ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

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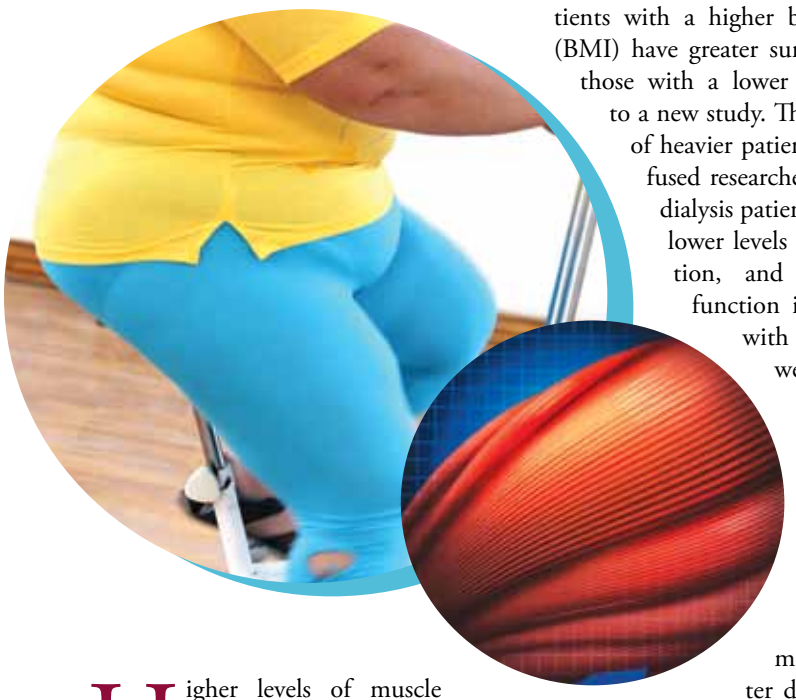
Muscle and Fitness Levels Linked to Dialysis Patients' Quality of Life



Higher levels of muscle mass contribute to higher quality of life for dialysis patients and could partially explain the "obesity paradox," in which dialysis patients with a higher body mass index (BMI) have greater survival times than those with a lower BMI, according to a new study. The longer survival of heavier patients has long confused researchers because obese dialysis patients generally have lower levels of physical function, and better physical function is also associated with better survival as well as better quality of life.

A new study in the *Clinical Journal of the American Society of Nephrology* used MRIs and other measures to better define body composition to tease out the relative effects of fat and muscle in these patients. Greater muscle mass was associated with better physical function among patients with similar BMIs. The results highlight the limitations of relying on BMI alone and imply that patients could benefit from interventions to increase muscle mass.

The study involved 105 maintenance hemodialysis patients at the University of Utah and at Vanderbilt University Medical Center. BMI is an easy but crude measure of body composition that does not differentiate how much of a person's weight is due to fat compared to muscle. So in addition to the patients' BMI, the researchers measured their waist circumference. To get a better idea of each patient's personal make-up, they used MRI to gauge the mid-thigh muscle level and amount of intra-abdominal fat. They assessed physical function by testing how far the patients could walk in six minutes and quality of life through questionnaires about physical function and mental health status. The patients were tested at the start of the study, after six months,

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Last Call for ESRD Seamless Care Organizations Issued

By Mark Lukaszewski

The Centers for Medicare & Medicaid Services (CMS) has announced a new—and likely its last—request for applications (RFA) for the ESRD Seamless Care Organizations (ESCOs).

If the RFA does not yield the expected 10 to 15 unique ESCO participants, CMS said it will consider scrapping the program. CMS emphasized that it reserves the right to terminate any model if it is not achieving the goals of the initiative. In its announcement, CMS stated that while it is "committed to improving care for beneficiaries with ESRD, the Agency reserves the right to decide not to move forward with the [Comprehensive ESRD Care] Model for any reason, as is true for all models."

Yet it is not all bad news for the future of the ESCO program. CMS has made vast improvements in this latest RFA, including changes to address rebasing concerns in years 4 and 5, and releasing proposed quality measures that would assess program participants' performance.

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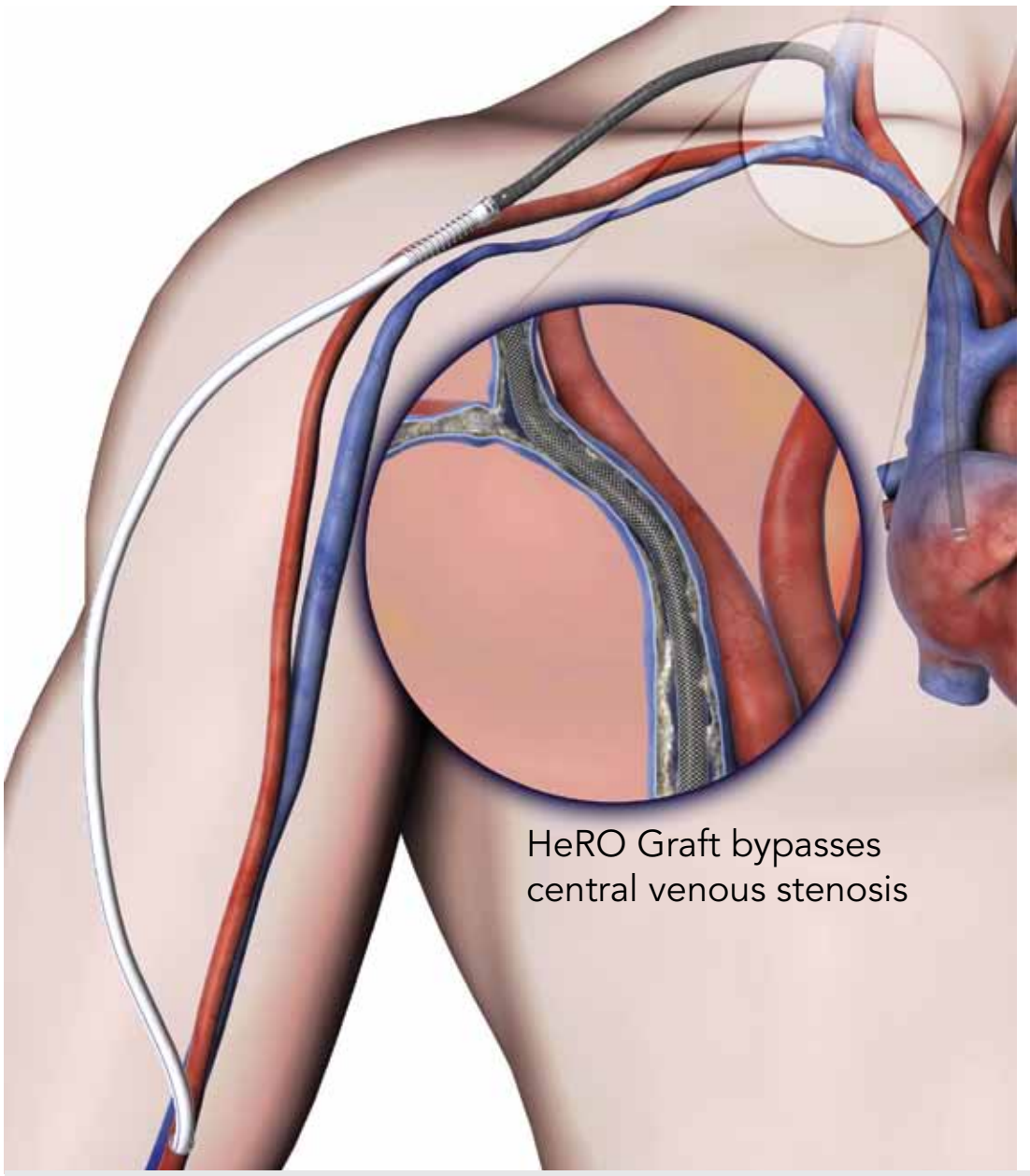
Inside



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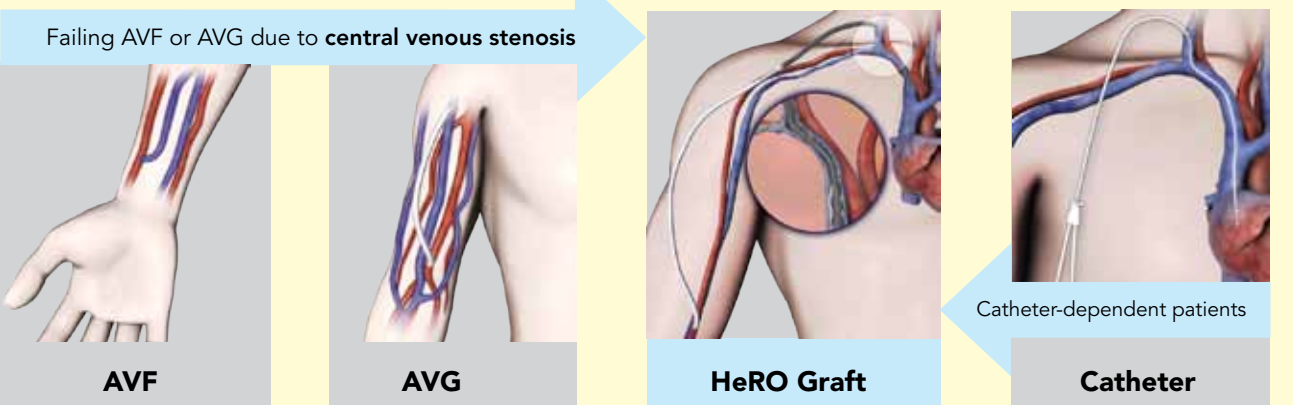

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References:
1) Katzman et al., J Vasc Surg 2009. 2) Gage et al., EJVES 2012. 3) Dageforde et al., JSR 2012.

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Muscle and Fitness

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and after 12 months.

The patients with higher BMI, greater waist circumference, and more abdominal fat had poorer scores on the walking test as well as worse scores on the quality-of-life questionnaires. Underweight patients also performed worse than patients with a normal BMI, a detail that could also reflect the effects of muscle mass.

"Because survival rates are better among dialysis patients with higher BMI, some people have argued that obesity is good in dialysis patients. This study is showing that it's much more nuanced than that," said lead study author Srinivasan Beddhu, MD, of the University of Utah School of Medicine in Salt Lake City. "Higher fat mass is associated with worse physical function, and more muscle mass is associated with better physical function. So from the point of view of physical function and quality of life, obesity is not good for dialysis patients."

Beddhu told *ASN Kidney News* that the relationship between mortality and BMI is complicated, with somewhat higher BMIs having a survival advantage even in the general population. In the U-shaped association, it seems bad to have either too much or too little fat. In the dialysis population, the curve shifts, with even higher levels of BMI having lower death risks. A higher BMI also seems to confer a survival advantage in patients with other chronic conditions such as heart failure and lung disease. "But that does not mean that fat is better than muscle," Beddhu said.

"This is a well-designed study where they have made careful measurements to try to separate out the influences of fat and muscle," said Kirsten Johansen, MD, professor of medicine at the University of California, San Francisco, School of Medicine and director of dialysis at the San Francisco VA Medical Canter, who was not involved in the study. Johansen said that the findings do not surprise her, but add important new data about the roles of fat and muscle.

"I've become convinced that, from a purely survival point of view, having a reserve of fat is good in case you get sick. But it isn't good for physical function," Johansen said. "I get nervous when people say patients who have higher body fat have better outcomes, so we should just let them be like that. These patients have really low levels of physical functioning and physical activity, so something that is having a negative impact on that may be having an impact on their quality of life, even if it is not negatively associated with survival. These data are highlighting once again that survival isn't everything."

The study's findings are consistent with other recent reports looking at the role of muscle mass in dialysis patients, according to Kamyar Kalantar-Zadeh, MD, MPH, PhD, chief of the division of nephrology and hypertension and professor of medicine at the University of California Irvine School of Medicine. Kalantar-Zadeh was the lead author of a similar study of almost 800 maintenance hemodialysis patients published in the *Clinical Journal of the American Society of Nephrology* in 2010. That study used mid-arm muscle circumference as a surrogate for lean body mass and triceps skinfold as a surrogate for fat mass. The study found that patients with more mid-arm muscle not only ranked higher on a mental health, quality-of-life scale but also had greater five-year survival rates. That finding of greater survival adds important information, considering that the study by Beddhu and colleagues was cross-sectional, giving a snapshot in time of the association of the patients' baseline levels with better quality of life.

Kalantar-Zadeh said that more studies are needed to go beyond associations and establish causation. "Dialysis patients have very high mortality and they have very poor quality of life. We need more studies to show whether doing something to increase muscle mass improves the outcomes in physical function and quality of life. If these associations are causal, interventions to increase muscle mass may improve patient outcomes," he said.

Johansen agreed that "we need longitudinal studies and intervention studies to see what happens if we have patients lose weight and build up muscle. Can we improve patients' functioning by doing these things?"

Beddhu echoed this assessment: "Because this study shows that higher muscle mass is associated with better physical function and quality of life in dialysis patients, interventions such as increased physical activity that decrease fat mass and increase muscle mass are likely to improve physical function, quality of life, and survival in dialysis patients. Such interventions need to be tested in clinical trials."

ESCOs

Continued from page 1

to reduce duplicative services and expenditures, the ACO would consolidate all aspects of care for patients with end stage renal disease (ESRD).

According to CMS, the initiative will identify, test, and evaluate new ways to optimize the quality of care for Medicare beneficiaries with ESRD. To do so, CMS will partner with health care providers and suppliers to test the effectiveness of a new payment- and service-delivery model with the goal of providing beneficiaries patient-centered, high-quality care resulting in improved outcomes and overall Medicare savings.

Positive changes to the ESCO application process

ASN believes that CMS's revised RFA was a step in the right direction and may entice organizations to participate in the program. The new RFA eliminates its original concept of reimbursing the program in years 4 and 5. This would have effectively penalized the highest performing ESCOs. This is a major change that will make the program more attractive to participants who are investing in costly resources and activities that will deliver better, higher-value care—the goal of the ESCO program.

Second, CMS said that allowing aggregation of beneficiary numbers and financial benchmarking information among smaller, non–large dialysis organization (LDO) providers is a positive change that might induce smaller providers to participate.

Finally, removing the requirement that nephrologists must be independent entities will likely make it possible for more nephrologists to consider becoming an ESCO-participant owner. Consequently, a nephrologist could be employed full or part time by another entity and still take an ownership share in the ESCO.

Outstanding challenges

Although CMS has made significant changes to attract greater participation, some are still concerned these changes may not be enough. Challenges to the program still remain. For instance, no end points have been established regarding what success will look like or how ESCOs will be judged as a success or a failure. The program is fundamentally an experiment, but in the scientific world one would never start a trial without first determining the end points being aimed for and what would define success.

Another major concern is how the ESCO program will incentivize kidney transplantation, one of the program's stated goals. Financial incentives in the current RFA do not seem to be aligned to promote transplantation, and CMS has not articulated any strategies to rectify this.

The proposed tecÚical expert panel (TEP) measure recommendations put forth were either not tested for dialysis patients or were recycled from general ACOs, not accounting for protocols that ESCOs would already be following. By making the proposed measures nonspecific to an ESCO population, CMS is increasing the administrative burden while not increasing patient quality. If the care organization is targeting a very specific population, the metrics should be as specific as possible to fit the unique needs of that population in order to optimize patient quality of life, satisfaction, and outcomes.

In addition, CMS does not take into account that ESCOs are incentivized to reduce expensive hospital-based care. This means that metrics designed to reduce hospitalizations and other expensive care may, in fact, be redundant administrative demands with no tangible effect on clinical outcomes. Finally, it is unclear how the metrics will interface with existing metrics in the Quality Incentive Program (QIP) as well as interpretative guidance in the Conditions for Coverage. Although it is stated that QIP metrics will be applied to the ESCO model, when QIP measures overlap with or supersede an ESCO measure, how will this be addressed? ASN, along with others from the kidney care community, has submitted comments to CMS regarding the proposed measures and will continue to work with CMS to produces patient-centered care for the ESCO program.

ASN remains hopeful that CMS can work within the community to finalize measures that fit the ESCO patient populations, and maintains that, if implemented appropriately, they could save costs while providing the highest care for patients.

The deadlines to apply for the ESCO program are June 23, 2014, for LDOs and September 14, 2014, for non-LDOs. CMS stated that the letters of intent will be used only for planning purposes and will not be binding. Applicants may access the application portal at https://innovationgov.force.com/rfa

Something to Say?

***ASN Kidney News* accepts correspondence in response to published articles. Please submit all correspondence to kidneynews@asn-online.org**

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KidneyNews

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- **Too rapid correction of serum sodium can cause serious neurologic sequelae**
- **Avoid fluid restriction during the first 24 hours of therapy**

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.

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March 2014

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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.
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Kidney Disease Biomarkers

Current Biomarkers in Kidney Disease: **Dawning of a New Era**

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By Joseph V. Bonventre

A biomarker is defined as a characteristic that can be objectively measured and evaluated as an indicator of normal biologic or pathogenic processes of pharmacological responses to a therapeutic intervention (1). Examples of biomarkers are proteins; lipids; microRNAs; genomic, metabolomic, or proteomic patterns; imaging determinations; electrical signals; and cells present on a urinalysis. This issue will focus primarily on serum and urine proteins. A partial list of candidate markers for kidney injury is presented in Figure 1 with corresponding sites of injury along the nephron.

Legacy kidney biomarkers include serum creatinine (sCr), blood urea nitrogen (BUN), urinary albumin/protein and volume excretion. However, sCr or BUN cannot distinguish injury from hemodynamic changes in the kidney that lead to appropriate changes in glomerular filtration rate (GFR), particularly when the changes are acute. Furthermore, sCr or BUN cannot change quickly enough with injury since individuals with normal renal function have a functional reserve that is brought into play in response to nephron injury. Other nephrons increase their function so that sCr and BUN may not move out of the "normal range" until there is a great deal of injury and potentially irreversible loss of nephrons. Thus GFR, whether measured by sCr or by more direct methods such as iohexol clearance, is a measure of function of the kidney which is clearly important but which may not move in sync with injury under all circumstances.

Having a biomarker that directly reflects injury, and is easily measured from a body fluid that is easily obtained, such as blood or urine, would change the paradigm to facilitate direct monitoring of injury rather than a secondary consequence of injury—a delayed reduction in GFR. By comparison to the field of cardiology we would move from a state of using changes in cardiac output or identification of heart failure as a reflection of myocardial injury to the use of troponin as a sensitive and specific marker of injury that physicians rely on and act upon. Of course there are other markers, besides troponin, that also provide additional information regarding the status of cardiac function. By analogy, multiple markers will be useful in nephrology, providing different information, for example about site of the injury, involvement of inflammation, and system associations. Some characteristics of an ideal biomarker are presented in Table 1. Biomarkers can be classified as predictive, prognostic, diagnostic, pharmacodynamic, or can be efficacy or surrogate markers (Table 2).

It is well recognized by regulatory agencies that a biomarker will not necessarily be informative in all contexts. In fact, the U.S. Food and Drug Administration (FDA) has developed a very thoughtful process by which they will "qualify" biomarkers in a "fit for purpose" contextualized way (2). There is a fundamental difference between "qualification" and "validation" of a biomarker. The latter term is best used to connote the validity and harmonization across many labs of the assay used to quantitate the biomarker.

In commenting on a major initiative of the FDA that focuses on biomarkers, Janet Woodcock, MD, current Director of the Center for Drug Evaluation and Research at the FDA, stated: "Most researchers agree that a new generation of predictive biomarkers would dramatically improve the efficiency of product development, help identify safety problems before a product is on the market (and even before it is tested in humans), and facilitate the development of new types of clinical trials that will produce better data faster" (3). The FDA has provided guidance that a biomarker can be considered "valid" if 1) it is measured in an analytical test system with well-established performance characteristics, and 2) there is an established scientific framework or body of evidence that elucidates the physiologic, pharmacologic, toxicologic, or clinical significance of the test result (4).

There has been a great enthusiasm of the pharmaceutical industry to work with academia and the regulatory agencies to identify new biomarkers that will facilitate drug development. As a result, much progress has been made on the preclinical identification of biomarkers that identify kidney injury due to a wide variety of toxins as well as ischemia with a very high level of sensitivity and specificity. This predictive safety testing consortium (PSTC) explored in great detail a number of urinary biomarkers and presented the results to the FDA and the European Medicines Agency (EMA) simultaneously. This was the first use of a framework allowing submission of a single application to the two agencies. The FDA and EMA concluded that they will allow drug companies to submit the results of seven new tests that evaluate kidney toxicity—four for tubular injury (KIM-1, albumin, clusterin, and trefoil factor-3) and three for glomerular changes or impaired tubular absorption (cystatin C, total protein, and β2 microglobulin) (5,6).

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Figure 1

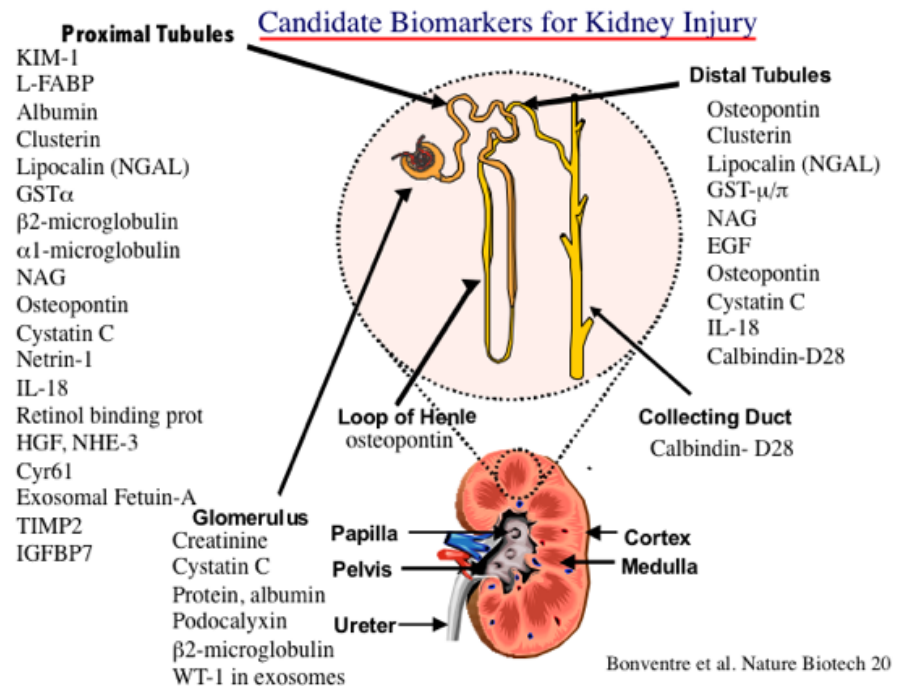

Table 1. Characteristics of an ideal blood or urinary biomarker

- Easy to measure with validated, reproducible technologies
- Stable in the blood or urine for time consistent with routine clinical use
- Devoid of interferences with other substances present in the biological fluid
- Unaffected by chemical composition of the fluid (e.g., urinary ionic strength and pH)
- Reflects risk, injury, outcome, and chronic sequelae with high sensitivity and high specificity
- Changes in measurements reflect efficacy of an intervention and/or recovery
- Identifies the specific site of injury (e.g., kidney tubule segment, glomerulus, endothelium, or interstitium)
- Understandable function of the marker in the kidney

Current Biomarkers

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Table 2. Classification of biomarkers

- **Predictive**—Identify subpopulations of subjects at higher risk for developing an outcome or more likely to respond to a therapy
- **Prognostic**—Informs likely course of disease progression or outcome
- **Diagnostic**—Characterizes onset and severity of a disease state
- **Efficacy**—Tracks the effectiveness of a treatment to mitigate a disease process
- **Pharmacodynamic**—Measures whether a particular biological response has occurred in response to a treatment
- **Surrogate**—Substitutes for a clinical end point ("a characteristic or variable that reflects how a patient feels, functions, or survives")

Initially this resulted in a great deal of momentum, but things have stalled. Why is this the case? Why have we not moved more rapidly to translate these findings in rats to humans? In many cases, when examined closely, the mechanisms of injury observed in rats carry over to humans. When studying the sensitivity and specificity of biomarkers for kidney injury in the rodent the gold standard is histological injury. The PSTC consortium was meticulous in examining multiple regions of the nephron and multiple compartments (tubular, interstitial, tubule, cortex, and outer and inner medulla) of the kidney. In humans this is not possible. Even in those patients in which biopsy material is available, only a small portion of the kidney is sampled and is likely not to reflect overall injury in an acute setting. As a result, the biomarkers have been generally evaluated using sCr as a gold standard. This leads to faulty conclusions because sCr is so flawed as a gold standard for acute injury. There can be significant injury without a change in sCr, and sCr can change due to hemodynamic factors without injury. We have pointed out the large impact the faulty gold standard has on evaluation of biomarkers (7). This has resulted in a large number of clinical studies where the receiver operator curve analysis (a standard way to evaluate biomarkers) reveals an area under the curve that is often between 0.7 and 0.85, much lower than values of 0.9 to 0.99 that have been reported in animals (8,9). This has introduced a level of caution in researchers, practitioners, and the diagnostics industry.

It can be argued that what really matters is not changes in laboratory values as an adjudicator of biomarker utility but longer term "hard" patient outcomes. While this is certainly true, it means that it may take many years to identify hard outcomes. For example, will an increase in a novel biomarker of kidney injury in a patient administered cisplatin, without a change in sCr, result in the development of hypertension and/or renal disease in later life? If we wait for these data we will lose the opportunity to employ these injury biomarkers. Especially in combination, they often provide a high negative predictive value even when compared to sCr.

Another reason for loss of momentum relates to studies of the kidney injury markers in chronic kidney disease (CKD). It is well known that acute kidney injury is associated with the development and/or progression of CKD (10). It therefore seems reasonable to assume these injury markers will predict progression of CKD, but the patient with CKD has multiple confounders that can potentially alter the rate of progression so that the relationship between a particular biomarker and progression is likely to be variable depending upon the study and the population—a fact that is being borne out in many studies. This does not, however, decrease the importance of a biomarker that provides mechanistic insight into an injury process that is important in the overall course of kidney disease. A list of some of the factors that have held back the clinical use of kidney biomarkers is included in Table 3.

In conclusion, over the last decade there has been intense interest in finding and qualifying new biomarkers of kidney injury. Biomarkers will enable us to diagnose kidney injury earlier and provide better information about the status of ongoing injury in patients with CKD as well as predict the likelihood of progression of disease. This will facilitate personalized medicine by better informing interventional, diagnostic, and therapeutic decision-making to minimize kidney injury and optimize interventional strategies. I am convinced that better kidney injury biomarkers will provide us with better tools that will result in better outcomes for our patients.

Table 3. What is holding back the use of kidney biomarkers?

- The "Gold Standard" problem
- Unknown thresholds to mark "normal" and "functionally important injury"
- Undue conservatism in not believing that preclinical studies inform the use and interpretation of biomarkers in man
- Therapeutic developers reluctance to incorporate biomarkers into clinical trials
- Diagnostic company timidness in aggressively developing biomarkers for clinical use
  - Expectations for study results in humans are unrealistic given the gold standard problem
  - Impacts harmonization of biomarker test values across lab sites

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Disclosures

Dr. Bonventre declares that he is co-inventor on KIM-1 patents that are assigned to Partners Healthcare. He is consultant to a number of companies in areas of patient kidney safety and development of new therapeutics including Sanofi, Thrasos, MediBeacon, Astellas, Mast, PTC, Keryx. He, or members of his family, own equity in Thrasos, Sentien, and MediBeacon.

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Biomarkers in Chronic Kidney Disease

By Nisha Bansal and Chi-Yuan Hsu

There has been considerable interest in studying novel biomarkers in chronic kidney disease (CKD) beyond the conventional clinical indices, such as serum creatinine, blood urea nitrogen, and urine protein or urine albumin. The motivation for this is similar to what has been outlined in other articles in this issue of *ASN Kidney News*. For example, novel biomarkers may improve our ability to better risk classify patients and guide clinical actions (e.g., closer follow-up and more intense treatment for patients at higher risk of progression of CKD), to identify high-risk patients for enrollment into clinical trials (as enriched enrollment of patients who are more likely to progress will enhance study power), and to better understand underlying biological pathophysiological mechanisms (which may in turn identify novel targets for treatment).

Under the sponsorship of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), a CKD Biomarker Consortium was formed in 2009. The consortium consists of investigators from more than a dozen academic medical centers and research institutions around the country, analyzing clinical data and stored biosamples and from numerous longitudinal cohorts.

Biomarkers of renal injury in the setting of CKD

One area of focus for the CKD Biomarker Consortium is to evaluate—among patients with CKD or those at high risk for CKD—urine injury biomarkers, many of which were initially identified in the arena of acute kidney injury (AKI). Examples of these urine injury biomarkers include urine kidney injury molecule-1 (KIM-1), urine neutrophil gelatinase associated lipocalin (NGAL), liver-type fatty acid binding protein (L-FABP) and beta-N-acetylglucosaminidase (NAG).

Preliminary results show that injury biomarkers are in fact often detectable in the urine of patients with CKD, albeit usually at concentrations much lower than that seen in the setting of AKI. Interestingly, a minority of seemingly stable ambulatory CKD patients have very high levels (1,2). Several studies have shown that elevations of these levels of urine injury biomarkers are independent risk factors for more rapid loss of kidney function in subsequent years (1–3). For example, in the Chronic Renal Insufficiency Cohort (CRIC) study, although median urine NGAL concentration was only 17.2 ng/mL (in 3386 patients), 5 percent of readings were between 178.9 ng/mL and 3069.6 ng/mL (1). In that study, even after adjusting for potential confounders such as baseline estimated glomerular filtration rate (eGFR) or urine protein, high urine NGAL level remained an independent risk factor for progression of CKD, defined as halving of eGFR or end stage renal disease (Table 1). However, this novel marker only very modestly improved prediction of outcome events (1).

Urine injury biomarkers may be associated with nonrenal outcomes

Kidney dysfunction, as traditionally assessed by eGFR and urine albumin-creatinine ratio, is strongly linked with higher future risk of cardiovascular disease and death (4,5). Recent investigations have also noted that urine injury biomarkers may also be associated with cardiovascular disease and death. A study of approximately 3000 older adults in the Health, Aging and Body Composition cohort with and without CKD (mean eGFR 79 mL/min/1.73 m^2) found that higher urine KIM-1 was independently associated with a 32 percent higher risk of incident heart failure, while there was no association of interleukin-18 (IL-18) with heart failure (6). In this same cohort, there was a modest association of higher urine KIM-1 with all-cause mortality (7). There was no association of KIM-1 with atherosclerotic disease and no association of IL-18 with atherosclerotic disease or death. However, the magnitude of the association of KIM-1 with these outcomes was smaller than that seen with urine albumin-creatinine ratio (6,7). These initial studies suggest that urine injury may possibly signal risk of numerous nonrenal outcomes. While these studies are observational and do not indicate causality, these data provide novel information about the link between kidney dysfunction and cardiovascular disease. Further studies are needed to explore these associations in different populations, including patients with known CKD.

Urine injury biomarkers in unique patient populations

Urine injury biomarkers have also been examined in unique populations, such as patients infected with the human immunodeficiency virus (HIV).

In a study of 908 HIV-infected women with preserved kidney function (mean eGFR 88 mL/min/1.73 m^2), high urine IL-18 levels were independently associated with 88 percent greater risk of all-cause mortality (8). There was no association of KIM-1 with higher risk of mortality (8). In this same cohort, IL-18 and KIM-1 were also independently associated with subsequent rapid decline of kidney function (9).

Interestingly, it has been suggested that elevations in urine injury biomarkers may also be an earlier manifestation of kidney injury induced by tenofovir, a commonly used nephrotoxic medication used to treat HIV. Among this cohort of HIV-infected women, three urine tubular biomarkers (NGAL, NAG and β-2-microglobulin) were measured before and after starting tenofovir (10). There were no differences in NGAL or NAG; however, β-2-microglobulin was 19 times more likely to be elevated after tenofovir initiation (10). In a cross-sectional study of 99 patients with HIV, of whom approximately half were on tenofovir therapy, spot concentrations of retinol-binding protein (RBP)—a low-molecular weight protein normally reabsorbed by the proximal tubule—were significantly higher in tenofovir users (11). As our understanding of these urine injury biomarkers increases, there may be further opportunities to study these biomarkers in other high-risk patient populations.

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Biomarkers of Acute Kidney Injury

By Suneel M. Udani and Jay L. Koyner

Over the past decade there has been an explosion of research investigating biomarkers of acute kidney injury (AKI). The research was borne out of the desire to replace serum creatinine, and in part urine output, as for a variety of reasons both serve as suboptimal tools in the diagnosis of acute renal tubular injury. The biomarker movement has been assisted by internationally accepted, standardized, consensus definitions of AKI. Whereas decades ago AKI definitions varied from study to study, the implementation and validation of the RIFLE (Risk, Injury, Failure, Loss and End Stage) and AKI Network criteria paved the way for the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines (1). In solidifying the definition of AKI these criteria have helped to quantify the growing number of AKI cases, facilitated the growth of the biomarker field, as well as allowed for the comparison of biomarkers and event rates across studies.

While initial investigations into several modern biomarkers of AKI demonstrated remarkable promise in the ability to detect AKI earlier than serum creatinine, subsequent attempts to validate these smaller studies in large-scale multicenter trials have failed to match the original success. Perhaps most importantly the intense investigation of biomarkers has demonstrated that AKI is a complex clinical syndrome that is often the result of multiple renal insults. For example, while AKI following cardiac surgery has traditionally been thought to be related to ischemic injury, in fact there are multiple factors that can impact the development and outcome of cardiac surgery–associated AKI, including ischemic injury; inflammatory response from, and duration of, cardiopulmonary bypass; need for postoperative mechanical ventilation; need for intra- and perioperative blood products; and preoperative comorbidities (most importantly CKD) amongst others. As nephrologists, we see AKI associated with a variety of clinical settings/factors including cardiac surgery, sepsis, nephrotoxins, and trauma. However comingling of these settings/issues in individual patients is extremely common, and as such it is unrealistic to expect one marker (known to upregulated due to inflammation or ischemia or some other injurious event) to be able to diagnose early AKI in all of these settings.

Research into the field of AKI biomarkers first set out to find the "renal troponin," which detects injury earlier than serum creatinine/urine output, and over the past several years countless studies have demonstrated that several modern biomarkers can do this. Whether it is data from the Endre and colleagues (2) from the EARLY ARF trial (investigating AKI in mixed medical-surgical intensive care units [ICUs]) or those from Parikh and colleagues from the TRIBE AKI (3,4) study (investigating AKI after adult and pediatric cardiac surgery) several biomarkers have been shown to detect AKI earlier than changes in serum creatinine. In these and other studies, many biomarkers (e.g., plasma and urine neutrophil gelatinase-associated lipocalin [NGAL], urine interleukin-18 [IL-18], or urinary kidney injury molecule-1 [KIM-1]) demonstrated mild to moderate success in predicting early AKI (areas under the curve [AUCs] of 0.60 to 0.80). However, given these results, some in the field have shifted their focus towards enhancing the AKI diagnostic capabilities via the utilization of modern biomarkers of AKI in conjunction with serum creatinine.

This idea has gained traction over the last 2 to 3 years with multiple groups demonstrating diagnostic and prognostic improvements when using modern biomarkers of AKI in conjunction with changes in serum creatinine. Utilizing biomarkers in the setting of small increases in serum creatinine or drops in urine output (e.g., KDIGO Stage 1 AKI) has been demonstrated to be effective in detecting those patients who will go on to develop more severe AKI (e.g., KDIGO Stage 3) or the future need for renal replacement therapy. In fact, a variety of biomarkers—including plasma NGAL, urinary albumin to creatinine ratio, urine IL-18, and the product of urine insulin-like growth factor-binding protein 7 (IGFBP7) and tissue inhibitor of metalloproteinases-2 (TIMP-2)—have all been shown to reliably forecast the future development of severe AKI when measured following adult cardiac surgery or early in the course of ICU admission/critical illness (5,6). Of note, besides modern biomarkers, recent data demonstrates that urine output in the 2 hours following a standardized high-dose furosemide challenge in euvolemic patients with early AKI also reliably forecasts progression to stage 3 AKI (7).

In addition to being used in the ICU in conjunction with serum creatinine, several recent studies have demonstrated that modern biomarkers can detect those patients at greatest risk for inpatient AKI at the time of emergency room (ER) arrival. Urine NGAL, serum cystatin C, and others have been shown to predict which patients will go on to develop AKI during their hospital stay (8,9). Perhaps more importantly, several of the ER studies have demonstrated that modern biomarkers can aid in distinguishing those with volume-responsive AKI from those with intrinsic renal tubular damage/acute tubular necrosis. This ability to distinguish those with a change in glomerular filtration/function but no change in tubular function (traditionally thought of a "prerenal" azotemia) from those with both a change in function and tubular damage is exactly what nephrologists have been looking for over the last decade. Separately, in 2012 Doi et al. (10) and Nejat et al. (11) published data in *Kidney International* that demonstrated several modern biomarkers (including NGAL, KIM-1, and urine Liver Fatty Acid Binding Protein [LFABP]) all had the ability to differentiate transient and sustained-intrinsic AKI in critically ill ICU patients. This ability to separate out those with readily reversible transient AKI from those with intrinsic tubular injury and acute tubular necrosis will be invaluable as nephrologists embark on clinical trials to treat and/or prevent AKI. In an attempt to maximize clinical trial funding, AKI investigators should attempt to enroll patients who will meet hard end points like KDIGO Stage 3. The need for renal replacement therapy and inpatient mortality will be of the utmost importance in order to maximize clinical trial funding. Table 1 summarizes the findings of several studies investigating modern biomarkers of AKI in a variety of clinical setting for several clinical end points.

Despite these data and their promise, modern biomarkers continue to have several limitations. First, biomarker performance has been measured against serum creatinine, which is not exactly a true gold standard. Second, as of March 2014, the U.S. Food and Drug Administration has not approved any of these biomarker assays for clinical use. In fact, several of the biomarkers have multiple commercially available research assays,

Table 1. Biomarker performance in detecting AKI in a variety of clinical settings*

	Perioperative AKI			Critically Ill			Emergency Room	
	Early Post-op AKI	AKI progression	Long-Term Mortality	Early Diagnosis of AKI	Type of AKI (Transient vs. Intrinsic)	Need for RRT	Early Diagnosis of AKI	Type of AKI (Transient vs. Intrinsic)
Urine NGAL	+	–	+	+	+	+	+	+
Blood NGAL	+	+	?	–	?	–	?	?
Blood CysC	+	–	?	+	+	+	?	?
Urine IL-18	+	+	+	+	+	+	+	+
Urine KIM-1	+	–	+	+	–	–	+	+
Urine LFABP	–	–	+	?	?	–	+	+
TIMP-2 IGFBP-7	?	?	?	+	?	+	?	?
Urine Protein/ Albumin	+	+	+	?	?	?	?	?

*AKI = acute kidney injury; CysC = cystatin C; IGFBP7 = insulin-like growth factor-binding protein 7; IL-18 = interleukin 18; KIM-1 = kidney injury molecule-1; LFABP = liver fatty acid binding protein; NGAL = neutrophil gelatinase associated lipocalin; op = operative; RRT = renal replacement therapy; TIMP-2 = tissue inhibitor of metalloproteinases-2; + = data published displays the ability to detect this aspect of AKI; – = data published does not display the ability to detect this aspect of AKI; ? = no large multicenter data published on this biomarker/aspect of AKI. Adapted and expanded from Koyner JL, Parikh CR. *Clin J Am Soc Nephrol* 2013; 8:1034–1042.

which only serve to confound the published literature. Finally, the ability to combine biomarkers to augment their diagnostic and prognostic performance remains statistically problematic.

In summary, there are several viable modern biomarkers of AKI. Each biomarker has its own individual profile, with some excelling at identifying early AKI while other can provide insight into the differential diagnosis of AKI (transient vs. intrinsic AKI). Over the next few years, undoubtedly new biomarkers will be discovered and established ones will be further validated. Eventually, biomarkers will be used as triggers for therapeutic AKI interventions or to risk-stratify patients to determine who would benefit from the early initiation of renal replacement therapy. Over the last decade nephrologists have laid the foundation for the next decade, which will see a shift towards these assays being used for clinical care while still being utilized in AKI research.

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Disclosure

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Biomarkers in Other Systemic Diseases: Cardio-Renal Syndrome

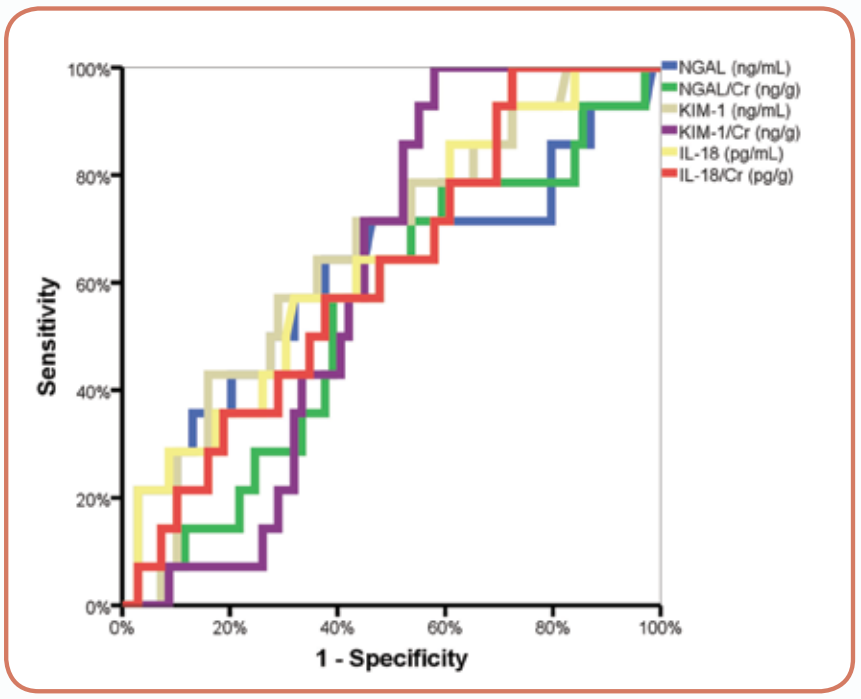
By W. H. Wilson Tang

Renal insufficiency is prevalent and clinically relevant in the setting of congestive heart failure. When admitted for acute decompensation, on average 1 out of 5 patients has a rise in serum creatinine, 1 out of 10 requires some form of dialysis, and 1 out of 20 requires long-term renal replacement therapies (1). These startling observations highlight the fact that adequate renal function plays a pivotal role in the clinical stability of heart failure. Hence, the term "cardio-renal syndrome" (CRS) has been coined to describe the extreme of cardio-renal dysregulation whereby therapy to relieve congestive symptoms of heart failure is limited by further decline in renal function (the 2004 National Heart, Lung, and Blood Institute [NHLBI] Working Group definition). However, the Acute Quality Dialysis Initiative (AQDI) has expanded this concept to a conceptual CRS classification scheme, which broadens the definitions to include a wide range of concomitant dysfunction between the heart and the kidneys (2). Unfortunately, such contemporary nomenclature is largely descriptive, and the lack of pathophysiologic basis has limited its clinical applicability in triaging distinct therapeutic approaches to individual patients while ignoring many confounding factors. Indeed, when both heart and kidney impairment progresses, as indicated by rising natriuretic peptide levels and worsening glomerular filtration rate, the long-term outcomes are the poorest (3). Nevertheless, the prognostic value of natriuretic peptides remains robust even though the range of the absolute values are higher than those without renal insufficiency.

There is a natural tendency for clinicians, researchers, and investigators alike to gravitate on quantifying renal dysfunction with an easily available metric that is useful in outcomes research. Indeed, a concerted effort was made to examine the clinical relevance of changes in daily serum creatinine during heart failure hospitalization. A rise in serum creatinine ≥0.3 mg/dL was deemed to provide the optimal sensitivity (65 percent) and specificity (81 percent) in predicting in-hospital mortality (4)—a threshold that has been used (and perhaps misused in retrospect) over the past decade in a wide range of outcomes research studies. Such a creatinine rise in patients (often termed "worsening renal function" or WRF) has been associated with an increase in length of hospital stay by 2.3 days, a 67 percent increase in risk of death within 6 months after discharge, and a 33 percent increased risk for readmission (5). However, several new observations have recently emerged regarding the complexity of creatinine changes during decongestive therapy and what they may imply. Improvement in renal function following decongestive therapy may not always reflect better clinical status, as evident that those whose fall in serum creatinine requires progressive renal impairment prior to admission (6). At the other end of the spectrum, the ability to achieve sustained decongestion despite worsening renal function (as evident by evolving hemoconcentration) has been associated with paradoxically better outcomes (7). Interestingly, the main determinants of worsening renal function during decongestion appeared to be inadequate systemic perfusion pressure (i.e., drop in systemic blood pressure during treatment) as well as inadequate responses to decongestive therapy (i.e., drop in net urine output) rather than changes in central hemodynamics or acute tubular injury as determined by novel AKI biomarkers (8–10 , Figure 1). These contemporary observations have thus revealed the increasingly clear picture that creatinine-based concepts of CRS may not account for concomitant large intravascular fluid shifts and the lack of true nephrotoxicity during aggressive decongestion—a concept that is still in evolution. Nevertheless, the good news is that not all rises in creatinine during decongestion for decompensated heart failure signal the grave consequence of AKI.

Perhaps the biggest challenge in contemporary approaches to CRS is the lack of effective "renal-sparing" or "renal-enhancing" therapies in the treatment of congestion for patients with heart failure. Much effort has been made over the past decade by investigators and industries alike. These included the clinical development of natriuretic peptide analogues, adenosine receptor antagonists, vasopressin receptor antagonists, and ultrafiltration—all have met with mixed results or off-target effects. Indeed, the treatment approach to acute decompensated heart failure has not changed over the past 3 decades, with the sole reliance on intravenous loop diuretics in various forms of dosing, route, and formulations, plus some adjunctive therapeutics. While future insightful mechanism biomarkers to guide therapeutic choices are still needed, they are more likely to be utilized to prevent rather than to react to AKI.

Figure 1. Receiver operator characteristic curve analysis for urinary biomarkers to predict acute kidney injury in the setting of acute decompensated heart failure (area under the curve 0.54 to 0.64) (Verbrugge FH, et al. *J Card* Fail 2013; 19:621–628). Cr = creatinine; IL-18 = interleukin-18; KIM-1 = kidney injury molecule-1; NGAL = neutrophil gelatinase associated lipocalin.



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Biomarkers in Acute Kidney Injury in Cirrhosis

By Daniel E. Carl and Arun J. Sanyal

Cirrhosis is a major contributor to the burden of disease in society, and much of the morbidity and mortality associated with cirrhosis is due to the complications of portal hypertension. Acute kidney injury (AKI) is a frequent complication in patients with cirrhosis, occurring in up to 20 percent of hospitalized patients (1). Despite the high rate of AKI in this patient population, there is often a delay in early diagnosis of AKI. Furthermore, there are clinical challenges in correctly diagnosing the etiology of AKI, which in turn can alter specific therapy. This article will focus on the current pitfalls in diagnosing AKI in cirrhosis and the use of biomarkers in this population.

The etiology of AKI in cirrhosis is often separated by functional and structural forms of injury. Approximately one-third of AKI occurrences in hospitalized patients with cirrhosis is from acute tubular necrosis (ATN), although the less common glomerular injury also needs to be screened. The remaining forms of AKI occur from decreased renal perfusion. The majority of these are volume-responsive prerenal azotemia (PRA), which accounts for approximately 45 percent of the AKI in the cirrhotic population. However, the other third of patients with AKI from decreased renal perfusion are not volume responsive, and have hepatorenal syndrome (HRS) (1). As treatment is different for each of these three types of AKI, the correct diagnosis is imperative. For example, HRS is treated with the vasoconstrictor agents norepinephrine, terlipressin, or midodrine in addition to albumin rescue (2,3). In addition, early diagnosis and subsequent treatment of HRS portends a better renal prognosis (4). The etiology of AKI can also dictate whether renal replacement is offered; specifically, patients not deemed a liver transplant candidate who are diagnosed with HRS are often not offered therapy. However, the converse is true in patients diagnosed with ATN, and missing the diagnosis of ATN can lead to denial of renal support to a patient. Further muddying the picture, infections are common in cirrhotic patients and can independently lead to all three types of AKI (ATN, PRA, and HRS); AKI in these patients may represent a continuum from functional to structural AKI.

When a clinician is investigating the etiology of AKI in cirrhosis, common studies used include: serum creatinine, urinalysis evaluation, urine sodium and fractional excretion of sodium (FENA), and urine microscopy evaluation. A percutaneous kidney biopsy could help in the correct diagnosis; however, it is frequently not performed in this patient population because of bleeding concerns. Wadei et al. (5) performed kidney biopsies in cirrhotic patients undergoing a liver transplant and found 41 percent had ATN despite non-classic urinary findings, which highlights the common yet likely underdiagnosed ATN lesion in cirrhosis. As prompt recognition and diagnosis of HRS is crucial in the management of the disease, it is therefore important to know the limitations of current methods to estimate GFR and indices of evaluating AKI.

Traditional methods of estimating GFR may be less reliable in cirrhosis compared to the general population, as both urea and creatinine production can be altered in cirrhosis. In addition, cirrhotic patients may have deceivingly low creatinine values, despite the presence of moderate or severe renal failure. This can occur from decreased muscle mass (6), increased renal tubular secretion of creatinine (7), as well as decreased hepatic creatine synthesis. Accordingly, it is well documented that cirrhotic patients can have a normal serum creatinine despite having a truly depressed GFR (6,8). Indeed, both measured as well as calculated creatinine clearances are falsely elevated in cirrhotic patients, and can overestimate inulin clearances by up to 74 percent (9). Traditionally, clinicians have used urine sodium, osmolality, as well as evaluation of urine sediment to help differentiate HRS from other causes of AKI. However, caution should be exercised with these traditional markers of renal function to evaluate the possibility of HRS. For example, patients with ATN in the setting of cirrhosis can have a low urinary sodium concentration, potentially a result from prolonged renal vasoconstriction (10). Conversely, patients with HRS and hyperbilirubinemia can infrequently have high urine sodium values (11,12). Furthermore, granular casts typically associated with ATN can also occur with persistent hyperbilirubinemia in HRS. As a result of these inconsistencies with urinary markers to differentiate ATN from HRS, the International Ascites Club removed these indices with publication of their revised guidelines in 2007 (13).

In summary, it is paramount to both diagnose AKI early as well as differentiate structural from a functional type of AKI. Serum creatinine is subject to many pitfalls in cirrhosis, and is also a late marker of kidney injury. Furthermore, it does not segregate between structural and functional AKI, particularly in cirrhosis. To this end, there has been a growing interest in nephrology to find and validate markers of structural kidney injury, especially those that will precede serum creatinine elevations. Interleukin-18 (IL-18), kidney injury molecule-1 (KIM-1), liver-type fatty acid binding protein (L-FABP), and neutrophil gelatinase associated lipocalin (NGAL) appear to have the most promise in defining structural, rather than functional, injury in this patient set.

Two studies separately investigated the utility of NGAL in differentiating structural (ATN) from functional (PRA or HRS). In the first, Fagundes et al. (14) studied urinary NGAL levels in 241 patients with cirrhosis, 84 of whom had renal dysfunction. They found uNGAL levels were significantly higher in those with ATN compared to PRA or HRS. uNGAL levels in HRS patients were at a level in between ATN and PRA. Moreover, upon review of the HRS cohort, uNGAL levels were higher in patients with an infectious mediated event compared to those who did not have an infection. Moreover, in this subset, uNGAL levels were close to those with ATN. In a second study, Verna et al. (15) measured uNGAL levels in 118 cirrhotic patients admitted to a single hospital. Similar to the preceding study, they also found uNGAL levels significantly higher in patients with intrinsic AKI compared to HRS or PRA, with uNGAL levels in HRS patients intermediate between the two groups. This difference in uNGAL between HRS and intrinsic AKI was in the absence of any difference in serum creatinine. Collectively, these two studies highlighted the promise uNGAL has in differentiating the different forms of AKI.

Finally, Belcher et al. (16) evaluated 76 patients with progressive AKI in a prospective, multicenter, blinder study. They found 53 percent had ATN, with the remainder having PRA (26 percent) or HRS (22 percent). FENA was lowest in the cohort diagnosed with HRS, although not statistically different from PRA or ATN. NGAL, L-FABP, IL-18, and KIM-1 were measured in all patients. The etiology of AKI was determined in a blinded manner, without knowledge of the biomarkers. Those identified with ATN had the highest levels of all four biomarkers, with HRS in the intermediate range similar to the two prior studies. Moreover, Belcher et al. found absolute value cutoffs for all four biomarkers to define those with ATN. The relative risk of ATN increased with the increasing number of positive biomarkers. In those patients with none of the four biomarkers above the cutoff, 17 percent had ATN. This increased to 73 percent if two of the biomarkers were positive and to 100 percent if all four were positive.

In conclusion, AKI in the cirrhotic population is a frequently encountered clinical problem, and is associated with a high mortality. Because of limitations in available laboratory tests, the diagnosis of AKI is frequently delayed and the etiology of AKI is incorrect. The introduction of new biomarkers that increase earlier than traditional markers, such as serum creatinine, allows for earlier identification of renal injury. Furthermore, these biomarkers hold promise for delineating structural versus functional AKI.

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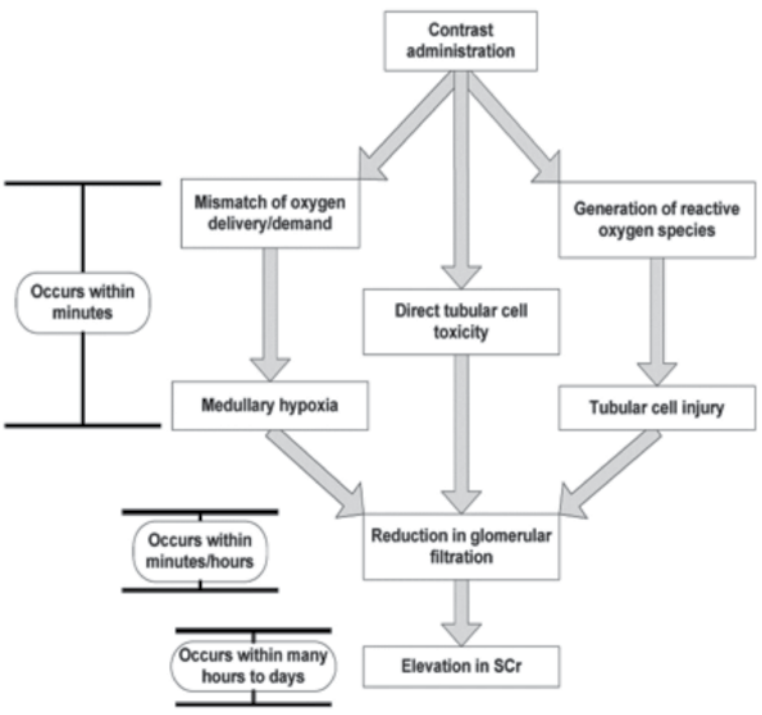
Biomarkers in Contrast-Induced Acute Kidney Injury

By Steven D. Weisbord, MD, MSc

Contrast-induced acute kidney injury (CI-AKI) is a common condition that is associated with serious, adverse short- and long-term outcomes. Despite substantial advancements in our understanding of CI-AKI, the capacity to effectively risk-stratify patients, diagnose incipient renal injury before elevations in serum creatinine (SCr) manifest, and identify patients at highest risk for adverse downstream events is limited. Blood and urine biomarkers of kidney injury hold promise as a means by which the risk-stratification, diagnosis, and prediction of prognosis of CI-AKI could be significantly enhanced, and the judicious implementation of cost-effective preventive care and treatment to mitigate adverse outcomes substantially improved.

Renal tubular injury in CI-AKI, which results from medullary hypoxia, generation of reactive oxygen species, and direct tubular toxicity of contrast media, occurs almost immediately following contrast administration. In a rat model of CI-AKI, Liss et al. (1) demonstrated a reduction in outer medullary renal blood flow within minutes of contrast administration, with the most pronounced decrement occurring within 10 to 20 minutes. Bakris et al. (2) documented increased oxygen free radical generation within 5 minutes and reduction in glomerular filtration of nearly 50 percent less than 20 minutes following contrast administration in dogs. Hofmann et al. (3) demonstrated that medullary blood flow in healthy human subjects decreased within 20 minutes following intravascular contrast administration. These and other studies confirm that the adverse hemodynamic and nephrotoxic effects of iodinated contrast develop within minutes following contrast administration. However, the diagnosis of CI-AKI in clinical practice is based on identifying elevations in SCr that typically manifest days following contrast administration (Figure 1). Consequently, provider and patient awareness of the development of CI-AKI is delayed or may not occur at all if follow-up assessment of SCr is not performed. As a result, supportive care to mitigate kidney damage, including correction of intravascular volume depletion and withdrawal of potentially nephrotoxic medications, may be delayed or not implemented. This lag in diagnosis underscores the strong need to identify other blood and/or urine markers that are sensitive and specific for early renal tubular injury, that identify patients with CI-AKI at the time of initial kidney insult, and that help inform the provision of appropriate care to attenuate the risk for progressive kidney damage.

Figure 1. Pathophysiology of contrast-induced acute kidney injury and timing of events



Prior studies of biomarkers in CI-AKI

Over the past decade there have been many studies investigating biomarkers for the risk stratification, diagnosis, and long-term prognosis of AKI. These studies focused largely on renal injury in the postoperative and intensive care unit settings. The predictive, diagnostic, and prognostic capacity of biomarkers in the context of iodinated contrast administration has been less well characterized. However, the studies that have been conducted to date demonstrate the potentially important role biomarkers may play in the setting of CI-AKI (Table 1) (4–15).

Table 1. Studies of biomarkers and contrast-induced acute kidney injury

Author	Pts (N)	Pts with CKD (N)	Biomarker	CIAKI N (%)
Alharazy et al.	100	100	s NGAL	11 (11)
Bachorzewska et al.	35	0	u/s NGAL	0 (0)
Bachorzewska et al.	100	0	u/s NGAL, s CyC*	11 (11)
Bachorzewska et al.	60	0	u/s NGAL, s CyC	6 (10)
Bachorzewska et al.	25	0	u/s NGAL, u L-FABP	NR
Briguori	410	410	s CyC	34 (8)
Briguori	294	≥142 £	s CyC	46 (16)
Hirsch et al.	91	0	u/p NGAL	11 (12)
Ling et al.	150	NR	u NGAL, u IL-18	13 (9)
Malyszko et al.	140	0	†	17 (12)
Nakamura et al.	96	69	u L-FABP	13 (14)
Shaker et al.	30	0	s NGAL, s CyC	2 (7)

*u denotes urine; s denotes serum; p denotes plasma
£ specific number of pts with CKD not specified
† panel included: u/s NGAL; uKIM-1,uL-FABP, ulL-18
NR denotes not reported

Nakamura et al. (11) demonstrated that preangiography urinary liver fatty acid binding protein (L-FABP) levels were higher among patients who developed CI-AKI than patients who did not (18.5±12.8 µg/g vs. 7.4±4.4 µg/g; p<0.01). Postangiography L-FABP levels increased among patients with CI-AKI, yet remained unchanged in patients without CI-AKI (46.8±30.5 µg/g vs. 8.0±6.2 µg/g; p<0.001). A subsequent study by Hirsch (8) demonstrated higher concentrations of urine neutrophil gelatinase-associated lipocalin (NGAL) (135±32 ng/mL vs. 11.6±2 ng/mL; p<0.001) and plasma NGAL (151±34 ng/mL vs. 36±4 ng/mL; p<0.001) 2 hours following angiography in patients with CI-AKI compared to patients without CI-AKI. Urine and plasma NGAL at 2 hours were strong independent predictors of CI-AKI (p<0.0001, respectively). In a study of 150 patients, Ling et al. (9) demonstrated that in addition to diagnosing kidney injury earlier than SCr, urine interleukin-18 (IL-18) levels 24 hours postangiography predicted the development of major adverse cardiac events over 17 months of follow-up (relative risk [RR] =2.09; p=0.001). More recently, in a study of 410 patients with CKD undergoing angiography, Briguori et al. (13) demonstrated that elevations in serum cystatin C (CyC) of ≥10 percent at 24 hours were 100 percent sensitive and 86 percent specific for the development of CI-AKI and were predictive of 1-year death and need for dialysis. Moreover, this threshold increase in serum CyC was more predictive of 1-year death and need for dialysis than elevations in SCr.

Notwithstanding these promising preliminary findings, there are certain methodological limitations to these studies. First, a large proportion of patients did not have baseline CKD, which is the principal risk factor for CI-AKI; consequently only a small minority developed CI-AKI. Second, since biomarker levels may be affected by baseline kidney function, the generalizability of findings from many of these studies to subjects with baseline CKD is not clear. Third, most studies did not track longer term outcomes. Thus, little is known about the ability of biomarkers to predict progressive kidney disease and other adverse events following CI-AKI. Lastly, several studies examined just one bio-

marker rather than a panel of biomarkers, limiting the capacity to determine if combinations of biomarkers are more predictive than a single biomarker. Notwithstanding these limitations, the findings of these studies suggest that biomarkers could potentially improve the ability to risk stratify patients, diagnose early CI-AKI, and identify risk for serious, adverse longer term sequelae.

CI-AKI is a common condition associated with adverse outcomes. Notwithstanding advancements in our understanding of risk factors for, pathophysiology of, and potential adverse events associated with CI-AKI, there remain significant limitations in our capacity to effectively and efficiently prevent, treat, and limit longer term effects of CI-AKI. Preliminary studies of blood and urine biomarkers in the setting of contrast administration suggest that biomarkers may be a means by which the care for patients at risk for and with CI-AKI could be improved. Large, well-designed studies that measure panels of biomarkers and that provide the opportunity to investigate "yet to be identified" biomarkers are needed to inform the delivery of evidence-based, effective care for the prevention and treatment of this iatrogenic condition.

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Disclosure

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Biomarkers in Kidney Transplantation: The Key is Disease Reclassification, Starting at The Biopsy

By Philip F. Halloran

Evolution of the biomarker concept

The search for biomarkers in body fluids is evolving into a broader quest for molecular phenotyping of tissue and disease reclassification. The original biomarker concept was too limited, failing to recognize that the interpretation of the molecular changes in body fluids requires a molecular understanding of the diseased tissue.

A molecular biomarker in nephrology implies a molecule that can be measured in body fluids as an indicator of a pathologic state in kidney tissue, perhaps avoiding biopsies by providing similar information. This demands that the biomarker is superior to current laboratory assessments such as creatinine and conventional urinalysis.

The problem with this concept is that the biomarker must perform in one dimension, perhaps even dichotomized by a cutoff, to deliver actionable new information. This expectation is flawed: molecular changes in human disease states do not operate in one dimension. Disease states have diagnosis, activity, stage, and prognostic information, and are imposed on aging and pre-existing diseases in the kidney or other organs. For example, in acute kidney injury (AKI), age, injury, and underlying diseases may all influence the levels of a biomarker, since many of the changes of AKI are also induced by chronic diseases (1). In some cases, a higher level of a biomarker is better than a lower level. If the marker indicates injury-repair, and the tissue has been injured, elevated levels of injury-repair molecules will indicate normal healing and their absence would be abnormal, like a wound that is not healing.

Molecular changes must be quantitative, and inter- and intralaboratory variation can create major problems. Molecular measurements delivered as laboratory-developed tests are difficult to normalize and standardize. Ideally, they should be measured centrally and normalized against a reference set.

Emerging lessons in how to use "big data"

An assessment of a disease state using laboratory tests is in fact a prediction of the unknowable true disease state. Molecular phenotyping adds a new dimension to increase the accuracy of this prediction (Figure 1).

Our approach is guided by new thinking about how "big data" should be used to create accurate predictions (2). As dramatized in the movie "Moneyball," the use of rich baseball databases added a statistical dimension to decision making in that sport, which had previously been based on expert opinion. The key was that the database included hard outcomes on which to train predictive equations—"Ws and Ls," wins and losses. Predictions from big databases in cancer are emerging using the same principle, capturing hard outcomes to build predictive equations using high dimensionality molecular platforms. Such predictions of the true disease state should be: 1) Bayesian, acknowledging prior probabilities and biases; 2) probabilistic, with estimates of potential for error; 3) updatable with new knowledge; and 4) consensus-seeking, including expert opinion.

The challenge is to assemble these pieces of information into an understanding for the individual patient (Figure 2).

Developing the Molecular Microscope

Using these principles, we developed a system for kidney transplant biopsy assessment, as recently reviewed (3). Our stepwise analysis is outlined in Table 1.

Our project related molecular changes in kidney biopsies to histologic changes, clinical phenotype (function, proteinuria, etc.), and outcomes, as well as specific diseases. We used indication biopsies as the centerpiece for disease understanding and reclassification. The project has captured more than 1000 indication biopsies from kidney transplant recipients and defined relationships among function, histology, outcome, and molecular changes measured by microarrays. Our understanding was helped by characterizing gene sets associated with biological changes in mouse models, permitting a sketch of the underlying biology—infiltration and activation of macrophages and effector T cells, tubulo-interstitial injury, and microcirculation injury, the types of diffuse changes that can be detected in a core biopsy.

We found that the prevailing classifications of diseases in transplants had major errors, for example interpretation of staining for complement factor C4d (4). We reclassified the diseases states based on conventional and molecular assessments. These biopsies became our reference set against which new biopsies can be assessed. We developed equations to turn microarray results into estimates of the diseases and the degree of tissue injury, and validated and calibrated the readouts. We integrate this with conventional assessments to create an overall view, which we envisage as that assembled by the clinician, not the pathologist.

The result is the Molecular Microscope system of equations, which currently provides estimates of the probability of: 1) T cell-mediated rejection (TCMR) score; 2) antibody-mediated rejection (ABMR) score; 3) atrophy-scarring score—extent of chronic damage; 4) acute kidney injury score—extent of recent parenchymal injury and ongoing injury repair; and 5) prognosis—the risk of progression to failure.

Lessons

The molecular phenotype of a biopsy is a reproducible dimension of the biopsy, but time and experience will be needed to define its full meaning. The molecular changes correlate with histologic and clinical phenotypes, but do not necessarily "agree" with them and are generally superior to histology or clinical parameters in predicting prognosis. The combined values of the molecular, histologic, and clinical assessments represent an opportunity for a consensus, not competition. Our goal for each biopsy and for each patient is to assign numerical values in multidimensional space, where N=1, a step toward precision medicine, and can be compared to her nearest neighbors in the reference set.

For example, the TCMR score is virtually always abnormal in typical TCMR, but there is considerable disagreement, which includes false negative histologic assessment of scarred tissue, confusing situations such as polyomavirus with TCMR, and false positive histologic diagnoses caused by sharing of lesions with other diseases.

The ABMR score, on the other hand, must assess a much more complex and pleiotropic phenotype. ABMR has a large dynamic range, from fulminant to indolent to inactive, and accrues time-dependent changes in the microcirculation. The ABMR molecular score may not be positive in patients who have relatively inactive ABMR. This is a new phenotype—histologic ABMR with low molecular activity. The histologic, clinical, and molecular states together create new disease classes, as has already happened in cancer, where complex multidimensional phenotypes are emerging as molecular measurements become standard of care.

The implication for biomarkers in body fluids is not necessarily bleak. They cannot provide the richness of phenotypic detail needed for disease reclassification and creation of new phenotypes, and as measurements in one dimension are unlikely to answer the unmet need for precision medicine. However, biomarkers in body fluids can be re-examined as useful additions to new multidimensional disease classifications to see how they contribute to care in the clinic, for example monitoring after biopsy.

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Figure 1. Approaching an unknowable truth: the actual state of a tissue

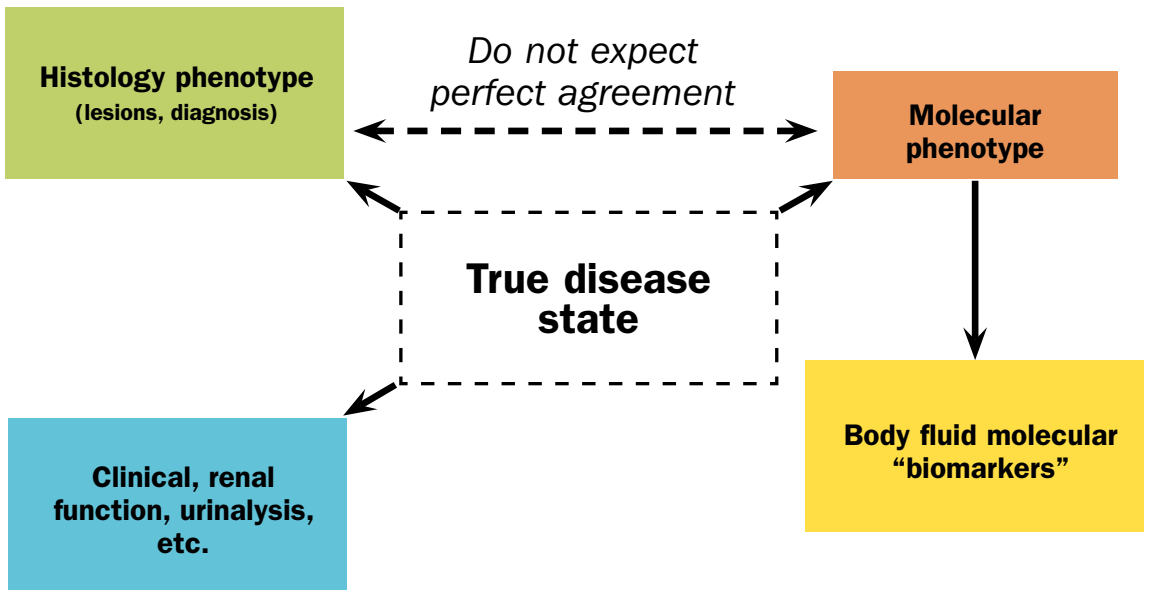
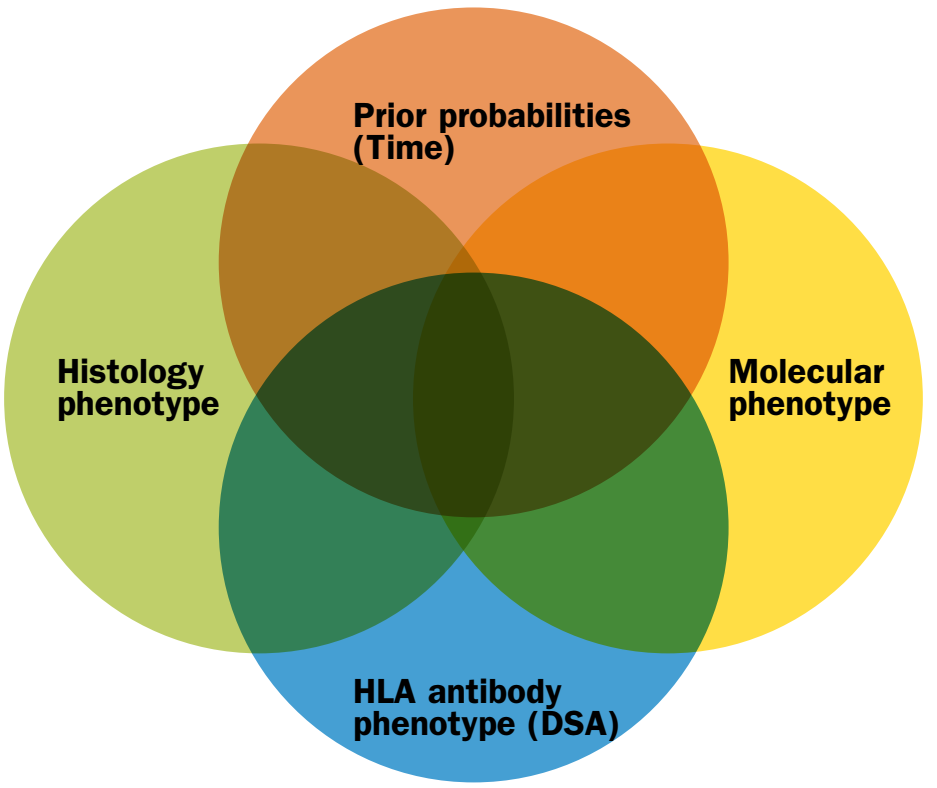


Figure 2. Incorporate prior probabilities and full phenotyping

This will produce new classifications



DSA = donor-specific antibodies; HLA = human leukocyte antigen.

Table 1. Steps in molecular biopsy phenotyping

- Focus on indication biopsies: phenotype
- Granularity: clinical, lab, histology, molecular
- Annotate the molecules: pathogenesis-based transcript sets – http://atagc.med.ualberta.ca/
- Correct the conventional classification: a **new reference standard pathology classification** – http://atagc.med.ualberta.ca/
- **Discover** the molecular classes – cross-validate
- **Validate** in new biopsy set
- **Engineer** the reporting system
- **Calibrate** the readouts: real time clinical meaning

Biomarkers and the FDA—Are We There Yet?

By Christine King

The burden of renal disease is continuing to increase not only in the U.S. population but worldwide, as comorbidity factors such as obesity and diabetes become more prevalent (1). This year, the CDC estimates that more than 10 percent of adults in the United States, approximately 20 million people, may have chronic kidney disease (CKD) in varying degrees of severity, with many people being unaware that they either have CKD or are at increased risk of developing it (2).

The prevalence of CKD, now and in the future, truly represents a public health challenge. The area of renal biomarker research holds much promise for providing better tools to meet the challenge of predicting and identifying renal injury, staging it, and monitoring the effectiveness of therapies. However, innovators often feel stymied by the regulatory requirements in obtaining clearance or approval for new devices. So, perhaps a more appropriate question for renal biomarker researchers and manufacturers is not "Biomarkers and the FDA—Are we there yet?", but rather "Biomarkers and the FDA—Where do we start?"

The regulatory process and criteria used by the Center for Devices and Radiological Health/Office of In Vitro Diagnostics and Radiological Health (CDRH/OIR) for evaluating the safety and effectiveness of biomarker devices are the same as with any diagnostic device. The FDA classifies all devices by risk. In other words, what is the impact of an incorrect result on the intended use population?

The amount of risk associated with a new device is dependent on its intended use. The intended use should state the purpose of the device, such as diagnosis, prognosis, monitoring, stratifying, or identifying specific populations. It should also specify the targeted population for the biomarker test such as renal allograft recipients, diabetics, or patients on certain drug therapies. The intended use and its designated population can be specific or broad depending on the purpose of the biomarker assay. The intended use should be formulated after the basic research and feasibility of the new biomarker and its assay has been completed and evaluated. These initial studies should be robust for characterizing the biomarker as "fit for purpose" by defining the clinical conditions under which the biomarker is to be used, and for the analytical validation of the assay used to measure the biomarker.

Feasibility studies should be designed to test the clinical hypothesis for the validity of the biomarker test in a small sampling of the proposed intended use population. It is during this phase of development that any applicable clinical cutoffs or algorithms are tested and then "locked" prior to commencing the pivotal clinical trial. The pivotal trial should validate the performance of the locked cutoffs and/or algorithms in the intended use population. If the data from the pivotal trial indicate that the cutoff(s) or algorithm(s) need to be modified to meet the intended use of the device, then a new pivotal study will need to be performed to validate the new cutoff/algorithm.

Analytical validity means that the device performance is reproducible over time (precision), specific for the target biomarker, and accurate. Analytical validity also could encompass linearity; detection limits (e.g., limit of the blank, limit of detection, and limit of quantitation); stability of the sample, reagent, controls and calibrators; and definition of a measuring range. The final submission to the FDA should include validation of analytical validity in addition to the clinical validity of the biomarker assay.

The pivotal clinical study to support the indications for use should be well designed to ensure that the right data, rather than just more data, is collected. The study populations should be appropriate for the intended use of the biomarker test, whether the use is diagnostic or prognostic, and should include individuals who represent the intended test population, including those who have or are at risk for developing the disease or condition. Sensitivity, specificity, positive predictive values (PPV), and negative predictive values (NPV) should be evaluated to determine how well the biomarker test is able to distinguish between those who have or are at risk for developing the disease or condition and those who are not.

Study end points also need to be considered in pivotal studies. The selection criteria should include how measurable or definable the end point is, and whether the intended use for the biomarker should be supported by a single, or multiple end points. Regardless of the number of end points, the acceptable performance criterion for the biomarker device and its ability to meet the end point(s) should be established prior to beginning the pivotal study. Also, if multiple end points are used, each end point should be distinguishable from the others in the study in order to prevent "double counting" of results and reduce variability or bias in outcome reporting.

Correlation with clinical diagnosis is one example of an end point. This end point is often used for diagnostic biomarker tests where the results of the device are compared to diagnosis of a disease or condition in the study population per current clinical practice or guidelines. Ideally, this type of study should include several different test sites—large and small, urban and rural—to account for variability in clinical practice, comorbidities, and patient demographics.

Longitudinal end points or outcomes may be appropriate for pivotal studies, especially for prognostic biomarkers. However, duration of the study and participant dropout are factors to be considered in this type of study design.

Studies may be performed prospectively or retrospectively. There are advantages and disadvantages to each type of design. The advantage to a prospective study is that the study conditions can be well defined for the particular intended use of the biomarker device. A disadvantage is that it may be difficult to determine the disease/condition prevalence in prospective studies so that there is adequate statistical power. It may also be difficult to estimate the length of time needed for the subject to reach the end point.

Retrospective data or samples may be used; however, the study protocol under which the samples were collected and stored needs to be well documented. The patient population, disease prevalence, and study population in a retrospective study needs to be the same as that specified in the intended use of the new biomarker device to avoid bias in the data, such as selection bias. Biomarker stability in the stored samples must be validated prior to beginning the pivotal study to determine whether retrospective testing will adequately substitute for prospective testing.

Some pitfalls to avoid when using retrospective study samples include the following: 1) the retrospective inclusion/exclusion criteria may not be appropriate for the intended use of the new biomarker; 2) samples or data may be missing; 3) the patient demographics may not mimic or match the intended use population; and 4) the biomarker recovery between the retrospective study and the intended use population may not be same, or the prevalence of the disease or condition as defined by the intended use may not be the same. The impact of the differences may prevent accurate calculations of PPV and NPV, or determination of risk. Additional information on FDA's current thinking on clinical study design for in vitro diagnostic devices can be found in FDA guidance documentation (3).

This has been only a brief discussion of "Where do we start?" for biomarker tests and the FDA. There is a mechanism for early interaction between the FDA and sponsors called the "Pre-Submission" process. Sponsors may submit their proposed study design to FDA for feedback (4). The process is informal and flexible and the FDA encourages this interaction early in the biomarker test development so that safe and effective new biomarkers for renal disease may soon be available to the public.

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Biomarkers and the Clinical Nephrologist

By Jennifer R. Charlton and Mark D. Okusa

Clinicians view kidney disease as a continuum where kidney failure results from a combination of patient susceptibility factors (diabetes, hypertension, or low nephron mass) combined with episodes of kidney injury (acute kidney injury [AKI]). Clinicians use traditional biomarkers such as serum creatinine, urine output, and albumin as indices of kidney function to diagnose, prognosticate, implement therapy, and monitor progression. These traditional biomarkers are far from ideal. Serum creatinine is a surrogate for kidney function, not injury, and often only signals the injury after several days. Creatinine is also a poor surrogate for renal reserve in assessing patients for chronic kidney disease (CKD) as more than 50 percent of a patient's nephrons have to be nonfunctional before it will increase. Urine output is hindered by diuretic use, inaccurate collection, and lack of specificity (1). There are many etiologies that lead to renal disease and complex compartments within the kidney that can be injured (vasculature, interstitium, glomeruli, and tubules). These factors make the development of specific biomarkers and the interpretation of these markers particularly challenging, but nonetheless critically important to assist the clinical nephrologist.

Biomarkers in AKI

Clinicians are challenged to recognize early and identify quickly the underlying causes of AKI in order to implement the appropriate therapies that may reduce the risk of progressive kidney disease. For example, many biomarkers have been tested to determine if they can distinguish prerenal AKI from intrinsic AKI with the latter due to tubule injury from medications, sepsis, or ischemic injury (2). During clinical AKI, there are alterations in the renal microcirculation and tissue oxygenation that ultimately lead to early cellular injury when cells release these markers into the plasma or urine which provide a window into the local environment of the kidney (1). Therefore, the baseline state of the kidney and the cumulative damage leading up to the episode of AKI play a role in the response to injury (1) and affect how we interpret these biomarkers.

Promising diagnostic markers of renal function and damage include cystatin C, neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), interleukin-18 (IL-18), and liver fatty acid binding protein (L-FABP). Each of these markers provides information regarding a different part of the nephron (3). Cystatin C is a small protein produced by all cells that is freely filtered and degraded by the proximal tubule and has become a clinically utilized biomarker. Also with glomerular injury and a disruption of the filtration barrier, albumin is excreted in the urine. When there is a tubular injury both albumin and cystatin C are not reabsorbed and are excreted in the urine. There are also markers that are released from damaged cells (N-Acetyl-β-o-glucosaminidase [NAG], α glutathione S-transferase [GST], π-GST, and collagen IV) and those that increase in response to damage (NGAL, KIM-1, L-FABP, and IL-18). NGAL is an iron-carrying protein that has been extensively studied with many attractive traits as a biomarker for AKI. It increases quickly within hours of renal injury and is both sensitive and specific. KIM-1 is also a promising marker for the detection of AKI as it is produced during proximal tubule injury and may be particularly useful in determining drug toxicity. These biomarkers open the door to patients with "subclinical AKI" who have undetectable changes in creatinine, but an increase in biomarkers reflecting kidney damage (3,7). In the current state of development, novel biomarkers must be interpreted with caution as not all perform well in every AKI setting (2).

Just as there are various segments of each nephron subject to injury, there are various causes of renal injury. Some injuries—such as cardiac surgery, contrast nephropathy, and nephrotoxins—have a known time of exposure, making clinical studies more straightforward. In other clinical scenarios, such as sepsis and hepatorenal disease, the time course and the primary injury can be obscured.

Beyond predicting the development of AKI, some biomarkers have been able to prognosticate severity and duration of AKI, likelihood for renal replacement therapy, and nonrecovery of function and death (4). These predictions appear to be stronger in the population where the timing of the renal insult is known (cardiac surgery) (4).

An ongoing dilemma in renal biomarker research is what should be the gold standard for the validation of these novel biomarkers. Just demonstrating the superiority to serum creatinine or urine output is a flawed approach and correlation between biomarkers and histologic damage does not occur in clinical trials. Therefore, the outcomes in AKI will not likely change until we gauge a biomarker's worth by its ability to provide a trigger for a clinical action (initiate or monitor therapy) (4). The association between these biomarkers and clinically relevant outcomes is needed (3).

There are still significant challenges in AKI biomarker research. First, we need to address patients with underlying CKD or in a setting where the renal health of the patient is not known prior to AKI (2). Second, we have to assess the usefulness of a biomarker to predict the progression to CKD as the time course may be long and variable. Finally, cutoffs for various markers, bedside utility, platform standardization, interlaboratory calibration (4), and the cost-benefit ratio of these biomarkers are all areas to address.

Biomarkers in CKD

Nephrologists require improved tools for the early diagnosis of the 26 million adult Americans who suffer from CKD and are at risk for developing ESRD (5). The most commonly utilized and validated biomarkers in CKD are eGFR and proteinuria. Similarly to AKI biomarkers, these biomarkers are retrospective or insensitive. Novel biomarkers are being studied in tubulointerstitial injury, glomerular injury, endothelial dysfunction, oxidative stress, inflammation, and fibrosis. As it is becomes more recognized that AKI is a prelude to CKD, the biomarkers assessed in AKI are also being tested in the setting of CKD (5).

Cystatin C, β-trace protein (BTP), and uric acid have been used as surrogates for kidney function, but require more rigorous validation in larger populations and are not being used in clinical practice (5). In clinical studies, NGAL concentration correlated to CKD staging, validated in various etiologies of CKD, and predicted kidney function decline. Other tubulointerstitial markers—such as KIM-1, NAG, and L-FABP—still need long-term studies in larger populations to ensure their validity as markers in CKD (5). Newer biomarkers sensitive to glomerular injury, such as nephrin, podocin, and podocalyxin, have been assessed in lupus, postinfectious, and IgA nephritis, and in their early stages seem to be specific to glomerular diseases (5). Other markers, such as C-reactive protein and IL-18, markers of inflammation and fibrosis, are being assessed in progressive kidney disease (5). Specific pathophysiologic mechanisms of primary renal diseases leading to CKD and elements of CKD progression are shared by all forms of progressive CKD, thus assessing both nonspecific and disease-specific markers is needed.

Biomarkers in transplantation

There is a large effort to investigate novel biomarkers that could guide titration of immunosuppressive medications tailored to the biologic suitability of the graft and recipient (6). Studies have unmasked a genetic signature that was highly sensitive and specific in patients experiencing chronic renal allograft rejection or tolerance (6). Additionally, urine proteomic analysis can distinguish chronic allograft injury from healthy controls and those patients with excellent graft function (6). Although promising, this area of research needs significantly more validation in a prospective fashion with larger cohorts of patients with attention to graft protection (6).

In summary, there is an intensive effort to develop novel biomarkers of kidney disease as currently used clinical biomarkers have shortcomings. There is hope, however, for implementing point-of-care use of panels of biomarkers in the near future. For the clinician, such tools will assist in therapy and counseling of their patients with the goal of improving outcomes.

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ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

Policy Update

Kidney Community Unites to Raise Awareness on Capitol Hill

By Kevin F. Erickson, MD, and Mallika L. Mendu, MD, MBA

On May 1, 2014, kidney patient and health professional advocates gathered in Washington, DC, for Kidney Community Advocacy Day. Since 2010, ASN has organized an annual congressional advocacy day to raise awareness about kidney disease and promote issues important to the kidney community.

Building on the momentum from the first-ever Summit of U.S. Kidney Organizations at the society's annual scientific meeting in 2013, more than 100 advocates from 14 organizations met with 133 congressional offices, including 19 members of Congress—triple the number of participants and double the number of meetings from ASN's congressional advocacy day in 2013.

All the advocates were divided into state teams and met with members of their congressional delegation to promote increased funding for kidney research and the Comprehensive Immunosuppressive Drug Coverage Act of 2013.

Kidney research funding

More than 20 million Americans have kidney disease, which can have a significant effect on patients' health and quality of life. When patients' kidneys stop working, they need a kidney transplant or dialysis.

Dialysis continues to be associated with high morbidity, mortality, and costs. Since the federal government pays for most of dialysis care, it has a significant incentive to fund research to prevent kidney disease progression and improve the health of patients on dialysis.

Yet kidney disease remains underfunded relative to other diseases; total federal investments in kidney research equal less than 1 percent of the federal cost for providing kidney disease care. Kidney Community Advocacy Day participants asked for an additional $150 million per year for 10 years above current funding levels to help address this disparity. More research will lead to better ways to diagnose, prevent, and treat kidney diseases of all kinds, improving the health of millions of Americans as well as reducing total federal expenses.

Comprehensive Immunosuppressive Drug Coverage Act of 2013

All patients with kidney failure receive Medicare coverage. For most patients with kidney failure, transplants are the optimal therapy. Medicare pays for kidney transplants, but only provides 36 months of immunosuppressive drug coverage for patients who do not qualify for Medicare because of age.

After 36 months, patients must find a way to pay for the expensive immunosuppressive drugs, and many patients have difficulty affording these medications. Because immunosuppressive medications are necessary to preserve the function of transplanted kidneys, some patients lose their transplanted kidney when they encounter difficulties in affording these medications and are forced to reduce or discontinue the prescribed treatment driven by economic necessity.

This is a tragedy for patients, their loved ones, and kidney donors who have provided a precious gift. In addition, patients return to dialysis when their transplants fail at an annual cost to Medicare of $90,000 compared to the less than $5000 annual cost to Medicare for the immunosuppressive drugs.

The Comprehensive Immunosuppressive Drug Coverage Act of 2013 would extend Medicare coverage for immunosuppressive drugs over a recipient's lifetime—protecting Medicare's investment in the transplant and ensuring that no patients will lose their kidney. As of press time, 16 senators and 116 representatives have signed onto the bill as co-sponsors.

Innovations in Kidney Research Congressional Briefing

In conjunction with Kidney Community Advocacy Day, ASN co-sponsored a standing-room only congressional briefing: "New Hope for Patients: Discussion of the latest cutting-edge breakthroughs in artificial kidney research." Congressional Kidney Caucus Co-chairs Rep. Tom Marino (R-PA) and Rep. Jim McDermott (D-WA) served as honorary sponsors and spoke about their strong support for the kidney community and additional research funding to develop cures.

The following advocates, experts, and scientists also spoke at the briefing: William Fissell, Jonathan Himmelfarb, Shuvo Roy, Murray Sheldon, Robert Star, and Melanie Stewart.

"Currently kidney disease is the 8th leading cause of death in the U.S., affecting over 20 million Americans, and costing the federal government over $79 billion annually, including $34 billion for treatment of end stage renal disease. But it doesn't have to be this way," Dr. Himmelfarb said. "There are innovators, inventors, and scientists working now on transformative tecÚologies that have the potential to make a fundamental difference for people living with kidney disease. Investing in research that spawns and supports innovation is the hope for the future."

Summing up the day, ASN President Sharon Moe, MD, FASN, said: "It was a successful day by all accounts. More groups participated than ever before, more congressional offices were visited, and our new advocacy message was well received. I have been visiting offices for the past five years. It is clear that the kidney community is being heard and the voice of the American Society of Nephrology is well-respected."

ASN is grateful to all who participated in Kidney Community Advocacy Day and will continue its efforts to engage Congress on these important legislative issues affecting patients with kidney disease.

Kevin F. Erickson, MD, and Mallika L. Mendu, MD, MBA, are ASN Public Policy Board Interns

Kidney Community Advocacy Day Participants

Alport Syndrome Foundation
American Association of Kidney Patients
American Kidney Fund
American Nephrology Nurses' Association
American Society of Nephrology
American Society of Pediatric Nephrology
Dialysis Patent Citizens
Home Dialyzors United
IGA Nephropathy Foundation of America
National Kidney Foundation
NephCure Foundation
PKD Foundation
Renal Physicians Association
Renal Support Network

ASN Public Policy Board Member Wolfgang Winkelmayer, MD, ScD, FASN, and Public Policy Board Intern Mallika L. Mendu, MD, MBA

(right to left) Rep. Larry Bucshon, MD, (R-IN) with ASN President Sharon Moe, MD, FASN, and ASN Executive Director Tod Ibrahim

ASN Councilor Mark Okusa, MD, FASN, (second from right) meeting with Rep. Robert Hurt's (R-VA) office

ASN Public Policy Board Member Raymond Hakim, MD, PhD, (third from right) and Policy Board Intern Kevin Erickson, MD (right)

ASN Acute Kidney Injury Advisory Group Chair Sarah Faubel, MD, (second from right) meeting with Rep. Joe Pitts's (R-PA) office

Journal View

Can random UAC detect microalbuminuria in diabetic patients?

For microalbuminuria screening in patients with diabetes, measuring urinary albumin concentration (UAC) in random urine samples offers sensitivity and specificity similar to those of the albumin-to-creatinine ratio (ACR), reports a study in *JAMA Internal Medicine*.

A meta-analysis was performed with the use of data on 2078 patients from 14 studies evaluating UAC and ACR in random urine samples. All studies included 24-hour urine collections as the criterion standard for diagnosis of microalbuminuria.

In bivariate random-effects models, the two tests offered similar diagnostic performances. Pooled sensitivity in detecting microalbuminuria was 0.85 for UAC and 0.87 for ACR. Specificity was 0.88 for both tests; diagnostic odds ratios were similar as well. Performance was similar by timing of sample as well as on analysis of seven studies in which patients underwent both UAC and ACR.

Measuring ACR in random urine samples has some disadvantages as a screening test for microalbuminuria, including the higher cost of urinary creatinine measurement. Studies comparing ACR with UAC for this purpose have yielded conflicting results.

The new meta-analysis suggests that UAC and ACR have similarly good performances for microalbuminuria screening in diabetic patients. With the rising incidence of diabetes and limited health care resources in many countries, the authors conclude, "UAC of random urine samples may become the screening tool of choice for the population with DM" [Wu H-Y, et al. Diagnostic performance of random urine samples using albumin concentration vs ratio of albumin to creatinine for microalbuminuria screening in patients with diabetes mellitus: a systematic review and meta-analysis. *JAMA Intern Med*, published online May 05, 2014. doi:10.1001/jamainternmed.2014.1363].

Diabetes complications—rates are down, but numbers are still high

Although the incidence of diabetes-related complications in the United States has decreased since 1990, the burden remains high because of rising prevalence of diabetes, according to a report in the *New England Journal of Medicine*.

The researchers compiled nationwide data from multiple sources to assess trends in diabetes-related complications from 1990 to 2010. Age-standardized to the United States population in 2000, the data showed decreased incidence rates for all five complications of interest. Relative decreases were 67.8 percent for acute myocardial infarction, 64.4 percent for death resulting from hyperglycemic crisis, 52.7 percent for stroke, 51.4 percent for lower-extremity amputations, and 28.3 percent for ESRD.

When 1995 was used as the start year rather than 1990, the decline in ESRD was more similar to that for the other outcomes. Absolute declines in cases per 10,000 persons per year were 95.6 for myocardial infarction, 58.9 for stroke, 30.0 for lower-extremity amputation, 7.9 for ESRD, and 2.7 for death resulting from hyperglycemic crisis.

However, once the rising prevalence of diabetes was taken into account, the reductions were significant only for myocardial infarction and death resulting from hyperglycemic crisis: by 32.2 and 42.0 percent, respectively. There was no significant change in the rates for amputation or stroke, and the ESRD rate increased by 90.9 percent: from 1.1 to 2.1 cases per 10,000 population.

The results suggest that improvements in preventive care have reduced the rates of important diabetes-related complications over the past two decades. However, as diabetes prevalence continues to rise, high numbers of complications persist nationwide. "The encouraging reductions in the rates of morbidity and hyperglycemia-related mortality in the population of adults with diabetes do not signify imminent reductions in the overall burden of diabetes-related complications," the researchers conclude [Gregg EW, et al. Changes in diabetes-related complications in the United States, 1990-2010. *N Engl J Med* 2014; 370:1514–1523].

Fewer adults will receive BP drugs under JNC8

Under the 2014 BP guideline of the Eighth Joint National Committee (JNC8), antihypertensive therapy will be recommended for significantly fewer adults in the United States, reports a study in the *Journal of the American Medical Association*.

The researchers used data on 16,372 adults from the National Health and Nutrition Examination Survey between 2005 and 2010 to assess the implications of the JNC8 2014 BP guideline, compared with the previous JNC7 BP guideline. Among younger adults aged 18 to 59, the percentage for whom antihypertensive therapy would be recommended decreased from 20.3 percent under JNC7 to 19.2 percent under JNC8. The decrease was even sharper for those aged 60 or older: from 68.9 to 61.2 percent.

The 2014 blood pressure guideline was also associated with an increase in the proportion of treatment-eligible adults meeting blood pressure targets: from 41.2 to 47.5 percent in those aged 18 to 59 and from 47.5 to 65.8 percent in those aged 60 or older.

Overall, 1.6 percent of adults aged 18 to 59 and 27.6 percent of those aged 60 or older were receiving antihypertensive drugs and meeting more stringent JNC7 targets. Under JNC8, some of these patients would be eligible for less stringent or no BP therapy.

The JNC8 guideline increased the systolic BP treatment goal from less than 140/90 to less than 150/90 mm Hg while increasing the target for patients with chronic kidney disease and diabetes from less than 130/80 to less than 140/90 mm Hg. The new study suggests that in comparison with JNC7, antihypertensive therapy will be recommended for fewer Americans under JNC8.

Under JNC8, more patients will be considered to have met BP targets, especially in those aged 60 and over. More study is needed to determine how the new guideline will affect overall BP levels and the resulting effects on cardiovascular disease outcomes [Navar-Boggan AM, et al. Proportion of US adults potentially affected by the 2014 hypertension guideline. *JAMA* 2014; 311:1424–1429].

Little benefit of spironolactone for heart failure with preserved ejection fraction

Treatment with spironolactone doesn't improve overall outcomes for heart failure patients with preserved left ventricular function, reports a trial in the *New England Journal of Medicine*.

The Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial included 3445 patients with symptomatic heart failure but an ejection fraction of 45 percent or higher. They were randomly assigned to double-blinded treatment with spironolactone, 15 to 45 mg/d, or placebo, added to existing therapy. A composite outcome of death resulting from cardiovascular causes, aborted cardiac arrest, or hospitalization for heart failure was assessed at a mean follow-up time of 3.3 years.

A primary outcome event occurred in 18.6 percent of patients receiving spironolactone and 20.4 percent with placebo. The difference was not significant; incidence rates were 5.9 and 6.6 events per 100 person-years, respectively. The rate of hospitalization for heart failure was lower in the spironolactone group: 12.0 versus 14.2 percent, hazard ratio 0.83.

The rates of all-cause mortality and hospitalization were also similar between groups. Patients receiving spironolactone had higher rates of increased serum creatinine and hyperkalemia but a lower rate of hypokalemia. There were no differences in serious adverse events, including serum creatinine of 3.0 mg/dL or higher or dialysis. The authors note that the study protocol included frequent patient monitoring.

For patients with heart failure and left ventricular dysfunction, mineralocorticoid-receptor antagonists reduce the risk of death and heart failure hospitalization. Some studies have reported that these drugs improve diastolic function in heart failure patients with preserved ejection fraction.

However, the TOPCAT trial found no overall reduction in cardiovascular outcomes with spironolactone added to existing therapy in this group of patients. The results suggest some reduction in hospitalization for heart failure in patients treated with spironolactone. In treated patients, close monitoring is warranted because of the heightened risk of hyperkalemia and increased creatinine levels [Pitt B, et al. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med* 2014; 370:1383–1392].

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Brief Summary: Consult full package insert for complete Prescribing Information.

INDICATIONS AND USAGE: Phoslyra® (calcium acetate oral solution 667 mg per 5 mL) is a phosphate binder indicated to reduce serum phosphorus in patients with end stage renal disease (ESRD). Management of elevated serum phosphorus levels usually includes all of the following: reduction in dietary intake of phosphate, removal of phosphate by dialysis, and inhibition of intestinal phosphate absorption with phosphate binders.

DOSAGE AND ADMINISTRATION: The recommended initial dose of Phoslyra for the adult dialysis patient is 10 mL with each meal. Increase the dose gradually to lower serum phosphorus levels to the target range, as long as hypercalcemia does not develop. Titrate the dose every 2 to 3 weeks until an acceptable serum phosphorus level is reached. Most patients require 15–20 mL with each meal.

CONTRAINDICATIONS: Patients with hypercalcemia.

WARNINGS AND PRECAUTIONS:

Hypercalcemia. Patients with end stage renal disease may develop hypercalcemia when treated with calcium, including calcium acetate (Phoslyra). Avoid the concurrent use of calcium supplements, including calcium-based nonprescription antacids, with Phoslyra. An overdose of Phoslyra may lead to progressive hypercalcemia, which may require emergency measures. Therefore, early in the treatment phase during the dosage adjustment period, monitor serum calcium levels twice weekly. Should hypercalcemia develop, reduce the Phoslyra dosage or discontinue the treatment, depending on the severity of hypercalcemia.

More severe hypercalcemia (Ca >12 mg/dL) is associated with confusion, delirium, stupor and coma. Severe hypercalcemia can be treated by acute hemodialysis and discontinuing Phoslyra therapy. Mild hypercalcemia (10.5 to 11.9 mg/dL) may be asymptomatic or manifest as constipation, anorexia, nausea, and vomiting. Mild hypercalcemia is usually controlled by reducing the Phoslyra dose or temporarily discontinuing therapy. Decreasing or discontinuing Vitamin D therapy is recommended as well.

Chronic hypercalcemia may lead to vascular calcification and other soft-tissue calcification. Radiographic evaluation of suspected anatomical regions may be helpful in early detection of soft tissue calcification.

The long-term effect of Phoslyra on the progression of vascular or soft tissue calcification has not been determined.

Hypercalcemia (>11 mg/dL) was reported in 16% of patients in a 3-month study of a solid dose formulation of calcium acetate; all cases resolved upon lowering the dose or discontinuing treatment.

Maintain the serum calcium-phosphorus product (Ca X P) below 55 mg^2/dL^2.

Concomitant Use with Medications. Hypercalcemia may aggravate digitalis toxicity. Phoslyra contains maltitol (1 g per 5 mL) and may induce a laxative effect, especially if taken with other products containing maltitol.

ADVERSE REACTIONS: No clinical trials have been performed with Phoslyra in the intended population. Because the dose and active ingredients of Phoslyra are equivalent to that of the calcium acetate gelcaps or tablets, the scope of the adverse reactions is anticipated to be similar.

Hypercalcemia is discussed elsewhere *[see Warnings and Precautions]*.

Clinical Trial 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 to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

In clinical studies, calcium acetate has been generally well tolerated.

The solid dose formulation of calcium acetate was studied in a 3-month, open-label, non-randomized study of 98 enrolled ESRD hemodialysis patients and in a two week double-blind, placebo-controlled, cross-over study with 69 enrolled ESRD hemodialysis patients. Adverse reactions (>2% on treatment) from these trials are presented in Table 1.

Table 1: Adverse Reactions in Patients with End-Stage Renal Disease Undergoing Hemodialysis

	Total adverse reactions reported for calcium acetate n=167	3-mo, open-label study of calcium acetate n=98	Double-blind, placebo-controlled, cross-over study of calcium acetate n=69	
			Calcium acetate	Placebo
Preferred Term	n (%)	n (%)	n (%)	n (%)
Nausea	6 (3.6)	6 (6.1)	0 (0.0)	0 (0.0)
Vomiting	4 (2.4)	4 (4.1)	0 (0.0)	0 (0.0)
Hypercalcemia	21 (12.6)	16 (16.3)	5 (7.2)	0 (0.0)

Calcium acetate oral solution was studied in a randomized, controlled, 3-arm, open label, cross-over, single-dose study comparing calcium acetate oral solution to a solid formulation in healthy volunteers on a controlled diet. Of the observed drug-related adverse reactions, diarrhea (5/38, 13.2%) was more common with the oral solution.

Postmarketing Experience. The following additional adverse reactions have been identified during post-approval of calcium acetate: dizziness, edema, and weakness.

DRUG INTERACTIONS: The drug interaction profile of Phoslyra is characterized by the potential of calcium to bind to drugs with anionic functions (e.g., carboxyl, carbonyl, and hydroxyl groups). Phoslyra may decrease the bioavailability of tetracyclines or fluoroquinolones via this mechanism.

There are no empirical data on avoiding drug interactions between calcium acetate or Phoslyra and most concomitant drugs. When administering an oral medication with Phoslyra where a reduction in the bioavailability of that medication would have a clinically significant effect on its safety or efficacy, administer the drug one hour before or three hours after Phoslyra or calcium acetate. Monitor blood levels of the concomitant drugs that have a narrow therapeutic range. Patients taking anti-arrhythmic medications for the control of arrhythmias and anti-seizure medications for the control of seizure disorders were excluded from the clinical trials with all forms of calcium acetate.

Ciprofloxacin. In a study of 15 healthy subjects, a co-administered single dose of 4 calcium acetate tablets (approximately 2.7 g) decreased the bioavailability of ciprofloxacin by approximately 50%.

USE IN SPECIFIC POPULATIONS

Pregnancy: Category C. Phoslyra contains calcium acetate. Animal reproduction studies have not been conducted with Phoslyra, and there are no adequate and well controlled studies of Phoslyra use in pregnant women. Patients with end stage renal disease may develop hypercalcemia with calcium acetate treatment *[see Warnings and Precautions]*. Maintenance of normal serum calcium levels is important for maternal and fetal well being. Hypercalcemia during pregnancy may increase the risk for maternal and neonatal complications such as stillbirth, preterm delivery, and neonatal hypocalcemia and hypoparathyroidism. Phoslyra treatment, as recommended, is not expected to harm a fetus if maternal calcium levels are properly monitored during and following treatment.

Labor and Delivery. The effects of Phoslyra on labor and delivery are unknown.

Nursing Mothers. Phoslyra contains calcium acetate and is excreted in human milk. Human milk feeding by a mother receiving Phoslyra is not expected to harm an infant, provided maternal serum calcium levels are appropriately monitored.

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

Geriatric Use. Clinical studies of calcium acetate did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

OVERDOSAGE: Administration of Phoslyra in excess of the appropriate daily dosage may result in hypercalcemia *[see Warnings and Precautions]*.

HOW SUPPLIED/STORAGE AND HANDLING: Phoslyra for oral administration is a clear solution containing 667 mg calcium acetate per 5 mL. Phoslyra is supplied in a 473 mL (16 oz) amber-colored, multiple-dose bottle, packaged with a marked dosing cup. Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature]. The shelf life is 24 months.

PATIENT COUNSELING INFORMATION: Inform patients to take Phoslyra with meals, adhere to their prescribed diets, and avoid the use of calcium supplements including nonprescription antacids. Inform patients about the symptoms of hypercalcemia *[see Warnings and Precautions and Adverse Reactions]*.

Advise patients who are taking an oral medication where a reduction in the bioavailability of that medication would have a clinically significant effect on its safety or efficacy to take the drug one hour before or three hours after Phoslyra.

Manufactured for:
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calcium acetate oral solution
667 mg per 5 mL

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INDICATION:

Phoslyra® (calcium acetate oral solution, 667 mg per 5 mL) is a phosphate binder (PB) indicated for the reduction of serum phosphorus in patients with end stage renal disease (ESRD). Phoslyra is administered orally with food.

IMPORTANT SAFETY INFORMATION:

- **Phoslyra is contraindicated in patients with hypercalcemia.**
- **Patients should have serum calcium levels closely monitored and their dose of Phoslyra adjusted or terminated to bring levels to normal.** No other calcium supplements should be given concurrently with Phoslyra.
- Phoslyra may decrease the bioavailability of tetracyclines or fluoroquinolones.
- There are no empirical data on avoiding drug interactions between calcium acetate or Phoslyra and most concomitant drugs. When administering an oral medication with Phoslyra where a reduction in the bioavailability of that medication would have a clinically significant effect on its safety or efficacy, administer the drug 1 hour before or 3 hours after Phoslyra or calcium acetate. Monitor blood levels of the concomitant drugs that have a narrow therapeutic range.
- The most common (>10%) adverse reactions experienced with Phoslyra are hypercalcemia, nausea, and diarrhea.
- Phoslyra may cause diarrhea with nutritional supplements that contain maltitol.

For additional important safety information, please see brief Prescribing Information on this page.

101731-02 Rev. A 08/2012

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