Findings

Fewer Adverse Renal Events with Balanced Crystalloids versus Saline

In both critically ill and non-critically ill adults, balanced crystalloids are associated with a lower risk of adverse renal events compared to saline, according to a pair of trials in The New England Journal of Medicine.

The “Saline Against Lactated Ringer’s or Plasma-Lyte in the Emergency Department” (SALT-ED) study included 13,347 adult patients seen in the emergency department (ED) and subsequently hospitalized outside the ICU. Over 16 months, the ED crossed-over monthly from treatment using balanced crystalloids (lactated Ringer’s solution or Plasma-Lyte A). Median volume of crystalloid administered in the ED was 1079 mL; about 88% of patients received their assigned solution.

The primary outcome of hospital-free days was not significantly different: median 25 days in both groups. Balanced crystalloids were associated with a significant reduction in major adverse kidney events within 30 days: 4.7% versus 5.6%, adjusted odds ratio 0.65. All-cause mortality, need for renal replacement therapy, and rate of persistent renal dysfunction were similar between groups.

In the “Isotonic Solutions and Major Adverse Renal Events Trial” (SMART), 15,802 adults in five ICUs were assigned to receive balanced crystalloids or saline. Balanced crystalloids were associated with a small but significant reduction in major adverse kidney events within 30 days: 14.3% versus 15.4%, OR 0.91. Thirty-day hospital mortality was also lower in the balanced-crystalloids group: 10.3% versus 11.1%. There was no significant difference in need for renal replacement therapy or persistent renal dysfunction.

The outcomes associated with the choice of isotonic crystalloid solutions are unclear, particularly outside of ICU settings. The SALT-ED trial shows no difference in hospital-free days with balanced crystalloids versus saline, but a lower incidence of major adverse kidney events with balanced crystalloids.


Higher UACR Linked to Cardiovascular Risk in Diabetes

Urinary albumin excretion is independently associated with a range of adverse cardiovascular outcomes in patients with type 2 diabetes, reports a study in JAMA Cardiology.

The study included data on 15,760 patients from the SAVOR-TIMI 53 study: a randomized, placebo-controlled trial of the oral hypoglycemic drug saxagliptin in patients with type 2 diabetes at high cardiovascular risk. Two-thirds of patients were men. Baseline urinary albumin to creatinine ratio (UACR) was less than 10 mg/g in 36.8% of patients, 10 to 30 mg/g in 24.7%, 30 to 300 mg/g in 28.1%, and greater than 300 mg/g in 10.4%.

At a median 2.1 years’ follow-up, rates of a primary composite outcome of cardiovascular death, myocardial infarction, and/or ischemic stroke increased progressively in each category of baseline UACR: 3.9%, 6.9%, 9.2%, and 28.1%, respectively. There were also stepwise increases for cardiovascular death, 1.4%, 2.6%, 4.1%, and 6.9%; and heart failure hospitalization, 1.5%, 2.5%, 4.0%, and 8.3%.

The UACR-related net reclassification improvement associated with these endpoints was 0.081, 0.129, and 0.056, respectively. Increases in cardiovascular risk associated with UACR values greater than 10 mg/g were observed at each stage of chronic kidney disease. The associations between UACR and cardiovascular outcomes remained significant on analysis including cardiac biomarkers, but were weakened.

Among those with type 2 diabetes, an elevated UACR is associated with reduced renal function and predicts an increased risk of renal failure and death. The new analysis shows that higher UACR is also associated with adverse cardiovascular outcomes at two years’ follow-up.

Added to established cardiac biomarkers, the UACR provides little incremental information on cardiovascular outcomes. However, the researchers note that UACR is routinely measured to assess chronic kidney disease in patients with type 2 diabetes, whereas cardiac biomarkers are not typically available. (Scirica BM, et al. Cardiovascular outcomes according to urinary albumin and kidney disease in patients with type 2 diabetes at high cardiovascular risk. JAMA Cardiol 2018; 3:155–163).
In CKD Patients with AF, Anticoagulation Increases Risks

In older adults with chronic kidney disease (CKD), new anticoagulant therapy for atrial fibrillation (AF) is associated with increased risks of ischemic stroke and hemorrhage, reports a study in the British Medical Journal.

From a UK general practice database, the researchers identified 6977 CKD patients newly diagnosed with AF. Of these, 2434 were started on anticoagulation within 60 days. Propensity scores were used to create matched pairs of patients, exposed or not exposed to anticoagulant therapy. Mean age was about 82 years. At a median follow-up of 506 days, rates of ischemic stroke, cerebral or gastrointestinal bleeding, and death from any cause were compared between groups.

The crude rate of ischemic stroke was 4.6 per 100 person-years after starting anticoagulants, compared to 1.5 for matched patients not taking anticoagulants. Rates of hemorrhage were 1.2 versus 0.4 per 100 person-years, respectively. Both adverse outcomes were significantly increased in the anticoagulant group: hazard ratio 2.60 for ischemic stroke and 2.42 for hemorrhage. All-cause mortality was paradoxically lower for patients starting anticoagulants: hazard ratio 0.82.

About one-third of patients with CKD also have AF. Decisions about anticoagulant therapy are complicated by the fact that stroke and bleeding risk both increase progressively as kidney function declines.

The results show increased rates of ischemic stroke and cerebral or gastrointestinal hemorrhage in older CKD patients who start anticoagulants after being diagnosed with AF. The reasons for the unexpected reduction in mortality are unclear. “These paradoxical findings emphasise the urgent need for adequately powered randomised controlled trials to provide clarity on correct clinical management,” the researchers conclude [Kumar S, et al. Ischaemic stroke, haemorrhage, and mortality in older patients with chronic kidney disease newly started on anticoagulation for atrial fibrillation: a population based study from UK primary care. BMJ 2018; 360:k342].

Continued on page 8

For the treatment of iron deficiency anemia in adult patients with chronic kidney disease (CKD) not on dialysis

Designed to be different

AURYXIA is the only oral iron tablet approved by the FDA for the treatment of iron deficiency anemia specifically in adult patients with CKD not on dialysis

- Proven effective in patients who were previously intolerant of or had an inadequate therapeutic response to traditional oral iron supplements
- Patients in the Phase III pivotal trial achieved results without the use of ESAs or IV iron
- 52% of patients achieved the primary endpoint of a hemoglobin increase of ≥1.0 g/dL by Week 16
- 18 percentage-point increase in mean TSAT at Week 16 from baseline
- Discontinuation rates due to adverse reactions were similar between AURYXIA and placebo (10% vs 9%)
- Convenient mealtime dosing
- Each tablet contains 210 mg of elemental iron

ESAs=erythropoiesis stimulating agents

Please see Brief Summary including patient counseling information on following page
Marijuana Users Aren’t at Increased Disease Risk

Current or past use of marijuana does not appear to affect the risk of developing kidney disease or decreased renal function, reports a study in The American Journal of Medicine.

The cross-sectional study included data from 5,995 respondents, aged 15 to 59, to the National Health and Nutrition Examination Survey from 2007 to 2014. Self-reported marijuana use, recent or past, was analyzed for association with renal outcomes: serum creatinine concentration, estimated glomerular filtration rate, and chronic kidney disease (stage 2 or higher).

In the nationally representative survey, 46.3% of respondents said they had never used marijuana, 39.3% were past users, and 14.4% were current users. Current marijuana users were more likely to be male, younger, and current alcohol users. Unadjusted data suggested higher mean serum creatinine and lower mean eGFR in past and current marijuana users.

However, on adjusted analysis, none of the three renal outcomes was associated with marijuana use. Serum creatinine and eGFR showed an increased trend in past and current marijuana users versus never users, but these were not statistically significant. Sensitivity analysis limited to respondents free of cardiovascular disease also found no significant associations.

As more states legalize medical and recreational marijuana, this use in the population is likely to increase. As for other acute and chronic health effects, little is known about how marijuana affects renal function. This study—the largest of its kind—finds no clinically significant effect of past or current marijuana use on serum creatinine, eGFR, microalbuminuria, or stage 2 or higher CKD.

Biologic Therapies for RA Reduce Kidney Risks

In patients with rheumatoid arthritis, treatment with biologic agents is associated with a lower risk of declining renal function and chronic kidney disease (CKD), reports a study in Kidney International.

Using a Department of Veterans Affairs database, the researchers identified 20,757 veterans diagnosed with RA between 2004 and 2006, with follow-up to 2013. All included patients had initially normal kidney function: estimated glomerular filtration rate (eGFR) 60 mL/min/1.73 m² or higher.

Treatment with biologic agents was examined for association with incident CKD, defined as eGFR less than 60 mL/min/1.73 m², with at least a 25% decrease; and change in renal function, classified as <-3, <-3, ≤0 (reference), and ≥30 mL/min/1.73 m². Treatment and control groups were propensity-matched, based on their likelihood of initiating biologic treatment.

Overall, 22% of patients received biologic agents: most commonly etanercept, followed by adalimumab and infliximab. Patients receiving biologic therapy were younger and less likely to be male and African American. They had lower eGFR, higher income, and less comorbidity.

Biologic therapy was associated with a lower incidence of CKD- hazard ratio 0.95 for a cutoff of under 60 mL/min/1.73 m² and 0.71 for under 45 mL/min/1.73 m². Patients receiving biologics were less likely to have progressive eGFR decline: nonmortality odds ratio 0.67 for an eGFR slope <-3 mL/min/1.73 m² and 0.76 for ≥30 mL/min/1.73 m² (relative to ≤3 to ≤0).

The yearly rate of eGFR decline slowed from -1.0 mL/min/1.73 m² before to −0.4 mL/min/1.73 m² after biologic treatment started.

Patients with RA are at elevated risk of kidney disease, likely via chronic inflammation and/or exposure to nephrotoxic drugs. Newer biologic agents used to reduce systemic inflammation in RA have been shown to have beneficial effects in lowering cardiovascular risk. This study findings suggest that biologic therapy reduces the risk of CKD and progressive decline in renal function in a nationwide cohort of veterans with RA. The associations are independent of known risk factors for CKD.


**Table 1: Adverse Reactions Reported in Two Clinical Trials in at least 5% of patients receiving AURYXIA**

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>AURYXIA % (N=99)</th>
<th>Placebo % (N=188)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Adverse Reaction</td>
<td>75</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td>5</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>22</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>21</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>18</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>10</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Disclosed doses</td>
<td>5</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

**Drug Interactions**

Oral administration of AURYXIA has to be taken at least 1 hour before or after AURYXIA and most concomitant oral drugs. For oral medications where a reduction in the bioavailability of that medication would have a clinically significant effect on its safety or efficacy, consider separation of the timing of the administration of the two drugs. The duration of separation depends upon the absorption characteristics of the medication concomitantly administered, such as the time to peak systemic levels and whether the drug is an immediate or an extended release product. Consider monitoring clinical responses or blood levels of concomitant medications that have a narrow therapeutic range.

**INDICATION AND USAGE**

AURYXIA is indicated for the treatment of iron deficiency anemia in adult patients with chronic kidney disease not on dialysis.

**CONTRAINDICATIONS**

AURYXIA is contraindicated in patients with iron overload syndromes (e.g., hemochromatosis).

**WARNINGS AND PRECAUTIONS**

Iron Overload: heart failure or AURYXIA may lead to excessive elevations in iron stores. Increases in serum ferritin and transferrin saturation (TSAT) have been observed in clinical trials. In a 26-week safety and efficacy trial evaluating the control of serum phosphate levels in patients with chronic kidney disease on dialysis in which concomitant use of intravenous iron was permitted, 55 (19%) of patients treated with AURYXIA had a ferritin level >1500 ngn/L, as compared with 13 (9%) of patients treated with active control. Assess iron parameters (e.g., serum ferritin and TSAT) prior to initiating AURYXIA and monitor iron parameters while on therapy. Patients receiving intravenous iron may require a reduction in dose or discontinuation of intravenous iron therapy.

**Risk of Overdose in Children Due to Accidental Ingestion**

Ingestion and resulting overdose of iron-containing products is a leading cause of fatal poisoning in children under 6 years of age. Advise parents of the risks to children and to keep AURYXIA out of the reach of children.

**ADVERSE REACTIONS**

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 adverse reaction rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Iron Deficiency Anemia in Chronic Kidney Disease Not on Dialysis

AURYXIA was studied in two trials, 170 subjects and 136 subjects with CKD-NDD were treated with AURYXIA. The AURYXIA group included a study of 117 patients treated with AURYXIA and 116 patients treated with placebo, with patients randomized to double-blind, double-dummy period and a study of 75 patients treated with AURYXIA and 73 treated with placebo in a 12-week randomized double-blind period. Dosage regimens in these studies ranged from 2.520 mg of ferric iron per day, equivalent to 1 to 12 tablets of AURYXIA.

Adverse reactions reported in at least 5% of patients treated with AURYXIA in these trials are listed in Table 1.