

Findings

New Model

Continued from page 7

g/L increase), proteinuria (OR of 1.65), coronary artery bypass graft (CABG) plus valve surgery (OR of 1.25 versus CABG only), cardiac procedures other than CABG (OR of 3.11), and emergent surgery (OR of 4.63).

A model comprising these eight variables had excellent performance, with c statistics of 0.87 in the derivation cohort and 0.83 in a validation cohort of 4467 patients. Net reclassification improve-

ment was 13.9% compared with the best existing prediction model (Cleveland Clinic Score).

On the basis of readily available clinical and laboratory data, the new model provides a practical and accurate tool for predicting the risk of AKI requiring renal replacement therapy after cardiac surgery. Although additional validation is needed, this simple score could be a useful aid in talking to patients about AKI risk before heart surgery [Pannu N, et al. A new model to predict acute kidney injury requiring renal replacement therapy after cardiac surgery. *CMAJ* 2016, in press]. ●

Healthy lifestyle lowers chronic kidney disease and mortality in type 2 diabetes

In the population with type 2 diabetes, even modest changes in lifestyle and dietary risk factors could have a substantial effect on chronic kidney disease (CKD) cases and deaths, suggests a study in *The American Journal of Kidney Diseases*.

The researchers analyzed the population-attributable fraction (PAF) of diabetes-related CKD and mortality associated with lifestyle factors and diet. The study included 6916 middle-aged adults with type 2 diabetes but without

severe albuminuria drawn from the international Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial Study. Median baseline urinary albumin-to-creatinine ratio was 6.6, and eGFR was 71.5 mL/min per 1.73 m².

The effects of “immediately modifiable personal behaviors” on CKD risk were analyzed using 5.5-year follow-up data. CKD was defined as moderate to severe albuminuria or at least a 5% annual decline in eGFR. The analysis accounted for competing risk of death.

During follow-up, 32.5% of patients developed albuminuria, 55.2% had a 5% or greater decline in eGFR, 12.3% met both CKD criteria, and 14.8% died. Daily physical activity was associated with reduced risk of both outcomes: PAF of 5.1% for CKD and 12.3% for death. Dietary improvements also had a significant effect—particularly increased consumption of vegetables.

Less than optimal diet, body weight, physical activity, tobacco use, and size of social network were associated with PAFs of 13.3% for CKD and 37.5% for death. Extrapolated to the US population of 17.8 million middle-aged adults with diabetes over 5.5 years, the findings suggested that achieving one modifiable lifestyle factor could reduce CKD incidence/progression by 274,000 and avoid 405,000 deaths.

Unfavorable dietary and lifestyle factors seem to be major contributors to the risk of CKD events and death among middle-aged Americans with type 2 diabetes. Although some of the PAFs reported in this study are not large, the results suggest that healthier diet and lifestyle changes could have a “substantial impact on population kidney health” [Dunkler D, et al. Population-attributable fractions of modifiable lifestyle factors for CKD and mortality in individuals with type 2 diabetes: A cohort study. *Am J Kidney Dis* 2016; 68:29–40]. ●

BRIEF SUMMARY

AURYXIA® (ferric citrate) tablets for oral use containing 210 mg of ferric iron equivalent to 1 g AURYXIA for oral use.

INDICATIONS AND USAGE

AURYXIA is a phosphate binder indicated for the control of serum phosphorus levels in patients with chronic kidney disease on dialysis.

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Iron Overload: Iron absorption from AURYXIA may lead to excessive elevations in iron stores. Increases in serum ferritin and transferrin saturation (TSAT) levels were observed in clinical trials. In a 56-week safety and efficacy trial in which concomitant use of AURYXIA and IV iron was permitted, 55 (19%) of patients treated with AURYXIA had a ferritin level >1500 ng/mL 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 IV iron may require a reduction in dose or discontinuation of IV iron therapy.

Accidental Overdose of Iron: Accidental overdose of iron-containing products is a leading cause of fatal poisoning in children under 6 years of age. Keep this product out of the reach of children. In case of accidental overdose, call a doctor or poison control center immediately.

Patients with Gastrointestinal Bleeding or Inflammation:

Patients with inflammatory bowel disease or active, symptomatic gastrointestinal bleeding were excluded from clinical trials. Safety has not been established in these populations.

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.

Adverse reactions to a drug are most readily ascertained by comparison with placebo, but there is little placebo-controlled experience with AURYXIA, so this section describes adverse events with AURYXIA, some of which may be disease-related, rather than treatment-related.

A total of 289 patients were treated with AURYXIA and 149 patients were treated with active control (sevelamer carbonate and/or calcium acetate) during the 52-week, randomized, open-label, active control phase of a trial in patients on dialysis. A total of 322 patients were treated with AURYXIA for up to 28 days in three short-term trials. Across these trials, 557 unique patients were treated with AURYXIA; dosage regimens in these trials ranged from 210 mg to 2,520 mg of ferric iron per day, equivalent to 1 to 12 tablets of AURYXIA. In these trials, adverse events reported for AURYXIA were similar to those reported for the active control group.

Adverse events reported in more than 5% of patients treated with AURYXIA in these trials included diarrhea (21%), nausea (11%), constipation (8%), vomiting (7%), and cough (6%).

During the 52-week active-control period, 60 patients (21%) on AURYXIA discontinued study drug because of an adverse event, as compared to 21 patients (14%) in the active control arm. Patients who were previously intolerant to any of the active control treatments (calcium acetate and sevelamer carbonate) were not eligible to enroll in the study. Gastrointestinal adverse reactions were the most common reason for discontinuing AURYXIA (14%). AURYXIA is associated with discolored feces (dark stools) related to the iron content, but this staining is not clinically relevant and does not affect laboratory tests for occult bleeding, which detect heme rather than non-heme iron in the stool.

DRUG INTERACTIONS

Doxycycline is an oral drug that has to be taken at least 1 hour before AURYXIA. Ciprofloxacin, an oral drug, should be taken at least 2 hours before or after AURYXIA. Oral drugs that can be administered concomitantly with AURYXIA are: amlodipine, aspirin, atorvastatin, calcitriol, clopidogrel, digoxin, diltiazem, doxercalciferol, enalapril, fluvastatin, glimepiride, levofloxacin, losartan, metoprolol, pravastatin, propranolol, sitagliptin, and warfarin. There are no empirical data on avoiding drug interactions between 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 reach peak systemic levels and whether the drug is an immediate release or an extended release product. Consider monitoring clinical responses or blood levels of concomitant medications that have a narrow therapeutic range.

USE IN SPECIFIC POPULATIONS

Pregnancy: Pregnancy Category B: There are no adequate and well-controlled studies in pregnant women. It is not known whether AURYXIA can cause fetal harm when administered to a pregnant woman. Animal reproduction studies have not been conducted.

The effect of AURYXIA on the absorption of vitamins and other nutrients has not been studied in pregnant women. Requirements for vitamins and other nutrients are increased in pregnancy. An overdose of iron in pregnant women may carry a risk for spontaneous abortion, gestational diabetes and fetal malformation.

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

Nursing Mothers: Data from rat studies have shown the transfer of iron into milk by divalent metal transporter-1 (DMT-1) and ferroportin-1 (FPN-1). Hence, there is a possibility of infant exposure when AURYXIA is administered to a nursing woman.

Pediatric Use: The safety and efficacy of AURYXIA have not been established in pediatric patients.

Geriatric Use: Clinical studies of AURYXIA included 106 subjects aged 65 years and older (33 subjects aged 75 years and older). Overall, the clinical study experience has not identified any obvious differences in responses between the elderly and younger patients in the tolerability or efficacy of AURYXIA.

OVERDOSAGE

No data are available regarding overdose of AURYXIA in patients. In patients with chronic kidney disease on dialysis, the maximum dose studied was 2,520 mg ferric iron (12 tablets of AURYXIA) per day. Iron absorption from AURYXIA may lead to excessive elevations in iron stores, especially when concomitant IV iron is used.

In clinical trials, one case of elevated iron in the liver as confirmed by biopsy was reported in a patient administered IV iron and AURYXIA.

PATIENT COUNSELING INFORMATION

Dosing Recommendations: Inform patients to take AURYXIA as directed with meals and adhere to their prescribed diets. Instruct patients on concomitant medications that should be dosed apart from AURYXIA.

Adverse Reactions: Advise patients that AURYXIA may cause discolored (dark) stools, but this staining of the stool is considered normal with oral medications containing iron. AURYXIA may cause diarrhea, nausea, constipation and vomiting. Advise patients to report severe or persistent gastrointestinal symptoms to their physician.

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