

variables during the first 3 ICU days were extracted from electronic medical records. Four machine learning algorithms—logistic regression, random forest, support vector machine, and extreme gradient boost—were used to train the models for prediction of in-hospital death and major adverse kidney events (MAKEs). The latter outcome was a composite of death, renal replacement therapy, and 50% or greater reduction in estimated glomerular filtration rate from baseline to 120 days after discharge.

The developed clinical models included 15 features for prediction of mortality and 14 for prediction of MAKEs. Predictive performance was evaluated using tenfold cross-validation in the derivation cohort, followed by external validation of 2333 patients from a different center.

The 15-variable clinical model outperformed the Se-

quential Organ Failure Assessment score for prediction of mortality in both the derivation cohort (area under the curve [AUC], 0.79 vs. 0.71) and the validation cohort (AUC, 0.71 vs. 0.74). In the validation cohort, among patients classified as being at >50% predicted risk of mortality, 41% actually died.

The 14-variable model also improved prediction of MAKEs compared with the maximum AKI KDIGO score (AUC, 0.78 vs. 0.66 in the derivation cohort and 0.66 vs. 0.73 in the validation cohort). Among patients at 50% or higher risk, 24.5% developed a MAKE.

AKI occurs in up to 50% of patients admitted to the ICU. Although clinical models are useful in predicting AKI risk, there are few tools for prediction of AKI recovery or outcomes.

The newly developed models perform well in predicting in-hospital mortality and MAKEs in a heterogeneous population of ICU patients with AKI. “[I]f further validated, [the models] could enable risk stratification for timely interventions that promote kidney recovery,” the researchers conclude. They have developed an online tool for predicting outcomes in critically ill adults with incident AKI within the first 3 days of an ICU stay, available at <http://phenomics.uky.edu/taki/> [Neyra JA, et al. Prediction of mortality and major adverse kidney events in critically ill patients with acute kidney injury. *Am J Kidney Dis*, published online ahead of print July 13, 2022. doi: 10.1053/j.ajkd.2022.06.004; [https://www.ajkd.org/article/S0272-6386\(22\)00774-0/fulltext](https://www.ajkd.org/article/S0272-6386(22)00774-0/fulltext)]. ■

causing maternal toxicity, malformations of limb bones increased in fetuses at 700 mg/kg/day or 154-times the 25 mg maximum clinical dose. Empagliflozin crosses the placenta and reaches fetal tissues in rats. In the rabbit, higher doses of empagliflozin resulted in maternal and fetal toxicity at 700 mg/kg/day, or 139-times the 25 mg maximum clinical dose. In pre- and postnatal development studies in pregnant rats, empagliflozin was administered from gestation day 6 through to lactation day 20 (weaning) at up to 100 mg/kg/day (approximately 16-times the 25 mg maximum clinical dose) without maternal toxicity. Reduced body weight was observed in the offspring at greater than or equal to 30 mg/kg/day (approximately 4-times the 25 mg maximum clinical dose). **Lactation: Risk Summary:** There is limited information regarding the presence of JARDIANCE in human milk, the effects of JARDIANCE on the breastfed infant or the effects on milk production. Empagliflozin is present in the milk of lactating rats [see Data]. Since human kidney maturation occurs *in utero* and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney. Because of the potential for serious adverse reactions in a breastfed infant, including the potential for empagliflozin to affect postnatal renal development, advise patients that use of JARDIANCE is not recommended while breastfeeding. **Data:** Empagliflozin was present at a low level in rat fetal tissues after a single oral dose to the dams at gestation day 18. In rat milk, the mean milk to plasma ratio ranged from 0.634 to 5, and was greater than one from 2 to 24 hours post-dose. The mean maximal milk to plasma ratio of 5 occurred at 8 hours post-dose, suggesting accumulation of empagliflozin in the milk. Juvenile rats directly exposed to empagliflozin showed a risk to the developing kidney (renal pelvic and tubular dilatations) during maturation. **Pediatric Use:** The safety and effectiveness of JARDIANCE have not been established in pediatric patients. **Geriatric Use:** In glycemic control studies in patients with type 2 diabetes mellitus, a total of 2721 (32%) patients treated with JARDIANCE were 65 years of age and older, and 491 (6%) were 75 years of age and older. JARDIANCE is expected to have diminished glycemic efficacy in elderly patients with renal impairment [see Use in Specific Populations]. The risk of volume depletion-related adverse reactions increased in patients who were 75 years of age and older to 2.1%, 2.3%, and 4.4% for placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg. The risk of urinary tract infections increased in patients who were 75 years of age and older to 10.5%, 15.7%, and 15.1% in patients randomized to placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg, respectively [see Warnings and Precautions and Adverse Reactions]. In heart failure studies, EMPEROR-Reduced included 1188 (64%) patients treated with JARDIANCE 65 years of age and older, and 503 (27%) patients 75 years of age

and older. EMPEROR-Preserved included 2402 (80%) patients treated with JARDIANCE 65 years of age and older, and 1281 (43%) patients 75 years of age and older. Safety and efficacy were similar for patients 65 years and younger and those older than 65 years. **Renal Impairment:** The efficacy and safety of JARDIANCE for glycemic control were evaluated in a study of patients with type 2 diabetes mellitus with mild and moderate renal impairment (eGFR 30 to less than 90 mL/min/1.73 m²) [see Clinical Studies]. In this study, 195 patients exposed to JARDIANCE had an eGFR between 60 and 90 mL/min/1.73 m², 91 patients exposed to JARDIANCE had an eGFR between 45 and 60 mL/min/1.73 m², and 97 patients exposed to JARDIANCE had an eGFR between 30 and 45 mL/min/1.73 m². The glucose lowering benefit of JARDIANCE 25 mg decreased in patients with worsening renal function. The risks of renal impairment, volume depletion adverse reactions and urinary tract infection-related adverse reactions increased with worsening renal function [see Warnings and Precautions]. Use of JARDIANCE for glycemic control in patients without established cardiovascular disease or cardiovascular risk factors is not recommended when eGFR is less than 30 mL/min/1.73 m². In a large cardiovascular outcomes study of patients with type 2 diabetes and established cardiovascular disease, there were 1819 patients with eGFR below 60 mL/min/1.73 m². The cardiovascular death findings in this subgroup were consistent with the overall findings [see Clinical Studies]. Studies of patients with heart failure [see Clinical Studies] enrolled patients with eGFR equal to or above 20 mL/min/1.73 m². No dose adjustment is recommended for these patients. There are insufficient data to support a dosing recommendation in patients with eGFR below 20 mL/min/1.73 m². Efficacy and safety studies with JARDIANCE did not enroll patients with an eGFR less than 20 mL/min/1.73 m². JARDIANCE is contraindicated in patients on dialysis [see Contraindications]. **Hepatic Impairment:** JARDIANCE may be used in patients with hepatic impairment [see Clinical Pharmacology].

OVERDOSAGE: In the event of an overdose with JARDIANCE, contact the Poison Control Center. Removal of empagliflozin by hemodialysis has not been studied.

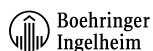
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Acetazolamide Improves Outcomes in Decompensated Heart Failure

In patients with acute decompensated heart failure with volume overload, adding acetazolamide to loop diuretic therapy increases the odds of successful decongestion, concludes a clinical trial report in *The New England Journal of Medicine*.

The multicenter Acetazolamide in Decompensated Heart Failure with Volume Overload (ADVOR) trial enrolled 519 hospitalized patients with acute decompensated heart failure (63% men; mean age, 78 years). Eligible patients had at least one clinical sign of volume overload (e.g., edema, pleural effusion, or ascites); an N-terminal pro-B-type natriuretic peptide level >1000 pg/mL or B-type natriuretic peptide level >250 pg/mL; and at least 1 month of oral maintenance therapy with furosemide 40 mg or equivalent.

Patients were randomly assigned to acetazolamide, 500 mg intravenously (IV) once daily or placebo added to IV loop diuretics at a dose equivalent to twice the oral maintenance dose. Groups were stratified based on left ventricular ejection fraction with a cutoff of 40%. The main outcome of interest was successful decongestion, defined as no evidence of volume overload within 3 days after randomization with no indications for escalated decongestive therapy.

Acetazolamide was associated with a significant increase in successful decongestion compared with placebo (42.2% vs. 30.5%; risk ratio, 1.46). Patients assigned to acetazolamide had a nonsignificant reduction in a composite secondary outcome of all-cause mortality or heart failure rehospitalization (29.7% and 27.8%, respectively).

The acetazolamide group showed evidence of increased diuretic efficiency with higher cumulative urine output and natriuresis. Rates of worsening kidney function, hypokalemia, hypotension, or adverse events were similar between groups.

Even with high-dose loop diuretics, many patients with acute decompensated heart failure continued signs of volume overload after discharge, associated with poor clinical outcomes. Added to loop diuretics, the carbonic anhydrase inhibitor acetazolamide reduces proximal tubular sodium reabsorption and thus, might improve diuretic efficiency.

The ADVOR results show an increase in successful decongestion with acetazolamide added to standardized loop diuretic therapy for acute decompensated heart failure with volume overload. “These findings highlight the importance of targeting congestion both early and aggressively and support the use of natriuresis as an indicator of diuretic response,” the researchers write [Mullens W, et al. Acetazolamide in acute decompensated heart failure with volume overload. *N Engl J Med*, published online ahead of print August 27, 2022. doi: 10.1056/NEJMoa2203094; <https://www.nejm.org/doi/10.1056/NEJMoa2203094>]. ■