

Do We Need to Test for CHD before Kidney Transplant?

Preoperative testing for coronary heart disease (CHD) does not reduce the risk of myocardial infarction (MI) or death in the early weeks after kidney transplantation, reports a study in *JAMA Internal Medicine*.

Using the US Renal Data System, the researchers identified 79,334 adults undergoing first-time kidney transplantation from 2000 through 2014. All were enrolled in Medicare for at least 1 year before and 1 year after transplant. The mean age was 56 years; 62% of patients were men, and 61% were White.

The researchers performed an instrumental variable (IV) analysis, with program-

level rates of preoperative CHD testing in the year of transplantation as the IV. Non-urgent CHD testing, invasive or non-invasive, was analyzed for an association with a primary composite outcome of death or MI during the first 30 days after transplantation.

A primary composite outcome event occurred in 5.3% of patients: acute MI in 2.9% of patients and death in 2.6%. From 2012 to 2014, program-level rates of preoperative CHD testing ranged from 56% in the top quintile to 24% in the bottom quintile.

In the main IV analysis, the CHD testing rate was unrelated to the 30-day risk of

MI or death: the rate difference of 1.9% was not statistically significant. The findings were consistent across most study periods. The exception was from 2000 to 2003 when CHD testing was associated with higher risk of primary outcome events: rate difference, 6.8%.

Screening for CHD before kidney transplantation is widely recommended and performed—despite a lack of evidence that it affects transplant outcomes. One study has suggested that patients selected for screening are a group at higher risk of MI. Until the results of an ongoing randomized trial are available, IV analysis provides a means

of drawing causal inferences from observational data.

Testing for CHD before kidney transplant does not reduce the risk of adverse outcomes during the early posttransplant period, the quasi-experimental study concludes. The results, added to ongoing interventional studies, “may pave the way to deescalating CHD testing before kidney transplantation,” the researchers conclude [Cheng XS, et al. Association of pretransplant coronary heart disease testing with early kidney transplant outcomes. *JAMA Intern Med* 2023; 183:134–141. doi: 10.1001/jamaintern-med.2022.6069]. ■

Traditional Risk Factors Explain Higher CKD Risk in Black Americans

The higher incidence of chronic kidney disease (CKD) among Black compared with White US adults is largely explained by traditional CKD risk factors, concludes a study in the *American Journal of Kidney Diseases*.

The analysis included 4198 Black and 7799 White participants from the “Reasons for Geographic and Racial Differences in Stroke” (REGARDS) study. All were at least 45 years old at enrollment in 2003–2007, with a baseline estimated glomerular filtration rate (eGFR) greater than 60 mL/min/1.73 m². CKD incidence and risk factors were compared between Black and White participants. The study definition of CKD was eGFR of less than 60 mL/min/1.73 m² with a decline of at least 40% from baseline or kidney failure. At 9.4 years’ follow-up, CKD incidence was 9%, ranging from 4% for adults aged 45 to 54 years to 18% in those aged 75 or older. Black race was associated with higher risk of eGFR change during follow-up, after adjustment for age, sex, and race.

However, the racial association was no longer significant in a fully adjusted model accounting for all risk factors. Independent risk factors for CKD included age, low income, residence in the Southeastern “Stroke Belt” states, systolic blood pressure, body mass index, diabetes, hyperlipidemia, and albuminuria.

Risk factors were similar on analysis of CKD incidence. For both eGFR change and CKD, albuminuria was a stronger risk factor in Black compared with White adults and for participants living in the Stroke Belt.

There are known racial disparities in the prevalence and associated costs of CKD in the US population. There are few data on the incidence of and risk factors for CKD in a contemporary US population, including possible differences by race, sex, or region.

Modifiable risk factors, such as diabetes, hypertension, and obesity, account for most of the increased incidence of CKD among Black Americans, the new results suggest. Further study is needed to clarify the importance of albuminuria and Stroke Belt residence as risk factors for incident CKD and eGFR decline [Cheung KL, et al. Risk factors for incident CKD in Black and White Americans: The REGARDS study. *Am J Kidney Dis*, published online ahead of print January 5, 2023. doi: 10.1053/j.ajkd.2022.11.015; https://www.ajkd.org/article/S0272-6386(23)00005-7/fulltext]. ■

JYNARQUE® (tolvaptan) tablets for oral use  
Brief summary of PRESCRIBING INFORMATION. See full prescribing information for JYNARQUE.

**WARNING: RISK OF SERIOUS LIVER INJURY**

- JYNARQUE (tolvaptan) can cause serious and potentially fatal liver injury. Acute liver failure requiring liver transplantation has been reported
- Measure ALT, AST and bilirubin before initiating treatment, at 2 weeks and 4 weeks after initiation, then monthly for the first 18 months and every 3 months thereafter. Prompt action in response to laboratory abnormalities, signs, or symptoms indicative of hepatic injury can mitigate, but not eliminate, the risk of serious hepatotoxicity.
- Because of the risks of serious liver injury, JYNARQUE is available only through a restricted distribution program under a Risk Evaluation and Mitigation Strategy (REMS) called the JYNARQUE REMS Program.

**INDICATIONS AND USAGE:** JYNARQUE is indicated to slow kidney function decline in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD).

**CONTRAINDICATIONS:** JYNARQUE is contraindicated in patients:

- With a history, signs or symptoms of significant liver impairment or injury. This contraindication does not apply to uncomplicated polycystic liver disease
- Taking strong CYP 3A inhibitors
- With uncorrected abnormal blood sodium concentrations
- Unable to sense or respond to thirst
- Hypovolemia
- Hypersensitivity (e.g., anaphylaxis, rash) to tolvaptan or any component of the product
- Uncorrected urinary outflow obstruction
- Anuria

**WARNINGS AND PRECAUTIONS**

**Serious Liver Injury:** JYNARQUE can cause serious and potentially fatal liver injury. Acute liver failure requiring liver transplantation has been reported in the post-marketing ADPKD experience. Discontinuation in response to laboratory abnormalities or signs or symptoms of liver injury (such as fatigue, anorexia, nausea, right upper abdominal discomfort, vomiting, fever, rash, pruritus, icterus, dark urine or jaundice) can reduce the risk of severe hepatotoxicity. To reduce the risk of significant or irreversible liver injury, assess ALT, AST and bilirubin prior to initiation of JYNARQUE, at 2 weeks and 4 weeks after initiation, then monthly for 18 months and every 3 months thereafter. At the onset of signs or symptoms consistent with hepatic injury or if ALT, AST, or bilirubin increase to >2 times ULN, immediately discontinue JYNARQUE, obtain repeat tests as soon as possible (within 48-72 hours), and continue testing as appropriate. If laboratory abnormalities stabilize or resolve, JYNARQUE may be reinitiated with increased frequency of monitoring as long as ALT and AST remain below 3 times ULN.

Do not restart JYNARQUE in patients who experience signs or symptoms consistent with hepatic injury or whose ALT or AST ever exceeds 3 times ULN during treatment with tolvaptan, unless there is another explanation for liver injury and the injury has resolved.

In patients with a stable, low baseline AST or ALT, an increase above 2 times baseline, even if less than 2 times upper limit of normal, may indicate early liver injury. Such elevations may warrant treatment suspension and prompt (48-72 hours) re-evaluation of liver test trends prior to reinitiating therapy with more frequent monitoring.

**JYNARQUE REMS Program:** JYNARQUE is available only through a restricted distribution program under a Risk Evaluation and Mitigation Strategy (REMS) called the JYNARQUE REMS Program, because of the risks of liver injury. Notable requirements of the JYNARQUE REMS Program include the following:

- Prescribers must be certified by enrolling in the REMS program.
- Prescribers must inform patients receiving JYNARQUE about the risk of hepatotoxicity associated with its use and how to recognize the signs and symptoms of hepatotoxicity and the appropriate actions to take if it occurs.
- Patients must enroll in the REMS program and comply with ongoing monitoring requirements.
- Pharmacies must be certified by enrolling in the REMS program and must only dispense to patients who are authorized to receive JYNARQUE.

**Hypernatremia, Dehydration and Hypovolemia:** JYNARQUE increases free water clearance and, as a result, may cause dehydration, hypovolemia and hypernatremia. Therefore, ensure abnormalities in sodium concentrations are corrected prior to initiation of therapy.

Instruct patients to drink water when thirsty, and throughout the day and night if awake. Monitor for weight loss, tachycardia and hypotension because they may signal dehydration.

During JYNARQUE therapy, if serum sodium increases above normal range or the patient becomes hypovolemic or dehydrated and fluid intake cannot be increased, then suspend JYNARQUE until serum sodium, hydration status and volume status is within the normal range.

**Co-Administration with Inhibitors of CYP 3A:** Concomitant use of JYNARQUE with drugs that are moderate or strong CYP 3A inhibitors (e.g., ketoconazole, itraconazole, lopinavir/ritonavir, indinavir/ritonavir, ritonavir, and cobicistat) increases tolvaptan exposure. Use with strong CYP 3A inhibitors is contraindicated; dose reduction of JYNARQUE is recommended for patients while taking moderate CYP 3A inhibitors

**ADVERSE REACTIONS**

**Clinical Trials 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 practice. JYNARQUE has been studied in over 3000 patients with ADPKD. Long-term, placebo-controlled safety information of JYNARQUE in ADPKD is principally derived from two trials where 1,413 subjects received tolvaptan and 1,098 received placebo for at least 12 months across both studies.

**TEMPO 3:4 -NCT00428948: A Phase 3, Double-Blind, Placebo-Controlled, Randomized Trial in Early, Rapidly-Progressing ADPKD:** The TEMPO3:4 trial employed a two-arm, 2:1 randomization to tolvaptan or placebo, titrated to a maximally-tolerated total daily dose of 60-120 mg. A total of 961 subjects with rapidly progressing ADPKD were randomized to JYNARQUE. Of these, 742 (77%) subjects who were treated with JYNARQUE remained on treatment for at least 3 years. The average daily dose in these subjects was 96 g daily.

Adverse events that led to discontinuation were reported for 15.4% (148/961) of subjects in the JYNARQUE group and 5.0% (24/483) of subjects in the placebo group. Aquaretic effects were the most common reasons for discontinuation of JYNARQUE. These included polyakiuria, polyuria, or nocturia in 63 (6.6%) subjects treated with JYNARQUE compared to 1 subject (0.2%) treated with placebo.

Table 1 lists the adverse reactions that occurred in at least 3% of ADPKD subjects treated with JYNARQUE and at least 1.5% more than on placebo.

Table 1: TEMPO 3:4, Treatment Emergent Adverse Reactions in ≥3% of JYNARQUE Treated Subjects with Risk Difference ≥ 1.5%, Randomized Period						
Adverse Reaction	Tolvaptan (N=961)			Placebo (N=483)		
	Number of Subjects	Proportion (%) <sup>a</sup>	Annualized Rate <sup>b</sup>	Number of Subjects	Proportion (%) <sup>a</sup>	Annualized Rate <sup>b</sup>
Increased urination <sup>c</sup>	668	69.5	28.6	135	28.0	10.3
Thirst <sup>d</sup>	612	63.7	26.2	113	23.4	8.7
Dry mouth	154	16.0	6.6	60	12.4	4.6
Fatigue	131	13.6	5.6	47	9.7	3.6
Diarrhea	128	13.3	5.5	53	11.0	4.1

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Adverse Reaction	Tolvaptan (N=961)			Placebo (N=483)		
	Number of Subjects	Proportion (%) <sup>a</sup>	Annualized Rate <sup>b</sup>	Number of Subjects	Proportion (%) <sup>a</sup>	Annualized Rate <sup>b</sup>
Dizziness	109	11.3	4.7	42	8.7	3.2
Dyspepsia	76	7.9	3.3	16	3.3	1.2
Decreased appetite	69	7.2	3.0	5	1.0	0.4
Abdominal distension	47	4.9	2.0	16	3.3	1.2
Dry skin	47	4.9	2.0	8	1.7	0.6
Rash	40	4.2	1.7	9	1.9	0.7
Hyperuricemia	37	3.9	1.6	9	1.9	0.7
Palpitations	34	3.5	1.5	6	1.2	0.5

<sup>a</sup>100x (Number of subjects with an adverse event)/N

<sup>b</sup>100x (Number of subjects with an adverse event/Total subject years of drug exposure)

<sup>c</sup>Thirst includes polydipsia and thirst

<sup>d</sup>Increased urination includes micturition urgency, nocturia, pollakiuria, polyuria

**REPRISE-NCT02160145: A Phase 3, Randomized-Withdrawal, Placebo-Controlled, Double-Blind, Trial in Late Stage 2 to Early Stage 4 ADPKD:** The REPRISE trial employed a 5-week single-blind titration and run-in period for JYNARQUE prior to the randomized double-blind period. During the JYNARQUE titration and run-in period, 126 (8.4%) of the 1496 subjects discontinued the study; 52 (3.5%) were due to aquaretic effects and 10 (0.7%) were due to liver test findings. Because of this run-in design, the adverse reaction rates observed during the randomized period are not described.

**Liver Injury:** In the two double-blind, placebo-controlled trials, ALT elevations >3 times ULN were observed at an increased frequency with JYNARQUE compared with placebo (4.9% [80/1637] versus 1.1% [13/1166], respectively) within the first 18 months after initiating treatment and increases usually resolved within 1 to 4 months after discontinuing the drug.

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

**Hepatobiliary Disorders:** Liver failure requiring transplant

**Immune System Disorders:** Anaphylaxis

**DRUG INTERACTIONS**

**CYP 3A Inhibitors and Inducers:** **CYP 3A Inhibitors:** Tolvaptan's AUC was 5.4 times as large and Cmax was 3.5 times as large after co-administration of tolvaptan and 200 mg ketoconazole. Larger doses of the strong CYP 3A inhibitor would be expected to produce larger increases in tolvaptan exposure. Concomitant use of tolvaptan with strong CYP 3A inhibitors is contraindicated. Dose reduction of JYNARQUE is recommended for patients while taking moderate CYP 3A inhibitors. Patients should avoid grapefruit juice beverages while taking JYNARQUE. **Strong CYP 3A Inducers:** Co-administration of JYNARQUE with strong CYP 3A inducers reduces exposure to JYNARQUE. Avoid concomitant use of JYNARQUE with strong CYP 3A inducers.

**V<sub>2</sub>-Receptor Agonist:** As a V<sub>2</sub>-receptor antagonist, tolvaptan will interfere with the V<sub>2</sub>-agonist activity of desmopressin (dDAVP). Avoid concomitant use of JYNARQUE with a V<sub>2</sub>-agonist.

**USE IN SPECIFIC POPULATIONS**

**Pregnancy: Risk Summary:** Available data with JYNARQUE use in pregnant women are insufficient to determine if there is a drug associated risk of adverse developmental outcomes. In embryo-fetal development studies, pregnant rats and rabbits received oral tolvaptan during organogenesis. At maternally non-toxic doses, tolvaptan did not cause any developmental toxicity in rats or in rabbits at exposures approximately 4- and 1-times, respectively, the human exposure at the maximum recommended human dose (MRHD) of 90/30 mg. However, effects on embryo-fetal development occurred in both species at maternally toxic doses. In rats, reduced fetal weights and delayed fetal ossification occurred at 17-times the human exposure. In rabbits, increased abortions, embryo-fetal death, fetal microphthalmia, open eyelids, cleft palate, brachymelia and skeletal malformations occurred at approximately 3-times the human exposure. Advise pregnant women of the potential risk to the fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage in the U.S. general population is 2-4% and 15-20% of clinically recognized pregnancies, respectively.

**Lactation: Risk Summary:** There are no data on the presence of tolvaptan in human milk, the effects on the breastfed infant, or the effects on milk production. Tolvaptan is present in rat milk. When a drug is present in animal milk, it is possible that the drug will be present in human milk, but relative levels may vary. Because of the potential for serious adverse reactions, including liver toxicity, electrolyte abnormalities (e.g., hypernatremia), hypotension, and volume depletion in breastfed infants, advise women not to breastfeed during treatment with JYNARQUE.

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

**Geriatric Use:** Clinical studies of tolvaptan did not include sufficient numbers of subjects aged 65 years 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.

**Use in Patients with Hepatic Impairment:** Because of the risk of serious liver injury, use is contraindicated in patients with a history, signs or symptoms of significant liver impairment or injury. This contraindication does not apply to uncomplicated polycystic liver disease which was present in 60% and 66% of patients in TEMPO 3:4 and REPRISE, respectively. No specific exclusion for hepatic impairment was implemented in TEMPO 3:4. However, REPRISE excluded patients with ADPKD who had hepatic impairment or liver function abnormalities other than that expected for ADPKD with typical cystic liver disease.

**Use in Patients with Renal Impairment:** Efficacy studies included patients with normal and reduced renal function. TEMPO 3:4 required patients to have an estimated creatinine clearance ≥60 mL/min, while REPRISE included patients with eGFR<sub>CKD-EPI</sub> 25 to 65 mL/min/1.73m².

**OVERDOSAGE:** Single oral doses up to 480 mg (4 times the maximum recommended daily dose) and multiple doses up to 300 mg once daily for 5 days have been well tolerated in trials 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. In patients with suspected JYNARQUE overdosage, assessment of vital signs, electrolyte concentrations, ECG and fluid status is recommended. Continue replacement of water and electrolytes until aquaresis abates. Dialysis may not be effective in removing JYNARQUE because of its high binding affinity for human plasma protein (>98%).

**PATIENT COUNSELING INFORMATION**

See FDA-Approved Patient Labeling (Medication Guide).

**To report SUSPECTED ADVERSE REACTIONS, contact Otsuka America Pharmaceutical, Inc. at 1-800-438-9927 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**