

Findings

Most US Adults with T2D Meet Criteria for GLP-1 RAs or SGLT2is, but Few Receive Them

More than 80% of American adults with type 2 diabetes (T2D) meet criteria for treatment with glucagon-like peptide-1 receptor agonists (GLP-1 RAs) or sodium-glucose cotransporter-2 inhibitors (SGLT2is), but few actually receive these medications, according to a research letter in the *Annals of Internal Medicine*.

The researchers analyzed data on 1330 adults with T2D from the National Health and Nutrition Examination Survey 2017–2020. Of these adults, 82.3% of patients met recommended criteria for GLP-1 RA or SGLT2i treatment. Criteria were met by all patients with established or high risk for atherosclerotic cardiovascular disease (ASCVD), heart failure, or chronic kidney disease (CKD). Ninety-seven percent of patients aged 65 years or older met treatment criteria, as did 70% of younger patients. Treatment criteria were met by 94.5% of Medicare patients.

Only 9.1% of patients were receiving either of these medications between 2017 and 2020, a time when they were not recommended for first-line treatment in many patients who would now be considered eligible. Treatment rates were 5.3% for SGLT2is and 3.7% for GLP-1 RAs.

Based on level A evidence, a 2022 consensus report by the American Diabetes Association and the European Association for the Study of Diabetes recommended GLP-1 RA treatment for patients with T2D with established or high risk for ASCVD. The report also recommended SGLT2is for patients with established ASCVD, CKD, or heart failure or high risk for ASCVD.

This study suggests that most US adults with T2D would meet those treatment criteria, including nearly all Medicare beneficiaries. During the period studied, only approximately 9% of eligible patients were receiving GLP-1 RAs or SGLT2is.

“However, at current drug pricing, using these two new medications as first-line agents among all eligible patients with T2D may not be cost-effective,” the researchers conclude. “[A]n assessment of cost-effectiveness may assist better targeting of interventions to achieve the greatest effect at a sustainable cost” [Tang S, et al. Recommended and prevalent use of glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter-2 inhibitors in a national population-based sample. *Ann Intern Med*, published online ahead of print February 28, 2023. doi: 10.7326/M22-3051; <https://www.acpjournals.org/doi/10.7326/M22-3051>]. ■

“No Opioids” for Major Urologic Cancer Surgery?

A “no-opioid” strategy greatly reduces the percentage of patients receiving opioid prescriptions after surgery for renal, bladder, or prostate cancer, reports a study in *JAMA Surgery*.

The cohort study included 647 opioid-naïve patients undergoing open or minimally invasive radical cystectomy, radical or partial nephrectomy, or radical prostatectomy at the authors’ referral center between 2017 and 2021. In a pre-intervention period (2017–2018), 202 patients were treated, 100 during an initial feasibility study or lead-in period (2019), and 384 during the in-

tervention period (2020–2021). The no-opioid intervention consisted of a pre-admission educational handout and post-discharge instructions for using non-opioid analgesics, without a routine opioid prescription. Acetaminophen and ibuprofen were the main non-opioid analgesics used.

The rate of opioid prescriptions at discharge decreased from 80.9% in the pre-intervention period to 57.9% during the lead-in period and to 2.2% in the intervention period. Median tablets prescribed were 14, 4, and 0, respectively. For procedures performed dur-

ing the intervention period, mean and median opioid dose was 0 tablets for prostate and bladder surgery. The mean number of tablets prescribed was 0.6 for open surgery and 0.3 for robotic kidney surgery.

The intervention did not increase calls or unplanned clinic or emergency department visits due to pain. Patient surveys from the no-opioid period showed low pain scores (mean 2.5) and high satisfaction scores. Of 10 patients in the intervention group who received additional opioid prescriptions, 8 had undergone kidney surgery.

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(sparsentan) tablets
200 mg/400 mg

FILSPARI™ (sparsentan) is indicated to reduce proteinuria in adults with primary immunoglobulin A nephropathy (IgAN) at risk of rapid disease progression, generally a urine protein-to-creatinine ratio (UPCR) ≥ 1.5 g/g.

This indication is approved under accelerated approval based on reduction of proteinuria. It has not been established whether FILSPARI slows kidney function decline in patients with IgAN. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory clinical trial.

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IMPORTANT SAFETY INFORMATION

BOXED WARNING: HEPATOTOXICITY AND EMBRYO-FETAL TOXICITY

Because of the risks of hepatotoxicity and birth defects, FILSPARI is available only through a restricted program called the FILSPARI REMS. Under the FILSPARI REMS, prescribers, patients and pharmacies must enroll in the program.

Hepatotoxicity

Some Endothelin Receptor Antagonists (ERAs) have caused elevations of aminotransferases, hepatotoxicity, and liver failure. In clinical studies, elevations in aminotransferases (ALT or AST) of at least 3-times the Upper Limit of Normal (ULN) have been observed in up to 2.5% of FILSPARI-treated patients, including cases confirmed with rechallenge.

Measure transaminases and bilirubin before initiating treatment and monthly for the first 12 months, and then every 3 months during treatment. Interrupt treatment and closely monitor patients who develop aminotransferase elevations more than 3x ULN.

FILSPARI should generally be avoided in patients with elevated aminotransferases ($>3x$ ULN) at baseline because monitoring for hepatotoxicity may be more difficult and these patients may be at increased risk for serious hepatotoxicity.

Embryo-Fetal Toxicity

FILSPARI can cause major birth defects if used by pregnant patients based on animal data. Therefore, pregnancy testing is required before the initiation of treatment, during treatment and one month after discontinuation of treatment with FILSPARI. Patients who can become pregnant must use effective contraception before the initiation of treatment, during treatment, and for one month after discontinuation of treatment with FILSPARI.

Please see additional Important Safety Information on adjacent page.

The no-opioid intervention—focused on pre-operative instruction and non-opioid alternatives—greatly reduced the use of opioid medications after major abdominopelvic surgery. The experience suggests that routine discharge opioid prescriptions can be eliminated with good pain control, low complication rates, and high patient satisfaction [Mian BM, et al. Implementation and assessment of no opioid prescription strategy at discharge after major urologic cancer surgery. *JAMA Surg*, published online ahead of print February 8, 2023. doi: 10.1001/jamasurg.2022.7652; <https://jamanetwork.com/journals/jamasurgery/fullarticle/2801213>]. ■

No Reduction in Recurrent Kidney Stones with Hydrochlorothiazide

In patients with recurring kidney stones, hydrochlorothiazide does not reduce the incidence of further recurrences compared with placebo, reports a clinical trial in *The New England Journal of Medicine*.

The trial enrolled 416 adult patients with recurrent kidney stones with at least two episodes over the past 10 years and any previous stone containing at least 50% calcium oxalate and/or calcium phosphate. Patients were randomly assigned to receive once-daily hydrochlorothiazide at a dose of 12.5, 25, or 50 mg or placebo. A primary composite end point of symptomatic or radiologic kidney stone recurrence was evaluated at a median fol-

low-up of 2.9 years.

No dose of hydrochlorothiazide was effective in reducing the risk of recurrent kidney stones. Compared with the 59% incidence with placebo, recurrence rates with hydrochlorothiazide were 59% at the 12.5-mg dose, 56% at the 25-mg dose, and 49% at the 50-mg dose. The symptomatic recurrence rate was similar across groups, with a 34% rate in the placebo group. The radiologic recurrence rate—a composite of stone growth or new stone formation—was lowest in the hydrochlorothiazide 25- and 50-mg dose groups.

Patients receiving hydrochlorothiazide had higher rates of hypokalemia, gout,

new-onset diabetes, skin allergy, and plasma creatinine >150% of baseline. Serious adverse events were no more common with hydrochlorothiazide versus placebo.

Kidney stones are a common and frequently recurrent problem. Hydrochlorothiazide is widely prescribed to prevent recurrent stones, despite limitations of the research on this issue.

This randomized, placebo-controlled trial finds no significant reduction in the frequency of recurrent kidney stones in high-risk patients taking hydrochlorothiazide. This is so across the range of once-

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Contraindications: FILSPARI is contraindicated in patients who are pregnant. Do not coadminister FILSPARI with angiotensin receptor blockers (ARBs), ERAs, or aliskiren.

Warnings and Precautions

- **Hepatotoxicity:** Elevations in ALT or AST of at least 3-fold ULN have been observed. To reduce the risk of potential serious hepatotoxicity, measure serum aminotransferase levels and total bilirubin prior to initiation of treatment, monthly for the first 12 months, then every 3 months during treatment. Advise patients with symptoms suggesting hepatotoxicity (nausea, vomiting, right upper quadrant pain, fatigue, anorexia, jaundice, dark urine, fever, or itching) to immediately stop treatment with FILSPARI and seek medical attention. If aminotransferase levels are abnormal at any time during treatment, interrupt FILSPARI and monitor as recommended. Consider re-initiation of FILSPARI only when hepatic enzyme levels and bilirubin return to pretreatment values and only in patients who have not experienced clinical symptoms of hepatotoxicity. Avoid initiation of FILSPARI in patients with elevated aminotransferases (>3x ULN) prior to drug initiation.
- **Embryo-Fetal Toxicity:** FILSPARI can cause fetal harm. Advise patients who can become pregnant of the potential risk to a fetus. Obtain a pregnancy test and advise patients who can become pregnant to use effective contraception prior to, during, and one month after discontinuation of FILSPARI treatment.
- **FILSPARI REMS:** FILSPARI is available only through a restricted program under a REMS called the FILSPARI REMS. Important requirements include:
 - Prescribers must be certified with the FILSPARI REMS by enrolling and completing training.
 - All patients must enroll in the FILSPARI REMS prior to initiating treatment and comply with monitoring requirements.
 - Pharmacies that dispense FILSPARI must be certified with the FILSPARI REMS and must dispense only to patients who are authorized to receive FILSPARI.
 Further information is available at www.filsparirems.com or 1-833-513-1325.
- **Hypotension:** There was a greater incidence of hypotension-associated adverse events, some serious, including dizziness, in patients treated with FILSPARI compared to irbesartan. In patients at risk for hypotension, consider eliminating or adjusting other antihypertensive medications and maintaining appropriate volume status. If hypotension develops, consider a dose reduction or dose interruption of FILSPARI.
- **Acute Kidney Injury:** Monitor kidney function periodically. Patients whose kidney function may depend in part on the activity of the renin-angiotensin system (e.g., patients with renal artery stenosis, chronic kidney disease, severe congestive heart failure, or volume depletion) may be at particular risk of developing acute kidney injury on FILSPARI. Consider withholding or discontinuing therapy in patients who develop a clinically significant decrease in kidney function while on FILSPARI.
- **Hyperkalemia:** Monitor serum potassium periodically and treat appropriately. Patients with advanced kidney disease, taking concomitant potassium-increasing drugs (e.g., potassium supplements, potassium-sparing diuretics), or using potassium-containing salt substitutes are at increased risk for developing hyperkalemia. Dosage reduction or discontinuation of FILSPARI may be required.

- **Fluid Retention:** Fluid retention may occur with ERAs, and has been observed with FILSPARI. If clinically significant fluid retention develops, after evaluation, consider modifying the dose of FILSPARI.

Most common adverse reactions (≥5%) are peripheral edema, hypotension (including orthostatic hypotension), dizziness, hyperkalemia, and anemia.

Drug interactions

- **Renin-Angiotensin System (RAS) Inhibitors and ERAs:** Do not coadminister FILSPARI with ARBs, ERAs, or aliskiren.
- **Strong and Moderate CYP3A Inhibitors:** Avoid concomitant use of FILSPARI with strong CYP3A inhibitors. Monitor blood pressure, serum potassium, edema, and kidney function regularly when used concomitantly with moderate CYP3A inhibitors.
- **Strong CYP3A Inducers:** Avoid concomitant use with a strong CYP3A inducer.
- **Antacids and Acid Reducing Agents:** Administer FILSPARI 2 hours before or after administration of antacids. Avoid concomitant use of acid reducing agents (histamine H2 receptor antagonist and PPI proton pump inhibitor) with FILSPARI.
- **Non-Steroidal Anti-Inflammatory Agents (NSAIDs), Including Selective Cyclooxygenase-2 (COX-2) Inhibitors:** Monitor for signs of worsening renal function.
- **CYP2B6, 2C9, and 2C19 Substrates:** Monitor for efficacy of the concurrently administered CYP2B6, 2C9, and 2C19 substrates and consider dosage adjustment in accordance with the Prescribing Information.
- **P-gp and BCRP Substrates:** Avoid concomitant use of sensitive substrates of P-gp and BCRP with FILSPARI.
- **Agents Increasing Serum Potassium:** Monitor serum potassium frequently. Concomitant use of FILSPARI with potassium-sparing diuretics, potassium supplements, potassium-containing salt substitutes, or other drugs that raise serum potassium levels may result in hyperkalemia.

Use in specific populations

- **Pregnancy / Females and Males of Reproductive Potential:** FILSPARI can cause fetal harm, including birth defects and fetal death, when administered to a pregnant patient and is contraindicated during pregnancy.
 - **Pregnancy Testing / Contraception:** Verify the pregnancy status and effective method of contraception prior to, during, and one month after discontinuation of FILSPARI treatment. The patient should contact their physician immediately for pregnancy testing if onset of menses is delayed or pregnancy is suspected.
- **Lactation:** Advise patients not to breastfeed during treatment with FILSPARI.
- **Hepatic Impairment:** Avoid use of FILSPARI in patients with any hepatic impairment (Child-Pugh class A-C).

For additional important safety information, please see Brief Summary of the full Prescribing Information on the following pages, and the full Prescribing Information, including BOXED WARNING.

Reference: FILSPARI Prescribing Information. San Diego, CA: Traverre Therapeutics, Inc.

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