MEDXCHANGE LIVE™ SPECIAL EDITION

DIABETIC KIDNEY DISEASE

Type 2 Diabetes and the Risk of Diabetic Kidney Disease

Worldwide, chronic kidney disease affects 8% to 16% of the population.[1] Diabetes mellitus is the most common cause of chronic kidney disease, leading to multiple complications including end-stage renal disease (ESRD), cardiovascular disease, infection, and death.[2,3] Due to an increased incidence of type 2 diabetes, the prevalence of diabetes mellitus has grown significantly throughout the world, leading to a major impact on development of chronic kidney disease (CKD).[3] Approximately 25% of all diabetic patients eventually develop CKD.[2] In addition, the increasing prevalence of chronic kidney disease in younger patients and obese patients with type 2 diabetes, a population associated with an accelerated course of complications, adds to the global burden of CKD.[4]

Chronic kidney disease in the setting of diabetes, or diabetic kidney disease (DKD), manifests clinically as reduced glomerular filtration rate (GFR) with or without albuminuria.[1–2,5–6] Therefore, albuminuria and/or a low GFR in patients with diabetes is referred to as DKD and is defined as a persistent abnormality in kidney structure or function (GFR <60 mL/min/1.73 m^2 or albuminuria ≥30 mg/gCr) for more than 3 months with a primary disease of diabetes.[1,6] Changes in demographics and treatments may affect the prevalence and clinical manifestations of DKD.[2]

Risk factors for DKD include higher uric acid level, older age, increased BMI, smoking, lower total cholesterol level, history of diabetic retinopathy, and high blood pressure, as well as a higher level of glycated hemoglobin A1c, HDL cholesterol, triglycerides, and estimated GFR (eGFR).[6,7] Over the past few decades, there has been a shift in the clinical manifestations of kidney disease in adults with diabetes associated with a decline in the prevalence of albuminuria and an increase in the prevalence of reduced eGFR.[2] Improved lowering of blood glucose levels and blood pressure control as well as the increased use of renin-angiotensin-aldosterone system (RAAS) inhibitors have contributed to this shift.[2,8]

Approximately **25%** of all diabetics will develop Chronic Kidney Disease.

Diabetes mellitus is the **most common** cause of CKD.

References on page 15

The Importance of Identifying Diabetic Kidney Disease in Patients with Type 2 Diabetes

DKD develops in approximately half of patients with type 2 diabetes[1-2] and may lead to multiple health complications, including ESRD, cardiovascular disease, infection, and death.[3-4] The number of deaths attributed to DKD is rising,[1,5] with approximately 90% of patients with DKD dying before requiring kidney replacement therapy.[6] Most patients with kidney damage or mildly reduced kidney function are unaware of their kidney disease, and 48% of patients with severely reduced kidney function but not on dialysis remain unaware.[7-8] Most patients are diagnosed with DKD when having a medical procedure or if eGFR and/or urine albumin-to-creatinine ratio is tested proactively by a clinician.[8]

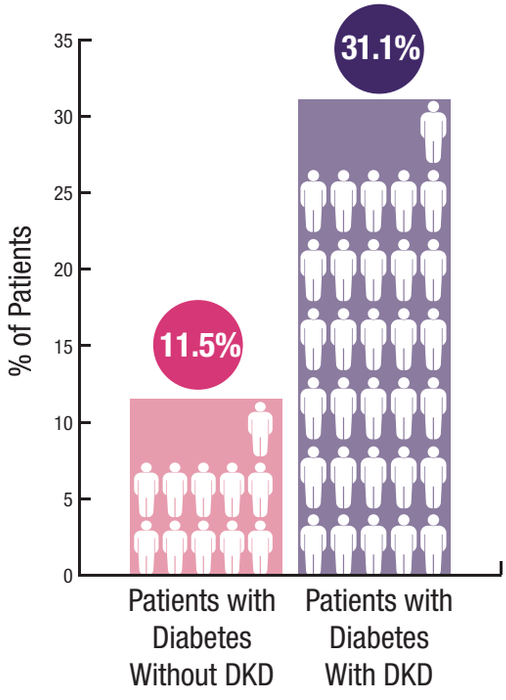
A study was conducted to assess the 10-year cumulative mortality for patients with diabetes with and without DKD (n=15,046) and found that patients with diabetes with DKD predominantly account for the increased mortality seen in patients with type 2 diabetes.[9] DKD was present in 9.4% of patients without type 2 diabetes and 42.3% of patients with type 2 diabetes.[9] Patients with diabetes with DKD had a higher standardized mortality compared with patients with diabetes without DKD (31.1% vs. 11.5%, respectively), with similar patterns for cardiovascular and non-cardiovascular mortality.[9]

Commonly in DKD the first clinical sign is moderately increased urine albumin excretion, with untreated albuminuria gradually worsening, GFR declining, and ESRD likely to result within 10 to 20 years.[10] The first symptom noticed is usually peripheral edema, which usually occurs at a very late stage.[10] Therefore, routine monitoring of urinary albumin-to-creatine ratio, eGFR, and blood pressure is necessary to identify those patients at risk for DKD.[10] Since DKD is a progressive disease, it requires early diagnosis and treatment to prevent progression to kidney replacement therapy, which is especially important in light of the growing awareness of other comorbidities associated with DKD, including heart disease.[11]

Identification and treatment of DKD complications may help improve quality-of-life and improve outcomes.[11-12] A study of patients with diabetes with protein leakage into their urine for 2 years (n=386) found that, over a 6-year period, DKD reverses itself with early detection and good control of blood glucose, blood pressure, cholesterol, and triglycerides.[12] In the study, patients with DKD diagnosed earliest had the best outcomes.[12] An additional study found that early detection of DKD in patients with diabetes led to a 3% decrease in kidney failure and gained 0.2 years in life expectancy.[13] Tests that allow earlier diagnosis and therefore treatment, such as biomarker tests, slow DKD progression and increase life expectancy for patients with diabetes.[13]

References on page 15

Proactive testing of eGFR and/or urine albumin-to-creatinine ratio typically identifies DKD.



[9]Adapted from: Afkarian M, et al. J Am Soc Nephrol. 2013;24:302–8.

Ten Key Steps to Managing Diabetic Kidney Disease in Patients with Type 2 Diabetes

Although DKD is often progressive and diagnosed when irreversible, there are key steps that healthcare providers and patients with type 2 diabetes can follow in an effort to slow DKD progression and increase life expectancy without complications or the need for renal replacement therapy.[1] The first step in treating DKD is to treat and control diabetes through blood glucose control and, if needed, to control hypertension, in an effort to delay or prevent kidney dysfunction and other complications associated with DKD.[2] The optimal management of DKD should also include treatment of albuminuria, avoidance of potential nephrotoxins, such as, nonsteroidal anti-inflammatory drugs, and adjustments to drug dosing if necessary, such as, many antibiotics and oral hypoglycemic agents.[3-4]

Patients with DKD will also require monitoring for treatment of potential complications, such as hyperkalemia, metabolic acidosis, hyperphosphatemia, vitamin D deficiency, secondary hyperparathyroidism, and anemia.[3] Ideally, hemoglobin $A1_C$ should be controlled as strictly as possible and the eGFR and urine albumin-to-creatinine ratio should be monitored routinely for progression, adding medication management with available treatments if necessary.[5] Other factors, such as blood pressure control, smoking cessation, weight loss, a low-protein diet, and cholesterol control, are also important key steps in the management of patients with DKD with type 2 diabetes.[1,4-8] Early detection and effective management of diabetes and cardiovascular risk factors are essential to reduce risk of morbidity and mortality in patients with DKD.[9]

> To manage DKD, treat albuminuria, avoid nephrotoxins, and adjust other treatments.

Ten Key Steps to Controlling DKD

References on page 15

Changes in the Pharmacologic Management of Diabetic Kidney Disease in Patients with Type 2 Diabetes

Currently, there is no cure for DKD for patients with type 2 diabetes, and management includes glycemic control, blockade of the RAAS, and lifestyle changes.[1] However, many patients still eventually progress to ESRD, leaving DKD to remain a major cause of morbidity and mortality and a leading cause of ESRD in patients with diabetes.[1-2]

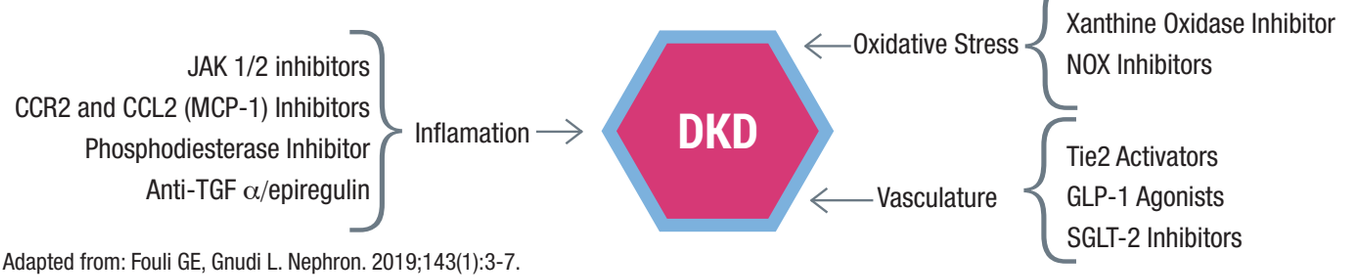
Identification and treatment of DKD complications, such as cardiovascular disease, anemia, malnutrition, mineral and bone disorders, depression, and reduced functional status, may help improve quality of life.[3] Historically, patients with type 2 diabetes and DKD and ESRD requiring dialysis were usually managed by Nephrologists, whereas patients with early-stage DKD were usually managed by Primary Care Physicians or Endocrinologists.[3] Today, the management of DKD involves an interdisciplinary approach in an effort to improve patient outcomes.[3] Therefore, due to the complex nature of DKD, referrals to the appropriate healthcare provider, including a Nephrologist, may be beneficial for patients with early-stage kidney disease.[3]

Intensified multifactorial interventions including blood pressure and glycemic control along with RAAS blockade and smoking cessation remain the standard of care to delay the development of DKD and progression to ESRD.[4-5] Although two decades have passed since the benefits of RAAS blockade were confirmed in clinical trials, the burden of DKD has persisted.[6] In recent years, over 20 completed clinical trials have provided a plethora of data that resulted in the transformation of diabetes care and kidney outcomes.[6] Novel agents are in use now for preventing DKD development and progression, including new types of glucose-lowering agents, Janus kinase inhibitors, and nonsteroidal mineralocorticoid receptor antagonists.[2] Moreover, new anti-hyperglycemic drugs have recently shown renoprotective effects, which represent major progress in optimizing the management of DKD in patients with type 2 diabetes.[5] Recent preclinical studies have identified novel therapeutic targets that may optimize renoprotection in the near future.[5] Besides strategies aimed to reduce oxidative stress and inflammation in the kidney, novel extra-renal approaches targeting stem cells, extracellular vesicles, and the microbiota are on the horizon with promising preclinical data.[5] The exact pathogenesis of diabetic nephropathy is still being researched, and recent advances have led to the development of several novel potential therapeutic targets.[1] The different experimental therapies that are currently being assessed can generally be separated into drugs targeting inflammation, drugs targeting oxidative stress, and drugs targeting the vascular system.[1,7]

> Sodium–glucose cotransporter 2 (SGLT-2) inhibition is an important therapeutic target for DKD.

DKD remains a very active field of research with multiple drugs in clinical trials.[1,4-7] Over the past three decades, discovery and elucidation of the role of sodium symporters in glucose reabsorption, and thereby glucose homeostasis, have pointed to sodium–glucose cotransporter 2 (SGLT-2) inhibition as a viable therapeutic target.[4,8] SGLT-2 inhibitors offer more promise than most other drugs under active investigation.[4,6]

Future and Experimental Therapies for Patients with DKD[1]



Adapted from: Fouli GE, Gnudi L. Nephron. 2019;143(1):3-7.

References on page 15

In adults who have T2D and diabetic nephropathy (ie, DKD) with albuminuria >300 mg/day,

INVOKANA® is the only SGLT2i proven to slow the progression of DKD

and reduce the risk of hospitalization for heart failure[1-4]

INVOKANA® is the only T2D therapy approved by the FDA to reduce the risk of end-stage kidney disease (ESKD), doubling of serum creatinine, cardiovascular (CV) death, and hospitalization for heart failure in adults who have T2D and diabetic nephropathy with albuminuria >300 mg/day[1]

In patients with DKD* and T2D

The landmark CREDENCE trial primary composite outcome[5]:

30% RRR

- **End-stage kidney disease†**
  (dialysis, transplant, or eGFR <15)
- **Doubling of serum creatinine**
- **Renal death‡**
- **CV death**

HR=0.70 (95% CI: 0.59, 0.82); *P*=0.00001

‡There were not enough events to evaluate the risk of renal death (placebo, n=5; INVOKANA®, n=2). **INVOKANA® is not indicated to reduce the risk of renal death.**
§Prespecified secondary endpoint.

- **Reduced risk of hospitalization for heart failure[6§]**
  39% RRR‖ in hospitalization for heart failure
- **Proven safety profile in patients with an eGFR of 30 to <90[1,5]**
  Similar overall AEs with INVOKANA® vs placebo (35.1 vs 37.9 per 100 patient-years), except for DKA and male GMI. No imbalance in fracture or amputation. Hypotension incidence was 2.8% vs 1.5%, respectively

Learn more at INVOKANAhcp.com.

INDICATIONS

INVOKANA® is indicated:

- as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
- to reduce the risk of major adverse cardiovascular events (cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke) in adults with type 2 diabetes mellitus and established cardiovascular disease (CVD)
- to reduce the risk of end-stage kidney disease (ESKD), doubling of serum creatinine, cardiovascular (CV) death, and hospitalization for heart failure in adults with type 2 diabetes mellitus and diabetic nephropathy with albuminuria >300 mg/day

INVOKANA® is not recommended in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

IMPORTANT SAFETY INFORMATION

WARNING: LOWER-LIMB AMPUTATION

- **An increased risk of lower-limb amputations associated with INVOKANA® use versus placebo was observed in CANVAS (5.9 vs 2.8 events per 1000 patient-years) and CANVAS-R (7.5 vs 4.2 events per 1000 patient-years), two large, randomized, placebo-controlled trials in patients with type 2 diabetes who had established cardiovascular disease (CVD) or were at risk for CVD.**
- **Amputations of the toe and midfoot were most frequent; however, amputations involving the leg were also observed. Some patients had multiple amputations, some involving both limbs.**
- **Before initiating, consider factors that may increase the risk of amputation, such as a history of prior amputation, peripheral vascular disease, neuropathy, and diabetic foot ulcers.**
- **Monitor patients receiving INVOKANA® for infection, new pain or tenderness, sores, or ulcers involving the lower limbs, and discontinue if these complications occur.**

CONTRAINDICATIONS

- Serious hypersensitivity reaction to INVOKANA®
- Patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2) who are being treated for glycemic control
- Patients on dialysis

Please read additional Important Safety Information and Brief Summary of full Prescribing Information, including Boxed WARNING for INVOKANA®, on the following pages.

Invokana™ (canagliflozin) tablets

AE=adverse event; CREDENCE=Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation; DKA=diabetic ketoacidosis; DKD=diabetic kidney disease; GMI=genital mycotic infection; HR=hazard ratio; RRR=relative risk reduction; SGLT2i=sodium-glucose co-transporter 2 inhibitor; T2D=type 2 diabetes.
eGFR is measured in mL/min/1.73 m^2.
*With albuminuria >300 mg/day.
†End-stage kidney disease was defined as dialysis for ≥30 days, kidney transplantation, or an eGFR <15 mL/min/1.73 m^2 sustained for ≥30 days.
‖RRR was calculated using the following formula: 100 x (1–HR).

References: 1. INVOKANA® [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals, Inc. **2.** Jardiance® [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc. **3.** Farxiga® [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP. **4.** Steglatro™ [prescribing information]. Whitehouse Station, NJ: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. **5.** Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med*. 2019;380(24):2295-2306. Supplementary appendix available at: doi:10.1056/NEJMoa1811744. **6.** Mahaffey KW, Jardine MJ, Bompoint S, et al. Canagliflozin and cardiovascular and renal outcomes in type 2 diabetes mellitus and chronic kidney disease in primary and secondary cardiovascular prevention groups. *Circulation*. 2019;140(9):739-750.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS and PRECAUTIONS

- **Lower-Limb Amputation:** An increased risk of lower-limb amputations associated with INVOKANA® use versus placebo was observed in CANVAS (5.9 vs 2.8 events per 1000 patient-years) and CANVAS-R (7.5 vs 4.2 events per 1000 patient-years), two randomized, placebo-controlled trials evaluating patients with type 2 diabetes who had either established cardiovascular disease or were at risk for cardiovascular disease. The risk of lower-limb amputations was observed at both the 100-mg and 300-mg once-daily dosage regimens.

  Amputations of the toe and midfoot (99 out of 140 patients with amputations receiving INVOKANA® in the two trials) were the most frequent; however, amputations involving the leg, below and above the knee, were also observed (41 out of 140 patients with amputations receiving INVOKANA® in the two trials). Some patients had multiple amputations, some involving both lower limbs.

  Lower-limb infections, gangrene, and diabetic foot ulcers were the most common precipitating medical events leading to the need for an amputation. The risk of amputation was highest in patients with a baseline history of prior amputation, peripheral vascular disease, and neuropathy.

  Before initiating, consider factors in the patient history that may predispose to the need for amputations, such as a history of prior amputation, peripheral vascular disease, neuropathy, and diabetic foot ulcers. Counsel patients about the importance of routine preventative foot care. Monitor patients for signs and symptoms of infection (including osteomyelitis), new pain or tenderness, sores, or ulcers involving the lower limbs, and discontinue if these complications occur.
- **Hypotension:** INVOKANA® causes intravascular volume contraction. Symptomatic hypotension can occur after initiating INVOKANA®, particularly in the elderly, and in patients with impaired renal function, low systolic blood pressure, or on diuretics or medications that interfere with the renin-angiotensin-aldosterone system. Before initiating INVOKANA®, volume status should be assessed and corrected. Monitor for signs and symptoms after initiating.
- **Ketoacidosis:** Ketoacidosis, a serious life-threatening condition requiring urgent hospitalization, has been identified in patients with type 1 and 2 diabetes mellitus receiving SGLT2 inhibitors, including INVOKANA®. Fatal cases of ketoacidosis have been reported in patients taking INVOKANA®. Before initiating INVOKANA®, consider factors in patient history that may predispose to ketoacidosis. For patients who undergo scheduled surgery, consider temporarily discontinuing INVOKANA® for at least 3 days prior to surgery. Monitor for ketoacidosis and temporarily discontinue in other clinical situations known to predispose to ketoacidosis. Ensure risk factors for ketoacidosis are resolved prior to restarting therapy. Educate patients on the signs and symptoms of ketoacidosis and instruct patients to discontinue INVOKANA® and seek medical attention immediately if signs and symptoms occur.
- **Acute Kidney Injury:** INVOKANA® causes intravascular volume contraction and can cause acute kidney injury. Acute kidney injury, requiring hospitalization and dialysis, has been reported. Initiation of INVOKANA® may increase serum creatinine and decrease eGFR. Before initiation, consider factors that may predispose patients to acute kidney injury. Consider temporarily discontinuing INVOKANA® in any setting of reduced oral intake or fluid losses; monitor patients for signs and symptoms of acute kidney injury. If it occurs, promptly discontinue and treat. Evaluate renal function prior to initiation and monitor periodically thereafter.
- **Urosepsis and Pyelonephritis:** Serious urinary tract infections, including urosepsis and pyelonephritis, requiring hospitalization have been reported in patients receiving SGLT2 inhibitors, including INVOKANA®. Treatment with SGLT2 inhibitors increases this risk. Evaluate for signs and symptoms and treat promptly.
- **Hypoglycemia With Concomitant Use With Insulin and Insulin Secretagogues:** INVOKANA® can increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue. A lower dose of insulin or insulin secretagogue may be required.
- **Necrotizing Fasciitis of the Perineum (Fournier's Gangrene):** Necrotizing fasciitis of the perineum, a rare but serious and life-threatening necrotizing infection requiring urgent surgical intervention, has been identified in postmarketing surveillance in female and male patients with diabetes mellitus receiving SGLT2 inhibitors, including INVOKANA®. Serious outcomes have included hospitalization, multiple surgeries, and death. If suspected, start treatment immediately with broad-spectrum antibiotics and, if necessary, surgical debridement. Discontinue INVOKANA®.
- **Genital Mycotic Infections:** INVOKANA® increases risk of genital mycotic infections, especially in uncircumcised males or patients with prior infections. Monitor and treat appropriately.
- **Hypersensitivity Reactions:** Hypersensitivity reactions, including angioedema and anaphylaxis, were reported with INVOKANA®; these reactions generally occurred within hours to days after initiation. If reactions occur, discontinue INVOKANA®, treat, and monitor until signs and symptoms resolve.
- **Bone Fracture:** Increased risk of bone fracture, occurring as early as 12 weeks after treatment initiation, was observed in patients using INVOKANA®. Prior to initiation, consider factors that contribute to fracture risk.

DRUG INTERACTIONS

- **UGT Enzyme Inducers:** Co-administration with rifampin lowered INVOKANA® exposure, which may reduce the efficacy of INVOKANA®. For patients with eGFR ≥60 mL/min/1.73 m^2, if an inducer of UGTs (eg, rifampin, phenytoin, phenobarbital, ritonavir) is co-administered with INVOKANA®, increase the dose to 200 mg (taken as two 100 mg tablets) once daily in patients currently tolerating INVOKANA® 100 mg. The dose may be increased to 300 mg once daily in patients currently tolerating INVOKANA® 200 mg and who require additional glycemic control. For patients with eGFR <60 mL/min/1.73 m^2, if an inducer of UGTs is co-administered with INVOKANA®, increase the dose to 200 mg (taken as two 100 mg tablets) once daily in patients currently tolerating INVOKANA® 100 mg. Consider adding another antihyperglycemic agent in patients who require additional glycemic control.
- **Digoxin:** There was an increase in the AUC and mean peak drug concentration of digoxin when co-administered with INVOKANA® 300 mg. Monitor appropriately.
- **Positive Urine Glucose Test:** Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.
- **Interference With 1,5-Anhydroglucitol (1,5-AG) Assay:** Monitoring glycemic control with 1,5-AG assay is not recommended in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.

USE IN SPECIFIC POPULATIONS

- **Pregnancy:** INVOKANA® is not recommended in pregnant women, especially during the second and third trimesters.
- **Lactation:** INVOKANA® is not recommended while breastfeeding.
- **Pediatric Use:** Safety and effectiveness in patients <18 years of age have not been established.
- **Geriatric Use:** Patients ≥65 years had a higher incidence of adverse reactions related to reduced intravascular volume, particularly with the 300-mg dose; more prominent increase in the incidence was seen in patients who were ≥75 years. Smaller reductions in HbA1c relative to placebo were seen in patients ≥65 years.
- **Renal Impairment:** The efficacy and safety of INVOKANA® for glycemic control were evaluated in a trial that included patients with moderate renal impairment (eGFR 30 to <50 mL/min/1.73 m^2). These patients had less overall glycemic efficacy, and patients treated with 300 mg per day had increases in serum potassium, which were transient and similar by the end of the study. Patients with renal impairment using INVOKANA® for glycemic control may be more likely to experience hypotension and may be at a higher risk for acute kidney injury. INVOKANA® is contraindicated in patients with ESKD on dialysis.
- **Hepatic Impairment:** INVOKANA® has not been studied in patients with severe hepatic impairment and is not recommended in this population.

OVERDOSAGE

- In the event of an overdose, contact the Poison Control Center and employ the usual supportive measures.

ADVERSE REACTIONS

- The most common adverse reactions associated with INVOKANA® (5% or greater incidence) were female genital mycotic infections, urinary tract infections, and increased urination.

cp-68813v4

Please read Brief Summary of full Prescribing Information, including Boxed WARNING for INVOKANA®, on the following pages.

Invokana™ (canagliflozin) tablets

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Janssen Pharmaceuticals, Inc.

Canagliflozin is licensed from Mitsubishi Tanabe Pharma Corporation.

 February 2020 cp-122493v2

INVOKANA®

(canagliflozin) tablets, for oral use
Brief Summary of Prescribing Information.

WARNING: LOWER LIMB AMPUTATION

- **An increased risk of lower limb amputations associated with INVOKANA use versus placebo was observed in CANVAS (5.9 vs 2.8 events per 1000 patient-years) and CANVAS-R (7.5 vs 4.2 events per 1000 patient-years), two large, randomized, placebo-controlled trials in patients with type 2 diabetes who had established cardiovascular disease (CVD) or were at risk for CVD *[see Warnings and Precautions]*.**
- **Amputations of the toe and midfoot were most frequent; however, amputations involving the leg were also observed. Some patients had multiple amputations, some involving both limbs *[see Warnings and Precautions]*.**
- **Before initiating, consider factors that may increase the risk of amputation, such as a history of prior amputation, peripheral vascular disease, neuropathy, and diabetic foot ulcers *[see Warnings and Precautions]*.**
- **Monitor patients receiving INVOKANA for infection, new pain or tenderness, sores or ulcers involving the lower limbs, and discontinue if these complications occur *[see Warnings and Precautions]*.**

INDICATIONS AND USAGE

INVOKANA® (canagliflozin) is indicated:

- as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
- to reduce the risk of major adverse cardiovascular events (cardiovascular death, nonfatal myocardial infarction and nonfatal stroke) in adults with type 2 diabetes mellitus and established cardiovascular disease (CVD).
- to reduce the risk of end-stage kidney disease (ESKD), doubling of serum creatinine, cardiovascular (CV) death, and hospitalization for heart failure in adults with type 2 diabetes mellitus and diabetic nephropathy with albuminuria > 300 mg/day.

Limitations of Use

INVOKANA is not recommended in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

CONTRAINDICATIONS

- Serious hypersensitivity reaction to INVOKANA, such as anaphylaxis or angioedema *[see Warnings and Precautions and Adverse Reactions]*.
- Patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2) who are being treated for glycemic control *[see Use in Specific Populations]*.
- Patients on dialysis *[see Use in Specific Populations]*.

WARNINGS AND PRECAUTIONS

Lower Limb Amputation: An increased risk of lower limb amputations associated with INVOKANA use versus placebo was observed in CANVAS (5.9 vs 2.8 events per 1000 patient-years) and CANVAS-R (7.5 vs 4.2 events per 1000 patient-years), two randomized, placebo-controlled trials evaluating patients with type 2 diabetes who had either established cardiovascular disease or were at risk for cardiovascular disease. The risk of lower limb amputations was observed at both the 100 mg and 300 mg once daily dosage regimens. The amputation data for CANVAS and CANVAS-R are shown in Tables 2 and 3, respectively *[see Adverse Reactions]*.

Amputations of the toe and midfoot (99 out of 140 patients with amputations receiving INVOKANA in the two trials) were the most frequent; however, amputations involving the leg, below and above the knee, were also observed (41 out of 140 patients with amputations receiving INVOKANA in the two trials). Some patients had multiple amputations, some involving both lower limbs.

Lower limb infections, gangrene, and diabetic foot ulcers were the most common precipitating medical events leading to the need for an amputation. The risk of amputation was highest in patients with a baseline history of prior amputation, peripheral vascular disease, and neuropathy.

Before initiating INVOKANA, consider factors in the patient history that may predispose to the need for amputations, such as a history of prior amputation, peripheral vascular disease, neuropathy and diabetic foot ulcers. Counsel patients about the importance of routine preventative foot care. Monitor patients receiving INVOKANA for signs and symptoms of infection (including osteomyelitis), new pain or tenderness, sores or ulcers involving the lower limbs, and discontinue INVOKANA if these complications occur.

Hypotension: INVOKANA causes intravascular volume contraction. Symptomatic hypotension can occur after initiating INVOKANA *[see Adverse Reactions]* particularly in patients with impaired renal function (eGFR less than 60 mL/min/1.73 m^2), elderly patients, patients on either diuretics or medications that interfere with the renin-angiotensin-aldosterone system (e.g., angiotensin-converting-enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs]), or patients with low systolic blood pressure. Before initiating INVOKANA in patients with one or more of these characteristics, volume status should be assessed and corrected. Monitor for signs and symptoms after initiating therapy.

Ketoacidosis: Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization have been identified in patients with type 1 and type 2 diabetes mellitus receiving sodium glucose co-transporter-2 (SGLT2) inhibitors, including INVOKANA. Fatal cases of ketoacidosis have been reported in patients taking INVOKANA. INVOKANA is not indicated for the treatment of patients with type 1 diabetes mellitus *[see Indications and Usage]*.

Patients treated with INVOKANA who present with signs and symptoms consistent with severe metabolic acidosis should be assessed for ketoacidosis regardless of presenting blood glucose levels, as ketoacidosis associated with INVOKANA may be present even if blood glucose levels are less than 250 mg/dL. If ketoacidosis is suspected, INVOKANA should be discontinued, patient should be evaluated, and prompt treatment should be instituted. Treatment of ketoacidosis may require insulin, fluid and carbohydrate replacement.

In many of the postmarketing reports, and particularly in patients with type 1 diabetes, the presence of ketoacidosis was not immediately recognized and institution of treatment was delayed because presenting blood glucose levels were below those typically expected for diabetic ketoacidosis (often less than 250 mg/dL). Signs and symptoms at presentation were consistent with dehydration and severe metabolic acidosis and included nausea, vomiting, abdominal pain, generalized malaise, and shortness of breath. In some but not all cases, factors predisposing to ketoacidosis such as insulin dose reduction, acute febrile illness, reduced caloric intake, surgery, pancreatic disorders suggesting insulin deficiency (e.g., type 1 diabetes, history of pancreatitis or pancreatic surgery), and alcohol abuse were identified.

Before initiating INVOKANA, consider factors in the patient history that may predispose to ketoacidosis including pancreatic insulin deficiency from any cause, caloric restriction, and alcohol abuse.

For patients who undergo scheduled surgery, consider temporarily discontinuing INVOKANA for at least 3 days prior to surgery *[see Clinical Pharmacology (12.2, 12.3) in Full Prescribing Information]*.

Consider monitoring for ketoacidosis and temporarily discontinuing INVOKANA in other clinical situations known to predispose to ketoacidosis (e.g., prolonged fasting due to acute illness or post-surgery). Ensure risk factors for ketoacidosis are resolved prior to restarting INVOKANA.

Educate patients on the signs and symptoms of ketoacidosis and instruct patients to discontinue INVOKANA and seek medical attention immediately if signs and symptoms occur.

Acute Kidney Injury: INVOKANA causes intravascular volume contraction *[see Warnings and Precautions]* and can cause acute kidney injury. There have been postmarketing reports of acute kidney injury, some requiring hospitalization and dialysis, in patients receiving SGLT2 inhibitors, including INVOKANA.

Increases in serum creatinine and decreases in estimated GFR may also be observed with initiation of INVOKANA *[see Adverse Reactions and Clinical Pharmacology (12.1) in Full Prescribing Information]*. Before initiating INVOKANA, consider factors that may predispose patients to acute kidney injury including hypovolemia, chronic renal insufficiency, congestive heart failure and concomitant medications (diuretics, ACE inhibitors, ARBs, NSAIDs). Consider temporarily discontinuing INVOKANA in the setting of reduced oral intake (such as acute illness or fasting) or fluid losses (such as gastrointestinal illness or excessive heat exposure); monitor patients for signs and symptoms of acute kidney injury. If acute kidney injury occurs, discontinue INVOKANA promptly and institute treatment.

Renal function should be evaluated prior to initiation of INVOKANA and monitored periodically thereafter.

Urosepsis and Pyelonephritis: There have been postmarketing reports of serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization in patients receiving SGLT2 inhibitors, including INVOKANA. Treatment with SGLT2 inhibitors increases the risk for urinary tract infections. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated *[see Adverse Reactions]*.

Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues: Insulin and insulin secretagogues are known to cause hypoglycemia. INVOKANA may increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue *[see Adverse Reactions]*. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with INVOKANA.

Necrotizing Fasciitis of the Perineum (Fournier's Gangrene): Reports of necrotizing fasciitis of the perineum (Fournier's gangrene), a rare but serious and life-threatening necrotizing infection requiring urgent surgical intervention, have been identified in postmarketing surveillance in patients with diabetes mellitus receiving SGLT2 inhibitors, including INVOKANA.

Cases have been reported in both females and males. Serious outcomes have included hospitalization, multiple surgeries, and death.

Patients treated with INVOKANA presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise, should be assessed for necrotizing fasciitis. If suspected, start treatment immediately with broad-spectrum antibiotics and, if necessary, surgical debridement. Discontinue INVOKANA, closely monitor blood glucose levels, and provide appropriate alternative therapy for glycemic control.

Genital Mycotic Infections: INVOKANA increases the risk of genital mycotic infections. Patients with a history of genital mycotic infections and uncircumcised males were more likely to develop genital mycotic infections *[see Adverse Reactions]*. Monitor and treat appropriately.

Hypersensitivity Reactions: Hypersensitivity reactions, including angioedema and anaphylaxis, have been reported with INVOKANA. These reactions generally occurred within hours to days after initiating INVOKANA. If hypersensitivity reactions occur, discontinue use of INVOKANA; treat and monitor until signs and symptoms resolve *[see Contraindications and Adverse Reactions]*.

Bone Fracture: An increased risk of bone fracture, occurring as early as 12 weeks after treatment initiation, was observed in patients using INVOKANA in the CANVAS trial *[see Clinical Studies (14.2) in Full Prescribing Information]*. Consider factors that contribute to fracture risk prior to initiating INVOKANA *[see Adverse Reactions]*.

ADVERSE REACTIONS

The following important adverse reactions are described below and elsewhere in the labeling:

- Lower Limb Amputation *[see Boxed Warning and Warnings and Precautions]*
- Hypotension *[see Warnings and Precautions]*
- Ketoacidosis *[see Warnings and Precautions]*
- Acute Kidney Injury *[see Warnings and Precautions]*
- Urosepsis and Pyelonephritis *[see Warnings and Precautions]*
- Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues *[see Warnings and Precautions]*
- Necrotizing Fasciitis of the Perineum (Fournier's gangrene) *[see Warnings and Precautions]*
- Genital Mycotic Infections *[see Warnings and Precautions]*
- Hypersensitivity Reactions *[see Warnings and Precautions]*
- Bone Fracture *[see Warnings and Precautions]*

Clinical Studies 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 the rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Pool of Placebo-Controlled Trials for Glycemic Control: The data in Table 1 is derived from four 26-week placebo-controlled trials where INVOKANA was used as monotherapy in one trial and as add-on therapy in three trials. These data reflect exposure of 1,667 patients to INVOKANA and a mean duration of exposure to INVOKANA of 24 weeks. Patients received INVOKANA 100 mg (N=833), INVOKANA 300 mg (N=834) or placebo (N=646) once daily. The mean age of the population was 56 years and 2% were older than 75 years of age. Fifty percent (50%) of the population was male and 72% were Caucasian, 12% were Asian, and 5% were Black or African American. At baseline the population had diabetes for an average of 7.3 years, had a mean HbA_{1C} of 8.0% and 20% had established microvascular complications of diabetes. Baseline renal function was normal or mildly impaired (mean eGFR 88 mL/min/1.73 m^2).

Table 1 shows common adverse reactions associated with the use of INVOKANA. These adverse reactions were not present at baseline, occurred more commonly on INVOKANA than on placebo, and occurred in at least 2% of patients treated with either INVOKANA 100 mg or INVOKANA 300 mg.

Table 1: Adverse Reactions from Pool of Four 26–Week Placebo-Controlled Studies Reported in ≥ 2% of INVOKANA-Treated Patients*

Adverse Reaction	Placebo N=646	INVOKANA 100 mg N=833	INVOKANA 300 mg N=834
Urinary tract infections‡	3.8%	5.9%	4.4%
Increased urination§	0.7%	5.1%	4.6%
Thirst#	0.1%	2.8%	2.4%
Constipation	0.9%	1.8%	2.4%
Nausea	1.6%	2.1%	2.3%
	N=312	**N=425**	**N=430**
Female genital mycotic infections†	2.8%	10.6%	11.6%
Vulvovaginal pruritus	0.0%	1.6%	3.2%
	N=334	**N=408**	**N=404**
Male genital mycotic infections¶	0.7%	4.2%	3.8%

INVOKANA® (canagliflozin) tablets

* The four placebo-controlled trials included one monotherapy trial and three add-on combination trials with metformin, metformin and sulfonylurea, or metformin and pioglitazone.

† Female genital mycotic infections include the following adverse reactions: Vulvovaginal candidiasis, Vulvovaginal mycotic infection, Vulvovaginitis, Vaginal infection, Vulvitis, and Genital infection fungal.

‡ Urinary tract infections include the following adverse reactions: Urinary tract infection, Cystitis, Kidney infection, and Urosepsis.

§ Increased urination includes the following adverse reactions: Polyuria, Pollakiuria, Urine output increased, Micturition urgency, and Nocturia.

¶ Male genital mycotic infections include the following adverse reactions: Balanitis or Balanoposthitis, Balanitis candida, and Genital infection fungal.

Thirst includes the following adverse reactions: Thirst, Dry mouth, and Polydipsia.

Note: Percentages were weighted by studies. Study weights were proportional to the harmonic mean of the three treatment sample sizes.

Abdominal pain was also more commonly reported in patients taking INVOKANA 100 mg (1.8%), 300 mg (1.7%) than in patients taking placebo (0.8%).

Placebo-Controlled Trial in Diabetic Nephropathy: The occurrence of adverse reactions for INVOKANA was evaluated in patients participating in CREDENCE, a study in patients with type 2 diabetes mellitus and diabetic nephropathy with albuminuria > 300 mg/day *[see Clinical Studies (14.3) in Full Prescribing Information]*. These data reflect exposure of 2,201 patients to INVOKANA and a mean duration of exposure to INVOKANA of 137 weeks.

The rate of lower limb amputations associated with the use of INVOKANA 100 mg relative to placebo was 12.3 vs 11.2 events per 1000 patient-years, respectively, in CREDENCE, an outcomes study of patients with type 2 diabetes and diabetic nephropathy, with 2.6 years mean duration of follow-up *[see Clinical Studies (14.3) in Full Prescribing Information]*.

In CREDENCE, incidence rates of adjudicated events of diabetic ketoacidosis (DKA) were 0.21 (0.5%, 12/2,200) and 0.03 (0.1%, 2/2,197) per 100 patient-years of follow-up with INVOKANA 100 mg and placebo, respectively *[see Warnings and Precautions]*. The incidence of acute kidney injury was similar between INVOKANA 100 mg and placebo in CREDENCE *[see Warnings and Precautions]*.

In CREDENCE, the incidence of hypotension was 2.8% and 1.5% on INVOKANA 100 mg and placebo, respectively *[see Warnings and Precautions]*.

Pool of Placebo- and Active-Controlled Trials for Glycemic Control and Cardiovascular Outcomes: The occurrence of adverse reactions for INVOKANA was evaluated in patients participating in placebo- and active-controlled trials and in an integrated analysis of two cardiovascular trials, CANVAS and CANVAS-R.

The types and frequency of common adverse reactions observed in the pool of eight clinical trials (which reflect an exposure of 6,177 patients to INVOKANA) were consistent with those listed in Table 1. Percentages were weighted by studies. Study weights were proportional to the harmonic mean of the three treatment sample sizes. In this pool, INVOKANA was also associated with the adverse reactions of fatigue (1.8%, 2.2%, and 2.0% with comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively) and loss of strength or energy (i.e., asthenia) (0.6%, 0.7%, and 1.1% with comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively).

In the pool of eight clinical trials, the incidence rate of pancreatitis (acute or chronic) was 0.1%, 0.2%, and 0.1% receiving comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively.

In the pool of eight clinical trials, hypersensitivity-related adverse reactions (including erythema, rash, pruritus, urticaria, and angioedema) occurred in 3.0%, 3.8%, and 4.2% of patients receiving comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. Five patients experienced serious adverse reactions of hypersensitivity with INVOKANA, which included 4 patients with urticaria and 1 patient with a diffuse rash and urticaria occurring within hours of exposure to INVOKANA. Among these patients, 2 patients discontinued INVOKANA. One patient with urticaria had recurrence when INVOKANA was re-initiated.

Photosensitivity-related adverse reactions (including photosensitivity reaction, polymorphic light eruption, and sunburn) occurred in 0.1%, 0.2%, and 0.2% of patients receiving comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively.

Other adverse reactions occurring more frequently on INVOKANA than on comparator were:

Lower Limb Amputation: An increased risk of lower limb amputations associated with INVOKANA use versus placebo was observed in CANVAS (5.9 vs 2.8 events per 1000 patient-years) and CANVAS-R (7.5 vs 4.2 events per

1000 patient-years), two randomized, placebo-controlled trials evaluating patients with type 2 diabetes who had either established cardiovascular disease or were at risk for cardiovascular disease. Patients in CANVAS and CANVAS-R were followed for an average of 5.7 and 2.1 years, respectively *[see Clinical Studies (14.2) in Full Prescribing Information]*. The amputation data for CANVAS and CANVAS-R are shown in Tables 2 and 3, respectively *[see Warnings and Precautions]*.

Table 2: CANVAS Amputations

	Placebo N=1441	INVOKANA 100 mg N=1445	INVOKANA 300 mg N=1441	INVOKANA (Pooled) N=2886
Patients with an amputation, n (%)	22 (1.5)	50 (3.5)	45 (3.1)	95 (3.3)
Total amputations	33	83	79	162
Amputation incidence rate (per 1000 patient-years)	2.8	6.2	5.5	5.9
Hazard Ratio (95% CI)	--	2.24 (1.36, 3.69)	2.01 (1.20, 3.34)	2.12 (1.34, 3.38)

Note: Incidence is based on the number of patients with at least one amputation, and not the total number of amputation events. A patient's follow-up is calculated from Day 1 to the first amputation event date. Some patients had more than one amputation.

Table 3: CANVAS-R Amputations

	Placebo N=2903	INVOKANA 100 mg (with up-titration to 300 mg) N=2904
Patients with an amputation, n (%)	25 (0.9)	45 (1.5)
Total amputations	36	59
Amputation incidence rate (per 1000 patient-years)	4.2	7.5
Hazard Ratio (95% CI)	--	1.80 (1.10, 2.93)

Note: Incidence is based on the number of patients with at least one amputation, and not the total number of amputation events. A patient's follow-up is calculated from Day 1 to the first amputation event date. Some patients had more than one amputation.

Renal Cell Carcinoma: In the CANVAS trial (mean duration of follow-up of 5.7 years) *[see Clinical Studies (14.2) in Full Prescribing Information]*, the incidence of renal cell carcinoma was 0.15% (2/1331) and 0.29% (8/2716) for placebo and INVOKANA, respectively, excluding patients with less than 6 months of follow-up, less than 90 days of treatment, or a history of renal cell carcinoma. A causal relationship to INVOKANA could not be established due to the limited number of cases.

Volume Depletion-Related Adverse Reactions: INVOKANA results in an osmotic diuresis, which may lead to reductions in intravascular volume. In clinical trials for glycemic control, treatment with INVOKANA was associated with a dose-dependent increase in the incidence of volume depletion-related adverse reactions (e.g., hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration). An increased incidence was observed in patients on the 300 mg dose. The three factors associated with the largest increase in volume depletion-related adverse reactions in these trials were the use of loop diuretics, moderate renal impairment (eGFR 30 to less than 60 mL/min/1.73 m^2), and age 75 years and older (Table 4) *[see Dosage and Administration (2.2) in Full Prescribing Information, Warnings and Precautions, and Use in Specific Populations]*.

Table 4: Proportion of Patients With at Least One Volume Depletion-Related Adverse Reaction (Pooled Results from 8 Clinical Trials for Glycemic Control)

Baseline Characteristic	Comparator Group* %	INVOKANA 100 mg %	INVOKANA 300 mg %
Overall population	1.5%	2.3%	3.4%
75 years of age and older†	2.6%	4.9%	8.7%
eGFR less than 60 mL/min/1.73 m^2†	2.5%	4.7%	8.1%
Use of loop diuretic†	4.7%	3.2%	8.8%

* Includes placebo and active-comparator groups
† Patients could have more than 1 of the listed risk factors

Falls: In a pool of nine clinical trials with mean duration of exposure to INVOKANA of 85 weeks, the proportion of patients who experienced falls was 1.3%, 1.5%, and 2.1% with comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. The higher risk of falls for patients treated with INVOKANA was observed within the first few weeks of treatment.

Genital Mycotic Infections: In the pool of four placebo-controlled clinical trials for glycemic control, female genital mycotic infections (e.g., vulvovaginal mycotic infection, vulvovaginal candidiasis, and vulvovaginitis) occurred in 2.8%, 10.6%, and 11.6% of females treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. Patients with a history of genital mycotic infections were more likely to develop genital mycotic infections on INVOKANA. Female patients who developed genital mycotic infections on INVOKANA were more likely to experience recurrence and require treatment with oral or topical antifungal agents and anti-microbial agents. In females, discontinuation due to genital mycotic infections occurred in 0% and 0.7% of patients treated with placebo and INVOKANA, respectively *[see Warnings and Precautions]*.

In the pool of four placebo-controlled clinical trials, male genital mycotic infections (e.g., candidal balanitis, balanoposthitis) occurred in 0.7%, 4.2%, and 3.8% of males treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. Male genital mycotic infections occurred more commonly in uncircumcised males and in males with a prior history of balanitis or balanoposthitis. Male patients who developed genital mycotic infections on INVOKANA were more likely to experience recurrent infections (22% on INVOKANA versus none on placebo), and require treatment with oral or topical antifungal agents and anti-microbial agents than patients on comparators. In males, discontinuations due to genital mycotic infections occurred in 0% and 0.5% of patients treated with placebo and INVOKANA, respectively.

In the pooled analysis of 8 randomized trials evaluating glycemic control, phimosis was reported in 0.3% of uncircumcised male patients treated with INVOKANA and 0.2% required circumcision to treat the phimosis *[see Warnings and Precautions]*.

Hypoglycemia: In all glycemic control trials, hypoglycemia was defined as any event regardless of symptoms, where biochemical hypoglycemia was documented (any glucose value below or equal to 70 mg/dL). Severe hypoglycemia was defined as an event consistent with hypoglycemia where the patient required the assistance of another person to recover, lost consciousness, or experienced a seizure (regardless of whether biochemical documentation of a low glucose value was obtained). In individual clinical trials of glycemic control *[see Clinical Studies (14.1) in Full Prescribing Information]*, episodes of hypoglycemia occurred at a higher rate when INVOKANA was co-administered with insulin or sulfonylureas (Table 5) *[see Warnings and Precautions]*.

Table 5: Incidence of Hypoglycemia* in Randomized Clinical Studies of Glycemic Control

Monotherapy (26 weeks)	**Placebo (N=192)**	**INVOKANA 100 mg (N=195)**	**INVOKANA 300 mg (N=197)**
Overall [N (%)]	5 (2.6)	7 (3.6)	6 (3.0)
In Combination with Metformin (26 weeks)	**Placebo + Metformin (N=183)**	**INVOKANA 100 mg + Metformin (N=368)**	**INVOKANA 300 mg + Metformin (N=367)**
Overall [N (%)]	3 (1.6)	16 (4.3)	17 (4.6)
Severe [N (%)]†	0 (0)	1 (0.3)	1 (0.3)
In Combination with Metformin (52 weeks)	**Glimepiride + Metformin (N=482)**	**INVOKANA 100 mg + Metformin (N=483)**	**INVOKANA 300 mg + Metformin (N=485)**
Overall [N (%)]	165 (34.2)	27 (5.6)	24 (4.9)
Severe [N (%)]†	15 (3.1)	2 (0.4)	3 (0.6)
In Combination with Sulfonylurea (18 weeks)	**Placebo + Sulfonylurea (N=69)**	**INVOKANA 100 mg + Sulfonylurea (N=74)**	**INVOKANA 300 mg + Sulfonylurea (N=72)**
Overall [N (%)]	4 (5.8)	3 (4.1)	9 (12.5)
In Combination with Metformin + Sulfonylurea (26 weeks)	**Placebo + Metformin + Sulfonylurea (N=156)**	**INVOKANA 100 mg + Metformin + Sulfonylurea (N=157)**	**INVOKANA 300 mg + Metformin + Sulfonylurea (N=156)**
Overall [N (%)]	24 (15.4)	43 (27.4)	47 (30.1)
Severe [N (%)]†	1 (0.6)	1 (0.6)	0
In Combination with Metformin + Sulfonylurea (52 weeks)	**Sitagliptin + Metformin + Sulfonylurea (N=378)**		**INVOKANA 300 mg + Metformin + Sulfonylurea (N=377)**
Overall [N (%)]	154 (40.7)		163 (43.2)
Severe [N (%)]†	13 (3.4)		15 (4.0)
In Combination with Metformin + Pioglitazone (26 weeks)	**Placebo + Metformin + Pioglitazone (N=115)**	**INVOKANA 100 mg + Metformin + Pioglitazone (N=113)**	**INVOKANA 300 mg + Metformin + Pioglitazone (N=114)**
Overall [N (%)]	3 (2.6)	3 (2.7)	6 (5.3)
In Combination with Insulin (18 weeks)	**Placebo (N=565)**	**INVOKANA 100 mg (N=566)**	**INVOKANA 300 mg (N=587)**
Overall [N (%)]	208 (36.8)	279 (49.3)	285 (48.6)
Severe [N (%)]†	14 (2.5)	10 (1.8)	16 (2.7)

* Number of patients experiencing at least one event of hypoglycemia based on either biochemically documented episodes or severe hypoglycemic events in the intent-to-treat population
† Severe episodes of hypoglycemia were defined as those where the patient required the assistance of another person to recover, lost consciousness, or experienced a seizure (regardless of whether biochemical documentation of a low glucose value was obtained)

Bone Fracture: In the CANVAS trial *[see Clinical Studies (14.2) in Full Prescribing Information]*, the incidence rates of all adjudicated bone fracture were 1.09, 1.59, and 1.79 events per 100 patient-years of follow-up to placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. The fracture imbalance was observed within the first 26 weeks of therapy and remained through the end of the trial. Fractures were more likely to be low trauma (e.g., fall from no more than standing height), and affect the distal portion of upper and lower extremities *[see Warnings and Precautions]*.

Laboratory and Imaging Tests*: Increases in Serum Creatinine and Decreases in eGFR*: Initiation of INVOKANA causes an increase in serum creatinine and decrease in estimated GFR. In patients with moderate renal impairment, the increase in serum creatinine generally does not exceed 0.2 mg/dL, occurs within the first 6 weeks of starting therapy, and then stabilizes. Increases that do not fit this pattern should prompt further evaluation to exclude the possibility of acute kidney injury *[see Warnings and Precautions and Mechanism of Action (12.1) in Full Prescribing Information]*. The acute effect on eGFR reverses after treatment discontinuation suggesting acute hemodynamic changes may play a role in the renal function changes observed with INVOKANA.

Increases in Serum Potassium: In a pooled population of patients (N=723) in glycemic control trials with moderate renal impairment (eGFR 45 to less than 60 mL/min/1.73 m^2), increases in serum potassium to greater than 5.4 mEq/L and 15% above baseline occurred in 5.3%, 5.0%, and 8.8% of patients treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. Severe elevations (greater than or equal to 6.5 mEq/L) occurred in 0.4% of patients treated with placebo, no patients treated with INVOKANA 100 mg, and 1.3% of patients treated with INVOKANA 300 mg.

In these patients, increases in potassium were more commonly seen in those with elevated potassium at baseline. Among patients with moderate renal impairment, approximately 84% were taking medications that interfere with potassium excretion, such as potassium-sparing diuretics, angiotensin-converting-enzyme inhibitors, and angiotensin-receptor blockers *[see Warnings and Precautions and Use in Specific Populations]*.

In CREDENCE, no difference in serum potassium, no increase in adverse events of hyperkalemia, and no increase in absolute (> 6.5 mEq/L) or relative (> upper limit of normal and > 15% increase from baseline) increases in serum potassium were observed with INVOKANA 100 mg relative to placebo.

Increases in Low-Density Lipoprotein Cholesterol (LDL-C) and non-High-Density Lipoprotein Cholesterol (non-HDL-C): In the pool of four glycemic control placebo-controlled trials, dose-related increases in LDL-C with INVOKANA were observed. Mean changes (percent changes) from baseline in LDL-C relative to placebo were 4.4 mg/dL (4.5%) and 8.2 mg/dL (8.0%) with INVOKANA 100 mg and INVOKANA 300 mg, respectively. The mean baseline LDL-C levels were 104 to 110 mg/dL across treatment groups.

Dose-related increases in non-HDL-C with INVOKANA were observed. Mean changes (percent changes) from baseline in non-HDL-C relative to placebo were 2.1 mg/dL (1.5%) and 5.1 mg/dL (3.6%) with INVOKANA 100 mg and 300 mg, respectively. The mean baseline non-HDL-C levels were 140 to 147 mg/dL across treatment groups.

Increases in Hemoglobin: In the pool of four placebo-controlled trials of glycemic control, mean changes (percent changes) from baseline in hemoglobin were -0.18 g/dL (-1.1%) with placebo, 0.47 g/dL (3.5%) with INVOKANA 100 mg, and 0.51 g/dL (3.8%) with INVOKANA 300 mg. The mean baseline hemoglobin value was approximately 14.1 g/dL across treatment groups. At the end of treatment, 0.8%, 4.0%, and 2.7% of patients treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively, had hemoglobin above the upper limit of normal.

Decreases in Bone Mineral Density: Bone mineral density (BMD) was measured by dual-energy X-ray absorptiometry in a clinical trial of 714 older adults (mean age 64 years) *[see Clinical Studies (14.1) in Full Prescribing Information]*. At 2 years, patients randomized to INVOKANA 100 mg and INVOKANA 300 mg had placebo-corrected declines in BMD at the total hip of 0.9% and 1.2%, respectively, and at the lumbar spine of 0.3% and 0.7%, respectively. Additionally, placebo-adjusted BMD declines were 0.1% at the femoral neck for both INVOKANA doses and 0.4% at the distal forearm for patients randomized to INVOKANA 300 mg. The placebo-adjusted change at the distal forearm for patients randomized to INVOKANA 100 mg was 0%.

INVOKANA® (canagliflozin) tablets

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

Ketoacidosis
Acute Kidney Injury
Anaphylaxis, Angioedema
Urosepsis and Pyelonephritis
Necrotizing Fasciitis of the Perineum (Fournier's gangrene)

DRUG INTERACTIONS

UGT Enzyme Inducers: Co-administration of canagliflozin with rifampin, a nonselective inducer of several UGT enzymes, including UGT1A9, UGT2B4, decreased canagliflozin area under the curve (AUC) by 51%. This decrease in exposure to canagliflozin may decrease efficacy.

For patients with eGFR 60 mL/min/1.73 m^2 or greater, if an inducer of UGTs (e.g., rifampin, phenytoin, phenobarbital, ritonavir) is co-administered with INVOKANA, increase the dose to 200 mg (taken as two 100 mg tablets) once daily in patients currently tolerating INVOKANA 100 mg. The dose may be increased to 300 mg once daily in patients currently tolerating INVOKANA 200 mg and who require additional glycemic control.

For patients with eGFR less than 60 mL/min/1.73 m^2, if an inducer of UGTs (e.g., rifampin, phenytoin, phenobarbital, ritonavir) is co-administered with INVOKANA, increase the dose to 200 mg (taken as two 100 mg tablets) once daily in patients currently tolerating INVOKANA 100 mg. Consider adding another antihyperglycemic agent in patients who require additional glycemic control *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3) in Full Prescribing Information]*.

Digoxin: There was an increase in the AUC and mean peak drug concentration (C_{max}) of digoxin (20% and 36%, respectively) when co-administered with INVOKANA 300 mg *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*. Patients taking INVOKANA with concomitant digoxin should be monitored appropriately.

Positive Urine Glucose Test: Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors as SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests. Use alternative methods to monitor glycemic control.

Interference with 1,5-anhydroglucitol (1,5-AG) Assay: Monitoring glycemic control with 1,5-AG assay is not recommended as measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.

USE IN SPECIFIC POPULATIONS

Pregnancy: Risk Summary: Based on animal data showing adverse renal effects, INVOKANA is not recommended during the second and third trimesters of pregnancy.

Limited data with INVOKANA in pregnant women are not sufficient to determine a drug-associated risk for major birth defects or miscarriage. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy *[see Clinical Considerations]*.

In animal studies, adverse renal pelvic and tubule dilatations that were not reversible were observed in rats when canagliflozin was administered during a period of renal development corresponding to the late second and third trimesters of human pregnancy, at an exposure 0.5-times the 300 mg clinical dose, based on AUC.

The estimated background risk of major birth defects is 6-10% in women with pre-gestational diabetes with a HbA_{1C} >7 and has been reported to be as high as 20-25% in women with a HbA_{1C} >10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations*: Disease-associated maternal and/or embryo/fetal risk*: Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, stillbirth and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

Animal Data: Canagliflozin dosed directly to juvenile rats from postnatal day (PND) 21 until PND 90 at doses of 4, 20, 65, or 100 mg/kg increased kidney weights and dose dependently increased the incidence and severity of renal pelvic and tubular dilatation at all doses tested. Exposure at the lowest dose was greater than or equal to 0.5-times the 300 mg clinical dose, based on AUC. These outcomes occurred with drug exposure during periods of renal

development in rats that correspond to the late second and third trimester of human renal development. The renal pelvic dilatations observed in juvenile animals did not fully reverse within a 1-month recovery period.

In embryo-fetal development studies in rats and rabbits, canagliflozin was administered for intervals coinciding with the first trimester period of organogenesis in humans. No developmental toxicities independent of maternal toxicity were observed when canagliflozin was administered at doses up to 100 mg/kg in pregnant rats and 160 mg/kg in pregnant rabbits during embryonic organogenesis or during a study in which maternal rats were dosed from gestation day (GD) 6 through PND 21, yielding exposures up to approximately 19-times the 300 mg clinical dose, based on AUC.

Lactation: Risk Summary: There is no information regarding the presence of INVOKANA in human milk, the effects on the breastfed infant, or the effects on milk production. Canagliflozin 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, advise women that use of INVOKANA is not recommended while breastfeeding.

Data: *Animal Data*: Radiolabeled canagliflozin administered to lactating rats on day 13 post-partum was present at a milk/plasma ratio of 1.40, indicating that canagliflozin and its metabolites are transferred into milk at a concentration comparable to that in plasma. Juvenile rats directly exposed to canagliflozin showed a risk to the developing kidney (renal pelvic and tubular dilatations) during maturation.

Pediatric Use: Safety and effectiveness of INVOKANA in pediatric patients under 18 years of age have not been established.

Geriatric Use: In 13 clinical trials of INVOKANA, 2,294 patients 65 years and older, and 351 patients 75 years and older were exposed to INVOKANA *[see Clinical Studies (14.1) in Full Prescribing Information]*.

Patients 65 years and older had a higher incidence of adverse reactions related to reduced intravascular volume with INVOKANA (such as hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration), particularly with the 300 mg daily dose, compared to younger patients; a more prominent increase in the incidence was seen in patients who were 75 years and older *[see Dosage and Administration (2.1) in Full Prescribing Information and Adverse Reactions]*. Smaller reductions in HbA_{1C} with INVOKANA relative to placebo were seen in older (65 years and older; -0.61% with INVOKANA 100 mg and -0.74% with INVOKANA 300 mg relative to placebo) compared to younger patients (-0.72% with INVOKANA 100 mg and -0.87% with INVOKANA 300 mg relative to placebo).

Renal Impairment: The efficacy and safety of INVOKANA for glycemic control were evaluated in a trial that included patients with moderate renal impairment (eGFR 30 to less than 50 mL/min/1.73 m^2) *[see Clinical Studies (14.1) in Full Prescribing Information]*. These patients had less overall glycemic efficacy, and patients treated with 300 mg per day had increases in serum potassium, which were transient and similar by the end of study. Patients with renal impairment using INVOKANA for glycemic control may also be more likely to experience hypotension and may be at higher risk for acute kidney injury *[see Warnings and Precautions]*.

Efficacy and safety studies with INVOKANA did not enroll patients with ESKD on dialysis or patients with an eGFR less than 30 mL/min/1.73 m^2. INVOKANA is contraindicated in patients with ESKD on dialysis *[see Contraindications and Clinical Pharmacology (12.1) in Full Prescribing Information]*.

Hepatic Impairment: No dosage adjustment is necessary in patients with mild or moderate hepatic impairment. The use of INVOKANA has not been studied in patients with severe hepatic impairment and is therefore not recommended *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*.

OVERDOSAGE

In the event of an overdose, contact the Poison Control Center. It is also reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment as dictated by the patient's clinical status. Canagliflozin was negligibly removed during a 4-hour hemodialysis session. Canagliflozin is not expected to be dialyzable by peritoneal dialysis.

PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

Lower Limb Amputation: Inform patients that INVOKANA is associated with an increased risk of amputations. Counsel patients about the importance of routine preventative foot care. Instruct patients to monitor for new pain or tenderness, sores or ulcers, or infections involving the leg or foot and to seek medical advice immediately if such signs or symptoms develop *[see Boxed Warning and Warnings and Precautions]*.

INVOKANA® (canagliflozin) tablets

Hypotension: Inform patients that symptomatic hypotension may occur with INVOKANA and advise them to contact their doctor if they experience such symptoms *[see Warnings and Precautions]*. Inform patients that dehydration may increase the risk for hypotension, and to have adequate fluid intake.

Ketoacidosis: Inform patients that ketoacidosis is a serious life-threatening condition and that cases of ketoacidosis have been reported during use of INVOKANA, sometimes associated with illness or surgery among other risk factors. Instruct patients to check ketones (when possible) if symptoms consistent with ketoacidosis occur even if blood glucose is not elevated. If symptoms of ketoacidosis (including nausea, vomiting, abdominal pain, tiredness, and labored breathing) occur, instruct patients to discontinue INVOKANA and seek medical attention immediately *[see Warnings and Precautions]*.

Acute Kidney Injury: Inform patients that acute kidney injury has been reported during use of INVOKANA. Advise patients to seek medical advice immediately if they have reduced oral intake (such as due to acute illness or fasting) or increased fluid losses (such as due to vomiting, diarrhea, or excessive heat exposure), as it may be appropriate to temporarily discontinue INVOKANA use in those settings *[see Warnings and Precautions]*.

Serious Urinary Tract Infections: Inform patients of the potential for urinary tract infections, which may be serious. Provide them with information on the symptoms of urinary tract infections. Advise them to seek medical advice if such symptoms occur *[see Warnings and Precautions]*.

Necrotizing Fasciitis of the Perineum (Fournier's Gangrene): Inform patients that necrotizing infections of the perineum (Fournier's gangrene) have occurred with INVOKANA. Counsel patients to promptly seek medical attention if they develop pain or tenderness, redness, or swelling of the genitals or the area from the genitals back to the rectum, along with a fever above 100.4°F or malaise *[see Warnings and Precautions]*.

Genital Mycotic Infections in Females (e.g., Vulvovaginitis): Inform female patients that vaginal yeast infection may occur and provide them with information on the signs and symptoms of vaginal yeast infection. Advise them of treatment options and when to seek medical advice *[see Warnings and Precautions]*.

Genital Mycotic Infections in Males (e.g., Balanitis or Balanoposthitis): Inform male patients that yeast infection of penis (e.g., balanitis or balanoposthitis) may occur, especially in uncircumcised males and patients with prior history. Provide them with information on the signs and symptoms of balanitis and balanoposthitis (rash or redness of the glans or foreskin of the penis). Advise them of treatment options and when to seek medical advice *[see Warnings and Precautions]*.

Hypersensitivity Reactions: Inform patients that serious hypersensitivity reactions, such as urticaria, rash, anaphylaxis, and angioedema, have been reported with INVOKANA. Advise patients to report immediately any signs or symptoms suggesting allergic reaction, and to discontinue drug until they have consulted prescribing physicians *[see Warnings and Precautions]*.

Bone Fracture: Inform patients that bone fractures have been reported in patients taking INVOKANA. Provide them with information on factors that may contribute to fracture risk *[see Warnings and Precautions]*.

Pregnancy: Advise pregnant women, and females of reproductive potential of the potential risk to a fetus with treatment with INVOKANA *[see Use in Specific Populations]*. Instruct females of reproductive potential to report pregnancies to their physicians as soon as possible.

Lactation: Advise women that breastfeeding is not recommended during treatment with INVOKANA *[see Use in Specific Populations]*.

Laboratory Tests: Inform patients that due to its mechanism of action, patients taking INVOKANA will test positive for glucose in their urine *[see Drug Interactions]*.

Missed Dose: If a dose is missed, advise patients to take it as soon as it is remembered unless it is almost time for the next dose, in which case patients should skip the missed dose and take the medicine at the next regularly scheduled time. Advise patients not to take two doses of INVOKANA at the same time.

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Sodium–Glucose Cotransporter-2 (SGLT-2) Inhibitors in Patients with Diabetic Kidney Disease and Type 2 Diabetes

Type 2 diabetes is a complex metabolic disorder associated with high cardiovascular risk, yet some treatment options are contraindicated in patients with concomitant heart disease.[1] However, novel medications to treat patients with type 2 diabetes, SGLT-2 inhibitors, are safe and effective and significantly reduce cardiovascular mortality and heart failure hospitalizations.[1] SGLT-2 inhibitors are a unique class of diabetic agents that have beneficial effects on weight, blood pressure, and arterial stiffness.[2-3] US Food and Drug Administration-approved SGLT-2 inhibitors include empagliflozin, dapagliflozin, and canagliflozin. The renal efficacy associated with these medications comes from their ability to restore a dysregulated tubuloglomerular feedback (TGF).[2] SGLT-2 inhibitors restore TGF by blocking proximal sodium and glucose absorption, which in turn reduces GFR.[2-4]

> SGLT-2 inhibitors reduce the risk of development or worsening of albuminuria, ESRD, and CV death through BP-lowering effects.

Evidence from clinical trials of SGLT-2 inhibitors indicate that these drugs improve outcomes in patients with type 2 diabetes and DKD including reducing the risk development or worsening of kidney problems and cardiovascular issues.[5-11] The first trial to demonstrate that a single intervention with SGLT-2 treatment reduced the need for kidney dialysis or transplantation or death due to ESRD was the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE).[5] This double-blind, randomized trial in patients with type 2 diabetes demonstrated that the risk of progression of DKD, kidney failure, ESRD dialysis, kidney transplantation, cardiovascular events, or death from renal or cardiovascular causes was lower in patients treated with an SGLT-2 inhibitor (canagliflozin) compared with placebo.[5] Canagliflozin also reduced glycemia, blood pressure, body weight, and albuminuria in these patients with type 2 diabetes.[6] In addition, integrated data from two clinical trials including over 10,000 patients demonstrated that canagliflozin was associated with a lower risk of cardiovascular events (ie, death, nonfatal myocardial infarction, or nonfatal stroke) versus placebo but a greater risk of amputation, along with a sustained 40% reduction in eGFR, decreased need for renal-replacement therapy, and lower death rate associated with renal issues.[6] The CANVAS Program, consisting of two double-blind, randomized trials also concluded that SGLT-2 treatment with canagliflozin was associated with a reduced risk of sustained loss of kidney function, attenuated eGFR decline, and a reduction in albuminuria along with reduced cardiovascular and renal outcomes.[7-8] In the DECLARE–TIMI 58 trial, treatment with the SGLT-2 inhibitor dapaglifozin resulted in a lower rate of cardiovascular death or hospitalization for heart failure.[9] Data from the EMPA-REG OUTCOME trial demonstrated that the SGLT-2 inhibitor empagliflozin markedly decreased the risk of cardiovascular events, including the risk of cardiovascular death, and delayed the progression of DKD.[10-11]

A systematic review and meta-analysis that was recently conducted to assess trial evidence from four of these studies that assessed three SGLT-2 inhibitors (empagliflozin [EMPA-REG OUTCOME[10-11]], canagliflozin [CANVAS Program[7-8] and CREDENCE[5]], and dapaglifozin [DECLARE–TIMI 58[9]]) provided additional evidence supporting the role of SGLT-2 inhibitors for kidney protection in patients with

type 2 diabetes.[12] Consistently across studies, SGLT-2 inhibitors substantially reduced the risk of ESRD, acute kidney injury, dialysis, transplantation, or death due to kidney disease.[12]

The benefits of SGLT-2 inhibition have been achieved in clinical trials when used in addition to the current standard of care.[5-13] Due to the increased cardiovascular risk associated with DKD and type 2 diabetes, SGLT-2 inhibitors may be considered as preferred add-on therapy for most patients.[2,14] The blood pressure-lowering effect of SGLT-2 inhibitors is maintained in patients with DKD and could potentially reduce renal burden and offer complementary effects with antihypertensives.[15] In addition, SGLT-2 inhibitors have demonstrated renoprotective potential, which may be partially dependent on the inhibition of glucose reabsorption.[16-17] Additional analyses and clinical trials will expand the current knowledge of the clinical efficacy and safety of SGLT-2 inhibitors in slowing the development and progression of DKD in patients with type 2 diabetes and can support that SLGT-2 inhibitors should be added to the current standard of care for patients with DKD and type 2 diabetes.[14-15] With the major progress that has been made in clinical trials over the past few years with the SLGT-2 medications, the outlook for patients with type 2 diabetes and DKD will greatly improve.[16-17]

SGLT-2 Inhibitors Substantially Reduced Risk of Dialysis, Transplantation, Injury, ESRD and Death Consistently Across Studies[12]

Results of data analysis for 4 trials assessing kidney outcomes after treatment with an SGLT-2 inhibitor:

- Empagliflozin
- Canagliflozin
- Dapagliflozin

Patients with Type 2 Diabetes Treated with SGLT-2 Inhibitor

N=38,723
Mean age=63 years
Men=65%

2.4%
(n=943) had acute kidney injury

0.86%
(n=335) developed ESRD

0.6%
(n=252) required required dialysis or transplantation or had death caused by kidney disease

Adapted from: Neuen BL, et al. Lancet Diab Endocrinol. 2019;7(11):845-54.

References on page 16

SGLT-2 inhibitors restore dysregulated tubuloglomerular feedback (TGF) blocking proximal sodium and glucose absorption, which in turn reduces GFR.

The Importance of Talking to Patients with Type 2 Diabetes about the Risk of Diabetic Kidney Disease

Patients with diabetes are at high risk for developing DKD as a result of high glycemia causing diabetic changes in the kidneys and high blood pressure causing vascular changes.[1-4] Educating patients about the risk of developing DKD is important because commonly patients remain asymptomatic with symptoms developing after DKD has progressed.[1-2] Therefore, patients with diabetes should be made aware that early symptoms of DKD may be nonspecific, such as fatigue or just not feeling well.[2] Some of the multiple factors leading to DKD can be controlled through patient behaviors; therefore, talking to patients with type 2 diabetes about the high risk of developing DKD and lifestyle changes they can make to protect their kidney health is an important part of medical care. [1]

> Some of the multiple factors leading to DKD can be controlled through patient behaviors.

Once established, DKD slowly and relentlessly progresses to ESRD, but studies have shown that progression can be slowed or may be even reversed through strict control of hyperglycemia.[2-4] Blood glucose level control can also reduce the risk of developing associated cardiovascular diseases.[2-4] The goal of maintaining a normal HbA1c <48 mmol/mol (or below 6%) may not be possible for some patients with diabetes, so a target level should be agreed upon with individual patients on a case by case basis.[2]

Medications available to minimize the risks associated with DKD and can be discussed with patients with type 2 diabetes.[1] For example, SGLT-2 inhibitors have been shown to improve systemic glucose homeostasis, the hypothesized mechanisms for kidney-protective effects of SGLT-2 inhibition, leading to current recommendations associated with the use of this class of antihyperglycemic agents in patients with diabetes with low eGFR.[4]

Although DKD is common in patients with type 2 diabetes, awareness of kidney disease is very low.[1] Patients can have kidney disease for a long time without having symptoms or knowing that they have the disease.[1-4] Many patients with DKD that has progressed to ESRD requiring transplant have little awareness of the risk of DKD and remain unaware of the possible lifestyle modifications that could have done to help prevent or slow the progression of DKD.[1] It is especially important to talk to patients with diabetes about kidney disease risk factors because they are more than twice as likely to develop DKD than those without diabetes.[1] By talking with patients who have diabetes about kidney disease and possible lifestyle modifications and medications that are available, patients and physicians can take steps together to slow the progression of DKD.

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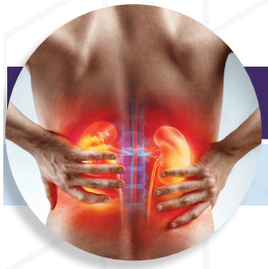

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