Residency Review

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SGLT2 Inhibitors — The Benefits Beyond Glucose

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Diabetes is a chronic disease affecting the way the body balances insulin and glucose. As of 2014 there are 422 million people living with diabetes in the world, and in 2016 there were an estimated 1.6 million deaths attributed to diabetes,[1] with atherosclerotic cardiovascular disease (ASCVD) being the leading cause of morbidity and mortality in people with type 2 diabetes (T2DM).[2]

According to the 2020 American Diabetes Association (ADA) Standards of Medical Care in Diabetes, metformin, along with lifestyle modifications, is the 1st line treatment option for all people with T2DM barring any contraindications.[3] There are many different drug classes for 2nd line and subsequent therapy choices for patients, with some classes benefitting specific patient groups more than others.[4] Specific medications have a greater benefit for patients with established ASCVD, heart failure, or chronic kidney disease (CKD), those looking to maximize weight loss/minimize weight gain, those at risk for hypoglycemia, and patients with other comorbidities or needs. This article will focus on the sodium glucose cotransporter 2 (SGLT2) inhibitors and the associated cardiovascular data and outcomes in people with diabetes.

In people with diabetes and established ASCVD, there is clinical evidence that adding an SGLT2 inhibitor to metformin therapy is beneficial, improving cardiovascular outcomes. There are currently four SGLT2 inhibitors on the market in the United States including canagliflozin (Invokana®), dapagliflozin (Farxiga®), empagliflozin (Jardiance®), and ertugliflozin (Steglatro®). The primary mechanism of action is to decrease blood glucose levels by increasing urinary glucose excretion. Canagliflozin, dapagliflozin, and empagliflozin have clinical trials supporting their cardiovascular benefit, but empagliflozin is the only one with an FDA approved indication to reduce the risk of major adverse cardiovascular death in adults with T2DM and cardiovascular disease.[2] Heart failure is another indication, along with established ASCVD, in which the most recent ADA guidelines recommend SGLT2 inhibitors as the 2nd line option for treatment after metformin due to the reduction in heart failure hospitalizations.

The Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG OUTCOME) trial assesses the effects of empagliflozin on cardiovascular (CV) morbidity and mortality in people with T2DM at high risk for cardiovascular events. This trial enrolled more than 7000 people with T2DM, an A1C of 7-9%, an estimated glomerular filtration rate (eGFR) of ≥30 ml/min/1.73m^2, and established cardiovascular disease. Participants in this trial were randomized 1:1:1 to receive empagliflozin 10mg, empagliflozin 25mg, or placebo. The primary composite outcomes were death from CV causes, non-fatal myocardial infarction (MI), or nonfatal stroke, collectively termed major adverse cardiovascular events (MACE), and the secondary composite outcome was primary outcome plus hospitalizations for unstable angina. The primary outcome occurred in a significantly lower percentage of patients in the empagliflozin groups as compared to the placebo group (10.5% vs 12.1%, P<0.001 for noninferiority and P=0.04 for superiority). Participants in the empagliflozin group also experienced significantly lower risk of CV death (hazard ratio 0.62; 95% CI 0.49-0.77; P<0.001) and any cause (hazard ratio 0.68; 95% CI 0.57-0.82, P<0.001), however there were no significant differences in the occurrence of MI or stroke. Despite having a dose-dependent metabolic and glycemic effect, the 10mg and 25mg doses of empagliflozin resulted in similar hazard ratios for cardiovascular outcomes. This trial also showed that empagliflozin was associated with small reductions in weight, waist circumference, uric acid levels, systolic and diastolic blood pressures, and small increases in both LDL and HDL cholesterol.[5]

The canagliflozin "sister" trials (CANVAS and CANVAS-R) assessed the effects of treatment with canagliflozin on cardiovascular and renal outcomes in people with T2DM at high risk for cardiovascular disease. This trial included patients ≥ 30 years old with symptomatic ASCVD or ≥ 50 years old with at least two risk factors for cardiovascular disease, an A1C of 7-10.5%, and an eGFR of at least 30 ml/min/1.73m^2. The two trials collectively enrolled over 10,000 patients with about 4,300 and 5,800 being enrolled in CANVAS and CANVAS-R respectively. Participants of the CANVAS trial were randomized 1:1:1 to canagliflozin 100mg, canagliflozin 300mg, or placebo; while CANVAS-R participants were randomized 1:1 to canagliflozin 100mg with an option to increase to 300mg at week 13 or placebo. The primary outcome of this trial was a composite of death from CV causes, nonfatal MI, or non-fatal stroke. Significantly fewer participants receiving canagliflozin had a primary outcome event compared to those receiving placebo (26.9 vs 31.5 participants, hazard ratio, 0.86; 95% CI, 0.75 to 0.97; P<0.001 for noninferiority; P=0.02 for superiority).[6] The canagliflozin and renal outcomes in type 2 diabetes and nephropathy (CREDENCE) trial once again assessed the impact of canagliflozin on cardiovascular events, but in this case, participants had both T2DM and kidney disease. Participants were randomly assigned 1:1 to either canagliflozin 100mg or placebo once daily. The results of this trial showed that those who received canagliflozin

had a significantly lower risk of experiencing a composite of cardiovascular death or hospitalization for heart failure (hazard ratio, 0.69; 95% CI, 0.57 to 0.83; P<0.001) and cardiovascular death, MI, or stroke (hazard ratio, 0.80; 95% CI, 0.67 to 0.95; P=0.01).[7] There is currently an ongoing clinical trial, Evaluation of ertugliflozin efficacy and safety cardiovascular outcomes (VERTIS-CV), looking to assess the impact of ertugliflozin on major adverse cardiovascular events in people with stable and established ASCVD.[8]

In addition to the benefit SGLT2 inhibitors have shown in ASCVD, they also show benefit in reducing heart failure and related hospitalizations. A few of the aforementioned trials also looked at the benefit of the trial drug in people with heart failure. The EMPA-REG OUTCOME trial showed that empagliflozin resulted in a significantly lower risk of hospitalization for heart failure when compared to placebo (2.7% vs 4.1%; hazard ratio, 0.65; 95% CI, 0.50 to 0.85; P=0.002).[5] The CREDENCE trial showed canagliflozin provided a lower risk for not only a composite of cardiovascular death or hospitalization for heart failure (hazard ratio, 0.69; 95% CI, 0.57 to 0.83; P<0.001), but also for hospitalization for heart failure alone (hazard ratio, 0.61; 95% CI, 0.47 to 0.80; P<0.001).[7] The dapagliflozin and cardiovascular outcomes in type 2 diabetes (DECLARE-TIMI) trial included more than 10,000 participants with and without ASCVD and assessed the impact of dapagliflozin on the primary efficacy outcome of MACE and a composite of cardiovascular death or hospitalization for heart failure. Dapagliflozin resulted in a lower rate of the composite outcome, which was attributed to the lower rate of heart failure hospitalizations (hazard ratio, 0.73; 95% CI, 0.61 to 0.88) since there was no difference in the rate of cardiovascular death between groups; this effect was similar amongst both groups with cardiovascular risk factors and those with established ASCVD.[9] Dapagliflozin in patients with heart failure and reduced ejection fraction (DAPA-HF) is a clinical trial comparing dapagliflozin to placebo with a primary outcome of a composite of worsening heart failure or cardiovascular death in participants who do not have diabetes. Almost 5000 participants with heart failure and an ejection fraction of ≤40% were randomized to receive either 10mg of dapagliflozin or placebo daily. The primary outcome occurred in 16.3% of people in the dapagliflozin group vs 21.2% in the placebo group (hazard ratio, 0.74; 95% CI, 0.65 to 0.85; P<0.001). The rates of an initial worsening heart failure event were also reduced in the dapagliflozin group (10% vs 13.7%; hazard ratio, 0.70; 95% CI, 0.59 to 0.83).[10] The cardiovascular events associated with SGLT2 inhibitors versus other glucose lowering drugs (CVD-REAL 2) trial set out to retrospectively examine a broad range of cardiovascular outcomes in over ten million patients started on SGLT2 inhibitors across six countries, a majority of which did not have established cardiovascular disease. This trial observed that initiation of an SGLT2 inhibitor (canagliflozin, dapagliflozin, and empagliflozin) versus other glucose lowering drugs was associated with a lower risk of hospitalization for heart failure (pooled HR: 0.64; 95% CI 0.5 to 0.82; p=0.001).[11] The empagliflozin outcome trial in patients with chronic heart failure with preserved ejection fraction (EMPEROR-Preserved) is an ongoing trial aiming to determine if empagliflozin can have a meaningful impact on the course of heart failure with preserved ejection fraction in people with and without T2DM.[12]

For the most part, these trials showed minimally significant differences between SGLT2 inhibitor and placebo in terms of adverse effects, however there were a few exceptions. The CANVAS trial showed that there was a higher risk of toe, foot, or leg amputations in patients treated with canagliflozin (6.3 vs. 3.4 participants with amputation per 1000 patient-years; hazard ratio of 1.97; 95% CI, 1.41 to 2.75), but the highest risk was amongst those who had a history of amputation or existing peripheral vascular disease.[6] However, the CREDENCE trial, also using canagliflozin, did not show any significant difference in the risk of lower limb amputations between treatment groups, but it did show a higher, but still low, rate of diabetic ketoacidosis (DKA) in the canagliflozin treatment group (2.2 vs 0.2 per 1000 patient-years).[7] The increased rate of DKA was mimicked in the DECLARE-TIMI trial which saw a small increase in diabetic ketoacidosis in the dapagliflozin group (0.3% vs. 0.1%; hazard ratio, 2.18; 95% CI, 1.10 to 4.30; P=0.02).[9] The most common adverse effect of SGLT2 inhibitors continues to be genital infections; in the DECLARE-TIMI trial, 0.9% (vs 0.1%) of patients in the dapagliflozin trial group had genital infections severe enough to drop out of the trial.[9] The EMPA-REG OUTCOME trial also showed an increased rate of genital infections amongst patients receiving empagliflozin, but reported no other adverse events.[5]

As evidenced by the aforementioned trials, SGLT2 inhibitors, although classified as antihyperglycemics, offer much more to patients than just managing blood glucose and lowering A1Cs. The EMPA-REG OUTCOME, CANVAS(-R), and CREDENCE trials showed that this class of medications can reduce CV mortality in people with diabetes. Additionally, the DECLARE-TIMI, DAPA-HF, and CVD-REAL 2 trials showed that these medications also reduce the risk of worsening or hospitalizations due to heart failure. Based on these trials, SGLT2 inhibitors are, after metformin, a great first option for the treatment of diabetes in patients with or at risk for ASCVD and those with heart failure. Like many other medications, SGLT2 inhibitors come with some adverse effects; however, when weighing the significant cardiovascular benefits against the potential adverse effects, these medications may be a viable option for many people with diabetes.

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Let's Bean Honest: SGLT2 Inhibitors and Kidney Protection

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The microvascular and macrovascular complications of diabetes have left approximately 30% of individuals affected by nephropathy.[1] Characterized by increased urinary albumin excretion (UAE) in the absence of other renal diseases, diabetic nephropathy (DN) is a growing health concern and the most common cause of end-stage renal disease (ESRD).[1] The stages of DN are distinguished between microalbuminuria (UAE >30 mg/24 hours and ≤300 mg/24 hours) and macroalbuminuria (UAE ≥300 mg/24 hours).[2] Known risk factors of DN consist of hyperglycemia, hypertension, dyslipidemia, smoking, obesity, and ethnic, familial and genetic predispositions.[1] The need to address diabetic nephropathy stems from its detrimental prognosis. Once diagnosed, the condition will progress until the patient requires dialysis or transplantation. Therefore, prevention is vital in the reduction of the onset and progression of diabetic kidney disease.

Renin-angiotensin-aldosterone system (RAAS) blockers, such as angiotensin II receptor blockers (ARBs) and angiotensin-converting enzyme (ACE) inhibitors, have been the primary pharmacologic treatment in preservation of kidney function in people with diabetes but are only partially effective in hindering DN development. Recently, sodium-glucose cotransporter 2 (SGLT2) inhibitors have demonstrated nephroprotectivity in various research studies and are becoming popular alternatives in the prevention of DN.

Due to the increased glucose filtered load in type 2 diabetes, there is an increased expression of SGLT2 localized in the proximal tubule of the kidney leading to amplified glucose reabsorption. The mode of action of SGLT2 inhibitors in diabetes treatment is to inhibit glucose reabsorption by excreting glucose via urine, resulting in reduced fasting and postprandial plasma glucose levels. This mechanism of glycemic control acts independently from endogenous insulin secretion and has additional benefits in blood pressure reduction and weight loss, both of which alleviate risk factors for DN.[1]

The nephroprotective properties of SGLT2 inhibitors are also attributed to an additional effect. Glomerular hyperfiltration is considered a potential risk factor in the development of DN. As nephrons become irreversibly damaged during the initiation and progression of diabetic kidney disease, hyperfiltration acts as a compensatory mechanism.[3] By inhibiting SGLT2, there is an additional reduction in sodium reabsorption, and via downstream effects, vasoconstriction of the afferent arteriole can occur to reduce hyperfiltration.

In recent trials determining cardiovascular benefit of SGLT2 inhibitors, researchers have simultaneously assessed kidney outcomes against placebo.[1] To determine a renoprotective effect, renoprotection was classified as reducing the risk of the composite of worsening kidney function, end-stage renal disease, or renal death.

The Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG) trial studied the long-term renal effects of empagliflozin (10mg or 25mg) against placebo. In the case of new or worsening nephropathy, defined as urine albumin-to-creatinine ratio (UACR) > 300mg/g, doubling of serum creatinine with an estimated glomerular filtration rate (eGFR) ≤45 ml/min/1.73 m^2, initiation of renal replacement therapy, or death due to renal disease, there was a 39% reduction in risk with use of empagliflozin. When reviewing each outcome individually, the empagliflozin study group had fewer incidences versus placebo in the following categories of incident or worsening nephropathy (12.7% vs. 18.8%; HR 0.61; 95% CI, 0.53 to 0.70; p<0.001), progression to macroalbuminuria (11.2% vs. 16.2%; HR 0.62; 95% CI, 0.54 to 0.72; p<0.001), and doubling of serum creatinine with an eGFR ≤45 ml/min/1.73 m^2 (1.5% vs. 2.6%; HR 0.56; 95% CI, 0.39-0.79; p<0.001).[4]

Consistent results were demonstrated in similar studies evaluating the effects of other SGLT2 inhibitors such as the Canagliflozin Cardiovascular Assessment Study-Renal (CANVAS-R), Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction (DECLARE-TIMI 58), and Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE). The CANVAS-R study explored the effects of canagliflozin on progression of albuminuria, defined as >30% increase in albuminuria and a change from either normoalbuminuria to microalbuminuria or macroalbuminuria, or from microalbuminuria to macroalbuminuria, in patients with previous cardiovascular events. Not only was the incidence of albuminuria progression less frequent among the intervention group (89.4 participants with an event per 1000 patient-years) than among those assigned placebo (128.7 participants with an event per 1000 patient-cases) (HR 0.73; 95% CI, 0.67-0.79), the study showed an association between canagliflozin use with regression of albuminuria (293.4 vs. 187.5 participants per 1000 patient-years; HR, 1.70; 95% CI, 1.51-1.91).[5]

Renal effects were a secondary endpoint in the DECLARE-TIMI 58 trial and specifically studied the cardiorenal composite of sustained decline of at least 40% in eGFR to less than 60mL/min/1.73m^2, end-stage renal disease (dialysis for at least 90 days, kidney transplantation, or confirmed sustained eGFR <15 mL/min/1.73m^2), or death from renal or cardiovascular causes. Patients on daily dapagliflozin experienced a lower incidence of composite cardiorenal outcomes when compared to placebo (4.3% vs. 5.6%; HR 0.76; 95% CI, 0.67-0.87; p<0.0001). Additionally, when considering composite renal-specific (1.5% vs 2.8%; HR 0.53; 95% CI, 0.43-0.66, p<0.0001) and sustained eGFR outcomes (1.4% vs. 2.6%; HR 0.54; 95% CI, 0.43-0.67; p<0.0001), dapagliflozin was significantly favorable in both categories.[6]

The CREDENCE trial was one of the first of its kind where the primary endpoint was focused on renal impact. The effects of daily canagliflozin 100mg were compared to placebo and evaluated the time to either ESRD, consisting of dialysis, transplantation, or sustained eGFR <15 mL/min/1.73m^2, doubling of serum creatinine, or death from renal or cardiovascular causes. The patient population included 4401 people diagnosed with type 2 diabetes and albuminuric chronic kidney disease with an eGFR of 30 to <90 mL/min/1.73m^2, albuminuria (ratio of albumin to creatinine >300 to 5000 mg/g), and were treated with RAAS blockers. The trial was stopped

early after reaching pre-specified efficacy criteria with a median follow-up of 2.62 years. The relative risk of the primary outcome of progression to ESRD, doubling of serum creatinine, and renal or cardiovascular death was 30% lower in the canagliflozin group than in the placebo group, with event rates of 43.2 and 61.2 per 1000 patient-years, respectively (HR 0.70; 95% CI, 0.59-0.82; p=0.00001). When assessing renal-specific outcomes, the intervention group had a 32% lower relative risk than placebo for ESRD (HR 0.68; 95% CI, 0.54-0.86; p=0.002). Additionally, the relative risk of the composite of ESRD, doubling of the serum creatinine level, or renal-specific death was lower by 34% in the canagliflozin group (HR, 0.66; 95% CI, 0.53 to 0.81; P<0.001).[7,8]

The Evaluation of Ertugliflozin Efficacy and Safety – Renal Outcomes (VERTIS RENAL) trial evaluated 5mg and 15mg of ertugliflozin versus placebo in people with type 2 diabetes who also had existing renal impairment categorized as stage 3 chronic kidney disease with an eGFR ≥45 to <60ml/min/1.73m^2. Although kidney-specific endpoints were not achieved in the study, results demonstrated a change in A1c from baseline by -0.2% (95% CI, – 0.5 to 0.1) and –0.4% (95% CI, – 0.6 to – 0.1) in the ertugliflozin 5 mg and 15 mg groups, respectively; not statistically significant versus placebo. However, body weight reduction was noted to be statistically significant (p<0.001) given the placebo group gained 0.5kg (95% CI, -0.1-1.0) while the ertugliflozin 5mg and 15mg group lost 1.3kg (95% CI, -1.9 to -0.8) and 1.4kg (95% CI, -2.0 to -0.8) respectively. This study in renally impaired participants demonstrated metabolic benefit and trends in glycemic improvement.[9]

As a class, SGLT2 inhibitors have demonstrated nephroprotective properties in both prevention and delayed progression of nephropathy in type 2 diabetes. The 2020 American Diabetes Association (ADA) Standards of Medical Care in Diabetes recommends SGLT2 inhibitors in people with type 2 diabetes who have established atherosclerotic cardiovascular disease and/or chronic kidney disease due to the cardiovascular mortality benefit and reduction in risk of kidney disease progression.[10] In particular, use of empagliflozin, canagliflozin, or dapagliflozin should be considered in patients with an estimated glomerular filtration rate ≥30 mL/min/1.73 m^2 and urinary albumin >30 mg/g creatinine, especially those with urinary albumin >300 mg/g creatinine.[11] It should be noted, the utilization of canagliflozin, empagliflozin, and dapagliflozin are contraindicated in patients with an eGFR <30 ml/min/1.73m^2, while ertugliflozin is contraindicated in patients with an eGFR <45 ml/min/1.73m^2. Nevertheless, SGLT2 inhibitors prove to be a beneficial adjunctive therapy with RAAS blockers in patients with current albuminuria and may assist in prevention of DN in asymptomatic patients. Due to the current data, in September 2019, the FDA approved canagliflozin for the indication of reducing risk of ESRD, worsening kidney function, cardiovascular death, and hospitalization for heart failure in adults with type 2 diabetes and diabetic kidney disease.[12] Trials specifically investigating renal outcomes with dapagliflozin (A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients with Chronic Kidney Disease (DAPA-CKD)) and empagliflozin (Clinical Trial of Empagliflozin Once Daily to Assess Cardio-renal Outcomes in Patients with Chronic Kidney Disease (EMPA-KIDNEY)) are ongoing.

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Summary of Clinical Trials Assessing SGLT2 Inhibitors

Trial Name	Participants	Intervention	Primary Outcome	Secondary Outcome	Renal Outcomes	Number Needed to Treat (NNT)
Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPAG-REG OUTCOME)[1,2]	7,020 patients	Empagliflozin 10mg, empagliflozin 25mg, or placebo	Death from CV causes, non-fatal MI, nonfatal stroke Occurred in 490 of 4687 (10.5%) patients in the empagliflozin group vs 282 of 2333 (12.1%) in the placebo group (HR 0.86; 95.02% CI, 0.74 to 0.99; P<0.001 for noninferiority and P=0.04 for superiority).	Primary outcome and hospitalization for unstable angina Occurred in 599 of 4687 patients (12.8%) in the empagliflozin group and 333 of 2333 patients (14.3%) in the placebo group (HR 0.89; 95% CI, 0.78 to 1.01; P<0.001 for noninferiority and P=0.08 for superiority).	Composite of doubling of serum creatinine with eGFR ≤45 ml/min/1.73 m^2, initiation of renal replacement therapy, or death from renal disease Occurred in 525 of 4124 patients (12.7%) in the empagliflozin group and 388 of 2061 patients (18.8% in the placebo group (HR 0.61; 95% CI, 0.53 to 0.70; P<0.001). When reviewing each outcome individually, the empagliflozin group had fewer incidences versus placebo in the following categories of incident or worsening nephropathy (12.7% vs. 18.8%; HR 0.61; 95% CI, 0.53 to 0.70; P<0.001), progression to macroalbuminuria (11.2% vs. 16.2%; HR 0.62; 95% CI, 0.54 to 0.72; P<0.001), and doubling of serum creatinine with an eGFR ≤45 ml/min/1.73 m^2 (1.5% vs. 2.6%; HR 0.56; 95% CI, 0.39 to 0.79; P<0.001).	Primary outcome = 62 Composite renal outcome = 72 Incident of or worsening nephropathy = 17 Progression to macroalbuminuria = 20 Doubling of serum creatinine with an eGFR ≤45 ml/min/1.73 m^2 = 91
Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes (CANVAS)[3]	10,134 patients (4334 CANVAS and 5790 CANVAS-R)	CANVAS: Canagliflozin 300mg, canagliflozin 100mg, or placebo CANVAS-R: Canagliflozin 100mg with option to increase to 300mg, or placebo	Composite of death from CV causes, nonfatal MI, or nonfatal stroke The rate was lower with canagliflozin than with placebo (26.9 vs. 31.5 participants per 1000 patient-years; HR 0.86; 95% CI, 0.75 to 0.97; P<0.001 for noninferiority; P=0.02 for superiority).	Death from any cause, death from cardiovascular causes, progression of albuminuria, and the composite of death from cardiovascular causes and hospitalization for heart failure Superiority was not shown for the first secondary outcome (death from any cause; P=0.24). Estimates for the fatal secondary outcomes, including death from any cause (HR 0.87; 95% CI, 0.74 to 1.01) and death from cardiovascular causes (HR 0.87; 95% CI, 0.72 to 1.06), are not considered to be significant.	Progression of albuminuria (>30% increase in albuminuria and a change from either normoalbuminuria to microalbuminuria or macroalbuminuria, or from microalbuminuria to macroalbuminuria) Occurred less frequently among participants assigned to canagliflozin than among those assigned to placebo (89.4 vs. 128.7 participants with an event per 1000 patient-years), corresponding to a hazard ratio of 0.73 (95% CI, 0.67 to 0.79).	Because the CANVAS Program was composed of 2 clinical trials with different treatment allocation ratios and different follow-up, it is not possible to estimate the NNT Progression of albuminuria = 29
Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes (DECLARE-TIMI)[4,5]	17,160 patients	Dapagliflozin 10mg or placebo	MACE and a composite of CV death or hospitalization for HF Dapagliflozin did not result in a lower rate of MACE (8.8% in the dapagliflozin group and 9.4% in the placebo group; HR 0.93; 95% CI, 0.84 to 1.03; P=0.17) but resulted in a lower rate of CV death or hospitalization for HF (4.9% vs. 5.8%; HR 0.83; 95% CI, 0.73 to 0.95; P=0.005), which reflected a lower rate of hospitalization for HF (HR 0.73; 95% CI, 0.61 to 0.88).	Renal composite outcome (sustained decrease of ≥40% of eGFR to ≤ 60 ml per minute, new ESRD, or death from renal or CV causes) or death from any cause A renal event occurred in 4.3% in the dapagliflozin group and in 5.6% in the placebo group (HR 0.76; 95% CI, 0.67 to 0.87), and death from any cause occurred in 6.2% and 6.6%, respectively (HR 0.93; 95% CI, 0.82 to 1.04).	Composite of sustained decline of ≥40% in eGFR to <60 ml/min/1.73 m^2, ESRD (defined as dialysis for at least 90 days, kidney transplantation, or confirmed sustained eGFR <15 ml/min/1.73 m^2), or death from renal causes In the overall population, the incidence of the renal-specific composite outcome was 1.5% in the dapagliflozin group and 2.8% in the placebo group (HR, 0.53; 95% CI, 0.43 to 0.66; P<0.0001). Dapagliflozin was also significantly favorable in sustaining eGFR outcomes (1.4% vs. 2.6%; HR 0.54; 95% CI, 0.43 to 0.67; P<0.0001).	Primary outcomes (Composite of CV death and HHF) = 112 Secondary outcome = 77

Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy (CREDENCE)[6]	4,401 patients	Canagliflozin 100mg or placebo	Composite of ESRD(dialysis for at least 30 days, kidney transplantation, or an eGFR of <15ml/min/1.73m^2 for at least 30 days), doubling of serum creatinine from baseline sustained for at least 30 days, or death from renal or CV causes. The event rate of the primary composite outcome was significantly lower in the canagliflozin group than in the placebo group (43.2 and 61.2 per 1000 patient-years, respectively), which resulted in a 30% lower relative risk (HR 0.70; 95% CI, 0.59 to 0.82; P=0.00001).	Composite of CV death or hospitalization for HF; a composite of CV death, MI, or stroke; hospitalization for HF; a composite of ESRD, doubling of the serum creatinine, or renal death; CV death; death from any cause; a composite of CV death, MI, stroke, or hospitalization for HF or for unstable angina Patients in the canagliflozin group had a lower risk of: the composites of CV death or hospitalization for HF (HR 0.69; 95% CI, 0.57 to 0.83; P<0.001), CV death, MI, or stroke (HR 0.80; 95% CI, 0.67 to 0.95; P=0.01), and hospitalization for HF (HR 0.61; 95% CI, 0.47 to 0.80; P<0.001). The relative risk of the composite of ESRD, doubling of the serum creatinine level, or renal death was lower by 34% in the canagliflozin group (HR 0.66; 95% CI, 0.53 to 0.81; P<0.001). When specifically assessing the incidence of ESRD, the canagliflozin group had a 32% lower relative risk than placebo (HR 0.68; 95% CI, 0.54 to 0.86; P=0.002).		Primary outcome = 22 Secondary outcome = 59
Ertugliflozin in Patients with Stage 3 Chronic Kidney Disease and Type 2 Diabetes Mellitus (VERTIS RENAL)[7]	467 patients	Ertugliflozin 5mg, ertugliflozin 15mg, or placebo	Change from baseline in A1c at week 26 Results demonstrated a change in A1c from baseline by -0.2% (95% CI, – 0.5 to 0.1) and –0.4% (95% CI, – 0.6 to – 0.1) in the ertugliflozin 5 mg and 15 mg groups, respectively. The placebo group demonstrated a change of -0.3% (95% CI, -0.4 to -0.1). There was no statistical significance between ertugliflozin against placebo.	Changes from baseline in A1c, body weight, systolic blood pressure, and fasting plasma glucose in the stage 3A chronic kidney disease cohort The ertugliflozin 5mg group demonstrated a change at week 26 in A1c from baseline by -0.2% (95% CI, -0.5 to 0.1) while the ertugliflozin 15mg group had a change of -0.4% (95% CI, -0.6 to -0.1). Body weight reduction was noted to be statistically significant (P<0.001) given the placebo group gained 0.5kg (95% CI, -0.1-1.0) while the ertugliflozin 5mg and 15mg group lost 1.3kg (95% CI, -1.9 to -0.8) and 1.4kg (95% CI, -2.0 to -0.8) respectively.		N/A
Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction (DAPA-HF)[8]	4,744 patients	Dapagliflozin 5mg, dapagliflozin 10mg, or placebo	Composite of worsening HF (hospitalization or an urgent visit resulting in IV therapy for HF) or CV death Occurred in 386 of 2373 patients (16.3%) in the dapagliflozin group and in 502 of 2371 patients (21.2%) in the placebo group (HR 0.74; 95% CI, 0.65 to 0.85; P<0.001).	Cardiovascular death, hospitalization for HF, worsening of renal function Cardiovascular death: 9.6% with dapagliflozin vs. 11.5% with placebo. Hospitalization for heart failure: 9.7% with dapagliflozin vs. 13.4% with placebo. Worsening of renal function: 1.2% with dapagliflozin vs. 1.6% with placebo (P=0.17).		Primary outcome = 21 Secondary outcomes: CV death = 53 HF hospitalization = 27

Cardiovascular events associated with SGLT2 inhibitors versus other glucose lowering drugs (CVD-REAL 2)[9]	235,064 patients initiated on an SLGT2i	Dapagliflozin, empagliflozin, ipragliflozin, canagliflozin, tofogliflozin, and luseogliflozin	Heart failure, all-cause death (ACD), cardiovascular death, MI, stroke, ischemic stroke, atrial fibrillation Initiation of SGLT-2i versus oGLD (other glucose lowering drug) was associated with a lower risk of ACD (pooled HR: 0.51; 95% CI: 0.37 to 0.70; P < 0.001) Initiation of SGLT-2i versus oGLD was associated with a lower risk of HHF (pooled HR: 0.64; 95% CI: 0.50 to 0.82; P=0.001) Initiation of SGLT-2i versus oGLD was associated with a lower risk of HHF or death (pooled HR: 0.60; 95% CI: 0.47 to 0.76; P< 0.001) Initiation of SGLT-2i versus oGLD was associated with a lower risk of MI (pooled HR: 0.81; 95% CI: 0.74 to 0.88; P< 0.001) Initiation of SGLT-2i versus oGLD was associated with a lower risk of stroke (pooled HR: 0.68; 95% CI, 0.55 to 0.84; P< 0.001).			Primary Outcome = 3.8

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Review of Fournier Gangrene for the Outpatient Clinician

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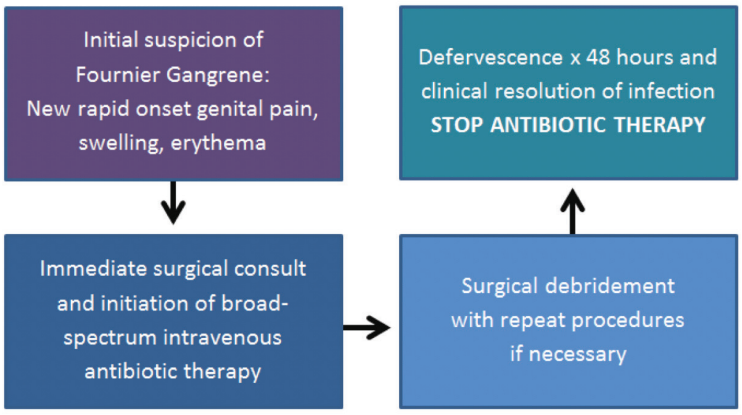
Fournier gangrene is a potentially life-threatening skin and soft tissue infection of the scrotum and penis or vulva. It typically occurs through contiguous spread from infections in the perianal or retroperitoneal regions along the fascial planes to the genitalia or through a urinary tract infection involving the periurethral glands.[1] It occurs most commonly in men, but may occur in women or in children as well. Fournier gangrene is a medical emergency with an estimated mortality rate of approximately 25%.[2,3] Patients suspected of having Fournier gangrene should receive immediate surgical consultation for debridement of involved tissue and initiation of intravenous broad-spectrum antibiotic therapy. The role of clinicians in the ambulatory setting is to recognize and triage any potential cases of Fournier Gangrene to receive emergent surgical evaluation and continued follow-up with patients upon discharge to ensure that no relapse of infection occurs.

Compared to other forms of necrotizing fasciitis which are typically monomicrobial, Fournier gangrene is more frequently polymicrobial with the potential for both aerobic and anaerobic organism involvement.[1] Causative organisms are typically those that are commensal to the perineal skin or genitalia, or those from the gastrointestinal tract. The most commonly implicated organisms include *Escherichia coli*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, and *Bacteroides fragilis*.[4] Upon presentation to the hospital, it is recommended that patients be started on broad-spectrum intravenous antimicrobial therapy that includes both aerobic and anaerobic coverage as seen in Figure 1, located below.[1] Cultures of surgically debrided tissue should be sent from the operating room and ideally can assist to narrow antimicrobial therapy targeting cultured pathogens. Regardless of culture results, anaerobic coverage should be retained within the antibiotic regimen due to the high frequency of anaerobic involvement and the difficultly to grow these pathogens in the clinical laboratory.[1]

Figure 1: General Treatment Approach to Fournier Gangrene



Patients presenting with Fournier Gangrene will most frequently report genital pain, swelling, and erythema.[4] Wound discharge, crepitation, or fluctuance may also be present. In cases of contiguous spread, adjacent cellulitis from the perineal or perineum may also be present. As the infection progresses, skin becomes macerated and expresses a feculent odor due to the presence of anaerobes within the infected soft tissues. Patients may also present with systemic signs of infection such as fever, hypotension, or tachycardia.

The total duration of antimicrobial therapy is highly dependent on the patient's clinical course. The Infectious Diseases Society of America (IDSA) Guidelines recommend that patients are continued on antibiotic therapy until they have defervesced for at least 48 hours and clinical resolution of infection has occurred.[1] A retrospective review by Lauerman & colleagues demonstrated that a total duration of antibiotic therapy of 7-days from last surgical debridement was not associated with an increased risk of mortality or recurrence compared to longer durations of therapy.[5] As only short courses of antibiotic therapy are typically required, patients presenting in the primary care setting will likely have completed antibiotic therapy and will require monitoring for potential relapse of infection. It is imperative for outpatient clinicians to conduct a physical exam on any patients complaining of new onset genital swelling and pain in order to properly triage patients should they need emergent surgical attention.

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