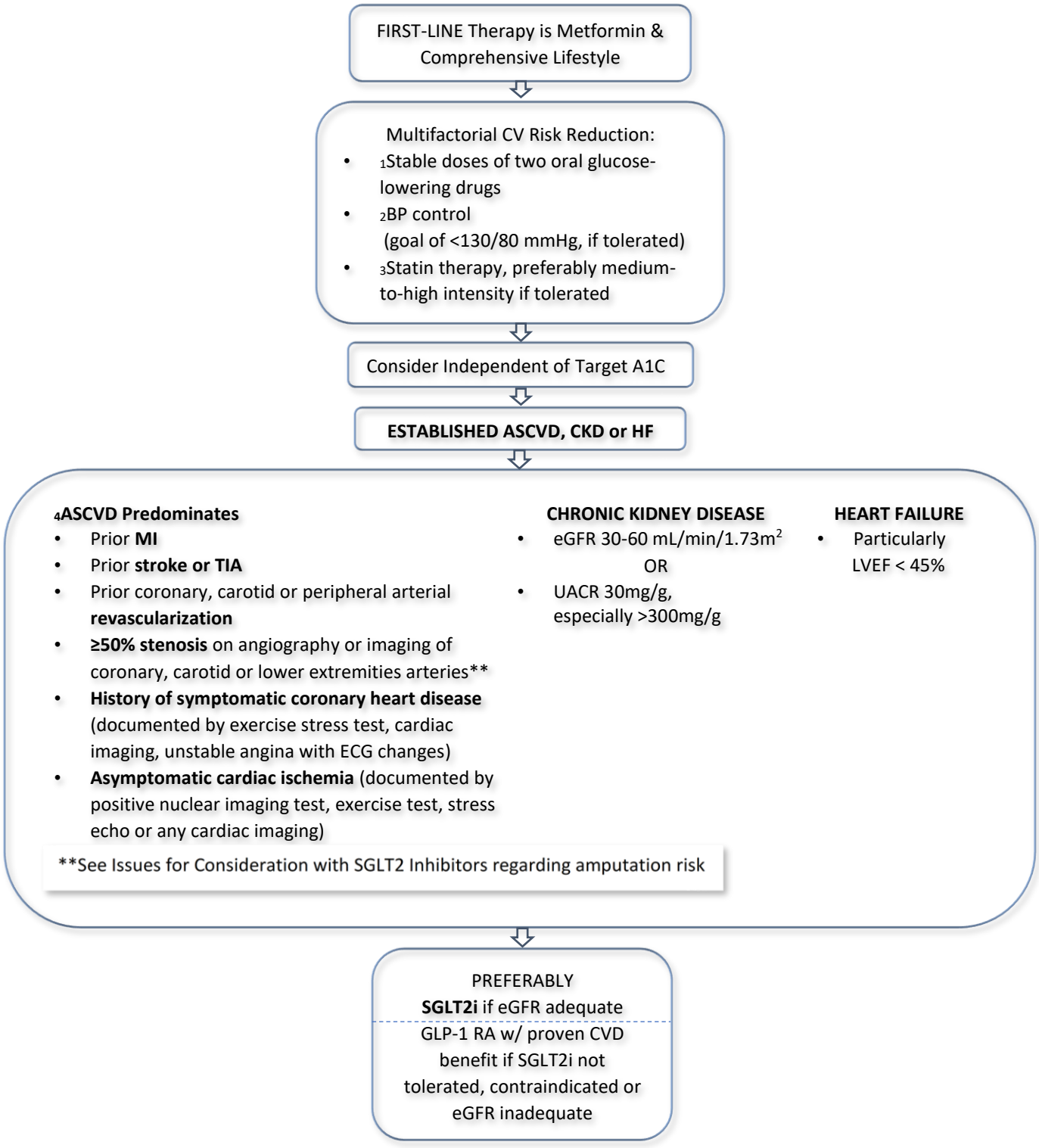
TYPE 2 DIABETES MACRO & MICROVASCULAR RISK REDUCTION

"For prevention and management of both ASCVD and heart failure, cardiovascular risk factors should be systematically assessed at least annually in patients with diabetes." – *ADA Standards of Medical Care in Diabetes 2020*



1Glycemic Control

Cardiovascular effects of formulary DM meds:

- **INSULIN – No CV Benefit**
  - Does NOT appear to prevent or increase MACE
- **METFORMIN (GLUCOPHAGE®) – CV Benefit**
  - United Kingdom Prospective Diabetes Study (UKPDS)
    - Metformin vs. SU or insulin
    - ↓ microvascular, macrovascular and all-cause mortality with metformin
  - Other trial w/ 390 patients for 4 years
    - Insulin-dependent DM with metformin added vs. placebo
    - Significant 40% reduction in macrovascular endpoints (i.e. MI, HF, stroke, amputation and sudden death)
  - Other trial - 46% reduction in MACE vs. SU after 5 years
- **SULFONYLUREAS – No CV Benefit**
  - Do not appear to increase risk of CV events
  - Meta-analysis of 115 trials
    - No difference in incidence of MACE though overall mortality increased
  - CAROLINA trial
    - Compared glimepiride vs. linagliptin
    - No evidence of increased CVD
- **PIOGLITAZONE (ACTOS®) – CV Benefit**
  - PROactive trial in 5238 patients
    - 16% significant decrease in composite of all-cause mortality, nonfatal MI or nonfatal stroke)
    - ↑ Hospitalization for heart failure
    - ↑ Weight gain & edema at higher doses
- **ACARBOSE (PRECOSE®) – Possible Benefit**
  - Study to Prevent Non-Insulin-Dependent DM (STOP-NIDDM) trial
    - 1429 patients assigned 100mg TID
    - Significant ↓ CV events by 49%
    - Further studies needed

2BP Control

GOALS

- Target of < 130/80 mmHg is appropriate if may be safely achieved
  - Older age, CKD & frailty increase risk of adverse events
  - A goal of <140/90 mmHg may be appropriate in these patients
- PREGNANCY: If pregnant with diabetes and preexisting hypertension, a BP target of ≤135/85 mmHg is suggested to reduce risk of accelerated maternal hypertension & minimize impaired fetal growth

TREATMENT

- Drug classes demonstrated to reduce CV events include:
  - ACE inhibitors or Angiotensin receptor blockers
    - 1st line for DM patients with UACR ratio ≥300mg/g
    - Should be considered, however, at any level of albuminuria
  - Thiazide-like diuretics
  - Dihydropyridine calcium channel blockers
- Note: Beta blockers may be used for treatment of prior MI, active angina or HF but have not been shown to decrease mortality as BP-lowering agents
- Resistant hypertension (↑BP despite lifestyle changes plus a diuretic & two other antihypertensives)
  - Add mineralocorticoid receptor antagonists (also reduce albuminuria & have additional CV benefits)
- Some evidence that HS dosing may reduce CV events

3Lipid Management

- Meta-analyses (>18,000 DM patients from 14 randomized trials, mean follow-up 4.3 years) demonstrate a 9% proportional reduction in all-cause mortality & 13% reduction in vascular mortality for each 39 mg/dL LDL reduction
- Primary Prevention
  - DM patients 40-75yo without ASCVD, use **moderate-intensity statin**
  - DM patients aged 20-39yo w/ additional ASCVD risk factors may benefit from statin
  - Patients w/ multiple ASCVD risk factors or aged 50-70yo may benefit from **high-intensity statin**
  - If 10-year ASCVD risk ≥20%, consider addition of ezetimibe to **maximally tolerated statin**
- Secondary Prevention
  - All DM patients of all ages should be treated w/ **high-intensity statin** (or maximally tolerated statin if necessary)
  - Very high-risk patients w/ LDL ≥70mg/dL on **maximally tolerated statin** could benefit from additional LDL lowering via ezetimibe
  - For patients who do not tolerate intended intensity, maximally tolerated dose should be used
- High-intensity statin therapy reduces LDL ≥50% and includes:
  - Atorvastatin 40-80mg
  - Rosuvastatin 20-40mg
- Moderate-intensity statin therapy reduces LDL 30-49% and includes formulary options:
  - Atorvastatin 10-20mg
  - Rosuvastatin 5-10mg
  - Pravastatin 40-80mg

Risk Calculator available at: http://tools.acc.org/ASCVD-Risk-Estimator-Plus

Glucagon-Like Peptide-1 (GLP-1) Considerations for Use, Precautions and Contraindications
(Liraglutide, Semaglutide, Dulaglutide, Exenatide, Exenatide Extended-Release, Lixisenatide)

Medications within class with proven CVD benefit include:

- *Dulaglutide (Trulicity®): REWIND trial – Significant outcomes include 12% reduction in primary composite (first occurrence of CV death, nonfatal MI or nonfatal stroke), 22% reduction in nonfatal stroke and 14% reduction in microvascular events (diabetic retinopathy or renal decline)*
- *Liraglutide (Victoza®): LEADER trial - Significant outcomes include 13% reduction in primary composite (first occurrence of death from CV causes, nonfatal MI or nonfatal stroke), 15% reduction in death from any cause, 22% reduction in death from CV causes, 14% reduction in MI and 22% reduction in nephropathy events*
- *Semaglutide (Ozempic® only): SUSTAIN-6 trial - Significant outcomes include 26% reduction in primary composite (first occurrence of death from CV causes, nonfatal MI or nonfatal stroke), 39% reduction in nonfatal stroke and 36% reduction in new or worsening nephropathy*

NOTE: Data is not intended to be comparative as no head-to-head studies exist, and baseline characteristics differ significantly between trials (i.e. only 31.5% of patients in REWIND trial have CV disease compared to 60% and 81% in SUSTAIN-6 and LEADER trials, respectively. Baseline A1C in REWIND was 7.2% vs. 8.7% in the other two studies)

Exclusion Criteria

- ❑ Type 1 diabetes
- ❑ [5]History of hypersensitivity to GLP-1 agonist or excipients
- ❑ [6]End-stage renal disease (ESRD) or CrCl < 30 mL/min (exenatide); eGFR < 45 mL/min/1.73m^2 (exenatide once-weekly); ESRD or eGFR < 15 mL/min/1.73m^2 (lixisenatide)[5]
- ❑ Personal or family history of medullary thyroid carcinoma or with Multiple Endocrine Neoplasia syndrome type 2 (excludes dulaglutide, exenatide once-weekly, liraglutide, lixisenatide and semaglutide)
- ❑ History of drug-induced, immune-mediated thrombocytopenia (exenatide products)
- ❑ Severe gastrointestinal disease (*i.e.*, gastroparesis)
- ❑ [7]History of pancreatitis
- ❑ History of diabetic retinopathy if using semaglutide injection (Not an absolute exclusion. See Issues for Consideration)
- ❑ Pregnancy (Not an absolute exclusion. See Issues for Consideration)
  Note: Per manufacturer labeling, discontinue semaglutide in women at least 2 months before a planned pregnancy due to the long washout period for semaglutide

[5]It is currently unknown if patients who experienced a hypersensitivity reaction to one GLP-1 agonist can safely use another.
[6]With all GLP-1 RAs, monitor renal function closely in patients with renal impairment reporting severe gastrointestinal reactions.
[7]Relative exclusions to use include triglyceride level > 1000 mg/dL, known gallstones with intact gallbladder and alcohol abuse.

•GLP-1 agonists in combination with alpha glucosidase inhibitors, meglitinides or DPP-4 inhibitors are not recommended due to lack of or insufficient data regarding their combined use. There is one randomized, controlled trial combining a GLP-1 agonist and a SGLT2 inhibitor. There were no increased adverse events with the combination, including volume-related events; however, care should be taken combining these two classes until more data become available.

• Insulin may be considered at any time prior to using a GLP-1 agonist; however, insulin is preferred if patient is symptomatic or the desired A1C reduction is beyond what is achievable by a GLP-1 agonist. In clinical trials the mean reduction in A1C when GLP1 agonists are used alone or added to oral hypoglycemic agents ranges from 0.7% to 1.8% across studies.
• Basal insulin should be titrated as feasible to an acceptable fasting blood glucose level unless unable to (e.g., hypoglycemia, patient unwilling or unable to intensify insulin dose)
• Consider addition of mealtime insulin instead of using a GLP-1 agonist; however, mealtime insulin should be used if patient is symptomatic or the desired A1C reduction is beyond what is achievable by a GLP-1 agonist. In clinical trials the mean reduction in A1C when used with insulin is approximately 1.2% (means ranging from 0.7% to 1.9% across studies).
• The data for GLP-1 agonists in combination with both basal and prandial insulin or with U500 insulin are very limited at present. Concomitant use of GLP-1 agonists with regimens containing basal insulin AND prandial insulin (including premixed formulations) or with U500 may be done on a case-by-case basis in consultation with an endocrinologist or diabetes specialist.

Issues for Consideration

• **Gallbladde**r: The GLP-1 agonists may be associated with an increased risk of bile duct and gallbladder disease. A population cohort study found increased risk with use of exenatide and liraglutide relative to use of two oral antidiabetic drugs. Events tended to occur within the first 180 days of use. The liraglutide clinical trials (LEADER and SCALE) showed an increased incidence of gallbladder-related events relative to placebo. Additionally, two small studies in healthy patients found decreased cholecystokinin-induced gallbladder emptying with exenatide and albiglutide vs. placebo which may increase the risk of gallstone formation. Patients should be educated and monitored for signs and symptoms of gallbladder disease (e.g., right upper quadrant pain, colicky pain)
• **Renal impairment**: Use with caution in patients with renal impairment, particularly during initiation of therapy and dose escalation. Acute renal failure and chronic renal failure exacerbation (sometimes requiring hemodialysis) have been reported; some cases have been reported in patients with no known pre-existing renal disease. The majority of reported cases occurred in patients with nausea/vomiting/diarrhea or dehydration.
• **Dehydration**: Avoid initiating in individuals whom the potential for dehydration poses a considerable risk (e.g., frail elderly, multiple co-morbid conditions, etc.)
• **Bariatric Surgery**: Use cautiously in patients who have undergone bariatric surgery due to the potential interaction the GLP-1 agonists may have on the gastrointestinal motor complications and gastric hormone changes associated with bariatric interventions. With bariatric surgery, there is increased GLP-1, changes in GI motility, and potential for hypoglycemia if a GLP-1 agonist is given.
• **Pregnancy**: In pregnant animals exposed to GLP-1 agonists, decreased maternal weight gain, decreased fetal growth, increased fetal or offspring abnormalities and neonatal deaths have occurred sometimes at doses reflecting those of human exposure. Limited data with GLP-1 agonists in pregnant women are not sufficient to determine a drug associated risk for major birth defects and miscarriage. Insulin is generally the preferred treatment during pregnancy. GLP-1 agonists should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
• **Lactation**: It is not known whether GLP-1 agonists are excreted in human milk. In animal studies, GLP-1 agonists were present in the milk of lactating rats and mice. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for a GLP-1 agonist and any potential adverse effects on the breastfed infant from a GLP-1 agonist or from the underlying maternal condition.
• **Diabetic Retinopathy**: In a 2-year trial involving patients with type 2 diabetes and high cardiovascular risk, more events of diabetic retinopathy complications (DRC) occurred in patients treated with injectable semaglutide (3.0%) compared to placebo (1.8%). The absolute risk increase for DRC was larger among

patients with a history of diabetic retinopathy at baseline (semaglutide 8.2%, placebo 5.2%) than among patients without a known history of diabetic retinopathy (semaglutide 0.7%, placebo 0.4%).

In patients with a history of diabetic retinopathy, the risk of DRC was further increased in those using insulin prior to the event. There was no increased risk in those using insulin without a history of diabetic retinopathy. While no data are available to support an interaction with insulin, use of insulin appears to identify those patients at highest risk of DRC.

Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy. The effect of long-term glycemic control with semaglutide on diabetic retinopathy complications has not been studied. Before considering injectable semaglutide, the provider should have the results of diabetic eye examination completed within past 1-2 years on file. Patients with a history of diabetic retinopathy should be monitored for progression of diabetic retinopathy. In a pooled analysis of glycemic control trials with oral semaglutide, diabetic retinopathy related adverse reactions during the trial were reported in 4.2% and 3.8% of patients receiving oral semaglutide and comparator respectively.

Sodium-Glucose Co-Transporter 2 Inhibitors (SGLT2i) Considerations for Use, Precautions and Contraindications (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin)

Medications within class with proven CVD benefit include:

- *Empagliflozin (Jardiance®): EMPA-REG OUTCOME trial – Significant outcomes include 14% reduction in time to first major adverse cardiovascular event (MACE),* ***38% reduction in time to CV death****, 35% reduction in time to first hospitalization for heart failure and 46% reduction in time to first renal composite outcome*
- *Canagliflozin (Inovkana®): CANVAS, CREDENCE trials - Significant outcomes include 14% (CANVAS) and 20% (CREDENCE) reduction in time to first MACE, 33% (CANVAS) and 39% (CREDENCE) reduction in time to first hospitalization for heart failure, 40% (CANVAS) and 34% (CREDENCE) reduction in time to first renal composite outcome (NOTE: CREDENCE specifically designed to assess primary outcomes associated with renal disease resulting in additional FDA indication of diabetic nephropathy with albuminuria)*
- *Dapagliflozin (Farxiga®): DECLARE-TIMI trial – Only significant outcome was 27% reduction in time to first hospitalization for heart failure*
- *Ertugliflozin (Steglatro®): VERTIS CV trial – Only significant outcome was 30% reduction in time to first hospitalization for heart failure*

NOTE: Data is not intended to be comparative as no head-to-head studies exist, and baseline characteristics differ significantly between trials

Exclusion Criteria

- ❑ History of a serious hypersensitivity reaction to an SGLT2 inhibitor
- ❑ On dialysis
- ❑ Pregnant or nursing
- ❑ Pancreatic disorders suggesting insulin deficiency (e.g., type 1 diabetes, recurrent pancreatitis, pancreatic surgery)
- ❑ History of frequent UTIs, those with indwelling catheters, need for self-catheterization, or known history of increased post void residual

• Insulin may be considered at any time prior to using empagliflozin; however, insulin is preferred if patient is symptomatic or the desired A1C reduction is beyond what is achievable by empagliflozin. In clinical trials the mean reduction in A1C when empagliflozin is used alone or added to oral hypoglycemic agents ranges from 0.7%-0.8%.

• Basal insulin should be titrated as feasible to an acceptable fasting blood glucose level unless unable to (e.g., hypoglycemia, patient unwilling or unable to intensify insulin dose)

• Consider addition of mealtime insulin; however, mealtime insulin should be used if patient is symptomatic or the desired A1C reduction is beyond what is achievable by empagliflozin. In clinical trials the mean reduction in A1C when empagliflozin is added to insulin ± metformin (and/or sulfonylureas) ranged from 0.6% to 1.0%.

Issues for Consideration

• **Hypotension**: SGLT2 inhibitors cause intravascular volume contraction. Symptomatic hypotension may occur after initiation of the SGLT2 inhibitor particularly in patients with eGFR <60mL/min/1.73m^2, elderly patients, those taking diuretics, or have low systolic blood pressure. Volume status should be assessed and corrected before initiating an SGLT2 inhibitor in patients with these characteristics. Monitor for signs and symptoms after initiating therapy.

• **Ketoacidosis**: There have been postmarketing reports of ketoacidosis, often with blood glucose levels <250mg/dL. Assess patients who present with signs and symptoms of metabolic acidosis for ketoacidosis, regardless of blood glucose level. If suspected, discontinue the SGLT2 inhibitor, evaluate and treat

promptly. Before initiating a SGLT2 inhibitor, consider risk factors for ketoacidosis (e.g., pancreatic insulin deficiency, alcohol abuse, caloric restriction). Patients on a SGLT2 inhibitor may require monitoring and temporary discontinuation of therapy in clinical situations known to predispose to ketoacidosis such as prolonged fasting due to acute illness or surgery.

• **Impairment in renal function**: SGLT2 inhibitors can increase serum creatinine and decrease eGFR. Elderly patients, those with impaired renal function or hypovolemia may be more susceptible to these changes. Periodic monitoring of renal function is recommended. More frequent monitoring is recommended in patients with eGFR <60mL/min/1.73m2.

• **Urosepsis and Pyelonephritis**: SGLT2 inhibitors increase the risk of urinary tract infections. There have been postmarketing reports of serious urinary tract infections including urosepsis and pyelonephritis in patients receiving SGLT2 inhibitors. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated.

• **Genital mycotic infections**: SGLT2 inhibitors increase the risk of genital mycotic infections. Patients with a history of genital mycotic infections were more likely to develop genital mycotic infections. Uncircumcised males were at a higher risk for developing genital mycotic infections.

• **Fournier's Gangrene**: Between March 2013 up to May2018 12 cases of Fournier's gangrene occurred in patients taking an SGLT2 inhibitor. Seven cases occurred in men and five in women, all which required hospitalization and surgery (one patient died). The average time to onset was 9.2 months (range 7 days to 25 months).

FDA indicates that this adverse event is very rare, with an estimated 1.7 million patients prescribed an SGLT2 inhibitor in 2017. Providers should instruct patients to promptly seek medical attention if they experience any symptoms of tenderness, erythema, or swelling in the genital or perineal area, fever, or malaise.

• **Hypersensitivity reactions**: Hypersensitivity reactions (e.g., generalized urticaria), some serious, have been reported. If hypersensitivity reactions occur, discontinue use and treat per standard of care. If the reaction was serious, the SGLT2 inhibitor should not be restarted (see contraindications).

• **Amputation**: Data from the CANVAS trials found that the use of canagliflozin was associated with approximately two-fold increased risk of lower limb amputations. Amputations most commonly occurred with the toe and middle of the foot but also involved the leg, below and above the knee. Some patients had more than one amputation and both limbs may have been affected. Events observed in the trials that preceded the need for amputation included lower limb infections, gangrene, diabetic foot ulcers, and ischemia.

The original labeling for canagliflozin included a Boxed Warning, which was later removed in August 2020. Although risk remains, incidence in new clinical data has demonstrated risk may have been overstated while further clinical benefits continue to be discovered. 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 canagliflozin for infections or ulcers of the lower limbs and discontinue if these occur. Instruct patients to notify their health care professionals right away if they notice any new pain or tenderness, sores or ulcers, or infections in their legs or feet.

It is not known whether the increased risk extends to other SGLT2 inhibitors such as empagliflozin. While an increase in lower extremity amputations has not been reported for empagliflozin, additional study is needed to assess if amputations are a class effect or limited to canagliflozin.

• **Increase in low-density lipoprotein (LDL-C)**: Dose-related increases in LDL-C occur. Monitor LDL-C and treat per standard of care.

• **Increase in hematocrit**: SGLT2 inhibitors may cause an increase in hematocrit resulting from intravascular volume contraction. The available evidence shows no increase in thromboembolic events.

• **Pregnancy Category C**: In rat studies, SGLT2 inhibitors may affect renal development and maturation. The timing of these effects corresponds to 2nd and 3rd trimester of human development; therefore, consider alternate therapy during pregnancy especially during the 2nd and 3rd trimester.

• **Lactation**: The SGLT2 inhibitors are secreted in milk of lactating rats. It is not known if they are excreted in human milk. Data in juvenile rats showed risk to the developing kidney during maturation. In humans, kidney maturation occurs in utero and in the first 2 years of life. Because of the potential for serious adverse reactions to the nursing infant, a decision should be made to discontinue the SGLT2 inhibitor or nursing taking into account the importance of the drug to the mother.

• **Empagliflozin dose-response effect**: There appears to be little difference in efficacy between the 10mg and 25mg dose. The difference in mean A1C reduction between the two doses is generally <0.2%. In the EMPA-REG trial the number needed to treat during a 3-year period to prevent 1 death was 41 (10mg) and 38 (25mg).