What is the prevalence of amputation for the SGLT2 inhibitors?

Background

Sodium-glucose co-transporter-2 (SGLT2) inhibitors represent 1 of 9 classes of oral medications approved for the treatment of type 2 diabetes (T2D).[1] These agents lower blood glucose by inhibiting reabsorption of glucose in the proximal renal tubule and promoting glucosuria, and they are associated with reductions in glycosylated hemoglobin (HbA1c) of approximately 0.5 to 1.0%. In their 2018 consensus statement on the management of T2D, the American Association of Clinical Endocrinologists (AACE) recognizes SGLT2 inhibitors as acceptable alternatives to metformin as initial therapy in patients with recent onset T2D or mild hyperglycemia (HbA1c <7.5%).[2] In their 2018 Standards of Medical Care in Diabetes, the American Diabetes Association (ADA) states that SGLT2 inhibitors are potential agents for addition to metformin in selected patients with uncontrolled HbA1c.[3]

At this time, 4 SGLT2 inhibitors are commercially available in the United States: canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin.[4] In addition to reductions in HbA1c, the SGLT2 inhibitors, as a class, have been associated with weight loss and decreased systolic blood pressure.[2] Empagliflozin and canagliflozin have also been associated with improvement in cardiovascular outcomes: empagliflozin was found to reduce the risk of all-cause and cardiovascular mortality and hospitalization for heart failure, and canagliflozin was found to reduce the risk of a composite of cardiovascular death, myocardial infarction, or nonfatal stroke. In addition to beneficial effects, several adverse effects have been reported with these agents. SGLT2 inhibitors, as a class, have been associated with increased risk of mycotic genital infections, slight increases in low-density lipoprotein cholesterol (LDL-C), and dehydration leading to renal impairment, hypotension, and syncope. Diabetic ketoacidosis has also been reported in association with these agents. Most recently, cases of Fournier's gangrene, or necrotizing fasciitis of the perineum, have been reported in patients using SGLT2 inhibitors.[5]

In May 2017, the Food and Drug Administration (FDA) issued a drug safety communication announcing confirmation of an increased risk of leg and foot amputations with canagliflozin.[6] The FDA reviewed data from 2 clinical trials: the Canagliflozin Cardiovascular Assessment Study (CANVAS) and the Study of the Effects of Canagliflozin on Renal Endpoints in Adult Participants with Type 2 Diabetes Mellitus (CANVAS-R). Based on their review, the FDA stated that a boxed warning would be added to the labels for canagliflozin-containing products describing this risk. A boxed warning to this effect was added to canagliflozin product labels in July 2017.[7,8] Notably, there is no mention of the risk of amputations in the prescribing information for dapagliflozin or empagliflozin.[9,10] The labels for ertugliflozin-containing products[11-13] include warnings for lower limb amputation, which the manufacturer based on observations from clinical trials of another SGLT2 inhibitor. The manufacturer further states that across 7 phase III trials for ertugliflozin, non-traumatic lower limb amputations were reported in 3 patients receiving 5 mg/day (0.2%), 8 patients receiving 15 mg/day (0.5%), and 1 patient in the control group (0.1%).

From a search of the literature, several studies were identified that evaluated the risk of amputation with SGLT2 inhibitors. These studies, as well as the findings of CANVAS and CANVAS-R, are described below.

CANVAS and CANVAS-R

CANVAS and CANVAS-R were randomized controlled trials sponsored by Janssen, the manufacturer of canagliflozin, and were intended to be assessed jointly in an integrated analysis known as the CANVAS Program.[14] The purpose of the trials was to determine the effects of canagliflozin on cardiovascular, kidney, and safety outcomes. The inclusion criteria for CANVAS and CANVAS-R were identical: both involved participants aged ≥30 years with T2D and HbA1c between 7.0% and 10.5%. Participants were also included if they had a history of symptomatic atherosclerotic cardiovascular disease, or were aged ≥50 years with 2 or more risk factors for cardiovascular disease, and all were required to have an estimated glomerular filtration rate (eGFR) >30 mL/min/1.73 m^2. In CANVAS, patients were randomized in a 1:1:1 ratio

to receive canagliflozin 300 mg/day, canagliflozin 100 mg/day, or placebo. In CANVAS-R, patients were randomized in a 1:1 ratio to receive canagliflozin at an initial dose of 100 mg/day, with an option to increase to 300 mg/day at week 13, or placebo. The primary outcome of both trials was a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke.

In total, there were 10,142 participants: 4330 in CANVAS and 5812 in CANVAS-R.[14] Approximately 96.0% (n=9734) completed the trials. The mean follow-up period was 188.2 weeks with a longer period in CANVAS (295.9 weeks) compared to CANVAS-R (108.0 weeks). Baseline characteristics were similar between treatment and placebo groups in both trials. (Most patients in CANVAS-R [71.4%] had their canagliflozin doses increased to 300 mg/day). The mean age of participants was 63.3 years, and 35.8% were female; 65.6% had a history of cardiovascular disease. With regard to the primary outcome, significantly fewer events were reported in patients receiving canagliflozin vs. placebo (26.9 vs. 31.5 participants with an event per 1000 patient-years; hazard ratio [HR] 0.86, 95% confidence interval [CI] 0.75 to 0.97). In terms of renal outcomes, findings were also favorable for canagliflozin. With regard to safety, serious adverse events occurred less frequently among patients receiving canagliflozin vs. placebo (104.3 vs. 120.0 participants per 1000 patient-years; HR 0.93, 95% CI 0.87 to 1.00); however, **there was a significantly higher risk of amputation of the toes, feet, or legs with canagliflozin vs. placebo (6.3 vs. 3.4 participants with amputation per 1000 patient-years; HR 1.97, 95% CI 1.41 to 2.75**). The highest absolute risk of amputation was observed among patients with a history of amputation (96.30 vs. 59.16 participants per 1000 patient-years; HR 2.15, 95% CI 1.11 to 4.19) or peripheral vascular disease (12.09 vs. 8.16 participants per 1000 patient-years; HR 1.39, 95% CI 0.80 to 2.40).[15]

The investigators concluded that patients with T2D and an elevated risk of cardiovascular disease had a lower risk of cardiovascular events when treated with canagliflozin vs. placebo; however, those treated with canagliflozin were also at a greater risk of lower limb amputation.[14] Neal et al asserted that the adverse effects reported in the CANVAS program were generally consistent with the known safety profile of canagliflozin and other SGLT2 inhibitor, but they noted that the increased risk of amputation was a new finding, for which the mechanism was unknown. They advised using caution when considering canagliflozin in patients at risk for amputation.

Additional literature – interventional studies

In addition to the CANVAS and CANVAS-R trials, clinical trials have been conducted evaluating the effects of other SGLT2 inhibitors. Jabbour et al conducted a pooled analysis of data from phase IIb and phase III clinical trials to evaluate the safety and tolerability of dapagliflozin.[16] The outcomes of interest included overall adverse events, serious adverse events, and specific adverse events, including lower limb amputation. Thirteen trials were included in the primary analysis: 3 phase IIb studies of 12 weeks' duration and 10 phase III studies of 24 weeks' duration. All of these trials were double-blind and randomized; patients received either dapagliflozin 10 mg/day (n=2360) or placebo (n=2295). A larger, longer-term pool of 30 placebo- or active comparator-controlled trials was used to assess lower limb amputation. The doses of dapagliflozin administered in the latter group of trials ranged from 2.5 to 50 mg/day, but the most frequently used doses were 5 and 10 mg/day.

In terms of overall adverse events, 60.0% of the dapagliflozin groups (1416/2360) and 55.7% of the placebo groups (1279/2295) reported experiencing at least 1 adverse event.[16] Most of these events were not deemed serious. Occurrence of at least 1 serious adverse event was reported by 5.1% of the dapagliflozin groups (120/2360) and 5.4% of the placebo groups (123/2295). **Lower limb amputation was rare and reported at similar rates between groups: 0.1% in the dapagliflozin group (8/9195) and 0.2% in the comparator groups (7/4629)**. Jabbour et al stated that there were no apparent between-group differences in the baseline characteristics of the patients who had an amputation; patients who had an amputation had a high prevalence of risk factors for amputation, including neuropathy, cardiovascular disease, dyslipidemia, and nephropathy. Time to amputation was also reportedly similar between groups. Jabbour et al reported that the time to onset was >150 days after initiation of treatment in 5 of the 8 patients who received dapagliflozin.

Jabbour et al concluded that the overall incidence of adverse events and serious adverse events was similar between dapagliflozin and placebo in phase IIb and III trials. As for amputations, the authors commented that a low frequency was observed in both dapagliflozin- and comparator-treated patients, but they also stated that the occurrence was too low to draw conclusions based on differences observed in baseline characteristics.

In another publication, Kohler et al conducted a pooled analysis of data from phase I through III trials to evaluate the safety and tolerability of empagliflozin in patients with T2D.[17] They assessed the occurrence of adverse events, including serious adverse events and specific events, including amputations. Data were pooled from 15 trials, ranging in duration from 8 days to 78 weeks, and 4 extension studies (52-week extensions to phase III trials). In all trials, patients were randomized to receive empagliflozin 10 mg/day (n=4221) or 25 mg/day (n=4196) or placebo (n=4203).

Overall, the incidences of adverse events and serious adverse events were higher in the placebo group than the empagliflozin groups.[17] Approximately 82.1% of patients in the placebo group (3449/4203) reported at least 1 adverse event (195.4 per 100 patient-years), compared to 80.6% of patients in the empagliflozin 10 mg/day group (3401/4221; 167.2 per 100 patient-years) and 80.6% of patients in the empagliflozin 25 mg/day group (3383/4196; 163.6 per 100 patient-years). Approximately 27.4% of patients in the placebo group (1150/4203) reported at least 1 serious adverse event (19.2 per 100 patient-years), compared to 24.2% of patients in the empagliflozin 10 mg/day group (1020/4221; 15.5 per 100 patient-years) and 25.1% of patients in the empagliflozin 25 mg/day group (1052/4196; 16.5 per 100 patient-years). Data on the frequency of lower limb amputations were manually reviewed by Kohler et al and included a review of pooled safety data and adverse event narratives. **The occurrence of lower limb amputations was 1.1% in all treatment groups (placebo: 46/4203; empagliflozin 10 mg/day: 46/4221; empagliflozin 25 mg/day: 48/4196)**. In total, there were 140 cases of lower limb amputations; 131 of these occurred in the EMPA-REG OUTCOME trial. While the proportions of patients receiving amputations were similar between empagliflozin and placebo in that trial, in both groups, the investigators noted that the risk of amputation was higher in patients with moderate renal impairment (eGFR 30 to <60 mL/min/1.73 m2) compared to those with no or mild renal impairment, and in patients with a history of peripheral artery disease, microvascular disease, or diabetic foot syndrome.

Kohler et al concluded that these findings were supportive of a favorable benefit-risk profile for empagliflozin compared to placebo in patients with T2D.[17] With regard to the risk of lower limb amputations, they found no evidence to suggest an increased risk with use of empagliflozin; however, they stated that their findings should be interpreted with caution due to the fact that the data were manually retrieved and concerns about validation.

In addition to these pooled analyses, a meta-analysis of randomized controlled trials was identified in which Li et al assessed the potential risks of diabetic foot syndrome and amputation associated with SGLT2 inhibitors.[18] Li et al identified randomized controlled trials of SGLT2 inhibitors evaluating the risk of diabetic foot syndrome and amputation that were published through June 14, 2017, and performed a random effects model to estimate odds ratios (ORs) and 95% CIs. They included 14 trials involving a total of 26,167 patients. The mean age ranged from 54.5 to 68.5 years, and the mean HbA1c ranged from 7.8% to 8.3%. The follow-up duration ranged from 52 weeks to 188.2 weeks – the longest follow-up period was for the CANVAS and CANVAS-R trials. Seven of the trials (n=19,781) reported any occurrence of amputations. No data were available to assess the amputation risk with dapagliflozin. **As a class, SGLT2 inhibitors were associated with an increased risk of amputation, but this was not statistically significant (OR 1.40, 95% CI 0.81 to 2.41). However, a subgroup analysis revealed a significant increase in the risk of amputation with canagliflozin compared to other oral antidiabetic drugs or placebo (OR 1.89, 95% CI 1.37 to 2.60)**. A separate analysis of empagliflozin revealed no significant difference in risk of amputation compared to other oral antidiabetic drugs or placebo (OR 1.02, 95% CI 0.71 to 1.48). Of the 14 trials, 12 (n=16,025) described the occurrence of diabetic foot syndrome. SGLT2 inhibitors were not associated with an increased risk of diabetic foot syndrome compared to placebo (OR 1.05, 95% CI 0.58 to 1.89). Li et al concluded that canagliflozin may be associated with an increased risk of amputation, but additional data are needed to conclude whether there is an association between amputation and the individual SGLT2 inhibitors.

Notably, at the time of this writing, no studies were identified evaluating the risk of amputations with ertugliflozin. However, as noted by the manufacturer in the prescribing information, amputations were reported in 12 patients across 7 phase III trials, 11 who received ertugliflozin and 1 who received the comparator treatment.[11-13]

Observational studies

In addition to the aforementioned studies, several observational studies were found in which investigators assessed the risk of amputations with SGLT2 inhibitors. Ryan et al conducted a meta-analysis of observational databases to compare the effectiveness of canagliflozin, SGLT2 inhibitors, and non-SGLT2 inhibitors on the risk of hospitalization for heart failure and amputation in patients with T2D.[19] They obtained data from 4 large administrative claims databases in the United States and conducted comparative analyses using a propensity score-adjusted new user-cohort design to determine the relative hazards of outcomes across new users of these drugs and in patients with established cardiovascular disease. Across the 4 databases, Ryan et al identified 142,800 new users of canagliflozin, 110,897 new users of other SGLT2 inhibitors (dapagliflozin and empagliflozin), and 460,885 new users of non-SGLT2 inhibitors. **In terms of amputations, the incidence among new users of canagliflozin ranged from 1.0 to 5.0 events per 1000 person-years in the on-treatment analysis. In comparison, the incidence of amputations ranged from 1.1 to 2.4 events per 1000 person-years among new users of dapagliflozin or empagliflozin, and 1.5 to 4.1 per 1000 person-years among new users of non-SGLT2 inhibitors**. When evaluating time to amputation, there were no statistically significant differences in hazards for new users of canagliflozin compared to new users of non-SGLT2 inhibitors (HR 0.75, 95% CI 0.40 to 1.41). No significant differences were observed when comparing new users of canagliflozin to new users of dapagliflozin or empagliflozin (HR 1.14, 95% CI 0.67 to 1.93). With regard to hospitalization for heart failure, the risk was found to be significantly lower with canagliflozin compared to other non-SGLT2 inhibitors (HR 0.39, 95% CI 0.26 to 0.60). In the subpopulation of patients with established cardiovascular disease, the incidences of amputation and hospitalization for heart failure were approximately double those of the overall new user cohorts.

Multiple cohort studies were identified which assessed the risk of amputations with SGLT2 inhibitors.[20-23] These studies are outlined in Table 1. All 4 studies were retrospective analyses of data from Truven MarketScan, a large administrative health claims database for members insured by employer-sponsored plans in the United States, and data were collected over similar time periods. SGLT2 inhibitors were compared to other classes of antidiabetic drugs, including dipeptidyl peptidase-4 (DPP4) inhibitors, glucagon-like peptide-1 (GLP-1) agonists, and older agents. In most of these studies, no significant differences were observed between SGLT2 inhibitors and comparators in the risk of amputation. However, Chang et al determined that there was a significant increase in risk of amputations with SGLT2 inhibitors compared to older agents, including sulfonylureas, thiazolidinediones, and metformin (adjusted HR 2.12, 95% CI 1.19 to 3.77). Notably, the follow-up periods for all of these studies were limited, ranging from 99 days to 1 year. All investigators commented on the need for larger studies with longer durations of follow-up to conclude the risk of amputation associated with use of SGLT2 inhibitors.

Table 1. Selected cohort studies evaluating risk of amputations associated with use of SGLT2 inhibitors.

Reference	Population/ data source	Exposures[a]	Incidence of amputations	Additional data
Yuan 2018[20]	Adult patients with T2D, exposure propensity score-matched. Mean age: 53 y; ~55% male; ~8% with peripheral vascular disease, 3% with renal impairment, 1% with congestive heart failure Truven MarketScan database April 1, 2013 – October 31, 2016	New exposure to: SGLT2 inhibitors (n=119,567) Non-SGLT2 inhibitor AHAs (n=226,623) Median duration of therapy: 0.33-0.43 y	Crude incidence (per 1000 person-years): SGLT2 inhibitors: 1.22 • Canagliflozin: 1.26 • Dapagliflozin: 0.96 • Empagliflozin: 1.39 Non-SGLT2 inhibitors: 1.87	Crude incidence of amputation (per 1000 person-years) in patients with established CV disease: SGLT2 inhibitors: 2.03 • Canagliflozin: 1.99 • Dapagliflozin: 1.28 • Empagliflozin: 3.42 Non-SGLT2 inhibitors: 3.29
Adimadhyam 2018[21]	Adult patients with T2D, propensity score-matched. Mean age: 54.7 y; 47.6% female; 4.5% with peripheral vascular disease, 13.3% with CV disease Truven MarketScan database April 1, 2013 – March 31, 2015	New exposure to: SGLT2 inhibitors (n=30,216) DPP4 inhibitors (n=30,216) Median follow-up: 0.6 y	SGLT2 inhibitors: 36 amputations Incidence: 1.62 per 1000 person-years Non-SGLT2 inhibitors: 24 amputations Incidence: 1.15 per 1000 person-years SGLT2 vs. DPP4: HR 1.38, 95% CI 0.83-2.31	Overall incidence of amputations was higher in groups at higher risk for amputations (aged >65 y, peripheral vascular disease at baseline, ≥1 vascular complication of diabetes at baseline) Risk of amputation was higher with dapagliflozin or empagliflozin vs. canagliflozin • Dapagliflozin/ empagliflozin: HR 2.25, 95% CI 0.78-6.47 • Canagliflozin: HR 1.15, 95% CI 0.64-2.07
Chang 2018[22]	Adult patients with T2D; significant differences in baseline characteristics. Mean age: 51.4-54.5 y; female: 43.3%-61.0%; congestive heart failure: 3.8%-4.9%; hypertension: 39.7%-59.8% Truven MarketScan database September 1, 2012 – September 30, 2015	New exposure to: Newer antidiabetic agents- SGLT2 inhibitors (n=39,869) DPP4 inhibitors (n=105,023) GLP-1 agonists (n=39,120) Older antidiabetic agents (SUs, metformin, or TZDs); n=769,894 Median observation time: 99-127 days	Number of amputations: • SGLT2 inhibitors: 18 • DPP4 inhibitors: 41 • GLP-1 agonists: 11 • Other agents: 231 Incidence (per 10,000 person-years): • SGLT2 inhibitors: 10.53 • DPP4 inhibitors: 8.52 • GLP-1 agonists: 7.10 • Other agents: 4.90	Adjusted HRs (95% CIs) for amputation were calculated, comparing SGLT2 inhibitors to the other classes: • DPP4 inhibitors: 1.50 (0.85-2.67) • GLP-1 agonists: 1.47 (0.64-3.36) • Other agents: 2.12 (1.19-3.77)

Reference	Population/ data source	Exposures[a]	Incidence of amputations	Additional data
Dawwas 2018[23]	Adult patients with T2D; propensity-matched. Mean age: 54 y; ~53% male; ~12% with ischemic heart disease, 3% with chronic kidney disease Truven MarketScan database January 2013 – December 2015	New exposure to: SGLT2 inhibitors (n=147,352) SUs (n=624,069) DPP4 inhibitors (n=300,607) Mean follow-up: 12 months	Crude incidence (per 1000 person-years): • SGLT2 vs. SU: 1.5 vs. 1.9 • SGLT2 vs. DPP4: 1.8 vs. 1.9	Comparative risk of amputation – HR (95% CI): • SGLT2 vs. SU: 0.74 (0.57-0.96) • SGLT2 vs. DPP4: 0.88 (0.65-1.15)

[a]SGLT2 inhibitors included canagliflozin, dapagliflozin, and empagliflozin.
AHAs=antihyperglycemic agents; CI=confidence interval; CV=cardiovascular; DPP4=dipeptidyl peptidase-4; GLP-1=glucagon-like peptide-1; HR=hazard ratio; SGLT2=sodium glucose co-transporter 2; SUs=sulfonylureas; T2D=type 2 diabetes; TZDs=thiazolidinediones; y=years.

Surveillance data

Two pharmacovigilance studies were identified in which investigators reviewed adverse events databases for reports of amputations associated with SGLT2 inhibitors.[24,25] Fadini and Avogaro reviewed the FDA Adverse Event Reporting System (FAERS) from its inception to March 31, 2017, and identified 66 reports of SGLT2 inhibitor-associated amputations.[24] Patients were aged ~60 years, and most were male. The average treatment duration was 1.5 years. Approximately 11% of patients had a diabetic foot wound, and 36% of cases involved at least 1 feature of diabetic foot syndrome. Most reports (86%, n=57) listed canagliflozin as the suspected/offending agent, and the frequency was 3.4 per 1000 reports. The frequency of reports implicating canagliflozin was significantly higher than those filed for non-SGLT2 inhibitors (proportional reporting ratio [PRR] 5.33, 95% CI 4.04 to 7.04). In comparison, reports involving dapagliflozin and empagliflozin were lower (dapagliflozin PRR 0.25, 95% CI 0.03 to 1.76; empagliflozin PRR 2.37, 95% CI 0.99 to 5.70).

Khouri et al reviewed VigiBase, the World Health Organization (WHO) global database of individual case safety reports, between January 2013 and December 2017 and identified 79 reports of lower limb amputations associated with SGLT2 inhibitors.[25] Among all of the antidiabetic agents, the PRR was increased only for SGLT2 inhibitors (5.55, 95% CI 4.23 to 7.29). Among the SGLT2 inhibitors, the PRR was increased for canagliflozin (7.09, 95% CI 5.25 to 9.57) and empagliflozin (4.96, 95% CI 2.89 to 8.50). Toe amputations, specifically, were reported at an increased rate for dapagliflozin (PRR 2.62, 95% CI 1.33 to 5.14).

Several limitations should be noted for these studies.[24,25] Like the previously described observational studies, these studies do not demonstrate a causal link between exposure to SGLT2 inhibitors and amputations. Additionally, FAERS and VigiBase are based on voluntary or spontaneous reporting and the records are often incomplete. Pharmacovigilance studies are also subject to biases affecting measures of disproportionality – e.g., time since marketing, media safety alerts, or selective notifications. PRRs are, therefore, not necessarily representative of the true risk of adverse events in clinical practice.

Conclusion

In summary, SGLT2 inhibitors may be associated with an increased risk of lower limb amputation. The first warnings of this risk were announced by the FDA, based on their review of the CANVAS and CANVAS-R trials, and were specific to canagliflozin.[6] There is a boxed warning describing the risk of lower limb amputations on the labels for canagliflozin-containing products.[7,8] However, there is no mention of amputation risk in the labels for dapagliflozin and

empagliflozin.[9,10] The manufacturer of ertugliflozin includes reports of amputations observed in phase III trials in the warnings section of the product labels but states that the warnings are based on observations of another SGLT2 inhibitor (presumably, canagliflozin).[11-13]

From a search of the literature, several studies have been conducted evaluating the risk of amputations with SGLT2 inhibitors.[14-25] While the reported incidences vary, most suggest that amputations are rarely occurring. The most cogent data are from the CANVAS and CANVAS-R trials, which were of robust design and were longer in duration than most of the reviewed studies.[14] Pooled analyses of clinical trials involving dapagliflozin and empagliflozin suggest that there may not be an increased risk of amputations with these agents.[16,17] Few data are available for ertugliflozin, precluding any conclusions regarding its association with amputations. Observational data have also been published, with mixed findings.[19-25] Additional large, prospective studies, designed to assess the safety of the individual SGLT2 inhibitors, are warranted to determine the true risk of amputations associated with these agents.

References

1. Triplitt CL, Repas T, Alvarez C. Diabetes mellitus. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey L. eds. *Pharmacotherapy: A Pathophysiologic Approach.* 10th ed. New York, NY: McGraw-Hill; http://accesspharmacy.mhmedical.com.gate.lib.buffalo.edu/content.aspx?bookid=1861&sectionid=146065891. Accessed September 25, 2018.
2. Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm – 2018 executive summary. *Endocr Pract*. 2018;24(1):91-120.
3. American Diabetes Association. Pharmacologic approaches to glycemic treatment: Standards of Medical Care in Diabetes – 2018. *Diabetes Care*. 2018;41(Supplement 1):S73-S85.
4. Sodium-glucose co-transporter 2 inhibitors. In: Facts & Comparisons. St. Louis (MO): Wolters Kluwer Health. [updated 9/14/18; accessed 9/25/18]. http://hubnet.buffalo.edu:2053/lco/action/doc/retrieve/tc/5545822.
5. US Food and Drug Administration (FDA). FDA Drug Safety and Availability: FDA warns about rare occurrences of a serious infection of the genital area with SGLT2 inhibitors for diabetes. August 29, 2018. https://www.fda.gov/Drugs/DrugSafety/ucm617360.htm. Accessed October 8, 2018.
6. US Food and Drug Administration (FDA). FDA Drug Safety Communication: FDA confirms increased risk of leg and foot amputations with the diabetes medicine canagliflozin (Invokana, Invokamet, Invokamet XR). May 16, 2017. https://www.fda.gov/Drugs/DrugSafety/ucm557507.htm. Accessed September 25, 2018.
7. US Food and Drug Administration (FDA). Drug Safety Labeling Changes. Invokana. https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm?event=searchdetail.page&DrugNameID=71. Accessed September 25, 2018.
8. Invokana® [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; 2018.
9. Farxiga® [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2017.
10. Jardiance® [package insert]. Ridgefield, CT: Boehringer Ingelheim; 2017.
11. Steglatro® [package insert]. Whitehouse Station, NJ: Merck and Co., Inc.; 2017.
12. Segluromet® [package insert]. Whitehouse Station, NJ: Merck Sharp and Dohme Corp.; 2017.
13. Steglujan™ [package insert]. Whitehouse Station, NJ: Merck Sharp and Dohme Corp.; 2017.
14. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. 2017;377(7):644-657.
15. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. Supplementary appendix. Available at: https://www-nejm-org.gate.lib.buffalo.edu/doi/suppl/10.1056/NEJMoa1611925/suppl_file/nejmoa1611925_appendix.pdf. Accessed September 26, 2018.

16. Jabbour S, Seufert J, Scheen A, Bailey CJ, Karup C, Langkilde AM. Dapagliflozin in patients with type 2 diabetes mellitus: a pooled analysis of safety data from phase IIb/III clinical trials. *Diabetes Obes Metab*. 2018;20(3):620-628.
17. Kohler S, Zeller C, Iliev H, Kaspers S. Safety and tolerability of empagliflozin in patients with type 2 diabetes: pooled analysis of phase I-III clinical trials. *Adv Ther*. 2017;34(7):1707-1726.
18. Li D, Yang JY, Wang T, Shen S, Tang H. Risks of diabetic foot syndrome and amputation associated with sodium glucose co-transporter 2 inhibitors: a meta-analysis of randomized controlled trials. *Diabetes Metab*. 2018. doi: 10.1016/j.diabet.2018.02.001. Epub ahead of print.
19. Ryan PB, Buse JB, Schuemie MJ, et al. Comparative effectiveness of canagliflozin, SGLT2 inhibitors, and non-SGLT2 inhibitors on the risk of hospitalization for heart failure and amputation in patients with type 2 diabetes mellitus: a real-world meta-analysis of 4 observational databases (OBSERVE-4D). *Diabetes Obes Metab*. 2018. doi: 10.1111/dom.13424. Epub ahead of print.
20. Yuan Z, DeFalco FJ, Ryan PB, et al. Risk of lower extremity amputations in people with type 2 diabetes mellitus treated with sodium-glucose co-transporter-2 inhibitors in the USA: a retrospective cohort study. *Diabetes Obes Metab*. 2018;20(3):582-589.
21. Adimadhyam S, Lee TA, Calip GS, Smith Marsh DE, Layden BT, Schumock GT. Risk of amputations associated with SGLT2 inhibitors compared to DPP-4 inhibitors: a propensity-matched cohort study. *Diabetes Obes Metab*. 2018. Doi: 10.1111/dom.13459. Epub ahead of print.
22. Chang HY, Singh S, Mansour O, Baksh S, Alexander GC. Association between sodium-glucose contransporter 2 inhibitors and lower extremity amputation among patients with type 2 diabetes. *JAMA Intern Med*. 2018;178(9):1190-1198.
23. Dawwas GK, Smith SM, Park H. Cardiovascular outcomes of sodium glucose cotransporter-2 inhibitors in patients with type 2 diabetes. *Diabetes Obes Metab*. 2018. doi: 10.1111/dom.13477. Epub ahead of print.
24. Fadini GP, Avogaro A. SGLT2 inhibitors and amputations in the US FDA Adverse Event Reporting System. *Lancet Diabetes Endocrinol*. 2017;5(9):680-681.
25. Khouri C, Cracowski JL, Roustit M. SGLT-2 inhibitors and the risk of lower-limb amputation: is this a class effect? *Diabetes Obes Metab*. 2018;20(6):1531-1534.