REVIEW

Canagliflozin in the treatment of type 2 diabetes: an evidence-based review of its place in therapy

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Introduction: Deciding on an optimal medication choice for type 2 diabetes is often challenging, due to the increasing number of treatment options. Canagliflozin is a novel glucose-lowering agent belonging to sodium–glucose co-transporter 2 (SGLT2) inhibitors.

Aim: The aim of this study was to examine and summarize the evidence based on the efficacy, safety, and cost-effectiveness of canagliflozin for type 2 diabetes.

Evidence review: Compared to placebo, canagliflozin 100 and 300 mg lower glycated hemoglobin (HbA1c) by ~0.6%–0.8%, respectively. Canagliflozin appears to be slightly more effective than dipeptidyl peptidase-4 (DPP-4) inhibitors in reducing HbA1c. It also has a favorable effect on body weight and blood pressure, both versus placebo and most active comparators. However, treatment with canagliflozin is associated with increased incidence of genital tract infections and osmotic diuresis-related adverse events. Based on short-term data, canagliflozin is not associated with increased risk for all-cause mortality and cardiovascular outcomes. Economic evaluation studies from various countries indicate that canagliflozin is a cost-effective option in dual- or triple-agent regimens.

Place in therapy: As monotherapy, canagliflozin could be used in patients for whom metformin is contraindicated or not tolerated. For patients on background treatment with metformin, canagliflozin appears to be superior to sulfonylureas with respect to body weight, blood pressure and risk for hypoglycemia, and to DPP-4 inhibitors in terms of lowering HbA1c, body weight, and blood pressure. Canagliflozin also seems to be cost-effective compared with sulfonylureas and DPP-4 inhibitors as add-on to metformin monotherapy, and compared with DPP-4 inhibitors as add-on to metformin and sulfonylurea.

Conclusion: Current evidence on intermediate efficacy outcomes, short-term safety and cost-effectiveness support the use of canagliflozin in patients on background treatment with metformin. Robust long-term data regarding the effect of canagliflozin on cardiovascular endpoints will be available upon completion of the Canagliflozin Cardiovascular Assessment Study (CANVAS) trial.

Keywords: canagliflozin, type 2 diabetes mellitus, evidence-based review, efficacy, safety, cost-effectiveness, tolerability, cardiovascular outcomes

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Core evidence clinical impact summary for canagliflozin

Outcome measure	Evidence	Implications
Disease-oriented evidence		
Glycemic efficacy versus placebo	Clear (pair-wise meta-analyses of randomized controlled trials [RCTs])	Canagliflozin 100 and 300 mg once daily reduce HbA1c by 0.6%–0.8%, respectively
		(Continued)

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Outcome measure	Evidence	Implications
Glycemic efficacy versus other antidiabetic agents	Clear versus sitagliptin (pair-wise meta-analyses of RCTs) Substantial versus other comparators (network meta-analyses of RCTs)	Canagliflozin 300 mg reduces HbA1c by 0.2% compared with sitagliptin 100 mg Canagliflozin may be slightly more effective in reducing HbA1c compared with other SGLT2 inhibitors, linagliptin, and saxagliptin, and appears to be of similar efficacy with sulfonylureas, pioglitazone, and glucagon-like peptide-1 receptor agonists (GLP-1 RA)
Reduction in body weight	Clear versus placebo and sitagliptin (pair-wise meta-analyses of RCTs) Substantial versus other comparators (network meta-analyses of RCTs)	Canagliflozin 100 and 300 mg confer reductions of 2 and 2.8 kg in body weight compared with placebo, respectively Canagliflozin seems to be more effective in reducing body weight compared with DPP-4 inhibitors
Reduction in arterial blood pressure	Clear versus placebo and sitagliptin (pair-wise meta-analyses of RCTs) Substantial versus other comparators (network meta-analyses of RCTs)	Compared with placebo, canagliflozin 100 and 300 mg reduce systolic blood pressure by 4.2 and 5.4 mmHg, respectively Canagliflozin reduces systolic blood pressure by 4 mmHg compared with sitagliptin Canagliflozin is superior to sulfonylureas and saxagliptin, and similar to pioglitazone, linagliptin, vildagliptin, and GLP-1 RA in terms of systolic blood pressure reduction
Patient-oriented evidence		
Hypoglycemia	Clear versus placebo and sitagliptin (pair-wise meta-analyses of RCTs) Substantial versus other comparators (network meta-analyses of RCTs)	Canagliflozin is associated with an increased risk for hypoglycemia compared with placebo (odds ratio ranging between 1.5 and 1.6) and is similar to sitagliptin Risk for hypoglycemia with canagliflozin seems to be lower compared with sulfonylureas, and similar to other DPP-4 inhibitors and GLP-1 RA
Urinary and genital tract infections	Clear (pair-wise and network meta-analyses of RCTs)	Incidence of urinary tract infections does not significantly differ between canagliflozin and placebo Incidence of genital infections is higher with canagliflozin compared with placebo (odds ratio ranging between 4.9 and 5.2) and compared with active control (excluding other SGLT2 inhibitors)
Intravascular volume reduction and osmotic diuresis	Substantial (pooled analyses of RCTs)	Canagliflozin is associated with an increased incidence of adverse events related to osmotic diuresis compared with placebo
Cardiovascular outcomes	Moderate (meta-analyses of short-term RCTs)	Canagliflozin is not associated with increased risk for all-cause mortality and cardiovascular outcomes
Economic evidence		
Monotherapy	Substantial (mostly conference abstracts of cost-effectiveness studies)	In the UK, canagliflozin as monotherapy appears to be cost-effective versus DPP-4 inhibitors, but not versus sulfonylureas or pioglitazone
Dual therapy	Substantial (mostly conference abstracts of cost-effectiveness studies)	As add-on to metformin, canagliflozin is likely to be cost-effective compared to sitagliptin in the UK, Ireland, France, Belgium, Sweden, Norway, Spain, Portugal, Slovakia, and the Czech Republic In comparison to sulfonylureas, canagliflozin seems cost-effective in Ireland, Belgium, Sweden, Norway, Poland, and the Czech Republic
Triple therapy	Substantial (mostly conference abstracts of cost-effectiveness studies)	As add-on to metformin and sulfonylurea, canagliflozin is likely to be cost-effective compared with sitagliptin in the UK, Ireland, France, Belgium, Norway, Spain, Portugal, Slovakia, the Czech Republic, Canada, and Brazil

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Core Evidence 2017:12

Introduction

It is estimated that, worldwide, more than 284 million people have diabetes, and this number is expected to reach 440 million by 2030.[1] Type 2 diabetes accounts for more than 90% of these cases[1] and is associated with high mortality and morbidity, given that the risk for developing cardiovascular disease is twofold in diabetic patients.[2] Moreover, the costs associated with management of type 2 diabetes and its complications are increasing, conferring a large economic burden on a global scale.[3]

Most patients with type 2 diabetes will eventually require a combination of different medications, to achieve or maintain glycemic control.[4] However, deciding on an optimal treatment choice often poses a major challenge, especially after failure with metformin monotherapy, due to the constantly increasing number of available antidiabetic medications.[4–6]

Canagliflozin is a novel oral antidiabetic agent belonging to the class of sodium–glucose co-transporter 2 (SGLT2) inhibitors.[7] Canagliflozin inhibits glucose reabsorption in the proximal tubule, leading to increased urinary glucose excretion and subsequently to reduction in plasma glucose concentration, in individuals with hyperglycemia.[8] Canagliflozin at a daily dose of 100 or 300 mg has received approval both in the USA [9] and Europe[10] for use in patients with type 2 diabetes, while its current placement in treatment algorithms is in second or third line of therapy.[5,11–13] The objective of this review is to update and summarize the evidence base with respect to the efficacy, safety, and cost-effectiveness of canagliflozin for type 2 diabetes.

Methods

Information on clinical efficacy and safety was based on data from pertinent systematic reviews and meta-analyses of randomized controlled trials (RCTs). These were identified through PubMed, using free text terms and MeSH (Medical Subject Headings) terms for canagliflozin, combined with search filters for systematic reviews[14] and RCTs.[15] Pairwise meta-analyses reporting direct comparisons between canagliflozin and its comparators were primarily selected. If such data were not available, we used information from individual RCTs or network meta-analyses. Economic evaluation evidence was retrieved from cost-effectiveness studies that compared canagliflozin with other antidiabetic agents and reported incremental cost-effectiveness ratio (ICER) values per quality-adjusted life year (QALY) gained. Such studies were identified through search of PubMed, using the keyword "canagliflozin" in combination with a search filter for economic studies.[16] In addition, we searched ISPOR (International Society for Pharmacoeconomics and Outcomes Research) Scientific Presentations Database[17] and the websites of the National Institute for Health and Care Excellence (NICE)[18] and the Canadian Agency for Drugs and Technologies in Health (CADTH).[19] All searches were run on 30 December 2016, while the study selection process, both for clinical and cost-effectiveness evidence, was conducted by one reviewer.

Clinical efficacy
Glycated hemoglobin

As monotherapy, canagliflozin 300 mg conferred a placebo-subtracted change in glycated hemoglobin (HbA1c) of −1.08% (95% confidence interval: −1.25, −0.90), based on data from two RCTs.[20] Similarly, a meta-analysis of studies assessing canagliflozin as add-on to metformin concluded that canagliflozin 100 and 300 mg reduced HbA1c by 0.59% (0.51, 0.67) and 0.74% (0.66, 0.82) compared with placebo.[21] Moreover, based on a meta-analysis of six placebo-controlled trials with a duration of at least 26 weeks, treatment with canagliflozin, either as monotherapy or add-on treatment, reduced HbA1c by 0.63% (0.49, 0.77) and 0.8% (0.62, 0.98) at a daily dose of 100 and 300 mg, respectively.[22] In addition, patients receiving canagliflozin were more likely to achieve the HbA1c target of <7% (risk ratio [RR] versus placebo 1.75% [1.54, 1.99] and 2.28% [1.91, 2.72] for canagliflozin 100 and 300 mg, respectively).[22]

Direct comparative evidence for canagliflozin versus other antidiabetic agents are available for metformin (one study),[23] glimepiride (one study),[24] and sitagliptin (three studies).[20] A 26-week RCT in drug-naïve patients demonstrated noninferiority of canagliflozin 100 and 300 mg, in terms of both HbA1c reduction and achievement of HbA1c <7%, compared with metformin.[23] In addition, in patients on background treatment with metformin, canagliflozin 300 mg provided durable glycemic improvements versus glimepiride over a period of 104 weeks (weighted mean difference [WMD] −0.18% [−0.29, −0.08]).[24] Furthermore, a meta-analysis of three RCTs showed that canagliflozin 300 mg significantly reduced HbA1c by 0.24% (0.09, 0.4) compared with sitagliptin 100 mg.[20]

Based on a network meta-analysis of SGLT2 inhibitors, canagliflozin 100 mg conferred greater HbA1c reductions compared with dapagliflozin 5 mg (−0.2% [−0.35, −0.05]) and empagliflozin 10 mg (−0.16% [−0.29, −0.03]), whereas canagliflozin 300 mg was more effective compared with all controls, including dapagliflozin 10 mg and empagliflozin 25 mg.[25] Conversely, in another network meta-analysis,

which assessed SGLT2 inhibitors as dual therapy, fewer patients achieved an HbA1c <7% with canagliflozin 100 mg compared with empagliflozin 10 and 25 mg, even though no significant differences were evident in terms of change in HbA1c from baseline.[26] When used as add-on to metformin monotherapy, a network meta-analysis combining data for both canagliflozin doses suggested that canagliflozin was more effective in reducing HbA1c than dapagliflozin, nateglinide, and saxagliptin and inferior to insulin glargine.[27] In a similar network meta-analysis of trials with patients on background treatment with metformin and sulfonylurea, canagliflozin led to greater reductions in HbA1c compared with empagliflozin, linagliptin, and sitagliptin and was of similar glycemic efficacy to dapagliflozin, thiazolidinediones, glucagon-like peptide-1 receptor agonists (GLP-1 RA), saxagliptin, vildagliptin, and insulin glargine.[28]

Fasting plasma glucose

Compared with placebo, fasting plasma glucose (FPG) was significantly reduced, both with canagliflozin 100 mg (−1.49 mmol/L [−1.68, −1.29]) and 300 mg (−1.8 mmol/L [−2.1, −10.49]), when administered as add-on to metformin.[21] Based on data from individual trials, canagliflozin 300 mg was more effective in reducing FPG compared with metformin (−0.5 mmol/L [−0.9, −0.1])[23] and glimepiride (−0.7 mmol/L [−0.9, −0.4]),[24] whereas canagliflozin 100 mg did not differ from metformin (−0.2 mmol/L [−0.6, 0.2]).[23] Moreover, a meta-analysis of two RCTs demonstrated a significant difference in FPG levels between canagliflozin 300 mg and sitagliptin 100 mg (−1.03 mmol/L [−1.29, −0.76]).[29] Regarding differences among individual SGLT2 inhibitors, canagliflozin 300 mg reduced FPG to a greater extent compared with dapagliflozin 5 and 10 mg and empagliflozin 10 and 25 mg, whereas canagliflozin 100 mg was superior to dapagliflozin 5 mg (−0.48 mmol/L [−0.83, −0.13]) and similar to all other comparators.[25]

Body weight

A meta-analysis of seven placebo-controlled trials demonstrated superiority of canagliflozin 300 mg with respect to body weight reduction (WMD −2.6 kg [−2.9, −2.3]).[30] This favorable effect was also evident in a meta-analysis of RCTs with a minimum duration of 24 weeks, which showed significant improvement in body weight versus placebo, both for canagliflozin 300 mg (−2.8 kg [−3.21, −2.39]) and 100 mg (−2 kg [−2.35, −1.65]).[25] Of note, based on data from six studies, the percent change from baseline in body weight versus placebo was −2.09% (−2.43, −1.75) and −2.66% (−3.18,

−2.14) for canagliflozin 100 and 300 mg, respectively.[21] In addition, in a pooled analysis of four placebo-controlled trials, 82–85% of patients treated with canagliflozin 100 and 300 mg, respectively, experienced weight loss, compared with 55% of placebo-treated patients.[31] Interestingly, each 1% reduction in weight loss was associated with a 0.045% reduction in HbA1c.[31] Approximately, 85% of the placebo-subtracted reductions in HbA1c were weight-loss independent, whereas 15% were weight-loss associated.[31]

Based on direct comparative evidence from head-to-head RCTs and a pair-wise meta-analysis, canagliflozin 300 mg was associated with significant reductions in body weight relative to metformin (−1.08 kg [−2.6, −1.1]),[23] glimepiride (−5.2% [−5.7, −4.6]),[24] and sitagliptin (−2.84 kg [−3.21, −2.48]).[20] With regard to canagliflozin 100 mg, results were similar versus glimepiride (−5.1% [−5.6, −4.5])[24] but less profound in comparison to metformin (−0.9 kg [−1.6, −0.2]).[23] Indirect data from a network meta-analysis of SGLT2 inhibitors suggest that canagliflozin 300 mg leads to greater weight reduction in comparison to dapagliflozin 5 mg (−0.89 kg [−1.43, −0.35]), whereas canagliflozin 100 mg does not seem to differ from other SGLT2 inhibitors.[25] Furthermore, in a network meta-analysis of various antidiabetic medications as add-on to metformin, canagliflozin was associated with a favorable effect on body weight compared with sulfonylureas, pioglitazone, insulin glargine, and individual dipeptidyl peptidase-4 (DPP-4) inhibitors, including linagliptin, saxagliptin, sitagliptin, and vildagliptin.[27] Of note, this meta-analysis combined data both for canagliflozin 100 and 300 mg, thus did not provide results for each dosing scheme separately.

Arterial blood pressure

Canagliflozin 100 mg reduced systolic blood pressure (SBP) and diastolic blood pressure (DBP) by 4.25 mmHg (3.21, 5.31) and 1.76 mmHg (0.96, 2.56), respectively, based on a meta-analysis of placebo-controlled trials.[22] In a similar manner, canagliflozin 300 mg was associated with a decrease of 5.4 mmHg (4.0, 6.8) in SBP and 2.1 mmHg (1.5, 2.8) in DBP, in comparison to placebo.[30] Notably, this blood pressure lowering effect seems to be enhanced in patients with baseline SBP ≥140 mmHg, as shown in a pooled subgroup analysis of four placebo-controlled studies.[32]

When compared with sitagliptin, a pair-wise meta-analysis of three RCTs demonstrated that canagliflozin 300 mg provided higher reductions both in SBP (WMD −4.09 mmHg [−5.29, −2.9]) and DBP (−2.06 mmHg [−2.82, −1.3]).[20] Moreover, a network meta-analysis concluded that

canagliflozin 300 mg reduced SBP to a greater extent than other SGLT2 inhibitors, whereas no differences were found for DBP and in comparisons of canagliflozin 100 mg with other SGLT2 inhibitors.[25] Finally, indirect comparisons suggest that canagliflozin is superior to glimepiride, glipizide, saxagliptin, and sitagliptin and similar to pioglitazone, linagliptin, vildagliptin, exenatide, and liraglutide, in terms of reducing SBP.[27]

Safety and tolerability

Hypoglycemia

An early pair-wise meta-analysis combining data from two studies on drug-naïve patients and one study on patients with background metformin therapy did not associate canagliflozin 300 mg with an increased hypoglycemic risk versus placebo (RR 1.13 [0.4, 3.2]).[20] However, incidence of any hypoglycemia was significantly higher, when canagliflozin was used as add-on to insulin or sulfonylurea (1.49 [1.14, 1.95], three studies).[20] Interestingly, more recent meta-analyses of placebo controlled-trials have associated canagliflozin with an increased risk for hypoglycemia, irrespective of background antidiabetic treatment (1.53 [1.15, 2.03], seven studies)[30] or as adjunct to metformin monotherapy (1.65 [1.02, 2.65], four studies).[21] Similarly, results from a network meta-analysis indicate that patients treated with canagliflozin 100 or 300 mg had more hypoglycemic episodes in comparison to placebo, with respective odds ratios (ORs) of 1.5 (1.3, 1.8) and 1.6 (1.3, 1.9).[25]

Based on data from head-to-head trials, canagliflozin was associated with similar and higher hypoglycemic risk in comparison to metformin[23] and glimepiride,[24] respectively. When canagliflozin was compared with sitagliptin, no significant difference in any hypoglycemia was evident between the two groups (RR 1.29 [0.82, 2.03], three studies).[20] Among SGLT2 inhibitors, indirect evidence from a network meta-analysis suggested that both canagliflozin doses increased incidence of hypoglycemia compared with dapagliflozin 10 mg and empagliflozin 10 mg.[25] Furthermore, an additional network meta-analysis concluded that canagliflozin as add-on to metformin was associated with lower rates of confirmed hypoglycemia versus sulfonylureas, nateglinide, and insulin glargine, whereas no differences were found versus other SGLT2 inhibitors, DPP-4 inhibitors, pioglitazone, and GLP-1 RA.[27]

Urinary and genital tract infections

The safety of SGLT2 inhibitors regarding infections of the genital and urinary tracts has been explored in a comprehensive systematic review and network meta-analysis of 52 RCTs involving more than 36,000 patients with type 2 diabetes.[33] Based on pooled effect estimates from this study, treatment with canagliflozin 100 or 300 mg resulted in similar rates of urinary tract infections (UTIs), relative to placebo, other individual SGLT2 inhibitors, and other active treatments (including metformin, glimepiride, sitagliptin, saxagliptin, and linagliptin, analyzed as a single control group).[33] However, incidence of genital infections was higher for both doses of canagliflozin compared with placebo (OR 4.88 [3.59, 6.64] and 5.23 [3.87, 7.09] for canagliflozin 100 and 300 mg, respectively) and active control (excluding SGLT2 inhibitors).[33] Of note, both the neutral effect of canagliflozin on UTIs and its increased risk for genital infections were also evident in an additional network meta-analysis of 38 RCTs.[25] Furthermore, pooled analyses of both placebo- and active-controlled trials suggested that patients randomized to canagliflozin had a small increase in incidence of UTIs, with no increase in serious or upper UTIs[34], and a significantly higher rate of genital mycotic infections, most of which were mild to moderate in intensity and responded to standard treatments.[35]

Intravascular volume reduction and osmotic diuresis

SGLT2 inhibitors increase glucose excretion by inhibiting renal glucose reabsorption, thus treatment with canagliflozin can potentially result in intravascular volume reduction and osmotic diuresis.[32] In a pooled analysis of data from four RCTs, the incidence of adverse events related to intravascular volume depletion, with hypotension, postural dizziness, and orthostatic hypotension being the most common, did not differ between canagliflozin and placebo.[32] Notably, the mean duration of these adverse events was longer in patients receiving canagliflozin 300 mg compared with canagliflozin 100 mg and placebo. In addition, both doses of canagliflozin were associated with an increased incidence of osmotic diuresis-related adverse events, mainly pollakiuria, thirst, and polyuria, most of which occurred within the first 6 weeks of treatment.[32]

Diabetic ketoacidosis and bone fractures

Following a US Food and Drug Administration (FDA) alert in 2015 concerning a potential increase in the risk for ketoacidosis with SGLT2 inhibitors,[36] the drug manufacturer conducted an analysis of diabetic ketoacidosis and related adverse events (ketoacidosis, metabolic acidosis, and acidosis), based on data for more than 17,500 patients from completed and ongoing trials with canagliflozin, through

May 2015.[37] A total of 13 acidosis-related serious events occurred in 12 patients, with an incidence of 0.07%, 0.11%, and 0.03% for canagliflozin 100 and 300 mg and comparator, respectively. Notably, six of these patients were later reported to have autoimmune diabetes, or having tested positive for GAD65 antibodies, whereas eight patients had significant comorbid conditions. Nevertheless, this study concluded that currently available evidence does not allow any clear inferences associating a particular clinical phenotype with an increased risk for developing diabetic ketoacidosis.[37]

Safety concerns have also been recently raised due to reports of bone fractures in clinical trials with SGLT2 inhibitors.[38] However, a network meta-analysis concluded that canagliflozin was not associated with an increased bone fracture risk compared with placebo (RR 1.15 [0.71, 1.88]), dapagliflozin, empagliflozin, or other antidiabetic medications.[39]

Cardiovascular outcomes and mortality

In pair-wise meta-analyses of trials with a duration of at least 12 weeks, canagliflozin did not differ from control in terms of all-cause mortality [OR 0.8 (0.45, 1.42), seven studies], cardiovascular death (0.57 [0.26, 1.24], six studies), myocardial infarction (six studies), and stroke (eight studies), while results were similar in sensitivity analyses including only placebo-controlled trials.[40] Moreover, based on pooled estimates from a network meta-analysis, canagliflozin had a similar effect on all-cause mortality, heart failure, and a composite outcome of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke compared with placebo, empagliflozin, dapagliflozin, and other active comparators.[41]

International regulatory authorities both in Europe and the USA have issued guidance for the pharmaceutical industry, which includes specific pre- and post-marketing requirements related to cardiovascular risk evaluation of new antidiabetic medications.[42,43] On this account, dedicated cardiovascular studies have been completed or are ongoing for most novel agents for type 2 diabetes. Notably, with Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes trial (EMPA-REG OUTCOME) study is a recently published RCT that demonstrated superiority of empagliflozin over placebo on all-cause and cardiovascular mortality, in patients with type 2 diabetes and high cardiovascular risk.[44] Robust long-term cardiovascular evidence for canagliflozin will be available in the near future, after completion of the Canagliflozin Cardiovascular Assessment Study (CANVAS), a double-blind, randomized, placebo-controlled trial, evaluating the effect of canagliflozin on the composite endpoint of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke, in patients with inadequate glycemic control and at an elevated risk for cardiovascular disease.[45]

Special populations

Chronic kidney disease

In the USA, canagliflozin 100 mg once daily is indicated for patients with moderate renal impairment, with an estimated glomerular filtration rate (eGFR) of 45 to <60 mL/min/1.73 m^2.[46] In Europe, canagliflozin has not been approved for patients with an eGFR <60 mL/min/1.73 m^2; however, in patients already treated with canagliflozin whose eGFR falls below 60 but not <45 mL/min/1.73 m^2, the dose should be adjusted to 100 mg once daily.[47]

Given that the urinary glucose excretion effect of SGLT2 inhibitors can be attenuated in patients with impaired renal function, the efficacy and safety of canagliflozin have been assessed over 52 weeks in a placebo-controlled trial recruiting exclusively patients with an eGFR ≥30 and <50 mL/min/1.73 m^2.[48] Based on this study, canagliflozin 100 and 300 mg conferred placebo-subtracted reductions in HbA1c of 0.27% (−0.001, 0.53) and 0.41% (0.14, 0.68); thus, both doses significantly reduced body weight and blood pressure. In addition, incidence of osmotic diuresis-related adverse events was higher in patients randomized to either dose of canagliflozin, whereas volume reduction-related adverse events and UTIs were more common in the canagliflozin 300 mg group.[48]

Elderly patients

Current guidelines advocate an individualized approach when treating older patients with type 2 diabetes.[4,5] In a 104-week placebo-controlled trial in patients aged 55–80 years, canagliflozin 100 and 300 mg reduced HbA1c by 0.49 (0.32, 0.65) and 0.6 (0.44, 0.77), respectively.[49] Similarly, both doses were associated with reductions in body weight and in SBP and DBP. However, in comparison to placebo, rates of osmotic diuresis- and volume depletion-related adverse events were higher with canagliflozin 100 and 300 mg, whereas incidence of bone fractures was higher with canagliflozin 300 mg.[49]

The favorable effect of canagliflozin on HbA1c, body weight, and blood pressure was also evident in patients older than 75 years, based on a pooled analysis of data from six placebo-controlled trials.[50] In the same analysis, a numerically higher incidence of UTIs, genital infections, and volume depletion events was noted in the elderly population; however, all these adverse events were generally not considered serious.[50]

Cost-effectiveness

Monotherapy

When choosing among different therapeutic options for type 2 diabetes, cost, along with clinical effectiveness, is an important parameter that should also be considered. The cost-effectiveness of canagliflozin as monotherapy was assessed in a health technology assessment (HTA) conducted by NICE in the UK.[51] Based on this economic evaluation, canagliflozin, as well as dapagliflozin and empagliflozin, was not cost-effective in comparison to sulfonylureas or pioglitazone. However, when compared with DPP-4 inhibitors, ICER values per QALY gained were <£29,300 for all SGLT2 inhibitors. Therefore, the HTA concluded that canagliflozin, dapagliflozin, and empagliflozin represented a cost-effective use of the UK National Health Service (NHS) resources as monotherapy, in patients for whom metformin is contraindicated or not tolerated, only when sulfonylureas and pioglitazone are not considered appropriate treatment options.

Regarding comparisons among individual SGLT2 inhibitors, the cost-effectiveness evidence from the NICE assessment did not support any differences between canagliflozin and dapagliflozin or empagliflozin.[51] Conversely, based on a cost-effectiveness analysis funded by the manufacturer, canagliflozin 300 mg in drug-naïve patients dominated both dapagliflozin and empagliflozin, whereas canagliflozin 100 mg yielded an ICER of £208 versus empagliflozin 25 mg and dominated dapagliflozin 10 mg and empagliflozin 10 mg.[52]

Finally, in a cost-effectiveness study in Sweden, canagliflozin (100 and 300 mg weighted average 80:20) was associated with an ICER of €1838, when compared with sulfonylureas.[53]

Dual therapy

As add-on to metformin, canagliflozin, assessed as a weighted average of 100 and 300 mg, dominated sitagliptin 100 mg in cost-effectiveness analyses conducted in the Swedish,[53] Norwegian,[54] and Portuguese[55] setting. This was also the case for canagliflozin 100 mg, based on economic evaluations in Spain[56] and Poland,[57] whereas canagliflozin 300 mg produced an ICER of €1813[56] and 45,008 zł[57] compared with sitagliptin, respectively. Results from additional country-specific analyses versus sitagliptin also suggest that canagliflozin is likely to be a cost-effective option adjunct to metformin, in Ireland,[58] France,[59] Belgium,[60] Slovakia,[61] and the Czech Republic.[62] Moreover, a NICE HTA for canagliflozin concluded that, due to small differences in costs and QALYs between canagliflozin and DPP-4 inhibitors, both canagliflozin 100 and 300 mg were recommended treatment options in patients inadequately controlled with metformin alone.[63]

Evidence from economic evaluations across different health care systems, including Sweden, Norway, Poland, Belgium, Ireland, and the Czech Republic, suggest that canagliflozin as add-on to metformin is cost-effective, compared with sulfonylureas.[53,54,57,60,62,64] In a similar manner, dapagliflozin 10 mg was also dominated by canagliflozin in two economic evaluations in the USA and Spain, utilizing the Economic and Health Outcomes Model for type 2 diabetes mellitus (ECHO-T2DM)[65] and the IMS Core Diabetes Model[66], respectively. Finally, a cost-effectiveness study in Ireland concluded that canagliflozin represented good value for money compared with the GLP-1 RA liraglutide, as adjunctive treatment to metformin.[67]

Triple therapy

Cost-effectiveness analyses in Canada[68] and Spain[56] demonstrated that both canagliflozin doses dominated sitagliptin 100 mg as third-line therapy in patients already on metformin and sulfonylurea. In particular, from the Canadian health care perspective, canagliflozin 100 and 300 mg provided QALY gains of 0.28 and 0.31, and cost savings of C$2560 and C$2217, respectively, over a time horizon of 40 years.[68] Canagliflozin also dominated sitagliptin across different countries, including Belgium,[60] France,[59] Norway,[54] and Portugal,[55] when both dosing schemes were assessed as a single intervention. Of note, additional economic evaluations concluded that canagliflozin was a cost-effective therapeutic option as add-on to metformin and sulfonylurea in Brazil,[69] Ireland,[58] Slovakia,[61] and the Czech Republic,[62] although it was associated with higher treatment costs compared with sitagliptin. Similarly, based on a NICE HTA, canagliflozin 100 and 300 mg, in triple-therapy regimens, had been shown to have a cost-effective use of NHS resources in the UK, despite small differences in costs and QALY estimates between canagliflozin and DPP-4 inhibitors.[63]

Place in therapy and conclusions

Metformin remains the optimal first-line treatment choice, given its well-established efficacy and safety profile, low treatment cost, and beneficial effect on cardiovascular endpoints.[70] Canagliflozin could be used as an alternative to DPP-4 inhibitors or other SGLT2 inhibitors in drug-naïve patients for whom metformin is contraindicated or not tolerated, while economic evaluation data, at least in the UK, suggest that a sulfonylurea or pioglitazone is likely to be more cost-effective options in these patients.

For patients on background treatment with metformin, canagliflozin appears to be superior to sulfonylureas with respect to body weight, blood pressure, and risk for hypoglycemia, and to DPP-4 inhibitors in terms of lowering HbA1c, body weight, and blood pressure. Moreover, across different health care systems, canagliflozin seems to be cost-effective compared with sulfonylureas and DPP-4 inhibitors as add-on to metformin monotherapy, and to DPP-4 inhibitors in triple-agent regimens (adjunct to metformin and a sulfonylurea). With regard to its safety profile, canagliflozin is associated with a higher incidence of genital infections, whereas adverse events related to osmotic diuresis or volume depletion are also a concern, especially in the elderly or in patients with renal impairment.

These conclusions are in line with the recently published guidelines for type 2 diabetes, issued by the American College of Physicians (ACP), which place SGLT2 inhibitors, including canagliflozin, as a second-line treatment option, along with sulfonylureas, thiazolidinediones, and DPP-4 inhibitors.[13] In accordance with a patient-centered approach, also advocated by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) position statement,[4,5] the ACP recommendations highlight that clinicians and patients should select among different therapeutic options after thoroughly discussing their comparative benefits, adverse effects, and costs.[13]

One should keep in mind that the evidence base for canagliflozin is limited by the lack of sufficient direct comparative data from head-to-head studies versus other antidiabetic medications. In fact, head-to-head RCTs for canagliflozin are available only versus sitagliptin (three studies), glimepiride (one study), and metformin (one study); therefore, conclusions about its comparative effectiveness against other agents are mostly based on indirect evidence from network meta-analyses.

In addition, the long-term cardiovascular profile of canagliflozin remains uncertain, until the forthcoming CANVAS trial will provide robust data regarding its effect on mortality and cardiovascular endpoints.[45] This was also the case with empagliflozin, which has recently received FDA approval to reduce the risk for cardiovascular death in patients with type 2 diabetes and cardiovascular disease,[71] based on the results of the EMPA-REG OUTCOME study.[44] However, it is still unknown, whether the findings of these cardiovascular studies are applicable to patients with a shorter duration of type 2 diabetes and a lower cardiovascular risk.

Disclosure

References

1. Farag YM, Gaballa MR. Diabesity: an overview of a rising epidemic. *Nephrol Dial Transplant.* 2011;26(1):28–35.
2. Sarwar N, Gao P, Sarwar N, et al; Emerging Risk Factors Collaboration. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet.* 2010;375(9733):2215–2222.
3. Liebl A, Khunti K, Orozco-Beltran D, Yale JF. Health economic evaluation of type 2 diabetes mellitus: a clinical practice focused review. *Clin Med Insights Endocrinol Diabetes.* 2015;8:13–19.
4. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care.* 2012;35(6):1364–1379.
5. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care.* 2015;38:140–149.
6. Matthews DR, Tsapas A. Four decades of uncertainty: landmark trials in glycaemic control and cardiovascular outcome in type 2 diabetes. *Diab Vasc Dis Res.* 2008;5(3):216–218.
7. Rosenstock J, Aggarwal N, Polidori D, et al. Dose-ranging effects of canagliflozin, a sodium-glucose cotransporter 2 inhibitor, as add-on to metformin in subjects with type 2 diabetes. *Diabetes Care.* 2012;35(6):1232–1238.
8. Polidori D, Sha S, Ghosh A, Plum-Morschel L, Heise T, Rothenberg P. Validation of a novel method for determining the renal threshold for glucose excretion in untreated and canagliflozin-treated subjects with type 2 diabetes mellitus. *J Clin Endocrinol Metab.* 2013;98(5):E867–E871.
9. Food and Drug Administration. FDA approves Invokana to treat type 2 diabetes. Available from: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm345848.htm. Accessed December 30, 2016.
10. European Medicines Agency. Invokana (canagliflozin). Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002649/human_med_001707.jsp&mid=WC0b01ac058001d124. Accessed December 30, 2016.
11. National Institute for Health and Care Excellence (NICE). Type 2 diabetes in adults management [NG28]. Available from: https://www.nice.org.uk/guidance/ng28/chapter/1-Recommendations. Accessed December 30, 2016.
12. CD Association. Pharmacologic management of type 2 diabetes: 2016 interim update. *Can J Diabetes.* 2016;40(3):193–195.
13. Qaseem A, Barry MJ, Humphrey LL, Forciea M; Clinical Guidelines Committee of the American College of Physicians. Oral pharmacologic treatment of type 2 diabetes mellitus: a clinical practice guideline update from the American College of Physicians. *Ann Intern Med.* 2017;166(4):279–290.
14. Search strategy used to create the systematic reviews subset on PubMed. Available from: https://www.nlm.nih.gov/bsd/pubmed_subsets/sysreviews_strategy.html. Accessed December 30, 2016.
15. The Cochrane highly sensitive search strategies for identifying randomized trials in PubMed. Available from: http://work.cochrane.org/pubmed. Accessed December 30, 2016.
16. CADTH's Database Search Filters. Available from: https://www.cadth.ca/resources/finding-evidence/strings-attached-cadths-database-search-filters. Accessed December 30, 2016.

17. The ISPOR Scientific Presentations Database. Available from: https://www.ispor.org/research_study_digest/index.asp. Accessed December 30, 2016.

18. National Institute for Health and Care Excellence (NICE). Available from: https://www.nice.org.uk/. Accessed December 30, 2016.

19. Canadian Agency for Drugs and Technologies in Health (CADTH). Available from: https://www.cadth.ca/. Accessed December 30, 2016.

20. Yang XP, Lai D, Zhong XY, Shen HP, Huang YL. Efficacy and safety of canagliflozin in subjects with type 2 diabetes: systematic review and meta-analysis. *Eur J Clin Pharmacol.* 2014;70(10):1149–1158.

21. Yang T, Lu M, Ma L, Zhou Y, Cui Y. Efficacy and tolerability of canagliflozin as add-on to metformin in the treatment of type 2 diabetes mellitus: a meta-analysis. *Eur J Clin Pharmacol.* 2015;71(11):1325–1332.

22. Xiong W, Xiao MY, Zhang M, Chang F. Efficacy and safety of canagliflozin in patients with type 2 diabetes: a meta-analysis of randomized controlled trials. *Medicine (Baltimore).* 2016;95(48):e5473.

23. Rosenstock J, Chuck L, Gonzalez-Ortiz M, et al. Initial combination therapy with canagliflozin plus metformin versus each component as monotherapy for drug-naive type 2 diabetes. *Diabetes Care.* 2016;39(3):353–362.

24. Leiter LA, Yoon KH, Arias P, et al. Canagliflozin provides durable glycemic improvements and body weight reduction over 104 weeks versus glimepiride in patients with type 2 diabetes on metformin: a randomized, double-blind, phase 3 study. *Diabetes Care.* 2015;38(3):355–364.

25. Zaccardi F, Webb DR, Htike ZZ, Youssef D, Khunti K, Davies MJ. Efficacy and safety of sodium-glucose co-transporter-2 inhibitors in type 2 diabetes mellitus: systematic review and network meta-analysis. *Diabetes, Obes Metab.* 2016;18(8):783–794.

26. Shyangdan DS, Uthman OA, Waugh N. SGLT-2 receptor inhibitors for treating patients with type 2 diabetes mellitus: a systematic review and network meta-analysis. *BMJ Open.* 2016;6(2):e009417.

27. Mearns ES, Sobieraj DM, White CM, et al. Comparative efficacy and safety of antidiabetic drug regimens added to metformin monotherapy in patients with type 2 diabetes: a network meta-analysis. *PLoS One.* 2015;10(4):e0125879.

28. Mearns ES, Saulsberry WJ, White CM, et al. Efficacy and safety of antihyperglycaemic drug regimens added to metformin and sulphonylurea therapy in type 2 diabetes: a network meta-analysis. *Diabet Med.* 2015;32(12):1530–1540.

29. Kaur K, Likar N, Dang A, Kaur G. Efficacy and safety of canagliflozin among patients with type 2 diabetes mellitus: a systematic review and meta-analysis. *Indian J Endocrinol Metab.* 2015;19(6):705–721.

30. Storgaard H, Gluud LL, Bennett C, et al. Benefits and harms of sodium-glucose co-transporter 2 inhibitors in patients with type 2 diabetes: a systematic review and meta-analysis. *PLoS One.* 2016;11(11):e0166125.

31. Cefalu WT, Stenlof K, Leiter LA, et al. Effects of canagliflozin on body weight and relationship to HbA1c and blood pressure changes in patients with type 2 diabetes. *Diabetologia.* 2015;58(6):1183–1187.

32. Weir MR, Januszewicz A, Gilbert RE, et al. Effect of canagliflozin on blood pressure and adverse events related to osmotic diuresis and reduced intravascular volume in patients with type 2 diabetes mellitus. *J Clin Hypertens (Greenwich).* 2014;16(12):875–882.

33. Li D, Wang T, Shen S, Fang Z, Dong Y, Tang H. Urinary tract and genital infections in patients with type 2 diabetes treated with sodium-glucose co-transporter 2 inhibitors: a meta-analysis of randomized controlled trials. *Diabetes Obes Metab.* 2017;19(3):348–355.

34. Nicolle LE, Capuano G, Fung A, Usiskin K. Urinary tract infection in randomized phase III studies of canagliflozin, a sodium glucose co-transporter 2 inhibitor. *Postgrad Med.* 2014;126(1):7–17.

35. Nyirjesy P, Sobel JD, Fung A, et al. Genital mycotic infections with canagliflozin, a sodium glucose co-transporter 2 inhibitor, in patients with type 2 diabetes mellitus: a pooled analysis of clinical studies. *Curr Med Res Opin.* 2014;30(6):1109–1119.

36. U.S. Food and Drug Administration. FDA drug safety communication: FDA warns that SGLT2 inhibitors for diabetes may result in a serious condition of too much acid in the blood. Available from: http://www.fda.gov/Drugs/DrugSafety/ucm446845.htm. Accessed December 30, 2016.

37. Erondu N, Desai M, Ways K, Meininger G. Diabetic ketoacidosis and related events in the canagliflozin type 2 diabetes clinical program. *Diabetes Care.* 2015;38(9):1680–1686.

38. Taylor SI, Blau JE, Rother KI. Possible adverse effects of SGLT2 inhibitors on bone. *Lancet Diabetes Endocrinol.* 2015;3(1):8–10.

39. Tang HL, Li DD, Zhang JJ, et al. Lack of evidence for a harmful effect of sodium-glucose co-transporter 2 (SGLT2) inhibitors on fracture risk among type 2 diabetes patients: a network and cumulative meta-analysis of randomized controlled trials. *Diabetes Obes Metab.* 2016;18(12):1199–1206.

40. Monami M, Dicembrini I, Mannucci E. Effects of SGLT-2 inhibitors on mortality and cardiovascular events: a comprehensive meta-analysis of randomized controlled trials. *Acta Diabetol.* 2017;54(1):19–36.

41. Tang H, Fang Z, Wang T, Cui W, Zhai S, Song Y. Meta-analysis of effects of sodium-glucose cotransporter 2 inhibitors on cardiovascular outcomes and all-cause mortality among patients with type 2 diabetes mellitus. *Am J Cardiol.* 2016;118(11):1774–1780.

42. European Medicines Agency. Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129256.pdf. Accessed December 30, 2016.

43. Food and Drug Administration. Guidance for industry diabetes mellitus–evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf. Accessed December 30, 2016.

44. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *New Engl J Med.* 2015;373(22):2117–2128.

45. Neal B, Perkovic V, de Zeeuw D, et al. Rationale, design, and baseline characteristics of the Canagliflozin Cardiovascular Assessment Study (CANVAS)–a randomized placebo-controlled trial. *Am Heart J.* 2013;166(2):217–223.e211.

46. Invokana (canagliflozin) tablets, for oral use. Prescribing information. Available from: https://www.icanimagine.com/sites/www.icanimagine.com/files/prescribing-information-invokana.pdf. Accessed December 30, 2016.

47. Invokana 100 mg and 300 mg film-coated tablets. Summary of product characteristics. Available from: https://www.medicines.org.uk/emc/medicine/28400#POSOLOGY. Accessed December 30, 2016.

48. Yale JF, Bakris G, Cariou B, et al. Efficacy and safety of canagliflozin over 52 weeks in patients with type 2 diabetes mellitus and chronic kidney disease. *Diabetes Obes Metab.* 2014;16(10):1016–1027.

49. Bode B, Stenlof K, Harris S, et al. Long-term efficacy and safety of canagliflozin over 104 weeks in patients aged 55–80 years with type 2 diabetes. *Diabetes Obes Metab.* 2015;17(3):294–303.

50. Sinclair AJ, Bode B, Harris S, et al. Efficacy and safety of canagliflozin in individuals aged 75 and older with type 2 diabetes mellitus: a pooled analysis. *J Am Geriatr Soc.* 2016;64(3):543–552.

51. National Institute for Health and Care Excellence (NICE) technology appraisal guidance. Canagliflozin, dapagliflozin and empagliflozin as monotherapies for treating type 2 diabetes. Available from: https://www.nice.org.uk/guidance/ta390. Accessed December 30, 2016.

52. Schroeder M, Johansen P, Willis M, Neslusan C. The cost-effectiveness of canagliflozin (CANA) versus dapagliflozin (Dapa) 10mg and empagliflozin (EMPA) 25mg in patients with type 2 diabetes mellitus (T2DM) as monotherapy in the United Kingdom. *Value Health.* 2015;18(7):A607.

53. Troelsgaard A, Knudsen MS, Kjellberg J, Schmidt A, Hemels M. Health economic evaluation of canagliflozin in the treatment of type 2 diabetes mellitus in Sweden. Available from: https://www.ispor.org/research_pdfs/46/pdffiles/PDB72.pdf. Accessed December 30, 2016.

54. Troelsgaard A, Huetson P, Kjellberg J, Hemels M, Knudsen M. Health economic evaluation of canagliflozin in the treatment of type 2 diabetes mellitus in Norway. *Value Health.* 2014;17(7):A345.

55. Troelsgaard A, Knudsen M, Maia-Lopes S, Luz M, Hemels M. Health economic evaluation of canagliflozin in the treatment of type 2 diabetes mellitus in Portugal. *Value Health.* 2014;17(7):A343–A344.

56. Nielsen AT, Pitcher A, Lovato E, et al. The cost-effectiveness of cana-gliflozin (cana) versus sitagliptin (sita) as an add-on to metformin or metformin plus sulphonylurea in the treatment of type 2 diabetes mel-litus in Spain. Available from: https://www.ispor.org/research_pdfs/49/pdffiles/PDB55.pdf. Accessed December 30, 2016.

57. Szmurlo D, Drzal R, Plisko R, Schubert A, Skrzekowska-Baran I. Cost effectiveness evaluation of canagliflozin in combination with metformin in the treatment of type 2 diabetes mellitus in Poland. *Value Health.* 2014;17(7):A346.

58. Bacon T, Willis M, Johansen P, Neslusan C, Nuhoho S, Worbes-Cerezo M. Is canagliflozin cost-effective compared to sitagliptin across mul-tiple lines of type 2 diabetes mellitus (T2dm) therapy in Ireland? *Value Health.* 2014;17(7):A345.

59. Granados D, Maurel F, Knudsen M, Troelsgaard A, Hemels M. Health economic evaluation of canagliflozin in the treatment of type 2 diabetes mellitus in France. *Value Health.* 2014;17(7):A344.

60. Lamotte M, Wyffels V, Knudsen MS, Troelsgaard A, Hemels M. Health economic evaluation of canagliflozin in the treatment of type 2 diabetes mellitus (t2dm) in Belgium. Available from: https://www.ispor.org/research_pdfs/46/pdffiles/PDB60.pdf. Accessed December 30, 2016.

61. Troelsgaard A, Pitcher A, Binder R, et al. Health economic evaluation of canagliflozin in the treatment of type 2 diabetes mellitus in Slovakia. *Value Health.* 2014;17(7):A345.

62. Troelsgaard A, Pitcher A, Vesela S, Lovato E, Hemels M. Health eco-nomic evaluation of canagliflozin in the treatment of type 2 diabetes mellitus in Czech Republic. *Value Health.* 2014;17(7):A342–A343.

63. National Institute for Health and Care Excellence (NICE) technology appraisal guidance. Canagliflozin in combination therapy for treating type 2 diabetes. Available from: https://www.nice.org.uk/guidance/ta315. Accessed December 30, 2016.

64. Bacon T, Willis M, Johansen P, Neslusan C, Nuhoho S, Worbes-Cerezo M. The cost-effectiveness of canagliflozin verse insulin-secretagogues (sul-phonylureas) or insulin in patients with type 2 diabetes mellitus (T2dm) as an add-on to metformin in Ireland. *Value Health.* 2014;17(7):A346.

65. Neslusan C, Teschemaker A, Martin S, Willis M, Johansen P. Cost-effectiveness analysis of canagliflozin (CANA) versus dapagliflozin (DAPA) as an add-on to metformin (MET) in patients with type 2 diabetes mellitus (T2DM) in the United States. Available from: https://www.ispor.org/research_pdfs/46/pdffiles/PDB62.pdf. Accessed Decem-ber 30, 2016.

66. Nielsen AT, Pitcher A, Lovato E, Schubert A, Hemels M, Neslusan C, González B. The cost-effectiveness evaluation of canagliflozin versus dapagliflozin in patients with type 2 diabetes mellitus inadequately controlled on metformin monotherapy in Spain. Available from: https://www.ispor.org/research_pdfs/49/pdffiles/PDB50.pdf. Accessed Decem-ber 30, 2016.

67. Bacon T, Willis M, Johansen P, Neslusan C, Nuhoho S, Worbes-Cerezo M. The cost-effectiveness of canagliflozin verse liraglutide in patients with type 2 diabetes (T2dm) failing to achieve glycaemic control on metformin monotherapy in Ireland. *Value Health.* 2014;17(7):A345.

68. Sabapathy S, Neslusan C, Yoong K, Teschemaker A, Johansen P, Willis M. Cost-effectiveness of canagliflozin versus sitagliptin when added to metformin and sulfonylurea in type 2 diabetes in Canada. *J Popul Ther Clin Pharmacol.* 2016;23(2):e151–e168.

69. Pititto L, Neslusan C, Teschemaker AR, et al. Cost-effectiveness of canagliflozin (Cana) versus sitagliptin (Sita) as add-on to metformin plus sulfonylurea in patients with type 2 diabetes mellitus (T2dm) in Brazil. *Value Health.* 2015;18(7):A864.

70. Kooy A, de Jager J, Lehert P, et al. Long-term effects of metformin on metabolism and microvascular and macrovascular disease in patients with type 2 diabetes mellitus. *Arch Intern Med.* 2009;169(6):616–625.

71. Food and Drug Administration News Release. FDA approves Jardiance to reduce cardiovascular death in adults with type 2 diabetes. Available from: http://www.fda.gov/NewsEvents/Newsroom/PressAnnounce-ments/ucm531517.htm. Accessed December 30, 2016.