REVIEW

Diabetes Management

Canagliflozin for Type 2 diabetes: an up-to-date evidence summary

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Practice points

- Canagliflozin is a sodium-glucose cotransporter 2 inhibitor that has received marketing authorization for treatment of Type 2 diabetes.
- It has an insulin independent mode of action inducing glucosuria by inhibition of glucose reabsorption in the proximal convoluted tubule.
- Several randomized controlled trials have corroborated the efficacy of canagliflozin both as monotherapy and in combination with other antidiabetic agents including insulin.
- Canagliflozin effectively lowers hemoglobin A_{1c} by approximately 0.8% relative to placebo, without increasing risk for hypoglycemia.
- Additional clinical benefits of canagliflozin include weight loss and reduction of blood pressure, which are attributed to loss of fat mass and osmotic diuresis.
- Use of canagliflozin is associated with an increased incidence of genital tract infections.
- Ongoing trials are expected to clarify the long-term safety and effect of canagliflozin on cardiovascular outcomes and microvascular complications.

SUMMARY Canagliflozin is a newly approved sodium-glucose cotransporter 2 inhibitor for Type 2 diabetes. It is used along with diet and exercise in patients who are intolerant to metformin, or as an adjunct to other antidiabetic agents including insulin when glycemic control is inadequate. Canagliflozin effectively lowers blood glucose without increasing risk for hypoglycemia. It also reduces body weight and blood pressure but is associated with increased incidence of genital tract infections. Caution is warranted for patients at risk for volume depletion, such as elderly subjects, patients treated with diuretics and patients with renal impairment. Based on local prescribing information, canagliflozin should not be initiated or its dose should be adjusted in patients with stage 3 chronic kidney disease or higher.

Sodium-glucose cotransporter 2 (SGLT2) inhibitors are the latest addition to the therapeutic armamentarium for Type 2 diabetes mellitus (T2DM). These oral agents have an insulin independent mechanism of action, inhibiting glucose reabsorption in the proximal convoluted tubule [1]. Canagliflozin is a member of the SGLT2 inhibitors class with marketing authorization in Europe, the USA and Japan. Starting dose is 100 mg once daily and can be uptitrated to 300 mg if glycemic

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control is inadequate [2]. Canagliflozin's efficacy and tolerability have been assessed in several clinical trials, while an ongoing study is expected to establish its effect on major cardiovascular outcomes in the near future. The purpose of this review is to provide an up-to-date summary of the available evidence for canagliflozin, focusing on its safety profile, its effect in special populations, and international data regarding its cost–effectiveness and recommendations for reimbursement.

Efficacy of canagliflozin

• Glycemic control

In a placebo controlled, dose finding study in T2DM patients treated with maximally tolerated dose of metformin, a dose response with regards to hemoglobin A_{1c} (HbA_{1c}) was observed for the once daily doses 50 to 300 mg of canagliflozin, with no additional effect for the twice daily 300 mg dose. These data support the choice of the once daily 100 and 300 mg doses [3]. Administration of canagliflozin 50 and 150 mg dosed twice daily as dual therapy with metformin produced consistent changes in HbA_{1c} relative to placebo. These findings support the comparability of the proposed dosing of the fixed dose combination of canagliflozin with metformin with that of once daily canagliflozin alone [4].

In a Phase III trial enrolling 584 patients with T2DM treated with diet and exercise alone, monotherapy with canagliflozin 100 and 300 mg resulted in significant reductions in hemoglobin A_{1c} relative to placebo after 26 weeks of treatment (-0.91%; 95% CI: -1.1 to -0.7 and -1.16%; 95% CI: -1.3 to -1.0, respectively) [5]. Moreover, among 1050 subjects with T2DM on metformin, two-year treatment with canagliflozin provided similar HbA_{1c} reduction benefits to glimepiride (-0.09%; 95% CI: -0.20–0.01 for canagliflozin 100 mg and -0.18%; -0.29 to -0.08 for canagliflozin 300 mg) [6]. When used on top of metformin, daily treatment with canagliflozin 300 mg (n = 367) was also superior to sitagliptin 100 mg (n = 366) after 52 weeks of treatment (relative change in HbA_{1c} -0.15%; 95% CI: -0.27 to -0.03) [7]. Finally, use of canagliflozin 300 mg in triple combination therapy in patients already treated with metformin and sulfonylurea resulted in greater HbA_{1c} reduction (-0.37%; 95% CI: -0.50 to -0.25) compared with sitagliptin 100 mg in a Phase III study with 756 participants [8].

• Body weight loss

A recent meta-analysis suggested that canagliflozin is associated with weight loss compared with placebo (-2.61%; 95% CI: -3.09 to -2.13) based on data from five randomized controlled trials [9]. Findings from two substudies utilizing dual-energy x-ray absorptiometry suggest that body weight reduction observed after treatment with canagliflozin is principally accounted for by fat mass loss. Moreover, assessment with computed tomography identified slightly greater changes in visceral rather than subcutaneous adipose tissue [10]. Body weight loss with canagliflozin was dose dependent, and ranged from 1.6 to 2.4% with 100 mg and from 1.8 to 3.8% with 300 mg dose [11].

• Blood pressure reduction

Arterial hypertension is a common complication among subjects with T2DM. Based on pooled results from 22 studies, canagliflozin was associated with a reduction in systolic blood pressure compared with control arms (-4.38 mmHg; 95% CI: -5.08 to -3.69). Reduction in systolic blood pressure was dose dependent and ranged from 2.6 to 5.7 mmHg and 3.5 to 7.9 mmHg with 100 and 300 mg, respectively [11]. A favorable effect on diastolic blood pressure was also noticed, though less pronounced (-2.02 mmHg; 95% CI: -2.48 to -1.56). The underlying mechanism is probably related to osmotic diuresis and natriuresis induced by canagliflozin [12].

Safety of canagliflozin

• Hypoglycemia

A recent meta-analysis showed that hypoglycemia rates did not differ between canagliflozin and placebo arms (risk ratio: 1.13; 95% CI: 0.40–3.20) [13]. Incidence of hypoglycemia was higher among patients receiving a sulfonylurea or insulin as allocation treatment or background therapy [9]. Among patients with stage 3 chronic kidney disease treated with insulin and/or sulfonylureas more subjects randomized to canagliflozin 100 or 300 mg experienced at least one hypoglycemic episode (41.9 and 43.8%, respectively) relative to placebo (29.2%) [14].

• Urinary & genital tract infections

Based on data submitted by the sponsor to the EMA, incidence of urinary tract infections (UTIs) was 4% among subjects treated with canagliflozin 100 mg (n = 833), 5.9% among patients receiving canagliflozin 300 mg (n = 834) and 4% in the placebo arms (n = 646). Only two

and one patients treated with canagliflozin 100 and 300 mg, respectively, experienced at least one serious event of UTI, while none such event was reported among subjects allocated to placebo [15].

Based on data from eight trials, genital mycotic infections (GMIs) were seen more commonly in patients treated with canagliflozin relative to placebo (risk ratio 3.76; 95% CI: 2.23–6.35) [13]. These infections occurred more often in females, were mainly of mild or moderate severity (vulvovaginitis in women and balanitis/balanoposthitis in men) and most of them were generally manageable with standard antifungal agents. Canagliflozin-treated women experiencing GMIs were more likely to have a history of vulvovaginitis (29%) compared with placebo (12%). Incidence of GMIs among female subjects was similar for both doses of canagliflozin (10.4 and 11.4% for 100 and 300 mg, respectively). Only 2 and 1% of females and males respectively had a recurrent GMI [16].

• Changes in lipid profile

Based on data submitted to regulatory authorities, treatment with canagliflozin was associated with a dose dependent increase in low-density lipoprotein cholesterol (LDL-C) (placebo corrected difference 4.5%; 95% CI: 1.4–7.6 for canagliflozin 100 mg and 8.0%; 95% CI: 4.9–11.1 for canagliflozin 300 mg). High-density lipoprotein cholesterol (HDL-C) levels also increased after treatment with canagliflozin 100 and 300 mg (5.4%; 95% CI: 3.6–7.2 and 6.3%; 95% CI: 4.5–8.2, respectively) but the LDL-C/HDL-C ratio remained essentially unchanged. Similar findings were also reported in a recent meta-analysis of canagliflozin [13]. Finally, triglyceride levels were reduced in canagliflozin-treated subjects (mean difference versus placebo -10.84 mg/dl; 95% CI: -17.07 to -4.62). The underlying pathophysiologic mechanism that drives this mild increase in LDL-C has not been fully elucidated, although it is speculated that hemoconcentration might play a role [13]. Mechanistic studies also suggest that the observed glucose deficit after treatment with SGLT2 inhibitors might result in enhanced lipid oxidation and higher free fatty acid concentrations in order to maintain energy balance [17]. Finally, a slightly lower proportion of subjects on canagliflozin 300 mg started a statin or modified its dose during the trial (1.6%; n = 834) compared with canagliflozin 100 mg (2.5%; n = 833) or placebo (2.5%; n = 646), but it is unlikely that such changes in statin use during the study period would significantly alter the effects of the drug on lipid levels [11].

• Changes in glucagon levels & endogenous glucose production

Beyond effective reduction of fasting plasma glucose, data from two mechanistic studies with other SGLT2 inhibitors, namely dapagliflozin and empagliflozin, showed consistent elevations in plasma glucagon levels and endogenous glucose production probably in compensation for the attendant energy deficit [17,18]. These hypothesis generating studies implicate that SGLT2 inhibitors might have complementary effects on glucose lowering when coadministered with incretin mimetics [19], which suppress glucagon secretion [20]. Albeit probably a class effect, whether canagliflozin induces similar changes in glucagon levels remains to be elucidated.

• Electrolyte changes

Electrolyte changes after treatment with canagliflozin are presented in **Table 1**. Although potassium levels were almost indifferent after 26 weeks of treatment with canagliflozin or placebo, transient increases in serum potassium were observed shortly after treatment with canagliflozin and tended to improve over time (change from baseline 0.11 and 0.14 mEq/l with canagliflozin 100 and 300 mg, respectively, compared with 0.09 mEq/l with placebo at week six). Adverse events related to hyperkalemia were more common among subjects with renal impairment – especially those treated with canagliflozin 300 mg – or patients receiving concomitant therapy with agents that precipitate hyperkalemia [11,15].

• Volume depletion

Adverse events related to volume depletion were observed in 71 (2.3%) and 105 (3.4%) subjects randomized to canagliflozin 100 (n = 3092) or 300 mg (n = 3085), as opposed to 49 subjects (1.5%) in control groups (n = 3262) [15]. These increases are probably attributed to osmotic diuresis induced by treatment with canagliflozin. The most commonly reported adverse events were hypotension and postural dizziness. Data from a mechanistic study showed that mean plasma volume decreased after 1 week treatment with canagliflozin 300 mg (placebo corrected difference -9.7%; 95% CI: -17.8 to -1.6), but this effect largely attenuated after 12 weeks

Table 1. Changes in serum electrolytes after 26 weeks treatment with canagliflozin. Pooled analysis of four placebo-controlled trials.

Serum parameter	Mean change from baseline to week 26[†]		
	Placebo	*Canagliflozin 100 mg*	*Canagliflozin 300 mg*
Sodium	0	0.2	0.2
Potassium	0.01	0.01	0.02
Calcium	0.01	0.06	0.10
Magnesium	-0.02	0.14	0.17
Phosphate	0.02	0.09	0.15
Chloride	-0.1	0.4	0.4
Bicarbonate	0.55	0.15	0.03

[†]Results are expressed in mEq/l except for changes in calcium and phosphate which are expressed in mg/dl.
Data taken from the US FDA briefing document on canagliflozin [11].

of treatment [21]. A higher, dose-related risk for volume depletion was observed in subgroups of patients with estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2, elderly subjects (≥65 years of age) and patients receiving concomitant therapy with angiotensin I-converting enzyme inhibitors, angiotensin II receptor blockers or loop diuretics. Higher HbA_{1c} levels and lower systolic blood pressure at baseline as well as longer duration of diabetes were also associated with increased risk for volume depletion [11].

• Fractures

A higher incidence of fractures was noted in patients treated with canagliflozin 100 (n = 58; 1.9%) and 300 mg daily (n = 54; 1.8%) compared with placebo (n = 47; 1.4%). Assessment of bone mineral density using dual-energy x-ray absorptiometry in a single canagliflozin study with 716 participants showed inconsistent changes after 52 weeks of treatment (differences for canagliflozin 300 mg versus placebo -0.7%; 95% CI: -1.4 to -0.1 for lumbar spine, 0.6%; 95% CI: -0.1–1.4 for femoral neck and 0.1%; 95% CI: -0.6–0.7 for distal forearm). Most fractures occurred shortly after initiation of treatment with canagliflozin, were located in the upper extremity and were related to falls potentially due to hypovolemia-related dizziness or hypotension [15].

• Cardiovascular events

A meta-analysis submitted by the sponsor to the US FDA did not identify a detrimental effect of canagliflozin on cardiovascular outcomes (composite endpoint including cardiovascular death, myocardial infarction, stroke and hospitalization for unstable angina). Overall, 130 such events were positively adjudicated by an independent blinded committee among subjects allocated to canagliflozin arms (n = 6396), as opposed to 71 events in patients assigned to control groups (n = 3327), resulting in a hazard ratio (HR) of 0.91 (95% CI: 0.68–1.22) [15]. This finding is in compliance with the FDA guidance for the evaluation of cardiovascular risk with new antidiabetic agents for T2DM [22]. Nevertheless, the HR for the component of nonfatal stroke was 1.46 (95% CI: 0.83–2.58). Moreover, an increased incidence of cardiovascular events (HR 6.5; 95% CI: 0.85–49.66) was noted during the first 30 days of the CANVAS trial enrolling patients with T2DM and a known history of or at high risk for cardiovascular disease. This imbalance was subsequently reversed [11]. Although this could represent a spurious finding, these limited data could also suggest that patients at increased cardiovascular risk may not experience a clear cardiovascular benefit from treatment with canagliflozin. Finally, adverse events related to congestive heart failure were less frequent with canagliflozin 100 and 300 mg (0.13 and 0.16%, respectively) compared with placebo (0.31%) [15].

Use of canagliflozin in special populations

• Elderly subjects

Use of canagliflozin in elderly patients was evaluated in a dedicated trial enrolling exclusively older subjects aged 55–80 years with or without background antidiabetic therapy. Treatment with canagliflozin in this subgroup of patients provided sustained glycemic efficacy (change in HbA_{1c} for canagliflozin 300 mg vs placebo -0.70%; $p < 0.001$) and weight reduction (-2.7 kg; $p < 0.001$). Patients with higher HbA_{1c} levels at baseline experienced greater improvements in glycemic status [23]. In a pooled analysis of four randomized controlled trials adverse events related to volume depletion were somewhat more common

in subjects ≥65 years of age compared with those <65 years [24]. Hence, initiation of canagliflozin in elderly subjects at 100 mg is reasonable given that the blood pressure lowering effects may be more relevant for safety reasons [15].

• Patients with renal impairment

Due to their mechanism of action, glycemic efficacy of SGLT2 inhibitors gradually declines with worsening renal function. Based on pooled findings from four randomized, placebo controlled trials with up to 26 weeks duration in patients with stage 3 chronic kidney disease (CKD, estimated Glomerular Filtration Rate ≥30 and <60 ml/min/1.73 m^2) canagliflozin sustained its glycemic efficacy (difference versus placebo in HbA_{1c} -0.38%; 95% CI: -0.50 to -0.26 for the 100 mg dose and -0.47%; 95% CI: -0.60 to -0.35). The HbA_{1c} reduction benefits with canagliflozin 300 mg were sustained after 52 weeks of treatment (difference vs placebo -0.41%; 95% CI: -0.68 to -0.14) [25]. For CKD patients treated with insulin and/or sulfonylureas hypoglycemia episodes were more common in subjects allocated to canagliflozin 100 and 300 mg groups (41.9 and 43.8%, respectively) compared with placebo (29.2%) [14]. Of note, a higher discontinuation rate was observed with canagliflozin 300 mg probably due to an increased incidence of volume-related adverse events such as dizziness and hypotension [14].

Both doses of canagliflozin sustain their glycemic efficacy in patients with estimated eGFR between 45 and 60 ml/min/1.73 m^2. The higher dose appears slightly more effective (mean differences in HbA_{1c} vs placebo -0.52 and -0.47% for 300 and 100 mg, respectively), however, it is also associated with a slightly increased rate of adverse events (i.e., volume depletion and electrolyte imbalances) [14]. Borderline clinically relevant HbA_{1c} reductions of 0.39 and 0.23% were observed with the 300 and 100 mg dose, respectively, in patients with eGFR between 30 and 45 ml/min/1.73 m^2 [14,15]. Due to safety considerations, the EMA recommends that canagliflozin should not be initiated in patients with eGFR <60 ml/min/1.73 m^2. For patients whose eGFR falls <60 ml/min/1.73 m^2 dose of canagliflozin should be maintained or adjusted to 100 mg daily. Finally, canagliflozin should be discontinued when eGFR is persistently below 45 ml/min/1.73 m^2 [2]. Similarly, the drug's prescribing information in the USA allow use of canagliflozin in patients with an eGFR less than 60 and up to 45 ml/min/1.73 m^2, but suggest that its dose is limited to 100 mg.

Recommendations for reimbursement & cost–effectiveness data

In the UK, a technology appraisal guidance has been recently issued by NICE based on cost–effectiveness data of canagliflozin submitted by the manufacturer [26]. The Economic and Health Outcomes-T2DM economic model was used, simulating individual patient outcomes over a lifetime horizon (40 years). Baseline characteristics for a hypothetical cohort of 1000 patients were sourced from the canagliflozin clinical trials and the National Health Service perspective was utilized. Based on exploratory analyses conducted by the Evidence Review Group by re-running some of the manufacturer's analyses, canagliflozin 100 and 300 mg compared with a sulfonylurea had an incremental cost–effectiveness ratio (ICER) of GB£1,579 and GB£5,368 per quality-adjusted life year (QALY) gained, respectively. In comparison to a dipeptidyl-peptidase 4 inhibitor, ICER values were GB£12,938 and GB£9,246 for the 100 and 300 mg dosage, respectively. Both dose regimens were dominated by a thiazolidinedione, meaning that they were more costly and less effective. Of note, the probability of canagliflozin being cost effective compared with dapagliflozin was estimated approximately 50% at a maximum acceptable ICER of GB£20,000 per QALY gained. As a final recommendation, the committee concluded that canagliflozin represents a cost effective use of National Health Service resources as dual therapy in combination with metformin, triple therapy combined with metformin and either a sulfonylurea or a thiazolidinedione, and as add-on to insulin. However, it is recommended as dual therapy in combination with metformin, only if a sulfonylurea is contraindicated or the patient is at significant risk for hypoglycemia.

Similarly, in Australia, the Pharmaceutical Benefits Advisory Committee has recently considered canagliflozin for listing on the Pharmaceutical Benefits Scheme, based on analyses submitted by the manufacturer [27]. Sitagliptin was the nominated comparator for these analyses and data were derived from one head-to-head study comparing canagliflozin with sitagliptin as add-on to metformin, and supplementary indirect comparisons from additional trials. The submission also included a cost minimization analysis comparing canagliflozin 300 mg with sitagliptin 100 mg.

In conclusion, the Pharmaceutical Benefits Advisory Committee recommended the listing of canagliflozin on the Pharmaceutical Benefits Scheme, accepting that canagliflozin is noninferior over sitagliptin in terms of comparative effectiveness. Nevertheless, it remained concerned regarding high rates of osmotic diuresis-related adverse events and genital mycotic infections, and stated that the cost of managing these infections should be accounted for in the economic analysis. Finally, the committee concluded that canagliflozin is noninferior in regard to efficacy and safety with dapagliflozin, but also noted the paucity of long-term data about the drug's renal and cardiovascular safety.

In the USA, a cost–effectiveness analysis based on data from one placebo-controlled trial concluded that monotherapy with canagliflozin is associated with lower costs and improved quality of life in comparison with lifestyle management alone [28]. Similarly, treatment with canagliflozin 100 and 300 mg improved QALYs at lower total costs (-US$2341 and -US$4526, respectively) compared with sitagliptin in patients inadequately controlled with metformin alone [28]. In addition, an economic simulation study on approximately 850 patients, identified from a US healthcare organization database, concluded that canagliflozin is more effective compared with sitagliptin at reducing healthcare costs associated with inadequate glycemic control [29]. Moreover, a cost utility analysis in the USA suggested that canagliflozin is associated both with lower costs and higher QALY gains compared with the other SGLT2 inhibitor dapagliflozin [30]. Interestingly, though, canagliflozin was reviewed in May 2013 by the US Department of Defense Pharmacy and Therapeutics (P&T) committee, which is responsible for managing available resources of the US military health system, based on pharmacoeconomic analyses [31]. The P&T committee concluded that canagliflozin has several safety concerns, is not cost effective and does not offer a clinically compelling advantage compared with other noninsulin antidiabetic agents. Thus, it recommended that canagliflozin should not be listed in the Uniform Formulary. Similarly, in Ireland, the National Centre for Pharmacoeconomics did not recommend reimbursement of canagliflozin on the grounds that it was associated with ICER values ranging from EUR€56,000 to EUR€156,846 per QALY which were above the accepted threshold of EUR€45,000 to demonstrate cost–effectiveness [32]. Moreover, the Institute for Quality and Efficiency in Healthcare in Germany stated in its benefit assessment that no added benefit of canagliflozin is proven over existing antidiabetic drugs neither as monotherapy nor as addition to other agents [33].

Conclusion

Canagliflozin effectively lowers HbA_{1c} and provides additional clinical benefits including weight loss and blood pressure reduction. It also confers low risk for hypoglycemia, unless used on top of insulin or secretagogues. It is generally well tolerated in the short term, but it is also associated with an increased risk for genital tract infections. Results for long-term safety and cardiovascular morbidity and mortality are pending. The drug has an insulin independent mode of action and ongoing studies are currently evaluating its potential place in the management of Type 1 diabetes.

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References

Papers of special note have been highlighted as:
• of interest; •• of considerable interest

1 Ferrannini E, Solini A. SGLT2 inhibition in diabetes mellitus: rationale and clinical prospects. *Nat. Rev. Endocrinol.* 8, 495–502 (2012).

2 European Medicines Agency. Summary of product characteristics. Invokana® (2014). www.ema.europa.eu/docs/en_GB

3 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* 35, 1232–1238 (2012).

4 Qiu R, Capuano G, Meininger G. Efficacy and safety of twice-daily treatment with canagliflozin, a sodium glucose co-transporter 2 inhibitor, added on to metformin monotherapy in patients with Type 2 diabetes mellitus. *J. Clin. Transl. Endocrinol.* 1, 54–60 (2014).

5 Stenlof K, Cefalu WT, Kim KA *et al.* Efficacy and safety of canagliflozin monotherapy in subjects with Type 2 diabetes mellitus inadequately controlled with diet and exercise. *Diabetes Obes. Metab.* 15, 372–382 (2013).

6 Langslet G, Cefalu WT, Leiter LA *et al.* Canagliflozin demonstrates durable glycaemic improvements over 104weeks compared with glimepiride in subjects with Type 2 diabetes mellitus on metformin. *Diabetologia* 56, S81 (2013).

7 Lavalle-Gonzalez FJ, Januszewicz A, Davidson J *et al.* Efficacy and safety of canagliflozin compared with placebo and sitagliptin in patients with Type 2 diabetes on background metformin monotherapy: a randomised trial. *Diabetologia* 56, 2582–2592 (2013).

• **A well-designed trial exploring the effect of canagliflozin relative to the dipeptidyl-peptidase 4 inhibitor sitagliptin in triple combination therapy.**

8 Schernthaner G, Gross JL, Rosenstock J *et al.* Canagliflozin compared with sitagliptin for patients with Type 2 diabetes who do not have adequate glycemic control with metformin plus sulfonylurea: a 52-week randomized trial. *Diabetes Care* 36, 2508–2515 (2013).

•• **A rigorous systematic review and meta-analysis summarizing the efficacy and safety of sodium-glucose cotransporter 2 inhibitors based on data from published and gray literature sources.**

9 Vasilakou D, Karagiannis T, Athanasiadou E *et al.* Sodium-glucose cotransporter 2 inhibitors for Type 2 diabetes: a systematic review and meta-analysis. *Ann. Intern. Med.* 159, 262–274 (2013).

• **Body composition analysis investigating weight change in patients treated with canagliflozin.**

10 Toubro S, Cefalu WT, Xie J *et al.* Canagliflozin, a sodium glucose co-transporter 2 inhibitor, reduces body weight mainly through loss of fat mass in subjects with Type 2 diabetes. *Diabetologia* 55, S313–S314 (2012).

11 US FDA. Briefing document. NDA 204042. Invokana (canagliflozin) tablets (2013). www.fda.gov/downloads/AdvisoryCommittees

12 Baker WL, Smyth LR, Riche DM, Bourret EM, Chamberlin KW, White WB. Effects of sodium-glucose co-transporter 2 inhibitors on blood pressure: a systematic review and meta-analysis. *J. Am. Soc. Hypertens.* 8, 262–275 (2014).

13 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.* 70, 1149–1158 (2014).

• **A pooled analysis of four randomized controlled trials investigating use of canagliflozin in patients with moderate renal impairment.**

14 Yamout H, Perkovic V, Davies M *et al.* Efficacy and safety of canagliflozin in patients with Type 2 diabetes and stage 3 nephropathy. *Am. J. Nephrol.* 40, 64–74 (2014).

15 European Medicines Agency. Assessment report. Canagliflozin. Procedure no. EMEA/H/C/002649/0000 (2013). www.ema.europa.eu/docs/en_GB

16 Ways K, Nyirjesy P, Sobel JD, Fung A, Gassmann-Mayer C, Usiskin K. Genital mycotic infections with canagliflozin in subjects with Type 2 diabetes mellitus. *Diabetologia* 56, S381 (2013).

17 Ferrannini E, Muscelli E, Frascerra S *et al.* Metabolic response to sodium-glucose cotransporter 2 inhibition in Type 2 diabetic patients. *J. Clin. Invest.* 124, 499–508 (2014).

18 Merovci A, Solis-Herrera C, Daniele G *et al.* Dapagliflozin improves muscle insulin sensitivity but enhances endogenous glucose production. *J. Clin. Invest.* 124, 509–514 (2014).

• **An informative editorial summarizing findings from mechanistic studies regarding metabolic response to therapy with sodium-glucose cotransporter 2 inhibitors.**

19 Cefalu WT. Paradoxical insights into whole body metabolic adaptations following SGLT2 inhibition. *J. Clin. Invest.* 124, 485–487 (2014).

20 Holst JJ, Christensen M, Lund A *et al.* Regulation of glucagon secretion by incretins. *Diabetes Obes. Metab.* 13, 89–94 (2011).

21 Sha S, Polidori D, Heise T *et al.* Effect of the sodium glucose co-transporter 2 inhibitor canagliflozin on plasma volume in patients with Type 2 diabetes mellitus. *Diabetes Obes. Metab.* 16, 1087–1095 (2014).

22 U.S. Food and Drug Administration. Guidance for industry. Diabetes mellitus — evaluating cardiovascular risk in new antidiabetic therapies to treat Type 2 diabetes. (2008). www.fda.gov/downloads/Drugs

23 Bode B, Stenlof K, Sullivan D, Fung A, Usiskin K. Efficacy and safety of canagliflozin treatment in older subjects with Type 2 diabetes mellitus: a randomized trial. *Hosp. Pract.* (1995) 41, 72–84 (2013)

24 Sinclair A, Bode B, Harris S *et al.* Efficacy and safety of canagliflozin compared with placebo in older patients with Type 2 diabetes mellitus: a pooled analysis of clinical studies. *BMC Endocr. Disord.* 14, 37 (2014).

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

26 National Institute for Health and Care Excellence. Canagliflozin in combination therapy for treating Type 2 diabetes (2014). www.nice.org.uk/guidance/ta315/resources

27 Australian Government, Department of Health, Pharmaceutical Benefits Advisory Committee. Public summary document. Canagliflozin, tablet, 100mg and 300mg, Invokana (2013). http://www.pbs.gov.au/industry/listing

28 Neslusan C, Johansen P, Willis M, Martin S. A health economic analysis of the long-term benefits and associated cost offsets of canagliflozin monotherapy in the U.S. *Diabetes* 62, A322 (2013).

29 Lafeuille MH, Grittner AM, Gravel J *et al.* Economic simulation of canagliflozin and sitagliptin treatment outcomes in patients with Type 2 diabetes mellitus with inadequate glycemic control. *J. Med. Econ.* 7, 1–13 (2014).

30 Neslusan C, Teschemaker A, Martin S, Willis M, Johansen P. PDB62 – 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. *Value Health* 17, A248 (2014).

31 Department of Defense. Pharmacy and therapeutics committee recommendations. Decision paper: canagliflozin (Invokana) (2013). http://pec.ha.osd.mil/P&T/PDF

32 National Centre for Pharmacoeconomics. Cost Effectiveness of canagliflozin (Invokana®) for adults with Type 2 diabetes mellitus to improve glycaemic control as monotherapy or add-on therapy with other anti-hyperglycaemic agents including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control (2014). www.ncpe.ie/wp-content/uploads/2013/04

33 Institute for Quality and Efficiency in Health Care. Canagliflozin – Benefit assessment according to §35a Social Code Book V (2014). www.iqwig.de/download/A14–12