

Canagliflozin

SGLT2 inhibitors

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Introduction

Nearly 26 million Americans have diabetes (about 8% of the population) of which 90 -95% is type 2 diabetes.^{1,2} Type 2 diabetes (T2DM) is associated with obesity and it is a major cause of morbidity and death worldwide.³ In the United States, it is a leading cause of kidney failure, non-traumatic limb amputation, and new cases of blindness among adults.³ It is also associated with an increased cardiovascular risk and is a major cause of heart disease and stroke.^{3,4} In 2007, the estimated costs associated with diabetes in the United States (direct and indirect) were \$174 billion.¹ A1C is a predictor of diabetes complications; the higher your A1C level, the higher your risk of diabetes complications (including kidney failure, blindness, damage to the nervous system, peripheral vasculature and skin, and limb amputation).^{4,5} According to current guidelines A1C levels of <6.5%^{6,7} or <7%⁸ are common treatment targets, but individualized goals may be higher (based on diabetes duration, age/life expectancy, comorbid conditions, known cerebrovascular disease or microvascular complications, hypoglycemia, and individual patient considerations).^{8,9} Initially, a trial of lifestyle modifications (such as healthy diet, weight loss, and exercise) is recommended, but pharmacotherapy is often required due to persistent elevated glucose levels.⁹ Insulin and sulfonylureas have been available for decades (since the early 1920's and the 1950's respectively)^{10,11}, and until 1995, these were the only available drug classes for patients affected by type 2 diabetes.¹² Currently, 12 classes of medications are FDA-approved for treating type 2 diabetes, including biguanides (e.g. metformin), thiazolidinediones, sulfonylureas, dipeptidyl peptidase-4 (DPP-4) inhibitors, meglitinides, glucagon-like peptide-1 (GLP-1) receptor agonists, amylin analogue, bromocriptine (dopamine agonist), alpha-glucosidase inhibitors, the bile acid sequestrant colesevelam, insulins, and the newly approved sodium-glucose co-transporter inhibitors (SGLT2).^{12,13}

Type 1 diabetics require insulin treatment due to a lack of insulin. Type 2 diabetes mellitus (T2DM) involves reduced insulin secretion or cellular insulin resistance.⁴ Therefore, the mechanisms of action of the medications for type 2 diabetes include stimulating insulin release, decreasing absorption or hepatic production of glucose, and improving insulin sensitivity of target organs.¹⁴ Oral agents become less effective as beta cell function declines and it may be necessary to add an injectable medication such as insulin (or to switch to insulin) to manage blood sugar levels.¹⁵ Estimates of the proportion of patients achieving the target HbA1c of <7% varies considerably for the different treatments and these have ranged from 26% with α -glucosidase inhibitors to 63% with exenatide.^{3,16}

It has been reported that T2DM augments the glucose homeostasis function of the kidney, including 10% of total glucose utilization in the body, up to 20% of all glucose production (via gluconeogenesis), and mediating glucose reabsorption, resulting in a three-fold increase in overall glucose production.³ An example provided in the literature is that normally in a healthy adult (GFR=125 mL/min) 180L of plasma is filtered through the kidneys every day.³ This would be about 180 g of glucose per day (average plasma glucose of 5 mmol/L) that is reabsorbed by the kidney and reabsorption from the glomerular filtrate increases in proportion to the plasma glucose concentration until the maximum transport capacity is reached. In a normal adult, excess glucose is then excreted whereas in diabetes the threshold of maximum glucose is increased (by up to 20%) and urinary glucose excretion (UGE) therefore begins at higher than normal plasma glucose levels.³ This mechanism has led to the development of a new class of hyperglycemia agents, the "SGLT2 inhibitors for diabetes: turning symptoms into therapy"¹⁷ (the title of a recent article in the Lancet). Sodium-dependent glucose transporter 1 (SGLT1) is the primary transporter responsible for gastrointestinal glucose and galactose absorption, and for about 10% of renal glucose reabsorption.^{3,18} Sodium-dependent glucose transporter 2 (SGLT2) is the transporter responsible for most of the glucose reabsorption performed by the kidney (about 90%).¹⁸ The drugs in this new SGLT2 class reduce blood glucose by acting on the kidneys as a 'glucoretic'.¹⁹ By inhibiting the subtype 2 sodium-glucose transport proteins (SGLT2), they lead to elimination of blood glucose through urine.¹⁹ In March 2013, canagliflozin became the first and only (to date) SGLT2 inhibitor to be approved in the United States.¹³ It is indicated as an adjunct to diet and exercise to improve

glycemic control in adults with type 2 diabetes mellitus.²⁰ Canagliflozin (Invokana) is available as once daily tablets (100 mg and 300 mg).²⁰ In January 2012, another drug in this class, dapagliflozin, was denied approval by the FDA because of concerns about a cancer signal, but this drug was approved in Europe in November 2012. Filing has been resubmitted in the US and includes several new studies and data from previously submitted studies.²¹ Empagliflozin has been filed for approval in the United States and the European Union²², and ipragliflozin²³, luseogliflozin²⁴, and tofogliflozin²⁵ have been filed for marketing approval in Japan.²⁶ Lexicon Pharmaceuticals has the first dual inhibitor of SGLT1 and SGLT2 in the pipeline (an orally-delivered, small molecule drug candidate; LX411).^{18,27} They have completed a Phase 2b trial in patients with type 2 diabetes, and initiation of Phase 3 studies is anticipated for the second half of 2013. Enrollment has been completed in a proof-of-concept trial in type 2 diabetes patients with renal impairment and enrollment is ongoing for a proof-of-concept trial in type 1 diabetes.¹⁸

National evidence-based type 2 diabetes guidelines (which include updated systematic reviews) have been revised to move towards a more patient centered approach to treatment management. A summary of current guidelines, and evidence and standards of care in Type 2 diabetes will be included in this review. This review will analyze the comparative effectiveness of canagliflozin for diabetes and incorporate important safety information. Differences in specific patient subpopulations or indications where canagliflozin may be more effective or safer than other available treatment options will be discussed. Canagliflozin's potential place in therapy will conclude this review. A well-conducted systematic review by Clar et al.²⁸ using the Cochrane risk of bias score for quality of assessment of studies, lists factors to consider when considering the SGLT2 inhibitors' place in therapy: effect on HbA1c, effect on weight (versus other drugs), adverse effects (particularly increased risk of genitourinary infections), duration of effectiveness, interactions with other drugs, ease of use, and cost.²⁸

Type 2 diabetes therapies

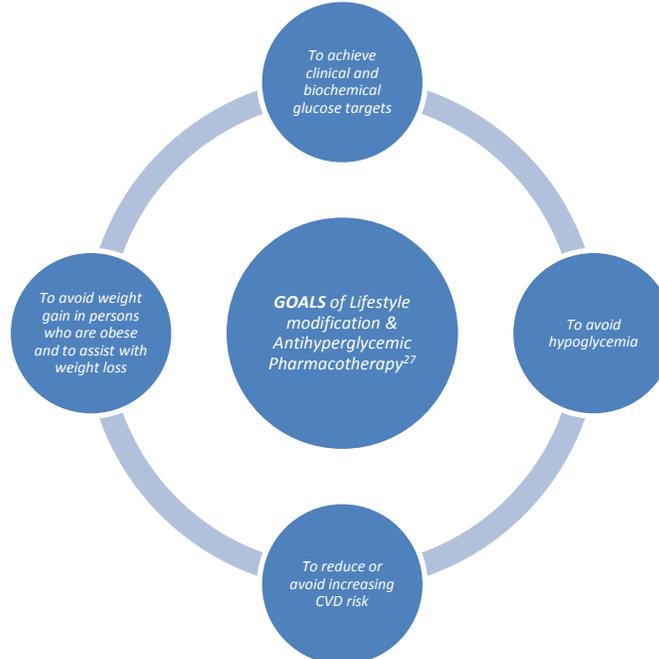
Appendix 1 contains a summary comparison table of the available type 2 diabetes medications in terms of classes, agents in classes, route of administration, mechanism of action, labeled indications, and notable adverse effects / limiting acceptability. Some drugs especially those that act mainly by stimulating insulin release, exhibit decreasing efficacy as duration of diabetes increases, and some have adverse effects such as weight gain and hypoglycemia.²⁸ The SGLT2 inhibitors are a new class of glucose-lowering agents of which canagliflozin is the only currently available product in the US. Appendix 2 contains information on canagliflozin in terms of uses and dosages, FDA information, contraindications, warnings and monitoring.

Methodology

A Medline and Cochrane Library literature search ending in August 2013 for systematic reviews and randomized controlled trials (RCTs) for canagliflozin, other SGLT2 inhibitors, and diabetic pharmacologic treatments was conducted. The Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Up To Date, the FDA website, ClinicalTrials.gov, The American Diabetes Association website, and the European Diabetes Association website were searched for safety information, systematic reviews, clinical trials, and guidelines. As per the hierarchy of evidence, high quality systematic reviews and evidence based guidelines were identified first. Published phase 3 randomized controlled trials were included for canagliflozin. After review of the sources, the following were reviewed: ADA Standards of Medical Care in Diabetes 2013²⁹ and five clinical treatment guidelines,^{6,9,30-32} three systematic review citations for SGLT2 inhibitors (of which one is a protocol³³ and two are reviews for which provisional abstracts were published by the Centre for Reviews and Dissemination)^{28,34} and several studies on ClinicalTrials.gov with corresponding publications.

Clinical Guidelines

⇒ Table 2 contains summary information from different guidelines.



Lifestyle optimization is the first step in management of type 2 diabetes, but often pharmacotherapy is needed.^{7,9} Metformin remains the cornerstone of type 2 anti-diabetic treatment. Advantages of metformin include low risk of hypoglycemia, can promote modest weight loss, it has a robust cardiovascular safety profile, and low cost.³⁰ If metformin alone is inadequate, the guidelines include various options as add-on therapy with a focus on individualized goals of treatment.

The SGLT2 inhibitor class was not included in the 2012 ADA/EASD^{8,9} or the 2012 ACP guidelines³² as canagliflozin was not approved yet, but this class was included in the new 2013 AACE guidelines.⁷ Another drug in this class was approved in Europe in November 2012 and NICE is currently in the process of updating their guidelines (see below).

The American Association of Clinical Endocrinologists (AACE) Guidelines Comprehensive Diabetes Management Algorithm⁷

The new AACE 2013 algorithm replaces the 2009 AACE/ American College of Endocrinology (ACE) Diabetes Algorithm for Glycemic Control. Their glycemic control algorithm lists drugs in a specific order as a suggested hierarchy of usage.⁷ It is also recommended that treatment be individualized based on attributes specific to patients and medications themselves. All FDA-approved medications are included in this algorithm making it the most comprehensive and updated guideline and it stratifies choice of therapies based on initial A1C level.³⁰ If the A1C is <7.5%, monotherapy with metformin is recommended. After metformin, GLP-1 receptor agonists are recommended as preferred agents due to their robust efficacy, weight loss and low hypoglycemic risk. DPP-4 inhibitors or alpha-glucosidase inhibitors are included as alternatives. SGLT-2 s, TZDs, and Sulfonylureas/glinides are included as options, but should be used with caution. The SGLT2 evaluation and recommendation is based on phase 3 clinical trials data. If the A1C is ≥7.5% (or not at goal), dual therapy with metformin and a second agent (GLP-1 analogue and DPP-4 inhibitor preferred) is recommended (see suggested order in table 2). Other options (see table 2) are included, and caution is advised with TZDs, SGLT2s, basal insulin, and sulfonylurea/glinides. If the A1C is >8%, a third medication may be considered (see table 2 for order; same medication cautions as for dual therapy), and if initial A1C is >9%

or if patients are receiving 2 oral agents or GLP-1 analogues and their A1C is >8% (or not at goal), insulin is recommended. Clinicians have limited experience with the SGLT2s and it is the AACEs consensus that the SGLT2 inhibitors' place in therapy remains undefined. It was proposed that these drugs will likely be used as add-on therapy to two or three other agents (including insulin) in patients who would benefit from weight loss. There are many decisions that physicians must make for every individual and this consensus statement recognizes that the schematics included cannot capture all of that.

American Diabetes Association and European Association for the Study of Diabetes (ADA/EASD) Guideline - Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement⁹

The ADA/EASD released a position statement in April 2012 which differed from previous published documents.⁹ The new position statement focused on a patient-centered approach by selecting second and third-line drugs on an individually-tailored basis taking into consideration patient preferences and tolerances. The position statement was not designed to be an algorithm, but rather to encourage physicians to critically evaluate the risk-to-benefit ratio for each patient, and recommendations were based on evidence and expert opinion.³⁵ Metformin remains the first-line recommended pharmacotherapy. The new position statement listed five different choices as add-on therapy to metformin treatment, and other drugs not shown may be used in selected patients.⁹ If triple therapy is necessary, the same dual therapy options can be considered, but insulin is most likely to achieve the A1c goal. The new position statement includes a summary table of the available glucose-lowering agents including information on advantages, disadvantages and cost as well as general recommendations.⁹ Considerations to guide the choice of pharmacological agents include efficacy, cost, potential side effects, effects on weight, comorbidities, hypoglycemia risk, and patient preferences.”²⁹

The general recommendations (ADA/EASD position statement⁹) state that other drugs not shown (alpha-glucosidase inhibitors: Acarbose, miglitol; bile acid sequestrant: colesevelam; dopamine agonists: bromocriptine; amylin mimetics: pramlintide) may be used in selected patients but they have modest efficacy and/or limiting side-effects.

Table 1. Summary table adapted from the ADA/EASD position statement⁹

	Sulfonylurea	Thiazolidinedione	DPP-4 Inhibitor	GLP-1 receptor agonist	Insulin
Efficacy	High	high	intermediate	high	highest
Hypoglycemia	moderate risk	low risk	low risk	low risk	high risk
Weight	Gain	gain	neutral	loss	gain
Major Side-effects	Hypoglycemia	edema, HF, fractures, ? MI (rosiglitazone) ? bladder cancer (pioglitazone)	Rare Urticarial/angioedema ? pancreatitis	GI ? Acute pancreatitis C-cell hyperplasia/ medullary thyroid tumors in animals	hypoglycemia

Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus: A Clinical Practice Guideline From the American College of Physicians (ACP)³²

This 2012 guideline include evidence of the comparative effectiveness of type 2 diabetes medications on intermediate outcomes (HbA1c, weight/BMI, LDL cholesterol, HDL cholesterol, triglycerides), long-term clinical outcomes (All-cause and cardiovascular mortality, cardiovascular and cerebrovascular morbidity, retinopathy, nephropathy, and neuropathy), safety (hypoglycemia, liver injury, GI event, CHF, macular edema, pancreatitis or cholecystitis, and fractures), and subgroups of adults aged 65 years or older. Key findings and the strength of evidence were presented in tables in the full text document. The SGLT2 inhibitor class was not included in this guideline. The evidence showed that most medications reduced HbA1c to a similar degree, but metformin was more effective as monotherapy and combination therapy for reducing

HbA1c levels, body weight, and plasma lipid levels. Evidence shows the risk for hypoglycemia with sulfonylureas, the heart failure risk with TZDs, and that metformin is associated with an increased risk for GI side effects. This guideline recommends monotherapy with metformin for initial pharmacotherapy (when lifestyle modifications and weight loss have failed to adequately improve hyperglycemia). It also recommends adding a second agent to metformin when this has failed, but no specific recommendations are made.

*International Diabetes Federation (IDF) Global Guideline for diabetes*³¹

The 2012 Global guideline recommendations³¹ were based on evidence and expert opinion. Metformin is recommended as initial monotherapy and sulfonylureas as second-line therapy (see table 2 for alternatives). Third-line (triple therapy) includes a third oral agent (DPP-4, TZD, or Alpha-glucosidase inhibitor) or insulin as the usual approach, but insulin could be considered earlier too.

*NICE Guidelines - Type 2 diabetes & Type 2 diabetes: newer agents*⁶

The National Institute for Health and Care Excellence (NICE) guidelines Type 2 diabetes (NICE clinical guideline 66) and Type 2 diabetes: newer agents (NICE clinical guideline 87) are currently in the process of being updated.³⁶ The current NICE guidelines also recommend metformin as first-line and suggest considering a sulfonylurea as a second option (if metformin is contraindicated) or adding to metformin if necessary (if not overweight; if a rapid therapeutic response is required due to hyperglycemic symptoms), and insulin as third-line-therapy. DPP-4 inhibitors (referring to sitagliptin) and thiazolidinediones (referring to pioglitazone) can be added as triple therapy (if unable to use insulin), but it is recommended to only continue treatment with these medications if the reduction in HbA1c is at least 0.5% in 6 months and the benefits and risks have been weighed and discussed with the patient.⁶ Exenatide is included in this NICE guideline 87 as an option to be added to metformin and a sulfonylurea if insulin is not acceptable or if the BMI ≥ 35 kg/m², but should only be continued if the patient has a reduction in HbA1c of at least 1% and a reduction of weight of $\geq 3\%$ of initial body weight in 6 months.⁶ Acarbose is included as an option for patients who are unable to use other glucose-lowering medications.⁶ Refer to table 6 for additional information.

*NICE Guideline Diabetes (type 2) - canagliflozin [ID554]*⁴

This NICE appraisal is currently being developed and is due in June 2014 (canagliflozin does not have a UK marketing authorization). The comments stated that “the inclusion of a monotherapy study in individuals intolerant of metformin is of some interest, but it is unlikely that this drug would offer such patients additional benefits above those agents already available.” This was also discussed at the scoping workshop and it was agreed that use in monotherapy would not be considered. The final scope includes dual therapy (for those inadequately controlled on monotherapy with metformin or a sulfonylurea), triple therapy (inadequately controlled on metformin+sulfonylurea or metformin/sulfonylurea+TZD/DPP-4 inhibitor/GLP-1 analogue), and add-on therapy to insulin (those on monotherapy with insulin or on insulin+up to 2 oral agents).

*NICE Guideline Diabetes (type 2) - dapagliflozin [ID427]*³⁷

In January 2012, dapagliflozin was denied approval by the FDA because of concerns about a cancer signal, but it was approved in Europe in November 2012. This NICE appraisal is currently being developed and the expected date of issue was June 2013, but the timelines have been extended to allow further resources to be applied to the evaluation of the manufacturer’s economic analysis. A summary of the Appraisal Committee’s key conclusions is available. Experts to the Committee stated that dapagliflozin was associated with a lower risk of hypoglycemia and it will provide a further option for people who are reluctant to start treatment with insulin because of fear of hypoglycemia or its impact on their lifestyle (fear of losing their driving license or job). Its adverse effect profile was different than those of other antidiabetic therapies and these were important considerations for the economic model. In terms of its place in therapy, recommendations were made as follows:

- Dual therapy: Combination with metformin is recommended as an option only if it is used as described for DPP-4 inhibitors in NICE clinical guideline 87 (see above). Combination with insulin or other antidiabetics is recommended as an option.
- Triple therapy: Combination with metformin and a sulfonylurea is NOT recommended (except as part of a clinical trial).

ADA Standards of Medical Care in Diabetes 2013²⁹

First-line monotherapy ^a	Dual therapy ^b (options to add to metformin)	Considerations based on:	Triple Therapy (options to add to metformin)	When to initiate insulin
Metformin	Another oral agent (e.g. sulfonylurea, TZD, DPP-4 inhibitor); GLP-1 agonist; Basal insulin	Patient-centered approach: Efficacy; Cost; Potential Side effects; Effects on weight; Comorbidities; Hypoglycemia; Risk; patient preferences	Readers are referred to the ADA/EASD position statement.	Consider insulin with/without additional agents from outset in newly diagnosed with markedly symptomatic and/or elevated blood glucose levels or A1C. Due to the progressive nature of type 2 diabetes, insulin therapy is eventually indicated for many patients with type 2 diabetes.

Table 2. Current Guidelines revised and adapted from Exciting Medication Updates in Diabetes Care³⁸

Guideline	First-line monotherapy ^a	Dual therapy ^b (options to add to metformin)	Considerations based on:	Triple Therapy (options to add to metformin)	When to initiate insulin
ADA/EASD⁹ 2012	Metformin	Another oral agent (e.g. sulfonylurea/glinide ^c , TZD, DPP-4 inhibitor); GLP-1 agonist; Basal insulin	Efficacy; Adverse effect profile; Cost; Injection preference; Patient preferences, needs and values; Glucose issue (fasting or prandial); dosing flexibility; Age; Weight; Chronic kidney disease	Same as for dual therapy; Insulin most likely to obtain A1c goal; Strongly consider if A1c≥8.5%	At diagnosis with significant hyperglycemic symptoms and/or dramatically elevated glucose > 300-350 mg/dL or A1c≥10%-12%
AACE³⁰ 2013	Metformin ^f (alternative in suggested order: GLP-1 agonist, DPP-4-i, AG-I, SGLT-2, TZD, SU/GLN)	In suggested order: GLP-1 agonist, DPP-4-i, TZD, SGLT-2, basal insulin, colesevelam, bromocriptine QR, AG-I, sulfonylurea/GLN	Individualized A1c target; Patient attributes (age, co-morbid conditions, duration of diabetes, risk of hypoglycemia, patient motivation, adherence, life expectancy, etc.); Medication attributes (risk of inducing hypoglycemia, weight gain, ease of use, cost, safety impact of kidney, heart or liver disease).	In suggested order: GLP-1 agonist, TZD, SGLT-2, basal insulin, DPP-4-i, colesevelam, bromocriptine QR, AG-I, sulfonylurea/GLN	Symptomatic patients (polyuria & weight loss) with entry A1c > 9%. Patients receiving 2 oral agents or GLP-1 with A1C >8% (or not at goal).
NICE⁶	Metformin	Sulfonylurea; DPP-4 inhibitor or TZD (if high risk for hypoglycemia); GLP-1 agonist (if BMI ≥35 kg/m ² ; if BMI lower & insulin unacceptable)	Risk of hypoglycemia Problem with weight gain Patient preference (occupational implications, social, recreational, or other issues e.g. with insulin)	DPP-4 inhibitor (refers to sitagliptin or vildagliptin), TZD (refers to pioglitazone) or GLP agonist Or Insulin (particularly with marked hyperglycemia)	A1c remains ≥7.5% despite other measures

Guideline	First-line monotherapy ^a	Dual therapy ^b (options to add to metformin)	Considerations based on:	Triple Therapy (options to add to metformin)	When to initiate insulin
ACP ³²	Metformin	Recommend add-on with persistent hyperglycemia, but no specific recommendation provided	Glycemic level reduction, reducing body weight, improving plasma lipid profiles, combination therapy: more effectively reduce A1C vs. more adverse effects	Not addressed	Not addressed
Global Guideline for Type 2 Diabetes³¹ 2012	Metformin ^d (unless contraindicated e.g. renal impairment)	Sulfonylurea (usual approach), and other medications are included as alternative approaches ^e	Availability; Cost; Efficacy; Side-effects; Effect on weight; Hypoglycemia risk; Long-term outcomes	Insulin or an oral agent (DPP-4, TZD, or Alpha-glucosidase inhibitor) as the usual approach for a third-line agent and GLP-1 agonists as an alternative approach	At triple therapy stage (if diabetes control remains unsatisfactory, the usual approach includes a third oral agent or insulin), but it may be considered earlier too.

^a If metformin is contraindicated, drugs from other classes (figure 2, position statement)⁹ such as sulfonylureas can be used as first-line therapy. A shorter-duration sulfonylurea, such as glipizide is less likely to cause hypoglycemia than the older, long-acting sulfonylureas.^{39,40} Other alternatives include thiazolidinediones, DPP-4 inhibitors, GLP-1 receptor agonists or repaglinide (particularly in patients with chronic kidney disease at risk for hypoglycemia).^{9,31,40}

^b Rapid-acting secretagogues (meglitinides) may be used in place of sulfonylureas. It should be considered in patients with irregular meal schedules or who develop postprandial hypoglycemia on sulfonylureas. Meglitinides may be associated with less hypoglycemia, but requires more frequent dosing.⁹

^c If non-insulin monotherapy at maximum tolerated dose do not achieve or maintain the A1C target over 3-6 months.⁸

^d The alternative approach is a sulfonylurea or an alpha-glucosidase inhibitor.³¹

^e The alternative approach is metformin (if not first line) or alpha-glucosidase inhibitor or DPP-4 inhibitor or TZD.

^f Upon diagnosis, monotherapy is recommended if A1C <7.5%, dual therapy if A1C 7.5% to 9%, and insulin if A1C >9%. If the treatment goal of <6.5% is not met within 3 months, AACE/ACE recommends intensifying therapy by adding another agent from a different class (dual therapy). SGLT-2 is based upon phase 3 clinical trial data.

Clinical Efficacy

Appendix 3 contains a comparison table with the different type 2 diabetic medications in terms of general efficacy and A1C lowering percentages. In March 2011, the AHRQ published an updated review (including metformin, second-generation sulfonylureas, thiazolidinediones, meglitinides, DPP-4 inhibitors, GLP-1 agonists as monotherapy and combination therapy). They reported that a high strength of evidence showed that most medications were similarly efficacious at lowering A1C by about 1% compared with baseline values (apart from the DPP-4 inhibitors which did not lower A1C to the same extent as metformin monotherapy), and by another 1% when added to monotherapy.¹² According to the new AACE 2013 guidelines, for patients with recent-onset T2DM and those with mild hyperglycemia (<7.5%), lifestyle modification and metformin monotherapy (1500 – 2000 mg/day) is generally sufficient and most patients will achieve their glycemic goal.³⁰ They included the SGLT2 inhibitors in their review, but stated that the SGLT2 evaluation and recommendation is based on phase 3 clinical trials data.

Systematic Reviews

The AHRQ systematic review on the comparative effectiveness of oral medications for type 2 diabetes was updated in 2011 (summary in appendix 4) and therefore did not include the new SGLT2 inhibitors.¹² We have identified three systematic review citations for SGLT2 inhibitors (of which one is a protocol³³ and two are reviews for which provisional abstracts were published by the Centre for Reviews and Dissemination^{28,34}; table 3). Musso et al.³⁴ (Search results through Dec 2010) included 13 RCTs (7 with dapagliflozin: 2943 participants, 2 with canagliflozin: 548 participants, 3 with BI 10773/empagliflozin: 536 participants, and 1 with LX4211: 36 participants) that evaluated these agents over periods of 2 to 48 weeks. This review concluded that SGLT2 inhibitors effectively reduce HbA1c and fasting plasma glucose values; they also reduce body mass index, blood pressure, and serum uric acid; and that overall, was safe, without major adverse events.³⁴ Adverse events included a mildly increased risk of mild hypoglycemic events (mostly with insulin therapy), and an increased risk of urinary and genital tract infections (significantly dose-related).³⁴ Limitations are stated as small number, size and duration of studies.³⁴ Larger RCTs of adequate power and duration are needed to confirm these findings. Clar et al.²⁸ (searches updated July 2012) included 8 RCTs (7 with dapagliflozin: 3398 participants, and only 1 canagliflozin trial: 451 participants) with only 2 trials against active comparators.²⁸ Even though the latter was a more recent review, they included fewer studies as their focus was on real-world use of SGLT2 inhibitors so they excluded studies of less than 8 weeks of duration (vs as short as 2 weeks were included in Musso et al.³⁴), and they reviewed SGLT2 inhibitors as combination therapy (not monotherapy).²⁸ The limited amount of studies included is a limitation, but this more recent review by Clar et al.²⁸ appears to be a well-conducted review that followed the principles recommended in the Cochrane Handbook for Systematic Reviews of Intervention, with a clearly defined protocol and inclusion/exclusion criteria, two independent reviewers, a comprehensive literature search, and they used the Cochrane Risk of Bias tool for the quality assessment. These two systematic reviews reached similar conclusions for SGLT2 inhibitors in terms of efficacy (they are effective in reducing HbA1c and fasting plasma glucose); they reduce BMI, serum uric acid and blood pressure; and they have an increased risk of UTIs.^{28,34}

Table 3. SGLT2 Systematic Review(s)

Author	Year	Title	Objective(s)	Summary	Reason(s) provided for review/Authors' Conclusion
Raval AD, et al. ³³	Published Online: 16 FEB 2011	Dapagliflozin for type 2 diabetes mellitus	To assess the effects of dapagliflozin for type 2 diabetes mellitus.	This is the <u>protocol</u> for a review and there is no abstract.	There were no current reviews on dapagliflozin in T2DM (2011), however they mentioned one older review: Brooks 2010 Brooks AM, Thacker SM. Dapagliflozin for the treatment of type 2 diabetes. Annals of Pharmacotherapy 2009; 43 (7): 1286–93. Limitation of this review: it did not address potential clinical outcome like mortality or vascular complications. New RCTs have been published since this review (2009).
Musso G, et al. ³⁴ Centre for Reviews and Dissemination - Database of Abstracts of Effects Reviews of Effects (Provisional Abstract)	2012	A novel approach to control hyperglycemia in type 2 diabetes: sodium glucose co-transport (SGLT) inhibitors. Systematic review and meta-analysis of randomized trials	To assess efficacy and safety of the new antidiabetic drugs sodium glucose co-transport-2 (SGLT2) inhibitors in T2DM.	Included 13 RCTs (through Dec 2010), but limitations are stated as small number, size and duration of studies "Dapagliflozin significantly reduced HbA1c (weighted mean difference (WMD) -0.52%; 95% CI -0.46, -0.57%; P < 0.00001) fasting plasma glucose (WMD -18.28 mg/dL; 95% CI -20.66, -15.89; P < 0.00001), body mass index (WMD -1.17%; -1.41, -0.92%; P < 0.00001), systolic (WMD -4.08 mmHg; -4.91, -3.24), and diastolic (WMD -1.16 mmHg; -1.67, -0.66) blood pressure, and serum uric acid (WMD -41.50 µmol/L; -47.22, -35.79). Other SGLT2 inhibitors showed similar results. Dapagliflozin treatment increased the risk of urinary (OR 1.34; 1.05–1.71) and genital (OR 3.57; 2.59–4.93) tract infection; it also mildly increased the risk of hypoglycemia (OR 1.27; 1.05–1.53) when co-administered with insulin." ³⁴	"Pending confirmation from larger RCTs, this analysis shows SGLT2 inhibitors are safe and effective for hyperglycemia treatment in T2DM." ³⁴
Clar C, et al. ²⁸ Centre for Reviews and Dissemination - Database of Abstracts of Effects Reviews of Effects (Provisional Abstract)	2012	Systematic review of SGLT2 receptor inhibitors in dual or triple therapy in type 2 diabetes (Provisional abstract)	To assess the clinical effectiveness and safety of the SGLT2 receptor inhibitors in dual or triple therapy in type 2 diabetes.	73 possible inclusions were identified, but after exclusions only 7 dapagliflozin (3398 participants) & 1 canagliflozin trials (451 participants; one trial is limitation) were included with only 2 trials against active comparators (searches updated July 2012). Note: inclusion criteria were for dual/triple therapy and not as monotherapy (no trials of triple therapy included). They used the Cochrane risk of bias score for quality assessment of the studies. Authors stated that trial quality appeared good. "Dapagliflozin 10 mg reduced HbA1c by -0.54% (weighted mean differences (WMD), 95% CI -0.67 to -0.40) compared to placebo, but there was no difference compared to glipizide. Canagliflozin reduced HbA1c slightly more than sitagliptin (up to -0.21% vs sitagliptin). Both dapagliflozin and canagliflozin led to weight loss (dapagliflozin WMD -1.81 kg (95% CI -2.04 to -1.57), canagliflozin up to -2.3 kg compared to placebo)." ²⁸	"Dapagliflozin appears effective in reducing HbA1c and weight in type 2 diabetes, although more safety data are needed." ²⁸ The authors stated that more data on safety are needed (with the FDA having concerns about breast and bladder cancers).

Randomized Controlled Trials (RCTs)

Canagliflozin was studied in over 10,300 patients in nine global, randomized and double-blind placebo- or active comparator-controlled trials as monotherapy and in combination with other agents (metformin, sulfonyleurea, metformin and sulfonyleurea, metformin and TZD and insulin).^{20,41-43} These trials were all sponsored by Johnson & Johnson Research & Development, L.L.C.⁴⁴

The Media Fact Sheet from Janssen Research & Development, LLC, 2012 provides the following explanation of the phase 3 Program:

- “CANTATA (CANagliflozin Treatment And Trial Analysis) includes multiple studies assessing the glucose-lowering efficacy and safety of canagliflozin in adult patients diagnosed with type 2 diabetes failing to achieve glycemic control on diet and exercise and on the background of a variety of commonly used oral antihyperglycemic agents or insulin.
- CANVAS (CANagliflozin cardiovascular Assessment Study) assesses the general safety, tolerability and cardiovascular safety of canagliflozin in approximately 4,300 adult patients with type 2 diabetes, who also have either a history or high risk of cardiovascular disease.”⁴¹

Appendix 5 contains a summary of the published randomized controlled trials. Active comparator phase III trials were identified on Clinicaltrials.gov, including efficacy comparisons of canagliflozin with sitagliptin (DPP-4 inhibitor) and glimepiride (sulfonyleurea). The primary endpoint in all the phase 3 RCTs was the change in baseline A1c at specified durations (apart from the CANVAS study which is major adverse cardiovascular events), and across trials, canagliflozin has been shown to be modestly effective in lowering HbA1c, and these studies also explored change in body weight as a secondary endpoint which showed weight loss for canagliflozin. Other important secondary endpoints included percentage of subjects obtaining an A1c <7.0% and fasting plasma glucose levels.⁴⁵ A phase 3 study was also conducted in patients with chronic kidney disease which demonstrated that the efficacy of canagliflozin is attenuated as renal function declines (efficacy on glycemic parameters and body weight reduction was less compared to normal populations).⁴⁶ This is expected due to the lower eGFR and therefore lower glucose excretion and this may also be the reason for the lower rates of adverse effects compared to other phase 3 studies.⁴⁶ Some limitations of these studies include lack of blinding details and randomization methodology description; potential bias; duration of studies (longer-term studies will be needed to evaluate the durability of the effects of canagliflozin); findings may not be generalizable to patients using other AHA regimens, those with milder or more severe hyperglycemia at baseline, or specific ethnic groups (did not include a high proportion of black/African-American/Hispanic patients).

Safety and adverse effects

Canagliflozin phase 3 studies included 9 clinical studies in T2DM adult patients and special populations; adults 55 to 80 years of age (2034 patients ≥65 years; and 345 patients ≥75 years), patients with moderate renal impairment, and patients with or at high risk of cardiovascular disease.^{20,41,42} Canagliflozin should not be used to treat people with type 1 diabetes or in diabetic ketoacidosis.⁴³ No adequate and well-controlled studies were conducted in pregnant women and it should therefore only be used if the potential benefit justifies the potential risk to the fetus (category C).²⁰ The safety and effectiveness of canagliflozin in pediatric patients (<18 years old), patients with severe hepatic impairment, or in patients with severe renal impairment (eGFR <30 mL/minute/1.73 m²), with ESRD, or receiving dialysis have not been established.²⁰ Canagliflozin is not expected to be effective in these renally impaired patients.²⁰

The most common adverse effects^{20,47} associated with canagliflozin (5% or greater incidence) were female genital infections (mycotic and vulvovaginal candidiasis), urinary tract infections, and increased urination.²⁰

Two recent systematic reviews for SGLT2 inhibitors stated that in all the cases the reported UTIs and genital tract infections were not severe and resolved with simple treatment.^{28,34} Other important adverse effects^{20,47,48} include impairment in renal function (canagliflozin increases serum creatinine and decreases eGFR, hypovolemic patients may be more susceptible), hyperkalemia, increases in Low-Density Lipoprotein/LDL-C (4.4 mg/dL with 100 mg and 8.2 mg/dL with the 300 mg)⁴⁵, male genital mycotic infections (balanitis), hypersensitivity reactions, and hypovolemia/decreases in intravascular volume and symptoms associated with it as a result of osmotic diuresis (hypotension, postural dizziness, orthostatic hypotension, syncope, dehydration, headache). Patients at increased risk for the latter were those over 75 years of age, use of loop diuretics and moderate renal impairment (eGFR 30 to less than 60 mL/min/1.73 m²).⁴⁵ It is also important to note that canagliflozin can increase the risk of hypoglycemia when combined with insulin and insulin secretagogues (known to cause hypoglycemia).^{20,34} Hemoglobin elevations, reduction in serum uric acid levels, slightly higher incidence of fracture and dose-related increases in magnesium and phosphate have been reported.^{20,47,48}

It is important to note that prior to approval of canagliflozin, safety concerns were highlighted by FDA staff in a briefing paper for the advisory panel meeting which included cardiac events in the first 30 days of treatment, fracture risks and risks in patients with renal impairment.⁴⁹ The recommendation for approval of canagliflozin was supported by a 10-5 vote by the FDA advisory panel.⁴⁹ As a result of the emerging cardiovascular risk profiles of T2DM medications (e.g. rosiglitazone and its CV risk), the FDA require greater evidence of cardiovascular safety for new T2DM medications⁴⁸ and as a condition of approval of canagliflozin, the FDA has requested a long-term cardiovascular outcomes study and 4 other postmarketing studies (an enhanced pharmacovigilance program to monitor for malignancies, serious cases of pancreatitis, severe hypersensitivity reactions, photosensitivity reactions, liver abnormalities, and adverse pregnancy outcomes, a bone safety study, and two pediatric studies under the Pediatric Research Equity Act (PREA)).^{17,43,49} Long-term data on the effects of canagliflozin (and other SGLT2 inhibitors) on cardiovascular outcomes in T2DM patients are not yet available.³ Apart from the well-known CV risk factors (such as increased body weight, blood pressure, and LDL cholesterol), elevated serum uric acid levels have been reported to be an independent risk factor for CV disease.³ Due to canagliflozin's reductions in blood pressure, body weight, A1C, and uric acid, it may have a favorable overall effect which may benefit obese patients with high CV risk.^{3,50} However, the increase in LDL-C and other potential unknown effects may have the opposite effect. A recent review on the potential of SGLT2 inhibitors to reduce cardiovascular risk in patients with T2DM, stated that with "canagliflozin, increases in HDL-cholesterol and LDL-cholesterol have been observed, with a minimal effect on the total cholesterol:HDL-cholesterol ratio, and small and inconsistent changes in triglycerides."^{3,51,52} A long-term ongoing major cardiovascular study (CANVAS - CANagliflozin cardioVascular Assessment Study; started December 2009 for up to 9 years) will evaluate "canagliflozin compared to placebo on CV events including CV death, heart attack, and stroke in patients with T2DM, whose diabetes is not well controlled at the beginning of the study and who have a history of CV events or have a high risk for CV events."⁵³ This study will "define the effects of canagliflozin on biomarkers and provide data on cardiovascular safety against established regulatory parameters."⁵⁴ The Primary Outcome Measures are Major adverse cardiovascular events, including CV death, nonfatal MI, and nonfatal stroke. Secondary Outcome Measures include a standard measure of fasting insulin secretion; progression of albumin in the urine; and effectiveness of lowering blood glucose.⁵³

Dapagliflozin was denied approval by the FDA because of concerns about a cancer signal. During dapagliflozin's clinical development program, there were 9 cases of bladder cancer (0.2% of patients) with dapagliflozin vs 1 (0.04% of patients) with the comparator, and 9 cases of breast cancer (0.4% of females) with dapagliflozin vs. 1 (0.09% of females) with the comparator.³ However, this drug was approved in Europe in November 2012 and filing has been resubmitted in the US and includes several new studies and data from previously submitted studies.²¹

Canagliflozin has an emerging profile and the drug's long-term safety is unknown.

Place in therapy

Factors and limitations of currently available classes to consider when considering the SGLT2 inhibitors' place in therapy^{28,42}:

- Effect on glycemic control: SGLT2 inhibitors are effective in reducing HbA1c.
- Effect on weight (versus other drugs): Obesity (a common comorbidity in T2DM) contributes to hyperglycemia by inducing insulin resistance, whereas weight loss is proposed to contribute to improvement in glycemic control. Glucosuria associated with canagliflozin has been reported to be about 80-120 g per day, which causes weight loss.^{51,55} Sulfonylureas, insulin, and TZDs are associated with weight gain. If metformin monotherapy is not effective, subcutaneous GLP-1 agonists and SGLT2 inhibitors are the only 2 options that are associated with weight loss. The other recommended agents not mentioned are all weight neutral (apart from pramlintide which is an option only in selected patients).^{7,51}
- Adverse effects: Particularly increased genital and urinary infections with the SGLT2 inhibitors (enhanced glycosuria may predispose to bacterial and mycotic growth).³⁴ The incidence and severity of hypoglycemia is expected to be low with the SGLT2 inhibitors. Sulfonylureas are associated with hypoglycemia, and Nauck et al.⁵⁶ reported a significantly higher incidence of hypoglycemia in the sulfonylurea group than with dapagliflozin.²⁸ Also, insulin and insulin secretagogues are known to cause hypoglycemia. Some drugs have GI side-effects (e.g. metformin, GLP-1 agonists) or are known to cause fluid retention (e.g. TZDs, sulfonylureas, insulin).
- Limited efficacy or durability: Some drugs such as the sulfonylureas and DPP-4 inhibitors lack durability.^{7,42}
- Interactions with other drugs: Drug interactions with canagliflozin include (a) UDP-Glucuronosyl Transferase (UGT) enzyme inducers (e.g. rifampin, phenytoin, phenobarbital, ritonavir) – these decrease the exposure to canagliflozin and an increase in canagliflozin dose from 100 mg to 300 mg should be considered (if currently tolerating 100 mg, with eGFR > 60 mL/min/1.73m², and additional glycemic control is needed). Another antihyperglycemic agent should be considered in patients with an eGFR of 45 to less than 60mL/min/1.73m² (moderate renal impairment) receiving concurrent therapy with a UGT inducer (as the dose is limited to 100 mg in these patients) (b) Digoxin – increases in concentration of digoxin has been seen with the 300 mg canagliflozin dose so monitoring of digoxin levels is recommended with concomitant use.
- Ease of use: Canagliflozin is taken orally once daily before the first meal of the day.
- Reduced cost: Sulfonylureas or insulin. Sulfonylureas are available at very low cost and it is unlikely that a new class such as the SGLT2 inhibitors will be cost-effective compared to them. They do not require special injectable instructions and may be more readily available in some settings. They have also been used for many years and therefore have a long-term safety profile.

Special populations with different individual circumstances require different choices in therapy. For example, physicians managing patients with chronic kidney disease have limited options as several agents are restricted (e.g. metformin due to risk of lactic acidosis, thiazolidinediones if fluid overload is an issue) or should be used with caution due to safety concerns (e.g. sulfonylureas and insulin can lead to sodium retention, weight gain and hypoglycemia).⁴⁶ The findings of the canagliflozin phase 3 study in T2DM patients with chronic kidney disease suggests that it may be an appropriate option in this patient population, but additional studies are needed to assess its efficacy and safety. Dapagliflozin did not demonstrate HbA1c

lowering efficacy in this population and it is not known whether this was due to differences between the drugs in this class or the study designs.^{46,57}

Utah Medicaid Utilization Data

There have been four fills for Canagliflozin:

Patient	Sex	Age	Fill Date	RX Date	Generic	Brand	Form	Qty	Days
X	M	62	7/9/2013	5/15/2013	Canagliflozin	INVOKANA TAB 100MG	Tablet	30	30
			9/10/2013	5/15/2013	Canagliflozin	INVOKANA TAB 100MG	Tablet	30	30
Y	M	36	7/30/2013	7/30/2013	Canagliflozin	INVOKANA TAB 300MG	Tablet	30	30
			8/30/2013	7/30/2013	Canagliflozin	INVOKANA TAB 300MG	Tablet	30	30

The medication history was reviewed for these patients going back one year.

Patient X's medication history includes Janumet (metformin/sitagliptin), pioglitazone, and glimepiride. He is currently filling prescriptions for:

- Invokana 100 mg (30)
- Pioglitazone 45 mg (30)
- Janumet (sitagliptin 50/metformin 1000 x60)

This patient filled prescriptions for Glimepiride 4 mg (60) and Janumet (sitagliptin 50/metformin 1000 x60) for a few months, then pioglitazone 45 mg (30) was added to his regimen for a few months, and then glimepiride was replaced by Invokana.

Patient Y's medication history includes metformin, pioglitazone, and glipizide. This patient is currently filling prescriptions for:

- Metformin 500 mg ER (60)
- Pioglitazone 30 mg (30)
- Glipizide 10 mg (60)
- Invokana 300 mg (30)

This patient filled prescriptions for metformin 500 mg ER (60) and pioglitazone 30 mg (30) for a few months, then glipizide 10 mg (60) was added to the regimen, and then Invokana 300 mg. Adherence appears to be a potential issue with patient Y, he was not started on 100 mg, and both of these patients are taking antihyperglycemics from 4 different classes in which case the prescriber(s) may wish to consider insulin. These patients will therefore be added to our monthly patients to be reviewed in full and if appropriate, letters will be sent to the prescriber(s).

Conclusions

Canagliflozin has been shown to be modestly effective in lowering HbA1c, and it has a low risk of hypoglycemia. It has also been shown to cause weight loss, reduced FPG and BP, increased HDL, and reduced uric acid. Due to canagliflozin's reductions in blood pressure, body weight, A1C, and uric acid, it may have a favorable overall effect which may benefit obese patients with high CV risk.^{3,50} However, the increase in LDL-C and other potential unknown effects may have the opposite effect. Notable side-effects include increased urinary and genital mycotic infections (which were not severe and resolved with simple treatment^{28,34}), and increased LDL-C.⁷ Concerns regarding CV and fracture risks and risks in patients with renal impairment were highlighted by the FDA. A long-term cardiovascular outcomes study and 4 other postmarketing studies (an enhanced pharmacovigilance program, a bone safety study, and two pediatric studies) were required as a

condition of approval^{17,49}. Long-term data on the effects of canagliflozin (and other SGLT2 inhibitors) on cardiovascular outcomes in T2DM patients are not yet available. The findings of the canagliflozin phase 3 study in T2DM patients with chronic kidney disease suggests that it may be an appropriate option in this patient population, but efficacy is attenuated with declining renal function and additional studies are needed to assess its efficacy and safety.⁴⁶

Utilization data for canagliflozin in the Utah Medicaid population is limited with only 4 fills (2 patients) to date. According to the ADA Standards of Medical Care in Diabetes 2013²⁹, current clinical guidelines^{9,30,31} and recent systematic reviews and meta-analyses of randomized controlled trials⁵⁸, metformin remains the cornerstone of type 2 anti-diabetic treatment. Advantages of metformin include low risk of hypoglycemia, can promote modest weight loss, and it has a robust cardiovascular safety profile.³⁰ If metformin alone is inadequate, the guidelines include various options as add-on therapy with a focus on individualized goals of treatment. Global and European guidelines suggest that sulfonylureas are an appropriate second-line therapy whereas current US guidelines are moving towards an individualized approach based on attributes of the patient and medications. The SGLT2 inhibitor class was included in the AACE guideline⁷, and NICE guidelines are currently being updated. It was agreed at the NICE scoping workshop that use in monotherapy would not be considered.⁴ Clinicians have limited experience with the SGLT2s and it is the AACEs consensus that the SGLT2 inhibitors' place in therapy remains undefined. It was proposed that these drugs will likely be used as add-on therapy to two or three other agents (including insulin) in patients who would benefit from weight loss. Patient acceptability remains unanswered and it has been suggested in a recent Lancet article, "SGLT2 inhibitors... turning symptoms into therapy", that only time will tell whether increased frequency of genitourinary infections will be acceptable for patients with diabetes who are prone to such infections and the authors conclude: "Meanwhile, the diabetes community is itching to learn new findings from relevant mechanistic and outcome studies to help establish the place of SGLT2 inhibitors in treatment of type 2 diabetes."¹⁷

Appendix 1 – Comparison of Antidiabetic Agents^{20,30,59-67}

Class	Agents in class	Route of administration	Mechanism of action	Labeled Indications	Notable Adverse Effects / Limiting Acceptability ^{9,30,68,69}
Alpha-glucosidase Inhibitors (AG-i)	Acarbose Miglitol	Oral tablets	Lower postprandial glucose. Competitive inhibitor of alpha-glucosidase (gut enzyme), resulting in delayed breakdowns of complex carbohydrates, thus delaying polysaccharide absorption.	Adjunct to diet and exercise to lower blood glucose in patients with Type 2 diabetes mellitus	Bloating, flatulence, diarrhea
Amylin Mimetics	Pramlintide	Injectable solution; subcutaneous	Synthetic analog of human amylin which works by prolonging gastric emptying (leading to feeling of early satiety), reduces postprandial glucagon secretion, and centrally-mediate appetite suppression	Adjunctive treatment with mealtime insulin in Type 1 diabetes mellitus Adjunctive treatment with mealtime insulin in Type 2 diabetes mellitus, with or without concurrent sulfonylurea and/or metformin	Nausea, hypoglycemia
Biguanides	Metformin Metformin/Alogliptin Metformin/Glipizide Metformin/Glyburide Metformin/Linagliptin Metformin/Pioglitazone Metformin/Repaglinide Metformin/Rosiglitazone Metformin/Saxagliptin Metformin/Sitagliptin	Oral tablets	Decreases hepatic glucose production, decreasing intestinal absorption of glucose and improving insulin sensitivity in muscle and fat	First-line management of Type 2 diabetes mellitus <u>Unlabeled Indications:</u> Gestational diabetes mellitus (GDM); polycystic ovary syndrome (PCOS); prevention of Type 2 diabetes mellitus	Nausea, lactic acidosis, Vitamin B12 deficiency
Bile acid sequestrant	Colesevelam	Oral tablets	Unknown; may reduce glucose absorption, may reduce hepatic insulin resistance (reduction in hepatic glucose production), may affect mediators of glucose metabolism	Type 2 diabetes (combination therapy with insulin or oral antidiabetic agents) Dyslipidemia	GI intolerance (nausea, bloating, constipation), increased triglycerides
Dipeptidyl peptidase IV Inhibitors (DPP-4-i)	Alogliptin Alogliptin/Metformin Alogliptin/Pioglitazone Linagliptin Linagliptin/Metformin Saxagliptin Saxagliptin/Metformin Sitagliptin Sitagliptin/Metformin Sitagliptin/Simvastatin	Oral tablets	Inhibits dipeptidyl peptidase IV (DPP-IV) enzyme resulting in prolonged active incretin levels resulting in increased insulin synthesis & release and decreased glucagon secretion	Management of Type 2 diabetes mellitus as an adjunct to diet and exercise as monotherapy or in combination with other antidiabetic agents	Pancreatitis

Dopamine Agonist	Bromocriptine=> Cycloset®	Oral tablets	Mechanism of action is unknown in type 2 diabetes. Believed to affect circadian rhythms (reversal of insulin resistance and decreases in glucose production, without increasing serum insulin concentrations) mediated in part by dopaminergic activity.	Management of type 2 diabetes mellitus (noninsulin dependent, NIDDM) as an adjunct to diet and exercise	Nausea, orthostasis
Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists	Exenatide Liraglutide	Injectable solution; subcutaneous	Analogs of the hormone incretin which increase glucose-dependent insulin secretion, decrease inappropriate glucagon secretion, increase B-cell growth/replication, slow gastric emptying, and decrease food intake	Treatment of Type 2 diabetes mellitus *May also improve hypertension in patients with diabetes	Headache, nausea, diarrhea. May be associated with pancreatitis, renal insufficiency, and thyroid cell cancer in rodents (Victoza)
Insulins	<u>Rapid-acting</u> Aspart: Novolog Glulisine: Apidra Lispro: Humalog <u>Short-acting</u> Regular: Humulin, Humulin R, Novolin <u>Intermediate-acting</u> NPH: Humulin N, Novolin N <u>Intermediate to Long-acting</u> Detemir <u>Long-acting</u> Glargine <u>Combination Products</u> Aspart protamine + Aspart Lispro protamine + Lispro NPH + Regular: Humulin 70/30, Novolin 70/30	Injectable solution; subcutaneous, intravenous	Insulin acts via specific membrane-bound receptors on target tissues to regulate metabolism of carbohydrate, protein, and fats. Target organs for insulin include the liver, skeletal muscle, and adipose tissue	Treatment of Type 1 diabetes mellitus and Type 2 diabetes mellitus to improve glycemic control	Weight gain, hypoglycemia
Meglitinides (GLN)	Nateglinide Repaglinide Repaglinide/Metformin	Oral tablets	Phenylalanine derivatives which stimulate insulin release and reduce postprandial hyperglycemia	Management of Type 2 diabetes mellitus as monotherapy or in combination with metformin or a thiazolidinedione	Hypoglycemia (rare), slight increases in serum uric acid, dizziness
Sodium-Glucose Cotransporter 2 (SGLT-2) Inhibitor	Canagliflozin	Oral tablets	Inhibits sodium-glucose co-transporter 2 (SGLT2) in the proximal renal tubules=>reduces reabsorption of filtered glucose from the tubular lumen and lowers the renal threshold for glucose (RT _G). SGLT2 is the main site of filtered glucose reabsorption. It results in increased urinary excretion of glucose, thereby reducing plasma glucose concentrations.	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	Urinary tract and genital infections (fungal), increased urination, may increase LDL

Sulfonylureas (SU)	Chlorpropamide Glimepiride Glimepiride/Pioglitazone Glimepiride/Rosiglitazone Glipizide Glipizide/Metformin Glyburide Glyburide/Metformin Tolazamide Tolbutamide	Oral tablets	Stimulates insulin release, reduces glucose output and increases insulin sensitivity	Management of Type 2 diabetes mellitus as monotherapy or in combination with metformin or insulin	Hypoglycemia
Thiazolidinediones (TZD)	Pioglitazone Pioglitazone/Alogliptin Pioglitazone/Glimepiride Pioglitazone/Metformin Rosiglitazone Rosiglitazone/Glimepiride Rosiglitazone/Metformin	Oral tablets	Agonists for peroxisome proliferator-activated receptor-gamma (PPARgamma) which influences the production of a number of gene products involved in glucose and lipid metabolism; improves insulin sensitivity	Management of Type 2 diabetes mellitus as monotherapy or in combination with a sulfonylurea, metformin, or sulfonylurea plus metformin	Weight gain, fluid retention (may contribute to heart failure), fracture risk, increased risk of bladder cancer (pioglitazone), increased risk of cardiovascular adverse effects (rosiglitazone)

Appendix 2 - Sodium-Glucose Co-Transporter Inhibitor(s) (SGLT2)

Table 4. Invokana (canagliflozin) label and FDA approval information^{13,20,70}

Note: An FDA-approved patient medication guide must be dispensed with this medication.

Treatment	Generic	Labeled indication	FDA Approval	Dosage Form(s)	FDA/DEA Classification	Usual Dose from Product Labeling/Lexicomp	Maximal Recommended Dose
Canagliflozin (Invokana)	No	Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus Limitation of Use: Should not be used for the treatment of type 1 diabetes or diabetic ketoacidosis.	03/29/2013	Oral tablet: 100 mg 300 mg	Rx only	<p>Note: If present, correct volume depletion prior to initiation.</p> <p>Initial: 100 mg once daily prior to first meal of the day; may increase to 300 mg once daily (only in patients with eGFR \geq60 mL/minute/1.73 m²)</p> <p>RENAL: <u>eGFR 45 to <60 mL/minute/1.73 m²:</u> Maximum 100 mg once daily. <u>Concurrent UDP-glucuronosyl transferase (UGT) enzyme inducers (eg, rifampin, phenytoin, phenobarbital, ritonavir) and eGFR 45 to <60 mL/minute/1.73 m² at baseline:</u> consider use of another antidiabetic agent. <u>eGFR 30-45 mL/minute/1.73 m²:</u> Use not recommended. In patients <u>already taking canagliflozin</u> (when baseline eGFR was >45 mL/minute/1.73 m²) that experience a <u>persistent decrease in eGFR to <45 mL/minute/1.73 m²,</u> canagliflozin should be discontinued. <u>eGFR <30 mL/minute/1.73 m² & ESRD receiving hemodialysis:</u> Use is contraindicated.</p> <p>HEPATIC: <u>Mild-to-moderate impairment</u> (Child-Pugh class A, B): No dosage adjustment necessary. <u>Severe impairment</u> (Child-Pugh class C): Use not recommended (has not been studied).</p>	300 mg once daily

Canagliflozin - Contraindications, Warnings, and Monitoring^{20,70}

Contraindications: History of severe hypersensitivity to canagliflozin, severe renal impairment, end-stage renal disease (ESRD), or on dialysis.

Warnings & Monitoring: Hypotension has been associated with canagliflozin treatment.

In geriatrics, there was a higher incidence of adverse reactions related to reduced intravascular volume (such as hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration), particularly with the 300 mg dose and in patients 75 years and older.²⁰ In patients with moderate renal impairment, there was a higher incidence of adverse effects related to reduced intravascular volume and renal function. These patients were also more likely to experience increases in potassium with the 300 mg dose.²⁰

Assessment and correction of *volume status and hypovolemia* in patients with renal impairment, the elderly, in patients with low systolic blood pressure or on diuretics, ARBs, or ACE inhibitors is recommended. It is recommended that *renal function* be monitored (baseline and periodically during treatment). It is recommended to monitor *potassium levels* for hyperkalemia (periodically after initiation in renal impairment and those predisposed to hyperkalemia), *serum magnesium and phosphate*, and *LDL-C*. Patients should also be monitored and treated if indicated for genital mycotic infections, and hypersensitivity reactions (discontinued and monitored).

Appendix 3 – Efficacy and Kidney Disease

Table 5. Efficacy, and kidney disease^{9,30}

Medication	Efficacy	A1C lowering	Kidney Disease ^{30,71,72}
Alpha-glucosidase inhibitors	lower ⁹ / modest A1C lowering ⁷	0.4-0.7% ^{30,73} 0.5-1% ^{9,69}	Not recommended in CKD (specifically if serum creatinine >2 mg/dL).
Amylin Mimetics	Lower or equivalent overall A1C lowering vs. other therapies ⁹	0.5-1% ⁶⁸	Pramlintide: CrCl >20 mL/minute: No dosage adjustment necessary. CrCl ≤20 mL/minute & dialysis: No dosage adjustment provided in manufacturer's labeling (has not been studied). ⁷⁴ Not recommended if CKD stage 4 or greater ⁷⁵
Biguanide	Compares favorably to other therapies ⁷ ; high ⁹	1-1.5% ^{9,30,76}	Contraindicated if serum creatinine level ≥1.4 mg/dL in women and ≥1.5 mg/dL in men and in patients with abnormal clearance
Bromocriptine	lower ⁹ / slight glucose lowering ⁷	0.5% ^{30,77} 0.5-1% ⁹	No dose adjustment; predominantly metabolized in liver; use with caution in CKD (no studies in patients with reduced GFR) ⁷⁵
Colesevelam	lower ⁹ / modest glucose lowering ⁷	0.4-0.6% ^{30,78} 0.5-1% ⁹	No dose adjustment
DPP-4 Inhibitor	lower ⁹ / intermediate/modest A1C lowering ⁷	0.5-0.9% ^{30,79,80} 0.5-1% ⁹	Linagliptin – predominantly non-renal elimination – no dose adjustment. Most DPP-4 inhibitors require dose adjustment (excreted by kidney).
GLP-1 agonist	high ⁹ /robust A1C lowering ⁷	0.8-2.0% ^{30,81} 1-1.5% ⁹	Liraglutide => not excreted via kidney => no restrictions in CKD (but not tested in end-stage renal disease/kidney transplant patients). Exenatide should be used with caution in stage 3 CKD and avoided if CrCl <30mL/min.
Insulin	highest	1.5-3.5% ⁶⁸	May increase risk of hypoglycemia; dosage adjustment (insulin requirements may be reduced) & monitoring may be necessary ⁸²
Meglitinides	reduced A1C lowering ^{7,9} Repaglinide more effective than nateglinide	0.5-1% ⁹	Repaglinide: adjust dose in severe renal impairment (CrCl 20-40 mL/min); not studied CrCl <20 mL/min or hemodialysis Nateglinide: No dose adjustments; dialysis => reduced medication exposure and plasma protein binding. Severe renal dysfunction => more susceptible to glucose-lowering effect; use with caution. ⁷¹
SGLT-2	Clinicians have little experience ⁷	0.45-0.92% ³⁰ 0.7-1% ⁶⁹	eGFR 45-<60 mL/min/1.73 m ² : Maximum 100 mg once daily. Not recommended if eGFR 30-45 mL/min/1.73 m ² ; contraindicated if eGFR <30 mL/minute/1.73 m ² & ESRD receiving hemodialysis
Sulfonylurea	high ⁹ / relatively potent A1C lowering ⁷	0.4-1.2% ³⁰ 1-1.5% ⁹	All excreted renally => lower starting doses. Use with caution as hypoglycemia risk may be higher (due to higher blood levels and prolonged half-life in CKD)
TZD	high ⁹ / relatively potent A1C lowering ⁷	0.7-1.2% ^{30,83} 1-1.5% ⁹	Pioglitazone => not excreted renally => no dose adjustment Rosiglitazone => no dosage adjustment ⁸⁴ Caution: risk of fluid retention & heart failure – avoid in patients with advanced kidney failure (especially if they have preexisting heart failure) ⁸⁵

Appendix 4 – AHRQ updated 2011 review

First-line monotherapy	Dual therapy (options to add to metformin)	Considerations based on:	Triple Therapy, insulin, and future research
<p>Evidence supports: metformin; most medications similarly efficacious at lowering hemoglobin A1C by about 1% (compared with baseline values); exception: DPP-4 inhibitor class did not lower A1c to the same extent as metformin when used as monotherapy; evidence still sparse regarding long-term outcomes and the comparative efficacy of the oral medications; metformin more favorable effect on body weight; Metformin decreased low-density lipoprotein cholesterol (LDL-C) relative to pioglitazone, sulfonylureas, and DPP-4 inhibitors.</p>	<p>Combination therapies could decrease A1c levels more than monotherapies; addition of most oral medications to monotherapy further improved glycemic control by lowering A1C by another 1% (compared to baseline values); two-drug combinations compared with each other demonstrated similar reductions in A1c</p>	<p>Weight gain: oral metformin and injectable GLP-1 agonists not associated with weight gain. Greatest risks of mild-to-moderate hypoglycemia: sulfonylureas and 2-drug combinations (sulfonylureas had a 4-fold higher risk of mild-to-moderate hypoglycemia compared with metformin alone, and, in combination with metformin, had more than a 5-fold increased risk compared with metformin plus a thiazolidinedione). Increased risk for heart failure and cardiovascular events: Thiazolidinediones (relative to sulfonylureas). Increased risk for hip and nonhip fractures: Thiazolidinediones (relative to metformin). Gastrointestinal upset: Metformin (compared with TZD users). Macrovascular and microvascular outcomes: low strength and insufficient evidence apart from metformin which was associated with lower all-cause mortality and cardiovascular-disease mortality. CHF - low strength evidence: higher risk for combination therapy with rosiglitazone (compared to metformin+sulfonylurea) and moderate strength evidence: higher risk for TZD monotherapy (compared to sulfonylurea)</p>	<p>Future research should strive to include triple combination regimens. Studies of the addition of basal or premixed insulin compared to metformin or TZDs are lacking</p>

Appendix 5 – Published Canagliflozin RCTs

From ClinicalTrials.gov, published trials, and Canagliflozin for type 2 diabetes mellitus (National Horizon Scanning Centre)⁴⁴

Trial	CANTATA-M (phase 3) ClinicalTrials.gov identifier: NCT01081834	CANTATA-D (phase 3) ClinicalTrials.gov Identifier: NCT01106677	CANTATA-D2 (phase 3) ClinicalTrials.gov identifier: NCT01137812
Publication	Stenloff et al. 2013 ⁸⁶	Lavalle-Gonzales, et al. 2013 ⁸⁷	Schernthaner et al. 2013 ⁸⁸
Comparators	Canagliflozin 100 mg & 300 mg vs sitagliptin 100 mg or placebo	Canagliflozin vs sitagliptin or placebo	Canagliflozin 300 mg vs sitagliptin 100 mg
Location	17 countries: EU, USA & other countries.	22 countries: EU, USA and other countries.	17 countries: EU, USA, Canada and other countries.
Date conducted	Between 08 February 2010 and 18 August 2011	Between 07 April 2010 and 17 August 2012	Between 30 June 2010 and 09 March 2012
Population & treatment allocation	n= 678 patients were enrolled; 587 patients in the main study and 91 patients in the high glycemic substudy. 584 patients in the main study and all 91 patients in the high glycemic substudy received at least one dose of study drug and were included in the modified intent-to-treat (mITT) analyses sets and the safety analyses sets. Adults with type 2 diabetes mellitus; inadequate glycemic control with diet and exercise alone. The Stenloff et al. study report is for the 26-week, randomized, double-blind, placebo-controlled, phase 3 trial, subjects (N=584) who received canagliflozin 100 or 300 mg or placebo once daily. Main study: mean HbA1c=8% & 4.3 years mean diabetes duration; Substudy: mean HbA1c=10.6% & 4.9 years mean diabetes duration.	n=1,284 were randomly allocated to the 4 treatment arms; Adults with type 2 diabetes mellitus; aged ≥ 18 and ≤ 80 years who had inadequate glycaemic control (HbA1c $\geq 7.0\%$ [53 mmol/mol] and $\leq 10.5\%$ [91 mmol/mol]) on metformin therapy; Randomised to canagliflozin 100mg or 300mg, once daily for 52 weeks, or sitagliptin 100mg once daily for 52 weeks, or placebo, once daily for 26 weeks followed by sitagliptin 100mg once daily for 26 weeks. All patients also take protocol-specified stable doses of metformin for 52 weeks. All patients received at least 1 dose of study drug and were included in the modified intent-to-treat (mITT) analysis set (used for the Week 26 and week 52 efficacy analyses). All 1,284 patients were included in the Week 26 and Week 52 safety analysis sets.	n=756 randomly allocated to the 2 treatment arms in the study. n=755 patients received at least 1 dose of study drug and were included in the modified intent-to-treat (mITT) analysis set and the safety analysis set. Adults with type 2 diabetes mellitus; inadequate glycaemic control on metformin and sulfonylurea therapy; Included patients: mean duration of diabetes: 9.2 years with a mean A1C of 8.1%
Objective/Aim(s)	To evaluate the efficacy and safety of canagliflozin in subjects with T2DM inadequately controlled with diet and exercise.	To evaluate the efficacy and safety of canagliflozin compared with sitagliptin and placebo in patients with type 2 diabetes mellitus who are receiving treatment with metformin monotherapy (i.e., treatment with a single drug) and have inadequate glycemic (blood sugar) control.	To evaluate the efficacy and safety of canagliflozin compared with sitagliptin in patients with type 2 diabetes mellitus inadequately controlled with metformin plus sulfonylurea.
Design	RCT - active & placebo, double blind, parallel-group, 3 arm, multicenter study	RCT - active & placebo, double blind, 4-Arm, Parallel Group, Multicenter Study	RCT- active-controlled, double-blind, multicenter study

Reporting groups	(a) Main Study: Placebo/Sitagliptin - placebo once daily for 26 weeks and were then switched to 100 mg of sitagliptin once daily until Week 52 (b) Main Study: Canagliflozin 100 mg - 100 mg of canagliflozin once daily for 52 weeks (c) Main Study: Canagliflozin 300 mg - 300 mg of canagliflozin once daily for 52 weeks (d) High Glycemic Substudy: Canagliflozin 100 mg - 100 mg of canagliflozin once daily for 26 weeks (e) High Glycemic Substudy: Canagliflozin 300 mg - 300 mg of canagliflozin once daily for 26 weeks	(a) Placebo/Sitagliptin - Each patient received matching placebo once daily for 26 weeks and were then switched from placebo to 100 mg of sitagliptin once daily until Week 52. Placebo and sitagliptin were given with protocol-specified doses of metformin immediate release. (b) Canagliflozin 100 mg - Each patient received 100 mg of canagliflozin once daily for 52 weeks with protocol-specified doses of metformin immediate release. (c) Canagliflozin 300 mg - Each patient received 300 mg of canagliflozin once daily for 52 weeks with protocol-specified doses of metformin immediate release. (d) Sitagliptin 100 mg - Each patient received 100 mg of sitagliptin once daily for 52 weeks with protocol-specified doses of metformin immediate release.	(a) Canagliflozin 300 mg - Each patient received 300 mg of canagliflozin once a day for 52 weeks with protocol-specified doses of metformin and sulfonylurea. (b) Sitagliptin 100 mg - Each patient received 100 mg of sitagliptin once a day for 52 weeks with protocol-specified doses of metformin and sulfonylurea.
OUTCOMES & RESULTS	Stenloff et al. reports the results of the 26-week core treatment period and the placebo-controlled study component is referred to as the 'main study'.		The greatest difference was shown in those with the highest baseline A1cs ($\geq 9.0\%$). Overall discontinuation rate: High (38.5%) - 44% of the sitagliptin group and 33% in the canagliflozin group.
Primary outcome	HbA1c (change from baseline in haemoglobin A1c (HbA1c) at week 26) 100 mg & 300 mg reduced HbA1c to a greater extent than placebo (-0.77, -1.03, 0.14% respectively; $p < 0.001$ for both)	Change in HbA1c From Baseline to Week 26 At week 26, canagliflozin 100 mg and 300 mg reduced HbA1c vs placebo (-0.79%, -0.94%, -0.17%, respectively; $p < 0.001$). At week 52, canagliflozin 100 mg and 300 mg demonstrated non-inferiority, and canagliflozin 300 mg demonstrated statistical superiority, to sitagliptin in lowering HbA1c (-0.73%, -0.88%, -0.73%, respectively); differences (95% CI) vs sitagliptin were 0% (-0.12, 0.12) and -0.15% (-0.27, -0.03), respectively.	HbA1c (change from baseline in haemoglobin A1c (HbA1c) at week 52) Canagliflozin 300 mg demonstrated noninferiority and, in a subsequent assessment, showed superiority to sitagliptin 100 mg in reducing A1C (-1.03% [-11.3 mmol/mol] and -0.66% [-7.2 mmol/mol], respectively; least squares mean difference between groups, -0.37% [95% CI, -0.50 to -0.25] or -4.0 mmol/mol [-5.5 to -2.7])." More patients discontinued from the study due to loss of glycemic control in the sitagliptin arm (22.5% vs 10.6%).
Secondary outcomes	Proportion of subjects achieving HbA1c < 7.0%; change from baseline in fasting plasma glucose (FPG), 2-h postprandial glucose (PPG) and systolic blood pressure (BP); and percent change in body weight, high-density lipoprotein cholesterol (HDL-C) and triglycerides. Greater percentage of patients obtained HbA1c < 7% compared to placebo (NNT=2-4) Both canagliflozin doses significantly decreased FPG, 2-h PPG, body weight and systolic BP ($p < 0.001$ for all), and increased HDL-C compared with placebo ($p < 0.01$ for both).	FPG; body weight; postprandial plasma glucose concentrations; proportion of patients achieving HbA1c < 7% and < 6.5%; systolic and diastolic blood pressure; fasting plasma lipids. Canagliflozin 100 mg and 300 mg reduced body weight vs placebo (week 26: -3.7%, -4.2%, -1.2%, respectively; $p < 0.001$) and sitagliptin (week 52: -3.8%, -4.2%, -1.3%, respectively; $p < 0.001$). Both canagliflozin doses reduced FPG and systolic BP vs placebo (week 26) and sitagliptin (week 52) ($p < 0.001$).	Change in fasting plasma glucose (FPG) and systolic blood pressure (BP), Percent change in body weight, triglycerides, and HDL cholesterol. Greater reductions in FPG (-29.9 vs. -5.9 mg/dL), body weight (-2.5 vs. 0.3%), and systolic BP (-5.1 vs. 0.9 mmHg) were observed with canagliflozin versus sitagliptin ($P < 0.001$). Canagliflozin raised HDL-C relative to sitagliptin (% change, 7.6 vs 0.6) and LDL-C (% change 11.7 vs 5.2).

Adverse effects	"Overall incidences of AEs were modestly higher with canagliflozin versus placebo; rates of serious AEs and AE-related discontinuations were low and similar across groups. Incidences of genital mycotic infections, urinary tract infections and osmotic diuresis-related AEs were higher with canagliflozin; these led to few discontinuations. The incidence of hypoglycaemia was low across groups."	Overall AE and AE-related discontinuation rates were generally similar across groups, but higher with canagliflozin 100 mg. Genital mycotic infection and osmotic diuresis-related AE rates were higher with canagliflozin; few led to discontinuations. Hypoglycaemia incidence was higher with canagliflozin.	Overall AE rates were similar with canagliflozin (76.7%) and sitagliptin (77.5%); incidence of serious AEs and AE-related discontinuations was low for both groups. Higher incidences of genital mycotic infections and osmotic diuresis-related AEs were observed with canagliflozin, which led to one discontinuation. Hypoglycemia rates were similar in both groups.
Authors' conclusion	Canagliflozin treatment improved glycaemic control, reduced body weight and was generally well tolerated in subjects with T2DM inadequately controlled with diet and exercise."	Canagliflozin improved glycaemia and reduced body weight vs placebo (week 26) and sitagliptin (week 52) and was generally well tolerated in patients with type 2 diabetes on metformin.	Findings suggest that canagliflozin may be a new therapeutic tool providing better improvement in glycemic control and body weight reduction than sitagliptin, but with increased genital infections in subjects with type 2 diabetes using metformin plus sulfonylurea.

Trial	CANTATA-SU (phase 3) ClinicalTrials.gov Identifier: NCT00968812	An Efficacy, Safety, and Tolerability Study of Canagliflozin in Patients With Type 2 Diabetes Mellitus Who Have Moderate Renal Impairment (phase 3); ClinicalTrials.gov Identifier: NCT01064414	A Safety and Efficacy Study of Canagliflozin in Older Patients (55 to 80 Years of Age) With Type 2 Diabetes Mellitus. ClinicalTrials.gov Identifier: NCT01106651	Dose-ranging effects of canagliflozin, a sodium-glucose cotransporter 2 inhibitor, as add-on to metformin in subjects with type 2 diabetes, Phase IIB, ClinicalTrials.gov Identifier: NCT00642278
Publication	Cafalu et al. 2013 ⁵¹	Yale et al. 2013 ⁴⁶	Bode et al. 2013 ⁸⁹	Rosenstock et al. 2012 ⁵²
Comparators	Canagliflozin 100 mg or 300 mg, or glimepiride starting dose of 1mg (up-titrated to 6 mg or 8 mg per day) orally once daily. All patients continue taking metformin.	Canagliflozin 100 mg or 300 mg vs. placebo	Canagliflozin 100 mg or 300 mg vs. placebo	Canagliflozin 50, 100, 200, or 300 mg once daily (QD) or 300 mg twice daily (BID), sitagliptin 100 mg QD, or placebo.
Location	19 countries: EU, USA, Canada and other countries.	19 countries: EU, USA, Canada and other countries.	17 countries worldwide.	13 countries worldwide.
Date conducted	Between 28 August 2009 and 25 January 2013	Between 02 March 2010 and 19 January 2012	Between 12 April 2010 and 14 June 2013.	Between 27 March 2008 and 28 January 2009

Population & treatment allocation	Patients with T2DM, 18 to 80 years of age, inclusive, who are not optimally controlled on metformin monotherapy; glycosylated haemoglobin A1c (HbA1c) of 7.0-9.5%; Body mass index (BMI) ≥ 22 to ≤ 45 kg/m ² at screening; fasting plasma glucose (FPG) ≤ 270 mg/dL (15 mmol/L) at Week -2; n=1450 of 1452 randomised patients received at least one dose of glimepiride (n=482), canagliflozin 100 mg (n=483), or canagliflozin 300 mg (n=485).	≥ 25 years; type 2 diabetes mellitus who had inadequate glycaemic control (HbA1c ≥ 7.0 and $\leq 10.5\%$); reduced renal function - stage 3 CKD (eGFR ≥ 30 and < 50 ml/min/1.73 m ²), Randomised to canagliflozin 100mg or 300mg, once daily for 52 weeks, or placebo once daily for 52 weeks. All arms in addition to standard of care for diabetes (American Heart Association regimen). Mean baseline HbA1c: 8%; Mean age: 68.5 year; Mean BMI: 33.0 kg/m ² ; Mean duration of T2DM: 16.3 years; Mean baseline eGFR: 39.4 ml/min/1.73 m ²	n = 716, aged 55 to 80 years (mean, 63.6 years) with glycosylated hemoglobin (HbA1c) levels $\geq 7.0\%$ to $\leq 10.0\%$ were randomized. Seven hundred fourteen received canagliflozin 100 mg or 300 mg or placebo (1:1:1) daily.	n= 451 randomized to canagliflozin 50, 100, 200, or 300 mg once daily (QD) or 300 mg twice daily (BID), sitagliptin 100 mg QD, or placebo.
Objective/Aim(s)	To demonstrate the efficacy, safety, and tolerability of canagliflozin compared with glimepiride in patients with type 2 diabetes mellitus with inadequate control despite treatment with metformin.	To evaluate the efficacy and safety of canagliflozin in subjects with T2DM and stage 3 chronic kidney disease [CKD; estimated glomerular filtration rate (eGFR) ≥ 30 and < 50 ml/min/1.73 m ²] (this is a more restricted range rather than to < 60 ml/min/1.73 m ²)	To evaluate the efficacy and safety of 2 different doses of canagliflozin compared with placebo in older patients (55 to 80 years of age) with type 2 diabetes mellitus (T2DM) with inadequate control on their current diabetes treatment regimen.	To evaluate the effects of canagliflozin in type 2 diabetes mellitus inadequately controlled with metformin monotherapy.
Design	RCT - active-controlled, double-Blind, 3-Arm Parallel-Group, 2-Year (104-Week), multicenter study, phase 3 non-inferiority trial	RCT - placebo-controlled	RCT - placebo-controlled, Parallel-Group, Multicenter Study	RCT - double-blind, placebo-controlled, parallel-group, multicenter, dose-ranging study

Reporting groups	<p>(a) Canagliflozin 100 mg - received 100 mg canagliflozin once daily with protocol-specified doses of metformin for 104 weeks.</p> <p>(b) Canagliflozin 300 mg - received 300 mg canagliflozin once daily with protocol-specified doses of metformin for 104 weeks.</p> <p>(c) Glimpiride - received glimepiride, at protocol-specified doses, once daily in combination with protocol-specified doses of metformin for 104 weeks. Data are presented for Baseline to Week 52.</p>	<p>(a) Placebo - received matching placebo once daily for 52 weeks.</p> <p>(b) Canagliflozin 100 mg - received 100 mg canagliflozin once daily for 52 weeks.</p> <p>(c) Canagliflozin 300 mg - received 300 mg of canagliflozin once daily for 52 weeks.</p>	<p>(a) Placebo: Baseline to Week 26 - receive matching placebo once daily for 104 weeks with/without stable doses of antihyperglycemic agent(s) taken at the time of study entry. Data are presented for Baseline to Week 26.</p> <p>(b) Canagliflozin 100 mg: Baseline to Week 26 - receive 100 mg canagliflozin once daily for 104 weeks with/without stable doses of antihyperglycemic agent(s) taken at the time of study entry. Data are presented for Baseline to Week 26.</p> <p>(c) Canagliflozin 300 mg: Baseline to Week 26 - receive 300 mg canagliflozin once daily for 104 weeks with/without stable doses of antihyperglycemic agent(s) taken at the time of study entry. Data are presented for Baseline to Week 26.</p>	<p>Canagliflozin 50 mg Daily Each patient received 50 mg of canagliflozin (JNJ-28431754) once daily (in the morning) for 12 weeks with matching placebo once daily (in the evening).</p> <p>(a) Canagliflozin 100 mg Daily - received 100 mg canagliflozin once daily (in the morning) for 12 weeks with matching placebo once daily (in the evening).</p> <p>(b) Canagliflozin 200 mg Daily - received 200 mg canagliflozin once daily (in the morning) for 12 weeks with matching placebo once daily (in the evening).</p> <p>(c) Canagliflozin 300 mg Daily - received 300 mg canagliflozin once daily (in the morning) for 12 weeks with matching placebo once daily (in the evening).</p> <p>(d) Canagliflozin 300 mg Twice Daily - received 300 mg canagliflozin twice daily for 12 weeks.</p> <p>(e) Sitagliptin 100 mg Daily - received 100 mg sitagliptin once daily (in the morning) for 12 weeks with matching placebo once daily (in the evening).</p>
OUTCOMES & RESULTS		<p>Yale et al. 2013 report on the 26-week, double-blind, core treatment period. The 26-week, double-blind, extension period's data to be reported in a separate publication.</p>		
Primary outcome	<p>Change in HbA1c from baseline to week 52 with a non-inferiority margin of 0.3% for the comparison of each canagliflozin dose with glimepiride. If non-inferiority was shown, they assessed superiority on the basis of an upper bound of the 95% CI for the difference of each canagliflozin dose versus glimepiride of less than 0.0%.</p>	<p>Change in HbA1c from baseline to week 26</p>	<p>Change in HbA1c from baseline to week 26</p>	<p>Change in A1C from baseline through week 12.</p>

	Canagliflozin 100 mg was non-inferior to glimepiride/similar effect (least-squares mean difference -0.01% [95% CI -0.11 to 0.09]); canagliflozin 300 mg was superior to glimepiride (-0.12% [-0.22 to -0.02])	Canagliflozin 100 and 300 mg reduced HbA1c from baseline compared with placebo at week 26 (-0.33, -0.44 and -0.03%; p < 0.05).	At week 26, treatment with canagliflozin 100 mg and 300 mg significantly reduced HbA1c levels compared with placebo (-0.60%, -0.73%, -0.03%, respectively; P < 0.001); more subjects achieved HbA1c levels < 7.0% with both canagliflozin doses compared with placebo (P < 0.001).	Canagliflozin was associated with significant reductions in A1C from baseline (7.6-8.0%) to week 12: -0.79, -0.76, -0.70, -0.92, and -0.95% for canagliflozin 50, 100, 200, 300 mg QD and 300 mg BID, respectively, versus -0.22% for placebo (all P < 0.001) and -0.74% for sitagliptin.
Secondary outcomes	Percentage of Patients Experiencing at Least 1 Hypoglycemic Event From Baseline to Week 52; Percent Change in Body Weight From Baseline to Week 52; Change Per Year in HbA1c as a Measure of Durability of Glycemic Control	FPG; fasting plasma lipids; body weight; systolic and diastolic blood pressure; proportion of patients achieving HbA1c <7%; proportion of patients receiving rescue therapy; renal function; glycaemic control.	Proportion of subjects achieving HbA1c levels < 7.0%, change from baseline in fasting plasma glucose (FPG) level and systolic blood pressure (BP), and percent change from baseline in body weight, triglyceride levels, and high-density lipoprotein cholesterol (HDL-C) level.	Change in fasting plasma glucose (FPG), body weight, and overnight urinary glucose-to-creatinine ratio.
	Canagliflozin was associated with reductions in body weight (unlike glimepiride), and a lower incidence of hypoglycaemia episodes.	Numerical reductions in FPG (but not statistical significant) and higher proportions of subjects reaching HbA1c < 7.0% were observed with canagliflozin 100 and 300 mg versus placebo (27.3, 32.6 and 17.2%). Both doses were also associated with reductions in body weight (thought to be related to loss of calories/glucose excretion, but also osmotic diuretic effect - patients with renal impairment tend to have sodium & fluid retention), and blood pressure (osmotic effect)	Both canagliflozin doses significantly reduced body weight, FPG level, and systolic BP, and increased HDL-C level compared with placebo (P < 0.001); low-density lipoprotein cholesterol level was increased with both canagliflozin doses compared with placebo.	FPG was reduced by -16 to -27 mg/dL, and body weight was reduced by -2.3 to -3.4%, with significant increases in urinary glucose-to-creatinine ratio.

Adverse effects	39 (8%) patients had serious adverse events in the glimepiride group versus 24 (5%) in the canagliflozin 100 mg group and 26 (5%) in the 300 mg group. In the canagliflozin 100 mg and 300 mg groups versus the glimepiride group, they recorded a greater number of genital mycotic infections (women: 26 [11%] and 34 [14%] vs five [2%]; men: 17 [7%] and 20 [8%] vs three [1%]), urinary tract infections (31 [6%] for both canagliflozin doses vs 22 [5%]), and osmotic diuresis-related events (pollakiuria: 12 [3%] for both doses vs one [$<1\%$]; polyuria: four [$<1\%$] for both doses vs two [$<1\%$]).	Overall AE rates were similar for canagliflozin 100 and 300 mg and placebo (78.9, 74.2 and 74.4%). Slightly higher rates of urinary tract infections and AEs related to osmotic diuresis and reduced intravascular volume were observed with canagliflozin 300 mg compared with other groups. The same AEs that were seen in other phase 3 studies (genital mycotic infections, small increase in UTIs, and osmotic diuresis AEs e.g. polyuria) were seen, but at lower rates in this study. Transient changes in renal function parameters that trended towards baseline over 26 weeks were observed with canagliflozin.	The overall AE incidence was slightly higher with canagliflozin 300 mg than with canagliflozin 100 mg or placebo (78.0%, 72.2%, 73.4%, respectively). Serious AE and AE-related discontinuation rates were low across groups. Both canagliflozin doses were associated with higher rates than placebo of genital mycotic infections, urinary tract infections, and osmotic diuresis-related AEs (i.e. pollakiuria, polyuria). Documented hypoglycemia rates were modestly higher with both canagliflozin doses compared with placebo.	Adverse events were transient, mild to moderate, and balanced across arms except for a non-dose-dependent increase in symptomatic genital infections with canagliflozin (3-8%) versus placebo and sitagliptin (2%). Urinary tract infections were reported without dose dependency in 3-9% of canagliflozin, 6% of placebo, and 2% of sitagliptin arms. Overall incidence of hypoglycemia was low.
Authors' conclusion	Canagliflozin provides greater HbA1c reduction than glimepiride, and is well tolerated in patients with type 2 diabetes receiving metformin. These findings support the use of canagliflozin as a viable treatment option for patients who do not achieve sufficient glycaemic control with metformin therapy.	Canagliflozin improved glycaemic control and was generally well tolerated in subjects with T2DM and Stage 3 CKD.	Canagliflozin improved glycemic control, reduced body weight and systolic BP, and was generally well tolerated in older subjects with T2DM who were on background therapy with a variety of blood glucose-lowering agents.	Canagliflozin added onto metformin significantly improved glycemic control in type 2 diabetes and was associated with low incidence of hypoglycemia and significant weight loss. The safety/tolerability profile of canagliflozin was favorable except for increased frequency of genital infections in females.

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