**Name of journal: World Journal of Diabetes**

**ESPS Manuscript NO: 9134**

**Columns: Minireview**

Canagliflozin-current status in the treatment of type 2 diabetes mellitus with focus on clinical trial data

BhatiaJ *et al.* Canagliflozin in type 2 diabetes

Jagriti Bhatia, Nanda Gamad, Saurabh Bharti, Dharamvir Singh Arya

**Jagriti Bhatia, Nanda Gamad, Saurabh Bharti, Dharamvir Singh Arya,** Department of Pharmacology, All India Institute of Medical Sciences, New Delhi-110029, India

**Author contributions:** All the authors contributed in collection of data on CFZ; Bhatia J and Gamad N were involved in writing the manuscript; Gamad N and Bharti S compiled the table no. 1 (Summary of clinical trials of CFZ) and table no. 2 (Summary of adverse events observed in the CFZ clinical trials) in the manuscript; Arya DS did the final editing of the review article.

**Correspondence to: Dr. Jagriti Bhatia,** Department of Pharmacology, All India Institute of Medical Sciences, Gautam Nagar, New Delhi 110029, India. [jagriti2012@gmail.com](mailto:jagriti2012@gmail.com)

**Telephone:** +91-11-26594266 **Fax:** +91-11-26584121

**Received:** January 22, 2014 **Revised:** April 3, 2014

**Accepted:** April 17, 2014

**Published online:**

**Abstract**

Canagliflozin (CFZ) is a member of new class of glucose lowering agents, sodium-glucose co-transporter (SGLT) inhibitors, which got approval by FDA. It has insulin independent action by blocking the transporter protein SGLT2 in the kidneys, resulting in urinary glucose excretion and reduction in blood glucose levels. In clinical trials, CFZ significantly decreased HbA1c level when administered either as monotherapy or as combined therapy with other anti-diabetic drugs. Intriguingly, it showed additional benefits like weight reduction and lowering of blood pressure. The commonly observed side effects were urinary and genital infections. It has exhibited favorable pharmacokinetic and pharmacodynamic profiles even in patients with renal and hepatic damage. Hence, this review purports to outline CFZ as a newer beneficial drug for type 2 diabetes mellitus.

© 2014 Baishideng Publishing Group Co., Limited. All rights reserved.

**Key words: Type 2 diabetes mellitus;** Sodium-glucose co-transporter **2; canagliflozin; clinical trial; safety profile**

**Core tip: This review article focuses upon the current pharmacokinetic, pharmacodynamic and clinical trial data on the newly introduced** sodium-glucose co-transporter **2 inhibitor, canagliflozin, for the treatment of type 2 diabetes mellitus. It also discusses briefly about the safety profile and future prospective of canagliflozin.**

Bhatia J, Gamad N, Bharti S, Arya DS. Canagliflozin-current status in the treatment of type 2 diabetes mellitus with focus on clinical trial data.

**Available from: URL:**

**DOI:**

**INTRODUCTION**

Diabetes mellitus (DM) is a metabolic disorder characterized by insulin resistance, hyperglycemia and progressive pancreatic β-cell dysfunction. Poorly controlled hyperglycemia leads to irreversible microvascular and macrovascular complications like visual impairment and blindness, kidney failure, peripheral neuropathy, myocardial infarction, stroke and lower limb amputation. In 2012, worldwide > 371 million people suffered from diabetes. Out of which 4.8 million people died due to its complications. This global burden is estimated to increase to 552 million by 2030[1]. This implies that the available drugs for DM are not able to maintain or achieve good glycemic control. Potential adverse events like gastrointestinal disturbances (with biguanides like metformin, α-glucosidase inhibitors like acarbose, GLP-1 agonists like exenatide, amylin agonists like pramlintide), hypoglycemia (with insulin, secretagogues like sulfonylureas and meglitinides), weight gain (with insulin, secretagogues like sulfonylureas and meglitinides, thiazolidinediones like pioglitazone) and risk of cardiovascular disease (with thiazolidinediones like pioglitazone) limit their dosage; and ensuing β-cell failure limits their effectiveness. Current guidelines recommend a target HbA1c value of < 7.0%, with patient-centered approach allowing some flexibility in terms of the actual target, and treatment with lifestyle changes and drugs for better glycemic control in diabetics. But the target HbA1c is rarely achieved with a single anti-diabetic agent and in only about half of adult patients with diabetes taking combination therapy[2,3]. Hence, there is ongoing hunt for newer efficacious and safer treatment strategies.

Kidney plays a pivotal role in maintaining glucose homeostasis through specialized transporters- SGLT1 and SGLT2- present in the proximal convoluted tubule (PCT). Together, they absorb almost all of the glucose filtered in the glomerulus. SGLT1 is a low capacity, high affinity transporter present mostly in small intestine, some in S3 segment of PCT in kidney, and in heart. It is responsible for approximately 10% of glucose reabsorption in the kidney. While SGLT2 is a high capacity, low affinity transporter present almost exclusively in S1 segment of PCT, responsible for approximately 90% of glucose reabsorption[4,5]. But kidney was never the target for treatment of diabetes until phlorizin was discovered. Phlorizin was isolated from the apple trees in 1835 and was initially tested for fever, infectious diseases and malaria. It was noticed that high doses caused glycosuria and chronic administration in dogs caused polydipsia and polyuria with normoglycemia. Subsequent detection of SGLT1 and SGLT2 in kidney, their role in glucose reabsorption and confirmation of inhibitory action of phlorizin on these transporters in animal studies paved way to consider phlorizin in the treatment of type 2 diabetes mellitus (T2DM). However, phlorizin was not clinically developed due to its poor pharmacokinetics and side effects attributed to SGLT1 inhibition such as glucose-galactose malabsorption, dehydration and diarrhea[6,7]. Later on T-1095 was discovered, a derivative of phlorizin which had comparatively better pharmacokinetic profile. Nevertheless, it was discontinued in the Phase-II clinical trial[8]. Meanwhile, it was observed that there was upregulation of SGLT2 and increase in maximum tubular transport of glucose in diabetic patients[9]. The underline defect in patients with familial renal glycosuria is also attributable to SGLT2 gene mutation. The patients with gene defect excrete increased amount of glucose in urine and are clinically asymptomatic[10]. These two observations with SGLT2 transporter *i.e*., the upregulation of SGLT2 in diabetes and its role in familial renal glycosuria, triggered research that ultimately led to the discovery of specific SGLT2 inhibitors viz. sergliflozin and remogliflozin. Unfortunately, these drugs too exhibited unfavorable pharmacokinetic profile, efficacy and side effect and hence did not progress in clinical trials[11].

Dapagliflozin is the first SGLT2 inhibitor that came to the European market in 2012. FDA approved dapagliflozin on 8th January, 2014[12]. It was initially rejected by FDA due to serious concerns about bladder and breast cancer[13]. Canagliflozin was the first of its kind to get approval from FDA on March 29, 2013. Currently it is in phase-II trial for the treatment of obesity in the USA and Europe[14]. Ipragliflozin, empagliflozin and many other SGLT2 inhibitors are under different phases of clinical trials.

This article reviews the available data on the pharmacokinetics, the pharmacodynamics and the therapeutic potential and safety of CFZ.

**SEARCH METHODOLOGY**

PubMed, ClinicalTrials.gov and Google scholar databases were used for mining the data. Following MESH words were used in the above mentioned databases: canagliflozin, canagliflozin and SGLT2, canagliflozin and diabetes, canagliflozin and pharmacokinetics, canagliflozin and pharmacodynamics and canagliflozin and adverse events. Up to date information was included till 31st March 2014.

**PHARMACOKINETIC PROPERTIES**

When CFZ is taken orally it gets rapidly absorbed from gastrointestinal tract in a dose dependent manner with the dose range of 50-300 mg and mean oral bioavailability of approximately 65%. Median t1/2 is 1-2 hours and steady state concentration is achieved after 4 to 5 days of daily intake of 100 mg and 300 mg. Maximum plasma concentration (Cmax) is not altered in renal injury. It accumulates in the plasma up to 36% following multiple doses of 100 and 300 mg. The plasma protein binding is 99%, which is constant irrespective of its plasma concentrations or hepatic or renal damage[15,16]. It is metabolized into two inactive *O*-glucuronide metabolites (M5 and M7). Major *O*-glucuronidation is by UGT1A9 and UGT2B4, while CYP3A4 mediated oxidative metabolism accounts for only 7%. Single oral radioactive [14C] CFZ to healthy subjects demonstrated 41.5%, 7.0% and 3.2% of administered radioactive dose in feces as CFZ, a hydroxylated metabolite and an *O*-glucuronide metabolite, respectively. The amount of CFZ excreted in urine in unchanged form is less than 1%, whereas the urine excretion of its metabolites namely M7 is 21%-32% and M5 is 7%-10%. Studies conducted so far have shown no clinically significant effect of age, sex, BMI/weight and race on pharmacokinetics of CFZ[15,16].

**PHARMACODYNAMIC PROPERTIES**

CFZ primarily inhibits SGLT2 in kidney and is responsible for increased urinary glucose excretion and reduction in blood glucose levels. It also inhibits SGLT1 in intestine and its potency on SGLT1 is 160 times lesser as compared to SGLT2[15,16]. It reduces glucose absorption by 31% in first hour and 20% by next hour of food intake. So, when given before meal, it reduces postprandial glucose excursions[15,17]. This insulin independent action is unique and differentiates CFZ from other available anti-diabetic agents. Moreover, there is dose dependent reduction in the renal threshold for glucose excretion (RTG) with maximal suppression of RTG from 240 mg/dL to ~70-90 mg/dL at the dose of 300 mg. Unlike other oral hypoglycemic drugs, CFZ is tolerated well in mild to moderate hepatic and renal failure patients. However, it is contraindicated in patients with Egfr < 30 mL/min per 1.73 m2, end stage kidney disease and patients on dialysis[15].

**DOSAGE AND ADMINISTRATION**

The recommended starting dose of CFZ is 100 mg once daily to be taken before the first meal of the day. If patients with eGFR of ≥ 60 mL/min per 1.73 m2 tolerate CFZ 100 mg once daily and require additional glycemic control, then dose can be increased to 300 mg once daily. Volume depletion has to be corrected in patients prior to the initiation of CFZ to compensate for CFZ induced increased urination[15].

**DRUG INTERACTIONS**

UGT inducers (*e.g*., rifampin, phenytoin, phenobarbital, ritonavir) increase the metabolism of CFZ, thereby reducing active CFZ levels in the blood. Thus, the dose of CFZ may be increased from 100 to 300 mg in such patients. On the other hand, CFZ increases Area Under the Curve (AUC) for digoxin and hence patients on digoxin treatment should be monitored[15].

**THERAPEUTIC POTENTIAL**

CFZ has shown promising results in many preclinical and clinical studies of T2DM. A study in Zucker fatty rats and Zucker diabetic fatty rats with CFZ (3-30 mg/kg) decreased renal threshold for glucose and increased urinary glucose excretion (UGE). This resulted in decreased blood glucose, HbA1c, weight gain, dose dependent increased fatty acid metabolism, de novo lipogenesis and improved insulin sensitivity in these animals[18].

Table 1 lists the published clinical trials on CFZ use as monotherapy and combined therapy. The CANTATA Trials (CANagliflozin Treatment And Trial Analysis) evaluated CFZ as monotherapy or as an add-on therapy to metformin, metformin and sulphonylurea and metformin and pioglitazone. These trials were randomized; double blind, placebo- or active-controlled with primary endpoint of finding the change in HbA1c at the end of 26 or 52 wk from baseline. In a trial using CFZ as monotherapy, both the doses 100 mg and 300 mg produced a statistically significant decrease in HbA1c (*P <* 0.001), body weight (-2.8% by 100 mg and -3.9% by 300 mg *vs* placebo, *P <* 0.001) as well as systolic blood pressure (-3.7 mmHg by 100 mg and -5.4 mmHg by 300 mg *vs* placebo, *P <* 0.001)[19]. Similar significant results were obtained in combined therapy trials viz. CANTATA-D (Dual therapy trial- CFZ compared with Sitagliptin)[20] and CANTATA-MP (CFZ compared with metformin and pioglitazone)[21].

The CANTATA-SU (CFZ compared with Sulphonylurea) trial established reductions in HbA1c in the glimepiride and CFZ 100 mg groups but greater reductions occurred in CFZ 300 mg group. CFZ 100 mg was reviewed as non-inferior where as CFZ 300 mg group was considered as superior to glimepiride arm. There was greater reduction in body weight, BP and greater rise in HDL levels in CFZ group[23]. CANTATA-MSU (CFZ compared with metformin and sulphonylurea) results also demonstrated statistically significant reductions (*P <* 0.001) in HbA1c, FBG and body weight[24]. In another CANTATA-D2 (Triple therapy trial- CFZ compared with Sitagliptin) trial, at the end of 52 wk, it was showed that CFZ 300 mg was superior to sitagliptin 100 mg when added to sulphonylurea and metformin, in reducing HbA1c, fasting blood glucose (FBG), body weight and systolic blood pressure. There was also significant increase in HDL (*P <* 0.001) in CFZ groups as compared to sitagliptin 100 mg[25].

CANTATA trials have unveiled various interesting clinical observations of CFZ use in the management of T2DM patients. CFZ improved glycemic control without a concomitant increase in the occurrence of hypoglycemia. It lowered RTG but lowering of RTG remained above the hypoglycemic threshold (60-70 mg/dL) and since UGE occurs below the RTG, the incidence as well as risk of hypoglycemia with CFZ was minimal[19,26]. Further, the amplified UGE of 80-120 g/d accounted for net loss of calories (approximately 400 kcal/d) that contributed to the weight loss, which was maintained over the trial period of 52 wk[24,26]. This weight loss was predominantly from loss of fat mass rather than lean body mass[22]. The reversal of glucotoxicity and weight loss together helped to improve beta cell function as indicated in improvement in HOMA-%B (Homeostasis Model Assessment estimating steady state beta cell function in percentage)[19,21,24,26]. The mechanism for increased LDL-C with CFZ is not known, however, improvement in HDL-C and triglycerides was likely to be due to improved glycemic control and weight loss associated with CFZ[19,21,22]. Mild reduction in BP was also observed in the trial participants. This was due to the mild osmotic diuretic response to UGE and natriuretic effect of CFZ[24]. Thus, in nutshell, CFZ can reduce blood glucose levels and has the least risk of producing hypoglycemia as compared to other anti-diabetic agents. In addition, it can also modify the insulin resistance, reduce weight and BP and increase HDL-C. These diverse effects are specific to CFZ and would explain the better outcome with CFZ treated patients as compared to other anti-diabetic agent treatment groups. The CANTATA trials have concluded that CFZ could be taken as an initial drug for T2DM patients whose glycemic control is not achieved with diet and exercise; and also as an effective alternative to sulphonylurea, sitagliptin or pioglitazone in dual therapy with metformin.

CFZ was also studied as an add-on to insulin therapy in a 28-day trial. Participants were T2DM patients not optimally controlled with insulin and receiving up to one oral antihyperglycemic agent. Both the CFZ doses (100 mg and 300 mg) showed greater reduction in HbA1c, body weight and FBG[26].

The effects of various doses of CFZ (50, 100, 200, 300 mg OD and 300 mg BD) have also been assessed in a 12-week trial in T2DM patients under stable metformin therapy. CFZ demonstrated greater reduction in FBG and body weight at all doses as compared to sitagliptin[27].

Three studies conducted trials in special patient population. One study was on adults with T2DM aged 55 to 80 years, not controlled on diet and exercise together with an antihyperglycemic agent. This trial showed that CFZ is equally effective in this age group[15]. In the second study, CFZ showed significant reduction in HbA1c in T2DM patients with or without an antihyperglycemic agent, on regular diet and exercise with moderate renal impairment[28]. The third trial done on T2DM patients with stage 3 chronic kidney disease (CKD) established the safety and efficacy of CFZ in these patients as well[29].

**SAFETY PROFILE**

Overall, CFZ is well tolerated. The distinctive concern is about increased risk of genital mycotic infections and urinary tract infections (UTI). The data from the four pooled 26-week placebo-controlled trials including monotherapy trial and three add-on combination trials with metformin, metformin and suphonylurea or metformin and pioglitazone; demonstrated female genital mycotic infections in 3.2% of patients in placebo, 10.4% in CFZ 100 mg and 11.4% of patients in CFZ 300 mg groups. The incidence of genital mycotic infection was less in males with rates of 0.6% in placebo, 4.2% in CFZ 100 mg and 3.7% in CFZ 300 mg groups. UTI presented at the rate of 4% in the placebo, 5.9% in 100 mg dose and 4.3% in the 300 mg dose groups[15].

Other common adverse events reported were increased urination, vulvovaginal pruritus, thirst, constipation and nausea. The risk of hypoglycemia in patients with CFZ was generally low. Volume depletion-related adverse reactions such as dizziness, hypotension and dehydration were higher in elderly patients, 65 years or older, particularly with the 300 mg daily dose, in comparison to younger patients. There were mild and transient changes in eGFR, albumin-creatinine ratio and BUN in early phase of the study in stage 3 CKD patients. However, 26-week treatment caused return of these parameters to baseline; there was also an increase in serum potassium and magnesium in these patients[15,29]. Some studies showed increase in LDL-C and hematocrit[15]. These short-term studies have shown no significant changes in vital signs or ECG finding with CFZ use. A long term prospective study to evaluate the efficacy and adverse effect profile of CFZ is already underway[30]. The summary of adverse events of CFZ is depicted in Table 2.

**CONCLUSION**

Clinical trial data for CFZ reveal that its glucose lowering efficacy is superior to usual gold standard drugs with the added benefit of weight loss. FDA has already approved CFZ monotherapy in adjuvant to diet and exercise. So far, none of the serious concerns which surround dapagliflozin are seen in CFZ trials. Furthermore, its insulin independent action is an important advantage as this essentially means that its glucose-lowering efficacy should not decrease significantly with progression of diabetes. CFZ is also compatible with other anti-diabetic therapies, including insulin, and might therefore be of value at any stage in the natural history of T2DM. CFZ with its multi dimensional properties can be beneficial in the disease cluster of obesity, hypertension and diabetes. Further, there is a low propensity to cause hypoglycemia in patients as glucose is reabsorbed by SGLT1 in kidney. In addition to the reported side effects of CFZ like UTI, genital mycotic infections, volume depletion and hypotension, the high cost of CFZ may prove to be a limiting factor in its wide spread use. However, for the time being CFZ has been proven to be safe and well tolerated and it is for the further long term studies to establish it more firmly as a major breakthrough in the clinical armamentarium for patients with diabetes.

**REFERENCES**

1 Global diabetes plan at a glance 2011-2021. International diabetes federation. Brussels, Belgium: IDF Expert Meeting: www.idf.org/sites/default/files/Global\_Diabetes\_Plan\_Final.pdf (2010, last accessed 31st March 2014)

2 **Inzucchi SE**, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, Peters AL, Tsapas A, Wender R, Matthews DR. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2012; **35**: 1364-1379 [PMID: 22517736 DOI: 10.2337/dc12-0413]

3 American Diabetes Association. Standards of medical care in diabetes--2012. *Diabetes Care* 2012; **35** Suppl 1: S11-S63 [PMID: 22187469 DOI: 10.2337/dc12-s011]

4 **Kanai Y**, Lee WS, You G, Brown D, Hediger MA. The human kidney low affinity Na+/glucose cotransporter SGLT2. Delineation of the major renal reabsorptive mechanism for D-glucose. *J Clin Invest* 1994; **93**: 397-404 [PMID: 8282810 DOI: 10.1172/JCI116972]

5 **Bailey CJ**. Renal glucose reabsorption inhibitors to treat diabetes. *Trends Pharmacol Sci* 2011; **32**: 63-71 [PMID: 21211857 DOI: 10.1016/j.tips.2010.11.011]

6 **Mackenzie GM**. An experimental study of blood glycolysis. The effects of thyroid and adrenal extracts and phlorhizin on glycolysis in vitro. *J Exp Med* 1915; **22**: 757-765 [PMID: 19867956 DOI: 10.1084/jem.22.6.757]

7 **Ehrenkranz JR**, Lewis NG, Kahn CR, Roth J. Phlorizin: a review. *Diabetes Metab Res Rev* 2005; **21**: 31-38 [PMID: 15624123 DOI: 10.1002/dmrr.532]

8 **Isaji M**. SGLT2 inhibitors: molecular design and potential differences in effect. *Kidney Int Suppl* 2011; : S14-S19 [PMID: 21358697 DOI: 10.1038/ki.2010.511]

9 **Freitas HS**, Anhê GF, Melo KF, Okamoto MM, Oliveira-Souza M, Bordin S, Machado UF. Na(+) -glucose transporter-2 messenger ribonucleic acid expression in kidney of diabetic rats correlates with glycemic levels: involvement of hepatocyte nuclear factor-1alpha expression and activity. *Endocrinology* 2008; **149**: 717-724 [PMID: 17962340 DOI: 10.1210/en.2007-1088]

10 **Santer R**, Kinner M, Lassen CL, Schneppenheim R, Eggert P, Bald M, Brodehl J, Daschner M, Ehrich JH, Kemper M, Li Volti S, Neuhaus T, Skovby F, Swift PG, Schaub J, Klaerke D. Molecular analysis of the SGLT2 gene in patients with renal glucosuria. *J Am Soc Nephrol* 2003; **14**: 2873-2882 [PMID: 14569097 DOI: 10.1097/01.ASN.0000092790.89332.D2]

11 **Washburn WN**. Evolution of sodium glucose co-transporter 2 inhibitors as anti-diabetic agents. *Expert Opin Ther Pat* 2009; **19**: 1485-1499 [PMID: 19852718 DOI: 10.1517/13543770903337828]

12 FDA approves Farxiga to treat type 2 diabetes. U.S. Food and Drug Administration. http: //www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm380829.htm. (2014, last accessed 31st March 2014)

13 **Rosenwasser RF**, Sultan S, Sutton D, Choksi R, Epstein BJ. SGLT-2 inhibitors and their potential in the treatment of diabetes. *Diabetes Metab Syndr Obes* 2013; **6**: 453-467 [PMID: 24348059]

14 **Elkinson S**, Scott LJ. Canagliflozin: first global approval. *Drugs* 2013; **73**: 979-988 [PMID: 23729000 DOI: 10.1007/s40265-013-0064-9]

15 Janssen Pharmaceuticals Inc. InvokanaTM (canagliflozin) tablets, for oral use: US prescribing information. http: //www.janssenmd.com/pdf/invokana/PI-INVOKANA.pdf. (2013, last accessed 31st March 2014)

16 Janssen Pharmaceuticals Inc. Endocrinologic and Metabolic Drugs Advisory Committee. Canagliflozin as an Adjunctive Treatment to Diet and Exercise Alone or Co-administered with Other Antihyperglycemic Agents to Improve Glycemic Control in Adults with Type 2 Diabetes Mellitus.www.fda.gov/downloads/AdvisoryCommittees/.../UCM334551.pdf. ‎ (2013, last accessed 31st March 2014)

17 **Polidori D**, Sha S, Mudaliar S, Ciaraldi TP, Ghosh A, Vaccaro N, Farrell K, Rothenberg P, Henry RR. Canagliflozin lowers postprandial glucose and insulin by delaying intestinal glucose absorption in addition to increasing urinary glucose excretion: results of a randomized, placebo-controlled study. *Diabetes Care* 2013; **36**: 2154-2161 [PMID: 23412078 DOI: 10.2337/dc12-2391]

18 **Liang Y**, Arakawa K, Ueta K, Matsushita Y, Kuriyama C, Martin T, Du F, Liu Y, Xu J, Conway B, Conway J, Polidori D, Ways K, Demarest K. Effect of canagliflozin on renal threshold for glucose, glycemia, and body weight in normal and diabetic animal models. *PLoS One* 2012; **7**: e30555 [PMID: 22355316 DOI: 10.1371/journal.pone.0030555]

19 **Stenlöf K**, Cefalu WT, Kim KA, Alba M, Usiskin K, Tong C, Canovatchel W, Meininger G. Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise. *Diabetes Obes Metab* 2013; **15**: 372-382 [PMID: 23279307 DOI: 10.1111/dom.12054]

20 Janssen Research & Development, LLC. The CANTATA-D Trial (CANagliflozin Treatment and Trial Analysis-DPP-4 Inhibitor. Comparator Trial). http: //clinicaltrials.gov/ct2/show/record/NCT01106677?term=CANTATA-D&rank= 1& sect=X0125 (2010, last accessed 31st March 2014)

21 **Guthrie R**, Goldenberg R, Vijapurkar U, Yee J, Meininger G, Stein P. Efficacy and safety of canagliflozin in subjects with type 2 diabetes mellitus on metformin and pioglitazone [abstract]. 4th World Congress on Controversies to Consensus in Diabetes, Obesity and Hypertension; 8-11 November 2012; Barcelona, Spain

22 **Forst T**, Guthrie R, Goldenberg R, Yee J, Vijapurkar U, Meininger G, Stein P. Efficacy and safety of canagliflozin over 52 weeks in patients with type 2 diabetes on background metformin and pioglitazone. *Diabetes Obes Metab* 2014; : [PMID: 24528605 DOI: 10.1111/dom.12273]

23 **Cefalu WT**, Leiter LA, Yoon KH, Arias P, Niskanen L, Xie J, Balis DA, Canovatchel W, Meininger G. Efficacy and safety of canagliflozin versus glimepiride in patients with type 2 diabetes inadequately controlled with metformin (CANTATA-SU): 52 week results from a randomised, double-blind, phase 3 non-inferiority trial. *Lancet* 2013; **382**: 941-950 [PMID: 23850055 DOI: 10.1016/S0140-6736(13)60683-2]

24 **Wilding JP**, Mathieu C, Vercruysse F, Usiskin K, Deng L, Canovatchel W. Canagliflozin, a sodium glucose co-transporter 2 inhibitor, improves glycaemia in subjects with type 2 diabetes inadequately controlled with metformin plus sulphonylurea [abstract no. 766]. *Diabetologia* 2012; **55** Suppl 1: S315-S316

25 **Schernthaner G**, Gross JL, Rosenstock J, Guarisco M, Fu M, Yee J, Kawaguchi M, Canovatchel W, Meininger G. 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* 2013; **36**: 2508-2515 [PMID: 23564919 DOI: 10.2337/dc12-2491]

26 **Devineni D**, Morrow L, Hompesch M, Skee D, Vandebosch A, Murphy J, Ways K, Schwartz S. Canagliflozin improves glycaemic control over 28 days in subjects with type 2 diabetes not optimally controlled on insulin. *Diabetes Obes Metab* 2012; **14**: 539-545 [PMID: 22226086 DOI: 10.1111/j.1463-1326.2012.01558.x]

27 **Rosenstock J**, Aggarwal N, Polidori D, Zhao Y, Arbit D, Usiskin K, Capuano G, Canovatchel W. Dose-ranging effects of canagliflozin, a sodium-glucose cotransporter 2 inhibitor, as add-on to metformin in subjects with type 2 diabetes. *Diabetes Care* 2012; **35**: 1232-1238 [PMID: 22492586 DOI: 10.2337/dc11-1926]

28 **Yale JF**, Bakris G, Xi L, Figueroa K, Wajs E, Usiskin K, Meininger G. Canagliflozin, a sodium glucose co-transporter 2 (SGLT2) inhibitor, improves glycaemic control and is well tolerated in type 2 diabetes mellitus (T2DM) subjects with moderate renal impairment [abstract no. 759]. *Diabetologia* 2012; **55** Suppl 1: S312

29 Janssen Research & Development, LLC. An Efficacy, Safety, and Tolerability Study of Canagliflozin in Patients With Type 2 Diabetes Mellitus Who Have Moderate Renal Impairment. http: //clinicaltrials.gov/ct2/show/results/NCT01064414?term=NCT01064414&rank=1§=X4305#othr (2010, last accessed 31st March 2014)

30 Janssen Research & Development, LLC. CANVAS - CANagliflozin cardioVascular Assessment Study. http: //clinicaltrials.gov/show/NCT01032629 (2009, last accessed 31st March 2014)

**P-Reviewers:** Georgescu A, Tamemoto H **S-Editor:** Wen LL **L-Editor:** **E-Editor:**

**Table 1 Summary of clinical trials of canagliflozin**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **References/Trial name**  **(*n =* sample size)** | **Study population and duration of the study** | **Study drugs** | **Change in HbA1c from the baseline (in percent)** | **Change in FBG from baseline** | **Change in body weight from baseline** | **Other parameters**  **(Least square mean change)** |
| Stenlof *et al*[19]  (*n =* 584) | T2DM patients on diet and exercise with inadequate glycemic control  Duration of the study  = 26 wk | CFZ = 100 mg/300 mg OD *vs* PL | -0.77% to  -1.03%  (CFZ 100 mg/300 mg, *P <* 0.001 *vs* PL) | -27 mg/dL to  -35 mg/dL  (CFZ 100 mg/300 mg, *P <* 0.001 *vs* PL) | % Body weight reduction  -2.8% to  -3.9%  (CFZ 100 mg/300 mg, *P <* 0.001 *vs* PL) | ΔPPBG = -43 to  -59 mg/dL (CFZ 100 mg/300 mg)  ΔSBP = -3.3 to -5.0 mmHg (CFZ 100 mg/300 mg,  *P <* 0.001 *vs* PL)  ΔDBP = -1.7 to  -2.1 mmHg (CFZ 100 mg/300 mg *vs* PL)  ΔHDL = CFZ 100 mg = +11.2%  (*P <* 0.001 *vs* PL)  CFZ 300 mg = +10.6%  (*P <* 0.01 *vs* PL)  ΔLDL = +2.9% to +7.1%  (CFZ 100 mg/300 mg *vs* PL)  ΔTG = +2.5% to  -2.3 (CFZ 100 mg/300 mg *vs* PL)  HOMA-%B =  +9.9% to +20.3%  (CFZ 100 mg/300 mg *vs* PL) |
| CANTATA-D[20]  (*n =* 1284) | 26-week extension study  T2DM patients with inadequate glycemic control on protocol specified MET-IR monotherapy with HbA1c: 7.0% to 10.5%, FBG< 270 mg/dL | CFZ = 100 mg/300 mg OD + MET-IR *vs* PL+ MET-IR for first 26 wk  CFZ = 100 mg/300 mg OD + MET-IR *vs* SITA 100 mg + MET-IR for next 26 wk | At the end of 26 wk  -0.79% to  -0.94%  (CFZ 100 mg/300 mg, *P <* 0.001 *vs* PL)  SITA =  -0.82%  At the end of 52 wk  -0.73% to  -0.88%  (CFZ 100 mg/300 mg)  SITA =  -0.73% | At the end of 26 wk  -27.3 mg/dL to  -37.8 mg/dL  (CFZ 100 mg/300 mg, *P <* 0.001 *vs* PL)  SITA =  -20.2 mg/dL  At the end of 52 wk  -26.2 mg/dL to  -35.2 mg/dL  (CFZ 100 mg/300 mg, *P <* 0.001 *vs* SITA)  SITA =  -17.7 mg/dL | At the end of 26 wk  % Body weight reduction  -3.7% to  -4.2%  (CFZ 100 mg/300 mg, *P <* 0.001 *vs* PL)  SITA =  -1.2%  At the end of 52 wk  -3.8% to  -4.2%  (CFZ 100 mg/300 mg, *P <* 0.001 *vs* SITA)  SITA =  -1.3% | At the end of 26 wk  ΔPPBG = -47.9 mg/dL to  -57.1mg/dL  (CFZ 100 mg/300 mg, *P <* 0.001 *vs* PL)  SITA = -49.3 mg/dL  ΔSBP =  -3.84 mmHg to  -5.06 mmHg  (CFZ 100 mg/300 mg,  *P <* 0.001 *vs* PL)  SITA = -1.83 mmHg  ΔTG = CFZ 100 mg = +1.6%, *P =* 0.7 *vs* PL, CFZ 300 mg = -1.4%, *P =* 0.2 *vs* PL  SITA = +1.0%  ΔHDL = +10.4% to +12.1%  (CFZ 100 mg/300 mg, *P <* 0.001 *vs* PL)  SITA = +5%  At the end of 52 wk  ΔSBP =  -3.53 mmHg to  -4.65 mmHg  (CFZ 100 mg/300 mg,  *P <* 0.001 *vs* SITA)  SITA = -0.66 mmHg  ΔTG = CFZ 100 mg = +1.9%,  *P =* 0.46 *vs* SITA  CFZ 300 mg  = +2.7%, *P =* 0.32 *vs* SITA  SITA = -0.4%  ΔHDL = +11.2% to +13.3%  (CFZ 100 mg/300 mg,  *P <* 0.001 *vs* SITA)  SITA = +6.0% |
| Guthrie *et al* [21,22]  CANTATA-MP  (*n =* 344) | 26-week extension study  T2DM patients currently treated with PPAR gamma agent (PIO or ROSI) and MET with HbA1c:  7-10.5% and FBG< 270 mg/dL | CFZ = 100 mg/300 mg OD + MET + PIO *vs* PL + MET + PIO  for first 26 wk  CFZ = 100 mg/300 mg OD + MET + PIO *vs* SITA 100 mg + MET + PIO  for next 26 wk | At the end of 26 wk  -0.89% to  -1.03%  (CFZ 100 mg/300 mg, *P <* 0.001 *vs* PL)  At the end of 52 wk  -0.92% to  -1.03%  (CFZ 100 mg/300 mg) | At the end of 26 wk  -26.8 mg/dL to  -33.2 mg/dL  (CFZ 100 mg/300 mg, *P <* 0.001 *vs* PL)  At the end of 52 wk  -26.7 mg/dL to  -31.5 mg/dL  (CFZ 100 mg/300 mg) | At the end of 26 wk  -2.8% to  -3.8%  (CFZ 100 mg/300 mg, *P <* 0.001 *vs* PL)  At the end of 52 wk  -2.7% to  -3.7%  (CFZ 100 mg/300 mg) | At the end of 26 wk  ΔSBP = CFZ 100 mg = -5.30 mmHg (*P =* 0.005 *vs* PL)  CFZ 300 mg =  -4.70 mmHg (*P =* 0.016 *vs* PL)  ΔTG = CFZ 100 mg = +3.2%  (*P =* 0.034 *vs* PL)  CFZ 300 mg =  -1.7%  (*P =* 0.003 *vs* PL)  ΔHDL = CFZ 100 mg = +7.2% (*P =* 0.01 *vs* PL)  CFZ 300 mg = +8.9% (*P <* 0.001 *vs* PL)  HOMA-%B =  +15.19% to +18.14%  (CFZ 100 mg/300 mg, *P <* 0.01 *vs* PL)  At the end of 52 wk  ΔSBP = -3.4 to -3.7 mmHg (CFZ 100 mg/300 mg)  ΔDBP = -2.5 to  -2.7 mmHg (CFZ 100 mg/300 mg)  ΔHDL = CFZ 100 mg = +7.0%  CFZ 300 mg = +11.4%  ΔLDL = +10.9% to +14.3%  (CFZ 100 mg/300 mg)  ΔTG = +4.7% to  -0.6% (CFZ 100 mg/300 mg) |
| Cefalu *et al*[23]  CANTATA-SU  (*n =* 1450) | T2DM patients with HbA1c:  7-9.5% on stable MET therapy  ≥ 1500 mg/d, BMI = 22-45kg/m2, FBG≤ 270mg/dL  Duration of the study  = 52 wk | CFZ = 100 mg/300mg OD + MET *vs* GLIM 6mg/8mg OD + MET | -0.82% to  -0.93%  (CFZ 100 mg/300 mg)  GLIM =  -0.81% | -1.35 mmol/L to  -1.52 mmol/L  (CFZ 100 mg/300 mg)  GLIM =  -1.02 mmol/L | -4.2% to  -4.7%  (CFZ 100 mg/300 mg, *P <* 0.001 *vs* GLI)  GLIM = 1% | ΔSBP = -3.3 to -4.6 mmHg  (CFZ 100 mg/300 mg)  GLIM = +0.2 mmHg  ΔDBP = -1.8 to -2.5 mmHg  (CFZ 100 mg/300 mg)  GLIM = -0.1 mmHg  ΔTG =  CFZ 100 mg = -3.7%  CFZ 300 mg = +2.3%  GLIM = +9.5%  ΔHDL =  CFZ 100 mg = +7.9%  CFZ 300 mg = +9.0%  GLIM = 0.3%  ΔLDL = +9.6% to +14.1%  (CFZ 100 mg/300 mg)  GLIM = +5% |
| Wilding *et al* [24]  CANTATA-MSU  (*n =* 469) | 26-week extension study  T2DM patients currently treated with MET and SU with HbA1c: 7-10.5% and FBG < 270 mg/dL | CFZ = 100 mg/300 mg OD + MET + SU *vs* PL + MET + SU | At the end of 26 wk  -0.85% to  -1.06%  (CFZ 100 mg/300 mg, *P <* 0.001 *vs* PL) | At the end of 26 wk  -18.2 mg/dL to  -30.5 mg/dL  (CFZ 100 mg/300 mg, *P <* 0.001 *vs* PL) | At the end of 26 wk  -2.1% to  -2.6%  (CFZ 100 mg/300 mg, *P <* 0.001 *vs* PL) | At the end of 26 wk  ΔSBP =  CFZ 100 mg = -4.89 mmHg (*P =* 0.07 *vs* PL)  CFZ 300 mg = -4.27 mmHg (*P =* 0.2 *vs* PL)  ΔTG =  CFZ 100 mg = +5.4%  (*P =* 0.256 *vs* PL)  CFZ 300 mg = +8.5%  (*P =* 0.57 *vs* PL)  ΔHDL =  CFZ 100 mg = +5.7% (*P =* 0.153 *vs* PL)  CFZ 300 mg = +6.5% (*P =* 0.056 *vs* PL) |
| Schernthaner *et al*[25]  CANTATA-D2  (*n =* 755) | T2DM patients currently treated with MET and SU with HbA1c: 7-10.5% and FBG < 300 mg/dL  Duration of the study  = 52 wk | CFZ = 300 mg OD + MET + SU *vs* SITA =  100 mg OD + MET + SU | CFZ 300 mg = -1.03% (*P <* 0.001 *vs* SITA)  SITA =  -0.66% | CFZ 300 mg =  -29.9 mg/dL (*P <* 0.001 *vs* SITA)  SITA = -5.85 mg/dL | CFZ 300 mg = -2.5% (*P <* 0.001 *vs* SITA)  SITA = +0.3% | ΔSBP = CFZ 300 mg = -5.06 mmHg  (*P <* 0.001 *vs* SITA)  SITA = +0.85 mmHg  ΔTG =  CFZ 300 mg = +9.6% (*P =* 0.554 *vs* SITA)  SITA = +11.9%  ΔHDL =  CFZ 300 mg = 7.6% (*P <* 0.001 *vs* SITA)  SITA = +0.6% |
| Devineni *et al*[26]  (*n =* 29) | T2DM patients not optimally controlled on insulin and up to one oral AHA with BMI: 25-45 kg/m2, FBG: 3.3-5.5 mmol/L, HbA1c: 7-10.5% and serum creatinine: <132.6 μmol/L for males and <123.8 μmol/L for women  Duration of the study  = 28 days | CFZ 100 mg OD/300 mg *bid* + Insulin + upto one AHA *vs* PL + Insulin + upto one AHA | -0.73% to  -0.92%  (CFZ 100 mg/300 mg) | -2.11 mmol/L to  -2.35 mmol/L  (CFZ 100 mg/300 mg) | -0.73 kg to  -1.19 kg  (CFZ 100 mg/300 mg) | ΔUGE =  +71.9 g/d to +129.2 g/d |
| Rosenstock *et al*[27]  (*n =* 451) | T2DM patients under stable MET monotherapy (≥1500 mg/d) with HbA1c:  7-10%, BMI: 24-45 kg/m2, serum creatinine:  <1.5mg/dL for males and  <1.4 mg/dL for females  Duration of the study  = 12 wk | CFZ = 50/  100/200/  300 mg OD or 300 mg *bid* + MET *vs* PL + MET *vs*  SITA  100 mg OD + MET | CFZ 50 mg =  -0.79%  100 mg =  -0.76%  200 mg =  -0.70%  300 mg =  -0.92%  300 mg *bid* =  -0.95%  SITA =  -0.74% | CFZ 50 mg = -16.2 mg/dL  100 mg =  -25.2 mg/dL  200 mg =  -27.0 mg/dL  300 mg =  -25.2 mg/dL  300 mg *bid* =  -3.4 mg/dL  SITA =  -12.6mg/dL | CFZ 50 mg = -2.3%  100 mg =  -2.6%  200 mg =  -2.7%  300 mg =  -3.4%  300 mg *bid* = -3.4%  SITA =  -0.6% | ΔSBP = -3.3 to -5 mmHg  (CFZ 100 mg/300 mg)  SITA = -0.8 mmHg  ΔDBP =  -1.7 to -2.1 mmHg  (CFZ 100 mg/300 mg)  SITA = -0.6mmHg  ΔTG =  CFZ 100 mg = +2.5%  CFZ 300 mg = -2.3%  ΔHDL =  CFZ 100 mg = +11.2%  CFZ 300 mg = +10.6%  ΔLDL = +2.9% to +7.1% (CFZ 100 mg/300 mg)  HOMA-%B =  CFZ 50-300 mg OD = 6 to 18%  CFZ 300 mg *bid* = 16%  SITA = 10% |
| ClinicalTrials. gov identifier: NCT01064414 [29]  (*n =* 272) | 26-week extension study  T2DM patients with or without AHA, on regular diet and exercise with moderate renal impairment | CFZ = 100 mg/300 mg OD with or without AHA *vs* PL with or without AHA | At the end of 26 wk  -0.33% to  -0.44%  (CFZ 100 mg, *P =* 0.01 *vs* PL, CFZ 300 mg, *P <* 0.001 *vs* PL) | At the end of 26 wk  CFZ 100 mg  = -14.9 mg/dL,  *P =* 0.02  CFZ 300mg  = -11.7 mg/dL,  *P =* 0.06 | Information was not available | Information was not available |

OD: Once daily; FBG: Fasting blood glucose; PL: Placebo; CFZ: Canagliflozin; ΔSBP: Change in systolic blood pressure from baseline; ΔDBP: Change in diastolic blood pressure from baseline; ΔHDL: Change in blood HDL level from baseline; ΔLDL: Change in blood LDL level from baseline; ΔTG: Change in blood triglycerides level from baseline; ΔPPBG: Change in postprandial blood glucose from baseline; MET: Metformin; SU: Sulphonylurea; SITA: Sitagliptin; PIO: Pioglitazone; ROSI: Rosiglitazone; AHA: Antihyperglycemic agent; IR: Immediate release; GLIM: Glimepride; HOMA-%B: Homeostasis Model Assessment estimating steady state beta cell function in percentage.

**Table 2 Summary of adverse events observed in the canagliflozin clinical trials**

|  |  |  |  |
| --- | --- | --- | --- |
| **S. No** | **ClinicalTrials.gov identifier** | **Adverse events** | **References** |
| 1 | NCT01081834 | Increased incidence of AEs in CFZ groups  Serious AEs and AE related discontinuations similar in all groups  Increased incidence of UTI, genital mycotic infections and osmotic diuresis related AEs in CFZ groups  Moderate increase in BUN, serum creatinine and decrease in serum uric acid | Stenlof *et al*[19] |
| 2 | NCT01106677 | AEs similar across all groups  Higher incidence of pollakiuria in CFZ groups– 5.71% with 100 mg CFZ and 2.72% with 300mg CFZ v/s 0.55% of PL | [20] |
| 3 | NCT01106690 | Vulvovaginal mycotic infections: 2.65% to 5.26% v/s 0% of placebo  Pollakiuria: 6.14% to 9.42% v/s 0.87% of placebo  Increased rate of hypoglycemic event with CFZ 300 mg (5.26% v/s 1.74% of PL) | Guthrie *et al*[21] |
| 4 | NCT00968812 | Osmotic diuresis related AEs in 3% of CFZ groups as compared to <1% in placebo groups  Genital infections and increase in LDL cholesterol more in CFZ groups | Cefalu *et al*[23] |
| 5 | NCT01106625 | Superficial genital mycotic infection: 16.0% to 21.0% v/s 5% in women and 3.4% to 6.6% v/s 1.3% in men  More subjects treated with CFZ had ≥1 hypoglycemic episodes | Wilding *et al*[24] |
| 6 | NCT01137812 | Genital mycotic infections: 9.2% of CFZ 300 mg v/s 0.5% of SITA  Osmotic diuresis related AEs: 2.4% of CFZ 300 mg v/s 1.3% of SITA  Higher incidence of increased TG in CFZ groups | Schernthaner *et al*[25] |
| 7 | Not available | Similar rate of AEs and discontinuations across all groups  No serious AEs | Devineni *et al* [26] |
| 8 | NCT00642278 | Non dose dependent increase in incidence of genital infections (3-8% v/s 2% of SITA) and UTI (3-9% v/s 2% of SITA) in CFZ groups  Low incidence of hypoglycemia  Small increase in LDL cholesterol in CFZ groups | Rosenstock *et al* [27] |
| 9 | NCT01064414 | AEs similar across all groups  Increased incidence of hypoglycemic events in CFZ groups- 14.44% with 100 mg CFZ and 11.24% with 300mg CFZ v/s 4.44% of PL | [29] |

AEs: Adverse events; CFZ: Canagliflozin; UTI: Urinary tract infections; SITA: Sitagliptin; LDL: Low-density lipoprotein.