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Systematic Review of Sodium Glucose Co-transporter Type 2 (SGLT2) Inhibitors in the Treatment of Patients with Diabetes Mellitus Type 2

A 2011 Center for Disease Control and Prevention (CDC) report estimated that nearly 26 million Americans have diabetes. In 2014, the CDC reported that about 40% of US adults will develop diabetes, primarily type 2, in their lifetime, and more than 50% of ethnic minorities will be affected. This is substantially higher than previous estimates.

Therefore, the importance of the therapy of this condition is of absolute importance. The decision related to the therapeutic choice should be based on the evidence of its efficacy, side effects, on the cost-benefit analysis, and plenty of other factors. Where and how are SJSM students looking for the evidence?

Habeeba Sirajudin

SYSTEMATIC REVIEW OF SODIUM GLUCOSE CO-TRANSPORTER 2 (SGLT2) INHIBITORS IN THE TREATMENT FOR PATIENTS WITH DIABETES MELLITUS TYPE 2

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Abstract:

Diabetes type 2 is one of the most prevalent diseases with an incidence of more than one million cases per year and is associated with billions of dollars in medical costs each year (1). It is also a progressive disease that can result in significant complications that affect multiple organ systems. Therefore, it is critical that blood glucose levels are monitored closely and controlled tightly. There are many pharmacological treatment options available for Type 2 diabetes once management with diet and exercise fails. However, present treatment options are associated with significant adverse events and have also shown to be less effective with respect to time. Sodium Glucose Co-Transporter 2 (SGLT2) inhibitors are a new class of anti-diabetic medications that are associated with fewer adverse events and work independently of insulin. The objective of this paper was to assess the safety and effectiveness of FDA approved SGLT2 inhibitors as monotherapy.

In this systematic review, randomized control trials and trials comparing other hypoglycemic agents with SGLT2 inhibitors were looked at and mean changes in HbA1C levels, fasting plasma glucose levels, blood pressure, weight, urinary tract infection (UTI) events, genital infection events, hypotensive events, and hypoglycemic events were recorded. Confidence intervals were then calculated to determine the significance of changes.

Fourteen articles were reviewed for data collection. Results showed a mean decrease of 1.02% in HbA1C levels, decrease of 2.6 kg, a mean decrease of 3.65mmHg in blood pressure, mean decrease of 23.06 in fasting plasma glucose with 10mg dapagliflozin. Dapagliflozin was also associated with a mean of 1.38% of hypoglycemic events, 4.96% of people had UTI events, 5.8% of genital infections, and 0.68% of hypotensive events. Results of 100mg of canagliflozin showed a mean decrease of

1.71% in HbA1C levels, a mean decrease of 2.5 kg in body weight, a mean decrease of 2.76mmHg in blood pressure, a mean decrease of 24mg/dL in fasting plasma glucose. The mean percent of hypoglycemic events in 100mg canagliflozin group were 0.51%, mean percent of 4.8% UTI's, 4.86% genital infections and a mean percent of 0.46% of hypotensive events.

Dapagliflozin 10mg and canagliflozin 100mg both appear to be effective and safe as monotherapy for patients with DM-2; although, more trials assessing the safety by looking at other factors such as carcinogenic potential and effect on the renal system are needed.

Keywords: SGLT2 inhibitors, dapagliflozin, canagliflozin

Introduction:

Diabetes is one of the most common diseases present today with its prevalence on the rise every year. According to the National Diabetes Statistics Report, 29.1 million people in the United States during the year 2013 were diagnosed with having diabetes and in the year 2012 with an incidence of 1.7 million people (1). Furthermore, DM-2 is associated with $174 billion in medical costs (1).

Type 2 Diabetes Mellitus (T2DM) is characterized by hyperglycemia due to inadequate secretion of insulin by the pancreatic beta cells and also due resistance of insulin in the peripheral organs (1). T2DM is a progressive disease which can lead to numerous macrovascular complications such as myocardial infarction, amputation, stroke, as well as microvascular complications such as nephropathy, retinopathy, and neuropathy (2). These complications result in increased mortality and morbidity in patients diagnosed with T2DM. Therefore, it is crucial that glucose levels in patients

diagnosed with T2DM are adequately controlled. Previous studies have demonstrated that every 1% decrease in hemoglobin A1C (HbA1C) is associated with a 35% reduction in the risk of microvascular complications (2).

Initial management for patients with T2DM is lifestyle change which includes a change in diet and reduction in weight. When non pharmacological treatment fails, antihyperglycaemic agents are introduced, with metformin being the first agent (3). Other antihyperglycaemic agents include sulfonylureas, glitazones, alpha glucosidase inhibitors, etc. Many of these agents have shown to be associated with adverse side effects such as lactic acidosis, gastrointestinal disturbances, and weight gain which can worsen insulin resistance (5). Furthermore, the use of metformin is contraindicated in patients with renal failure. Previous studies have also shown that because of the side effects and because T2DM is a progressive disease, monotherapy failure is achieved faster and the need to combine medications is increased (5).

In a healthy adult approximately 180g of glucose is filtered from the renal glomeruli each day and almost all of the filtered glucose is reabsorbed and returned back to circulation (4). Glycosuria occurs when renal threshold of glucose has been reached; that is after reabsorbing approximately 160-180mg/dl of glucose, glucose is excreted in urine. 98% of the urinary glucose is reabsorbed back to the circulation by the SGLT2, which is located in the proximal renal tubules (5). In T2DM SGLT2 are upregulated because of high plasma glucose levels, which leads to glucose conservation and hyperglycemia (4). Inhibiting SGLT2 activity decreases reabsorption of glucose and lowers plasma glucose concentration.

Sodium glucose cotransporter 2 (SGLT2) inhibitors are a novel therapeutic class of antihyperglycaemic agents that have shown to provide long term glycaemic control with minimal adverse effects (3).

A number of SGLT2 inhibitors are currently at different phases of development (e.g.: ertugliflozin, luseogliflozin, tofoglifozin ipragliflozin, remogliflozin) with dapagliflozin and canagliflozin currently approved in the United States (4). In this systematic review, the goal is to evaluate the efficacy, risks, benefits, and safety of the FDA approved SGLT2 inhibitors.

The goal of this article is to study the effectiveness of SGLT2 inhibitors as monotherapy for patients with DM2. The review of the evidence for effectiveness was undertaken systematically.

Methods:

We reviewed articles that studied the effectiveness of FDA approved SGLT2 inhibitors as monotherapies for DM2. The main outcomes that were looked at to determine the efficacy of SGLT2 inhibitors was the glycolated hemoglobin (HbA1C), changes in body weight, changes in blood pressure, changes in fasting plasma glucose levels from baseline. Safety of SGLT2 inhibitors was evaluated by looking at the incidence of hypoglycemic and hypotensive events. The incidence of urogenital infections was also considered to assess the safety.

We reviewed articles that utilized randomized controlled trials (that is those that used placebo, life-style, or other hypoglycemic agents). Furthermore, we looked at trials that were published between 2006 and 2014, and those that lasted for at least 12 weeks. This was because it was in 2006 that the first recording of dapagliflozin was noted, and as for the 12 weeks it takes at least 8 weeks to

measure a change in HbA1C (5). All articles that were utilized were not restricted on the basis of ethnicity or the duration of the disease. We also only reviewed articles where the dose of SGLT2 inhibitors was listed as efficient.

The mean changes from trials were recorded and graphed. Confidence intervals and P-values were calculated to determine if changes were significant or not.

The search methods utilized to identify studies included Medline, PubMed, DynaMed, Federal Drug Agency, American Diabetes Association (conference abstracts), and bibliographies of retrieved articles.

The key words that were utilized to find articles included SGLT2 inhibitors, canagliflozin, dapagliflozin, sodium glucose inhibitors, sodium glucose transport inhibitors, sodium glucose co-transporters, sodium glucose co-transporter 2, and sodium glucose co-transporter 2 inhibitors.

Results:

After retrieving articles and analyzing the literature according to the study protocol it was determined that dapagliflozin 10 mg and canagliflozin 100mg were the doses that were considered to be efficient. Eight articles were found that provided information comparing dapagliflozin 10mg and placebo, three articles were found comparing dapagliflozin 10mg with metformin 500mg, and three articles were found that compared canagliflozin 100mg with placebo. All of the articles reviewed consisted of trials that lasted for twelve weeks or longer.

Table 1 depicts the mean changes in HbA1C (%), fasting plasma glucose (mg/dL), body weight (kg), and blood pressure (mmHg).

HbA1C levels showed a mean change of HbA1C levels based on the eight articles found was -1.02% with dapagliflozin 10mg and -0.24% in the placebo group (CI: -1.05,-0.51; P<0.05). The mean change was -1.13% and -1.12% in the dapagliflozin 10mg vs metformin 500mg group respectively (CI: -1.21,-0.90; P>0.05). The mean change in canagliflozin 100mg vs placebo was -0.71% and +0.3% in the placebo group respectively (CI: -2.26,0.24; P<0.05).

Levels of body weight showed a mean decrease of -2.52kg in the dapagliflozin 10mg group and a decrease of -0.10kg in the placebo group (CI: -3.54, -1.29; P<0.05). There was a mean decrease of -2.6kg in the dapagliflozin 10mg vs a decrease of -1.2kg in the metformin 500mg group (CI: -2.26,-0.54; P<0.05). The mean drop in the canagliflozin 100mg group was -2.5 kg and -0.4kg in the placebo group (CI: -4.82, 0.56; P>0.05).

Levels of blood pressure depict that there was a mean drop of -3.65mmHg in the dapagliflozin 10mg group and a mean drop of -0.38mmHg in the placebo group (CI: -4.97, -1.55; P<0.05). There was a mean drop of -2.76mmHg in the dapagliflozin 10mg group and -1.47mmHg in the metformin 500mg group (CI: -2.80, 0.21 P>0.05). The mean in the canagliflozin 100mg group was -2.76mmHg and in the placebo group it was 0 (CI: -5.28, -0.25; P<0.05)

Levels of FPG showed that there was a mean decrease of -23.06mg/dL in the dapagliflozin 10mg group and a mean increase of 2.51mg/dL in the placebo group (CI: -34.46,-16.69; P<0.05). The mean was -12. 59 in the dapaglilozin 10mg group compared to -18.93 in the metformin 500mg group (CI: -12.59, -0.07; P<0.05). The mean in the canagliflozin 100mg group was -24 and in the placebo was 1.9 (CI: -31.54, -20.26; P<0.05).

Table 2 depicts the mean changes noted in urinary tract infections (UTI), genital infections, hypotensive events, and hypoglycemic events.

The mean percent of hypoglycemic events were 1.38% in the dapagliflozin 10mg group and 1.53% in the placebo group (CI: -1.19,0.88; P>0.05). Mean percent noted in the dapagliflozin 10mg group were 2.06% vs 6.4% in the metformin 500mg group (CI: -8.67, -0.11; P<0.05). Mean percent noted in the canagliflozin 100mg group were 0.51% and 0.24% in the placebo group (CI: -0.28,0.84; P>0.05).

The mean percent of UTI's noted in the dapagliflozin 10mg group was 4.96% and 1.54% in the placebo group (CI: 1.72, 5.13; P<0.05). The mean percent in dapagliflozin 10mg vs metformin 500mg was 4.5% and 2.2% respectively (CI: -0.45, 4.92; P>0.05). The mean percent in canagliflozin 100mg was 4.8% and 0.63% in the placebo group (CI: 0.88, 7.44; P<0.05).

The mean percent of genital infections noted in the dapagliflozin 10mg group was 5.8% and 0.48% in the placebo group (CI: 4.27, 6.35; P<0.05). The mean in the dapagliflozin 10mg group compared to the metformin 500mg group was 8.56% and 1.83% respectively (CI: 5.5, 7.8; P<0.05). The mean in the canagliflozin 100mg group was 4.86% and in the placebo group a mean on 0.88% (CI: 1.5, 6.46; P<0.05).

The mean percent of hypotensive events was 0.68% in the dapagliflozin 10mg and 0.59% in the placebo group (CI: -0.60, 0.78; P>0.05). The mean in the dapagliflozin 10mg vs metformin 500mg was 1.39% and 3.06% respectively (CI: -3.92, 0.59; P>0.05). The mean percent in the canagliflozin 100mg group was 0.46% and 0.11% in the placebo group (CI: -0.71, 1.42; P>0.05).

HbA1C

article	dapagliflozin	placebo
1	-0.85	-0.18
2	-0.89	-0.23
3	-1.11	-0.29
4	-1.19	-0.2
5	-1.45	-0.6
6	-0.53	-0.08
7	-1.35	-0.37
8	-0.82	0.02

HbA1C

article	dapagliflozin	metformin
9	-0.89	-1.12
10	-1.19	-1.35
11	-1.32	-0.9

HbA1C

article	canagliflozin	placebo
12	-0.7	-0.2
13	-0.77	1.2
14	-0.66	-0.1

Body weight

article	dapagliflo	placebo
1	-2.7	-0.95
2	-3.2	-0.27
3	-2.25	-1.6
4	-2	-0.9
5	-2.6	1.1
6	-1.63	2.2
7	-2.2	0.8
8	-3.6	-1.2

Body weight

article	dapagliflozin	metformin
9	-2.2	-1.09
10	-2.5	-1.4
11	-3.2	-1.21

Body weight

article	canagliflozin	placebo
12	-2.6	-2.1
13	-2.8	-0.3
14	-2.2	1.2

Blood Pressure (mmHg)

article	dapagliflozin	placebo
1	-6.4	2.4
2	-3.6	-0.9
3	-2.3	-1.2
4	-3.2	-0.2
5	-4.2	-3.6
6	-3.1	-1.3
7	-3.6	-0.1
8	-2.8	1.8

Blood Pressure (mmHg)

article	dapagliflozin	metformin
9	-3.6	-1.09
10	-2.6	-1.22
11	-2.1	-2.1

Blood Pressure (mmHg)

article	canagliflozin	placebo
12	-2.8	-0.2
13	-4.3	0.3
14	-1.2	-0.1

FPG

article	dapagliflozin	placebo
1	-21	-6
2	-28.8	-4.1
3	-31.6	2.5
4	-22.2	3.5
5	-11.2	11.17
6	-10.6	17.21
7	-31.94	-4.1
8	-27.2	-0.1

FPG

article	dapagliflozin	metformin
9	-28.8	-18.2
10	-25	-17.5
11	-22	-21.1

FPG

article	canagliflozin	placebo
12	-27	-0.1
13	-24	2.3
14	-21	3.5

Table 1.

Hypoglycemic

article	dapagliflozin	placebo
1	3.4	1.7
2	2	2.9
3	1.2	1.5
4	2.1	1.2
5	1.5	0.65
6	0.54	2
7	0.1	0.4
8	0.2	1.9

Hypoglycemic

article	dapagliflozin	metformin
9	3.2	9
10	1.5	6.1
11	1.32	4.1

Hypoglycemic

article	canagliflozin	placebo
12	0.34	0.2
13	0.9	0.15
14	0.3	0.36

UTI events

article	dapagliflozin	placebo
1	6	1.1
2	6.6	0.42
3	5.3	2
4	4	0.9
5	7.9	3.7
6	4.8	1.5
7	1.33	1.9
8	3.8	0.8

UTI events

article	dapagliflozin	metformi
9	4.2	3.1
10	6.1	2.2
11	3.2	1.5

UTI events

article	canagliflozin	placebo
12	7	1
13	4.2	0
14	3.2	0.9

Genital infections

article	dapagliflozin	placebo
1	5.9	0
2	4.5	1
3	3.6	0.8
4	6.9	0.2
5	5.1	0.9
6	6.2	0.8
7	7.4	0
8	6.8	0.2

Genital infections

article	dapagliflozin	metformin
9	7.9	2
10	8.6	2
11	9.2	1.5

Genital infections

article	canagliflozin	placebo
12	6	0.25
13	5	2
14	3.6	0.4

Hypotensive events

article	dapagliflozin	placebo
1	0	2
2	1	1
3	1.9	0.9
4	0.9	0.11
5	0.8	0.4
6	0.6	0.2
7	0.2	0
8	0.1	0.16

Hypotensive events

article	dapagliflozin	metformin
9	2.1	4.3
10	1.2	3.1
11	0.89	1.78

Hypotensive events

article	canagliflozin	placebo
12	0	0.32
13	1.2	0.02
14	0.2	0

Table 2.

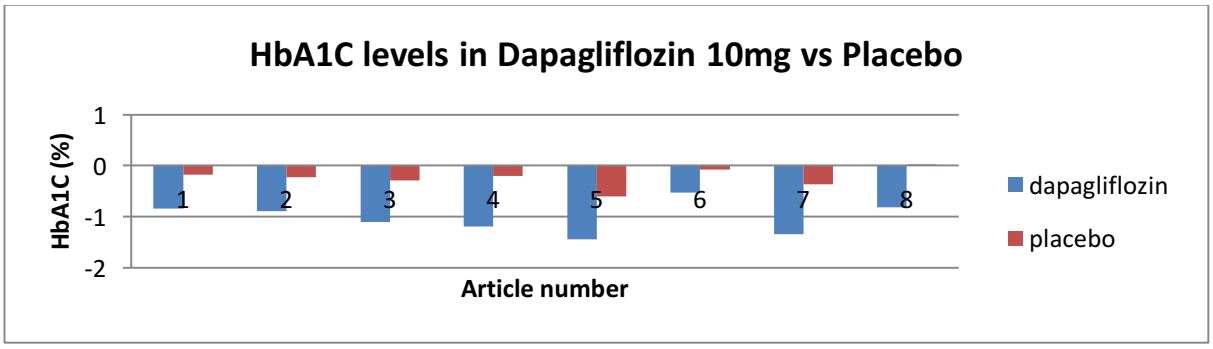


Figure 1.

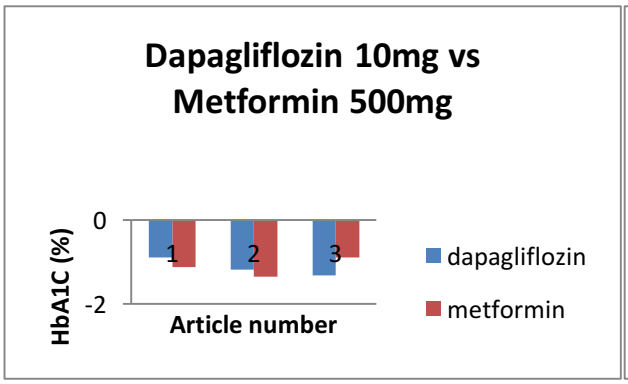


Figure 2.

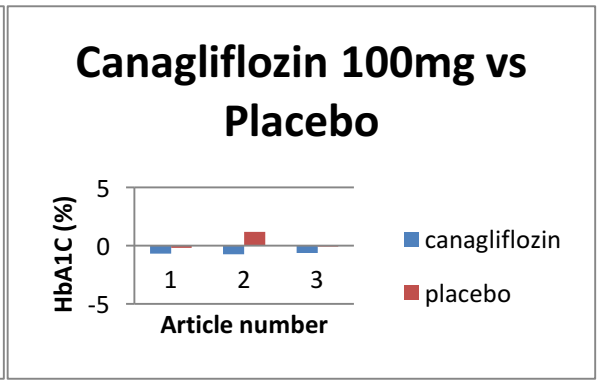
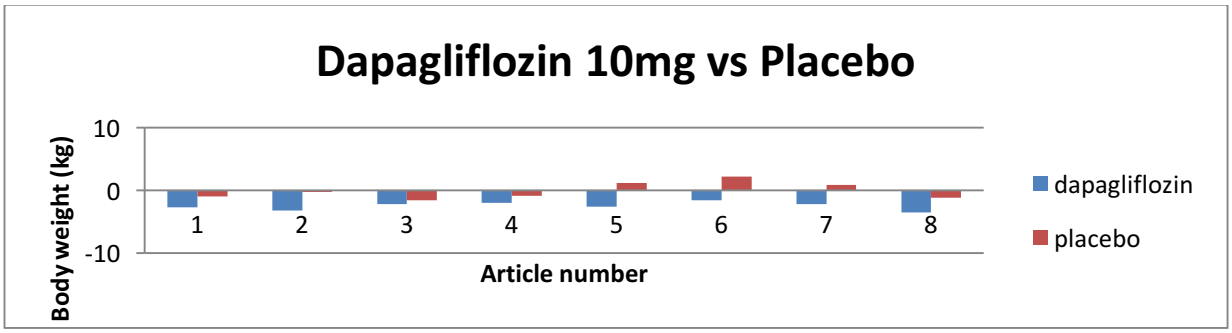


Figure 3.

Figure 1, Figure 2, and Figure 3 show the mean changes in the respective articles in a graphical form. It can be seen from the graphs that SGLT2 inhibitors led to a decrease in the HbA1C levels compared to placebo and metformin. The mean decreases in HbA1C level are noted above.



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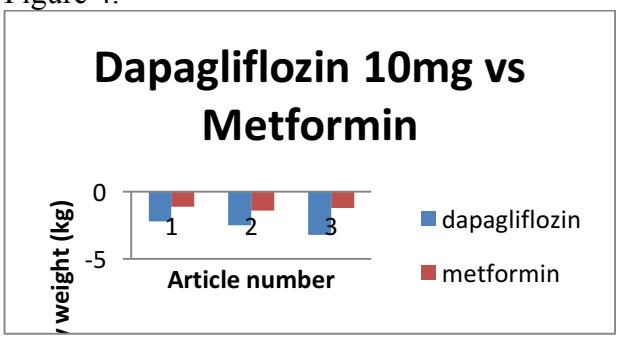

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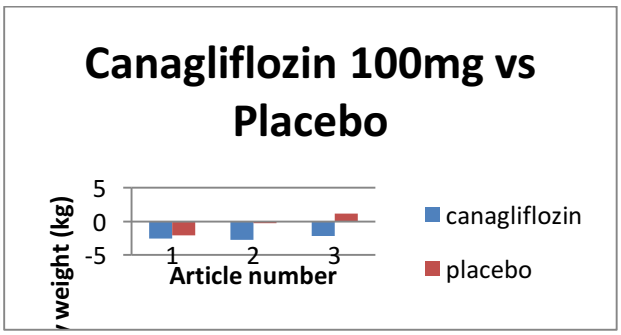
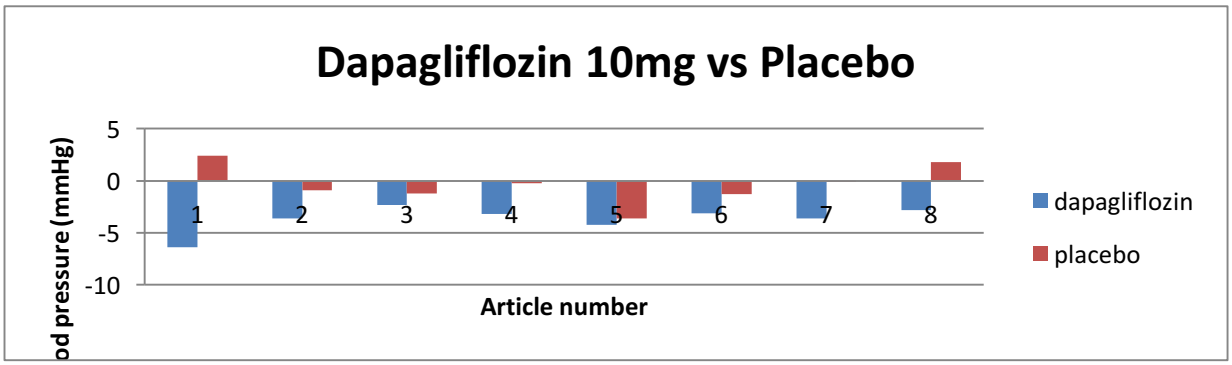


Figure 6.

Figure 4, Figure 5, and Figure 6 show the mean changes in the respective articles in a graphical form. It can be seen from the graphs that SGLT2 inhibitors led to a decrease in the mean body weight compared to placebo and metformin. The mean changes are noted above.



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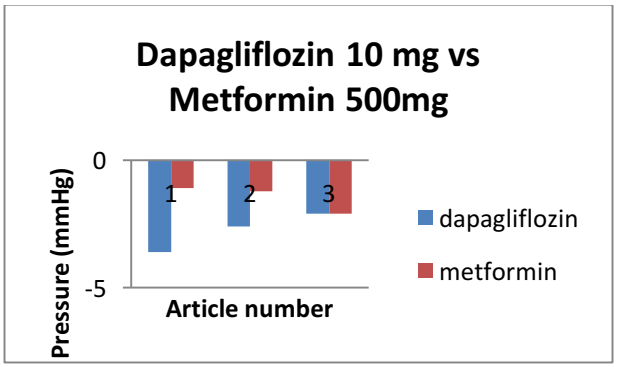

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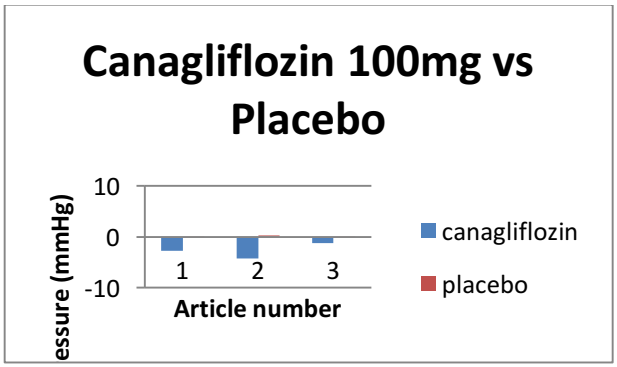
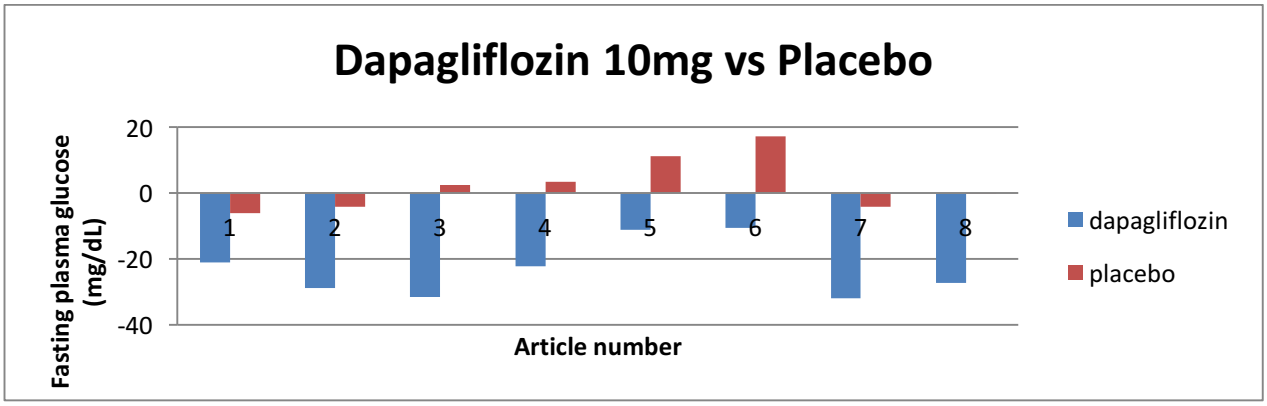


Figure 9.

Figure 7, Figure 8, and Figure 9 show the mean changes in the respective articles in a graphical form. It can be seen from the graphs that SGLT2 inhibitors led to a decrease in the mean blood pressure compared to placebo and metformin. The mean decreases are noted above.



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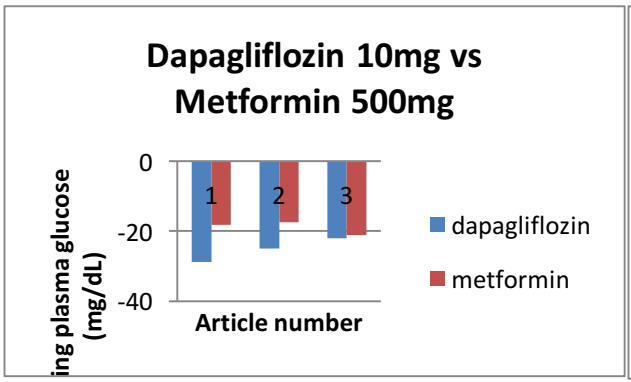

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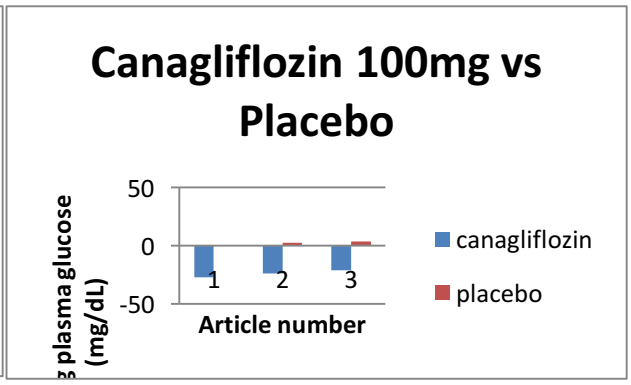
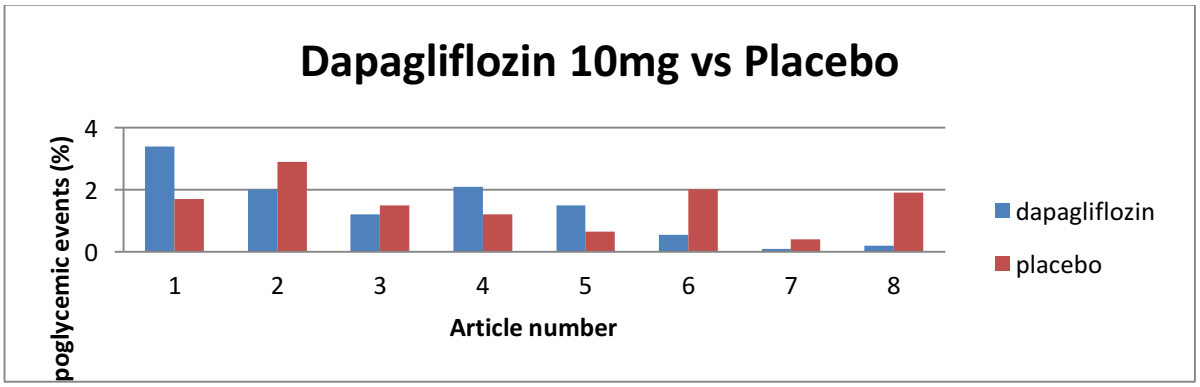


Figure 12.

Figure 10, Figure 11, and Figure 12 show the mean changes in the respective articles in a graphical form. It can be seen from the graphs that SGLT2 inhibitors led to a decrease in the mean fasting plasma glucose compared to placebo and metformin. The mean changes are noted above.



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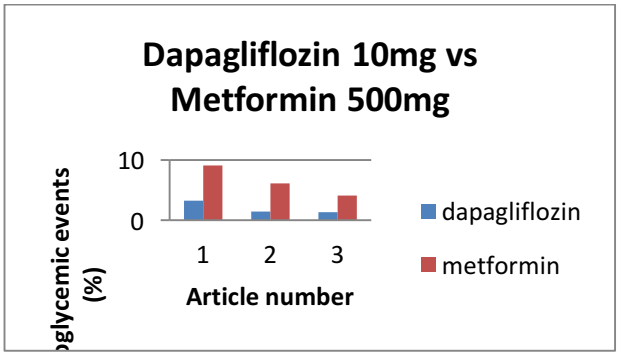


Figure 14.

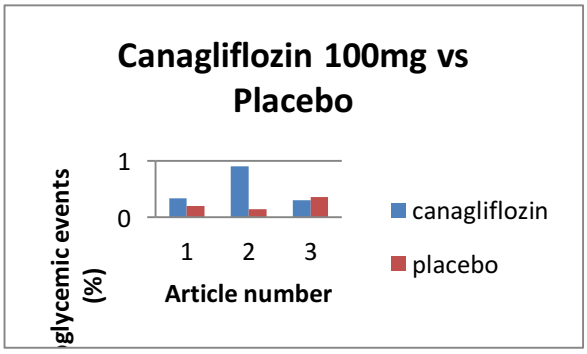
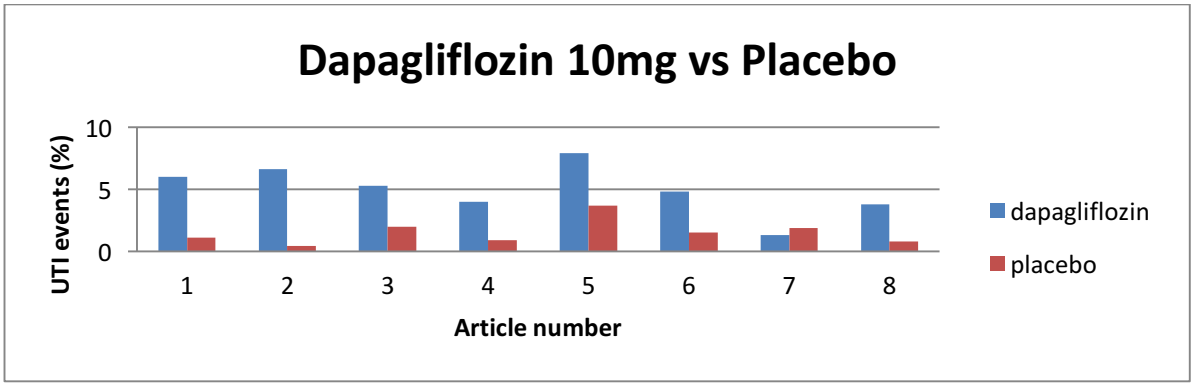


Figure 15.

Figure 13, Figure 14, and Figure 15 show the mean changes in the respective articles in a graphical form. It can be seen from the graphs that SGLT2 inhibitors led to a decrease in the mean percent of

people experiencing hypoglycemic events compared metformin and a slight increase when compared to placebo. The mean changes are noted above.



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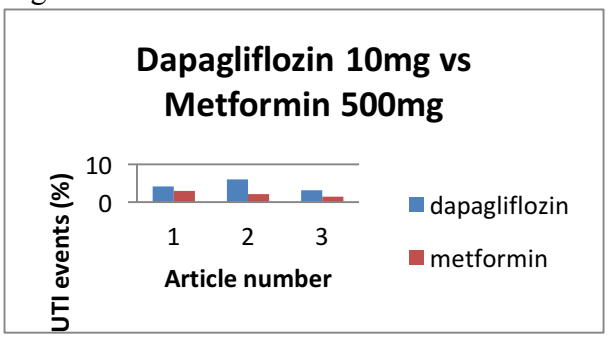

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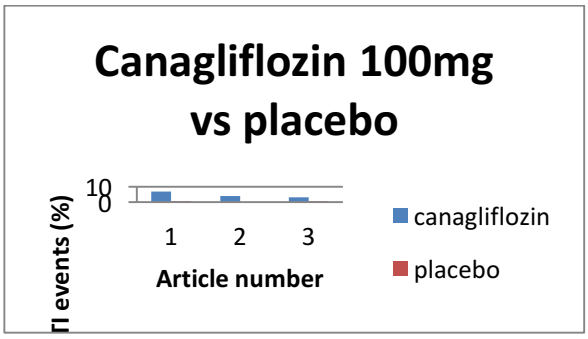

Figure 18.

Figure 16, Figure 17, and Figure 18 show the mean percentage of UTI events noted in the respective articles in a graphical form. It can be seen from the graphs that SGLT2 inhibitors led to an increase in the number of UTI events noted. The increases are noted in the placebo and the metformin group. The numerical values of the mean changes are noted above.

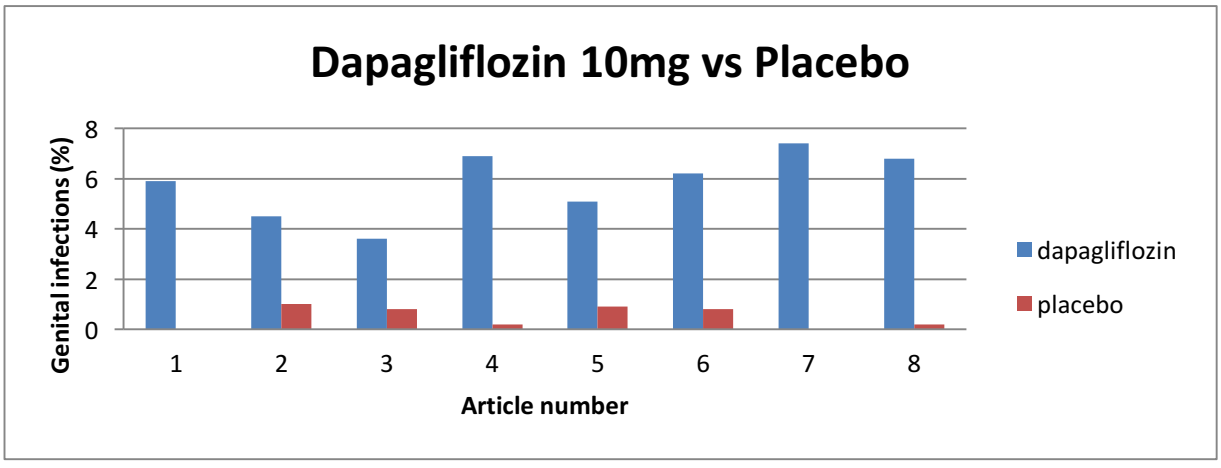

Figure 19.

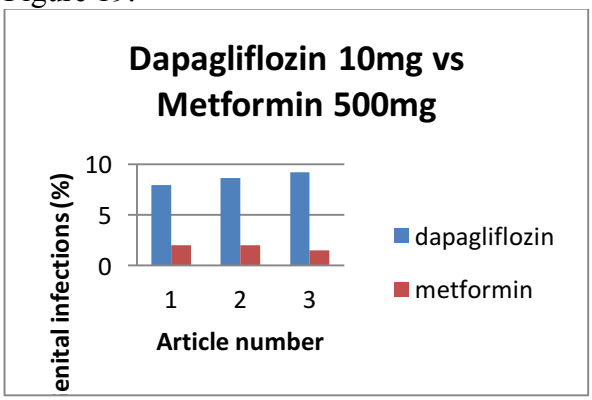

Figure 20.

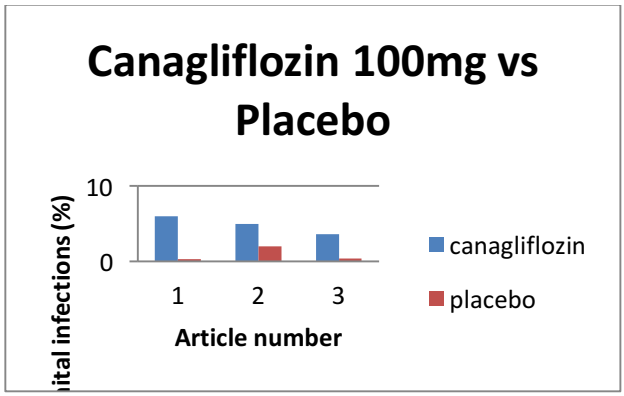

Figure 21.

Figure 19, Figure 20, and Figure 21 show the mean changes in the percent of genital infections noted in the respective articles in a graphical form. It can be seen from the graphs that SGLT2 inhibitors led to an increase in the percent of genital infections, the increase can be seen in both the placebo group as well as the metformin group. The numerical values of the mean changes are noted above.

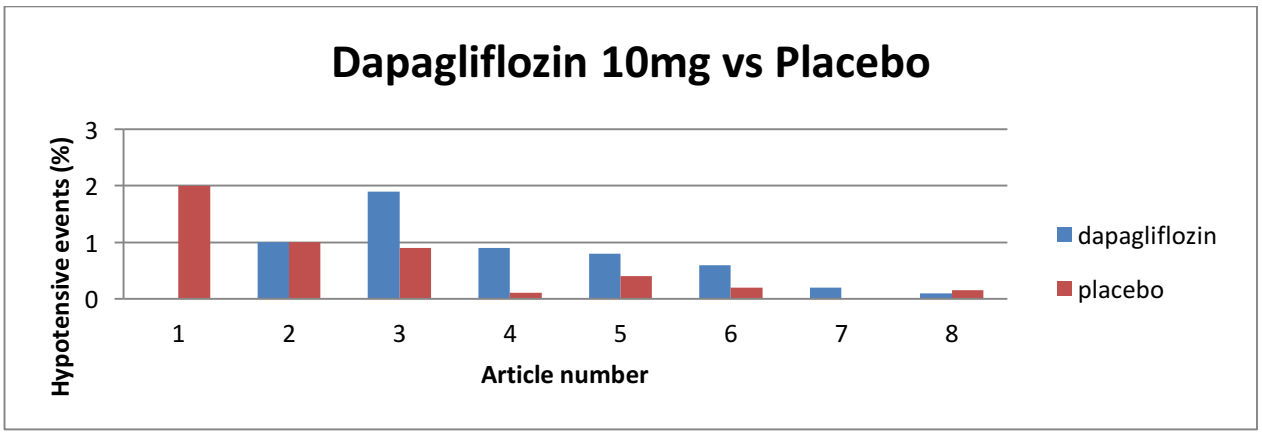

Figure 22.

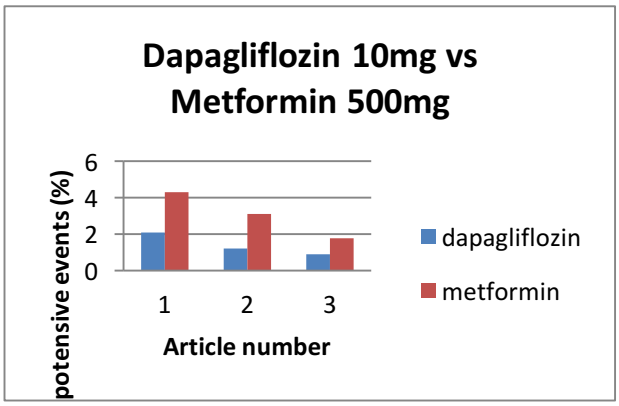

Figure 23.

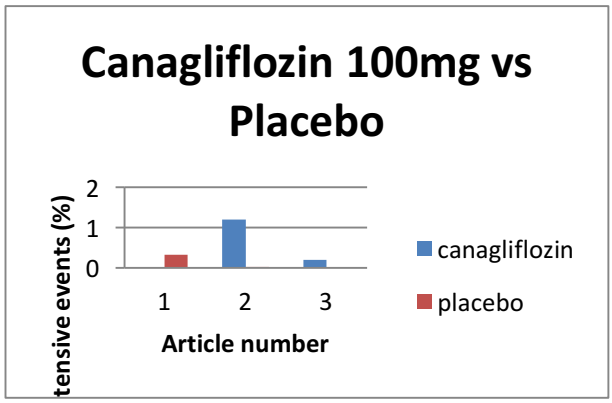

Figure 24.

Figure 22, Figure 23, and Figure 24 show the mean percentage of hypotensive events noted in the respective articles in a graphical form. It can be seen from the graphs that the number of hypotensive events is noted in the group treated with metformin. There is an increase in the percent of events noted in the SGLT2 inhibitors group compared to the placebo group. The numerical values of the mean changes are noted above.

Discussion:

Diabetes is a critical condition that affects at 29.1 million people in just the United States (1). Based on the results acquired by reviewing articles that focused on randomized control trials, it was determined that SGLT2 inhibitors are effective in decreasing HbA1C levels, body weight, blood pressure, and fasting plasma glucose and also having low numbers of hypoglycemic events. The main results of the articles reviewed show that the HbA1C values were significantly different in the dapagliflozin vs the placebo group and in the canagliflozin vs the placebo group. Though there were no significant differences between changes in HbA1C values in dapagliflozin and metformin, dapagliflozin may be a better option because it is known that metformin can result in critical adverse

events such as lactic acidosis. In addition, studies have shown that when metformin is combined with insulin it may lead to hypoglycemic events (7).

SGLT2 inhibitors exert their effects without having an effect on beta cell or tissue insulin sensitivity; therefore they can be used efficiently either as monotherapy or in combination with insulin without causing significant hypoglycemic events.

The adverse events that were evaluated in the articles reviewed included hypoglycemic events, hypotensive events, genital infections, and UTI events.

In terms of hypoglycemic events, analysis of the means showed that there was a significant difference between dapagliflozin and metformin, but there were no significant differences between the SGLT2 inhibitors and placebo groups.

It is known that diabetics are prone to genital infections. In terms of genital infections, there was a significant difference between SGLT2 inhibitors vs placebo and also between dapagliflozin and metformin. There was significant difference between the number of UTI events noted in SGLT2 inhibitors vs placebo, however, it was noted that the infections were mild and easily treatable. There was no difference between the number of UTI events noted in the dapagliflozin group vs the metformin group.

Limitations:

The majority of the studies reviewed lasted for 12-26 weeks with only four to five articles lasting for 48 weeks. Sulfonylureas lose their efficacy with respect to time because of loss of beta cell capacity; therefore, studies with long term data in terms of maintaining the respective efficacy are

needed (22). Furthermore, data regarding side effects on the renal system and specific cardiovascular events are limited. A few previous studies also associate SGLT2 inhibitors with potential carcinogenic risk, specifically bladder and breast cancer (8). However, studies are limited and those following our protocol were not found.

Future practice:

It would be interesting to see the effects of administering the medication in different forms such as injections. Interactions with other drugs, especially in people taking numerous medications for commodities should also be considered (3).

Conclusion:

SGLT2 inhibitors are a new class of anti-hyperglycemic medications that work by inhibiting the reabsorption of glucose in the proximal tubules of the kidneys. After doing a systematic review and evaluating its safety and efficacy by looking at the changes in HbA1C, FPG, blood pressure, body weight, hypoglycemic events, hypotensive events, UTI events, and genital infection events, it can be concluded that SGLT2 inhibitors appear to be safe and effective as T2DM monotherapy. They were shown to decrease HbA1C levels, FPG levels, weight, and blood pressure. There was also a low risk for hypoglycemic and hypotensive events. The number of UTI and genital infections experienced was higher; however, infections were mild and easily managed.

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References:

1. Centers for Disease Control and Prevention. *National Diabetes Statistics Report: Estimates of Diabetes and Its Burden in the United States, 2014*.
2. American Diabetes Association. Standards of medical care in diabetes—2014. *Diabetes Care.* 2014;37(Suppl 1):S14-S80.
3. SGLT2 Inhibitors: A New Emerging Therapeutic Class in the Treatment of Type 2 Diabetes Mellitus. *SGLT2 Inhibitors: A New Emerging Therapeutic Class in the Treatment of Type 2 Diabetes Mellitus*.
4. SGLT2 Inhibitors: A New Treatment Option for Type 2 Diabetes. *SGLT2 Inhibitors: A New Treatment Option for Type 2 Diabetes*.
5. Diabetes Care. *Dapagliflozin Monotherapy in Type 2 Diabetic Patients With Inadequate Glycemic Control by Diet and Exercise*.
6. List, J. F., V. Woo, E. Morales, W. Tang, and F. T. Fiedorek. Sodium-Glucose Cotransport Inhibition With Dapagliflozin in Type 2 Diabetes. *Diabetes Care* 32.4 (2009): 650-57.
7. Ferrannini, E., S. J. Ramos, A. Salsali, W. Tang, and J. F. List. Dapagliflozin Monotherapy in Type 2 Diabetic Patients With Inadequate Glycemic Control by Diet and Exercise: A Randomized, Double-blind, Placebo-controlled, Phase 3 Trial. *Diabetes Care* 33.10 (2010): 2217-224.
8. Zhang, L., Y. Feng, J. List, S. Kasichayanula, and M. Pfister. Dapagliflozin Treatment in Patients with Different Stages of Type 2 Diabetes Mellitus: Effects on Glycaemic Control and Body Weight. *Diabetes, Obesity and Metabolism* 12.6 (2010): 510-16
9. Henry, R. R., Murray HM, Marmolejo MH, Hennicken D, Ptaszynska A, and List JF. Dapagliflozin, Metformin XR, or Both: Initial Pharmacotherapy for Type 2 Diabetes, a Randomised Controlled Trial. *International Journal of Clinical Practice* 66.5 (2012): 446-56.
10. Parikh, S., Wilding, J., Jabbour, S. and Hardy, E. (2014), Dapagliflozin in type 2 diabetes: effectiveness across the spectrum of disease and over time. *International Journal of Clinical Practice.* Available at: http://onlinelibrary.wiley.com/enhanced/doi/10.1111/ijcp.12531/. Retrieved on January 2015.
11. Zhang, Mei, Lin Zhang, Bin Wu, Haolan Song, Zhenmei An, and Shuangqing Li. Dapagliflozin Treatment for Type 2 Diabetes: A Systematic Review and Meta-analysis of Randomized Controlled Trials. *Diabetes/Metabolism Research and Reviews* (2013).Avbalable at: http://onlinelibrary.wiley.com/enhanced/doi/10.1002/dmrr.2479. Retrieved on January 2015.

12. Kaku, K., Inoue, S., Matsuoka, O., Kiyosue, A., Azuma, H., Hayashi, N., Tokudome, T., Langkilde, A. M. and Parikh, S. (2013), Efficacy and safety of dapagliflozin as a monotherapy for type 2 diabetes mellitus in Japanese patients with inadequate glycaemic control: a phase II multicentre, randomized, double-blind, placebo-controlled trial. *Diabetes, Obesity and Metabolism,* 15: 432–440.
13. Bailey, C. J., Iqbal, N., T'joen, C. and List, J. F. (2012), Dapagliflozin monotherapy in drug-naïve patients with diabetes: a randomized-controlled trial of low-dose range. *Diabetes, Obesity and Metabolism*, 14: 951–959.
14. Henry, R. R., Murray, A. V., Marmolejo, M. H., Hennicken, D., Ptaszynska, A. and List, J. F. (2012), Dapagliflozin, metformin XR, or both: initial pharmacotherapy for type 2 diabetes, a randomised controlled trial. International Journal of Clinical Practice, 66: 446–456.
15. Ferrannini E, Ramos SJ, Salsali A, Tang W, List JF. Dapagliflozin Monotherapy in Type 2 Diabetic Patients With Inadequate Glycemic Control by Diet and Exercise: A randomized, double-blind, placebo-controlled, phase 3 trial. *Diabetes Care* 2010;33(10):2217-2224. doi:10.2337/dc10-0612.
16. Nauck, Michael A. Update on Developments with SGLT2 Inhibitors in the Management of Type 2 Diabetes. *Drug Design, Development and Therapy* 8 (2014): 1335–1380.
17. Bhatia, Jagriti et al. Canagliflozin-Current Status in the Treatment of Type 2 Diabetes Mellitus with Focus on Clinical Trial Data. *World Journal of Diabetes* 5.3 (2014): 399–406.
18. Davis, C. S., Fleming, J. W. and Warrington, L. E. (2014), Sodium glucose co-transporter 2 inhibitors: A novel approach to the management of type 2 diabetes mellitus. American Assoc Nurse Prac, 26: 356–363.
19. Stenlöf, Kaj, William T. Cefalu, Kyoung-Ah Kim, Esteban Jodar, Maria Alba, Robert Edwards, Cindy Tong, William Canovatchel, and Gary Meininger. Long-term Efficacy and Safety of Canagliflozin Monotherapy in Patients with Type 2 Diabetes Inadequately Controlled with Diet and Exercise: Findings from the 52-week CANTATA-M Study. *Current Medical Research and Opinion* (2013): 1-13.
20. Stenlöf, K., Cefalu, W. T., Kim, K.-A., Alba, M., Usiskin, K., Tong, C., Canovatchel, W. and Meininger, G. (2013), Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise. *Diabetes, Obesity and Metabolism,* 15: 372–382.
21. Ptaszynska, Agata, Kristina M. Johnsson, Shamik J. Parikh, Tjerk W. A. De Bruin, Anne Marie Apanovitch, and James F. List. Safety Profile of Dapagliflozin for Type 2 Diabetes: Pooled Analysis of Clinical Studies for Overall Safety and Rare Events. *Drug Safety* 37.10 (2014): 815-29.
22. Kahn SE. Clinical review 135: the importance of beta-cell failure in the development and progression of type 2 diabetes. *J Clin Endocrinol Metab* 2001; 86: 4047–58.