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# A POST MARKETING SURVEILLANCE STUDY (CLINICAL AUDIT) OF INVOKANA (CANAGLIFLOZIN) AND FORXIGA (DAPAGLIFLOZIN) IN PATIENTS WITH TYPE 2 DIABETES

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**ABSTRACT**: *Invokana and Forixga is a sodium-glucose co-transporter 2 (SGLT2) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus, a new class of agents developed for oral diabetic medication was studied for effectiveness and safety. An Improved glycaemic control and weight loss has been demonstrated in clinical trials but effectiveness outside of the trial environment has not yet been reported. A systematic clinical case study was performed to note an audit of type 2 diabetes patients initiated on invokana and forixga along with their concomitant medication in a diabetes specialist outpatient centre at kiran clinic centre, hyderabad. a total of 40 out patients were selected based on the inclusion and exclusion critreria of the study. out of 40 people included in the study , 46% had a reduction in glycated haemoglobin (hba1c) of >1%, 33% had no reduction; 20% had weight loss >5kg, 6% had weight loss >10kg and 24% had no weight reduction. Improvements in hba1c, weight, and blood pressure were consistent with those reported in earlier clinical trials. It was observed that the rate at which discontinuation of the medication was higher than the earlier reported results. But the interesting fact was more than 50 % of the population were able to tolerate the medication of invokana and forixga and were able to stop and reduce the one or more diabetic medications. Both invokana and forixga is effective in improving the overall glycaemic control. They also reduced the blood pressure levels, weight loss, and helps in reducing the need for concomitant diabetes medications. However, they are not tolerated as well in real-patient world as in the case of participants of clinical trials.*

**Key words**: Invokana, Forixga, Diabetes, Glycated Haemoglobin, Glycaemic control, SGLT2

**INTRODUCTION**:

Dapaglifozin and canagliflozin are the first PBS-listed agents from a new class of oral antidiabetics agents known as SGLT2 inhibitors. This class represents a novel insulin-independent approach for treatment of type 2 diabetes that relies on the role of the kidneys in glucose homeostasis. SGLT2 is a low-affinity, high-capacity sodium-coupled glucose transporter located on the luminal side of the renal proximal tubule and accounts for most glucose reabsorption in the kidneys (1).

In non-diabetic people around 180 g per day of glucose is freely filtered by the kidneys but nearly all is reabsorbed by SGLT2, with loss in urine occurring only when plasma glucose exceeds a threshold for reabsorption (2). In type 2 diabetes, even when hyperglycemia occurs, filtered glucose continues to be reabsorbed, leading to persistently elevated blood glucose concentrations (3, 4). By selectively and reversibly inhibiting SGLT2, dapagliflozin and canagliflozin lower plasma glucose levels through decreased reabsorption of glucose and increased urinary glucose excretion, creating a diuretic effect. The current global markets of all SGLT2 are depicted in (Figure 1).

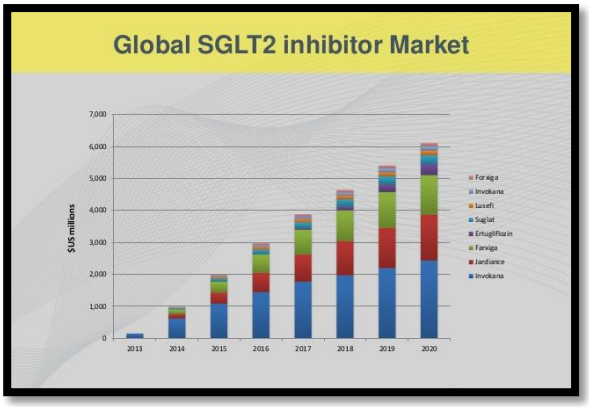


**Figure: 1. Global Market trend of SGLT2 inhibitors in the treatment of diabetes.**

Both dapagliflozin and canagliflozin are TGA approved as an adjunct to diet and exercise for glycaemic control in adults with type 2 diabetes mellitus as: monotherapy when OHA is contraindicated or not tolerated add-on dual combination therapy, with OHA or insulin (dapagliflozin and canagliflozin) or with other anti-hyperglycaemic agents (canagliflozin only). Only dual

combination therapy with metformin or a sulfonylurea is PBS subsidized.

Treatment are benefited with SGLT2 inhibitors is dependent on kidney function, so efficacy may be affected in people with kidney impairment (3,4). Dapagliflozin is contraindicated in people with moderate or severely impaired kidney function (eGFR < 60 mL/min/1.73 m 2 or CrCL < 60 mL/min) (4). Canagliflozin is contraindicated in people with severely impaired kidney function, including patients receiving dialysis (eGFR < 30 mL/min/1.73m 2 or CrCL < 30 mL/min), or with eGFR persistently < 45mL/min/1.73 m 2 or CrCL persistently < 45mL/min. SGLT2 inhibitors contribute to osmotic diuresis and elevated urinary volume, with an accompanying reduction in sodium reabsorption in the kidneys.

Considering the diuretic effect of SGLT2 inhibitors before starting dapagliflozin or canagliflozin, especially in people who have reduced intravascular volume or those at risk of volume depletion. This includes people already taking diuretics or medicines with a diuretic effect and those with a history of hypotension. Before starting dapagliflozin or canagliflozin in older people consider that they are more likely to have impaired kidney function and risk of volume depletion, which may be exacerbated by other concurrent medicines (3,4). A starting dose of canagliflozin 10 mg once daily is recommended in patients aged 75 years or older. As a result of limited therapeutic experience, starting dapagliflozin in patients 75 or older is not recommended.

In comparison with other combination therapies, both dapagliflozin and canagliflozin provide similar improvements in HbA1c levels when combined with concomitant medication of OHA. The long-term safety profile of SGLT2 inhibitors is not yet known and there are insufficient data to determine effects on macrovascular disease or diabetes-related complications and

mortality. It is unclear how elevated glycosuria associated with the mechanism of action for SGLT2 inhibitors impacts the urogenital tract, particularly with respect to urogenital infections. A post marketing study was undertaken to understand and also to monitor the affects and side effects of both the drugs. Given the mechanism of action of SGLT2 inhibitors, adverse effects such as genital infection (5,6) and UTIs, volume depletion (hypovolaemia-related events and haemo concentration) and kidney safety and hypoglycemia have been a focus of safety and tolerability in clinical trials to date. A clinical audit study is designed to understand and assess the combinational treatment of both inovakana and forxiga.

**MATERIALS AND METHODS**:

The study was designed on context to the real-world scenario, an observational, non-randomized single centre study was planned. The study comprised of a systematic clinical audit of notes and electronic records from people with type 2 diabetes with dapagliflozin and canagliflozin initiated in the diabetes specialist outpatient centre of a Kiran Diabetic Clinic, Hyderabad. The records of all people prescribed dapagliflozin and canagliflozin before 5$^{th}$ May 2015 were analyzed (n=40). People with no follow-up data were excluded (n=26).

Randomized data were collected on patient demographics, disease profile, concurrent medications, and outcomes. The demographic and disease information collected comprised patient age, gender, diabetes type and duration, renal function, and baseline measurement of HbA1c, weight, BMI, and blood pressure. All recorded clinical measurements were taken from routine data. Where no baseline measurement was available for HbA1c, weight, or blood pressure, the most recent available measurement within the preceding three months was used. A small number of people had dapagliflozin and canagliflozin stopped by their General practioner and there was no documented

reason for this discontinuation in the secondary care notes. In these cases the general practitioner was contacted for additional information and asked about any drug related adverse effects. Where people stopped taking dapagliflozin, data from subsequent visits were excluded from the analysis here. All collected data were sense checked and apparently anomalous values were rechecked in the clinical records.

**STATISTICAL ANALYSES**:

To evaluate change in the outcome parameters of HbA1c, weight, and blood pressure over time, patient follow-up data were grouped by three month periods. The median change in each outcome parameter was calculated for each three month group. Where people attended more than one follow-up appointment in a single three month period, the last appointment data was used. We performed a linear regression analysis to identify predictors of reduction in HbA1c, weight, and blood pressure in people taking dapagliflozin and cangafloxicin. People who failed to start dapagliflozin or who stopped taking it during the follow-up period were excluded. Change from baseline for the outcome measures of HbA1c, weight, and blood pressure were calculated. We assume a significance level of $p < 0.05$ and report model performance using R-square and adjusted R-square values. The analysis was undertaken using origin software 7.0 version.

**Ethical considerations**:

This study was designed as a measure of clinical audit of routine practice for the purpose of improving treatment methodologies leading to patient management and as such did not require ethics committee review (7).

**RESULTS:**

All people (n=40) who had been prescribed inovakana and forxiga were initially included for analysis. Three people were excluded as their notes were unavailable. Six people were excluded as they failed to attend any follow-up appointments. Four people were excluded

because they were not yet due to attend follow-up and four were excluded because they chose not to start taking dapagliflozin. The majority of participants had complete data (an initial value and follow-up measurements) on HbA1c (n=38; 82%), weight (n=40; 92%), and blood pressure (n=40; 99%). Those with incomplete data for an outcome measure were excluded from the analysis of that outcome measure. The included cohort (n=40) attended one or more follow-up appointments and comprised 23% women, mean age 58.9 (range 50-75) years, with a mean duration of type 2 diabetes of 9.1 (range 1-20) years. The mean weight of the cohort was 94.7 (range 30-105) kg and BMI 33.7 (range 22-52) kg/m2. The mean duration of follow-up was 180 (range 7-231; standard deviation 115) days. The shortest duration of follow-up was an urgent appointment requested because the patient had developed a widespread rash. Dapagliflozin was stopped at this visit. The mean number of follow-up appointments included was 1.57 (range 1-4).

Efficacy studies of the included people in the study, 82 (85%) had follow-up within the first three months of starting dapagliflozin and cangafloricin, 30 (32%) at 4-6 months. Average changes at the follow-up visit are shown in Table 1. Six people had no response to dapagliflozin with no improvement in HbA1c and no weight reduction (Table 2). It was evident that HbA1c response was sustained during the treatment duration. Weight and blood pressure continued to improve during the year of follow-up treatment with both invokana and forxiga. Of those people who tolerated dapagliflozin through the follow-up period, 26 (42%) were able to stop or reduce one or more other diabetes medications, whereas 18 (26%) patients had medication.

**Table 1 Changes in outcome measures at final follow-up visit in patients with type 2 diabetes treated with dapagliflozin and canaglifoxicin.**

| Outcome measure (units) | n (%) | Mean baseline value (SEM) | Mean change from baseline(SEM) | 95% confidence interval |
|---|---|---|---|---|
| **HbA1c (%)** | 38 (94) | 8.51 (0.19) | **-0.93 (0.23)** | -1.38 to -0.40 |
| **HbA1c (mmol/mol)** | 38 (94) | 78.4 (2.1) | **-9.2 (2.5)** | -13.2 to -3.2 |
| **Weight (kg)** | 40 (100) | 88.3 (2.6) | **-2.4 (0.5)** | -2.2 to -1.2 |
| **Systolic BP (mmHg)** | 40(100) | 124 (2) | **-3.3 (2.3)** | -9.5 to 0.6 |
| **Diastolic BP (mmHg)** | 40 (100) | 76 (1) | **-3.3 (1.3)** | -7.5 to -1.8 |

**Table 2 Response to dapagliflozin and canagliflozin treatment in patients with type 2 diabetes ('real-world Scenario').**

| Outcome measures | n (%) | Response | % |
|---|---|---|---|
| **HbA1c reduction** | 38 (94) | No response | 23 |
| | | Reduction < 1% | 22 |
| | | Reduction > 1% | 40 |
| **Weight loss** | 36 (92) | No response | 24 |
| | | Weight loss < 5kg | 38 |
| | | Weight loss > 5kg and <10kg | 10 |
| | | Weight loss > 10kg | 3 |
| **Systolic BP reduction (mmHg)** | 40 (100) | No response | 33 |
| | | Reduction Hg < 5mm | 10 |
| | | Reduction > 5mmHg | 57 |
| **Diastolic BP reduction (mmHg)** | 40 (100) | No response | 38 |
| | | Reduction < 5mmHg | **12** |
| | | Reduction > 5mmHg | 50 |

**Table 3 Clinical predictors of change in HbA1c in patients taking dapagliflozin and canagliflozin (n=40)**

| Clinical characteristic | Coefficient (95% confidence limits) | p value |
|---|---|---|
| **Age (years)** | -0.007 (-0.023 to 0.009) | 0.668 |
| **Female** | -0.437 (-0.747 to -0.126) | 0.164 |
| **Diabetes duration (years)** | 0.010 (-0.015 to 0.034) | 0.693 |
| **BMI (kg/m2)** | 0.014 (-0.010 to 0.037) | 0.561 |
| **Baseline HbA1c (%)** | -0.598 (-0.686 to -0.511) | <0.001 |
| **Model R-square 0.459, adjusted R-square 0.419** | | |

**Table 4 Clinical predictors of weight change in patients taking dapagliflozin & canagliflozin (n=40) (kg)**

| Clinical characteristic | Coefficient (95% confidence limits) | p value |
|---|---|---|
| **Age (years)** | 0.011 (-0.031 to 0.052) | 0.795 |
| **Female** | -0.480 (-1.288 to 0.328) | 0.554 |
| **Diabetes duration (years)** | 0.002 (-0.061 to 0.065) | 0.976 |
| **BMI (kg/m2)** | -0.144 (-0.208 to -0.081) | 0.026 |
| **Baseline HbA1c (%)** | -0.165 (-0.409 to 0.079) | 0.502 |
| **Model R-square 0.072, adjusted R-square 0.006** | | |

**Table 5 Clinical predictors of reduction in systolic blood pressure (mmHg) in patients taking dapagliflozin and canagliflozin (n=40)**

| Clinical characteristic | Coefficient (95% confidence limits) | p value |
|---|---|---|
| **Age (years)** | -0.272 (-0.404 to 0.066) | 0.432 |
| **Female** | 1.134 (-2.029 to 6.401) | 0.687 |
| **Diabetes duration (years)** | -0.045 (-0.378 to 0.248) | 0.756 |
| **BMI (kg/m2)** | -0.341 (-0.572 to 0.090) | 0.389 |
| **Baseline HbA1c (%)** | -0.687 (-2.009 to 0.358) | 0.412 |
| **Baseline systolic BP (mmHg)** | -0.482 (-0.664 to -0.392) | <0.001 |
| **Model R-square 0.291, adjusted R-square 0.163** | | |

**Table 6 Clinical predictors of reduction in diastolic blood pressure (mmHg) in patients taking dapagliflozin and canagliflozin (n=40)**

| Clinical characteristic | Coefficient (95% confidence limits) | p value |
|---|---|---|
| **Age (years)** | -0.210 (-0.362 to -0.151) | 0.038 |
| **Female** | -0.733 (-3.211 to 1.103) | 0.651 |
| **Diabetes duration (years)** | 0.186 (-0.010 to 0.268) | 0.288 |
| **BMI (kg/m2)** | -0.168 (-0.378 to -0.004) | 0.243 |
| **Baseline HbA1c (%)** | -0.388 (-1.085 to 0.210) | 0.435 |
| **Baseline systolic BP (mmHg)** | -0.156 (-0.316 to -0.110) | 0.031 |
| **Model R-square 0.212, adjusted R-square 0.078** | | |

Higher HbA1c at baseline was associated with a greater reduction in HbA1c whilst taking dapagliflozin (Table 3). Reduction in HbA1c was independent of age, gender, duration of diabetes. Higher BMI at baseline was associated with greater weight loss (Table 4). Baseline weight was not associated with the degree of weight loss. Weight loss was independent of age and gender, duration of disease, and baseline HbA1c. Higher baseline blood pressure was associated with a greater reduction in both systolic and diastolic blood pressure (Tables 5 and 6). Older age was weakly associated with a greater reduction in diastolic blood pressure during the exposure time.

Adverse effects were recorded for 12 (18%) people. Increased urine flow (nocturia and polyuria) was the most common adverse effect (3 people) followed by genital candidiasis (2), postural hypotension (1), dyspepsia (1), thirst (1), dry mouth (1), rash (2), erectile dysfunction (1), fatigue (1), back pain (1), palpitations (1), and urinary incontinence (1). The person reporting urinary incontinence had a previous history of incontinence which returned whilst taking dapagliflozin alone. The two people reporting rash had developed a widespread

erythematous rash with associated pruritus within the first three days of taking dapagliflozin necessitating discontinuation.

A total of 4 (10%) people stopped taking dapagliflozin during the follow-up period. Four people were advised to stop because of deterioration in their renal function (three of these had an improvement in glucose control prior to stopping), two because they felt it added to an already large pill burden (which may be improved in future by fixed dose combinations) and 7 because of adverse effects. The most common adverse effect leading to discontinuation of dapagliflozin was genital candidiasis. Most people with reported polyuria (3) elected to continue taking dapagliflozin and canagliflozin. Similarly, most people with nocturia (3) elected to continue during the treatment period.

**DISCUSSION:**

This study of real-world data suggests and demonstrates that dapagliflozin and canagaflozin is effective at reducing HbA1c with >48% of the people who tolerated dapagliflozin achieving a reduction in HbA1c >2%. Significant reductions in weight and blood pressure were also confirmed in our study. The clinical response to dapagliflozin and canagliflozin was independent of age and duration of diabetes and the greatest improvement in HbA1c was seen in those with the poorest control at baseline. Similarly the greatest reduction in weight and blood pressure was seen in those with the highest BMI and blood pressure at baseline. BMI and not baseline weight was associated with weight loss, which suggests that the degree of obesity is an predictor for weight loss. As considerable numbers could either reduce or stop other oral therapies (OHA) or insulin, there may be additional cost benefits from a pharmacoeconomic perspectives.

Dapagliflozin improves glycaemic control by preventing glucose reuptake by SGLT2 in the proximal tubule of the kidney (8, 9). Inhibition of SGLT2 can prevent the renal reabsorption of glucose in the systemic circulation. The resulting glucosuria also promotes reduction in the weight (4). The action is independent of insulin secretion and insulin action and does not predispose to hypoglycemia (3). Inhibition of SGLT2 can promote urinary sodium loss (10,11) which, along with weight reduction and an osmotic diuresis, may be partially responsible for the blood pressure lowering effects observed (12). People who were experienced with polyuria or nocturia condition were likely to continue to take the agents, although several adverse effects were observed leading to 12% of the cohort discontinuing forixga and invokana therapy. The glycosuria induced by dapagliflozin and canagliflozin can potentially lead to the UTIs and genital infections, predominantly causing or giving rise to candidiasis (9, 13) the adverse effects most likely leading to the discontinuation of the treatment.

**LIMITATIONS OF THE STUDY:**

The routinely collected data was used to assess the prevalence of side effects which are likely to lead to some underestimation of their frequency. The minor side effects may not be reported in clinics as they were over looked during the treatment period. However major adverse events or effects are forcing the patients to discontinue dapagliflozin and canagliflozin are almost certainly documented. The routinely collected data in the clinics also had some missing values for the outcome measures of HbA1c, weight, and blood pressure. We cannot determine retrospectively if there was a bias towards missing data in a particular subpopulation although we suspect that missing data are mostly random. Our real-world data scenario was confounded by changes to other medications and there is no control group for comparison. However the general trend was observed during the follow-up period

was towards less concomitant medication, suggesting that the beneficial effects seen in this group of patients are mostly attributed to dapagliflozin and canagliflozin treatment. The linear regression analysis of factors associated with HbA1c, weight, and blood pressure changes is limited by small sample size and heteroskedacity in both outcome measures. The higher variability in HbA1c, weight, and blood pressure change with higher initial values is likely to be an intrinsic property associated with the data.

**CONCLUSIONS**:

The data in the real-world scenario presented here may have greater generalisability to clinical practice, than data from clinical trials as patients with multiple co-morbidities or on multiple oral antidiabetic agents were included in the population analyzed and are usually excluded from clinical trials. This study mainly emphasized on the small population of patients with diabetes referred for specialist management in secondary care and therefore may not be applicable to all patients in the primary care setting. These data confirm that dapagliflozin and canagliflozin is effective as a treatment in clinical practice but clinicians should account for a higher level of intolerance to the side effects of associated with the drugs in clinical practice than that which is reported in clinical trials. In those who tolerated, the commonly clustered metabolic risk factors of poor glycaemic control, obesity, and hypertension were all significantly improved. There was also a reduction in the use of other oral antidiabetic agents and insulin in these populations suggesting an improved patient management.

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