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Original Research Article

Expert Opinion on the Prescription Practice of Oral Hypoglycemic Agents for the Management of Type 2 Diabetes Mellitus in India

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Abstract: ***Background*:** In India, the prevalence of diabetes is constantly rising in both urban and rural settings. The innovation of newer drugs and the combination of available drugs to treat diabetes has also been increasing. So, this study aimed to understand the practice of clinicians and their perspective towards prescribing appropriate oral hypoglycemic agents for individuals diagnosed with type 2 diabetes mellitus (T2DM) in India. ***Methods*:** This cross-sectional survey was conducted among diabetologists who provided consent to participate in the survey on their prescription pattern of oral hypoglycemic agents for management of T2DM individuals. ***Results*:** Majority of physicians preferred sitagliptin and dapagliflozin fixed dose combination (FDC) (84.42%) for T2DM individuals with high-risk. The experts also mentioned the FDC reduces time in range (40.04%) when sodium glucose cotransporter-2 inhibitors (SGLT2i) and Dipeptidyl peptidase-4 inhibitors (DPP4i) FDC was given. Sitagliptin and dapagliflozin combination therapy was given majorly to newly diagnosed T2DM individuals with cardiovascular risk (CV risk) (67.07%). Sitagliptin and dapagliflozin FDC for 16 weeks reduces 1.5 to 2% of glycated hemoglobin (HbA1c) (40.63%). ***Conclusion*:** Sitagliptin and dapagliflozin FDC was effective for T2DM individuals with high-risk and for newly diagnosed T2DM (and with CV risk). The combination also showed benefit in reducing blood pressure and weight loss when compared to SGLT2 inhibitors monotherapy. Hospitalization rate and CV risk was reduced in individuals who take sitagliptin and dapagliflozin FDC.

Keywords: Type 2 diabetes mellitus, oral hypoglycemic agents, sitagliptin, dapagliflozin, glycated hemoglobin.

INTRODUCTION

The global incidence and prevalence of diabetes increases at a higher rate every year. In the International Diabetes Federation (IDF) Atlas 2021, it was predicted that 643 million people will be diagnosed with diabetes by the year 2030 and 784 million by 2045 [1]. In India, the prevalence of diabetes is constantly rising in both urban and rural settings. In 1972, the prevalence of diabetes in the rural and urban were 2.4% and 3.3% respectively. However, in 2015 – 2019, the rural and urban prevalence of diabetes were increased as 15% and 19% respectively [2].

In a recent study, the lifetime risk of diabetes among young women and men was studied and estimated as 64.6% and 55.5% respectively, where women have higher risk for development of diabetes than man [3]. Expenses towards oral hypoglycemic drugs, insulin, hospitalization, or any other direct or indirect expenses have impact on the socio-economic countries [4]. Although combined therapies have been taken into consideration for the management of diabetes mellitus, some patients were not adequately controlled with their targeted blood glucose level.

Metformin combined with lifestyle changes remains the first choice of OHA (oral hypoglycemic agent) for newly diagnosed individuals with type 2 diabetes mellitus (T2DM) [5]. However, the OHA for individuals need to be personalised based on the individual's requirement and the protocol. In recent, there were several newer therapies and fixed dose combinations (FDC's) of several molecules are available to attain the targeted blood sugar level. Contrarily, the perspectives and preferences of clinicians in managing T2DM were not clear. So, this study aimed to understand the practice towards prescribing or selecting appropriate

oral hypoglycemic agents for individuals diagnosed with type 2 diabetes mellitus in India.

MATERIALS AND METHODS

A cross sectional, questionnaire based survey was carried out among diabetologists involved in treating diabetes mellitus in the major Indian cities from June 2022 to December 2022.

Questionnaire

The questionnaire booklet named TREAT TO TARGET study was sent to the diabetologists who were willing to participate in this study. The TREAT TO TARGET study questionnaire contains 26 questions and were used to obtain information about the recent trends in the management of type 2 diabetes. The study was conducted after getting approval from Bangalore Ethics, an Independent Ethics Committee which is recognized by the Indian Regulatory Authority, Drug Controller General of India.

Participants

An invitation was sent to leading diabetologists in treating diabetes mellitus in the month of March 2022 for participation in this Indian survey. About 534 doctors from major cities of all Indian states representing the geographical distribution shared their willingness to participate and provide necessary data. The participants were informed not to discuss the questions/ answers before and while answering the questions with anyone or online and are asked to answer them on their own. A written informed consent was obtained from each diabetologist before initiation of the study.

Statistical Analysis

The data were analyzed by using descriptive statistics where the categorical variables were presented as percentages to provide a clear understanding of their distribution. The frequency of occurrence and the corresponding percentage were used to represent the distribution of each variable. Microsoft Excel was used to visualize the distribution of the categorical variables, pie, and bar charts.

RESULTS

A total of 534 doctors participated in the survey. Finally, 507 doctor's responses were included for the analysis, as others (n=27) were excluded as no response was noted. The majority of physicians preferred sitagliptin and dapagliflozin FDC (84.42%), followed by empagliflozin and linagliptin FDC (9.86%) and vildagliptin and dapagliflozin FDC (5.72%) (Figure 1). Majority of the experts mentioned the FDC reduces time in range (40.04%), followed by moderate impact in time in range (32.54%), increases time in range (24.26%), no role (2.96%) and the question was not attempted by 1 (0.2%) expert. Majority of the clinicians (43.39%) highlighted 30% to 50% of Indian T2DM individuals respond to DPP-4 inhibitor therapy, followed by 10% to 30% by 157 (30.97%) clinicians, more than 50% by 82 (16.17%) clinicians and only 5% to 10% response for DPP IV inhibitor therapy by 47 (9.27%) clinicians.

Majority (37.67%) of the clinicians responded as 20% to 40% of T2DM individuals were associated with cardiovascular and renal failure risk. Followed by 40% to 60% of risk was responded by 188 (37.08%) clinicians, 10% to 20% of risk by 86 (16.96%) clinicians and more than 50% risk was mentioned by 41 (8.09%) clinicians. Majority of the physicians recommended sitagliptin and dapagliflozin combination therapy for newly diagnosed T2DM with cardiovascular risk (67.06%), followed by individuals with HbA1c level of 7.5% at diagnosis (13.02%), HbA1c level of 9% at diagnosis (11.24%), and newly diagnosed T2DM individuals (8.48%). Majority of the experts mentioned SGLT2i and DPP4i FDC therapy helped in all the options provided (improves both insulin resistance & beta cell function, offers rapid & sustained glycemic control, and helps in reducing body weight & blood pressure) (34.91%), followed by offering rapid and sustained glycemic control (26.82%), improves both insulin resistance & beta cell function (20.51%), and helps in reducing body weight & blood pressure (extra glycemic benefits) (17.55%).

Majority of the experts mentioned 1.5% to 2% reduction of HbA1c levels with sitagliptin and dapagliflozin FDC for 16 weeks of therapy (40.63%), followed by 1% to 1.5% reduction by 204 experts (40.24%), more than 2% reduction (10.65%), and reduction of 0.5% to 0.9% (8.28%) (Figure 2). Majority of the experts mentioned 1.5% to 2% reduction of HbA1c levels with sitagliptin and dapagliflozin and metformin triple OAD therapy (45.76%), followed by 1% to 1.5% reduction by 178 experts (35.11%), more than 2% reduction (11.05%), and reduction of 0.5% to 0.9% (7.89%).

The clinicians highlighted 15% to 30% reduction of weight and blood pressure with sitagliptin and dapagliflozin FDC therapy (40.43%), followed by 30% to 45% reduction by 145 experts (28.6%), more than 50% reduction by 78 experts (15.38%), and 10% to 15% by 78 experts (15.38%). Majority of them mentioned synergistic benefit in blood pressure & body weight reduction (41.03%), followed by improving patient compliance (28.99%), synergistic benefit in targeted glycemic goal (21.89%), and less UTI infections (7.89%) (Figure 3). Experts also mentioned CVOT (Cardiovascular outcome trial) trial availability (60.16%), followed by better glycemic reduction (21.3%), and glycemic durability (18.34%) as benefits of sitagliptin and dapagliflozin FDC therapy over vildagliptin and dapagliflozin therapy in T2DM individuals.

Experts (50.3%) mentioned FDC 'ominous octet' are not addressed by DPP-4 inhibitors FDC therapy. In the rest, 164 (32.35%) clinicians mentioned

few parameters are addressed and 87 clinicians mentioned it addresses (17.16%). Also, they mentioned the FDC would reduce the risk of rate of hospitalisation and CV risk (76.33%), followed by no risk (18.54%), and no significant role (4.93%).

The sitagliptin and dapagliflozin combination therapy can achieve targeted HbA1c level (less than 7%) by 51% to 60% as mentioned by 35.7% of clinical experts, followed by 40% to 50% (31.36%), 61% to 70% (17.95%), and more than 17% (14.79%). Majority of the experts mentioned risk-reduction approach (52.66%), and by gluco-centric approach (47.14%). The responses of experts on major challenge with triple OAD therapy were majorly risk of hypoglycemia (41.81%), followed by dose titration (31.76%), and missed dose challenge (26.23%).

The DPP4 inhibitors, SGLT2 inhibitors and biguanide FDC was majorly chosen by the experts (54.83%) as a first line in HbA1c above 9% in newly diagnosed T2DM individuals, followed by DPP-4 inhibitors and metformin FDC (27.81%), and SGLT2 inhibitors monotherapy (17.16%) (Figure 4). Majority of the experts preferred DPP-4 Inhibitors, SGLT2i and biguanide FDC (45.56%) as drug of choice in uncontrolled T2DM, followed by SGLT2i and DPP-4 inhibitors FDC (33.53%), and add-on with SGLT2i therapy (20.71%).

The clinicians recorded 40–50 mg/dl of fasting blood glucose reduction observed with sitagliptin, dapagliflozin and metformin triple OAD therapy (38.66%), followed by 35-45 mg/dl (23.27%), 50-60 mg/dl (20.71%), and 60-70 mg/dl (17.16%) (Figure 5). Further, most of the experts observed 70-80 mg/dl of post-prandial blood glucose (PPBG) reduction in individuals with T2DM at 16 weeks of sitagliptin, dapagliflozin and metformin FDC (42.8%), followed by 60-70 mg/dl (25.84%), more than 90 mg/dl (16.17%), and 80-90 mg/dl (14.99%). They also observed 6 to 8 individuals with more than 9% HbA1c values per day (37.48%), followed by less than 5 (27.22%), 8 to 10 individuals (20.91%), and minimum 10 T2DM individuals (14.2%).

The sitagliptin, dapagliflozin and metformin triple OAD therapy reduces the risk of glycemic variability as noted by 80.87% of clinicians, followed by increased risk of glycemic variability (10.85%), and no role (8.09%). Majority of the physicians mentioned sitagliptin, dapagliflozin and metformin FDC therapy provides CV and renal safety with weight neutral therapy (42.21%), followed by improving patient's compliance with efficacious therapy (26.82%), beneficial to long standing T2DM individuals (15.58%), and replace convention triple OAD therapy (15.19%). Majority of the experts mentioned early initiation of DPP-4 inhibitors and SGLT2i combination therapy reduced insulin dose (42.8%), followed by delaying the use of insulin (42.01%), and no requirement for insulin dose (14.99%). Majority of the experts mentioned the use of sitagliptin, dapagliflozin and metformin FDC therapy over pioglitazone triple FDC therapy has CVOT trial clearance (46.55%), followed by significant HbA1c reduction (25.05%), and renal safe & weight neutral therapy (28.21%).

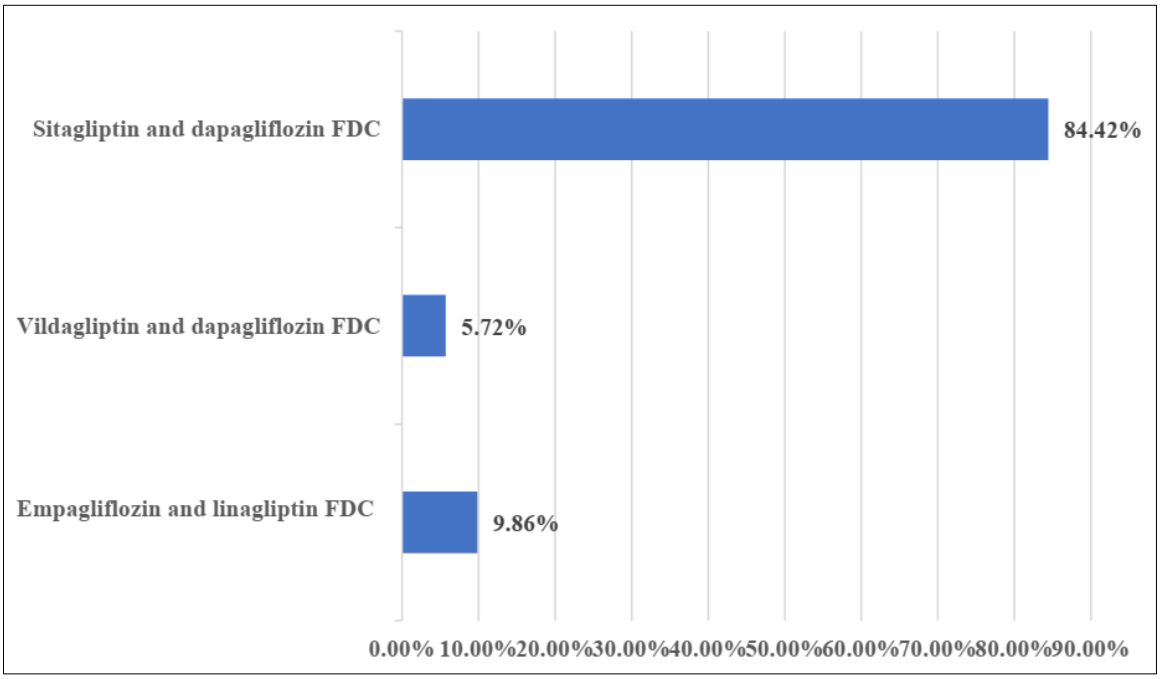

Figure 1: Respondents experience on DPP4i and SGTL2i's FDC for T2DM management with high-risk individuals

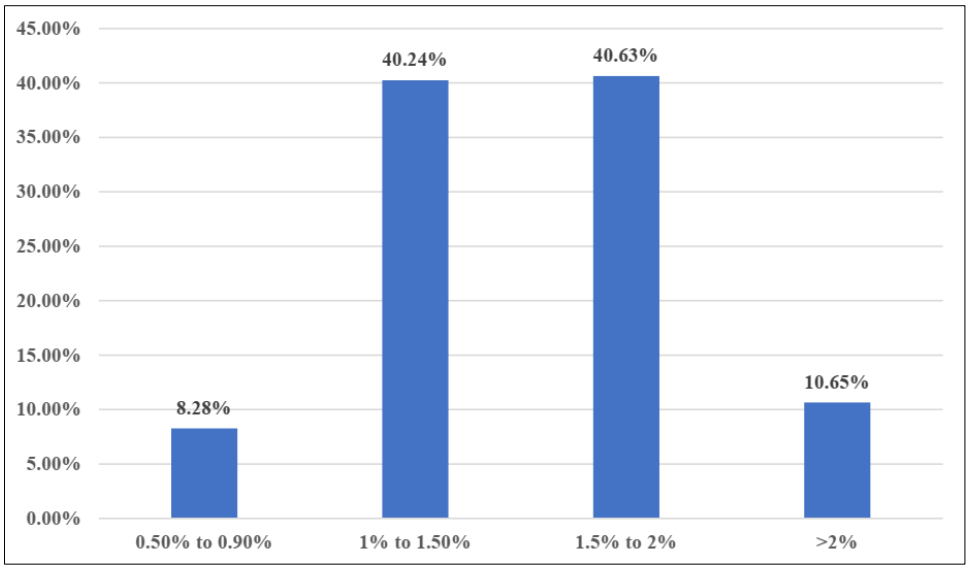

Figure 2: Respondents experience on the percentage reduction of HbA1c level with sitagliptin and dapagliflozin FDC in 16 weeks

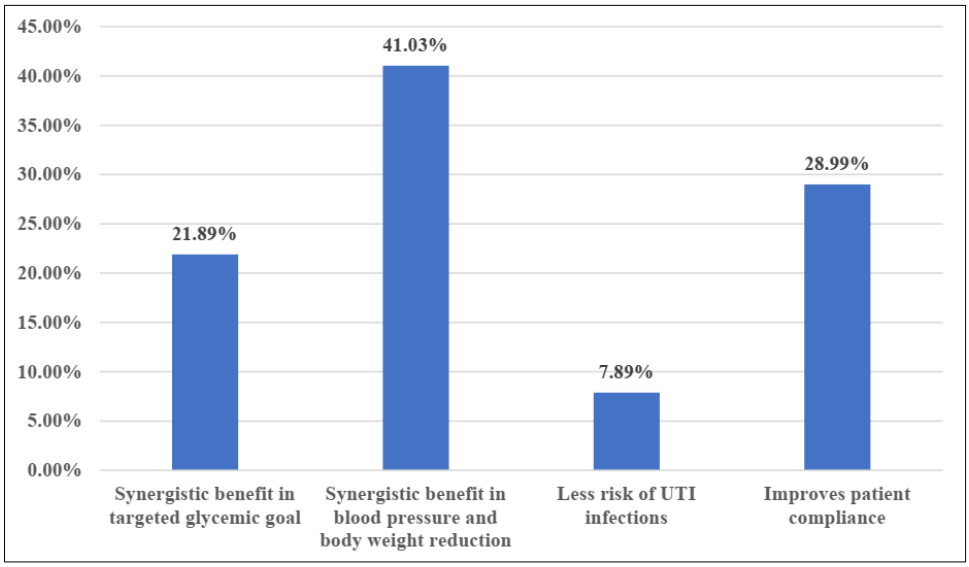

Figure 3: Respondents experience on the major significant advantage of sitagliptin and dapagliflozin FDC therapy as compared to SGLT2 inhibitor monotherapy

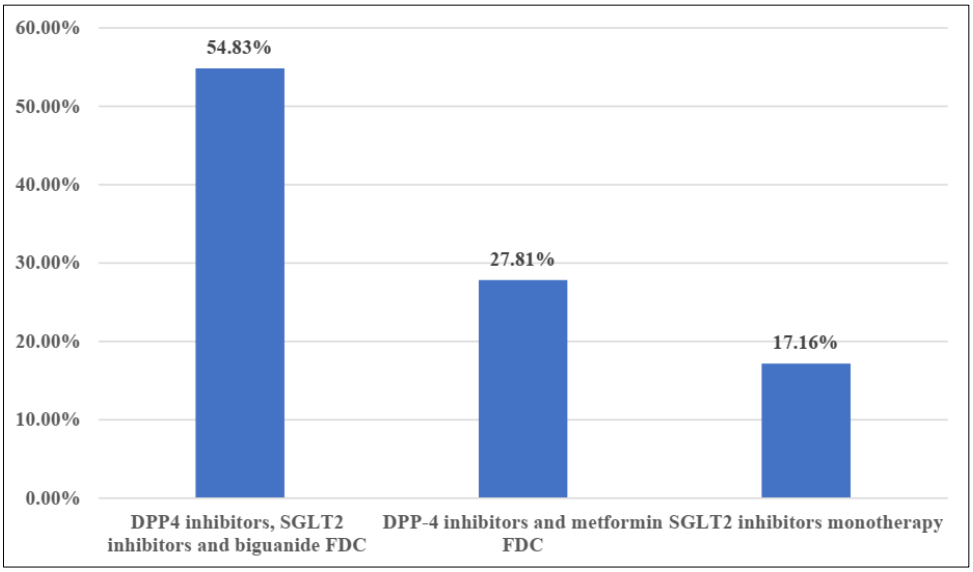

Figure 4: Respondents preference on the first line therapy in HbA1c above 9% in newly diagnosed T2DM individuals

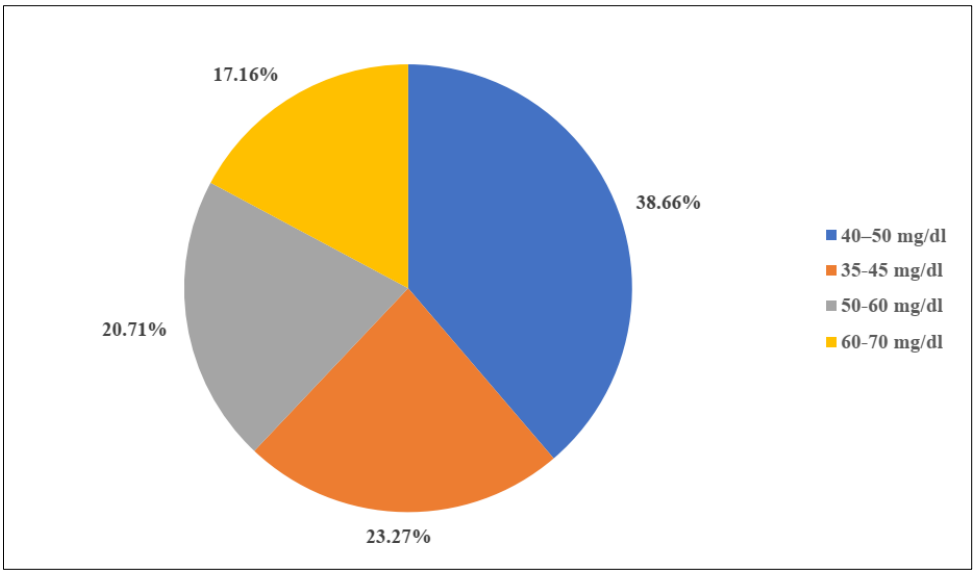

Figure 5: Respondents experience on the fasting blood glucose reduction observed with sitagliptin, dapagliflozin and metformin triple OAD therapy

DISCUSSION

In FDC of SGLT2i and DPP4i with respect to time in range, majority of the doctors mentioned it concerns with reducing time in range (40.04%), whereas only 32.54% doctors mentioned the moderate impact in time in range which was the appropriate response. The real DAPSI (real-world study for dapagliflozin and sitagliptin) study showed FDC of sitagliptin and dapagliflozin FDC showed benefits for T2DM with high-risk in Indian settings [6].

In our study, sitagliptin and dapagliflozin FDC therapy was preferred by the clinicians for high-risk T2DM individuals and its preferred (over vildagliptin and dapagliflozin FDC) by the clinicians for cardiovascular outcome trial. In comparison to a placebo, the analysis revealed a drop of HbA1c values of about 0.6 to 0.7% with use of vildagliptin and sitagliptin (DPP-4 inhibitors over 12 and 52 weeks), respectively [7]. In our study, majority of the clinicians mentioned, 1.5 to 2% of HbA1c level reduction after intake of sitagliptin and dapagliflozin FDC for 16 weeks which was almost triple than the Cochrane review report. In 21 different countries, including India, with varying income levels, the Prospective Urban Rural Epidemiology study compared the rates of cardiovascular events, all-cause mortality, and CV mortality among 143,567 adults with and without diabetes.

The study found that the rates of CVD, all-cause mortality, and CV mortality were significantly higher among adults with diabetes in low-income countries as compared to middle- and high-income countries [8]. Individuals with diabetes have higher cardiovascular risk on comparison with individuals without diabetes [9]. Hence, our study the physicians mentioned risk reduction approach should be focused as a treatment strategy in the centre stage while treating individuals with diabetes. Numerous trials have shown that in patients with poorly controlled type 2 diabetes, SGLT2i/DPP4i significantly reduced weight and improved glycemic control without raising the risk of hypoglycemia [10, 11].

The physicians mentioned SGLT2i and DPP4i FDC therapy improves both insulin resistance & beta cell function, offers rapid & sustained glycemic control, helps in reduction of body weight and reduction of blood pressure other than glycemic benefits. Similar to our study clinician's opinion, the Asian Indian patient group with type 2 diabetes is greatly impacted by the combination's wide range of therapeutic outcomes, which include improved glycemia and adiposity, decreased metabolic and vascular risk, safety, and ease of sustained compliance [12].

Further, one of the main limitations of this study was, the clinicians were selected based on their own interest and limitation to access the wide range of diabetologists exists. The details of diabetologists like years of experience, were not included or collected in the survey. Hence, we could not correlate with the individual's response and their experience in the field. So, this study results needs be analysed with more participants representing from all over the country.

CONCLUSION

It was noted that sitagliptin and dapagliflozin FDC was effective for high-risk individuals with T2DM. Sitagliptin and dapagliflozin combination therapy was recommended for newly diagnosed T2DM (and with CV risk). This combination also showed benefit in reducing blood pressure and weight loss when compared to SGLT2 inhibitors monotherapy. Hospitalization rate and CV risk was reduced in individuals who take sitagliptin and dapagliflozin FDC.

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Conflict of Interest: None declared

Ethical Approval: This study was approved by the Independent Ethics Committee.

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