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Efficacy and Safety of Vildagliptin and Remogliflozin as Add-On Therapy to Metformin in Patients of Type 2 Diabetes Mellitus

An open-label comparative study

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Abstract

Objectives: Metformin is considered as first-line drug in Type 2 Diabetes Mellitus (T2DM).

However, as disease progresses with heightened insulin resistance and declining β -cell function, use of metformin alone is often inadequate to achieve optimum glucose level. The aim of this study was to evaluate safety and efficacy of remogliflozin in comparison to vildagliptin as add-

on drug to metformin in T2DM. **Methods:** This prospective, randomized study was conducted at ESIC Hospital, Faridabad, India between February 2020 to January 2021, recruited patients with T2DM with HbA1c $\geq 6.5\%$ taking metformin at daily dosage of ≥ 1500 to ≤ 3000 mg for ≥ 3

months with age between 35-70 years. Patients were randomly assigned into 1:1 ratio to receive

either vildagliptin (50mg) or remogliflozin (100mg) twice daily for 90 days. The primary

endpoint was change in HbA1c levels from baseline to end of 90 days whereas secondary

endpoints were changes in lipid profile and weight. **Results:** 60 patients underwent

randomization of which, 30 each were assigned to receive either vildagliptin or remogliflozin.

On analysis it was found that decrement in mean HbA1c levels was significantly higher in

remogliflozin group than in vildagliptin group (-8.1% vs. -2.4% , $P < 0.001$). Also, there was

more significant weight loss in remogliflozin treated patients (-5.2% vs. -0.6% , $P < 0.01$). Both

treatments were well tolerated over the course of study. **Conclusions:** Compared to vildagliptin, remogliflozin was significantly more effective in glycemic control and weight loss in T2DM and therefore can be considered as add-on drug in T2DM not adequately controlled by metformin monotherapy.

Keywords: Remogliflozin; Vildagliptin; Metformin; Type 2 Diabetes Mellitus; Efficacy; Safety; Glycaemic Control; Weight Loss.

Advances in Knowledge

- In our study primary endpoint was change in HbA1c levels from baseline to the end of 90 days whereas secondary endpoints were changes in lipid profile and weight from baseline to the end of study. Safety assessment was also done during the duration of the study.
- 60 patients underwent randomization of which, 30 each were assigned to receive either vildagliptin or remogliflozin.
- On analysis it was found that decrement in mean HbA1c levels was significantly higher in the remogliflozin group than in the vildagliptin group (-8.1% vs. -2.4%, $P < 0.001$). Moreover, remogliflozin was superior to vildagliptin in reducing mean body weight (-5.2% vs. -0.6%, $P < 0.01$). Both the treatments were well tolerated over the course of study.
- To the best of our knowledge our study was distinctive where efficacy and safety of remogliflozin, a novel SGLT2 inhibitor was compared with vildagliptin, a commonly prescribed DPP4-inhibitor as add-on therapy to metformin in patients with type 2 diabetes mellitus.

Application to Patient Care

- Metformin is considered as first-line therapy for treatment of patients with T2DM. However, as the disease progresses with heightened insulin resistance and declining β -cell function, use of metformin alone is often inadequate to achieve the optimum glucose level.
- ADA recommends DPP4 inhibitor or SGLT2 inhibitor, as an add-on therapy when the HbA1c target of $\leq 6.5\%$ is not attained after 3 months treatment with metformin alone in management of T2DM.
- In our study we observed that in comparison to vildagliptin, remogliflozin was significantly more effective in glycaemic control and has more significant weight loss potential as add-on drug to metformin in treatment of patients with T2DM. Thus, can potentially be used as an

add-on drug in obese patients with type 2 diabetes mellitus not adequately controlled by metformin monotherapy.

Introduction

Diabetes mellitus stands as a prevalent chronic condition worldwide, leading to a rise in both illness and death rates.¹ In 2010, approximately 6.4% of adults, totalling 285 million individuals, were affected by diabetes, and this figure is predicted to grow to 7.7% encompassing 439 million people by 2030.¹ Notably, India witnessed an estimated 62.4 million diabetic patients in 2011, with projections indicating a staggering increase to 101.2 million cases by 2030.¹ The current guidelines for the comprehensive management of type 2 diabetes advocate a patient-focused strategy to determine the appropriate pharmacological treatments.² Apart from achieving optimal glycaemic control, several other factors affect the selection of anti-diabetic agents, including their impact on body weight, the risk of causing hypoglycaemia, and the presence of other comorbidities.² Type 2 Diabetes Mellitus (T2DM) is a gradually advancing condition that necessitates the intensification of treatment over time to maintain glycaemic control.³ Metformin is considered as first-line drug for the management of T2DM.³ Nevertheless, as the disease progresses, characterized by increased insulin resistance and decreased beta cell function, relying solely on metformin often proves insufficient in attaining the optimum glucose level.³ Since metformin act by enhancing insulin sensitivity, the addition of therapy utilizing an insulin-independent pathway may be beneficial.³

The joint position statement of the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) recommends the usage of one of the six commonly employed antihyperglycemic agents entailing sulfonylurea, thiazolidinedione, dipeptidyl peptidase-4 (DPP4) inhibitor, sodium-glucose cotransporter subtype-2 (SGLT2) inhibitor, glucagon-like peptide-1 (GLP-1) receptor agonist, or basal insulin analogue, as an add-on therapy when the HbA1c target of $\leq 6.5\%$ is not attained following a three-month period of treatment with metformin alone.⁴ DPP4 inhibitors and SGLT2 inhibitors are widely used therapies for T2DM that are associated with a low incidence of hypoglycemia.⁵ DPP4 inhibitor are body-weight neutral⁶, whereas SGLT2 inhibitors promote weight loss and reduce systolic blood pressure.⁷ According to 2017 American Association of Clinical Endocrinologists (AACE)

and American College of Endocrinology (ACE) comprehensive glycaemic control algorithm, ranks SGLT2 inhibitors higher than DPP4 inhibitors in the recommended order of use, both as standalone therapy and as an add-on treatment in the management of T2DM.⁸

Vildagliptin, a potent and selective inhibitor of dipeptidyl peptidase-4 (DPP-4), improves glycaemic control by increasing the availability of endogenous incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulintropic polypeptide (GIP).⁹ Complementing the pharmacological effect of metformin, vildagliptin enhances glucose-dependent insulin secretion and suppresses glucagon release, thereby improving glycaemic control, and contributing to weight-neutrality and reduced hypoglycemia.¹⁰ Remogliflozin, a novel SGLT2 inhibitor, is to be administered as prodrug remogliflozin etabonate.¹¹ Inhibition of SGLT2 (which is selectively expressed in the proximal convoluted tubules of kidney) leads to increased excretion of glucose in urine, resulting in reduced blood glucose concentrations and has therapeutic benefit in T2DM.¹² The recommended dose of remogliflozin etabonate for the treatment of T2DM in India is 100 mg twice daily.¹³ This study was proposed with the hypothesis that remogliflozin may be non-inferior to vildagliptin in the treatment of type 2 diabetes mellitus as add-on therapy to metformin.

Methods

Study Design

The study was a prospective, randomized, open-label, parallel-group, interventional and comparative study, registered with the Clinical Trials Registry of India (CTRI). The study protocol was approved by institutional ethics committee of Maulana Azad Medical College, New Delhi on 1st November 2019. Prior to the initiation of the study written informed consent was obtained from all the patients involved in the study. Privacy was maintained during data collection and subjects were ensured of complete confidentiality about the information they share in the study.

Study population

The study enrolled 60 outpatients with type 2 diabetes mellitus managed at medicine OPD at Lok Nayak Jai Prakash Hospital in New Delhi, India. The enrollment began in February 2020 and

ended in January 2021. The inclusion criteria were as follows: (1) Patients with diagnosis of type 2 diabetes mellitus with HbA1c > 6.5 % (48 mmol/mol); (2) those taking metformin at dosage of ≥ 1500 to ≤ 3000 mg/day for ≥ 3 months; (3) those aged between 35 and 70 years of all sexes; (4) those who provided written informed consent to participate in the study. The following exclusion criteria were used: (1) Patients with type 1 diabetes or secondary diabetes; (2) those taking any other glucose-lowering agents other than metformin; (3) those with hepatic dysfunction [AST or ALT ≥ 2.5 times of upper normal limit (UNL) or bilirubin > 2 times of UNL]; (4) those with renal dysfunction [estimated glomerular filtration rate (eGFR) as per MDRD formula < 45 ml/min/1.73 m²]; (5) those with genitourinary tract infections; (6) those with lower limb cellulitis or ulcer; (7) patients with known case of osteoporosis; (8) patients allergic to the study medications; (9) those who were pregnant or breastfeeding; (10) those who did not give consent.

Randomization, study intervention and study outcomes

Following the acquisition of informed consent, eligible patients were divided randomly into two groups in a 1:1 ratio. One group received vildagliptin (50 mg; twice daily), while the other group received remogliflozin (100 mg; twice daily), both as additional medication to their existing metformin intake at dosage between ≥ 1500 to ≤ 3000 mg/day, for the duration of 90 days. The randomization process utilized a computer-based dynamic allocation method to ensure a balanced distribution of key baseline characteristics, such as age, gender, metformin dose, HbA1c levels, lipid-profile, and body weight. The primary endpoint was change in HbA1c from baseline to the end of 90 days whereas the secondary endpoints were changes in the lipid parameters and the body weight, relative to baseline.

Data collection schedule

During the patient recruitment day, a comprehensive medical history was gathered, and a thorough general and systemic examination was conducted, with particular focus on identifying any potential complications related to diabetes mellitus. Additionally, the patients underwent various essential investigations, including liver and kidney function tests, routine urine examination, HbA1c, lipid profile, fundus examination, and ECG. After the initial assessment, the patients were scheduled for a follow-up visit after 90 days. During the follow-up visit, they

underwent similar examinations and investigations as performed on the recruitment day. All the relevant details were carefully recorded in a pre-designed clinical proforma for accurate documentation and analysis.

Safety evaluation

Throughout the study, the patients' well-being was closely monitored for any adverse events (AEs), via telephonic communication and regular in-person visits to the medicine outpatient department (OPD) where they received their prescribed treatment drugs. The patients were reassured that they could reach out to the researchers at any time if they experienced any form of discomfort during the study. Any AEs that occurred were documented. Additionally, the researchers maintained regular contact with the patients, checking on their well-being and ensuring they adhered to the prescribed treatment and instructions.

Statistical analysis

The collected data were transformed into variables, coded and entered in Microsoft Excel spreadsheet 2019. The data were analysed and statistically evaluated using SPSS software version 25.0. The quantitative data were expressed in mean \pm standard deviation, difference between two groups were tested by student's t-test (unpaired) or Mann Whitney 'U' test for normal and non-normal data respectively. The qualitative data were expressed in frequency and percentage, differences between the proportions were tested by Fisher's exact test or Chi-square test for parametric and non-parametric distributions respectively. P value < 0.05 was considered statistically significant. Safety analysis included all treated patients.

Results

Clinical Characteristics

In this study, 548 patients were screened, out of which 488 were excluded from the study (481 did not meet eligibility criteria, 7 did not give consent). 60 patients were enrolled and randomized, and 57 completed the study and were included in the final analysis, 28 and 29 patients in the vildagliptin and remogliflozin groups, respectively (Figure 1). Two patients (one in each group) were excluded after randomization due to protocol violation as they started taking glucose-lowering agents other than study medications. The baseline demographic, clinical, and

laboratory characteristics of the study population were comparable between the both treatment groups (Table 1).

Superiority of remogliflozin regarding the primary and secondary endpoints

The improvement in the HbA1c levels was significantly more pronounced in the remogliflozin group than in the vildagliptin group after 90 days of treatment [-0.67 ± 0.24 vs. -0.20 ± 0.22 ; $P < 0.001$ (Table 2, Figure 2)]. The weight loss was also significantly more in the remogliflozin group than in the vildagliptin group relative to the baseline levels [-3.73 ± 1.91 vs. -0.4 ± 1.52 (kg); $P < 0.01$ (Table 3)]. Regarding the lipid parameters, there were significant decrement in total cholesterol, triglycerides, LDL and VLDL levels in the remogliflozin group when compared with levels in the vildagliptin group [-2.33 ± 9.54 vs. 6.47 ± 4.85 ; $P = 0.001$, -1.1 ± 9.32 vs. 6.3 ± 6 ; $P < 0.01$, -1.70 ± 7.78 vs. 4.13 ± 3.57 ; $P = 0.02$; -0.27 ± 5.22 vs. 4.07 ± 3.6 ; $P < 0.01$ (mg/dl), respectively (Table 3). Also, the increment in HDL level in the remogliflozin group was more significantly pronounced when compared to the vildagliptin group [1.30 ± 4.63 vs. -1.6 ± 3.27 ; $P = 0.03$ (Table 3)].

Safety Outcomes

During the study, 19 of 28 patients (67.8%) in the vildagliptin group and 17 of 29 patients (58.6%) in the remogliflozin group reported adverse events (AEs). The nature of AEs was mild in nature like dizziness or weakness, nausea, headache, diarrhoea, joint pain, genital infection, urinary tract infection (UTI), constipation, cough, nasopharyngitis and abdominal pain. (Figure 3). Most of the AEs were self-limiting and resolved spontaneously during the course of study thus, treatment protocol was not altered. No subjects in either group were withdrawn because of AEs. No significant differences in AEs were found between the groups. No serious AEs including hypoglycaemia were observed in either group.

Discussion

This prospective randomized study was done to evaluate efficacy and safety of remogliflozin, a novel SGLT2 inhibitor in comparison to vildagliptin, a commonly prescribed DPP4 inhibitor in the treatment of type 2 diabetes mellitus. We enrolled 60 patients with type 2 diabetes mellitus with inadequate glycaemic control (average HbA1c level, 8.30% or 67 mmol/mol) on metformin

alone. After 90 days of treatment, we observed that remogliflozin in comparison to vildagliptin, as an add-on therapy to metformin, is superior to vildagliptin in terms of glycaemic control, lipid-lowering potential and weight loss capacity. Both the medications were well tolerated and no serious adverse events were observed during the course of study.

A randomized, double-blind, active- and placebo-controlled trial was conducted to evaluate efficacy and safety of twice-daily remogliflozin etabonate for the treatment of type 2 diabetes mellitus.¹⁵ In this 90 days study, 336 treatment-naïve subjects with type 2 diabetes and an HbA1c between 7.0 to 9.5% were randomized to remogliflozin etabonate (50 mg, 100 mg, 250 mg, 500 mg or 1000 mg twice daily), matching placebo or 30 mg pioglitazone once daily.¹⁵ The results indicated that the twice-daily administration of remogliflozin etabonate led to a dose-dependent improvement in glycaemic control, with statistically significant reductions in body weight compared to the placebo group.¹⁵ Additionally, the treatment was generally well-tolerated by the participants.¹⁵ In our study, we observed that in the group administered with remogliflozin 100 mg twice daily, after 90 days showed improvement in glycaemic control in terms of decrement in mean HbA1C levels from baseline by 8.1% which was comparable to previous study which showed decrement by 11.9%.¹⁵ In terms of effect on lipid profile, the study showed 1.3% decrement in mean total cholesterol levels, 1.5% decrement in mean LDL levels, and 0.9% decrement in mean VLDL levels

Our findings were in contrast to findings of previous study by Sykes et al¹⁵ which showed rather increment in total cholesterol, LDL and VLDL levels by 2.5%, 4.9% and 1.2% respectively. This can be attributed to the limitations of our study which were small sample size and short duration. However, we also observed, 1.7% decrement in mean triglycerides levels and 3% increment in mean HDL levels, these findings were comparable to previous study by Sykes et al¹⁵ which showed 3.5% decrement in triglycerides level and 6.5% increment in HDL levels. The overall changes in lipid profiles in the remogliflozin treatment group may in part reflect improvements in glycaemia and a change in insulin sensitivity, as insulin activates lipoprotein lipase to hydrolyze triglycerides, resulting in a decrease in triglycerides level, increase in HDL-cholesterol concentration and a shift in the processing of particles towards cholesterol-rich lower-density particles.¹⁶

A similar pattern of lipid changes has been documented with canagliflozin, reflecting a 2.0-6.1% increase in LDL cholesterol, a 6.1-6.8%, increment in HDL cholesterol and a decrement of 5.4-10.2% in triglycerides.¹⁷ Though, the lipid-lowering potential of remogliflozin was statistically more in comparison to vildagliptin but meagre increment makes it unsuitable to be used as an alternative to standard lipid-lowering drugs for treating type 2 diabetes patients with dyslipidaemia.

In our study, patients receiving remogliflozin at end of 90 days showed statistically significant reduction in mean body weight from baseline at 5.2% which was comparable to previous study which showed 5% reduction in body weight.¹⁵ Similar findings were also previously observed in DIVERSITY-CVR trial where body weight loss of $\geq 3.0\%$ was significantly achieved in the dapagliflozin group in comparison to sitagliptin.¹⁸ Reported adverse events were mild and self-limiting in both the groups and comparable to findings in previous study by Sykes *et al*¹⁵ where overall rate of adverse events in the remogliflozin treatment groups did not differ from that in the placebo group and none were reported as serious. We did not observe any episode of hypoglycaemia in either group similar to findings in previous study by Sykes *et al*¹⁵ where no subjects in the remogliflozin or pioglitazone treatment groups were withdrawn because of hypoglycaemia or other adverse events. These data indicate that both remogliflozin and vildagliptin can be used to improve glycaemic control while minimizing hypoglycemic episodes in management of patients with type 2 diabetes.

Our study has few limitations which should be mentioned. First, this was an open-label study and second, all patients were of Indian ethnicity as we recruited patients from medicine OPD where patients were receiving drugs as part of their standard care. The Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) reported that East Asians had the greatest HbA1c level response to sitagliptin, a DPP4 inhibitor of the same class as vildagliptin.²⁰ Thirdly, the sample size of our study was small with short duration of follow-up as it was planned as a pilot study. The sample size was not calculated and participant recruitment done on that basis. Nonetheless, promising results of our study has encouraged the researchers to further evaluate potential of remogliflozin including its impact on renal and cardiovascular outcomes in T2DM. To further

validate the generalizability of our findings, it is requisite to conduct future trials with a larger number of participants, adequate representation of different ethnicities, and long-term observation.

Conclusion

To our knowledge, our study was first to directly evaluate the efficacy and safety of remogliflozin in comparison to vildagliptin as add-on therapy to metformin in patients with inadequately controlled type 2 diabetes mellitus. Our study showed that remogliflozin was superior to vildagliptin in terms of glycaemic control after 90 days of treatment. Additionally, loss in body weight occurred more significantly in the remogliflozin group.

Conflicts of Interest

The authors declare no conflict of interests.

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No funding was received for this study.

Authors' Contribution

VS conceptualized the study. VS analyzed and interpreted the data. VS and BS drafted the manuscript. SC and SG reviewed the manuscript critically. VS and BS revised the manuscript. All authors approved the final version of the manuscript.

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Table 1: Patients Characteristics at Baseline.

Characteristics	Vildagliptin group (N=28)	Remogliflozin group (N=29)	*P-value
Age (years)	50.57±10.01	49.10±9.36	0.50
Sex			
Male/Female	14 (50)/14 (50)	15 (51.7)/14 (48.3)	0.89
Metformin Daily Dosage (gm)			0.86
1.5/2/2.5	6 (21.4)/20 (71.4)/2 (7.2)	5 (17.2)/21 (72.4)/3 (10.4)	
HbA1c (%)	8.31±0.92	8.30±1.05	0.99
Lipid Parameters (mg/dl)			
Total Cholesterol	198.67±40.26	192.40±36.85	0.28
Triglyceride	174.35±55.68	166.37±53.39	0.29
LDL	111.43±21.12	115.33±26.14	0.27
HDL	40.53±8.22	43.10±7.15	0.22
VLDL	34.27±12.05	30.37±12.57	0.11
Body Weight (kg)	65.27±10.49	71.40±14.03	0.09

Data are presented as frequency (percentage) or mean±standard deviation, as appropriate; *P-values for between-groups comparison were obtained using the Student t-test (unpaired) and Fisher's exact test for continuous and categorical variables, respectively and value <0.05 was considered statistically significant; HbA1c-glycated haemoglobin, LDL-low-density lipoprotein, HDL-high-density lipoprotein, VLDL- very low-density lipoprotein.

388 **Table 2:** Comparison of mean change in HbA1c (%) level from baseline to day 90.

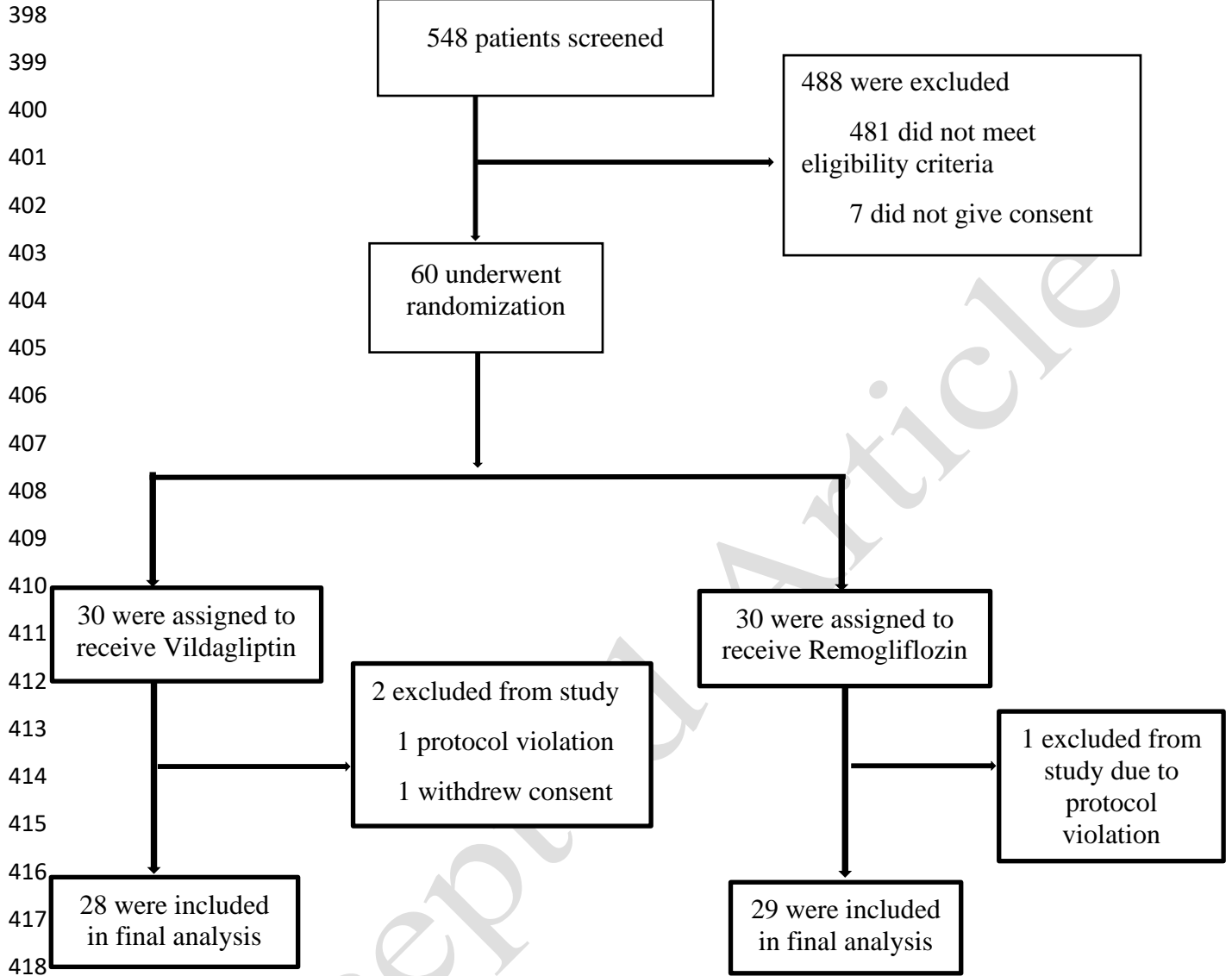
HbA1c (%)	Vildagliptin group (N=28)	Remogliflozin group (N=29)	* <i>P</i> -value
Baseline	8.31±0.92	8.30±1.05	0.99
Day 90	8.10±0.84	7.62±1.00	0.05
Mean change	-0.20±0.22	-0.67±0.24	< 0.001

389 Data are presented as mean±standard deviation; **P*-values for between-group comparisons were
390 obtained using Student t-test (unpaired) and value <0.05 was considered statistically significant;
391 HbA1c-glycated hemoglobin.

392
393 **Table 3:** Comparison of mean change in the secondary endpoints from baseline.

HbA1c (%)	Vildagliptin group (N=28)	Remogliflozin group (N=29)	* <i>P</i> -value
ΔTotal Cholesterol (mg/dl)	6.47±4.85	-2.33±9.54	0.001
ΔTG level (mg/dl)	6.3±6.1	-1.1±9.32	< 0.01
ΔLDL level (mg/dl)	4.13±3.57	-1.70±7.78	0.02
ΔHDL level (mg/dl)	-1.6±3.27	1.30±4.63	0.03
ΔVLDL level (mg/dl)	4.07±3.6	-0.27±5.22	< 0.01
ΔBody Weight (kg)	-0.4±1.52	-3.73±1.91	< 0.01

394 Data are presented as mean±SD; **P*-values for between-group comparisons were obtained using
395 Student t-test (unpaired) and value <0.05 was considered statistically significant; SD-Standard
396 Deviation, Δ-amount of change from baseline to day 90, TG-Triglycerides, LDL-low-density
397 lipoprotein, HDL-high-density lipoprotein, VLDL-very low-density lipoprotein.



419 **Figure 1:** Flow chart of patients' enrollment, allocation and analysis.

420

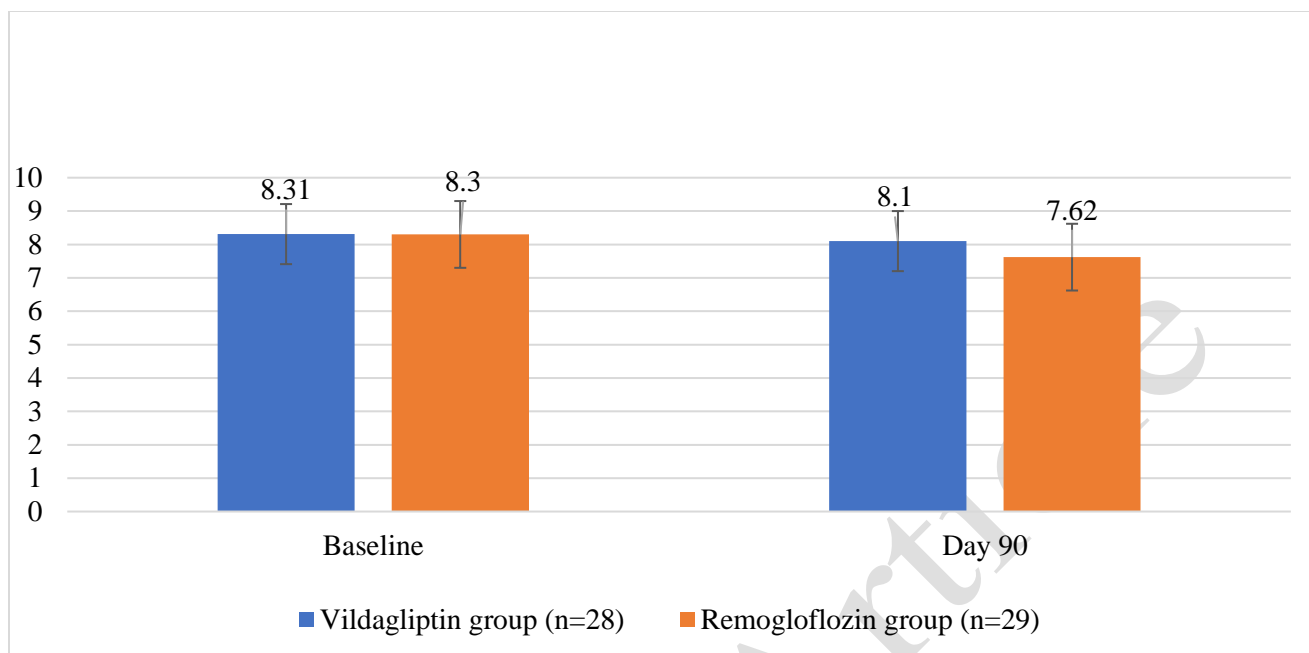


Figure 2: Comparison of HbA1c (%) level at baseline & day 90 between the groups.

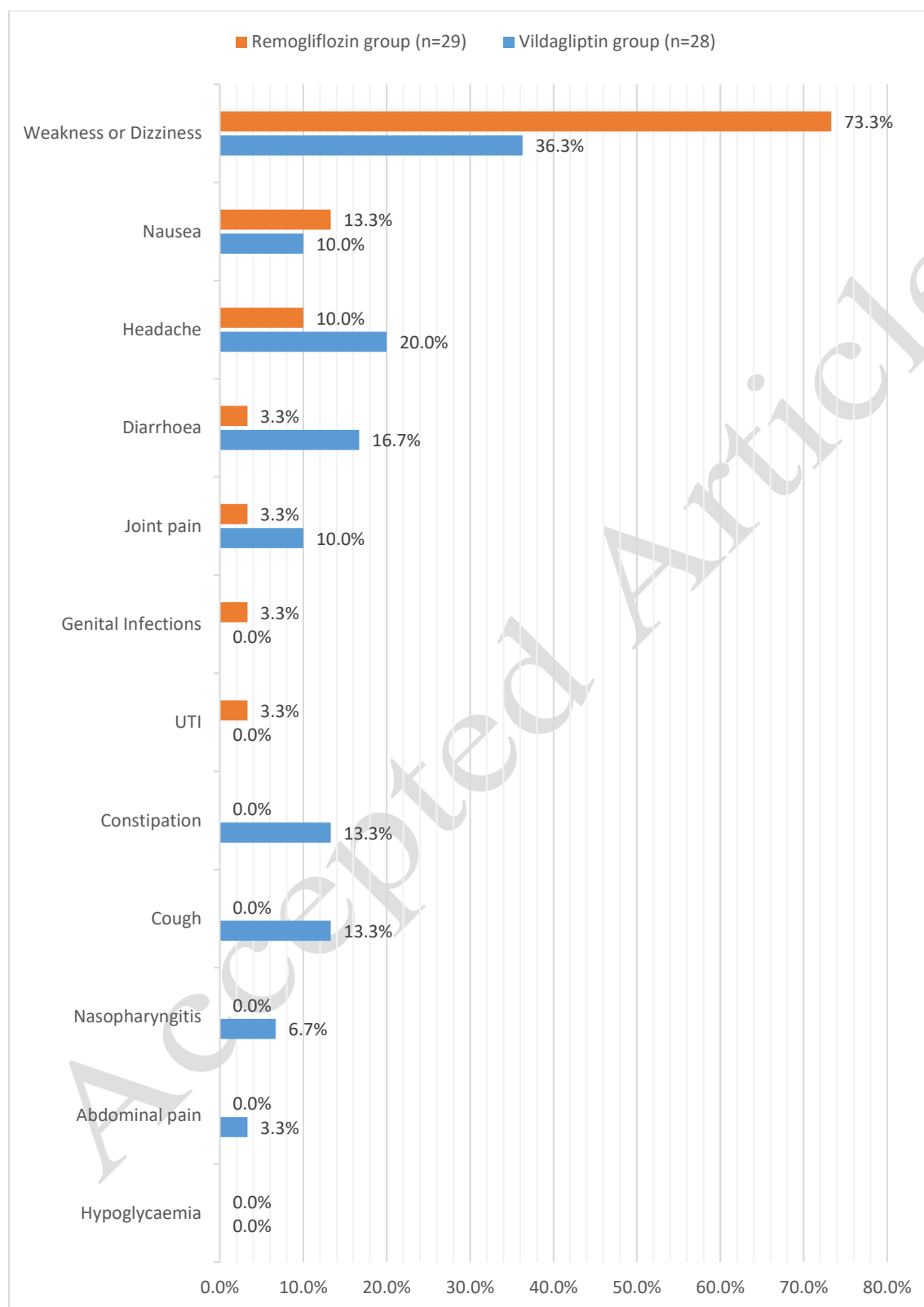


Figure 3: Comparison of adverse events between the groups.