ORIGINAL ARTICLE

Improved Clinical Outcomes with the Combination Therapy of a Glucagon-like Peptide-1 Receptor Agonists and a Sodium-glucose Cotransporter-2 Inhibitor in Overweight/Obese People with Type 2 Diabetes: Real-world Evidence from the Indian Subcontinent

Anant Nigam*

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Abstract

Objective: Type 2 diabetes (T2D) mellitus is increasing exponentially in India, with overweight/obesity being prime contributors. This study aimed at assessing the clinical impact of the combination therapy of a glucagon-like peptide-1 receptor agonist (GLP-1RA) injection (inj.) and a sodium-glucose cotransporter-2 inhibitor (SGLT-2i) in overweight/obese patients from the Indian subcontinent.

Methods: In two real-world evidence (RWE) studies (RWE1 and 2), we retrospectively observed the effect of the combination therapy of a GLP-1RA, injection dulaglutide (DU) 1.5 mg/week, and an SGLT-2i, canagliflozin (CAN) 100 mg/day at weeks 16, 32, and 52 on HbA1c, body weight (weight), systolic blood pressure (SBP), lipids, change in doses of antidiabetic agents (ADA) and antihypertensive agents (AHA) in overweight/obese Asian Indian subjects with T2D, who had suboptimal glycemic control.

Results: A total of 95 T2D patients [51 males (M), 44 females (F)] completed the two RWE studies. In RWE 1, 40 patients (20 M/20 F), mean [standard deviation (SD)] age 49.4 (10.7) years (Y), weight 92.6 (6.6) kg, body mass index (BMI) 30.6 (2.3) kg/m^2, duration of T2D 8.1 (3.2) Y, completed the study. At week 32, the mean (SD) reduction in A1c (%) was −1.3% [8.4 (0.7) to 7.1 (0.3); $p < 0.01$] and mean (SD) weight (kg) loss was −5.5 [92.6 (6.6) to 87.9 (7.02); $p < 0.00001$]. This group was then followed up until week 52. In RWE 2, 55 patients (31 M/24 F), age 51 (5.8) Y, weight 92.6 ± 3.4 kg, BMI 31.1 ± 2.1 kg/m^2, SBP 142.4 ± 3.9 mm Hg, estimated glomerular filtration rate (eGFR) 62 ± 5 mL/minute/1.73 m^2, with 8.4 ± 3.3 Y duration of diabetes met the inclusion criteria. In 71% of subjects, A1c decreased by −1.4% [8.5 ± 0.4 to 7.1 ± 0.2; $p < 0.0001$] at week 16 and was 6.8 ± 0.3 ($p = 0.0002$) in 18% at week 32.

Conclusion: A statistically significant (SS) improvement in glycemic control, weight, and improvement in cardiovascular (CV) risk factors was observed with the GLP-1RA/SGLT-2i combination, which was well tolerated.

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Introduction

An exponential increase in the number of people with diabetes in India from 77 million in 2019 to 101 million in 2030 is anticipated.[1] The prevalence of obesity in developing countries and, in particular, abdominal adiposity in certain ethnic populations like the South Asians, has increased significantly. This in turn has led to an increased burden of type 2 diabetes (T2D), cardiovascular (CV) disease, and the related morbidity and mortality.[2] The risk of developing T2D increases by 1.5% among overweight/obese individuals and by 0.5% among nonoverweight individuals for each unit rise in body mass index (BMI).[3] Zhang et al., in a survey on the prevalence of risk factors in patients with undiagnosed T2D, found that 82.6 and 61.9% of patients had hypercholesterolemia and hypertension, respectively; 56.8% were obese, and an additional 29.5% were overweight.[4]

Both obesity and T2D have been labeled as epidemics, and the prevalence of abdominal adiposity continues to increase in adults.[5] The excess accumulation of abdominal adipose tissue and visceral adiposity (VA) poses a greater risk of developing T2D and CV disease than peripheral obesity.[6] Data suggest that weight loss is a key factor in the control and prevention of coronary artery disease (CAD), T2D, hyperlipidemia, cardiorespiratory failure, and other chronic degenerative diseases.[7] A reduction in diabetes-related complications and a significant improvement in CV risk factors can be expected in patients with T2DM if weight gain can be prevented or a modest weight reduction of about 5% can be achieved.[8]

Current recommendations suggest that the initial antidiabetic agents (ADA) used in therapy in T2DM be based on comorbidities and be focused on treatment factors and management needs of patients. T2D is a progressive, complex metabolic disorder. Metformin (MET) monotherapy often fails to produce a sustained reduction in A1c, and thus, early combination therapy has been suggested. Initial combination therapy provides a greater and more durable A1c reduction due to the synergistic and complementary mode of action of ADA.[9,10] This has been validated by the VERIFY (Vildagliptin Efficacy in Combination with MET for Early Treatment of T2D) trial.[11] The glucagon-like peptide-1 receptor agonist (GLP-1RA)/sodium-glucose cotransporter-2 inhibitor (SGLT-2i) combination therapy corrects most of the pathophysiologic abnormalities of the ominous octet, provides effective glycemic control with weight loss but without an increased risk of hypoglycemia (hypo). It also offers enhanced cardio-renal benefits.[12]

Obesity/overweight is a well-recognized CV risk factor.[13] In patients with indicators of high CV risk, atherosclerotic cardiovascular disease (ASCVD), heart failure (HF), or chronic kidney disease (CKD), it is recommended that agents like a GLP-1RA or an SGLT-2i with proven CV benefits be used, independent of baseline A1c, individualized A1c target, or MET use. For patients on a GLP-1RA who are not meeting A1c goals, an SGLT-2i may

Director, Nigam Diabetes Center, Jaipur, Rajasthan, India; *Corresponding Author

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be added, and vice versa.[9] The GLP-1RA/SGLT-2 combination therapy has favorable and augmented effects on weight loss with little or almost no risk of hypo.[14,15] This is in sharp contrast to the most commonly used ADA agents like insulin secretagogues (SU, meglitinides), glitazones, and INS, which cause weight gain.[16] Randomized controlled trials (RCTs) and other nonrandomized studies have shown that the GLP-1RA/SGLT-2i combination provides effective glycemic control compared to monotherapy with either agent alone. The indication to use a GLP-1RA in patients with multiple CV risk factors (like obesity) for ASCVD is based on the Researching Cardiovascular Events with a Weekly Incretin in Diabetes (REWIND) trial, where patients were randomly assigned to a weekly injection of dulaglutide (DU) or a placebo.[17]

In patients without ASCVD, HF, CKD, or indicators of high ASCVD risk, the American Diabetes Association suggests the use of agents based on glycemic efficacy and patient-centered treatment factors like preventing weight gain and minimizing hypo. GLP-1RA and SGLT-2i promote weight loss and help in meeting these goals.[9,18]

The addition of basal INS to oral agents is a well-established strategy in patients who have a long duration of diabetes, are obese, and require agents with greater potency to reduce A1c.[9] Data suggest that the glycemic efficacy of an injectable GLP-1RA is similar to or greater than that of basal INS, with a lower risk of hypo and the benefit of weight loss.[19,20] Thus, in obese patients with T2D, the addition of a GLP-1RA is a better option vis-à-vis basal INS. Here are reported two retrospective observational real-world evidence (RWE1, 2) studies on the dual therapy of a GLP-1RA and an SGLT-2i in overweight/obese Asian Indian subjects who did not achieve glycemic targets on their preceding therapy.[21,22]

Study Design and Methods

Both RWE1 and RWE2 retrospective observational studies were carried out in overweight/obese Asian Indian subjects with T2D in a specialized diabetes care center in North India. These evaluated the effect of the combined therapy of a GLP-1RA (injection DU 1.5 mg, Eli Lilly and Company, Indianapolis, IN 46285, United States of America) and an SGLT-2i (tablet canagliflozin (CAN) 100 mg, Janssen Pharmaceuticals, Inc., Titusville, NJ 08560) on A1c, body weight, SBP, and changes in doses of ADA including INS and antihypertensive agents (AHA).[21,22]

For both RWE1 and RWE2, patients with T2D, aged 20–75 years, BMI ≥27 kg/m^2, A1c ≥8.0%, and estimated glomerular filtration rate (eGFR) >45 mL/minute/m^2 were eligible for inclusion. Patients with a past medical history of pancreatitis and T1 diabetes were excluded from the study.

In RWE1, injection DU 1.5 mg weekly subcutaneously (SC) was added to the ongoing CAN therapy (100 mg oral daily) for a minimum of 16 weeks and other ADA therapies. The primary endpoints were changes in A1c and body weight from baseline at weeks 16 and 32, and secondary endpoints were side effects of DU and CAN and events of hypo.[21] All parameters were finally assessed at week 52. In RWE2, therapy was initiated with a combination of injection DU (1.5 mg weekly SC) and CAN (100 mg oral daily) in patients not achieving glycemic control on MET, SU, and/or INS. The primary endpoints were changes in A1c, body weight, SBP, lipids, and doses of previous ADA and AHA from baseline at weeks 16, 32, and 52. Key secondary endpoints were side effects of DU, CAN, and events of hypo.[22] Titration of existing therapy (INS) and oral agents (other than MET) was done based on individualized self-monitoring of blood glucose (SMBG) targets after 4 weeks or earlier if symptoms of hypo were reported or if blood sugars were out of the set target for each patient. Statistical calculations were done using Microsoft Excel 10 and were validated by checking the electronic health records for accuracy.

Results

In RWE1, 43 subjects (22 M, 21 F) were enrolled, but 40 completed the study (2 M went missing on follow-up and 1 F underwent bariatric surgery). In RWE2, 55 patients (31 M, 24 F) completed the study. Table 1 shows the baseline data of patients RWE 1 and 2.

In RWE1, a statistically significant (SS) reduction of A1c of −1.3% [8.4 (0.7) to 7.1 (0.3), $p < 0.01$] (Fig. 1A) and weight of −5.5 kg [92.6 (6.6) to 87.9 (7.02); $p < 0.00001$] (Fig. 1B) was seen.[21] A1c and weight benefits were maintained in 65% of subjects until week 52 (Table 2). In RWE2A1c decreased in 71% patients by −1.4% [8.5 ± 0.4 to 7.1 ± 0.2, $p < 0.0001$] (week 16) (Fig. 2A) and by week 32 dropped to 6.8 ± 0.3 ($p = 0.0002$) in 18%. At week 16, weight reduced by −4.1 kg (92.6 ± 3.4 to 88.5 ± 3.6, $p < 0.0001$) and 68% lost another 3.3 ± 0.7 kg ($p < 0.0001$) (week32) (Fig. 2B). Durability of A1c and weight was seen until week 52 (Table 2).

Composite of A1c and Weight Loss

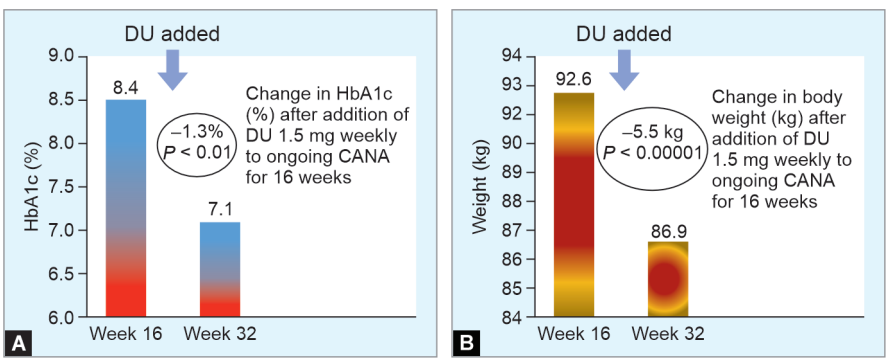
A composite of A1c ≤ 7% and weight loss of 5–10% was seen in 57 and 64% of patients in RWE1 and RWE2, respectively. Weight loss >10% and A1c ≤ 7% was observed in 12 and 17% of patients in RWE1 and RWE2, respectively (Fig. 3).

Doses of Antidiabetic Agents and Basal INS

In RWE1, by week 16, only half the dose of SU was needed in 30% of patients and had

Table 1: Baseline patient characteristics of RWE1 and RWE2

	RWE1	*RWE2*
Males	20	31
Females	20	24
Age mean (SD) years	49.4 (10.7)	51 (5.8)
BMI mean (SD) kg/m^2	30.6 (2.3)	31.1 (2.1)
Weight mean (SD) kg	92.6 (6.6)	92.6 (3.4)
Duration of diabetes mean (SD) years	8.1 (3.2)	8.4 (3.3)
HbA1c mean (SD)%	9.2 (0.4)	8.5 (0.4)
SBP mean (SD) mm Hg	140.5 (3.5)	142.4 (3.9)
eGFR mean (SD) mL/minute/1.73m^2	68 (3)	62 (5)
Patients on MET (%)	87	83
Patients on sulfonyl urea (%)	65	60
Patients on basal insulin (%)	67	71
Patients on SU + insulin (%)	42	40

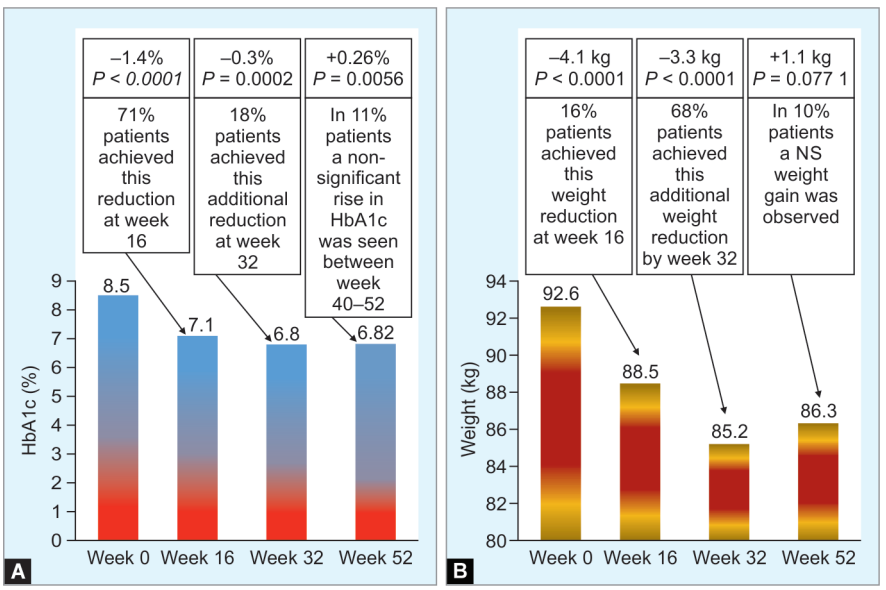


Figs 1A and B: Effect on HbA1c and weight after addition of a GLP-1RA to SGLT-2i and other therapies in RWE1[21]

Table 2: Baseline and follow-up values of demographic characteristics, laboratory values, and changes in various parameters at baseline, week 16, 32, and 52

	RWE1				*RWE2*			
	Baseline	*Week 16*	*Week 32*	*Week 52*	*Baseline*	*Week 16*	*Week 32*	*Week 52*
HbA1c (%) Mean (SD)	9.2 (0.4)	8.4 (0.7)	71%:7.1 (0.3)	65%:7.0 (0.4) 20%:7.2 (0.6) 15%:6.9 (0.2)	8.5 (0.4)	71%:7.1 (0.2) 29%:7.4 (0.5)	18%:6.8 (0.3) 74%:6.9 (0.4) 08%:7.1 (0.6)	80%:6.9 (0.3) 09%:7.0 (0.4) 11%:7.06 (0.5)
Weight (kg) Mean (SD)	94.1 (4.5)	92.6 (6.6)	83%: 87.9 (7.02) 17%:88.0 (6.5)	65%: 83.2 (3.9) 35%:82.9 (4.2)	92.6 (3.4)	70%: 88.5 (3.6) 30%:89.5 (3.9)	68%: 85.2 (0.7) 32%:86.1 (1.2)	90%: 84.91 (4.0) 10%:82.3 (3.8)
SBP mean (SD) (mm Hg)	148 (4.0)	144 (3.7)		143 (4.1)	142.4 (3.9)	139 (2.3)	138.3 (2.8)	138.2 (2.2)
TGL Mean (SD) (mg/dL)	171 (7.0)			147 (7.9)	189.6 (8.1)			168.4 (6.9)
LDLC Mean (SD) (mg/dL)	112s (8.8)			108 (8.1)	107.5 (4.7)			104.2 (4.9)
Change in doses of medication								
SU	65% (n = 26) were on SU	In 30% (n = 8): Dose halved in 43% (n = 11): SU stopped		In 61% (n =11): SU stopped	60% (n = 33)	In 56% (n = 18): dose halved in 15% (n = 5): SU stopped		In 49% (n = 16): SU stopped
Basal INS Mean (SD) dose	16 (3.1) U	43%: 12 (2.1) U 14%: stopped		68%: 10(2.3) U 22%:stopped	18 (3.1)	50%: 12 (2.2) U 15%: stopped		73%: 10 (1.8) U 27%: stopped
Doses of AHA	–	39%: decrease in doses 19%: stopped one category		6%: required stoppage		53%: decrease in doses 24%: stopped one category		11%: required stoppage of all AHA

AHA, antihypertensive agents; LDLC, low-density lipoprotein cholesterol; SBP, systolic blood pressure; SU, sulfonylurea; TGL, triglycerides; INS, insulin



Figs 2A and B: (A) This shows the effect of the combination therapy of Inj DU and CAN on HbA1c in obese type 2 diabetic Asian Indian patients in RWE2[22]; (B) This shows the effect of the combination therapy of Inj DU and CAN on weight in obese type 2 diabetic Asian Indian patients in RWE2[22]

to be stopped in 43%. By week 52, 61% did not require SU for optimal glycemic control (Table 2). In RWE2, by week 16, the dose of SU had been halved in 56% of patients and stopped in 15%. By week 52, SU had to be discontinued in 49% of patients.[22] In both RWE1 and RWE2, basal INS doses had to be reduced by week 16. By week 52, 22% and 27% of patients needed the stoppage of INS in RWE1 and RWE2, respectively (Table 2).

Systolic Blood Pressure and Doses of Antihypertensive Agents

A SS reduction in SBP of −4.0 mm Hg, $p < 0.0001$ (RWE1, Table 2) and a −4.1 mm Hg, $p < 0.0001$ reduction was seen in RWE2 was seen.[22] A decrease in doses of AHA and the need to discontinue one or both AHA by week 52 was seen in both RWE 1 (Table 2) and RWE 2.[22]

Effect on Lipids

Table 2 shows a reduction in triglycerides (TGL) and LDL-cholesterol (LDL-C) in RWE1

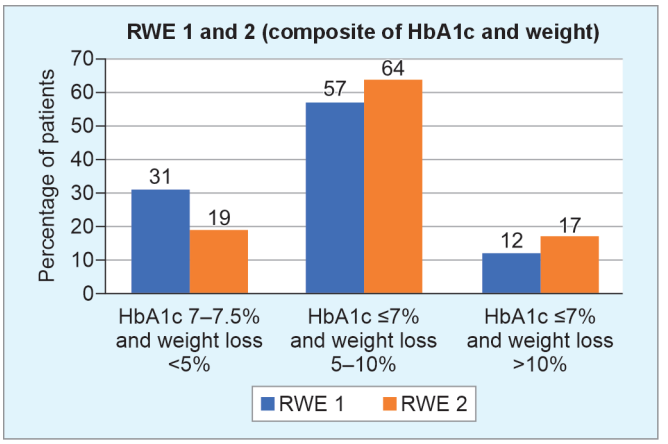


Fig. 3: Effect on the composite of HbA1c and weight in RWE1 and RWE2 at the end of 24 weeks

of –24 mg/dL ($p < 0.0001$) and –3 mg/dL ($p = 0.0002$), respectively. In RWE2, TGL, and LDL-C decreased by –21.2 mg/dL ($p < 0.0001$) and –3.3 mg/dL ($p = 0.0004$), respectively.[22]

Side Effects

In RWE1, nausea and vomiting were observed in 20% of subjects, with none having to discontinue therapy.[21] Genital and urinary tract infections were reported in 5.9% (2 F, 1 M) and 3.6%, respectively, with CAN in RWE2, but no patient had to pause therapy. With DU, nausea occurred in 18.1%, vomiting in 14.5%, and diarrhea in 7.2%, but therapy was not discontinued in any patient. Minor episodes of hypoglycemia occurred in 7.5% ($n = 3$) of patients, where the dose of SU and INS had to be reduced.[22]

Discussion

A multifactorial approach to managing hyperglycemia in T2D has been shown to reduce diabetes complications, and an annual assessment of CV risk factors is thus recommended.[14] The current recommendation is to prescribe a GLP-1RA or SGLT-2i with proven CV benefits (GLP-1RAs: DU, injectable Semaglutide, Liraglutide; SGLT-2is: Canagliflozin, Empagliflozin, Dapagliflozin) in patients with T2D at high risk for ASCVD (examples: obesity/overweight, dyslipidemia, hypertension, smoking) or those with ASCVD (examples: acute coronary syndrome or MI, coronary artery bypass, stroke, peripheral artery disease of probable atherosclerotic origin), HF, or CKD. This usage should be independent of baseline or individualized A1c target or MET use. Only DU, among the current GLP-1RAs, has demonstrated a reduction in CV events, both in people with and without CV risk factors.[17] Other factors, such as patient preferences, cost, side effects, and their effect (I) on body weight and (II) on hypoglycemic risk, should be considered.[9]

In patients without established ASCVD or CKD, both GLP-1RA and SGLT-2i are important agents to consider if there is a pressing need to reduce weight gain, promote weight loss, and reduce the risk of hypo.[17] In addition, a GLP-1RA/SGLT-2i combination therapy has synergistic effects in decreasing A1c, body weight, and other CV risk factors.[17]

Overweight and obesity are very important comorbidities with T2D, and a loss of body weight of about 5% has been shown to result in improved control.[23] Clinical trials with weight-loss medications in T2DM have shown improvements in A1c and fasting plasma glucose (FPG).[24] With weight loss, a reduction in the requirement and doses of ADA, AHA, and anti-lipid agents has also been observed.[21]

While RCTs remain the gold standard, RWE studies provide important information about treatment effectiveness and outcomes in routine practice.[25]

In both of our RWE studies, a SS and durable reduction in A1c of –1.3 to –1.4% was observed when patients received dual therapy with GLP-1RA (DU 1.5 mg) and SGLT-2i (CAN 100 mg).[21,22] Stable glycemic control was seen in both RWE studies up to week 52 in the majority of our patients (Table 2). Other RWE studies using a DU/SGLT-2i combination have also observed a drop in A1c of –1.3 to –2.2%.[26,27] In the 24-week long AWARD-10 [The Assessment of Weekly Administration of LY2189265 (DU) in Diabetes] trial, there was an almost similar decline in A1c of –1.34 and –1.21% for 1.5 and 0.75 mg weekly DU, respectively, vs placebo when patients with uncontrolled T2D (A1c ≥7.0% and ≤9.5%) on ongoing SGLT2i therapy were randomly assigned to weekly DU 1.5, 0.75, or a placebo.[17] In a meta-analysis conducted in patients on a GLP-1/SGLT-2i combination therapy, A1c levels were significantly decreased and maintained for over 1 year.[25,28]

A significant reduction in the doses of SU and basal INS in a sizable number of patients, with the need to also discontinue in others, was seen as early as week 16 in both RWE studies (Table 2). It has been predicted that for an average decrease of 5% body weight, doses of SU, INS, and any ADA could be reduced by 39, 42, and 49%, respectively. The same investigators also reported that for every 5% body weight reduction, the relative odds of stopping SU, INS, and any ADA were 1.24, 1.30, and 1.37, respectively.[29] We hypothesize that the reduction in ADA doses is due to the overall decrease in body weight, which leads to a fall in insulin resistance and, thus, improvement in insulin sensitivity.

In both our RWE, significant weight loss was observed.[14,22] The durability of this weight loss was observed even at week 52 (Fig. 2 and Table 2). A weight loss of –2.6–6.4 kg was noted in other RWE studies.[24,25] However, body weight reduction in RWE studies was greater than that seen in the AWARD-10 trial (0.9–3.0 kg for DU 1.5 mg). The magnitude of weight loss was less than additive.[30] A meta-analysis also confirmed further weight reduction after a GLP-1RA was added to ongoing SGLT2 therapy.[31] The suppression of appetite and decrease in gastrointestinal motility caused by GLP-1RA, combined with glycosuria and the resultant calorie loss due to SGLT2i therapy is the explanation for the substantial loss of weight with this combination.[32,33] Thus, the combination of a GLP-1RA/SGLT-2i, when used in overweight/obese T2DM patients, has been found to be distinctly useful in achieving A1c and weight goals.

Figure 3 shows that a composite of A1c ≤7% and weight loss of 5–10% was achieved in 57 and 64% of RWE1 and RWE2 patients, respectively. A weight loss of >10% was also observed in 12% (RWE1) and 17% (RWE2). Similar results have been observed in RCTs and also in a meta-analysis using the combination.[34,35]

As seen in Table 2, a durable drop in SBP over a year was seen in both our RWE studies. This required a decrease in the doses of AHA and even discontinuation of one category of AHA. These changes could be seen as early as week 16. A meta-analysis of three RCTs confirmed similar findings on SBP, which was additive, although no changes were observed in diastolic blood pressure. Mechanisms postulated for this reduction in SBP include natriuresis (both), reduction in intravascular volume and/or alteration in intrarenal hemodynamics (SGLT-2i), and vasodilation (GLP-1RA).[36,37] The overall decrease in body

weight and insulin resistance with GLP-1RA/SGLT-2i may also explain this drop in SBP.

We observed a reduction in triglyceride and LDL-C in both our studies, which was sustained for a year. A 10% lower level of LDL-C was observed in the SUSTAIN-9 trial (Efficacy and Safety of Semaglutide Once-Weekly Versus Placebo as Add-On to SGLT-2i in Subjects with T2D Mellitus trial).[38] A significant decrease in both total and LDL cholesterol has been reported. However, there was no change in either HDL cholesterol or triglycerides.[39]

In a meta-analysis that pooled data from eight studies with 1,895 patients with T2DM, dual therapy with GLP-1RA/SGLT-2i vs monotherapy with either agent showed greater reductions in A1c, body weight, FPG, 2-hour postprandial glucose (2h PG), systolic blood pressure (SBP), BMI, and LDL-C. These reductions in A1c, body weight, and FPG were sustained for more than one year, although the effects gradually declined over time.[34]

Most observations made in this meta-analysis are in concordance with our two RWE studies.

The combination of DU and CAN was well tolerated in both our studies, as has also been reported.[40] Nausea, vomiting, and diarrhea were the most common adverse events (AEs) observed with DU, and genital and urinary tract infections were seen with CAN in a small percentage of patients. However, none discontinued therapy.[24,25] Similar AE were observed in the Award-10 Trial.[17]

Glucagon-like peptide-1 receptor agonist and SGLT-2i have a low inherent risk of hypoglycemia. Minor episodes of hypoglycemia were seen in both our RWE studies, only in patients on SU and/or insulin, at about 4 weeks after initiation of therapy. If doses of SU and insulin are adjusted in time, these episodes of hypoglycemia can be avoided.

Strength and Limitation

The strength of our RWE studies was the lack of dropout among subjects recruited in the study group and a long-term follow-up of up to 52 weeks. Waist circumference (WC) is a surrogate marker of visceral adiposity. Our inability to measure WC in both our RWE studies is a limitation of our study. If it had been measured, we would have been able to determine the decrease in visceral adiposity after therapy with GLP-1RA/SGLT-2i.

Conclusion

Dual therapy of GLP-1RA/SGLT-2i provides a significant decrease in A1c and body weight. Improvement in CV risk factors like blood pressure and lipids was also observed. These effects were sustained up to 1 year of the study, confirming durability and consistency in results. This combination therapy is well tolerated and is a useful therapeutic option in overweight/obese patients with T2D.

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Author Contributions

Study concept and design: AN; acquisition of data: AN; analysis and interpretation of data: AN; drafting of the manuscript: AN; critical revision of the manuscript: AN; statistical analysis: AN; administrative, technical, or material support: AN; and study supervision: AN.

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