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Metabolic and cardiovascular benefits with SGLT-2 inhibitors and GLP-1 receptor agonists combination therapy in type 2 diabetes

Singh AK *et al*. GLP-1RA and SGLT-2I dual therapy in T2DM

Awadhesh Kumar Singh, Ritu Singh

Abstract

Both GLP-1 receptor agonists (GLP-1RA) and SGLT-2 inhibitors (SGLT-2I) are relatively newer class of anti-diabetic agents that lower HbA1c moderately and decrease body weight and systolic blood pressure (SBP) modestly. Combination therapy with GLP-1RA plus SGLT-2I have shown a greater reduction in HbA1c, body weight and SBP compared to either agent alone without any significant increase in hypoglycemia and other side effects. Since several agents from each class of these drugs have shown an improvement in cardiovascular (CV) and renal outcomes in their respective cardiovascular outcome trials (CVOT), combination therapy is theoretically expected to have additional CV and renal benefits. In this comprehensive opinion review, we found HbA1c lowering with GLP-1RA plus SGLT-2I to be less than additive compared to the sum of HbA1c lowering with either agent alone, although body weight lowering was nearly additive and the SBP lowering was found to be more than additive. Our additional meta-analysis of CV outcomes with GLP-1RA plus SGLT-2I combination therapy from the pooled data of 5 CVOT demonstrated a similar reduction in 3-point major adverse cardiovascular event compared to GLP-1RA or SGLT-2I alone, against placebo. Interestingly, a greater benefit in reduction of heart failure hospitalization with GLP-1RA plus SGLT-2I combination therapy was noted in the pooled meta-analysis of 2

randomized controlled trials. Future adequately powered trials can confirm whether additional CV or renal benefit is truly exerted by combination of GLP-1RA plus SGLT-2I therapy.

Key Words: GLP-1 receptor agonists; SGLT-2 inhibitors; Combination therapy, Metabolic outcomes; Cardiovascular outcomes; Renal outcomes

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Core Tip: GLP-1 receptor agonists (GLP-1RA) plus SGLT-2 inhibitors (SGLT-2I) dual therapy causes a greater reduction in HbA1c, body weight and systolic blood pressure (SBP), compared to either agent alone with similar adverse events. However, lowering of HbA1c, body weight and SBP with combination therapy appeared to be less, nearly equal and more than additive, respectively. Our meta-analysis from 5 cardiovascular outcome trials suggests a similar reduction in major adverse cardiovascular events with dual therapy compared to GLP-1RA or SGLT-2I alone, but an additional benefit in heart failure hospitalization is likely. Future trials are needed to confirm these findings.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) has a complex nature of pathophysiology and therefore most patients will eventually require a combination of antidiabetic agents (ADD) with different mechanisms of action to achieve optimal glycemic control. GLP-1 receptor agonists (GLP-1RA) are relatively newer class of ADD that lower plasma glucose both by enhancing insulin secretion and inhibiting glucagon secretion[1]. SGLT-2 inhibitors (SGLT-2I) are another newer class of ADD that lowers plasma glucose by promoting urinary glucose excretion through kidney by inhibiting glucose reabsorption[2]. Notably, both classes of these drugs have shown a favorable effect on body weight and blood pressure. Importantly, several recent cardiovascular (CV) outcome trials (CVOT) conducted with SGLT-2I or GLP-1RA have shown that certain agents within each class can reduce the incidence of CV events and mortality in people with T2DM[3,4]. In this comprehensive opinion review, we attempt to answer three contemporary questions: (1) What is the rational of this combination in type 2 diabetes; (2) What additional metabolic control can we achieve with this combination therapy; and (3) Do we get an additional CV and renal benefit by combining both drugs?

WHAT IS THE RATIONAL OF THIS COMBINATION IN TYPE 2 DIABETES?

Since both GLP-1RA and SGLT-2I works through a different mechanism of actions (MOA) in different organs, combination therapy with these agents is expected to have a complementary or perhaps a synergistic effect on metabolic outcomes. Combination of GLP-1RA and SGLT-2I can potentially correct seven of the eight pathophysiologic defects (ominous octet) of T2DM[5]. GLP-1RA lowers plasma glucose concentration by augmenting insulin secretion and inhibiting glucagon secretion *via* β-cells and α-cells in pancreas respectively, in a glucose-dependent manner[1,6]. SGLT-2I lowers plasma glucose concentration by producing glucosuria which in turn causes a compensatory and "paradoxical" increase in endogenous glucose production (EGP) accompanied by a significant increase in plasma glucagon as well as a significant decrease in the fasting plasma insulin concentration. Thus, SGLT-2I administration can lead to a marked

increase in plasma glucagon-to-insulin ratio (GIR) by a tune of 50%-100%[7,8]. This increase in EGP by SGLT-2I appears to counterbalance or offset nearly 40%-50% of the amount of glucose that is lost in the urine during glucosuria and therefore attenuates overall decrease in HbA1c caused by the SGLT-2I class of drugs[7]. Since increase in plasma glucagon-to-insulin ratio contributes to an increase in EGP caused by SGLT-2I (at least in part), any pharmacological agents that reverse this ratio and in turn prevent an increase in EGP would amplify the decrease in HbA1c by SGLT-2I[9,10]. This led to believe that addition of GLP-1RA to SGLT-2I would stimulate insulin secretion and inhibit glucagon secretion and thus can prevent an increase in plasma glucagon-to-insulin ratio and hence expected to mitigate any increase in EGP caused by SGLT-2I allowing an amplification of plasma glucose lowering with SGLT-2I in combination with GLP-1RA. Indeed, in a study (n = 36) that evaluated the acute effect of single dose of liraglutide (GLP-1RA), canagliflozin (SGLT-2I) and combination of liraglutide plus canagliflozin, on serum insulin, glucagon and EGP found that acute administration of a single dose of liraglutide prevented the insulin decline and blocked the glucagon rise observed with canagliflozin, although it did not inhibit the increase in EGP[11]. Similarly, a 16-wk trial (n = 45) that evaluated the chronic effect of liraglutide, canagliflozin and liraglutide plus canagliflozin combination therapy on serum insulin, glucagon and EGP, found that canagliflozin caused a significant 9% increase in EGP ($P < 0.05$) accompanied by a significant 50% increase ($P < 0.05$) in plasma GIR, while liraglutide inhibited EGP and reduced plasma glucagon concentration. Interestingly, EGP increased by a significant 15% ($P < 0.05$) in canagliflozin plus liraglutide combination arm, despite the fact that canagliflozin induced plasma glucagon concentration was blocked by liraglutide and no change in plasma insulin from the baseline was observed[12]. These findings hint that factor other than insulin and glucagon may contribute to the stimulation of EGP with SGLT-2I induced glucosuria and these include contribution of renal gluconeogenesis which is insensitive to plasma glucagon concentration[13].

Other logic of this combination therapy also stems from the fact that while SGLT-2I cause significant reduction of body weight, chronic administration may lead to a

plateau effect due to compensatory increase in appetite which may partially offset weight reductions[14]. Contrarily, GLP-1RA delays gastric emptying and is associated with appetite suppression, therefore combination may overcome SGLT-2I induced hyperphagia. Figure 1 summarizes the potential effect of combining SGTL-2I and GLP-1RA therapy. Importantly, early initiation of GLP-1RA and SGLT-2I in combination do not potentiate hypoglycemia and adverse events significantly and shall allow a timely achievement of glycemic goals. Consequently, this combination has the potential of lowering the risks of diabetes-related morbidity and mortality in patients with T2DM especially in the light of positive CV and renal outcomes with these agents as demonstrated in their respective CV and renal outcome trials[15].

WHAT ADDITIONAL METABOLIC CONTROL CAN WE ACHIEVE WITH THIS COMBINATION THERAPY?

Several short- and long-term randomized controlled trials (RCTs)[12,16-23] and observational studies[24-30] (ranging from 12-104 wk), and meta-analysis of RCTs[31-34] have assessed the efficacy and safety of GLP-1RA and SGLT-2I combination therapy either simultaneously or sequentially. All these studies have demonstrated a significantly greater benefit on metabolic outcomes (HbA1c, body weight and systolic blood pressure) with combination therapy compared to either agent alone or placebo. Table 1 summarizes the results from both randomized and observational studies, while Table 2 summarizes the results of meta-analysis. Collectively, reduction in HbA1c, body weight and SBP was significantly greater with GLP-1RA plus SGLT-2I combination therapy compared to the placebo, GLP-1RA alone or SGLT-2I alone. However, in these RCTs HbA1c lowering with simultaneous combination therapy of GLP-1RA and SGLT-2I was found to be less than additive compared to the sum of HbA1c lowering with either agent. Notably, body weight lowering appeared to be nearly additive, while SBP lowering was more than additive with simultaneous GLP-1RA and SGLT-2I combination therapy when compared to the sum effect with either agent alone across RCTs. Table 3 summarizes these findings from RCTs. From the safety perspective, no

obvious increase in odds of severe hypoglycemia was noted with combination therapy compared to either agent alone. Similarly, no obvious increase in gastrointestinal (GI) side effect or genital tract infection (GTI) was observed with GLP-1RA and SGLT-2I combination therapy compared with GLP-1RA or SGLT-2I alone, respectively.

The less than additive effect on HbA1c is commonly observed with many combination treatments including SGLT-2I plus metformin or SGLT-2I plus DPP-4 inhibitors or SGLT-2I plus GLP-1RA. It may be at least partly due to the "floor effect", as the efficacy of each individual agent depends on baseline HbA1c. When given in combination, one ADD would lower HbA1c more rapidly than the other due to the differential time to onset of action for each drug thereby resulting in a smaller "effective baseline HbA1c" for the second ADD of combination therapy. Thus, the second ADD would then have a smaller decline in HbA1c compared with its use in monotherapy, given the lower starting glycaemic load. Secondly, it could be related to the MOA of the individual components. Thirdly, despite a notable reduction in GIR and EGP with GLP-1RA alone, there was no decrease in EGP with combination therapy of GLP-1RA plus SGLT-2I which can partly explain less than additive effect on HbA1c. Summarily, overall effect on HbA1c with combination therapy depends upon multiple factors including onset of action and MOA of each drug and may not necessarily be synergistic despite having complimentary MOA. Another unique finding that has emerged about simultaneous GLP-1RA and SGLT-2I dual therapy compared to either therapy alone is related to weight reduction in short term *vs* long-term trial. In the longest conducted RCT (DURATION-8; 26-, 52- and 104-wk), Δweight reduction with GLP-1RA plus SGLT-2I dual therapy (exenatide QW and dapagliflozin combination) and GLP1-RA therapy (exenatide QW) alone decreased over time when compared to Δweight reduction at 28 wk[16-18]. Contrarily, SGLT-2I (dapagliflozin) recipients alone achieved greater Δ weight reduction at 104 wk compared with Δweight reduction at 28 wk. This hint to a time-dependent diminution in body weight lowering attributed to GLP-1RA rather than the SGLT-2I and therefore this finding defies the logic of "plateau" effect on body weight reduction with long term use of SGLT-2I. Lastly, it is unclear whether

simultaneous initiation or sequential administration of GLP-1RA and SGLT-2I has any difference in metabolic outcome based on available evidence. This is because all available studies that has evaluated sequential administration were primarily placebo-controlled trials. To know the metabolic outcome differences between simultaneous vs. sequential approach one requires comparison of three-arm trials- arm with simultaneous GLP-1RA plus SGLT-2I combination vs. arm with GLP-1RA initiation and subsequent addition of SGLT-2I *vs* arm with SGLT-2I initiation and subsequent addition of GLP-1RA.

Several other studies with combination therapy with GLP-1RA plus SGLT-2I are currently under progress that can further enlighten their synergistic metabolic effect as compared to either therapy alone. Dapagliflozin plus exenatide on central regulation of appetite in diabetes type 2 (DECREASE; NCT03361098) is a double-blind, 16-weeks, RCT (n = 65) investigating the separate and combined actions of GLP-1RA plus SGLT-2I on food intake, body weight and the activity within the central satiety and reward circuits in response to food-related stimuli and whether the combination can prevent the increased intake observed with SGLT2-I in obese T2DM[35]. Effects of combined dapagliflozin and exenatide *vs* dapagliflozin and placebo on ectopic lipids in patients with uncontrolled type 2 diabetes mellitus (EXENDA, NCT003007329) is a triple-blind, 24-wk, RCT (n = 34) investigating the effect of combination therapy *vs* SGLT-2I alone on hepatic lipid content (primary outcome) and myocardial as well as pancreatic lipid content (secondary outcome) as measured by magnetic resonance spectroscopy[36]. Another randomized, controlled, double blind study is undergoing to assess mechanistic effects of combination therapy of dapagliflozin with exenatide QW *vs* dapagliflozin alone in obese (BMI > 30 kg/m^2) patients with type 2 diabetes mellitus (RESILIENT; EudraCT 2015-005242-60). This study is evaluating the effect of exenatide QW plus dapagliflozin *vs* dapagliflozin alone compared with placebo, on adjusted mean reduction in total body fat mass (as determined by dual-energy X-ray absorptiometry, DEXA) after 32 wk of treatment (n = 110)[37]. A 6 wk (n = 17), open-label, randomized, cross-over study to evaluate the albuminuria lowering effect of

dapagliflozin, exenatide and their combination in patients with type 2 diabetes (DECADE, EudraCT 2017-004709-42) is also currently underway[38]. Results from these studies of GLP-1RA plus SGLT-2I dual therapy would further add to our knowledge.

DO WE GET AN ADDITIONAL CV AND RENAL BENEFIT BY COMBINING BOTH DRUGS?

The mechanism by which both SGLT-2I and GLP-1RA exert their CV benefit appears to be mostly independent of glucose lowering and likely to be complementary owing to their differential mechanisms of action and differential CV benefit. Available data from CVOT and renal outcome trials does hint that GLP-1RA primarily reduce the risk of atherosclerotic cardiovascular diseases (ASCVD) event (ischemic stroke benefits being greater), with a modest effect on kidney function and minimal effect on heart failure; whereas SGLT-2I significantly reduce the risk of heart failure and improve kidney function with a modest effect on ASCVD. Consequently, it is alluring to consider that combination therapy of SGLT-2I and GLP-1RA would achieve greater metabolic and cardio-renal benefits in patients with T2DM, compared with either class of drug alone. This has gained further importance in the light of latest American Diabetes Association and the European Association for the Study of Diabetes consensus report[39] and the European Society of Cardiology guidelines[40] that has put SGLT-2I, GLP-1RA and its combination therapy much early in hierarchy in presence of high CV risk, despite the unclarity on whether beneficial CV effects of individual GLP-1RA and SGLT-2I are retained or enhanced or mitigated in combination therapy. To date, no dedicated randomized CVOT have yet evaluated the cardio-renal outcomes with combination therapy of these two drug classes. A real-world propensity-matched study (n = 25168) using insurance claims databases from the United States found addition of SGLT-2I to GLP-1RA therapy to be associated with a lower major adverse cardiovascular event and heart failure hospitalization compared to initiation with sulfonylureas, in people with T2DM[41]. Another 12-mo randomized blinded study (n = 160) reported a significant increase of global myocardial work index with GLP-1RA plus SGLT-2I combination

therapy (17.4%) or GLP-1RA alone (12.7%) compared with insulin (3.1%) or SGLT-2I (2%). Similarly, a significantly ($P < 0.05$ for all comparisons) greater decline of pulse wave velocity (PWV) including central and brachial systolic blood pressure was observed with GLP-1RA plus SGLT-2I combination therapy (PWV, 13%) or SGLT-2I (PWV, 10.1%) as compared with GLP-1RA (PWV, 8.6%) or insulin (PWV, 3.6%). The dual therapy of GLP-1RA plus SGLT-2I showed a significantly ($P < 0.05$) greatest effect on all measured markers in patients with left ventricular ejection fraction < 55%[42]. Summarily, GLP-1RA and SGLT-2I dual therapy showed a significantly greater improvement of endothelial glycocalyx thickness (a marker of endothelial dysfunction), myocardial work index and a greater reduction in arterial stiffness compared with insulin therapy, despite a similar glucose reduction.

The study of combination therapy with GLP-1RA plus SGLT-2I in recently conducted CVOT have been rare. The prevalence of baseline SGLT-2I use in GLP-1RA CVOT ranged from 0% to 5.3%, the exception being AMPLITUDE-O study of efpeglenatide where 15.2% ($n = 618$) were using SGLT-2I at the baseline[43-45]. Likewise, the prevalence of baseline GLP-1RA use in SGLT-2I CVOT ranged from 2.5% to 4.4% (CANVAS, $n = 407$; DECLARE-TIMI, $n = 750$; VERTIS-CV, $n = 277$)[45-48]. To understand the CV effect of GLP-1RA plus SGLT-2I combination therapy, we systematically reviewed the literature and pooled the data of primary three-point major adverse cardiovascular event (3P-MACE) outcome from 5 CVOT that reported the results against placebo[43,45-48]. Figure 2 represents the search criteria and flow diagram according to PRISMA statements. Additionally, we also pooled the data of HHF and renal composite that was available for 2 RCT-AMPLITUDE-O and DECLARE-TIMI[45,47]. Table 4 summarizes the findings from 5 CVOT that reported the outcomes stratified on combination therapy users. Subsequently, a meta-analysis was conducted by applying the inverse variance-weighted averages of pooled logarithmic hazard ratio (HR) using fixed-effects model with Comprehensive Meta-Analysis software Version 3, Biostat Inc. Englewood, NJ, United States. A two-sided P value of < 0.05 was considered statistically significant. Heterogeneity was measured using Higgins I^2 and Cochrane Q statistics and it was

considered low ($I^2 \leq 25\%$) or moderate (> 25%-50%) or high (> 50%)[49]. While we did not use Cochrane tool to assess the bias risk assessment considering the robust quality of trials included in this meta-analysis, publication bias for CV outcome was evaluated by applying funnel plot using the "trim and fill" adjustment, rank correlation test and the Egger's test. A sensitivity exclusion analysis was additionally performed to determine whether any subgroups included in this meta-analysis could have influenced the aggregate result or changed the heterogeneity significantly. Our meta-analysis of 5 CVOT (n = 40, 760) that reported the outcome with or without combination therapy, found a significant reduction in composite of 3P-MACE (HR 0.90; 95%CI: 0.85-0.96; P = 0.001), without any heterogeneity. This finding was similar regardless of baseline GLP-1RA or SGLT-2I use: GLP-1RA without SGLT-2I (1 RCT; n = 3458; HR 0.74; 95%CI: 0.58-0.94; P = 0.02), SGLT-2I without GLP-1RA (3 RCT; n = 34106; HR 0.92; 95%CI: 0.86-0.99; P = 0.02) and GLP-1RA plus SGLT-2I combination therapy (5 RCT; n = 3,196; HR 0.77; 95%CI: 0.59-1.01; P = 0.06), without any significant heterogeneity and interaction ($P_{interaction}$ = 0.12) (Figure 3). Sensitivity influence analysis showed that no individual subgroup significantly affected the aggregate results or heterogeneity (Supplementary Table 1). No obvious publication bias was noted amongst 3 subgroups and Trim and Fill imputed point estimates were exactly similar to the final results (Supplementary Figure 1). Our analysis suggests no incremental or attenuated 3P-MACE benefits with GLP-1RA plus SGLT-2I combination therapy, although that needs to be confirmed through large adequately powered clinical trials. Nonetheless, our findings are congruent to two recent network meta-analysis that did not report additional CV benefit with GLP-RA and SGLT-2I combination therapy[50,51].

Unlike 3P-MACE, a possible additive beneficial effect on heart failure and renal events with GLP-1RA and SGLT-2I combination therapy is very likely mechanistically, in particular because both drug classes have shown a consistent reduction in urinary protein excretion and rate of estimated glomerular filtration rate (eGFR) decline. Since both classes of drugs cause natriuresis (albeit by different mechanism), a synergistic effect on HHF reduction is also mechanistically possible. Indeed, in post hoc subgroup

analysis of DECLARE-TIMI (n = 750) stratified on baseline GLP-1RA use, a greater benefit ($P_{interaction}$ = 0.014) on HHF was noted in patients with baseline dapagliflozin plus GLP-1RA users (HR 0.20; 95%CI: 0.07-0.60) compared to dapagliflozin alone (HR 0.77; 95%CI: 0.64-0.92)[47]. Similarly, a greater benefit ($P_{interaction}$ = 0.03) on composite of CV death/HHF was also noted in DECLARE-TIMI in patients with baseline dapagliflozin plus GLP-1RA users (HR 0.37; 95%CI: 0.18-0.78) compared with dapagliflozin alone (HR 0.86; 95%CI: 0.75-0.98)[47]. However, the benefit of dapagliflozin on renal endpoints in DECLARE-TIMI was similar ($P_{interaction}$ = 0.49) amongst baseline dapagliflozin plus GLP-1RA users (HR 0.36; 95%CI: 0.11-1.15) compared to dapagliflozin alone or GLP-1RA non-users (HR 0.54; 95%CI: 0.43-0.67)[47]. A post-hoc analysis of the CANVAS program also noted a similar effect on the composite renal outcome in canagliflozin plus GLP-1RA users *vs* GLP-1RA non-users ($P_{interaction}$ = 0.43)[46].

Similar trends were also noted in GLP-1RA CVOT although it was inconsistent. In an exploratory analysis of AMPLITUDE-O with GLP-1RA efpeglenatide (n = 618), a nonsignificant trend ($P_{interection}$ = 0.35) of greater HHF reduction was observed in baseline efpeglenatide plus SGLT-2I users (HR 0.23; 95%CI: 0.05-0.97) *vs* SGLT-2I nonusers (HR 0.70; 95%CI: 0.42-1.17)[45]. Similarly, improvement in renal composite outcome in AMPLITUDE-O were insignificantly ($P_{interection}$ = 0.38) greater in baseline efpeglenatide plus SGLT-2I users (HR 0.52; 95%CI: 0.33-0.83) compared to SGLT-2 non-users (HR 0.70; 95%CI: 0.59-0.83)[45]. Notably, a propensity matched post-hoc analysis (n = 1144) of EXSCEL reported a nominally significant reduction in all-cause mortality (adjusted HR 0.38, 95%CI: 0.16-0.90), CV death (0.17; 95%CI: 0.04-0.77) and improvement in estimated eGFR slope (+1.94 mL/min; 95%CI: 0.94-2.94 mL/min/1.73 m^2/year) with exenatide QW plus SGLT-2I combination therapy compared to the placebo[43]. Importantly, exenatide QW plus SGLT-2I combination also demonstrated a nominally significant reduction in all-cause mortality (HR 0.41; 95%CI: 0.17-0.95), CV death (HR 0.21; 95%CI: 0.05-0.93) and improved eGFR slope (+2.38 mL/min; 95%CI:

1.40-3.35 mL/min/1.73 m^2/year) as compared to exenatide QW alone in a propensity-matched analysis of 1150 participants[43].

Our meta-analysis from the pooled data of 2 RCT that reported the outcomes of HHF and renal composite suggested a greater benefit ($P_{interaction}$ = 0.02) on HHF outcomes with GLP-1RA plus SGLT-2I dual therapy (HR 0.21; 95%CI: 0.08-0.50, P < 0.001) compared with GLP-1RA without SGLT-2I (HR 0.70; 95%CI: 0.42-1.17; P = 0.17) and SGLT-2I without GLP-1RA (HR 0.77; 95%CI: 0.64-0.92; P = 0.005) against placebo (Figure 4). No significant difference ($P_{interection}$ = 0.11) was noted on the composite of renal outcome between combination therapy (HR 0.50; 95%CI: 0.32-0.76; P = 0.001), GLP-1RA without SGLT-2I (HR 0.70; 95%CI: 0.59-0.83, P < 0.001) and SGLT-2I without GLP-1RA (HR 0.54; 95%CI: 0.43-0.67; P < 0.001) against placebo (Figure 5). Collectively, these findings hint to a possible synergistic CV and renal effect of GLP-1RA plus SGLT-2I combination therapy. Nevertheless, some caution must be exercised while interpreting these findings in the light of following limitations. Limitations include exploratory, post-hoc analysis, with a small number of participants in each subgroup compounded by a very small number of events (9 events of HHF in AMPLITUDE-O and 14 events for renal outcome in DELCARE-TIMI in combination arm); uncategorized type of heart failure; results with wide confidence interval (imprecise point estimates); allocation bias; applying the aggregate trial-level results for the meta-analysis in the absence of individual patient data; inclusion of adjusted HR from propensity-matched analysis of EXSCEL and no correction made for multiplicity in the subgroups analysis. Moreover, baseline GLP-1RA or SGLT-2I addition to SGLT-2I or GLP-1RA CVOT respectively, may have been determined by the patient preference, cost, availability of treatment and local guidelines, and thus preclude true randomization. Future randomized trial PRECIDENTD (PREvention of CardIovascular and DiabEtic kidNey disease in Type 2 Diabetes) which has been planned to evaluate cardiovascular and renal outcomes with either SGLT-2I or GLP-1RA or both, in nearly 9000 T2DM having high CV risk, shall further enlighten the effect of combination therapy[52].

CONCLUSION

GLP-1RA plus SGLT-2I combination therapy lower HbA1c, body weight and SBP significantly greater than GLP-1RA or SGLT-2I therapy alone. While HbA1c lowering with this combination therapy is less than additive compared to the sum of HbA1c lowering with individual agents, body weight lowering seems to be nearly additive and SBP lowering is found to be more than additive. Importantly, combination therapy with GLP-1RA and SGLT-2I do not potentiate hypoglycemia or GI side effects or GTI compared to either agent alone. While 3P-MACE risk reduction with GLP-1RA plus SGLT-2I combination therapy appears to be similar compared with either GLP-1RA or SGLT-2I alone, improvement in HHF and possibly renal outcomes could be likely additive. Future adequately powered large RCT are needed to confirm additional benefit of GLP-1RA plus SGLT-2I combination therapy on CV, renal and mortality outcomes.

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