SGLT2 Inhibitors in Combination Therapy: From Mechanisms to Clinical Considerations in Type 2 Diabetes Management

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The progressive nature of type 2 diabetes (T2D) requires practitioners to periodically evaluate patients and intensify glucose-lowering treatment once glycemic targets are not attained. With guidelines moving away from a one-size-fits-all approach toward setting patient-centered goals and allowing flexibility in choosing a second-/third-line drug from the growing number of U.S. Food and Drug Administration–approved glucose-lowering agents, keen personalized management in T2D has become a challenge for health care providers in daily practice. Among the newer generation of glucose-lowering drug classes, sodium–glucose cotransporter 2 inhibitors (SGLT2is), which enhance urinary glucose excretion to lower hyperglycemia, have made an imposing entrance to the T2D treatment armamentarium. Given their unique insulin-independent mode of action and their favorable efficacy–to–adverse event profile and given their marked benefits on cardiovascular-renal outcome in moderate-to-high risk T2D patients, which led to updates of guidelines and product monographs, the role of this drug class in multidrug regimes is promising. However, despite many speculations based on pharmacokinetic and pharmacodynamic properties, physiological reasoning, and potential synergism, the effects of these agents in terms of glycemic and pleiotropic efficacy when combined with other glucose-lowering drug classes are largely understudied. In this perspective, we review the currently emerging evidence, discuss prevailing hypotheses, and elaborate on necessary future studies to clarify the potential risks and benefits of using an SGLT2i in dual combination with metformin and triple combination with a glucagon-like peptide 1 receptor agonist, dipeptidyl peptidase 4 inhibitor, or other glucose-lowering agent that is recommended by the American Diabetes Association and European Association for the Study of Diabetes (i.e., a sulfonylurea, thiazolidinedione, or insulin) to treat patients with T2D.

Over the past decade, type 2 diabetes (T2D) management guidelines have moved forward from a one-size-fits-all recommendation toward a patient-centered approach (1–4). Two observations from landmark diabetes trials have encouraged this treatment personalization that balances the benefits of glycemic control with its potential risks in the context of cardiovascular risk reduction, which includes lifestyle adaptations, blood pressure (BP) control, and lipid management. First, in particular in patients with long-standing T2D, strict glycemic control may increase the risk of hypoglycemia, resulting in reduced quality of life and possibly increased cardiovascular risk, emphasizing the importance of drug classes with low hypoglycemia risk. Second, while glucose lowering per se reduces or prevents the onset and development of microvascular

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complications, the impact of glucose control on cardiovascular-renal complications is much more modest and emerges only after many years, emphasizing the importance of drug classes with cardiovascular-renal benefit. Although this concept of personalization is highly appealing, many health care providers are confronted with the predicament of how to pursue this approach in clinical practice, in particular when multiple drugs are indicated.

The preferred and most used first-line pharmacotherapy to manage hyperglycemia in T2D is indisputably metformin. Yet, six drug classes are currently recommended by the American Diabetes Association (ADA) and European Association for the Study of Diabetes for combination therapy on top of metformin: sodium–glucose cotransporter 2 inhibitors (SGLT2is), glucagon-like peptide 1 receptor agonists (GLP-1RAs), dipeptidyl peptidase 4 inhibitors (DPP-4is), sulfonylureas, thiazolidinediones, and basal insulin. All of these drug classes possess specific modes of action, safety profiles, and cardiovascular-renal effects, which raises the question of which combination strategy should be initiated after metformin monotherapy failure. Ideally, the quantitative or net effect of a combination is additive (i.e., sum of expected actions of two drugs alone) or superadditive (i.e., greater than the expected sum), which implies the use of glucose-lowering drug classes that mechanistically address different components of the prevailing pathophysiological defects and/or one drug favorably altering the actions of the other. Management strategies should exploit these combination effects to maximize treatment outcome.

Since SGLT2is and GLP-1RAs exhibit a low hypoglycemia risk and members of these drug classes demonstrated significant reductions in major adverse cardiovascular event (MACE) and mortality outcomes in recently reported cardiovascular outcomes trials (CVOTs) for safety, these drug classes have gained particular attention. In this perspective, we focus on SGLT2is in dual combination with metformin and triple combination with other glucose-lowering drug classes in T2D management.

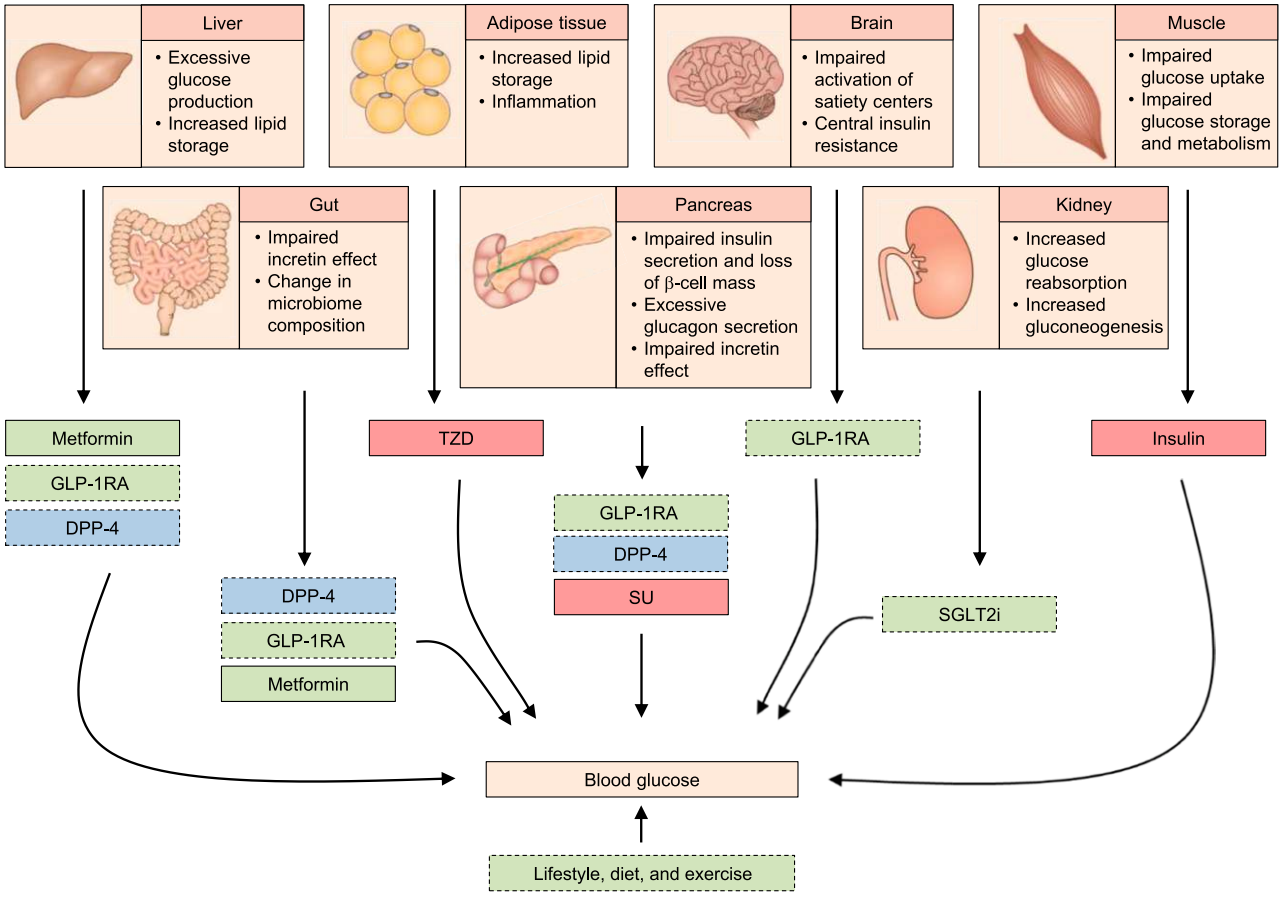

Figure 1—Pathophysiology and drug targets. T2D is a heterogeneous disorder with a complex pathophysiology, in which genetic and environmental factors contribute to dysfunction of various organ systems that control glucose homeostasis (5,6). Insulin resistance of liver, adipose, and skeletal muscle tissue results in respectively impaired insulin-induced reduction of HGP, lipolysis, and impaired insulin-stimulated glucose uptake (5). Hyperglycemia evolves when pancreatic β-cells are unable to secrete sufficient insulin to overcome insulin resistance (i.e., β-cell failure). In addition, α-cell dysfunction, characterized by fasting and postprandial hyperglucagonemia, stimulates HGP, which further augments hyperglycemia. Moreover, the efficacy of gut-derived incretin hormones GLP-1 and GIP to facilitate meal-related insulin release and glucagon suppression is impaired. The kidneys contribute to hyperglycemia by increasing tubular glucose reabsorption, presumably through upregulation of SGLT2 and increased renal gluconeogenesis (7). Last, in the development of T2D, impaired activation of satiety centers in the brain stimulates excessive food intake, and insulin resistance in the brain may alter central control of metabolic homeostasis (45). Pleiotropic drug effects are illustrated by the frame and color of the boxes. Green indicates body weight loss, blue indicates body weight neutrality, and red indicates body weight gain. A dotted frame indicates blood pressure reduction, and a solid frame indicates blood pressure neutrality. SU, sulfonylurea; TZD, thiazolidinedione.

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PATHOPHYSIOLOGY OF HYPERGLYCEMIA IN T2D

The pathophysiology of T2D involves various organs that control glucose homeostasis, as reviewed extensively elsewhere and summarized in Fig. 1 (5,6). We highlight the increased glucose reabsorption, impaired incretin effect, and impaired activation of satiety centers in the brain, as these pathophysiological defects have emerged as either established or potential therapeutic targets.

The renal reabsorption of glucose is controlled by two symporters that cotransport sodium and glucose. SGLT2 is situated at the first two convoluted segments of the proximal tubule and, under physiological conditions, reabsorbs ~90% of the filtered glucose, whereas the remaining 10% is reabsorbed by SGLT1 located in the adjacent straight segment. In T2D, the maximal reabsorption capacity is raised, which prevents glycosuria and energy loss but adds to the persistence of hyperglycemia.

In response to food intake, gut endocrine cells secrete glucose-dependent insulinotropic polypeptide (GIP) and GLP-1. Both incretins have glucose-dependent insulinotropic and glucagon-suppressing effects (7), which cause oral glucose uptake to result in a 50–70% greater insulin response than glucose infused intravenously despite equality in plasma glucose levels, a finding called the incretin effect. Due to rapid degradation by DPP-4 and the liver, systemic concentrations are low and insufficient to explain the full capacity of the incretin effect, suggesting that GLP-1 mainly acts via local paracrine or autocrine rather than systemic actions. Although plasma incretin levels are not affected, the incretin effect is impaired or even absent in T2D, which contributes to the disrupted glycemic control (8).

Food intake is the result of complex interactions between nutrients, hormones, neuropeptides, and several different brain areas. Important central nervous system structures that control energy balance and adjust food intake (i.e., homeostatic feeding) are the brainstem and hypothalamus, as they receive, convey, and integrate peripheral signals of changes in nutrients, hormones, and neuropeptides. Other areas such as the corticolimbic circuits are involved in the cognitive, emotional, and rewarding properties of food intake (i.e., nonhomeostatic or hedonic feeding). In T2D, impaired activation of satiety centers stimulates excessive food intake, and insulin resistance in the brain may alter central control of metabolic homeostasis (9).

SGLT2is

At present, four oral agents (i.e., canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin) are approved for the treatment of T2D by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency, either as monotherapy or in combination with other glucose-lowering drug classes.

Glycemic Control

According to a 2013 meta-analysis, the glucose-lowering efficacy of SGLT2is in T2D patients without severe renal impairment and baseline HbA_{1c} of 6.9–9.2% is on average 0.79% when used as monotherapy and 0.61% when used as additional therapy (10). Since hyperglycemia increases the filtered glucose load, the glycemic efficacy of this drug class in particular is amplified at high baseline levels. Conversely, since the filtered glucose load in patients with impaired renal function is reduced, the glucose-lowering efficacy parallels renal function and gradually declines to HbA_{1c} reductions of 0.3–0.4% in estimated glomerular filtration rate (eGFR) range 30–59 mL/min/1.73 m^2 and no effect $<$30 mL/min/1.73 m^2 (11). SGLT2is increase plasma glucagon levels and stimulate hepatic glucose production (HGP), which restricts their glucose-lowering capacity. Considering that their mode of action is independent of insulin resistance and β-cell failure, SGLT2is are effective in all individuals with T2D and preserved renal function.

Pleiotropic Effects

SGLT2is have several pleiotropic effects. First, SGLT2is induce weight loss of 2–3 kg, which starts with a fast decline of 1–2 kg in the first weeks, which may be the result of acute osmotic diuresis by blockade of the SGLT2 receptor (12). Thereafter, body weight declines more gradually over 20 weeks, which can be related to reductions in fat mass, and subsequently reaches a plateau phase (13). Interestingly, this 2- to 3-kg weight loss observed at the plateau phase is less than expected based on the calculated loss of calories excreted in the urine, which would equal a weight reduction of ~11 kg. Since SGLT2is do not alter resting or postprandial energy expenditure (14), the discrepancy between expected and observed weight loss implies that caloric intake is increased. Second, according to a 2017 meta-analysis, SGLT2is cause persistent reductions in systolic BP (SBP) and diastolic BP (DBP) of ~5 and 2 mmHg, respectively (15). Several mechanisms that may underlie this antihypertensive effect have been suggested: *1*) plasma volume contraction by osmotic diuresis; *2*) weight loss; *3*) improvements in vascular stiffness by reductions in body weight, hyperglycemia-associated oxidative stress, and/or endothelial glycocalyx protection from sodium overload; *4*) reduced sympathetic nervous system activity; and *5*) lower serum uric acid concentrations (16). Third, SGLT2is modestly alter lipid profiles by reductions in plasma triglycerides and increases in HDL cholesterol and LDL cholesterol (11). Fourth, although the effects on liver histology are unknown, SGLT2is attenuate several factors associated with nonalcoholic steatohepatitis (NASH) and nonalcoholic fatty liver disease (NAFLD), such as weight gain, elevated alanine aminotransferase, high liver fat index, and visceral fat (17). Fifth, SGLT2is induce natriuresis, which might improve whole-body sodium balance and volume status (18), and are associated with improved endothelial function and reduced vascular stiffening, decreasing the demand placed on cardiac tissue that causes left ventricular hypertrophy (19). Sixth, a study by Cherney et al. (20) suggested that in type 1 diabetes, SGLT2is reduce intraglomerular pressure by enhancing urinary sodium delivery to the macula densa, thereby activating tubuloglomerular feedback (TGF) and increasing afferent renal arteriolar resistance. While such mechanistic data are not available in T2D, eGFR trajectories in phase 3 trials indicate acute reductions in glomerular hyperfiltration by means of an initial drop and subsequent stabilization of renal function over time, halting the natural decline in eGFR. Last, presumably through reductions in intraglomerular pressure, SGLT2is attenuate albuminuria by 30–40% (18). Interestingly, the effects of SGLT2i on body weight, BP, and albuminuria appear to be independent of eGFR (21).

Outcomes in CVOTs

Cardiovascular safety and benefit of SGLT2is empagliflozin and canagliflozin

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Table 1—Reported cardiovascular and renal outcome trials in T2D (CVOTs)

Name of clinical trial	Intervention	Population	Follow-up (years)	Primary outcome	Key secondary outcome	CV death	MI¶	Stroke¶	HHF	Unstable angina hospitalization	All-cause mortality	Worsening of nephropathy†
					SGLT2is							
EMPA-REG OUTCOME ($n = 7,020$)	Empagliflozin vs. placebo	T2D patients with established CVD	3.1	3-point MACE 0.86 (0.74–0.99)	4-point MACE 0.89 (0.78–1.01)	0.62 (0.49–0.77)	0.87 (0.70–1.09)	1.18 (0.89–1.56)	0.65 (0.50–0.85)	0.99 (0.74–1.34)	0.68 (0.57–0.82)	0.61 (0.53–0.70)
CANVAS Program ($n = 10,142$)	Canagliflozin vs. placebo	T2D patients with established CVD or ≥2 CV risk factors	2.4	3-point MACE 0.86 (0.75–0.97)#	All-cause and CV mortality	0.96 (0.77–1.18)** 0.87 (0.72–1.06)#	0.89 (0.73–1.09)#	0.87 (0.69–1.09)#	0.67 (0.52–0.87)#	NA	0.87 (0.74–1.01)** 0.90 (0.76–1.07)#	0.60 (0.47–0.77)#
					GLP-1RAs							
ELIXA ($n = 6,068$)	Lixisenatide vs. placebo	T2D patients with a recent acute coronary event (<180 days before screening)	2.1	4-point MACE 1.02 (0.89–1.17)	Expanded MACE 1.00 (0.90–1.11)	0.98 (0.78–1.22)	1.03 (0.87–1.22)	1.12 (0.79–1.58)	0.96 (0.75–1.23)	1.11 (0.47–2.62)	0.94 (0.78–1.13)	NA
LEADER ($n = 9,340$)	Liraglutide vs. placebo	T2D patients with established CVD, kidney disease, or HF or ≥1 CV risk factors	3.8	3-point MACE 0.87 (0.78–0.97)	Expanded MACE 0.88 (0.81–0.96)	0.78 (0.66–0.93)	0.86 (0.73–1.00)	0.86 (0.71–1.06)	0.87 (0.73–1.05)	0.98 (0.76–1.26)	0.85 (0.74–0.97)	0.78 (0.67–0.92)
SUSTAIN-6* ($n = 3,297$)	Semaglutide vs. placebo	T2D patients with established CVD, CKD, or HF or ≥1 CV risk factors	2.1	3-point MACE 0.74 (0.58–0.95)	Expanded MACE 0.74 (0.62–0.89)	0.98 (0.65–1.48)	0.74 (0.51–1.08)	0.61 (0.38–0.99)	1.11 (0.77–1.61)	0.82 (0.47–1.44)	1.05 (0.74–1.50)	0.64 (0.46–0.88)
EXSCEL ($n = 14,752$)	Exenatide QW vs. placebo	T2D patients with or without established CVD	3.2	3-point MACE 0.91 (0.83–1.00)	Individual components of MACE	0.88 (0.76–1.02)	0.97 (0.85–1.10)	0.85 (0.70–1.03)	0.94 (0.78–1.13)	1.05 (0.94–1.18)	0.86 (0.77–0.97)	NA
					DPP-4is							
SAVOR-TIMI 53 ($n = 16,492$)	Saxagliptin vs. placebo	T2D patients with a history of or multiple risk factors for CVD	2.1	3-point MACE 1.00 (0.89–1.12)	Expanded MACE 1.02 (0.94–1.11)	1.03 (0.87–1.22)	0.95 (0.80–1.12)	1.11 (0.88–1.39)	1.27 (1.07–1.51)	1.19 (0.89–1.60)	1.11 (0.96–1.27)	1.08 (0.88–1.32)
EXAMINE ($n = 5,380$)	Alogliptin vs. placebo	T2D patients with recent ACS (15–90 days before randomization)	1.5	3-point MACE 0.96 (95% UL ≤1.16)	4-point MACE 0.95 (95% UL ≤1.14)	0.85 (0.66–1.10)	1.08 (0.88–1.33)	0.91 (0.55–1.50)	1.19 (0.90–1.58)	0.90 (0.60–1.37)	0.88 (0.71–1.09)	NA
TECOS ($n = 14,671$)	Sitagliptin vs. placebo	T2D patients with established CVD	3.0	4-point MACE 0.98 (0.89–1.08)	3-point MACE 0.99 (0.89–1.10)	1.03 (0.89–1.19)	0.95 (0.81–1.11)	0.97 (0.79–1.19)	1.00 (0.83–1.20)	0.90 (0.70–1.16)	1.01 (0.90–1.14)	NA
					Thiazolidinediones							
PROactive ($n = 5,238$)	Pioglitazone vs. placebo	T2D patients with established CVD	2.8	Expanded MACE 0.90 (0.80–1.02)	3-point MACE 0.84 (0.72–0.98)	0.94 (0.74–1.20)	0.83 (0.65–1.06)	0.81 (0.61–1.07)	1.41 (1.10–1.80	0.78 (0.55–1.11)	0.96 (0.78–1.18)	NA
TOSCA.IT ($n = 3,028$)	Pioglitazone vs. sulfonylurea	T2D patients without recent CV events (>6 months) or CHF	4.8	Expanded MACE 0.96 (0.74–1.26)	Expanded MACE 0.88 (0.65–1.21)	2.24 (0.69–7.28)	0.87 (0.48–1.55)	0.79 (0.41–1.53)	1.57 (0.76–3.24)	NA	1.10 (0.75–1.61)	NA

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Table 1—Continued

Name of clinical trial	Intervention	Population	Follow-up (years)	Primary outcome	Key secondary outcome	CV death	MI¶¶	Stroke¶	HHF	Unstable angina hospitalization	All-cause mortality	Worsening of nephropathy†
						Insulin						
DEVOTE (n = 7,637)	Insulin degludec vs. insulin glargine	T2D patients with established CVD, CKD, or HF or ≥1 CV risk factors	2.0	3-point MACE 0.91 (0.78–1.06)	Expanded MACE 0.92 (0.80–1.05)	0.96 (0.76–1.21)	0.85 (0.68–1.06)	0.90 (0.65–1.23)	NA	0.95 (0.68–1.31)	0.91 (0.78–1.06)	NA

Adapted from Cefalu et al. (99). Four members of two different drug classes demonstrated cardiovascular (CV) benefit in CVOTs. In EMPA-REG OUTCOME, empagliflozin demonstrated a 14% reduction in primary end point 3-point MACE, mainly driven by a 38% reduction in cardiovascular death. Moreover, a 35% risk reduction in HHF emerged after several months, suggesting acute effects on renal and systemic hemodynamic function or direct effects on the cardiovascular system. Also, new-onset or worsening nephropathy was reduced by 39%. The secondary outcomes of CANVAS and CANVAS-R have been revised to prioritize cardiovascular death, all-cause mortality, and HF and to improve the outcomes MI and stroke. Instead of reporting the separated dose effects, the results of both studies and doses were combined and reported as the CANVAS Program. Canagliflozin reduced the primary end point 3-point MACE by 14% and HHF risk by 33%. The composite renal outcome was reduced by 40%. In LEADER, liraglutide reduced primary end point 3-point MACE by 13%, with reduction of equal size in all three components. In SUSTAIN-6, semaglutide reduced the primary end point 3-point MACE by 26%, with the greatest reductions in the stroke category. In conclusion, the benefit of SGLTis is likely related to reductions in HF, which is dissimilar to the more antiatherogenic reductions seen with GLP-1RAs. All outcomes are HR (95% CI), except for EXAMINE secondary outcome, which gives a 95% upper limit. 95% UL, upper limit of 95% CI; ACS, acute coronary syndrome; CHF, congestive heart failure; DEVOTE, A Trial Comparing Cardiovascular Safety of Insulin Degludec Versus Insulin Glargine in Patients With Type 2 Diabetes at High Risk of Cardiovascular Events; NA, not assessed/not reported. *Powered to rule out an HR upper margin ≥1.8; superiority hypothesis not prespecified. #Nontruncated integrated data (refers to pooled data from CANVAS, including before 20 November 2012 plus CANVAS-R). **Truncated integrated data set (refers to pooled data from CANVAS after 20 November 2012 plus CANVAS-R; prespecified in treating hierarchy as the principal data set for analysis for superiority of all-cause mortality and CV death in the CANVAS Program). ¶Reported for fatal and nonfatal events in all trials except EXAMINE, ELIXA, SUSTAIN-6, PROactive, and TOSCA.IT, which reported for nonfatal events only. †Worsening nephropathy was defined as doubling of creatinine level, initiation of dialysis, renal transplantation, or creatinine >6.0 mg/dL (530 μmol/L) in SAVOR-TIMI 53; as the new onset of macroalbuminuria (urine ACR >300 mg/g) or a doubling of the serum creatinine level and an eGFR of ≤45 mL/min/1.73 m^2, the need for continuous renal-replacement therapy, or death from renal disease in LEADER, SUSTAIN-6, and EMPA-REG OUTCOME; and as 40% reduction in eGFR, renal-replacement therapy, or death from renal causes in CANVAS. Worsening nephropathy was a prespecified exploratory adjudicated outcome in SAVOR-TIMI 53, LEADER, SUSTAIN-6, and CANVAS but not in EMPA-REG OUTCOME.

were demonstrated in the BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) trial and the Canagliflozin Cardiovascular Assessment Study (CANVAS) Program (i.e., two studies, CANVAS and CANVAS-Renal [CANVAS-R], jointly reported) (22,23). Importantly, nearly all included patients were adequately treated with statins and BP-lowering agents, most notably renin-angiotensin-aldosterone system (RAAS) inhibitors (~80%). In EMPA-REG OUTCOME, the incidence of cardiovascular death was reduced, whereas in both EMPA-REG OUTCOME and the CANVAS Program, a reduction in hospitalization for heart failure (HHF) and incident or worsening of nephropathy was observed (Table 1) (22–24). Since the subtle improvements in cardiovascular risk factors are unlikely to contribute to the large and early benefit, there has been much speculation about the underlying mechanisms. In a post hoc analysis of EMPA-REG OUTCOME, plasma volume contraction, estimated by hematocrit concentration, has been put forward (25). Other explanations include alterations of cardiac substrate metabolism and direct effects on the cardiomyocyte (26,27).

Adverse Effects

SGLT2is are well tolerated and have a low hypoglycemia risk in patients not using sulfonylureas or insulin. The main adverse effect is a four- to fivefold increased risk of genital mycotic infection (11). Rare episodes of diabetic ketoacidosis (DKA), particularly in patients with long-standing T2D, have been reported, which prompted the FDA to issue a warning about this potential complication. SGLT2is have the propensity to cause DKA due to a reduced availability of carbohydrates caused by SGLT2i-induced glycosuria, a shift in substrate utilization from glucose to fat oxidation, and the promotion of hyperglucagonemia, stimulating ketogenesis (28). Finally, in the CANVAS Program, canagliflozin was associated with a higher risk of bone fractures and lower-limb amputations (22), which have not been reported with other SGLT2is.

SGLT2 INHIBITION IN COMBINATION THERAPY

Since the glucose-lowering mechanism of SGLT2is does not interact with drugs that improve β-cell function or insulin

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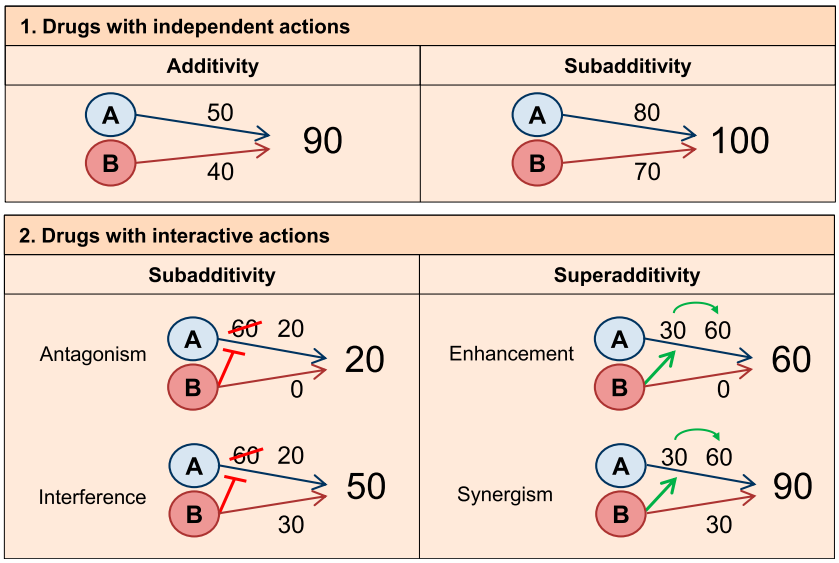

Figure 2—Mechanistic principles for net effects of drugs in combination therapy. The quantitative or net effect of two or more drugs depends on whether the individual drug effects are independent or interactive. When drug effects are independent, the quantitative effect is either additive or subadditive. When drug effects interact, the quantitative effect can be subadditive by antagonism or interference, or superadditive by enhancement or synergism. The effect of the individual drugs is indicated next to the arrows, and the net effect of the combination is indicated by the number at the right of each pair. The maximum effect is 100. A represents drug A, and B represents drug B. The top panel illustrates mechanisms for drugs with independent actions, with additivity occurring if tissue responsiveness permits both drug A and drug B to exert their full effect (left) but with subadditivity occurring if tissue responsiveness is the limiting factor for the total magnitude of response possible (right). The bottom panel illustrates mechanisms for drugs with interactive actions. The left side of the bottom panel illustrates two possibilities for subadditivity: simple antagonism (top), in which drug B reduces the effect of drug A threefold (indicated by the red inhibition line) but has no effect on its own, and interference (bottom), in which drug B reduces the effect of drug A threefold (indicated by the red inhibition line), preventing it from exerting its full response, but drug B nonetheless has a beneficial effect on its own. The right side of the bottom panel illustrates two possibilities for superadditivity: enhancement, in which drug B increases the effect of drug A twofold (green arrow) but has no effect on its own (top), and synergism, in which drug B exerts a useful effect on its own in addition to its twofold enhancement of the effects on drug A (bottom).

sensitivity, combination therapy might result in additive efficacy (Fig. 2). Moreover, the efficacy of SGLT2is may be hampered by increased caloric intake and increased HGP, disadvantages that can be mitigated by concomitant treatment with another agent. Also, other agents might have pleiotropic effects that modulate cardiovascular-renal risk differently. Therefore, combination therapy with SGLT2is has potential benefits on both the preservation of glycemic control and cardiovascular-renal complications (Table 2) (29–31).

SGLT2is and GLP-1RAs

GLP-1RAs

Since exogenous GLP-1, in contrast to GIP, still exerts an insulinotropic effect in T2D patients, GLP-1RAs were developed to mimic the effects of native GLP-1, reducing blood glucose by stimulating insulin and suppressing glucagon secretion in a glucose-dependent manner (Fig. 1). Seven GLP-1RAs, namely short-acting exenatide, liraglutide, and lixisenatide and long-acting exenatide, semaglutide, dulaglutide, and albiglutide have been approved by the FDA and the European Medicines Agency for the treatment of T2D. GLP-1RAs reduce HbA_{1c} levels by ~1%, which varies between agents based on their mode of action (32). Short-acting GLP-1RAs are injected preprandially, causing suppressed postprandial glucagon levels and decreased gastric emptying rates, which prolongs the rate of glucose entry into the duodenum and blunts the absorption of meal-derived glucose, collectively lowering postprandial hyperglycemia. Because of the uninterrupted insulin stimulation, long-acting GLP-1RAs have a more pronounced effect on HbA_{1c} and fasting plasma glucose (FPG). The lack of efficacy of long-acting GLP-1RAs in reducing meal-related hyperglycemia might be explained by rapid tachyphylaxis of GLP-1RA–induced gastric emptying deceleration (33).

GLP-1RAs induce several pleiotropic effects. The associated weight loss of ~3 kg is the result of delayed gastric emptying, peripheral vagal nerve stimulation, and central nervous system activation, which collectively promote satiety, decrease hunger sensation, and ultimately lead to a reduction in food intake, involving brain areas associated with both homeostatic and hedonic feeding (9,34). Moreover, GLP-1RAs cause SBP and DBP reductions of ~3 and 1 mmHg, respectively (35), and improvements in lipid profiles by reductions in LDL cholesterol, total cholesterol, and triglycerides (36). In addition, GLP-1RAs activate several anti-inflammatory pathways, including reductions in oxidative stress via reactive oxygen species, nuclear factor-κB binding/activation, expression of inflammatory cytokines and C-reactive protein, and increases in adiponectin (37). Also, GLP-1RAs seem to have beneficial effects on NASH and NAFLD by reductions in body weight, de novo hepatic lipogenesis, oxidative stress, inflammatory cytokines, and endoplasmatic reticulum stress and improvements in hepatic insulin sensitivity, triglyceride handling, and neural regulation of hepatic metabolism (38,39). In the Liraglutide Efficacy and Action in Non-Alcoholic Steatohepatitis (LEAN) trial, liraglutide reduced liver enzymes and oxidative stress and improved liver histology in patients NAFLD and T2D (40).

The CVOTs investigating lixisenatide (Evaluation of Lixisenatide in Acute Coronary Syndrome [ELIXA]), liraglutide (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results [LEADER]), semaglutide (Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes [SUSTAIN-6]), and exenatide (Exenatide Study of Cardiovascular Event Lowering [EXSCEL]) all reported cardiovascular safety (Table 1) (41–44). LEADER and SUSTAIN-6 demonstrated cardiovascular benefit, whereas the improved cardiovascular outcome in EXSCEL just missed statistical significance (hazard ratio [HR] 0.91; 95%

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Table 2—Expected and demonstrated net effects in combination therapy with SGLT2is in T2D

			MET + SGLT2i				
	MET	SGLT2i	+GLP-1RA	+DPP-4i	+TZD	+SU	+Insulin
Insulin secretion	=	↓	↑	↑	↓	↑	↓
Glucagon secretion	↓	↑	=*	=	↑?	↓	↓
HGP	↓	↑	↑*	↑	↑	↓?	↓
Insulin sensitivity	↑	↑	↑↑	↑/↑↑	↑↑	↑	↑
Body weight	=/↓	↓	↓↓*	↓*	↑*	↓*	=*
Food intake	=/↓	↑	↓	↑?	↑?	↑?	↑?
SBP	=	↓	↓↓*	↓*	↓↓*	↓/=*	↓*
HDL/LDL ratio	=	=	↓*	=*	=/↑*	= *	=/↑*
Diuresis (osmotic and natriuretic)	=?	↑	↑↑	↑↑	↑/=	↑?	↑/=
Cardiovascular events	=	↓	↓↓	↓	↓	↓?	↓?
HF events	=	↓	↓	↓/=	↓/=	↓?	↓?
New or worsening of nephropathy	=?	↓	↓↓	↓	↓	↓?	↓?

MET, metformin; SU, sulfonylurea derivative; TZD, thiazolidinedione; =, no effect; ↑, an increased effect; ↓, a decreased effect; ↑↑ or ↓↓, a stronger net effect than SGLT2i on top of metformin alone; ?, unstudied single-drug effects. All combined effects are expected effects based on single-drug effects, except for *, which are demonstrated net effects in combination studies.

CI 0.83–1.00; $P = 0.06$ for superiority). ELIXA could not demonstrate cardiovascular benefit. The cardiovascular benefit of liraglutide was driven by reductions in both all-cause and cardiovascular mortality, whereas semaglutide mainly affected nonfatal stroke. These benefits of GLP-1RA treatment are likely mediated by antiatherosclerotic mechanisms, which could be the result of the activated anti-inflammatory pathways. The renal outcome improved with both liraglutide and semaglutide, mainly driven by reductions in macroalbuminuria. In all CVOTs, GLP-1RAs reduced progression of albuminuria over time ranging from 22 to 46%, yet it remains uncertain whether these effects are truly independent of glucose control as HbA_{1c} differences between groups were considerable (45). However, in response to a comment, the authors of LEADER showed that adjustment for HbA_{1c}, body weight, and SBP did not alter the composite renal outcome (46). In the same study, liraglutide decelerated the eGFR decline by 2% (−7.44 vs. −7.82 mL/min/m^2 in 36 months) from baseline compared with placebo, most evidently in patients with baseline eGFR 30–59 mL/min/1.73 m^2. In prepublished results of the Study Comparing Dulaglutide With Insulin Glargine on Glycemic Control in Participants With Type 2 Diabetes and Moderate or Severe Chronic Kidney Disease (AWARD-7) (47), a randomized open-label study comparing once-weekly (QW) dulaglutide (0.75 mg or 1.5 mg) with insulin glargine plus prandial insulin lispro in 576 T2D subjects with stage 3–4 chronic kidney disease (CKD), dulaglutide showed greater reductions in albuminuria (albumin-to-creatinine ratio [ACR] of −27.7 and −26.7, respectively, vs. −16.4 in the placebo group) and again decelerated the eGFR decline slightly compared with insulin glargine. The mechanisms responsible for these renal benefits are not completely understood. Current suggestions involve the effect of reductions in body weight and BP, anti-inflammatory effects, and alteration of renal hemodynamics either by inhibition of vasodilation of the afferent renal arteriole by activation of TGF via downregulation of the sodium-hydrogen exchanger isoform 3 receptor located prior to the macula densa or by inhibition of factors that cause constriction of the efferent arteriole, such as reactive oxygen species, RAAS components, and endothelin-1. Moreover, it has been suggested that GLP-1RAs act on neural regulation centers of sodium and water homeostasis. Paradoxically, GLP-1RAs also cause direct GLP-1R–mediated and indirect nitric oxide–dependent vasodilation of the afferent arteriole, causing an increase in glomerular pressure. The effect on renal function is thus a complex balance between direct afferent vasodilatory actions and inhibition of pathways associated with glomerular hyperfiltration. Since T2D patients have impaired nitric oxide–dependent vasodilatory capacity, the presence of glomerular hyperfiltration could well be essential for incretin therapies to exert their renoprotective effect (45,48).

Common adverse effects of GLP-1RAs are nausea and occasional vomiting, which are usually mild to moderate and transient (49). In SUSTAIN-6, increased rates of retinopathy were observed, more likely caused by rapid glucose reductions than drug-specific effects. The putative relationship between GLP-1RAs and pancreatitis has been extensively debated (50). In a comprehensive 2017 meta-analysis, there was no association between acute pancreatitis and GLP-1RAs (51). This was confirmed by the 2017 meta-analysis of all CVOTs of GLP-1RAs by Bethel et al. (52).

Glycemic Control

Two clinical trials have examined the glucose-lowering efficacy of SGLT2is combined with GLP-1RAs in T2D patients. In DURATION-8 (53), 695 metformin-treated participants were allocated to dapagliflozin 10 mg, exenatide 2 mg, or dapagliflozin plus exenatide 2/10 mg. Combination therapy reduced HbA_{1c} by 2.0% from baseline 9.3%, which was significantly more than exenatide or dapagliflozin alone (Fig. 3) (53). In Study of Dulaglutide (LY2189265) in Participants With Type 2 Diabetes Mellitus (AWARD-10) investigating 424 patients randomly assigned to 24-week dulaglutide 1.5 and 0.75 mg or placebo added to ongoing SGLT2i treatment and metformin, combination therapy led to significant greater HbA_{1c} reductions of 1.34 and 1.21%, respectively, vs. 0.54% with placebo from a mean baseline of 8.0% (54). In a post hoc subgroup analysis of CANVAS involving 95 patients with baseline HbA_{1c} of 7.9–8.3%, addition of canagliflozin to GLP-1RA treatment reduced HbA_{1c} by 1.00% (95% CI 0.65–1.35) for 100 mg and 1.06% (95% CI 0.69–1.43) for 300 mg compared with placebo (55). The achieved net glycemic efficacy of the combination is subadditive, which could be explained by the interactive effects on glucagon and HGP, but could also be the result of a more comprehensive interactive effect. As elegantly explained by Polidori et al. (56), the glucose-lowering efficacy of all glucose-lowering agents depends on the level of hyperglycemia, which means that subadditivity can be expected

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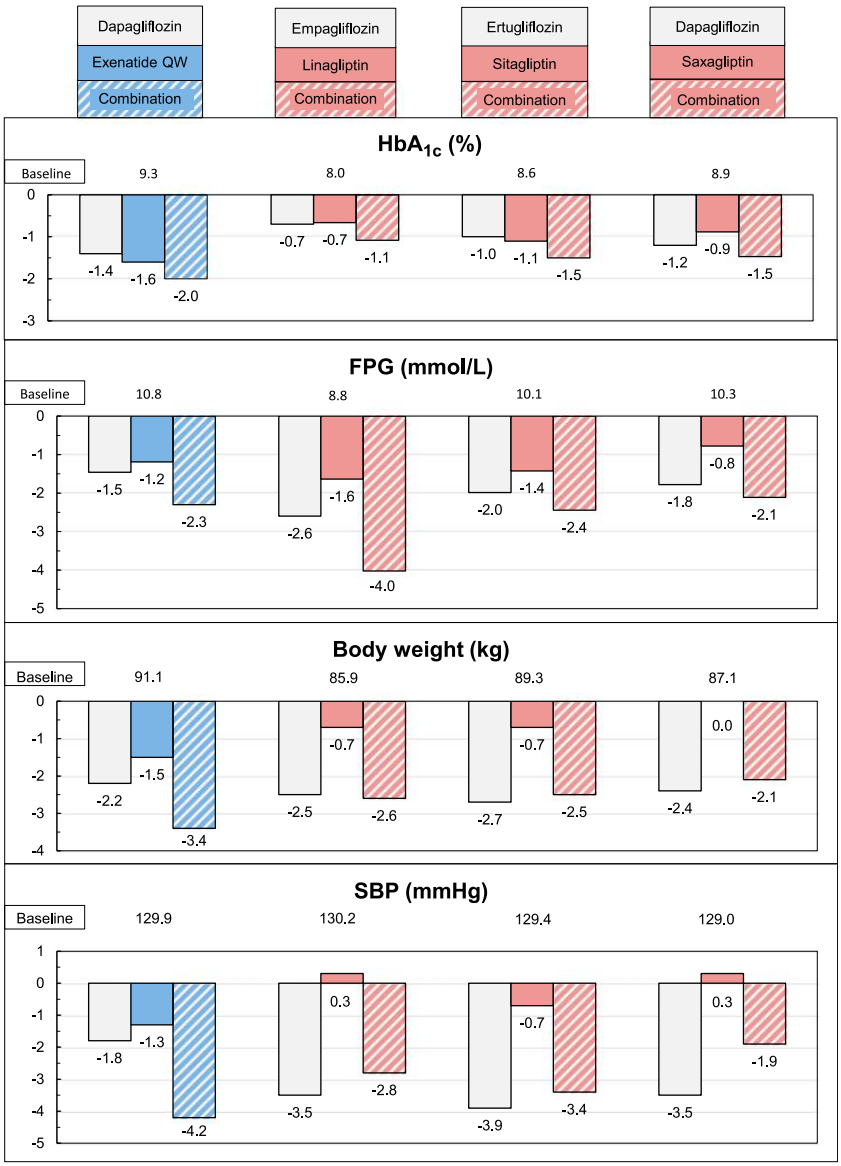

Figure 3—Additivity in glycemic and pleiotropic effects. Reductions from baseline in combination therapy vs. either agent alone. At the moment, four studies have investigated the net effects of glucose-lowering combination therapy with SGLT2is on top of metformin, one with GLP-1RAs and three with DPP-4is. Frías et al. (53) investigated the effect of 28-week exenatide 2 mg QW in combination with dapagliflozin 10 mg once daily (QD) on top of metformin in 695 T2D patients. DeFronzo et al. (96) investigated the effects of 52- and 24-week empagliflozin and linagliptin on top of metformin in 686 T2D patients. Given data derive from 24-week empagliflozin 10 mg QD and linagliptin 5 mg QD, except for SBP data, which derive from 52-week therapy in the same dose. Pratley et al. (97) assessed the effects of 52- and 26-week ertugliflozin and sitagliptin in 1,233 T2D patients on top of metformin. Data derive from 26-week ertugliflozin 5 mg QD and sitagliptin 100 mg QD. Rosenstock et al. (98) assessed the effects of 24-week dapagliflozin 10 mg QD and saxagliptin 5 mg QD in 534 T2D patients on top of metformin.

for all possible combinations that do not evoke synergism. Unfortunately, this combination does not result in the glycemic synergy so hoped for but is subadditive as a result of interference.

Pleiotropic Effects

In DURATION-8, a nearly additive net body weight reduction of 3.41 kg (mean baseline weight 91 kg) in patients receiving combination treatment was observed. Moreover, a net SBP reduction of 4.2 mmHg from baseline 131 mmHg suggested synergy and a possible interaction between drugs (Fig. 3). No significant differences in lipid levels between the treatment groups were observed. AWARD-10 demonstrated that addition of dulaglutide to ongoing SGLT2i treatment further reduced body weight by 3.1 and 2.6 kg and SBP by 4.5 and 3.2 mmHg for the 1.5 and 0.75 mg doses, respectively. In the context of DURATION-8, it is remarkable that addition of dulaglutide in AWARD-10, in particular in the low dose, struggles to significantly stand out against placebo. This could be explained by the substantial HbA_{1c}, FPG, body weight, and SBP reductions seen in the placebo group, which reveal an ongoing SGLT2i effect. For instance, background SGLT2i treatment was initiated mostly just 3–6 months prior to randomization, which is before the body weight plateau phase. Although it seems that dulaglutide has added benefits even on top of ongoing SGLT2i effects, it is not entirely possible to separate and quantify the GLP-1RA- and SGLT2i-induced actions given the design of the trial. In the post hoc analysis of CANVAS, placebo-subtracted reductions when canagliflozin 100 or 300 mg was added to GLP-1RA therapy were 2.7 and 3.3 kg in body weight and 7.0 and 6.9 mmHg in SBP, respectively. The effect on lipids was again neutral. The combined effect on NASH and NAFLD has not been studied; however, since both drug classes improve related etiologic factors and reduce visceral fat and GLP-1RAs demonstrated efficacy in liver histology, the combination has additive potency in the treatment of these diseases (40,57).

Both drug classes exert distinct renal benefits, which combined could lead to additive or synergistic effects on the preservation of renal function. For instance, as glucagon induces glomerular hyperfiltration via TGF-mediated dilatation of the afferent arteriole, a reduction of glucagon by incretin therapy could potentiate the effects of SGLT2is on TGF. Combination therapy thus has promising renal benefits, which call for further study.

Outcomes in CVOTs

Cardiovascular safety or benefit has not been studied for this combination. As both agents reduce cardiovascular risk through different mechanisms (atherogenic and volume related, respectively), they might produce an additive cardiovascular benefit, a hypothesis that requires further study. Conversely, there is also the possibility that beneficial effects can be limited by interference. For instance, the substrate shift hypothesis

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regarding the benefits of SGLT2i on heart failure (HF) postulates beneficial effects of increased ketogenesis on the heart. GLP-1RAs could mitigate this effect by lowering glucagon levels.

Adverse Events

The combination of GLP-1RAs and SGLT2is is associated with a low hypoglycemia risk due to their glucose-dependent efficacy. The risk of DKA might be offset by the glucagon-suppressing properties of GLP-1RAs. In both DURATION-8 and AWARD-10, combination therapy was well tolerated and side effects were not different than those that could be expected from either agent alone.

Pathophysiological Rationale

The stimulation of insulin and suppression of glucagon by GLP-1RAs complements the insulin-independent pathophysiological defect targeted by SGLT2is and compensates for the SGLT2i-induced increase of HGP. Despite this elegant rationale, the net glycemic efficacy is subadditive. DeFronzo et al. (58) investigated this result in more detail, showing that liraglutide indeed inhibited canagliflozin-induced increments in glucagon levels but failed to antagonize the rise in HGP, an observation that needs additional study. The combination results in nearly additive body weight loss, suggesting that deceleration of gastric emptying and reduction of food intake by GLP-1RAs do not limit the weight-reducing efficacy by glycosuria with SGLT2is. It remains unclear whether GLP-1RAs suppress SGLT2i-induced hyperphagia. Last, the net effect on BP was superadditive, suggesting synergy, which could be a favorable pleiotropic effect.

SGLT2is AND DPP-4is

DPP-4is

Although DPP-4is were developed to prevent the rapid degradation of native GLP-1, inhibition also leads to augmented concentrations of several other DPP-4 substrates. As such, the glucose-lowering capacities of this drug class are probably not limited to the induced prolonged postprandial rise in endogenous GLP-1 (Fig. 1) but also involve increased concentrations of other glucoregulatory substrates (59). DPP-4is are less potent than GLP-1RAs and lower postprandial glucose by ~3.0 mmol/L, FPG by 1.0–1.5 mmol/L, and HbA_{1c} by 0.77% from a mean baseline of 8.05% (60,61). This is mainly achieved through increased insulin and suppressed glucagon secretion, which results in reduced HGP. Currently, five DPP-4is are available in Europe and the U.S., namely sitagliptin, vildagliptin, saxagliptin, alogliptin, and linagliptin.

The drug class alters cardiovascular-renal risk factors to a smaller extent than GLP-1RAs. DPP-4is are considered weight neutral, lower SBP and DBP by ~3 and 1 mmHg, respectively (62), and modestly improve total cholesterol and triglyceride concentrations (45). In comparison with GLP-1RAs, DPP-4is possess distinct glucose-independent anti-inflammatory and antifibrotic properties, which could be mediated indirectly via DPP-4 substrates or directly, as DPP-4is affect T-cell development, T-cell activation, and immune regulation (45).

The CVOTs of alogliptin (Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care [EXAMINE]), saxagliptin (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53 [SAVOR-TIMI 53]), and sitagliptin (Trial Evaluating Cardiovascular Outcomes With Sitagliptin [TECOS]) all demonstrated cardiovascular safety (Table 1) but indicated no trend toward benefit (63–65). Unexpectedly, in SAVOR-TIMI 53 and numerically but nonsignificantly in EXAMINE, DPP-4i use was associated with an increase in HHF without an increase in mortality, which prompted the FDA to issue a safety warning for the whole drug class for this potential complication. Plausible mechanistic explanations are lacking, and given the absence of any harmful signals in TECOS, it seems unlikely that these results can be extrapolated to DPP-4is per se.

The effect of DPP-4is on renal disease in T2D is inconclusive. Combined data from 13 placebo-controlled clinical trials showed reduced renal disease events by ~16% (66). In SAVOR-TIMI 53, saxagliptin reduced the ACR by 34 mg/g but did not affect hard renal outcome. In the Efficacy, Safety & Modification of Albuminuria in Type 2 Diabetes Subjects With Renal Disease With LINAgliptin (MARLINA-T2D) trial investigating 360 patients with microalbuminuria despite RAAS blockade, 24-week linagliptin did not significantly change eGFR or lower albuminuria (67). EXAMINE only reported change in eGFR from baseline, which was not altered by alogliptin, and TECOS reported slight reductions in eGFR (1.34 mL/min/1.73 m^2) and ACR (0.18 mg/g), of which the clinical implication is unknown.

The adverse event profile of DPP-4is is mild, with placebo-like event rates. As mentioned earlier, the increased HHF has resulted in an FDA safety warning on the labels of agents of this drug class. Although the incidence is low, usage is associated with an increased risk of pancreatitis (50,68).

Glycemic Control

In phase 3 trials investigating combination therapy versus either SGLT2is or DPP-4is alone, HbA_{1c} was reduced by ~1.2–1.5%, which was significantly more than either agent alone (Fig. 3). A meta-analysis by Cho et al. (69) summarized the effects of 10 SGLT2i/DPP-4i combination studies, mostly on top of metformin. Combination therapy versus DPP-4is alone resulted in significantly greater reductions (0.62%; 95% CI 0.51–0.73; $P < 0.001$), with slightly larger reductions when an SGLT2i was added to a DPP-4i (0.70%; 95% CI 0.54–0.85; $P < 0.001$) compared with initial combination therapy (0.51%; 95% CI 0.37–0.65). Combination therapy compared with SGLT2is alone resulted in significantly higher reductions in HbA_{1c} (0.32%; 95% CI 0.22–0.48; $P < 0.001$). Initial combination proved to be equally as effective as add-on strategies. After stratification by baseline HbA_{1c} levels, the additional reduction by SGLT2is as estimated from combination therapy versus DPP-4is alone showed reductions proportional to baseline HbA_{1c}. In contrast, combination therapy versus SGLT2is alone resulted in modest reductions regardless of baseline HbA_{1c}. Interestingly, the authors thereafter suggest that additional glucose control is significant when SGLT2is are combined with or added to DPP-4is but not vice versa, as was also suggested previously (30). The stimulation of HGP by SGLT2i-induced glycosuria might be so powerful that it limits the glycemic efficacy of DPP-4is in this combination. Similar to combination with GLP-1RAs, the net glycemic efficacy is not synergistic but subadditive as a result of interference.

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Pleiotropic Effects

Unlike combination therapy with GLP-1RAs, phase 3 combination trials versus either agent alone with SGLT2is and DPP-4is indicate that the additive BP and body weight reductions are not significantly different in comparison with SGLT2i alone (Fig. 3). Cho et al. (69) demonstrate that this applies for both initial combination and the add-on studies. Moreover, post hoc data of CANVAS do not indicate significant differences in lipid profiles of patients also treated with DPP-4is, suggesting that combined use does not relevantly affect lipid levels. Interestingly, DPP-4is are associated with increased urinary sodium excretion (70,71). Lovshin et al. (70) recently suggested, based on a mechanistic study using fractional lithium excretion, that DPP-4is block sodium reabsorption differently than SGLT2is, at a location downstream of the macula densa, thereby not altering TGF and renal hemodynamic functions, which explains the mild-to-neutral effects on eGFR trajectories and albuminuria. Yet, DPP-4is could still improve renal function via GLP-1R–mediated effects or via other DPP-4 substrates associated with sodium excretion or anti-inflammatory effects such as SDF-1α, neuropeptide Y, PYY, substance P, and BNP (45).

Outcomes in CVOTs

The cardiovascular outcomes of SGLT2is combined with DPP-4is have not been investigated. In the reported CVOTs that examined DPP-4is, SGLT2is were not used as background therapy. Vice versa, in EMPA-REG OUTCOME, DPP-4i use was almost associated with worse outcome in the subgroup analysis of the primary outcome, but the small numbers (23 events in 198 patients) are not convincing (HR 1.27 [95% CI 0.82–1.98] vs. 0.81 [95% CI 0.70–0.95]; *P* for interaction 0.06). The CANVAS Program did not report such an analysis. Therefore, the cardiovascular-renal outcome of combined use is unknown; however, given that DPP-4is only modestly alter risk factors and do not induce cardiovascular-renal benefit, it is unlikely that these agents will majorly improve SGLT2i-induced benefits.

Adverse Events

SGLT2is have potential adverse effects that could be ameliorated when combined with DPP-4is. For instance, the rate of genital infections is lowered by 26% when used in this combination, which has been attributed to DPP-4i effects on the immune system (72). Moreover, although speculative, the increased rate of HHF associated to saxagliptin may be counteracted by the cardioprotective effects of SGLT2is. The risk of DKA may be lower due to an enlarged insulin/glucagon ratio. Other adverse effects will probably be independent and thus additive.

Pathophysiological Rationale

When considering the SGLT2i/DPP-4i combination, baseline HbA_{1c} and drug sequence are important factors that determine glycemic efficacy. Although the combination results in a clinically relevant reduction of HbA_{1c} and FPG, addition of a DPP-4i to ongoing SGLT2i therapy reduces glycemic levels modestly, and it seems unlikely that DPP-4is can offset SGLT2i-induced increments in glucagon levels and HGP. However, synergism might still be possible on pleiotropic targets such as the preservation of renal function.

SGLT2is AND OTHER GLUCOSE-LOWERING AGENTS

SGLT2is and Sulfonylureas

Sulfonylureas are frequently used as second-line therapy due to their well-established efficacy and low costs. By depolarizing the β-cell membrane, sulfonylureas stimulate insulin secretion and, according to a 2010 meta-analysis, thereby lower HbA_{1c} by ~1.0–1.25% when used on top of metformin (73). Their effect on BP and lipids is neutral. Common adverse effects are hypoglycemia and weight gain (74). The durability of this drug class is weak, which is often related to induced β-cell failure. Although sulfonylureas have been used for several decades, the cardiovascular-renal safety of sulfonylureas has not been studied properly. Two ongoing studies, Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus (CARMELINA) (NCT01897532) and Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients With Type 2 Diabetes (CAROLINA) (NCT01243424), which are designed to demonstrate the cardiovascular safety of linagliptin versus placebo and active comparator glimepiride, respectively, could via an indirect comparison help to finally narrow this long existing gap in our knowledge.

The effect of combination therapy versus either agent alone has not been investigated, and as a consequence, the quantitative effects are unclear. Phase 3 trials showed that adding SGLT2is to sulfonylurea therapy causes greater glycemic efficacy than placebo (75,76). In combination, SGLT2is might reduce the sulfonylurea-induced β-cell stress by lowering the β-cell afterload. Moreover, the addition of SGLT2is to sulfonylureas reduces body weight, lowers BP, and has no effect on lipids (77–79). In EMPA-REG OUTCOME, sulfonylurea usage in 2,014 patients did not alter the cardiovascular benefit of empagliflozin (HR 0.87; 95% CI 0.69–1.11; *P* for interaction 0.83).

SGLT2is and Thiazolidinediones

Thiazolidinediones, agonists of the peroxisome proliferator–activated receptor γ, improve insulin sensitivity by sensitizing muscle, liver, and adipose tissue to insulin and preserve β-cell function, collectively improving glycemic control (80). Since rosiglitazone is associated with significant increases in the risk of myocardial infarction (MI) (81), pioglitazone is currently the most preferred agent. In the efficacy and tolerability trial of the Pioglitazone 027 Study Group, pioglitazone lowered HbA_{1c} on top of metformin by 0.8% compared with placebo (mean baseline 9.8–9.9%) (82). Pioglitazone induces weight gain due to adipogenesis but lowers BP and improves lipid profiles (80). Pioglitazone has potentially harmful side effects, which include increased fracture risk, edema, and HF (80,83). The underlying mechanism of edema and HF could be fluid retention and plasma volume expansion, which result from sodium reabsorption in the renal collecting duct. In the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive), pioglitazone significantly reduced the main secondary end point 3-point MACE (all-cause mortality, nonfatal MI, stroke) but not the primary extended MACE due to an increase in leg revascularization (84). Also, in subgroup analyses involving patients with established MI (85) or stroke (86), reoccurrence of these events was significantly reduced, indicating a benefit on

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atherosclerotic outcome. This result was confirmed by the Insulin Resistance Intervention After Stroke (IRIS) study (87), which demonstrated that in patients who had insulin resistance along with a recent history of ischemic stroke or transient ischemic attack, pioglitazone significantly reduces the event rate of fatal or nonfatal MI and stroke (HR 0.76; 95% CI 0.62–0.93; *P* = 0.007). However, Thiazolidinediones or Sulfonylureas Cardiovascular Accidents Intervention Trial (TOSCA.IT) showed that the incidence of cardiovascular events was similar when sulfonylureas (mostly glimepiride and gliclazide) were compared with pioglitazone, without significant differences in risk of HF. Probably due to the healthy population, the event rates in TOSCA.IT were so low that the study was terminated early on the basis of a futility analysis. These results thus have to be interpreted with caution. The efficacy and tolerability of empagliflozin added to pioglitazone was assessed in the EMPA-REG PIO studies (88,89). At week 24, empagliflozin reduced HbA_{1c} by ~0.7% compared with placebo from a baseline of 8.1–8.2% in 498 T2D patients. Body weight decreased by ~1.5 kg with empagliflozin, whereas placebo resulted in an increase of ~0.3 kg. Addition of canagliflozin to pioglitazone (90) or addition to pioglitazone without metformin (91) resulted in similar effects. Overall, addition of SGLT2is to pioglitazone on top of metformin reduces HbA_{1c} and BP and ameliorates but does not halt weight gain and edema (31). The beneficial effects of pioglitazone on atherosclerotic outcomes stroke and MI could additively improve cardiovascular outcome when combined with SGLT2is. Since pioglitazone has shown to improve hepatic fat content and liver histology (80), the combination might be effective in the treatment of NASH and NAFLD. Theoretically, the much-debated pioglitazone-associated adverse effects edema and HF could be offset by SGLT2is. An additive or synergistic effect on BP and weight gain, together with SGLT2i-induced plasma contraction, could result in cardioprotection, but this hypothesis needs further research.

SGLT2is and Insulin

While increasing insulin dosages will correct any level of hyperglycemia, treatment intensification is hampered by increased weight gain and hypoglycemia risk. Weight gain results in the need for higher insulin dosages and, as such, creates a vicious circle. Therefore, clinical practice strategies pursue lower insulin dosages by adding other glucose-lowering agents that increase insulin sensitivity or lower insulin need. In a meta-analysis of seven phase 3 studies in 4,235 insulin-treated patients (including basal and basal-bolus regimens), addition of an SGLT2i caused HbA_{1c} reductions of 0.56%, reduced FPG by 0.95 mmol/L, and induced weight loss of 2.63 kg, and insulin dose was decreased by 8.79 IU from mean of ~65 IU compared with placebo (92). Additionally, the SGLT2i-induced reductions in BP are maintained on an insulin background (93–95). In EMPA-REG OUTCOME, SGLT2is maintained their cardiovascular benefit in patients who were on insulin (2,252 patients, HR 0.93; 95% CI 0.75–1.13; *P* for interaction 0.28). In the meta-analysis mentioned earlier, an increased risk of drug-related adverse events of 36% was observed, and urinary tract infections and genital infections increased by 29% and 357%, respectively (92). Last, the propensity of SGLT2is to cause DKA can be amplified when SGLT2i causes a reduction in the dose of concomitant insulin therapy.

CONCLUSIONS

Clinical Considerations

When balancing risks and benefits of glycemic control and pursuing cardiovascular risk reduction, a patient-centered approach requires numerous considerations, including glycemic efficacy, hypoglycemia risk, history of cardiovascular disease (CVD), weight control, adverse effects, renal effects, delivery method, costs, and patient preferences. The differences in the current (inter)national guidelines illustrate the challenge of such a holistic approach. The ADA's *Standards of Medical Care in Diabetes—2018* (1) offers a free choice from the six discussed drug classes recommended after initiation of metformin, and we support the recently added recommendation that T2D patients with established CVD should be treated with an agent that reduces cardiovascular events and/or mortality. Considering the CVOTs (Table 1), we advocate the use of GLP-1RAs in patients with CVD of atherosclerotic origin and SGLT2is in patients with diabetes-related HF and/or CKD. Although the freedom of choice provides opportunities for thorough patient- and disease-based individualization, it assumes a comprehensive knowledge of the T2D treatment armamentarium (Fig. 1), in particular when combination therapy is indicated (Table 2). The National Institute for Health and Care Excellence guideline (2) focuses on the use of DPP-4is, pioglitazone, and sulfonylureas. The use of SGLT2is is restricted to patients with a significant hypoglycemia risk or to those in which metformin and sulfonylureas are contraindicated or not tolerated. Triple therapy with SGLT2is is not the first recommendation and is advised on top of metformin with pioglitazone or sulfonylurea. GLP-1RAs can be considered as triple therapy in severely overweight patients and/or to reduce obesity-associated comorbidities but are not mentioned in combination with SGLT2is. Although this guideline takes hypoglycemia risk into account, it seems to favor cost-effectiveness over cardiovascular benefit, weight control, and safety-to-efficacy profile. The current American Association of Clinical Endocrinologists and American College of Endocrinology algorithm (3) recommends a hierarchy of use for all FDA-approved agents in mono-, dual, and triple therapy. On top of metformin, the suggested order is GLP-1RAs, SGLT2is, DPP-4is, thiazolidinediones, basal insulin, colesevelam, bromocriptine, α-glucosidase inhibitors, and sulfonylureas/glinides. In triple therapy, this order remains, except for DPP-4is, which drop down below basal insulin. The hierarchy provides support, but the fixed character is reminiscent of a one-size-fits-all approach. It is clear that guidelines face an insoluble dilemma to either offer support in a more stepwise or simplified approach that impedes individualization or offer freedom of choice in a holistic patient-centered approach, leaving health care providers without direction or endorsement.

The five possible combinations with SGLT2is on top of metformin discussed in this perspective all showed greater net glycemic efficacy than either agent alone and resulted in clinically meaningful reductions of HbA_{1c}. Yet, none of them demonstrated (super)additive glycemic efficacy, which could be explained by the observation that the glycemic efficacy of all drug classes depends on baseline

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hyperglycemia, causing interference (Fig. 2) (56). Nonetheless, even combinations with GLP-1RAs or DPP-4is were subadditive (Fig. 3), which suggests that the potent glycosuria-driven action of SGLT2is on glucagon and HGP cannot sufficiently be counteracted by the incretin therapies to evoke synergism. The glycemic rationale for a specific drug combination for an individual patient thus lies in the prevailing pathophysiological defects rather than a demonstrated superior net glycemic efficacy of one combination over the other.

In contrast, the combined net pleiotropic effects are various. From an SGLT2i-centered point of view, a combination with GLP-1RAs seems most attractive, showing additive effects in body weight and even synergism in SBP reduction (Fig. 3). Moreover, this combination couples the two drug classes that demonstrated cardiovascular-renal benefit. Although these benefits have enthused many and revised T2D management, several questions remain. First, what mechanisms underlie the benefits? Second, are these benefits class effects? Third, are these benefits generalizable to all T2D patients? Fourth, what is the benefit of one drug class over the other? Ultimately, will these benefits remain in combination therapy?

Future Perspective

At present, we do not know the answers to these questions. The increasing number of mechanistic trials and future CVOTs that investigate cardiovascular and/or renal effects will possibly answer the first two questions but will not demonstrate generalizability or head-to-head risks and benefits. Unfortunately, it is unlikely that these questions will ever be answered by dedicated randomized clinical trials due to the costs and feasibility of such trials, let alone for combination therapy. Therefore, in order to maximize the effect of a patient-centered approach and exploit the benefits of combination therapy, we call for the use of well-designed observational studies in the real-life setting to clarify the individual benefits of one agent and one combination over the other.

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