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REVIEW

Practical combination therapy based on pathophysiology of type 2 diabetes

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Philip A Levin

MODEL Clinical Research, Endocrinology, Department of Medicine, Greater Baltimore Medical Center, Baltimore, MD, USA

Abstract: Type 2 diabetes is a complex, chronic, and progressive condition that often necessitates the use of multiple medications to achieve glycemic goals. Clinical guidelines generally recommend intensifying pharmacotherapy if glycemic goals are not achieved after 3 months of treatment. However, for many patients with type 2 diabetes, treatment intensification is delayed or does not occur. Initiating combination therapy early in the disease course has the potential to delay disease progression and improve patient outcomes. Guidelines generally provide a list of agents that may be used in combination regimens and emphasize individualization of treatment. The purpose of this review is to discuss the rationale for combination therapy, considering treatment effects on pathophysiologic aspects of type 2 diabetes and individual drug profiles. The combination of newer antidiabetes therapies with complementary mechanisms of action provides the opportunity to target multiple sites of tissue, organ, and cellular dysfunction.

Keywords: type 2 diabetes, combination therapy, oral antidiabetes drugs, insulin

Introduction

More than 415 million adults worldwide are estimated to have diabetes, with an increase to 642 million expected by 2040.[1] Type 2 diabetes (T2D) is the most common type of diabetes in adults, and the prevalence is expected to increase largely because of a parallel increase in the prevalence of obesity.[1] There have been significant advances in the understanding of glucose homeostasis and the pathophysiology of T2D over the past few decades.[2] It is now understood that glucose concentrations are maintained by a complex network of finely tuned feedback mechanisms involving multiple organs and hormonal systems and that dysfunctions in this network contribute to the development and progression of insulin resistance and β-cell failure, hallmarks of T2D.[2] Although there is still much to be learned about the disease process,[2] current understanding suggests that early intervention with targeted pharmacotherapy to correct multiple sites of dysfunction might slow T2D progression and improve patient outcomes.

Treatment guidelines recommend metformin as initial oral pharmacotherapy for most adults,[3,4] although study findings show that only 58% of patients are started on metformin in clinical practice.[5] Guidelines consistently advise follow-up at 3 months and a general stepwise approach to pharmacotherapy with the addition of another antidiabetes agent if glycemic goals are not met[3,4]; however, many patients with T2D are subject to notable delays in treatment intensification, generally referred to as clinical inertia.[6] A retrospective cohort study in patients with T2D and glycated hemoglobin

Correspondence: Philip A Levin
MODEL Clinical Research, Greater Baltimore Medical Center, 6535 N Charles Street, Suite 400 N, Baltimore, MD 21204, USA
Tel +1 410 828 7417
Email pal3420@yahoo.com

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(A1C) ≥7% or ≥8% taking one oral antidiabetes drug (OAD) found that the median time to treatment intensification with an additional OAD was 2.9 and 1.6 years, respectively, and more than 7.2 and 6.9 years in patients already taking two OADs.[6] A recent retrospective database study found that in nearly 80% of patients with uncontrolled glycemia despite two OADs, a third OAD was added to the treatment regimen rather than insulin, which provided greater A1C reduction and lower health care costs, suggesting resistance to prescribing and taking insulin in current practice.[7] These prolonged periods of inadequate glycemic control can have a detrimental effect on long-term outcomes.[6,8]

Guidelines from the American Association of Clinical Endocrinologists (AACE) suggest early use of combination pharmacotherapy for patients with high A1C at treatment initiation (Figure 1).[3] AACE recommends initial treatment with dual therapy for patients with an A1C ≥7.5% and advancement to triple therapy if A1C goals are not met after 3 months. For patients with an A1C >9.0% and no hyperglycemia symptoms (eg, polyuria, polydipsia, polyphagia), initial pharmacotherapy with three antidiabetes agents may be appropriate.[3] AACE guidelines further note that combination therapy should include medications with complementary mechanisms of action to maximize effectiveness[3,9] to correct multiple sites of dysfunction. Targeting multiple sites of dysfunction using combination therapy early in the disease course may also produce more durable efficacy, particularly when using agents that preserve β-cell function.[10] The purpose of this review is to discuss the rationale for combination therapy based on the pathophysiology of T2D, providing an overview of the underlying defects in T2D and the primary mechanisms of action of commonly used antidiabetes medications for a greater insight into their use in combination.

Pathophysiology of T2D

Feedback regulation to maintain glucose homeostasis and the critical role of β-cells

In glucose-tolerant individuals, a feedback loop between β-cells and insulin-sensitive tissues maintains normal glucose homeostasis. In this cyclic process, insulin secreted in response to β-cell stimulation suppresses glucose production in the liver and facilitates uptake of glucose, amino acids, and fatty acids in adipose tissue and muscle. Plasma glucose concentrations are maintained within a narrow range (70–90 mg/dL) and are primarily regulated by the hormones insulin, glucagon, and incretins, with input from the central

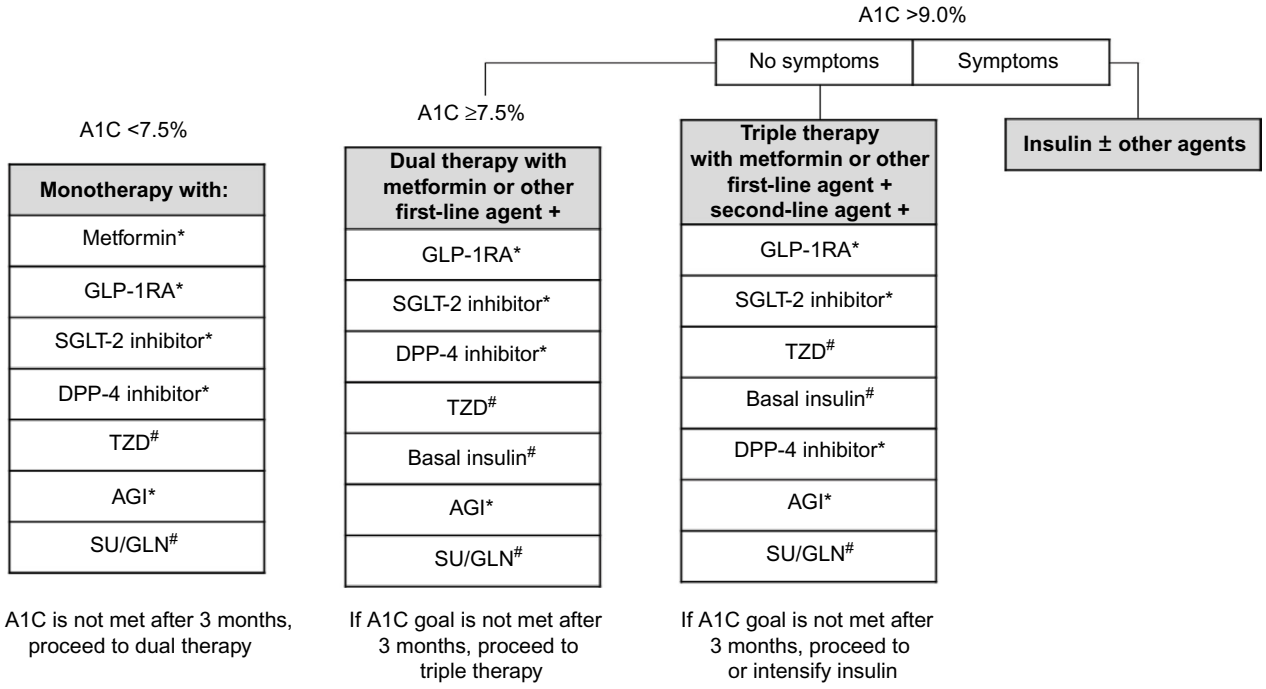

Figure 1 Treatment algorithm based on A1C at entry.

Notes: Order of medications suggests hierarchy of usage by the AACE. Adapted with permission from American Association of Clinical Endocrinologists © 2016 AACE. Garber AJ, Abrahamson MJ, Barzilay JI, et al. AACE/ACE comprehensive type 2 diabetesmanagement algorithm 2016. *Endocr Pract*. 2016;22:84–113.[3] *Indicates few adverse events or possible benefits. #Use with caution.

Abbreviations: A1C, glycated hemoglobin; AACE, American Association of Clinical Endocrinologists; ACE, American College of Endocrinology; AGI, α-glucosidase inhibitor; DPP-4, dipeptidyl peptidase-4; GLN, glinide; GLP-1RA, glucagon-like peptide-1 receptor agonist; SGLT-2, sodium-glucose cotransporter-2; SU, sulfonylurea; TZD, thiazolidinedione.

and peripheral nervous systems.[11] Pancreatic glucagon plays an important role in maintaining glucose homeostasis by stimulating glycogenolysis and gluconeogenesis, metabolic processes in the liver and kidney that convert glycogen and other substrates (lactate, amino acids, glycerol) to free glucose for circulation in the fasted state.[12,13] It is estimated that renal glucose release accounts for 20% of overall endogenous glucose release and ~40% of all gluconeogenesis.[14] Glycogen is also stored in the skeletal muscle; however, muscle glycogen is not directly available to other tissues because it lacks the enzyme glucose-6-phosphatase needed to produce glucose.[14] When exogenous glucose is available, insulin suppresses glycogenolysis and gluconeogenesis. In patients with T2D, however, hepatic insulin resistance results in the inability of normal concentrations of insulin to inhibit glycogenolysis and gluconeogenesis,[15] resulting in increases in basal hepatic glucose production (HGP) and hyperglycemia in the fasted state.[16]

Normally functioning adipose tissue is one of the key regulatory tissues involved in maintaining lipid and glucose homeostasis.[17] Thus, when adipose tissue is in a state of chronic low-level inflammation as occurs with obesity, a multitude of pathologies emerge, including peripheral insulin resistance.[18,19] Preclinical studies have shown macrophage accumulation occurring at the onset of weight gain, and inflammation and macrophage-specific gene expression are upregulated in correlation with increased adiposity.[20] In both animals and humans, macrophage accumulation is in direct proportion to adipocyte size and body mass index.[21] This increased infiltration of macrophages into adipose tissue perpetuates the production of proinflammatory molecules, including free fatty acids that impair insulin sensitivity, which initiate additional activation and infiltration of peripheral monocytes and macrophages.[20,21] Eventually, the continued state of inflammation and impaired insulin signaling in adipose tissue leads to lipolysis, necrosis, and the development of systemic insulin resistance.[20]

The β-cell is highly attuned to changes in insulin sensitivity and can maintain glucose homeostasis by increasing insulin secretion during the early stages of insulin resistance. When the β-cell can no longer produce enough insulin to compensate for a diminished insulin response, glucose concentrations rise.[2] Exposure to chronically elevated glucose concentrations leads to production of reactive oxygen species that cause oxidative stress and increased production of free fatty acids, leading to glucolipotoxicity. This in turn interferes with β-cell compensatory mechanisms, collectively contributing to worsened β-cell function and apoptosis.[2,22] The overall extent to which β-cell function is impaired determines the severity of hyperglycemia, and the progressive failure of β-cells accounts for the transition from impaired glucose tolerance to T2D.[2] The rate at which β-cell impairment occurs varies among patients, although certain factors, most notably poor metabolic control and duration of T2D, contribute to progression.[23]

Multiple genetic and environmental factors also contribute to the development of insulin resistance and β-cell dysfunction.[2] Insulin resistance and reduced β-cell function are largely heritable and present in individuals with normal glucose tolerance but at risk for hyperglycemia (eg, first-degree relatives of patients with T2D).[24,25] Obesity, nutrient composition (particularly intake of saturated fats), and other factors, such as age-related declines in β-cell response, also contribute to glucose intolerance.[2,26] A genetic propensity for obesity has also been demonstrated[27]; obesity and related insulin resistance are thought to arise when genes for abnormal body adiposity interact with certain environmental factors (eg, increased caloric intake, decreased energy expenditure).[2] Although it is not yet known how genes interact with the environment to cause progressive β-cell dysfunction, and there is inherent variability among patients, current data suggest that both a genetic propensity for β-cell dysfunction and increased body adiposity may be necessary for the interaction with environmental factors that results in T2D.[2]

Dysfunction in other body systems

Gastrointestinal tract

In healthy subjects, more insulin is secreted after nutrient ingestion compared with a similar nutrient load given intravenously.[28] The gastrointestinal-derived incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic hormone (GIP), are largely responsible for this effect and primarily stimulate insulin secretion in a glucose-dependent manner by acting at their receptors on β-cells.[28] GLP-1 has also been shown to directly inhibit glucagon secretion via GLP-1 receptors on pancreatic α cells or indirectly by stimulating insulin and somatostatin secretion.[29] In vivo, GLP-1 and GIP facilitate β-cell proliferation and inhibit apoptosis, in addition to stimulating insulin secretion. GLP-1 also slows gastric emptying and decreases food intake, likely through multiple mechanisms.[29,30] Under basal conditions, circulating GLP-1 and GIP concentrations are low but rise rapidly in the postprandial state and then decline as GIP and GLP-1 are rapidly degraded by enzymes, primarily dipeptidyl peptidase-4 (DPP-4).[31] In patients with T2D, the insulinotropic response to GIP is notably reduced,[32] which

likely accounts for much of the decrease in incretin activity.[33] In contrast, the insulinotropic response to GLP-1 remains largely intact in T2D,[28] although certain patient factors, such as high body mass index or high glucagon concentrations, may reduce GLP-1 secretion.[33]

Kidney

In glucose-tolerant subjects, nearly all glucose filtered by the renal glomeruli is reabsorbed by the proximal tubule for recirculation.[34] Glucose is excreted into the urine to help maintain glucose homeostasis only if the maximum glucose transport capacity is exceeded.[34] Glucose reabsorption from the glomerular filtrate is primarily mediated by sodium-glucose cotransporter-2 (SGLT-2), a low-affinity, high-capacity transporter located in the proximal convoluted tubule, in a process independent of insulin secretion or action.[34] Compared with subjects with normal glucose tolerance, patients with T2D have increased renal glucose uptake and release in the postprandial state.[35] As the threshold for glucose reabsorption increases, uptake continues despite elevated plasma glucose concentrations, minimizing glucosuria and exacerbating the hyperglycemic environment.[36] In addition, the kidneys also contribute to glucose release through increased gluconeogenic activity.[14]

Brain

The nervous system also plays an important role in metabolic regulation. Through direct and indirect pathways, the nervous system controls glucose metabolism, affecting insulin and glucagon secretion and HGP.[2] The hypothalamus, in particular, is an important mediator of β-cell function and plasma insulin concentrations.[2,37] Insulin action at the hypothalamus also plays a critical role in regulating appetite and body weight,[2,35] and high-fat diets have been shown to lead to inflammatory signaling in the hypothalamus and subsequent insulin and leptin resistance.[38] Decreased activity at this site is associated with the development of obesity, which is consistent with imaging studies showing structural changes (increased gliosis) in the hypothalamus of obese subjects.[2,39] In preclinical studies, disruptions in circadian rhythms were associated with the development of insulin resistance and obesity,[40] as well as an increase in β-cell dysfunction and apoptosis.[41]

It is apparent that continuous interactions between β-cells and insulin-sensitive tissues and input from other essential organs, such as the brain, kidney, and gastrointestinal tract, collectively ensure an adequate supply of glucose to tissues and organs while keeping plasma glucose concentrations within a specific range to prevent hypoglycemia or hyperglycemia. However, disruptions in these interactions by genetic or environmental triggers, such as inherited insulin resistance, β-cell dysfunction, or obesity, lead to a series of interconnected disturbances that contribute to the development and progression of T2D.

Actions of commonly used antidiabetes medications

New approaches to targeted pharmacotherapy have been developed in response to a better understanding of the underlying pathophysiology of T2D. Knowledge about the mechanisms of action of the more traditional agents has also increased in recent years. Table 1 summarizes the primary actions and key clinical effects of each class of commonly used antidiabetes medications.

As recognized by the AACE, many patients will not reach glycemic goals with monotherapy and will require a combination of antidiabetes medications.[3] However, association recommendations are generally not prescriptive with regard to which treatments to use in combination; rather, individualized treatment is emphasized. Current knowledge provides a sensible rationale for choosing medications that act in a synergistic manner (eg, improved insulin sensitivity and increased insulin secretion) to control glycemia, minimize adverse effects, including hypoglycemia, and correct underlying pathologies.

Suppression of HGP

The primary action of metformin is as an agonist of 5-adenosine monophosphate-activated protein kinase, which reduces HGP by inhibiting gluconeogenesis in the liver. Additionally, metformin yields improved hepatic insulin sensitivity and decreased fasting plasma insulin concentrations.[10,42] Data also indicate that metformin has a beneficial effect on lipid metabolism secondary to improved insulin sensitivity and may help reverse hepatic steatosis,[43,44] a condition closely associated with insulin resistance.[42] Because 5-adenosine monophosphate-activated protein kinase actions also lead to reduced growth of human cancer cells, an antitumorigenic role has also been suggested for metformin,[45] which is supported by a meta-analysis demonstrating a significant 50% reduction in hepatocellular carcinoma incidence in patients with diabetes receiving metformin versus not receiving metformin.[46]

Insulin sensitizers

Thiazolidinediones (TZDs), synthetic peroxisome proliferator-activated receptor-γ agonists,[47] are potent

Table 1 Overview of antidiabetes medications

	Mechanism of action	Protective effects on β-cell function and/or mass	Expected A1C% decrease, monotherapy (%)	Risk for hypoglycemia[3]	Weight	Common side effects/warnings and precautions[b,3,4,51]
Metformin	Decreases HGP (primary) Decreases fasting plasma insulin concentrations and improves insulin resistance[42]	Probable (limited preclinical trials)[159]	1.4[73]	Neutral	Loss (–0.64 kg)[73]	GI side effects Contraindicated in renal impairment, acidosis
GLP-1RAs	Increases insulin secretion and decreases glucagon secretion by activating the GLP-1 receptors; slows gastric emptying and increases satiety[51]	Yes (preclinical and clinical trials)[89]	0.8–2.0[a,9]	Neutral	Loss (1–4 kg)[a,9]	GI side effects Increased heart rate Potential for increased risk of acute pancreatitis
SGLT-2 inhibitors	Inhibits renal glucose reabsorption and increases urinary glucose excretion[51]	Yes (preclinical and clinical trials)[92]	<1.2[160]	Neutral	Loss (up to 4.7 kg)[a,160]	Genital infection Potential for serious urinary tract infection[133] Polyuria, volume depletion, hypotension, and dizziness Increased LDL-C and transient increase in creatinine
DPP-4 inhibitors	Increases insulin secretion and decreases glucagon production by increasing concentrations of GLP-1 and GIP[51]	Yes (preclinical and clinical trials)[91]	0.5–0.9[9]	Neutral	Neutral[3]	Potential for increased risk of acute pancreatitis Potential for increased risk for hospitalizations for HF
TZDs	Reduces insulin resistance in skeletal muscle, liver, and adipose tissue[10]	Yes (preclinical and clinical trials)[87]	0.7–1.2[9]	Neutral	Gain (3–4 kg)[161]	Edema/HF Risk for bone fracture Potential for HF due to fluid retention Increased LDL-C (rosiglitazone)
SUs	Stimulate insulin secretion from pancreatic β-cells[162]	No (possible adverse effect on β-cells)[85,86]	0.4–1.2[9]	Moderate to severe	Gain (1–4 kg)[162]	Low durability Potential for increased CV risk
Basal insulin analogs	Increases glucose disposal and decreases HGP by activating insulin receptors[51]	Yes (clinical trials)[163]	1.5–1.8[9]	Moderate to severe	Gain (1–3 kg more vs other antidiabetes medications)[9]	Allergic reactions and injection site reactions Edema

Notes: [a]Includes monotherapy and add-on therapy evaluations. [b]Not inclusive of all treatment-related adverse effects or warnings.
Abbreviations: A1C, glycated hemoglobin; CV, cardiovascular; DPP-4, dipeptidyl peptidase-4; GI, gastrointestinal; GIP, glucose-dependent insulinotropic hormone; GLP-1, glucagon-like peptide-1; GLP-1RA, glucagon-like peptide-1 receptor agonist; HF, heart failure; HGP, hepatic glucose production; LDL-C, low-density lipoprotein cholesterol; SGLT-2, sodium-glucose cotransporter-2; SU, sulfonylurea; TZD, thiazolidinedione.

insulin sensitizers in the liver, muscle, and adipose tissue[48–50]; evidence has shown TZDs to additionally alleviate lipotoxicity by transporting lipid deposits out of muscle, liver, and β-cells.[10] Similar to that of metformin, the insulin-sensitizing effects of TZDs may counteract hepatic steatosis.[44]

Insulin secretagogues

Sulfonylureas (SUs) primarily increase insulin secretion by binding to the adenosine triphosphate-sensitive potassium (K_{ATP}) channel on pancreatic β-cell plasma membranes.[51–53] Specifically, SUs bind to the SU receptor 1, a subunit on the K_{ATP} channel, and induce closure.[53] As a result, concentrations of intracellular potassium rise, the β-cell membrane is depolarized, and insulin-containing secretory granules move to the cell surface for release into circulation.[53,54]

In contrast to the actions of SUs, the actions of incretin-based therapies are glucose-dependent.[55] Incretin mimetics, or GLP-1 receptor agonists (GLP-1RAs), primarily increase insulin secretion and decrease glucagon secretion by activating the GLP-1 receptor.[30,31] Delayed gastric emptying has also been associated with GLP-1RAs and shown to occur within minutes of administration.[29] It is likely that this effect, as well as enhanced satiety and reduced food intake, involves interactions between the central and peripheral nervous systems.[29]

It is estimated that the half-life of biologically active GLP-1 in circulation is less than 2 minutes because of rapid degradation by DPP-4 activity.[56,57] By inhibiting the DPP-4 enzyme and thereby increasing the half-life of endogenous incretin hormones in circulation, DPP-4 inhibitors indirectly increase stimulation of GLP-1 receptors.[58] DPP-4 inhibitors are rapidly absorbed following oral administration and competitively and reversibly bind to the active site of DPP-4, reducing DPP-4 activity by 70% to 90% and, consequently, increasing GLP-1 concentrations approximately 1.5- to 4-fold at therapeutic doses.[59] Preclinical and clinical evidence has demonstrated the benefits of DPP-4 pharmacologic inhibition, including increased concentrations of GIP and GLP-1, stimulation of insulin in circulation, improved glucose tolerance and insulin sensitivity, suppressed plasma glucagon, and prevention of weight gain.[29] The clinical efficacy of DPP-4 inhibitors has been demonstrated in randomized controlled trials showing significant reductions from baseline in fasting plasma glucose, postprandial glucose, and A1C.[59] DPP-4 inhibitors typically provide mean A1C reductions ranging from approximately 0.4% to 1.0% as monotherapy and from 0.7% to 1.2% in combination therapy regimens.[59]

Insulin independent agents

SGLT-2 inhibitors reduce elevated glucose concentrations through increased glucosuria by decreasing renal glucose reabsorption.[34] The mechanism of action of SGLT-2 inhibitors is independent of insulin and may therefore complement a variety of other antidiabetes medications that are insulin dependent.[34] It is also theorized that because SGLT-2 inhibitors target renal glucose handling, efficacy should not be compromised as further declines in β-cell function and increased insulin resistance occur.[34]

The α-glucosidase inhibitors (AGIs) primarily reduce postprandial plasma glucose concentrations through the competitive and reversible inhibition of α-glucosidase located in the brush border of the small intestine.[60] Following nutrient ingestion, α-glucosidase hydrolyzes complex carbohydrates to monosaccharides for absorption. Thus, AGIs obstruct the degradation of starches and sucrose and delay carbohydrate reabsorption in a nonsystemic manner.[60] However, a patient's diet may alter efficacy. Studies indicate that AGIs may have a more potent effect in patients who consume a typical Eastern diet (whole grains, vegetables, fruits) compared with patients whose diet is characterized as Western (processed meat, high-fat dairy products, refined grains).[60,61]

Central nervous system

The development of therapies that target the central nervous system to reduce glucose concentrations is challenging.[2] Bromocriptine, a quick-release sympatholytic D2-dopamine agonist, is currently the only approved antidiabetes medication that has a centrally mediated mechanism of action.[2] Although the mechanism by which bromocriptine lowers plasma glucose concentrations is unknown, it is believed that early-morning treatment with bromocriptine resets circadian rhythms of hypothalamic dopamine and serotonin and thereby improves insulin sensitivity.[62]

Bile acid sequestrants

Bile acid sequestrants were initially developed to treat hypercholesterolemia; therefore, these agents have significant lipid-lowering properties.[63] The mechanism by which colesevelam reduces plasma glucose concentrations is not fully understood, although study findings suggest that colesevelam reduces hyperglycemia by improving tissue glucose metabolism in both the fasting (increased plasma glucose clearance) and postprandial (increased glycolytic disposal of oral glucose) states.[64] Colesevelam has also been associated with increased GLP-1 and GIP plasma concentrations, which likely contribute to observed improvements in β-cell function and increased glycolytic disposal.[64]

The American Diabetes Association currently does not favor the use of AGIs, colesevelam, or bromocriptine because of modest effects on glucose lowering, frequent dosing schedules, and occurrence of side effects.[51] Therefore, discussion of the use of these agents in combination is limited in this review.

Basal insulin

Many patients will eventually require insulin to maintain glycemic control.[51] The primary mechanism of action of insulin and its analogs is the activation of insulin receptors.[51] Thus, insulin analogs lower plasma glucose concentrations by stimulating peripheral glucose uptake and inhibiting HGP.[65,66] Although various formulations of insulin are available, guidance from the AACE recommends initial insulin therapy with long-acting basal insulin analogs because basal formulations are associated with less glycemic variability and a lower risk for hypoglycemia compared with neutral protamine Hagedorn, an intermediate-acting insulin.[3] Several types

Table 2 Potential regimens for targeted combination therapy to address major pathophysiologic defects[a]

	Dual therapy										Triple therapy						Basal insulin				
	MET +					TZD +			SGLT-2i +		MET + DPP-4i +		MET + SGLT-2i				Insulin +				
Pathophysiologic improvement	**GLP-IRA**	**SGLT-2i**	**DPP-4i**	**TZD**	**SU**	**GLP-IRA**	**SGLT-2i**	**DPP-4i**	**GLP-IRA**	**DPP-4i**	**TZD**	**SU**	**GLP-IRA**	**DPP-4i**	**TZD**	**SU**	**MET**	**GLP-IRA**	**SGLT-2i**	**DPP-4i**	**TZD**
Enhance endogenous insulin/sensitivity	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Preserve β-cell function[b]	Yes	Likely	Likely	Yes	–	Yes	Yes	Yes	Yes	Likely	Yes	–	Yes	Likely	Yes	–	Yes[c]	Yes[c]	Yes[c]	Yes[c]	Yes[c]
Decrease body weight	Yes	Yes	–	No	No	Yes	Yes	No	Yes	Yes	No	No	Yes	Yes	Likely	Likely	No	Yes	Yes	No	No

Notes: [a]Potential improvements based on individual therapeutic profiles. Not inclusive of all potential combination regimens (– indicates improvement not likely). [b]Available data indicate beneficial effects on β-cell function with DPP-4 inhibitors and SGLT-2 inhibitors, although effects are not as well established as those associated with GLP-IRAs or TZDs. [c]Early insulin therapy may exert protective effects on the β-cells.
Abbreviations: DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-IRA, glucagon-like peptide-1 receptor agonist; MET, metformin; SGLT-2i, sodium-glucose cotransporter-2 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione.

of long-acting basal insulin analogs are available in the US, including insulin glargine (Lantus® [Sanofi-Aventis, Bridgewater, NJ, USA] and Toujeo® [Sanofi-Aventis]), insulin detemir (Levemir® [Novo Nordisk, Bagsværd, Denmark]), and insulin degludec (Tresiba® [Novo Nordisk]).[51,66,67] Although both formulations of insulin glargine provide prolonged activity and thus allow once-daily dosing, Toujeo is a concentrated glargine, and its duration of action exceeds that of Lantus (approximately 36 vs 24 hours).[68] In addition, Toujeo has been shown to significantly reduce nighttime low blood sugar events compared with Lantus (P=0.0002).[69] Insulin detemir or Levemir is also associated with a constant duration of action, but similar to that of Lantus (approximately 24 hours), and may be administered once or twice daily in divided doses.[66] Of the currently available long-acting basal insulin analogs, Tresiba provides the longest duration of effect, lasting at least 42 hours, primarily because of delayed absorption of insulin degludec from the subcutaneous tissue into systemic circulation.[67]

Potential combinations to improve pathophysiologic dysfunction

Enhancing endogenous insulin action

There are many combination regimens that have the potential to address multiple sites of pathophysiologic dysfunction of T2D, and those that may exert complementary effects are outlined in Table 2. The combination of metformin and a TZD has been suggested[10] because metformin reduces HGP by inhibiting gluconeogenesis in the liver but is only a weak sensitizer in the muscle,[42,70,71] and TZDs are potent insulin sensitizers in liver, muscle, and adipose tissue.[48] Metformin and TZDs individually have a robust effect on A1C, and each exerts its actions through different pathways, providing an additive effect on glucose lowering.[10] Metformin and TZDs are also associated with a low risk for hypoglycemia,[3] making these agents appealing for use in combination. However, because metformin primarily relies on renal function for elimination,[72] it is contraindicated in patients with renal disease or dysfunction.[73] Metformin is also associated with gastrointestinal adverse effects that may lead to discontinuation for some patients but may dissipate with continued use or with dosing adjustments.[74] TZDs have been shown to have beneficial effects on cognitive disorders related to insulin resistance in the central nervous system in studies in mice[75] and to exert favorable effects on cardiovascular (CV) risk markers in patients with T2D.[76] However, TZDs are associated with an increased risk for weight gain and

fluid retention, which may worsen or lead to congestive heart failure (HF).[77,78]

Insulin secretagogues, such as SUs or incretin-based therapies, may also act in a complementary manner to metformin by facilitating insulin secretion. SUs are associated with moderate glycemic efficacy, although these agents are recommended for patients with a disease duration of less than 5 years[55] because the mechanism of action is dependent on functioning β-cells.[53] In addition, because SUs act independently of plasma glucose concentrations, the main risk is hypoglycemia, which may be exacerbated by coadministration with other drugs, especially those that inhibit SU metabolism via the cytochrome P450 2C9 isozyme.[79] To avoid hypoglycemia, the addition of a DPP-4 inhibitor or a GLP-1RA to metformin may be considered instead. Although GLP-1RAs are associated with a more robust effect on A1C lowering compared with DPP-4 inhibitors,[80] each has been shown to improve glycemic control without increasing the risk for hypoglycemia.[51] GLP-1RAs are also associated with gastrointestinal side effects, particularly transient nausea, which may be attributed to delayed gastric emptying.[80] Preclinical and clinical studies also demonstrate additional complementary actions between metformin and a DPP-4 inhibitor or a GLP-1RA. In vivo, metformin increased circulating concentrations of active GLP-1 but did not affect the activity of the DPP-4 enzyme.[81] Thus, as demonstrated in healthy subjects, metformin and a DPP-4 inhibitor increased GLP-1 concentrations through two separate pathways, providing an additive increase in GLP-1 concentrations.[82] Similar benefits were observed with metformin in combination with exogenous GLP-1 administration in patients with T2D, although findings in this study suggested that metformin enhanced injected active GLP-1 concentrations by inhibiting DPP-4 activity.[83]

Preserving β-cell function

Maintaining β-cell function is a key aspect in delaying disease progression,[84] and as noted above, the efficacy of drugs that depend on β-cell function for their actions, such as the SUs, declines as β-cell function declines.[10] Furthermore, results of in vitro studies have suggested that prolonged exposure to SUs may in fact cause disturbances in islet cell function[85] and may induce β-cell apoptosis as a secondary effect to the closure of the K_{ATP} channel.[86]

In contrast, substantial evidence has demonstrated that TZDs positively affect β-cells by improving insulin secretory capacity and function, preserving structure and mass, and exerting protective effects from oxidative stress.[87] Preclinical studies have also shown that GLP-1RAs and DPP-4 inhibitors improve or preserve β-cell mass by promoting β-cell proliferation and inhibiting apoptosis.[30,88] Clinical trials in patients with T2D further demonstrate that GLP-1RAs preserve β-cell function and sensitivity to glucose with a durable effect,[89,90] and DPP-4 inhibitors sustain β-cell function during 2 years of treatment.[91] More recently, SGLT-2 inhibitors have been shown to improve β-cell function in patients with T2D, despite having no direct effect on pancreatic β-cells, through the reversal of glucotoxicity and improved insulin sensitivity.[92] Therefore, the combination of a TZD with a DPP-4 inhibitor, GLP-1RA, or SGLT-2 inhibitor may provide both insulin-sensitizing and insulin secretory effects, in addition to helping preserve β-cell function.

Promoting weight loss

Treatment-related effects on weight are also important to consider because weight gain can worsen insulin resistance and thereby diminish efficacy.[89] TZDs are associated with weight gain, in part due to fluid retention and fat cell proliferation,[93] as are SUs, as a secondary effect on adipocyte K_{ATP} channels.[94] Metformin is associated with weight loss or is weight neutral and has been shown to maintain efficacy across all body weight categories, including patients who are overweight or obese,[55] providing a rationale for use in combination. Because AGIs slow intestinal carbohydrate digestion and absorption,[51] weight gain is not expected, and treatment has been shown to minimize weight gain when used in combination with SUs.[95] However, because AGIs have limited potency in lowering A1C and are also commonly associated with gastrointestinal side effects, their use in combination regimens may not always be suitable.[3]

For patients in whom weight loss is difficult, the use of a GLP-1RA with an SGLT-2 inhibitor may be particularly beneficial because GLP-1RAs slow gastric emptying, increase satiety, and reduce food intake,[29] and SGLT-2 inhibitors decrease weight through increased caloric loss via glucosuria.[3] Additionally, GLP-1RA s and SGLT-2 inhibitors reduce blood pressure in patients with T2D, possibly as a secondary effect of weight loss and other factors, such as the mild osmotic diuretic effect of the SGLT-2 inhibitors.[34,96] In a recent retrospective analysis, patients had a two-fold greater weight loss with GLP-1RA and SGLT-2 inhibitor combination therapy (−7.2 kg) compared with patients taking an SGLT-2 inhibitor alone (−3.0 kg).[97] Because the actions of GLP-1RAs are distinct from those of SGLT-2 inhibitors, the reduction in weight is likely additive when used in combination. DPP-4 inhibitors may also complement SGLT-2 inhibitors in this regard. Inhibition of the DPP-4 enzyme is

associated with prevention of weight gain,[29] and clinical study findings have shown an initial combination therapy with a DPP-4 inhibitor and an SGLT-2 inhibitor in treatment-naïve patients to significantly reduce weight compared with a DPP-4 inhibitor administered alone.[98]

Triple oral combination therapy

Much of the previous discussion has focused on potential dual therapy combinations; however, some patients with high A1C may require initial triple oral pharmacotherapy or intensified treatment with a third agent if dual therapy regimens do not provide adequate glycemic control. In patients with more recent disease, triple oral therapy with metformin, an SU, and a DPP-4 inhibitor may help address key disease aspects, including decreased insulin secretion and increased HGP. SUs in this population may also provide greater efficacy because β-cell function may still be intact. In patients with inadequate glycemic control despite metformin and SU dual therapy, the addition of a DPP-4 inhibitor, an SGLT-2 inhibitor, or a TZD has been shown to improve glycemic control.[99,100] However, as previously mentioned, SUs increase the risk for hypoglycemia,[3] making a TZD in combination with metformin and a DPP-4 inhibitor or an SGLT-2 inhibitor an alternative choice if avoiding hypoglycemia is a primary treatment goal.[101,102] TZDs in these combinations should also provide additive benefits on β-cell function and mass, although adverse effects on body weight may limit use. Triple therapy with metformin, a DPP-4 inhibitor, and an SGLT-2 inhibitor has also been shown to be efficacious in reducing A1C without increasing the risk for hypoglycemia or weight gain.[103–107] Based on the respective mechanisms of action, this particular combination allows improved insulin sensitivity and enhanced insulin production, with additional clinical benefits on weight and blood pressure. In addition, SGLT-2 inhibitors are associated with a rise in fasting plasma glucagon concentrations and endogenous glucose production, which could limit efficacy.[108,109] However, preclinical studies have shown the suppressive effects of metformin on HGP to counteract the rise in endogenous glucose production and thereby enhance the glucose-lowering properties of SGLT-2 inhibitors.[110] DPP-4 inhibitors, which suppress glucagon secretion and therefore inhibit endogenous glucose production,[111] have been shown to reduce SGLT-2 inhibitor-induced increases in glucagon when used concomitantly.[112]

Combination with basal insulin

In general, the initiation of insulin should be considered for patients with initial A1C >9% and symptomatic hyperglycemia or for patients with A1C >8.0% despite dual therapy and/or long-standing T2D, because adding a third antidiabetes drug in this scenario will be less likely to achieve glycemic targets (Figure 1).[3] Although previous guidance has suggested delaying the initiation of insulin therapy until after several rounds of treatment failure, more recent recommendations suggest initiating insulin earlier, often in combination with DPP-4 inhibitors, SGLT-2 inhibitors, or GLP-1RAs.[3] Research also supports the early use of insulin to protect β-cell function through the rapid reversal of glucolipotoxicity.[113]

Weight gain is common with insulin therapy and has been attributed to the correction of severe hyperglycemia leading to rebuilding of muscle and fat mass, as well as increased caloric retention resulting from decreased glucosuria.[93] In addition, patients experiencing hypoglycemia may increase their food intake.[93] For patients requiring increasing insulin doses, TZDs have been suggested as adjunct therapy to help reduce insulin daily doses and establish glycemic control.[51] Although TZDs may additionally help to preserve β-cell function,[87] weight gain and fluid retention associated with TZD therapy may be exacerbated with concomitant insulin use,[114] limiting use in some patients. In patients taking SU therapy, it is generally recommended that the dose be reduced or treatment stopped after starting basal insulin.[3]

In patients with T2D receiving basal insulin, controlled clinical trials support the use of incretin-based therapies or SGLT-2 inhibitors. For example, in patients on background insulin glargine with or without OADs, add-on exenatide for 30 weeks was associated with significantly greater reductions from baseline in A1C (−1.74% vs −1.04%, $P<0.001$) and weight (−1.8 vs +1.0 kg) versus add-on placebo, with no increased risk for hypoglycemia.[115] Additional clinical studies of other GLP-1RAs added to existing basal insulin regimens have demonstrated similar results.[116,117] Clinical trials of add-on DPP-4 inhibitor therapy to basal insulin (or other insulin formulations) have also demonstrated significant improvements in A1C without an increased risk for weight gain or hypoglycemia versus controls.[118–121] Importantly, findings observed from clinical trials of basal insulin in combination with incretin-based therapies are consistent with those from real-world observational studies.[122,123] Available clinical trial data have also shown that the addition of an SGLT-2 inhibitor to basal insulin or other formulations (with or without other OADs) effectively reduces A1C and weight and maintains a low risk for hypoglycemia.[124–126] Of interest, insulin detemir may have a more favorable effect on weight compared with other basal insulin formulations, and patients treated with

detemir plus other OADs have been shown to consistently experience weight loss.[127,128]

Based on clinical trial findings, the AACE suggests a DPP-4 inhibitor, GLP-1RA, or SGLT-2 inhibitor in combination with basal insulin to decrease basal and postprandial glucose and weight gain, without increasing the risk for hypoglycemia and weight gain.[3] With more complex insulin regimens, SGLT-2 inhibitors are also suggested to reduce the amount of insulin needed.[51] Consistently, clinical trials have shown that patients treated with GLP-1RAs, DPP-4 inhibitors, and SGLT-2 inhibitors in combination with insulin (basal and other formulations) require fewer increases in daily insulin doses compared with controls.[115,116,118,119,124–126] DPP-4 inhibitors and SGLT-2 inhibitors have the advantage of oral administration; however, because patients are already receiving insulin injections, the route of administration may not be a primary factor in the treatment selection.[129] In addition, injection pens with single administration of combination basal insulin and GLP-1RA (insulin degludec and liraglutide and insulin glargine and lixisenatide fixed ratio) are currently in development.[130,131]

More recently, there has been concern about whether SGLT-2 inhibitors are associated with an increased risk of diabetic ketoacidosis (DKA), particularly in patients with a recent reduction in concomitant insulin dose.[132] Based on postmarketing reports of 73 cases in patients treated with SGLT-2 inhibitors (March 2013–June 2015), the US Food and Drug Administration required labeling of SGLT-2 inhibitors to include warnings of an increased risk of DKA.[133] More expansive reviews of data have shown that most patients had only slightly elevated plasma glucose concentrations (euglycemic DKA), and some cases occurred in patients with type 1 diabetes.[132] In addition, data from the clinical development programs for the three US-approved SGLT-2 inhibitors have shown no clear association between DKA and SGLT-2 inhibitor treatment.[132] For example, in the EMPA-REG OUTCOME trial in 7,020 patients, the incidence of DKA was ≤0.1% and did not differ between empagliflozin and placebo groups.[134] A similar incidence rate of <0.1% for DKA was also reported from the clinical development programs for canagliflozin (N=17,596) and dapagliflozin (N>18,000).[132,135] The AACE has also undertaken a rigorous examination of this potential risk and concluded that the occurrence of DKA in treated patients is infrequent, and the risk–benefit ratio remains in favor of continued SGLT-2 inhibitor use, with no changes in current recommendations required.[136] Regulatory agencies and pharmaceutical companies will continue to monitor this potential risk, and attention to risk factors for euglycemic DKA, such as reductions in concomitant insulin doses, has been advised when treating patients with SGLT-2 inhibitors.[132]

CV safety

The effect of antidiabetes therapies on CV outcomes remains a major concern. Research has reported mixed findings as to whether SUs or insulin are associated with an increased risk for CV events.[137–140] Prescribing information for glipizide, glyburide, and glimepiride includes a warning of an increased risk of CV mortality with the first-generation SU, tolbutamide, versus insulin as add-on to diet or diet alone.[141–143] Although the use of SUs in patients with CV risk appears to be declining in clinical practice,[144] recent findings of an increased risk for mortality and CV events with treatment warrant continued caution.[145,146] For example, initial SU monotherapy in a German cohort of patients with T2D significantly increased the risk of major CV events, overall mortality, and T2D-related hospitalization compared with initial metformin monotherapy (all $P<0.001$).[146] Findings from a systematic review additionally found an increased risk of all-cause mortality and CV-related mortality with SUs compared with other antidiabetes drugs and a significantly higher risk of myocardial infarction (vs DPP-4 inhibitors) in randomized clinical trials, which was also confirmed in observational studies.[145] Further, the risk of stroke was significantly higher in patients treated with SUs in clinical trials versus those treated with DPP-4 inhibitors, GLP-1RAs, TZDs, or insulin.[145]

TZDs have been associated with HF, attributed to treatment-induced fluid retention.[3,51] These agents are therefore contraindicated in patients with preexisting HF, and the prescribing information for pioglitazone and rosiglitazone contains warnings for congestive HF.[77,78] Although there is not yet conclusive evidence to establish CV benefit with this treatment,[147] fewer patients with T2D had a CV disease event with bromocriptine quick-release as add-on to standard of care compared with placebo in a 1-year trial.[148]

CV outcome trials

Findings have been published from three CV outcome trials for DPP-4 inhibitors showing no increased risk for major CV events with alogliptin, saxagliptin, or sitagliptin, respectively, versus placebo as add-on to standard of care.[149–151] However, a potential for an increased risk of hospitalization for HF versus placebo was observed in patients treated with saxagliptin[149] and in a subgroup of patients with no

history of HF at baseline treated with alogliptin.[152] A recent observational cohort study using data from a US insurance claims database evaluated the risk of hospitalization for HF between patients with T2D treated with DPP-4 inhibitors or an SU and between patients treated with saxagliptin or sitagliptin.[153] In patients with no baseline CV disease, DPP-4 inhibitors were associated with a significantly lower risk of hospitalization for HF compared with those treated with an SU (P=0.013). The risk of hospitalization for HF between saxagliptin and sitagliptin in patients with or without baseline CV disease and between DPP-4 inhibitors and SUs in patients with baseline CV disease was not significantly different.[153] Additional CV outcome studies for linagliptin are ongoing.[154,155] Until additional findings are known, it is recommended that DPP-4 inhibitors be used with caution, or not at all, in patients with preexisting HF.[4]

In the EMPA-REG OUTCOME CV outcomes trial in patients with T2D and established CV disease, empagliflozin as add-on to standard of care was associated with significantly lower rates of major CV events (ie, death from CV causes, nonfatal myocardial infarction, nonfatal stroke), primarily driven by a significant reduction in death from CV causes, as well as death from any cause and hospitalization for HF compared with add-on placebo.[134] CV outcome trials for dapagliflozin and canagliflozin are underway and are expected to be completed in 2017 (canagliflozin) and 2019 (dapagliflozin). Each trial includes patients with T2D at high risk for CV events.[156,157] Most of the GLP-1RA CV trials are ongoing, although one study for lixisenatide recently reported preliminary findings.[158] In this study, no increased risk for major CV events was observed in patients with a recent acute coronary syndrome event treated with lixisenatide versus placebo.[158]

Conclusion

The multitude of therapeutic options for T2D adds to the complexity of managing patients with this disease but also allows clinicians to readjust and rebalance treatment over time as physiologic changes occur throughout the course of the disease. As understanding of the pathophysiology of T2D grows, it is becoming apparent that early use of targeted combination therapy has the potential to slow disease progression, potentially through the correction of known pathologies and the preservation of β-cell function. Obesity plays a central role in the development and worsening of T2D, and thus it can be argued that treatments that facilitate weight loss may be most beneficial. Whereas the underlying pathophysiology of T2D should be a key factor in choosing which medications to combine, the treatment choice must also be individualized to patients' needs and tolerability. Based on individual therapeutic profiles, the newer incretin-based therapies and SGLT-2 inhibitors are appropriate for use in combination with one another or in combination with more traditional agents (eg, metformin, TZDs, insulin) to reduce A1C without increasing the risk of hypoglycemia. In addition, because these newer agents act on different pathways, the beneficial actions on glycemia and weight are likely additive when used in combination. Although clinical inertia remains an issue, emerging research helps to support and advocate for the use of early combination therapy as a practical approach to preempt the development of long-term complications and disease progression.

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