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REVIEW

Combination Glucose-Lowering Therapy Plans in T2DM: Case-Based Considerations

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ABSTRACT

Type 2 diabetes mellitus (T2DM) is a complex disease, and while lifestyle interventions remain the cornerstone of therapy, most patients will also require pharmacotherapy. Current diabetes treatment guidelines and algorithms recommend an individualized approach to setting glycemic goals and selecting treatment. Although a single antihyperglycemic agent may be appropriate as the initial T2DM pharmacotherapy, the progressive nature of the disease due to declining pancreatic β-cell function will result in the vast majority of T2DM patients eventually requiring two or more antihyperglycemic agents. The American Association of Clinical Endocrinologists/American College of Clinical Endocrinology T2DM management algorithm recommends initial dual agent combination therapy when a single agent is unlikely to achieve their target glycemia, i.e., for those patients with an HbA1c $\geq$ 7.5 and an individualized HbA1c target of $<$ 7.5%. The American Diabetes Association Standards of Care recommend combination pharmacotherapy for those patients presenting with very elevated HbA1c levels (e.g., $\geq$ 9% and $<$ 10%). Metformin (if well tolerated and not contraindicated) is the initial pharmacologic choice for most patients; selection of another antihyperglycemic agent to the regimen will depend on the presence of atherosclerotic cardiovascular disease and other patient-specific factors (e.g., age, known duration of T2DM, history of or risk for hypoglycemia and/or adverse consequences from hypoglycemia, other comorbidities, and available resources), along with drug-specific factors (e.g., risk for hypoglycemia, potential effects on weight, drug adverse event profiles, and cost). Combination therapy may be administered as a multi-pill regimen, a single-pill combination (i.e., fixed-dose combination oral therapy), or as a combination of oral and/or injectable therapies. This paper provides two illustrative case presentations to demonstrate how current treatment recommendations and algorithms can be used to guide the selection of non-insulin-based combination therapy for patients with T2DM in primary care settings and discusses the relative merits of several possible approaches for each patient.

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a progressive disease associated with declining pancreatic β-cell function, which is typically accompanied by insulin resistance. Treatment regimens that combine lifestyle interventions with pharmacologic antihyperglycemic monotherapy often lack durability over time [1]. Consequently, many patients continue to have glycated hemoglobin (HbA1c) levels above goal, with clinical inertia contributing to delays in the escalation of treatment for persistent hyperglycemia [2, 3]. Barriers to the intensification of therapy (despite inadequate glycemic control) include patient concerns with potential side effects associated with some therapies and escalating costs related to new or additional medications [4].

Evidence from comparative effectiveness analyses suggests that the addition of some second, non-insulin antihyperglycemic agents to initial therapy can lower HbA1c levels by approximately one percentage point [5, 6]. Data show that two-drug combinations provide reductions in plasma HbA1c levels of approximately − 0.5% to − 1.0% compared with that achieved by the individual components [7], although the baseline level is an important determinant of the magnitude of the on-treatment reduction in HbA1c. Multiple single-pill combination (i.e., fixed-dosed combination [FDC]) products are commercially available in the USA for the treatment of T2DM (Table 1). Due to the reduction in pill burden, FDCs can lead to enhanced regimen adherence, which may result in improved control of glycemic parameters, and lowered overall costs of disease management [7].

This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

CURRENT GUIDELINES AND ALGORITHMS: PATIENT-CENTERED INDIVIDUALIZED CARE AND COMBINATION TREATMENT

The 2015 position statement from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) on the management of hyperglycemia [8], the 2018 standards of care from the ADA [9, 10], and the 2018 comprehensive diabetes management algorithm from the American Association of Clinical Endocrinologists (AACE) and the American Collage of Endocrinology (ACE) [11] recommend an individualized approach to setting HbA1c goals and selecting treatment. This care model implies that multiple factors need to be considered regarding treatment decisions, including patient risk for adverse consequences from hypoglycemia and weight gain, individual preferences regarding treatment goals, the presence of comorbidities or complications (e.g., cardiovascular disease [CVD]), duration of T2DM, and overall life expectancy [8]. Therapeutic lifestyle interventions, including medical nutrition therapy and appropriately prescribed physical activity to promote healthful body weight, are the foundation of T2DM management in the current guidelines, but usually will need to be combined with antihyperglycemic pharmacotherapy. Finally, the evidence-based recommendations that are most salient to primary care are summarized in the ADA Standards of Medical Care in Diabetes—2018 Abridged for Primary Care Providers [12] or in the 2018 AACE/ACE algorithm [11].

Metformin, when tolerated and not contraindicated, is usually the preferred first-line pharmacotherapy, although some patients may require initial insulin therapy because of marked hyperglycemia [8, 9, 11]. For combination therapy with metformin, the 2018 AACE glycemic control algorithm suggests several agents according to the therapeutic hierarchy shown in Fig. 1 [11]. In the ADA 2018 algorithm, second-line therapies added to metformin include either an oral agent (sulfonylurea [SU], thiazolidinedione [TZD], dipeptidyl peptidase-4 [DPP-4] inhibitor, or

Table 1 Single-pill oral combination products approved in the USA for the treatment of T2DM

Generic name	Brand name	Doses	General dosage and administration[a]
DPP-4 inhibitor and metformin			
Alogliptin and metformin	Kazano®	12.5/500 mg 12.5/1000 mg	Individualize starting dose based on the patient's current regimen BID with food, with gradual dose escalation to minimize GI side effects due to metformin Maximum daily dose: alogliptin 25 mg/metformin 2000 mg
Linagliptin and metformin	Jentadueto®	2.5/500 mg 2.5/850 mg 2.5/1000 mg	Individualize starting dose based on the patient's current regimen BID with food, with gradual dose escalation to minimize GI side effects due to metformin Maximum daily dose: linagliptin 5 mg/metformin 2000 mg
Linagliptin and metformin XR	Jentadueto® XR	2.5/1000 mg 5/1000 mg	Individualize starting dose based on the patient's current regimen Give once daily with a meal Maximum daily dose: linagliptin 5 mg/metformin XR 2000 mg
Saxagliptin and metformin XR	Kombiglyze® XR	5/500 mg 5/1000 mg 2.5/1000 mg	Individualize starting dose based on the patient's current regimen QD with the evening meal, with gradual dose escalation to minimize GI side effects due to metformin Maximum daily dose: saxagliptin 5 mg/metformin XR 2000 mg Limit the saxagliptin dosage to 2.5 mg daily for patients also taking strong cytochrome P450 3A4/5 inhibitors (e.g., ketoconazole)
Sitagliptin and metformin	Janumet®	50/500 mg 50/1000 mg	Individualize starting dose based on the patient's current regimen BID with meals, with gradual dose escalation to minimize GI side effects due to metformin Maximum daily dose: sitagliptin 100 mg/metformin 2000 mg
Sitagliptin and metformin XR	Janumet® XR	100/1000 mg 50/500 mg 50/1000 mg	Individualize starting dose based on the patient's current regimen QD, preferable with the evening meal, with gradual dose escalation to minimize GI side effects due to metformin Maximum daily dose: sitagliptin 100 mg/metformin XR 2000 mg
DPP-4 inhibitor and TZD			
Alogliptin and pioglitazone	Oseni®	12.5/15 mg 12.5/30 mg 12.5/45 mg 25/15 mg 25/30 mg 25/45 mg	Dosage should be individualized Starting dose should not exceed a daily dose of alogliptin 25 mg/pioglitazone 45 mg Can be taken with or without food

Table 1 continued

Generic name	Brand name	Doses	General dosage and administration[a]
SU/glinide and metformin			
Glipizide and metformin	Generic available	2.5/250 mg 2.5/500 mg 5/500 mg	Dosage should be individualized Starting dose should not exceed the daily doses of glipizide or metformin already being taken BID with the morning and evening meals; may start 2.5/250 mg QD in antihyperglycemic agent-naïve patients, with gradual dose escalation to avoid hypoglycemia due to glipizide and minimize GI side effects due to metformin Maximum daily dose: glipizide 20 mg/metformin 2000 mg
Glyburide and metformin	Glucovance®	1.25/250 mg 2.5/500 mg 5/500 mg	Dosage should be individualized Starting dose should not exceed the daily doses of glyburide (or SU equivalent) or metformin already being taken BID with the morning and evening meals, with gradual dose escalation to avoid hypoglycemia due to glyburide and minimize GI side effects due to metformin Maximum daily dose: glyburide 20 mg/metformin 2000 mg
Repaglinide and metformin	PrandiMet®	1/500 mg 2/500 mg	Individualize starting dose based on the patient's current regimen Start with repaglinide 1 mg/metformin 500 mg BID unless the patient is already taking higher co-administered doses; gradual dose escalation to reduce the risk of hypoglycemia with repaglinide Give in divided doses within 15 min prior to meals; patients who skip a meal should skip the repaglinide/metformin dose for that meal Maximum daily dose: repaglinide 10 mg/metformin 2500 mg daily or repaglinide 4 mg/metformin 1000 mg per meal
TZD and metformin[b]			
Pioglitazone and metformin	Acto*Plus* Met®	15/500 mg 15/850 mg	Individualize starting dose based on the patient's current regimen Administer in divided daily doses with meals to reduce the GI side effects due to metformin Maximum daily dose: pioglitazone 45 mg/metformin 2550 mg; maximum daily dose is pioglitazone 15 mg/metformin 850 mg in patients taking strong CYP2C8 inhibitors (e.g., gemfibrozil)

Table 1 continued

Generic name	Brand name	Doses	General dosage and administration[a]
Pioglitazone and metformin XR	Acto*Plus* Met® XR	15/1000 mg 30/1000 mg	Individualize starting dose based on the patient's current regimen Administer in divided daily doses with meals to reduce GI side effects due to metformin Maximum daily dose: pioglitazone 45 mg/metformin XR 2000 mg; maximum daily dose is 15/1000 mg in patients taking strong CYP2C8 inhibitors (e.g., gemfibrozil)
Rosiglitazone and metformin	Avandamet®	2/500 mg 4/500 mg 2/1000 mg 4/1000 mg	Individualize starting dose based on the patient's current regimen Generally administered in divided doses with meals, with gradual dose escalation to reduce GI side effects largely due to metformin Maximum total daily dose: rosiglitazone 8 mg/metformin 2000 mg
SGLT2 inhibitor and metformin			
Canagliflozin and metformin	Invokamet®	50/500 mg 50/1000 mg 150/500 mg 150/1000 mg	Individualize starting dose based on the patient's current regimen BID with meals, with gradual dose escalation to reduce GI side effects due to metformin Maximum daily dose: canagliflozin 300 mg/metformin 2000 mg
Canagliflozin and metformin XR	Invokamet® XR	50/500 mg 50/1000 mg 150/500 mg 150/1000 mg	Individualize starting dose based on the patient's current regimen Two tablets QD with the morning meal Maximum daily dose: canagliflozin 300 mg/metformin XR 2000 mg
Dapagliflozin and metformin XR	Xigduo® XR	2.5/1000 mg 5/500 mg 5/1000 mg 10/500 mg 10/1000 mg	Individualize starting dose based on the patient's current regimen QD in the morning with meals, with gradual dose escalation to minimize GI side effects due to metformin Maximum daily dose: dapagliflozin 10 mg/metformin XR 2000 mg
Empagliflozin and metformin	Synjardy®	5/500 mg 5/1000 mg 12.5/500 mg 12.5/1000 mg	Individualize starting dose based on the patient's current regimen BID with meals, with gradual dose escalation to reduce GI side effects due to metformin Maximum daily dose: empagliflozin 25 mg/metformin 2000 mg
Empagliflozin and metformin XR	Synjardy® XR	5/1000 mg 10/1000 mg 12.5/1000 mg 25/1000 mg	Individualize starting dose based on the patient's current regimen QD in the morning with meals, with gradual dose escalation to minimize GI side effects due to metformin Maximum total daily dose: empagliflozin 25 mg/metformin XR 2000 mg

Table 1 continued

Generic name	Brand name	Doses	General dosage and administration[a]
Ertugliflozin and metformin	Segluromet®	2.5/500 mg 2.5/1000 mg 7.5/500 mg 7.5/1000 mg	Individualize starting dose based on the patient's current regimen BID with meals, with gradual dose escalation Maximum total daily dose: 7.5 mg ertugliflozin/1000 mg metformin BID
SGLT2 inhibitor and DPP-4 inhibitor			
Dapagliflozin and saxagliptin	Qtern®	10/5 mg	Should only be administered to patients who tolerate 10 mg dapagliflozin QD in the morning with or without food: dapagliflozin 10 mg/saxagliptin 5 mg
Empagliflozin and linagliptin	Glyxambi®	10/5 mg 25/5 mg	Start with empagliflozin 10 mg/linagliptin 5 mg QD in the morning with or without food Dose may be increased to empagliflozin 25 mg/linagliptin 5 mg QD
Ertugliflozin and sitagliptin	Steglujan®	5/100 mg 15/100 mg	Recommended starting dose is 5 mg ertugliflozin/100 mg sitagliptin QD in the morning, with or without food Dose may be increased to 15 mg ertugliflozin/100 mg sitagliptin QD

BID twice daily, *DPP-4* dipeptidyl peptidase-4, *GI* gastrointestinal, *QD* once daily, *SGLT2* sodium glucose cotransporter 2, *SU* sulfonylurea, *T2DM* type 2 diabetes mellitus, *TZD* thiazolidinedione, *XR* extended-release

[a] Information in this table is based on the prescribing information for the available agents. Please see individual prescribing information for dosage with regard to renal impairment, hepatic impairment, drug interactions, special populations, and warnings and precautions

[b] Single-pill combination products containing TZD/SU are available: rosiglitazone/glimepiride (Avandaryl®) and pioglitazone/glimepiride (Duetact®); please refer to prescribing information for details

sodium glucose cotransporter 2 [SGLT2] inhibitor) or an injectable therapy (glucagon-like peptide-1 receptor agonist [GLP-1 RA] or basal insulin) (Fig. 2) [9]. Rather than identify a specific hierarchy for second-line therapies, the ADA suggests consideration of the relative advantages and disadvantages of each medication class to guide treatment individualization (e.g., HbA1c-lowering effect, associated hypoglycemia risk, effects on body weight, major side effects, and costs) [8].

Recommendations for when to initiate either antihyperglycemic monotherapy or dual combination therapy differ somewhat between the algorithms [9, 11]. For patients with goal HbA1c $\leq$ 6.5%, the AACE algorithm recommends initial monotherapy if baseline HbA1c is $<$ 7.5% and initial dual combination therapy if baseline HbA1c is $\geq$ 7.5% [11], whereas the ADA recommends initial dual therapy in patients with baseline HbA1c $\geq$ 9.0% [9]. For patients with substantially elevated HbA1c levels at baseline ($>$ 9%), the AACE/ACE algorithm recommends dual or triple combination therapy. In patients with baseline HbA1c levels $>$ 9% and who are symptomatic, the recommendation includes insulin as a third agent [11]. For patients with baseline HbA1c levels $>$ 10%, the ADA recommends basal insulin therapy (usually with metformin and possibly another non-

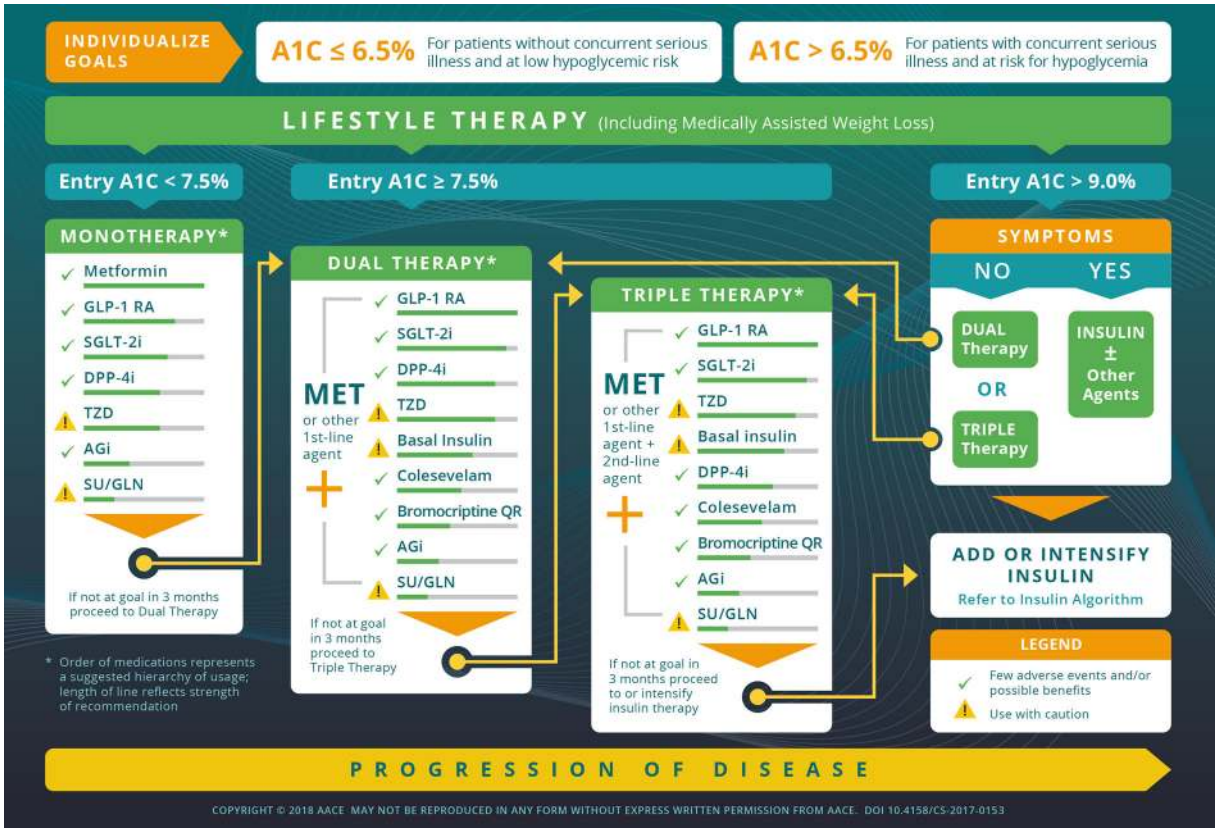


Fig. 1 The AACE and ACE glycemic control algorithm. *A1C* glycated hemoglobin, *AACE/ACE* American Association of Clinical Endocrinologists/American College of Endocrinology, *AGi* alpha-glucosidase inhibitor, *DPP-4i* dipeptidyl peptidase-4 inhibitor, *GLN* glinide, *GLP-1 RA* glucagon-like peptide-1 receptor agonist, *MET* metformin, *QR* quick release, *SGLT-2i* sodium glucose cotransporter 2 inhibitor, *SU* sulfonylurea, *TZD* thiazolidinedione. Reprinted with permission from American Association of Clinical Endocrinologists © 2018 AACE. Garber AJ, Abrahamson MJ, Barzilay JI, et al. AACE/ACE comprehensive type 2 diabetes management algorithm 2018. Endocr Pract. 2018;24(1):91–120

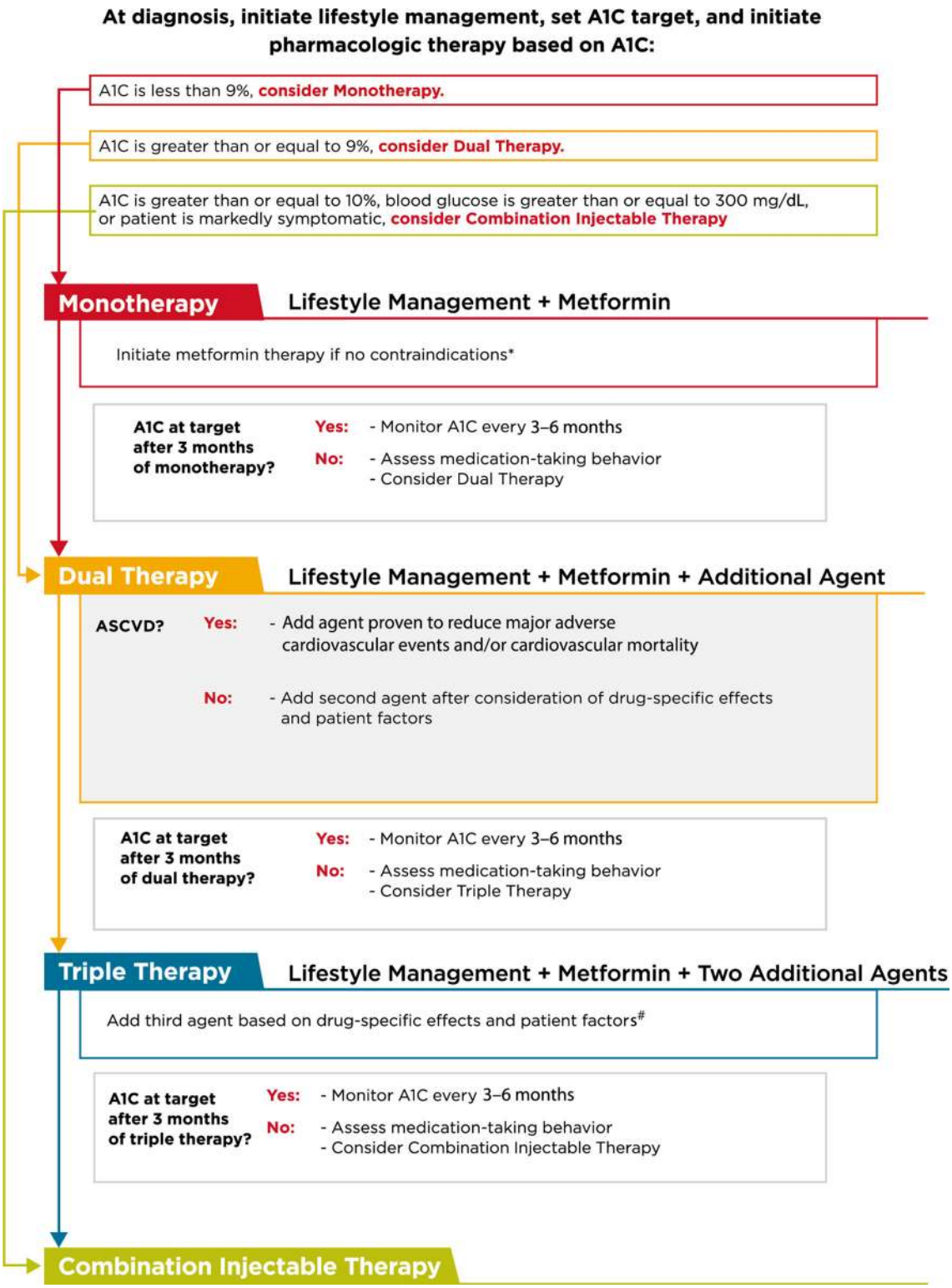
insulin agent). Depending on patient response to this approach, the regimen can be escalated with rapid-acting insulin or another GLP-1 RA [9]. Both organizations recommend advancing therapy when glycemic control is not achieved or maintained after 3 months (i.e., monotherapy to dual therapy, dual therapy to triple therapy and/or injectable agents [including insulin] if needed) [9, 11]. The following sections present model discussions of two hypothetical cases to demonstrate how patient care can be individualized, and suggest combination regimens with appropriate antihyperglycemic agents in accordance with current recommendations.

APPLYING THE ALGORITHMS

Case 1

Traveling Professional with Newly Diagnosed T2DM and Comorbid Conditions

A 52-year-old man with a history of hypertension was recently diagnosed with T2DM at a yearly health screening offered through his employer for renewal of his medical and prescription coverage. His primary care physician evaluated him 1 month later. At the time he was seen, his blood pressure (BP) in the clinic was well controlled (130/80 mmHg) on lisinopril 10 mg daily. His body mass index (BMI) was


At diagnosis, initiate lifestyle management, set A1C target, and initiate pharmacologic therapy based on A1C:
A1C is less than 9%, consider Monotherapy.
A1C is greater than or equal to 9%, consider Dual Therapy.
A1C is greater than or equal to 10%, blood glucose is greater than or equal to 300 mg/dL, or patient is markedly symptomatic, consider Combination Injectable Therapy
Monotherapy
Lifestyle Management + Metformin
Initiate metformin therapy if no contraindications*
A1C at target after 3 months of monotherapy?
Yes: - Monitor A1C every 3–6 months
No: - Assess medication-taking behavior
- Consider Dual Therapy
Dual Therapy
Lifestyle Management + Metformin + Additional Agent
ASCVD?
Yes: - Add agent proven to reduce major adverse cardiovascular events and/or cardiovascular mortality
No: - Add second agent after consideration of drug-specific effects and patient factors
A1C at target after 3 months of dual therapy?
Yes: - Monitor A1C every 3–6 months
No: - Assess medication-taking behavior
- Consider Triple Therapy
Triple Therapy
Lifestyle Management + Metformin + Two Additional Agents
Add third agent based on drug-specific effects and patient factors#
A1C at target after 3 months of triple therapy?
Yes: - Monitor A1C every 3–6 months
No: - Assess medication-taking behavior
- Consider Combination Injectable Therapy
Combination Injectable Therapy

◀**Fig. 2** Antihyperglycemic therapy in T2DM: general recommendations. *If a patient is intolerant of, or has contraindications to metformin, agents from another class should be considered. #GLP-1 receptor agonists and DPP-4 inhibitors should not be prescribed in combination. Agents with evidence of cardiovascular risk reduction should be considered for patients with established atherosclerotic cardiovascular disease. Reproduced with permission from American Diabetes Association [10], https://doi.org/10.2337/dc18-S008 and http://care.diabetesjournals.org/content/41/Supplement_1/S73

28 kg/m^2. His blood work indicated T2DM with an HbA1c of 8.3%. His post-prandial C-peptide level was modestly elevated (4 nmol/L), a result also supporting a diagnosis of T2DM. He had no history of CVD. An ophthalmology evaluation revealed no evidence of retinopathy. While he reported a busy lifestyle with frequent work-related travel, he indicated that he is motivated to pursue lifestyle changes.

Case Discussion

The presence of T2DM and hypertension is certainly associated with increased CVD risk. For this patient, a BP target of $< 140/90$ or $< 130/< 80$ mmHg is desirable [11]. Lifestyle interventions, including medical nutrition therapy and appropriately prescribed physical activity, are important for the management of both conditions [9]. A target HbA1c goal of $< 7.0\%$, or even $\leq 6.5\%$ (if it can be accomplished without hypoglycemia), would seem appropriate because of the short duration of the patient's disease, his potential for long life expectancy, and the absence of known CVD.

However, because of his high baseline HbA1c level ($> 7.5\%$), this patient is unlikely to achieve an HbA1c of $\leq 6.5\%$ with single-agent antihyperglycemic treatment. Therefore, the clinician suggested initial combination therapy with metformin and another oral agent as recommended by the 2018 AACE/ACE algorithm [11]. The potential benefit of initial combination therapy for those with higher baseline HbA1c levels was assessed in a post hoc analysis of patients who received the metformin/sitagliptin single-pill combination vs. metformin monotherapy as initial treatment [13]. Among those with a baseline HbA1c of $> 7.5\%$ to 9.0%, 48.6% who initiated single-pill combination therapy achieved an HbA1c of $\leq 6.5\%$, and 69.4% achieved an HbA1c $< 7.0\%$ at week 18 vs. 23.1% ($p < 0.001$) and 46.7% ($p < 0.01$) of patients who initiated metformin monotherapy [13]. A randomized controlled study of combination therapy with linagliptin and metformin vs. linagliptin alone in newly diagnosed T2DM patients with marked hyperglycemia at baseline (mean HbA1c 9.8%) demonstrated that at week 24, 61% of patients in the linagliptin/metformin group, vs. 40% in the linagliptin group, achieved an HbA1c concentration of $< 7.0\%$ at week 24 ($p = 0.0008$) [14]. A systematic review and meta-analysis of 15 randomized clinical trials further supports the glycemic benefits of initial combination therapy with metformin plus an additional oral antihyperglycemic agent (TZD, insulin secretagogue, DPP-4 inhibitor, or SGLT2 inhibitor) compared with metformin alone [15]. Initial combination therapy resulted in significant improvements compared with monotherapy for changes in HbA1c (weighted mean difference [WMD] -0.43%; 95% confidence interval [CI] -0.56 to -0.30), reductions in fasting plasma glucose (WMD -14.30 mg/dL; 95% CI -16.09 to -12.51), and attainment of goal HbA1c $< 7\%$ (relative risk [RR] 1.40; 95% CI 1.33–1.48).

For this patient, metformin is a logical choice for one of the agents in a combination regimen. Of the options listed for add-on therapy in the ADA algorithm, an SU or a TZD may not be the best choices for this overweight patient because they are associated with weight gain [9]; also, these agents are listed as lower priority options in the AACE algorithm (Fig. 1) [11]. Although the addition of a GLP-1 RA to metformin is an efficacious option recommended in both algorithms, some patients may be reluctant to use an injectable agent early in the course of their T2DM. Therefore, this clinician suggested initial combination therapy with metformin and either a DPP-4 inhibitor or an SGLT2 inhibitor for this patient, which is consistent with current treatment guidance.

Efficacy Considerations with a Combination of Metformin and a DPP-4 Inhibitor

The combination of metformin and a DPP-4 inhibitor provides agents with complementary mechanisms of action. Whereas metformin

decreases hepatic glucose production, increases insulin sensitivity (to a very modest degree) [16], and increases GLP-1 secretion from the intestinal L-cell, the DPP-4 inhibitors increase insulin secretion by inhibiting the degradation of incretin hormones—GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) [17]. The combination of these two therapeutic classes can provide clinically relevant glycemic control [9, 11].

Not surprisingly, results from several studies have shown that initial combination therapy with metformin and a DPP-4 inhibitor provides greater improvement in glycemic control than monotherapy with either agent [14, 18–20]. For example, results from a 24-week study with linagliptin plus metformin demonstrated greater placebo-corrected reductions in HbA1c with initial combination therapy than monotherapy with either component: − 1.7% for linagliptin 5 mg/metformin 2000 mg, − 1.3% for linagliptin 5 mg/metformin 1000 mg, − 1.2% for metformin 2000 mg, − 0.8% for metformin 1000 mg, and − 0.6% for linagliptin 5 mg (all $p < 0.0001$) [18]. Participants who continued combination therapy in a 1-year extension maintained their HbA1c reductions. The retrospective Comparative Outcomes Study of Metformin Intervention versus Conventional (COSMIC) Approach study examined the durability of initial combination therapy with sitagliptin and metformin in 890 patients with a mean baseline HbA1c of 8.6 ± 1.1%, who were followed every 3–6 months in routine clinical practice [20]. After 1 year of combination treatment, 72.2% of patients had an HbA1c reduction of ≥ 0.8% or attained a target HbA1c ≤ 7.0%. After 4 years, 35.4% of the patients maintained the response, with a mean HbA1c of 7.0 ± 0.9%. In another double-blind study, 316 patients with T2DM (mean baseline HbA1c, 9.8%) were randomized to linagliptin 5 mg once daily plus metformin twice daily (2000 mg/day maximum) or to linagliptin monotherapy [14]. The 24-week adjusted mean (± standard error) changes from baseline in HbA1c were − 2.8 ± 0.1% with the combination and − 2.0 ± 0.1% with linagliptin monotherapy, a treatment difference of − 0.8% (95% CI − 1.1 to − 0.5; $p < 0.0001$) [14].

Safety Considerations with Metformin and DPP-4 Inhibitor Combination

Each antihyperglycemic agent has a well-characterized risk–benefit profile that will need to be considered along with existing comorbidities (e.g., CVD, history of pancreatitis and/or pancreatic cancer, degree of renal dysfunction) when deciding on an appropriate therapeutic regimen. As a class, DPP-4 inhibitors are generally safe and well tolerated, and are associated with a low risk of hypoglycemia (except when used with insulin or insulin secretagogues) and weight neutrality [21].

Cardiovascular safety is another consideration with regard to T2DM therapy selection. Data from three prospective, randomized, long-term cardiovascular outcome trials (CVOTs) demonstrated that the DPP-4 inhibitors alogliptin (Cardiovascular Outcomes Study of Alogliptin in Patients with Type 2 Diabetes and Acute Coronary Syndrome; EXAMINE), saxagliptin (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction; SAVOR-TIMI 53), and sitagliptin (Trial to Evaluate Cardiovascular Outcomes after Treatment with Sitagliptin; TECOS), when given in addition to standard care, do not increase or decrease the risk of major adverse cardiovascular events (MACE) in patients with a previous cardiovascular event or at risk for such an event [22–24]. However, results for the risk of hospitalization for heart failure were conflicting, with a statistically significant increase in risk reported for saxagliptin [24, 25], a nonsignificant increase with alogliptin [23, 26], and no increase with sitagliptin [22, 27]. As a result, a warning regarding the use of saxagliptin and alogliptin in patients with known heart failure risk factors was added to the prescribing information for saxagliptin and alogliptin [28–30].

While heart failure has not been associated with therapy with either linagliptin or sitagliptin, a warning was recently added to the US prescribing information for these agents [31, 32], in response to the association noted between heart failure and DPP-4 inhibitor treatment observed in CVOTs for two other members of this class (SAVOR-TIMI 53 and EXAMINE). However, to date, the number of

heart failure events identified in clinical studies with linagliptin has been small, and reported in studies that were not specifically designed to assess cardiac failure. At present, two cardiovascular outcome trials (Cardiovascular Outcome Trial of Linagliptin Versus Glimepiride in Type 2 Diabetes; CAROLINA) [33, 34] and (Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients with Type 2 Diabetes Mellitus; CARMELINA) [35] are underway to assess the long-term impact of linagliptin treatment on cardiovascular outcomes.

Consistent with the results of CVOTs to date, a recent meta-analysis of data from 36 randomized trials of 54,664 patients reported by Rehman et al. [36] found no increase in risk of all-cause mortality, cardiovascular mortality, myocardial infarction, or stroke, but revealed a modest but significant increase in the risk of heart failure (RR 1.13; 95% CI 1.01–1.26) with DPP-4 inhibitors compared with placebo [36].

Post-marketing cases of acute pancreatitis and pancreatic cancer have been reported in patients receiving incretin-based therapy [21]. However, clearly identifying a pancreas-related safety signal with any T2DM treatment is challenging, because the incidence of pancreatitis in patients with T2DM is approximately threefold higher than in age- and sex-matched patients without T2DM [37]. The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) carefully studied post-marketing and clinical trial data and concluded that current evidence does not support a causal relationship between incretin-based therapies and pancreatitis or pancreatic cancer. They further indicated that warnings regarding possible risks of pancreatitis and pancreatic cancers are adequately reflected in DPP-4 inhibitor labeling, and that they would continue to monitor data from ongoing trials, including the CVOTs.

In the SAVOR-TIMI 53 trial, the risks for acute pancreatitis were very low and similar between saxagliptin and placebo, whereas rates of pancreatic cancer were numerically, but not significantly, lower with saxagliptin [38]. In the TECOS trial, pancreatitis and pancreatic cancer were uncommon events, with no significant difference between the sitagliptin and placebo groups in the reported rates of each. However, pancreatitis did develop in a numerically larger number of sitagliptin-treated participants, whereas pancreatic cancer developed in fewer sitagliptin-treated participants [9]. A meta-analysis combining data from these two trials, as well as the EXAMINE study, demonstrated a significantly increased risk of acute pancreatitis with DPP-4 inhibitor treatment vs. placebo (odds ratio [OR] 1.7; 95% CI 1.13–2.82; $p = 0.013$) [39]. These results are consistent with findings from the meta-analysis reported by Rehman et al. [36], which showed an increased risk of acute pancreatitis with DPP-4 inhibitor therapy (RR 1.57; 95% CI 1.03–2.39) [36].

As a practical matter, patients who are receiving incretin-based therapy need to be aware of the signs and symptoms of pancreatitis, and should discontinue these agents if clinical manifestations are detected. In cases where pancreatitis is confirmed, these medications should not be restarted. At present, it is unknown if a history of pancreatitis will lead to a higher risk of pancreatitis in patients taking incretin-based therapy. However, FDA prescribing information for albiglutide [40], dulaglutide [41], exenatide [42], and liraglutide [43] recommend discontinuation if pancreatitis is suspected, and use of a different agent if pancreatitis is confirmed. In patients with a history of pancreatitis, FDA prescribing information for albiglutide [40], dulaglutide [41], and exenatide [42] recommend the use of a different antidiabetic therapy, and this guidance would seem reasonable for patients taking DPP-4 inhibitors as well. Liraglutide has been studied in a limited number of patients who have a history of pancreatitis, and as a result, it is not known if these patients are at higher risk for development of pancreatitis [43].

Efficacy Considerations with Metformin and SGLT2 Inhibitor Combination

The SGLT2 inhibitors represent a recently available class of oral antihyperglycemic agents with a unique mechanism of action that is independent of insulin. They reduce hyperglycemia by inhibiting the reabsorption of glucose from the proximal tubule of the kidney,

leading to urinary glucose excretion. Because the glycemic efficacy of SGLT2 inhibitors is dependent on renal function, particularly the estimated glomerular filtration rate (eGFR), SGLT2 inhibitor treatment is contraindicated in those with severe renal impairment (eGFR < 30 mL/min/1.73 m^2), end-stage renal disease, or on dialysis [44, 45]. Treatment with dapagliflozin should not be initiated (and should be discontinued) in patients with an eGFR < 60 mL/min/1.73 m^2 [49], and empagliflozin and canagliflozin should not be initiated (and should be discontinued) in patients with an eGFR < 45 mL/min/1.73 m^2 [44, 45]. The dose of canagliflozin should be limited to 100 mg once daily in patients with an eGFR of 45 to < 60 mL/min/1.73 m^2. Also, in patients who have an eGFR ≥ 60 mL/min/1.73 m^2 and who tolerate 100 mg once daily, the canagliflozin dose can be increased to 300 mg once daily if additional glycemic control is needed [45]. Ertugliflozin should not be initiated in patients with an eGFR of 30 to < 60 mL/min/1.73 m^2, or used in patients with an eGFR < 30 mL/min/1.73 m^2. In patients with an eGFR of 30 to < 60 mL/min/1.73 m^2, ongoing use of ertugliflozin is not recommended [46].

The complementary mechanisms of action of metformin and an SGLT2 inhibitor allow the combination to provide good efficacy and relative safety [9]. Six single-pill combinations of metformin and an SGLT2 inhibitor are available in the USA: canagliflozin/metformin [47], canagliflozin/metformin extended-release (XR) [48], dapagliflozin/metformin XR [49], empagliflozin/metformin [50], empagliflozin/metformin XR [50], and ertugliflozin/metformin [51] (Table 1). Pharmacokinetic studies have demonstrated that these single-pill combinations are bioequivalent to the monotherapies administered separately [48, 52].

Results from several studies demonstrate that initial combination therapy with an SGLT2 inhibitor and metformin or metformin XR leads to reductions in HbA1c and body weight that are greater than those achieved with either agent as initial monotherapy [53, 54]. For example, in two 24-week trials of drug-naïve patients with T2DM, reductions in HbA1c from baseline (9.03–9.21%) were significantly greater with dapagliflozin 5 or 10 mg plus metformin XR (5 mg, − 2.05%; 10 mg, − 1.98%) than with either agent as monotherapy (dapagliflozin 5 mg, − 1.19%; 10 mg, − 1.45%; metformin − 1.35% and − 1.44%; all $p < 0.0001$). Body weight was significantly reduced with combination therapy (5 mg, − 2.7 kg; 10 mg, − 3.3 kg) vs. metformin (− 1.29 and − 1.36 kg; $p < 0.0001$) [54]. Approximately half of patients receiving combination therapy reached their HbA1c goal. Reductions in systolic BP (SBP) were modest in the SGLT2 inhibitor treatment arms (− 2.9 to − 4.2 mmHg). Similarly, a 26-week study of 1186 treatment-naïve patients with T2DM demonstrated that both initial combination regimens of canagliflozin 100 or 300 mg plus metformin significantly reduced HbA1c from a mean baseline of 8.8% compared with metformin alone (median dose, 2000 mg/day) (treatment differences, − 0.46% and − 0.48%, respectively; $p = 0.001$) or canagliflozin alone (treatment differences, − 0.40% and − 0.36%, respectively; $p = 0.001$) [53]. In addition, greater proportions of patients achieved an HbA1c target of $< 7\%$ with the canagliflozin 100 and 300 mg plus metformin combinations than with metformin monotherapy (50%, 57%, and 43%, respectively). Weight loss was significantly greater with combination therapy (100 or 300 mg) vs. monotherapy (− 3.2, − 3.9 vs. − 1.9 kg; both $p = 0.001$). Modest, non-significant reductions in SBP were observed in the two combination arms compared with metformin monotherapy. Also, a 24-week, placebo-controlled trial evaluated the initial combination therapy of empagliflozin (12.5 or 5 mg twice daily) plus metformin (500 or 1000 mg twice daily) vs. the respective monotherapies in drug-naïve patients with T2DM [53]. Reductions in HbA1c from baseline (8.6–8.9%) were significantly greater in patients receiving empagliflozin and metformin twice daily than in those receiving empagliflozin once daily (treatment difference, − 0.57% to − 0.72%; $p < 0.001$) or metformin twice-daily regimens (treatment difference, − 0.33% to − 0.79%; $p < 0.001$) [53]. At week 24, decreases in weight from baseline were significantly greater with empagliflozin and metformin twice daily compared with the metformin twice-daily

regimens (treatment difference, − 2.2 to − 2.5 kg; $p < 0.001$) [53]. The proportions of patients on combination therapy who achieved an HbA1c of < 7% ranged from 57% to 70% at 24 weeks. A significant reduction in SBP was seen with empagliflozin plus metformin twice daily compared with the metformin twice-daily regimens (treatment difference, − 2.8 to − 4.0 mmHg; $p < 0.05$) [53].

Finally, a 26-week, double-blind trial evaluated the efficacy and safety of ertugliflozin in T2DM patients who were inadequately controlled (HbA1c, 7.0–10.5%) after a minimum of 8 weeks of metformin therapy (≥ 1500 mg/day) [55]. Patients ($N = 621$) were randomized 1:1:1 to placebo, or ertugliflozin 5 or 15 mg QD.

The baseline HbA1c was 8.1%, and at week 26, the placebo-adjusted least-squares mean (95% CI) change was − 0.7% (− 0.9, − 0.5; ertugliflozin 5 mg) and − 0.9% (− 1.0, − 0.7; ertugliflozin 15 mg), both $p < 0.001$ [55]. At week 26, the mean (SD) reductions from baseline in HbA1c were larger in patients who had higher HbA1c levels at baseline (< 8.0%: placebo, 0 [0.9]; ertugliflozin 5 mg, − 0.4 [0.7]; ertugliflozin 15 mg, − 0.5 [0.6]); and in patients with HbA1c ≥ 9.0% at baseline, the reductions were − 0.8 [1.0], − 1.7 [1.1], and − 1.8 [0.8], respectively [55]. At week 26, reductions in fasting plasma glucose were significantly greater with ertugliflozin and metformin, when compared to placebo and metformin (treatment difference, − 1.4 to − 2.1 mmol/L; $p < 0.001$). Also at week 26, more patients on ertugliflozin 5 mg (35%) or 15 mg (40%) had HbA1c levels < 7.0% compared to patients on placebo (16%) [55].

Other parameters also demonstrated favorable changes after 26 weeks of treatment with ertugliflozin. These include reductions in body weight, which were significantly greater with ertugliflozin and metformin vs. placebo and metformin (treatment difference, − 0.7 to − 1.6 kg; $p < 0.001$), and in DBP, with a reported treatment difference of − 1.4 ($p = 0.013$) to − 2.0 mmHg ($p = 0.001$) with metformin and ertugliflozin (5 and 15 mg, respectively) vs. placebo [55].

Cardiovascular Considerations with the Combination of Metformin and an SGLT2 Inhibitor

The EMPAgliflozin Removal of Excess Glucose: Cardiovascular OUTCOME Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME®) study ($N = 7020$), the first CVOT to report results for this class, examined the effect of empagliflozin in addition to standard care in patients with T2DM and established CVD [56]. Approximately 75% of all patients were receiving metformin as part of their background therapy at baseline. Patients receiving empagliflozin (pooled 10 and 25 mg doses) experienced significantly lower rates of 3-point MACE (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) than those in the placebo group over a median observation period of 3.1 years (10.5% vs. 12.1%; hazard ratio [HR] 0.86; 95% CI 0.74–0.99; $p = 0.04$ for superiority). Importantly, patients treated with empagliflozin also experienced significantly lower rates of death from cardiovascular causes (38% relative risk reduction) and death from any cause (32% relative risk reduction), but no differences in the relative risks for myocardial infarction or stroke. On the basis of the results of this trial, empagliflozin received an indication to reduce the risk of cardiovascular death in adult patients with T2DM and established CVD [44]. Of note, empagliflozin was associated with reduced risk of hospitalization for heart failure (35% relative risk reduction; $p = 0.002$) [56]. The composite renal endpoint of incident or worsening nephropathy was also significantly reduced in the empagliflozin group (39% relative risk reduction; $p < 0.001$); however, unlike cardiovascular events, renal events were not prospectively adjudicated [57].

Recently, data from the Canagliflozin Cardiovascular Assessment Study (CANVAS) was combined with data from the CANVAS-Renal (CANVAS-R) study and analyzed using an integrated approach. The CANVAS Program included 10,142 patients from both studies with T2DM who had a history of symptomatic atherosclerotic CVD and were aged 30 years or older or who had two or more risk factors for CVD and were aged 50 years or older [58]. Patients were randomly assigned to either

canagliflozin (100 or 300 mg once daily) or placebo on top of standard care. At baseline, approximately 77% of the patients were on metformin. The mean follow-up time was 188 weeks (median approximately 126 weeks) [58].

The rate of the primary outcome (3-point MACE: cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) was significantly lower with canagliflozin than with placebo (26.9 vs. 31.5 participants/1000 patient-years; HR 0.86; 95% CI 0.75–0.97; $p = 0.02$ for superiority). The results also suggested canagliflozin was associated with benefits with regard to renal outcomes (progression of albuminuria [HR 0.73; 95% CI 0.67–0.79]; composite outcome of a sustained 40% reduction in eGFR, need for renal-replacement therapy, or death from renal causes [HR 0.60; 95% CI 0.47–0.77]) [58].

The Comparative Effectiveness of Cardiovascular Outcomes in New Users of Sodium-Glucose Cotransporter-2 Inhibitors (CVD-REAL) study was a large retrospective, observational analysis of data from patients with T2DM that examined whether results from the CVOTs could be applied in real-world clinical practice to patients with a broader CV risk profile [59]. This study was based on data from health records across six countries (Denmark, Germany, Norway, Sweden, UK, and USA) and included 154,528 new users of SGLT2 inhibitor therapy who were matched with an equal number of new users of other antihyperglycemic agents. The primary outcome was the risk of hospitalization for heart failure; secondary outcomes were all-cause death and the composite of heart failure hospitalization or all-cause death [59]. Canagliflozin, dapagliflozin, and empagliflozin accounted for 53%, 42%, and 5% of the total exposure time in the SGLT2 inhibitor class, respectively. Treatment with SGLT2 inhibitors was associated with a lower risk of heart failure hospitalization (HR 0.61; 95% CI 0.51–0.73; $p < 0.001$), death (HR 0.49; 95% CI 0.41–0.57; $p < 0.001$), and the composite of heart failure hospitalization or death (HR 0.54; 95% CI 0.48–0.60; $p < 0.001$) compared with treatment with other antihyperglycemic drugs [59]. Although the results from CVD-REAL suggest that the reported cardiovascular benefits of SGLT2 inhibitors are a class effect, observational studies do not provide the same level of evidence as randomized controlled clinical trials because of biases that may result from variable patient and/or data selection, and limited standardization of patient outcomes [60].

Safety Considerations with Metformin and SGLT2 Inhibitor Combinations

As a class, the SGLT2 inhibitors have a generally favorable benefit-to-risk profile. Because of their mechanism of action, this class is not associated with an increased risk of hypoglycemia, unless combined with insulin or insulin secretagogues [44–46, 61, 62]. In trials of dapagliflozin, canagliflozin, or empagliflozin in combination with metformin as initial combination therapy, there were no significant differences in the incidence of hypoglycemia between canagliflozin plus metformin vs. metformin monotherapy [53], dapagliflozin plus metformin vs. metformin monotherapy [54], or empagliflozin plus metformin vs. metformin monotherapy [53]. However, when ertugliflozin was added to the regimens of T2DM patients inadequately controlled on metformin, the rates of documented hypoglycemia were higher in the ertugliflozin groups (7.2% in the 5 mg arm, 7.8% in the 15 mg arm, compared to 4.3% in the placebo arm) [55]. As discussed above, therapy with SGLT2 inhibitors is also associated with modest weight loss.

The most common adverse events (AEs) associated with use of SGLT2 inhibitors are considered related to the pharmacologically elevated level of glucose in the urine, increasing the risk of osmotic diuresis, genital mycotic infections, and less frequently, urinary tract infections (UTIs). Osmotic diuresis and subsequent intravascular volume contraction may lead to volume-related AEs, such as hypotension, particularly in elderly individuals or those who have predisposing risk factors (e.g., low SBP, diuretic use) [44–46, 62]. Genital mycotic infections are the most frequent SGLT2-associated AE, and occur more frequently in women, uncircumcised men, and in patients with a history of such infections [44–46, 62, 63].

Patients can be counseled to exercise proper hygiene [64].

Data showing a risk of UTIs associated with SGLT2 inhibitor therapy are inconsistent. Analysis of data from 12 randomized clinical trials of dapagliflozin as monotherapy, or as add-on therapy, showed a slight increase in risk of UTIs with dapagliflozin 5 and 10 mg (5.7% and 4.3%, respectively) vs. placebo (3.7%) [65]. In contrast, a meta-analysis of 10 randomized canagliflozin trials reported a similar incidence of UTIs between canagliflozin and placebo (RR 1.19; 95% CI 0.82–1.73; $p = 0.36$) or other comparators (RR 1.18; 95% CI 0.84–1.64; $p = 0.34$) [66]. In a pooled analysis of data from 17 clinical trials and six extension studies with empagliflozin, the incidence of events consistent with UTI was similar for placebo and empagliflozin 10 and 25 mg (11.3, 10.4, and 9.4/100 patient-years, respectively) [67]. Of note, post-marketing reports have identified infrequent, yet serious kidney infections, including urosepsis and pyelonephritis, arising in patients with UTIs taking SGLT2 inhibitors [68]. Patients should be evaluated for signs and symptoms of UTIs, and such infections should be treated promptly when indicated [44–46, 62]. In addition, a warning and precaution regarding the potential for acute kidney injury (AKI) has been added to US SGLT2 inhibitor labels following reports from post-marketing surveillance [68]. Before therapy initiation, clinicians should consider if patients have predisposing factors for renal insult (e.g., hypovolemia; chronic renal insufficiency; congestive heart failure; concomitant medication use, such as diuretics, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, or nonsteroidal anti-inflammatory drugs) [44–46, 62]. If AKI does occur, SGLT2 inhibitor therapy should be promptly discontinued.

In addition, rare, but serious, cases of diabetic ketoacidosis (DKA) have been reported in conjunction with SGLT2 inhibitor use in post-marketing surveillance [68]. Some of these cases were reported as euglycemic DKA, where blood glucose levels were not markedly elevated (i.e., < 250 mg/dL), a distinction that can make the initial diagnosis more difficult [69]. Many cases of DKA were reported in either T2DM patients who were also treated with insulin or in type 1 diabetes patients (SGLT2 inhibitors are not indicated for the treatment of type 1 diabetes) [70]. Moreover, patients presenting with DKA often had a predisposing factor such as a significant concurrent illness, myocardial infarction, severe infection, stroke, surgery, or reduced insulin doses; or were experiencing stressful situations such as reduced food and fluid intake, excessive exercise, or recent alcohol intake [69, 70]. Since the initial case reports, data from clinical trial programs have confirmed that the incidence of DKA in patients on SGLT2 inhibitors is infrequent [11, 55, 67, 69–71].

Other less common AEs need to be considered when selecting among SGLT2 inhibitor therapies. In pooled data from nine clinical trials, canagliflozin was associated with bone fractures (1.4, 1.5, and 1.1/100 patient-years for canagliflozin 100, 300 mg, and comparators, respectively) [45]. A meta-analysis showed that the increase in bone fracture risk was primarily driven by results from the CANVAS trial that included older patients with increased risk of CVD and a low baseline eGFR, and suggested that it may be related to indirect effects such as falls resulting from AEs related to volume depletion [72]. In the adjudicated analysis of CANVAS Program data, higher rates of all bone fractures were reported for canagliflozin compared with placebo (15.4 vs. 11.9 participants with fracture/1000 patient-years; HR 1.26; 95% CI 1.04–1.52), with a similar pattern for low-trauma fractures (11.6 vs. 9.2 participants with fracture/1000 patient-years; HR 1.23; 95% CI 0.99–1.52) [58]. However, these events were not homogenously reported between the CANVAS and CANVAS-R studies; all bone fractures and low-trauma fractures were higher in the canagliflozin arm vs. placebo in the CANVAS study (both $p \leq 0.005$), but not in the CANVAS-R study.

Regarding other SGLT2 inhibitors, a pooled analysis of clinical trial data reported no increase in fracture risk with empagliflozin compared with placebo [67]. For dapagliflozin, a numeric imbalance of fractures was reported in a study of patients with moderate renal impairment, but this concern is not listed under

warnings and precautions in the US prescribing information for this agent [62]. Data from the CANVAS Program also demonstrated a low incidence, but an increased risk of amputation with canagliflozin (6.3 vs. 3.4 participants/1000 patient-years for canagliflozin vs. placebo, respectively; HR 1.97; 95% CI 1.41–2.75). The amputations were primarily at the level of the toe or metatarsal [58]. The risk was highest among patients with a history of amputation or peripheral vascular disease. As a result of these findings, the FDA has required the addition of a boxed warning to the prescribing information for canagliflozin-containing products [45, 47, 48, 73].

Finally, initial clinical trials indicated potentially higher rates of breast cancers and bladder cancers with dapagliflozin treatment, but these reports may have been artifacts of early vigilance. No such associations have been reported in subsequent clinical trials (as would be expected if these were drug-related adverse events), although the prescribing information notes the imbalance in the number of cases between treatment groups in the early studies, and states that the agent should not be used in patients with active bladder cancer, and should be used with caution in those with a prior history [74]. These AEs have also not been associated with other SGLT2 inhibitors, including empagliflozin [67] or canagliflozin [75].

The above combinations include metformin, and gastrointestinal (GI) symptoms are well-recognized side effects of metformin therapy. In contrast to immediate-release (IR) formulations, the delivery system for XR formulations provides a slower release of metformin into the upper GI tract, which may improve GI tolerance [76]. In one small study, most patients who switched from metformin IR to XR reported improvement in GI AEs (e.g., diarrhea) [77]. These findings are consistent with a retrospective study that showed significantly lower frequencies of any GI AE, and diarrhea, in patients switched from metformin IR to XR formulations [78]. Minimization of patient-reported AEs may facilitate patient adherence. An analysis of data from 2074 patients with T2DM who participated in the US National Health and Wellness survey showed significantly lower regimen adherence and decreased satisfaction with therapy by those who reported more than one tolerability issue; this trend magnified as the number of reported tolerability issues increased [79]. Patient adherence is important to the overall success of any therapeutic approach. A meta-analysis of data from seven studies reported improved patient adherence (10–13% higher) when patients with T2DM were started on a single-pill combination tablet. This analysis suggested that patients with T2DM who were treated with single-pill combination tablets may also report improved satisfaction and lower direct medical costs when compared to patients on regimens requiring the consumption of multiple pills every day [80].

Case Conclusion

Initial combination therapy with metformin, paired with a DPP-4 inhibitor or an SGLT2 inhibitor (or a combination of a DPP-4 inhibitor and an SGLT2 inhibitor in patients with a contraindication or intolerance to metformin [81] in accordance with the current AACE algorithm), would be reasonable treatment options for this young patient who does not have overt CVD, but who does have related risk factors including hypertension, elevated HbA1c levels, and excess body weight. The patient could be started on a single-pill combination due to his busy lifestyle. He should be taught to perform self-monitoring of blood glucose (SMBG) at a frequency determined by him and his clinician. Over time, SMBG values could help inform his clinician of any potential need to adjust the dosing or choice of agent in the patient's antihyperglycemic regimen, and also to monitor the ongoing impact of lifestyle choices on his blood glucose levels.

Although the patient in this case has a history of hypertension and is overweight, he does not meet the high-risk inclusion criteria that characterized the EMPA-REG OUTCOME or the CANVAS patient populations. However, results from the CVD-REAL study suggest that high-risk patients with T2DM who do not have established CVD may benefit from treatment with SGLT2 inhibitors. If an SGLT2 inhibitor is included in the initial regimen, the patient should have a baseline renal function and

volume status assessment, and a follow-up appointment to repeat these measures within a month or two after starting treatment.

For agents in which dose adjustments are recommended depending on patient factors, the necessary assessments and adjustments should be scheduled as needed. In addition, at the follow-up visit, the patient's progress toward meeting his BP, glucose, and HbA1c goals should be monitored. At that assessment, the patient's regimen, including pharmacotherapy, can be adjusted as needed.

Case 2

Obese T2DM Patient with Elevated Glucose Levels

A 42-year-old woman with T2DM has returned to her primary care clinician for a follow-up visit. She reports good adherence to her twice-daily metformin 1000 mg regimen; however, her SMBGs indicate elevations in blood glucose, averaging 180–200 mg/dL. She is concerned that she may need a second agent. Her BP is 130/80 mm Hg on lisinopril 10 mg daily. Her height is 5′2″ (1.57 m) and she weighs 170 lb (77.1 kg), indicating a BMI of 31 kg/m^2 and is therefore considered obese [82]. Her blood work shows an HbA1c level of 8.2%.

Case Discussion

Of the available add-on antihyperglycemic agents, weight gain is associated with TZDs, SUs, glinides, and insulin; weight neutrality is associated with DPP-4 inhibitors and alpha-glucosidase inhibitors; and weight loss is generally seen with GLP-1 RAs and SGLT2 inhibitors [8, 11]. Given her weight loss goals and the need for an HbA1c reduction of approximately − 1.2%, a GLP-1 RA would be a reasonable choice to add to her current metformin therapy. This strategy is supported by current algorithms and provides an option for substantial HbA1c lowering while minimizing hypoglycemia and offering the potential for modest weight loss [83].

The addition of a GLP-1 RA to metformin is a good option due to the complementary mechanisms of action of the two agents. The GLP-1 RAs have varying structural homology to human GLP-1 with attached moieties (including long-chain fatty acids, immunoglobulins, or albumin), which confer resistance to DPP-4 degradation and other properties leading to protracted action [84]. With enhanced pharmacodynamics, these agents mimic GLP-1 and stimulate insulin release from the pancreas, suppress glucagon secretion (both in a glucose-dependent manner), inhibit gastric emptying, and may lower overall appetite and food intake [17].

Another option would be the addition of both a DPP-4 inhibitor and an SGLT2 inhibitor. The combination of these two agents provides two complementary mechanisms of action; the SGLT2 inhibitor leads to urinary excretion of glucose, and the DPP- 4 inhibitor limits the degradation of endogenous incretin hormones GLP-1 and GIP. Finally, basal insulin could be added to the existing metformin regimen to reduce this patient's hyperglycemia [85], but the initiation, titration, and optimization of "add-on" insulin therapies is beyond the scope of this review. For a detailed discussion of the inclusion of insulin and related therapies in an antihyperglycemic regimen, please see the relevant guidelines [8, 9, 11]. The remainder of the case discussion will focus on the first two options mentioned.

Efficacy Considerations with a Combination of Metformin and a GLP-1 RA

Controlled trials in individuals with T2DM have shown that the addition of a GLP-1 RA to metformin therapy provides greater improvements in glycemic control than the addition of a DPP-4 inhibitor [86, 87]. For example, in the Diabetes therapy Utilization: Researching changes in A1c, weight and other factors Through Intervention with exenatide ONce weekly (DURATION-2) trial of patients on background metformin, significantly greater improvements in HbA1c from baseline to week 26 were demonstrated in patients who received exenatide extended-release (− 1.5%) than those who received either sitagliptin (− 0.9%) or pioglitazone (− 1.2%), and significantly greater weight loss was observed (exenatide, − 2.3 kg; sitagliptin, − 0.8 kg; pioglitazone, + 2.8 kg)

[87]. Similarly, a meta-analysis of 21 controlled trials demonstrated a more robust reduction in HbA1c with longer-acting GLP-1 RA therapy (liraglutide or exenatide LAR [extended-release] once daily) compared with twice-daily exenatide or DPP-4 therapy when added to metformin [88].

With newer once-weekly GLP-1 RA therapies, reductions from baseline in HbA1c range from − 0.7% to − 1.6% with the use of long-acting GLP-1 RA as monotherapy (e.g., exenatide extended-release, dulaglutide [41], or albiglutide [40, 89]). These agents are also efficacious as components of dual-therapy combination regimens. For example, the Assessment of Weekly AdministRation of LY2189265 (dulaglutide) in Diabetes-6 (AWARD-6) trial compared once-daily liraglutide to once-weekly dulaglutide in T2DM patients who were inadequately controlled on metformin (mean baseline HbA1c, 8.1%) [90]. A total of 269 participants in each group completed 26 weeks of treatment. The mean reduction in HbA1c in the dulaglutide arm was − 1.42% vs. − 1.36% in the liraglutide arm (treatment difference, − 0.06%; 95% CI − 0.19 to 0.07; $p < 0.0001$ for noninferiority) [90]. While both treatment groups demonstrated significant weight loss after 26 weeks of treatment, the difference from baseline was less in the dulaglutide arm, − 2.90 vs. − 3.61 kg, than in the liraglutide arm (treatment difference, 0.71 kg; 95% CI 0.17–1.26); $p = 0.011$ [90]. No significant differences were reported in the rates of nausea, diarrhea, dyspepsia, or vomiting, and rates of discontinuation due to AEs were similar between the two groups (6% each). Hypoglycemia rates were also similar in each group, and no cases of severe hypoglycemia were reported [90].

Several studies have also demonstrated that the glycemic efficacy of add-on GLP-1 RA treatment is similar or modestly superior to that of add-on basal insulin therapy, with benefits regarding body weight and hypoglycemia [91–95]. However, the basal insulin titration was not always optimal in some of these studies, and patients generally had baseline HbA1c levels between 8.0% and 8.5%. It is likely that at some higher level of HbA1c, basal insulin might provide greater HbA1c reductions. A post hoc analysis of some of these studies showed that even patients with mean HbA1c levels between 9% and 10% had equivalent or modestly better glycemic lowering with a GLP-1 RA [96]. Nevertheless, these findings suggest that GLP-1 RAs can be an appropriate alternative to basal insulin therapy in some circumstances, and might be used as the first injectable agent in many type 2 diabetes patients, especially those who are overweight or obese.

Safety Considerations with a Combination of Metformin and a GLP-1 RA

The GLP-1 RAs have a well-characterized safety and tolerability profile. The most common AEs associated with GLP-1 RA therapy are GI related, including diarrhea, nausea, and vomiting [89]. These usually tend to be dose related and self-limiting as treatment progresses. For those products with more than one dosing option, slower dose titration (thereby slowing the exposure to the drug) can help limit the GI AEs [89]. Hypoglycemia has been reported with GLP-1 RAs, but this effect is less common, and usually seen in combination with insulin or insulin secretagogues [97].

Before starting GLP-1 RA therapy, clinicians should consider a patient's baseline risk for pancreatitis or pancreatic cancer, including any history of pancreatitis or family history of pancreatic cancer. Although preclinical studies suggest associations between incretin-based therapy and pancreatitis or pancreatic cancer, retrospective observational trials have not confirmed this association nor have the FDA and EMA reviews of the available data identified any causal association, as discussed in case 1 [98]. Meta-analyses of large, randomized clinical trials have not demonstrated an association between GLP-1 RAs and pancreatic cancer [99, 100]. In addition, no association between GLP-1 RA therapy and pancreatic cancer was identified in several large CVOTs with these agents [101–103].

In a similar fashion, an increase in thyroid C-cell hyperplasia, adenomas, and medullary thyroid carcinomas (MTC) have been reported in rodents after treatment with once-daily and once-weekly GLP-1 RAs [40, 41, 43, 104],

although the human relevance of these findings is unknown [98].

Cardiovascular Considerations with a Combination of Metformin and a GLP-1 RA

The Evaluation of Lixisenatide in the Acute Coronary Syndrome (ELIXA) trial, the first reported GLP-1 RA CVOT, demonstrated no increased CVD risk with lixisenatide; however, it was not associated with a reduced CVD risk compared with placebo in patients with T2DM who experienced an acute coronary syndrome event within the previous 180 days ($N = 6068$). The incidence of the primary 4-point MACE (cardiovascular death, myocardial infarction, stroke, or hospitalization for unstable angina) was similar in both treatment arms (13.4% vs. 13.2%; HR 1.02; 95% CI 0.89–1.17; $p < 0.001$ for noninferiority; $p = 0.81$ for superiority) [103]. Also, there were no significant differences in the rates of hospitalization for heart failure (HR 0.96; 95% CI 0.75–1.23) or in the rate of death from cardiovascular causes (HR 0.94; 95% CI 0.78–1.13) [103].

In comparison, results from the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial with the longer-acting liraglutide ($N = 9340$, median follow-up 3.8 years) and the Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6) with once-weekly semaglutide ($N = 3297$, median follow-up 2.1 years) [101] showed significantly lower rates of composite MACE outcomes. In the LEADER trial, the rate of the primary MACE outcome (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) was significantly lower in the liraglutide group than in the placebo group (13.0% vs. 14.9%; HR 0.87; 95% CI 0.78–0.9; $p < 0.001$ for noninferiority; $p = 0.01$ for superiority) [102]. The rates of cardiovascular death, and death from any cause, were lower in the liraglutide group than in the placebo group (4.7% vs. 6.0%; HR 0.78; 95% CI 0.66–0.93; $p = 0.007$), as were deaths due to any cause (8.2% vs. 9.6%; HR 0.85; 95% CI 0.74–0.97; $p = 0.02$) [102]. On the basis of findings from the LEADER trial, the US FDA recently approved an indication for liraglutide to reduce the risk of MACE, comprising CV death, nonfatal myocardial infarction, or nonfatal stroke, in adults with T2DM and established CVD [43].

In the SUSTAIN-6 trial with semaglutide, the primary outcome (the first occurrence of a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) occurred in 6.6% of patients receiving semaglutide and in 8.9% of patients on placebo (HR 0.74; 95% CI 0.58–0.95; $p < 0.001$ for noninferiority) [101]. The rates of nonfatal stroke were 1.6% in the semaglutide arm and 2.7% in the placebo arm (HR 0.61; 95% CI 0.38–0.99; $p = 0.04$). However, there were no significant differences in the rates of nonfatal myocardial infarction or cardiovascular death [101]. Semaglutide has recently been approved for use by the FDA as an adjunct to diet and exercise to improve glycemic control in adults with T2DM [105].

Considerations with SGLT2/DPP-4 Single-Pill Combination Added to Metformin

Another option for this patient would be add-on therapy with a single-pill combination of SGLT2/DPP-4 inhibitors. A study reported by DeFronzo et al. examined the efficacy of the empagliflozin/linagliptin single-pill combination as second-line therapy in patients with T2DM who were inadequately controlled on metformin [106]. Adjusted mean reductions in HbA1c from baseline (mean 7.90–8.02%) were significantly greater with empagliflozin 25 mg/linagliptin 5 mg (− 1.19%) and empagliflozin 10 mg/linagliptin 5 mg (− 1.08%) compared with linagliptin 5 mg (− 0.70%; treatment differences, − 0.50% and − 0.39%, respectively; both $p < 0.001$) and vs. empagliflozin 25 mg (− 0.62%) and empagliflozin 10 mg (− 0.66%; treatment differences, − 0.58% and − 0.42%, respectively; both $p < 0.001$) at week 24. Reductions in HbA1c with both doses of empagliflozin/linagliptin were maintained at week 52 [106].

The single-pill combination of dapagliflozin/saxagliptin [107] is another alternative combination add-on therapy for this patient. The efficacy of this combination was confirmed in

patients who were poorly controlled on a background regimen of metformin XR (1500 mg/day) with HbA1c values between ≥ 8.0% and ≤ 12.0% (mean 8.94 ± 1.13%) [108], which were higher than the mean baseline HbA1c reported by DeFronzo et al. [106]. Patients were randomized to saxagliptin plus dapagliflozin (5 and 10 mg/day; $n = 179$), saxagliptin (5 mg/day) plus placebo ($n = 176$), or dapagliflozin (10 mg/day) plus placebo ($n = 179$) in a double-blind design. After 24 weeks of treatment, the adjusted mean change from baseline HbA1c was − 1.5% (triple combination) vs. − 0.9% with saxagliptin and metformin (difference, − 0.59%; $p < 0.0001$) and –1.2% with dapagliflozin and metformin (difference, − 0.27%; $p < 0.02$) [108]. In addition, an HbA1c of < 7% was achieved by 41% of patients on triple therapy, 18% of those on saxagliptin and metformin, and 22% of patients on dapagliflozin and metformin. Reported rates of AEs were low in all arms, with urinary and genital infections at ≤ 1% in patients receiving triple therapy. There were no reports of major hypoglycemia, and any hypoglycemia was infrequent in all arms [108].

A recent study compared the efficacy and safety of the combination of ertugliflozin and sitagliptin, vs. each individual agent, as add-on therapies in T2DM patients who were inadequately controlled on metformin monotherapy [109]. Patients with HbA1c ≥ 7.5% and ≤ 11.0% on metformin ≥ 1500 mg/day ($n = 1233$) were randomized to ertugliflozin (ertu; 5 or 15 mg/day), sitagliptin (sita; 100 mg/day) or both agents (ertu 5 or 15 mg/sita 100 mg) in addition to metformin.

At week 26, reductions from baseline in least-squares mean HbA1c levels were greater with either of the two ertu 5 or 15 mg/sita 100 mg combinations (− 1.5% each) than with either agent alone (− 1.0%, − 1.1%, and − 1.1% for ertu 5 or 15 mg, and sita 100 mg, respectively), $p < 0.001$ for either combination vs sitagliptin monotherapy [109]. In addition, an HbA1c of < 7.0% was achieved by 26.4%, 31.9%, 32.8%, 52.3%, and 49.2% of patients in the ertu 5 mg, ertu 15 mg, sita 100 mg, and the ertu 5/sita 100 and ertu 15/sita 100 groups, respectively. Also at week 26, significantly greater reductions in body weight were reported with both combination regimens − 1.8 kg for ertu 5 mg/sita 100 mg, and − 2.3 kg for ertu 15 mg/sita 100 mg, beyond sita 100 mg alone, where the reduction was − 0.7 kg (both $p \leq 0.001$). At week 26, SBPs were significantly reduced with both combination regimens, − 2.8 mmHg for ertu 5 mg/sita 100 mg, and − 3.0 mmHg for ertu 15 mg/sita 100 mg, beyond the − 0.7 mmHg reduction noted for sita 100 mg alone (both $p \leq 0.005$) [109].

As expected, genital mycotic infections were more common among ertugliflozin-treated patients, with rates of 4.1% and 2.4% in male patients treated with ertu 5 or 15 mg/sita 100 mg, vs. 0% for male patients treated with sita 100 mg ($p < 0.05$ for ertu 5/sita 100 mg vs. sita 100 mg) [109]. Among female patients, genital mycotic infections were also more common among those treated with ertugliflozin, with rates of 5.0% and 7.6% in ertu 5 or 15 mg/sita 100 mg, vs. 1.1% in the sita 100 mg arm ($p < 0.05$ for ertu 15/sita 100 mg vs. sita 100 mg). However, for other AEs, including symptomatic hypoglycemia, AEs related to hypovolemia, or urinary tract infections, the reported rates were similar between groups [109].

Case Conclusion

This patient has an HbA1c of 8.2% on metformin and lifestyle interventions and needs additional antihyperglycemic pharmacotherapy. A single oral agent is unlikely to allow her to reach her glycemic target. Because of her obesity, pharmacotherapy associated with some weight loss would be beneficial. The two best potential options would be either a GLP-1 RA or the combination of a DPP-4 inhibitor and an SGLT2 inhibitor added to metformin. Either option could allow her to approach her glycemic goals. The single-pill combinations of empagliflozin/linagliptin or dapagliflozin/saxagliptin might be good choices, which many patients may prefer owing to convenience.

SUMMARY

Given the nature of the normal progression of T2DM over time, most patients eventually will

require combinations of antihyperglycemic therapies, in addition to lifestyle interventions, to reach or maintain their glycemic targets. When to initiate combination therapy and which agents to use can represent complex choices. For many patients, management of their T2DM would most likely benefit from earlier use of a combination therapy regimen. This is especially true in cases where reliance on simple lifestyle changes and a single antihyperglycemic agent is unlikely to achieve and maintain selected glycemic targets.

For patients with substantial hyperglycemia, early introduction of combination therapy may lead to more rapid attainment of therapeutic goals [110, 111]. Metformin is the usual choice for initial pharmacotherapy in patients who do not need insulin at the time of diagnosis. The choice of add-on therapy, however, should be based on patient-specific variables, such as the risk of developing hypoglycemia and any associated adverse consequences, relative need to avoid weight gain, existing comorbidity profile, financial resources and personal support systems available, and the patient's overall motivation to pursue lifestyle changes and maintain regimen adherence. Current recommendations for the management of T2DM have evolved from a more uniform, stepwise approach to a more individualized approach. For some patients, an oral single-pill combination will be a good choice, whereas other patients will require a combination of oral and injectable therapies.

Newer T2DM management regimens that include both incretin-based treatments and SGLT2 inhibitors are becoming well-established options due to their novel and complementary mechanisms of action, robust reductions in HbA1c levels, efficacy in reducing body weight and BP, and generally good safety profile. Taken together, these attributes have allowed these agents to find an earlier role in treatment algorithms.

As the case discussions presented here demonstrate, current position statements and algorithms from the ADA and AACE/ACE can be used to guide combination therapy selection for patients with T2DM in primary care. After considering drug-specific and patient factors, the ADA currently recommends that patients with T2DM and established atherosclerotic CVD begin antihyperglycemic therapy with lifestyle management and metformin, and subsequently incorporate an agent proven to reduce MACE and CV mortality; currently these are empagliflozin and liraglutide [10]. In these patients, canagliflozin may be considered to reduce MACE, based on drug-specific and patient factors [10]. These guidelines are also expected to evolve as new data from additional long-term outcomes studies become available.

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