Update on Management of Type 2 Diabetes for Cardiologists

Mohammed Qureshi, M.D.; *Emily Gammoh,* M.D.; *Jawairia Shakil,* M.D.; *Richard Robbins,* M.D.

HOUSTON METHODIST HOSPITAL, HOUSTON, TEXAS

ABSTRACT: The management of type 2 diabetes mellitus has evolved over the last several years as new antidiabetic agents continue to arrive and change the goals of diabetes care. In 2008, the U.S. Food and Drug Administration mandated that all new antidiabetic agents must demonstrate cardiovascular (CV) safety, which has led to a series of CV outcome trials. In this article, we review the key findings from these CV outcome trials and their impact on diabetes care guidelines.

INTRODUCTION

Medical literature is rife with guidelines, meta-analyses, and treatment recommendations for optimal diabetes management. Given the association between diabetes and heart disease, cardiologists often assume the role of caring for diabetic patients or, at the very least, assisting in their care. Although previous studies focusing on tight glycemic control demonstrated modest delays in progression of microvascular complications (e.g., retinopathy, nephropathy, and neuropathy), very few have actually shown clinically significant reductions in cardiac events or strokes.

Over the past 40 years, the principal outcomes that clinicians use to judge optimal care of a patient with type 2 diabetes mellitus (T2DM) have shifted from optimal glycemic control (i.e., HbA1c) to a new emphasis on preventing macrovascular disease, specifically cerebrovascular and cardiac events. As a result, the last two decades have produced a number of new classes of T2DM medications, some of which have been associated with reductions in cardiovascular (CV) end points.

New management guidelines for T2DM emphasize a multidimensional approach that promotes cardiovascular health by optimizing weight loss, nutrition, exercise, hypertension, and hyperlipidemia. This review presents a synopsis of the most recent guidelines from the American Diabetes Association (ADA), the American College of Endocrinology (ACE), and the American Association of Clinical Endocrinologists (AACE), with a focus on trials that have measured cardiovascular outcomes.

OPTIMIZING CARE OF ADULTS WITH TYPE 2 DIABETES MELLITUS

Comprehensive care for patients with T2DM requires a multifaceted approach, which is reflected in the AACE and ADA updated 2018 guidelines.[1] Lifestyle modifications focus on nutrition, physical activity, sleep, and smoking cessation. Avoiding foods with a high glycemic index, increasing consumption of plant-based foods, limiting intake of salt and saturated/trans fats, and reaching an ideal weight are now central elements.[2] As shown by the Diabetes Prevention Program (DPP) study, lowering caloric intake facilitates weight loss and controls glucose, lipids, and blood pressure.[3] According to the Action for Health in Diabetes (Look AHEAD) trial, increasing physical activity directly correlates with significant weight loss.[2] Thus, the AACE and ACE recommend at least 150 minutes of moderately intense physical activity per week for patients with T2DM.[2] Attaining 6 to 9 hours of sleep per night reduces inflammatory cytokines, enabling better control of blood glucose and blood pressure.[2] In addition, smoking cessation is paramount to prevent the added risk of CV disease in patients with T2DM.[1]

Uncontrolled hypertension can accelerate CV disease.[2] A recent meta-analysis by Bangalore et al. revealed that systolic blood pressure ≤ 135 mm Hg correlated with decreased nephropathy and stroke risk and a reduction in all-cause mortality compared to systolic blood pressure ≤ 140 mm Hg.[4,5] More aggressive blood pressure control of < 130 mm Hg further decreased stroke risk but saw an increased risk of serious adverse events (SAEs). The AACE recommends a target blood pressure of < 130/80 mm Hg for patients with T2DM but advocates for individualized goals to prevent SAEs.[2]

Insulin resistance increases the risk of atherosclerotic CV disease (CVD).[6] The AACE and ACE have stratified atherosclerotic CVD risk in patients with T2DM as high risk, very high risk, and extreme risk; based on each patient's risk, they have published goals for low-density lipoproteins, non-high-density lipoproteins, apolipoprotein B, and triglycerides.[2] Appropriate treatment of dyslipidemia in patients with T2DM requires moderate- to high-intensity statins, and additional lipid-lowering drugs can be added to reach lipid goals.[2]

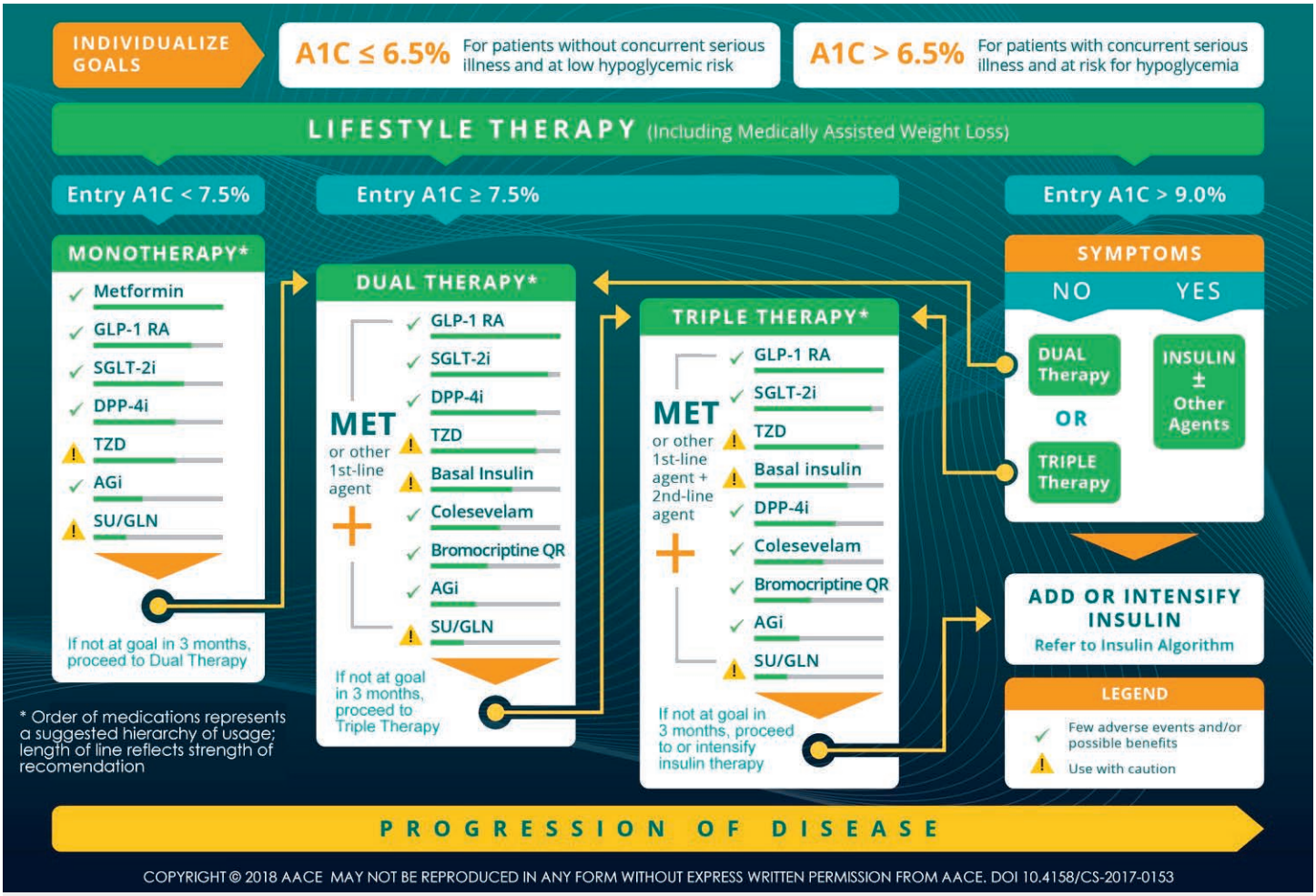

Figure 1.
2018 AACE/ACE glycemic control algorithm. Reprinted with permission from American Association of Clinical Endocrinologists © 2018. Endocr Pract. 2018;24:90-120. AACE: American Association of Clinical Endocrinologists; ACE: American College of Endocrinology

ANTIDIABETIC AGENTS AND THEIR CV EFFECTS: REVIEW OF CV OUTCOME TRIALS

Metformin

Metformin is the most common diabetes medication prescribed worldwide and is recommended as first-line therapy for T2DM (Figure 1).[7] The usual starting dose is 500 mg twice daily; however, maximum benefit is achieved at 2,000 mg per day.[8] Metformin is used as monotherapy if the initial A1c level is less than 7.5% but is usually prescribed with one or more additional medications if the starting A1c is above 7.5%. This treatment regimen is derived from the United Kingdom Prospective Diabetes Study, which evaluated the benefits and risk of different diabetes medications in patients with type 2 diabetes. Use of metformin monotherapy in obese patients with newly diagnosed T2DM was associated with a 32% reduction in the aggregate diabetes-related end point, which included sudden death and myocardial infarction (MI) ($P = .011$), as well as a 36% reduction in all-cause mortality ($P = .011$).[9] In addition, the metformin group demonstrated persistent risk reductions for any diabetes-related end point (21%, $P = .01$), MI (33%, $P = .005$), and all-cause mortality (27%, $P = .002$) during the 10-year post-trial follow-up of the survivor cohort.[9]

A meta-analysis by Lamanna et al. of 35 randomized trials–including 7,171 participants treated with metformin and 11,301 treated with a comparator–showed that metformin reduced adverse CV events (MI, stroke, peripheral artery disease, and cardiovascular death) compared to placebo/no therapy (MH-OR 0.79, 95% CI, 0.64-0.98, $P = .031$) but not against active comparators (MH-OR 1.03, 95% CI, 0.72-1.77, $P = .89$).[10]

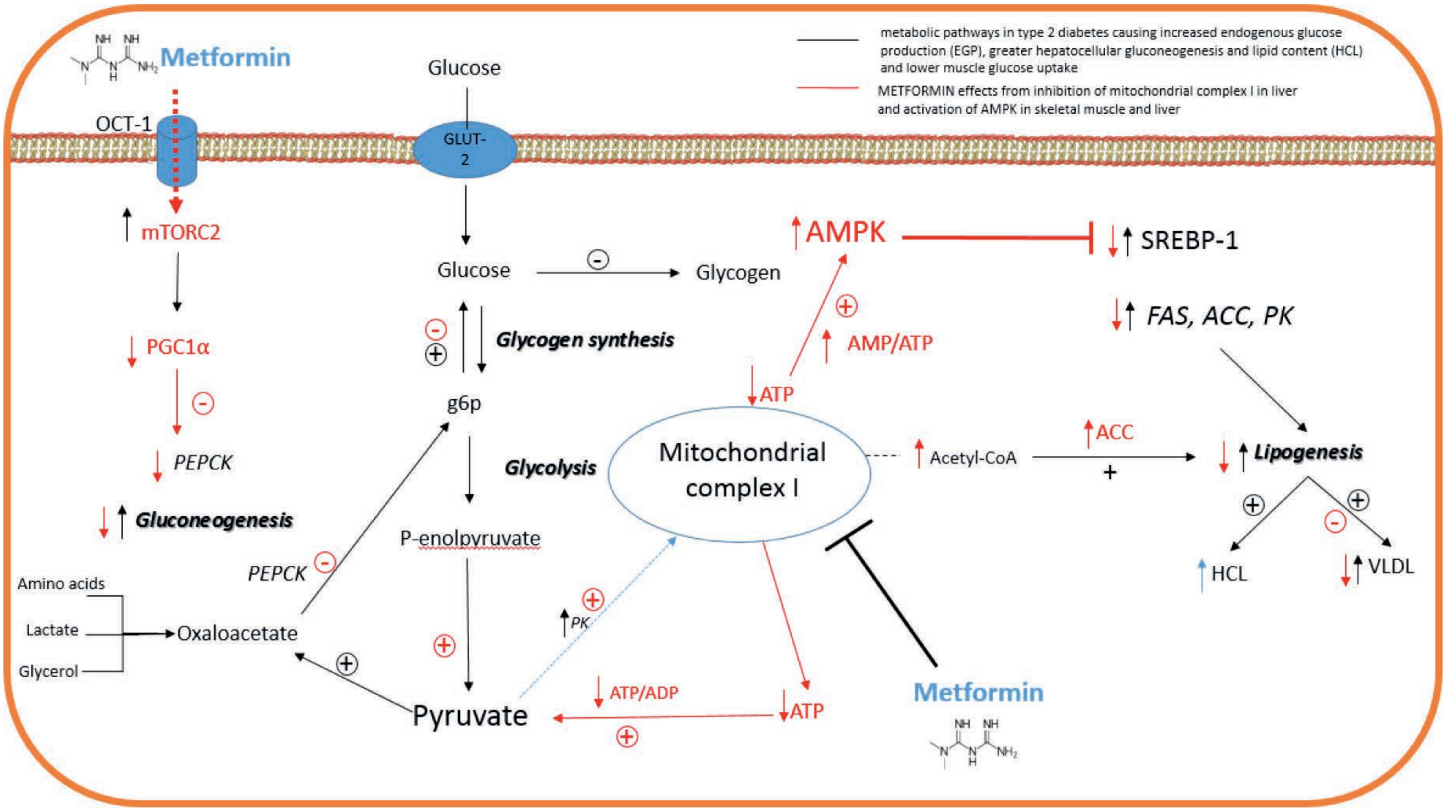

Figure 2.
Metformin effect on glycogen synthesis and inhibition of gluconeogenesis at the hepatocellular level. It inhibits mitochondrial complex I, which decreases ATP/ADP ratio, thereby enhancing pyruvate-kinase, and inhibits gluconeogenesis. The increase in AMP/ATP ratio and AMP-activated protein kinase (AMPK) switches from ATP-consuming anabolic to ATP-generating catabolic pathways. This decreases expression and activities of ACC and SREBP-1 with down regulation of lipogenic enzymes (e.g., FAS) and increases pyruvate kinase activity, reducing hepatic VLDL. Metformin-induced suppression of gluconeogenesis is mediated by liver kinase B1 (LKB1), which phosphorylates AMPK and, via mammalian target-of-rapamycin C2 (mTORC2), reduces PPARγ coactivator 1α (PGC1α), which regulates phosphoenolpyruvate carboxykinase (PEPCK), in turn reducing glycogen production. ACC: acyl-CoA synthetase; HCL: hepatocellular lipid content; G6P: glucose-6-phosphate; FAS: fatty acyl-CoA synthetase; PK: pyruvate kinase; PPAR: peroxisome proliferator-activated receptor; SREBP: sterol regulatory element-binding protein; TG: triglyceride; VLDL: very-low-density lipoprotein

The analysis also found that metformin was not associated with significant harm or benefit related to CV events (MH-OR 0.94 [0.82-1.07], $P = .34$). Another meta-analysis of 35 trials representing 7,960 participants suggested that metformin was moderately protective when compared to other oral diabetes agents and placebo,[11] while a paper by Bailey and Day tracing the herbal roots of metformin noted that it offers a unique range of effects that counter insulin resistance without the side effects of other treatments.[12]

In summary, metformin has a good cardiovascular safety profile (Figure 2), is relatively safe to use in patients with mild to moderate chronic kidney disease, is inexpensive, and lowers HbA1c. Lactic acidosis is a very rare but potentially fatal adverse effect.

Sulfonylureas

Sulfonylureas act by binding to receptors on pancreatic beta cells, leading to increased secretion of insulin.[13] The most common side effects include weight gain and hypoglycemia.[14] A recent meta-analysis of 116 randomized clinical trials including 45,488 patients did not find a significant increase in major adverse cardiac events (MACE) or MI with use of sulfonylureas but did find a statistically significant increase in the risk of stroke and all-cause mortality.[15] Another meta-analysis of 37 randomized clinical trials including 37,650 patients looked specifically at second- and third-generation sulfonylureas and found no correlation between sulfonylureas and all-cause or CV mortality, MI, or stroke.[16]

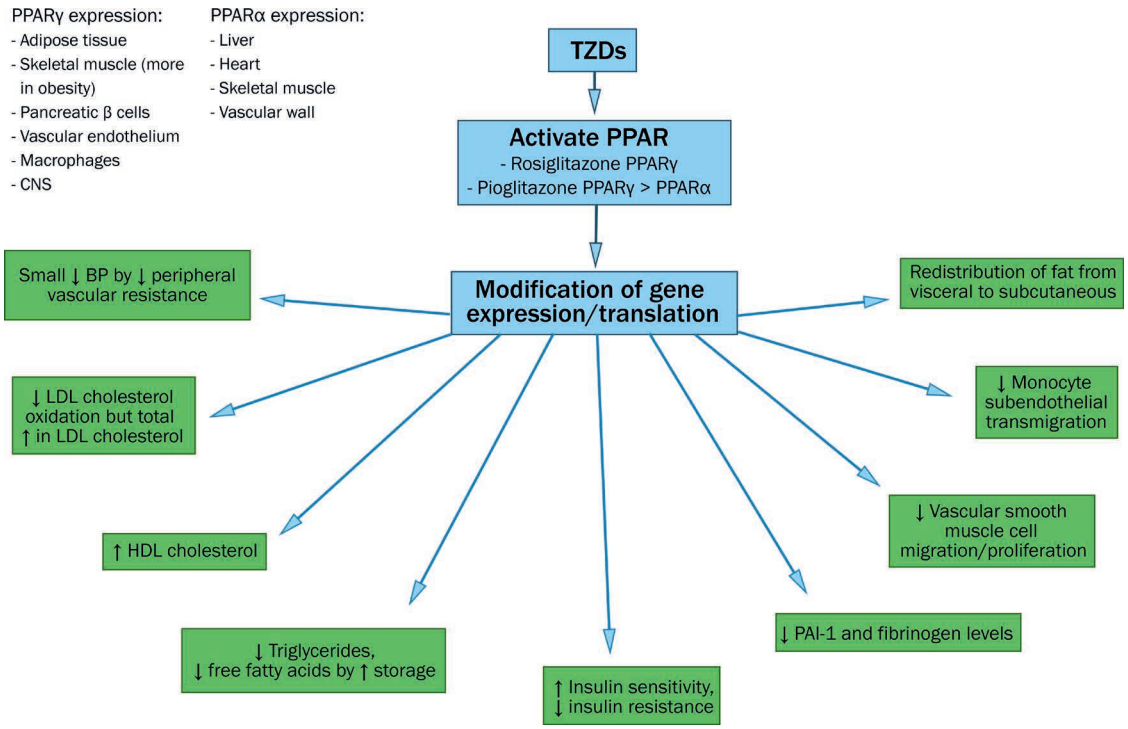

Figure 3.
Cardiovascular effects of thiazolidinediones. TZDs: thiazolidinediones; PPAR: peroxisome proliferator-activated receptor; BP: blood pressure; LDL: low-density lipoprotein; HDL: high-density lipoprotein; PAI-1: plasminogen activator inhibitor-1; CNS: central nervous system

These contradictory findings can be attributed to various causes. For example, the randomized controlled trials in the aforementioned meta-analyses were not powered to detect cardiovascular events. Also, the observational studies used varying approaches to study design and data analysis that may have introduced time lag, selection, and other types of bias.[17]

Thiazolidinediones

Thiazolidinediones (e.g., pioglitazone) activate peroxisome proliferator-activated receptor (PPAR) gamma, thereby increasing downstream sensitivity to insulin (Figure 3).[13] ADA guidelines do not recommend their use as first-line therapy due to unfavorable side effects (Table 1).[18] The PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) and Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) trials evaluated CV outcomes of pioglitazone and rosiglitazone, respectively, and reported a statistically significant increase in congestive heart failure with thiazolidinediones, but this did not translate to an increase in CV mortality.[19,20]

The 2005 PROactive trial, which evaluated the macrovascular effects of pioglitazone in diabetic patients, revealed a statistically significant decline in all-cause mortality, MI, and stroke, favoring pioglitazone over placebo.[19] These findings were congruent with a meta-analysis of 19 randomized controlled trials in 2007, which enrolled 16,390 patients and revealed a lower all-cause mortality rate, MI, and stroke with pioglitazone versus control (HR 0.82; 95% CI, 0.72-0.94).[21]

More recently, the IRIS trial, a randomized, multicenter, double-blinded trial examining the use of pioglitazone in insulin-resistant patients after an ischemic stroke or transient ischemic attack, found a statistically significant reduction in stroke and MI in patients who received pioglitazone.[22] The CV benefits with pioglitazone are not fully understood but may in part be due to altered lipid/lipoprotein metabolism and decreased vascular inflammation.[23,24]

Alpha-Glucosidase Inhibitors

Alpha-glucosidase inhibitors (AGIs) blunt intestinal carbohydrate metabolism and diminish postprandial hyperglycemia.[25] AGIs are associated with weight loss (1 kg vs placebo), an HbA1c reduction of 0.8%, and low hypoglycemia risk and should be avoided in patients with renal insufficiency.[18,25,26]

Two trials provide the majority of CV outcome data regarding this class of antidiabetic agents. In the Study to Prevent NIDDM (STOP NIDDM) trial, acarbose, when compared to placebo, was shown to delay the onset of T2DM in patients with prediabetes (32% vs 42% developed T2DM, respectively; 95%

DRUG CLASS (DRUGS AVAILABLE)	MECHANISM OF ACTION	CLINICAL EFFECTS	SIDE EFFECTS	CARDIOVASCULAR EFFECTS
Biguanides (Metformin)	Reduce hepatic gluconeogenesis by inhibiting mitochondrial respiratory-chain complex 1	Reduce HbA1C 1-2%; increase insulin sensitivity; slight weight loss; improve LDL-C; neutral effect on blood pressure	GI; contraindicated in patients with CKD with eGFR < 30; use caution in patients with eGFR < 45 and in hypoxic states	Reduce MACE as an add-on agent; benefit of monotherapy in prediabetes and early diabetes
Sulfonylureas (chlorpropamid, glyburide, glipizide, glimepiride)	Bind sulfonylurea receptor and block potassium ATP channels, increasing insulin secretion	Reduce HbA1c by 1-1.5%; neutral on lipids; slight increase in weight and blood pressure	Hypoglycemia; weight gain	Blunted ischemic preconditioning with glipizide or glyburide; no clear evidence of risk or benefit
Thiazolidinediones (rosiglitazone, pioglitazone)	Bind peroxisome-proliferator-activated receptor gamma, causing a downstream effect of decreasing insulin resistance	Reduce HbA1c by 1-1.5%; pioglitazone lowers TG, LDL particle concentration, LDL particle size, and increases HDL	Edema, CHF risk increases with this class of medications; rosiglitazone risk > pioglitazone; increased fracture risk	Reduced aggregate CV end points with pioglitazone
Alpha glucosidase inhibitors (acarbose, miglitol)	Competitively inhibit intestinal alpha glucosidase, blunting intestinal CHO metabolism	Reduce HbA1c by 0.8%; weight reduction by 1 kg vs placebo; diminish postprandial hyperglycemia; slow the progression from prediabetes to T2DM	GI side effects including diarrhea and flatulence; low risk of causing hypoglycemia; should be avoided in patients with renal insufficiency	No reduction in composite MACE end points vs placebo; no clear evidence of risk or benefit
DPP4 Inhibitors (sitagliptin, saxagliptin, linagliptin, alogliptin)	Inhibit breakdown of dipeptidyl peptidase 4 enzyme; increase endogenous incretin hormones (GLP1 and GIP)	Reduce HbA1c by 0.5%-0.8%; weight neutral; low risk of causing hypoglycemia; can be used in renal insufficiency	GI side effects including diarrhea, abdominal pain, and rarely pancreatitis	No reduction in composite MACE end points vs placebo FDA recommends discontinuation of alogliptin and saxagliptin in patients who develop heart failure
Amylin mimetics (pramlintide)	Simulate endogenous amylin hormone; slow gastric emptying; induce early satiety; blunt pancreatic glucagon secretion	Reduce HbA1c by 0.3%-1.0%; weight loss 0.5 kg -1.8 kg vs placebo; low risk of causing hypoglycemia; can be used in renal insufficiency	GI side effects including nausea and abdominal pain	No reduction in composite MACE end points; no clear evidence of risk or benefit
Insulin and Insulin analogs	Mimic the effects of endogenous insulin	Reduce HbA1c 1.5-3.5%; neutral on blood pressure; decrease total cholesterol, LDL cholesterol, triglycerides	Hypoglycemia; weight gain	No positive or negative effect on CV outcomes

** See review by Ahmed Yehya for CV effects of GLP-1 and SGLT2*

Table 1.
Antidiabetic agents and their CV effects.***** MACE: major adverse cardiac events; CKD: chronic kidney disease; TG: triglyceride; LDL: low-density lipoprotein; HDL: high-density lipoprotein; GI: gastrointestinal: CHF: chronic heart failure; CHO: carbohydrate; CV: cardiovascular

CI, 0.63-0.90, $P = .0015$).[27] Although retrospective post hoc analysis of secondary outcomes showed a reduced incidence of MI with acarbose vs placebo (1 vs 12; $P = .0226$) and any CV event (15 vs 32; $P = .0326$), the overall proportion of patients with these CV events was small (N = 1429) and the analysis was done retrospectively.[27]

The Acarbose Cardiovascular Evaluation (ACE) trial evaluated for MACE, including CV death, MI, stroke, unstable angina, and heart failure.[28] The cohort included patients with newly discovered prediabetes who had a CV event within the preceding 3 months. Patients were subsequently started on acarbose versus placebo. The trial found that the number of patients in both groups experienced similar primary MACE events (14.4% vs 14.7%, respectively; 95% CI, 0.86-1.11, $P = .73$;), indicating no reduction in CV risk with acarbose.[28]

Dipeptidyl Peptidase 4 Inhibitors

Dipeptidyl peptidase 4 (DPP4) inhibitors (e.g., sitagliptin, saxagliptin, alogliptin) prevent DPP4 from breaking down endogenous incretin hormones (GLP1 and GIP). This amplifies the ability of postprandial GLP1 and GIP to suppress glucagon and promote glucose-dependent insulin secretion.[29] DPP4 inhibitors decrease HbA1c levels by 0.5% to 0.8%, are weight neutral, have a low risk of hypoglycemia, and can be used in patients with renal insufficiency with appropriate dose adjustment.[29] According to the most recent AACE/ACE glycemic control algorithm, DPP4 inhibitors can be initiated as first-line monotherapy or used with another antidiabetic agent as dual therapy.[2]

Three trials have evaluated this medication class for its cardiovascular effects. Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction (SAVOR-TIMI 53), Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE), and Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) are multicenter, randomized, double-blind, placebo-controlled, noninferiority trials that compared saxagliptin, alogliptin, and sitagliptin, respectively.[28] The primary composite end point in each trial evaluated MACE. Hospitalization for heart failure was included as a secondary end point in SAVOR TIMI 53 and TECOS and as an extended primary end point in EXAMINE. All three trials reported neutral effects on the composite MACE end points, indicating overall safety related to CV death, MI, and stroke, with no added benefit or improvement in CV outcomes when compared to placebo.[28] EXAMINE showed a possible increased risk for hospitalization related to heart failure with alogliptin (3.9% vs 3.3%, respectively; 95% CI, 0.90-1.58, $P = 1.19$). The precise effect on heart failure remains unclear but is unlikely to be a class effect since no correlation was seen with sitagliptin in the TECOS trial. Currently, the U.S. Food & Drug Administration (FDA) recommends discontinuing alogliptin and saxagliptin in patients who develop heart failure.[30] Linagliptin is currently being evaluated in two additional trials—Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients With Type 2 Diabetes (CAROLINA) and Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus (CARMELINA)—although outcomes are not yet available.

Amylin-Mimetics

Amylin analogs (pramlintide) slow gastric emptying, induce early satiety, blunt pancreatic glucagon secretion, and reduce prandial insulin requirements.[18] According to the 2018 AACE/ACE glycemic control algorithm, their precise role remains unclear, but they are only indicated for use with basal bolus insulin regimens.[2] Amylin analogs are associated with weight loss and an HbA1c reduction of between 0.3% and 1.0%, and they have a low risk of hypoglycemia.[31]

The CV safety of amylin analogs was assessed in a pooled analysis of five randomized controlled clinical trials that were undertaken between 2002 and 2009. The pooled data showed no difference in the incidence of primary MACE in the pramlintide group versus control group (4.7% vs 4.5%, respectively; RR: 1.034; 95% CI, 0.69-1.54).[31]

Insulin and Insulin Analogs

Type-2 diabetes is characterized by the progression of insulin resistance to insulin deficiency and requires exogenous insulin to control hyperglycemia. Glargine, a basal insulin with a 24-hour duration of action, is most commonly initiated for treatment of uncontrolled T2DM. The Outcome Reduction With Initial Glargine Intervention (ORIGIN) trial examined the effect of glargine on CV and other outcomes when used to target normal fasting plasma glucose.[32] After a 6-year follow-up, the investigators found no effect of glargine on CV outcomes compared with guideline-suggested glycemic control and no effect on blood pressure.[32] Weight gain is a common side effect of glargine use and may incur a negative effect on cardiovascular outcomes.[33]

New synthetic insulin analogs have recently emerged, such as degludec, an ultra-long-acting, once-daily basal insulin. The Trial Comparing Cardiovascular Safety of Insulin Degludec Versus Insulin Glargine in Subjects With Type 2 Diabetes at High Risk of Cardiovascular Events (DEVOTE) trial looked at the safety and efficacy of degludec compared to glargine and found it to be noninferior to glargine with regard to CV

outcomes and risk factors but superior with regard to severe hypoglycemia.[34]

SUMMARY

Ever since the FDA mandated that all new antidiabetic agents demonstrate CV safety, various CV trials have shown neutral CV effects while others have exhibited CV benefits (Table 1). The focus of T2DM management has shifted over the past several years from optimal glycemic control to a new emphasis on prevention of macrovascular disease. In all seven drug classes discussed in this review, HbA1c remains the standard of judging the success of a drug's ability to control glucose intolerance. To our knowledge, studies have not been conducted that attempt to identify a unique dosage of any drug that targets MACE rather than HbA1c. In an attempt to promote CV health, new guidelines stress a multifactorial approach for T2DM management with an emphasis on weight loss, nutrition, exercise, hypertension, and hyperlipidemia, as published by the 2018 ADA and AACE/ACE guidelines. These important updates will enable all health care providers to deliver the highest level of care for the management of T2DM.

KEY POINTS

- Management of type-2 diabetes requires a multidimensional approach to promote cardiovascular health by optimizing weight loss, nutrition, exercise, hypertension, and hyperlipidemia.
- As mandated by the U.S. Food & Drug Administration, all new antidiabetic agents must demonstrate cardiovascular (CV) safety, which has led to a series of CV outcome trials in recent years.
- The various CV trials have shown some antidiabetic agents to have neutral CV effects while others have exhibited CV benefit.

Conflict of Interest Disclosure:
The authors have completed and submitted the *Methodist DeBakey Cardiovascular Journal* Conflict of Interest Statement and none were reported.

Keywords:
type 2 diabetes mellitus, diabetes management, cardiovascular outcome trials, cardiovascular safety, major adverse cardiac events

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