Reducing Cardiovascular Events in Your Patients with Type 2 Diabetes Mellitus

Scott Urquhart, PA-C, DFAAPA; Davida Kruger, MSN, APRN-BC, BC-ADM

CONTINUING MEDICAL EDUCATION

LEARNING OBJECTIVES

After reading this article, the clinician should be able to:

1. Describe why glycemic control alone is insufficient to prevent long-term adverse cardiovascular outcomes
2. Characterize the cardiovascular complications observed in type 2 diabetes mellitus
3. Describe the results of cardiovascular outcome trials of glucose-lowering medications for type 2 diabetes mellitus, focusing on medications shown to reduce cardiovascular events
4. Individualize glucose-lowering medication shown to reduce cardiovascular events in patients with type 2 diabetes mellitus and with or without established atherosclerotic cardiovascular disease, heart failure, or chronic kidney disease

TARGET AUDIENCE

Family physicians and clinicians who wish to gain increased knowledge and greater competency regarding primary care management of diabetes mellitus.

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FACULTY

Davida Kruger, MSN, APRN-BC, BC-ADM, Certified Nurse Practitioner, Henry Ford Health System, Division of Endocrinology, Diabetes and Bone Disease, Detroit, MI; Scott Urquhart, PA-C, DFAAPA, Past President, American Society of Endocrine PAs (ASEPA), Adjunct Clinical Professor, PA Program, James Madison University, Diabetes and Thyroid Associates, Fredericksburg, VA

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CASE SCENARIO

A 67-year-old woman was diagnosed with type 2 diabetes mellitus (T2DM) 7 years ago. At the time, her glycated hemoglobin (A1c) was 8.7% and body mass index (BMI) 34.6 kg/m^2. After 10 months of lifestyle management, her A1c was 8.2% and her BMI 32.8 kg/m^2. Metformin was added and titrated to 1 g twice daily. Currently, her A1c is 7.6%, BMI 33.1 kg/m^2, blood pressure 138/94 mm Hg, and low-density lipoprotein cholesterol (LDL-C) 86 mg/dL. Her estimated glomerular filtration rate is 74 mL/min/1.73 m^2 with no evidence of albuminuria. She was diagnosed with 75% obstruction of the left anterior descending coronary artery 1.5 years ago. In addition to metformin, her current medications are hydrochlorothiazide 25 mg, rosuvastatin 20 mg, both once daily, isosorbide dinitrate 20 mg three times daily, and nitroglycerin prn.

What change would you make to her treatment plan for T2DM?

CARDIOVASCULAR RISK IN TYPE 2 DIABETES MELLITUS

As shown by the Framingham Heart Study 4 decades ago, T2DM is an independent cardiovascular (CV) risk factor, conferring a greater risk of CV disease in men and women with diabetes mellitus compared with those without diabetes mellitus (relative risk [RR], 2.1 and 2.6, respectively).[1] The risk is especially high in men and women with diabetes mellitus versus without diabetes mellitus for intermittent claudication (RR, 3.6 and 5.7, respectively) and heart failure (HF) (RR, 2.1 and 4.6, respectively). In fact, peripheral arterial disease is the most common initial presentation of CV disease in persons with T2DM (hazard ratio, 2.98).[2] Generally, the risk of cardiovascular events increases with the duration of T2DM. For example, the risk of both myocardial infarction (MI) and HF in persons with T2DM for 20 or more years is approximately twice the risk compared with persons with T2DM for less than 5 years.[3]

As shown by the United Kingdom Prospective Diabetes Study, glycemic lowering reduces CV events. For every 1% reduction of the A1c, the incidence of HF is reduced 16%, MI 14%, and stroke 12%.[4] Lower extremity amputation or fatal peripheral vascular disease is reduced 43% for every 1% reduction of the A1c. These findings are an important reminder of 2 key points to consider when managing patients with T2DM. (1) A treat-to-target approach to achieve and maintain glycemic targets is important.[5] (2) Reducing the blood glucose is important, but a key treatment objective is to reduce microvascular and macrovascular disease.

Other cardiovascular risk factors

In addition to T2DM, there are other independent modifiable risk factors for CV disease, including smoking, obesity, hyperlipidemia, and hypertension. It is, therefore, critical that all major risk factors for CV disease be identified and appropriately managed. The American Diabetes Association (ADA) does not recommend routine screening for coronary heart disease in asymptomatic patients provided that identified CV risk factors are appropriately managed.[6] Screening should be considered in patients with atypical cardiac symptoms, such as unexplained dyspnea or chest discomfort, if there are signs or symptoms of associated vascular disease, or if abnormalities on the electrocardiogram are noted.[6]

In the case scenario above, further treatment of the patient's body weight, blood pressure, and elevated LDL-C is needed to achieve recommended targets and reduce CV risk.[7-9] An angiotensin converting enzyme inhibitor or angiotensin receptor blocker should be considered as a component of antihypertensive therapy and for kidney protection. Other components of comprehensive management of patients with T2DM include antiplatelet therapy, physical activity, regular examination of eyes, mouth/teeth, skin, feet, and kidney function, as well as diabetes distress and overall quality of life.

Communication about cardiovascular risk

Communicating with patients with diabetes mellitus about CV risk is important since the majority are not aware that CV disease is the leading cause of death in patients with T2DM as shown by the "For Your Sweet Heart" survey.[10] Moreover, the survey showed that half of patients with T2DM do not realize that they are at an increased risk for CV disease and related macrovascular events. Becoming aware of this association would prompt 88% to modify their diet and 81% to talk with their health care provider. At the minimum, it is suggested that discussion with the patient with T2DM about CV risk address the following 3 questions[11]:

- What is a heart attack?
- What is my risk of having a heart attack?
- How can I reduce my risk?

The discussion might include the consequences of CV disease, including not only mortality, but reduced functioning and quality of life, as well as pain. It also may be helpful to compare the patient's risk for a CV event with a person of average risk using the American College of Cardiology ASCVD Risk Estimator (https://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate/). Similarly, comparing the patient's A1c, blood pressure, and cholesterol with recommended targets can help the patient focus on the path to improved CV health, beginning with a shared decision making process to develop a treatment plan.

CARDIOVASCULAR OUTCOME TRIALS

US Food and Drug Administration 2008 guidance

Approximately 20 years following publication of the

TABLE Medications for type 2 diabetes mellitus showing cardiovascular benefit

Medication	CVOT(s)	Use/prevention	MACE[a]	HF benefit	Renal benefit
GLP-1 Receptor Agonists					
Albiglutide[14]	HARMONY	2°	✔		
Dulaglutide[15,16]	REWIND	1° & 2°	✔		✔
Liraglutide[17,18]	LEADER	1° & 2°	✔		✔
Semaglutide[19]	SUSTAIN 6[b]	1° & 2°	✔		✔
Sodium Glucose Cotransporter-2 Inhibitors					
Canagliflozin[20,21]	CANVAS/-R, CREDENCE	1° & 2°	✔	✔	✔
Dapagliflozin[22,23]	DECLARE-TIMI 58	1° & 2°		✔	✔
Empagliflozin[24-26]	EMPA-REG OUTCOME	2°	✔	✔	✔

Abbreviations: CVOT, cardiovascular outcome trial; HF, heart failure; MACE, major adverse cardiovascular event.

[a]Composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke

[b]Injectable route of administration

Framingham Heart Study showing an increased risk of CV disease in patients with diabetes mellitus, a meta-analysis of 42 randomized controlled trials was published suggesting that rosiglitazone increased the risk of MI in patients with T2DM.[12] Further investigation several years later allayed these concerns, but in the interim, the US Food and Drug Administration (FDA) issued a guidance in 2008 requiring industry sponsors to demonstrate in a clinical trial that a new medication for T2DM is not associated with an unacceptable increase in CV risk compared to placebo as part of standard care in patients at increased risk of a CV event.[13] The guidance applies to all medications for T2DM developed since 2008, including the dipeptidyl peptidase-4 inhibitors (DPP-4is), glucagon-like peptide-1 receptor agonists (GLP-1RAs) (except exenatide twice-daily, since it was approved prior to issuance of the FDA guidance), and sodium glucose cotransporter-2 inhibitors (SGLT-2is).

The primary endpoint of a CV outcome trial (CVOT) is the incidence of a major adverse CV event (MACE), which is a composite of CV death, nonfatal MI, and nonfatal stroke. Most CVOTs also investigate other CV events, eg, HF and kidney function. The trials should be long enough to obtain enough events and to provide data on longer-term CV risk. They should include patients with T2DM at higher risk of CV events, eg, advanced disease, advanced age, or renal impairment.

The FDA guidance specifies that a finding of noninferiority, ie, safety comparable to placebo, is demonstrated if the upper limit of the two-sided 95% confidence interval (CI) for the estimated risk ratio is less than 1.3. If noninferiority is demonstrated, further investigation to assess CV risk reduction is allowed. A risk ratio less than 1 indicates superiority, demonstrating that the new medication reduces CV risk compared to placebo as part of standard care.

Overview of cardiovascular outcome trials

One or more CVOT has been completed for all 4 DPP-4is (alogliptin, linagliptin, saxagliptin, sitagliptin), 6 GLP-1RAs (albiglutide, dulaglutide, exenatide once-weekly, liraglutide, lixisenatide, injectable and oral semaglutide), and 3 SGLT-2is (canagliflozin, dapagliflozin, empagliflozin). The VERTIS-CV trial for ertugliflozin is ongoing. Most of the trials have included patients at high risk of CV disease (1° prevention) as well as patients with established CV disease (2° prevention). All completed CVOTs have demonstrated the new medication for T2DM is noninferior to placebo as part of standard care, thereby providing reassurance that it poses no increased CV risk.

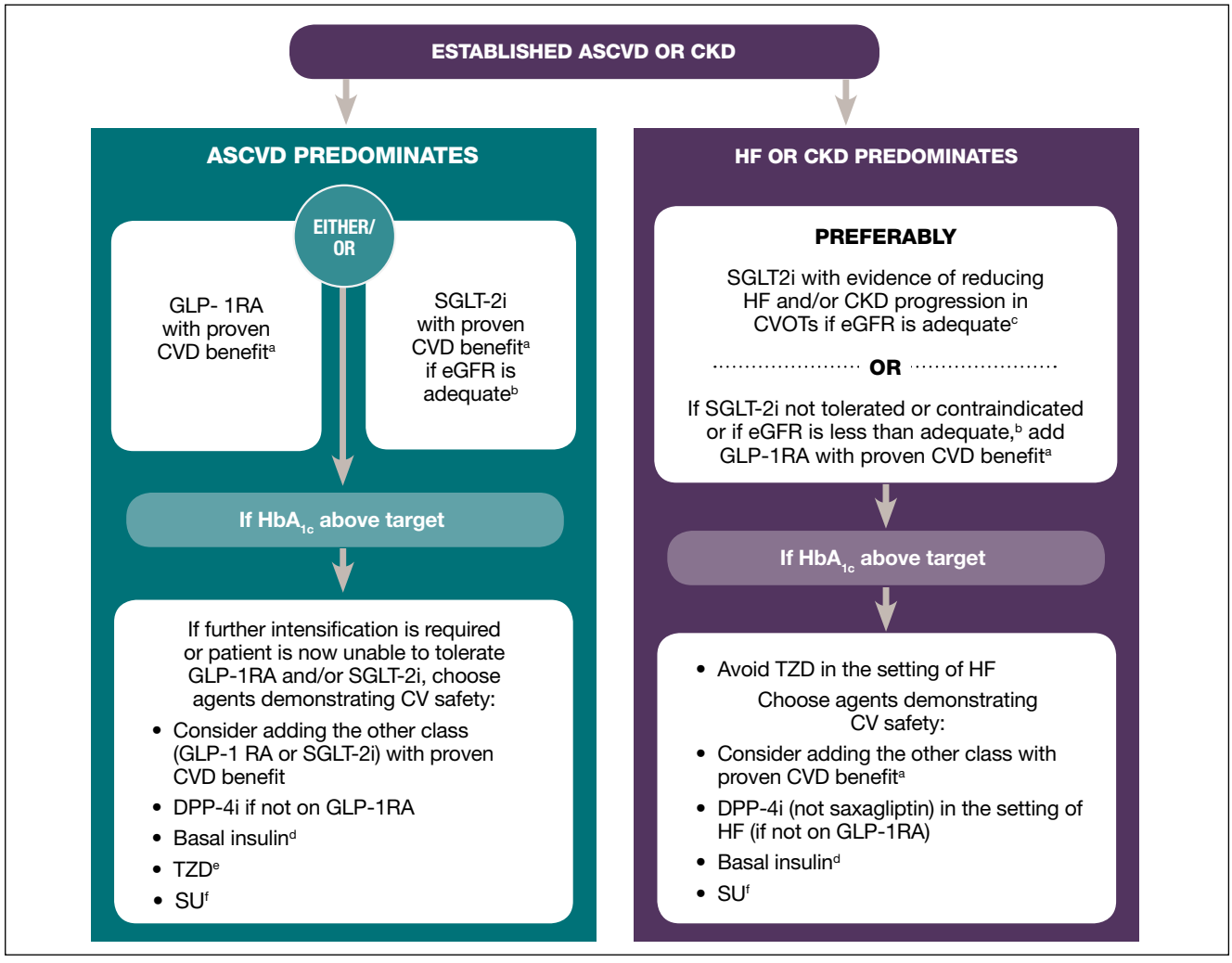
In addition, superiority, ie, significant reduction in CV risk, has been demonstrated for the primary endpoint (MACE) for the GLP-1RAs albiglutide, dulaglutide, liraglutide, and injectable semaglutide and the SGLT-2is canagliflozin and empagliflozin (**TABLE**).[14-26] Furthermore, the GLP-1RAs dulaglutide, liraglutide, and semaglutide have shown a reduction in kidney events, while empagliflozin, canagliflozin, and dapagliflozin have shown a reduction in kidney events, as well as HF events, in CVOTs.

It is also worth noting that the safety of insulin glargine U-100 has been shown to be noninferior to standard care for MACE in a head-to-head trial. [27] The safety of degludec was compared with glargine U-100 in a head-to-head trial showing degludec to be noninferior to glargine U-100 for MACE.[28] Finally, in its review of the new drug application for glargine U-300, the FDA concluded that there is no safety concern with glargine U-300 compared with glargine U-100.[29]

PATIENT-CENTRIC APPROACH TO DIABETES CARE

A key principle of the ADA Standards of Medical Care in

FIGURE Treatment of patients with type 2 diabetes mellitus and established atherosclerotic cardiovascular disease or chronic kidney disease who do not achieve glycemic control with first-line therapy of metformin and comprehensive lifestyle management[31]



Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; CVOTs, cardiovascular outcome trials; DPP-4i, dipeptidyl peptidase-4 inhibitor; FDA, US Food and Drug Administration; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; $HbA1_c$, hemoglobin A1c; HF, heart failure; SGLT-2i, sodium glucose cotransporter-2 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione.

[a] Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1RA, liraglutide is FDA approved to reduce the risk of MACE in adults with type 2 diabetes and established CVD; liraglutide and dulaglutide showed superiority for MACE outcomes in large CVOTs; semaglutide showed superiority for MACE outcomes in a safety CVOT. These results were primarily in patients with known ASCVD although there was consistent benefit in the dulaglutide trial in patients with and without established ASCVD. For SGLT-2i, evidence modestly stronger for empagliflozin > canagliflozin.

[b] Be aware that SGLT-2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use.

[c] Empagliflozin, canagliflozin, and dapagliflozin have shown reduction in HF and reduction in CKD progression in CV outcome trials.

[d] Degludec or glargine U-100 have demonstrated CV safety.

[e] Low dose may be better tolerated though less well studied for CVD effects.

[f] Choose later generation sulfonylurea with lower risk of hypoglycemia.

Diabetes – 2019 is for the provision of patient-centered diabetes care, ie, care that is respectful of and responsive to individual patient preferences, needs, and values, and that ensures that patient values guide all clinical decisions.[30] Medication-specific factors are an important consideration as well and include effectiveness in glycemic lowering, adverse events (particularly hypoglycemia and weight change), route of administration, cost, and contraindications/warnings.

According to the ADA, the following classes of medications are recommended for a patient *without established* atherosclerotic CV disease (ASCVD) or chronic kidney disease (CKD) who does not achieve adequate glycemic control with metformin and lifestyle management in the following situations[31]:

- Compelling need to minimize hypoglycemia: DPP-4i, GLP-1RA, SGLT-2i, thiazolidinedione
- Compelling need to minimize weight gain or promote weight loss: GLP-1RA with good efficacy for weight loss or SGLT-2i
- Cost is a major issue: sulfonylurea or thiazolidinedione

For patients *with established* ASCVD or CKD who do not achieve adequate glycemic control with metformin and lifestyle management, the ADA now provides specific recommendations for combination glucose-lowering therapy (**FIGURE,** previous page).[31] These diabetes medications do not replace the need for other therapy for ASCVD, HF, or CKD as recommended in current guidelines.

Patients where established atherosclerotic cardiovascular disease predominates

For a patient where established ASCVD predominates, the addition of either a GLP-1RA or SGLT-2i with proven CV disease benefit as reflected in FDA-approved labeling is recommended. Based on the results of the CVOTs, the FDA-approved indication for the following medications has been updated to include the following:

- Canagliflozin: to reduce the risk of MACE in adults with T2DM and established CV disease and to reduce the risk of end-stage kidney disease, doubling of serum creatinine, cardiovascular death, and hospitalization for heart failure in adults with T2DM and diabetic nephropathy with albuminuria >300 mg/d[32]
- Empagliflozin: to reduce the risk of CV death in adult patients with T2DM and established CV disease[33]
- Liraglutide: to reduce the risk of MACE in adults with T2DM and established CV disease[34]

An SGLT-2i should not be initiated in a patient with an estimated glomerular filtration rate <45 mL/min/1.73 m^2. For GLP-1RAs, the strongest evidence is for liraglutide, dulaglutide, and semaglutide and for SGLT-2is, empagliflozin over canagliflozin. It should be noted that this hierarchy was determined by the ADA Standards of Care panel based on available evidence, but that the CVOTs were not head-to-head comparisons of the new medication with active treatment.

Patients where established heart failure or chronic kidney disease predominates

For a patient where HF or CKD predominates, an SGLT-2i with evidence of reducing HF and/or CKD progression is preferred provided that the eGFR is ≥45 mL/min/1.73 m^2.[31] Therefore, canagliflozin, dapagliflozin, or empagliflozin are recommended for patients with established HF or CKD.[20-26] Note that the FDA-approved indication for canagliflozin has been expanded to include a benefit in patients with CKD based upon the results of the CREDENCE trial.[35] If an SGLT-2i is not tolerated, the addition of a GLP-1RA with proven CV benefit is recommended. For a patient with CKD, dulaglutide, liraglutide, or semaglutide would be preferred due to their demonstrated benefits in slowing progression of kidney disease.[15,17-19]

CASE SCENARIO (SUMMARY)

This patient's inadequate glycemic control with metformin and lifestyle management indicates the need for treatment intensification. Since she has established ASCVD, the use of a GLP-1RA or SGLT-2i with proven CV benefit is recommended. Of these, the use of a medication with an approved ASCVD-related indication would be preferred, ie, canagliflozin, empagliflozin, and liraglutide.

If the patient had established HF or CKD, an SGLT-2i with proven CV benefit is recommended, ie, canagliflozin, dapagliflozin, and empagliflozin. Additional therapy to address comorbidities as recommended in current guidelines also would be necessary.

Finally, while it may be preferable to use medications approved by the FDA for reducing CV risk in patients with T2DM and established CV disease, insurance coverage may necessitate consideration of other medications in the same class. In this case, those shown to provide a CV benefit may be preferred. ●

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