Cardiovascular Risk Reduction in Patients with Type 2 Diabetes

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ABSTRACT

- *Objective*: To review the assessment of cardiovascular risk and prevention of vascular disease in patients with type 2 diabetes mellitus (T2DM).
- *Methods*: Literature and guidelines were reviewed and the evidence is presented around a clinical case.
- *Results*: T2DM has a high prevalence and confers significant lifetime risk for macrovascular disease, including stroke, heart disease, and peripheral arterial disease. There is strong evidence to support nonpharmacologic interventions, such as smoking cessation and weight loss, and pharmacologic interventions, such as statin therapy, in order to decrease lifetime risk. The effectiveness of an intervention as well as the strength of the evidence supporting an intervention differs depending on the stage of the disease.
- *Conclusion*: Once a patient is diagnosed with T2DM, it is important to recognize that their lifetime risk for vascular disease is high. Starting at this stage and continuing throughout the disease course, cardiovascular risk should be assessed in an ongoing manner and evidence-based interventions should be implemented whenever they are indicated. Using major guidelines as a framework, we provide an evidence-based approach to the reduction of vascular risk in these patients.

Key words: *cardiovascular disease, diabetes, prevention, risk assessment, risk factors.*

Type 2 diabetes (T2DM) is considered epidemic in the developed world, and is rapidly increasing in the developing world. Since 1980, there has been a near quadrupling of the number of adults with diabetes worldwide to an estimated 422 million in 2014 [1]. Because diabetes affects the whole body vascular system, there is a significant burden of vascular complications directly attributable to diabetes. Although the rates of diabetes-related complications are declining, the burden of disease remains high due to the increasing prevalence of diabetes [2]. The tremendous burden of diabetes and its complications on the population make it imperative that all health care practitioners understand the vascular effects of diabetes as well as evidence-based interventions that can mitigate them. In this review, we present an approach to the assessment, prevention, and treatment of cardiovascular disease in patients with T2DM.

CASE STUDY

A 38-year-old male presents to his family physician's office for a routine check-up. He is obese and a smoker, has no other health issues, and is taking no medications. He is sent for routine bloodwork and his A1c and fasting glucose are elevated and are diagnostic for diabetes. He returns to the clinic to discuss his results.

- **How are cardiovascular risk and risk factors assessed in a patient with diabetes?**

There are many risk scores and risk calculators available for assessing cardiovascular risk. The Framingham Risk Score is the most commonly employed and takes into account the most common risk factors for cardiovascular risk, including cholesterol level, age, gender, and smoking status. Unfortunately, because a patient with diabetes may have a high lifetime risk but low or moderate short-term risk, these risk scores tend to underestimate overall risk in the population with diabetes [3,4]. Furthermore, since early intervention can decrease lifetime risk, it is important to recognize the limitations of these risk scores.

In a patient with diabetes, cardiovascular risk is conferred by all of the classical risk factors, including

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age, gender, blood pressure, cholesterol, and smoking. In addition, there are a number of risk factors specific to diabetes, such as diabetes duration, glycemic control, and the presence of microvascular complications [5] (**Table 1**). Complete assessment of lifetime cardiovascular risk must take into accounts all of these factors.

Table 1. Cardiovascular Risk Factors in Patients with Diabetes

Classical Risk Factors
Age
Male gender
Hypertension
Smoking
Cholesterol (LDL)
Family history
Chronic kidney disease
Diabetes-Specific Risk Factors
Duration of diabetes
Glycemic control
Presence of microvascular complications (retinopathy, neuropathy, microalbuminuria)

- **What interventions should be used for primary prevention at this stage?**

A number of interventions can decrease lifetime risk for cardiovascular disease in persons with diabetes. First, smoking increases risk for all forms of vascular disease, including progression to end-stage renal disease, and is an independent predictor of mortality. Smoking cessation is one of the most effective interventions at decreasing these risks [6]. Second, lifestyle interventions such as diet and exercise are often recommended. The Look AHEAD trial studied the benefits of weight loss and exercise in the treatment of T2DM through a randomized control trial involving more than 5000 overweight patients with T2DM. Patients were randomly assigned to intensive lifestyle interventions targeting weight loss or a support and education group. Although the Action for Health in Diabetes (Look AHEAD) trial did not demonstrate clinical outcome benefit with this intensive intervention, there was improvement in weight, cholesterol level, blood pressure, and glycemic control, and clinical differences may have been related to study power or differences in cardioprotective medication use [7]. Furthermore, at least 1 large randomized trial of dietary intervention in high-risk cardiovascular patients, half of whom had diabetes (Prevención con Dieta Mediterránea [PREDIMED]), showed significant benefits in cardiovascular disease, reducing the incidence of major cardiovascular events [8]. According to most diabetes guidelines, diet and exercise continue to be stressed as initial management for all patients with diabetes [9–12].

In addition, although intensive glucose control decreases microvascular complication rates, it has been more difficult to demonstrate a reduction in cardiovascular disease with more intense glycemic control. However, long-term follow-up of the United Kingdom Prospective Diabetes Study (UKPDS) cohort, a population that was earlier in their diabetes course, clearly demonstrated a reduction in cardiovascular events and mortality with better glycemic control over the long term [13,14]. For those who are later in their diabetes course, meta-analyses of glycemic control trials, along with follow-up studies, have also shown that better glycemic control can reduce cardiovascular events, but not mortality [15–17]. Therefore, glucose lowering should be pursued for cardiovascular risk reduction, in addition to its effects on microvascular complications.

It is well established that a multifactorial approach to cardiovascular risk reduction in patients with type 2 diabetes is effective. In the Steno-2 study, 160 patients with type 2 diabetes were randomly assigned to receive multidisciplinary, multifactorial intensive target-based lifestyle and pharmacologic intervention or standard of care. The intensive therapy group all received smoking cessation counseling, exercise and dietary advice, vitamin supplementation, and an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB). Acetylsalicylic acid (ASA) was added for all patients with clinical macrovascular disease. Dyslipidemia, hypertension, and hyperglycemia were all treated in a protocolized way if lifestyle interventions did not achieve strict targets. During the mean 7.8 years of follow-up, the adjusted hazard ratio for a composite of cardiovascular death and macrovascular disease was 0.47 (95% confidence interval [CI] 0.22 to 0.74; $P = 0.01$) [18]. These patients were followed for an additional 5.5 years in an observational study with no further active intervention in both groups. Over the entire period, there was an absolute risk reduction of 20% for

death from any cause, resulting in a number needed to treat of 5 for 13 years [19]. As a result of these compelling data, guidelines from around the world support a multifactorial approach, with the Canadian Diabetes Association (CDA) guidelines [20] promoting the use of the "ABCDES" of vascular protection:

A – A1C target

B – Blood pressure target

C – Cholesterol target

D – Drugs for vascular protection

E – Exercise/Eating

S – Smoking cessation

- **Is any particular dietary pattern recommended?**

There is a large and ever-growing number of dietary patterns that are marketed to improve weight and cardiovascular health. Unfortunately, however, few of these interventions have been studied rigorously, and most dietary interventions are found to be unsustainable in the long term. In the case of motivated patients, there are some specific dietary patterns with high-quality evidence to recommend them. The simplest intervention is the implementation of a vegetarian or vegan diet. Over 18 months, this has been shown to improve fasting glucose and cholesterol profile, and promote weight loss [21]. In another study, a calorie-restricted vegetarian diet led to a reduction in diabetes medication in 46% of participants (versus 5% with conventional diet) [22].

A Mediterranean diet is comprised of large amounts of fruits, vegetables, legumes, nuts, and whole grains. In addition, it includes moderate consumption of olive oil, dairy, fish and poultry, with low consumption of red meat. This dietary pattern has been extensively studied, and in a meta-analysis has been shown to improve glycemic control, blood pressure, and lipid profile [23]. The PREDIMED study evaluated the efficacy of 2 versions of the Mediterranean diet, one supplemented with olive oil or mixed nuts, for reducing cardiovascular events. This multicenter randomized control trial of 7447 participants at high cardiovascular risk (48.5% of whom had diabetes) was stopped early due to benefit. Both versions of the diet reduced cardiovascular events by 30% over 5 years of follow-up [8].

The Dietary Approaches to Stop Hypertension (DASH) diet is similar to the Mediterranean diet in focusing on fruits, vegetables, low-fat dairy, whole grains, nuts, fish, and poultry, while avoiding red meat. In addition, it explicitly recommends avoiding sweets and sweetened beverages, as well as dietary fat. In a trial of patients with diabetes matched for moderate sodium intake, the DASH diet has been shown to decrease A1c, blood pressure, and weight and improve lipid profile within 8 weeks [24,25].

In addition to these specific dietary patterns, specific foods have been shown to improve glycemic control and cardiovascular risk profile, including mixed unsalted nuts, almonds, dietary pulses, and low-glycemic versus high-glycemic index carbohydrates [26–31].

In accordance with CDA, American Diabetes Association (ADA), and European Association for the Study of Diabetes (EASD) guidelines, we recognize that a variety of diets can improve the cardiovascular risk profile of a patient [12,32,33]. Therefore, we suggest a tailored approach to dietary changes for each individual patient. This should, whenever possible, be undertaken with a registered dietitian, with emphasis placed on the evidence for vascular protection, improved risk profile, patient preference, and likelihood of long-term sustainability.

- **Should therapy for weight loss be recommended for this patient?**

There are currently a number of effective strategies for achieving weight loss, including lifestyle interventions, pharmacotherapy, and surgery. The evidence base for dietary interventions for diabetes is reviewed above. The Look AHEAD study randomized 5145 overweight or obese patients with T2DM to intensive lifestyle intervention for weight loss through promotion of decreased caloric intake and increased physical activity, or usual diabetes support and education. After a median follow-up of 9.6 years, the study was stopped early on the basis of a futility analysis despite greater weight loss in the intervention group throughout the study. However, other benefits were derived including reduced need for medications, reduced sleep apnea, and improved well-being [7].

Pharmacotherapy agents for weight loss have been approved by various regulatory agencies. None has as yet

Table 2. Initial and Periodic Risk Assessments in Patients with Type 2 Diabetes

	Diagnosis	3 Mo	6 Mo	9 Mo	1 Yr
A1c	X	X	X	X	X
Blood pressure	X	X	X	X	X
Smoking status	X	X	X	X	X
Diet/exercise	X	X	X	X	X
Lipid profile	X		X (if positive)		X
Albumin: creatinine and serum creatinine	X	X (if positive)			X
Foot examination	X				X
Dilated retinal exam	X				X

shown a reduction in cardiovascular events. Therefore, these cannot be recommended as therapies for vascular protection at this time.

Bariatric surgery is an effective option for weight loss in patients with diabetes, with marked and sustained improvements in clinically meaningful outcomes when compared with medical management. The longest study of bariatric surgery is the Swedish Obesity Study, a prospective case-control study of 2010 obese patients who underwent bariatric surgery and 2037 matched controls. After a median of 14.8 years of follow-up, there was a reduction in overall mortality (hazard ratio [HR] 0.71) and decreased incidence of diabetes (HR 0.17), myocardial infarction (HR 0.71), and stroke (HR 0.66). Diabetes remission, defined as normal A1c off of antihyperglycemic therapy, was increased at 2 years (odds ratio [OR] 13.3) and sustained at 15 years (OR 6.3) [34–36]. Randomized controlled trials of bariatric surgery have thus far been small and do show some decreases in cardiovascular risk factors [37–40]. However, these have not yet been of sufficient duration or size to demonstrate a decrease in cardiovascular event rate. Although local policies may vary in referral recommendation, the Obesity Society, ADA, and CDA recommend that patients with a body mass index greater than 40 kg/m^2, or greater than 35 kg/m^2 with an obesity-related comorbidity such as diabetes, should be referred to a center that specializes in bariatric surgery for evaluation [41–43].

Case Continued

After the initial diagnosis, the patient was seen by a registered dietitian and followed a Mediterranean diet for some time but has since stopped. He is seen regularly for follow-up of his diabetes at 3- to 6-month intervals. He initially lost some weight but has unfortunately regained the weight. He tells you proudly that he finally quit smoking. He was started on metformin about 6 months after diagnosis to address his glycemic control. He continues on the metformin now as his only medication.

The patient returns to clinic for his usual follow-up visit approximately 5 years after initial diagnosis. He is feeling well with no new medical issues. He has no clinically apparent retinopathy or macrovascular complications. On examination, his blood pressure is 140/90 mm Hg and the remainder of the exam is unremarkable. His bloodwork shows an A1c of 8% and a low-density lipoprotein cholesterol (LDL-C) level of 124 mg/dL. His albumin-to-creatinine ratio is normal.

- **How often should cardiovascular risk be reassessed?**

Every patient visit should be seen as an opportunity to assess and reduce cardiovascular risk. The factors to assess include glycemic control, blood pressure, lifestyle, and smoking status. In addition, for the patient not on lipid-lowering therapy, a fasting cholesterol profile should be checked at diagnosis and then periodically every 1 to 5 years thereafter. If therapy is initiated, this interval should be decreased to every 3 to 6 months. Patients should be screened for microvascular complications at least once per year after diagnosis, with a complete foot examination, urinary albumin-to-creatinine ratio, and dilated retinal examination (**Table 2**) [44,45].

- **When should initiating pharmacotherapy to reduce risk in primary prevention be considered?**

In the population with diabetes, statins and renin-angiotensin-aldosterone inhibition are the mainstays of pharmacotherapy for cardiovascular risk reduction. In the presence of clinical macrovascular disease, the standard of care includes both of these therapies. However, there is also a great deal of data that supports the use of these therapies for primary prevention.

Statins

Major studies on the benefits of statin therapy in people with diabetes have consistently shown decreased cardiovascular disease and mortality. The Heart Protection Study included a subgroup of patients with diabetes in which patients over the age of 40 were randomly assigned to simvastatin or placebo. Consistently across all subgroups, there was a relative risk reduction of 22% to 33% for the primary outcome of first cardiovascular event over 5 years. This effect was maintained even in those who did not have elevated LDL-C at randomization [46]. Similarly, the Collaborative Atorvastatin Diabetes Study (CARDS) randomized patients with T2DM, over age 40, with at least 1 other vascular risk factor to atorvastatin 10 mg or placebo. They found a 37% risk reduction in time to first event over 4 years with atorvastatin, with consistent results across all subgroups [47].

Based on these studies, it is recommended that all patients with diabetes be placed on statin therapy to reduce vascular risk at age 40 years (CDA, ADA, American College of Cardiology/American Heart Association [ACC/AHA]) [20,45,48]. If under age 40 years, statin therapy should be considered in the presence of other risk factors (ADA, ACC/AHA) [45,48], or if diabetes duration is more than 15 years and age is greater than 30 years, or there are micro- or macrovascular complications (CDA) [20].

Renin-Angiotensin-Aldosterone Inhibition

Similar to research into statin therapy, a considerable amount of research has been dedicated to renin-angiotensin-aldosterone system (RAAS) blockade for the primary purpose of vascular risk reduction, even in the absence of hypertension, in those with diabetes. In a prespecified substudy of the Heart Outcomes Prevention Evaluation (HOPE) trial, known as MICRO HOPE, patients with diabetes who were older than 55 years of age, with at least 1 other cardiovascular risk factor, were randomized to receive ramipril 10 mg daily or placebo. In this study, ramipril reduced the risk for myocardial infarction (22%), stroke (33%), cardiovascular death (37%), and all-cause mortality (24%) over 4.5 years [49]. In the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET), patients at high risk for cardiovascular disease were randomized to telmisartan 80 mg or ramipril 10 mg. In the diabetes subgroup, there were similar risk reductions and no statistical difference between the groups [50]. A 2012 meta-analysis assessed the benefits of RAAS blockade compared with placebo for primary prevention in high-risk individuals, or secondary prevention in those with established vascular disease. A reduction in cardiovascular death, all-cause mortality, fatal or nonfatal myocardial infarction, and stroke was seen across all subgroups, including those with and without diabetes or hypertension [51].

The CDA currently recommends that an ACE inhibitor or ARB be given to all patients with diabetes who are 55 years of age or older, or have macro- or microvascular disease, for the primary purpose of decreasing risk for vascular disease, even in the absence of hypertension. An agent and dose with proven vascular protective benefit should be chosen when selecting an ACE inhibitor or ARB [20].

- **Should this patient start ASA therapy?**

Whether to start daily low-dose ASA for primary prevention of coronary artery disease has been a long-standing question in patients with diabetes. The benefits of ASA therapy with regards to coronary artery disease have long been known from a secondary prevention standpoint, and given the low risk and long experience, primary prevention seemed reasonable. However, no high-quality randomized controlled trials enrolling large numbers of patients with diabetes have been performed in the current era of medical therapy, specifically in the era of widespread statin use. The initial studies examining ASA use in primary prevention were analyzed in a meta-analysis in 1994 and showed a trend towards benefit for ASA in patients with diabetes [52]. Further trials increased the number of diabetes patient-years studied but did not change the initial result. Five meta-analyses have been

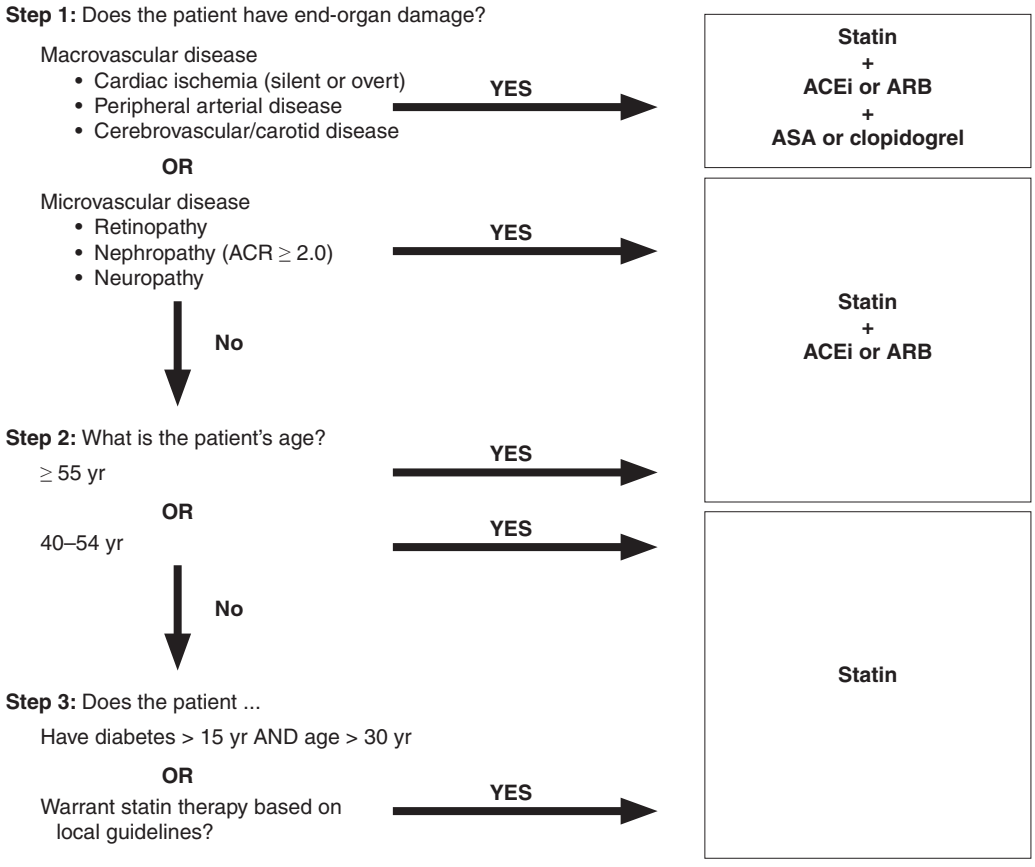

Figure. Pharmacotherapy for vascular benefit. ACEi = angiotensin-converting enzyme inhibitor; ACR = albumin:creatinine ratio; ARB = angiotensin receptor blocker; ASA = acetylsalicylic acid. (Adapted from reference 20.)

conducted on the currently available trials, and all but one do not show a significant reduction in coronary artery disease or stroke in patients with diabetes [53–57]. In addition, ASA is known to cause a small absolute increase in the risk for gastrointestinal hemorrhage that is consistent across all studies, with a number needed to harm of approximately 100 over 2.5 years. Therefore, the possible small absolute benefit that was seen in ASA trials with regards to coronary artery disease in the era before statin therapy must be weighed against the known risk of bleeding. Because of this, the CDA and European Society of Cardiology have recommendations against the routine use of ASA for primary prevention in patients with diabetes [12,20].

Since these meta-analyses, one further trial has been completed, the Japanese Primary Prevention Project (JPPP). In a subset of 4903 patients with diabetes, there was no significant benefit to ASA 100 mg for primary prevention of cardiovascular disease [58]. In the near future, 2 large trials looking specifically at patients with diabetes are planned, ASCEND [59] and ACCEPT-D [60], which will help definitively answer the question of whether ASA is beneficial for primary prevention in the era of widespread statin usage.

A summary of pharmacotherapy for cardiovascular risk reduction is shown in the **Figure**.

Case Continued

The patient is started on a statin because of his elevated LDL-C level in the context of being over the age of 40 years with T2DM. He is also started on an ACE inhibitor to address the hypertension. In addition, a dipeptidyl peptidase-4 inhibitor is added to his metformin to address the elevated A1c. He continues to follow up every 3 to 6 months.

Six years later, he experiences an episode of retrosternal chest discomfort while exercising. He is brought to hospital and is found to have a non-ST elevation myocardial infarction. He is admitted to hospital, undergoes percutaneous revascularization of a single lesion, and is discharged to a rehabilitation center. He is discharged on aspirin, clopidogrel, an ACE inhibitor, a beta blocker, and a high-intensity statin. His blood pressure is well managed, and he has lost further weight since he was last seen. When he returns to clinic, he wonders if there is anything more he can do to prevent further events.

- **What secondary prevention of cardiovascular disease is recommended for patients with T2DM?**

Optimal secondary prevention following a major vascular event includes a combination of pharmacologic and nonpharmacologic interventions. In the population without diabetes, evidence supports smoking cessation, exercise, cardiac-specific rehabilitation, antiplatelets, RAAS antagonists, beta-blockade, and statins. Most of the trials that led to this standard suite of interventions had large diabetes subgroups. Therefore, there is no difference in the secondary prevention of cardiovascular disease in the population with diabetes with regard to these interventions.

- **Have any antihyperglycemic agents been shown to reduce cardiovascular events?**

Metformin

Due to its long history and safety profile, metformin is considered the first-line antihyperglycemic agent in most of the developed world. Despite this, there are few high-quality studies specifically assessing the efficacy of metformin at decreasing cardiovascular event rate. The landmark UKPDS trial compared intensive to conventional glycemic therapy. In a substudy, 753 overweight patients were randomized to metformin or conventional therapy. Diabetes-related death, all-cause mortality, and any diabetes endpoint were all decreased significantly in the metformin group [13]. Furthermore, 10 years of post-trial observational follow-up showed continued benefit in the metformin group despite loss of difference in glycemic control [14]. However, the cardiovascular benefit of metformin in the current era is controversial, with conflicting results from different meta-analyses [61,62].

A summary of the vascular effects observed during trials of antihyperglycemic agents is shown in **Table 3**.

Empagliflozin

Many large randomized, controlled cardiovascular outcome trials have been completed or are ongoing looking at the cardiovascular safety of newer antihyperglycemic agents. The majority of the completed trials have shown a neutral effect, suggesting that the agents are safe. However, in September 2015, the first cardiovascular outcome trial of an antihyperglycemic agent with a positive result was published. The Empagliflozin Cardiovascular Outcome Event Trial (EMPA-REG OUTCOME) randomized 7020 patients with T2DM and cardiovascular disease (defined as nonacute myocardial infarction, multivessel coronary artery disease, unstable angina, nonacute stroke, or occlusive peripheral arterial disease) to placebo or 1 of 2 doses of empagliflozin. The primary outcome of cardiovascular mortality, nonfatal myocardial infarction, or stroke was reduced by 14% in the empagliflozin-treated group. Key secondary outcomes of all-cause mortality (HR 0.68) and heart failure hospitalization (HR 0.65) were also statistically different in favor of the empagliflozin arm [63].

On the basis of this trial's results, empagliflozin should be considered for treatment of all patients with type 2 diabetes and known cardiovascular disease. It is as yet unknown whether this effect will translate to the other members of the sodium-glucose co-transporter 2 (SGLT-2) inhibitor class, although results of studies involving other SGLT-2 inhibitors are expected in the next 2 to 3 years.

Liraglutide

In 2016, the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial reported results of its cardiovascular safety trial. In this trial, 9340 patients with either established vascular disease or risk factors for vascular disease were randomized to daily liraglutide or placebo injections. The primary composite outcome of cardiovascular death, nonfatal myocardial infarction, or stroke was reduced by 13%. A key secondary outcome of all-cause mortality also showed a significant reduction (HR 0.85). There was no reduction in hospitalization for heart failure [64].

Table 3. Comparison of Vascular Effects with Antihyperglycemic Agents

Agent	Study	Patient Population	Key CV Results	Key Exclusion Criteria
CV BENEFIT				
Metformin	UKPDS [13]	753 overweight patients randomized to intensive metformin vs conventional therapy	Compared with conventional therapy: All cause mortality RR 0.64	Serum creatinine > 2 mg/dL
	UKPDS post-trial monitoring [14]	Post-trial monitoring: 279 overweight patients in metformin group vs 309 in conventional therapy arm	Observational follow-up: Mortality RR 0.73 MI RR 0.67	
Empagliflozin	EMPA-REG OUTCOME [63]	7020 patients with T2DM and nonacute macrovascular disease (CAD, CVD, or PAD)	Composite CV outcome* HR 0.86 All-cause mortality HR 0.68	Liver disease, eGFR < 30 mL/min
Liraglutide	LEADER [64]	9340 patients > 50 yr with established CVD, or > 60 with multiple CV risk factors	Composite CV outcome* HR 0.87 All-cause mortality HR 0.85	DPP-4 inhibitor or rapid-acting insulin use, family history of medullary thyroid cancer or MEN2, acute MI or stroke
Semaglutide	SUSTAIN-6 [65]	3297 patients > 50 yr with established CVD, heart failure, or CKD, or > 60 with 1 risk factor	Composite CV outcome* HR 0.74	
NO CV BENEFIT OR HARM				
Saxagliptin	SAVOR-TIMI [66]	16,492 patients > 40 yr with established CVD or > 55 with ≥ 1 CV risk factor	Composite CV outcome* HR 1.00 (no significant difference [noninferiority $P < 0.001$]) Hospitalization for heart failure HR 1.27 (95% CI 1.07 to 1.51; $P = 0.007$)	Serum creatinine > 6 mg/dL, incretin therapy
Alogliptin	EXAMINE [67]	5380 patients with acute coronary syndrome within 15 to 90 days before randomization	Composite CV outcome* HR 0.96 (no significant difference [superiority $P = 0.32$])	Unstable cardiac disorders (arrhythmia, heart failure, refractory angina), ESRD requiring dialysis
Sitagliptin	TECOS [68]	14,671 patients > 50 yr with established CVD	Composite CV outcome* HR 0.98 (no significant difference [noninferiority $P < 0.001$]) No significant difference in hospitalization for heart failure	eGFR < 30 mL/min, incretin therapy
Lixisenatide	ELIXA [69]	Patients with an acute coronary event within 180 days	Composite CV outcome† HR 1.02 (no significant difference [noninferiority $P < 0.001$)]	eGFR < 30 mL/min

CKD = chronic kidney disease; CV = cardiovascular; CVD = cardiovascular disease; DPP-4 = dipeptidyl peptidase 4; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; HR = hazard ratio; MI = myocardial infarction; RR = relative risk.

*Composite CV outcome = CV death, nonfatal myocardial infarction, nonfatal ischemic stroke.

†Composite CV outcome = CV death, nonfatal myocardial infarction, nonfatal stroke, or unstable angina.

Semaglutide

Most recently, the Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6) was completed, assessing cardiovascular safety of a once-weekly injectable glucagon-like peptide-1 (GLP-1) analogue. This nonin-

feriority trial studied 3297 patients with type 2 diabetes over the age of 50 years with established macrovascular disease, chronic heart failure, or chronic kidney disease (stage III or higher), or over the age of 60 years with at least 1 other cardiovascular risk factor. The patients were randomized to 1 of 2 doses of once-weekly semaglutide or placebo injection. A composite cardiovascular outcome of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke was decreased by 26% in the pooled semaglutide group. This was driven primarily by a reduction in nonfatal stroke, with no statistically significant reduction in nonfatal myocardial infarction or cardiovascular mortality. Significant secondary outcomes showed a reduction in new or worsening nephropathy (HR 0.64), and an unexpected increase in retinopathy (HR 1.76) [65].

All of these trials utilized their respective agents as add-on to existing antihyperglycemic therapy. Therefore, first-line antihyperglycemic therapy in a patient with T2DM remains metformin. For the patient with established vascular disease or who is at high risk for developing vascular disease, add-on therapy using an antihyperglycemic agent with proven cardiovascular benefits, such as empagliflozin or liraglutide, is suggested [9,11]. Semaglutide is not yet available for clinical use. The choice between these agents should be based on patient preference, cost, side effect profile, and absence of contraindications.

Currently, there are more studies underway with similar designs with different agents. As these studies are reported in the upcoming years, it is hoped that the options for reduction of cardiovascular risk will increase, and that we will have multiple antihyperglycemic agents that will provide not only glycemic benefit but also cardiovascular risk reduction.

Case Conclusion

The patient continues to abstain from smoking. He follows up with a dietitian and is enrolled in an exercise program. He remains on his cardiac medications. For glycemic control, he continues on his previous antihyperglycemic therapy and an antihyperglycemic agent with proven cardiovascular benefit is added. With these interventions, he understands that his risk is mitigated, but given his history and previous event, he remains at high risk for future vascular disease.

Conclusion

The care of a patient with diabetes requires a multifactorial approach. All patients are at risk for developing the vascular complications of diabetes, and it is these complications that ultimately result in the nearly doubled risk of mortality in patients with diabetes. Various trials have shown that targeted interventions can and do reduce the risk for cardiovascular disease in a measurable way. Above and beyond targeted interventions, we now know that strict multifactorial interventions can result in a clinically significant reduction in both mortality and cardiovascular disease. This multifactorial approach is supported by guidelines around the world [12,44,45]. A standardized approach to the assessment of risk and the application of interventions is critical. More recent data show that specific antihyperglycemic therapies can also reduce cardiovascular events above and beyond their glycemic effects. The rates of cardiovascular events in patients with diabetes have declined over time, and hopefully this trend will continue as further research supports additional interventions.

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