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REVIEW

Management of type 2 diabetes: consensus of diabetes organizations

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Abstract

Despite the advances in diabetes management, people with diabetes are not reaching their target glycemic goals. Healthcare professionals often fail to initiate, escalate, or de-intensify therapy when indicated. There are several organizations that provide guidance on the management of diabetes to assist the practitioner in achieving improved glycemic control, and this can cause confusion to the practitioner on which organizations' guidance to follow. Diabetes mellitus is associated with an elevated risk of cardiovascular disease, and there have been studies that suggest some antidiabetic medications increase cardiovascular risk and some reduce cardiovascular risk. Diabetes organizations recommend the individualization of treatment goals and choices of drug therapy that will be safe and effective. Healthcare professionals should be knowledgeable and equipped to decide on the best treatment regimen for each of their patients with type 2 diabetes (T2D) and be familiar with how to utilize the different organizations' philosophies in treating their patients.

Keywords: cardiovascular outcomes, consensus, diagnostic criteria, management of type 2 diabetes, renal outcomes, treatment goals, type 2 diabetes.

Citation

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Introduction

Battling diabetes is a global challenge. Diabetes is not a disease of rich or poor nations but all nations. It is projected that the number of diabetics globally will increase from 387 million in 2014 to 592 million by 2035.[1] The World Health Organization 2016 Global Report on diabetes has reported that the prevalence of diabetes has nearly doubled since 1980, rising from 4.7 to 8.5% in the adult population.[2] In 2015, it was reported that the cost of diabetes worldwide was 1.31 trillion US dollars of which two-thirds were direct medical costs and one-third were indirect costs, such as loss of productivity.[3] Despite the increasing numbers of new diabetic medications and technology, people with diabetes are not achieving their target glycemic goals, which results in poor health outcomes.[4,5] Both the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) suggested that tight glycemic control, HbA1c <7% (53 mmol/mol), demonstrated a reduction in microvascular complications and possibly macrovascular complications.[5] Professional consensus reports identify how and when treatments should be used, but healthcare providers often fail to initiate or escalate therapy when indicated. The term 'clinical inertia' defines the failure of healthcare providers to advance therapy or de-intensify treatment when it is appropriate.[4,5] The causes of clinical inertia are multifactorial. The contributing factors are physician, patient, and health system related. Some key factors are poor communication between health providers and the patient, no team approach to care, fear of hypoglycemia, adverse events, and affordability of medications. The professional organizations that guide the management of diabetes are the American Diabetes Association (ADA), European Association for the Study of Diabetes (EASD), American Association of Clinical Endocrinology/American College of Endocrinology (AACE/ACE), Endocrine Society, and American College of Physicians (ACP). These organizations agree on the individualization of treatment based on patient-specific factors to reduce morbidity and mortality. The approach to therapeutic recommendations for the treatment of hyperglycemia in people with T2D varies for each organization. This often leads to confusion among healthcare professionals on how to select the appropriate medications and when to intensify therapy. To overcome clinical inertia, healthcare professionals need to be educated on how to use the diabetes organizations' recommendations for the treatment of hyperglycemia in people with T2D. The goal of this review is to assist healthcare professionals on how to use

each organization's document and to differentiate among their target goals and recommendations for the treatment of people with T2D.

Diagnosis of type 2 diabetes and target goals

The current recommendations by the professional organizations to diagnose prediabetes and diabetes are based on one or four glucose abnormalities: fasting plasma glucose (FPG), random elevated glucose with symptoms, glycated hemoglobin (HbA1c), and abnormal oral glucose tolerance test. The current recommendations are summarized in Table 1.[6–10] Unless there is a clear diagnosis of diabetes where a patient demonstrates symptomatic hyperglycemia and a random blood glucose ≥200 mg/dL (11.1 mmol/L), the diagnosis of diabetes will require repeating the measurement.[6–10] The repeat test can be from the same sample or on a subsequent day.[6–10] If two different tests demonstrate the diagnosis of diabetes, additional testing is not needed.[6–10] Healthcare providers need to be aware of conditions that may affect the HbA1c levels such as not using a standardized laboratory, sickle cell disease, blood loss or recent transfusion, iron deficiency anemia, erythropoietin therapy, hemodialysis, second and third trimester of pregnancy, and postpartum.[6,11] Plasma blood glucose should be used in those circumstances to diagnose diabetes.[6,11] Screening for asymptomatic T2D can lead to its earlier diagnosis and treatment. Each organization has criteria for screening and how often patients should be tested. Some of the risk factors for developing T2D includes age above 45, ethnic/racial background (African American, Alaska Native, American Indian, Asian American, Hispanic/Latino, Native Hawaiian, or Pacific Islanders), family history, history of gestational diabetes, polycystic ovary syndrome, sedentary lifestyle, and metabolic syndrome (obesity, increased waist circumference, hypertension [HTN], and hyperlipidemia). The Diabetes Prevention Program Research Group studied adults in the United States that were at high risk for T2D. The study was designed to see if lifestyle changes (intensive training in diet and exercise) or treatment with metformin would reduce the incidence of diabetes in persons at high risk.[12] The incidence

Table 1. Diagnostic criteria for diabetes.[69]

	Normal	Impaired fasting glucose	Diabetes
American Diabetes Association/European Association for the Study of Diabetes/American College of Physicians/ Endocrine Society[6–9]			
FPG	<100 mg/dL	100–125 mg/dL	≥126 mg/dL
	(5.6 mmol/L)	(5.6–6.9 mmol/L)	(7.0 mmol/L)
2-hour	<140 mg/dL	140–199 mg/dL	≥200 mg/dL
OGTT	(7.8 mmol/L)	(7.8–11.0 mmol/L)	(11.1 mmol/L)
HbA1c	<5.7%	5.7–6.4%	≥6.5%
	(39 mmol/mol)	(39–46 mmol/mol)	(48 mmol/mol)
American Association of Clinical Endocrinologists/American College of Endocrinology[7]			
FPG	<100 mg/dL	100–125 mg/dL	≥126 mg/dL
	(5.6 mmol/L)	(5.6–6.9 mmol/L)	(7.0 mmol/L)
2-hour	<140 mg/dL	140–199 mg/dL	≥200 mg/dL
OGTT	(7.8 mmol/L)	(7.8–11.0 mmol/L)	(11.1 mmol/L)
HA1c	<5.5%	5.5–6.4%	≥6.5%
	(37 mmol/mol)	(37–46 mmol/mol)	(48 mmol/mol)
International Diabetes Federation[10]			
FPG	<100 mg/dL	100–125 mg/dL	≥126 mg/dL
	(5.6 mmol/L)	(5.6–6.9 mmol/L)	(7.0 mmol/L)
2-hour	<140 mg/dL	140–199 mg/dL	≥200 mg/dL
OGTT	(7.8 mmol/L)	(7.8–11.0 mmol/L)	(11.1 mmol/L)
HbA1c			≥6.5%
			(48 mmol/mol)

Classic symptoms (polyuria, polydipsia, polyphagia, unexplained weight loss, weakness, blurred vision) and a random blood glucose ≥200 mg/dL (11.1 mmol/L).
Any test abnormality will require repeating the test. If two different tests demonstrate the diagnosis of diabetes additional testing is not needed.
FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; HbA1c, glycated hemoglobin.

of diabetes was reduced by 58% with lifestyle changes and by 31% with metformin as compared to placebo.[12] Similar results were seen in other studies such as the Finnish Diabetes Prevention Study that looked at just lifestyle changes (intensive training in diet and exercise).[13] Lifestyle changes should include an individualized plan that addresses dietary changes, physical activity, weight loss, smoking cessation, and psychological support.[14,15] The consensus statement from the ADA/EASD for 2019 and the recently published ADA Standards of Care 2020 focus on a patient-centered approach to care.[14] The consensus of all the major diabetes organizations is that glycemic treatment targets should be individualized and take into consideration the patient's age, comorbidities, life expectancy, risk of hypoglycemia, and patient preferences.[7,14–16] Target glycemic goals differ among the different organizations and are summarized in Table 2. The ACP guidelines changed in 2018 where they raised the goal of the HbA1c levels to be 7–8% for most patients with type 2 diabetes.[16] The Endocrine Society, the ADA, the American Association of Clinical Endocrinologists, and the American Association of Diabetes Educators issued a joint statement strongly disagreeing with the ACP and proposing new guidelines.[17,18] These organizations believe that the ACP did not take into consideration the differences of the patient populations in the trials Action to Control Cardiovascular Risk in Diabetes (ACCORD), Action in Diabetes and Vascular Disease – PreterAx and DiamicroN Modified Release Controlled Evaluation (ADVANCE), UKPDS, and Veterans Affairs Diabetes Trial (VADT), which analyzed the long-term benefits of lower HbA1c levels and the positive impact of newer medications.[16–18] Common HbA1c target goals advocated by the other diabetes organizations are levels of 6.5–7% for most patients with T2D. Higher HbA1c goals are individualized based on risk for adverse effects such as hypoglycemia, comorbidities, age, life expectancy, and patient preferences. The Endocrine Society and the American Diabetes Association/EASD have addressed specific HbA1c target goals for the elderly, which are included in Table 2.[19,20] Abnormal glucose metabolism and cardiovascular disease (CVD) are risk factors for each other.[8,21,22] Cardiovascular risk is significantly higher in patients with T2D.

Cardiovascular disease and diabetes

T2D is associated with an elevated risk of cardiovascular disease, which remains the leading cause of morbidity and mortality in this patient population.[23] Since 2001, the National Cholesterol Education Program-Adult Treatment Panel NCEP-ATP guidelines consider diabetes a risk equivalent to coronary heart disease (CHD).[24] The former recommendation stemmed from a Finnish study, [25] where T2D patients without any previous CHD events had comparable mortality risk when compared to nondiabetic patients with a previous cardiovascular event. The latest literature proposes that the CHD risk in T2D patients varies. A systematic review of 13 studies evaluating 45,108 people with or without diabetes, indicated that CHD risk was 43% lower in diabetic patients with no previous CHD compared to those without T2D with a prior myocardial infarction.[26] The 2019 American College of Cardiology (ACC)/American Heart Association (AHA) Guidelines

Table 2. Treatment goals for adult patients with type 2 diabetes.[7,10,19,20,86]

	ADA/EASD	AACE/ACE	IDF	ACP	Endocrine Society
HbA1c Individual Goal					
%	<6.5	<6.5	<7.0	7–8	<7.0
mmol/L	48	48	53	53	53
HbA1c General Goal					
%	<7.0	<6.5	<7.0	7.0–8.0	<7.0
mmol/L	53				
HbA1c >65 Years Old Goal					
%	<7.5–<8.5				>7.0–8.5
mmol/L	58–69				53–69
Fasting Plasma Glucose Goal					
mg/dl	80–130	<110	<110		
mmol/L	4.5–7.2	<6	<6		
Postprandial Plasma Glucose Goal					
mg/dl	<180	<140	<180		
mmol/L	<10	<7.8	<10		

AACE, American Association of Clinical Endocrinology; ACE, American College of Endocrinology; ACP, American College of Physicians; ADA, American Diabetes Association; EASD, European Association for the Study of Diabetes; HbA1c, glycated hemoglobin; IDF, International Diabetes Federation.

Table 3. Prevention of CVD.[29,32]

Risk enhancers in patients with diabetes
• Long duration (≥10 years for T2D or ≥20 years for type 1 diabetes mellitus)
• Albuminuria ≥30 mcg albumin/mg creatinine
• eGFR <60 mL/min/1.73 m^2
• Retinopathy
• Neuropathy
• ABI <0.9

ABI, ankle–brachial index; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; T2D, type 2 diabetes mellitus.

on the Primary Prevention of Cardiovascular Disease[27] recognize risk enhancers in diabetic patients summarized in Table 3. The guidelines categorize high-risk patients based on the calculation of atherosclerotic cardiovascular disease (ASCVD) outcomes. ACC developed a tool to assess the 10-year risk for the first ASCVD event as listed in Table 4. ASCVD can be defined as acute coronary syndrome (ACS), a history of myocardial infarction (MI), stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease presumed to be of atherosclerotic origin.[28] Hypertension and dyslipidemia, common comorbidities coexisting with T2D, are considered strong risk factors for ASCVD. Current ADA guidelines emphasize the importance of controlling individual cardiovascular risk factors in preventing or reducing ASCVD risks in patients with diabetes. An additional risk factor for morbidity and mortality from cardiovascular disease is heart failure (HF). Recent trials demonstrated a higher incidence of HF hospitalizations in those patients with T2D compared to those without diabetes.[29] The ADA recommends evaluating cardiovascular risk factors in patients with T2D annually. These risk factors include obesity (BMI >30 adult, >95th% in children), hypertension, hyperlipidemia, smoking, chronic kidney disease, presence of albuminuria, and family history of premature coronary disease.[29] The guidelines strongly recommend treating modifiable risk factors when applicable to decrease the incidence of cardiovascular disease in diabetic individuals.

Table 4. ASCVD.[29,32]

ASCVD risk-enhancing factors
• **Family history of premature ASCVD** - Males, age <55 years - Females, age <65 years
• **Primary hypercholesterolemia** - LDL-C 160–189 mg/dL [4.1–4.8 mmol/L] - Non-HDL-C 190–219 mg/dL [4.9–5.6 mmol/L]
• **Metabolic syndrome** Factors: (tally of 3 makes the diagnosis) - Increased waist circumference - Elevated triglycerides (≥150 mg/dL) - Elevated blood pressure - Elevated glucose - Low HDL-C (<40 mg/dL in men; <50 mg/dL in women)
• **Chronic kidney disease** - eGFR 15–59 mL/min per 1.73 m^2 with or without albuminuria; not treated with dialysis or kidney transplantation
• **Chronic inflammatory conditions** - Conditions such as psoriasis, rheumatoid arthritis, or HIV/AIDS
• **History of premature menopause (before age 40) and history of pregnancy-associated conditions that increase later ASCVD risk such as preeclampsia**
• **High-risk race/ethnicities** (e.g. South Asian ancestry)
• **Lipid/biomarkers:** Associated with increased ASCVD risk - Persistently elevated, primary hypertriglyceridemia (≥175 mg/dL) - If measured: ◦ **Elevated high-sensitivity C-reactive protein** (≥2.0 mg/L) ◦ **Elevated Lp(a)** ≥50 mg/dL or ≥125 nmol/L constitutes a risk-enhancing factor especially at higher Lp(a) ◦ **Elevated apoB** ≥130 mg/dL corresponds to an LDL-C >160 mg/dL and constitutes a risk-enhancing factor ◦ **ABI** <0.9

ABI, ankle–branchial index; apoB, apolipoprotein B-100; ASCVD, atherosclerotic cardiovascular disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein a.

Management of hyperlipidemia

Although ASCVD risk factors are considered for selection of statin intensification therapy in the previous editions of the guidelines, the latest ACC/AHA guidelines[30] suggest treating all diabetic patients between the ages of 40 and 75 and low-density lipoprotein (LDL) levels >70 mg/dL, with a moderate-intensity statin without assessing their ASCVD 10-year risk. Diabetic individuals with additional ASCVD risk factors should be initiated on high-intensity statins with an LDL reduction goal of >50%. These additional risk enhancers include long duration (≥10 years for type 2 diabetes or ≥20 years for type 1 diabetes), albuminuria ≥30 mcg albumin/mg creatinine, estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2, ankle–brachial index <0.9, and the presence of neuropathy and retinopathy.[28] The ADA suggests a similar approach to the management of hyperlipidemia in diabetics. Recent ADA guidelines recommend initiating a moderate-

Table 5. Overview of statin therapy.[28,30]

High intensity (decrease LDL-C >50%)	Moderate intensity (decrease LDL-C 30–<50%)
Atorvastatin 40–80 mg	Atorvastatin 10–20 mg
Rosuvastatin 20–40 mg	Rosuvastatin 5–10 mg
Patients with ACS and LDL>50 mg/dL who could not tolerate high dose statins Use moderate-intensity statin and ezetimibe	Simvastatin 20–40 mg
	Pravastatin 40–80 mg
	Lovastatin 40 mg
	Fluvastatin XL 80 mg

LDL-C, low-density lipoprotein cholesterol.

intensity statin in all diabetic individuals between the ages of 40 and 75 years.[29] The updated recommendation is to initiate a high-intensity statin for patients who have multiple risk factors for cardiovascular disease. A comprehensive list for statin therapy is outlined in Table 5. Collectively ADA and ACC/AHA do not endorse a specific target goal for LDL levels, in contrast to recommendations provided by AACE. In 2019, AACE updated its guidelines for the management of dyslipidemia and the prevention of cardiovascular disease.[31] The guidelines advocate that the treatment goals for dyslipidemia should be individualized according to the patient's ASCVD risk. Diabetic patients without any additional risk factors are classified into the 'high risk' group with a target LDL goals of <100 mg/dL and non-HDL-C goal <130 mg/dL. T2D with additional risk factors is considered 'very high risk' and therefore should achieve LDL levels <70 mg/dL and non-HDL-C levels <100 mg/dL.

Management of hypertension

Hypertension is defined as a sustained blood pressure (BP) >140/90 mmHg and remains common among patients with T2D.[29] As stated previously, hypertension is considered a major risk factor for macrovascular complications. Moreover, numerous studies have shown that antihypertensive therapy reduces ASCVD events, HF, and microvascular complications.[29] ADA guidelines advise a BP target of <130/80 mmHg for hypertensive individuals with T2D and high ASCVD risk of >15%.[29] For patients with a lower cardiovascular risk, the ADA recommends a BP goal of <140/80 mmHg.[29] The most recent AACE[32] guidelines recognize that elevated BP in patients with T2D has been associated with an increased risk of cardiovascular events. The AACE recommends that a BP goal should be individualized with a suggested target of <130/80 mmHg, which has been deemed appropriate for most patients. In 2017, the ACC in conjunction with the AHA and other organizations published the Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults.[33] The ACC/AHA guideline suggests a BP goal of <130/80 mmHg for all patients including patients with T2D.

Diabetes and risk factors for HF

T2D is a risk factor for the development of HF. Recent evidence shows an increased risk of morbidity and mortality in patients with established HF and T2D. In the Framingham Heart Study, T2D increased the risk of HF incidence by two-fold in men and four-fold in women, after adjusting for other CV risk factors.[34] Data from other literature have shown that poor glycemic control may lead to the development of HF. With each 1% increase in HbA_1c, the risk of HF increases by 8–36%.[35,36] In recent trials, concomitant diabetes in patients with HF has shown an increased risk of death. When considering pharmacotherapy for T2D in patients with HF, it is important to evaluate the currently available literature on the effects of antidiabetic treatment modalities on HF symptoms and exacerbations. Historically, metformin was avoided in patients with HF. Recent evidence suggests a survival benefit of using metformin in HF patients, and as of 2006, the Food and Drug Administration (FDA) has removed HF as a contraindication for metformin.[37] Thiazolidinediones are associated with increased rates of HF events and should not be used in this patient population.[38] In the SAVOR-TIMI 53 (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus – Thrombolysis in Myocardial Infarction 53) trial, the risk of HF hospitalization was increased by 27%.[39] Increased HF hospitalization risk was not shown to be significantly greater for alogliptin and sitagliptin when compared to placebo in the EXAMINE (Examination of Cardiovascular Outcomes with Alogliptin *versus* Standard of Care) and the TECOS (Trial Evaluating Cardiovascular Outcomes with Sitagliptin) trials, respectively.[40,41] Both SGLT2 inhibitors and glucagon-like peptide-1 (GLP-1) agonists may be beneficial in reducing HF hospitalizations in patients with T2D, as discussed in the next section of this paper.

T2D Treatment Modalities and Cardiovascular Disease Risk

Cardiovascular safety data

A wide selection of therapies is available for the treatment of T2D. The evaluation of these therapies on cardiovascular risk permits a clinician to make a precise decision on the management of T2D. In 2008, the US FDA issued Guidance for Industry to establish the safety of a new antidiabetic therapy to treat diabetes.[42] The Guidance for sponsors states that therapy will not result in an unacceptable increase in cardiovascular risk. Moving forward, the proposal for new

phase 2 and phase 3 clinical trials will have appropriate study designs for the inclusion of cardiovascular mortality, MI, and stroke. The studies may include evaluation of hospitalization for ACS, urgent revascularization procedures, and possibly other endpoints.[42] These recommendations were motivated by the high prevalence of cardiovascular disease in diabetic patients. Additionally, potential increased cardiovascular risk with the use of the peroxisome proliferator-activated receptor (PPAR) agonist rosiglitazone propelled this FDA Guidance to be issued.[43] Cardiac safety concerns were observed with increased deaths and major cardiovascular events during the development program of the PPAR agonist muraglitazar[44] increased mortality with intense glucose control in the ACCORD trial[45] and increased risk for congestive HF with pioglitazone[38] and rosiglitazone.[46]

Currently, several trials are reporting significant reductions in cardiovascular events with SGLT2 inhibitors and GLP-1 agonists. Empagliflozin: Cardiovascular Outcomes and Mortality in Patients with Type 2 Diabetes Mellitus (EMPA-REG)[47] is a double-blind placebo-controlled trial. The study randomly assigned 7020 adult T2D patients with established CVD to receive a placebo or 10 or 25 mg of the SGLT2 inhibitor empagliflozin after a run-in period. Individuals with body mass index ≤45 kg/m^2, hemoglobin A1c (HbA1c) of 7–10%, and an eGFR >30 mL/min/1.73 m^2 were included. At the end of the study period, the empagliflozin group met the primary endpoint of reducing major cardiac adverse events (MACE) (composite of cardiovascular death, nonfatal MI, or nonfatal stroke) by 14% with a *p*-value <0.001. When given in addition to standard of care, empagliflozin reduced the risk of cardiovascular death by 38%, all-cause death by 32%, and hospitalization for HF by 35% in comparison with placebo. Treatment of only 39 patients with empagliflozin on top of standard care (ACE-inhibitors, statins, and aspirin) prevents one death over a period of 3 years. Empagliflozin compares favorably to ramipril, preventing one death in 56 individuals over a treatment period of 5 years. [48] The overall incidence of nephropathy in chronic kidney disease (CKD) patients was reduced. This was observed after treatment with empagliflozin as compared with placebo (hazard ratio [HR]: 0.58; 95% CI: 0.47–0.71; $p<0.001$). Empagliflozin decreased the risk of acute renal failure by 1.4%.[47] Overall, EMPA-REG was an important trial examining SGLT2-I and CV efficacy and safety outcomes. The dependable design of the trial, with >99% of patients having an established CVD resulted in a strong recommendation for the use of empagliflozin in the updated ADA guidelines.[49]

Similarly, canagliflozin reduced the occurrence of MACE in a group of subjects with, or at high risk for, ASCVD in the CANVAS Program Collaborative Group. The Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes (CANVAS) study[50] demonstrated that canagliflozin was superior to placebo at preventing cardiovascular events. Patients with T2D were randomized to canagliflozin 100 or 300 mg arms (n=5795) *versus* placebo (n=4347). Inclusion criteria encompassed patients with T2D and high cardiovascular risk ≥30 years old and a history of symptomatic atherosclerotic cardiovascular disease. In addition, individuals ≥50 years old with two of the following were enrolled: diabetes duration >10 years, systolic BP >140 mm Hg on antihypertensive therapy, current smoking, albuminuria, or high-density lipoprotein cholesterol <38.7 mg/dL. The primary outcome was the composite incidence of cardiovascular death, MI, or stroke. Canagliflozin significantly reduced MACE compared to placebo ($p=0.02$ for superiority, $p<0.001$ for noninferiority). The benefit for canagliflozin appeared to be similar for patients with reduced ejection fraction (HFrEF) and preserved ejection fraction (HFpEF). An alarming secondary outcome of increased amputations was observed in the canagliflozin group 6.3 participants per 1000 patient-years *versus* 3.4 participants per 1000 patient-years in the placebo group ($p<0.05$). Progression of albuminuria was reduced in the canagliflozin group 89.4 participants per 1000 patient-years *versus* 128.7 participants per 1000 patient-years ($p<0.05$).[50] Both trials verified that SGLT2 inhibitors reduced hospitalization for HF.[47,50]

Dapagliflozin was assessed in the DECLARE-TIMI 58[51] (Dapagliflozin Effect on Cardiovascular Events – Thrombolysis in Myocardial Infarction) trial that randomized 17,150 patients with T2D with either known cardiovascular disease or at least two risk factors for cardiovascular disease. The primary efficacy outcomes were MACE and a composite of cardiovascular death or hospitalization for HF. Secondary outcomes focused on the renal effects of dapagliflozin. The results of this trial indicate that dapagliflozin is noninferior for reducing MACE in patients with T2D and high CV risk. Dapagliflozin reduced HF hospitalizations, in addition to uncovering the beneficial effect on renal outcomes that were reported. Furthermore, among patients with HFrEF, dapagliflozin reduced HF hospitalizations, CV, and all-cause mortality. However, this group comprised only about 4% of the total population. Different from canagliflozin,[51] there was no clear safety signal regarding increased amputations and or risk. These findings are consistent with other trials conducted with (SGLT-2) inhibitors.

Ertugliflozin is presently being evaluated in the Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial (VERTIS) trial.[52] The primary objective of this trial is to evaluate the noninferiority of ertugliflozin *versus* placebo on MACE. Secondary objectives are to demonstrate the superiority of ertugliflozin *versus* placebo on time to CV death or hospitalization for HF CV death and the composite for renal outcomes/renal death, dialysis/transplant, or doubling of serum creatinine from baseline. Results from this trial are pending and anticipated to be finalized by December 2019.

The injectable GLP-1 receptor agonists liraglutide and semaglutide have also shown promising cardiovascular benefits. In people with T2D with ASCVD or increased risk for ASCVD, the addition of liraglutide decreased MACE and mortality.[53] Similarly, semaglutide had favorable outcomes on cardiovascular endpoints in high-risk subjects.[54] Liraglutide was

evaluated in the liraglutide and cardiovascular outcomes in T2D (LEADER) trial.[53] LEADER was a double-blind placebo-controlled study that randomized a total of 9340 patients. Individuals with T2D, HbA1c values >7%, and high cardiovascular risk were assessed for the primary composite outcome of the first occurrence of death from CVD causes, nonfatal MI, or nonfatal stroke. The primary composite outcome occurred in fewer patients in the liraglutide group (608 of 4668 patients [13.0%]) than in the placebo group (694 of 4672 [14.9%]) (HR: 0.87; 95% CI: 0.78–0.97; $p<0.001$ for noninferiority; $p=0.01$ for superiority). Death from CVD causes occurred in fewer patients in the liraglutide group (219 patients [4.7%]) than in the placebo group (278 [6.0%]) (HR: 0.78; 95% CI: 0.66–0.93; $p=0.007$).

Semaglutide, a once-weekly GLP-1 analog, significantly reduced the risk of the primary composite endpoint of time to the first occurrence of either CV death, nonfatal MI, or nonfatal stroke in the Semaglutide and Cardiovascular Outcomes, Efficacy, and Safety in Type 2 Diabetes (SUSTAIN 6) trial.[55] Semaglutide was evaluated in 3297 adults with T2D at high CV risk. The primary outcome occurred in 108 of 1648 patients (6.6%) in the semaglutide group and in 146 of 1649 patients (8.9%) in the placebo group (HR: 0.74; 95% CI: 0.58–0.95; $p<0.001$ for noninferiority). Nonfatal MI occurred in 2.9% of the patients receiving semaglutide and in 3.9% of those receiving placebo (HR: 0.74; 95% CI: 0.51–1.08; $p=0.12$); nonfatal stroke occurred in 1.6% and 2.7%, respectively (HR: 0.61; 95% CI: 0.38–0.99; $p=0.04$). The results indicate a substantial 39% decrease in nonfatal stroke by 39% and a nonsignificant 26% decrease in nonfatal MI and a neutral outcome in CV death after 2 years of treatment.[55]

The PIONEER 6 investigators in the Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes study[56] assessed CV outcomes of once-daily oral semaglutide in a randomized, double-blind, placebo-controlled trial involving 3183 patients at high CV risk (age of ≥50 years with established CV or CKD, or age of ≥60 years with CV risk factors only). Results for components of the primary outcome were as follows: death from CV causes, 15 of 1591 patients (0.9%) in the oral semaglutide group and 30 of 1592 (1.9%) in the placebo group (HR: 0.49; 95% CI: 0.27–0.92); nonfatal MI, 37 of 1591 patients (2.3%) and 31 of 1592 (1.9%), respectively (HR: 1.18; 95% CI: 0.73–1.90); and nonfatal stroke, 12 of 1591 patients (0.8%) and 16 of 1592 (1.0%), respectively (HR: 0.74; 95% CI: 0.35–1.57).

The Lixisenatide in Patients with T2D and Acute Coronary Syndrome (ELIXA) study[57] evaluated T2D patients with previous MI or hospitalization for unstable angina within the previous 180 days. The trial was designed with adequate statistical power (LIST) to assess whether lixisenatide was noninferior as well as superior to placebo. The 6068 patients who underwent randomization were followed for 25 months. A primary endpoint event occurred in 13.4% in the lixisenatide group and in 13.2% in the placebo group, which showed the noninferiority of lixisenatide to placebo ($p<0.001$) yet did not demonstrate superiority ($p=0.81$). Significant differences between groups were not observed in the rate of hospitalization for HF or the rate of death. A *post hoc* analysis[58] of the ELIXA trial assessed change in eGFR and urinary albumin-to-creatinine ratio (UACR) from baseline. It was reported that lixisenatide was associated with a 23% lower risk for the first macroalbuminuria event without baseline macroalbuminuria ($p=0.0174$).

Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes (EXCEL) was an international trial of a broad population of T2D patients with or without CVD.[59] EXCEL enrolled 14,752 patients between June 2010 and September 2015 with a median follow-up of 3.2 years. The primary endpoint was outlined from previous trials and included the first occurrence of death from cardiovascular causes, nonfatal MI, and nonfatal stroke. Exenatide, administered once weekly, was not superior to placebo with respect to efficacy ($p=0.06$). The incidence of MACE did not differ significantly between patients who received exenatide and those who received placebo.

The Albiglutide and Cardiovascular Outcomes in Patients with T2D and Cardiovascular Disease (Harmony Outcomes)[60] trial aimed to determine the safety and efficacy of albiglutide in preventing cardiovascular death, MI, or stroke. Participants were randomly assigned to groups to receive albiglutide and placebo. A total of 9463 patients were evaluated for a median duration of 1.6 years and were assessed for the primary outcome. The primary composite outcome occurred in 338 of 4731 (7%) of patients in the albiglutide group and in 428 of 4732 (9%) of participants in the placebo group (HR: 0.78; 95% CI: 0.68–0.90), which indicated that albiglutide was superior to placebo ($p=0.0006$). In patients with T2D and CVD, albiglutide was superior to placebo with respect to MACE. The evidence-based glucagon-like peptide 1 receptor agonists should, therefore, be considered as part of a comprehensive strategy to reduce the risk of cardiovascular events in patients with T2D.

CV safety trials with DDP 4 inhibitors include SAVOR-TIMI 53,[61] EXAMINE,[40] Effect of Sitagliptin on Cardiovascular Outcomes in T2D (TECOS),[41] Cardiovascular Outcome Trial of Linagliptin *Versus* Glimepiride in Type 2 Diabetes (CAROLINA),[54] and Cardiovascular Safety and Clinical Outcome with Linagliptin (CARMELINA).[62]

These trials incorporate a prospective blinded evaluation of CV events in patients at an increased risk (e.g. advanced age, preexisting CVD, renal disease). Primary MACE endpoint includes CV death, nonfatal MI, and nonfatal stroke. The linagliptin and sitagliptin studies also include hospitalization for unstable angina as a part of primary MACE endpoint and CARMELINA[62] has a renal endpoint.

SAVOR-TIMI 53[61] was the first CV outcome study for DPP-4 inhibitors to be published. The investigators enrolled 16,492 patients from May 2010 through December 2011. A primary endpoint event of cardiovascular death, nonfatal MI, or nonfatal ischemic stroke occurred in 613 patients in the saxagliptin group (7.3%) and in 609 patients in the placebo group (7.2%)

(HR: 1.00; 95% CI: 0.89–1.12; p=0.99 for superiority and p<0.001 for noninferiority). A major secondary endpoint event of CV death, nonfatal MI, nonfatal ischemic stroke, hospitalization for unstable angina, coronary revascularization, or HF occurred in 1059 patients in the saxagliptin group (12.8%), and in 1034 patients in the placebo group (12.4%) (HR: 1.02; 95% CI: 0.94–1.11; p=0.66). Saxagliptin was associated with significantly improved glycemic control and reduced the development and progression of microalbuminuria.

The results of EXAMINE trial[40] showed that the rates of major composite events were not increased with alogliptin as compared with placebo after a 40-month follow-up. A total of 5380 participants were randomized to alogliptin and the placebo groups. The primary endpoint was a composite of death from CV causes, nonfatal MI, or nonfatal stroke. The primary endpoint occurred at similar rates in the alogliptin and placebo groups (in 11.3% and 11.8% of patients, respectively, HR: 0.96; the upper boundary of the one-sided repeated CI: 1.16; p<0.001 for noninferiority; p=0.32 for superiority). Alogliptin was neutral on CV morbidity or mortality and did not worsen preexisting HF. In addition, assessment of pro-BNP concentration from baseline to 6 months did not reveal any significant changes.

The TECOS study[41] randomized 14,735 patients from December 2008 through July 2012. The primary composite CV outcome occurred in 839 patients in the sitagliptin group (11.4%) and 851 in the placebo group (11.6%). There was no significant between-group difference in the primary composite CV outcome (HR: 0.98; 95% CI: 0.88–1.09; p<0.001 for noninferiority (per-protocol analysis) (HR in the intention-to-treat analysis: 0.98; 95% CI: 0.89–1.08; p=0.65 for superiority). TECOS demonstrated noninferiority in terms of risk of a four-point MACE outcome, with no increased risk of hospitalizations due to HF.

The Vildagliptin in Ventricular Dysfunction Diabetes (VIVIDD)[62] study evaluated the effect of vildagliptin on ejection fraction compared to placebo in diabetic patients with HF. This small trial with 254 patients indicated that vildagliptin did not have an unfavorable effect on left ventricular ejection fraction (LVEF), although an increase in left ventricular end-diastolic volume was observed (p=0.007). Baseline LVEF was 30.6±6.8% in the vildagliptin group and 29.6±7.7% in the placebo group. The adjusted mean change in LVEF was 4.95±1.25% in vildagliptin-treated patients and 4.33±1.23% in placebo-treated patients, a difference of 0.62 (95% CI: –2.21–3.44; p=0.667).

CAROLINA[63] is the first active-comparator cardiovascular outcome trial for a DPP-4 inhibitor. The trial is designed to evaluate the cardiovascular safety of linagliptin compared to glimepiride in 6033 adults with T2D. Participants enrolled had to have a high cardiovascular risk or established history for cardiovascular disease. In addition, the results for this trial would be advantageous to practice as the median follow-up for included patients was beyond 6 years.

CARMELINA[64], another study with linagliptin, was a multinational, randomized, placebo-controlled clinical trial that involved 6979 adults. CARMELINA evaluated linagliptin on CV and kidney safety outcomes in adults with T2D at high risk for cardiovascular and/or kidney disease. The primary outcome was the first occurrence of the composite of CV death, nonfatal MI, or nonfatal stroke. Secondary outcomes included time to the first occurrence of adjudicated death due to renal failure, ESRD, or decrease in eGFR from baseline. During a median follow-up of 2.2 years, the primary outcome occurred in 12.4% in the linagliptin group and 12.1% in the placebo groups (p<0.001) for noninferiority. The secondary outcome occurred in 9.4% and 8.8% linagliptin and placebo groups, respectively (p=0.62). In adults with T2D, linagliptin addition demonstrates long-term cardiovascular safety compared with placebo in individuals at high risk for cardiovascular and/or kidney disease.

Dulaglutide and cardiovascular outcomes in T2D (REWIND)[65], a double-blind, randomized placebo-controlled trial, assessed the effect of the GLP-1 receptor agonist dulaglutide on MACE when added to the existing antihyperglycemic therapy. Patients were randomized at 371 sites between Aug 18, 2011, and Aug 14, 2013. Participants randomly assigned to receive dulaglutide (n=4949) or placebo (n=4952) and were followed up for a median of 5.4 years. The primary composite outcome (first occurrence of the composite endpoint of nonfatal MI, nonfatal stroke, or death from CV causes) occurred in 594 (12.0%) participants in the dulaglutide group and in 663 (13.4%) in the placebo group (HR: 0.88; 95% CI: 0.79–0.99; p=0.026). All-cause mortality did not differ between groups (536 [10.8%] in the dulaglutide group *versus* 592 [12.0%] in the placebo group; HR: 0.90; 95% CI: 0.80–1.01; p=0.067). Based on this trial, dulaglutide could be considered for the management of glycemic control in older patients with either previous CVD or CVD risk factors.[65]

Renal safety data

The evidence supporting the benefit of antihyperglycemic drugs and the improvement of renal outcomes continues to accumulate as well. Empagliflozin was evaluated in the Empagliflozin and Progression of Kidney Disease in T2D (EMPA-REG) trial[66] to determine the long-term renal effects of empagliflozin. Patients with an estimated glomerular filtration rate of at least 30 mL/min were randomly assigned to receive empagliflozin 10 or 25 mg or placebo. Renal outcomes included incident or worsening nephropathy (progression to macroalbuminuria, doubling of the serum creatinine level, initiation of renal-replacement therapy, or death from renal disease) and incident albuminuria. Incident or worsening nephropathy occurred in 525 of 4124 patients (12.7%) in the empagliflozin group and in 388 of 2061 (18.8%) in the placebo group (HR in the empagliflozin group: 0.61; 95% CI: 0.53–0.70; p<0.001). A significant relative risk reduction of 44% in the doubling of the serum creatinine level was observed: 70 of 4645 patients (1.5%) in the empagliflozin group and 60 of 2323 (2.6%)

in the placebo group. Renal-replacement therapy was initiated in 13 of 4687 patients (0.3%) in the empagliflozin group and in 14 of 2333 patients (0.6%) in the placebo group, demonstrating a relative risk reduction of 55% in the empagliflozin group.

The randomized, double-blind Canagliflozin and Renal Outcomes in T2D and Nephropathy (CREDENCE) trial was stopped early after an interim analysis indicated substantial renal and cardiovascular protective benefits. The study investigators randomized 4401 patients with T2D plus CKD who were followed for an average of 2.62 years. The primary outcome, a composite of end-stage kidney disease (dialysis, transplantation, or a sustained estimated GFR of <15 mL/min), a doubling of the serum creatinine level, or death from renal or cardiovascular causes was 30% lower in the canagliflozin group than in the placebo group, with event rates of 43.2 and 61.2 per 1000 patient-years, respectively (HR: 0.70; 95% CI: 0.59–0.82; p=0.00001). A 34% reduction was found in the renal composite outcome of ESRD, doubling of serum creatinine, or death from renal causes (p<0.001), and a 32% reduction was found in the relative risk of ESRD (p=0.002).[67]

The CARMELINA randomized clinical trial[64] mentioned previously evaluated linagliptin on kidney outcomes in patients with T2D at high risk of CV and kidney events. The study enrolled 6979 adults with T2D of whom 57% had CV disease and 74% had kidney disease. After a median follow-up of 2.2 years, renal events occurred in 9.4% of the linagliptin group and 8.8% of the placebo group (HR: 1.04; 95% CI: 0.89–1.22; p=0 .62).

The DECLARE-TIMI 58 trial[51] established a prespecified secondary cardiorenal composite outcome defined as a sustained decline of at least 40% in eGFR to less than 60 mL/min, end-stage renal disease (defined as dialysis for at least 90 days, kidney transplantation, or confirmed sustained eGFR <15 mL/min) or death from renal causes. In this subanalysis of DECLARE-TIMI 58, the cardiorenal secondary composite outcome was significantly reduced with dapagliflozin *versus* placebo (HR: 0.76; 95% CI: 0.67–0.87; p<0·0001). The trial identified a 46% reduction in sustained decline in eGFR by at least 40% to less than 60 mL/min (120 [1.4%] *versus* 221 [2.6%]; HR: 0.54 [95% CI: 0.43–0.67]; p<0.0001). The risk of end-stage renal disease or renal death was also lower in the dapagliflozin group than in the placebo group (11 [0.1%] *versus* 27 [0.3%]; HR: 0.41 [95% CI: 0.20–0.82]; p=0.012).

The renal outcomes of dulaglutide were evaluated in the REWIND trial. In this exploratory analysis, researchers investigated the renal component of the composite microvascular outcome, defined as the first occurrence of new macroalbuminuria (UACR >33·9 mg/mmol), a sustained decline in eGFR of 30% or more from baseline, or chronic renal-replacement therapy. The renal outcome developed in 848 (17.1%) participants in the dulaglutide group and in 970 (19.6%) participants in the placebo group (HR: 0.85; 95% CI: 0.7–0.93; p=0.0004). The clearest effect was for new macroalbuminuria (HR: 0.77; 95% CI: 0.68–0.87; p<0.0001). Sustained decline in eGFR of 30% or more had a HR of 0.89 (0.78–1.01; p=0.066) and HR 0.75 (0.39–1.44; p=0.39) for chronic renal-replacement therapy. Long-term use of dulaglutide was associated with reduced composite renal outcomes in people with T2D.[68]

The vast amount of recently published data from CV outcome trials places pressure on clinical guideline groups to continuously update their recommendations. Treatment algorithms take into consideration data from CV outcome trials on the CV and renal protective aspects of antidiabetics. These recommendations aim at providing a resource not only to endocrinologists but to cardiologists, nephrologists, and primary care physicians in the region. The next section of this paper will discuss the different treatment modalities for T2D and their place in therapy.

Comprehensive management of type 2 diabetes

The ADA and American Association of Clinical Endocrinologists/American College of Endocrinology publish updated recommendations on the management of patients with T2D every January to provide guidance to healthcare professionals on how to manage this challenging disease. The ADA also provides clinical updates throughout the year. Evidence-based recommendations reflect new therapies and management approaches for individualized therapy and optimal care. The ADA/EASD published the 2018 consensus report jointly on providing a patient-centered care approach to managing hyperglycemia in T2D.[14] The patient-centered care approach does not rely on a HbA1c number or an algorithm, but assesses patient-specific factors that impact choice of treatment as in Figure 1.[14,69] The ADA/EASD consensus has also addressed the importance of having the patient share in the decision of their management plan to have patients engage in their management. Based on recent findings from cardiovascular outcome trials, the consensus report guides healthcare professionals on how to manage hyperglycemia in patients with atherosclerotic cardiovascular disease, CKD, and HF. The consensus also considers in patients without ASCVD or CKD the need to minimize hypoglycemia and weight gain, promote weight loss, and consider the costs of therapy as shown in Figure 1.[14,69] The AACE/ACE glycemic control algorithm centers treatment guidance based on a patients' entry HbA1c value (<7.5%, >7.5% or >9%).[15] The order of medications and the number of medications suggested by AACE/ACE is presented in the algorithm as a hierarchy of recommended usage, and the strength of the expert consensus recommendation is represented by the length of a colored line as shown in Figure 2.[15] Compared to the ADA/EASD and AACE/ACE, the other diabetes organizations (ACP, International Diabetes Federation [IDF] and Endocrine Society) do not provide easy to follow guidance on how to treat patients with T2D. The ACP and IDF organizations published treatment recommendations for patients with T2D in 2017.[10,70] All the organizations agree on individualizing therapy with a patient-centered approach to guide the choice of medication.

Figure 1. ADA/EASD glucose-lowering medication in type 2 diabetes overall approach.[14, 69] (Reprinted with permission from the American Diabetes Association.)

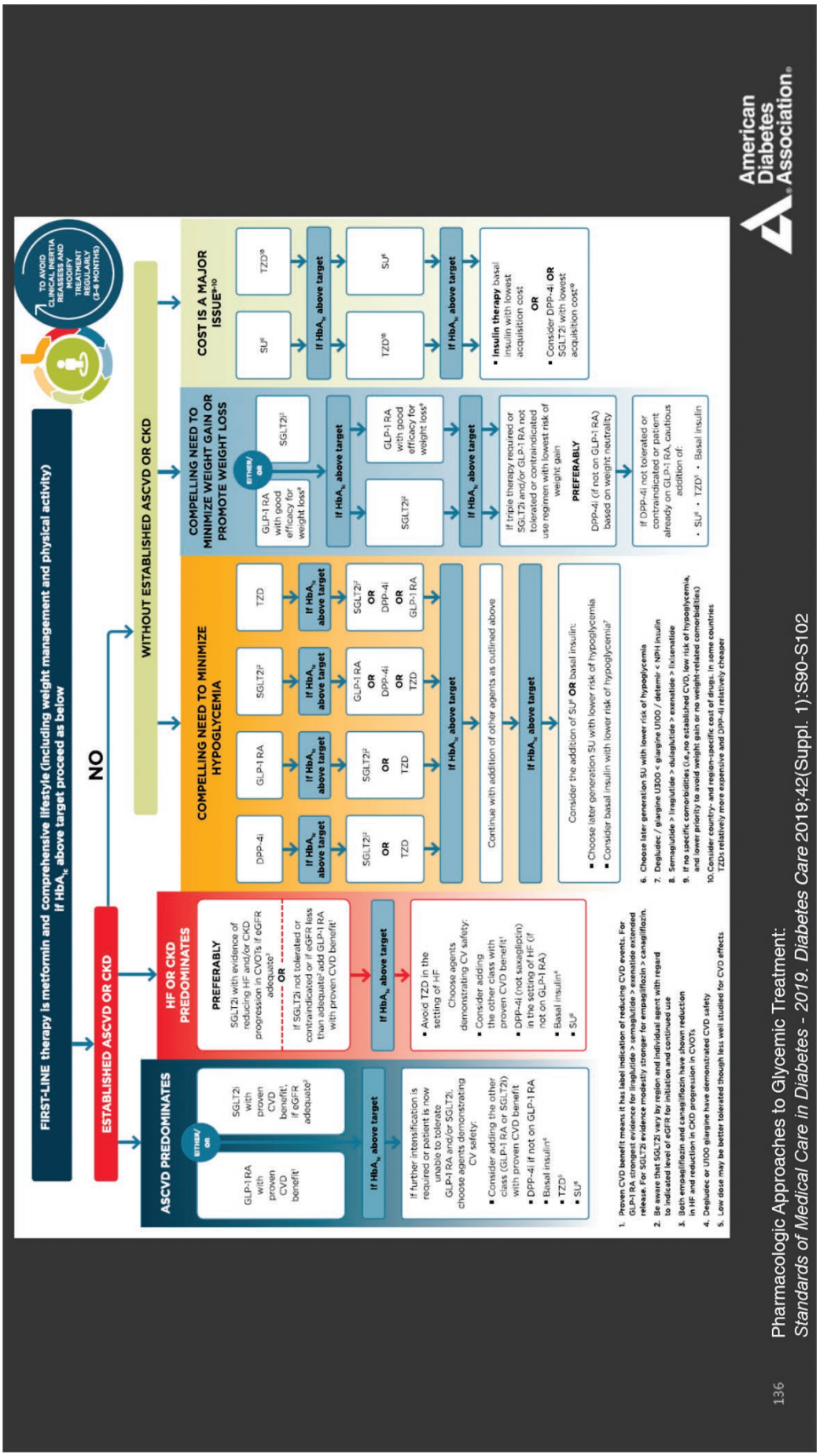
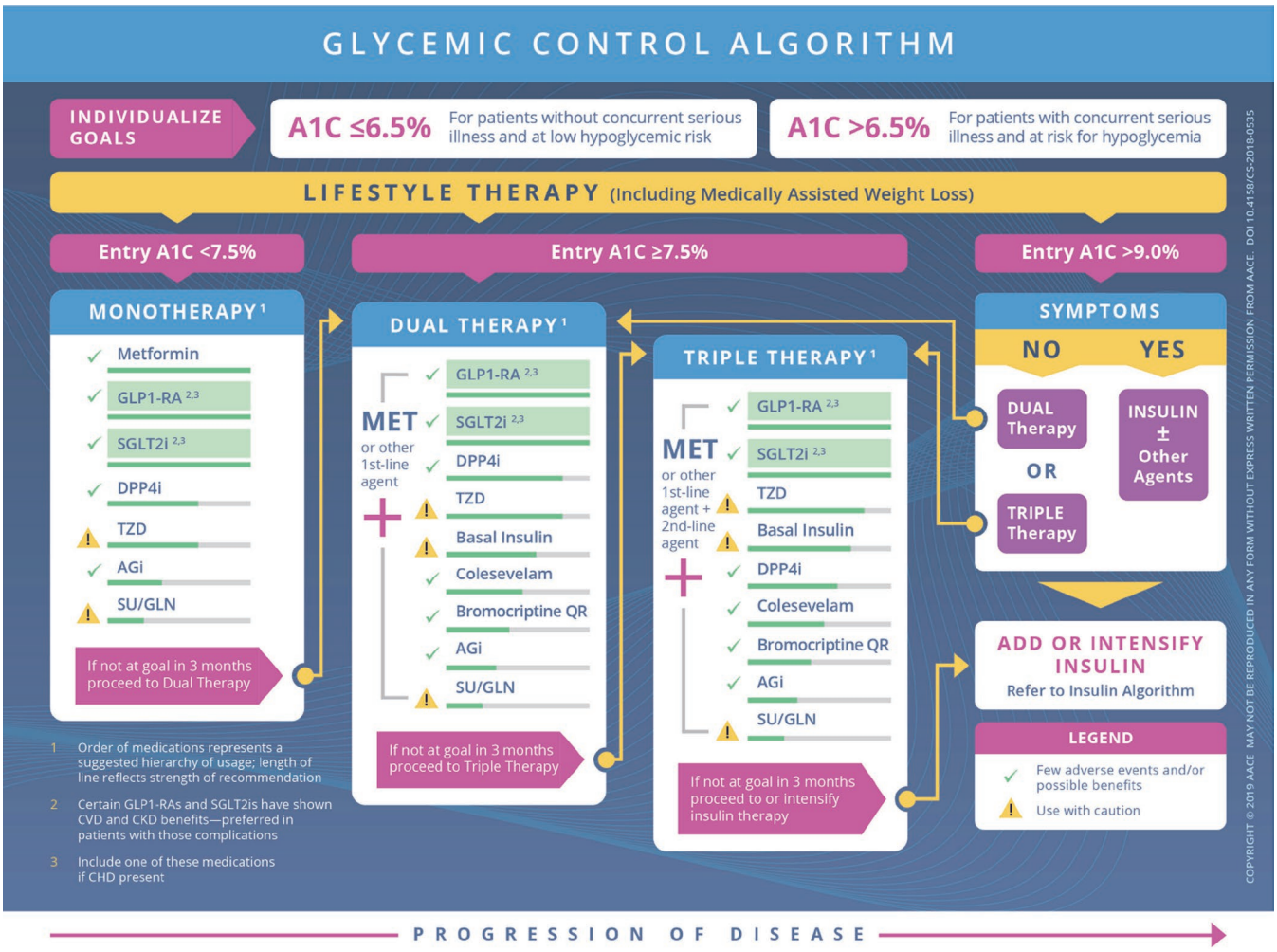


Figure 2. AACE/ACE glycemic control algorithm.[15] (Reprinted with permission from the American Association of Clinical Endocrinologists and American College of Endocrinology.)



The consensus for treating T2D is to incorporate lifestyle management such as medical nutrition therapy, exercise, weight loss, smoking cessation counseling, psychosocial care, and diabetes self-management education into a patient's treatment plan.[70,71] The cornerstone for the treatment of T2D has been metformin unless there are contraindications. An overview of precautions and contraindications for metformin is summarized in Table 6. Metformin is effective, safe, low in cost, does not cause weight gain or hypoglycemia, and may reduce cardiovascular events and mortality.[10,14,15,19,69,70] The European Society of Cardiology in collaboration with the EASD released updated 2019 guidelines for diabetes, prediabetes, and heart disease recommending SGLT-2 inhibitors and GLP-1 agonists as first-line therapy for people with diabetes who have heart disease or at the risk of heart disease.[72] Recommending to start a patient on dual therapy depends on the diabetes organization. The ADA/EASD recommends considering dual therapy in a newly diagnosed patient if they have an HbA1c >1.5% (12.5 mmol/mol) above their glycemic target.[14,69] AACE/ACE recommends starting with dual therapy if the entry HbA1c is >7.5% or triple therapy when the entry level is >9%.[15] Therapy should be reassessed every 3–6 months and modified to avoid clinical inertia.[69] When the HbA1c is above the individualized target and medications have reached the maximum dose for the patient, then other drugs may be added to therapy. Other antihyperglycemic medications are added to therapy based on patient comorbidities, adverse effect profiles, and cost. Based on the cardiovascular outcomes and renal trials, there is now guidance on using certain GLP-1 receptor agonists and SGLT-2 inhibitors that have demonstrated CVD, renal, and HF benefit; see Table 7 for a description of trials. Studies have demonstrated that GLP-1 agonists (liraglutide, dulaglutide, and semaglutide) and SGLT-2 inhibitors (empagliflozin, and canagliflozin) with proven CVD benefit should be prescribed to patients with T2D and ASCVD.[46,48–50,52,54,55,65] Oral semaglutide eliminates the barrier of injection and may increase the usage of GLP-1 receptor agonists. PIONEER 6 trial has demonstrated oral semaglutide is safe for patients with T2D and high CV risk.[56,73] Among patients with T2D in whom HF exists or is of special concern, SGLT-2 inhibitors (empagliflozin, canagliflozin, and dapagliflozin) have been shown to lower the risk of HF hospitalizations.[14,43,69,74,75] There are several SGLT-2 inhibitor outcome trials: Empagliflozin

Table 6. Overview of precautions and contraindications for oral antidiabetic medications.[10,14,15]

Biguanide: metformin
• *Diarrhea and abdominal discomfort*
• *B-12 deficiency*
• *History of DKA, lactic acidosis, metabolic acidosis (contraindication)*
• *Renal Adjustment (eGFR <30 contraindicated)*
Sulfonylureas: glyburide, glipizide, glimepiride, glibenclamide, gliclazide
• *Hypoglycemia*
• *Weight gain*
• *Diarrhea, nausea*
• *Caution renal insufficiency*
• *Uncertain cardiovascular safety*
Meglitinides: repaglinide, nateglinide
• *Hypoglycemia*
• *Weight gain*
• *Uncertain cardiovascular safety*
• *Must be taken with meals*
Thiazolidinediones: pioglitazone, rosiglitazone
• *Weight gain*
• *Macular edema*
• *Edema/increased risk of CHF (avoid NYHA class III/IV CHF)*
• *Rosiglitazone increases LDL*
• *Fracture risk*
• *Avoid in increased liver function tests*
SGLT-2 inhibitors: canagliflozin, dapagliflozin, empagliflozin, ertugliflozin
• *Urinary tract infections*
• *Genital fungal infections*
• *Necrotizing fasciitis (Fournier's Gangrene)*
• *Hypotension*
• *Dehydration*
• *Fracture risk (canagliflozin)*
• *Amputation risk (canagliflozin)*
• *Euglycemia ketoacidosis*
• *Increase in LDL*
• *Increase serum creatinine (acute kidney injury)*
• *Bladder cancer risk (dapagliflozin)*
Dipeptidyl peptidase-4 inhibitors: sitagliptin, saxagliptin, alogliptin, linagliptin, vildagliptin
• *Joint pain*
• *Pancreatitis (rare)*
• *Hypersensitivity reactions*
• *Heart failure risk (saxagliptin, alogliptin)*
α-Glucosidase inhibitors: acarbose, miglitol
• *Diarrhea, flatulence, abdominal pain*
• *Avoid in severe renal or hepatic disease*
• *Hypoglycemia must be treated with glucose, not sucrose or complex carbohydrates*
• *Must take with food*
Bile acid sequestrant: colesevelam
• *Constipation, nausea, bloating*
• *Increased triglycerides*
• *Space doses with other medications*
Dopamine receptor agonist: bromocriptine
• *Orthostatic hypotension*
• *Dizziness, headache, somnolence*
• *Nausea, vomiting, diarrhea*
• *Worsen psychiatric disorders*
Injectable antidiabetic medications
Glucagon-like peptide-1 (GLP-1) agonists: exenatide, lixisenatide, dulaglutide, liraglutide, semaglutide (available orally and injectable)
• *Black box warning: medullary thyroid carcinoma and multiple endocrine neoplasia syndrome type 2*
• *Nausea, vomiting, diarrhea*
• *Jittery feeling, headache, dizziness*
• *Hypoglycemia risk with sulfonylureas and insulin*
• *Risk of acute pancreatitis*
• *Risk of cholelithiasis*
• *Caution gastroparesis*
• *Avoid all GLP-1 agonists in severe renal impairment*
• *Caution retinopathy and semaglutide titrate slowly*
Amylin analog: pramlintide acetate
• *Hypoglycemia*
• *Nausea, vomiting, anorexia*
• *Caution with gastroparesis*
Insulin:
• *Hypoglycemia*
• *Weight gain*
• *Possible injection site reactions or erratic absorption from not rotating sites*
• *Incorrect use of pen or technique of injecting insulin can affect blood sugar*
• *Not storing insulin correctly and using expired insulin can affect blood sugar*
• *Multiple injections may be required with different insulin*
• *Frequent dose adjustments*
• *Misidentification, inaccurate dosing, incorrect timing*
• *Inhaled insulin requires lung function monitoring; cannot be used if you have asthma, COPD, smoker, lung cancer, dexterity problems, children*

(*Continued*)

Table 7. CVD and renal benefits.[47,50–75]

Patient population	Design/follow-up	Primary outcome	Secondary outcome
Glucagon-like peptide-1 receptor agonist trials			
LEADER (liraglutide)			
T2D patients with established CV disease or CV risk factors	9340 patients were randomized to Liraglutide 0.6–1.8 mg group or to placebo. Patients were followed for 3.8 years	Composite outcome (first occurrence of death from CV causes, nonfatal MI, or nonfatal stroke). Significantly lower in liraglutide group (608/4668 [13.0%]) than in placebo group (694/4672 [14.9%]) (HR: 0.87; 95% CI: 0.78–0.97; $p<0.001$ for noninferiority; $p=0.01$ for superiority)	Lower mortality due to CV causes in the liraglutide group (219 [4.7%]) *versus* placebo group (278 [6.0%]) (HR: 0.78; 95% CI: 0.66–0.93; $p=0.007$).All-cause mortality was lower with liraglutide (381 [8.2%]) than placebo (447 [9.6%]) (HR: 0.85; 95% CI: 0.74–0.97; $p=0.02$). Rates of nonfatal MI, nonfatal stroke, and HF hospitalization were lower with liraglutide than placebo (nonstatistically significant)
SUSTAIN-6 (semaglutide)			
Most patients (83.0%) had established CVD or CKD, or both	3297 patients randomized to receive once-weekly semaglutide (0.5 or 1.0 mg) or placebo for 104 weeks	Primary outcome (CV death, nonfatal MI, nonfatal stroke) occurred in 108/1648 patients (6.6%) in semaglutide group and 146/1649 patients (8.9%) in placebo group (HR: 0.74; 95% CI: 0.58–0.95; $p<0.001$ for noninferiority). Nonfatal MI occurred in 2.9% of semaglutide patients and 3.9% of placebo patients (HR: 0.74; 95% CI: 0.51–1.08; $p=0.12$) nonfatal stroke occurred in 1.6% and 2.7%, respectively (HR: 0.61; 95% CI: 0.38–0.99; $p=0.04$)	Rates of death from CV causes were similar in each group. Rates of new or worsening nephropathy were lower in semaglutide group, but rates of retinopathy complications were significantly higher (HR: 1.76; 95% CI: 1.11–2.78; $p=0.02$)
PIONEER-6 (semaglutide)			
T2D patients with established CKD or CVD or high risk of CVD	3183 patients were randomly assigned to receive oral semaglutide (14 mg/day) or placebo for a median follow-up of 15.9 months	Primary outcome (CV death, nonfatal MI, nonfatal stroke). CV death occurred in 15 of 1591 patients (0.9%) in the oral semaglutide group and 30 of 1592 (1.9%) in the placebo group (HR: 0.49; 95% CI: 0.27–0.92); nonfatal myocardial infarction, 37 of 1591 patients (2.3%) and 31 of 1592 (1.9%), respectively (HR: 1.18; 95% CI: 0.73–1.90); and nonfatal stroke, 12 of 1591 patients (0.8%) and 16 of 1592 (1.0%), respectively (HR: 0.74; 95% CI: 0.35–1.57)	Death from any cause occurred in 23 of 1591 patients (1.4%) in the oral semaglutide group and 45 of 1592 (2.8%) in the placebo group (HR: 0.51; 95% CI: 0.31–0.84)
ELIXA (lixisenatide)			
T2D patients with MI or hospitalization for unstable angina in ≤180 days	6068 patients with received lixisenatide or placebo for 25 months	Primary event was observed in 406 (13.4%) patients in the lixisenatide group and in 399 (13.2%) in the placebo group (HR: 1.02; 95% CI: 0.89–1.17), $p<0.001$ for noninferiority and $p=0.81$ for superiority	No difference was observed for the rates of hospitalization for heart failure (HR: 0.96; 95% CI: 0.75–1.23) and the rate of death (95% CI: 0.78–1.13).

(*Continued*)

Table 7. (*Continued*)

Patient population	Design/follow-up	Primary outcome	Secondary outcome
EXSCEL (exenatide ER)			
T2D patients of whom 73.1% had previous CVD	14,752 patients received subcutaneous injections of extended-release exenatide at a dose of 2 mg or matching placebo once weekly and followed for 3.2 years	Exenatide once-weekly did not increase the incidence MACE (a composite endpoint of CV death, myocardial infarction) or nonfatal stroke, compared to placebo (HR, 0.91; 95% CI: 0.83–1.00; $p<0.001$ for noninferiority)	The rates of death from CVD causes, fatal or nonfatal MI and stroke, hospitalization for heart failure, acute coronary syndrome, and the incidence of acute pancreatitis, pancreatic cancer, medullary thyroid carcinoma, and serious adverse events did not differ significantly between the two groups
Harmony Outcomes (albiglutide)			
Patients >40 y/o with T2D and CVD	9463 patients were randomized to receive SC injection of albiglutide (30–50 mg) or matched volume of placebo once a week	The primary composite outcome occurred in 338/4371 (7%) patients in the albiglutide group and in 428/4732 (9%) of patients in the placebo group (HR: 0.78; 95% CI: 0.68–0.90), indicates albiglutide was superior to placebo ($p<0.0001$ for noninferiority; $p=0.0006$ for superiority)	The incidence of acute pancreatitis, pancreatic cancer, medullary thyroid carcinoma, and other serious adverse events did not differ between the two groups
REWIND (dulaglutide)			
T2D patients aged at least 50 years with a previous CVD event or CVD risk factors	9901 participants randomly assigned to either weekly subcutaneous injection of dulaglutide (1.5 mg) or placebo with a mean follow-up of 5.4 years	The primary outcome (first occurrence of the composite endpoint of nonfatal MI, nonfatal stroke, or death from CV causes) occurred in 594 (12.0%) participants in the dulaglutide group and in 663 (13.4%) participants in the placebo group (HR: 0.88, 95% CI: 0.79–0.99; $p=0.026$)	All-cause mortality did not differ between groups (536 [10.8%] in the dulaglutide group *versus* 592 [12.0%] in the placebo group; HR: 0.90; 95% CI: 0.80–1·.1; $p=0.067$). 2347 (47.4%) participants assigned to dulaglutide reported a gastrointestinal adverse event during follow-up compared with 1687 (34.1%) participants assigned to placebo ($p<0.0001$) Renal outcome developed in 848 (17.1%) participants in the dulaglutide group and in 970 (19.6%) participants in the placebo group (HR: 0.85; 95% CI: 0.77–0.93; $p=0.0004$). New macroalbuminuria (HR: 0.77; 95% CI: 0.68–0.87; $p<0.0001$), with HRs of 0.89 (0.78–1.01; $p=0.066$) for sustained decline in eGFR of 30% or more and 0.75 (0.39–1.44; $p=0.39$) for chronic renal-replacement therapy

(*Continued*)

Table 7. (*Continued*)

Patient population	Design/follow-up	Primary outcome	Secondary outcome
Dipeptidyl peptidase 4 (DPP-4) inhibitor trials			
SAVOR-TIMI 53 (saxagliptin)			
T2D patients who had a history of, or were at risk for, CVD events	16,492 patients were randomized to saxagliptin or placebo and followed for a median of 2.1 years	A primary endpoint event occurred in 613 (7.3%) patients in the saxagliptin group and in 609 (7.2%) patients in the placebo group (HR: 1.00; 95% CI: 0.89–1.12; p=0.99 for superiority; p<0.001 for noninferiority)	Composite endpoint of cardiovascular death, MI, hospitalization for unstable angina, coronary revascularization, stroke, or heart failure occurred in 1059 (12.8%) patients in the saxagliptin group and in 1034 (12.4%) patients in the placebo group (HR: 1.02; 95% CI: 0.94–1.11; p=0.66)
EXAMINE (alogliptin)			
Patients with T2D and either an acute MI or unstable angina requiring hospitalization within the previous 15–90 days	5380 patients were randomized to alogliptin or placebo in addition to existing antihyperglycemic and cardiovascular drug therapy were followed for 40 months	A primary endpoint event (composite of death from CVD causes, nonfatal MI, or nonfatal stroke) occurred in 305 (11.3%) of patients assigned to alogliptin and in 316 (11.8%) of patients assigned to placebo groups (HR: 0.96; CI: 1.16; p<0.001 for noninferiority)	Glycated hemoglobin levels were significantly lower with alogliptin than with placebo p<0.001. No differences were observed between the incidences of cancer hypoglycemia, pancreatitis, and initiation of dialysis between alogliptin and placebo groups
Patients with T2D and CVD	14,671 patients were randomized to sitagliptin or placebo and were followed for a median of 3 years	Primary cardiovascular outcome (composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina) occurred in 839 (11.4%) patients in the sitagliptin group and 851 (11.6%) patients in the placebo group. Sitagliptin was noninferior to placebo for the primary composite cardiovascular outcome (HR: 0.98; 95% CI: 0.88–1.09; p<0.001)	Rates of hospitalization for heart failure did not differ between the two groups (HR: 1.00; 95% CI: 0.83–1.20; p=0.98). There were no significant between-group differences in rates of acute pancreatitis (p=0.07) or pancreatic cancer (p=0.32)
CAROLINA (linagliptin)			
Adults with T2D and increased CV risk or established cardiovascular disease	6033 patients were randomized to linagliptin *versus* glimepiride with a median follow-up of more than 6 years	Met its primary endpoint (noninferiority for linagliptin *versus* glimepiride in time to the first occurrence of CV death, nonfatal MI or nonfatal stroke (3P-MACE)	Not available
CARMELINA (linagliptin)			
Adults with T2D HbA1c of 6.5–10.0%, high CV risk (history of vascular disease and urine-albumin creatinine ratio [UACR] >200 mg/g), and high renal risk (reduced eGFR and micro- or macroalbuminuria)	6979 patients were randomized to linagliptin 5 mg once daily or placebo and followed for a median duration of 2.2 years	Primary outcome (first occurrence of the composite of CV death, nonfatal MI, or stroke) occurred in 434/3494 (12.4%) in the linagliptin group and in 420/3485 (12.1%) in the placebo groups (absolute incidence rate difference, 0.13 [95% CI: −0.63–0.90] per 100 person-years) (HR: 1.02; 95% CI: 0.89–1.17; p<0.001 for noninferiority)	The secondary outcome (first occurrence of adjudicated death due to renal failure, or sustained 40% or higher decrease in eGFR from baseline) occurred in 327/3494 (9.4%) in the linagliptin group and in 306/3485 (8.8%) in the placebo group (absolute incidence rate difference, 0.22 [95% CI: −0.52 to −0.97] per 100 person-years) (HR: 1.04; 95% CI: 0.89–1.22; p=0.62)

(*Continued*)

Table 7. (*Continued*)

Patient population	Design/follow-up	Primary outcome	Secondary outcome
(VIVIDD) vildagliptin			
Patients 18–85 y/o with T2D and HF (New York Heart Association functional class I to III and left ventricular ejection fraction [LVEF] <0.40)	254 patients were randomized to vildagliptin 50 mg twice a day (n=128) or placebo (n=126) for 52 weeks	Primary objective (LVEF from baseline) the mean change in LVEF was reported to be 4.95 (±1.25%) in the vildagliptin group and 4.33% (±1.23%) in the placebo group; a difference of 0.62% (95% CI: −2.21–3.44; p=0.667)	The decrease in HbA1c from baseline to 16 weeks (main secondary endpoint) was greater in the vildagliptin group compared to placebo −0.62% (95% CI: −0.93 to −0.30%; p<0.001)
Sodium-glucose cotransporter (SGLT) 2 inhibitor trials			
EMPA-REG (empagliflozin)			
Patients with T2D, high risk or CV events, BMI ≤ 45	7028 patients were randomized to empagliflozin 10 or 25 mg compared to placebo	The primary outcome (three-point MACE: CV death, nonfatal MI, or stroke) occurred in 490/4687(10.5%) patients in pooled empagliflozin group and in 282/2333 (12.1%) in placebo group (HR: 0.86; 95% CI: 0.74–0.99; p=0.04 for superiority)	Empagliflozin group had significantly lower rates of death from CV causes (3.7%, *versus* 5.9% 38% RR reduction), and hospitalization for HF (2.7% *versus* 4.1%, 35% RR reduction), and death from any cause (5.7% *versus* 8.3%, respectively; 32% RR reduction). No significant differences between groups were seen in rates of MI or stroke. Incident or worsening nephropathy occurred in 12.7% of empagliflozin patients and 18.8% of placebo patients (HR: 0.61; 95% CI: 0.53–0.70; p<0.001). Serum creatinine level doubled in 1.5% empagliflozin patients *versus* 2.6% of placebo patients (significant RR reduction of 44%)
CANVAS (canagliflozin)			
Participants with T2D and high cardiovascular risk	10,142 participants were randomly assigned to receive canagliflozin or placebo and were followed for a mean of 188.2 weeks	The rate of the primary outcome (three-point MACE: CV death, nonfatal stroke, or MI) was lower in the canagliflozin group compared with placebo (occurring in 26.9 *versus* 31.5 participants per 1000 patient-years; HR: 0.86; 95% CI: 0.75–0.97; p<0.001 for noninferiority; p=0.02 for superiority)	Results showed a possible benefit of canagliflozin on renal outcomes (not statistically significant) progression of albuminuria (HR: 0.73; 95% CI: 0.67–0.79) and composite outcome of a sustained 40% reduction in the estimated GFR, need for renal-replacement therapy, or death from renal causes (HR: 0.60; 95% CI: 0.47–0.77)
CREDENCE (canagliflozin)			
Patients with T2D and albuminuric chronic kidney disease with eGFR >30 mL/min	4401 patients were randomized to canagliflozin 100 mg/day or placebo, with a median follow-up of 2.62 years	The primary outcome (a composite of end-stage kidney disease (dialysis, transplantation, or a sustained estimated GFR of <15 mL per minute per 1.73 m^2), a doubling of the serum creatinine level, or death from renal or CV causes) was 30% lower in the canagliflozin group than in the placebo group,	The relative risk of the renal-specific composite of end-stage kidney disease, a doubling of the creatinine level, or death from renal causes was lower by 34% (HR: 0.66; 95% CI: 0.53–0.81; p<0.001), and the relative risk of end-stage kidney disease was lower by 32% (HR: 0.68; 95% CI: 0.54–0.86; p=0.002). The canagliflozin group also had a

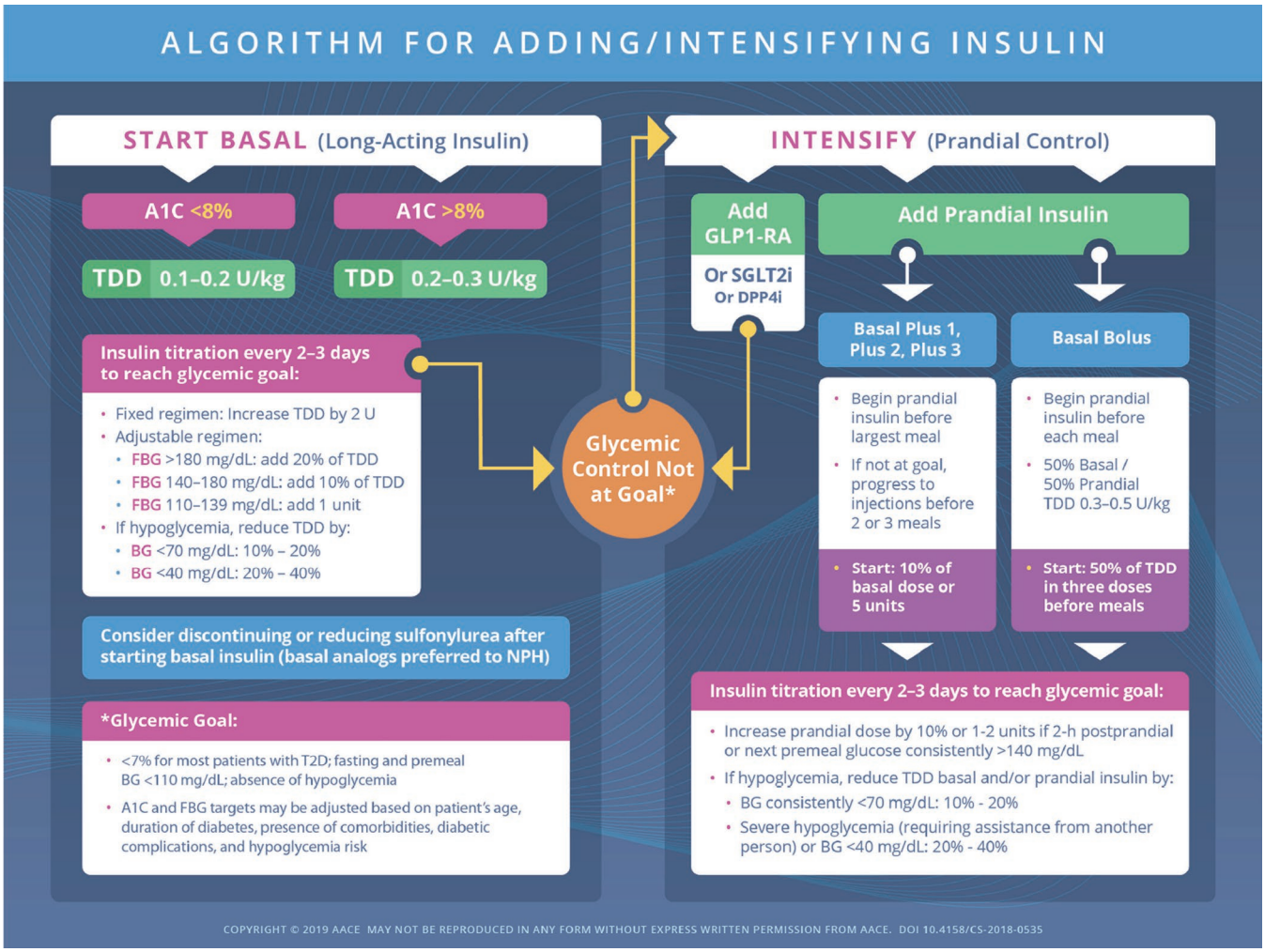
(*Continued*)

Table 7. (*Continued*)

Patient population	Design/follow-up	Primary outcome	Secondary outcome
		with event rates of 43.2 and 61.2 per 1000 patient-years, respectively (HR: 0.70; 95% CI: 0.59–0.82; p=0.00001)	lower risk of CV death, MI, or stroke (HR: 0.80; 95% CI: 0.67–0.95; p=0.01) and hospitalization for heart failure (HR: 0.61; 95% CI: 0.47–0.80; p<0.001). There were no significant differences in the rates of amputation or fracture
DECLARE-TIMI (dapagliflozin)			
Patients with T2D who had or were at risk for atherosclerotic cardiovascular disease	17,160 patients were randomized	The primary safety outcome a composite of MACE (cardiovascular death, MI, or ischemic stroke) dapagliflozin met the prespecified criterion for noninferiority to placebo 95% CI: <1.3; p<0.001 for noninferiority). In the primary efficacy outcomes of MACE dapagliflozin did not result in a lower rate of MACE (8.8% in the dapagliflozin group *versus* 9.4% in the placebo group; HR , 0.93; 95% CI: 0.84–1.03; p=0.17) and a primary efficacy outcome (composite of CV death or hospitalization for HF) were lower in the dapagliflozin group compared to placebo (4.9% *versus* 5.8%; hazard ratio: 0.83; 95% CI: 0.73–0.95; p=0.005)	A renal event occurred in 4.3% in the dapagliflozin group and in 5.6% in the placebo group (HR: 0.76; 95% CI: 0.67–0.87), and death from any cause occurred in 6.2% and 6.6%, respectively (HR: 0.93; 95% CI: 0.82–1.04). Diabetic ketoacidosis was more common with dapagliflozin than with placebo (0.3% *versus* 0.1%, p=0.02). Rate of genital infections that led to discontinuation of the regimen or that were considered to be serious adverse events was higher in the dapagliflozin group (0.9% *versus* 0.1%, p<0.001)
VERTIS (ertugliflozin)			
Patients, ≥40 y/o with T2D (A1C 7.0–10.5%) and established vascular disease of the coronary, cerebral, and/or peripheral arterial systems	8237 patients were randomized	Ongoing trial	Ongoing trial

Outcome Trial in Patients with Chronic HF with Preserved Ejection Fraction (EMPEROR-PRESERVE), Empagliflozin Outcome Trial in Patients with Chronic HF with Reduced Ejection Fraction (EMPEROR-REDUCED) and Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure (DELIVER) looking at the efficacy of SGLT-2 inhibitors in patients with established HF (patients with diabetes and without diabetes) in reducing or preserving ejection fraction. A meta-analysis of seven cardiovascular trials (REWIND, PIONEER-6, Harmony outcomes, EXSCEL, SUSTAIN-6, LEADER, ELIXA) showed that GLP-1 agonists reduced major adverse cardiovascular events by 12%, all-cause mortality by 12%, and hospitalizations for HF by 9% in patients with T2D.[76] SGLT-2 inhibitors (empagliflozin, canagliflozin, and dapagliflozin) have been shown to reduce CKD progression, but should be considered in the treatment of patients with T2D only if the eGFR is adequate.[14,15,67,69,77,78] SGLT-2 inhibitors may cause acute kidney injury especially in patients that are dehydrated or on nonsteroidal anti-inflammatory drugs (NSAID). In clinical trials, GLP-1 agonists liraglutide (LEADER trial), semaglutide (SUSTAIN-6 trial), and dulaglutide (REWIND trial) have demonstrated that treatment with a GLP-1 agonist can reduce albuminuria.[45,55,68,79] The Pioneer 5 trial showed that renal safety was consistent in the GLP-1 receptor agonist class.[80] Pioglitazone and metformin may also have potential benefits in atherosclerotic cardiovascular disease, and pioglitazone may also reduce stroke risk.[14,15] Insulin resistance has been suggested to accelerate ASCVD. Both pioglitazone and metformin are insulin sensitizers and may be beneficial in the treatment of patients with T2D and ASCVD by decreasing insulin resistance in skeletal muscle, liver, and adipocytes. The thiazolidinediones such as pioglitazone are not recommended in patients with symptomatic HF and contraindicated in New York Heart Association (NYHA) class III and IV HF. As this class of medication causes fluid retention, there

Figure 3. AACE/ACE algorithm for adding/intensifying insulin.[14, 15, 69] (Reprinted with permission from the American Association of Clinical Endocrinologists and American College of Endocrinology.)



is an increased risk of HF.[10,14,15,19,69] Metformin is discouraged in patients with acute HF with hypoperfusion.[81] The CAROLINA and CARMELINA cardiovascular outcome trials for linagliptin have shown cardiovascular safety.[63,64] Saxagliptin and alogliptin DPP-4 inhibitors have been shown to have a slight increased risk of HF and should be avoided in patients with preexisting HF.[15] Both SGLT-2 inhibitors and GLP-1 receptor agonists are excellent choices for minimizing weight gain in patients with T2D, but the GLP-1 receptor agonists promote more weight loss than SGLT-2 inhibitors. The DPP-4 inhibitors and metformin are weight neutral, but the thiazolidinediones, sulfonylureas, meglitinides, and insulin cause weight gain.[10,14,15,56,69] When considering a pharmacologic agent to utilize in patients with T2D, hypoglycemia must be considered. Patients at risk for hypoglycemia should use classes of medications with a lower risk of hypoglycemia such as metformin, SGLT-2 inhibitors, GLP-1 receptor agonists, DPP-4 inhibitors, thiazolidinediones, or the α-glucosidase inhibitors.[10,14,15,56,69] The antidiabetic classes of medications with the highest risk of hypoglycemia are the secretagogues (sulfonylureas and meglitinides) and insulins.[10,14,15,69,70] When considering antidiabetic medications there is a need to consider all the medication precautions and contraindications listed in Table 6. Cost is another consideration when recommending specific medications for patients with diabetes. Insurance carriers all have their own formularies that list their preferred drugs. Healthcare coverage will allow only certain medications to be covered. There are many patients who have high co-pays or need to pay out of pocket for their medications, and this can be very costly. The medications that are prescribed most often and low in cost are metformin, sulfonylureas, thiazolidinediones, and human insulin.[14,69] Medications that are prescribed most often and are high in cost are the insulin analogs, GLP-1 receptor agonists, SGLT-2 inhibitors, and DPP-4 inhibitors.[14,69]

T2D is a progressive disease in which the pancreas cannot synthesize and secrete sufficient insulin to meet the demands of insulin-resistant patients. Both the AACE/ACE and ADA/EASD recommend insulin therapy when patients with T2D fail to achieve their individualized target ranges. The AACE/ACE recommends insulin therapy be considered on diagnosis with or without other agents when the patient has

Figure 4. ADA/EASD intensifying to injectable therapies.14, 15,69 (Reprinted with permission from the American Diabetes Association.)

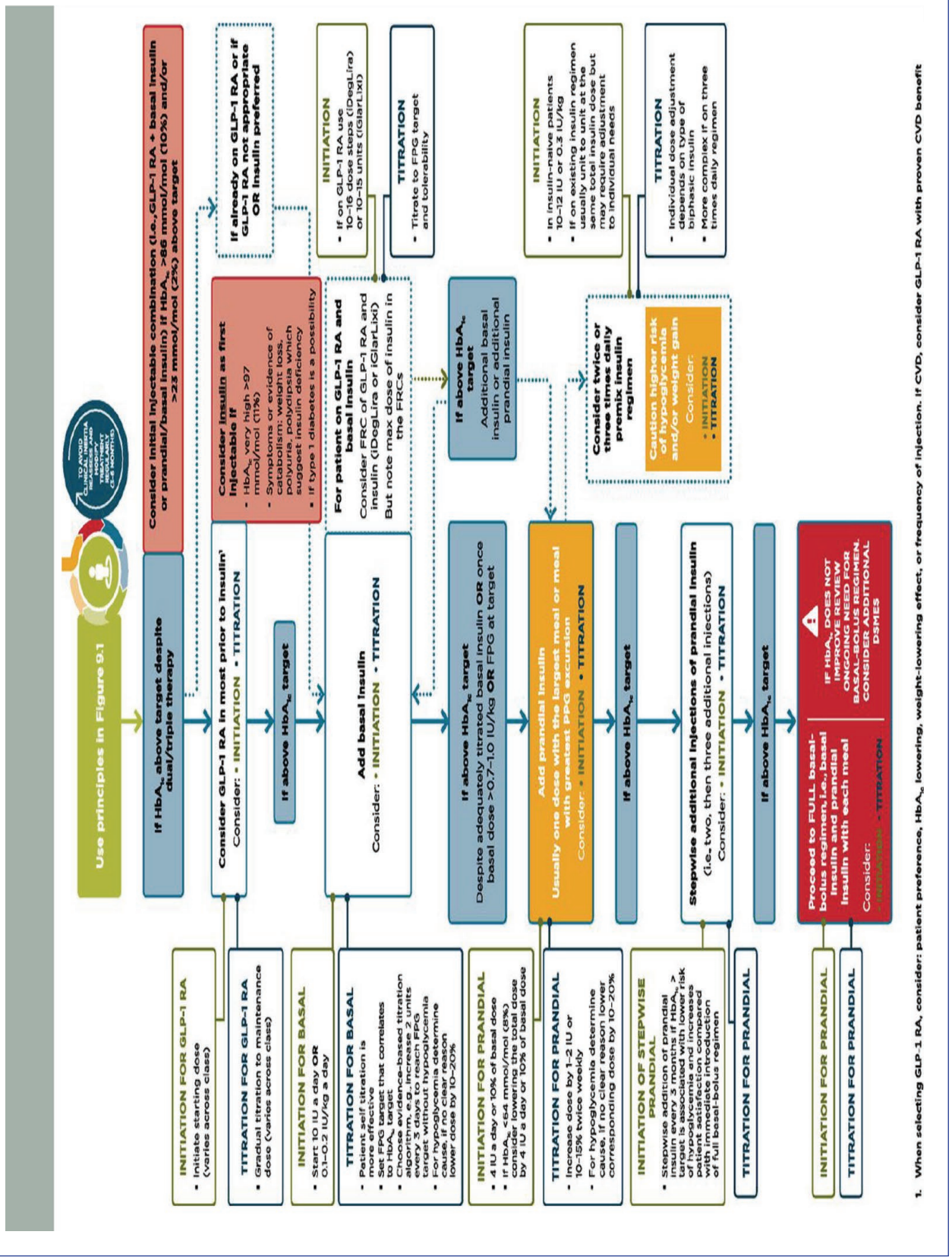


Table 8. Insulin preparations.[14,15,87,88]

Basal insulin
• NPH (human) (Humulin® N, Novolin® N) U-100
• glargine U-100 (Lantus®)
• glargine (Basaglar®) 'follow-on biologic' U-100
• glargine U-300 (Toujeo®) Longer acting than Lantus®; Basaglar®
• detemir U-100 (Levemir®)
• degludec U-100, U-200 (Tresiba®) Longest acting
• regular (human) (Humulin® R) U-500 (Basal/Bolus)
Combination basal insulin/GLP-1 agonist
• degludec/liraglutide (Xultophy®)
• lixisenatide/glargine (Soliqua®) 100/33
Bolus insulin
Rapid-acting insulin
• lispro (Humalog®) U-100 and U-200; Junior pen ½ unit
• lispro (Admelog®) 'follow-on biologic' U-100
• aspart (Novolog®) U-100; Fiasp® works a little faster and glucose lowering is better in the first 90 minutes
• glulisine (Apidra®) U-100
Short-acting insulin
• regular (human) (Humulin® R, Novolin® R) U-100
Inhaled insulin
• Powdered insulin cartridge (Afrezza®) onset right away
Premixed insulin
• Humulin® 50/50 (50% NPH, 50% regular)
• Humulin® 70/30 (70% NPH, 30% regular)
• Humalog® Mix 75/25 (75% insulin lispro protamine suspension (NPH) and 25% insulin lispro rDNA origin) equivalent to 70% NPH, 30% lispro
• Humalog® Mix 75/25 Pen (same as previously mentioned)
• Humalog® 50/50 vial and pen (50% NPH, 50% lispro)
• Novolin® 70/30 (70% NPH, 30% regular)
• Novolin® 70/30 Pen Fill (70% NPH, 30% regular)
• Novolin® 70/30 Prefilled (70% NPH, 30% regular)
• Novolog® 70/30 (70% insulin aspart protamine suspension 30% insulin aspart)
• Novolog® 70/30 Pen (same as previously mentioned)
• ReliOn/Novolin® 70/30 (70% NPH, 30% regular)
• Ryzodeg® 70/30 (70% degludec/30% aspart)

symptoms of hyperglycemia and an HbA1c level above 9% (74.9 mmol/mol).[15] The type of insulin is not recommended by the organization. If on diagnosis the patient does not have symptoms and the HbA1c is >9% (74.9 mmol/mol), the organization recommends dual or triple therapy in which basal insulin therapy may be an option.[15] Basal insulin may still be recommended for patients who do not achieve their HbA1c target goal. The dose of their basal insulin is determined by the HbA1c being <8% (63.9 mmol/mol) or >8% (Figure 3).[15] The ADA/EASD recommends insulin therapy be considered when the patient has symptoms of hyperglycemia and weight loss or an HbA1c of 11% (>97 mmol/mol).[14,69] The organization recommends considering combination injectable agents when the HbA1c is >10% (86 mmol/mol) and/or 2% (>23 mmol/mol) above target.[14,69] Injectable combination agents recommended by the ADA/EASD organizations are a GLP-1 receptor agonist with basal insulin or using both prandial insulin and basal insulin together (Figure 4).[14,69] Therapy should be evaluated every 3–6 months and adjusted based on patient-specific targets.

The prices of the newer insulin analogs have increased in recent years, so, as a result, many patients with diabetes cannot afford to buy insulin analogs. Over the years, insulin preparations have been developed to be less immunogenic and mimic the pancreatic release of insulin. Table 8 provides a list of the most common insulin products used by healthcare professionals. Basal insulin analogs have less hypoglycemia especially nocturnal, less variability, more predictability, longer duration of action and fewer injections than human insulin.[82] NPH insulin peaks leading to a greater risk of hypoglycemia and is also given usually twice a day.[82] Patients cannot skip meals and all meals should be carbohydrate consistent at the same time each day. A systemic review and network meta-analysis published in the Annals of Internal Medicine compared basal insulin analogs used for patients with type 2 diabetes and found they did not differ substantially in their glucose-lowering effect.[83] They also stated degludec and glargine 300 may have a lower risk of nocturnal hypoglycemia than the other insulin analogs.[83] Weight gain may be less for determir and glargine 300.[82,83] Prandial insulin analogs have been developed to mimic the pancreatic secretion of insulin when a person eats. These analogs have a faster onset and shorter duration of action than regular insulin.[82] Regular insulin needs to be taken 30 minutes before eating, and the analogs can be taken at the start of the meal or immediately after a meal.[82] Premixed insulin contains a combination of basal insulin and prandial insulin in one injection but tends to have an increased risk for hypoglycemia. Premixed insulin should be used only in patients who have consistent meals. Concentrated formulations (U-200, U-300, and U-500) of insulin are available for patients who require large doses of insulin. Insulin is now available as 'biosimilar' or 'follow-on' formulations that are less expensive and not identical to the original insulin due to a different manufacturing process. For individuals who cannot afford insulin analogs, attention has also been brought to using human insulin products. A study published in *JAMA* evaluated the implementation of a Health Plan Program switching patients from analog insulin to human insulin and showed there was a small increase in population-level HbA1c.[83] The World Health Organization has also published guidelines for treatment intensification in T2D and type of insulin in type 1 and type 2 diabetes in low-resource settings.[84] The recommendation from the WHO was to use short- and intermediate-acting human insulin to manage blood glucose in adults with type 1 and type 2 diabetes unless they have frequent episodes of hypoglycemia at which point long-acting insulin analogs would be used.[85] One must take into consideration that frequent episodes of hypoglycemia can cause hypoglycemia unawareness and serious adverse effects that can cause death.[86–88]

The management of patients with T2D has become complex with the growing number of medications and formulations that have been approved over the past few years. All the medications approved to treat diabetes lower the glucose levels by acting on different pathways that contribute to hyperglycemia. In selecting a treatment regimen for a patient with T2D, the regimen needs to be tailored to fit that specific individual patient. Healthcare providers must take into consideration several factors when selecting a drug treatment regimen: individualized glycemic targets, age of the patient, life expectancy, comorbidities, cardiovascular risk reduction and renal protection, avoidance of hypoglycemia and other side effects of medications, weight control, cost, and patient preferences to successfully manage a patient with T2D. Healthcare providers need to deliver patient-centered care. Adherence to therapy will depend on the patient being involved with decisions on their therapy. Diabetes is a progressive disease, and it is important to initiate, escalate, or sometimes de-intensify therapy when necessary to avoid 'clinical inertia.' The response to therapy should be assessed at regular intervals for efficacy and safety, and healthcare providers should adjust regimens to maintain glycemic targets. Healthcare providers need to work together with their patients on how to achieve agreed-upon glycemic targets.

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References

1. Dagogo-Jack S. 2015 Presidential address: 75 years of battling diabetes-our global challenge. *Diabetes Care*. 2016;39:3–9. https://doi.org/10.2337/dc15-1818
2. World Health Organization. Diabetes fact sheet. October 30, 2018. https://www.who.int/news-room/fact-sheets/detail/diabetes. Accessed April 11, 2019.
3. Zhang P, Gregg E. Global economic burden of diabetes and its implications. The *Lancet Diabetes Endocrinol*. 2017;5(6):404–405. https://doi.org/10.1016/S2213-8587(17)30100-6
4. American Diabetes Association. Summary of Proceedings of the American Diabetes Association Summit "Overcoming Therapeutic Inertia: Accelerating Diabetes Care For Life". 2019; 1–26. https://professional.diabetes.org
5. Khunti K, Seidu S. Therapeutic inertia and the legacy of dysglycemia on the microvascular and macrovascular complications of diabetes. *Diabetes Care*. 2019;42:349–351. https://doi.org/10.2337/dci18-0030
6. American Diabetes Association. Classification and diagnosis of diabetes: standards of medical care in diabetes 2019 *Diabetes Care*. 2019;42(Suppl. 1):S13–S28. https://doi.org/10.2337/dc19-S002
7. Handelsman Y, Bloomgarden ZT, Grunberger G, et al. American Association of Clinical Endocrinologists and American College of Endocrinology clinical practice guidelines for developing a diabetes mellitus comprehensive care plan—2015. *Endocr Pract*. 2015;21(Suppl. 1):1–87. https://doi.org/10.4158/EP15672.GL
8. Siu AL. Screening for abnormal blood glucose and type 2 diabetes mellitus: U.S. preventive services task force recommendation statement. *Ann Intern Med*. 2015;163(11):861–868. https://doi.org/10.7326/M15-2345
9. Saudek CK, Herman WH, Sacks DB, et al. A new look at screening and diagnosing diabetes mellitus. *J Clin Endocrinol Metab*. 2008;93:2447–2453. https://doi.org/10.1210/jc.2007-2174
10. International Diabetes Federation. Recommendations for managing type 2 diabetes in primary care, 2017. https://ihsgonline.com/wp-content/uploads/2017/09/IDF-T2D-CPR-2017_Guidelines_interactive.pdf. Accessed April 11, 2019.
11. Lisi DM. Applying recent A1C recommendations in clinical practice. *US Pharm*. 2018;43(10):15–22. https://doi.org/10.1007/s11892-016-0792-9
12. Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002;346(6):393–403. https://doi.org/10.1056/NEJMoa012512
13. Tuomilehto J, Lindström J, Eriksson JG, et al. Finnish diabetes prevention study group. *N Engl J Med*. 2001;344(18):1343–1350. https://doi.org/10.1056/NEJM200105033441801
14. Davies MJ, D' Alessio DA, Fradkin J, et al. Management of hyperglycaemia in type 2 diabetes, 2018: a consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia*. 2018; 61(12): 2461–2498. https://doi.org/10.1007/s00125-018-4729-5
15. Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm-2019 executive summary. *Endocr Pract*. 2019;25(1):69–100. https://doi.org/10.4158/CS-2018-0535
16. Qaseem A, Wilt TJ, Kansagara D, et al. Hemoglobin A1c targets for glycemic control with pharmacologic therapy for nonpregnant adults with type 2 diabetes mellitus: a guidance statement update from the American College of Physicians. *Ann Intern Med*. 2018;168(8):569–576. https://doi.org/10.7326/M17-0939
17. Endocrine News. Endocrine Society, ADA, AACE, AADE Strongly Disagree with ACP's Recent Diabetes Statement. March, 2018. https://endocrinenews.endocrine.org/endocrine-society-ada-aace-aade-strongly-disagree-acps-recent-diabetes-statement/. Accessed April 11, 2019.
18. Ladd J. ACP says A1C up to 8% is okay in type 2, but other groups object. Now what? *Pharmacy Today*. 2018;24(5):28. https://www.pharmacytoday.org/article/S1042-0991(18)30574-7/fulltext. Accessed January 20, 2020.
19. LaRoith D, Biessels GJ, Braithwaite SS, et al. Treatment of diabetes in older adults: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2019;104(5):1520–1574. https://doi.org/10.1210/jc.2019-00198

20. American Diabetes Association. Older adults: standards of medical care in diabetes—2019. *Diabetes Care*. 2019;42(1):S139–S147. https://doi.org/10.2337/dc19-S012
21. Cefalu WT, Rosenstock J, LeRoith D, et al. Getting to the "Heart" of the matter on diabetic cardiovascular disease: "Thanks for the Memory". *Diabetes Care*. 2016;39(5):664–667. https://doi.org/10.2337/dc16-0405
22. Shan D, Desai S. Cardiometabolic risk, metabolic syndome, and diabetes: dysmetabolism and cardiovascular risk. *Pract Diabetol*. 2015;34(1):11–16.
23. The Emerging Risk Factors Collaboration. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet*. 2010;375(9733):2215–2222. https://doi.org/10.1016/S0140-6736(10)60484-9
24. Expert Panel on Detection, Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of The National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). *JAMA*. 2001;285(19):2486–2497. https://doi.org/10.1001/jama.285.19.2486
25. Haffner SM, Lehto S, Ronnemaa T, et al. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med*. 1998;339(4):229–234. https://doi.org/10.1056/NEJM199807233390404
26. Bulugahapitiya U, Siyambalapitiya S, Sithole J, et al. Is diabetes a coronary risk equivalent? Systematic review and meta-analysis. *Diabet Med*. 2009;26(2):142–148. https://doi.org/10.1111/j.1464-5491.2008.02640.x
27. Nishimura RA, O'Gara PT, Bavaria JE, et al. 2019 AATS/ACC/ASE/SCAI/STS expert consensus systems of care document: a proposal to optimize care for patients with valvular heart disease: a joint report of the American Association for Thoracic Surgery, American College of Cardiology, American Society of Echocardiography, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2019. https://doi.org/10.1016/j.jacc.2018.10.007
28. American Diabetes Association. Cardiovascular disease and risk management. Standards of medical care in diabetes 2019. *Diabetes Care*. 2019;42(Suppl. 1):S103–S123. https://doi.org/10.2337/dc19S010
29. McAllister DA, Read S, Kerssens J, et al. Incidence of hospitalization for heart failure and case-fatality among 3.25 million people with and without diabetes. *Circulation*. 2018;138(24):2774–2786. https://doi.org/10.1161/CIRCULATIONAHA.118.034986
30. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2018;73(24):e285–e350. https://doi.org/10.1016/j.jacc.2018.11.003
31. 2017 AACE/ACE Guidelines for the Management of Dyslipidemia and Prevention of Cardiovascular Disease Task Force. *Endocr Pract*. 2017; 23(Suppl 2) S1-63. https://doi.org/10.4158/EP171764.GL
32. Clinical practice guidelines for healthy eating for the prevention and treatment of metabolic and endocrine diseases in adults. Clinical practice guidelines for healthy eating. *Endocr Pract*. 2013;19(Suppl. 3). https://doi.org/10.4158/EP13155.GL
33. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2018;71:e127–e248. https://doi.org/10.1016/j.jacc.2017.11.006
34. Kannel WB, McGee DL. Diabetes and cardiovascular disease: the Framingham study. *JAMA*. 1979;241:2035–2203. https://doi.org/10.1001/jama.1979.03290450033020
35. Iribarren C, Karter AJ, Go AS, et al. Glycemic control and heart failure among adult patients with diabetes. *Circulation*. 2001;103:2668–2673. https://doi.org/10.1161/01.CIR.103.22.2668
36. Pazin-Filho A, Kottgen A, Bertoni AG, et al. HbA 1c as a risk factor for heart failure in persons with diabetes: the Atherosclerosis Risk in Communities (ARIC) study. *Diabetologia*. 2008; 51:2197–2204. https://doi.org/10.1007/s00125-008-1164-z
37. Romero SP, Andrey JL, Garcia-Egido A, et al. Metformin therapy and prognosis of patients with heart failure and new-onset diabetes mellitus: a propensity-matched study in the community. *Int J Cardiol*. 2013;166:404–412. https://doi.org/10.1016/j.ijcard.2011.10.141
38. Lincoff AM, Wolski K, Nicholls SJ, et al. Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. *JAMA*. 2007;298:1180–1188. https://doi.org/10.1001/jama.298.10.1180
39. Scirica BM, Braunwald E, Raz I, et al.; For the SAVOR-TIMI 53 Steering Committee and Investigators. Heart failure, saxagliptin, and diabetes mellitus: observations from the SAVOR-TIMI 53 randomized trial. *Circulation*. 2014;130:1579–1588. https://doi.org/10.1161/CIRCULATIONAHA.114.010389
40. White WB, Bakris GL, Bergenstal RM, et al. EXamination of CArdiovascular outcoMes with alogliptIN versus standard of carE in patients with type 2 diabetes mellitus and acute coronary syndrome (EXAMINE): a cardiovascular safety study of the dipeptidyl peptidase 4 inhibitor alogliptin in patients with type 2 diabetes with acute coronary syndrome. *Am Heart J*. 2011;162:620–626. https://doi.org/10.1016/j.ahj.2011.08.004

41. Green JB, Bethel MA, Paul SK, et al. Rationale, design, and organization of a randomized, controlled Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) in patients with type 2 diabetes and established cardiovascular disease. *Am Heart J*. 2013;166:983–989. https://doi.org/10.1016/j.ahj.2013.09.003
42. U.S. Food and Drug Administration. Guidance for Industry. Diabetes mellitus evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes, December 2008. www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf. Accessed April 11, 2019.
43. Hiatt WR, Kaul S, Smith RJ. The cardiovascular safety of diabetes drugs–insights from the rosiglitazone experience. *N Engl J Med*. 2013;369:1285–1287. https://doi.org/10.1056/NEJMp1309610
44. Nissen SE, Wolski K, Topol EJ. Effect of muraglitazar on death and major adverse cardiovascular events in patients with type 2 diabetes mellitus. *JAMA*. 2005;294:2581–2586. https://doi.org/10.1001/jama.294.20
45. Gerstein HC, Miller ME, Byington RP, et al.; Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med*. 2008;358(24):2545–2559. https://doi.org/10.1056/NEJMoa0802743
46. Kahn SE, Haffner SM, Heise MA, et al.; ADOPT Study Group. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N Engl J Med*. 2006; 355:2427–2443. https://doi.org/10.1056/NEJMoa066224
47. Zinman B, Wanner C, Lachin JM, et al.; EMPA- REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373:2117–2128. https://doi.org/10.1056/NEJMoa1504720
48. Yusuf S, Sleight P, Pogue J et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med*. 2000; 342(3):145–153. https://doi.org/10.1056/NEJM200001203420301
49. Zinman B, Inzucchi SE, Lachin JM, et al. Rationale, design, and baseline characteristics of a randomized, placebo-controlled cardiovascular outcome trial of empagliflozin (EMPA-REG OUTCOME). *Cardiovasc Diabetol*. 2014;13:102. https://doi.org/10.1186/1475-2840-13-102
50. Neal B, Perkovic V, Mahaffey KW, et al.; CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. 2017;377(7):644–657. https://doi.org/10.1056/NEJMoa1611925
51. Wiviott, SD, Raz, I, Bonaca, MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes (DECLARE TIMI 58). *N Engl J Med*. 2019;380:347–357. https://doi.org/10.1056/NEJMoa1812389
52. Cannon CP, McGuire DK, Pratley R., et al. Design and baseline characteristics of the eValuation of ERTugliflozin efflcacy and Safety CardioVascular outcomes trial (VERTIS-CV). *Am Heart J*. 2018;206:11–23. https://doi.org/10.1016/j.ahj.2018.08.016
53. Marso SP, Daniels GH, Brown-Frandsen K, et al.; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2016;375(4):311–322. https://doi.org/10.1056/NEJMoa1603827
54. Zweck E, Roden M. GLP-1 agonists and cardiovascular disease: drug specific or class effects? *Lancet*. 2019;7:89–90. https://doi.org/10.1016/S2213-8587(18)30351-6
55. Marso SP, Bain S, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2016;375:1834–1844. https://doi.org/10.1056/NEJMoa1607141
56. Husain M, Birkenfeld AL, Donsmark M, et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2019;381:841–851. https://doi.org/10.1056/NEJMoa1901118
57. Pfeffer MA, Claggett B, Diaz R, et al. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. *N Engl J Med*. 2015;373:2247–2257. https://doi.org/10.1056/NEJMoa1509225
58. Muskiet MA, Tonneijck L, Huang Y, et al. Lixisenatide and renal outcomes in patients with type 2 diabetes—a post-hoc analysis of the ELIXA trial. *Diabetes*. 2018;67(Suppl. 1). https://doi.org/10.2337/db18-1060-P
59. Holman RR, Bethel MA, Mentz RJ, et al. EXSCEL Study Group. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2017;377(13):1228–1239. https://doi.org/10.1056/NEJMoa1612917
60. Hernandez AF, Jennifer BG, Janmohamed S, et al. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomized placebo-controlled trial. *Lancet*. 2018;392:1519–1529. https://doi.org/10.1016/S0140-6736(18)32261-X
61. Scirica BM, Bhatt DL, Braunwald E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med*. 2013;369:1317–1326. https://doi.org/10.1056/NEJMoa1307684
62. McMurray JJV, Ponikowski P, Bolli GB, et al. Effects of vildagliptin on ventricular function in patients with type 2 diabetes mellitus and heart failure: a randomized placebo-controlled trial. *JACC Heart Fail*. 2018; 6(1):8–17. https://doi.org/10.1016/j.jchf.2017.08.004
63. Boehringer Ingelheim. 2019 Boehringer Ingelheim and Lilly announce the CAROLINA® cardiovascular outcome trial of Tradjenta® met its primary endpoint of non-inferiority compared with glimepiride. [Press Release] https://www.boehringer-ingelheim.us/press-release/boehringer-ingelheim-and-lilly-announce-carolina-cardiovascular-outcome-trial.
64. Rosentock J, Perkovic V, Johansen OE, et al.; CARMELINA investigators. Cardiovascular events in adults with type 2 diabetes and high cardiovascular and renal risk. The CARMELINA randomized clinical trial. *JAMA*. 2019;321(1):69–79. https://doi.org/10.1001/jama.2018.18269

65. Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double blind randomised placebo-controlled trial. *Lancet*. 2019;394(10193):121–130. https://doi.org/10.1016/S0140-6736(19)31149-3
66. Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med*. 2016;375:323–334. https://doi.org/10.1056/NEJMoa1515920
67. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med*. 2019;380:2295–2306. https://doi.org/10.1056/NEJMoa1811744
68. Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and renal outcomes in type 2 diabetes: an exploratory analysis of the REWIND randomized, placebo-controlled trial. *Lancet*. 2019;394(10193):131–138. https://doi.org/10.1016/S0140-6736(19)31150-X
69. American Diabetes Association. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes-2019. *Diabetes Care*. 2019; 42(1):S90–S102. https://doi.org/10.2337/dc19-S009
70. Qaseem A, Barry MJ, Humphrey LL, et al. Oral pharmacologic treatment of type 2 diabetes mellitus: a clinical practice guideline update from the American College of Physicians. *Ann Intern Med*. 2017;166(4):279–290. https://doi.org/10.7326/M16-1860
71. American Diabetes Association. Lifestyle management: standards of medical care in diabetes-2019. *Diabetes Care*. 2019; 42(1):S46–S60. https://doi.org/10.2337/dc19-S005
72. Cosentino F, Grant PJ, Aboyans V, et al. 2019 ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: The Task Force for diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD). *Euro Heart J*. 2019;ehz486. https://doi.org/10.1093/eurheartj/ehz486
73. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2019;381: 2075–2077. https://doi.org/10.1056/NEJMoa1913157
74. Cefalu WT, Kaul S, Gerstein HC, et al. Cardiovascular outcomes trials in type 2 diabetes: where do we go from here? Reflections from a diabetes care editors' expert forum. *Diabetes Care*. 2018;41:14–31. https://doi.org/10.2337/dci17-0057
75. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2019;381:1995–2008. https://doi.org/10.1056/NEJMoa1911303
76. Kristensen SL et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet Diabetes Endocrinol*. 2019;7(10):776–785. https://doi.org/10.1016/S2213-8587(19)30249-9
77. Kelly MS, Lewis J, Huntsberry AM, et al. Efficacy and renal outcomes of SGLT2 inhibitors in patients with type 2 diabetes and chronic kidney disease. *Postgrad Med*. 2019;131(1):31–42. https://doi.org/10.1080/00325481.2019.1549459
78. Cook J, Ayers J, Sisson E. SGLT2 inhibitors: cardiovascular benefits beyond glycemic control. *ADCES Pract*. 2018;6(3):34–39. https://doi.org/10.1177/2325160318762127
79. Johannes FE, Orsted DD, Brown-Frandsen K, et al.; LEADER Steering Committee. Liraglutide and renal outcomes in type 2 diabetes. *N Engl J Med*. 2017;377:839–848. https://doi.org/10.1056/NEJMoa1616011
80. Mosenzon O, Blicher TM, Rosenlund S, et al. Efficacy and safety of oral semaglutide in patients with type 2 diabetes and moderate renal impairment (PIONEER 5): a placebo-controlled, randomized, phase 3a trial. *Lancet Diabetes Endocrinol*. 2019;7(7):515–527. https://doi.org/10.1016/S2213-8587(19)30192-5
81. Flory J, Lipska K. Metformin in 2019. *JAMA*. 2019;321(19):1926–1927. https://doi.org/10.1001/jama.2018.15333
82. Grunberger G. Insulin analogs-are they worth it? Yes! *Diabetes Care*. 2014;37(6):1767–1770. https://doi.org/10.2337/dc14-0031
83. Madenidou AV, Paschos P, Karagiannis T, et al. Comparative benefits and harms of basal insulin analogues for type 2 diabetes: a systemic review and network meta-analysis. *Ann Intern Med*. 2018;169(3):165–174. https://doi.org/10.7326/M18-0443
84. Luo J, Khan NF, Manetti T, et al. Implementation of a health plan program for switching from analogue to human insulin and glycemic control among medicare beneficiaries with type 2 diabetes. *JAMA*. 2019;321(4):374–384. https://doi.org/10.1001/jama.2018.21364
85. Roglic G, Norris SL. Medicines for treatment intensification in type 2 diabetes and type of insulin in type 1 and type 2 diabetes in low-resource settings: synopsis of the World Health Organization guidelines on second-and-third line medicines and type of insulin for the control of blood glucose levels in nonpregnant adults with diabetes mellitus. *Ann Intern Med*. 2018;169:394–397. https://doi.org/10.7326/M18-1149
86. Seaquist ER, Anderson J, Childs B, et al. Hypoglycemia and diabetes: a report of a Workgroup of the American Diabetes Association and the Endocrine Society. *J Clin Endocrinol Met*. 2013;98(5):1845–1859. https://doi.org/10.1210/jc.2012-4127
87. Drugs for type 2 diabetes. *The Medical Letter on Drugs and Therapeutics* 2017;59(1512). https://secure.medicalletter.org/article-share?a=1512a&p=tml&title=Drugs%20for%20Type%202%20Diabetes&cannotaccesstitle=1 Accessed May 28, 2019.
88. Insulins for type 2 diabetes. *The Medical Letter on Drugs and Therapeutics* 2019;61(1571). https://secure.medicalletter.org/article-share?a=1571a&p=tml&title=Insulins%20for%20Type%202%20Diabetes&cannotaccesstitle=1 Accessed May 28, 2019