CONTENTS

The ART

The SCIENCE

PREFACE

The Art and Science of Diabetes Care and Education (Art and Science), now in its sixth edition, continues to be the comprehensive, evidence-based, authoritative reference for diabetes care and education specialists (DCES), nurses, dietitians, nutritionists, pharmacists, physicians, and other health care professionals (HCPs) and community professionals. Since the first edition was published in 2006, *Art and Science* has offered the essential tools and resources to help translate foundational principles, recommendations, and guidelines into the strategies necessary to ensure proper management and achievable health behaviors for people living with diabetes.

The following global and chapter specific revisions have been made to the sixth edition:

- ***Updated*** to the American Diabetes Association (ADA) *Standards of Care in Diabetes* 2023 (*Standards of Care*).
- ***Revised*** language and terminology that is person-first, strength-based, and empowering to help improve communication and enhance the motivation, health, and well-being of PWD (refer to the Foreword on page xv).
- ***New*** to this edition is the *Insulin Pump Therapy and Automated Insulin Delivery Systems* Appendix at the back of this book. The appendix was added to support persons with both type 1 diabetes and type 2 diabetes using insulin pumps.

Chapter 4, *Healthy Coping,* the addiction section was updated to be consistent with industry standards in the field of addiction. The eating disorders section is expanded and updated to cover the 3 most common eating disorders in PWD, defined by the American Psychiatric Association (APA), and current research on diabetes and eating disorders. Other revisions to this chapter include updates to Table 4.3, *Depression, Anxiety, and Diabetes-Related Stress: Informal Screen Questions,* which was revised to be to be consistent with the APA and current research.

Chapter 6, *Being Active,* the Physical Activity Pyramid was removed from the chapter and replaced with a stronger emphasis on daily movement. The physical activity recommendations were updated to include the latest guidelines for type 2 diabetes from the American College of Sports Medicine *2022 Consensus Statement.* Alternate physical activity studies and details were added including qigong, sprint interval training, and high-intensity interval training. The use of continuous glucose monitoring devices and time-in-range measurements and the impact of being active sections were expanded, as well as heat-related illness and activity risk in PWD, and the importance of regular exercise around bariatric surgery, and exercise barriers

Chapter 11, *Diabetes Education Program Management,* is updated with discussions on the vision for the specialty, and related resources, to illustrate new opportunities in diabetes self-management education and support services, the national diabetes prevention program, delivering services via telehealth, and social determinants of health considerations.

Chapter 12, *Transitional Care,* The medication use section is updated to reflect new recommendations and literature for safe medication use when transitioning to different settings, including holding SGLT2 inhibitors prior to scheduled surgeries.

Chapter 13, *Pathophysiology of the Metabolic Disorder,* includes updates to the diabetes statistics in the United States, epidemiology (race and ethnic prevalence) statistics, the 2014 data for maps of trends in diabetes and obesity, and the pathophysiology stages in the development of type 1 diabetes.

FOREWORD

The Association of Diabetes Care and Education Specialists (ADCES) publication, *The Art and Science of Diabetes Care and Education*, affectionately known as the *Art and Science*, was first published in 2006. As we celebrate the 50th anniversary of our specialty organization in 2023, it is important to reflect on how far diabetes care and education specialists (DCES) have come over the years. This beloved book, which presents evidence and instructions to support the work of the DCES, has been shaped and updated to reflect the evolution of the diabetes care and education landscape over time.

One area that has become increasingly visible and more frequently discussed in diabetes care and education is the impact of our words and messages on the people we care for and about. The *language movement* in diabetes started several decades ago; however, it did not gain real traction until the 2010s.

A study, commissioned by ADCES (then known as the American Association of Diabetes Educators) and published in 2015, explored perspectives of health professions faculty and nursing students on diabetes education as a career path. Results of open-ended questions surveys revealed that nursing students overwhelmingly felt frustrated at the thought of working with people who have diabetes. These students saw people with diabetes as *not caring about themselves, not taking care of themselves,* and *being "non-compliant.*

Staff members at the ADCES and members of the research team decided to pursue this problem; they predicted that if the messages around diabetes were changed, more health care professions students might be willing to work in diabetes. This group gathered a writing team to develop a *paper* on the topic of language in diabetes.[1] Almost immediately it became clear that more than a *paper* was needed, and the team recruited additional volunteer writers from the American Diabetes Association (ADA). This writing team developed the following principles that guided them as they wrote a *paper* for publication:

- Diabetes is a complex and challenging disease involving many factors and variables
- Stigma that has historically been attached to a diagnosis of diabetes can contribute to stress and feelings of shame and judgment
- Every member of the health care team can serve people with diabetes more effectively through a respectful, inclusive, and person-centered approach
- Person-first, strengths-based, empowering language can improve communication and enhance the motivation, health, and well-being of people with diabetes

The resulting article, *The Use of Language in Diabetes Care and Education*,[1] was published jointly by ADCES and ADA in late 2017. This paper has been used to support a more robust language movement among diabetes health care professionals in the United States and internationally. Since that time, ADCES has continued to promote person-centered, strengths-based, and empowering messages in spoken and written content and all the programs they offer. Prominent in the ADCES 2020 revised competencies for the DCES is the use of person-centered and nonjudgmental language. Changing our language helps the DCES more effectively communicate with people who have diabetes as well as fellow clinicians, and the evidence supporting such change is steadily growing.

of the fastest-growing global health emergencies of the 21st century.[2] Certainly, there is a distinction, never more apparent than now, between communicable and noncommunicable health emergencies. And the importance of developing systems to rapidly respond to emerging health concerns cannot be minimized. At the same time, it is critical to focus on other life-threatening, chronic conditions. The negative impact exerted by diabetes mellitus on individuals and society is never-ending. The magnitude of the impact will be most apparent in countries with the fewest resources, but diabetes knows no boundaries. Even within the wealthiest countries, including the United States, the effects of diabetes and prediabetes continue to exert significant damage on population health.[3] Without change, 15 million people are projected to *prematurely* die every year from noncommunicable diseases.[4] Fifteen million translates to more than 28 individuals every minute, of every day, 365 days of the year.

There are 3 primary forms of diabetes:

1. Type 1 diabetes (T1D)
2. Type 2 diabetes (T2D)
3. Gestational diabetes

Each of these is discussed in detail in later chapters of this publication. Type 2 diabetes is the most common form of diabetes. It affects up to 95% of all persons with the disease.[2,3] The development of T2D is associated with genetics, epigenetics, and is compounded by modifiable environmental risk factors including obesity, physical inactivity, and poor nutrition.[2,5] Although the onset of T2D can be delayed or prevented by disrupting the association of 1 or more risk factors, continued worldwide growth makes it clear T2D has moved beyond pandemic levels into *syndemic* proportions.[3,6] Strong evidence supports the positive impact of impact of health behaviors on T2D, and new data suggest that the use of monoclonal antibodies may delay the onset of T1D as well.[7,8] Once diagnosed, long-term complications of either T1D or T2D can be prevented or delayed with targeted diabetes management strategies.[3,6,9,10] Among these complications are related cardiometabolic conditions.[3] In fact, major cardiovascular events and vascular and nerve damage leading to lower-extremity amputations are among the leading causes of hospitalizations in adults with diabetes, far outpacing complications associated with hypo- and hyperglycemic events.[3] Strategies such as person-centered care, education, and ongoing support to facilitate health behaviors aimed at achieving and maintaining target glucose levels are essential components of comprehensive care that impact both the immediate outcomes as well as the related comorbidities that often develop in persons with diabetes (PWD).

Global Impact of Diabetes

In the *Atlas of Diabetes,* published biennially, the International Diabetes Federation (IDF) addresses the global impact of diabetes.[2] According to 2021 data, the total estimated prevalence of diabetes in adults has more than tripled since 2000 and currently affects 537 million worldwide.[2] Expected to rise another 25% over the next decade, the IDF is projecting a worldwide prevalence of diabetes of over 700 million by 2045. This far surpasses previous projections. While growth is expected throughout the world, the largest increases are expected to occur as countries continue to develop and their economies improve such as in Africa, the Middle East, North Africa, Southeast Asia, and South and Central America.[2,3] Worldwide, T2D continues to account for approximately 90% of all diabetes[2] and is slightly more common in men than in women. In many countries, including the United States, T2D is far more common in non-White and older adult populations.[2,3,11] Type 2 diabetes is often a condition associated with aging; while a rising 10.5% of the overall adult population has diabetes, nearly 25% of those over aged 65 years are shown to have diabetes.[2,3]

Across the United States, in addition to the estimated 37.3 million PWD, another 88 million adults have prediabetes, bringing the total number of Americans with or at risk for diabetes to over 120 million.[3,12,13] Projections suggest that by 2050 as many as 1 in 3 adults throughout the world will have diabetes.[2,14,15] China, India, and the United States continue to lead the world in cases of diabetes, a situation not likely to change in the future despite the rapid rise in disease in other areas of the world.[2,3]

Because diabetes affects all segments of society, the impact of this disease is far-reaching. In 2010, an estimated 4 million deaths were attributed to diabetes worldwide, with the proportionate number of deaths from diabetes in middle-aged women sometimes reaching nearly 25%.[16] By 2017, the annual death rate attributable to diabetes had exceeded 4 million worldwide.[2] In the United States, diabetes is ranked as the eighth-leading cause of death.[17] However, it is generally believed estimates of mortality due to diabetes are greatly underestimated because the cause of death in PWD is often ascribed to other conditions including heart disease and stroke, both of which rank higher on the list.[17] Global targets to reduce premature death from noncommunicable diseases by 30% by 2030 have been established.[4] Despite unprecedented rapid advances in technology, health care systems in most countries are unprepared to deal with the consequences associated with a pandemic of this magnitude.[18] Public health initiatives promoting an understanding of the multifactorial nature of diabetes and its complications combined with targeted approaches to identify and treat

other than TGs and cholesterol, are involved in these systems and include very low-density lipoproteins (VLDL), low-density lipoproteins (LDL-C), and high-density lipoproteins (HDL-C).[6] **Figure 20.1** depicts the exogenous and endogenous lipid transport system.

Dyslipidemia in PWD is typically composed of elevated TGs and decreased HDL-C, with LDL-C elevations comparable to those of PWD. However, the particle size of the LDL-C in PWD tends to be smaller and denser, which can increase atherogenicity.[6]

The small, dense LDL-C particles often seen with diabetes raise the risk for heart disease.

The abnormalities in the small, dense LDL-C composition are partially due to hypertriglyceridemia and are associated with a threefold increased risk of coronary heart disease (CHD).[7] This increased risk is caused by the particles' ability to enter blood vessel walls more easily than the normal, large, and less-dense LDL-C particles thus, endothelial function is impaired and susceptibility to thrombosis increases.[8]

However, serum LDL-C may be less predictive of CHD risk than other measurements. Therefore, non-HDL-C (calculated as total cholesterol [TC] – HDL-C) has been recommended as an alternative to LDL-C because of data suggesting it may be a better predictor of CHD risk than LDL-C.[9] Furthermore, non-HDL-C represents an individual's entire atherogenic lipoprotein burden and is easily measured during a non-fasting state.

Elevated TGs are a key contributor to low HDL-C.

Elevated TG levels can result from 2 abnormalities: overproduction of VLDL and impaired lipolysis of TGs. Persons with T2D overproduce TG-rich VLDL, a result of elevated free fatty acid levels, hyperglycemia, obesity, and insulin resistance.[10] Impaired lipolysis of VLDL TGs is thought to be due to a reduction in lipoprotein lipase activity.[10]

HDL-C is the major lipoprotein responsible for removing excess cholesterol from peripheral tissues, which is known as reverse cholesterol transport. Therefore, suboptimal levels of HDL-C can result in increases in TGs, VLDL, and LDL-C.[6] Low levels of HDL-C is a known risk factor for CHD; however, studies involving medications that raise HDL-C have not been shown to reduce ASCVD risk.[11-13]

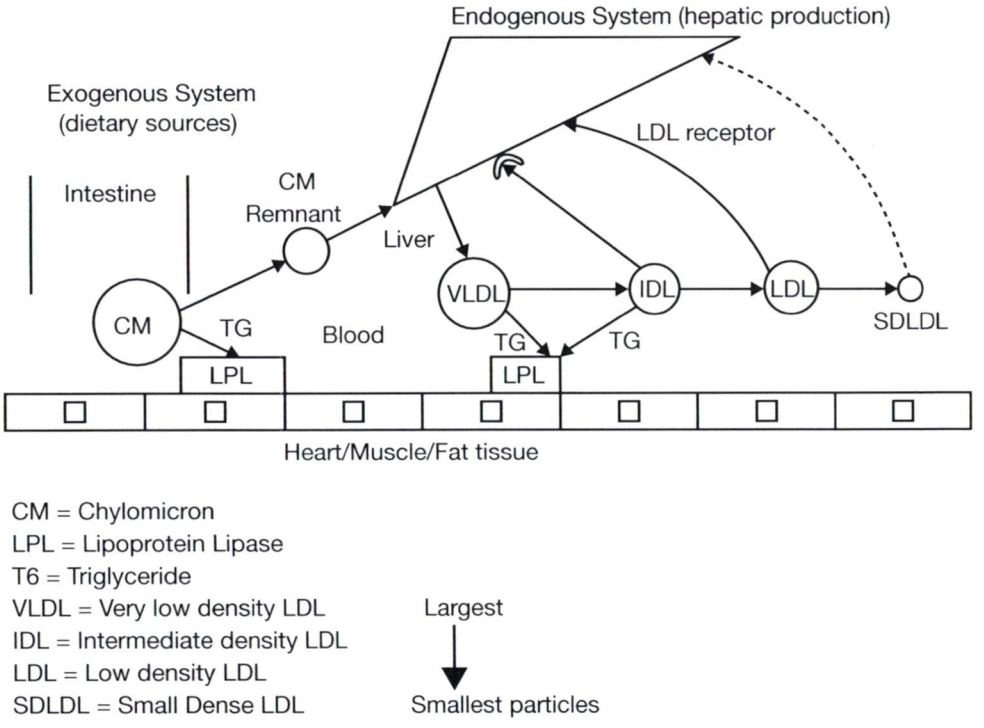

FIGURE 20.1 Exogenous and Endogenous Lipid Transport Systems

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Dosing. Statins are generally administered once daily. Because of their short half-life, lovastatin, fluvastatin, pravastatin, and simvastatin may be taken in the evening to coincide with nighttime cholesterol synthesis.[17] However, morning dosing is appropriate if evening dosing results in missed administration. Atorvastatin, rosuvastatin, and pitavastatin may be taken at any time of day. The dosage is based on the desired statin intensity according to an individual's risk.[9]

Low-intensity doses are only appropriate for:

- Individuals unable to tolerate moderate- or high-intensity doses;
- Individuals at higher risk of adverse effects due to unavoidable drug-drug interactions; and
- Asian populations, who are known to have a greater response to statin therapy than other groups.[9]

Pregnancy, Precautions, and Contraindications. Statins are not recommended in pregnancy and in women who are breastfeeding; they should be used cautiously in those with significantly impaired renal or hepatic function.[9]

Adverse Effects. Statins are generally well tolerated with minimal adverse effects, especially with appropriate monitoring. However, several statin-associated adverse effects involving the musculoskeletal, metabolic, liver, neurological, and other systems have been reported.[9,18]

Statin-associated muscle symptoms (SAMS) are the most commonly reported adverse effect, with reports ranging from 10% to 25% of those on statin therapy.[18]

TABLE 20.3 HMG-CoA Reductase Inhibitors (Statins): Dosage Information[9]

Drug	Trade Name	Common Dose	Common Frequency
Atorvastatin	Lipitor	10 to 80 mg	Once daily
Fluvastatin	Lescol	20 to 40 mg	Once or twice daily
	Lescol XL	80 mg	Once daily
Lovastatin	Mevacor	10 to 40 mg	Once or twice daily
	Altoprev	10 to 60 mg extended-release	Once daily
Pitavastatin	Livalo Zypitamag	1 to 4 mg	Once daily
Pravastatin	Pravachol	10 to 80 mg	Once daily
Rosuvastatin	Crestor	5 to 40 mg	Once daily
Simvastatin	Zocor	10 to 40 mg	Once daily

Muscle pain, stiffness, and/or achiness often develop bilaterally and involve large muscle groups (eg, thighs, back), while cramping is unilateral and involves smaller muscles in the hands and/or feet. Terms used to describe SAMS vary and include *myopathy*, *myositis*, and *myalgia*. Interestingly, SAMS can occur in those with normal creatine kinase (CK) levels, while some individuals can have elevated CK levels but no muscle symptoms. Rarely (0.1% of statin users), persons develop rhabdomyolysis, which is evident by a CK greater than 10 times the upper limit of normal and symptoms of fever, nausea, tachycardia, and dark-colored urine.[18] SAMS are most common with high-intensity statin therapy, concomitant use of drugs that interact with statins, those of advanced age, the female gender, lower body mass index, alcohol use, and regular exercisers. Therefore, instruct persons to report any experience of muscle weakness, tenderness, pain, or fever.

Vitamin D status may be considered a modifiable risk factor for muscle-related adverse effects of statins, and supplementation of vitamin D (particularly when ≤20 ng/mL) may improve statin tolerance.[9]

Statins have also been associated with causing new-onset diabetes (as reported in the JUPITER Study).[18] Several meta-analyses including several statin trials observed a small but statistically significant increase in the risk of new-onset diabetes in statin users.[18] However, a post-hoc analysis of the JUPITER study found that new-onset diabetes developed only in those individuals enrolled in the trial who had at least 1 risk factor for diabetes.[19] Furthermore, rosuvastatin 20 mg daily reduced the risk of or delayed 3 ASCVD events for every new case of diabetes. Thus, the benefit of statin therapy exceeded the diabetes risk in those at high risk of developing diabetes. Mechanisms for statin-associated diabetes are unclear. It appears that there is merely an *association* but no definitive evidence that statins *cause* or *worsen* diabetes.[9]

Significant elevations of liver enzymes can occur and are more common during the first 12 weeks of therapy.[20] Statin therapy should be discontinued when liver enzymes exceed 3 times the upper limit of normal. Of note, there have been few reports of statins directly causing liver failure.[20] While measuring liver enzymes before statin initiation and at the time of the next lipid panel after initiation is reasonable, there are currently no recommendations to routinely monitor liver enzymes.[9]

Drug Interactions. Most statins are metabolized through multiple complex mechanisms that primarily involve the cytochrome P-450 pathway in the liver.[21] However, the degree to which statins are involved with

Mechanism of Action. Niacin reduces the catabolism of HDL and selectively decreases the excretion of HDL apo-A-1, stimulating reverse cholesterol transport in hepatic cells.[6,24] Additionally, niacin reduces hepatic VLDL production, resulting in a reduction of LDL-C, thereby lowering TG and LDL-C levels.

Dosing. Niacin is available in immediate-release, sustained-release, and extended-release doses; these formulations should not be interchanged. Therapy should be started with small doses and titrated up as necessary and tolerable.[24] Sustained-release nicotinic acid can be initiated at 250 mg twice daily and titrated up as tolerated to a maximum dose of 2 g per day, administered in a single or divided dose. Single doses can be given at bedtime with a low-fat snack.[24] Dosage information is outlined in **Table 20.10**.

Pregnancy, Precautions, and Contraindications. Niacin should be avoided in pregnancy to reduce fetal risks.[24] Caution should be used in persons with preexisting gout, heavy alcohol use, or renal dysfunction. Liver dysfunction, active peptic ulcer disease, and arterial bleeding are contraindications.

Adverse Effects. The adverse effects of niacin are a limitation to its use. Common adverse effects include headache; hypotension; and GI discomfort, such as nausea, vomiting, and diarrhea; as well as the more notorious dermatological reactions of flushing, pruritis, and rash.[11,24] Flushing typically decreases with continuous use and can be reduced by taking niacin with meals. Aspirin taken once daily, 30 minutes prior to the niacin dose, can also minimize flushing.[24]

Persons on large doses of niacin, greater than 2 g per day, may be at increased risk of hepatotoxic effects. Significant elevation of liver enzymes can occur. Discontinue treatment when liver enzymes are greater than 3 times the upper limit of normal.[24]

Drug Interactions. Niacin is known to inhibit the release of insulin from the beta cell, resulting in hyperglycemia. This is especially notable in those newly diagnosed with T2D and in those with prediabetes, in whom beta-cell production of insulin has not been diminished or exhausted. Alcohol and hot drinks can increase flushing and pruritis effects. Rhabdomyolysis may occur when used in combination with statins.[24]

Monitoring. A baseline lipid profile, liver enzymes, uric acid, and glucose levels should be performed prior to initiating niacin therapy and repeated at 6-week intervals while adjusting the dosage. Lipid profiles should be reviewed at 3- to 6-month intervals. Glucose levels should be monitored regularly, especially in those newly diagnosed or with prediabetes. Liver enzymes should also be monitored at 12-week intervals during the first year of treatment.[24]

Instructions. Niacin should be taken 30 minutes after an aspirin or with a low-fat snack to minimize flushing effects. Advise persons to avoid taking niacin with hot beverages or alcohol. Glucose levels need to be monitored to identify glycemic elevations. Educate persons on the signs and symptoms of myopathy, such as persistent muscle or joint pain, especially if they are concurrently on a statin.

Bempedoic Acid (Nexletol)

Nexletol is a first-in-class agent that primarily affects LDL-C and non-HDL lipoproteins. The approval of Nexletol was ascertained based on its ability to safely lower LDL-C. Because of the relatively sparse outcome data, Nexletol is currently not solely recommended for PWD, but it remains a second-line agent for persons with ASCVD and/or who are statin intolerant.[16]

Mechanism of Action. Nexletol is a pro-drug that is activated by enzymes found only in the liver. After conversion to the active molecule, inhibition occurs at ATP-citrate lyase. ATP-citrate lyase is an enzyme upstream of HMG-CoA reductase involved in cholesterol synthesis. As a result of decreased cholesterol synthesis, LDL receptors are upregulated in the liver, and thereby enhance the removal of LDL-C from the blood.[16]

Dosing. Nexletol and the combination bempedoic acid/ezetimibe (180/10 mg) are administered once daily. No dosage adjustment is required due to altered kidney function or mild-moderate liver disease. Because Nexletol has not been studied in severe liver disease, caution is advised for use in persons with advanced hepatic disease.[16] Dosage information is outlined in **Table 20.11**.

TABLE 20.10 Niacin: Dosage Information[9]

Drug	Trade Name	Common Dose	Common Frequency
Niacin sustained release	Niaspan	500 to 1,000 mg	Once daily
Nicotinic acid immediate release	Niacin	100 to 1,000 mg	1 to 3 times daily
Nicotinic acid sustained release	Slo-Niacin	250 mg	Once or twice daily

Pregnancy, Precautions, and Contraindications. The safety of Nexletol has not been evaluated in pregnancy and therefore should be avoided to reduce risks. Caution is warranted in persons with a history of tendon rupture and gout.[16]

Adverse Effects. Nexletol may increase uric acid levels. Laboratory monitoring of uric acid should occur prior to initiation as clinically necessary. An increased incidence of tendon rupture was observed in clinical trials. Counseling on managing tendon swelling is recommended prior to initiating bempedoic acid. Other common adverse effects reported for bempedoic acid in clinical studies include upper respiratory tract infections, bronchitis, muscle spasms, abdominal pain, anemia, back pain, and elevated liver enzymes.[16]

Drug Interactions. Bempedoic acid may increase the concentrations of simvastatin and pravastatin. Doses greater 20 mg with simvastatin and 40 mg with pravastatin should be avoided with concomitant Nexletol treatment.[16]

Monitoring. Baseline lipid panel, liver enzymes, and uric acid levels should be measured prior to Nexletol treatment. A lipid panel is also recommended in 4 to 12 weeks after starting Nexletol to assess LDL-C treatment response.[16]

Instructions. Nexletol should be taken once daily without regard to meals.[16]

Inclisiran

Inclisiran (Leqvio) is a first-in-class agent that primarily reduces LDL-C. Inclisiran's approval was solely based on its ability to safely lower LDL-C. Cardiovascular outcome trials for inclisiran are ongoing and its effect on cardiovascular outcomes is unknown at this time.[16]

Mechanism of Action. Inclisiran is a subcutaneously delivered small interfering ribonucleic acid (siRNA) agent that binds to the ribonucleic acid-inducing silencing complex (RISC) in the liver. The interaction between RISC and inclisiran causes hepatic translation of PCSK9 to be inhibited. With PCSK9 production inhibited LDL receptors are upregulated on hepatocytes further enhancing the removal of LDL-C.[16]

Dosing. Inclisiran is a subcutaneous injection that is only approved for administration by a HCPs. There is only one dose for inclisiran (284 mg) and dose adjustments for kidney or liver disease are not recommended. However, caution is advised in severe liver disease due to lack of study data in this population. The second dose of inclisiran is administered 3 months after the initial dose. Once the first 2 doses are complete, dosing should occur every 6 months.[16] Dosage information is outlined in **Table 20.12.**

Pregnancy, Precautions, and Contraindications. The safety of inclisiran has not been evaluated in pregnancy and therefore should be avoided to reduce risks. There are no other contraindications to inclisiran therapy.[16]

Adverse Effects. Injection site reactions are the most common adverse effects reported with inclisiran. Arthralgias, urinary tract infections, diarrhea, bronchitis, and pain in the extremities were also reported in clinical trials at a low incidence.[16]

Drug Interactions. There are no known drug interactions with inclisiran.[16]

Monitoring. A baseline lipid panel is recommended prior to starting inclisiran. A second lipid panel to assess LDL-C reduction with inclisiran treatment may be checked as early as 30 days.[16]

Instructions. Inclisiran must be administered by a clinician through subcutaneous delivery. Prior authorization by the insurance company will be required for coverage and should be completed prior to administration.[16]

Combination Therapies

Although statins are highly effective therapies for reducing LDL-C and ASCVD risk, there remains a high degree of risk for recurrent ASCVD events in many persons.[9] Therefore, nonstatin therapies that have been shown to further reduce ASCVD risk when used in combination with maximally tolerated statin therapy are preferred over other nonstatin agents.

Ezetimibe can provide up to an additional 25% reduction in LDL-C when combined with statin therapy and has been shown to also reduce ASCVD risk in

TABLE 20.11 Bempedoic Acid: Dosage Information

Drug	Trade Name	Common Dose	Common Frequency
Bempedoic acid	Nexletol	180 mg	Once daily
Bempedoic acid/ezetimibe	Nexlizet	180 mg/ 10 mg	Once daily

additional costs, and risk for adverse effects. Any consideration of adding drug therapy to reduce ASCVD risk should involve a discussion with their HCPs about the risks and benefits.[9]

First-Line Therapy

Statins remain the initial drug of choice for PWD. In persons unable to tolerate any statin, non-statin therapies shown to further reduce ASCVD risk (eg, ezetimibe, PCSK9 mAbs, icosapent ethyl) may be considered as reasonable alternatives. Two or more lipid-lowering agents may be necessary for some persons. Lipid profiles, adverse effects, as well as management by the PWD must be routinely monitored.

Hypertension

Blood pressure is the product of cardiac output (CO) and total peripheral resistance (TPR), where CO is the result of stroke volume and heart rate. The pathophysiology of hypertension in most people is a multifactorial process that occurs due to the body's inability to maintain the homeostasis between CO and TPR.[34]

Two important systems exist that work to maintain normal BP: the autonomic nervous system and the renin-angiotensin-aldosterone system (RAAS).[34] Evidence suggests that the RAAS is part of the multifactorial progression of diabetes, CVD, and renal disease. Through RAAS inhibition, BP is reduced and albuminuria can be reversed. Studies have also shown that RAAS inhibition can decrease ASCVD and slow the progression of diabetes.[35,36]

Renin-Angiotensin-Aldosterone System

Understanding of the RAAS has evolved over the decades and continues to do so. The RAAS regulates the balance of fluid volume, electrolytes, and blood volume in the body. Changes in the RAAS result in changes in vascular tone and sympathetic nervous system activity.

Stimulation of the RAAS leads to vasoconstriction, sodium retention, smooth muscle proliferation, and increased antidiuretic hormone in the vasculature.[37-39] In the kidney, activation of the RAAS is associated with intraglomerular hypertension, a precursor of proteinuria. Endothelial cells line the glomerulus as well as the blood vessels and function as the gatekeeper for cardiovascular and renal systems.[38,39] Abnormal RAAS activity can impair endothelium-dependent vasodilation in persons with T2D, resulting in decreased acetylcholine stimulation and enhanced oxidative stress.[38,39] These changes lead to insulin resistance, endothelial dysfunction, and microalbuminuria.

To briefly review, the RAAS begins with a release of renin, an enzyme synthesized in the kidney, in response to changes within or outside the kidney. Renin then acts on angiotensinogen, a hepatic peptide, to create angiotensin-I (AT-I). Angiotensin-converting enzyme (ACE), located in the pulmonary and vascular endothelium, converts AT-I to angiotensin-II (AT-II).[37-39] Angiotensin-converting enzyme converts approximately 30% of circulating AT-I to AT-II. Other enzymes, such as chymase, tonin, and cathepsin-G, are responsible for the remaining 70% of AT-II production.[39,40] This peptide, AT-II, binds to AT-I receptors, which are primarily in vascular and myocardial tissue, to increase vasoconstriction, sympathetic activity, and aldosterone secretion. These increases result in peripheral vascular resistance, vasoconstriction and increased heart rate, and fluid retention, respectively, which contribute to the development of hypertension.[38-40]

Diagnosis of Hypertension in Adults

The 2017 multi-society guideline, led by the AHA and ACC, provided a comprehensive, evidence-based guideline for diagnosing and classifying persons with hypertension.[41] A major update in this guideline was the change in how BP is classified.

Blood pressure is now classified into 4 stages:

1. Normal (systolic blood pressure [SBP] <120 mmHg and diastolic blood pressure [DBP] <80 mmHg)
2. Elevated BP (SBP 120 to 129 mmHg and DBP <80 mmHg)
3. Stage 1 hypertension (SBP 130 to 139 mmHg OR DBP 80 to 89 mmHg)
4. Stage 2 hypertension (SBP ≥140 OR DBP ≥90).[41]

Diagnosis and classification of hypertension is determined from the average of ≥2 BP readings obtained from ≥2 separate clinic visits; it is measured using an appropriately sized cuff with the person in a seated position, after a ≥5-minute rest. Out-of-office BP readings are recommended for diagnostic confirmation, especially as persons may have higher office BPs compared to out-of-office measurements.[41]

Treatment: Managing Hypertension in Adult Persons With Diabetes

As with lipid management, current guidelines for blood pressure management recommend a *risk-based* approach that incorporates both ASCVD risk and BP in driving

alpha-adrenergic agonists, should be avoided when possible in older adults.[43] Older adults are more likely to take multiple medications making pill burden and medication costs key considerations in this group. Thus, BP goals and the aggressiveness of treating hypertension must be individualized.

Diagnosis of Hypertension in Children and Adolescents

Updated guidelines on the diagnosis and management of hypertension in pediatric persons was published in 2017.[44] This guideline reiterates that having hypertension in childhood greatly increases the likelihood of hypertension in adulthood. Like the adult guidelines, the term *prehypertension* was replaced with *elevated BP* and new normative BP tables were developed according to age, sex, and height percentile. Blood pressure should be measured at every routine visit beginning at age 3 years, and those children noted to have elevated BP or hypertension should have their BP repeated and confirmed on 3 separate days.[44] Ambulatory BP monitoring is also highly recommended to confirm a diagnosis of hypertension. Hypertension in childhood is defined as an average systolic or diastolic BP ≥95th percentile for age, sex, and height.

Treatment in Children and Adolescents

Health behavior modifications are key in managing hypertension in this population; however, pharmacotherapy should not be withheld if BP remains elevated after health behavior modifications or if the hypertension is associated with diabetes or chronic kidney disease. Optimal BP in these persons is <90th percentile for age, sex, and height, or <130/80 mmHg in adolescents aged >13 years.[44]

Like most adults with diabetes, the pharmacologic treatment of hypertension should begin with an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB). Long-acting calcium channel blockers and thiazide diuretics may be considered if single drug therapy is not sufficient to achieve optimal BP.

Pharmacotherapy: Hypertension in Persons With Diabetes

Many classes of agents used to treat high BP target different mechanisms in the treatment of hypertension (**Table 20.13**).[41] However, several classes are preferred and traditionally used as first-line therapy because of their BP-lowering and/or renal-protection effects in PWD.[1,41] The benefit of medications that target the RAAS is their ability

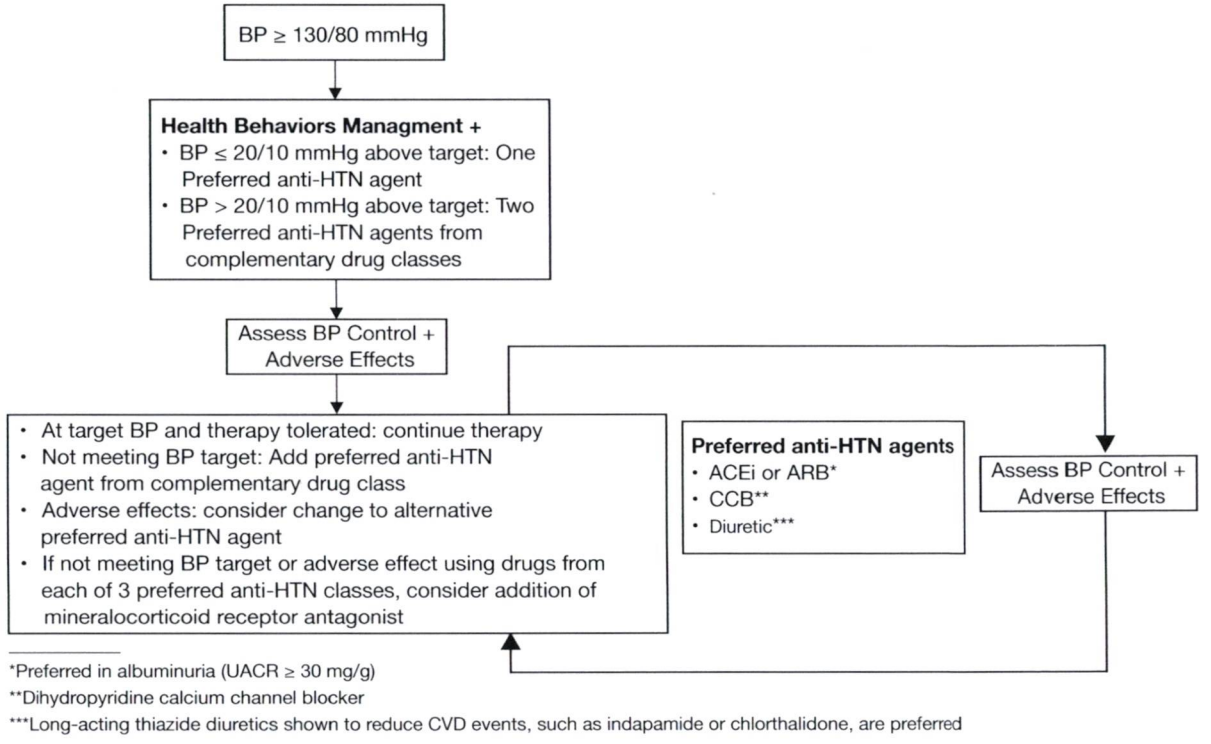

FIGURE 20.2 Summary of Treatment Recommendation[1,41]