

# Patient-Centered Care in Type 2 Diabetes Mellitus



By Amie D. Brooks, Pharm.D., FCCP, BCPS, BCACP

Reviewed by Krystal L. Edwards, Pharm.D., FCCP, BCPS; Rita Morelli, Pharm.D., BCACP; and S. Rochelle Sullivan, Pharm.D., BCACP

## LEARNING OBJECTIVES

1. Apply components of patient-centered care to the management of patients with diabetes.
2. Using patient-specific information, assess health literacy, psychological health, and patient activation in the management of diabetes.
3. Design individualized strategies for diabetes-related goal setting, education, and therapeutic management.
4. Justify system-level strategies for enhancing patient-centered care of diabetes.
5. Develop evidence-based, patient-specific glycemic and nonglycemic goals of therapy for patients with type 2 diabetes.

## ABBREVIATIONS IN THIS CHAPTER

ASCVD	Atherosclerotic cardiovascular disease
CCM	Chronic care model
CV	Cardiovascular
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DM	Diabetes mellitus
DSME	Diabetes self-management education
DSMS	Diabetes self-management support
MI	Myocardial infarction
PCMH	Patient-centered medical home
SBP	Systolic blood pressure
T2DM	Type 2 diabetes mellitus

## INTRODUCTION

There have been many advancements in pharmacologic agents for the treatment of type 2 diabetes mellitus (T2DM) during the past 3 decades. At the same time, evidence in support of interventional approaches, the relationship between clinical parameters and chronic complications, and effective self-management behaviors has grown exponentially and has informed providers and patients of effective strategies for controlling blood glucose and other risk factors to minimize the risk of complications.

Despite the growing armamentarium of treatment options and knowledge, many patients with diabetes do not meet evidence-based goals and continue to experience preventable complications. That discrepancy between optimal control and actual control can be attributed to multiple variables that include clinician, patient, and system factors. Central to all of them is the concept of patient-centered care. Successful diabetes care requires a patient's consistent self-care behaviors such as attention to diet, exercise, preventive care measures, drug adherence, and self-monitored blood glucose.

In the area of chronic illnesses, diabetes exemplifies the direct relationship between patient behavior and clinical outcomes. The standard of care in T2DM includes emphasis on self-management education provided through interprofessional teams. True implementation of patient-centered care in diabetes requires knowledge of the components of that patient-centered care, as well as consideration of and attention to patient-specific factors that may influence outcomes. In addition, shared decision-making in daily clinical practice requires the application and synthesis of contemporary evidence that examines the goals of therapy in patients with diabetes.

## Defining Patient-Centered Care

Emphasized by the American Diabetes Association (ADA), the National Institute for Health and Care Excellence, and the Institute of Medicine, a patient-centered approach to care has increasingly become both a parameter of quality assessment and a widely acknowledged core value. In the setting of T2DM, patient-centered care is associated with increased patient satisfaction, improved patient-provider communication, and enhanced patient well-being (IOM 2001; Kimmonth 1998).

The concept of patient-centered care is generally understood, but its specific definition is not universally agreed upon. The literature describes conceptual models with core concepts that are linked to positive outcomes such as increased patient satisfaction, decreased symptom burden, increased efficiency of care, and decreased utilization (Little 2001; Stewart 2000). Although the terminologies differ, commonly referenced key components include the concepts of (1) patient as person (disease and illness experience), (2)

biopsychosocial perspective (consideration of whole person), (3) shared power and responsibility, and (4) patient-provider relationship (therapeutic alliance) (Mead 2000).

A provider's efforts to understand the patient as a person and the way the patient experiences disease are crucial to a patient-centered approach. Because patients experience illness in individual ways, that personal narrative can motivate behaviors or decisions that influence health. For example, the financial implications of a diagnosis or an individual therapy may motivate a patient to avoid seeking medical attention for symptoms. Similarly, social or cultural norms may shape a patient's perspective of an illness, a symptom, or a therapy, even if those norms are refuted by factual information from a credible health care professional.

In addition to considering a patient as an experiencing individual, the biopsychosocial perspective incorporates a broadened view of the patient-provider encounter to include consideration of nonmedical influences (e.g., social, psychological, health literacy, other factors) on illness, health promotion, and behavior modification. That perspective shifts the focus of health care from a primarily reactive approach addressing acute and chronic illness to a more comprehensive and proactive approach that includes preventive health care (physical, social, psychological) and wellness. That biopsychosocial component of patient-centered care encourages health care professionals to consistently incorporate nonmedical influences into care plans rather than deem those influences beyond their practice scope.

To further value a patient's perspective and unique characteristics, patient-centered medicine promotes shared responsibility and power rather than a paternalistic approach in which the patient defers to medical authority. In other words, patient autonomy and participation are paramount. In contrast to that patient-centered approach, the provider-centered approach creates a power dynamic that puts the provider in control. In that situation, patient-provider encounters focus on the skills and knowledge of the clinician, with closed questioning and directions given by the provider to the patient and perhaps a caregiver. The illusion of control in the provider-centered, paternalistic approach often shatters when the patient autonomously decides to not adhere to or implement a therapy or a monitoring plan. A more effective approach involves a shift from patient cooperation to mutual participation of the health care provider and the patient in shared decision-making.

A natural extension of the first three components of patient-centered medicine is the patient-provider relationship. Historically, the concept of bedside manner has been regarded as a bonus rather than an integral element of effective health care. The patient-centered approach places high value on the therapeutic alliance that a healthy patient-provider relationship can represent. At a minimum, the relationship should consist of a provider who demonstrates empathy, effective listening, a shared understanding of health-related goals,

### BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- National guideline recommendations for clinical goals (glycemia, blood pressure, lipids) in patients with type 2 diabetes mellitus
- Potential chronic microvascular and macrovascular complications of type 2 diabetes
- Oral and parenteral agents used in the treatment of diabetes, including their mechanisms of action, pharmacokinetics, dosing, adverse reactions, warnings and precautions, contraindications, and drug interactions

### ADDITIONAL READINGS

The following resources are available for readers wishing additional background information on this topic.

- [American Diabetes Association. Standards of Medical Care in Diabetes—2015.](#)
- [American Diabetes Association/European Association for the Study of Diabetes Position Statement. Management of Hyperglycemia in Type 2 Diabetes, 2015: A Patient-Centered Approach.](#)
- [American Association of Clinical Endocrinologists and American College of Endocrinology. Clinical Practice Guidelines for Developing a Diabetes Mellitus Comprehensive Care Plan—2015.](#)
- [American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 American College of Cardiology/American Heart Association Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults.](#)

and mutual trust. Emphasis on those four key components ensures that care is individualized, respectful, and responsive to patient preferences, needs, and values. It is an approach that places the patient at the center of care as the final driver of therapy and other health care decisions.

### **The Centrality of the Patient**

Science is the fundamental basis of clinical practice, and health care professionals spend years working with textbooks and laboratory experiments before interacting with patients. Therefore, the incorporation of evidence-based principles into practice is a relatively easy transition for most providers. However, effective implementation of the patient-centered approach requires a broader skill set that draws on such areas as communication, professionalism, and empathy. Incorporation of these principles will require an understanding of the evidence that supports a meaningful relationship between clinical outcomes and patient-specific characteristics such as health-literacy, depression, and patient activation.

### **Health Literacy**

Health literacy includes functional, interactive, critical, and numeracy skill components (Al Sayah 2012). The functional skills consist of reading, writing, and interpreting written information. The interactive component includes the ability to listen to, comprehend, and communicate health-related information such as communicating personal health history to a new provider. The critical components consist of decision-making and navigation of the health care system for selection of a health care plan or the locations of providers or services. The numeracy skills involve the interpretation of numeric data such as dosages, food labels, and test results (e.g., self-monitored blood glucose). Available studies sometimes evaluate the effect of health literacy and numeracy separately.

Low health literacy is a strong predictor of both poor health status (AMA 1999) and poor health outcomes (Berkman 2011; DeWalt 2004). In fact, the predictive relationship between health status and limited health literacy has been demonstrated as stronger than the components of age, education level, and race (AMA 1999). In the setting of diabetes, limited health literacy and limited numeracy have been associated with less diabetes-related knowledge and less recognition of symptoms (DeWalt 2004; Williams 1998), poor glycemic control (Cavanaugh 2008; Schillinger 2002), more difficulty in estimating portion sizes and interpreting food labeling (Huizinga 2009; Rothman 2006), and diminished self-care (Karter 2010; Cavanaugh 2008).

It is important to note that health literacy and disease knowledge, although related, are two distinct components. For instance, a patient with low health literacy may be able to correctly answer disease-specific questions if they are administered verbally. Many studies have demonstrated an inverse relationship between health literacy and A1C (Ishikawa 2011;

Tang 2008; Powell 2007; Schilliner 2003). Assessment of health literacy may facilitate a more individualized, patient-centered approach to care in the setting of diabetes. Table 1-1 summarizes some commonly used, validated instruments to assess health literacy in clinical practice.

Numeracy is an essential component of health literacy in the setting of diabetes. Several health literacy instruments include an evaluation of numeracy (see Table 1-1). Diabetes self-care includes routine review and interpretation of numerical information such as self-monitored blood glucose, food quantification from food labels, and drug dosages—especially in the case of insulin. As may be expected, numeracy is more strongly correlated with glycemic control than is general health literacy (Osborn 2009; Cavanaugh 2008). When assessing health literacy for the purposes of patient-centered care in diabetes, the clinician should ideally use a validated tool that has a numeracy component.

### **Self-Efficacy and Patient Activation**

Self-efficacy is a patient's confidence in the ability to perform a goal-directed behavior. In patients with diabetes, a correlation between self-efficacy, self-care behaviors and glycemic control has been demonstrated (Wallston 2007). A similar concept—patient activation—incorporates not only a level of confidence but also the patient's knowledge and skill level as it involves health care. Patients with high levels of activation are more likely to obtain preventive care and practice positive self-care behaviors (Mosen 2007).

Self-management education is consistently recommended for patients with diabetes, but the method and manner in which education is provided are also important. The mere sharing of knowledge does not translate to improved outcomes. A tailored approach to self-management education and an assessment of patient activation are preferred. Fortunately, patient activation is developmental, and positive changes have been associated with improved outcomes. The Patient Activation Measure (PAM) 13 is a validated tool that assesses degree of patient activation. Its questions can be answered either verbally or in written form by the patient. The measure consists of 13 items designed to enable a clinician to assess a patient as falling into one of four PAM levels (Hibbard 2009). Table 1-2 shows the four levels of activation recognized as a patient progresses toward effective self-management. In a study of patients with T2DM, PAM was found to be predictive of glycemic control and hospitalizations (Woodard 2014).

To build confidence and facilitate a patient's progression through the levels of activation over time, education tailored to patient activation level focuses on the identification of goals with high likelihood of success (Hibbard 2007). For example, patients at activation level 1 benefit from understanding their own behavior patterns and developing an awareness of self. Patients at level 2 benefit from beginning to make small, achievable changes in behavior that are patient specific but may include general things such as reducing the daily number

**Table 1-1.** Health Literacy Assessment Tools

Health literacy instrument	Description and Components	Scoring	Administration	Advantages	Disadvantages
Test of Functional Health Literacy in Adults (TOFHLA) (Parker 1995)	Measurement of health information comprehension Use of actual health care items (e.g., pill bottles, appointment slips) 17 numeracy items, 3 reading comprehension passages	Health literacy: Adequate (75–100) Marginal (60–74) Inadequate (0–59)	About 22 minutes of total administration time	Used extensively in clinical studies Multiple numeracy items Gold standard for health literacy testing	Administered by clinicians, long administration time, poor translation to computer-adapted format
S-TOFHLA (Parker 1999)	Shortened form of the TOFHLA, with goal of increasing practical use Two reading comprehension passages	Health literacy: Adequate (23–36) Marginal (17–22) Inadequate (0–16)	About 8 minutes of total administration time	Reading comprehension items that correlate well with original, gold standard instrument More practical for clinical use compared with the TOFHLA because of reduced administration time	Numeracy items removed because of poor correlation with original tool
<u>Newest Vital Sign</u> (Weiss 2005)	Six-item questionnaire using a food label to assess reading comprehension and numeracy	Each item is worth one point, and scores rank likelihood of limited health literacy: 0–1 = high 2–3 = possible 4–6 = most likely adequate health literacy	About 3 minutes of total administration time	Available in English and Spanish Minimal administration time Assessment of comprehension and numeracy	Not studied as extensively as TOFHLA or REALM <b>Contains numeracy assessment</b>

Rapid Estimate of Adult Literacy in Medicine (Baker 1999; Davis 1993)	Validated health literacy screening tool that provides reading grade estimate for patients who score below ninth-grade level: 66 items	Limited health literacy (at or below sixth-grade reading level) Marginal (seventh- to eighth-grade reading level) Adequate (at or above ninth-grade reading level)	About 3 minutes of total administration time.	Used extensively in research and clinical practice Practical for use in clinical practice because of short administration time	No numeracy assessment, no comprehension of health-related information (only reading ability)
REALM–Short Form (Arozullah 2007)	7-item word recognition		Total administration time less than 2 minutes	Practical because of short administration time Excellent correlation with 66-item REALM	
Short Assessment of Health Literacy–Spanish and English (Lee 2010)	18 items combining word recognition (based on terms in REALM instrument) and comprehension assessed by way of multiple-choice options	Each item is worth one point, and a score of <14 = low health literacy	About 3 minutes of total administration time.	Validated in both English and Spanish Minimal administration time/practical	Not studied as extensively as TOFHLA or REALM No <b>assessment of numeracy</b>

Information from Davis TC, Long SW, Jackson RH, et al. Rapid estimate of adult literacy in medicine: a shortened screening instrument. *Fam Med* 1993;25:391-5; Arozullah AM, Yarold PR, Bennett CL, et al. Development and validation of a short-form, rapid estimate of adult literacy in medicine. *Med Care* 2007;45:1026-33; Baker DW, Williams MV, Parker RM, et al. Development of a brief test to measure functional health literacy. *Patient Educ Couns* 1999;38:33-42; Lee SD, Stucky B, Lee J, et al. Short assessment of health literacy–Spanish and English: a comparable test of health literacy for Spanish and English speakers. *Health Serv Res* 2010;45:1105-20; Parker RM, Baker DW, Williams MV, et al. The test of functional health literacy in adults: a new instrument for measuring patients' literacy skills. *J Gen Intern Med* 1995;10:537-41; Baker DW, Williams MV, Parker RM, et al. Development of a brief test to measure functional health literacy. *Patient Educ Couns* 1999;38:33-42; and Weiss BD, Mays MZ, Martz W, et al. Quick assessment of literacy in primary care: the newest vital sign. *Ann Fam Med* 2005;3:514-22.

**Table 1-2.** Patient Activation Measure

Level	Description
1	Patient tends to be overwhelmed and therefore unprepared to play a significant role in health care.
2	Patient lacks knowledge and self-confidence for self-care.
3	Patient begins to take action but lacks skill and confidence to support effective self-care.
4	Patient has adopted many positive self-care behaviors but may not be able to maintain them in the face of life stressors.

of sugary beverages, parking farther from a store entrance, and limiting desserts to three times weekly. At level 3, it is usually appropriate for patients to adopt new and healthy behaviors. It is important that the patient and provider set goals that are reasonable and achievable. For instance, for a sedentary patient, that may include walking for 15 minutes three times a week. At level 4, education focuses on collaboratively developing strategies for relapse prevention and on maintaining goals during stressful situations.

### **Psychosocial Influences**

The integration of physical health and mental health is a component of the biopsychosocial perspective of the patient-centered approach and an increasingly recognized priority in primary care. Depression is prevalent in patients with diabetes and has been associated with lower levels of self-care behaviors such as exercise and glucose monitoring (Dirmaier 2010). The assessment, evaluation, and treatment of psychological illness should be of routine concern to clinicians caring for patients with diabetes (Ducat 2014; Hermanns 2013). Box 1-1 summarizes validated tools that are commonly used in primary care to screen for depression.

Routine screening for depression in primary care remains controversial primarily because of the lack of randomized controlled evidence to support benefit, as well as the substantial resource commitment needed to integrate mental health and primary care. It is imperative that the ambulatory care pharmacist working in diabetes care be able to interpret and seamlessly integrate depression-screening findings into practice.

## **PATIENT-CENTERED CARE DELIVERY IN DIABETES**

### **Barriers to Patient-Centered Care**

There are many barriers to patient-centered care delivery. The fee-for-service reimbursement model, in which providers are paid based on episodic and unbundled health care services, incentivizes many patient encounters but not higher-quality care. This model has decreased the allotted time for each patient, limiting the opportunities to identify patient-specific factors in the clinical decision-making process, as well

### **Box 1-1. Depression-Screening Tools**

- **Beck Depression Inventory** (requires subscription): 21-item multiple-choice questionnaire assessing cognitive and somatic symptoms of depression for the previous 7 days. Higher values indicate more-intensive depressive symptoms. Each of the 21 items is scored 0–3. Sum total score of more than 10 is indicative of depression.
- **Center for Epidemiologic Studies Depression scale:** Patient self-report, 20-item questionnaire assessing frequency of occurrence of each symptom or thought pattern in previous week. Each item is based on a four-point scale (0 = rarely; 3 = most/all). Sum total of scores of more than 16 indicates depression.
- **Patient Health Questionnaire–9 (PHQ-9):** Questionnaire with nine items scored based on frequency of symptoms in previous 2 weeks. Each item is scored on a 0–3 scale. Severity of depression: less than 4 (no depression), 5–9 (mild), 10–14 (moderate), 15–19 (moderately severe), and 20–27 (severe).
- **Patient Health Questionnaire–2 (PHQ-2):** Abbreviated version of PHQ-9, with only two items scored 0–3 each based on frequency. A score of 3 or greater indicates likely depression and should be confirmed with the PHQ-9.
- **World Health Organization Five Well-being Index:** Administered by health care professional, five items with score of 0–5 for each based on degree of agreement. Total score of less than 13 indicates likely clinical depression. Multiplication of total score by 4 yields a percentage for monitoring of changes in well-being over time. A 10% difference is considered significant.

as the ability to provide the information necessary for true shared decision-making. Effective patient-centered care also requires an interprofessional team of clinicians and educators, which is not economically feasible for all practices. Finally, the patient-care delivery system is often fragmented with lack of communication, limited transitions-of-care capabilities, duplication of clinical services, and poor coordination. A strong combination of clinician efforts and system-level interventions is vital to consistent patient-centered care.

**Table 1-3.** Tailored Patient Educational Strategies

Patient characteristic	Clinician Strategy
Limited health literacy (Pignone 2005)	<ul style="list-style-type: none"><li>• Use written education materials at or below sixth-grade reading level</li><li>• Include photographs or illustrations in written educational material</li><li>• Use interactive/technology-based education</li><li>• Reiterate information, return-demonstration of skills, teach-back method</li></ul>
Low patient activation (Hibbard 2009)	<ul style="list-style-type: none"><li>• Increase patient self-awareness through use of self-care diary, monitoring, and documentation</li><li>• Increase self-efficacy through implementation of realistic goals at each encounter</li><li>• Share development of self-care plans that consider patient psychosocial influences</li></ul>
Depression (Hermanns 2013)	<ul style="list-style-type: none"><li>• Refer to appropriate health care team member for step-care therapy</li><li>• Communicate with primary care provider</li><li>• Focus on self-efficacy and realistic goal setting</li></ul>

Information from Hermanns N, Caputo S, Dzida G, et al. Screening, evaluation and management of depression in people with diabetes in primary care. *Prim Care Diabetes* 2013;7:1-10; Hibbard JH, Greene J, Tusler M. Improving the outcomes of disease management by tailoring care to the patient's level of activation. *Am J Manag Care* 2009;15:353-60; and Pignone M, DeWalt DA, Sheridan S, et al. Interventions to improve health outcomes for patients with low literacy. *J Gen Intern Med* 2005;20:185-92.

### Clinician Strategies for Effective Implementation

The ambulatory care clinical pharmacist may apply several strategies within the context of patient-centered care to address factors such as limited health literacy, patient activation, and psychosocial influences. Patient care providers must gain knowledge, skills, and attitudes consistent with the four key components of patient-centered care: (1) consistent consideration of the patient as a person, (2) adoption of the biopsychosocial perspective of care, (3) promotion of shared provider-patient responsibility, and (4) emphasis on the patient-provider relationship. The inclusion of those four components will begin to shape the expectations and experiences of patients in our health care systems. Ambulatory care clinical pharmacists are well positioned to implement or continue those practices. Deliberate and routine incorporation of assessments of health literacy, patient activation, and psychosocial influences is advisable so as to enhance the therapeutic alliance and implement individualized strategies to address those unique patient characteristics. Several methods of educational delivery have been studied and endorsed by experts; Table 1-3 summarizes strategies matched to relevant patient assessment.

#### **American Association of Diabetes Educators 7**

The American Association of Diabetes Educators 7 (AADE7) system encompasses a framework of diabetes self-management education, goal setting, follow-up, and performance measures for the implementation and assessment of a diabetes education program. The system is based on the seven self-care behaviors listed in Box 1-2. Incorporation of these

elements into each encounter can serve as a behavioral review of systems and lead to sharper focus on collaborative patient-pharmacist problem solving, goal setting, and decision-making related to self-care. Several tools and resources that support the framework are available for diabetes care educators and providers. The resources focus on defining successful diabetes self-management education (DSME) based on behavior change rather than solely on clinical measures.

#### **Self-Management Education and Support**

The ADA standards recommend a comprehensive and patient-centered approach to DSME and diabetes self-management support. The guideline recommendations have shifted from a didactic approach to a skills-based approach that incorporates the goals of supporting informed decision-making, self-care, problem solving, and collaboration to improve clinical outcomes and quality of life. The evidence-based benefits of DSME are well established and include improved clinical outcomes such as lower A1C, lower weight, improved quality of life, and lower

#### **Box 1-2. AADE7 Self-Care Behaviors**

- Healthy eating
- Being active
- Monitoring
- Taking medication
- Problem solving
- Reducing risks
- Healthy coping

health care costs (Norris 2002). The major components of DSME and diabetes self-management support are medical-nutrition therapy, physical activity, smoking cessation, psychosocial assessment and care, and immunizations. Table 1-4 summarizes specific recommendations within each component.

### Decision Aids

The routine use of decision aids in daily practice facilitates collaborative, patient-centered care. Decision aids are tools designed to involve a patient in health care decisions by providing clear and succinct illustrations or summaries of available options and pinpointing the relative advantages and disadvantages of each (Stacey 2003). Validated decision aids may be electronic or written, and

most are designed to be used during health care encounters. For example, an [electronic decision aid](#) the Mayo Clinic developed to assist with shared decision-making in the selection of diabetes therapy gives the patient a menu of issues to select from according to personal priorities. The menu includes effect on blood sugar, daily routine, daily sugar testing, low blood sugar, weight change, side effects, and cost. Patients may select any number of those issues for side-by-side comparison of all available diabetes medications. The side-by-side comparison is for dialogue between the patient and the provider in their shared decision-making.

A Cochrane systematic review indicated that decision aids increase knowledge, lower decisional conflict related to feeling uninformed, reduce the proportion of patients who remain

**Table 1-4.** ADA Diabetes Self-Management Education and Support Recommendations

Component	Specific Recommendations
Medical nutrition Therapy	<ul style="list-style-type: none"> <li>Promote and support healthy eating patterns with a variety of nutrient-dense foods in appropriate portions</li> <li>Address individual needs based on health literacy and numeracy, access, willingness and ability to make change, barriers to change, and personal and cultural preferences</li> <li>Provide positive messages about food choices, limiting those food choices only when indicated by scientific evidence</li> <li>Offer practical tools for daily meal planning, and avoid focusing on individual macro- or micronutrients</li> </ul>
Physical activity	<ul style="list-style-type: none"> <li>Specify at least 150 minutes of moderately intense aerobic activity weekly, spread over at least three days per week and with no more than 2 consecutive days without activity</li> <li>Reduce sedentary time by breaking up extended periods (&gt;90 minutes) of sitting</li> <li>Include resistance training twice each week</li> </ul>
Smoking cessation	<ul style="list-style-type: none"> <li>Advise all patients to avoid smoking and use of tobacco products</li> <li>Routinely include smoking cessation counseling in patient encounters</li> </ul>
Psychosocial assessment and care	<ul style="list-style-type: none"> <li>Assess psychological and social health as an ongoing and routine component of diabetes management</li> <li>Determine attitudes about illness, expectations for outcomes, affect/mood, quality of life, resources (financial, social, and emotional), and psychiatric history</li> <li>Screen routinely for depression and anxiety</li> <li>Prioritize older adults (&gt;65 years) with diabetes for depression screening and treatment</li> <li>Offer stepwise, collaborative care for patients with depression</li> </ul>
Immunizations	<ul style="list-style-type: none"> <li>Administer or prescribe annual influenza vaccine</li> <li>Administer or prescribe pneumococcal polysaccharide vaccine 23 (PPSV23) for all patients with diabetes who are older than 2 years of age</li> <li>Administer or prescribe for adults older than 65 years—if not previously vaccinated—pneumococcal conjugate vaccine 13 (PCV13) followed by PPSV23 &gt;12 months later</li> <li>Administer or prescribe for adults older than 65 years—if previously vaccinated with PPSV23—a follow-up in 6–12 months with PCV13</li> <li>Administer or prescribe for all previously unvaccinated adults aged 19–59 years a hepatitis B vaccination series, and consider it for those older than 60 years if other risk factors are present</li> </ul>

Information from American Diabetes Association. Foundations of care: education, nutrition, physical activity, smoking cessation, psychosocial care, and immunization. *Diabetes Care* 2015;38:s20-s30.

passive, and reduce the proportion of patients who remain undecided (Stacey 2003). Decision aids also demonstrate a positive effect on patient-practitioner communication and patient satisfaction. Various decision aids such as the [Mayo Clinic Diabetes Medication Choice Decision Aid](#), [Janssen Diabetes Medication Option Decision Aid](#), and [Mayo Clinic Statin Choice Decision Aid](#) have been studied in the context of diabetes and would be a valuable addition to daily practice for ambulatory care pharmacists involved in the care of patients with diabetes.

### System-Level Strategies for Effective Implementation

As the health care environment continues to shift from an episodic, acute-treatment, fee-for-service model to a coordinated, team-based, quality-focused model, the values of achieving quality clinical measures in chronic illness and of focusing on the patient experience as a whole become incentivized financially. Individual health care providers and health systems are interested in finding systematic methods for implementing patient-centered care in the setting of a deficit in primary care physicians. Ambulatory care clinical pharmacists are well positioned to serve as integral team members, and in many cases are already filling those roles. Historically, episodic care and fee-for-service payments have limited the sustainability of ambulatory care clinical service, whereas contemporary care models have the potential to more appropriately value pharmacists' contributions in achieving patient outcomes related to the care experience and quality clinical outcomes.

The [Chronic Care Model \(CCM\)](#) is an approach to providing care that integrates six key components: self-management support, decision support, information systems, organizational support, practice design, and community resources (ICIC 2015). The model includes systematic interventions that can improve care delivery to facilitate efficiency and that focus more on the patient. Evidence supports the CCM as an effective framework for improving the quality of diabetes care (Stellefson 2013).

One vehicle for implementing the CCM is the patient-centered-medical-home ([PCMH](#)), which has demonstrated evidence-based quality improvement in the primary care setting. The PCMH cornerstone is interprofessional team-based care, including the main elements of (1) commitment to quality and safety; and (2) care that is comprehensive, patient centered, coordinated, and accessible. The PCMH model encourages consistent use of evidence-based practices and clinical decision support tools to assist in shared decision-making. In addition, performance measurement and improvement, including patient experiences and satisfaction, are important elements. Safety and quality data are shared publicly in PCMH practices. Comprehensive care includes prevention, wellness, and acute and chronic care delivered by a team of care providers.

As the term implies, the patient-centered approach is paramount, and focus on the provider-patient relationship and shared decision making is emphasized. The coordination of care across the health system between specialists, hospitals, home health, long-term care, and community resources is critical in the PCMH system, with the greatest emphasis placed on coordination during transitions of care. High-quality and effective health care requires adequate patient access (e.g., provider availability during times of urgent need or illness, enhanced health center hours, around-the-clock electronic access). The PCMH approach aligns well with the concept of patient-centered care and evidence in effective diabetes management practices.

The accountable care organization ([ACO](#)) represents another model of care focusing on care coordination between providers and entities. Supported by the Centers for Medicare & Medicaid Services, an ACO is a group of doctors, hospitals, and other health care providers with the goal of coordinated, high-quality, and efficient care for patients with chronic illnesses. Through shared savings and advance-payment programs, ACOs are incentivized to meet 33 quality care standards, 6 of which are diabetes focused, and several of which are medication related or related to the patient experience and care delivery (patient centeredness).

Effective care for patients with diabetes is incentivized by quality-of-care measures that are reported and often made publicly available for patients and consumers in the choice of a health plan. The National Committee for Quality Assurance implemented the Healthcare Effectiveness Data and Information Set (HEDIS), a tool used by a many health plans to measure and compare quality health care performance. The tool offers multiple [measures](#) related to diabetes, including clinical indexes such as A1C, blood pressure, and smoking cessation. The committee annually updates and publishes [national benchmarks](#) along with financial incentives for degrees of achievement. A health plan's goal is to compare favorably with national and regional thresholds (25th, 50th, 75th percentiles) and the national benchmark. Recently, metrics involving patient centeredness of care were introduced in the Agency for Healthcare Research and Quality's Consumer Assessment of Healthcare Providers and Systems survey, which includes measures related to access, communication, coordination of care, comprehensiveness of care, self-management support, and shared decision-making. ACO quality measures relevant to diabetes include clinical (A1C, LDL, blood pressure, and tobacco and aspirin use), preventive health (immunizations), and general patient-centered measures (access, communication, shared decision-making, and health status). Routine requirements for reporting of those measures, with the inclusion of incentives for increasing the level of patient centeredness of care, enable ambulatory care pharmacists and health care institutions to determine areas of excellence and opportunities for quality improvement in patient care services for diabetes.

## PATIENT-CENTERED, EVIDENCE-BASED GOALS OF THERAPY

### Glycemic Goals

Individualization (a patient-centered approach) of glycemic goals is recommended by guidelines from the American Association of Clinical Endocrinologists (AACE), the ADA, and the National Institute for Health and Care Excellence. Current ADA recommendations include consideration of higher A1C targets (7%–8%) in patients with known histories of severe hypoglycemia; limited life expectancy; advanced microvascular or macrovascular complications; extensive comorbidities; long duration of diabetes; and difficulty in achieving the less-than-7% goal despite adequate education, close monitoring, and treatment (Inzucchi 2015). An overview of guideline-endorsed glycemic goals and considerations for less stringent goals can be found in Table 1-5.

Historical and contemporary evidence continues to frame our knowledge of the benefits and risks of lower A1C targets. The relationship between hyperglycemia and long-term complications is well established. After adjustment for other known risk factors, each 1% increase in A1C results in an 18% increase in the risk of CV events, a 13% increase in the risk of death, and a 37% increase in the risk of retinopathy or end-stage renal disease (Gerstein 2005; Selvin 2004; Stratton 2000).

The initial United Kingdom Prospective Diabetes Study (UKPDS) trials formed the historical perspective on glycemic goals demonstrating reduced risk of microvascular disease in

patients with type 2 diabetes with intensive (median A1C 7%) versus standard (median A1C 7.9%) glycemic control. Although UKPDS failed to demonstrate reduced risk of macrovascular complications in the intensive control group, the study was underpowered for the outcome. Subsequent prospective studies with intensive-versus-standard control goals—including the ACCORD clinical trial (mean A1C 6.4% vs. 7.53%), the ADVANCE trial (mean A1C 6.5% vs. 7.3%), and the VADT trial (mean A1C 6.9% vs. 8.4%)—sought to determine the effect of stricter glycemic control on macrovascular and microvascular risk (ACCORD 2010; ADVANCE 2007; Duckworth 2009). The patient population studied varied in each trial; however, overall results demonstrated a lack of macrovascular risk reduction, increased risk of hypoglycemia, and potential for increased mortality related to stricter control.

The effect on microvascular outcomes has been varied, with the greatest impact observed on reduction of surrogate markers of nephropathy. Follow-up studies have been conducted to determine the longer-term effect of strict control. To provide effective, evidence-based, patient-centered care in diabetes, the clinical pharmacist must be able to adequately evaluate and synthesize the results of those investigations so as to determine individualized goals. A careful review of the characteristics of the patient populations studied and of individual and composite results in those populations is imperative for appropriate application of the findings to individual patients, with attention to benefits versus risks. Table 1-6 provides a summary of key evidence.

**Table 1-5.** Guideline-Recommended A1C Goals

Guideline	A1C Goal	Considerations for Less Stringent Goal
ADA	<7% <sup>a</sup>	<ul style="list-style-type: none"> <li>History of severe hypoglycemia</li> <li>Limited life expectancy</li> <li>Advanced microvascular or macrovascular complications</li> <li>Extensive comorbid conditions</li> <li>Long-standing T2DM with difficulty in attaining general goal despite DSME, monitoring, and effective doses of multiple medications, including insulin</li> </ul>
AACE/ACE	≤6.5%	<ul style="list-style-type: none"> <li>History of severe hypoglycemia</li> <li>Limited life expectancy</li> <li>Advanced renal disease</li> <li>Macrovascular complications</li> <li>Extensive comorbid conditions</li> <li>Long-standing, asymptomatic T2DM with difficulty in attaining goal despite intensive efforts</li> </ul>
NICE	6.5% <sup>b</sup>	<ul style="list-style-type: none"> <li>Not addressed specifically</li> </ul>

<sup>a</sup>More-stringent goal (<6.5%) recommended for those with short duration of T2DM, long life expectancy, T2DM treated with lifestyle or metformin only, or significant cardiovascular disease (CVD) as long as the goal can be achieved without significant hypoglycemia or other adverse effects.

<sup>b</sup>Individualized based on patient-specific factors. Avoid pursuit of stringent goals <6.5%.

AACE = American Association of Clinical Endocrinologists; ACE = American College of Endocrinology; ADA = American Diabetes Association; DSME = diabetes self-management education; NICE = National Institute for Health and Care Excellence; T2DM = type 2 diabetes mellitus.

**Table 1-6.** Summary of Evidence: Glycemic Goals in Type 2 Diabetes Mellitus

Population	Glycemic targets	Initial Results	Follow-up Results
<b>UKPDS<sup>a,b</sup> (n=3867)</b>			
<ul style="list-style-type: none"> <li>• Mean age, 54 years</li> <li>• Newly diagnosed T2DM</li> <li>• Clinical ASCVD ~7.5% (exclusion criteria: angina, MI within past year, heart failure, &gt;1 vascular event)</li> </ul>	<p>A1C &lt;7% (intensive group) A1C 7%–7.9% (standard group)</p>	<ul style="list-style-type: none"> <li>• Median follow-up, 10 years</li> <li>• Mean A1C               <ul style="list-style-type: none"> <li>◦ 7.0% (intensive)</li> <li>◦ 7.9% (standard)</li> </ul> </li> <li>• <b>Microvascular (intensive)</b> <ul style="list-style-type: none"> <li>• 25% risk reduction in all microvascular end points (intensive) (p=0.0099) NNT = 42</li> </ul> </li> <li>• <b>Macrovascular (intensive)</b> <ul style="list-style-type: none"> <li>• Nonsignificant reduction in MI</li> <li>• No differences in mortality or CV mortality</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Conducted 10-year post-study conclusion (20 years of data)</li> <li>• Between-group differences in A1C lost within 1 year of study end</li> <li>• <b>Microvascular (intensive)</b> Sulfonylurea/insulin               <ul style="list-style-type: none"> <li>• 9% RRR: any diabetes-related end point (p=0.04) NNT = 37</li> <li>• 24% RRR: microvascular disease (p=0.001) NNT = 31</li> <li>• Metformin</li> <li>• 21% RRR: any diabetes-related end point (p=0.01) NNT = 12</li> </ul> </li> <li>• <b>Macrovascular (intensive)</b> Sulfonylurea/insulin               <ul style="list-style-type: none"> <li>• 15% RRR: MI (p=0.01) NNT = 36</li> <li>• 13% RRR: All-cause mortality (p=0.007) NNT = 29</li> <li>• Metformin</li> <li>• 33% RRR: MI (p=0.005) NNT = 16</li> <li>• 27% RRR: All-cause mortality (p=0.002) NNT = 14</li> </ul> </li> </ul>
<b>ACCORD<sup>c,d</sup>(n=10,251)</b>			
<ul style="list-style-type: none"> <li>• Mean age, 62.2 ± 6.8 years</li> <li>• Mean duration (DM) = 10 years</li> <li>• Mean A1C, 8.3% ± 1.1</li> <li>• Clinical ASCVD ~35%</li> </ul>	<p>A1C &lt;6% (intensive) A1C 7%–7.9% (standard)</p>	<ul style="list-style-type: none"> <li>• Mean follow-up, 3.5 years</li> <li>• A1C (median)               <ul style="list-style-type: none"> <li>◦ 6.4% (intensive)</li> <li>◦ 7.5% (standard)</li> </ul> </li> <li>• <b>Macrovascular (intensive)</b> <ul style="list-style-type: none"> <li>• Nonfatal MI HR 0.76 (95% CI 0.62–0.92) NNH = 100</li> <li>• CV death HR 1.35 (95% CI 1.04–1.76) NNH = 125</li> <li>• All-cause mortality HR 1.22 (95% CI 1.01–1.46) NNH = 100</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Mean follow-up 5 years</li> <li>• A1C               <ul style="list-style-type: none"> <li>◦ 7.2% (intensive)</li> <li>◦ 7.6% (standard)</li> </ul> </li> <li>• <b>Macrovascular (intensive)</b> <ul style="list-style-type: none"> <li>• Nonfatal MI HR 0.82 (95% CI 0.7–0.96) NNT = 500</li> <li>• CV death HR 1.29 (95% CI 1.04–1.60) NNH = 1000</li> <li>• All-cause mortality HR 1.19 (95% CI 1.03–1.38) NNH = 500</li> </ul> </li> </ul>

**Table 1-6.** Summary of Evidence: Glycemic Goals in Type 2 Diabetes Mellitus (*continued*)

Population	Glycemic Targets	Initial Results	Follow-up Results
<b>ADVANCE<sup>e,f</sup> (n=11,140)</b>			
<ul style="list-style-type: none"> <li>• Mean age, 66.6 ± 6 years</li> <li>• Mean duration (DM) = 8 years</li> <li>• Clinical ASCVD = 32%</li> </ul>	A1C <6.5% (intensive) A1C <7% (standard)	<ul style="list-style-type: none"> <li>• Median follow-up, 5 years</li> <li>• A1C                             <ul style="list-style-type: none"> <li>◦ 6.5% (intensive)</li> <li>◦ 7.3% (standard)</li> </ul> </li> <li><b>Composite (intensive)</b> <ul style="list-style-type: none"> <li>• Major microvascular and macrovascular events HR 0.90 (95% CI 0.82–0.98) NNT = 53</li> </ul> </li> <li><b>Microvascular (intensive)</b> <ul style="list-style-type: none"> <li>• Major events HR 0.86 (95% CI 0.77–0.97) NNT = 67</li> <li>• New or worsening nephropathy HR 0.79 (95% CI 0.66–0.93) NNT = 91</li> <li>• New onset microalbuminuria HR 0.91 (95% CI 0.85–0.98) NNT = 500</li> <li>• Macroalbuminuria HR 0.71 (95% CI 0.57–0.85) NNT = 83</li> </ul> </li> <li><b>Macrovascular (intensive)</b> <ul style="list-style-type: none"> <li>• Major macrovascular events HR 0.94 (95% CI 0.84–1.06)</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Mean follow up 5.4 years (n=8,494)</li> <li>• A1C                             <ul style="list-style-type: none"> <li>◦ 7.5% (intensive)</li> <li>◦ 7.5% (standard)</li> </ul> </li> <li><b>Microvascular (intensive)</b> Major microvascular events</li> <li><b>Macrovascular (intensive)</b> <ul style="list-style-type: none"> <li>• Major macrovascular events</li> <li>• HR 1.00 (95% CI 0.92–1.08)</li> <li>• Mortality HR 1.00 (95% CI 0.92–1.08)</li> </ul> </li> </ul>
<b>VADT<sup>g,h</sup> (n=1791)</b>			
<ul style="list-style-type: none"> <li>• Mean age, 60.5 ± 9 years</li> <li>• Mean duration (DM) = 11.5 years</li> <li>• Clinical ASCVD, ~40%</li> </ul>	A1C reduction of 1.5% (intensive) compared with standard	<ul style="list-style-type: none"> <li>• Median follow-up, 5.6 years</li> <li>• A1C                             <ul style="list-style-type: none"> <li>◦ 6.9% (intensive)</li> <li>◦ 8.4% (standard)</li> </ul> </li> <li><b>Microvascular (intensive)</b> <ul style="list-style-type: none"> <li>• No significant differences</li> </ul> </li> <li><b>Macrovascular (intensive)</b> <ul style="list-style-type: none"> <li>• Major macrovascular events HR 0.88 (95% CI 0.74–1.05)</li> <li>• CV death HR 1.32 (95% CI 0.81–1.42)</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Median follow up 9.8 years (n=1391)</li> <li>• A1C                             <ul style="list-style-type: none"> <li>◦ 7.8% (intensive)</li> <li>◦ 8.3% (standard)</li> </ul> </li> <li><b>Macrovascular (intensive)</b> <ul style="list-style-type: none"> <li>• Time to first major CV event HR 0.83 (95% CI 0.70–0.99)</li> <li>• CV mortality HR 0.88 (95% CI 0.64–1.20)</li> </ul> </li> </ul>

<sup>a</sup>UK Prospective Diabetes Study Group. Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;352:837-53.

<sup>b</sup>Holman R, Paul S, Bethel A, et al. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008;359:1577-1589.

<sup>c</sup>ACCORD Study Group. Effects of intensive blood pressure control in type 2 diabetes mellitus. *N Engl J Med* 2010;362:1575-85.

<sup>d</sup>Riddle MC, Ambrosius WT, Brillon DJ, et al.; Action to Control Cardiovascular Risk in Diabetes Investigators. Epidemiologic relationships between A1C and all-cause mortality during a median 3.4-year followup of glycemic treatment in the ACCORD trial. *Diabetes Care* 2010;33:983-90.

<sup>e</sup>Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation (ADVANCE) Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008;358:2560-72.

<sup>f</sup>Zoungas S, Chalmers J, Neal B, et al. Follow-up of blood pressure lowering and glucose control in type 2 diabetes. *N Engl J Med* 2014;371:1392-406.

<sup>g</sup>Duckworth W, Abraira C, Moritz T, et al; VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med* 2009;360:129-39.

<sup>h</sup>Hayward R, Reaven P, Wiitala W, et al. Follow-up of glycemic control and cardiovascular outcomes in type 2 diabetes. *NEJM* 2015;372:2191-207.

ASCVD = atherosclerotic cardiovascular disease; CV = cardiovascular; T2DM = type 2 diabetes mellitus; MI = myocardial infarction; RRR = regular rate and rhythm.

### **The UKPDS Trials**

The UKPDS trials randomized about 4000 patients (mean age, 53.3 years  $\pm$  8.6; 61% men; 81% white) with newly diagnosed T2DM to intensive (fasting plasma glucose <108 mg/dL) versus conventional control (fasting plasma glucose <270 mg/dL). Combinations of lifestyle interventions, sulfonylureas, metformin, and insulin were used to achieve target glucose levels. At the end of the mean 10-year follow-up, median A1C was 7% (95% CI, 6.4–8.2) in the intensive group and 7.9% (95% CI, 6.9–8.8) in the conventional group. The intensive control cohort demonstrated significant reductions in the primary end point of all diabetes complications (risk reduction 12%; 95% CI, 1–21;  $p=0.029$ ) and all microvascular end points (risk reduction 25%) that were driven by decreases in requirement for retinal photocoagulation and surrogate markers for renal disease. Subjects in the intensive group experienced more weight gain and hypoglycemia, and macrovascular outcomes did not differ significantly between the intensive and conventional groups; however, there was a trend toward decreased risk of myocardial infarction (MI) in the intensive control group (risk reduction 16%;  $p=0.052$ ) even though the study was not statistically powered to detect a difference in that outcome. A randomized subanalysis of overweight subjects (>120% of ideal body weight) treated with metformin demonstrated a 39% reduction in MI ( $p=0.01$ ) and a 36% reduction in all-cause mortality ( $p=0.01$ ). Diabetes-related and all-cause mortality did not differ between groups (UKPDS 33 1998; Stratton 2000).

### **The UKPDS Follow-Up**

The UKPDS follow-up study sought to determine the long-term effect of early, intensive glycemic control. More than 3000 subjects participated in the 10-year intention-to-treat analysis. Differences in A1C between the intensive and conventional groups were lost within 1 year of the discontinuation of study assignment. The 25% reduction in risk for microvascular end points was sustained, and statistically significant post-trial differences emerged favoring intensive therapy in MI (risk reduction 15%;  $p=0.01$ ) and all-cause mortality (risk reduction 13%;  $p=0.007$ ) (Holman 2008).

### **The ACCORD Trial**

Although a clear relationship between hyperglycemia and CV risk was established, the effect of intensive glycemic control on CV risk remained unclear. The objective of the ACCORD trial was to determine whether CV events would be reduced by targeting normal A1C (<6%) in middle-aged to older individuals with T2DM and preexisting or substantial risk of CVD (Gerstein 2008). The primary outcome was a composite of the first occurrence of nonfatal MI or nonfatal stroke or death from CV causes. More than 10,000 subjects were randomized to intensive (A1C goal <6%) or standard (7.0%–7.9%) control arms. Therapeutic regimens were individualized and not dictated by trial design. Subject characteristics at baseline

(approximate mean  $\pm$ SD) included age of 62.2 years ( $\pm$ 6.8), A1C 8.3% ( $\pm$ 1.1), and BMI 32.2 kg/m<sup>2</sup> ( $\pm$ 5.5). Sixty-four percent of study subjects were white and 19% were African American. More than 50% were current or former smokers. More than 30% were on insulin, and median duration of diabetes was 10 years.

The mean duration of follow-up was 3.5 years when the trial was stopped early because of higher mortality in the intensive control group. Significant differences in A1C attainment were observed as early as 4 months after randomization (median A1C of 6.7% in the intensive group and 7.5% in the standard control group). Results for the intensive versus standard control groups include primary outcome (HR 0.90; 95% CI, 0.78–1.04;  $p=0.16$ ) and mortality (HR 1.22; 95% CI, 1.01–1.46;  $p=0.04$ ). Mortality rate began to separate in the two study groups after 1 year, and the differences persisted throughout the duration of follow-up. Prespecified subgroup analysis indicated fewer fatal or nonfatal CV events in subjects in the intensive control group who had had no CV events before randomization ( $p=0.04$ ) or who had baseline A1Cs less than 8.0% ( $p=0.03$ ). The intensive control group experienced significantly more hypoglycemia ( $p<0.001$  for hypoglycemia requiring medical assistance and hypoglycemia requiring any assistance) and weight gain ( $p<0.001$ ).

### **The ACCORD Follow-Up**

The ACCORD study group subsequently published the results of a total study duration of 5 years, which included a mean of 3.7 years of intervention (intensive versus standard control) followed by a mean of 1.2 years of postintervention follow-up. During the post-trial follow-up, therapies were relaxed in the intensive and standard control arms, with median A1C of 7.2% in the intensive group at the end of the trial and 7.6% in the standard group. The incidence of the primary outcome remained nonsignificant during the post-trial follow-up (HR 0.91; 95% CI, 0.81–1.03;  $p=0.02$ ). Despite nonsignificance at the end of the intervention, the incidence of CV death reached statistical significance during the follow-up, favoring standard therapy (HR 1.29; 95% CI, 1.04–1.60;  $p=0.02$ ). The significantly higher rate of all-cause mortality in the intensive group persisted during the follow-up (1.53 vs. 1.27; 95% CI, 1.03–1.38;  $p=0.02$ ). Rates of severe hypoglycemia and other adverse effects in the follow-up did not differ significantly.

### **The ADVANCE Trial**

The ADVANCE trial was designed to evaluate the effect of an aggressive A1C goal of 6.5% or less on major vascular outcomes (ADVANCE Collaborative 2007). The primary outcomes were (1) a composite of macrovascular and microvascular events and (2) individual composites (composite macro and composite micro). More than 11,000 subjects with T2DM were randomized to intensive control (A1C <6.5%) versus standard control for a median duration of 5 years. Study participants

had a mean age of 66 years ( $\pm 6$ ) and a median baseline A1C of 7.5%, with a mean duration of diabetes of about 8 years. About one-third of subjects had histories of major macrovascular disease (e.g., MI, stroke), and about 10% had histories of major microvascular disease (e.g., macroalbuminuria, microvascular eye disease).

By the end of the study, subjects in the intensive control group had achieved a mean A1C of 6.5% compared with 7.3% in the standard control group. The risk of the primary composite of major macrovascular or microvascular events was lower in the intensive control group (HR 0.90; 95% CI, 0.82–0.98;  $p=0.01$ ), as was the incidence of major microvascular events (HR 0.86; 95% CI, 0.77–0.97;  $p=0.01$ ). The incidence of major macrovascular events did not differ significantly between groups (HR 0.94; 95% CI, 0.84–1.06;  $p=0.32$ ), and mortality was not significantly different. Intensive control resulted in a significant reduction in renal outcomes, including new or worsening nephropathy, new onset microalbuminuria, and macroalbuminuria. The incidence of severe hypoglycemia was greater in the intensive control group (HR 1.86; 95% CI, 1.42–2.40;  $p<0.001$ ). Although the primary combined composite outcome favored intensive therapy, this was driven primarily by the effect on renal outcomes. Although macrovascular outcomes did not differ between groups, it is important that event rates in the entire study were lower than expected, and thus, statistical power was lacking.

### **The ADVANCE Follow-Up**

A post-trial observational study (ADVANCE ON) with a median duration of 5.4 years post-trial was conducted to determine whether the glycemic control differences demonstrated in the original investigation resulted in long-term effect on vascular end points (Zoungas 2014). The primary outcomes were death from any cause and major macrovascular events (composite of nonfatal MI, nonfatal stroke, or death from any CV cause). All survivors of the original trial were invited to participate in the follow-up study, and 84% (about 8400) enrolled, with a random subset of 2000 subjects included in the biochemical analysis. Differences observed in A1C at the end of the ADVANCE trial were no longer evident at the initiation of the follow-up study, and levels remained relatively consistent through the conclusion of post-trial follow-up (7.2% in the intensive group and 7.4% in the standard group). No significant differences were observed in death from any cause, major macrovascular events, or major microvascular events. The intensive group demonstrated reduced risk of end-stage renal disease during the post-trial follow up (HR 0.54; 95% CI, 0.34–0.85;  $p=0.007$ ).

### **The VADT trial**

This open-label trial within Veterans Affairs medical centers sought to determine the effect of intensive glycemic control on CV events over a medial follow-up of 5.6 years (Duckworth 2009). Older veterans (mean age, 60.4 years), with mean

diabetes duration of 11.5 years and high CV risk (40% with prior event), were randomly assigned to standard or intensive control. Rather than a specific glycemic target, the goal in the intensive group was to achieve an absolute reduction of 1.5% in A1C compared with standard control. The primary outcome of interest was time to first occurrence of a major CV event (composite of MI, stroke, death from CV causes, congestive heart failure, CV surgery, inoperable cardiac disease, or amputation for ischemic gangrene). The intensive control group achieved an A1C of 6.9% versus 8.4% in the standard therapy group. There were no significant differences between the groups in either the primary outcome or any individual component of the primary outcome, and no difference was observed in the composite of microvascular complications. However, microalbuminuria and macroalbuminuria were significantly less common in the intensive control group. Hypoglycemia was more common in the intensive control group.

### **VADT Follow-Up**

As a follow-up to the VADT study, a post-trial observational study of 92.4% of the original subjects was conducted during a median 9.8 years. The primary outcome was the time to first major CV event (MI, stroke, new or worsening heart failure, amputation, or CV death). Secondary outcomes included CV mortality and all-cause mortality. The mean 1.5% difference in A1C (6.9% vs. 8.4%) observed in the primary trial was maintained for more than 1 year post-trial. At 3 years post-trial, the difference declined to 0.3%. Patients enrolled in the intensive arm had a significantly lower risk of the primary outcome compared with those in standard therapy (HR 0.83; 95% CI, 0.70–0.99;  $p=0.04$ ), which translates to an absolute risk reduction of 8.6 major CV events per 1000 person-years. There were no significant differences in CV mortality (HR 0.88; 95% CI, 0.64–1.20;  $p=0.42$ ) or total mortality (HR 1.05; 95% CI, 0.89–1.25;  $p=0.54$ ) (Hayward 2015).

### **Weighing Benefits and Risks**

The careful consideration of study data in the context of patient-specific factors and the provision of education for patients, caregivers, and other health care professionals—based on this evidence so they could collaboratively determine glycemic targets—is an important aspect for the ambulatory care clinical pharmacist. However, the individual trials do not provide clear answers in all scenarios. Weighing the benefits and risks associated with intensive glycemic control is complex and requires consideration of the evidence as a whole, and meta-analyses and post hoc analyses of existing data have provided additional insight. The disadvantages of intensive glycemic control, including the lack of benefit demonstrated in CV and all-cause mortality, are consistently confirmed in meta-analyses (Boussageon 2011; Hemmingsen 2011; Kelly 2009). Similarly, increased risk of severe hypoglycemia is consistently demonstrated. There are

some consistent benefits, but they are often overshadowed by negative findings.

The ACCORD trial and subsequent meta-analyses have demonstrated reduced risk of nonfatal MI, retinopathy, and albuminuria (new onset and progression from microalbuminuria to macroalbuminuria) with intensive control. The key to making patient-specific decisions regarding glycemic targets goes beyond the aggregate trial findings and involves examination of study subject characteristics and post hoc evaluations.

A baseline A1C of more than 8.5% was independently associated with increased mortality in the original ACCORD trial. Close examination of on-treatment predictors of mortality in the original ACCORD study has implicated two factors that may be related to mortality risk: inability to achieve rapid and sustained A1C reduction and severe hypoglycemia. The intensive therapy group demonstrated an increase in mortality; however, the highest mortality rate within the intensive group was among those with the highest mean on-treatment A1C. The excess risk occurred in intensive-group subjects with mean on-treatment A1C of more than 7% (Riddle 2010). In addition, the excess risk was demonstrated only in participants in the intensive group whose A1C did not decline or declined very little (<0.5%) after entering the trial. Therefore, the participants at highest risk were those who entered the intensive arm with high baselines A1C (>8.5%) and who were unable to achieve glycemic targets (sustained A1C >7%). Not surprisingly, severe hypoglycemia (requiring third-party assistance for resuscitation) was more common in the intensive group. However, trial participants in the intensive group, with known histories of severe hypoglycemia before the trial, were less likely to die than were those in the standard group with a prior severe event.

The highest incidence of severe hypoglycemia in the intensive group was in subjects with mean A1C between 7% and 8%, again implicating those unable to achieve a lower A1C. Additional analysis indicated that participants with more nonsevere hypoglycemia (serum glucose <70 mg/dL, no assistance required) during the trial had lower risk of death. Though it is not intuitive, these data support an emerging theory of so-called hypoglycemic preconditioning (Bonds 2010; Riddle 2010). The typical physiologic response to hypoglycemia includes the release of counterregulatory catecholamines resulting in increased platelet adhesion, increased heart rate, vasoconstriction, and potentially malignant arrhythmias. In patients with infrequent hypoglycemia, the physiologic response to severe hypoglycemia is likely to result in a more exaggerated catecholamine response. Conversely, in patients with multiple nonsevere episodes of hypoglycemia, the catecholamine response may be blunted, resulting in a potentially protective effect. In the case of ACCORD, because subjects were unable to reduce A1C to less than 7%, they were more vulnerable to death secondary to severe hypoglycemia; lack of prior exposure to hypoglycemia because of consistently

### Box 1-3. Evidence-Based Considerations for Less-Stringent A1C Goal

- Patients with histories of severe hypoglycemia requiring assistance
- Patients unable to reduce A1C more than 0.5% in first 4–12 months of therapy
- Patients with persistent A1C elevation (>8%) with no histories of mild or moderate hypoglycemia

elevated glucose may have prevented the potential preconditioning for fatal arrhythmias.

These data support strong considerations of patient-specific characteristics, including history of hypoglycemia, severe hypoglycemia, and early response to therapy (Box 1-3). In patients with no history of hypoglycemia or in those with histories of severe hypoglycemia requiring assistance, it would be potentially more risky to pursue an aggressive A1C goal. Similarly, in patients unable to reduce A1C more than 0.5% in the first 4–12 months of treatment, the continued pursuit of an aggressive A1C goal may lead to poor outcomes.

The timing of intervention is also important: The data seem to support that even though the risk of microvascular complications can be potentially mitigated at any time during the duration of T2DM, one of the keys to reducing macrovascular risk lies in setting more-aggressive glycemic goals early in the disease—in appropriate patients. The evidence supports that such early glycemic interventions can provide lasting benefits (the legacy effect) even if they are not sustained (Stratton 2000).

### Nonglycemic Goals of Therapy

Elevated blood pressure is a known risk factor for microvascular and macrovascular complications in patients with diabetes. The relationship is linear, with increasing risk mirroring increasing blood pressure. Though a large pool of data exists for the evaluation and comparison of various therapeutic agents in the treatment of hypertension for patients with diabetes, few studies examine the specific impact of different blood pressure targets.

Current ADA standards recommend a BP goal of lower than 140/90 mm Hg, with initiation of pharmacotherapy at the systolic threshold of 140 mm Hg and lifestyle interventions at 120 mm Hg. Further, the ADA recommends consideration of a lower goal (<130/80 mm Hg) in younger patients if it can be achieved without undue treatment burden, although *younger* is not specifically defined. The 2014 report of the [Eighth Joint National Committee](#) (JNC) also recommends initiation of antihypertensive therapy in patients with diabetes at a systolic BP threshold of 140 mm Hg and a target BP of less than 140/90 mm Hg (James 2013). This is in contrast to the prior recommendations in multiple editions of both the ADA and the JNC, including a target of less than 130/80 mm Hg for this population.

## Patient Care Scenario

A 60-year-old woman with a medical history of T2DM for 10 years (baseline A1C, 9.8%) hypertension for 15 years, cerebrovascular disease (stroke in 2010), and chronic kidney disease (estimated CrCl, 48 mL/minute; urine albumin:creatinine 100 mcg:mg) is being seen for routine follow-up. Her home drugs are insulin glargine 58 units subcutaneously daily, metformin 1000 mg orally twice daily, lisinopril 40 mg orally daily, and aspirin 81

mg orally daily. The patient tells of a history of frequent, mild hypoglycemia. She has completed several diabetes self-management education courses and self-monitors blood sugar twice daily. Her current A1C is 9.4% (9.6% 3 months ago), and her blood pressure is 144/86 mm Hg (142/84 3 months ago). Which A1C goal would be most appropriate for this patient?

### ANSWER

The determination of therapy goals for this patient requires consideration of multiple factors for weighing of benefits and risks. To determine the A1C goal, important considerations include duration of diabetes, baseline A1C, response to therapy, presence of comorbidities, and history of hypoglycemia. This patient has a relatively long duration of diabetes, which supports a less-stringent A1C goal because patients with the greatest evidence-based benefit of intensive therapy (UKPDS) were those with new diagnoses of diabetes; and those with less-favorable outcomes (ACCORD) had had longer durations. Early response to therapy was examined in a post hoc analysis of the ACCORD trial, and those patients with baseline A1Cs more than 8.5% and with minimal (<0.5% reduction) or no response to therapy had less-favorable outcomes.

This patient has had a persistently elevated A1C (more than 8.5% at baseline) with minimal (<0.5%) reduction despite receiving self-management education and follow-up. Those factors also support a less-stringent A1C goal for this patient. The patient's vascular complications represent another reason to consider a less-stringent A1C goal, because patients in ACCORD had more-significant vascular disease and poorer outcomes with intensive therapy.

Two patient-specific factors support a more-stringent A1C goal: the presence of nephropathy and history of frequent, mild hypoglycemia. Patients in the intensive arm

of the ADVANCE study demonstrated decreased risk of progression to macroalbuminuria. Patients in the intensive arm of the ACCORD study with histories of frequent, mild, hypoglycemia were less likely to have unfavorable outcomes than were those with no histories of hypoglycemia. Overall, the risks of a stringent A1C goal outweigh the risks in this patient. Therefore, the evidence supports a less-stringent goal (i.e., A1C 7%–8%) for this patient.

1. UK Prospective Diabetes Study Group. Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;352:837-53.
2. ACCORD Study Group. Effects of intensive blood pressure control in type 2 diabetes mellitus. *N Engl J Med* 2010;362:1575-85.
3. Gerstein HC, Miller ME, Byington RP, et al. Effects of intensive glucose lowering in type 2 diabetes. The action to control cardiovascular risk in diabetes study group. *N Engl J Med* 2008;358:2545-59.
4. ADVANCE Collaborative Group. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomized controlled trial. *Lancet* 2007;370:829-40.

The ACCORD trial, which compared an intensive systolic BP target of less than 120 mm Hg with a standard of less than 140 mm Hg and which did not demonstrate significant reduction in a composite CV outcome among patients in the intensive arm, is cited in reference to those changes. The guidelines of the American Society of Hypertension (ASH) and the International Society of Hypertension concur by recommending a BP target of less than 140/90 mm Hg for most patients and citing lack of evidence for more-intensive goals (Weber 2014). In contrast to ASH, ADA, and JNC 8, the [American Association of Clinical Endocrinologists' clinical practice guidelines](#) for diabetes recommend a target BP of less than 130/80 mm Hg for most patients, acknowledging a lack of randomized controlled data but citing expert consensus based on observational and epidemiological data (AACE 2015). A thorough understanding of the evidence from ACCORD—in the context of additional data—will enable the clinician to incorporate patient-specific factors and take a

patient-centered approach when developing therapy goals related to blood pressure.

Early evaluations of blood pressure lowering, including the Hypertension Optimal Treatment study, demonstrated evidence of improved outcomes with an intensive diastolic BP goal (<80 mm Hg) when compared with a standard goal (<85 mm Hg) (Hanssen 1998). Landmark trials such as the Systolic Hypertension in the Elderly Program and UKPDS provided data that supported improved microvascular and macrovascular outcomes in patients achieving end-of-study BP values ranging from 143 mm Hg to 144 mm Hg systolic and from 68 mm Hg to 82 mm Hg diastolic (UKPDS 1998; Curb 1996).

The International Verapamil SR-Trandolapril study compared hypertension treatment strategies (calcium channel antagonist versus  $\beta$ -blocker) rather than blood pressure goals in patients with diabetes, but the results provided meaningful insights into desirable blood pressure targets (Bakris 2004). More than 6000 study subjects with diabetes were evaluated

for a mean duration of 2.7 years. The primary outcome (composite of all-cause death, nonfatal MI, or nonfatal stroke) was significantly lower in subjects with end-of-study BP less than 140/90 mm Hg, with a linear relationship extending to 110/60 mm Hg. The Appropriate Blood Pressure Control in Non-Insulin-Dependent Diabetes Mellitus trial investigated the effect of an intensive BP target (diastolic blood pressure [DBP] goal, 75 mm Hg) compared with a moderate target (DBP 80–90 mm Hg) on microvascular and macrovascular outcomes in patients with T2DM for more than 5 years (Schrier 2007). Mean end-of-study BP was 133/78 mm Hg in the intensive group and 139/86 mm Hg in the moderate control group. All-cause mortality was significantly lower (5.5% vs. 10.7%,  $p < 0.037$ ) in the intensive BP control group, and nephropathy progression (to microalbuminuria and macroalbuminuria) was decreased. Further analysis of normotensive (DBP 80–89 mm Hg) diabetic patients randomized to intensive control (DBP decrease of 10 mm Hg) or moderate (no change) control demonstrated reduction in retinopathy and stroke in the intensive cohort (mean end-of-study BP of 128/75 mm Hg) (Schrier 2007).

Although more contemporary evidence, including the ALLHAT trial and the Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension trial, were not designed to assess BP targets, subjects who achieved blood pressures in the 132–135 mm Hg systolic and 79–84 mm Hg diastolic ranges experienced CV risk reductions (Jamerson 2008; ALLHAT 2003). The Multifactorial Intervention and Cardiovascular Disease in Patients with Type 2 Diabetes study evaluated the effect of two BP targets (<130/80 mm Hg and <135/85 mm Hg) on microvascular and macrovascular outcomes in patients with diabetes and albuminuria (Gaede 2003). The intensive therapy group had reductions in the risk of CVD, nephropathy, retinopathy, and autonomic neuropathy compared with the less intensive group. Multiple observational studies support an association between blood pressure and renal function in patients with diabetes (Ninomiya 2009; Gerstein 2001; Dineen 1997). Current [Kidney Disease: Improving Global Outcomes](#) guidelines recommend a blood pressure goal of less than 130/80 mm Hg for patients with diabetes and micro- or macroalbuminuria (Kidney Disease 2012), but that recommendation was given a low grade because it is based primarily on observational data and only one randomized trial (Gaede 2003).

The composite of these findings led to the logical assumption that blood pressure values lower than 130/80 mm Hg may lead to further decreases in macrovascular and microvascular risk. Scrutiny of that assumption, as a basis for guideline recommendations, subsequently led to clinical studies designed to evaluate outcomes as they relate to predefined targets. Table 1-7 summarizes findings relevant to blood pressure in the ACCORD, ADVANCE, and ADVANCE ON studies.

The ACCORD BP study evaluated the effect of a systolic blood pressure target of less than 120 mm Hg (compared with

a target of less than 140 mm Hg) on CV outcomes in high-risk patients with T2DM (ACCORD Study Group 2010). The primary outcome was a composite of first occurrence of major CV events (nonfatal MI, nonfatal stroke, or CV death). Patients enrolled in the trial had a 10-year mean duration of diabetes, and more than one-third had prior CV events. One-half of the subjects were former or current smokers and had mean BMIs in the obese range. There were no significant between-group differences in the primary outcome. All-cause and CV mortality rates were similar between the two groups. Significantly fewer strokes (all and nonfatal) were demonstrated in the intensive treatment arm, along with significantly less macroalbuminuria (although microalbuminuria did not differ). More-adverse effects—including hypokalemia, elevated SCr, and decreased estimated glomerular filtration rate—were observed in the intensive target group.

The ADVANCE and ADVANCE ON studies did not specifically compare blood pressure targets, but data from achieved blood pressure results may inform goal setting (Zoungas 2104). In addition, the concept of a legacy effect on CV risk with blood pressure reduction can be considered in the context of the post-trial follow-up data from ADVANCE ON.

The ADVANCE study randomized more than 11,000 patients with T2DM to a fixed combination of perindopril (2–4 mg) and indapamide (0.625–1.25 mg) or placebo in addition to current antihypertensive therapy. The intent-to-treat analysis examined the effect of intervention on the primary composite outcome of major macrovascular and microvascular events (death from CV disease, nonfatal stroke, or nonfatal MI; and new or worsening nephropathy or retinopathy). End-of-study blood pressures were lower in the intervention group (134–136/73–74 mm Hg) compared with placebo (139–141/73–78 mm Hg). The intervention group resulted in a 9% relative risk reduction in primary composite outcome, a 14% relative risk reduction in all-cause mortality, and an 18% relative risk reduction in total coronary events. Microvascular outcomes, including total renal events and new microalbuminuria, were significantly reduced in the intervention group as well. Cerebrovascular events did not differ between groups.

Even though the findings from the trial support the use of an angiotensin-converting-enzyme inhibitor/thiazide diuretic combination in the treatment of hypertension in the setting of diabetes, the end-of-study blood pressure achievements cannot be ignored. The blood pressures achieved in ADVANCE represent the lowest values demonstrated in a clinical trial with no protocol-driven blood pressure target, and they presumably contributed to the positive effect demonstrated on microvascular and macrovascular outcomes. The ADVANCE ON investigation consisted of a post-trial observational study of surviving patients from ADVANCE that examined two prespecified primary outcomes: death from any cause and major macrovascular events (a composite of nonfatal MI, nonfatal stroke, or death from CV disease). More than 8000 of the original subjects (about 83%) participated

**Table 1-7.** Summary of Evidence: Blood Pressure Goals

		<b>ACCORD BP (2010)</b>	<b>ADVANCE (2007) (BP arm)</b>	<b>ADVANCE ON (2014) (BP arm)</b>
Subjects (mean follow-up)		n=4733 Mean age 62 years; 48% women; 34% CVD at baseline; mean BP 139/76 mm Hg (4.7 years)	n=11,140 Mean age 66 years; 43% women; 32% macrovascular disease at baseline; mean BP 145/81 mm Hg (4.3 years)	n=9787 Mean age 67 years; 59% women; 30% vascular disease; mean BP 144/80 mm Hg (post-trial median 5.9 years; total follow-up 9.9 years)
Intervention(s)		Intensive BP control (target <120/80 mm Hg) vs. standard BP control (target <140/90 mm Hg)	Fixed combination perindopril/indapamide vs. placebo No blood pressure target identified Other BP medications used at primary care physician's discretion	No intervention; post-trial follow-up to determine whether differences observed in ADVANCE persisted. No control of BP regimens or targets
Mean achieved BP (mm Hg)	Standard	SBP 133.5 (95% CI 133.1–133.8) DBP 70.5 (95% CI 70.2–70.8)	141/77 <sup>a</sup>	As above Differences in BP between intervention and standard groups became insignificant 6 months after conclusion of original trial.
	Intensive	SBP 119.3 (95% CI 118.9–119.7) DBP 64.4 (95% CI 64.1–64.7)	135/75 <sup>a</sup>	
Outcomes Hazard Ratio Intervention Group (95% CI)		<b>Macrovascular</b> Primary outcome (first occurrence of major CV event): HR 0.88 (0.73–1.06) <i>NNT = 454/1 year</i> Any stroke 0.59 (CI 0.39–0.89) <i>NNT = 476/1 year</i> Nonfatal stroke 0.63 (0.41–0.96) <i>NNT = 588/1 year</i> Mortality 1.07 (0.85–1.35)	Death (any) 0.86 (0.75–0.98); p=0.03 <i>NNT = 83</i> <b>Composite</b> Major macro and microvascular events: 0.91 (0.83–0.99); p=0.041 <i>NNT = 77</i> <b>Macrovascular</b> Major macrovascular events: 0.92 (0.81–1.04); p=0.16 Total coronary events: 0.86 (0.76–0.98); p=0.020 <i>NNT = 83</i> <b>Microvascular</b> Major microvascular events: 0.91 (0.8–1.04); p=0.16 All renal events: 0.79 (0.73–0.85); p<0.001 <i>NNT = 22</i>	Death (any) 0.91 (0.84–0.99); p=0.03 <i>NNT = 67</i> <b>Macrovascular</b> Composite 0.92 (0.85–1.00); p=0.06 Death CV cause = 0.88 (0.77–0.99); p=0.04 <i>NNT = 100</i> <b>Microvascular</b> Major events 1.05 (0.92–1.21); p=0.47

<sup>a</sup>Extrapolated from trial figures.

Information from ACCORD Study Group. Effects of intensive blood pressure control in type 2 diabetes mellitus. *N Engl J Med* 2010;362:1575-85; ADVANCE Collaborative Group. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomized controlled trial. *Lancet* 2007;370:829-40; and Zoungas S, Chalmers J, Neal B, et al. Follow-up of blood pressure lowering and glucose control in type 2 diabetes. *N Engl J Med* 2014;371:1392-1406.

in the follow-up. Initial post-trial evaluations occurred at a median of 3.5 years after the original trial ended, with a total follow-up time frame (in trial and post-trial) of almost 10 years.

After the original trial ended, blood pressure differences between groups were attenuated within 6 months, and levels remained similar for the rest of the post-trial period (mean end of study BP 144.1/80.4 ±21.3/10.8). Significant differences in macrovascular outcomes, including all-cause mortality and death from CV causes, persisted in the post-trial follow-up for the intervention group, which achieved lower BP. Those findings indicate the potential presence of a legacy effect in the treatment of blood pressure in patients with diabetes. If CV benefits can be seen years later in spite of similar degree of control, early initiation of effective therapies to achieve target blood pressure levels is imperative.

Systematic reviews and meta-analyses have provided additional factors for consideration. A Cochrane review included five major clinical trials that compared more- and less-intensive blood pressure targets (Arguedas 2013). It is important that only one study to date (ACCORD) has specifically examined the systolic blood pressure target, whereas other data have focused examination on the diastolic target. The Cochrane review found a significant reduction in incidence of stroke with lower systolic blood pressure (SBP) targets but no effect on mortality and significant increase in risk of serious adverse effects. Further, review of the DBP data demonstrated a trend toward reduction in mortality in the intensive control cohort, with no significant differences in stroke, MI, or heart failure. A broad and more recent meta-analysis consisting of 40 studies with varying outcomes analyzed the association of microvascular and macrovascular outcomes according to achieved systolic

### Box 1-4. Clinical Considerations for Blood Pressure Target Less Than 130/80 mm Hg

1. A patient with treated hypertension and current blood pressure less than 130/80 mm Hg without adverse drug events
2. A patient with high risk of cerebrovascular disease (prior stroke or transient ischemic attack, multiple stroke risk factors beyond hypertension and diabetes)
3. A patient with mild, nonproliferative diabetic retinopathy
4. A patient with any significant degree of albuminuria

blood pressure (>130 mm Hg vs. <130 mm Hg) (Emdin 2015). There was no significant difference in coronary events at a systolic BP of less than 140 mm Hg. However, treatment was associated with lower risks of stroke (RR 0.72; 95% CI, 0.57–0.90), albuminuria (RR 0.86; 95% CI, 0.81–0.90), and retinopathy (RR 0.87; 95% CI, 0.76–0.99) in the SBP-less-than-130-mm-Hg stratum.

Based on the collective evidence, it is reasonable to target a blood pressure of less than 140/90 mm Hg in the majority of patients with T2DM and hypertension. Box 1-4 lists patient-specific exceptions for consideration of a lower target (<130/80 mm Hg) if it can be achieved without adverse effects or undue treatment burden.

### Cholesterol

[ADA recommendations](#) regarding CV risk factor management with cholesterol-lowering drugs are in alignment with the [2013 American College of Cardiology/American Heart Association \(ACC/AHA\) cholesterol treatment guidelines](#) and are summarized in Table 1-8 (Stone 2014). Specific LDL

**Table 1-8.** ACC/AHA 2013 Lipid Guidelines for Patients with T2DM Aged 40–75 Years

#### Estimated 10-year ASCVD risk <7.5%

*Moderate intensity*

Daily dose = mean LDL reduction of 30%–49%

Atorvastatin 10–20 mg

Rosuvastatin 5–10 mg

Simvastatin 20–40 mg

Pravastatin 40–80 mg

Lovastatin 40 mg

Fluvastatin XL 80 mg

Fluvastatin 40 mg twice daily

Pitavastatin 2–4 mg

#### Estimated 10-year ASCVD risk ≥7.5%

*High intensity*

Daily dose = mean LDL reduction of ≥50%

Atorvastatin 40–80 mg

Rosuvastatin 20–40 mg

Information from Stone N, Robinson J, Lichtenstein, et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults. *Circulation* 2014;129:S1-S45.

**Table 1-9.** NLA and AACE/ACE Lipid Guidelines for Patients with Diabetes

<b>NLA Guidelines</b>			
<b>Risk Group</b>	<b>LDL Target</b>	<b>Non-HDL Target</b>	<b>Nonstatin Therapy</b>
High <sup>a</sup>	<100 mg/dL	<130 mg/dL	Bile acid sequestrants, niacin, or ezetimibe when LDL goal cannot be met with statin alone or statin intolerance High-dose omega-3 fatty acids, fibrates, or niacin to achieve non-HDL goal or for very high triglycerides (> 500 mg/dL)
Very high <sup>b</sup>	<70 mg/dL	<100 mg/dL	
<b>AACE/ACE Guidelines</b>			
Moderate <sup>c</sup>	<100 mg/dL	<130 mg/dL	Bile acid sequestrants, niacin, or ezetimibe when LDL goal cannot be met with statin alone or statin intolerance High-dose omega-3 fatty acids, fibrates, or niacin to achieve non-HDL goal or for TG (> 500 mg/dL)
High <sup>d</sup>	<70 mg/dL	<100 mg/dL	

<sup>a</sup>0–1 ASCVD risk factors [age (>45 years men or >55 years women), premature family history of ASCVD (<55 years men, <65 years women), smoking, hypertension (>140/90 mm Hg or on medication), low HDL (men <40 mg/dL, women <50 mg/dL)].

<sup>b</sup>Clinical ASCVD, >2 major ASCVD risk factors, or end organ damage (chronic kidney disease, proteinuria >30 mcg/mg, or retinopathy).

<sup>c</sup>Absence of clinical ASCVD, absence of risk factors (hypertension, family history, low HDL, smoking).

<sup>d</sup>Presence of clinical ASCVD or >1 risk factor.

targets have been abandoned in favor of identifying appropriate statin intensity based on estimated CV risk. The guidelines do not endorse combination therapy to achieve LDL or non-HDL targets, citing a paucity of evidence. In contrast, the guidelines of the [National Lipid Association \(NLA\)](#) and the [AACE/ACE](#), which are summarized in Table 1-9, continue to advise that treatments target lipid levels and the use of combination therapy when necessary to reach lipid goals. Patients with diabetes commonly present with patterns of lipid abnormalities that include high TG and/or low HDL. In addition, some patients do not achieve historical LDL targets even on high-intensity statin, leading to the consideration of combination therapy. The ambulatory care clinical pharmacist should be familiar with the evidence regarding those issues to be able to inform patient-specific goal setting and therapy selection.

Unfortunately, therapeutic strategies aimed at decreasing TG and/or increasing HDL with combination therapy have failed to demonstrate any significantly improved outcomes (Boden 2011; Ginsberg 2010; Keech 2005). The Fenofibrate Intervention and Event Lowering in Diabetes investigation randomly assigned about 10,000 patients with T2DM (about 25% with CVD) to micronized fenofibrate (200 mg daily) or placebo (no statin therapy in either group) for a mean duration of 5 years (Keech 2005). Enrolled subjects had TC of 116–251 mg/dL and TG of 89–443 mg/dL, with TC/HDL ratios of 4 or more at study entry. The primary outcome involved coronary events (coronary-heart-disease death or

nonfatal MI) and was not significantly affected by the addition of fenofibrate.

The Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglyceride study randomly assigned patients (n=3000) to statin therapy (simvastatin 40–80 mg daily) plus extended release niacin (1500-2000mg) versus statin monotherapy (titrated to LDL 40–80 mg/dL). Subjects had established CVD, moderate LDL (<180 mg/dL), low HDL (<40 mg/dL for men and <50 mg/dL for women), and TG in the 150–400 mg/dL range (Boden 2011). About one-third of enrolled patients had diabetes. The primary CV outcome was a composite, including first event of death from coronary heart disease, nonfatal MI, ischemic stroke, hospitalization for an acute coronary syndrome or symptom-driven coronary, or cerebrovascular revascularization. The investigation was halted early because of lack of benefit observed in the primary outcome. The ACCORD LIPID study randomly assigned more than 5000 patients who had diabetes and were at high risk of CVD to receive simvastatin (open-label adjusted to LDL goal; mean dose about 20mg) alone or in combination with blinded fenofibrate 160mg (renally adjusted) for about 4.5 years (Ginsburg 2010). The primary outcome was first occurrence of a major CV event (nonfatal MI, nonfatal stroke, or death from CV cause). Combination therapy did not reduce the rate of fatal or nonfatal CV events compared with simvastatin alone.

In general, high TG (>200 mg/dL) should be treated with lifestyle modifications; however, patients with very high TG

(>500 mg/dL) may need immediate treatment with a fibrin acid derivative or fish oil product to decrease the risk of pancreatitis. Similarly, low HDL levels should be corrected through lifestyle modifications such as smoking cessation. Although combination therapy can improve the serum lipid profile, those changes have not resulted in significant beneficial patient-oriented outcomes. Furthermore, combination therapy increases patient risks, including hepatic damage and rhabdomyolysis. Evidence-based practice supports primarily statin-based lipid regimens, with emphasis on lifestyle modifications to correct TG and/or HDL levels that remain outside the desirable range.

## CONCLUSION

Patient-centered care in the context of diabetes requires knowledge and the application of key components such as patient as person, biopsychosocial perspective, shared decision-making, and patient-provider relationship. Those components can be enhanced by a thorough assessment of

patient health literacy, self-efficacy, activation, and depression. Such a thorough assessment enables the ambulatory care clinical pharmacist to tailor an approach to patient education and health management. Service-level strategies, including the AADE7 framework and use of decision aids, focus on encouraging and measuring behavior change and on shared decision-making. Though many barriers to patient-centered care continue to exist, system-level strategies such as the CCM, PCMH, and ACO are still capable of providing health systems with structures and incentives that support patient-centered-care initiatives.

As ambulatory care clinical specialists, pharmacists must continue to stay abreast of evidence regarding the effect of more- and less-aggressive goals of therapy, which are summarized in Table 1-10. Knowledge of that evidence leads to integration with patient-specific factors that in turn lead to collaborative determination—with the patient and other members of the health care team—of the most appropriate glycemic and nonglycemic goals of therapy.

**Table 1-10.** Summary of Evidence-Based Goals of Therapy

Clinical Parameter	A1C	BP	Lipids
<i>General goal</i>	<7% <sup>a</sup> <6.5% <sup>b</sup>	<140/90 mm Hg	Moderate- to high-intensity statin <sup>c,d</sup> LDL <100 mg/dL <sup>b,e,f</sup>
<i>Special considerations</i>	A1C 7%–8% History of severe hypoglycemia requiring assistance Patients unable to reduce A1C >0.5% in first 4–12 months of therapy Patients with persistent A1C elevation (>8%) with no histories of mild or moderate hypoglycemia	BP <130/80 mm Hg Treated hypertension and current blood pressure <130/80 mm Hg without adverse drug events High risk of cerebrovascular disease (prior stroke or transient ischemic attack, multiple stroke risk factors beyond hypertension and diabetes) Mild, nonproliferative diabetic retinopathy Any significant degree of albuminuria	Current evidence does not support decreased CV risk with addition of nonstatin therapies

<sup>a</sup>American Diabetes Association. Standards of medical care 2015. *Diabetes Care* 2015;38(Suppl. 1):S33-57.

<sup>b</sup>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.

<sup>c</sup>Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2013;00:000–000. Moderate intensity for ASCVD risk <7.5%, high intensity for ASCVD risk >7.5%.

<sup>e</sup>Jacobson T, Ito M, Maki K, et al. National lipid association recommendations for patient-centered management of dyslipidemia: part 1 – executive summary. *J Clin Lipidol* 2014;8:473-88.

<sup>f</sup>LDL <70 mg/dL for patients with CVD and T2DM.

## Practice Points

- A patient-centered approach to care in diabetes is endorsed by major guidelines.
- Implementation of that approach requires knowledge of the four major concepts of patient-centered care (patient as person, biopsychosocial perspective, shared decision-making, and patient-provider relationship) as well as a comprehensive patient assessment that includes health literacy, patient activation, and psychosocial influences.
- Provider-level interventions such as diabetes self-management education, inclusion of the AADE7 as a behavioral review of systems, and routine use of decision aids can improve the patient centeredness of care.
- System-level interventions that include adoption of the Chronic Care Model or implementation of a patient-centered medical home can encourage and incentivize a patient-centered approach to care.
- Individualized goal setting in diabetes is essential and should be evidence based and patient specific.
- Current evidence supports patient-specific consideration of less-stringent A1C goals for patients with (1) histories of severe hypoglycemia, (2) lack of or minimal response to therapy (<0.5% A1C reduction) in the first 4–12 months after treatment, (3) limited life expectancy, and/or (4) vascular complications. Evidence supports a more stringent A1C goal for patients with new diagnoses or short disease durations.
- Current evidence supports patient-specific consideration of a more stringent blood pressure goal (<130/80 mm Hg) for patients with proteinuria, those with mild retinopathy, or those at high risk of cerebrovascular disease.
- Nonstatin lipid-lowering therapies have not demonstrated efficacy as add-on therapy in patients on appropriate-intensity statins who have elevated triglycerides or non-HDL cholesterol.

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# Self-Assessment Questions

1. A 52-year-old man with type 2 diabetes mellitus (T2DM) has been lost to follow-up for more than a year. At his last visit (about 14 months ago), he was maxed out on two oral agents and the potential of insulin initiation was introduced. His A1C was 11%. Today, the clinical pharmacist talks with the patient about his dietary habits, physical activity, and occupation. She asks him to describe how he felt after the last visit and his rationale for deciding to skip subsequent appointments. He shares that he drives a truck for a living, and after the last visit he was concerned about the idea of starting insulin because of the potential effect on his employment. Which component of patient-centered care best aligns with the pharmacist's approach to identifying the patient's motivation for missing scheduled appointments?

  - A. Patient as person
  - B. Bio-psychosocial perspective
  - C. Shared responsibility
  - D. Patient-provider relationship
2. A 60-year-old man is newly diagnosed with T2DM (random plasma glucose 380 mg/dL, A1C 12%). The patient is new to your practice and you hope to assess his health literacy to effectively provide patient-tailored education and review therapy options including insulin. Which one of the following would best assess this patient's numeracy and comprehension in less than 5 minutes?

  - A. TOHFLA
  - B. REALM-SF
  - C. SAHL-S&E
  - D. NVS
3. A 56-year-old man with T2DM (A1C 9.5%) is referred to your ambulatory care specialty service. You have a prior relationship with the patient, having worked with him on smoking cessation 1 year ago. The patient shares that he is confident in his ability to accomplish diabetes-related goals because of his success in smoking cessation. Additionally, a comprehensive assessment by members of an interprofessional diabetes care team yields the following results: s-TOHFLA score of 15, PHQ-9 score of 3, and PAM level of 4. Which one of the following is the greatest concern as you develop your care plan with this patient?

  - A. Self-efficacy
  - B. Health literacy
  - C. Mental health
  - D. Patient activation
4. A 46-year-old woman presents to the clinical pharmacist's office for follow-up diabetes care. She expresses interest in improved glycemic control and weight loss. At her last visit she was feeling overwhelmed. She was advised to keep a food and blood sugar diary. Today, she acknowledges a link between her intake of orange juice and elevated blood sugar. She also acknowledges limited physical activity and a need to exercise more. Today she indicates that she is nervous about her ability to succeed in self-care and has not implemented any changes. She would like to establish some specific goals to work toward. She agrees to limit orange juice to twice weekly and avoid concentrated sweets. At today's visit prior to implementing actions related to goals, which one of the following best describes this patient's level of patient activation per the Patient Activation Measure (PAM)?

  - A. Level 1
  - B. Level 2
  - C. Level 3
  - D. Level 4
5. A 54-year-old woman with T2DM is referred to your ambulatory care clinical pharmacy service. She has a 5-year history of diabetes with A1C values in the 8%–10% range despite a three-drug regimen. She admits to feeling overwhelmed by her diabetes diagnosis and she has not adopted positive self-care behaviors despite completion of a diabetes self-management education class series. When asked about her nutrition and exercise, she provides nonspecific answers such as "I'm on my feet a lot" and "I eat different stuff every day." She intermittently monitors blood sugar and does not record readings other than the memory in her glucometer. Which one of the following is the most appropriate goal for this patient encounter?

  - A. Document nutrition, exercise, and blood sugar in a diabetes diary
  - B. Limit intake of sugary beverages
  - C. Eat five servings of vegetables each day
  - D. Exercise for 15 minutes daily
6. An adult patient with T2DM undergoes mental health screening with the [PHQ-2](#) instrument. The patient indicates the following answers:  
*Over the past 2 weeks, how often have you been bothered by any of the following problems?*

  1. Little interest or pleasure in doing things: "more than half the days"
  2. Feeling down, depressed or hopeless: "several days"

Which one of the following is best to recommend for this patient?

  - A. Provide tailored diabetes education
  - B. Complete PHQ-9 screening
  - C. Initiate citalopram 20 mg daily
  - D. Refer to mental health specialist

7. An ambulatory care clinical pharmacist is looking for a tool that will assist him with patient-centered care in his diabetes-specialty practice. He is specifically interested in a system that he can easily implement without system-level buy in. He would like to measure performance based on a combination of behavior change and clinical metrics. Which one of the following would best serve this purpose?
  - A. Clinical decision-aids
  - B. AADE-7 framework
  - C. Chronic care model
  - D. Patient-centered medical home
8. A 63-year-old woman with T2DM is referred to your practice for diabetes education and management. Assessment data include A1C 9.2%, SCr 1.1 mg/dL, NVS = 0, PAM = 4, PHQ 9 = 2. Which one of the following is the best next step for this patient?
  - A. Referral for step-wise collaborative care
  - B. Use of interactive/technology-based education
  - C. Development of self-awareness
  - D. Focus on self-efficacy
9. An ambulatory care clinical pharmacist implements routine use of decision-aids for diabetes pharmacotherapy and statin use into her diabetes-specialty service. Which component of patient-centered care does this intervention most significantly affect?
  - A. Patient as person
  - B. Bio-psychosocial perspective
  - C. Shared decision making
  - D. Patient-provider relationship
10. An ambulatory care clinical pharmacist is appointed to the practice management committee in a freestanding physician group practice. The committee's charge is to recommend system level quality improvement efforts to improve their patient-centered medical home (PCMH) model, specifically in the area of care coordination. Which initiative would best address this goal?
  - A. Patient access to electronic health record
  - B. An after-hours urgent care call line
  - C. A transitions of care clinic
  - D. Consumer Assessment of Healthcare Providers and Systems (CAHPS) survey
11. A health plan is striving to improve performance on **HEDIS** measures based upon **national benchmarks**. A needs assessment is performed to identify areas for improvement in diabetes care. Results indicate mean A1C 9.4%, 40% of patients with A1C < 8%, 94% with appropriate A1C testing, 75% with annual eye exam, and 15% with A1C > 9%. Which patient group would be the highest priority for identification and intervention?
  - A. Patients with A1C 8%–9%
  - B. Patients with no A1C in past 6 months
  - C. Patients with no annual eye examinations
  - D. Patients with A1C >9%

- A. Patients with A1C 8%–9%
- B. Patients with no A1C in past 6 months
- C. Patients with no annual eye examinations
- D. Patients with A1C >9%

**Questions 12 and 13 pertain to the following case.**

S.V. is a 64-year-old man with a history of T2DM (15 years) and a current A1C of 8.6%. He is taking metformin, exenatide, and glargine insulin. S.V. shares a history of consistently elevated blood sugar with his A1C in the 8%–9% range since diagnosis despite completion of a diabetes self-management education program, routine contact with diabetes self-management support team, and adherence to medications. He reports no history of severe hypoglycemia but has had relatively frequent, mild hypoglycemia over the past several years. S.V.'s medical history is also significant for hypertension, stage 3 chronic kidney disease, stable angina, and osteoarthritis.

12. Based upon available evidence, which patient characteristic provides the strongest rationale for selecting an A1C target of 7%–8% for S.V.?
  - A. Age greater than 60 years
  - B. Persistently elevated A1C
  - C. Frequent mild hypoglycemia
  - D. Chronic kidney disease
13. Intensive therapy is implemented in S.V. with the goal to rapidly achieve an A1C target of < 6%. According to the findings in the ACCORD study, for which one of the following outcomes is S.V. most at risk?
  - A. Retinopathy
  - B. Albuminuria
  - C. Nonfatal myocardial infarction
  - D. Death
14. A 52-year-old woman is newly diagnosed with T2DM. Her medical history is significant for hypertension and obesity. She has no history of cardiovascular disease. Based upon the findings from the UKPDS trial, which is the most appropriate A1C goal for this patient?
  - A. < 6%
  - B. < 6.5%
  - C. < 7%
  - D. 7–8%

**Questions 15 and 16 pertain to the following case.**

K.K. is a 63-year-old African American woman with a 5-year history of T2DM. She has had mild, frequent hypoglycemia for the past few years. She comes to the clinic today for follow-up on her blood pressure. Her medical history is also significant for hypertension, coronary artery disease (NSTEMI 2010), cerebrovascular disease (CVA 2012), peripheral arterial disease, and distal polyneuropathy. K.K.'s current medications

include metformin 1000 mg twice daily, glipizide 10 mg twice daily, lisinopril 10 mg once daily, amlodipine 10 mg once daily, hydrochlorothiazide 25 mg once daily, gabapentin 600 mg three times daily, and clopidogrel 75 mg once daily. Objective data include BP 144/92 mm Hg, HR 78 beats/minute, and SCr 1.1 mg/dL.

15. Based upon evidence, which patient characteristic most supports consideration of an A1C goal of 7%–8% in K.K.?
- A. Age
  - B. History of hypoglycemia
  - C. Duration of diabetes
  - D. Macrovascular complications
16. Based upon available evidence, what patient characteristic most supports consideration of a blood pressure goal of < 130/80 mm Hg in K.K.?
- A. Age > 60 years
  - B. Diabetes duration ≥ 5 years
  - C. Coronary artery disease
  - D. Cerebrovascular disease
17. A 61-year-old man with T2DM, hypertension, and proteinuric stage 3 chronic kidney disease presents to the ambulatory care clinical pharmacist for follow-up. His chief complaint today includes recent severe hypoglycemia with loss of consciousness. He has a history of severe hypoglycemia and is hesitant to change insulin doses because he fears recurrence. Current drugs include insulin glargine 60 units once daily, insulin aspart 20 units three times daily before meals, lisinopril 20 mg daily, chlorthalidone 25 mg daily, and aspirin 81 mg daily. His vitals include BP 136/82 mm Hg and heart rate 68 beats/minute. Serum laboratory values include SCr 1.6 mg/dL and A1C 8.2%. Urine laboratory values include albumin:creatinine 200 mcg:mg. Based upon evidence and patient-specific data, which one of the following is the best goal of therapy for this patient?
- A. A1C < 8%, BP < 130/80 mm Hg
  - B. A1C < 8%, BP < 140/90 mm Hg
  - C. A1C < 7%, BP < 130/80 mm Hg
  - D. A1C < 7%, BP < 140/90 mm Hg
18. A 60-year-old woman with newly diagnosed T2DM (A1C 8%) is referred for diabetes education and management. She presents with a blood pressure of 148/94 mm Hg and heart rate 84 beats/minute. At her primary care physician visit earlier in the week, she had a blood pressure of 146/94 mm Hg. Her physician indicates he would prefer to wait on starting an antihypertensive. Which clinical trial best justifies the early initiation of antihypertensive therapy in this patient based upon the legacy effect?
- A. ACCORD BP
  - B. ABCD
  - C. ADVANCE ON
  - D. INVEST
19. A 56-year-old woman with T2DM (baseline ASCVD risk 5%) on simvastatin 20 mg daily for cardiovascular risk reduction has a fasting serum lipid panel including TC 168 mg/dL, HDL 38 mg/L, and TG 320 mg/dL. Based upon the evidence reviewed, which one of the following is best to recommend for this patient?
- A. Lifestyle modification alone.
  - B. Lifestyle modification and add fenofibrate.
  - C. Lifestyle modification plus add niacin.
  - D. Lifestyle modification and change simvastatin to fenofibrate.
20. A 58-year-old man with T2DM is currently treated with atorvastatin 80 mg daily to decrease cardiovascular risk. Before starting medication, his 10-year ASCVD risk was calculated at 15%. His current serum lipid panel includes TC 170 mg/dL, HDL 32 mg/dL, and TG 300 mg/dL. Based upon available evidence, which one of the following is best to recommend for this patient?
- A. Continue current therapy
  - B. Switch to rosuvastatin
  - C. Add fenofibrate
  - D. Add niacin