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In the Clinic®

Type 2 Diabetes

Screening and Prevention

Diagnosis and Evaluation

Treatment

Practice Improvement

Type 2 diabetes is a prevalent illness that causes major vascular, renal, and neurologic complications. Prevention and treatment of diabetes and its complications are of paramount importance. Many new treatments have emerged over the past 5–10 years. Recent evidence shows that newer treatments may substantially reduce risk for cardiac and renal disease, suggesting that it may be necessary to change existing treatment paradigms. This review summarizes the evidence supporting diabetes prevention and treatment, focusing on aspects that are commonly in the purview of primary care physicians.

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Diabetes is among the most common illnesses encountered by internists. An estimated 30.3 million persons (9.4%) in the United States have diabetes, and only 23.1 million of these cases have been diagnosed (1). Incidence is increasing because of the aging and changing ethnic mix of the population and because of increasing obesity. On the basis of current trends, prevalence is expected to nearly double by 2050 (2).

Diabetes is a leading cause of vision loss, amputation, and end-stage renal disease in the United States (3). In addition, it is a substantial risk factor for atherosclerotic disease, which is the leading cause of morbidity, mortality, and expenditures in persons with diabetes.

Although care and complication rates showed improvements through 2010 (4), there has recently been a concerning resurgence in rates of complications, particularly among younger adults (5).

Screening and Prevention

Should we screen for type 2 diabetes?

Current data suggest that about 1 in 4 persons with type 2 diabetes are unaware of their disease (1). Diabetes has a long asymptomatic phase, during which some people develop early complications, such as background retinopathy or microalbuminuria. Some groups have therefore suggested that screening should be done every 3 years in persons older than 45 years and in those younger than 45 years who have risk factors (see the Box: Risk Factors for Type 2 Diabetes) (6).

However, no clinical trials have shown that screening improves health outcomes. In a large-scale trial in the United Kingdom, screening for diabetes among high-risk persons did not lead to changes in outcomes during 10 years of follow-up (7). Evidence from modeling studies is inconsistent, and whether screening is likely to substantially improve outcomes or be cost-effective when applied broadly is unclear (8–10). There is thus a lack of consensus on who should be screened, the magnitude of benefit (if any), and how often screening should be done.

In a cluster randomized trial in 33 practices in the United Kingdom, 15 089 patients who were at high risk for diabetes on the basis of responses to questionnaires were invited for screening. Seventy-three percent were screened, and 3% were ultimately diagnosed with previously unknown diabetes. After 9.6 years of follow-up, there was no difference in overall (hazard ratio [HR], 1.06 [95% CI, 0.90–1.25]), cardiovascular (HR, 1.02 [CI, 0.75–1.38]), or diabetes-related (HR, 1.26 [CI, 0.75–2.10]) mortality between patients who were screened and those who were not (7).

Risk Factors for Type 2 Diabetes

- Age >45 years
- First-degree relative with type 2 diabetes
- African American, Hispanic, Asian, Pacific Islander, or Native American race/ethnicity
- History of gestational diabetes or delivery of infant weighing ≥9 lb
- Polycystic ovary syndrome
- Overweight, especially abdominal obesity
- Cardiovascular disease, hypertension, dyslipidemia, or other features of metabolic syndrome

Who is likely to benefit from screening?

Diabetes screening is most likely to improve outcomes in patients with risk factors for cardiovascular disease, particularly if treatment goals differ for those with

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and without diabetes. For example, lipid management guidelines suggest a risk-based approach using a risk calculator for initiation of lipid-lowering therapy. However, lipid-lowering therapy is recommended for all patients with diabetes, regardless of underlying risk (11). Thus, knowledge of diabetes status alters the likelihood of recommending treatment and may argue for screening of patients who would otherwise not be candidates for lipid-lowering therapy. However, to date there have been no formal evaluations of the effects of diabetes screening on lipid treatment recommendations.

Diabetes is more likely to be detected in persons with risk factors for it (Box: Risk Factors for Type 2 Diabetes). However, beyond the increased prevalence of disease, there is no consistent evidence supporting improved clinical outcomes with screening, and recommendations are based largely on expert opinion.

Can type 2 diabetes be prevented?

Several high-quality randomized trials have shown that changes in diet and exercise lead to substantial reductions in progression to type 2 diabetes in persons with "prediabetes," defined as impaired fasting glucose level or impaired glucose tolerance. These programs achieved modest weight loss (generally 5%–7%) but were markedly effective.

In a randomized, unblinded, controlled trial of 522 overweight Finnish patients with impaired glucose tolerance (mean age, 55 years), an intervention aimed at a 5% reduction in weight decreased the incidence of newly diagnosed type 2 diabetes from 23% to 11% over 3 years. The intervention involved personal counseling sessions to encourage a reduction in total and saturated fat intake to less than 30% and 10% of energy consumed, respectively; an increase in fiber intake; and moderate exercise for at least 30 minutes per day (12).

The Diabetes Prevention Program, a randomized controlled trial that involved 3234 U.S. patients with prediabetes (mean age, 51 years; mean body mass index, 34 kg/m^2), showed that a lifestyle modification program aimed at a 7% weight loss reduced the cumulative incidence of diabetes from 29% to 14% over 3 years (relative risk, 0.42 [CI, 0.34–0.52]) compared with placebo (13). Ten-year follow-up found persistence of the initial effect of lifestyle modification, although the rates in both groups were similar after the study period, implying that the intervention must be maintained for benefit to continue (14).

A randomized controlled trial involving 577 Chinese adults with impaired glucose tolerance assigned to diet, exercise, both, or neither found that incidence of diabetes over 6 years was 68% among persons in the "neither" group, 44% in the diet group, 41% in the exercise group, and 46% in the "both" group. All 3 interventions resulted in statistically significant reductions in progression to diabetes (15).

Some medications can prevent diabetes onset in patients with prediabetes.

In the medication group of the Diabetes Prevention Program, metformin (850 mg twice daily) reduced cumulative incidence of diabetes from 29% to 22% over 3 years (relative risk, 0.69 [CI, 0.57–0.83]), a significant reduction but smaller than that observed with the lifestyle intervention (13). Ten-year follow-up again showed persistence of the initial effect, although the rates in the metformin and placebo groups were similar after the study period (14).

In the randomized, double-blind, international STOP-NIDDM (Study to Prevent Non-Insulin-Dependent Diabetes Mellitus), which involved 1429 patients with impaired glucose tolerance, acarbose (100 mg 3 times daily) reduced incidence of diabetes from 42% to 32% compared with placebo. The relative risk reduction over 3 years was 25% (16).

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The DREAM (Diabetes Reduction Assessment with ramipril and rosiglitazone Medication) trial randomly assigned 5269 adults without previous cardiovascular disease but with impaired fasting glucose level, impaired glucose tolerance, or both to rosiglitazone, 8 mg/d, or placebo and to rosiglitazone, up to 15 mg/d, or placebo. After a median of 3 years, 11.6% of patients who received rosiglitazone developed diabetes or died versus 26.0% of those who received placebo (HR, 0.40 [CI, 0.35–0.46]). Cardiovascular event rates were statistically similar in both groups (17).

The implications of diabetes screening for prevention have not been fully elucidated, but screening is generally necessary to identify the high-risk prediabetes population. However, because lifestyle and dietary modification are likely to benefit everyone regardless of diabetes status, the advantages of labeling patients as "prediabetic" are uncertain. The most reasonable option is to consider screening in persons who are at particularly high risk (those with multiple risk factors) and to implement preventive measures, such as medication therapy and lifestyle modification, in persons with high-risk prediabetes (18).

Screening and Prevention... Little trial evidence shows clinical benefit from broad-based screening programs for type 2 diabetes. The single large-scale trial did not show benefit at 10 years, and modeling studies have yielded inconsistent results. However, programs aimed at modest weight loss can prevent diabetes in persons with prediabetes, and medication may be indicated for those who cannot achieve lifestyle goals. Because diet and exercise programs tend to be beneficial regardless of blood glucose levels, screening may be best for persons at particularly high risk, especially to identify those who may benefit from medications to prevent diabetes (18). Guidelines for lifestyle change suggest that loss of about 7% of body weight and 150 minutes of exercise per week are enough to substantially reduce diabetes risk.

CLINICAL BOTTOM LINE

Diagnosis and Evaluation

What are the diagnostic criteria for type 2 diabetes in nonpregnant adults?

Clinicians should confirm the diagnosis of diabetes in persons with classic symptoms (polyuria, polydipsia, polyphagia, and weight loss) or evidence of complications (retinopathy, nephropathy, neuropathy, impotence, acanthosis nigricans, or frequent infections). Many tests can be used to diagnose type 2 diabetes; however, because of ease of use and reliability, the current recommendation is to measure hemoglobin A_{1c} (HbA_{1c}) levels, with a threshold of 6.5% or higher being diagnostic for diabetes (6). Other tests can also be used, including measurement of fasting plasma glucose levels, with a level of 7.0 mmol/L (126 mg/dL) or higher confirmed by testing on a different day being diagnostic for diabetes. Alternatively, diabetes can be diagnosed in persons with classic symptoms and a nonfasting glucose level of 11.1 mmol/L (200 mg/dL) or higher confirmed by a second test. Finally, an oral glucose tolerance test (OGTT)

Table 1. **Diagnostic Criteria for Type 2 Diabetes**

Diagnosis	*Hemoglobin A_{1c} Level, %*	*Fasting Plasma Glucose Level*	
		mmol/L	mg/dL
Prediabetes	5.7–6.4	5.6–6.9	100–125
Diabetes	≥6.5	≥7.0	≥126

could be used, with a 2-hour plasma glucose level of 11.1 mmol/L (200 mg/dL) considered diagnostic for diabetes.

Prediabetes can be diagnosed in persons with an HbA_{1c} level of 5.7%–6.4%, a fasting glucose level of 5.6–6.9 mmol/L (100-125 mg/dL), or a 2-hour plasma glucose level of 7.8–11.0 mmol/L (140-199 mg/dL) on an OGTT (**Table 1**).

What should the initial evaluation of patients with newly diagnosed type 2 diabetes include?

Clinicians should conduct a detailed history and physical examination, including review of diet and physical activity and assessment of cardiovascular, cerebrovascular, and erectile dysfunction. The initial evaluation should include blood pressure measurement and inspection for possible diabetes complications via cardiovascular, neurologic, skin, and foot examinations. Laboratory tests should assess levels of glucose control (HbA_{1c} level), cholesterol levels, and nephropathy (urinary microalbumin–creatinine ratio and serum creatinine). Liver function testing should be considered in those who are likely to need lipid-lowering therapy and because nonalcoholic fatty liver disease is prevalent among patients with type 2 diabetes. At diagnosis, ophthalmologic assessment should be done to evaluate for retinopathy.

Diagnosis and Evaluation... Type 2 diabetes is common and should be considered when patients present with suggestive symptoms (such as polyuria or polydipsia), signs (such as acanthosis nigricans), or complications (such as retinopathy) of the disease. The diagnosis can be confirmed by HbA_{1c} levels of 6.5% or higher or fasting plasma glucose levels above 7.0 mmol/L (>126 mg/dL) on 2 occasions at least 1 day apart. Random plasma glucose levels and an OGTT can also be used to diagnose type 2 diabetes. Newly diagnosed patients should be examined for hypertension, as well as neurologic, ophthalmologic, and podiatric complications. The initial laboratory evaluation should include an assessment of glucose control, a lipid profile, and measurement of urinary microalbumin–creatinine ratio.

CLINICAL BOTTOM LINE

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What are the components of nondrug therapy for patients with type 2 diabetes?

Lifestyle changes, primarily diet and exercise, are the cornerstones of management of type 2 diabetes and should be considered first-line therapy unless severe hyperglycemia requires immediate medical treatment. No one diet or exercise regimen is appropriate for all patients with diabetes, and an individualized assessment should be used to develop a feasible strategy. The American Diabetes Association lifestyle management guidelines (19) can be accessed at http://care.diabetesjournals.org/content/42/Supplement_1/S46.

In a study of patients with newly diagnosed type 2 diabetes, diet initially reduced HbA_{1c} levels by 2.25%. However, control deteriorated over time, and most patients eventually required drug therapy (20).

A meta-analysis of 34 randomized trials that compared exercise (aerobic with or without resistance training) versus no exercise in patients with type 2 diabetes showed that exercise significantly improved glycemic control and reduced waist circumference and blood pressure, even though neither weight nor body mass index was significantly reduced (21).

What is the role of home glucose monitoring?

Home glucose monitoring allows patients and providers to assess glucose control longitudinally, can provide real-time feedback on the effects of glucose treatments, and should be used for testing if symptoms of hyperglycemia or hypoglycemia are present. It is considered part of the standard of care for persons receiving insulin therapy to allow sensible dose adjustments, particularly with shorter-acting insulin preparations. The optimum frequency of home monitoring has not been formally evaluated and is usually at the discretion of the patient and provider. Its role in guiding oral therapy is unclear; a formal evidence review found a small reduction in HbA_{1c} levels at 6 months, but this benefit subsided by 12 months, suggesting that self-monitoring has no sustained effect (22).

Patients are generally advised to monitor fasting and preprandial glucose levels. However, postprandial measurement may be helpful in persons with elevated HbA_{1c} levels despite normal fasting levels. Observational data suggest that postprandial glucose excursions may be tied to cardiovascular risk (23), leading some experts to recommend routine postprandial monitoring. However, thus far no trials have shown that treatment of these excursions reduces cardiovascular risk.

What is the target HbA_{1c} level?

No single HbA_{1c} target applies to all patients with type 2 diabetes. Most organizations and quality measurement groups advocate a target of 7% or less for most patients, based on the results of the UKPDS (U.K. Prospective Diabetes Study) (20). However, the results from the UKPDS and other studies of intensive glucose control are inconsistent.

In the UKPDS, patients with newly diagnosed diabetes were randomly assigned to more versus less intensive glucose control. Patients in the intensive group achieved an HbA_{1c} level of 7.0% compared with 7.9% among those in the control group. Persons maintaining better control had reduced risk for early, asymptomatic microvascular outcomes but did not have clear benefits for either cardiovascular outcomes or symptomatic microvascular complications, such as vision loss, amputation, or end-stage renal disease (20). In a 20-year follow-up

study, the group initially assigned to intensive control had lower rates of myocardial infarction (16.8 vs. 19.6 per 1000 patient-years) and death (26.8 vs. 30.3 per 1000 patient-years), even though differences in glycemic control were not maintained between groups (24).

The VADT (Veterans Affairs Diabetes Trial) studied 1791 veterans with diabetes (mean age, 60.4 years; mean diabetes duration, 11.5 years; 40% with a prior cardiovascular event). The group assigned to intensive control had a target HbA_{1c} level that was 1.5% lower than in the control group. The achieved levels were 6.9% in the intensive group and 8.4% in the control group. No significant effects on the primary end point (a composite of cardiovascular events, heart failure, vascular surgery, and amputation), total mortality, or microvascular events were found (25). In a 15-year follow-up study, patients randomly assigned to intensive control did not have lower rates of mortality (HR, 1.02 [CI, 0.88–1.18]) or cardiovascular disease (HR, 0.91 [CI, 0.78–1.06]). However, during a median of 7.1 years while HbA_{1c} levels differed between groups, there was a reduction in cardiovascular events (HR, 0.83 [CI, 0.70–0.99]) (26).

These results are not fully in accord with each other but suggest that there may be a small benefit to cardiovascular risk with treatment to an HbA_{1c} level of about 7%. This possible benefit, plus a presumed eventual benefit in microvascular outcomes that will likely take more than 20 years to realize, has led the American College of Physicians to suggest an HbA_{1c} goal between 7% and 8% for most patients (27). However, despite the aforementioned evidence, some experts advocate more aggressive targets for glycemic control or treatment to near-normal glucose levels when possible (HbA_{1c} level <6%).

In ACCORD (Action to Control Cardiovascular Risk in Diabetes), a study of 10 251 U.S. patients with diabetes (mean age, 62.2 years; median diabetes duration, 10 years; 35% with a prior cardiovascular event), the group assigned to intensive therapy had target HbA_{1c} levels less than 6.0%, whereas the group assigned to conventional therapy had target levels ranging from 7.0%–7.9%. The achieved levels were 6.4% and 7.5%. The trial was stopped early because of a 22% increase in total mortality in the intensive control group (5.0% vs. 4.0%; P = 0.04). The overall main end point (nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death) did not differ between groups. Hypoglycemia and weight gain were also more prevalent in the intensive control group (28). Long-term follow-up of this population suggested an ongoing increase in risk for cardiovascular events (29).

ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron - MR Controlled Evaluation), a multinational study of 11 140 patients with diabetes (mean age, 66 years; mean diabetes duration, 8 years; 32% with a prior cardiovascular event), comprised an intensive control group with a target HbA_{1c} level of 6.5% or lower and a control group. The HbA_{1c} level was 6.5% in the intensive control group and 7.3% in the control group. The intensive control group had reduced nephropathy (4.1% vs. 5.2%; P = 0.006), but there were no differences in cardiovascular events or mortality (30).

Interpretation and reconciliation of the results of the major glucose-lowering trials are difficult. Moderate glucose control (mean HbA_{1c} level of 7%) may eventually provide small benefit in decreasing cardiovascular events and mortality and in early asymptomatic microvascular outcomes. It is likely but has not been proved that longer-term benefit in symptomatic microvascular outcomes, such as vision loss, end-stage renal disease, and amputation, will eventually occur, but only in the distant future because such benefits have not been demonstrated even in studies with 20 years of follow-up. More aggressive control (for example, HbA_{1c} target <6.5%), at least in the shorter term, does not seem to provide substantial benefit and may increase mortality due to higher rates of cardiovascular events. Further, it is unclear whether specific subgroups of patients are more prone to harms or benefits as the result of aggressive control.

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53. Billings LK, Doshi A, Gouet D, et al. Efficacy and safety of IDegLira versus basal-bolus insulin therapy in patients with type 2 diabetes uncontrolled on metformin and basal insulin: the DUAL VII randomized clinical trial. Diabetes Care. 2018;41:1009-16. [PMID: 29483185]
54. Cushman WC, Evans GW, Byington RP, et al; ACCORD Study Group. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med. 2010; 362:1575-85. [PMID: 20228401]
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56. Qaseem A, Wilt TJ, Rich R, et al; Clinical Guidelines Committee of the American College of Physicians and the Commission on Health of the Public and Science of the American Academy of Family Physicians. Pharmacologic treatment of hypertension in adults aged 60 years or older to higher versus lower blood pressure targets: a clinical practice guideline from the American College of Physicians and the American Academy of Family Physicians. Ann Intern Med. 2017;166: 430-7. [PMID: 28135725]
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58. LaRosa JC, Grundy SM, Waters DD, et al; Treating to New Targets (TNT) Investigators. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med. 2005; 352:1425-35. [PMID: 15755765]

The most logical conclusion from these studies is that moderate control (HbA_{1c} level of 7%–8%, which may vary depending on diabetes duration) will probably provide the majority of achievable benefit for most people with type 2 diabetes because most of them are older than 65 years and are therefore less likely to benefit from intensive control given the long time horizon but are also more likely to experience treatment-related harms. However, because younger or otherwise healthy patients with a longer life expectancy (≥20 years) may eventually realize benefit from more intensive control (for example, HbA_{1c} level <7%), glycemic targets should be adjusted depending on life expectancy and comorbid conditions. Evidence from modeling studies suggests that the time horizon for benefit may cause the burden of therapy (particularly injectable agents) to outweigh the benefits for many patients with type 2 diabetes (31).

When should treatment include drugs?

Once an HbA_{1c} goal has been established, pharmacologic management should be instituted if diet and exercise do not achieve the goal. In general, aside from patients with mild HbA_{1c} elevations, if diet and exercise do not accomplish the targeted reduction in glycemic values within approximately 6–8 weeks, pharmacologic therapy should be initiated. Patients with severe hyperglycemia or symptoms may require pharmacologic intervention immediately, sometimes with insulin.

How should physicians select therapies from among the many drug options other than insulin?

Table 2 provides an overview of the classes of noninsulin agents available to treat type 2 diabetes. Studies that may help to guide the selection of treatments for patients with type 2 diabetes are outlined here.

The UKPDS found that, in patients who exceeded ideal body weight by 20%, metformin was superior to sulfonylureas and insulin in reducing mortality despite identical levels of glycemic control (32). Metformin was also associated with lower rates of hypoglycemia and weight gain than insulin or sulfonylureas. Metformin should not be used in persons with severe renal insufficiency (glomerular filtration rate <30 mL/min/1.73 m^2), acute decompensated heart failure, or severe liver disease.

If metformin is contraindicated or not tolerated, the choice of oral agent should be dictated by patient preferences regarding potential adverse effects, efficacy, and cost. Although there was little known difference between drug classes in the past, more recent data show that some drug classes provide benefit in cardiovascular and renal outcomes. Of note, this benefit may be independent of glucose control (33).

In the EMPA-REG trial, 7020 patients with type 2 diabetes and high cardiovascular risk were randomly assigned to placebo or to 10 or 25 mg of the sodium–glucose cotransporter-2 (SGLT-2) inhibitor empagliflozin. The pooled empagliflozin group had a composite cardiovascular risk of 10.5% versus 12.1% in the placebo group (HR, 0.86 [CI, 0.74–0.99]). There was also a significant reduction in all-cause mortality (5.7% vs. 8.3%; HR, 0.68 [CI, 0.57–0.82]), with the difference largely explained by reductions in cardiovascular mortality (34). Renal outcomes also improved in this trial, with lower rates of doubling of serum creatinine level and initiation of renal replacement therapy (35).

In the CREDENCE (Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation) trial, 4401 patients

who had type 2 diabetes, a glomerular filtration rate of 30–89 mL/min/1.73 m^2, and albuminuria and were using renin–angiotensin blockade were randomly assigned to canagliflozin or placebo. There was a significant reduction in the composite end point of end-stage renal disease, doubling of creatinine level, or death due to renal or cardiovascular causes (43.2 vs. 61.2 per 1000 patient-years; HR, 0.70 [CI, 0.59–0.82]). Reductions were seen in renal outcomes, including end-stage renal disease, and in cardiovascular outcomes (36).

In the DECLARE–TIMI 58 (Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58) trial, 17 160 patients with type 2 diabetes (10 186 without baseline cardiovascular disease) were randomly assigned to dapagliflozin or placebo, with a primary outcome of cardiovascular death, myocardial infarction, or stroke and a second composite of cardiovascular death and hospitalization for heart failure (37). Secondary outcomes included a composite renal failure outcome and all-cause mortality. The trial found no difference in the primary outcome but reductions in hospitalization for heart failure (HR, 0.73 [CI, 0.61–0.88]) and renal end points (HR, 0.76 [CI, 0.67–0.87]).

A trial randomly assigned 9340 patients with type 2 diabetes and high cardiovascular risk to the glucagon-like peptide-1 (GLP-1) receptor agonist liraglutide or placebo. Over 3.8 years, there was a lower rate of a composite of cardiovascular events with liraglutide (13.0% vs. 14.9%; HR, 0.87 [CI, 0.78–0.97]), including a reduction in total mortality (8.2% vs. 9.6%; HR, 0.85 [CI, 0.74–0.97]) and cardiovascular mortality (4.7% vs. 6.0%; HR, 0.78 [CI, 0.66–0.93]) (38).

A trial randomly assigned 3297 patients with type 2 diabetes and high cardiovascular risk (83.0% with prior cardiovascular or chronic kidney disease) to once-weekly semaglutide or placebo. Patients who received semaglutide had lower risk for a composite cardiovascular end point (6.6% vs. 8.9%; HR, 0.74 [CI, 0.58–0.95]). There were no differences in mortality. Rates of nephropathy were reduced in the semaglutide group (3.8% vs. 6.1%; HR, 0.64 [CI, 0.46–0.88]), but rates of worsening retinopathy requiring treatment were higher (2.0% vs. 1.8%; HR, 1.76 [CI, 1.11–2.78]) (39). In a trial of oral semaglutide versus placebo, a composite cardiovascular end point was not significantly reduced, but total mortality was (1.4% vs. 2.8%; HR, 0.51 [CI, 0.31–0.84]),

59. Cannon CP, Braunwald E, McCabe CH, et al; Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 Investigators. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med. 2004;350:1495-504. [PMID: 15007110]
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Table 2. **Noninsulin Medications Available in the United States for Type 2 Diabetes**

Drug Class	*Name*	*Initial Dose*	*Maximum Dose*	*Usual Dose*
Biguanides	Metformin	500 mg twice daily or 850 mg/d	2550 mg/d	500–1000 mg twice daily
	Metformin extended release	500 mg/d	2000 mg/d	1500–2000 mg/d
Sulfonylureas	Glimepiride	1–2 mg/d	8 mg/d	4 mg/d
	Glipizide	2.5–5 mg/d	40 mg/d	10–20 mg/d (or twice daily)
	Glipizide sustained release	5 mg/d	20 mg/d	5–20 mg/d (or twice daily)
	Glyburide	2.5–5 mg/d	20 mg/d	5–20 mg/d (or twice daily)
	Glyburide micronized	0.75–3 mg/d	12 mg/d	3–12 mg/d (or twice daily)
Thiazolidinediones	Pioglitazone	15–30 mg/d	45 mg/d	15–45 mg/d
	Rosiglitazone	4 mg/d (or twice daily)	8 mg/d	4–8 mg/d (or twice daily)
α-Glucosidase inhibitors	Acarbose	25 mg/d (with meals)	100 mg 3 times daily	50–100 mg 3 times daily
	Miglitol	25 mg/d (with meals)	100 mg 3 times daily	25–100 mg 3 times daily
Nonsulfonylurea insulin secretagogues	Repaglinide	0.5 mg before meals	4 mg before meals (16 mg/d); wait 1 wk between dose increases	0.5–4 mg with meals
	Nateglinide	120 mg 3 times daily before meals (60 mg 3 times daily if near glycemic goals)	120 mg 3 times daily before meals	60–120 mg 3 times daily before meals
Dipeptidyl peptidase-4 inhibitors	Sitagliptin	100 mg/d	100 mg/d	100 mg/d
	Saxagliptin	2.5 mg/d	5 mg/d	5 mg/d
	Linagliptin	5 mg/d	5 mg/d	5 mg/d
	Alogliptin	25 mg/d	25 mg/d	25 mg/d
Sodium–glucose cotransporter-2 inhibitors	Canagliflozin	100 mg/d	300 mg/d	100–300 mg/d
	Empagliflozin	10 mg/d	25 mg/d	10–25 mg/d
	Dapagliflozin	5 mg/d	10 mg/d	5–10 mg/d
	Ertugliflozin	5 mg/d	15 mg/d	5–15 mg/d
Glucagon-like peptide-1 agonists*	Exenatide	5 mcg twice daily (≤60 min before meals)	10 mcg twice daily	5–10 mcg/d
	Exenatide extended release	2 mg once per week	2 mg once per week	2 mg once per week
	Liraglutide	0.6 mg/d	1.8 mg/d	1.2 mg/d
	Dulaglutide	0.75 mg/wk	1.5 mg/wk	0.75–1.5 mg/wk
	Lixisenatide	10 mcg/d	20 mcg/d	20 mcg/d
	Semaglutide	0.25 mg/wk	1 mg/wk	0.5 mg/wk
	Semaglutide (oral)	7 mg/d	14 mg/d	7–14 mg/d

** All are injectable aside from oral semaglutide.*

63. Bowman L, Mafham M, Wallendszus K, et al; ASCEND Study Collaborative Group. Effects of aspirin for primary prevention in persons with diabetes mellitus. N Engl J Med. 2018;379:1529-39. [PMID: 30146931]
64. Sussman JB, Vijan S, Choi H, et al. Individual and population benefits of daily aspirin therapy: a proposal for personalizing national guidelines. Circ Cardiovasc Qual Outcomes. 2011;4:268-75. [PMID: 21487091]
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66. Brenner BM, Cooper ME, de Zeeuw D, et al; RENAAL Study Investigators. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med. 2001;345: 861-9. [PMID: 11565518]
67. Hansson L, Lindholm LH, Niskanen L, et al. Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomised trial. Lancet. 1999;353: 611-6. [PMID: 10030325]
68. Parving HH, Lehnert H, Bröchner-Mortensen J, et al; Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study Group. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. N Engl J Med. 2001;345:870-8. [PMID: 11565519]
69. Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm - 2019 executive summary. Endocr Pract. 2019;25:69-100. [PMID: 30742570]

driven primarily by a reduction in cardiovascular mortality (40).

The REWIND trial compared dulaglutide with placebo in 9901 persons with type 2 diabetes and high cardiovascular risk (31.5% had a prior cardiovascular event; the remainder had various combinations of cardiovascular risk factors) (41). The primary outcome was a composite of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death. Dulaglutide led to a reduction in cardiovascular outcomes (HR, 0.88 [CI, 0.79–0.99]). In a post hoc exploratory analysis, the investigators also found a reduction in renal end points (HR, 0.85 [CI, 0.77–0.93]), primarily new-onset macroalbuminuria (42).

Taken together, these data strongly suggest that newer agents, particularly SGLT-2 inhibitors and GLP-1 receptor agonists, reduce total mortality, primarily through a reduction in cardiovascular mortality. These agents should therefore be strongly considered as first-line agents in persons unable to take metformin; choices between them may be dictated by patient preferences (injectable vs. oral agents, adverse effect profile) and individual risk factors. For example, liraglutide is approved by the U.S. Food and Drug Administration as a weight loss medication and may be particularly helpful in patients with obesity (43).

Most patients with diabetes have worsening glycemic control over time. Increasing the dose of existing oral agents is generally the first step to maintain control, but the response from dose escalation is limited. Patients therefore often require the addition of 1 or more oral agents. On the basis of the aforementioned trials, SGLT-2 inhibitors and GLP-1 receptor agonists should both be considered for second- and/or third-line treatment as needed. Dipeptidyl peptidase-4 inhibitors are reasonable options for glucose control, although trials have not demonstrated the cardiovascular benefits seen with metformin, SGLT-2 inhibitors, and GLP-1 receptor agonists (44–46). Sulfonylureas can cause hypoglycemia and weight gain (20) and have less convincing evidence of cardiovascular benefits than other drugs. Thiazolidinediones can increase risk for heart failure and fracture, although they probably do not increase total cardiovascular events (47, 48). Short-acting agents, such as α-glucosidase inhibitors (acarbose, miglitol) and nonsulfonylurea insulin secretagogues (nateglinide, repaglinide), are administered before meals and may be useful in persons with inconsistent mealtimes. Several combination formulations of oral agents are available and may provide advantages in convenience or cost for some patients. Adverse effects should also be considered when choosing agents.

When should physicians consider insulin therapy?

Patients who are unable to achieve glycemic goals with noninsulin medications, whether alone or in combination, are candidates for insulin therapy. Other indications include a desire for rapid reduction of blood glucose levels in persons with severe symptoms; some experts recommend early initiation for persons with markedly elevated HbA_{1c} levels at diagnosis because of the possibility of prolonging β-cell function (29).

Many insulin formulations are available, separated primarily by their onset of action and duration (**Table 3**). No particular regimen is clearly superior; in 1 randomized trial, median HbA_{1c} levels were similar among biphasic, prandial, and basal insulin, although rates of hypoglycemia were lowest in the basal insulin group (49). Most patients have a 1%–2% decrease in HbA_{1c} levels

after starting insulin therapy (50, 51). When intensive glycemic control is planned, a fasting glucose level below 6.7 mmol/L (<120 mg/dL) is a reasonable goal. The primary risks of insulin therapy are hypoglycemia and weight gain (20). Patients must be warned about these possibilities and educated to recognize and treat hypoglycemia.

At the start of insulin therapy, most patients can be treated with a once-daily injection. Those without hypoglycemia can often be effectively treated with a single bedtime dose of neutral protamine Hagedorn (NPH) or basal analogue insulin combined with an oral agent, such as metformin. This can reduce insulin dosing to once daily at bedtime, which is often more acceptable to patients (52).

In patients with normal fasting glucose levels or high risk for hypoglycemia, a basal analogue may be the first choice, although they are considerably more expensive than NPH insulin. Evidence suggests lower rates of hypoglycemia with basal analogues, particularly newer, long-acting analogues, such as degludec. Typical starting doses of insulin are 0.1–0.2 U/kg of body weight.

Some patients need twice-daily insulin to achieve glycemic targets, but more frequent injections (such as preprandial injections) are often not necessary for persons with type 2 diabetes. However, if HbA_{1c} levels remain elevated despite normal fasting glucose levels, prandial insulin may be considered. For those receiving high doses of insulin, the U-500 (highly concentrated) formulation can be used.

Fixed-dose combinations, such as basal insulin and GLP-1 receptor agonists, are also available. These achieve glycemic control similar to that with basal plus prandial insulin injections but are associated with lower rates of hypoglycemia and often avoid the weight gain associated with insulin (53).

Aside from glycemic control, what other clinical interventions reduce complications?

Hypertension is a major risk factor for diabetes complications. However, aggressive treatment to a blood pressure target of 120/80 mm Hg does not lead to improved diabetes outcomes compared with a target of 140/90 mm Hg (54). Despite this, the current guidelines from the American College of Cardiology and the American Heart Association suggest a blood pressure target of 130/80 mm Hg for patients with diabetes (55), although other organizations, including the American College of Physicians, recommend a target of 140/90 mm Hg (56).

Current evidence is not clear on the optimal choice of drugs for blood pressure control. All drug classes are effective, although many patients use angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs) as the initial agent for blood pressure control because of their beneficial renal effects. Other agents should be added as needed to achieve blood pressure goals, with choices dictated by comorbid conditions, adverse effects, and patient preferences.

Table 3. **Onset and Mechanisms of Action of Various Types of Insulin**

Class	*Onset of Action*	*Peak of Action*	*Duration of Action*
Rapid-acting (insulin analogues lispro, aspart, glulisine)	≤30 min	0.5–3 h	3–5 h
Short-acting (human regular)	0.5–1 h	2–5 h	Up to 12 h
Concentrated insulin (U-500)	0.5–1 h	6–8 h	Up to 24 h
Intermediate-acting (human NPH)	1.5–4 h	4–12 h	Up to 24 h
Long-acting (insulin analogues glargine, detemir, degludec)	0.8–4 h	Relatively peakless	Up to 24–42 h
Ultra-long-acting (glargine U-300)	6 h	Relatively peakless	Up to 5 d to steady state
Human insulin mixtures			
70% NPH/30% regular	0.5–2 h	2–12 h	Up to 24 h
50% NPH/50% regular	0.5–2 h	2–5 h	Up to 24 h
Analogue mixtures			
75% lispro protamine/25% lispro	<15 min	1–2 h	Up to 24 h
50% lispro protamine/50% lispro	<15 min	1–2 h	Up to 24 h
70% aspart protamine/30% aspart	10–20 min	1–4 h	Up to 24 h
Inhaled insulin (Afrezza [MannKind])	12–15 min	1 h	2.5–3 h

NPH = neutral protamine Hagedorn.

Use of lipid-lowering agents is also a priority in patients with diabetes. For primary prevention, recent guidelines suggest using a risk-based approach to select patients for lipid-lowering therapy. Nearly all patients with diabetes who are older than 40 years meet treatment thresholds and are therefore likely to benefit from statin therapy, regardless of their initial low-density lipoprotein cholesterol level (11). Optimal low-density lipoprotein cholesterol targets, particularly in primary prevention, are not well established; however, most trial evidence suggests that moderate statin doses are recommended for most patients with type 2 diabetes (57). For secondary prevention, statin use should be encouraged in almost all patients. There is evidence that higher-dose statins (for example, simvastatin or atorvastatin, 80 mg) may be more effective than lower-dose statins in patients with existing coronary artery disease (58, 59). Combination therapy with statins and fibrates does not seem to improve cardiovascular outcomes in patients with diabetes (60), although ezetimibe may have modest additional benefit in high-risk patients already using a statin (61). Newer agents, such as proprotein convertase subtilisin/kexin type 9 inhibitors, may also offer modest benefit in high-risk patients who are already receiving maximal tolerated statin doses, but these agents are injectable and expensive (62).

The benefit of aspirin therapy in preventing cardiovascular disease in patients with type 2 diabetes is unclear. A recent randomized controlled study of aspirin in patients with type 2 diabetes found an absolute reduction in serious vascular events of 1.1% but an increase in bleeding risk of 0.9%, suggesting no net benefit (63). Although the evidence is not clear, consideration of underlying cardiovascular and bleeding risk may identify patients who are most likely to benefit from aspirin therapy (64). Patients with a history of heart disease should take 75–325 mg of aspirin per day.

Retinal examination reduces incidence of vision loss in patients with type 2 diabetes. The frequency of examination for patients without high-risk retinal lesions can range from 1–3 years depending on underlying risk (65). Measurement of the urinary microalbumin–creatinine ratio allows detection of early diabetic nephropathy; albuminuria is also a risk factor for cardiovascular disease. Clinical trials have shown that treatment of albuminuria with ACE inhibitors or ARBs reduces risk for progression to end-stage renal disease (66–68). As noted earlier, newer classes of glucose-lowering agents, particularly SGLT-2 inhibitors, also show impressive reductions in renal disease outcomes (35, 36). Neuropathy screening and foot care are essential in reducing risk for amputation. Painful neuropathy is uncommon in type 2 diabetes but can be treated with various agents (**Table 4**).

How frequently should physicians see patients with type 2 diabetes, and what should be included in follow-up visits?

There is no direct evidence on the ideal frequency of visits for patients with type 2 diabetes. Expert opinion and the recommended frequency of monitoring of HbA_{1c} levels suggest that quarterly visits are reasonable. For patients with stable disease, this can be reduced to every 6 months (3).

When should a specialist be consulted?

Meta-analyses show that diabetes education by a certified educator is effective in improving many key domains in diabetes care, including glycemic control, although the durability of these effects is not clear.

Consultation with an endocrinologist is helpful for addressing questions about diagnosis or when glucose management becomes difficult (for example, in patients with highly labile blood glucose levels). Patients who are pregnant or are contemplating pregnancy should be referred for assistance with glucose control because poor control is associated with adverse fetal outcomes.

Ophthalmologic examination, whether by an ophthalmologist or optometrist or via retinal photography, should be done every 1–3 years depending on prior examination results and level of glucose control. Other conditions, such as known retinopathy, glaucoma, and cataracts, may necessitate more frequent examination.

Nephrologic evaluation is required for patients with a glomerular filtration rate less than 30 mL/min/1.73 m^2. Earlier referral can be considered, although interventions to reduce progression center around risk factor control and use of ACE inhibitors or ARBs as outlined earlier. Referral should also be considered if the origin of renal insufficiency is unclear. Patients with hyperkalemia, acidemia, or difficulty with controlling blood pressure may also benefit.

Table 4. **Therapies to Reduce Neuropathy Symptoms***

Agent	*Notes*
Tricyclic antidepressants	RCT evidence shows efficacy Start with small bedtime dose and titrate to efficacy Anticholinergic adverse effects common; use with particular caution in elderly persons
Duloxetine	Approved for diabetic neuropathy by the U.S. Food and Drug Administration Not appropriate with liver disease or substantial alcohol use
Capsaicin cream	RCT evidence shows efficacy Causes burning sensation that often decreases over time
Antiepileptic agents	Carbamazepine, gabapentin, and pregabalin have RCT evidence of efficacy

RCT = randomized controlled trial.
** There are no data on the relative efficacy of the medications listed. Patient preference should be considered for dosing and administration, along with comorbid conditions and adverse effect profiles, to determine initial choice of agent.*

Podiatric evaluation is helpful for management of lesions, such as calluses or deformities, which require intervention to reduce risk for foot ulcers and amputation.

When should patients with type 2 diabetes be hospitalized?

Some patients with severe, symptomatic hyperglycemia may require hospitalization, particularly at the time of diagnosis. Diabetic ketoacidosis or hyperosmolar coma requires hospitalization for management. Diabetes complications may require hospitalization; for example, cellulitis or osteomyelitis may require intravenous antibiotics or surgery.

Treatment... The goal of treating type 2 diabetes is to achieve glycemic targets on an individual basis according to life expectancy and patient preferences. Patients should achieve at least moderate control (HbA_{1c} level <8.0% in most cases) to minimize hyperglycemia and because microvascular risk increases exponentially above this level. More aggressive targets (for example, <7.0%) should be reserved for patients with a long life expectancy because reductions in advanced diabetes complications take 15–20 years to accrue.

CLINICAL BOTTOM LINE

What measures do U.S. stakeholders use to evaluate the quality of care for patients with type 2 diabetes?

The National Committee on Quality Assurance, through the Healthcare Effectiveness Data and Information Set program, recommends several measures of diabetes care (see the Box: Quality Measures for Diabetes). It is important to note that these recommendations do not perfectly align with clinical targets.

Quality Measures for Diabetes

Eye examination

- Percentage of patients who received a retinal or dilated eye examination by an eye care professional (optometrist or ophthalmologist) during the reporting year or during the prior year if patient has low risk for retinopathy (not taking insulin, HbA_{1c} level <8.0%, and no evidence of retinopathy in the prior year)

HbA_{1c} management

- Percentage of patients who have had ≥1 HbA_{1c} test in the measurement year

HbA_{1c} management control

- Percentage of patients whose most recent HbA_{1c} level was <8.0% (good control)
- Percentage of patients whose most recent HbA_{1c} level was >9.0% (poor control)
- Percentage of patients whose most recent HbA_{1c} level was <7.0% (selected population likely to benefit from tight control)

Blood pressure management

- Percentage of patients with blood pressure <140/90 mm Hg documented in the past year

Medical attention for nephropathy (use of an ACE inhibitor/ARB or screening for albuminuria)

What do professional organizations recommend regarding the care of patients with type 2 diabetes?

Several professional associations publish guidelines for diabetes care. These guidelines do not always agree on all aspects, and the nature of the organization inevitably influences its recommendations. The following organizations are 4 of the most commonly cited sources.

The American College of Physicians conducted systematic reviews of the evidence to inform guidelines on glucose management in patients with type 2 diabetes (27). Blood pressure control is discussed in a separate guideline (56).

The American Diabetes Association releases standards of diabetes care annually. The standards are broad and encompass most relevant areas of screening, prevention, and management (3).

The American Association of Clinical Endocrinologists updated its guidelines in 2019 (69).

The U.S. Preventive Services Task Force recommends screening for elevated blood glucose level (not specifically diabetes) every 3 years in adults who are at increased risk for diabetes (see the Box: Risk Factors for Type 2 Diabetes). This recommendation is based on the evidence supporting the efficacy of diabetes prevention programs. More detail and finalized recommendations can be accessed at www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/screening-for-abnormal-blood-glucose-and-type-2-diabetes.

In the Clinic
Tool Kit

Type 2 Diabetes

Patient Information

https://medlineplus.gov/howtopreventdiabetes.html
https://medlineplus.gov/spanish/howtopreventdiabetes.html
Information in English and Spanish on how to prevent diabetes from the National Institutes of Health MedlinePlus.

www.niddk.nih.gov/health-information/diabetes/overview/what-is-diabetes
www.niddk.nih.gov/health-information/informacion-de-la-salud/diabetes/informacion-general/que-es
Information for patients in English and Spanish on types of diabetes from the National Institute of Diabetes and Digestive and Kidney Diseases.

www.niddk.nih.gov/health-information/diabetes/overview/managing-diabetes
Information for patients on managing diabetes from the National Institute of Diabetes and Digestive and Kidney Diseases.

https://professional.diabetes.org/search/site?f%5B0%5D=im_field_dbp_ct%3A32&retain-filters=1
Patient education library from the American Diabetes Association, in English and other languages.

Information for Health Professionals

https://professional.diabetes.org/content-page/practice-guidelines-resources
The 2019 Standards of Medical Care in Diabetes from the American Diabetes Association, updated yearly.

http://diabetes.acponline.org
Latest information on type 2 diabetes from the American College of Physicians Diabetes Monthly.

www.niddk.nih.gov/health-information/communication-programs/ndep/health-professionals
Information for health professionals on diabetes from the National Institute of Diabetes and Digestive and Kidney Diseases.

WHAT YOU SHOULD KNOW ABOUT TYPE 2 DIABETES

What Is Type 2 Diabetes?

Diabetes is a common condition where there is too much sugar in your blood. Insulin is a hormone that turns sugar into energy. Most people with diabetes make some insulin, but it does not work to keep the blood sugar under control. This is called type 2 diabetes. High sugar levels in your blood over time may lead to:

- Vision loss
- Kidney damage
- Nerve damage
- Foot ulcers
- Heart disease
- Possible amputation from infections

What Are the Signs and Symptoms?

- Extreme thirst and/or hunger
- Fatigue
- Frequent need to urinate
- Unexpected weight loss
- Blurred vision
- Tingling or numbness in the hands or feet

Some people with diabetes may not have symptoms at first and do not know they have the disease.

What Are Other Risk Factors?

- Age 45 years or older
- African American, Hispanic, Asian, Pacific Islander, or Native American race/ethnicity
- Being overweight or obese
- Having a close relative with type 2 diabetes
- A history of diabetes in pregnancy

Can I Prevent It?

A healthy diet and regular exercise may prevent type 2 diabetes. Even a small amount of weight loss and 30 minutes of exercise a day can reduce your risk.

How Is It Diagnosed?

- Your health care provider will ask you about your medical history, including your current diet and exercise regimen, and do a physical examination.
- Diabetes is diagnosed by measuring the level of sugar in your blood. You may need to fast before some tests.
- Your hemoglobin A_{1c} (HbA_{1c}) level is assessed with a simple blood test that measures your average blood sugar over the past 3 months and does not require fasting.

- Your provider will check your blood pressure, cholesterol levels, and kidney function.
- You will need an eye examination to check for any problems.

How Is It Treated?

People with diabetes need to improve blood sugar control in their bodies.

- Lifestyle changes, such as losing weight and exercising regularly, improve blood sugar control without medication.
- If lifestyle changes do not improve blood sugar control, you may need medicine.
- There are many different types of medicines for type 2 diabetes, including several new oral and injectable medicines. Not all people with type 2 diabetes need to take injectable medicines or check their blood sugar at home.
- Talk to your provider about what your average blood sugar target (HbA_{1c} level) should be.
- Make sure your blood pressure and cholesterol are controlled to help prevent complications.
- The best treatment plan for you is one that you can afford and will stick with. Talk about the cost and convenience of treatment plans with your health care provider.

Questions for My Doctor

- Do I need to change my diet and start exercising?
- What is an optimal blood sugar target (HbA_{1c} level) for me?
- Do I have to check my blood sugar? When, and how often?
- What are the symptoms of low blood sugar? What should I do when I have these symptoms?
- How should I care for my feet?
- How often should I make follow-up visits?
- Do I need to see other medical specialists?

For More Information

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American College of Physicians
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American College of Physicians
www.acponline.org/practice-resources/patient-education/online-resources/diabetes

American Diabetes Association
www.diabetes.org/diabetes/type-2

Patient Information