such problems is of paramount importance. Patients with symptoms or signs of neuropathy should check their feet daily and take precautions (footwear) aimed at preventing calluses or ulcerations. If foot deformities are present, a podiatrist should be involved.

Chronic, painful diabetic neuropathy is difficult to treat but may respond to duloxetine, amitriptyline, gabapentin, valproate, pregabalin, or opioids. Two agents, duloxetine and pregabalin, have been approved by the U.S. Food and Drug Administration (FDA) for pain associated with diabetic neuropathy, but no treatments are satisfactory. No direct comparisons of agents are available, and it is reasonable to switch agents if there is no response or if side effects develop. Referral to a pain management center may be necessary. Because the pain of acute diabetic neuropathy may resolve over time, medications may be discontinued as progressive neuronal damage from DM occurs.

Therapy of orthostatic hypotension secondary to autonomic neuropathy is also challenging. A variety of agents have limited success (fludrocortisone, midodrine, clonidine, octreotide, and yohimbine), but each has significant side effects. Nonpharmacologic maneuvers (adequate salt intake, avoidance of dehydration and diuretics, and lower extremity support hose) may offer some benefit.

GASTROINTESTINAL/GENITOURINARY DYSFUNCTION

Long-standing type 1 and 2 DM may affect the motility and function of the gastrointestinal (GI) and genitourinary systems. The most prominent GI symptoms are delayed gastric emptying (gastroparesis) and altered small- and large-bowel motility (constipation or diarrhea). Gastroparesis may present with symptoms of anorexia, nausea, vomiting, early satiety, and abdominal bloating. Microvascular complications (retinopathy and neuropathy) are usually present. Nuclear medicine scintigraphy after ingestion of a radiolabeled meal may document delayed gastric emptying, but may not correlate well with the patient's symptoms. Noninvasive "breath tests" following ingestion of a radiolabeled meal have been developed, but are not yet validated. Although parasympathetic dysfunction secondary to chronic hyperglycemia is important in the development of gastroparesis, hyperglycemia itself also impairs gastric emptying. Nocturnal diarrhea, alternating with constipation, is a feature of DM-related GI autonomic neuropathy. In type 1 DM, these symptoms should also prompt evaluation for celiac sprue because of its increased frequency. Esophageal dysfunction in long-standing DM may occur but is usually asymptomatic.

Diabetic autonomic neuropathy may lead to genitourinary dysfunction including cystopathy and female sexual dysfunction (reduced sexual desire, dyspareunia, reduced vaginal lubrication). Symptoms of diabetic cystopathy begin with an inability to sense a full bladder and a failure to void completely. As bladder contractility worsens, bladder capacity and the postvoid residual increase, leading to symptoms of urinary hesitancy, decreased voiding frequency, incontinence, and recurrent urinary tract infections. Diagnostic evaluation includes cystometry and urodynamic studies.

Erectile dysfunction and retrograde ejaculation are very common in DM and may be one of the earliest signs of diabetic neuropathy (Chap. 67). Erectile dysfunction, which increases in frequency with the age of the patient and the duration of diabetes, may occur in the absence of other signs of diabetic autonomic neuropathy.

TREATMENT GASTROINTESTINAL/GENITOURINARY DYSFUNCTION

Current treatments for these complications of DM are inadequate. Improved glycemic control should be a primary goal, because some aspects (neuropathy, gastric function) may improve. Smaller, more frequent meals that are easier to digest (liquid) and low in fat and fiber may minimize symptoms of gastroparesis. Metoclopramide has been used but is now restricted in both the United States and Europe and not advised for long-term use. Gastric electrical stimulatory devices are available but not approved. Diabetic diarrhea in the absence of bacterial overgrowth is treated symptomatically (Chap. 349).

Diabetic cystopathy should be treated with scheduled voiding or self-catheterization. Drugs that inhibit type 5 phosphodiesterase are effective for erectile dysfunction, but their efficacy in individuals with DM is slightly lower than in the nondiabetic population (Chap. 67). Sexual dysfunction in women may be improved with use of vaginal lubricants, treatment of vaginal infections, and systemic or local estrogen replacement.

CARDIOVASCULAR MORBIDITY AND MORTALITY

CVD is increased in individuals with type 1 or type 2 DM. The Framingham Heart Study revealed a marked increase in PAD, coronary artery disease, MI, and CHF (risk increase from one- to fivefold) in DM. In addition, the prognosis for individuals with diabetes who have coronary artery disease or MI is worse than for nondiabetics. CHD is more likely to involve multiple vessels in individuals with DM. In addition to CHD, cerebrovascular disease is increased in individuals with DM (threefold increase in stroke). Thus, after controlling for all known cardiovascular risk factors, type 2 DM increases the cardiovascular death rate twofold in men and fourfold in women.

The American Heart Association has designated DM as a "CHD risk equivalent," and type 2 DM patients without a prior MI have a similar risk for coronary artery–related events as nondiabetic individuals who have had a prior MI. However, the cardiovascular risk assessment in type 2 DM should encompass a more nuanced approach. Cardiovascular risk is lower and not equivalent in a younger individual with a brief duration of type 2 DM compared to an older individual with long-standing type 2DM. Because of the extremely high prevalence of underlying CVD in individuals with diabetes (especially in type 2 DM), evidence of atherosclerotic vascular disease (e.g., cardiac stress test) should be sought in an individual with diabetes who has symptoms suggestive of cardiac ischemia or peripheral or carotid arterial disease. The screening of asymptomatic individuals with diabetes for CHD, even with a risk-factor scale, is not recommended because recent studies have not shown a clinical benefit. The absence of chest pain ("silent ischemia") is common in individuals with diabetes, and a thorough cardiac evaluation should be considered prior to major surgical procedures.

The increase in cardiovascular morbidity and mortality rates in diabetes appears to relate to the synergism of hyperglycemia with other cardiovascular risk factors. Risk factors for macrovascular disease in diabetic individuals include dyslipidemia, hypertension, obesity, reduced physical activity, and cigarette smoking. Additional risk factors more prevalent in the diabetic population include microalbuminuria, macroalbuminuria, an elevation of serum creatinine, abnormal platelet function and endothelial dysfunction The possibility of atherogenic potential of insulin is suggested by the data in nondiabetic individuals showing higher serum insulin levels (indicative of insulin resistance) in association with greater risk of cardiovascular morbidity and mortality. However, treatment with insulin and the sulfonylureas did not increase the risk of CVD in individuals with type 2 DM.

TREATMENT CARDIOVASCULAR DISEASE

In general, the treatment of coronary disease is not different in the diabetic individual (Chap. 293). Revascularization procedures for CHD, including percutaneous coronary interventions (PCI) and coronary artery bypass grafting (CABG), may be less efficacious in the diabetic individual. Initial success rates of PCI in diabetic individuals are similar to those in the nondiabetic population, but diabetic patients have higher rates of restenosis and lower long-term patency and survival rates in older studies.

Aggressive cardiovascular risk modification in all individuals with DM and glycemic control should be individualized, as discussed in Chap. 418. In patients with known CHD and type 2 DM, an ACE inhibitor (or ARB), a statin, and acetylsalicylic acid (ASA; aspirin) should be considered. Past trepidation about using beta blockers in individuals who have diabetes should not prevent use of these agents because they clearly benefit diabetic patients after MI. In