as an alternative approach.[627] Other evaluations requiring a variety of expensive devices have a low sensitivity and specificity for CAN and are not recommended for use in clinical care.[614]

As CAN progresses, persons may present with resting tachycardia with fixed heart rate (>100 bpm), exercise intolerance, nondipping BP and reverse dipping BP, and in most advanced cases with orthostatic hypotension (a fall in systolic or diastolic BP by >20 mm Hg or >10 mm Hg, respectively, upon standing without an appropriate increase in heart rate).[547] Orthostatic hypotension is usually easy to document in the office by measuring the BP supine and after standing. However, as with symptoms, the specificity of the signs for CAN is low, and thorough differential is required.[547] In a symptomatic person with a history of poor glucose control presenting with resting tachycardia or postural hypotension, clinicians may not need to perform additional CAN tests given costs and burden after excluding other potential causes.[547]

Management of CV Autonomic Neuropathy

Intensive glucose control is most effective to prevent CAN in T1D as documented by a 45% reduction in risk with intensive glucose control in the Diabetes Control and Complications Trial, a benefit that persisted during the Epidemiology of Diabetes Interventions and Complications study with a 30% reduction in incident CAN over an additional 14 years of follow-up.[542,628,629] Glucose control as part of a multifactorial intervention that also targeted hypertension, dyslipidemia, and lifestyle demonstrated a 63% reduction in the rate of progression to CAN in a small T2D cohort participating in the Steno-2 trial.[630] Analyses from the ACCORD trial reported that, after adjusting for multiple other risk factors, intensive glucose treatment significantly reduced CAN risk by 16% compared to standard intervention in a large cohort of more than 8 000 participants with T2D in the ACCORD trial over a mean 5-year follow-up.[611] As for DPN, lifestyle modifications with diet and exercise have shown benefit in CAN prevention.[631]

Management of orthostatic hypotension involves both behavioral and pharmacological interventions. Behavioral supportive measures include: (1) avoiding abrupt changes in body position; (2) avoiding actions that elevate intraabdominal and intrathoracic pressures; (3) avoiding medications that would exacerbate hypotension such as tricyclic antidepressants, phenothiazines, and diuretics; (4) raising the head of the bed during sleep; (5) following a schedule of small and frequent meals to minimize postprandial hypotension; (6) considering physical counterpressure maneuvers such as leg crossing and squatting; and (7) hydrating with fluids and salt, if not contraindicated.[547] Pharmacological therapy includes midodrine and the more recent droxidopa, both of which are FDA approved for the management of orthostatic hypotension and may be considered in persons who fail nonpharmacological interventions. However, it is recommended to proceed with a very slow titration and use the minimally effective dose to avoid undesirable side effects. In selected severe cases, low-dose fludrocortisone may be also an option.[547]

Gastrointestinal Autonomic Neuropathy

GI neuropathies may involve any portion of the GI tract with manifestations including esophageal dysmotility, gastroparesis (delayed gastric emptying), constipation, diarrhea, and fecal incontinence.[547] Among these, gastroparesis may the most common condition providers may consider in clinical practice.

Earlier prevalence data on gastroparesis are limited and inconsistent. However, more recent data from larger community-based studies reported that cumulative incidence of gastroparesis over 10 years was 5% in T1D compared with T2D (1%) and controls (1%). The prevalence of GI symptoms that could mimic gastroparesis increased substantially in recent years in the United States and other countries, although these are nonspecific.

Screening and Diagnosis in Clinical Care

A careful history may unveil symptoms such as early satiety, fullness, bloating, nausea, vomiting, dyspepsia, and abdominal pain. However, all these symptoms are nonspecific and resemble many other conditions, do not correspond with the severity of gastroparesis, and are poorly associated with abnormal gastric emptying.[547] Thus, gastroparesis may be clinically silent in the majority of cases and symptoms and many persons may only present with unexplained early postprandial hypoglycemia followed by later hyperglycemia.[547]

Importantly, besides organic causes such as gastric outlet obstruction or peptic ulcer disease, hyperglycemia, hypoglycemia, and acute changes in BG are well documented to alter gastric emptying.[547] A critical consideration is that several medications widely used in persons with DM, especially opioids, that have been unfortunately prescribed extensively for pain management, and GLP-1 RAs, directly affect gastric emptying and could mimic gastroparesis or cause iatrogenic gastroparesis.[547] Therefore, a thorough differential to exclude all these factors known to affect gastric emptying (including esophagogastroduodenoscopy and/or a barium study of the esophagus, stomach, and upper GI tract), careful documentation of medication intake, and performing CGM if available should always be considered before conducting more specialized testing for gastroparesis and a firm diagnosis is established.

The diagnostic gold standard is the measurement of gastric emptying with scintigraphy of digestible solids at 15-minute intervals for 4 hours after food intake. Optimization of glucose levels prior to scanning is needed to avoid false-positive results. However, this test is burdensome, time consuming, not readily available, and costly. Recently, the use of 13C-octanoic acid breath test has been FDA approved and emerged as a much easier to use alternative.[547]

Other Forms of Diabetic Neuropathies

Other forms of diabetic neuropathies are mononeuritis such as cranial nerve palsies or entrapment neuropathies (eg, carpal tunnel syndrome, ulnar entrapment, and peroneal entrapment, among others).[632-635] There may also be atypical variants of diabetic neuropathy such as small-fiber neuropathies, which present predominantly with pain and autonomic features.[636,637] Risk factors include metabolic syndrome, IFG, and IGT.[638-640]

Question 9: How should antihyperglycemic agents be prioritized in persons with T2D at high risk for or with established CVD?

Recommendation 9.1

In persons with T2D and established ASCVD or at high risk for ASCVD, use GLP-1 RAs with proven CV benefits to reduce the risk of myocardial infarction, stroke, or CV death regardless of other glucose-lowering or CV therapies and independent of A1C.
Grade A; BEL 1

Recommendation 9.2

In persons with T2D and established ASCVD or very high ASCVD risk, use SGLT2is with proven CV benefits to reduce the risk of hospitalization for HF, major adverse CV events (MACE), or CV death regardless of background glucose-lowering therapy, CV therapy, or A1C.
Grade A; BEL 1

Recommendation 9.3

In persons with T2D and established HF (regardless of ejection fraction, background glucose-lowering or HF therapies, or A1C), use