

# World Journal of *Diabetes*

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## Cardiac autonomic neuropathy: Risk factors, diagnosis and treatment

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### Abstract

Cardiac autonomic neuropathy (CAN) is a serious com-

plication of diabetes mellitus (DM) that is strongly associated with approximately five-fold increased risk of cardiovascular mortality. CAN manifests in a spectrum of things, ranging from resting tachycardia and fixed heart rate (HR) to development of "silent" myocardial infarction. Clinical correlates or risk markers for CAN are age, DM duration, glycemic control, hypertension, and dyslipidemia (DLP), development of other microvascular complications. Established risk factors for CAN are poor glycemic control in type 1 DM and a combination of hypertension, DLP, obesity, and unsatisfactory glycemic control in type 2 DM. Symptomatic manifestations of CAN include sinus tachycardia, exercise intolerance, orthostatic hypotension (OH), abnormal blood pressure (BP) regulation, dizziness, presyncope and syncope, intraoperative cardiovascular instability, asymptomatic myocardial ischemia and infarction. Methods of CAN assessment in clinical practice include assessment of symptoms and signs, cardiovascular reflex tests based on HR and BP, short-term electrocardiography (ECG), QT interval prolongation, HR variability (24 h, classic 24 h Holter ECG), ambulatory BP monitoring, HR turbulence, baroreflex sensitivity, muscle sympathetic nerve activity, catecholamine assessment and cardiovascular sympathetic tests, heart sympathetic imaging. Although it is common complication, the significance of CAN has not been fully appreciated and there are no unified treatment algorithms for today. Treatment is based on early diagnosis, life style changes, optimization of glycemic control and management of cardiovascular risk factors. Pathogenetic treatment of CAN includes: Balanced diet and physical activity; optimization of glycemic control; treatment of DLP; antioxidants, first of all  $\alpha$ -lipoic acid (ALA), aldose reductase inhibitors, acetyl-L-carnitine; vitamins, first of all fat-soluble vitamin B1; correction of vascular endothelial dysfunction; prevention and treatment of thrombosis; in severe cases-treatment of OH. The promising methods include prescription of prostacyclin analogues, thromboxane A2 blockers and drugs that contribute into strengthening and/or normalization of  $\text{Na}^+$ ,  $\text{K}^+$ -ATPase (phosphodiesterase inhibitor), ALA, dihomogamma-linolenic acid (DGLA),  $\omega$ -3 polyunsaturated fatty acids ( $\omega$ -3 PUFAs), and the simultaneous prescription of ALA,  $\omega$ -3 PUFAs and DGLA, but the future investigations

are needed. Development of OH is associated with severe or advanced CAN and prescription of nonpharmacological and pharmacological, in the foreground midodrine and fludrocortisone acetate, treatment methods are necessary.

**Key words:** Diabetes mellitus; Risk factors; Cardiac autonomic neuropathy; Screening for cardiac autonomic neuropathy; Cardiovascular reflex tests; Orthostatic hypotension; Heart rate variability; Prophylaxis; Treatment

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**Core tip:** Cardiac autonomic neuropathy (CAN) is a serious complication of diabetes mellitus, which is strongly associated with increased risk of cardiovascular mortality. Although it is common complication, the significance of CAN has not been fully appreciated and there are no unified treatment algorithms for today. In this review we have analyzed the existing data about the known risk factors, screening and diagnostic algorithm, staging of CAN and possible treatment, including effectiveness of lifestyle modification, intensive glycemic control; treatment of diabetic dyslipidemia; antioxidants; vitamins; correction of vascular endothelial dysfunction; prevention and treatment of thrombosis; treatment of orthostatic hypotension.

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## INTRODUCTION

It was estimated that there were 415 million people with diabetes mellitus (DM) aged 20-79 years in 2015, and the number was predicted to rise to 642 million by 2040<sup>[1]</sup>. The development of cardiac autonomic neuropathy (CAN) is associated with the lesion of the autonomic nervous system (ANS), and may be accompanied by coronary vessels ischemia, arrhythmias, "silent" myocardial infarction (MI), severe orthostatic hypotension (OH) and sudden death syndrome<sup>[2-6]</sup>. At the early stages CAN can be subclinical and it becomes clinically evident as the disease progresses<sup>[7-9]</sup>.

Based on the CAN Subcommittee of the Toronto Consensus Panel on Diabetic Neuropathy<sup>[5]</sup> and the American Diabetes Association (ADA)<sup>[3]</sup>, CAN is defined as the impairment of cardiovascular autonomic control in patients with DM following the exclusion of other causes. Cardiovascular autonomic reflex tests (CARTs) are usually used for CAN diagnosis and staging<sup>[5,10]</sup>.

CAN treatment is a complex process, that includes: Lifestyle modification; reducing insulin resistance (IR); tight glucose control; management of diabetic dyslipidemia (DLP); antioxidants; vitamins; treatment of myocardial metabolic abnormalities; thrombosis;

management of OH; symptomatic treatment of concomitant diseases and others<sup>[11-18]</sup>. This study was aimed to review the existing data about the risk factors, prophylaxis, early diagnosis, treatment, and treatment perspectives of patients with DM and CAN.

The PubMed and MEDLINE, Scopus, BIOSIS, EMBASE, Google Scholar and Springer Online Archives Collection were used to conduct a search of the literature. Keywords used were "cardiac autonomic neuropathy", "silent myocardial infarction", "sudden death syndrome", "heart rate variability", "orthostatic hypotension", "cardiovascular autonomic reflex tests" in combination with the term "diabetes" for the years from 1990 until today. In addition, a manual search of some reference lists of relevant reviews and trials was performed.

## RISK FACTORS FOR CAN

The risk of developing autonomic dysfunction in DM depends on several factors. However, two of them are common to both type 1 DM (T1DM) and type 2 DM (T2DM): Degree of glycemic control and disease duration. Inadequate glucose control plays an important role in the initial pathophysiology [microcirculation dysfunction due to nitric oxide (NO) loss, oxidative stress (OS) and accumulation of free radicals with lesion of Schwann cell] as well as in its progression (neuronal apoptosis and axonal degeneration)<sup>[19-21]</sup>.

The pathophysiological mechanism of diabetic neuropathies development is multifactorial, and there is enough evidence that small-fiber diabetic polyneuropathy (DPN) and even CAN may precede DM<sup>[22]</sup>.

Several studies reported the important role of cardiovascular risk factors, such as systolic blood pressure (BP), triglycerides (TGs) level, body mass index (BMI) and smoking, in the development of CAN<sup>[21]</sup>.

Even more important, however, were the results of the Intensified Multifactorial Intervention in Patients With Type 2 Diabetes and Microalbuminuria (Steno 2) study, in which the intensified multifactorial intervention (hyperglycemia, DLP, hypertension, and microalbuminuria) in patients with T2DM reduced the risk of CAN progression by 68%<sup>[23,24]</sup>. The role of intensive control in preventing and slowing the progression of CAN in patients with T1DM is also well-known: In the Diabetes Control and Complications Trial (DCCT), its prevalence was reduced by 53%<sup>[21,25]</sup>.

The main predictors for the development of CAN in patients with T2DM are age, gender, ethnicity and presence of microvascular complications [nephropathy, retinopathy, and peripheral neuropathy (PNP)]<sup>[6]</sup>. In a cohort of 1000 T2DM people, the development of CAN 7.5 years of follow-up was correlated with older age and the presence of microvascular disease<sup>[26]</sup>. In terms of gender, in a multicenter study of 3250 patients with DM, there was no difference in the prevalence of CAN between men and women (men 35% and women 37%)<sup>[27]</sup>. However, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study which involved more than 8000 T2DM patients, CAN was more prevalent in

**Table 1 Cardiac autonomic neuropathy in type 1 and type 2 diabetes mellitus: Differences in relation to risk factors and natural history<sup>[21]</sup>**

Risk factors	Type 1 DM	Type 2 DM
Age	+	+
Gender (female)	+	-
Obesity	-	+
Hyperinsulinemia	NA	+
Duration of DM	++	++
Smoking	+	+
HbA1c	++	++
Hypertension	++	+
Retinopathy	++	+
Hypertriglyceridemia	+	+
Classical DPN	++	++
Microalbuminuria	++	++
Dyslipoproteinemia (> LDL and < HDL)	+	(+)
Prevalence at diagnosis of DM	7.70%	5%
Prevalence after 10 yr	38%	65%
Prevalence (random)	25%	34%

++: Strong association; +: Moderate association; -: Not found; (+): Controversial; NA: Not applicable; DM: Diabetes mellitus; LDL: Low-density lipoprotein; HDL: High-density lipoprotein.

women (2.2% in women and 1.4% in men for severe; 4.7% in women and 2.6% in men for moderate to severe)<sup>[28]</sup>.

According to data obtained from cross-sectional or longitudinal studies clinical predictors or correlates of CAN were age, diabetes duration, glycemic control, the presence of other chronic DM complications, such as diabetic retinopathy, DPN, diabetic nephropathy, and renal failure<sup>[5,19,22,29,30]</sup>. The value of several cardiovascular risk factors in development of CAN has also been reported: Hypertension, smoking (only in cross-sectional studies), decreased high-density lipoprotein cholesterol (HDL-C), increased low-density lipoprotein cholesterol (LDL-C), TGs levels, obesity in T2DM (with some controversy), insulin levels in T2DM, waist circumference, cardiovascular disease, and use of anti-hypertensive drugs<sup>[5,19,29-31]</sup>. Current data that differentiate CAN in T1DM and in T2DM in terms of risk factors and natural history are summarized in Table 1<sup>[21]</sup>.

Possible factors associated with high mortality and sudden death due to autonomic neuropathy are<sup>[27]</sup>: Cardiorespiratory arrest/increased perioperative and peri-intubation risk; silent myocardial ischaemia (SMI)/infarction; hypertension; ventricular arrhythmias/prolongation of the QT interval (QTi); resting tachycardia; orthostatic hypotension (OH); exaggerated BP responses with supine position and exercise; flattening of the nocturnal reduction of BP and heart rate (HR); abnormal diastolic/systolic left ventricular function; impaired cardiovascular responsiveness; poor exercise tolerance; heat intolerance due to defective sympathetic thermoregulation; hypoglycemia unawareness; increased risk of severe hypoglycemia; obstructive sleep apnoea syndrome; susceptibility to foot ulcers and amputations

due to arteriovenous shunting and sudomotor dysfunction.

## MORBIDITY AND MORTALITY IN CAN

Reduced heart rate variability (HRV) has been shown to have direct independent consequences in terms of morbidity and mortality in patients with prediabetes and DM<sup>[32]</sup>. Development of autonomic dysfunction in T1DM is accompanied by the four time higher risk of mortality<sup>[33,34]</sup>.

CAN is strongly associated with increased mortality<sup>[5,35,36]</sup>, and in some studies with morbidity, such as stroke, coronary artery disease (CAD) and SMI. A diminished Valsalva heart rate (HR) ratio was significantly associated with development of SMI<sup>[5,37]</sup>. According to the European Epidemiology and Prevention of Diabetes (EURODIAB) study autonomic dysfunction was associated with coexisting cardiovascular disease (CVD), glycated hemoglobin (HbA<sub>1c</sub>) level, duration of T1DM and was diagnosed in one-third of patients<sup>[32]</sup>. Results from the ACCORD trial again confirmed the association of CAN and mortality. These investigations showed that the individuals in this trial with baseline CAN were 1.55-2.14 times as likely to die as individuals without CAN<sup>[5,28]</sup>. Furthermore, CAN in the presence of DPN was the highest predictor of CVD mortality. There is also strong evidence, based on studies in patients with T1DM and patients with T2DM that prolongation of QT<sub>i</sub> is an independent predictor of cardiovascular deaths and all-cause mortality<sup>[5,8,34,35,38]</sup>.

There is definitive evidence for a predictive value of CAN on overall mortality (class I) and some evidence on morbidity (class II). Prolongation of QT<sub>i</sub> (class II), tachycardia (class II) and non-dipping status (class III) are associated with increased mortality rate. Poor glycemic control in T1DM (class I), and a combination of obesity, DLP, hypertension and poor glycemic control in T2DM (class II) are established risk factors for CAN<sup>[5]</sup>.

## CLASSIFICATION OF DIABETIC AUTONOMIC NEUROPATHIES<sup>[39]</sup>

CAN, that is associated with reduction in HRV, resting tachycardia, OH and sudden death syndrome; Gastro-intestinal, that includes diabetic gastropathy, enteropathy and colonic hypomotility; Urogenital, that includes erectile dysfunction, diabetic cystopathy and female sexual dysfunction; Sudomotor dysfunction with development of gustatory sweating and distal hyperhidrosis; Abnormal pupillary function; Hypoglycemia unawareness.

### Classification of diabetic CAN<sup>[5]</sup>

**Subclinical phase:** Decreased HRs variability.

**Early phase:** Resting tachycardia.

**Advanced stage:** Exercise intolerance; Cardiomyopathy with left ventricular dysfunction; OH; Silent myocardial

**Table 2** Abnormalities associated with cardiovascular autonomic neuropathy at the level of cardiovascular system and peripheral vascular function<sup>[5,45,46]</sup>

Cardiovascular system	Peripheral vascular function
Perioperative instability	↑ Peripheral blood flow and warm skin
Resting tachycardia	↑ Arteriovenous shunting and swollen veins
Loss of reflex heart rate variations	↑ Venous pressure
Hypertension	Leg and foot oedema
Exercise intolerance	Loss of protective cutaneous vasomotor reflexes
Orthostatic hypotension	Loss of venoarteriolar reflex with microvascular damage
Postprandial hypotension	↑ Transcapillary leakage of macromolecules
Silent myocardial ischaemia	↑ Medial arterial calcification
Left ventricular dysfunction and hypertrophy	-
QT interval prolongation	-
Impaired baroreflex sensitivity	-
Non-dipping, reverse dipping	-
Sympathovagal imbalance	-
Dysregulation of cerebral circulation	-
↓ Sympathetically mediated vasodilation of coronary vessels	-
↑ Arterial stiffness	-

ischaemia.

## SCREENING AND DIAGNOSIS

Cardiovascular autonomic neuropathy is by far one of the most studied forms among the various forms of diabetic autonomic neuropathies<sup>[40,41]</sup>. Screening for CAN should be performed in T2DM patients at diagnosis and T1DM patients after 5 years of disease, in particular those at greater risk for CAN due to a history of poor glycemic control ( $HbA_{1c} > 7\%$ ), or the presence of one major CVD risk factor, or other chronic complications of DM (level B). CAN screening may be also required in asymptomatic patients for pre-operative risk assessment before major surgical procedures (level C)<sup>[5]</sup>. Assessment of symptoms and signs, associated with CAN should be considered in patients with hypoglycemia unawareness (level C). Patients with chronic complications of DM should be screened for CAN symptoms and signs and in case of the presence tests excluding other drug effects/interactions or comorbidities that could mimic CAN should be performed (level E)<sup>[2,5,39]</sup>. CAN assessment can be used for cardiovascular risk stratification and as a marker for increased risk of intraoperative cardiovascular lability.

## CLINICAL IMPACT OF CAN

### Clinical manifestations of CAN

Symptomatic manifestations of CAN include sinus tachycardia, exercise intolerance and OH. Depending on studied diabetic populations OH was present in 6%-32% of patients with DM<sup>[5,21,42]</sup>. The symptoms of OH, such as dizziness, light-headedness, fainting, blurred vision were found out in 4%-18% of diabetic patients<sup>[5,22]</sup>. Orthostatic intolerance symptoms may be worse in the early morning, during prolonged standing, after meals, or physical activity<sup>[5,43,44]</sup>, that may contribute to the associated with CAN burden (Table 2).

Light-headedness, palpitations, weakness, faintness,

and syncope are the most common symptoms of CAN, that occurs upon standing<sup>[5,45,46]</sup> (Table 2). It may be considered to perform screening among patients with unawareness of hypoglycemia, as this condition may be associated with CAN<sup>[30,39,45,47-50]</sup>.

Development of OH is associated with advanced disease stage and is easy to recognize in the office. There is no compensatory increase in the HR, despite hypotension in most cases of CAN<sup>[5,39,46,51]</sup>. CAN diagnosis includes evaluation of symptoms (Table 3) and signs of CAN (higher resting HR, presence of OH and impaired HRV). In patients with microvascular and neuropathic complications should be performed evaluation for symptoms and signs of autonomic neuropathy (level E)<sup>[39,49,52]</sup>.

## CAN ASSESSMENT

### Assessment of CAN symptoms

According to the Rochester Diabetic Neuropathy Study the correlation between the autonomic deficits and symptoms was weak in patients with T1DM and absent in T2DM patients<sup>[5,43,44]</sup>.

### Assessment of CAN signs

**Resting tachycardia:** A fixed HR that is unresponsive to moderate exercise, stress or sleep indicates almost complete cardiac denervation<sup>[8,32,53]</sup>. Higher resting HR ( $> 78$  bpm) compared with lower resting HR ( $< 58$  bpm) and a rise in HR with time have been shown to be independent risk predictors for all-cause and CVD mortality<sup>[5,32,36]</sup>.

**Exercise intolerance:** Autonomic dysfunction impairs exercise tolerance, reduces response in HR and BP, and blunts increases in cardiac output in response to exercise. To avoid hazardous levels of intensity of exercise patients with CAN need to rely on their perceived exertion, not HR. Presently, there is inadequate evidence to



**Table 3** Symptoms and signs associated with diabetic cardiovascular autonomic neuropathy<sup>[39]</sup>

Cardiovascular autonomic neuropathy	
Resting tachycardia	
Abnormal blood pressure regulation	Nondipping Reverse dipping
Orthostatic hypotension (all with standing)	Light-headedness Weakness Faintness Visual impairment Syncope
Orthostatic tachycardia or bradycardia and chronotropic incompetence (all with standing)	Light-headedness Weakness Faintness Dizziness Visual impairment Syncope
Exercise intolerance	

recommend routine screening of asymptomatic diabetic patients with an exercise ECG test<sup>[5,8,32]</sup>.

**OH:** OH is an excessive fall in BP level (is a drop of > 20 mmHg systolic or/and > 10 mmHg diastolic BP) within 3 min of standing and a fall of 30 mmHg systolic BP when a person assumes a standing position. OH is characterized by symptoms that occur after standing: Lightheadedness, weakness, faintness, dizziness, palpitations, blurred vision, and even nausea and syncope<sup>[5,8,32,43,51]</sup>.

**Orthostatic tachycardia syndrome:** Symptoms compatible with orthostasis, such as feeling faint or dizzy, circumoral paresthesia may be caused by postural tachycardia syndrome (POTS), neurocardiogenic syncope, inappropriate sinus tachycardia, or abnormalities in baroreceptor function<sup>[5,8,32]</sup>.

**QTi prolongation:** Prolongation of QTi has been defined as a QTc (corrected QT for HR)  $\geq 450$  ms in men and  $\geq 460$  ms in women<sup>[54]</sup>. Hyperinsulinemia can induce reversible prolongation of QTi in healthy subjects, hyperglycemia and acute hypoglycemia can induce the prolongation of QTi in both healthy and diabetic patients<sup>[38,55,56]</sup>. In patients with T1DM prolongation of QTc was found out during overnight hypoglycemia and support an arrhythmic basis for the "dead in bed" syndrome<sup>[5,57]</sup>.

**Impaired HRV:** Decrease in HRV is the earliest clinical indicator of CAN. In health people the HR has a high degree of beat-to-beat variability and HRV fluctuates increasing with inspiration and decreasing with expiration. Impaired HRV is a strong, independent predictor of increased mortality after acute MI<sup>[8,46]</sup>.

**Reverse dipping and non-dipping pattern:** At night, normal individuals exhibit reduction in nocturnal BP, associated with predominance of vagal tone and decreased sympathetic activity. In diabetic patients with CAN this pattern is altered, resulting in predominance of sympathetic tone during night and development

of nocturnal hypertension. This is associated with a development of left ventricular (LV) hypertrophy and increased cardiovascular morbidity and mortality rate in patients with DM and CAN<sup>[5,46]</sup>. In research and management of arterial hypertension ambulatory blood pressure monitoring (ABPM) is a standard tool with regard to diagnostic, prognostic, and therapeutic issues<sup>[58]</sup>. CAN was associated with both violations of the circadian variation in BP, namely non-dipping or reverse dipping condition. So, ABPM may be useful in detecting of the circadian variation in BP violations, orthostatic and postprandial hypotension, and in achieving BP goals. The presence of non-dipping or reverse dipping in ABPM requires CAN testing and may suggest the presence of CAN<sup>[5]</sup>.

**"Silent" myocardial ischemia/cardiac denervation syndrome:** "Silent" ischemia in diabetic patients can either result from CAN, from autonomic dysfunction attributable to CAD itself, or from both. Altered pain thresholds, subthreshold by ischemia not sufficient to induce pain and dysfunction of the afferent cardiac autonomic nerve fibers have all been suggested as possible mechanisms<sup>[32,59]</sup>. Development of nausea, vomiting, cough, dyspnea, tiredness and electrocardiography (ECG) changes are the features of an MI in patients with CAN<sup>[8]</sup>.

#### **CAN and "dead in bed" syndrome**

Sudden, unexpected deaths occur among subjects with CAN<sup>[60]</sup>. Imaging of myocardial sympathetic innervation has shown that predisposition to arrhythmias may also be related to intracardiac sympathetic imbalance<sup>[61,62]</sup>. In the Rochester Diabetic Neuropathy Study<sup>[61,63]</sup>, the investigators found that all cases of sudden death in individuals with and without DM had severe CAD or LV dysfunction.

#### **Intraoperative cardiovascular liability**

Development of DM is accompanied by the two-three times higher risk of perioperative cardiovascular morbidity and mortality<sup>[32,64]</sup>. Preoperative screening



**Table 4 Cardiovascular autonomic reflex tests<sup>[29,42]</sup>**

Test	Technique	Normal response and values
Beat-to-beat HRV	With the patient at rest and supine, heart rate is monitored by ECG while the patient breathes in and out at 6 breaths per minute, paced by a metronome or similar device	A difference in HR of > 15 beats per minute is normal and < 10 beats per minute is abnormal. The lowest normal value for the expiration-to inspiration ratio of the R-R interval decreases with age: age 20-24 yr, 1.17; 25-29, 1.15; 30-34, 1.13; 35-39, 1.12; 40-44, 1.10; 45-49, 1.08; 50-54, 1.07; 55-59, 1.06; 60-64, 1.04; 65-69, 1.03; and 70-75, 1.02
Heart rate response to standing	During continuous ECG monitoring, the R-R interval is measured at beats 15 and 30 after standing	Normally, a tachycardia is followed by reflex bradycardia. The 30:15 ratio should be > 1.03, borderline 1.01-1.03
Heart rate response to the Valsalva maneuver	The subject forcibly exhales into the mouthpiece of a manometer to 40 mmHg for 15 s during ECG monitoring	Healthy subjects develop tachycardia and peripheral vasoconstriction during strain and an overshoot bradycardia and rise in BP with release. The normal ratio of longest R-R to shortest R-R is > 1.2, borderline 1.11-1.2
Systolic blood pressure response to standing	Systolic BP is measured in the supine subject. The patient stands and the systolic BP is measured after 2 min	Normal response is a fall of < 10 mmHg, borderline fall is a fall of 10-29 mmHg and abnormal fall is a decrease of > 30 mmHg
Diastolic blood pressure response to isometric exercise	The subject squeezes a handgrip dynamometer to establish a maximum. Grip is then squeezed at 30% maximum for 5 min	The normal response for diastolic BP is a rise of > 16 mmHg in the other arm, borderline 11-15 mmHg

HRV: Heart rate variability; ECG: Electrocardiography; BP: Blood pressure; HR: Heart rate.

for CAN should be performed in patients with reduced hypoxic-induced ventilatory drive<sup>[32]</sup> and identify patients with greater intraoperative complications risk<sup>[8,32]</sup>. Thus, resting HR is not a specific sign of CAN (class IV). After exclusion of other causes OH suggests an advanced CAN that should be confirmed by cardiovascular autonomic reflex tests (CARTs) (class I). Specific but insensitive CAN indices are QT<sub>i</sub> prolongation (class II), OH (class III) and reverse dipping (class III)<sup>[32]</sup>.

## DIAGNOSTIC TESTING FOR CAN

### Cardiovascular autonomic reflex tests

CARTs are considered as gold-standard measures of autonomic function<sup>[32]</sup>. Postural change of BP (OH) and sustained isometric muscular strain provide indices of sympathetic function, whereas the HR variations during deep breathing, lying-to-standing (HR tests) and Valsalva maneuver are indices mainly of parasympathetic function. Diagnostic tests of CAN are summarized in Table 4. The normal, borderline and abnormal values in tests of cardiovascular autonomic function are summarized in Table 5.

According to CAN subcommittee in the Toronto Diabetic Neuropathy Consensus Panel, CAN diagnostic criteria are divided as follows: A positive one test is early diagnosis of CAN; the presence of two or three positive tests is required for definitive diagnosis of CAN; the presence of OH combined with one of the previous criteria is defined as severe CAN<sup>[5]</sup>.

The main clinical indications of the autonomic reflex tests<sup>[5,52,65]</sup>: Diagnosis and staging of CAN in T2DM patients (at diagnosis and annually thereafter); diagnosis and staging of CAN in T1DM patients (5 years after diagnosis and annually thereafter); stratification of cardiovascular risk: In pre-operative testing, pre-physical activity, indication of selective beta-blocker, and suspected silent

ischemia; differential diagnosis of other manifestations of CAN (regardless of DM duration): Assess whether gastroparesis, erectile dysfunction, OH, dizziness, syncope, or tachycardia in diabetic persons are due to dysautonomia; evaluate the progression of autonomic failure and monitor response to therapy (e.g., continuous infusion of insulin, post-transplants, and use of antioxidants); differential diagnosis of other causes of neuropathy such as autoimmune autonomic neuropathy (chronic inflammatory demyelinating polyneuropathy, celiac disease, amyotrophy) or toxic-infectious neuropathy (alcohol, primary neuritic Hansen's disease, human immunodeficiency virus) as well as in cases where the presence of autonomic neuropathy is disproportionate to the sensory-motor neuropathy.

To the most sensitive and specific diagnostic tests available for CAN evaluation belongs HRV, muscle sympathetic nerve activity (MSNA), baroreflex sensitivity (BRS), plasma catecholamines, and heart sympathetic imaging<sup>[50,66]</sup>.

### Short-term ECG recording

The short-term ECG recordings can be analyzed by dedicated software in the frequency domain. This method usually uses the Fourier method, which transform R-R intervals into waves with three basis components: Very low frequency  $\leq 0.04$  Hz (VLF); low frequency 0.04-0.15 Hz (LF) and high frequency 0.15-0.4 Hz (HF). LF represents combined effects of sympathetic and parasympathetic influence, whereas HF represents vagal activity. A decrease in HF is a sign of parasympathetic dysfunction, in the early stages of autonomic dysfunction in DM, when sympathetic predominance is observed it leads to an increase in LF/HF<sup>[67]</sup>. It is not clear if classical Ewing's tests or time-domain methods are better for diagnosis of CAN. However, Ewing's tests are simpler and can be more easily implemented during routine clinical use.

**Table 5** Normal, borderline and abnormal values in tests of cardiovascular autonomic function<sup>[27]</sup>

	Normal	Borderline	Abnormal
Tests reflecting mainly parasympathetic function			
Heart rate response to Valsalva Manoeuvre (Valsalva ratio)	$\geq 1.21$	1.11–1.20	$\leq 1.10$
Heart rate (R-R interval) variation	$\geq 15$ beats/min	11–14 beats/min	$\leq 10$ beats/min
During deep breathing (maximum-minimum heart rate) immediate heart rate response to standing (30:15 ratio)	$\geq 1.04$	1.01–1.03	$\leq 1.00$
Tests reflecting mainly sympathetic function			
Blood pressure response to standing (fall in systolic blood mmHg mmHg mmHg pressure)	$\leq 10$	11–29	$\geq 30$
Blood pressure response to sustained handgrip (increase in diastolic blood pressure)	$\geq 16$ mmHg	11–15 mmHg	$\leq 10$ mmHg

**HR variability**

Possible mechanisms, which can affect HR are: Efferences of sympathetic and parasympathetic nervous system to the sinus node, ionic changes in the sinus node, neurohumoral influences, local temperature changes. The short-term HRV is essentially determined by the sympathetic and parasympathetic efferences and stretch of the sinus nod under resting conditions.

The state of sympathetic and parasympathetic is responsible for a physiologic variation in the HR and HRV. The evaluation of HRV can be performed in the time and frequency domains<sup>[5,50,66]</sup>.

Time domain measures include the standard deviation of 5-min average of normal R-R intervals (SDANN), the difference between the longest and shortest R-R intervals and the root-mean square of the difference of successive R-R intervals (RMSSD). The number of instances per hour in which two consecutive R-R intervals differ by more than 50 ms over 24 h (pNN50) can be calculated by longer recordings. All these indices explore the parasympathetic activity<sup>[67]</sup>.

It is obvious that reduction in HRV is associated with CAN, but this method has no standard values for diagnosis CAN<sup>[68,69]</sup>. Also during 24 h recording many factors can have an influence on HRV parameters, such as concomitant illness, use of medication, and lifestyle factors (exercise, stress, smoking, etc.). The analysis of ECG recordings in conjunction with respiration and beat-to-beat BP recordings is the best approach to HRV testing (level C).

**HR turbulence**

HR turbulence (HRT) is a method for CAN detection by Holter-based technique<sup>[70,71]</sup>.

**Baroreflex sensitivity**

The interesting approach that combines information derived from BP and HR is BRS that can be done with several methods: Spontaneous BP variations can be measured and drugs or physical manoeuvres can be applied to modify BP. None of the BRS tests available today shown a clinically relevant difference or definite advantage over the others<sup>[72]</sup>. Although the results of some studies in diabetic patients suggest an early impairment of BRS, the diagnostic accuracy of BRS measures was evaluated in very few studies<sup>[50,73]</sup>. Cardiac vagal BRS is a independent

prognostic index for cardiovascular mortality in the general (class II). The presence of early abnormalities with respect to CARTs warrant the clinical use of BRS in identifying subjects at risk for CAN (classes II–III).

**Muscle sympathetic nerve activity**

Blunted responsiveness to physiological hyperinsulinemia or glucose ingestion and increased resting MSNA have been described among T2DM with neuroadrenergic autonomic dysfunction and obesity. MSNA abnormalities reverse with weight loss<sup>[50,66]</sup>, but in contrast, T1DM is associated with a by about half decrease in the number of bursts<sup>[74]</sup>. MSNA allows direct and continuous measurement of sympathetic nerve traffic (class I). Resting MSNA might be increased in early T2DM, possibly due to hyperinsulinemia and type 1 diabetes is associated with a MSNA reduction (class IV). This technique requires specialized personal, is difficult, time-consuming, invasive, and cannot be repeated often (class II)<sup>[50]</sup>.

**Cardiovascular sympathetic tests and catecholamine assessment**

The determination of norepinephrine in plasma is in principle the biochemical equivalent of MSNA. While norepinephrine clearance is low in idiopathic autonomic neuropathy, this was not in the case of CAN<sup>[50,75]</sup>. The plasma catecholamine measurements can not be mandatory recommended for routine CAN diagnosis in clinical practice (level C)<sup>[50]</sup>.

**Heart sympathetic imaging**

Cardiac sympathetic innervation is possible to assess by using radiolabelled sympathomimetic amines or catecholamines ( $[^{123}\text{I}]$ -meta-iodobenzylguanidine (MIBG),  $[^{11}\text{C}]$ -meta-hydroxyephedrine (HED), 6- $[^{18}\text{F}]$  dopamine, and  $[^{11}\text{C}]$ -epinephrine<sup>[50,76–78]</sup>). Regional differences in vesicular uptake or retention was determined in subjects with T1DM and CAN by analysing the washout rates of  $[^{11}\text{C}]$ -epinephrine parallels those of  $[^{11}\text{C}]$ -HED<sup>[50,79,80]</sup>.

Scintigraphic tracers directly assess the structural integrity of the sympathetic nervous system supply to the heart (class III). Heart sympathetic imaging has greater sensitivity to detect changes in sympathetic neuronal function and/or structure<sup>[50,81]</sup>. The indices of myocardial perfusion and LV dysfunction in T1DM correlate with scintigraphic data (class III).

**Table 6** Diagnostic algorithm for diabetic cardiac autonomic neuropathy<sup>[3,39]</sup>

Symptoms		Signs/diagnostic tests	Differential workup
Resting tachycardia	Palpitations could be asymptomatic	Clinical exam: Resting heart rate > 100 bpm	Anemia hyperthyroidism fever  CVD (atrial fibrillation, flutter, other) Dehydration Adrenal insufficiency Some medications Smoking, alcohol, caffeine Recreational drugs (cocaine, amphetamines, methamphetamine, mephedrone) Adrenal insufficiency
Orthostatic hypotension	Light-headedness  Weakness Faintness Visual impairment Syncope	Clinical exam: A reduction of > 20 mmHg in the systolic blood pressure or > 10 mmHg in diastolic blood pressure	Intravascular volume depletion Blood loss/acute anemia Dehydration Pregnancy/postpartum CVD Alcohol Medication Antiadrenergics Antianginals Antiarrhythmics Anticholinergics Diuretics ACE inhibitors/angiotensin receptor blocker Narcotics Neuroleptics Sedatives

CAD: Coronary artery disease; CVD: Cardiovascular disease.

**Diagnostic testing for orthostatic symptoms**

A standard test for establishing the cause of postural symptoms is the head-up tilt-table study. Other functional syndromes may also be revealed, such as paradoxical orthostatic bradycardia syndrome and the vasoconstrictor syndrome (paradoxical orthostatic hypertensive syndrome, also known as OH)<sup>[8]</sup>.

**Diagnostic algorithm for diabetic CAN (Table 6)****Differential diagnosis of diabetic neuropathies:**

Differential diagnosis of diabetic neuropathies should be performed by excluding other causes of neuropathy (Table 7), by undertaking a medication history and family history and performing relevant testing (*e.g.*, blood count, folic acid, serum B<sub>12</sub>, metabolic panel, thyroid hormones)<sup>[49]</sup>.

**Neuropathy end points for research and clinical practice<sup>[3,39]</sup>:**

For clinical trials the recommended CAN measures include: standardized CARTs that are specific, sensitive, simple<sup>[5,39,49,82,83]</sup>; HRV indices<sup>[39,45,50,84]</sup>; resting QTc and HR<sup>[28,34,39,85]</sup>; other methods are expensive and time-consuming, require trained personnel (baro-reflex sensitivity, cardiac sympathetic imaging, and microneurography)<sup>[5,39,50,86]</sup>.

**Diagnostic criteria for CAN**

The CAN Subcommittee of the Toronto Consensus Panel on Diabetic Neuropathy established four reasons why

the diagnosis of CAN is relevant to clinical practice<sup>[5]</sup>: For diagnosing and staging the different clinical forms of CAN: Initial, definite, and advanced or severe; for stratifying the degree of cardiovascular risk and the risk of other diabetic complications; for the differential diagnosis of clinical manifestations and their respective treatment; to adapt the goal of HbA<sub>1c</sub> in each patient: For example, those with initial stages of CAN should have a more intensive glycemic control while patients with severe CAN should have a less aggressive glycemic control due to the risk of asymptomatic hypoglycemia. CARTs are the “gold” standard clinical tests for cardiovascular autonomic neuropathy<sup>[5]</sup>. In the CAN Subcommittee of the Toronto Consensus Panel statement are defined criteria for CAN definition and severity<sup>[5,6]</sup>. For the early CAN diagnosis only one abnormal CART result (among the 7 tests: 5 CARTs and HRV tests in time- and frequency-domains) is sufficient; definite CAN should be confirmed by 2 or 3 abnormal tests and severe CAN can be indicated by development of OH<sup>[5,71,87]</sup>.

**Staging of CAN**

Ewing *et al.*<sup>[42]</sup> (1985) proposed a classification based on “early involvement” (two borderline test results or one abnormal result on HR test), “definite involvement” (two or more abnormal results on HR tests), and “severe involvement” (development of OH).

The following CARTs are the “gold” standard for clinical autonomic testing: HR response to deep breathing,

**Table 7 Differential diagnosis of diabetic neuropathies<sup>[39]</sup>**

Metabolic disease	Thyroid disease (common) Renal disease
Systemic disease	Systemic vasculitis Nonsystemic vasculitis Paraproteinemia (common) Amyloidosis
Infectious	Human immunodeficiency virus Hepatitis B Lyme
Inflammatory	Chronic inflammatory demyelinating polyradiculoneuropathy
Nutritional	B12 Postgastroplasty Pyridoxine Thiamine Tocopherol Industrial agents, drugs, and metals Industrial agents Acrylamide Organophosphorous agents
Drugs	Alcohol Amiodarone Colchicine Dapsone Vinka alkaloids
Metals	Platinum Taxol Arsenic Mercury
Hereditary	Hereditary motor, sensory, and autonomic neuropathies

standing, and Valsalva manoeuvre, and BP response to standing (class II); these CARTs are sensitive, specific, reproducible, easy to perform, safe and standardized (classes II and III); the Valsalva manoeuvre is not advisable in the presence of increased risk of retinal haemorrhage and proliferative retinopathy (class IV). Age is the most relevant factor affecting HR tests (class I); a definite diagnosis of CAN and CAN staging requires more than one HR test and the OH test (class III)<sup>[5]</sup>.

## PREVENTION OF THE CAN

Prevention of diabetic neuropathies focuses on lifestyle modifications and tight glucose control. Early optimization of glucose control in patients with T1DM (class A) and a multifactorial approach targeting glycaemia among other cardiovascular risk factors in patients with T2DM (class C) were considered for prevention or delay of CAN development<sup>[39]</sup>.

## TREATMENT OF THE CAN

Implementation of tight glucose control as early as possible to prevent or delay the development of CAN in the course of T1DM (class A); consider a multifactorial approach in the course of T2DM (class C).

CAN treatment is a complex process, that includes: Lifestyle modification; reducing IR; intensive glycemic control; treatment of DLP; antioxidants, first of all

$\alpha$ -lipoic acid (ALA), aldose reductase inhibitors, acetyl-L-carnitine; vitamins, first of all fat-soluble vitamin B<sub>1</sub>; correction of vascular endothelial dysfunction; prevention and treatment of thrombosis; in severe cases-treatment of OH<sup>[88]</sup>.

### Glucose control

In the DCCT intensive glucose control reduced the risk of CAN development by 45% and in the Epidemiology of Diabetes Interventions and Complications (EDIC) study, this risk was reduced by 31%<sup>[39,48]</sup>.

The large sample size in DCCT/EDIC, the robust definitions used for CAN and the highly reproducible and sensitive testing protocol support tight glycemic control for prevention or delay of CAN development in the course of T1DM. In contrast, intensive glucose control has not consistently lowered the risk of CAN development in T2DM<sup>[39,47]</sup>. Lifestyle modification, tight glycemic control and targeting cardiovascular disease risk factors reduced the risk of CAN development by 60% in patients with T2DM<sup>[24,39]</sup>.

### Lifestyle modifications

Lifestyle modifications include rational nutrition and optimal level of physical activity and correction of obesity. Active lifestyle is accompanied by the three times less risk of increased mortality rate than sedentary lifestyle (less than 1000 kcal/wk)<sup>[89]</sup>.

The ADA does not recommend a specific diet over another for the diabetic patients and lists three different diets for individuals who have or are at risk of having DM (low-carbohydrate, low-fat calorie-restricted or Mediterranean diet)<sup>[90]</sup>. Although there are no studies looking at the cardiovascular outcome in diabetic patients only there is some cardiovascular benefit of adhering to a Mediterranean diet in diabetic patients.

Although the DPP<sup>[39,91]</sup> and the Impaired Glucose Tolerance Neuropathy (IGTN) study<sup>[39,92]</sup> reported benefits of lifestyle modification on diabetic symmetrical sensory neuropathy (DSPN) and CAN measures, respectively, these trials did not include DM patients. The best models to date regarding effectiveness of intensive lifestyle intervention come from the DPP<sup>[24]</sup>, the Steno-2 Study, the Italian supervised treadmill study<sup>[93]</sup>, and the University of Utah T2DM study<sup>[94]</sup>. The risk of adverse events or exercise-induced injury through decreased cardiac responsiveness to exercise, impaired thermoregulation, OH, impaired night vision due to impaired papillary reaction, and greater susceptibility to hypoglycemia can be increased in patients with autonomic neuropathy<sup>[5]</sup>. CAN is considered also as an independent risk factor for development of SMI and cardiovascular death<sup>[28]</sup>. Therefore, individuals with diabetic CAN should undergo cardiac investigation before beginning physical activity more intense than that to which they are accustomed<sup>[3]</sup>.

Most peripheral neuropathy affects the extremities, particularly the lower legs and the feet, but also the hands, whereas damage to the ANS may lead to imbalances



between the sympathetic and parasympathetic nerve fibers that innervate the heart and blood vessels, as well as abnormalities in HR control and vascular dynamics. To prescribe or engage in exercise that is both safe and effective, health care providers and patients with DM need to increase their understanding of the pathophysiological nature of neuropathies and the physical activity hurdles that may arise from the presence of a neuropathy. With proper care and preventative measures, patients with DM that experience either type of neuropathy can benefit from regular participation in mild to moderate aerobic, resistance, and balance activities, assuming they take any potential alterations into account to ensure that exercise is safe and effective<sup>[95,96]</sup>. Individuals with CAN should be screened and receive physician approval and possibly an exercise stress test before exercise initiation. Exercise intensity is best prescribed using the HR reserve method with direct measurement of maximal HR<sup>[95,96]</sup>.

Individuals with autonomic neuropathy (particularly CAN) should avoid high-intensity physical activities unless they have been cleared by a physician to participate: They should also avoid physical exertion in hot or cold environments since dehydration may be a risk for those who have difficulty with thermoregulation; individuals must be made aware that hypotension may occur after vigorous activities; recumbent cycling or water aerobics may be safer activities for individuals with OH; for better accuracy, individuals should monitor exercise intensity using the HR reserve method using a measured maximal HR, if possible, or use perceived exertion. The results indicate that 6-mo aerobic exercise training improves the cardiac ANS function in T2DM patients. However, more favourable effects are found in T2DM patients with definite CAN<sup>[97]</sup>.

### Glucose control

The DCCT and the follow-up observational EDIC study (DCCT/EDIC) stands as the pivotal trial demonstrating clear and persistent benefits of tight glucose control for both DSPN and CAN in patients with T1DM<sup>[47,48,94,98-100]</sup>. DCCT enrolled patients with T1DM who were randomly assigned to intensive or conventional insulin therapy<sup>[47,48,101-103]</sup>. The risk reduction in incident CAN with intensive therapy during DCCT was 45%<sup>[47,48,101,103]</sup>. The DCCT/EDIC has furthered the understanding of the role of glucose control in the development and progression of neuropathy<sup>[47,48,103,104]</sup>. The Kumamoto trial, the first randomized controlled trial to report beneficial effects of tight glucose control, reported no differences on CAN measures<sup>[47,105]</sup>. The UKPDS trial enrolled 3,867 relatively young patients with newly diagnosed T2DM. By the end of the trial, intensive glucose control had no effect on DSPN or CAN<sup>[47,106,107]</sup>. The VADT trial randomized 1,791 veterans with T2DM to either intensive or standard glucose control. After approximately 5.6 years of follow-up, there were no differences in the rates of new DSPN in the intensive vs standard arm, despite significant differences in the mean HbA<sub>1c</sub> between groups<sup>[47,108,109]</sup>. The ADDITION trial did not obtain baseline evaluations

for DSPN or CAN, preventing objective evaluations of change in DSPN or CAN with intervention<sup>[110-112]</sup>.

### Drugs for treatment of hypercholesterolemia

**The 3-hydroxy-3-methylglutaryl-coenzyme reductase inhibitors:** The 3-hydroxy-3-methylglutaryl-coenzyme (HMG-CoA) reductase inhibitors (lovastatin, pravastatin, fluvastatin, simvastatin, atorvastatin, rosuvastatin, pitavastatin). By inhibiting HMG-CoA reductase, statins block the pathway for synthesizing cholesterol in liver. The reduction in cholesterol level induces an increased expression of the low density lipoprotein receptor (LDLR), which results in decreased concentration of LDL-C and other apolipoprotein B (apoB)-containing lipoproteins<sup>[113]</sup>.

Secondary prevention statin studies such as MRC/BHF Heart Protection Study (HPS) showed significant risk reduction among individuals with DM. Based on this, the primary prevention of CVD with atorvastatin in T2DM in the Collaborative Atorvastatin Diabetes Study (CARDS) was designed to assess the effects of aggressive lipid lowering on the primary prevention of atherosclerotic CVD in individuals with T2DM. In individuals with average or mildly elevated LDL-C at baseline (mean 117 mg/dL), an LDL-C reduction to a mean of 82 mg/dL was accompanied by a 37% reduction in major cardiovascular events compared with placebo. CARDS, which originally planned a mean follow-up of 4 years, was terminated 2 years early because of the significant benefit achieved in the statin group<sup>[114,115]</sup>.

**Cholesterol absorption (ezetimibe):** In summary, cholesterol absorption inhibitors<sup>[113,115]</sup>: ↓ LDL-C 10%-18% by inhibiting intestinal absorption of cholesterol and decreasing delivery to the liver (primarily); ↓ ApoB 11%-16%; ↓ LDL-C 25%, total LDL-C 34%-61% (in combination with statins); ↓ LDL-C 20%-22% and apo B 25%-26% without reducing increasing HDL-C (in combination with fenofibrate). Ezetimibe: Usual recommended starting daily dosage 10 mg; dosage range 10 mg<sup>[115]</sup>.

### PCSK9 inhibitors (proprotein convertase subtilisin/kexin type 9) inhibitors (alirocumab, evolocumab):

Two monoclonal antibody inhibitors of PCSK9, a protein that regulates the recycling of LDLR, have recently been approved by the Food and Drug Administration (FDA)<sup>[116,117]</sup>. Alirocumab and evolocumab are subcutaneously injectable LDL-lowering agents capable of further reducing LDL approximately 60% when added to maximum statin therapy<sup>[118-122]</sup>. Alirocumab: Usual recommended starting daily dosage 75 mg every 2 wk; dosage range 75-150 mg every 2 wk. Evolocumab. Usual recommended starting daily dosage 140 mg every 2 wk or 420 mg once mo; dosage range not applicable<sup>[115]</sup>.

**Fibric acid derivatives (gemfibrozil, fenofibrate, fenofibric acid):** Fibrates are agonists of peroxisome

proliferator-activated receptor- $\alpha$  (PPAR- $\alpha$ ), acting *via* transcription factors regulating various steps in lipid and lipoprotein metabolism<sup>[113,123]</sup>. Fenofibrate: Usual recommended starting daily dosage 48-145 mg; dosage range 48-145 mg; Gemfibrozil: Usual recommended starting daily dosage 1.200 mg; dosage range 1.200 mg; Fenofibric acid: Usual recommended starting daily dosage 45-135 mg; dosage range 45-135 mg<sup>[115]</sup>.

**Niacin (nicotinic acid):** Nicotinic acid has been reported to decrease fatty acid influx to the liver and the secretion of VLDL by the liver; this effect appears to be mediated in part by the effects on hormone-sensitive lipase in the adipose tissue. Nicotinic acid has key action sites in both liver and adipose tissue. In the liver nicotinic acid is reported to inhibit diacylglycerol acyltransferase-2 (DGAT-2) that results in the decreased secretion of VLDL particles from the liver, which is also reflected in reductions of both IDL and LDL particles. Nicotinic acid raises HDL-C and apolipoprotein A1 (apoA1) primarily by stimulating apoA1 production in the liver<sup>[124]</sup>. The effects of nicotinic acid on lipolysis and fatty acid mobilization in adipocytes are well established<sup>[125,126]</sup>. Nicotinic acid (immediate-release): Usual recommended starting daily dosage 250 mg; dosage range 250-3000 mg; Nicotinic acid (extended-release): Usual recommended starting daily dosage 500 mg; dosage range 500-2000 mg<sup>[115]</sup>.

**Bile acid sequestrants:** In summary, bile acid sequestrants<sup>[115,127]</sup>: ↓ LDL-C (primarily) 15%-25% by binding bile acids and preventing their reabsorption in the ileum; ↓ glucose and HbA<sub>1c</sub> (approximately 0.5%) (colesevelam); is FDA approved to treat T2DM. Cholestyramine: Usual recommended starting daily dosage 8-16 g; dosage range 4-24 g; Colestipol: Usual recommended starting daily dosage 2 g; dosage range 2-16 g; Colesevelam: Usual recommended starting daily dosage 3.8 g; dosage range 3.8-4.5 g; Ezetimibe/simvastatin: Usual recommended starting daily dosage 10/20 mg; dosage range 10/10-10/80 mg; Extended-release niacin/simvastatin: Usual recommended starting daily dosage 500/20 mg; dosage range 500/20-1.000/20 mg<sup>[115]</sup>.

#### **Inhibitors of microsomal TG transfer protein**

Within the lumen of the endoplasmic reticulum, lomitapide inhibits microsomal TG transfer protein (MTP), which prevents the formation of apoB, and, thus, the formation of VLDL and chylomicrons as well. Altogether, this leads to a reduction of LDL-C. Lomitapide, the MTP inhibitor, and mipomersen, the antisense oligonucleotides against apo B, have shown their efficacy in lowering LDL-C in recent phase III trials and they were already approved for treating patients with homozygous familial hypercholesterolemia<sup>[128]</sup>. Lomitapide: Usual recommended starting daily dosage 5 mg, with subsequent titration; dosage range 5-60 mg<sup>[115]</sup>.

#### **Antisense apolipoprotein B oligonucleotide (mi-**

**pomersen *via* subQ injection):** Mipomersen is a second-generation antisense oligonucleotide targeted to human apoB-100, large protein synthesized by the liver that plays a fundamental role in human lipoprotein metabolism. Mipomersen predominantly distributes to the liver and decreases the production of apoB-100, the primary structural protein of the atherogenic lipoproteins including LDL, thereby reducing plasma LDL-C and apoB-100 concentrations<sup>[129]</sup>. Mipomersen (SubQ injection): Usual recommended starting daily dosage 200 mg once weekly, with subsequent titration; dosage range 200 mg once weekly<sup>[115]</sup>.

**Omega-3 fatty acids:** Omega-3 polyunsaturated fatty acids (PUFAs) (eicosapentaenoic acid and docosahexaenoic acid) are used at pharmacological doses to lower TGs. Prescription of omega-3 fatty acids (2-4 g/d) results in decreased plasma concentration of TGs and VLDL concentration<sup>[113]</sup>.

In summary, omega-3 fatty acids<sup>[115]</sup>: ↓ TG 27%-45%, TC 7%-10%, VLDL-C 20%-42%, apoB 4%, and non-HDL-C 8%-14% in individuals with severe hypertriglyceridemia, most likely by reducing hepatic VLDL-TG synthesis and/or secretion and enhancing TG clearance from circulating VLDL particles. Other potential mechanisms of action include<sup>[115]</sup>: ↑  $\beta$ -oxidation; ↓ inhibition of acyl-CoA; 1,2-diacylglycerol acyltransferase; ↓ decreased hepatic lipogenesis; ↑ increased plasma lipoprotein activity; ↓ LDL-C 5% (Icosapent ethyl); ↑ LDL-C 45% (omega-3-acid ethyl esters). Omega-3-acid ethyl esters (Lovaza): Usual recommended starting daily dosage 4 g per day; dosage range 4 g per day. Icosapent ethyl (Vascepa®) Usual recommended starting daily dosage 4 g per day; dosage range 4 g per day<sup>[115]</sup>.

#### **Specific features of DLP in insulin resistance and type 2 diabetes**

Diabetic DLP is a cluster of plasma lipid and lipoprotein abnormalities that are metabolically interrelated. The increase in large VLDL particles in T2DM initiates a sequence of events that generates atherogenic remnants, small TG-rich dense HDL particles and small dense LDL<sup>[113,130-132]</sup>.

#### **Evidence for low-density lipoprotein-lowering therapy**

The Cholesterol Treatment Trialists' meta-analysis further indicates that subjects with T2DM will have a relative risk reduction that is comparable to that seen in non-diabetic patients, but being at higher absolute risk, the absolute benefit will be greater, resulting in a lower number needed to treat<sup>[113,133,134]</sup>.

#### **Triglycerides and high-density lipoprotein cholesterol**

Clinical benefits achieved by the treatment of atherogenic DLP (high TGs and low HDL-C) are still a matter of discussion. Although the Helsinki Heart Study reported a significant reduction in CVD outcomes with gemfibrozil, neither the Fenofibrate Intervention and Event Lowering

in Diabetes (FIELD) nor the ACCORD study showed a reduction in total CVD outcomes<sup>[113,135-137]</sup>.

### **Treatment strategies for patients with T2DM and metabolic syndrome**

Recommendations for the treatment of DLP in DM<sup>[113]</sup>: In all patients with T1DM and in the presence of microalbuminuria and/or renal disease, LDL-C lowering (at least 50%) with statins as the first choice is recommended irrespective of the baseline LDL-C concentration (class I, level C)<sup>[113,138,139]</sup>; in patients with T2DM and CVD, and in patients without CVD who are > 40 years of age with one or more other CVD risk factors, the recommended goal for LDL-C is < 1.8 mmol/L (< 70 mg/dL), for non-HDL-C is < 2.6 mmol/L (< 100 mg/dL) and for apoB is < 80 mg/dL (class I, level B)<sup>[133,139]</sup>.

In all patients with T2DM and no additional risk factors and/or evidence of target organ damage, LDL-C < 2.6 mmol/L (< 100 mg/dL) is the primary goal. Non-HDL-C < 3.4 mmol/L (< 130 mg/dL) and apoB < 100 mg/dL are the secondary goals (class I, level B)<sup>[133,139]</sup>.

### **Fatty acids metabolism disorders**

Vasoactive prostanoids, metabolites and dihomono- $\gamma$ -linolenic acid (DGLA) are necessary for the normal nerve conductivity and blood flow. According to the data from double-blind, placebo-controlled studies prescription of DGLA to patients with DPN was accompanied by the increase in the speed of nerve conductivity. Prescription of L-carnitine can be recommended as one of the lipid-lowering therapy components to T2DM patients<sup>[140,141]</sup>.

### **Antioxidant therapy**

Hyperglycemia-induced OS and nitrosative stress has been singled out as one of the major links between DM and diabetic complications; leads to generation of free radicals due to autooxidation of glucose and glycosylation of proteins<sup>[142,143]</sup>. The persistent increase in reactive oxygen species (ROS) and reactive nitrogen species (RNS) accompanied by a decrease in antioxidant (AO) activity leads to the occurrence of OS and nitrosative stress which can cause endothelial dysfunction, IR, and eventually leads to diabetic microvascular and macrovascular complications<sup>[144]</sup>. Reactive species can be eliminated by a number of enzymatic and nonenzymatic antioxidant mechanisms. Superoxide dismutase (SOD) immediately converts  $\text{O}_2^-$  to hydrogen peroxide ( $\text{H}_2\text{O}_2$ ), which is then detoxified to water either by catalase in the lysosomes or by glutathione peroxidase (GPx) in the mitochondria. Another enzyme that is important is glutathione reductase (GSR), which regenerates glutathione that is used as a hydrogen donor by GPx during the elimination of  $\text{H}_2\text{O}_2$ <sup>[142,143]</sup>.

Hyperlipidemia in the presence of hyperglycemia generates additional ROS that are also implicated in cell dysfunction<sup>[143,145]</sup>. OS has been implicated in causing nerve damage in several animal, human, and experimental models of diabetes<sup>[143,146]</sup>. The mechanisms involved in OS-induced nerve dysfunctions include

generation of ROS, increased RNS, lipid peroxidation (LPO), deoxyribonucleic acid (DNA) damage, and reduction in cellular antioxidants<sup>[143,147]</sup>. Increased ROS and RNS together with reductions in the AO defense mechanisms within the neurons contribute to the manifestations of DPN which include nerve blood flow impairment, endoneurial hypoxia, nerve degeneration, axonal atrophy. Recent findings implicate free radicals in the development of DN in addition to the impairment of AO defense system in T2DM<sup>[142]</sup>.

Also, induction of aldose reductase enzyme depletes the reduced form of nicotinamide adenine dinucleotide phosphate (NADPH), a requirement for the regeneration of the cellular AO, reduced glutathione (GSH), contributing to OS<sup>[7,143,148,149]</sup>. Intra- and inter-molecular cross-linking reactions with proteins, lipids, or DNA lead to the formation of stable, covalent, and irreversible adducts collectively referred to as advanced glucose end-products (AGEs) that accumulate within cells with age<sup>[143,148]</sup>. Increased formation of AGEs leads to the elevation of OS and subsequently damage to cells and tissues, an occurrence that has been found in experimental animals and in humans<sup>[150]</sup>. AGEs have also been shown to decrease axonal transport within neurons leading to their degeneration<sup>[143,151]</sup>.

Antioxidants are available endogenously as a physiological defense mechanism of the cell or obtained exogenously from diet. The enzymatic AO systems, such as copper, zinc, manganese and selenium, SOD, GPx, GSR, and catalase may remove the ROS directly or sequentially, preventing their excessive accumulation and consequent adverse effects. Non-enzymatic AO systems consist of scavenging molecules that are endogenously produced such as GSH, ubiquinol, and uric acid or derivatives of the diet such as vitamins A, C and E, carotenoids, lipoic acid (LA); coenzyme Q<sub>10</sub> (CoQ<sub>10</sub>); and cofactors like albumin, vitamins B<sub>1</sub>, B<sub>3</sub>, folic and uric acids<sup>[152,153]</sup>. Vitamins C, E and LA are involved in the termination of the LPO process<sup>[152]</sup>. The abilities of flavonoids to scavenge free radicals have also been reported<sup>[143]</sup>. However, in the case of macrovascular/microvascular complications, the antioxidant therapy is beneficial together with BP control, management of atherogenic DLP, and optimal glucose control<sup>[143,153,154]</sup>.

### **Strategies targeted directly against reactive oxygen species and reactive nitrogen species<sup>[143]</sup>**

Diabetes-induced nerve dysfunction is established to be caused by an increase in the overproduction of ROS and RNS. It was therefore hypothesized that antioxidants or agents that directly scavenge free radicals can reduce the formation or progression of ROS reactions which in turn decreases OS thereby improving DPN conditions<sup>[143]</sup>. Some of the most important antioxidants include ALA, vitamins A, C, and E, acetyl L-carnitine, taurine, and melatonin.

**ALA:** ALA can be biosynthesized in plants and animals where it is metabolized to dihydrolipoic acid (DHLA)

upon uptake into cells. Both ALA and DHLA are potent free radical scavengers that are also involved in the regeneration of vitamins C and E and oxidized GSH within the cell<sup>[155]</sup>. ALA is also a cofactor for a number of mitochondrial enzymes<sup>[143]</sup>. ALA is known to reduce OS by inhibiting hexosamine and AGEs pathways<sup>[143]</sup>.

ALA, a critical co-factor for mitochondrial dehydrogenase reactions, is another compound with free radical-scavenging activity<sup>[156,157]</sup>. ALA was found to increase glucose transport in muscle cells in culture by stimulating translocation of glucose transporter type 4 (GLUT4) from internal pools to the plasma membrane<sup>[153]</sup>.

Treatment with ALA protected the insulin receptor from oxidative damage, maintaining its functional integrity in cultured adipocytes. Oral administration of ALA significantly increased insulin-mediated glucose uptake, presumably by modulating insulin sensitivity in patients with T2DM<sup>[153]</sup>. ALA600SOD (an oral formulation of ALA and SOD) improved symptoms and electroneurographic parameters among subjects with DPN<sup>[158]</sup>.

#### **Vitamins A, B<sub>1</sub>, B<sub>3</sub>, C and E**

Dietary antioxidant vitamins such as vitamins A, C, and E detoxify free radicals directly and also interact with recycling processes to create reduced forms of the vitamins. Antioxidant vitamins have a number of biological activities such as immune stimulation and prevention of genetic changes by inhibiting DNA damage induced by the ROS metabolites<sup>[159]</sup>.

**Vitamin A:** Vitamin A has a plethora of cellular actions. Besides modulating gene expression, cell growth and differentiation, this vitamin may also act as AO, although the mechanisms of action in this role are not fully deciphered<sup>[159]</sup>. The AO potential of carotenoids (vitamin A) depends on their distinct membrane-lipid interactions, while some carotenoids can decrease LPO, others can stimulate it<sup>[159]</sup>.

**Vitamin B<sub>1</sub>:** Thiamine derivatives are cofactor for enzymes involved in the production of chemical energy from carbohydrates and fat. Thiamine deficiency (TD) may be associated with specific and selective neuronal cell death and damage of the blood-brain barrier. DM might be considered as TD state, if not in absolute terms at least relative to the increased requirements deriving from accelerated and amplified glucose metabolism in non-insulin dependent tissues that, like the vessel wall, are prone to complications. The TD in clinical diabetes may increase the fragility of vascular cells to the adverse effects of hyperglycemia and there by the increase of the risk of developing microvascular complications<sup>[160]</sup>.

**Nicotinamide (vitamin B<sub>3</sub>):** The vitamin plays an important role in mitochondrial energy generation and DNA repair. Deficiency of nicotinamide is associated with dermatological, gastrointestinal, hematological and

nervous system dysfunction. Sensory neuropathy due to vitamin B<sub>3</sub> deficiency is characterized by decreased sensation to touch and vibration<sup>[154]</sup>.

**Vitamin C:** Ascorbic acid serves as a cofactor for hydroxylation and function of monooxygenase enzymes in the synthesis of sub-tissues (collagen), neurotransmitters and carnitine. Ascorbic acid is an antioxidant acting as an enzymatic cofactor in maintaining tissue integrity and plays an important role in formation of epithelial and endothelial barriers and aids in regeneration of oxidized vitamin E<sup>[154]</sup>.

Vitamin C has a role in scavenging ROS and RNS by becoming oxidized itself. The oxidized products of vitamin C, ascorbic radical and dehydroascorbic radical are regenerated by GSH, the reduced form of nicotinamide adenine dinucleotide (NADH) or NADPH. In addition, vitamin C can reduce the oxidized forms of vitamin E and GSH. There is paucity of information on the role of vitamin C in DPN despite evidence that it normalizes sorbitol concentration in the blood, scavenges LPO, and regenerates GSH in diabetes<sup>[143]</sup>. In a prospective cohort study, vitamin C intake was found to be significantly lower among incident cases of T2DM<sup>[153]</sup>.

**Vitamin E:** Vitamin E is a group of fat-soluble compounds that includes the AO compound alpha-tocopherol, which is a lipid-soluble AO that increases resistance of LDL-C to oxidation, reduces smooth muscle cell proliferation, and reduces adhesiveness of platelets to collagen<sup>[154]</sup>. It inhibits LPO by scavenging reactive oxygen species and preserving cell membranes. Neurological conditions associated with vitamin E deficiency includes: Posterior spinal columns disease, spinocerebellar ataxia, peripheral neuropathy, and optic neuropathy<sup>[154]</sup>.

Vitamin E has been reported to alleviate symptoms of DM and diabetes-induced complications in animals through reduction in OS biomarkers. In clinical trials, vitamin E did not however show a significant relief of the symptoms of microvascular and macrovascular complications despite reducing OS biomarkers in the subjects<sup>[143]</sup>.

The lack of performance of vitamin E may not however be unconnected to the fact that the design of each study was not targeted directly at diabetes end-points such as HbA<sub>1c</sub> < 7% levels, BP < 130/180 mmHg, avoiding hypoglycemic events, and maintaining weights but rather at complications that may have multiple causal factors<sup>[143]</sup>. Vitamin E supplementation reduced blood glucose and HbA<sub>1c</sub> levels significantly and had a neuroprotective effect on the total myenteric population, without affecting intestinal area or thickness of the intestinal wall or muscular tunic<sup>[143,161]</sup>.

Vitamin doses may also be part of the problem, as the effect of vitamins depends on dietary concentrations and/or supplement intake. The wide variety of doses reached with diet and supplements, and the lack of an established "pharmacological" dose of vitamins, makes



it difficult to ascertain the true net effect of vitamin status or supplementation needed to generate beneficial effects<sup>[161-163]</sup>. Other AOs are taurine, acetyl L-carnitine, and N-acetylcysteine which have been demonstrated to reduce the progression of DPN<sup>[15]</sup>.

### Strategies targeted against individual OS pathways<sup>[143]</sup>

The pathways of hyperglycemia-induced OS discussed earlier are potential therapeutic targets in DPN. Some of the interventions have resulted in specific therapies, for example, aldose reductase inhibitors (ARIs), protein kinase C (PKC) inhibitors, and anti-AGE agents.

**Aldose reductase inhibitors:** Therefore, ARIs are agents that reduce the flux of glucose into the polyol pathway thereby preventing the harmful effects of excess sorbitol and fructose in neurons. Results from *in vivo* and *in vitro* animal studies highlighted the positive effect of inhibiting ARI on DPN<sup>[143]</sup>. These studies have been the foundation for embarking on several clinical trials with ARIs with AO activities such as Fidarestat (SNK-860), Epalrestat, and Ranirestat (AS-3201)<sup>[143]</sup>. Among the ARIs that have made it to clinical trials, Epalrestat was licensed in Japan while others [e.g., Tolrestat (AY-2773), Zenarestat (FK-366; FR-74366), and Ponalrestat] were withdrawn due to inefficacy or safety concerns<sup>[143]</sup>. ARIs prevent the progression of DPN, enhance sural motor and sensory nerve conduction velocities (NCV), and improve wrist and ankle F-wave latency together with alleviating neuropathic pain<sup>[143,164]</sup>. In addition, it is reported that the prescription of eparestat may improve subjective neuropathy symptoms, sensory and motor nerve conduction velocity<sup>[143]</sup>.

**Protein kinase C inhibitors:** PKC is involved in the activation of key regulatory proteins responsible for nerve function and synthesis of neurotransmitters. Inhibiting PKC was reported to suppress neuropathic pain. Ruboxistaurin, a specific inhibitor of neuronal protein kinase C (PKC1B) that possesses antioxidant effects, improves NCV and endoneurial blood flow in diabetic rats. In clinical trials, Ruboxistaurin reduces the progression of DPN<sup>[143]</sup> but fails to achieve its primary end-points, vibration detection threshold and symptoms reduction. Ruboxistaurin had effects on diabetic DPN in some studies, but the evidence is not enough for meta-analysis and firm conclusion.

**Anti-advanced glucose end-products agents:** Anti-AGE agents prevent the formation and accumulation of AGEs. They also counteract the AGE-receptor for AGE interactions that might aggravate the OS damage in DPN. Examples are benfotiamine, aminoguanidine, and aspirin which are known for their AO properties through the inhibition of AGEs formation<sup>[7,143]</sup>.

### Benfotiamine

Benfotiamine (BFT) has been reported to increase

transketolase enzyme activity which directs AGE substrates to the pentose phosphate pathway resulting in the reduction of hyperglycemic damage. It also inhibits the increase in UDP-N-acetylglucosamine that induces the hexosamine pathway activity ultimately reducing tissue AGEs<sup>[143,165-167]</sup>. In combination with pyridoxamine and cyanocobalamin, BFT improves the vibration perception threshold, motor function, and symptom score<sup>[143,168]</sup>.

### Aminoguanidine

Aminoguanidine has been reported to react with 3-deoxyglucosone, a precursor of AGE, thereby trapping the reactive carbonyls and preventing the formation of AGEs although it has been withdrawn from clinical trial as a result of toxicity<sup>[143,169]</sup>.

### Aspirin

Aspirin has been reported to inhibit the production of pentosidine, a cross-linking AGE, by scavenging free radicals and chelating metal ions in collagen incubated with glucose *in vitro*<sup>[170]</sup>.

### Strategies targeted at mitochondria<sup>[143]</sup>

It has been demonstrated that excess superoxide anion radicals, hydroxyl radicals, and H<sub>2</sub>O<sub>2</sub> are produced during the generation of adenosine triphosphate (ATP) in mitochondria under hyperglycemic conditions contributing to increased oxidative damage<sup>[143]</sup>.

**Coenzyme Q:** Coenzyme Q (a mitochondrial antioxidant) or ubiquinone may decrease OS not only by quenching reactive oxidant species but also by "recoupling" mitochondrial oxidative phosphorylation, thereby reducing superoxide production<sup>[153,156]</sup>. CoQ<sub>10</sub> supplements can be either the oxidized form (ubiquinone) or reduced form (ubiquinol) as both forms seem pretty equally potent in increasing circulating levels of total CoQ<sub>10</sub> in the body. "Total CoQ<sub>10</sub>" refers to the sum of both forms, since CoQ<sub>10</sub> can readily swap between forms as it acts in the body<sup>[171]</sup>. Ubiquinone and ubiquinol form a pair of molecules known as a REDOX couplet (reduction/oxidation) which is a property that is crucial for the functioning of CoQ<sub>10</sub> within the electron transport chain, where it transports electrons from complex I and II to complex III. CoQ<sub>10</sub> is an important micronutrient acting on the electron transport chain of the mitochondria with two major functions: (1) synthesis of ATP; and (2) a potent antioxidant. Deficiency in CoQ<sub>10</sub> is often seen in patients with T2DM<sup>[171]</sup>. CoQ<sub>10</sub> also has the ability to prevent LPO from either inhibiting lipid peroxyl radicals and has been noted to restore α-tocopherol from its radical state back to its AO state<sup>[171]</sup>. Protein carbonylation has also been noted to be reduced with CoQ<sub>10</sub> (direct inhibition of protein oxidation) but has been noted to not influence the conversion of NO into peroxynitrite. *Via* its AO potential, ubiquinone can protect DNA from excess oxidation from H<sub>2</sub>O<sub>2</sub> and potentially act as an anticarcinogen (as noted in human lymphocytes at least)<sup>[171]</sup>.

Deficiency in CoQ<sub>10</sub> is often present among pati-

ents with T2DM due to various reasons. As a potent antioxidant, CoQ<sub>10</sub> is assumed to scavenge excessive ROS and provide protection to cells, especially mitochondria from oxidative damage. Therefore, restoration of CoQ<sub>10</sub> level among patients with T2DM by supplementation of exogenous CoQ<sub>10</sub> could potentially alleviate OS, preserve mitochondrial function, and eventually lead to improvement of glycemic control<sup>[171]</sup>. In DM, CoQ<sub>10</sub> has been reported to show promising therapeutic potential<sup>[171]</sup>. The standard dose for CoQ<sub>10</sub> is generally 90 mg for a low dose and 200 mg for the higher dose, taken once daily with a meal due to its reliance on food for absorption<sup>[171]</sup>.

### **Telmisartan**

Telmisartan is a well-known unique angiotensin II (Ang II) type 1 receptor blocker (ARB) that exerts a powerful AO effect. Furthermore, a number of properties like the best binding affinity to Ang II type 1 receptors, the maximum plasma half life and the highest lipophilicity among the presently available ARBs make this molecule a long lasting antioxidant<sup>[172]</sup>. Telmisartan has a potential neuro-protective effect on PNP; this is mediated through its anti-inflammatory effects and its dual properties as an ARB, and a partial PPAR- $\gamma$  ligand<sup>[172]</sup>. Usual adult dose for hypertension: Initial dose: 40 mg orally once a day. Maintenance dose: 40 to 80 mg orally once a day. Usual adult dose for cardiovascular risk reduction: 80 mg orally once a day.

### **Metformin**

Both American and European guidelines recommend metformin as the first-line agent for the pharmacological management of T2DM and preventing its complications<sup>[3]</sup>. It possesses AO property and causes reduction of albumin excretion rate in the urine of diabetic patients. In addition, it decreases the production of AGEs, improves free radical defense system by its ability to directly scavenge oxygenated free radicals and thereby reduces intracellular ROS levels. The glycemic control-independent neuroprotective and antineuropathic effects of metformin recently reported in animal studies<sup>[173]</sup>. Usual adult dose for T2DM: Initial dose: 500 mg PO bid or 850 mg PO qd. Dose titration: Increase in 500 mg weekly increments or 850 mg every 2 wk as tolerated. Maintenance dose: 2.000 mg daily in divided doses. Maximum dose: 2500 mg/d.

### **Pioglitazone**

Thiazolidinedione (TZD) drugs such as pioglitazone are approved by the FDA for the treatment of T2DM. TZDs also reduce the molecular and behavioral sequelae of neurological disease. Positive and protective effects of TZD group of drugs, like pioglitazone, in the amelioration of AO enzyme levels in renal histopathology and renal tissue associated with diabetic nephropathy has recently been investigated by many researchers. Increased expression of nuclear transcription factor p65 in renal tubules and glomeruli during diabetic nephropathy has

been reduced by pioglitazone therapy thereby showing protection from renal pathophysiology. But TZDs has limited clinical uses due to the occurrence of fluid retention, hemodilution, and heart failure in about 15% of patients. Usual adult dose for T2DM: Initial dose: 15-30 mg PO with meal qDay initial; may increase dose by 15 mg with careful monitoring to 45 mg qDay maximum. Some drugs with AO properties which have antioxidant effect in patients with DM are shown in Table 1<sup>[163]</sup>.

### **Triple antioxidant therapy**

Participants with T1DM with early complications were randomly assigned to a combination AO regimen or to placebo. Allopurinol (300 mg qd), ALA (600 mg bid) and nicotinamide (750 mg bid), or matched PO placebos were administered for 24 mo. The administration of each individual active drug or placebo component was titrated in consecutive weeks (first ALA, then nicotinamide, finally allopurinol) such that the participant began receiving full therapeutic doses of all the medications 3 wk postrandomisation. In cohort of T1DM patients with mild-to-moderate CAN, a combination AO treatment regimen did not prevent progression of CAN, had no beneficial effects on myocardial perfusion or DPN, and may have been detrimental. However, a larger study is necessary to assess the underlying causes of these findings<sup>[83]</sup>.

### **Correction of vascular endothelial dysfunction**<sup>[174,175]</sup>

**Trimetazidine:** Prescription of this medication is accompanied by glucose metabolism improvement, endothelin-1 reduction in patients with diabetic cardiomyopathy, significantly contributes to the improvement of ejection fraction (EF) in patients with heart failure<sup>[174,175]</sup>.

**Perhexiline:** Prescription of this pharmacological agent to patients with HF significantly improve the EF and VO<sub>2</sub>max, but unfortunately, the clinical use is limited because of the increased risk of PNP development and hepatotoxicity<sup>[175,176]</sup>.

**Ranolazine:** Unfortunately the prescription of this drug with possible metabolism modification properties is associated with the increased possibility of QTc prolongation<sup>[175,177]</sup>.

**Beta blockers:** Prescription of beta blockers, particularly the  $\beta_1$ -selective, is associated with endothelial protective effects. In patients with essential hypertension prescription of nebivolol was accompanied by endothelium-dependent vasodilator function improvement<sup>[178-183]</sup>. Endothelium-dependent responses in patients with essential hypertension were improved after prescription of carvedilol (non-selective  $\beta_{1,2}$  antagonist with  $\alpha$ -antagonist property), but this can be due its antioxidant capacity<sup>[182,183]</sup>. The combined prescription of angiotensin-converting enzyme inhibitor and carvedilol was accompanied with more pronounced endothelium-dependent vasodilator

responses<sup>[184]</sup>.

**Calcium channel blockers:** Prescription of dihydropyridine calcium channel blockers is accompanied by endothelial protective effect, mainly mediated by reduction in LPO and associated ROS generation<sup>[183,185,186]</sup>. Prescription of isradipine to cholesterol-fed rabbit was associated with endothelial function improvement<sup>[183,187]</sup>.

Prescription of some dihydropyridines (amlodipine, nifedipine and azelnidipine) was associated with decrease of leucocyte activation and interleukin-6 and C-reactive protein levels<sup>[183,188]</sup>, also improvement of endothelial function by treatment with amlodipine was found<sup>[183,189,190]</sup>.

The combination of statins with amlodipine produces more beneficial effect on endothelial function in rats with DM<sup>[191,192]</sup>. Thus, prescription of dihydropyridine calcium channel blockers is suitable for treatment of endothelial dysfunction.

**Phosphodiesterase-5 inhibitors:** Phosphodiesterase-5 (PDE5) is highly specific for hydrolysis of cyclic nucleotides monophosphate, such as cyclic guanosine monophosphate (cGMP), which is a molecular messenger involved in regulation of vascular function, axon guidance, the modulation of DPN and pain perception<sup>[193-195]</sup>. PDE5 inhibitors including sildenafil, tadalafil, and vardenafil, are primarily used as pharmacological agents for the treatment of erectile dysfunction, but they also have a potential therapeutic application for the treatment of neurovascular dysfunction, neuroinflammatory and neurodegenerative diseases by inducing accumulation of cGMP and activation of cGMP dependent protein kinase, e.g., PKG, signaling pathways<sup>[195,196]</sup>. Clinical study demonstrates that PDE5 inhibitors are safe and generally well tolerated with no serious side effects in patients. Sildenafil improves vascular function and blood supply to the vasa nervorum while ameliorating neurological function of neuropathy in diabetic patients<sup>[197]</sup>.

The considerably longer duration of action for tadalafil may permit less frequent dosing and could potentially reduce adverse effects associated with treatment. Moreover, the absorption and activity of tadalafil is unaffected by food ingestion, age, diabetes, or mild to moderate hepatic insufficiency. Also, tadalafil did not lower systemic BP in clinical trials<sup>[198]</sup>.

The angiopoietin-Tie (ANG/Tie) signaling system was identified as a vascular-specific receptor tyrosine kinase pathway that is essential for vessel development. PDE5 inhibitor-induced activation of the cGMP/PKG and ANG/Tie2 signaling pathways promotes neurovascular remodeling both directly through these signaling pathways to ameliorate neurovascular function, and indirectly *via* endothelial cells and Schwann cells, which produce neurotrophic factors and provide a permissive restorative microenvironment in the sciatic nerve. Both direct and indirect approaches, in concern, improve neurological function of diabetic neuropathy<sup>[199]</sup>.

### **Ivabradine, the cardiac pacemaker “funny” [I<sub>f</sub>] inhibitor:**

Ivabradine is a heart-rate-lowering agent that acts by selectively and specifically inhibiting the  $I_f$ , a mixed  $\text{Na}^+$ - $\text{K}^+$  inward current that controls the spontaneous diastolic depolarization in the sinoatrial node and hence regulates the HR<sup>[200,201]</sup>. Ivabradine slows down HR and exerts cardioprotective effects<sup>[183,202,203]</sup>.

According to data obtained from clinical studies the influence of ivabradine on flow-mediated vasodilation is nonsignificant, so the effects of this drug are controversial<sup>[183,204,205]</sup>. In patients with stable CAD without heart failure, the additional prescription of the cardiac pacemaker “funny” [I<sub>f</sub>] inhibitor was associated with increased frequency of atrial fibrillation<sup>[183,206]</sup>.

### **Prevention and treatment of thrombosis**

Administration of antiplatelet agents (acetylsalicylic acid, clopidogrel and others) can lead to prevention of blood clots, stenocardia and development of MI. Clopidogrel is more effective medication for the reduction of cardiovascular risk factors<sup>[207,208]</sup>.

### **Treatment of OH**

Treatment of OH should involve both non pharmacological and pharmacological interventions. Non-pharmacologic treatment should be the initial approach. OH should be treated by volume repletion with fluids and salt. Patients should be advised to avoid hot baths, to get out of bed slowly and if their diabetes is being treated with insulin, patients should administer this medication while lying down<sup>[8,209,210]</sup>. Although there are concerns on risk of supine hypertension by administration of fludrocortisones, rescription of low-dose may be beneficial in supplementing volume repletion<sup>[8,209,210]</sup>.

Pharmacological intervention includes prescription of mineralocorticoids and/or adrenergic agonists. Supplementary salt intake together with mineralocorticoid (fludrocortisones) increases plasma volume. In generally it is ineffective until edema develops, which carries a risk of causing hypertension and congestive HF<sup>[81]</sup>. Prescription of adrenergic agonist (ephedrine, midodrine, clonidine) is effective in some patients, but titration of this medications should be performed gradually<sup>[81]</sup>. The somatostatin analog (octreotide) can also be prescribed to patients with refractory OH after eating<sup>[7]</sup>.

OH can be aggravated by different forms of therapy [e.g. tricyclic antidepressant (amitriptyline)] used for the treatment of other complications (e.g., painful sensory neuropathy). Therefore, careful attention to other medications that may aggravate OH in these patients is mandatory<sup>[8,211]</sup>. Similarly, the use of  $\beta$ -adrenergic blockers may benefit the tachycardia and anticholinergics, the orthostatic bradycardia. Pyridostigmine (inhibitor of acetylcholinesterase) has also been shown to improve symptoms and orthostatic BP for patients with POTS and HRV in healthy young adults<sup>[8,212]</sup>. Treatment with somatostatin (Octreotide) can be recommended for patients with pooling of blood in the splanchnic bed, and

prescription of erythropoietin for patients with contracted plasma volume<sup>[8]</sup>. Sympathomimetic drugs (midodrine) are the first-line medicines in the treatment of patients with OH<sup>[3,39,81]</sup>. The titration of midodrin should be performed gradually to efficacy.

## CONCLUSION

CAN is common and often underdiagnosed complication of DM which is strongly associated with increased rate of cardiovascular morbidity and mortality. As the development and progression of cardiovascular denervation can be slowed down and is partly reversible in the early disease stages, it is recommended to perform screening for that complication among DM patients. A variety of methods can be used for CAN assessment, but the "gold" standard clinical tests are CARTs. The basic CAN prevention and treatment tools are intensive glycemic control, lifestyle modification and management of CVD risk, but the unified algorithm and known disease modifying treatment is lacking.

CAN treatment is a complex process, that includes: Lifestyle modification; reducing IR; intensive glycemic control; treatment of DLP, antioxidants, vitamins, correction of vascular endothelial dysfunction, prevention and treatment of thrombosis and OH. The new possible perspective areas of CAN treatment are administration of thromboxane A<sub>2</sub> blockers and prostacyclin analogues, PDE5 inhibitors, ALA,  $\omega$ -3 PUFAs, DGLA and the combined prescription of ALA, DGLA and  $\omega$ -3 PUFAs. In addition the combined administration of ALA,  $\omega$ -3 PUFAs and benfotiamine promotes reduction of chronic inflammation markers and increase of HRV parameters, that might be useful in preventing the development and progression of CAN. Development of OH is associated with severe or advanced CAN and prescription of nonpharmacological and pharmacological, in the foreground midodrine and fludrocortisone acetate, treatment methods are necessary.

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