DIABETE OGGI

prevenzione e cura al centro del cambiamento

SID Società Italiana di Diabetologia

AMD Associazione Medici Diabetologi

Latina, 7 giugno 2025

Focus sulla cardiopatia autonomica

Dott.ssa Ilenia D'Ippolito

UOC Endocrinologia e Diabetologia - Policlinico di Tor Vergata
Dipartimento di Medicina dei Sistemi - Università di Tor Vergata
Roma

PTV FONDAZIONE PTV POLICLINICO TOR VERGATA

TOR VERGATA UNIVERSITÀ DEGLI STUDI DI ROMA

La dr.sa Ilenia D'Ippolito dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- Abbott
- Novo Nordisk

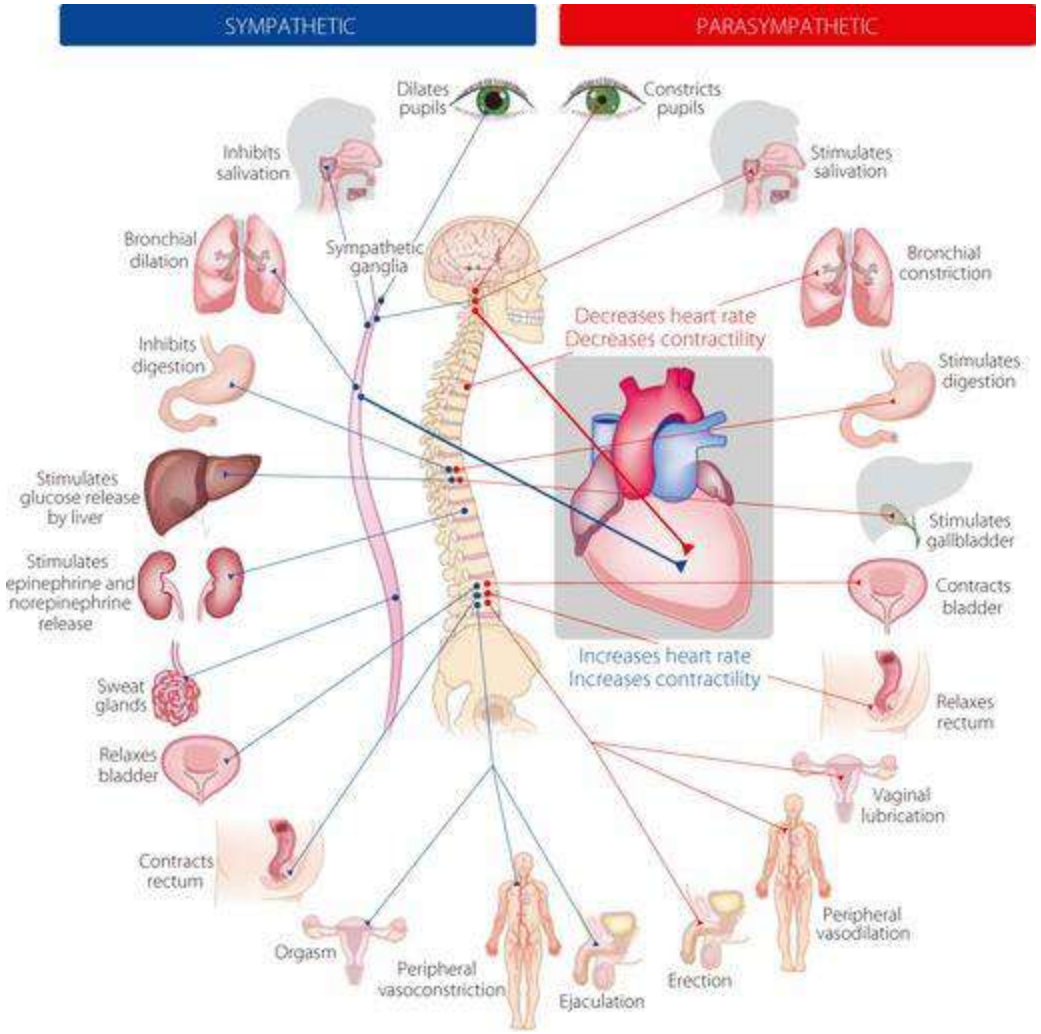
Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente aspecifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).

Agenda

- Diabetic autonomic neuropathy and cardiovascular autonomic neuropathy: definitions, epidemiology and natural history of CAN
- CAN: impact on mortality and morbility
- Diagnosis of diabetic autonomic neuropathy
- Autonomic symptoms in diabetic neuropathy
- COMPASS 31 for the assessment of autonomic symptoms
- CAN: the issue of underdiagnosis
- CAN management

Diabetic autonomic neuropathy and cardiovascular autonomic neuropathy: definitions

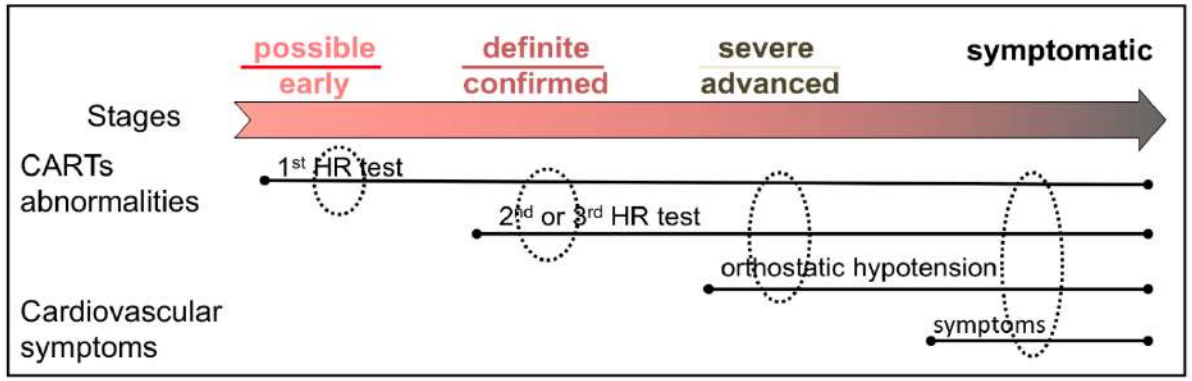
- Diabetic autonomic neuropathy (DAN) is classically defined as an autonomic nervous system disorder in the setting of diabetes or prediabetes after exclusion of other causes.
- DAN is a systemic disorder, which includes several clinical manifestations and leads to significant increase in morbidity and mortality.
- The most common manifestation of DAN is cardiovascular autonomic neuropathy (CAN), defined as an alteration of autonomic control of the cardiovascular system in the setting of diabetes, after exclusion of other causes.



Tesfaye S et al for The Toronto Neuropathy Expert Group. *Diabetes Care, 2010*
Spallone V et al on behalf of the Toronto Consensus Panel on Diabetic Neuropathy. *Diabetes Metab Res Rev 2011*
Vinik AI et al J Diabetes Investig. 2013;4:4-18

Epidemiology and natural history of CAN

- Prevalence of CAN in diabetes: 20%
- Prevalence of CAN in prediabetes: 11.4% (including IFG and IGT)
- The risk of developing CAN increases with age, duration of diabetes and suboptimal metabolic control reaching to 65% in patients with long disease duration.



777 patients with T2D (ADDITION – Denmark) evaluetad for CAN at 6 and 13 years from T2D diagnosis.

Prevalence of confirmed CAN increased from 9.1 to 15.1 with a total incidence of 11.9% and an annual incidence of 1.8%.

CAN status regressed in 41 patients: **8 patients with confirmed CAN changed to no CAN.**

Andersen ST et al Diabetes Care. 2018 Dec;41(12):2586-2594

In 759 subjects with T2D and CAN retrospectively followed for 2-3 years

Regression of CAN status in 13 out of 40 patients

9 patients with confirmed CAN changed to no CAN

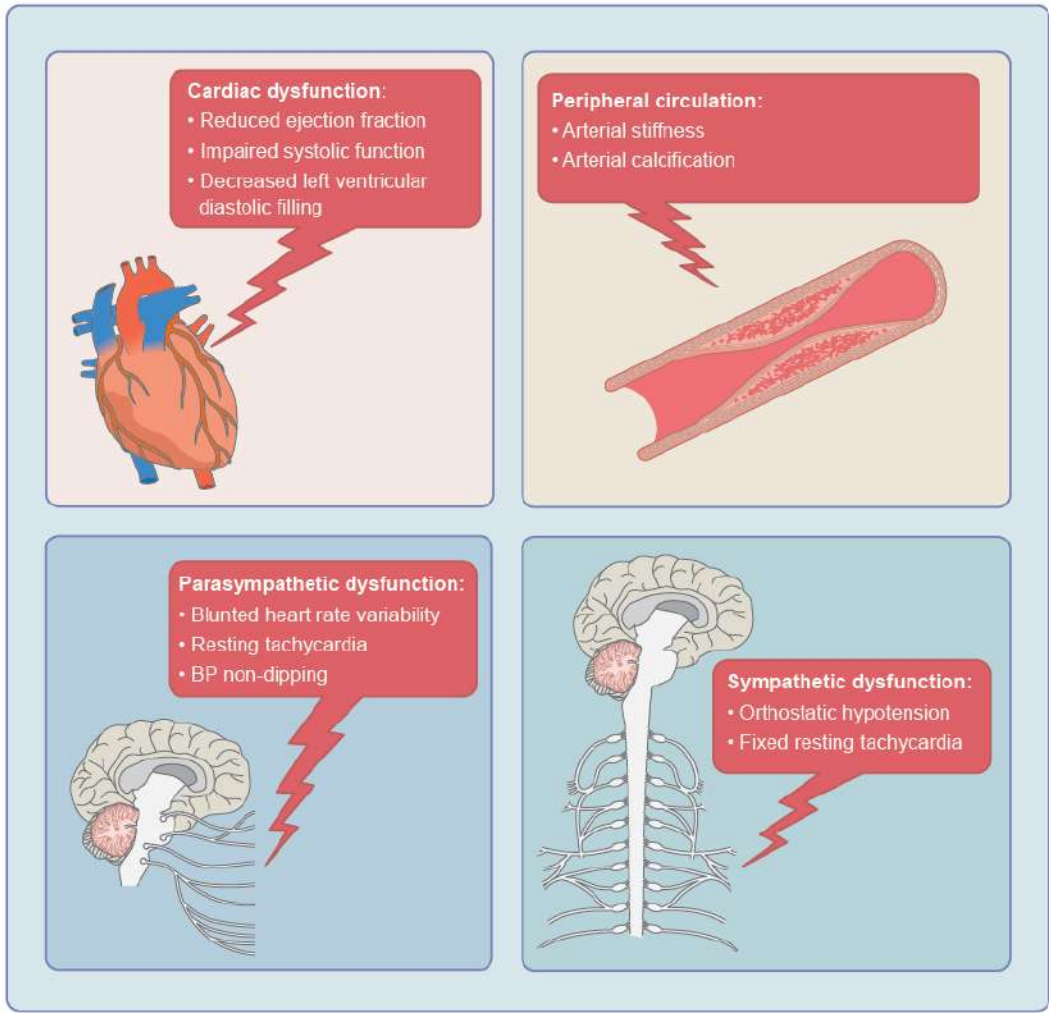
Factors related to CAN *regression*:

- Age (youger)
- Tight glycemic control
- Body weight reduction

Jun JE et al Cardiovasc Diabetol. 2019 Mar 11;18(1):29

Williams SM, et al. Diabetes Ther. 2019 Dec;10(6):1995-2021
Vinik AI, et al., Diabetes Care. 2003 May;26(5):1553-79
Eleftheriadou A, et al., Diabetologia. 2024 67:2611–2625

CAN: impact on mortality and morbility



- CAN is a strong predictor of all-cause mortality and cardiovascular disease (CVD) mortality, even for populations at higher CVD risk.

- Orthostatic hypotension, when due to advanced CAN, is associated with an additional increase in mortality risk over that driven by HRV abnormalities

CAN is a strong predictor of vascular morbidities:

- Silent myocardial ischemia
- Coronary artery disease
- Cardiovascular morbidity
- Perioperative instability
- Stroke

Recent evidences from a subanalysis of the ACCORD study (7,866 subjects; 60% male, 40% female) indicates that the presence of cardiovascular autonomic neuropathy in women is associated with a 67–78% increase in all-cause mortality and up to a 330% increase in cardiovascular mortality. No significant association was observed in men.

Pop-Busui, et al., *Diabetes Care*. 2010;33:1578–1584
Spallone V, and Toronto Consensus Panel on Diabetic Neuropathy. Diabetes Metab Res Rev. 2011 Oct;27(7):639-53.
Eleftheriadou A, et al., Diabetologia. 2024 67:2611–2625
Zhou Z, et al., J Am Heart Assoc. 2025 Jan 21;14(2):e034626.

Diagnosis of diabetic autonomic neuropathy

- Symptoms and signs of autonomic neuropathy should be assessed in people with diabetes starting at diagnosis of type 2 diabetes and 5 years after the diagnosis of type 1 diabetes, and at least annually thereafter, and with evidence of other microvascular complications, particularly kidney disease and diabetic peripheral neuropathy

- Screening can include asking about orthostatic dizziness, syncope, early satiety, erectile dysfunction, changes in sweating patterns, or dry cracked skin in the extremities

- Signs of autonomic neuropathy include orthostatic hypotension, a resting tachycardia, or evidence of peripheral dryness or cracking of skin.

Guidelines of scientific societies on screening and diagnosis of CAN in clinical practice

	Toronto Consensus (2011)	Position Statement ADA (2017)	Position Statement AACE/ACE (2018)	SID/AMD Standards (2018)
Symptoms	**Screening**	**Screening**	**Screening**	**Screening**
Signs	**Screening**	**Screening Diagnosis**	**Screening**	**Screening**
CARTs	**Gold standard for diagnosis**	**Possible In asymptomatic patients**	**Screening**	**Diagnosis**
HRV (time- and frequency-domain indices)	**Prognostic information**	**Research**	**In addition to CARTs**	**Research**
Candidates	In particular in those at greater risk for CAN; universal screening of symptoms and signs	In presence of microvascular complications and/or hypoglycaemia unawareness	Those with type 2 from diagnosis, or type 1 after 5 years	In particular in presence of high cardiovascular risk and complications

American Diabetes Association Professional Practice Committee. 2025 Jan
Tesfaye S et al for The Toronto Neuropathy Expert Group. *Diabetes Care, 2010*
Spallone V. Diabetes Metab J. 2019;43:3-30

Cardiovascular autonomic reflex tests: CARTS

Deep Breathing

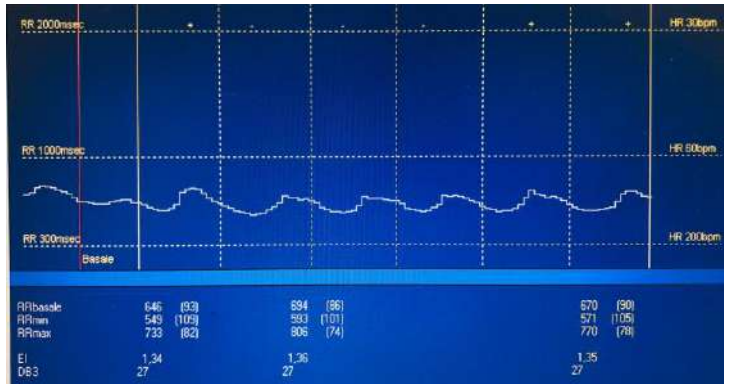
- Heart rate changes with breathing**: rising during inspiration and falling during expiration**.
- This pattern is called **respiratory sinus arrhythmia** and is controlled by the **parasympathetic nervous system**.
- Results are analyzed as the **Expiration/Inspiration (E/I) ratio**—comparing RR intervals during expiration and inspiration—or as the difference between maximum and minimum heart rates during the test.

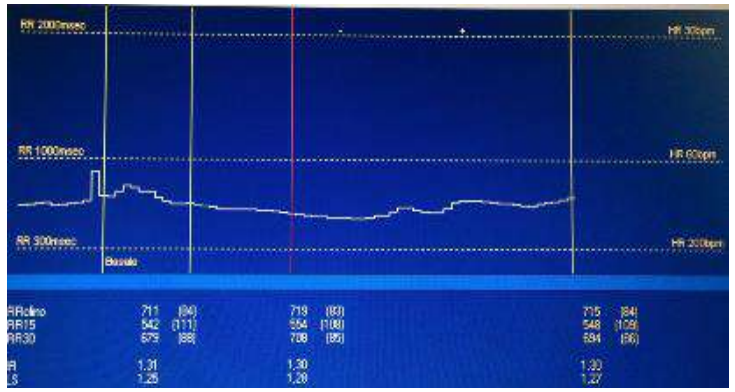
Lying-to-standing

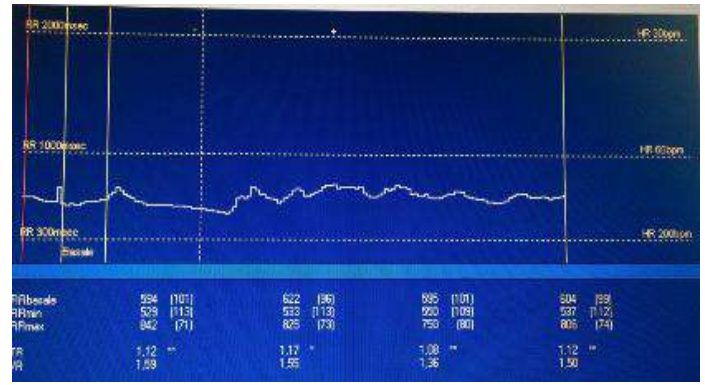
- Heart rate **increases upon standing** to maintain adequate cardiac output, then gradually decreases. The peak heart rate typically occurs between the 10th and 20th beat after standing, while a decrease is usually observed between the 25th and 35th beat. This response is mediated by the **parasympathetic nervous system**.
- The result is expressed as the **30/15 ratio**, calculated by dividing the longest RR interval (between the 25th and 35th beats) by the shortest RR interval (between the 10th and 20th beats) after standing.

Valsalva Maneuver

- The Valsalva maneuver involves a **forced expiration against resistance with an open glottis**, leading to changes in heart rate and blood pressure and **triggering reflex tachycardia** and peripheral vasoconstriction. Upon release, venous return and blood pressure rebound, leading to reflex bradycardia.
- The **Valsalva ratio**—used to evaluate autonomic function—is calculated by dividing the longest RR interval after expiration by the shortest RR interval during expiration.







During the execution continuous heart rate monitoring is required. Visual inspection of the ECG trace is essential to exclude artifacts and/or any type of cardiac arrhythmias from the analysis. Age-related normal ranges of heart rate tests are strictly required.

Spallone V, Bax G, Bellavere F, Esposito K, Melga P, Morganti R, Quadri R, Scionti L, Viviani G, per il Gruppo di Studio SID "Neuropatia Diabetica" Raccomandazioni sull'uso dei test cardiovascolari nella diagnosi di neuropatia autonomica diabetica

Heart Rate Variability (HRV) indices

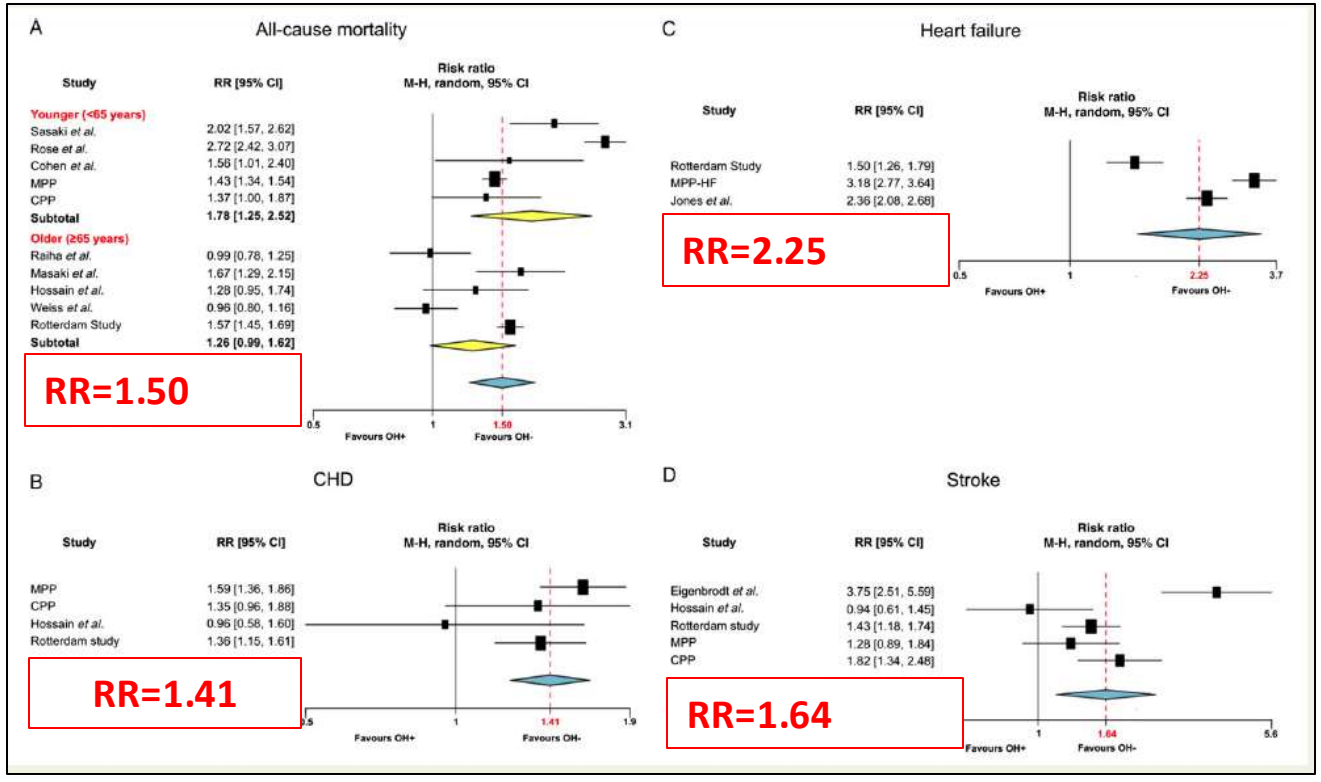
- A reduction in HRV has been associated with the early stages of clinical CAN.
- The electrocardiogram (ECG) recordings were initially longer in duration, usually over a period of 24 h but recent data has demonstrated that recording of shorter duration can provide equally reliable information.
- Five-minute HRV indices refer to the analysis of fluctuations in the time intervals between heartbeats, measured over a five-minute period to assess cardiovascular autonomic neuropathy.
- Five-minute HRV can be useful but it requires careful data management and expert interpretation.
- It is advisable to use it in combination with other monitoring parameters to diagnose cardiovascular autonomic neuropathy.
- Emerging evidence indicates that heart rate variability (HRV) measures obtained from a standard resting ECG may offer a reliable method for detecting cardiovascular autonomic neuropathy (CAN). This supports the potential role of resting ECG as a practical and effective screening tool for CAN in both clinical and research contexts.

Dimitropoulos G, Tahrani AA, Stevens MJ. World J Diabetes. 2014 Feb 15;5(1):17-39
Zhang Z, et al., J Diabetes Res. 2020 Oct 30;2020:5316769.
Pop-Busui R, et al., J Diabetes Investig. 2022 Jan;13(1):125-133.

Orthostatic Hypotension (OH)

- Orthostatic hypotension (OH) is defined as a sustained reduction of systolic blood pressure (SBP) ≥20 mmHg or diastolic blood pressure (DBP) ≥10 mmHg within 3 minutes of active standing or on a head-up tilt test.
- In patients with supine hypertension SBP/DBP decline ≥30/15 mmHg could be more appropriate to diagnose OH.
- Supine hypertension is defined as SBP of ≥ 140 mmHg and/or DBP of ≥ 90 mmHg, measured after at least 5 min of rest in the supine position.

- OH is a major manifestation of CAN in patients with diabetes
- OH is considered a specific (but not sensitive) sign of CAN (sensitivity 50%, specificity 95%).
- The presence of OH identifies an advanced or severe stage of CAN.
- Considering its ease of execution and clinical and prognostic relevance, scientific societies recommend to perform OH test in diabetic population.



Spallone V et al Clin Auton Res 2009 19:58–64
Williams B et al Eur Heart J. 2018;39:3021-3104
Freeman R N Engl J Med 2008;358:615-24
Spallone V et al NMCD 2011;21;69-78
Spallone V et al Diabetes Metab Res Rev. 2011;27:639-53
Ricci F, et al., Eur Heart J. 2015 Jul 1;36(25):1609-17

Autonomic symptoms in diabetic neuropathy

Autonomic symptoms have epidemiological impact influence on morbidity and quality of life.
Scientific guidelines and experts recommend to assess autonomic symptoms in people with diabetes.

Cardiovascular symptoms

- Tachycardia
- Exercise intolerance
- Orthostatic symptoms:
  light-headedness, dizziness, blurred vision, neck pain, fainting when standing up

Gastrointestinal symptoms

- Gastric symptoms
- Diarrhoea, fecal incontinence, constipation

Urinary symptoms

Erectile dysfunction

Sweating abnormalities

- Gustatory sweating
- Anhidrosis and compensatory hyperhidrosis

Pupillary abnormalities

Tesfaye S et al for Toronto Diabetic Neuropathy Expert Group. *Diabetes Care. 2010;33:2285-93*
Spallone V et al for Toronto Consensus Panel on Diabetic Neuropathy. *Diabetes Metab Res Rev. 2011;27:639-53.*
Pop-Busui R et al. for American Diabetes Association. *Diabetes Care. 2017;40:136-154.*
Spallone V et al. for Diabetic Neuropathy Study Group of the Italian Society of Diabetology. *Nutr Metab Cardiovasc Dis 21:69-78, 2011.*

COMPASS 31 for the assessment of autonomic symptoms

COMPASS 31 is a short simplified version (31 item) of COMPASS questionnaire, developed from Autonomic Symptom Profile (*Suarez 1999*, *Sletten 2012*).

COMPASS 31 is validated in **Italian** (*Pierangeli 2015*), **Croatian/Serbian** (Drulovic 2017), **Korean** (Ahn 2021), **Danish** (Brinth 2021), **German** (Hilz 2022)

ASP - Autonomic Symptom Score	
169 items, 11 domains	
Orthostatic intolerance	Secretomotor dysfunction
Syncope	Sleep dysfunction
Male sexual failure	Vasomotor symptoms
Bladder dysfunction	Pupillomotor symptoms
Diarrhea	
Constipation	**11 weighted subscale scores and 1 total score**
Upper gastrointestinal symptoms	

COMPASS - Composite Autonomic Symptom Score	
84 items: 72 in 11 autonomic domains plus 12 for understatement and psychosomatic indexes	
Orthostatic intolerance	Secretomotor dysfunction
Syncope	Sleep dysfunction
Male erectile dysfunction	Vasomotor symptoms
Bladder dysfunction	Pupillomotor symptoms
Diarrhea	
Constipation	**11 weighted subscale scores and 1 total score plus 2 validity scores**
Gastroparesis	

COMPASS 31	
31 items, 6 domains	
Orthostatic intolerance	Secretomotor dysfunction
~~Syncope~~	~~Sleep dysfunction~~
~~Male erectile dysfunction~~	Vasomotor
Bladder dysfunction	Pupillomotor
Gastrointestinal symptoms	**6 weighted subscale scores and 1 total score**

Drulovic J et al Croat Med J 2017;58:342–348
Ahn JH et al *PLoS ONE 2021;16: e0258897.*
Brinth L et al *Dan Med J. 2021;69:A07210576.*
Hilz MJ et al *Neurol Sci. 2022;43:365-371.*

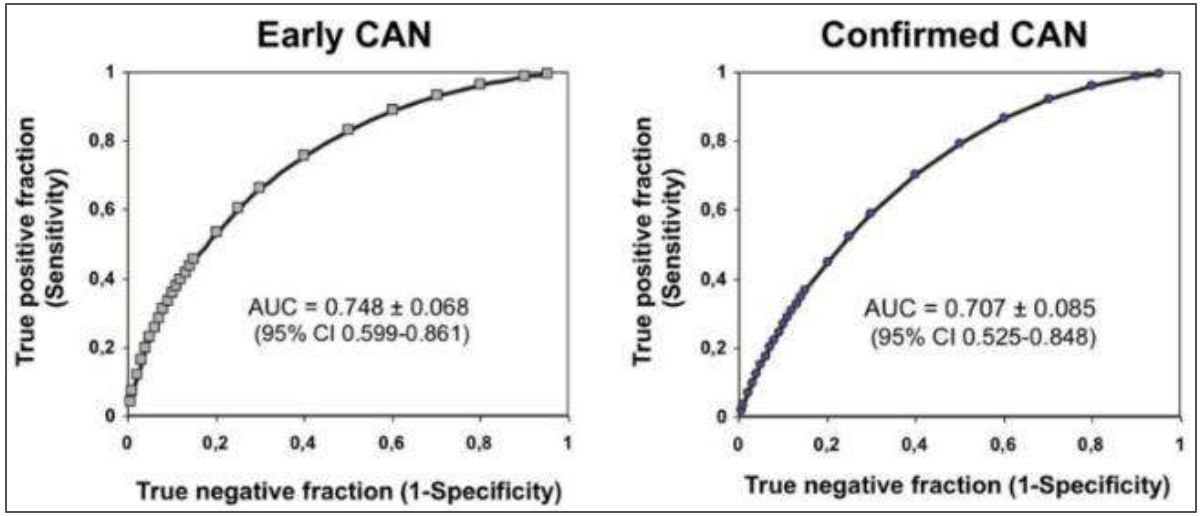
Suarez GA et al *Neurology* 1999; 52:523-528;
Sletten DM et al *Mayo Clin Proc* 2012; 87:1196-1201;
Pierangeli G et al *Neurol Sci 2015;36:1897-902.*

Validation of the Composite Autonomic Symptom Score 31 (COMPASS 31) for the assessment of symptoms of autonomic neuropathy in people with diabetes

Greco C, Di Gennaro F, D'Amato C, Morganti R, Corradini D, Sun A, Longo S, Lauro D, Pierangeli G, Cortelli P, Spallone V.

Diabet Med. 2017;34:834-838

COMPASS 31 validated for diabetic CAN with a fair diagnostic accuracy (sensitivity and specificity of 75% and 65%, respectively)(*Greco 2017*).



At the Cut-off of 16 and 17 COMPASS 31 Total Weighted have acceptable sensitivity for CAN

CAN

Cut-off	OR	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR^+	LR^-
16	5.5	75	65	37	90	2.1	0.38

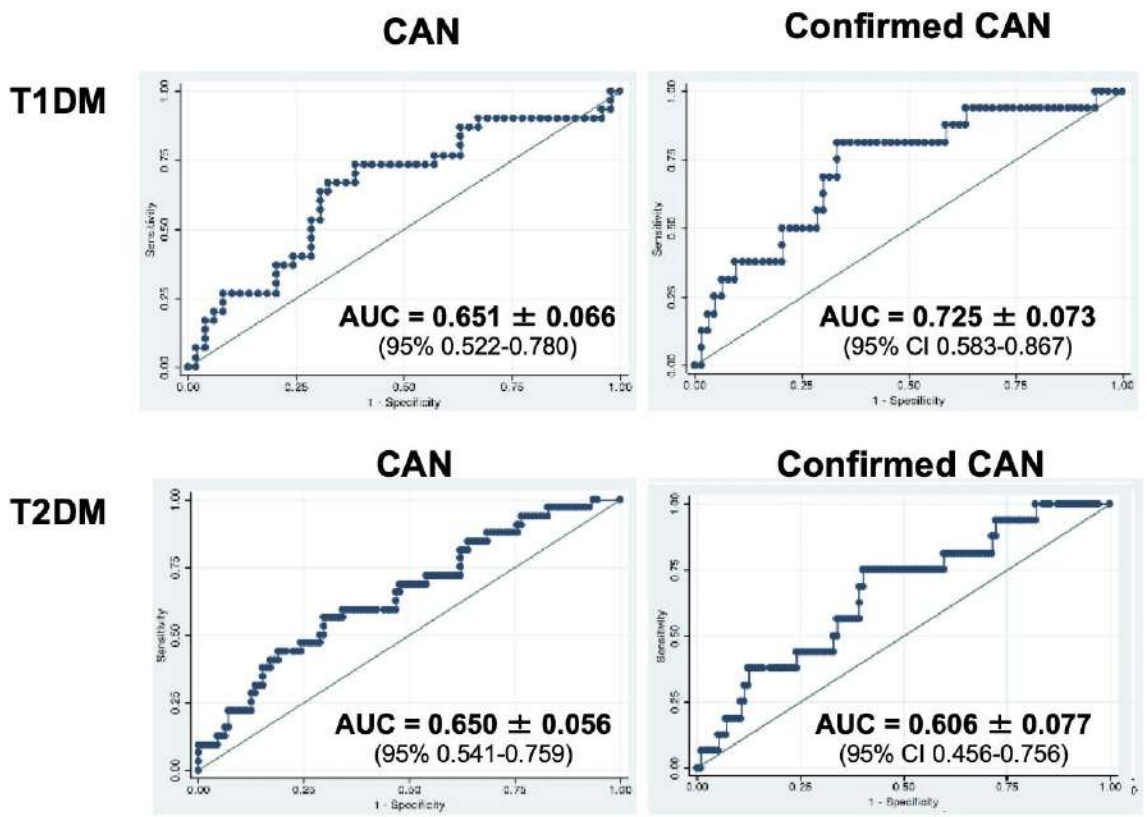
CAN confirmed

Cut-off	OR	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR^+	LR^-
17	4.7	70	67	25	93	2.1	0.45

OR: odds ratio
PPV: positive predictive value
NPV: negative predictive value
LR^+: likelihood ratio for positive result
LR^-: likelihood ratio for negative result

Does the diagnostic value of the questionnaire for autonomic symptoms COMPASS 31 differ between type 1 and type 2 diabetes?

ROC plots for COMPASS 31 TWS in distinguishing between participants with and without CAN in T1DM and T2DM



Diagnostic characteristics of COMPASS 31 TWS for CAN in T1DM and T2DM

	CAN (early and confirmed)		Confirmed CAN	
Cut-off 16.44	**Sensitivity**	**Specificity**	**Sensitivity**	**Specificity**
T1DM	65.5% (48.2-82.8)	62.0% (48.5-75.4)	**81.2%** (62.1-100)	60.3% (48.2-72.4)
T2DM	68.7% (52.7-84.8)	52.2% (43.0-61.5)	66.7% (42.8-90.5)	49.2% (40.6-57.9)

When considering the diagnostic validity of COMPASS 31 for CAN and DPN separately in patients with T1DM and T2DM, **the diagnostic performance for confirmed CAN seems to be better in type 1 than in type 2 diabetes**.

D'Ippolito I et al Diabetologia 2021; 64 (Suppl 1)- S307-S308

CAN: the issue of underdiagnosis

- Cardiovascular autonomic diabetic neuropathy (CAN) is still an under diagnosed complication of diabetes despite its epidemiological impact, its prognostic relevance and its involvement in the patients' quality of life.

- Among the possible reasons of this worldwide lack of attention about CAN diagnosis, in particular for screening and early manifestations, there is a limited access to CARTs, which need a professional and skilled team, an adequate instrumentation, patients' compliance and standardized performances.

- To manage this relevant problem, scientific community is trying to process and validate different possible solutions including simplification of CARTs procedure or the alternative use of short-term HRV indices but a possible approach could be also limiting the burden of a universal referral to CARTs by identifying the best candidates for CAN screening.

Spallone V et al. Diabetes Metab Res Rev 2011;27:639-53
Tesfaye S et al. Diabetes Care 2010;33: 2285-93

Clinical scoring systems for the risk of cardiovascular autonomic neuropathy in type 1 and type 2 diabetes: A simple tool

Menduni M, D'Amato C, Leoni M, Izzo V, Staltari M, Greco C, Abbatepassero A, Seminara G, D'Ippolito I, Lauro D, Spallone V.

J Peripher Nerv Syst. 2022 Aug 27.

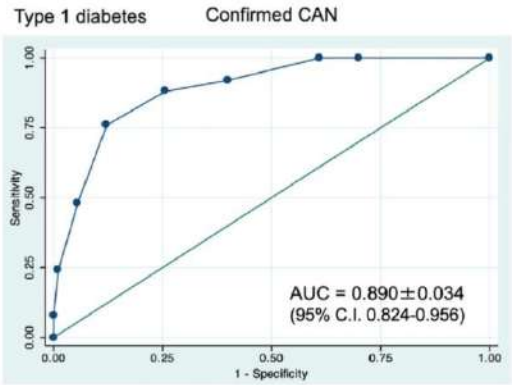
In 115 participants with type 1 diabetes and 161 with type 2 diabetes (age 63.1 ± 8.9 years), strength of associations of confirmed CAN (based on 2 abnormal CARTs) with clinical variables was used to build a CAN risk score.

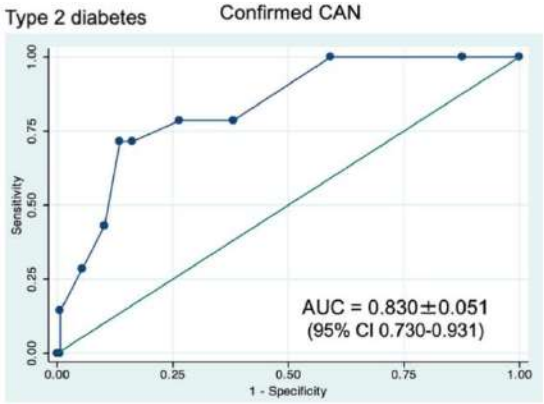
CAN risk score for type 1 diabetes		
Variable	Criterion	Score
Heart rate (bpm)	≥80	2
HbA1c	≥8%	2
Retinopathy and/or nephropathy	Yes	2
Systolic BP (mmHg)	≥140	1
HDL (mg/dl)	≤40 or ≤50*	1
Cardiovascular disease	Yes	1
Smoking	Yes	1
Range		0-10

* according to male or female sex

CAN risk score for type 2 diabetes		
Variable	Criterion	Score
Retinopathy	Yes	3
Insulin treatment	Yes	2
Heart rate (bpm)	≥80	1
HbA1c	>8%	1
Microalbuminuria	Yes	1
Cardiovascular disease	Yes	1
Physical Activity	No	1
Range		0-10

Area under the ROC curve (AUC) of CAN risk score for confirmed CAN in type 1 and type 2 diabetes





Diagnostic performance of CAN risk score for confirmed CAN and CAN (early and confirmed) in type 1 and in 2 diabetes

Type 1 diabetes

Cut-off	CAN	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Youden's J
4	Confirmed CAN	88.0 (CI 73.3-100.7)	74.4 (CI 65.4-83.4)	48.9 (CI 34.3-63.5)	95.7 (CI 91.0-100.5)	0.62
4	CAN (early and confirmed)	69.0 (CI 55.1-83.0)	78.1 (CI 68.6-87.6)	64.4 (CI 50.5-78.4)	81.4 (CI 72.3-90.5)	0.47

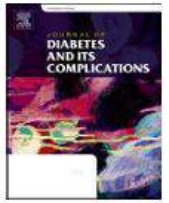
Type 2 diabetes

Cut-off	CAN	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Youden's J
4	Confirmed CAN	78.6 (CI 57.1-100.1)	73.5 (CI 66.3-80.1)	22.0 (CI 10.5-33.4)	97.3 (CI 94.3-100.3)	0.521
4	CAN (early and confirmed)	64.5 (CI 47.7-81.3)	76.9 (CI 69.7-84.2)	40.0 (CI 26.4-53.6)	90.1 (CI 84.5-95.6)	0.414

External validation of a clinical risk score for the presence of cardiovascular autonomic neuropathy in type 1 diabetes

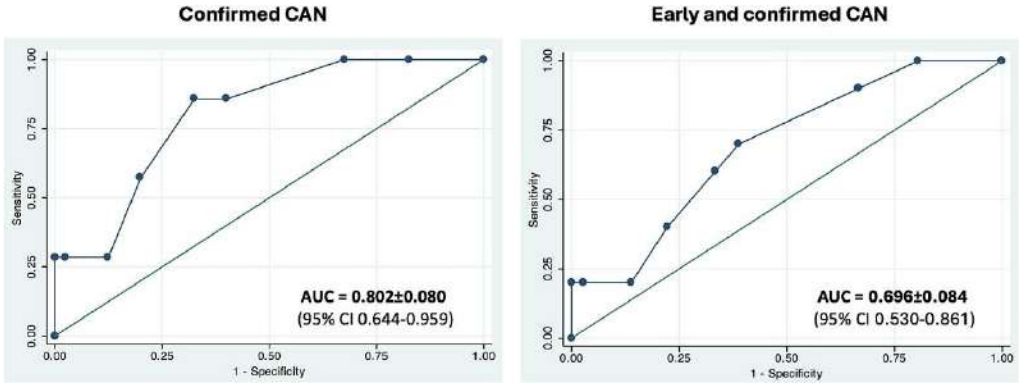
Pietro Pertile, Ilenia D'Ippolito, Beatrice De Santis, Aikaterini Andreadi, Davide Lauro, Vincenza Spallone

J Diabetes Complications, 2025 Jul



47 participants with type 1 diabetes (age 63.1 ± 8.9 years), this study validated the CAN Risk Score's diagnostic value to identify CART candidates and reducing the need for universal screening.
It is simple to apply in clinical practice, relying on standard categorical clinical data.

Diagnostic accuracy of CAN Risk Score for confirmed CAN and overall (early and confirmed) CAN measured using area under the ROC curve (AUC)

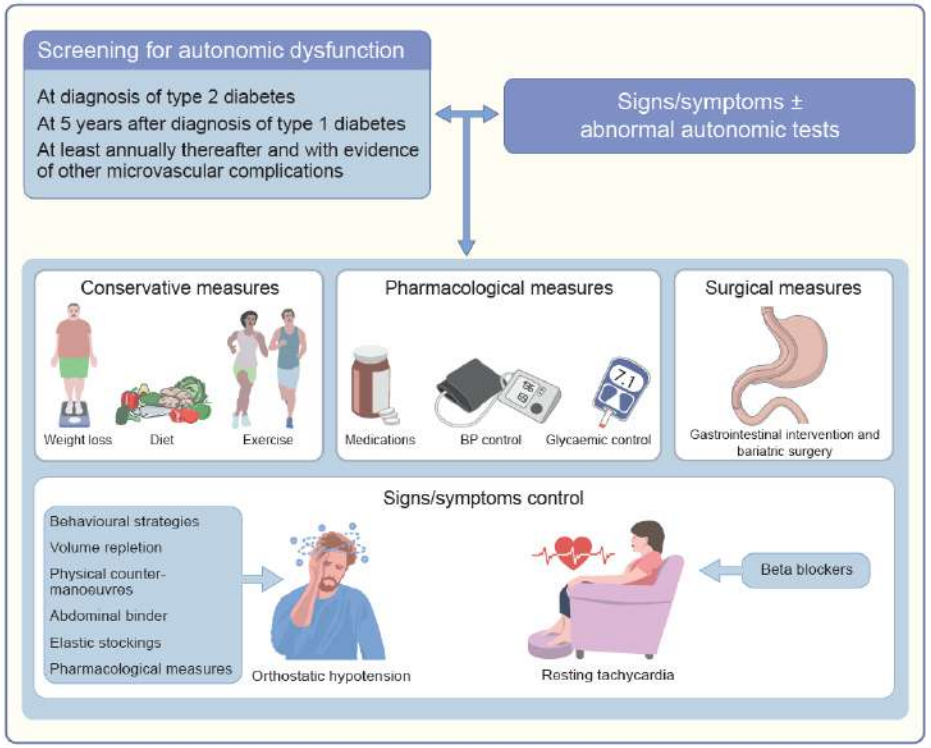


Cut-off ≥4	CAN (early and confirmed)	Confirmed CAN
Sensitivity	63.64% (CI 35.21% - 92.07%)	**85.71**% (CI 59.78% - 111.64%)
Specificity	66.67% (CI 51.27% - 82.07%)	67.50 % (CI 52.98% - 82.02%)
Positive predictive value	36.84% (CI 15.15% - 58.53%)	31.58% (CI 10.68% - 52.48%)
Negative predictive value	**85.71**% (CI 72.75% - 98.67%)	**96.43**% (CI 89.56% - 103.30%)
Youden's J	0.30	0.53

CAN management

<u>Non pharmacological measures</u>:

- Optimizing glycemic control
- Weight loss
- Diet
- Physical activity



<u>Pharmacological measures</u>:

- **ACE inhibitors /ARBs**: first-line for hypertension and microalbuminuria in diabetes. Possible role in CAN prevention
- **β-blockers**: Indicated for high resting heart rate in CAN. Improving HRV and diastolic coronary perfusion. Lowering heart rate may reduce CV risk
- **Statins**: Key in dyslipidemia treatment (T1D and T2D) Some studies: ↓ risk of polyneuropathy (dose-dependent). Some studies show neutral effect.
- **Alpha-Lipoic Acid (ALA)**: Antioxidant; reduces hyperglycemia-induced oxidative stress. No current guideline recommendation for CAN.

- **SGLT2-i**: Possible autonomic effects:
  - ↓ norepinephrine expression
  - improved renal hemodynamics
  - ↓ BP without ↑ HR

  Direct effect on CAN remains inconclusive, but potential benefit exists

- **GLP1-RA**: Limited direct evidence on CAN benefit

Eleftheriadou A, et al., Diabetologia. 2024 67:2611–2625
Pop-Busui R, et al., Diabetes Care 40(1):94–100.
The DCCT/EDIC Study Research Group, N Engl J Med. 2005, 353(25):2643–2653.
Fisher VL, Tahrani AA Diabetes Metab Syndr Obes Targets Ther. 2017,10:419–434

OH treatment

Treatment is recommended in symptomatic forms to attend symptoms (not to normalize BP fall)

Non-pharmacological measures

Exclusion of Exacerbating Agents
- Antihypertensive medications
- Tricyclic antidepressants
- Psychoactive substances

Avoidance of Precipitating Factors
- Rapid postural changes (e.g., sudden standing upon awakening)
- Prolonged supine positioning
- Intense physical activity, particularly postprandial
- Exposure to high ambient temperatures
- Large or high-carbohydrate meals
- Alcohol consumption

Non-Pharmacological Interventions
- Head-of-bed elevation (≈20°) during sleep
- Ensuring adequate hydration and salt intake
- Consumption of frequent, small-volume meals
- Regular isotonic physical activity at low to moderate intensity

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Preventive Strategies (Prior to Symptom Onset)
- Lower limb counter-pressure maneuvers (e.g., leg crossing)
- Use of portable seating (e.g., folding chair) during prolonged standing or high-risk situations

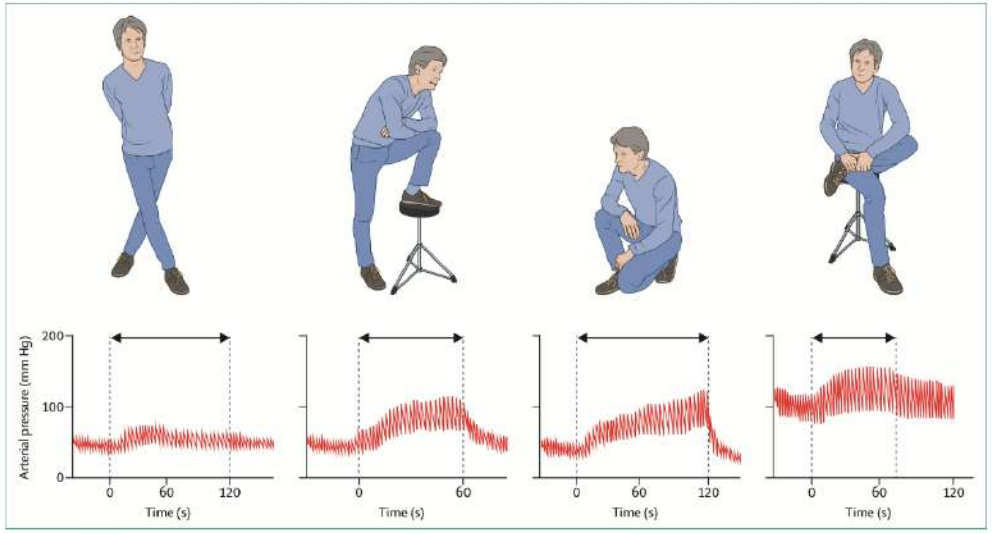

Figure 4: Physical countermanoeuvres to increase blood pressure in patients with orthostatic hypotension

Pharmacological measures

- Midodrine
- Fludrocortisone (off-label)
- Droxidopa, acarbose, octreotide, desmopressin, erythropoietin, pyridostigmine, atomoxetine (off-label)

Spallone V et al Diabetes Metab Res Rev 27:639–653,2011.
Low P et al J Clin Neurol. 2015;11:220-6.
Wieling W et a J Intern Med. 2015;277:69-82.
Fedorowski A et al Circ Arrhythm Electrophysiol 2022;15:e010573.
Wieling W et al., J Hypertens. 2009 May;27(5):935-8.

Agenda

- Diabetic autonomic neuropathy and cardiovascular autonomic neuropathy: definitions, epidemiology and natural history of CAN
- CAN: impact on mortality and morbility
- Diagnosis of diabetic autonomic neuropathy
- Autonomic symptoms in diabetic neuropathy
- COMPASS 31 for the assessment of autonomic symptoms
- CAN: the issue of underdiagnosis
- CAN management

Key Points

Prevalence and Risk Factors

CAN is a common complication of both type 1 and type 2 diabetes. It can develop early and its risk increases progressively with advancing age, longer diabetes duration, and suboptimal glycemic control.

Prognostic Significance

CAN is a strong, independent predictor of both all-cause and cardiovascular mortality.

Screening Recommendations

Guidelines recommend screening for signs and symptoms of CAN:

- At diagnosis of **type 2 diabetes**
- **Five years** after diagnosis of **type 1 diabetes**
- Annually thereafter, especially in the presence of other microvascular complications (e.g., nephropathy, peripheral neuropathy)

Diagnostic Tools

- **Cardiovascular Autonomic Reflex Tests** are the gold standard for diagnosis.
- **Orthostatic Hypotension** is a major clinical manifestation and a specific, though not sensitive, indicator of advanced CAN.
- Scientific societies recommend OH testing due to its simplicity and prognostic relevance.

Symptom Assessment

- Autonomic symptoms contribute significantly to morbidity and reduced quality of life.
- The COMPASS-31 is a validated instrument for the assessment of autonomic symptoms.

Management

- No disease-modifying therapies are currently available.
- **Lifestyle modifications** are recommended for prevention.
- Treatment is recommended for symptomatic CAN to relieve symptoms.


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CAN and hypoglycemia: a complex and bidirectional relationship

Impaired Awareness of Hypoglycemia (IAH) is defined as a loss of sympathetic warning signs and CAN may contribute in its pathogenesis.

- Hypoglycemia can reduce HRV and baroreflex sensitivity.
- Hypoglycemia-predominant patterns are associated with reduced cardiovagal tone.
- CAN and hypoglycemia may impair cardiac autonomic regulation, increasing arrhythmia risk.
- Hypoglycemia may cause axonal damage via metabolic disruption.

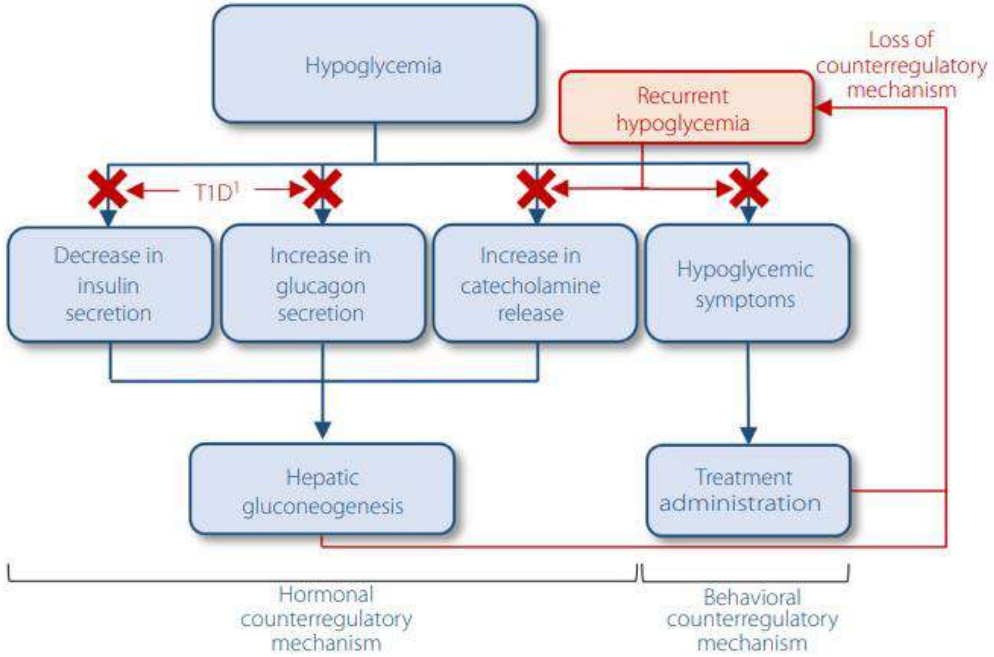

Figure 1 | Hypoglycemia counterregulatory mechanisms and the impacts of type 1 diabetes (T1D) and recurrent hypoglycemia on these mechanisms. [1]Or advanced type 2 diabetes.

Lin YK, et al., J Diabetes Investig. 2020 Nov;11(6):1388-1402.
Kaze AD, et al., JCI Insight 7(22):e156334.
Jaiswal M, et al., Diabetes Care 2014; 37: 2616–2621.