Cardiopatia autonomica

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Neuropatia autonomica diabetica cardiovascolare

- ***impatto clinico***
- ***diagnosi e sua rilevanza***
- ***terapia patogenetica***
- ***trattamento delle forme sintomatiche***

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DOCUMENTI

Raccomandazioni sull'uso dei test cardiovascolari nella diagnosi di neuropatia autonomica diabetica

Vincenza Spallone, Giuseppe Bax, Federico Bellavere, Katherine Esposito, Pierluigi Melga, Roberto Morganti, Roberto Quadri, Luciano Scionti, Giorgio Viviani, per il Gruppo di Studio SID "Neuropatia Diabetica"

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Nutrition, Metabolism & Cardiovascular Diseases

REVIEW

Recommendations for the use of cardiovascular tests in diagnosing diabetic autonomic neuropathy☆

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endorsement dell'AINV

Reviews/Commentaries/ADA Statements
REVIEW ARTICLE

Diabetic Neuropathies: Update on Definitions, Diagnostic Criteria, Estimation of Severity, and Treatments

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on behalf of the Toronto Diabetic Neuropathy Expert Group*

Diabetes Care 33:2285–2293, 2010

DIABETES/METABOLISM RESEARCH AND REVIEWS
Diabetes Metab Res Rev 2011; 27: 639–653.
Published online in Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1002/dmrr.1239

REVIEW ARTICLE

Cardiovascular autonomic neuropathy in diabetes: clinical impact, assessment, diagnosis, and management

Vincenza Spallone[1]*
Dan Ziegler[2,3] Roy Freeman[4]
Luciano Bernardi[5]
Simona Frontoni[1]
Rodica Pop-Busui[6]
Martin Stevens[7]
Peter Kempler[8] Jannik Hilsted[9]
Solomon Tesfaye[10]
Phillip Low[11] Paul Valensi[12] on behalf of The Toronto Consensus Panel on Diabetic Neuropathy†

DIABETES/METABOLISM RESEARCH AND REVIEWS
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REVIEW ARTICLE

Methods of investigation for cardiac autonomic dysfunction in human research studies

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Martin Stevens[3]
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Solomon Tesfaye[10]
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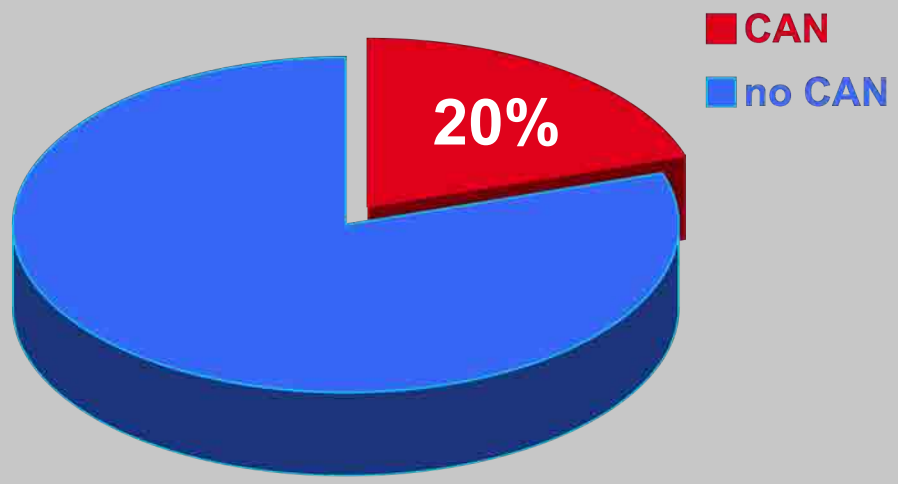
Diabetic autonomic neuropathy: definition

Diabetic autonomic neuropathy (DAN) is a disorder of the autonomic nervous system in the setting of diabetes or metabolic derangements of pre-diabetes after the exclusion of other causes.

Cardiovascular autonomic neuropathy (CAN) is defined as the impairment of autonomic control of the cardiovascular system *in the setting of diabetes after exclusion of other causes. CAN is usually documented using several cardiovascular autonomic reflex tests.*

Tesfaye S et al for The Toronto Neuropathy Expert Group. ***Diabetes Care 33:2285-2293, 2010***
Spallone V et al on behalf of the Toronto Consensus Panel on Diabetic Neuropathy. ***Diabetes Metab Res Rev 27:639–653,2011***

Diabetic autonomic neuropathy: epidemiology



CAN is present in one diabetic patient out of 5

Prevalence increases with
- ***age: until 38% in type 1 and 44% in type 2 of 40-70 years old***
- ***diabetes duration: until 35% in type 1 and 65% in type 2***

Neil HAW et al. *Diabetic Med 1989*
Ziegler D et al. *Diabetic Med 1993*
Valensi P et al. *Metabolism 1993*
Stephenson J et al. *Diabetologia 1994*
O'Brien IAN et al. *Q J Med 1986*
Töyry JP et al. *Diabetes 1996*
May O et al. *J Intern Med 2000*
Low P et al. *Diabetes Care 2004*
Ko S-H et al *Diabetes Care 2008*
Pop-Busui R et al. *Circulation 2009*
Abbott C et al. *Diabetes Care 2010*

Spallone V et al on behalf of the Toronto Consensus Panel on Diabetic Neuropathy. *Diabetes Metab Res Rev 27:639–653,2011*

Spectrum of clinical forms of DAN

Roma,
9-11 novembre 2012

Clinical forms may present with signs and symptoms regarding heart, vessels, gut, bladder, erectile and sudomotor function.

- Cardiovascular system
- Respiratory system
- Gastrointestinal system
- Urogenital system
- Hormonal secretion
- Pupillary function
- Sudomotor function

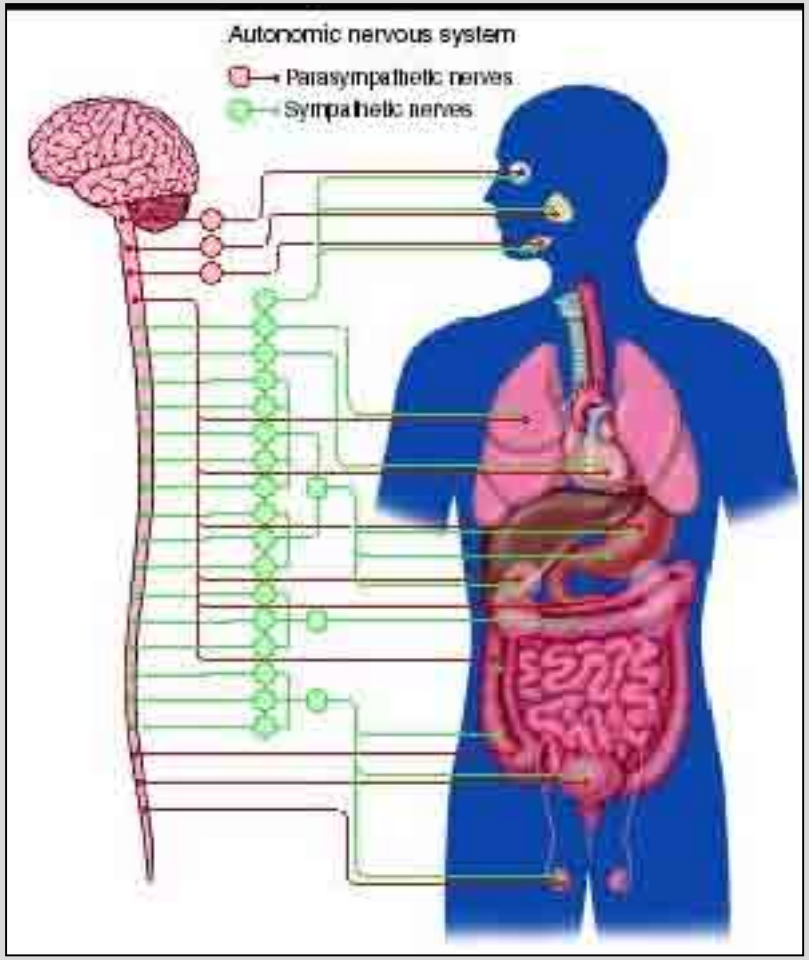
Cardiovascular symptoms
- tachycardia
- exercise intolerance
- orthostatic symtpoms

Gastrointestinal symptoms
- gastric symtpoms
- diarrhoea, fecal incontinence, stipsis

Urinary symptoms

Erectile dysfunction

Sweating abnormalities



www.biologyreference.com

CAN as a predictor of mortality

Meta-analysis of 15 studies (1966-2001)

2900 patients followed for 1-16 years

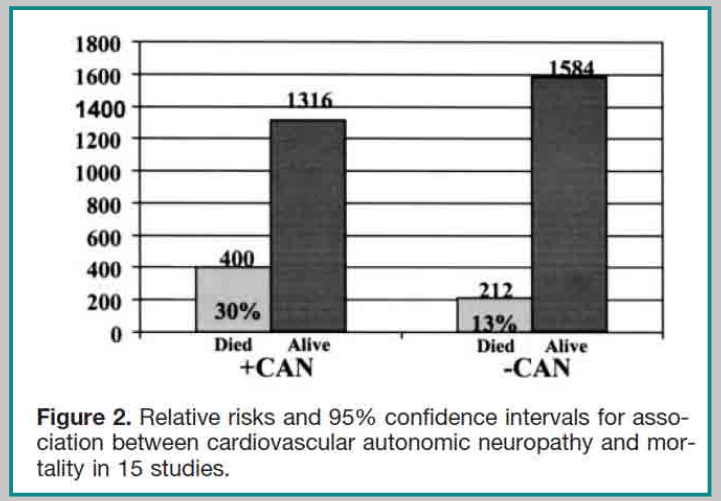
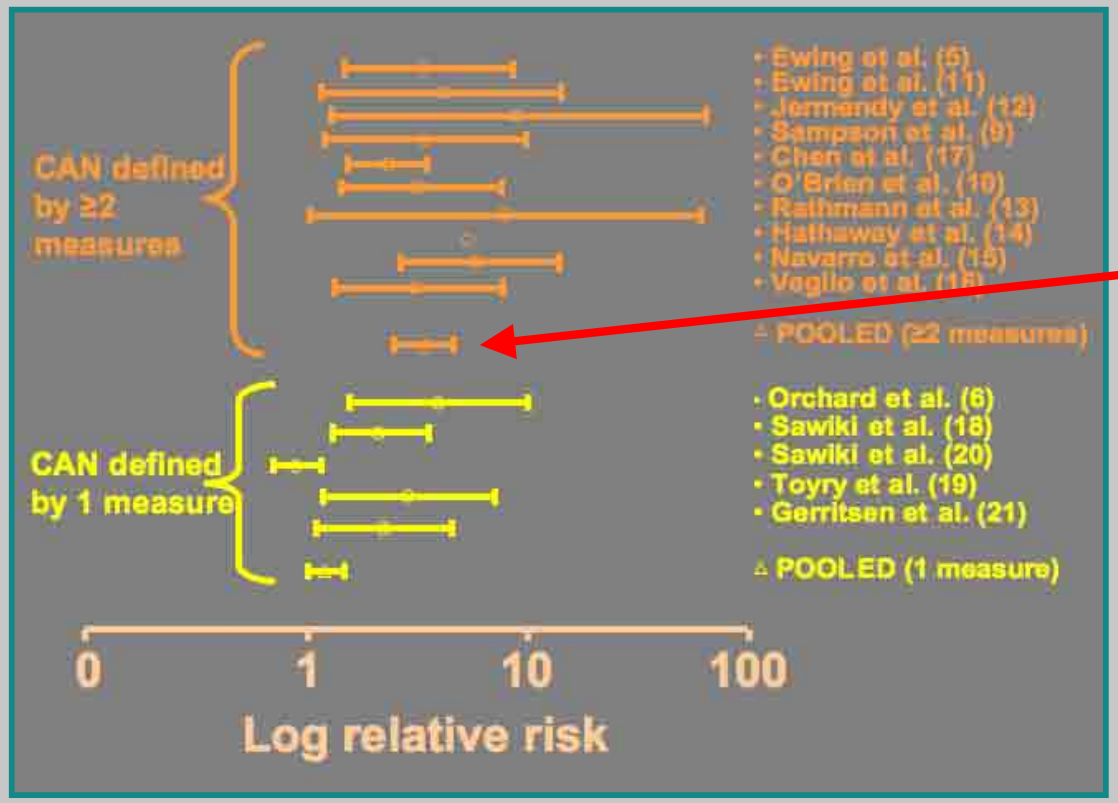


Figure 2. Relative risks and 95% confidence intervals for association between cardiovascular autonomic neuropathy and mortality in 15 studies.



RR = 3.65
(95% C.I. 2.66-4.47)
with 2 abnormal tests

RR = 2.14
(95% C.I. 1.83-2.51)
with at least 1 abnormal test

Maser RE et al. *Diabetes Care 6:1895–190, 2003*
Vinik A and Ziegler D. *Circulation 115;387-397, 2007*

CAN as a predictor of vascular morbidities

- **Association with perioperative instability during surgery** (in 7 out of 8 studies)
- **Association with or independent predictor value for**
  - ***silent myocardial ischemia***
  - coronary artery disease
  - cardiovascular morbidity
  - stroke in type 2 diabetes (in 4 studies)
- **Progression promoter of diabetic nephropathy** (in 6 out of 8 studies)

Sundkvist G et al. *Diabetes Care 1993*;
Weinrauch LA et al. *Am J Hypertens 1998*;
Burger AJ et al. *Int J Cardiol 2002*;
Forsèn A et al. *Diabet Med 2004;21:852-8;*
Maguire AM et al *Diabetes Care 2007*;
Brotman DJ et al. *J Am Soc Nephrol 2010*

Burgos LG et al *Anesthesiology 1989*;
Linstedt U et al *Anaesthesist 1993*;
Kitamura A et al *Anesthesiology 2000*;
Keyl C et al. *Anesth Analg 1999*

Vinik A et al. *Diabetes Care 2003;*
Wackers FJ et al *Diabetes Care 2004;*
Young LH et al *JAMA 2009;*
Liao P et al. *Diabetes 2002*;
Astrup et al *Diabetes Care 2006;*
Toyry JP et al *Stroke 1996;*
Cohen JA et al, *Auton Neurosci 2003; 31;108:73-8*
Cordolo CRL et al *Stroke 2003;*
Ko SH et al *Diabetic Med 2008*

Spallone V et al on behalf of the Toronto Consensus Panel on Diabetic Neuropathy. *Diabetes Metab Res Rev 27:639–653,2011*

CAN and cardiovascular morbidity

Abnormalities associated with CAN at the level of cardiovascular system and peripheral vascular function

- Forms of cardiovascular morbidity
- Risk markers or factors for mortality and morbidity
- Potential pathogenetic link between CAN and mortality/morbidity

Cardiovascular system

- Perioperative instability
- Exercise intolerance
- Postprandial hypotension
- Silent myocardial ischemia
- Orthostatic hypotension
- Resting tachycardia
- QT interval prolongation
- Nondipping, reverse dipping
- Impaired BRS
- Loss of reflex heart rate variations
- Reduced HRV
- Sympatho-vagal imbalance
- Cardiac sympathetic dysinnervation
- Dysregulation of cerebral circulation
- ⇓ Sympathetically mediated vasodilation of coronary vessels
- Left ventricular dysfunction
- ↑ Arterial stiffness

Peripheral vascular function

↑ Peripheral blood flow and warm skin
↑ Arteriovenous shunting and swollen veins
↑ Venous pressure and oedema
- Loss of protective cutaneous vasomotor reflexes
- Loss of venoarteriolar reflex with oedema and microvascular damage

↑ Incapillary permeability
- Medial arterial calcification

Spallone V et al on behalf of the Toronto Consensus Panel on Diabetic Neuropathy. *Diabetes Metab Res Rev 27:639–653,2011*
Bernardi L et al *on behalf of the Toronto Consensus Panel on Diabetic Neuropathy. Diabetes Metab Res Rev 27:654-664,2011*

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Simona Frontoni[1] behalf of The Toronto
Rodica Pop-Busui[6] Consensus Panel on Diabetic
Martin Stevens[7] Neuropathy†
Peter Kempler[8] Jannik Hilsted[9]

Clinical impact of CAN

Recommendations

- **CAN is a risk marker of mortality (level A) as well as a risk marker and likely a risk factor for cardiovascular morbidity (level B), and possibly a progression promoter of diabetic nephropathy (level C).**
- Orthostatic hypotension is associated with a worse prognosis than cardiovagal neuropathy (level C).
- QTi prolongation has prognostic value in diabetes (level B).
- Non-dipping status is associated with an adverse cardiovascular prognosis in diabetes (level C).
- Non-dipping status predicts the progression from micro and macroalbuminuria to renal failure in type 2 diabetes (level C).

Methods of CAN assessment

- Assessment of symptoms
- Assessment of signs
- Cardiovascular tests based on heart rate and BP
- Ambulatory BP Monitoring (ABPM) for dipping status
- HRV time- and frequency-domain indices
- BRS measures
- Scintigraphic studies
- Muscle Sympathetic Nerve Activity (MSNA)
- Cathecolamine assessment

Clinical diagnosis	Research	End-points
no	no	no
yes	yes	no
yes	yes	yes
yes	yes	no
yes	yes	yes
possible	yes	yes
no	yes	yes
no	yes	possible
no	yes	possible

Modified from Spallone V et al on behalf of the Toronto Consensus Panel on Diabetic Neuropathy. *Diabetes Metab Res Rev 27:639–653,2011*

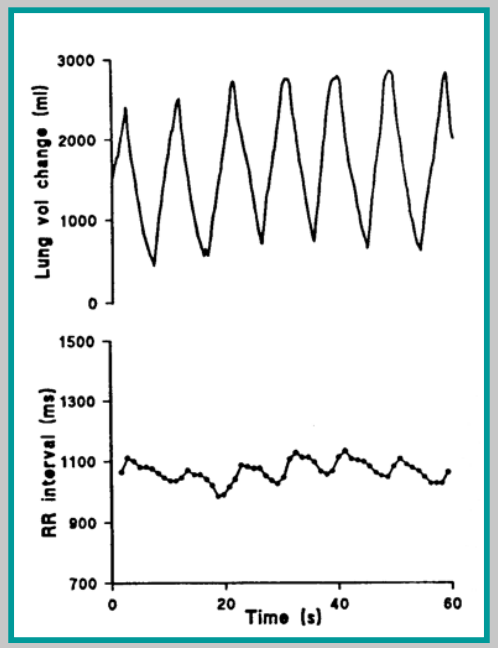
Cardiovascular Reflex Tests

- measure the heart rate and BP response to provocative physiological manoeuvres
- established measures of autonomic function and the gold standard in autonomic testing (Class II, Level A)

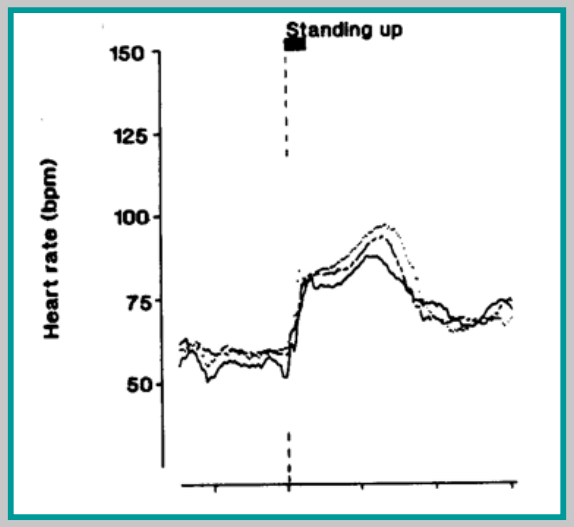
Heart rate tests
- deep breathing (Deep Breathing)
- standing (Lying to Standing)
- Valsalva manoeuvre

Orthostatic hypotension test

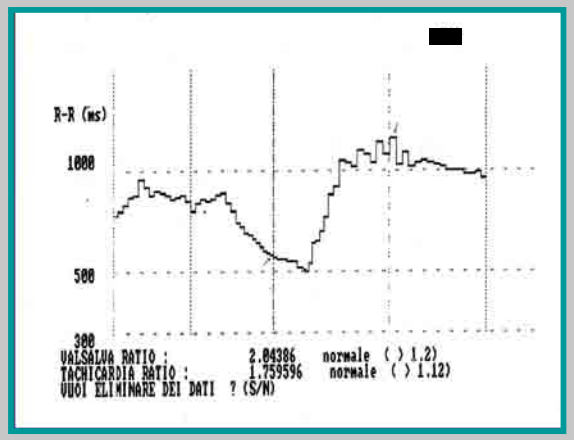
Deep Breathing



Lying to standing



Valsalva manoeuvre



Anonymous. *Neurology 46: 873-880, 1996;* England JD et al. *Neurology 72:177-184, 2009;*
Spallone V et al. on behalf of Diabetic Neuropathy Study Group of the Italian Society of Diabetology. *Nutr Metab Cardiovasc Dis 21:69-78, 2011.*
Spallone V et al on behalf of the Toronto Consensus Panel on Diabetic Neuropathy. *Diabetes Metab Res Rev 27:639–653,2011*

Confounding factors that can impact reliability of CARTs

- Patients' compliance and standardisation
- Age
- Respiratory pattern
- Body position
- Basal heart rate and BP
- Physical exercise
- Coffee, alcohol, smoking
- Meals
- Obesity
- Hypoglycaemia, hyperglycaemia
- Insulin
- Respiratory, cardiovascular diseases
- Drugs

Spallone V et al on behalf of the Toronto Consensus Panel on Diabetic Neuropathy. *Diabetes Metab Res Rev 2011;*
Spallone V et al on behalf of the Diabetic Neuropathy Study Group of the Italian Society of Diabetology *Nutr Metab Cardiovas Dis* 2011

Table 3. Confounding factors on cardiovascular autonomic testing

Physiological confounders	Advice	Recommendation
Standardization	Follow the standard procedures in performing tests and control or minimize the influence of confounding factors	Standardization of testing procedure and control of confounding factors are essential to the reliability of cardiovascular tests
Patients' compliance	Provide detailed information to the subject	Instructions to patients and their familiarization with the tests allow a better standardization of stimuli
Age	Use normal age-related values	Age-related normal reference values are strictly required to correctly interpret the results of all the heart rate-based cardiovascular tests (level B)
Respiratory pattern	Control for respiratory pattern	Accurate instruction on timed deep breathing and on avoidance of deep or irregular breaths after the Valsalva manoeuvre and after standing is advisable (level C)
Body position	Allow a sufficient supine rest before orthostatic test	Adequate supine rest before standing is necessary to increase reproducibility and test reliability
Basal heart rate and blood pressure	Caution in interpreting the results of heart rate tests with a resting heart rate >100 bpm and of orthostatic hypotension test with supine systolic blood pressure >160 mmHg or <120 mmHg	No correction is needed for the resting heart rate (level C), the possible confounding effect of supine systolic blood pressure should be taken into account when evaluating orthostatic hypotension test (level B)
Physical exercise	Avoid strenuous exercise 24 h before testing	Patients should be requested to avoid strenuous physical exercise in the 24 h preceding the tests
Coffee, alcohol, smoking	Avoid consumption of coffee and alcohol, and smoking before testing	Patients should be requested to avoid caffeine beverages, smoking, and alcohol at least 2 h prior to the tests
Meals	Avoid testing just after main meals	It is advisable to perform the tests at least 2 h after a light meal
Pathophysiological confounders		
Intercurrent diseases	Avoid testing in the presence of intercurrent diseases associated with fever, infection, or dehydration	It is advisable to avoid testing during acute disease, stressful condition, fever, infection, dehydration
Hypoglycaemia, hyperglycaemia	Avoid testing during hypoglycaemia or marked hyperglycaemia	Tests should not be performed during hypoglycaemia or marked hyperglycaemia (level C)
Insulin	Avoid testing just after short-acting insulin administration	Tests should be performed at least 2 h after short-acting insulin administration (level C)
Respiratory and cardiovascular disease	Control for associated diseases	Test results should be interpreted with caution in presence of respiratory or cardiovascular diseases, in particular heart failure (level C)
Drugs	Control for medications	An appropriate wash-out of interfering drugs, particularly diuretics, sympatholytic agents and psychoactive drugs should be pursued, if not feasible, results should be interpreted with caution

Confounding factors that can impact reliability of CARTs

- Patients' compliance and standardisation
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- Respiratory pattern
- Body position
- Basal heart rate and BP
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Body		idance of deep
Basal		fter the
		nd after
		(level C)
		efore standing
		se
		st reliability
		for the resting
		e possible
		f supine
		e should be
		hen evaluating
Physic		on test (level B)
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		ercise in the
		sts
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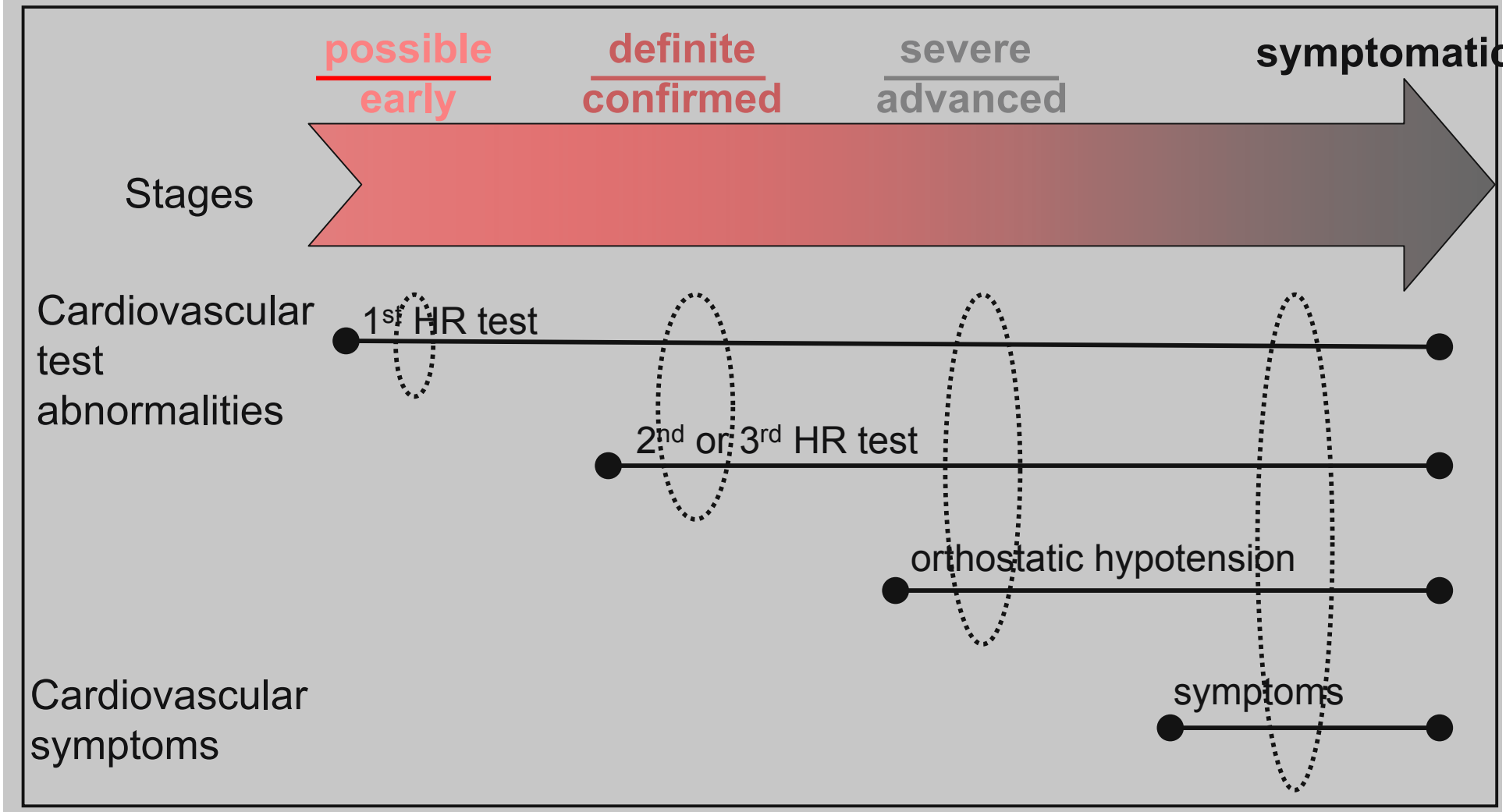
CAN stages



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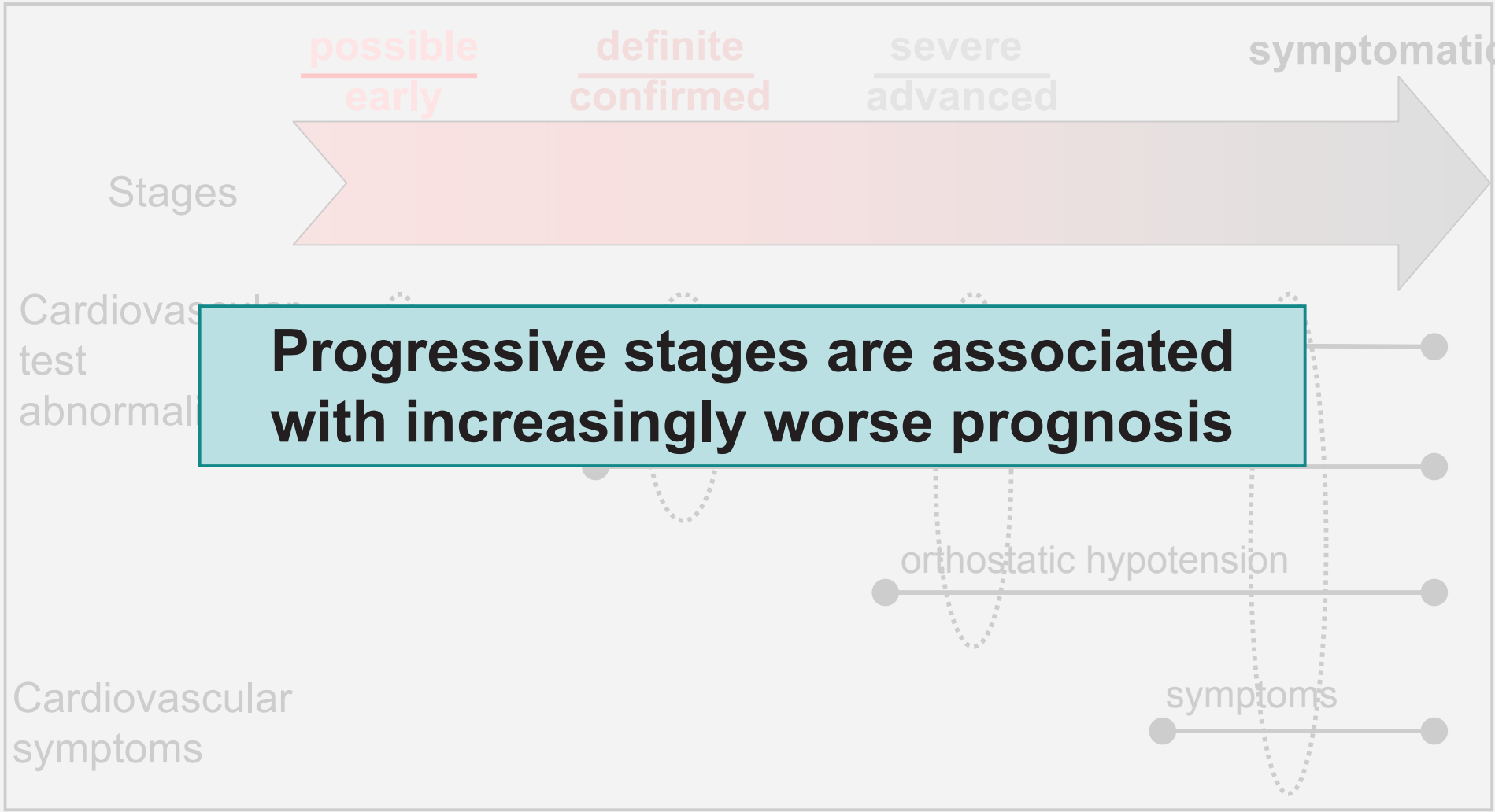

Progressive stages are associated with increasingly worse prognosis

Spallone V et al on behalf of the Toronto Consensus Panel on Diabetic Neuropathy. *Diabetes Metab Res Rev 27:639–653,2011*

Cardiovascular autonomic tests and suggested indications for their use

	Clinical diagnosis	Research	End-point in clinical trials
HR cardiovascular tests	Yes	Yes	Yes
Orthostatic hypotension test	Yes	Yes	No (low sensitivity)
QT interval	Yes (additional information and risk stratification)	Yes	No (low sensitivity)
ABPM for dipping status	Yes (risk stratification)	Yes	No (low sensitivity)
HRV time- and frequency-domain indices	Yes (early additional information and risk stratification)	Yes	Yes
BRS measures	No (early additional information and risk stratification but low availability)	Yes	Yes
Scintigraphic studies	No (low availability, limited standardisation)	Yes	Yes
MNSA	No (low availability, limited data in CAN)	Yes	Possible (used in life-style intervention trials in obesity)
Catecholamine assessment	No (low availability)	Yes	Possible (used in life-style intervention trials in obesity)

Spallone V et al on behalf of the Toronto Consensus Panel on Diabetic Neuropathy. *Diabetes Metab Res Rev 2011*

Correlati clinici della Neuropatia Autonomica Cardiovascolare

- Età
- Durata diabete
- Controllo glicemico
- Retinopatia, nefropatia
- Polineuropatia sensitivomotoria
- Fattori di rischio cardiovascolare
  - pressione arteriosa
  - BMI e obesità (tipo 2) (dati controversi)
  - circonferenza vita
  - fumo (solo studi trasversali)
  - colesterolemia (alto LDL e basso HDL)
  - trigliceridemia
- Insulinemia (tipo 2)
- Malattia cardiovascolare
- Farmaci antiipertensivi (tipo 2)

Spallone V et al on behalf of the Toronto Consensus Panel on Diabetic Neuropathy. *Diabetes Metab Res Rev 27: 639-653, 2011*

Prevention and treatment of CAN

Lifestyle intervention

- **weight loss and/or physical activity (in prediabetes and in small, mostly open studies in type 2 diabetes)**
- **slow breathing in type 1 diabetes (on BRS)**

Disease modifying treatments

- **glycaemic control (in type 1 diabetes)**
- **multifactorial cardiovascular risk intervention (in type 2 diabetes)**
- α-lipoic acid, aldose reductase inhibitors, C-peptide, Vitamin E (limited unconfirmed data)

Carnethon MR et al *Diabetes Care 2006; 29:914–919*
Maser RE e Lenhard MJ. *Curr Diab Rev 2007*
Loimaala A et al *Diabetes 2003; 52:1837–1842*
Zoppini G et al Diabet Med 2007;24: 370–6
Kanaley JA et al *Int J Obes (Lond) 2009;33:1198-206*

Rosengård-Bärlund M et al Diabetologia 2011;54:1862-70
Anonymous *Diabetologia 1998; 41: 416–423*
Pop-Busui R et al *Circulation 2009; 119: 2886–2893.*
Gaede P et al *N Engl J Med 2008; 358: 580–591.*
Ziegler D et al *Diabetes Care 1997; 20: 369–373.*

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Management of Cardiovascular Autonomic Neuropathy

Conclusions

- **Intensive diabetes therapy retards the development of CAN in type 1 diabetes (level A).**
- **Intensive multifactorial cardiovascular risk intervention retards the development and progression of CAN in type 2 diabetes (level B).**
- **Lifestyle intervention may improve HRV in pre-diabetes (level B) and diabetes (level B).**

Recommendations

- Diabetes therapy in patients with type 1 and type 2 diabetes should consider the individual risk profile and comorbidities (class I).
- Lifestyle intervention should be offered as a basic preventive measure (class I).
- Given the limited evidence from very few large scale randomized clinical trials, recommendations cannot be given for pharmacological and non-pharmacological treatments of CAN.

Treatment of clinical consequences of CAN

Treatments targeted to clinical consequences of CAN

- **sympathovagal unbalance**: avoid drugs which may lead to sympathetic activation and HRV reduction, prefer those with possible favourable effect on HRV (i.e. ACE inhibitors, ARBs**)**
- **tachycardia:** cardioselective β blockers
- **nondipping:** in hypertensive subjects bedtime treatment with ≥ 1 hypertension medication
- **nocturnal hypertension:** non pharmacological measures, transdermal nitroglycerine (low dose)
- **orthostatic hypotension:** non pharmacological measures, midodrine or fludrocortisone

Aronson D ***Diabetologia 1997; 40: 476–481***
Hermida RC et al ***Diabetes Care 2011; 34:1270–1276***
Shannon J et al ***Hypertension 1997;30:1062-1067***
Freeman R ***N Engl J Med 2008; 358: 615–624***

Trattamento sintomatico dell'ipotensione ortostatica nelle neuropatie autonomiche

Quando?

Solo se presenti sintomi ortostatici

Obiettivi del trattamento

Minimizzare i sintomi (non mirare a valori pressori normali)

Come?

- Identificare altre cause di ipotensione ortostatica
- Educare a strategie comportamentali
- Misure non farmacologiche
- Se inefficaci misure farmacologiche

Trattamento non farmacologico dell'ipotensione ortostatica nelle neuropatie autonomiche

Identificare altre cause di ipotensione ortostatica

- deplezione di volume
- ipotensivi (alfalitici), psicofarmaci (antidepressivi triciclici)

Evitare situazioni favorenti

- alzarsi in piedi rapidamente (al risveglio)
- prolungata stazione eretta
- sforzo durante minzione e defecazione
- attività fisica intensa (primo mattino e dopo i pasti)
- esposizione al caldo, docce e bagni troppo caldi
- pasti abbondanti ricchi di carboidrati
- assunzione di alcol

Trattamento farmacologico dell'ipotensione ortostatica nelle neuropatie autonomiche

Misure non farmacologiche

- dormire con la testa del letto sollevata (20°)
- adeguato apporto di liquidi e sale (almeno 1.5 L di acqua al giorno e 4-6 g di sale)
- pasti piccoli e frequenti
- esercizio fisico prudente (incluso il nuoto)
- calze elastiche in ortostatismo
- contromanovre fisiche
  - incrociare le gambe stando in piedi
  - accovacciarsi
  - piegare in avanti il busto a braccia incrociate
  - comprimere l'addome
  - sollevare un piede su una sedia
  - sedersi su seggiolino portatile (38 cm)
- se sintomi ortostatici in acuto bere 2 bicchieri da 250 ml di acqua in rapida successione

Trattamento farmacologico dell'ipotensione ortostatica nelle neuropatie autonomiche

Farmaci di 1ª linea

- **Fluoroidrocortisone acetato**
- **Midodrina**

Farmaci di 2ª linea

- Desmopressina (DDAVP) *(per poliuria notturna)*
- Eritropoietina ricombinante (rHuEPO) *(se coesiste anemia)*
- Octreotide *(per ipotensione postprandiale)*
- Caffeina *(per ipotensione postprandiale)*
- Acarbosio *(per ipotensione postprandiale)*

Cardiovascular autonomic neuropathy in diabetes: clinical impact, assessment, diagnosis, and management

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Management of CAN

Conclusions

- Symptomatic orthostatic hypotension may be improved by non-pharmacological measures (level B) and by midodrine (level A) and/or fludrocortisone (level B).
- Drug treatment of **symptomatic** orthostatic hypotension in diabetic patients with CAN may be challenging and should be thoroughly **balanced between the goal of increasing standing blood pressure and the avoidance of a marked increase in supine blood pressure (level C).**

Recommendations

- The first therapeutic approach in symptomatic orthostatic hypotension should consider the **exclusion of drugs exacerbating orthostatic hypotension, correction of volume depletion (class I), and other non-pharmacological measures (class IIa).**
- Pharmacotherapy of symptomatic orthostatic hypotension should include **midodrine (class I) or fludrocortisone or a combination of both in non-responders to monotherapy** (class IIa).
- **Because of the limited evidence, the potential risk of any pharmacological treatment should be thoroughly weighed against its possible benefit (class I).**

Cardiopatia autonomica: *take home message*

- **La CAN è una complicanza frequente.**
- **Interessa diverse funzioni cardiovascolari ed è marker di rischio di morbilità e mortalità cardiovascolare.**
- **I test cardiovascolari sono il gold standard per la sua diagnosi e ne consentono la stadiazione.**
- **I segni clinici di CAN - seppur tardivi - sono identificabili nella pratica clinica.**
- **La diagnosi di CAN è rilevante nella pratica clinica per la diagnosi e il trattamento delle forme cliniche, e per la stratificazione del rischio di complicanze cardiovascolari.**
- **Vi sono evidenze sulla azione preventiva del controllo glicemico nel diabete di tipo 1, non su terapie patogenetiche.**
- **Il trattamento dell'ipotensione ortostatica ha come obiettivo il controllo dei sintomi e comprende misure non farmacologiche e farmacologiche.**