Prise en charge de l'hypotension orthostatique liée à la polyneuropathie diabétique

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CINFO Adultes & Enfants

Déclaration de conflits d’intérêt potentiels de Paul Valensi

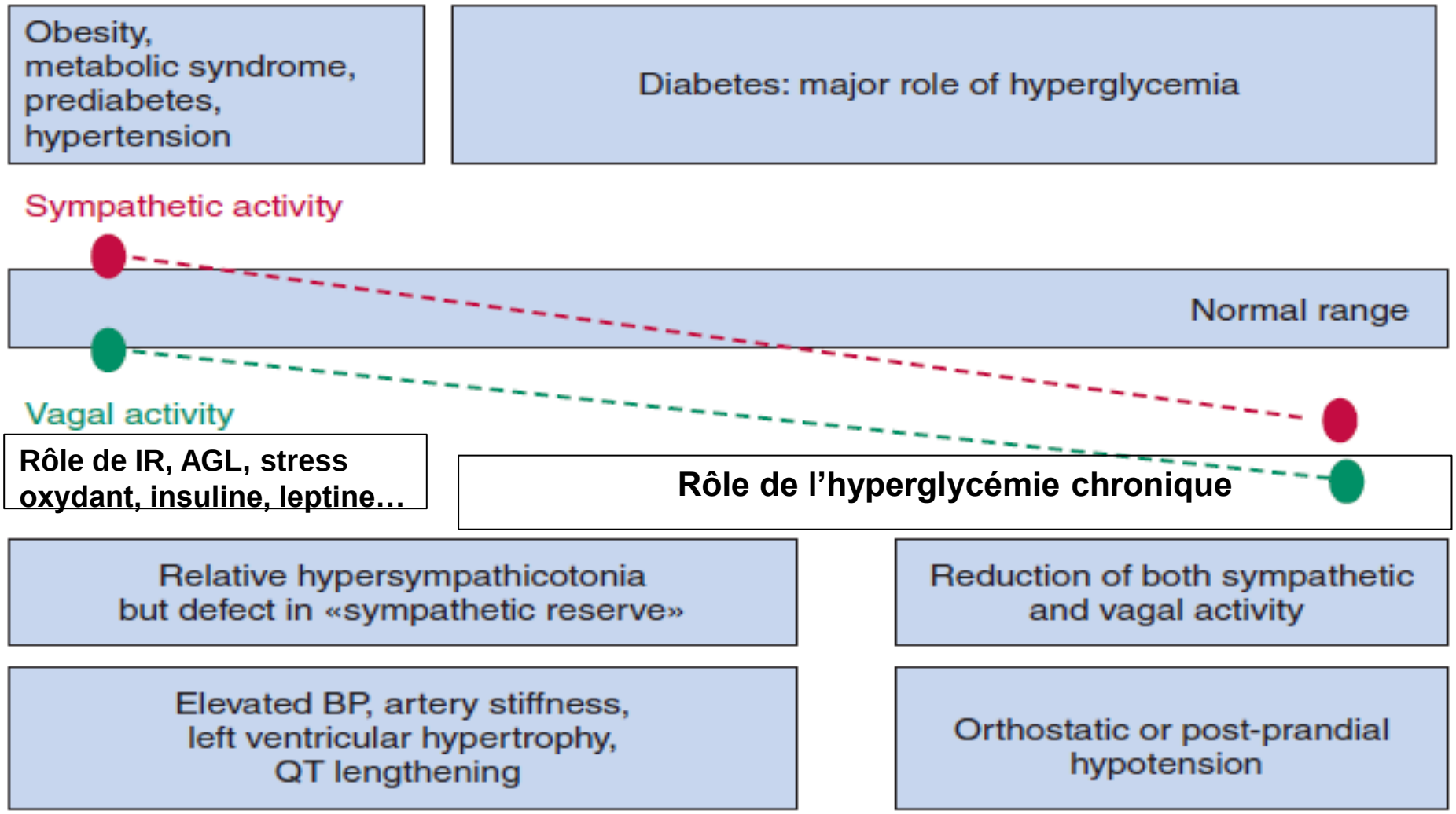
- **Conférences** à la demande de Abbott, Bayer, Bristol Myers Squibb (BMS)-AstraZeneca (AZ), Eli-Lilly, GlaxoSmithKline (GSK), Hikma, Merck Santé, Merck Sharp Dohme (MSD), Novo Nordisk, Novartis, Pierre Fabre, Sanofi, Servier, Stendo
- **Crédits de recherche** de la part de Abbott, Bayer, BMS-AZ, GSK, Merck Santé, Novo Nordisk
- **Participation à des Comités d’Experts** pour Abbott, Astra Zeneca, BMS, Boehringer Ingelheim, Daiichi-Sankyo, GSK, Kowa, Lilly, MSD, Novo Nordisk, Sanofi
- **Expert pour l’HAS, l’AFSSAPS, l’ANSM**
- **Membre de la Task Force ESC/EASD sur Diabetes, Prediabetes and CVD 2013 et 2019**

Introduction

- **NAC asymptomatique:** détectée par l'analyse des variations de fréquence cardiaque, fréquente

- **NAC symptomatique:** hypotension orthostatique (HO), peu fréquente, symptomatique ou non éventuellement associée à d'autres manifestations dysautonomiques

CHANGES IN VAGAL AND SYMPATHETIC ACTIVITY IN THE DIABETES CONTINUUM



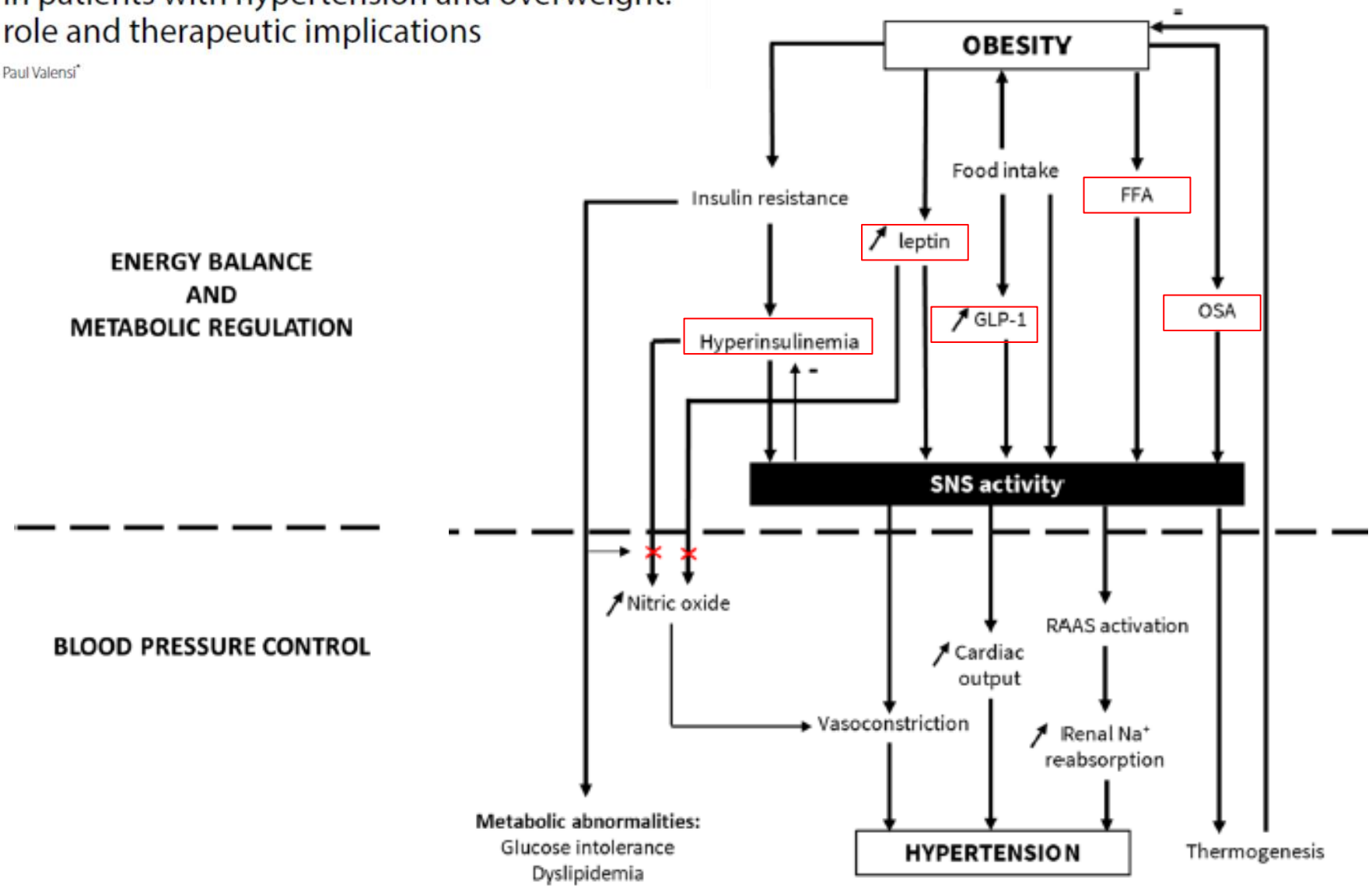
Valensi P. In: Diabetes in Cardiovascular Disease: A Companion to Braunwald's Heart Disease. Elsevier 2014

REVIEW Open Access

Autonomic nervous system activity changes in patients with hypertension and overweight: role and therapeutic implications

Paul Valensi*

Valensi Cardiovasc Diabetol (2021) 20:170



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Autonomic nervous system activity changes in patients with hypertension and overweight: role and therapeutic implications

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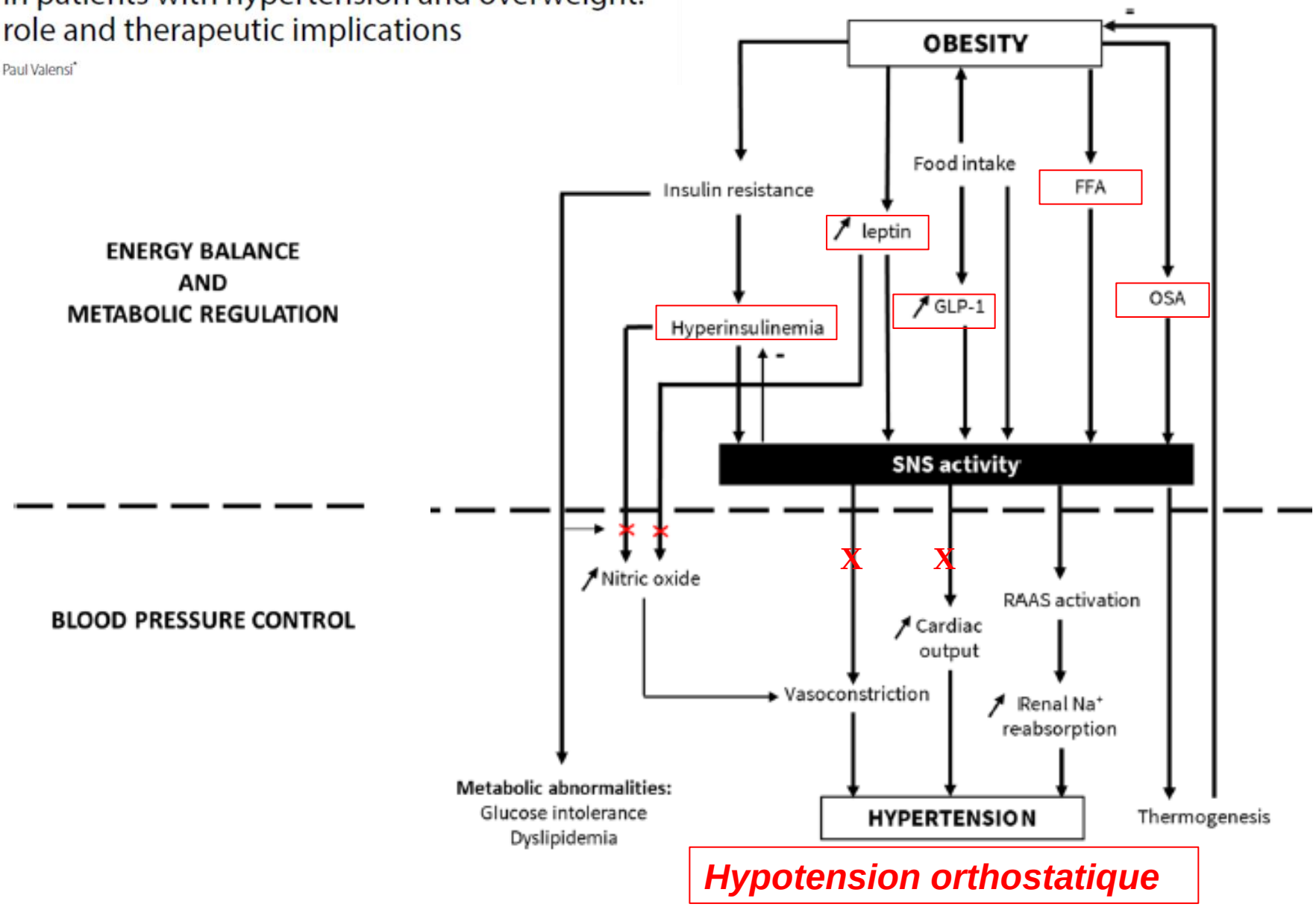


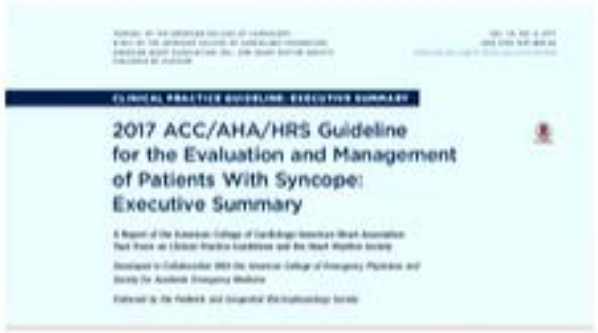
Hypotension orthostatique

Plan

- **Définitions et types**
- **Diagnostic**
- **Fréquence et déterminants**
- **Mécanismes**
- **Pronostic**
- **HO et profil tensionnel des 24h et hypotension post-prandiale**
- **Bilan de la dysautonomie**
- **Prévention et traitement**

The North American Cardiology consensus 2017

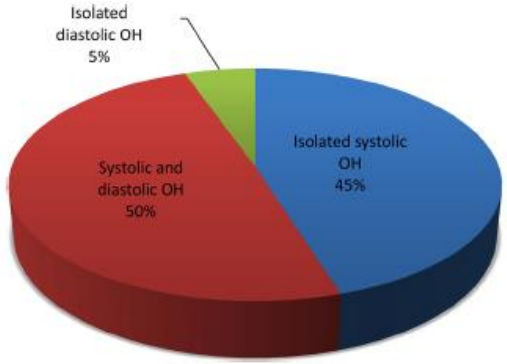
Les mêmes sous-types que les guidelines 2011


CLINICAL PRACTICE GUIDELINE: EXECUTIVE SUMMARY

2017 ACC/AHA/HRS Guideline for the Evaluation and Management of Patients With Syncope: Executive Summary

Shen et al. JACC 2017;70:e39-110

Orthostatic hypotension (OH)	A drop in systolic BP of ≥20 mm Hg or diastolic BP of ≥10 mm Hg with assumption of an upright posture (13).
■ **Initial (immediate) OH**	A transient BP decrease within 15 s after standing, with presyncope or syncope (13,14).
■ **Classic OH**	A sustained reduction of systolic BP of ≥20 mm Hg or diastolic BP of ≥10 mm Hg within 3 min of assuming upright posture (13).
■ **Delayed OH**	A sustained reduction of systolic BP of ≥20 mm Hg (or 30 mm Hg in patients with supine hypertension) or diastolic BP of ≥10 mm Hg that takes >3 min of upright posture to develop. The fall in BP is usually gradual until reaching the threshold (13).
■ **Neurogenic OH**	A subtype of OH that is due to dysfunction of the autonomic nervous system and not solely due to environmental triggers (such as dehydration or drugs) (15,16). Neurogenic OH is due to lesions involving the central or peripheral autonomic nerves.



95% des patients avec HO répondent au critère de PAS

Fedorowski et al. Clin Auton Res 2017;27:167-173

Practical Instructions for the 2018 ESC Guidelines for the diagnosis and management of syncope

Active standing

Recommendations	Class[a]	Level[b]
Indications		
Intermittent determination by sphygmomanometer of BP and HR while supine and during active standing for 3 min are indicated at initial syncope evaluation.[20,103,104]	I	C
Continuous beat-to-beat non-invasive BP and HR measurement may be preferred when short-lived BP variations are suspected, such as in initial OH.[20,103,104]	IIb	C
Diagnostic criteria		
Syncope due to OH should be considered likely when there is an asymptomatic fall in systolic BP from baseline value ≥20 mmHg or diastolic BP ≥10 mmHg, or a decrease in systolic BP to <90 mmHg, and symptoms (from history) are consistent with OH.[6,20,103,104]	IIa	C
Syncope due to OH should be considered likely when there is a symptomatic fall in systolic BP from baseline value ≥20 mmHg or diastolic BP ≥10 mmHg, or a decrease in systolic BP to <90 mmHg, and not all of the features (from history) are suggestive of OH.[6,20,103,104]	IIa	C
POTS should be considered likely when there is an orthostatic HR increase (>30 b.p.m. or to >120 b.p.m. within 10 min of active standing) in the absence of OH that reproduces spontaneous symptoms.[6,20,103,104]	IIa	C
Syncope due to OH may be considered possible when there is an asymptomatic fall in systolic BP from baseline value ≥20 mmHg or diastolic BP ≥10 mmHg, or a decrease in systolic BP to <90 mmHg, and symptoms (from history) are less consistent with OH.[6,20,103,104]	IIb	C

Syncope due to OH is confirmed when there is a fall in SBP from baseline ≥ 20 mmHg or DBP ≥ 10 mmHg or a decrease in SBP to < 90 mmHg that reproduces spontaneous symptoms

Brignole et al. Eur Heart J 2018;39:e43-80

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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 33:1–3, 2010

Diabetes Metab Res Rev 2011

- V Spallone, D Ziegler, R Freeman, L Bernardi, S Frontoni, R Pop-Busui, M Stevens, P Kempler, J Hilsted, P Low, P Valensi.
Cardiovascular autonomic neuropathy in diabetes: clinical impact, assessment, diagnosis, and management

- L Bernardi, V Spallone, M Stevens, J Hilsted, S Frontoni, R Pop-Busui, D Ziegler, P Kempler, R Freeman, P Low, S Tesfaye, P Valensi.
Investigation methods for cardiac autonomic function in human research studies

Toronto Consensus. 2009

Détecter et grader la NAC: batterie recommandée

Recherche d'une hypotension orthostatique

Baisse de la PAS de ≥ 20mmHg (plutôt 30) et/ou de la PAD de ≥ 10 mmHg dans les 3 minutes suivant le passage en orthostatisme
En l'absence de facteur iatrogène
Témoigne d'une atteinte sympathique

Epreuves standardisées

- **Méthode de référence: simple, validée, sensible, spécifique, reproductible (A)****
- **Tests évaluant la variabilité de la fréquence cardiaque**
  respiration profonde, Valsalva (CI si rétinopathie proliférante), orthostatisme actif
- **CV intra-sujets: 6-13% ***
- **Evaluent surtout l'activité vagale cardiaque**

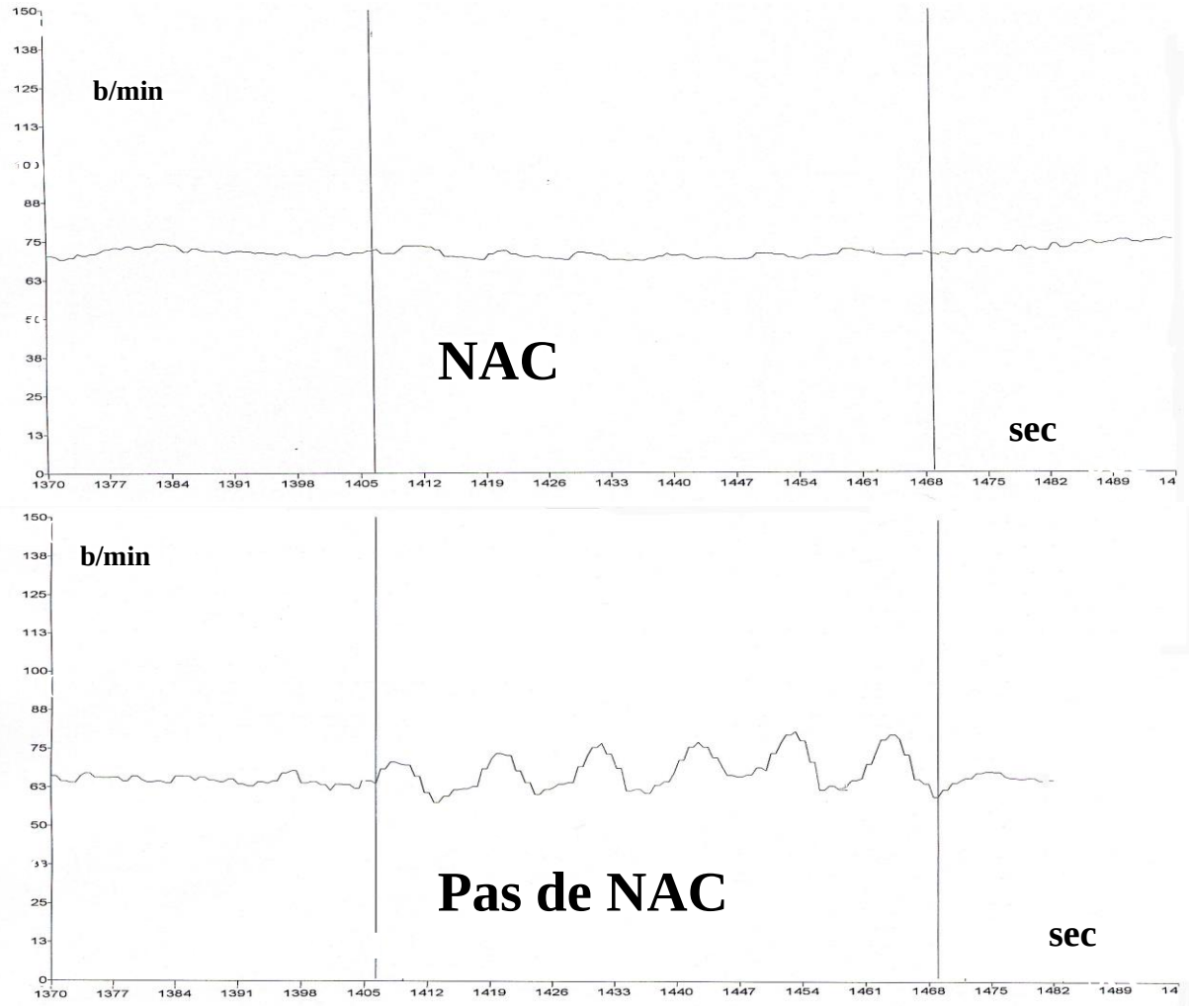
Ecarter une autre étiologie de NAC et d'HO

A faire dès la découverte du DT2 et après 5 ans de DT1,
particulièrement chez les patients à risque élevé de NAC:
mauvais équilibre glycémique, fdr cardiovasculaire, neuropathie périphérique,
complications macro ou microvasculaires (B), puis annuellement*

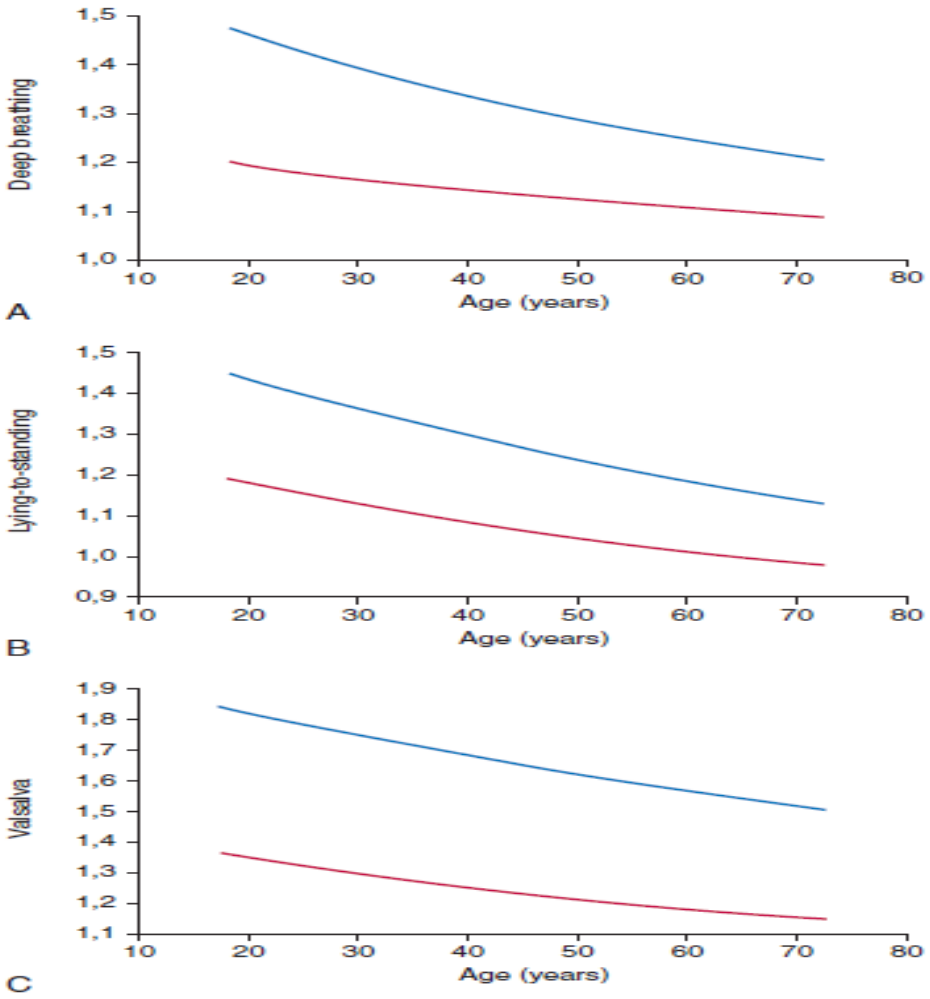
** Valensi et al. Diabet Med 1993 ; 10 : 933-9*

*** Consensus de Toronto. Spallone et al. DMRR 2011;27:639-53*

Test de respiration profonde à 6 cycles/minute



Influence de l'âge



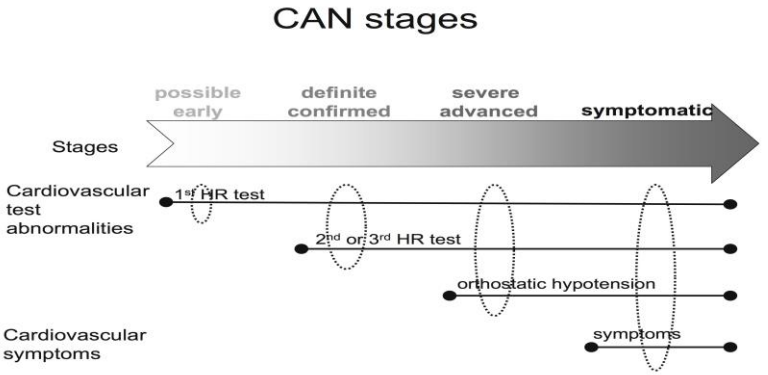
Valensi P. In: Diabetes in Cardiovascular Disease: A Companion to Braunwald's Heart Disease. Elsevier 2014

Staging CAN

Toronto consensus meeting

Trois grades de NAC

- **Possible ou débutante:** un test cardiovagal anormal
- **Définie ou confirmée:** ≥ 2 tests cardiovagaux anormaux
- **Sévère ou avancée:** hypotension orthostatique (témoin d'une atteinte sympathique) en plus des tests cardiovagaux anormaux



Consensus de Toronto. Spallone et al. DMRR 2011;27:639-53

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Prevalence of subclinical CAN in diabetic patients
CAN was assessed using standard tests of HRV and the detection of postural hypotension

- In the French Multicentre Study
- 396 asymptomatic normotensive diabetic patients: 151 T1D and 245 T2D
- Cardiac vagal neuropathy:
  - possible (1 test) 31%
  - **definite (2 or 3 tests) 20%**
- **Postural hypotension : 10.3%**
- CAN was associated with longer diabetes duration and worse glycemic control
- More prevalent in overweight T2D patients: 60.6 *vs* 40% (p=0.03)

Valensi et al. Metabolism 2003;52:815-820

- Prévalence de la NAC: 9 à 15% avec une incidence annuelle de 1,8%

Spallone et al. Diabetes Metab Res Rev. 2011

- Incidence moindre dans l'étude ADDITION: DT2 pris en charge intensivement à la découverte du diabète ***Andersen et al. Diabetes Care 2018;41:2586-94***

Corrélats de la NAC

- **Age**
- **Durée diabète**
- **Contrôle glycémique**
- **Présence d'une PND**
- **Rétinopathie, néphropathie**
- **HTA**
- **Autres fdr: obésité, dyslipidémie**

Valensi et al. Metabolism 2003;52:815-820

Spallone V. Diabetes Metab J 2019;43:3-30

Prévalence et incidence de l'HO dans une grande population de patients DT2 hypertendus

ACCORD-BP study: une population à fort risque d'HO

PA mesurée assis puis après 1, 2 et 3 minutes d'orthostatisme, à l'inclusion puis à 12 et 48 mois

HO définie par baisse de PAS de ≥ 20 mmHg ou PAD ≥ 10 mmHg

Sur la durée totale du suivi, 20% de patients avec HO. Faible relation avec symptomes au lever

Participants Analyzed	Intensive Group % (n/n)	Standard Group % (n/n)	*P* Value
Participants with data at all 3 visits			
Prevalence			
Baseline	18.7 (86/461)	16.8 (78/465)	0.49
12 mo	10.2 (47/461)	11.6 (54/465)	0.53
48 mo	12.2 (56/461)	12.9 (60/465)	0.77
Incidence			
12 mo*	7.7 (29/375)	9.8 (38/387)	0.31
48 mo†	9.8 (34/346)	8.6 (30/349)	0.58
Resolution			
12 mo‡	79.1 (68/ 86)	79.5 (62/ 78)	0.95
48 mo§	70.2 (33/ 47)	75.9 (41/ 54)	0.52

Pas d'augmentation du risque de développer une HO malgré le traitement anti-hypertenseur intensif, comme dans SPRINT

Fleg et al. Hypertension 2016;68:888-95

ACCORD-BP: Comparaison des patients avec ou sans HO en analyses multivariées

Baseline Characteristic	Odds Ratio	95% Confidence Interval	*P* Value
Systolic BP, mm Hg	1.013	1.007–1.018	<0.0001
Current vs never smokers	1.382	1.095–1.743	0.006
Peripheral neuropathy	1.076	0.920–1.257	0.36
Hemoglobin A1c, %	1.088	1.014–1.167	0.02
β-Blockers	1.240	1.033–1.288	0.02
α-Blockers	1.701	1.018–2.843	0.04
Insulin	1.242	1.030–1.497	0.02

Fleg et al. Hypertension 2016;68:888-95

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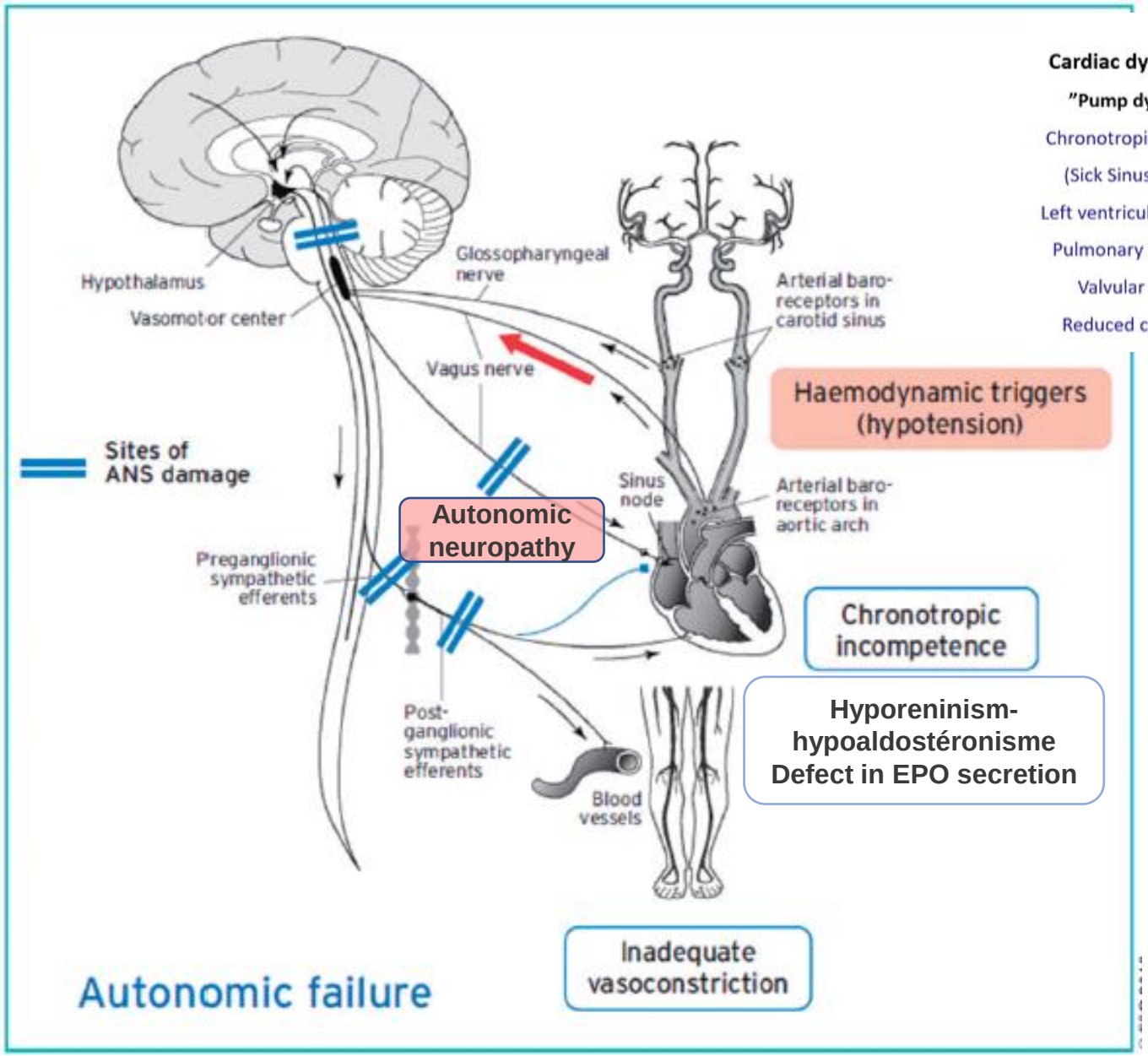
Pathophysiology

Immediately after standing, there is gravitationally mediated redistribution of the blood volume, and a pooling of 300–800 ml of blood in the lower extremities and splanchnic venous capacitance system. As a consequence, venous return to the heart falls and cardiac filling pressure is reduced. This results in diminished stroke volume and cardiac output. In response, sympathetic outflow to the heart and blood vessels increases and cardiac vagal nerve activity decreases. These autonomic adjustments increase vascular tone, heart rate and cardiac contractility, and stabilize arterial pressure. During standing, contraction of lower body skeletal muscle prevents excessive pooling and augments venous return to the heart.

Orthostatic hypotension is caused by an excessive fall of cardiac output or by defective or inadequate vasoconstrictor mechanisms. The focus of this consensus statement is neurogenic orthostatic hypotension, i.e., orthostatic hypotension due to inadequate release of norepinephrine from sympathetic vasomotor neurons leading to vasoconstrictor failure.

HO associée au diabète: causes centrale et périphérique



D'après Brignole et al. Eur Heart J 2018;39:e43-80

La vasoréactivité microcirculatoire en réponse à l'activation sympathique est altérée chez les patients DT2
Défaut de réserve sympathique et de vasomotion

Group/Parameter	Deep-Breathing	
	%	Slope
NIDDM patients (n = 42)	43.4 ± 6.0	7.4 ± 0.8
Controls (n = 14)	79.1 ± 23.0	11.9 ± 1.3
P	.04	.003

Valensi et al. Metabolism 1997;46:235-41

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Mauvais pronostic associé à HO

First Author - Study Cohort	Year	Death, any cause	CV death	HF	CAD/MI	Stroke	Atrial Fibrillation	Subclinical ASCVD/TOD
Raiha et al.	1995	■	■		■	■		
Masaki et al. - HHP	1998	■						
Eigenbrodt et al. - ARIC Stroke	2000					■		
Hossain et al.	2001	■			■	■		
Sasaki et al.	2005	■						
Cohen et al.	2006	■						
Rose et al. - ARIC	2006	■	■					
Weiss et al.	2006	■						
Verwoert et al. - Rotterdam Study	2008	■		■	■	■		
Fedorowski et al. - MPP	2010	■			■	■	■	
Fedorowski et al. - MPP HF	2010			■				
Jones et al. - ARIC HF	2012			■				
Agarwal et al. - ARIC	2013						■	
Alagiakrishnan et al. - CHS	2013	■		■	■	■		
Casiglia et al. - LEOGRA	2013			■	■	■	■	
Fedorowski et al. - CPP	2013	■			■	■		
Chou et al. - Taiwan NHIRD	2015	■			■	■		
Magnusson et al. - MPP	2015							■
Fleg et al. – ACCORD BP	2016	■	■	■	■	■		
Ricci et al. - MPP	2017	■	■					
Juraschek et al. - AASK	2018	■		■	■	■		
Juraschek et al. - ARIC	2018	■	■	■	■	■		■
Ko et al. - FHS	2018						■	
Yasa et al. - MDCS	2018	■	■	■	■	■	■	

Fedorowski et al. Kardiol Pol 2019;77:1020-7

Conséquences cardio-vasculaires du déséquilibre de la balance vago-sympathique

Altérations de l'activité du système nerveux autonome

Réduction de l'activité vagale

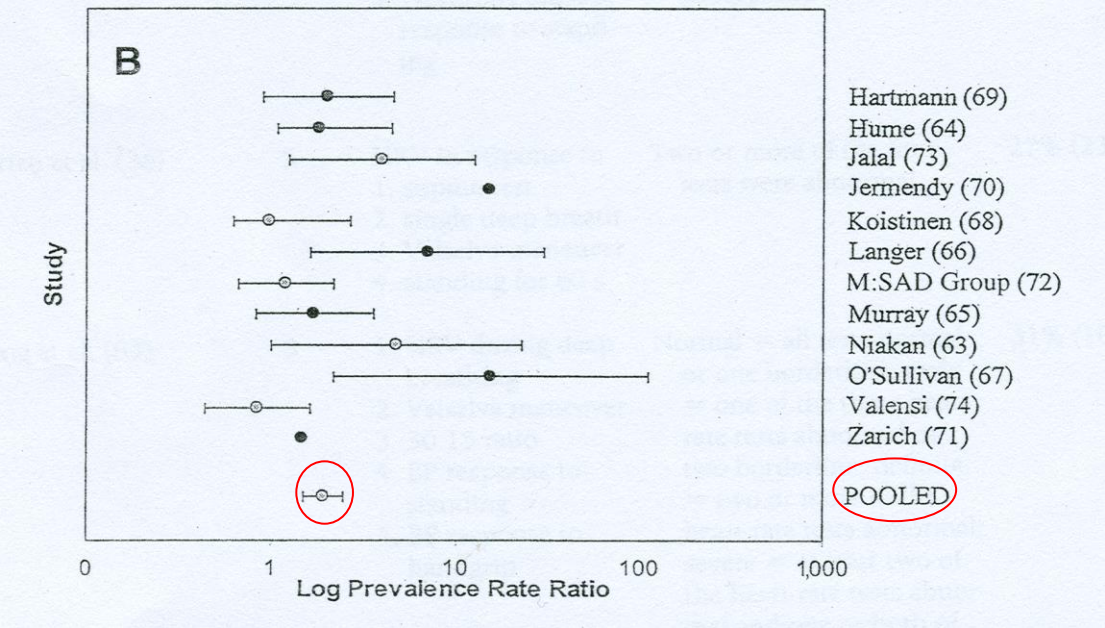
Prédominance sympathique

- Hypertension
  Non dipping
  Rigidité artérielle
- Ischémie myocardique silencieuse
  Réduction de la réserve coronaire
- Intolérance à l'effort
- HVG
  Dysfonction VG
  Insuffisance cardiaque
- Arythmie
- Microangiopathie

Complications cardiovasculaires

Assess the cv disorders associated to CAN

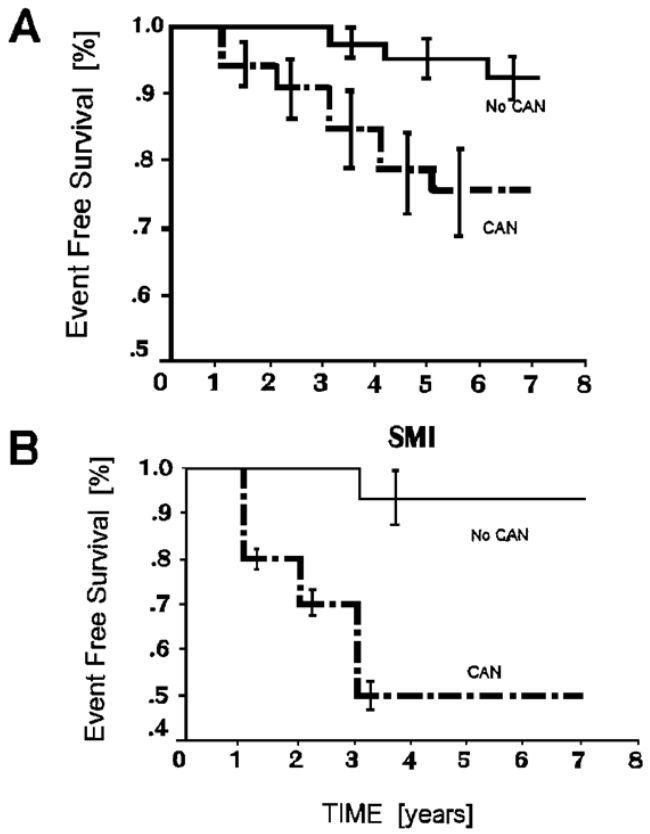
Association NAC-ischémie myocardique silencieuse
Données poolées de 12 études (1468 patients)



Relative risk for SMI = 1.96 (p < 0.001)

Vinik et al. Diabetes Care 2003 ; 26 : 1553-79

La NAC aggrave le pronostic chez les diabétiques avec ischémie myocardique silencieuse



Valensi et al. Diabetes Care 2001;24:339-44

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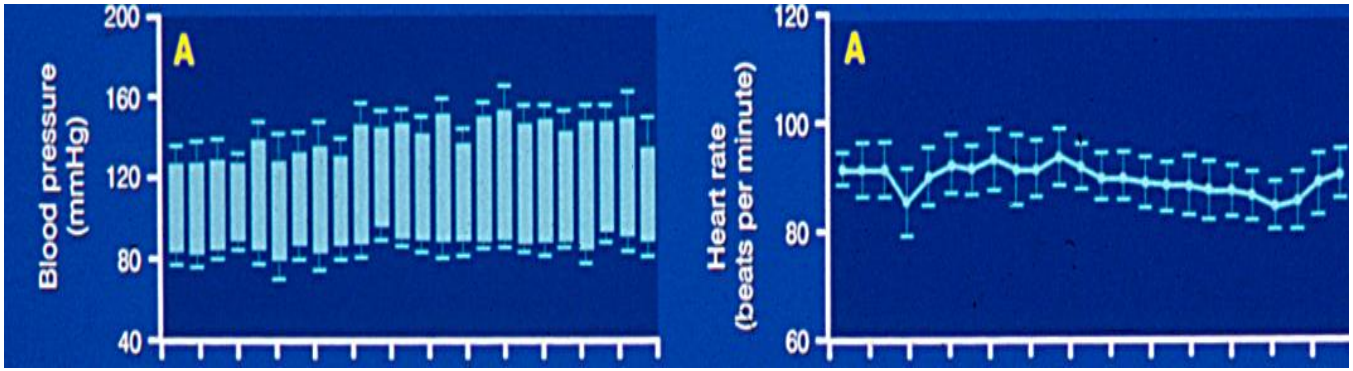
Higher prevalence of hypertension in the patients with abnormal cardiovagal tests

Number of abnormal CAN function tests	0	1	2	3 or 4	*P*-value
Type 1 diabetes	3.6	14.8	23.1	36.4	< 0.0001
Type 2 diabetes	14.7	27.9	42.9	87.5	< 0.0001
All subjects with diabetes	12.0	23.0	35.0	58.0	< 0.0001

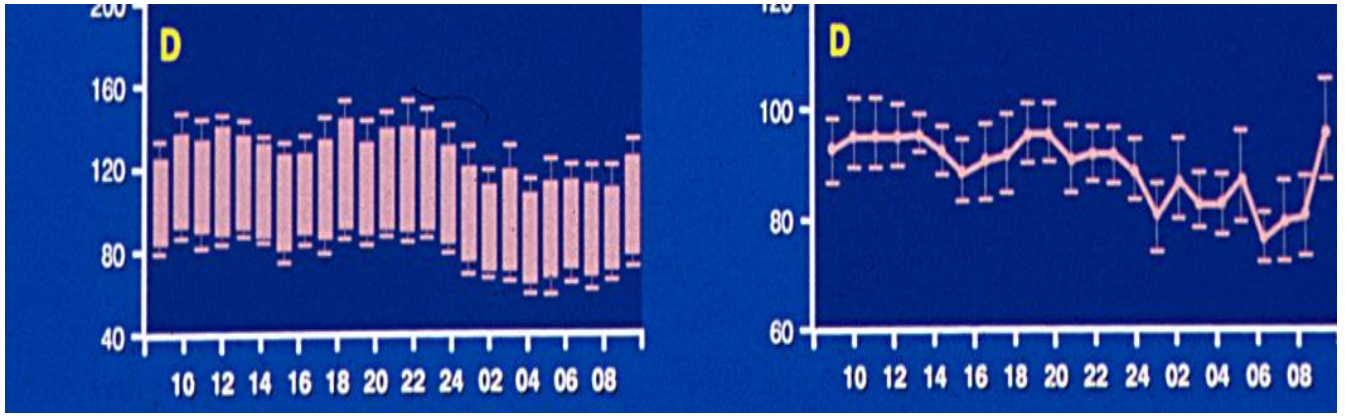
Ayad et al. Diabet Med 2010;77:804-11

CAN, non or reverse dipping

NAC+

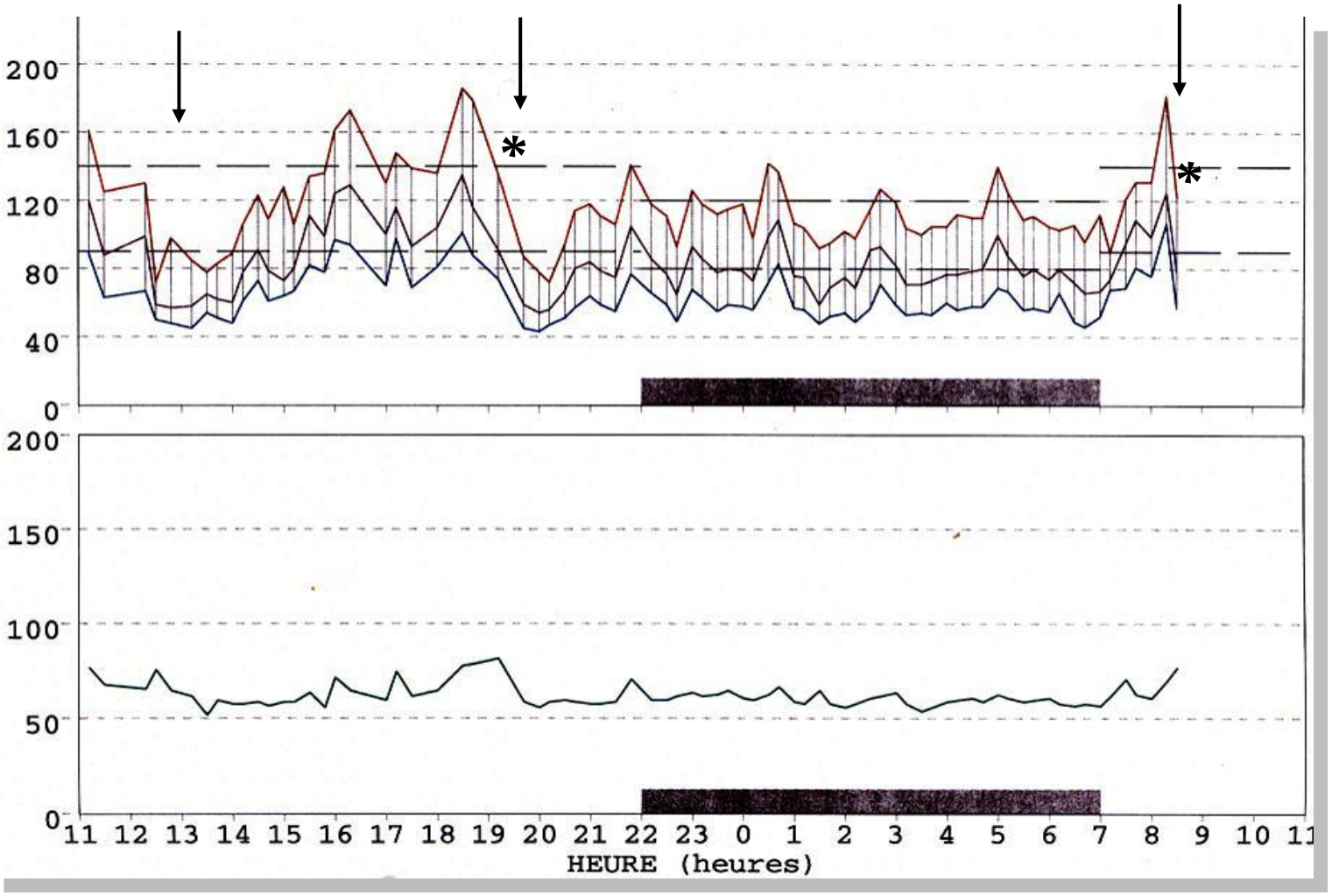


NAC-



Liniger et al. Diabetic Med 1991;8:420-7

Baisse tensionnelle en période post-prandiale, source de malaises



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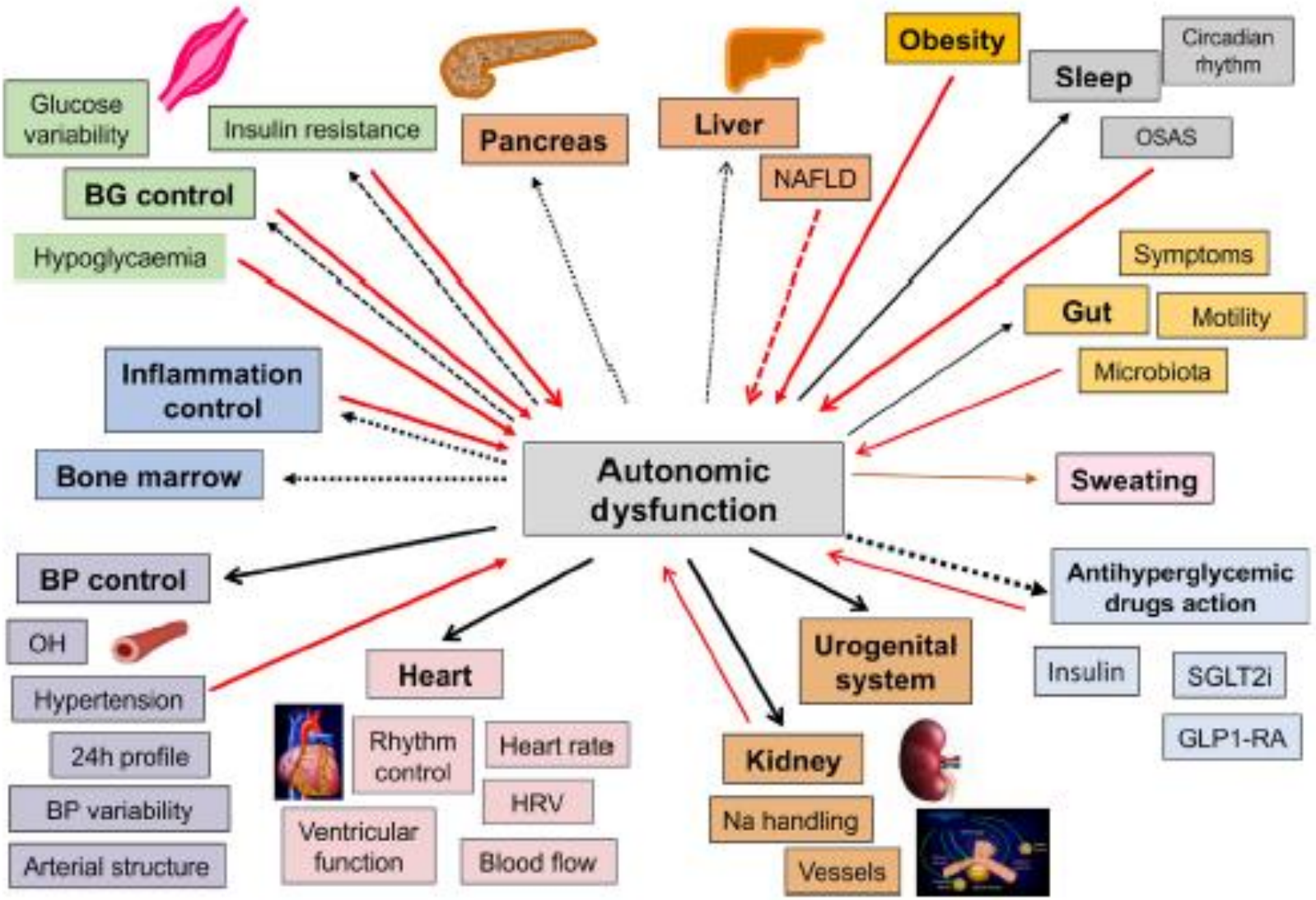
Les cibles multiples de la dysautonomie diabétique



Spallone & Valensi. Diabetes Metab 2021;47:101224

Pourquoi rechercher une NAC ?

- **Pour affirmer l'origine dysautonomique**

  d'une hypotension orthostatique ou post-prandiale,

  d'une tachycardie inexpliquée

  d'hypoglycémies non ressenties

  d'un reverse dipping

  d'un QT long

  de manifestations digestives ou génito-urinaires sans atteinte d'organe *(classe I, B,C)*

- **Pour le traitement adapté des désordres associés à la NAC**

  tachycardie, hypotension orthostatique, nondipping, allongement du QT

- **Pour affiner l'estimation du RCV et rechercher une maladie coronaire silencieuse**

Consensus de Toronto. Spallone et al. DMRR 2011;27:639-53

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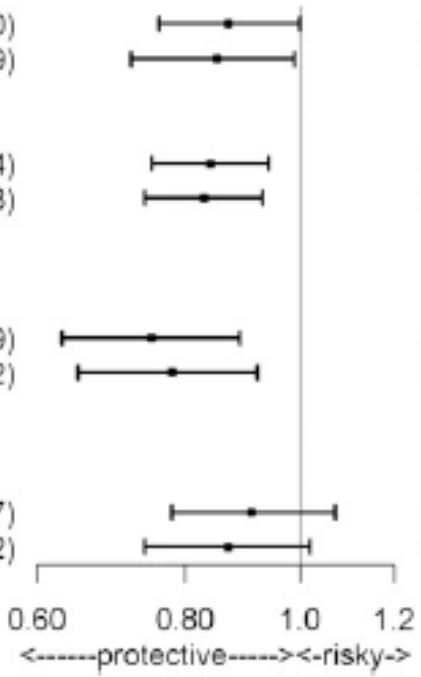
Effets préventifs du contrôle glycémique intensifié sur la NAC
L'étude DCCT/EDIC chez lez diabétiques de type 1

Test and Group	DCCT Baseline	DCCT Closeout	EDIC Year 13/14
CAN prevalence, n (%)*			
INT	24 (3.9)	43 (7.1)	179 (28.9)§
CONV	31 (5.3)	57 (9.9)	208 (35.2)
R-R Variation ≤15, n (%)			
INT	20 (3.3)	39 (6.6)	147 (23.8)§
CONV	25 (4.3)	53 (9.5)	178 (30.2)
Valsalva ratio ≤1.5, n (%)			
INT	31 (5.2)	42 (7.4)	145 (26.0)
CONV	30 (5.2)	51 (9.3)	146 (30.4)

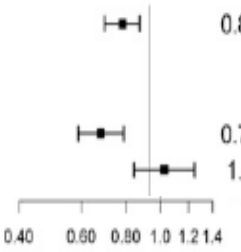
Pop-Busui et al. Circulation 2009;119:2886-93

ACCORD: effets du contrôle des fdr sur la NAC chez les patients DT2

Interventions	OR	95%CI	P value
Intensive glycemic control vs. standard glycemic control			
Before transition			
Minimally adjusted model	0.87	(0.76, 1.00)	0.053
Fully adjusted model	0.85	(0.72, 0.99)	0.042
All follow-up			
Minimally adjusted model	0.84	(0.75, 0.94)	0.003
Fully adjusted model	0.83	(0.74, 0.93)	0.002
Intensive BP control vs. standard BP control			
Minimally adjusted model	0.75	(0.63, 0.89)	0.001
Fully adjusted model	0.78	(0.65, 0.92)	0.004
Fenofibrate + statin vs. placebo + statin			
Minimally adjusted model	0.91	(0.78, 1.07)	0.262
Fully adjusted model	0.87	(0.74, 1.02)	0.078



Subgroup	OR	95%CI	P value	P value for interaction
Total	0.84	(0.75, 0.94)	0.003	
Previous cardiovascular event				0.001
No	0.73	(0.63, 0.85)	0.00003	
Yes	1.1	(0.91, 1.34)	0.33	



Tang Y et al. Diabetes Care 2021;44:164-73

Chez les patients diabétiques avec HO

- **Bilan cardiaque plus poussé:**
  - **échocardiographie**
  - **holter ECG 24h**
  - **recherche maladie coronaire silencieuse (CAC,…)**
- **Contrôle tensionnel avec encore plus de précautions. MAPA**
- **Contrôle glycémique en évitant les hypoglycémies. Intérêt du CGM**
- **Risque accru d'HO sous inhibiteurs du SGLT2 [1]. Probablement dû aux effets diurétiques et dépresseurs du sympathique [2]**

1. Bhanu C et al. Plos Med 2021;18:e1003821
2. Spallone & Valensi Diabetes Metab 2021;47:101224

Mesures non pharmacologiques en présence d'une HO

Intervention
Patient and family education for:
Reasons for symptoms
Safety measures to avoid OH-related falls
Recognition of presyncopal symptoms
Avoidance of triggers (ie, heat exposure, over-exertion, alcohol, hot tubs, dehydration)
Caution with valsalva-like maneuvers (avoiding strain with defecation, urination)
Patient diary to record physical activity and meals; further ambulatory blood-pressure monitoring (with patient activity diary) can help identify presence of postprandial hypotension as well as supine hypertension at night
Counterpressure maneuvers for preventing symptoms and emergency management of symptoms
Crossing legs upon standing
Abdominal and leg muscle pumping/contractions
Bending forward or squatting
Activity and positioning
Avoid prolonged sitting or standing. If prolonged inactivity, do ankle pumps & cross/uncross legs
Avoid abrupt change from lying to standing (ie, sit at the edge of the bed for a minute before standing) or sitting to standing
Rise gradually from sitting to standing (ie, after being inactive or sitting on the toilet)
Sit after eating or exercise (ie, for 20 minutes); record symptoms related to meals or exercise
Drinking fluids to ensure hydration
Additional oral water bolus (ie, about 400–500 mL within 5 minutes) may help when symptomatic, before arising in the morning, before exercise or after eating (if not contraindicated due to comorbidities)
Bolus drinking may not be appropriate for patients at risk for fluid overload (ie, heart failure, end-stage kidney disease)
Compression garments if properly fit and patient is able to apply, remove, and tolerate
Abdominal binder may reduce symptoms for patients before an outing or event
Full leg compression stockings (eg, ankle to hips compression stockings at 22–32 mm Hg, not just calves or thighs)
Coping, support, and integrative therapies, such as, cognitive behavior strategies, support groups, and mindfulness stress reduction techniques, have been effective in similar populations and anecdotally recommended by clinicians
Due to limited evidence, negative studies, and potential side effects, avoid indiscriminate recommendation for:
Lower limb compression stockings
Sleeping with head of bed elevated
Increasing salt in diet

Fedorowski et al. Circ Arrhythm Electrophysiol 2022;15:e010573

Traitements pharmacologiques proposés si HO
Méfiance si HTA et cardiopathie

Drugs	Mechanism(s)	Adverse events
Droxidopa (100–600 mg tid)*	Norepinephrine precursor	Headache, nausea, supine hypertension
Midodrine (2.5–10 mg bid or tid)*	Direct α1-adrenoreceptor agonist	Goose bumps, paresthesia, pruritus, supine hypertension, urinary urgency
Fludrocortisone (0.05–0.3 mg qd)	Mineralocorticoid (volume expander), increases sodium reabsorption and enhances sensitivity of α-adrenoreceptors	Supine hypertension and hypokalemia
Pyridostigmine (30–60 mg bid or tid)	Acetylcholinesterase inhibitor	Gastrointestinal symptoms, urinary urgency
Atomoxetine (18 mg qd)	Norepinephrine reuptake inhibitor	Supine hypertension, urinary urgency
Octreotide (0.2–1.6 mg/kg qd, subcutaneous)	Somatostatin analog reducing postprandial splanchnic hyperemia induced by gastrointestinal vasodilatory peptides	Injection site discomfort, erythema, gastrointestinal disturbances, flushing, cholelithiasis, hyperglycemia, supine hypertension
Desmopressin (nasal spray, 5–40 mg qd; oral, 100–800 mg qd)	V1a (vascular smooth muscle) and V2 (distal convoluted tubule and collecting ducts of the kidney) receptor agonist. Vasopressin analogue (volume expander), increases water reabsorption and reduces nocturia	Limited data, safety issues unclear
Ephedrine/pseudoephedrine (25/30–50/60 mg 3× per day)	Direct and indirect α1-adrenoreceptor agonist	Nausea, supine hypertension

Arrêter β– et utiliser un IEC de courte demi-vie
Eviter les médicaments qui allongent le QT

EPO

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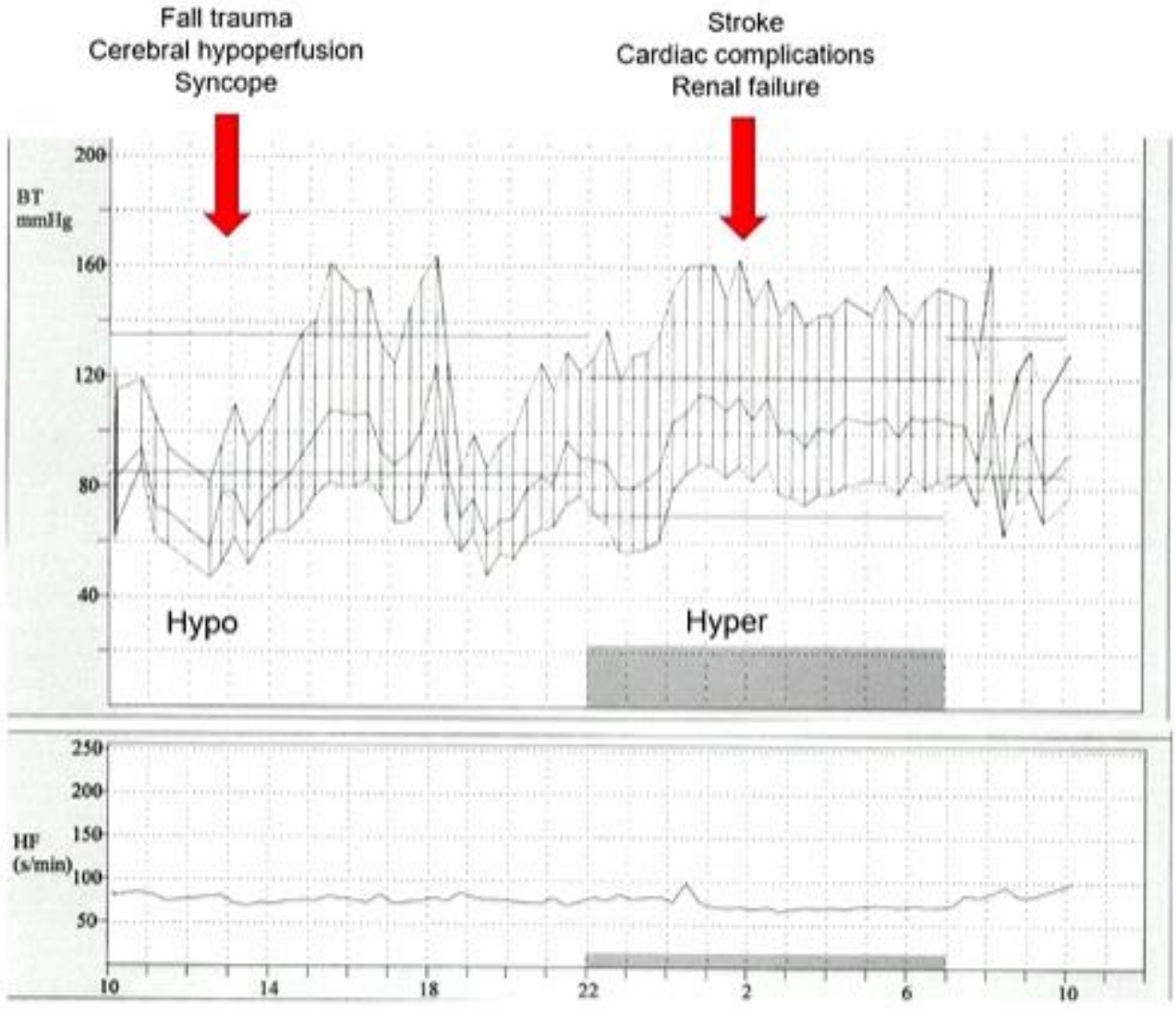
Le dilemme thérapeutique de l'HO



24h ambulatory BP monitoring