Corso di Aggiornamento A.I.N.V.
"LA DISAUTONOMIA NELLA PRATICA CLINICA: diagnosi e strategie terapeutiche"
4 Ottobre 2024 - Treia (MC)

Il Sessione

Novità nella gestione e nella terapia delle patologie del SN Autonomo

Ruolo protettivo dei SGLT2 inibitori

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Duality of interest declaration

In the last 2 years I had financial relationship (speaker's honorarium, board member, advisory panel) with the following companies:

- Meda Pharma S.p.A., Italy
- Nevro Medical Ltd., UK
- Theras Lifetech S.r.l., Italy
- Wörwag Pharma GmbH & Co, Germany

Agenda

- Il contesto: impatto epidemiologico e prognostico della neuropatia autonomica cardiovascolare (CAN) nel diabete
- Pertinenza della CAN alla malattia cardiovascolare e renale
- Dal beneficio nei trial clinici ai meccanismi fisiopatologici: il ruolo del SNA nelle azioni dei SGLT2i
- Prospettive terapeutiche: farmaci protettivi sul SNA nel diabete

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Global, regional, and national burden of disorders affecting the nervous system, 1990–2021: a systematic analysis for the Global Burden of Disease Study 2021

GBD 2021 Nervous System Disorders Collaborators*

Lancet Neurol. 2024 Apr;23(4):344-381

As **the leading cause of disability-adjusted life-years** (DALYs), affecting more than 40% of the global population, **nervous system health loss** should be a public health priority.

The 10 conditions with the highest age-standardised DALYs in 2021 were

1. stroke,
2. neonatal encephalopathy,
3. migraine,
4. Alzheimer's disease and other dementias,
5. **diabetic neuropathy**,
6. meningitis,
7. epilepsy,
8. neurological complications due to preterm birth,
9. autism spectrum disorder,
10. nervous system cancer.

Diabetic neuropathy the 5th neurological condition causing chronic disability globally.

Prevalence of diabetic cardiovascular autonomic neuropathy (CAN)

Prevalence in diabetes

20% in unselected population

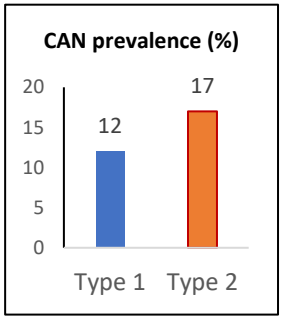
Incidence in T1DM ↑ 1.7% year of duration **up to 44%**

Incidence in T2DM ↑ 4.6-6% year of duration **up to 65%**

Prevalence in adolescents and young adults

SEARCH Study

12% in T1DM
17% in T2DM

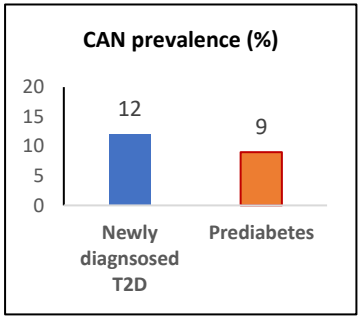


Prevalence at diagnosis in T2DM

12-17% in population studies (overall CAN)

Prevalence in prediabetes

9% in a population study (confirmed CAN)



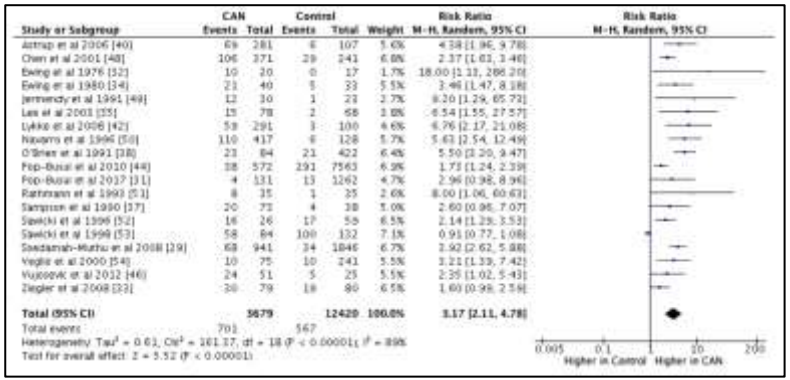
Eleftheriadou A et al *Diabetologia. 2021;64:288-303*
Ratzmann KP et al *J Diabetes Complications 1991; 5: 1-5.*
Töyry JP et al *Diabetes 1996; 45: 308-315.*
Zoppini G et al *Diabetes Care. 2015;38:1487-93.*
Ko SH et al *Diabetes Care 2008; 31: 1832-1836*

Ziegler D et al *Diabetologia. 2015;58:1118-28.*
Ziegler D et al Diabetes Care 1992; 15: 908-911
Spallone V et al *Diabetes Metab Res Rev 2011;27:639–653*
Braffett BH et al *Diabetes 2020;69:1000–1010*
Jaiswal M et al *Pediatr Diabetes. 2018;19:680-689*

CAN as a risk marker for mortality: a meta-analysis

Meta-analysis of 19 studies: 3679 patients with and 12 420 without cardiovascular autonomic neuropathy (CAN) for the outcome of all-cause mortality and 16 studies (2875 patients with and 11 722 without CAN) for cardiovascular events.

Forrest plot with risk ratio (RR) of overall CAN for all-cause mortality



CAN for all-cause mortality
RR: **3.17**

RR for all-cause mortality was
- **in type 1 > in type 2** diabetes (3.76 Vs. 1.94)
- with a **definite CAN > early CAN** (3.88 Vs. RR 2.3)

Chowdhury M et al *BMJ Open Diab Res Care 2021;**9**:e002480*

CAN as a predictor of vascular morbidities

Perioperative instability

(7 of 8 studies)

Arrhythmias

Heart failure

Silent myocardial ischemia

(13 studies)

Coronary artery disease

Cardiovascular morbidity

Events recurrence

(2 of 3 studies)

Stroke

(5 studies in T2DM)

Progression promoter of diabetic nephropathy

(13 of 14 studies)

CAN for cardiovascular events
RR: **3.16**

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

Cardiac autonomic neuropathy and risk of incident heart failure among adults with type 2 diabetes

Kaze AD, Yuyun MF, Erqou S, Fonarow GC, Echouffo-Tcheugui JB.

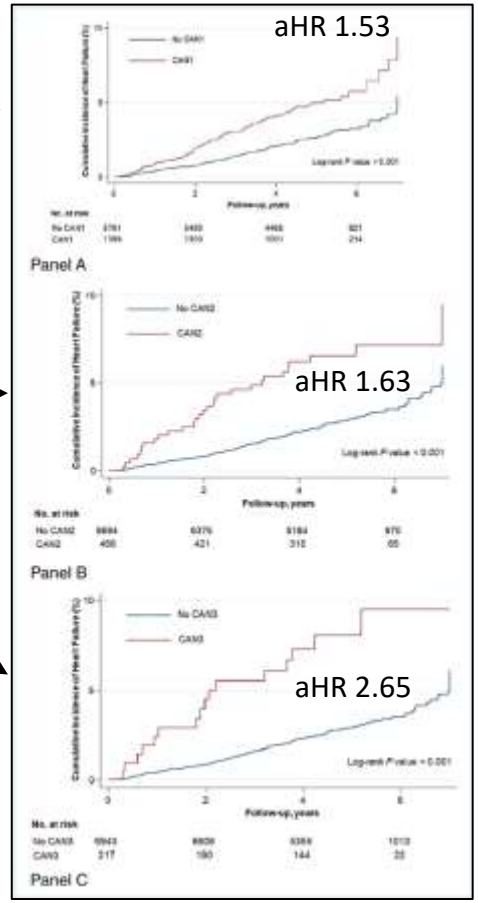
Eur J Heart Fail. 2022;24:634-641.

Risk of incident heart failure (HF) in the ACCORD study, including 7160 participants (age 62.3 years) with T2DM and without HF at baseline, followed for 4.9 years.
CAN diagnosis based on 10-sec HRV indexes (SDNN and rMSSD), QTi and resting heart rate (HR)

Definition of CAN

- SDNN <8.2 ms and rMSSD <8.0 ms
- SDNN <7.815 ms and QTI >104.32%
- SDNN <7.815 ms, QTI >104.32%, HR >77 bpm

Incidence of HF



Conclusion: CAN was associated with increased risk of incident HF (between 1.53 and 2.65), independently of known risk factors and might be considered in the estimation of HF in T2DM.

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

Potential pathogenetic links between CAN and mortality/morbidity

Resting tachycardia

QT interval prolongation

Impaired baroreflex sensitivity

Loss of reflex heart rate variations

Cardiac sympathetic dysinnervation

Left ventricular dysfunction

Orthostatic hypotension

Reverse dipping

↑ Arterial stiffness

↑ Arterial calcification

Sympatho-vagal imbalance

Dysregulation of cerebral circulation

⇓ Sympathetically mediated vasodilation of coronary vessels

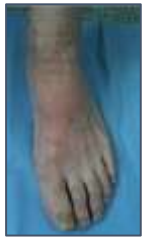
Myocardial flow reserve dysregulation

Altered BP and albuminuria circadian rhythms

Changes in glomerular hemodynamics

Dysregulation of EPO production

↑ Peripheral blood flow
↑ Arteriovenous shunting
↑ Venous pressure



Warm skin

Swollen veins

Edema

Loss of protective cutaneous vasomotor and venoarteriolar reflexes
↑ Capillary permeability

Medial arterial calcification

Dryness

Spallone V et al *Diabetes Metab Res Rev 2011; 27:654-664*
Zobel EH et al *Diabetes 2019;68:1277–1286*
Hjortkjær HØ et al *Diab Vasc Dis Res. 2019;16:98-102.*

Predictive value of CAN for progression of diabetic nephropathy

Author (year)	**N° and Type**	**CAN testing**	**Follow-up** (years)	**Kidney function outcomes**
Sundkvist (1993)	35 with T1D	DB, Tilt test	10	CAN predictor of Δ GFR And associated with ↓ GFR
Weinrauch (1998)	26 with T1D with proteinuria	DB, LS, VM	1	VM predictor of Δ creatinine and renal failure
Burger (2002)	23 with T1D with macro	DB, LS, VM, HRV indices	1	HRV indexes associated with Δ GFR ≥8 ml/min
Forsèn (2004)	58 with T1D	DB, Tilt test, OH	7-14	DB associated with 14 years UAE OH predictor of 7 years Δ GFR
Astrup (2006)	388 with T1D with micro-macro	DB	10	DB not predictor of Δ GFR
Maguire (2007)	137 with T1D with normo	Pupillary light test	12	Small pupil size predictor of microalbuminuria
Kim (2009)	156 with T2D with normo	DB, LS, VM, OH	9	DB predictor of Δ eGFR
Brotman (2010) ARIC Study	13241 (1523 with diabetes)	HR, HRV indices	16	HR and HRV predictors of ESRD
Tahrani (2014)	204 with T2D without ESRD	DB, LS, VM, OH	2.5	CAN predictor of eGFR decline
Orlov (2015) !st Joslin Kidney Study	204 with T1D with normo 166 with T1D with micro	MCR during DB	14	MCR<20 predictor of eGFR loss (OR 4.09) and of CKD stage ≥3
Yun (2015)	755 with T2D without CKD	DB, LS, VM, OH	9.6	Confirmed CAN predictor of CKD stage ≥3 (HR 2.62)
Bjerre-Christensen (2021)	329 with T1D	DB, LS, VM	6.1	Confirmed CAN predictor of albuminuria progression (+7.8% per year) not of eGFR
Yun (2022)	2033 with T2D	DB, LS, VM, OH	2.9	Confirmed CAN predictor of incident CKD (HR 1.56)
Tang (2024) PERL /ACCORD Study	469 with T1D 7973 with T2D	HRV indices	3.2 4.9	HRV predictor of eGFR decline HR 2.11-2.5 (T1D); HR 1.39-1.54 (T2D)

DB: deep breathing; LS: lying to standing; VM: Valsalva manoeuvre; HRV: heart rate variability; MCR: Mean Circular Resultant; GFR: glomerular filtration rate; ESRD: end-stage renal disease; CKD: Chronic Kidney Disease; OH, orthostatic hypotension; UAE, urinary albumin excretion;

CAN is a progression promoter of diabetic nephropathy in 13 out of 14 studies

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

Predictive value of nondipping on the progression of diabetic nephropathy

Author	**Type (n)**	**ABPM parameter**	**Follow-up** (years)	**Progression outcome**
Poulsen (1994)	44 with T1D and normo	Night/day ratio	3.1	No for microalbuminuria
Farmer (1998)	26 with proteinuria	Non-dipping	6	RR 2.7 for GFR
Nakano (1999)	257 with T2D and normo-micro-macro	**Rising**	4.5	**RR 16.2 for haemodialysis**
Lurbe (2002)	75 with T1D and normo	Non-dipping	5.2	RR 1.9 for microalbuminuria
Lengyel (2003)	53 with T1D and normo	Δ DBP	5	Predictor of albuminuria
Palmas (2008)	957 with T2D and normo-micro	**Rising**	2.5	**HR 1.68 for progression**
Knudsen (2009)	112 with T2D	Δ BP	9.5	HR 1.06 for progression
Marcovecchio (2009)	509 young with T1D	Δ BP	2.2	No for microalbuminuria

- *Debatable evidence for the development of microalbuminuria in patients with T1D*
- ***Stronger evidence for the progression to renal failure or dialysis in patients with T2D***

Spallone V *Curr Diab Rep. 2018;18:137.*

Mechanisms of the association between CAN and nephropathy

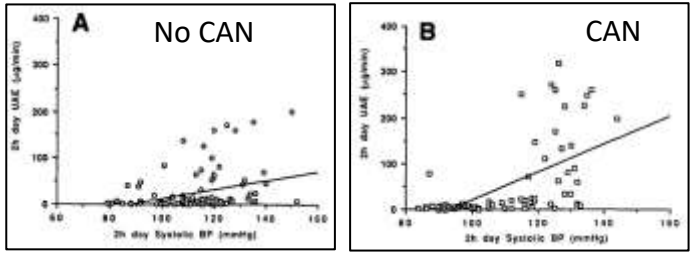
Diabetic autonomic neuropathy/dysfunction associated with

Loss of neurally mediated adjustment in renal hemodynamics → **Steeper relation between simultaneous systolic BP and albumin excretion**

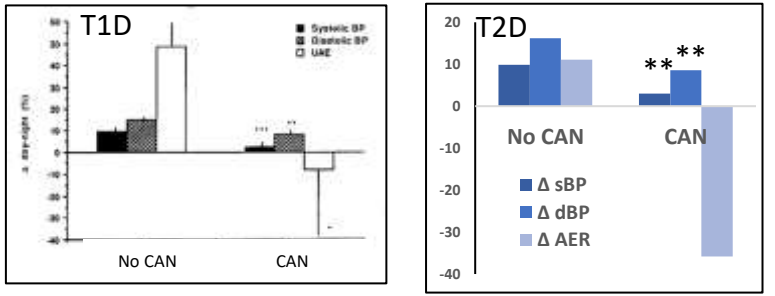
Abnormal circadian profile of sympathovagal activity → **Nondipping/rising Loss of circadian rhythm of albumin excretion**

EPO dysregulation → **EPO deficiency anaemia**

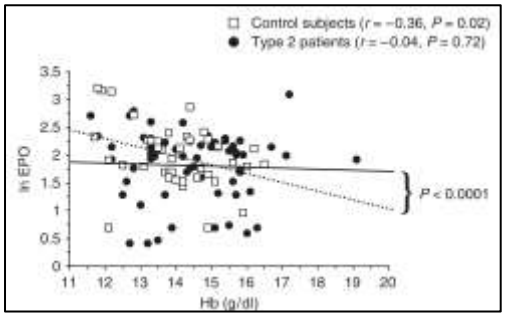
Relation between contemporary 2h SBP and AER in T1D



Day-night change in sBP, dBP and AER in T1D and T2D according to CAN



Relationship between EPO and Hb in T2D and controls



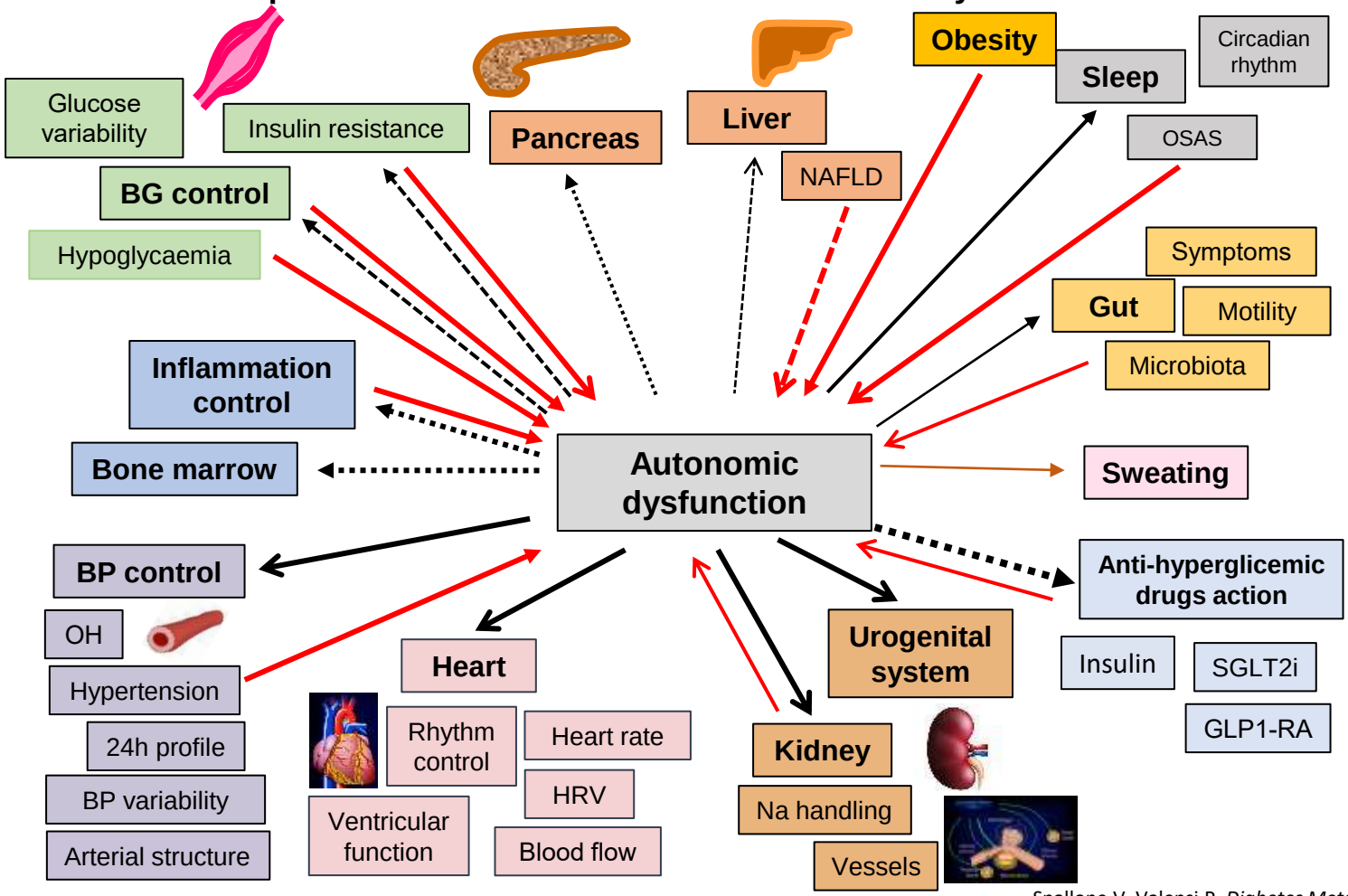
Autonomic score independent predictor of HT in T2D

Multiple linear regression analysis for haematocrit (Ht) in 64 patients with T2D, including also sex, BMI, duration, creatinine, 24h AER, 24h dBP

Variable	Coefficient	P-value
Autonomic score	**-0.40**	**0.011**
ESR (mm/h)	-0.073	0.012
Ferritin (µ/l)	0.007	0.012

Spallone V et al *Diabetes. 1993;42:1745-52*
Spallone V et al *Diabetes Care. 1994;17:578-84.*
Spallone V et al *Diabet Med. 2004 ;21:1174-80.*

Multifaceted pattern of *zones of influence* of autonomic dysfunction in diabetes



Spallone V, Valensi P. *Diabetes Metab. 2021;47:101224.*

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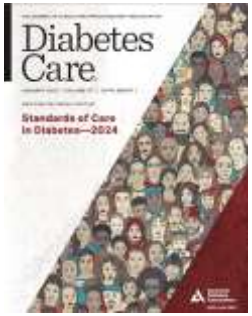
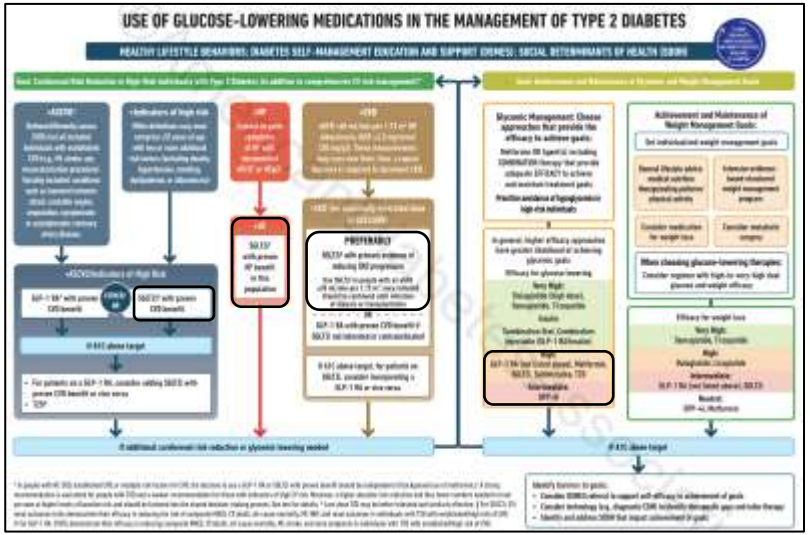




KDIGO 2024 CLINICAL PRACTICE GUIDELINE FOR THE EVALUATION AND MANAGEMENT OF CHRONIC KIDNEY DISEASE

Kidney Int. 2024 Apr;105(4S):S117-S314

3.7 Sodium-glucose cotransporter-2 inhibitors (SGLT2i)

Recommendation 3.7.1: **We recommend treating patients with type 2 diabetes (T2D), CKD, and an eGFR ≥20 ml/min per 1.73 m2 with an SGLT2i (1A).**

Recommendation 3.7.2: **We recommend treating adults with CKD with an SGLT2i for the following (1A):**

- **eGFR ≥20 ml/min per 1.73 m2 with urine ACR ≥200 mg/g (≥20 mg/mmol), or**
- **heart failure, irrespective of level of albuminuria.**

Recommendation 3.7.3: **We suggest treating adults with eGFR 20 to 45 ml/min per 1.73 m2 with urine ACR <200 mg/g (<20 mg/mmol) with an SGLT2i (2B).**

- Diabete e CKD
- Diabete e CVD o alto rischio
- Diabete e HF
- Diabete T2D non a target glicemico

- CKD con e senza diabete
- CVD o alto rischio con diabete
- HF con e senza diabete

ESC European Society of Cardiology — European Heart Journal (2021) 42, 3227–3337 doi:10.1093/eurheartj/ehab484

ESC GUIDELINES

2021 ESC Guidelines on cardiovascular disease prevention in clinical practice

Developed by the Task Force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies

With the special contribution of the European Association of Preventive Cardiology (EAPC)

ESC European Society of Cardiology — European Heart Journal (2022) 00, 1–110

ESC GUIDELINES

2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death

Developed by the task force for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death of the European Society of Cardiology (ESC)

Endorsed by the Association for European Paediatric and Congenital Cardiology (AEPC)

Recommendations for glucose-lowering treatment for patients with diabetes

Recommendations	Class[a]	Level[b]
SGLT2 inhibitors		
Empagliflozin, canagliflozin, or dapagliflozin are recommended in patients with T2DM and CVD, or at very high/high CV risk,[c] to reduce CV events.[306,308,309,311]	I	A
Empagliflozin is recommended in patients with T2DM and CVD to reduce the risk of death.[306]	I	B

Recommendation Table 10 — Recommendations for treatment with heart failure medication

Recommendations	Class[a]	Level[b]
Optimal medical treatment including ACE-I/ARB/ARNIs, MRAs, beta-blockers, and SGLT2 inhibitors is indicated in all heart failure patients with reduced EF.[343–347]	I	A

Presumed mechanisms of SGLT2i actions

Heart failure

- Osmotic diuresis and natriuresis
- Direct cardiac effects
- ↓ Sympathetic nervous system
- ↑ Myocardial efficiency
- ↑ O2 delivery through EPO stimulation
- ↓ Inflammation and oxidative stress
- Metabolic effects

SGLT2 overexpressed in cardiomyocytes of explanted heart from diabetic

Marfella R et al Pharmacol Res. 2022;184:106448

Kidney disease

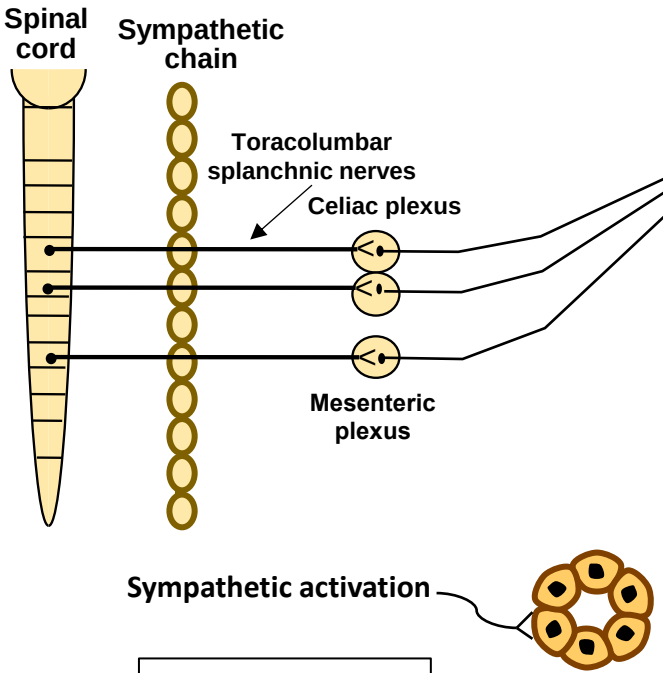
- Metabolic effects
- ↓ BP and arterial stiffness
- Restoration of tubuloglomerular feedback
- ↓ Workload regarding ATP production
- ↓ Inflammation, fibrosis and oxidative stress
- ↓ Uric acid

*'The unexpected and impressive reductions in important clinical endpoints observed in large-scale clinical trials … have led investigators **from the bedside back to the bench** to improve the understanding of the drugs in this class and elucidate their mechanisms of action.'*

Zelniker TA & Braunwald E. *J Am Coll Cardiol. 2020;75:435-447.*

SGLT2i and Sympathetic Nervous System share the same target cells

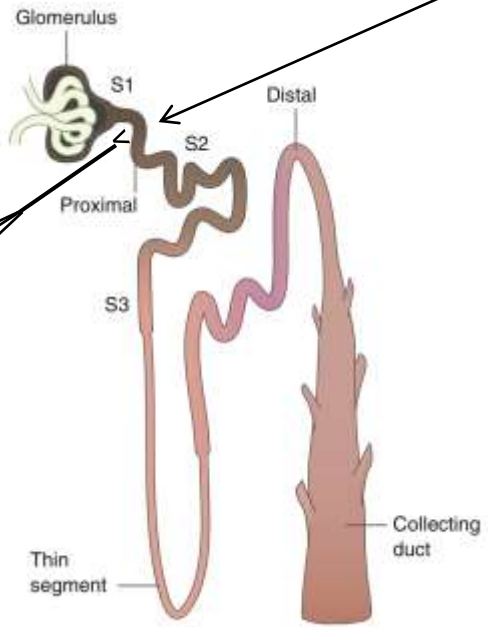
Sympathetic Innervation



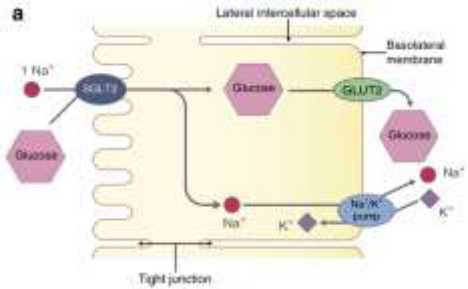
↑ Na reabsorption
↓ Natriuresis

Nephron

SGLT2



Glucose reabsorption



+ SGLT2i

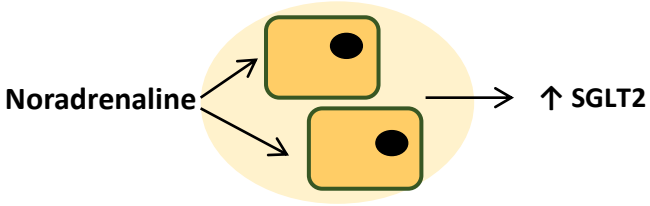
↑ Glucosuria
↑ Natriuresis

Di Bona G et al *Am J Physiol Regul Integr Comp Physiol 2010; 298: R245–R253*
Ghezzi C et al *Diabetologia 2018; 61:2087–2097*

Interaction between SGLT2i and Sympathetic Nervous System: preclinical studies

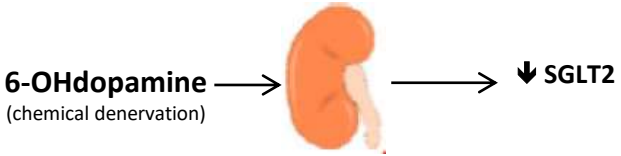
In vitro study

Human proximal tubule cells

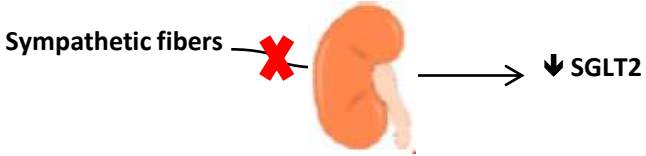


In vivo studies

BPH/2J (neurogenic hypertensive) **mice**

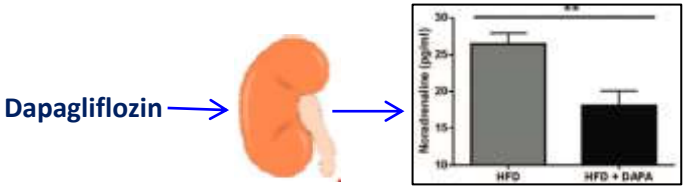


OLETF rats



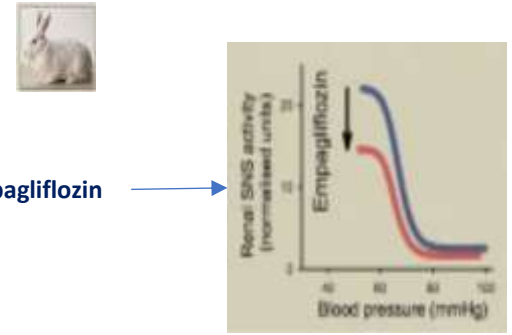
In vivo studies

C57BL6/J high-fat diet (HFD) mice



Tyrosine hydroxylase
Noradrenaline

Alloxan-diabetic rabbit



Renal SNA baroreflex

A crosstalk between SNS and SGLT2 regulation with sympathetic upregulation of SGLT2 and sympatho-inhibitory effect of SGLT2is

Matthews WB et al *J Hypertens 2017; 35:2059–2068;* Herat LY et al *JACC Basic Transl Sci. 2020;5(2):169-179;* Gueguen C et al *Diabetologia 2020;63:1424-1434;* Rafik K et al *Diabetologia 2015;58:2885–98*

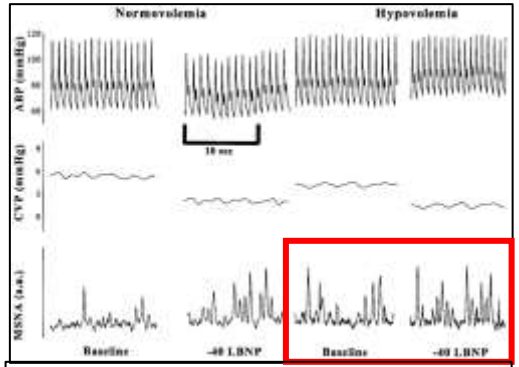
Spallone V. *Diabetes Metab J. 2019;43:3-30.*
Spallone V and Valensi P. *Diabetes Metab 2021;47:101224.*

Interaction between SGLT2i and Sympathetic Nervous System: clinical studies

Healthy normotensive males

Diuretic-induced hypovolemia

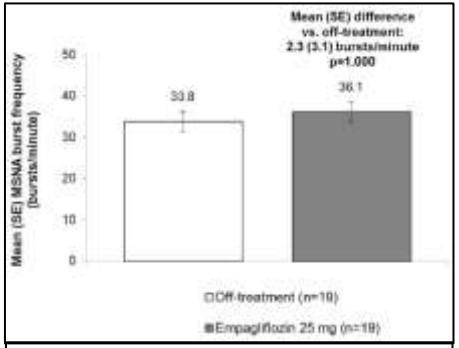
↑ Muscle Sympathetic Nerve Activity (**MNSA**)



Δ in arterial BP, CVP, and MSNA from baseline to -40 mmHg LBNP during diuretic hypovolemia and normovolemia.

Human T2DM

4 days of **empagliflozin** (25 mg) → ↓Weight ↓BP ↑Diuresis → **= MSNA**



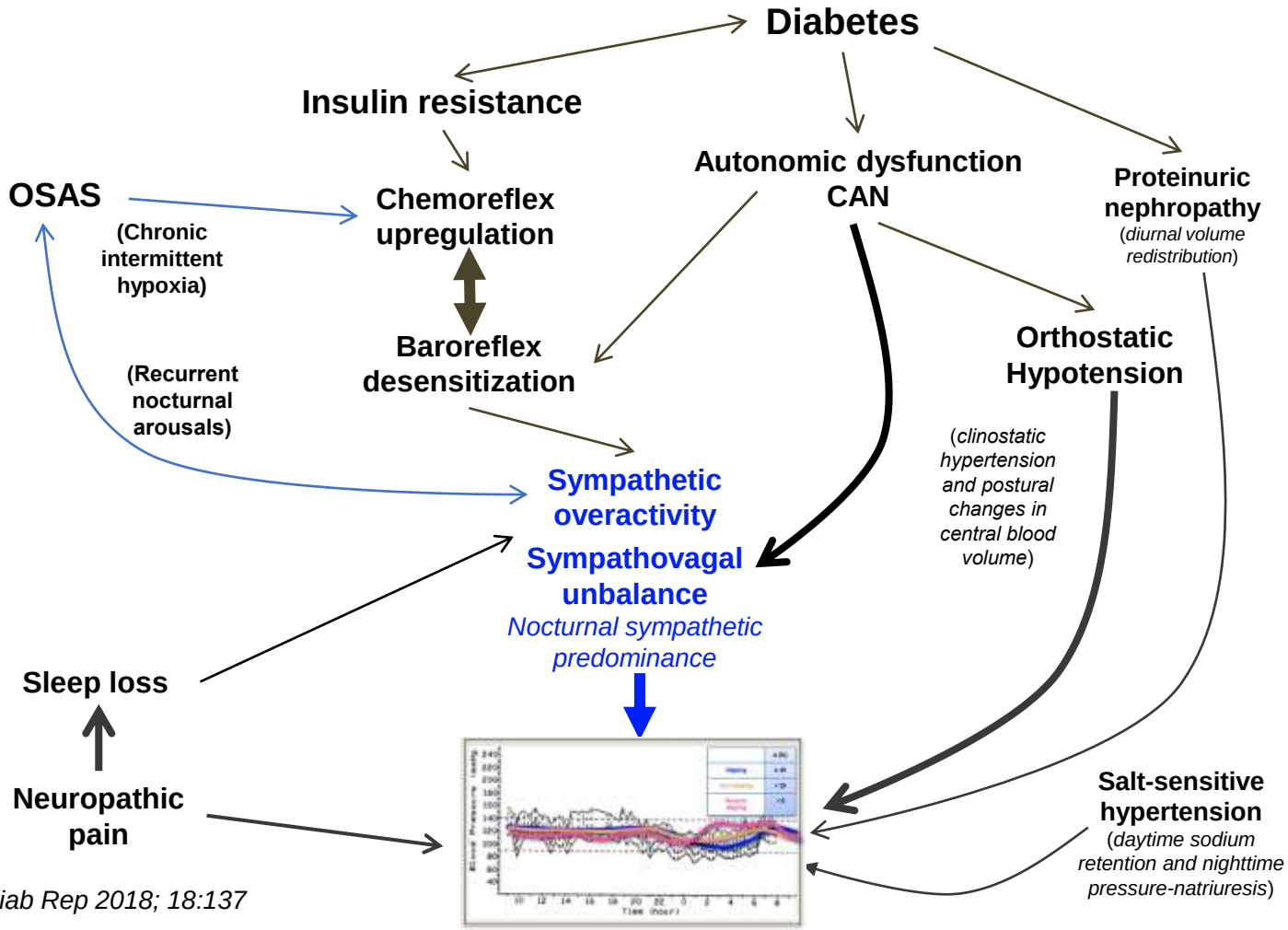
MSNA burst frequency off-treatment and on day 4 of treatment with empagliflozin 25 mg

SGLT2i trials in T2DM → ↓Weight ↓BP ↑Diuresis → **= Heart rate**

Kimmerly DS et al *Am J Physiol Heart Circ Physiol. 2002;282:H645-55.;* Ryan KL et al *Front Physiol 2012;3:110.* ; Jordan J et al *J Am Soc Hypertens. 2017;11:604-612.*; Sano M et al. *J Diabetes Investig. 2018 May;9(3):638-641;* Garg V et al *Metabol Open. 2020;7:100039.*

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

Multifactorial pathogenesis of nondipping in diabetes: the main role of sympathovagal unbalance



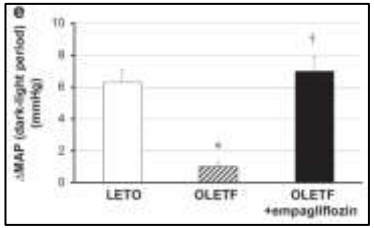
Spallone V. *Curr Diab Rep 2018; 18:137*

Interaction between Sympathetic Nervous System and SGLT2i: effects on circadian BP profile

Metabolic syndrome rats

Salt treated obese OLETF rats

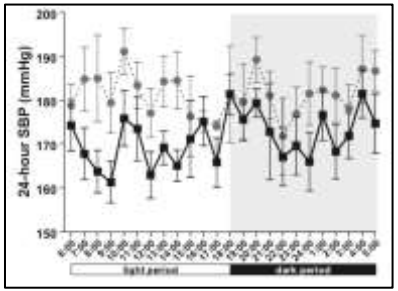
Empaglifozin → Prevention of salt-induced hypertension and nondipping

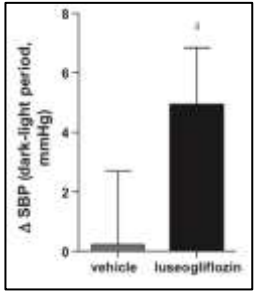


Δ mean arterial pressure (MAP) in vehicle-treated LETO, vehicle-treated OLETF and empagliflozin-treated OLETF rats

SHRcp rats

Luseoglifozin → Dipping restoration





Human T2DM

Meta-analyses of 6 and 7 trials
EMPA-REG BP trial
Black patients with hypertension
Patients with uncontrolled nocturnal BP

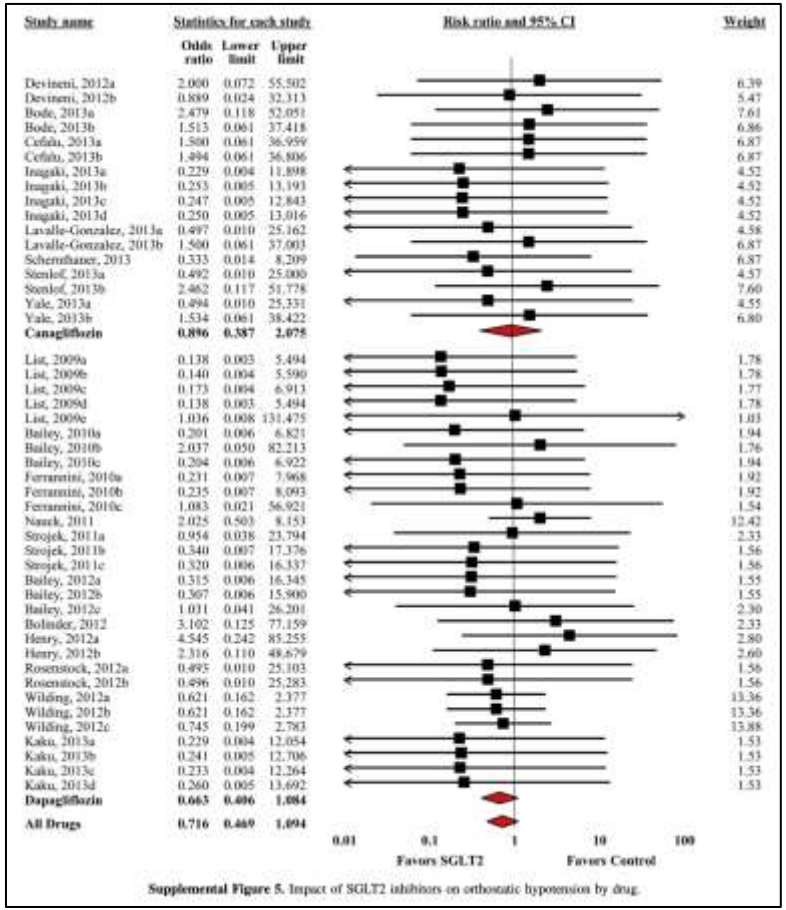
SGLT2i → No preferential BP-lowering effects on night-time vs daytime systolic BP

Takeshige Y et al *Hypertens Res. 2016 Jun;39(6):415-22;* Rahman A et al. *Clin Exp Pharmacol Physiol 2017; 44:522–5;* Chilton R et al *Diabetes Obes Metab. 2017;19:1620-1624;* Baker WL et al *J Am Heart Assoc. 2017;6:e005686;* Kario K et al *Circulation 2019;139:2089-9;* Ferdinand KC et al *Circulation. 2019;139:2098-2109;* Georgianos PI et al *Diabetes Care. 2019;42:693-700.*

Spallone V. *Diabetes Metab J. 2019;43:3-30.*
Spallone V and Valensi P. *Diabetes Metab 2021;47:101224.*

SGLT2i and risk of symptomatic OH

27 RCTs (12,960 participants with T2D)



Supplemental Figure 5. Impact of SGLT2 inhibitors on orthostatic hypotension by drug.

Baker WL et al *J Am Soc Hypertens 2014;8:262–275*

SGLT2i and risk of OH events

16 RCTs (12,749 participants with T2D)

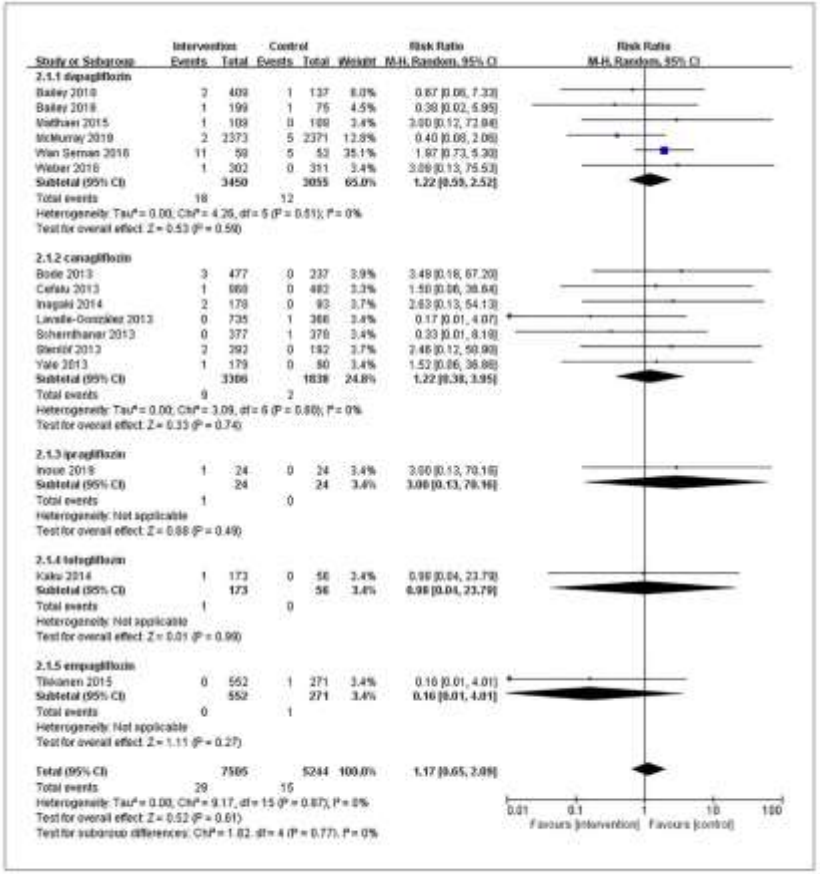


Figure 3. Forest plot of different SGLT2 inhibitors versus control for orthostatic hypotension.

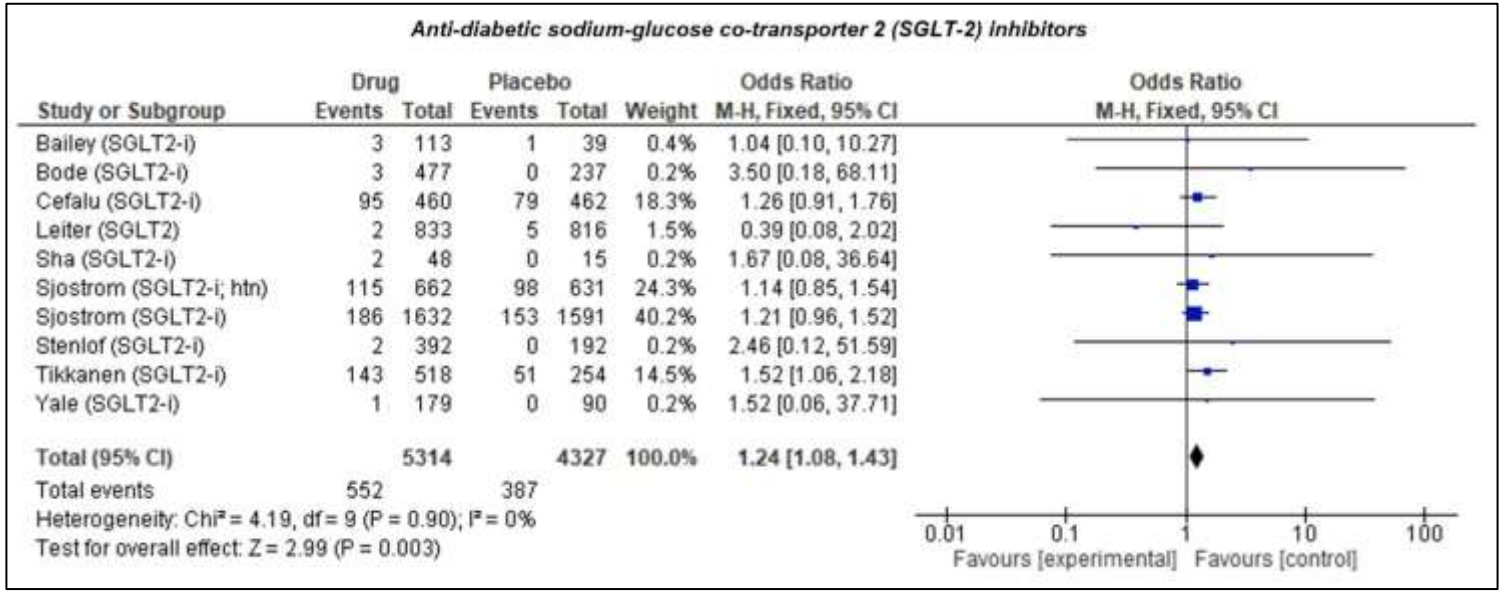
Rong X et al *Diab Vasc Dis Res. 2020;17:1479164120953625.*

Drug-induced orthostatic hypotension: A systematic review and meta-analysis of randomised controlled trials

Bhanu C, Nimmons D, Petersen I, Orlu M, Davis D, Hussain H, Magammanage S, Walters K.

PLoS Med. 2021 Nov 9;18(11):e1003821.

SGLT2i and OH risk



Drug	Odds ratio (95% CI)	P
SGLT2i	1.24 (1.08-1.43)	0.003

Conclusions: Drugs targeting multiple parts of the BP reflex pathway causing OH may carry cumulative risk, suggesting that **individuals with polypharmacy could benefit from routine postural BP monitoring.**

Methods of investigation for cardiac autonomic dysfunction in human research studies

Bernardi L, Spallone V, Stevens M, Hilsted J, Frontoni S, Pop-Busui R, Ziegler D, Kempler P, Freeman R, Low P, Tesfaye S, Valensi P; Toronto Consensus Panel on Diabetic Neuropathy
Diabetes Metab Res Rev. 2011;27:654-64.

Heart rate variability (HRV)

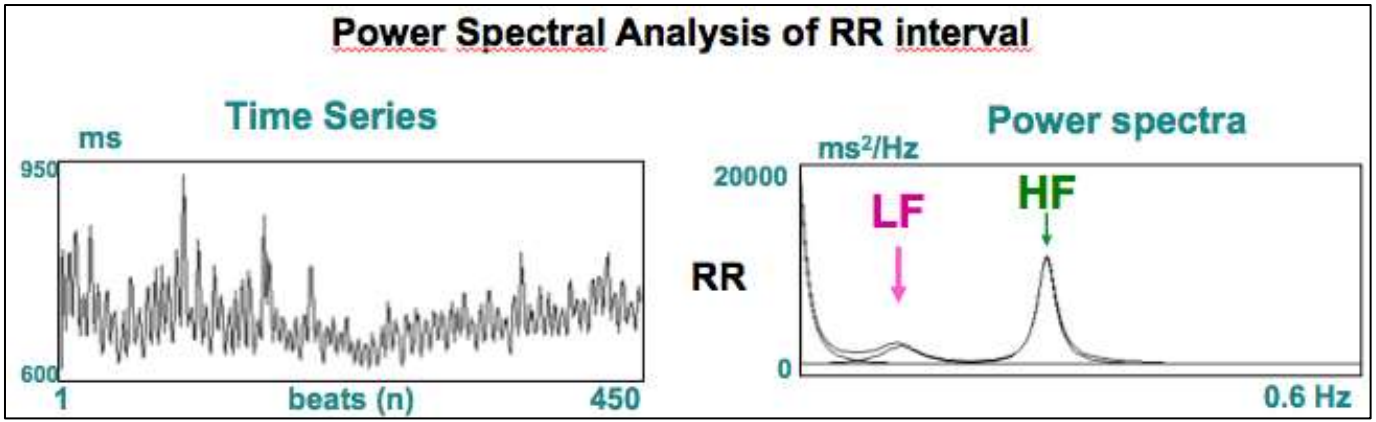
Time domain
(statistical measures)
- SDNN (ms)
- SDANN (ms)
- RMSSD (ms)
- SDNN index (ms)
- NN50
- pNN50 (%)

Indexes of parasympathetic activity
- time-domain indexes of global HRV
- total spectral power of HRV
- spectral power in the HF region

Index of sympathetic activity
- the relative proportion (% of global HRV) and not the absolute power of LF

Frequency domain
(short-term, 5 min)
- VLF (ms^2)
- LF (ms^2)
- LF norm (nu)
- HF (ms^2)
- HF norm (nu)
- LF/HF

Frequency domain
(long-term, 24h)
- Total power
- ULF (ms^2)
- VLF (ms^2)
- LF (ms^2)
- LF norm (nu)
- HF (ms^2)
- HF norm (nu)
- LF/HF



Sassi R et al *Europace. 2015;17:1341-53*.

HRV assessment provides information on autonomic – parasympathetic and sympathetic – modulation of the cardiovascular system
Reduced HRV has prognostic value after MI and in the general and diabetic population.

Trials with SGLT2i and autonomic measures as outcome

Author (year)	Population	Design	GLT2i	Follow-up	Autonomic measures	Results with SGLT2i
Garg et al (2020)	66 T2DM with stable CAD (most on βblockers)	Post-hoc exploratory analysis of EMPA-HEART Cardiolink-6	Empaglifozin 10 mg/day (Vs. placebo)	6 months	24h HRV indexes (SDNN, SDANN, r-MSSD, HF, LF, LF:HF)	No ≠ Vs. placebo but SDNN and SDANN increased with placebo
Shimizu W et al (2020)	96 T2DM post AMI (most on βblockers)	Randomized double-blind placebo-controlled trial	Empagliflozin 10 mg/day (Vs. placebo)	24 weeks	24h HRV indexes (SDNN, SDANN, r-MSSD, HF, LF, LF:HF)	↑ SDNN, SDANN, r-MSSD, HF, LF ↓ LF:HF and abnormal heart rate turbulence in SGLT2i group No differences inter-group
Ang L et al (2021)	41 T2DM	Randomized cross-over single blinded	Dapagliflozin 5-10 mg/day (Vs. glimepiride 2-4 mg/day)	12 + 12 weeks	3 CARTs, LF, HF, SDNN, r-MSSD	No change in CARTs and short HRV indexes
Van Bommel et al (2020)	44 T2DM	Secondary analysis of RED trial (randomized, open-label, comparator-controlled, parallel-group	Dapagliflozin 10 mg/die (Vs. gliclazide 30 mg/day)	12 weeks	LF, HF, LF:HF, SDNN, r-MSSD	No changes intra- or differences inter-group
Ishibashi F et al (2022)	113 T2DM with HbA1c >8%	Open comparison study	Dapaglifozin 5-10 mg/day, Tofoglifozin 20 mg/day, Ipraglifozin 25-50 mg/day (Vs. non SGLT2i)	3 years	CV-RR	No change in CV-RR (but in NCS)
Hamaoka T et al (2022)	18 T2DM with and without heart failure	Uncontrolled, open study	Dapagliflozin 5 mg/day	12 weeks	MSNA, cardiac BRS, sympathetic BRS	↓ MSNA (greater in HF Vs. non HF) No change in cBRS and sBRS
Sardu C et al (2022)	324 T2DM with VVS	Multicenter observational study	Empagliflozin 10-25 mg/day Canagliflozin 100 mg/day (Vs. non SGLT2i)	1 year	24h HRV (LF:HF) 123^{I}-MIBG myocardial scintigraphy VVS recurrence	↓ HR, ↓LF/HF and ↑ 24 HRV ↑ H/M_{late} ↓ VVS recurrence (vasodepressor) (-45%)

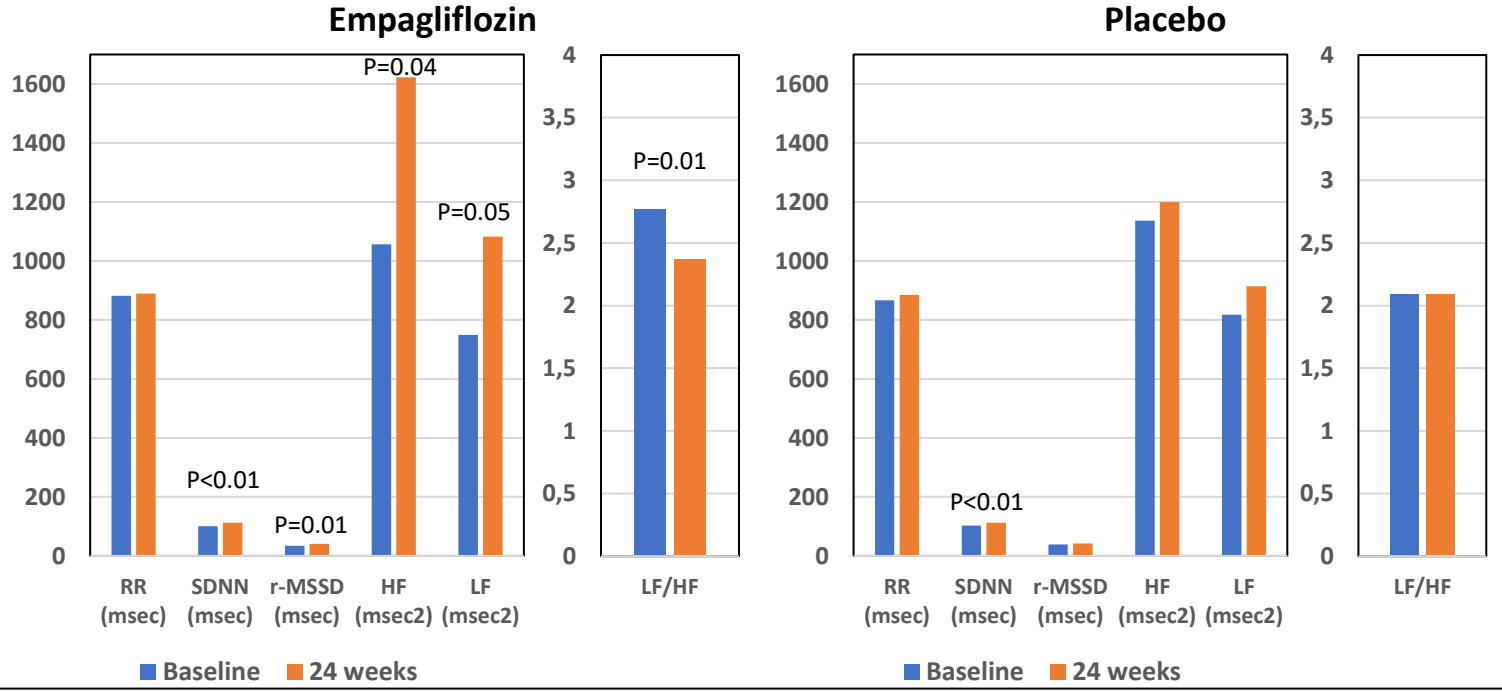
AMI, acute myocarfial infarction; CART, cardiovascular autonomic reflex test; HF high frequency; H/M_{late}: late heart-to-mediastinum ratio; HRV, heart rate variability; LF, low frequency; LF:HF, Low to high frequency ratio; 123^{I}-MIBG, $^{1}23$I-meta- iodobenzylguanidine; NCS, nerve conduction study; r-MSSD, the root-mean-square of the difference between successive RRs; SDNN, the standard deviation of NN intervals; SDANN, standard deviation of the 5 minute average NN intervals; T2DM, type 2 diabetes mellitus; VVS: vaso vagal syncope

Effects of empagliflozin versus placebo on cardiac sympathetic activity in acute myocardial infarction patients with type 2 diabetes mellitus: the EMBODY trial

Shimizu W, Kubota Y, Hoshika Y, Mozawa K, Tara S, Tokita Y, Yodogawa K, Iwasaki YK, Yamamoto T, Takano H, Tsukada Y, Asai K, Miyamoto M, Miyauchi Y, Kodani E, Ishikawa M, Maruyama M, Ogano M, Tanabe J; EMBODY trial investigators

Cardiovasc Diabetol. 2020;19:148.

The 1st randomized double-blind placebo-controlled trial to evaluate the effects of empagliflozin vs placebo on HRV indices.
96 patients with type 2 diabetes, 2 weeks post-AMI (most of them taking beta-blockers) randomized to empagliflozin 10 mg or placebo



In the empagliflozin group **most primary outcomes improved**, in the placebo group only SDNN improved. Among secondary outcomes, **heart rate turbulence improved only in the empagliflozin group** whereas cardiac MIBG scintigraphy improved in both groups**. No differences in the intergroup comparison.**

Effect of SGLT-2 inhibitors on cardiac autonomic function in type 2 diabetes mellitus: a meta-analysis of randomized controlled trials

Patoulias D, Katsimardou A, Fragakis N, Papadopoulos C, Doumas M.

Acta Diabetol. 2023 Jan;60(1):1-8

Do SGLT-2 inhibitors affect CAN indices, in patients with T2DM?

Meta-analysis of 4 parallel group or cross-over RCTs with SGLT2i Vs. placebo or active comparator (247 subjects with T2DM)

Primary efficacy outcome: LF/HF, secondary efficacy outcomes: SD of all 5 min mean normal RR intervals (SDANN) and square root of the mean of the squares of differences between adjacent RR intervals (r-MSSD).

Results: **SGLT-2 inhibitor treatment did not have a significant effect on LF/HF, on SDNN or on r-MSSD**.

Overall risk of bias graded as low across the selected RCTs.

LF/HF

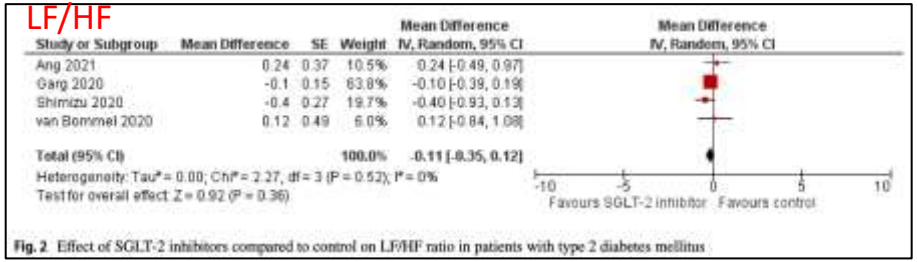


Fig. 2 Effect of SGLT-2 inhibitors compared to control on LF/HF ratio in patients with type 2 diabetes mellitus

R-MSSD

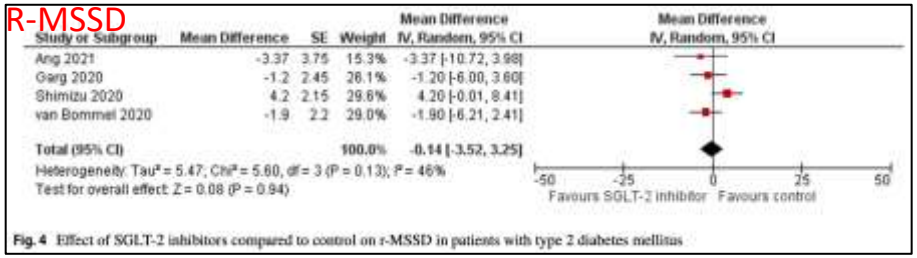


Fig. 4 Effect of SGLT-2 inhibitors compared to control on r-MSSD in patients with type 2 diabetes mellitus

SDNN

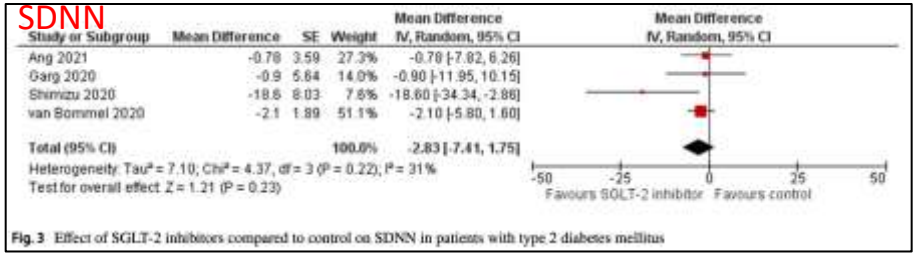


Fig. 3 Effect of SGLT-2 inhibitors compared to control on SDNN in patients with type 2 diabetes mellitus

Conclusions: SGLT-2 inhibitor treatment in T2DM does not seem to provide any significant beneficial effect on CAN indices.

Reasons of caution in interpreting results

- Use of betablockers
- Not homogeneous autonomic measures and methods (short and 24h HRV)
- Spectral analysis methodology
- Differences in BMI, HbA1c, comorbidities, primary/secondary outcomes

EMPYREAN study is ongoing (134 patients with T2D, strict selection criteria, 24h HRV outcomes and 24 weeks duration)

Motoki H et al *ESC Heart Fail. 2020 Oct;7(5):3134-3141*

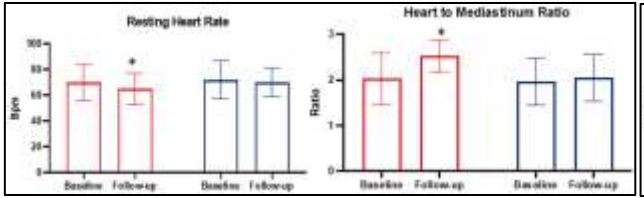
SGLT2-inhibitors reduce the cardiac autonomic neuropathy dysfunction and vaso-vagal syncope recurrence in patients with type 2 diabetes mellitus: the SCAN study

Sardu C, Massimo Massetti M, Rambaldi P, Gatta G, Cappabianca S, Sasso FC, Santamaria M, Volpicelli M, Ducceschi V, Signoriello G, Paolisso G, Marfella R

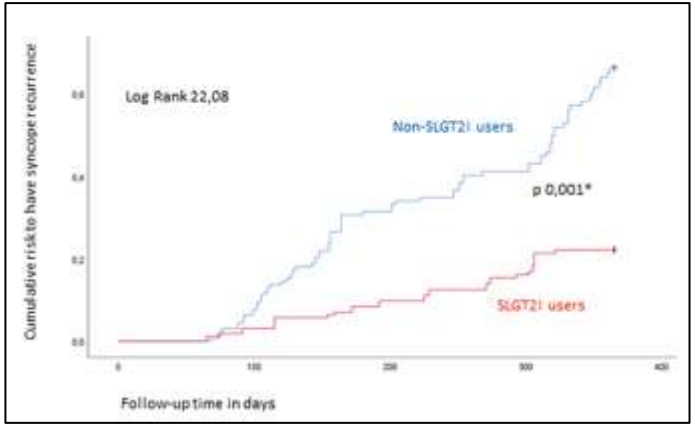
Metabolism. 2022 Jun 19:155243.

In a prospective multicenter study, in 324 T2DM patients with vaso-vagal syncope (VVS), divided into 161 SGLT2i-users vs. 163 Non-SGLT2i users, 24h HRV indexes, 123^{I}-MIBG myocardial scintigraphy and VVS recurrence were evaluated at 1 year follow-up.

The SGLT2i-users vs. Non-SGLT2i users:
↑ glucose homeostasis
↓ values of inflammatory markers
↓ resting HR
↑ 24 HRV indices
↓ LF/HF
↑ H/M_{late} (late heart-to-mediastinum ratio)



The SGLT2i-users vs. Non-SGLT2i users: ↓ VVS (vasodepressor*) recurrence events
(* a fall in SBP without changes in HR during head-up tilt test)



Predictors of 1-year VVS recurrence (Cox regression analysis)
- H/M_{late} (HR: 0.710)
- **SGLT2i therapy (HR 0.550)** **Risk-45%**

Conclusions: The indexes of cardiac denervation predicted the VVS recurrence, while **the SGLT2i reduced the risk of VVS recurrence**.

Sudden cardiac death (SCD) and autonomic modulation by SGLT2i

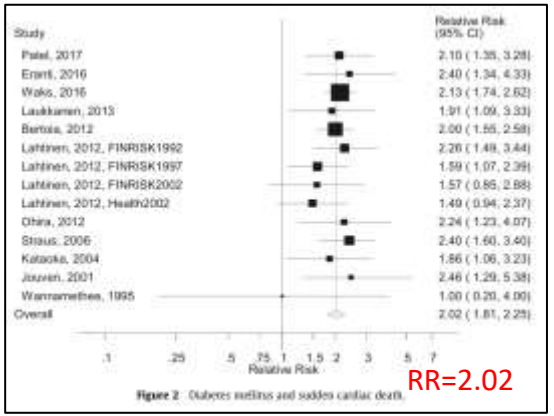
Epidemiology

50% of all cardiovascular deaths in the general population

Zeppenfeld K at al for ESC Scientific Document Group. *Eur Heart J. 2022 Aug 26:ehac262.*

Risk is doubled in diabetic population

Population-based studies
(3610 cases of SCD, 249,225 participants)



Aune D et al *Nutr Metab Cardiovasc Dis. 2018;28:543-556.*

ANS and SCD

- ANS recognized as a promoter of SCD
- Proarrhythmic conditions as heart failure and MI characterised by SNS hyperactivity
- Experimental evidence of autonomic role but not conclusive association with diabetic CAN or with autonomic indices after MI

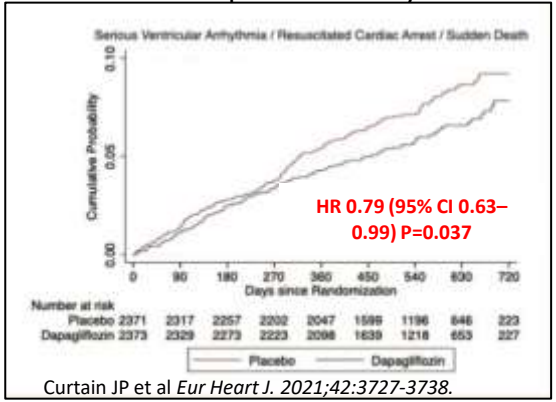
Suarez GA et al J Neurol Neurosurg Psychiatry 2005;76:240–245; Barthel P et al *Diabetes Care. 2011;34:1833-7;* Jungen C et al *Am J Physiol Heart Circ Physiol 2019;317: H1328-H1341*

Sudden cardiac death (SCD) and autonomic modulation by SGLT2i

SGLT2i and SCD

- Experimental evidence of anti-arrhythmogenic effect of SGLT2i
- Post hoc analysis of DAPA-HF shows a lower risk of VA, cardiac arrest, or SD
- Meta-analyses show conflicting results
- EMPA-ICD trial in T2D with ICD/CRT-D reduced the number of VA
- Ongoing clinical trial in patients with CRT device (ERASE-trial)
- **No consistent mechanism identified for the antiarrhythmic properties.**

DAPA-HF post-hoc analysis



Curtain JP et al *Eur Heart J. 2021;42:3727-3738.*

Meta-analysis for SGLT2i effects on SCD

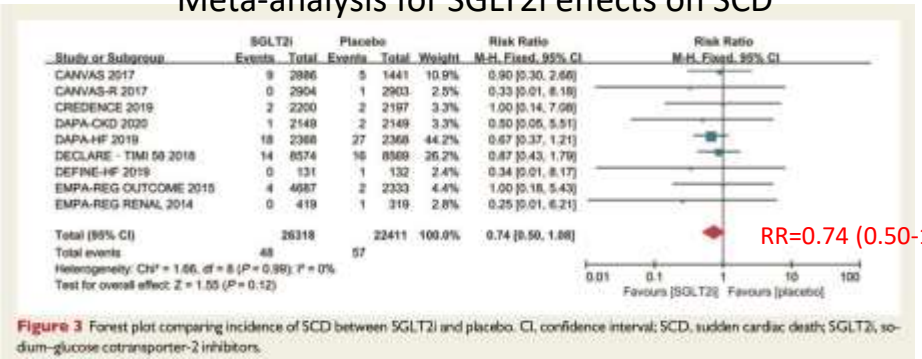


Figure 3 Forest plot comparing incidence of SCD between SGLT2i and placebo. CI, confidence interval; SCD, sudden cardiac death; SGLT2i, sodium-glucose cotransporter-2 inhibitors.

Sfairopoulos D et al *Europace 2022; 24:20-30*

ICD: implanted cardioverter defibrillator
CRT: cardiac resynchronization therapy device

Curtain JP et al *Eur Heart J. 2021;42:3727-3738*
Li H-L et al *Cardiovasc Diabetol. 2021;20:100*
Fernandes GC et al *Heart Rhythm 2021;18:1098-105*
Yin Z et al *Front. Cardiovasc. Med. 2022;9:902923*
Sfairopoulos D et al *Europace 2022; 24:20-30*
von Lewinski D et al *Am Heart J. 2022 Apr;246:152-160*

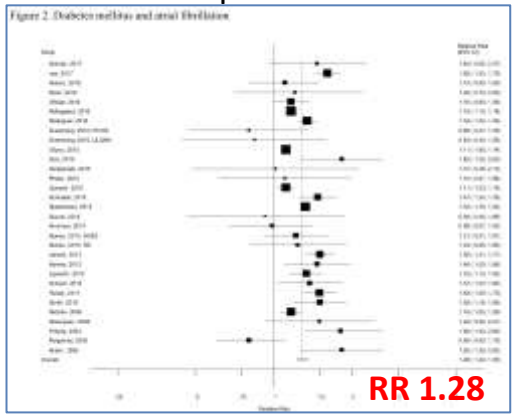
Atrial fibrillation (AF) and autonomic modulation by SGLT2i

Epidemiology

↑ risk in diabetic population (RR 1.28)

Aune D et al *J Diabetes Complications. 2018;32:501-511.*

Atrial Fibrillation prevalence in diabetes



ANS and AF

Possible role of autonomic dysfunction in AF

ARIC Study

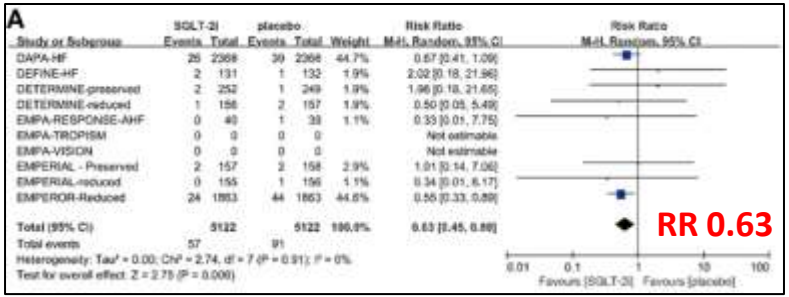
-1 SD SDNN +14% AF
-1 SD HF +12% AF

Agarwal SK et al *J Am Coll Cardiol. 2017 Jan 24;69(3):291-299.*

SGLT2i and AF

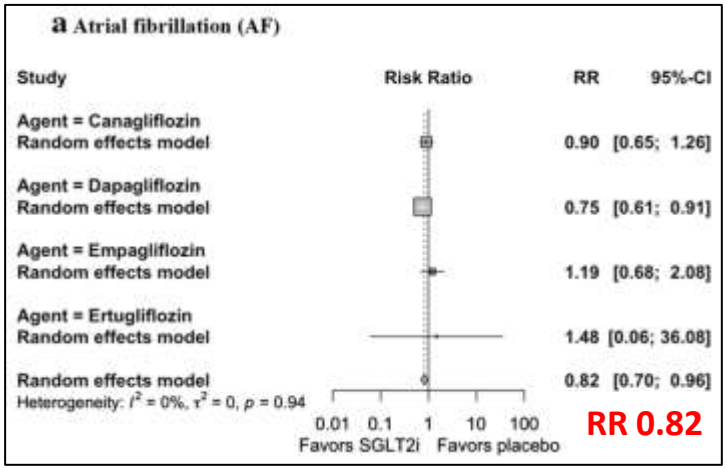
Reduced risk of AF (-18% and -37%)

SGLT2i and risk of Atrial Fibrillation



Li H-L et al *Cardiovasc Diabetol. 2021;20:100.*

SGLT2i and risk of Atrial Fibrillation



Yin Z et al *Front. Cardiovasc. Med. 2022;9:902923.*

Hypoxia in diabetic kidney

Tissues are hypoxic in diabetes

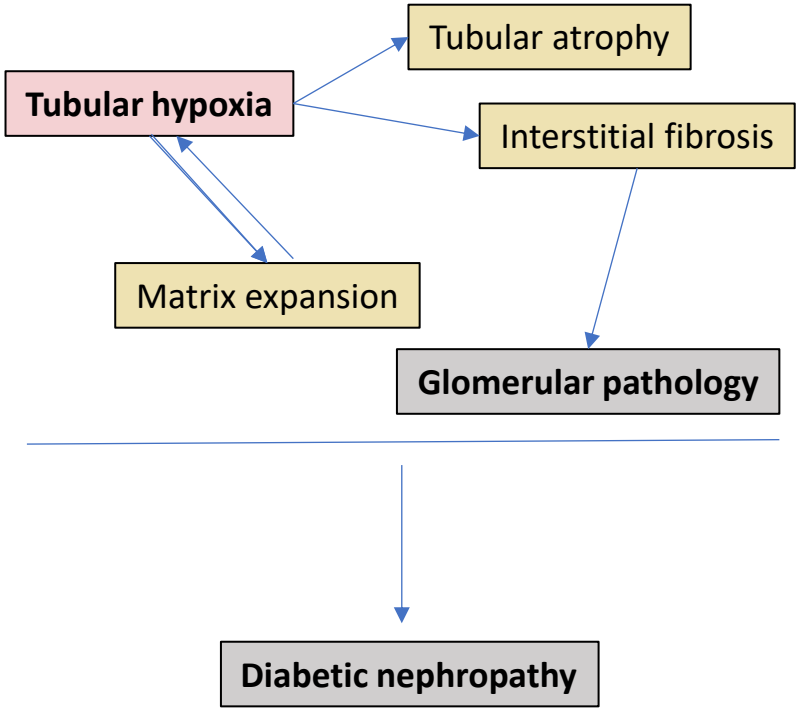
Response to hypoxia

Hypoxia → ↑ HIF-1α
Hypoxia → ↑ HIF-2α

Diabetes → HIF-1 signalling dysregulation

HIF: hypoxia-inducible factor

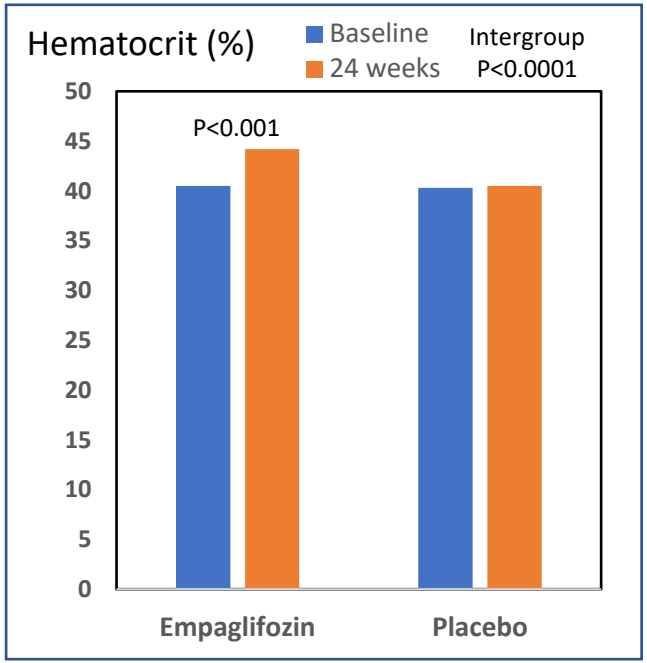
Kidney hypoxia in diabetic nephropathy



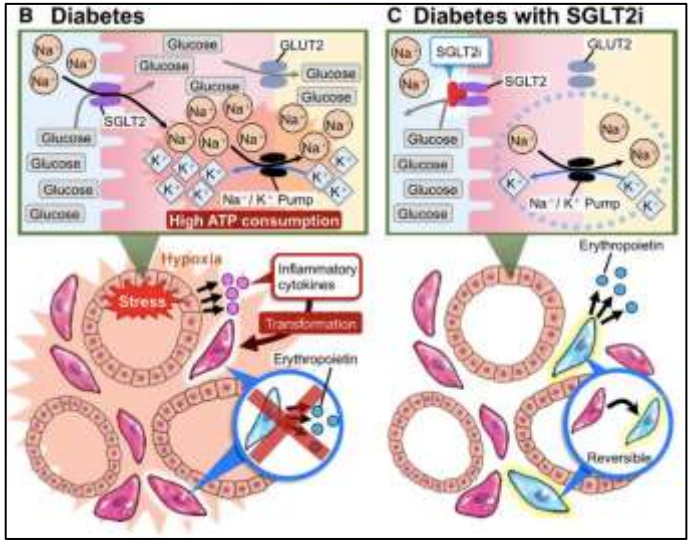
Catrina S-B and Zheng X *Diabetologia 2021;64:709-716*
Packer M *Am J Kidney Dis. 2021;77:280-286*

SGLT2i effects on chronic hypoxia of kidney associated with diabetes

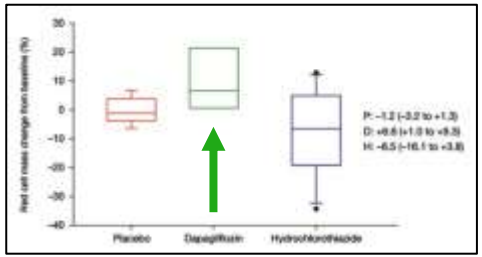
EMBODY trial: empaglifozin increased Ht

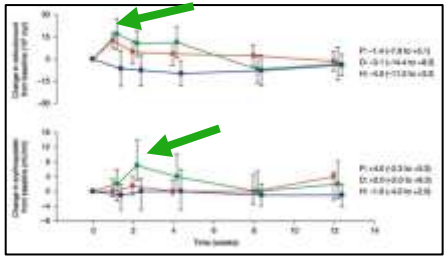


SGLT2i might restore EPO producing cells by reducing hypoxia



Dapaglifozin increased red cell mass, reticulocytes and EPO production



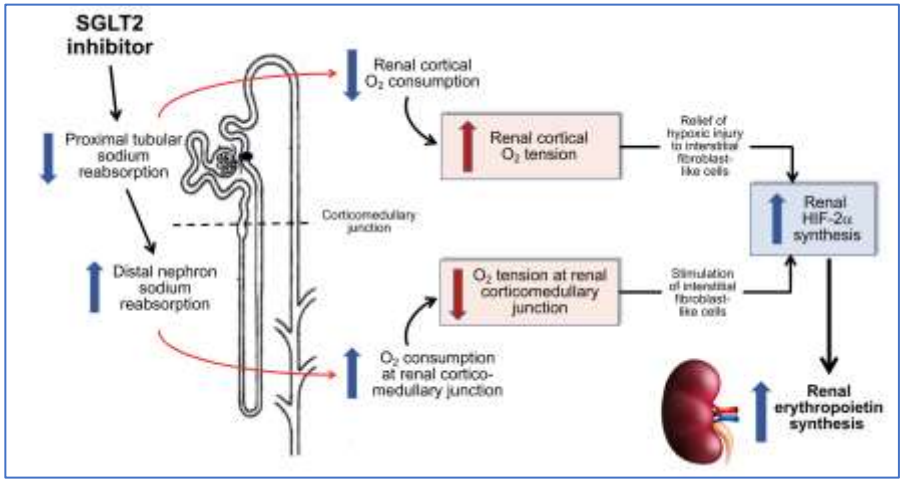


Shimizu W et al *Cardiovasc Diabetol. 2020;19:148.*
Sano M & Goto S. *Circulation. 2019;139:1985–1987*
Lambers Heerspink HJ et al. *Diabetes Obes Metab 2013;15:853–62.*

Mechanisms of enhanced renal EPO synthesis by SGLT2i: hypoxia and/or non-hypoxia-related mechanisms

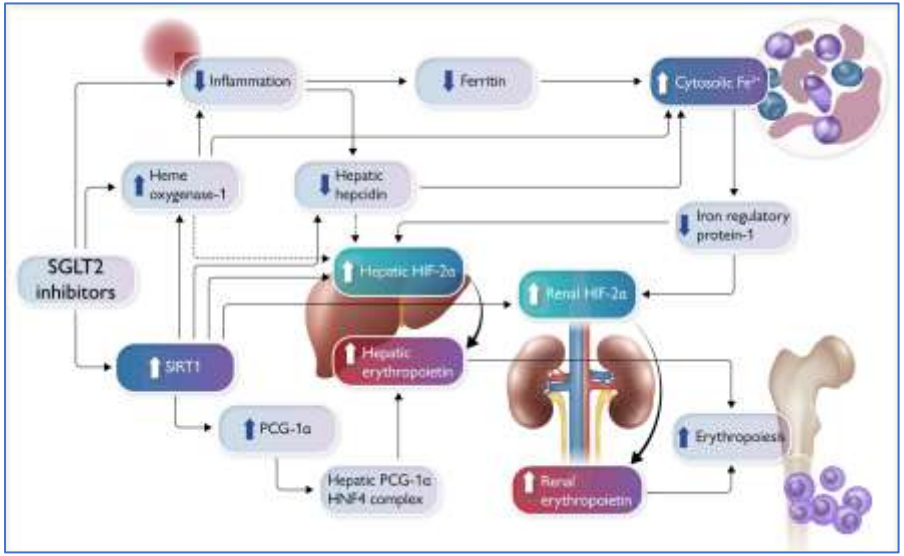
SGLT2i

↓ Na and glucose transport and O2 consumption in the proximal tube (↓ cortical hypoxia) and ↑ Na and glucose transport and O2 consumption downstream (↑ in the deep cortex and outer medulla)



Improvement in cortical hypoxia with SGLT2i confirmed with qualitative studies, not confirmed with quantitative studies; cortico-medullary junction hypoxia not found in non-diabetics

Starvation state with upregulation of nutrients deprivation signals as SIRT1 that activates HIF-2

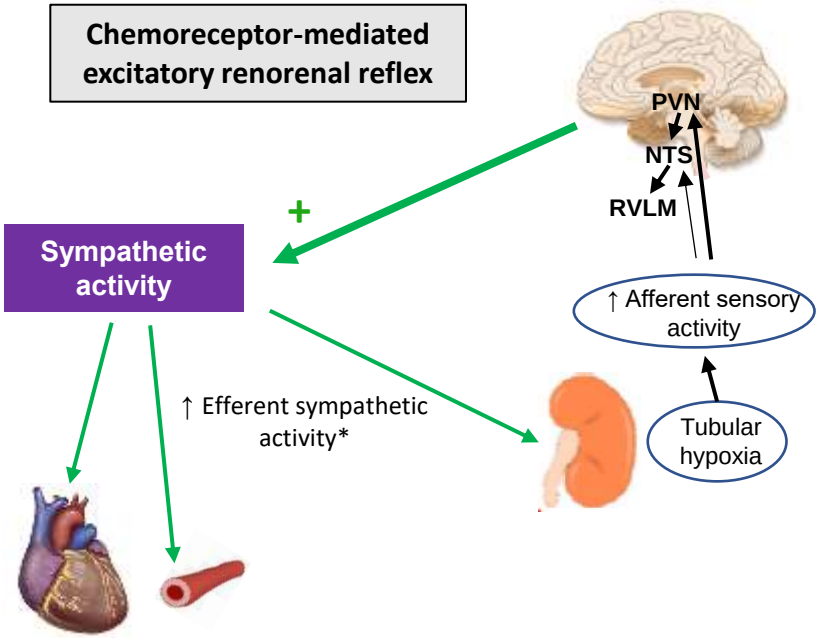


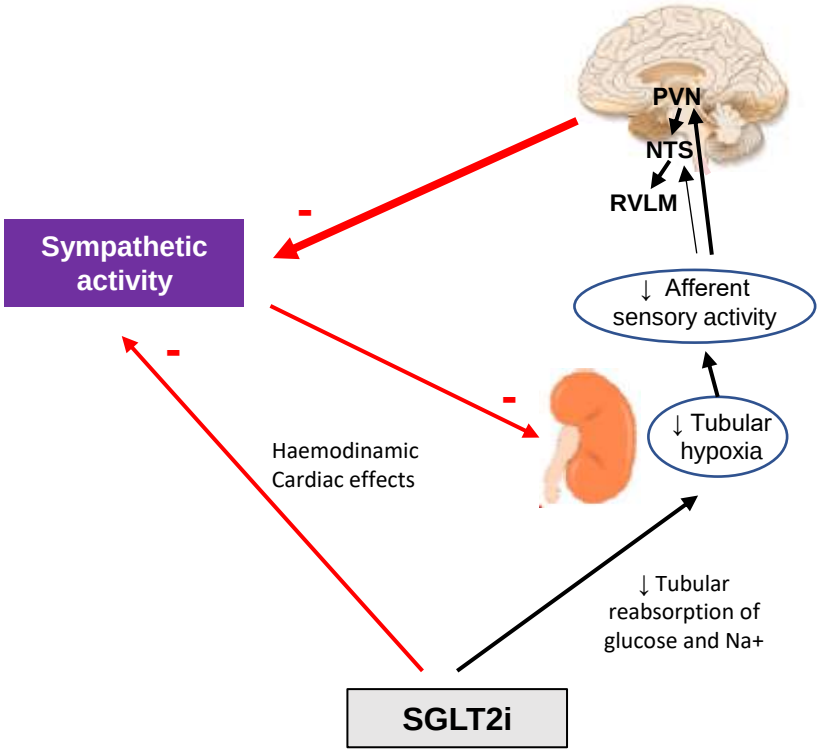
Still a hypothesis needing ad hoc studies

HIF-2α, hypoxia-inducible factor-2α

Packer M *Eur Heart J. 2023 Dec 21;44(48):5027-5035*

Influences of SGLT2i on autonomic function in diabetes and conditions of sympathetic overactivity





*Systemic
PVN: paraventricular nucleus
RVLM: rostral ventrolateral medulla
NTS: nucleus of solitary tract

Modified from Spallone V & Valensi P. *Diabetes Metab. 2021;47:101224.*

Acute effects of dapagliflozin on renal oxygenation and perfusion in type 1 diabetes with albuminuria: A randomised, double-blind, placebo-controlled crossover trial

Laursen JC, Søndergaard-Heinrich N, de Melo JML, Haddock B, Rasmussen IKB, Safavimanesh F, Hansen CS, Størling J, Larsson HBW, Groop PH, Frimodt-Møller M, Andersen UB, Rossing P

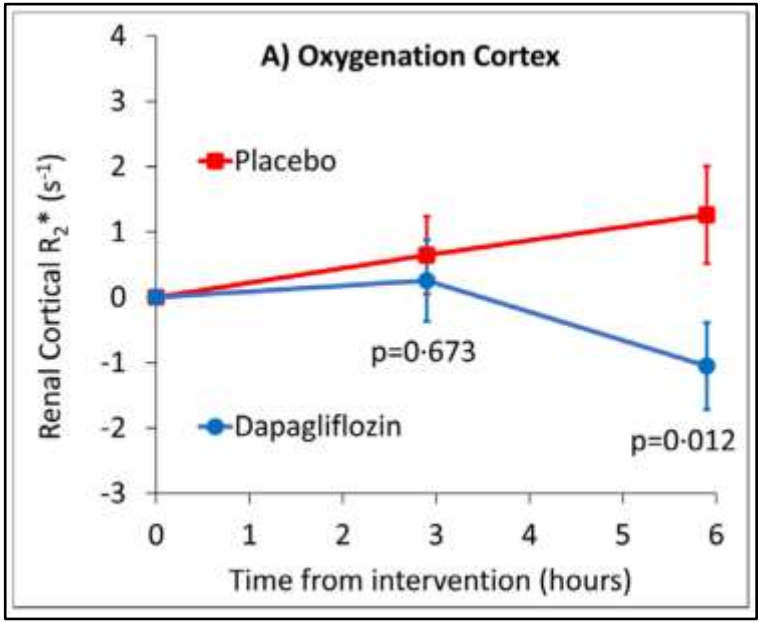
EClinicalMedicine. 2021 Jun 28;37:100895.

Design: crossover RCT in 15 microalbuminuric T1DM using a single 50 mg dose of dapagliflozin and placebo.

Methods: Blood Oxygen Level Dependent (BOLD) **MRI to assess renal oxygenation** (R2*, low value means high tissue oxygenation), perfusion and flow before and after ingestion.

Results: DAPA associated with ↓ in renal cortical R2* at 6 hours Vs. placebo.

No changes of SaO_2, renal tissue perfusion, renal blood flow, BP, HR, BRS



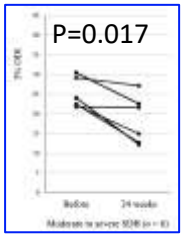
Interpretation: High dose of dapagliflozin acutely improved renal cortical oxygenation without changing renal perfusion or blood flow as for an **increase in renal cortical oxygenation** consequent to ↓ O_2 demand **due to a reduced tubular transport workload in the proximal tubules**.
It remains to be determined whether the same effects can be achieved with lower doses, with chronic treatment and in type 2 diabetes.

Effects of SGLT2i on OSA

Open-label, single arm study in 30 patients with T2D and OSA

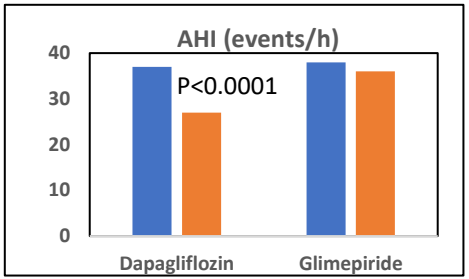
Dapagliflozin → ↓ O_2 Desaturation Index (ODI) in moderate-severe OSA

ODI



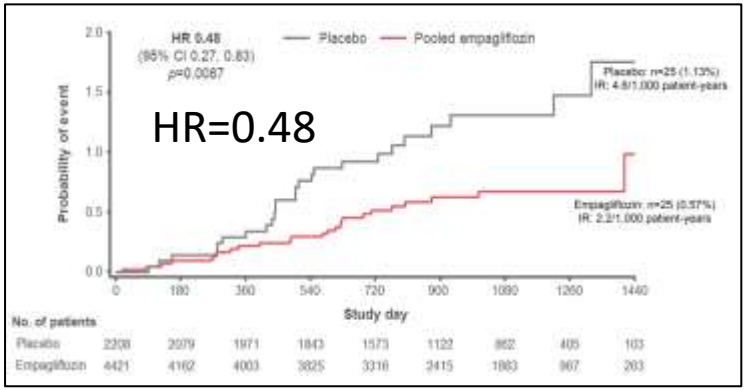
Case-control study in 36 patients with T2D and OSA

Dapagliflozin → ↓ Apnea-Hypopnea Index (AHI) →



EMPA-REG OUTCOME trial

Empagliflozin → - 52% new-onset OSA (mainly not mediated by OSA risk factors)

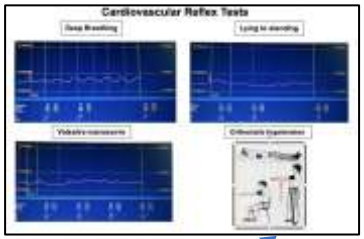


Kaplan-Meier estimates for time to 1st OSA event

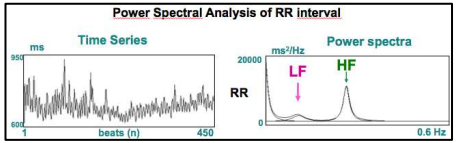
Furukawa S et al *Endocr J 2018;65: 953–961*
Tang Y et al *Nutr Diabetes. 2019;9:32*.
Neeland IJ et al *Diabetes Care 2020;43:3007-3015.*

Effects of SGT2i on autonomic related measures and outcomes in humans

CARTs

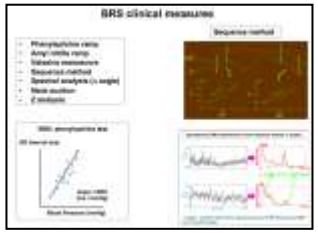


HRV

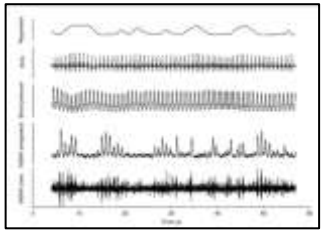


SDNN,r-MSSD,LF, HF, LF:HF

BRS

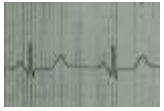


MSNA

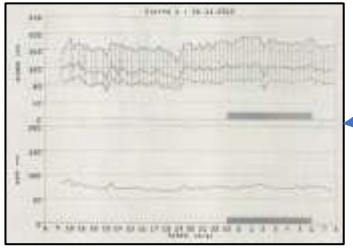


Miglis MG *Academic Press. 2017;227-244*

HR



ABPM



Confirmed effect (≠ or ↓)

No effect

Possible effect (↑)

No effect

Possible effect (↓)

SGLT2i

No effect on dipping

Possible effect (↓)

Possible effect (↓)

Non conclusive data

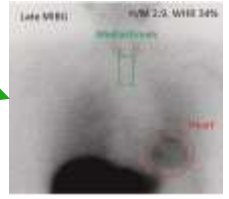
Possible effect (↓)

Possible effect (↓)

Possible effect (↑)

Cathecolamines

Heart innervation (^{123}I-MIBG)



Sardu C et al *Metabolism. 2022 Jun 19:155243*

OSA

Vaso-vagal syncope

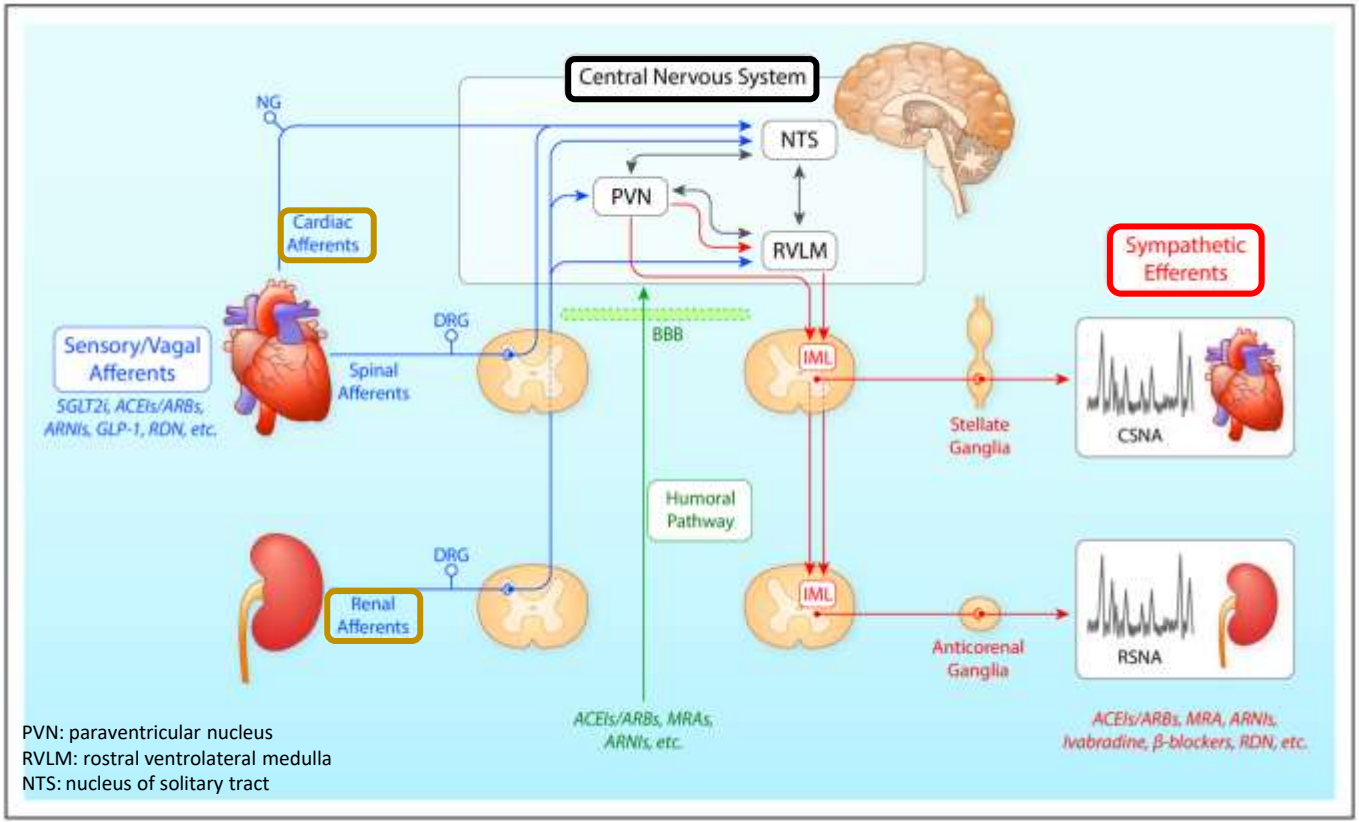
Sudden Cardiac Death

Ventricular arrhythmias

Atrial fibrillation

Updated from Spallone V. 32nd Neurodiab Annual Meeting Bergen 2022

Neural and humoral connection between the heart and the kidneys via the CNS and the potential therapeutic target sites in cardiorenal syndrome



Integration of **cardiac and renal afferents** (and other visceral inputs) in **CNS** (NTS, PVN and RVLM) to regulate **sympathetic outflow is** critical for heart and kidney function under normal conditions and the cardiorenal syndrome.

Innervated kidneys play as the origin as well as the target of SNS activation.

Patel KP et al *Circ Res. 2022;130:1601-1617.*

Agenda

- Il contesto: impatto epidemiologico e prognostico della neuropatia autonomica cardiovascolare (CAN) nel diabete
- Pertinenza della CAN alla malattia cardiovascolare e renale
- Dal beneficio nei trial clinici ai meccanismi fisiopatologici: il ruolo del SNA nelle azioni dei SGLT2i
- **Prospettive terapeutiche: farmaci protettivi sul SNA nel diabete**

Disease-modifying intervention for CAN

Lifestyle intervention

- **Weight loss** obtained by bariatric surgery or caloric restriction diet in subjects with T2DM (7 most uncontrolled and non randomized studies)
- **Physical exercise** mainly in T2DM and without CAN (29 studies, **7 RCTs**)

→ ↓HR and ↑ HRV indexes and BRS
↑ sympathovagal balance

Disease-modifying treatments

- **glycaemic control** effective in T1DM (DCCT and EDIC)
- **multifactorial cardiovascular risk intervention effective in T2DM** (Steno-2 trial, ACCORD study) (not in ADDITION)

- **α-lipoic acid** effective in DEKAN study (*Ziegler 1997*), and in 1 open study (Tankova 2004), with borderline efficacy (*Lee 2017*), ineffective in combination with allopurinol and nicotinamide (*Pop-Busui 2013*); improvement in DB (predicted by ACE inhibitors use) in NATHAN 1 study (*Ziegler 2016*); safe

- **ARIs** (no ponalrestat) effective in a meta-analysis on HRV and 30:15, more effective with HbA1c <8% and duration <9.5 years; safe (*Hu 2014*)

- C-peptide in T1DM
- Benfotiamine in T2DM (open study)

- Vitamin E
- ω-3 PUFA treatment in T2DM
- Vitamin D in T1DM (open study)
- Vitamin B12 in T2DM (open study, not in 1 RCT)

- β-blockers (metoprolol)
- **ACE inhibitors and ARB** (quinapril, trandolapril, losartan) effective in 4/7 small studies (2 controlled)

Weight loss
Alam I et al *Auton Neurosci. 2009;151:168-73;* Sjoberg N et al *J Appl Physiol (1985). 2011;110:1060-4;* Maser RE et al *Surg Obes Relat Dis. 2013;9:221-6;* Kokkinos A et al *Obes Surg. 2013;23:31-8;* Lips MA et al *Eur J Endocrinol. 2013;169:383-90;* Straznicky N et al. *Front. Physiol. 2016;7:516;* Casellini CM et al *PLoS ONE 2016; 11(5): e0154211.*

Physical exercise
Voulgari C et al *Metab Clin Exp. 2013;62:609–21* ; Villafaina S et al *Curr Diab Rep 2017;17: 110;* Röling M et al *Curr Diab Rep 2017; 17: 125;* Bhati P et al *Diabetes Metab Syndr 2018; 12:69–78 ; Bellavere F et al Nutr Metab Cardiovasc Dis. 2018;28:226-233; Cassidy S et al Diab Vasc Dis Res. 2019;16:69-76;* Bönhof GJ et al *Diabetologia 2022;65:1048-1057*

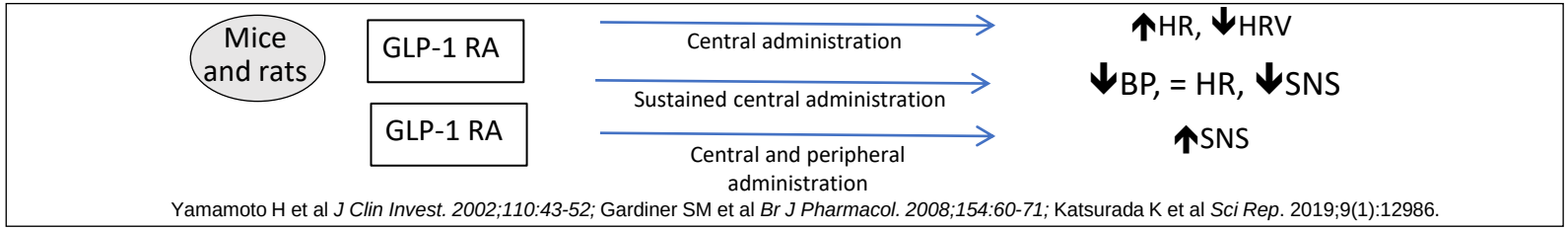
Glycaemic control
Martin CL et al *Diabetes Care 2014;37:31–38;* Gaede P et al *Diabetologia 2016;59:2298–2307;* Charles M et al *Diabetologia 2013; 56:101–108 ; Tang Y et al Diabetes Care 2021;44:164–173*

α-lipoic acid and ARI
Ziegler D et al *Diabetes Care 1997; 20: 369–373;* Tankova et al *Rom J Intern Med. 2004;42:457-64;* Lee SJ et al *Diabetes Metab J 2017;41:275-283;* Pop-Busui R et al *Diabetologia. 2013;56:1835–1844;* Ziegler D et al *J Diabetes Complications. 2016;30:350–356;* Hu X et al *PLoS ONE 2014; 9(2): e87096*

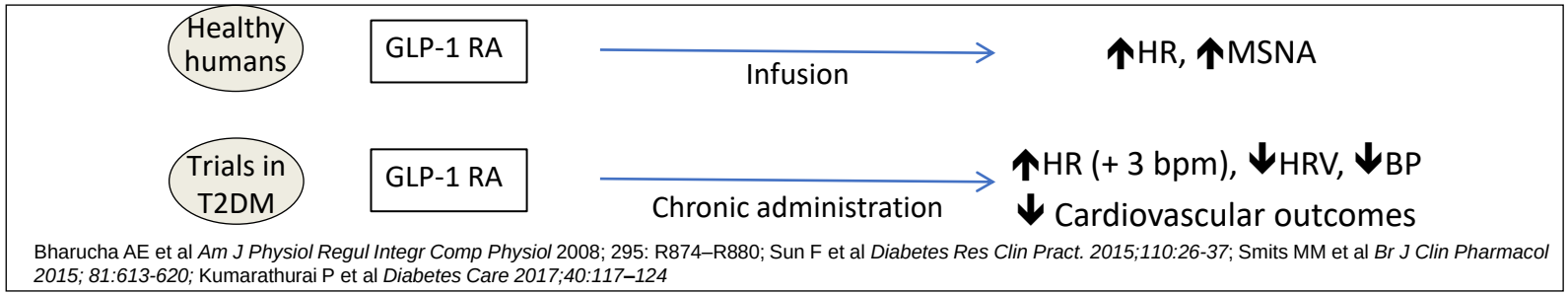
C-peptide, Vitamin E, Benfotiaminne, Vitamin D, β-blockers, ω-3 PUFA, Vitamin B12
Johansson BL et al *Diabet Med. 2000;17:181–189.;* Manzella D et al *Am J Clin Nutr 2001;73: 1052-1057.;* Serhiyenko VA et al *Int J Endocrinol (Ukraine) 2020;16:257-264;* Ebbehoj E et al *Diabetologia 2002; 45: 965-975* **;** Santini V et al *Nutr Metab Cardiovasc Dis. 2007;17:712-8.;* Silva LSD et al *Front Endocrinol (Lausanne). 2020;11:605681;* Yoshioka K et al *Horm Metab Res. 1995;27:43-4;* Didangelos T et al *Nutrients. 2021;13:395*

ACEi, ARB and others
Kontopoulos AG et al *Diabetes Care 1997; 20: 355-361;* Malik RA et al *Lancet 1998; 352: 1978-1981;* Athyros VG et al *Acta Cardiol 1998; 53: 201-209;* Maser RE et al *J Diabetes Complications. 2003;17:286-91.;* Kubba S et al *Neurol India 2003; 51: 355-358;* Didangelos TP et al *J Diabetes Complications 2006; 20: 1-7;* Didangelos TP et al *J Diabetes Res. 2017;2017:6719239.*

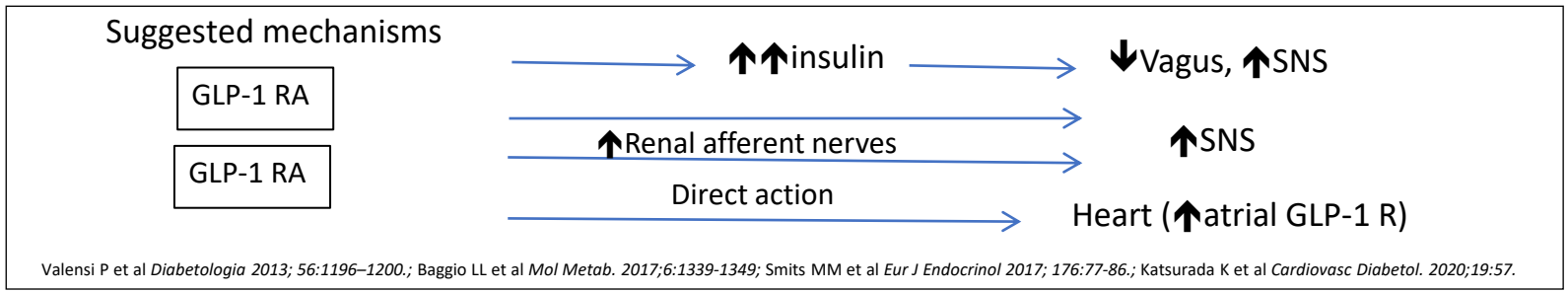
GLP-1 Receptor Agonists and autonomic nervous system



Yamamoto H et al *J Clin Invest. 2002;110:43-52;* Gardiner SM et al *Br J Pharmacol. 2008;154:60-71;* Katsurada K et al *Sci Rep*. 2019;9(1):12986.



Bharucha AE et al *Am J Physiol Regul Integr Comp Physiol* 2008; 295: R874–R880; Sun F et al *Diabetes Res Clin Pract. 2015;110:26-37*; Smits MM et al *Br J Clin Pharmacol 2015; 81:613-620;* Kumarathurai P et al *Diabetes Care 2017;40:117–124*



Valensi P et al *Diabetologia 2013; 56:1196–1200.;* Baggio LL et al *Mol Metab. 2017;6:1339-1349;* Smits MM et al *Eur J Endocrinol 2017; 176:77-86.;* Katsurada K et al *Cardiovasc Diabetol. 2020;19:57.*

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

Trials with GLP1-RA and autonomic measures as outcome

Author (year)	Population	GLP1-RA	Follow-up (weeks)	Heart Rate	Autonomic measures
Jaiswal (2015)	46 T2DM (32 with DPN)	Exenatide (Vs. glargine)	18	=	No change in CARTs, HRV indexes
Nakatani (2016)	60 T2DM	Liraglutide (Vs. lixisenatide)	4	↑ with liraglutide	↑ 24h LF:HF with liraglutide
Kumarathurai (2017)	39 T2DM with CAD	Liraglutide (Vs. placebo)	12	↑	↓ 24h HRV indexes
Smits (2017)	57 T2DM	Liraglutide (Vs. placebo)	12	↑	No change in HRV indexes
Cacciatori (2017)	28 T2DM	Exenatide-ER	26	↑	↑ DB ↓ VR ↓ LF:HF
Tonneijck (2018)	34 T2DM	Lixisenatide (Vs glulisine)	8	=	No change in LF:HF
Hansen (2019)	99 T1DM	Liraglutide (Vs. placebo)	24	↑	No change in CARTs, HRV indexes
Brock (2019)	39 T1DM with DPN (35 with OH)	Liraglutide (Vs. placebo)	26	=	No change in HRV indexes, BRS, CVT
Nyström (2019)	62 T2DM (with heart failure)	Liraglutide (Vs. glimepiride)	18	↑	No change in 24h HRV indexes

BRS: Baroreflex sensitivity; CAD: Coronary artery disease; CART, cardiovascular autonomic reflex test; CVT: Cardiac vagal tone; DB: Deep breathing; DPN: Diabetic polyneuropathy; HRV, heart rate variability; LF:HF: Low to high frequency ratio; OH: Orthosttaic hypotension; T2DM, type 2 diabetes mellitus; VR: Valsalva ratio

Kumarathurai P et al *Diabetes Care 2017;40:117–124;*
Nakatani Y et al *Diabetes Care 2016;39:e22-23*;
Cacciatori V et al *J Endocr Soc 2017; 2:53-62;*
Tonneijck *Hypertension*. 2018;72:314-322
Hansen CS et al *Front. Endocrinol. 2019,10:242*
Brock C et al Br J Clin Pharmacol. 2019; 85:2512-2523
Nyström *T et al Endocrinol Diab Metab.* 2019;2:e00058

Discrepancies in the available preclinical and clinical findings suggesting possible species-specific patterns of GLP1 receptors in addition to differences between GLP1-RAs.

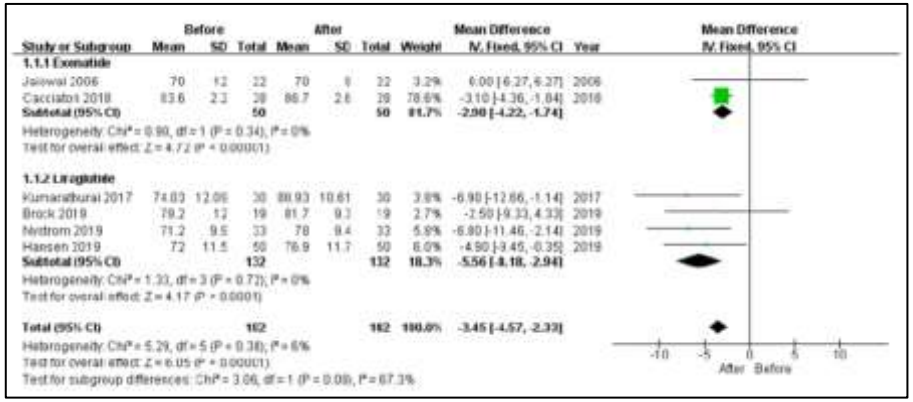
Effect of the Glucagon-Like Peptide-1 Receptor Agonists on Autonomic Function in Subjects with Diabetes: A Systematic Review and Meta-Analysis

Greco C, Santi D, Brigante G, Pacchioni C, Simoni M.

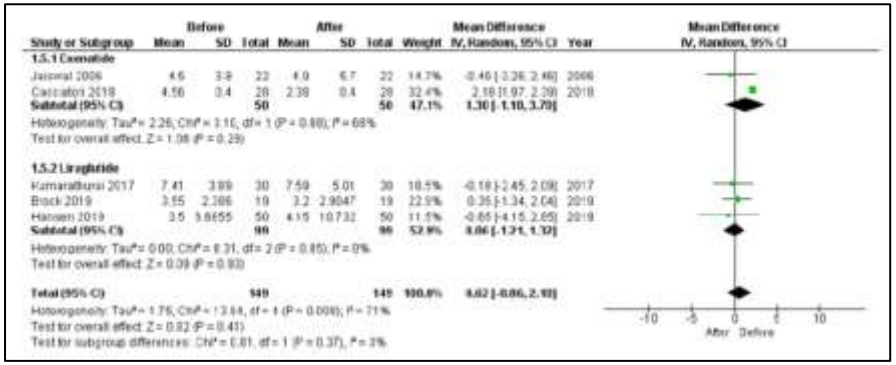
Diabetes Metab J. 2022 Apr 12.

Meta-analysis of 6 studies (182 individuals with diabetes, mostly type 2) exploring GLP-1RA actions on autonomic measures

Heart rate (HR) mean difference

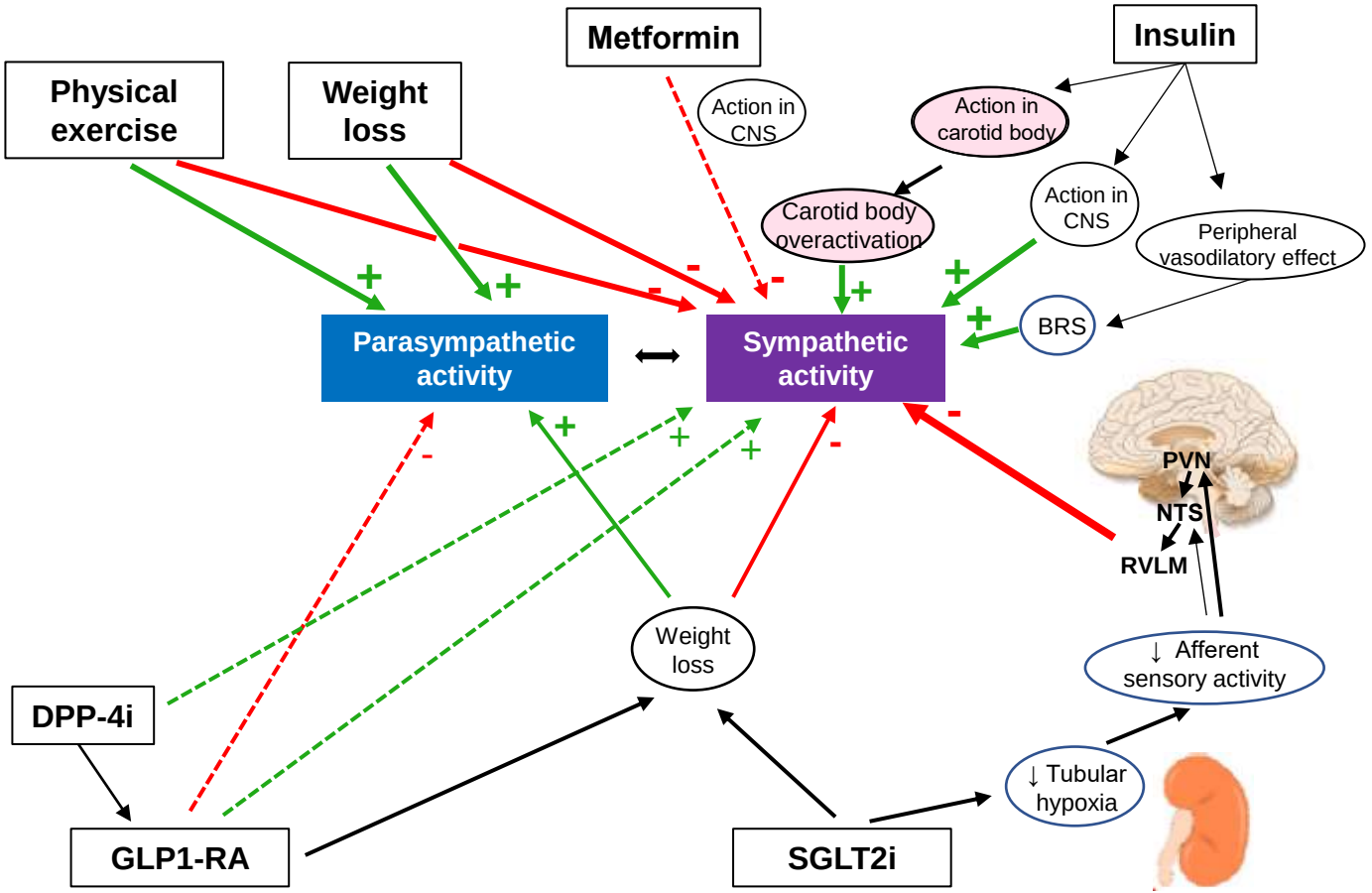


LF/HF ratio mean difference



HR increased after treatment with GLP1-RA (↑3.45 bpm, P<0.001), whereas LF/HF did not change

Influences of therapeutic interventions on autonomic function in diabetes



Spallone V & Valensi P. *Diabetes Metab. 2021;47:101224.*

Conclusioni

- L’interesse/conoscenza sui circuiti nervosi che regolano il controllo autonomico di cuore e reni è in costante crescita con un ruolo centrale riconosciuto all'innervazione renale.
- Il diabete offre un punto di osservazione privilegiato in quanto associato sia alla disfunzione/neuropatia autonoma conseguente a fattori metabolici sia alla sindrome cardiorenale.
- Gli studi disponibili suggeriscono il coinvolgimento del sistema nervoso autonomo nelle molteplici azioni dei SGLT2i.
- La complessità della rete impedisce di esplorarla completamente quando si mira a un singolo outcome.
- Un approccio multidisciplinare e integrato alla ricerca auspicabile.

La prospettiva autonomica può aiutare a comprendere la malattia cardiorenale e gli effetti dei nuovi farmaci, favorire le scelte terapeutiche e aprire nuove opportunità di ricerca.

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Società Italiana di Diabetologia
Neuropathy Study Group of Italian Society of Diabetology (SID)

AINV
Italian Society for Neurovegetative Research

NEURODiab
Diabetic Neuropathy Study Group (NEURODiab)

Thank you for attention

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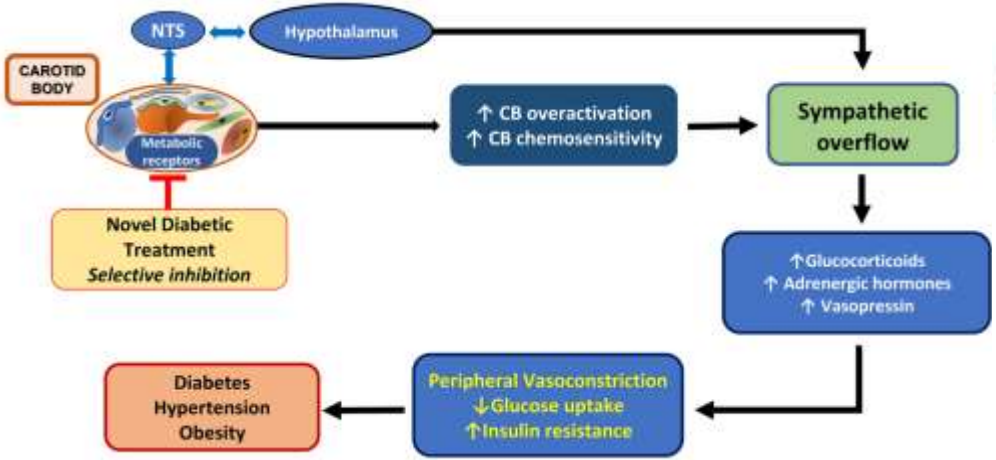
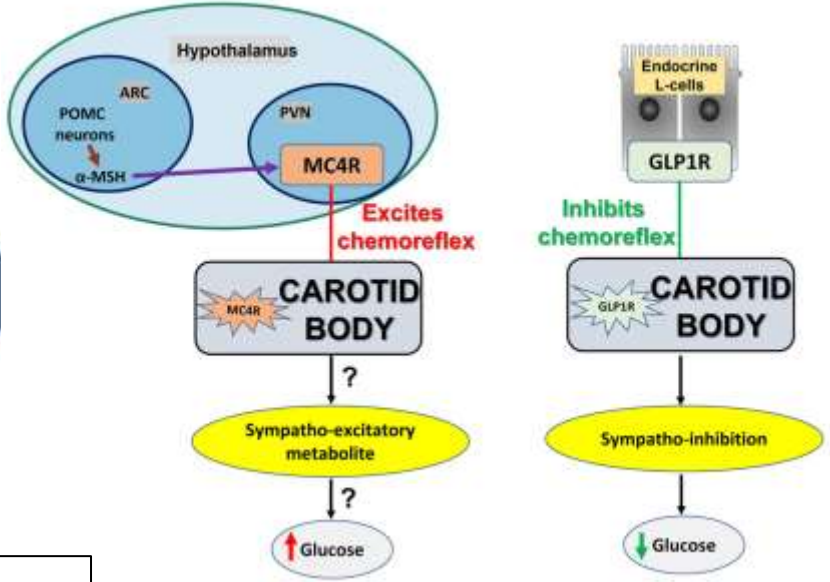
Carotid body: an emerging target for cardiometabolic co-morbidities

Thakkar P et al *Exp Physiol. 2023 May;108(5):661-671.*

Overactivity of Carotid body triggers sympathetic overflow with metabolic and cardiovascular consequences



Carotid body as potential target for cardiometabolic homeostasis via GLP1R and MC4R pathway



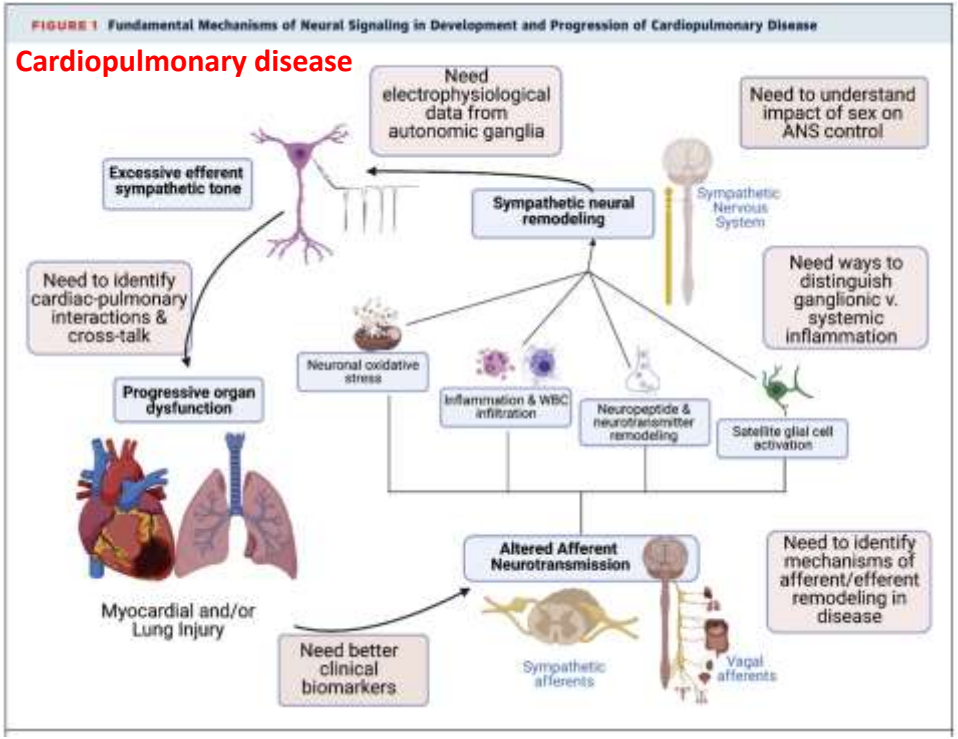
In rat and human

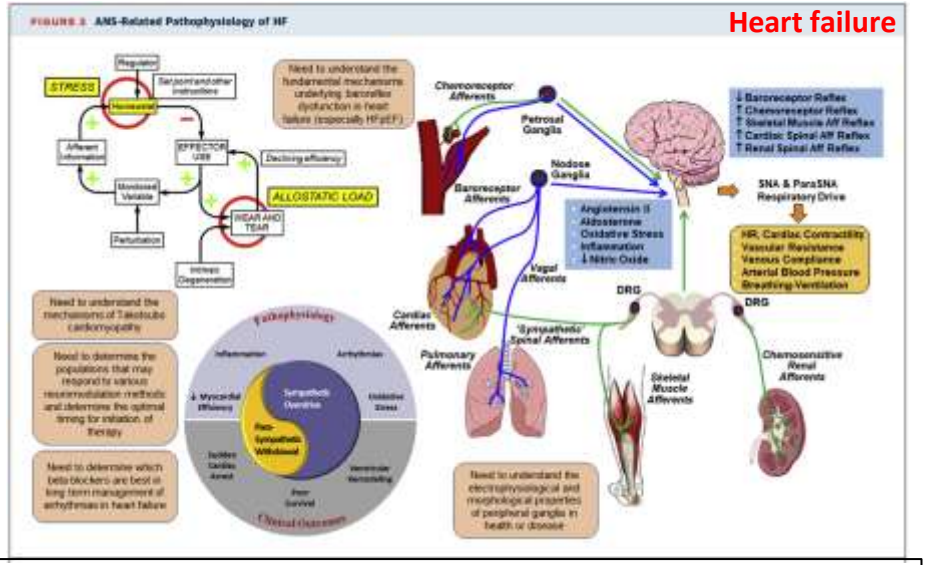
- GLP1Rs are expressed in the carotid body
- Activation of GLP1Rs in the carotid body acutely suppresses the peripheral chemoreflex-evoked sympathetic response

Pauza AG et al *Circ Res. 2022 Mar 4;130(5):694-707.*

New perspectives in research on autonomic neural mechanisms of cardio-pulmonary-renal disease and development of autonomic-focused therapeutics

Workshop of US National Heart, Lung, and Blood Institute and the National Institutes of Health
Knowledge gaps and research priorities in autonomic neural cardiopulmonary regulation for multidisciplinary collaborations*





Highlights

- **ANS is a key regulator** of cardiopulmonary and sleep/circadian pathophysiology
- **Understanding cardiopulmonary SNS and PNS** structure/function over disease time-course and cell type interactions **is essential**.
- In vitro ANS and **experimental** and computational **integrative studies are necessary**.
- Clarifying sex-and race-specific cardiopulmonary and sleep/circadian influence on **ANS response to neurotherapeutics interventions** is critical for personalized strategies.

*basic, translational, and clinical researchers in neuroscience and cardiopulmonary disorders

Mehra R et al *JACC Basic Transl Sci. 2022;7:265-293*

Sudden cardiac death (SCD) and autonomic modulation

SNS hyperactivity

↓ refractory period
↓ action potential duration
↑ regional heterogeneity in refractoriness and repolarization
→ intracellular calcium overload

→ Re-entry Afterdepolarization → Ventricular arrhythmia

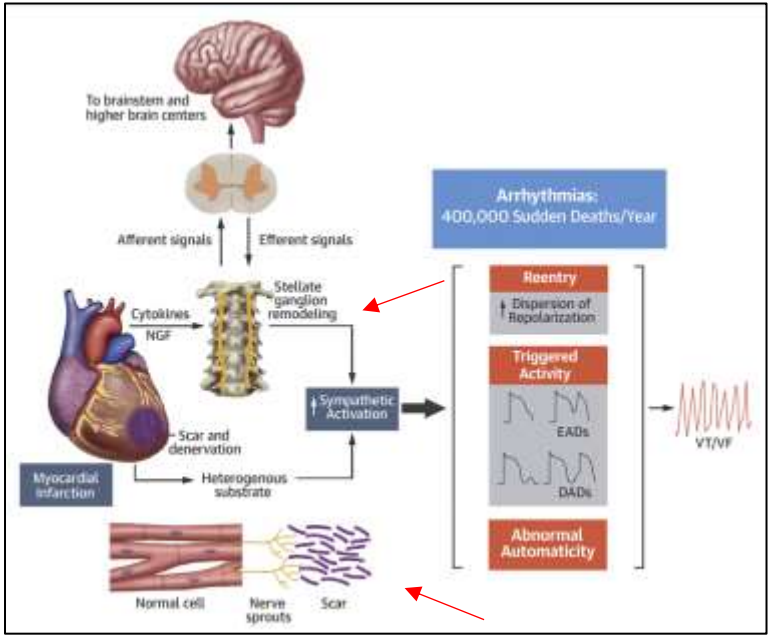
Myocardial infarction and heart failure

Neuro-cardiac SNS remodelling

- ↑ activity and neuronal remodelling in stellate ganglion (also mediated by ↑ **activity of renal nerves**)
- Regional heterogeneous hyper-innervation along border zones of injured myocardium

Inflammatory and neurohormonal activation

- Neuronal phenotypic switching from adrenergic to cholinergic phenotypes
- Stimulation of renal sympathetic afferents and amplification of central sympathetic signalling



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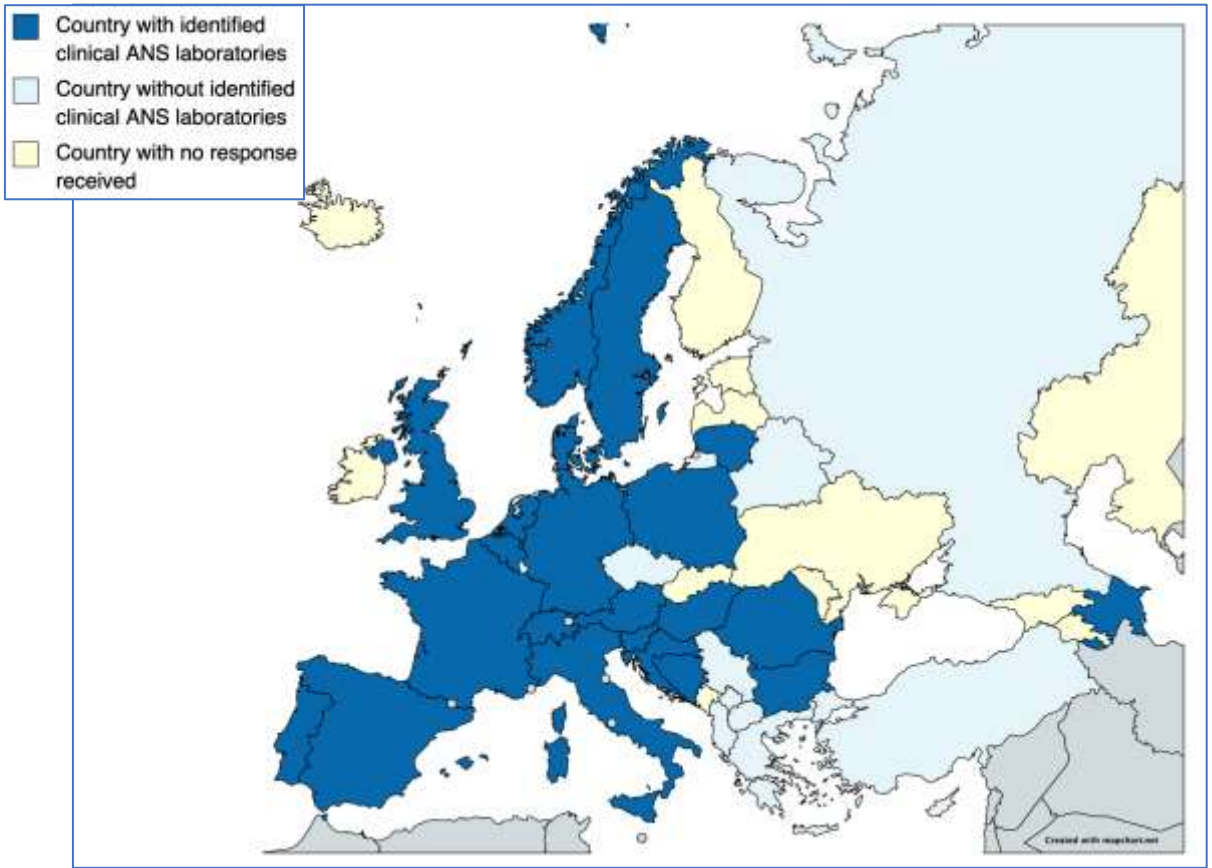
Clinical autonomic nervous system laboratories in Europe

A joint survey of the European Academy of Neurology and the European Federation of Autonomic Societies

Habek M, Leys F, Krbot Skorić M, Reis Carneiro D, Calandra-Buonaura G, Camaradou J, Chiaro G, Cortelli P, Falup-Pecurariu C, Granata R, Guaraldi P, Helbok R, Hilz MJ, Iodice V, Jordan J, Kaal ECA, Kamondi A, Pavy Le Traon A, Rocha I, Sellner J, Senard JM, Terkelsen A, Wenning GK, Berger T, Thijs RD, Struhal W, Fanciulli A; Collaborators of the European Network of Clinical ANS laboratories.

Eur J Neurol. 2022 Dec;29(12):3633-3646.

Distribution of clinical ANS laboratories across Europe (51 countries)



Aim: to identify the neurology-driven or interdisciplinary **clinical ANS laboratories in Europe**, their characteristics, and regional differences

Identified **84 laboratories in 22 countries**: 46 (55%) answered the survey

1 ANS laboratory in

- 11 out of 12 from
  - 6 Western Europe
  - 5 Northern Europe
- 11 out of 21 from (*p* = 0.021)
  - 6 Southern Europe
  - 4 Eastern Europe
  - 1 Greater Europe

Conclusions: Disparities in the availability of healthcare services for people with ANS disorders across European countries