Ente Ospedaliero Cantonale

Ipertensione difficile da trattare

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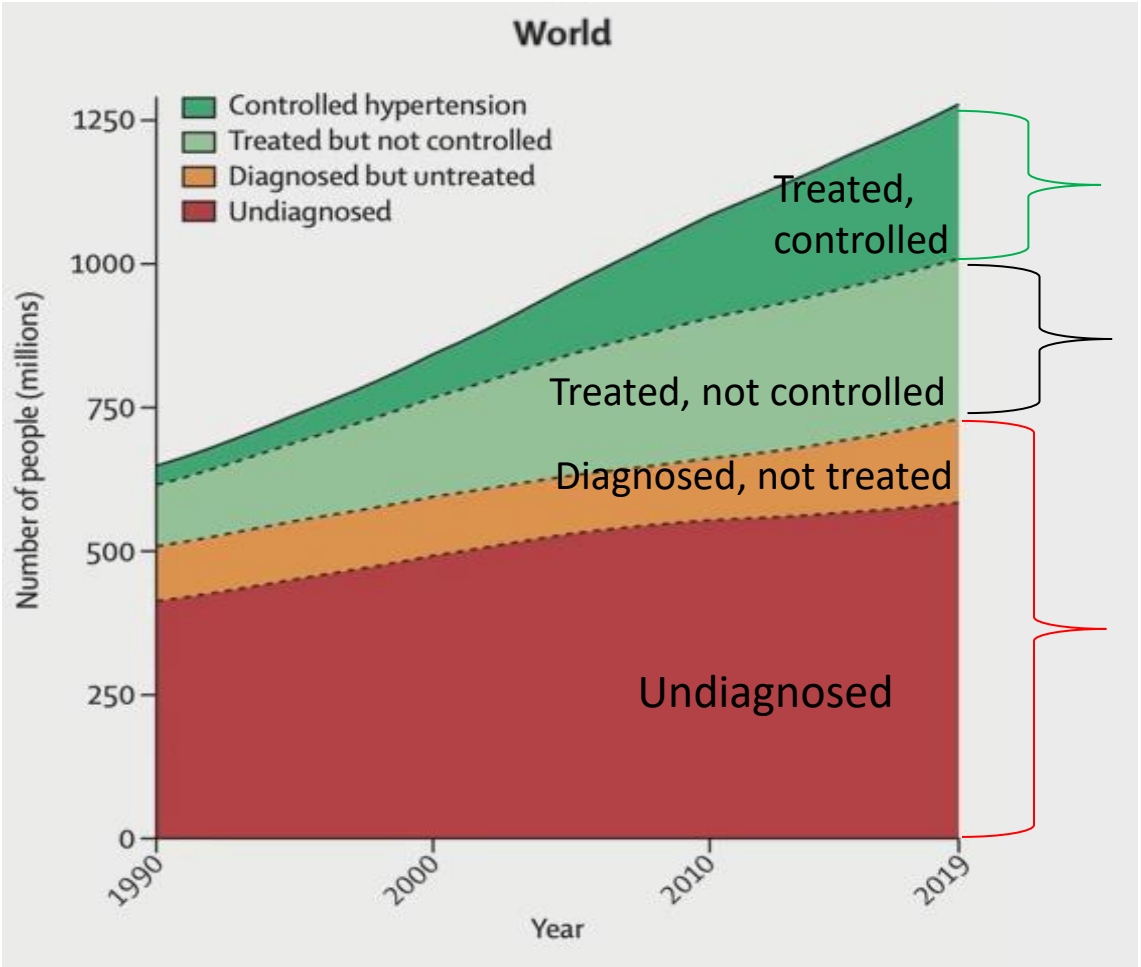
Epidemiologia



Vanno bene

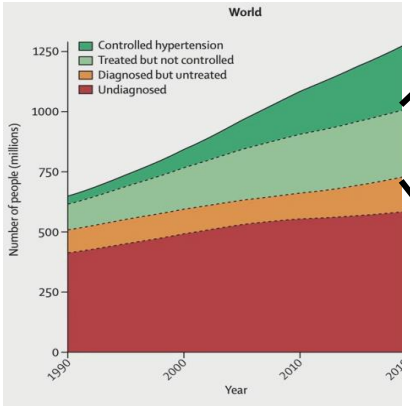
Ce ne occupiamo, ma non vanno bene

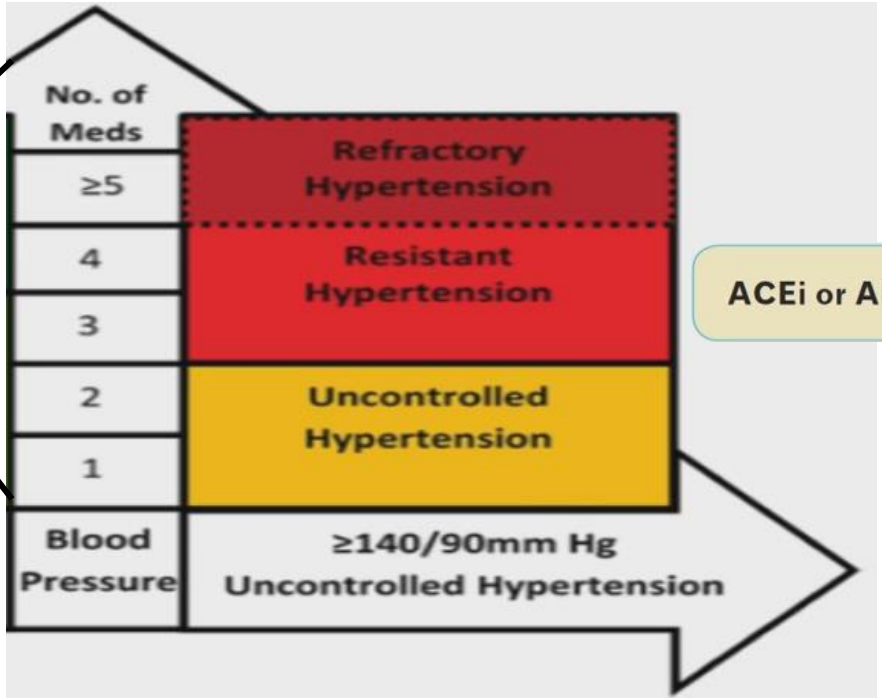
Nessuno se ne occupa …

NCD Risk factor Collaboration, Lancet 2021

3 termini differenti per uno stesso concetto

Treated but not controlled



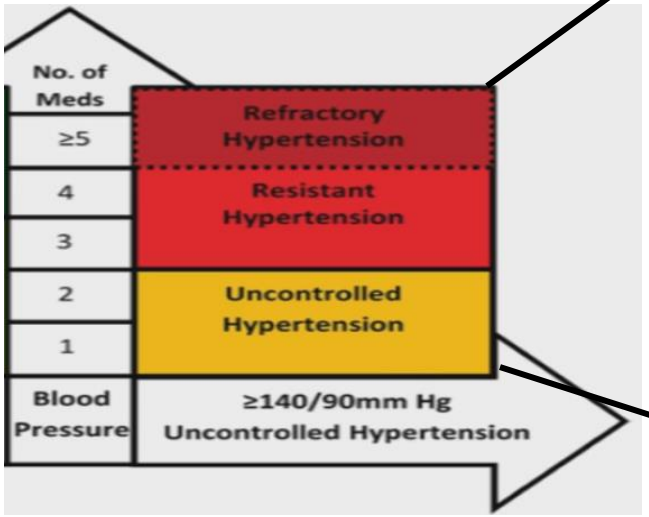


ACEi or ARB + CCB + diuretic

Calhoun, Current Opin Nephrol Hypertens, 2017

Urge un cambio di approccio

Treated but not controlled



Popolazione eterogenea
con 1 caratteristica in comune
'Ipertensione non controllata'

Domandiamoci il perché ?!

Uncontrolled HT

EUROSPIRE III: 40-50% of all hypertensive patients

Pseudoresistant HTN
5-20%

- White coat effect
- Poor adherence
- Intolerance to treatment
- Not optimized treatment

True resistant HTN
2-5%

Secondary HTN
3-5%

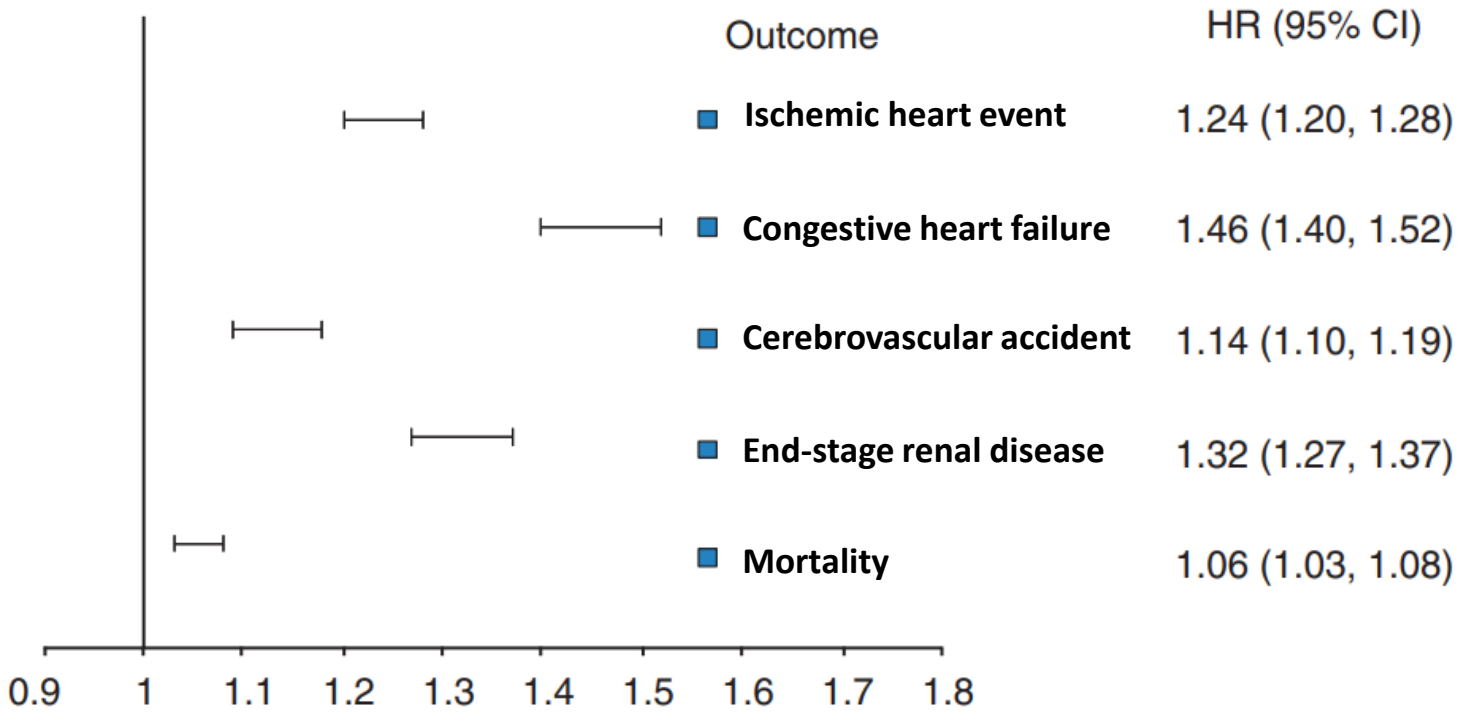
Il nuovo concetto di: «Ipertensione veramente resistente»

Recommendations	Class	Level
Uncontrolled HT 	I	C
— pseudo-resistant HT 		
— secondary HT 		
 **= true resistant HT**		

Definition of true resistant HT, ESH Guidelines 2023

rHT→↗↗ rischio cardiovascolare

470,386 individuals with resistant vs. non-resistant HT



Sim et al. Kidney Int, 2015

HT pseudo-resistente: la prima causa di ipertensione non controllata

Uncontrolled HT

EUROSPIRE III: 40-50% of all hypertensive patients

Pseudoresistant HTN
5-20%

- **White coat effect**
- **Poor adherence**
- **Not optimized treatment**
- **Intolerance to treatment**

True resistant HTN
2-5%

Secondary HTN
3-5%

HT pseudo-resistente : definizione

“high blood pressure that

seems to resist treatment,

when other factors are raising

blood pressure and

making treatment difficult”

Fattori interferenti

Inappropriate treatment
- Drug class
- Low dosis

Obesity

Non-adherence

Physical inactivity

CKD

Sleep apnea
Sleep deprivation

Drugs

Interfering medicines

Salt
Alcohol
Smoke

Il ruolo importante dell'anamnesi

Non-adherence

Inappropriate treatment
- Drug class
- Low dosis

Obesity

CKD

ANAMNESI

Physical inactivity

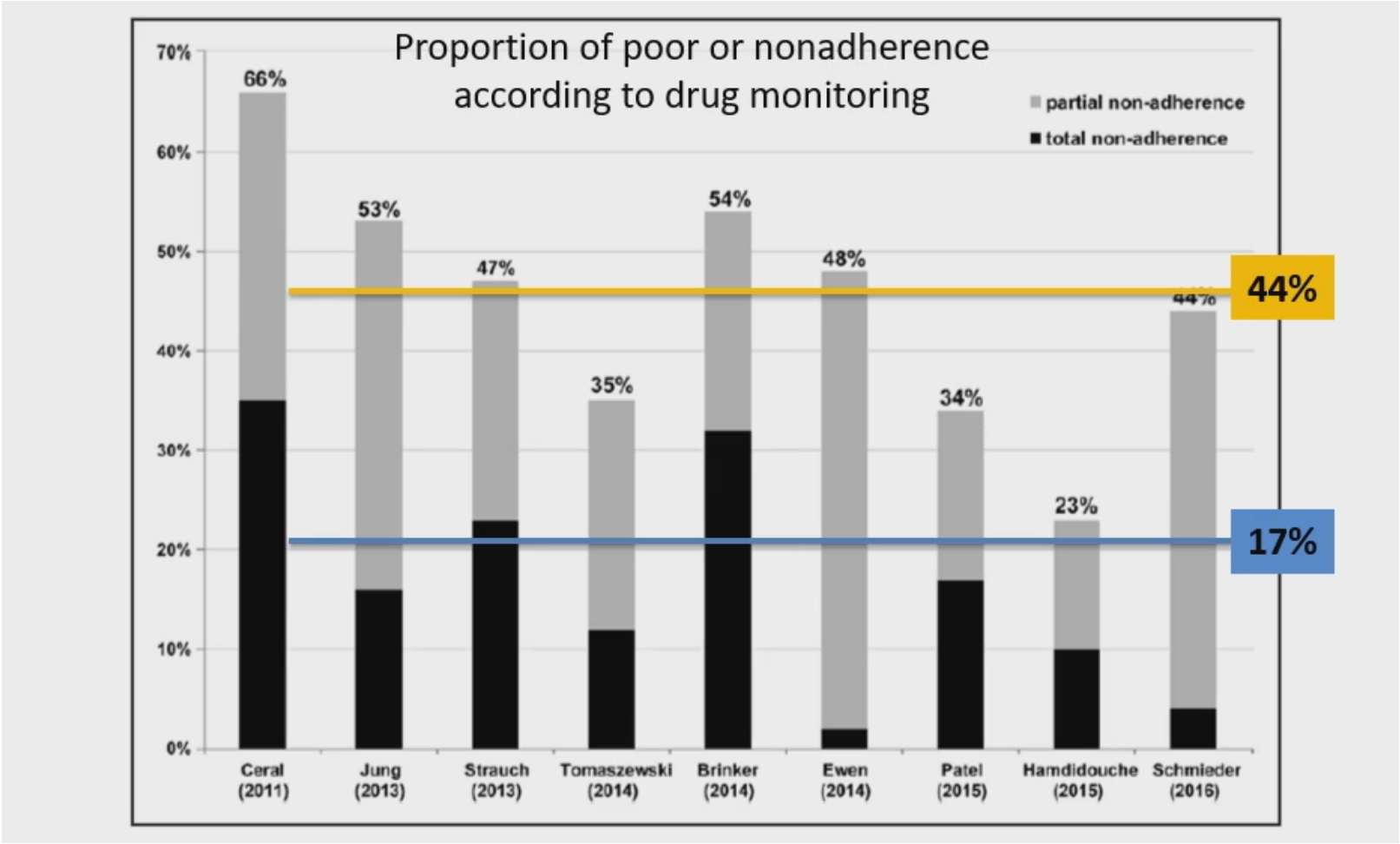
Sleep apnea
Sleep deprivation

Drugs

Interfering medicines

Salt
Alcohol
Smoke

Gli anti-ipertensivi agiscono bene, ma ...

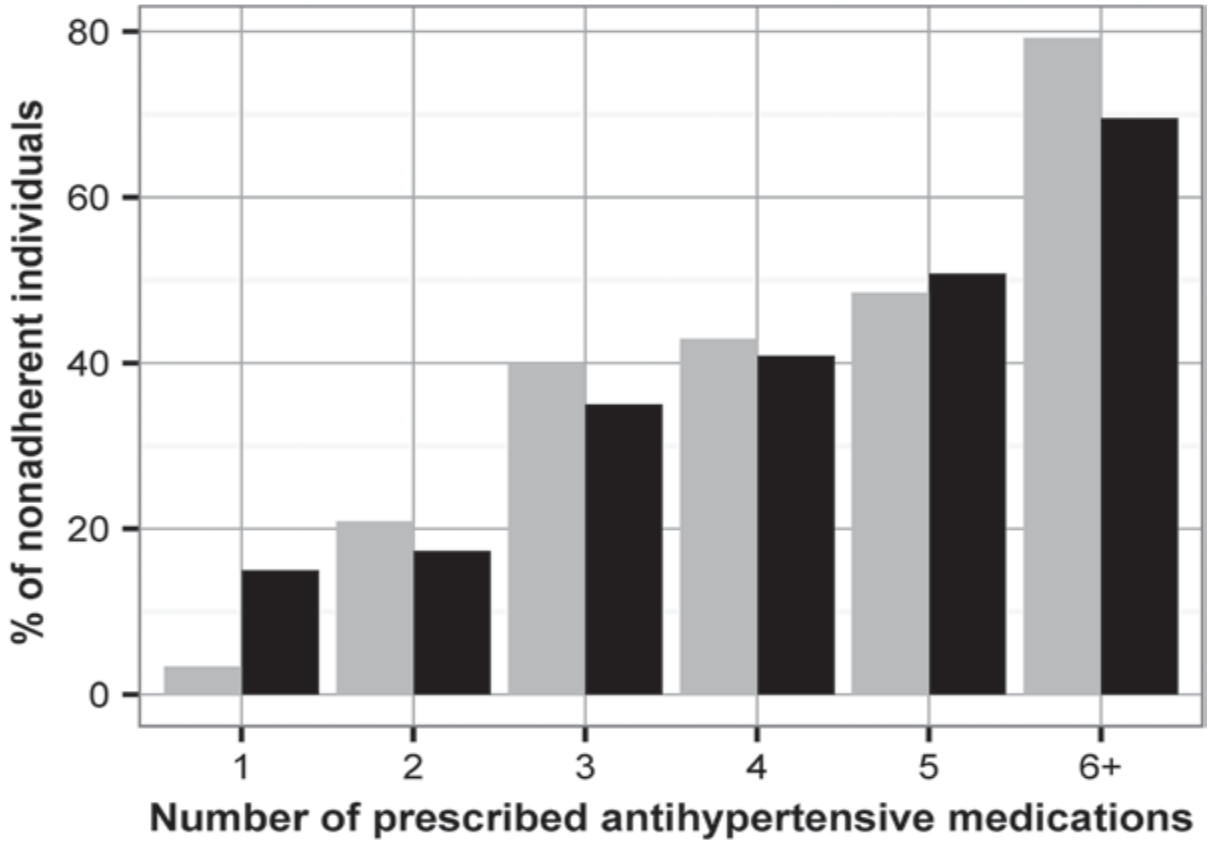


Berra E, Hypertension 2018

Ragioni di ridotta aderenza

Tomaszewski et al. Wlad Lek, 1999

La non-aderenza è proporzionale al N° di cpr prescritte



UK

Czeck republic

Gupta et al. 2017; 69:1113-20

Inerzia clinica

= incapacità degli operatori sanitari di iniziare o intensificare il trattamento quando indicato (cioè quando la pressione arteriosa non è nel target)

Philipps LS. Ann Intern Med, 2001

Linee guida

Prefer SPCs at any step

Step 1
Dual combination

Step 2
Triple combination

Step 3
Add further drugs

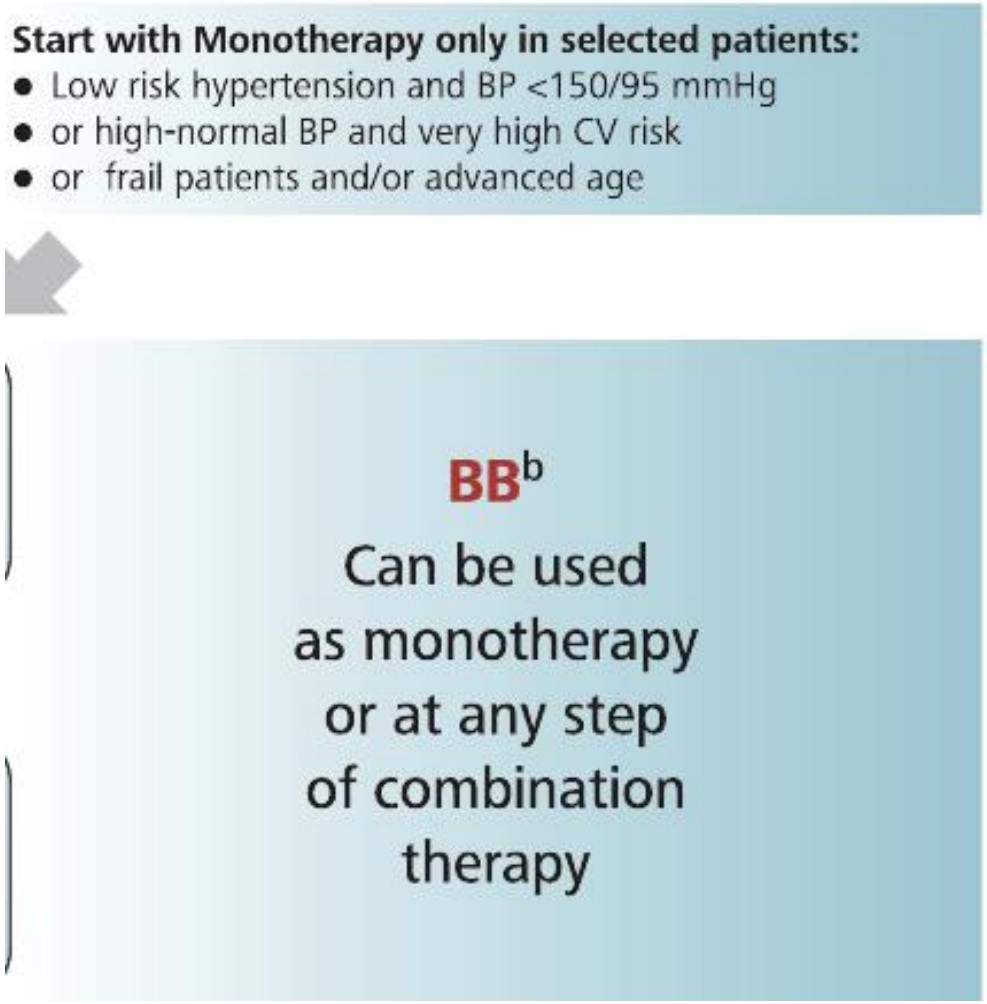
Start with Dual Combination Therapy in most patients

ACEi or ARB + CCB or $_{T/TL}$Diuretic[a]
Increase to full-dose if well tolerated
→ up to ~ 60% controlled[c]

ACEi or ARB + CCB + $_{T/TL}$Diuretic
Increase to full-dose if well tolerated
→ up to ~ 90% controlled[c]

ESH Guidelines, 2023

Linee guida



ESH Guidelines, 2023

Ipertensione secondaria: forse non così rara come si pensa …

Uncontrolled HTN

EUROSPIRE III: 40-50% of all hypertensive patients

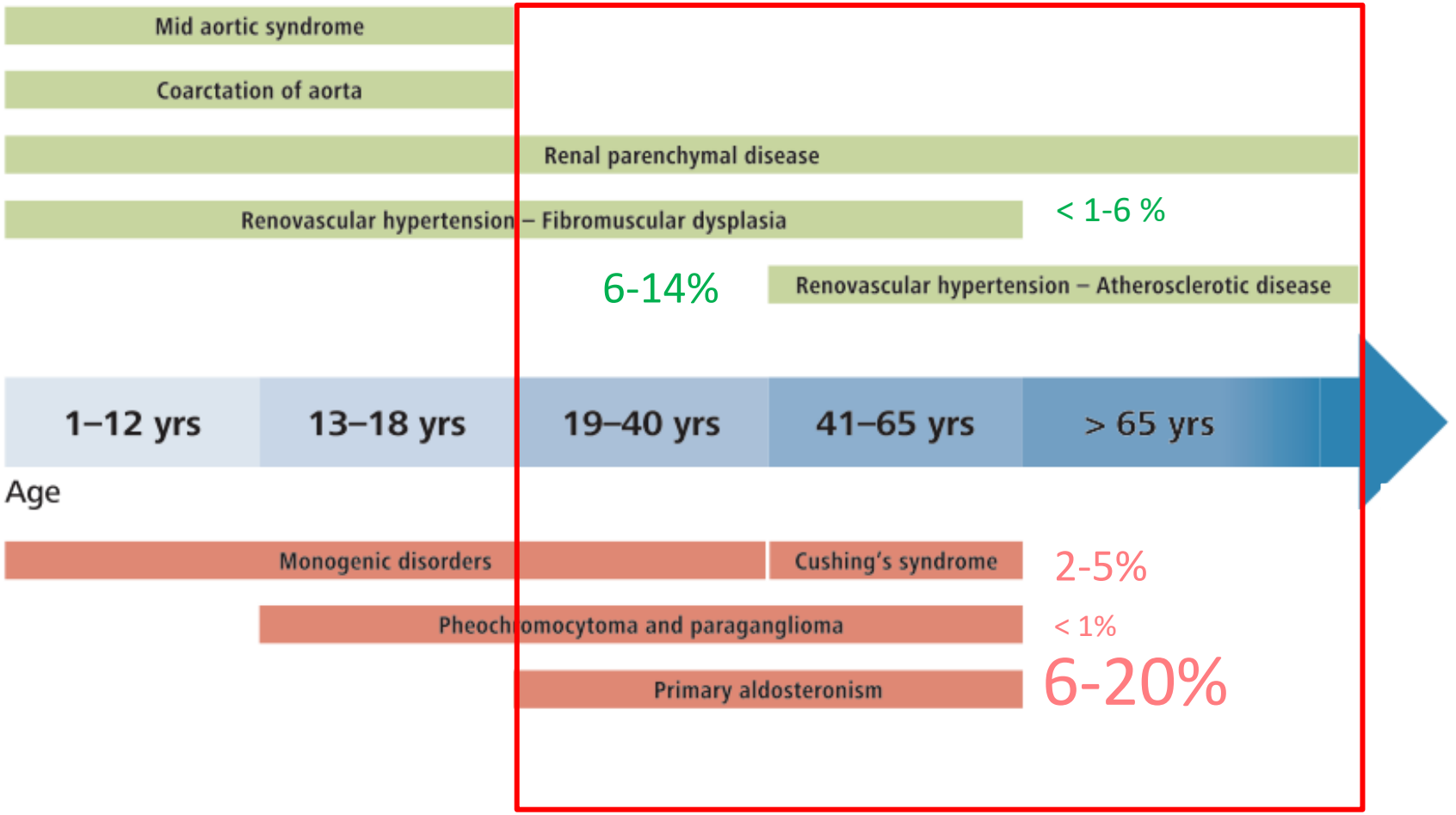
Pseudoresistant HTN
5-20%

- White coat effect
- Poor adherence
- Not optimized treatment
- Intolerance to treatment

True resistant HTN
2-5%

Secondary HTN
3-5%

Forme secondarie di HT secondo l'età



ESH-ESC Guidelines 2023

Ipertensione secondaria: indicazioni al depistaggio

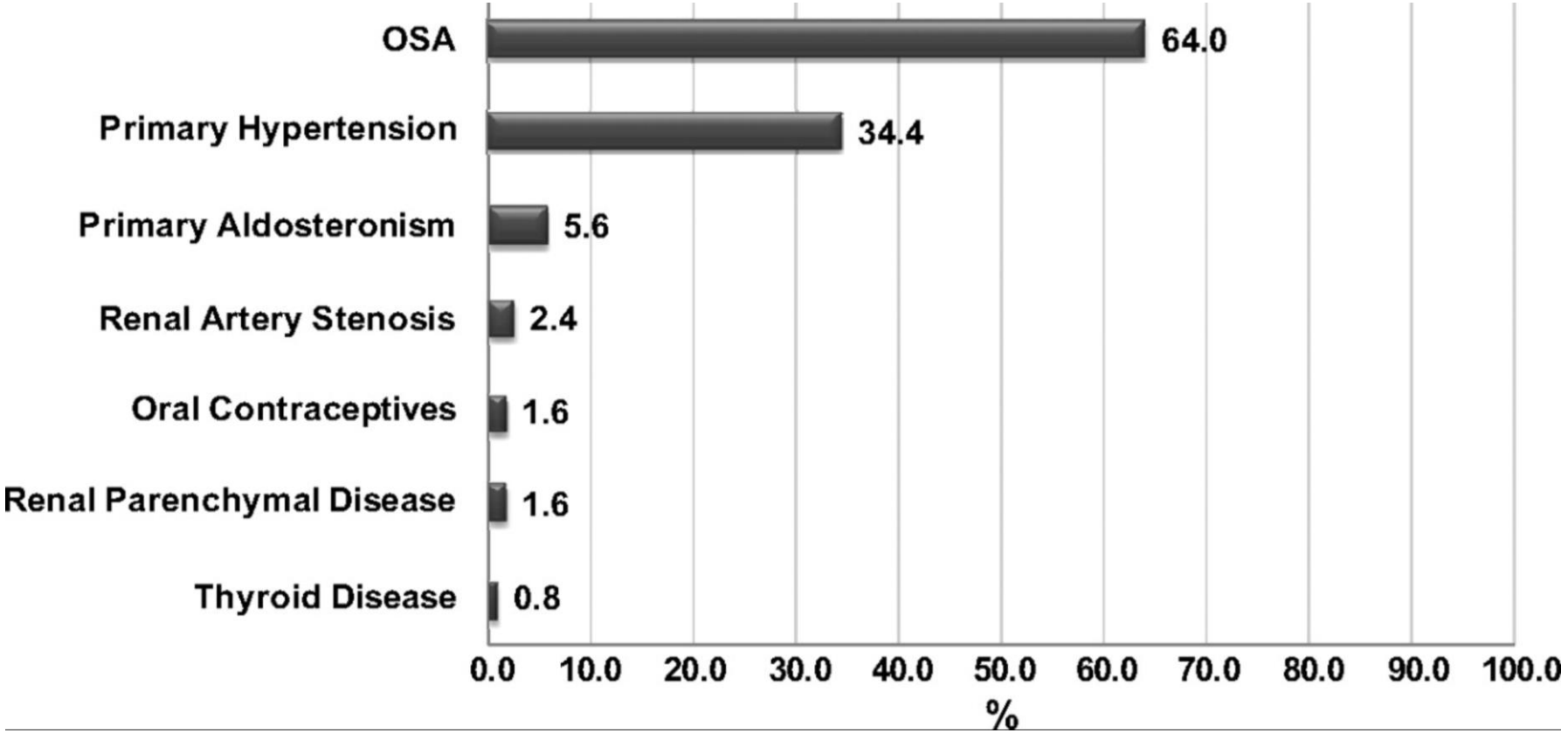
1. **Apparent resistant HT**
2. **Younger patients** (< 40y) with grade 2 or 3 HT or HT of any grade **in childhood**
3. **Severe (grade 3)** HT or **malignant** HT
4. Hypertensive **emergency**
5. **Sudden onset** of HT
6. **Acute worsening** of BP control in patients with previously well controlled by treatment
7. **Severe/extensive organe damage**, particularly if disproportionate for the duration and severity of BP elevation

ESH-ESC Guidelines 2023

Ipertensione secondaria: indicazioni al depistaggio

8. **Clinical or biological features** suggestive of endocrine causes of HT, of atherosclerotic renovascular disease or fibromuscular dysplasia or of obstructive sleep apnea
9. Severe HT in **pregnancy** or acute worsening of BP control in pregnant women with preexisting HT

Le apnee ostruttive del sonno sono la causa N°1 delle forme secondarie di HT



Pedrosa, Hypertension 2011

Link tra apnee e rHT

Recurrent apneas/hypopneas
Respiratory efforts (arousals)

Systemic metabolic effects of SA

SNS hyperactivity	Inflammation
Oxidative stress	Hypercoagulability
Vascular rigidity	RAAS hyperactivity

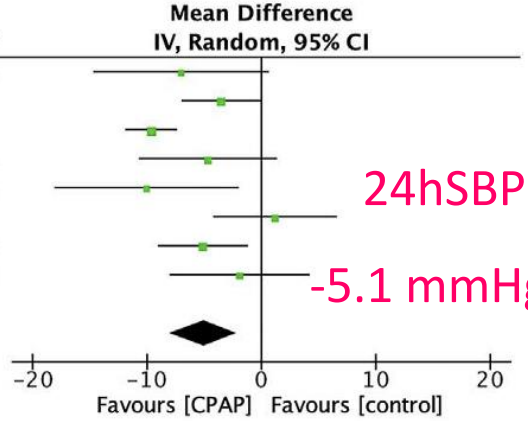
HT
Hyperhydratation

Efficacia della CPAP in caso di rHT

A

Study or Subgroup	CPAP Mean	CPAP SD	CPAP Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI	Year
Lozano 2010 (28)	-7.6	10.9	20	-0.6	13.7	21	8.6%	-7.00 [-14.56, 0.56]	2010
Martinez-Garcia 2013 (29)	-4.7	10.92	98	-1.2	12.78	96	16.0%	-3.50 [-6.85, -0.15]	2013
Pedrosa 2013 (31)	-6.5	3.3	19	3.1	3.3	16	18.2%	-9.60 [-11.79, -7.41]	2013
Lloberes 2014 (27)	-2.3	10.8	27	2.35	11.9	29	11.0%	-4.65 [-10.60, 1.30]	2014
Oliveira 2014 (25)	-10	14	24	0	13.88	23	8.1%	-10.00 [-17.97, -2.03]	2014
Muxfeldt 2015 (30)	0.8	14.13	46	-0.4	13.45	60	12.1%	1.20 [-4.12, 6.52]	2015
Zou 2018 (32)	-2.3	10.6	43	2.8	7.5	47	15.0%	-5.10 [-8.93, -1.27]	2018
Joyeaux-Faure 2018 (26)	-4	9.3537	19	-2.12	9.3537	18	10.9%	-1.88 [-7.91, 4.15]	2018
Total (95% CI)			**296**			**310**	**100.0%**	**-5.06 [-7.98, -2.13]**	

Heterogeneity: $Tau^2 = 11.02$; $Chi^2 = 22.62$, df = 7 (P = 0.002); $I^2 = 69\%$
Test for overall effect: Z = 3.39 (P = 0.0007)



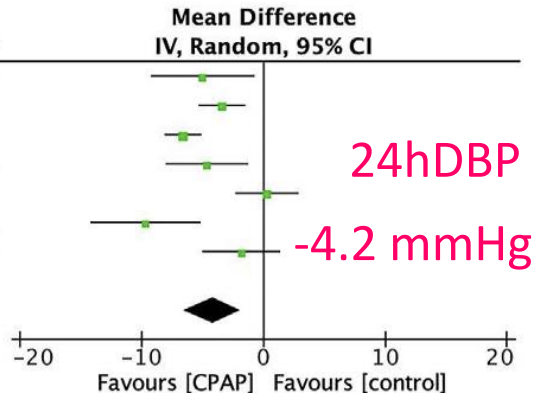
24hSBP

-5.1 mmHg

B

Study or Subgroup	CPAP Mean	CPAP SD	CPAP Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI	Year
Lozano 2010 (28)	-4.9	6.4	20	0.1	7.3	21	11.6%	-5.00 [-9.20, -0.80]	2010
Martinez-Garcia 2013 (29)	-3.9	7.38	98	-0.5	5.8	96	16.9%	-3.40 [-5.27, -1.53]	2013
Pedrosa 2013 (31)	-4.5	1	10	2.1	2.7	16	17.6%	-6.60 [-8.06, -5.14]	2013
Lloberes 2014 (27)	-4.4	6	27	0.25	6.7	29	13.5%	-4.65 [-7.98, -1.32]	2014
Muxfeldt 2015 (30)	-0.2	7.32	46	-0.5	5.45	60	15.4%	0.30 [-2.23, 2.83]	2015
Joyeaux-Faure 2018 (26)	-4	6.9338	19	5.69	6.9338	18	11.0%	-9.69 [-14.16, -5.22]	2018
Zou 2018 (32)	-1.2	7.7	43	0.6	7.4	47	14.0%	-1.80 [-4.93, 1.33]	2018
Total (95% CI)			**263**			**287**	**100.0%**	**-4.21 [-6.50, -1.93]**	

Heterogeneity: $Tau^2 = 7.12$; $Chi^2 = 31.25$, df = 6 (P < 0.0001); $I^2 = 81\%$
Test for overall effect: Z = 3.62 (P = 0.0003)



24hDBP

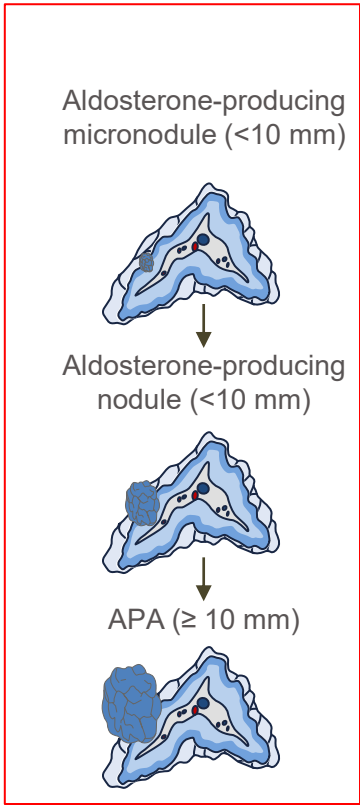
-4.2 mmHg

Labarca, Sleep medicale rev 2021

HT e CPAP: indicatori di risposta

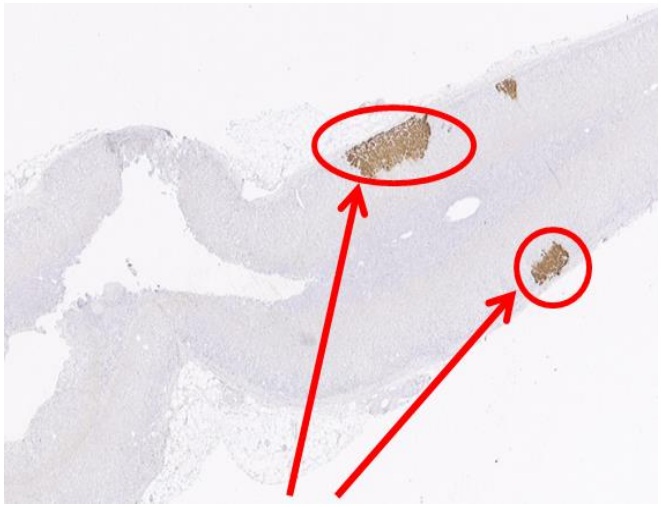
1. HT resistenti
2. Paziente con sonnolenza diurna
3. Pazienti con ipertensione notturna / non-dipper

Iperaldosteronismo primario (PA)

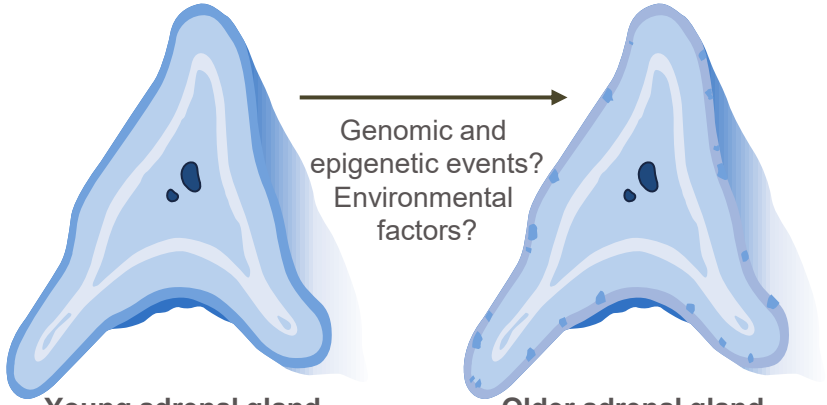


A, et al. J Clin Endocrinol Metab. 2013;98:1409–16; 2. Baudrand R, et al. Hypertension. 2017;69:950–6

Iperaldosteronismo primario (PA)

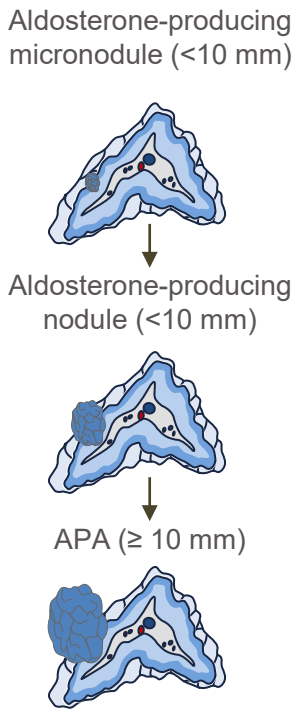


Aldosterone producing cell clusters
with somatic mutations
KCNJ5, CACNA1D, *ATP1A1*, and *ATP2B3*



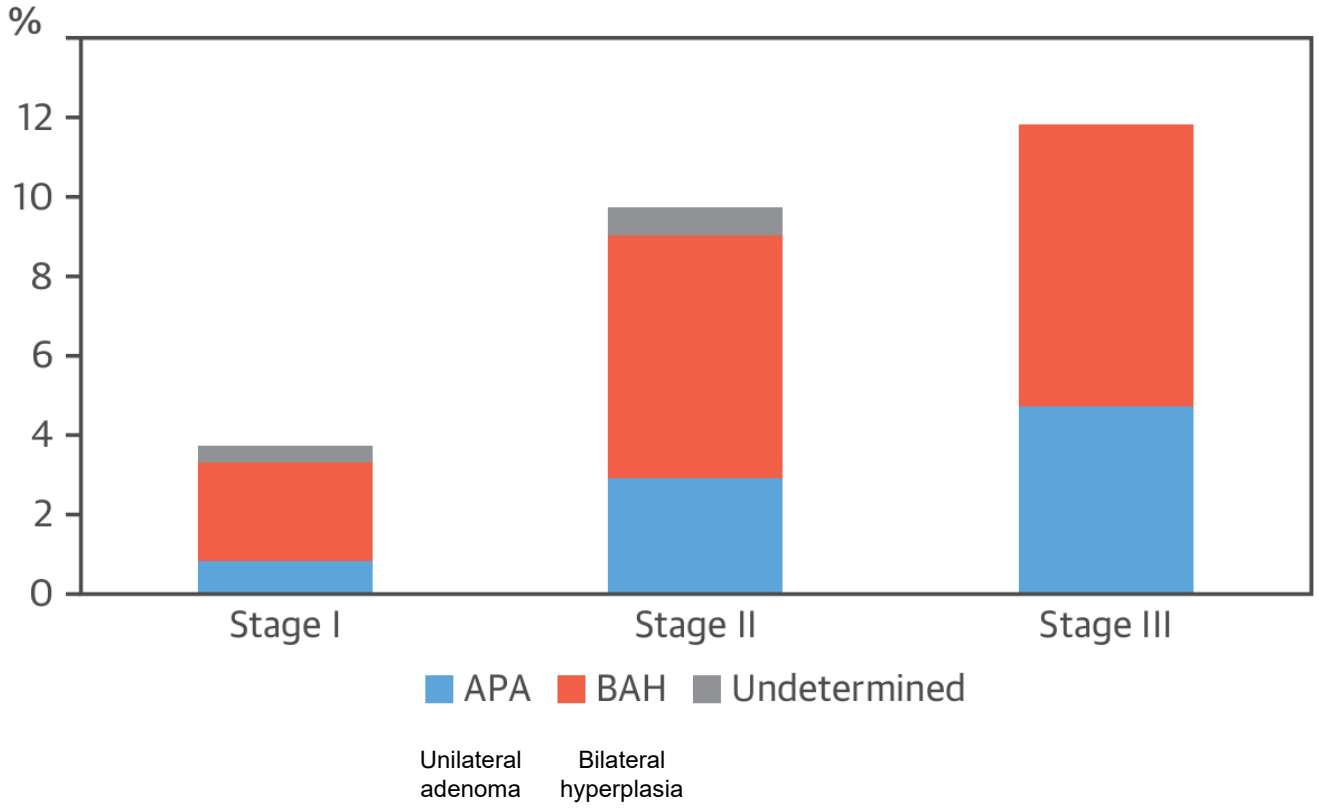
Young adrenal gland
Continuous ZG CYP11B2 expression

Older adrenal gland
Discontinuous ZG CYP11B2 expression with APCC



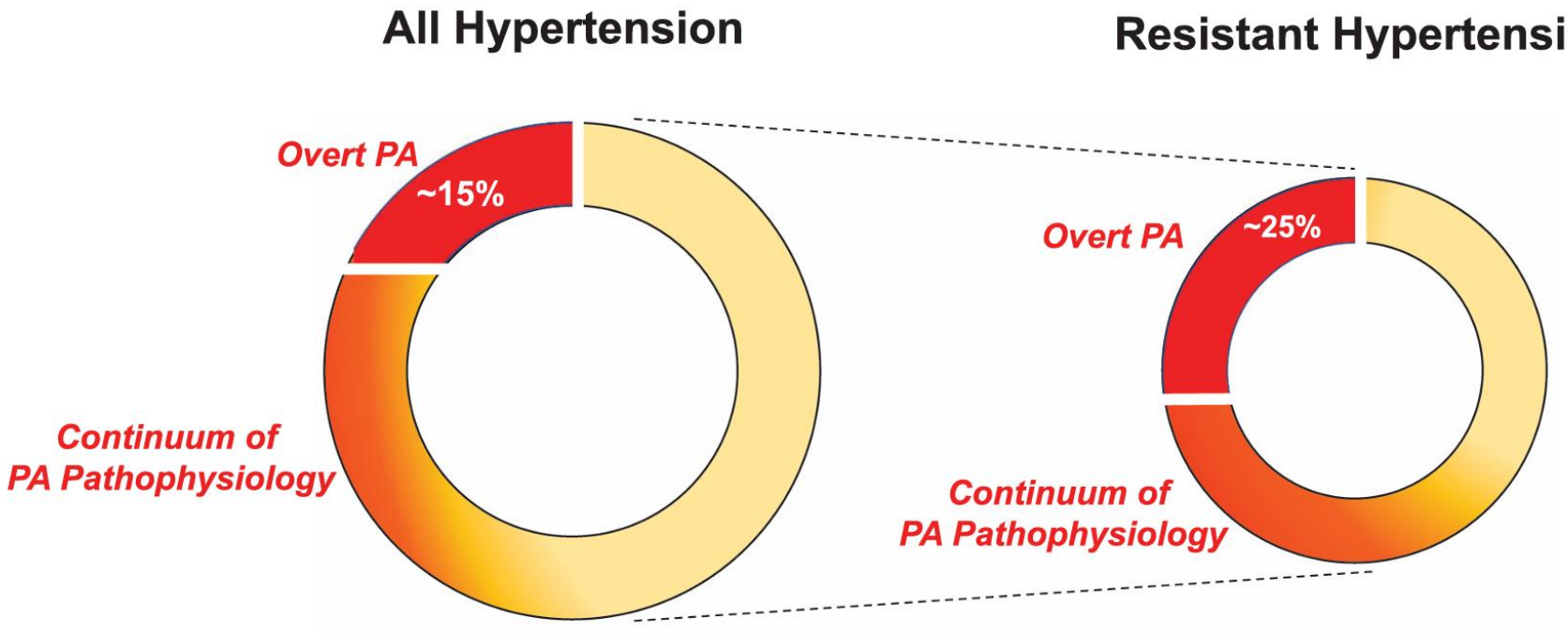
A, et al. J Clin Endocrinol Metab. 2013;98:1409–16; 2. Baudrand R, et al. Hypertension. 2017;69:950–6

Prevalenza dell'iperaldosteronismo primario



Monticone et al. Prevalence and Clinical Manifestation of PA. JACC 2017, 69: 1811-20

Prevalenza dell'iperaldosteronismo primario



Vaidya et al.. Am J Hypertens. 2022

PA: booster del rischio CV

Aldosterone Dysregulation vs Essential HTN[a]:	
Outcome	**OR (95% CI)**
CAD	1.77 (1.10-2.83)
Atrial Fibrillation	3.52 (2.06-5.99)
Heart Failure	2.05 (1.11-3.78)
Stroke	2.58 (1.93-3.45)

Monticone et al. CV events and HMOD in PA compared with essential HT. Lancet Diabets Endocrinol. 2018

PA: indicazioni allo screening

	Association of endocrin. 2006	Endocrine society 2016	French Society of HT 2016	ESH 2023	ESC 2024	Endocrine society 2025
Resistant HT	■	■	■	■	■	■
Unexplained or diuretic-induced hypokaliemia	■	■	■	■	■	■
HT < 40 years		■	■	■	■	■
Adrenal incidentaloma		■	■	■	■	■
BP > 150 mmHg					■	■
All HT patients					■	■
HT with sleep apnea		■		■	■	■
HT with atrial fibrillation		■		■	■	■
Extensive target organ damage			■		■	■
Suspected familial form		■			■	■

PA: indicazioni allo screening

Highest priority
Resistant HT, HT with hypokaliemia

High priority
Young HT patients, adrenal incidentaloma + HT

Moderate priority
Severe HT, severe organe damage, AF, OSAS

Low priority
Older patients, with well-contolled HT

Amar, ESH Congress 2025

Screening del PA: considerazioni generali

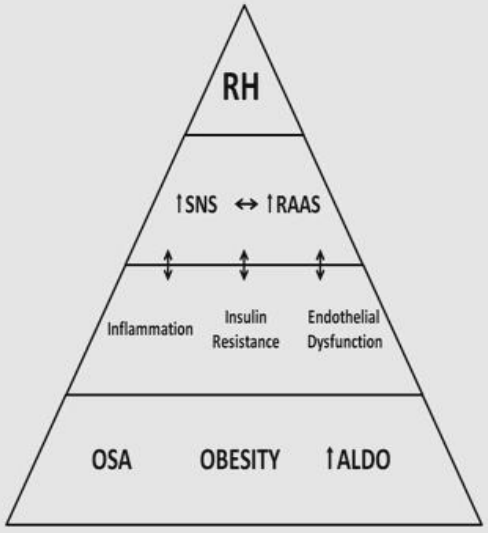
- Il test di screening consiste nel dosaggio dell'aldosterone plasmatico e della renina, interpretando il loro rapporto (rapporto aldosterone-renina, ARR)
- l'ARR dipende dal tipo di **test utilizzato e dalle unità**
- Le tecniche di dosaggio e gli standard variano **a seconda del laboratorio**
- La determinazione del cut-off diagnostico è complessa
- Ampia **variabilità inter- ed intraindividuale**

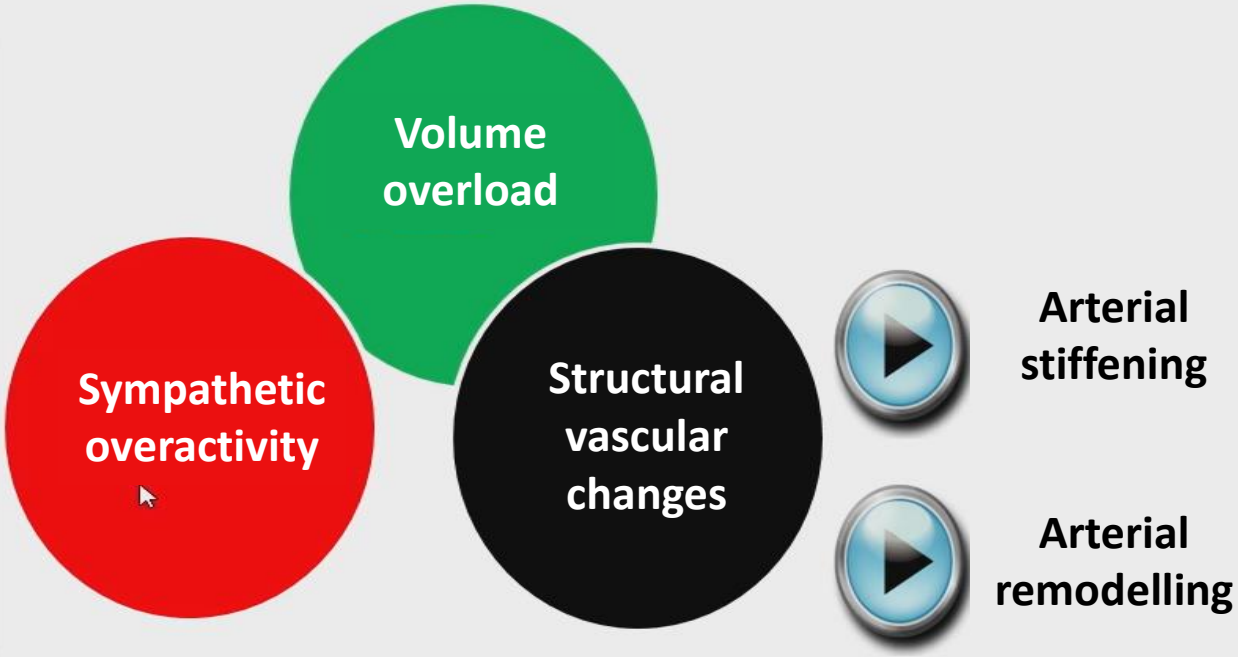
Screening del PA: considerazioni generali

- Necessità di **standardizzare le condizioni** per ridurre al minimo i risultati falsi positivi e falsi negativi:
  - Interrompere farmaci interferenti
  - Ottimizzare gli apporti di sale ed il potassio plasmatico
  - Test più sensibile se eseguito al mattino
  - Prelievo da via venosa (ad es. venflonTM) per evitare l'aumento della renina indotto dallo stress

Sembra semplice, ma…

Meccanismi implicati nella «resistenza»

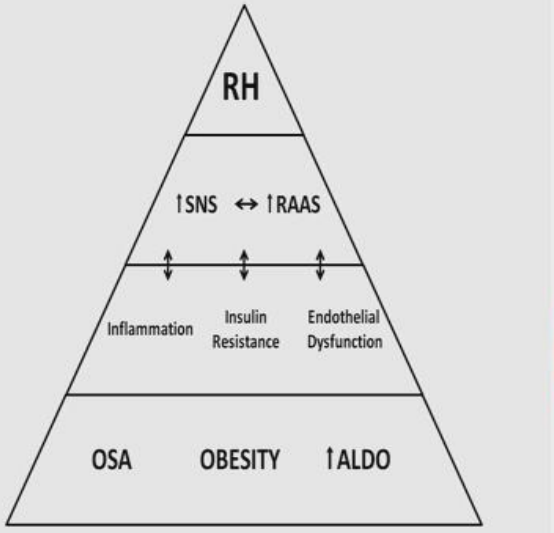


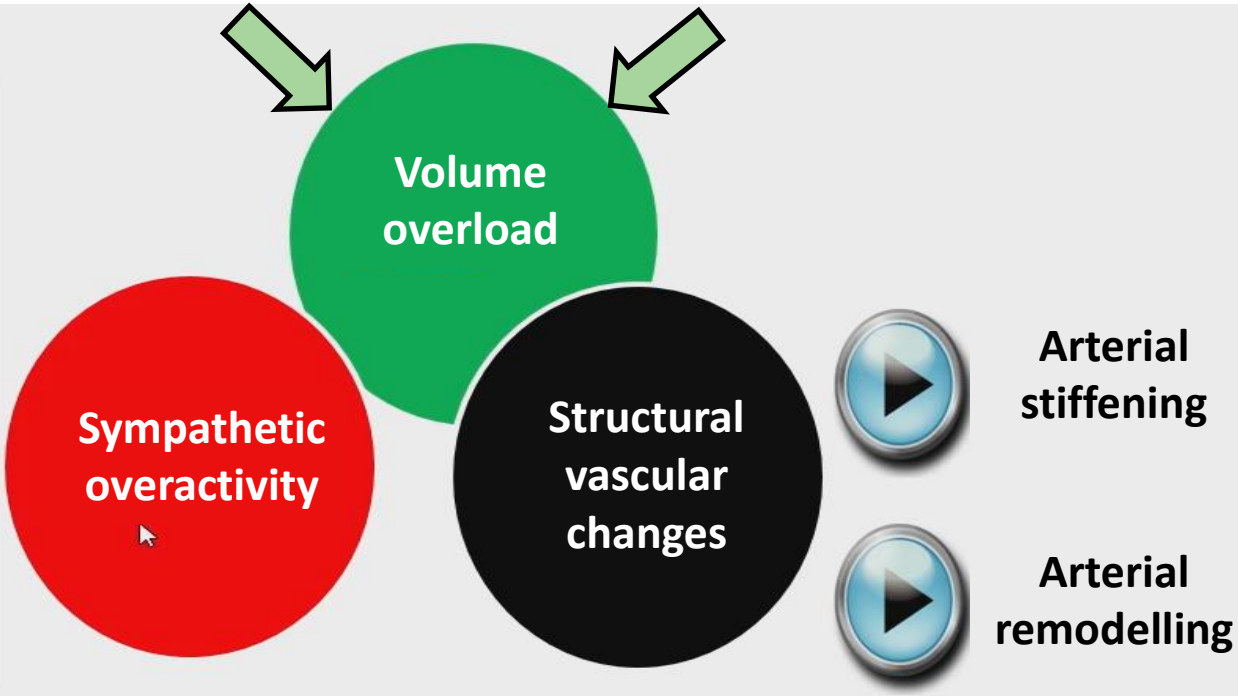


Tsioufis et al. J International J Hypertension, 2010

Il ruolo della deplezione di sodio

Dieta povera in sodio **Diuretici**





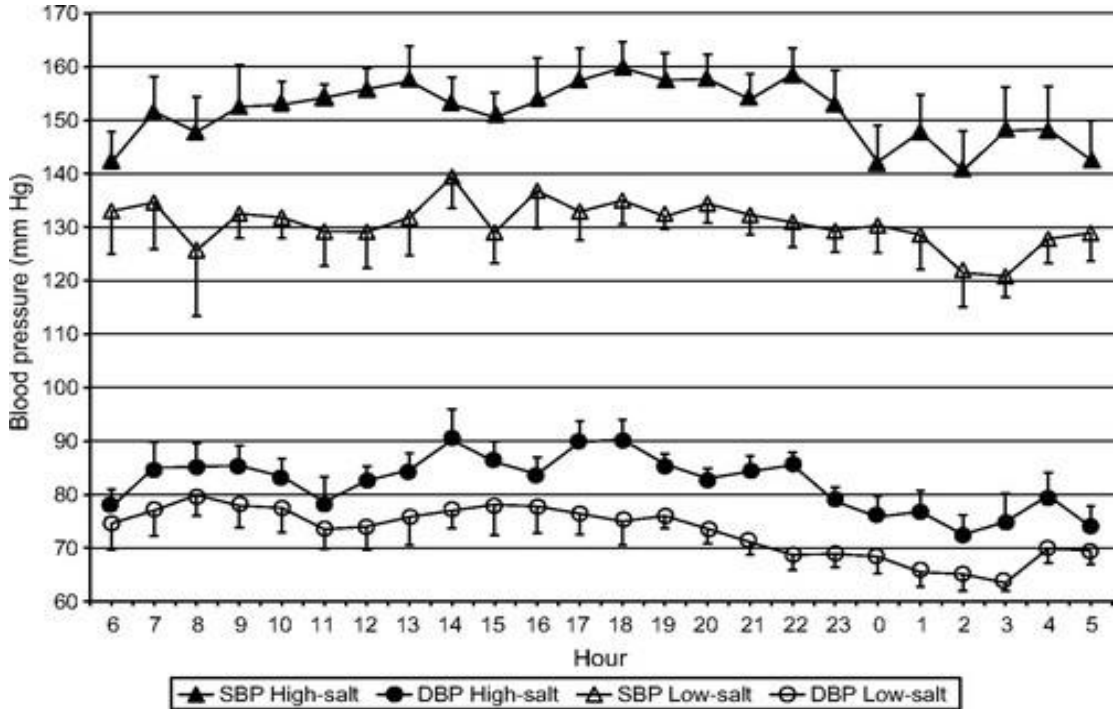
Tsioufis et al. J International J Hypertension, 2010

Dieta ricca vs. povera in sale

N = 12 HTr patients

Cross-over study

Mean daytime SBP/DBP ⇩ 20.7/9.6 mmHg



High salt diet: 15 g/24h

Low salt diet: 3 g/24h

High salt diet

Low salt diet

Pimenta et al. Hypertension, 2009

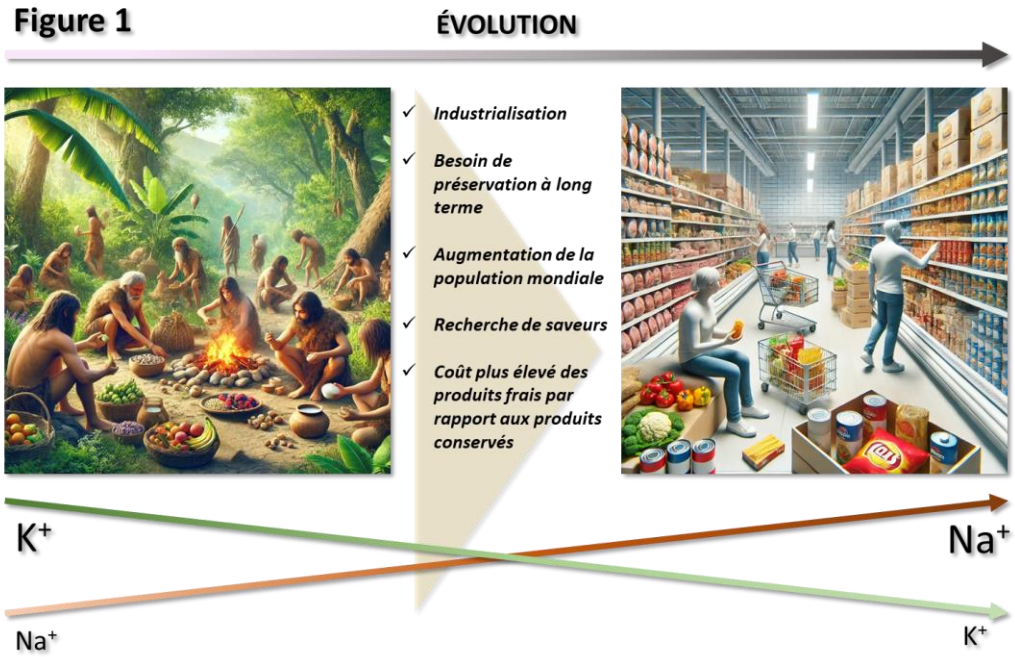
Interventi di lifestyles

Lifestyles intervention		
Weight reduction	1	A
Dietary salt restricion < 5g/day	1	B
Increase dietary potassium	1	B
Salt substitutes (KCl)	1	A
Daily physical activity	1	B
Alcohol intake reduction	1	B
Smoking cessation	1	B
Stress reduction	2	C

Lifestyle changes - reccomendations, ESH Guidelines, 2023

Sodio e potassio

Figure 1



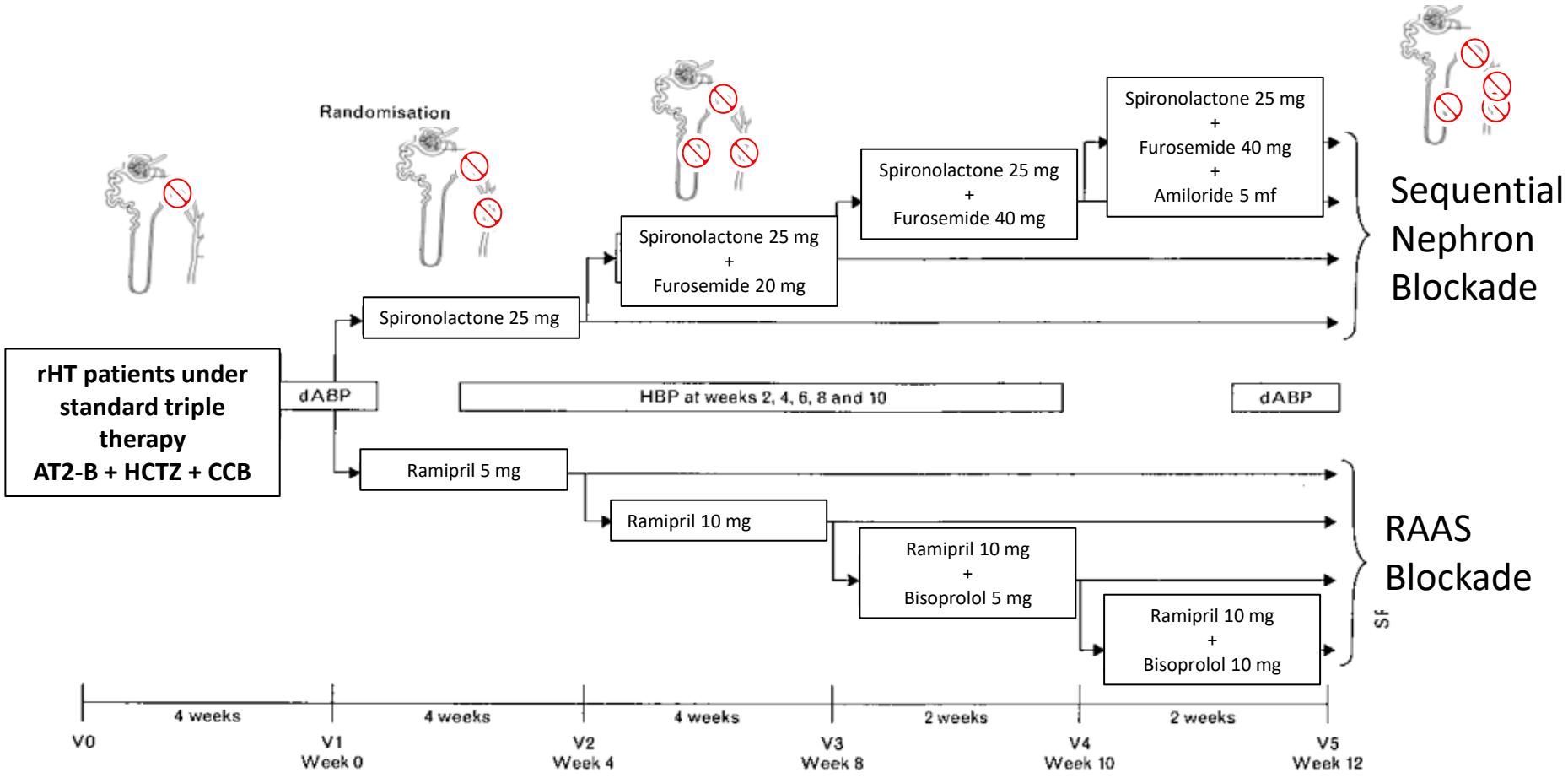
≃10 g	250 mmol	**K⁺**	60 mmol	≃ 2,5 g
≃0,6 g	10 mmol	**NaCl**	150 mmol	≃ 9,0 g

25 **Ratio K⁺/NaCl** 0,4

Raccomandations OMS	
K⁺	**> 3,5 g/j**
NaCl	**< 5,0 g/j**

Cozzo et al, Sel, potassium et hypertension artérielle : un ménage à trois. RMS, 09.2025

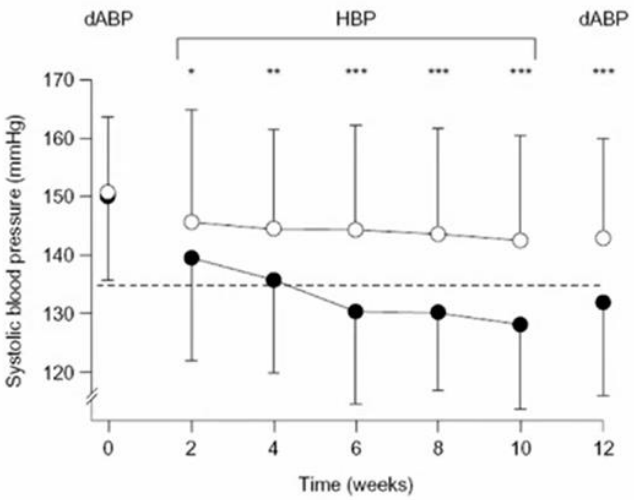
Strategie farmacologiche a confronto



Bobrie et al. J Hypertension, 2012

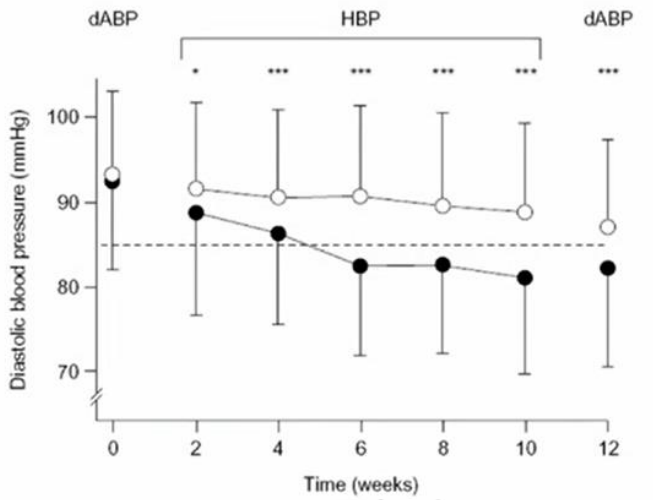
Strategie farmacologiche a confronto

● Sequential Nephron Blockade
○ Sequential RAAS Blockade



Mean difference in dABP

SBP: 10 mmHg (95% CI 7-14 mmHg)



Mean difference in dABP

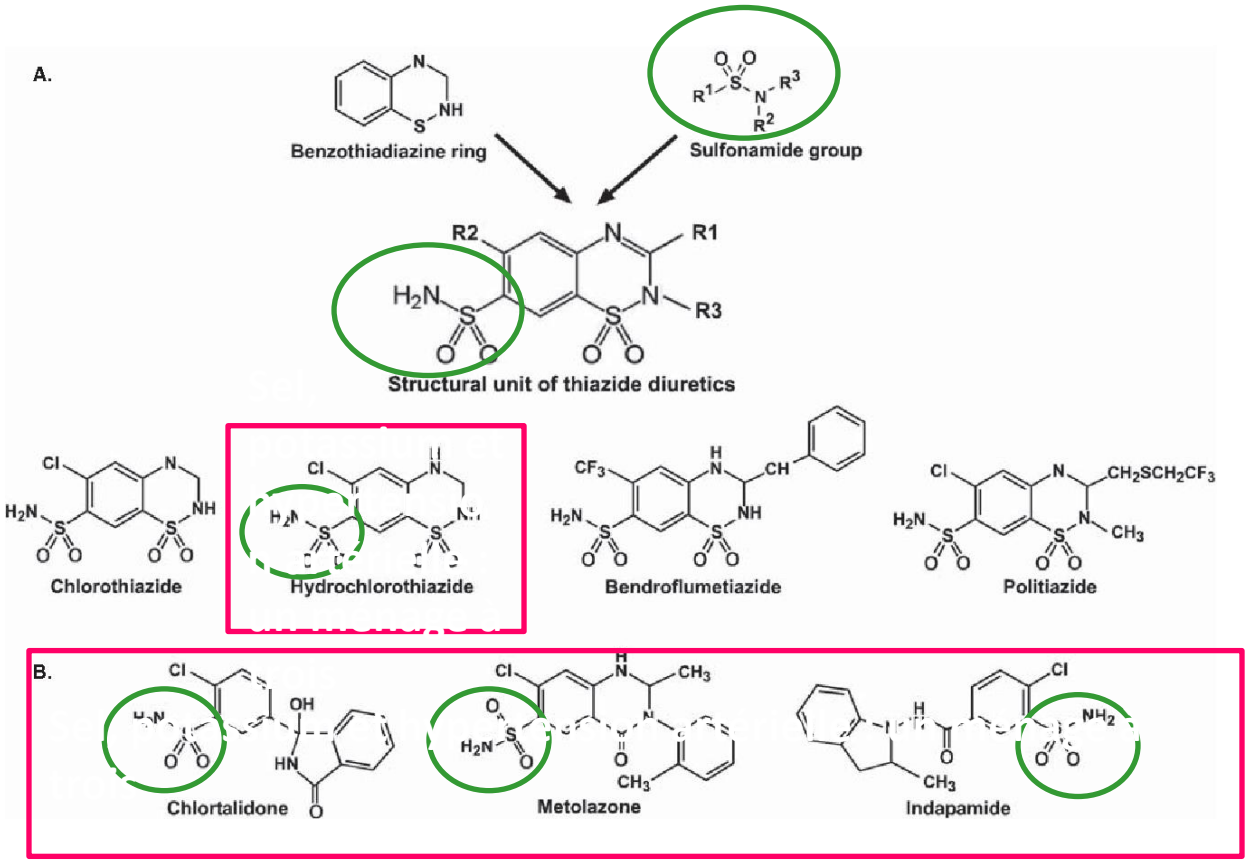
DBP: 4 mmHg (95% CI 2-7 mmHg)

Ernst et al. N Engl J Med, 2009

Diuretici a confronto

Tiazidici

Tiazidici-like



Diuretici a confronto

	HCTZ	Indapamide	CLT
T1/2 (h)	6-15	12-24	40-60
Equidosis (mg)	25 mg	1.5	12.5

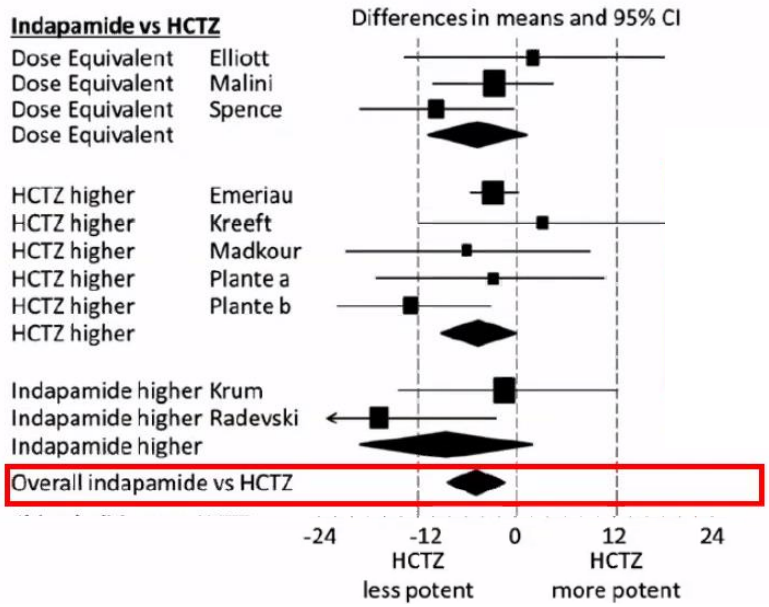
	HCTZ	Indapamide	CLT
K_{pl}	-	- -	- - -
$Glucose_{pl}$	+	≠	+
$Uric\ acid_{pl}$	+	++	++
$Lipid_{pl}$	+	≠	+/-
GFR	-	≠	-

HCTZ = Hydrochlorothiazide, CLT = Chlortalidone

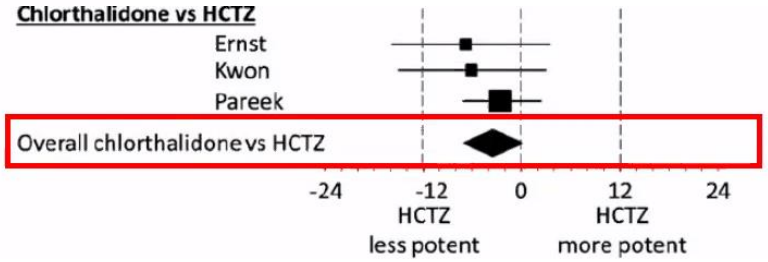
Ernst et al. N Engl J Med, 2009

Tiazidici-like >> HCTZ

Indapamide vs HCTZ on SBP



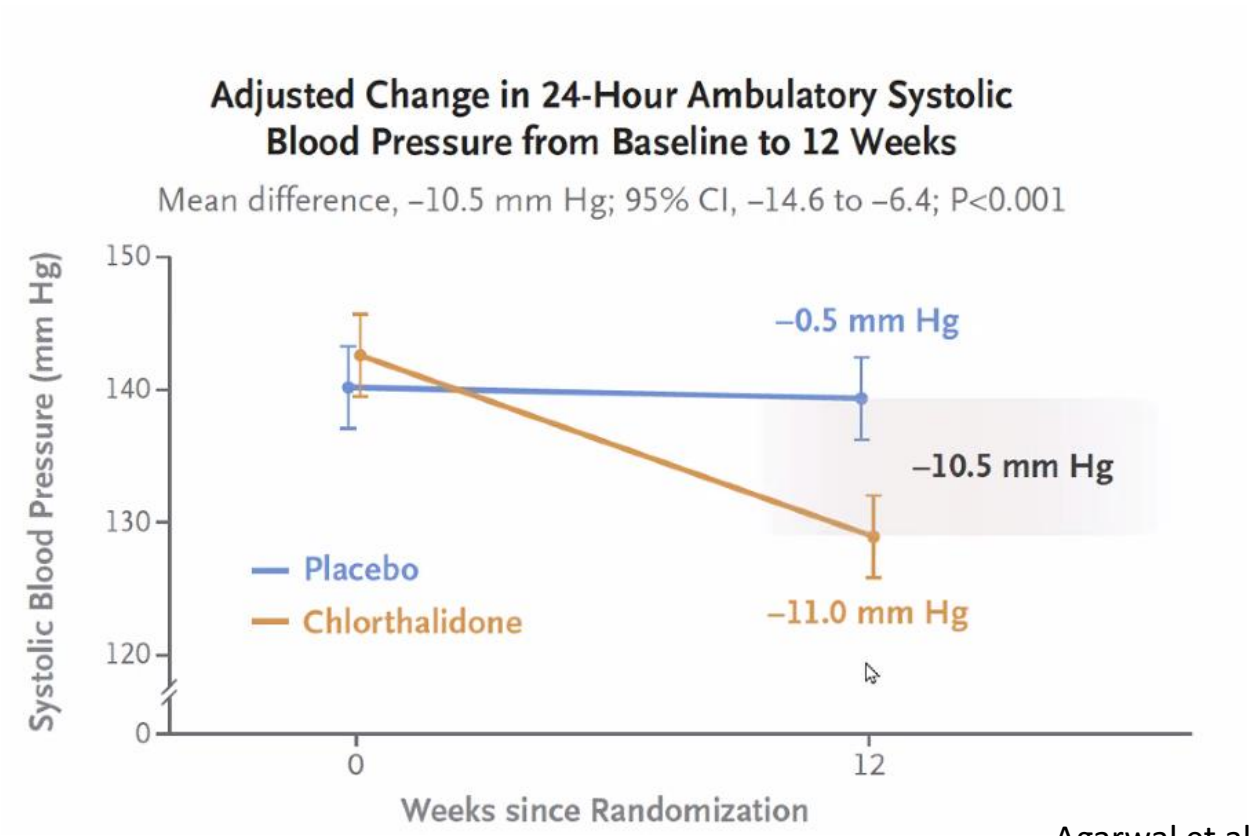
Chlortalidone vs HCTZ on SBP



Roush et al. Hypertension, 2015

Clortalidone

160 patients with CKD Stage 4 (eGFR 15-30 ml/min/1.73m2)
Treated, uncontrolled HT (confirmed by 24h-ABPM)
R: Chlortalidone vs Placebo; initial dose 12.5 mg, increases every 4 weeks to 50 mg

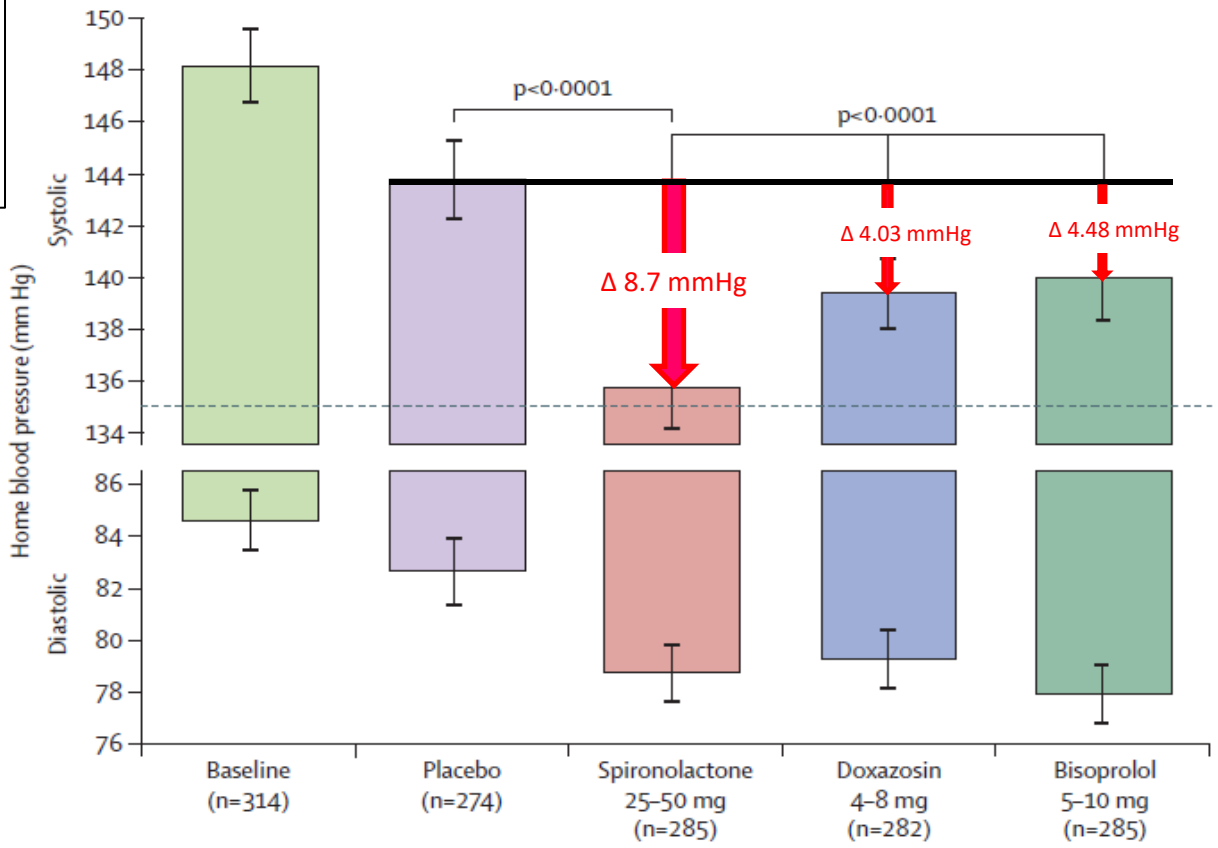


Agarwal et al. N Engl J Med, 2021

Spironolattone è 1. scelta in rHT

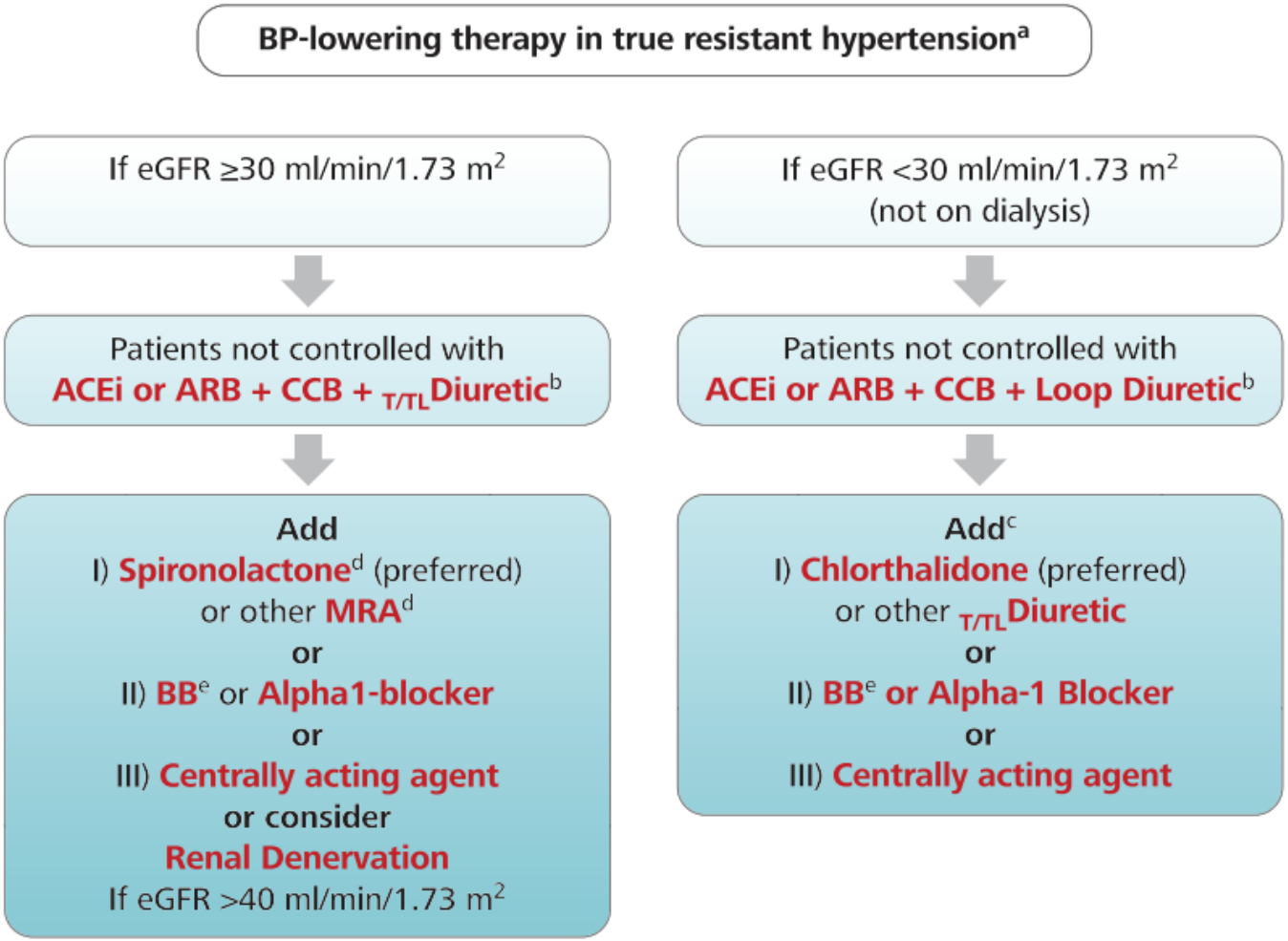
rHT patients under standard triple therapy
RAAS-B + HCTZ + CCB

Effect after 6-weeks therapy on BP



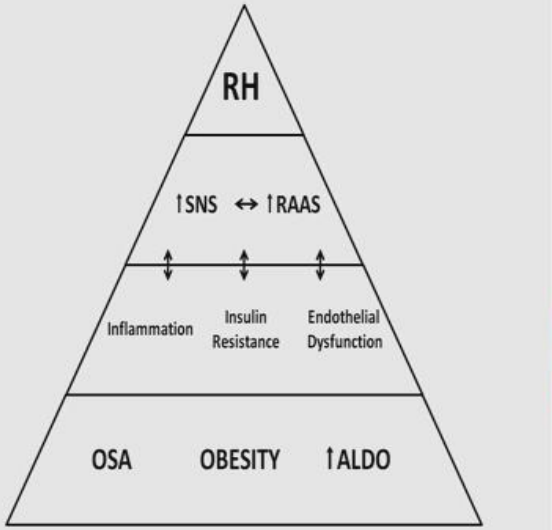
Williams B et al. Lancet Diabetes Endocrinol, 2018

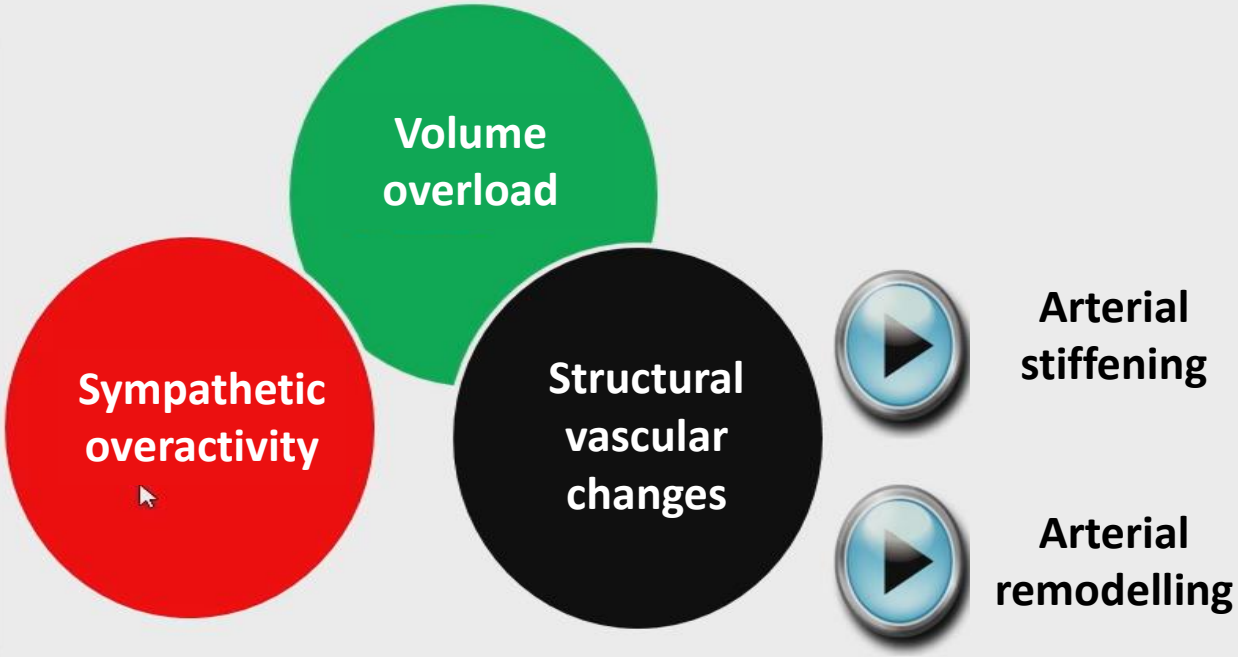
Linee guida



ESC-ESH Guidelines, 2023

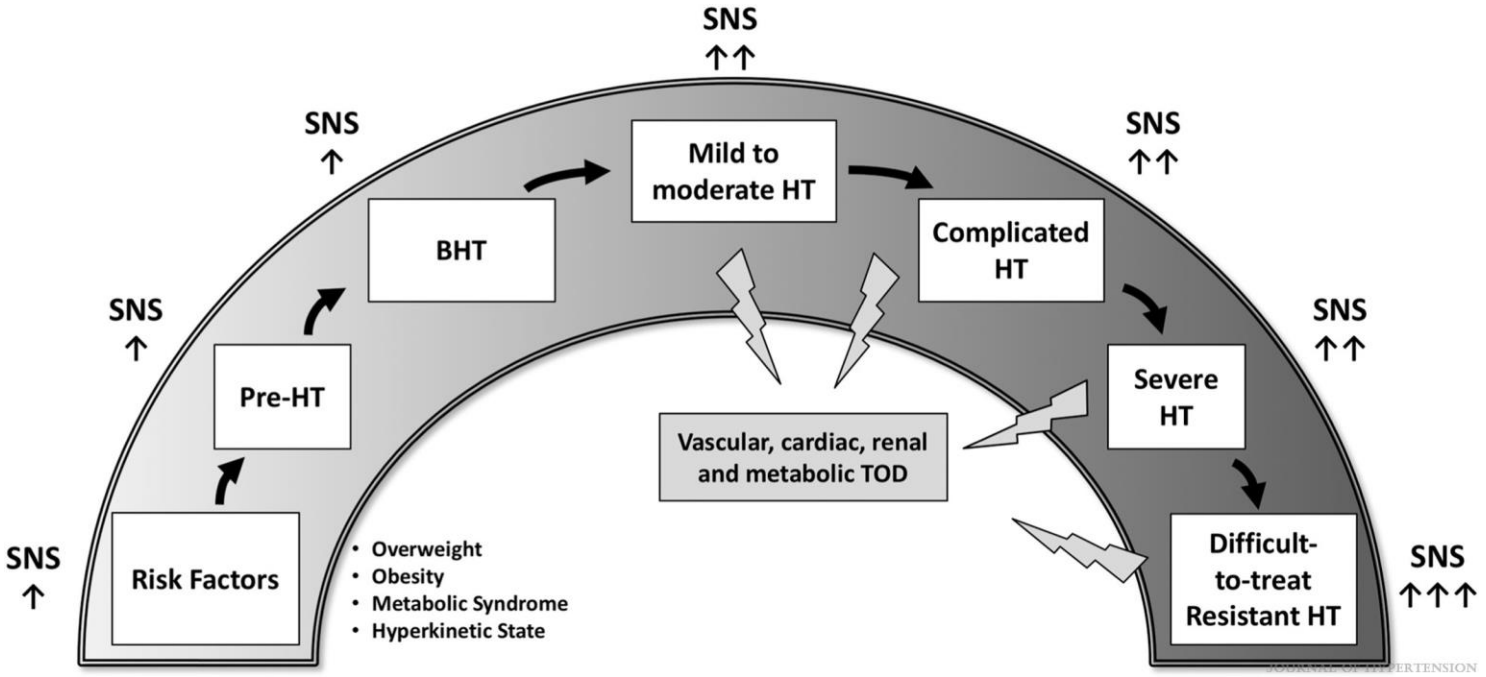
Overdrive del sistema simpatico





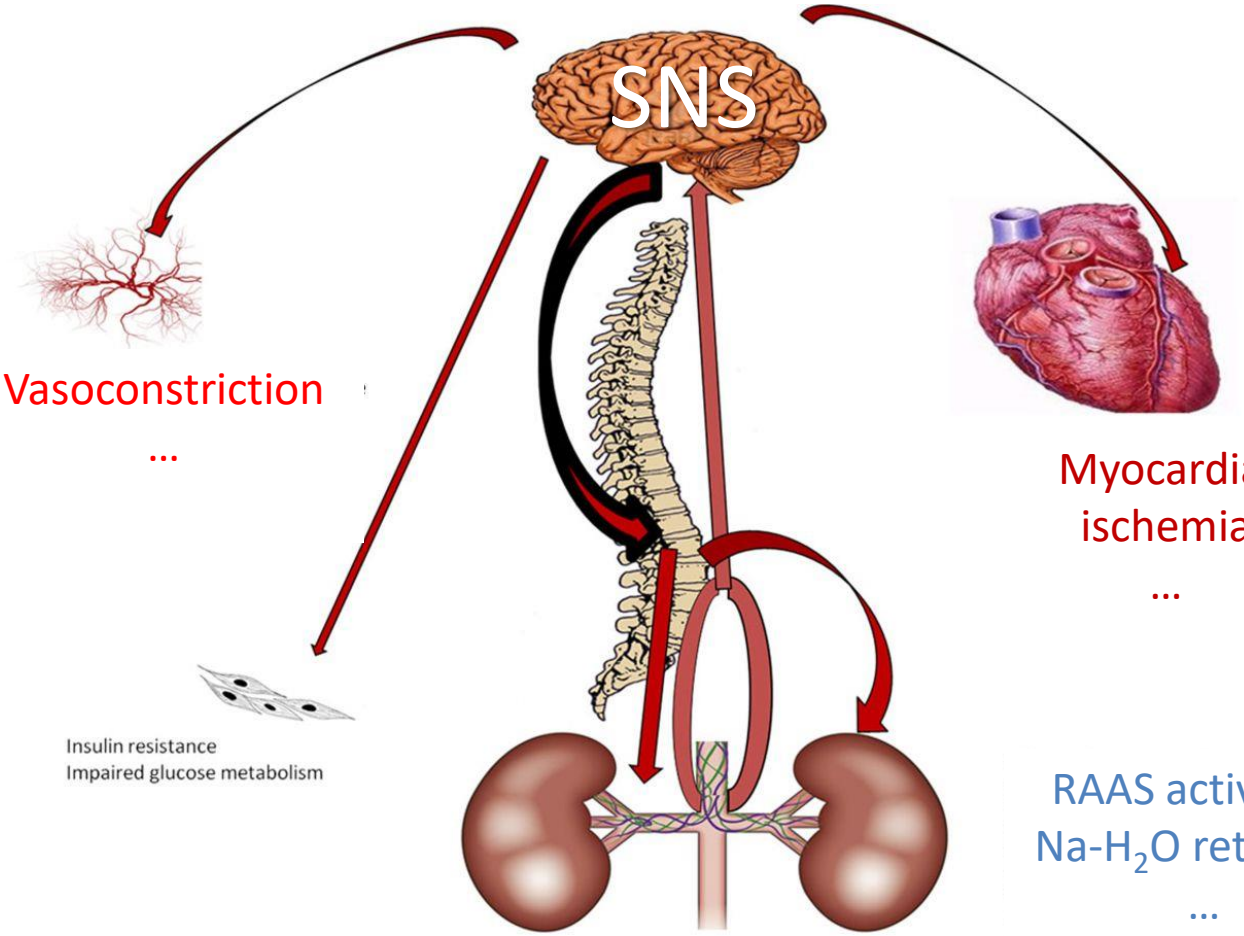
Tsioufis et al. J International J Hypertension, 2010

Overdrive del SNS



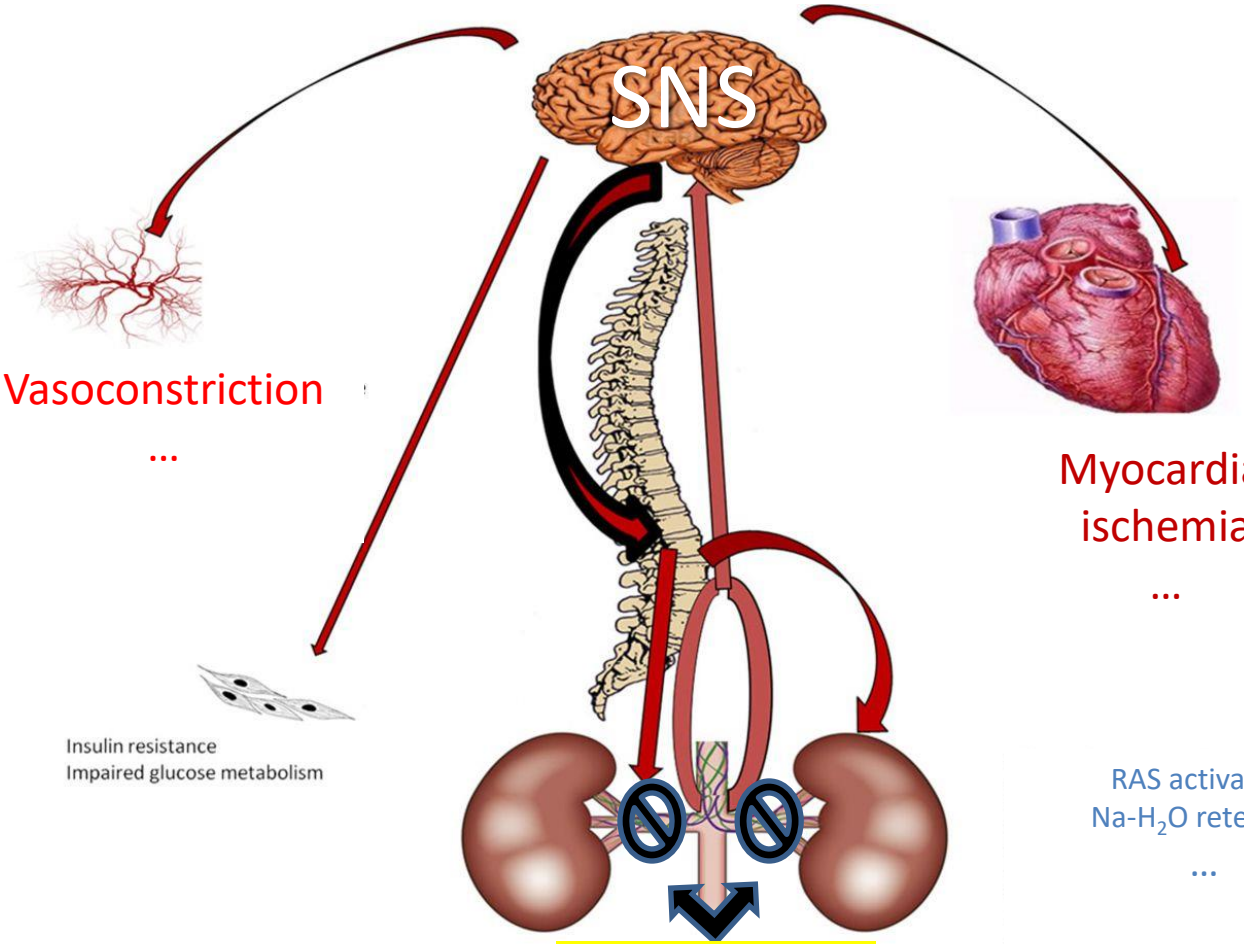
Grassi et al. J International J Hypertension, 2023

Overdrive del SNS



P ılation, 2014

Implicazioni terapeutiche



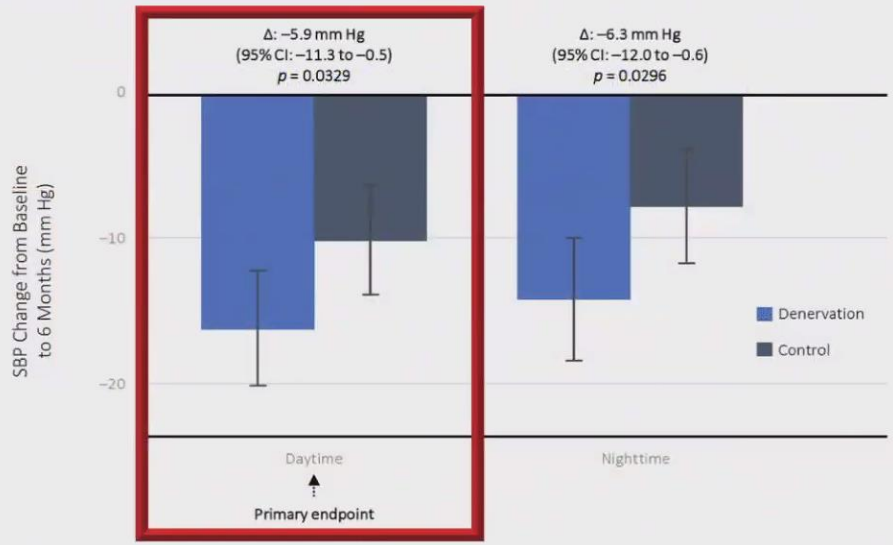
Papademetriou et al. J Circulation, 2014

DNR: efficacia a breve termine

DENER-HTN

Azizi M, et al., Lancet 2015

CHANGE IN AMBULATORY SBP @ 6 MONTHS



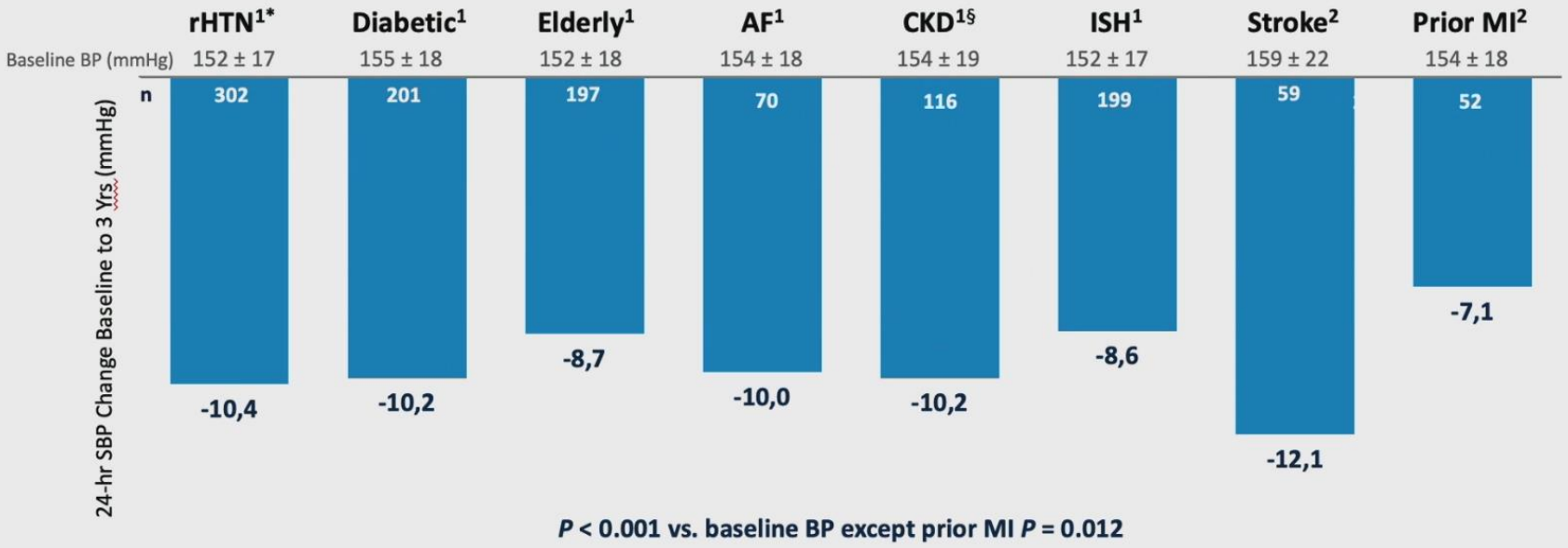
RENAL DENERVATION SUPERIOR TO OPTIMAL MEDICAL THERAPY ALONE

DNR: efficacia a lungo termine

GLOBAL SYMPLICITY REGISTRY (GSR)

Mahfoud F, et al., EuroPCR conference, Paris, 2022

CHANGES IN 24-HOUR SYSTOLIC BLOOD PRESSURE @ 3 YEARS IN HIGH-RISK SUBGROUPS



P < 0.001 vs. baseline BP except prior MI *P* = 0.012

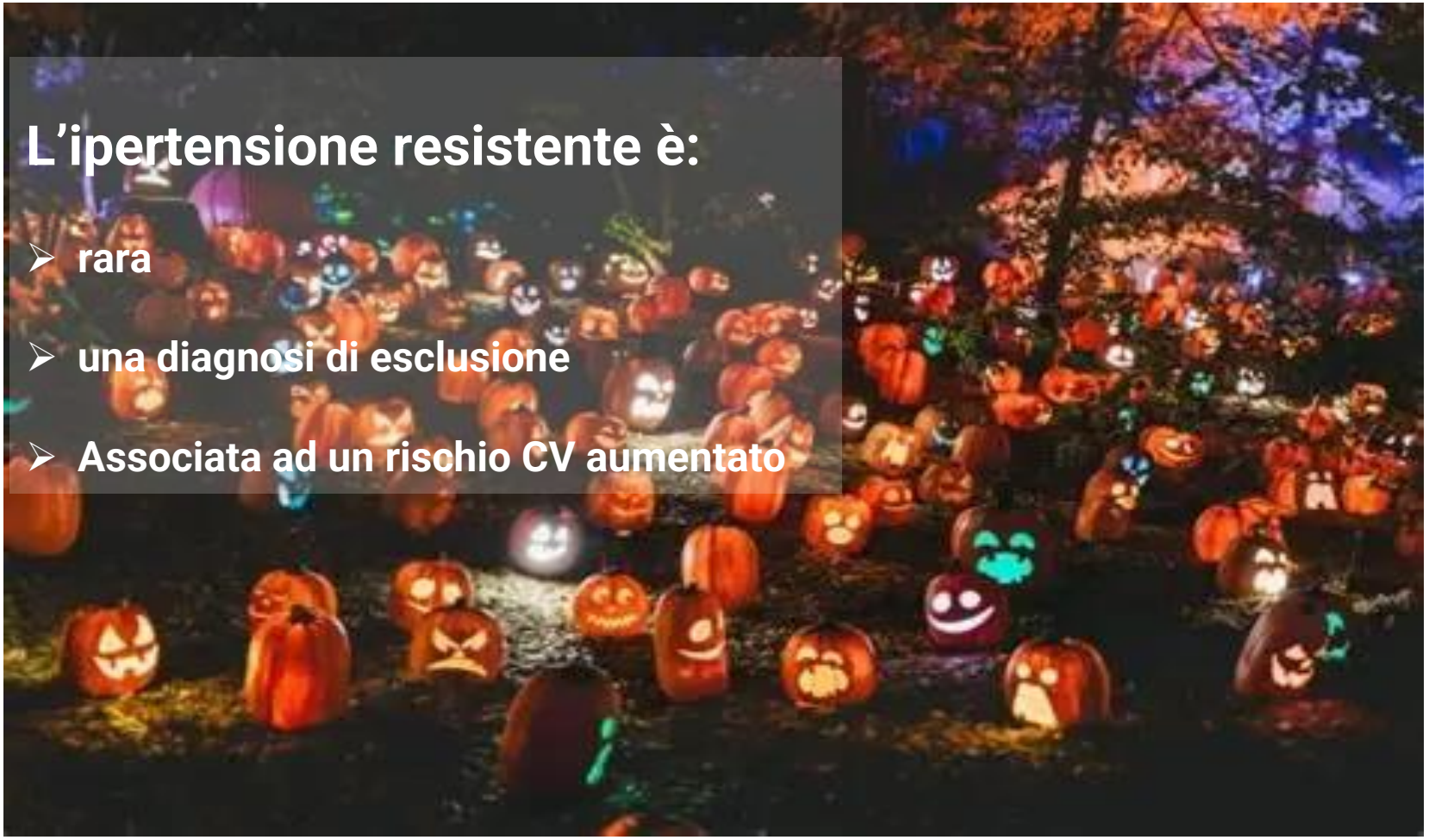
Denervazione renale

Use of renal denervation

Recommendations and statements	CoR	LoE
RDN can be considered as a treatment option in patients with an eGFR >40 ml/min/1.73m^2 who have uncontrolled BP despite the use of antihypertensive drug combination therapy, or if drug treatment elicits serious side effects and poor quality of life.	II	B
RDN can be considered as an additional treatment option in patients with true resistant hypertension if eGFR is >40 ml/min/1.73m^2.	II	B
Selection of patients to whom RDN is offered should be done in a shared decision-making process after objective and complete patient's information.	I	C
RDN should only be performed in experienced specialized centers to guarantee appropriate selection of eligible patients and completeness of the denervation procedure.	I	C

ESC-ESH Guidelines, 2023

Take home messages



Take home messages

Il nostro ruolo é “scardinare" l’ipotesi della resistenza:

- Identificando i fattori di "pseudo-resistenza"
- Ottimizzando la terapia farmacologica e comportamentale
- Escludendo le forme secondarie

Take home messages

La stategia terapeutica in caso di “true rHT” é:

- Rinforzare le misure comportamentali
- Rinforzare la terapia diuretica
- Considerare la denervazione renale come aggiunta o alternativa alla terapia farmacologica

RECIPE FOR SUCCESS

1. Appropriate treatment
2. Adherent patient
3. Proactive – «inertia-free» physician

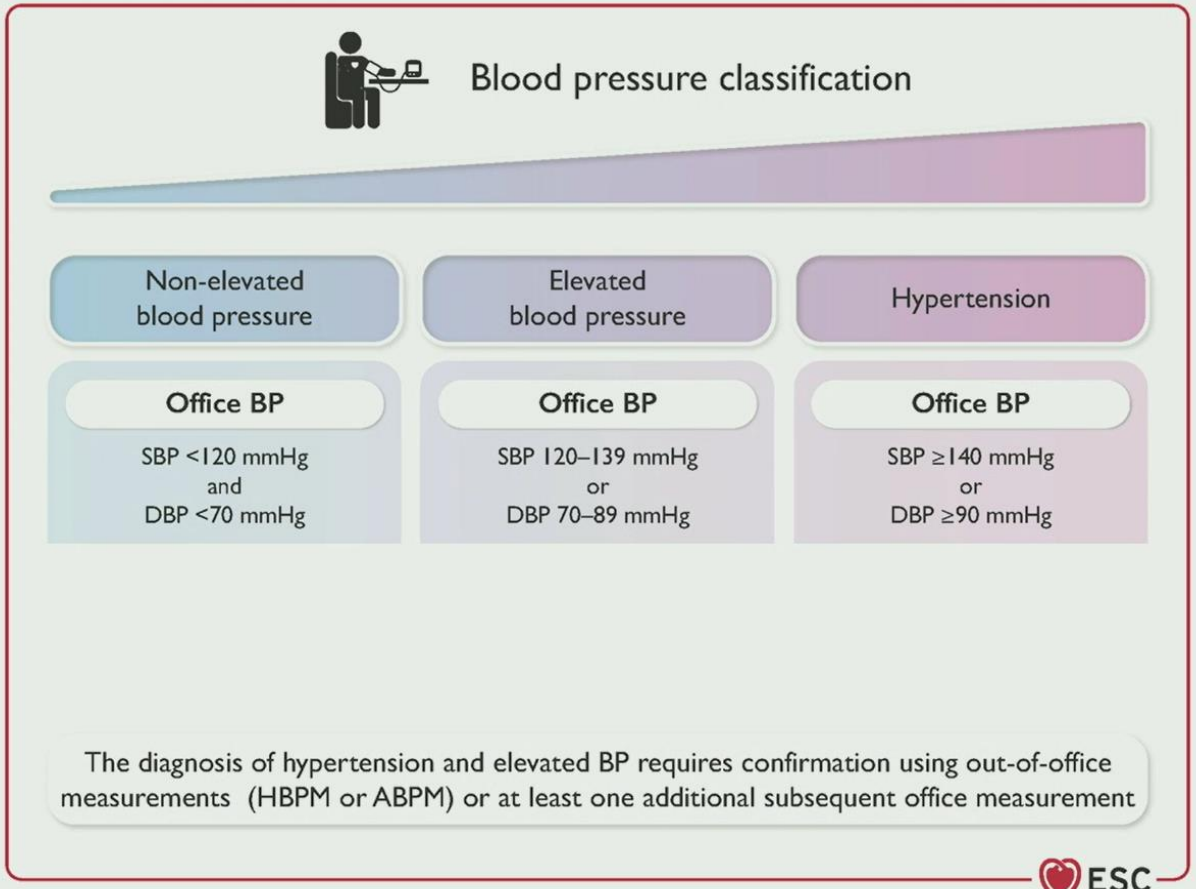
New 2024 ESC categories

Simplified to:

-Non-elevated
<120/70 mmHg

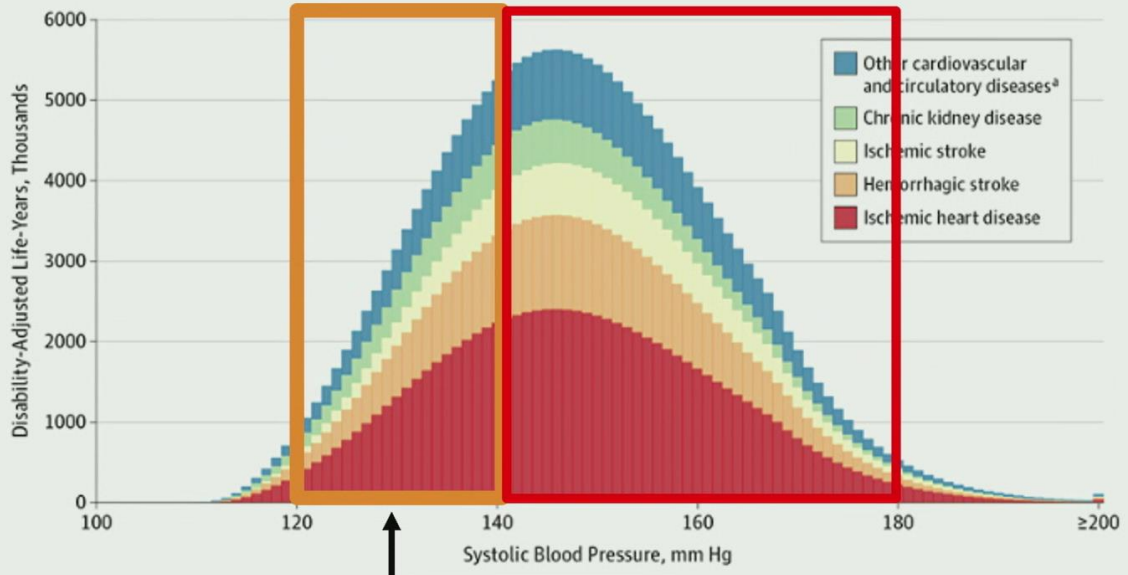
-Elevated
120-139/70-89 mmHg

-Hypertension
≥140/90 mmHg



Large burden of CVD events occurring among individuals with elevated BP

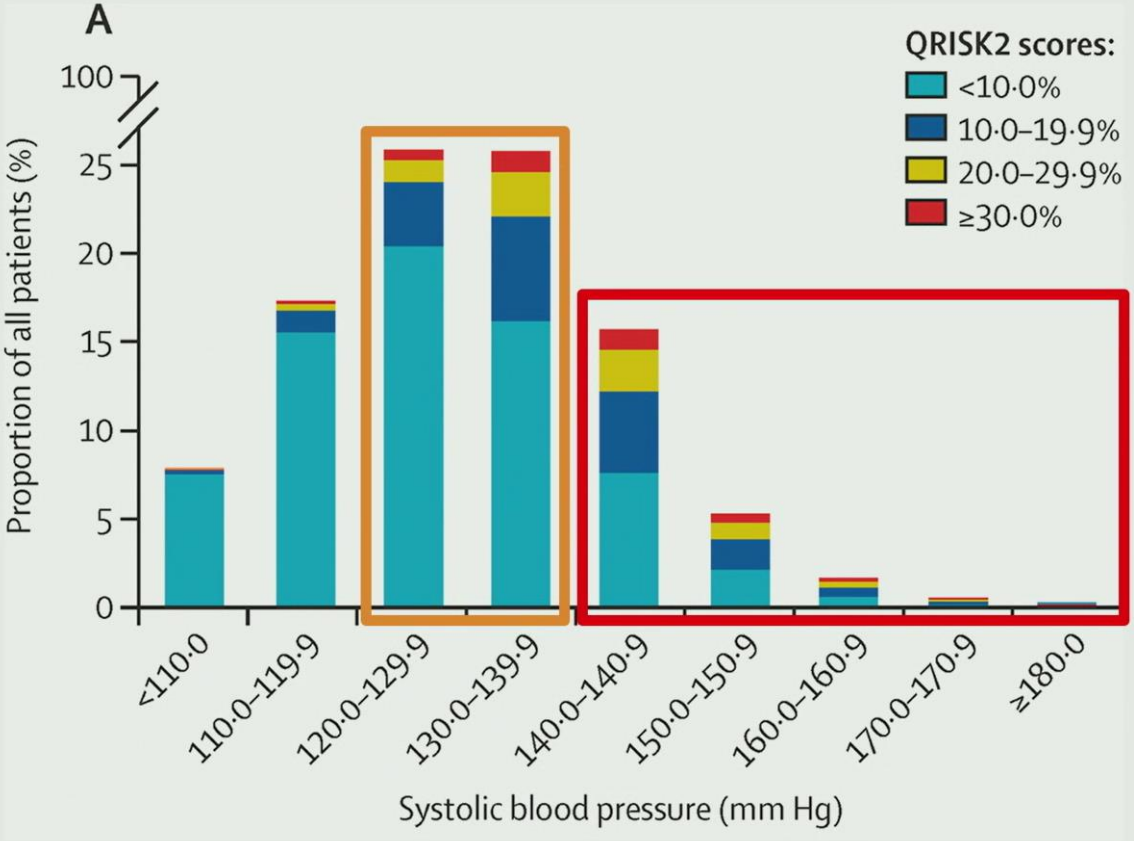
Figure 2. Projected Global Disability-Adjusted Life-Years by Systolic Blood Pressure Level and Cause, 2015



~ 30% of the disability adjusted life years (DALYs) lost related to CVD occur in individuals with SBP between ~120 - 140

Forouzanfar MH, et al. JAMA. 2017;317:165-182

Cardiovascular risk stratified by BP



Herrett E, et al. Lancet Healthy Longev. 2022; 3:e22-e30