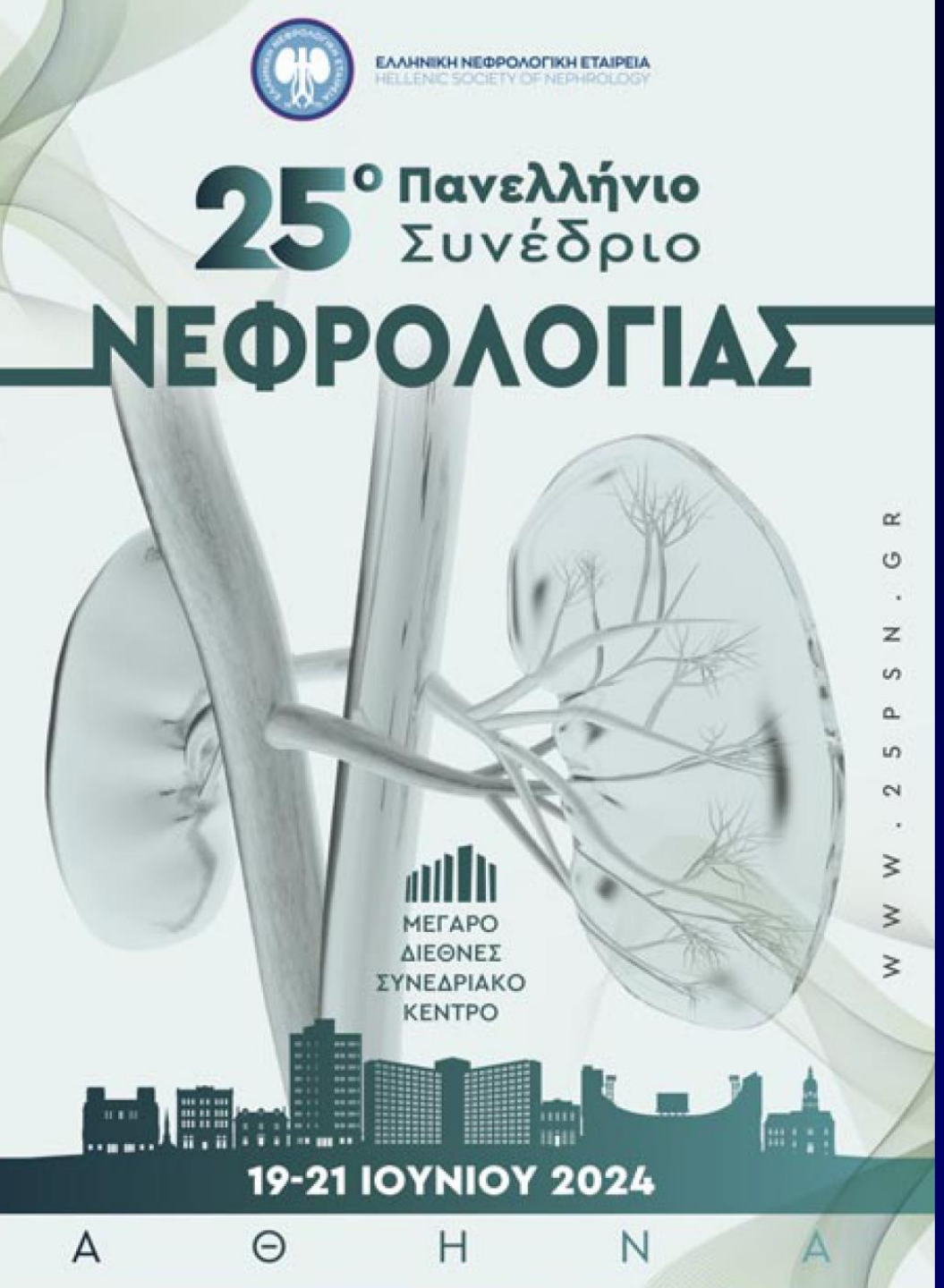

Resistant Hypertension in CKD

Pantelis A. Sarafidis, MD, MSc, PhD

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Chair, 1st Department of Nephrology,
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Thessaloniki, Greece

Disclosures

- Advisor to: Bayer, Astra-Zeneca, Primeview, Healthink, Recor Medical, Boehringer Ingelheim, Menarini, Baxter and Astellas
- Speaker for: AstraZeneca, Bayer, Genesis Pharma, Astellas, Boehringer Ingelheim, Springer, Menarini , Peervoice, WebMD, AICME and Science Collected
- Institutional research support received from Boehringer Ingelheim, Genesis Pharma, AstraZeneca and Vianex
- Member of clinical trial committees for Bayer and CSL Behring
- Associate Editor, Journal of Human Hypertension; Theme Editor, Nephrology Dialysis and Transplantation
- Council Member, ERA; Chair, European Renal Best Practice (ERBP); Past Chair, “Hypertension and the Kidney” WG, European Society of Hypertension

Definitions of various forms of resistant hypertension

REVIEWS

Resistant hypertension—its identification and epidemiology

Pantelis A. Sarafidis, Panagiotis Georgianos and George L. Bakris

NATURE REVIEWS | NEPHROLOGY VOLUME 9 | JANUARY 2013 | 51

Sarafidis P, Georgianos P, Bakris G. Nature Reviews Nephrology 2012

Ανθεκτική Υπέρταση

Επιδημιολογία – Έμμεσα στοιχεία

Epidemiology of Resistant Hypertension
Indirect Evidence

For several years, information on epidemiology of Resistant Hypertension derived from 3 types of studies:

(1) retrospective cohort studies,

(2) data on the control of hypertension from population studies

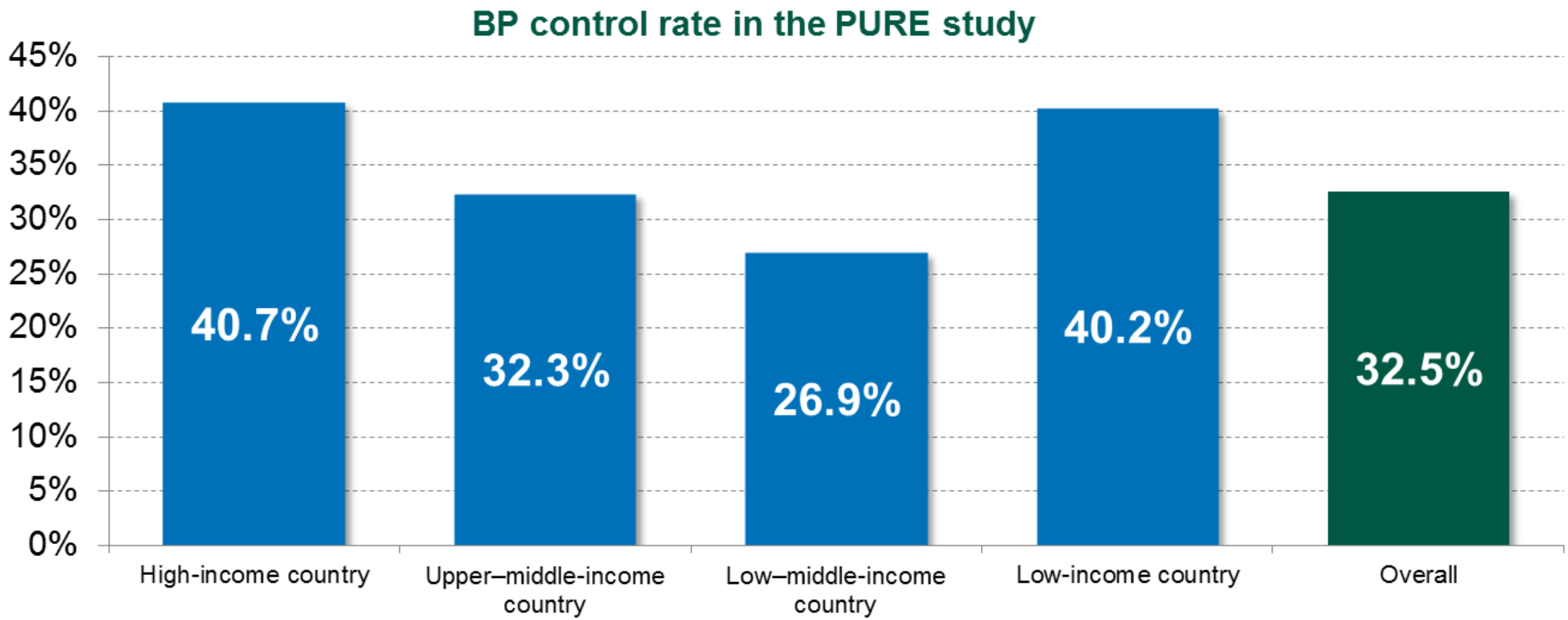
(3) data from the selected populations of major outcome trials

The prevalence was estimated depending on the population studied:

- General: 2-5 %
- Hypertension Centers/Nephrology Clinics: 15-50%

Sarafidis P. J Clin Hypertens 2011

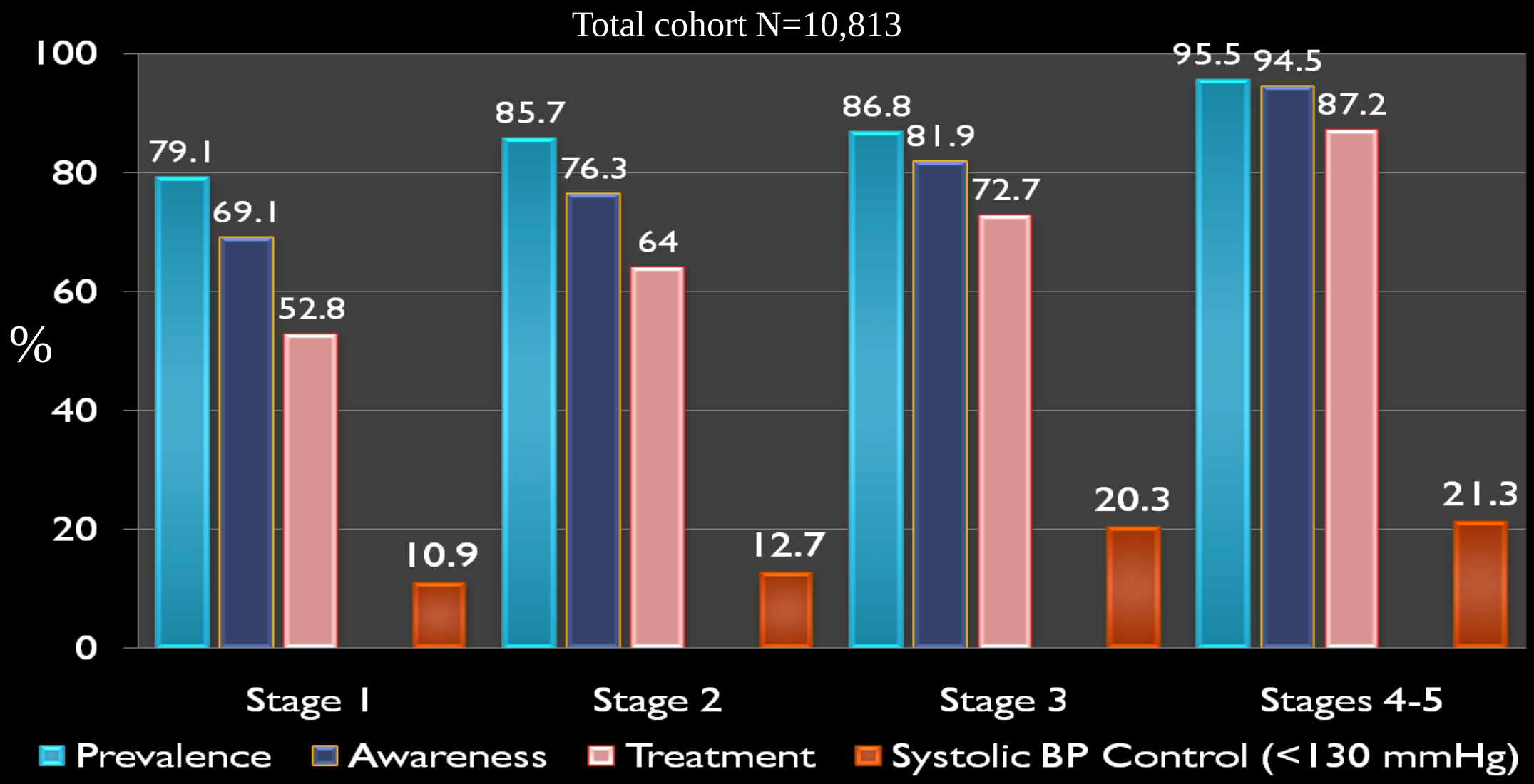
2 out 3 treated hypertensive patients have uncontrolled BP (17 countries



International, multicentre, cross-sectional study of 153 996 adults, 35-70 years old

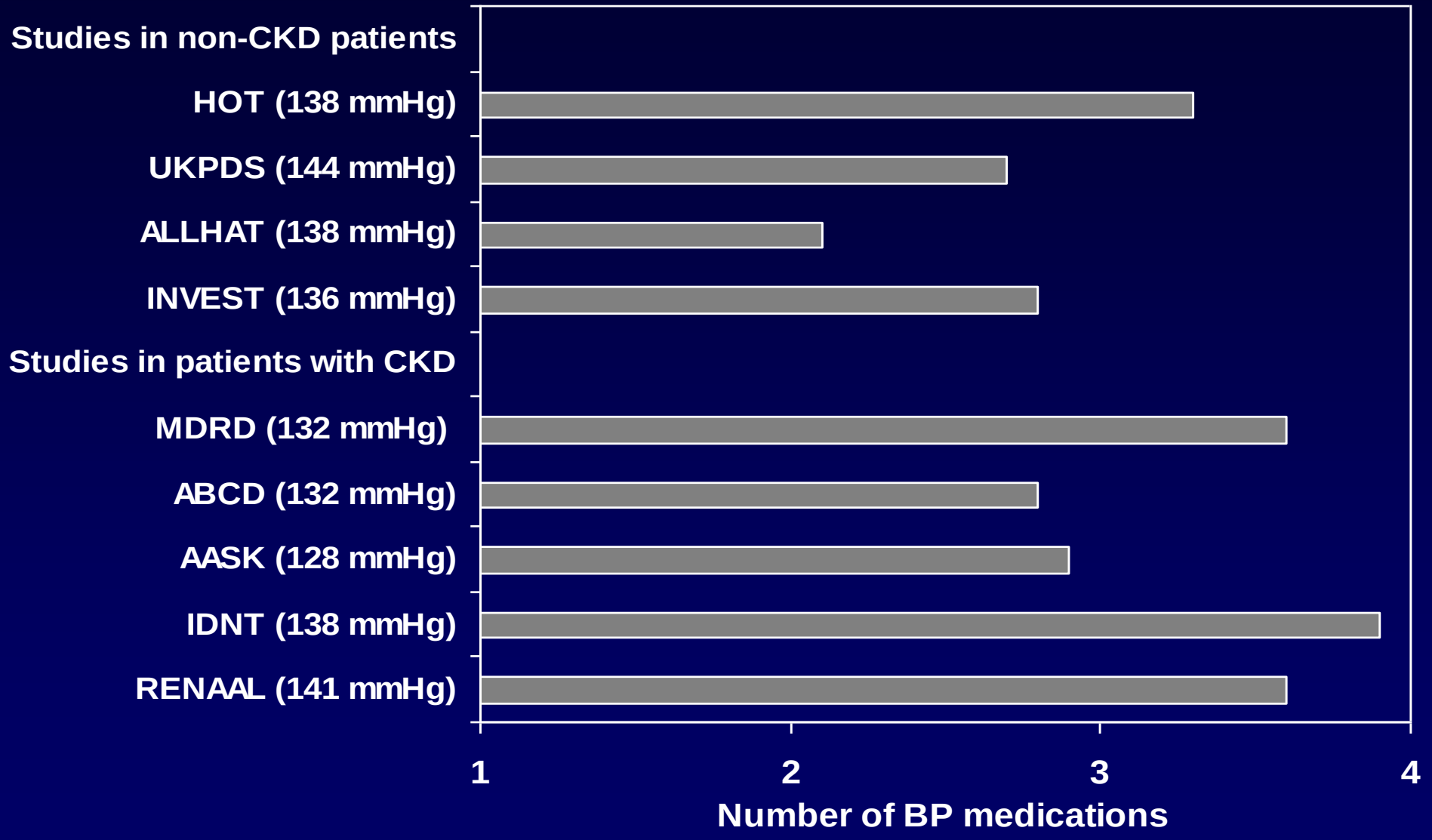
Chow CK et al. *JAMA*. 2013;310(9):959-968.

Prevalence, Awareness, Treatment, and Control of Hypertension to Goal (<130/80 mmHg) by CKD stage



Sarafidis P, et al. Am J Med 2008

Mean antihypertensive drug number in major outcome trials



Sarafidis PA & Bakris GL, J Clin Hypertens 2008

Ανθεκτική Υπέρταση

Επιδημιολογία – Άμεσα στοιχεία σε ασθενείς με και χωρίς ΧΝΝ

Prevalence of Resistant Hypertension

• An accurate determination of RH prevalence would require prospective cohort studies in a large hypertensive populations performing estimations after forced titration and ensuring adherence to maximal tolerated doses of at least three antihypertensive medications, including a diuretic (& excluding cases of pseudo-resistance)

• A less informative alternative would be cross-sectional studies in large samples of unselected hypertensive patients with detailed recording of medications

Sarafidis P. J Clin Hypertens 2011

Sarafidis P, Georgianos P, Bakris G. Nature Reviews Nephrology 2012

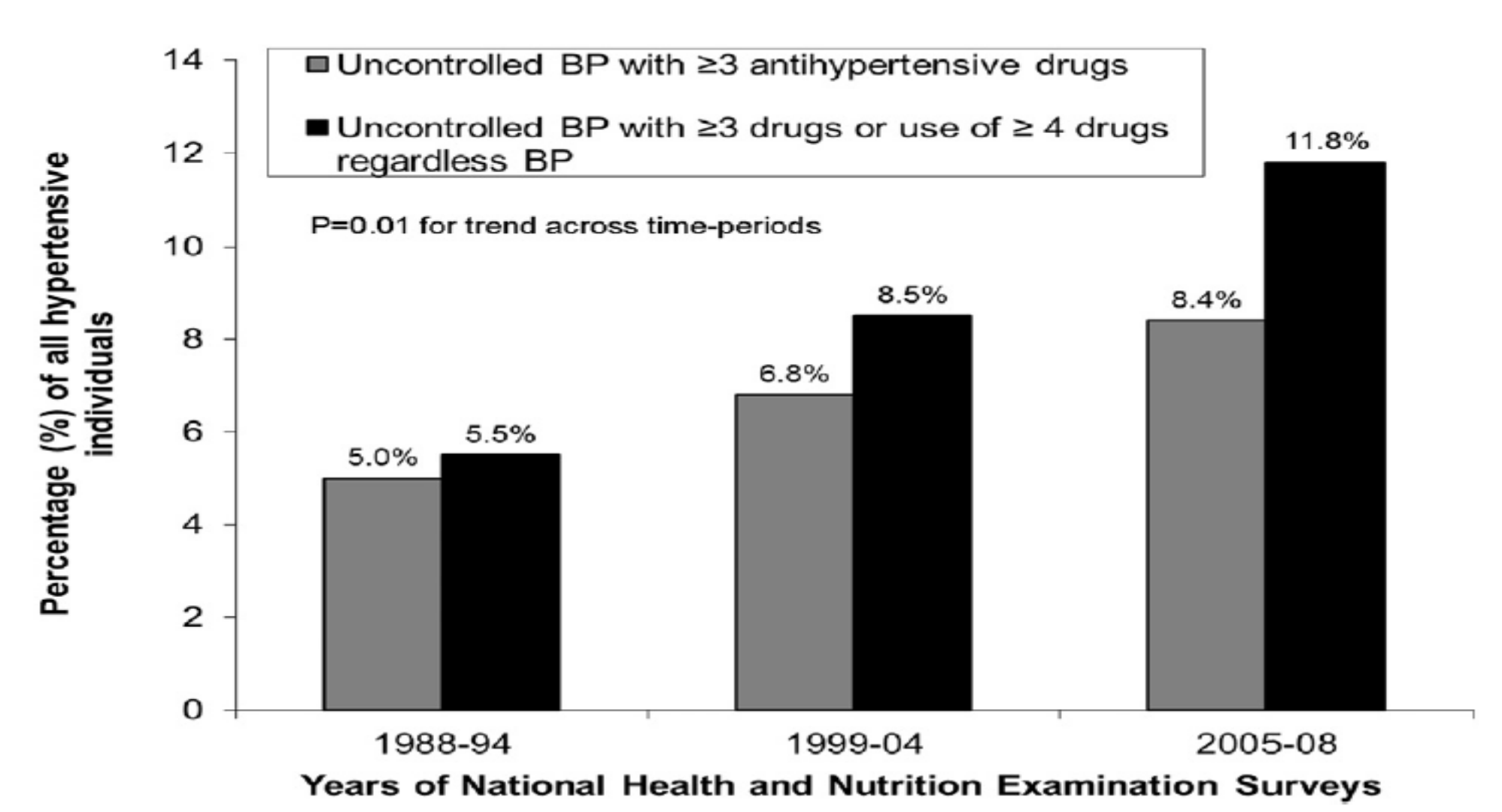
Prevalence of Resistant Hypertension in US: NHANES 2003-2008

Classification	No. of Participants	Among All Hypertensive Adults, % (SE)	Among Drug-Treated Hypertensive Adults, % (SE)
Uncontrolled, no drug treatment	1520	30.7 (1.2)	
Controlled hypertension, ≤3 drugs	2035	40.8 (1.1)	58.9 (1.2)
Uncontrolled hypertension, ≤2 drugs	1136	19.6 (0.8)	28.3 (1.1)
Resistant hypertension, uncontrolled, ≥3 drugs or controlled ≥4 drugs	539	8.9 (0.6)	12.8 (0.9)

Uncontrolled indicates a mean systolic pressure of ≥140 or diastolic ≥90 mm Hg.

Persell et al. Hypertension 2011

Trends in Prevalence of Resistant Hypertension



Egan M et al. Circulation 2011

Sarafidis P, et al. Seminars in Nephrology 2014

2017 AHA/ACC BP Clinical Practice Guideline

Estimates of Resistant Hypertension

- On the basis of the previous cutoff of 140/90 mm Hg, the prevalence of resistant hypertension is approximately 13% in the adult population.
- Estimates suggest the prevalence would be about 4% higher with the newly recommended control target of <130/80 mm Hg (subject to validation in future study).
- Multiple single-cohort studies have indicated that common risk factors for resistant hypertension include older age, obesity, CKD, black race, and DM.

Whelton et al., Hypertension 2017

Prevalence of RH in CKD patients

Study ID	Population characteristics	Definition of resistant hypertension	Prevalence estimates
Tanner et al. (22) cJASN 2013	10.700 hypertensive adults participating in the REGARDS study	Uncontrolled BP>140/90 mmHg with ≥3 antihypertensive drugs or use of >4 antihypertensive drugs regardless of BP	15.8% for eGFR≥60ml/min/1,73m^2; 24.9% for eGFR 45-59 ml/min/1.73m^2; 33.4% for eGFR≤45 ml/min/1.73m^2
De Nicola et al. (20) JACC 2013	436 hypertensive CKD patients, defined as office BP>130/80mmHg and eGFR<60ml/min/1.73m^2 or eGFR between 60-90ml/min/1.73m^2 and albuminuria >300mg/day	Uncontrolled office BP>130/80 mmHg with ≥3 antihypertensive drugs, including a diuretic, or >4 drugs and ABP> 125/75 mmHg	A total of 100 out of 436 patients (22.9%) were classified as resistant hypertensives

Sarafidis P, et al. Seminars in Nephrology 2014

Prevalence of RH in CKD patients

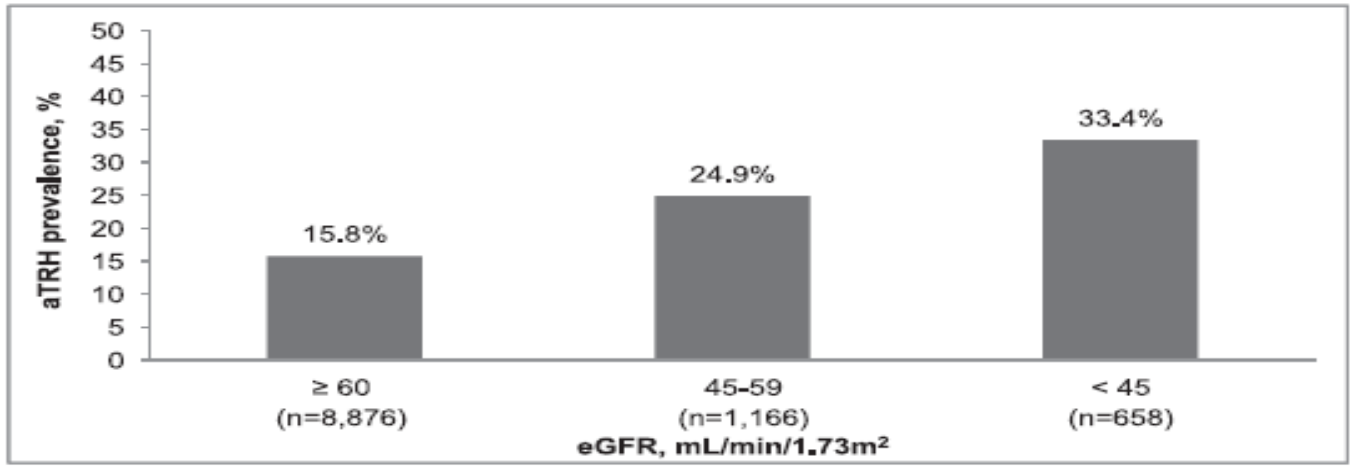


Figure 1. | Prevalence of apparent treatment-resistant hypertension (aTRH) by estimated GFR (eGFR) among Reasons for Geographic and Racial Differences in Stroke (REGARDS) study participants.

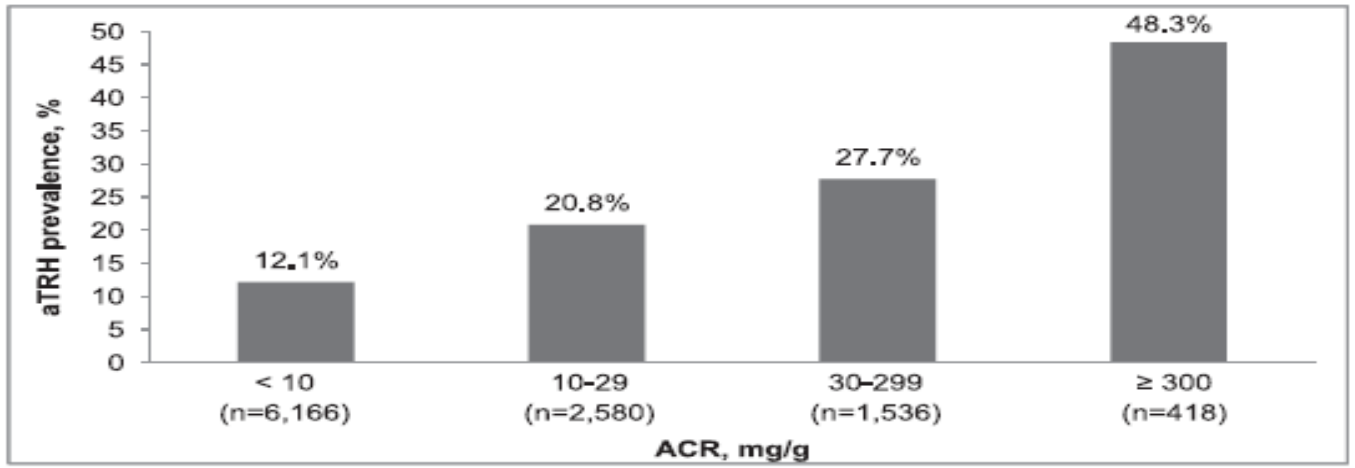
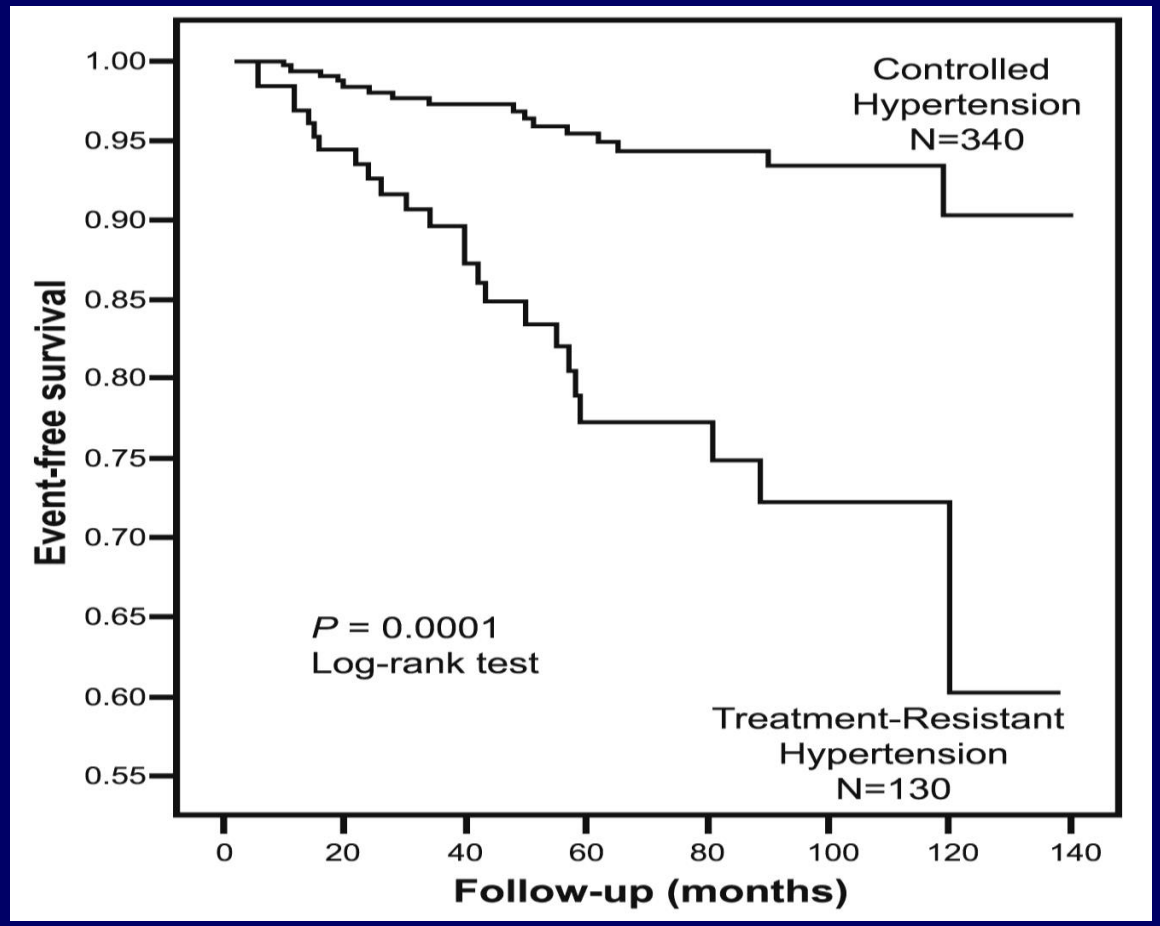


Figure 2. | Prevalence of aTRH by albumin-to-creatinine ratio (ACR) among REGARDS study participants.

Tanner et al. Clin J Am Soc Nephrol 2013

Prognosis of Resistant Hypertension



CV Event Rate (5-year follow-up)	
Controlled Hypertension	5%
Treatment Resistant	19%

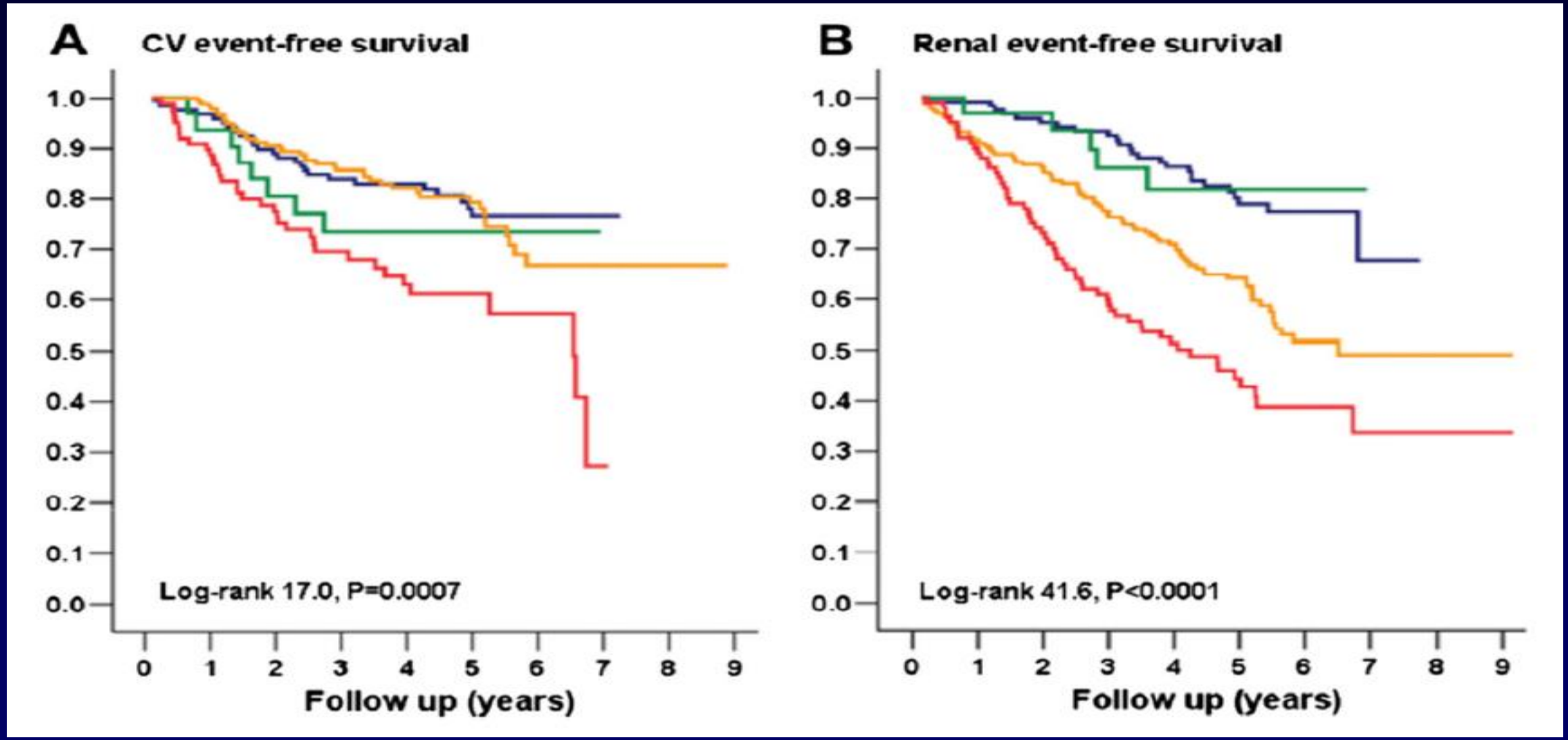
Differences between groups were apparent from very early in the follow-up period, indicating the urgent need for BP control in patients with treatment-resistant hypertension.

Note: Study did not include outcomes in untreated hypertensives or in patients with uncontrolled hypertension on 1-2 antihypertensive medications.

CV=cardiovascular.

Adapted from Pierdomenico SD, et al. *Am J Hypertens.* 2005;18:1422-1428.

Prognosis of Resistant Hypertension in CKD



De Nicola et al. J Am Coll Cardiol 2013

Ανθεκτική Υπέρταση

«Ψευδο-ανθεκτική» ΑΥ σε ασθενείς με και χωρίς ΧΝΝ

Causes of Pseudo-Resistant Hypertension

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ISSN 0735-1097/08/$34.00
doi:10.1016/j.jacc.2008.08.036

STATE-OF-THE-ART PAPER

Resistant Hypertension

An Overview of Evaluation and Treatment

Pantelis A. Sarafidis, MD, PHD,* George L. Bakris, MD, FAHA, FASN†

Thessaloniki, Greece; and Chicago, Illinois

Physician inertia (failure to change or increase dose regimens when not at goal)

Sarafidis P & Bakris G. J Am Coll Cardiol 2008

2023 ESH Guidelines

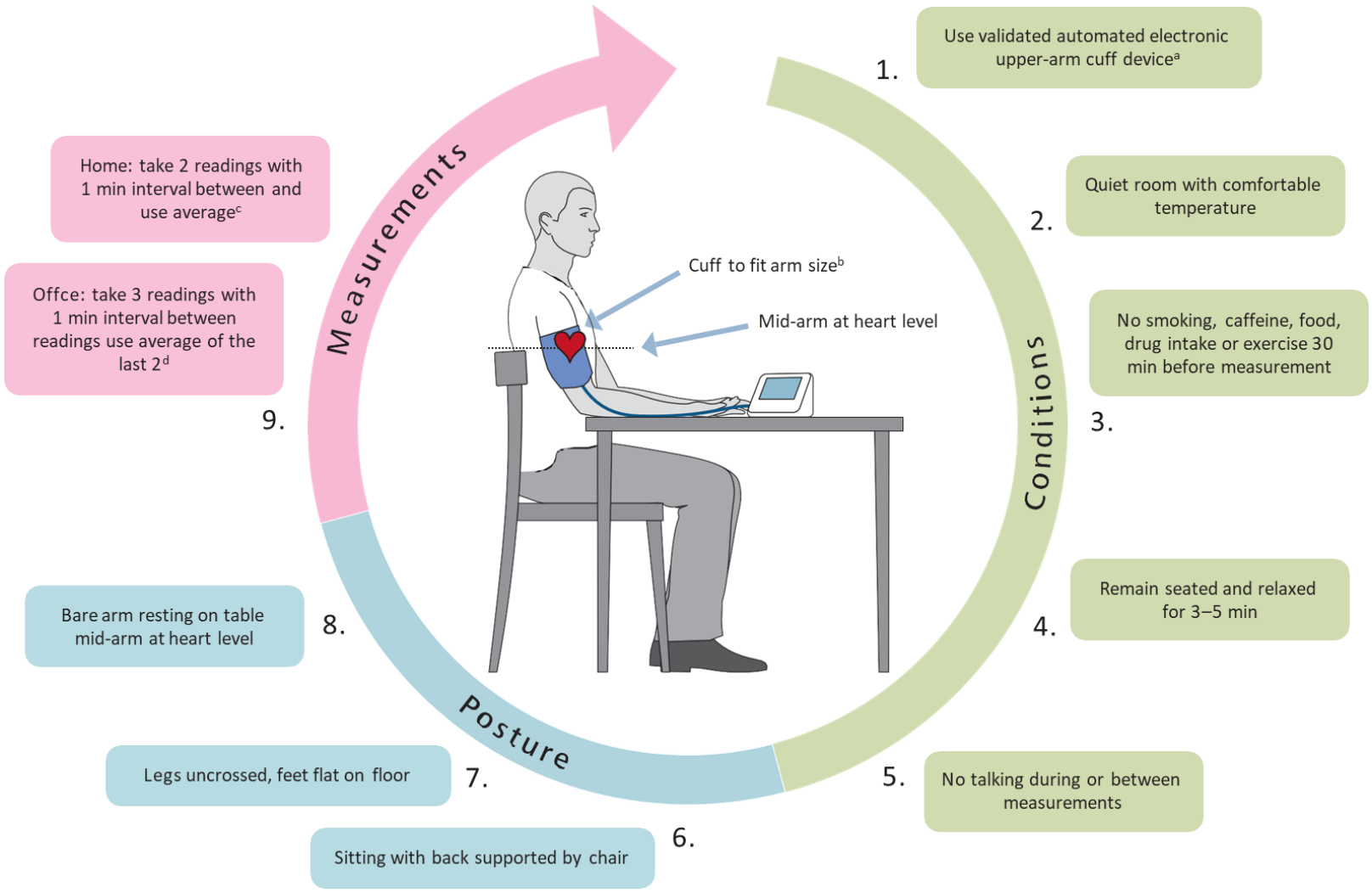
2023 ESH Guidelines for the management of arterial hypertension

The Task Force for the management of arterial hypertension of the European Society of Hypertension

Endorsed by the International Society of Hypertension (ISH) and the European Renal Association (ERA)

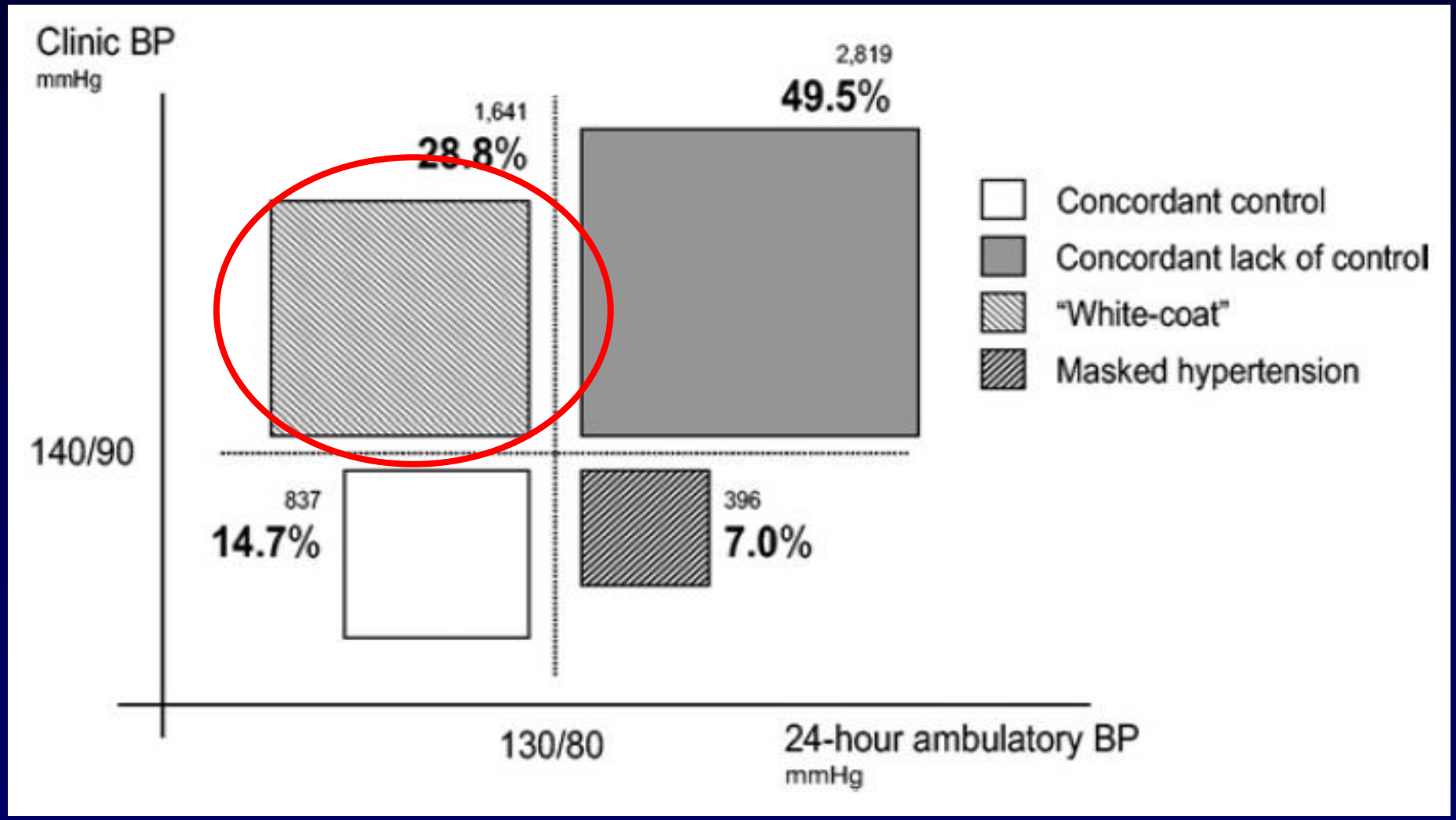
Authors/Task Force Members: Giuseppe Mancia (Chairperson)[a,*], Reinhold Kreutz (Co-Chair)[b,*], Mattias Brunström[c], Michel Burnier[d], Guido Grassi[e], Andrzej Januszewicz[f], Maria Lorenza Muiesan[g], Konstantinos Tsioufis[h], Enrico Agabiti-Rosei[i], Engi Abd Elhady Algharably[b], Michel Azizi[j,k], Athanase Benetos[l], Claudio Borghi[m], Jana Brguljan Hitij[n], Renata Cifkova[o,p], Antonio Coca[q], Veronique Cornelissen[r], J. Kennedy Cruickshank[s], Pedro G. Cunha[t,u], A.H. Jan Danser[v], Rosa Maria de Pinho[w], Christian Delles[x], Anna F. Dominiczak[y], Maria Dorobantu[z], Michalis Doumas[aa], María S. Fernández-Alfonso[bb,cc], Jean-Michel Halimi[dd,ee,ff], Zoltán Járai[gg], Bojan Jelakovic[hh], Jens Jordan[ii,jj], Tatiana Kuznetsova[kk], Stephane Laurent[ll], Dragan Lovic[mm], Empar Lurbe[nn,oo,pp], Felix Mahfoud[qq,rr], Athanasios Manolis[ss], Marius Miglinas[tt,uu], Krzystof Narkiewicz[vv], Teemu Niiranen[ww,xx], Paolo Palatini[yy], Gianfranco Parati[zz,aaa], Atul Pathak[bbb], Alexandre Persu[ccc], Jorge Polonia[ddd], Josep Redon[oo,eee,fff], Pantelis Sarafidis[ggg], Roland Schmieder[hhh], Bart Spronck[iii], Stella Stabouli[jjj], George Stergiou[kkk], Stefano Taddei[lll], Costas Thomopoulos[mmm], Maciej Tomaszewski[nnn,ooo], Philippe Van de Borne[ppp], Christoph Wanner[qqq], Thomas Weber[rrr], Bryan Williams[sss], Zhen-Yu Zhang[ttt], and Sverre E. Kjeldsen[uuu]

Recommendations for BP measurements in the office and at home



Pseudo-Resistant Hypertension

White-Coat Effect in CKD

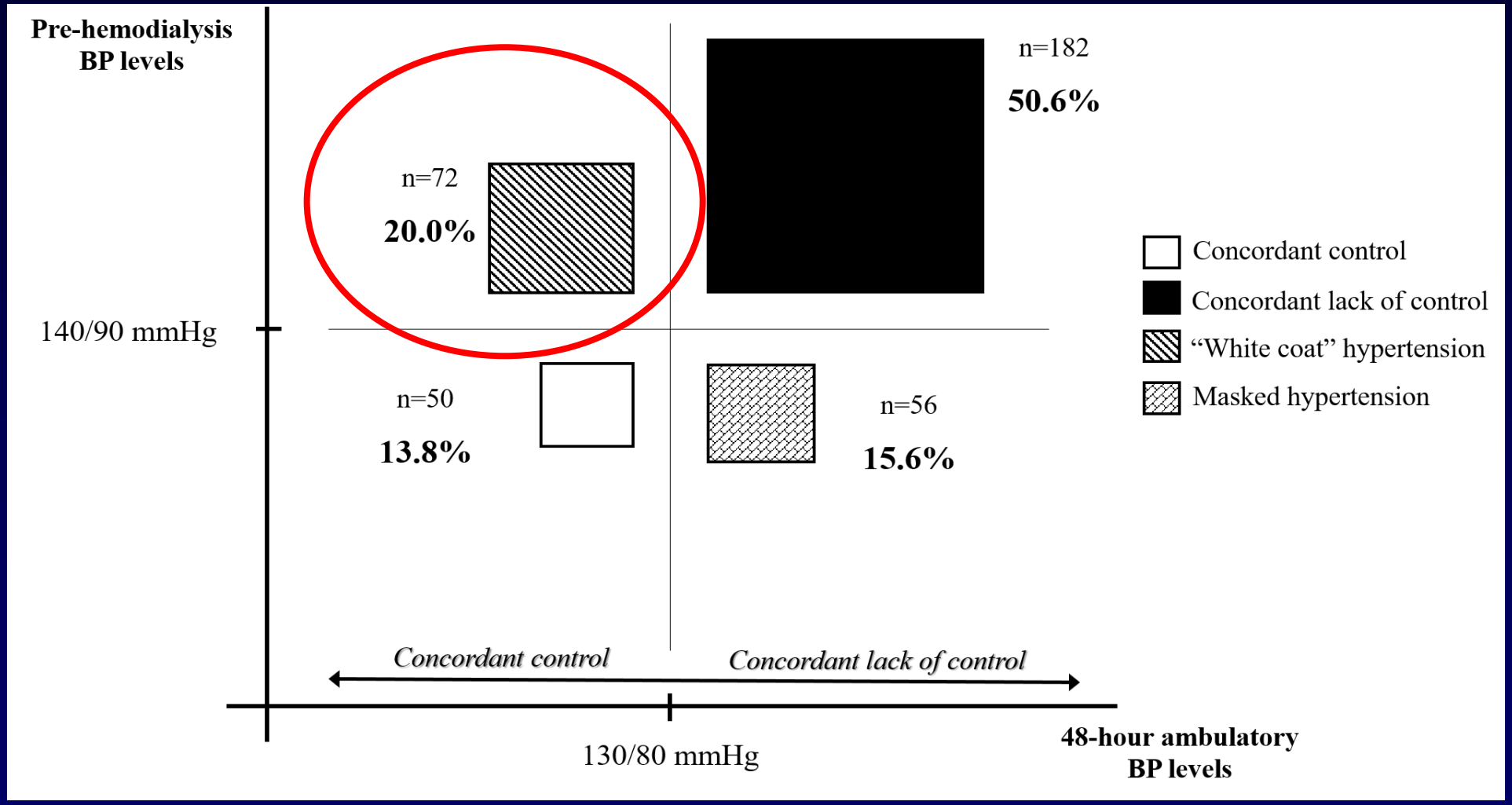


Gorostidi M, Sarafidis P, de la Sierra A, et al. Am J Kidn Dis 2013

Pseudo-Resistant Hypertension

White-Coat Effect in Hemodialysis

n=396



Sarafidis P, et al. Nephrol Dial Transplant 2018

Pseudo-Resistant Hypertension
Poor Adherence

Identifying non-compliance is important, but to deal with it effectively we also need to understand its nature

Non-compliance

Don’t forget the number of pills!!

Intentional non-compliance
(missing/altering doses for personal reasons)

- Active process
- Associated with beliefs about condition and treatment
- Can be driven by side effects
- Also affected by economic/lifestyle issues (skipping doses/taking smaller doses to make medication last longer)

Unintentional non-compliance
(forgetting to take medication)

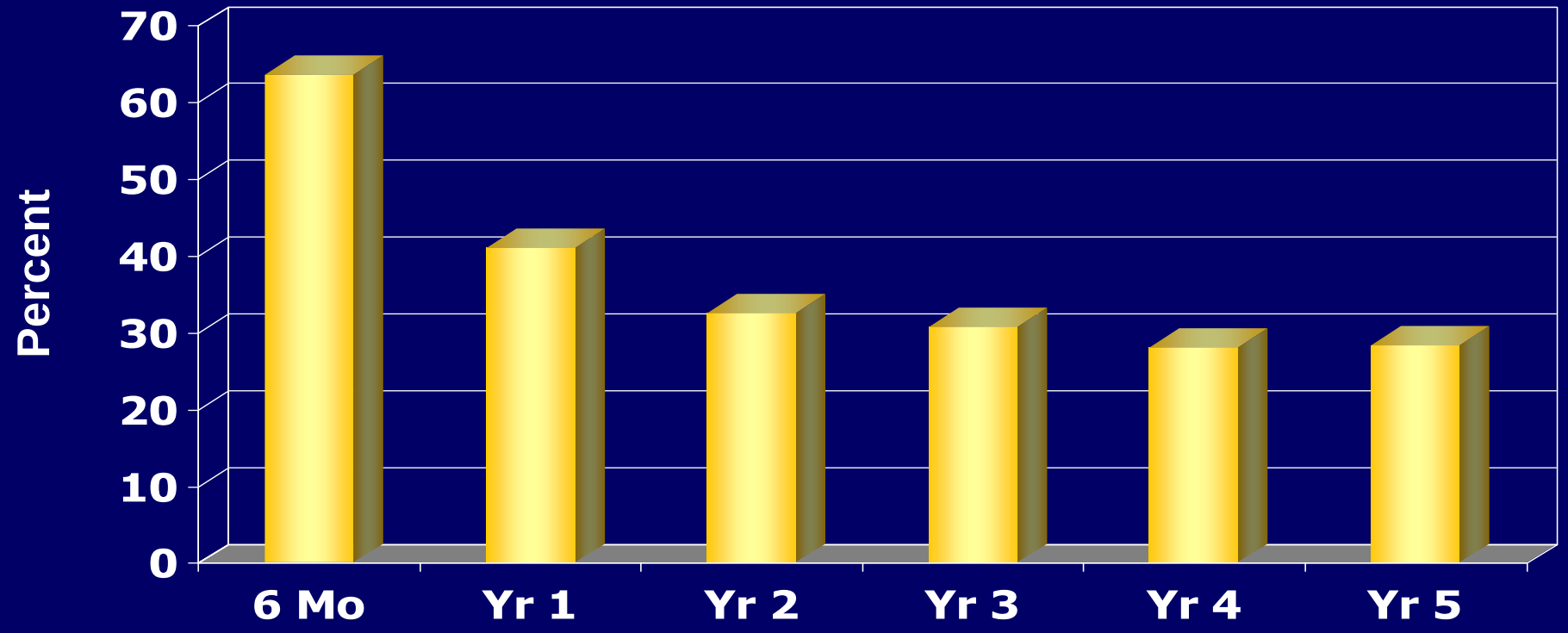
- Passive process
- Associated with demographics (especially in the elderly)

WHO. 2003. http://www.who.int/chp/knowledge/publications/adherence_introduction.pdf.
Kjeldsen et al. Int J Clin Pharm 2011;33:565–72, Wroe. J Behav Med 2002;25:355–72

Therapeutic Inertia: A Problem Present Even When Drugs Are Free

ALLHAT

Proportion of Participants on 2 or More Drugs with BP ≥ 140/90 Who Had Their Drugs Increased[1]



Adapted from Cushman WC et al. *J Clin Hypertens* 2002;4(6):393-404.

[1]Increased= ↑in dose of step 1 blinded drug, an ↑ in the number of drugs prescribed, or a change in prescription without a change in the # of drugs.

Ambulatory BP monitoring (ABPM)

Specific recommendations and statements	CoR	LoE
ABPM is recommended in addition to OBPM to improve CV risk prediction due to better reproducibility and prognostic value than OBPM, although lacking data on treatment benefit from RCTs.	II	B
ABPM is recommended to identify white-coat hypertension, masked hypertension and nocturnal BP phenotypes. Repeated ABPM may be necessary because these phenotypes have a limited reproducibility.	I	B
ABPM should be used to diagnose true resistant hypertension.	I	B
ABPM should be measured using upper arm-cuff automated BP monitors validated according to an established protocol. www.stridebp.org	I	C
The recommended frequency of measurements is 20 minutes during day and night to minimize the risk of missing day or night periods.	I	C

True resistant hypertension

Recommendations and statements	CoR	LoE
It is recommended that hypertension is defined as true resistant hypertension when SBP is ≥ 140mmHg or DBP is ≥ 90 mmHg provided that: -maximum recommended and tolerated doses of a three-drug combination comprising a RAS blocker (either an ACEi or an ARB), a CCB and a Thiazide/Thiazide-like diuretic were used -adequate BP control has been confirmed by ABPM -various causes of pseudo-resistant hypertension (especially poor medication adherence) and secondary hypertension have been excluded.	I	C
If confirmation of true resistant hypertension by ABPM is not feasible, HBPM may be used	II	C

Ανθεκτική Υπέρταση

Αίτια στη ΧΝΝ

- Drug-induced
  - Nonsteroidal anti-inflammatory drugs (including cyclo-oxygenase-2 inhibitors)
  - Sympathomimetics (decongestants, anorectics)
  - Cocaine, amphetamines, other illicit drugs
  - Oral contraceptive hormones
  - Adrenal steroid hormones
  - Erythropoietin
  - Cyclosporine and tacrolimus
  - Licorice (included in some chewing tobacco)
  - Over-the-counter dietary and herbal supplements (e.g., ginseng, yohimbine, ma huang, bitter orange)
- Excess alcohol intake
- Volume overload
  - Excess sodium intake
  - Volume retention from kidney disease
  - Inadequate diuretic therapy
- Associated conditions
  - Obesity
  - Diabetes mellitus
  - Older age
- Identifiable causes of hypertension
  - Renal parenchymal disease
  - Renovascular disease
  - Primary aldosteronism
  - Obstructive sleep apnea
  - Pheochromocytoma
  - Cushing's syndrome
  - Thyroid diseases
  - Aortic coarctation
  - Intracranial tumors

Factors contributing to resistant hypertension

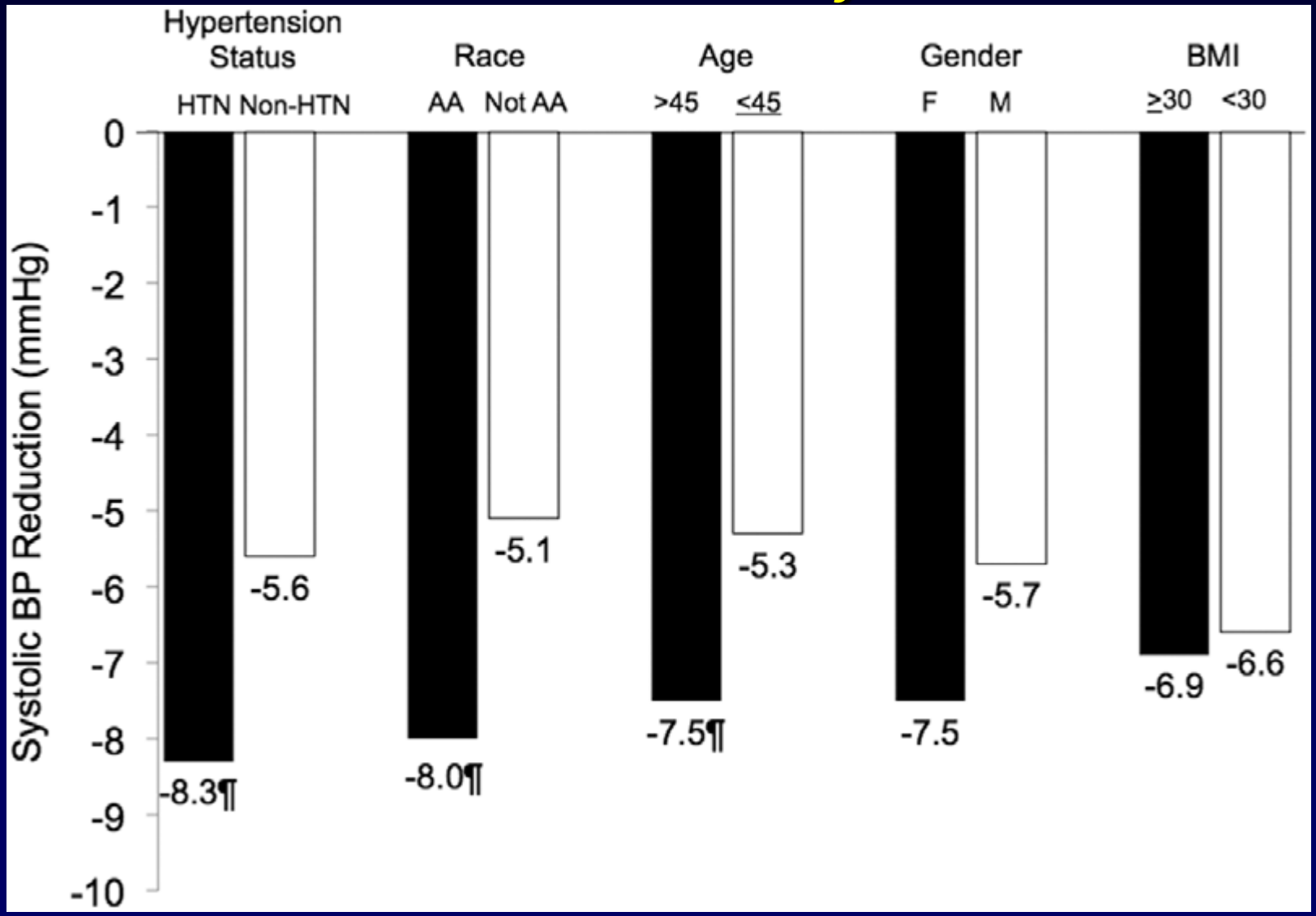
Sarafidis P & Bakris G.
J Am Coll Cardiol 2008

Patient Groups with High Prevalence of Sodium-Sensitivity

- Fixed factors
  - Middle and older-aged persons
  - African-Americans
  - Genetic Factors
  - Individuals with:
    - Hypertension
    - Diabetes
    - Chronic Kidney Disease
- Modifiable
  - Low potassium intake
  - Poor quality diet

Elijovich F, Weinberger MH, Anderson CAM, et al. Salt sensitivity of blood pressure: a scientific statement from the AHA. Hypertension. 2016;68:e7-46.

Salt and Hypertension
The DASH Study



Sacks F.M. et al. N Engl J Med 2001; Vollmer WM Ann Intern Med. 2001

Resistant Hypertension

Chronic Kidney Disease

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STATE-OF-THE-ART PAPER

Resistant Hypertension

An Overview of Evaluation and Treatment

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Thessaloniki, Greece; and Chicago, Illinois

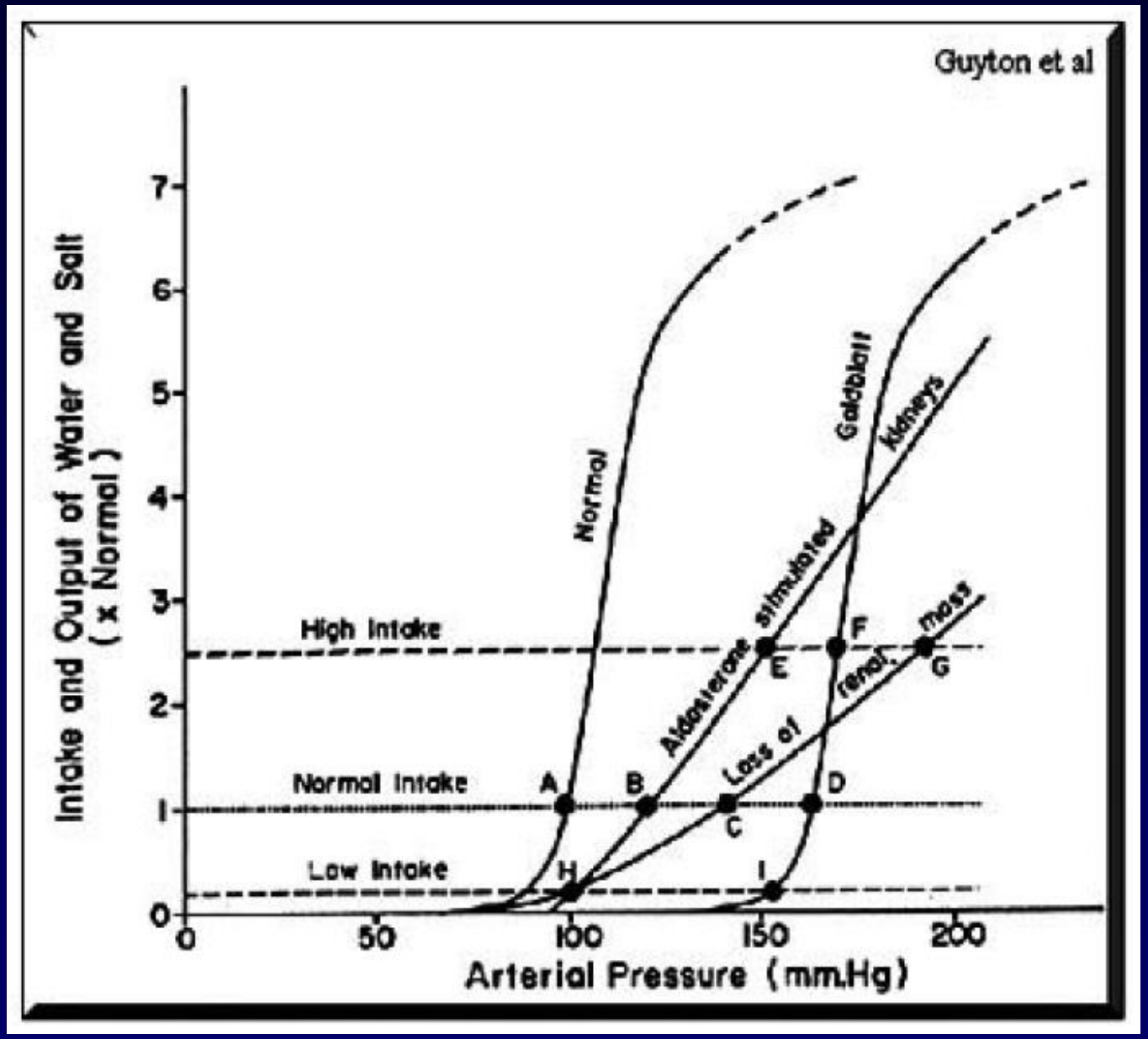
Sarafidis P & Bakris G. J Am Coll Cardiol 2008

Pathogenesis of hypertension in CKD

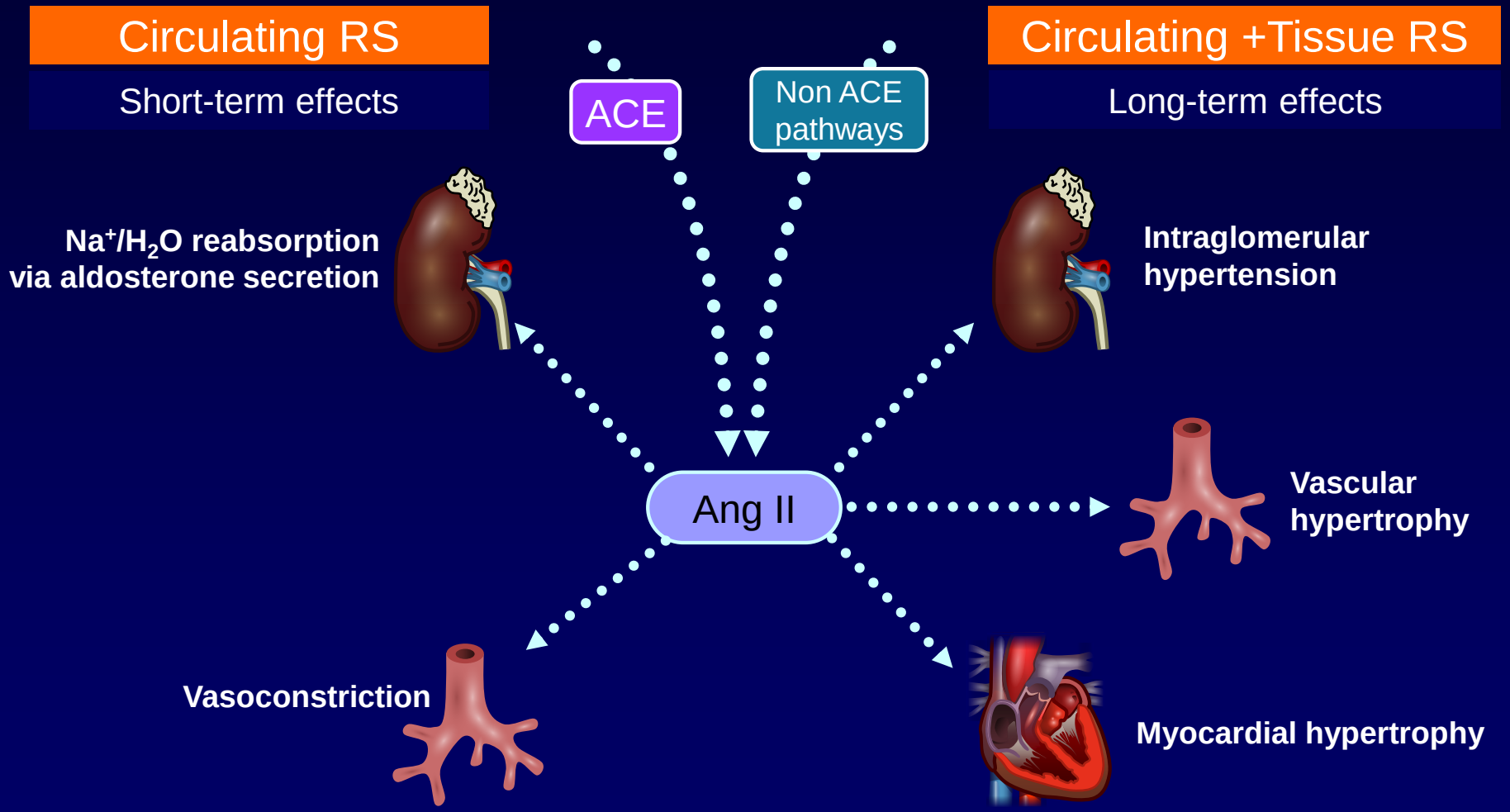
- Pre-existing essential hypertension
- Extracellular fluid volume expansion
- Renin-angiotensin-aldosterone system stimulation
- Increased sympathetic activity
- Endogenous digitalis-like factors
- Prostaglandinds/bradykinins
- Alterations in endothelium-derived factors (nitric oxide/endothelin)
- Increased body weight
- Erythropoietin administration
- Parathyroid hormone secretion/increased intracellular calcium/hypercalcemia
- Calcification of arterial tree
- Renal artery disease
- Chronic allograft dysfynction
- Cadaver allografts, esp. from a donor with family history of hypertension
- Cyclosporine, tacrolimus other immunosuppressive/corticosteroid therapy

P.A. Sarafidis, G.L. Bakris. Kidney disease and hypertension. In: Lip G and Hall J (eds). Comprehensive Hypertension. Elsevier, London, 2007

Sodium Sensitivity in CKD

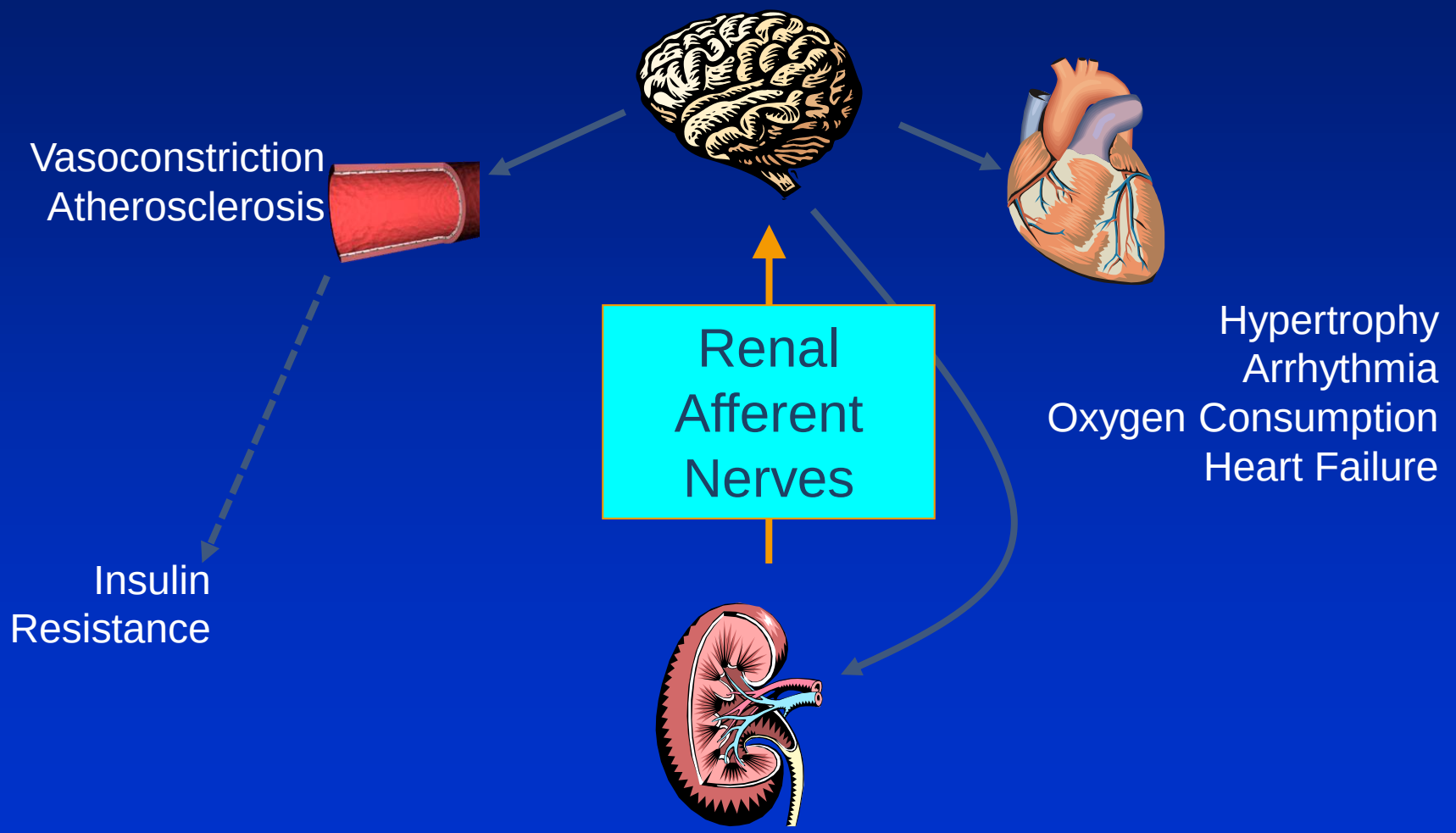


Circulating and local tissue renin systems have different effects on the CV system

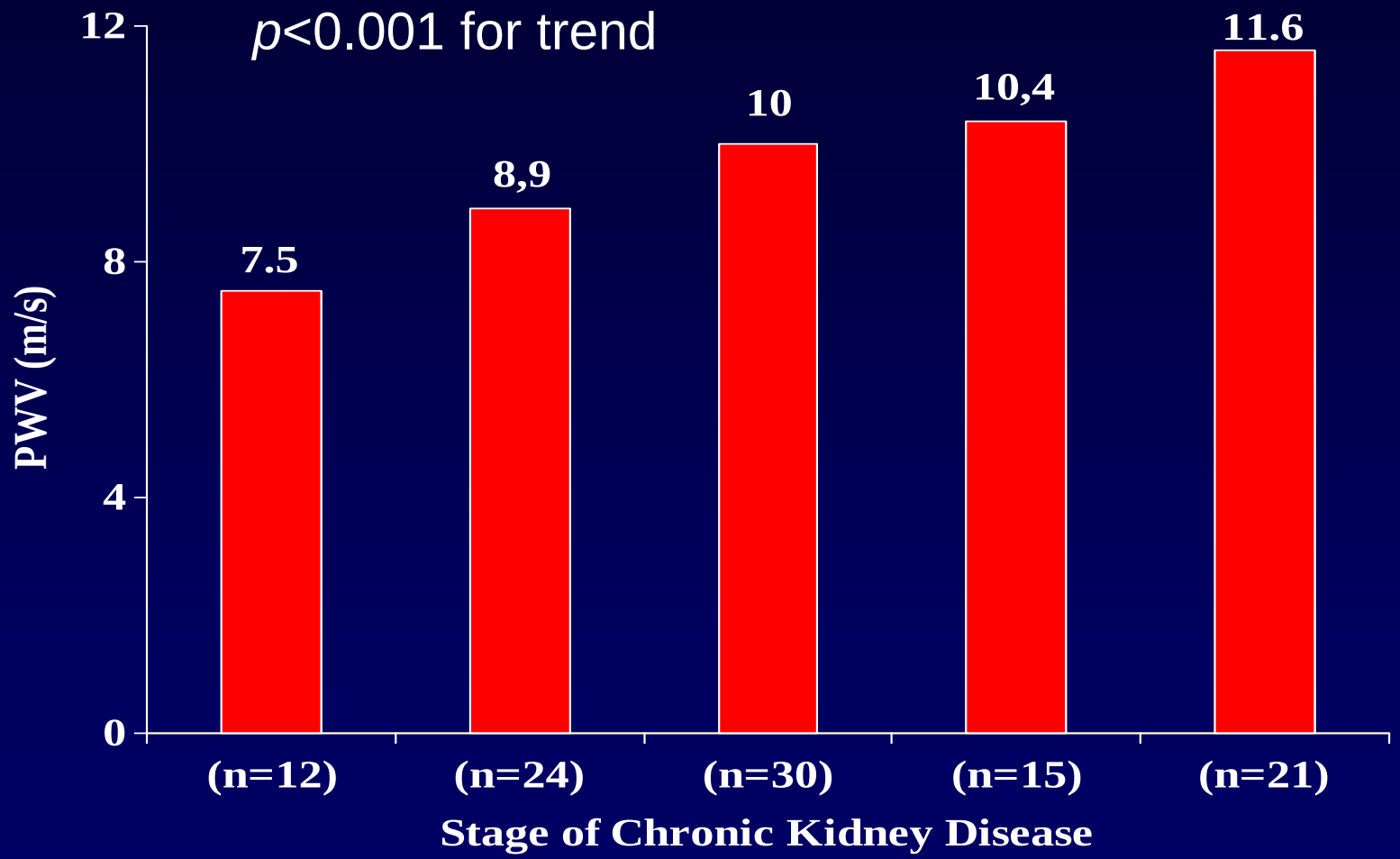


Modified from: Dzau VJ. 1993

Renal Sympathetic Afferent Nerves: Kidney as Origin of Central Sympathetic Drive



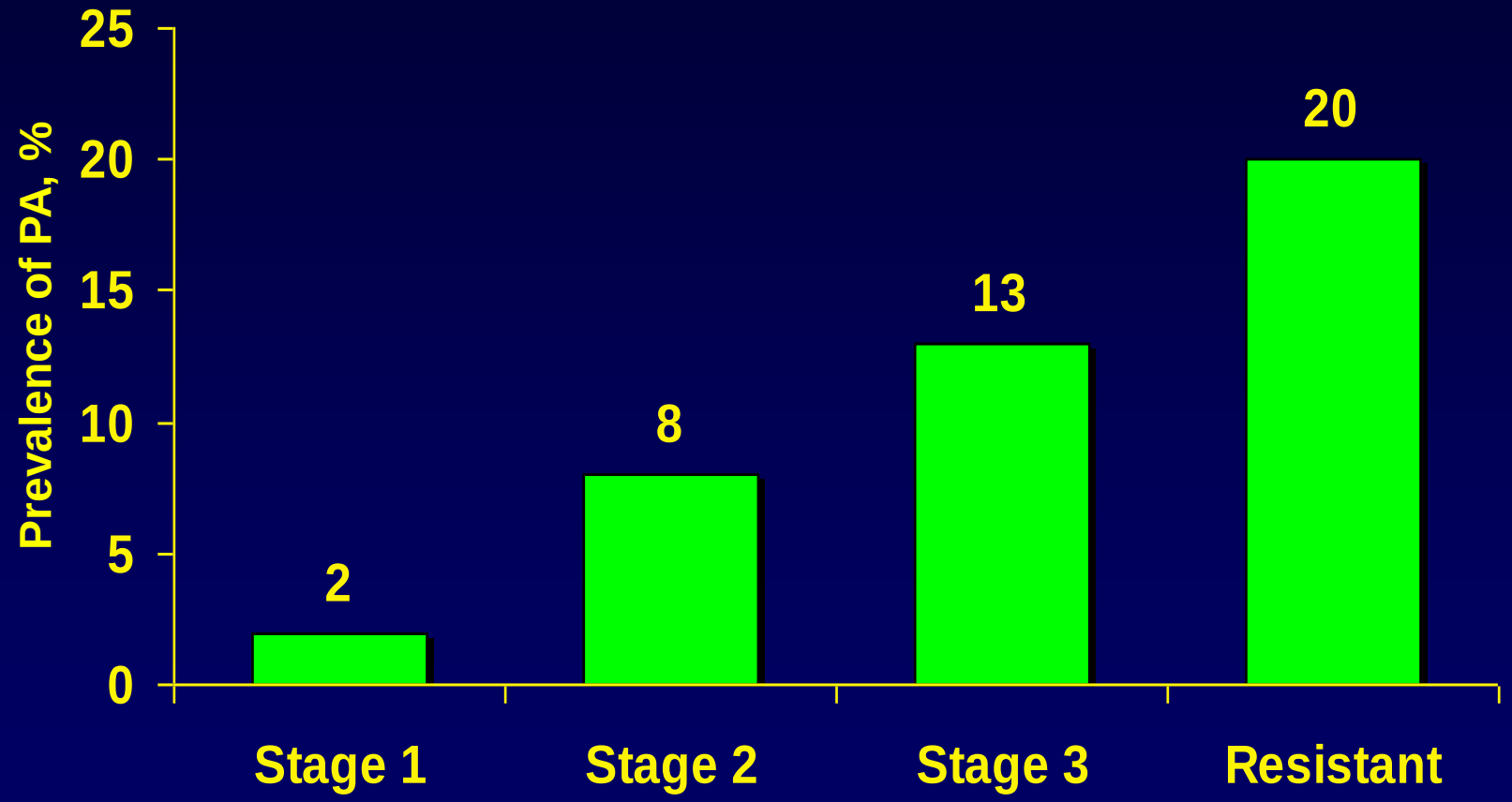
Pulse Wave Velocity Increases as Renal Function Decreases



AJKD 45:494, 2005

Resistant Hypertension

Primary Aldosteronism



Mosso L, et al. Hypertension. 2003;42:161-165.
Calhoun DA, et al. 2002. Hypertension. 2002;40:892-896.

Clinical phenotypes of ARVD that should prompt investigations

Nephrol Dial Transplant, 2023, 0, 1–16
https://doi.org/10.1093/ndt/gfad095
Advance access publication date: 18 May 2023

Atherosclerotic renovascular disease: a clinical practice document by the European Renal Best Practice (ERBP) board of the European Renal Association (ERA) and the Working Group Hypertension and the Kidney of the European Society of Hypertension (ESH)

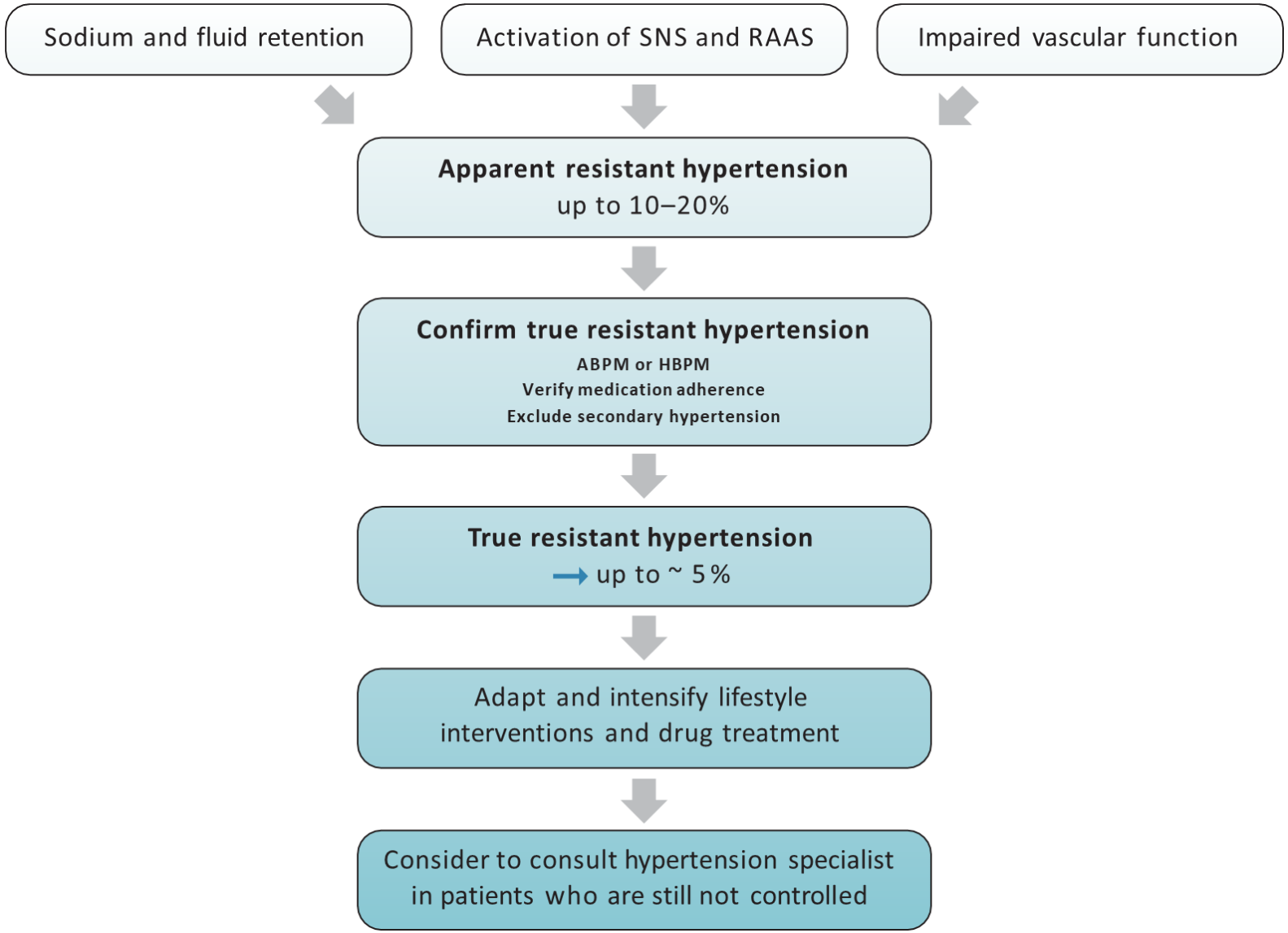
Pantelis A. Sarafidis[1], Marieta Theodorakopoulou[1], Alberto Ortiz[2], Beatriz Fernandez-Fernández[2], Ionut Nistor[3,4], Roland Schmieder[5], Mustafa Arici[6], Athanasios Saratzis[7], Patricia Van der Niepen[8], Jean-Michel Halimi[9], Reinhold Kreutz[10], Andrzej Januszewicz[11], Alexandre Persu[12,†] and Mario Cozzolino[13,†]

Sarafidis et al. *Nephrol Dial Transplant* 2023

Ανθεκτική Υπέρταση

Αντιμετώπιση σε ασθενείς με ΧΝΝ

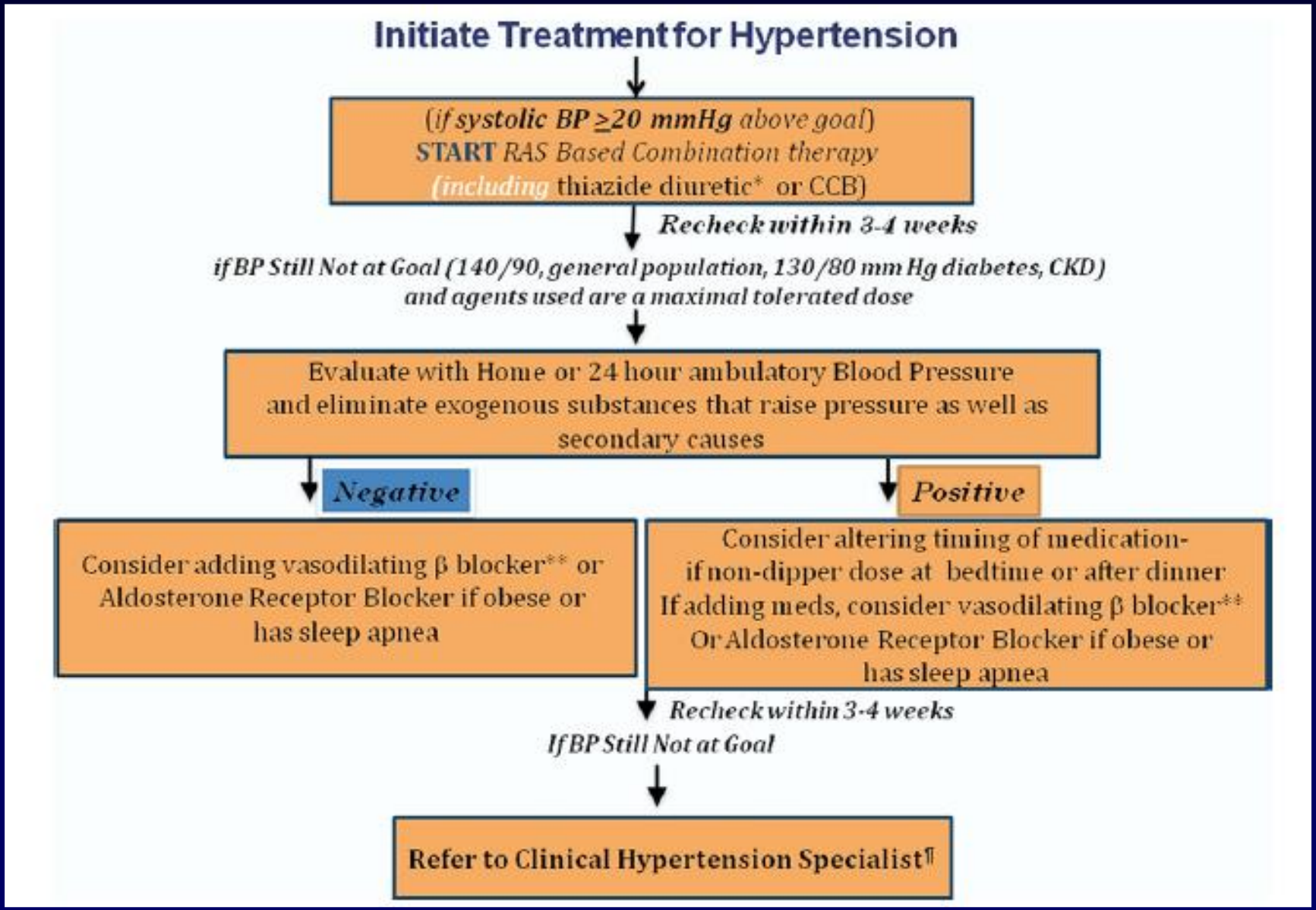
Characteristics of true resistant hypertension



Lifestyle interventions

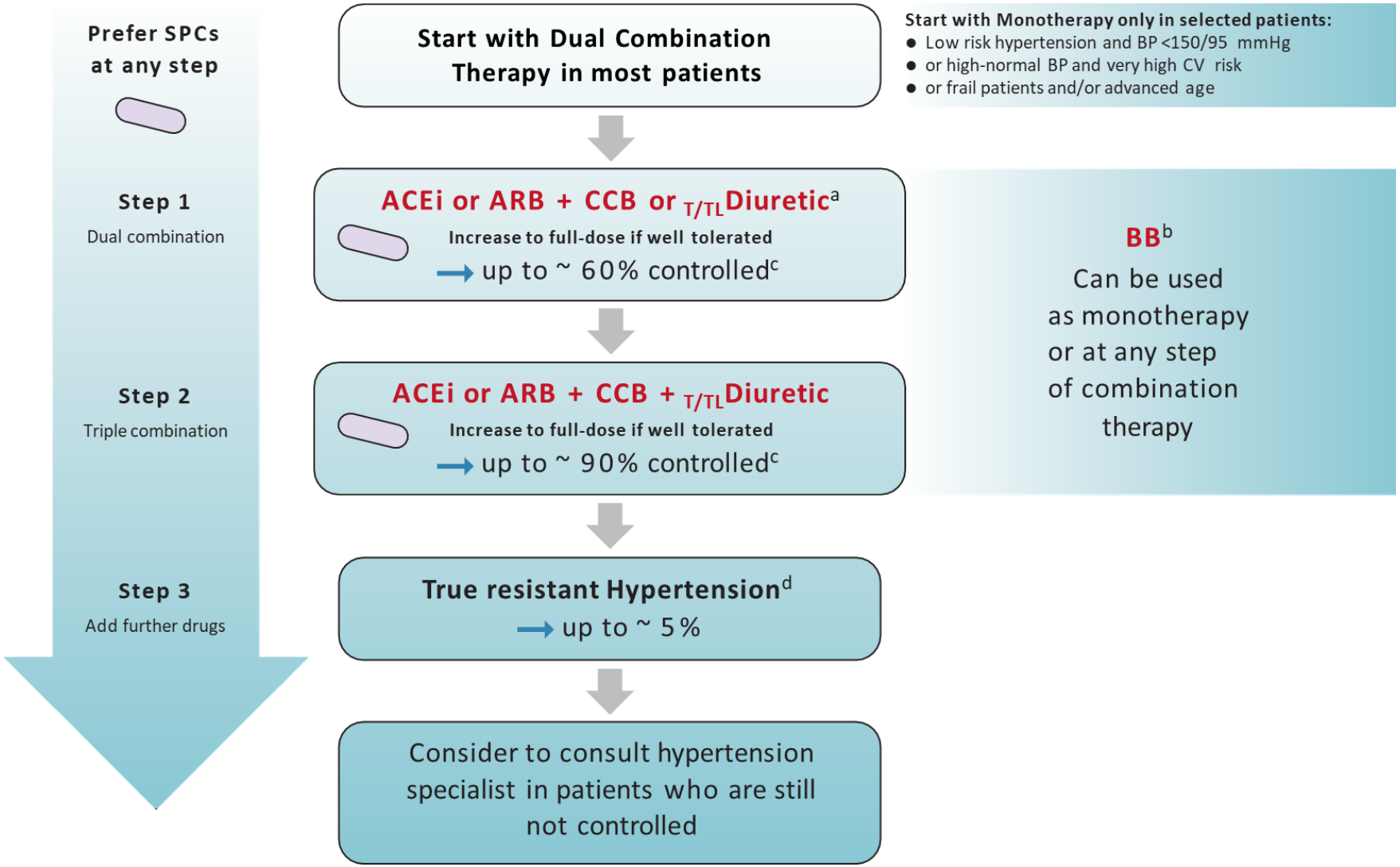
Recommendations and statements	CoR	LoE
In adults with elevated BP who are overweight or obese, weight reduction is recommended to reduce BP and improve CV outcomes.	I	A
Preferred dietary products include vegetables, fruits, beans, nuts, seeds, vegetable oils, and fish and poultry among meat products. Fatty meats, full-fat dairy, sugar, sweetened beverages, and sweets should be limited. Overall, a healthy dietary patterns including more plant-based and less animal-based food is recommended.	I	B
In adults with hypertension consuming a high sodium diet (most Europeans), salt substitutes replacing part of the NaCl with KCl is recommended to reduce BP and the risk for CVD.	I	A
Dietary salt (NaCl) restriction is recommended for adults with elevated BP to reduce BP. Salt (NaCl) restriction to < 5 g (~2.0 g sodium) per day is recommended.	I	B
Increased potassium consumption, preferably via dietary modification, is recommended for adults with elevated BP, except for patients with advanced CKD.	I	B
Daily physical activity and structured exercise is recommended for adults with elevated BP to reduce BP and improve cardiovascular risk profile. It is recommended to strive for at least 150-300 minutes of aerobic exercise a week of moderate intensity, or 75-150 minutes a week of aerobic exercise of vigorous intensity or an equivalent combination. Sedentary time should also be reduced and supplemented with dynamic resistance exercise (2-3 times per week).	I	B

Treatment Algorithm for Resistant Hypertension

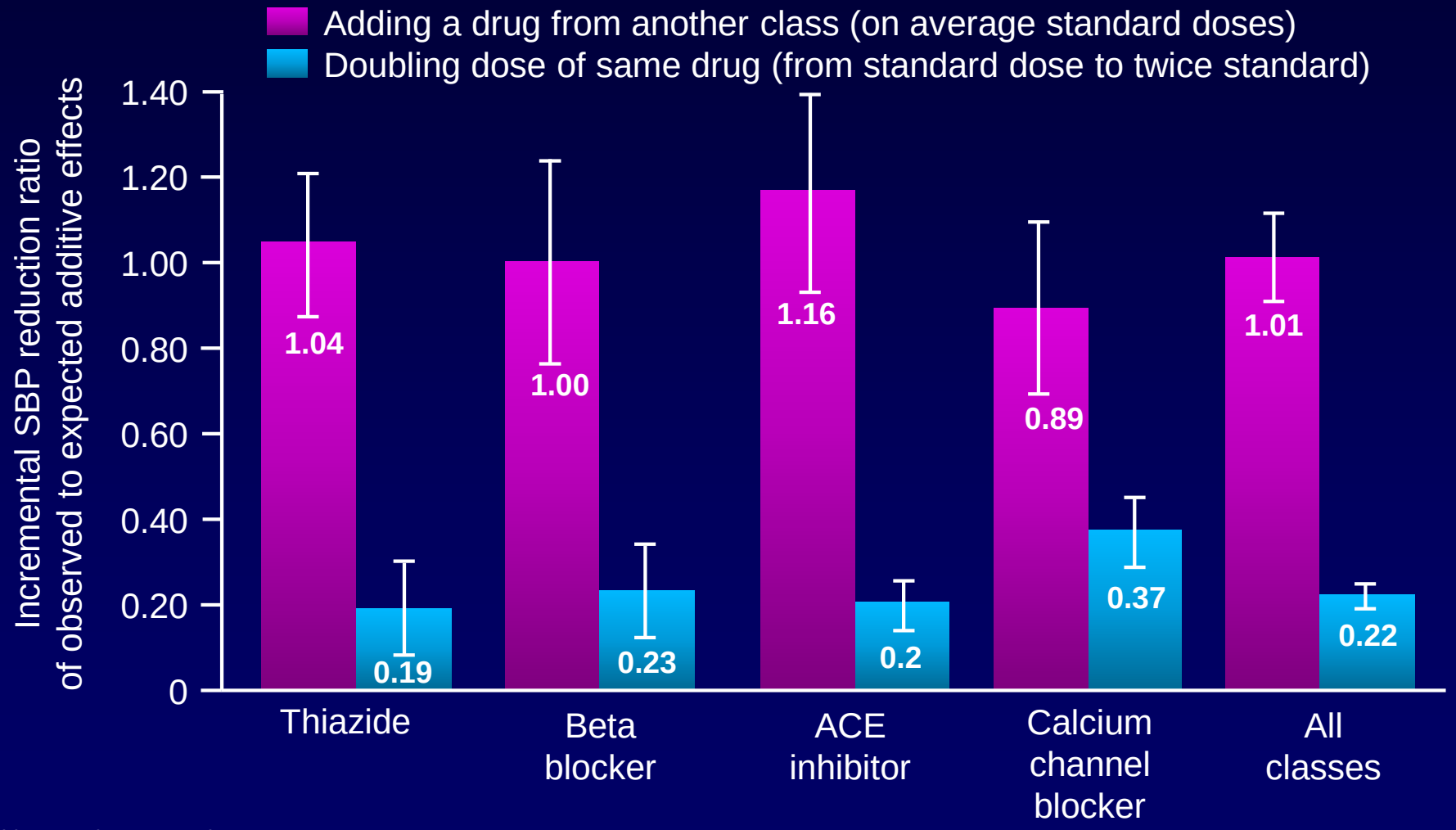


Sarafidis P & Bakris G, J Am Coll Cardiol 2008

General BP-lowering strategy in patients with hypertension



Ratio of Observed to Expected Incremental BP-Lowering Effects of Adding a Drug or Doubling the Dose According to Drug Class



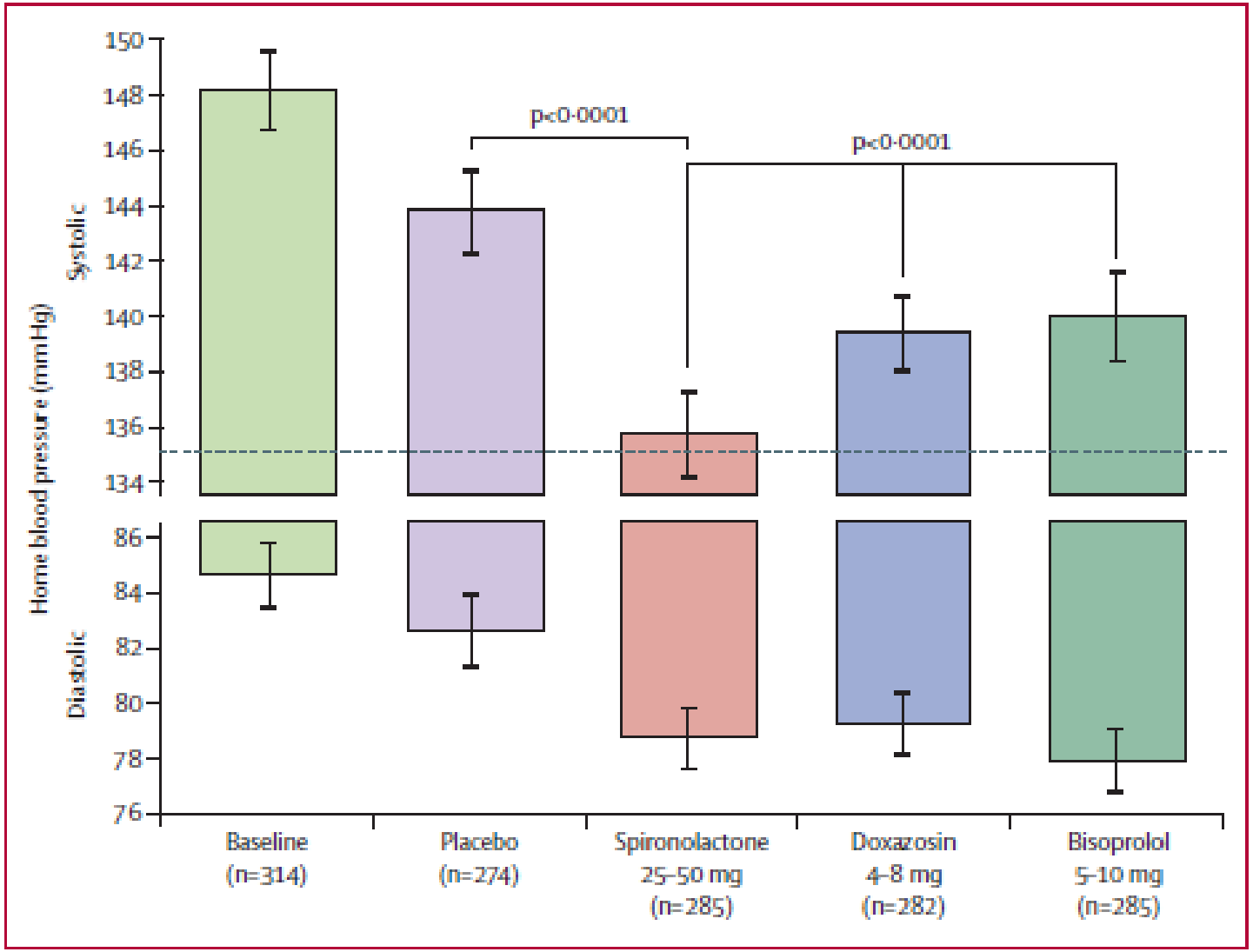
Wald DS et al. *Am J Med.* 2009;122:290-300.

Diuretics in CKD: Special Considerations

- Thiazide diuretics become less effective when GFR decreases to less than 40 mL/min/1.73 m^2
- To control BP in patients with a GFR less than that level, a loop diuretic (ie, furosemide, torsemide) is very likely to be needed.
- If furosemide is used, it should be dosed adequately (ie, 2 to 3 times instead of once daily) as it has a very short duration of action (3 to 6 hours).

Sarafidis P. et al, Am J Kidney Dis 2007
Sarafidis P & Bakris G, J Clin Hypertens 2008

The PATHWAY-2 Cross-Over trial



Williams B, et al. Lancet 2015

Predictors of Hyperkalemia Risk following Hypertension Control with Aldosterone Blockade

American Journal of Nephrology

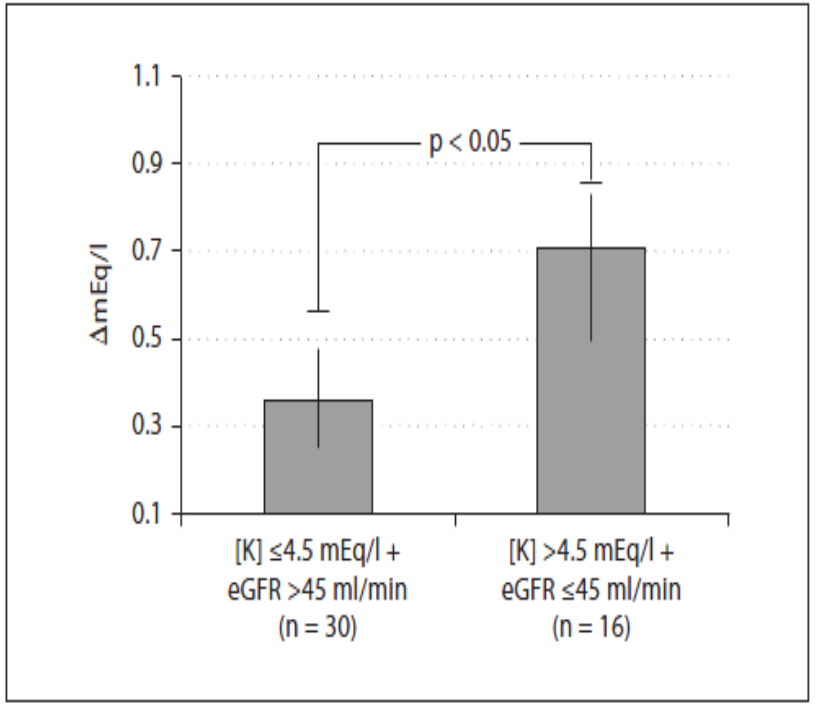


Fig. 2. Increases from baseline in serum potassium as a function of baseline level and kidney function as assessed by eGFR.

Table 2. OR of hyperkalemia development following aldosterone antagonism in nephropathy

Variable	OR	p
Baseline eGFR ≤45 ml/min/1.73 m^2	2.97 (1.14–21.3)	<0.03
+ Serum potassium >4.5 mEq/l	8.71 (2.89–24.8)	<0.01
+ >30% reduction in eGFR	7.76 (2.13–22.8)	<0.01
+ >15 mm Hg in systolic BP	3.98 (0.89–27.1)	0.18

Khosla, Kalaitzidis & Bakris. Am J Nephrol 2009

Clorthalidone in patients with CKD Stage 4: the CLICK study

- 160 patients with CKD 4
- 24-h SBP >130 or DBP>80 mmHg on >1 drug
- ACEI or ARB or β-blocker
- 24-h SBP >160 or DBP>100 mmHg excluded

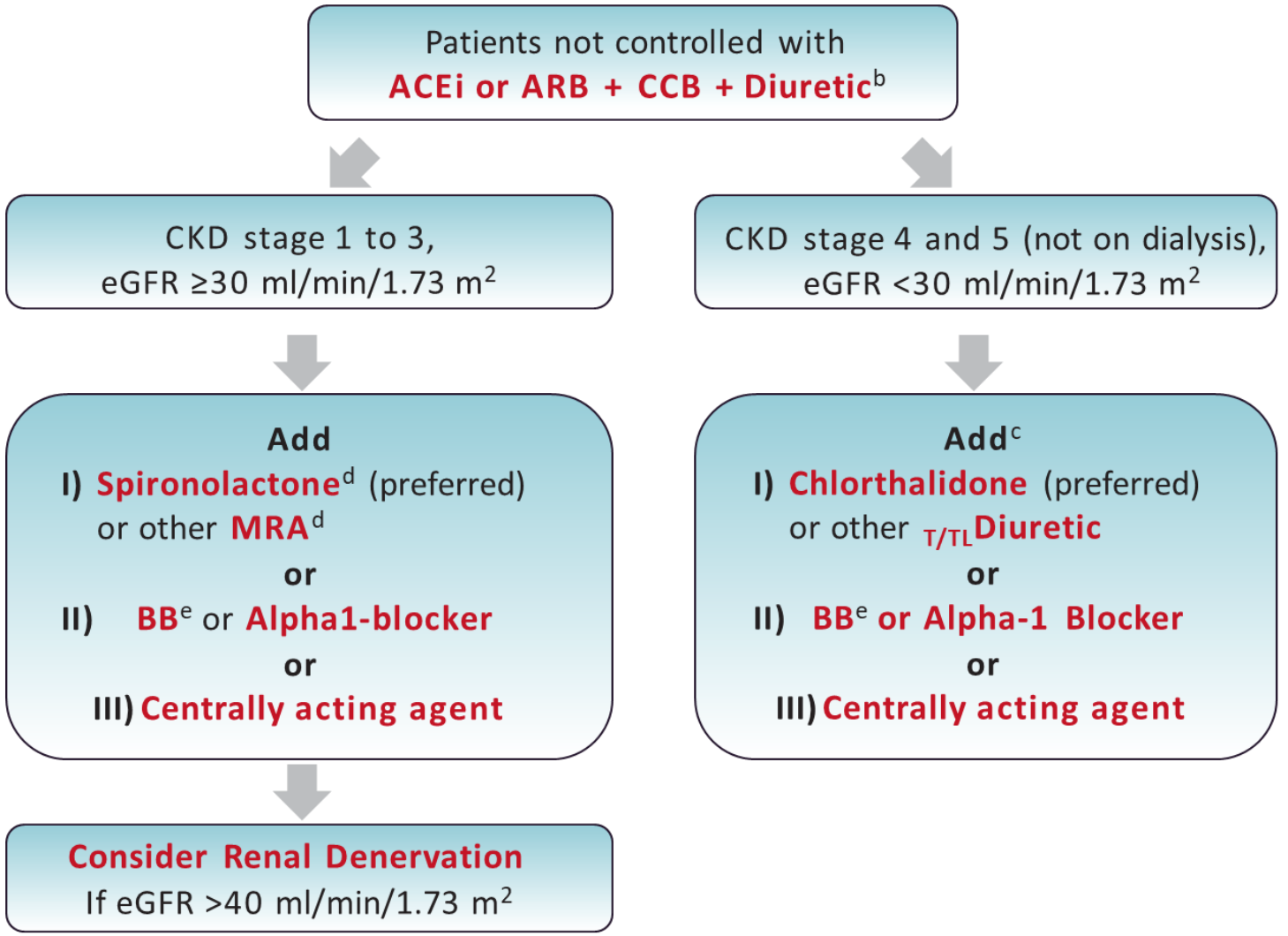
- eGFR 23.2±4.2 ml/min/1.73 m2
- 67% with very high albuminuria
- 76% with DM, 60% on loop diuretics

- Primary Outcome Change in 24-h SBP at 12 weeks

Variable	Chlorthalidone (N=81)	Placebo (N=79)	Treatment Effect (95% CI)†
Systolic blood pressure			
24-hr blood pressure — mm Hg			
At randomization	142.6±8.1	140.1±8.1	
Adjusted change at 12 wk (95% CI)	−11.0 (−13.9 to −8.1)	−0.5 (−3.5 to 2.5)	−10.5 (−14.6 to −6.4)‡
Daytime blood pressure — mm Hg			
At randomization	145.2±8.8	142.7±8.8	
Adjusted change at 12 wk (95% CI)	−11.3 (−14.4 to −8.3)	−0.7 (−3.9 to 2.5)	−10.6 (−15.0 to −6.3)
Nighttime blood pressure — mm Hg			
At randomization	138.0±10.0	135.4±10.2	
Adjusted change at 12 wk (95% CI)	−10.5 (−15.2 to −5.8)	0.6 (−3.0 to 4.2)	−11.1 (−16.6 to −5.6)
Diastolic blood pressure			
24-hour blood pressure — mm Hg			
At randomization	74.6±10.1	72.8±9.3	
Adjusted change at 12 wk (95% CI)	−4.9 (−6.6 to −3.2)	−1.0 (−2.8 to 0.7)	−3.9 (−6.3 to −1.5)
Daytime blood pressure — mm Hg			
At randomization	77±10.6	75.1±9.5	
Adjusted change at 12 wk (95% CI)	−5.4 (−7.3 to −3.6)	−1.3 (−3.1 to 0.6)	−4.2 (−6.8 to −1.6)
Nighttime blood pressure — mm Hg			
At randomization	70.4±10.5	68.9±10.2	
Adjusted change at 12 wk (95% CI)	−4.7 (−7.5 to −2.0)	−0.6 (−2.8 to 1.6)	−4.1 (−7.4 to −0.9)

Agarwal et al. N Engl J Med 2022

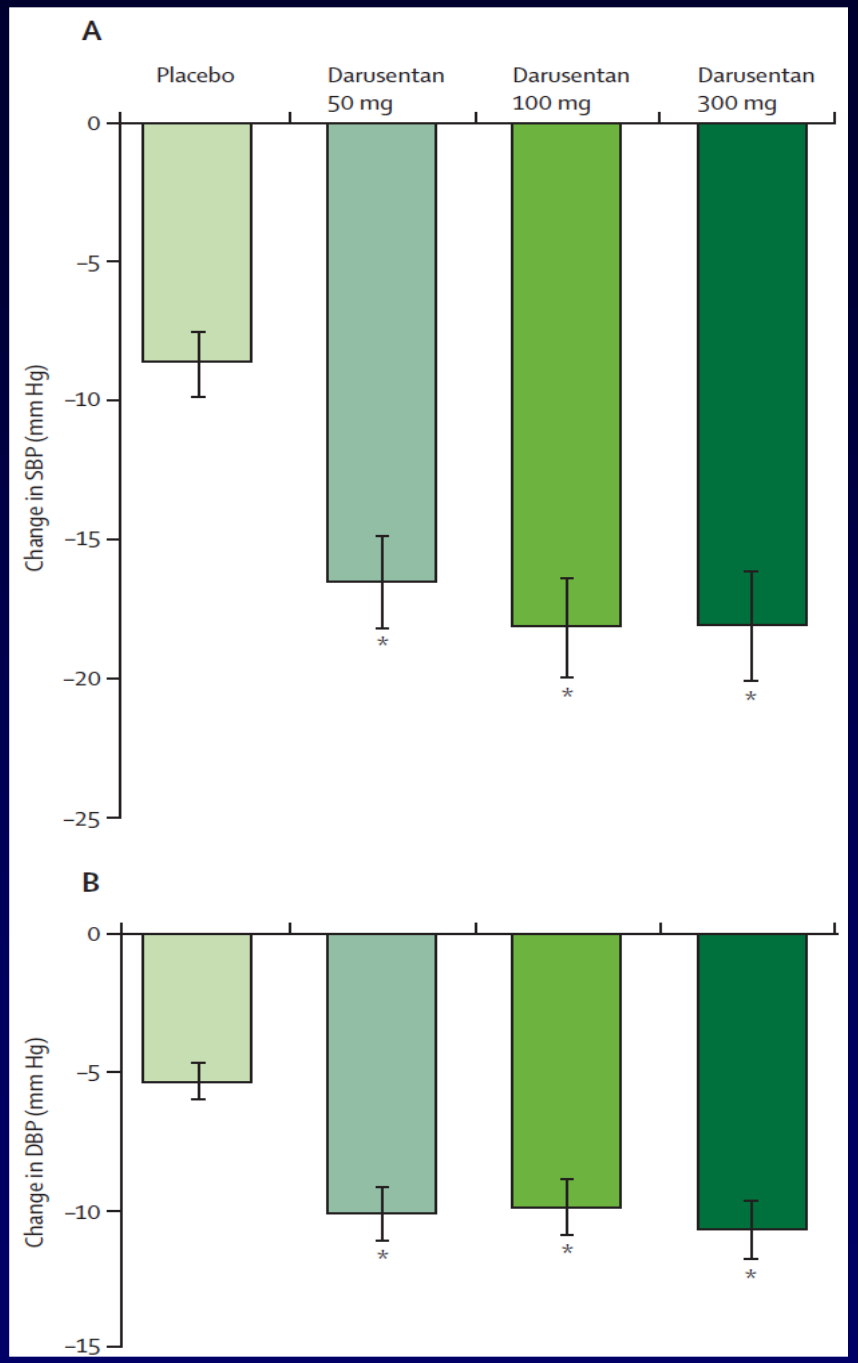
BP-lowering strategy in true resistant hypertension[a]



Ανθεκτική Υπέρταση

Θεραπείες υπό μελέτη

Darusentan in Resistant Hypertension



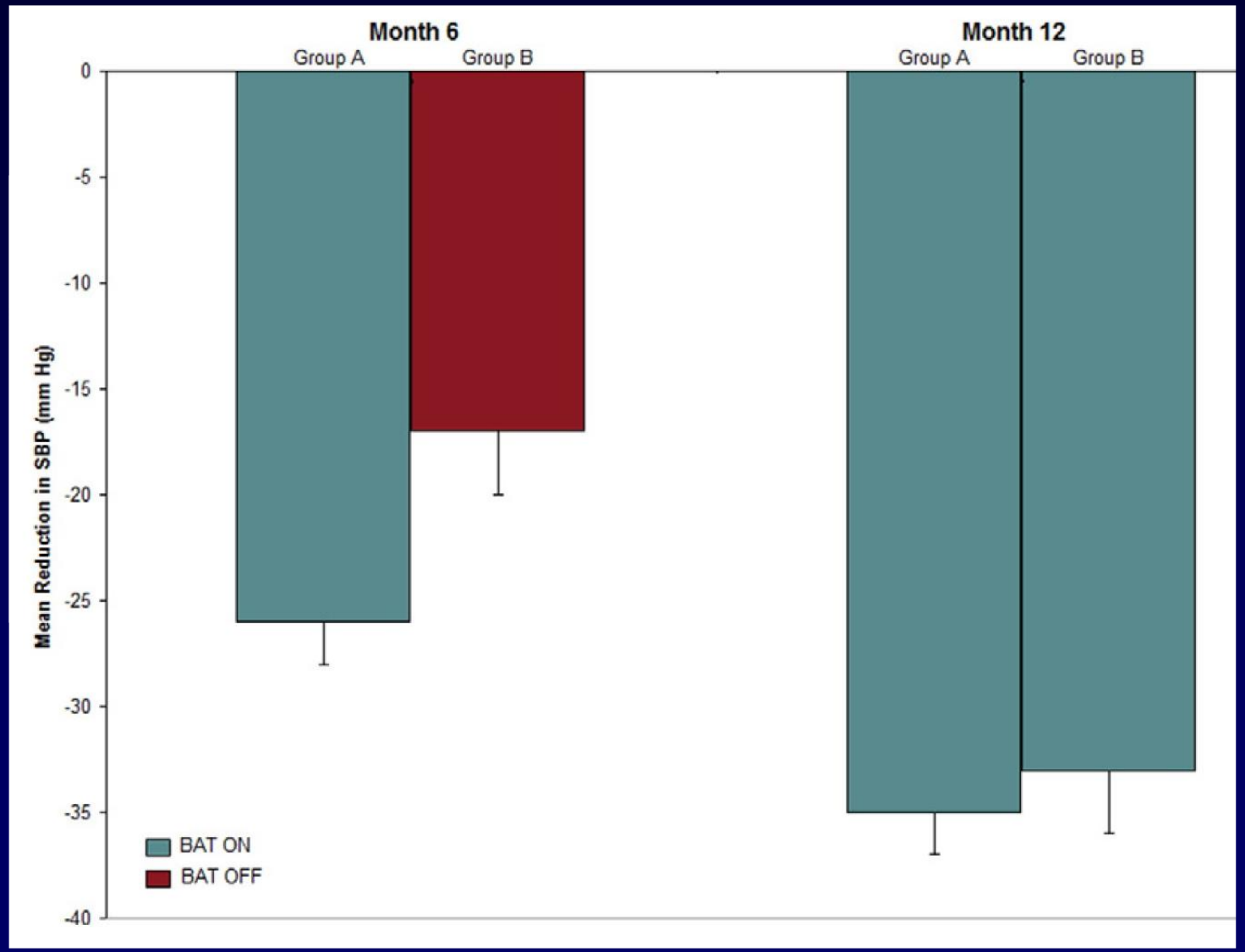
Randomised, double-blind study, n=379

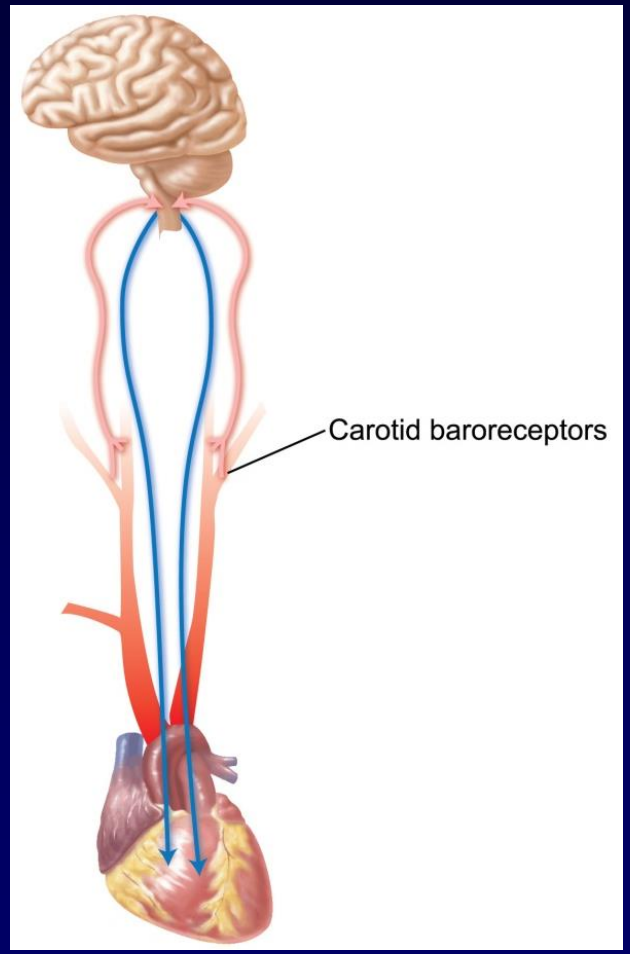
Oedema or fluid retention occurred in 67 (27%) patients given darusentan compared with 19 (14%) given placebo

Weber MA, et al. Lancet 2009; 374:1423-1431

Baroreflex activation in RH: The Rheos System (CVRx)

N=265 patients with RH





Bisognano, et al. JACC 2011

Iliac AV fistula in RH: The Rox Study

N=83 patients with office SBP >140 mmHg and ABP >135/85 mmHg on drugs
Implantation of AV coupler vs no treatment. Follow-up=6 months

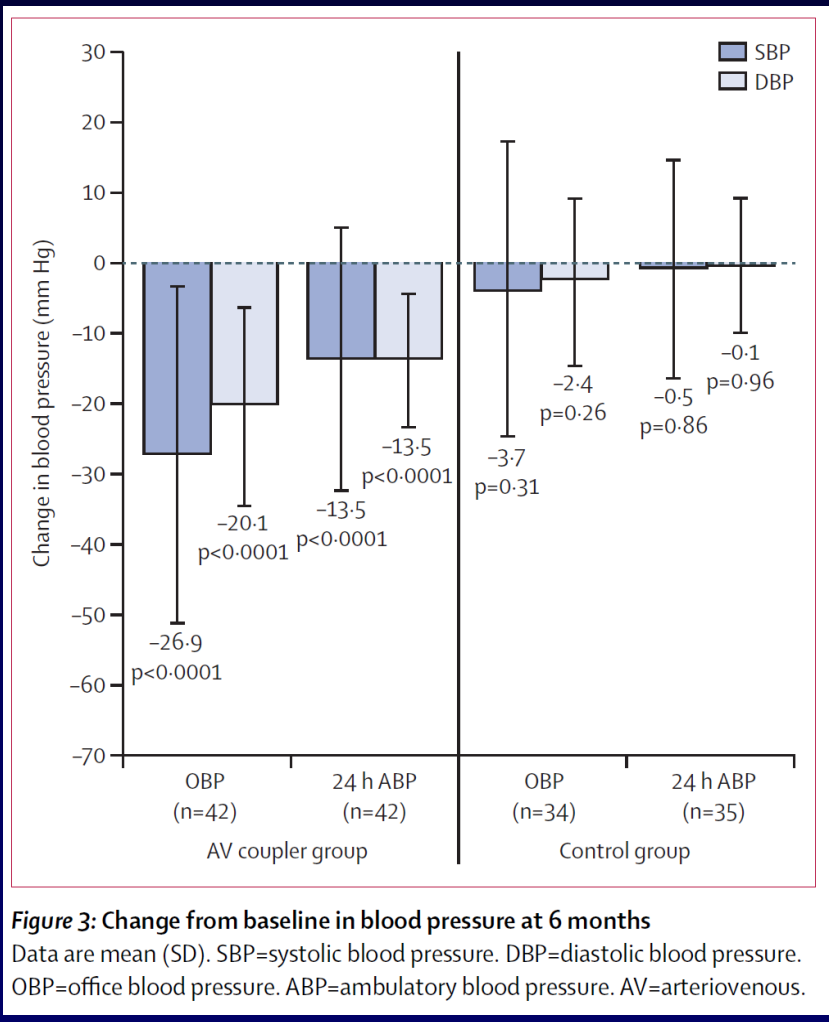


Figure 3: **Change from baseline in blood pressure at 6 months**
Data are mean (SD). SBP=systolic blood pressure. DBP=diastolic blood pressure. OBP=office blood pressure. ABP=ambulatory blood pressure. AV=arteriovenous.

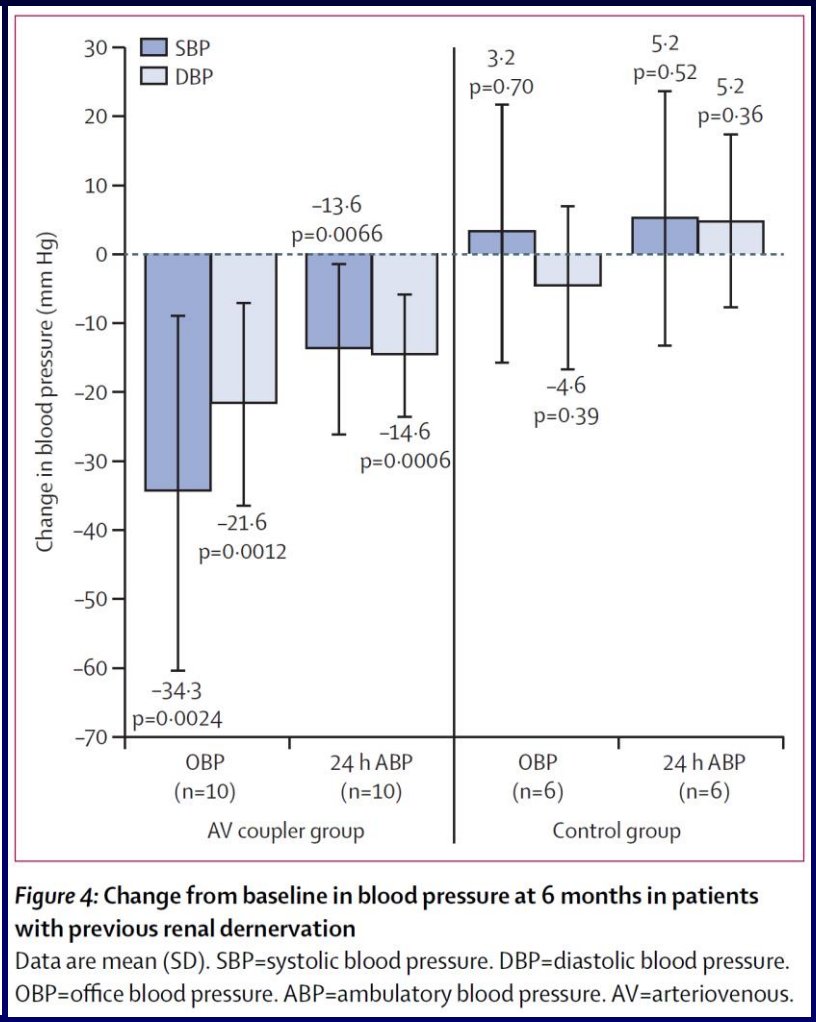
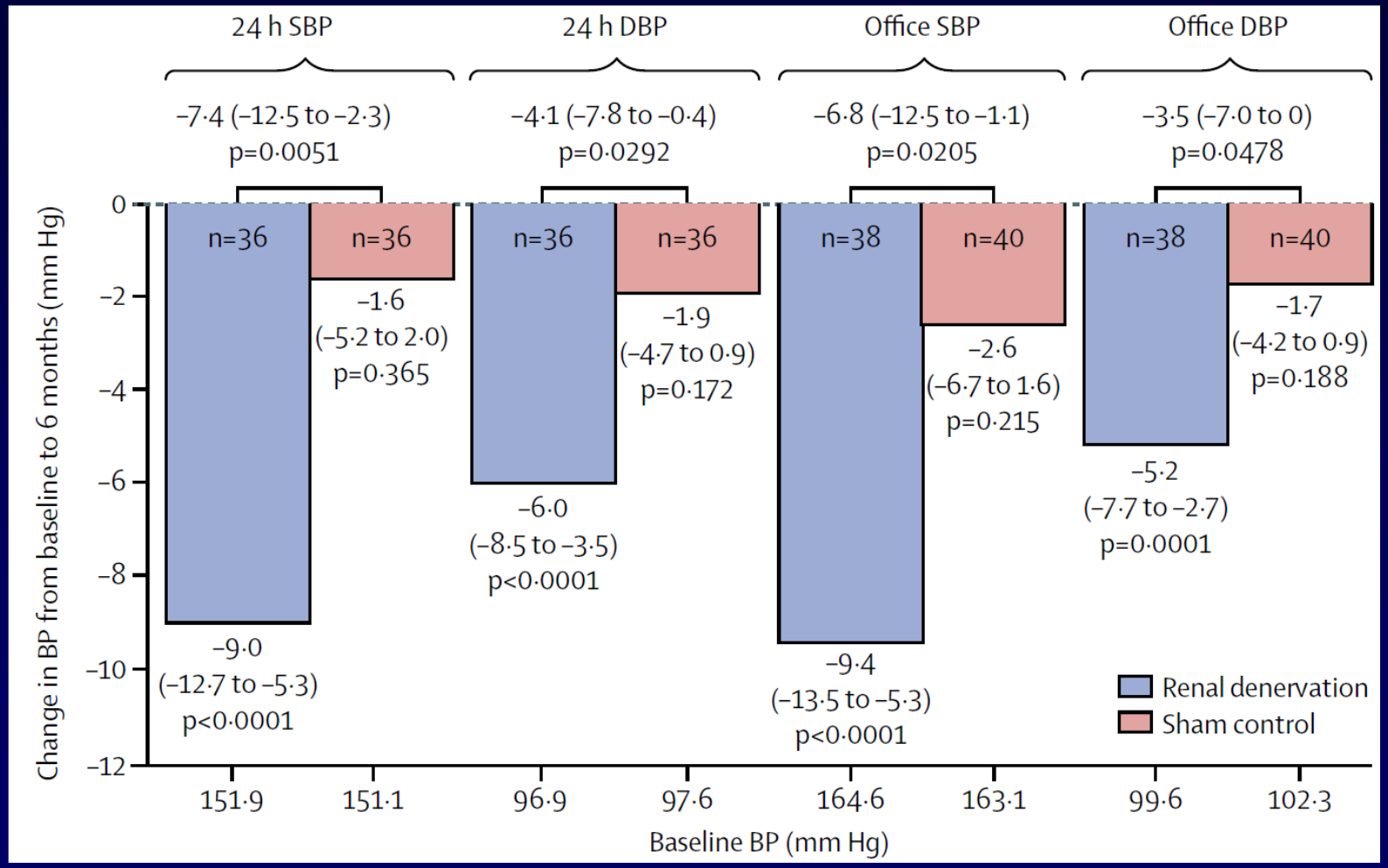


Figure 4: **Change from baseline in blood pressure at 6 months in patients with previous renal dernervation**
Data are mean (SD). SBP=systolic blood pressure. DBP=diastolic blood pressure. OBP=office blood pressure. ABP=ambulatory blood pressure. AV=arteriovenous.

Lobo, et al. Lancet 2015

The SPYRAL HTN-ON MED study

N=80 patients with office SBP 150-180 mmHg and DBP>90 mm Hg
24-h SBP 140-170 mm Hg at second screening
1-3 antihypertensive drugs with stable doses for at least 6 weeks. F-U=6 months



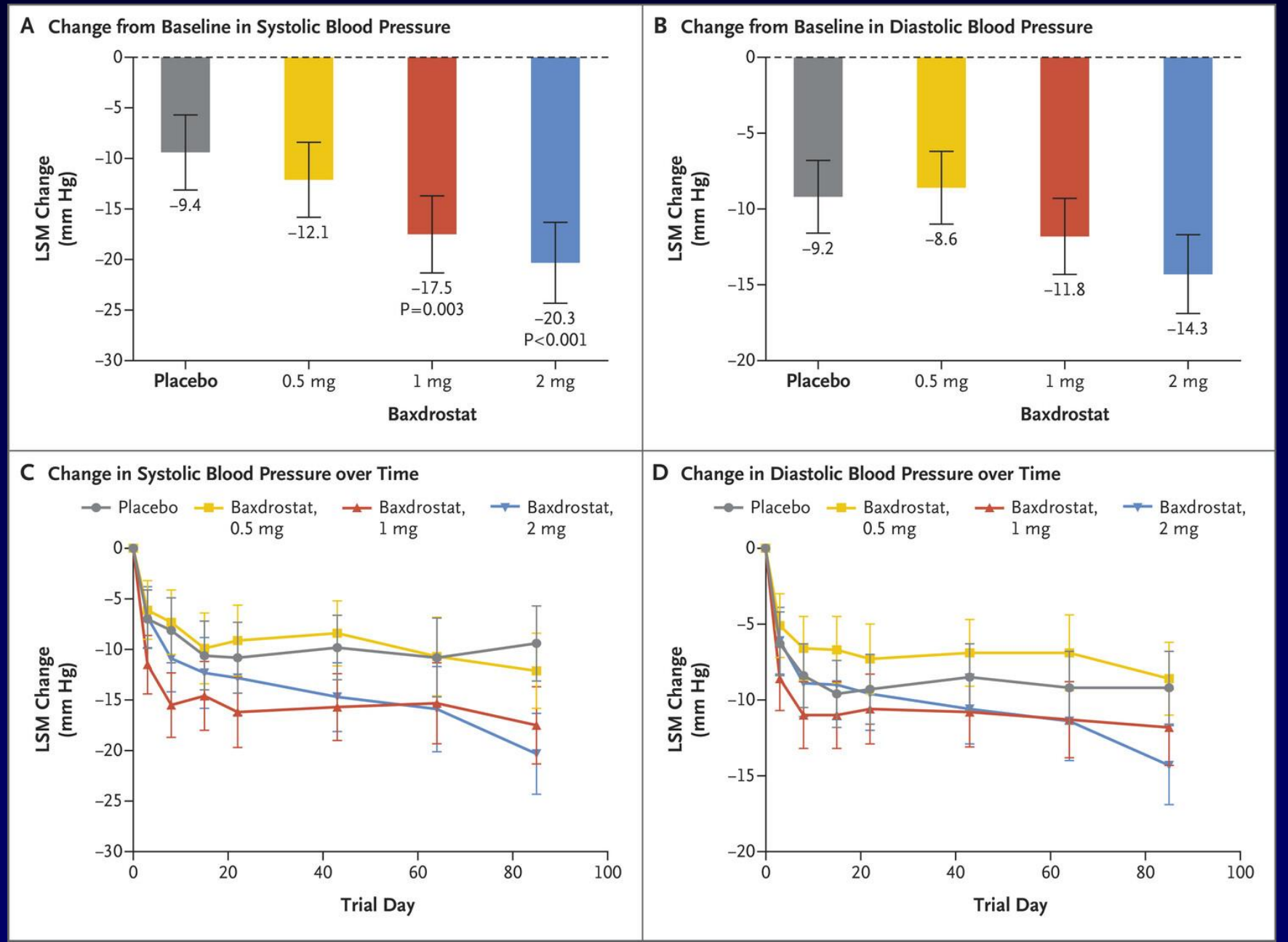
Kandzari, et al. Lancet 2018

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.	IIb	B
RDN can be considered as an additional treatment option in patients with resistant hypertension if eGFR is >40 ml/min/1.73m^2	IIb	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
Renal denervation should only be performed in experienced specialized centers to guarantee appropriate selection of eligible patients and completeness of the denervation procedure.	I	C

Baxdrostat for Resistant Hypertension

N=248 patients with office BP 130/80 mm Hg or higher, receiving stable doses of at least three antihypertensive agents



Freeman, et al. N Engl J Med 2022

Zilebesiran, an RNA Interference Therapeutic Agent for Hypertension

Desai, et al. N Engl J Med 2023

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Zilebesiran, an RNA Interference Therapeutic Agent for Hypertension

Desai AS et al. DOI: 10.1056/NEJMoa2208391

CLINICAL PROBLEM

Nearly half of patients with hypertension do not reach guideline-recommended blood-pressure targets. Zilebesiran is an investigational RNA interference therapeutic agent that inhibits the production of angiotensinogen, the precursor of angiotensin, which plays a key role in the pathogenesis of hypertension.

CLINICAL TRIAL

Design: A four-part, multicenter, phase 1 study assessed the safety and blood-pressure–lowering effects of zilebesiran in adults ≤65 years of age with treated or untreated hypertension.

Intervention: 107 patients were enrolled. In Part A, patients were randomly assigned to a single subcutaneous dose of zilebesiran (at one of seven doses ranging from 10 to 800 mg) or placebo. In Part B, zilebesiran (800 mg) or placebo was administered under low- and high-salt dietary conditions, and in Part E, irbesartan was added to zilebesiran (800 mg). (Part C was removed during a protocol amendment, and Part D is ongoing.) The primary end point was the frequency of adverse events.

RESULTS

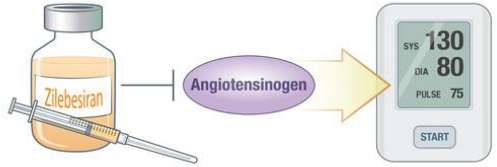
Safety: Overall, adverse events were not more frequent with zilebesiran than with placebo. Five zilebesiran recipients had mild, transient injection-site reactions. No patient received interventions for hypotension, hyperkalemia, or worsening of renal function.

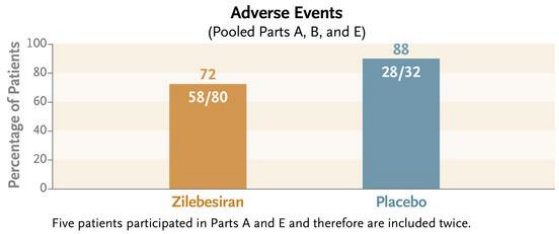
Efficacy: In Part A, single doses of zilebesiran of ≥200 mg were associated with dose-dependent decreases in blood pressure that were apparent by week 8 and were sustained for up to 24 weeks. In Part B, a high-salt diet appeared to attenuate the blood-pressure–lowering effects of zilebesiran. In Part E, irbesartan appeared to enhance the effects of zilebesiran.

LIMITATIONS AND REMAINING QUESTIONS

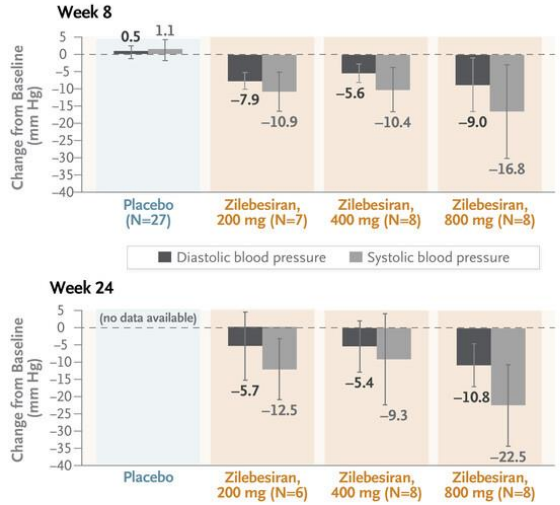
- The efficacy end points were exploratory.
- The study was too small and short to fully assess safety.
- Whether zilebesiran has the teratogenic effects of other renin–angiotensin system inhibitors is unknown.

Links: Full Article | NEJM Quick Take | Science behind the Study





Five patients participated in Parts A and E and therefore are included twice.



CONCLUSIONS

In patients with hypertension, the investigational RNA interference therapeutic agent zilebesiran was associated with mild injection-site reactions and led to dose-dependent decreases in blood pressure that were sustained at 24 weeks of follow-up.

The next wave: investigational antihypertensive drugs for HTN Management

Drug Name	Phase of Development	Company	Target Indication	Notes
Aprocitentan	Phase 3	Janssen/Idorsia	Resistant hypertension	Idorsia filed an NDA with the FDA for difficult-to-control hypertension in December 2022
XXB750	Phase 2	Novartis	Resistant hypertension and HFpEF	Pursuing indications for Resistant Hypertension and HFpEF
Zilebesiran	Phase 2	Alnylam	Uncontrolled hypertension	Novel mechanism of action
IONIS-AGT-LRx	Phase 2	Ionis Pharmaceuticals	Uncontrolled hypertension	Novel antisense oligonucleotide inhibitor
Baxdrostat	Phase 2	AstraZeneca/CinCor	Resistant hypertension	underwhelming performance in phase 2 HALO trial
Lorundrostat	Phase 2	Mineralys	Uncontrolled hypertension	Positive results from phase 2

https://www.drugdiscoverytrends.com/the-next-wave-10-promising-investigational-antihypertensive-drugs-to-watch/

Conclusions

- Cross-sectional studies estimate the prevalence of RH in 12% of the general hypertension and >30% of patients with advanced CKD
- RH in CKD patients is associated with worse renal and CV outcomes
- Factors of “pseudo-resistance” (white coat effect and poor adherence) should be excluded also in CKD
- Identifiable causes (primary aldo, RAS) may be present
- Among numerous causes of RH in CKD, excess sodium intake & impaired sodium removal are the most prominent
- Reduction of sodium intake and modification of diuretics are the cornerstones of treatment
- Spironolactone provides effective BP reduction also in CKD but should be used with caution

Καλό ταξίδι δάσκαλε!