

ADVANCES IN CARDIAC ARRHYTHMIAS

and

GREAT INNOVATIONS IN CARDIOLOGY

XXVII GIORNATE CARDIOLOGICHE TORINESI



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Università degli Studi di Torino
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SCU Medicina Interna, Centro Ipertensione Arteriosa
Torino

Management of severe hypertension: the approach

How to recognize and how to treat
difficult blood pressure control patient

Franco Veglio, MD, CHS

Documentation and treatment of hypertension: in a family medicine resident clinic

- In the USA, uncontrolled hypertension contributes to 1000 deaths a day.
- US\$ 131 billion a year in healthcare costs.

aTRH

- **Apparent treatment-resistant hypertension**

aTRH is defined as uncontrolled hypertension despite the use of ≥ 3 antihypertensive medication classes.

or **controlled hypertension** while treated with ≥ 4 antihypertensive medication classes.

Definition of Resistant Hypertension

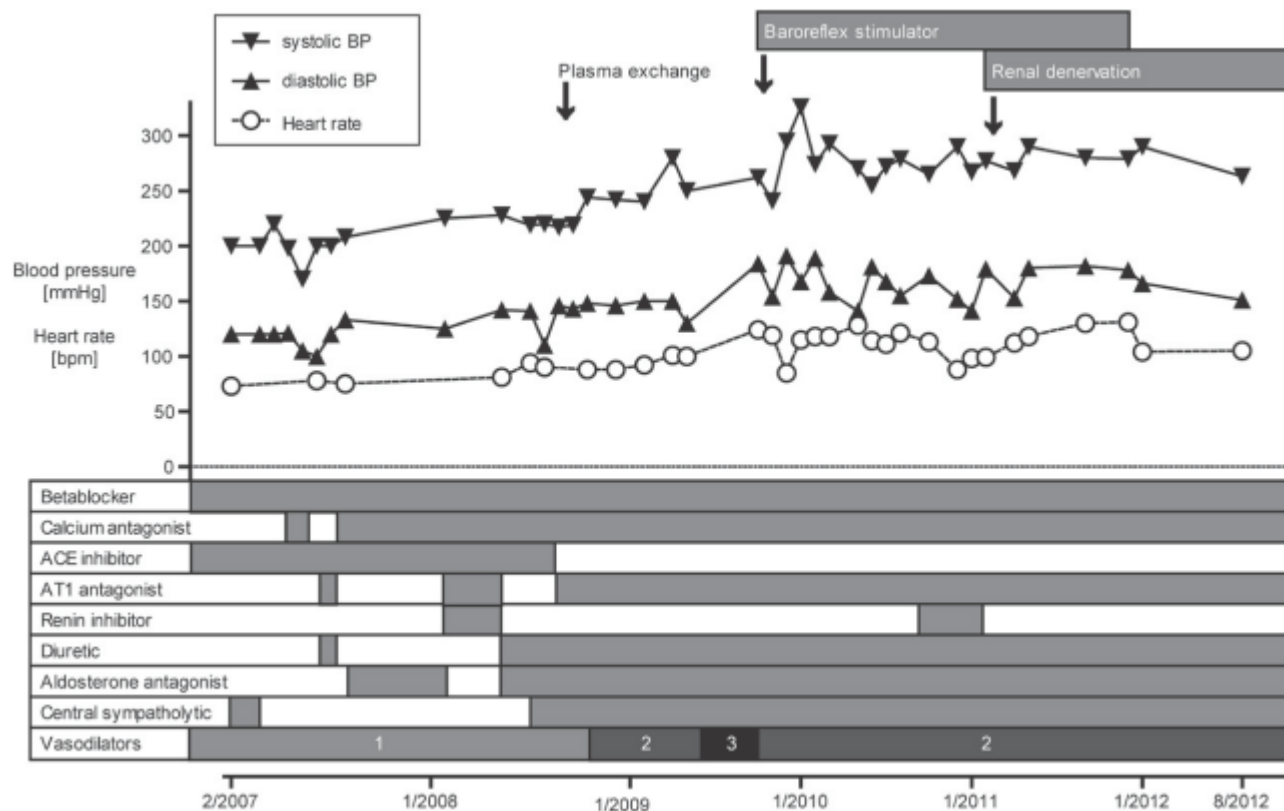
by Blood Pressure Monitoring

RHT categories	Office BP	Mean home BP	Mean daytime BP	Mean daytime and nighttime BP
Controlled RHT	<140/90 mm Hg	<135/85 mm Hg	<135/85 mm Hg	<135/85 mm Hg and <120/70 mm Hg
Masked RHT	<140/90 mm Hg	≥135/85 mm Hg	≥135/85 mm Hg	≥135/85 mm Hg or ≥120/70 mm Hg
White-coat RHT	≥140/90 mm Hg	<135/85 mm Hg	<135/85 mm Hg	<135/85 mm Hg and <120/70 mm Hg
→ True RHT	≥140/90 mm Hg	≥135/85 mm Hg	≥135/85 mm Hg	≥135/85 mm Hg or ≥120/70 mm Hg

Hypertension Grand Rounds

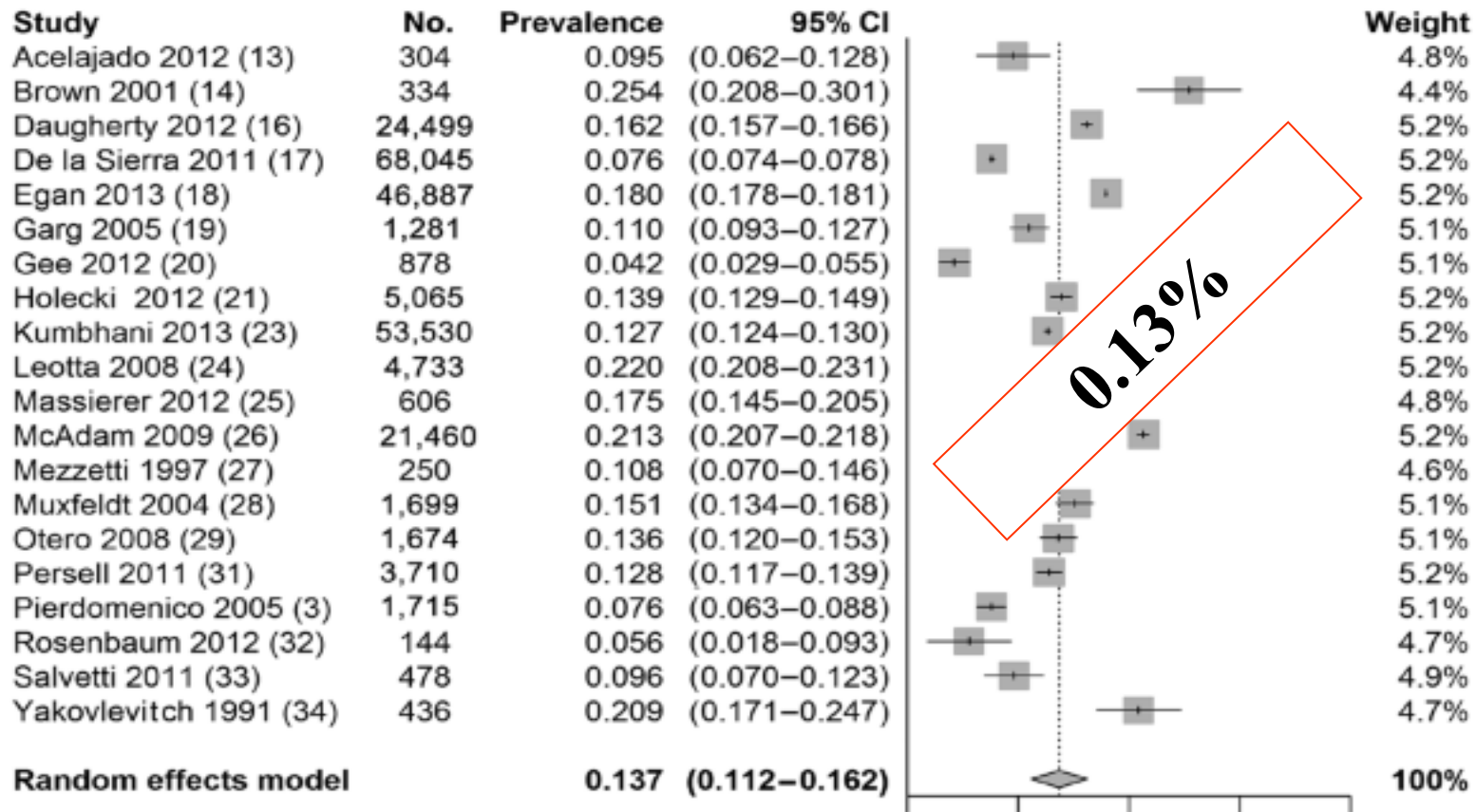
Truly Refractory Hypertension

Christoph Schroeder, Karsten Heusser, Julia Brinkmann, Jan Menne, Hanno Oswald, Hermann Haller, Jens Jordan, Jens Tank, Friedrich C. Luft



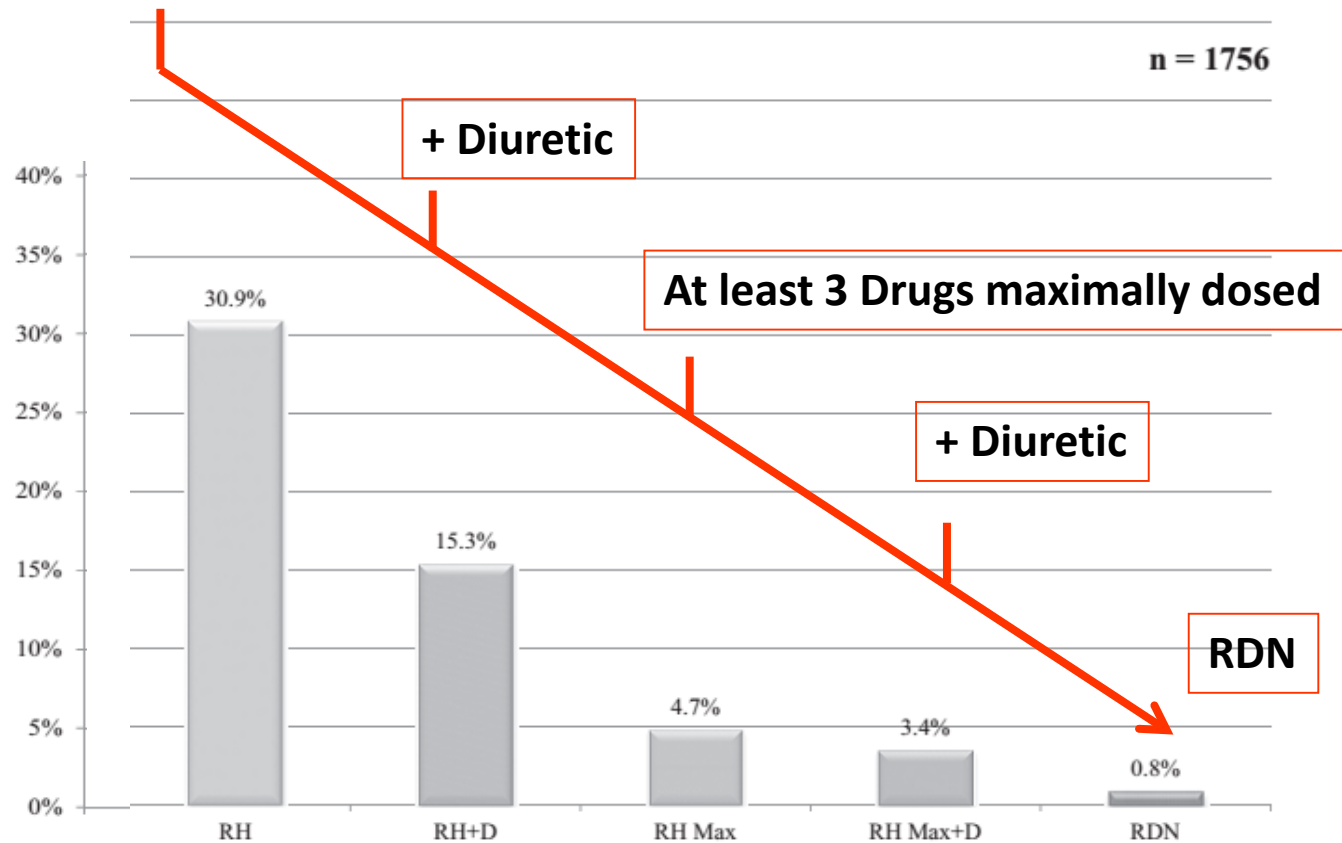
“Device refractory hypertension”

PREVALENCE OF aTRH

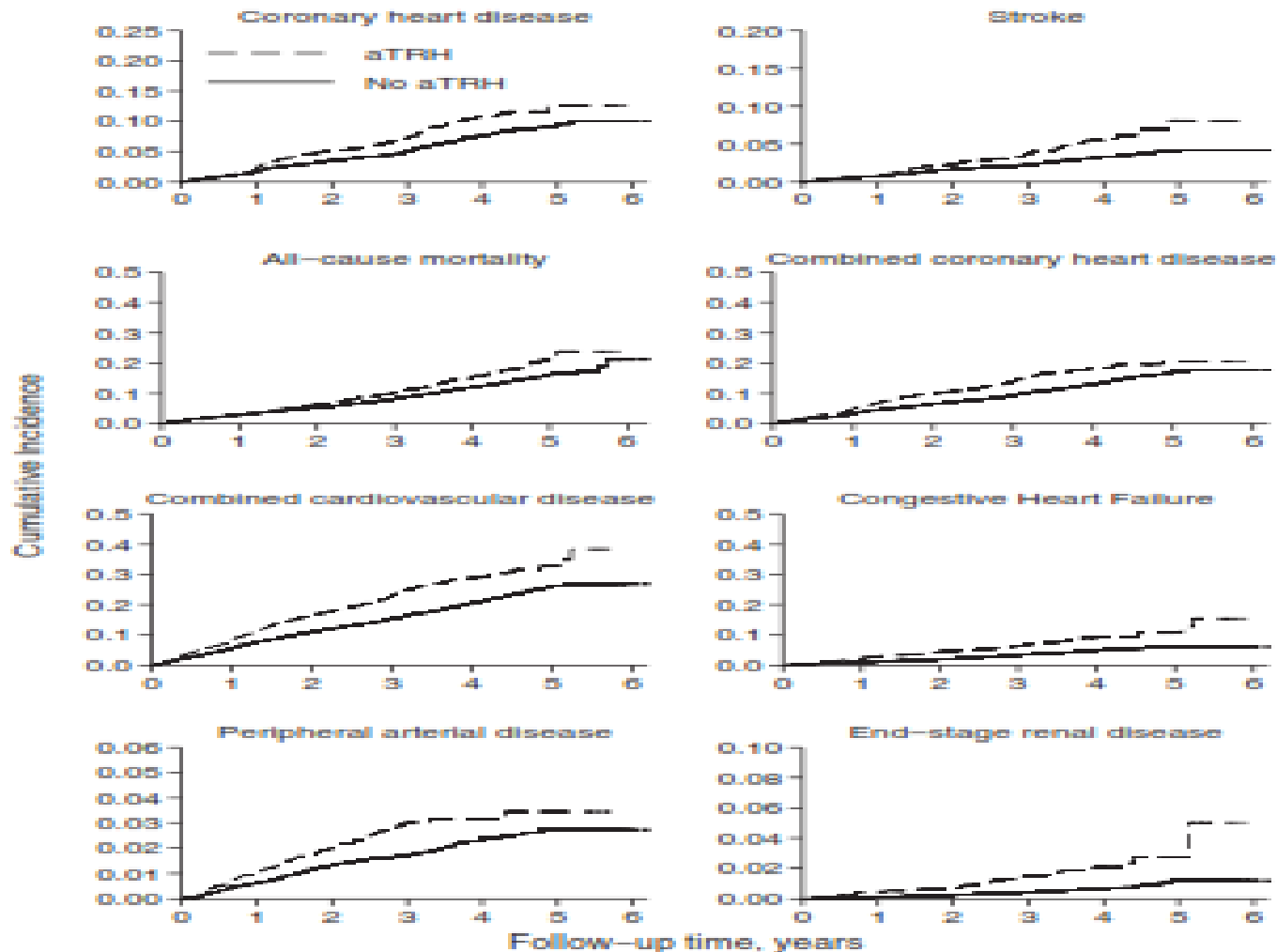


PREVALENCE OF RESISTANT HYPERTENSION

SBP>140 \geq 3 Drugs or controlled with \geq 4 Drugs



Prognosis of aTRH



Clinical Management of Resistant Hypertension

Practical recommendations from the Italian Society of Hypertension (SIIA)

Franco Veglio • Guido Grassi • Giuseppe Mancia •
Massimo Volpe

Published online: 15 August 2013

Factors contributing to pseudo-resistant hypertension

Clinician-related factors

- Inappropriate blood pressure measurement technique
- Treatment inadequacy
 - Inadequate doses
 - Suboptimal drug combinations
- Clinical inertia (failure to optimize or enhance antihypertensive therapy when needed)
- Poor communication skills
- Complex therapeutic regimens (particularly with simultaneous presence of other drug regimens)

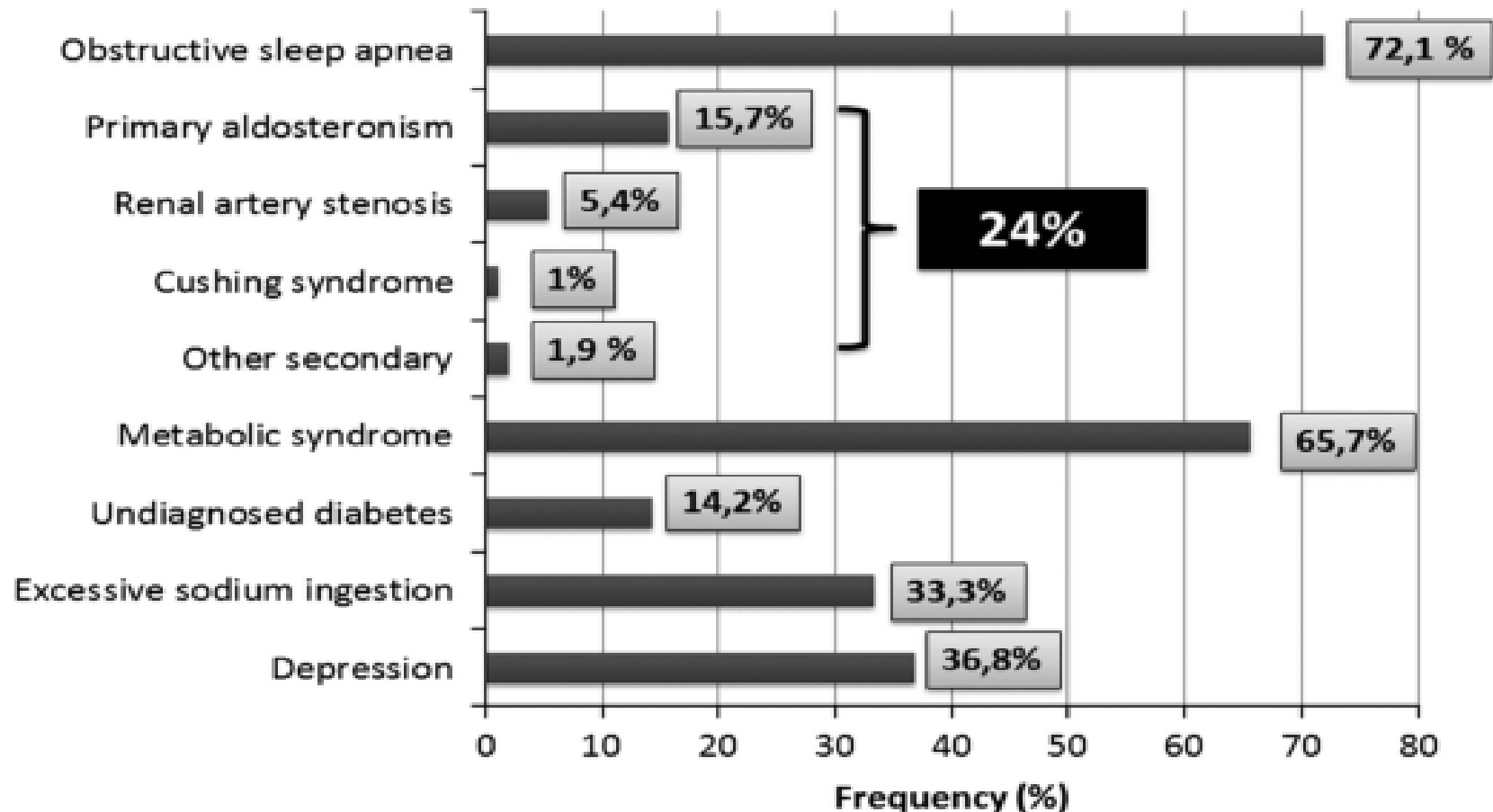
Patient-related factors

- White coat effect
- Drug related adverse events
- Lack of motivation
- Poor communication skills
- Concomitant use of oral contraceptives
- Concomitant use of NSAIDs or sympathomimetic drugs
- Memory loss, psychiatric illness or cognitive impairment (elderly patients)
- Cost of therapy (in some health care systems)

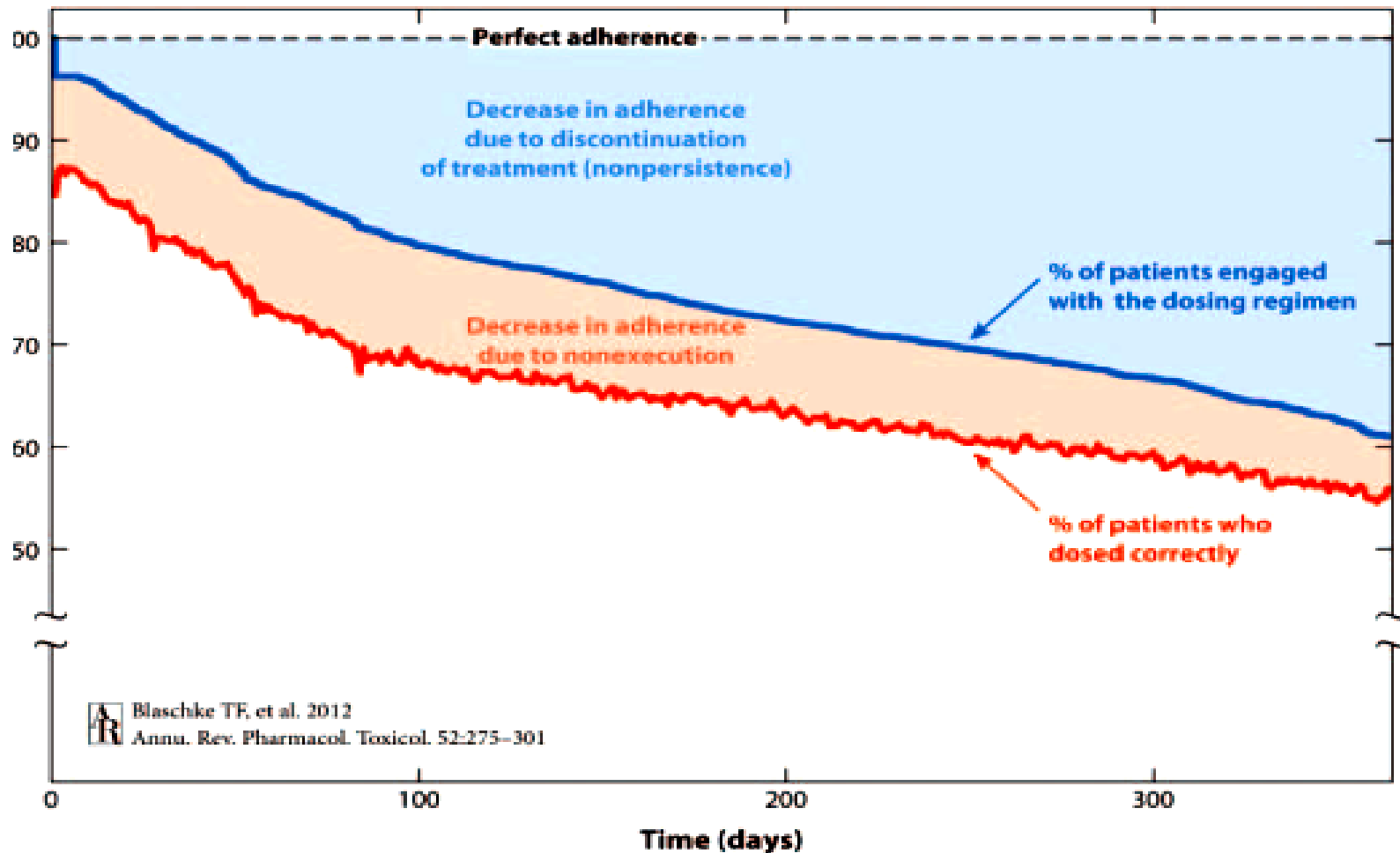
Other factors

- Obstructive sleep apnea
- Nephropathy or chronic kidney disease
- Primary or secondary hyperaldosteronism
- Severe atherosclerosis of arterial walls (elderly patients)
- Aortic valve sclerosis resulting in hemodynamically significant regurgitation

Prevalence of pseudoresistant hypertension phenotypes

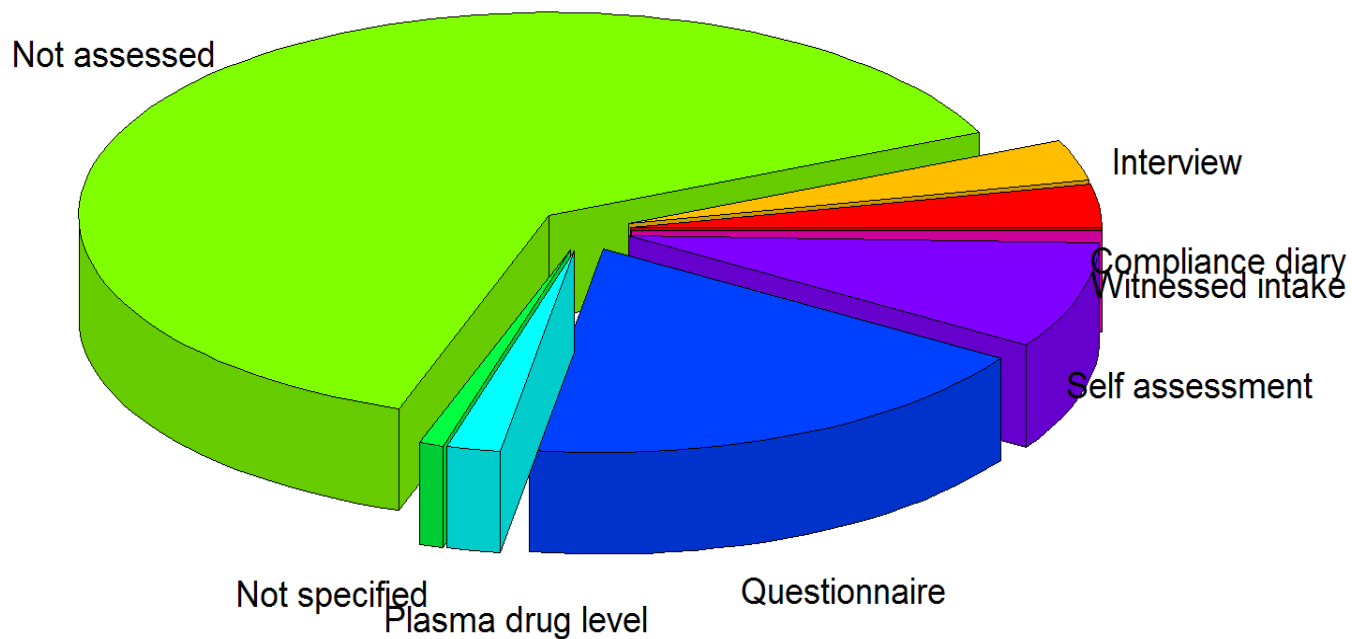


Measuring, Analyzing, and Managing Drug Adherence in Resistant Hypertension

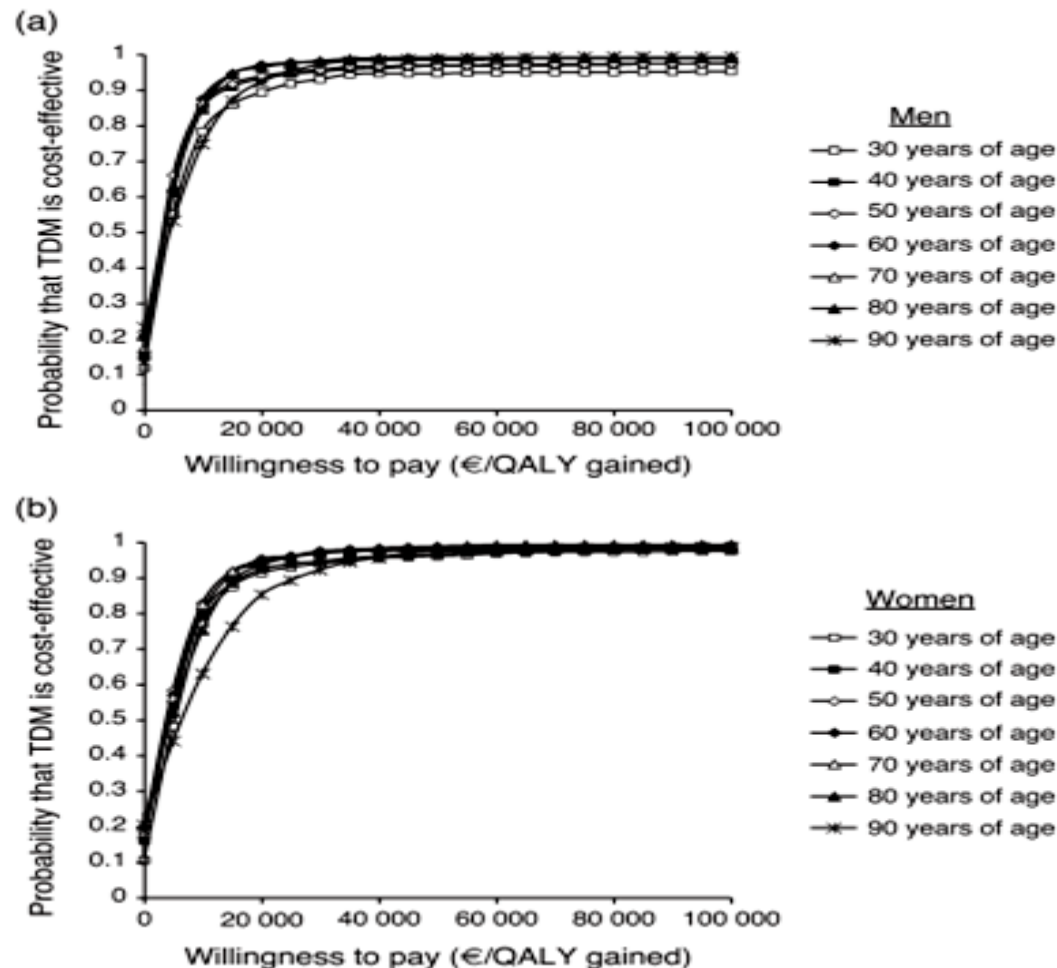


RADIOFREQUENCY RENAL DENERVATION

Characteristics of the included studies: **Adherence to antihypertensive therapy**

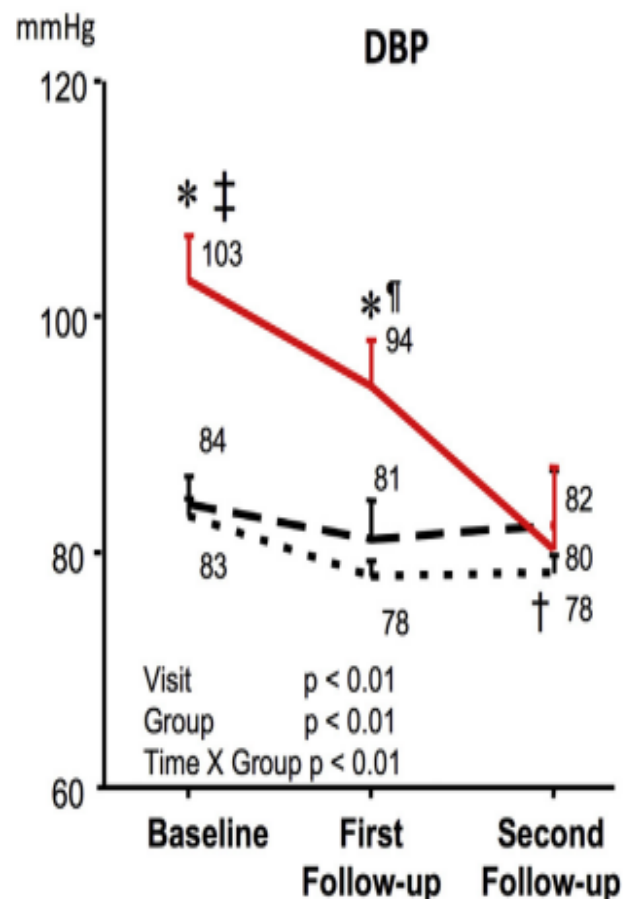
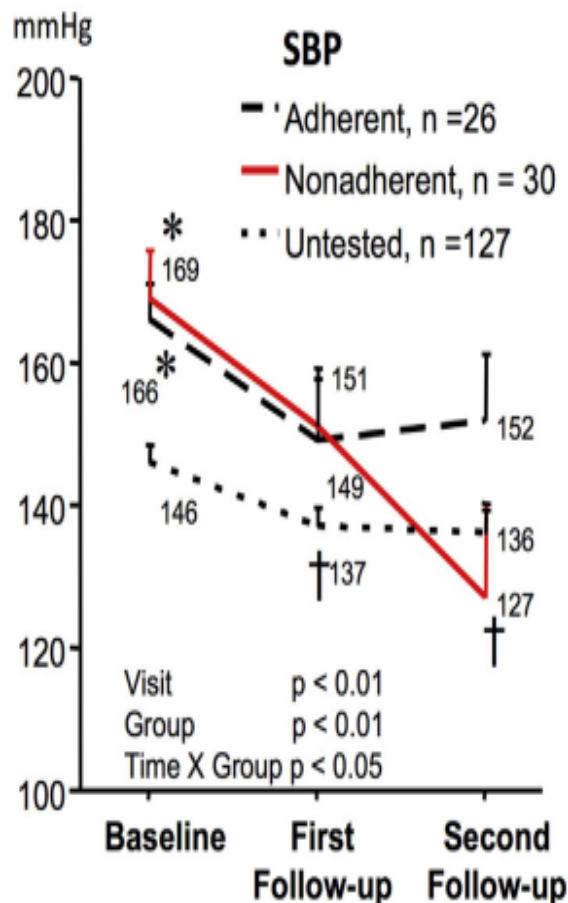


Potential cost-effectiveness of therapeutic drug monitoring in patients with resistant hypertension



Therapeutic Drug Monitoring Facilitates
Blood Pressure Control in Resistant Hypertension

C



Chromatographic Analysis

 Laboratorio di Farmacologia Clinica e Farmacogenetica	Therapeutic Drug Monitoring	7PG01_ipertensivi Rev. 0 Pag. 1 di 1

Università degli Studi di Torino / ASL TO2

INVIARE IL CAMPIONE A: C/A DR. ANTONIO D'AVOLIO

DIP. DI SCIENZE MEDICHE - Laboratorio di Farmacologia Clinica e Farmacogenetica (Resp. Dr. Antonio D'Avolio)
Padiglione Q, Ospedale "Amedeo di Savoia" C.so Svizzera 164, 10149 Torino; Tel. 011.4393979; Fax: 011.4393882; e-mail:
info@tdm.torino.org

Scheda di accompagnamento del campione ANTI-IPERTENSIVI

Studio:	TDM-TO
Reparto inviante:	Medicina Interna 4, AOU Molinette
Telefono:	011 6336959
Email:	centroiperten.torino@libero.it

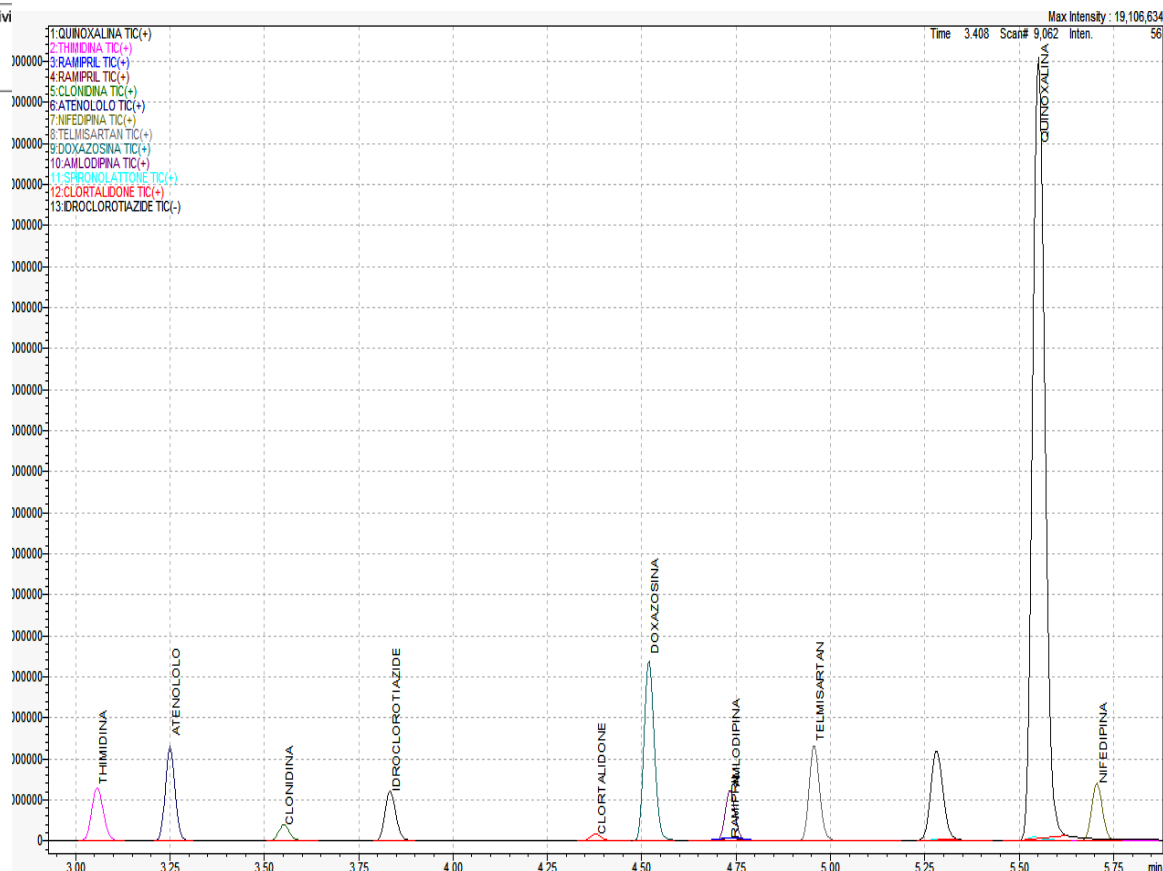
Dati paziente:		
ID _____	Peso (Kg) _____	Sesso M <input type="checkbox"/> F <input type="checkbox"/>
Data di nascita _____	Altezza (cm) _____	

Terapia antiipertensiva in corso					
Farmaco	Dose(mg)	n.co/die	Inizio T(g/m/a)	U.D. (g/m/a)	h U.D. h pasto vicino U.D.
Amlodipina <input type="checkbox"/>			///	///	
Atenololo <input type="checkbox"/>			///	///	
Clortalidone <input type="checkbox"/>			///	///	
Idroclorotiazide <input type="checkbox"/>			///	///	
Ramipril <input type="checkbox"/>			///	///	
Telmisartan <input type="checkbox"/>			///	///	
Olmesartan <input type="checkbox"/>			///	///	
Clonidina <input type="checkbox"/>			///	///	
Nifedipina <input type="checkbox"/>			///	///	
Doxazosina <input type="checkbox"/>			///	///	
Spironolattone <input type="checkbox"/>			///	///	

Informazioni del campione			
Liquido biologico	Data prelievo (g/m/a)	h prelievo	Farmaco da dosare
PLASMA □/URINE □	///	///	Amlodipina
PLASMA □/URINE □	///	///	Atenololo
PLASMA □/URINE □	///	///	Clortalidone
PLASMA □/URINE □	///	///	Idroclorotiazide
PLASMA □/URINE □	///	///	Ramipril
PLASMA □/URINE □	///	///	Telmisartan
PLASMA □/URINE □	///	///	Olmesartan
PLASMA □/URINE □	///	///	Clonidina
PLASMA □/URINE □	///	///	Nifedipina
PLASMA □/URINE □	///	///	doxazosina
PLASMA □/URINE □	///	///	spironolattone

Altri farmaci concomitanti (ipertensivi e non)		
.....
.....
.....
.....

TDM Plasmatico → **2 provetta 7mL "tappo verde LH"**; TDM Urinario → **provetta di urina 10mL/24h (n. 1 provette)+ spot-10ml urine (n.1 provetta)**
 Far pervenire al Laboratorio di Farmacologia Clinica e Farmacogenetica Padiglione Q Dr. Sciandra/D'Avolio in **breve tempo** **n.3 vials con 1,5 ml x di plasma.**
 Si dichiara che il prelievo è stato eseguito, stoccato ed inviato secondo le indicazioni presenti nel sito www.tdm-torino.org: SI ☐ NO ☐



Clinical Management of Resistant Hypertension

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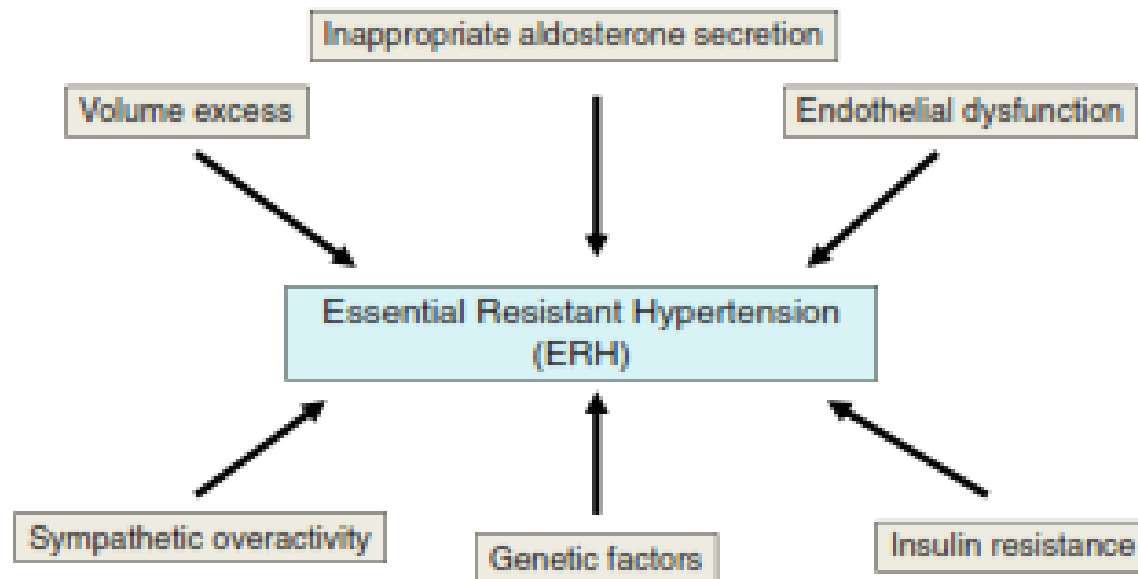
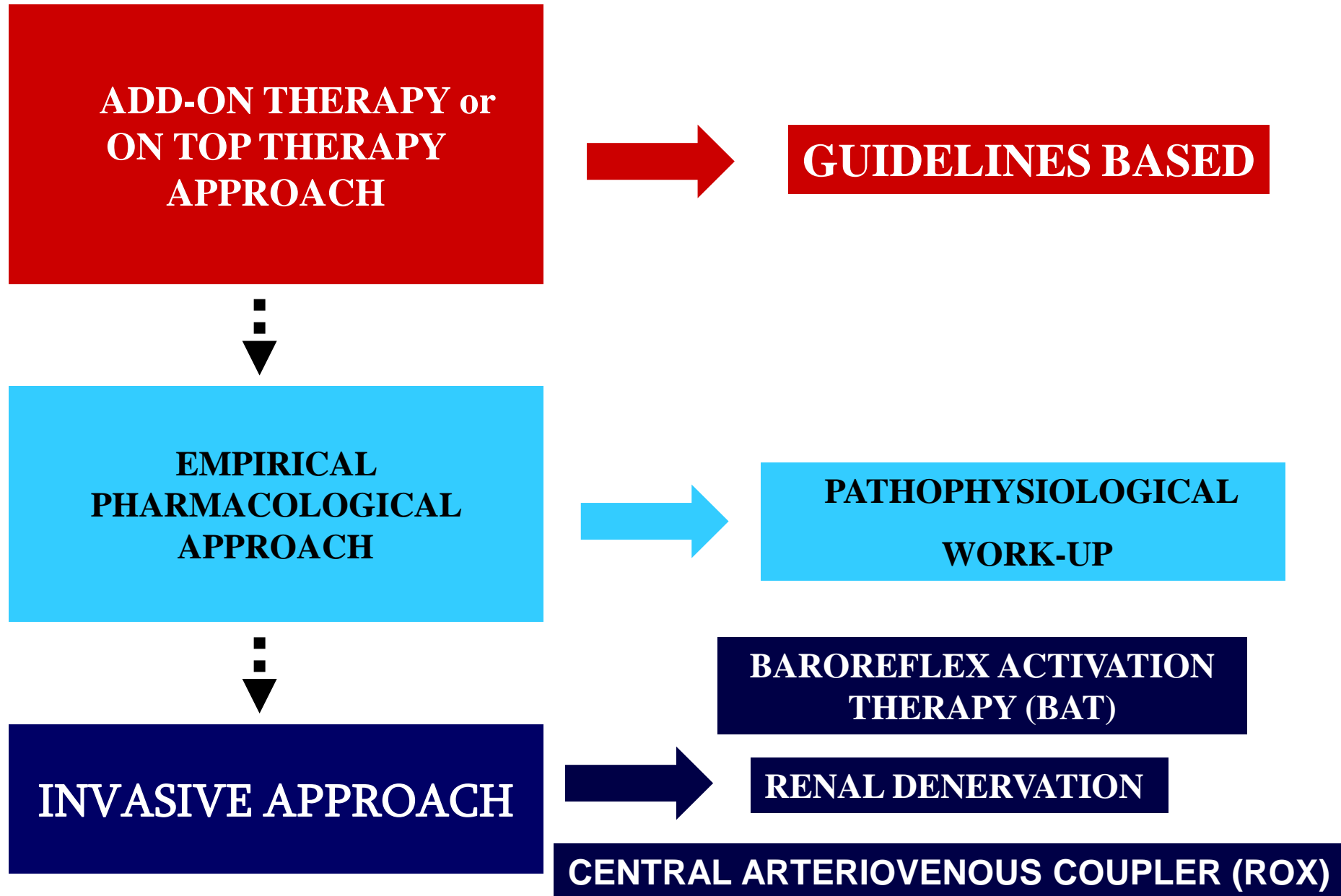


Fig. 1 Main pathophysiological mechanisms of ERH

CLINICAL STRATEGIES IN RESISTANT HYPERTENSION



Clinical Clues Helpful in Drug Selection in the Management of Resistant Hypertension

Clinical and biochemical clues suggesting
the need for a more potent diuretic regimen

High sodium intake

Size of patient

Presence of edema

Low plasma renin activity

Blood urea nitrogen, creatinine, and uric acid levels
unchanged by current diuretic

Chronic renal disease

Clinical Clues Helpful in Drug Selection in the Management of Resistant Hypertension

Clinical circumstances suggesting the presence of neurogenic hypertension

Conditions associated with both blood pressure elevation and increased sympathetic tone

- Acute stroke

- Sleep apnea

- Alcoholism

- Paroxysmal hypertension

Clinical situations suggestive of neurogenic hypertension

- Hypertension refractory to drug combinations that target sodium/volume and the renin-angiotensin system

- Absence of clinical and biochemical clues of volume excess

- Labile or paroxysmal hypertension

- Unexplained severe hypertension

- Hypertension with sinus tachycardia

Psychological factors

Simulated effect of underlying hypertension pathology on response to different antihypertensive therapies.

	DRI	ARB	ACEi	HCTZ	MR blocker	CCB (amlo)
Systemic Vascular Resistance (+)						
Preglomerular Resistance (+)						
Afferent Resistance (+)	*	*	*			
Proximal Sodium Reabs. Rate (+)						
Distal Sodium Reabs. Rate (+)						
Collecting Duct Sodium Reabs. Rate (+)				*		
Glomerular Hydraulic Conductance (-)	*	*	*	*	*	
Number of nephrons (-)				*	*	
Renin Secretion Rate (+)				*		
Aldosterone Secretion Rate (+)				*		
Renal Sympathetic Nerve Activity (+)	*	*	*			*

Mechanism-based algorithm for treating Resistant hypertension

2 Drugs Regimen

Anti Volume + Anti RAS

Clinical clues of volume excess



Step 1: Option A: optimize diuretic

Clinical clues of neurogenic HTN



Option B: treat neurogenic HTN

Add (or substitute) β or $\alpha + \beta$ Blockade

Step 2:

Option A + Option B

Step 3:

Add spironolactone or CCB (if not yet prescribed)

Step 4:

Add hydralazine or central α -agonist

Management of hypertension: summary of NICE guidance

Step 4 (Resistant hypertension)

- If clinic blood pressure remains higher than 140/90 mm Hg after treatment with the optimal or best tolerated doses of the drug combination mentioned in step 3 (an ACE inhibitor or an ARB combined with a calcium channel blocker and a diuretic), consider adding a third drug to the regimen, and consider adding a fourth antihypertensive drug and/or seeking expert advice. (Updated recommendation) *[Based on low quality observational evidence]*

3 DRUGS REGIMEN

(Updated recommendation) *[Based on low quality observational evidence]*

- If further drug treatment at step 4 is not effective, consider an α blocker or β blocker. (Updated recommendation) *[Based on low quality observational studies]*

α Blocker or β Blocker

- For treatment of resistant hypertension:
 - Consider further diuretic treatment with low dose spironolactone (25 mg once daily) if the blood potassium concentration is 4.5 mmol/L or lower. Use particular caution in patients with reduced renal function and low glomerular filtration rate because they have an increased risk of hyperkalaemia
 - Consider higher dose thiazide-like diuretic treatment if the blood potassium concentration is higher than 4.5 mmol/L.

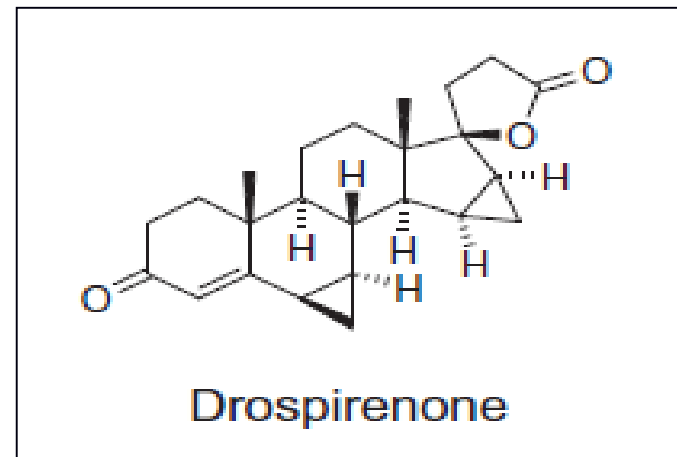
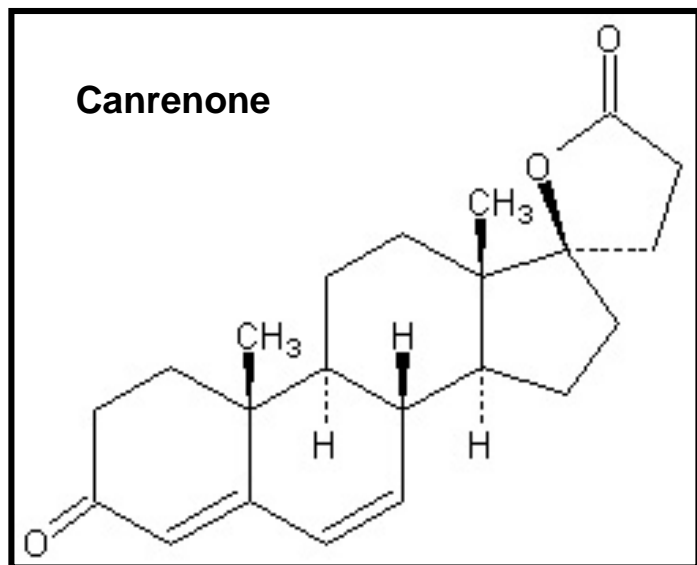
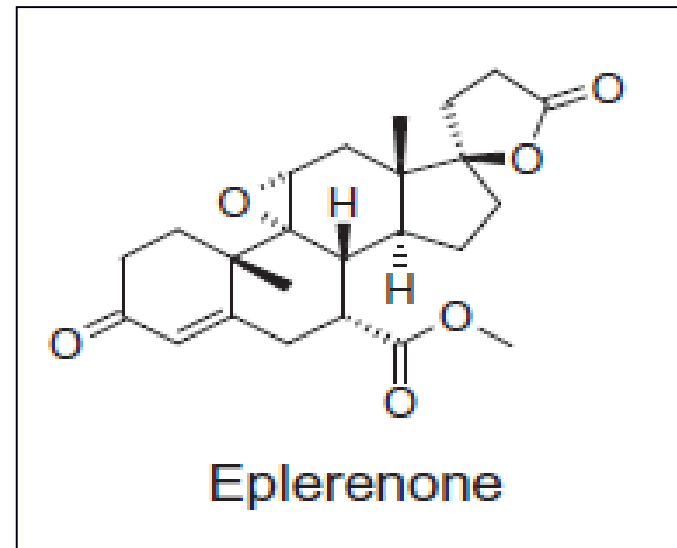
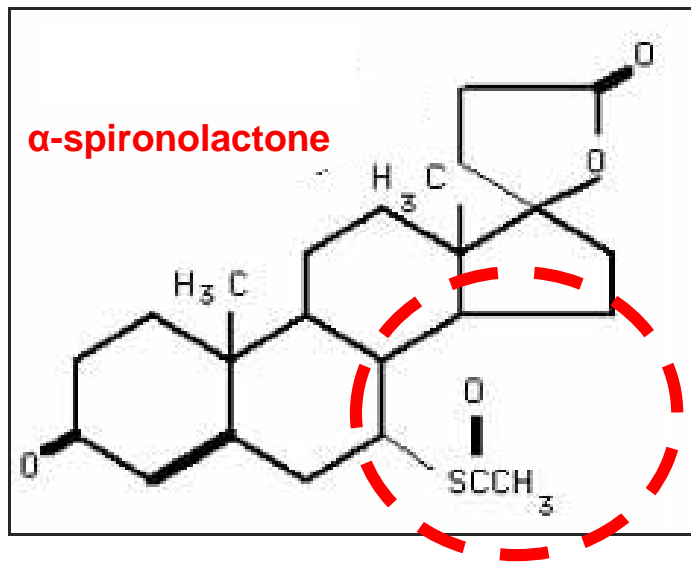
SPIRONOLACTONE 25 mg

If blood pressure remains uncontrolled with the optimal or maximum tolerated doses, seek expert advice if not yet obtained. (Updated recommendation) *[Based on the experience and opinion of the GDG]*

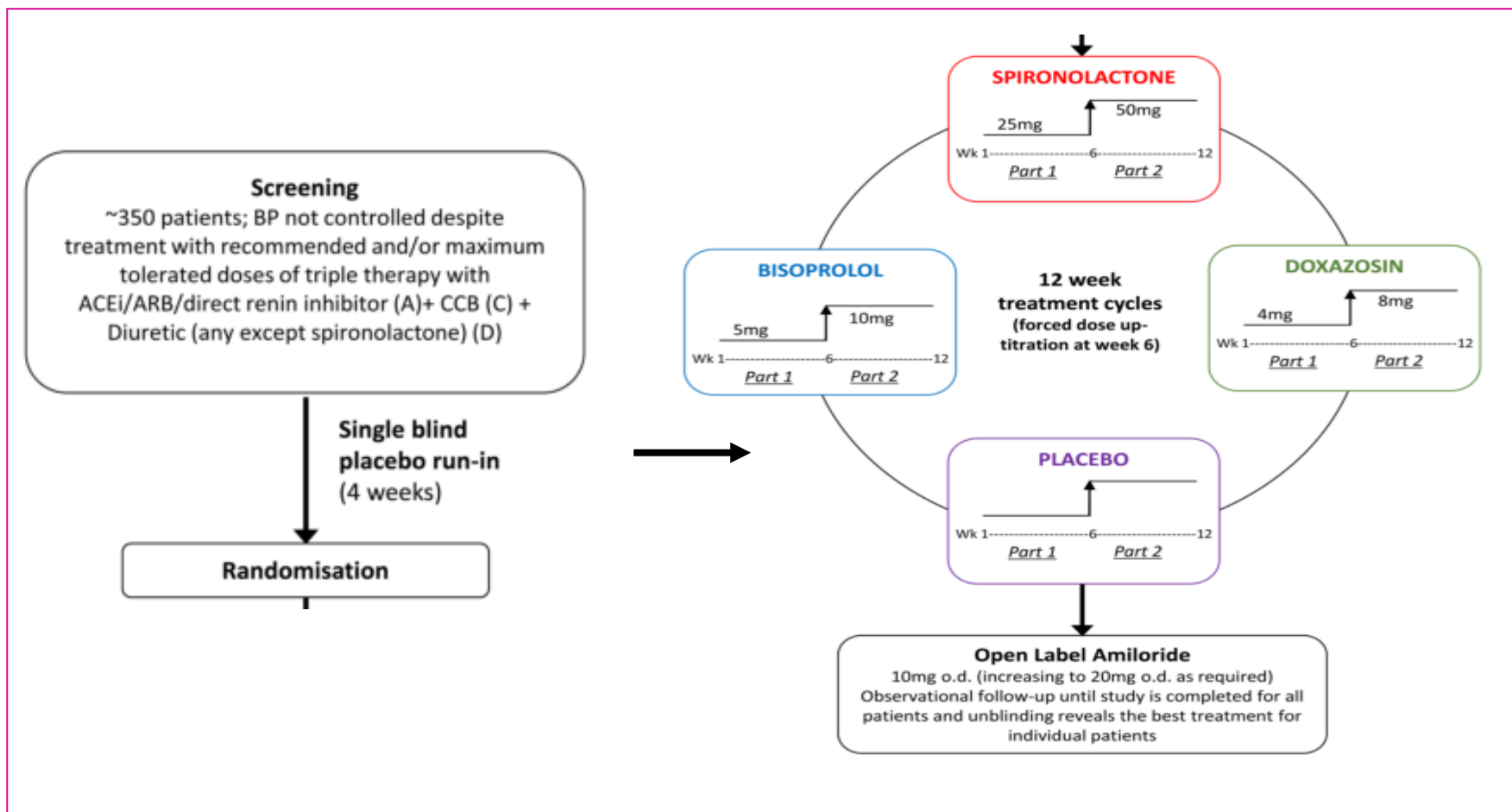
SPECIALIST

Molecular structure of ARAs

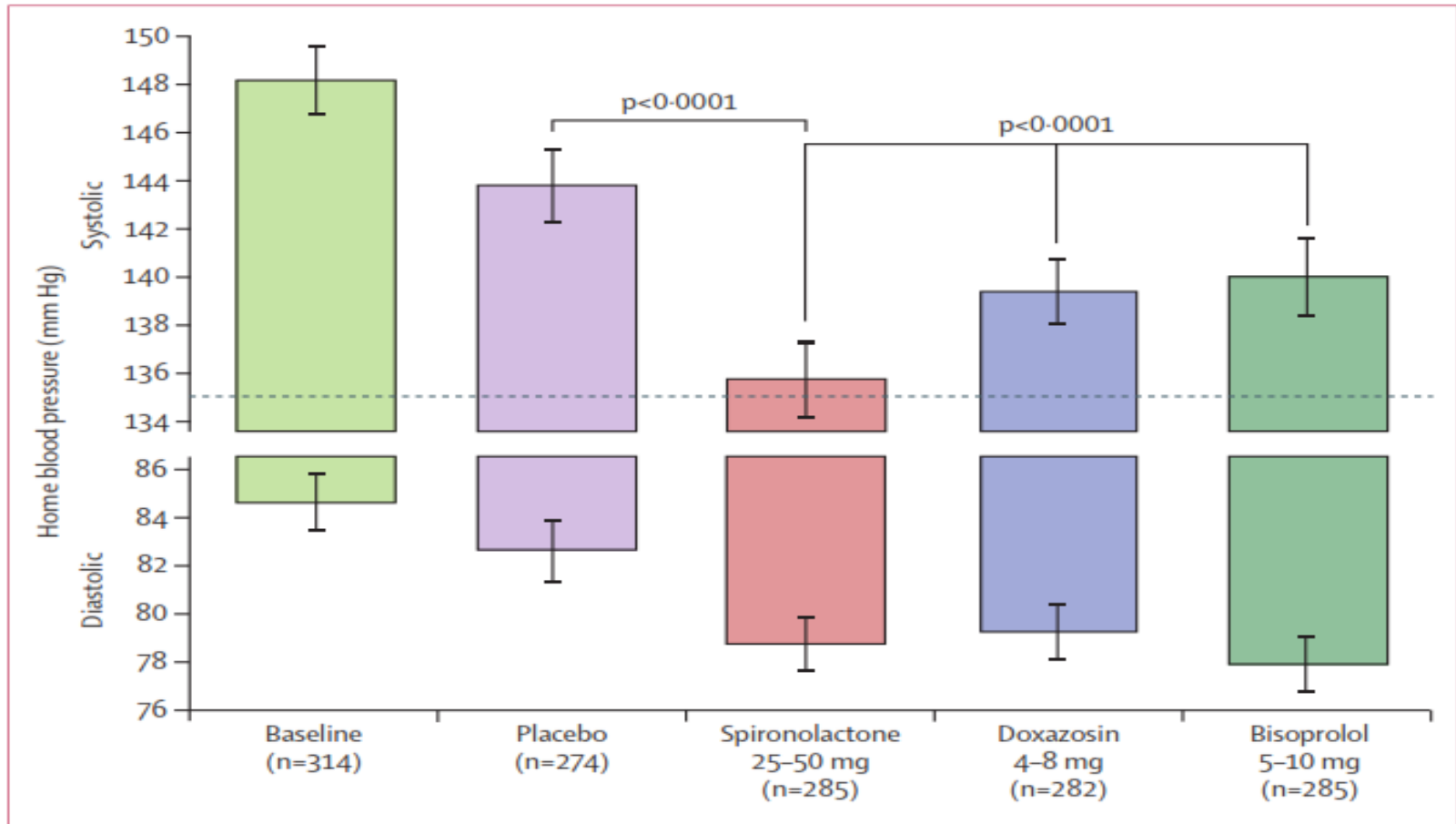
(Facultative Diuretics)



PATHWAY-2



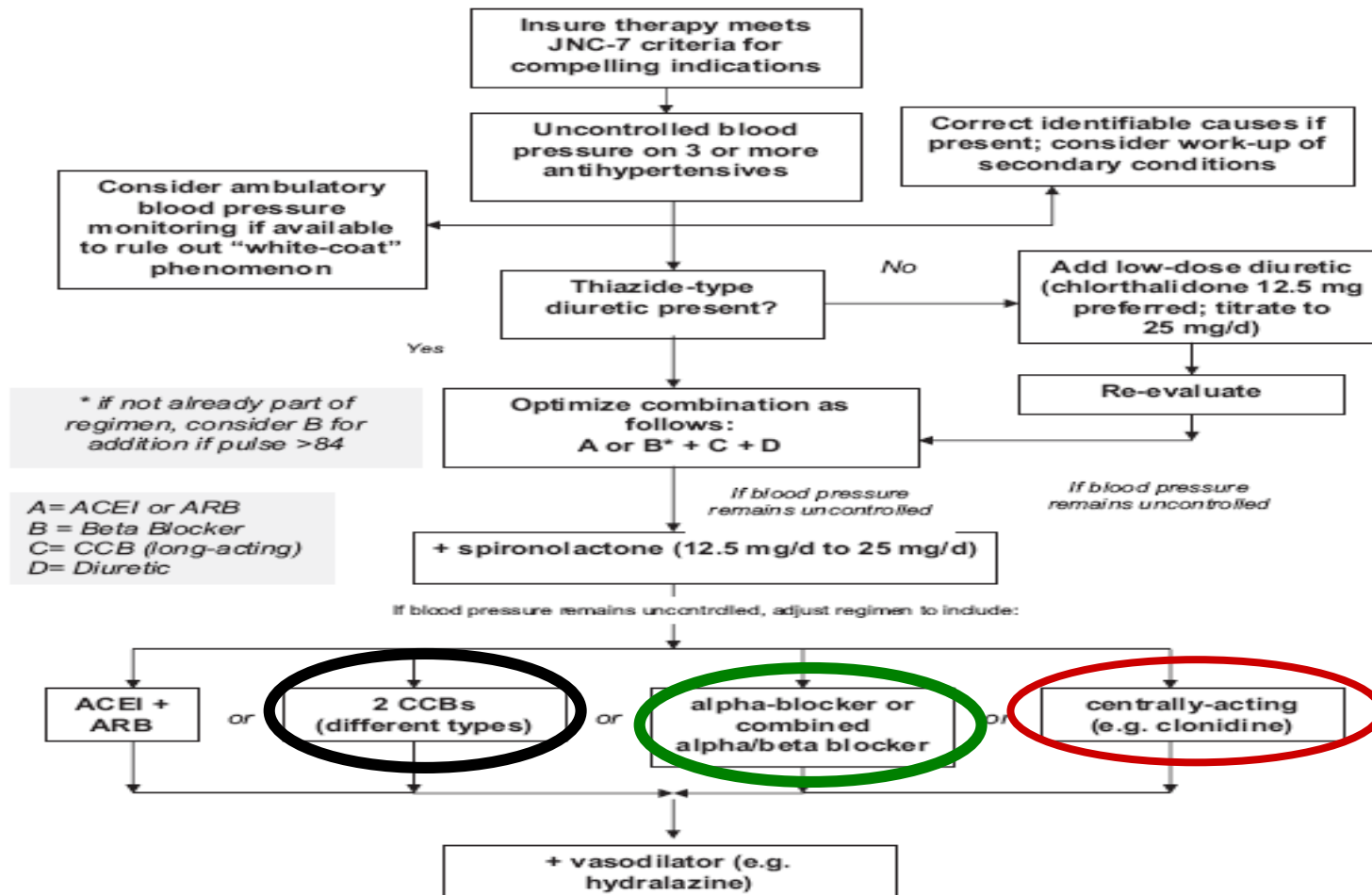
PATHWAY-2



Williams, Lancet 2015

UNUSUAL COMBINATION THERAPIES

JNC-7 Algorithm for the treatment of resistant hypertension



Additional Options

for the Treatment of Resistant Hypertension

**Combined α - and β -blocker (carvedilol, labetalol)
or β -blocker (non- α -blocking) + α -blocker**

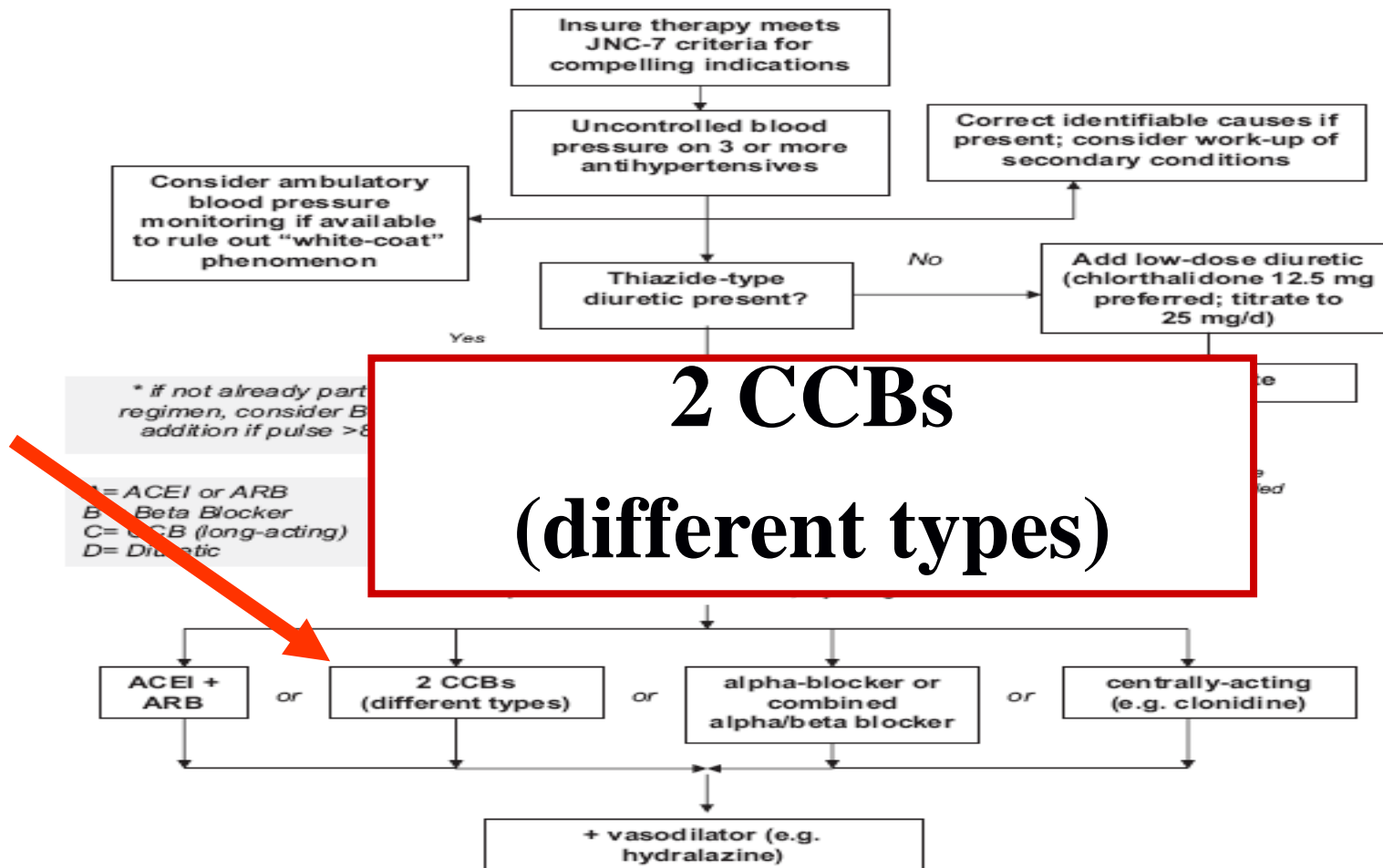
Aldosterone antagonist

Non-DHP CCB + DHP CCB

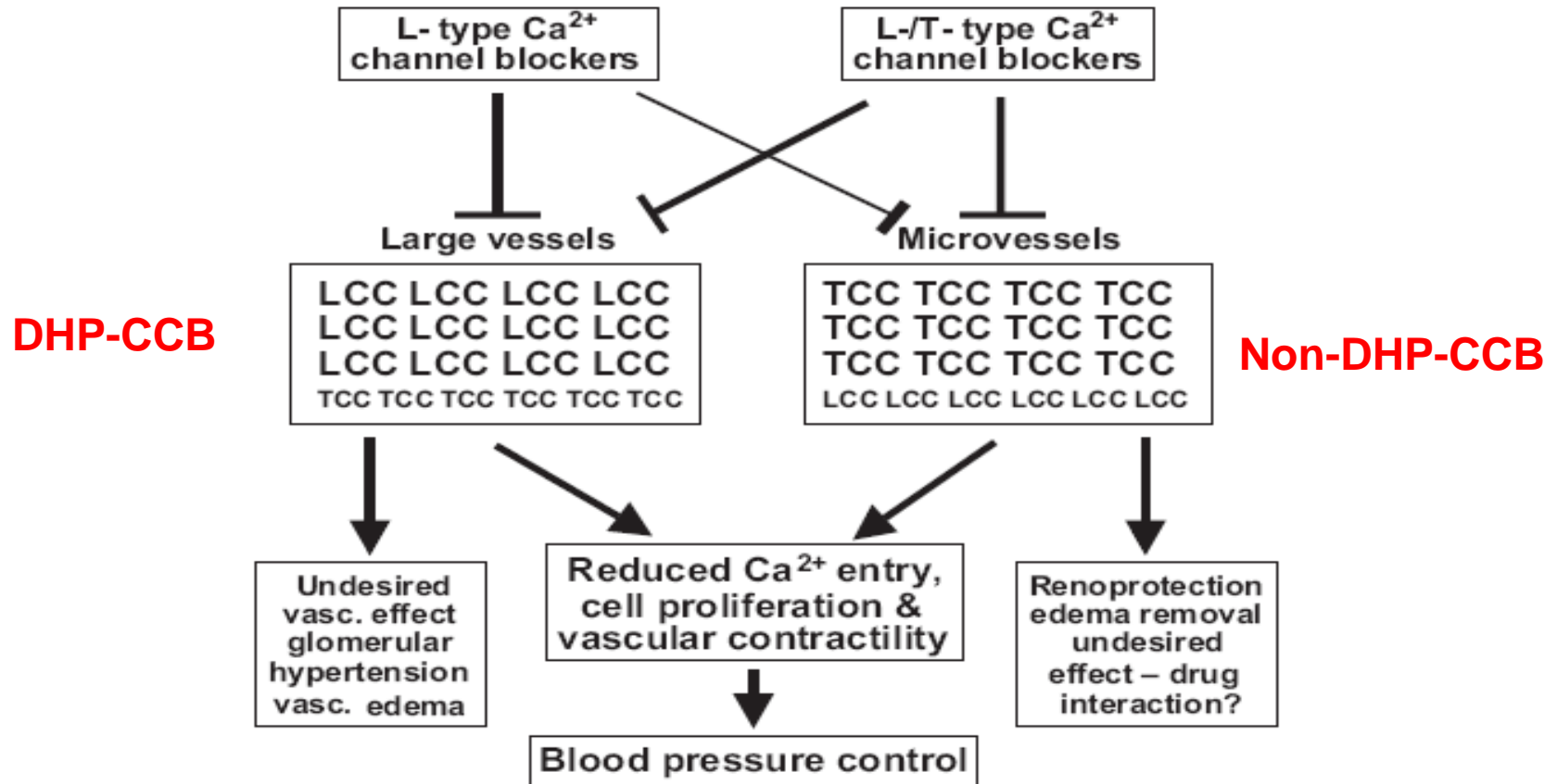
Vasodilator – **Minoxidil (with a β -blocker + loop diuretic)**

Centrally acting agent

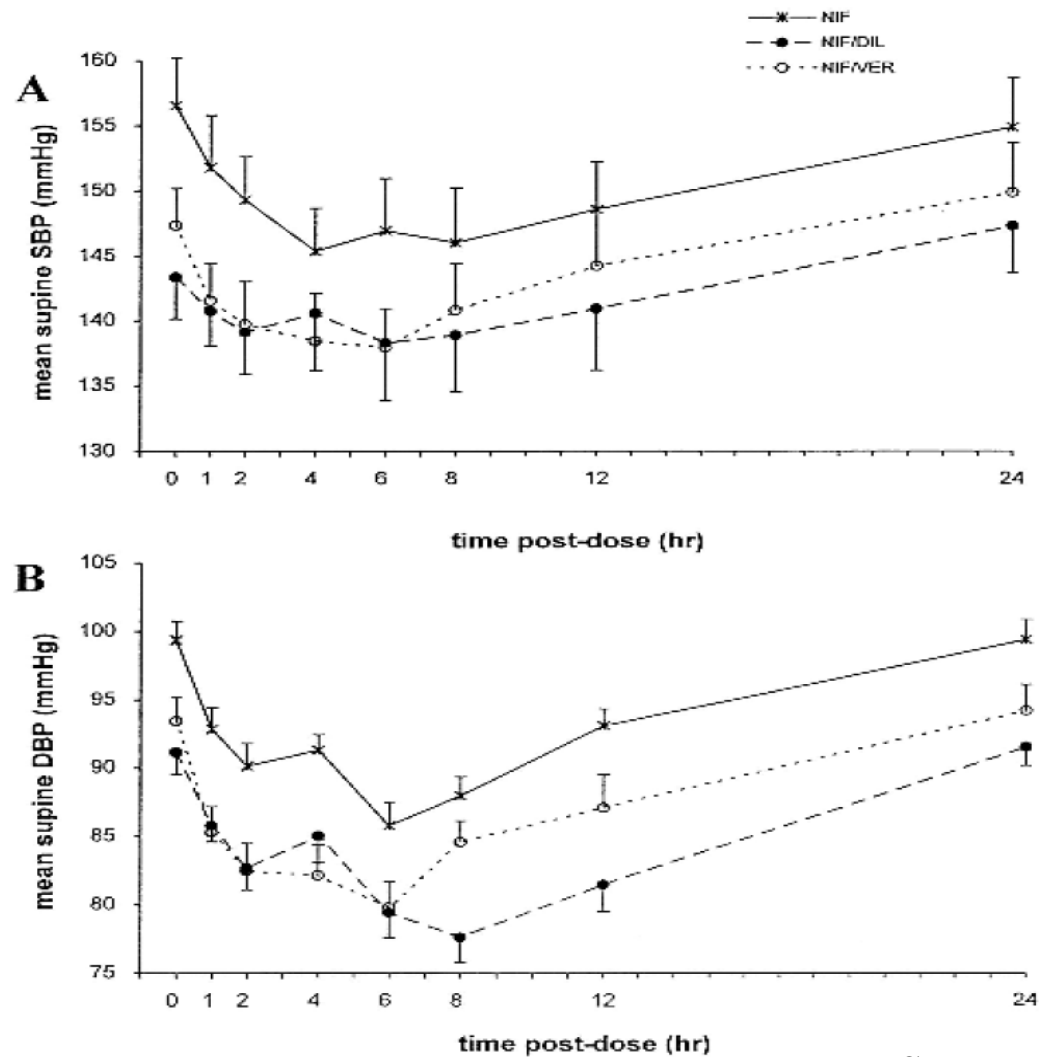
JNC-7 Algorithm for the treatment of resistant hypertension



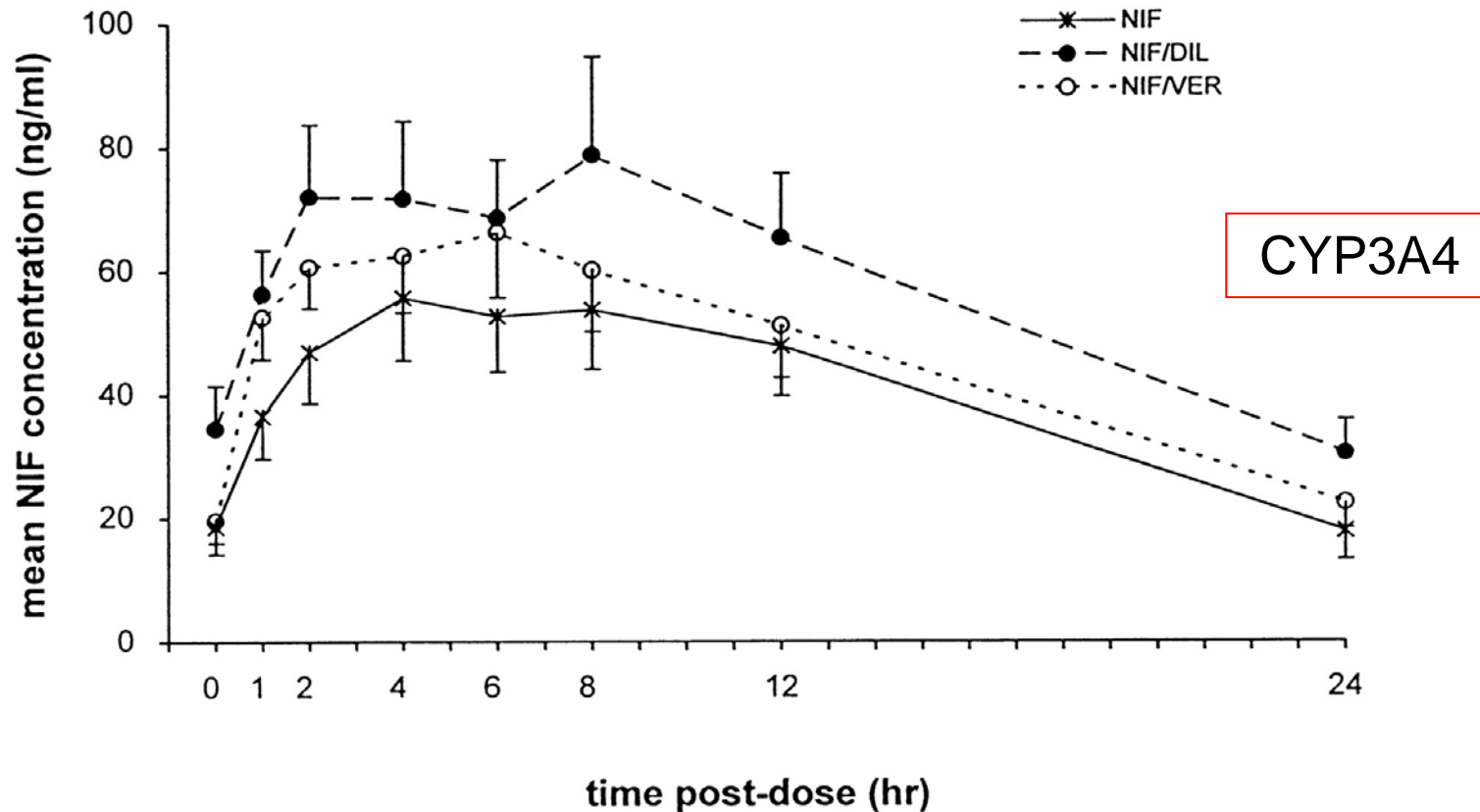
Effects of L-type and combined L-/T-type Ca²⁺ channel blockers in large and microvessels.



Comparison of Nifedipine Alone and With Diltiazem or Verapamil in Hypertension



Nifedipine (NIF) Cp versus time after steady-state oral dosing of study medication



Saseen,

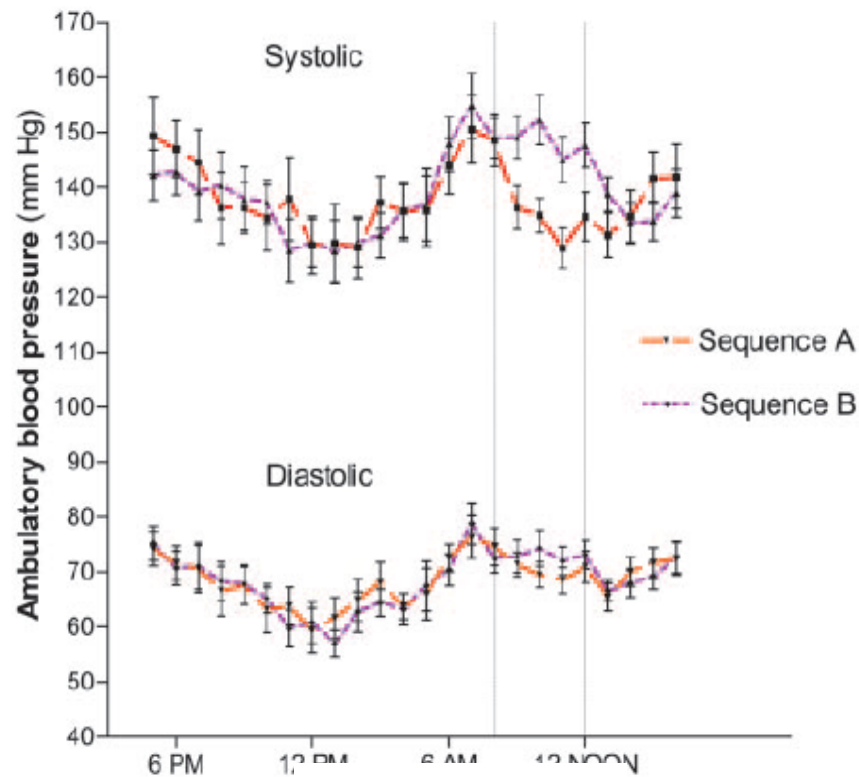
Hypertension, 1996

Long-Term Effectiveness of Extended-Release Nitrate for the Treatment of Resistant Systolic Hypertension

Editorial Commentary

Nitrates as Adjunct Hypertensive Treatment A Possible Answer to Resistant Systolic Hypertension

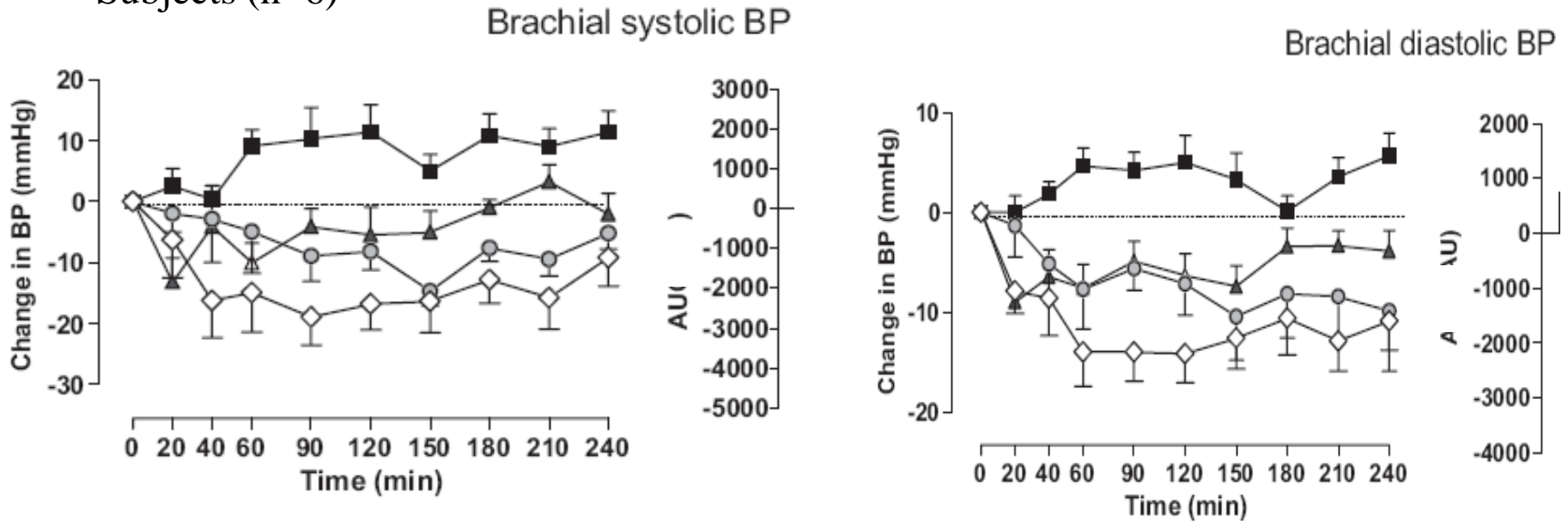
Subjects (n=16)



Stokes, Curr Opin *Hypertension*, 2010

Combination of Organic Nitrate and Phosphodiesterase Type 5 Inhibitor in Treatment-Resistant Hypertension

Subjects (n=6)



Placebo ■

Sildenafil ▲

ISMN ○

Combined sildenafil and ISMN ◇

The Future

	Drug	Preclinical stage	Phase 1-3	Pharmaceutical industry
Dual vasopeptidase inhibitor				
Dual neprilysin-ACE inhibitor	Ilepatril (AVE7688)	..	Phase 3	Sanofi-Aventis
Dual neprilysin-ECE inhibitor	Daglutril (SLV306)	..	Phase 2	Solvay Pharmaceuticals
Dual ARNI	LCZ696	..	Phase 3	Novartis Pharmaceuticals
Aldosterone-synthase inhibitor	LCI699	..	Phase 2*	Novartis Pharmaceuticals
Endothelin antagonist	Bosentan Darusentan	..	Phase 2 Phase 3*	Actelion Pharmaceuticals Gilead Sciences
Nitric oxide donor				
Nitric oxide-releasing drugs	Nitrosyl-cobinamide	Yes
Nitric oxide-releasing hybrids	Nitric oxide-losartan Nitric oxide-telmisartan	Yes Yes	Cayman Chemicals Cayman Chemicals
CINOD	Naproxcinod	..	Phase 3	NicOx
Renin-prorenin blocker	..	Yes
ACE-2 activator	..	Yes
Aminopeptidase-A inhibitor	QGC001	Yes	..	Quantum Genomics Corp
Vaccine				
Angiotensin 1 vaccine	PMD3117	..	Phase 2	Protherics Inc
Angiotensin 2 vaccine	Cyt006-AngQb	..	Phase 2	Cytos Biotechnology AG
Dual AT1R/ETA antagonist	PS-433540	..	Phase 2	Ligand Pharmaceuticals
Novel dual ARB and partial PPAR-γ agonist	..	Yes
AGE breaker	Alagebrium (ALT-711)	..	Phase 2*	Synvista Therapeutics

We have only listed molecules described in the text. ACE=angiotensin-I converting enzyme. ARNI=dual-acting angiotensin receptor-neprilysin inhibitor. CINOD=cyclo-oxygenase-inhibiting nitric-oxide donator. ARB=angiotensin-receptor blocker. PPAR-γ=peroxisome proliferator-activated receptor-γ. AGE=advanced glycation end-product. *Development stopped.

INVASIVE APPROACH TO RESISTANT HYPERTENSION

BAROREFLEX ACTIVATION THERAPY (BAT)

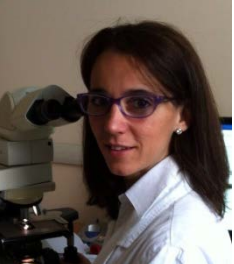
(Scheffers, J Am Coll Cardiol 2010), available since 2009

RENAL DENERVATION (RDN)

(Krum, Lancet 2010)

Central arteriovenous coupler (ROX)

(Lobo, Lancet 2015)



Internal Medicine and Hypertension Division
University of Turin, Italy