DIU d'HTA

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HYPERTENSION ARTERIELLE RESISTANTE

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HTA RESISTANTE

OBJECTIFS PEDAGOGIQUES

DEFINITION ET SES LIMITES

PREVALENCE, PRONOSTIC ET CARACTERISTIQUES CLINIQUES

MEDICAMENTS ET SUBSTANCES EXOGENES

RECHERCHE D'HTA SECONDAIRE

ADAPTATION MEDICAMENTEUSE

ALTERNATIVES NON MEDICAMENTEUSES

NECESSITE D'UNE DEMARCHE SYSTEMATIQUE STANDARDISEE

Niveau tensionnel moyen et prévalence de l'hypertension artérielle chez les adultes de 18 à 74 ans, ÉNNS 2006-2007.

Godet-Thobie H et al. BEH 16 décembre 2008

Hommes	18-34 ans	35-44 ans	45-54 ans	55-64 ans	65-74 ans	18-74 ans	[IC95 %]
Mesure dans l'année (%)	68,3	86,4	96,5	92,7	97,5	86,5	[83,1-89,9]
Prévalence de l'HTA (%)	4,0	19,5	42,6	62,4	69,9	34,1	[29,8-38,4]
HTA connue* (%)	21,5	22,9	40,5	55,2	59,9	46,9	[39,4-54,5]
HTA connue traitée* (%)	**	55,7	60,3	85,5	91,4	77,4	[67,2-87,6]
HTA traitée contrôlée* (%)	**	**	46,8	43,5	33,9	41,8	[32,3-51,3]
Femmes	**18-34 ans**	**35-44 ans**	**45-54 ans**	**55-64 ans**	**65-74 ans**	**18-74 ans**	**[IC95 %]**
Mesure dans l'année (%)	87,5	88,1	89,5	93,6	95,7	90,2	[87,9-92,6]
Prévalence de l'HTA (%)	5,6	13,1	31,4	43,7	65,0	27,8	[24,7-30,8]
HTA connue* (%)	22,3	55,5	52,9	62,0	68,6	58,8	[52,4-65,2]
HTA connue traitée* (%)	**	60,8	78,4	91,5	94,9	86,6	[81,1-92,1]
HTA traitée contrôlée* (%)	**	**	64	59,4	49,6	58,5	[51,1-65,8]

* HTA connue= proportion d'hypertendus connus parmi les hypertendus.
HTA connue traitée= proportion d'hypertendus traités par médicaments à action antihypertensive parmi les hypertendus connus.
HTA traitée contrôlée= proportion d'hypertendus contrôlés parmi les hypertendus traités.
** Effectifs insuffisants.
Champ : France métropolitaine 18-74 ans.
Source : Étude ENNS, 2006-2007.

Outpatient Hypertension Treatment, Treatment Intensification, and Control in Western Europe and the United States.

Wang YR et al. Arch Intern Med. 2007; 167: 141-147.

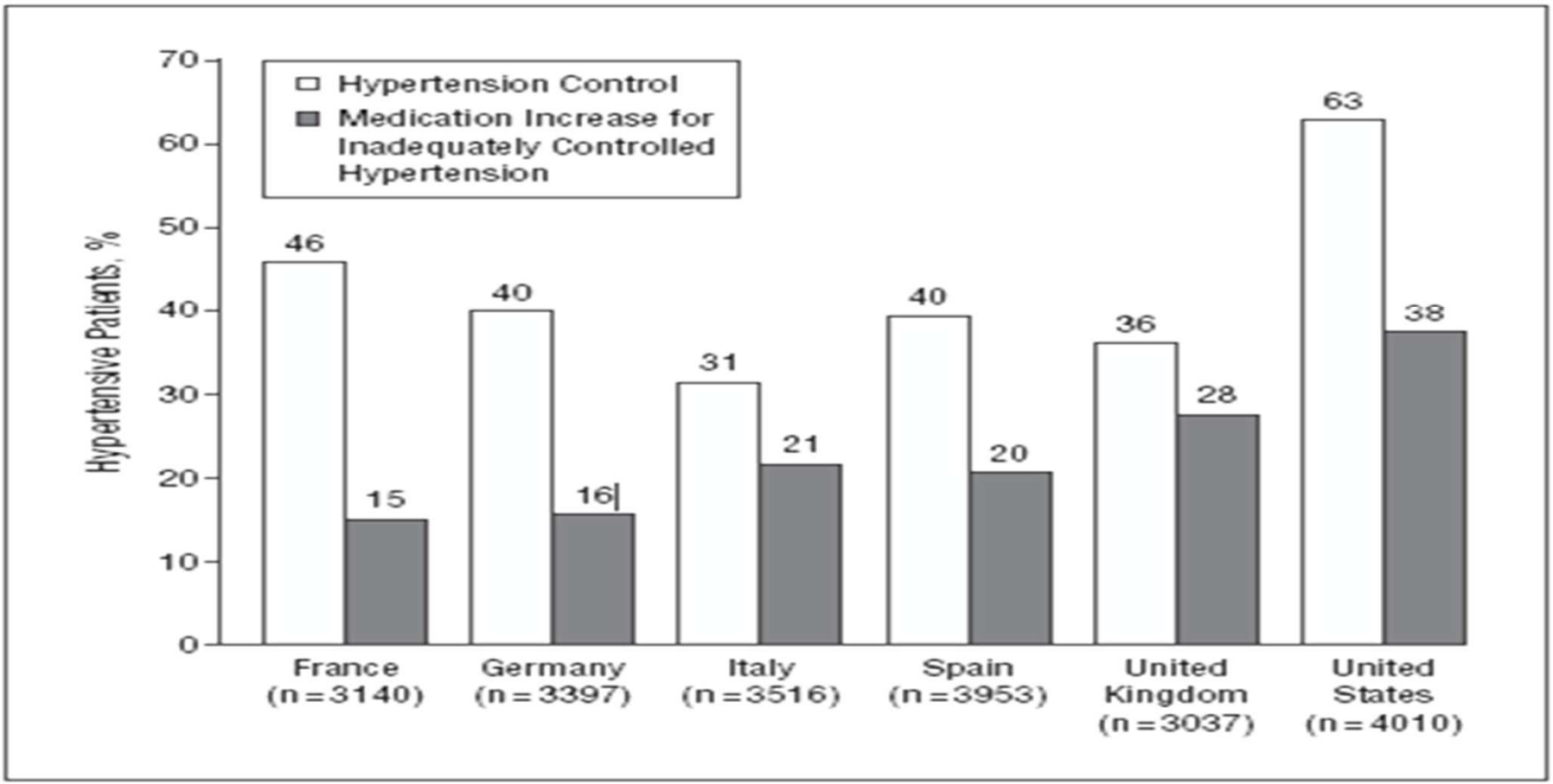


Figure 2. Cross-national differences in hypertension control (defined as a latest systolic blood pressure level of <140 mm Hg and a diastolic blood pressure level of <90 mm Hg) and medication increase for those with inadequately controlled hypertension.

HTA RESISTANTE : DEFINITIONS

ESH 2007

Lorsque des mesures de style de vie et au moins trois médicaments à doses suffisantes n'ont pas réussi à abaisser les pressions systolique et diastolique à des valeurs inférieures à l'objectif.

2007 ESH-ESC guidelines for the management of arterial hypertension.
J Hypertens 2007; 25: 1105-1187.

ESH 2013

L'hypertension artérielle est définie comme résistante au traitement quand une stratégie thérapeutique qui comprend :

- **des mesures appropriées en matière de style de vie,**
- **un diurétique et deux autres antihypertenseurs appartenant à des classes différentes à des doses adéquates,**

ne parvient pas à diminuer la valeur des PAS et PAD en dessous de 140 et 90 mmHg, respectivement.

2013 ESH-ESC guidelines for the management of arterial hypertension.
J Hypertens 2013; 31: 1281–1357.

HTA RESISTANTE : LIMITES DES DEFINITIONS 1

ESH 2013 : Modalité de mesure de la PA : Mesure clinique

Spanish ABPM Registry (December 2009):

- 68 045 treated patients,

- 8 295 (12.2%) had RH (OBP ≥140 and/or 90 mmHg despite ≥3 antihypertensive drugs, 1 of them being a diuretic).

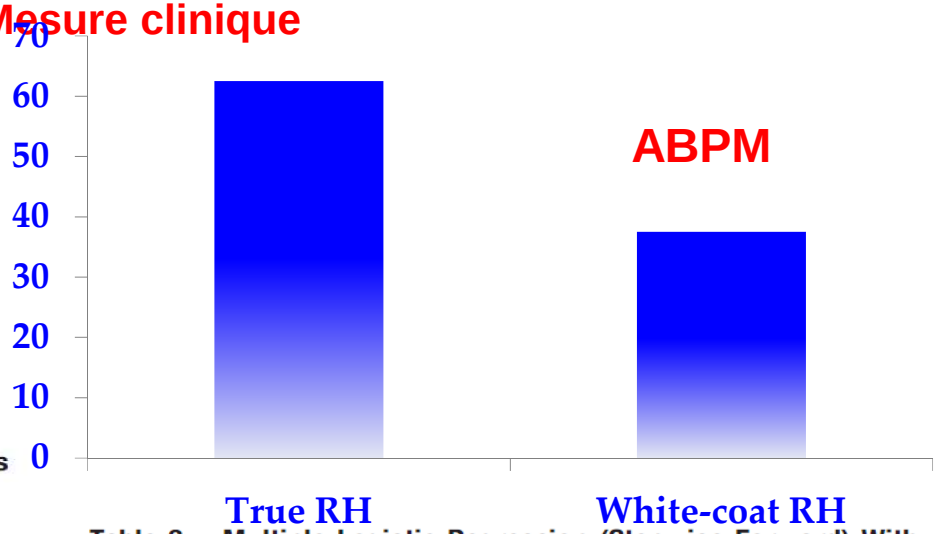


Table 2. Differences in Office, Daytime, and Nighttime BP, as Well as Circadian Pattern Distribution, Between RH Patients With Normal or Elevated 24-Hour BP

Parameter	True RH (N=5182)	White-Coat RH (N=3113)	*P*
Office SBP	164±18	157±15	<0.001
Office DBP	90±13	87±12	<0.001
Daytime SBP	145±13	122±8	<0.001
Daytime DBP	81±12	70±8	<0.001
Nighttime SBP	136±17	113±10	<0.001
Nighttime DBP	72±11	61±8	<0.001
Circadian SBP pattern distribution			<0.001
Extreme dippers, %	5.3	6.3	
Dippers, %	29.9	32.7	
Nondippers, %	42.5	43.3	
Risers, %	22.3	17.7	
Circadian DBP pattern distribution			<0.001
Extreme dippers, %	16.1	20.4	
Dippers, %	39.3	43.1	
Nondippers, %	32.5	26.8	
Risers, %	12.1	9.6	

Values are in millimeters of mercury. RH indicates resistant hypertension; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 3. Multiple Logistic Regression (Stepwise Forward) With Clinical Variables Showing Differences Between True and White-Coat–Resistant Hypertensive Patients

Parameter	MOR	95% CI	*P*
Age, y	0.99	0.98 to 1.00	0.002
Sex, (males vs females)	1.23	1.02 to 1.49	0.031
Duration of hypertension, y	1.02	1.01 to 1.03	0.001
Smokers (yes vs no)	1.25	1.01 to 1.44	0.041
Diabetics (yes vs no)	1.26	1.10 to 1.39	0.002
Creatinine, μmol/L	1.01	1.00 to 1.02	0.028
HDL cholesterol, mmol/L	NS	NS	0.693
Triglycerides, mmol/L	NS	NS	0.113
LVH by ECG (yes vs no)	1.22	1.02 to 1.38	0.033
Previous CV disease (yes vs no)	1.22	1.02 to 1.38	0.034
Treatment with ≥4 AH drugs (≥4 vs 3)	NS	NS	0.460

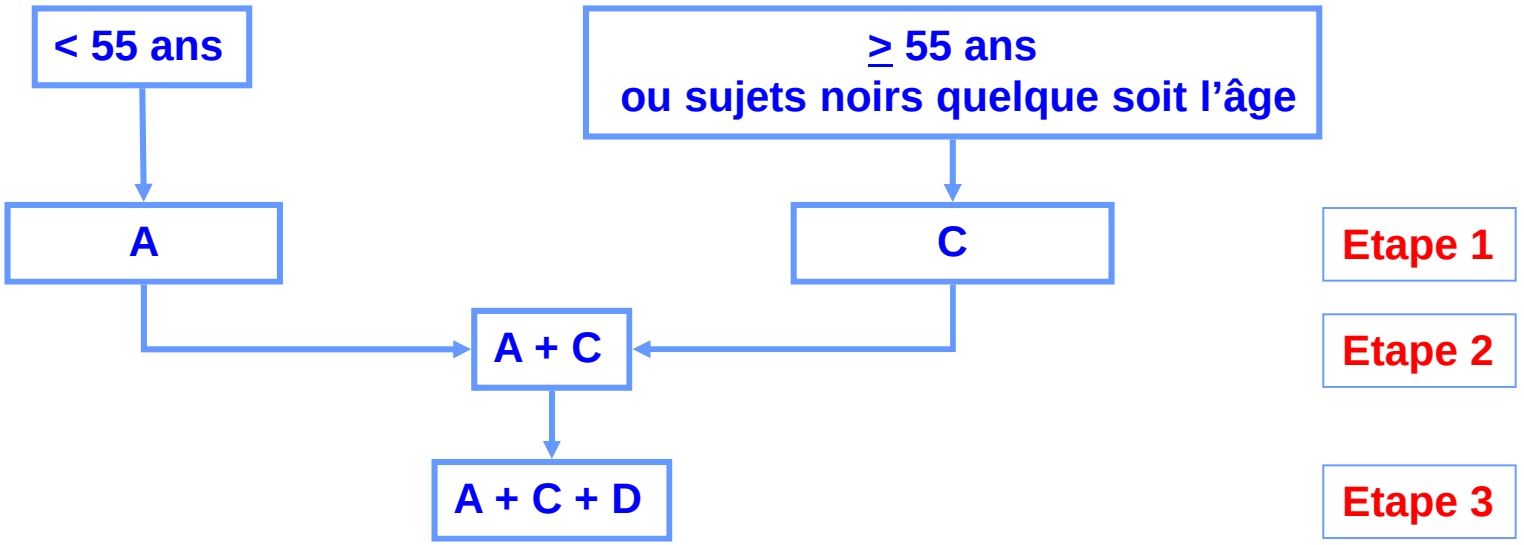
MOR indicates multivariate odds ratio; LVH, left ventricular hypertrophy; ECG, electrocardiogram; CV, cardiovascular; AH, antihypertensive; HDL, high-density lipoprotein.

De la Sierra. Hypertension 2011; 57: 898-902.

HTA RESISTANTE : LIMITES DES DEFINITIONS 2

ESH 2013 : « un diurétique et deux autres antihypertenseurs » : pas de précision sur le type de diurétique et sur les classes de ces deux autres antihypertenseurs !

Management of hypertension: summary of NICE Guidance.



A = IEC ou ARA 2. C = Antagonistes calciques. D = Diurétiques thiazidiques ou apparentés : **chlortalidone (12.5-25.0 mg/j) ou indapamide (1.5 mg LP/j ou 2.5 mg/j), de préférence au thiazidique conventionnel tels que bendroflumethiazide ou hydrochlorothiazide.**

Krause T, et al. Management of hypertension: summary of NICE guidance. BMJ 2011;343:d4891.

HTA RESISTANTE : LIMITES DES DEFINITIONS 3

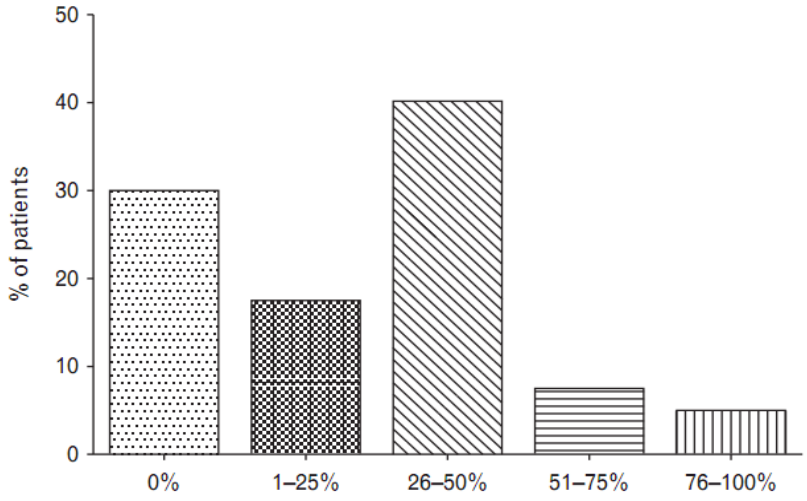
JNC VII : « chez un patient observant du traitement »

JAMA 2003; 289: 2560-72.

TABLE 3. Comparison between adherent and nonadherent patients

	Adherent ($n=36$)	Nonadherent ($n=40$)	*P*
Age (years)	60 (53–69)	58 (49–67)	0.147
Male, *n* (%)	24 (66.7%)	20 (50%)	0.168
Hypertension since (years)	15 (7–23)	10 (5–21)	0.113
SBP (mmHg)	166 (151–177)	175 (163–201)	0.011
DBP (mmHg)	95 (84–100)	101 (90–101)	0.023
Heart rate	67 (61–76)	77 (65–87)	0.019
Antihypertensive tablets per day	6 (5–8)	7 (5–9)	0.102
BMI	30 (28–35)	31 (28–36)	0.847
Smoker, *n* (%)	17 (47.2%)	15 (37.5%)	0.487
Family history of hypertension, *n* (%)	32 (80.0%)	34 (94.4%)	0.740
Concomitant disease or target organ damage, *n* (%)	31 (86.1%)	38 (95.0%)	0.246
Antihypertensive tablets per day	6 (5–8)	7 (5–9)	0.102
Fixed-dose combination, *n* (%)	26 (72.2%)	28 (70.0%)	1.000

Variables are expressed as median and inter quartile range (IQR) or as proportions as appropriate.



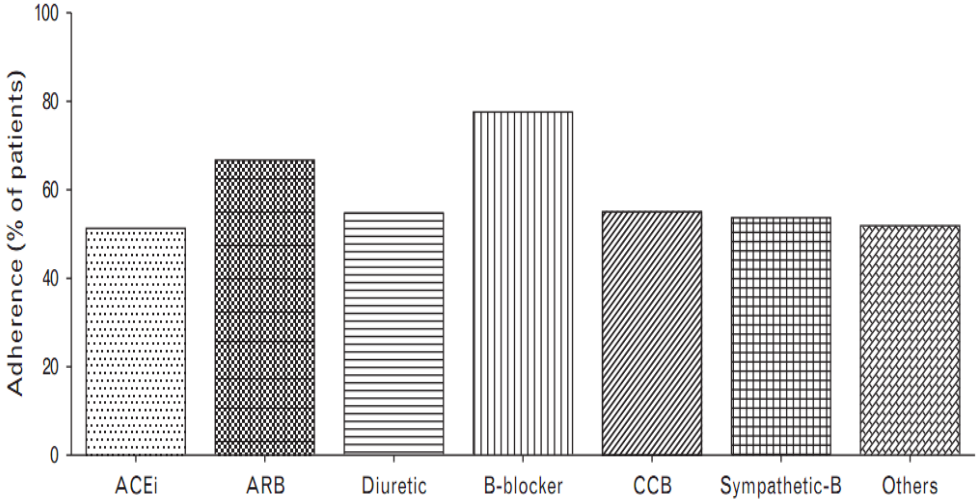


FIGURE 3 Percentage of prescribed drugs taken by nonadherent patients.

Jung O. et al. J Hypertens 2013; 31: 766-74.

ADHERENCE TO MEDICATION

"Drugs don't work in patients who don't take them". ***C. Everett Koop.***

Major Predictors of Poor Adherence to Medication

- Presence of psychological problems, particularly depression
- Presence of cognitive impairment
- **Treatment of asymptomatic disease**
- Inadequate follow-up or discharge planning
- **Side effects of medication**
- **Patient's lack of belief in benefit of treatment**
- Patient's lack of insight into the illness
- Poor provider–patient relationship
- Presence of barriers to care or medications
- Missed appointments
- **Complexity of treatment**
- Cost of medication, copayment, or both

Osterberg L, Blaschke T. N Engl J Med 2005; 353: 487-97.

HTA RESISTANTE : DEFINITIONS

SFHTA 2013

1. Il est recommandé de définir une HTA résistante comme une HTA non contrôlée en consultation (PA ≥ 140/90 mmHg chez un sujet de moins de 80 ans, ou PAS ≥ 150 mmHg chez un sujet de plus de 80 ans) et confirmée par une mesure en dehors du cabinet médical (automesure ou mesure ambulatoire de la pression artérielle), malgré une stratégie thérapeutique comprenant des règles hygiéno-diététiques adaptées et une trithérapie antihypertensive, depuis au moins 4 semaines, à dose optimale, incluant un diurétique.

2. a) La trithérapie antihypertensive doit comporter, outre un diurétique thiazidique, un bloqueur du SRA (ARA2 ou IEC) et un inhibiteur calcique. D'autres classes pharmacologiques sont à utiliser en cas d'intolérance ou d'indications préférentielles.
b) Dans l'HTA résistante, un diurétique thiazidique doit être utilisé : l'hydrochlorothiazide à un dosage d'au moins 25 mg/j ou l'indapamide.
c) En cas d'insuffisance rénale stades 4 et 5 (eDFG<30 ml/min/1.73 m2), le thiazidique doit être remplacé par un diurétique de l'anse (furosémide, bumétamide) prescrit à une posologie adaptée à la fonction rénale.

3. Il est recommandé de rechercher une mauvaise observance : questionnaire, dosages médicamenteux, décompte des médicaments…

HTA RESISTANTE : LIMITES DES DEFINITIONS 4

ESH 2013 : « un diurétique et deux autres antihypertenseurs à des doses adéquates » : pas de précision sur les doses adéquates !

SFHTA 2013 : « trithérapie antihypertensive, depuis au moins 4 semaines, à dose optimale, incluant un diurétique. » : pas de précision sur les doses adéquates !

Prescription à la dose optimale recommandée dans l'autorisation de mise sur le marché.

Parfois différente d'un pays à l'autre.

JNC 8

Table 4. Evidence-Based Dosing for Antihypertensive Drugs

Antihypertensive Medication	Initial Daily Dose, mg	Target Dose in RCTs Reviewed, mg	No. of Doses per Day
ACE inhibitors			
Captopril	50	150-200	2
Enalapril	5	20	1-2
Lisinopril	10	40	1
Angiotensin receptor blockers			
Eprosartan	400	600-800	1-2
Candesartan	4	12-32	1
Losartan	50	100	1-2
Valsartan	40-80	160-320	1
Irbesartan	75	300	1
β-Blockers			
Atenolol	25-50	100	1
Metoprolol	50	100-200	1-2
Calcium channel blockers			
Amlodipine	2.5	10	1
Diltiazem extended release	120-180	360	1
Nitrendipine	10	20	1-2
Thiazide-type diuretics			
Bendroflumethiazide	5	10	1
Chlorthalidone	12.5	12.5-25	1
Hydrochlorothiazide	12.5-25	25-100[a]	1-2
Indapamide	1.25	1.25-2.5	1

JAMA. 2014;311(5):507-520. doi:10.1001/jama.2013.284427

Prevalence of Optimal Treatment Regimens in Patients With Apparent Treatment-Resistant Hypertension Based on Office Blood Pressure in a Community-Based Practice Network

Egan BM et al. Hypertension. 2013; 62: 691-697.

2007–2010

468 877 hypertensive patients

147 635 (31.5%) uncontrolled

44 684 (30.3%) ≥3 BP medications

of whom 22 189 (15.0%) optimal therapy (diuretic and ≥2 other BP medications at ≥50% of maximum recommended hypertension doses).

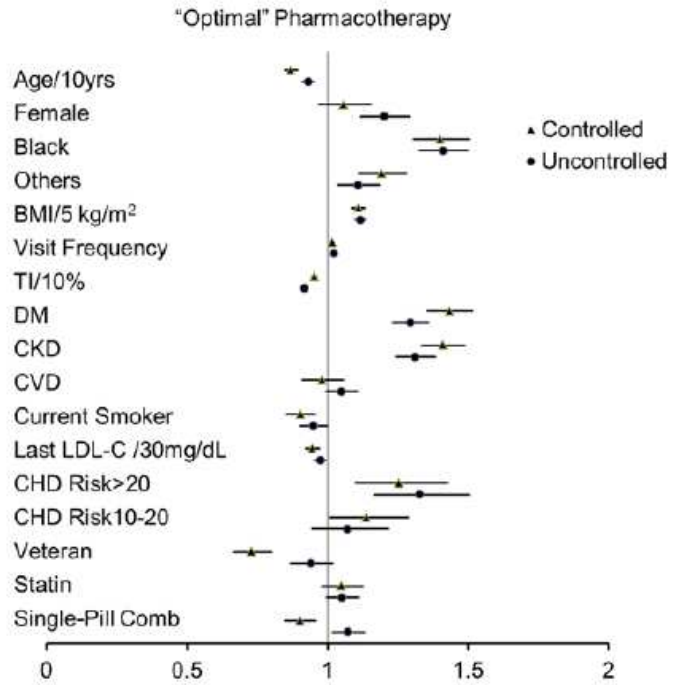
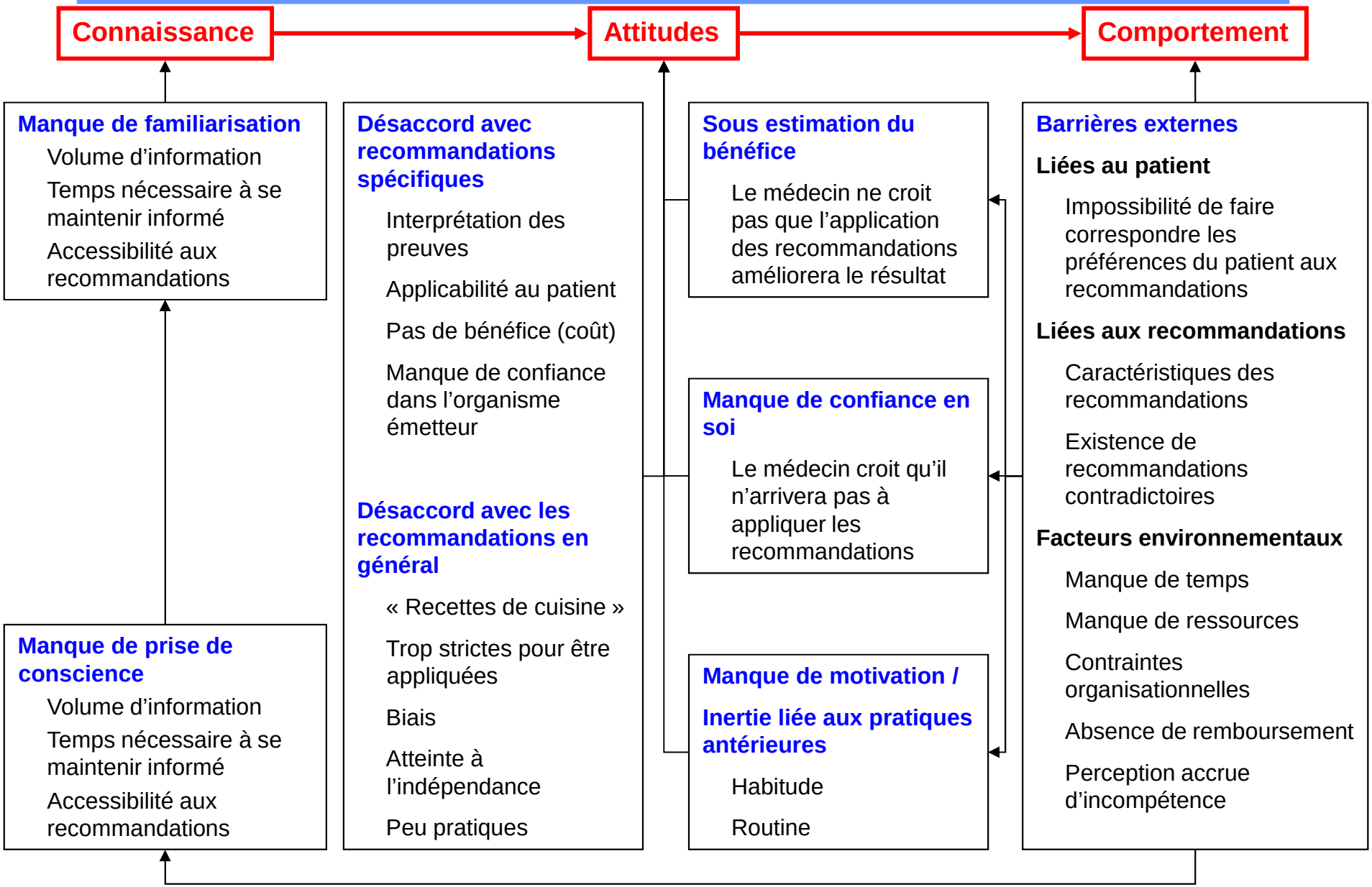


Figure 1. The independent relationship is shown between various clinical factors and the relative probability (odds ratio, 95% confidence interval) of receiving prescriptions for optimal pharmacotherapy for patients with controlled and uncontrolled apparent treatment-resistant hypertension. BMI indicates body mass index; CHD, coronary heart disease; CKD, chronic kidney disease; CVD, cardiovascular disease; DM, diabetes mellitus; LDL-C, low-density lipoprotein cholesterol; and TI, therapeutic inertia (visits with uncontrolled blood pressure [BP] without medication change/visits with uncontrolled BP).

Why Don't Physicians Follow Clinical Practice Guidelines?: A Framework for Improvement

Cabana MD et al. JAMA. 1999; 282:1458-1465



Physician-related barriers to the effective management of uncontrolled hypertension.

Oliveria SA et al. Arch Intern Med 2002; 162: 413-420.

- **5 145 patients avec diagnostic d'HTA (CIM 9) en 6 mois**
- **314 patients non contrôlés dont 231 interviews téléphoniques :**
  69 ans ; 50% blancs; 152/84 mmHg ; 94% traités.
- **21/ 26 (81%) médecins ont répondu au questionnaire et donné informations sur 270 visites patients (taux de réponse : 86%).**

Connaissance du JNC VI (%)	52
En accord avec JNC VI (%)	76
Appliquent JNC VI (toujours ou habituellement) (%)	76

- **Motifs de non augmentation (%)**

Poursuivre mesures PA avant changement traitement	35
Satisfait de la réponse tensionnelle	30
Motif de la visite indépendant de l'HTA	29
PAD satisfaisante	16
HTA limite	10

- **Analyse multivariée (OR)**

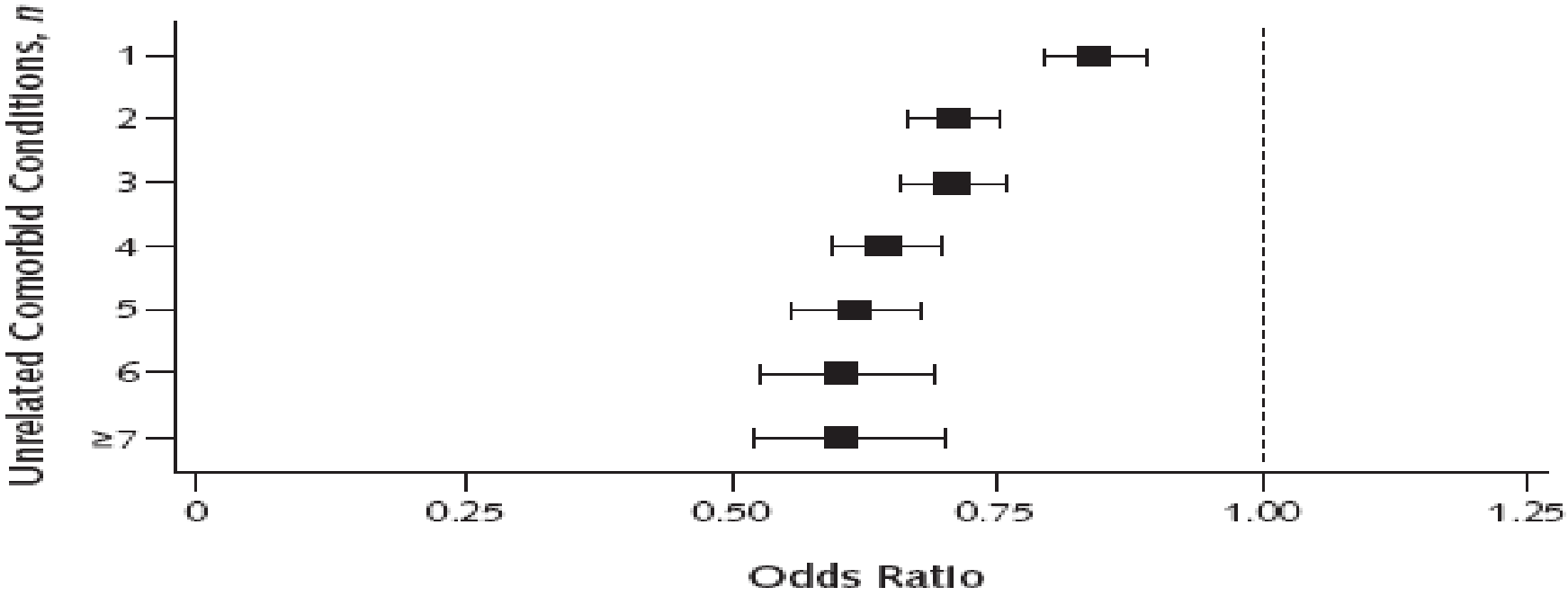
Augmentation de TTT dans les 6 mois précédents	2.88 (1.42-5.96)
Niveau tensionnel obtenu	2.96 (1.53-5.83)

Effect of Unrelated Comorbid Conditions on Hypertension Management.

Turner BJ. Ann Intern Med. 2008; 148: 578-586.

Examination of a database derived from electronic medical records collected during routine care of a cohort of primary care: 15 459 patients with uncontrolled hypertension who made 70 557 visits to 200 clinicians (01/2004 – 12/2006).

Adjusted association of unrelated comorbid conditions with management of uncontrolled hypertension



The role of clinical uncertainty in treatment decisions for diabetic patients with uncontrolled blood pressure.

Kerr EA et al. Ann Intern Med. 2008; 148: 717-727.

1169 diabetic patients (2005-2006).

Despite an average SBP of 154 mmHg, only 49% of patients had a change in a BP treatment (medication intensification or planned follow-up within 4 weeks).

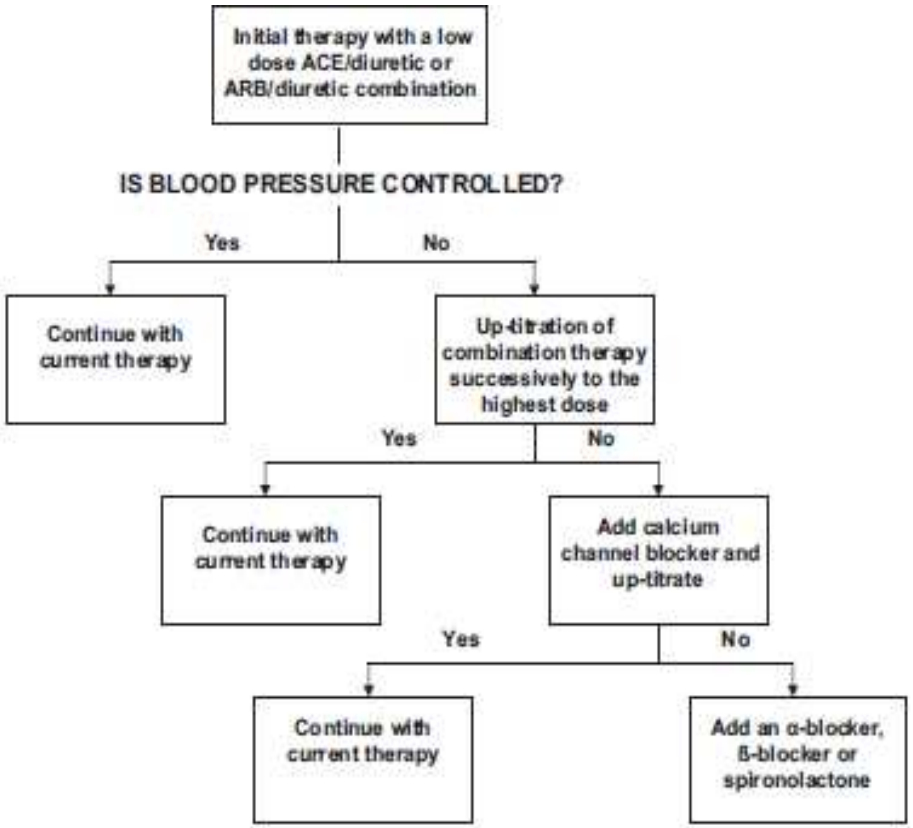
Factors of intensification			p
OBP < 140/90 vs. ≥ 140/90 mmHg or no OBP	13%	61%	<0.001
HBPM < 140/90 vs. ≥ 140/90 mmHg or no HBPM	18%	52%	<0.001
OSBP goal > 130 mmHg vs < 130 mmHg	33%	52%	0.008
Discussion of medication issues vs no	23%	52%	<0.001

A Simplified Approach to the Treatment of Uncomplicated Hypertension: A Cluster Randomized, Controlled Trial.

Feldman RD. et al. Hypertension 2009; 53: 646-653.

Table 2. Baseline Characteristics of the Practices and Patients

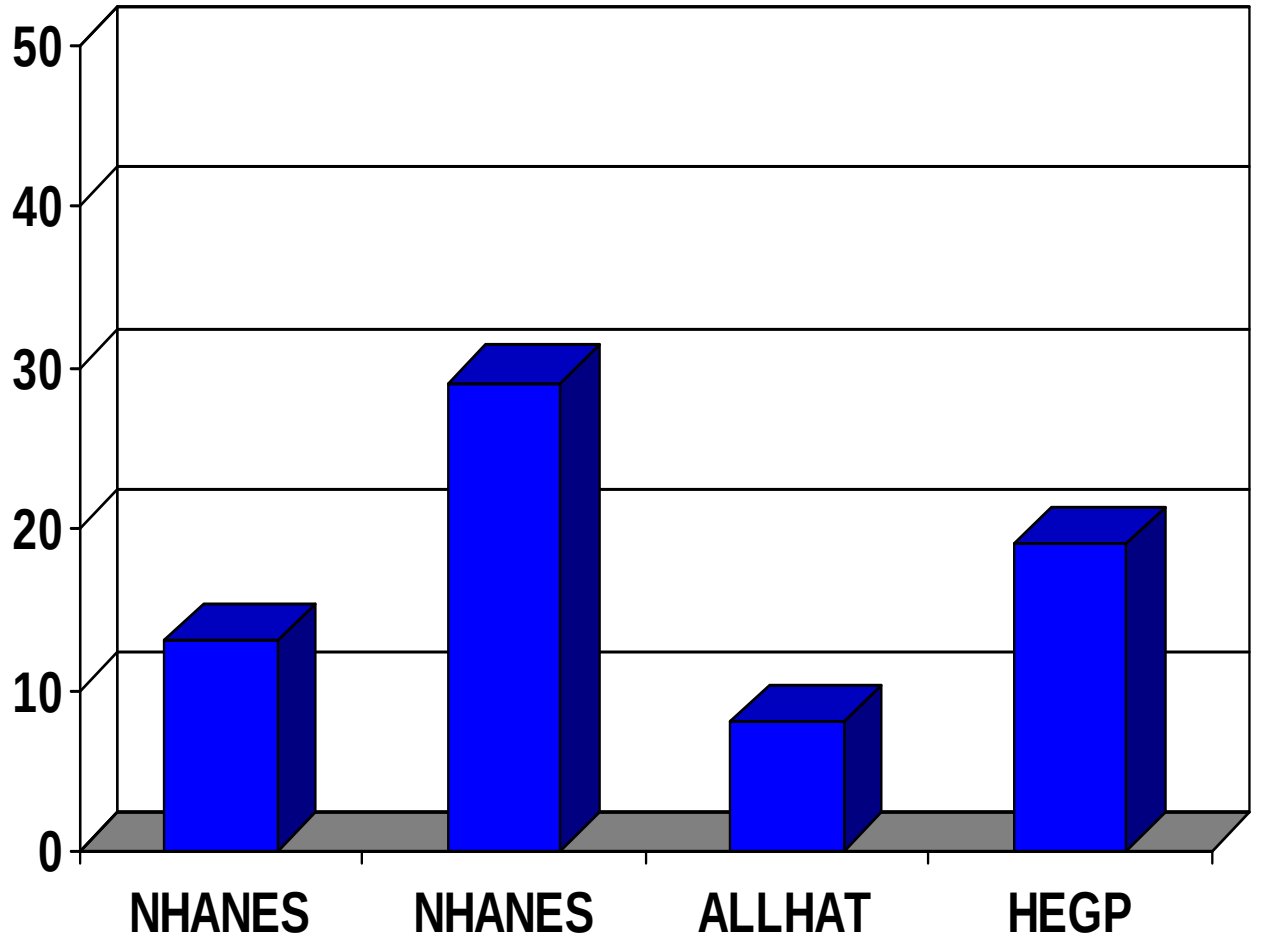
Practice/Patient Characteristics	Guideline Care	STITCH Care
Practices	27	18
Median cluster size (range)	46 (25 to 50)	46 (26 to 50)
Proportion of physicians graduated before 1984, n (%)	11 (40.7)	8 (44.4)
Mean recruitment duration by cluster, d	140	169
Urban location, n (%)	25 (92.6)	17 (94.4)
Men, n (%)	20 (74.1)	15 (83.3)
Patients		
No. of patients	1246	802
Recruitment duration, d	503	531
Age, mean (range), y	60.9 (18.6 to 93.0)	61.9 (20.4 to 92.8)
Women, %	53	56
Diabetic, %	15.9	15.1
Baseline SBP, mean (SD), mm Hg	153.4 (14.9)	155.1 (13.7)
Baseline DBP, mean (SD), mm Hg	87.7 (10.9)	88.1 (10.9)



Patients achieving target:
STITCH-care: 64.7%
Guidelines-care: 52.7%
absolute difference: 12.0% [1.5%- 22.4%]

(Simplified Treatment Intervention To Control Hypertension [STITCH])

HTA RESISTANTE : PREVALENCE



Persell SD. Hypertension. 2011; 57: 1076-1080.
Egan BM. Circulation. 2011; 124: 1046-1058.
ALLHAT-LLT. JAMA. 2002; 288: 2998-3007.
Savard S. J Am Coll Cardiol. 2012; 60: 2422-4.

HTA RESISTANTE : PREVALENCE

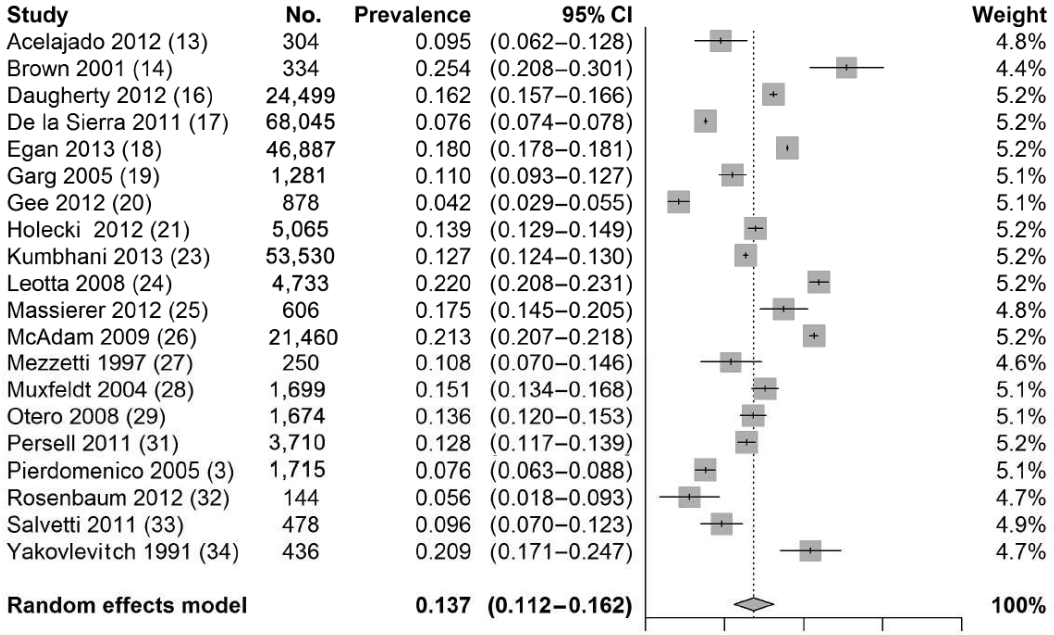


Figure 2. Forest plot for the pooled prevalence of resistant hypertension from 20 observational studies. The effect size (prevalence) of each study is represented by the small, solid vertical line, and its 95% confidence interval (CI) is shown by the solid horizontal line. The dashed vertical line represents the pooled prevalence, and the diamond represents its 95% CI. The size of the shaded squares symbolize the weight each study was assigned in the pooling.

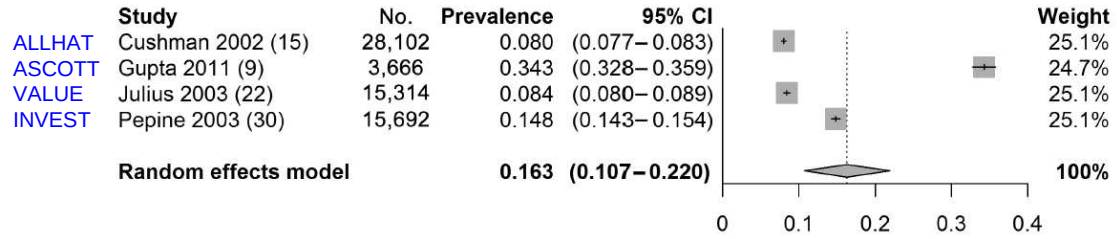
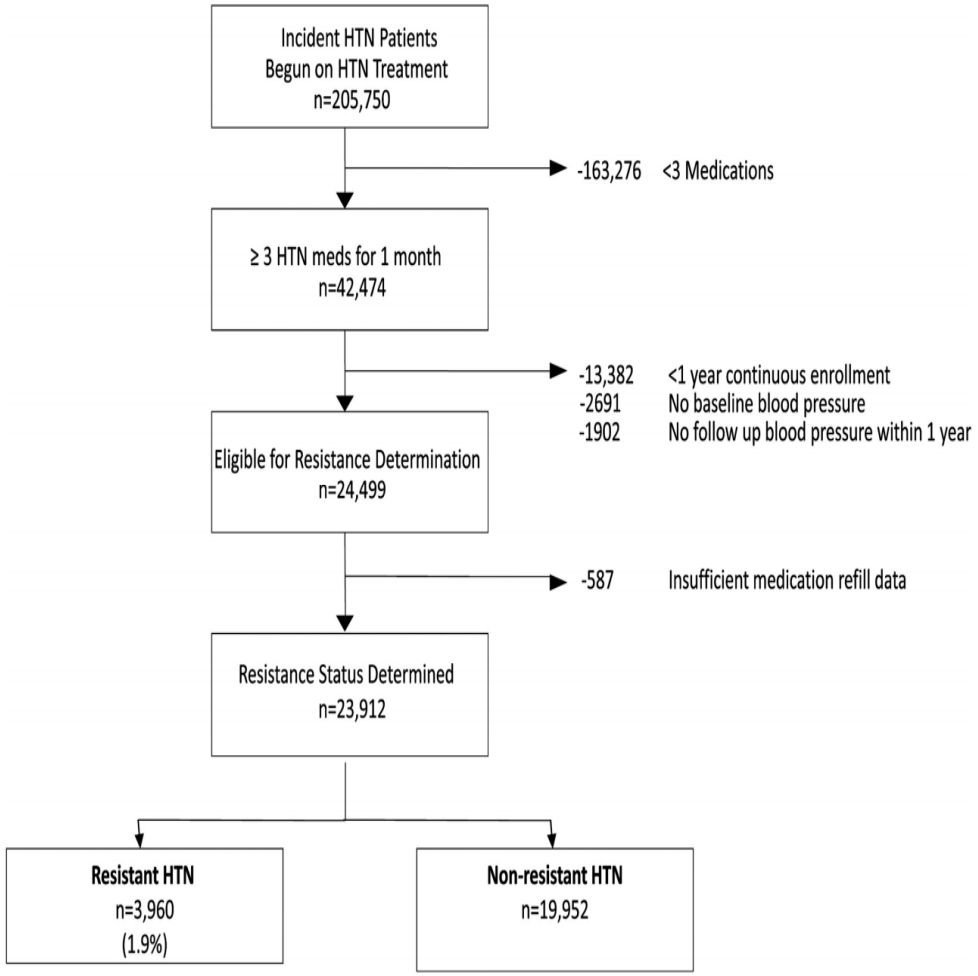


Figure 3. Forest plot for the pooled prevalence of resistant hypertension from 4 randomized control trials (RCTs). The effect size (prevalence) of each study is represented by the small, solid vertical line, and its 95% confidence interval (CI) is shown by the solid horizontal line. The dashed vertical line represents the pooled prevalence, and the diamond represents its 95% CI. The size of the shaded squares symbolize the weight each study was assigned in the pooling.

Achelrod D. Am J Hypertens. 2015 ; 28: 355-61.

HTA RESISTANTE

INCIDENCE



Après un suivi médian de 1,5 an après le début du traitement

PRONOSTIC

Table 2. Cardiovascular Outcomes Among Patients in the Primary Outcomes Analysis According to Resistance Status

Outcome	Resistant	Nonresistant	Total
Death	54 (2.1)	290 (1.9)	344 (1.9)
Myocardial infarction	9 (0.4)	81 (0.5)	90 (0.5)
Stroke	15 (0.6)	76 (0.5)	91 (0.5)
Congestive heart failure	10 (0.4)	43 (0.3)	53 (0.3)
Chronic kidney disease	365 (14.5)	1607 (10.4)	1972 (10.9)
Total events	453 (18.0)	2097 (13.5)	2550 (14.1)
Total patients	2521	15 515	18 036

Values are n (%).

Augmentation du risque d'évènement CV :
HR : 1.47 (95% CI,1.33–1.62; P<0.001)
(suivi médian de 3,8 ans)

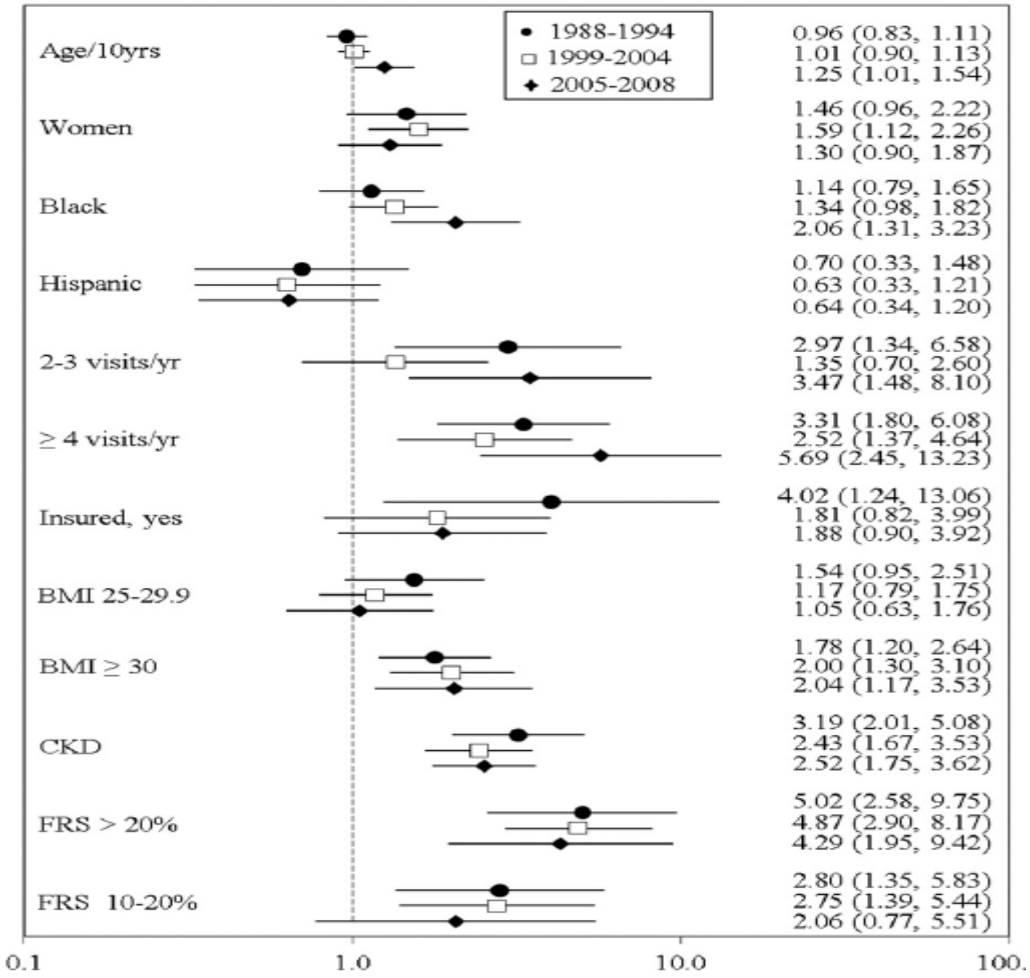
Daugherty SL et al. Circulation. 2012; 125: 1635-1642.

HTA RESISTANTE : CARACTERISTIQUES CLINIQUES 1

NHANES

Relations indépendantes entre les variables cliniques sélectionnés et la variable dépendante, l'hypertension résistante à 3 médicaments.
Odds ratios multivariés et intervalles de confiance à 95%.

Groupe de référence : patients hypertendus non contrôlés.



Egan BM. Circulation. 2011;124:1046-1058

HTA RESISTANTE : CARACTERISTIQUES CLINIQUES 2 : SAOS

Table 2 Baseline polysomnographic data

	Controlled hypertension ($n = 22$)	Refractory hypertension ($n = 42$)	P
OSA, n (%)	12 (55)	34 (81)	0.03
AHI (numbers of hours of sleep)	16.5 ± 2.7	24.9 ± 3.2	0.13
Mean SaO_2 (%)	94.1 ± 0.5	94.5 ± 0.3	0.49
Lowest SaO_2 (%)	83.8 ± 1.7	84.0 ± 1.1	0.91
Time in bed (min)	406.9 ± 8.7	396.1 ± 11.9	0.46
Sleep onset latency (min)	15.0 ± 2.5	25.4 ± 4.4	0.30
Total sleep time (min)	321.4 ± 9.5	281.9 ± 14.1	0.02
Wake after sleep onset (min)	70.6 ± 6.7	84.7 ± 8.8	0.51
Sleep efficiency (%)	79.0 ± 1.7	69.7 ± 3.0	0.01
Stages 1 and 2 sleep (min)	219.9 ± 8.7	207.3 ± 10.4	0.43
Slow wave sleep (min)	38.3 ± 5.1	27.6 ± 4.0	0.11
REM sleep (min)	63.2 ± 4.9	47.0 ± 4.5	0.02
Arousal index (number per hour of sleep)	19.2 ± 2.6	26.8 ± 3.3	0.11

Values are expressed as means ± SEM. AHI, apnea–hypopnea index; OSA, obstructive sleep apnea; REM, rapid eye movement; SaO_2, oxygen saturation.

Table 4 Odds of having refractory hypertension, multivariate logistic regression

Factors	OR	95% CI	P
Presence of OSA	3.994	1.191–13.388	0.02
Reduced REM sleep time (min)	1.025	1.002–1.049	0.03

Variables included in the multivariate analysis were the presence of OSA, reduced total sleep time, reduced sleep efficiency and reduced REM sleep. CI, confidence interval; OR, odds ratio; OSA, obstructive sleep apnea; REM, rapid eye movement.

Ruttanaumpawana P et al. J Hypertens 2009; 27: 1439–1445.

HTA RESISTANTE : BILAN 1

Médicaments et substances ayant une action vaso-pressive

- Anti-angiogéniques
- Ciclosporine, tacrolimus
- Erythropoïétine
- Œstrogènes de synthèse (contraception orale)
- Sympathomimétiques
- Venlafaxine

- Alcool
- Cocaïne, amphétamines
- Herbes (ephedra ou ma huang)

Substances ayant une action sur la volémie

- Corticostéroïdes
- Inhibiteur de CYP17A1
- Réglisse
- Apports sodés

Médicaments et substances pouvant interférer avec le métabolisme et/ou l'action des antihypertenseurs

- Anti-inflammatoire non stéroïdien
- Inhibiteur de CYP3A4 : pamplemousse, macrolides, antifongiques azolés …

Interrogatoire long, difficile, systématisé

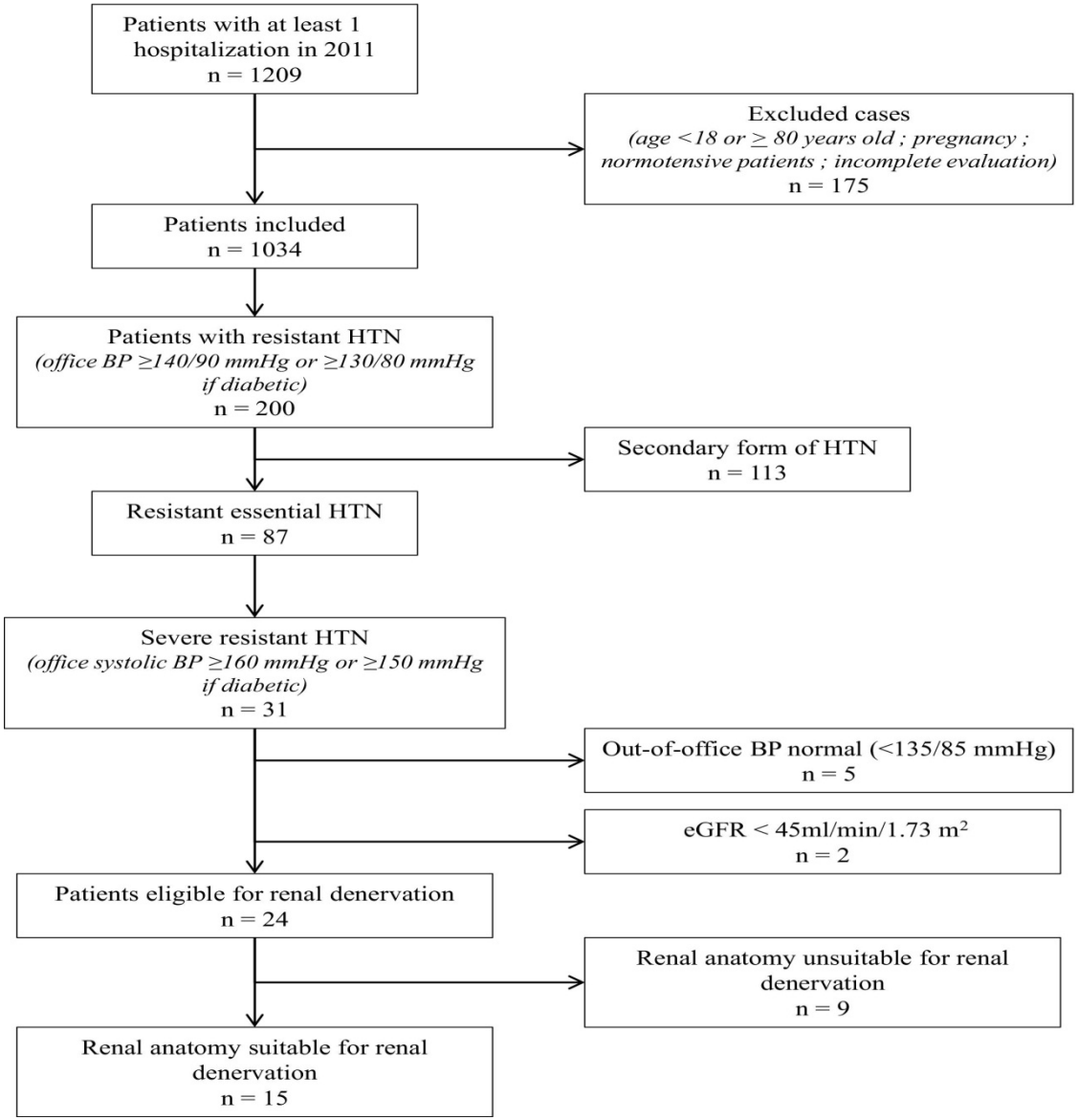
Questionnaire « HY-QUEST »

- Préparation de la consultation par le patient
- Aide à l'exhaustivité des questions

www.centre-hypertension.org

Postel-Vinay N et al. J Hypertens 2014; 32: 693-8.

HTA RESISTANTE : BILAN 2



Savard S. J Am Coll Cardiol. 2012; 60: 2422-4.

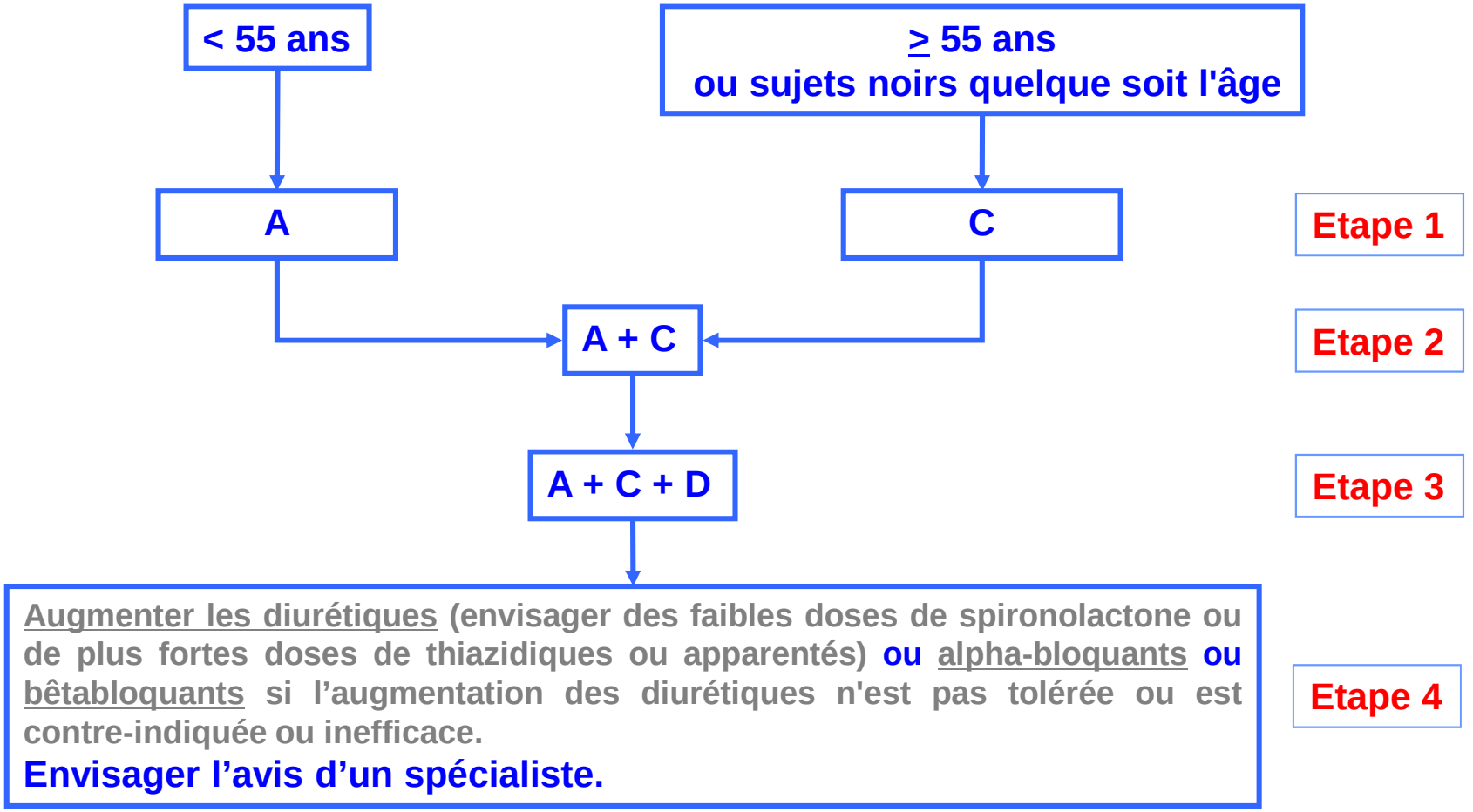
Recherche d'HTA secondaire en milieu spécialisé

- **HAP (20% ?)**
- **Maladie rénale chronique**
- **Sténoses artérielles rénales**
- **Phéochromocytomes / Paragangliomes**
- **Cushing**
- **Coarctation de l'aorte**

Examens complémentaires

- **Iono sang et créatininémie, natriurèse, créatininurie, protéinurie des 24h**
- **Angioscanner abdominal**
- **Echo Doppler Art rénales**
- **Rénine et aldostérone plasmatiques**
- **Méta- et normétanéphrines urinaires des 24h**
- **Cortisol libre urinaire des 24h,**
- **Test de freinage rapide par la déxaméthasone 1 mg**
- **Oxymétrie nocturne, polygraphie de ventilation, enregistrement polysomnographique.**

Management of hypertension: summary of NICE Guidance.



A = IEC ou ARA 2. C = Antagonistes calciques. D = Diurétiques thiazidiques ou apparentés : **chlortalidone (12.5-25.0 mg/j) ou indapamide (1.5 mg LP/j ou 2.5 mg/j), de préférence au thiazidique conventionnel tels que bendroflumethiazide ou hydrochlorothiazide.**

Krause T et al. BMJ 2011;343:bmj.d4891

Lifestyle interventions to reduce raised blood pressure: a systematic review of randomised controlled trials.

Dickinson HO et al. J Hypertens 2006; 24: 215–233.

			Net reduction in blood pressure (mmHg)												
			Systolic blood pressure (SBP)				Diastolic blood pressure (DBP)				Withdrawals[a]			
Type of intervention	*n*	*N*	MD	(95% CI)	I^2	Size, *P*	MD	(95% CI)	I^2	Size, *P*	*n*	RD	(95% CI)	I^2
Diet	14	1339	−6.0	(−8.6 to −3.4)	72%	0.49	−4.8	(−6.9 to −2.7)	81%	0.25	12	0.04	(−0.02 to 0.09)	65%
Diet (excl. [28])	13	1256	−5.0	(−7.0 to −3.1)	52%	0.81	−3.7	(−5.1 to −2.4)	52%	0.59	12	0.04	(−0.02 to 0.09)	65%
Exercise	21	1346	−6.1	(−10.1 to −2.1)	87%	0.57	−3.0	(−4.9 to −1.1)	74%	0.45	17	0.03	(−0.01 to 0.08)	19%
Exercise (excl. [49])	20	1270	−4.6	(−7.1 to −2.0)	65%	0.13	−2.4	(−4.0 to −0.7)	58%	0.21	16	0.04	(−0.01 to 0.08)	26%
Relaxation	23	1231	−4.0	(−6.4 to −1.6)	62%	0.93	−3.1	(−4.7 to −1.5)	70%	0.68	12	0.04	(−0.01 to 0.09)	38%
Alcohol restriction	4	305	−3.8	(−6.1 to −1.4)	0%	0.71	−3.2	(−5.0 to −1.4)	0%	0.73	1	−0.09	(−0.25 to 0.08)	*
Sodium restriction	7	491	−4.7	(−7.2 to −2.2)	59%	0.21	−2.5	(−3.3 to −1.8)	5%	0.002	3	0.02	(−0.09 to 0.13)	4%
Sodium restriction (excl. [94])	6	450	−3.6	(−4.6 to −2.5)	0%	0.43	−2.5	(−3.2 to −1.7)	4%	0.008	3	0.02	(−0.09 to 0.13)	4%
Combined interventions	6	374	−5.5	(−8.8 to −2.3)	51%	0.41	−4.5	(−6.9 to −2.0)	53%	0.70	5	0.05	(−0.02 to 0.13)	12%
Calcium supplements	13	461	−2.5	(−4.4 to −0.6)	42%	0.90	−0.8	(−2.1 to 0.4)	48%	0.64	4	0.00	(−0.06 to 0.06)	0%
Magnesium supplements	12	527	−1.3	(−4.0 to 1.5)	62%	0.14	−2.2	(−3.4 to −0.9)	47%	0.78	8	0.00	(−0.04 to 0.03)	0%
Potassium supplements	5	398	−11.3	(−25.2 to 2.7)	98%	0.57	−5.0	(−12.4 to 2.4)	99%	0.23	3	−0.02	(−0.07 to 0.02)	0%
Potassium suppl. (excl. [133])	4	350	−3.9	(−8.6 to 0.8)	73%	0.96	−1.5	(−6.2 to 3.1)	96%	0.26	3	−0.02	(−0.07 to 0.02)	0%
Fish oil supplements	8	375	−2.3	(−4.3 to −0.2)	0%	0.10	−2.2	(−4.0 to −0.4)	34%	0.03	5	0.02	(−0.04 to 0.07)	28%

n, Number of included trials; *N*, number of participants assessed; MD, mean difference between treatment and control; CI, confidence interval; I^2, % of variation between trials not explained by sampling variation [11]; Size, *P*, *P* value for relationship between treatment effect and size of trial [12]; RD, risk difference. *, Not enough trials. [a]For parallel trials only.

Resistant Hypertension.
Comparing Hemodynamic Management to Specialist Care.

Taler SJ et al. Hypertension 2002; 39: 982-988.

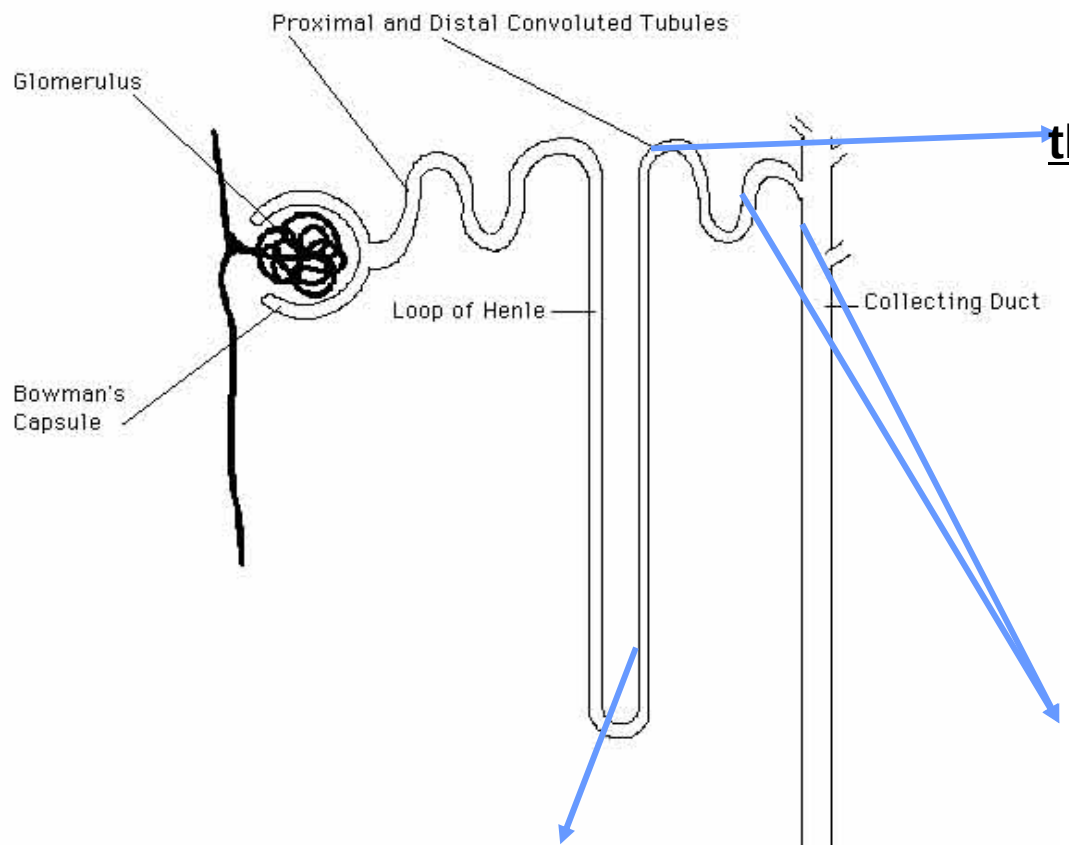
104 resistant hypertension patients randomized to drug selection:
• based on serial hemodynamic measurements (thoracic bioimpedance) and a predefined algorithm,
• directed by a hypertension specialist,
in a 3-month intensive treatment program.

Cardiac index	Systemic vascular resistance index	Medication choices
low	high	1. Add or increase C, A or direct vasodilator 2. Reduce B 3. Evaluate Δ TBI: if reduced, add or intensify D
high	low	1. Add B or central agonist 2. Reduce vasodilators 3. Evaluate ΔTBI: if reduced, add or intensify D
normal	normal	Evaluate ΔTBI: if reduced, add or intensify D

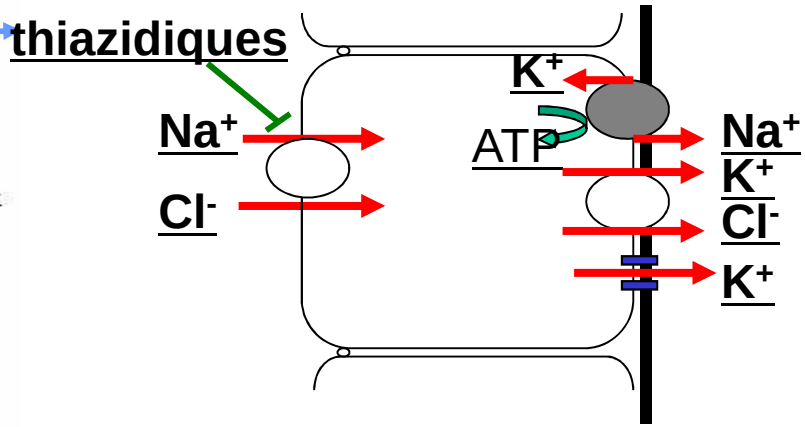
Resistant Hypertension.
Comparing Hemodynamic Management to Specialist Care.

Taler SJ et al. Hypertension 2002; 39: 982-988.

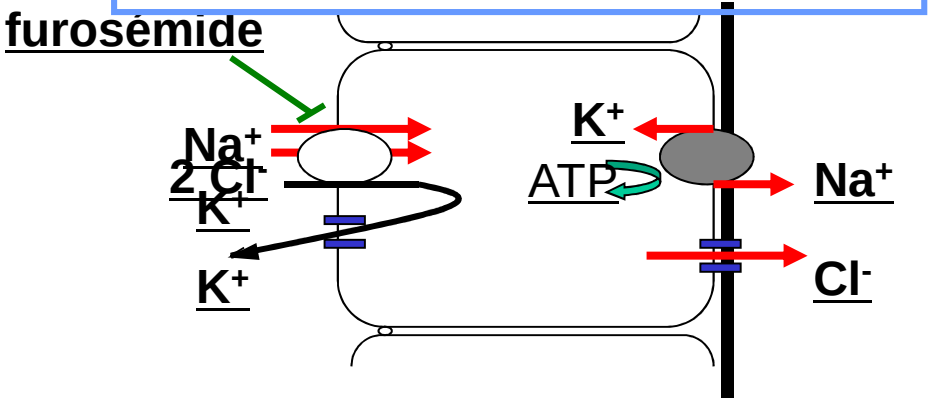
	Hemodynamic care	p	Specialist care
n	50		54
Age, y	67±2		64±2
BMI, kg/m²	31.4±1.0		32.7±1.2
Diabetes mellitus	16 (32)		18 (33)
BP, mmHg	169±3 / 87±2		173±3 / 91±2
HR, bpm	66±1	*	72±2
No. of medications	3.6±0.1		3.6±0.1
DDD	1.1±0.1		1.2±0.2
obstructive sleep apnea	9 (18)		11 (20)
	After 3 months of treatment		
BP, mmHg	139±2 / 72±1	*/*	147±2 / 79±1
Control ≤ 140/90 mmHg	28 (56)	*	18 (33)
No. of medications	4.3±0.1	*	4.1±0.1
DDD	2.1±0.2	*	1.4±0.1



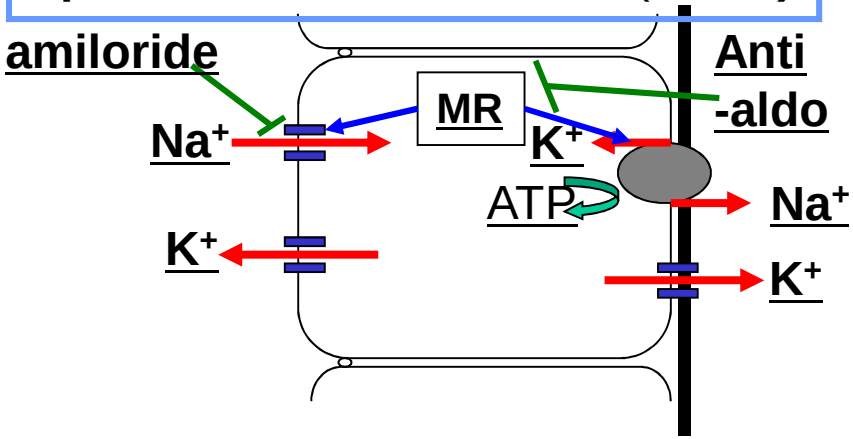
Na^+Cl^- Co-transporter (NCC)



$Na^+K^+Cl^-$ Co-transporter (NKCC2)



Epithelial sodium channel (ENaC)



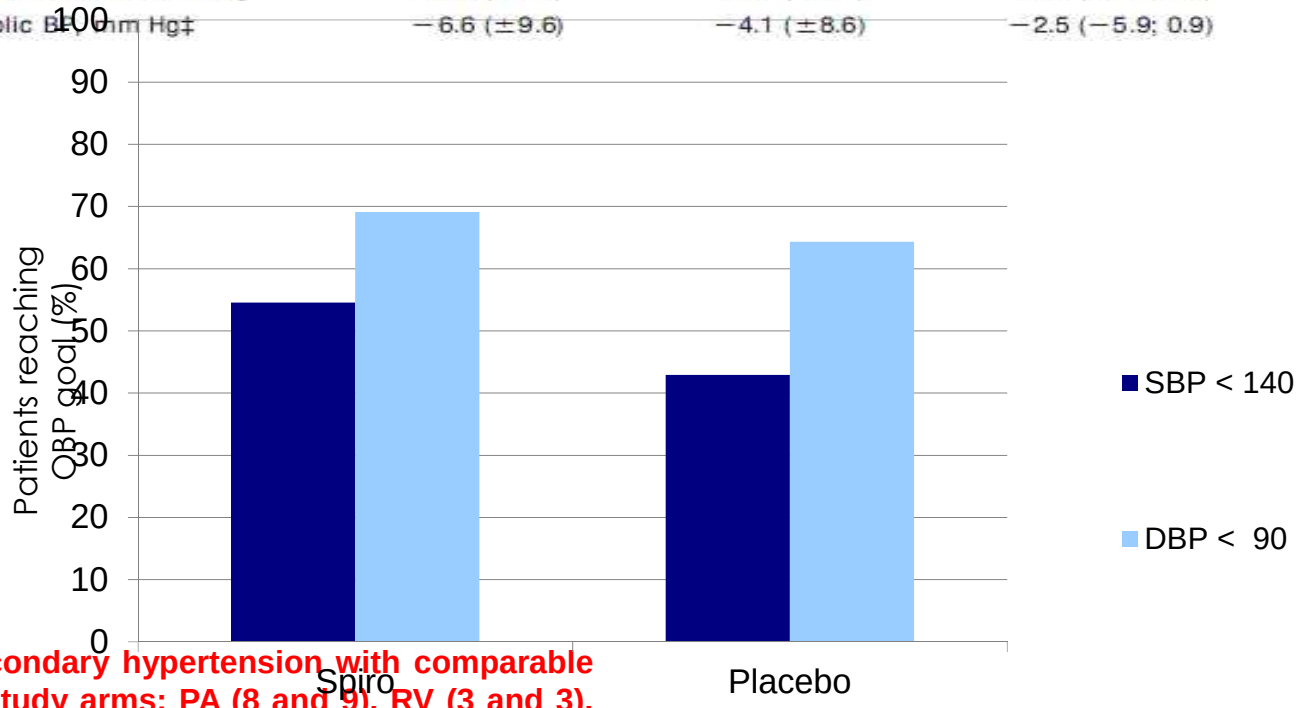
RESISTANCE TO DIURETIC TREATMENT

- **Sodium balance cancellation** *(Freis 1958)*
- **Extracellular volume contraction (thiaz): ⇘ filtered NaCl, ⇗ NaCl proximal reabsorption** *(Walter 1986)*
- **Antinatriuretic effect: NaCl reabsorption downstream of the diuretic action site** *(Wilcox 1983)*
- **Epithelial cells hypertrophy and ⇗ number of NaCl transporter in the distal tubule (furosemide)** *(Kaissling 1988; Ellison D. 1989)*
- **Sodium intake (mouse): high salt regimen: undetectable cytoplasmic ENaC sub-units; low salt regimen: detectable ENaC sub-units in the apex cells of the proximal and collector tubules** *(Loffing 2003)*
- **Loop diuretics treatment (rats): ⇗ NKCC2 and ENaC** *(Na 2003)*
- **Thiazides treatment (rats) : ⇗ NCC and ENaC** *(Na 2003)*
- **Aldosterone exposition (Xenopus laevis ovocytes): ⇗ α ENaC expression and apical transfert of ENaC sub-units** *(Loffing 2003)*
- **Spironolactone treatment (rats): ⇘ NCC and α and γENaC, then regulation via MR which don't block ENaC redistribution related to sodium diet.** *(Nielsen 2003)*

Addition of Spironolactone in Patients With Resistant Arterial Hypertension (ASPIRANT).

Table 2. Change of Patient Characteristics at 8 Weeks Compared to Baseline

Patient Characteristics	Spironolactone (n=55)	Placebo (n=56)	Between-Group Difference*	P†
Systolic BP				
ABPM daytime systolic BP, mm Hg	−9.3 (±12.6)	−3.9 (±12.1)	−5.4 (−10.0; −0.8)	0.024
ABPM nighttime systolic BP, mm Hg	−11.2 (±17.6)	−2.6 (±17.7)	−8.6 (−15.2; −2.0)	0.011
24-h ABPM systolic BP, mm Hg	−13.8 (±11.8)	−4.0 (±12.7)	−9.8 (−14.4; −5.2)	0.004
Office systolic BP, mm Hg‡	−14.6 (±15.6)	−8.1 (±14.8)	−6.5 (−12.2; −0.8)	0.011
Diastolic BP				
ABPM daytime diastolic BP, mm Hg	−4.2 (±8.0)	−3.2 (±8.2)	−1.0 (−4.0; 2.0)	0.358
ABPM nighttime diastolic BP, mm Hg	−5.6 (±10.5)	−2.6 (±11.0)	−3.0 (−7.0; 1.0)	0.079
24-h ABPM diastolic BP, mm Hg	−4.2 (±7.0)	−3.2 (±7.7)	−1.0 (−3.7; 1.7)	0.405
Office diastolic BP, mm Hg‡	−6.6 (±9.6)	−4.1 (±8.6)	−2.5 (−5.9; 0.9)	0.079

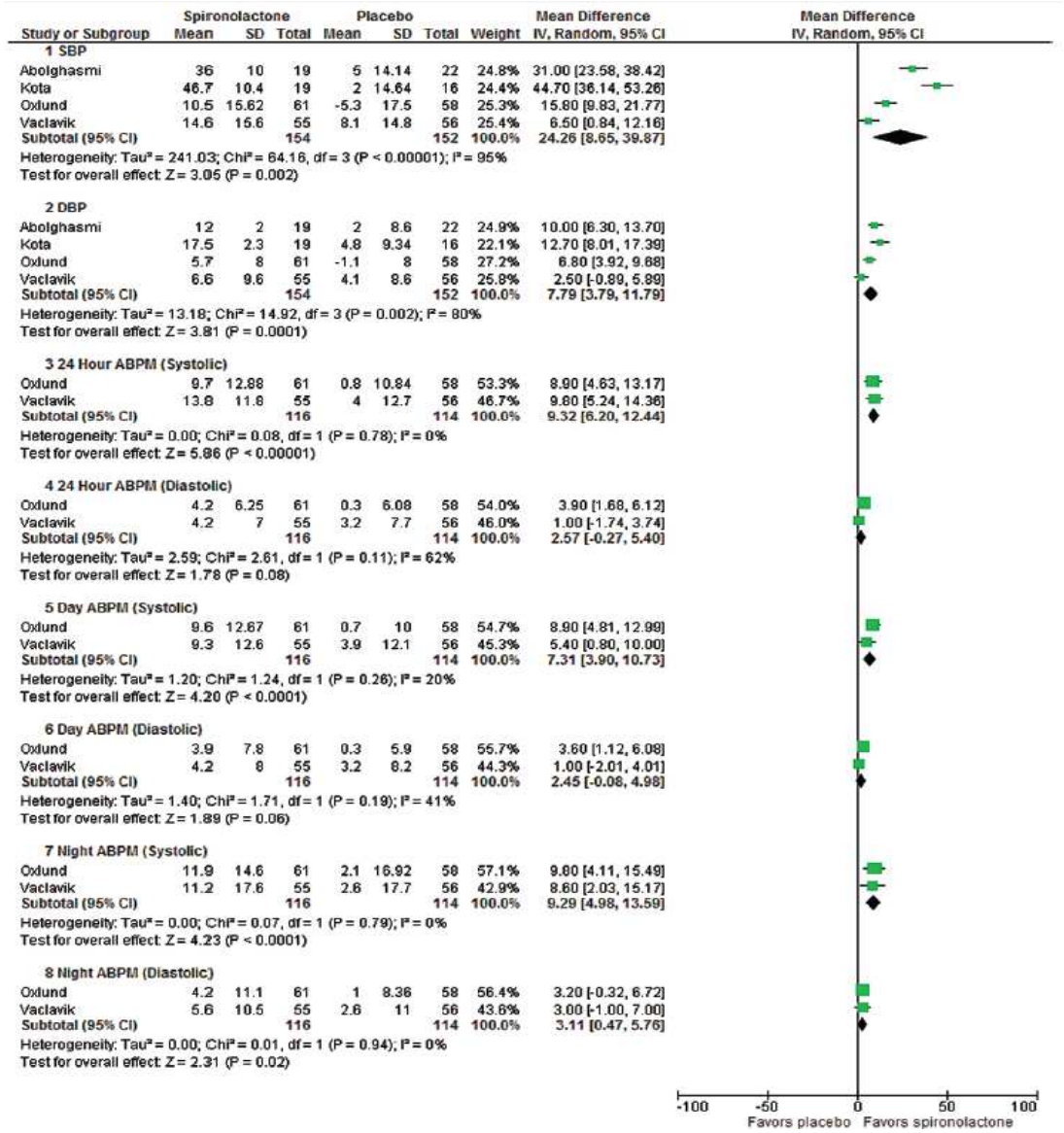


28 pts (24%) had secondary hypertension with comparable distribution in both study arms: PA (8 and 9), RV (3 and 3), OSA (1 and 2), and nephrogenic hypertension (1 and 1).

Vaclavík J. et al. Hypertension 2011;57:1069-1075.

The Effects of Aldosterone Antagonists in Patients With Resistant Hypertension: A Meta-Analysis of Randomized and Non randomized Studies.

Dahal K et al. Am J Hypertens. 2015;28:1376-85.

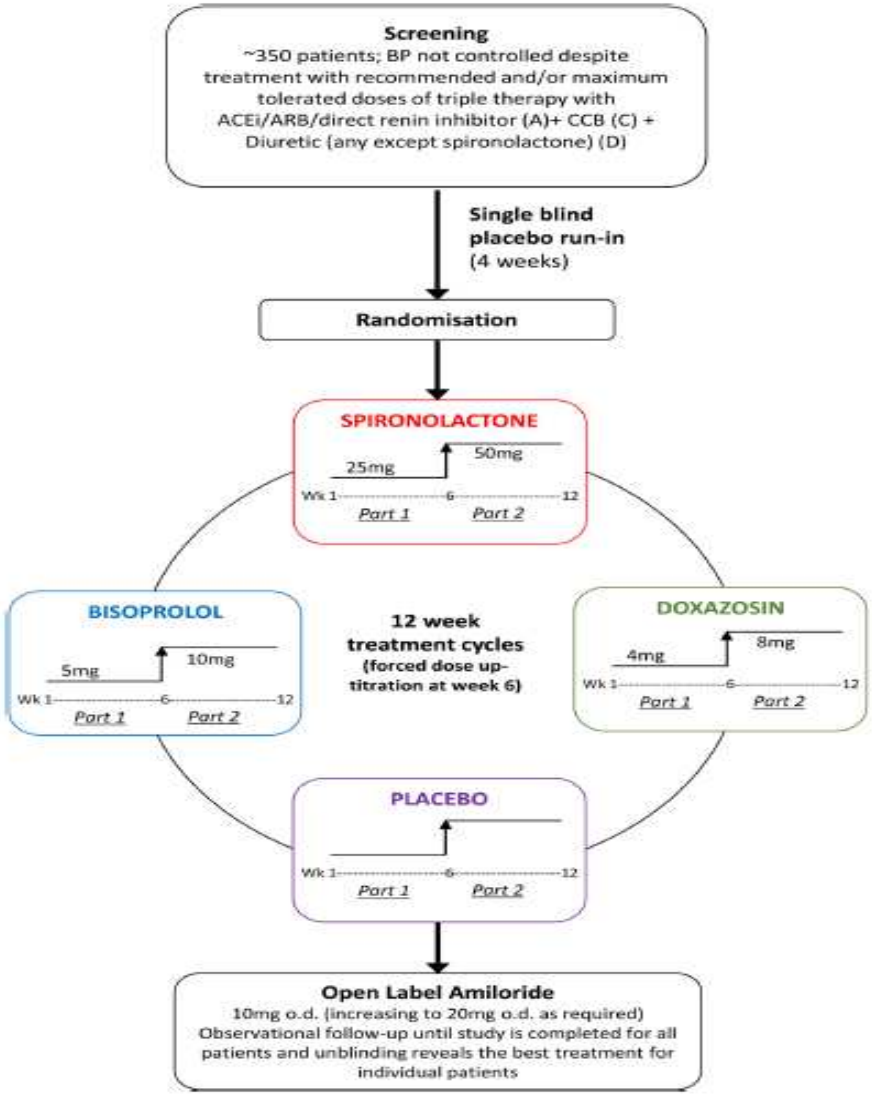


Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial.

Williams B. et al. for The British Hypertension Society's PATHWAY Studies Group. Lancet. 2015;386:2059-68.

PATHWAY: Prevention And Treatment of Hypertension With Algorithm-based therapy

	Mean (SD) or N (%)
Age (years)	61·4 (9·6)
Sex	
Male	230 (69%)
Female	105 (31%)
Weight (kg)	93·5 (18·1)
Smoker	26 (7·8%)
Home	
Systolic blood pressure (mm Hg)	147·6 (13·2)
Diastolic blood pressure (mm Hg)	84·2 (10·9)
Heart rate (beats per min)	73·3 (9·9)
Clinic	
Systolic blood pressure (mm Hg)	157·0 (14·3)
Diastolic blood pressure (mm Hg)	90·0 (1·5)
Heart rate (beats per min)	77·2 (12·2)
24 h urine (mmol/24 h)	
Sodium	137·1 (71·8)
Potassium	70·5 (29·5)
Blood electrolytes (mmol/L)	
Sodium	139·6 (3·0)
Potassium	4·1 (0·5)
eGFR (mL/min)	91·1 (26·8)
Diabetic	46 (14%)



Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial.

Williams B. et al. for The British Hypertension Society's PATHWAY Studies Group. Lancet. 2015;386:2059-68.

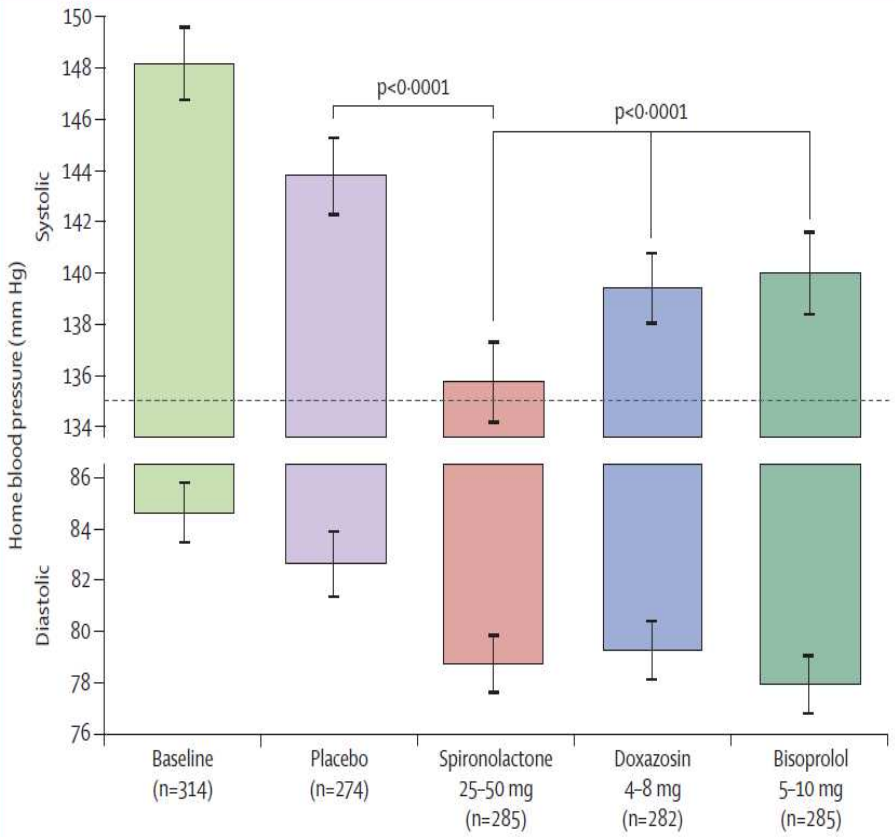


Figure 2: Home systolic and diastolic blood pressures comparing spironolactone with each of the other cycles

The top and bottom of each column represents the unadjusted home systolic and diastolic blood pressures, respectively, averaged across the mid-cycle (low-dose) and end-of-cycle (high-dose) visits (6 weeks and 12 weeks) in which patients received the drug. Error bars represent 95% CI. Comparisons are as described under methods for the primary endpoint.

	Blood pressure (mm Hg)	Change from baseline (mm Hg)
Mean		
Spironolactone	134·9 (134·0 to 135·9)	−12·8 (−13·8 to −11·8)
Doxazosin	139·0 (138·0 to 140·0)	−8·7 (−9·7 to −7·7)
Bisoprolol	139·4 (138·4 to 140·4)	−8·3 (−9·3 to −7·3)
Placebo	143·6 (142·6 to 144·6)	−4·1 (−5·1 to −3·1)
Mean differences		
Spironolactone *vs* placebo	8·70 (−9·72 to −7·69)	p<0·0001
Spironolactone *vs* mean bisoprolol and doxazosin	−4·26 (−5·13 to −3·38)	p<0·0001
Spironolactone *vs* doxazosin	−4·03 (−5·04 to −3·02)	p<0·0001
Spironolactone *vs* bisoprolol	−4·48 (−5·50 to −3·46)	p<0·0001

Data are mean (95% CI). Home systolic blood pressure throughout the treatment cycle for each drug (includes data from mid-cycle at week 6 and the final visit at week 12). Least squares means from mixed effects models adjusted for baseline covariates. Hierarchical primary endpoints each tested only if the preceding tests were significant.

Table 2: **Home systolic blood pressure averaged across both visits for each cycle**

Supplementary Table S7. Home systolic BP control rates

	HSBP		Patients	Met target		Least squares estimate (95% CI)	Odds ratio	p-value
	Baseline	Final	(n)	(r)	r/n (%)			
Control								
Spironolactone	148·3	133·9	282	163	57·8	58·0 (52·0, 63·7)		
Doxazosin	147·8	138·8	276	115	41·7	41·5 (35·8, 47·5)	0·52 (0·37, 0·73)	<·001
Bisoprolol	147·7	139·6	280	122	43·6	43·3 (37·5, 49·2)	0·55 (0·39, 0·78)	<·001
Placebo	147·8	143·5	270	66	24·4	23·9 (19·1, 29·4)	0·23 (0·16, 0·33)	<·001

BP control rates refer to patients achieving a home systolic BP of <135mmHg. Odds ratios from logistic regression models adjusted for baseline.

Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial.

Williams B. et al. for The British Hypertension Society's PATHWAY Studies Group. Lancet. 2015;386:2059-68.

- **At least 50 patients with hypokaliemia suggesting Primary hyperaldosteronism.**
- **Bendroflumethiazide: less effective than Chlortalidone or Indapamide.**
- **Baseline HBPM: 148/84 mmHg.**
- **Low exposure time (6 weeks) to the maximal dose of Spironolactone (50 mg/j) insufficient to assess tolerance (very low percentage of side effects, including gynecomastia and impotence).**

Supplementary Table S8. Adverse events

	Doxazosin		Bisoprolol		Spironolactone		Placebo		p value
	n	%	n	%	n	%	n	%	
Dizziness	36	6.0	72	12.2	36	6.1	26	4.5	0.091
Fatigue	10	3.3	18	6.1	22	7.4	9	3.1	0.283
Muscle spasms	20	6.6	5	1.7	3	1.0	0	0.0	<.001
Bradycardia	5	1.7	3	1.0	19	6.4	2	0.7	<.001
Dizziness postural	28	4.6	10	1.7	2	0.3	2	0.3	<.001
Nasopharyngitis	4	1.3	14	4.7	10	3.4	3	1.0	0.015
Oedema peripheral	0	0.0	13	4.4	4	1.3	2	0.7	<0.001
Diarrhoea	2	0.7	8	2.7	11	3.7	3	1.0	0.025
Dyspnoea exertional	1	0.3	9	3.1	4	1.3	0	0.0	0.002
Syncope	1	0.3	4	1.4	0	0.0	0	0.0	0.036
Tachycardia	0	0.0	6	1.0	0	0.0	0	0.0	0.029
Skin lesion	0	0.0	0	0.0	3	1.0	0	0.0	0.045

Distinct patients reporting adverse events with each preferred term. Terms listed are those that occurred in at least 5% of patients on any treatment, or were significantly different between treatments ($p<0.05$, Fisher's exact test)

Sequential nephron blockade versus sequential renin angiotensin system blockade in resistant hypertension: a prospective, randomized, open blinded endpoint study.

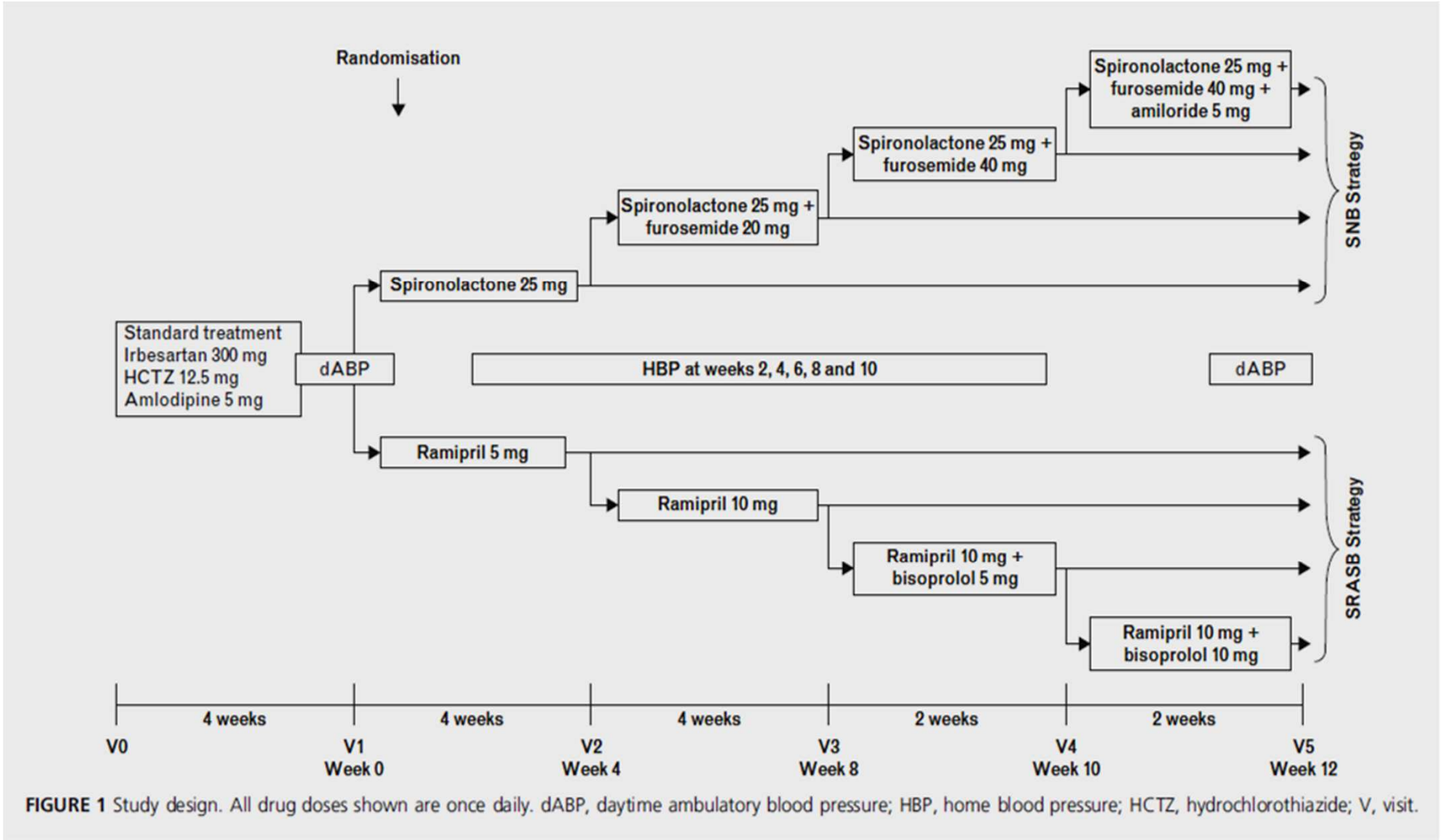
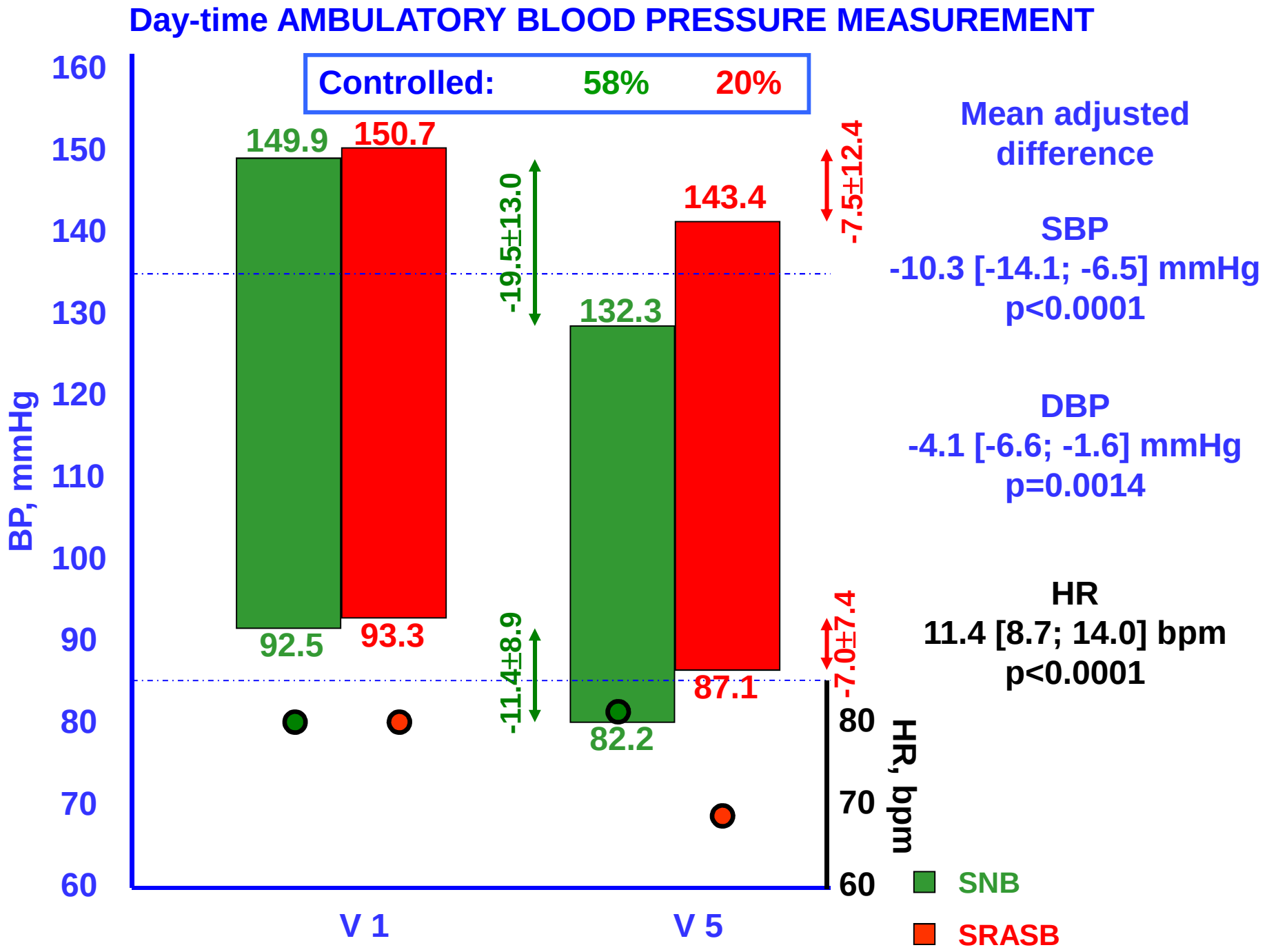


FIGURE 1 Study design. All drug doses shown are once daily. dABP, daytime ambulatory blood pressure; HBP, home blood pressure; HCTZ, hydrochlorothiazide; V, visit.

Bobrie G. et al. J Hypertens. 2012; 30: 1656-64.


Day-time AMBULATORY BLOOD PRESSURE MEASUREMENT
Controlled: 58% 20%
BP, mmHg
160
150
140
130
120
110
100
90
80
70
60
149.9
150.7
92.5
93.3
-19.5±13.0
-11.4±8.9
143.4
132.3
87.1
82.2
-7.5±12.4
-7.0±7.4
HR, bpm
80
70
60
V 1
V 5
Mean adjusted difference
SBP
-10.3 [-14.1; -6.5] mmHg
p<0.0001
DBP
-4.1 [-6.6; -1.6] mmHg
p=0.0014
HR
11.4 [8.7; 14.0] bpm
p<0.0001
SNB
SRASB

A selective endothelin-receptor antagonist to reduce BP in patients with treatment-resistant hypertension.

Weber MA et al. Lancet 2009; 374: 1423–31.

	Placebo (n=132)	Darusentan 50 mg (n=81)	Darusentan 100 mg (n=81)	Darusentan 300 mg (n=85)
Age (years)				
<65 (n=233)	-8·8 (1·5)	-16·4 (2·3); p=0·0020	-17·2 (2·4); p=0·0014	-19·5 (2·4); p<0·0001
≥65 (n=146)	-8·3 (2·1)	-16·8 (2·3); p=0·0091	-19·4 (2·9); p=0·0038	-15·8 (3·4); p=0·0554
Sex				
Women (n=191)	-9·9 (1·8)	-19·9 (2·4); p=0·0002	-18·3 (2·9); p=0·0035	-20·2 (2·8); p=0·0009
Men (n=188)	-7·1 (1·7)	-13·5 (2·3); p=0·0222	-18·0 (2·3); p=0·0003	-16·1 (2·7); p=0·0036
Comorbidity status				
Diabetes (n=153)	-7·2 (1·9)	-13·7 (2·3); p=0·0104	-18·4 (3·1); p=0·0013	-13·4 (3·0); p=0·0724
CKD (n=96)	-7·6 (2·4)	-11·1 (4·1); p=0·2722	-17·5 (4·0); p=0·0292	-16·0 (4·3); p=0·0514
Neither diabetes nor CKD (n=176)	-10·1 (1·9)	-18·9 (2·6); p=0·0051	-17·8 (2·3); p=0·0114	-22·2 (2·8); p=0·0003
Number of background antihypertensive drugs				
Exactly three (n=159)	-8·7 (1·6)	-15·1 (2·6); p=0·0136	-19·8 (3·1); p=0·0007	-18·3 (2·7); p=0·0009
≥Four (n=220)	-8·5 (1·8)	-17·4 (2·2); p=0·0017	-17·1 (2·3); p=0·0040	-17·9 (2·8); p=0·0070

Data are mean (SE). p values indicate changes from baseline compared with placebo. CKD=chronic kidney disease.

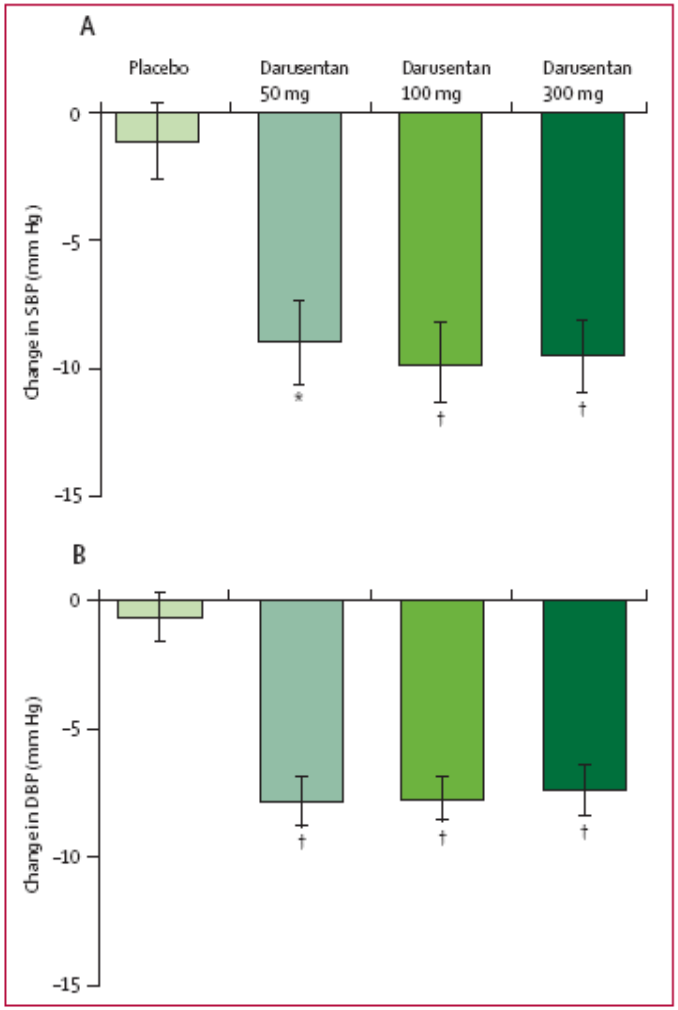


Figure 3: Changes from baseline in mean 24-h ambulatory blood pressure after 14 weeks

Oedema or fluid retention occurred in 67 (27%) patients given darusentan compared with 19 (14%) given placebo. One patient in the placebo group died (sudden cardiac death), and 5 patients in the 3 darusentan dose groups combined had cardiac-related SAE.

Blood-pressure reduction with LCZ696, a novel dual-acting inhibitor of the angiotensin II receptor and neprilysin: a randomised, double-blind, placebo-controlled, active comparator study.

Ruilope LM et al. Lancet. 2010;375: 1255-66.

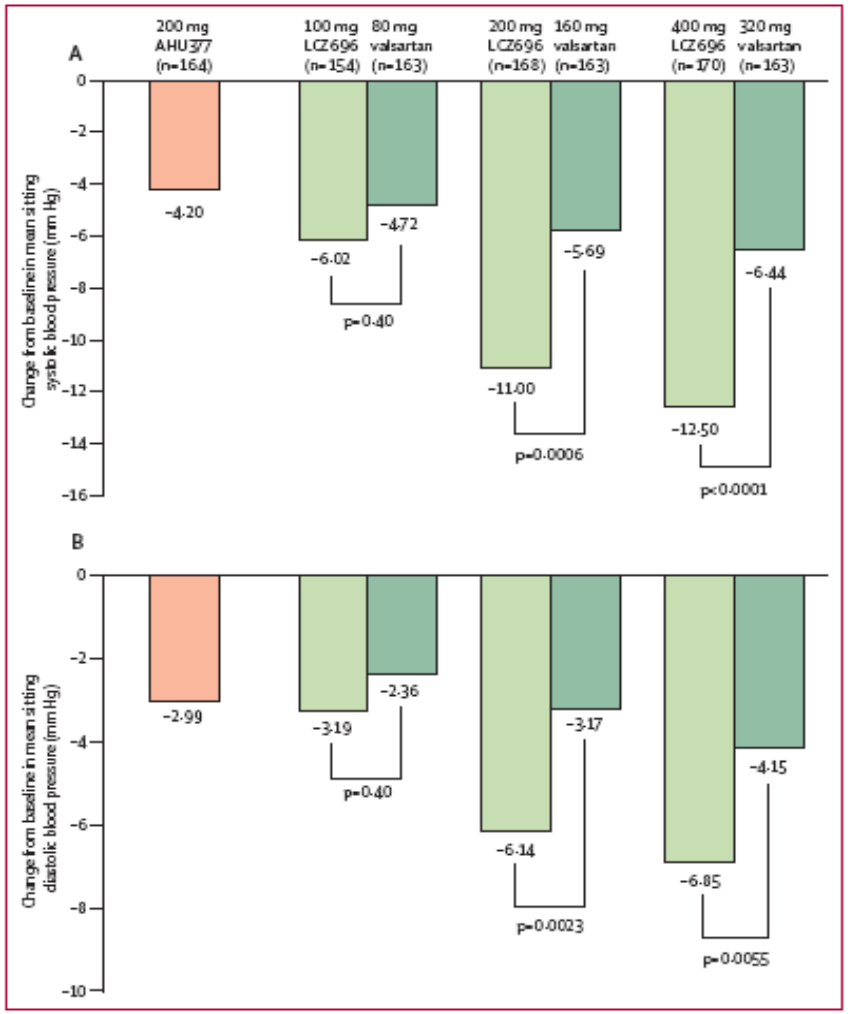
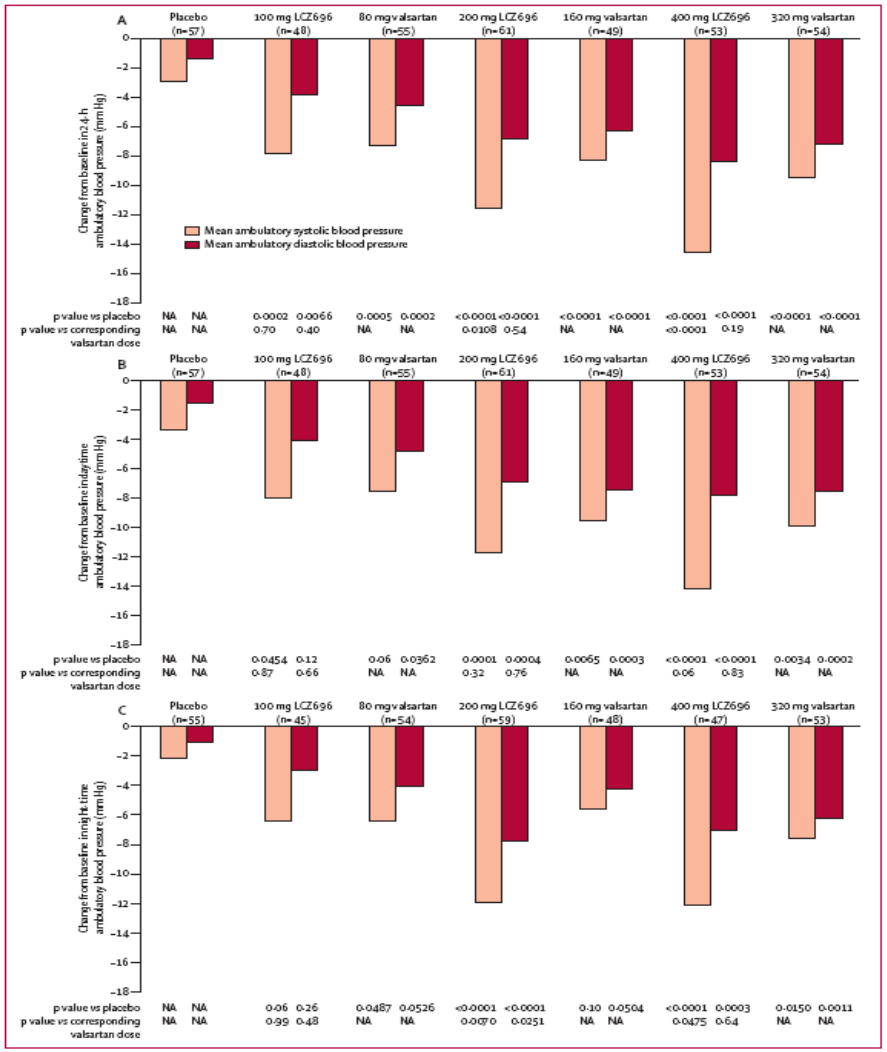
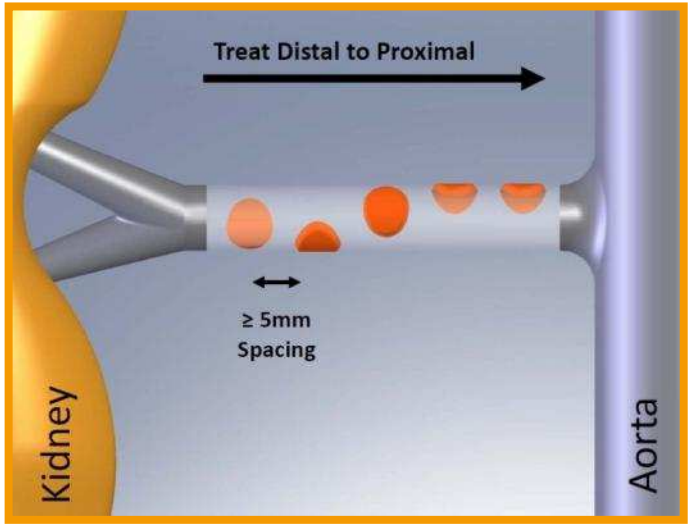
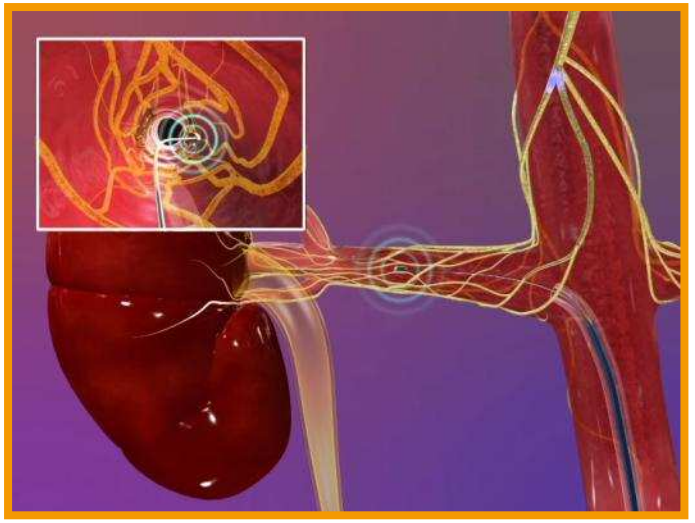


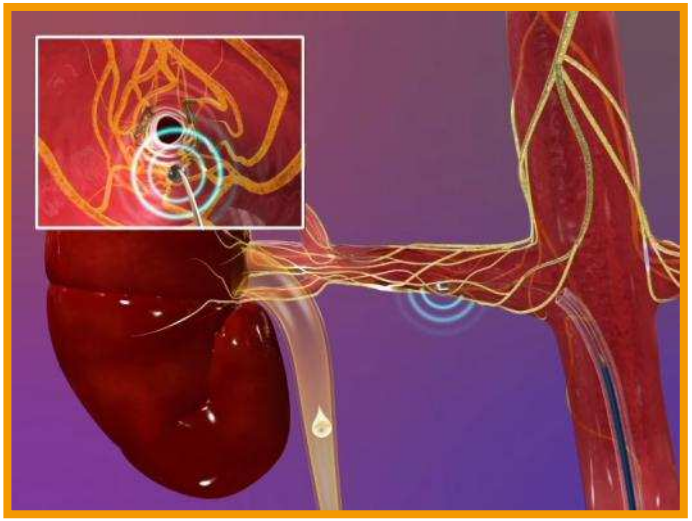
Figure 2: Change in placebo-subtracted mean sitting systolic blood pressure (A) and mean sitting diastolic blood pressure (B) during the 8-week treatment period
Patients who discontinued the study drug without a blood pressure measurement after randomisation were excluded.

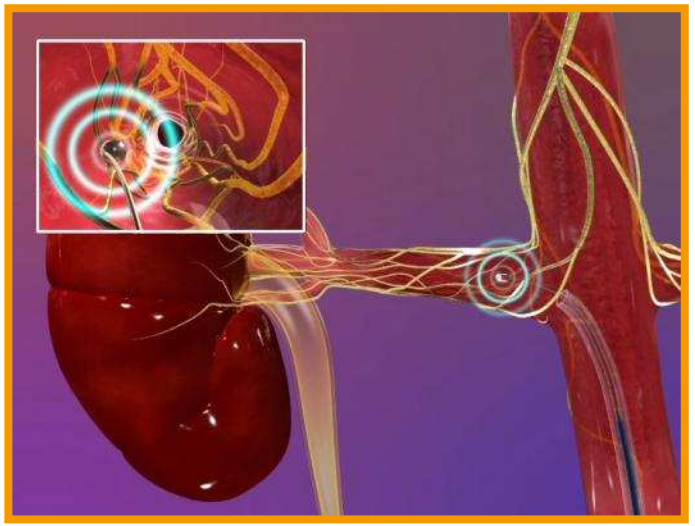


DENERVATION RENALE









Symplicity HTN-2 Investigators. Lancet 2010; 376: 1903–09.

Management of Uncontrollable Hypertension With a Carotid Sinus Stimulation Device.

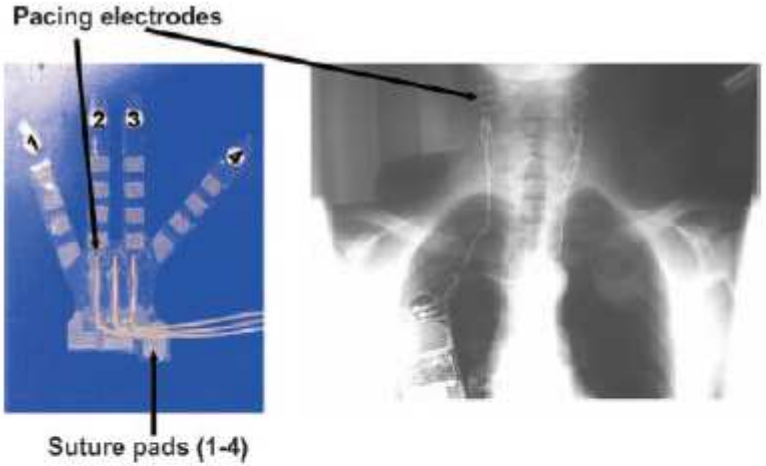


Figure 1. A, Electrode system that is implanted on both carotid sinuses is shown. The adventia is stimulated directly. Pacing electrodes and suture pads of the electrodes are prepared to accommodate placement close to the carotid bifurcation. B, Chest roentgenogram after implantation showing the electrodes in place and the stimulator that is somewhat larger than a conventional pacemaker.

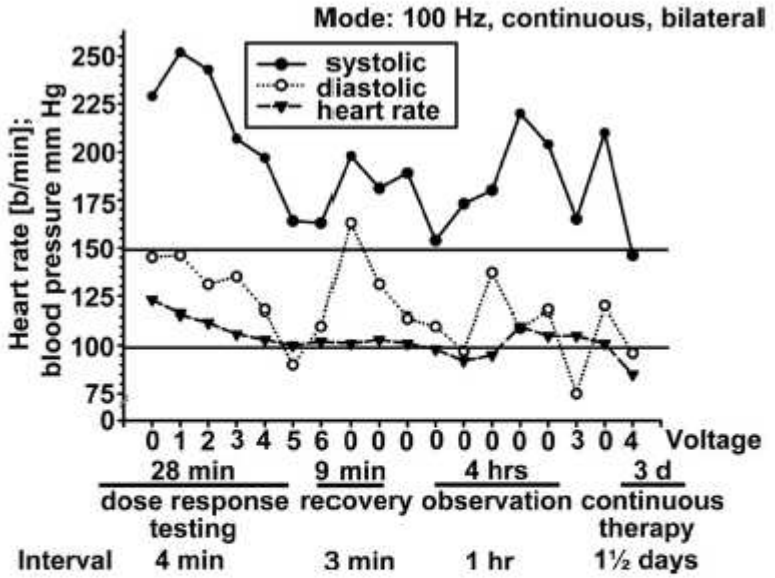


Figure 2. Dinamap blood pressure measurements of the patient during a hypertensive crisis are shown. Systolic blood pressure decreased >45 mm Hg, and diastolic blood pressure decreased 50 mm Hg. Thereafter, the device was shut off, and blood pressure increased over 4 hours. Continuation of the stimulus resulted in blood pressure decreases to the previous stimulation values. Voltage is indicated on the *x* axis. The stimulation was bilateral with on a continuous square-wave pattern at a frequency of 100 Hz and a pulse width of 480 μs.

Mohaupt MG et al. Hypertension. 2007; 50: 825-828.

HTA RESISTANTE : CE QU'IL FAUT RETENIR

1. Pour poser le diagnostic d'HTAR, on devra donc dans un premier temps et de façon systématique s'assurer que :

- **la trithérapie comporte un bloqueur du système rénine, un antagoniste calcique et un diurétique ;**
- **chacun de ces 3 composants est à dose optimale ;**
- **l'observance est correcte ;**
- **l'HTA est effectivement résistante par MAPA ou AMT.**

2. L'HTAR concerne près de 20% des hypertendus. L'HTAR a un mauvais pronostic CV.

3. Interrogatoire systématisé à la recherche des médicaments et substances :

- **ayant une action vaso-pressive,**
- **augmentant la volémie,**
- **interférant avec le métabolisme et/ou l'action des antihypertenseurs.**

Questionnaire « HY-QUEST » : préparation de la consultation par le patient et aide à l'exhaustivité des questions (www.centre-hypertension.org)

4. Recherche systématique d'une HTA secondaire en milieu spécialisé.

5. Augmenter les traitements en augmentant la déplétion sodée. Possibilité de traitements non médicamenteux (système sympathique et baro-réflexe).

6. DEMARCHE STANDARDISEE.