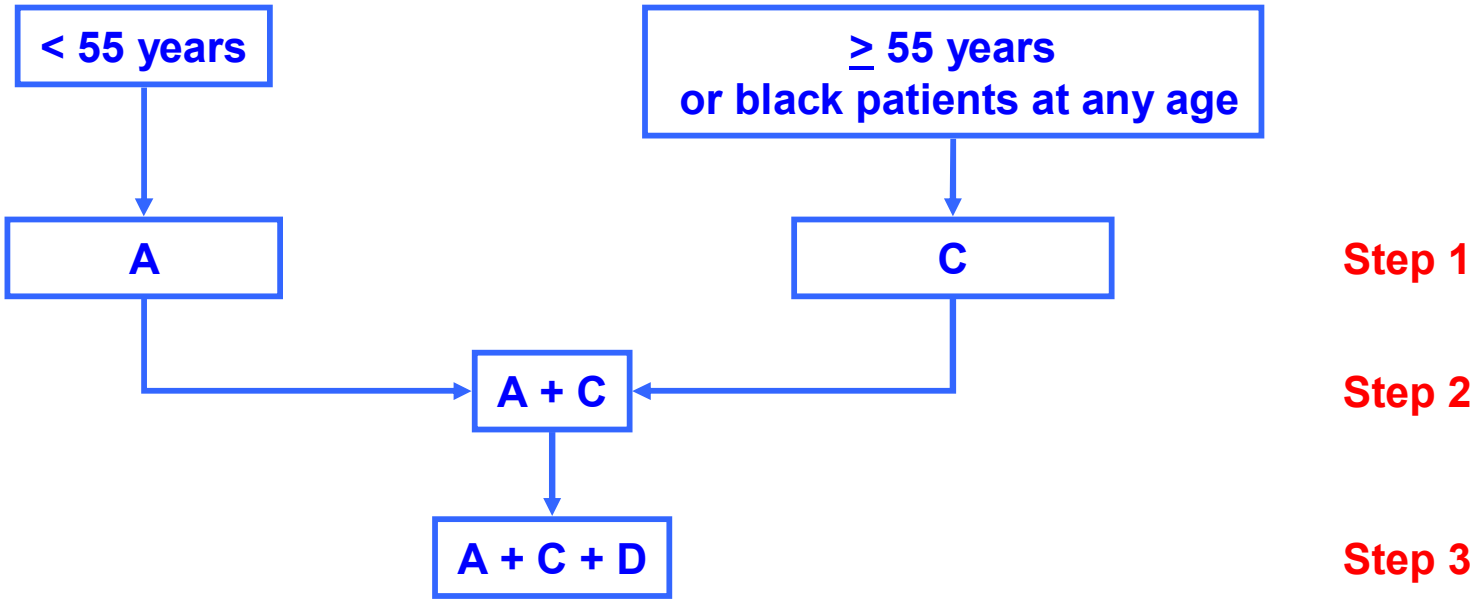
ANALYSE ET TRAITEMENT DES HTA RESISTANTES

G.Bobrie, M. Azizi, P-P Plouin. **HEGP - Paris**

Management of hypertension: summary of NICE Guidance.

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



A = ACE inhibitor or ARB. C = Calcium channel blocker. D = Thiazide-like diuretic : **chlortalidone (12.5-25.0 mg o.d) or indapamide (1.5 mg modified release o.d or 2.5 mg o.d), in preference to a conventional thiazide diuretic such as bendroflumethiazide or hydrochlorothiazide.**

REFRACTORY HYPERTENSION: DEFINITIONS

• 2007 ESH-ESC guidelines for the management of arterial hypertension. *J Hypertens 2007; 25: 1105-1187.* **« When lifestyle measures and at least three drugs in adequate doses has failed to lower systolic and diastolic BP to goal. »**

• ESH recommendations for BP measurement. *J Hypertens 2003; 21: 821-48.*

« Clinical BP measurement consistently greater than 140/90 mmHg with three antihypertensive drugs… ».

• The Seventh Report of the Joint National Committee. *JAMA 2003; 289: 2560-72.* **« the failure to reach goal BP in patients who are adhering to full doses of an appropriate three-drug regimen that includes a diuretic. »**

• Diagnostic et prise en charge de l'HTA essentielle de l'adulte. *ANAES 2005.*

« PA restant au-dessus de la cible thérapeutique fixée (le plus souvent 140/90 mmHg) chez un patient traité par une association de 3 médicaments dont un diurétique ou parfois 2 médicaments antihypertenseurs à doses maximales ».

• Resistant Hypertension: Diagnosis, Evaluation, and Treatment. A Scientific Statement From the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. *Circulation.* 2008;117:e510-e526.

Resistant hypertension is defined as BP that remains above goal in spite of the concurrent use of 3 antihypertensive agents of different classes. Ideally, one of the 3 agents should be a diuretic and all agents should be prescribed at optimal dose amounts. Although arbitrary in regard to the number of medications required, resistant hypertension is thus defined in order to identify patients who are at high risk of having reversible causes of hypertension and/or patients who, because of persistently high blood pressure levels, may benefit from special diagnostic and therapeutic considerations. As defined, resistant hypertension includes patients whose blood pressure is controlled with use of more than 3 medications. That is, patients whose blood pressure is controlled but require 4 or more medications to do so should be considered resistant to treatment.

Uncontrolled and Apparent Treatment Resistant Hypertension in the United States,1988 to 2008.

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

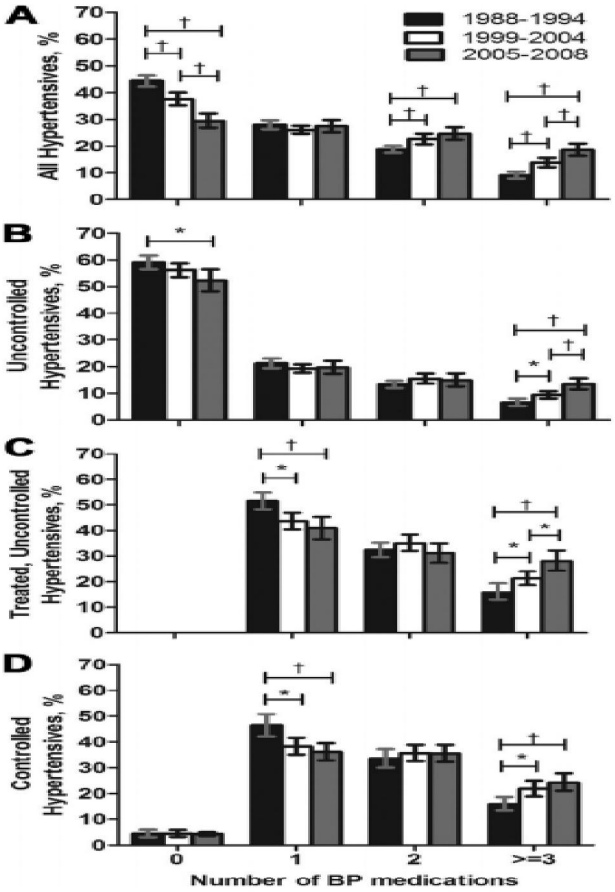


Figure 1. The percentages of hypertensive patients who reported taking 0, 1, 2, and ≥3 antihypertensive (blood pressure [BP]) medications for (**A**) all, (**B**) all uncontrolled, (**C**) treated uncontrolled, and (**D**) treated controlled patients in the different National Health and Nutrition Examination Survey (NHANESs). Symbols over a trio of columns indicate significant changes in the percentage of patients reportedly taking a given number of antihypertensive medications across the 3 NHANES time periods. *$P<0.01$; †$P<0.001$.

Prevalence of Resistant Hypertension in the United States, 2003–2008.

Persell SD. Hypertension 2011; 57: 1076-80.

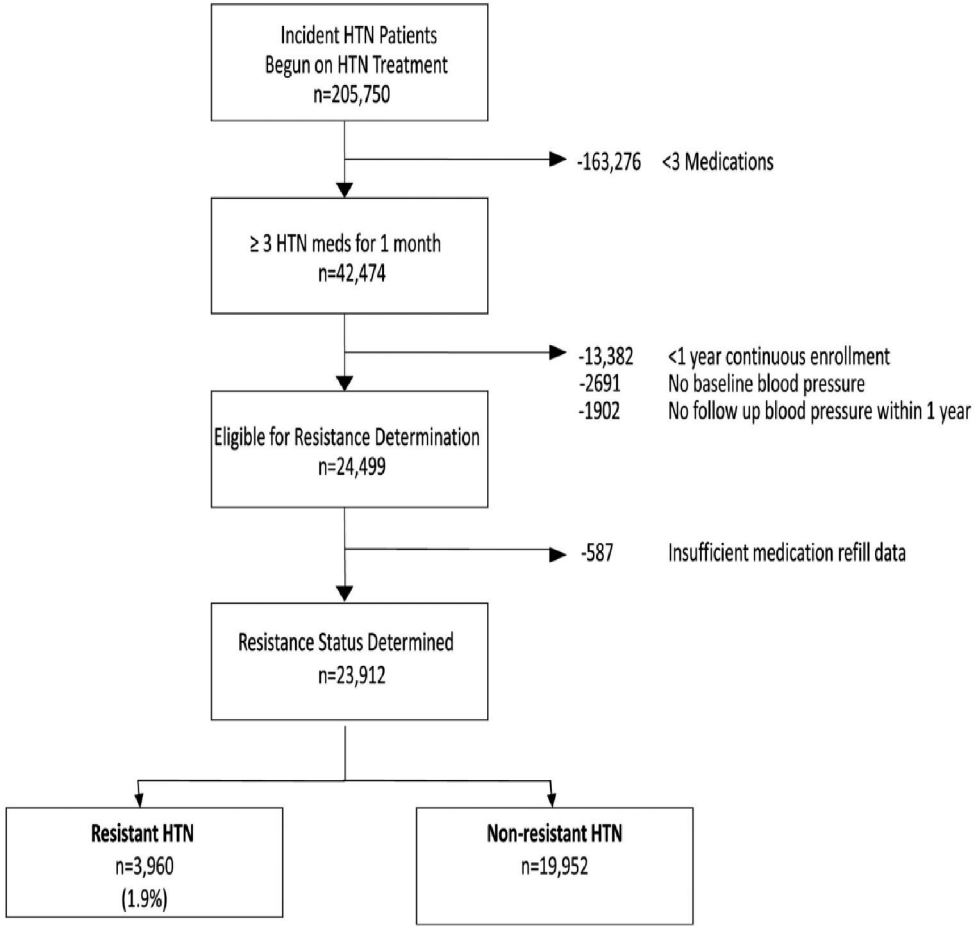
Table 1. Classification of Adults With Hypertension in the United States

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.

Incidence and Prognosis of Resistant Hypertension in Hypertensive Patients.

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



A median of 1.5 years from initial treatment

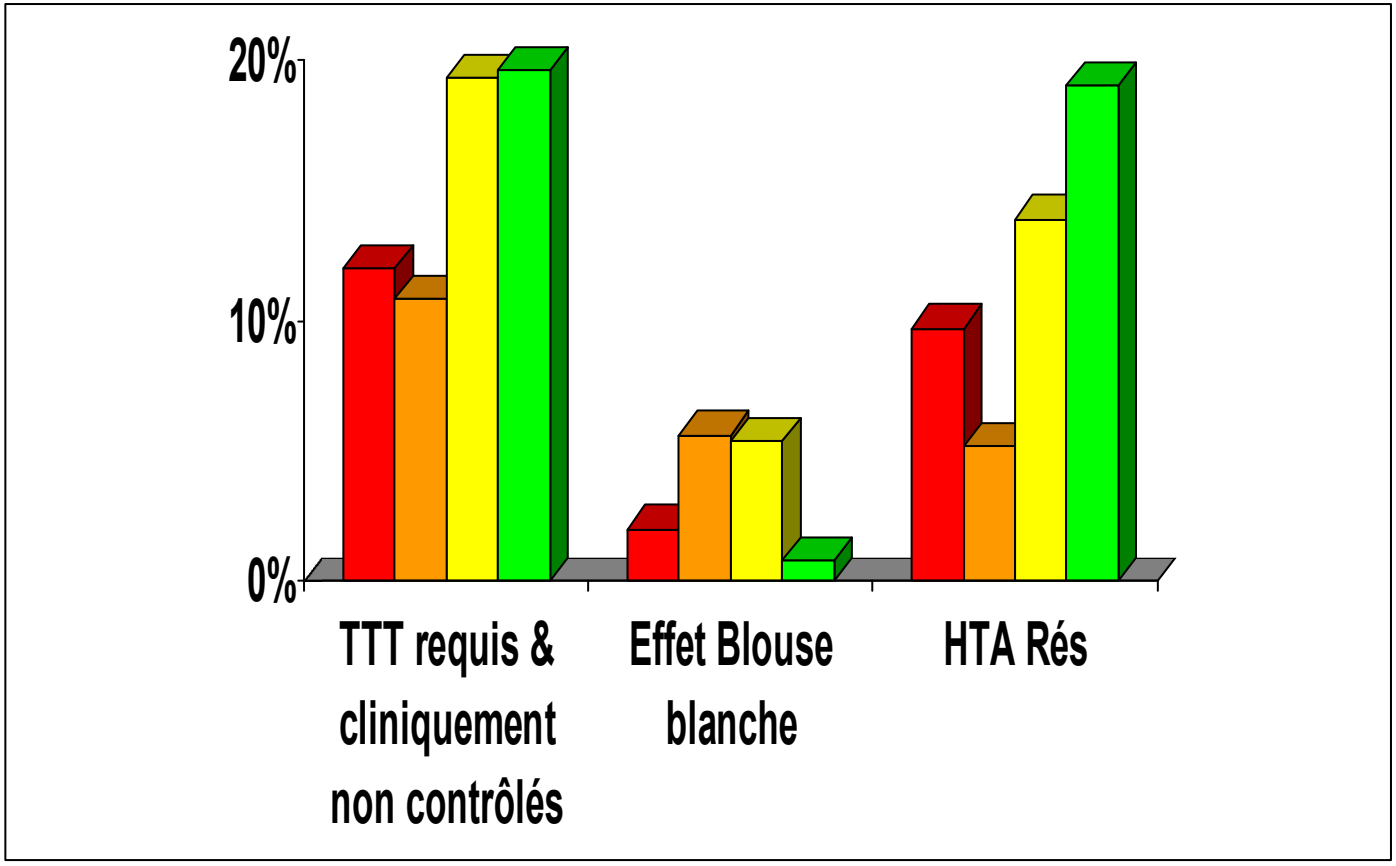
Table 2. Cardiovascular Outcomes Among Patients in the Primary Outcomes Analysis According to Resistance Status

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 (%).

Increased risk of adverse CV outcomes (HR, 1.47; 95% CI,1.33–1.62; P<0.001) (median FU 3.8 years)

HTA RESISTANTE AU TRAITEMENT
PREVALENCE



Bobrie (n=257 nouveaux) (1995)
Mezzetti (n=250 MAPA av ttt) (1997)
Brown (n=611 > 140/90) (2001)
Veglio (n=2500) (2001)

Predictors of Uncontrolled Hypertension in Ambulatory Patients.

Knight EL et al. Hypertension 2001; 38: 809-814.

525 hypertendus, analyse multivariée

Variable	Odds of Poor Control	95% Confidence Interval
Age group*		
55–64 y	1.26	0.71–2.24
65–74 y	2.50	1.49–4.19
≥75 y	2.56	1.45–4.52
Site**		
VAMC	0.63	0.40–1.01
Hospital	0.94	0.42–2.11
No. of antihypertensive drugs during the study period***		
0	0.90	0.41–1.98
2	1.91	1.25–2.91
3	2.53	1.50–4.28
4 or 5	4.70	2.22–9.95
Angina	0.33	0.20–0.56
Lack of knowledge of appropriate SBP	1.55	1.09–2.20
Attributed a specific side effect to a specific antihypertensive medication	2.06	1.41–3.01

Prevalence of Resistant Hypertension in the United States, 2003–2008.

Persell SD. Hypertension. 2011; 57: 1076-1080.

Table 2. Drug-Treated Hypertension Among Adults in the 2003–2008 National Health and Nutrition Examination Survey

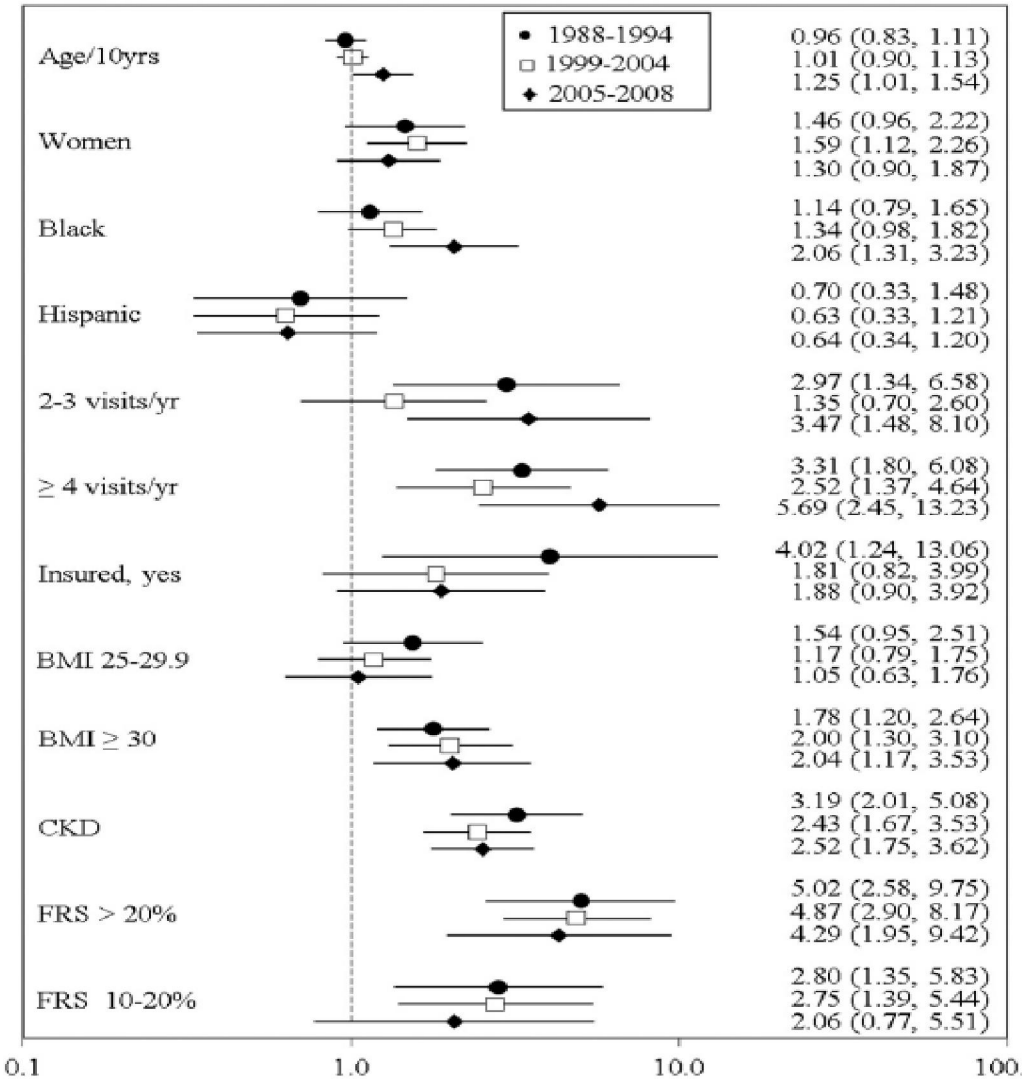
Characteristic	Resistant Hypertension, Uncontrolled, ≥3 Drugs or Controlled ≥4 Drugs (N= 539)	Uncontrolled Hypertension, ≤2 Drugs (N=1136)	P*	Controlled Hypertension, ≤3 Drugs (N=2035)	P*
Age in y, mean	66.4 (0.9)	64.7 (0.5)	0.1	59.5 (0.5)	<0.001
Women, %	53.8 (2.4)	59.2 (1.8)	0.07	53.8 (1.3)	0.9
Race/ethnicity, %			0.02		0.002
Mexican American	1.9 (0.6)	4.4 (1.1)		3.5 (0.7)	
White, non-Hispanic	72.6 (2.8)	75.9 (2.9)		77.8 (1.9)	
Black, non-Hispanic	18.5 (2.3)	13.7 (2.0)		12.6 (1.5)	
Other/multiracial	7.1 (1.7)	6.0 (0.9)		6.0 (0.9)	
Body mass index in kg/m^2, mean†	32.4 (0.5)	29.7 (0.2)	<0.001	31.0 (0.2)	0.01
Estimated GFR in mL/min, mean‡	69.1 (1.5)	78.9 (0.9)	<0.001	80.2 (0.7)	<0.001
Estimated GFR <60 mL/min, %‡	33.7 (2.6)	19.4 (1.6)	<0.001	16.5 (0.9)	<0.001
Serum potassium, mmol/L, %‡	4.03 (0.02)	4.00 (0.01)	0.4	4.00 (0.01)	0.4
Albumin:creatinine ratio, %§			<0.001		<0.001
<30 mg/g	61.0 (2.1)	75.8 (1.5)		86.8 (0.8)	
30 to 300 mg/g	26.2 (2.3)	20.1 (1.4)		11.3 (0.8)	
>300 mg/g	12.8 (2.2)	4.1 (0.7)		1.9 (0.3)	
Coronary heart disease, %	22.0 (2.6)	12.1 (1.6)	<0.001	9.4 (1.2)	<0.001
Heart failure, %	10.0 (2.0)	3.9 (0.8)	<0.001	4.1 (0.5)	<0.001
Diabetes mellitus, %	35.2 (2.6)	20.2 (1.1)	<0.001	20.0 (1.0)	<0.001
Stroke, %	10.1 (1.7)	5.8 (0.8)	0.02	3.8 (0.5)	<0.001

Uncontrolled and Apparent Treatment Resistant Hypertension in the United States, 1988 to 2008.

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

The independent relationships between selected clinical variables and the dependent variable, apparent treatment-resistant hypertension (uncontrolled on 3 BP medications), as multivariable odds ratios and 95% confidence intervals for the 3 National Health and Nutrition Examination Survey periods.

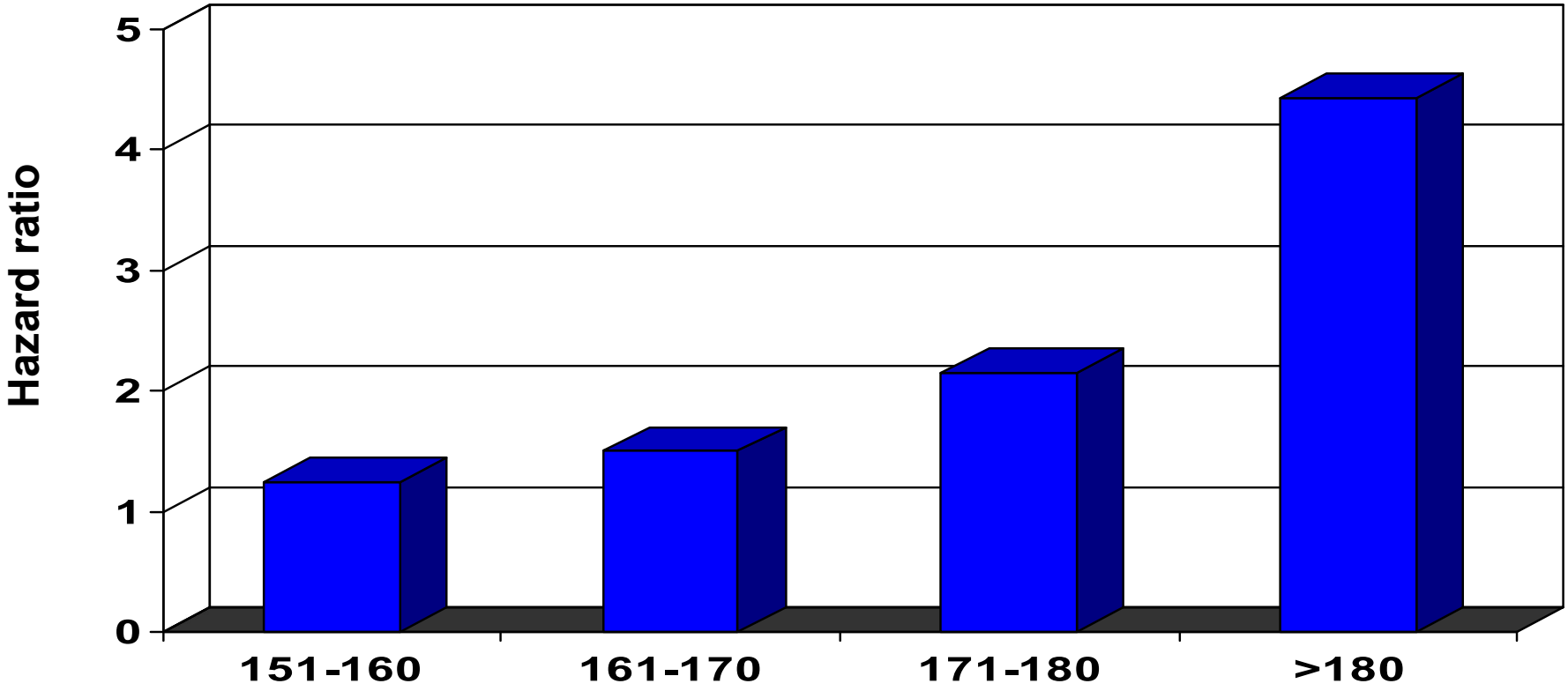
The reference group is all uncontrolled hypertensive patients.



Baseline predictors of resistant hypertension in the Anglo-Scandinavian Cardiac Outcome Trial (ASCOT): a risk score to identify those at high-risk.

Gupta AK et al. J Hypertens 2011; 29: 2004–2013

Predictors of development of resistant hypertension among 3666 previously untreated (or newly diagnosed) hypertensive patients



ADHERENCE TO MEDICATION

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

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

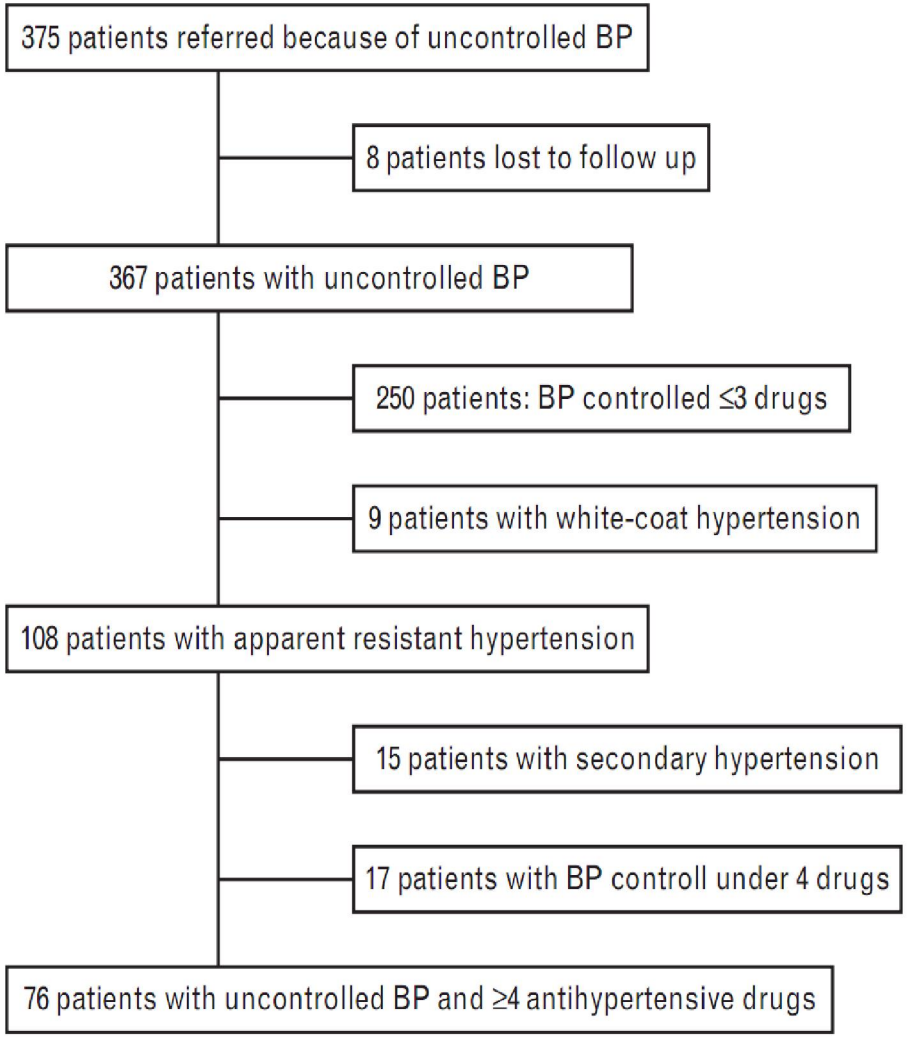
Major Predictors of Poor Adherence to Medication

- 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

Resistant hypertension? Assessment of adherence by toxicological urine analysis

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

2004 and 2011



	N = 76
Age (years)	58 (51–69)
Hypertension – *n* (%)	
Grade I	20 (26.3%)
Grade II	31 (40.8%)
Grade III	25 (32.9%)
Hypertension since (years)	12 (5–22)
Male – *n* (%)	44 (57.9%)
BMI >30 kg/m^2, *n* (%)	70 (92.1%)
Smoker, *n* (%)	32 (42.1%)
Family history of hypertension, *n* (%)	66 (86.8%)
Concomitant disease and/or target organ damage, *n* (%)	69 (90.8%)
Diabetes mellitus type II	24 (31.6%)
Dyslipidemia, *n* (%)	57 (75.0%)
Albuminuria (30–300 mg/day)	6 (7.9%)
Proteinuria (>300 mg/day)	21 (27.6)
eGFR (45–60 ml/min)	7 (9.2%)
Left ventricular hypertrophy	66 (86.8%)
Coronary artery disease	6 (7.9%)
Cerebrovascular disease	6 (7.9%)
Peripheral occlusive disease	3 (3.9%)

Variables are expressed as median and interquartile range (IQR) or as proportions as appropriate. eGFR, estimated glomerular filtration rate.

In the 76 patients, 388 antihypertensive drugs were prescribed. Liquid chromatography-mass spectrometry analysis performed for 368 drugs, (except lercanidipine and nitrates).

Resistant hypertension? Assessment of adherence by toxicological urine analysis

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

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.

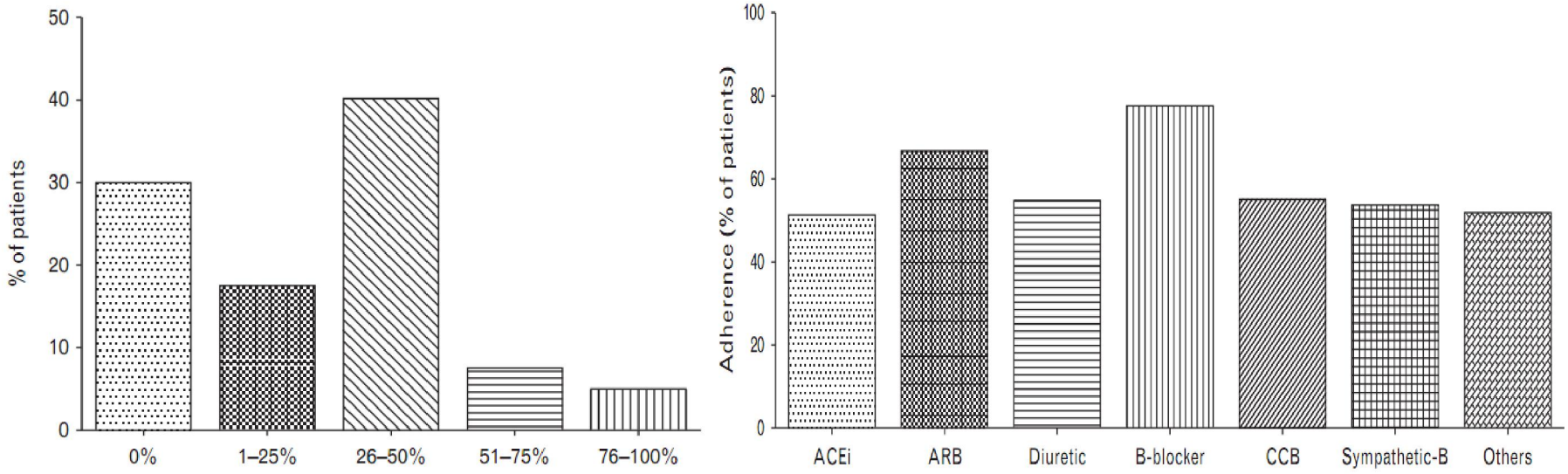


FIGURE 3 Percentage of prescribed drugs taken by nonadherent patients.

A Systematic Review of the Effects of Home Blood Pressure Monitoring on Medication Adherence.

Ogedegbe G and Schoenthaler A. J Clin Hypertens. 2006; 8: 174–180.

Table I. Characteristics of Studies Included in the Systematic Review

Study (year)	Duration of Intervention	N	Completed Follow-Up (%)		Adherence Measure	Statistical Improvement in Adherence
			Intervention	Control		
Bailey et al.[6] (1999)	8 wk	62	97	97	Pill count	No
Binstock et al.[8] (1988)	1 yr	111	100	100	Self-report	No
Friedman et al.[11] (1996)	6 mo	267	85	92	Pill count	Yes
Haynes et al.[13] (1976)	6 mo	38	100	95	Pill count	Yes
Girvin et al.[12] (2004)	6 mo	136	97	97	Pill count	No
McKenney et al.[15] (1992)	24 wk	67	94	97	Electronic monitoring device	Yes
Mehos et al.[16] (2000)	6 mo	36	98	97	Pharmacy records	No
Ogbuokiri[18] (1980)	5 mo	24	79*		Pill count	Yes
Rudd et al.[19] (2004)	6 mo	150	94	91	Electronic monitoring device	Yes
Vrijens and Goetghebeur[22] (1997)	6 wk	628	n/a	n/a	Electronic monitoring device	Yes
Zarnke et al.[23] (1997)	8 wk	31	100	98	Self-report	No

n/a=not applicable; *lost to follow-up not differentiated among conditions

Of the 11 RCTs, six (54%) reported statistically significant improvement in medication adherence attributed to the intervention. Five of these six studies were complex interventions.

Influence of Weight Reduction on Blood Pressure
A Meta-Analysis of Randomized Controlled Trials

Neter J et al. Hypertension. 2003; 42: 878-884.

An average net weight reduction of 5.1 kg was associated with a reduction in SBP of 4.44 mm Hg (95% CI, 5.93-2.95) and in DBP of 3.57 mm Hg (95% CI, 4.88-2.25).

TABLE 2. Changes in SBP and DBP in 25 RCTs of Weight Reduction and BP, Overall and in Subgroups

		SBP, mm Hg†		DBP, mm Hg†	
Stratum	No. of Strata*	Unadjusted	Adjusted‡	Unadjusted	Adjusted‡
Overall	34	−4.44 (−5.93; −2.95)	−4.78 (−5.76; −3.80)	−3.57 (−4.88; −2.25)	−3.56 (−4.31; −2.81)
Age					
≤45 years	15	−4.19 (−6.19; −2.20)	−4.74 (−6.35; −3.12)	−3.17 (−5.04; −1.31)	−3.69 (−4.96; −2.43)
>45 years	19	−4.74 (−6.95; −2.52)	−4.80 (−6.48; −3.13)	−3.94 (−5.76; −2.12)	−3.43 (−4.63; −2.23)
Gender					
<50% females	21	−4.75 (−6.54; −2.97)	−5.05 (−6.10; −3.99)	−4.04 (−5.61; −2.48)	−3.89 (−4.66; −3.12)
≥50% females	13	−3.74 (−6.40; −1.07)	−3.91 (−5.69; −2.13)	−2.53 (−4.82; −0.24)	−2.50 (−3.93; −1.08)
Hypertension§					
No	17	−4.06 (−6.01; −2.16)	−4.46 (−5.71; −3.21)	−2.35 (−4.05; −0.65)	−2.62 (−3.63; −1.42)
Yes	17	−4.95 (−7.25; −2.64)	−4.73 (−6.40; −3.06)	−4.92 (−6.73; −3.12)	−4.36 (−5.72; −3.00)
Race‖					
White	14	−3.19 (−4.79; −1.59)	. . .	−2.50 (−3.00; −1.99)	. . .
Black	4	−4.67 (−8.86; −0.49)	. . .	−3.08 (−4.92; −1.23)	. . .
Asian	4	−8.77 (−11.91; −5.64)	. . .	−9.81 (−11.17; −8.44)	. . .
Intervention					
Energy restriction	19	−4.93 (−6.84; −3.02)	−4.33 (−5.70; −2.97)	−4.25 (−5.95; −2.55)	−2.84 (−3.80; −1.87)
Physical activity	6	−1.73 (−5.14; 1.69)	−4.74 (−7.60; −1.88)	−1.93 (−5.07; 1.22)	−4.65 (−6.84; −2.45)
Combined intervention	7	−5.15 (−7.78; −2.51)	−5.66 (−7.52; −3.81)	−3.12 (−5.60; −0.64)	−4.44 (−5.68; −3.19)
Initial BMI					
<30 kg/m²	15	−4.14 (−4.95; −3.33)	−4.59 (−5.70; −3.49)	−2.61 (−3.29; −1.93)	−3.11 (−4.01; −2.21)
≥30 kg/m²	13	−4.09 (−4.87; −3.31)	−4.05 (−5.06; −3.05)	−2.75 (−3.39; −2.11)	−2.77 (−3.50; −2.04)
Weight reduction					
≤5 kg	16	−2.44 (−4.38; −0.49)	−2.70 (−4.59; −0.81)	−1.97 (−3.71; −0.21)	−2.01 (−3.47; −0.54)
>5 kg	18	−6.24 (−8.06; −4.41)	−6.63 (−8.43; −4.82)	−4.97 (−6.62; −3.31)	−5.12 (−6.48; −3.75)
Antihypertensive drugs¶					
No	26	−3.77 (−5.33; −2.22)	−4.11 (−5.23; −3.00)	−2.97 (−4.39; −1.55)	−2.91 (−3.66; −2.16)
Yes	8	−7.00 (−10.02; −3.98)	−6.70 (−8.71; −4.69)	−5.49 (−8.06; −2.93)	−5.31 (−6.64; −3.99)

Association between refractory hypertension and obstructive sleep apnea.

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

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

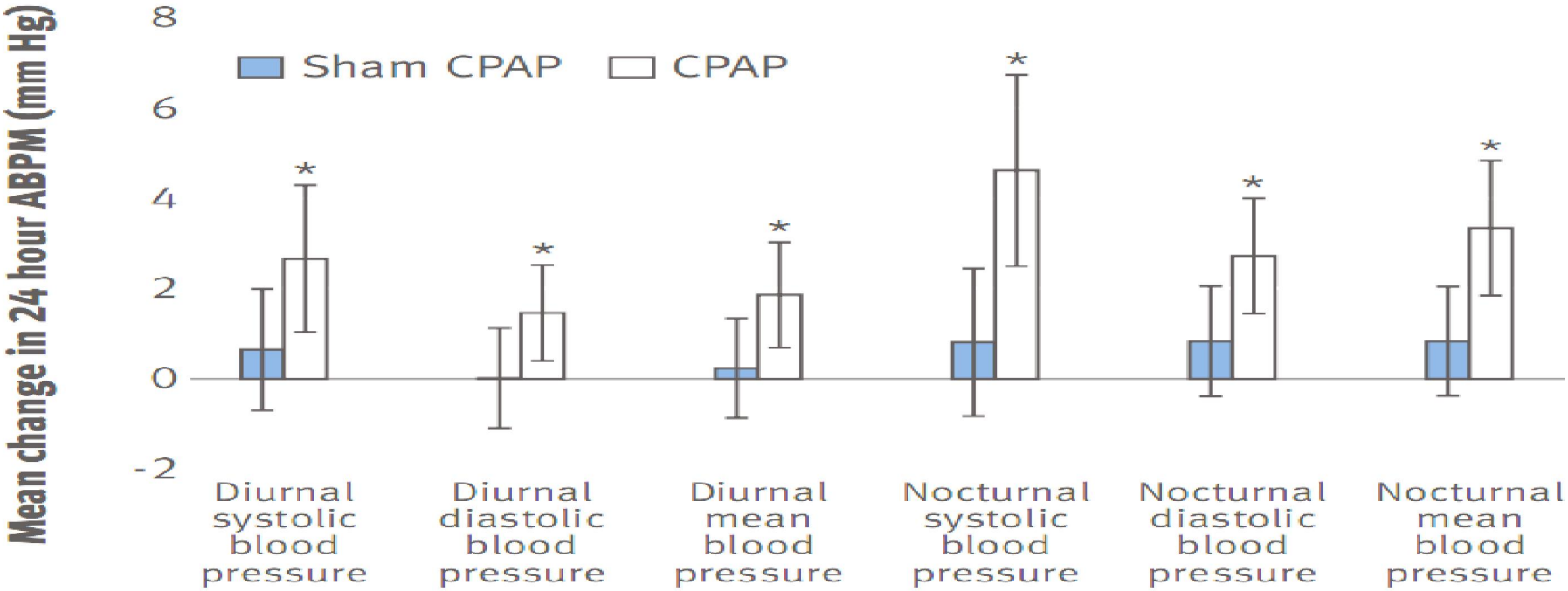
Factors	OR	95% CI	P
Presence of OSA	3.994	1.191–13.388	0.02
Reduced REM sleep time (min)	1.025	1.002–1.049	0.03

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.

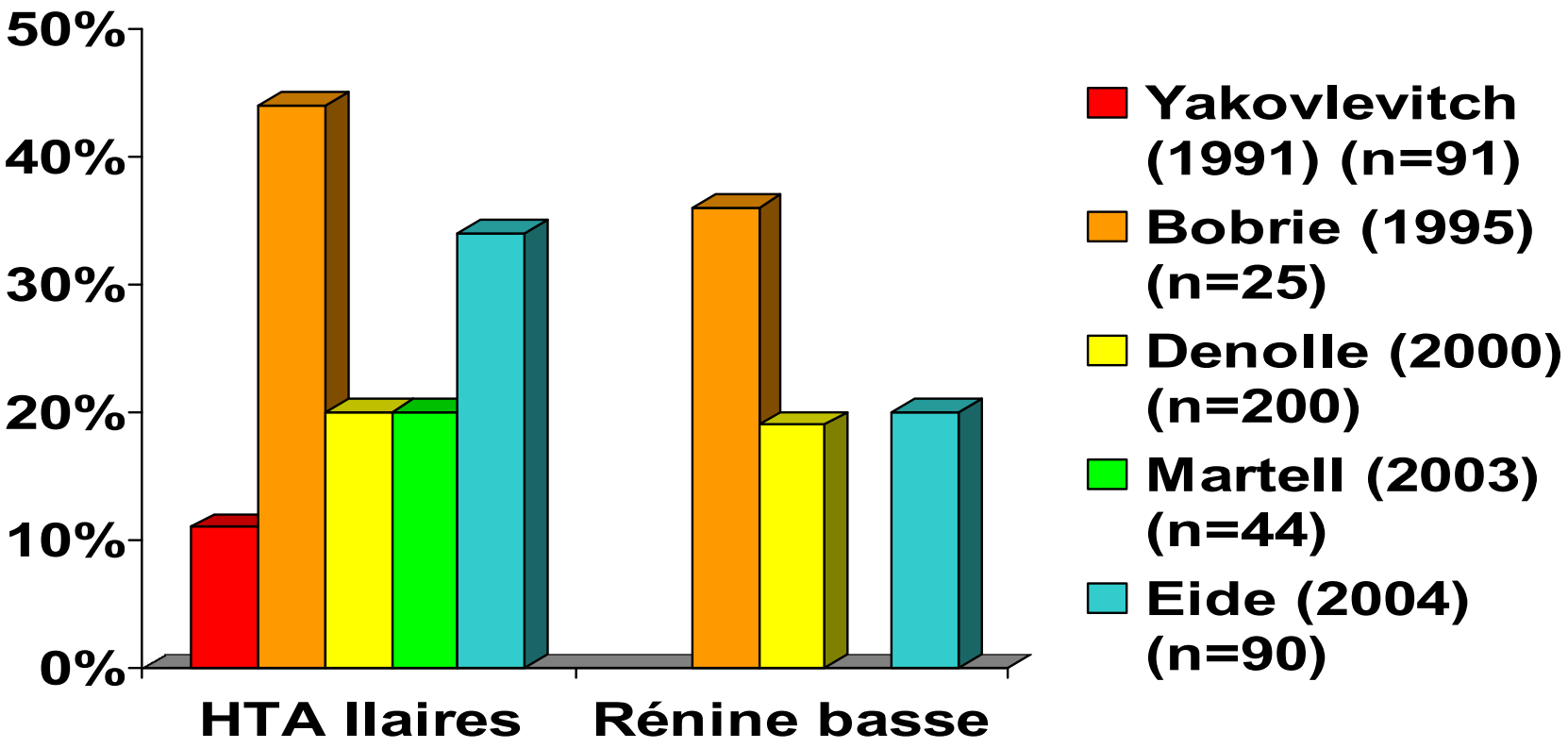
Continuous positive airway pressure as treatment for systemic hypertension in people with obstructive sleep apnoea: randomised controlled trial.

Duran-Cantolla J. BMJ 2010; 341: c5991

340 patients recently diagnosed as having hypertension (≥140 and/or 80mmHg) and an apnoea-hypopnoea index of >15 events/hour of sleep.
CPAP (n=169) or sham CPAP(n=171) for three months.
277(81%) men; mean age 52.4(SD10.5) years, BMI 31.9(5.7), Epworth sleepiness scale score of 10.1(4.3), apnoea-hypopnoea index of 43.5(24.5).



HTA RESISTANTE AU TRAITEMENT
HTA SECONDAIRES



NEPHROPATHIE ET I. RENALE

STENOSE ARTERIELLE RENALE

HAP & HYPERCORTICISME & PHEOCHROMOCYTOME

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

Addition of Spironolactone in Patients With Resistant Arterial Hypertension (ASPIRANT). A Randomized Double-Blind Placebo-Controlled Trial.

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

Addition of 25mg of spironolactone on BP in patients with RH.

Table 1. Patient Demographics and Baseline Characteristics (Completed Study Set)

Patient Characteristics	Spironolactone Group (n=55)	Placebo Group (n=56)
Demographic characteristics		
Age, years	61.4 (±9.6)	60.1 (±9.4)
Sex (female)	18 (32.7%)	24 (42.9%)
Height, cm	173.1 (±8.9)	170.7 (±8.3)
Weight, kg	96.9 (±17.1)	94.1 (±17.3)
BMI, kg/m^2	32.3 (±5.1)	32.3 (±5.3)
Heart rate, bpm	67.8 (±10.4)	70.0 (±9.2)
Mean baseline BP		
Office systolic BP, mm Hg*	154.9 (±10.4)	153.5 (±12.0)
Office diastolic BP, mm Hg*	92.6 (±10.7)	90.6 (±10.9)
ABPM systolic daytime BP, mm Hg	144.7 (±14.8)	140.1 (±16.2)
ABPM diastolic daytime BP, mm Hg	83.6 (±11.1)	80.9 (±10.4)

Table 1. Continued

Patient Characteristics	Spironolactone Group (n=55)	Placebo Group (n=56)
Medication at randomization		
Angiotensin-converting enzyme inhibitor	42 (76.4%)	43 (76.8%)
β-blocker	41 (74.5%)	47 (83.9%)
Calcium channel blocker	49 (89.1%)	43 (76.8%)
Diuretics	55 (100.0%)	56 (100.0%)
Angiotensin II receptor blocker	25 (45.5%)	27 (48.2%)
α-blocker	8 (14.5%)	5 (8.9%)
Centrally acting antihypertensives	32 (58.2%)	31 (55.4%)
Other antihypertensives	2 (3.6%)	0 (0.0%)
Median no. of antihypertensives	4 (3; 6)	4 (3; 6)

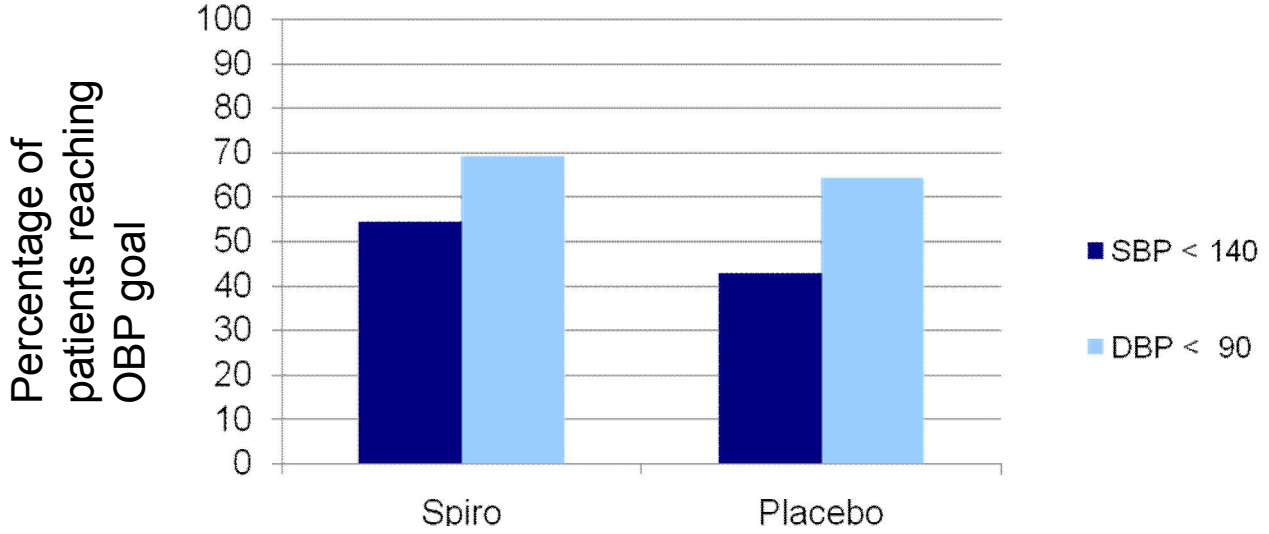
Data are mean (SD) when normally distributed and median (5th and 95th percentile range) when they have non-normal distributions. Categorical variables are number (percentage). None of the baseline parameters is statistically significantly different between the groups

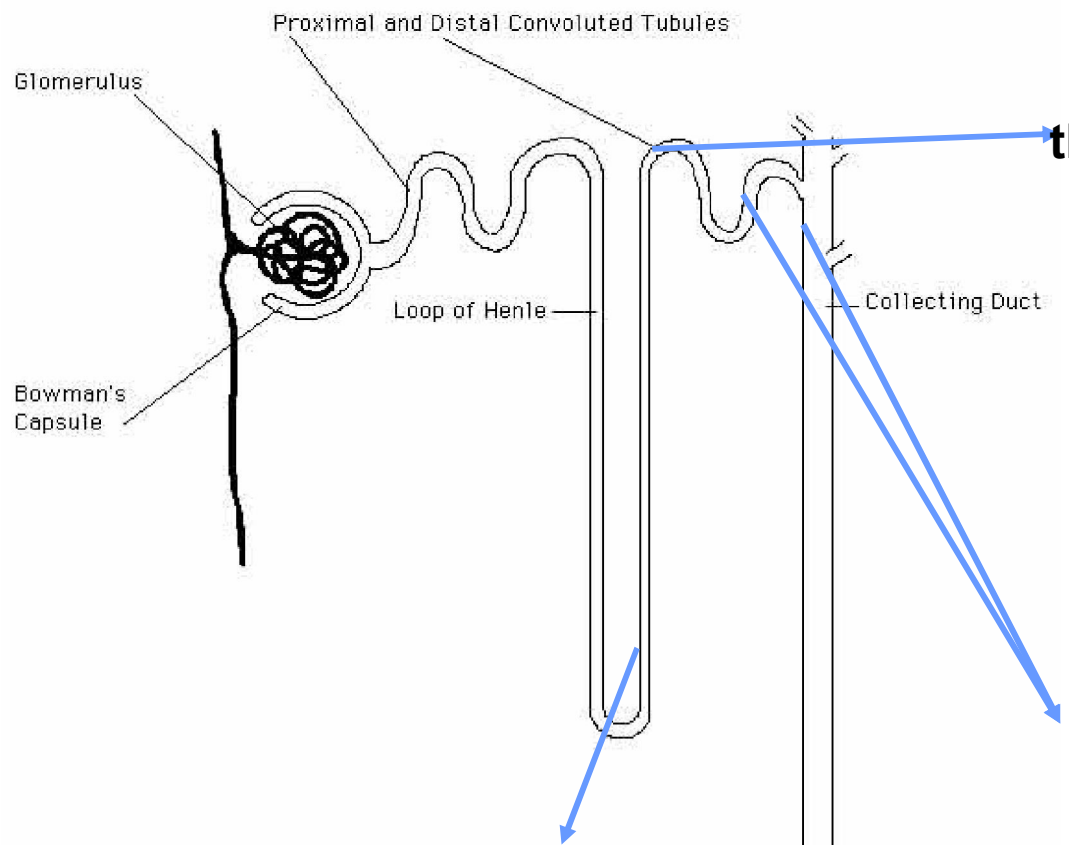
Addition of Spironolactone in Patients With Resistant Arterial Hypertension (ASPIRANT).
A Randomized Double-Blind Placebo-Controlled Trial.

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

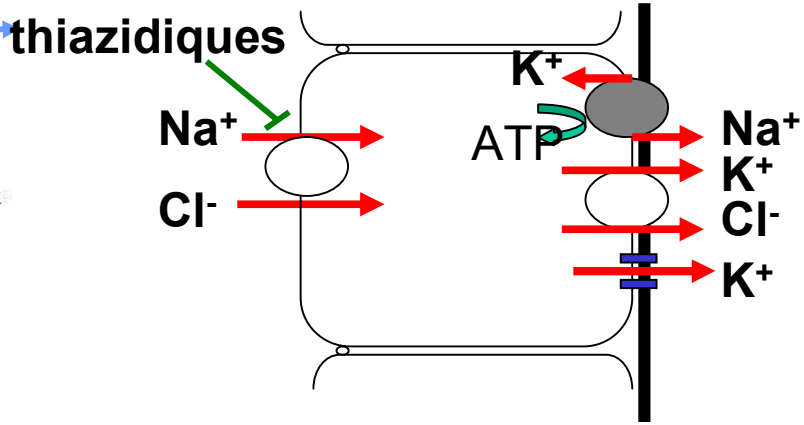
Table 2. Change of Patient Characteristics at 8 Weeks Compared to Baseline

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

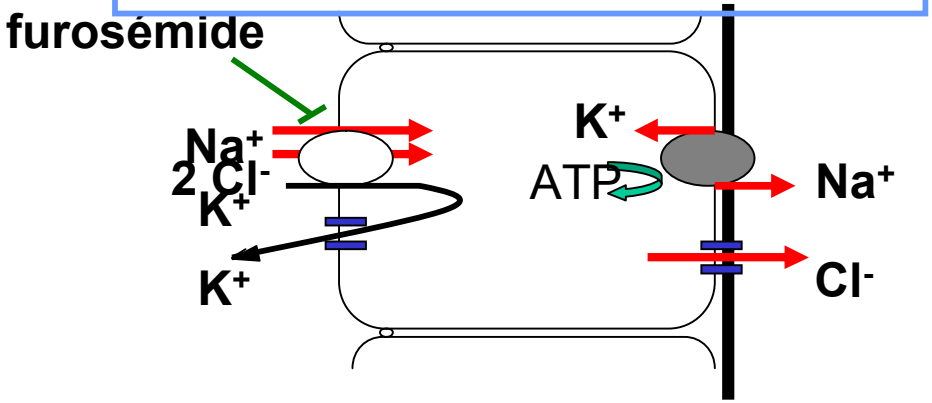




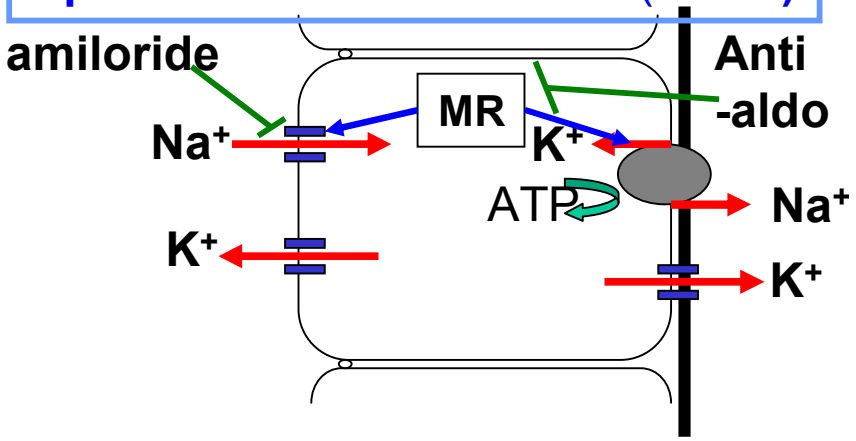
Na^+Cl^- Co-transporter (NCC)



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



Epithelial sodium channel (ENaC)



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

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

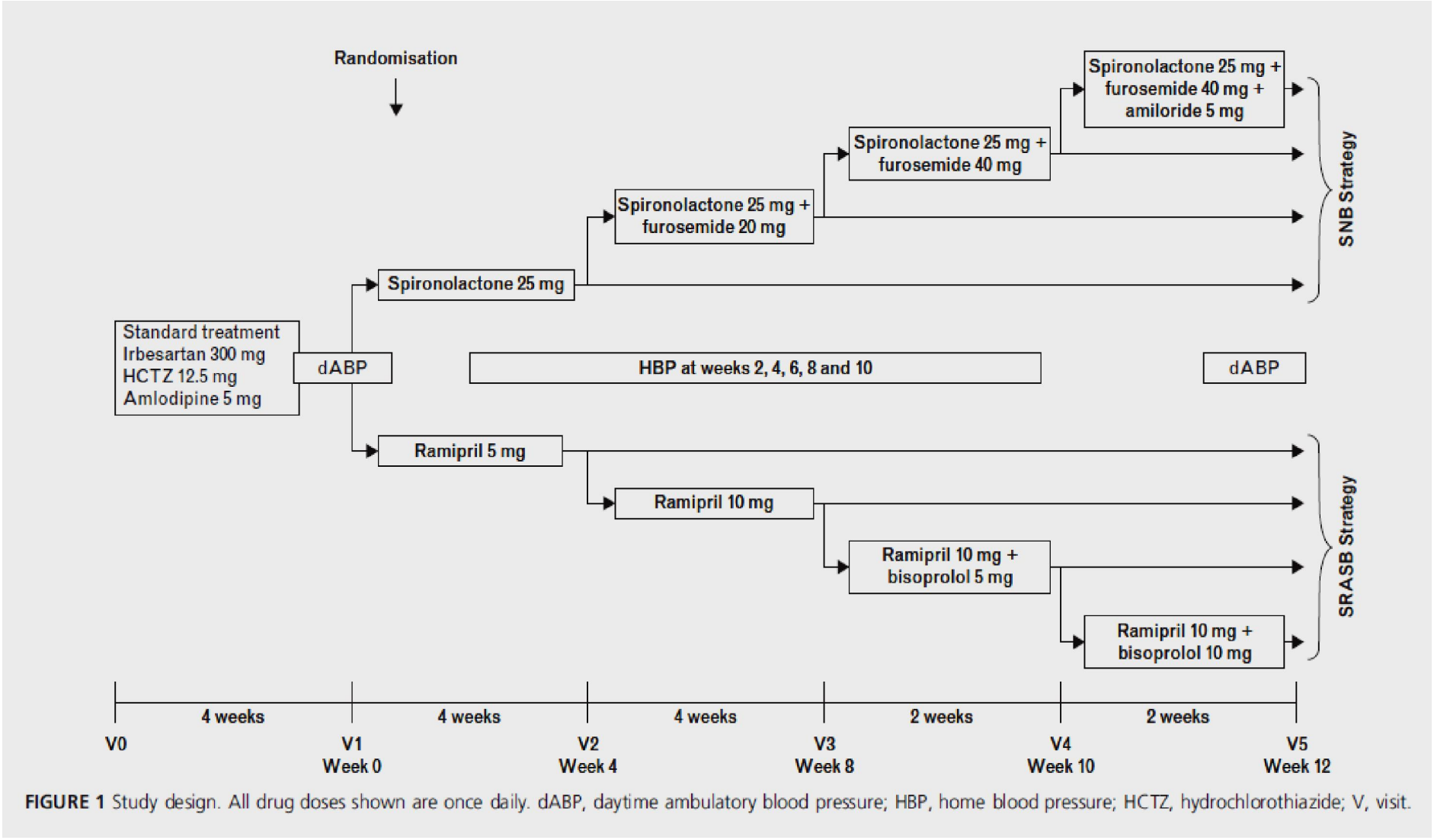


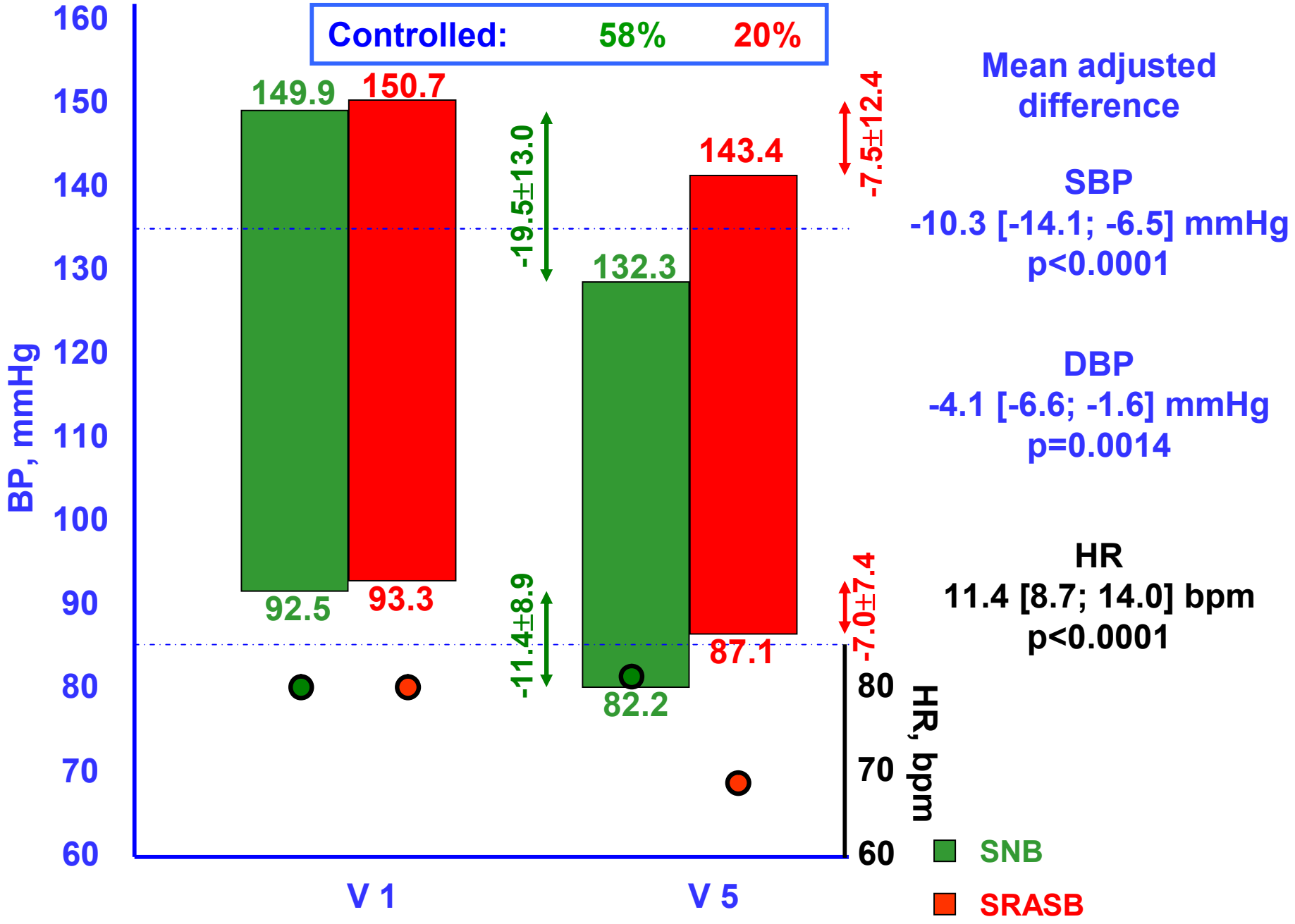
FIGURE 1 Study design. All drug doses shown are once daily. dABP, daytime ambulatory blood pressure; HBP, home blood pressure; HCTZ, hydrochlorothiazide; V, visit.

BASELINE CHARACTERISTICS

(after a standardized 4-week 3 drug-regimen) (Med [IQR])

	SNB-group N=85	SRASB-group N=82	p
Males, n (%)	64 (75.3)	62 (75.6)	0.9622
Black, n (%)	22 (25.9)	17 (20.7)	0.4316
Age, y	56.7 [50.7-62.3]	55.0 [46.7-63.5]	0.5881
BMI, kg/m²	28.7 [25.9-32.4]	28.0 [25.9-30.8]	0.1125
Obesity (BMI >30 kgm²), n (%)	35 (41.2)	27 (32.9)	0.2445
Diabetes, n (%)	15 (17.6)	18 (22.0)	0.6896
Glycemia, mmol/L	6.0 [5.5-6.5]	5.8 [5.3-6.4]	0.3067
HbA1c, %	5.7 [5.3-6.1]	5.5 [5.2-6.0]	0.2791
Never smokers, n (%)	45 (52.9)	35 (42.7)	0.2019
Cholesterolemia, mmol/L	4.8 [4.0-5.4]	4.5 [4.0-5.2]	0.1982
Triglyceridemia, mmol/L	1.3 [0.9-1.6]	1.1 [0.7-1.7]	0.2554
Creatininemia, µmol/L	84 [76-103]	81.5 [73-95]	0.1193
eGFR (MDRD), ml/mn/1.73m²	80 [69-96]	87 [75-101]	0.0539
Uricemia, µmol/L	352 [295-398]	344 [272-391]	0.2385
Protidemia, g/L	69 [66-73]	68 [66-71]	0.2325
U Na / U Creat, mmol/mmol	10.4 [8.0-13.3]	11.4 [8.6-14.7]	0.1263
Microalbuminuria, mg/24h	10 [6-23]	10 [5-18]	0.6983
Natremia, mEq/L	141 [139-142]	141 [139-142]	0.7775
Kaliemia, mEq/L	3.9 [3.6-4.2]	3.9 [3.6-4.2]	0.3227

Day-time AMBULATORY BLOOD PRESSURE MEASUREMENT

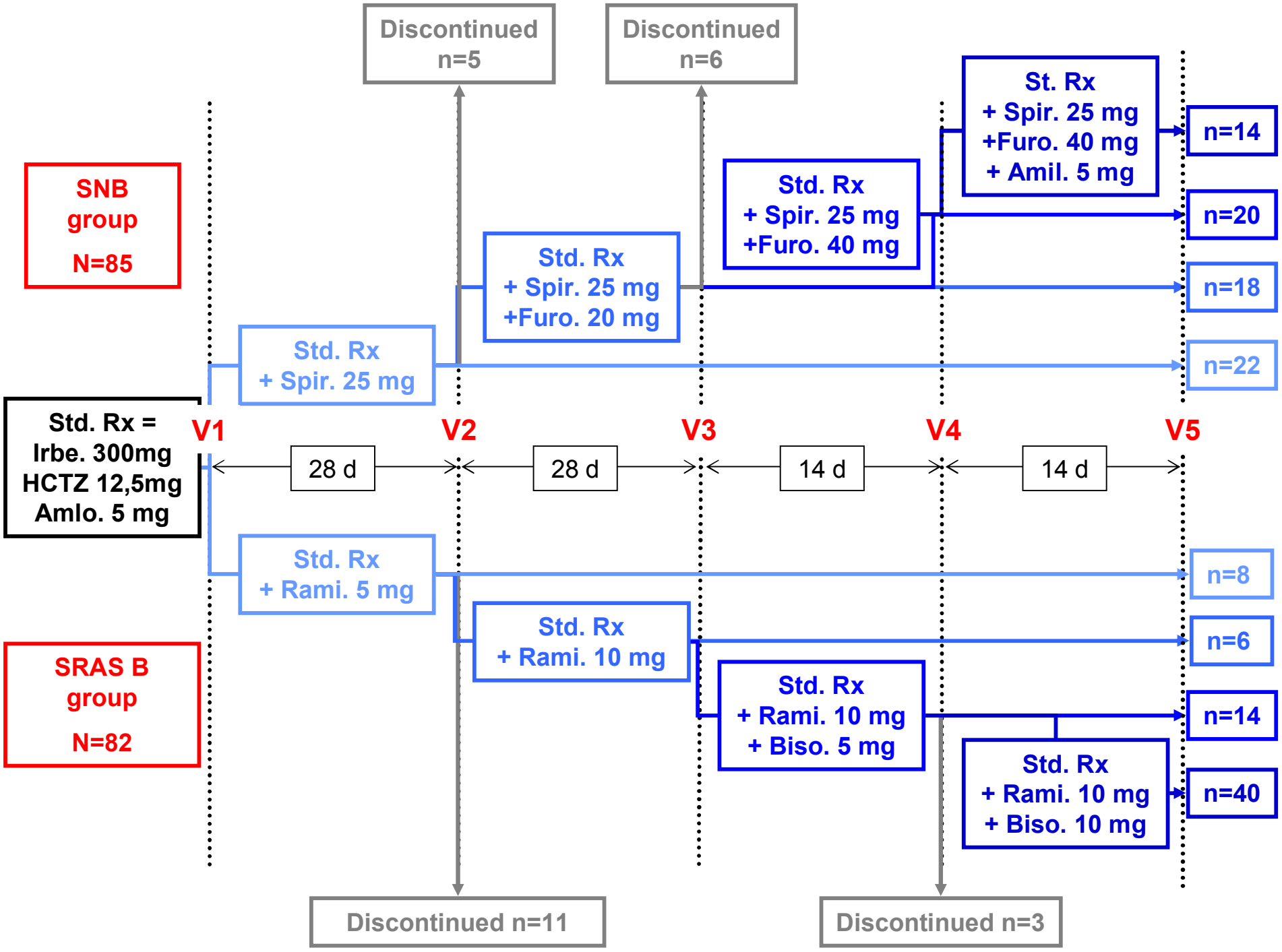


Mean adjusted difference

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



FINAL CHARACTERISTICS (Med [IQR])

	SNB-group N=85	SRASB-group N=82	p
Creatininemia, µmol/L	98 [84-118]	86 [71-101]	<0.0001
Weight, kg	84.0 [77.0-90.0]	82.5 [75.0-92.4]	0.0627
Uricemia, µmol/L	399 [324-449]	359 [289-398]	<0.0001
Protidemia, g/L	70 [67-74]	69 [65-71]	0.0759
U Na / U Creat, mmol/mmol	10.4 [8.3-13.3]	9.7 [7.7-13.8]	0.1264
Natremia, mEq/L	139 [137-140]	140 [139-141]	<0.0001
Kaliemia, mEq/L	4.2 [3.9-4.5]	3.9 [3.7-4.3]	<0.0001
Glycemia, mmol/L	6.1 [5.6-6.8]	6.0 [5.4-6.4]	0.4630
HbA1c, %	5.9 [5.5-6.5]	5.6 [5.3-5.9]	0.0003
Cholesterolemia, mmol/L	4.9 [4.1-5.4]	4.4 [3.8-5.2]	0.1851
Triglyceridemia, mmol/L	1.4 [0.9-1.9]	1.1 [0.8-1.7]	0.3548

ADVERSE EVENTS

	Total	Diuretics combination	RASB combination
SAE with protocol discontinuation	0		
SAE without protocol discontinuation	9	4	5
AE with protocol discontinuation	13	7	6
Asthenia, vertigo		4	1
Cough			1
ARF (creatininemia increase > 35%)		1	
Hyperkaliemia, hyponatremia		1	
Hyponatremia			1
Bradycardia			1
Headache			2
Erectile dysfunction		1	
AE without protocol discontinuation	75	41	34
Asthenia, vertigo		5	7
Cough			2
ARF (creatininemia increase > 35%)		1	
Hyperkaliemia		2	
Hypokaliemia		1	3
Hyponatremia		3	
AV dysfunction, bradycardia			3
Headache			2
Gout			1
Erectile dysfunction		5	
Gynaecosmastia		0	0
Miscellaneous		24	16

DEVICE-BASED ANTIHYPERTENSIVE THERAPY

Therapeutic Modulation of the Autonomic Nervous System

SUBSTANCES VASOPRESSIVES

AINS

Alcool

Cocaïne

Réglisse

Sympathicomimétiques

Anti-VEGF

Corticoïdes

Erythropoïétine

Oestrogènes de synthèse

Tacrolimus (*FK-506, Prograf*®)

Ciclosporine (*Sandimmun*®, *Neoral*®)

The effects of cyclooxygenase-2 inhibitors and NSAI therapy on 24-h BP in patients with hypertension, osteoarthritis, and type 2 DM.

Sowers JR et al. Arch Intern Med 2005; 165: 161-8.

Characteristic	Celecoxib (n = 136)	Rofecoxib (n = 138)	Naproxen (n = 130)
Patient Baseline Characteristics			
Age, y	61.8	63.6	63.6
Sex, % (M/F)	38/62	41/59	40/60
Race, %			
White	75	76	77
Black	15	15	13
Other	10	9	10
Weight, kg	90.6	90.9	92.2
24-h SBP, mm Hg	131.9	132.1	134.3
24-h DBP, mm Hg	75.8	76.2	76.0
24-h pulse pressure, mm Hg	56.2	55.9	58.3
Glycosylated hemoglobin, %	7.0	7.0	7.0
Nonfasting plasma glucose, mg/dL	154.2	138.0	142.0
Serum creatinine, mg/dL	0.86	0.87	0.87
Osteoarthritis index, %			
Hip	16	11	10
Knee	84	89	90
Antihypertensive Therapies†			
Combination	84 (62)	85 (64)	84 (66)
ACE inhibitor	114 (84)	109 (83)	106 (83)
ARB	24 (18)	24 (18)	19 (15)
Calcium channel blocker	38 (28)	40 (30)	39 (30)
β-Blocker	24 (18)	30 (23)	28 (22)
Diuretic	55 (40)	54 (41)	52 (41)
Other	17 (13)	13 (10)	7 (6)

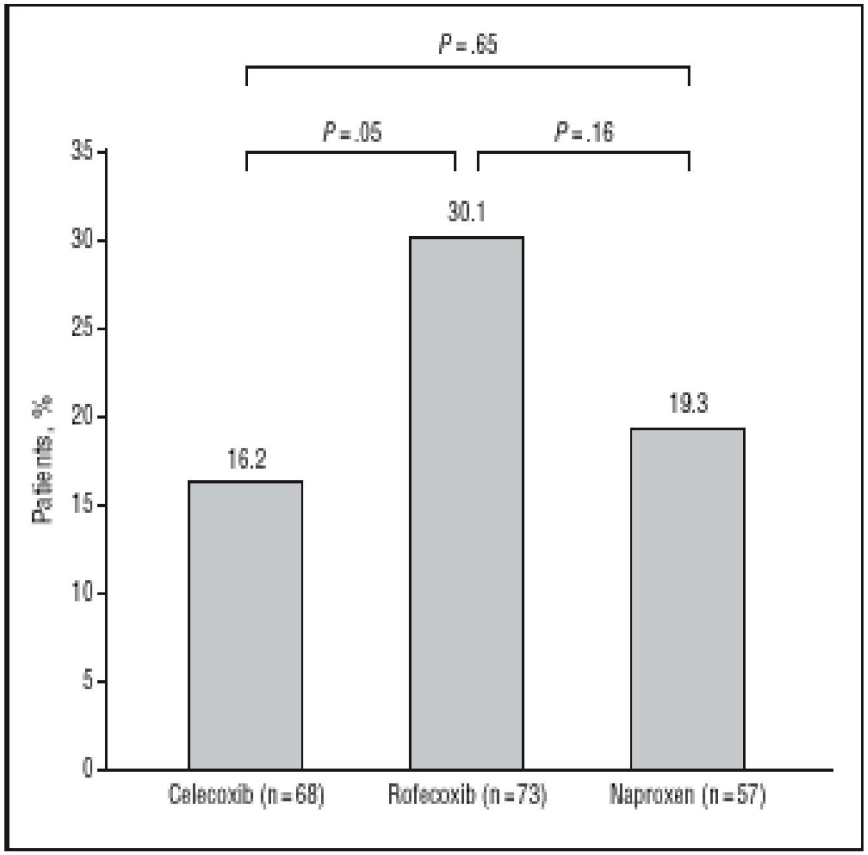


Figure 2. Percentage of baseline normotensive patients who became hypertensive at week 6. *Normotensive* is defined as an ambulatory systolic blood pressure (SBP) lower than than 135 mm Hg. *Hypertensive* is defined as an ambulatory SBP of 135 mm Hg or higher. *P* values are based on a χ^2 test. Nearly twice as many patients in the rofecoxib treatment group became hypertensive compared with the celecoxib and naproxen treatment groups.

Home Blood-Pressure Monitoring in Patients Receiving Sunitinib.

Azizi M et al. N Engl J Med. 2008; 358: 95-7.

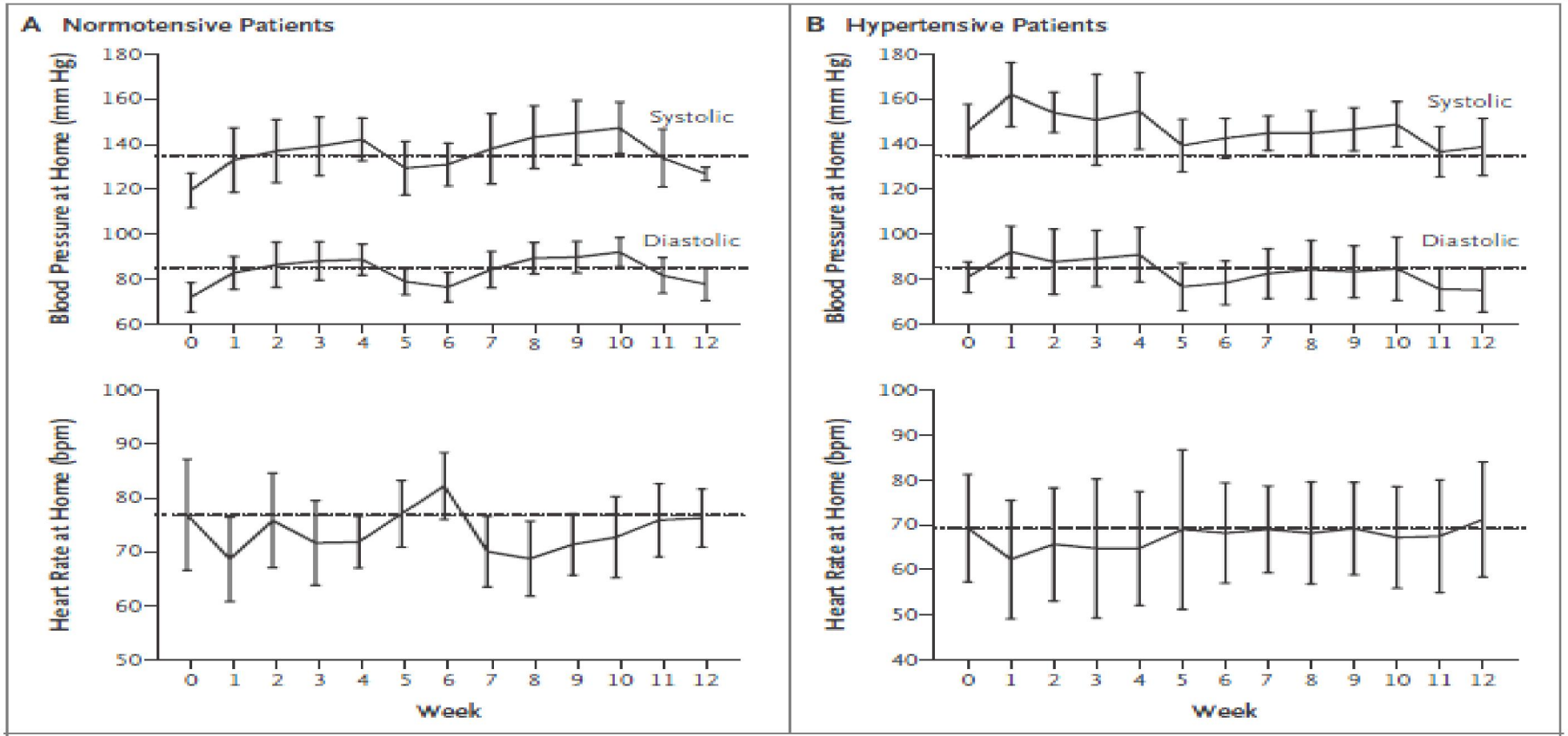


Figure 1. Changes in Systolic and Diastolic Blood Pressure and Heart Rate.

The graphs show the changes in mean blood pressure and heart rate as measured by teletransmitted results of home monitoring in patients with metastatic renal-cell carcinoma who were treated with two cycles of sunitinib at a dose of 50 mg daily for 4 weeks (shaded area), followed by 2 weeks without treatment. The results are shown separately for patients who were normotensive (Panel A) and those who were hypertensive (Panel B) before starting sunitinib treatment. In the graphs of home blood-pressure monitoring, the dotted line shows the blood-pressure threshold for the diagnosis of hypertension (systolic pressure, >135 mm Hg; or diastolic pressure, >85 mm Hg).[5] For changes in heart rate, the dotted line represents the baseline value. The I bars indicate the standard deviation.

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%

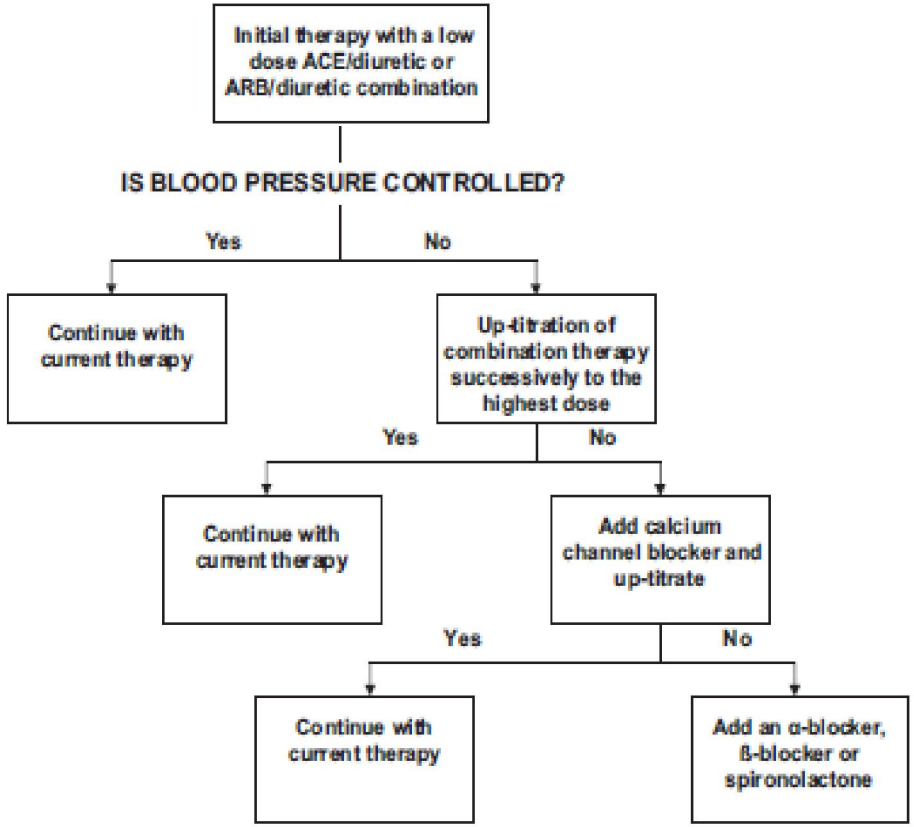
n, Number of included trials; *N*, number of participants assessed; MD, mean difference between treatment and control; CI, confidence interval; I^2, % of variation between trials not explained by sampling variation [11]; Size, *P*, *P* value for relationship between treatment effect and size of trial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

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])

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%).**

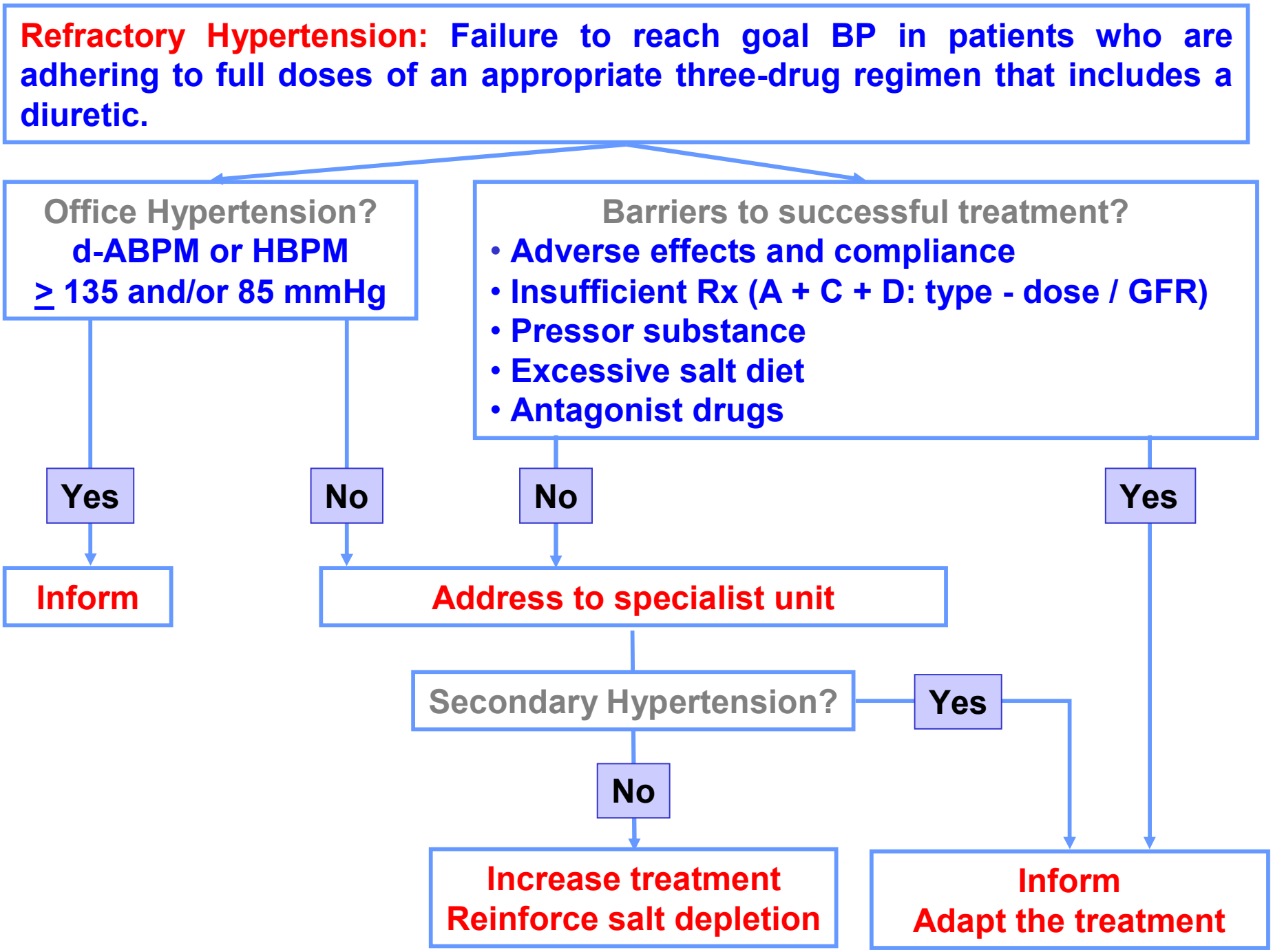
Connaissance du JNC VI (%)	52
En accord avec JNC VI (%)	76
Appliquent JNC VI (toujours ou habituellement) (%)	76

- **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

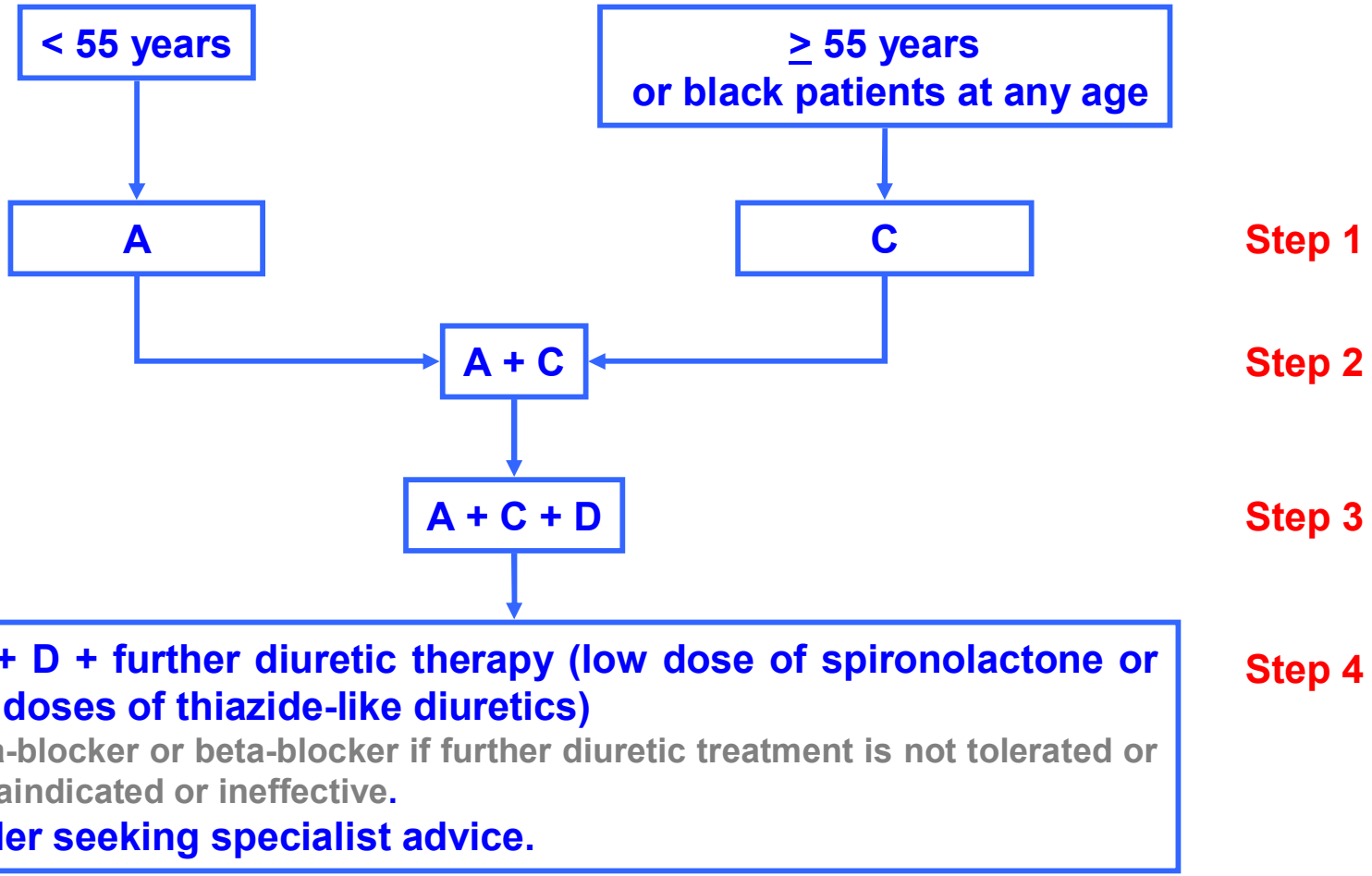
- **Analyse multivariée (OR)**

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



Management of hypertension: summary of NICE Guidance.

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



A = ACE inhibitor or ARB. C = Calcium channel blocker. D = Thiazide-like diuretic : **chlortalidone (12.5-25.0 mg o.d) or indapamide (1.5 mg modified release o.d or 2.5 mg o.d), in preference to a conventional thiazide diuretic such as bendroflumethiazide or hydrochlorothiazide.**