Atelier Groupe HTA

Inefficacité des BSRA en Afrique subsaharienne

Mythe ou réalité ?

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Pas de conflit d'intérêts

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STCCCV
Société Tunisienne de Cardiologie & de Chirurgie Cardio-Vasculaire

Hypertension artérielle en Afrique subsaharienne.

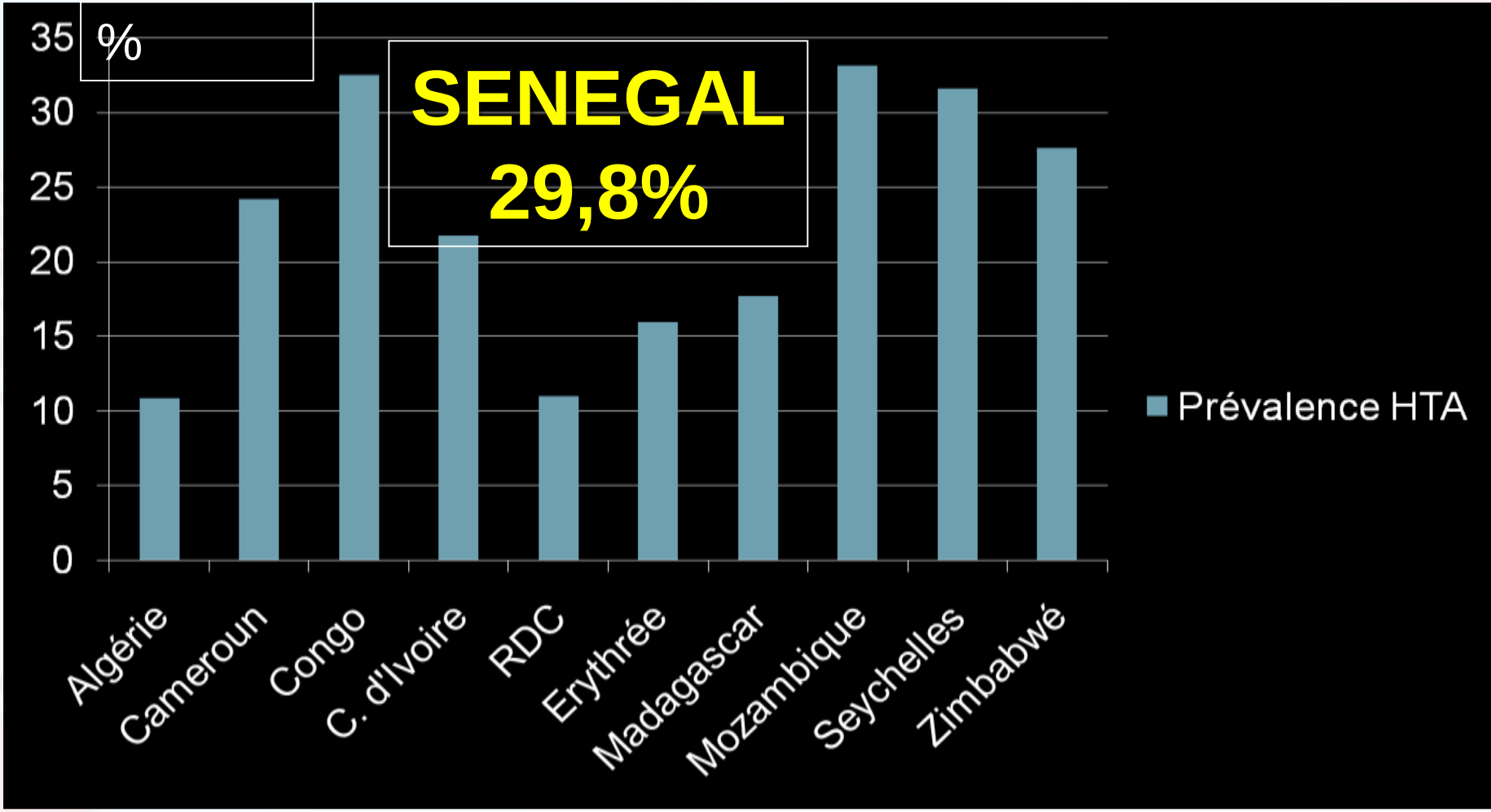
Quel profil d'HTA ?
Quel type d'hypertendu?

Transition épidémiologique en Afrique sub-saharienne

	Douala (2000)	N'djaména (1995)	Bamako (1994)	Ouaga (1991)	Abidjan (1991)
HTA	38,5	58	36,5	49,1	39,3
Valvulopathie rhumatismale	25,6	13,8	22,9	13	14,5
MCP	22,5	16	18,1	18,1	7,4
EPC	0,6	-	-	-	1,9
Maladie coronaire	0,9	3,1	2,2	1,8	6,5
Péricardites	5,8	9	2,5	3,5	8,8
Insuffisances cardiaques	5,8	3,1	13,6	9,8	-
CPC	4,8	4	1,1	2,3	3
Endocardites infectieuses	0,9	-	-	-	3,3

Bertrand E. Morbidité cardiovasculaire en Afrique subsaharienne en 1990-2000. Cardiol Trop 2000;26:87-89.

Prévalence de l'HTA en Afrique



Prévalence de l'HTA selon enquête STEPS en Afrique

HTA en Afrique subsaharienne

- L'HTA est le principal *facteur de risque cardio-vasculaire* en Afrique subsaharienne

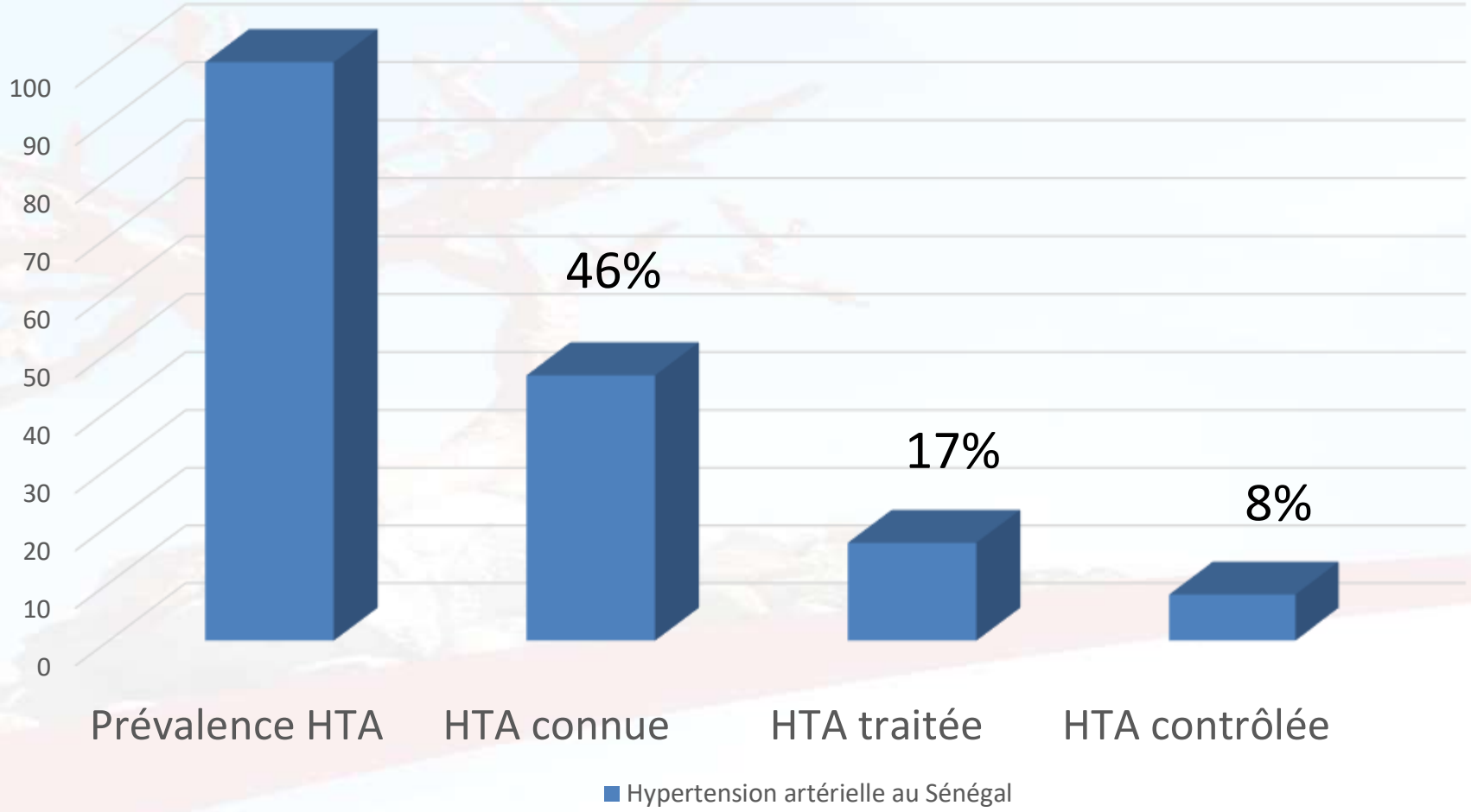
- Moins de 40 % des hypertendus diagnostiqués

- Moins de 30% des hypertendus diagnostiqués sous traitement médicamenteux.

- Entre 0,4% et 16,8% des patients traités sont contrôlés!!!

Hypertension In Sub-Saharan Africa : A Systematic Review. Hypertension 2007;50:1012-1018

Hypertension artérielle au Sénégal
(STEPS, OMS 2015)



Particularités de l'HTA du noir - africain

- Niveau de rétention hydro-sodée
- Activité rénine – Aldostérone
- Profil génétique - Phénotype
- Réponse thérapeutique aux antihypertenseurs

Efficacité des BSRA ? ? ?

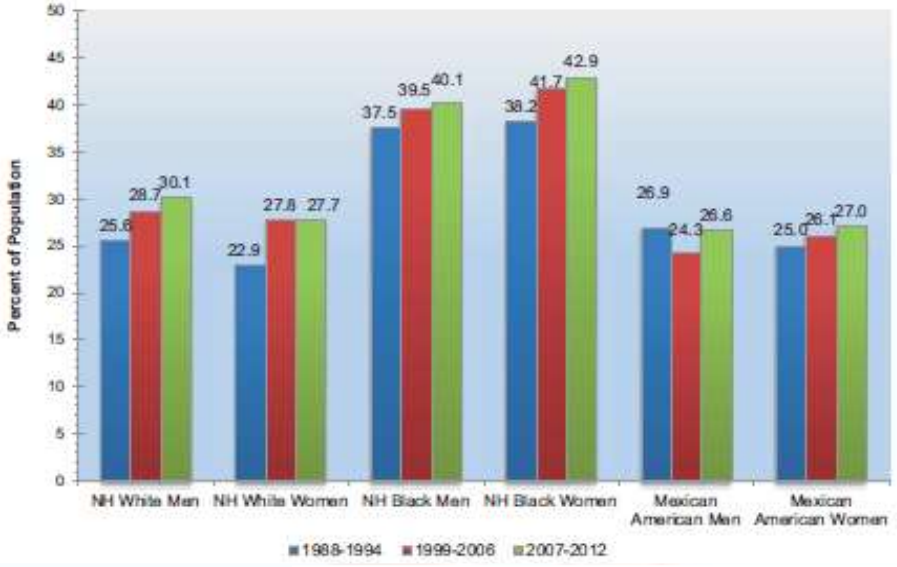
HTA en Afrique subsaharienne

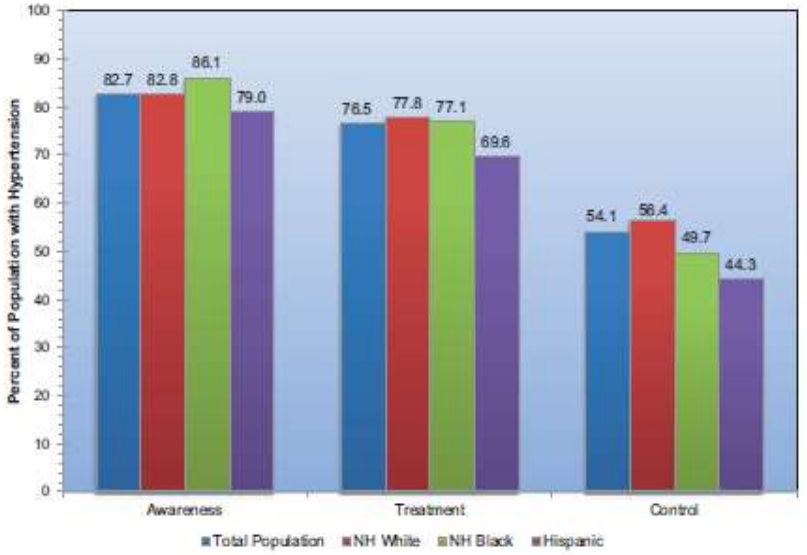
- HTA volontiers sévère
- Chiffres élevés ++++
- Lésions des organes cibles +++
  - Accidents vasculaires cérébraux
  - Insuffisance cardiaque
  - Insuffisance rénale

Hypertension In Sub-Saharan Africa : A Systematic Review. Hypertension 2007;50:1012-1018

Heart Disease and stroke statistics – 2015 Updated
A report from the American Heart Association

Circulation. 2015;131:e29–e322..





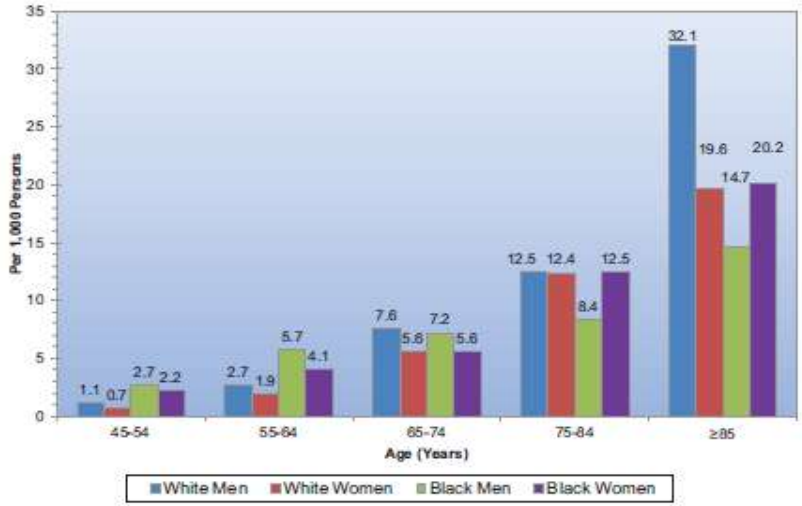


Chart 14-3. Annual rate of first cerebral infarction by age, sex, and race (Greater Cincinnati/Northern Kentucky Stroke Study: 1999). Rates for black men and women 45 to 54 years of age and for black men ≥75 years of age are considered unreliable. Source: Unpublished data from the Greater Cincinnati/Northern Kentucky Stroke Study.

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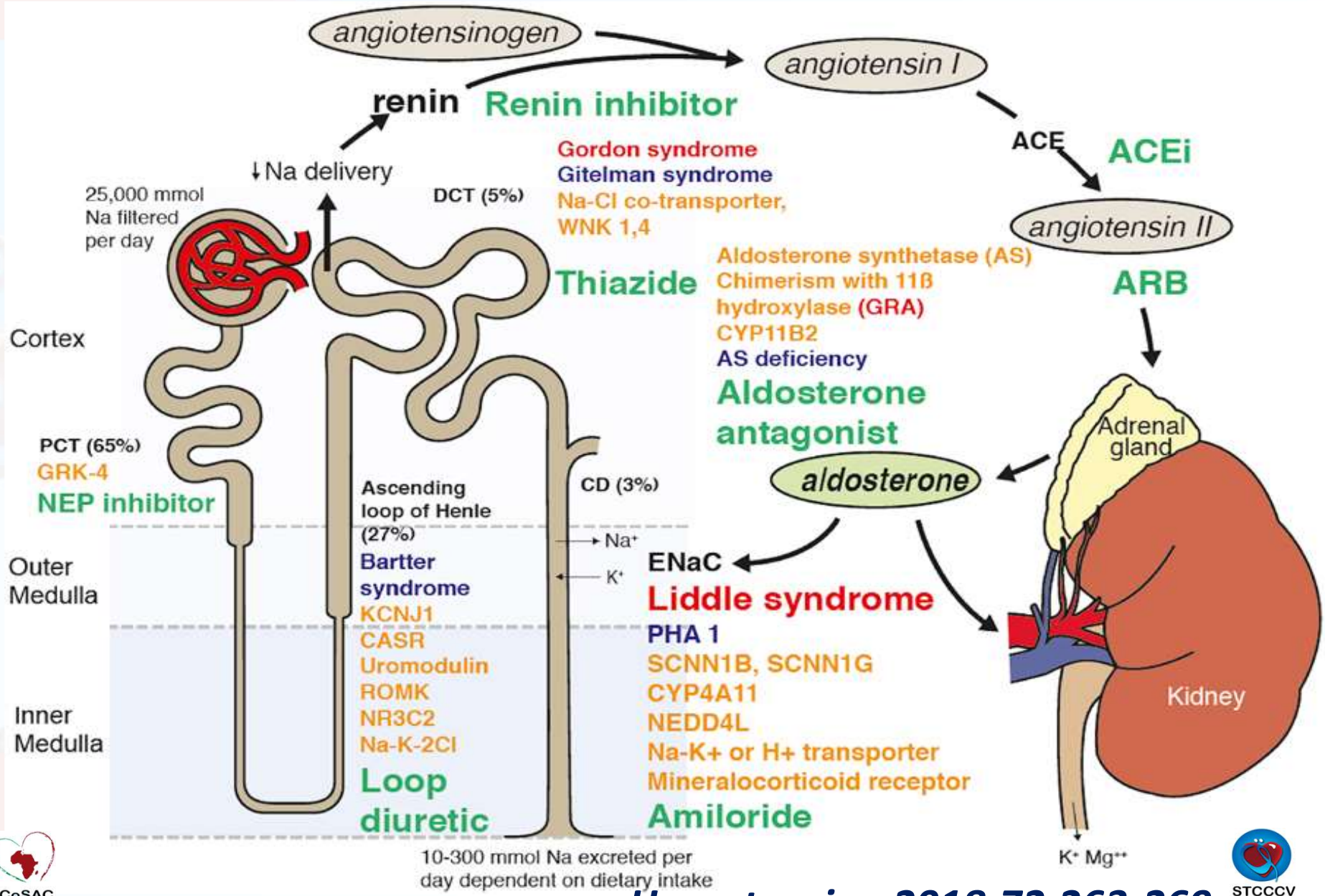
Hypertension artérielle chez le sujet noir

Particularités physiopathologiques ?

Système Rénine Angiotensine et Rétention hydrosodée



Hypertension 2018;72:263-269

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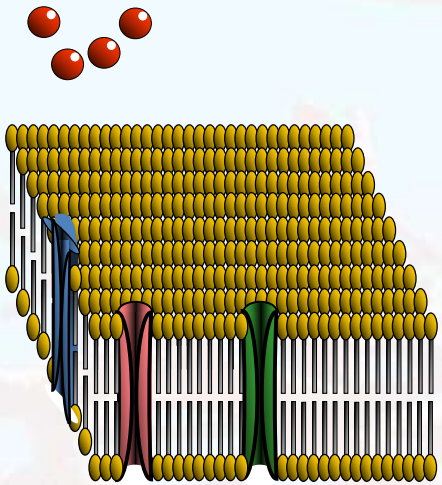
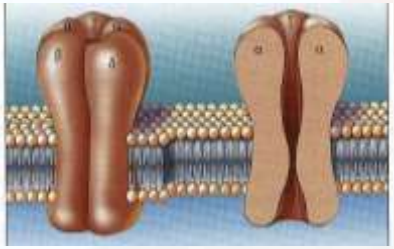
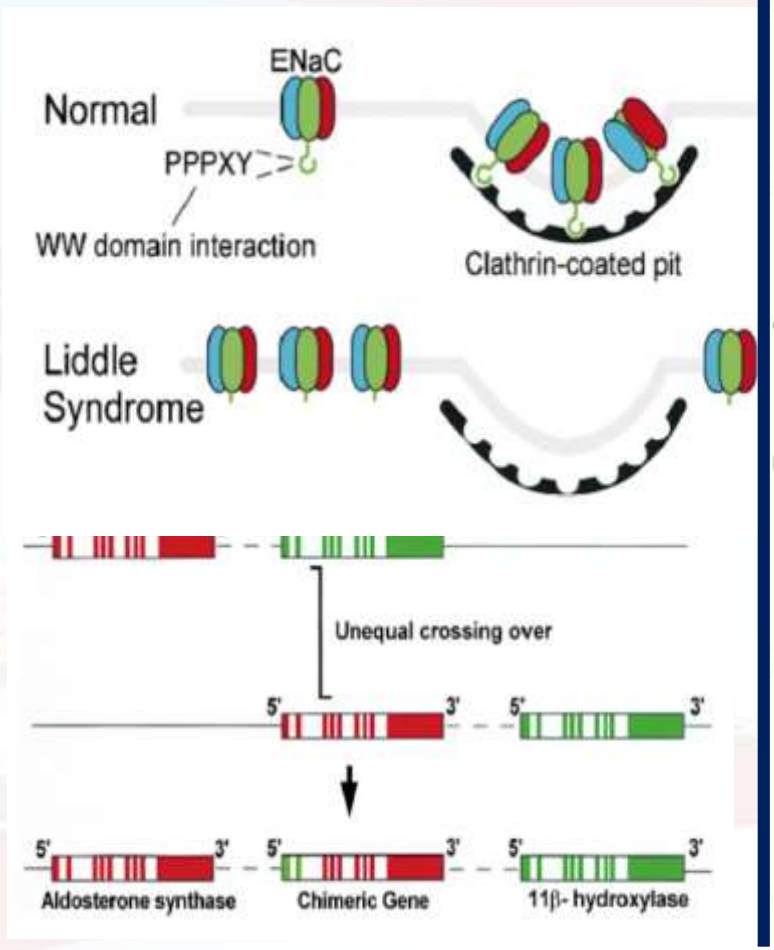
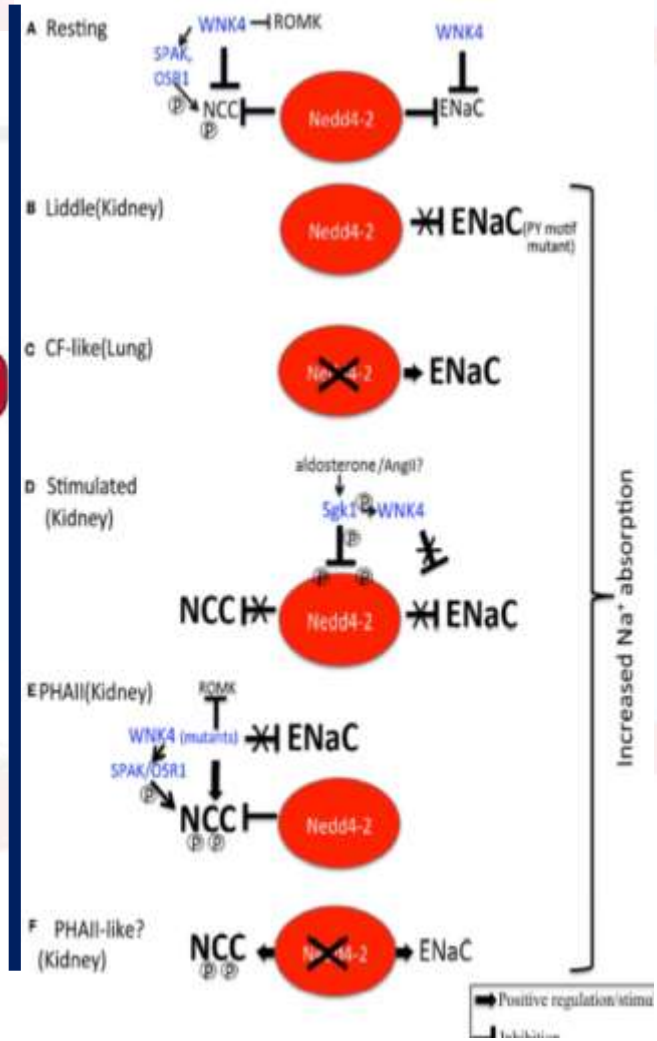
Hyperactivité des canaux sodiques: Rétention hydrosodée + + +

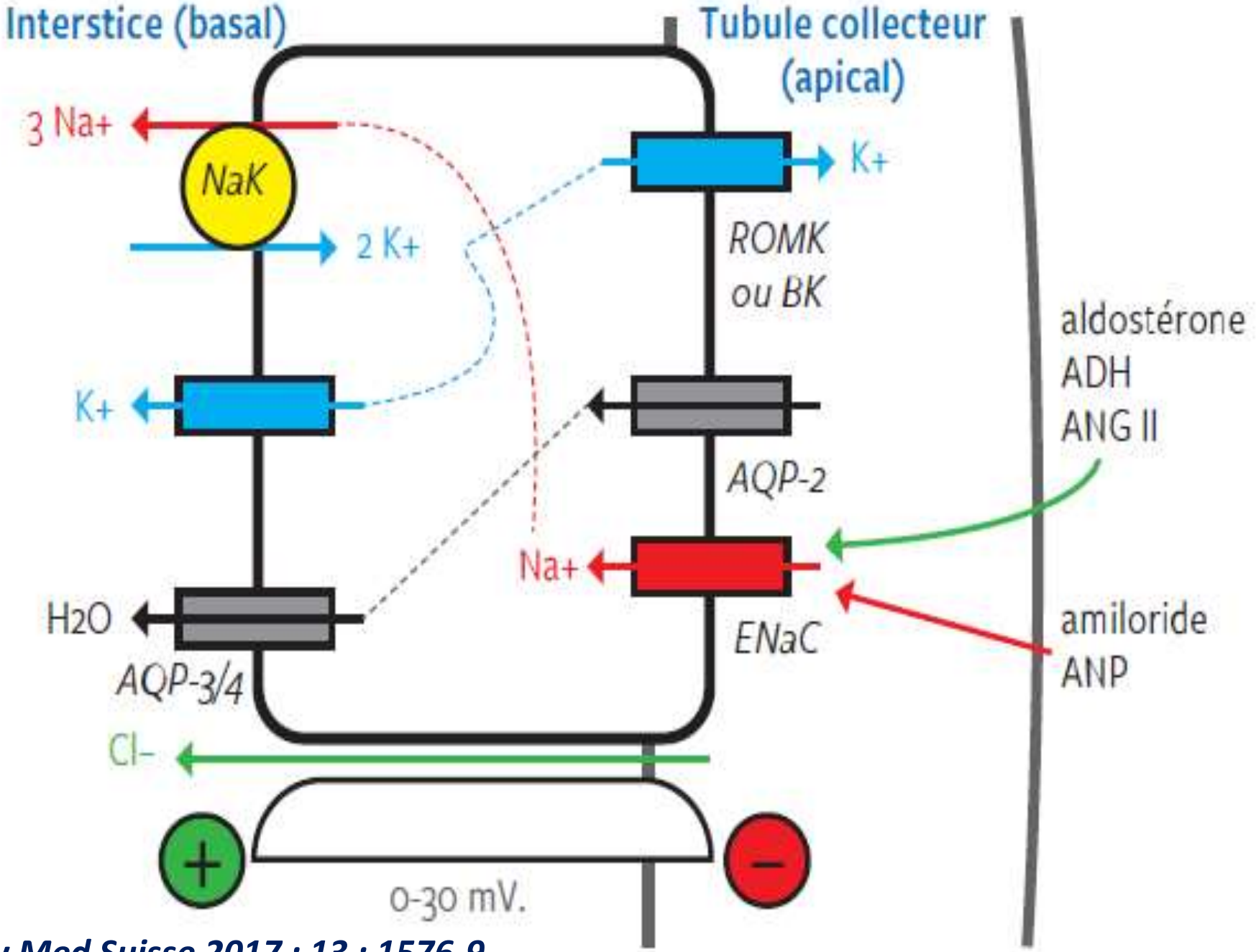








Molecular mechanisms of human hypertension. Cell. 2001;104:545–556.



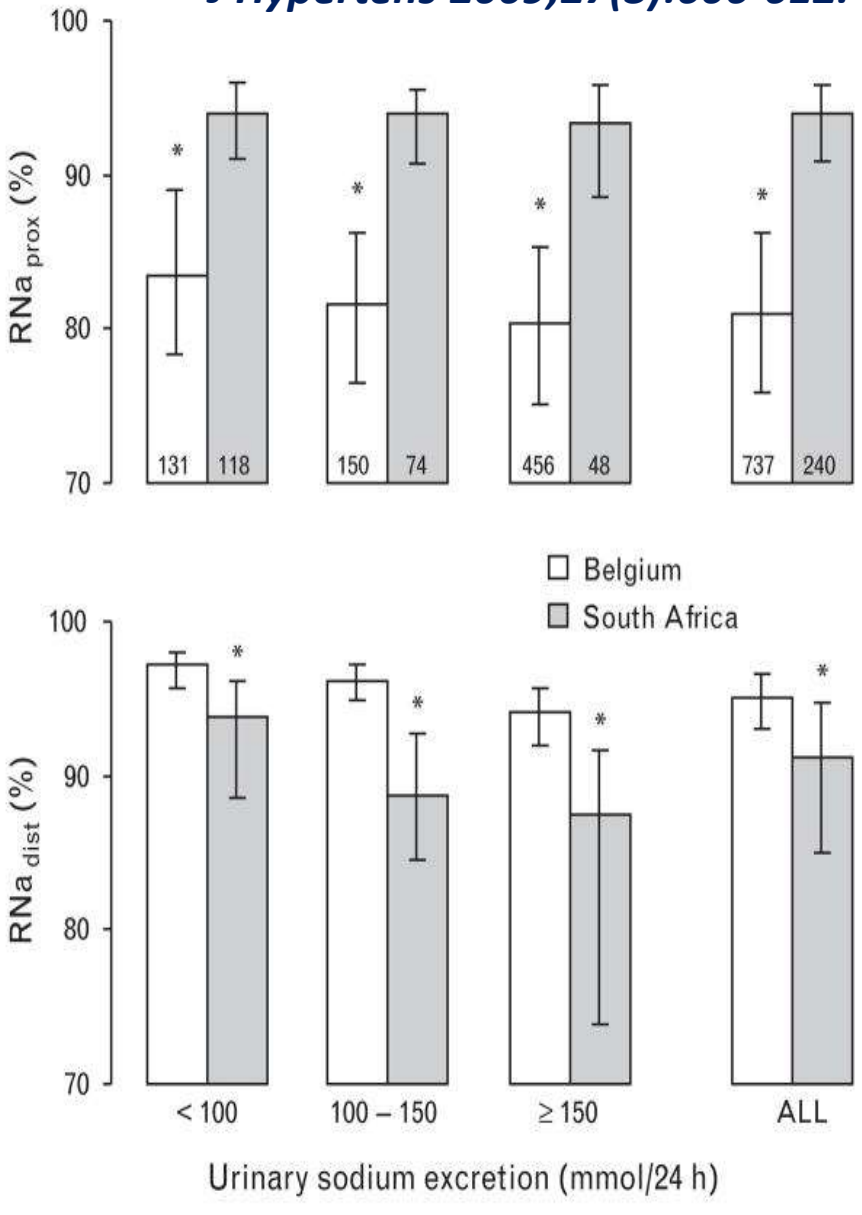
Rev Med Suisse 2017 ; 13 : 1576-9

Sujet africain = Rétention hydrosodée +++

Ethnic differences in proximal and distal tubular sodium reabsorption are heritable in black and white populations

J Hypertens 2009;27(3):606-612.

Variable	Black South Africans (n = 240)	White Belgians (n =737)
Women [n (%)]	149 (62.0)	374 (50.7)
Age (years)	42.7 ± 18.6	40.4 ±15.8
BMI (kg/m^2)	28.8 ± 7.1	25.0 ±4.4
Blood pressure		
Systolic blood pressure (mmHg)	131.0 ± 24.0	125.3 ±14.2
Diastolic blood pressure (mmHg)	84.3 ± 11.5	77.7 ±10.3
Hypertension [n (%)]	101 (42.1)	198 (26.9)
Antihypertensive therapy		
β-Blocker [n (%)]	1 (0.4)	57 (7.7)
Diuretic [n (%)]	39 (16.3)	30 (4.1)
ACE inhibitor [n (%)]	20 (8.3)	15 (2.0)
Current smoking [n (%)]	28 (11.7)	200 (27.1)
Current alcohol intake [n (%)]	53 (22.1)	428 (58.1)
Serum concentration		
Sodium (mmol/l)	137.0 ± 2.4	142.2 ±2.6
Lithium (μmol/l)	0.31 ± 0.16	0.31 ±0.16
Creatinine (μmol/l)	80.6 ± 15.9	78.3 ±15.4
Urinary excretion rate		
Sodium (mmol/h)	4.5 ± 2.3	8.3 ±5.2
Lithium (μmol/h)	0.13 ± 0.15	0.35 ±0.25
Creatinine (mmol/h)	0.44 ± 0.18	0.46 ±0.19
Renal clearances (ml/min)		
Sodium	0.46 (0.42–0.50)	0.81 (0.77–0.84)
Lithium	5.2 (4.7–5.8)	16.4 (15.8–17.1)
Creatinine	84.0 (78.3–90.2)	90.7 (88.2–93.2)
Renal sodium handling (%)		
RNa_{prox}	91.9 (91.1–93.1)	80.0 (79.4–80.6)
RNa_{dist}	86.3 (84.2–88.4)	93.9 (93.5–94.3)
FE_{Na}	0.55 (0.51–0.59)	0.88 (0.85–0.91)



Hypertension artérielle chez le sujet noir

Existe-t-il un phénotype africain ?

Quels phénotypes chez le sujet africain ? ? ?

	Age	Sex	PRA	Aldo	Aldo/renin ratio	Baseline systolic	Baseline diastolic
Primary aldosteronism phenotype: sequencing of *Cyp11B2*							
Kenya 1	48	M	2.7	421	156	189	115
2	42	F	1.5	379	253	191	132
3	75	M	1.2	402	335	212	102
4	51	M	0.3	306	1020	179	92
South Africa 1	60	M	0.3	179	597	160	90
2	62	M	1.5	309	206	146	88
3	58	F	0.5	381	762	201	134
4	52	M	0.5	147	294	184	125
5	50	M	0.9	760	844	180	130
Liddle phenotype: sequencing of *SCNN1B*, *NEDD4L*, *GRK4*, *UMOD*, and *NPPA*							
Kenya 1	69	M	4.5	68	15	150	100
2	17	F	9	61	7	156	110
South Africa 1	45	F	7.2	51	7	182	10
2	45	M	1.2	129	108	184	134
3	73	F	0.7	73	104	150	59
4	32	M	2.3	140	61	172	120
5	60	M	1.1	36	33	151	98
6	32	M	3	116	39	157	107
7	36	M	0.4	98.2	246	152	85

High frequency of variants of candidate genes in black Africans with low renin-resistant hypertension.
Am J Hypertens.2017;30:478–483

Hypertension 2018;72:263-269

Phénotype Liddle

❖ **Hyperactivité des canaux sodiques**

❖ **Activité rénine basse - Activité Aldostérone basse**

En Afrique du Sud

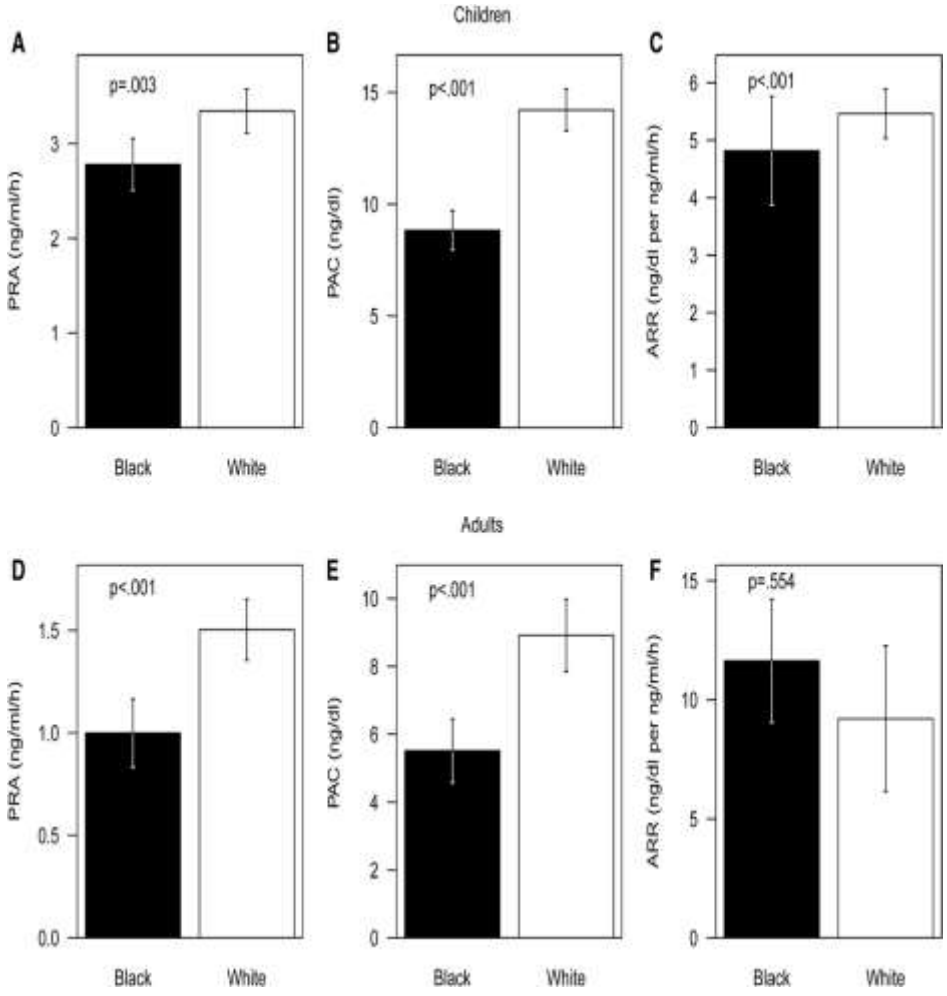
- Phénotype Liddle plus fréquent chez les blacks vs white, quelle que soit la consommation sodée

  S Afr Med J. 2001;91:594–599.

- Mutation SCNN1B (R563Q) correlée au phénotype Liddle chez les blacks et leurs descendants

  ***Hypertens*. 2003;21:921–926.**

Aux USA



***Hypertension*. 2014;63:1212-1218.)**

Toutefois, sujet africain = Variabilité génétique+++

PT NO.	Tribe	Country												
			NPPA	*SCNN1B*	*SCNN1B*	*SCNN1B*	*UMOD*	*UMOD*	*UMOD*	*GRK4*	*GRK4*	*GRK4*	*GRK4*	
LRLA			V32M	R206Q	G442V	R563Q	D25G	L180V	T585I	R65L	A116T	A142V	V486A	
4002	Colored	SA	GA									TT	TC	
4021	Colored	SA										CT	TC	
4024	Colored	SA	GA										CC	
4051	Xhosa	SA							CT	TT		TT	CC	
4053	Xhosa	SA		GA		GA		CG				CT	CC	
4059	Xhosa	SA		GA								TT	CC	
4065	MOZ	SA	GA				AG					CT	CC	
3019	Kikuyu	Kenya						CG		GT	GA	TT	CC	
3031	Kikuyu	Kenya			GT		AG			GT		TT	CC	
LRHA, CYP11B2			R30Q	N82D	P86A	R87G	C109R	C109Y	I112S	D147E	K152N	I248T	I339T	V386A	G435S
4005	Colored	SA		AG	CG	CG	TC	GA	TG	TA	GC	TC	TC		
4023	Colored	SA		AG	CG	CG	TC	GA	TG	TA	GC	TC			GA
4031	Colored	SA	GA	AG	CG	CG	TC	GA	TG	TA	GC	TC	CC		
4044	Xhosa	SA	GA	AG	CG	CG	TC	GA	TG	TA	GC	TC	TC		
4048	Colored	SA		AG	CG	CG	TC	GA	TG	TA	GC	TC			
3004	Kalenjin	Kenya		AG	CG	CG	TC	GA	TG	TA	GC	TC		TC	
3005	Kikuyu	Kenya		AG	CG	CG	TC	GA	TG	TA	GC	TC	TC		
3034	Kikuyu	Kenya		AG	CG	CG	TC	GA	TG	TA	GC	TC	CC		
3035	Kalenjin	Kenya		AG	CG	CG	TC	GA	TG	TA	GC	TC	CC		

High frequency of variants of candidate genes in black Africans with low renin-resistant hypertension.

Am J Hypertens.2017;30:478–483

Hypertension 2018;72:263-269

Hypertension artérielle chez le sujet noir

Quelle molécule préférentielle?

Efficacité du diurétique thiazidique

A Functional Variant of *NEDD4L* Is Associated With Hypertension, Antihypertensive Response, and Orthostatic Hypotension

Fang Luo, Yibo Wang, Xiaojian Wang, Kai Sun, Xianliang Zhou, Rutai Hui

Hypertension. 2009;54:796-801

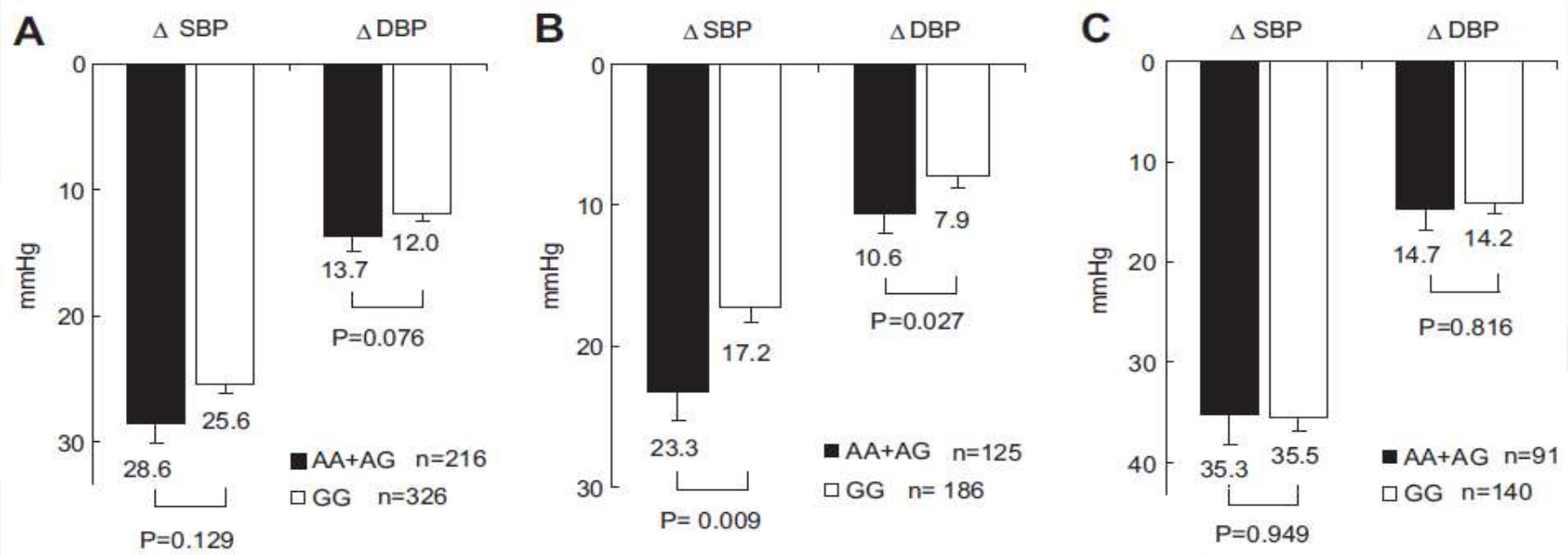


Figure. BP responses after 2 and 4 weeks of HCZT treatment. A, BP measurements in patients treated with HCTZ alone at the end of 2 weeks. B, BP measurements in patients treated with HCTZ alone at the end of 4 weeks. C, BP measurements in patients not treated with HCTZ or treated with HCTZ and another drug at the end of 4 weeks. The BP responses on the basis of rs4149601 are presented as means, and the bars represent the SEM. rSBP indicates the change in SBP from baseline; rDBP, change in DBP from baseline.

CARDIOVASCULAR JOURNAL OF AFRICA Vol 18, No. 4, July/August 2007 241

Review Article

Differences in hypertension between blacks and whites: an overview

JANE LINDHORST, NICOLE ALEXANDER, JULIET BLIGNAUT, BRIAN RAYNER

Molécules de choix:

- Diurétiques thiazidiques +++
- Inhibiteurs calciques +++

BSRA:

- Efficacité moindre en monothérapie
- Intérêt +++ en association (néphroprotection)

Faible Population black dans les grandes études

Étude	Année	Sujets	Sujets noirs (%)
ALLHAT	2002	42 452	35,6
HDFP	1979	10 940	44,3
MRFIT	1984	12866	7,2
SHEP	1991	4736	13,9
VA	1993	1292	48,0
HOT	1998	18790	3,1
TOMHS	1993	902	19,6
ABCD	1998	470	13,8
HTA avec HVG			
LIFE	2002	9194	5,8
CONVINCE	2003	16605	7,3
HTA et diabète			
UKPDS	1998	1148	7,6
HTA et insuffisance rénale			
MDRD	1995	840	7,9
AASK	2002	1094	100
HTA et diabète et insuffisance rénale			
RENAAL	2001	1513	15,2
IDNT	2001	1715	13,3

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)

JAMA. 2002;288:2981-2997

Table 1. Baseline Characteristics of the ALLHAT Participants*

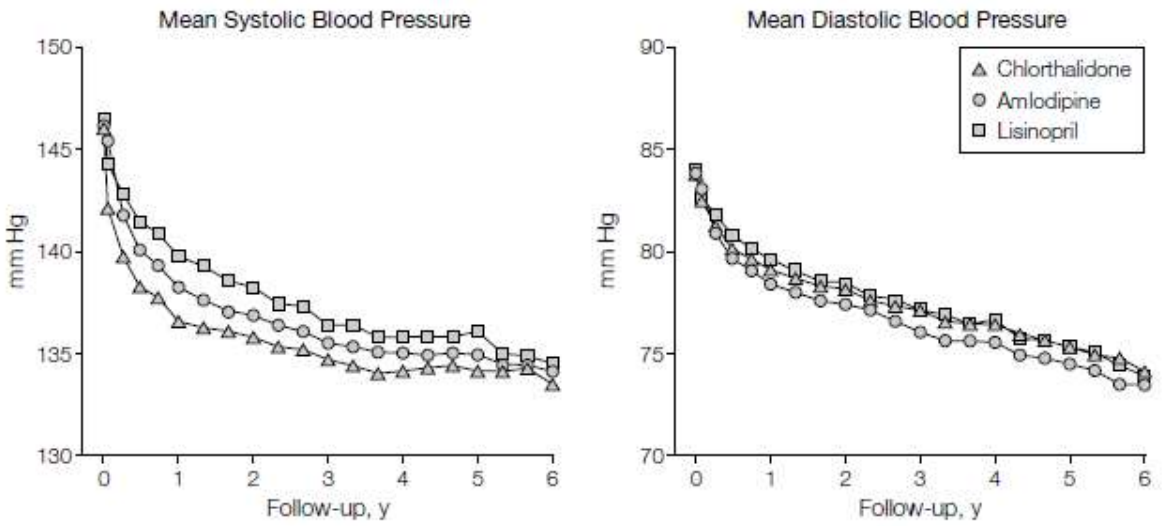
Characteristic	No. of Participants (%)		
	Chlorthalidone (n = 15 255)	Amlodipine (n = 9048)	Lisinopril (n = 9054)
Age, mean (SD), y	66.9 (7.7)	66.9 (7.7)	66.9 (7.7)
Age range, y			
55-64	6471 (42.4)	3844 (42.5)	3869 (42.7)
≥65	8784 (57.6)	5204 (57.5)	5185 (57.3)
Ethnicity			
White, non-Hispanic	7202 (47.2)	4305 (47.6)	4262 (47.1)
Black, non-Hispanic	4871 (31.9)	2911 (32.2)	2920 (32.3)
White Hispanic	1912 (12.5)	1108 (12.2)	1136 (12.5)
Black Hispanic	498 (3.3)	302 (3.3)	290 (3.2)
Other	772 (5.1)	422 (4.7)	446 (4.9)

Aux USA

40% de sujets blacks

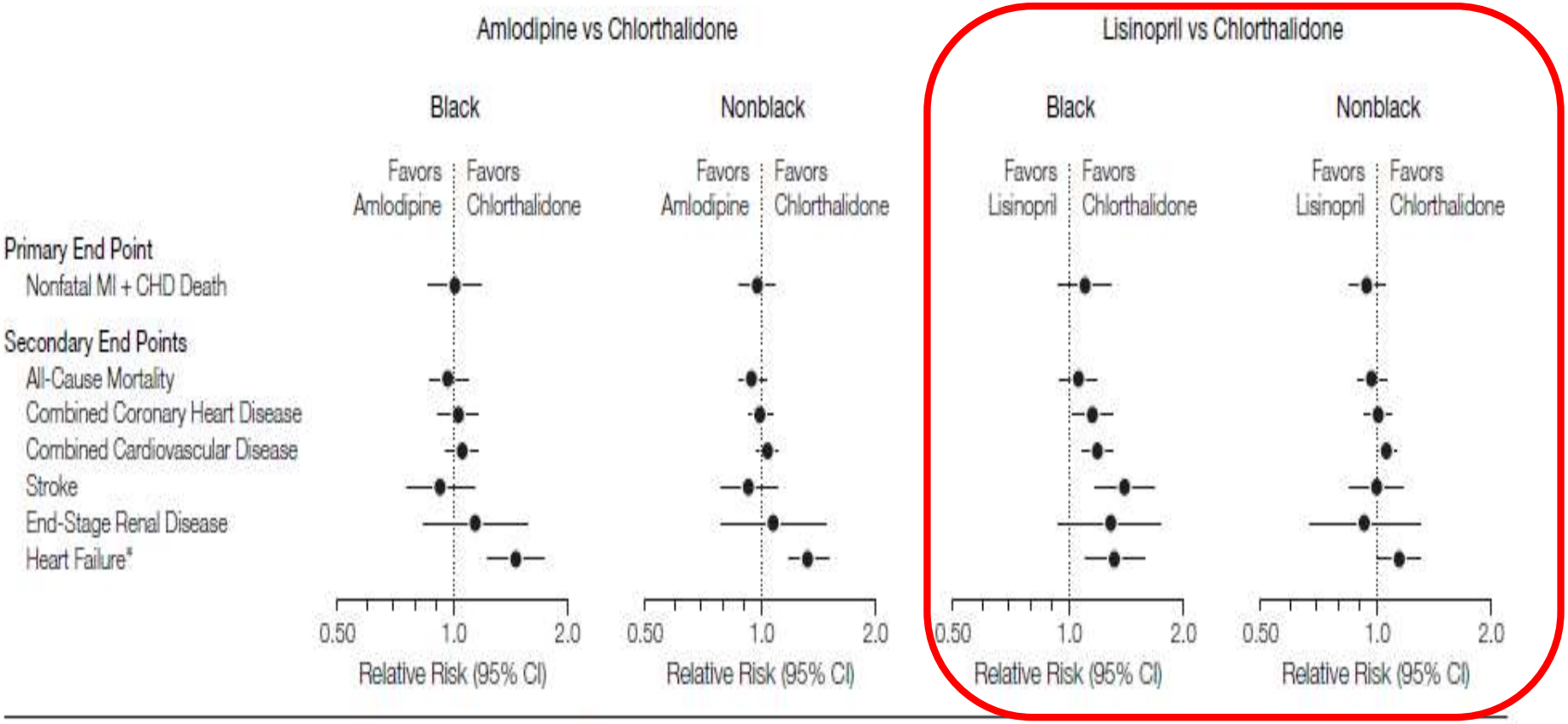
Supériorité du diurétique vs IEC

Figure 2. Mean Systolic and Diastolic Blood Pressure by Year During Follow-up



Outcomes in Hypertensive Black and Nonblack Patients Treated With Chlorthalidone, Amlodipine, and Lisinopril

JAMA. 2005;293:1595-1608



Scales are shown in natural logarithm. The proportional hazards assumption was violated for heart failure, so relative risks and 95% confidence intervals (CIs) were calculated using 2 × 2 tables. *Includes fatal, nonfatal hospitalized, and nonhospitalized treated. CHD indicates coronary heart disease; MI, myocardial infarction.

Faible Population black dans les grandes études

Étude	Année	Sujets	Sujets noirs (%)
ALLHAT	2002	42 452	35,6
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Odili et al. Trials 2012, 13:59
http://www.trialsjournal.com/content/13/1/59

TRIALS

RESEARCH Open Access

Progress report on the first sub-Saharan Africa trial of newer versus older antihypertensive drugs in native black patients

Augustine N Odili[1,2], Birinus Ezeala-Adikaibe[1,3], Mouhamadou B Ndiaye[5], Benedict C Anisiuba[3], Marius M
Chinwuba K Ijoma[3], Joseph Kaptue[4], Hilaire J Boombhi[6], Philip M Kolo[7], Elvis N Shu[8], Lutgarde Thijs[1],
Jan A Staessen[1,9*], Bab
Jean-René M'Buyamba-Kabangu

Abstract

Background: The epidemic surge in hypertension in sub-Saharan Africa
antihypertensive agents in Black patients recruited in this area of the world.
Antihypertensive agents in African Hypertensive patients (NOAAH) trial to compare,
single-pill combination of newer drugs, not involving a diuretic, with a combination of
diuretic.

Methods: Patients aged 30 to 69 years with uncomplicated hypertension (140 to
associated risk factors are eligible. After a four week run-in period off treatment,
randomized to once daily bisoprolol/hydrochlorothiazide 5/6.25 mg (R) or amlo
attain blood pressure <140/<90 mmHg during six months, the doses of biso
increased to 10 mg/day with the possible addition of up to 2 g/day α-meth

Results: At the time of writing of this progress report, of 206 patients enr
randomized. At randomization, the R and E groups were similar ($P \geq 0.1$
body mass index (28.2 kg/m^2), blood pressure (153.9/91.5 mmHg) and
treatment naïve patients (72.7%). After randomization, in the R and E
18.2/10.1 mmHg, 19.4/11.2 mmHg, 22.4/12.2 mmHg and 25.8/15.2
eight (n = 57), and 12 (n = 49), respectively. The control rate was
patients (24.5%) had progressed to the higher dose of R or E a
49 patients up to 12 weeks were confirmatory. Only two patie

Conclusions: NOAAH (NCT01030458) demonstrated that blood pressure control can be achieved fast in Black patients born and living in Africa with a simple regimen consisting of a single-pill combination of two antihypertensive agents. NOAAH proves that randomized clinical trials of cardiovascular drugs in the indigenous populations of sub-Saharan Africa are feasible.

Keywords: Antihypertensive therapy, Health policy and outcome research, Randomized clinical trial, Special populations

Table 1

Characteristic	Older drugs	Newer drugs	Difference (95% CI)	P
Number	69	71		
Anthropometrics				
Women, n (%)	33 (47.8)	42 (59.2)		0.23
	50.5 ± 8.6	50.9 ± 9.2	0.4 (−2.6 to 3.4)	0.78
	80.8 ± 14.6	76.9 ± 14.7	−4.0 (−8.9 to 0.9)	0.11
	167.8 ± 7.8	166.4 ± 9.0	−1.2 (−4.1 to 1.6)	0.39
	28.7 ± 4.6	27.8 ± 5.1	−0.9 (−2.5 to 0.8)	0.30
	94.5 ± 13.9	92.9 ± 11.5	−1.6 (−5.9 to 2.7)	0.47
	154.2 ± 11.0	153.7 ± 11.8	−0.5 (−4.3 to 3.3)	0.80
	92.2 ± 9.4	90.8 ± 10.3	−1.4 (−4.7 to 1.9)	0.41
	74.0 ± 9.5	73.1 ± 10.3	−0.9 (−4.2 to 2.4)	0.59
				0.74
				0.82
			−1.0 (−4.7 to 2.7)	0.60
		13 (18.3)		0.48
		1 (1.4)		0.35
		0 (0.0)		1.00
		22 (31.0)		1.00
Hemoglobin		± 1.7	−0.1 (−0.7 to 0.5)	0.74
Hematocrit, %			−0.2 (−2.0 to 1.7)	0.86
Glucose, mmol/L			−0.2 (−0.4 to 0.1)	0.19
Cholesterol, mmol/L	4.9 ± 1.1		−0.0 (−0.4 to 0.4)	0.86
Creatinine, μmol/L	86.1 ± 20.1		4.8 (−4.7 to 14.3)	0.32
ECG measurements				
Sokolow-Lyon index, mm	28.3 ± 7.7	29.8 ± 7.2	1.7 (−0.8 to 4.2)	0.18
Cornell index, mm × msec	1818 ± 836	1771 ± 594	−48 (−290 to 194)	0.70

Values are mean ± SD, number of participants (%), or the difference between the two groups (95% confidence interval). Older and newer drugs refer to the single-pill combinations of hydrochlorothiazide plus bisoprolol or valsartan plus amlodipine, respectively. The blood pressure measurements are averages of three consecutive readings in each participant.

ETUDE NOAAH

Etude NOAAH

« Newer vs Older anti hypertensive Agents in African with Hypertensive patients »

- **Première Etude en Afrique noire**, multicentrique, prospective, randomisée, en double aveugle chez des patients noirs hypertendus âgés de 30 à 69 ans sans complication. PA de 140/90 à 179/109 mm Hg + 2 facteurs de risque cardiovasculaire

- Durée de suivi: 24 semaines; 180 patients

- Bisoprolol/HCTZ (5/6.25) vs Amlodipine/valsartan (5/160)

- Si PA non controlée à 1 mois, passer à Bisoprolol 10 mg (bras older) ou Amlodipine 10 mg (bras Newer)

- Si toujours cible non atteinte, ajouter alpha méthyldopa

Etude NOAAH

« **N**ewer vs **O**lder anti hypertensive **A**gents in **A**frican with **H**ypertensive patients »

Caractéristiques	Anciens Produits (40)	Nouveaux Produits (40)	Valeur de p
PAS mmHg	19.5±1.2	24.8±1.2	<0.0001
PAD mmHg	12.0±0.8	13.2±0.9	0.12
FC, b/mn	9.7±1.0	-0.2±0.	<0.0001
Effets secondaires	35	9	<0,0001

Caractéristiques	Anciens Produits (40)	Nouveaux Produits (40)
Atteinte PA Cible	56,1%	71,6%

Chez les patients hypertendus noirs africains vivant en Afrique sub-saharienne

Supériorité de **Amlodipine-Valsartan** sur association **Bisoprolol/HCTZ**

CREOLE Study: Comparison of Three Combination Therapies in Lowering Blood Pressure in Black Africans

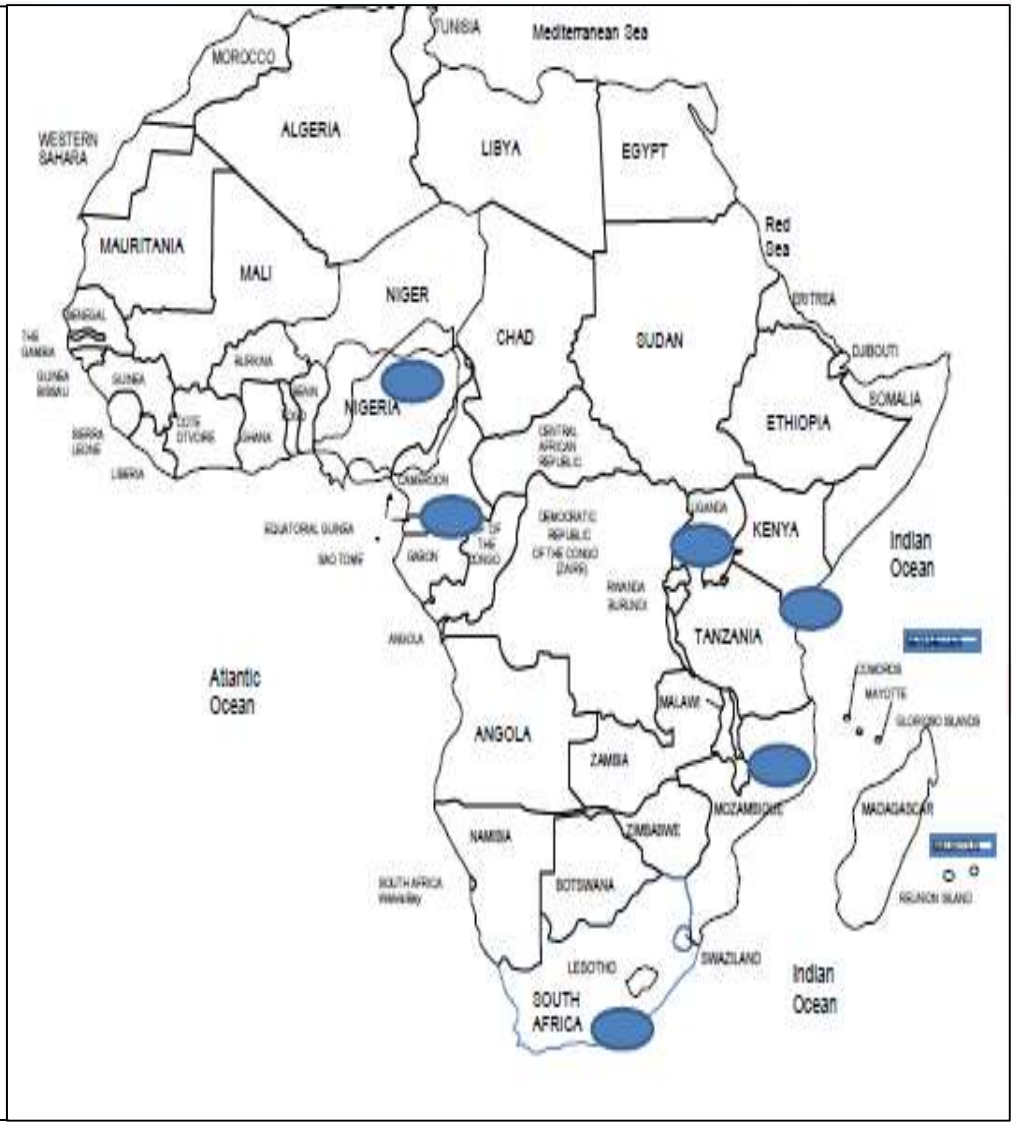
CREOLE Study

Study Medications

Amlodipine + Perindopril (5/4 & 10/8mg)

Amlodipine + HCT (5/12.5 &10+25 mg)

Perindopril + HCT (4/12.5mg & 8+25 mg)

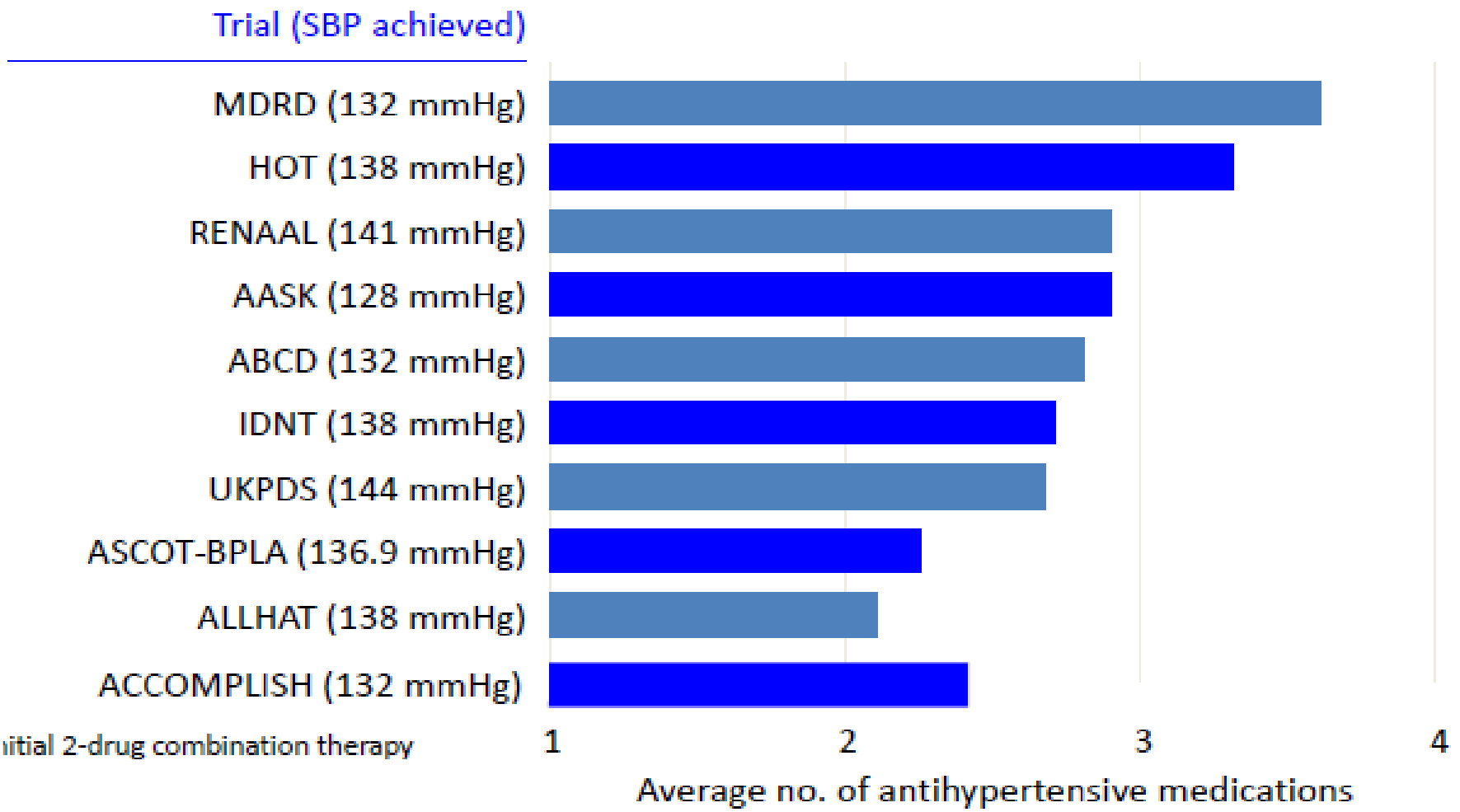


Hypertension artérielle chez le sujet noir

Recommandations internationales (SFHTA, ESC/ESH, AHA/ACC, PASCAR)

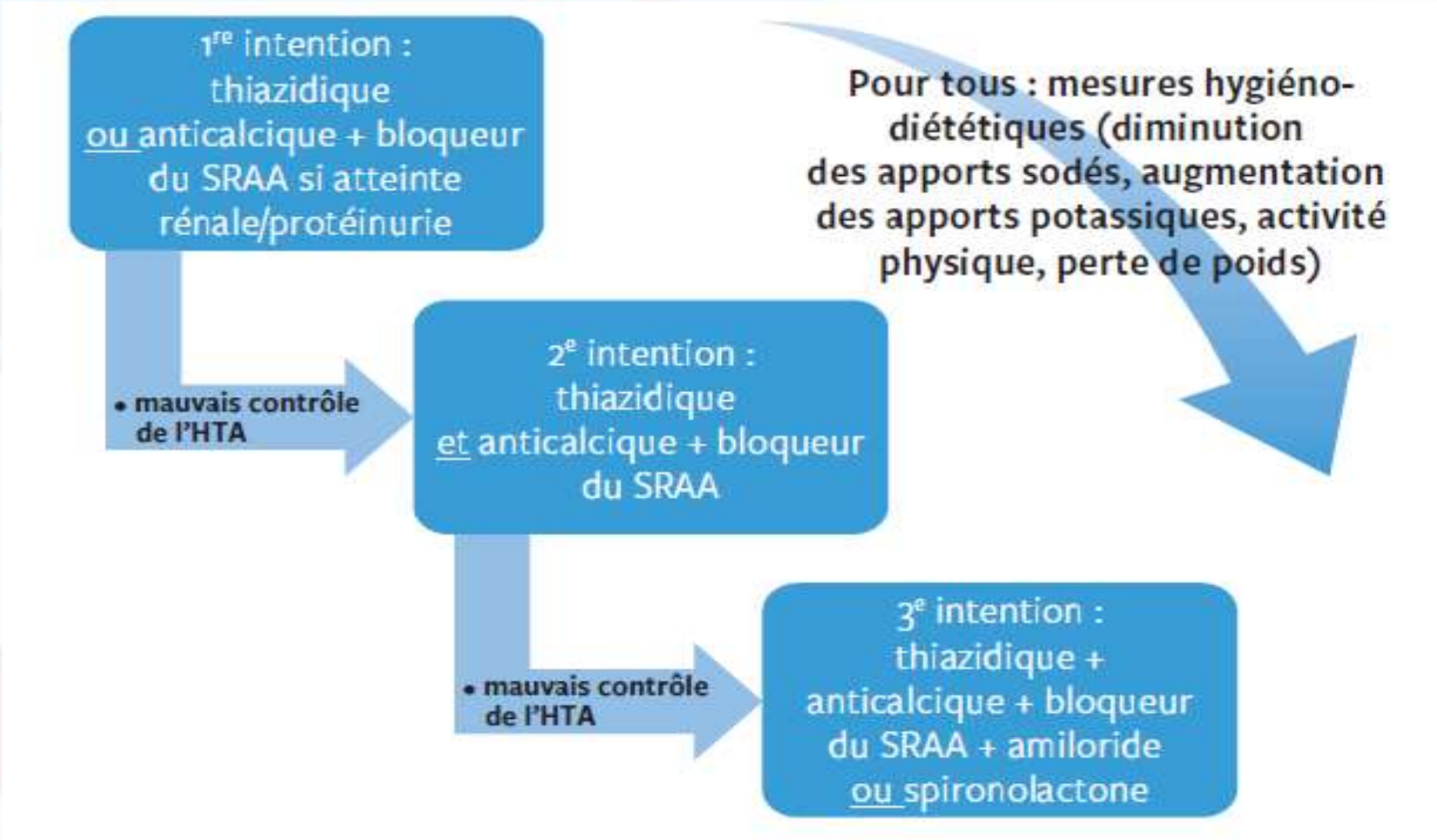
- **BSRA seraient moins efficaces chez les noirs vs blancs**
- **BSRA majorés par association aux thiazidiques ou aux inhibiteurs calciques**
- **Sont recommandés, si monothérapie:**
  - **Inhibiteurs calciques**
  - **Diurétiques thiazidiques**
- **BSRA restent incontournables en association et dans les indications préférentielles (insuffisance cardiaque, néphropathies chroniques, protéinurie)**

Multiple Antihypertensive Agents are Needed to Reach BP Goal



Bakris et al. Am J Med 2004;116(5A):30S–8; Dahlöf et al. Lancet 2005;366:895–906
Jamerson et al. Blood Press 2007;16:80–6; Jamerson et al. N Engl J Med 2008;359:2417–28

Traitement de l'HTA chez le sujet noir



Hypertension artérielle chez le sujet noir

Limites de l'application des résultats des études actuelles,

au sujet noir d'Afrique subsaharienne

- Extrapolation d'études sur des populations noires non africaines

- Environnements différents
- Diverses caractéristiques socio-culturelles
- Réponses thérapeutiques non uniformes
- Absence d'étude sur les noirs d'Afrique subsaharienne

Conclusion

- Peu d'étude sur des patients noirs subsahariens
- Les recommandations actuelles chez le noir africain sont des extrapolations d'études effectuées ailleurs
- Etude NOAAH: étude pionnière en Afrique subsaharienne. Nécessité d'études de grande envergure sur des populations noires d'Afrique subsaharienne
- BSRA incontournables essentiellement en association.
- Nécessité de recommandations **africaines** basées sur des études **africaines**.

Merci

Lac rose
Dakar, Sénégal

CoSAC
Le congrès des Sociétés Africaines de Cardiologie

STCCCV
Société Tunisienne de Cardiologie & de Chirurgie Cardio-Vasculaire