HTA en 2022

UNIVERSITÉ DE GENÈVE
FACULTÉ DE MÉDECINE

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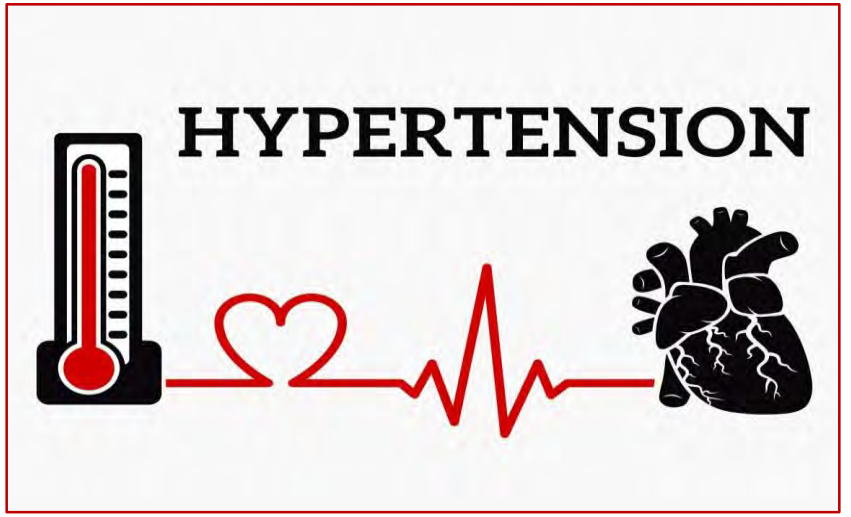
PLAN

- ✓Epidémiologie quand tu nous tiens
- ✓Une cible à atteindre malgré l’âge
- ✓Maximaliser ou Ajouter?
- ✓Adherence: that is the question
- ✓Du sel, toujours et encore du sel….
- ✓Le retour en force de la chlortalidone



Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants

*NCD Risk Factor Collaboration (NCD-RisC)**

Population 20-79 ans
184 pays

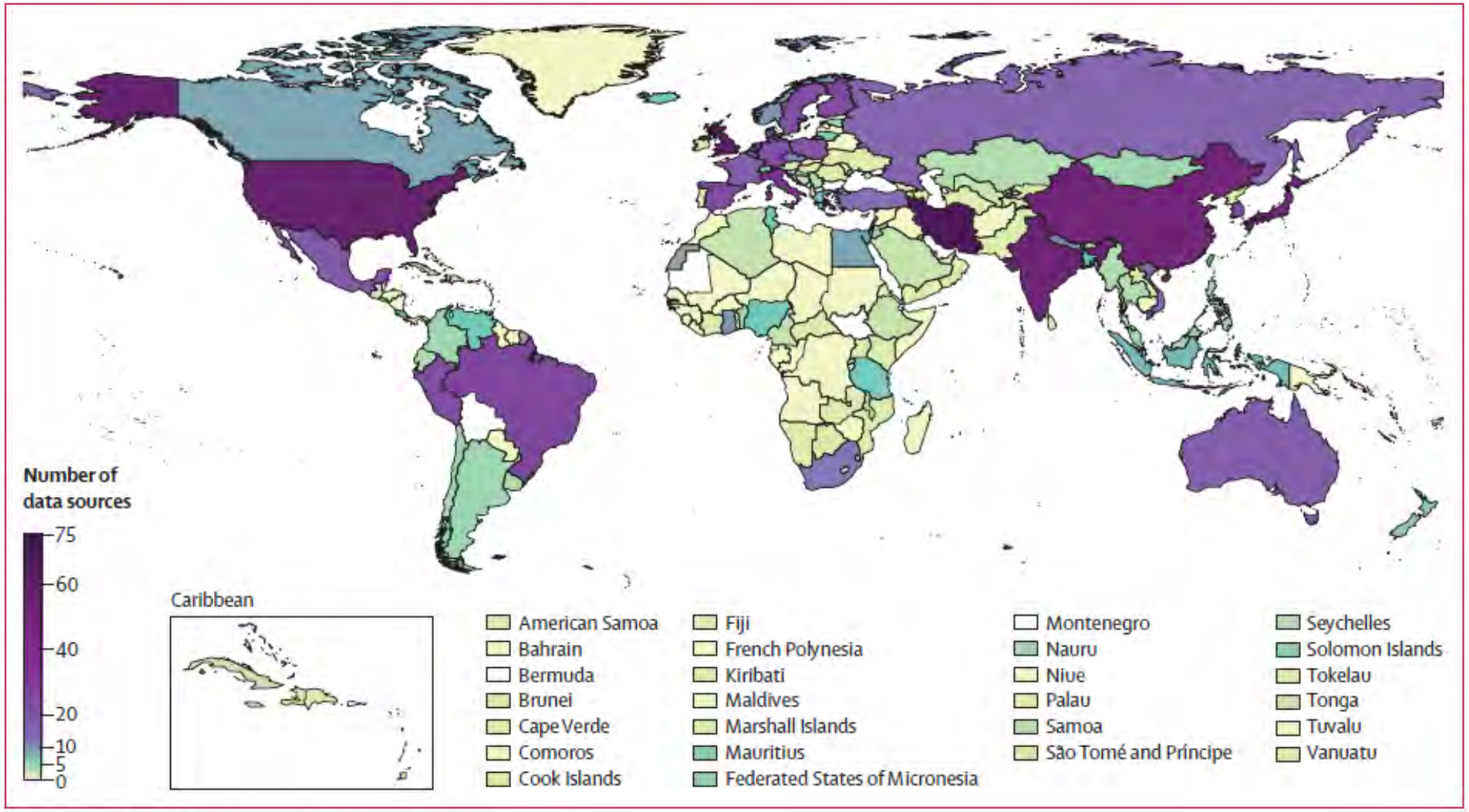
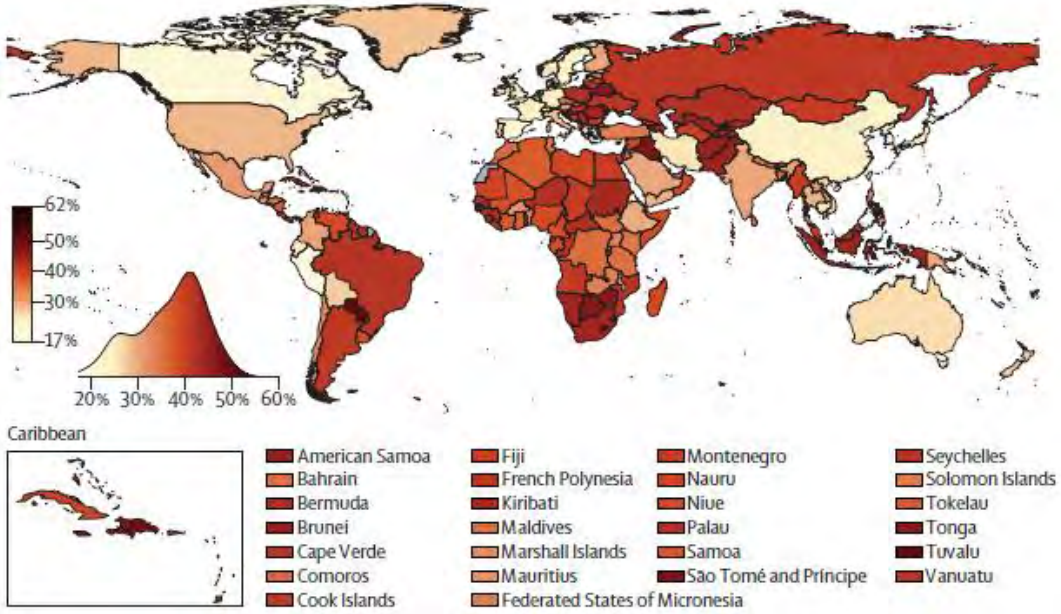
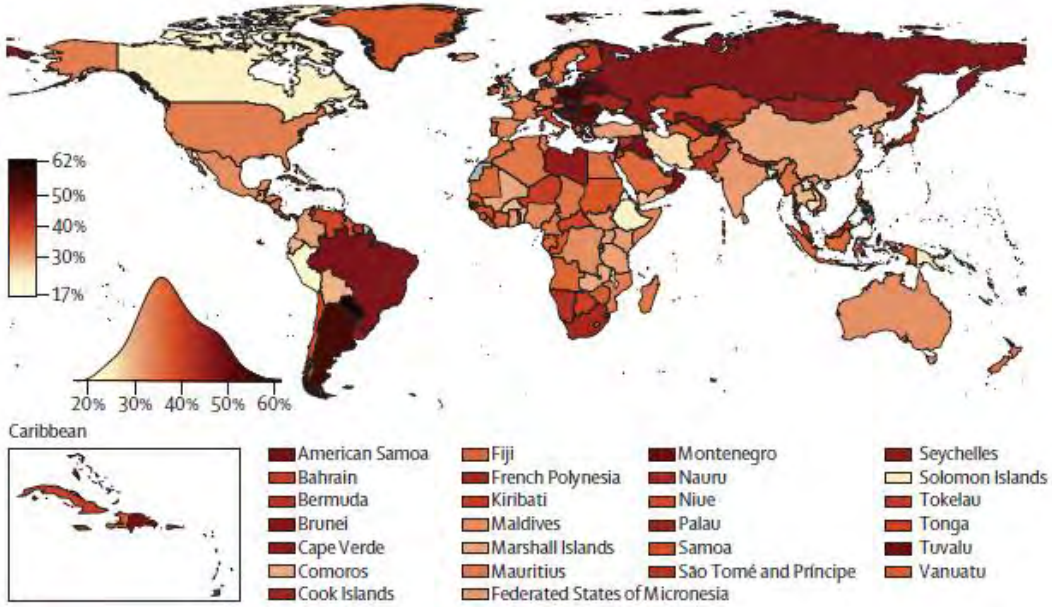


Figure 1: Number of data sources by country

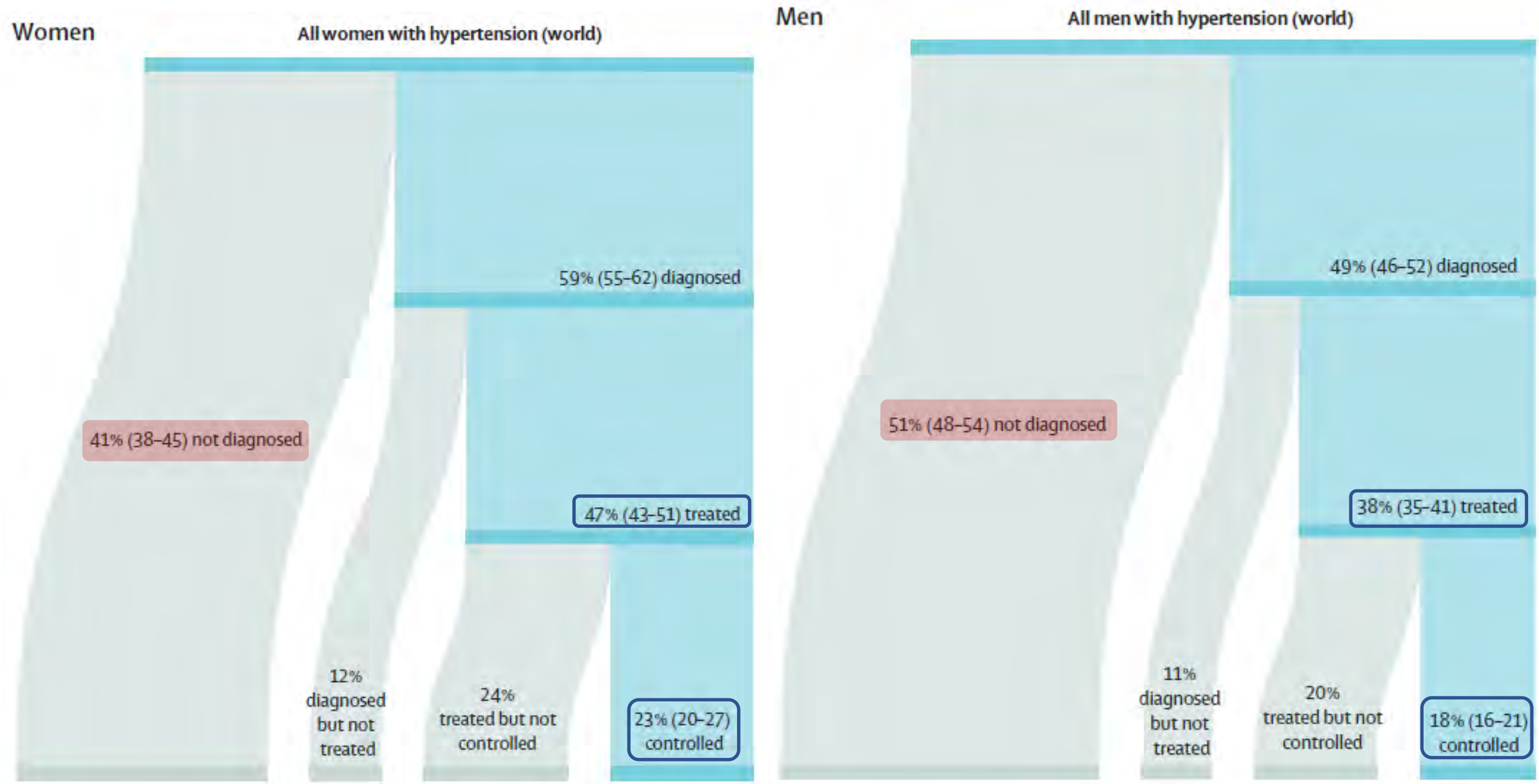
Prévalence 2019 selon sexe, standardisé par âge

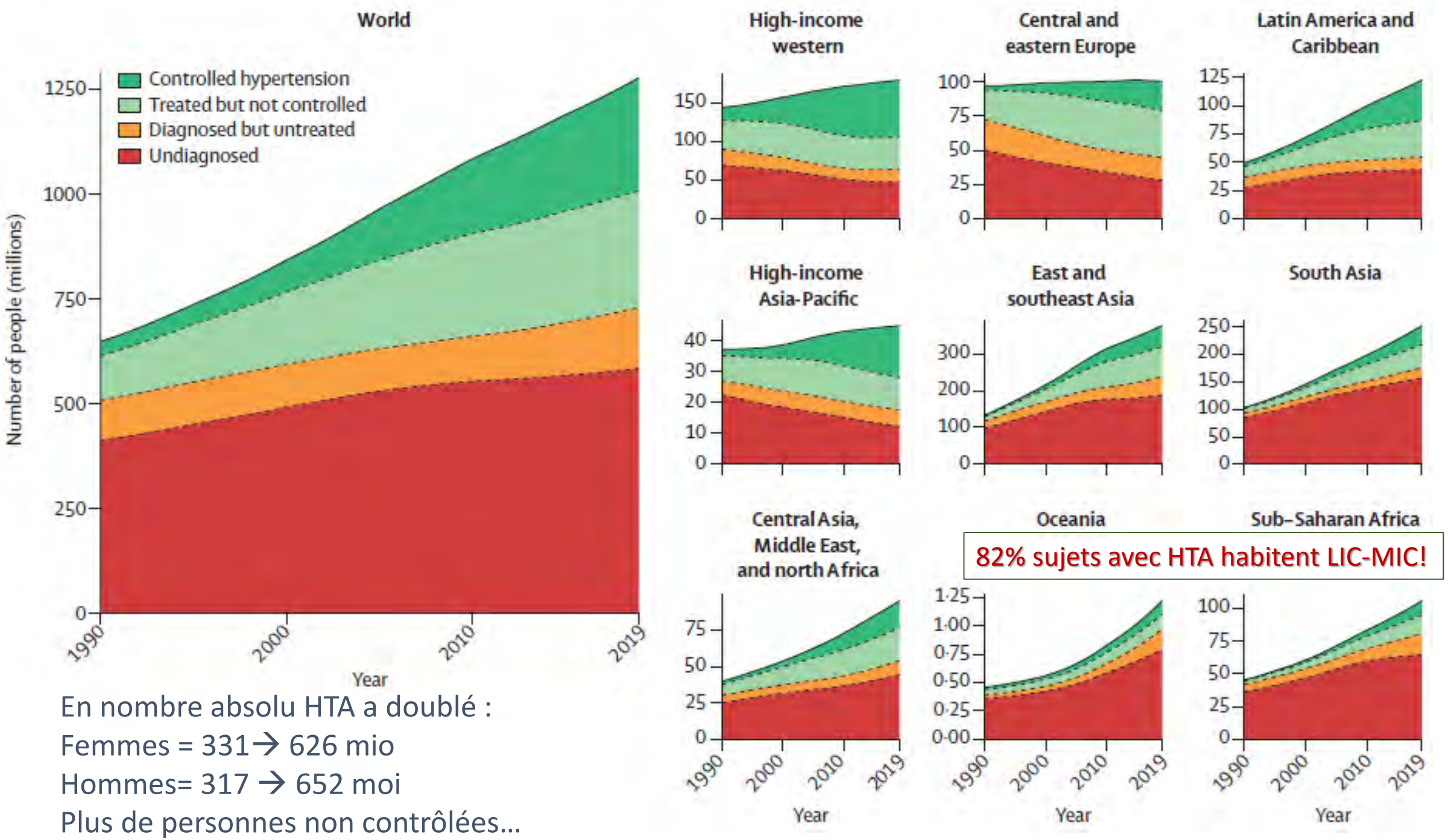


Prévalence 2019 Femme:
32% (30-34), stable
mais ⇧ dans Low IC par rapport à réduction High IC



Prévalence 2019 Homme:
34% (32-37), stable
mais ⇧ dans Low IC


Women
All women with hypertension (world)
59% (55–62) diagnosed
41% (38–45) not diagnosed
47% (43–51) treated
12% diagnosed but not treated
24% treated but not controlled
23% (20–27) controlled
Men
All men with hypertension (world)
49% (46–52) diagnosed
51% (48–54) not diagnosed
38% (35–41) treated
11% diagnosed but not treated
20% treated but not controlled
18% (16–21) controlled



En nombre absolu HTA a doublé :

Femmes = 331→ 626 mio

Hommes= 317 → 652 moi

Plus de personnes non contrôlées…

82% sujets avec HTA habitent LIC-MIC!

Data years	Survey/Study name/Citation	Level of representative-ness	Rural, urban, or both	Age range used in the global analysis		Sample size used in the global analysis		Information on diagnosis	Type of blood pressure measurement device*
				Female	Male	Female	Male		
1992-1993	The Swiss MONICA Study Wave III	Subnational	both	30-74	30-74	1,532	1,414	Yes	Random-zero mercury
2003-2006	Cohorte Lausannoise (CoLaus)	Community	urban	35-75	35-75	3,288	2,978	Yes	Digital oscillometric
2007-2012	Bus Santé Study	Subnational	urban	30-74	30-74	2,437	2,354	Yes	Digital oscillometric
2009-2012	Cohorte Lausannoise (CoLaus)	Community	urban	40-79	40-79	2,664	2,327	Yes	Digital oscillometric
2013-2016	Bus Santé	Subnational	urban	30-74	30-74	1,806	1,667	Yes	Digital oscillometric
2014-2017	Cohorte Lausannoise (CoLaus)	Community	urban	45-79	45-79	2,119	1,760	Yes	Digital oscillometric

Women aged 30-79 years	Hypertension (%)	Detection/ awareness (%)	Treatment (%)	Control (%)
North Western Europe				
Austria	30.2 (19.3-42.8)	65.1 (40.6-85.0)	53.7 (31.0-76.5)	27.1 (7.7-57.0)
Belgium	26.1 (20.5-32.2)	73.4 (62.5-82.9)	65.0 (52.6-76.0)	42.3 (27.6-58.2)
Denmark	28.6 (21.7-36.0)	58.1 (43.7-72.1)	27.3 (17.5-38.4)	10.2 (4.3-19.1)
Finland	30.6 (24.1-37.4)	70.8 (59.7-80.6)	53.9 (40.4-67.0)	29.1 (16.2-43.7)
Germany	25.0 (17.0-34.2)	70.8 (57.0-83.4)	65.0 (48.6-79.8)	48.0 (25.3-70.7)
Greenland	28.4 (18.3-39.9)	59.0 (39.0-77.8)	46.3 (25.4-67.9)	29.3 (10.4-54.9)
Iceland	24.2 (16.7-32.8)	82.0 (69.4-91.2)	71.8 (55.3-85.6)	52.9 (30.3-75.2)
Luxembourg	24.2 (18.4-30.4)	59.6 (46.3-72.2)	51.3 (37.3-64.6)	33.7 (19.2-50.8)
Netherlands	24.8 (18.0-32.3)	55.0 (39.5-69.4)	46.5 (32.6-61.2)	26.5 (13.4-43.3)
Norway	25.5 (16.8-36.0)	66.4 (41.9-86.4)	45.6 (25.9-67.1)	28.7 (10.1-55.4)
Sweden	24.6 (18.5-31.4)	55.1 (42.4-67.1)	39.8 (27.1-53.0)	19.2 (8.7-33.1)
Switzerland	17.5 (11.9-24.2)	73.8 (61.0-84.7)	56.8 (40.7-72.0)	39.4 (21.6-59.5)

Data years	Survey/Study name/Citation	Level of representative-ness	Rural, urban, or both	Age range used in the global analysis		Sample size used in the global analysis		Information on diagnosis	Type of blood pressure measurement device*
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Men aged 30-79 years	Hypertension (%)	Detection/ awareness (%)	Treatment (%)	Control (%)
North Western Europe				
Austria	37.5 (24.7-51.5)	61.7 (37.8-82.6)	54.3 (33.0-75.2)	27.5 (8.9-54.1)
Belgium	33.8 (26.5-41.4)	62.0 (50.3-72.7)	55.2 (44.2-66.0)	34.7 (22.8-47.9)
Denmark	43.3 (34.3-52.2)	54.1 (41.4-66.8)	25.1 (17.5-33.8)	8.8 (4.0-15.8)
Finland	41.0 (33.0-49.5)	65.9 (55.6-75.4)	48.8 (38.4-58.8)	27.0 (15.9-39.2)
Germany	34.4 (24.5-45.0)	72.2 (58.8-83.9)	61.1 (46.5-74.5)	43.2 (23.1-63.8)
Greenland	37.9 (25.2-51.2)	50.3 (33.0-68.0)	38.4 (21.9-56.7)	19.7 (5.9-40.8)
Iceland	30.9 (22.3-40.6)	82.8 (72.2-91.1)	71.0 (56.8-82.8)	50.9 (29.3-71.4)
Luxembourg	36.6 (29.0-44.4)	58.8 (47.3-70.0)	51.1 (38.9-63.1)	26.8 (15.4-40.5)
Netherlands	36.2 (27.4-44.8)	48.8 (35.4-62.6)	39.6 (28.7-51.6)	20.5 (9.9-35.4)
Norway	35.3 (24.4-47.3)	62.4 (39.6-82.6)	47.8 (30.3-66.3)	28.8 (10.1-52.5)
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Switzerland	26.4 (19.3-34.5)	72.7 (61.4-82.9)	55.8 (42.3-68.9)	35.2 (19.3-52.9)

Appendix Table 4. Status of hypertension risk factors, and policies and programmes related to hypertension prevention, detection, treatment and control in seven countries with high hypertension treatment rates.

Country	Factors related to hypertension prevention*	Factors related to hypertension detection, treatment and control
Canada	- Mean BMI: 27 kg/m^2 in women and 27.5 kg/m^2 in men, an increase of 2-2.5 kg/m^2 since 1990. - Average sodium intake: ~3.7 g/day. - Availability of vegetables and of starchy roots and fruits increased since 1990. - Smoking prevalence: 12% in women and 17% in men, a 40-50% relative reduction since 2000.	- The healthcare system is funded through personal and corporate taxes. - 100% public insurance coverage for physician consultations and for drugs provided in hospitals. Payment needed for prescriptions. Private benefit plans cover varying proportions of prescriptions. - National effort to improve hypertension control is coordinated by the Canadian Hypertension Education Program (CHEP), started in 1999. CHEP included three workforces on recommendation, implementation and outcome evaluation. Key features in CHEP include: annual update of guidelines; tailored knowledge dissemination; and coordinated implementation and outcome evaluation. - Hypertension guidelines were first published in 1977 with annual update since 1999. Since 1993, guidelines recommended immediate treatment for people with BP ≥160/100 mmHg and recommended immediate treatment based on other risks for people with BP between 140/90 and 160/100 mmHg.
Costa Rica	- Mean BMI: 28 kg/m^2 in women and 27 kg/m^2 in men, an increase of 3.5 kg/m^2 in women and 2.5 kg/m^2 in men since 1990. - Average sodium intake: ~3.2 g/day. - Availability of vegetables and of starchy roots and fruits increased since 1990. - Smoking prevalence: 6% in women and 17% in men, a ~30% relative reduction since 2000.	- Healthcare system is funded by 70% public resources, 27% out of pocket spending, and 3% private insurance in 2010. Government covers children and pregnant women not covered through other means, retried people and homeless people. - Single-payer health system (CCSS) with universal lifetime coverage, serving 95% of the population and providing strong safety net for the poor. Low inequality in health service access and health outcomes nationally. - A wide nationwide network of primary care facilities organised in a community-based clinic model (EBAIS). Hypertension prevention and detection is part of the planned care for adults and carried out in primary care. - Antihypertensive medications are in the list of essential medicines. No co-payment for drugs accessed via the public sector. - Evidence-based national guidelines for hypertension management that is adapted to local resources.

And so what?

1ère étude donnant telle information sur HTA dans le monde

- Depuis 1990, nombre de personnes avec HTA a doublé
- Surtout en relation avec augmentation dans LIC-MIC
- Détection, traitement et control bas dans pays les + pauvres

Limitations:

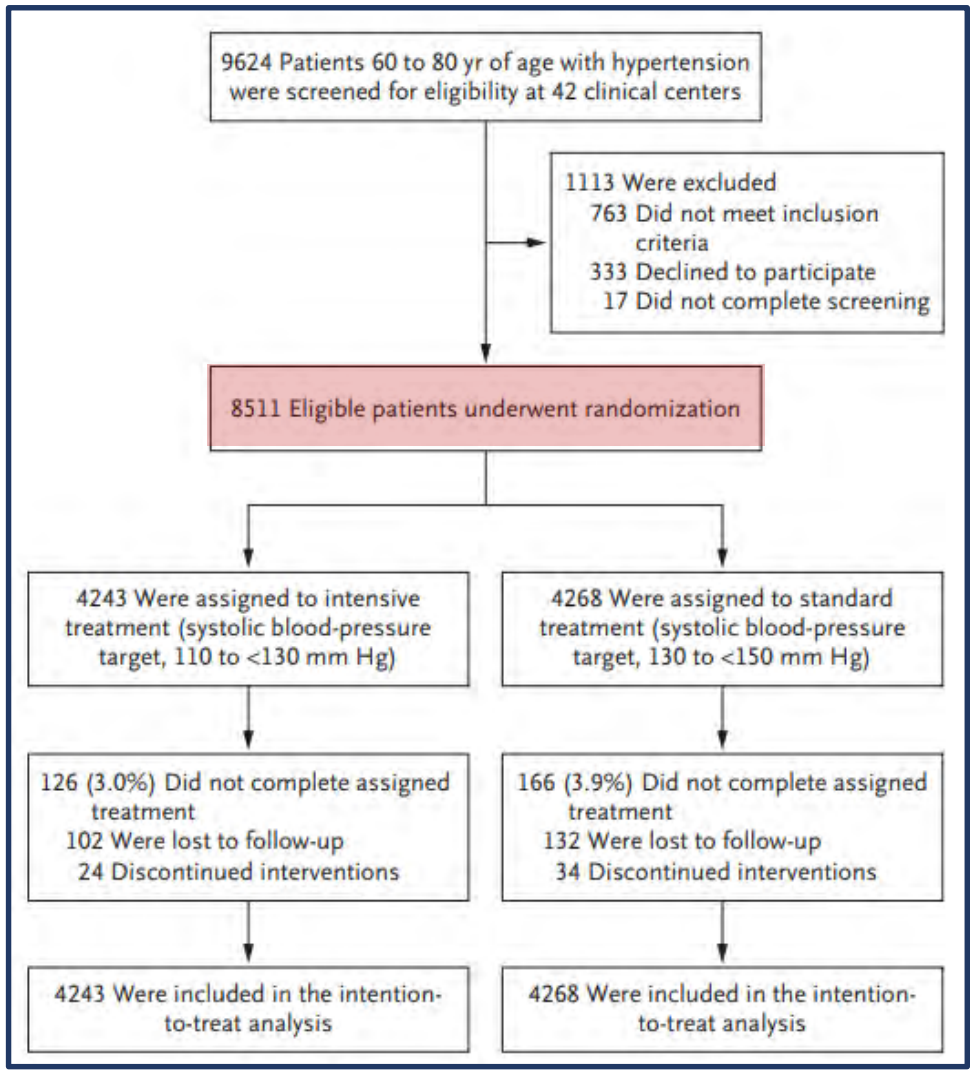
❖Information manque dans certains pays.

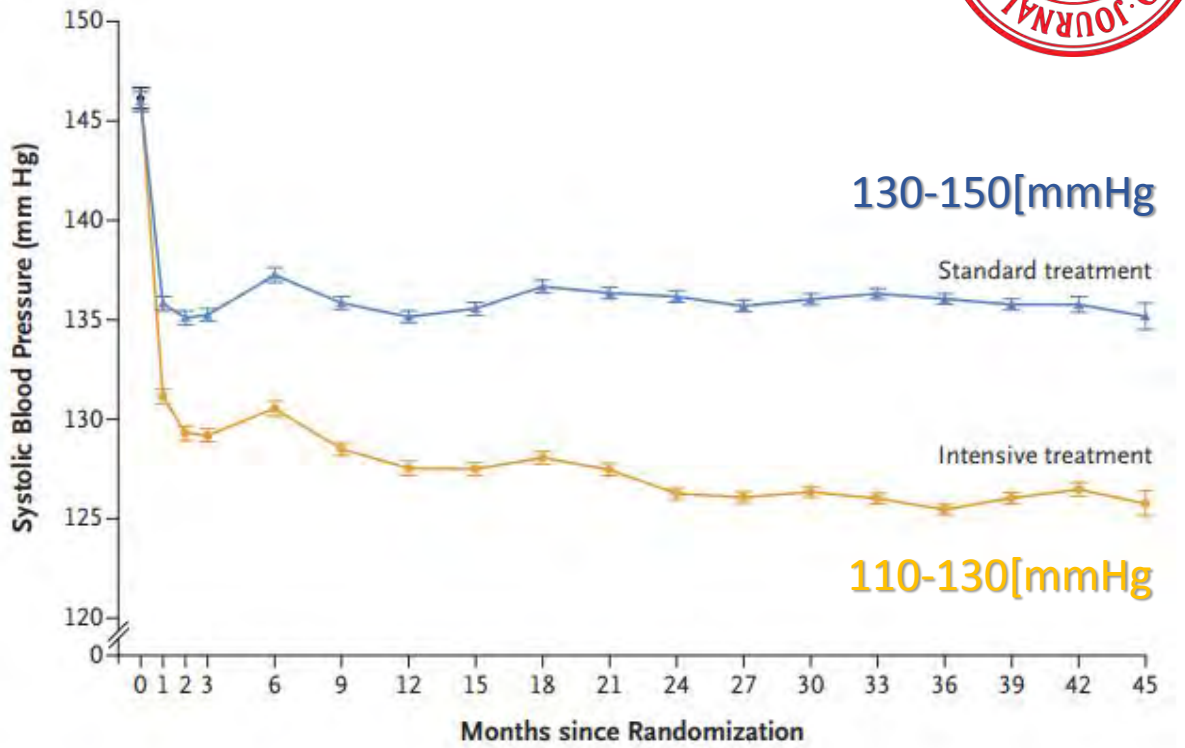
❖Méthode mesure PA diffèrent, souvent 1 visite

❖Pas accès aux types de traitement

STEP:Trial of Intensive Blood-Pressure Control in Older Patients with Hypertension

Zhang W et al.





No. with Data								
Standard treatment	4268	4139	4086	4092	4072	3954	3857	1885
Intensive treatment	4243	4128	4086	4049	4050	3969	3894	1850
Mean No. of Medications								
Standard treatment	1.4	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Intensive treatment	1.5	1.7	1.8	1.8	1.9	1.9	1.9	1.9

Lower incidence of cardiovascular events in intensive arm (110-130mmHg) rather than standard treatment (130-150mmHg)

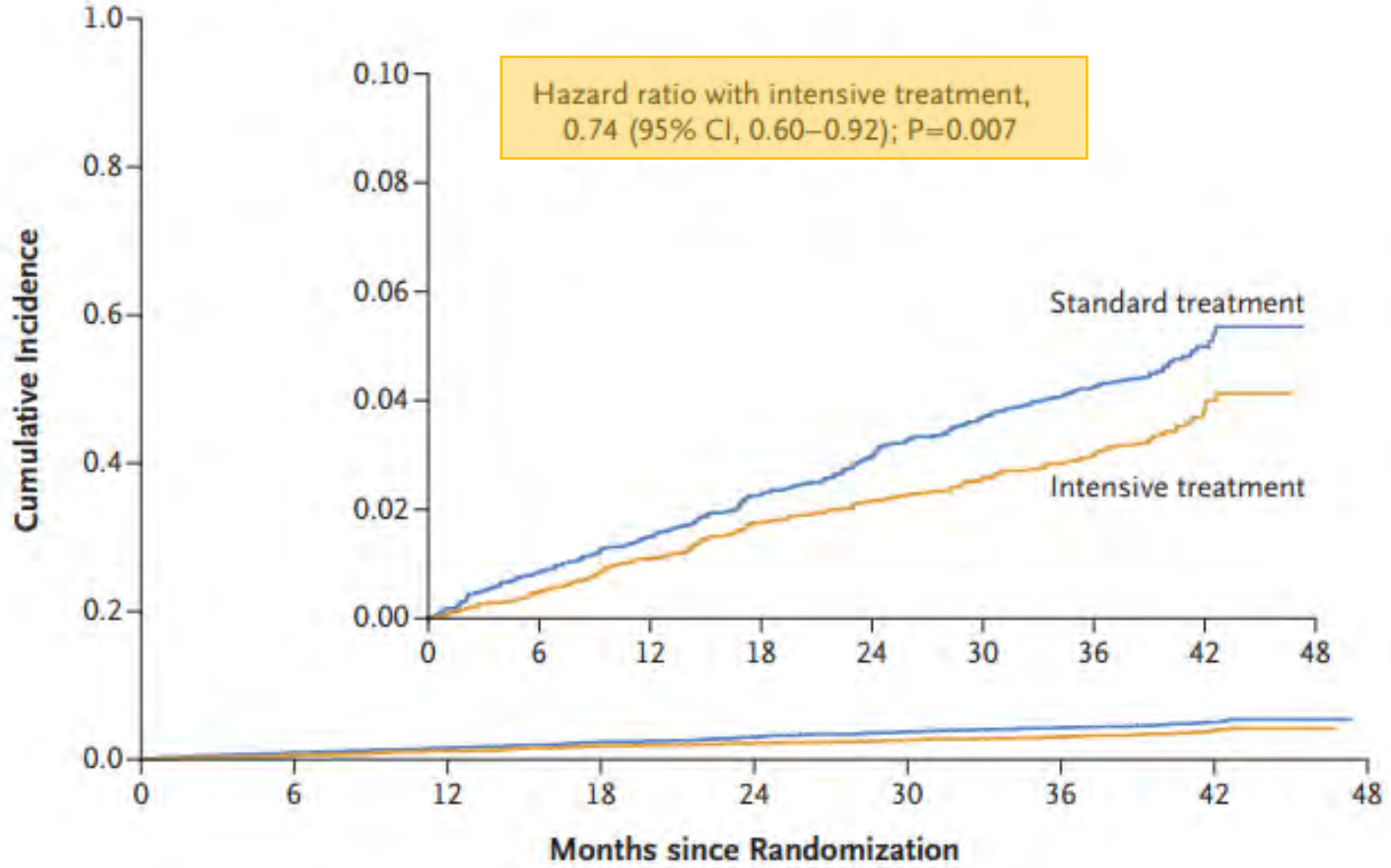
Primary composite outcome:

- Stroke ++
- Acute coronary syndrome ++
- Acute decompensated heart failure ++
- Coronary revascularization
- Atrial fibrillation
- Death from CV causes

Suivi médian: 3.3 ans

Fin prématurée car benefice+++

→Events: 3.5 % vs 4.6%



No. at Risk								
Standard treatment	4268	4147	4070	4000	3938	3849	3664	1200
Intensive treatment	4243	4174	4109	4039	3970	3867	3694	1234

And so what?

- ✓Confirme dans population âgée résultats de Sprint
- ✓Pas de differences d'effets secondaires: vertiges, syncopes, fractures, IRA
- ✓Hypotension orthostatique + fréquente dans bras intensif: 3.4 vs 2.6%

Limitations:

- ❖Exclusions patients avec AVC ou institutionnalisés
- ❖Index de fragilité non validé utilise
- ❖Nombre de medicaments pour cibles bas: 1.9 (intensif) vs 1.5 (standard)
- ❖Méthodes de mesures TA diverses: effet sur adhésion?
- ❖ Cible TAS 150 et non 140?

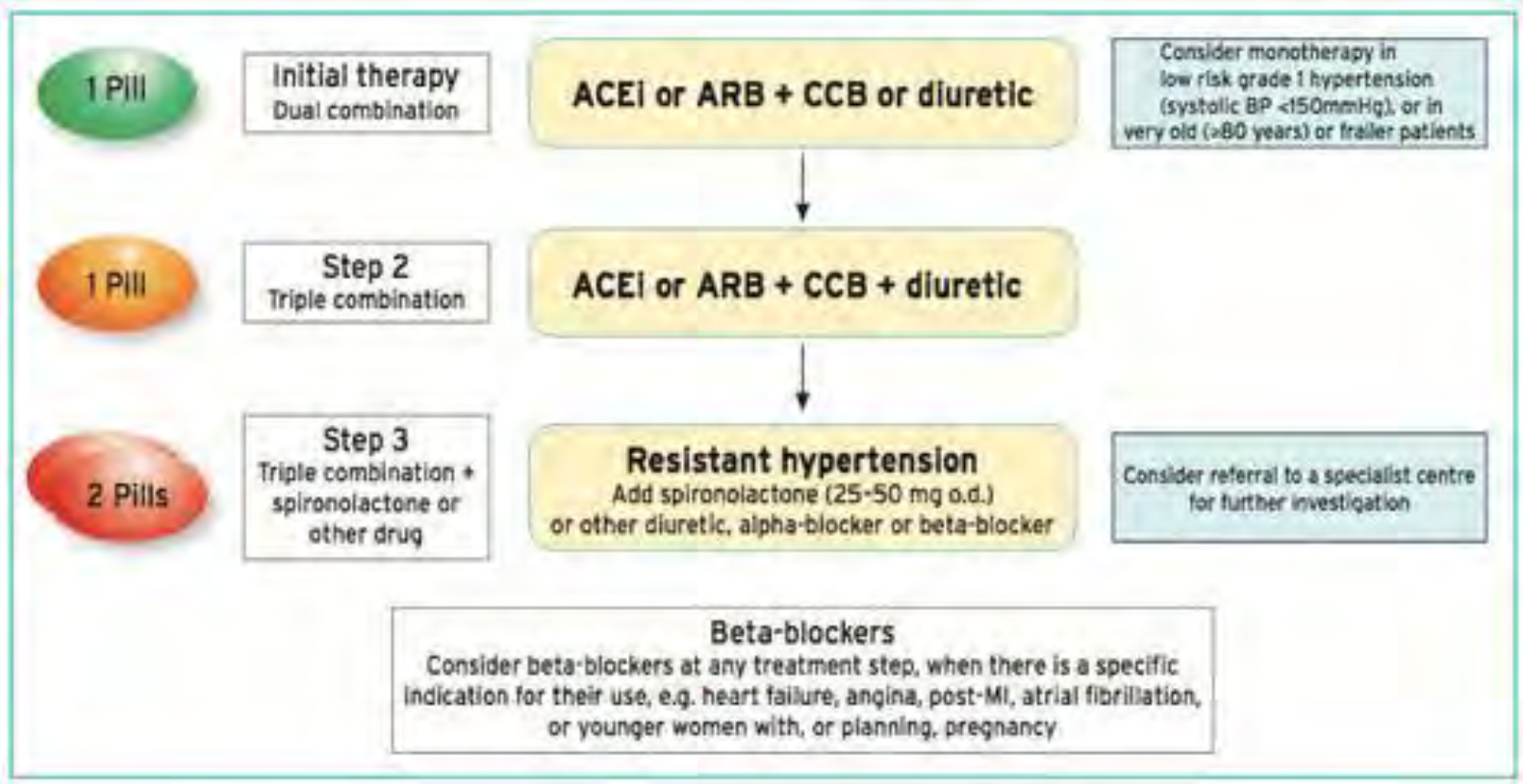
ORIGINAL RESEARCH

Annals of Internal Medicine

Adding a New Medication Versus Maximizing Dose to Intensify Hypertension Treatment in Older Adults

A Retrospective Observational Study

Carole E. Aubert, MD, MSc; Jeremy B. Sussman, MD, MS; Timothy P. Hofer, MD, MSc; William C. Cushman, MD; Jin-Kyung Ha, PhD; and Lillian Min, MD, MSHS



ESH European Society of Hypertension

Adding a New Medication Versus Maximizing Dose to Intensify Hypertension Treatment in Older Adults

A Retrospective Observational Study

Objective: To assess the 1. frequency of intensification by adding a new medication versus maximizing dose, as well as the association of each method with intensification 2. sustainability and follow-up systolic blood pressure (SBP). 3.

Design: Large-scale, population-based, retrospective cohort study. Observational data were used to emulate a target trial with 2 groups, new medication and maximizing dose, who underwent intensification of their drug regimen.

Setting: Veterans Health Administration (2011 to 2013).

Patients: Veterans aged 65 years or older with hypertension, an SBP of 130 mm Hg or higher, and at least 1 antihypertensive medication at less than the maximum dose.

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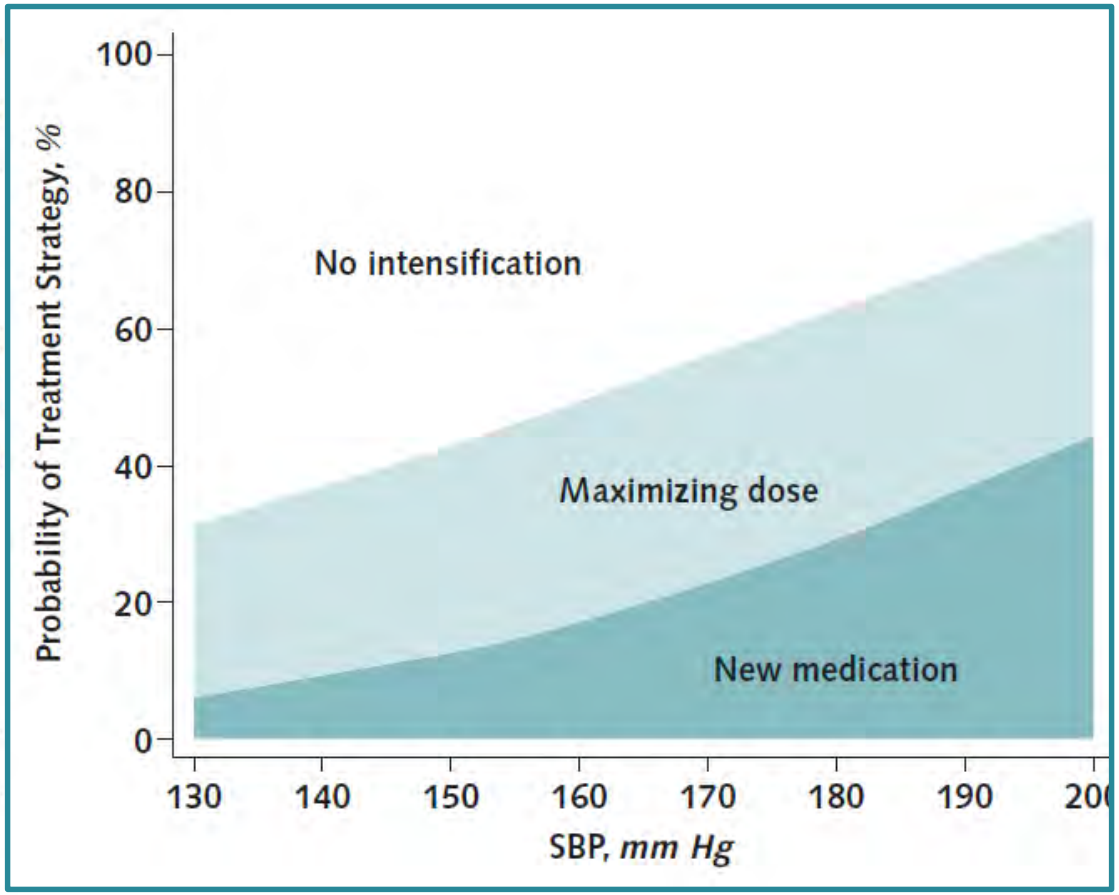


Patients aged ≥65 y, with hypertension, established VA primary care (*n* = 1 311 111)

Excluded (*n* = 824 109)
- No visit 1 July 2011 to 30 March 2012
- SBP <130 mm Hg
- No antihypertensive
- All antihypertensives at maximum dose

Baseline visit with SBP (*n* = 487 002)

Excluded (*n* = 308 440)
- No intensification: 306 736
- Death: 1704

Eligible patients (*n* = 178 562)

Treatment weights*

New medication (*n* = 45 575)

Dose maximizing (*n* = 132 987)

Intensification sustainablity

Mean follow-up SBP

Intensification sustainablity

Mean follow-up SBP

Baseline variable assessment

–3 mo

T_0

3 mo

+12 mo

Death (*n* = 1510)

3-mo survival weights†

3-mo sustainability: *treatment weights* × 3-mo *survival weights*

Death (*n* = 8205)

12-mo survival weights†

12-mo sustainability: *treatment weights* × 12-mo *survival weights*

–3 mo

T_0

3 mo

+12 mo

Incomplete follow-up (no SBP or death) (*n* = 105 851)

3-mo censoring weights‡

3-mo SBP: *treatment weights* × 3-mo *censoring weights*

Incomplete follow-up (no SBP or death) (*n* = 17 767)

12-mo censoring weights‡

12-mo SBP: *treatment weights* × 12-mo *censoring weights*

Table. Baseline Characteristics of the Patients (*n* = 178 562), According to Treatment Strategy

Characteristic	New Medication (*n* = 45 575)	Maximizing Dose (*n* = 132 987)
Mean age (SD), *y*	75.5 (7.4)	75.9 (7.5)
Physician specialty, *n (%)*		
Geriatric care	706 (1.5)	2656 (2.0)
Hypertension-treating specialty care*	3026 (6.6)	8063 (6.0)
Systolic blood pressure		
Mean (SD), *mm Hg*	142.3 (10.6)	140.0 (9.3)
130–140 mm Hg, *n (%)*	23 498 (51.6)	82 389 (62.0)
140–160 mm Hg, *n (%)*	18 690 (41.0)	44 650 (33.6)
≥160 mm Hg, *n (%)*	3387 (7.4)	5948 (4.5)
Chronic conditions		
Mean number, in addition to hypertension (SD), *n*	3.5 (3.6)	3.5 (3.5)
Multimorbidity, *n (%)*†	38 003 (70.7)	94 984 (71.4)
Cardiac, cerebral, or peripheral vascular disease, *n (%)*	14 716 (32.3)	41 622 (31.3)
Heart failure/valve disorder, *n (%)*	6778 (14.9)	18766 (14.1)
Diabetes mellitus, *n (%)*	14 408 (31.6)	41 217 (31.0)
Arrhythmia, *n (%)*	4407 (9.7)	12 620 (9.5)
Current smoking, *n (%)*	4442 (9.7)	13 183 (9.9)
Antihypertensive medication		
Mean number of medications (SD), *n*	1.9 (0.9)	2.4 (1.1)
Mean standardized total dose (SD), *HDD unit*	2.0 (1.7)	2.3 (1.8)
ACEI/sartan/renin inhibitor, *n (%)*	24 214 (53.1)	93 555 (70.4)
β-Blocker, *n (%)*	20 751 (45.4)	69 721 (52.4)
Calcium-channel blocker, *n (%)*	15 515 (34.0)	59 601 (44.8)

Higher frequency of maximalising vs adding new treatment
Higher sustainability when maximalising

1. Frequency of intensification:

   maximal vs addition: 74.5% vs 25.5%

2. Intensification “sustainability”:

   Maximal vs additional: 65% vs 49.8% à 3-6 mois

   Additional: Average Treatment effect (ATE) -15.2% à 3-6 mois

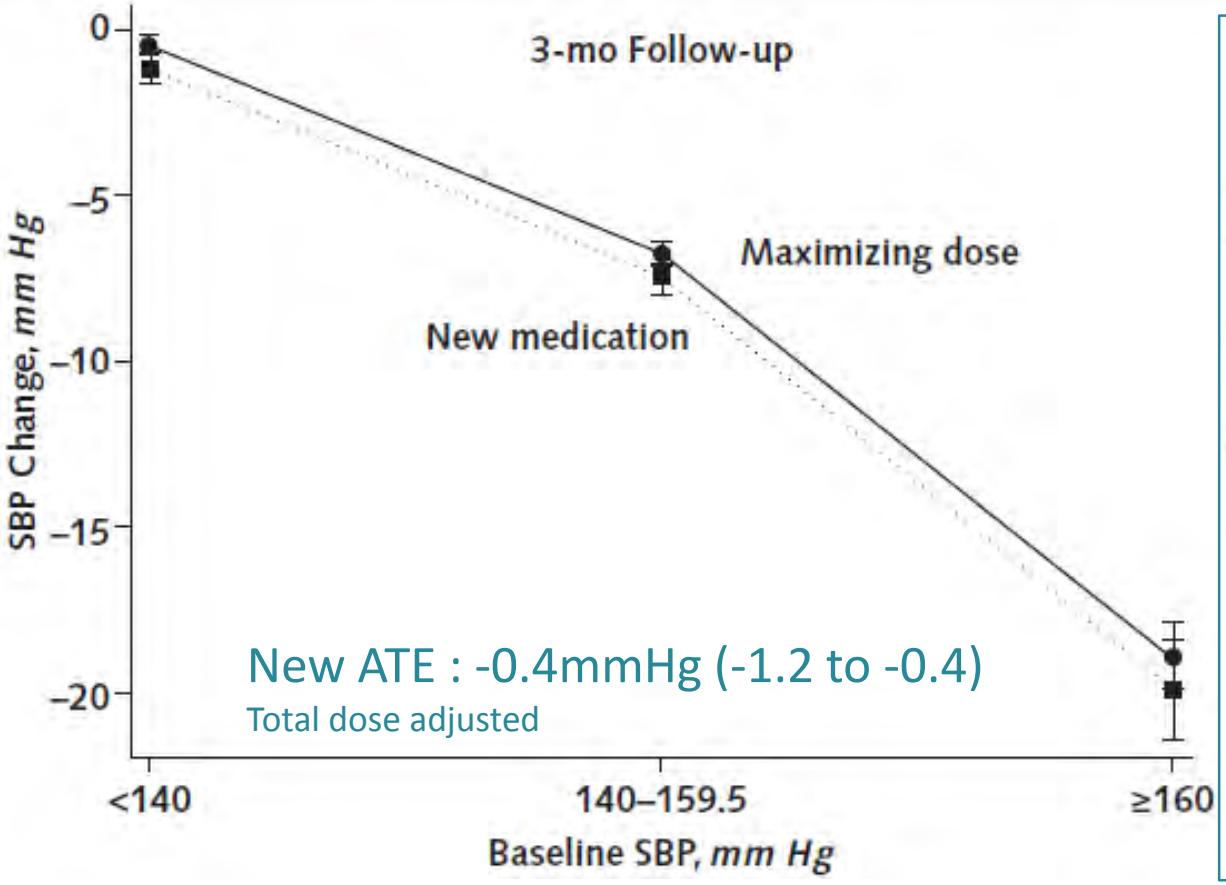
   indépendant de baseline SBP

   indépendant nombre medicament initial

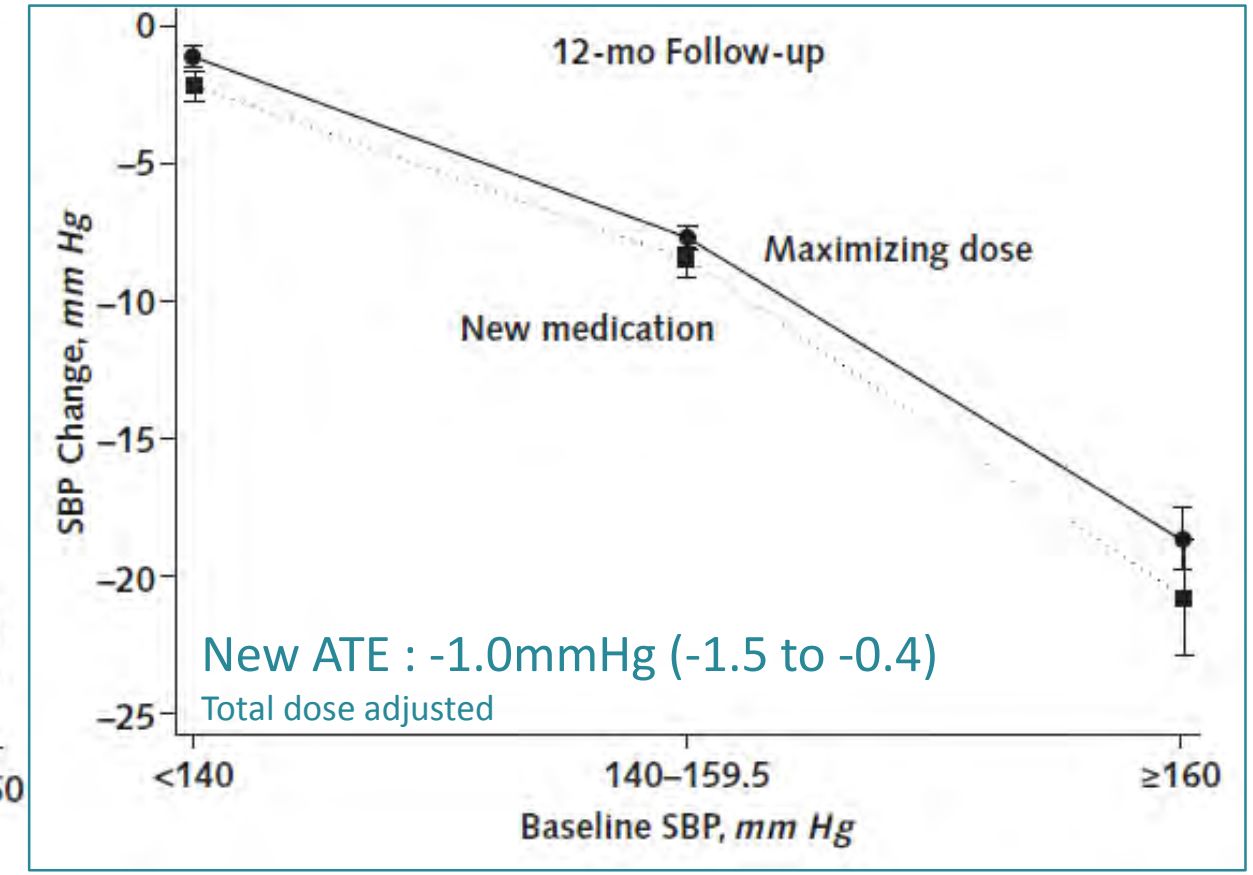
   pas de difference selon conditions CV

Decrease in SBP steeper by adding a new drug, even larger effect at higher baseline SBP

Figure 3. Change in SBP between baseline and follow-up, according to intensification approach and baseline SBP.



New ATE : -0.4mmHg (-1.2 to -0.4)
Total dose adjusted



New ATE : -1.0mmHg (-1.5 to -0.4)
Total dose adjusted

And so what?

Dose maximale ttt + prescrite dans population âgée avec comorbidités, prise + soutenue dans le temps mais effet sur SBP un peu plus faible

SBP reduction 5mmHg → reduction RR événement CV majeur de 10% / 4 ans

✓ Large echelle

✓ Design imitant RCT avec analyse type ITT

Limitations:

❖Database – données de registre (pharmacy records)

❖Limitée aux hommes

❖Ne tient pas compte de combinaisons

❖Outcome “dur” CV ou mortalité non considéré

Adherence to antihypertensive medication and incident CV events in Young adults with hypertension. Lee H et al.

- Nationwide health insurance database

✓123 390 participants free of prior cardiovascular disease

✓Initiating pharmacological treatment for hypertension 2004-2007

✓75.1% male and Age 20 to 44 years

Participants were categorized as:

- Adherent = proportion of days covered ≥0.8
- Nonadherent=proportion of days covered <0.8

to antihypertensive medication during the first year of treatment

Poor medication adherence is associated with higher risk of CVD events in young patients initiating an antihypertensive treatment

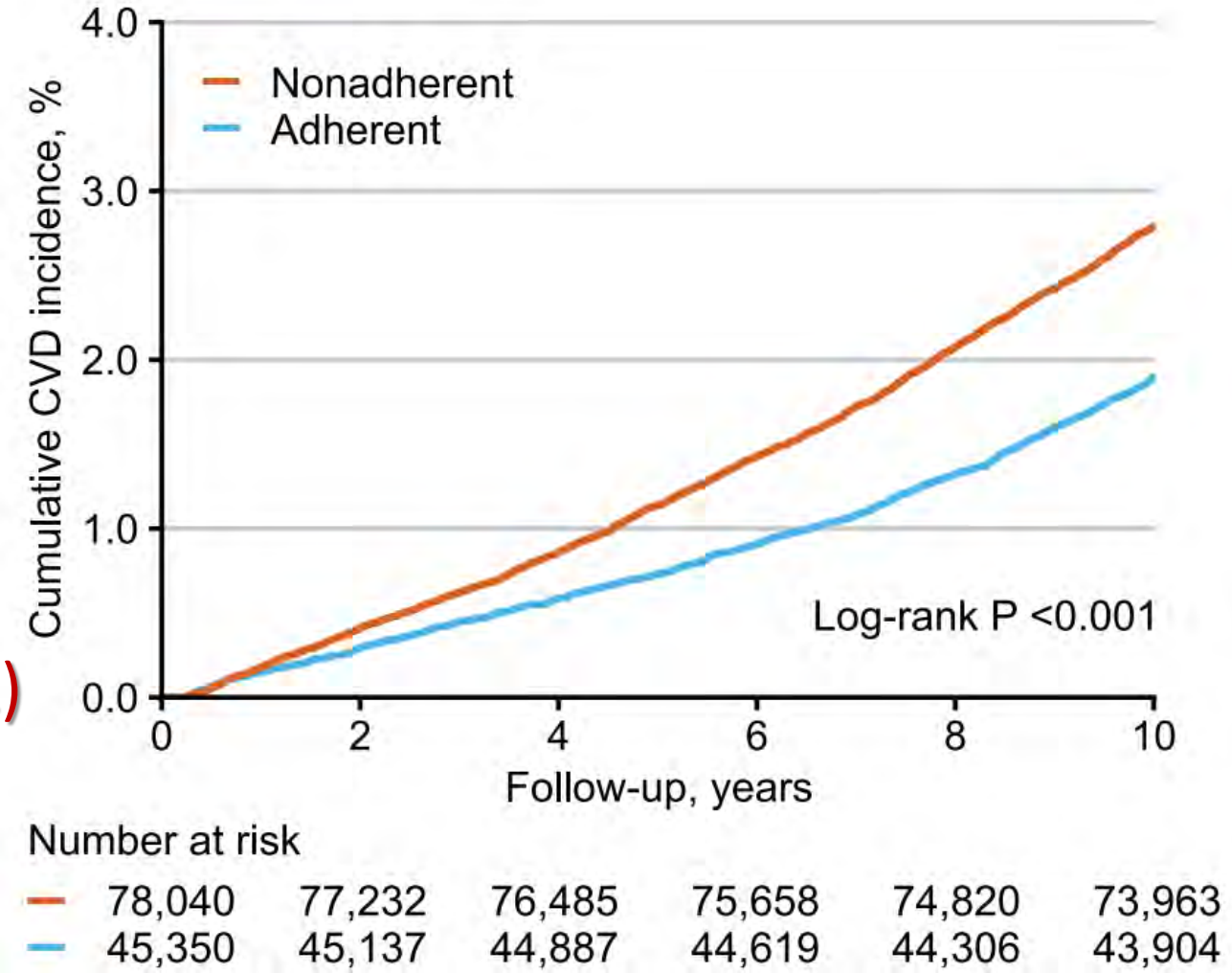
Primary CV composite outcome:

- myocardial infarction
- Stroke
- heart failure
- cardiovascular death

Suivi médian: 10 ans

→NonA: HR 1.57 (IC95%: 1.45-1.71)

→Effet dose-réponse (quartiles)



And so what?

1ère étude montrant association mauvaise adhesion et événements CV **chez jeunes avec risque CV initial bas**

✓Grand recrutement, Durée du suivi

→ Importance d'aborder la question de l'adherence tôt

Limitations:

❖Evaluation adhésion peu precise

❖Définition adhésion discutable

❖25% femme seulement


CAUTION
LOW SALT
AREA

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

24-Hour Urinary Sodium and Potassium Excretion and Cardiovascular Risk

Yuan Ma, Ph.D., Feng J. He, Ph.D., Qi Sun, M.D., Sc.D., Changzheng Yuan, Sc.D.,

- ✓6 prospective cohorts
- ✓2 x 24h urinary samples
- ✓General healthy population (n=10’709)
- ✓Age 51.5±12.6; 54.2% women

Primary outcome during 8.8 years Fup:

Coronary revasc. or non fatal MI or stroke

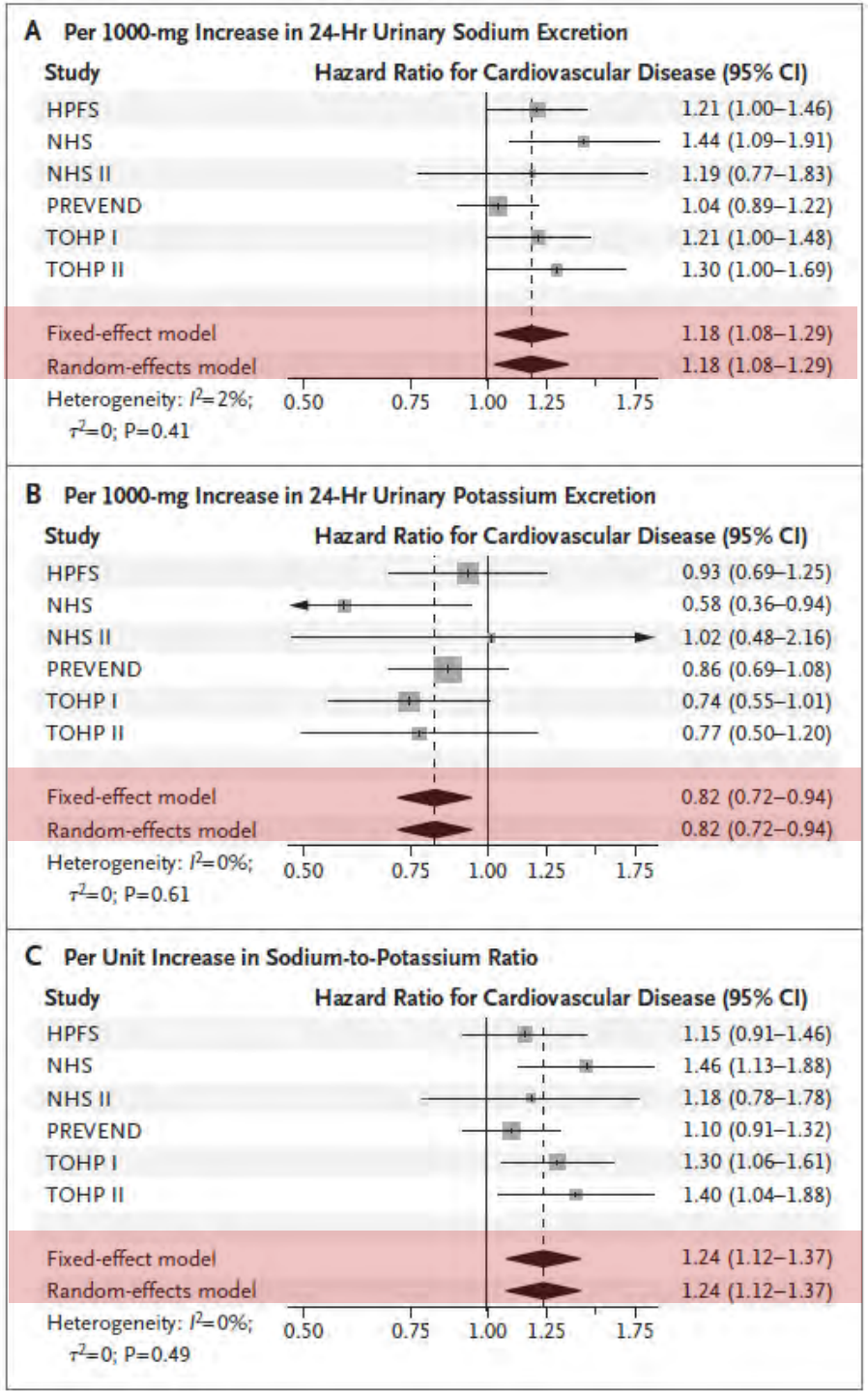
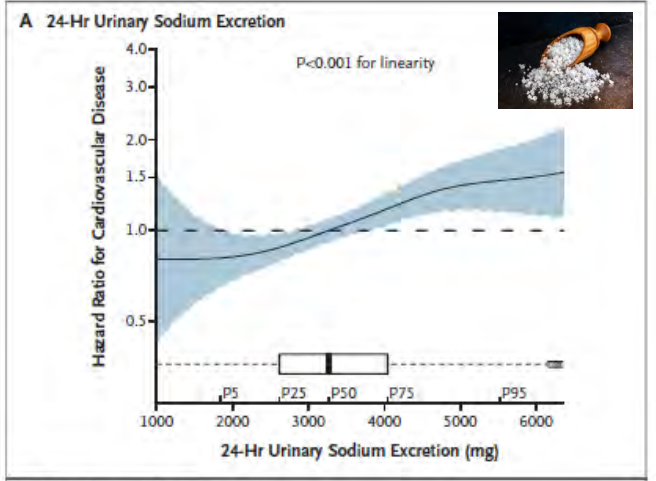
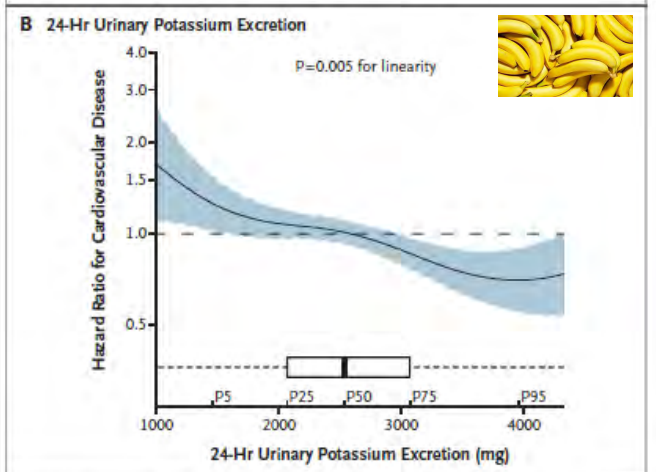


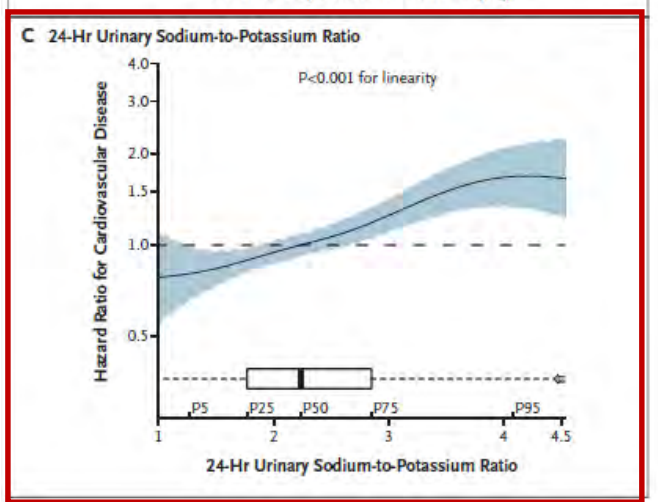
Table 2. Association of Sodium and Potassium Excretion with Cardiovascular Risk.*

CV events = 571 => 5.9 /1000personnes-années

Variable	Quartile of Urinary Biomarker				Hazard Ratio per 1000-mg Increase per Day†	P Value
	Quartile 1	Quartile 2	Quartile 3	Quartile 4		
24-Hr sodium excretion						
Median 24-hr sodium excretion — mg	2212	2942	3588	4692		—
Cardiovascular event — no. of events/ no. of participants	111/2677	139/2677	145/2679	176/2676	—	—
Hazard ratio (95% CI)						
Model 1	Reference	1.15 (0.89–1.49)	1.25 (0.86–1.80)	1.40 (1.07–1.82)	1.12 (1.04–1.21)	—
Model 2	Reference	1.25 (0.96–1.63)	1.44 (0.93–2.23)	1.60 (1.19–2.14)	1.18 (1.08–1.29)	<0.001
24-Hr potassium excretion						
Median 24-hr potassium excretion — mg	1755	2336	2784	3501		—
Cardiovascular event — no. of events/ no. of participants	148/2682	156/2674	140/2677	127/2676	—	—
Hazard ratio (95% CI)						
Model 1	Reference	1.02 (0.81–1.29)	0.88 (0.69–1.11)	0.74 (0.57–0.95)	0.85 (0.76–0.96)	—
Model 2	Reference	1.00 (0.78–1.26)	0.86 (0.67–1.11)	0.69 (0.51–0.91)	0.82 (0.72–0.94)	0.005
Sodium-to-potassium ratio						
Median ratio	1.5	2.0	2.4	3.4		—
Cardiovascular event — no. of events/ no. of participants	113/2676	116/2678	152/2679	190/2676	—	—
Hazard ratio (95% CI)†						
Model 1	Reference	1.02 (0.79–1.33)	1.43 (1.01–2.01)	1.76 (1.37–2.24)	1.27 (1.16–1.40)	—
Model 2	Reference	1.02 (0.78–1.33)	1.40 (0.99–1.99)	1.62 (1.25–2.10)	1.24 (1.12–1.37)	<0.001







A Per 1000-mg Increase in 24-Hr Urinary Sodium Excretion

Subgroup	No. of Events/ No. of Person-Yr	Hazard Ratio for Cardiovascular Disease (95% CI)
Age		
<65 yr	404/81,389	
≥65 yr	167/15,013	
Sex		
Male	380/42,783	
Female	191/53,619	
Baseline hypertension		
No	370/75,614	
Yes	201/20,788	
Weight status		
Normal	158/36,909	
Overweight or obese	408/58,617	
Years of follow-up		
<5 yr	318/51,485	
≥5 yr	302/93,566	

B Per 1000-mg Increase in 24-Hr Urinary Potassium Excretion

Subgroup	No. of Events/ No. of Person-Yr	Hazard Ratio for Cardiovascular Disease (95% CI)
Age		
<65 yr	404/81,389	
≥65 yr	167/15,013	
Sex		
Male	380/42,783	
Female	191/53,619	
Baseline hypertension		
No	370/75,614	
Yes	201/20,788	
Weight status		
Normal	158/36,909	
Overweight or obese	408/58,617	
Years of follow-up		
<5 yr	318/51,485	
≥5 yr	302/93,566	

0.6 0.8 1.0 1.2 1.4 1.6

Per Unit Increase in Sodium-to-Potassium Ratio

Subgroup	No. of Events/ No. of Person-Yr	Cardiovascular Disease (95% CI)
Age		
<65 yr	404/81,389	
≥65 yr	167/15,013	
Sex		
Male	380/42,783	
Female	191/53,619	
Baseline hypertension		
No	370/75,614	
Yes	201/20,788	
Weight status		
Normal	158/36,909	
Overweight or obese	408/58,617	
Years of follow-up		
<5 yr	318/51,485	
≥5 yr	302/93,566	

0.6 0.8 1.0 1.2 1.4 1.6

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 16, 2021 VOL. 385 NO. 12

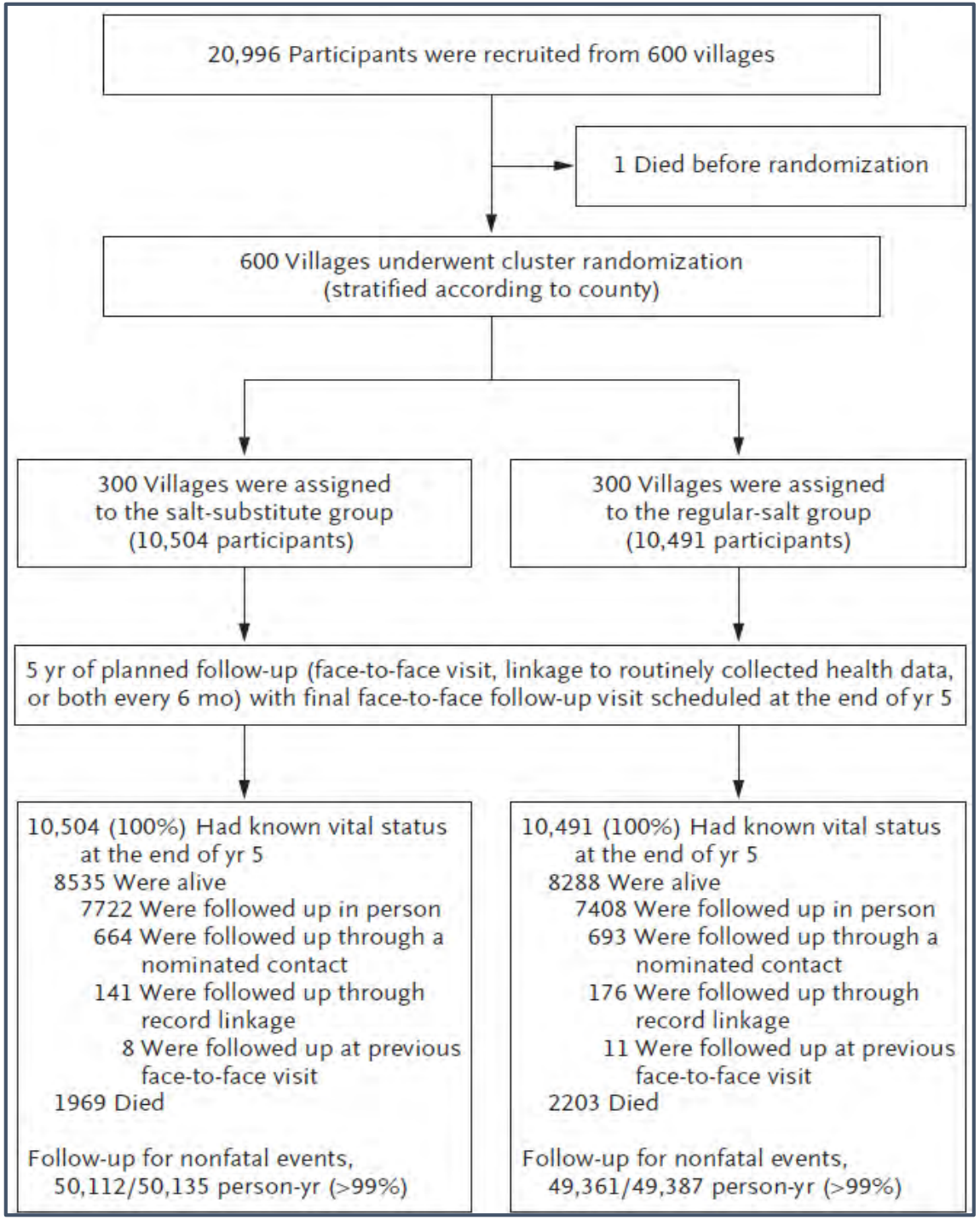
Effect of Salt Substitution on Cardiovascular Events and Death

Outcome I : Stroke (>24h or death from Stroke)

Outcome II: CV events or death

Death any cause

Safety outcome: HyperK

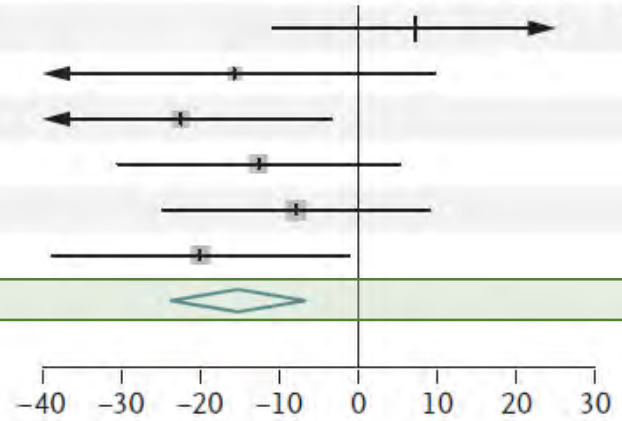


Mean Group differences: Sodium < Potassium

C 24-Hr Urinary Sodium Excretion (mmol)

Time Point	Salt Substitute (no. of participants)	Regular Salt (no. of participants)	Mean Difference (95% CI)
Baseline	276	268	9.96 (−12.39 to 32.32)
12 Mo	577	445	−15.69 (−41.05 to 9.66)
24 Mo	1,047	939	−22.45 (−41.52 to −3.37)
36 Mo	428	392	−12.55 (−30.41 to 5.31)
48 Mo	444	383	−7.89 (−24.73 to 8.95)
60 Mo	424	358	−19.95 (−38.71 to −1.20)
Fixed-Effects Model			**−15.21 (−23.72 to −6.70)**

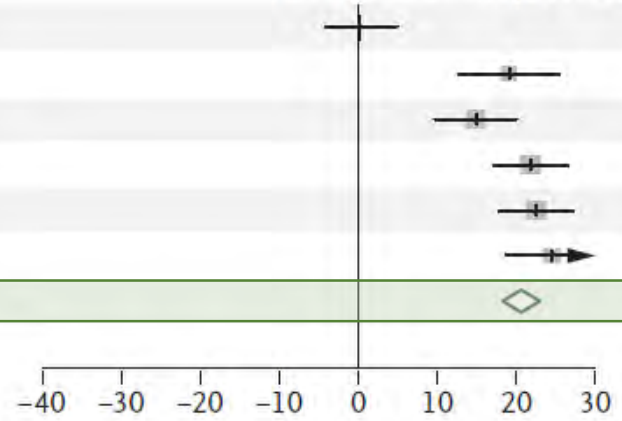
Heterogeneity: I^2=0%; P=0.81



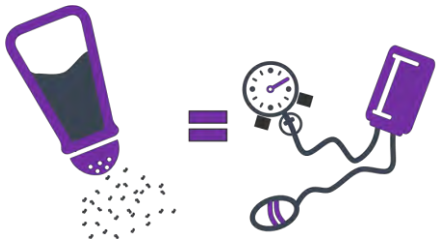
D 24-Hr Urinary Potassium Excretion (mmol)

Time Point	Salt Substitute (no. of participants)	Regular Salt (no. of participants)	Mean Difference (95% CI)
Baseline	276	268	0.63 (−3.36 to 4.62)
12 Mo	577	445	19.13 (12.82 to 25.45)
24 Mo	1,047	939	14.88 (9.73 to 20.03)
36 Mo	428	392	21.87 (17.15 to 26.60)
48 Mo	444	383	22.48 (17.78 to 27.18)
60 Mo	424	358	24.52 (18.74 to 30.30)
Fixed-Effects Model			**20.64 (18.30 to 22.98)**

Heterogeneity: I^2=47.4%; P=0.11

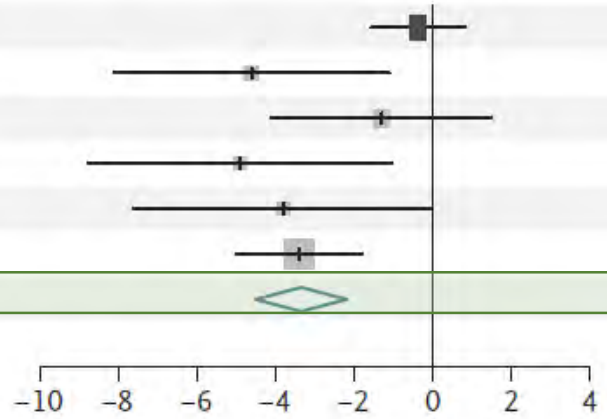


Mean Group differences: SBP> DBP



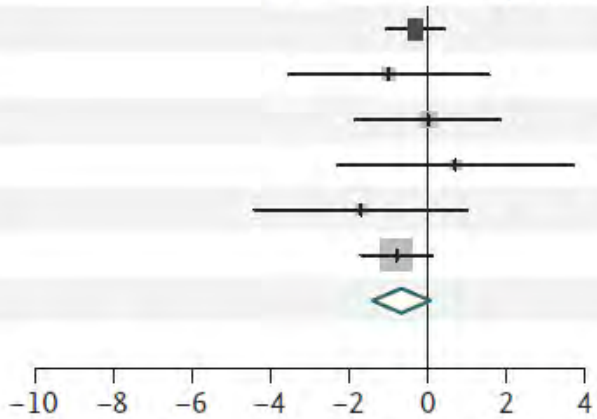
A Systolic Blood Pressure (mm Hg)

Time Point	Salt Substitute	Regular Salt	Mean Difference (95% CI)
	no. of participants		
Baseline	10,504	10,491	−0.40 (−2.50 to 1.70)
12 Mo	768	658	−4.60 (−8.10 to −1.10)
24 Mo	1,412	1,374	−1.30 (−4.10 to 1.50)
36 Mo	584	584	−4.90 (−8.75 to −1.05)
48 Mo	587	559	−3.80 (−7.60 to 0.00)
60 Mo	7,436	7,081	−3.40 (−5.00 to −1.80)
Fixed-Effects Model			−3.34 (−4.51 to −2.18)
Heterogeneity: I^2=0%; P=0.52			

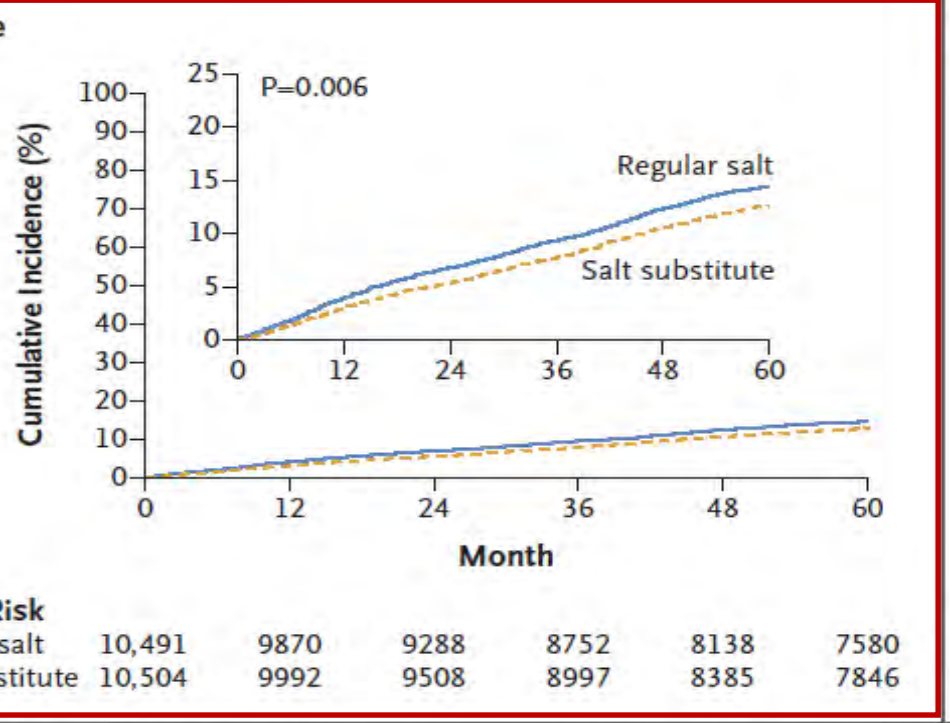


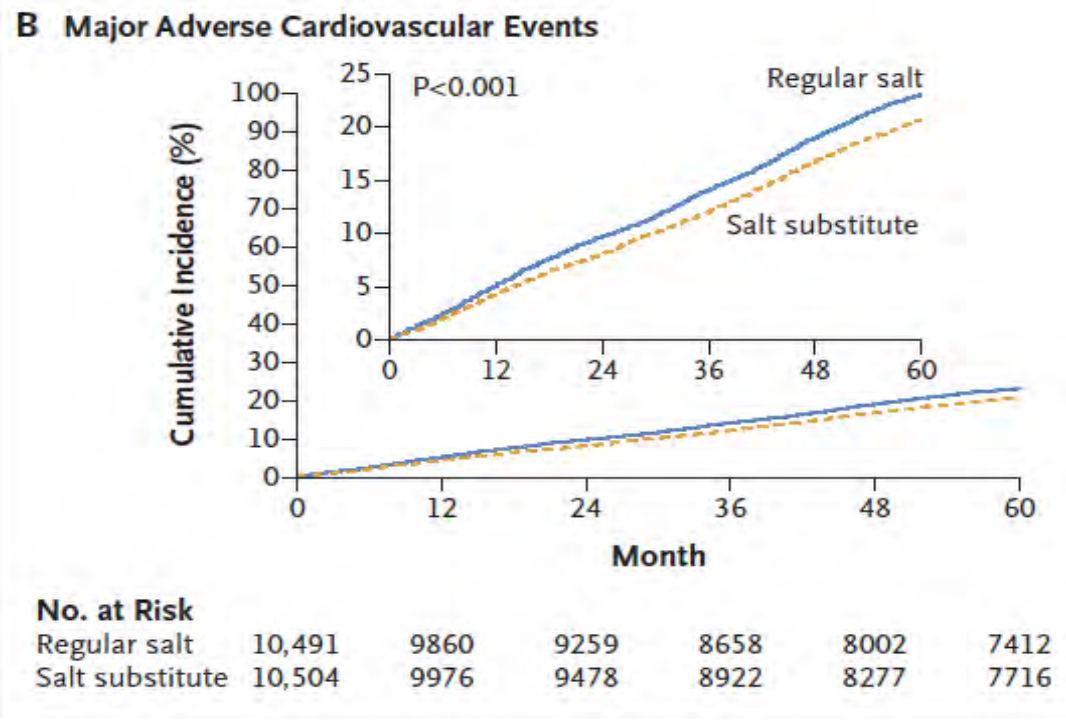
B Diastolic Blood Pressure (mm Hg)

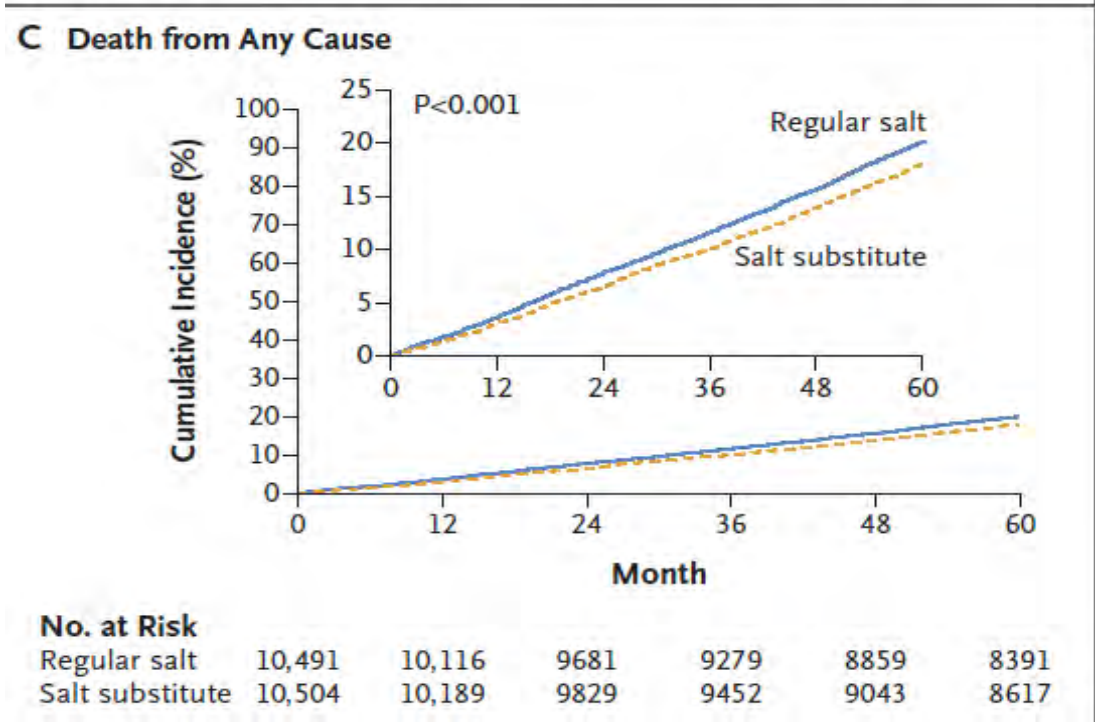
Time Point	Salt Substitute	Regular Salt	Mean Difference (95% CI)
	no. of participants		
Baseline	10,504	10,491	−0.30 (−1.55 to 0.95)
12 Mo	768	658	−1.00 (−3.55 to 1.55)
24 Mo	1,412	1,374	0.00 (−1.85 to 1.85)
36 Mo	584	584	0.70 (−2.30 to 3.70)
48 Mo	587	559	−1.70 (−4.40 to 1.00)
60 Mo	7,436	7,081	−0.80 (−1.70 to 0.10)
Fixed-Effects Model			**−0.67 (−1.39 to 0.05)**
Heterogeneity: I^2=0%; P=0.73			

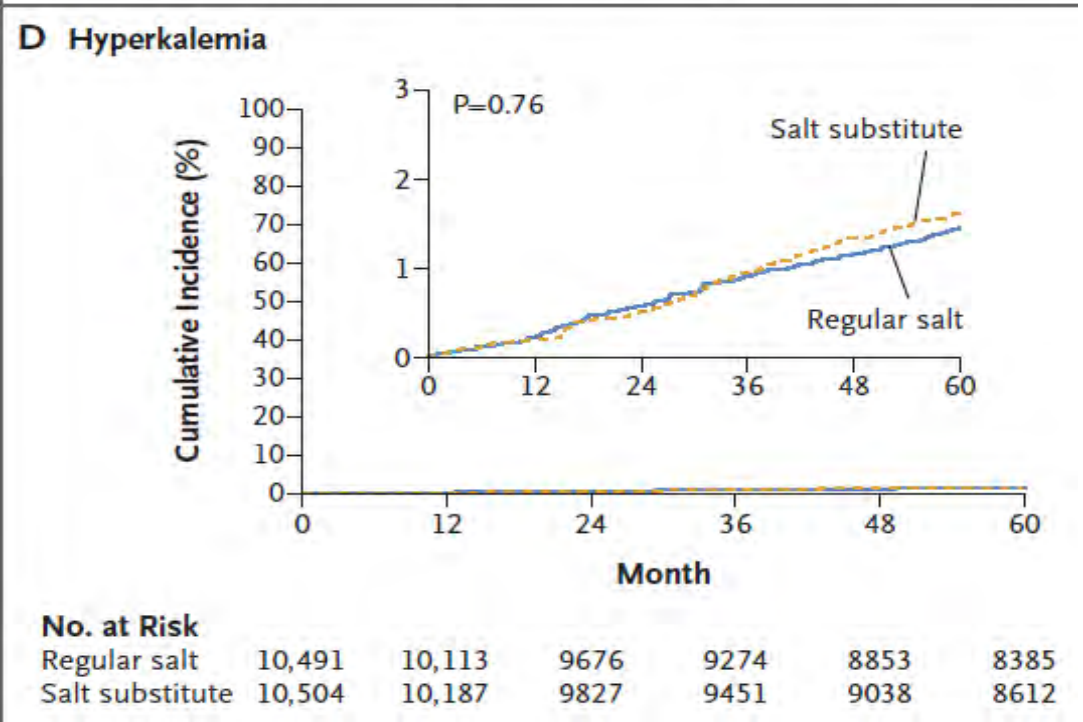


Outcome I


A Stroke
P=0.006
Regular salt
Salt substitute
Cumulative Incidence (%)
Month
No. at Risk
Regular salt 10,491 9870 9288 8752 8138 7580
Salt substitute 10,504 9992 9508 8997 8385 7846


B Major Adverse Cardiovascular Events
P<0.001
Regular salt
Salt substitute
Cumulative Incidence (%)
Month
No. at Risk
Regular salt 10,491 9860 9259 8658 8002 7412
Salt substitute 10,504 9976 9478 8922 8277 7716


C Death from Any Cause
P<0.001
Regular salt
Salt substitute
Cumulative Incidence (%)
Month
No. at Risk
Regular salt 10,491 10,116 9681 9279 8859 8391
Salt substitute 10,504 10,189 9829 9452 9043 8617


D Hyperkalemia
P=0.76
Salt substitute
Regular salt
Cumulative Incidence (%)
Month
No. at Risk
Regular salt 10,491 10,113 9676 9274 8853 8385
Salt substitute 10,504 10,187 9827 9451 9038 8612

Outcomes	Salt Substitute	Regular Salt	Rate Ratio (95% CI)	P Value
	no. of events per 1000 person-yr			
Stroke	29.14	33.65	0.86 (0.77–0.96)	P=0.006
Major Adverse CV Events	49.09	56.29	0.87 (0.80–0.94)	P<0.001
Death from Any Cause	39.28	44.61	0.88 (0.82–0.95)	P<0.001
Hyperkalemia	3.35	3.30	1.04 (0.80–1.37)	P=0.76

And so what?

- ✓Longue durée, large échelle, randomisée, c/o patients à haut risque
- ✓Effet médié par ↓ TA mais encore?
- ✓Effet probablement encore sous-estimé.
  - Adhérence incomplète au régime
  - Consommation de sel à l'extérieur de la maison
  - Utilisation de substitut de sel dans le groupe contrôle

Limitations:

- ❖↓ consommation de sel minime: -15mmol (=0.8g): → effet plutôt protecteur du K+?
- ❖Récolte d'informations limitées
- ❖Hyperkaliémie: pas de mesures périodique K : sous-estimation?
- ❖Généralisation?
  - Population sélectionnée « salt sensitive »
  - Apport moyen de sel élevé en Chine par rapport à autres pays (11g vs 9g)
  - Potentiellement pas applicable chez patients IRC

RESEARCH SUMMARY

Chlorthalidone for Hypertension in Advanced Chronic Kidney Disease

Agarwal R et al. DOI: 10.1056/NEJMoa2110730

CLINICAL PROBLEM

Thiazides or thiazide-like diuretics are important for blood-pressure management in patients with essential hypertension, but their safety and efficacy in the treatment of hypertension in patients with advanced chronic kidney disease are poorly understood.

CLINICAL TRIAL

Design: A randomized, double-blind, placebo-controlled trial examined the safety and efficacy of the thiazide-like diuretic chlorthalidone in patients with stage 4 chronic kidney disease and poorly controlled hypertension.

Intervention: 160 patients were randomly assigned to add chlorthalidone (12.5 mg per day, with titration to 50 mg per day as needed) or placebo to their antihypertensive regimen. Patients were receiving an average of 3.4 antihypertensive drugs at baseline. The primary outcome was the change in 24-hour ambulatory systolic blood pressure from baseline to 12 weeks.

RESULTS

Efficacy: At 12 weeks, the reduction in 24-hour systolic blood pressure was significantly greater in the chlorthalidone group than in the placebo group.

Safety: Adverse events occurred in 91% of patients in the chlorthalidone group and 86% of patients in the placebo group. Increases in serum creatinine level, hypokalemia, hypomagnesemia, hyponatremia, hyperglycemia, hyperuricemia, and dizziness occurred more often with chlorthalidone.

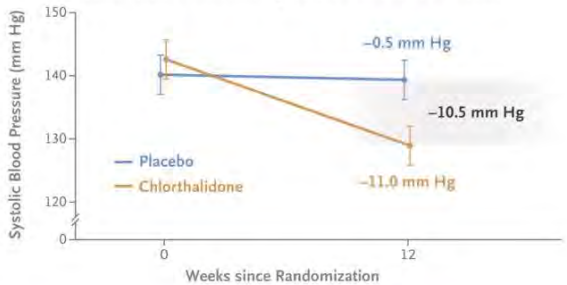
LIMITATIONS AND REMAINING QUESTIONS

- The number of patients was relatively small, with disproportionately few women, Asian patients, and Hispanic patients.
- Chlorthalidone was associated with a reduction in albuminuria; whether this would translate into cardiovascular and kidney protection in patients with chronic kidney disease is unknown.
- The safest approach to concomitant use of chlorthalidone and loop diuretics in patients with chronic kidney disease remains to be determined, given the possibility of more patients with hypokalemia, increases in serum creatinine level, or both.

Links: Full Article | NEJM Quick Take

Adjusted Change in 24-Hour Ambulatory Systolic Blood Pressure from Baseline to 12 Weeks

Mean difference, −10.5 mm Hg; 95% CI, −14.6 to −6.4; P<0.001



Adverse Events during the Treatment Period

no. with event/total no. (%)	Chlorthalidone	Placebo
Increase in serum creatinine level (>25% from baseline)	33/74 (45)	10/77 (13)
Hypokalemia	8/81 (10)	0
Hypomagnesemia	19/81 (23)	13/79 (16)
Hyponatremia	9/81 (11)	6/79 (8)
Hyperglycemia	13/81 (16)	4/79 (5)
Hyperuricemia	16/81 (20)	7/79 (9)
Dizziness	20/81 (25)	13/79 (16)

CONCLUSIONS

In patients with advanced chronic kidney disease and poorly controlled hypertension, the addition of chlorthalidone to other antihypertensive medications improved blood-pressure control at 12 weeks as compared with placebo.

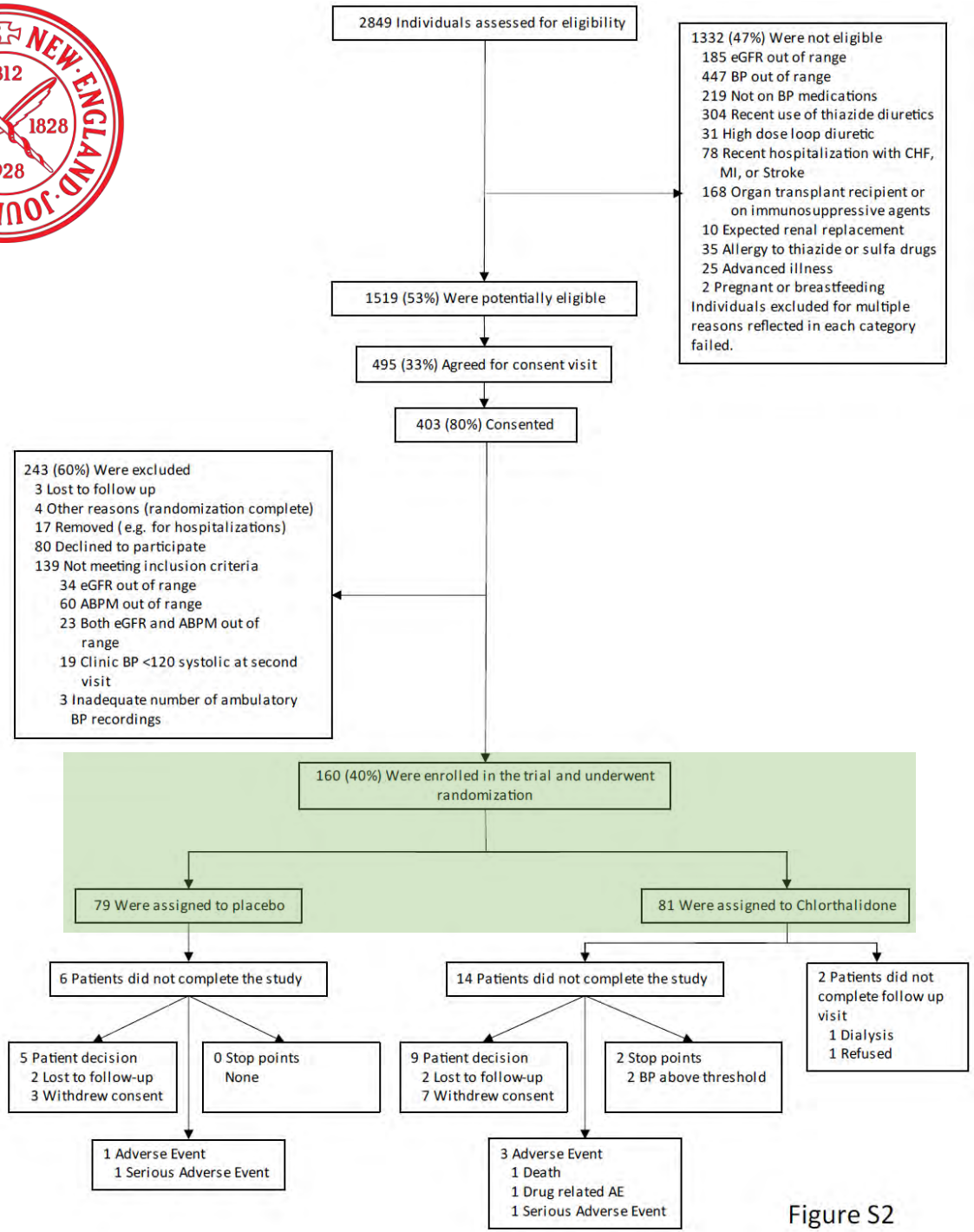
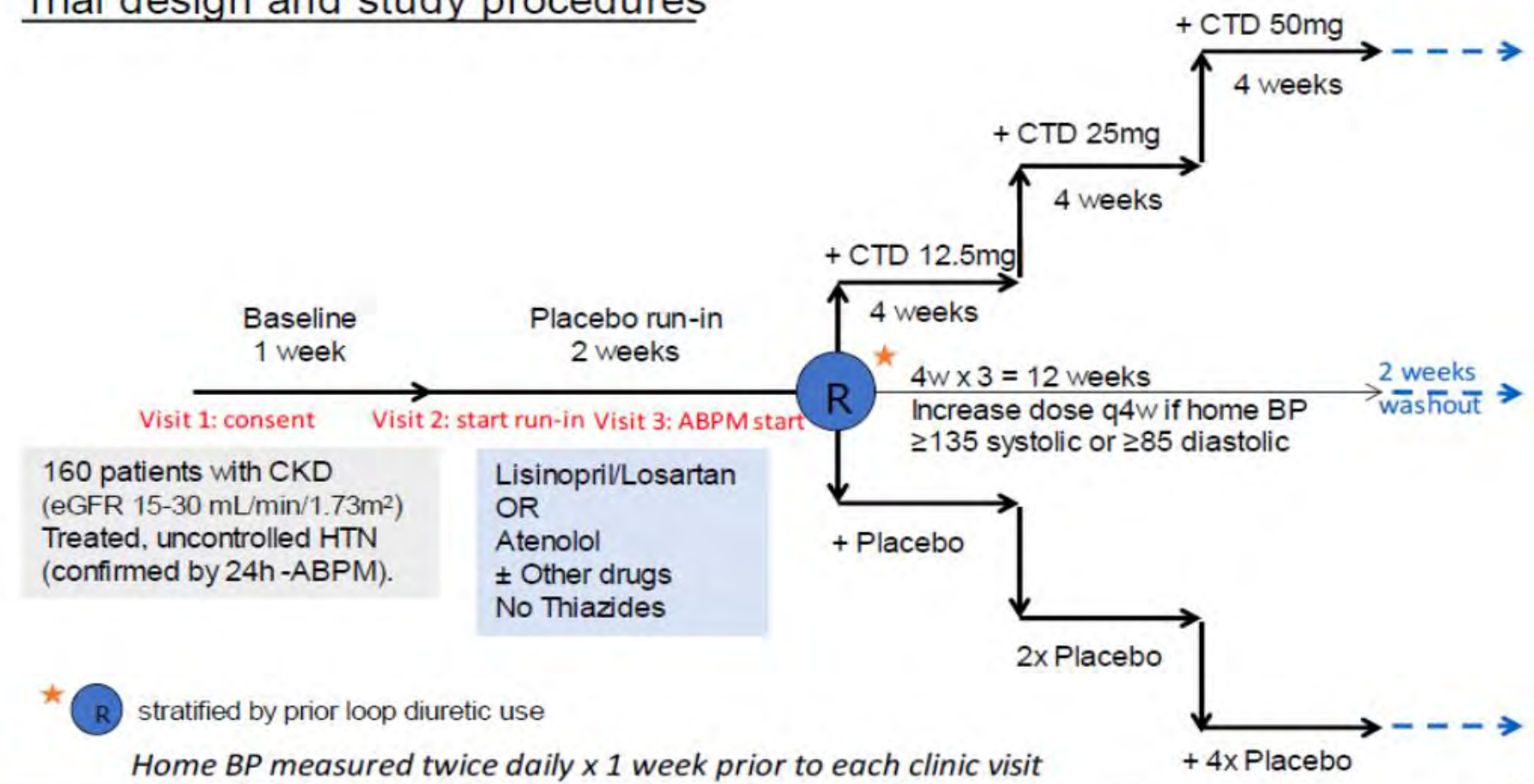


Figure S2

Trial design and study procedures

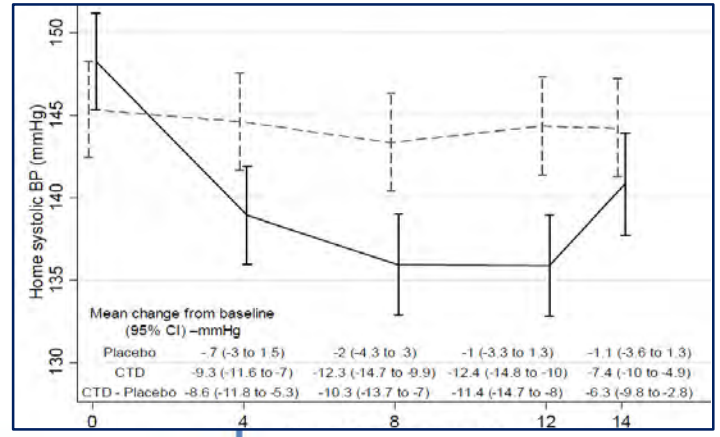


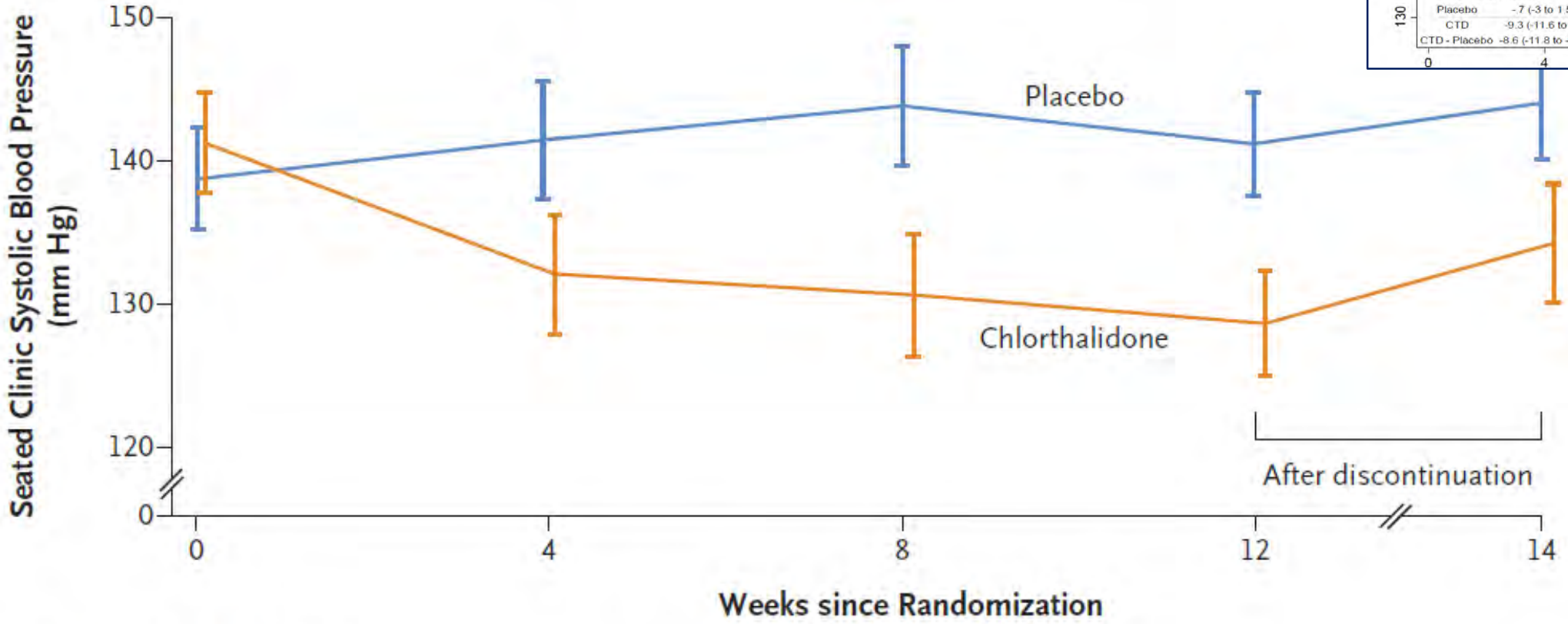
TOD MARKER
•UACR

VOLUME MARKERS
•Renin/aldo
•NT-proBNP
•Body volume

Measurements	Time →	Visit 4: ABPM end And randomize Week 0	Visit 5: titrate 1 Week 4	Visit 6: titrate 2 Week 8	Visit 7: ABPM start / Visit 8: ABPM end Week 12	Visit 9: post washout Week 14
24h ambulatory BP + 24 h urine		x			x	
Home BP (BID x 1w), Clinic BP		x	x	x	x	x
Markers of target organ damage		x	x	x	x	x
Markers of volume		x	x	x	x	x

Visits before randomization are in red font, post randomization but during exposure in blue font, and following washout in green font.

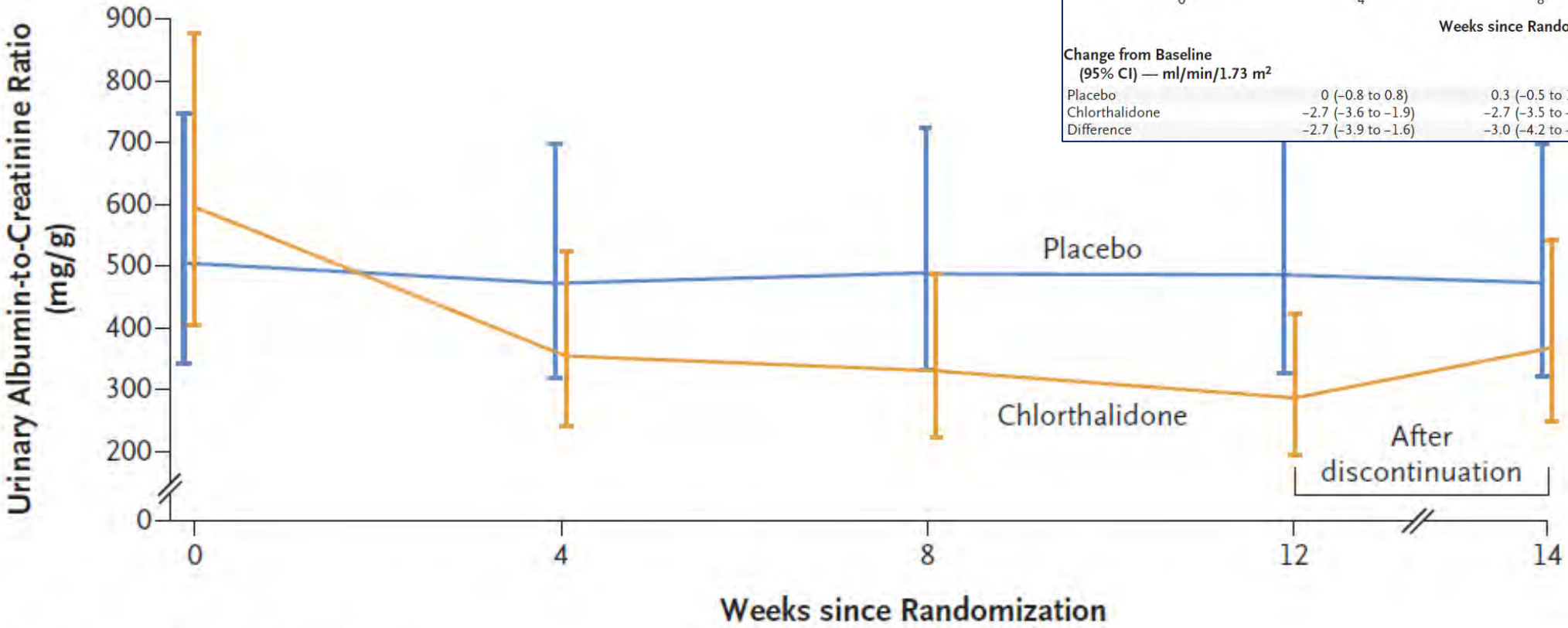


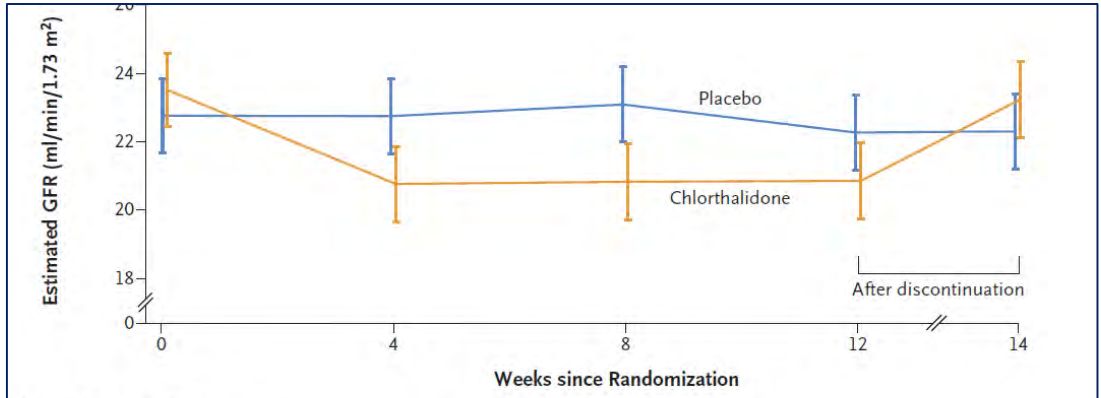


Mean Change from Baseline (95% CI) — mm Hg

Placebo	2.7 (–0.9 to 6.3)	5.1 (1.4 to 8.8)	2.4 (–0.6 to 5.5)	5.3 (1.8 to 8.8)
Chlorthalidone	–9.2 (–12.9 to –5.5)	–10.6 (–14.5 to –6.8)	–12.6 (–15.8 to –9.5)	–7.0 (–10.7 to –3.3)
Difference	–11.9 (–17.1 to –6.7)	–15.7 (–21.0 to –10.5)	–15.1 (–19.4 to –10.7)	–12.3 (–17.5 to –7.2)

A





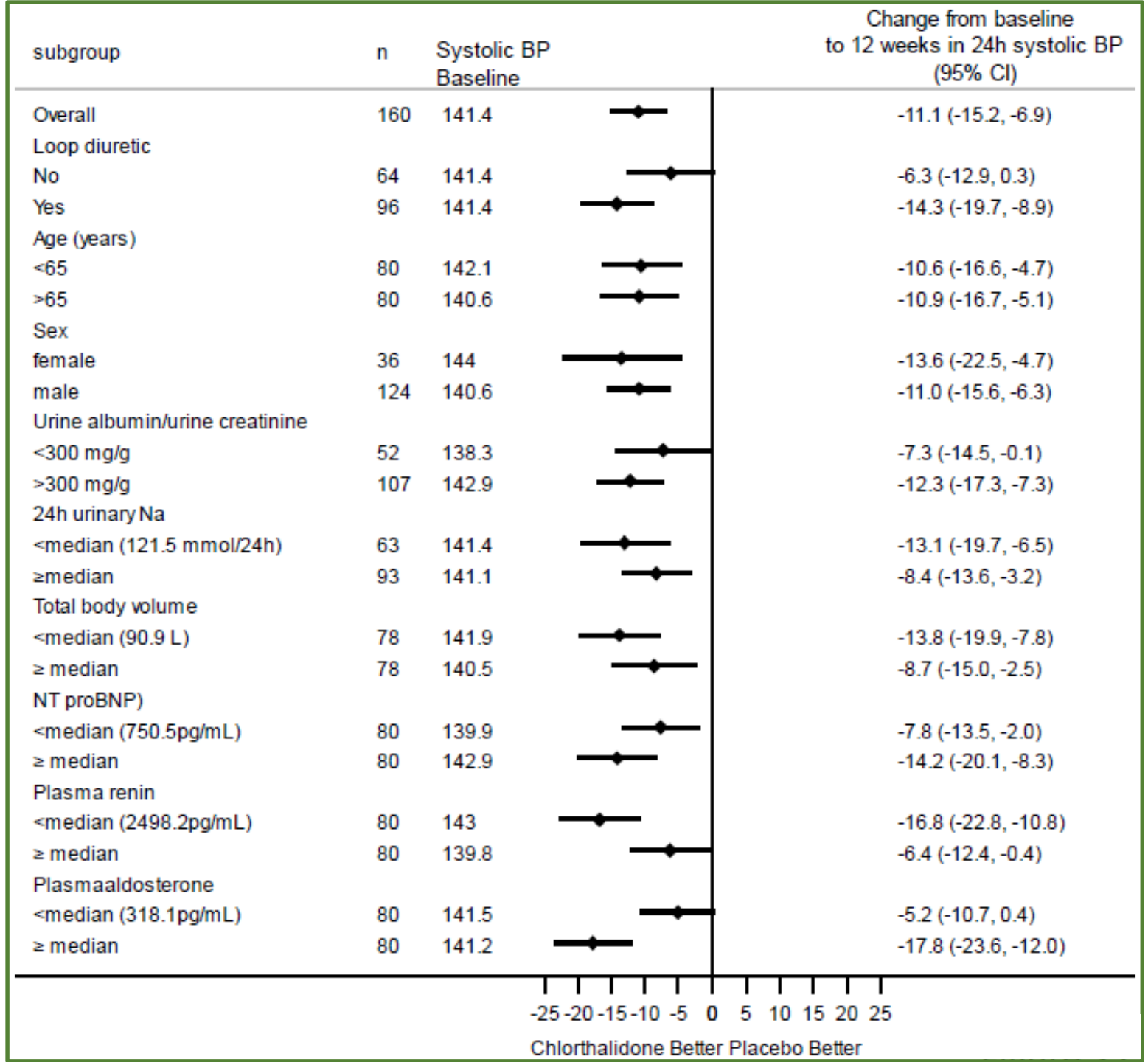
Change from Baseline (95% CI) — ml/min/1.73 m²				
Placebo	0 (−0.8 to 0.8)	0.3 (−0.5 to 1.1)	−0.5 (−1.3 to 0.3)	−0.5 (−1.3 to 0.4)
Chlorthalidone	−2.7 (−3.6 to −1.9)	−2.7 (−3.5 to −1.9)	−2.7 (−3.5 to −1.8)	−0.3 (−1.1 to 0.6)
Difference	−2.7 (−3.9 to −1.6)	−3.0 (−4.2 to −1.9)	−2.2 (−3.3 to −1.0)	0.2 (−1.0 to 1.4)

Percent Change from Baseline (95% CI)				
Placebo	−7 (−20 to 9)	−3 (−17 to 13)	−4 (−18 to 12)	−6 (−21 to 11)
Chlorthalidone	−41 (−49 to −30)	−45 (−53 to −35)	−52 (−59 to −43)	−38 (−48 to −26)
Percentage-point difference	−36 (−49 to −21)	−43 (−54 to −28)	−50 (−60 to −37)	−34 (−48 to −16)

Analyse sous-groupes

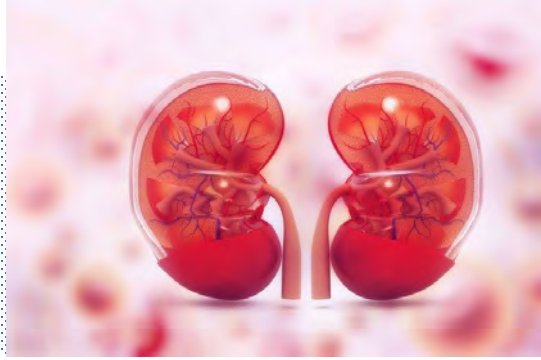
Pas de différence effet selon:

- Diurétique anse
- Âge
- Sexe
- Albuminurie
- Excrétion urinaire
- Volume total
- BNP
- Taux de rénine, aldostérone



subgroup	n	Systolic BP Baseline	Change from baseline to 12 weeks in 24h systolic BP (95% CI)
Overall	160	141.4	-11.1 (-15.2, -6.9)
Loop diuretic			
No	64	141.4	-6.3 (-12.9, 0.3)
Yes	96	141.4	-14.3 (-19.7, -8.9)
Age (years)			
<65	80	142.1	-10.6 (-16.6, -4.7)
>65	80	140.6	-10.9 (-16.7, -5.1)
Sex			
female	36	144	-13.6 (-22.5, -4.7)
male	124	140.6	-11.0 (-15.6, -6.3)
Urine albumin/urine creatinine			
<300 mg/g	52	138.3	-7.3 (-14.5, -0.1)
>300 mg/g	107	142.9	-12.3 (-17.3, -7.3)
24h urinary Na			
<median (121.5 mmol/24h)	63	141.4	-13.1 (-19.7, -6.5)
≥median	93	141.1	-8.4 (-13.6, -3.2)
Total body volume			
<median (90.9 L)	78	141.9	-13.8 (-19.9, -7.8)
≥ median	78	140.5	-8.7 (-15.0, -2.5)
NT proBNP)			
<median (750.5pg/mL)	80	139.9	-7.8 (-13.5, -2.0)
≥ median	80	142.9	-14.2 (-20.1, -8.3)
Plasma renin			
<median (2498.2pg/mL)	80	143	-16.8 (-22.8, -10.8)
≥ median	80	139.8	-6.4 (-12.4, -0.4)
Plasmaaldosterone			
<median (318.1pg/mL)	80	141.5	-5.2 (-10.7, 0.4)
≥ median	80	141.2	-17.8 (-23.6, -12.0)

And so what?



1ère étude démontrant efficacité chlortalidone dans IRC avancée

- ✓Effet sur la pression artérielle
- ✓Effet sur l'albumurie ? Néphroprotection

Limitations:

- ❖ Etude de petite taille, suivi court
- ❖ IECA/ARA2 ou BB comme 1ère ligne?
- ❖ 77% d'hommes – peu de femmes
- ❖40% africains, mais pas d'anticalcique d'office?

TAKE HOME MESSAGES

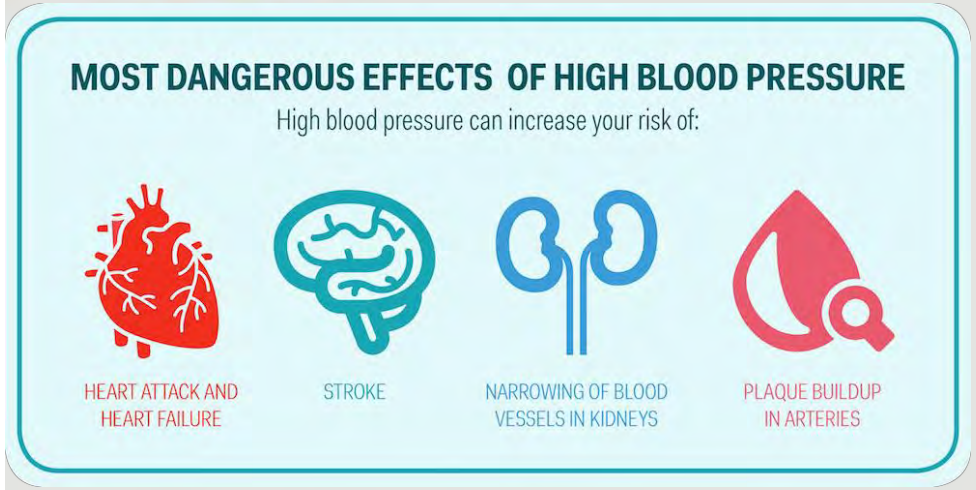
- Depuis 1990, nombre de personnes avec HTA a doublé dans le monde

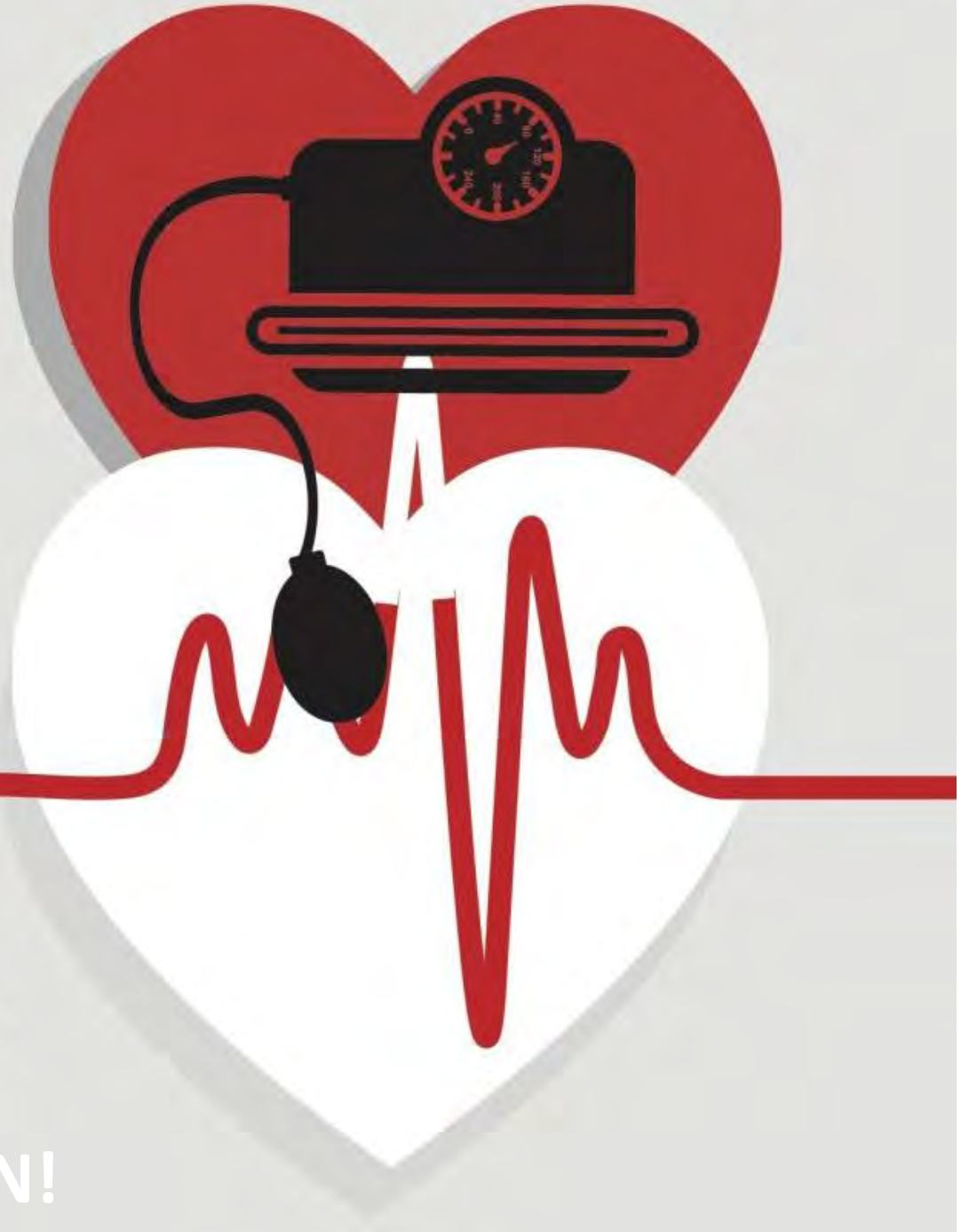
- Dans population 60-80 ans, sans atcd d'AVC, cibles 110-130mmHg, semble diminuer risque événements CV à 3 ans
- Ajouter un nouveau médicament diminue d'avantage SBP, mais moins tenable

- Mauvaise adhésion chez jeune hypertendu augmente événements CV à 10 ans

- Peu de sel mais avec du potassium diminue le risque d'AVC et événements CV
- Avantage des substituts de sel

- La chlortalidone est efficace pour baisser la PA dans l'IRC avancée





17 MAI

Journée mondiale contre l'hypertension

MERCI POUR VOTRE ATTENTION!