Les diurétiques thiazidiques sont'ils mort?

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OUI!

Et NON (pour les non-thiazide)

Conflit d'intérêt potentiel

Type d'affiliation	Nom de la compagnie	Période
Consultant	Servier, Merck, Abbott, Sanofi, Takeda, Shire, Forest Lab., Valeant	2011-2016
Conférencier	Merck, Abbott, Sanofi, Takeda, Shire, Boehringer, Janssen, Amgen, Lilly, Servier, Valeant	2011-2016
Subvention de recherche	Novartis, Servier, Valencia	2011-2016

Objectifs

- Connaître les différences pharmacocinétique entre les diurétiques thiazidiques;
- Connaître les grandes études démontrant les différences en terme de réduction des événements cardiovasculaire entre les diurétiques thiazidiques;
- Savoir faire un choix éclairé d'un diurétique thiazidique.

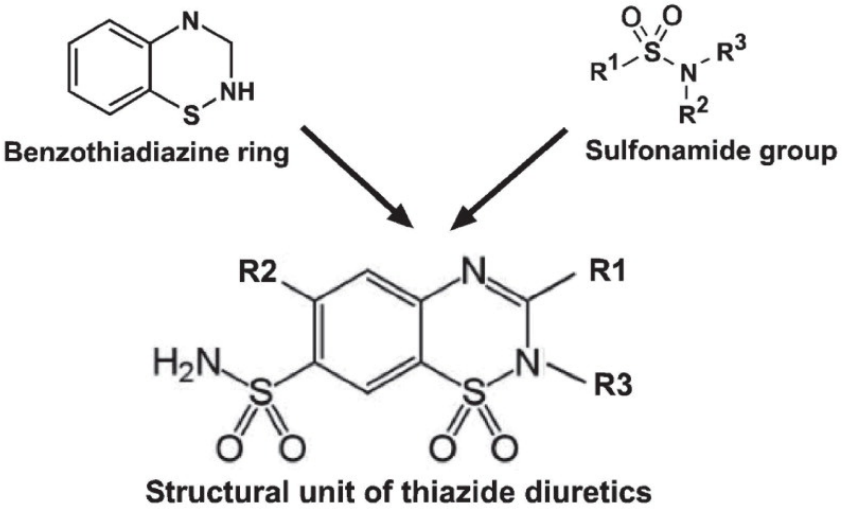
Sujets chauds en HTA

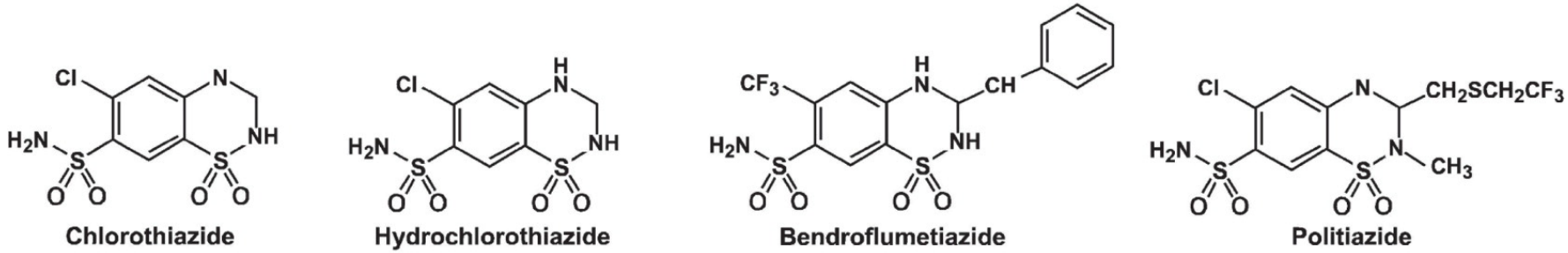
- Tx HTA chez les patients à haut risque cardiovasculaire, chez les personnes âgées…
- Rôle de la neuromodulation en HTA…
- Effets anti-HTA des anti-SGLT2…
- Le meilleur médicament pour le bon patient, médicaments à éviter…
- Les cibles de TA…étude SPRINT…
- Les diurétiques thiazidiques et non-thiazidiques
- …

HTA et diurétiques thiazidiques: sont-ils tous égaux??

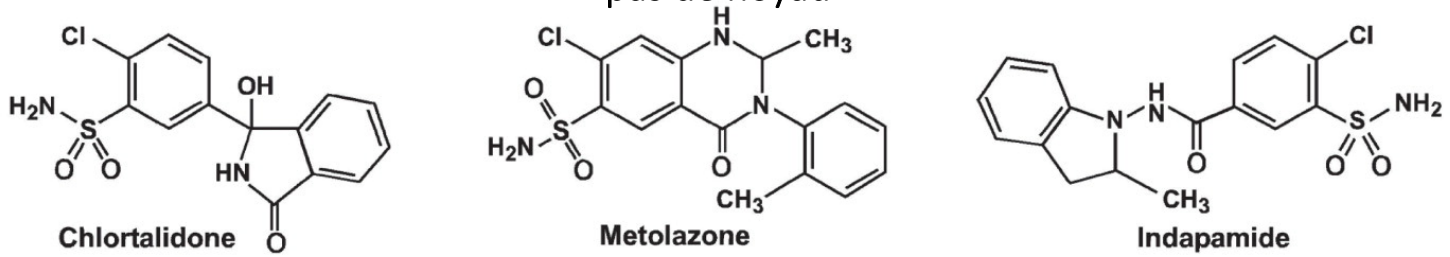
Comparaison indapamide (IND)
Chlorthalidone (CTLD)
hydrochlorothiazide (HCTZ)

Représentation schématique de la structure moléculaire de quelques diurétiques thiazidiques et 'thiazide-like'

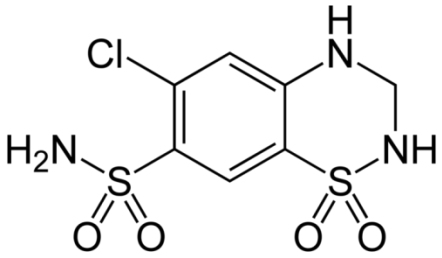




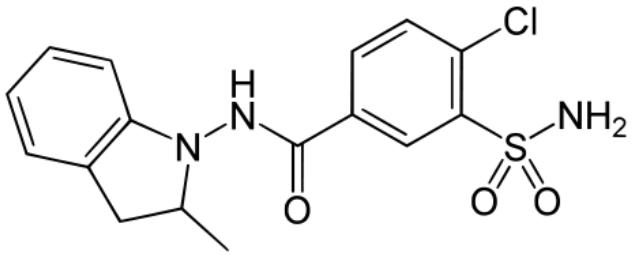
'Thiazide-like': pas de noyau benzothiadiazine



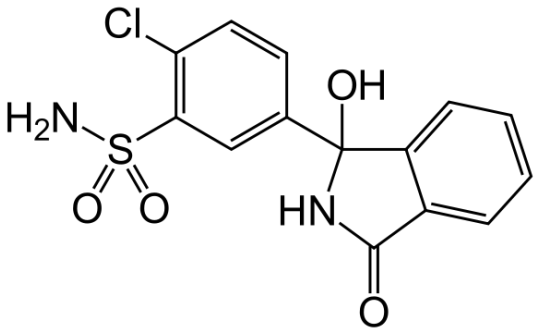
Thiazide et ‘thiazide-like’ prescrits en Amérique du Nord



Hydrochlorothiazide
thiazide



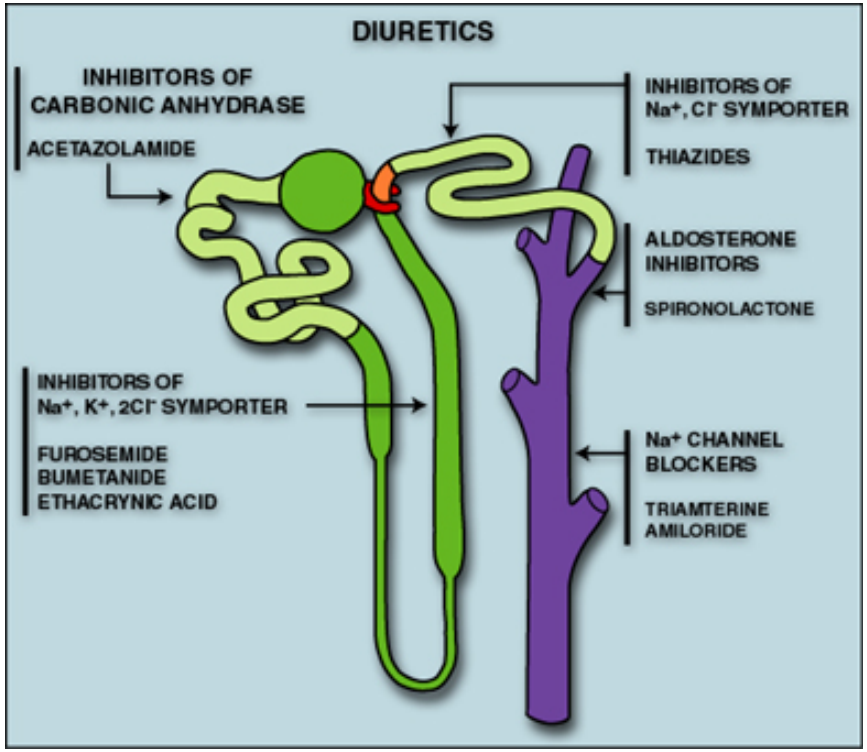
Indapamide
Sulfamoyl benzamide



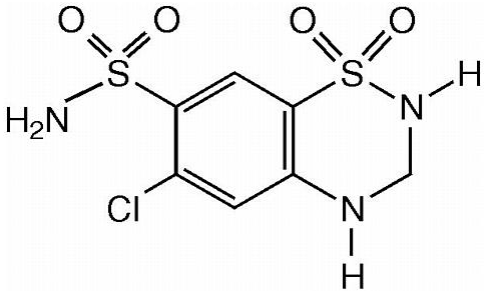
Chlorthalidone
benzensulfonamide

Les thiazidiques ne sont pas une même classe

Agissent tous au même site d'action, mais n'ont pas tous la même durée d'action ou la même structure chimique

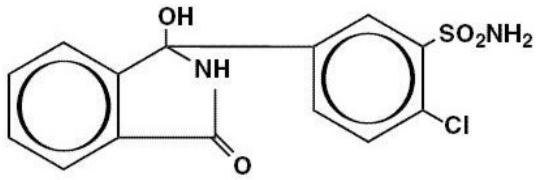


Thiazidique

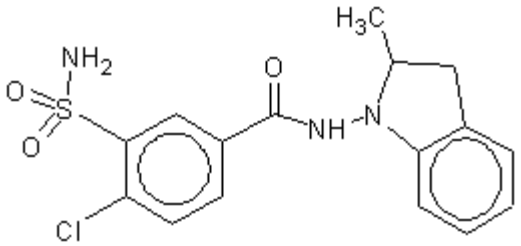


HCTZ

Non-thiazidique

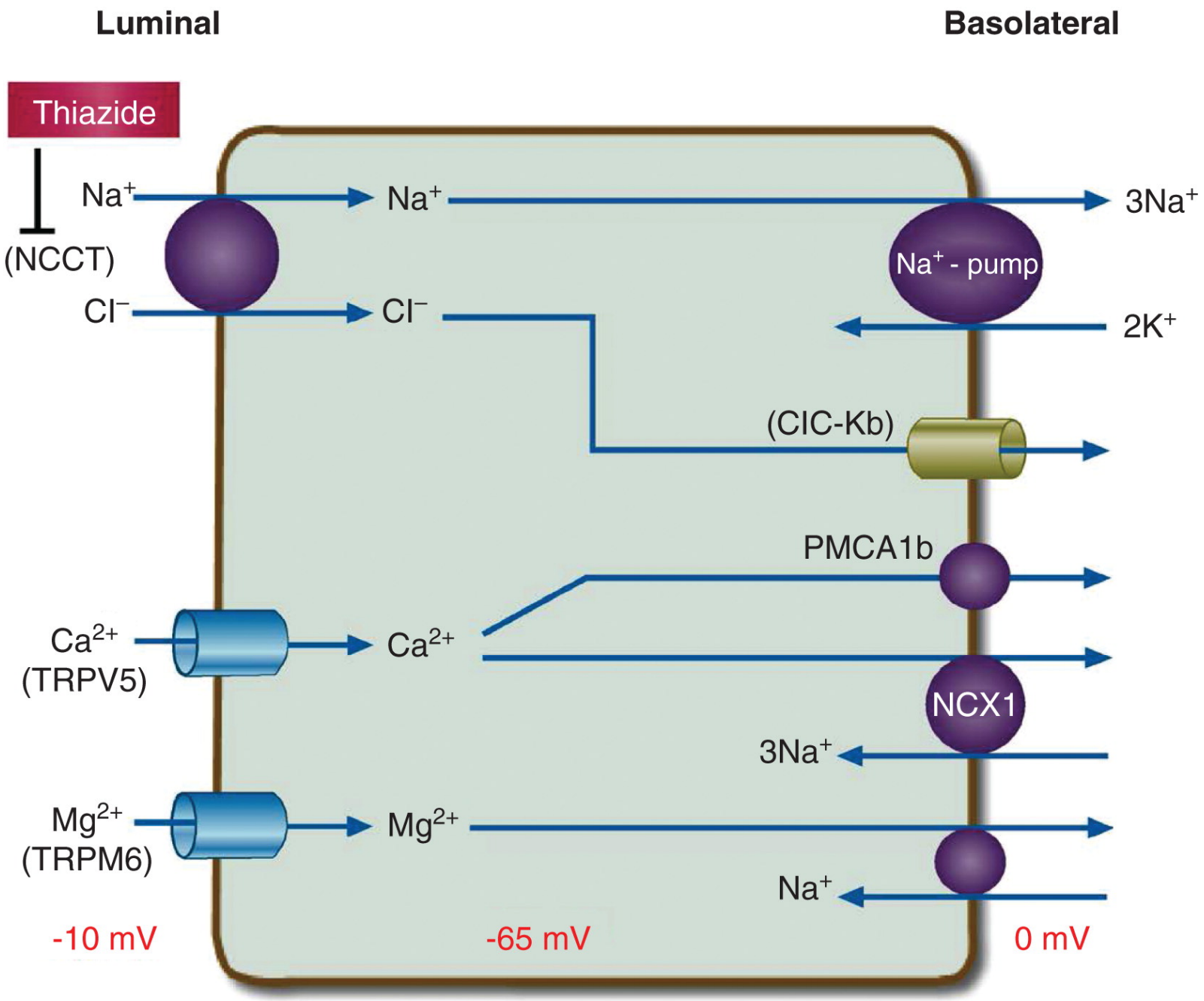


chlorthalidone



indapamide

Mécanisme d'action des thiazides et 'thiazides like'



Mécanismes d'action des thiazides et 'thiazides like' pour **la baisse de TA**

- **BAISSE DU VOLUME PLASMATIQUE**
  - **NATRIURÈSE (1/3?)**
  - **Risque d'hypoK, HypoNa, Hyperuricémie**
- **BAISSE DE LA RÉSISTANCE VASCULAIRE PÉRIPHÉRIQUE (2/3?)**
  - **Bloqueurs de canaux K, Na et/ou calcique?**
- **Effets métaboliques communs (hypoNa, hypoK, hyperuricémie)**
- **EFFETS MÉTABOLIQUES défavorables (dlp, glycémie) sauf indapamide**

Indapamide en HD chez des patients anuriques

Table V. Mean values of body weight, blood pressure, and heart rate in hypertensive hemodialysis patients

Treatment group	Body weight (lb)	Blood pressure (mm Hg)					Heart rate (bpm)	
		Supine		Standing				
		Systolic	Diastolic	Systolic	Diastolic	MABP	Supine	Standing
Placebo period								
Predialysis	167	175	99	172	101	124	92	90
Postdialysis	163	164	93	146	88	112	99	84
Active period								
Predialysis	165	165*	95*	160*	97*	118*	91	86
Postdialysis	160	150*	87*	137*	81*	104*	93	89
Follow-up period								
Predialysis	165	165	100	160	97	120	100	90
Postdialysis	162	148	90	137	85	108	96	93

MABP = mean arterial blood pressure.
*$p < 0.05$.

Conclusions. The findings of this study substantiate our own observations that indapamide does not accumulate in hypertensive patients undergoing maintenance hemodialysis. Furthermore, the calculated t½ of indapamide in the hypertensive hemodialysis patients was found to be very similar to the indapamide t½ that we observed in hypertensive patients with normal and compromised renal function and reported on in the first part of this study (range of t½, 15 to 21 hours). Similar results on the

Effet anti-HTA de l'indapamide
-Effet diurétique 1/3
-Effet vasodil. / BCC? 2/3

(Am Heart J 106:237, 1983.)

Comparaisons diurétiques thiazidiques et non-thiazidiques

- Comparaison IND, CTLD et HCTZ
  - Pharmacocinétique
  - Effets sur la TA
  - Effets métaboliques
  - Effets cliniques: morbidité cardiovasculaire, mortalité

Pharmacocinétique

	Biodisponibilité (%)	Demie-vie (hr)	Durée d'action (hr)
Hydrochlorothiazide	70	6-14	6-15
Indapamide	95	14-25	30
Chlorthalidone	65	40-60	40-72

Expert Opin. Pharmacother. (2014)15 :527-547

Pharmacodynamique

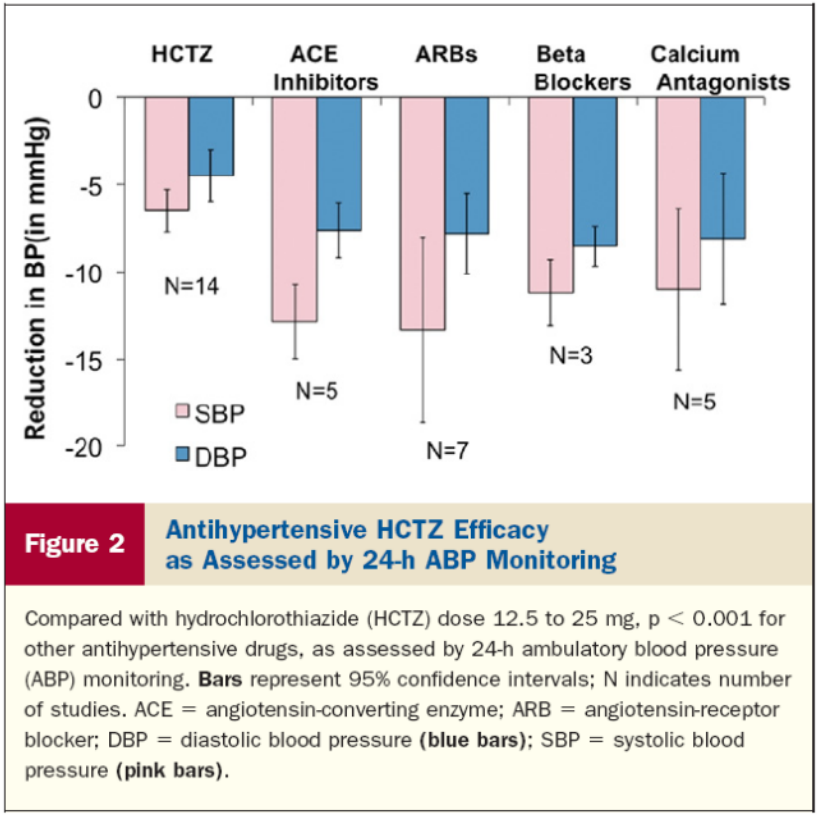


Figure 2 **Antihypertensive HCTZ Efficacy as Assessed by 24-h ABP Monitoring**

Compared with hydrochlorothiazide (HCTZ) dose 12.5 to 25 mg, $p < 0.001$ for other antihypertensive drugs, as assessed by 24-h ambulatory blood pressure (ABP) monitoring. **Bars** represent 95% confidence intervals; N indicates number of studies. ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; DBP = diastolic blood pressure **(blue bars)**; SBP = systolic blood pressure **(pink bars)**.

Ne pas faire!

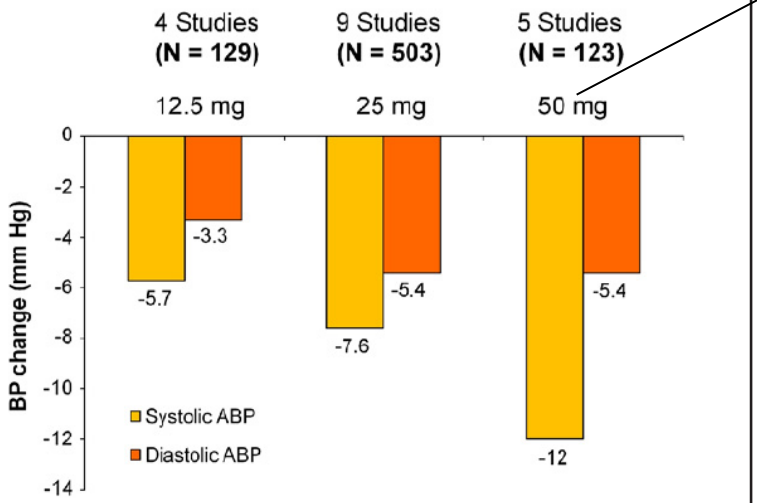
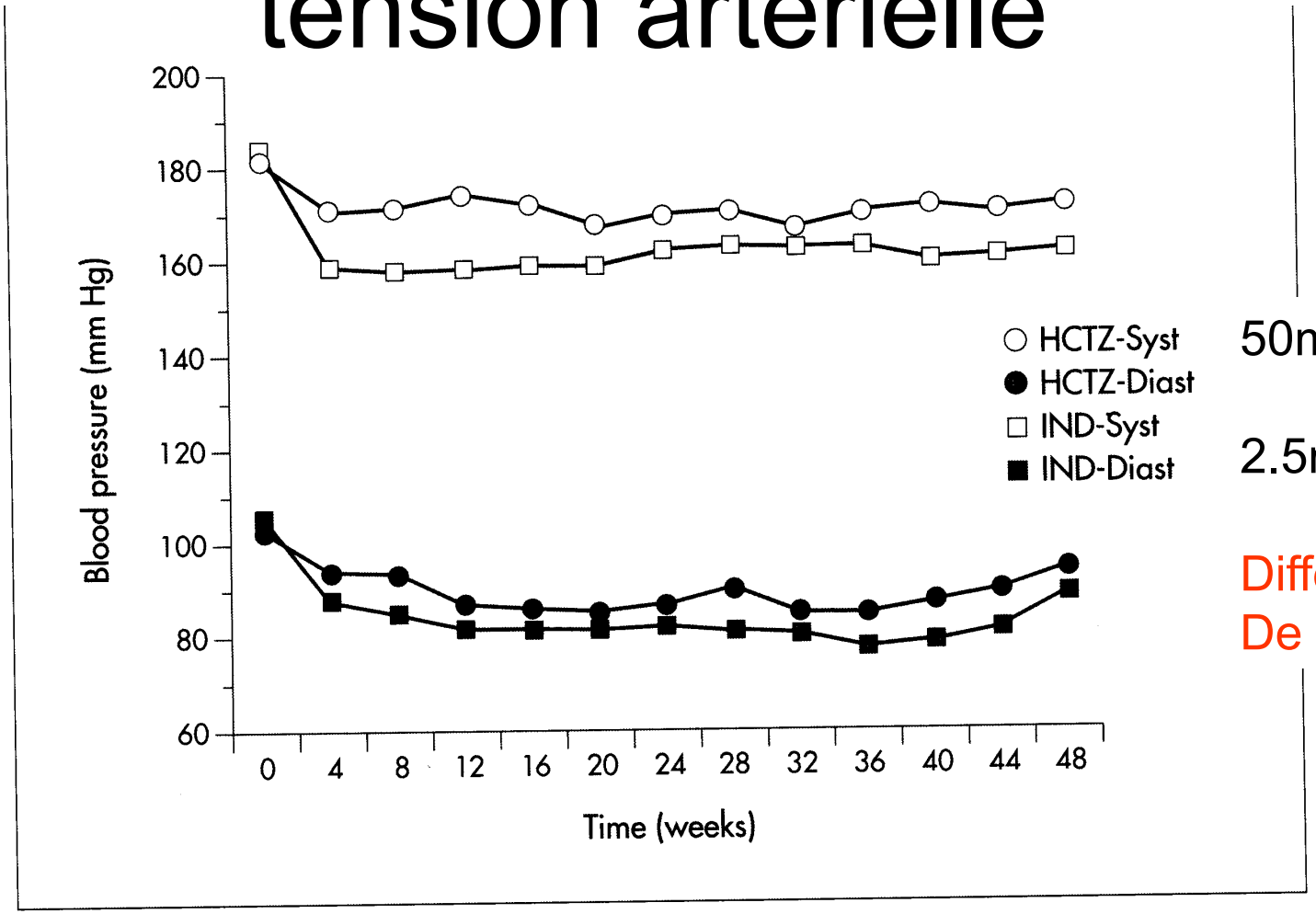


Figure 7 **Dose Response Curve With Hydrochlorothiazide**

Systolic ambulatory blood pressure (ABP) is indicated by **yellow bars**; diastolic ABP is indicated by **red bars**. Compared with HCTZ 25 mg ABP: p = NS versus 12.5 mg (both systolic and diastolic), p = 0.0001 versus 50 mg systolic, and p = NS versus 50 mg diastolic. N indicates number of patients. HCTZ = hydrochlorothiazide; NS = not significant.

Indapamide vs HCTZ – tension artérielle



50mg HCTZ

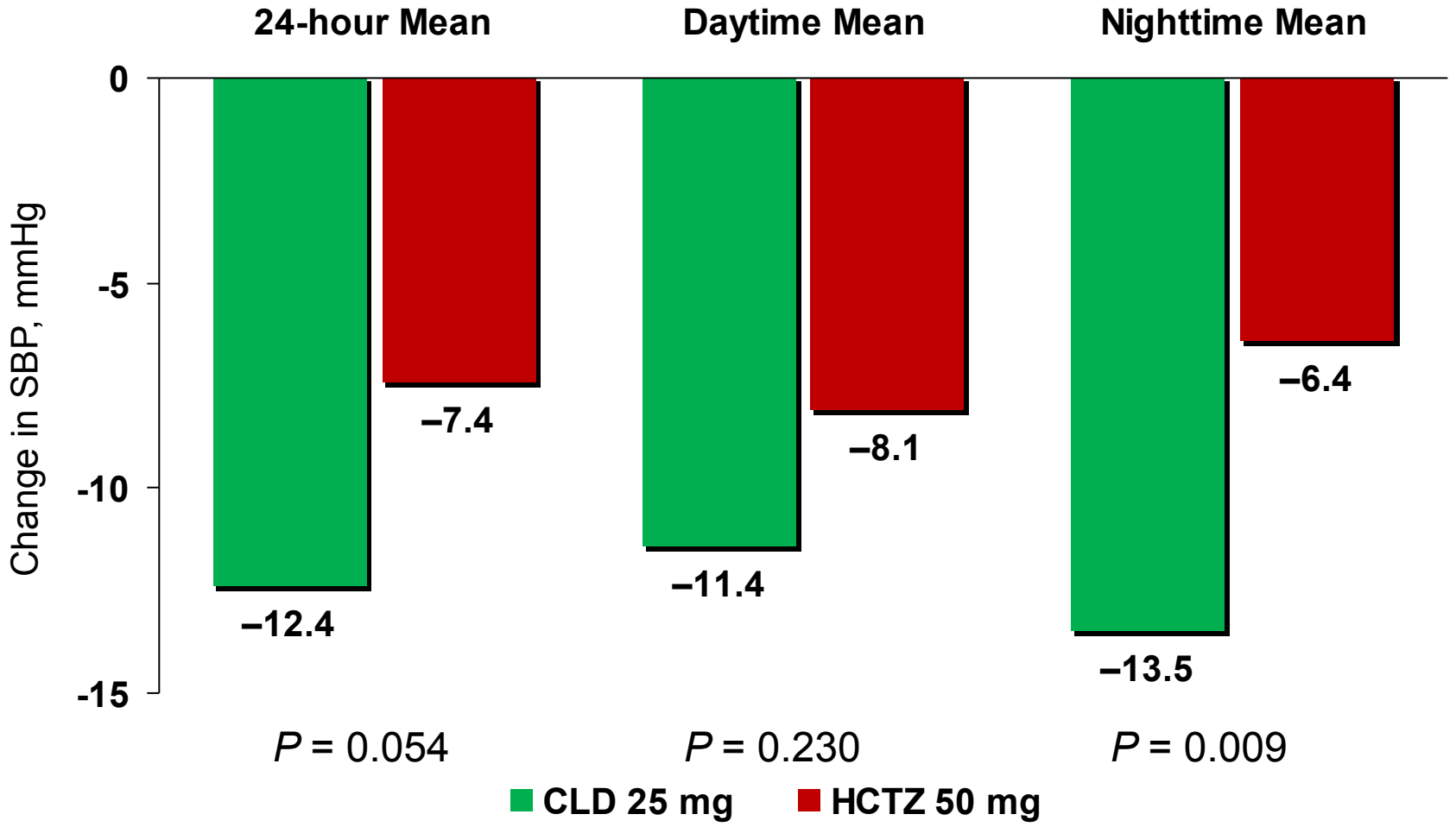
2.5mg ind.

Différence
De 8/5 mmHg

Figure 1. Systolic and diastolic blood pressure values before and during 48 weeks of active treatment with either hydrochlorothiazide or indapamide.

Plante *et al. Amer J Med* 1988;84:98-103.

Chlorthalidone 25 mg vs HCTZ 50 mg: Effects on SBP



Randomized, single-blind, 8-week active treatment crossover study comparing daily CLD 12.5 mg (forced titration to 25 mg) and daily HCTZ 25 mg (forced treatment to 50 mg) in untreated hypertensive patients (N = 24 completed both treatments).
CLD = chlorthalidone; HCTZ = hydrochlorothiazide; SBP = systolic blood pressure

Ernst ME, et al. *Hypertension.* 2006;47:352–358.

Différence de 5 mmHg

Table 1 | Pooled summary of HCTZ and chlorthalidone clinical trials included in the analysis

Antihypertensive trial characteristics	HCTZ ($n = 108$)	Chlorthalidone ($n = 29$)
Total data points (SBP and serum potassium), all subjects[a]	6,063	4,380
Duration (weeks), mean (±s.d.)	10.6 (8.5)	32.2 (21.3)
Dose (mg), mean (±s.d.)	42.7 (37.1)	31.6 (25.2)
Dose (mg), median	33.0	25.0
Dose (mg), range	3–450	12.5–200
Baseline SBP (mm Hg), mean (±s.d.)	162.8 (8.6)	165.8 (9.0)
Change in SBP (mm Hg), mean (±s.d.)	−17 (5.6)	−23 (6.7)
Change in SBP (mm Hg), median	−17	−26
Baseline potassium (mEq/l), mean (±s.d.)	4.22 (0.12)	4.38 (0.14)
Change in potassium (mEq/l), mean (±s.d.)	−0.36 (0.19)	−0.45 (0.16)
Change in potassium (mEq/l), median	−0.31	−0.40

[a]Some studies included dose-titrations and reported SBP and serum potassium data at different time points throughout the study; each subject could therefore provide more than one data point for SBP and serum potassium in these studies.
HCTZ, hydrochlorothiazide; SBP, systolic blood pressure.

Effets métaboliques des thiazides

- Augmentation de la glycémie (sauf indapamide)
  - ***ALLHAT: Circ Cardiovasc Qual Outcomes*. 2012;5:153-162.: nouveaux diabétiques:** 7.5% with chlorthalidone, 5.6% with amlodipine, and 4.3% with lisinopril: augmentation de 3.2%!
- Augmentation du cholestérol total et des triglycérides (sauf indapamide)
- Effets métaboliques communs:
  - HypoKaliémie
  - HyponNatrémie
  - Hyperuricémie

Potassium

Group by Dose Level	Study name	Statistics for each study: Difference in means	Lower limit	Upper limit	p-Value
Dose Equivalent	Bhigjee (Black patients)	0.370	-0.204	0.944	0.206
Dose Equivalent	Bhigjee (Indian Patients)	-0.220	-0.690	0.250	0.358
Dose Equivalent	Elliott	0.100	-1.170	1.370	0.877
Dose Equivalent	Malini	-0.020	-0.170	0.130	0.794
Dose Equivalent	Spence	0.020	-0.311	0.351	0.906
Dose Equivalent		-0.008	-0.136	0.119	0.897
HCTZ Higher	Kreeft	0.300	-1.679	2.279	0.766
HCTZ Higher	Plante b	0.440	-0.834	1.714	0.498
HCTZ Higher		0.399	-0.672	1.470	0.465
INDAP Higher	Krum	-0.250	-0.633	0.133	0.200
INDAP Higher	Radveski	-0.100	-2.892	2.692	0.944
INDAP Higher		-0.247	-0.626	0.132	0.201
Overall		-0.054	-0.296	0.188	0.661

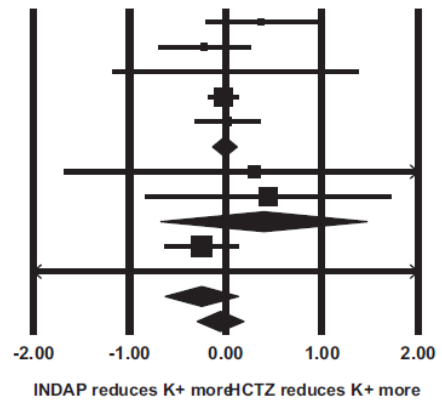
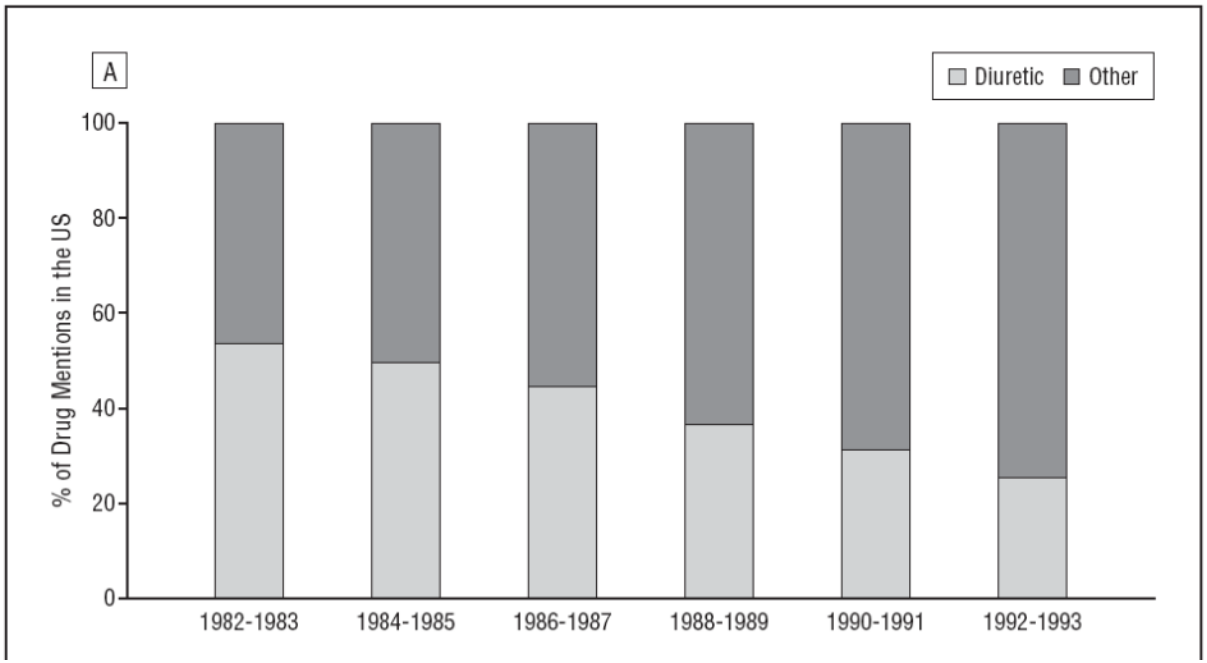


Figure 2. For the effects on serum potassium in mEq/L, random effects, DerSimonian–Laired meta-analysis comparing hydrochlorothiazide (HCTZ) and indapamide (INDAP). There was no heterogeneity across trials. HCTZ-higher trials weighted the overall effect by 1% compared with 10% from INDAP-higher trials, indicating a slight bias toward INDAP causing a greater hypokalemic effect. CI indicates confidence interval.

(*Hypertension*. 2015;65:1041-1046.



Arch Intern Med. 2009;169(20):1851-1856

Table 1. Effects of antihypertensive agents on serum lipid profile

Drug	Total cholesterol*	LDL cholesterol*	Triglycerides*	HDL cholesterol*	Comments
Diuretics	↑[†]	NS (↑[‡])	↑[‡]	NS (↓[§])	
β-Blockers	NS (↑)	NS (↓)	↑	↓	
β-1 selective	NS (↑)	NS (↓[¶])	↓ (↑[¶])	NS (↓)	
ISA	↓	↓[¶]	↓ (↑[¶])	↑ (↓)	
α-Blockers	↓	↓	↓	↑	Effects blunted when used with β-blockers
ACE inhibitors	NS (↓)	NS (↓)	↓	NS (↑)	
Vasodilators	↓	↓	NS**	↑	
Calcium channel blockers	– (↑)	– (↑)	– (↓)	– (↑)	
Sympatholytics	↓	NS (↑)	NS (↑)	↓	
Angiotensin-II receptor blockers	↓	↓	↓	↑	No meta-analysis available

*Data in parentheses are from meta-analysis of only randomized trials.
[†]More prominent in black patients.
[‡]More prominent in men.
[§]In diabetes patients.
[¶]Less prominent than with nonselective β-blockers.
**Statistically significant decrease among black patients.
ACE—angiotensin-converting enzyme; HDL—high-density lipoprotein; ISA—intrinsic sympathomimetic activity; LDL—low-density lipoprotein; NS—not statistically significant.

Tableau 1. Effets du traitement par l'indapamide sur le profil lipido-lipoprotéinique sanguin

Référence	Nb. de malades	Durée	Modification du cholésterol					Modification des triglycérides
			Total	VLDL	LDL	HDL	LDL/HDL	
Gerber et coll. (90)	69	2 mois	NS	NS	NS	NS	→	NS
Colo et coll. (94)	27	2 mois	NS	NS	NS			NS
Cardona (89)	30	4 mois	NS	NS	NS	+29%	baisse*	−28%
Horgan et coll. (95)	17	6 mois	NS					NS
Meyer-Sabellek et coll. (63)	20	6 mois	NS	NS	NS	+16%	baisse	NS
Belin (64)	311	9 mois	NS					NS
Baba et coll. (88)	67	12 mois	NS			NS		
Goto et coll. (68)	98	12 mois	NS			NS		
Leonetti et coll. (72)	173	12 mois	NS			NS		NS
Scalabrino et coll. (91)	15	24 mois	NS	NS	NS	NS	→	NS
Demanet et coll. (96)	12	24-36 mois	NS					

*(VLDL + LDL)/HDL

- Les non-thiazides auraient aussi des effets vasculaires favorables supplémentaires que les thiazides n'ont pas.

Woodman R, Brown C, Lockette W. Chlorthalidone decreases platelet aggregation and vascular permeability and promotes angiogenesis. *Hypertension*. 2010;56:463–470. doi: 10.1161/HYPERTENSIONAHA.110.154476.

Rendu F, Bachelot C, Molle D, Caen J, Guez D. Indapamide inhibits human platelet aggregation *in vitro*: comparison with hydrochlorothiazide. *J Cardiovasc Pharmacol*. 1993;22(suppl 6):S57–S63.

Comparaisons diurétiques thiazidiques et thiazidiques-like

- Basé sur le profil pharmacocinétique et pharmacodynamique et métabolique plus favorable aux non-thiazides, il est plausible que leur effet sur les maladies cardiovasculaires soit plus favorable

- Aucune étude comparative directe

Études avec issues importantes

Diurétique	Étude	Résultats	Commentaires
Chlorthalidone (CTLD)	**ALLHAT**[1] N=33 357	Pas de différence dans l'issue primaire	La TAs était significativement plus élevé avec amlodipine et lisinopril (0.8 et 2 mm Hg, respectivement) vs CTLD
	SHEP[2] N=4736	Réduction de 36% AVC (*P*=0.0003)	NNT=3 pour prévenir 1 AVC; NNT=18 pour prévenir 1 événement CV.
	MRFIT[3] N=12 868	Réduction de 41% mortalité et 58% moins de MCV	Switch HCTZ à CTLD: 28% réduction du risque de mortalité CV (*P*<0.04)
Indapamide (IDP)	**PATS**[4] N=5665	Réduction de 29% des AVC (*P*=0.0009)	NNT=34 pour prévenir 1 AVC
	HYVET[5] N=3845	-30% AVC fatal/nonfatal AVC (*P*=0.06); -39% AVC fatal (*P*=0.05); -21% mortalité de toute cause (*P*=0.02); -23% mortalité CV (*P*=0.06).	Réduction moyenne de TA de 15.0/6.1 mm Hg traitement actif vs placebo.
	PROGRESS[6] N=9000	Réduction de 29% des AVC (*P*<0.0001)	Ajout de périndopril ne change rien, 9/4 mm Hg réduction moyenne de TA
Hydrochlorothiazide (HCTZ)	**OSLO HT Trial**[7] N=785	5x plus de mortalité CV avec HCTZ vs placebo (14 vs 3 (*P*<0.01), respectivement)	HCTZ: réduction de TA 17/10 mm Hg BP vs placebo
	MRFIT[3] N=12 868	Augmentation de 41% mortalité et 58% de MCV	Switch HCTZ à CTLD: 28% réduction du risque de mortalité CV (*P*<0.04)
	ANBP2[8] N=6083	Augmentation Mortalité et MCV (11%, *P*=0.05)	Enalapril vs HCTZ (comparés à **ALLHAT**[1])
	ACCOMPLISH[9] N=11506	Augmentation Mortalité et MCV 20% (*P*<0.0001)	Amlodipine vs HCTZ (tous sur benazepril) (comparés à **ALLHAT**[1])

1. ALLHAT. *JAMA.* 2002;288:2981-2997. **2.** SHEP. *JAMA.* 1991;265:3255-3264. **3.** MRFIT. *Circulation.* 1990;82:1616-1628. **4.** PATS. *Chin Med J.* 1995;108:710-717. **5.** Beckett NS, et al. *N Engl J Med.* 2008;358:1887-1898. **6.** PROGRESS. *Lancet.* 2001 ;358:1033-1041. **7.** Leren P, et al. *Drugs.* 1986;31:41-45. 8. NEJM 2003;348:583-592. 9. ACCOMPLISH.NEJM. 2008;359:2417-2428.

HCTZ: est-ce seulement une question de dose?? NON

HCTZ Trial	Results	HCTZ dose
OSLO HT Trial[1] **N=785**	5x plus de mortalité CV avec HCTZ vs placebo (14% vs 3% (*P*<0.01), respectivement)	50 mg die
MRFIT[2] **N=12 868**	Augmentation de 41% mortalité et 58% de MCV	> 50 mg die 28% < 50 mg die 72%
ANBP2[3] **N=6083**	Augmentation Mortalité et MCV (11%, *P*=0.05)	12.5-25 mg die
ACCOMPLISH[4] **N=11506**	Augmentation Mortalité et MCV 20% (*P*<0.0001)	12.5-25 mg die

Conclusions: aucune dose d'HCTZ ne semble sécuritaire (semble pire à partir de 50 mg die)

1. Leren P, et al. *Drugs.* 1986;31:41-45. **2.** MRFIT. *Circulation.* 1990;82:1616-1628. 3. NEJM 2003;348:583-592. 4. ACCOMPLISH.NEJM. 2008;359:2417-2428.

Étude de Oslo

3. Discussion

The fact that hypertension is a well established coronary risk factor has given faith to the expectation that lowering of elevated blood pressure by means of drugs would be an effective preventive measure against coronary heart disease. In that respect the result of the Oslo Hypertension Study is disappointing, but consistent with other random-

Leren P, et al. *Drugs.* 1986;31:41-45

sponding age groups of women, 2.4 and 2.2. The inability of drug treatment of hypertension to influence the impact of coronary heart disease is clearly a major health problem and a challenge to the medical profession. The reasons for it are unknown, but some speculative suggestions have been proposed. For example, adverse metabolic effects of the commonly used antihypertensives have been supposed to counteract the beneficial effect of pressure lowering. Diuretics have been the main drugs in most of these trials, and several studies have shown adverse effects of these on blood lipids

Leren P, et al. *Drugs.* 1986;31:41-45

antihypertensive drugs. This might be of special importance for the long term treatment of mild hypertension in young people.

Leren P, et al. *Drugs.* 1986;31:41-45

Hypertension

The clinical management of primary hypertension in adults

Clinical Guideline 127

Methods, evidence, and recommendations

August 2011

Recommandations UK

GDG Guideline Development Group

Consequently, the GDG recommended that when thiazide-type diuretics are used for the treatment for primary hypertension, thiazide-like diuretics, e.g. chlortalidone (12.5mg -25mg od) or indapamide (1.5mg SR or 2.5mg o.d.) should be preferred to conventional thiazide diuretics, e.g. bendroflumethiazide or hydrochlorthiazide. The GDG did not consider it necessary to recommend

https://www.nice.org.uk/guidance/cg127/chapter/1-Guidance#choosing-antihypertensive-drug-treatment-2

Opinion d'expert

J. J. DiNicolantonio

Article highlights.

- Evidence for the use of hydrochlorothiazide (HCTZ) is lacking; indeed, two large trials have shown that HCTZ increases cardiovascular death and coronary artery disease compared to placebo and usual care. Despite this fact, HCTZ is the most widely prescribed thiazide diuretic in the US.
- Chlorthalidone and indapamide have the greatest evidence for reducing morbidity and mortality of the thiazide diuretics. These agents should no longer be classified as 'thiazide diuretics' but as 'non-thiazide sulfonamide diuretics' and should be recommended over HCTZ.

This box summarizes key points contained in the article.

OSLO1980 et ANBP2 1997

Expert Opin. Pharmacother. (2012) 13(6):807-814

Chlorthalidone Compared With Hydrochlorothiazide in Reducing Cardiovascular Events

Systematic Review and Network Meta-Analyses

George C. Roush, Theodore R. Holford, Achuta K. Guddati

Abstract—Hydrochlorothiazide (HCTZ) is widely used for hypertension, and prescriptions for HCTZ outnumber those for chlorthalidone (CTDN) by >20-fold in 2 recent surveys. Some have recently expressed a preference for CTDN. However, head-to-head trials testing the effect of the 2 drugs on cardiovascular events (CVEs) are lacking. We conducted a systematic review of randomized trials in which 1 arm was based on either HCTZ or CTDN followed by 2 types of network meta-analyses, a drug-adjusted analysis and an office systolic blood pressure–adjusted analysis. Nine trials were identified: 3 based on HCTZ and 6 based on CTDN. In the drug-adjusted analysis (n=50946), the percentage of risk reduction in congestive heart failure for CTDN versus HCTZ was 23 (95% CI, 2–39; P=0.032); and in all CVEs was 21 (95% CI, 12–28; P<0.0001). In the office systolic blood pressure–adjusted analysis (n=78350), the percentage of risk reduction in CVEs for CTDN versus HCTZ was 18 (95% CI, 3–30; P=0.024). When the reduction in office systolic blood pressure was identical in the 2 arms, the risk for CVEs in HCTZ arms was 19% higher than in its nondiuretic comparator arms (P=0.021). Relative to HCTZ, the number needed to treat with CTDN to prevent 1 CVE over 5 years was 27. In conclusion, CTDN is superior to HCTZ in preventing cardiovascular events. This cannot be attributed entirely to the lesser effect of HCTZ on office systolic blood pressure but may be attributed to the pleomorphic effects of alternative medications or to the short duration of action of HCTZ. (***Hypertension***. **2012;59:1110-1117.)** • **Online Data Supplement**

Table 2. OSBP and Relative Risk for Cardiovascular Outcomes

Trial: Step 1 Comparison	Mean Achieved OSBP			Relative Risk				
	Diuretic Arm	Nondiuretic Arm	Diuretic Minus Nondiuretic Arm	ACM	CHD	CVA	CHF	CVEs
HCTZ trials								
Oslo: HCTZ vs usual care	NA	NA	−17.0	1.07	1.44	0/7†	0/1	0.82
ANBP2: HCTZ vs enalapril	144.0	144.0	0.0	1.11	1.16	1.11	1.18	1.14
ACCOMPLISH: HCTZ vs amlodipine	132.5	131.6	+0.9	1.11	NA	1.19	1.04	1.25‡
CTDN trials								
HDFP: CTDN vs referred care	134.5	143.3	−8.8	0.83†	0.84*	0.64†	NA	0.80‡
SHEP: CTDN vs placebo	142.8	155.1	−12.4	0.87	0.75*	0.64‡	0.46‡	0.68‡
ALLHAT: CTDN vs lisinopril	135.1	137.3	−2.2	1.00	0.95	0.87*	0.84‡	0.91‡
ALLHAT: CTDN vs amlodipine	135.1	136.1	−1.1	1.04	1.00	1.08	0.72‡	0.96
ALLHAT: CTDN vs doxazosin	135.9	138.3	−2.4	0.93	0.97	0.79†	0.56‡	0.83‡
SHELL: CTDN vs lacidipine	143.2	142.0	+1.2	0.81	1.18	1.04	0.83	0.99

(*Hypertension*. 2012;59:1110-1117.)

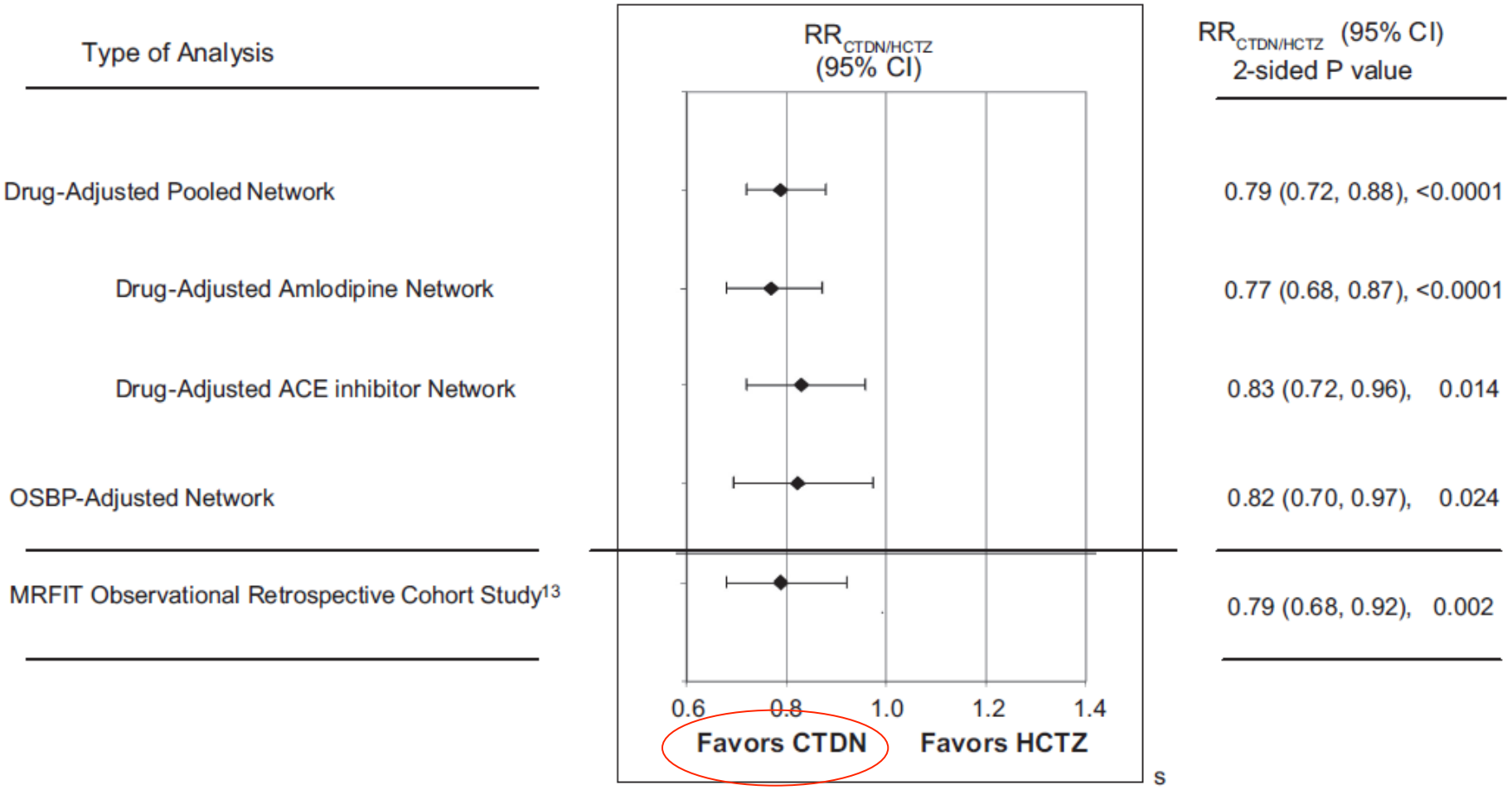


Figure 2. $RR_{\text{chlorthalidone (CTDN)/hydrochlorothiazide (HCTZ)}}$ for cardiovascular events by type of analysis. RR indicates relative risk.

(*Hypertension*. 2012;59:1110-1117.)

Perspectives

That many millions of patients are being treated with an inferior antihypertensive agent becomes more likely in view of these results. Our 21% estimate of RR reduction from CTDN compared with HCTZ is identical to that from the retrospective cohort analysis of MRFIT, which used a different study design and a different population. Because CTDN's superiority was found in 2 different types of network analyses, and because network analyses have been thought to be methodologically superior to observational studies,[21] the present results move support for CTDN to a level above that of observational studies but not yet at the level of a head-to-head randomized trial. For some, these results imply that such a trial is no longer necessary, whereas, for others, it becomes even more urgent. New pharmaceutical preparations of CTDN, including scored 25-mg tablets and combinations with other common antihypertensives, would erase the practical advantage of HCTZ and would be more in accord with the best available evidence. These results support previous recommendations[7] that, in trials comparing medications with thiazide-like diuretics, the more appropriate comparator is CTDN. Finally, the inferiority of HCTZ cannot be explained entirely on the basis of HCTZ's lesser effect on OSBP. Rather, the reasons for HCTZ's inferiority may include pleomorphic effects of alternative medications or HCTZ's short duration of action, which may leave critical nighttime BP inadequately controlled.

(*Hypertension*. 2012;59:1110-1117.)

Effects of Thiazide-Type and Thiazide-Like Diuretics on Cardiovascular Events and Mortality

Systematic Review and Meta-Analysis

Rik H.G. Olde Engberink, Wijnanda J. Frenkel, Bas van den Bogaard, Lizzy M. Brewster, Liffert Vogt, Bert-Jan H. van den Born

***Hypertension*. 2015;65:1033-1040**

Primary Analysis

In comparison with placebo, TT (RR, 0.67 [0.56–0.81]; I^2=37%) and TL diuretics (RR, 0.67 [0.60–0.75]; I^2=0%) significantly reduced the number of CVE (Figure S2). In addition, TT and TL diuretics significantly reduced the number of cerebrovascular events (TT: RR, 0.52 [0.38–0.69]; I^2=25% and TL: RR, 0.68 [0.57–0.80]; I^2=0%) and heart failure (TT: RR, 0.36 [0.16–0.84]; I^2=14% and TL: RR, 0.47 [0.36–0.61]; I^2=0%) compared with placebo. In contrast to TT diuretics, treatment with TL diuretics also resulted in a significant reduction of coronary events (RR, 0.76 [0.61–0.96]; I^2=0%) and all-cause mortality (RR, 0.84 [0.74–0.96]; I^2=0%).

Next, we compared thiazide diuretics with studies that used other antihypertensive therapy as control treatment. TT diuretics did not show a significant benefit on any of the outcomes. TL diuretics, however, more effectively reduced heart failure (RR, 0.71 [0.53–0.95]; I^2=91%), and showed similar risk reductions for CVEs (RR, 0.86 [0.72–1.04]; I^2=88%), cerebrovascular events (RR, 0.93 [0.86–1.01]; I^2=0%), coronary events (RR, 1.01 [0.95–1.07]; I^2=0%), and all-cause mortality (RR, 1.00 [0.95–1.05]; I^2=0%) when compared with studies that used other antihypertensive therapy as control treatment.

***Hypertension*. 2015;65:1033-1040**

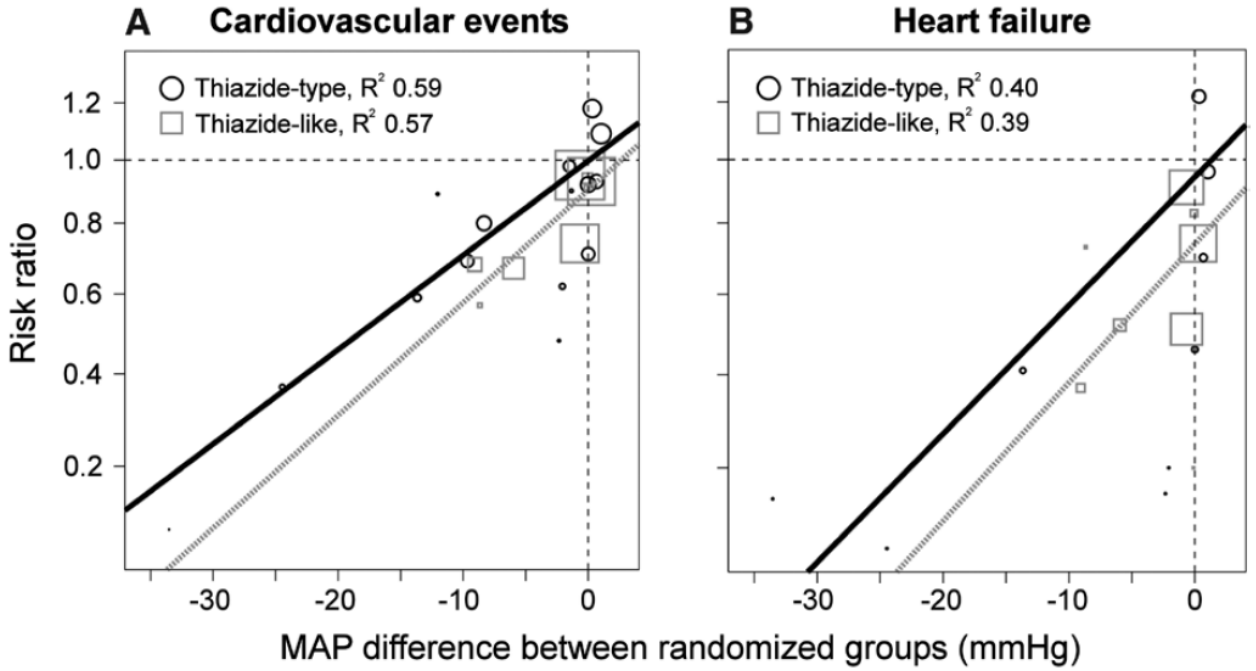


Figure. Blood pressure (BP) adjusted analysis. Association between the risk ratios of cardiovascular events (CVEs) and heart failure, and the difference in achieved mean arterial pressure (MAP) reduction between treatment and control group. Circles and squares represent individual trials and have a size proportional to the calculated weight. Analyzing *y*-intercept, thiazide-like diuretics showed a significant additional 12% risk reduction of CVE (**A**; *P*=0.049) and a 21% risk reduction of heart failure (**B**; *P*=0.023) when compared with thiazide-type diuretics, independent of office BP reduction. A significant extra risk reduction for CVE (*P*=0.028) was seen when larger MAP reductions were achieved with thiazide-like diuretic treatment.

***Hypertension*. 2015;65:1033-1040**

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Systematic Review and Meta-Analysis

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Novelty and Significance

What Is New?

- This meta-analysis provides evidence that thiazide-like (TL) diuretics are superior to thiazide-type (TT) diuretics in preventing heart failure and cardiovascular events when comparable blood pressure reductions are achieved.
- Our data suggest that TT and TL diuretics have a similar incidence of adverse events when comparable blood pressure reductions are achieved.

What Is Relevant?

- TT and TL diuretics are among the most commonly prescribed drugs for the treatment of hypertension. Although most guideline do not distinguish between these 2 classes, prescriptions for TL diuretics are far outnumbered by prescriptions for TT diuretics. As the available evidence from indirect comparisons suggest that TL diuretics are superior to TT diuretics, millions of patients may receive suboptimal treatment.

Summary

TL diuretics seem to be superior when compared with TT diuretics in preventing heart failure and cardiovascular events when comparable blood pressure reduction are achieved.

Hypertension. 2015;65:1033-1040

Cardioprotective Effect of Thiazide-Like Diuretics: A Meta-Analysis

Peng Chen, Sandip Chaugai, Fujie Zhao, and Dao Wen Wang

CONCLUSIONS

Pooled analyses of available RCTs suggests that application of TD in hypertensive patients results in a reduction in the risk of CVs (24%), especially heart failure (38%). However, the beneficial effects are mainly confined to thiazide-like diuretics with only a modest trend toward protection observed with thiazide-type diuretics, suggesting that thiazide-like diuretics offer greater cardioprotection. Considering the high prevalence of hypertension globally, widespread use of thiazide-like diuretics may be expected to improve clinical outcomes and optimize the cost of care. The results of this study provide a convincing evidence to improve the status of thiazide-like diuretics in treatment of hypertension.

Études récentes avec thiazides et thiazides-like

-HOPE3 2016: Atacand + HCTZ chez le patient à risque intermédiaire: Négatif

-SPRINT 2015: Chlorthalidone surtout dans le traitement intensif: Positif

-HYVET 2008: Indapamide vs placebo chez la personne âgée: Positif

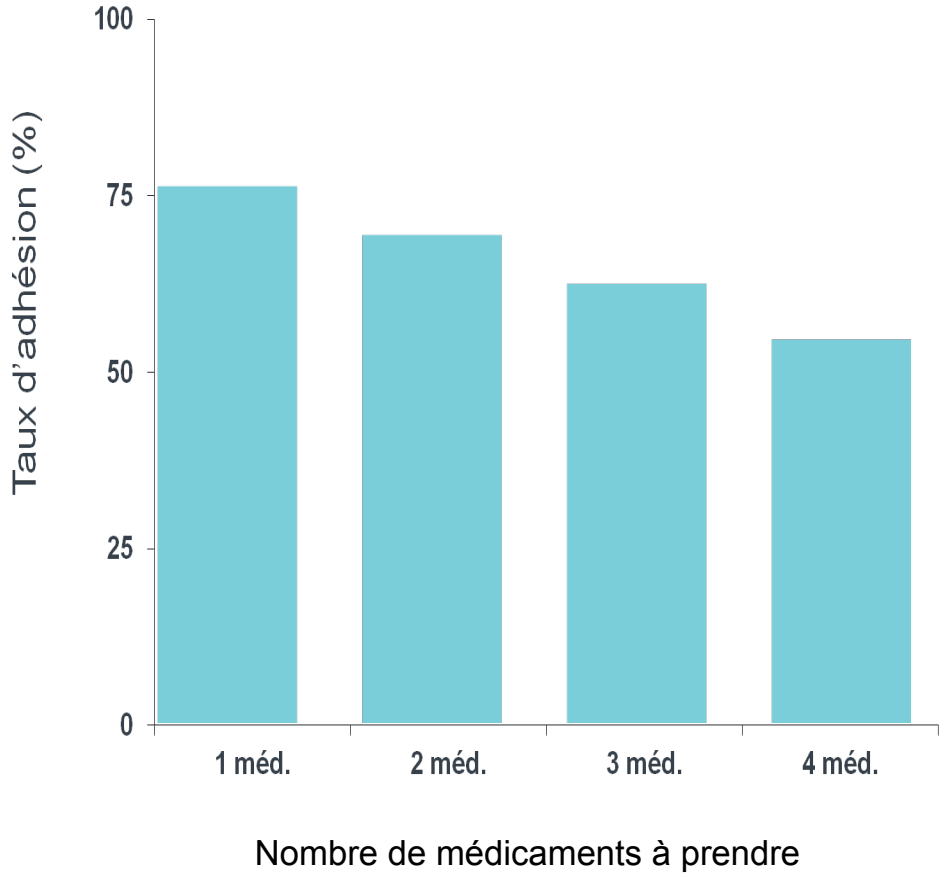
-Accomplish: IECA + amlodipine vs HCTZ: Négatif

Comparaisons diurétiques thiazidiques et thiazidique-like

- Comparaison IND, CTLD et HCTZ
  - Pharmacocinétique: IND, CTLD > HCTZ
  - Effets sur la TA: IND, CTLD > HCTZ
  - Effets métaboliques: IND > CTLD et HCTZ
  - Effets cliniques: morbidité, mortalité: pas de comparaison directe: IND, CTLD > HCTZ
- L'indapamide et CTLD semblent globalement supérieures comparées à l'HCTZ!!
- L'indapamide semble se démarquer car moins d'effets métaboliques
- Conclusion: éviter HCTZ, préférer CTLD et surtout indapamide

- Éviter HCTZ: Enjeux principaux:
  - Effets néfastes: Briser les combos avec HCTZ (défavorise observance)
  - VS
  - Effets bénéfiques: Fonder ses traitements sur les données probantes positives avec indapamide et chlorthalidone (favoriser résultats), chronothérapie?

L'ADHÉSION AU TRAITEMENT ANTIHYPERTENSEUR *DIMINUE* AVEC *L'AUGMENTATION* DU NOMBRE DE COMPRIMÉS À PRENDRE



Fung V, et al. *Clin Ther* 2007;29:972-84.

PECH : TRAITEMENT DE L'HYPERTENSION SYSTOLO-DIASTOLIQUE EN *L'ABSENCE* D'AUTRES FACTEURS CONTRAIGNANTS

CIBLE < 140/90 mmHg

TRAITEMENT INITIAL ET MONOTHÉRAPIE

Modification des habitudes de vie

L'association de deux médicaments de première intention peut être envisagée comme traitement initial si la tension artérielle dépasse les valeurs cibles de ≥ 20 mmHg pour la TAS ou de ≥ 10 mmHg pour la TAD.

Choix de combos avec indapamide et chlorthalidone

- Tous les combos sont faits avec l'hydrochlorothiazide pour des raisons historiques.
- Sauf:
  - Périndopril-indapamide (Coversyl plus)
    - Doses: 4/1.25 et 8/2.5
  - Azylsartan-chlorthalidone (Edarbyclor):
    - Doses: 40/12.5, 40/25

Conclusions

- Aucune étude ne supporte l'utilisation de l'HCTZ
- Éviter HCTZ tel que recommandé par le NICE depuis 2011
- Préférer chlorthalidone et indapamide
- Au total: avantage pour l'indapamide car moins d'effets métaboliques

Merci de votre attention!!

Questions ?

Commentaires ?