Nouveaux médicaments de l'HTA : nouveaux monocomposants? ou nouvelles associations?

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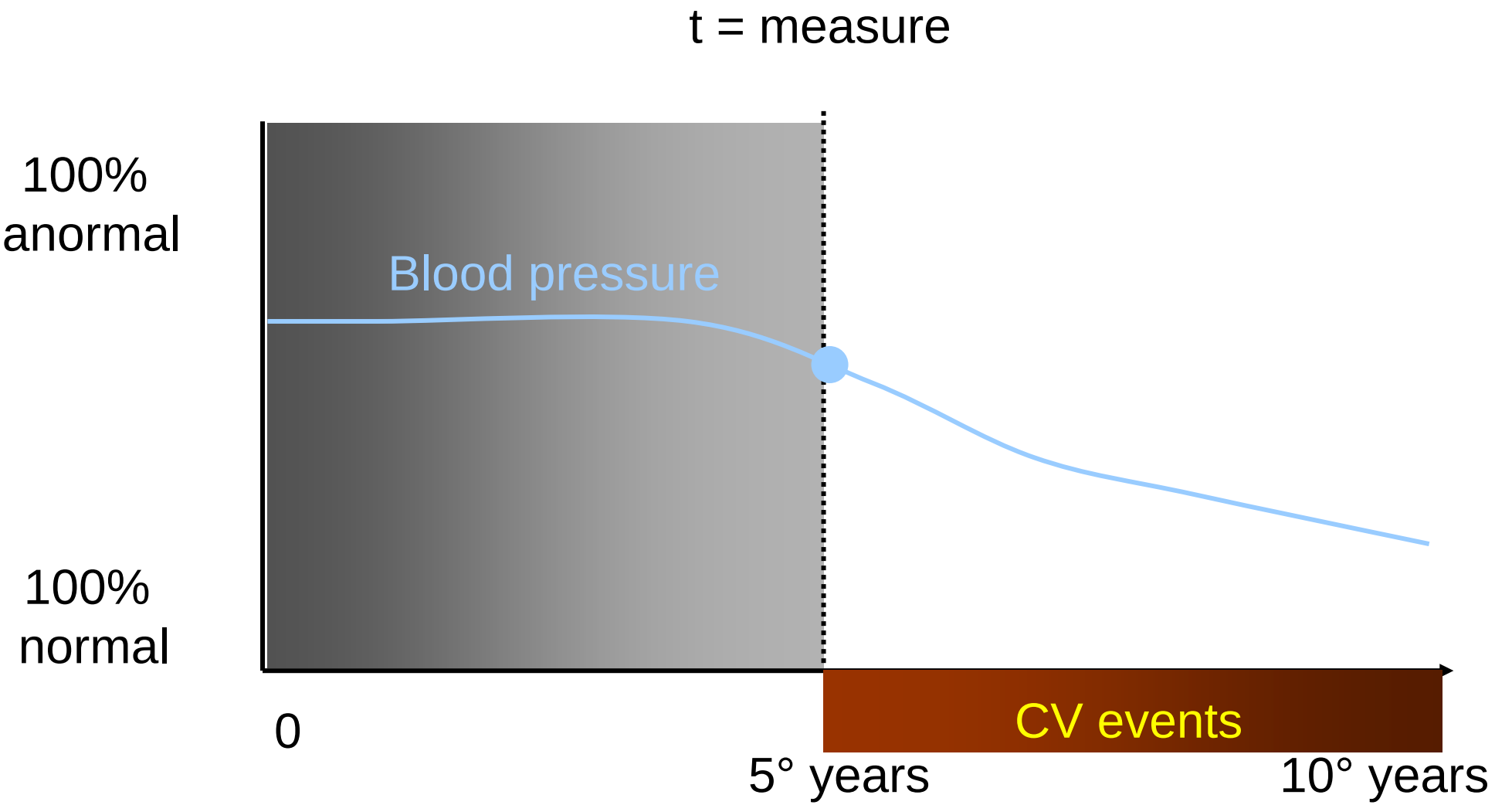
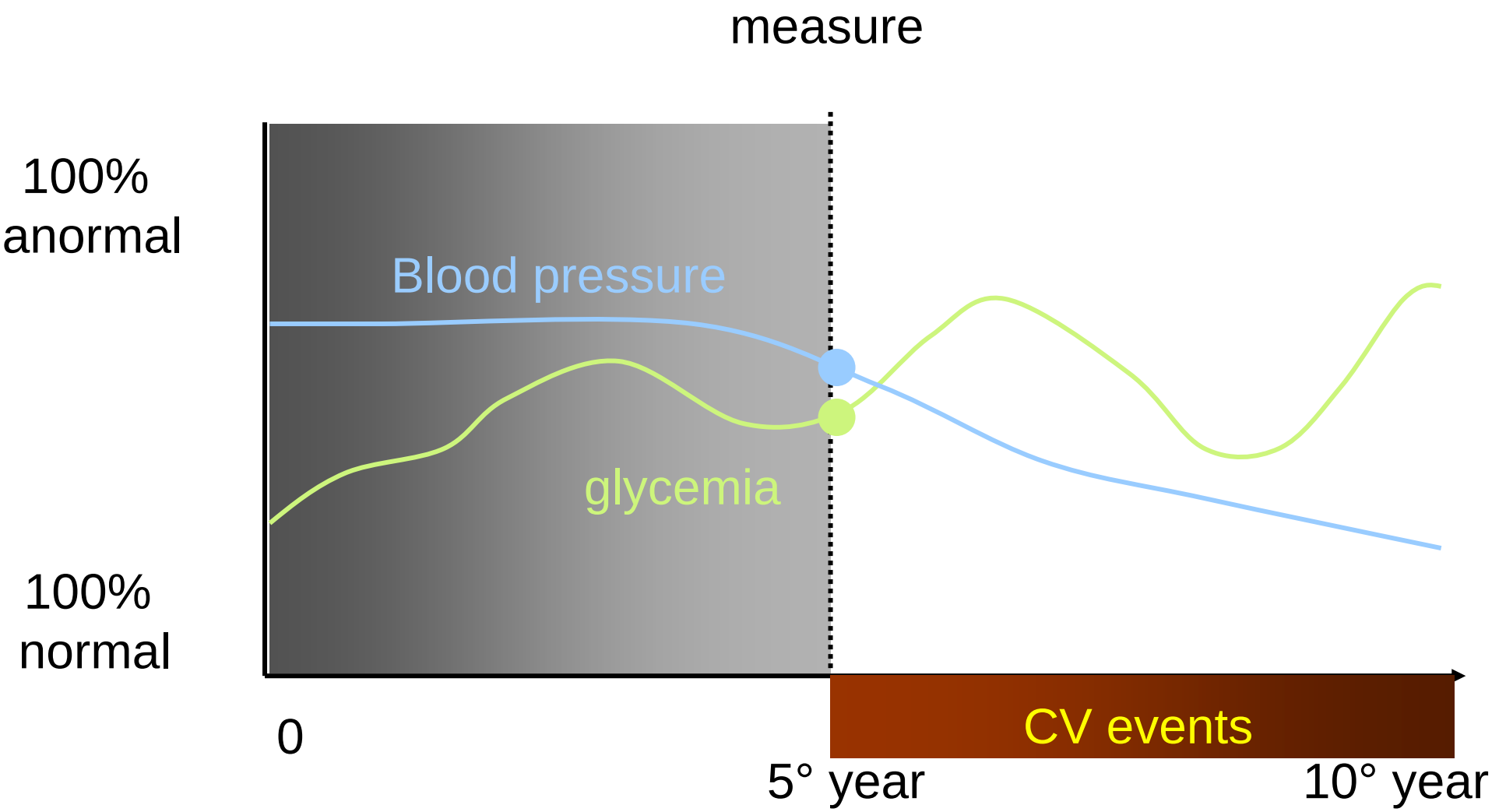
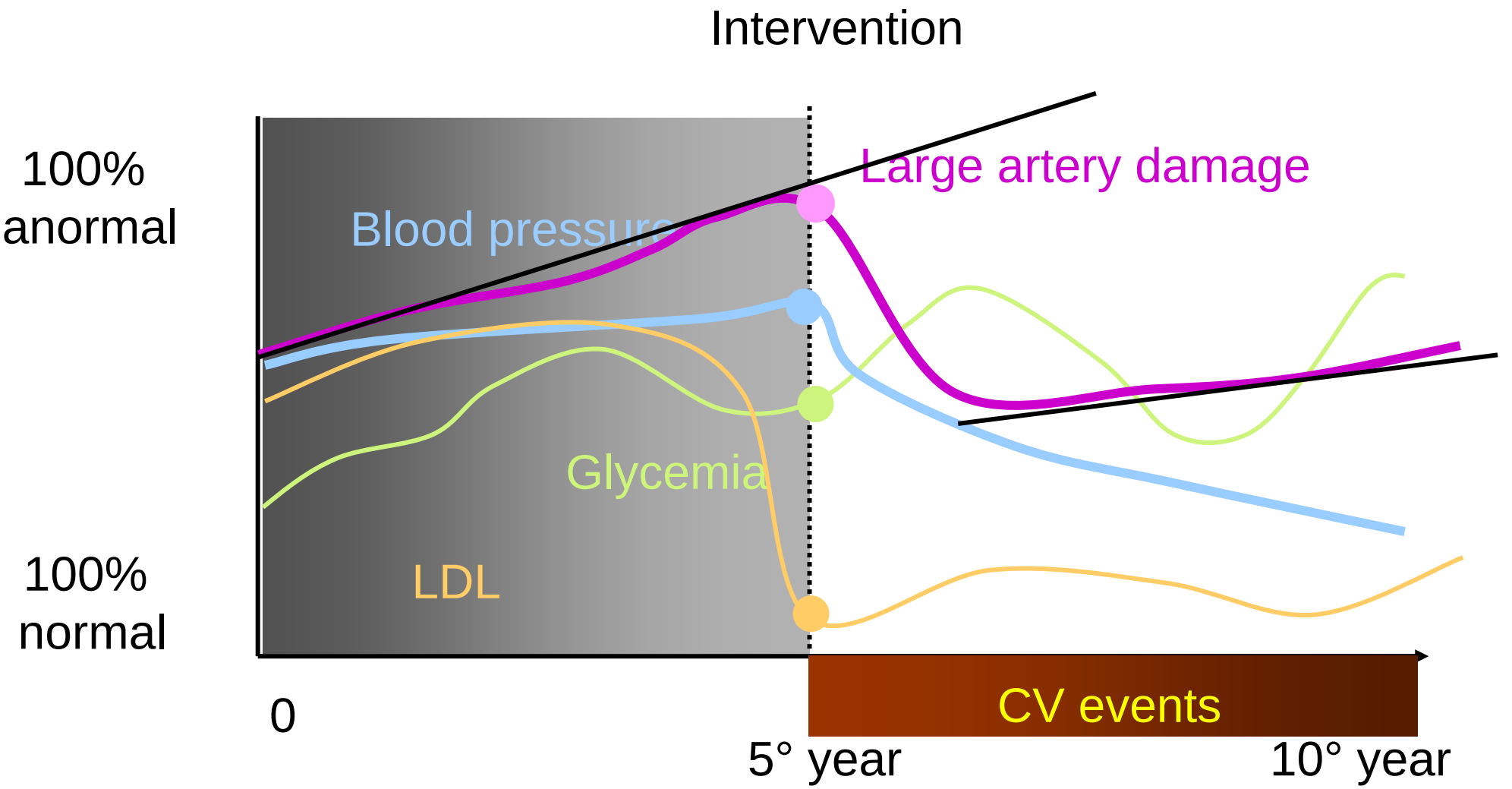
Target organ damage is an integration of time*multiple risk factors



Target organ damage is an integration of time*multiple risk factors



Target organ damage is an integration of time*multiple risk factors



Approches conceptuelles du traitement de l'HTA (I)

1. Normalisation insuffisante (< 30% HT et <10% HTet DT2)
   - observance insuffisante
   - efficacité insuffisante : cibles, contre-régulations
   - surtout dans des populations où le risque est élevé (DT2+IRC) donc à fort gain de traitement

2. « Shift of paradigm » PAD → PAS
   60% des ISH n'ont jamais fait d'IDH

3. Co-morbidités : DT2, obésité, insuffisance coronaire, artérite, insuffisance cardiaque, …

Approches conceptuelles du traitement de l'HTA (II)

4. Atteinte des organes cibles et biomarqueurs

- lesquels?

  - HVG, microalbuminurie
  - ↗ rigidité artérielle, ↗ EIM carotidienne, dysfonction endothéliale
  - biomarqueurs d'atteinte vasculaire : CRP, etc…

- critères de substitution?

Approches conceptuelles du traitement de l'HTA (III)

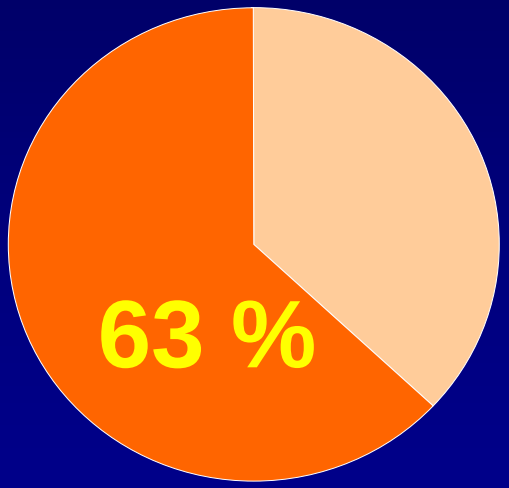
1. Normalisation insuffisante
2. « Shift of paradigm » PAD → PAS
3. Co-morbidités : DT2, obésité, insuffisance coronaire, artérite, insuffisance cardiaque, …
4. Atteinte des organes cibles et biomarqueurs

Associations d'anti-hypertenseurs

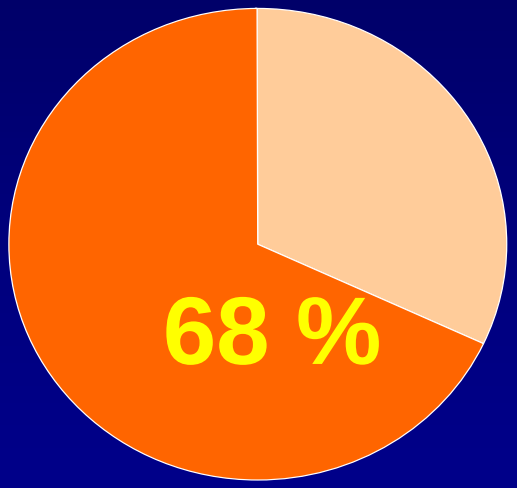
The HOT study

% de patients nécessitant une association anti-HTA pour atteindre la PAD cible

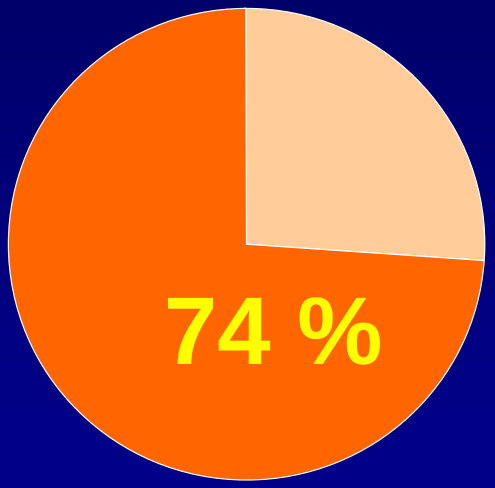
≤ 90 mm Hg



≤ 85 mm Hg



≤ 80 mm Hg



Monotherapy

Combination

Hansson L et al., Lancet 1998

Plurithérapies
au cours des grands essais thérapeutiques

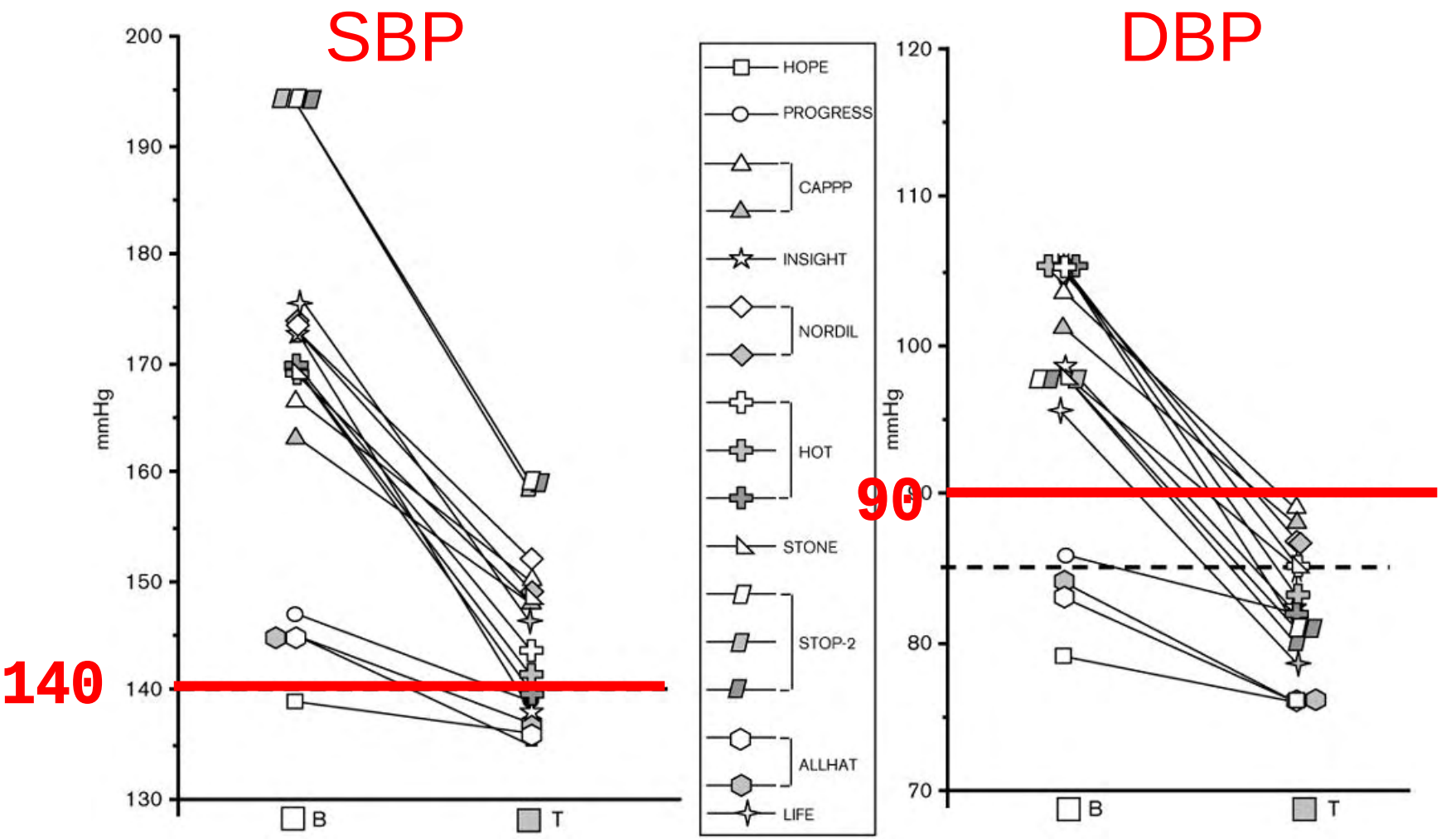
Essais	% patients recevant ≥ 2 TT anti-HTA en fin d'étude
ALLHAT	40 - 43%
ASCOT	86 - 91%
LIFE	90 - 91%
VALUE	65 - 73%

Approches conceptuelles du traitement de l'HTA (III)

1. Normalisation insuffisante
2. « Shift of paradigm » PAD → PAS
3. Co-morbidités : DT2, obésité, insuffisance coronaire, artérite, insuffisance cardiaque, …
4. Atteinte des organes cibles et biomarqueurs

Associations d'anti-hypertenseurs

SBP is more difficult to normalize than DBP in large clinical trials



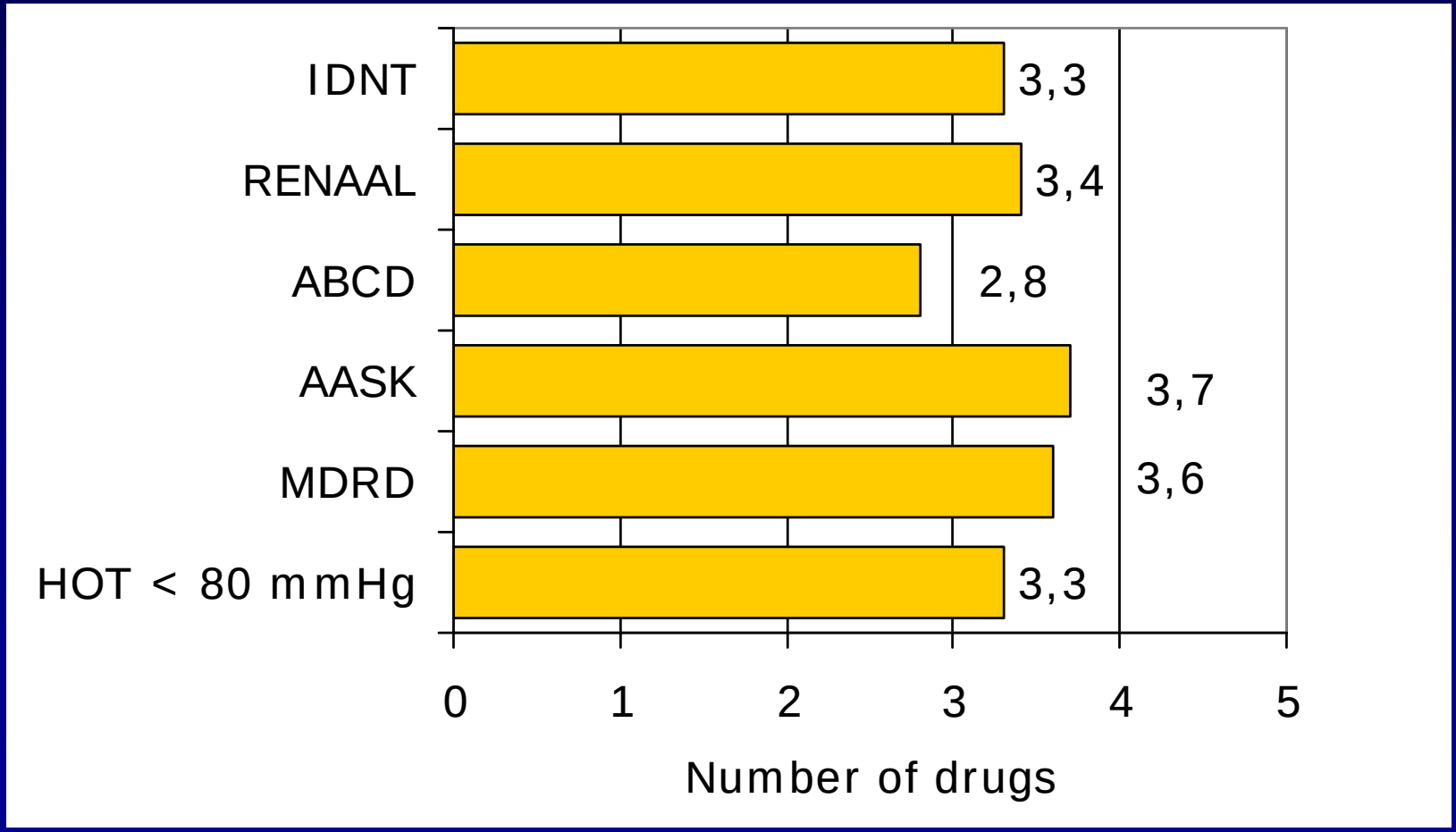
Mancia et al. J Hypertens 2002;20:1461-1464

Approches conceptuelles du traitement de l'HTA (III)

1. Normalisation insuffisante
2. « Shift of paradigm » PAD → PAS
3. Co-morbidités : DT2, obésité, insuffisance coronaire, artérite, insuffisance cardiaque, insuffisance rénale, …
4. Atteinte des organes cibles et biomarqueurs

Associations d'anti-hypertenseurs

Average number of drugs required for BP control in recent trials in hypertensive patients with diabetes and/or renal disease



Approches conceptuelles du traitement de l'HTA (III)

1. Normalisation insuffisante
2. « Shift of paradigm » PAD → PAS
3. Co-morbidités : DT2, obésité, insuffisance coronaire, artérite, insuffisance cardiaque, …
4. Atteinte des organes cibles et biomarqueurs

Associations d'anti-hypertenseurs

Atteinte des organes cibles et risque CV

- Hypertrophie VG (HVG)
- Protéinurie
- EIM carotidienne
- Rigidité artérielle
- Dysfonction endothéliale

Critère intermédiaire

- …

Atteinte des organes cibles et risque CV

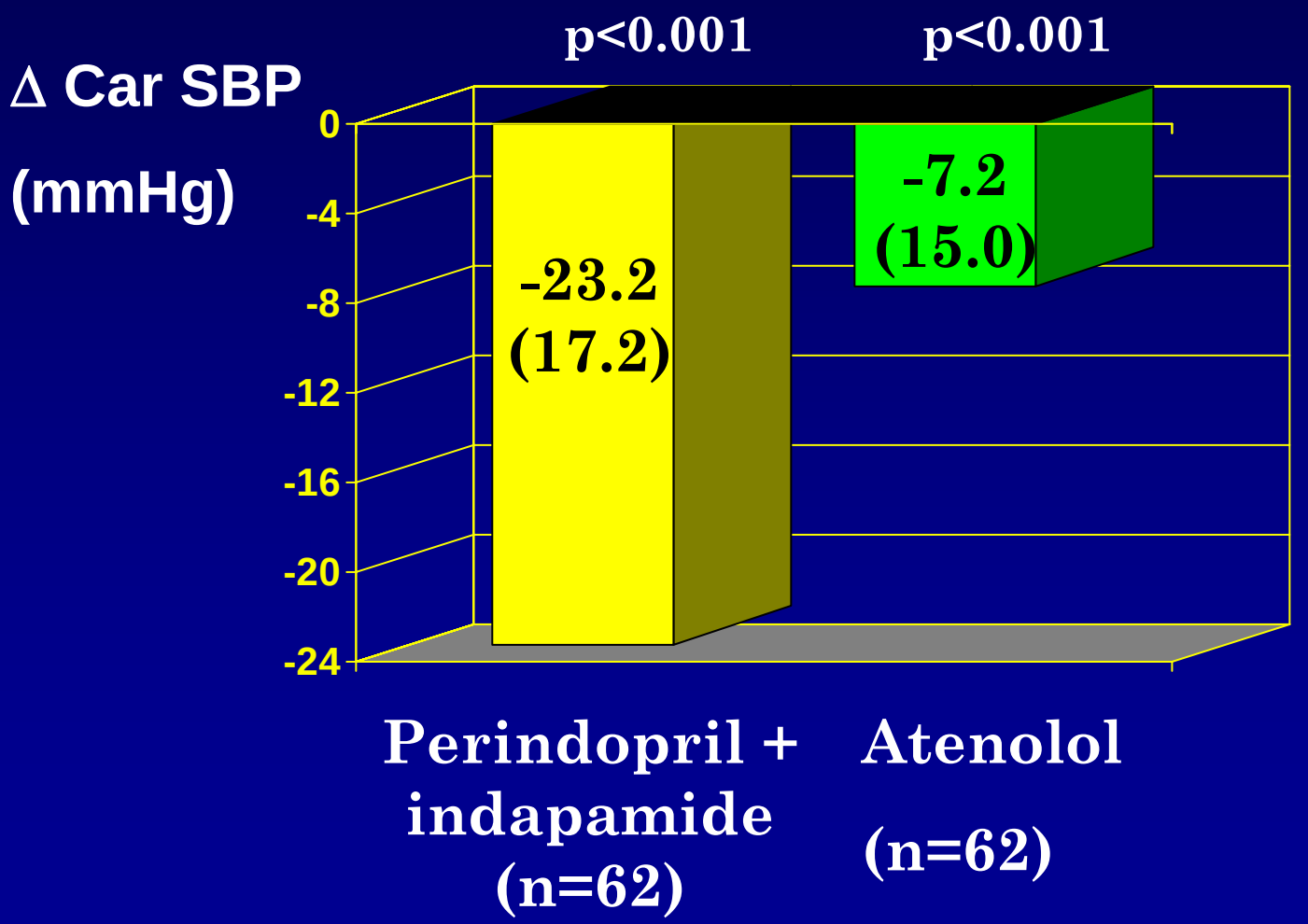
- Hypertrophie VG (LIFE)
- Protéinurie (RENAAL)
- EIM carotidienne ?
- Rigidité artérielle (Guerin, 2001)
- Dysfonction endothéliale ?

Critère intermédiaire
et critère de substitution

- …

Etude REASON : Carotid tonometry
Carotid Systolic blood pressure (C-SBP)

Asmar R et al. Hypertension 2001



Δ adjusted= -14.4 mmHg

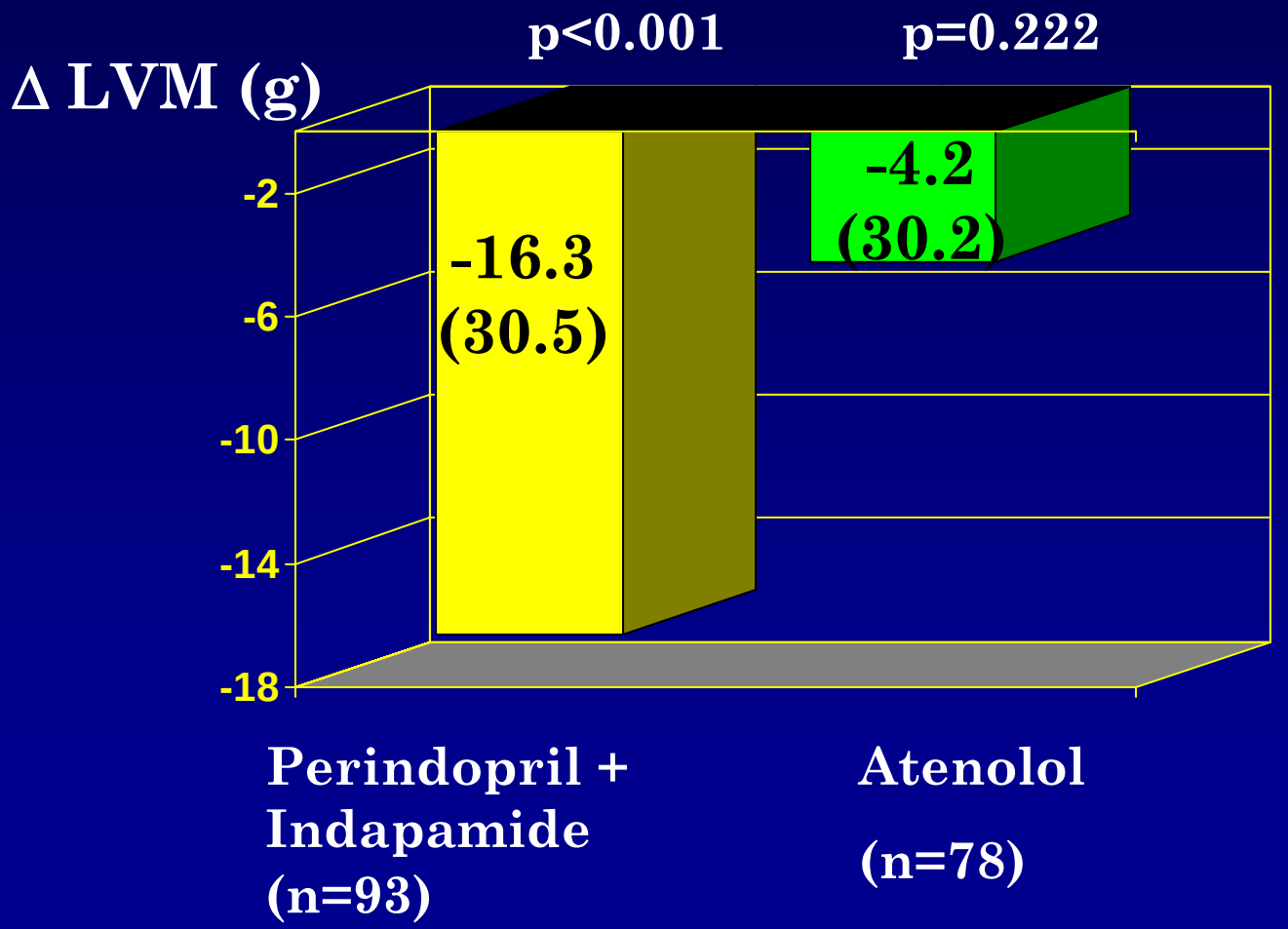
[-19.7 ; -9.0]

p<0.001

adjusted test on age, sex and baseline (p<0.001)

Etude REASON : Echocardiographie
Left Ventricular Mass (LVM)

Asmar R et al. Hypertension 2001



Δ adjusted = -9.7g

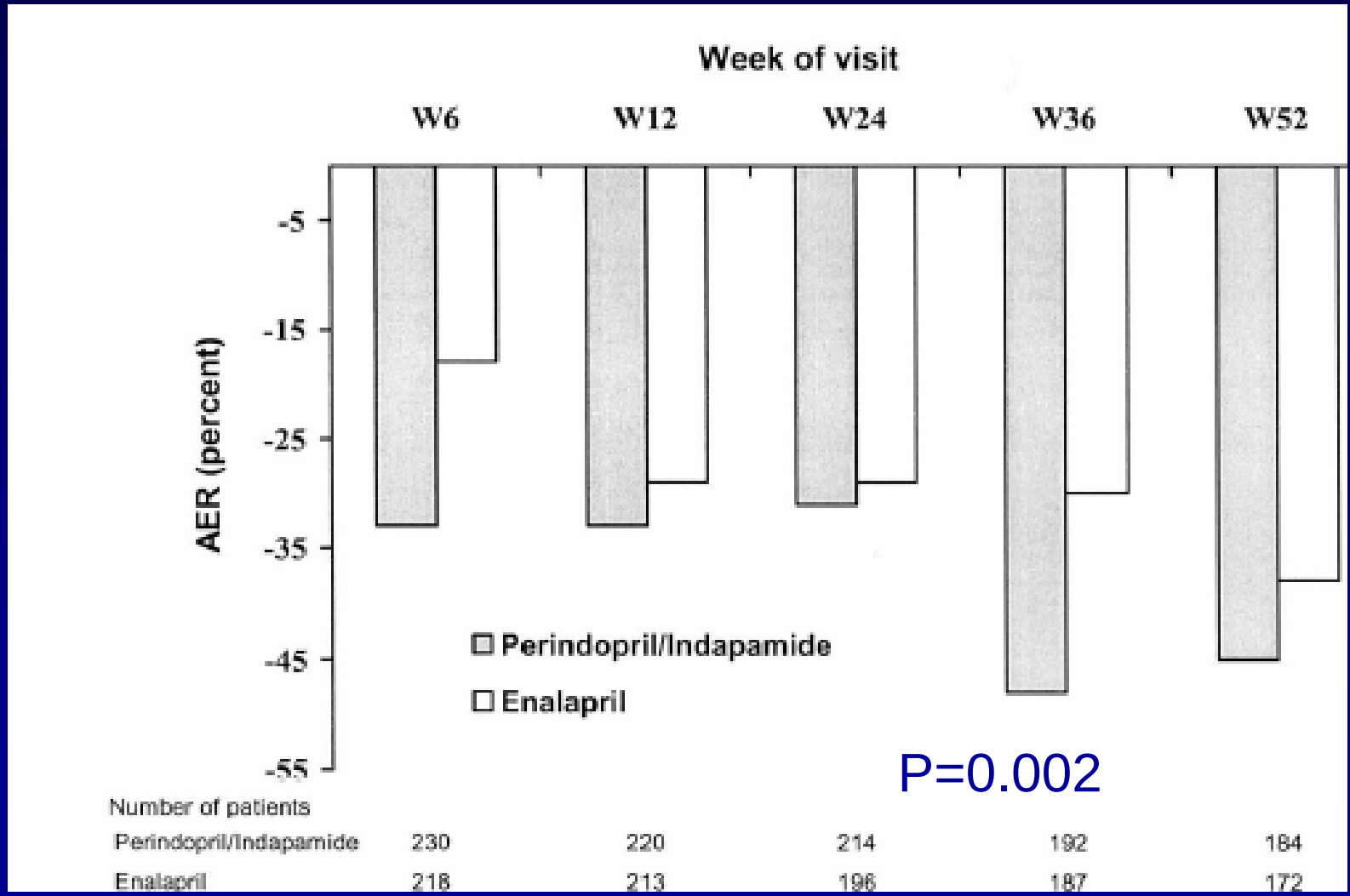
[-17.7 ; -1.8]

p=0.016

adjusted test on age, sex (p=0.044), LVM baseline (p<0.001)

Etude PREMIER : Réduction de l'albuminurie (%)

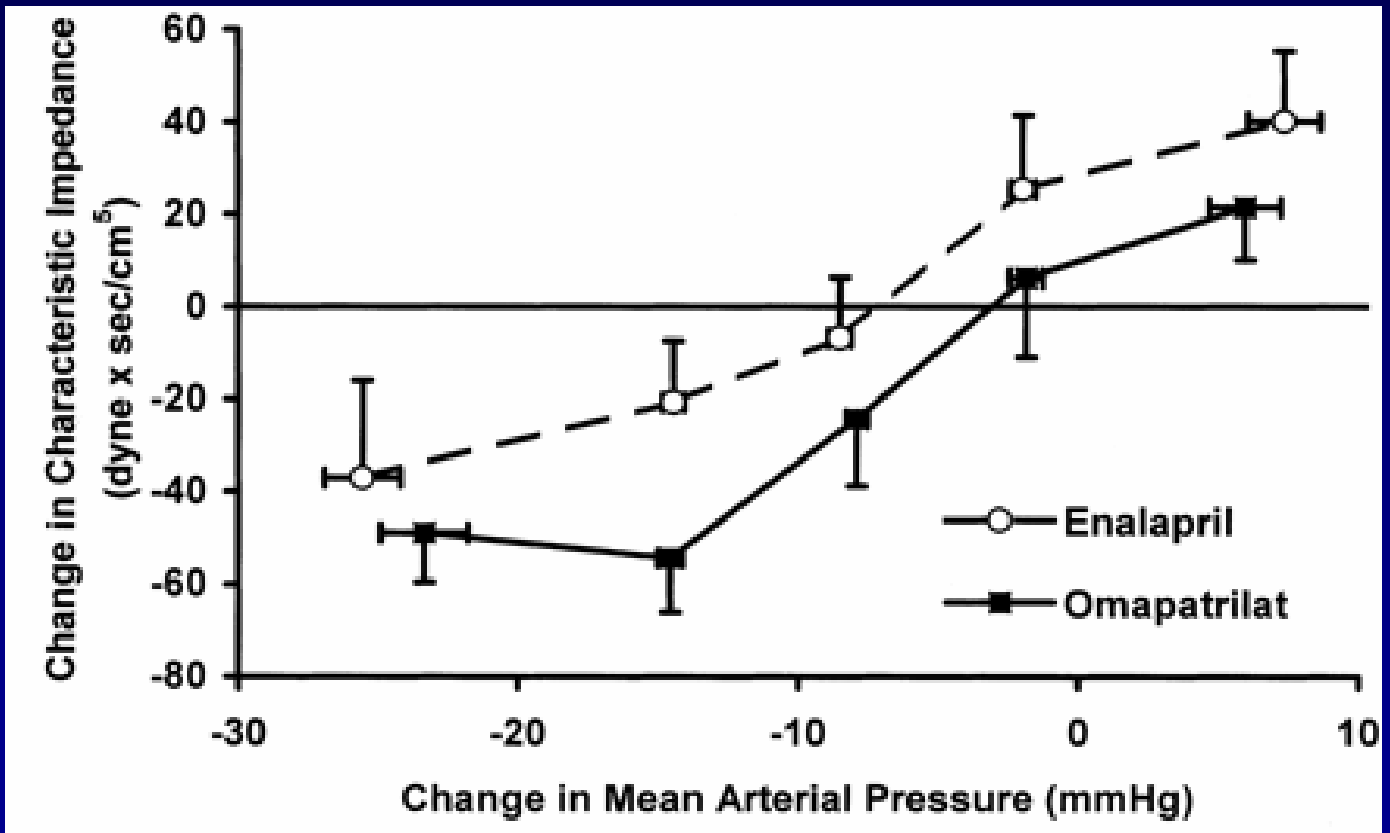
Mogensen CE, et al. Hypertension, 2003



Omapatrilat (NEPI + ACEI) reduces pulse pressure and proximal aortic stiffness in patients with systolic hypertension

Mitchell G et al. Circulation 2002

- study design : 12 W, randomized, double-blind,
- parallel groups : enalapril 40 mg (n=87) or omapatrilat 80 mg (n=80)*
- characteristic impedance : Δ carotid pressure / Δ aortic flow in early systole



Enalapril	11	16	18	20	22
Omapatrilat	24	18	19	11	8
Total	35	34	37	31	30

Années 1985-2000

Controverse sur le choix de la monothérapie de première intention

Années 2000-2010

Réflexion sur le choix des associations d’anti-HTA

Quelles associations ?

1. Selon les recommandations

2. Avec ou sans beta-bloquant?

3. En développement

Recommandations HAS 2005

« Prise en charge des patients adultes atteints d'hypertension artérielle essentielle »

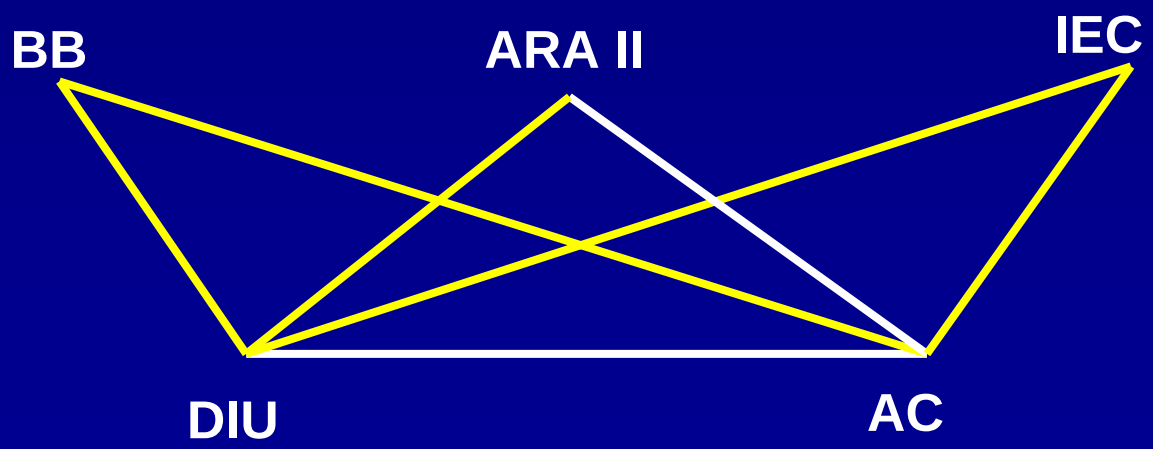
- **Bithérapies fixes**

A faibles doses

- Première intention, en alternative à la monothérapie
- Synergiques, améliorent le contrôle de la PA

À doses habituelles

- En deuxième intention
- Synergiques, améliorent l'observance



Pharmacological class	Effects	Combination drug
CCB (C)	Σ activation	β-blockers (B)
	RAAS activation	ACEI (A)

ACCOMPLISH

Pharmacological class	Effects	Combination drug
CCB (C)	Σ activation	β-blockers (B)
	RAAS activation	ACEI (A)
Diuretics (D)	RAAS activation	ACEI (A)

ACCOMPLISH

Pharmacological class	Effects	Combination drug
CCB (C)	Σ activation	β-blockers (B)
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Diuretics (D)	RAAS activation	ACEI (A)
	Σ Activation	β-blockers (B)

Pharmacological class	Effects	Combination drug
CCB (C)	Σ activation	β-blockers (B)
	RAAS activation	ACEI (A)
Diuretics (D)	~~RAAS activation~~	~~ACEI (A)~~
	Σ Activation	β-blockers (B)

No alpha-blockade

Pharmacological class	Effects	Combination drug
CCB (C)	Σ activation RAAS activation	β-blockers (B) ACEI (A)
Diuretics (D)	RAAS activation Σ Activation	ACEI (A) β-blockers (B)
ACE inhibitors or ARB (A)	« Renin » effect + « Volume » effect	Diuretics (D)

Choix Pragmatique

- Le choix des associations est le plus souvent pragmatique et dépend
  - De la tolérance+++
  - De l'expérience préalable du patient

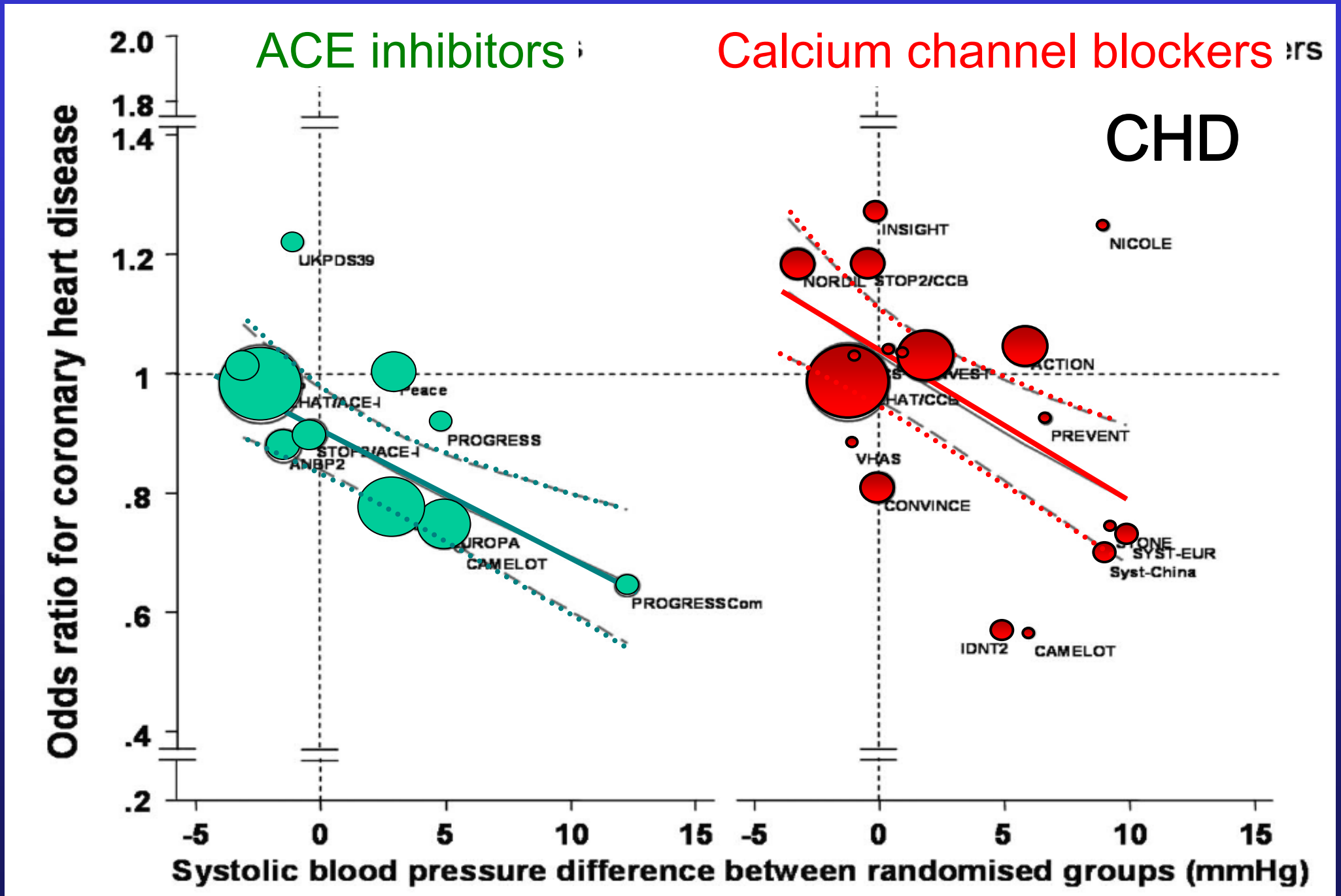
+++ Choix par défaut +++

Existe t'il un effet préventif différentiel entre les classes d'antihypertenseurs pour les événements indépendant de la pression?

Metaanalysis 2005
(Verdecchia P. *Hypertens*. 2005;46:386-392.)

- ACEi > CCB for coronary artery prevention
- CCB > ACEi for stroke prevention
- ACEi = BB or Diuretics for stroke and CHD
- CCB < BB/D for CHD and > BB/D for stroke

28 outcome trials
comparing either ACEIs or CCBs with diuretics, β-blockers, or placebo
- 179 122 patients,
- 9509 incident cases of CHD (myocardial infarction and coronary death)
- 5971 cases of stroke



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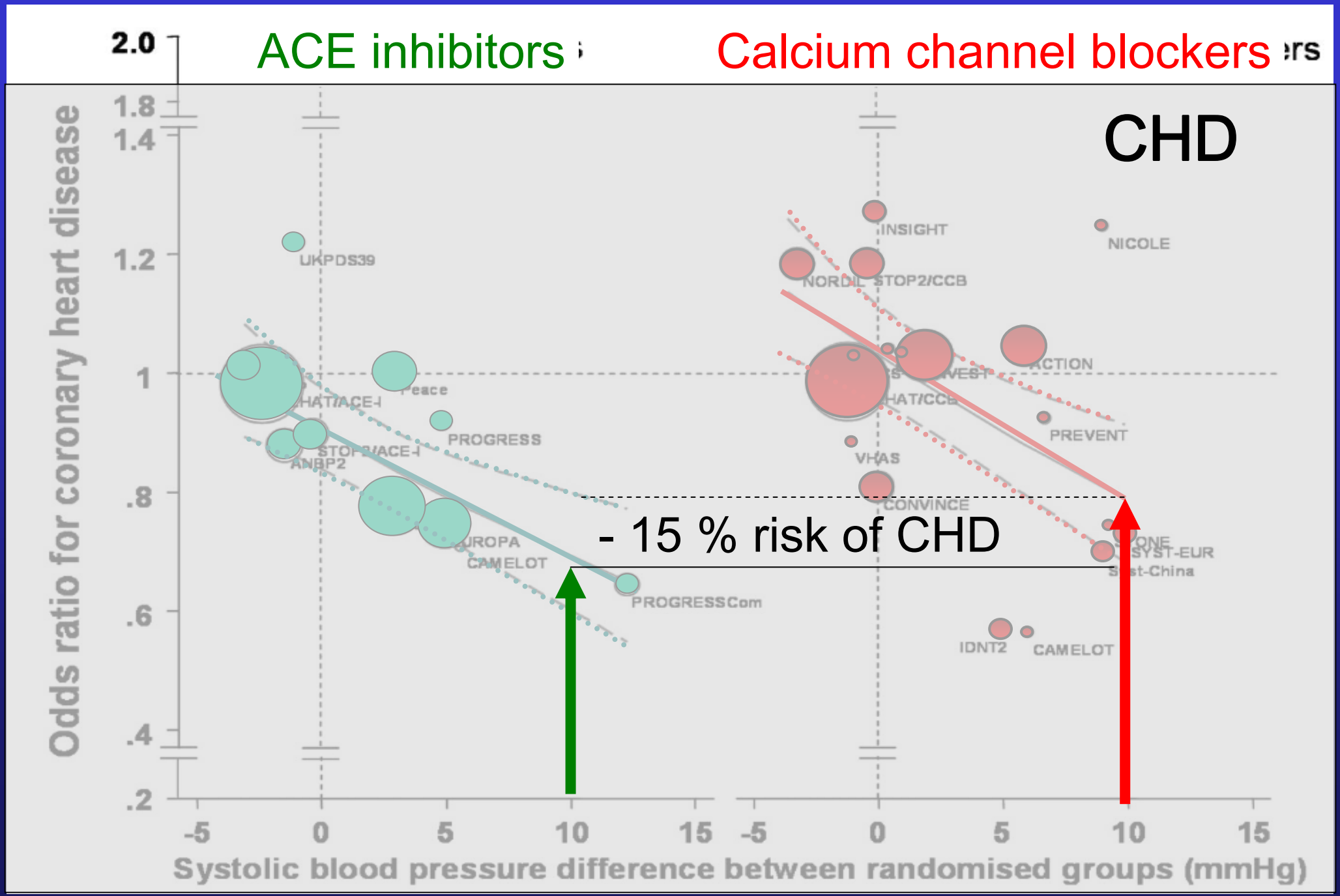

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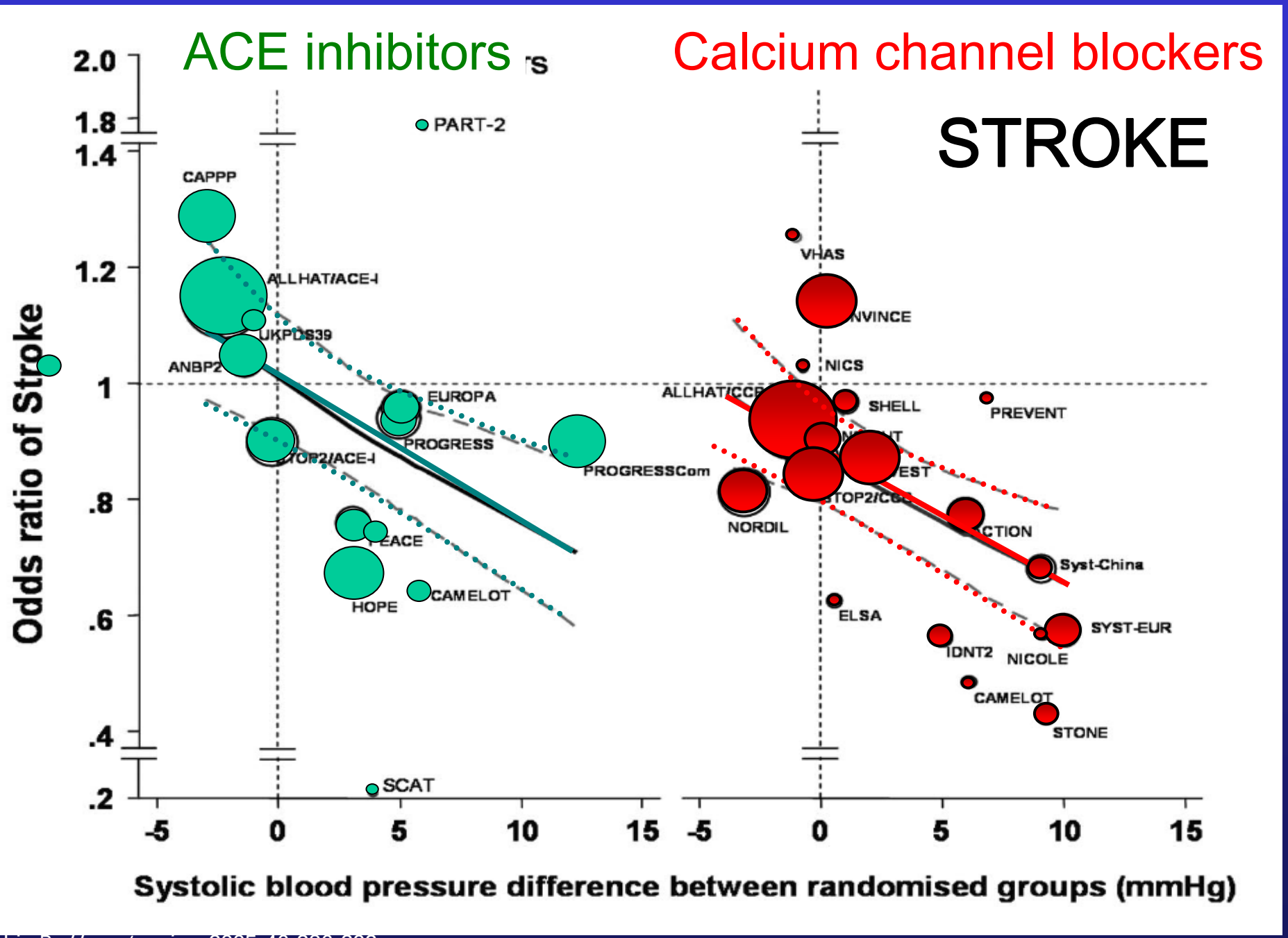

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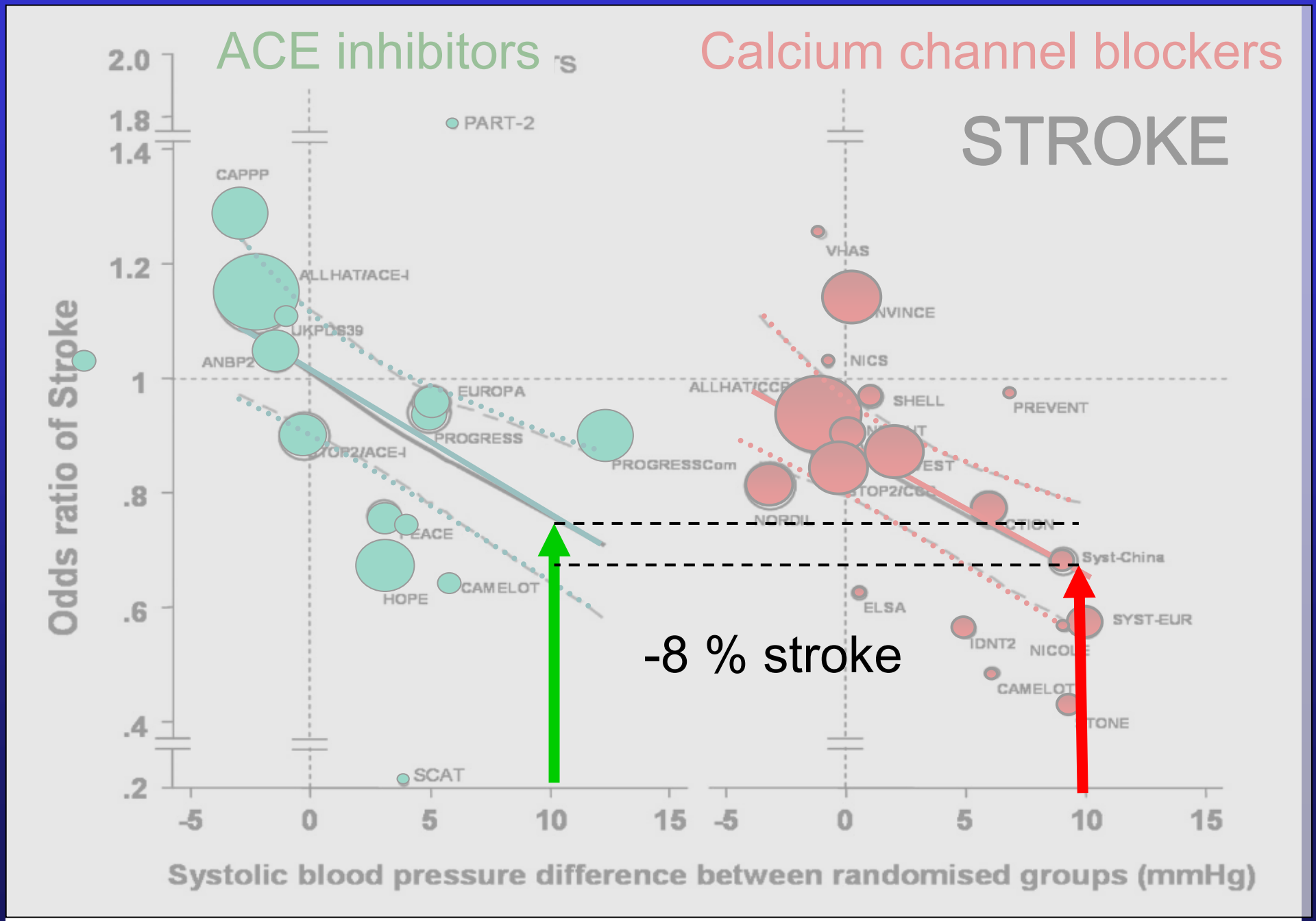
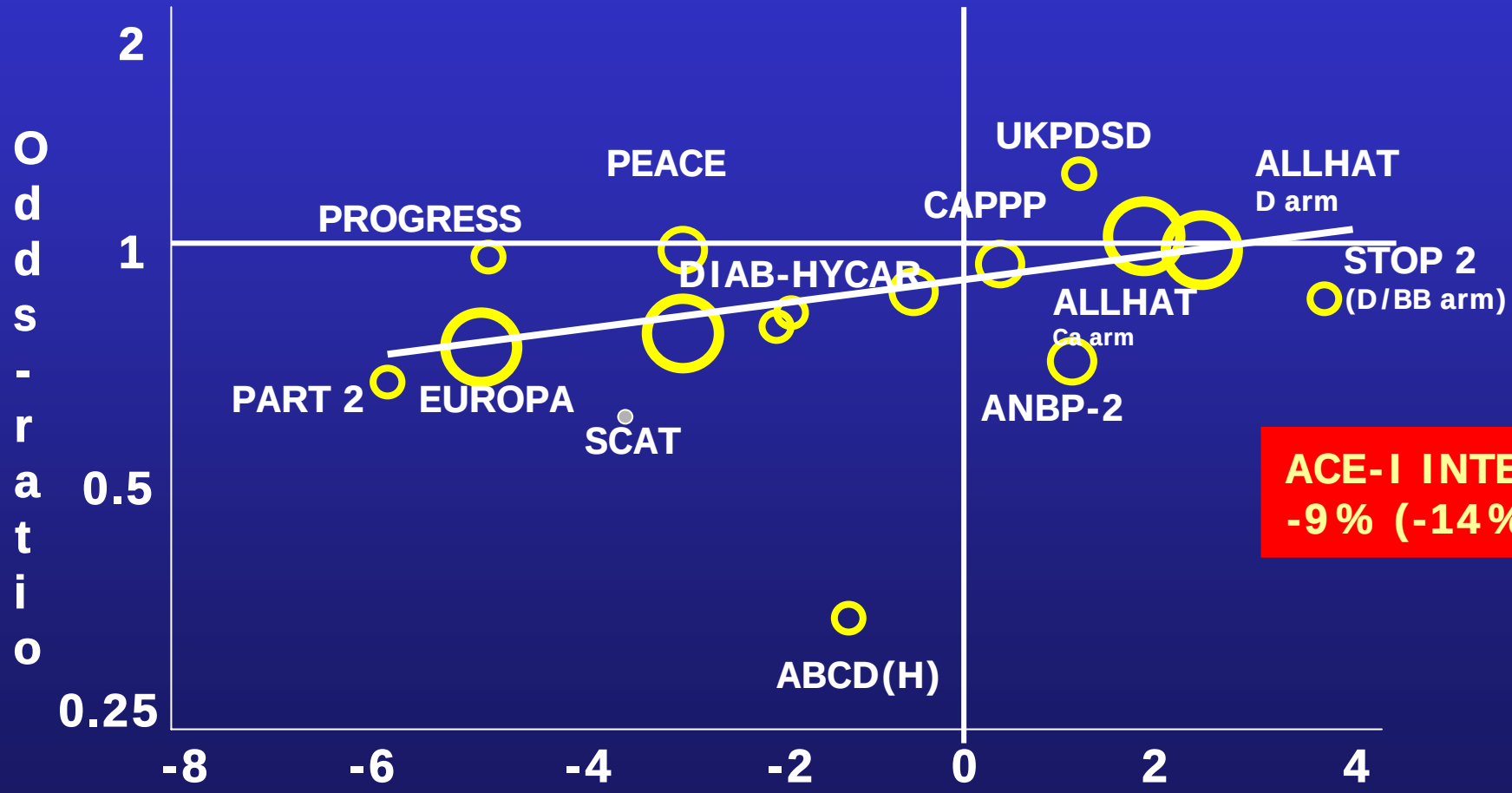


Verdecchia P. *Hypertension*. 2005;46:386-392.

J Hypertens. 2007;25:951-8

ACEI versus ARB in CHD prevention

Coronary heart disease: ACEI



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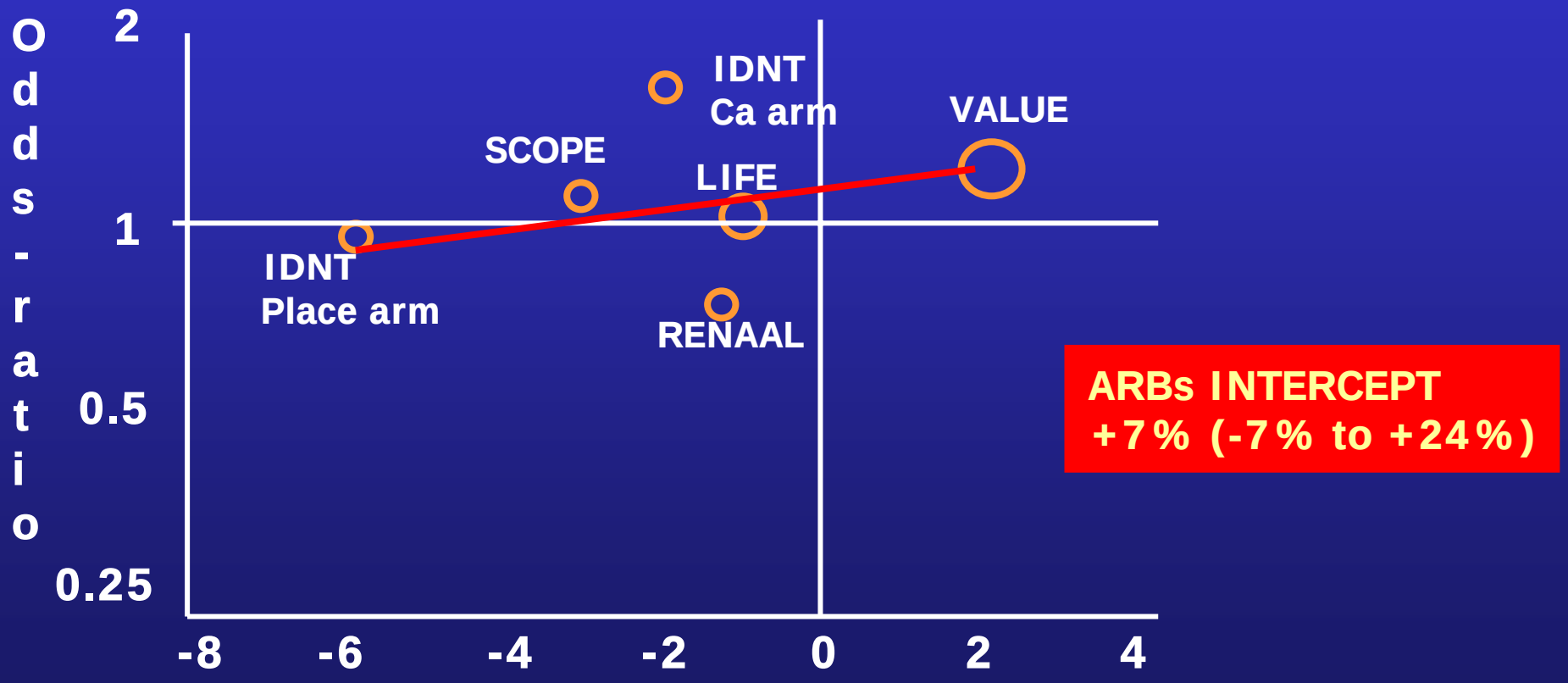
ACEI versus ARB in CHD prevention

Coronary heart disease: ARB

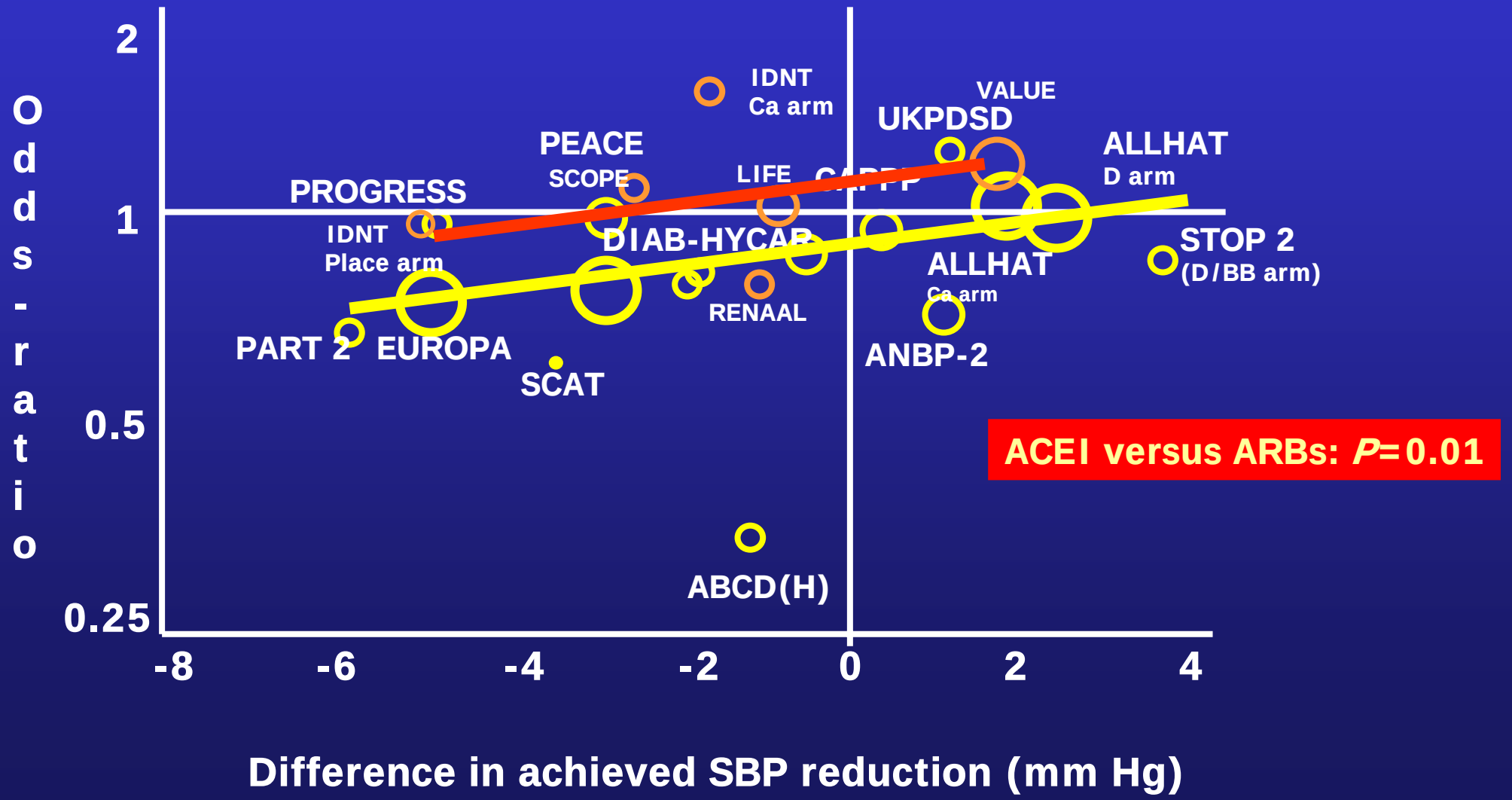


ARBs INTERCEPT +7% (-7% to +24%)

J Hypertens. 2007;25:951-8

ACEI versus ARB in CHD prevention

Coronary heart disease: ARB



Blood pressure-dependent and independent effects of agents that inhibit the renin–angiotensin system

- 146 838 hypertensives or patients at elevated CVD risk
- 22 666 major cardiovascular events
  - Comparable BP dependent reductions in risk with ACEI and ARB
  - ACEI produced a BP-independent reduction in risk of CHD 9% (3–14%), NOT ARBs (P=0.002)
  - For stroke and heart failure ➔ no evidence of any blood pressure-independent effects of either ACEI or ARB.

Quelles associations ?

1. Selon les recommandations

2. Avec ou sans beta-bloquant?

3. En développement

Antihypertenseurs

Classes pharmacologiques actuelles

- Diurétiques
- Bêtabloquants
- Antagonistes calciques
- IECA : inhibiteurs de l'enzyme de conversion de l'Ang I
- Antagonistes de l'Ang II
- Alphabloquants
- Centraux

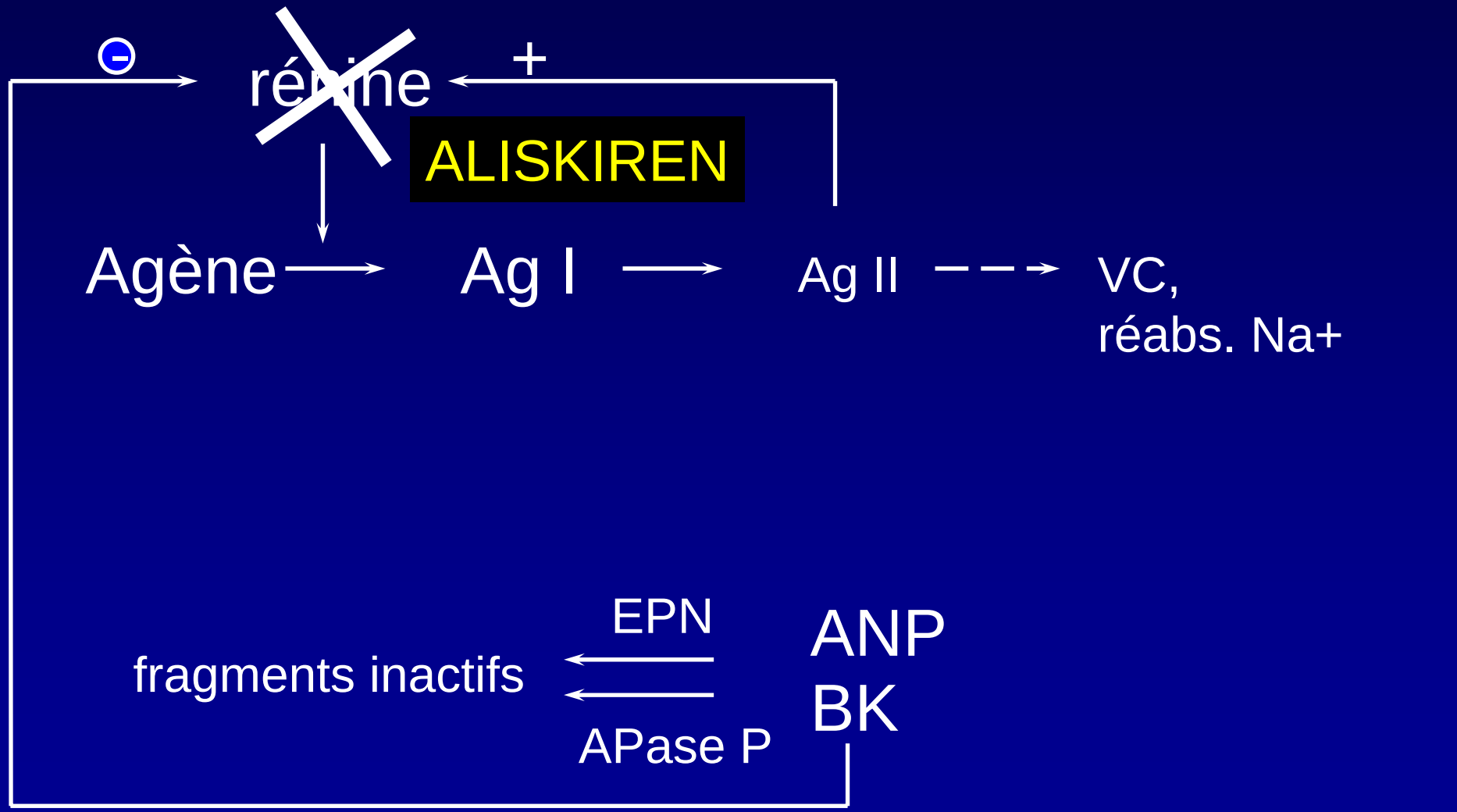
Nouvelles classes

- Inhibiteurs de la rénine
- IEPN : Inhibiteurs de l'endopeptidase neutre
- Antialdosterones sélectifs :

  - MR antagonistes : éplérénone

  - Inhibiteurs de l'aldostérone synthétase : fadrazole
- IECE : inhibiteurs de l'enzyme de conversion de l'endothéline
- Antagonistes de l'endothéline…

Inhibiteurs mixtes de l'endopeptidase neutre et de l'enzyme de conversion : contre-régulation des systèmes rénine-angiotensine, bradykinine et ANP



Renin inhibitors

- Advantages
  - New class+++
  - Long duration of action
  - Good tolerance
  - Better kidney protection?
- Questions
  - Better efficacy on all target organ damage protection?
  - Efficacy on clinical events protection
  - Relative position versus ACEi and ARB?

Antihypertenseurs

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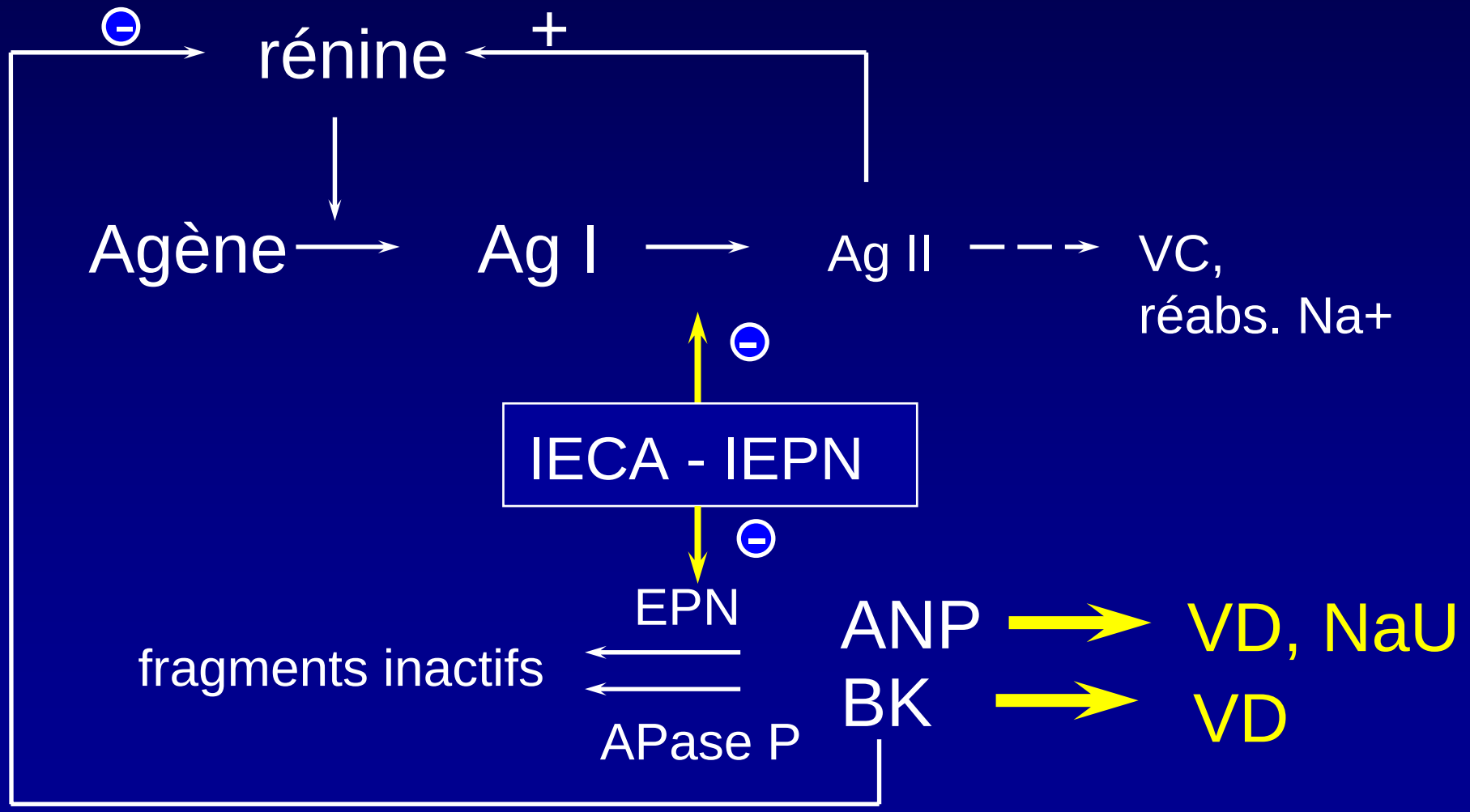
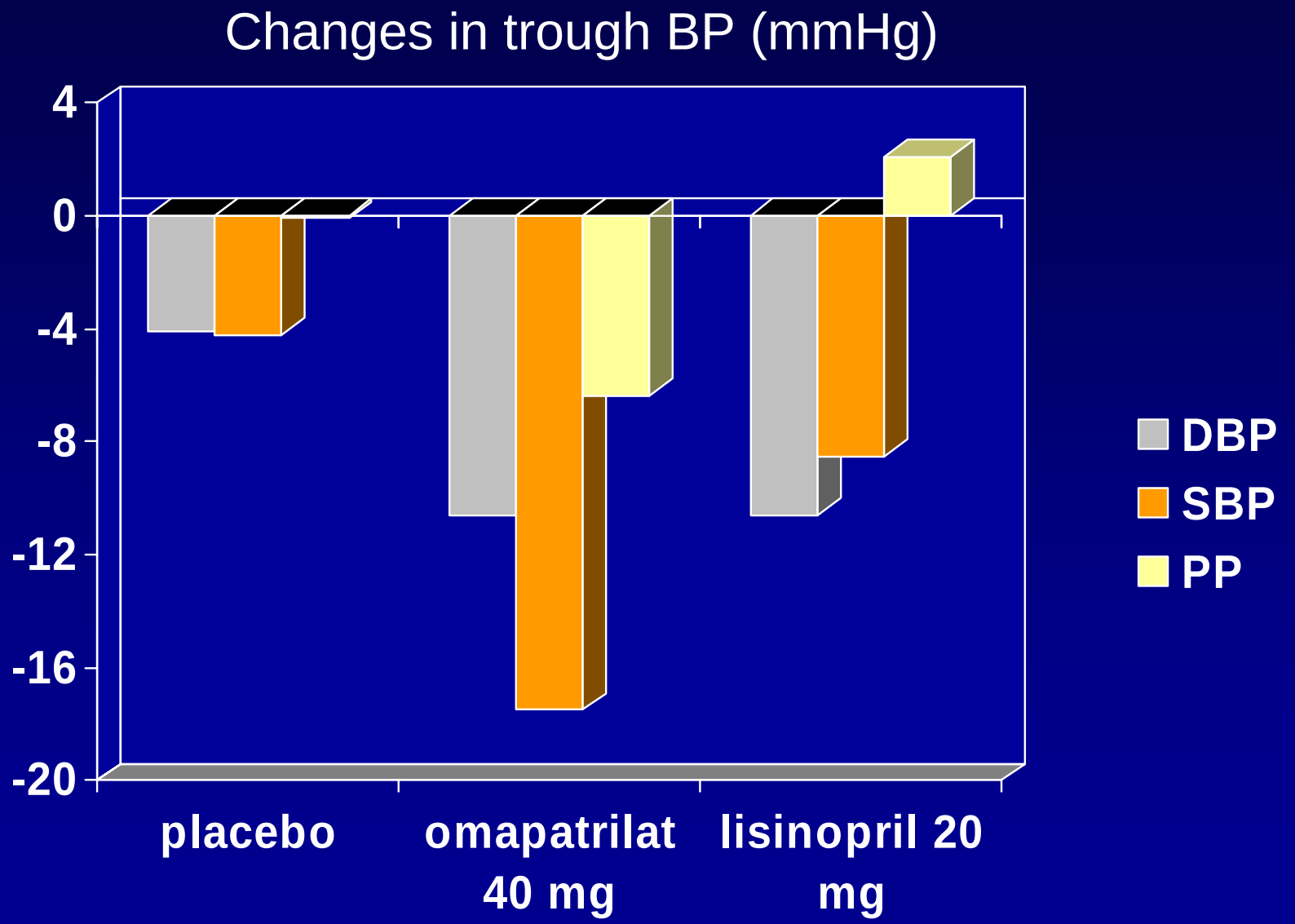


Antihypertensive effects of omapatrilat (NEPI + ACEI) in elderly hypertensive patients



OCTAVE: Severity of Angioedema

	Omapatrilat (n=12,609)	Enalapril (n=12,557)	Absolute Difference
No treatment, or treated with antihistamines only	162 (1.28%)	65 (0.52%)	0.76%
Treated with epinephrine or steroids; no airway compromise	110 (0.87%)	21 (0.17%)	0.71%
Airway compromise • Treatment with epinephrine • Mechanical airway protection	 1 1	 0 0	 -- --
TOTAL	274	86	--

H. Black 2002; Data on file, Bristol-Myers Squibb

Nouveaux inhibiteurs de la NEP

- très sélectifs pour la NEP >>> pour l'ACE,
  et l'aminopeptidase P (BK)

- pas de modifications de ET, BK, Ag II

- combinaison à IEC, ARA2

- Problème des angio-oedèmes
  - moindre incidence théorique
    si pas d'inhibition de l'aminopeptidase P

Stratégie d'association:
Efficacité anti-hypertensive
Prévention des évènements cardiovasculaires

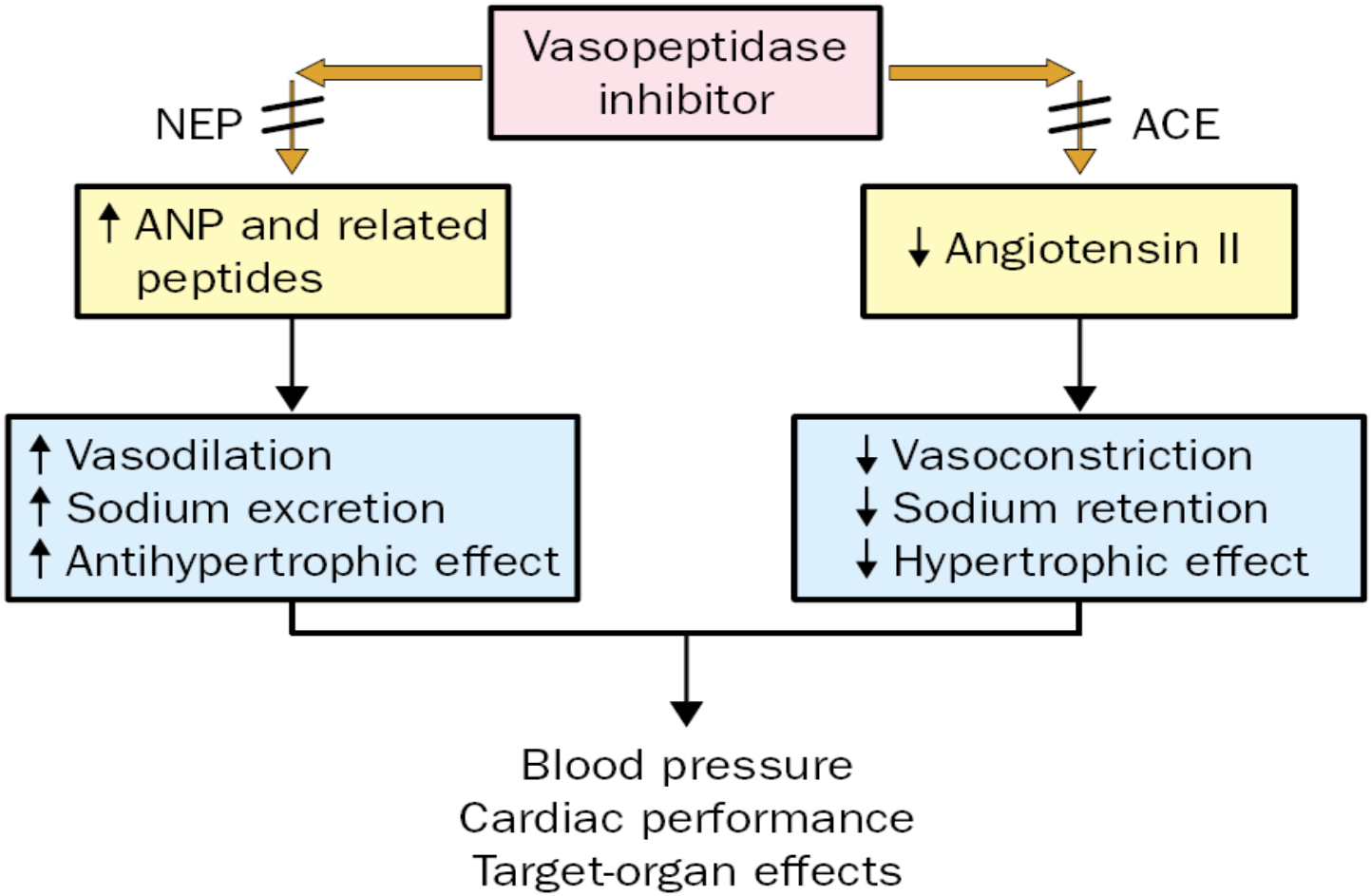
IEPN + IECA > IEC + DIU

ou

IEPN + ARA2 > IEC + DIU

?

Dual-Acting Angiotensin Receptor–Neprilysin Inhibitor (ARNi)



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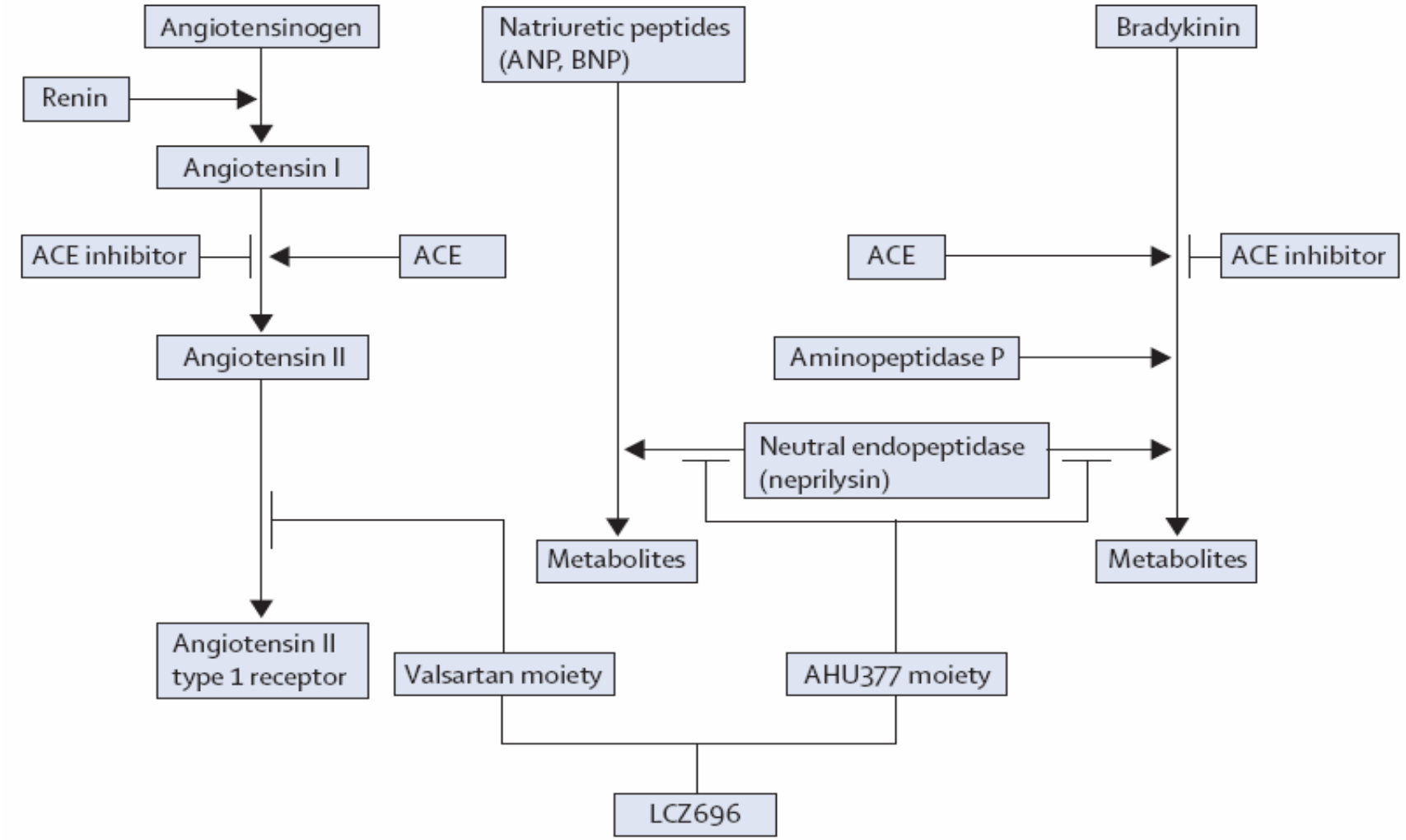
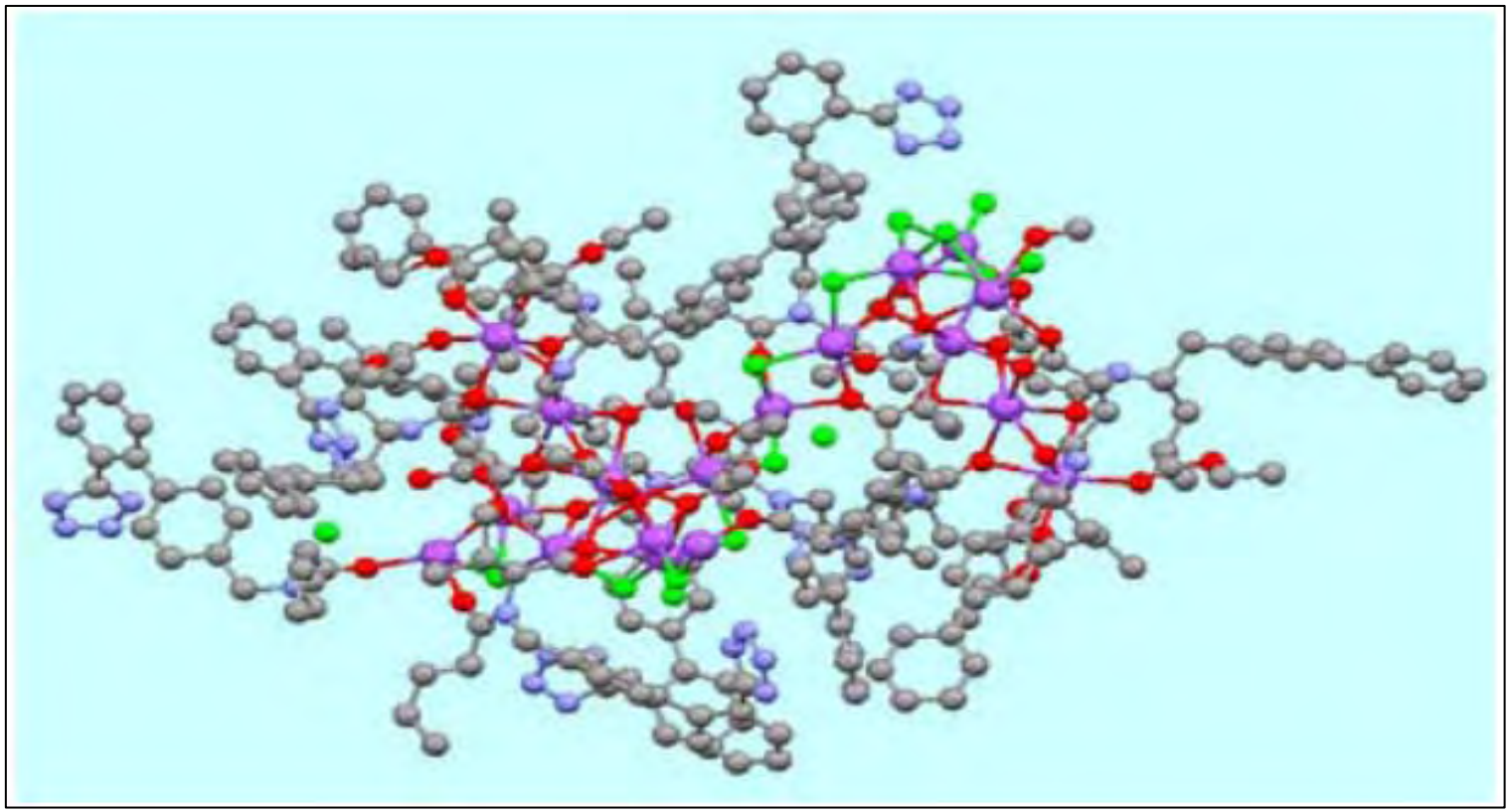


LCZ696 : a dual-Acting Angiotensin Receptor–Neprilysin Inhibitor (ARNi)

Single molecule in which the molecular moieties of valsartan and the molecular moieties of the NEP inhibitor prodrug AHU377 are present in a 1:1 molar ratio.



Gu J et al. J Clin Pharmacol, 2010;50:401-414

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

Ruilope et al. Lancet 2010; 375:1255-1266

1328 patients aged 18–75 years with mild-to-moderate hypertension
DBP: 90/95 to 109 mmHg, 8-week treatment

Washout 4 Weeks

Treatment 8 Weeks

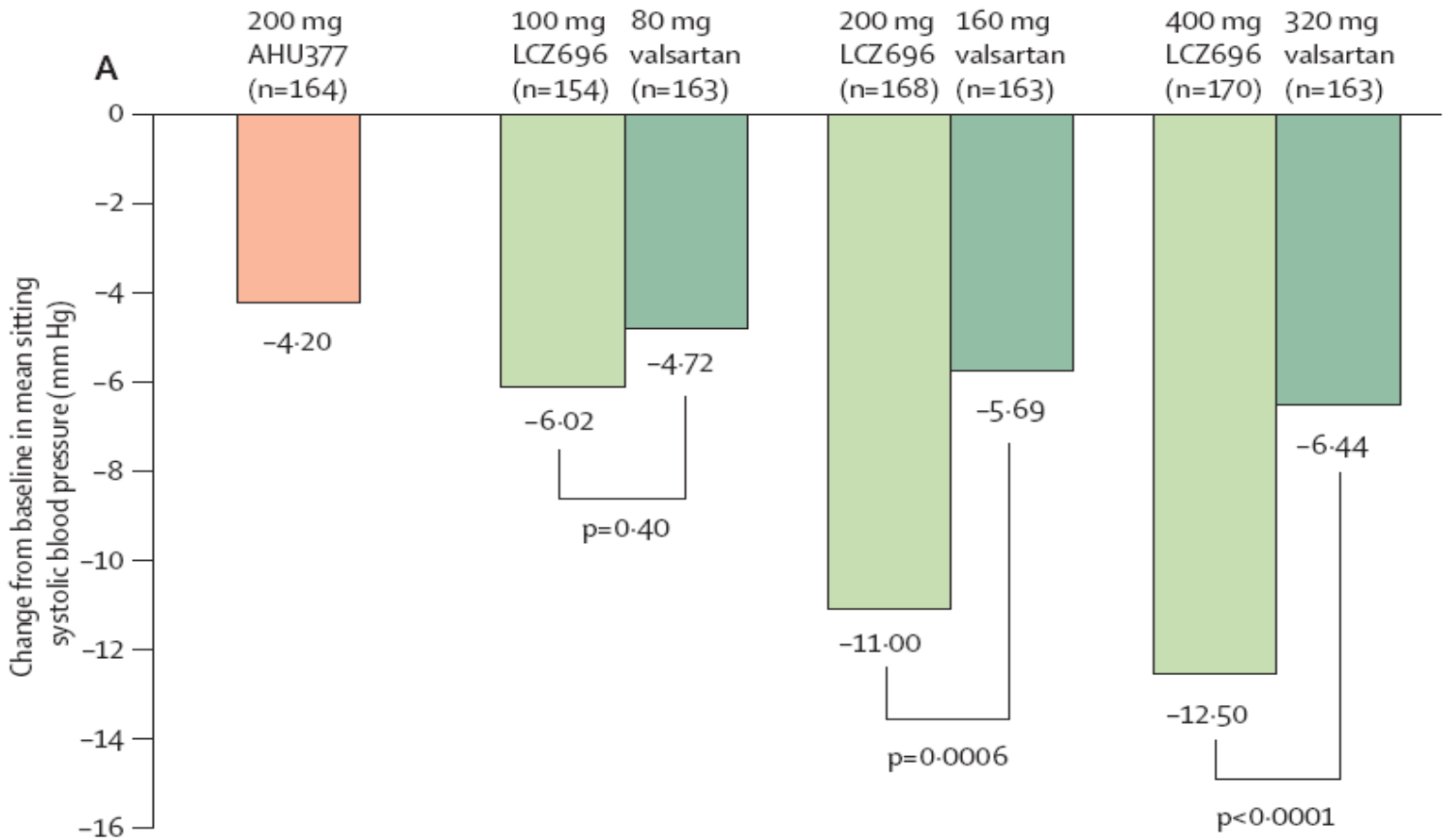
- **Placebo**
- **AHU377 200 mg**
- **LCZ696 100 mg**
- **LCZ696 200 mg**
- **LCZ696 400 mg**
- **Valsartan 80 mg**
- **Valsartan 160 mg**
- **Valsartan 320 mg**

Withdrawal 1 Week

BP reduction with LCZ696, a novel dual-acting inhibitor of the angiotensin II receptor and neprilysin

Ruilope et al. Lancet 2010; 375:1255-1266

Placebo-corrected change in SBP (mmHg)



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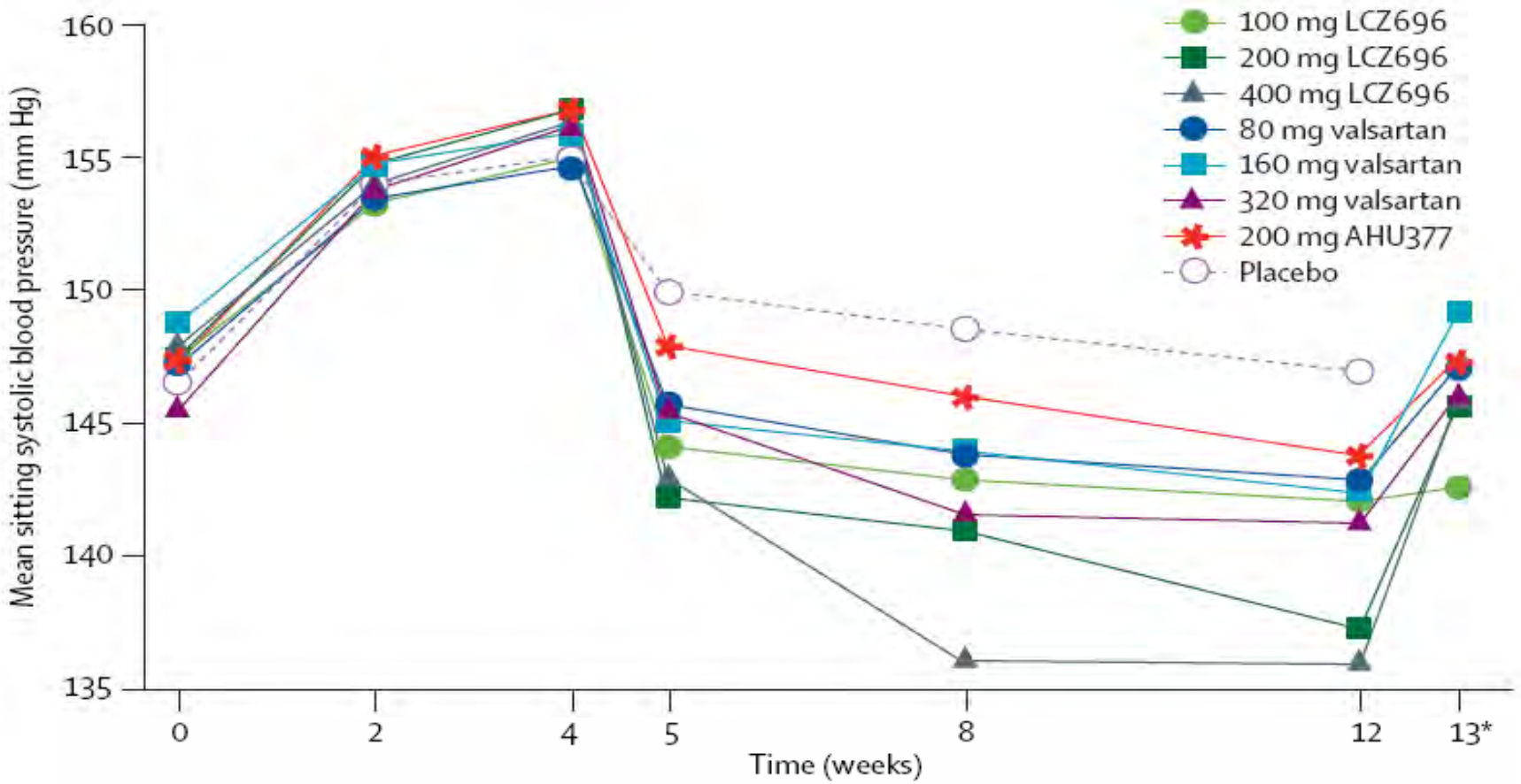
Mean sitting SBP (mmHg)



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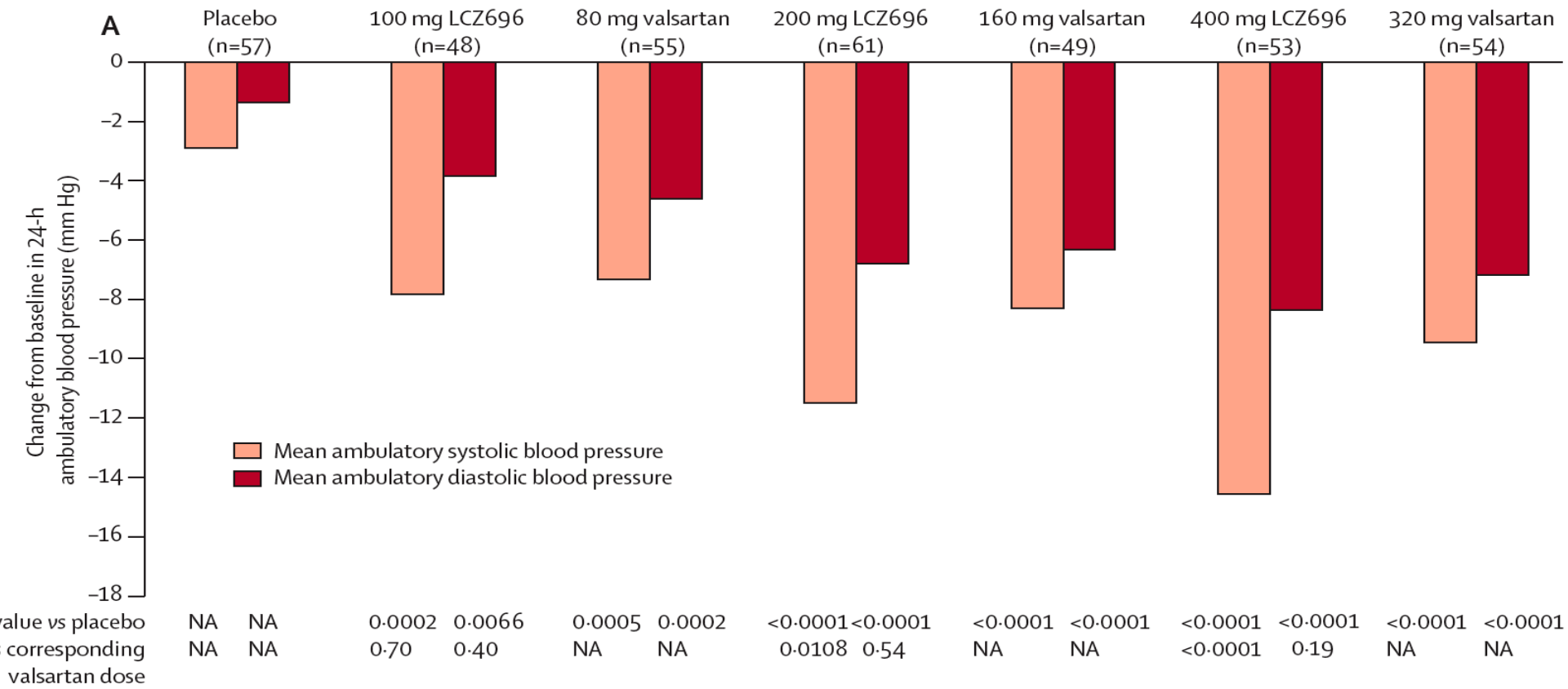
Change in Ambulatory BP over the 8 week period



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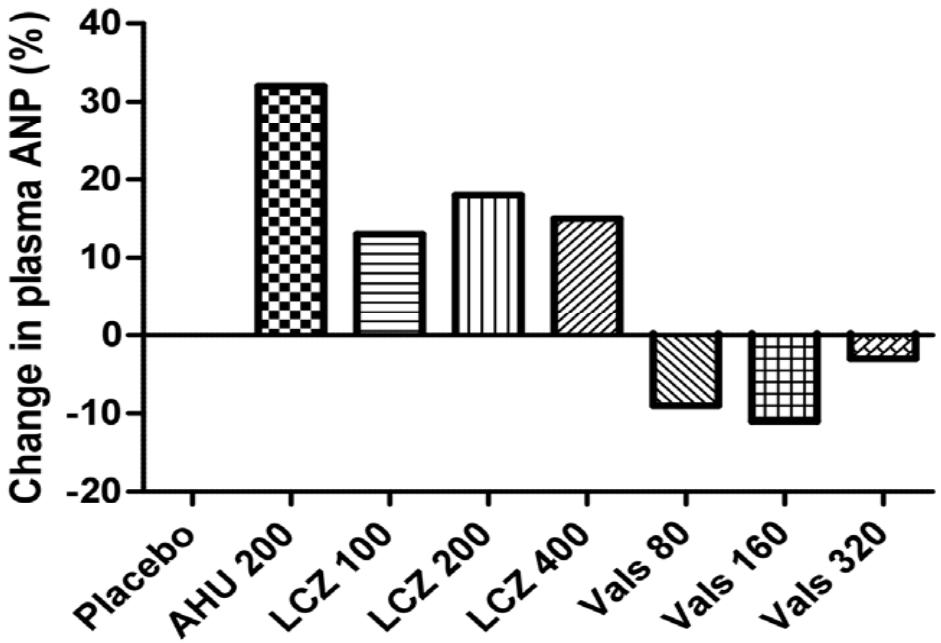
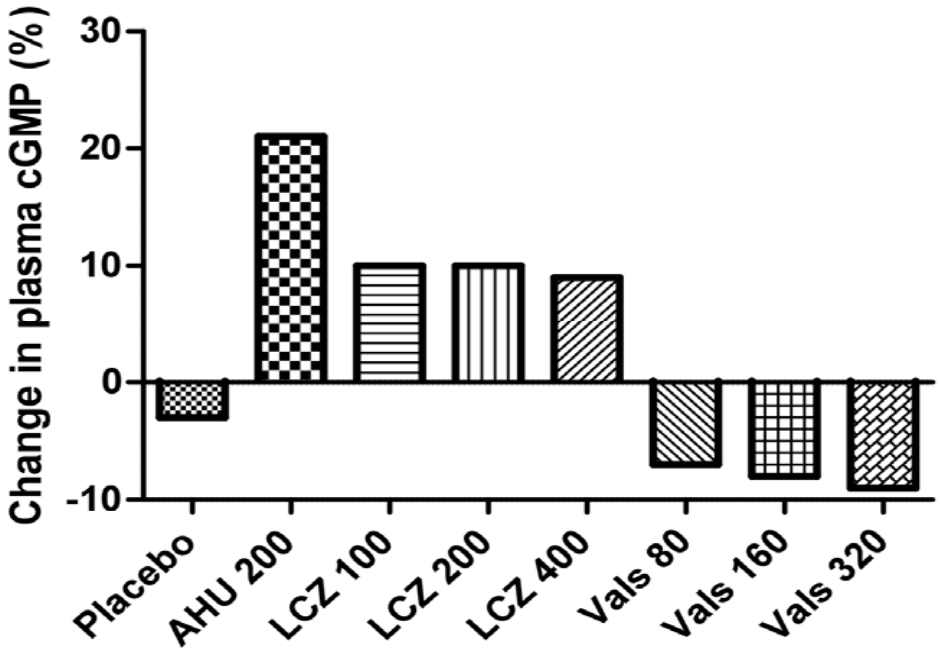
Ruilope et al. Lancet 2010; 375:1255-1266

Effect on plasma ANP and cGMP

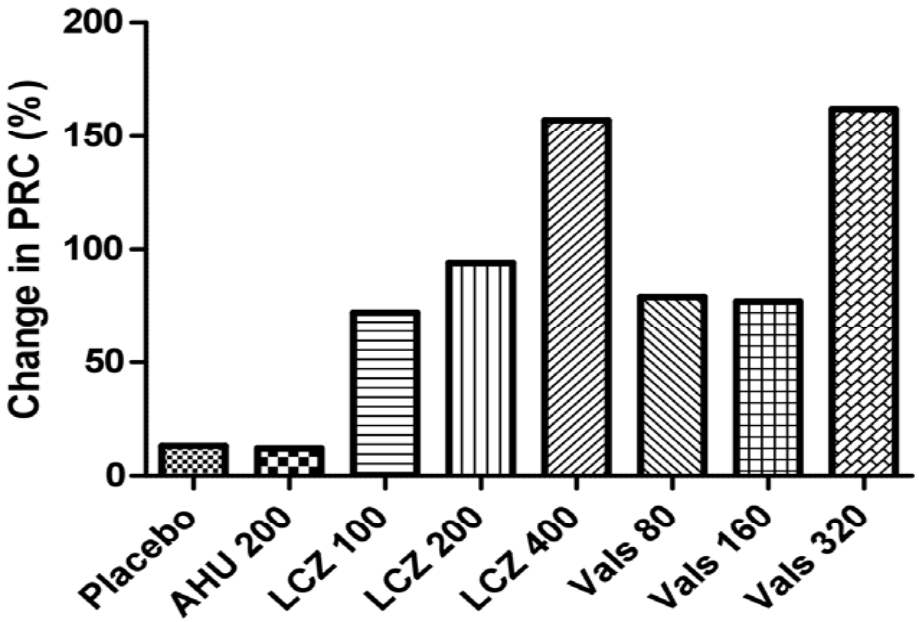


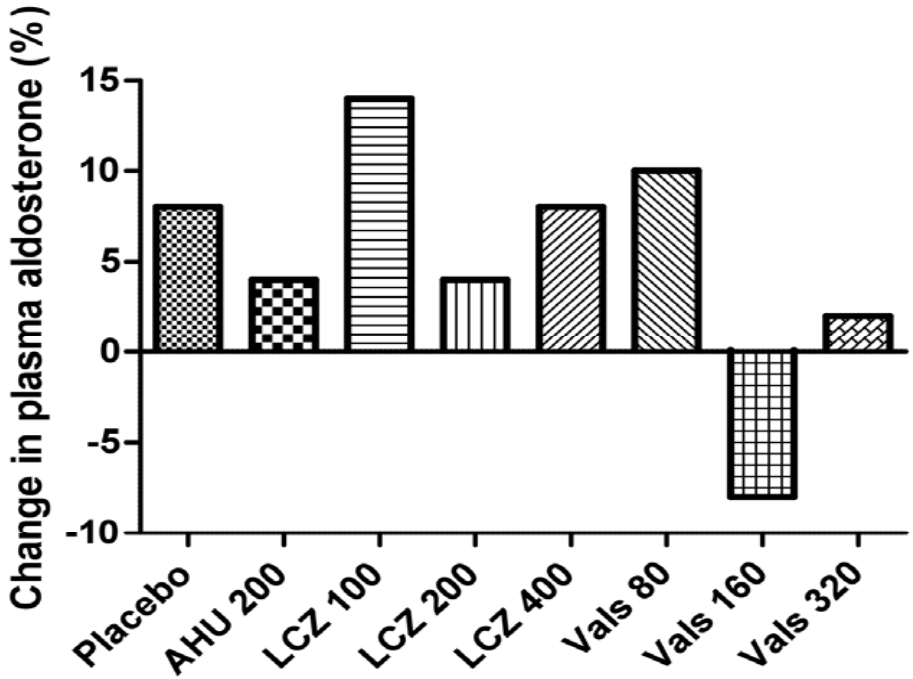


BP reduction with LCZ696, a novel dual-acting inhibitor of the angiotensin II receptor and neprilysin

Ruilope et al. Lancet 2010; 375:1255-1266

Effect on plasma renin and aldosterone





Antihypertenseurs

Classes pharmacologiques actuelles

- Diurétiques
- Bêtabloquants
- Antagonistes calciques
- IECA : inhibiteurs de l'enzyme de conversion de l'Ang I
- Antagonistes de l'Ang II
- Alphabloquants
- Centraux

Nouvelles classes

- Inhibiteurs de la rénine
- IEPN : Inhibiteurs de l'endopeptidase neutre
- Antialdosterones sélectifs :

  - MR antagonistes : éplérénone

  - Inhibiteurs de l'aldostérone synthétase : fadrazole
- IECE : inhibiteurs de l'enzyme de conversion de l'endothéline
- Antagonistes de l'endothéline…

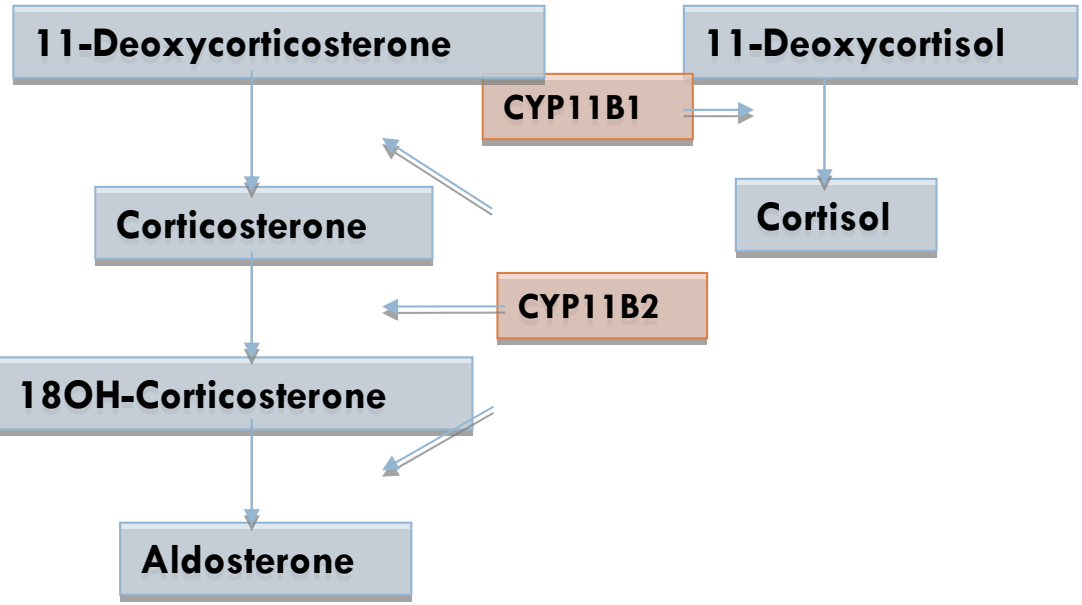
New Pharmacological Approach : Inhibition of Aldosterone Synthase : Rationale

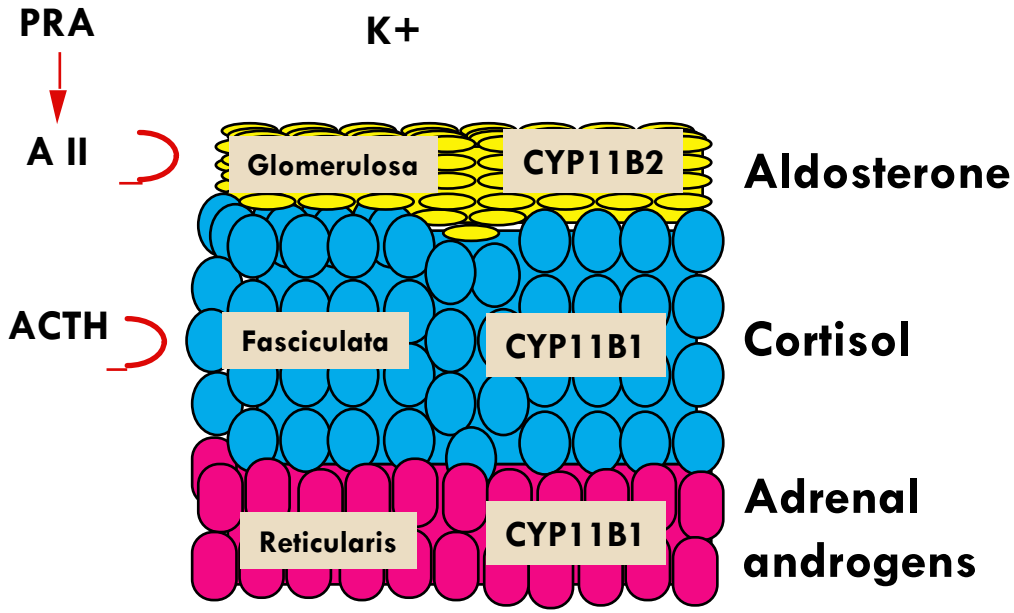
1. Pathophysiological role of Aldosterone
   - BP, potassium and sodium homeostasis
   - Cardiovascular and renal diseases pathophysiology and prognosis

2. Beneficial effects of MR antagonists
   - Heart failure
   - LV dysfunction after myocardial infarction
   - Proteinuric nephropathies

3. Limitations of MR antagonism
   - Spironolactone side effects
   - Failure of eplerenone in patients with PA : unmet medical need
   - Nongenomic effects of aldosterone not blocked by MR antagonism

New Pharmacological Approach : Inhibition of Aldosterone Synthase : Enzymatic pathway





1. Aldosterone synthase is approximately 93% homologous to 11-b hydroxylase, the product of the CYP11B1 gene, which catalyzes the conversion of 11-deoxycortisol to cortisol
2. CYP11B1 and CYP11B2 genes map to human chromosome 8q21-22
3. CYP11B1: ZF; CYP11B2 : ZG

New Pharmacological Approach : Inhibition of Aldosterone Synthase : Compound LCI699

- Structurally derived from FAD286A, a non-steroidal aromatase inhibitor
- IC50 on CYP11B2 : 1.6 ± 0.1nM, on CYP11B1 : 9.9 ± 0.9nM
- Good but incomplete specificity on CYP11B2
- Rapid absorption (tmax ~ 1 hour).
- Half-life ~ 4 hour, no accumulation
- Exposure dose-linear and dose-proportional within the dose range 0.5 to 3 mg.
- Well tolerated following 2-week oral administration for doses <3mg/day in healthy normotensive males on a controlled salt diet

Menard J. et al. JACC 2010; 55: A61.E583

New Pharmacological Approach : Inhibition of Aldosterone Synthase : Compound FAD286A

- Dose-dependent decrease of plasma and urine aldosterone concentrations and increase in PRA in SHRs on a low Na/High K diet

  J Ménard et al. J. Hypertens 2006;24: 1147

- Prevention of death, and reduction of cardiac hypertrophy and albuminuria in dTGR to human renin and angiotensinogen

  Fiebeler et al. Circulation. 2005;111:3087

- Improvement of LV hemodynamics, remodelling, and function, in a rat model of CHF to a similar extent than spironolactone

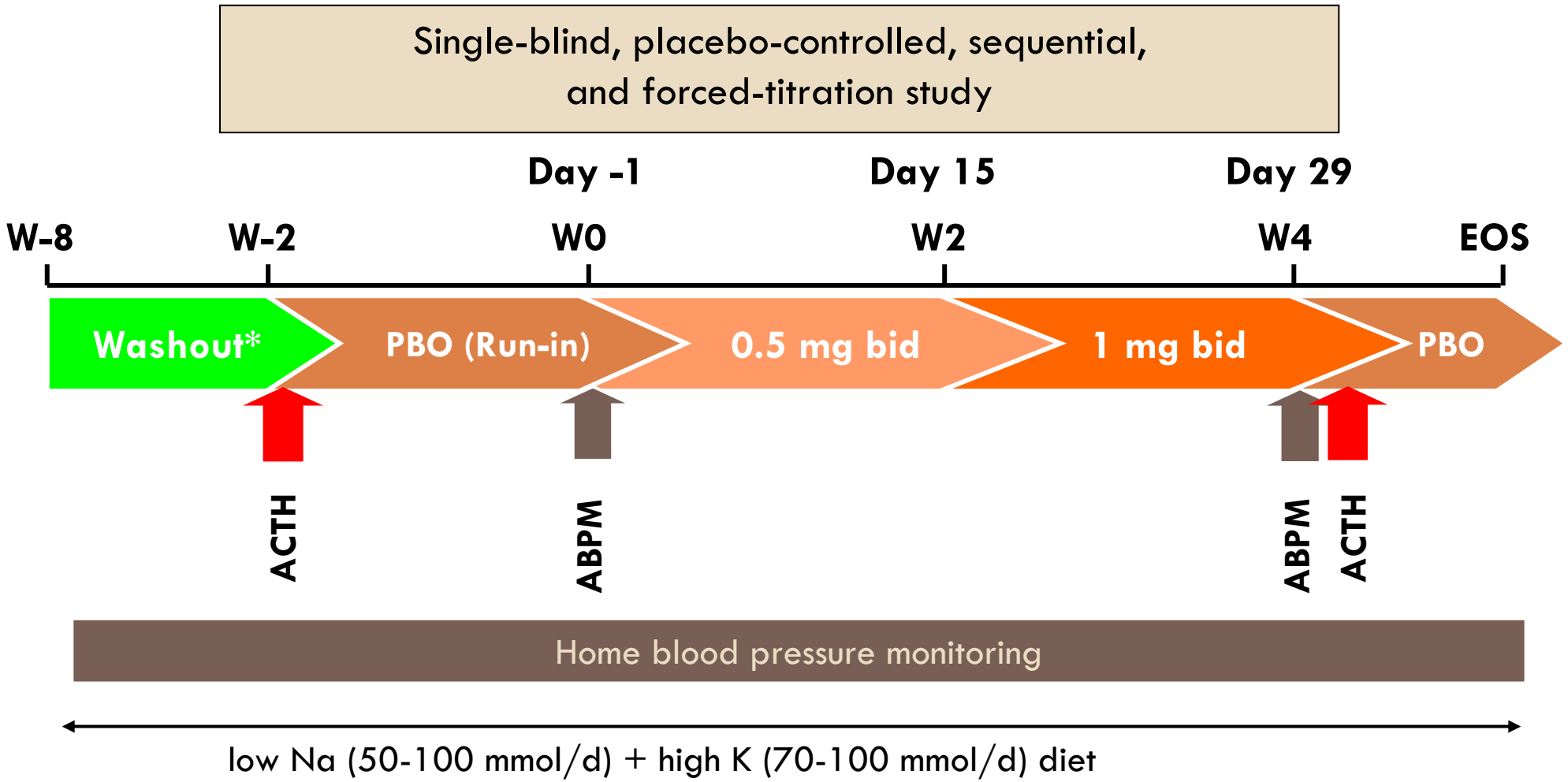
  Mulder P et al. Eur Heart J. 2008; 29 : 2171

- Prevention of albuminuria and azotemia and reduction of LVH and fibrosis in uniNx rats treated with Ang II and high salt diet to a similar extent than spironolactone

  Lea WB et al Kidney 2009; 75: 936

Inhibition of Aldosterone Synthase with LCI699 : patients with primary aldosteronism

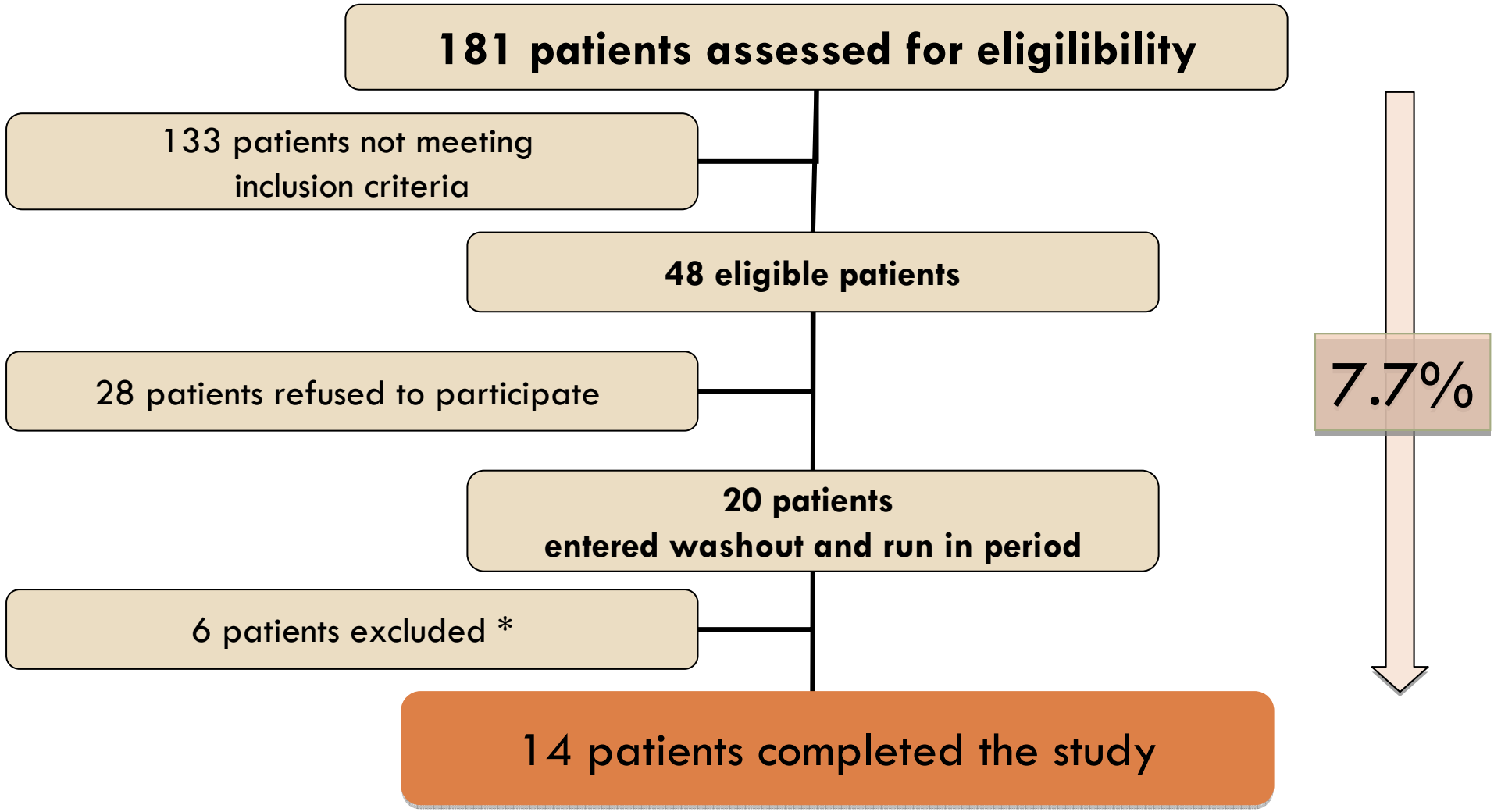
Amar et al. Hypertension 2010; 56:831-8



* 2- to 6-week washout period, to stop all antihypertensive medication interfering with the RAAS

Inhibition of Aldosterone Synthase with LCI699 : patients with primary aldosteronism

Amar et al. Hypertension 2010; 56:831-8



* abnormal test result: n=3; AE: acute AF, HBP >170/105 mmHg), protocol violation: n= 1

Inhibition of Aldosterone Synthase with LCI699 : patients with primary aldosteronism

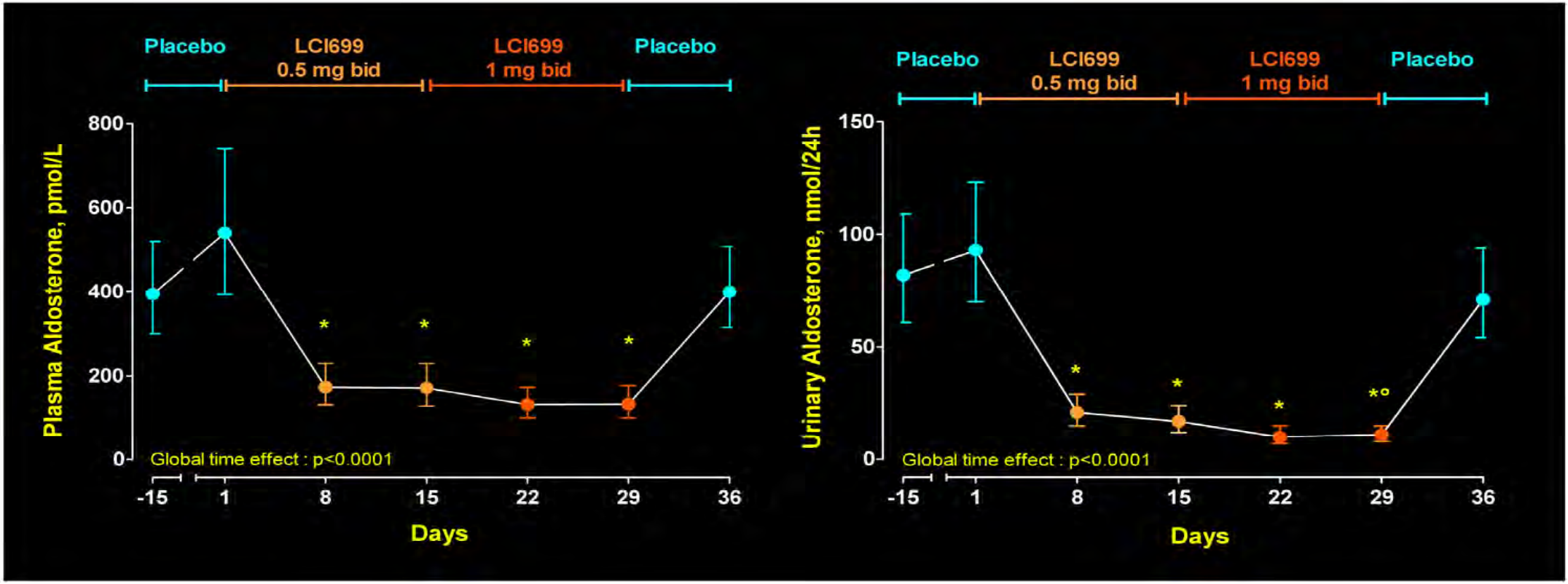
Amar et al. Hypertension 2010; 56:831-8

Clinical Characteristics: n=14	
Age (years)	50.3 ± 6.7
Male sex (n/N)	13/14
Office SBP (mmHg)	151 ± 17
Office DBP (mmHg)	91 ± 12
AHT score (n)	2 (1;3)
BMI (kg/m^2)	28.6 ± 3.0
Unilateral adrenal tumor on CT scan and/or lateralized AVS (n/N)	8/14
Time interval between diagnosis and inclusion (months)	6 (0.3;25)

Inhibition of Aldosterone Synthase with LCI699 : patients with primary aldosteronism

Amar et al. Hypertension 2010; 56:831-8

Effects on plasma and urinary aldosterone

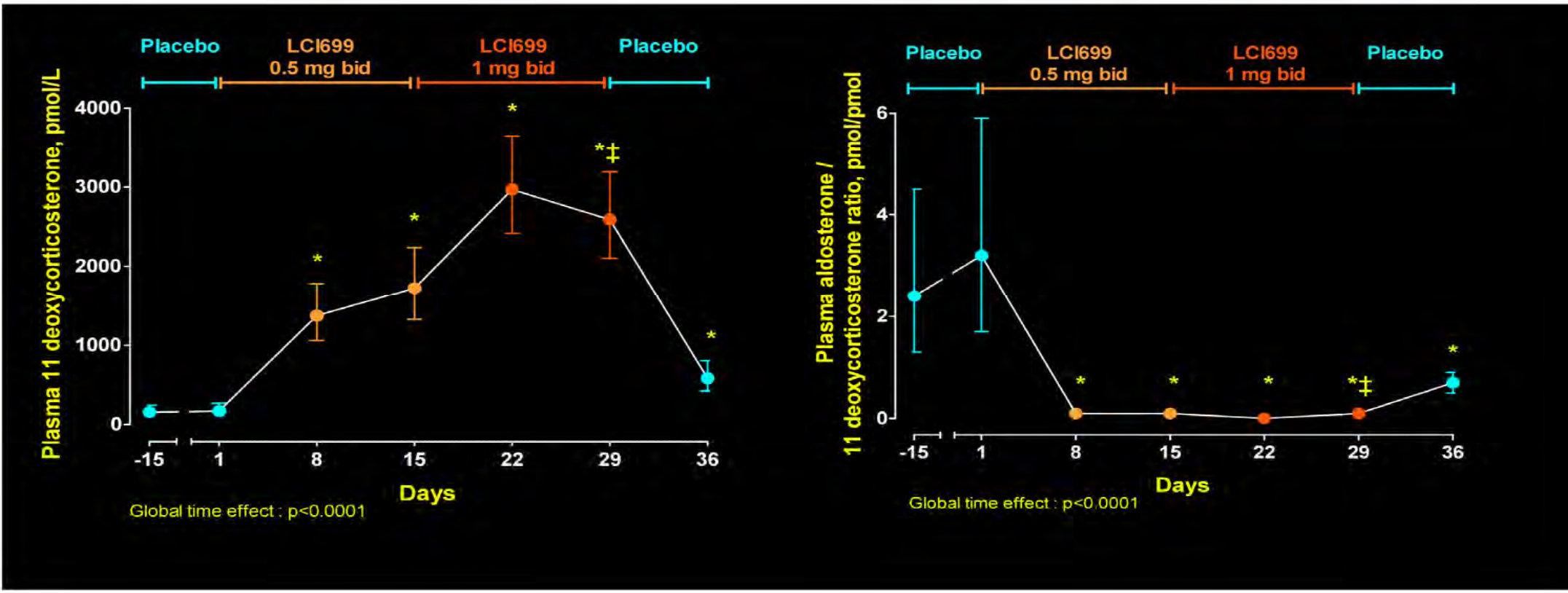


* adjusted P<0.0001 vs Day 1 and ° adjusted P<0.001 vs Day 15

Inhibition of Aldosterone Synthase with LCI699 : patients with primary aldosteronism

Amar et al. Hypertension 2010; 56:831-8

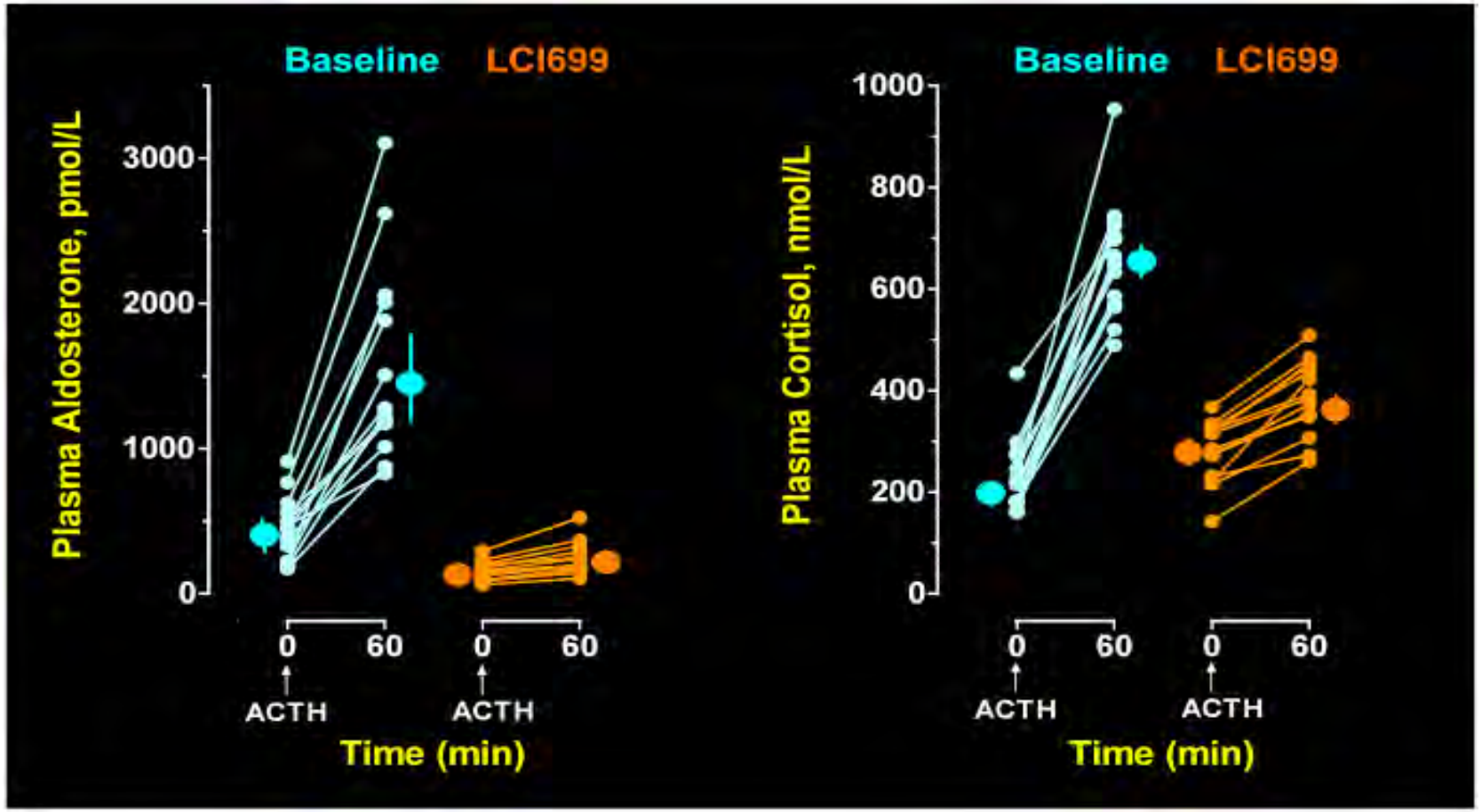
Dose-dependently increase of plasma 11 deoxycorticosterone and decrease of the aldosterone/DOC ratio



Inhibition of Aldosterone Synthase with LCI699 : patients with primary aldosteronism

Amar et al. Hypertension 2010; 56:831-8

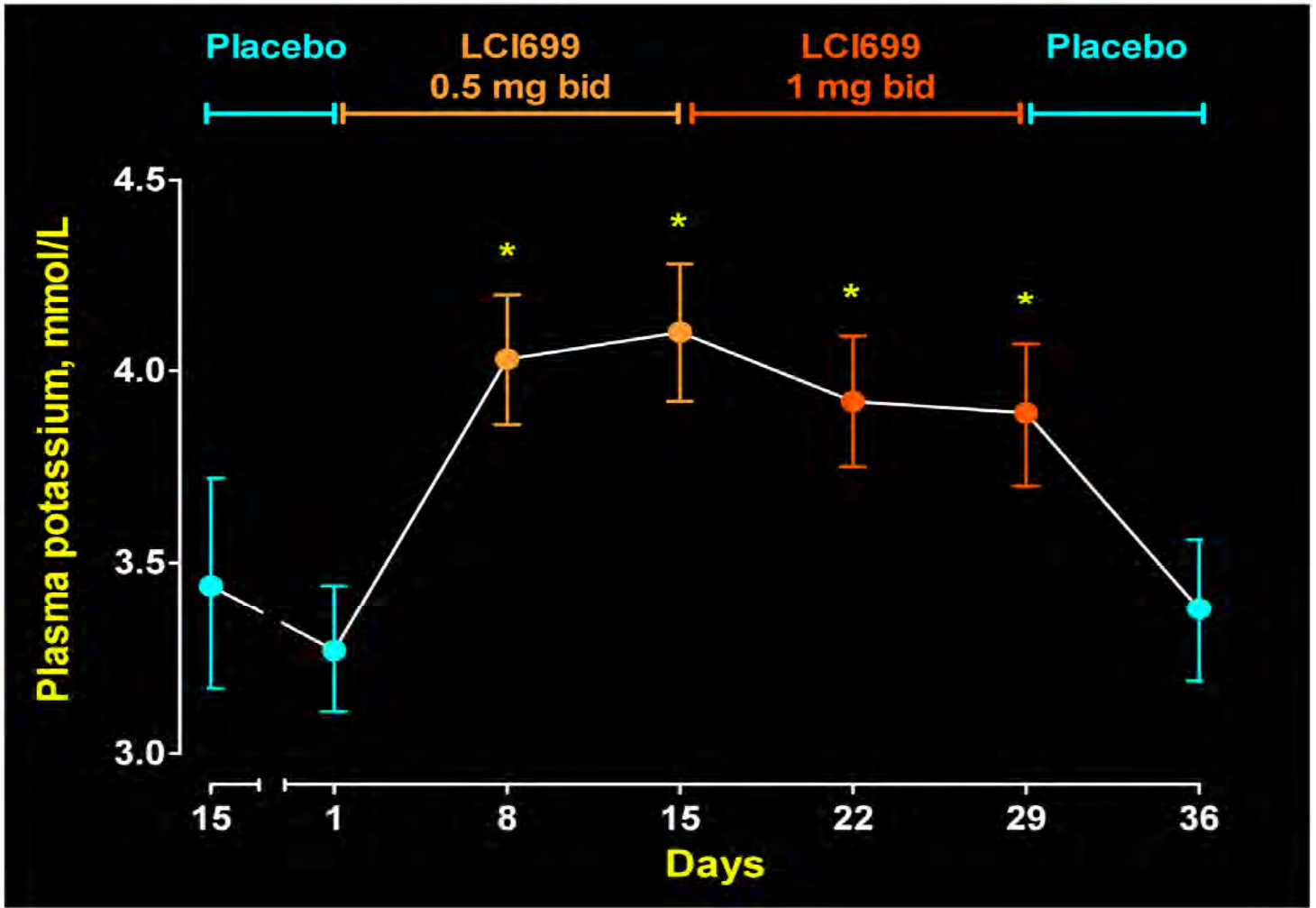
LCI699 blunts both aldosterone and cortisol responses to ACTH stimulation



Inhibition of Aldosterone Synthase with LCI699 : patients with primary aldosteronism

Amar et al. Hypertension 2010; 56:831-8

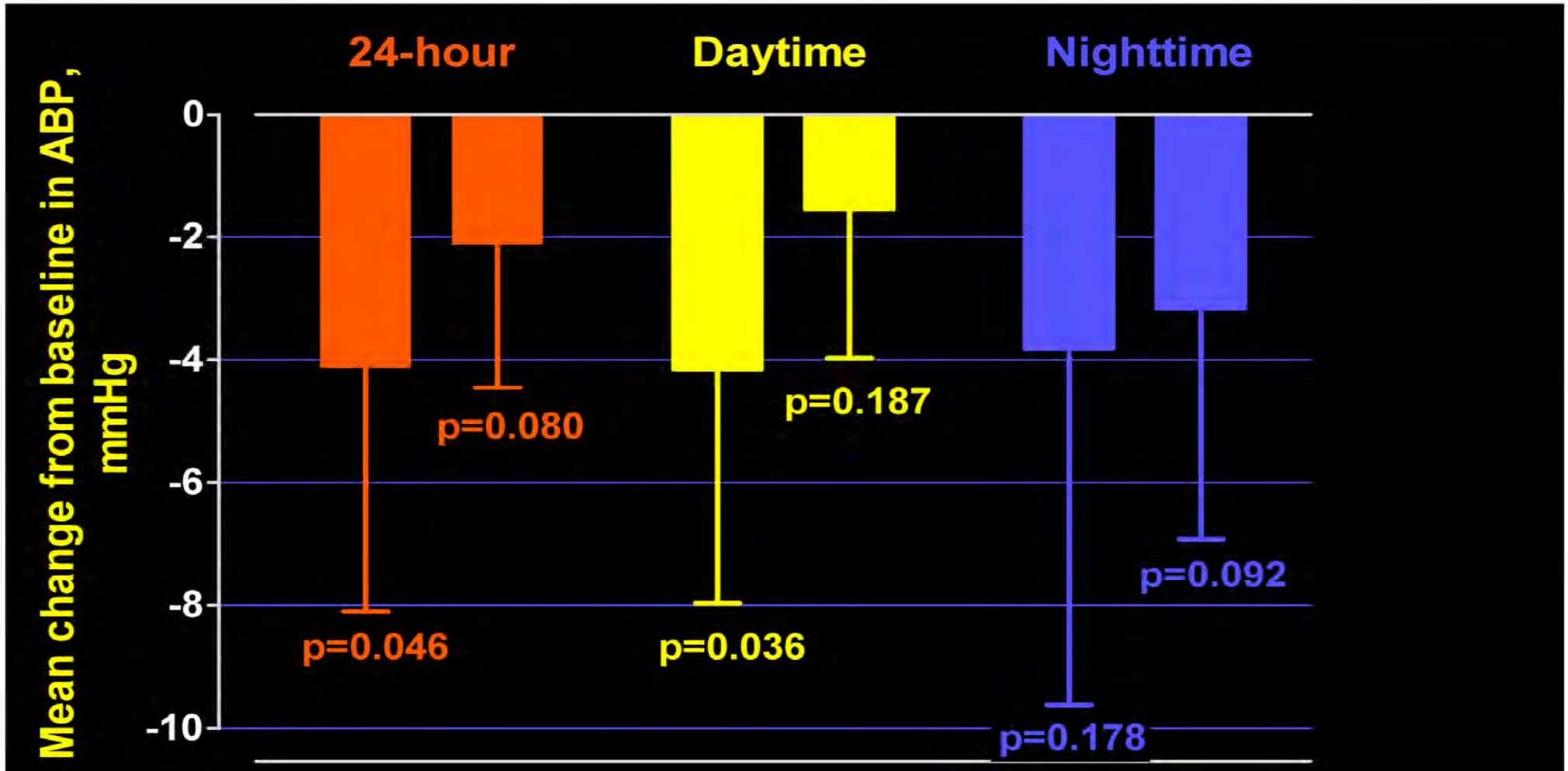
Effect on plasma potassium



Inhibition of Aldosterone Synthase with LCI699 : patients with primary aldosteronism

Amar et al. Hypertension 2010; 56:831-8

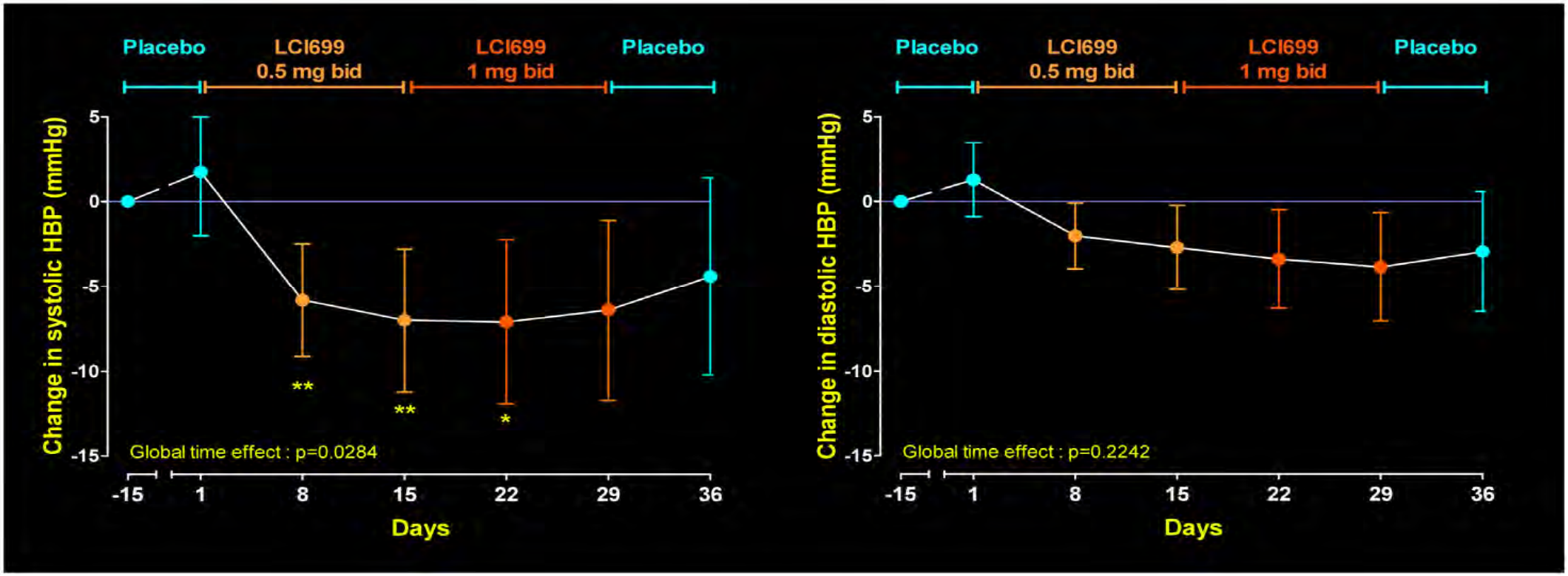
Effect on mean ambulatory blood pressure at week 4



Inhibition of Aldosterone Synthase with LCI699 : patients with primary aldosteronism

Amar et al. Hypertension 2010; 56:831-8

Effect on teletransmitted home blood pressure



Stratégie d'association:
Efficacité anti-hypertensive
Prévention des évènements cardiovasculaires

Surtout utiles dans les populations à haut risque CV

IEC / ARA2 + DIU + A Ca^{++}

Blocage du SRAA incontournable, à optimiser, en raison du phénomène d'échappement de l'aldostérone

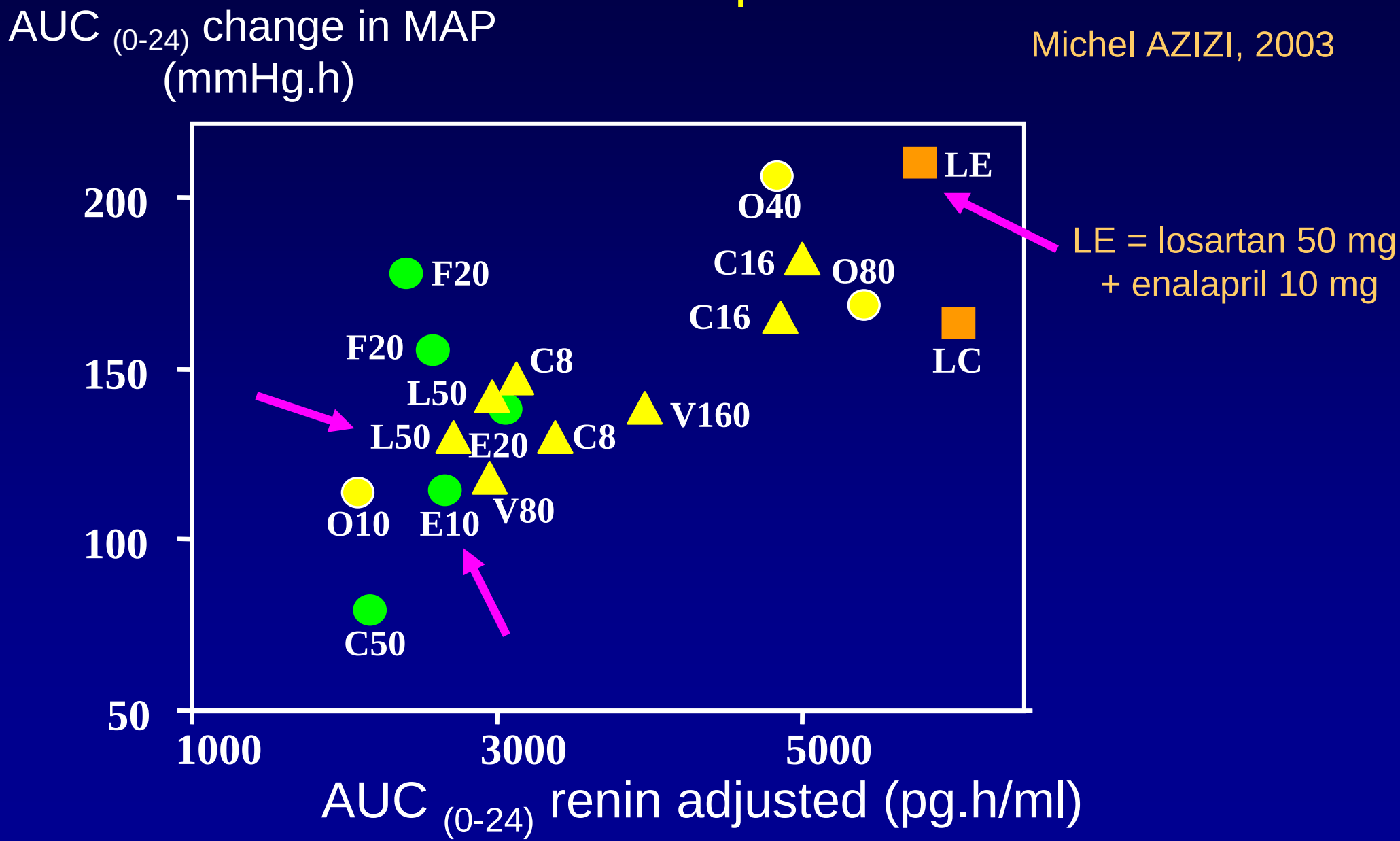
IEC / ARA2 + anti-aldo + DIU + A Ca^{++}

Innovations thérapeutiques
Associations fixes de première intention

- Nouvelles bithérapies fixes ?
  - IEC + ARA 2

Potency order of different RAS blockers on BP and plasma renin

Michel AZIZI, 2003

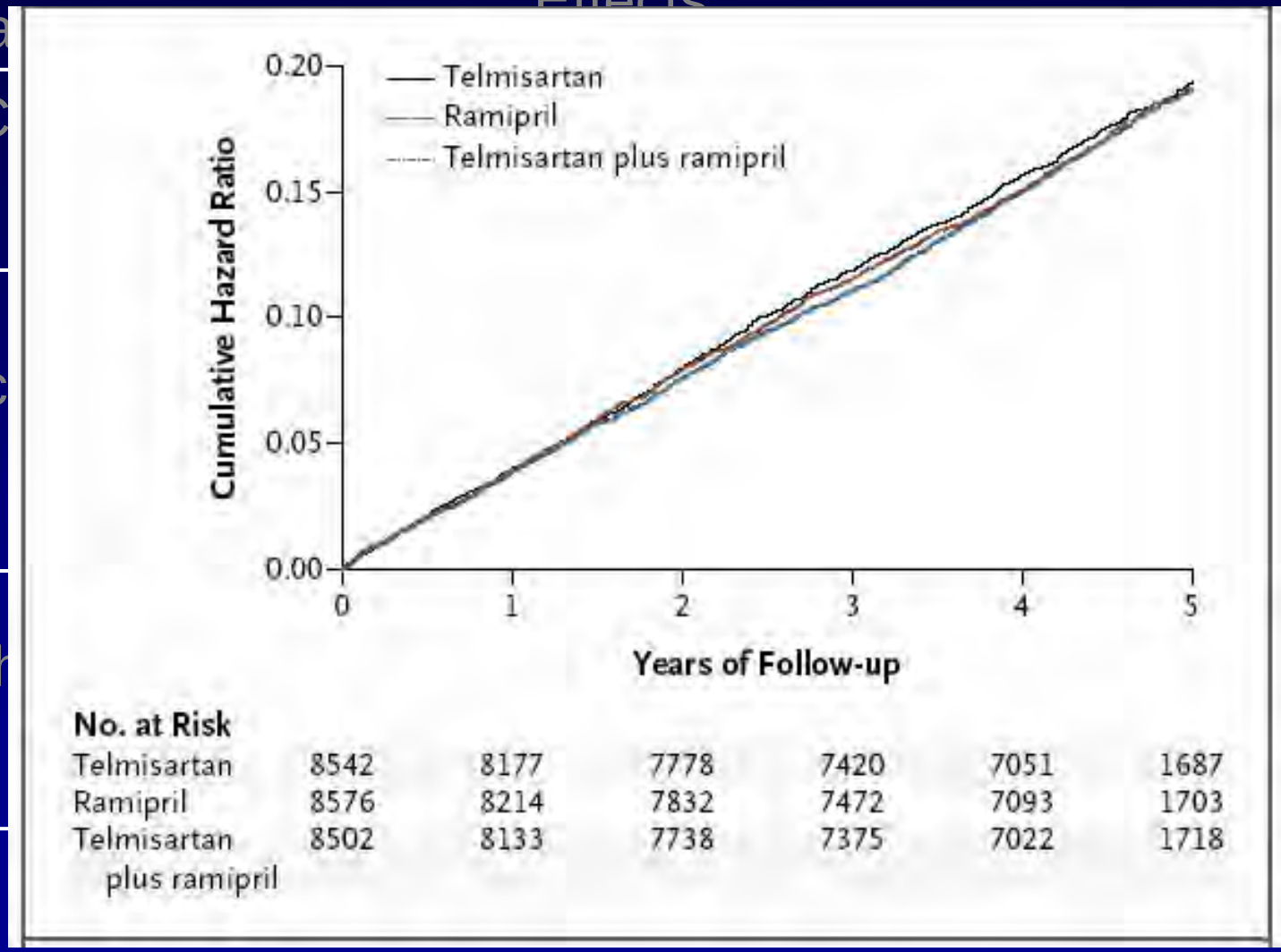


ONTARGET

Pharmacological class	Effects	Combination drug
CCB (C)	Σ activation	β-blockers (B)
	RAAS activation	ACEI (A)
Diuretics (D)		CEI (A)
		blockers (B)
ACE inhibitors or ARB (A)	« Renin » effect + « Volume » effect	Diuretics (D)

ACEi + ARB

ONTARGET



No. at Risk						
Telmisartan	8542	8177	7778	7420	7051	1687
Ramipril	8576	8214	7832	7472	7093	1703
Telmisartan plus ramipril	8502	8133	7738	7375	7022	1718

Innovations thérapeutiques
Associations fixes de première intention

- Nouvelles bithérapies fixes ?
  - IEC + ARA 2
  - IEC + A Ca^{++}

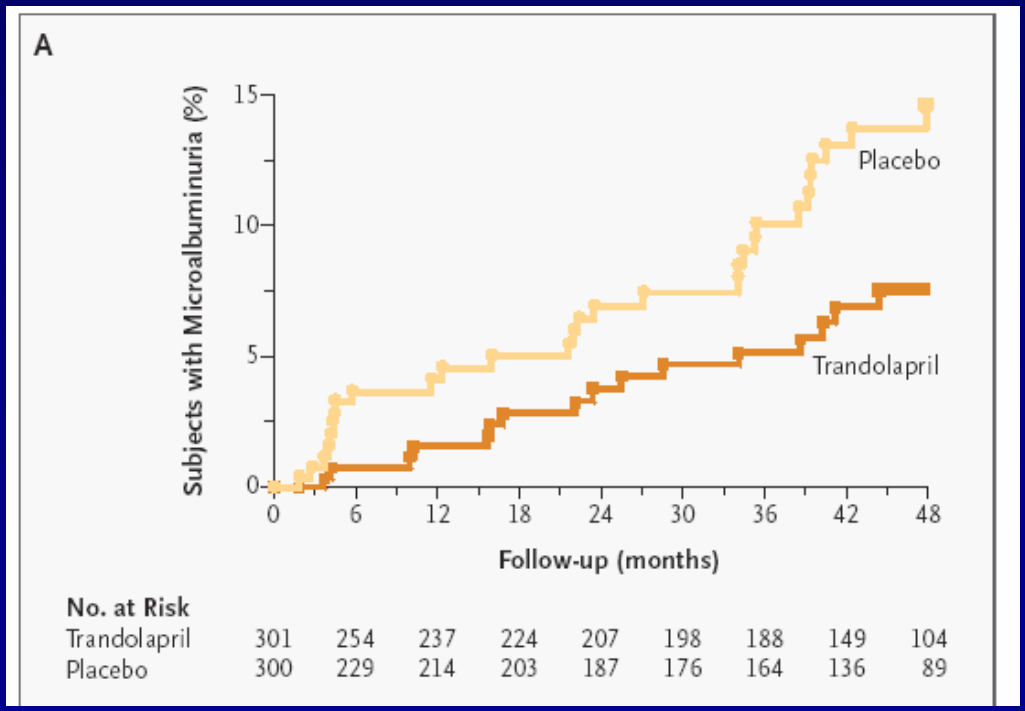
ASCOT
ACCOMPLISH

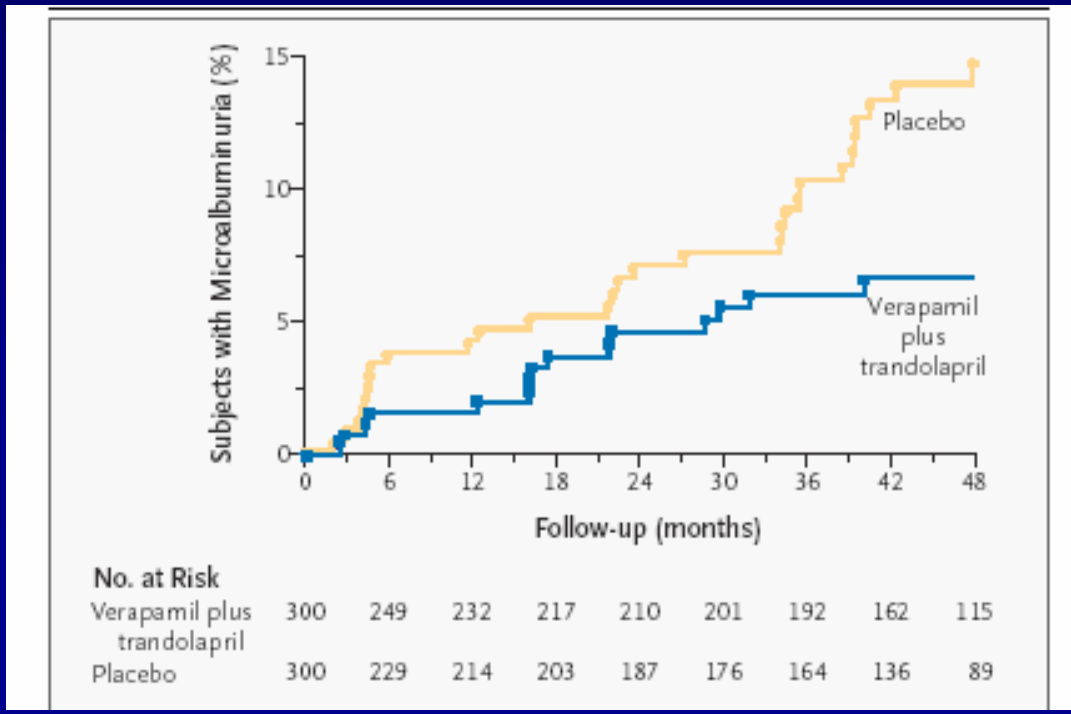
Etude BENEDICT

Ruggenenti P et al. NEJM, 2004

Critère I : apparition d'une microalbuminurie chez le DT2 HT

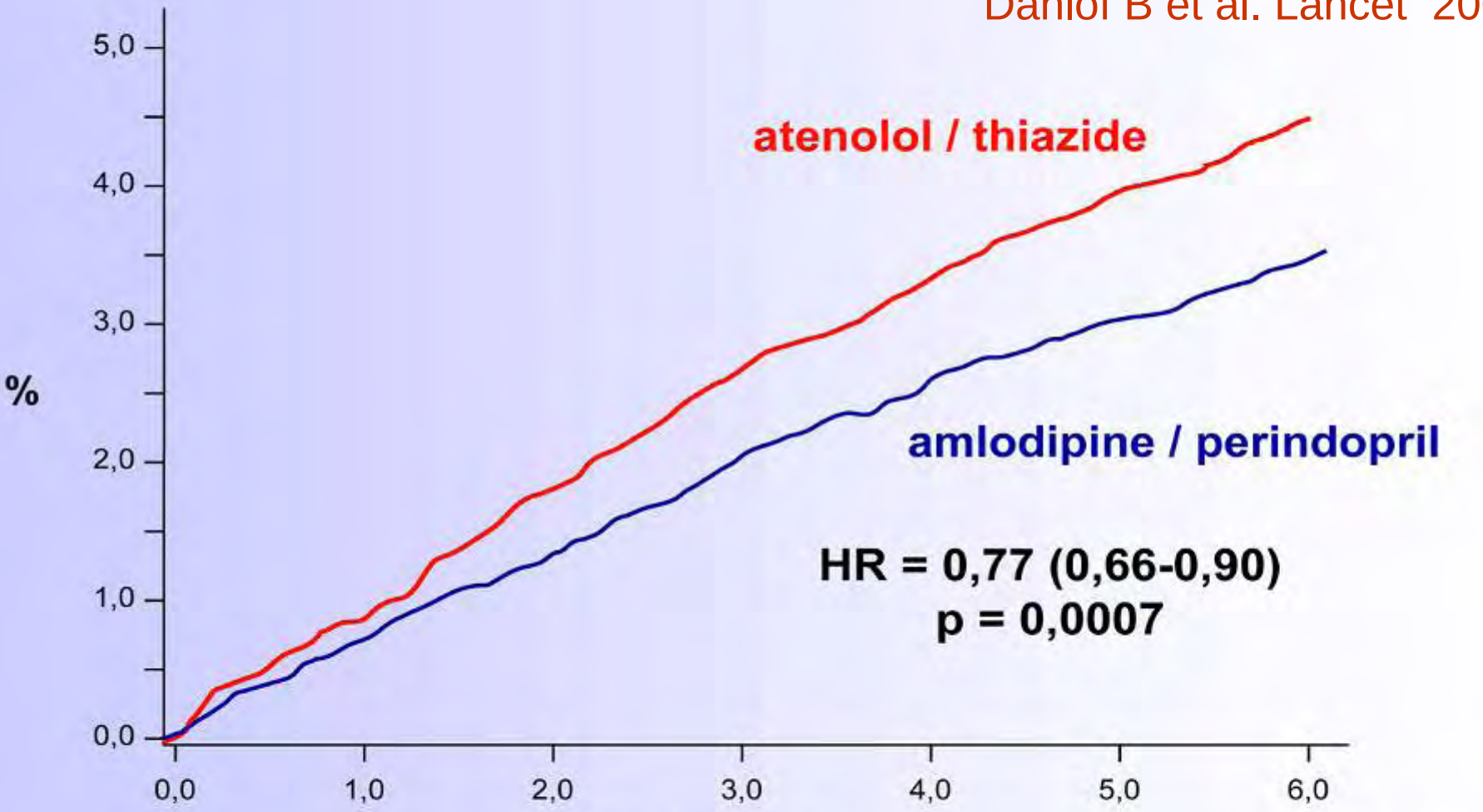
Vérapamil + Trandolapril # Trandolapril > placebo





Fatal and non fatal strokes

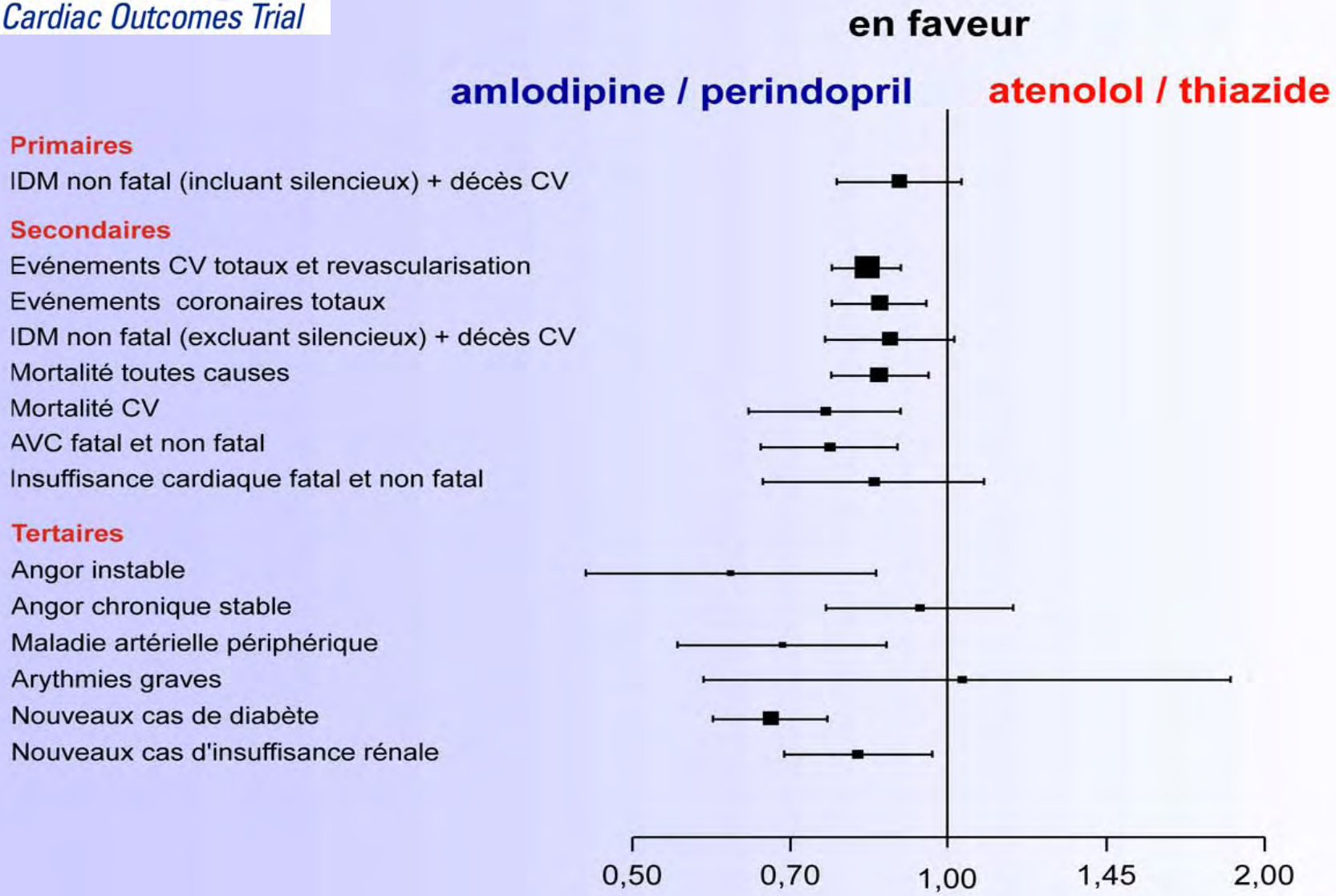
Dahlof B et al. Lancet 2005



ascot

Anglo-Scandinavian ascot Cardiac Outcomes Trial

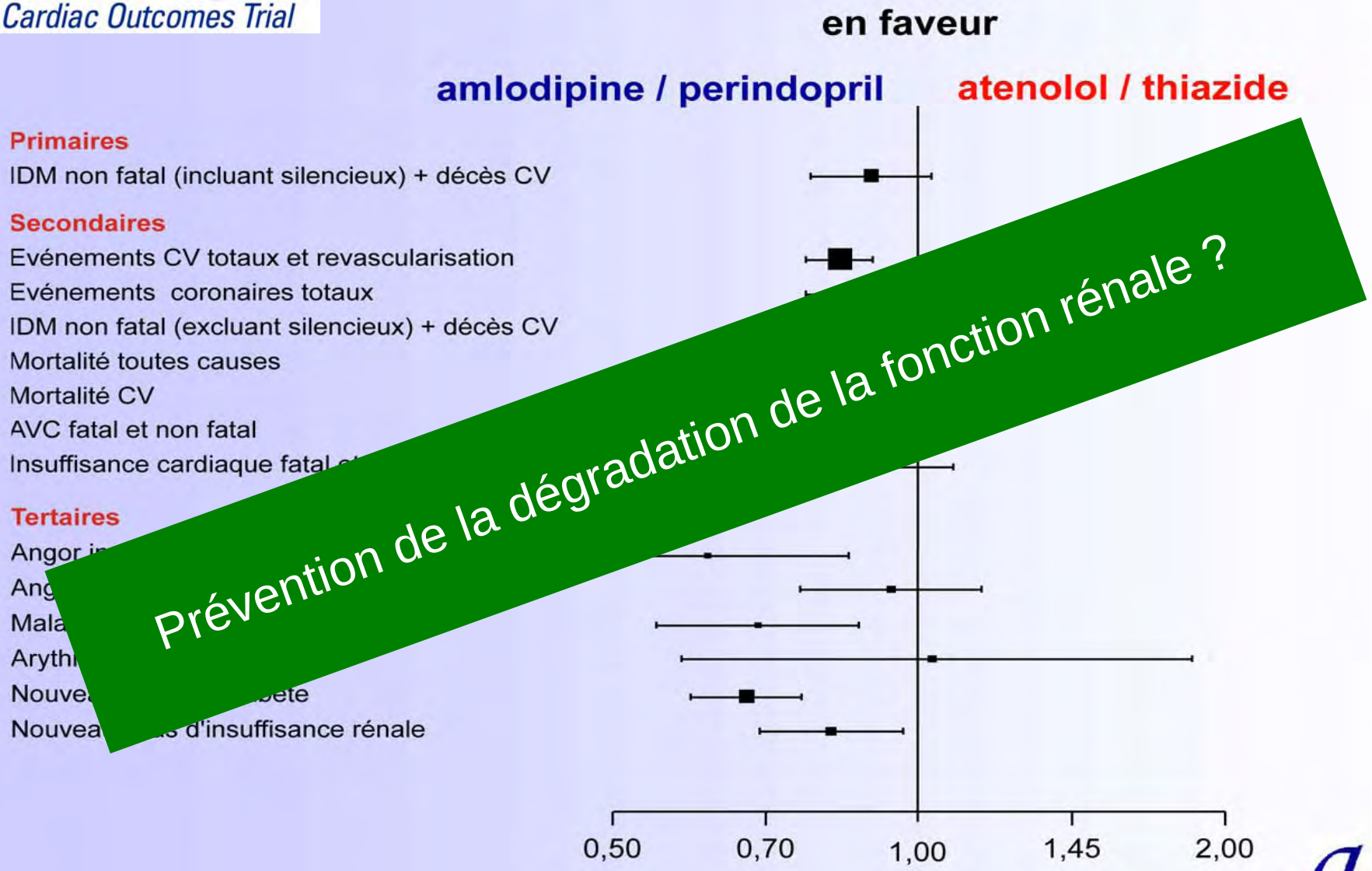
Résultats sur les différents critères



ascot

Anglo-Scandinavian ascot Cardiac Outcomes Trial

Résultats sur les différents critères

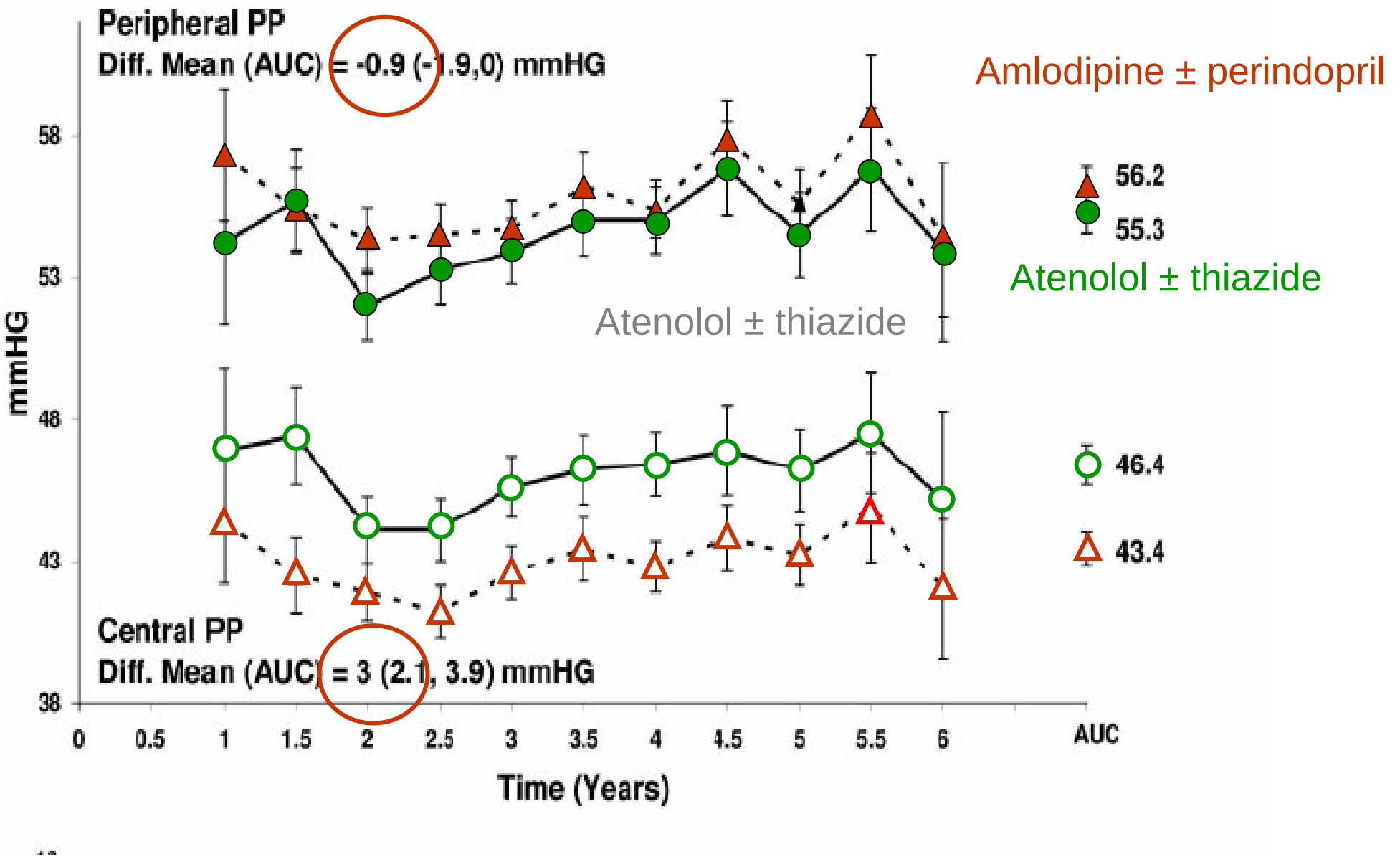


Prévention de la dégradation de la fonction rénale ?

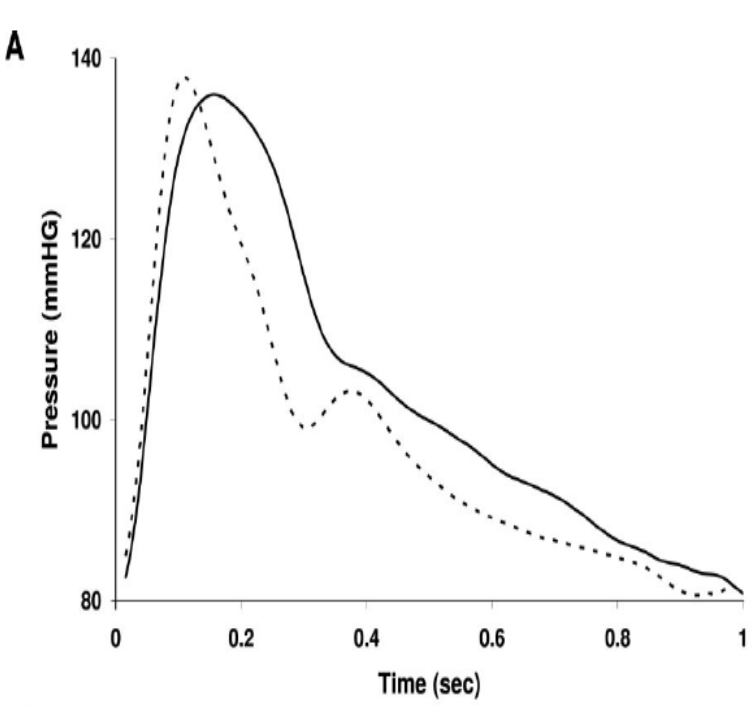
ascot

ACC - March 8, 2005 - Preliminary data

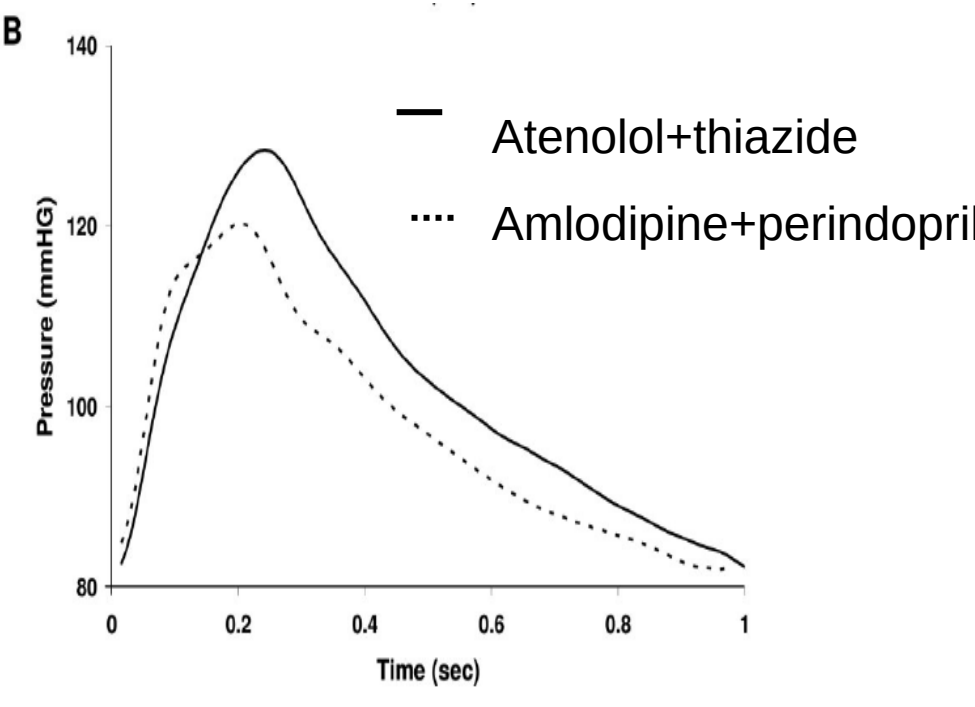
CAFE study : Williams B et al. Circulation 2006



Effect of atenolol or amlodipine+perindopril on pressure wave morphology the CAFÉ trial



Peripheral BP



Central BP

+++ Central pulse pressure : independent predictor of CV outcomes +++

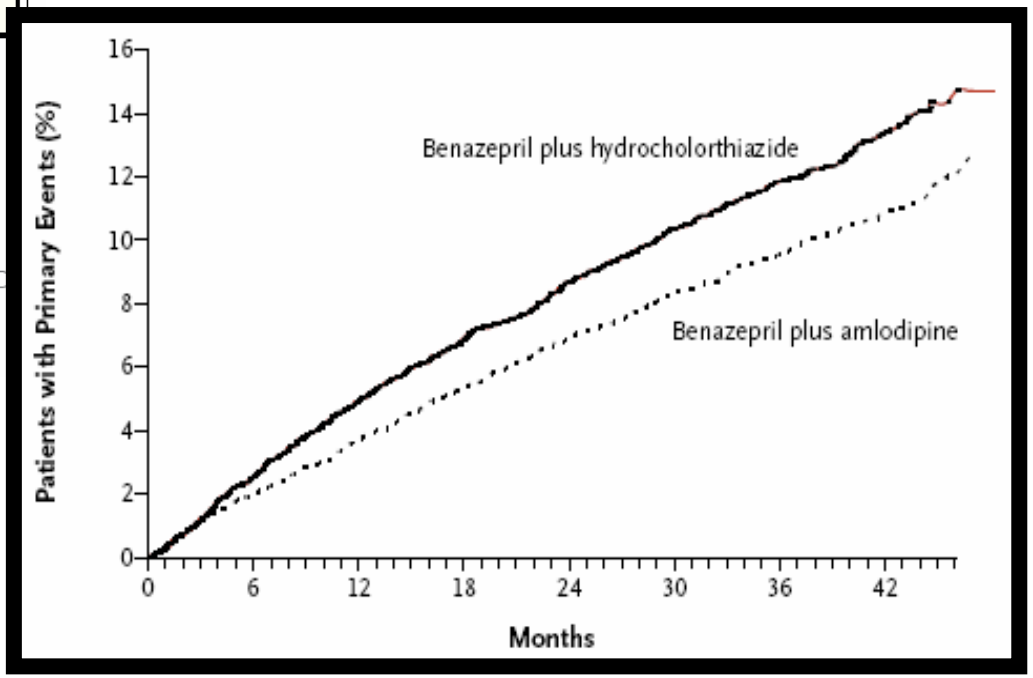
The NEW ENGLAND JOURNAL of MEDICINE

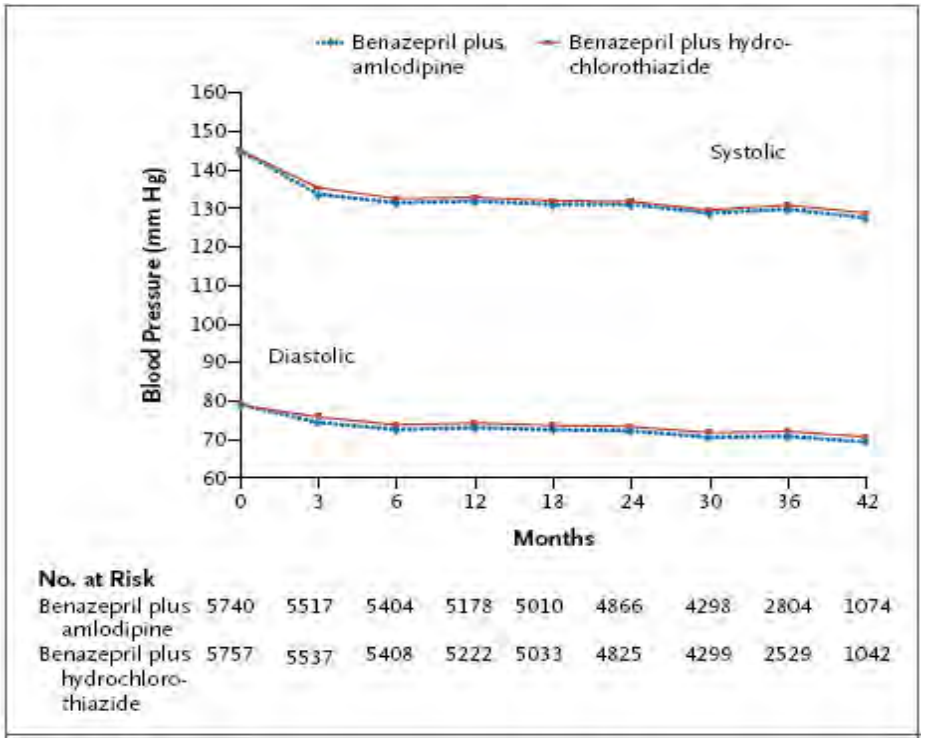
ESTABLISHED IN 1812 DECEMBER 4, 2008 VOL. 359 NO. 23

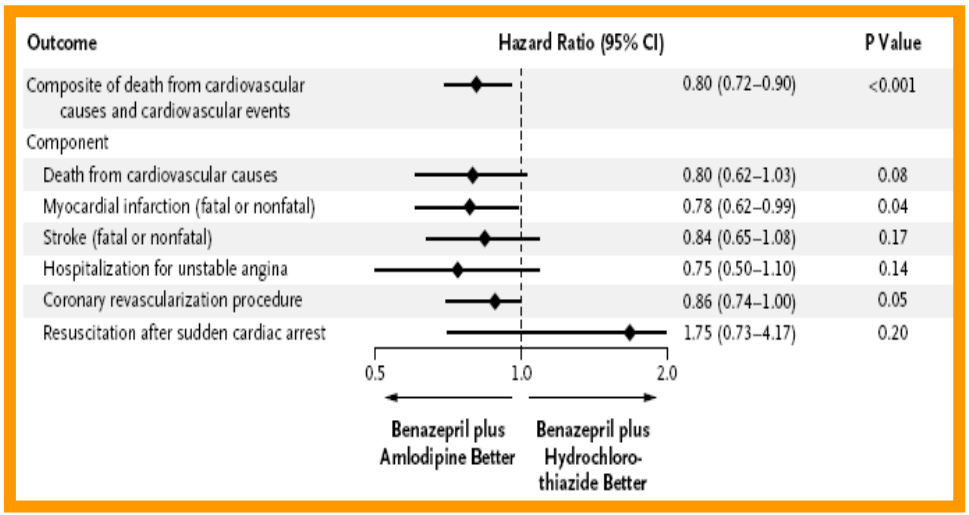
Benazepril plus Amlodipine or Hydrochlorothiazide for Hypertension in High-Risk Patients

Kenneth Jamerson, M.D., Michael A. Weber, M.D., George L. Bakris, M.D., Björn Dahlöf, M.D., Bertram Pitt, M.D., Victor Shi, M.D., Allen Hester, Ph.D., Jitendra Gupte, M.S., Marjorie Gatlin, M.D., and Eric J. Velazquez, M.D., for the ACCOMPLISH trial investigators*

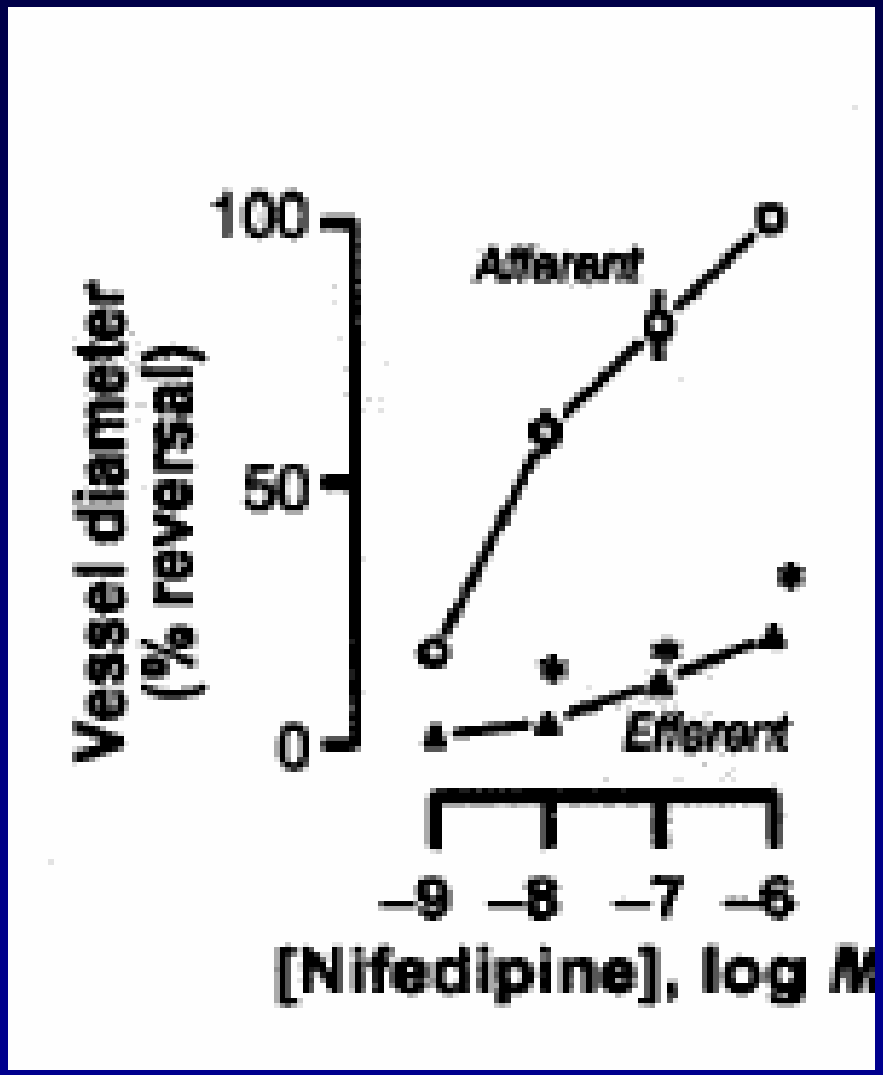
Primary endpoint: CV event or death from CV cause

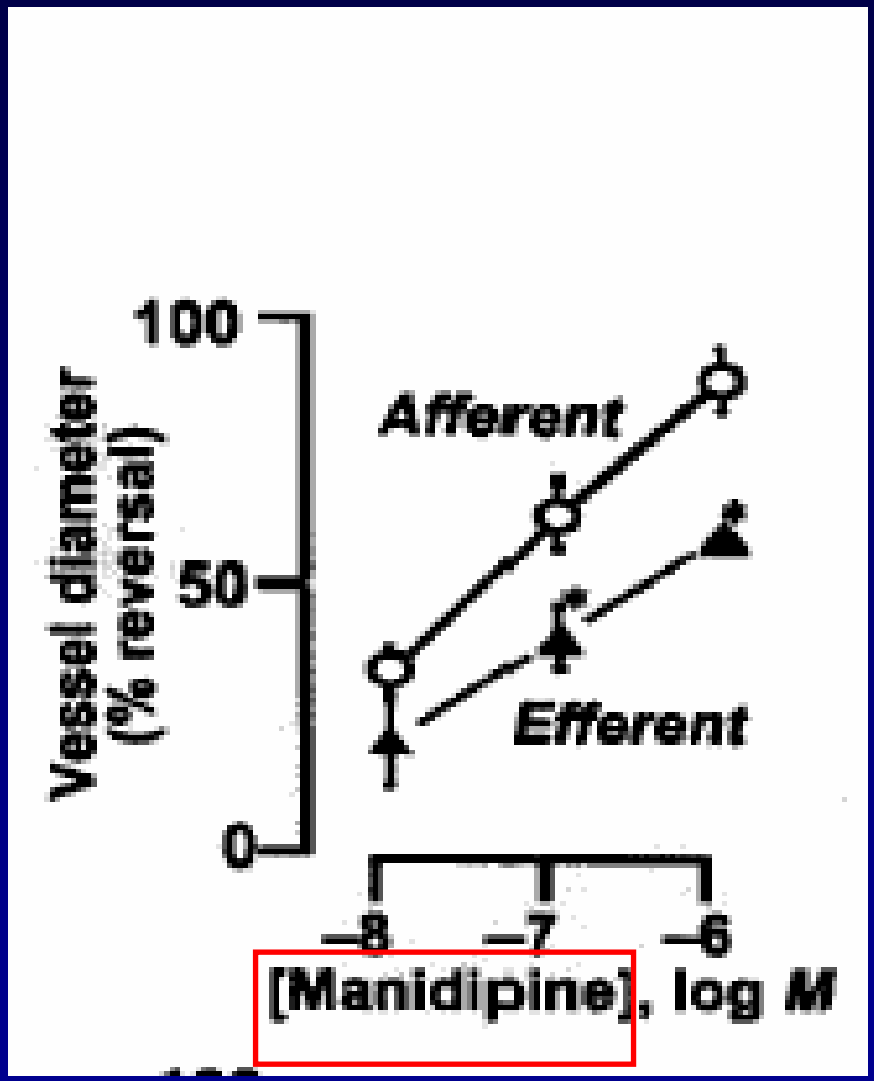






Efferent VD effect of manidipine



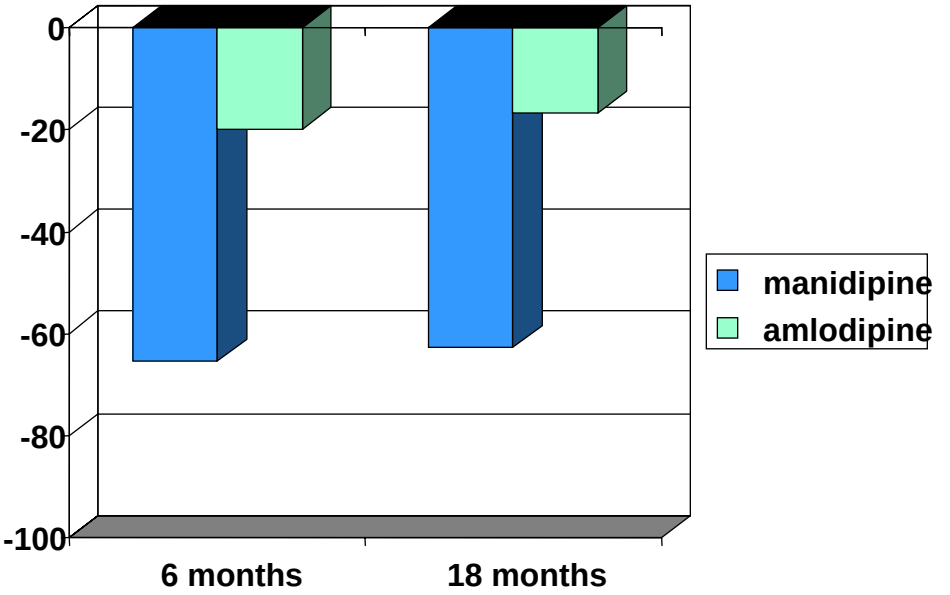


Am J Nephrol 2003; 23:229-244 DOI: 10. 1159/00002054

Reduction of microalbuminuria with manidipine versus amlodipine

- 91patients withdiabetes type 2 and hypertension+microalbumuria
  - 18 months treatment
- Manidipine better tolerated than amlodipine

Reduction in microalbuminuria (%)



Expert Rev Cardiovasc Ther. 2008

Other clinical evidence with manidipine

- Equivalent tolerance and efficacy on blood pressure of manidipine/delapril versus olmesartan/HCTZ
  - in elderly hypertensives (1)
    - Less orthostatic hypotension
  - in diabetic hypertensives (2)
  - In obese patients
    - Decreased insulin resistance and inflammation (4)
- Manidipine versus amlodipine
  - in diabetic hypertensives
    - Less microalbuminuria (3)
  - In elderly hypertensives
    - Similar BP reduction (5)

(1) Fogari et al, Hypertens Res. 2008
(2) Roca-Cusachs et al, J Hypertens. 2008
(3) Expert Rev Cardiovasc Ther. 2008
(4) Fogari et al, Intern Med 2008
(5) Payeras et al, Clin Drug invest 2007

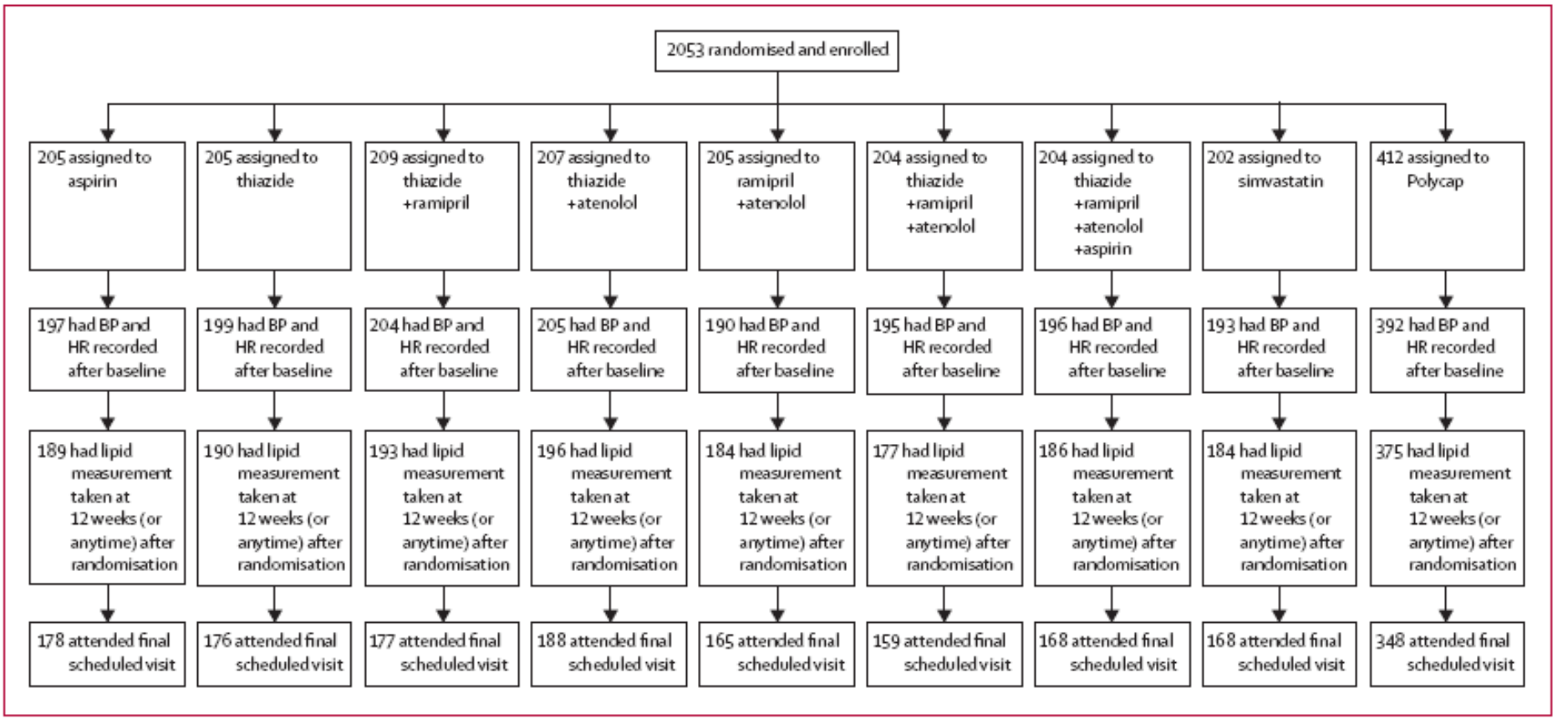
Prévention primaire des évènements cardiovasculaires chez l'hypertendu sans autre FR CV

Tri-thérapie anti-HTA ?

ou

1 anti-HTA + 1 statine + 1 AAS ?

The polypill approach

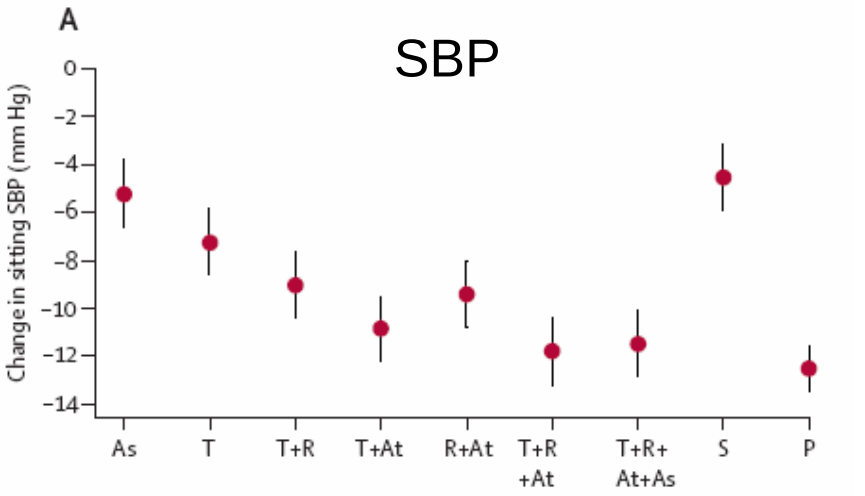


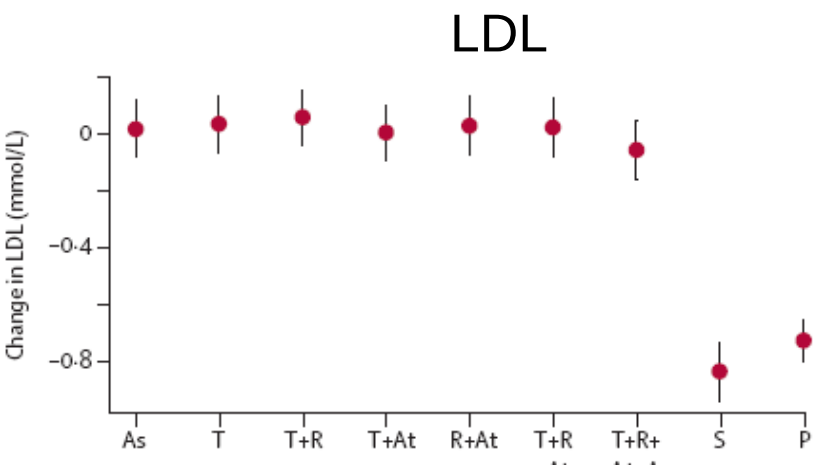
Lancet 2009

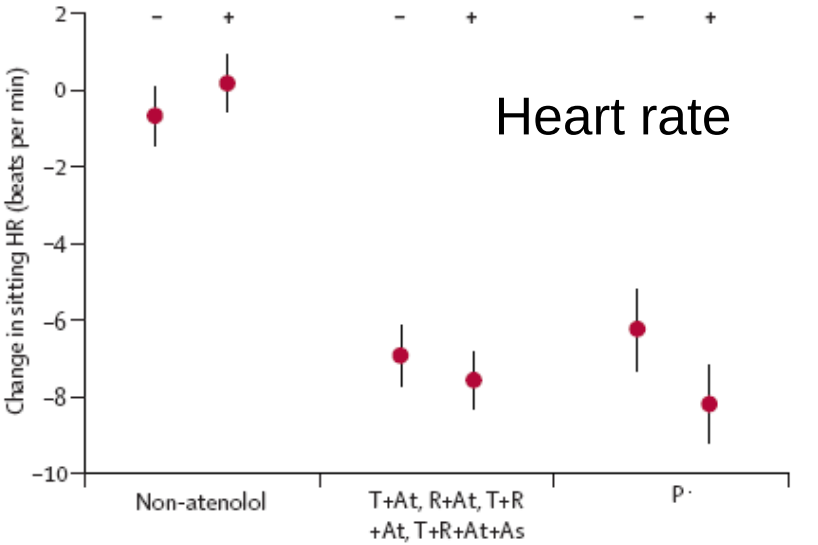
The polypill approach

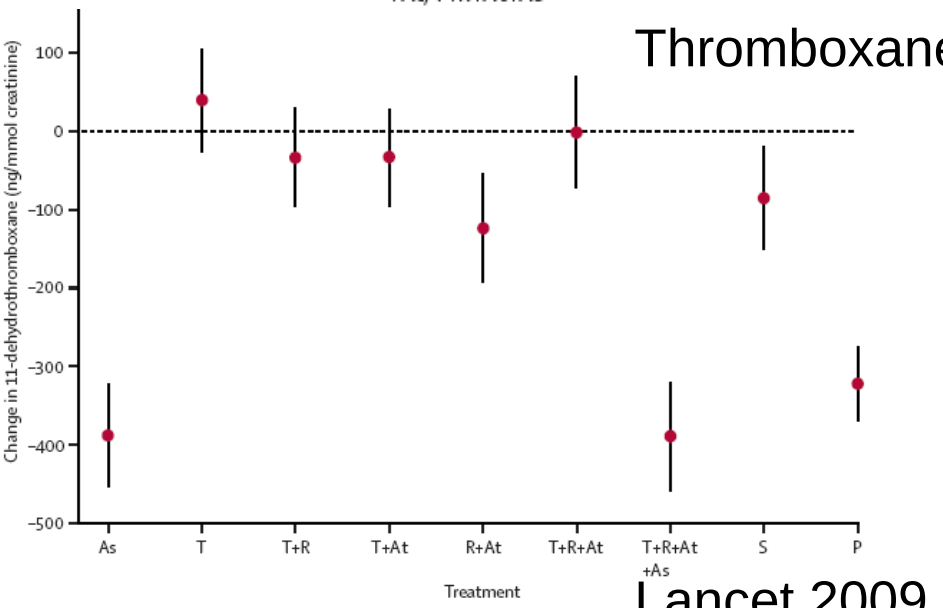
- **The combination of three blood-pressure-lowering drugs at low doses, with a statin, aspirin, and folic acid (the polypill), could reduce cardiovascular events by more than 80% in healthy individuals.**
- Polycap ➔ low doses of thiazide (12·5 mg), atenolol (50 mg), ramipril (5 mg), simvastatin (20 mg), and aspirin (100 mg) per day

Wald and Law, BMJ 2003

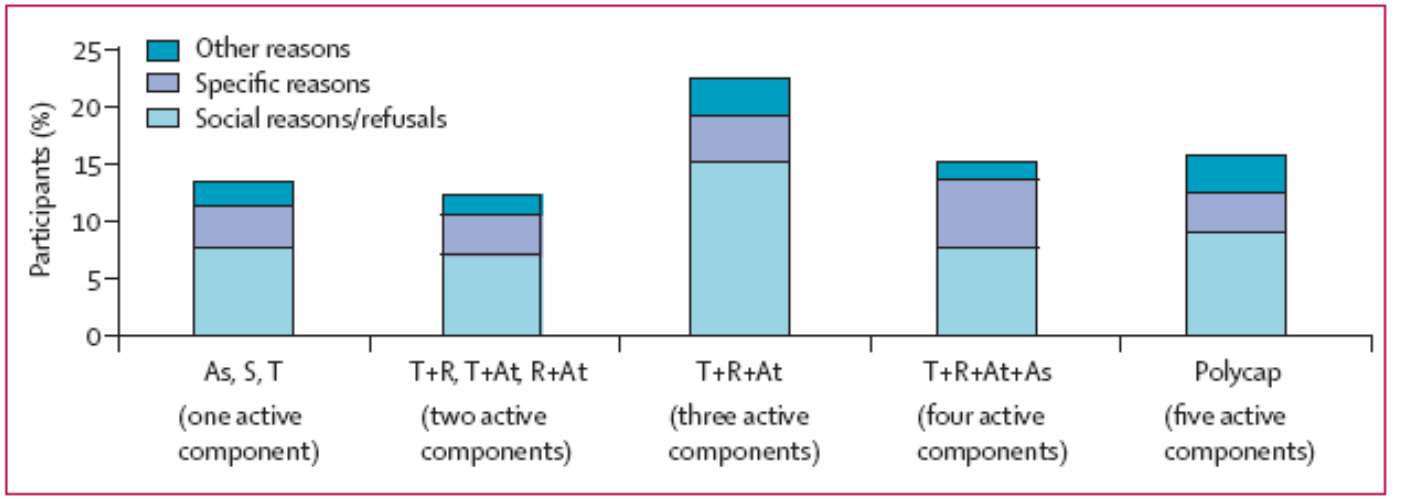

A
SBP
Change in sitting SBP (mm Hg)
0
-2
-4
-6
-8
-10
-12
-14
As
T
T+R
T+At
R+At
T+R +At
T+R+ At+As
S
P

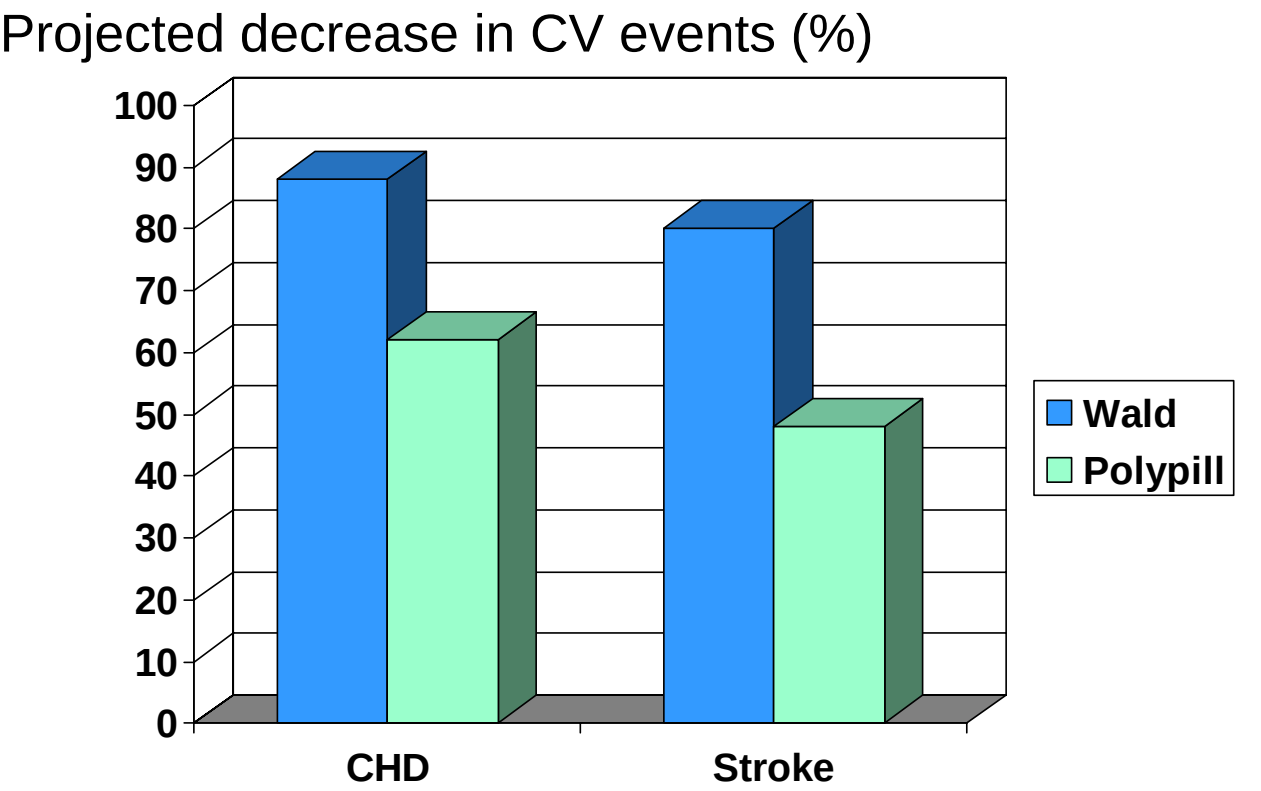

LDL
Change in LDL (mmol/L)
0
-0·4
-0·8
As
T
T+R
T+At
R+At
T+R
T+R+
S
P


Heart rate
Change in sitting HR (beats per min)
2
0
-2
-4
-6
-8
-10
-
+
-
+
-
+
Non-atenolol
T+At, R+At, T+R +At, T+R+At+As
P


Thromboxane
Change in 11-dehydrothromboxane (ng/mmol creatinine)
100
0
-100
-200
-300
-400
-500
As
T
T+R
T+At
R+At
T+R+At
T+R+At +As
S
P
Treatment

Lancet 2009


Other reasons
Specific reasons
Social reasons/refusals
Participants (%)
25
20
15
10
5
0
As, S, T
(one active component)
T+R, T+At, R+At
(two active components)
T+R+At
(three active components)
T+R+At+As
(four active components)
Polycap
(five active components)


Projected decrease in CV events (%)
100
90
80
70
60
50
40
30
20
10
0
CHD
Stroke
Wald
Polypill

New generation combos

- Triple associations mid/full dose
  - ACEi or ARB + Calcium antagonist + diuretic
    - Potential fall of SBP by more than 50 mmHg
    - Potential rate of control > 80 % at initiation
    - Tolerance better than monotherapy
- Polypil
  - Takes into account the multifactorial origin of risk
  - Multiple components of generic drugs
  - Low dose
  - Low price