Prévention médicamenteuse des complications de l'HTA : les grands essais

Pr. Jacques Blacher

Unité hypertension artérielle, prévention et thérapeutique cardiovasculaires
Centre de diagnostic et de thérapeutique, Hôtel-Dieu, Paris

Mars 2017

Déclaration de liens d'intérêt de Jacques Blacher :

- Absence de participation financière dans le capital d'une entreprise liée aux médicaments.

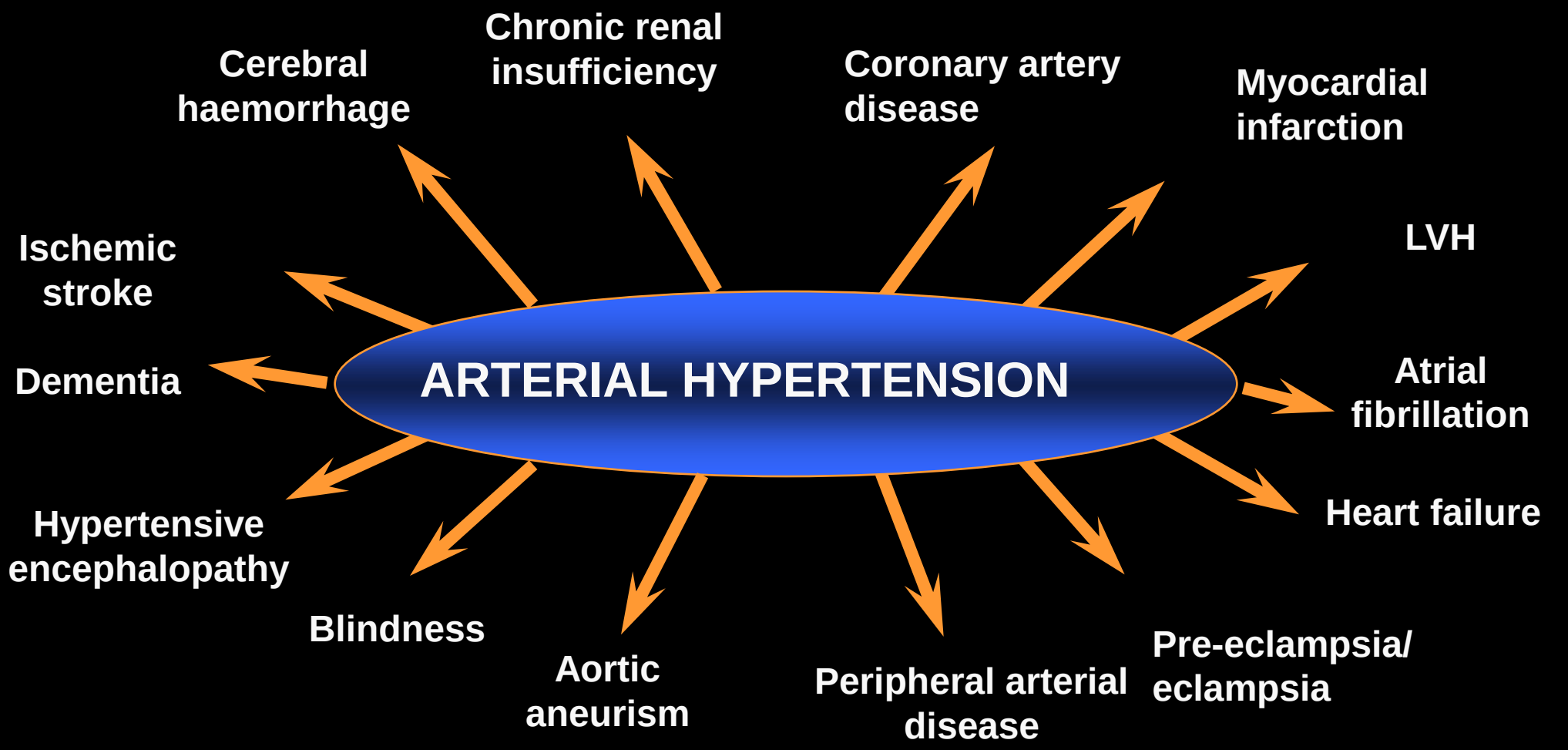
- Interventions ponctuelles en rapport avec des entreprises liées aux médicaments (essais cliniques, travaux scientifiques, comités scientifiques, rapports d'expertise, conférences, colloques, actions de formation, participation à divers symposia, rédaction de brochures...) avec, le cas échéant, facturation d'honoraires ; et ceci avec la majorité des entreprises du médicaments commercialisant des produits cardiovasculaires et autres produits en rapport avec mes domaines de spécialité (Amgen, Astra-Zeneca, Bayer, Boehringer Ingelheim, Bouchara, Daiichi Sankyo, Egis, Ferring, Ipsen, Lilly, Le Quotidien du Médecin, Medtronic, Menarini, MSD, Novartis, Pharmalliance, Pierre Fabre, Pileje, Sanofi Aventis, Saint Jude, Servier, Takeda).

- HAS, ANSM, CNAM, MGEN

Plan

- Observation / intervention
- Veterans / MRC / SHEP
- ALLHAT
- LIFE et ARA II - Problème de posologies - IEC
- ASCOT
- ACCOMPLISH
- HYVET
- SPRINT
- Méta-analyses

Hypertension : silent killer



Age-specific relevance of usual BP to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies.

Prospective Studies Collaboration Lancet 2002; 360: 1903–13*

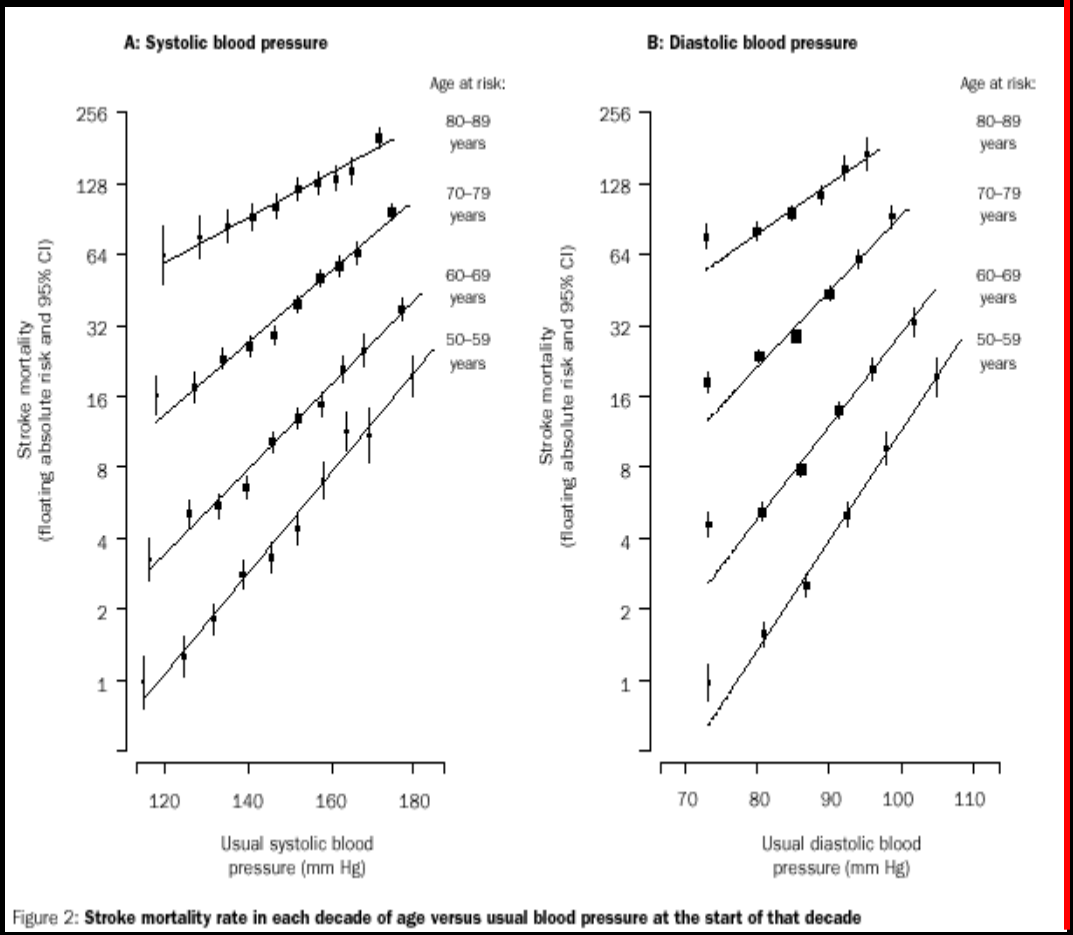


Figure 2: **Stroke mortality rate in each decade of age versus usual blood pressure at the start of that decade**

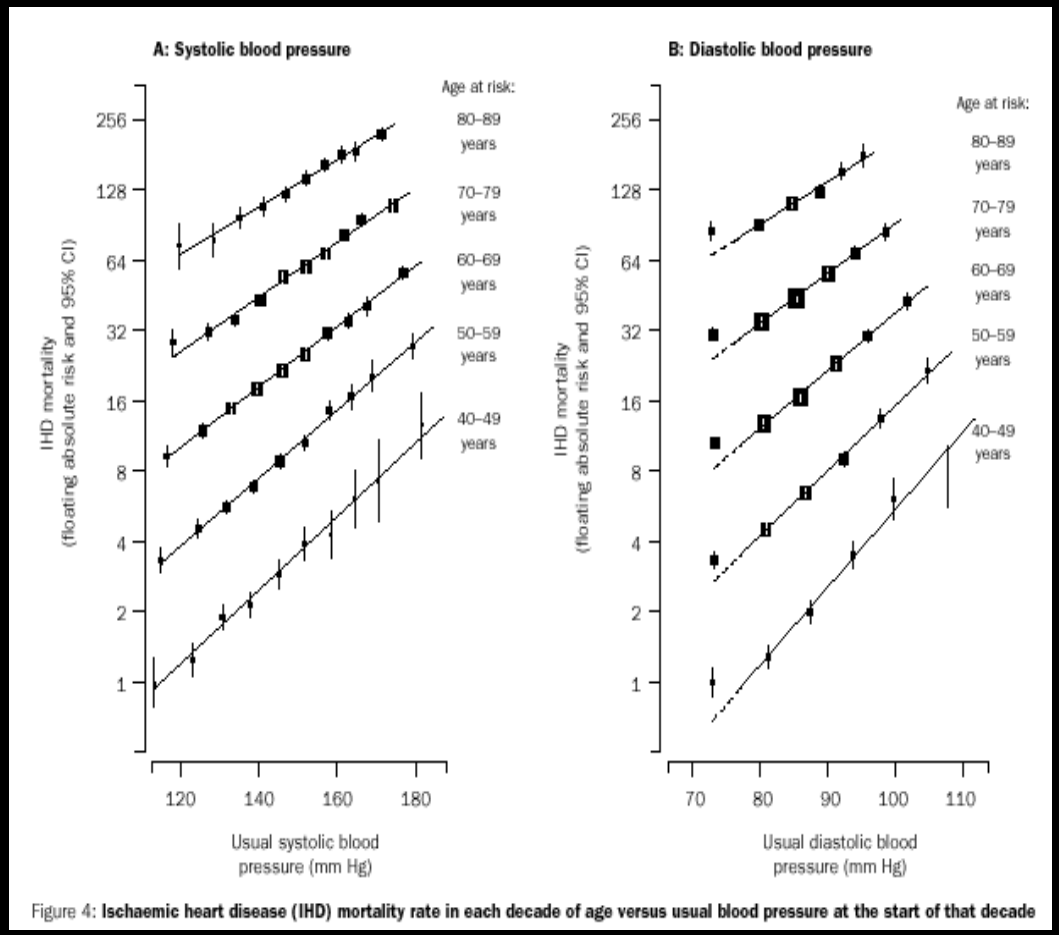
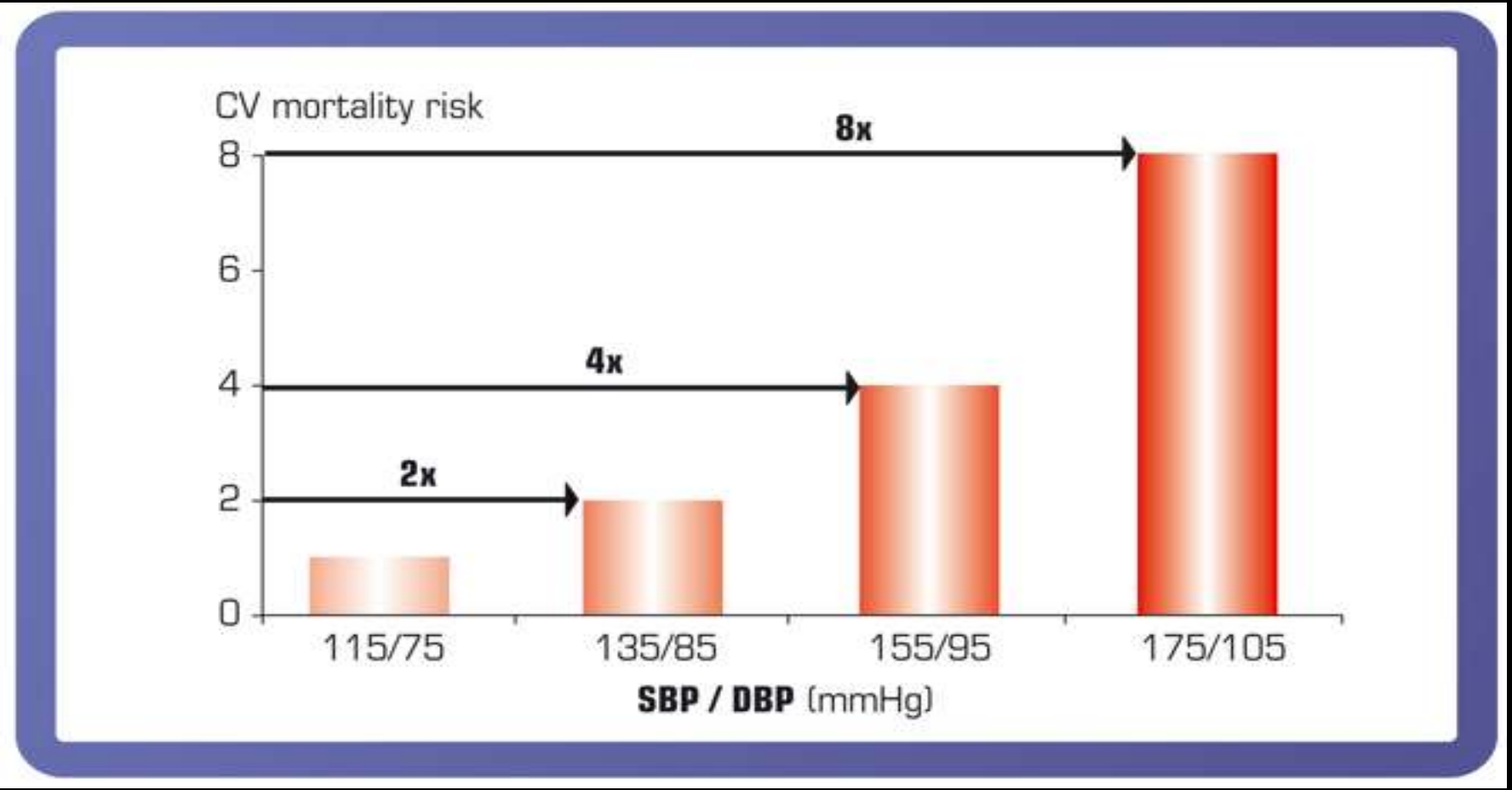


Figure 4: **Ischaemic heart disease (IHD) mortality rate in each decade of age versus usual blood pressure at the start of that decade**

Pour chaque augmentation de 10 mmHg de PAS ou de 5 mmHg de PAD, le risque moyen de mortalité cérébro-vx augmente de 40% et cardiaque ischémique de 30%.

Le risque de mortalité cardiovasculaire double pour chaque augmentation de PAS/PAD de 20/10 mmHg



* Individus âgés de 40–69 ans

Lewington et al. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002 ; 360 : 1903–13.

Dans les années 50, il n'était pas évident qu'il faille baisser la pression artérielle des hypertendus.

- Crainte d'effets délétères à type d'hypoperfusion des organes vitaux.
- (*Perera GA. Hypertensive vascular disease: description and natural history. J Chronic Dis 1955;1:33-42*).

Trois pionniers pensaient tout autrement, ils tentaient de réduire les chiffres de PA… … de façons bien différentes :

- **Walter KEMPLER pensait que le secret résidait dans l'alimentation. Il mettait ses patients à la diète et observait une réduction pondérale et une réduction tensionnelle.**

- **Le régime était exclusivement composé de riz et de fruits, faible en calories, faible en lipides, faible en protéines et faible en sodium (2 g de sel).**

- **(*Kempner W. Treatment of hypertensive vascular disease with rice diet. Am J Med 1948;4:545-577).***

Trois pionniers pensaient tout autrement, ils tentaient de réduire les chiffres de PA… … de façons bien différentes :

- Reginald SMITHWICK, chirurgien, pensait que la solution était … chirurgicale.

- Voie d'abord xyphopubienne :
  - sympathectomie bilatérale dorso-lombaire +
  - résection des ganglions sympathiques +
  - exérèse de la quasi-intégralité de l'innervation splanchnique.

- La pression artérielle baissait et certains patients survivaient.

- *(Smithwick RH. Surgical treatment of hypertension. Am J Med 1948:4:744-59).*

Trois pionniers pensaient tout autrement, ils tentaient de réduire les chiffres de PA…

… de façons bien différentes :

- **Robert WILKINS croyait en l'approche pharmacologique, tout d'abord avec des drogues anti-hypertensives que l'histoire n'a pas retenu:**
  - **Pentaquine (anti-paludéen),**
  - **Rauwolfia Serpentina,**
  - **Alcaloïdes du Veratrum,**
  - **Ganglioplégiques,**
  - **Hydralazine…**

- ***Freis ED, Wilkins RW. The effects of pentaquine in patients with hypertension. Proc Soc Exp Biol Med 1947;64:455-458.***
- ***Wilkins RW. New drug therapies in arterial hypertension. Ann Intern Med 1952;37:1144-1155.***
- ***Wilkins RW, Judson WE. The use of Rauwolfia serpentina in hypertensive patients. N Engl J Med 1953;248:48-5***

- **Jusqu'à l'avènement de l'Hydrochlorothiazide**

- ***Hollander W, Wilkins RW. Chlorothiazide: a new type of drug for the treatment of arterial hypertension. BMQ 1957;8:69-75.***

Plan

- Observation / intervention
- Veterans / MRC / SHEP
- ALLHAT
- LIFE et ARA II - Problème de posologies - IEC
- ASCOT
- ACCOMPLISH
- HYVET
- SPRINT
- Méta-analyses

Démonstration de l'efficacité du traitement anti-hypertenseur

Groupes	Nombre	PA diastolique	Evénements CV
Placebo	70	121	27 (39 %)
Traité	73	121	2 (2,7 %)

Patients ayant une PAD comprise entre 115 et 129 mmHg

Traitements actifs : Hydrochlorothiazide, Hydralazine, Réserpine

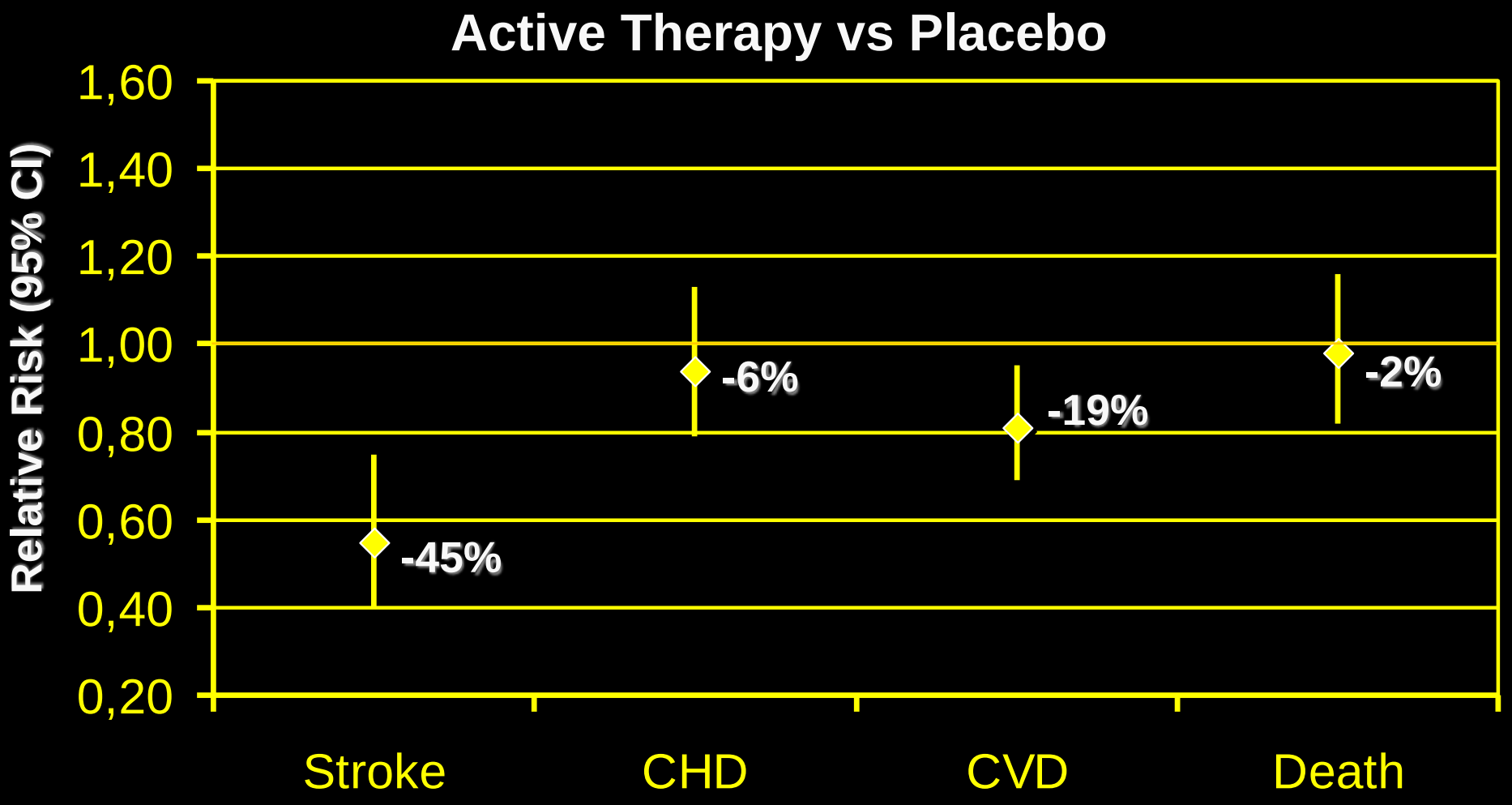
Veterans Administration Cooperative Study, JAMA 1967

MRC Trial: Design

- N: 17,354; 52% men
- Age: 35-64 years
- BP: diastolic BP 90 to 109 mm Hg
- Design: 3 treatment groups
- Treatment: bendrofluazide vs propranolol vs placebo
- Diastolic BP difference: 6 mm Hg
- Duration: 5.5 years

MRC Working Party. *BMJ*. 1985;291:97-104.

MRC Trial: Endpoints



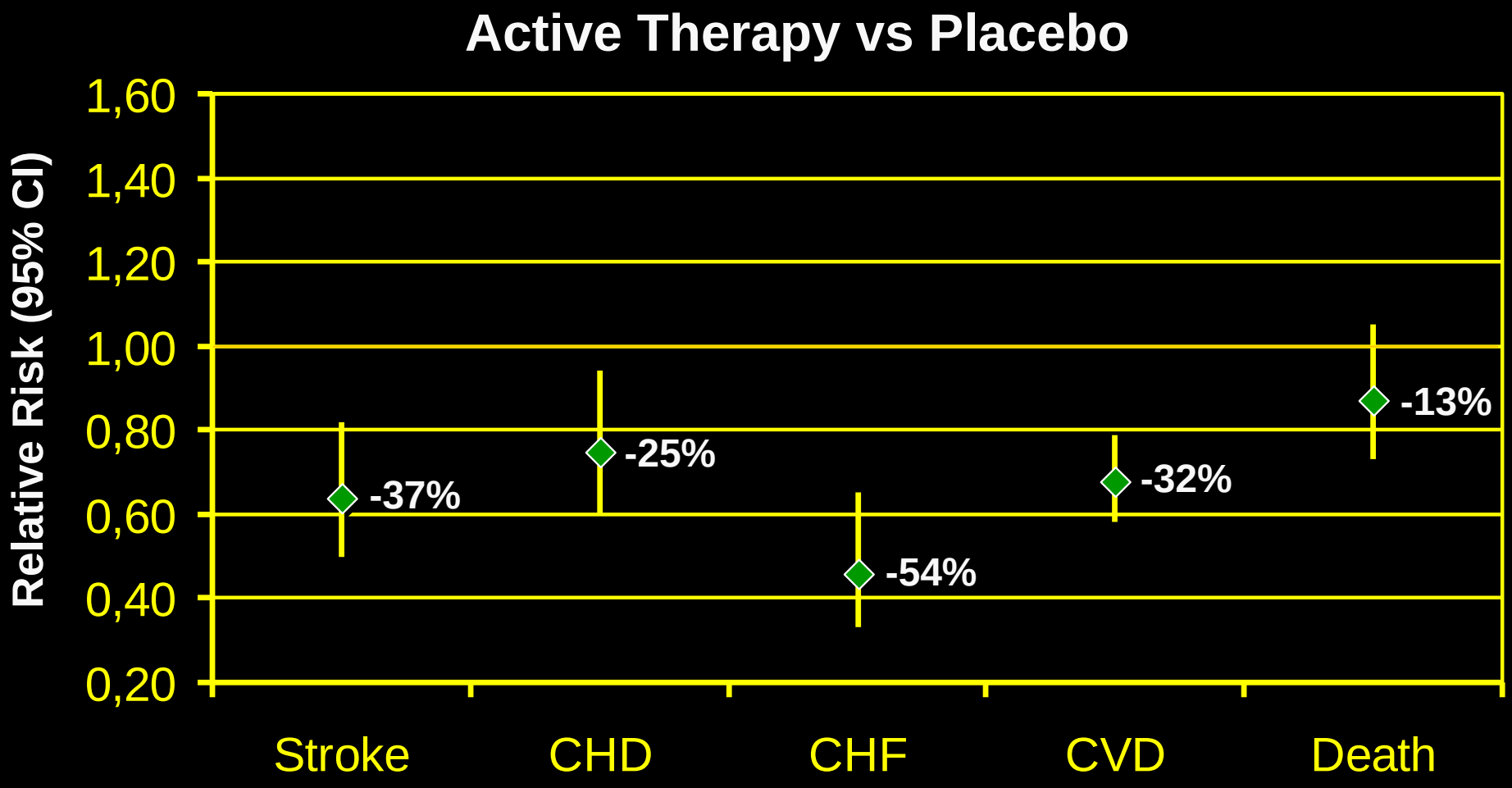
MRC Working Party. *BMJ*. 1985;291:97-104.

SHEP Trial: Design

- N: 4736; 43% male
- Age: >60 years
- BP: systolic BP 160-219 mm Hg and diastolic BP <90 mm Hg
- Design: placebo-controlled, double-blind
- Active treatment: chlorthalidone (atenolol as step 2)
- Systolic BP difference: 12 mm Hg
- Duration: 4.5 years

SHEP Cooperative Research Group. *JAMA*. 1991;265:3255-3264.

SHEP Trial: Endpoints

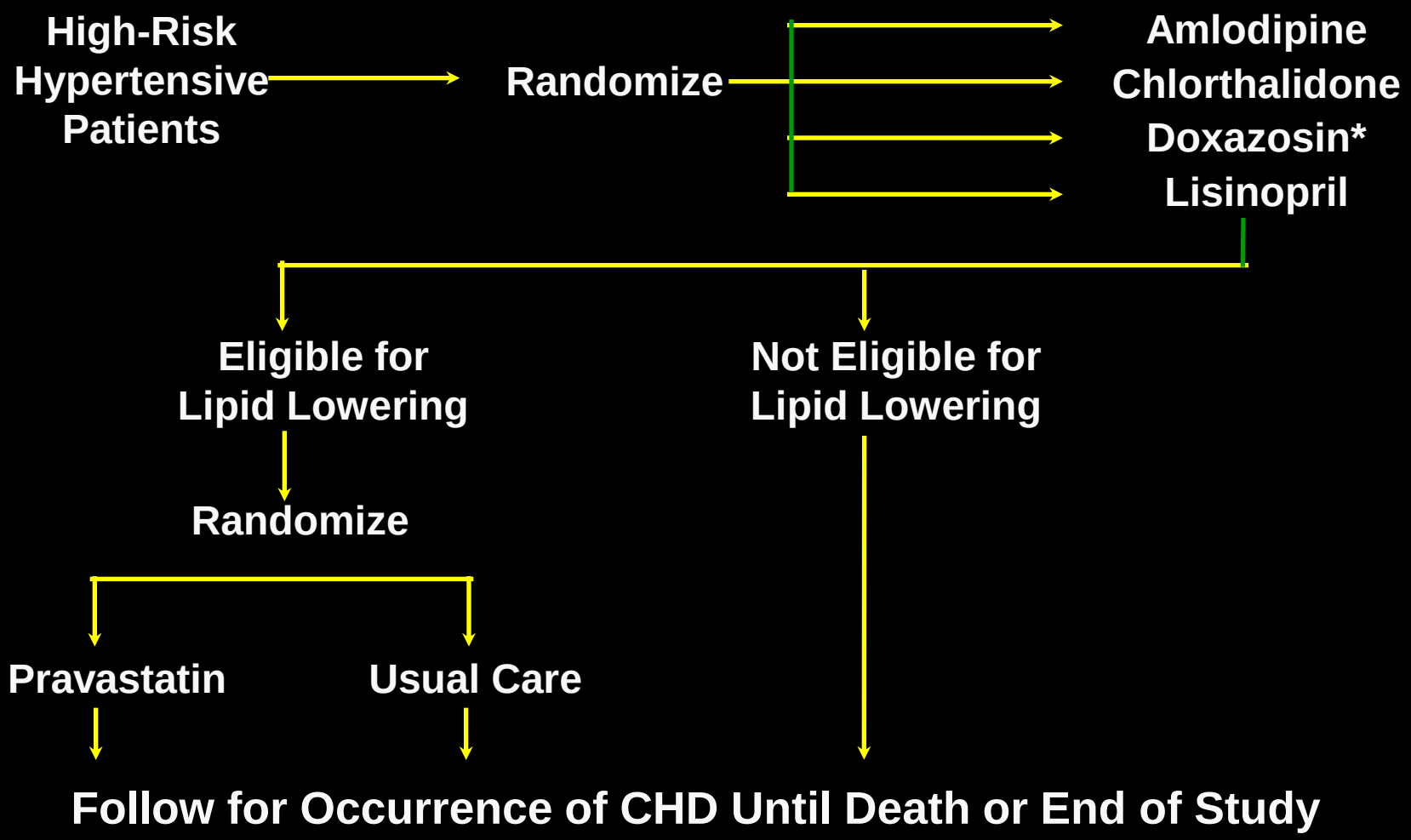


SHEP Cooperative Research Group. *JAMA*. 1991;265:3255; Kostis et al. *JAMA*. 1997;278:212-216.

Plan

- Observation / intervention
- Veterans / MRC / SHEP
- ALLHAT
- LIFE et ARA II - Problème de posologies - IEC
- ASCOT
- ACCOMPLISH
- HYVET
- SPRINT
- Méta-analyses

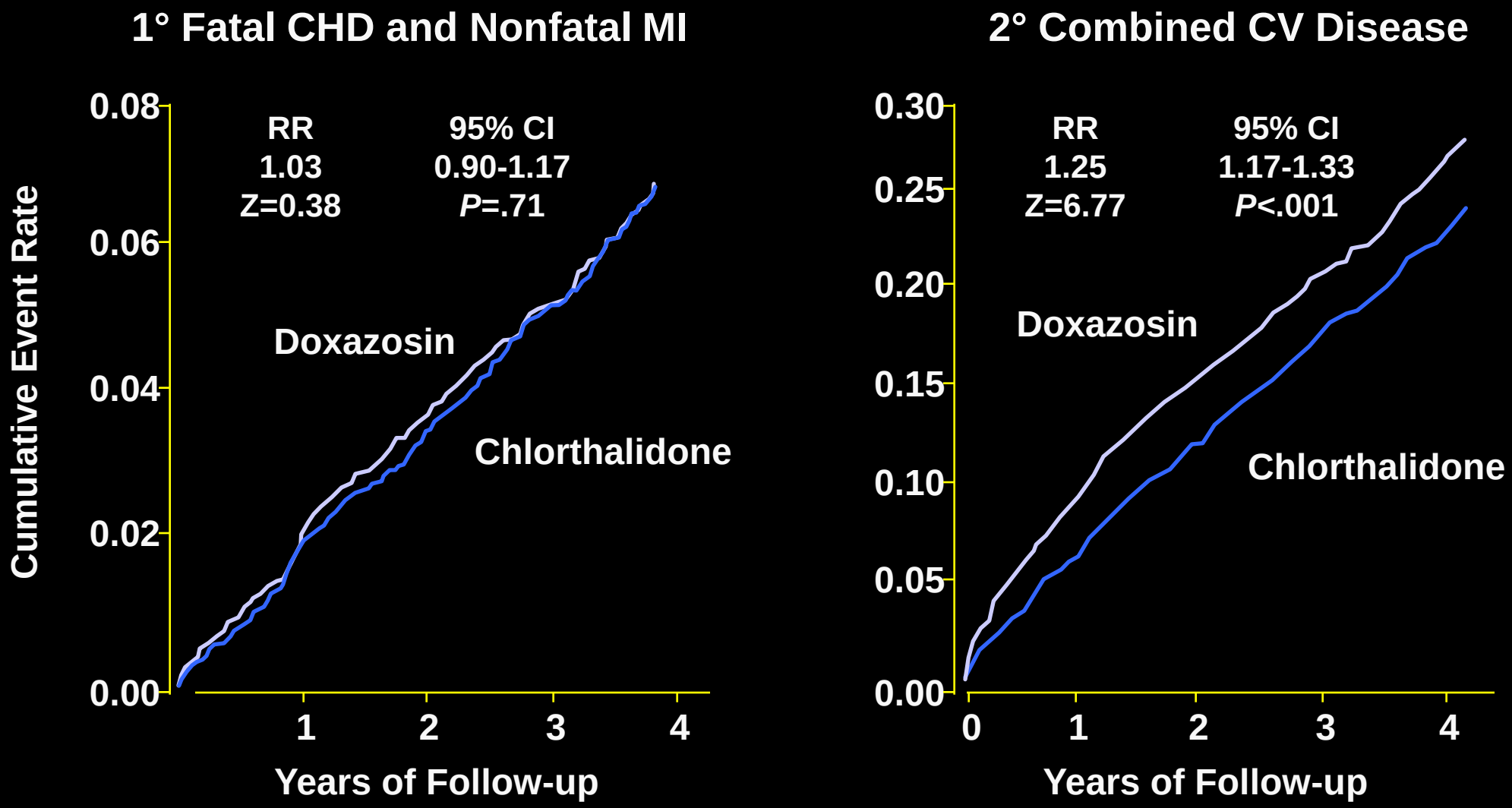
ALLHAT: Study Design



*On January 24, 2000, the National Heart, Lung, and Blood Institute decided to discontinue the doxazosin arm of the antihypertensive trial and report results.

ALLHAT Collaborative Research Group. *JAMA*. 2000;283:1967-1975; Davis et al. *Am J Hypertens*. 1996;9:342-360.

ALLHAT: Primary and Secondary Endpoints (Doxazosin vs Chlorthalidone)



ALLHAT Collaborative Research Group. *JAMA*. 2000;283:1967-1975.

Summary and Conclusions 1

- ALLHAT is the largest hypertension trial with great clinical relevance
- ALLHAT emphasizes the importance of controlling systolic BP
- ALLHAT demonstrates that aggressive treatment is necessary to achieve systolic BP goals
- ALLHAT shows that multiple medications often are required to get to BP goal

ALLHAT Collaborative Research Group. *JAMA*. 2002;288:2981-2997.

Summary and Conclusions 2

- In ALLHAT, patients taking amlodipine had results comparable to the diuretic for the primary endpoint of CHD death and nonfatal MI, and the secondary endpoints of total mortality, stroke, combined CHD, combined CVD, and renal disease
- In ALLHAT, amlodipine was efficacious and safe for lowering BP in a broad range of hypertensive patients (older and younger patients, African Americans, patients with diabetes)

ALLHAT Collaborative Research Group. *JAMA*. 2002;288:2981-2997.

Summary and Conclusions 3

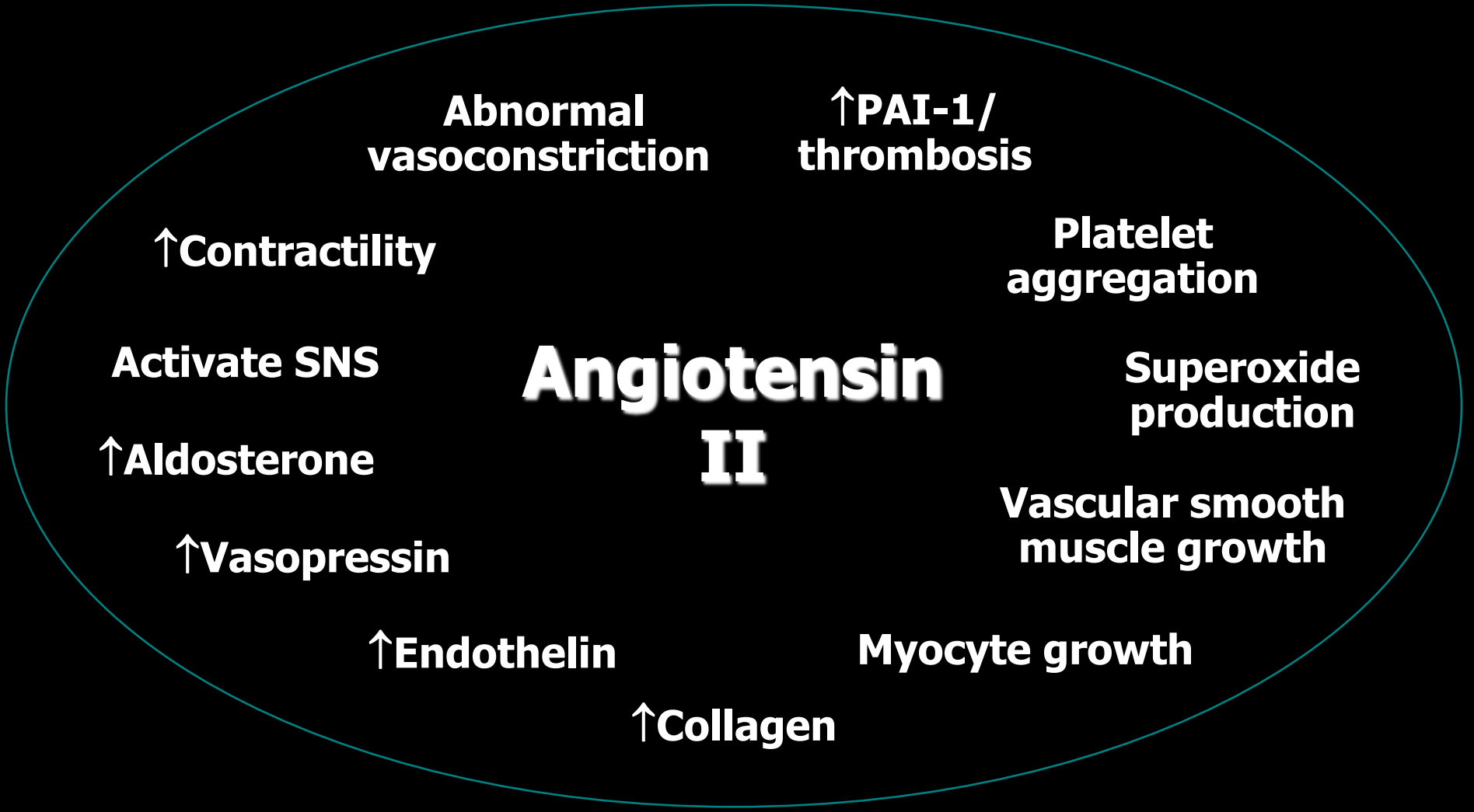
- **ALLHAT demonstrated that the lisinopril-based treatment was not as effective as the diuretic for reducing systolic BP**
- **Contrary to expectations, ALLHAT showed that results for the group taking lisinopril were not superior to the diuretic group with regard to CHD and CVD morbidity and mortality in the overall hypertensive population and in diabetics**

ALLHAT Collaborative Research Group. *JAMA*. 2002;288:2981-2997.

Plan

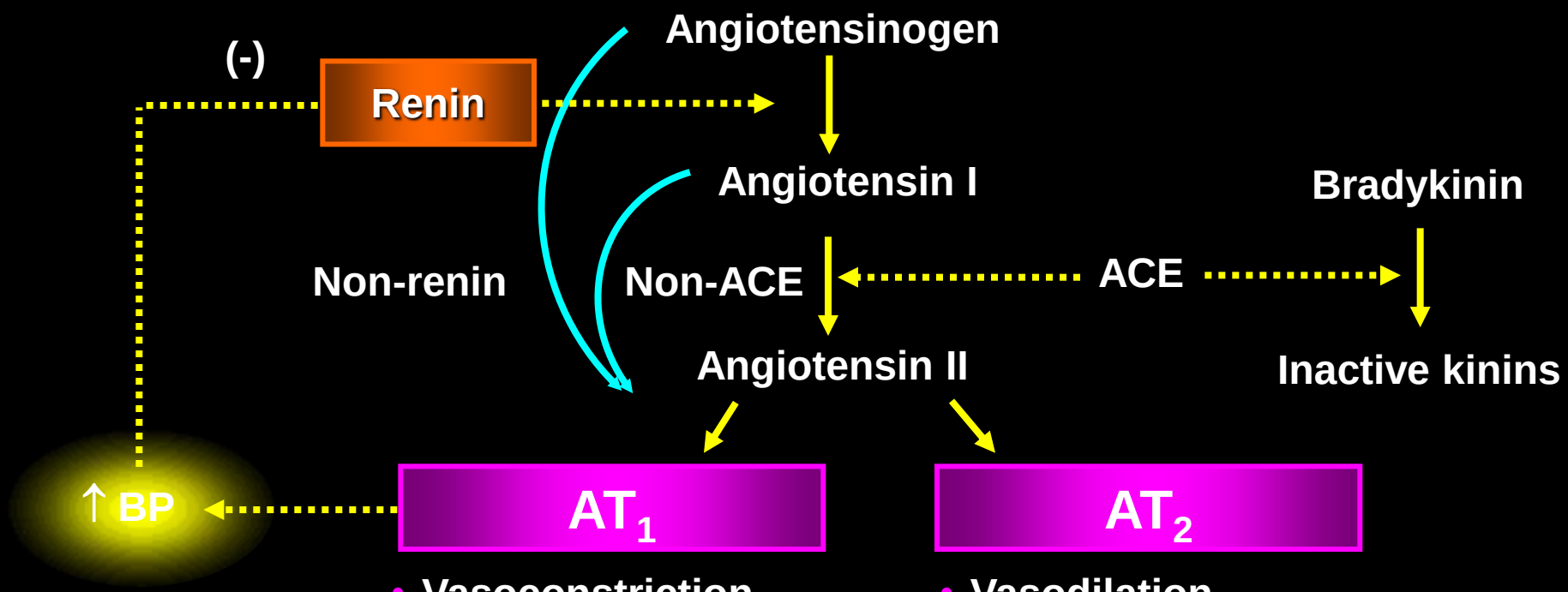
- Observation / intervention
- Veterans / MRC / SHEP
- ALLHAT
- LIFE et ARA II - Problème de posologies - IEC
- ASCOT
- ACCOMPLISH
- HYVET
- SPRINT
- Méta-analyses

Pathophysiologic Effects of Angiotensin II



Burnier M, Brunner HR. *Lancet*. 2000;355:637–645.

Renin-angiotensin-aldosterone system



- Vasoconstriction
- Aldosterone secretion
- Catecholamine release
- Proliferation
- Hypertrophy

- Vasodilation
- Inhibition of cell growth
- Cell differentiation
- Injury response
- Apoptosis

Ellis et al. *Pharmacotherapy* 1996;16:849–60
Carey et al. *Hypertension* 2000;35:155–63

LIFE

- Population : 9193 patients avec HTA
  et HVG-ECG

- Losartan 50-100 mg + HCTZ (n=4605)
  versus Atenonol 50-100 mg + HCTZ (n=4588)

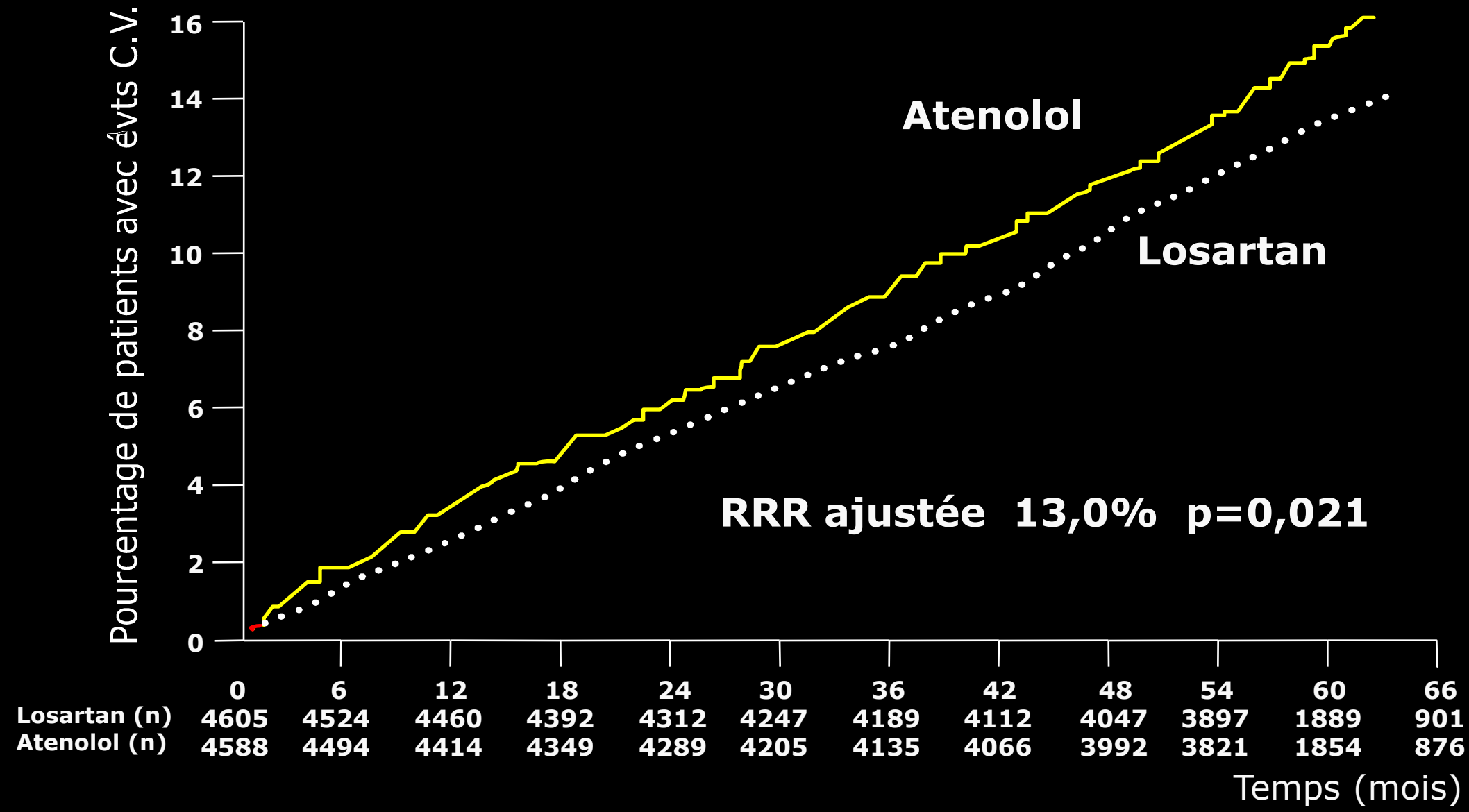
- Suivi moyen : 4,8 ans

- Critère principal : morbidité/mortalité
  (IDM, AVC, DC CV)

Losartan **I**ntervention **F**or **E**ndpoint reduction hypertension study

LIFE

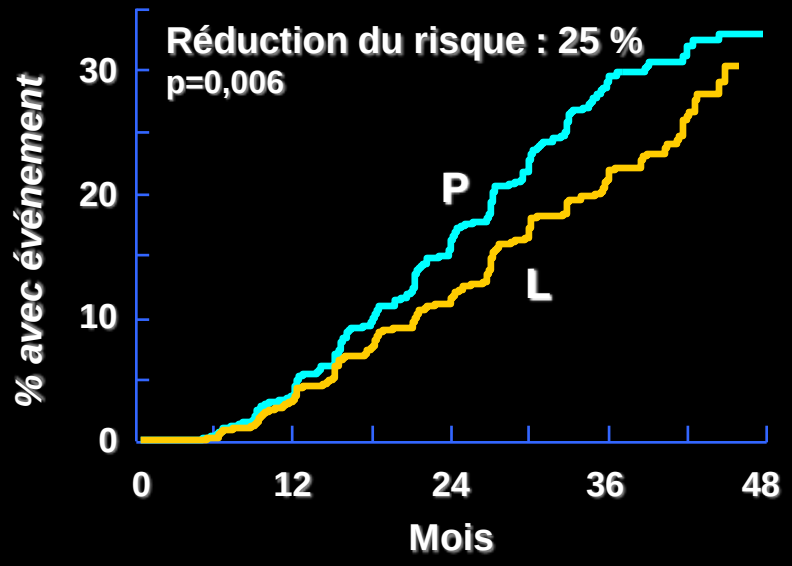
Critère principal (mortalité CV, AVC, IDM)



Etude RENAAL

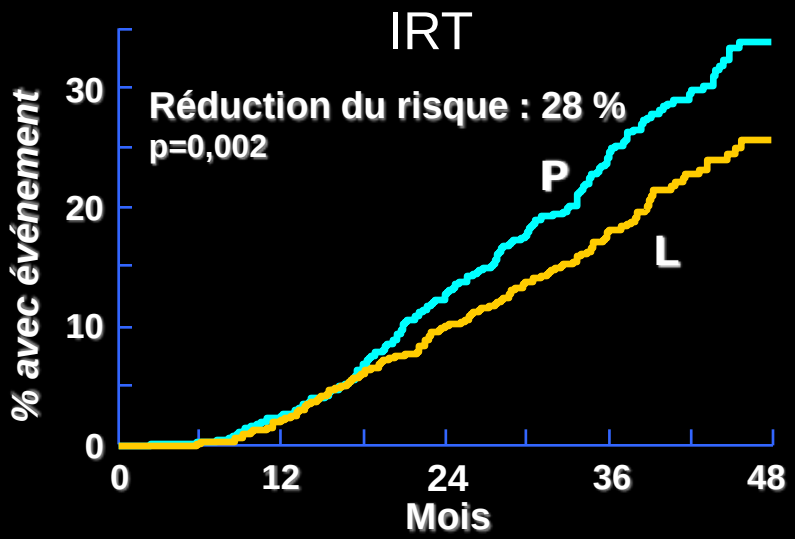
Composants du critère d'évaluation combiné

Doublement de la créatininémie



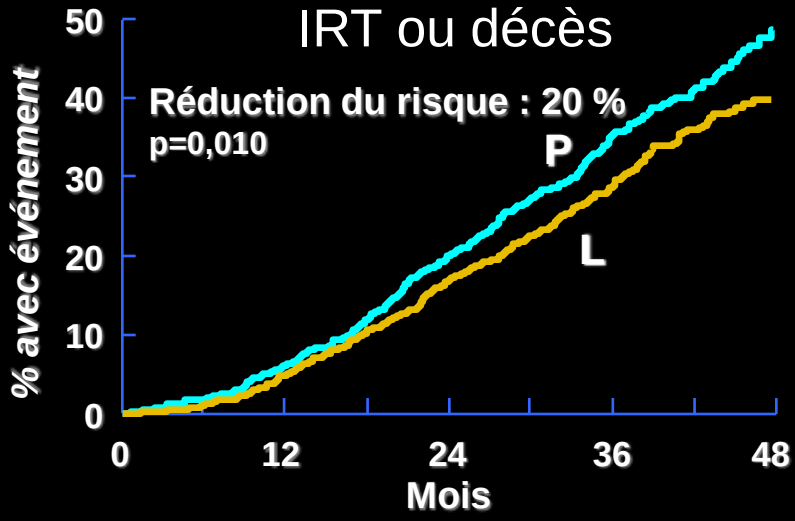
P (+ TC)	762	689	554	295	36
L (+ TC)	751	692	583	329	52

IRT



P (+ TC)	762	715	610	347	42
L (+ TC)	751	714	625	375	69

IRT ou décès

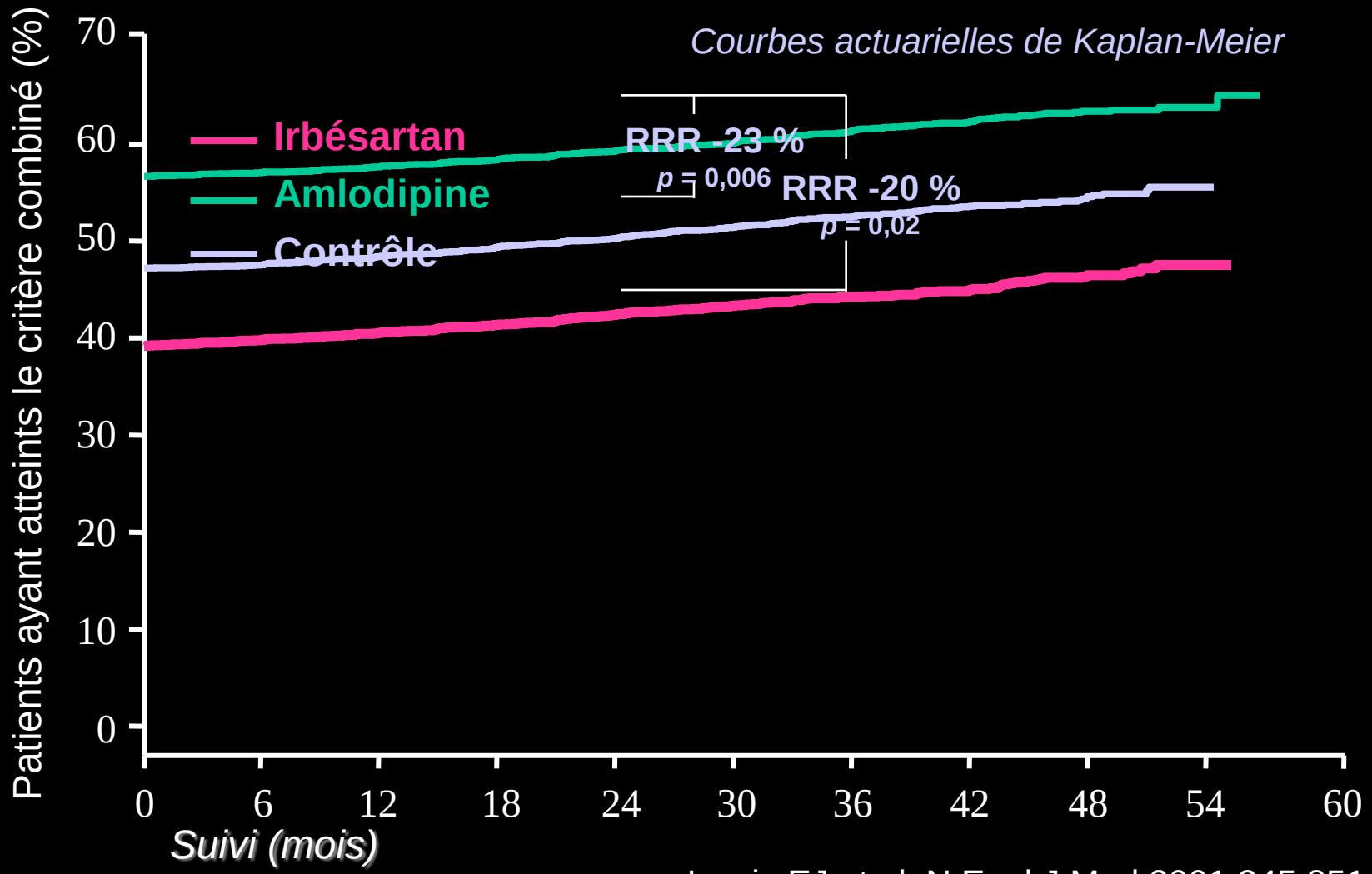


P (+ TC)	762	715	610	347	42
L (+ TC)	751	714	625	375	69

Brenner BM et col. New Engl J Med 2001; 345(12):861-869

IDNT: Objectif principal

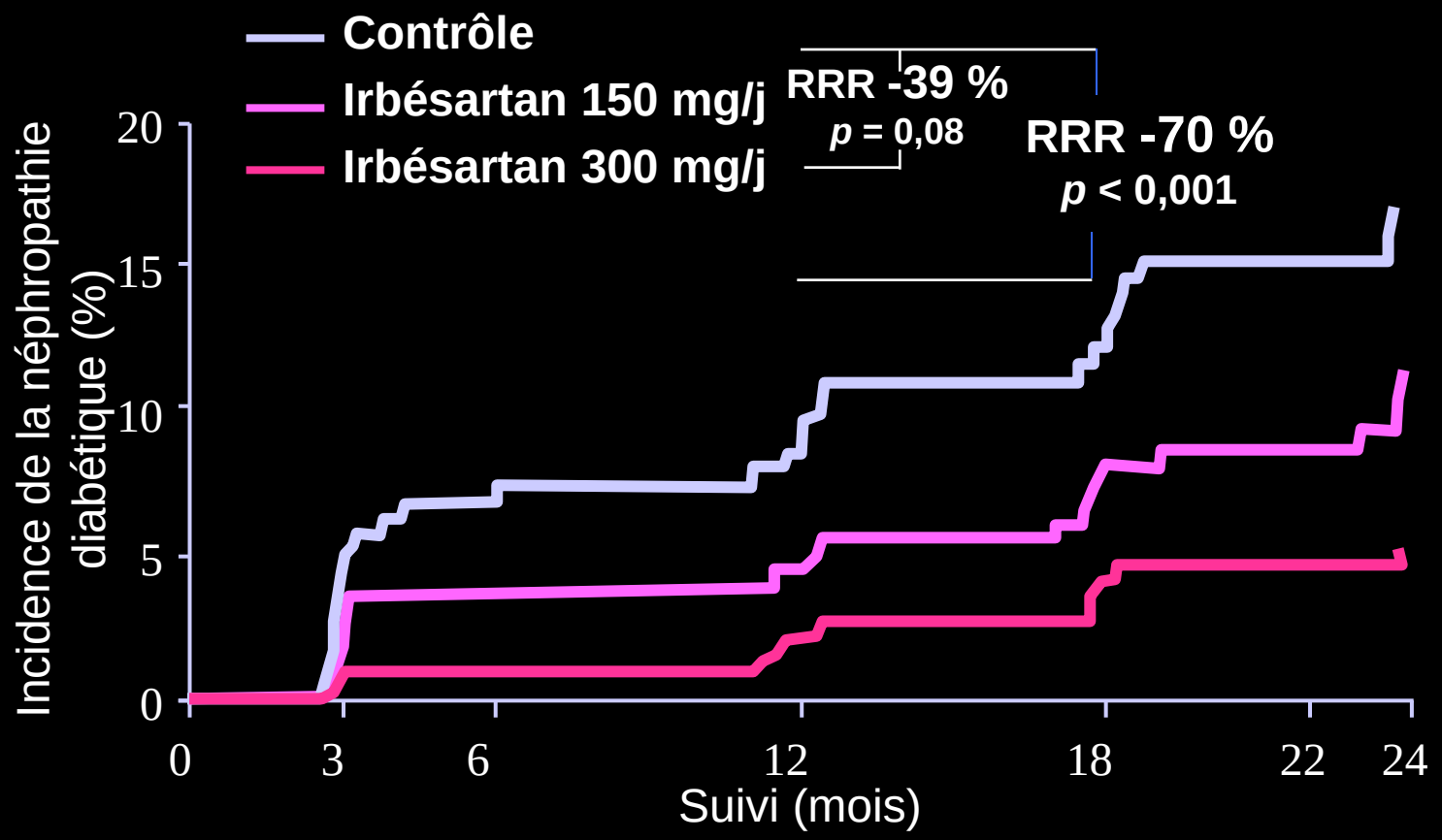
Doublement de la créatininémie, IRT ou décès



Lewis EJ et al. N Engl J Med 2001;345:851-60

IRMA 2: Objectif principal

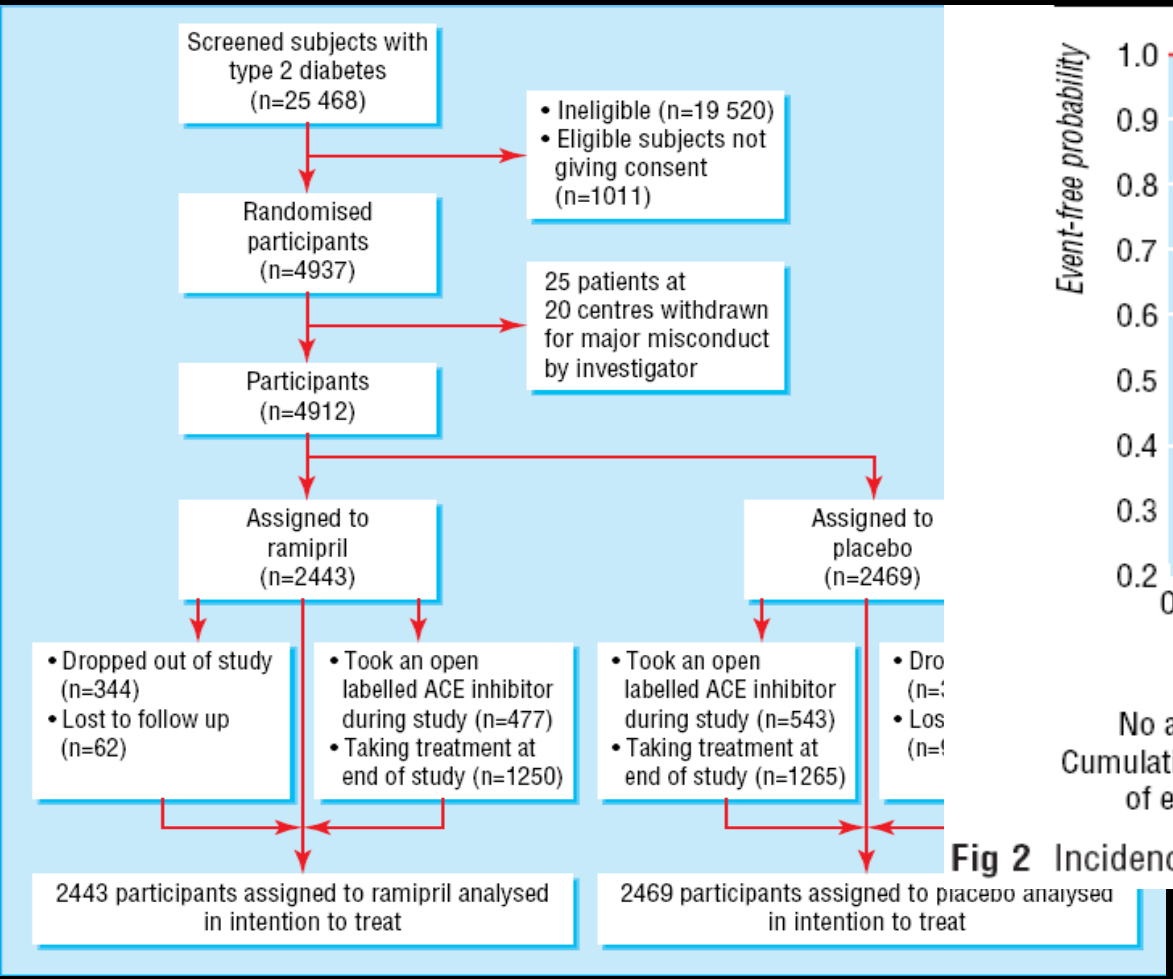
Apparition d'une protéinurie avérée



Parving HH *et al*. N Engl J Med 2001;345:870-878

Effects of low dose ramipril on cardiovascular and renal outcomes in patients with type 2 diabetes and raised excretion of urinary albumin: randomised, double blind, placebo controlled trial (the DIABHYCAR study)

Michel Marre, Michel Lievre, Gilles Chatellier, Johannes F E Mann, Philippe Passa, Joël Ménard, on behalf of the DIABHYCAR Study Investigators



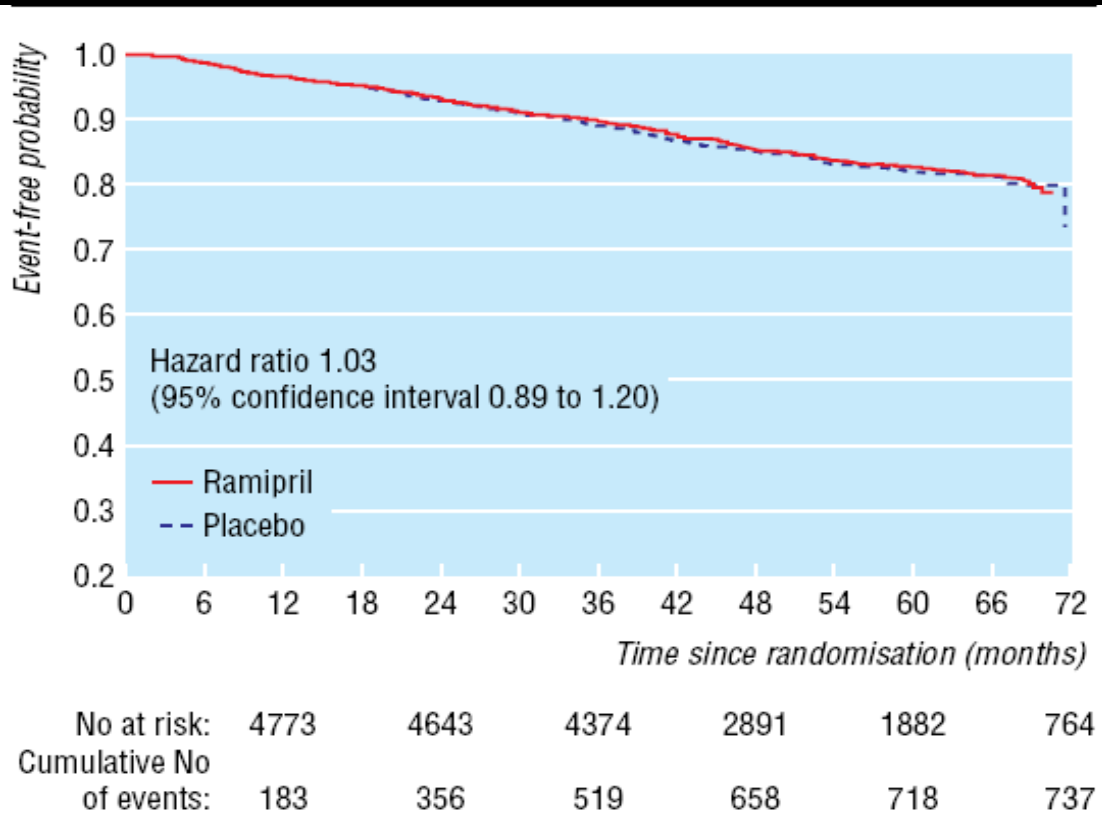


Fig 2 Incidence of the primary end point according to treatment group

BMJ 2004;328;495

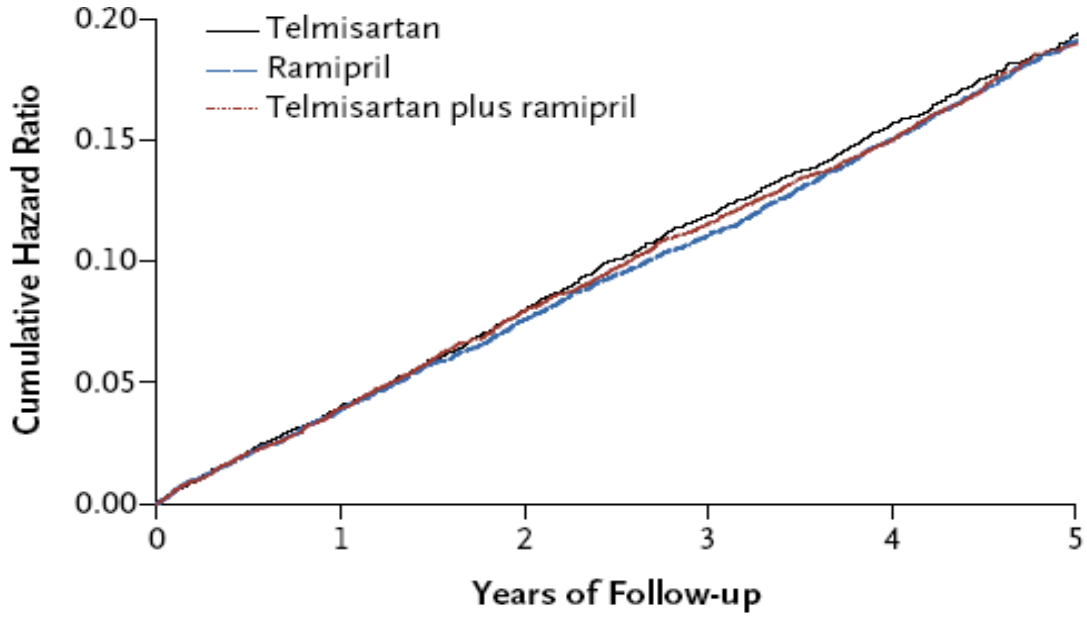
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 10, 2008 VOL. 358 NO. 15

Telmisartan, Ramipril, or Both in Patients at High Risk for Vascular Events

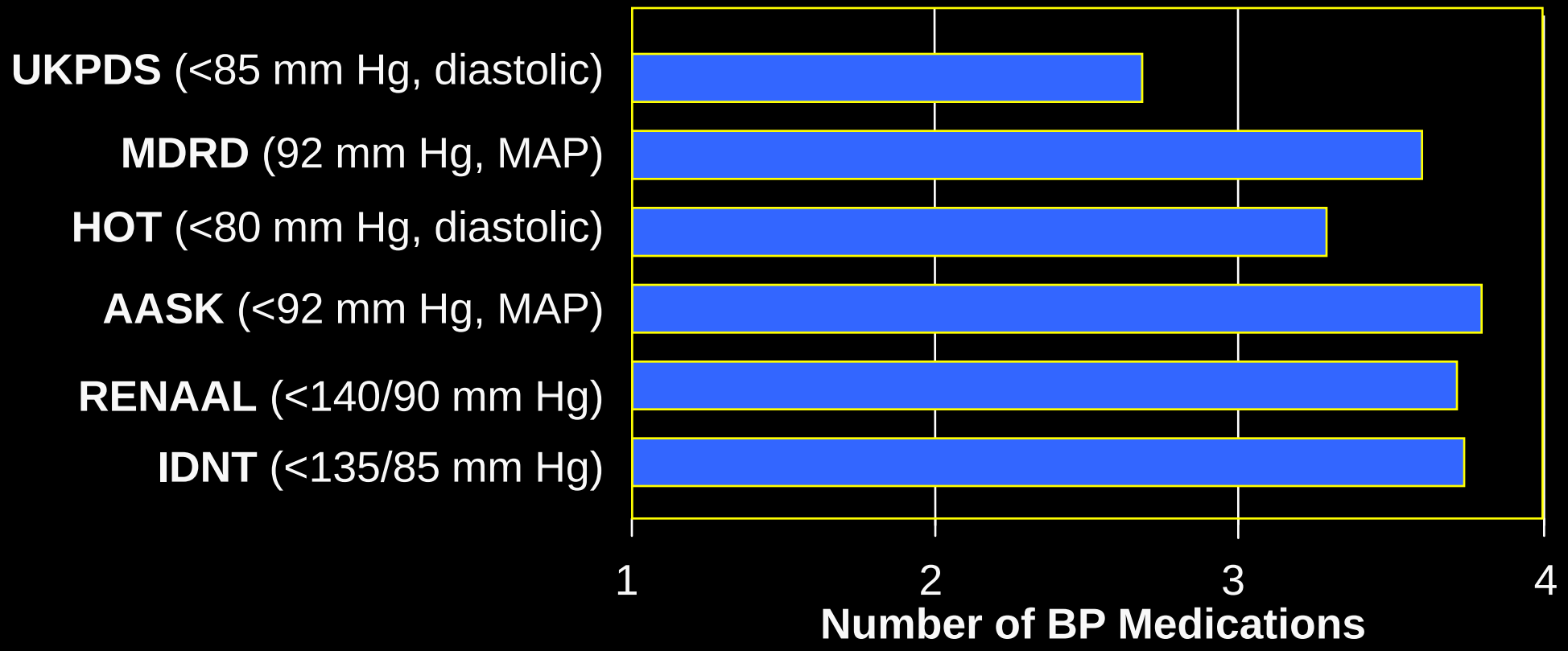
The ONTARGET Investigators*

ONTARGET Primary Outcome



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

Hypertension in High-Risk Patients: Number of Agents Used to Treat BP



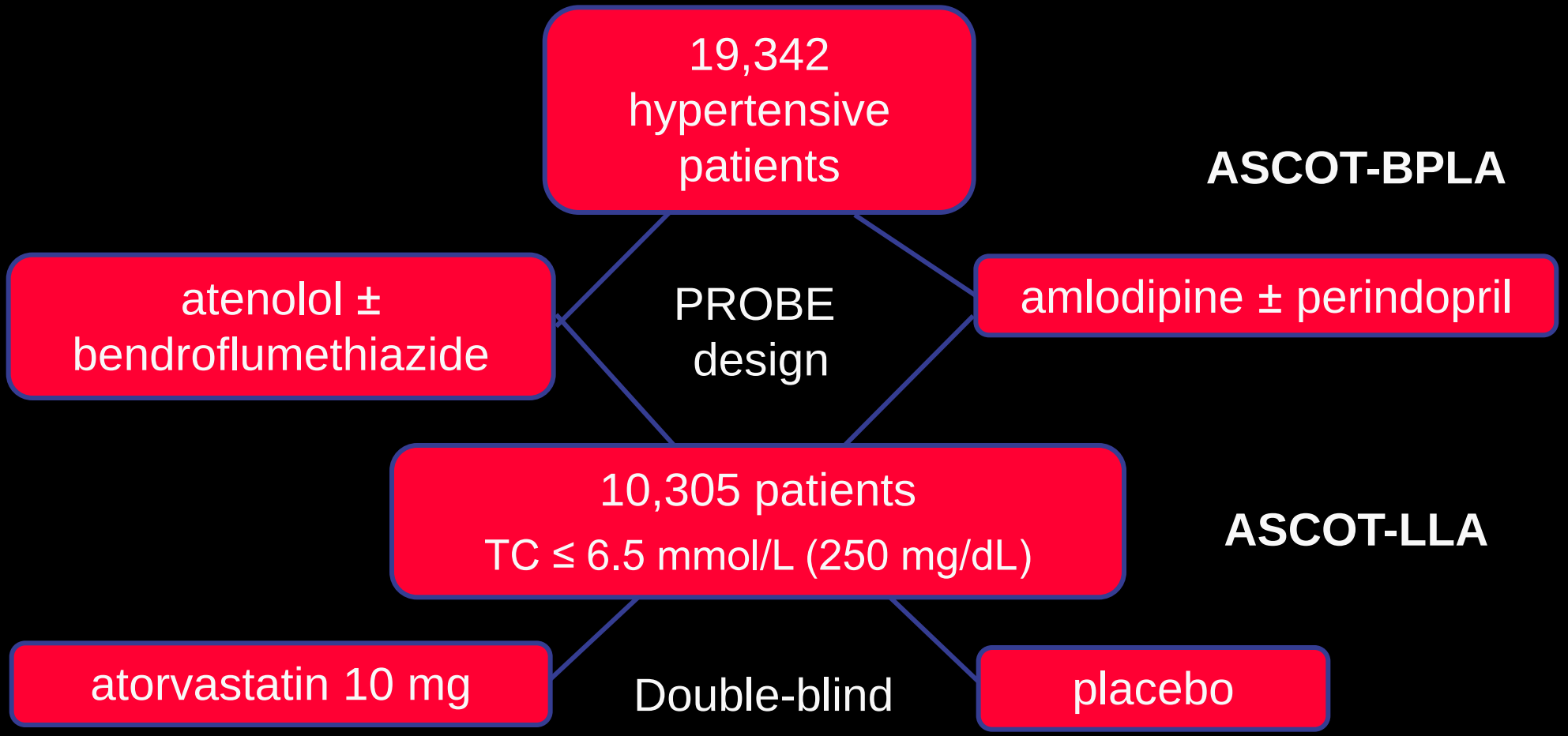
UKPDS=United Kingdom Prospective Diabetes Study; MDRD=Modification of Diet in Renal Disease; HOT=Hypertension Optimal Treatment; AASK=African American Study of Kidney Disease; RENAAL=Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan; IDNT=Irbesartan Diabetic Nephropathy Trial; MAP=mean arterial pressure.

Bakris et al. *Am J Kidney Dis*. 2000;36:646-661; Brenner et al. *N Engl J Med*. 2001;345:861-869; Lewis et al. *N Engl J Med*. 2001;345:851-860.

Plan

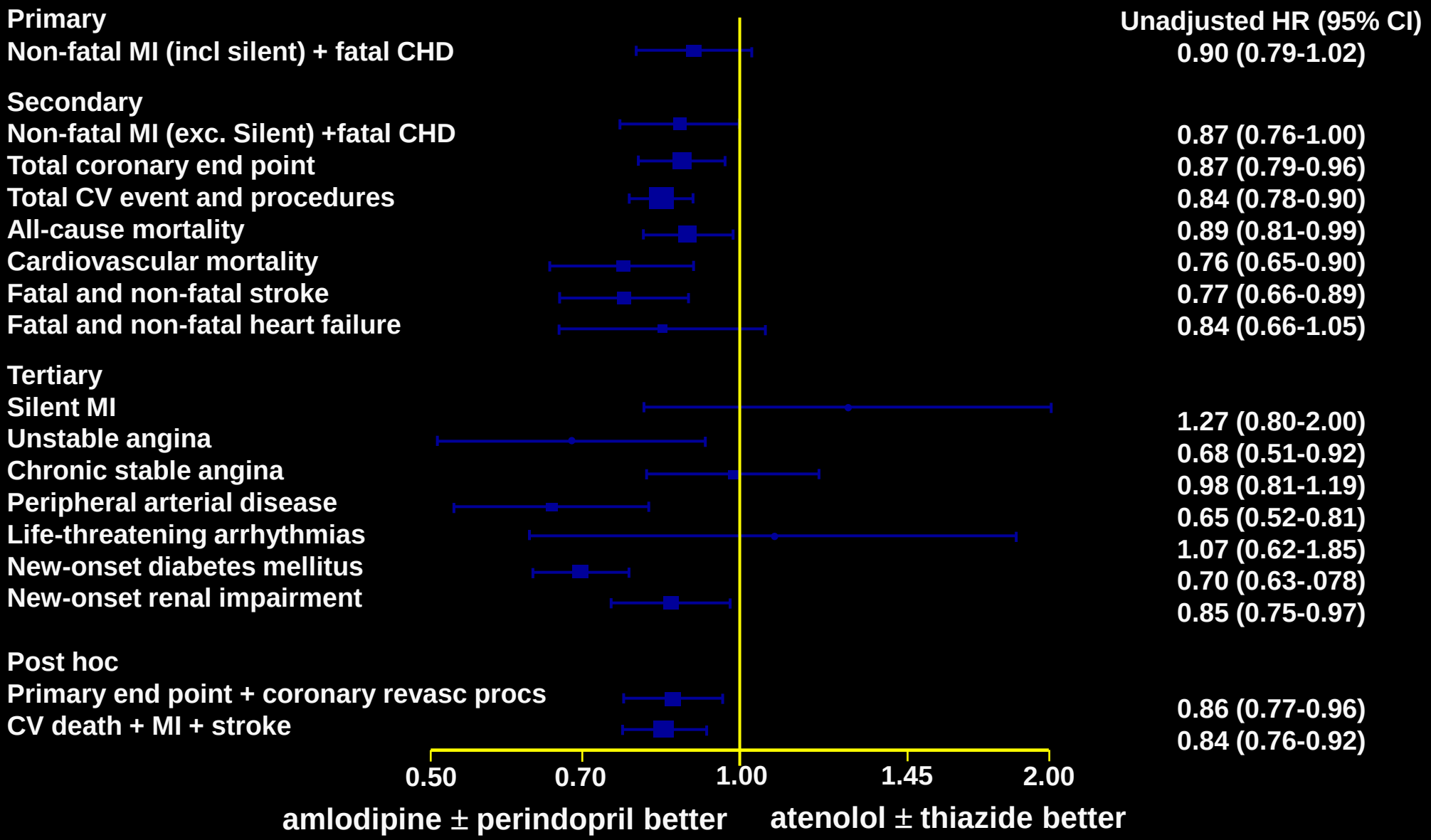
- Observation / intervention
- Veterans / MRC / SHEP
- ALLHAT
- LIFE et ARA II - Problème de posologies - IEC
- ASCOT
- ACCOMPLISH
- HYVET
- SPRINT
- Méta-analyses

ASCOT-BPLA



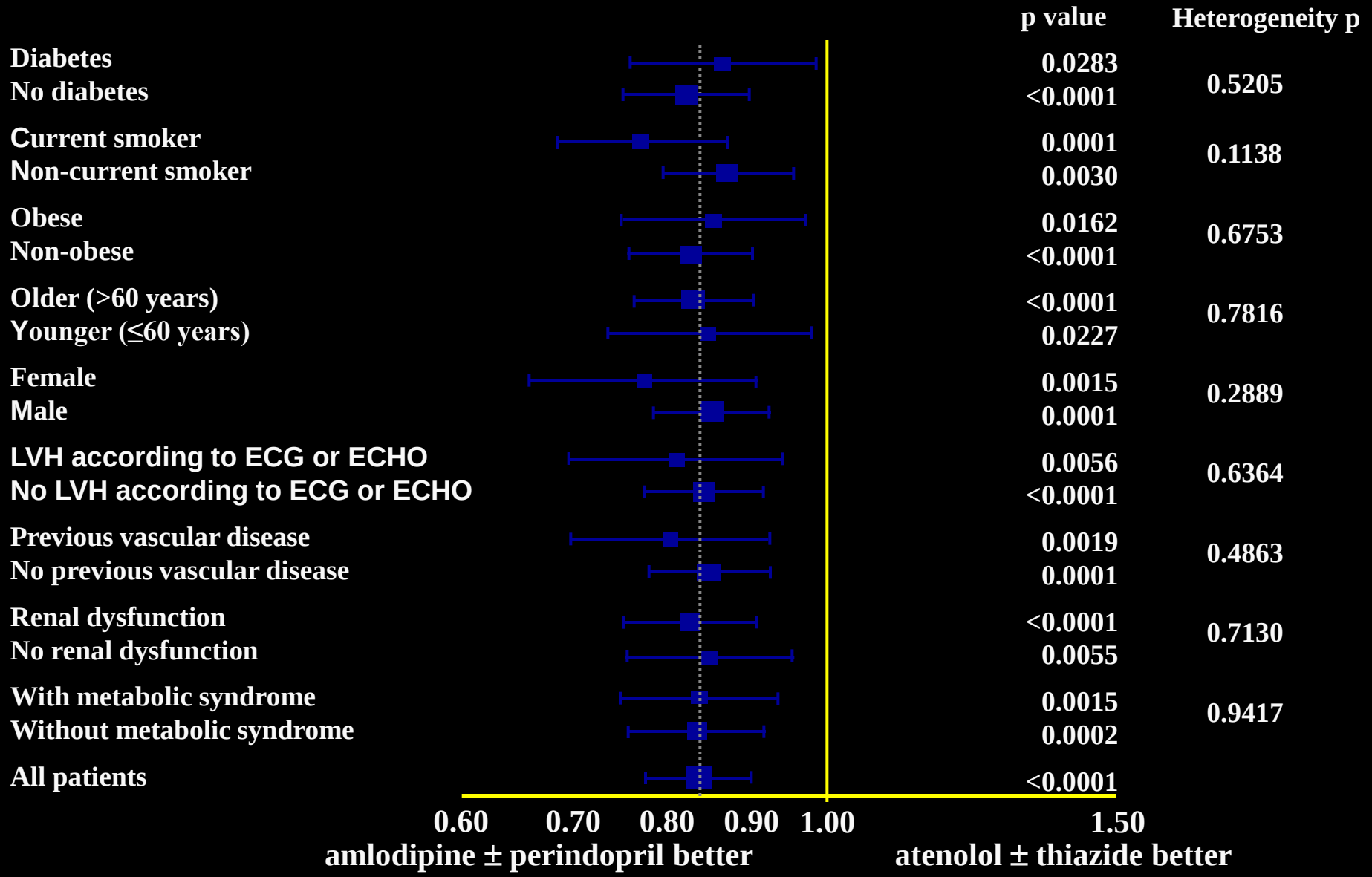
Investigator-led, multinational randomised controlled trial

ASCOT-BPLA: summary of all end points



Dahlöf B, *et al. Lancet*. 2005;366:895-906.

Total CV events and procedures among subgroups



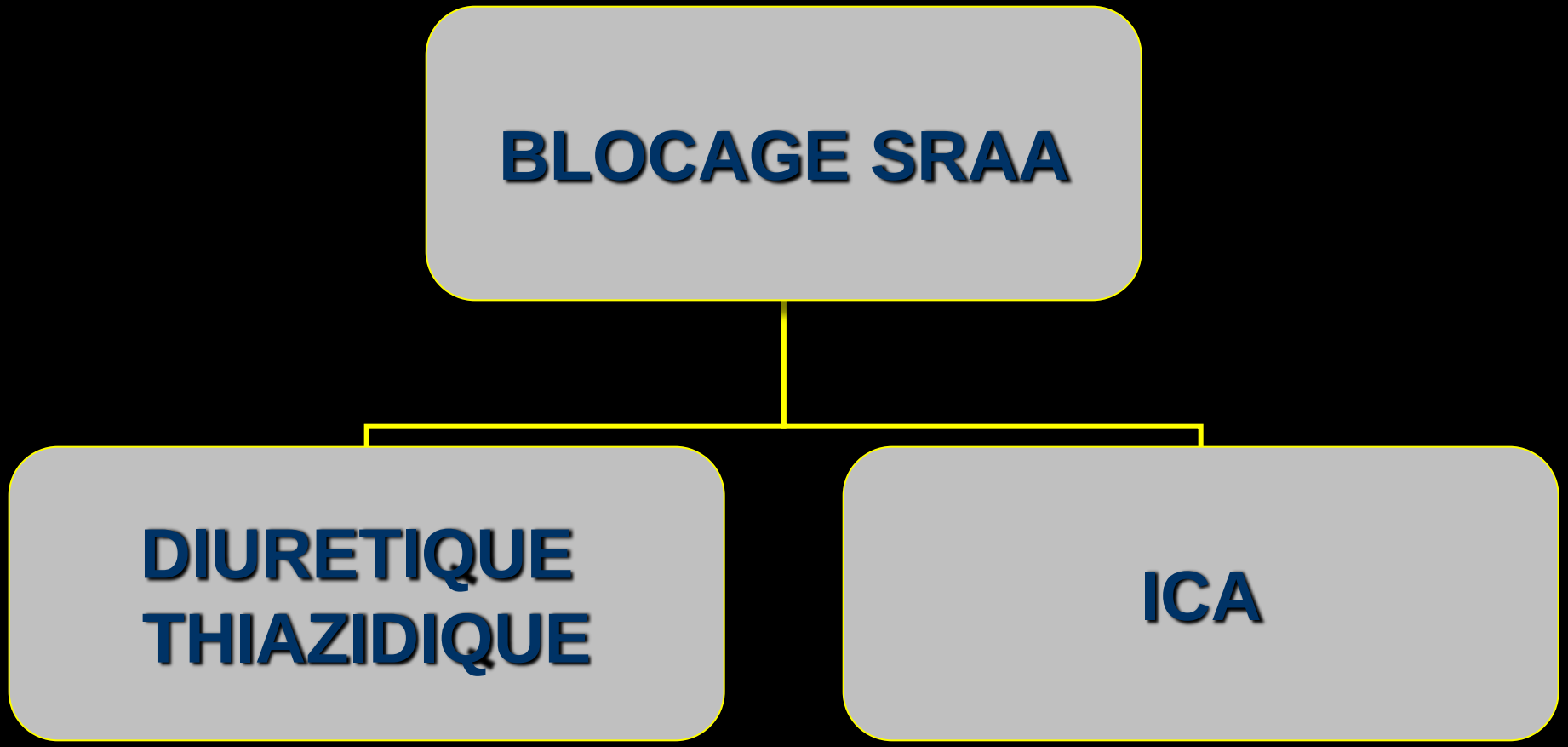
The area of the blue square is proportional to the amount of statistical information

Dahlöf B, *et al. Lancet*. 2005;366:895-906.

Plan

- Observation / intervention
- Veterans / MRC / SHEP
- ALLHAT
- LIFE et ARA II - Problème de posologies - IEC
- ASCOT
- ACCOMPLISH
- HYVET
- Méta-analyses
- Recommandations

Les bithérapies les plus « en vogue »



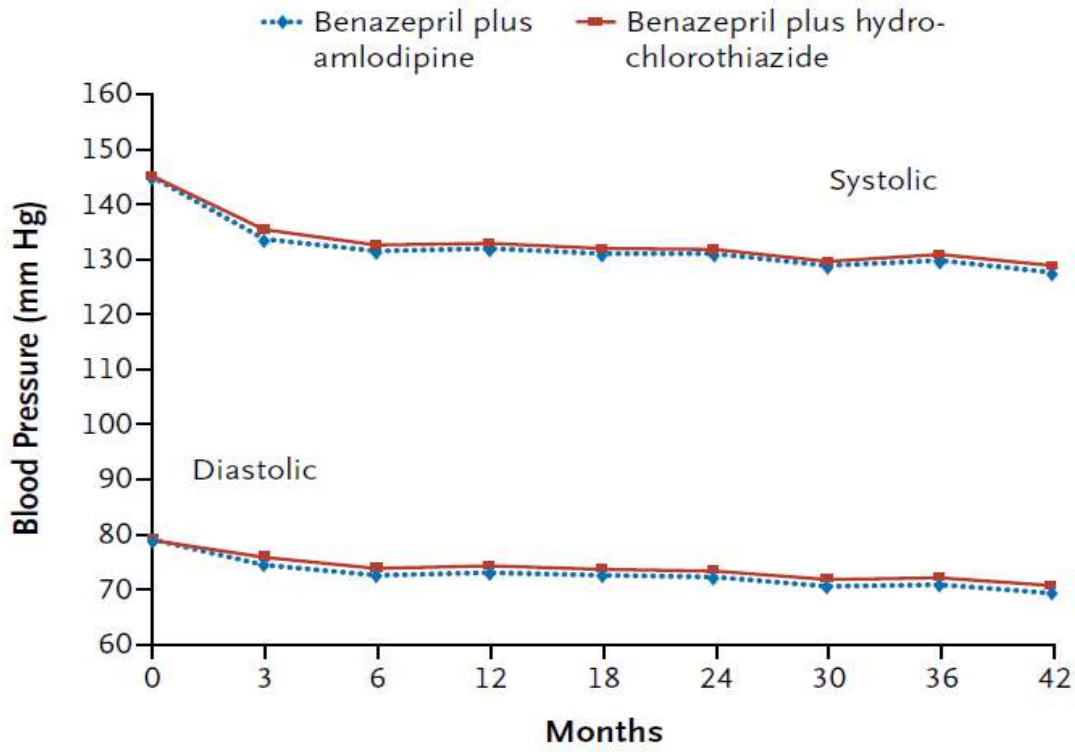
The NEW ENGLAND JOURNAL of MEDICINE

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*

N Engl J Med 2008;359:2417-28.

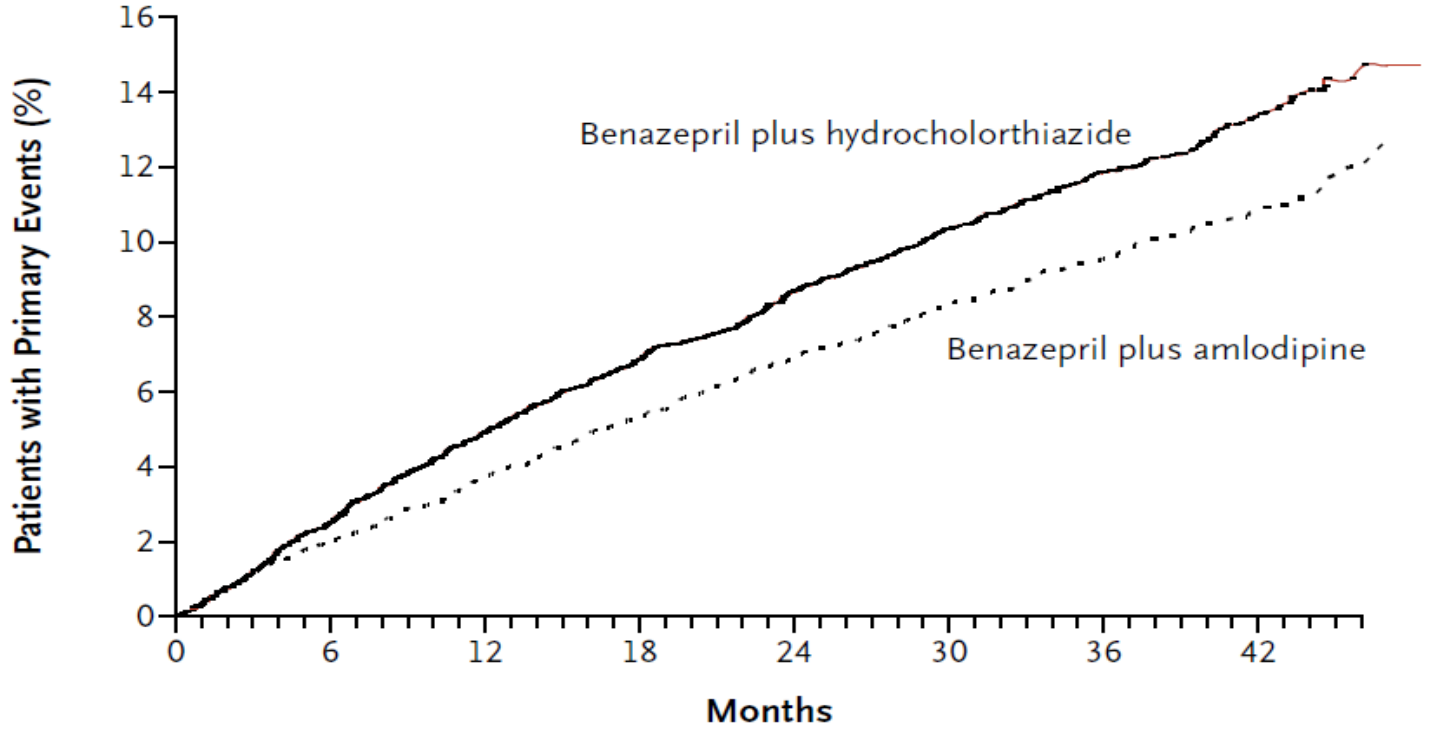


No. at Risk

Benazepril plus amlodipine	5740	5517	5404	5178	5010	4866	4298	2804	1074
Benazepril plus hydrochlorothiazide	5757	5537	5408	5222	5033	4825	4299	2529	1042

Figure 1. Effects of Treatment on Systolic and Diastolic Blood Pressure over Time.

The mean systolic and diastolic blood pressures after dose adjustment were 131.6/73.3 mm Hg in the benazepril–amlodipine group and 132.5/74.4 mm Hg in the benazepril–hydrochlorothiazide group. The mean difference in blood pressure between the two groups was 0.9 mm Hg systolic and 1.1 mm Hg diastolic ($P<0.001$ for both comparisons).



No. at Risk							
Benazepril plus amlodipine	5512	5317	5141	4959	4739	2826	1447
Benazepril plus hydrochlorothiazide	5483	5274	5082	4892	4655	2749	1390

Figure 2. Kaplan–Meier Curves for Time to First Primary Composite End Point.

There were 552 patients with events (9.6%) in the benazepril–amlodipine group, as compared with 679 patients with events (11.8%) in the benazepril–hydrochlorothiazide group. The relative risk reduction was 20% (hazard ratio, 0.80; 95% CI, 0.72 to 0.90; P<0.001).

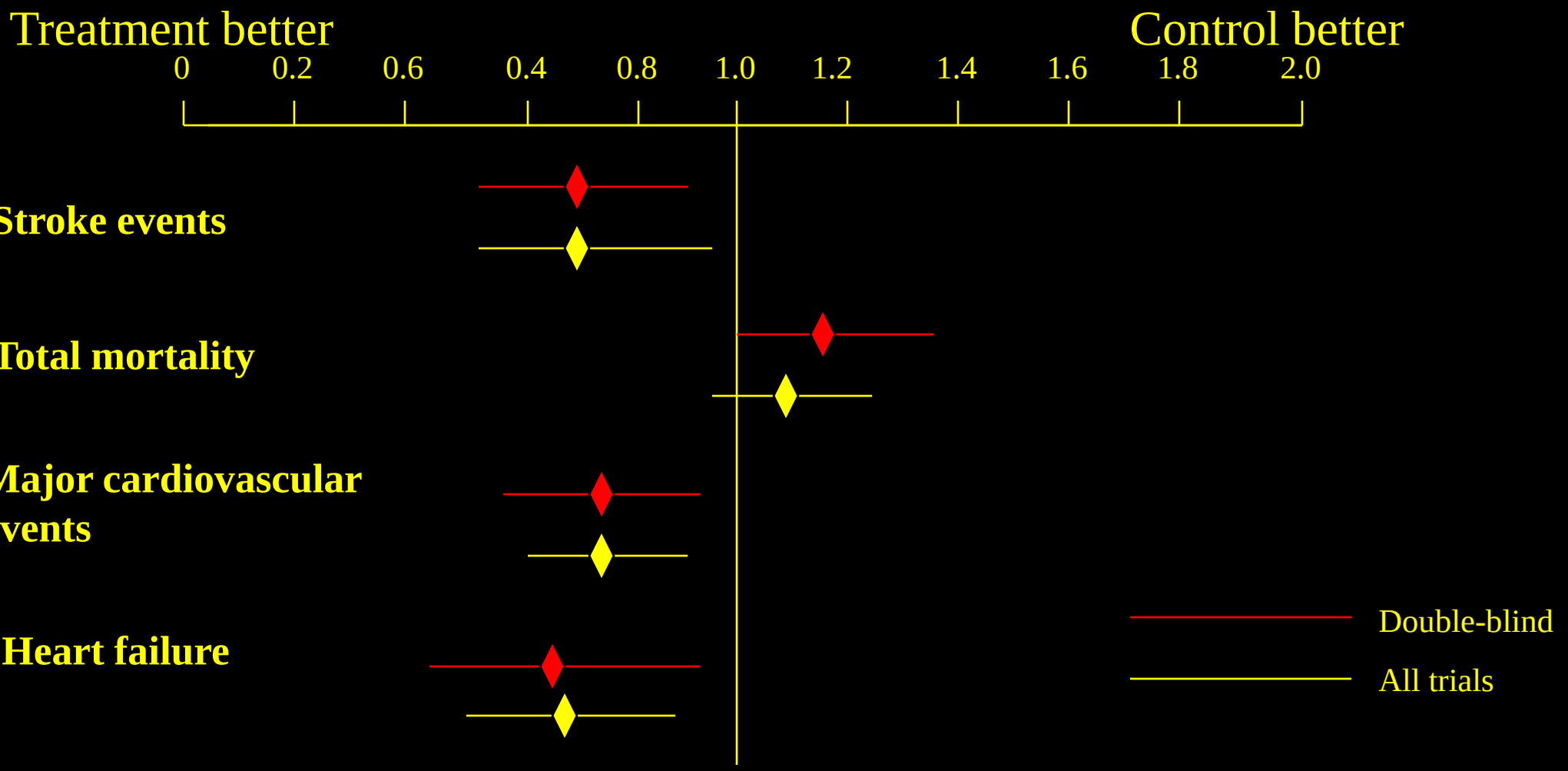
Plan

- Observation / intervention
- Veterans / MRC / SHEP
- ALLHAT
- LIFE et ARA II - Problème de posologies - IEC
- ASCOT
- ACCOMPLISH
- HYVET
- Méta-analyses
- Recommandations

Effect of antihypertensive therapy over 80 years

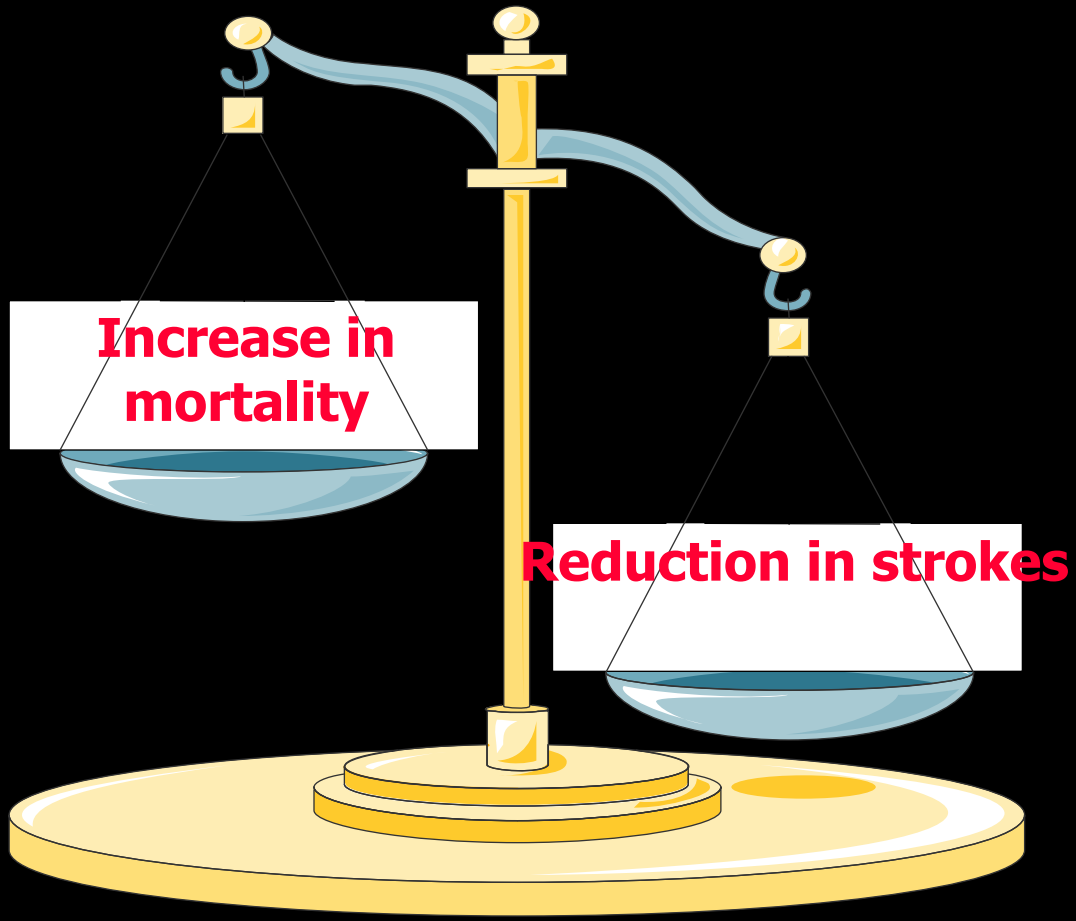
Meta-analysis of Randomised Controlled Trials

(n=1670, mean age = 83, SBP/DBP=180/84)



Gueyffier F et al. Lancet 1999:353:793-96

To treat or not to treat?
That is the question



This dilemma provided the rationale for the

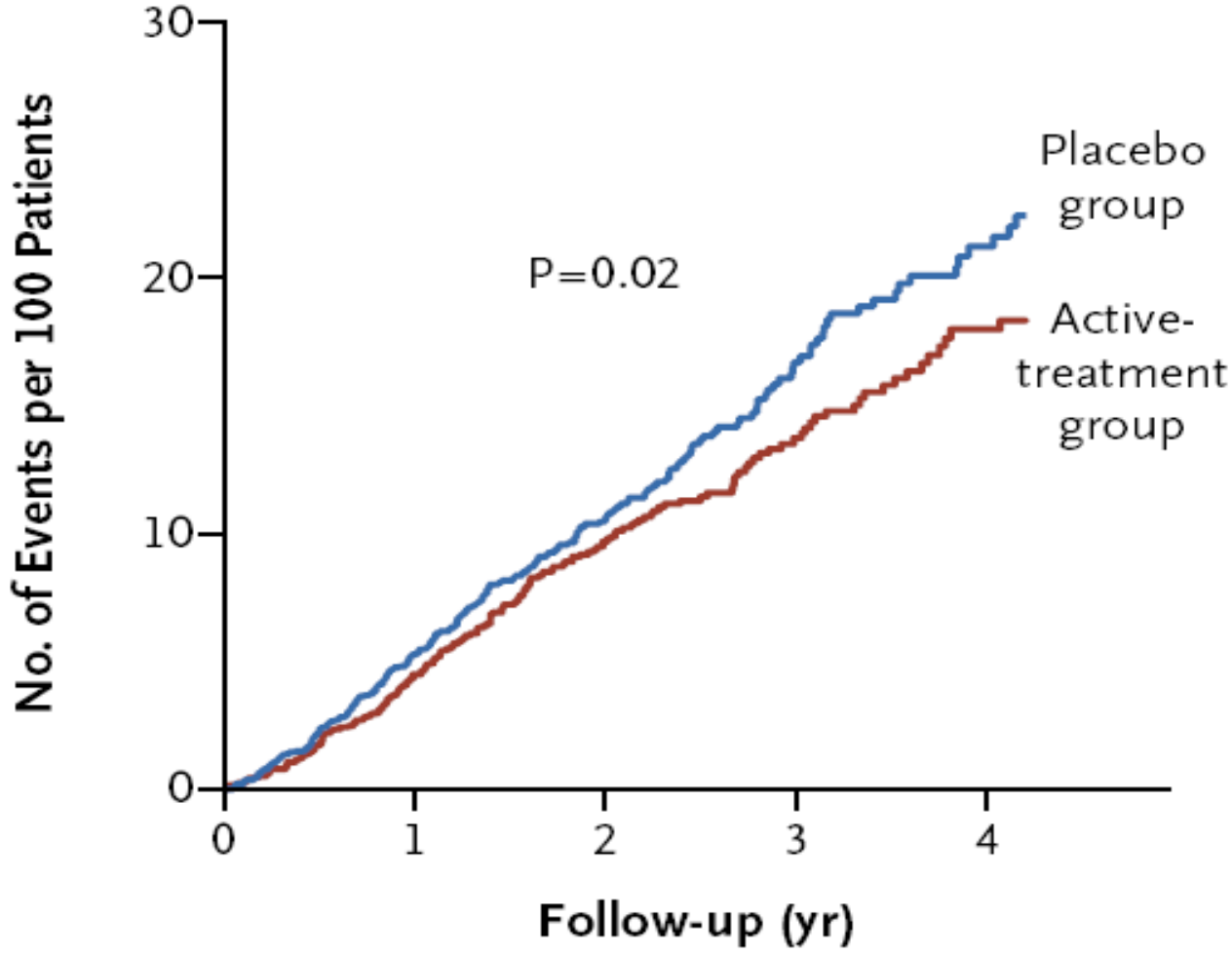
HYpertension in the **V**ery **E**lderly **T**rial

The NEW ENGLAND JOURNAL of MEDICINE

Treatment of Hypertension in Patients 80 Years of Age or Older

Nigel S. Beckett, M.B.,Ch.B., Ruth Peters, Ph.D., Astrid E. Fletcher, Ph.D., Jan A. Staessen, M.D., Ph.D., Lisheng Liu, M.D., Dan Dumitrascu, M.D., Vassil Stoyanovsky, M.D., Riitta L. Antikainen, M.D., Ph.D., Yuri Nikitin, M.D., Craig Anderson, M.D., Ph.D., Alli Belhani, M.D., Françoise Forette, M.D., Chakravarthi Rajkumar, M.D., Ph.D., Lutgarde Thijs, M.Sc., Winston Banya, M.Sc., and Christopher J. Bulpitt, M.D., for the HYVET Study Group*

B **Death from Any Cause**



No. at Risk

Placebo group	1912	1492	814	379	202
Active-treatment group	1933	1565	877	420	231

Plan

- Observation / intervention
- Veterans / MRC / SHEP
- ALLHAT
- LIFE et ARA II - Problème de posologies - IEC
- ASCOT
- ACCOMPLISH
- HYVET
- SPRINT
- Méta-analyses

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 26, 2015 VOL. 373 NO. 22

A Randomized Trial of Intensive versus Standard Blood-Pressure Control

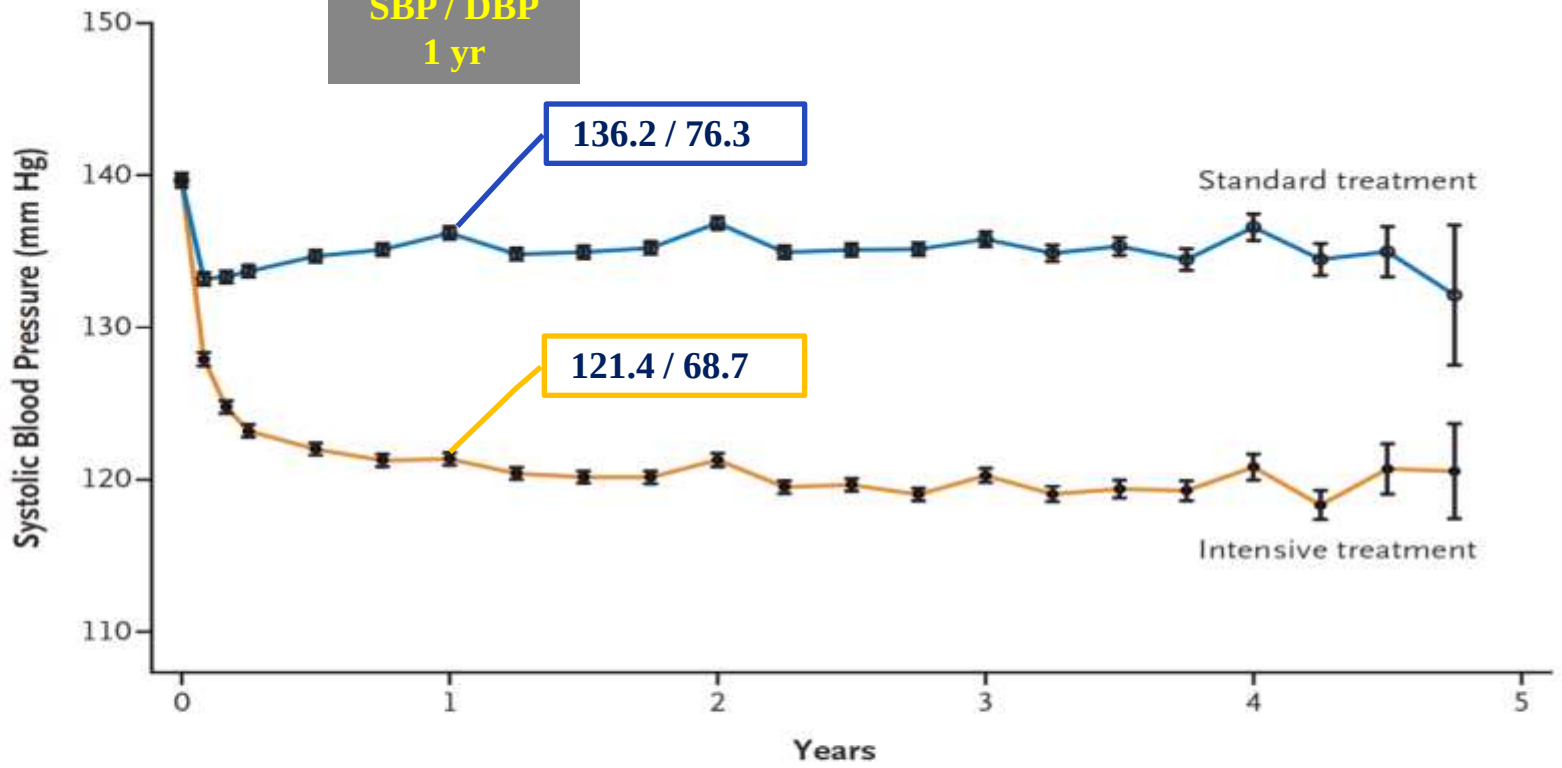
The SPRINT Research Group*

SPRINT was sponsored by the NHLBI, with cosponsorship by the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute of Neurological Disorders and Stroke, and the National Institute on Aging.

This article was published on November 9, 2015, at NEJM.org.

N Engl J Med 2015;373:2103-16.

SBP / DBP
1 yr



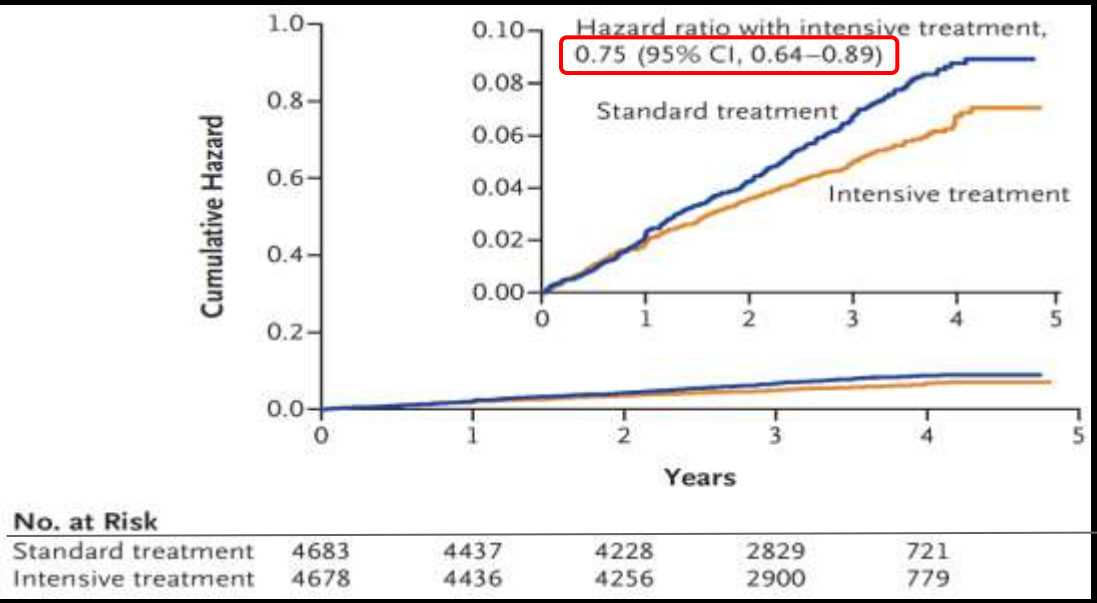
No. with Data										
Standard treatment	4683	4345	4222	4092	3997	3904	3115	1974	1000	274
Intensive treatment	4678	4375	4231	4091	4029	3920	3204	2035	1048	286
Mean No. of Medications										
Standard treatment	1.9	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.9
Intensive treatment	2.3	2.7	2.8	2.8	2.8	2.8	2.8	2.8	2.8	3.0

Early termination of the study
Median follow-up of 3.26 yrs

N Engl J Med 2015;373:2103-16.

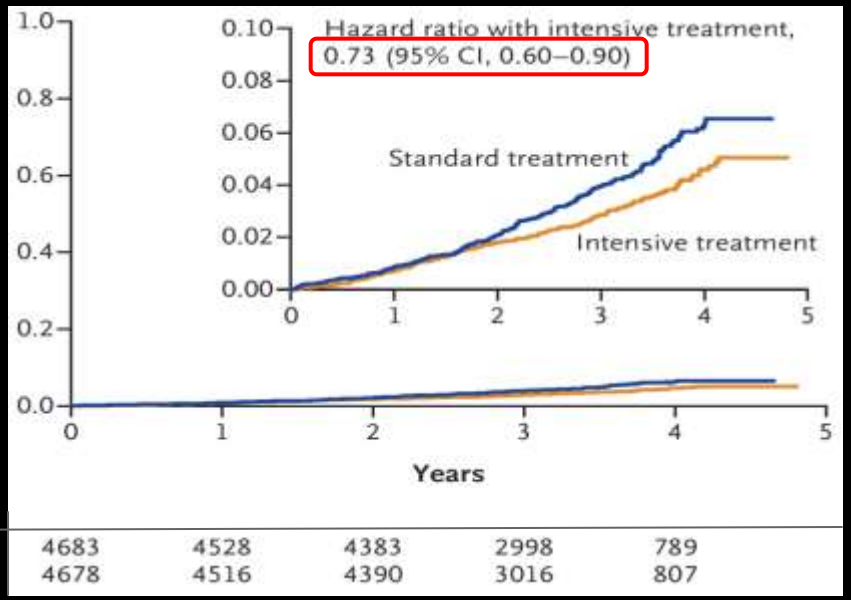
SPRINT - Outcomes

A. Primary Outcome



No. at Risk					
Standard treatment	4683	4437	4228	2829	721
Intensive treatment	4678	4436	4256	2900	779

B. Death from Any Cause



	4683	4528	4383	2998	789
	4678	4516	4390	3016	807

N Engl J Med 2015;373:2103-16.

SPRINT – Adverse events

Variable	Intensive Treatment (N=4678)	Standard Treatment (N=4683)	Hazard Ratio	P Value
	no. of patients (%)			
Serious adverse event*	1793 (38.3)	1736 (37.1)	1.04	0.25
Conditions of interest				
Serious adverse event only				
Hypotension	110 (2.4)	66 (1.4)	1.67	0.001
Syncope	107 (2.3)	80 (1.7)	1.33	0.05
Bradycardia	87 (1.9)	73 (1.6)	1.19	0.28
Electrolyte abnormality	144 (3.1)	107 (2.3)	1.35	0.02
Injurious fall†	105 (2.2)	110 (2.3)	0.95	0.71
Acute kidney injury or acute renal failure‡	193 (4.1)	117 (2.5)	1.66	<0.001
Emergency department visit or serious adverse event				
Hypotension	158 (3.4)	93 (2.0)	1.70	<0.001
Syncope	163 (3.5)	113 (2.4)	1.44	0.003
Bradycardia	104 (2.2)	83 (1.8)	1.25	0.13
Electrolyte abnormality	177 (3.8)	129 (2.8)	1.38	0.006
Injurious fall†	334 (7.1)	332 (7.1)	1.00	0.97
Acute kidney injury or acute renal failure‡	204 (4.4)	120 (2.6)	1.71	<0.001
Monitored clinical events				
Adverse laboratory measure§				
Serum sodium <130 mmol/liter	180 (3.8)	100 (2.1)	1.76	<0.001
Serum sodium >150 mmol/liter	6 (0.1)	0		0.02
Serum potassium <3.0 mmol/liter	114 (2.4)	74 (1.6)	1.50	0.006
Serum potassium >5.5 mmol/liter	176 (3.8)	171 (3.7)	1.00	0.97
Orthostatic hypotension¶				
Alone	777 (16.6)	857 (18.3)	0.88	0.01
With dizziness	62 (1.3)	71 (1.5)	0.85	0.35

Automated compared to manual office blood pressure and to home blood pressure in hypertensive patients

Jan Filipovský[a,b], Jitka Seidlerová[a,b], Zdeněk Kratochvíl[a], Petra Karnosová[a,b], Markéta Hronová[a] and Otto Mayer Jr[a,b]

[a]Department of Internal Medicine II; [b]Biomedical Centre, Charles University, Medical Faculty in Pilsen, Pilsen, Czech Republic

ABSTRACT

We studied the relationships of automated blood pressure (BP), measured in the healthcare centre, with manual office BP and home BP. Stable outpatients treated for hypertension were measured automatically, seated alone in a quiet room, six times after a 5 min rest with the BpTRU device, and immediately afterwards using the auscultatory method. Home BP was measured in a subgroup during 7 days preceding the visit. The automated, office and home BP values were 131.2 ± 21.8/77.8 ± 12.1 mmHg, 146.9 ± 20.8/85.8 ± 12.4 mmHg and 137.7 ± 17.7/79.4 ± 8.2 mmHg, respectively. Limits of agreement between office and automated BP (2 SDs in Bland–Altman plots) were +42.6 to −12.6/+22.6 to −6.6 mmHg for systolic/diastolic BP; for home and automated BP they were +45.8 to −25.8/+20.8 to −12.6 mmHg. For patients with two visits, intraclass correlation coefficients of BP values measured during the first and second visits were 0.66/0.72 for systolic/diastolic automated BP and 0.68/0.74 for systolic/diastolic office BP. Automated BP was lower than home BP and no more closely related to home BP than to office BP. It did not show better repeatability than office BP. Whether automated BP and the "white-coat effect", calculated cas the office BP–automated BP difference, have clinical and prognostic importance deserves further studies.

ARTICLE HISTORY

Received 5 June 201
Accepted 14 Decemb
Published online 4 Fe
2016

KEYWORDS

Automated office blo
pressure; blood press
measurement; home
pressure; white-coat

Etude SPRINT : synthèse

Au prix d'une augmentation significative de nombreux effets adverses

tenter d'atteindre une PAS inférieure à 120 mmHg

mesurée au dinamap dans une pièce ou le patient est seul, sans hypotension orthostatique,

plutôt qu'inférieure à 140 mm Hg

mesurée au dinamap dans une pièce ou le patient est seul, sans hypotension orthostatique

(équivalent à 130-135 vs. 150-155 mmHg en mesure au cabinet médical)

réduit significativement la mortalité totale et les événements CV majeurs

chez des hypertendus non diabétiques, sans antécédents cérébro-vasculaires

Plan

- Observation / intervention
- Veterans / MRC / SHEP
- ALLHAT
- LIFE et ARA II - Problème de posologies - IEC
- ASCOT
- ACCOMPLISH
- HYVET
- SPRINT
- Méta-analyses

Effects of blood pressure lowering on outcome incidence in hypertension: 7. Effects of more vs. less intensive blood pressure lowering and different achieved blood pressure levels – updated overview and meta-analyses of randomized trials

Costas Thomopoulos[a], Gianfranco Parati[b,c], and Alberto Zanchetti[d,e]

Journal of Hypertension 2016, 34:613–622

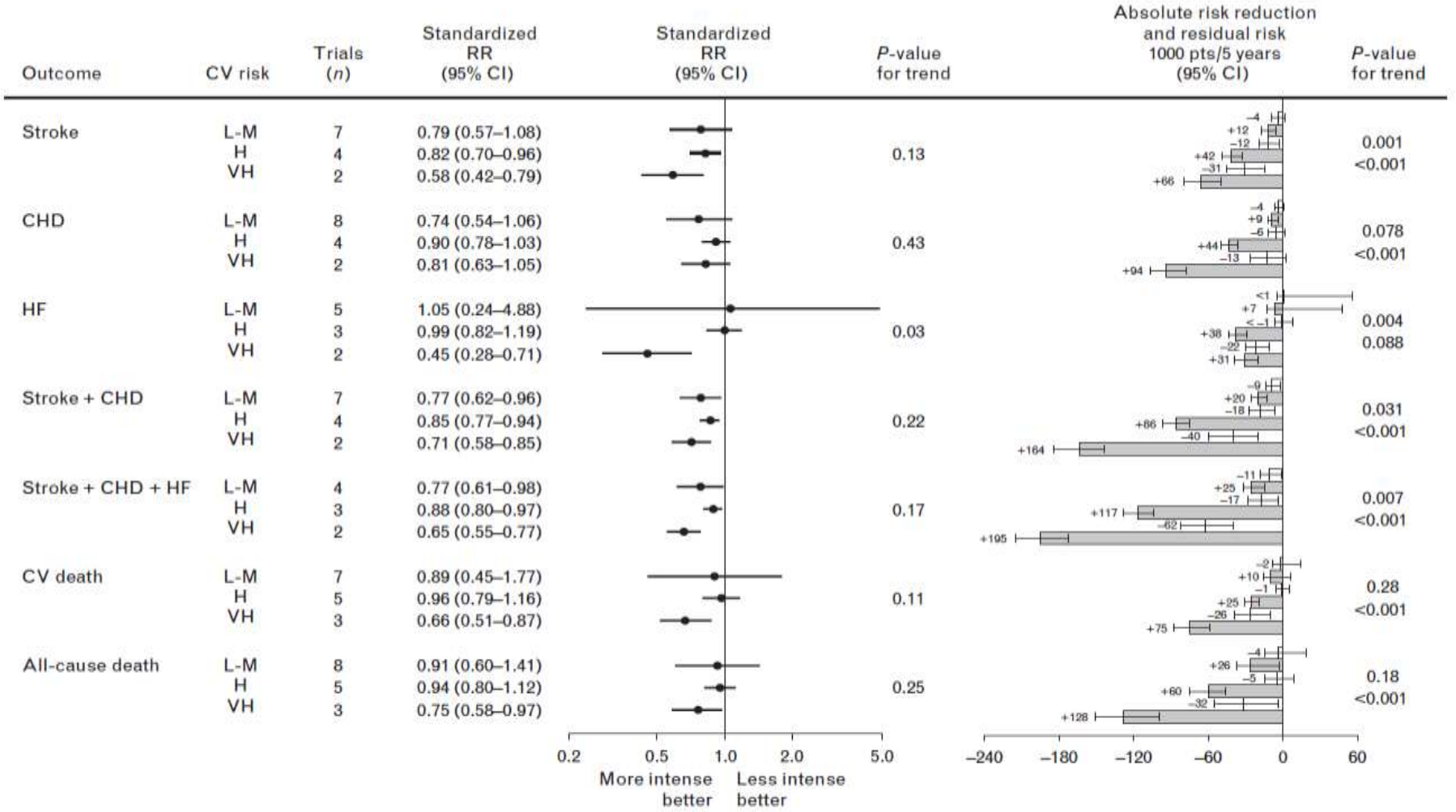


FIGURE 3 Effects of more vs. less intense BP lowering in trials stratified by different levels of cardiovascular (CV) risk: low-moderate (L-M), high (H), very high (VH). Standardized Mantel–Haenszel risk ratios (RR) are to a SBP/DBP difference of −10/−5 mmHg. The white histograms of the column absolute risk reduction and residual risk represent the absolute risk reductions as numbers (and 95% CI) of events prevented every 1000 patients more intensely treated for 5 years using the standardized RR; the gray histograms represent the residual risk as numbers (and 95% CI) of residual events every 1000 patients more intensely treated for 5 years. The two columns headed *P* value for trend refer, the first, to the standardized RR, and the second to absolute risk reduction (value above) and residual risk (value below). CHD, coronary heart disease; HF, heart failure; pts, patients.

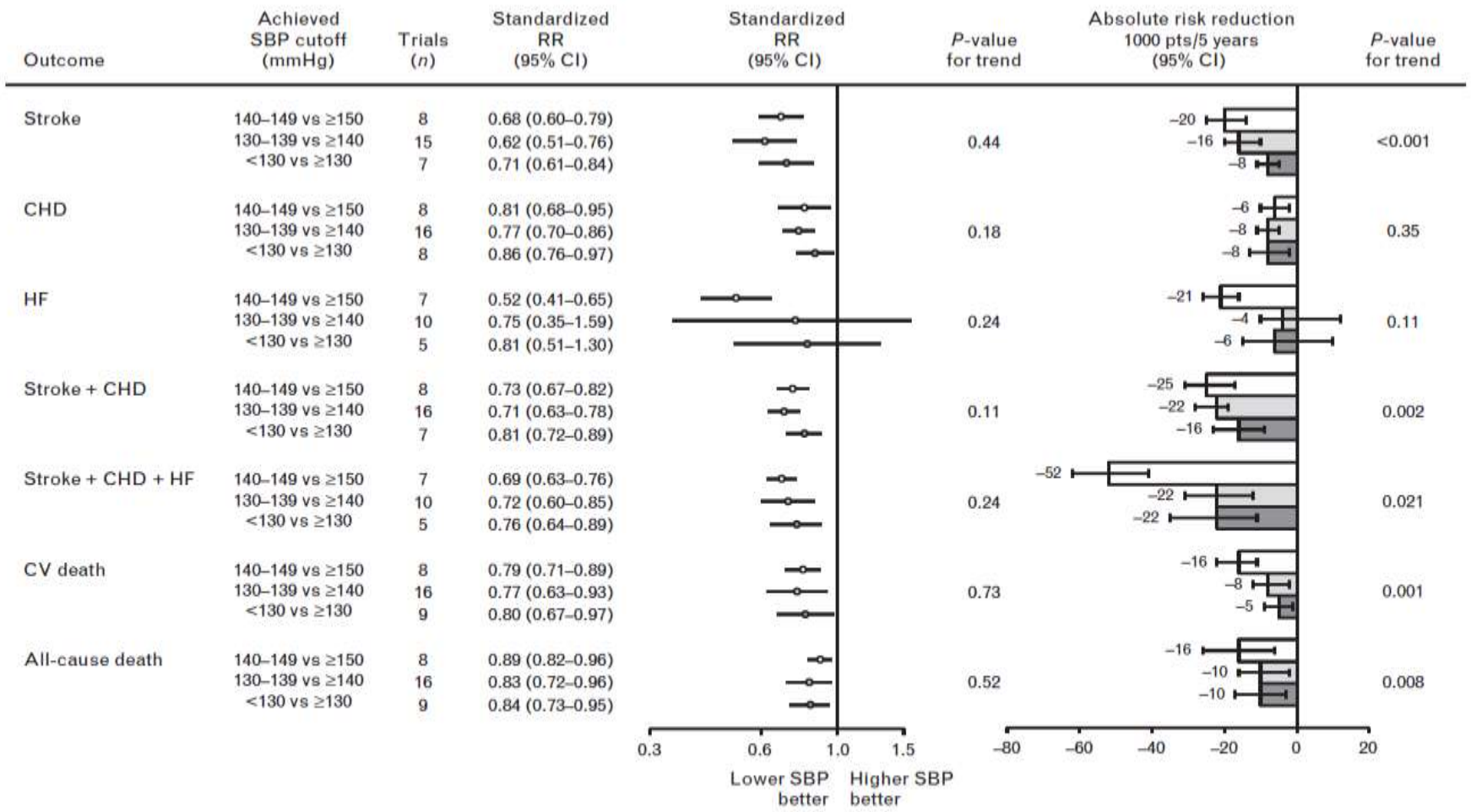


FIGURE 5 Effects of BP lowering in trials of active treatment vs. placebo and more vs. less intense treatment (considered together), stratified in three strata with mean SBP achieved by active or more intense treatment vs. mean SBP achieved in the placebo or less intense treatment: 140–149 vs. at least 150 mmHg; 130–139 vs. at least 140 mmHg; less than 130 vs. at least 130 mmHg. Standardized RR is to a SBP/DBP difference of −10/−5 mmHg. The histograms of the column Absolute risk reduction represent the numbers (and 95% CI) of events prevented every 1000 patients actively or more intensely treated for 5 years using the standardized RR. The two columns headed *P* value for trend refer, the first, to the standardized RR, and the second to absolute risk reduction. Mean SBP/DBP achieved in the three strata of achieved SBP were (from above downward): 143.3/76.4 vs. 157.1/82.1; 137.2/81.0 vs. 144.3/84.8; 125.8/76.3 vs. 134.9/79.4. BP, blood pressure; CHD, coronary heart disease; CI, confidence interval; CV, cardiovascular; HF, heart failure; pts, patients; RR, Mantel–Haenszel risk ratio.