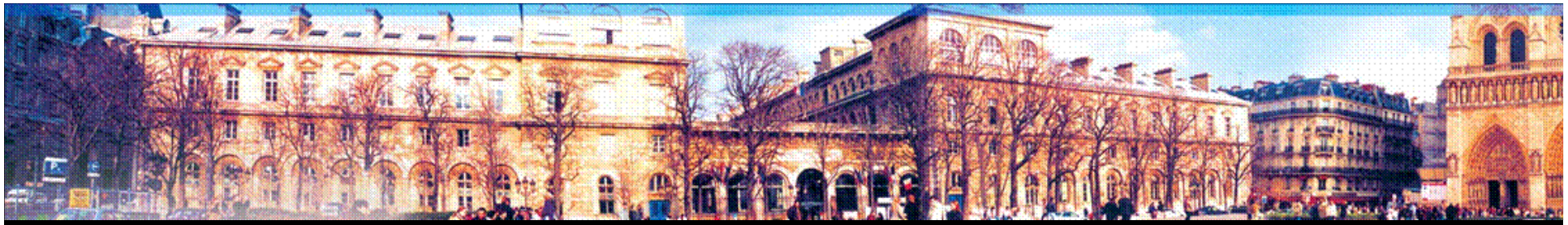

Prévention médicamenteuse des complications de l'HTA : les grands essais

Pr. Jacques Blacher
Unité hypertension artérielle, prévention et thérapeutique cardiovasculaires
Centre de diagnostic et de thérapeutique, Hôtel-Dieu, Paris

Mars 2014

Plan

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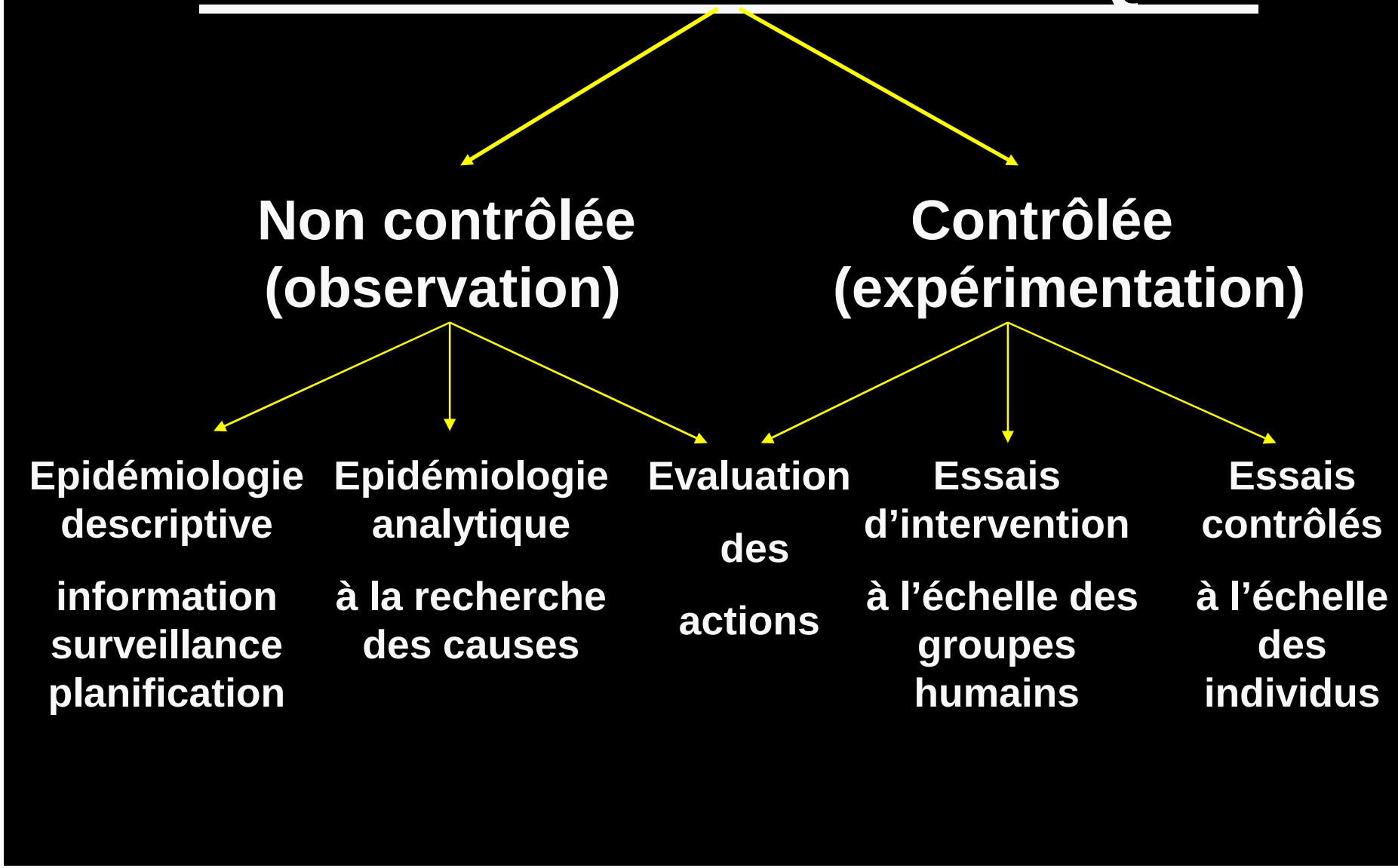
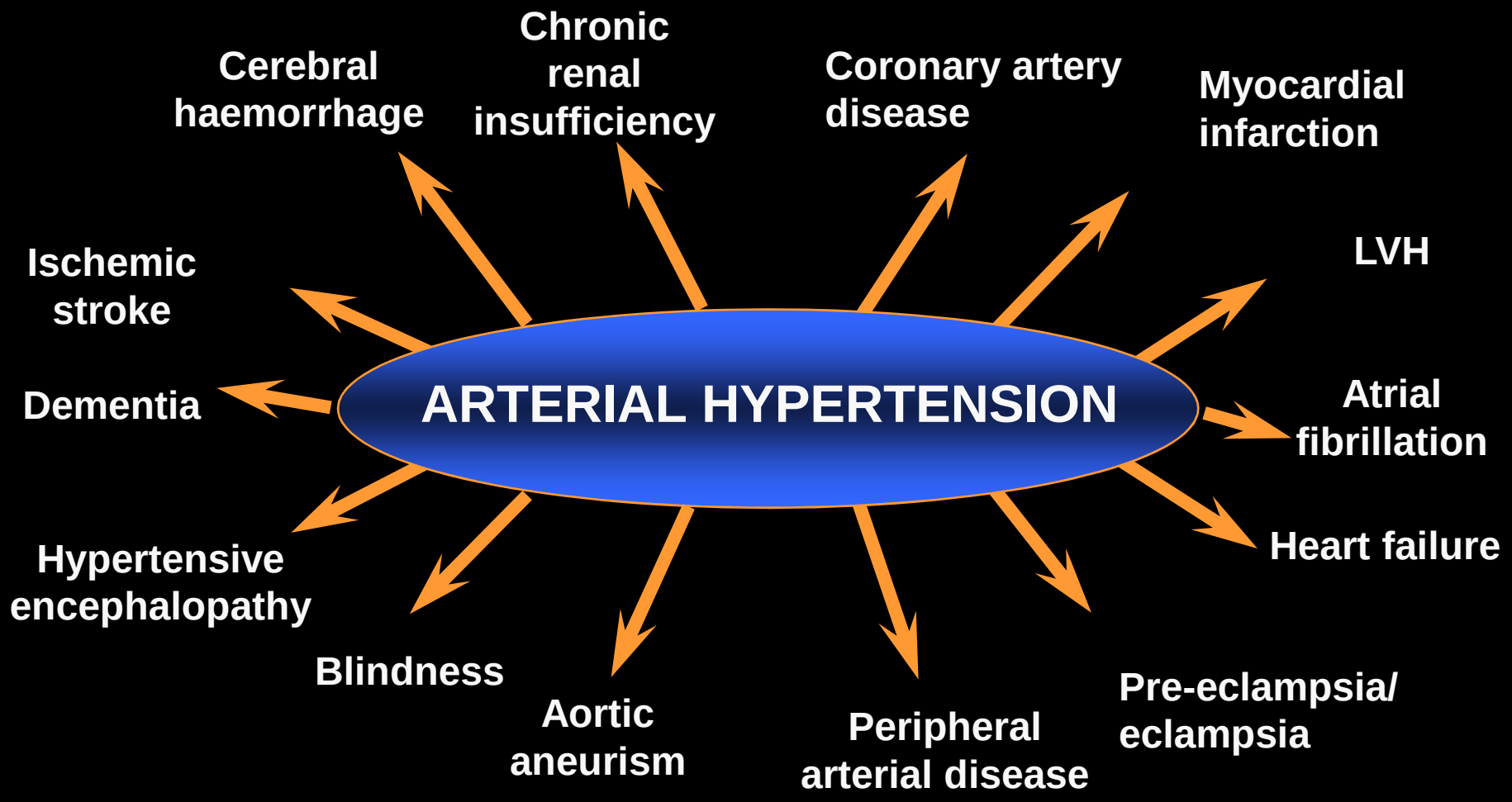
- HYVET
- Méta-analyses
- Recommandations

ETUDE EPIDEMIOLOGIQUE



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

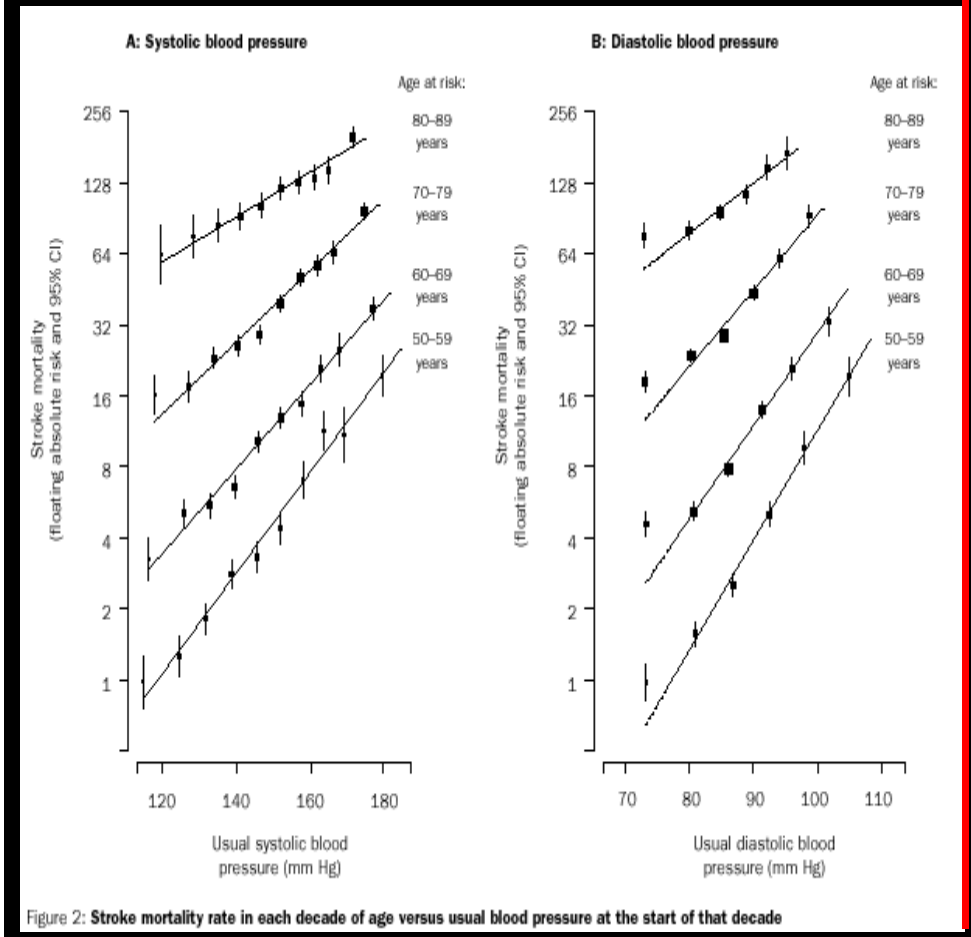


Figure 2: **Stroke mortality rate in each decade of age versus usual blood pressure at the start of that decade**

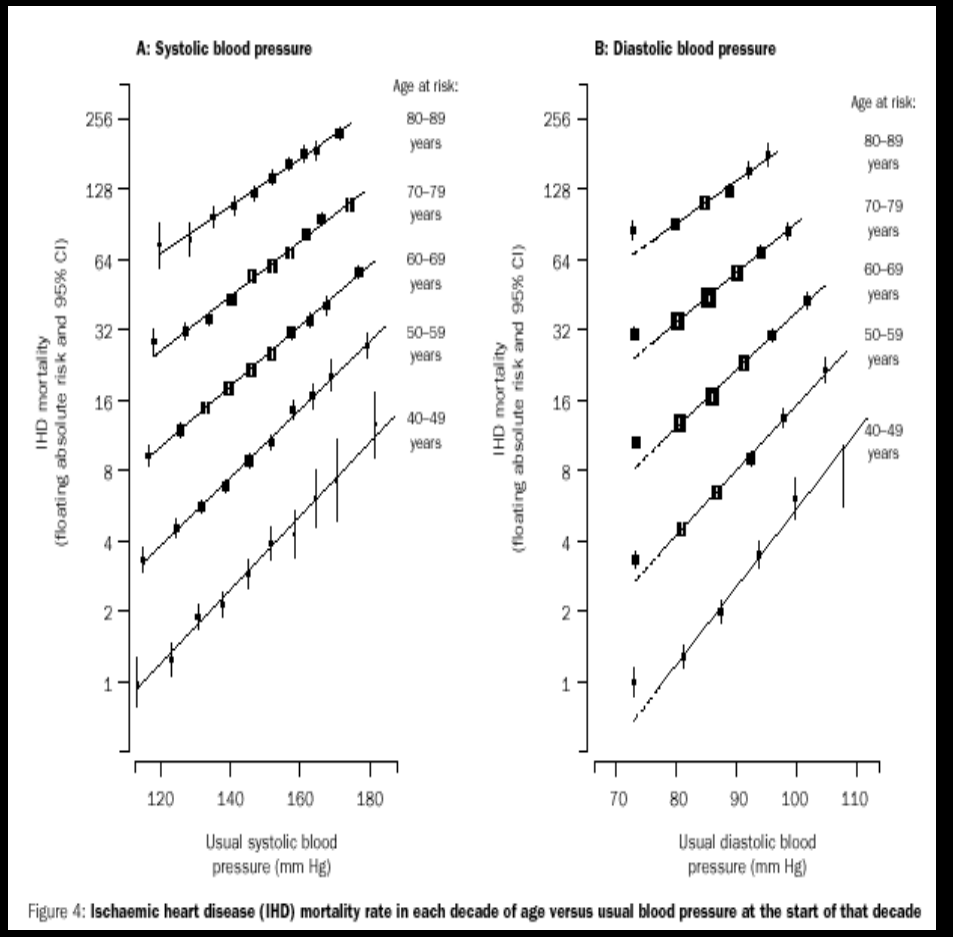
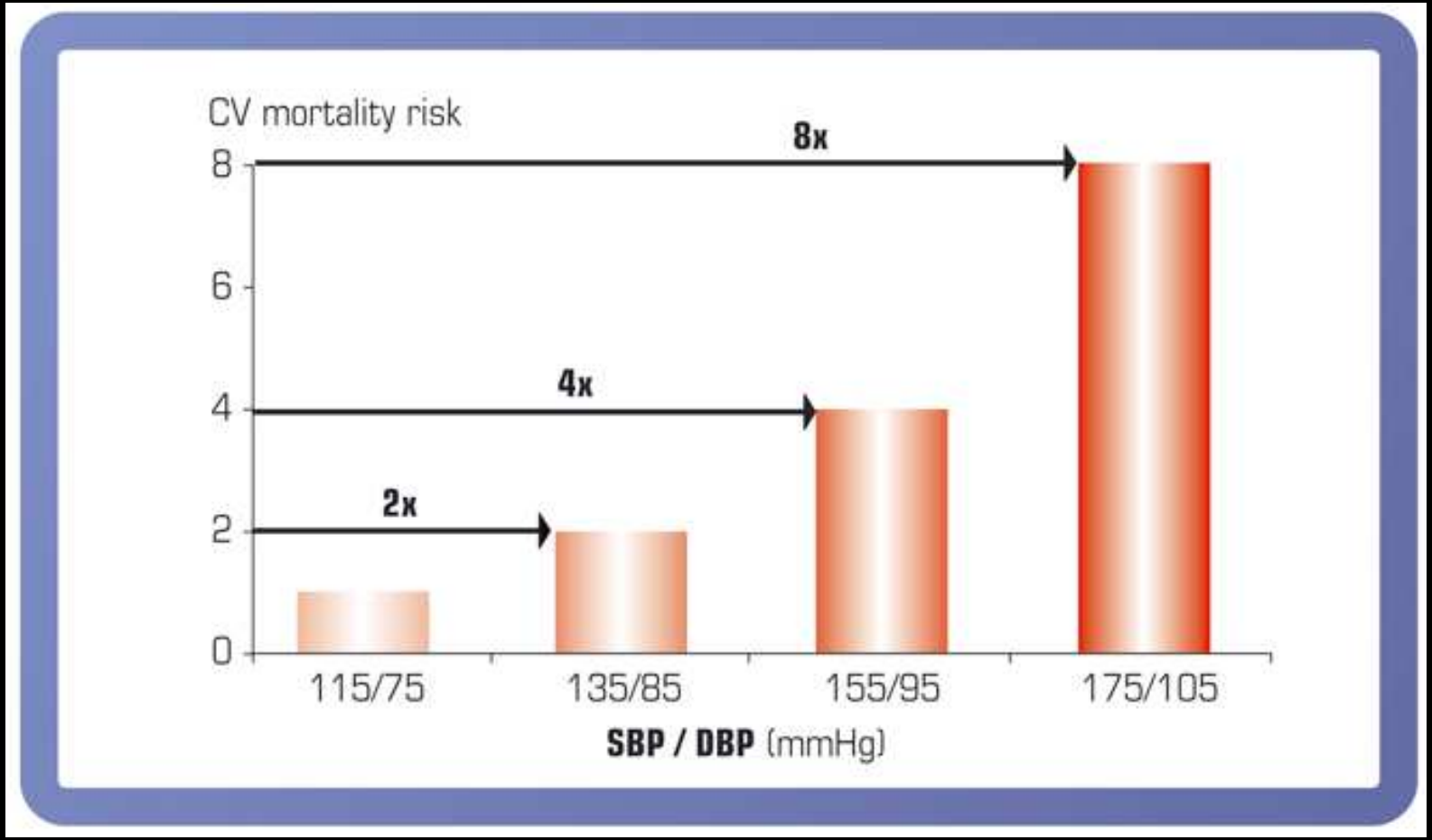


Figure 4: **Ischaemic heart disease (IHD) mortality rate in each decade of age versus usual blood pressure at the start of that decade**

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%.

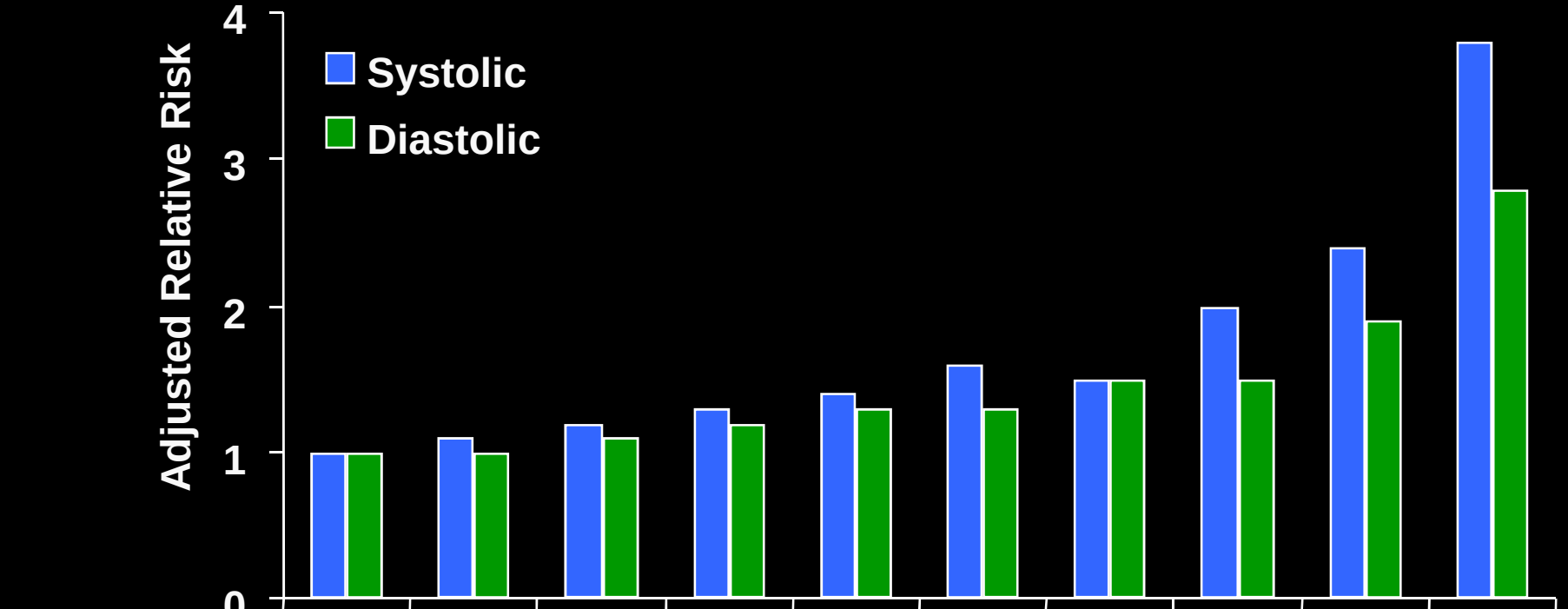
Le risque de mortalité cardiovasculaire double pour chaque augmentation de PAS/PAD de 20/10 mmHg



* 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.

Risk of CHD Death According to Systolic BP and Diastolic BP in MRFIT



Stamler et al. *Arch Intern Med*. 1993;153:598-615.

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*.

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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

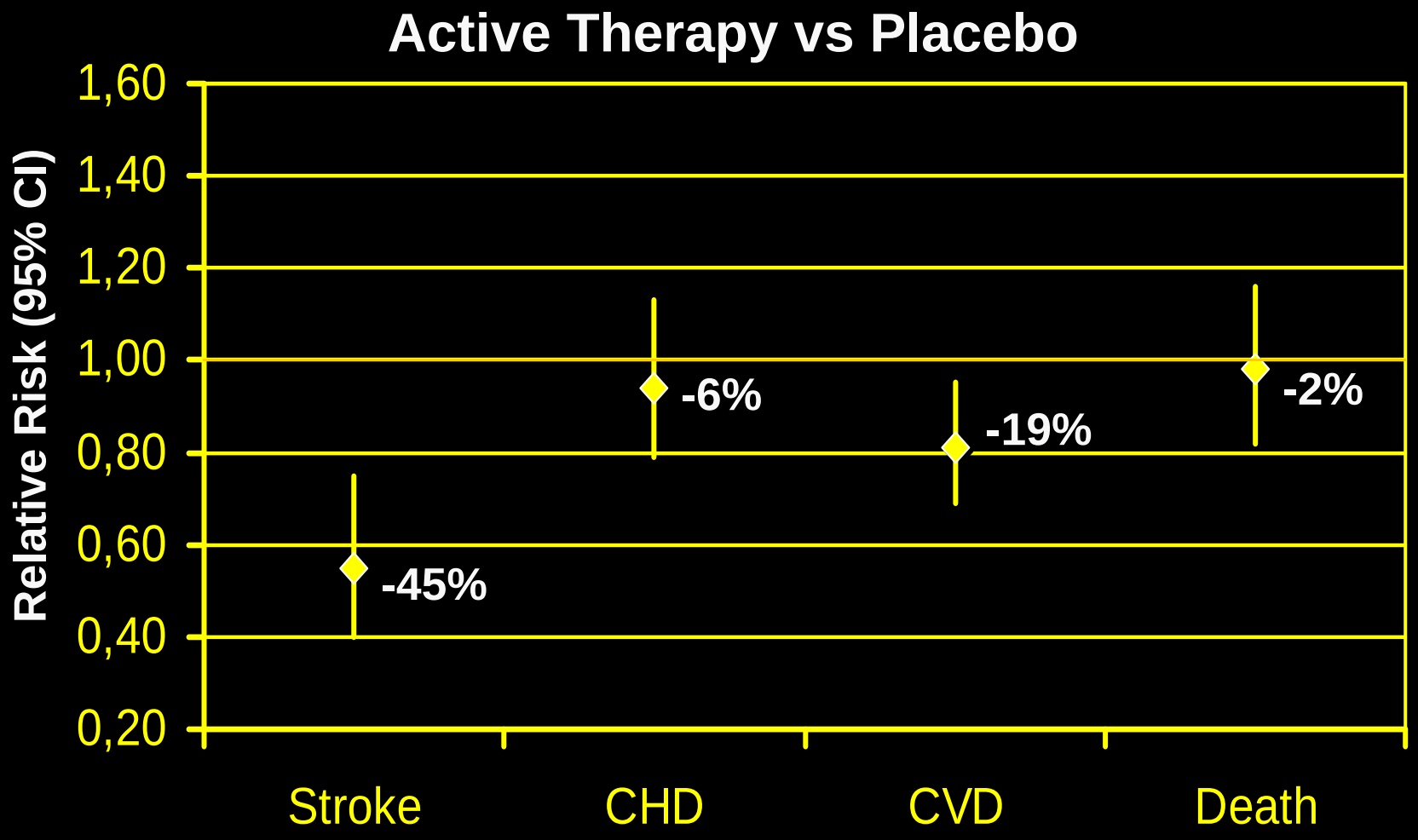
Veterans Administration Cooperative Study, JAMA 1967

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



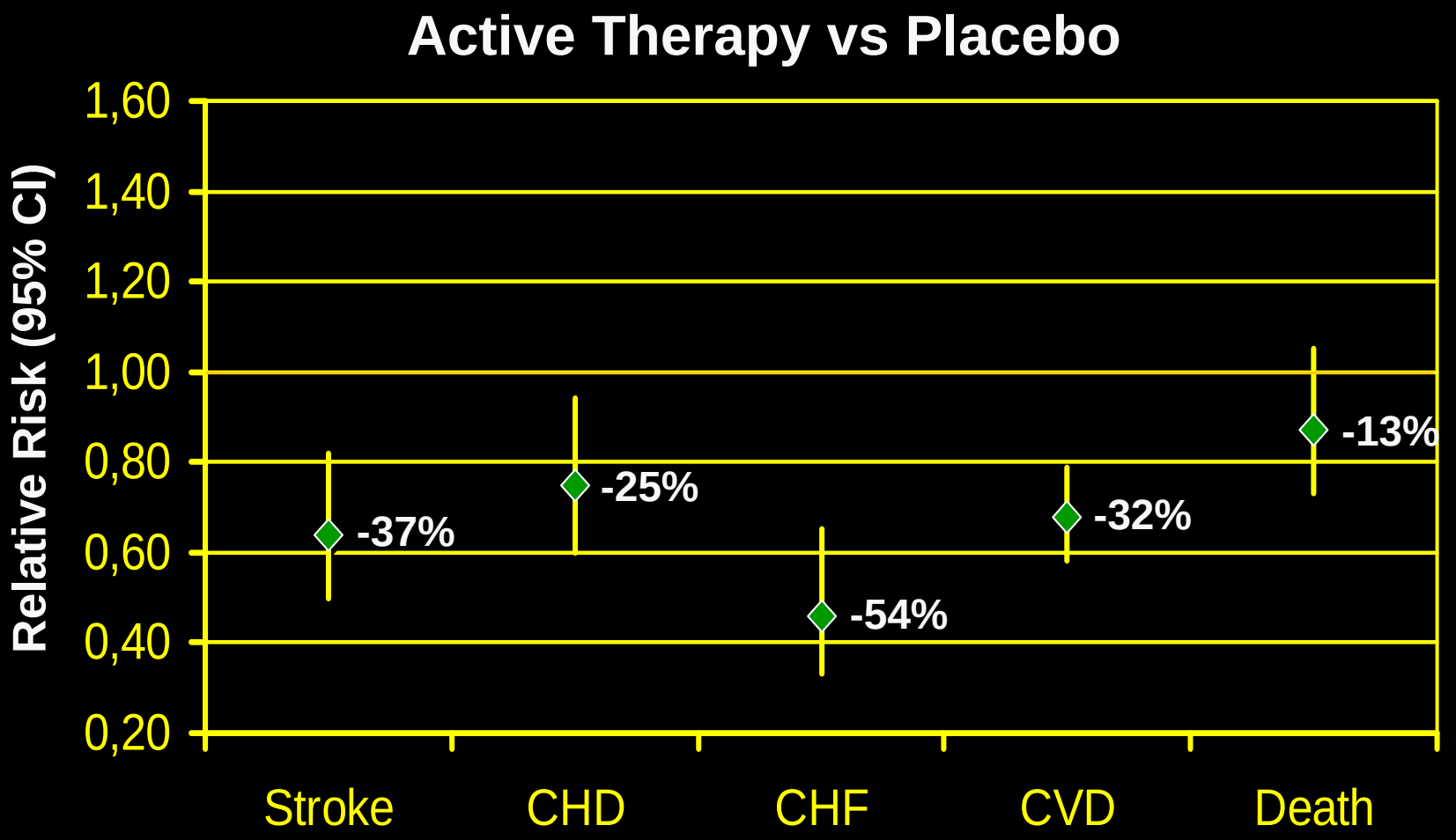
MRC Working Party. *BMJ*. 1985;291:97-104.

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.

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ALLHAT: Design

- Practice-based randomized clinical trial in high-risk patients with hypertension
- Patients 55 years and older; intention to recruit broad-based population including women, blacks, patients with diabetes
- Double-blinded assignment to initial antihypertensive therapy with amlodipine, chlorthalidone, lisinopril, or doxazosin
- Substudy: open-label pravastatin vs usual care in planned 20,000 moderately hypercholesterolemic patients
- Planned follow-up: 6 years

Davis et al. *Am J Hypertens*. 1996;9:342-360; Grimm et al. *Hypertension*. 2001;37:19-27.

ALLHAT: Hypothesis

- **The combined incidence of fatal CHD and nonfatal MI will be lower in hypertensive patients randomized to**
  - **an ACEI, or**
  - **a CCB, or**
  - **an alpha-adrenergic blocker**

  as first-line therapy than in those randomized to a thiazide-like diuretic

Davis et al. *Am J Hypertens*. 1996;9:342-360.

ALLHAT: Primary Endpoint

- **Combined CHD deaths[1] and nonfatal MI[2]**

[1]Excluded stroke deaths.

[2]By discharge summary, face sheet, including suspect MI with thrombolysis, or biennial ECG.

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

ALLHAT: Prespecified Secondary Endpoints

- All-cause mortality
- Combined CHD (CHD or revascularization procedures or hospitalized angina)
- Stroke
- Combined CVD (combined CHD, stroke, CHF, or PAD)
- Renal disease (ESRD/ slope and reciprocal of serum creatinine)
- Hospitalized gastrointestinal bleeding
- Cancer
- LVH
- Health-related quality of life
- Major costs of medical care

Davis et al. *Am J Hypertens*. 1996;9:342-360.

ALLHAT: Criteria for HF Evaluation

Must have 1 from each category:

Category "A"

- Paroxysmal nocturnal dyspnea
- Dyspnea at rest
- NYHA Classification III
- Orthopnea

Category "B"

- Rales
- Ankle edema
- Tachycardia
- Cardiomegaly by CXR
- CXR characteristic of CHF
- S_3 gallop
- Jugular venous distention

ALLHAT Manual of Operations, 5.3.4.

ALLHAT: Entry Criteria

- **Untreated systolic and/or diastolic hypertension (>140/90 mm Hg but <180/110 mm Hg at 2 visits), OR**
- **Treated hypertension (>160/100 mm Hg on 1-2 antihypertensive drugs at visit 1; >180/110 mm Hg at visit 2, when medication may have been partially withdrawn)**
- **Age >55 years old**
- **At least 1 additional risk factor for CV morbidity, including:**
  - Old MI or stroke
  - History of revascularization
  - Other documented ASCVD
  - Type 2 diabetes mellitus
  - Cigarette smoking
  - Low HDL cholesterol
  - LVH

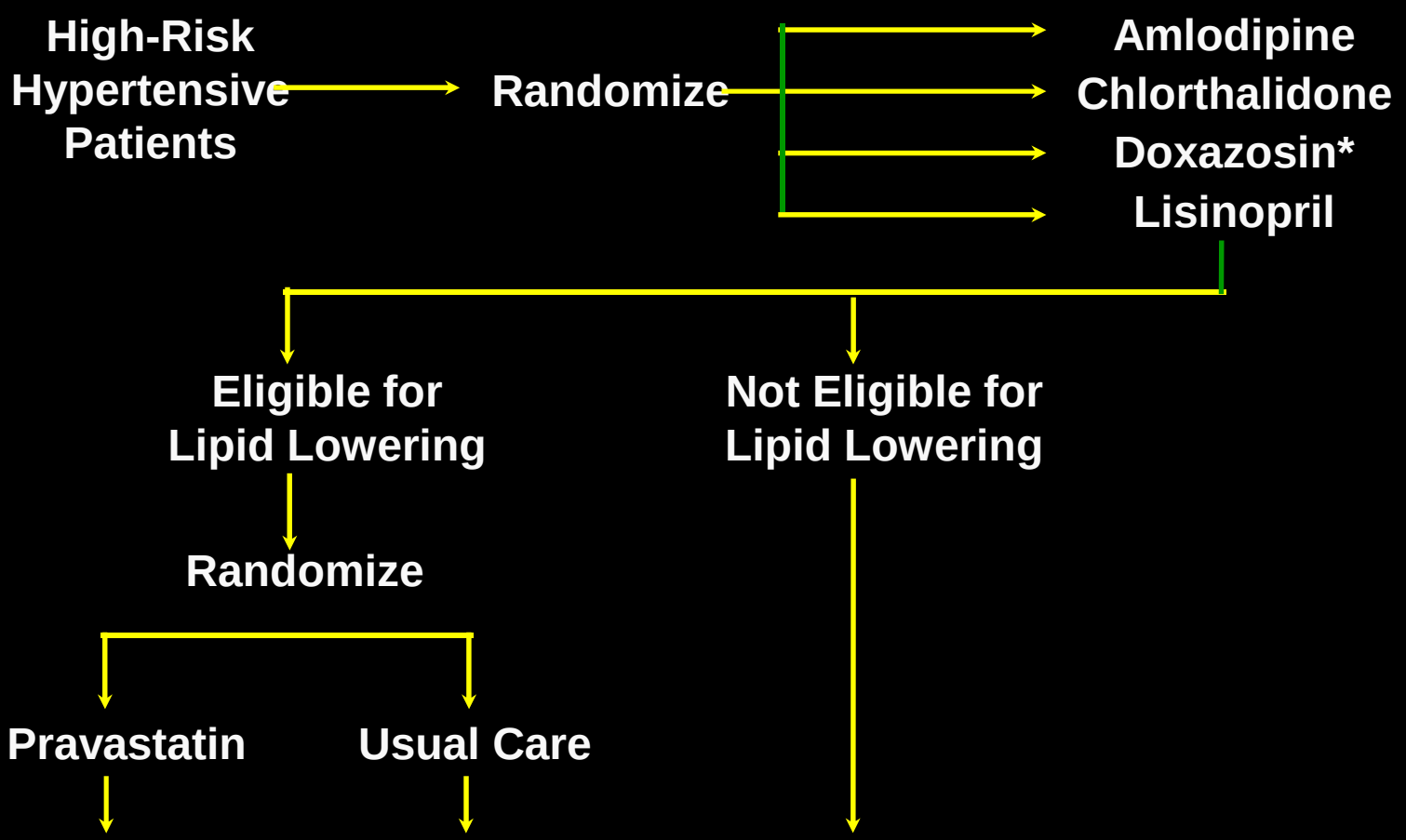
Davis et al. *Am J Hypertens*. 1996;9:342-360.

ALLHAT: Exclusion Criteria

- Recent MI or stroke (<6 months)
- Symptomatic CHF
- Known LVEF <35%
- Known renal insufficiency (creatinine >2.0 mg/dL)
- Requirement for more than 2 drugs to achieve BP control

Davis et al. *Am J Hypertens*. 1996;9:342-360.

ALLHAT: Study Design



Follow for Occurrence of CHD Until Death or End of Study

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

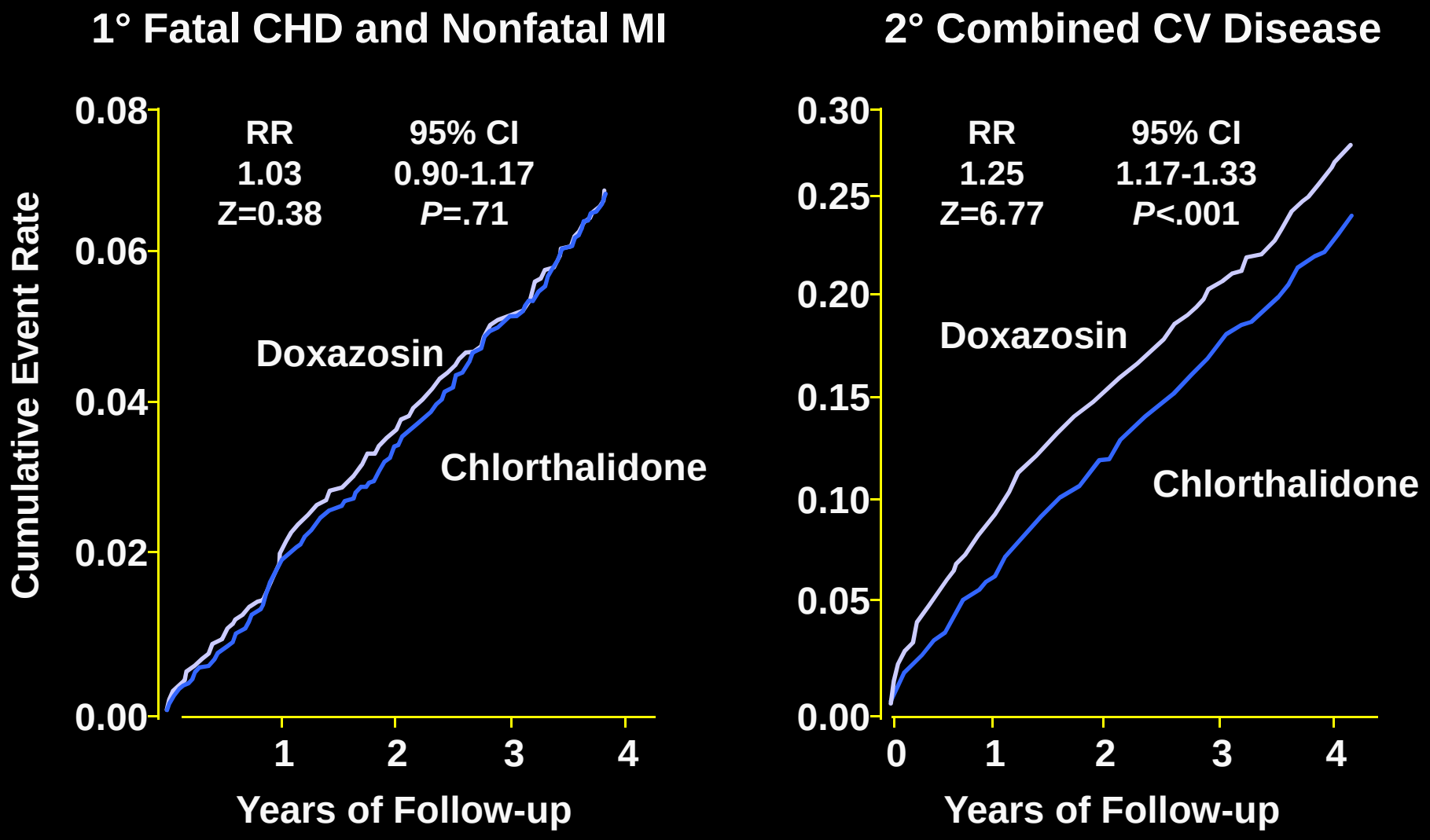
ALLHAT Collaborative Research Group. *JAMA*. 2000;283:1967-1975; Davis et al. *Am J Hypertens*. 1996;9:342-360.

ALLHAT: Statistics

- Intention-to-treat analysis
- 83% power to detect a 16% reduction in the risk of the primary outcome between chlorthalidone and each other arm
  at a 2-sided alpha = .0178
  (to account for the original 3 comparisons)

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

ALLHAT: Primary and Secondary Endpoints (Doxazosin vs Chlorthalidone)



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

Decision to Drop the Doxazosin Arm of ALLHAT

- January 24, 2000—NHLBI Director accepts recommendation of independent review to terminate doxazosin arm for the following reasons:
  - Unlikely to find a significant difference in the primary outcome between doxazosin and chlorthalidone arms
  - Statistically significant 25% higher rate of major secondary endpoint—combined CVD outcomes, principally CHF
- Doxazosin arm was not discontinued for safety reasons

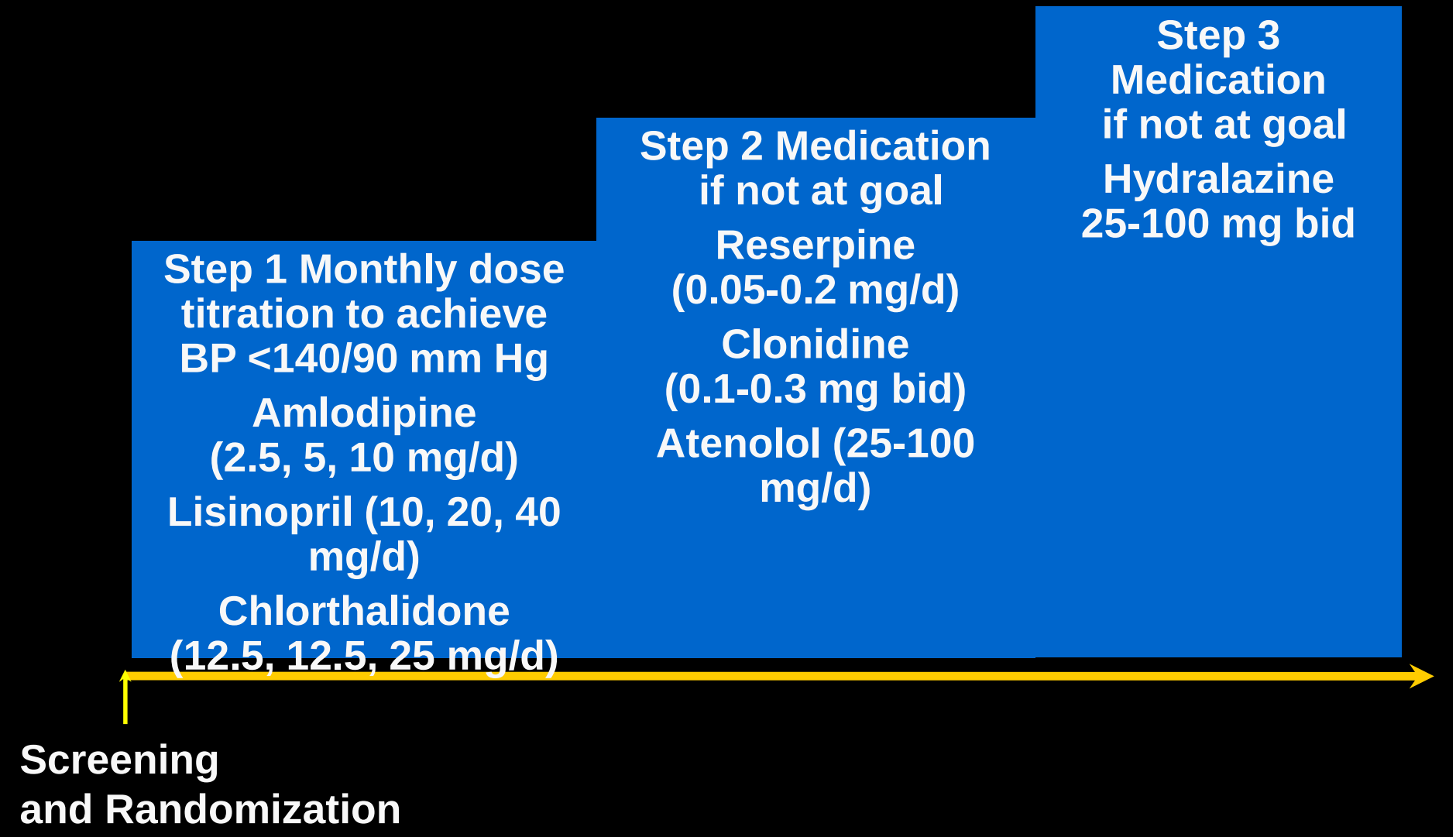
Data on file. Pfizer Inc, New York, NY.

ALLHAT: BP Treatment

- **BP goal <140/90 mm Hg**
- **Visit BP was the average of 2 seated measurements**
- **Unless original drug regimen required tapering for safety reasons, subjects continued prior meds until randomization and receipt of study drug**
- **Nonpharmacologic treatments in accordance with national guidelines**
- **Dose titration of randomized drug approximately monthly until at goal (chlorthalidone 12.5, 12.5, 25 mg/day; amlodipine 2.5, 5, 10 mg/day; lisinopril 10, 20, 40 mg/day)**

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

ALLHAT: Study Medications



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

ALLHAT: Baseline Characteristics

	Chlorthalidone	Amlodipine	Lisinopril
No. Randomized	15,255	9048	9054
Women, %	47.0	47.3	46.2
Age, y	66.9	66.9	66.9
White, non-Hispanic, %	47.2	47.6	47.1
Black, non-Hispanic, %	31.9	32.2	32.3
White Hispanic, %	12.5	12.2	12.5
Black Hispanic, %	3.3	3.3	3.2
Other, %	5.1	4.7	4.9
Baseline BP (mm Hg) (overall)	146/84	146/84	146/84
Cig. smoker, %	21.9	21.9	21.9
ASCVD, %	51.8	51.0	51.7
Type 2 diabetes, %	36.2	36.7	35.5
LVH by ECG, %	16.2	16.9	16.3
LVH by echocardiogram, %	4.6	4.6	4.5

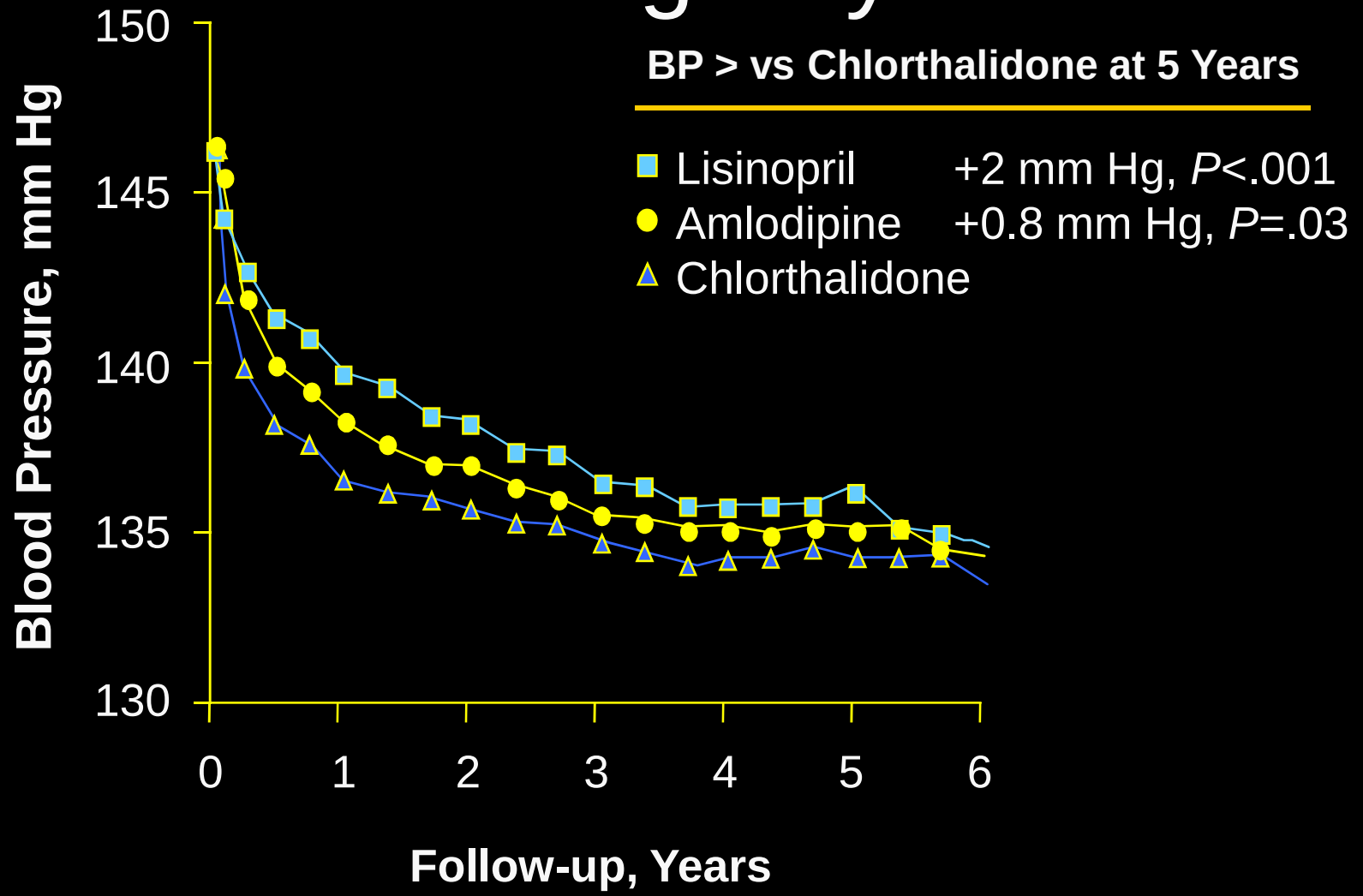
ALLHAT Collaborative Research Group. *JAMA*. 2002;288:2981-2997.

ALLHAT Follow-up Status

- Mean length of follow-up: 4.9 years
- At closeout, unknown vital status in 2.7% chlorthalidone, 2.8% amlodipine, 3.0% lisinopril patients
  - Distributions of most baseline factors similar among 3 groups
  - Unknown vital status participants assigned to lisinopril less likely to be black, more likely to be women, have untreated hypertension, evidence
    of CHD or ASCVD, and lower mean serum glucose

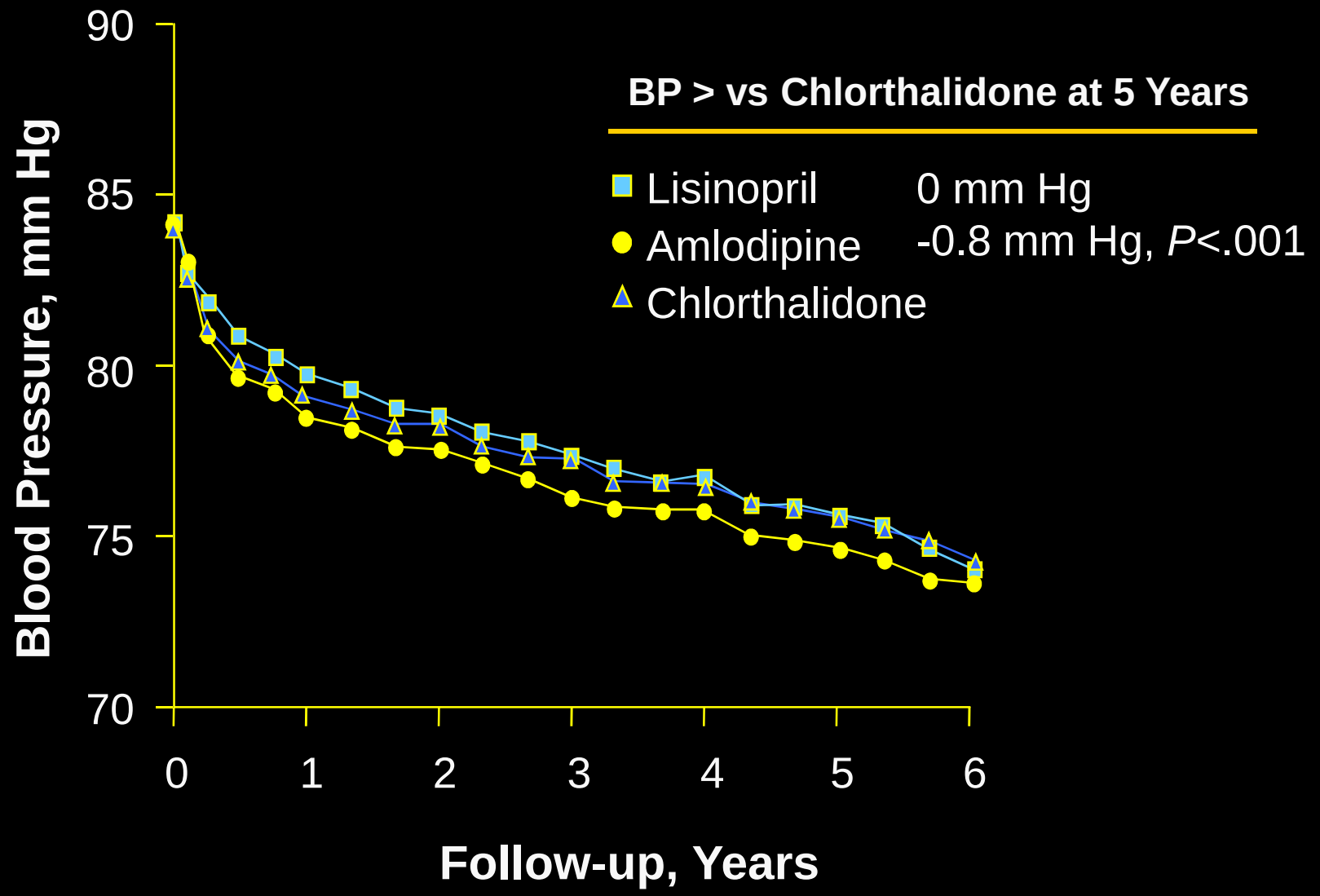
ALLHAT Collaborative Research Group. *JAMA*. 2002;288:2981-2997.

ALLHAT: Average Systolic BP



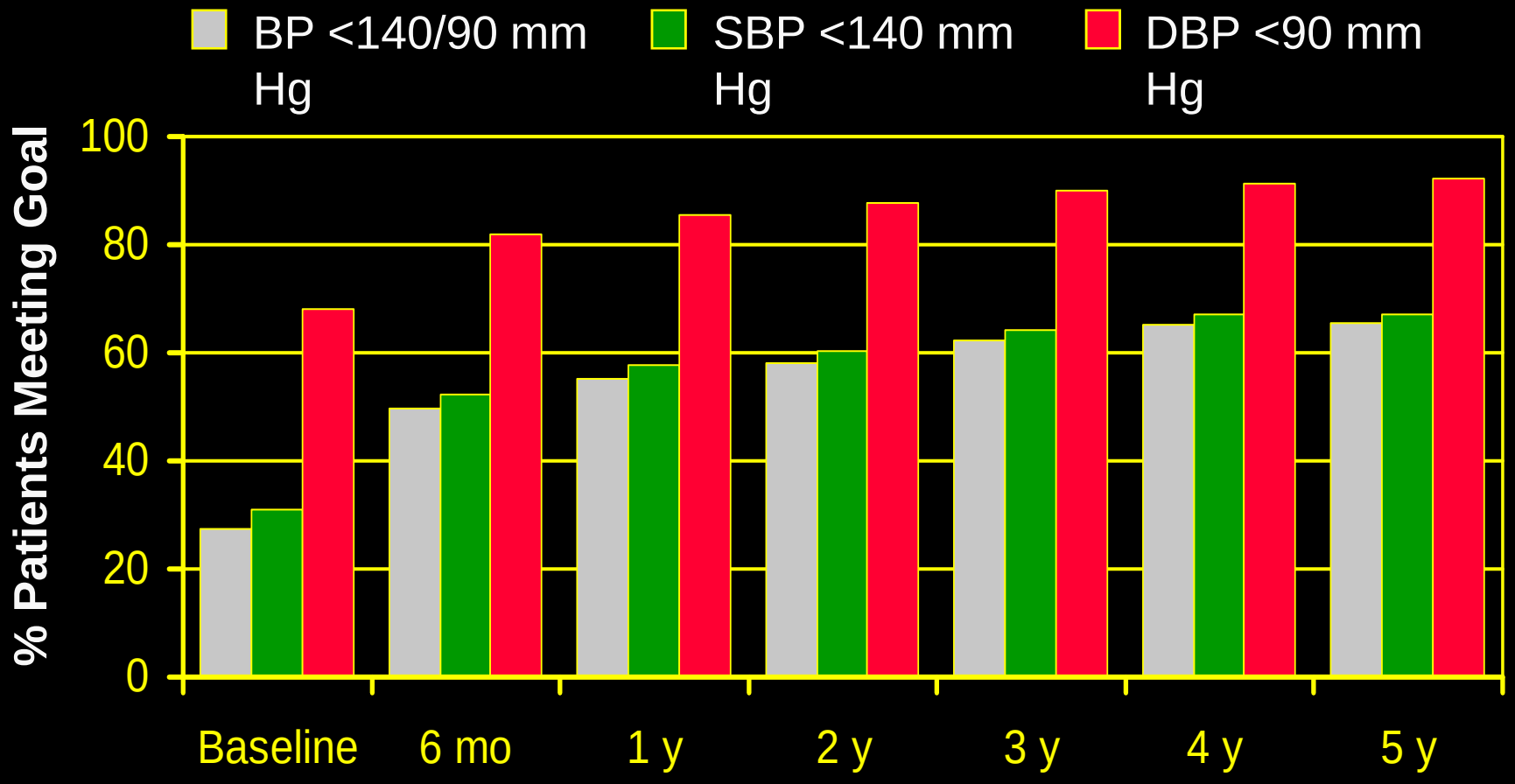
ALLHAT Collaborative Research Group. *JAMA*. 2002;288:2981-2997.

ALLHAT: Average Diastolic BP



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

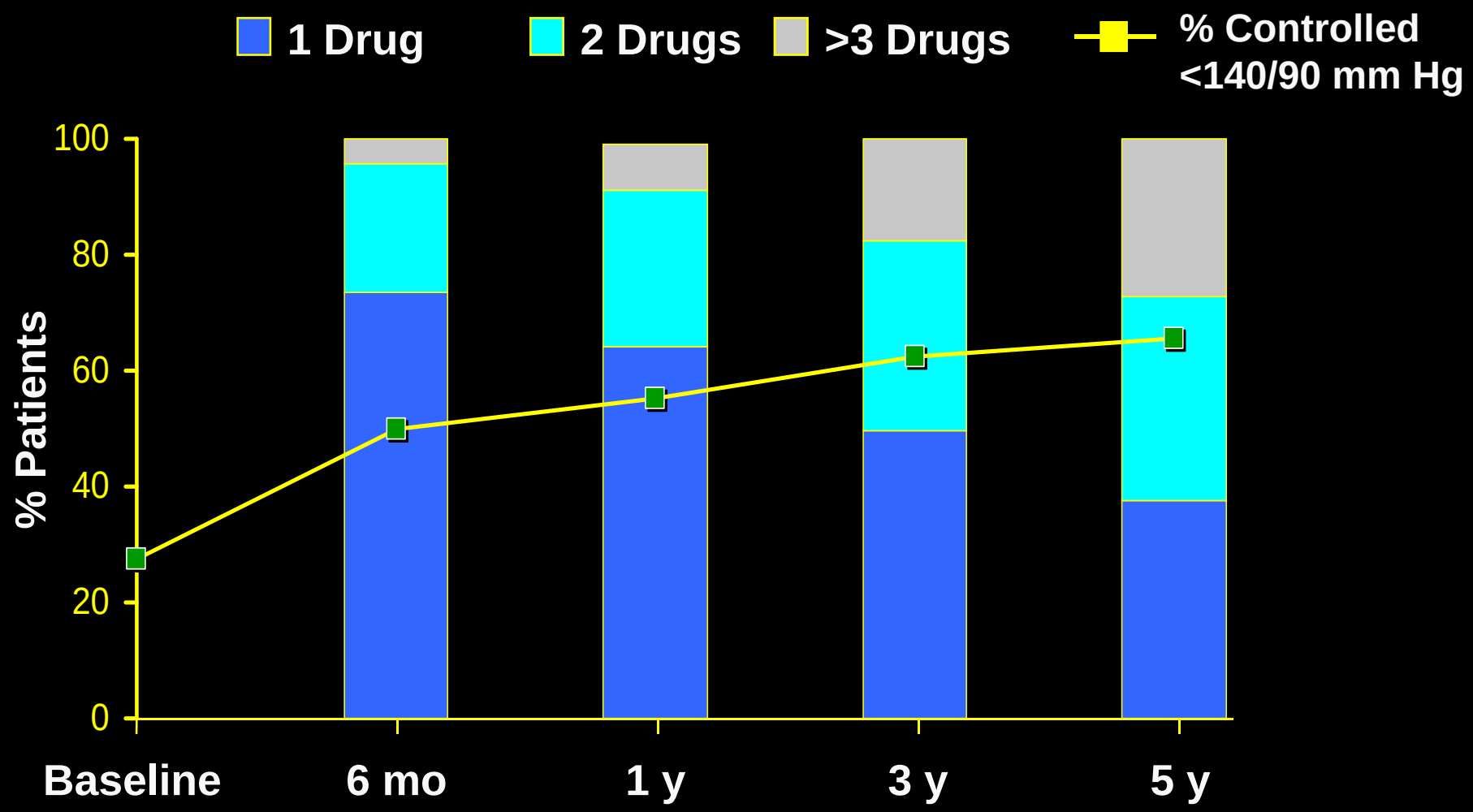
BP Control in ALLHAT Participants: % Meeting Goal by Year of Follow-up



Mean BP	145/83	140/81	138/79	137/78	136/77	135/76	13 5/75
No drugs	–	1.3	1.4	1.6	1.7	1.8	2.0

Cushman et al. *J Clin Hypertens*. 2002;4:393-404.

Medication Use and BP Control in ALLHAT



Cushman et al. *J Clin Hypertens*. 2002;4:393-404.

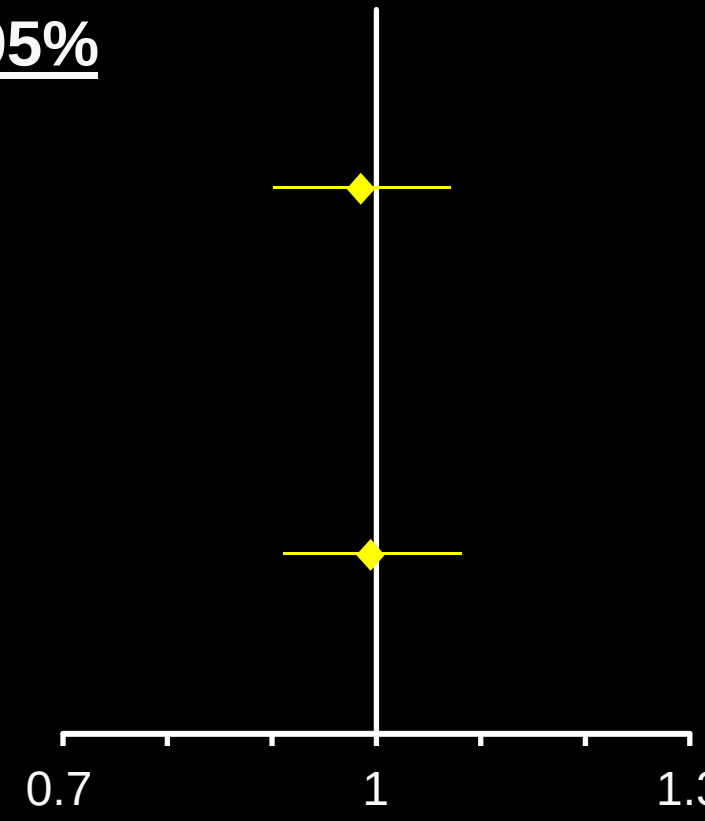
ALLHAT BP Control Implications

- Systolic BP was more difficult to control than was diastolic BP
  - Diastolic BP <90 mm Hg in 92% of participants
  - Systolic BP <140 mm Hg in 67% of participants
- Average of 2 drugs required for BP control in 2/3 of participants, primarily to control systolic BP
- Clinical practice data suggest that the majority of patients will require at least 2 antihypertensive medications to achieve the goal of <140/90 mm Hg
- Achieving lower goals, as is recommended for patients with diabetes, will likely require even more drugs

Cushman et al. *J Clin Hypertens*. 2002;4:393-404.

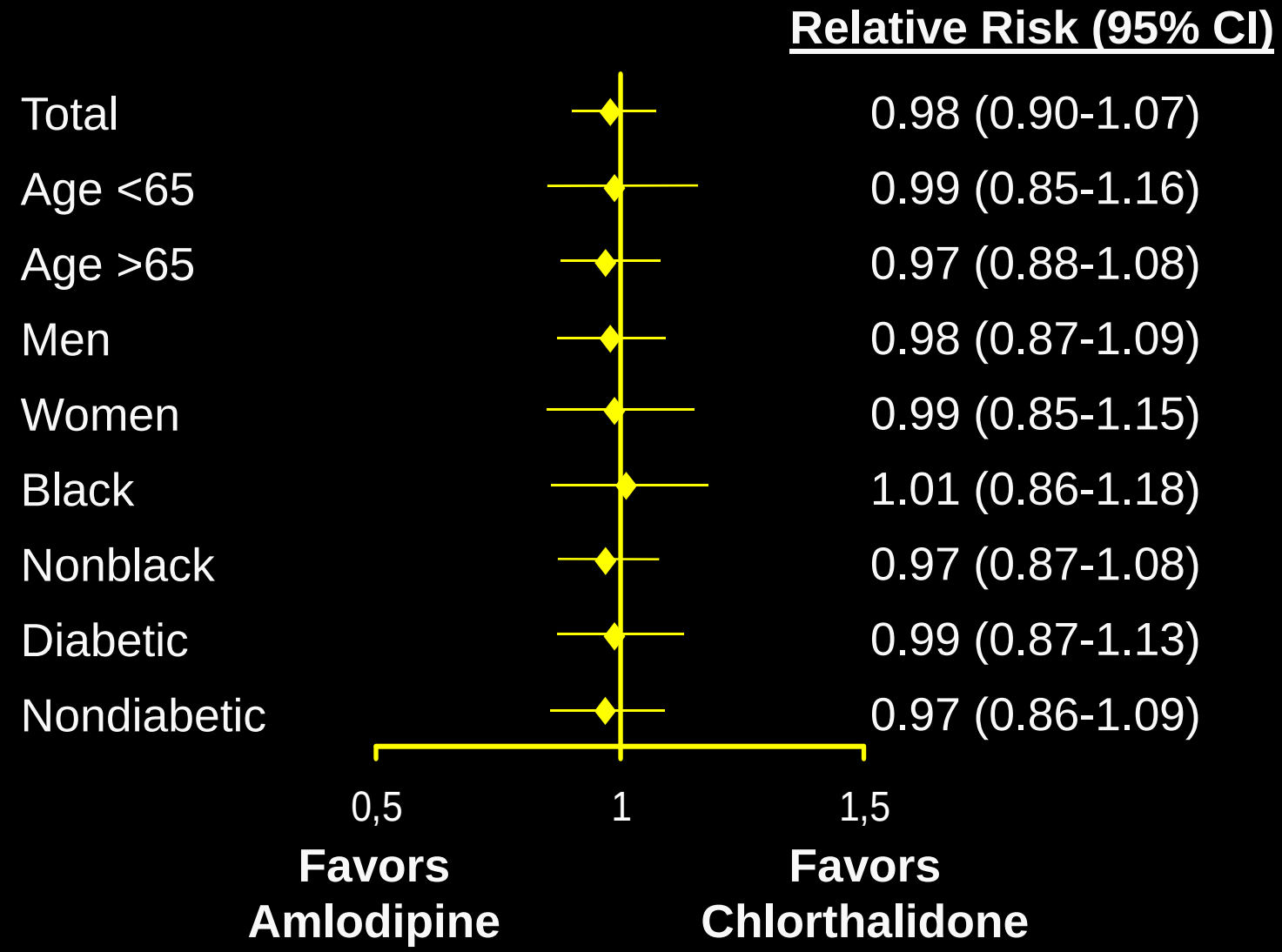
ALLHAT Primary Endpoint: CHD Death and Nonfatal MI

	Relative Risk (95% CI)
Amlodipine	0.98 (0.90-1.07)
Lisinopril	0.99 (0.91-1.08)



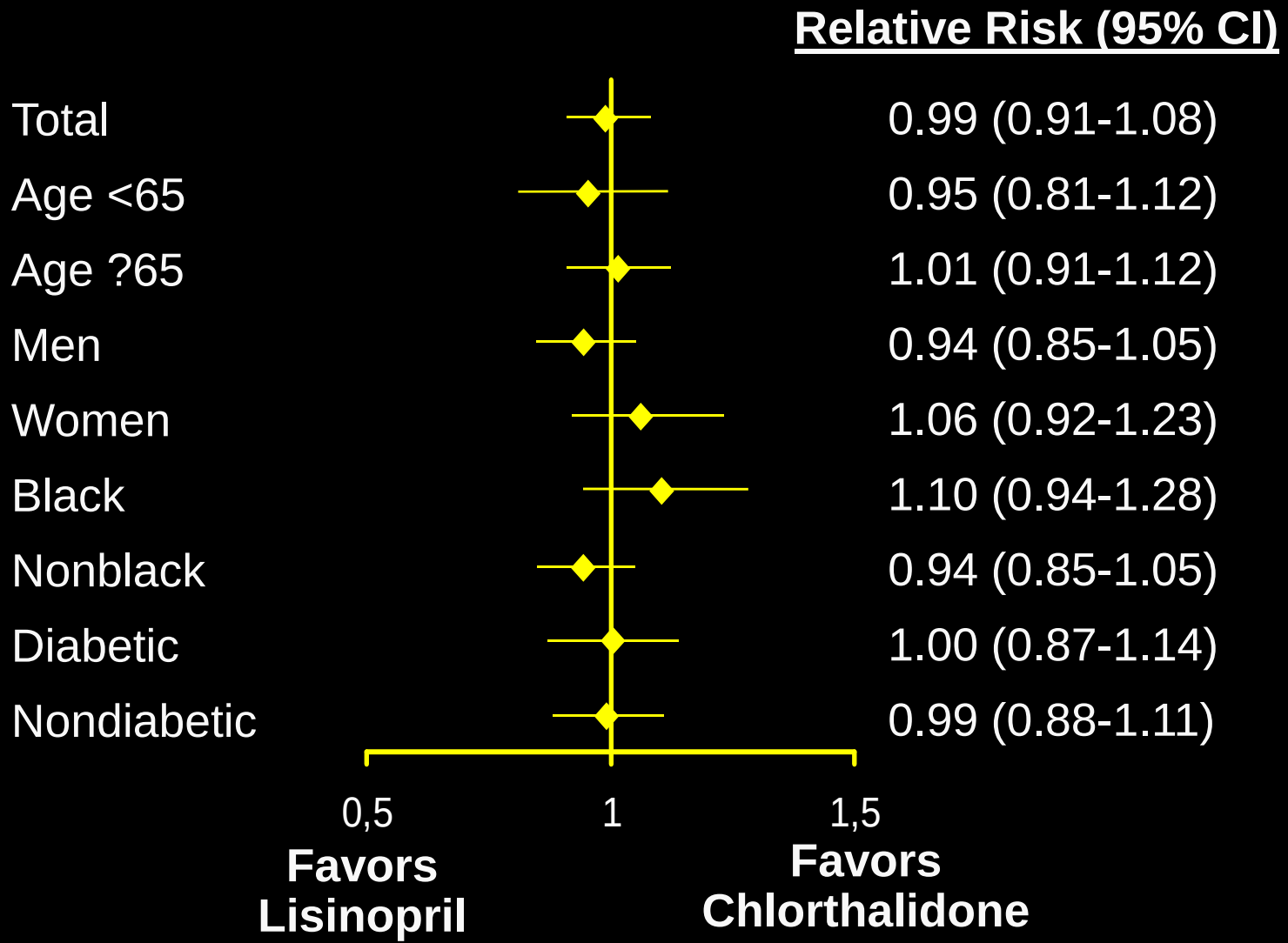
ALLHAT Collaborative Research Group. *JAMA*. 2002;288:2981-2997.

ALLHAT: Amlodipine vs Chlorthalidone
Primary Endpoint (Nonfatal MI + CHD Death) Subgroups



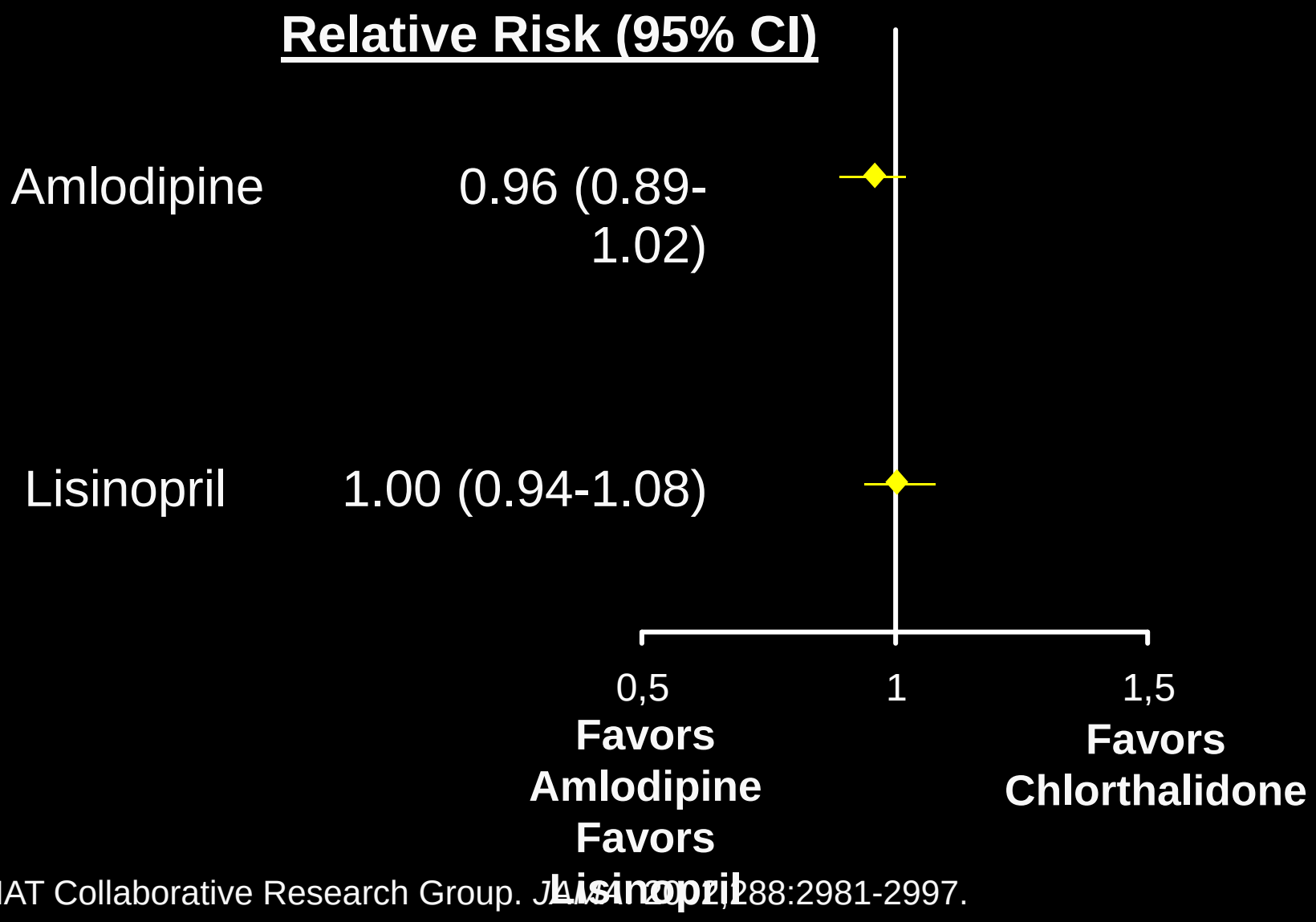
ALLHAT Collaborative Research Group. *JAMA*. 2002;288:2981-2997.

ALLHAT: Lisinopril vs Chlorthalidone
Primary Endpoint (Nonfatal MI + CHD Death) Subgroups



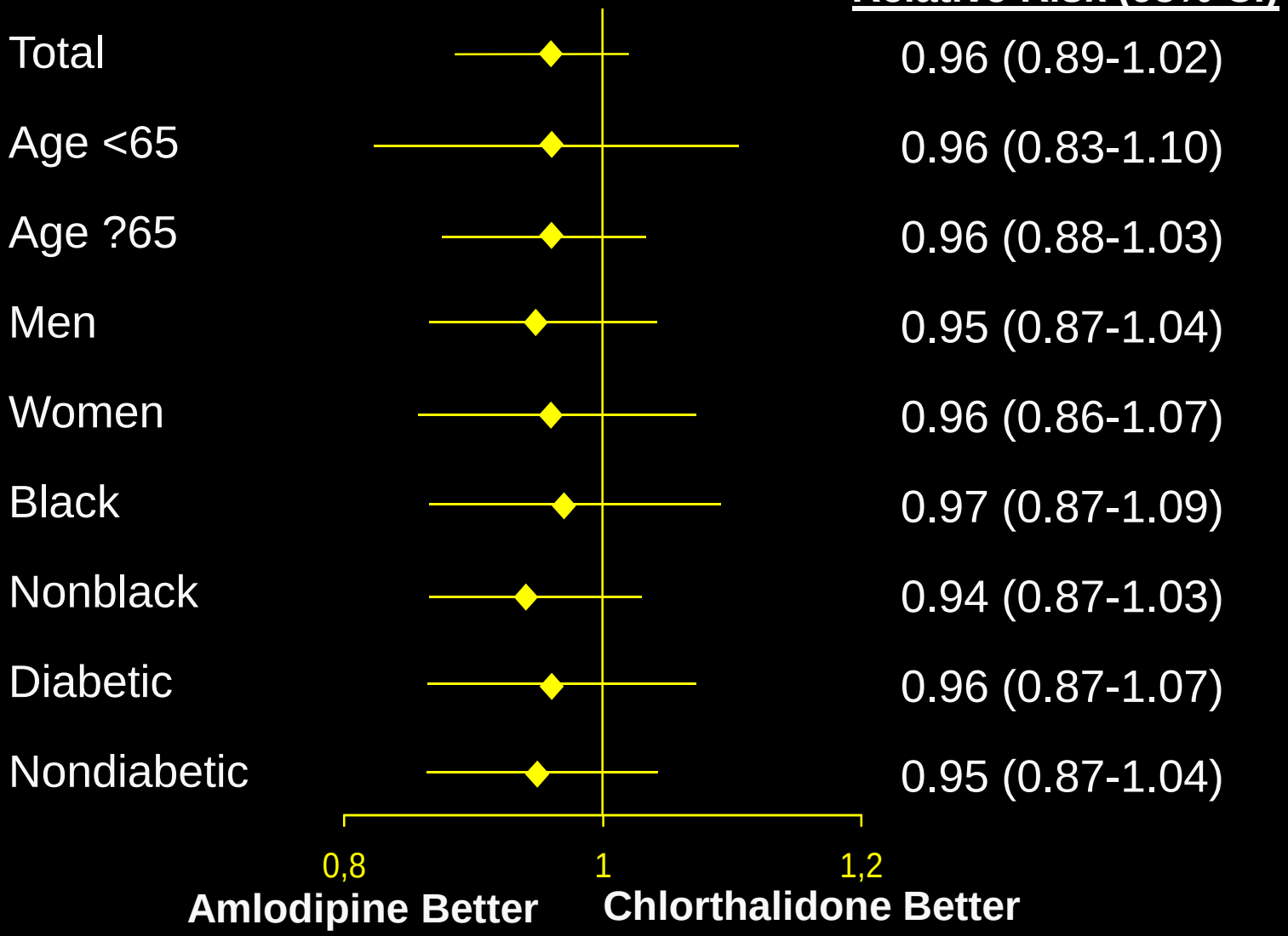
ALLHAT Collaborative Research Group. *JAMA*. 2002;288:2981-2997.

ALLHAT: Secondary Endpoints: Total Mortality



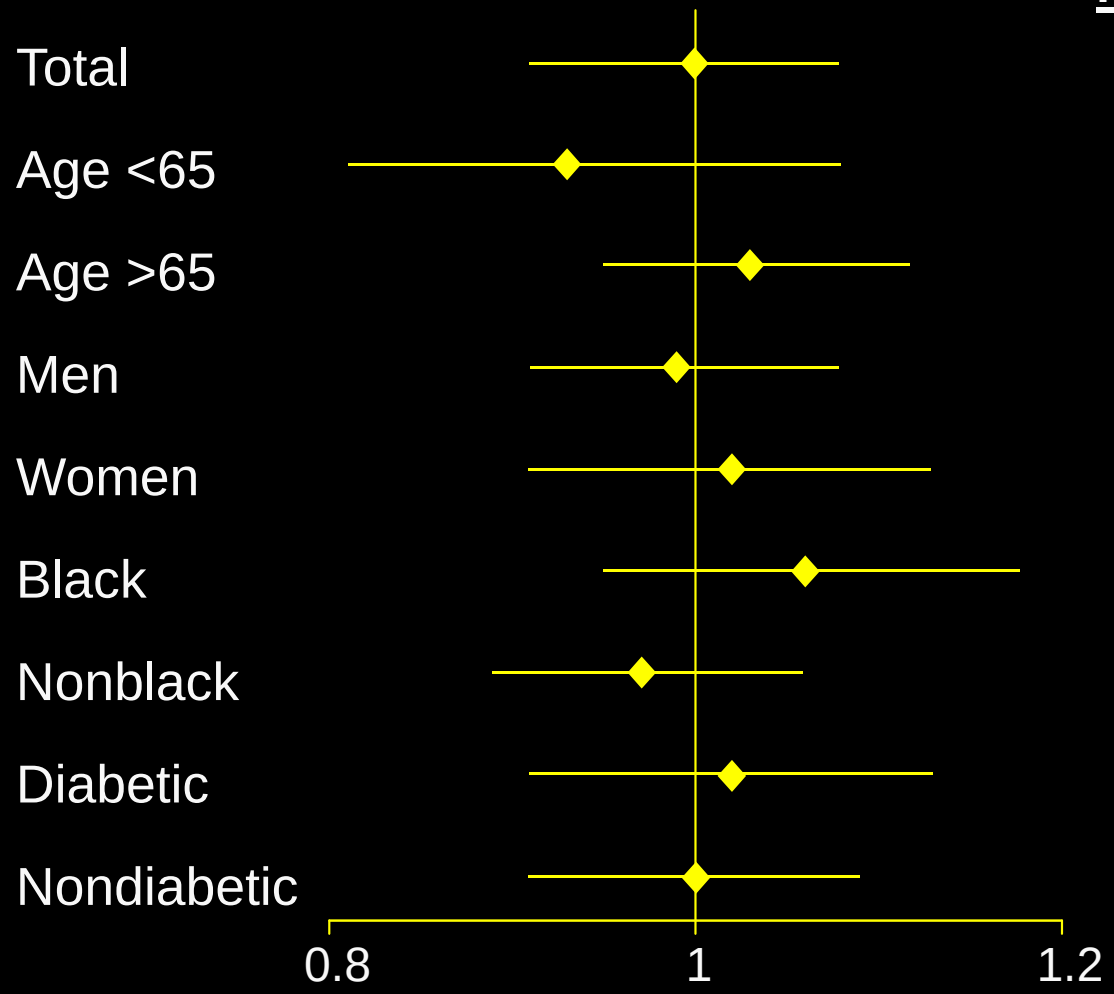
ALLHAT Collaborative Research Group. *JAMA*. 2002;288:2981-2997.

ALLHAT: Total Mortality (Amlodipine vs Chlorthalidone) Subgroups



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

ALLHAT: Total Mortality (Lisinopril vs Chlorthalidone) Subgroups



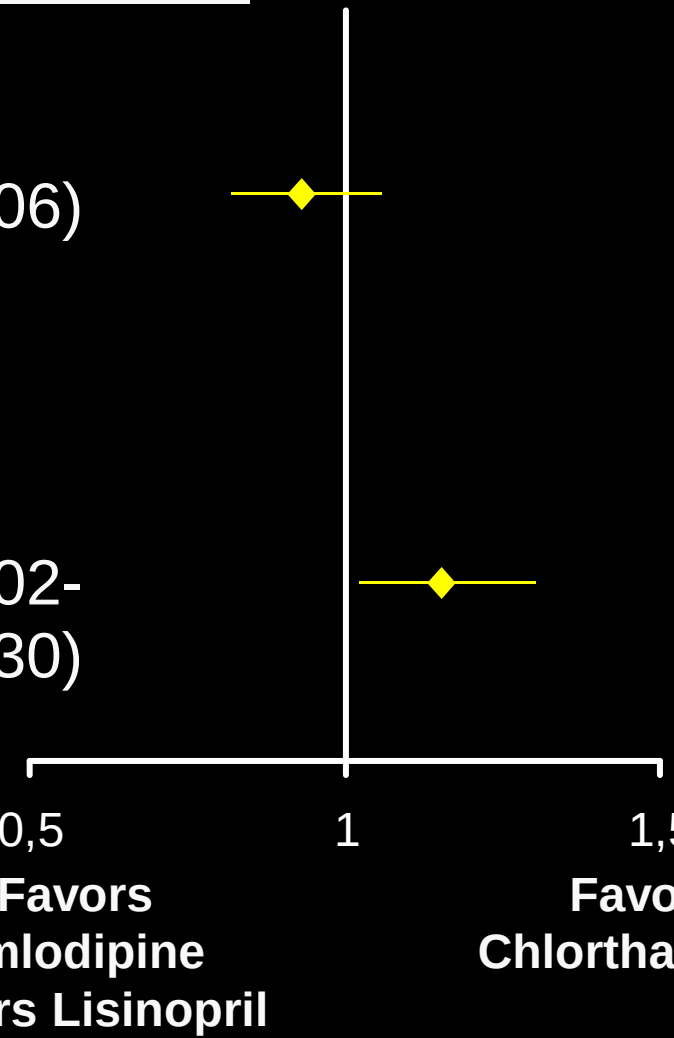
ALLHAT Collaborative Research Group. *JAMA*. 2002;288:2981-2997.

ALLHAT: Secondary Endpoints: Stroke

Relative Risk (95% CI)

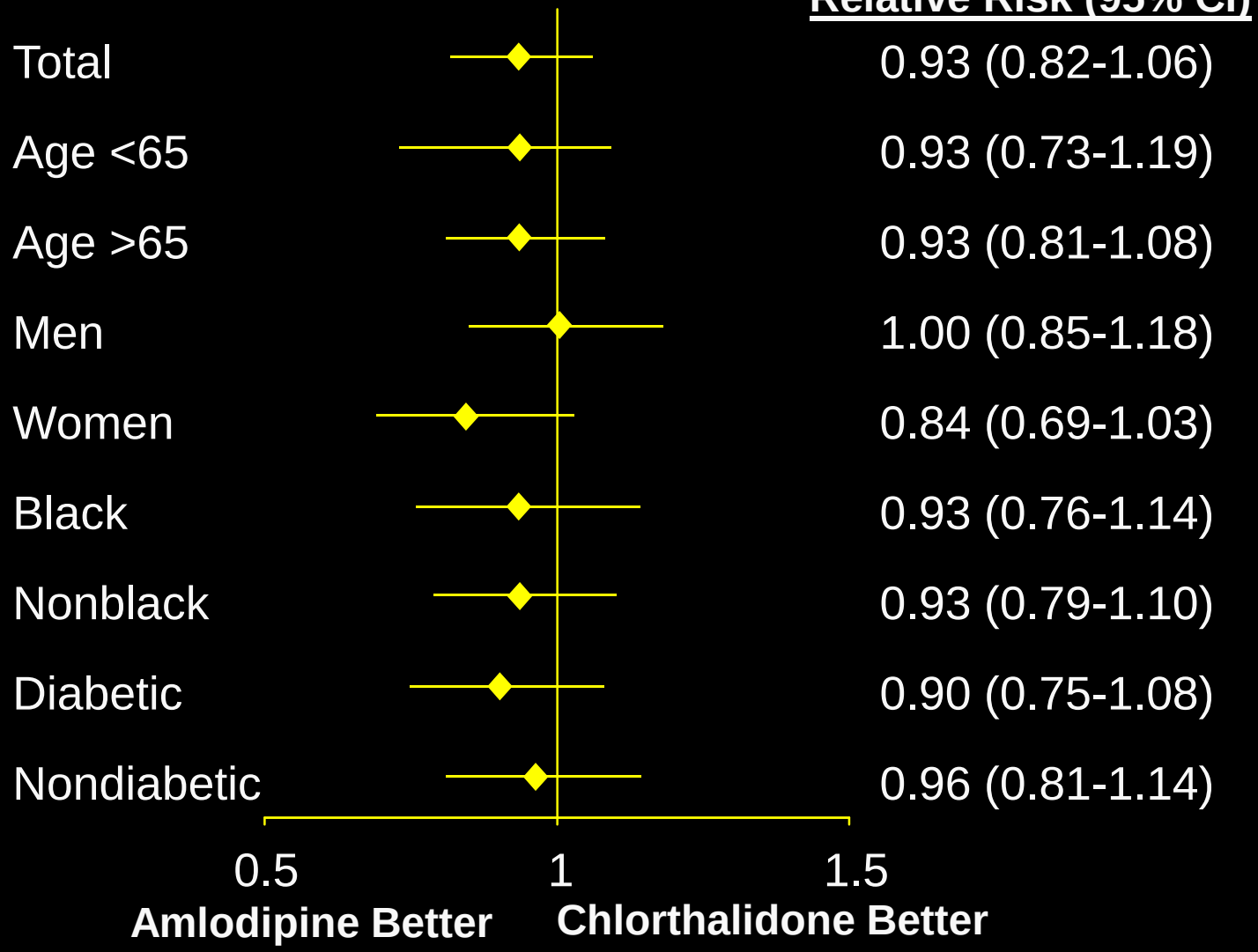
Amlodipine 0.93 (0.82-1.06)

Lisinopril 1.15 (1.02-1.30)



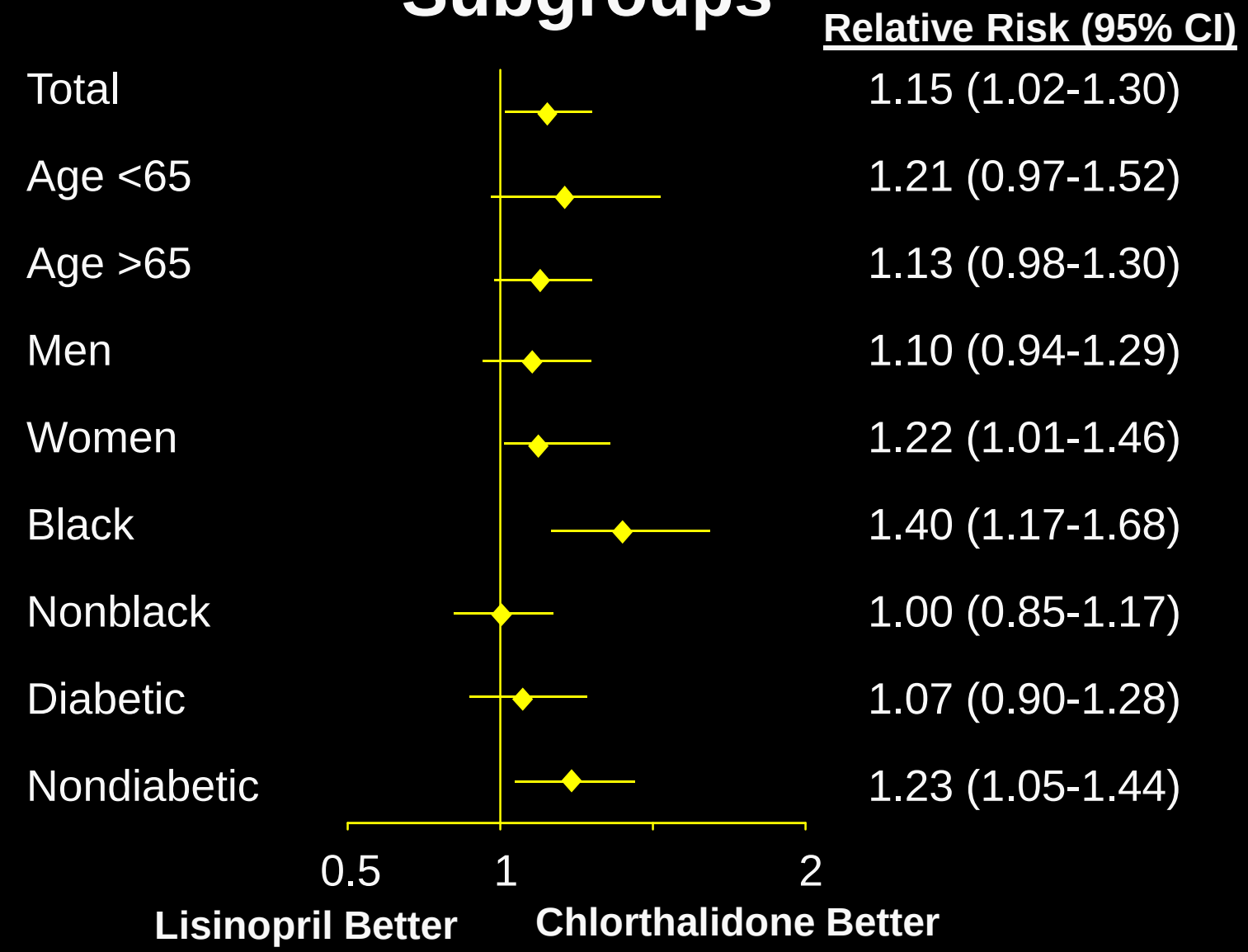
ALLHAT Collaborative Research Group. *JAMA*. 2002;288:2981-2997.

ALLHAT: Stroke (Amlodipine vs Chlorthalidone) Subgroups



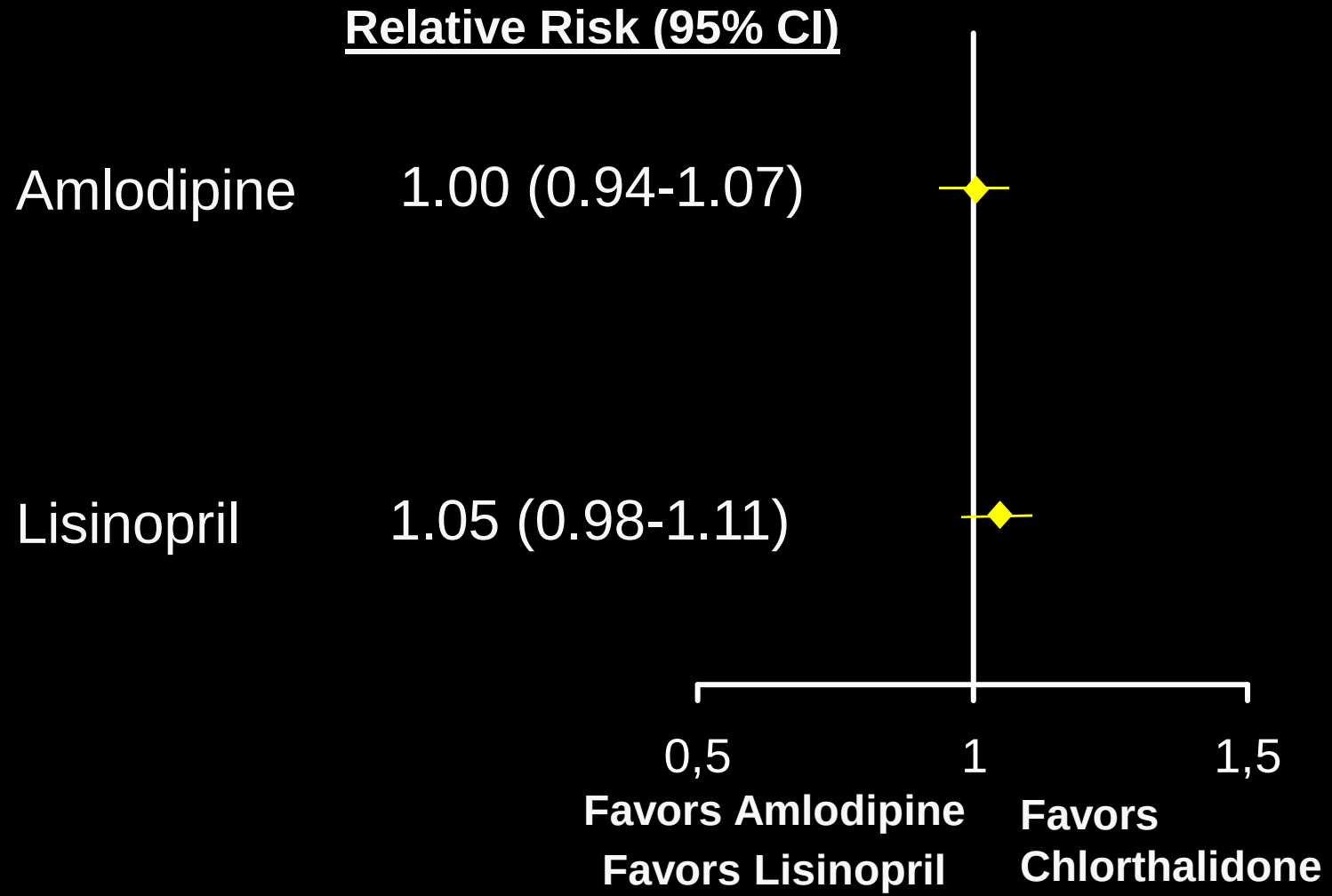
ALLHAT Collaborative Research Group. *JAMA*. 2002;288:2981-2997.

ALLHAT: Stroke (Lisinopril vs Chlorthalidone) Subgroups



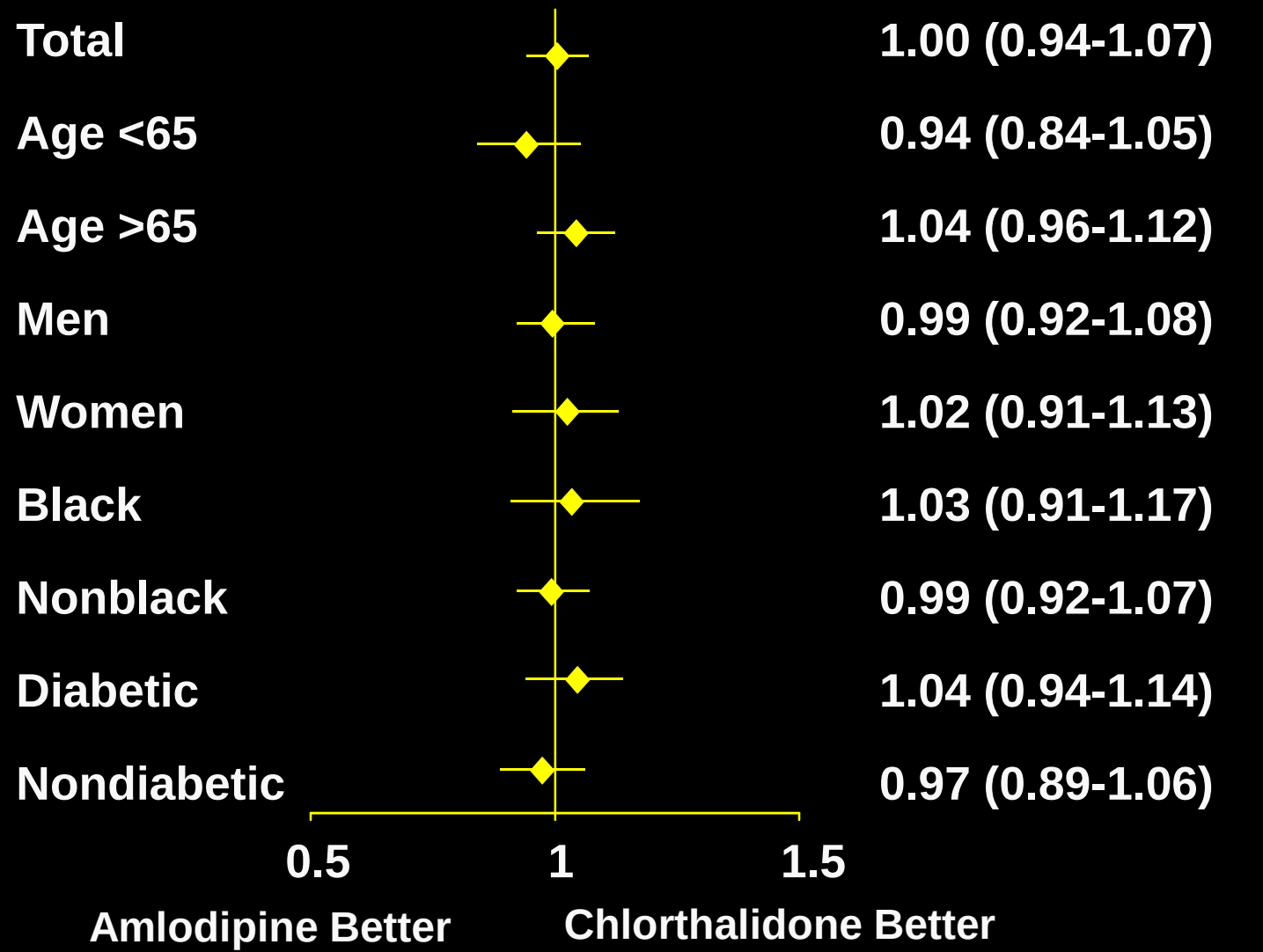
ALLHAT Collaborative Research Group. *JAMA*. 2002;288:2981-2997.

ALLHAT: Secondary Endpoints: Combined CHD



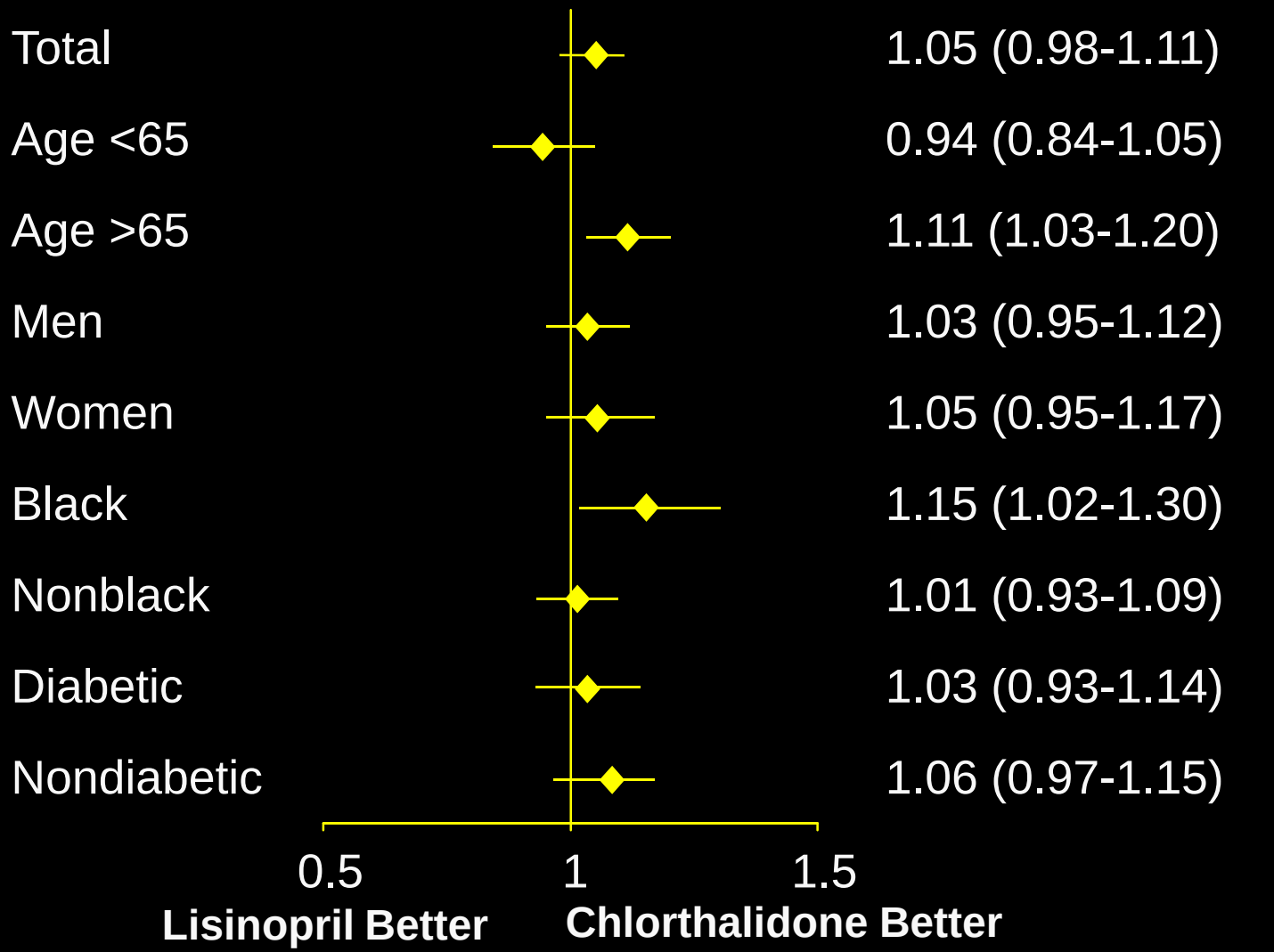
ALLHAT Collaborative Research Group. *JAMA*. 2002;288:2981-2997.

ALLHAT: Combined CHD (Amlodipine vs Chlorthalidone) Subgroups



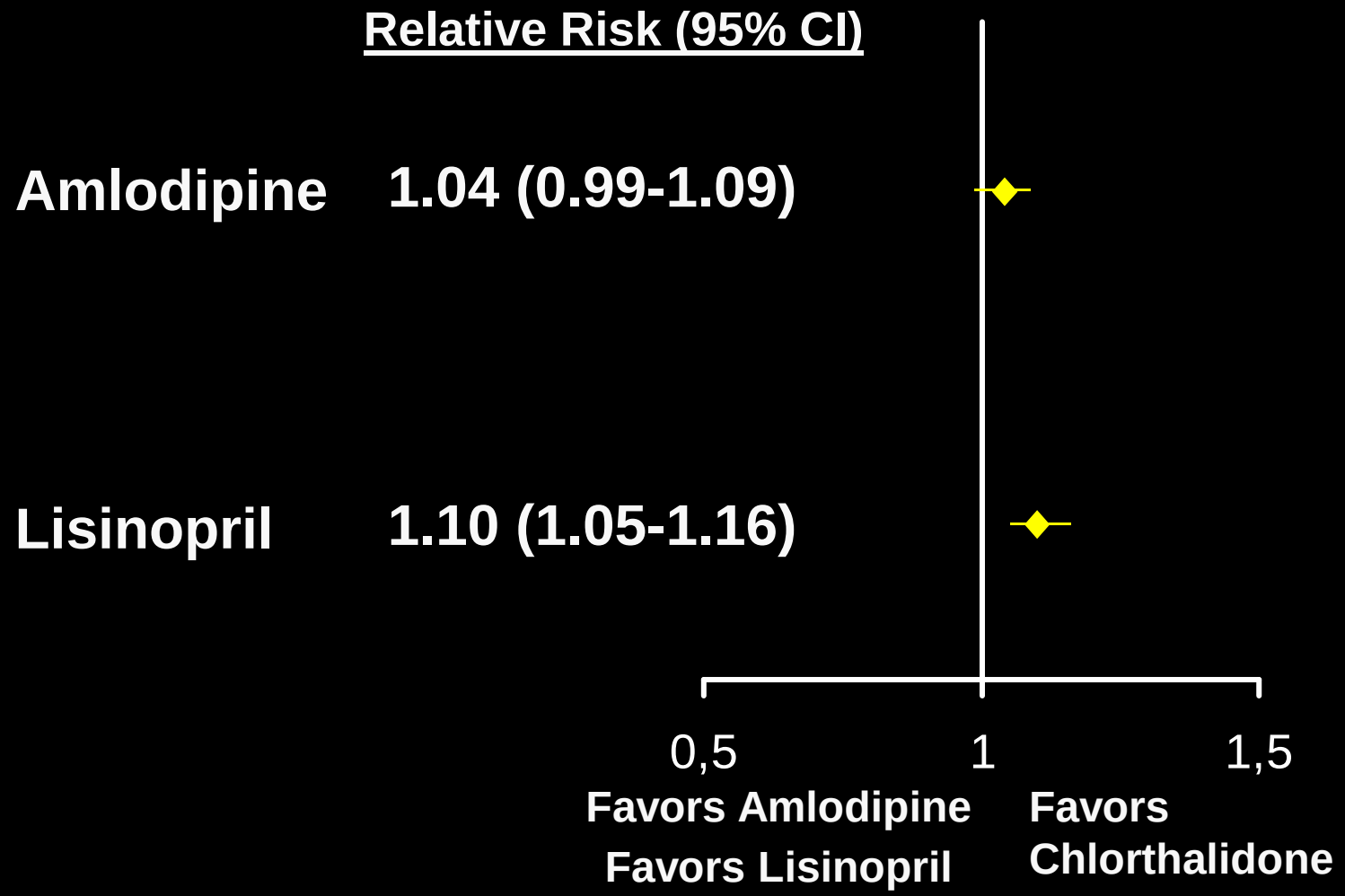
ALLHAT Collaborative Research Group. *JAMA*. 2002;288:2981-2997.

ALLHAT: Combined CHD (Lisinopril vs Chlorthalidone) Subgroups



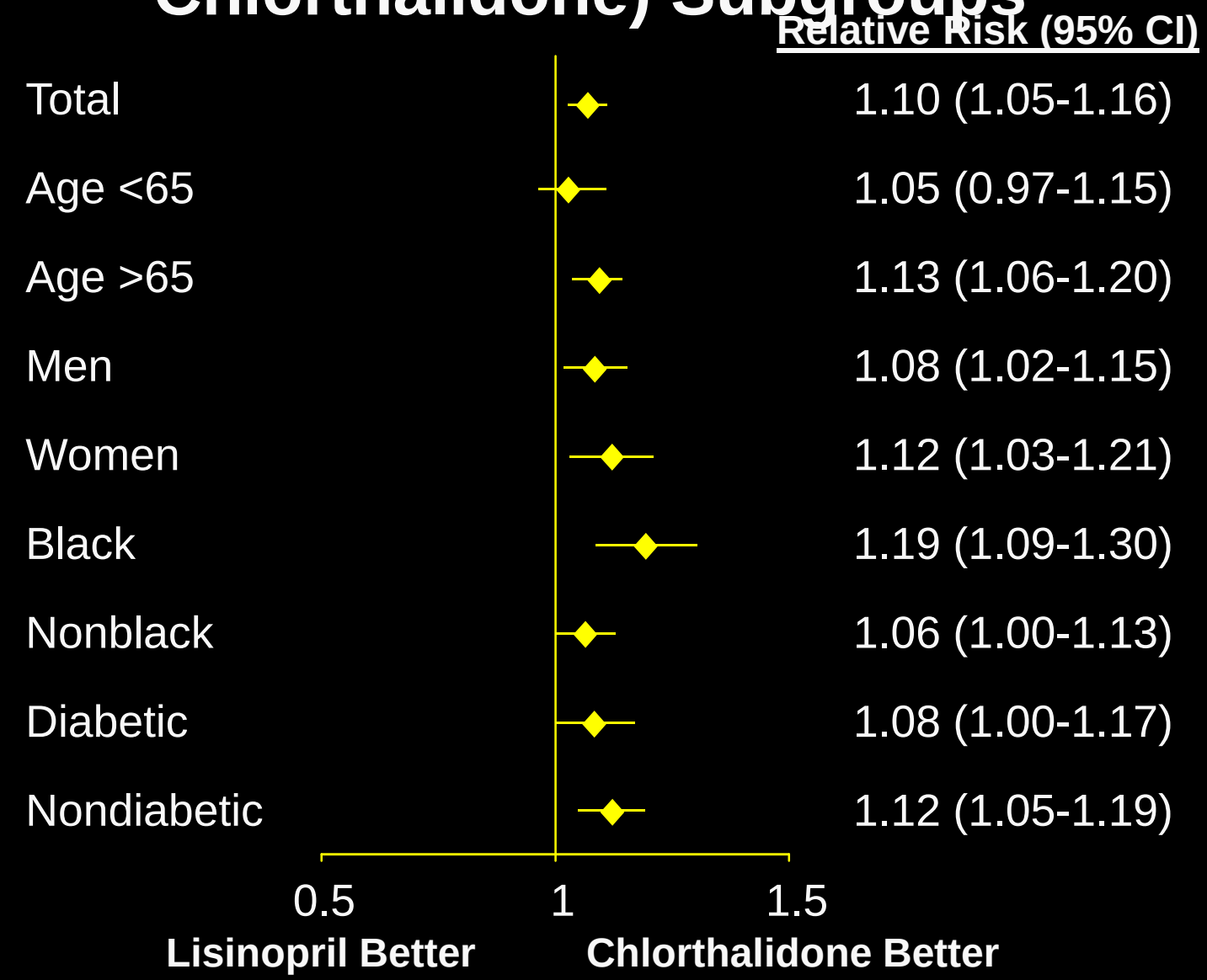
ALLHAT Collaborative Research Group. *JAMA*. 2002;288:2981-2997.

ALLHAT: Secondary Endpoints: Combined CVD



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

ALLHAT: Combined CVD (Lisinopril vs Chlorthalidone) Subgroups



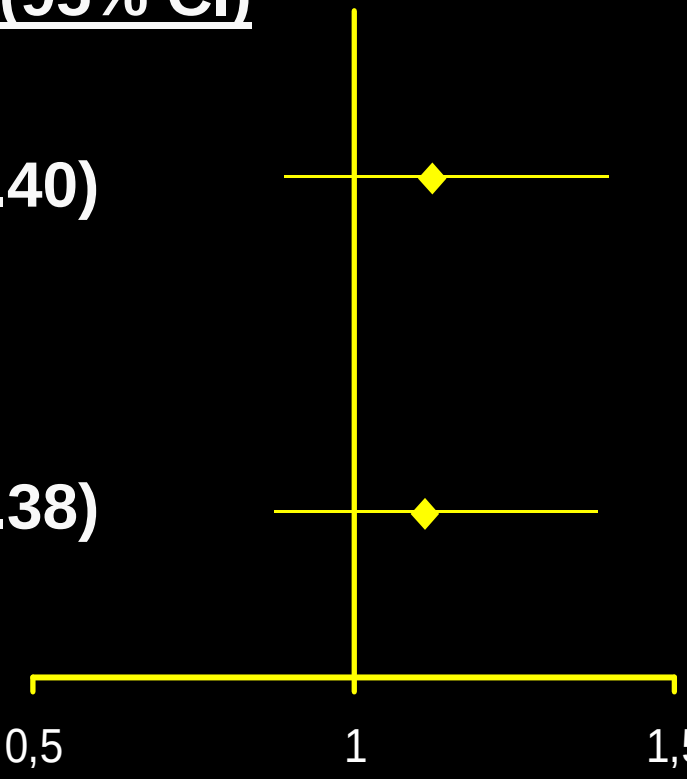
ALLHAT Collaborative Research Group. *JAMA*. 2002;288:2981-2997.

ALLHAT: Secondary Endpoints: ESRD

Relative Risk (95% CI)

Amlodipine 1.12 (0.89-1.40)

Lisinopril 1.11 (0.88-1.38)



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

ALLHAT: Components of Secondary Endpoints*: Heart Failure (Not Prespecified)

Relative Risk (95% CI)

Heart failure
(fatal, nonfatal, hospitalized or treated)

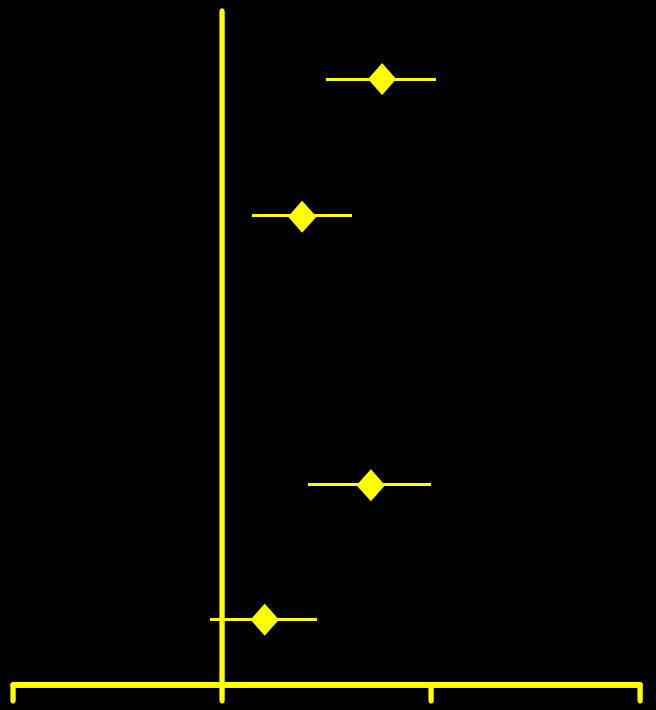
Amlodipine 1.38 (1.25-1.52)

Lisinopril 1.19 (1.07-1.31)

Hospitalized/Fatal HF

Amlodipine 1.35 (1.21-1.50)

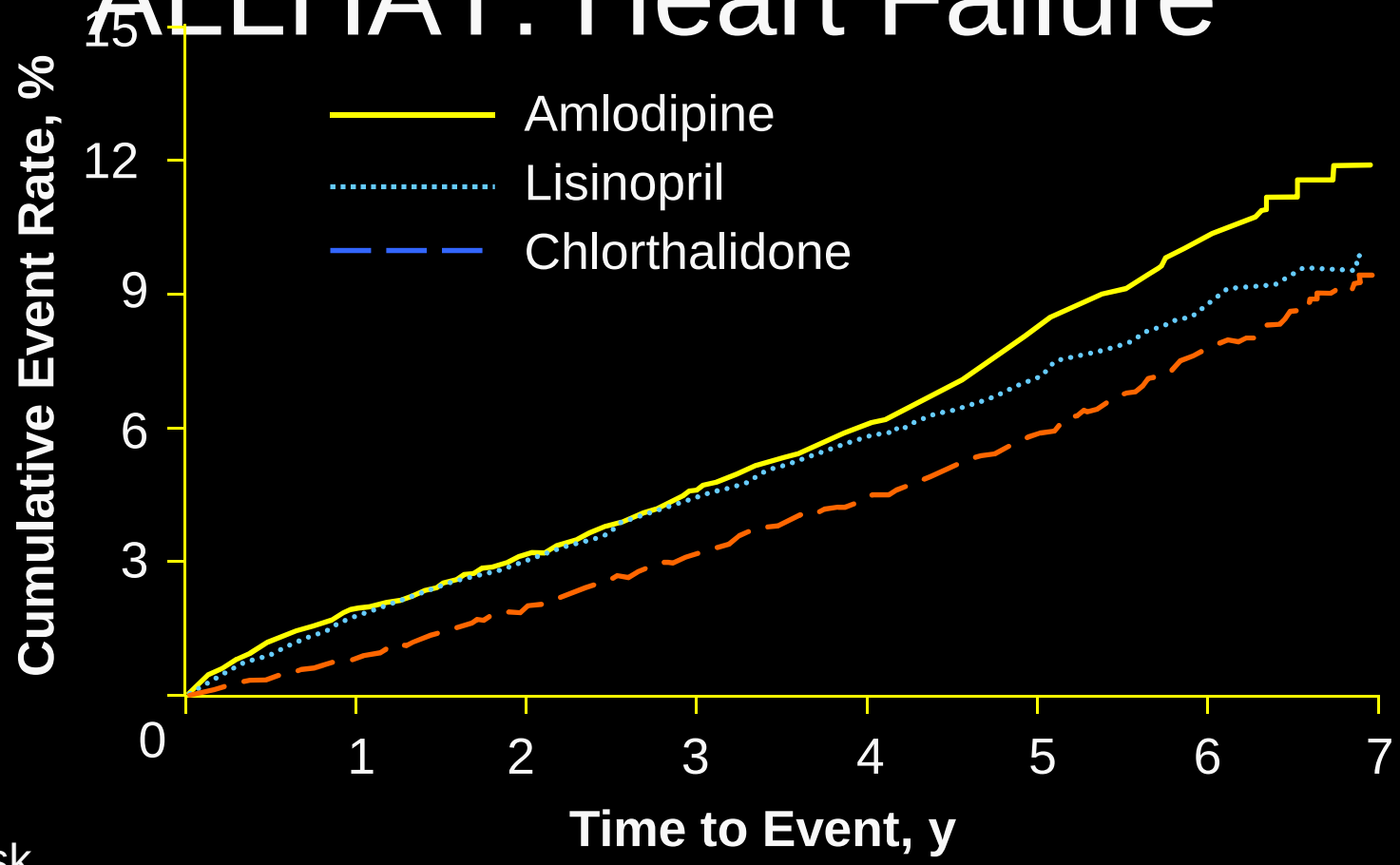
Lisinopril 1.10 (0.98-1.23)



*Heart failure is a component of combined CVD.

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

ALLHAT: Heart Failure*

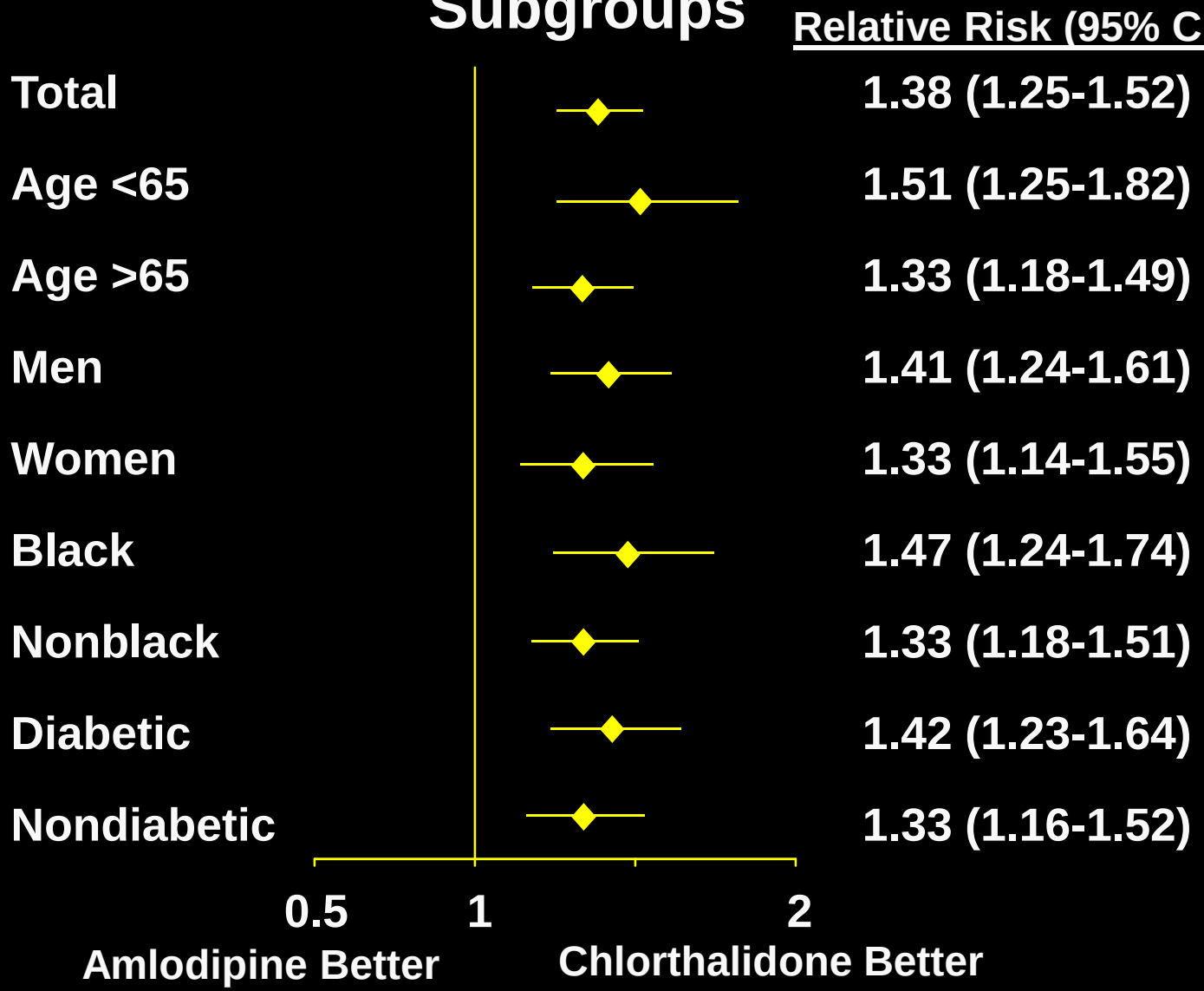


No. at Risk								
Chlorthalidone	15,255	14,528	13,898	13,224	11,511	6369	3015	384
Amlodipine	9048	8535	8185	7801	6785	3775	1780	210
Lisinopril	9054	8496	8096	7689	6698	3789	1837	313

*Heart failure was not a prespecified endpoint.

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

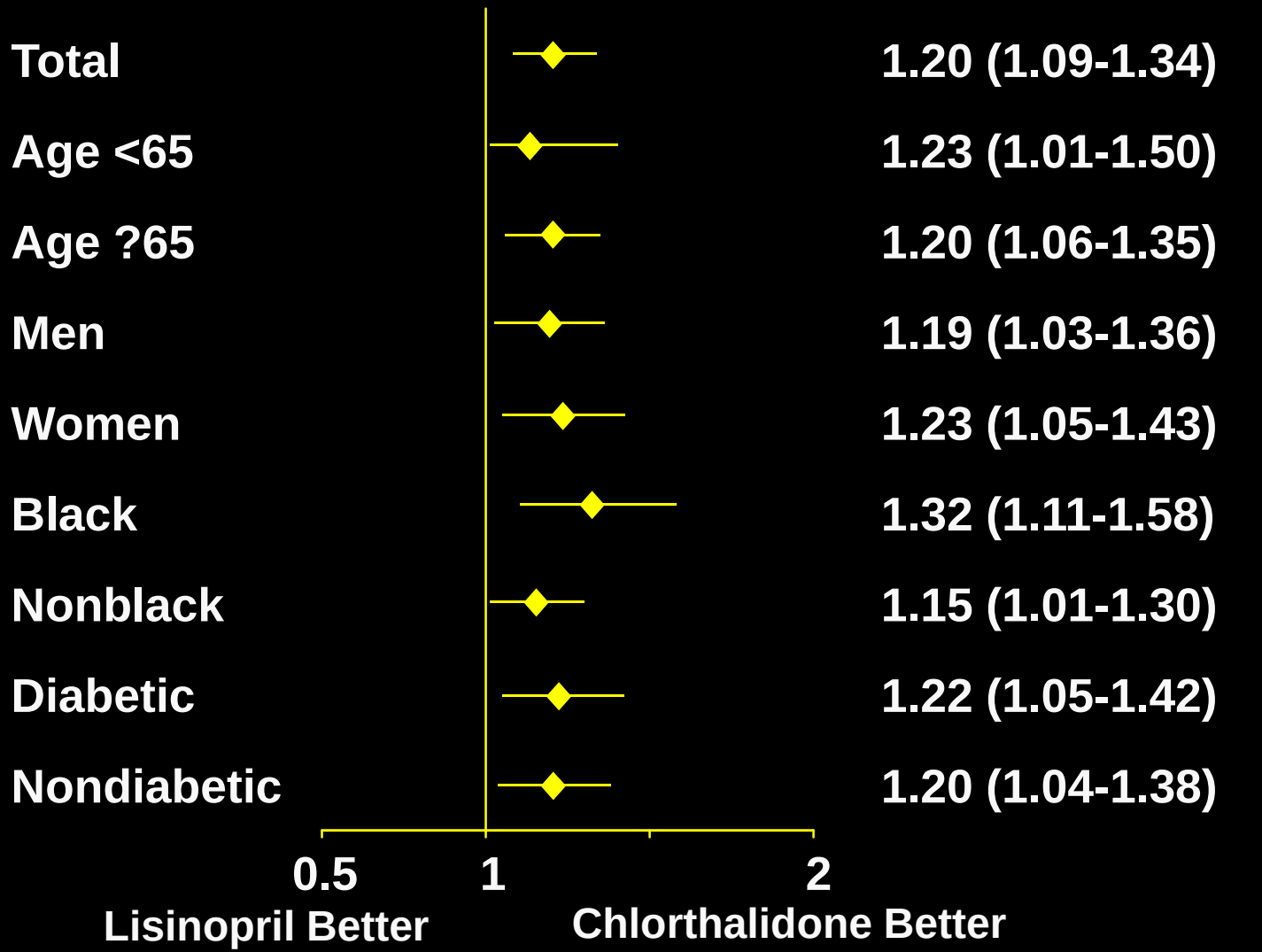
ALLHAT: Heart Failure* (Amlodipine vs Chlorthalidone)



*Heart failure was not a prespecified endpoint.

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

ALLHAT: Heart Failure* (Lisinopril vs Chlorthalidone) Subgroups



*Heart failure was not a prespecified endpoint.

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

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

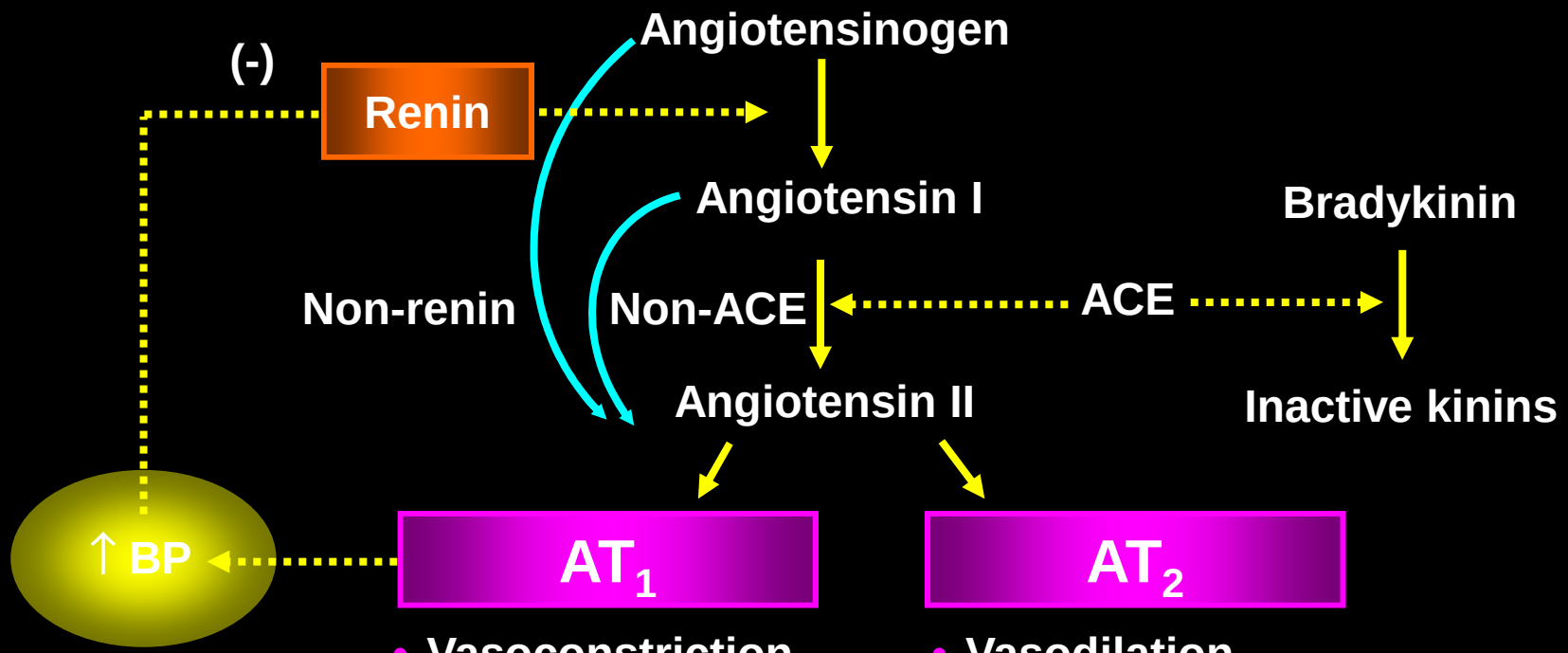
- **ALLHAT demonstrated that the lisinopril-based treatment was not as effective as the diuretic for reducing systolic BP**
- **Contrary to expectations, ALLHAT showed that results for the group taking lisinopril were not superior to the diuretic group with regard to CHD and CVD morbidity and mortality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

Renin-angiotensin-aldosterone system

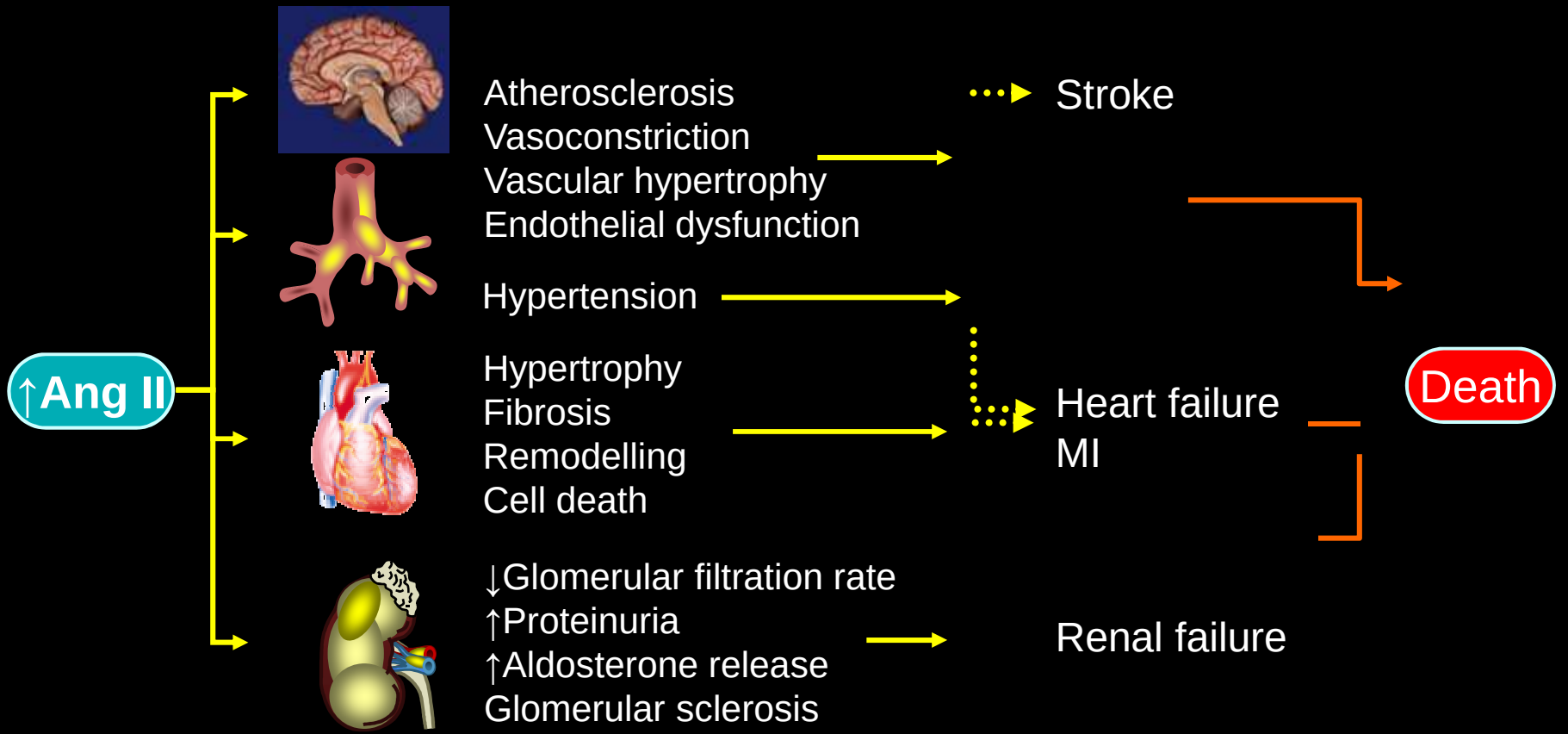


- Vasoconstriction
- Aldosterone secretion
- Catecholamine release
- Proliferation
- Hypertrophy

- 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

Chronic Activation of the Renin System Contributes to End-organ Damage



Adapted from Anderson, Goodfriend, and Phillips In: Hypertension Primer, 2003.

LIFE

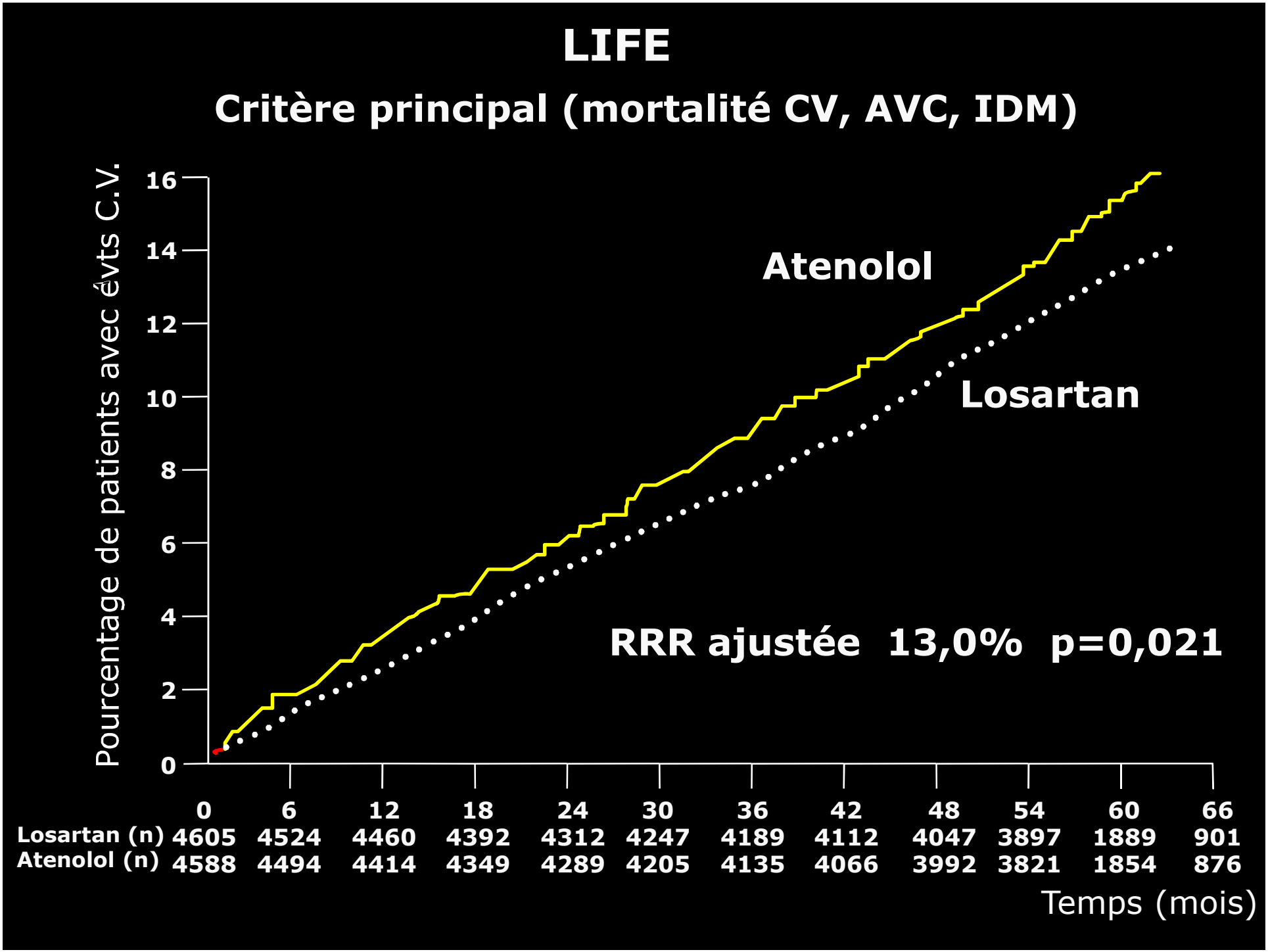
- Population : 9193 patients avec HTA
  et HVG-ECG

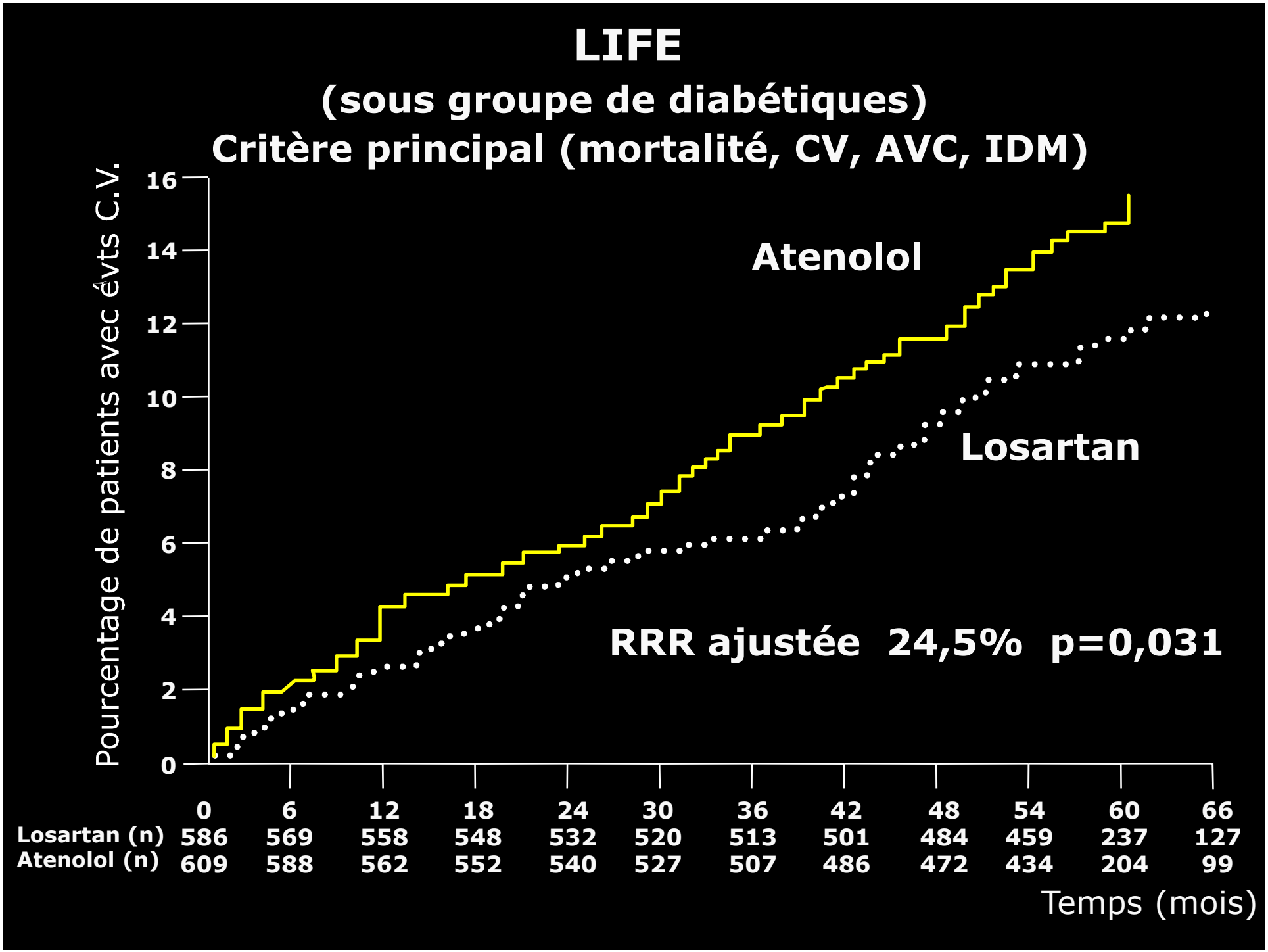
- Losartan 50-100 mg ± HCTZ (n=4605)
  versus Atenonol 50-100 mg ± HCTZ (n=4588)

- Suivi moyen : 4,8 ans

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

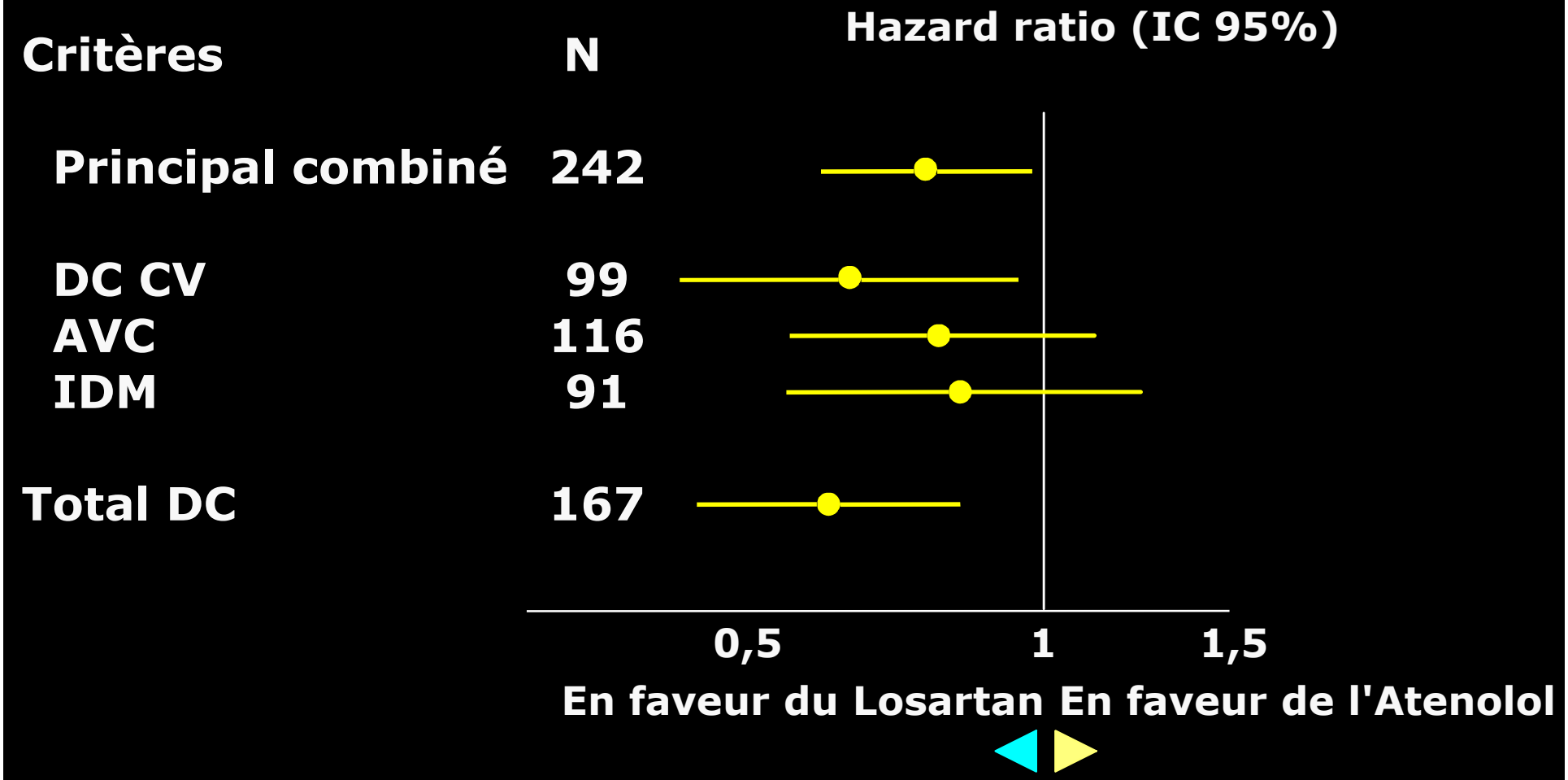
Losartan **I**ntervention **F**or **E**ndpoint reduction hypertension study


LIFE
Critère principal (mortalité CV, AVC, IDM)
Pourcentage de patients avec évts C.V.
16
14
12
10
8
6
4
2
0
Atenolol
Losartan
RRR ajustée 13,0% p=0,021
0 6 12 18 24 30 36 42 48 54 60 66
Losartan (n) 4605 4524 4460 4392 4312 4247 4189 4112 4047 3897 1889 901
Atenolol (n) 4588 4494 4414 4349 4289 4205 4135 4066 3992 3821 1854 876
Temps (mois)


LIFE
(sous groupe de diabétiques)
Critère principal (mortalité, CV, AVC, IDM)
Pourcentage de patients avec évts C.V.
16
14
12
10
8
6
4
2
0
Atenolol
Losartan
RRR ajustée 24,5% p=0,031
0 6 12 18 24 30 36 42 48 54 60 66
Losartan (n) 586 569 558 548 532 520 513 501 484 459 237 127
Atenolol (n) 609 588 562 552 540 527 507 486 472 434 204 99
Temps (mois)

LIFE

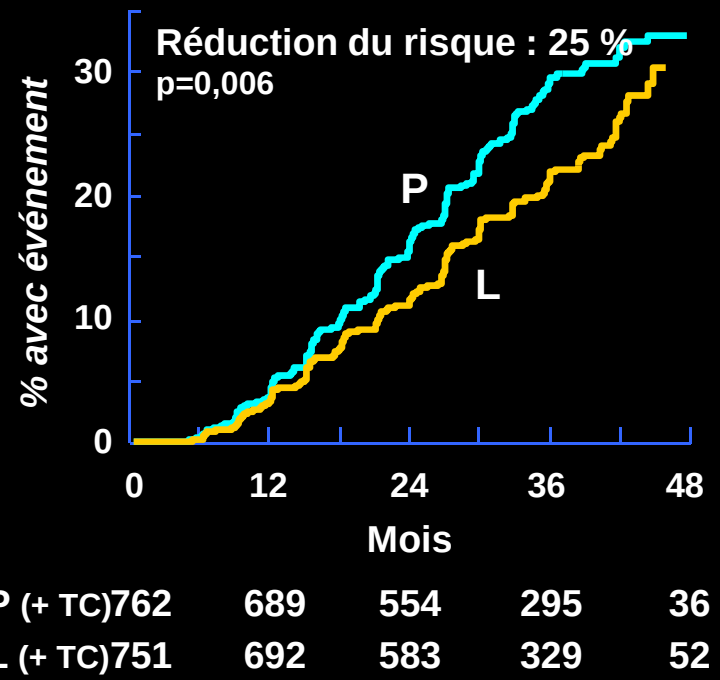
(sous groupe de diabétiques)
Critère principal (mortalité CV, AVC, IDM)
(n = 1195)



Etude RENAAL

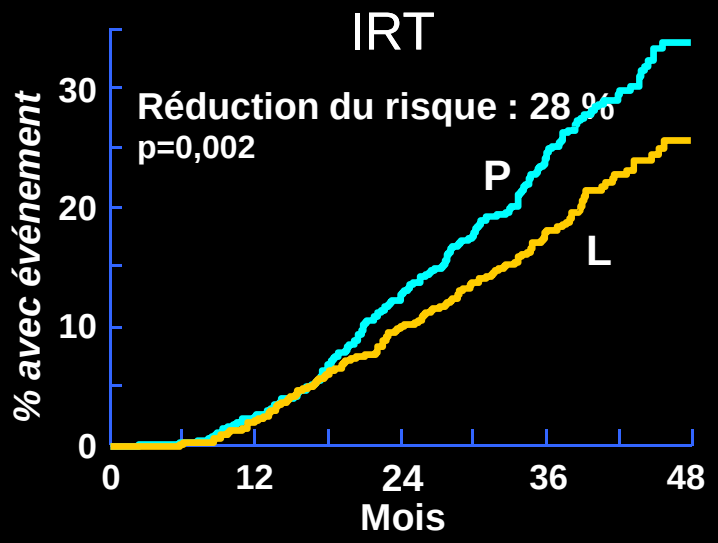
Composants du critère d'évaluation combiné

Doublement de la créatininémie



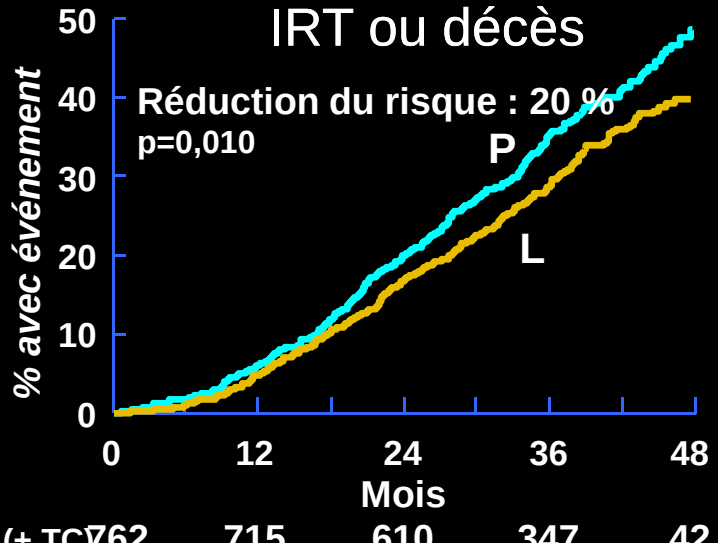
P (+ TC)	762	689	554	295	36
L (+ TC)	751	692	583	329	52

IRT



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

IRT ou décès

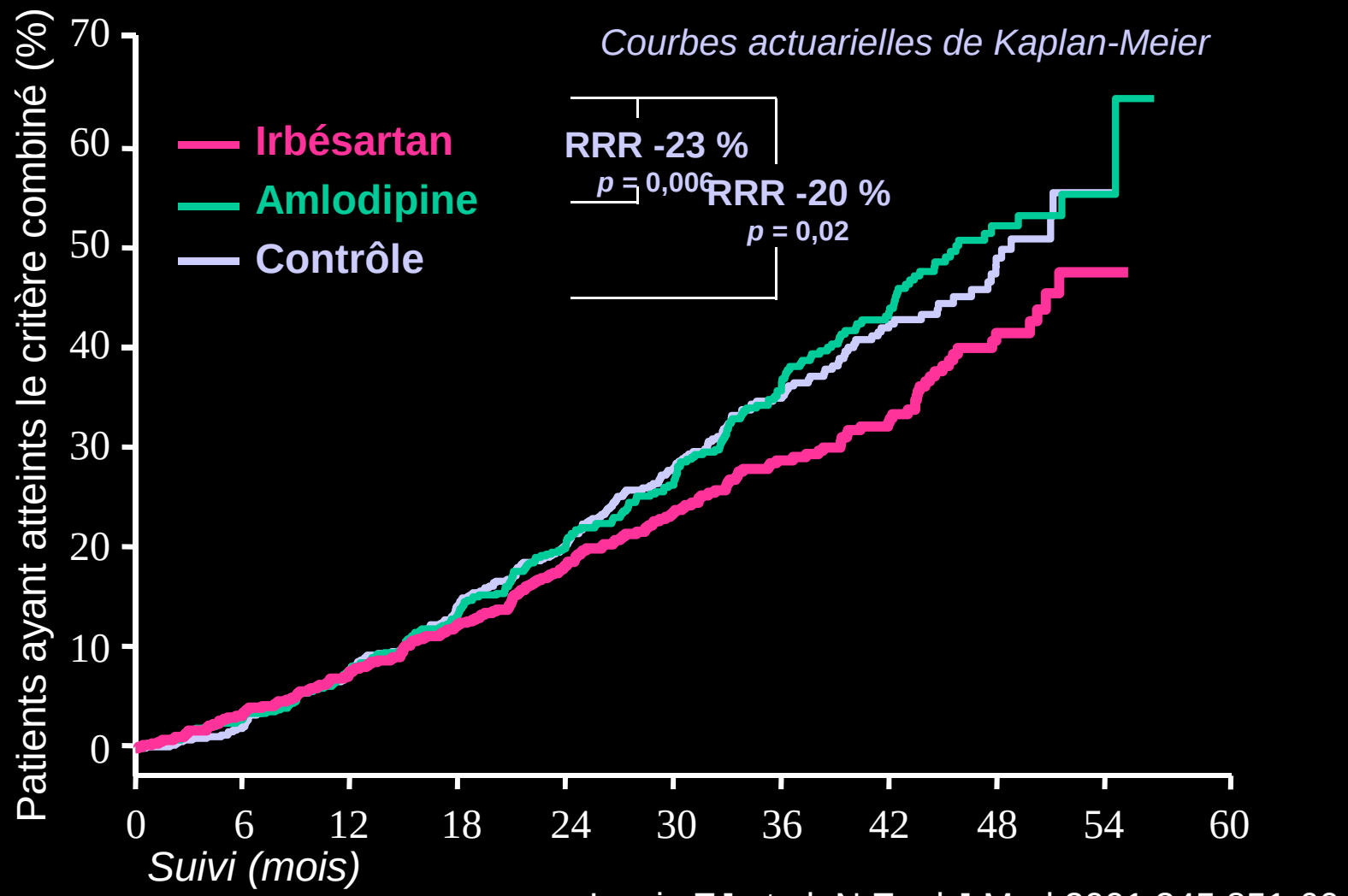


P (+ TC)	762	715	610	347	42
L (+ TC)	751	714	625	375	69

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

IDNT: Objectif principal

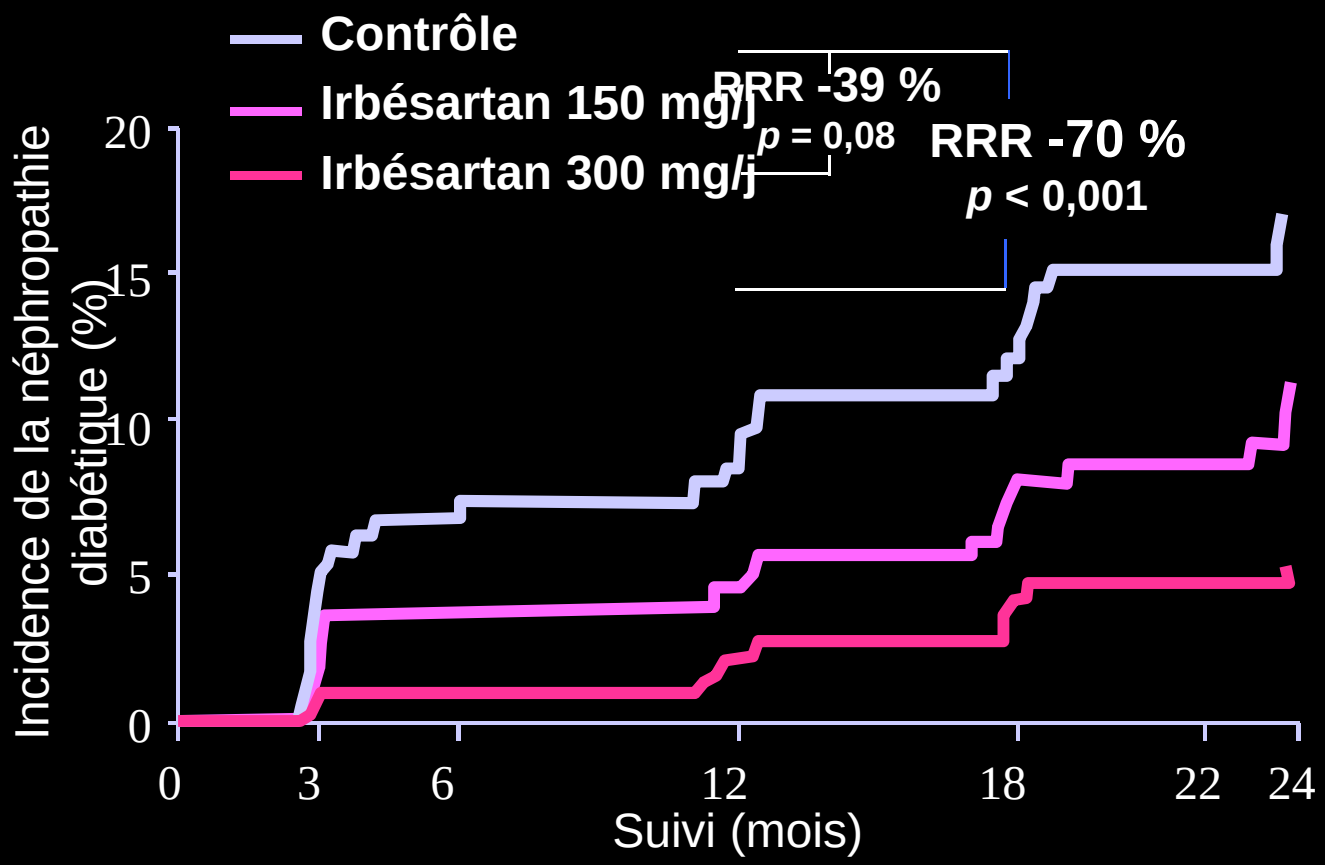
Doublement de la créatininémie, IRT ou décès



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

Taux de patients traités par classe thérapeutique prescrite en 2000 et 2006

% de patients traités au moins 1 fois dans l'année par cette classe thérapeutique	2000	2006
Sartans	19,8	36,7
IEC	33,3	28,7
Diurétiques	53,4	54,7
Diurétiques thiazidiques	37,4	41
Bêtabloquants	39,1	38,9
Inhibiteurs calciques	29	29
Autres antihypertenseurs	12,5	9
Antidiabétiques oraux	13,9	17,2
Hypolipémiants	36,2	44,8
Statines	22	33,7
Antiagrégants	24,7	28,5

Samson S et coll. *Points de repère* n°10, oct. 2007.

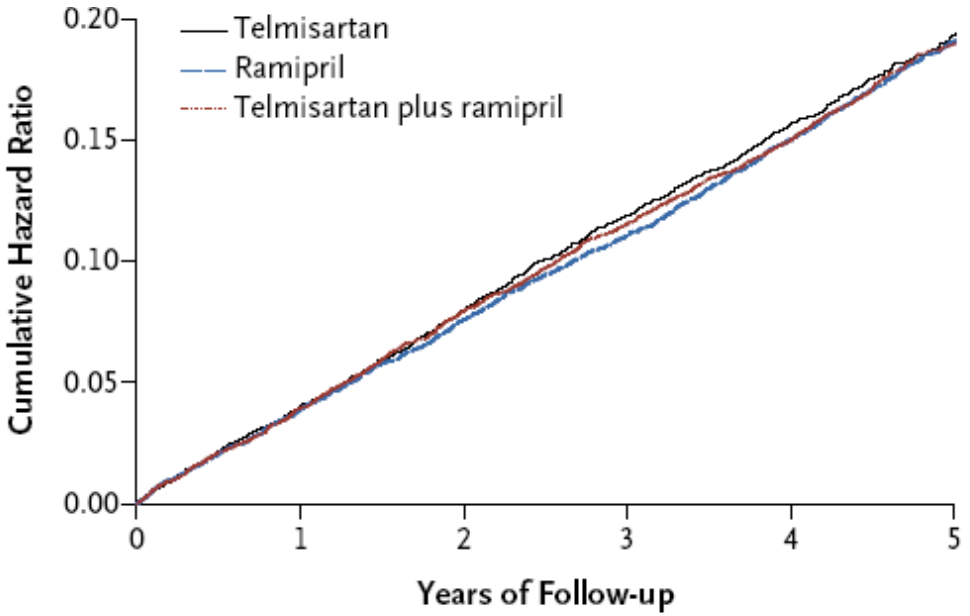
The NEW ENGLAND JOURNAL of MEDICINE

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

HAUTE AUTORITÉ DE SANTÉ

BON USAGE DES MEDICAMENTS

Les inhibiteurs du système rénine-angiotensine dans l'HTA essentielle non compliquée

Comment choisir entre IEC et sartans ?

Les données cliniques actuelles ne permettent pas de différencier les IEC et les sartans en termes d'efficacité antihypertensive et d'impact sur la morbi-mortalité

Selon les données cliniques actuelles[4], la tolérance des IEC et celle des sartans sont similaires en dehors de la toux

- En France, le recours aux sartans a fortement progressé depuis l'année 2000, aboutissant à une pratique atypique par rapport à nos voisins européens. La part des sartans (seuls ou associés) dans la prescription des inhibiteurs du SRA est aujourd'hui de 55 % en France, alors qu'elle est de 44 % en Espagne, de 41 % en Italie et de 27 % au Royaume-Uni comme en Allemagne (CNAMTS, décembre 2007).
- Treize IEC (dont six sont génériqués) et sept sartans (dont aucun n'est encore génériqué) sont actuellement commercialisés en France. Le coût du traitement d'une HTA par un sartan est en général supérieur au coût du traitement par un IEC.

CONCLUSION

- Selon les études comparatives publiées, les IEC et les sartans ont une efficacité antihypertensive et une tolérance similaires dans l'HTA essentielle non compliquée. Seule les différencie la survenue d'une toux sèche, plus fréquente sous IEC, mais cédant à l'arrêt du traitement. En revanche, le coût du traitement est en général plus élevé avec un sartan qu'avec un IEC.
- Aussi, lorsque le médecin est amené à prescrire un inhibiteur du système rénine-angiotensine pour traiter une HTA essentielle, il est recommandé de prescrire plutôt un IEC qu'un sartan en première intention et de réserver les sartans aux patients ayant une toux sous IEC.

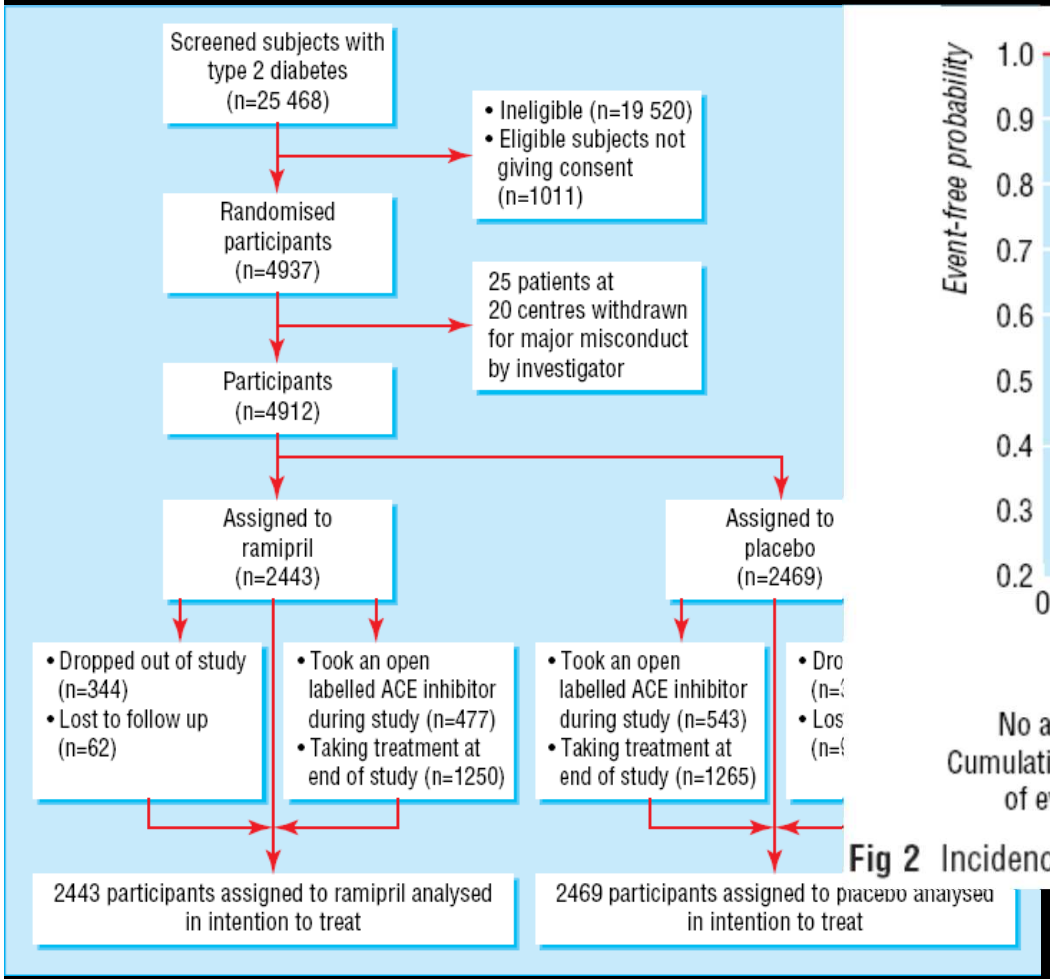
HAS

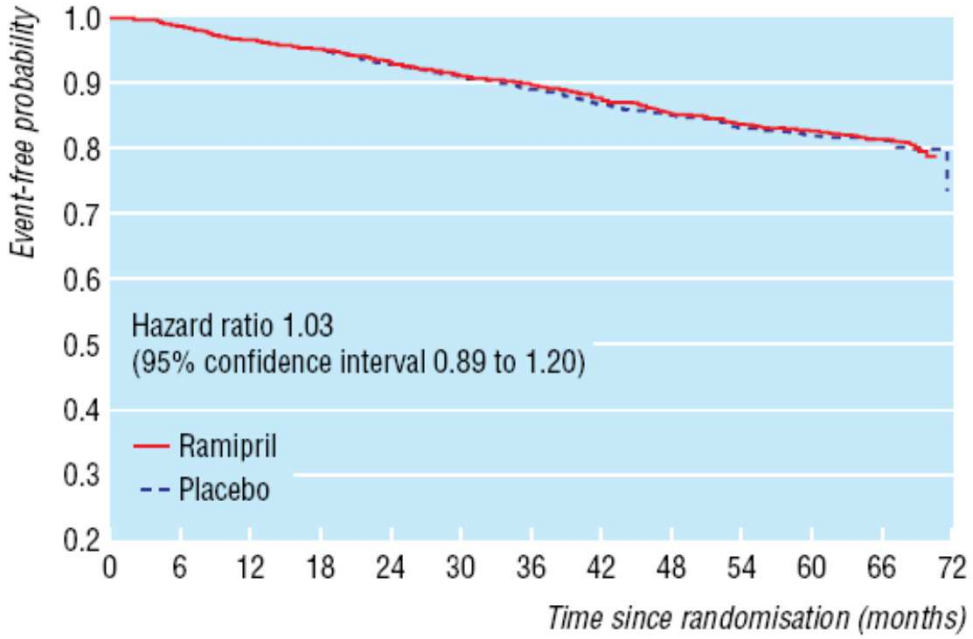
Comme l'ensemble des publications de la HAS, ce document est disponible sur
www.has-sante.fr

Octobre 2008

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

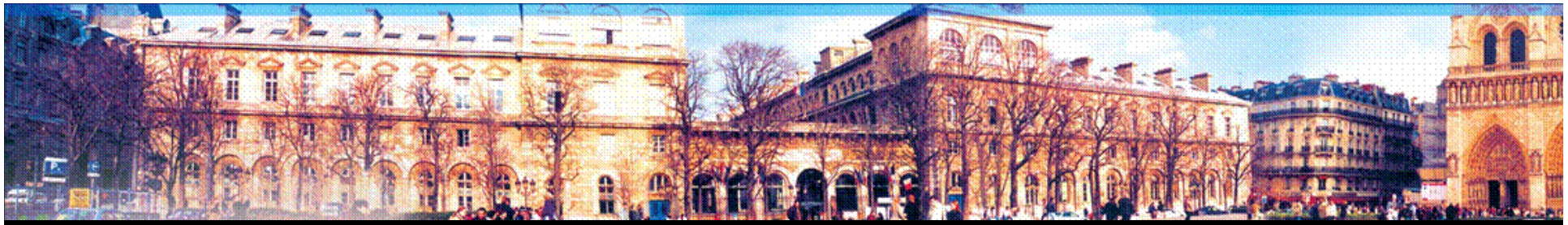




No at risk:	4773	4643	4374	2891	1882	764
Cumulative No of events:	183	356	519	658	718	737

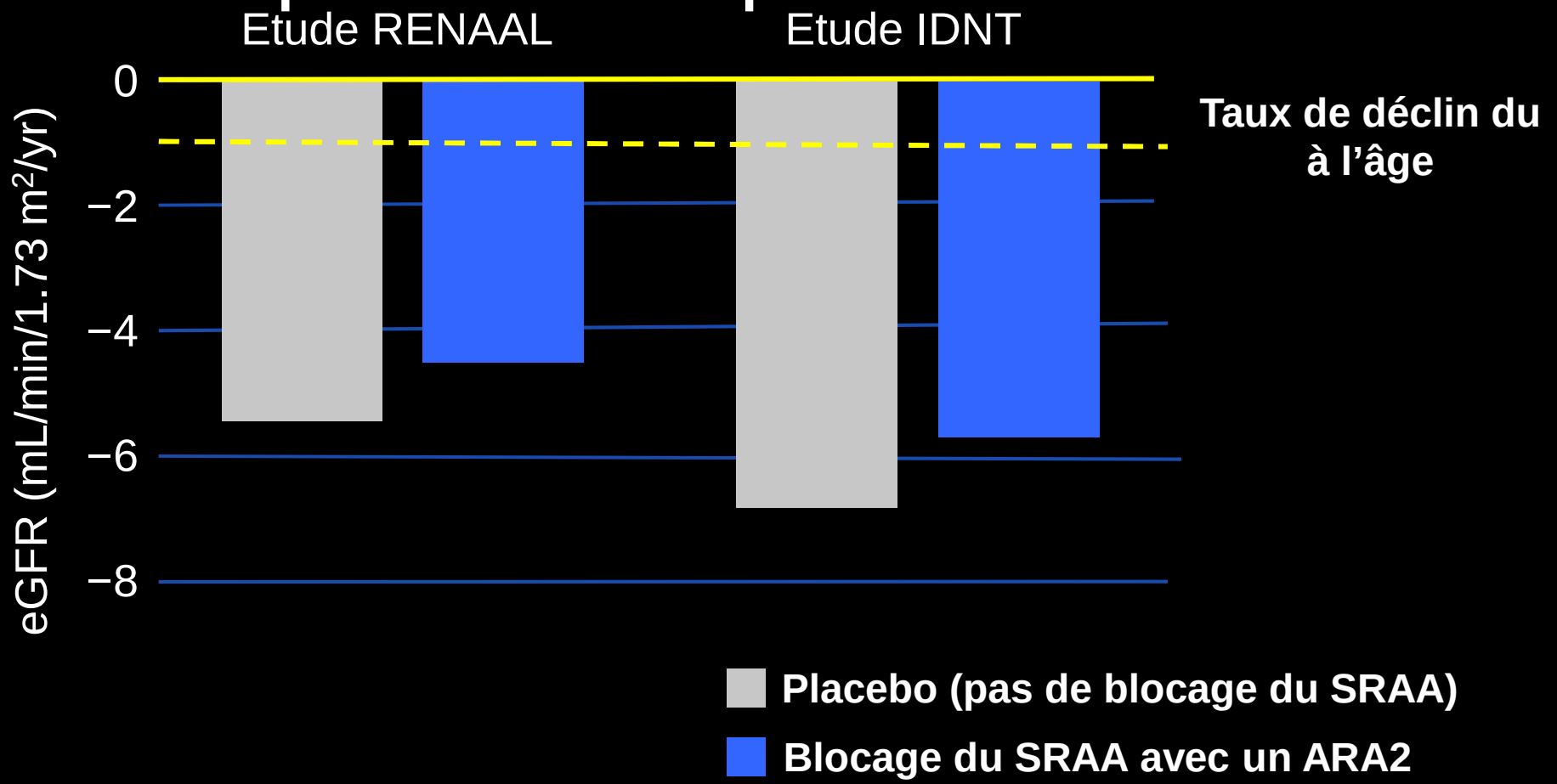
Fig 2 Incidence of the primary end point according to treatment group

BMJ 2004;328;495



Au-delà du blocage du SRAA ?

Malgré un traitement par ARA2, le taux de déclin de la fonction rénale est plus élevé que celui attendu



Weber MA & Giles TD. Rev Cardiovasc Med 2006

Effects of Dietary Sodium and Hydrochlorothiazide on the Antiproteinuric Efficacy of Losartan

Liffert Vogt,* Femke Waanders,* Frans Boomsma,† Dick de Zeeuw,*‡ and Gerjan Navis*‡

*Department of Internal Medicine, Division of Nephrology and ‡Department of Clinical Pharmacology, University Medical Center Groningen, University of Groningen, Groningen, and †Department of Internal Medicine, Section of Vascular Pharmacology, Erasmus Medical Center, Rotterdam, Netherlands

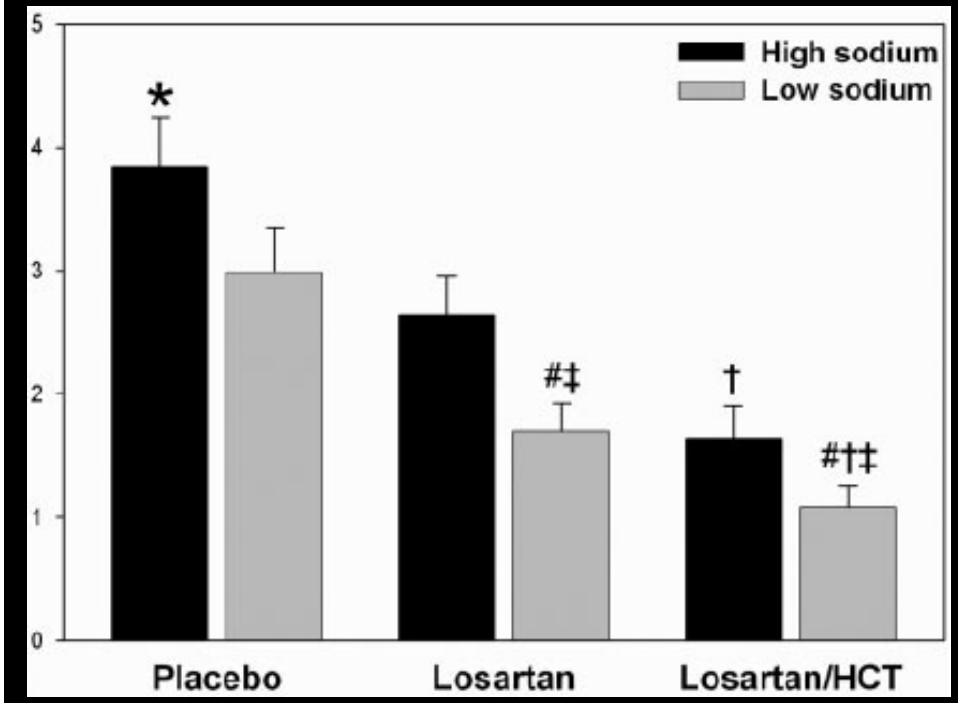
ABSTRACT

There is large interindividual variability in the antiproteinuric response to blockade of the renin-angiotensin-aldosterone system (RAAS). A low-sodium diet or addition of diuretics enhances the effects of RAAS blockade on proteinuria and BP, but the efficacy of the combination of these interventions is unknown. Therefore, this randomized, double-blind, placebo-controlled trial to determine the separate and combined effects of a low-sodium diet and hydrochlorothiazide (HCT) on proteinuria and BP was performed. In 34 proteinuric patients without diabetes, mean baseline proteinuria was 3.8 g/d, and this was reduced by 22% by a low-sodium diet alone. Losartan monotherapy reduced proteinuria by 30%, and the addition of a low-sodium diet led to a total reduction by 55% and the addition of HCT to 56%. The combined addition of HCT and a low-sodium diet reduced proteinuria by 70% from baseline (all $P < 0.05$). Reductions in mean arterial pressure showed a similar pattern (all $P < 0.05$). In addition, individuals who did not demonstrate an antiproteinuric response to losartan monotherapy did respond when a low-sodium diet or a diuretic was added. In conclusion, a low-sodium diet and HCT are equally efficacious in reducing proteinuria and BP when added to a regimen containing losartan and especially seem to benefit individuals who are resistant to RAAS blockade. Combining these interventions in sodium status is an effective method to maximize the antiproteinuric efficacy of RAAS blockade.

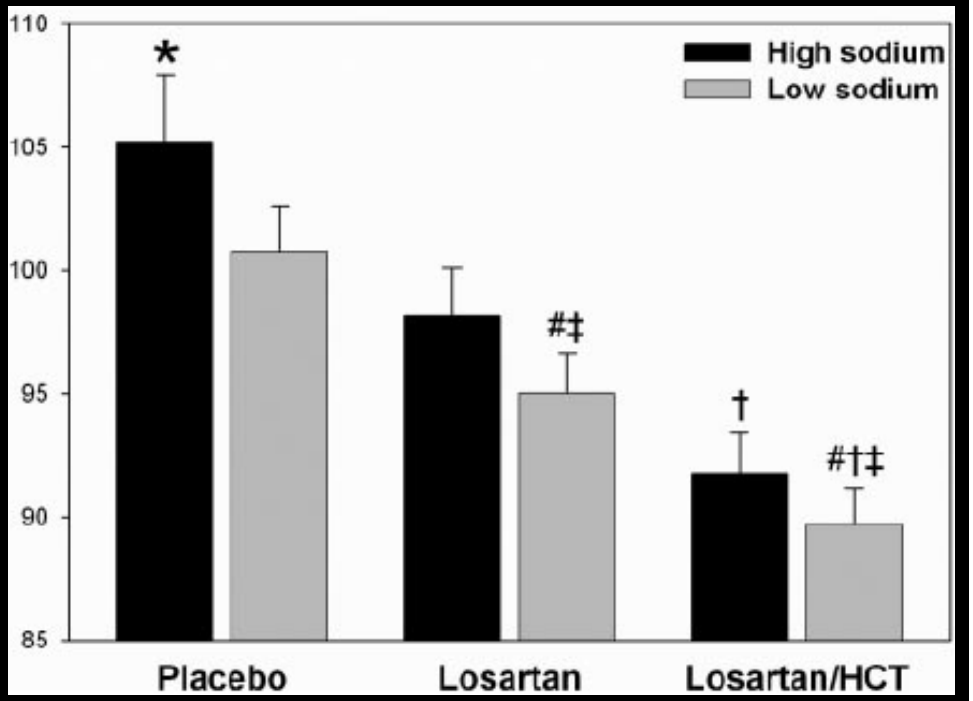
J Am Soc Nephrol 19: 999–1007, 2008. doi: 10.1681/ASN.2007060693

Bloquer SRAA + Diurétique + RSS

Protéinurie (g/g)



PAM (mm Hg)

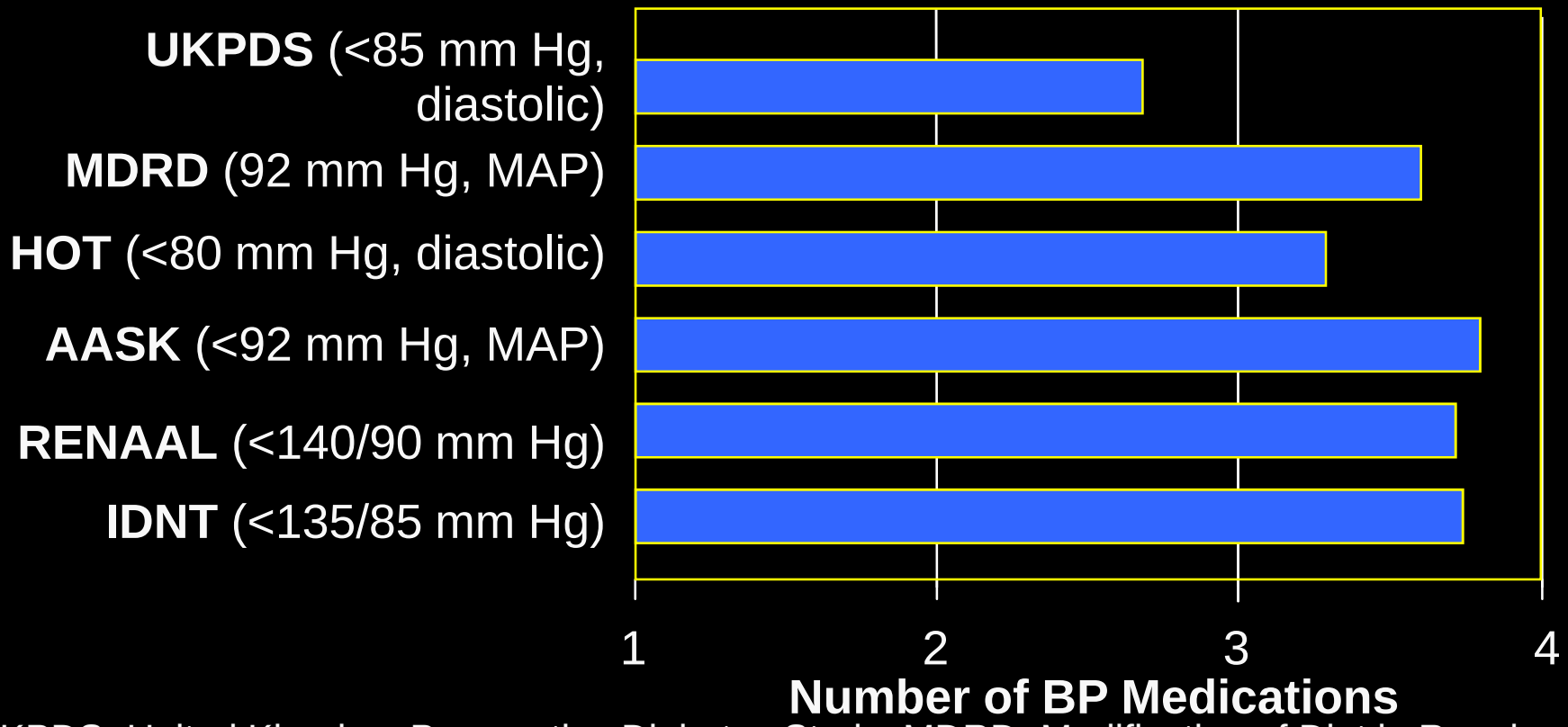


Vogt. JASN 2008,19,999-1007

Plan

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

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.

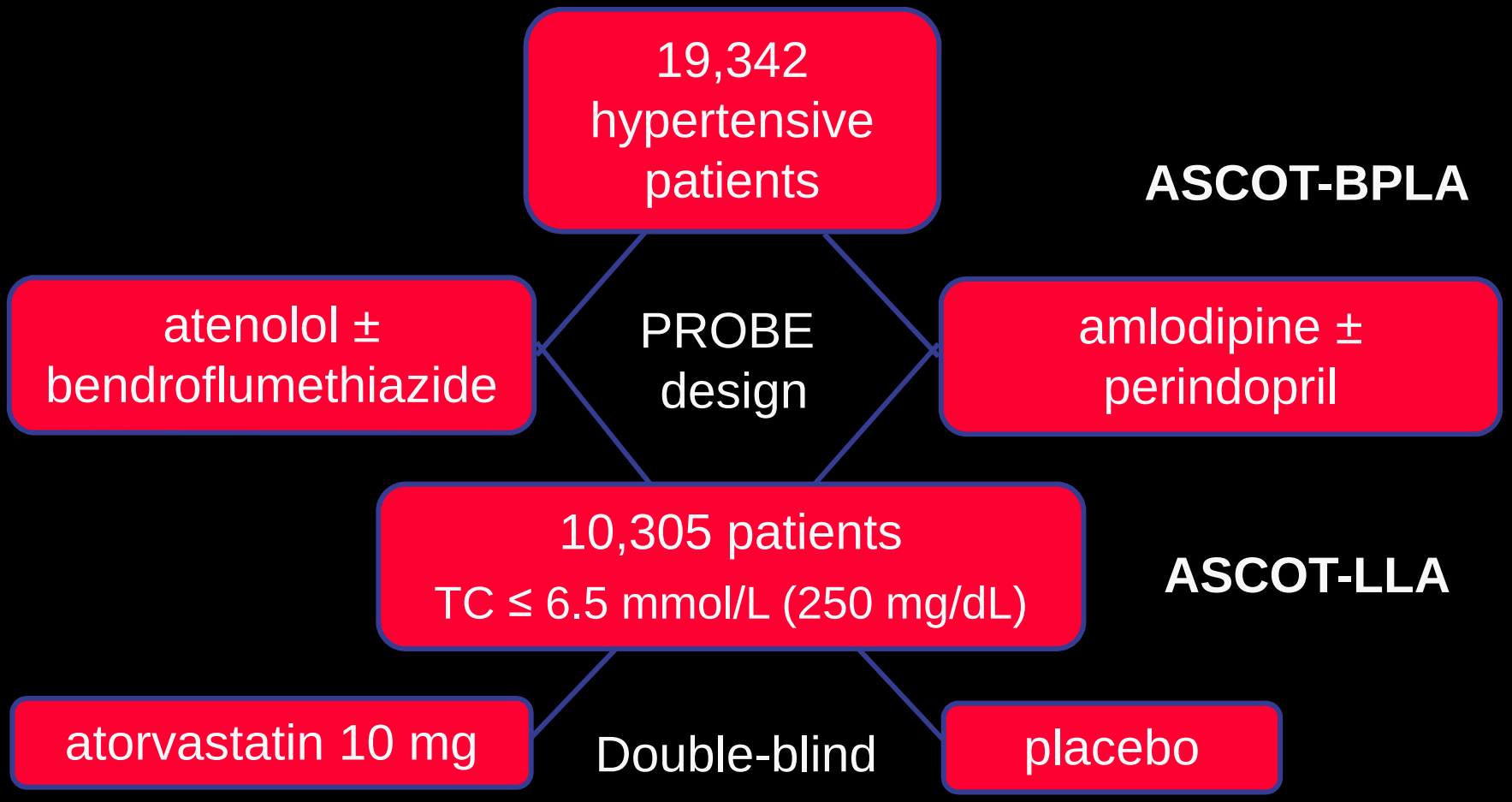
Anglo-Scandinavian ascot Cardiac Outcomes Trial

A randomised controlled trial of the prevention of CHD and other vascular events by BP and cholesterol lowering in a factorial study design

B. Dahlof (Co-chair), P. Sever (Co-chair), N. Poulter (Secretary)
H. Wedel (Statistician), G. Beevers, M. Caulfield, R. Collins
S. Kjeldsen, A. Kristinsson, J. Mehlsen, G. McInnes, M. Nieminen
E. O'Brien, J. Östergren, on behalf of the ASCOT Investigators

ascot

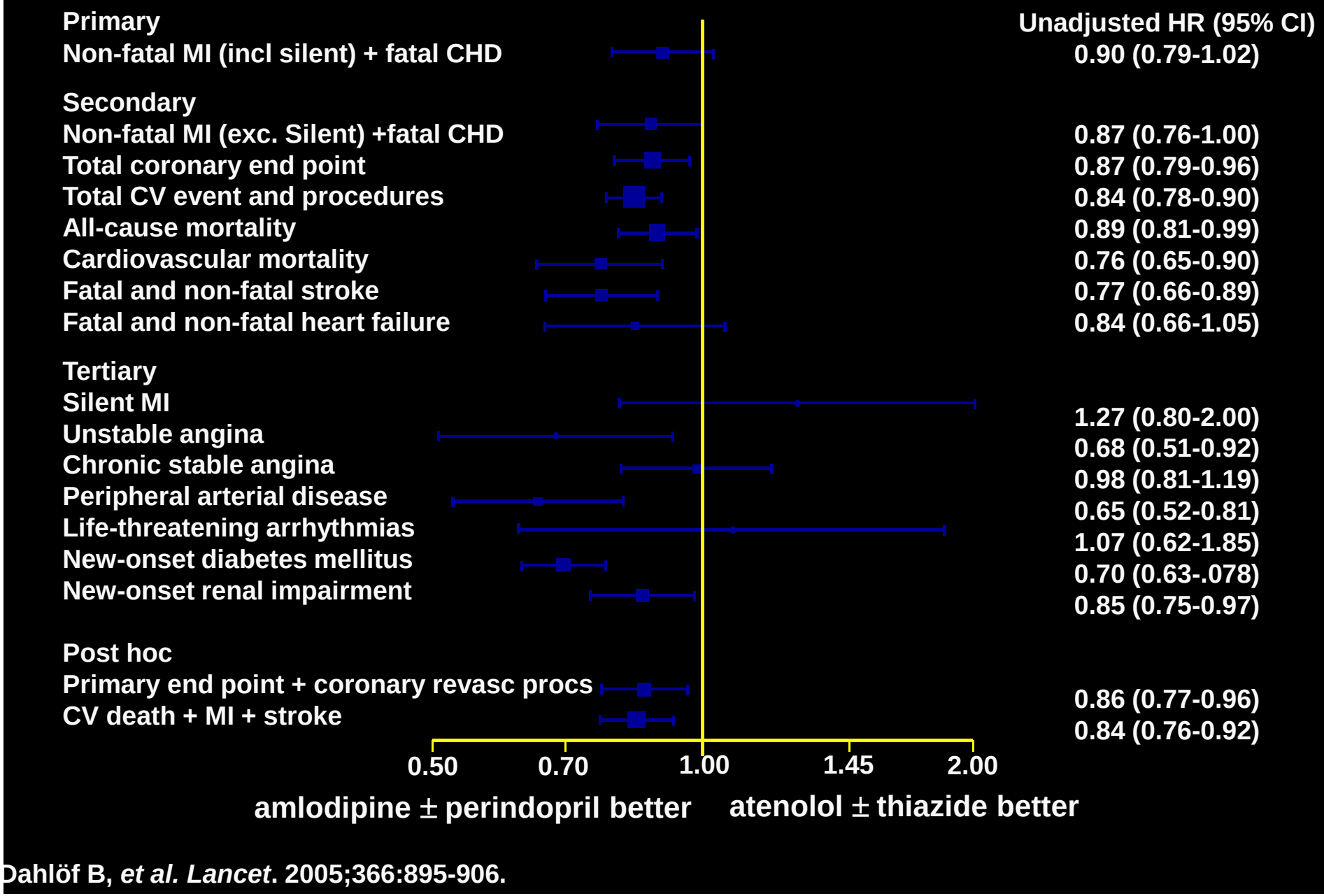
ASCOT-BPLA



Investigator-led, multinational randomised controlled trial

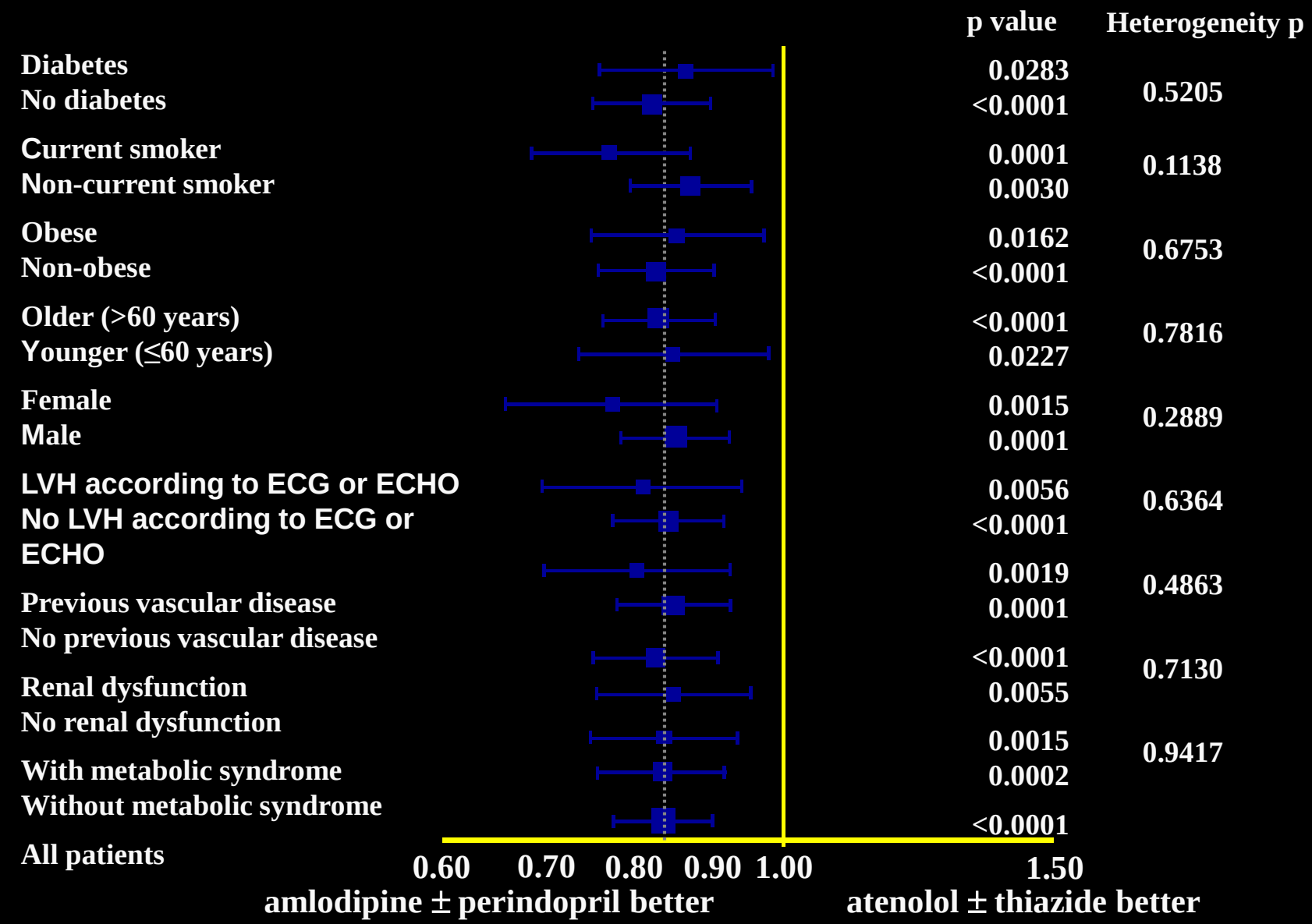
www.ascotstudy.org

ASCOT-BPLA: summary of all end points



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

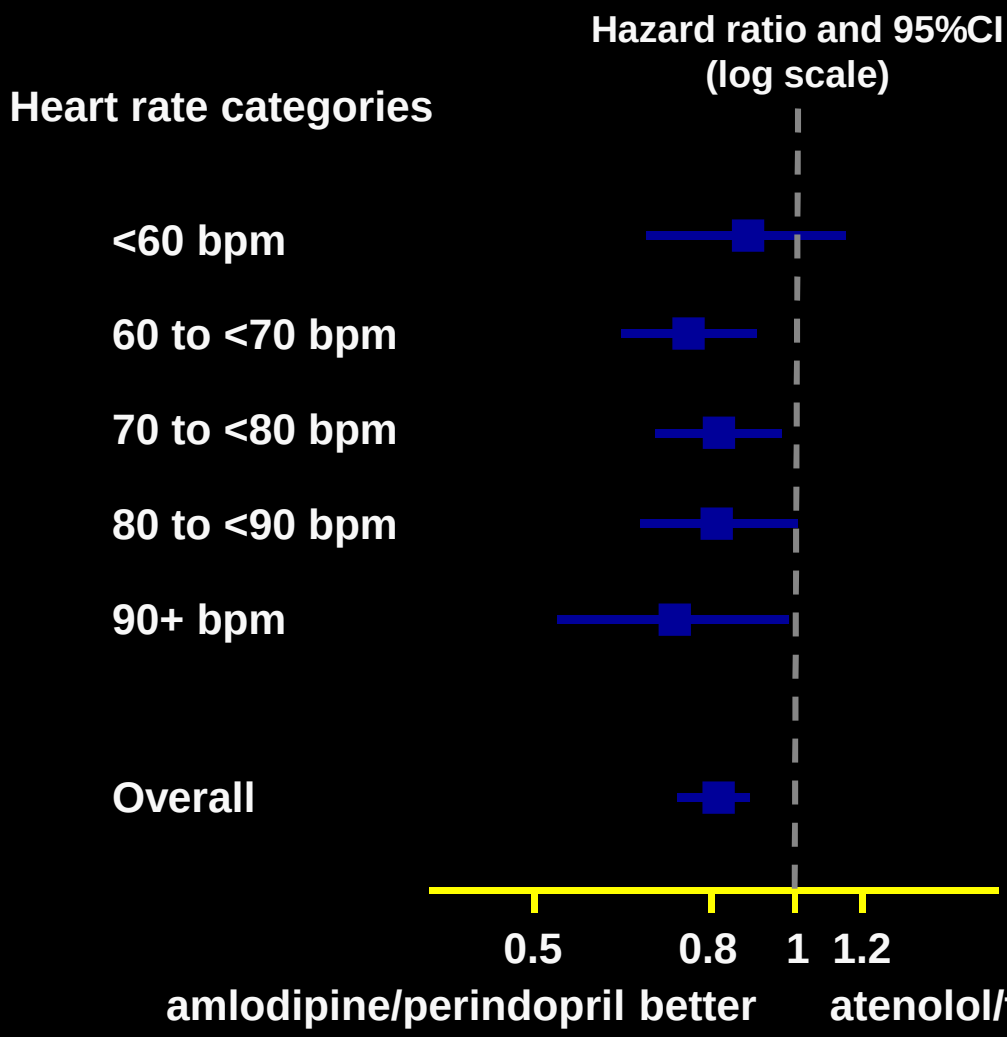
Total CV events and procedures among subgroups



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

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

Total Cardiovascular Events and Procedures



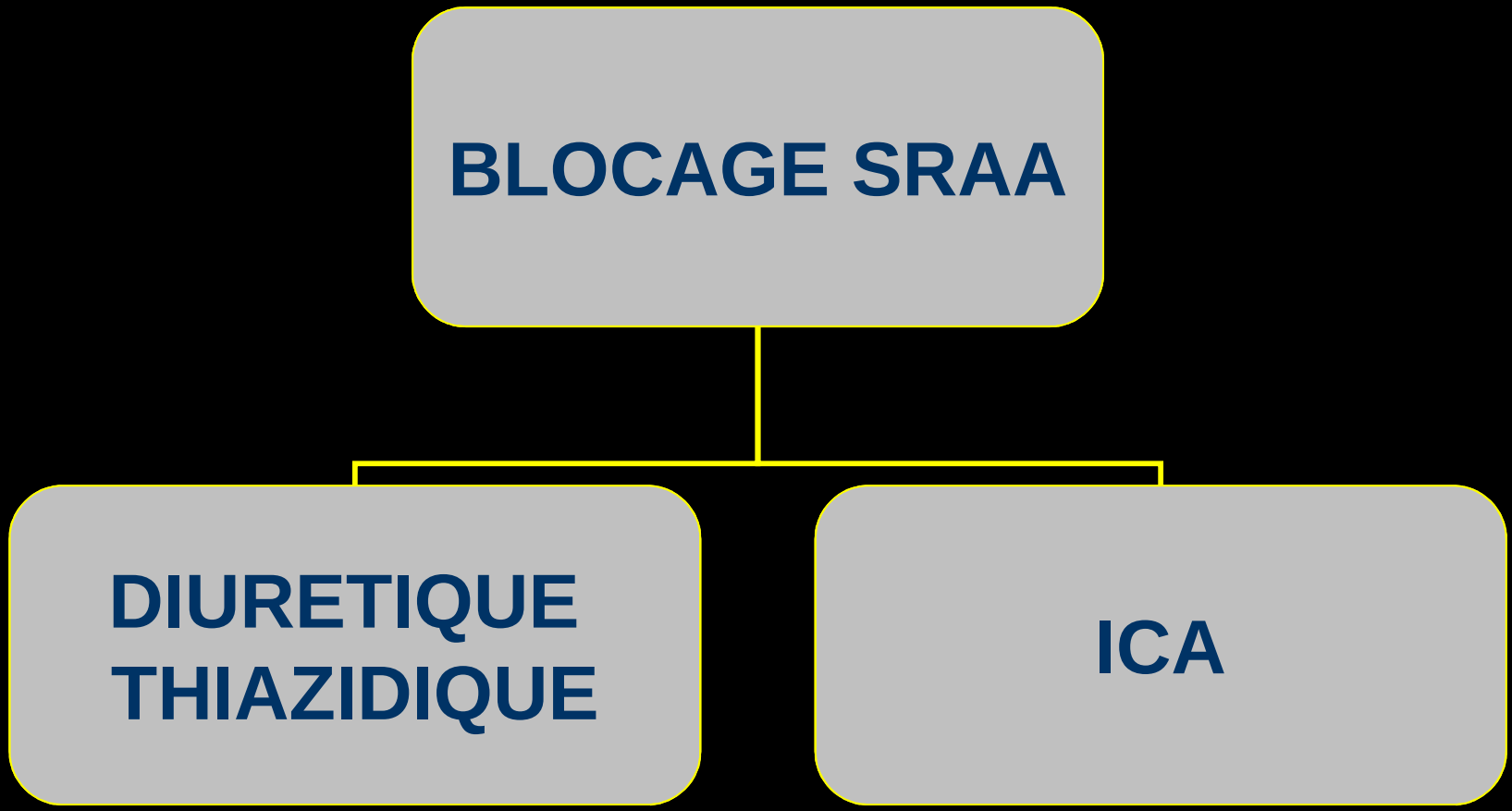
Heart rate categories	No of events/patients amlodipine/ perindopril	atenolol/ thiazide
<60 bpm	125/688	116/724
60 to <70 bpm	308/1842	230/1748
70 to <80 bpm	329/2003	2839/2050
80 to <90 bpm	210/12050	183/1236
90+ bpm	103/623	79/640
Overall	1075/6361	891/6398

Interaction p-value (trend)* = 0.814

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

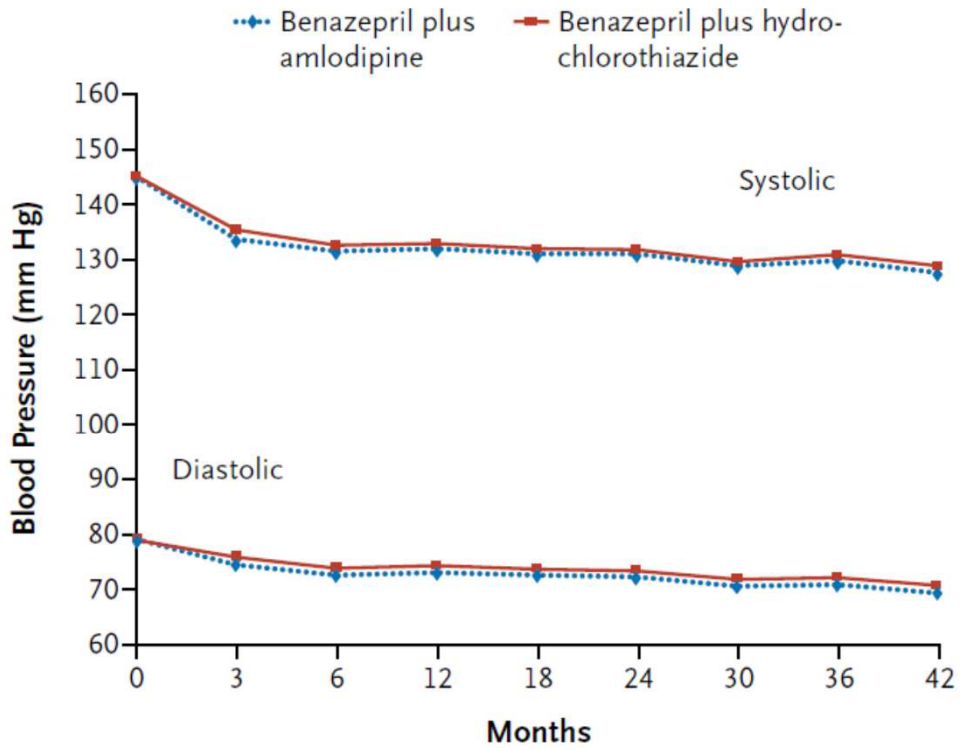
Kenneth Jamerson, M.D., Michael A. Weber, M.D., George L. Bakris, M.D., Björn Dahlöf, M.D., Bertram Pitt, M.D., Victor Shi, M.D., Allen Hester, Ph.D., Jitendra Gupte, M.S., Marjorie Gatlin, M.D., and Eric J. Velazquez, M.D., for the ACCOMPLISH trial investigators*

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

ACCOMPLISH : caractéristiques à la randomisation

Table 1. (Continued.)

Characteristic	Benazepril–Amlodipine Group (N = 5744)	Benazepril–Hydrochlorothiazide Group (N = 5762)
Risk factors — no. (%)		
Previous myocardial infarction	1337 (23.3)	1372 (23.8)
Previous stroke	762 (13.3)	736 (12.8)
Previous hospitalization for unstable angina	653 (11.4)	671 (11.6)
Diabetes mellitus	3478 (60.6)	3468 (60.2)
Renal disease‖	352 (6.1)	353 (6.1)
Estimated glomerular filtration rate <60	1047 (18.2)	1030 (17.9)
Previous coronary revascularization	2044 (35.6)	2073 (36.0)
Coronary-artery bypass grafting	1248 (21.7)	1197 (20.8)
Percutaneous coronary intervention	1055 (18.4)	1123 (19.5)
Left ventricular hypertrophy**	763 (13.3)	758 (13.2)
Other		
Current smoking	641 (11.2)	658 (11.4)
Dyslipidemia	4221 (73.5)	4319 (75.0)
Atrial fibrillation	376 (6.5)	403 (7.0)

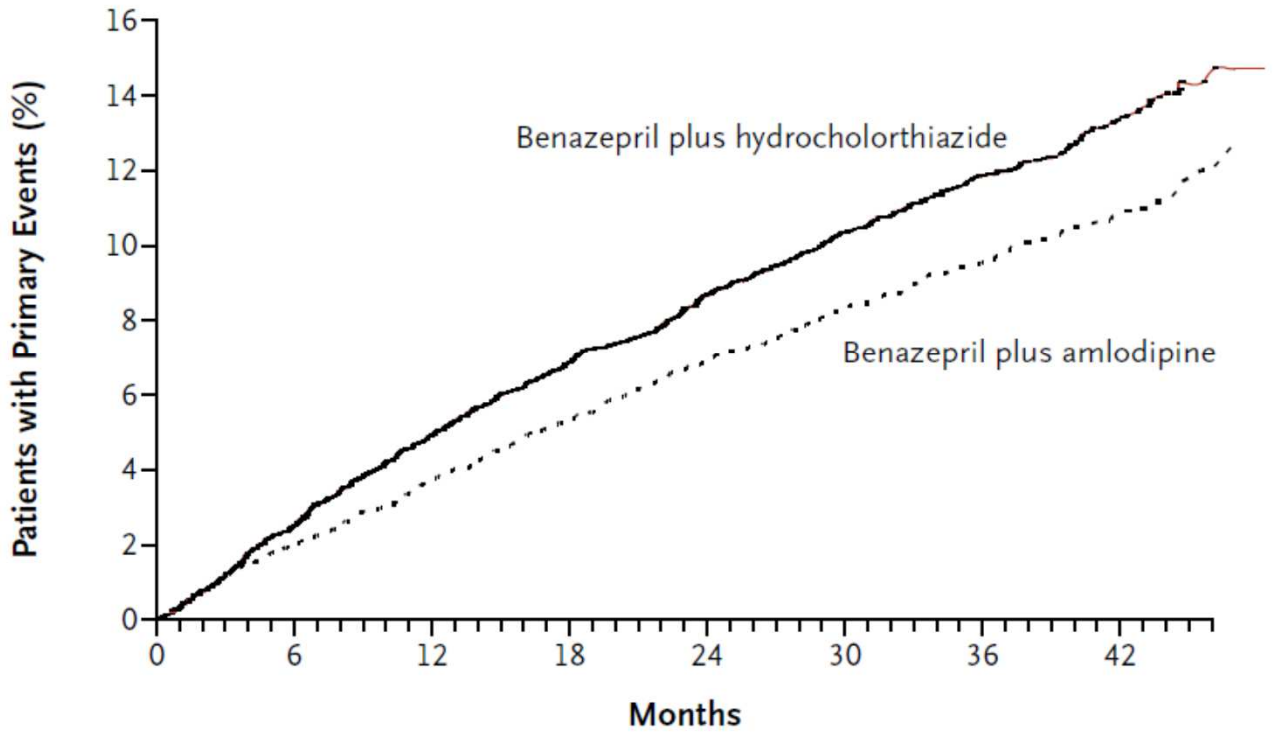


No. at Risk

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).

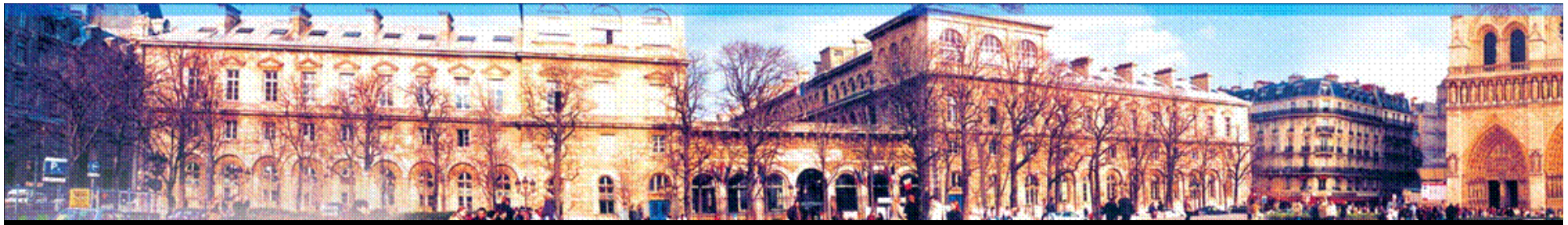


No. at Risk

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).



Le flacon compte autant que l’ivresse (en matière d’hypertension)

Plan

- Observation / intervention
- Veterans / MRC / SHEP
- ALLHAT
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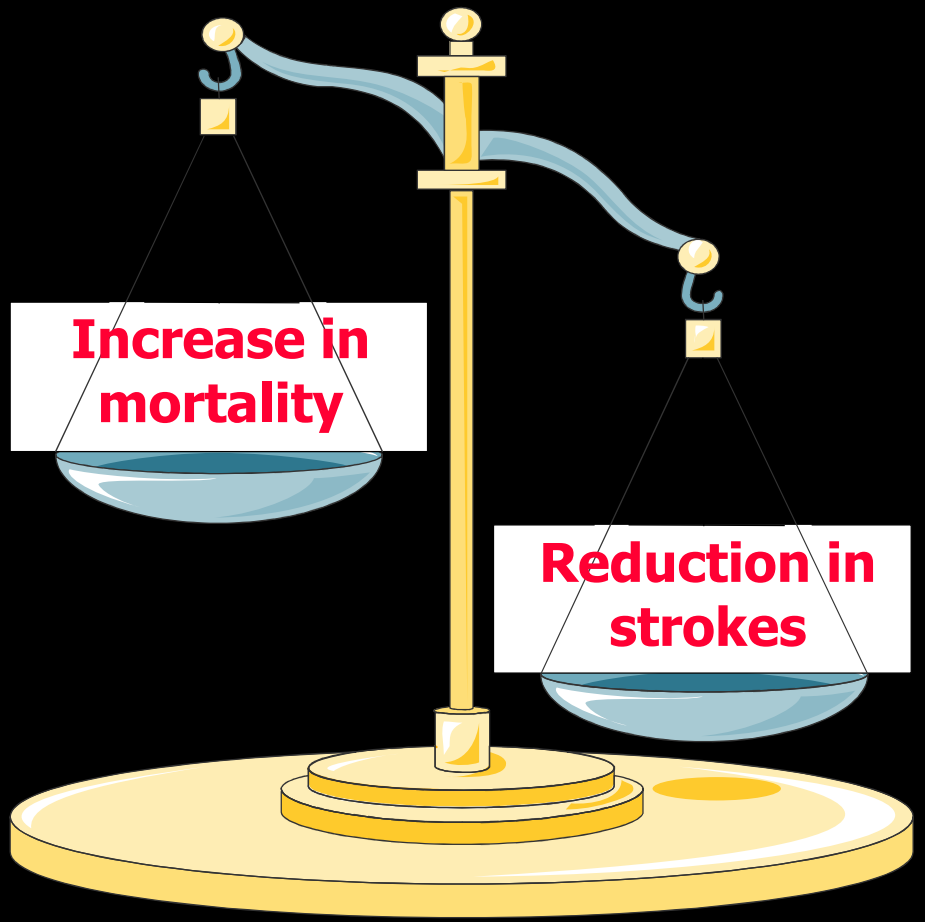
- ASCOT
- ACCOMPLISH
- HYVET
- Méta-analyses
- Recommandations

To treat or not to treat? That is the question



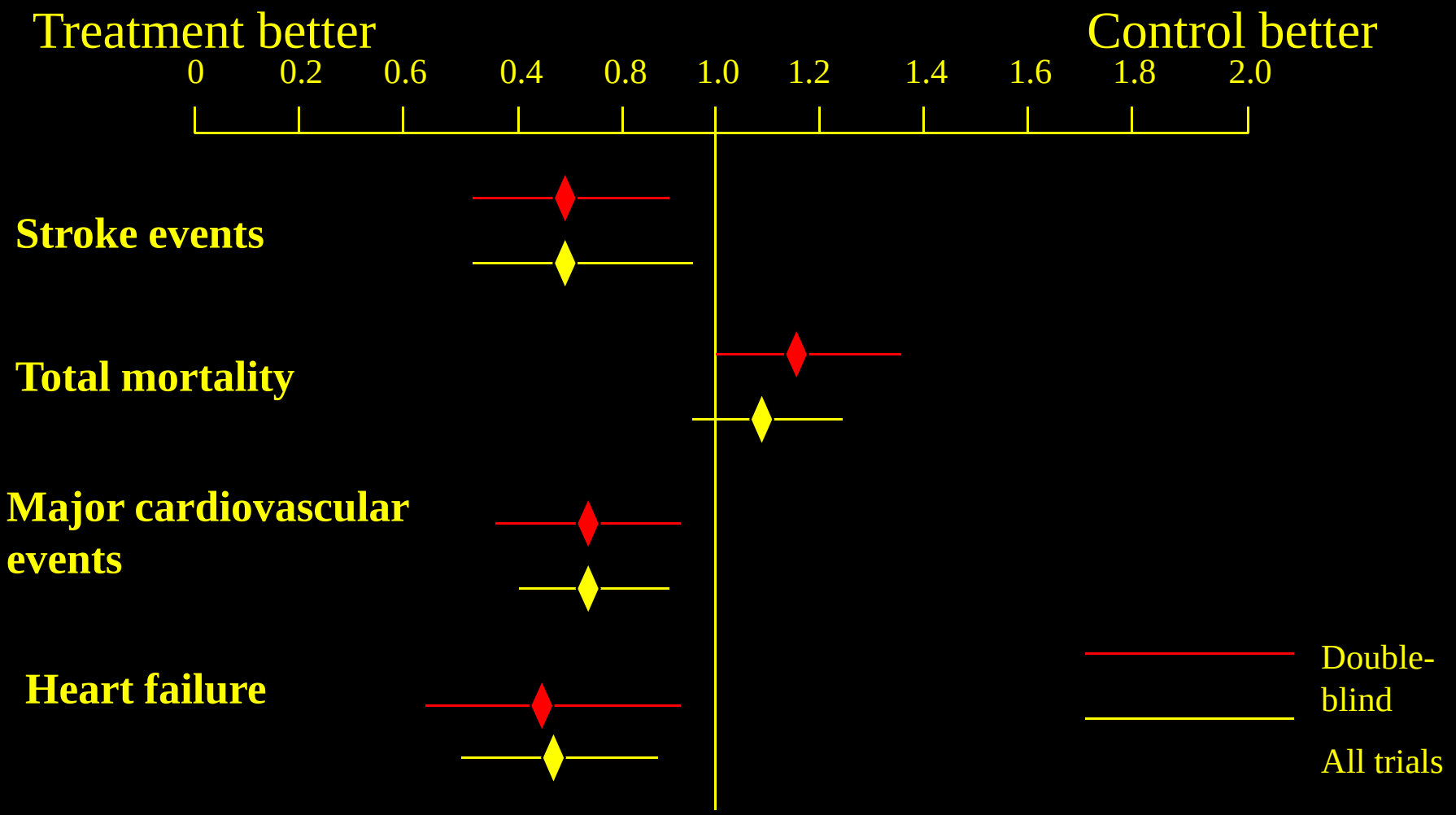
This dilemma provided the rationale for the

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

Effect of antihypertensive therapy over 80 years

Meta-analysis of Randomised Controlled Trials

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

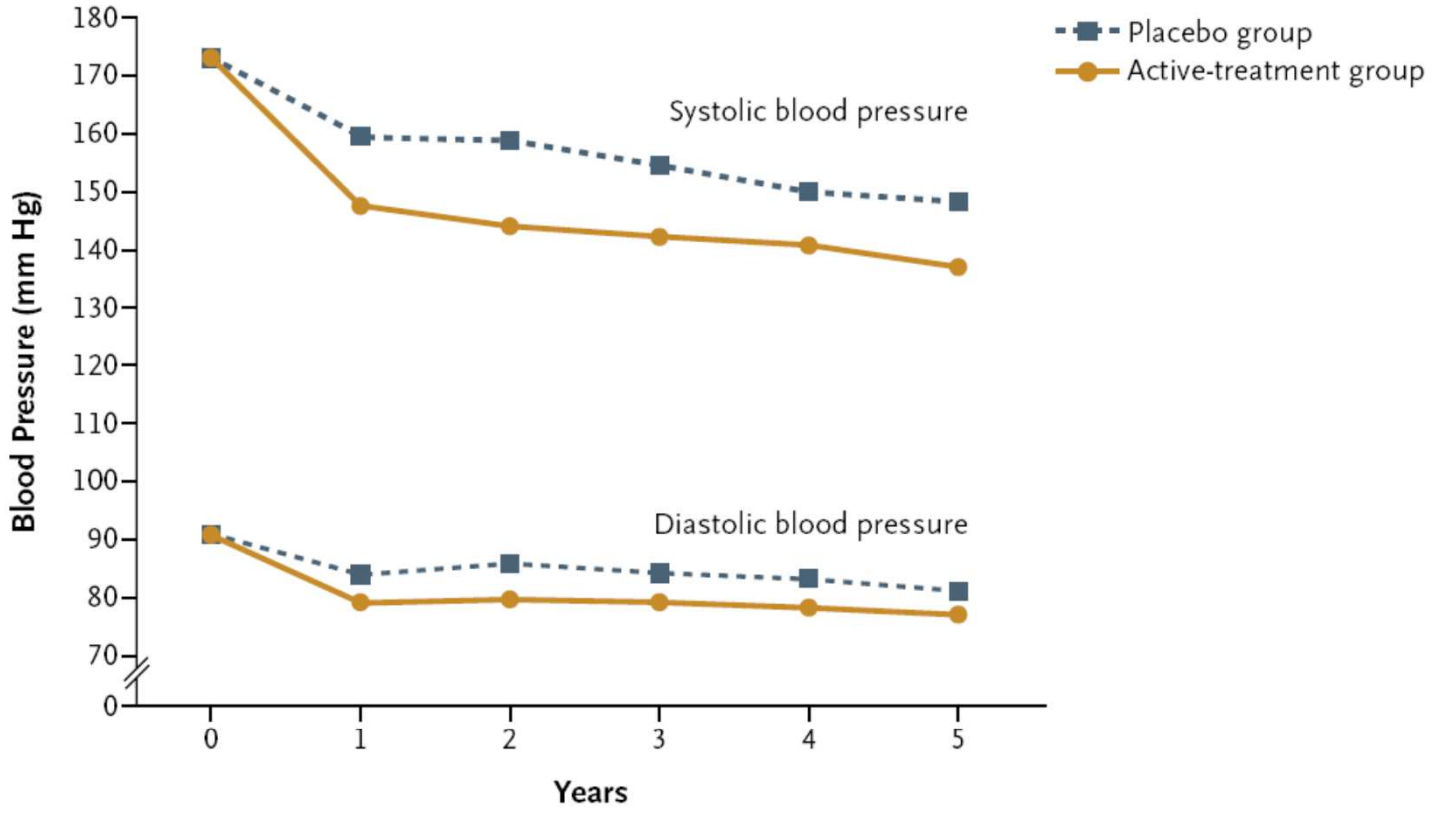


Gueyffier F et al. Lancet 1999:353:793-96

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*



No. at Risk

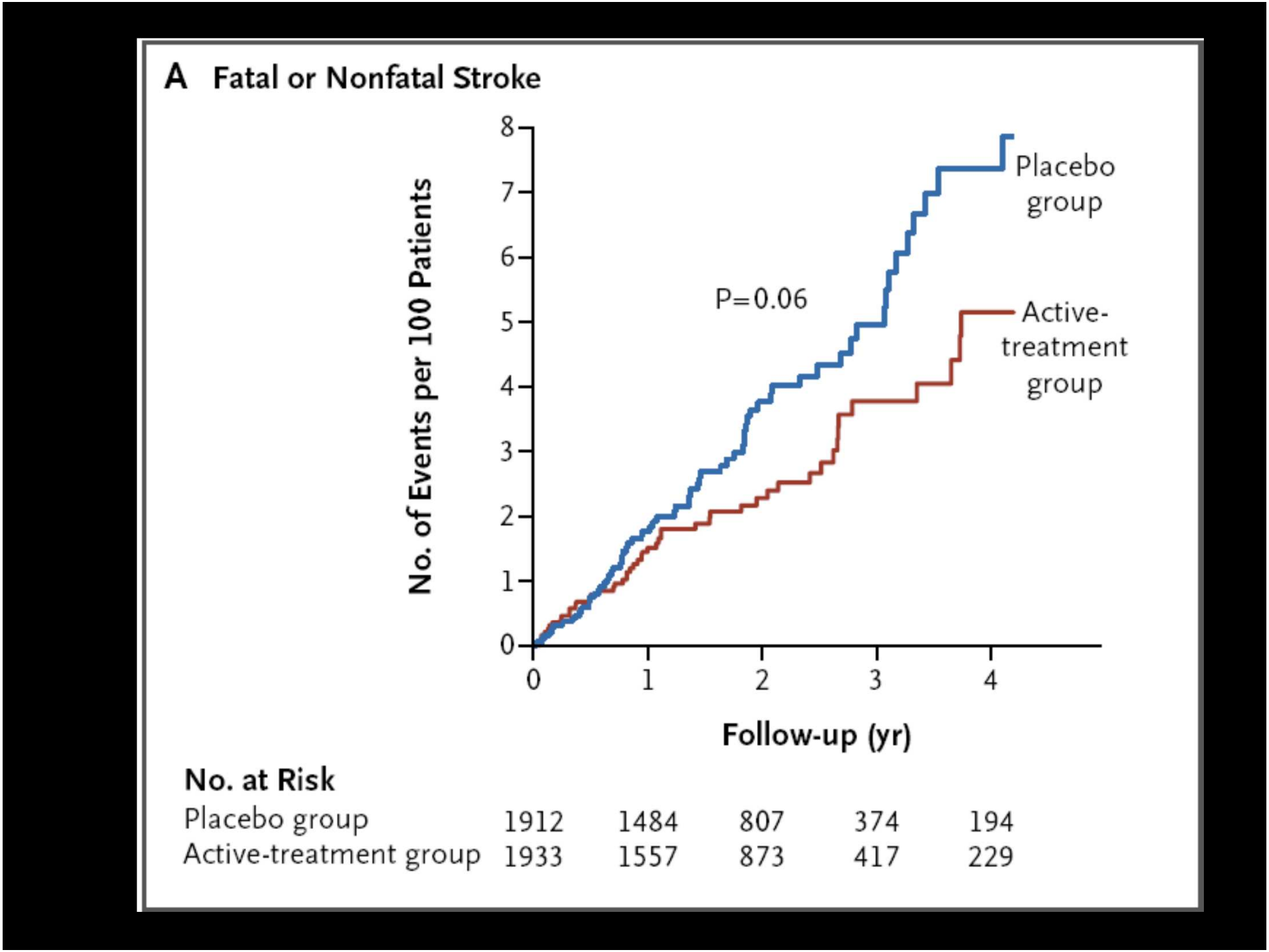
Placebo group	1912	1468	701	330	191	116
Active-treatment group	1933	1540	754	373	207	118

Figure 2. Mean Blood Pressure, Measured While Patients Were Seated, in the Intention-to-Treat Population, According to Study Group.

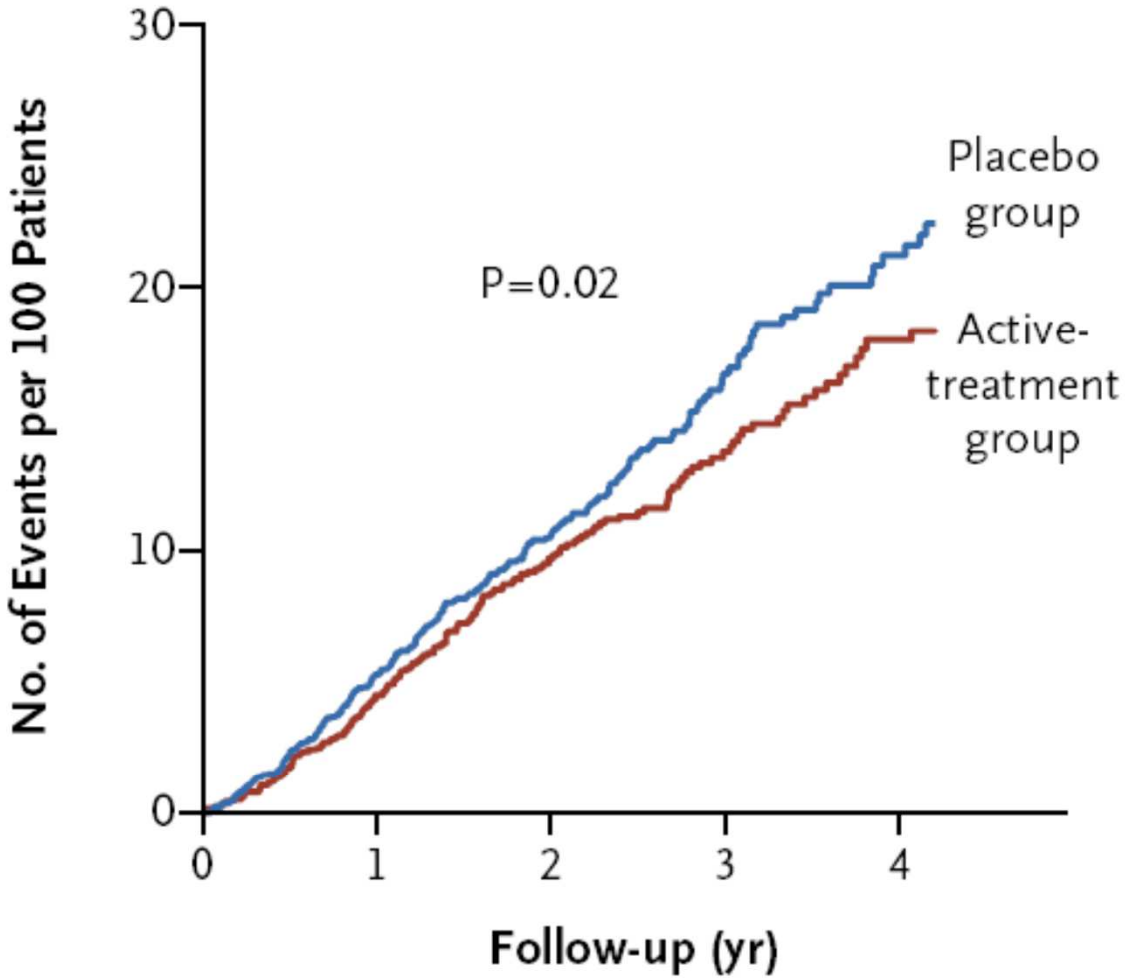
Table 2. Main Fatal and Nonfatal End Points in the Intention-to-Treat Population.

End Point	Rate per 1000 Patient-Yr (No. of Events)		Unadjusted Hazard Ratio (95% CI)	P Value
	Active	Placebo		
	no. (%)			
Stroke				
Fatal or nonfatal	12.4 (51)	17.7 (69)	0.70 (0.49–1.01)	0.06
Death from stroke	6.5 (27)	10.7 (42)	0.61 (0.38–0.99)	0.046
Death				
From any cause	47.2 (196)	59.6 (235)	0.79 (0.65–0.95)	0.02
From noncardiovascular or unknown causes	23.4 (97)	28.9 (114)	0.81 (0.62–1.06)	0.12
From cardiovascular cause	23.9 (99)	30.7 (121)	0.77 (0.60–1.01)	0.06
From cardiac cause*	6.0 (25)	8.4 (33)	0.71 (0.42–1.19)	0.19
From heart failure	1.5 (6)	3.0 (12)	0.48 (0.18–1.28)	0.14
Fatal or nonfatal				
Any myocardial infarction	2.2 (9)	3.1 (12)	0.72 (0.30–1.70)	0.45
Any heart failure	5.3 (22)	14.8 (57)	0.36 (0.22–0.58)	<0.001
Any cardiovascular event†	33.7 (138)	50.6 (193)	0.66 (0.53–0.82)	<0.001

* Death from cardiac causes was defined as fatal myocardial infarction, fatal heart failure, and sudden death.
† Any cardiovascular event was defined as death from cardiovascular causes or stroke, myocardial infarction, or heart failure.


A Fatal or Nonfatal Stroke
No. of Events per 100 Patients
8
7
6
5
4
3
2
1
0
P=0.06
Placebo group
Active-treatment group
0
1
2
3
4
Follow-up (yr)
No. at Risk
Placebo group 1912 1484 807 374 194
Active-treatment group 1933 1557 873 417 229

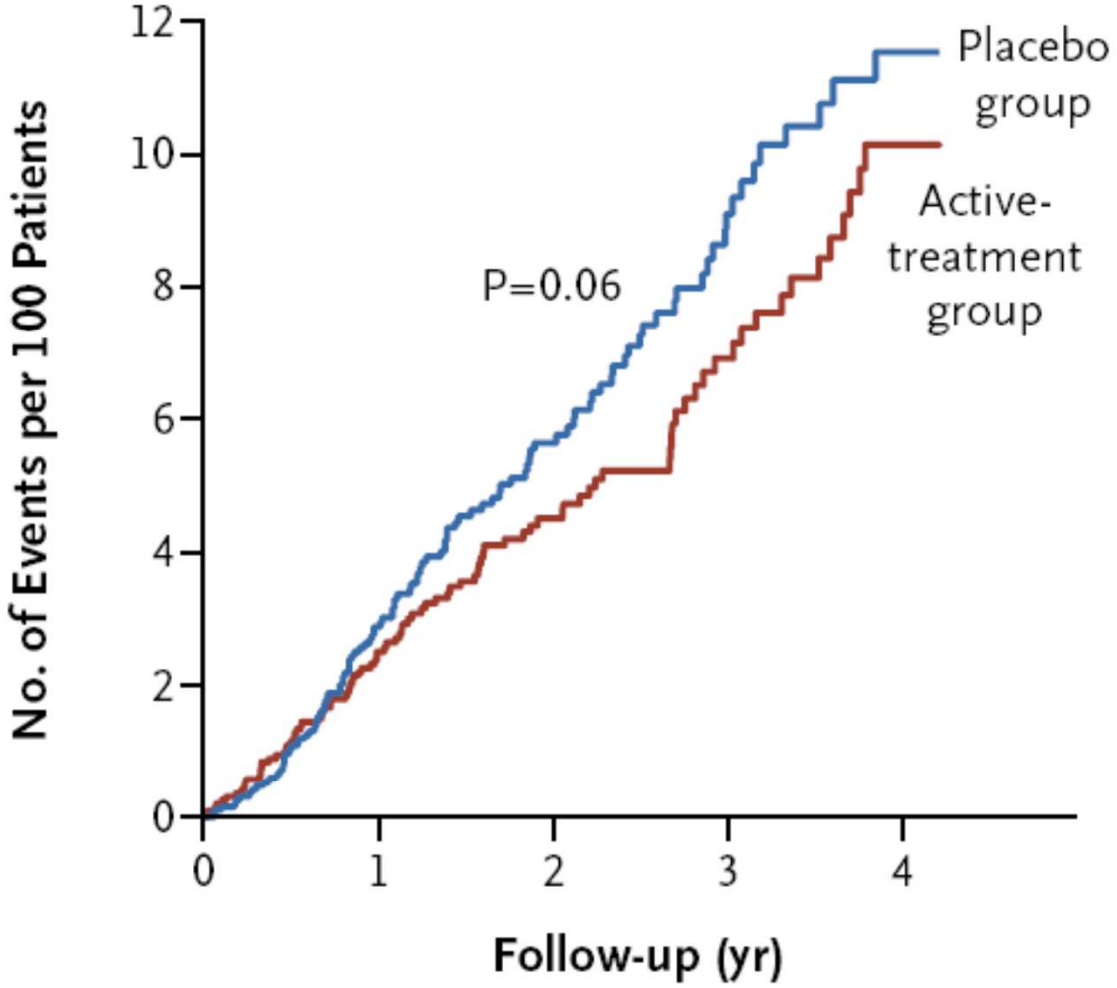
B **Death from Any Cause**



No. at Risk

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

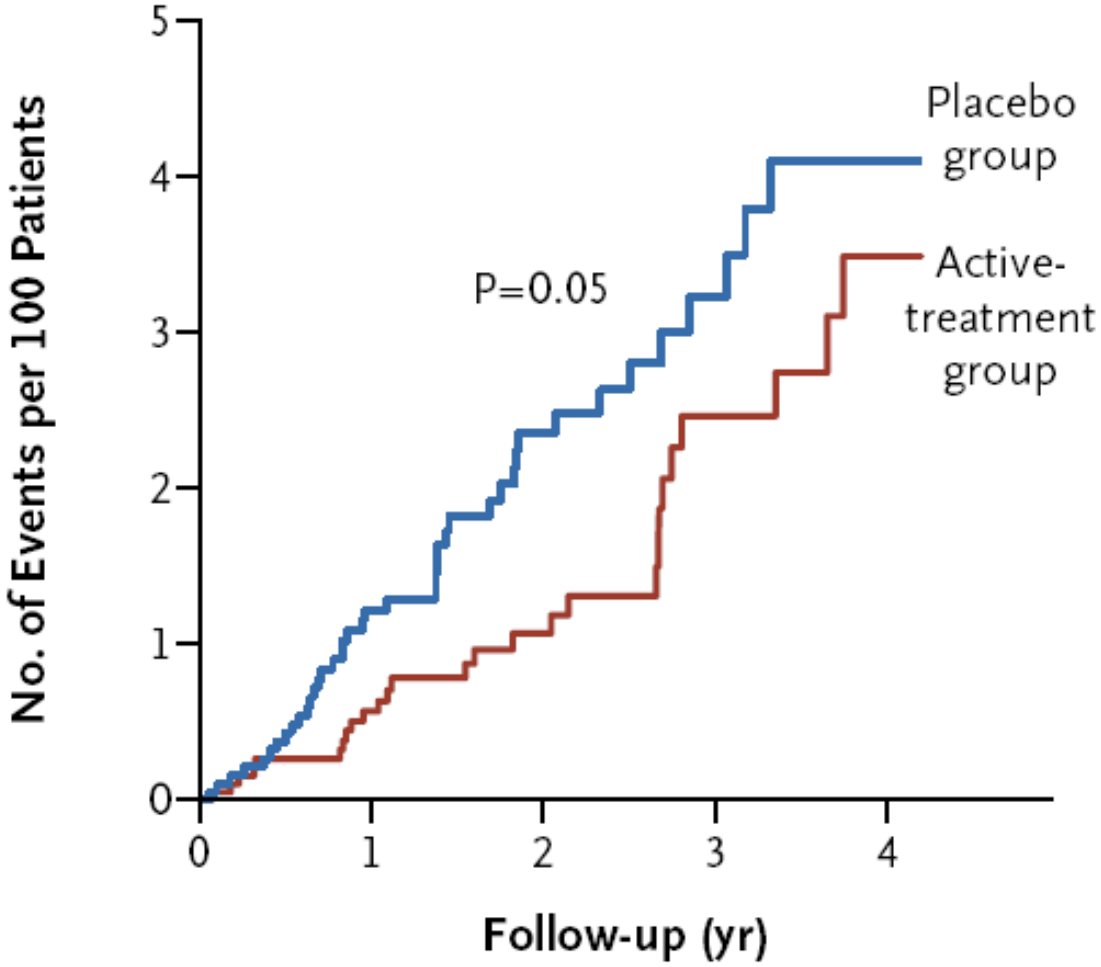
C **Death from Cardiovascular Causes**



No. at Risk

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

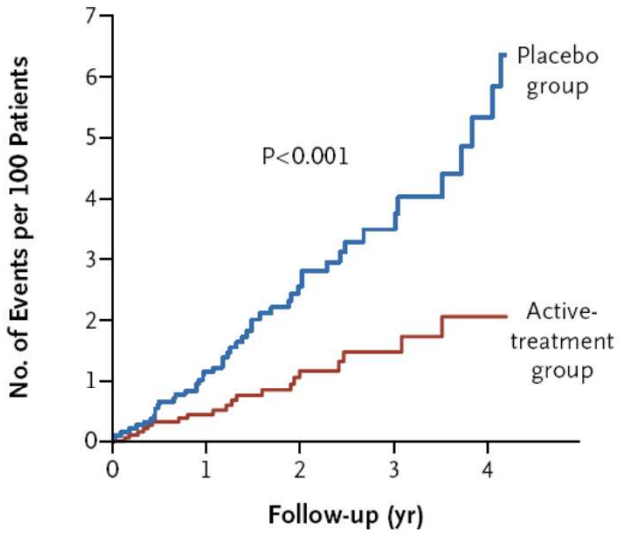
D Death from Stroke



No. at Risk

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

E Heart Failure



No. at Risk

Placebo group	1912	1480	794	367	188
Active-treatment group	1933	1559	872	416	228

Figure 3. Kaplan–Meier Estimates of the Rate of End Points, According to Study Group.

For the active-treatment group as compared with the placebo group, the unadjusted hazard ratios (95% CIs) were as follows: for fatal or nonfatal stroke, 0.70 (0.49 to 1.01) (Panel A); for death from any cause, 0.79 (0.65 to 0.95) (Panel B); for death from cardiovascular causes, 0.77 (0.60 to 1.01) (Panel C); for death from stroke, 0.61 (0.38 to 0.99) (Panel D); and for heart failure, 0.36 (0.22 to 0.58) (Panel E).

However, it would be premature to extrapolate the results from HYVET to patients in this age group who are more frail.

Plan

- Observation / intervention
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- HYVET
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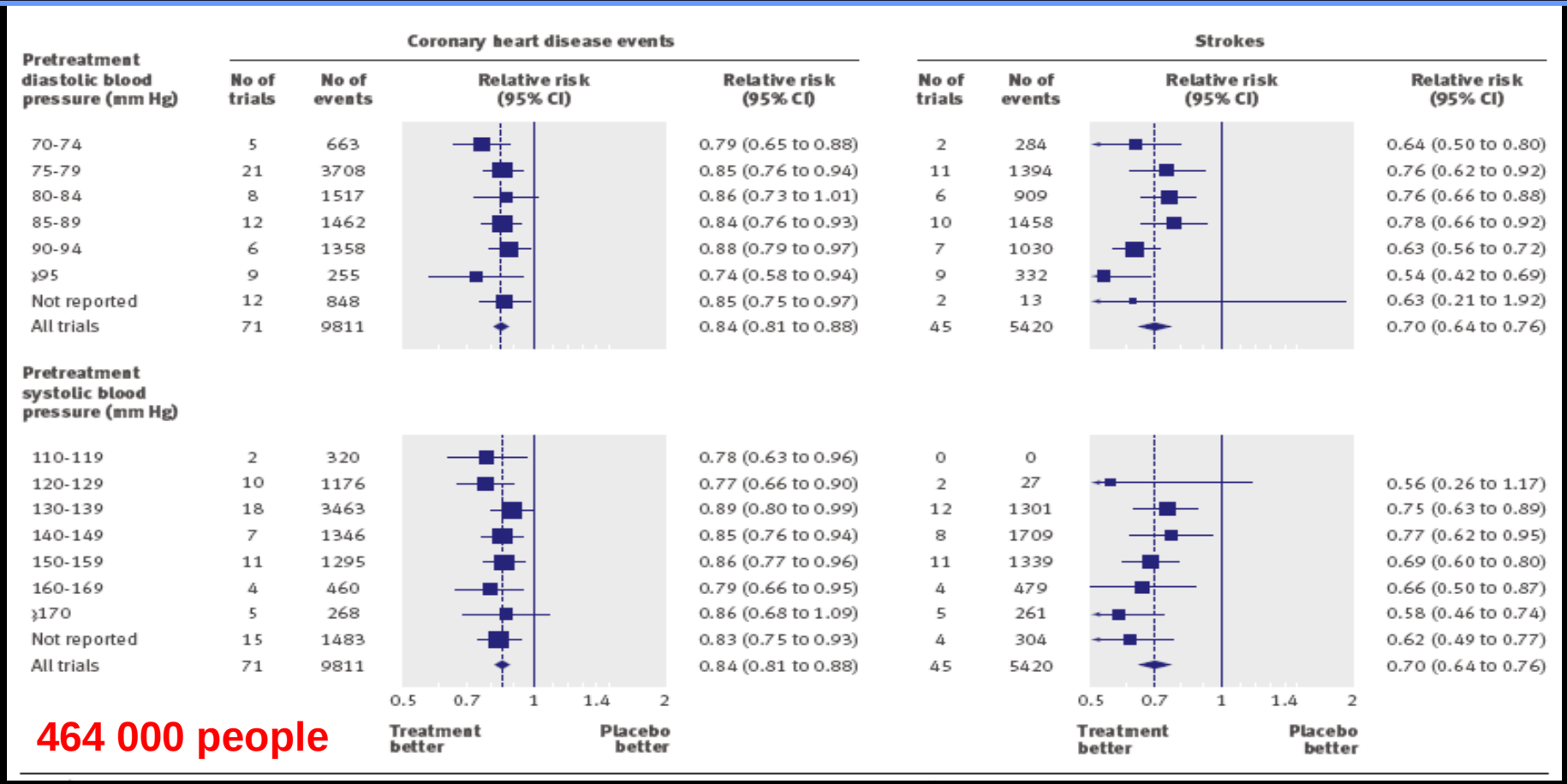
- Recommandations

Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies.

Law MR, Morris K. BMJ 2009; 338: b1665



464 000 people

Each reduction of 10 mmHg SBP or 5 mmHg DBP is associated with a 41% (33-48) reduction in stroke and a 22% (17-27) reduction in CHD.

Pharmacotherapy for mild hypertension (Review)

Diao D, Wright JM, Cundiff DK, Gueyffier F

THE COCHRANE COLLABORATION®

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2012, Issue 8

http://www.thecochranelibrary.com

Background

People with no previous cardiovascular events or cardiovascular disease represent a primary prevention population. The benefits and harms of treating mild hypertension in primary prevention patients are not known at present. This review examines the existing randomised controlled trial (RCT) evidence.

Objectives

Primary objective: To quantify the effects of antihypertensive drug therapy on mortality and morbidity in adults with mild hypertension (systolic blood pressure (BP) 140-159 mmHg and/or diastolic BP 90-99 mmHg) and without cardiovascular disease.

Search methods

We searched CENTRAL (2011, Issue 1), MEDLINE (1948 to May 2011), EMBASE (1980 to May 2011) and reference lists of articles. The Cochrane Database of Systematic Reviews and the Database of Abstracts of Reviews of Effectiveness (DARE) were searched for previous reviews and meta-analyses of anti-hypertensive drug treatment compared to placebo or no treatment trials up until the end of 2011.

Selection criteria

RCTs of at least 1 year duration.

Data collection and analysis

The outcomes assessed were mortality, stroke, coronary heart disease (CHD), total cardiovascular events (CVS), and withdrawals due to adverse effects.

Main results

Of 11 RCTs identified 4 were included in this review, with 8,912 participants. Treatment for 4 to 5 years with antihypertensive drugs as compared to placebo did not reduce total mortality (RR 0.85, 95% CI 0.63, 1.15). In 7,080 participants treatment with antihypertensive drugs as compared to placebo did not reduce coronary heart disease (RR 1.12, 95% CI 0.80, 1.57), stroke (RR 0.51, 95% CI 0.24, 1.08), or total cardiovascular events (RR 0.97, 95% CI 0.72, 1.32). Withdrawals due to adverse effects were increased by drug therapy (RR 4.80, 95%CI 4.14, 5.57), ARR 9%.

Authors' conclusions

Antihypertensive drugs used in the treatment of adults (primary prevention) with mild hypertension (systolic BP 140-159 mmHg and/or diastolic BP 90-99 mmHg) have not been shown to reduce mortality or morbidity in RCTs. Treatment caused 9% of patients to discontinue treatment due to adverse effects. More RCTs are needed in this prevalent population to know whether the benefits of treatment exceed the harms.

Plan

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

JNC VII JAMA
21 Mai 2003

Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document

Giuseppe Mancia[a], Stéphane Laurent[b], Enrico Agabiti-Rosei[c], Ettore Ambrosioni[d], Michel Burnier[e], Mark J. Caulfield[f], Renata Cifkova[g], Denis Clément[h], Antonio Coca[i], Anna Dominiczak[j], Serap Erdine[k], Robert Fagard[l], Csaba Farsang[m], Guido Grassi[n], Hermann Haller[o], Anthony Heagerty[p], Sverre E. Kjeldsen[q], Wolfgang Kiowski[r], Jean Michel Mallion[s], Athanasios Manolis[t], Krzysztof Narkiewicz[u], Peter Nilsson[v], Michael H. Olsen[w], Karl Heinz Rahn[x], Josep Redon[y], José Rodicio[z], Luis Ruilope[a1], Roland E. Schmieder[a2], Harry A.J. Struijker-Boudier[a3], Pieter A. van Zwieten[a4], Margus Viigimaa[a5] and Alberto Zanchetti[a6]

Journal of Hypertension 2009, 27:2121–2158

Correspondence to Professor Giuseppe Mancia, Clinica Medica, University of Milan-Bicocca, San Gerardo Hospital, Via Pergolesi 33, 20052 Monza, Milan, Italy

HAS

HAUTE AUTORITÉ DE SANTÉ

RECOMMANDATIONS POUR LA PRATIQUE CLINIQUE

PRISE EN CHARGE DES PATIENTS ADULTES ATTEINTS D'HYPERTENSION ARTÉRIELLE ESSENTIELLE

Issue date: June 2006

Hypertension

Management of hypertension in adults in primary care

This is a partial update of NICE clinical guideline 18

Programme Éducatif Canadien sur l'Hypertension

Canadian Hypertension Education Program

2010

Recommandations canadiennes pour le traitement de l'hypertension artérielle

Du nouveau et des rappels importants

Siegel D, Lopez J. Trends in antihypertensive drug use in the United States. Do the JNC V recommendations affects prescribing. JAMA 1997 ; 278 : 1745-8.

- **1992 (part de marché)**
- **AC : 33 %**
- **IEC : 25 %**
- **Béta - : 18 %**
- **Diur. : 16 %**

Siegel D, Lopez J. Trends in antihypertensive drug use in the United States. Do the JNC V recommendations affects prescribing. JAMA 1997 ; 278 : 1745-8.

- **1992 (part de marché)**
- **AC : 33 %**
- **IEC : 25 %**
- **Béta - : 18 %**
- **Diur. : 16 %**

- **1995 (part de marché)**
- **AC : 38 %**
- **IEC : 33 %**
- **Béta - : 11 %**
- **Diur. : 8 %**

RECOMMANDATION

PRISE EN CHARGE DE L'HYPERTENSION ARTÉRIELLE DE L'ADULTE

LES RENDEZ-VOUS DE L'HYPERTENDU

AVANT DE DÉBUTER LE TRAITEMENT

1) Confirmer le diagnostic, avec mesures tensionnelles en dehors du cabinet médical.
2) Mettre en place les mesures hygiéno-diététiques.
3) Réaliser un bilan initial.
4) Organiser une consultation d'information et d'annonce de l'HTA.

PLAN DE SOIN INITIAL (6 PREMIERS MOIS)

1) Objectif principal : contrôle de la pression artérielle dans les 6 premiers mois.
2) Privilégier cinq classes d'antihypertenseurs qui ont démontré une prévention des complications cardiovasculaires chez les hypertendus.
3) Choix individualisé du premier traitement antihypertenseur, tenant compte notamment de la persistance.
4) Privilégier les bithérapies (fixes) en cas d'échec de la monothérapie, puis une trithérapie si nécessaire.
5) S'assurer de la bonne tolérance.

PLAN DE SOIN A LONG TERME

1) HTA non contrôlée à 6 mois sous trithérapie: avis spécialisé après avoir vérifié la bonne observance et l'HTA en dehors du cabinet médical.
2) En cas d'HTA contrôlée, visite tous les 3 à 6 mois.
3) Dépister la mauvaise observance des traitements antihypertenseurs.
4) Favoriser la pratique de l'automesure tensionnelle.
5) Après 80 ans, objectif modulé sans dépasser 3 antihypertenseurs.
6) Après complication cardiovasculaire, ajustement des traitements et maintien de l'objectif tensionnel.