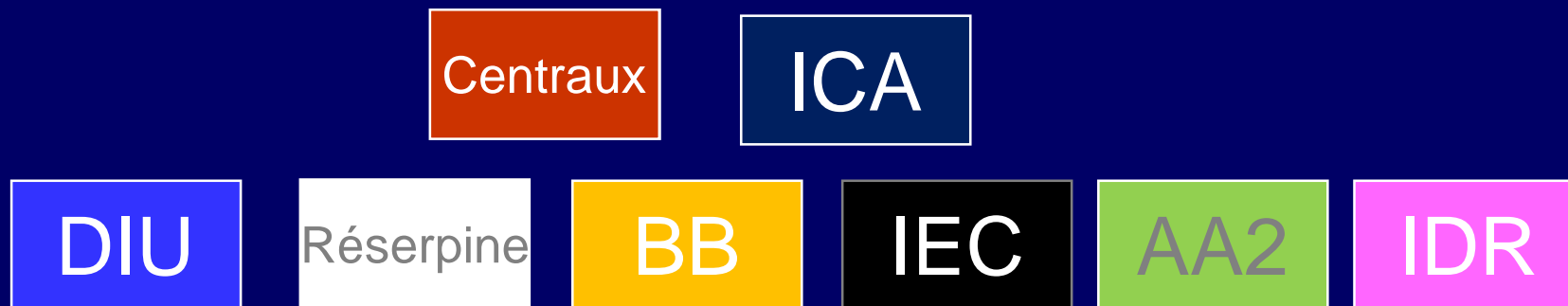


Lecture critique des grands essais sur l'HTA

Pr Xavier Girerd
Pôle Endocrinologie
Unité de Prévention des Maladies Cardiovasculaires
Groupe Hospitalier Pitié-Salpêtrière
Faculté Pierre et Marie Curie, Paris 6

L'historique des antihypertenseurs



Dates de lancement

1950 1960 1970 1980 1990 2000 2010

1960 - 1990

Efficacité préventive des
antihypertenseurs

Essais randomisés vs. Placebo

Clinical trials of antihypertensive therapy

Thiazide diuretics and/or beta-blockers vs. placebo

- Trials in malignant hypertension
 - Hamilton 1964
- Trials in mild to moderate hypertension
 - Active vs. placebo
 - 1970 - 1990
 - HDFP, MRC, Australian
- Trials in elderly hypertensives
 - Active vs. placebo
 - 1980-2008
 - MRC II, SHEP, SYST-EUR, HYVET

1990

La méta-analyse de *Collins* fait entrer le traitement diurétique/bêta-bloquant dans le panthéon des thérapeutiques de l'HTA.

Mild or moderate hypertension treated with diuretics
and/or beta-blockers

Collins R, Peto R, MacMahon S,
Lancet 1990; 335: 827-38.

Reductions in blood pressure of about 10–12 mm Hg
systolic and 5–6 mm Hg diastolic conferred relative
reductions in stroke risk of 38% and in risk of coronary
heart disease of 16% within just a few years of
beginning treatment.

1990 - 2010

Pourquoi utiliser les nouvelles classes
d'antihypertenseurs ?

Essais PROBE

Meta-analyses, Meta-régressions

Essais de morbi-mortalité avec des antihypertenseurs

Caractéristiques des populations

Prévention Primaire

HDFP
ABPT
MRC
SHEP
EWPHE
CAPPP
SCOPE
STOP
ALLHAT
JIKEI
HYVET

Traitement
de l'HTA
Prévention CV

Diabète, Néphropathie,
HVG, **haut risque CV**

IDNT
RENAAL
LIFE
VALUE
ASCOT
ACCOMPLISH

**Atteinte des
organes cibles**

Traitement
De l'HTA
Prévention CV

Prévention Secondaire

HOPE
PEACE
VALIANT
EUROPA
INVEST
PROGRESS
PROFESS
ONTARGET
TRANSCEND

Prévention CV

Clinical trials of antihypertensive therapy

ACEI, CCB, ARB vs. active

- Trials in patients with high CV risk
 - Secondary prevention after CHD
 - HOPE, INVEST, EUROPA, ACTION, PEACE, ONTARGET, TRANSCEND
 - Secondary prevention after stroke
 - PROGRESS, PROFESS
 - Diabetic nephropathy
 - RENAAL, IDNT, BENEDICT
 - Primary prevention in high CV risk
 - VALUE, LIFE, ASCOT
 - Diabetic type 2
 - DIAB-HYCAR, ADVANCE, ACCORD

2000

La méta-analyse des *trialists* affirme que les bénéfices des antihypertenseurs sont liés à la baisse tensionnelle indépendamment de la famille pharmacologique utilisée.

Effects of ACE inhibitors, calcium antagonists, and other blood pressure lowering drugs: results of prospectively designed overviews of randomised trials

Blood Pressure Lowering Treatment Trialists' Collaboration Lancet 2000; 355: 1955–64*

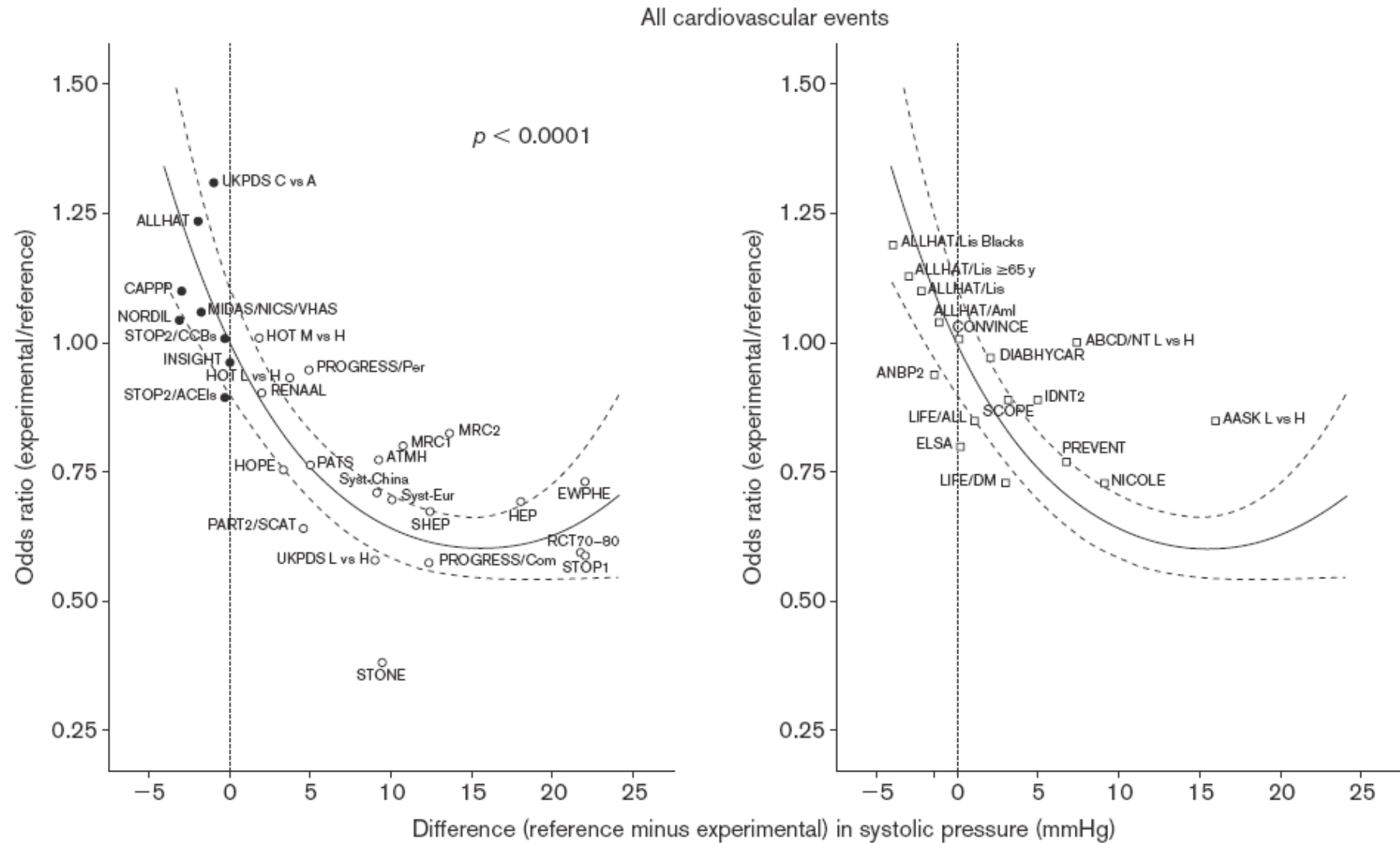
Strong evidence of benefits of ACE inhibitors and calcium antagonists is provided.

There is weaker evidence of differences between treatment regimens based on different drug classes.

2003

L'analyse en meta-régression de *Staessen* affirme que les bénéfices des antihypertenseurs sont liés à la baisse tensionnelle indépendamment de la famille pharmacologique utilisée.

Cardiovascular protection and blood pressure reduction: a meta-analysis



Cardiovascular prevention and blood pressure reduction: a quantitative overview updated until 1 March 2003

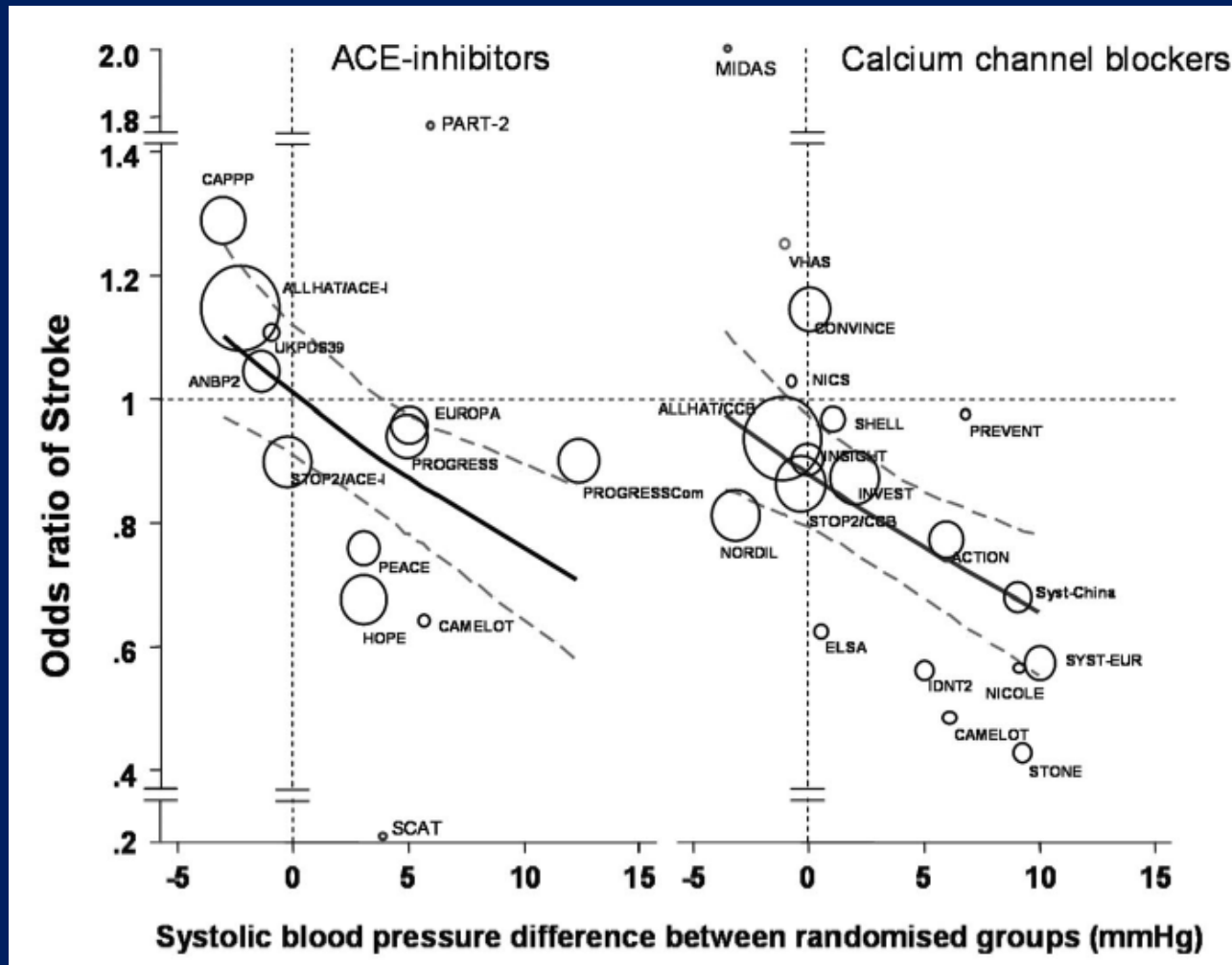
*Jan A. Staessen, Ji-Guang Wang and Lutgarde Thijs
J Hypertens 2003 21:1055–1076*

The hypothesis that new antihypertensive drugs, such as calcium-channel blockers, A-blockers, ACE inhibitors or AR1 blockers might influence cardiovascular prognosis over and beyond their antihypertensive effect remains unproven.

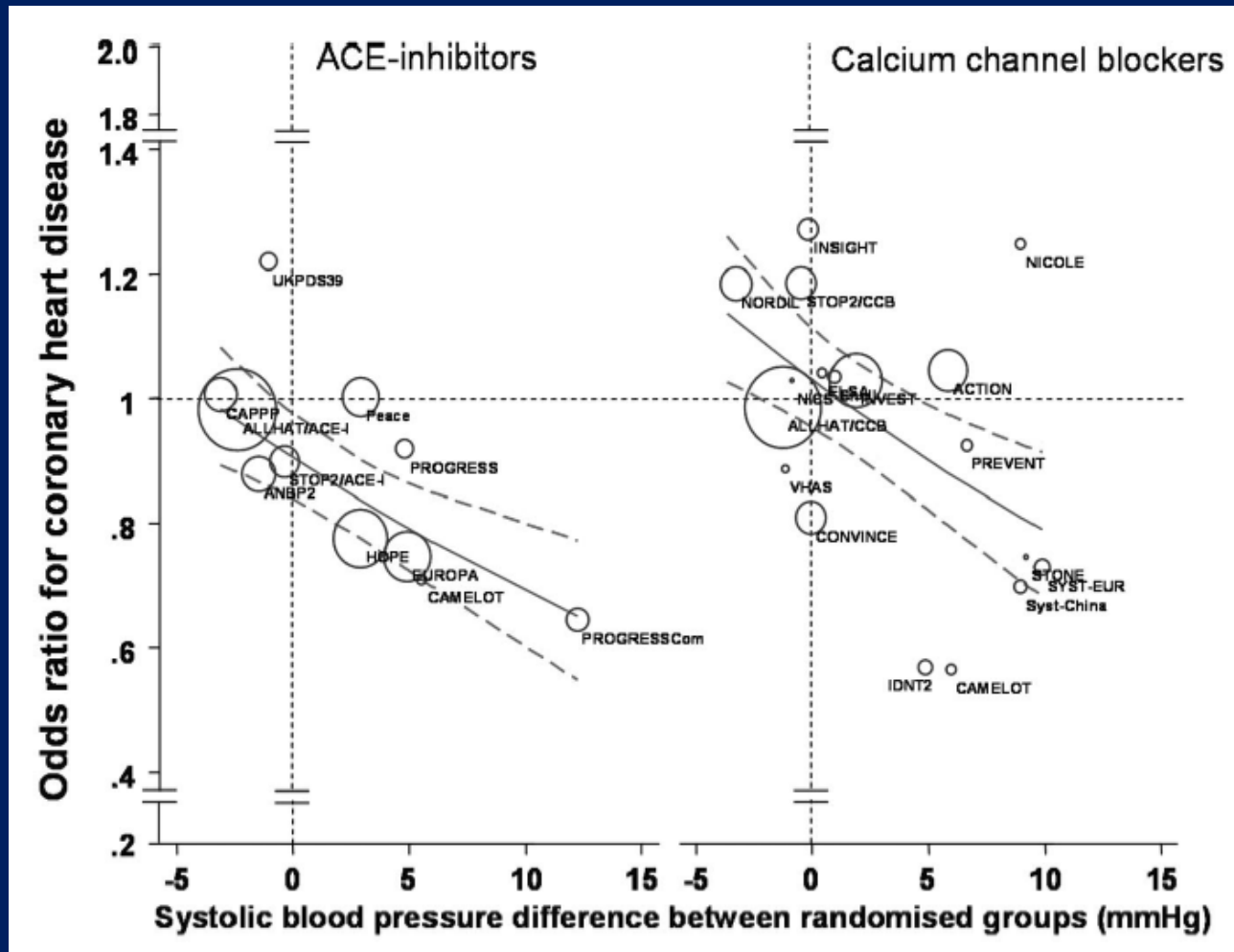
2005

L'analyse en méta-régression de *Verdecchia* affirme qu'il existe un bénéfice de prévention « au-delà de la baisse tensionnelle » pour les antagonistes calciques (Stroke) et pour les IEC (CHD).

Prevention of Stroke with ACEI or CCA



Prevention of CHD with ACEI or CCA

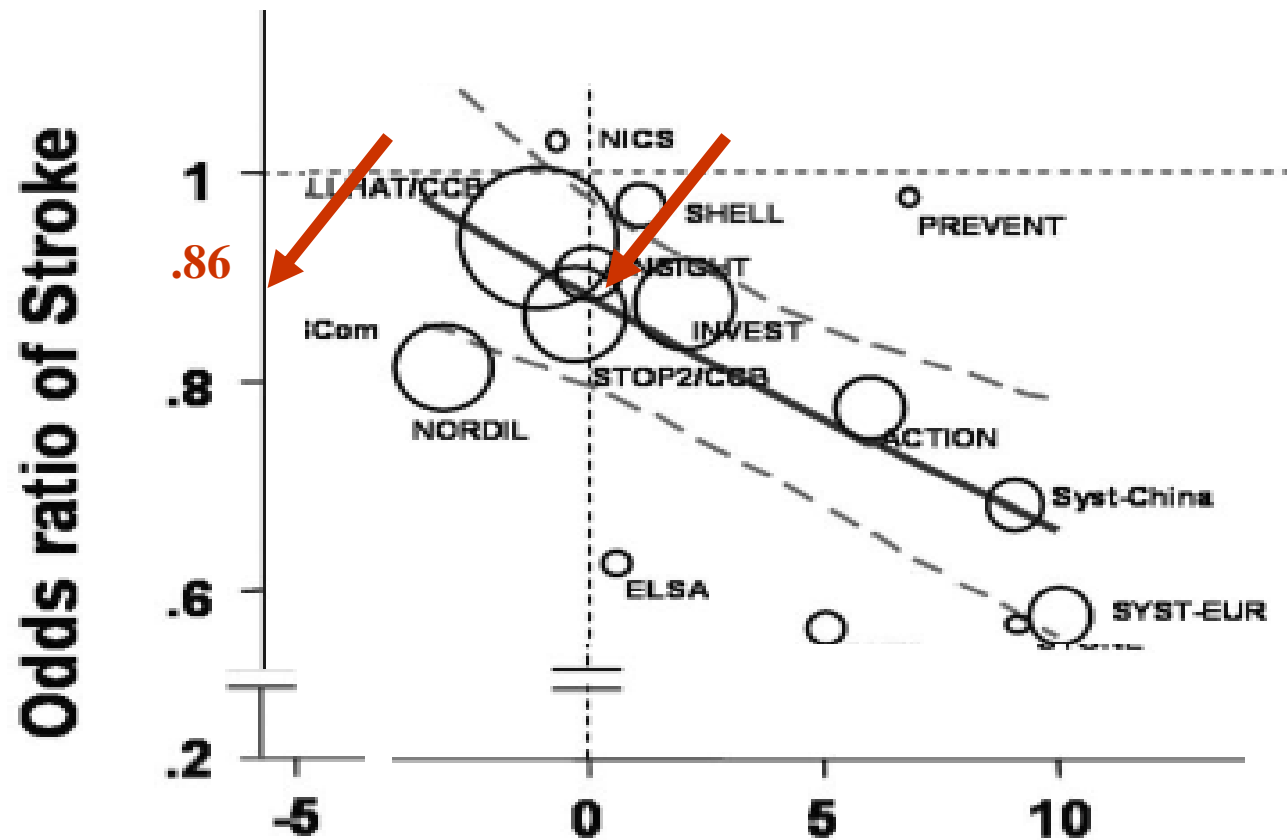


Angiotensin-Converting Enzyme Inhibitors and Calcium Channel Blockers for Coronary Heart Disease and Stroke Prevention

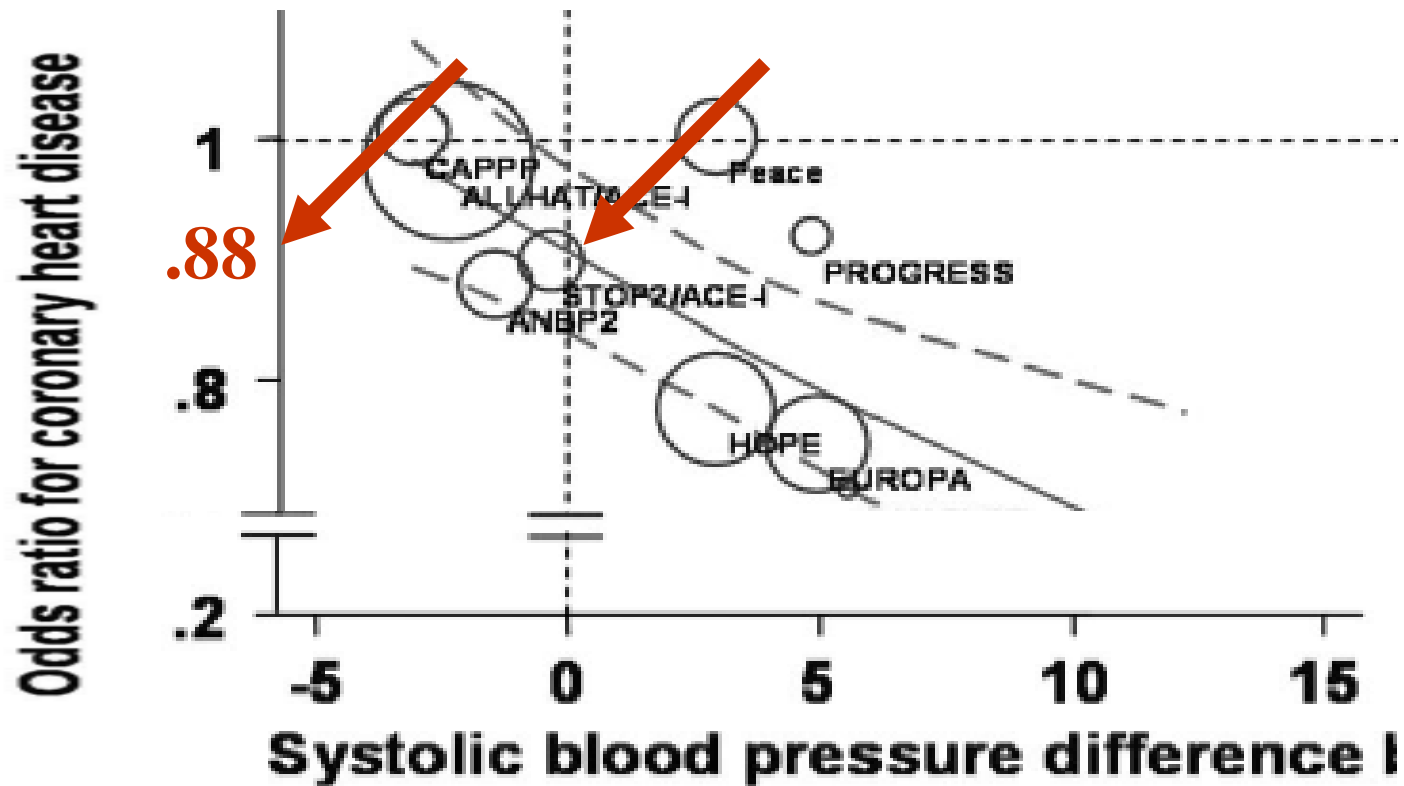
For 10 mmHg decrease in systolic BP in hypertensives treated with ACEIs or CCBs

- 25 % in stroke incidence
- 25 % in coronary heart disease incidence

Prevention of Stroke with CCA



Prevention of CHD with ACEI



Angiotensin-Converting Enzyme Inhibitors and Calcium Channel Blockers for Coronary Heart Disease and Stroke Prevention

Paolo Verdecchia, Gianpaolo Reboldi, Fabio Angeli, Roberto Gattobigio, Maurizio Bentivoglio, Lutgarde Thijs, Jan A. Staessen, Carlo Porcellati

(Hypertension. 2005;46:386-392.)

BP lowering is fundamental for prevention of CHD and stroke.

However, over and beyond BP reduction, ACEIs appear superior to CCBs for prevention of CHD, whereas CCBs appear superior to ACEIs for prevention of stroke.

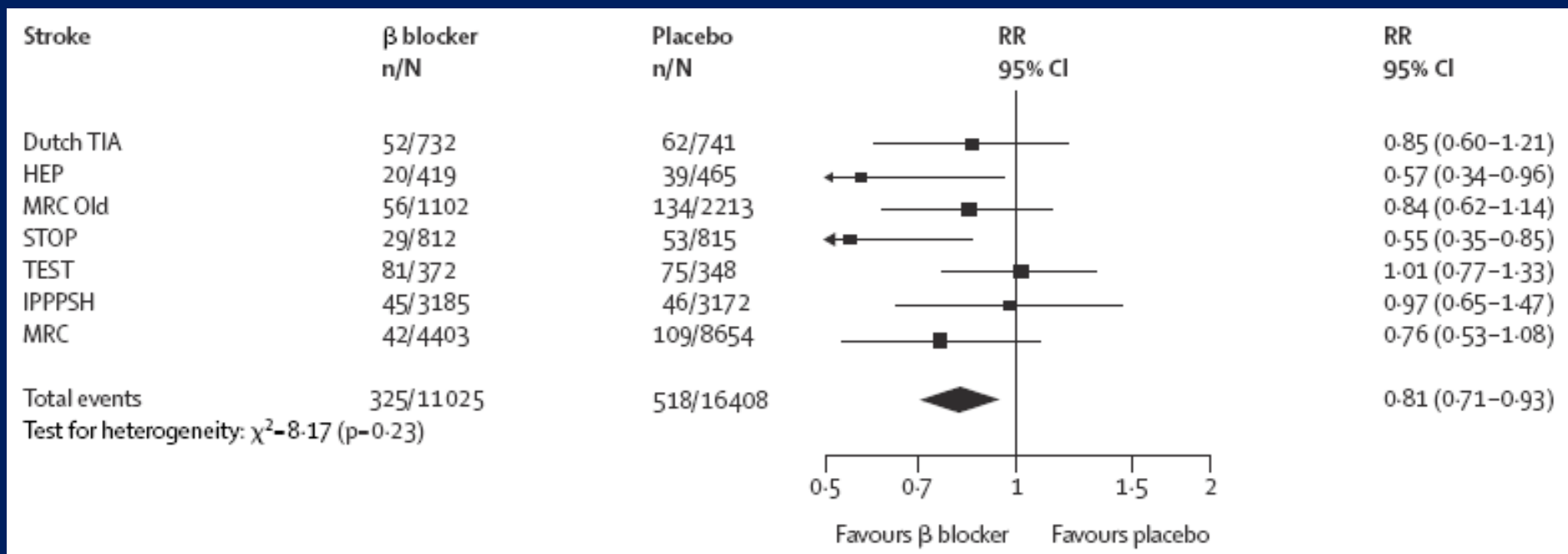
2005

La méta-analyse de *Lindholm* indique que dans le traitement de l'HTA, les bêta-bloquants, sont inférieurs aux autres antihypertenseurs pour la prévention des AVC.

Should β blockers remain first choice in the treatment of primary hypertension? A meta-analysis

Stroke

All Beta blockers vs. Placebo or no treatment

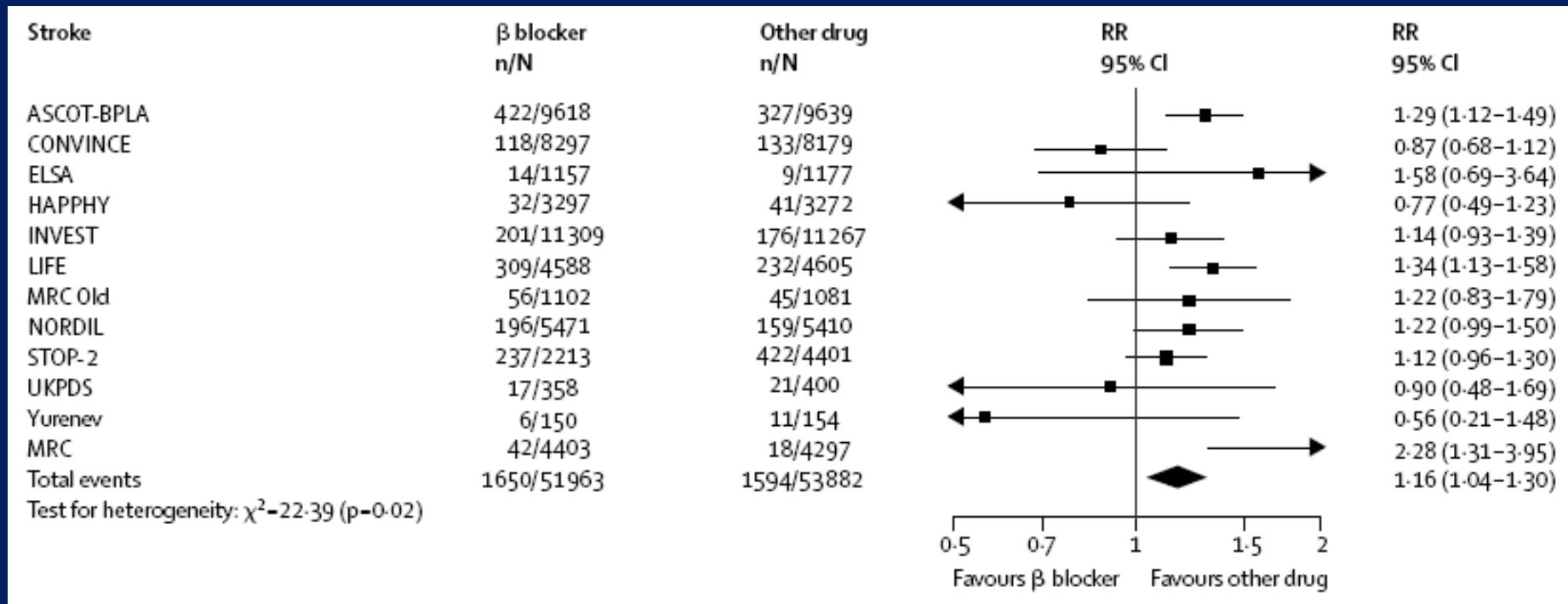


Lancet 2005;366:1545-53

Should β blockers remain first choice in the treatment of primary hypertension? A meta-analysis

Stroke

All Beta blockers vs. Other antihypertensive treatment



Lancet 2005;366:1545-53

Should β blockers remain first choice in the treatment of primary hypertension? A meta-analysis

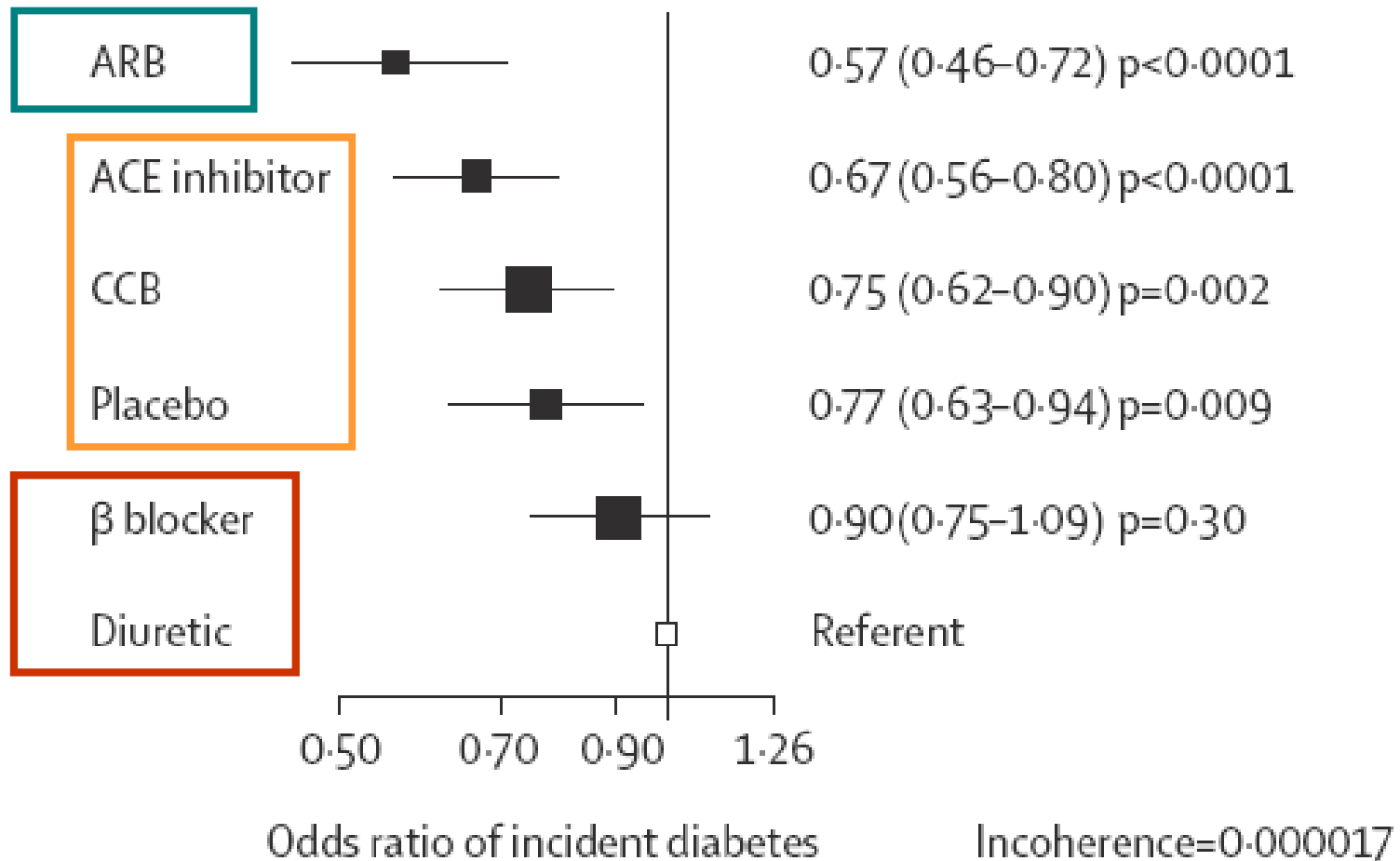
Lancet 2005;366:1545-53

Interpretation: In comparison with other antihypertensive drugs, the effect of β blockers is less than optimum, with a raised risk of stroke. Hence, we believe that β blockers should not remain first choice in the treatment of primary hypertension and should not be used as reference drugs in future randomised controlled trials of hypertension.

2007

La network meta-analysis de *Elliott* indique une augmentation de l'incidence du diabète chez l'hypertendu traité par bêta-bloquant et/ou diurétique thiazidique.

Incident diabetes in clinical trials of antihypertensive drugs: a network meta-analysis



Incident diabetes in clinical trials of antihypertensive drugs: a network meta-analysis

William J Elliott, Peter M Meyer

The association of antihypertensive drugs with incident diabetes is lowest for ARB and ACE inhibitors followed by CCB and placebo, β blockers and diuretics in rank order.

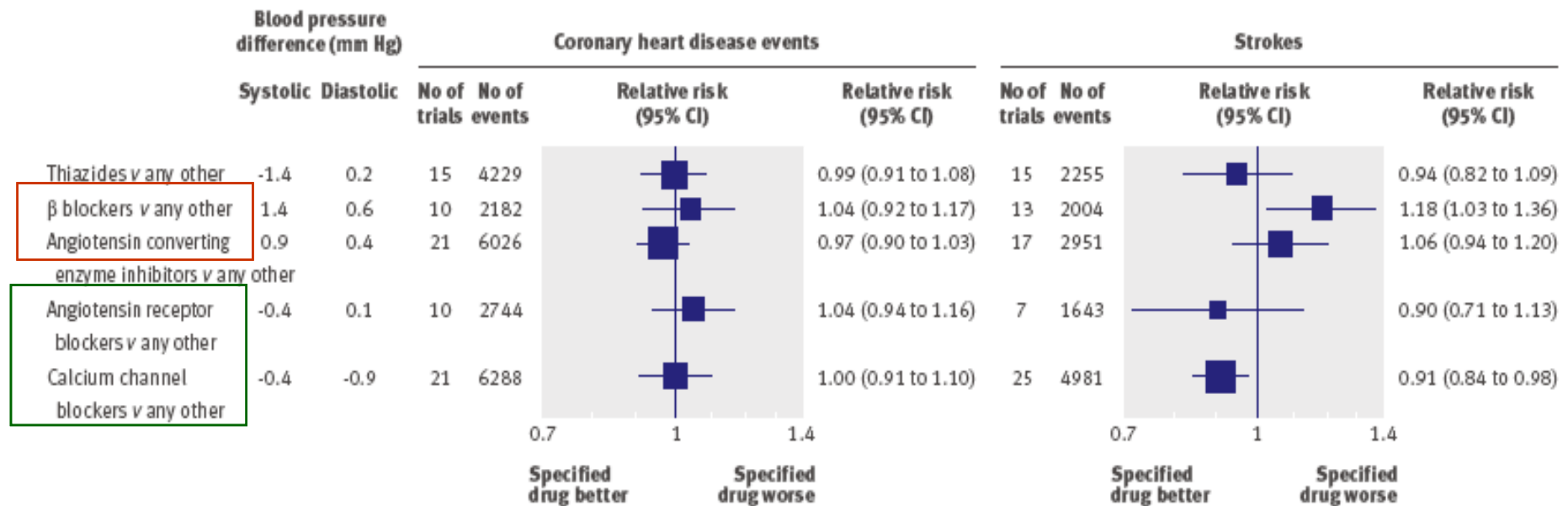
Lancet 2007; 369: 201–07

2009

La méta-analyse de *Law* confirme que, pour la prévention des AVC les bêta-bloquants, sont inférieurs aux antagonistes calciques et aux AA2.

Méta-analyse de 147 essais randomisés dans la prévention des maladies cardiovasculaires

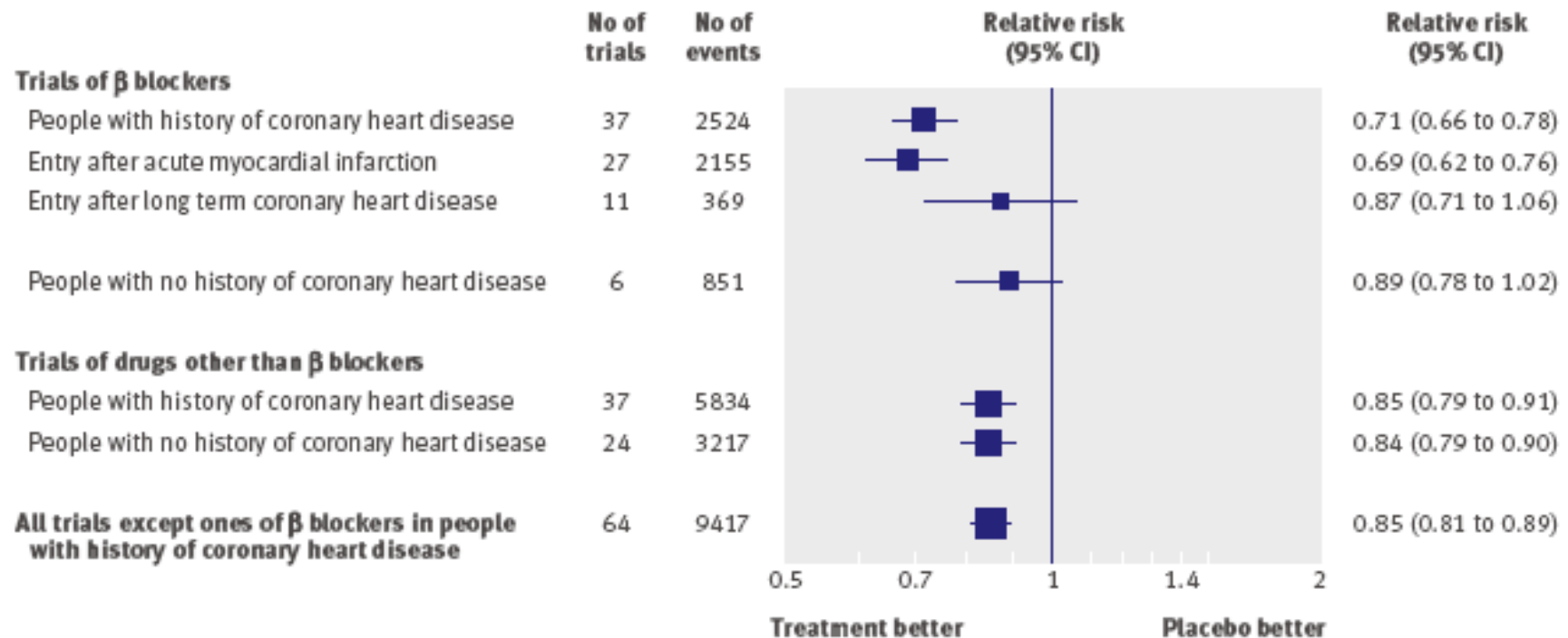
Bénéfices comparés des traitements



Les antagonistes calciques ou les AA2 sont plus efficaces que les Bêtabloquant ou les IEC pour la prévention des AVC.

Toutes les familles sont équivalentes pour la prévention de la maladie coronaire.

Prospective meta-analysis of 147 randomised trials in the prevention of cardiovascular disease



2008

La méta-analyse de *Reboldi* suggère
que pour la prévention des AVC les
AA2 sont supérieurs aux IEC.

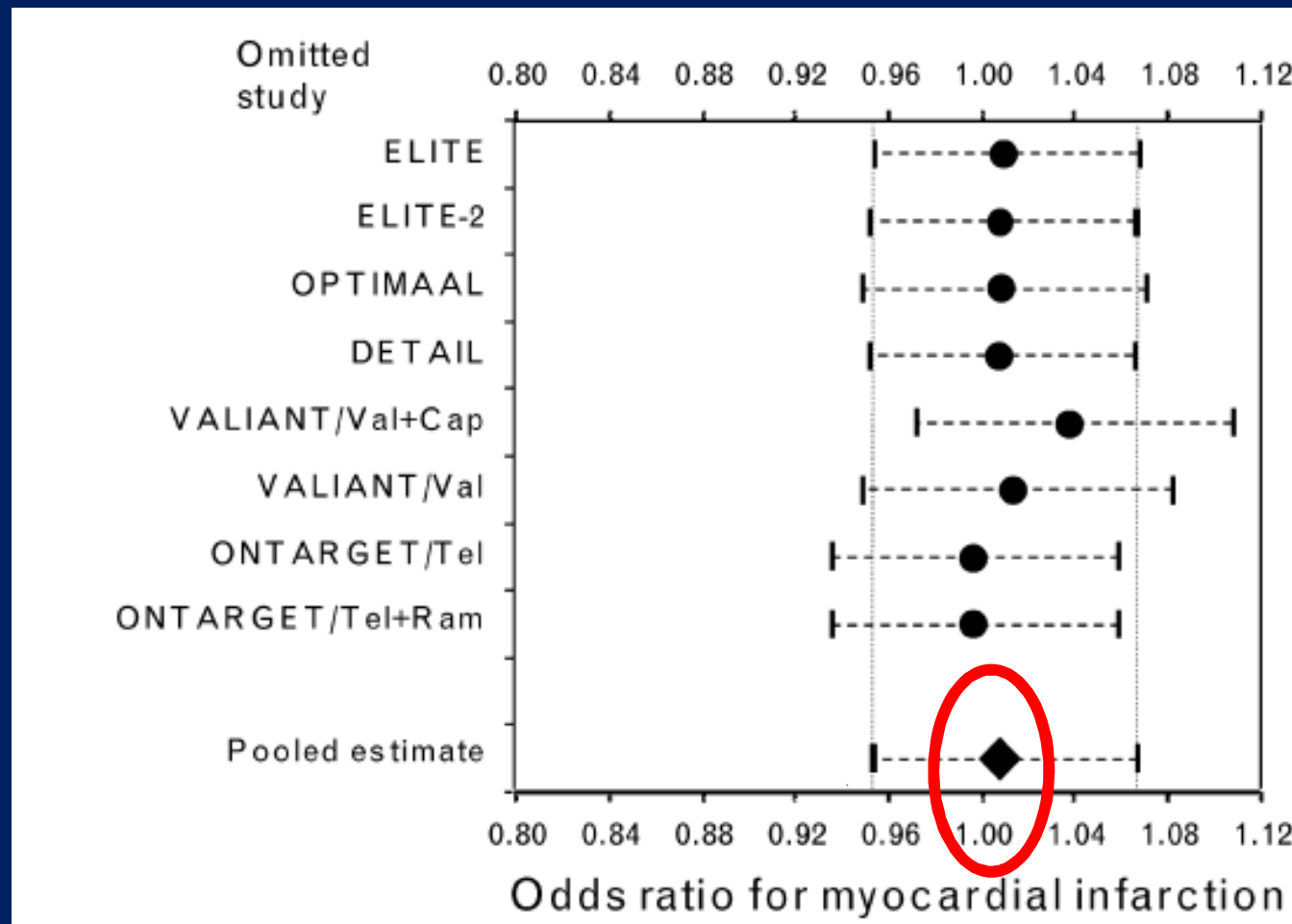
Comparison between angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on the risk of myocardial infarction, stroke and death: a meta-analysis

Gianpaolo Reboldi^a, Fabio Angeli^b, Claudio Cavallini^b, Giorgio Gentile^a, Giuseppe Mancia^c and Paolo Verdecchia^b

J Hypertens 2008;26:1282–1289

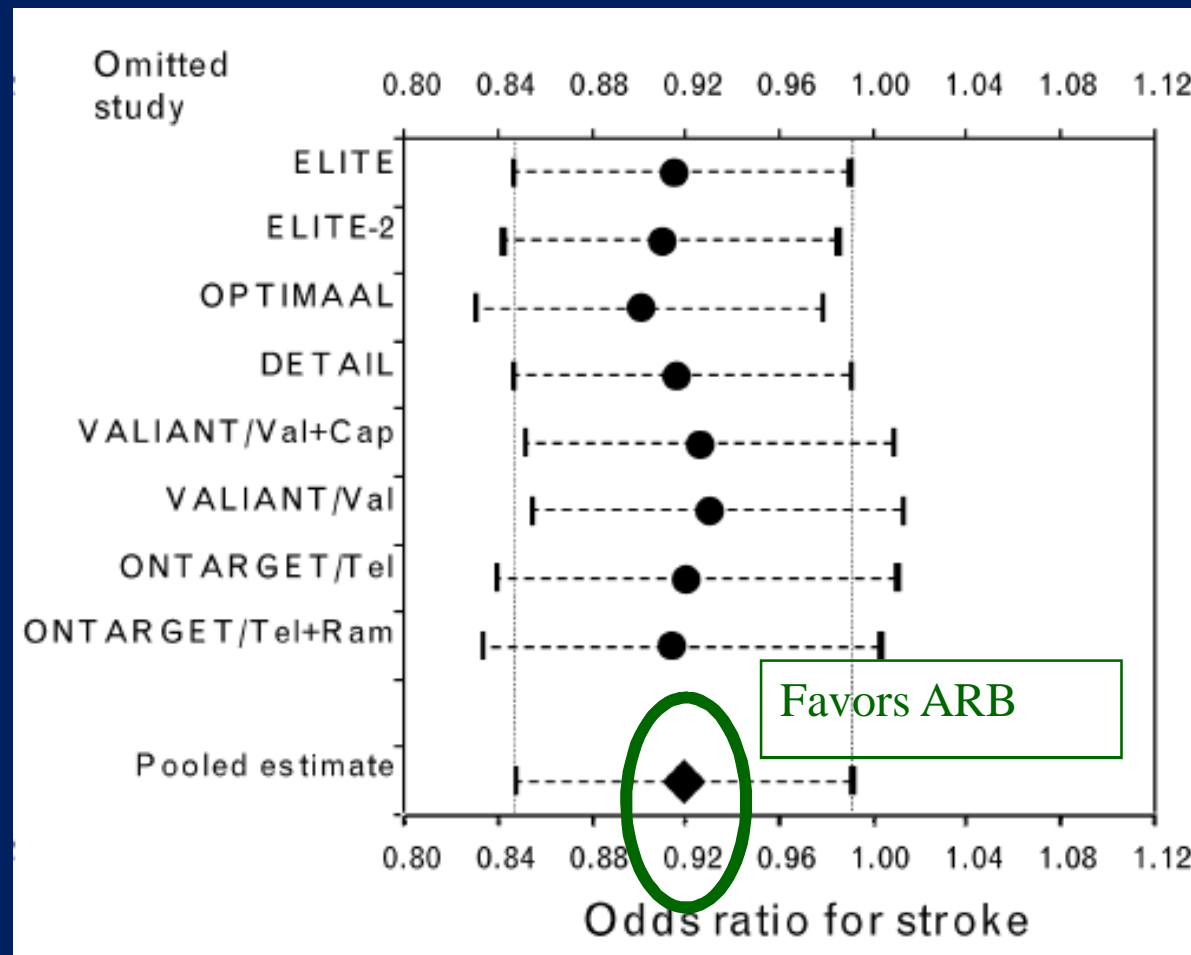
Study	ARB	ACEI	Publication year
ELITE [6]	Losartan	Captopril	1997
ELITE-II [7]	Losartan	Captopril	2000
OPTIMAAL [8]	Losartan	Captopril	2002
VALIANT/Val [9,28]	Valsartan	Captopril	2003, 2006
VALIANT/Val + Cap [9,28]	Valsartan	Captopril	2003, 2006
DETAIL [10]	Telmisartan	Enalapril	2004
ONTARGET/Tel [26]	Telmisartan	Ramipril	2008
ONTARGET/Tel + Ram [26]	Telmisartan	Ramipril	2008

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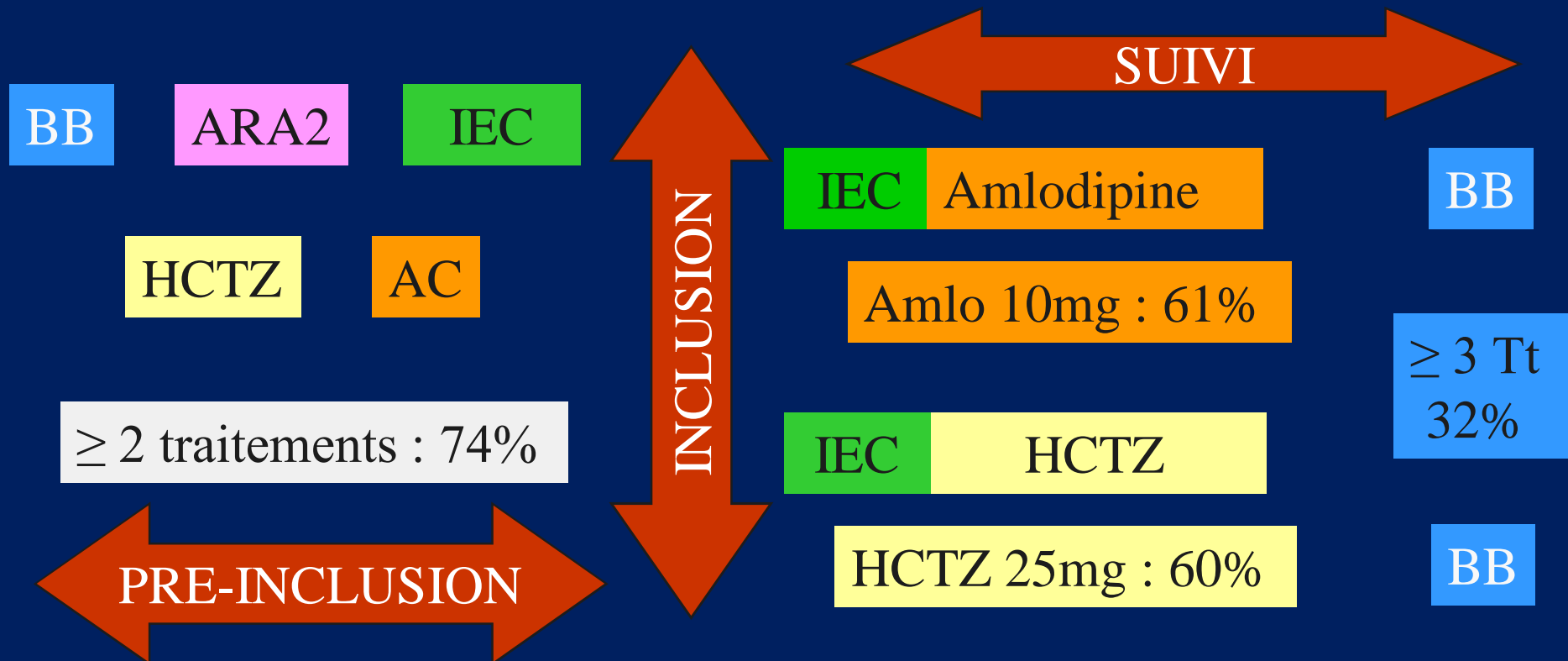
J Hypertens 2008;26:1282–1289

This overview suggests that angiotensin II receptor blockers are as effective as angiotensin-converting enzyme inhibitors on the risk of myocardial infarction, cardiovascular mortality and total mortality. Angiotensin II receptor blockers may be slightly more protective than angiotensin-converting enzyme inhibitors on the risk of stroke.

2008

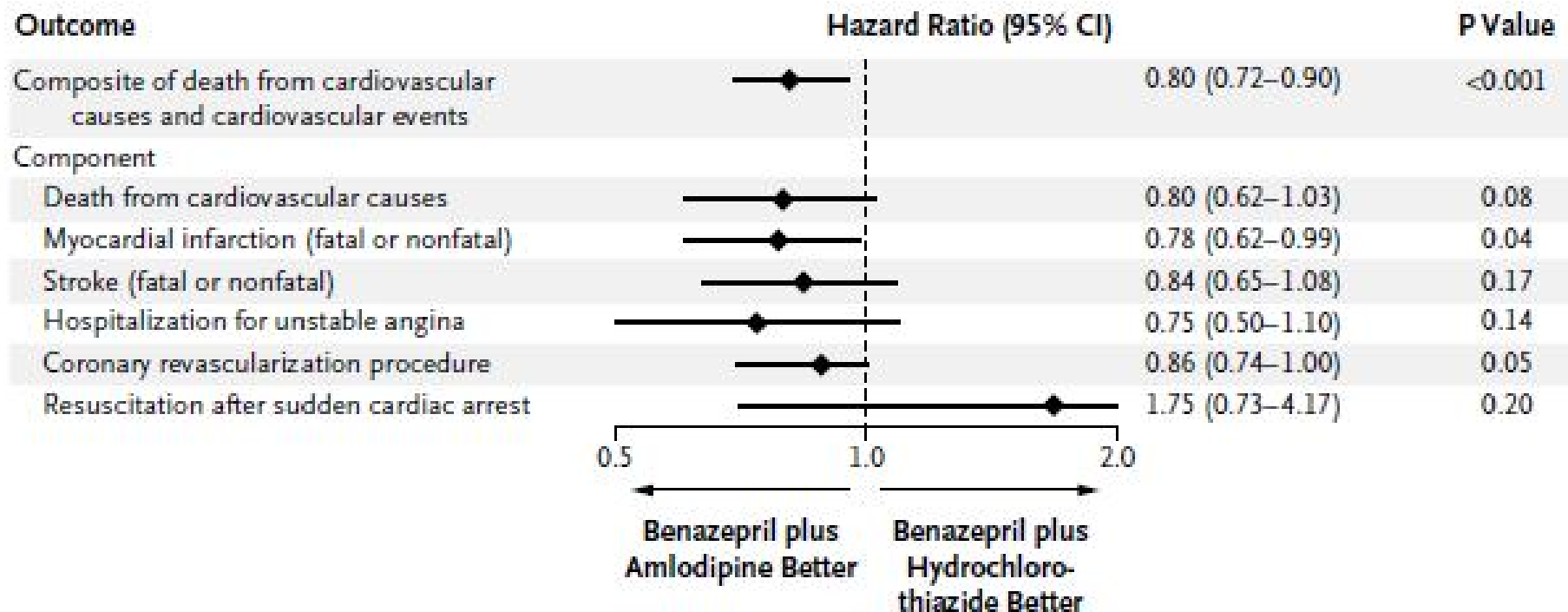
L'étude ACCOMPLISH indique une action préventive plus importante de l'amlodipine Vs. HCTZ en association à un IEC.

Stratégie d'utilisation des traitements antihypertenseurs dans ACCOMPLISH

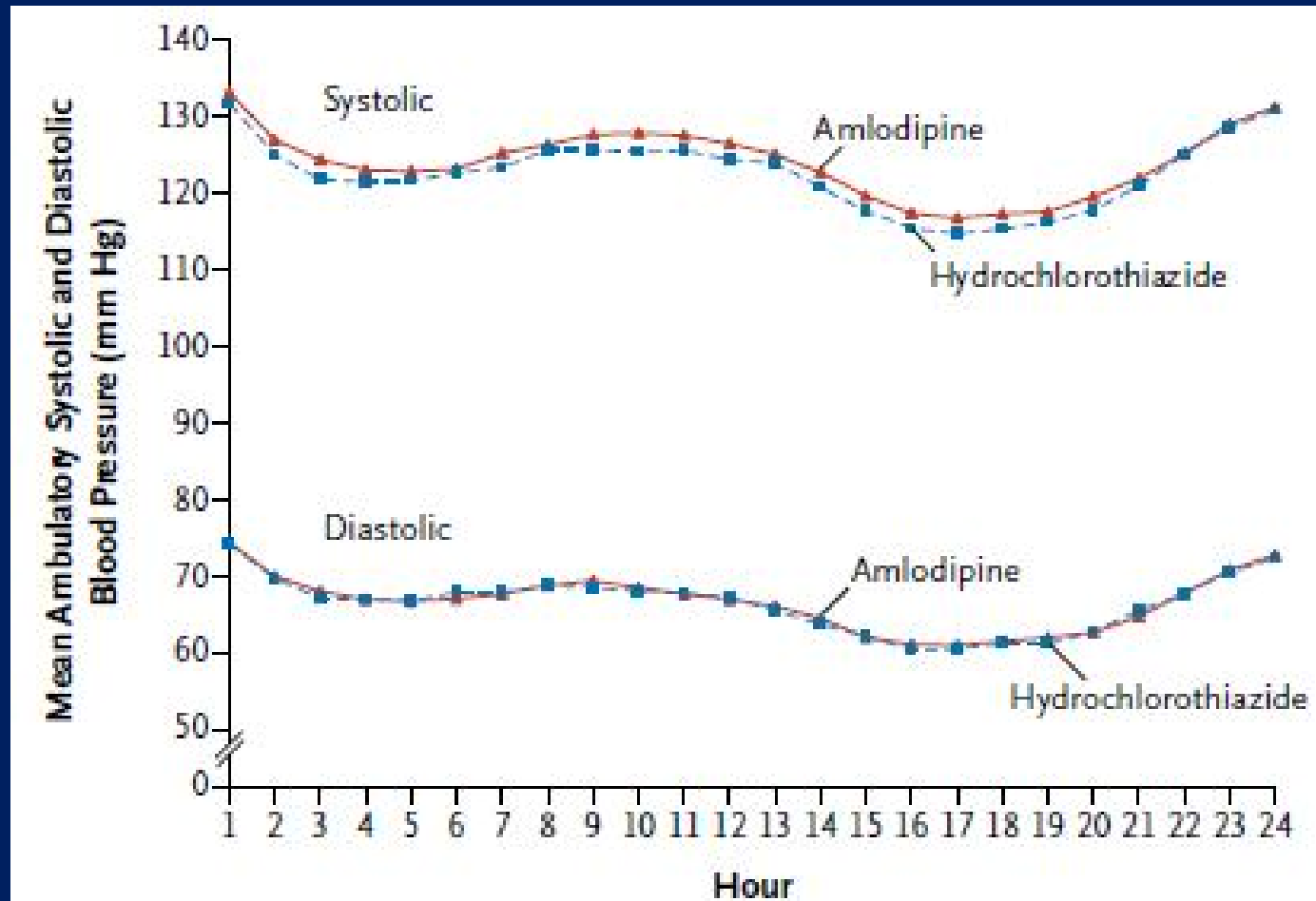


Benazepril plus Amlodipine or Hydrochlorothiazide for Hypertension in High-Risk Patients

Kenneth Jamerson,, Michael A. Weber,, George L. Bakris,



24-Hour Ambulatory Blood Pressure in the ACCOMPLISH Trial



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

Kenneth Jamerson,, Michael A. Weber,, George L. Bakris,

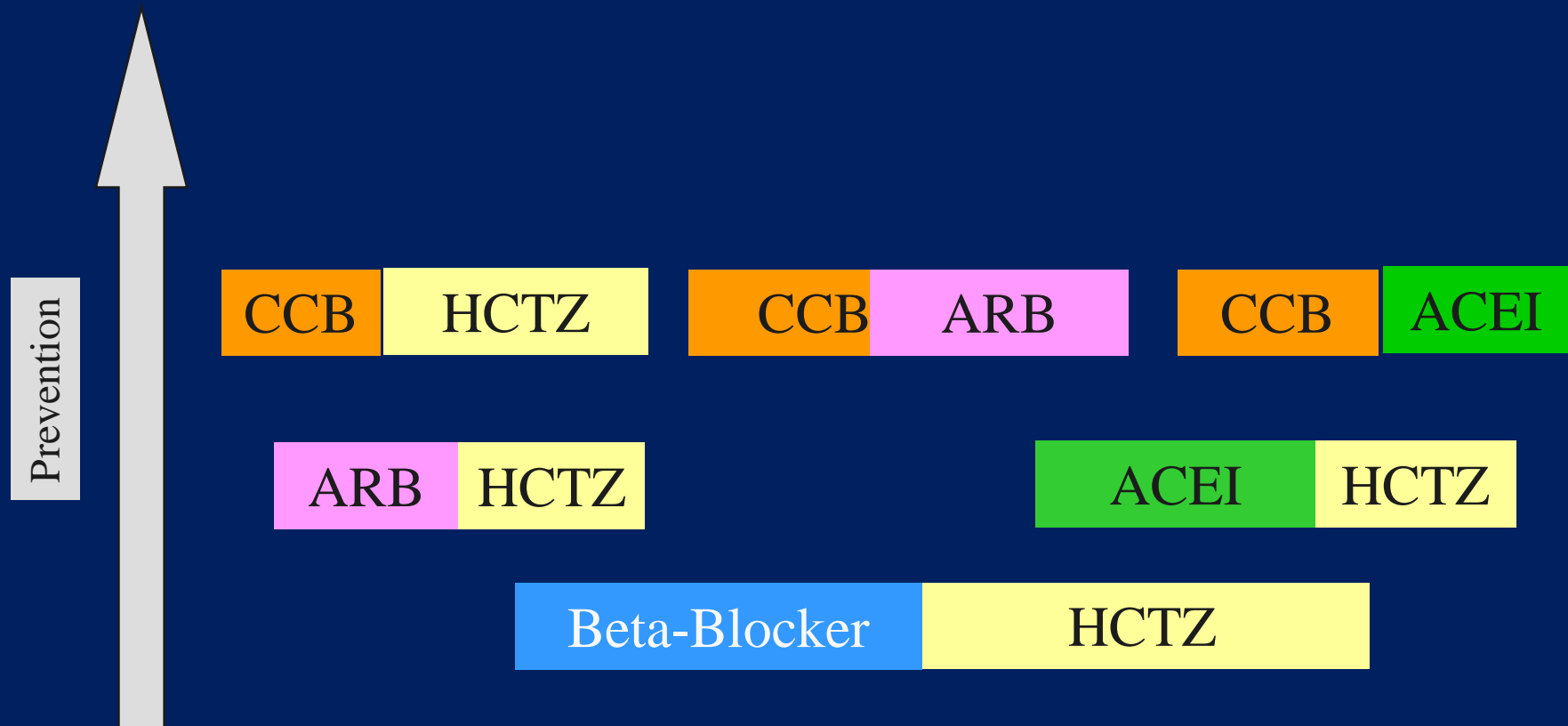
The benazepril–amlodipine combination was superior to the benazepril–hydrochlorothiazide combination in reducing cardiovascular events in patients with hypertension who were at high risk for such events.

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

2009

A partir de l'analyse de la littérature
l'ESH recommande, pour associer les
antihypertenseurs,
un IEC ou un ARA2
avec un diurétique thiazidique ou un
antagoniste calcique.

Cardiovascular prevention in subjects treated with combined antihypertensive therapy



Le choix d'une bithérapie en 2010

Selon l'ESH



Journal of Hypertension 2009, 27:2121-2158

2010

L'essai ACCORD indique que chez l'hypertendu diabétique, une PAS sous traitement < 140 mmHg, apporte une prévention des complications cardiovasculaires comparable à celle d'une PAS sous traitement < 120 mmHg.

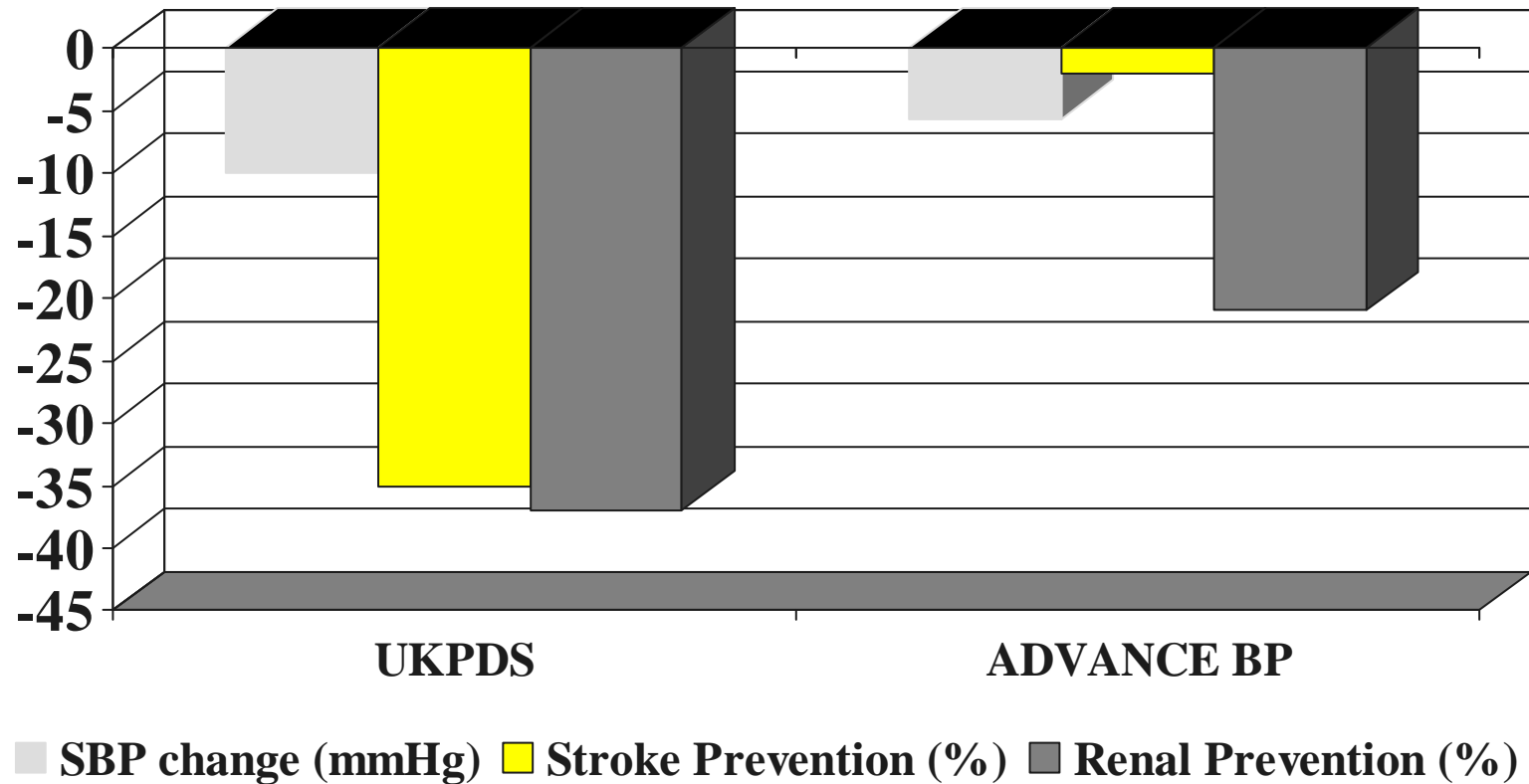
Macrovascular and microvascular complications in diabetes

Effect of blood pressure reduction

BP at inclusion

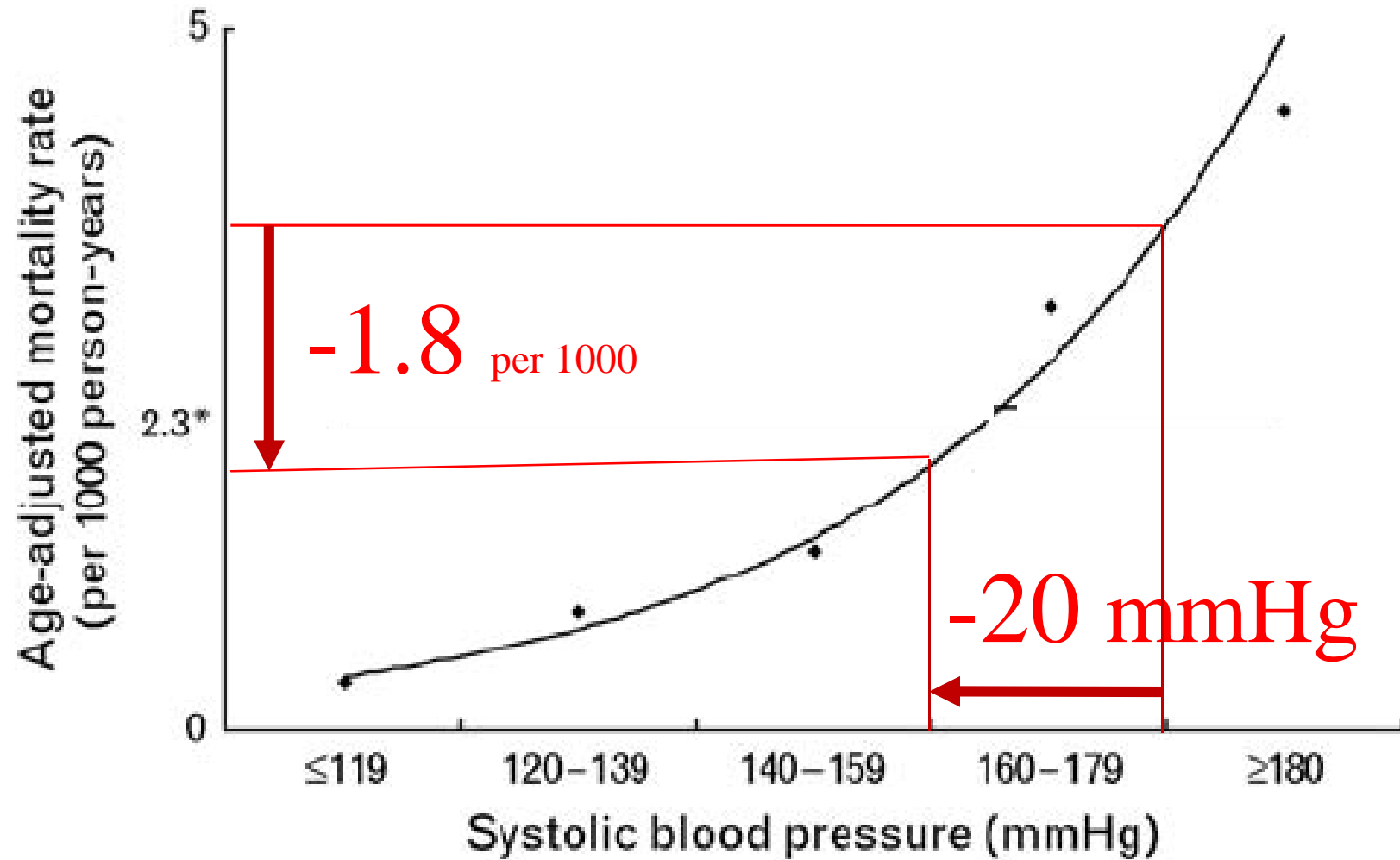
UKPDS 160/94

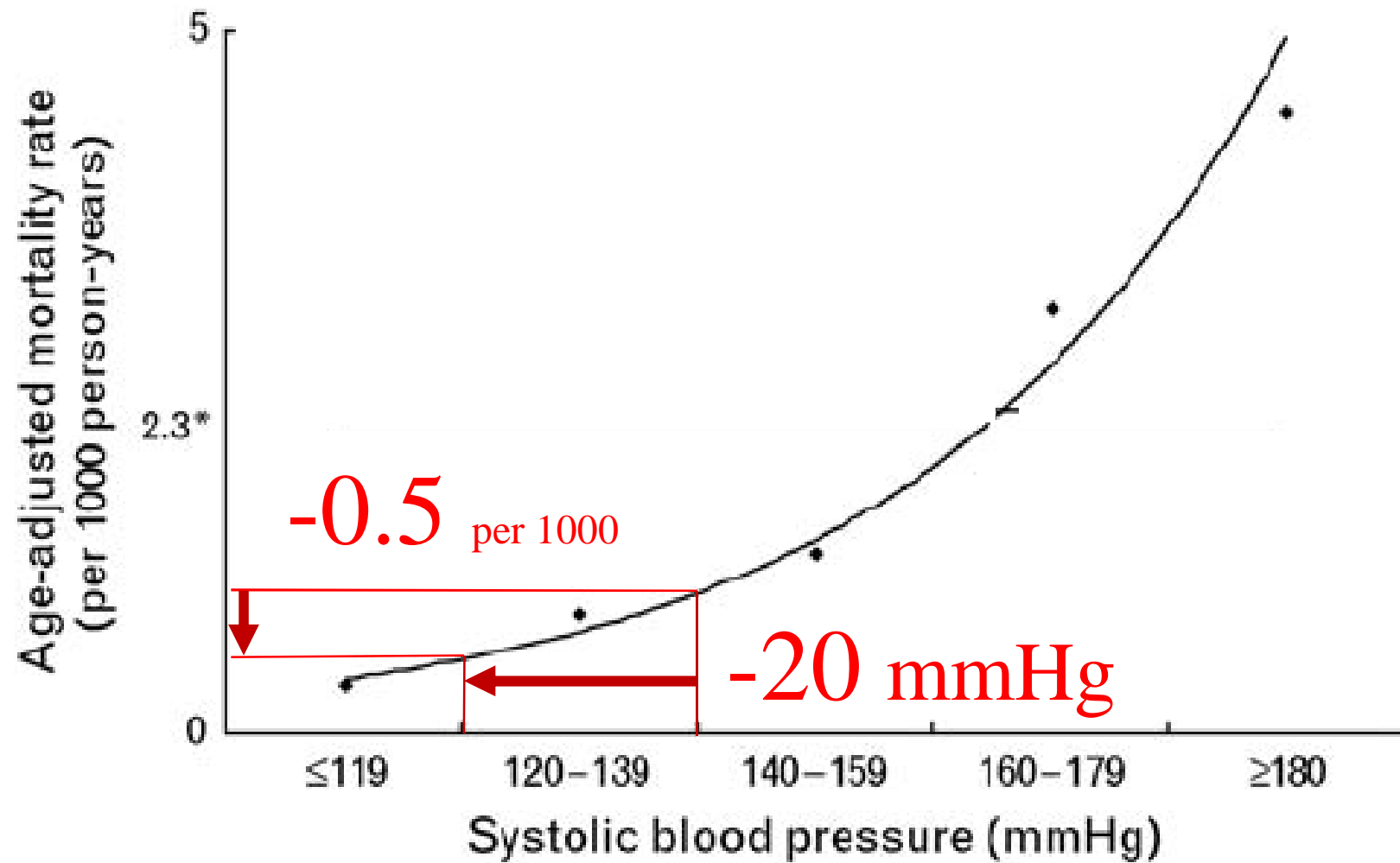
ADVANCE 145/81



UKPDS *BMJ* 2000;321:412-9

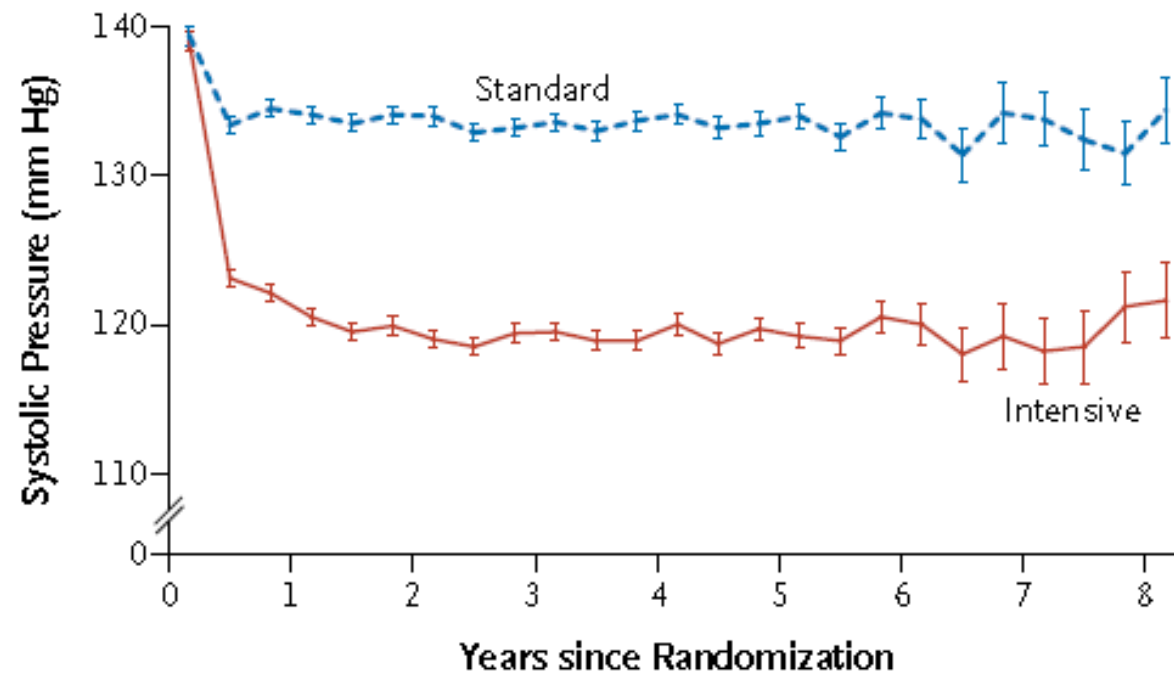
ADVANCE BP *Lancet* 2007; 370: 829-40.





Effects of Intensive Blood-Pressure Control in Type 2 Diabetes Mellitus

The ACCORD Study Group*



Mean No. of Medications Prescribed

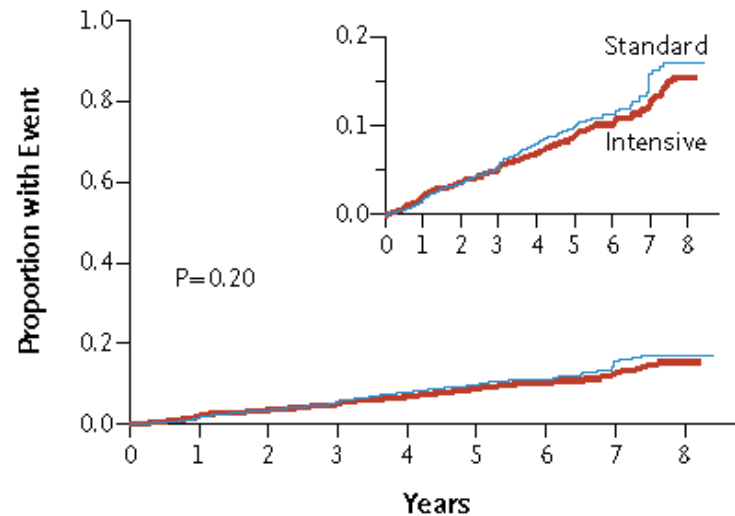
Intensive	3.2	3.4	3.4	3.5	3.5	3.5	3.4	3.4
Standard	1.9	2.1	2.1	2.2	2.2	2.3	2.3	2.3

published on March 14, 2010, at NEJM.org.

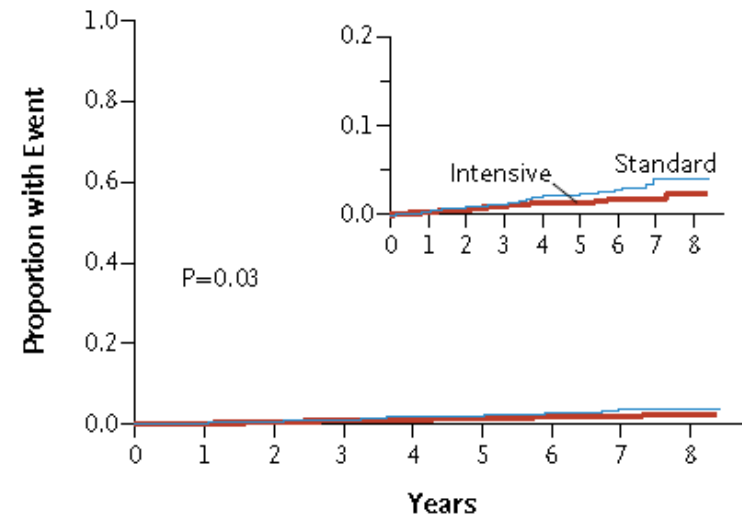
Effects of Intensive Blood-Pressure Control in Type 2 Diabetes Mellitus

The ACCORD Study Group*

A Primary Outcome



B Nonfatal Stroke

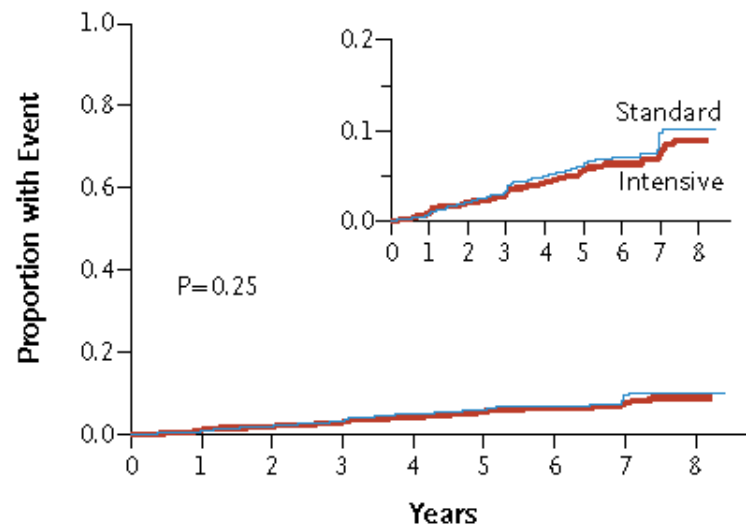


published on March 14, 2010, at NEJM.org.

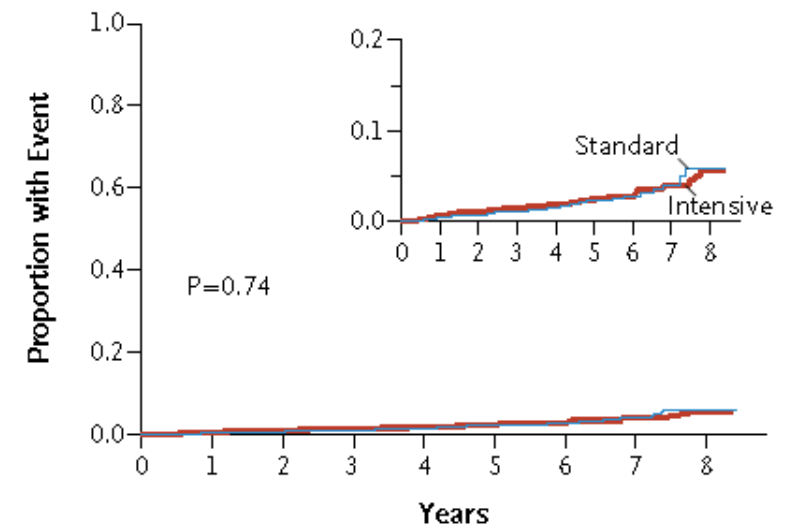
Effects of Intensive Blood-Pressure Control in Type 2 Diabetes Mellitus

The ACCORD Study Group*

C Nonfatal Myocardial Infarction



D Death from Cardiovascular Disease



published on March 14, 2010, at NEJM.org.

Effects of Intensive Blood-Pressure Control in Type 2 Diabetes Mellitus

The ACCORD Study Group*

In conclusion, the ACCORD BP trial evaluated the effect of targeting a systolic blood pressure of 120 mm Hg, as compared with a goal of 140 mm Hg, among patients with type 2 diabetes at high risk for cardiovascular events. The results provide no evidence that the strategy of intensive blood-pressure control reduces the rate of a composite of major cardiovascular events in such patients.

published on March 14, 2010, at NEJM.org.

2012 -2015


Les essais réalisés avec l'aliskiren pour le traitement de l'hypertension du diabétique avec néphropathie ou pour le traitement de l'hypertension du sujet âgé indiquent

Les essais thérapeutiques de morbi-mortalité en cours de réalisation avec l'aliskiren dans le traitement de l'HTA


2008 2009 2010 2011 2012 2013 2014 2015

A horizontal white arrow pointing to the right, spanning the width of the timeline from 2008 to 2015.

ALTITUDE : 8600 diabétiques de type 2 avec néphropathie,
aliskiren vs placebo + traitement conventionnel

A horizontal white bar representing the duration of the ALTITUDE trial, starting at the beginning of 2009 and ending at the end of 2012.

APPOLO : 12500 patients âgés avec PAS
entre 130 et 159 mmHg, aliskiren vs placebo

A horizontal white bar representing the duration of the APPOLO trial, starting at the beginning of 2013 and ending at the end of 2015.

Lecture critique des grands essais : de la théorie à la pratique

La baisse de la pression artérielle par des moyens pharmacologiques est efficace pour prévenir les complications cardiovasculaires des hypertendus.

Les familles pharmacologiques ont montré des propriétés préventives différentes et ne sont pas équivalentes.

Les résultats des essais de morbi-mortalité ne devraient pas être le seul critère permettant de différencier les médicaments antihypertenseurs.

« Ce que j'ai compris »

