
Symposium MENARINI


# ESC 2018: le « Brexit » des betabloquants

**Dr Salem ABDESSALEM**
TABARKA, TUNISIE

# Déclaration de conflits d'intérêts

Aucune action dans les firmes pharmaceutiques

Conférencier (sympo)

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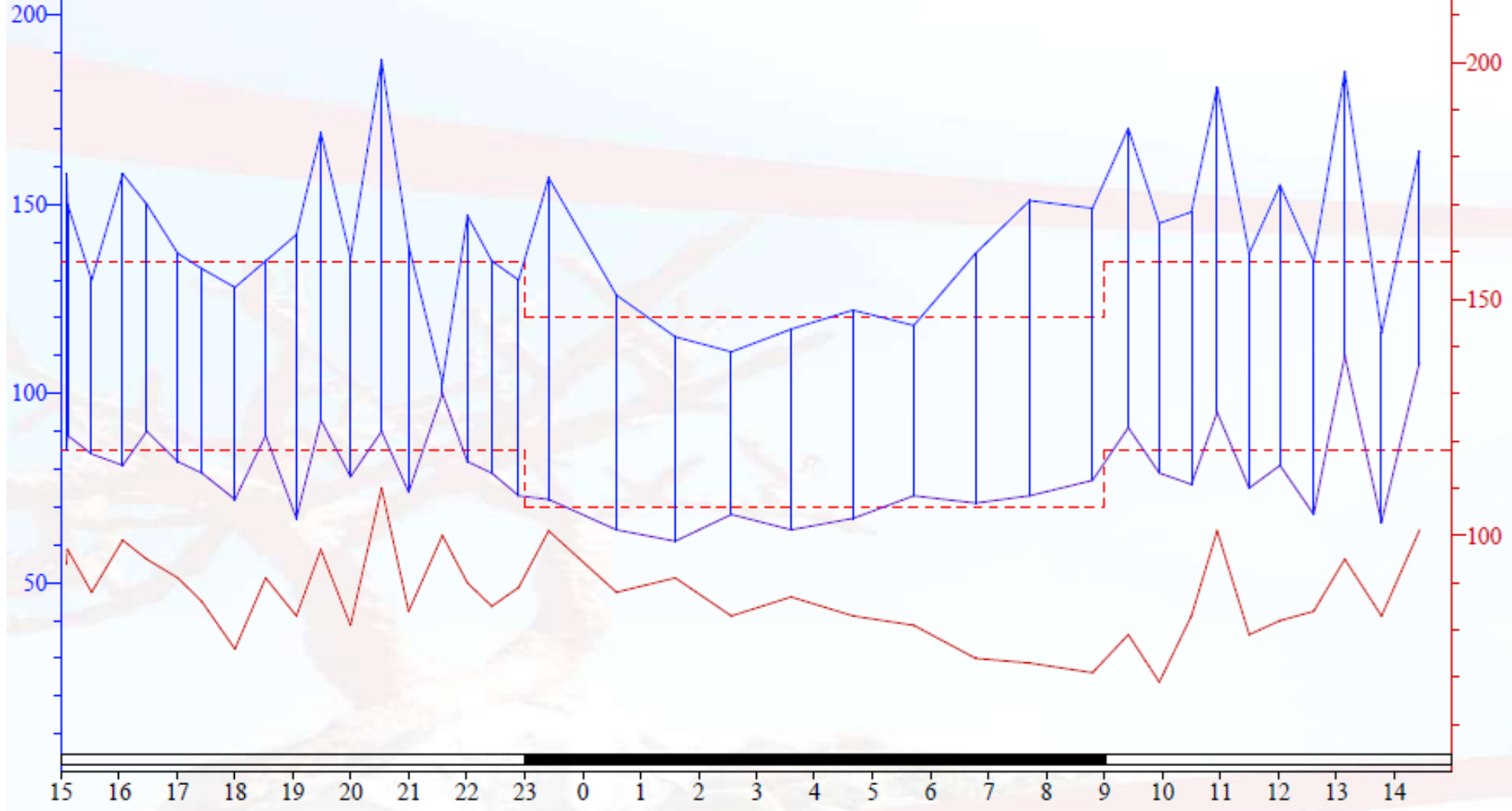
# Mr LUIGI, 46 ans

**Avocat d'affaire italien (Multinationale)**
**Résident en Tunisie, Très actif +++,**
**Obsessionnel.**
**Quelques cigarettes/j**
**Signes neurosensoriels d'HTA**
**TA= 160/100. BMI=27, TT=90**
**Rythme à 88/mn, Régulier**
**Pas de signes d'IC**
**ATCD DE sous ARA II**
**ECG Normal**




| | Tout | | | | Jour (09:00 - 23:30) | | | | Nuit (23:30 - 09:00) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Reference Value | 130/80mmHg | | | | 135/85mmHg | | | | 120/70mmHg | | | |
| | Valeur Max | Valeur Min | Valeur Moy | PP | Valeur Max | Valeur Min | Valeur Moy | PP | Valeur Max | Valeur Min | Valeur Moy | PP |
| Systole | 188 | 103 | 142 | 62.0 | 188 | 103 | 146 | 63.0 | 151 | 111 | 127 | 58.0 |
| Diastole | 110 | 61 | 79 | 62.0 | 110 | 66 | 83 | 63.0 | 77 | 61 | 68 | 58.0 |
| FC | 110 | 69 | 87 | | 110 | 69 | 89 | | 91 | 71 | 81 | |

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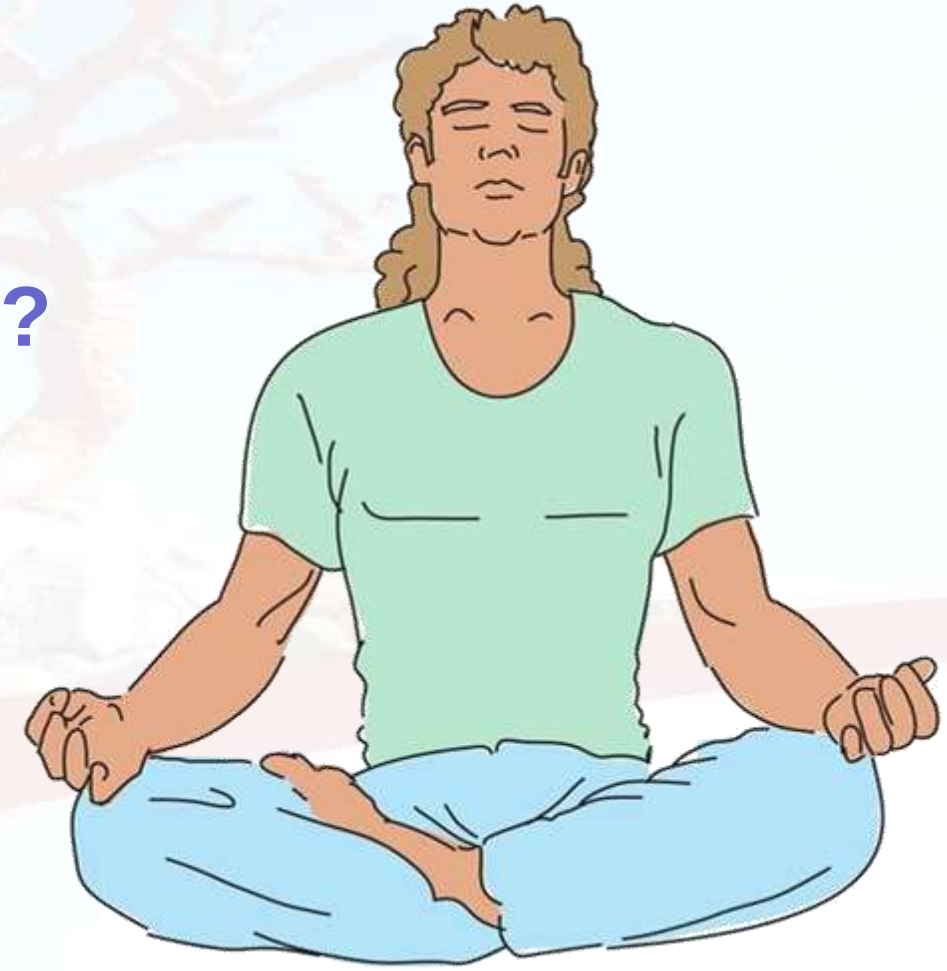
# Mr LUIGI, 54 ans

**Qui penserait à un bétabloquant en 1ère intention ?**

**Si oui lequel ?**



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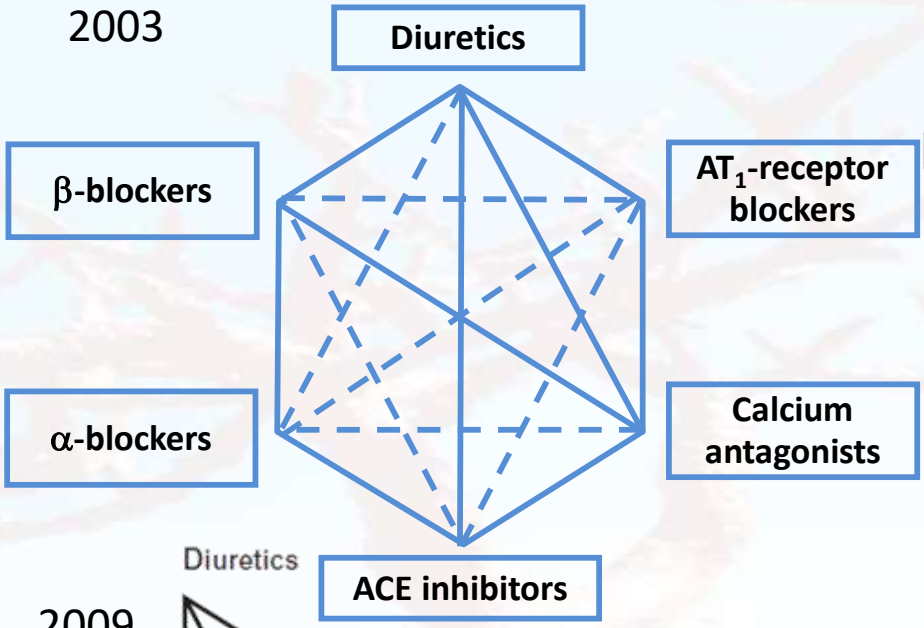
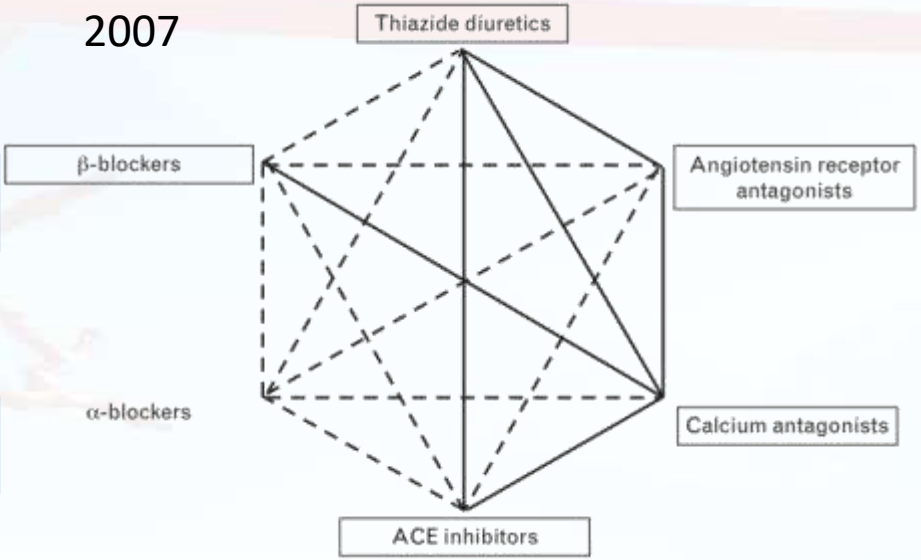
# Le Swing des Bétabloquants

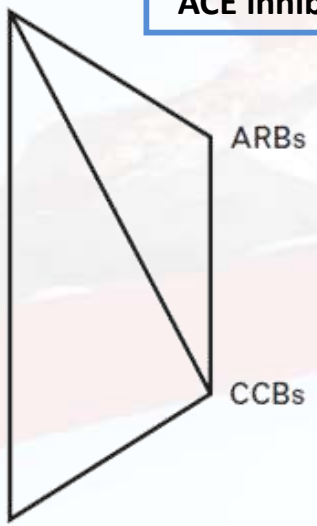
2003



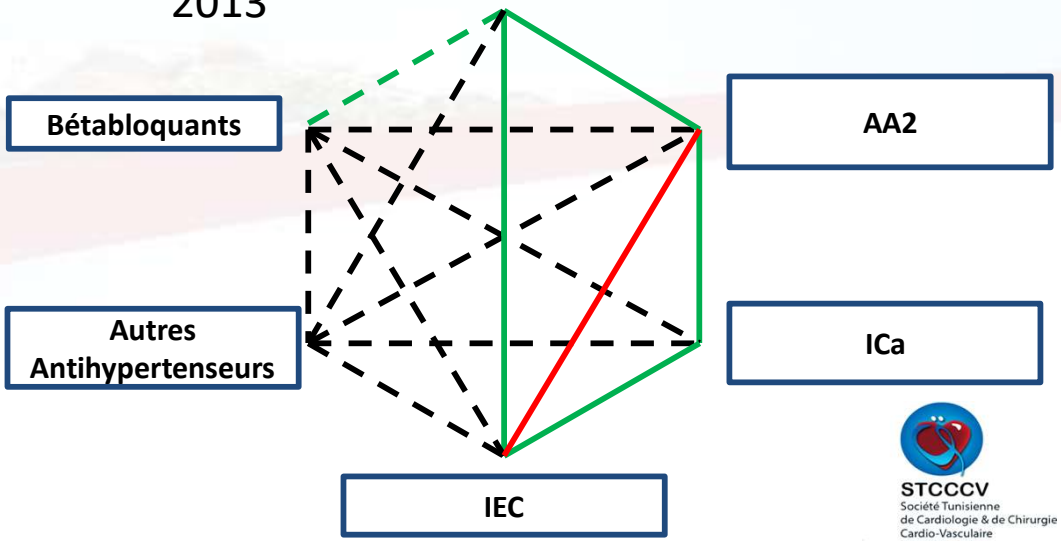

2007




2009




2013

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# 2018 ESC/ESH Guidelines for the management of arterial hypertension

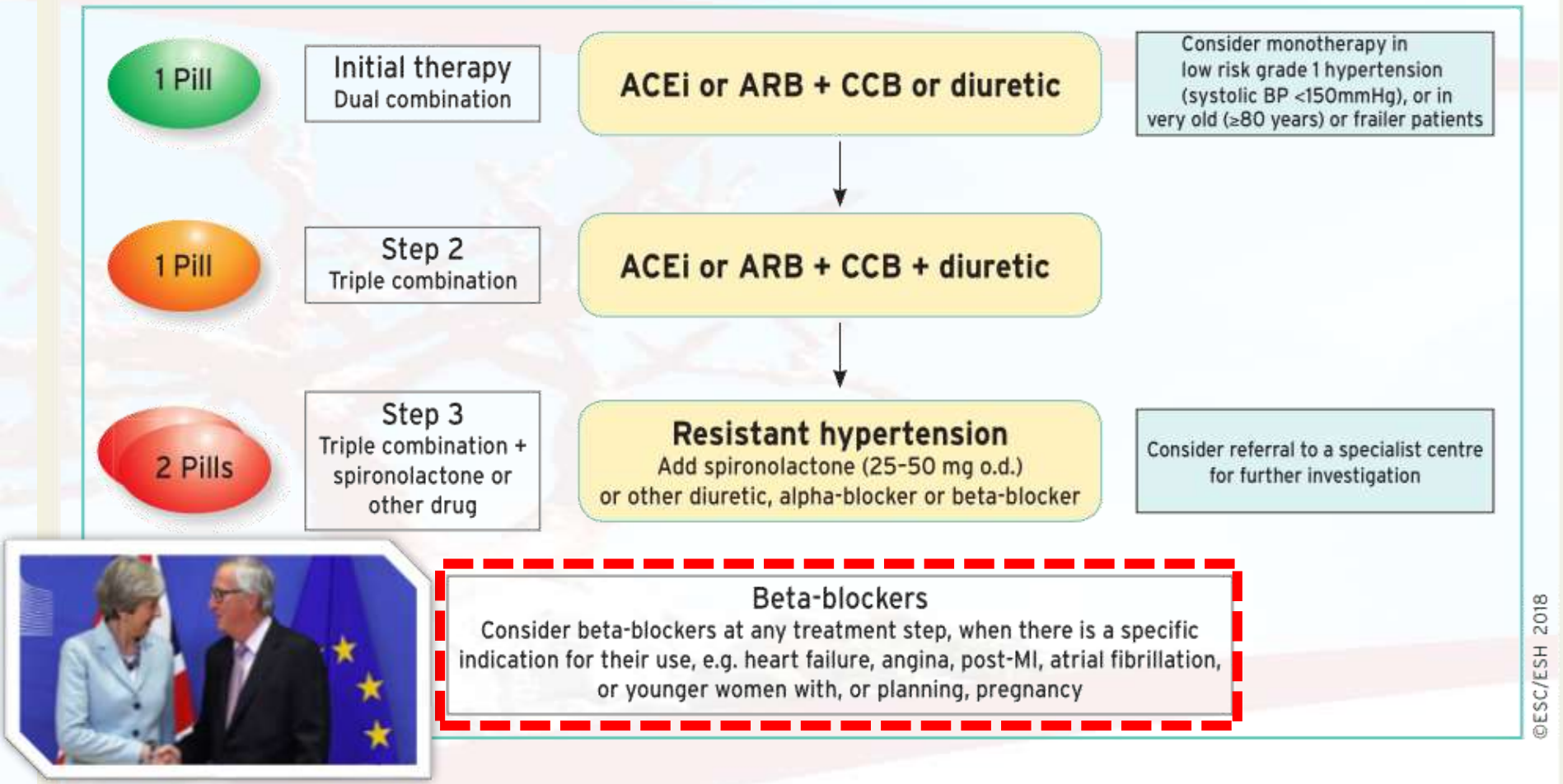


**Figure 4 Core drug treatment strategy for uncomplicated hypertension.** The core algorithm is also appropriate for most patients with HMOD, cerebrovascular disease, diabetes, or PAD. ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; HMOD = hypertension-mediated organ damage; MI = myocardial infarction; o.d. = omni die (every day); PAD = peripheral artery disease.

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**Table 4** Factors influencing cardiovascular risk in patients with hypertension

| Demographic characteristics and laboratory parameters |
|---|
| Sex[a] (men >women) |
| Age[a] |
| Smoking (current or past history)[a] |
| Total cholesterol[a] and HDL-C |
| Uric acid |
| Diabetes[a] |
| Overweight or obesity |
| Family history of premature CVD (men aged <55 years and women aged <65 years) |
| Family or parental history of early-onset hypertension |
| Early-onset menopause |
| Sedentary lifestyle |
| Psychosocial and socioeconomic factors |
| Heart rate (resting values >80 beats/min) |

Dudley Metropolitan Borough Council

NHS Dudley Clinical Commissioning Group

Dudley Hypertension Pathway

# When is it Appropriate to Use Beta-blockers in the Management of Hypertension?

**For new prescriptions** – beta blockers are not a preferred initial choice but may be considered in younger people, particularly:

- Those with an intolerance or contraindication to ACE-I / ARB
- Women of child bearing potential or in pregnancy (Labetalol)
- Patients with evidence of increased sympathetic drive

Here, D is best avoided (not absolutely contraindicated) to reduce the risk of new onset diabetes Mellitus.

**When reviewing those on existing beta blocker therapy**, if:

- BP is not well controlled (≥140/90mmHg) treatment should be revised according to the algorithm.
- BP is well controlled (≤140/90mmHg) long-term management should be considered as part of the routine review, there is no absolute need to replace the beta-blocker with an alternative agent.

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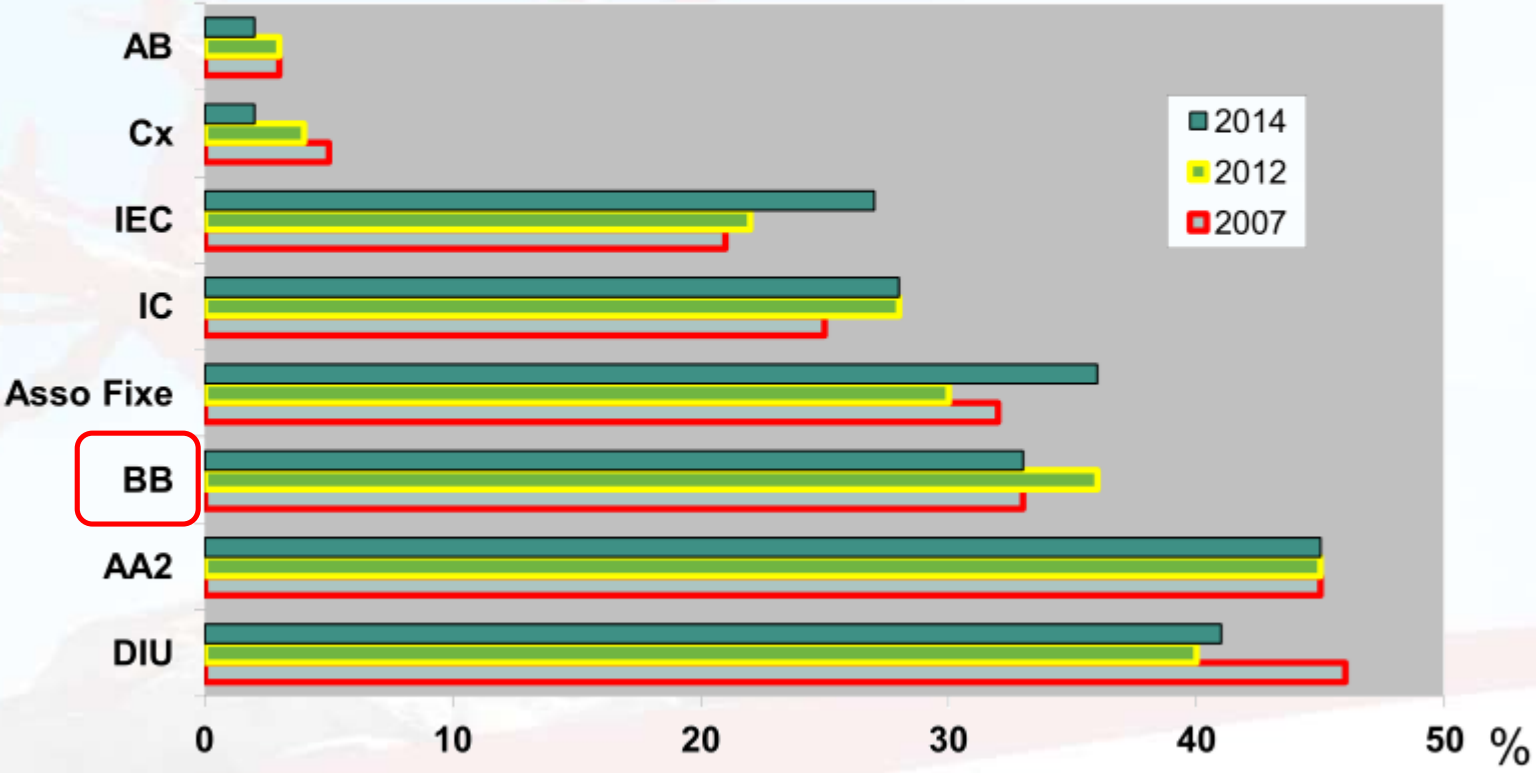
FLAHS
2007
2012
2014

# Utilisation des anti-hypertenseurs 2007 – 2012 – 2014

## Ordonnances des sujets traités

Texte




*Enquête FLAHS 2014 French League Against Hypertension Survey*
*Analyse pour 1057 hypertendus traités*

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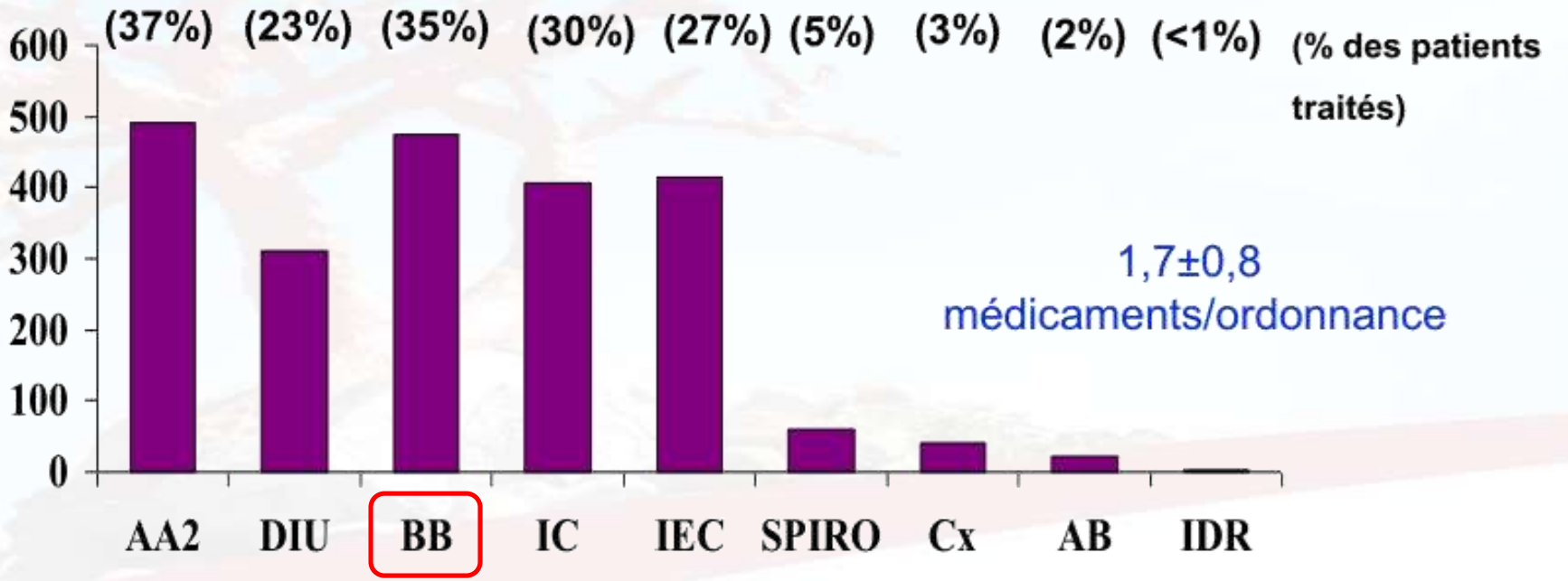
# Utilisation des anti-hypertenseurs en 2017

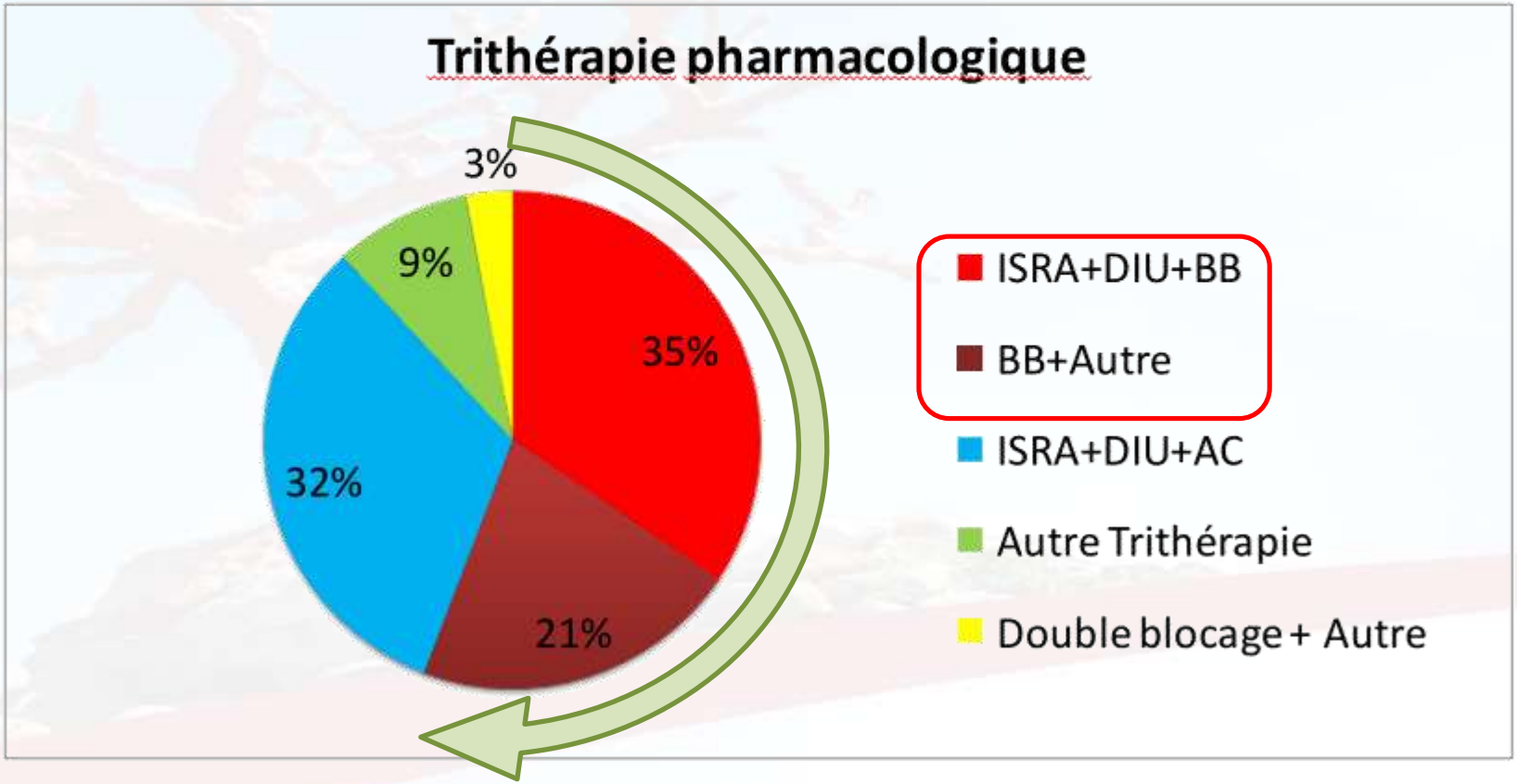
## Analyse de l'utilisation des classes pharmacologiques sur les ordonnances




1,7±0,8
médicaments/ordonnance

*Enquête FLAHS 2017- French League Against Hypertension Survey*
*Analyse pour 1334 hypertendus traités*

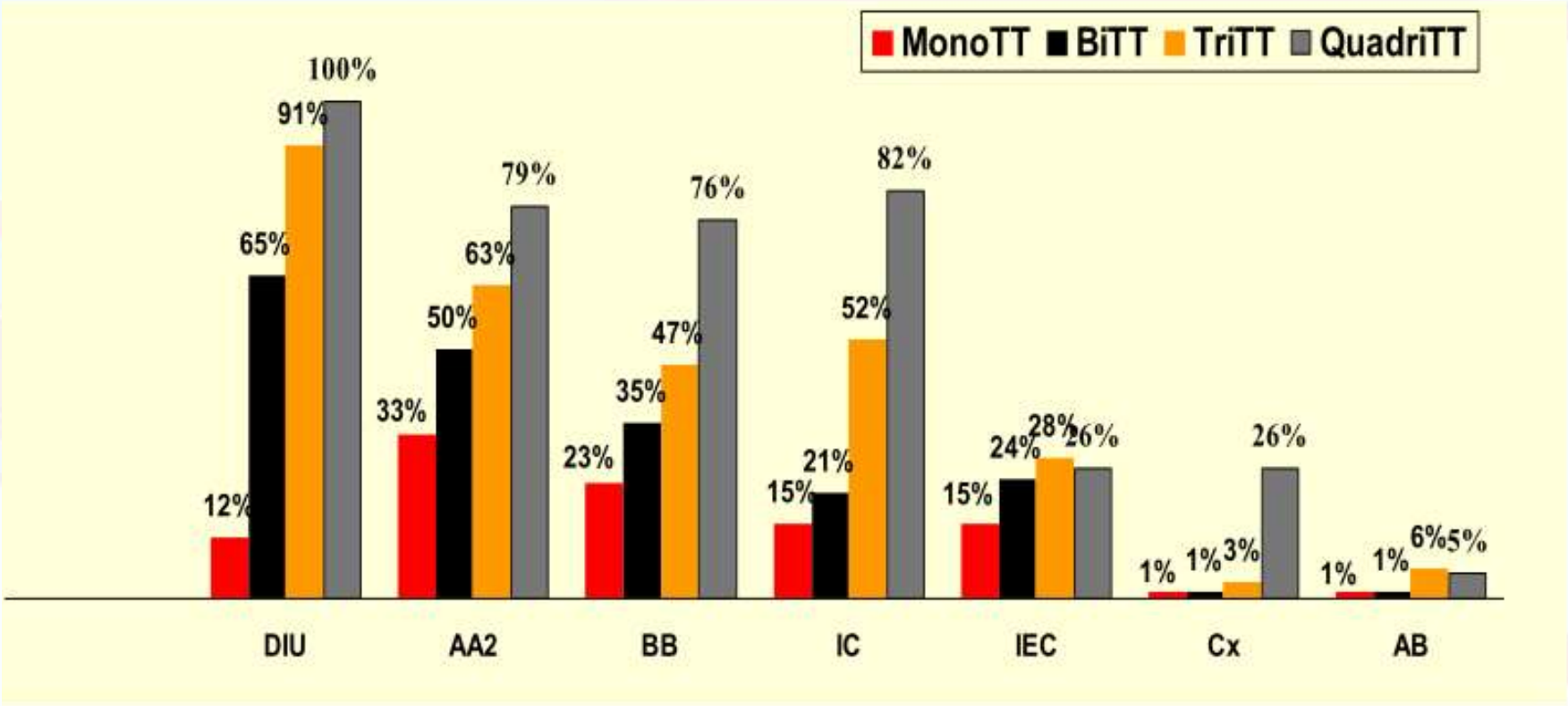
# Utilisation des associations en 2014
# Choix des associations d'antihypertenseurs chez les sujets traités par une **trithérapie** pharmacologique




*Enquête FLAHS 2012 - French League Against Hypertension Survey*
*Analyse pour 1054 hypertendus traités*

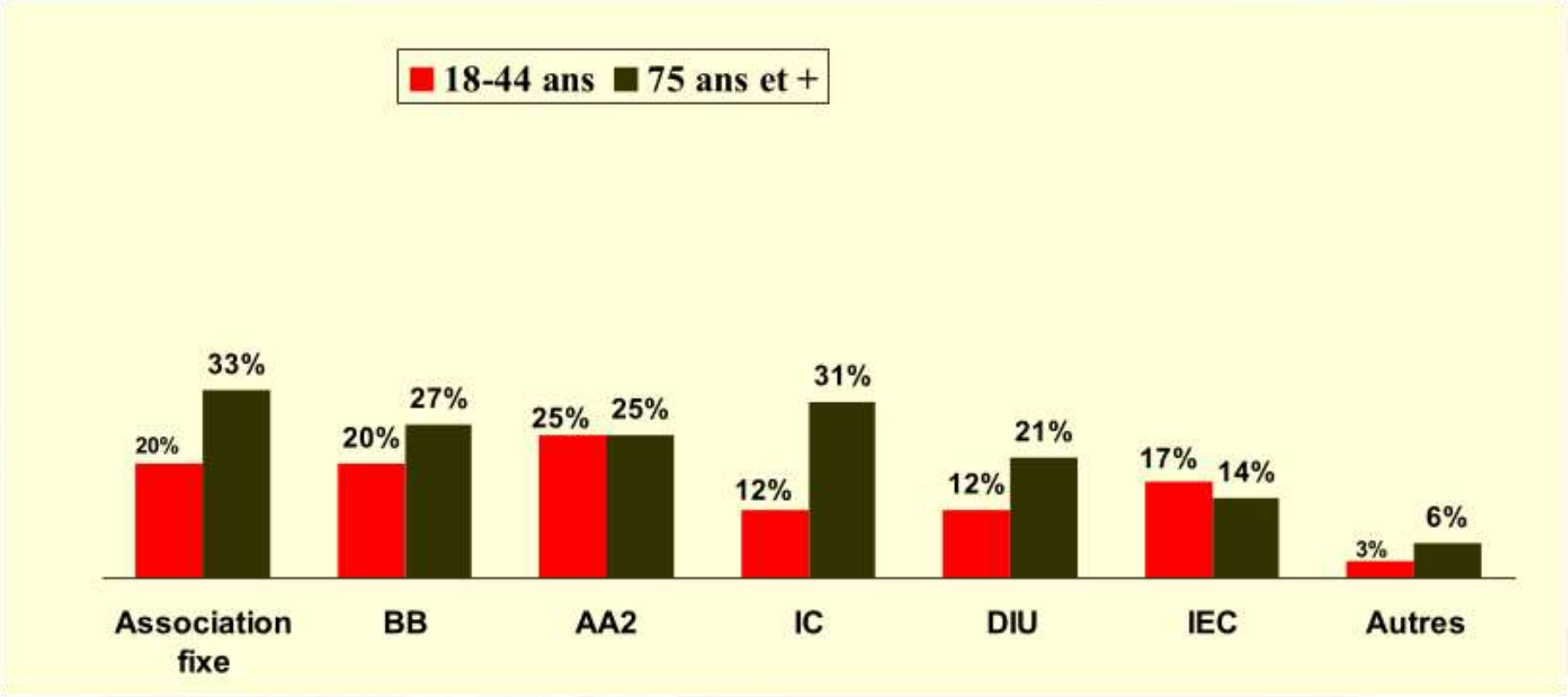
www.comitehta.org

**Figure 5 : Répartition de l'HTA traitée et non contrôlée selon le grade tensionnel et l'âge en 2009.**



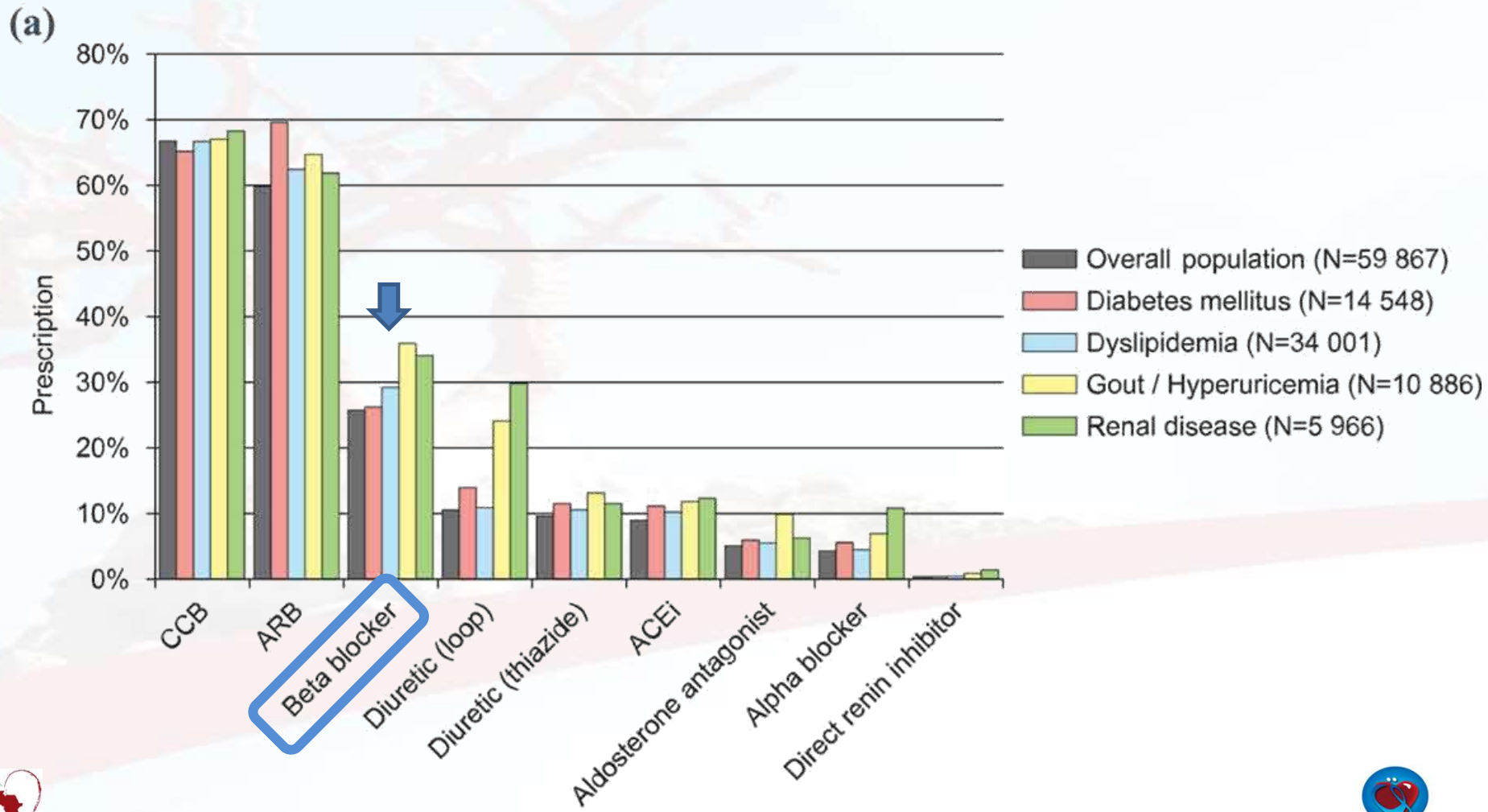

Une monothérapie, est un médicament diurétique sur 12% des ordonnances et 65% des bithérapies comportent un diurétique.
Une monothérapie est un AA2 sur 33% des ordonnances et 50% des bithérapies comportent un AA2.

# Figure 6: Utilisation des traitements antihypertenseurs selon l'âge en 2009.




Les associations fixes, les inhibiteurs calciques , les diurétiques et les bêta-bloquants sont des médicaments plus fréquemment utilisés chez les hypertendus de plus de 75 ans.

# prescription status of antihypertensive drugs in Japanese patients with hypertension in 2017

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# Le Swing des Bétabloquants

## Chez l'IC

## Chez le coronarien

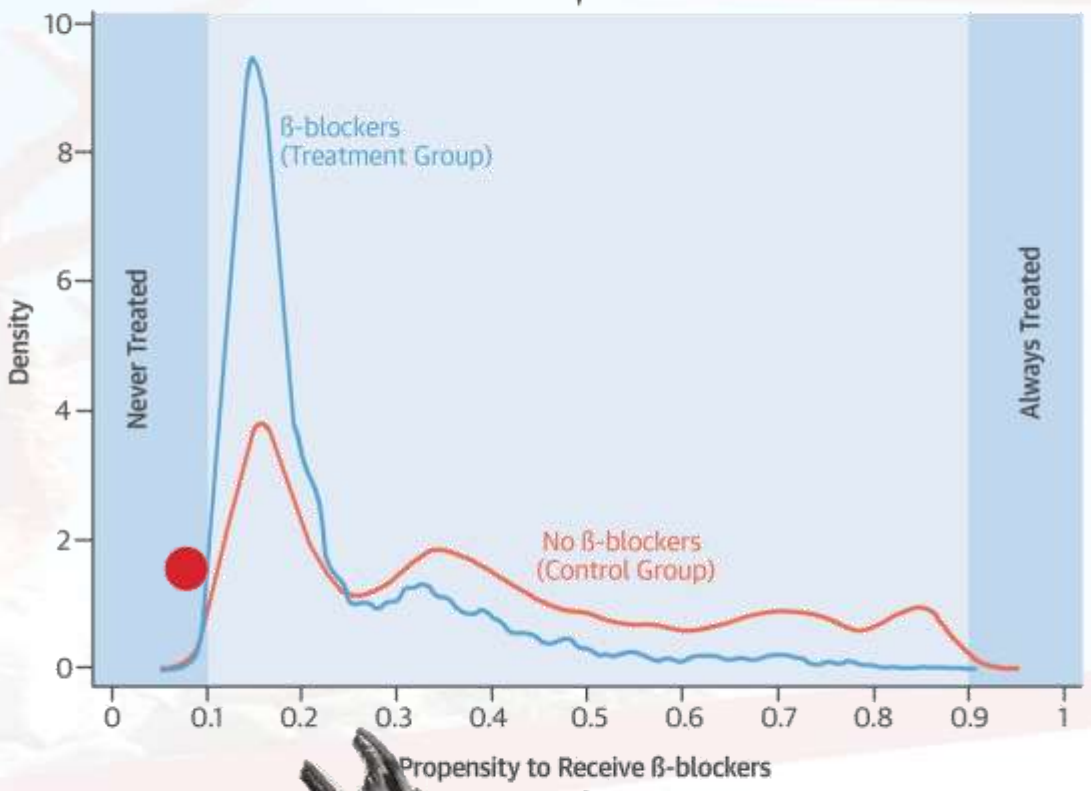
## après CAPRICORN?

**CENTRAL ILLUSTRATION: β-Blockers and Mortality After AMI Without HF**

Analytical Cohort of AMI Hospitalizations (n = 179,810)

Prescribed ß-blockers 170,475 (94.8%)

Not Prescribed ß-blockers 9,335 (5.2%)




Trimmed Propensity Score Analyses (n = 16,683)

ß-blocker Survival Time 4.7 (3.4-5.9) Months

No ß-blocker Survival Time 4.6 (4.0-5.2) Months

Dondo, T.B. et al. J Am Coll Cardiol. 2017;69(22):2710-20.

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# Les β-bloquants une histoire d'une grande famille hétérogène

Nonselective
Selective
Vasodilating

Propanolol
Metoprolol tartrate
Atenolol
Pindolol
Acebutolol
Penbutolol
Metoprolol Succinate
Carvedilol
Nebivolol

1960 1970 1980 1990 2000 2010

Nadolol
Timolol
Labetalol
Carteolol
Betaxolol
Bisoprolol

## The Nobel Prize in Physiology or Medicine 1988

Sir James W. Black

Born: 14 June 1924, Uddingston, Scotland

Died: 21 March 2010, ,

Affiliation at the time of the award: London University, King's College Hospital Medical School, London, United Kingdom

Prize motivation: "for their discoveries of important principles for drug treatment."

At the beginning of the 1960s, James Black developed the drug **propranolol**, which is a beta-blocker that has a calming effect on the heart by blocking the receptor for adrenaline.

## The Nobel Prize in Chemistry 2012

Robert J. Lefkowitz

Born: 15 April 1943, New York, NY, USA

Affiliation at the time of the award: Howard Hughes Medical Institute , Duke University Medical Center, Durham, NC, USA

Prize motivation: "for studies of G-protein-coupled receptors."

Prize share: 1/2

Brian K. Kobilka

Born: 30 May 1955, Little Falls, MN, USA

Affiliation at the time of the award: Stanford University School of Medicine, Stanford, CA, USA

Prize motivation: "for studies of G-protein-coupled receptors."

Prize share: 1/2

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**Franz H. Messerli, MD**

Professor of Medicine

Mount Sinai Health System

Icahn School of Medicine at Mount Sinai

Member, Vascular Medicine section of CARDIOLOGY TODAY Editorial Board

Editorial Review

# Beta blockers in hypertension – to use or not to use?

Kardiovaskulare Medizin 2008;11(4):117–123

*Sripal Bangalore, Franz H. Messerli*

St. Luke's-Roosevelt Hospital and Columbia University, New York, USA

## The North-American answer

When I talk about beta-blockers, there is one study that I always refer to: the Dutch TIA Trial, which was published in 1993.[5] In this study, patients had had either a stroke or a transient ischemic attack (TIA) and the authors hypothesized that beta-blockers would prevent vascular events in these patients. Over 1,400 patients who were already on aspirin were randomized to atenolol or placebo and followed for a mean of 2.6 years. Blood pressure was lowered effectively with atenolol when compared with placebo. However, there was absolutely no effect in terms of outcome, ie, death or fatal or nonfatal stroke. Where there was a difference from placebo, however, was in side effects such as hypotension, bradycardia, and erectile dysfunction, which were almost twice as common with atenolol. This is a classic study, 12 years old, but the results have never been disseminated to practicing physicians. If practicing physicians saw this they would not want to prescribe a drug that does not even reduce strokes better than placebo, yet causes impotence, hypotension, dizziness, cold extremities, and other side effects.

**Medscape: Are newer beta-blockers like carvedilol, bisoprolol, and nebivolol different from atenolol?**

**Dr. Messerli:** Carvedilol, bisoprolol, and nebivolol all have the potential to do better than atenolol, although we do not have any outcome studies in hypertension with these newer drugs. However, their hemodynamic profile looks much more attractive than looked the older ones like atenolol and metoprolol.

# Pourquoi un brexit des β -

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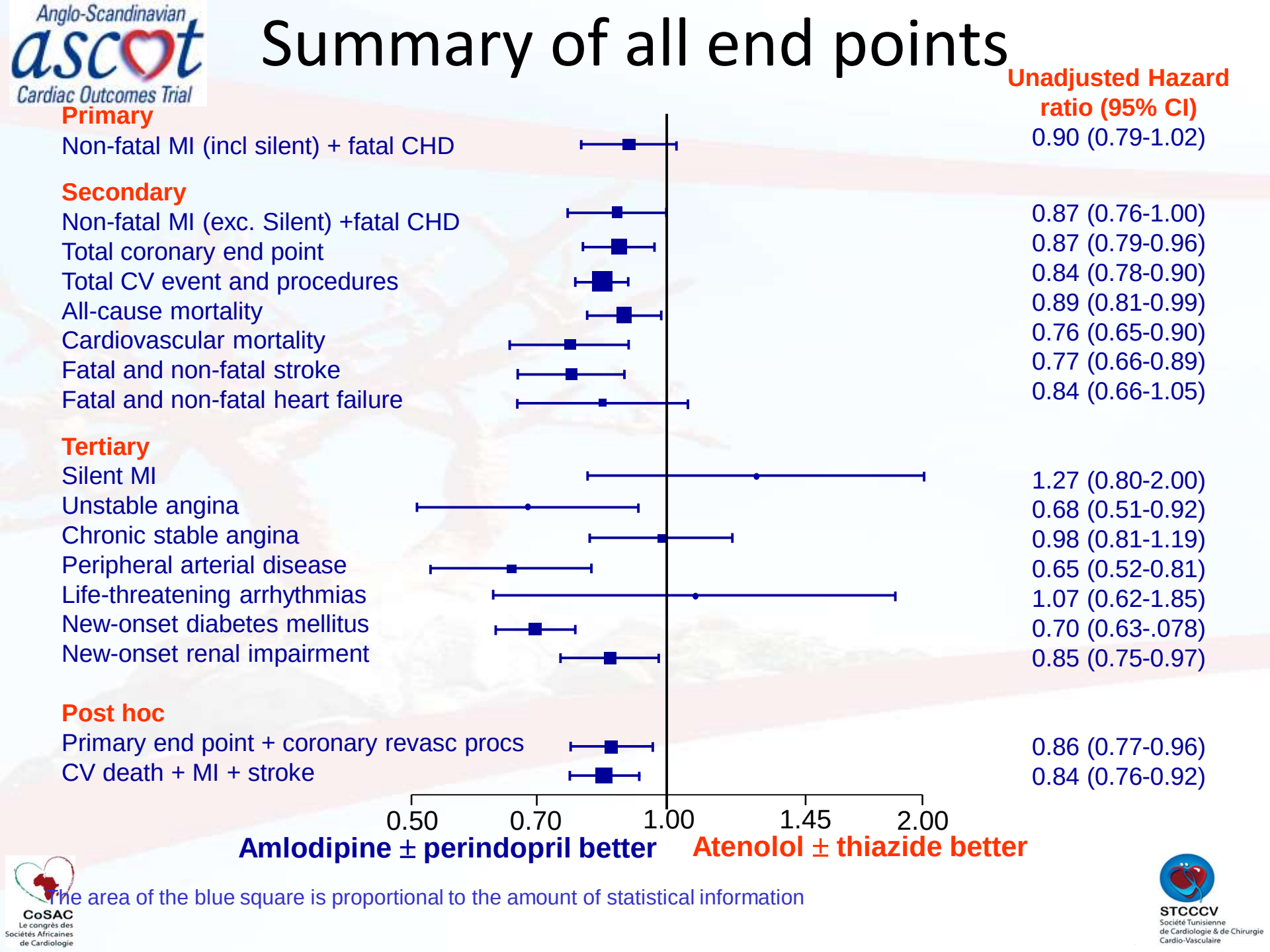
# Summary of all end points



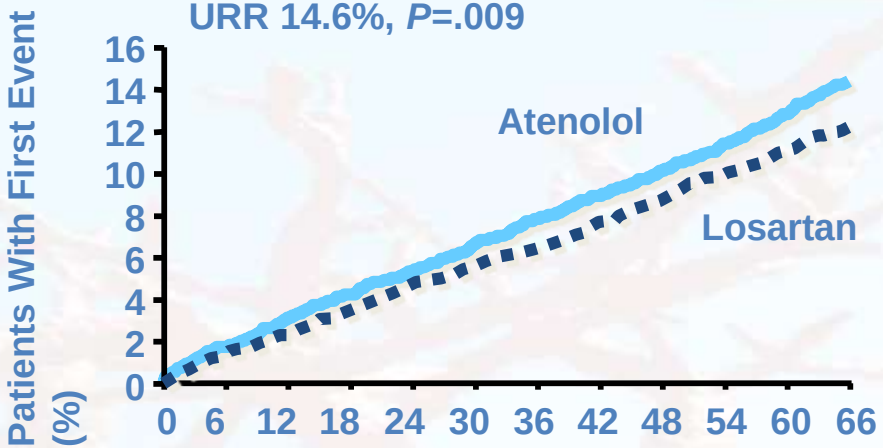

The area of the blue square is proportional to the amount of statistical information

# LIFE: Cumulative Event Rates

n=9,193

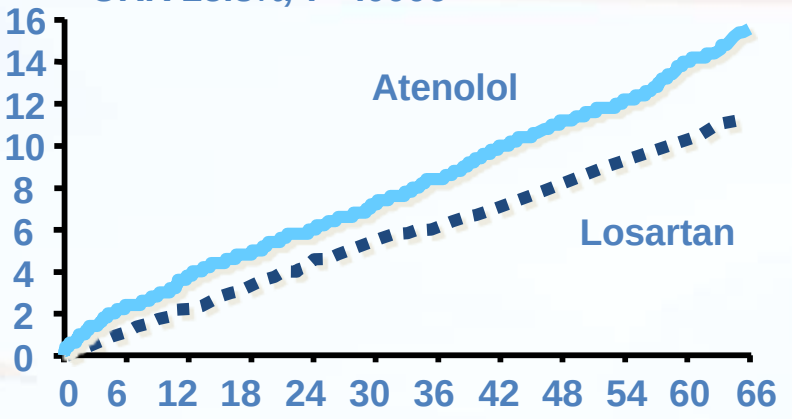
## Primary Composite Endpoint

ARR 13.0%, *P*=.021
URR 14.6%, *P*=.009



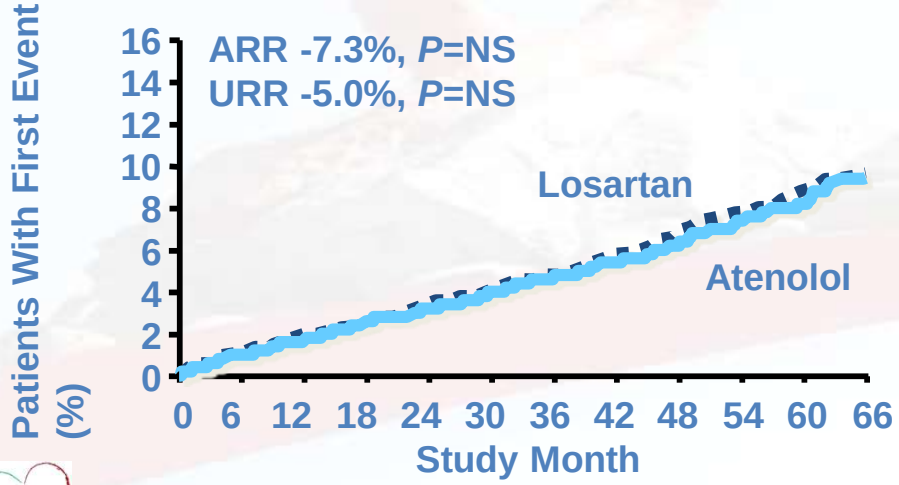

## Fatal/Nonfatal Stroke

ARR 24.9%, *P*=.001
URR 25.8%, *P*=.0006



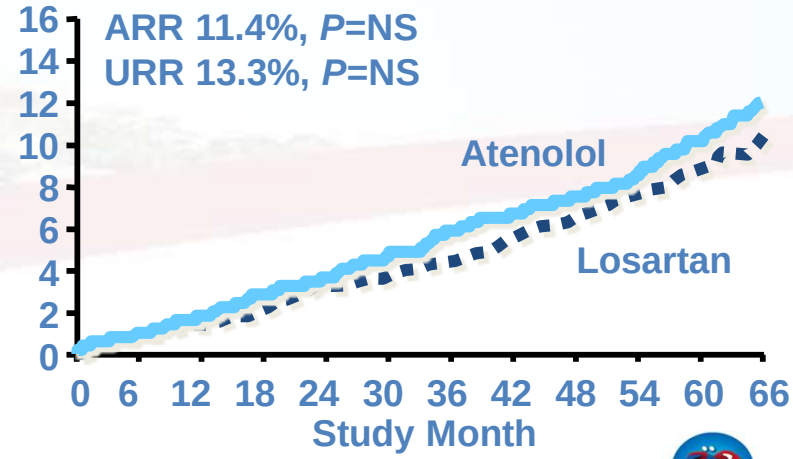

## Fatal/nonfatal MI

ARR -7.3%, *P*=NS
URR -5.0%, *P*=NS




## CV Mortality

ARR 11.4%, *P*=NS
URR 13.3%, *P*=NS




ARR=adjusted risk reduction; URR=unadjusted risk reduction

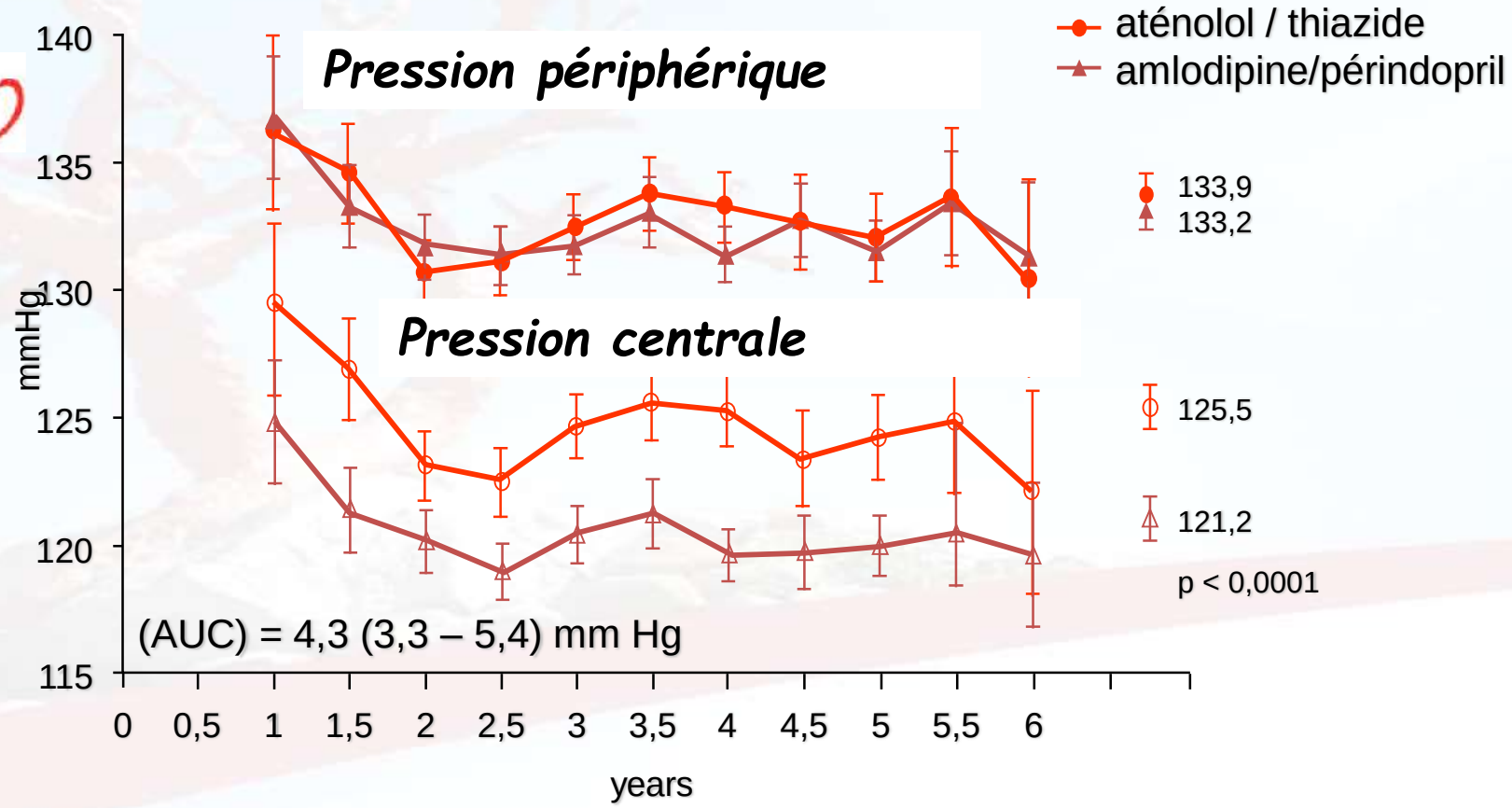
Dahlöf et al. *Lancet*. 2002;359:995-1003

# Follow-up 2006 Meta-Analysis: Atenolol vs Other Treatments

| End Point | Summary OR (95% CI) |
|---|---|
| Death | 1.10 (1.03-1.16) *P*=0.003 |
| CV Death | 1.13 (1.04-1.22) (*P*=0.005) |
| MI | 1.05 (0.97-1.14) *P*=0.19 |
| **Stroke** | 1.26 (1.15-1.38) *P*=0.0000006 |

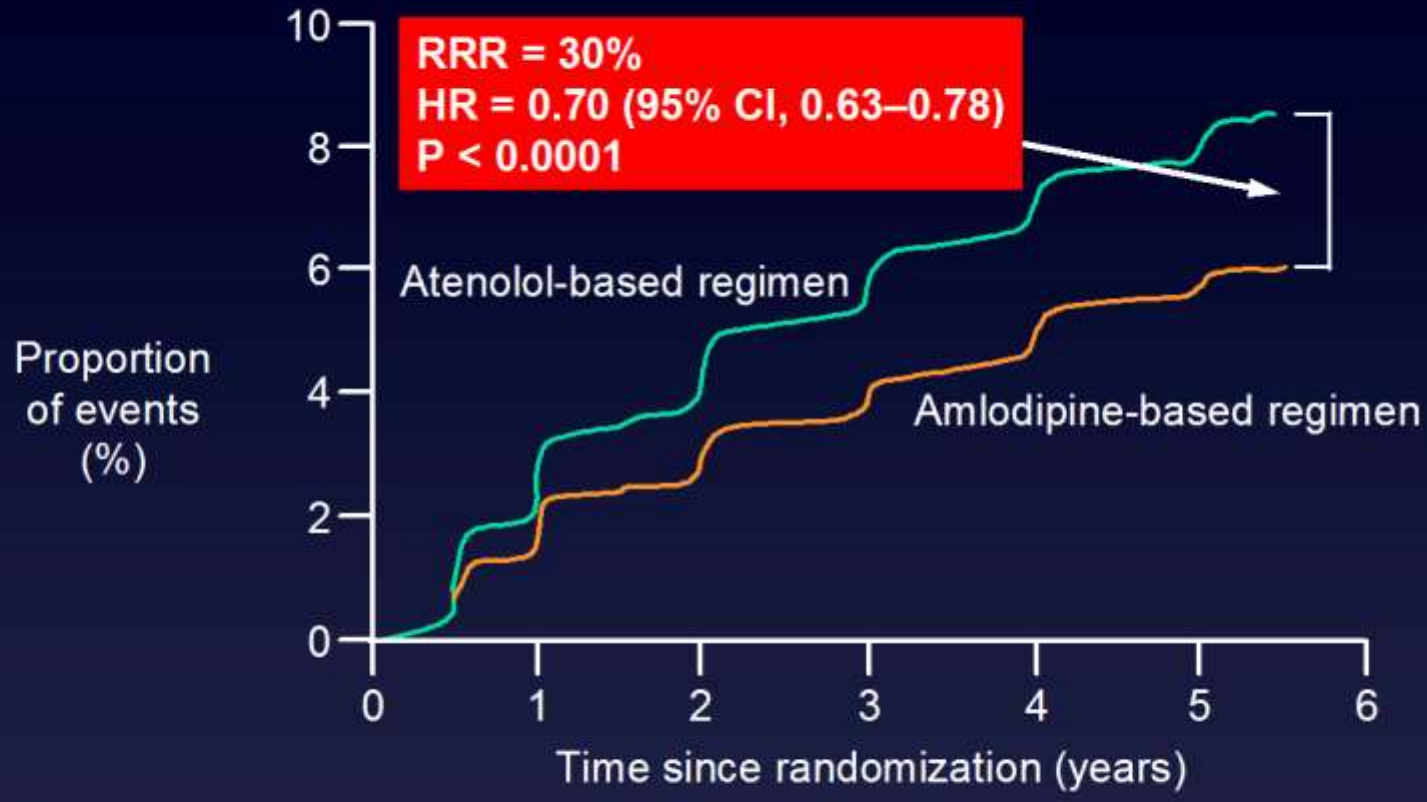
Elliott WJ. *JACC.* 2006;47 (Suppl):361A.

# Une plus grande efficacité sur la PA centrale




*CAFE Investigators: Circulation 2006, 113: 1213.*

# ASCOT-BPLA: New-onset diabetes




| Number at risk | | | | | | |
|---|---|---|---|---|---|---|
| Amlodipine-based regimen (567 events) | 9639 | 9383 | 9165 | 8966 | 8726 | 7618 |
| Atenolol-based regimen (799 events) | 9618 | 9295 | 9014 | 8735 | 8455 | 7319 |

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

# Les contre-exemples

# MRC trial of treatment of mild hypertension: principal results

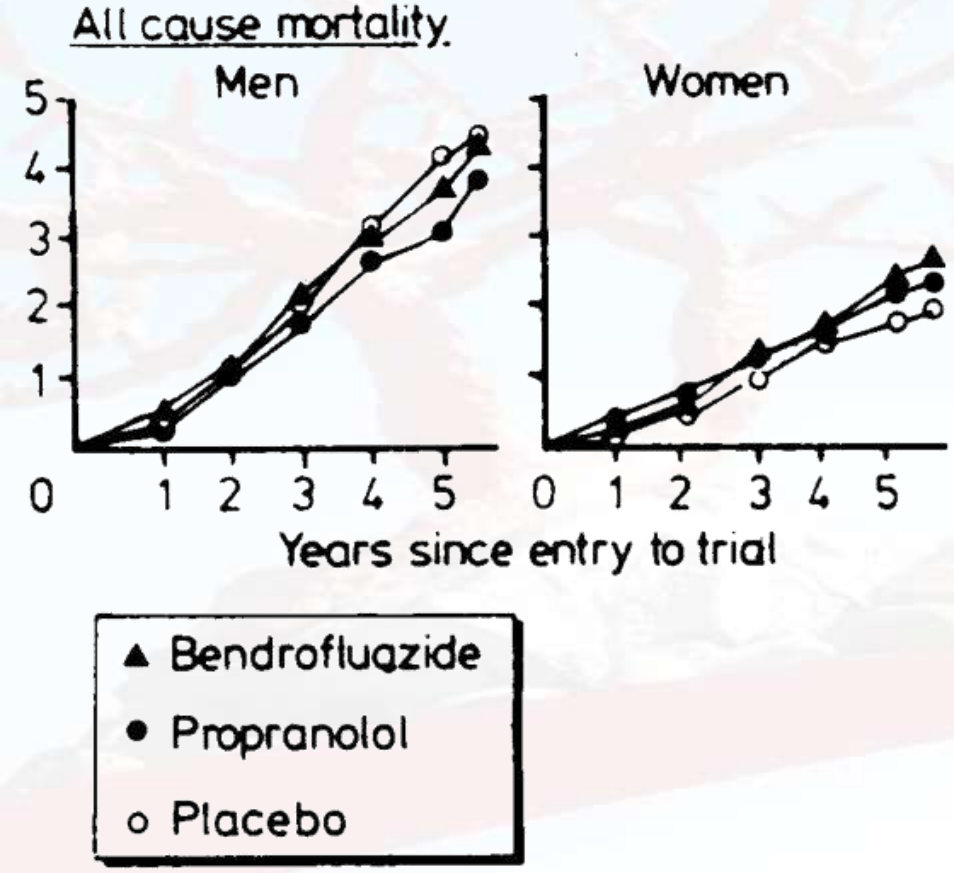
MEDICAL RESEARCH COUNCIL WORKING PARTY

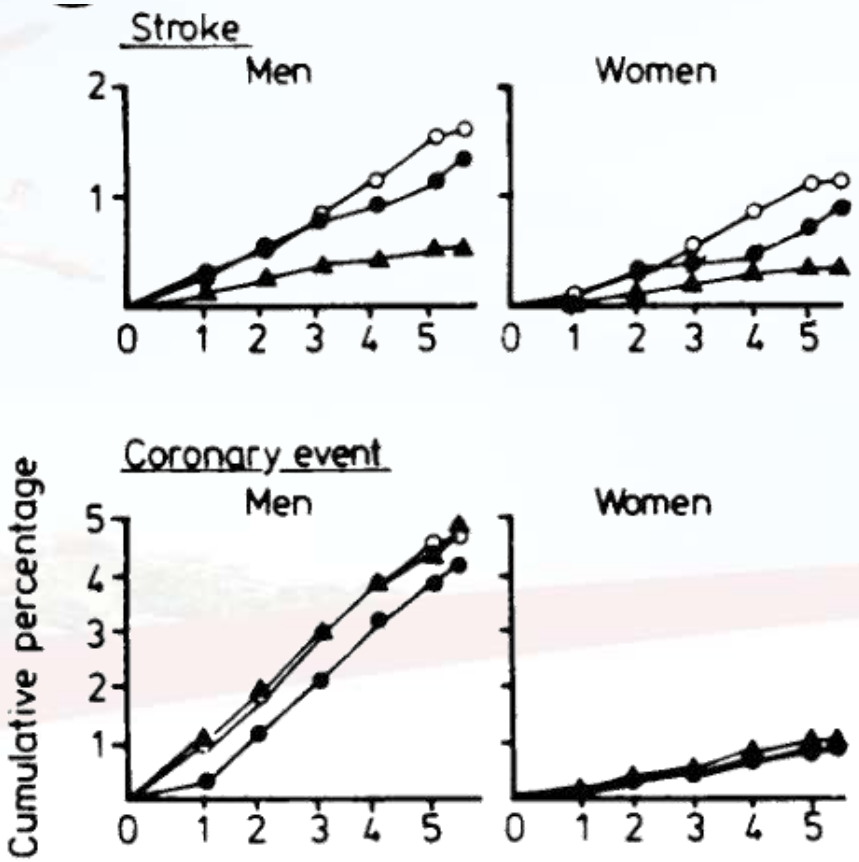
The main aim of the trial was to determine whether drug treatment of mild hypertension (phase V diastolic pressure 90-109 mm Hg) reduced the rates of stroke, of death due to hypertension, and of coronary events in men and women aged 35-64 years. Subsidiary aims were: to compare the course of blood pressure in two groups, one taking bendrofluazide and one taking propranolol, and to compare the incidence of suspected adverse reactions to these two drugs. The study was single blind and based almost entirely in general practices; 17 354 patients were recruited, and 85 572 patient years of observation have accrued. Patients were randomly allocated at entry to take bendrofluazide or propranolol or placebo tablets.

BRITISH MEDICAL JOURNAL VOLUME 291 13 july 1985

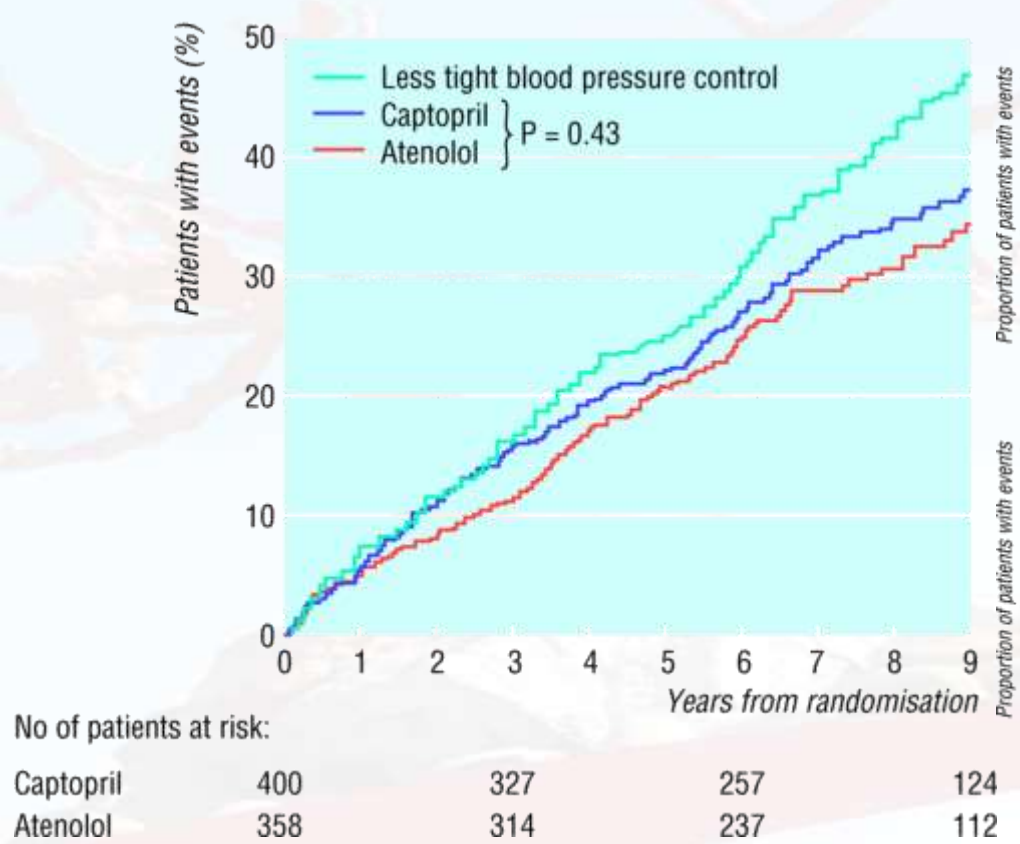
# MRC trial of treatment of mild hypertension: principal results

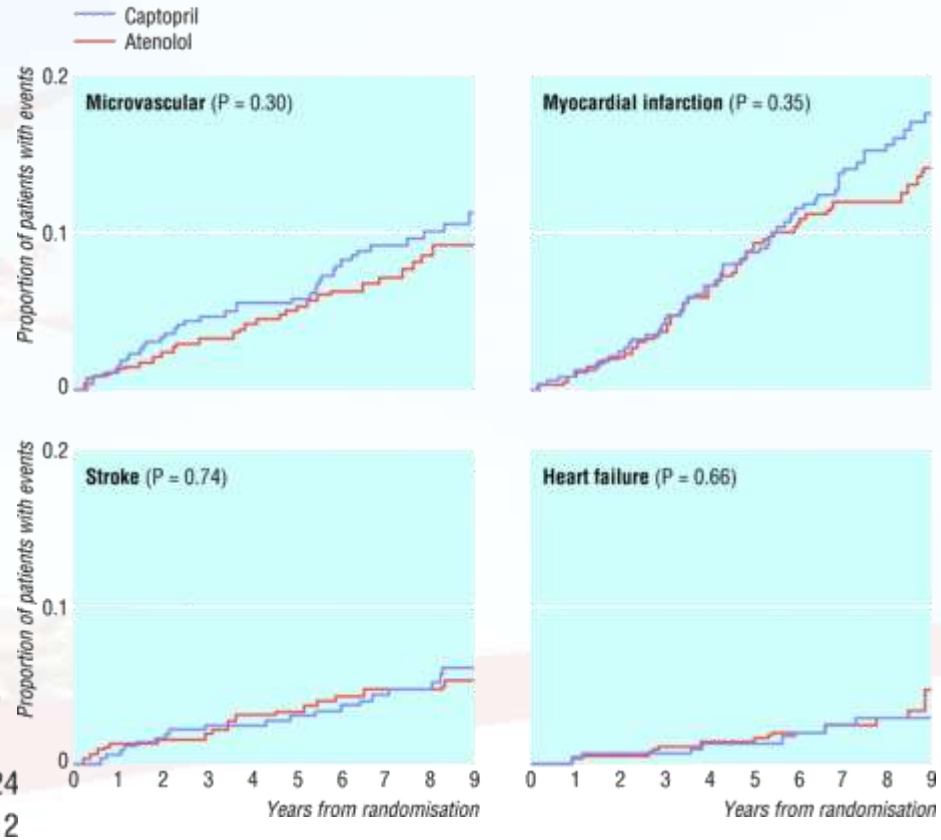
MEDICAL RESEARCH COUNCIL WORKING PARTY



# *Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39 (9 Years Trial +++)*




*BMJ 1998; 317 doi: https://doi.org/10.1136/bmj.317.7*

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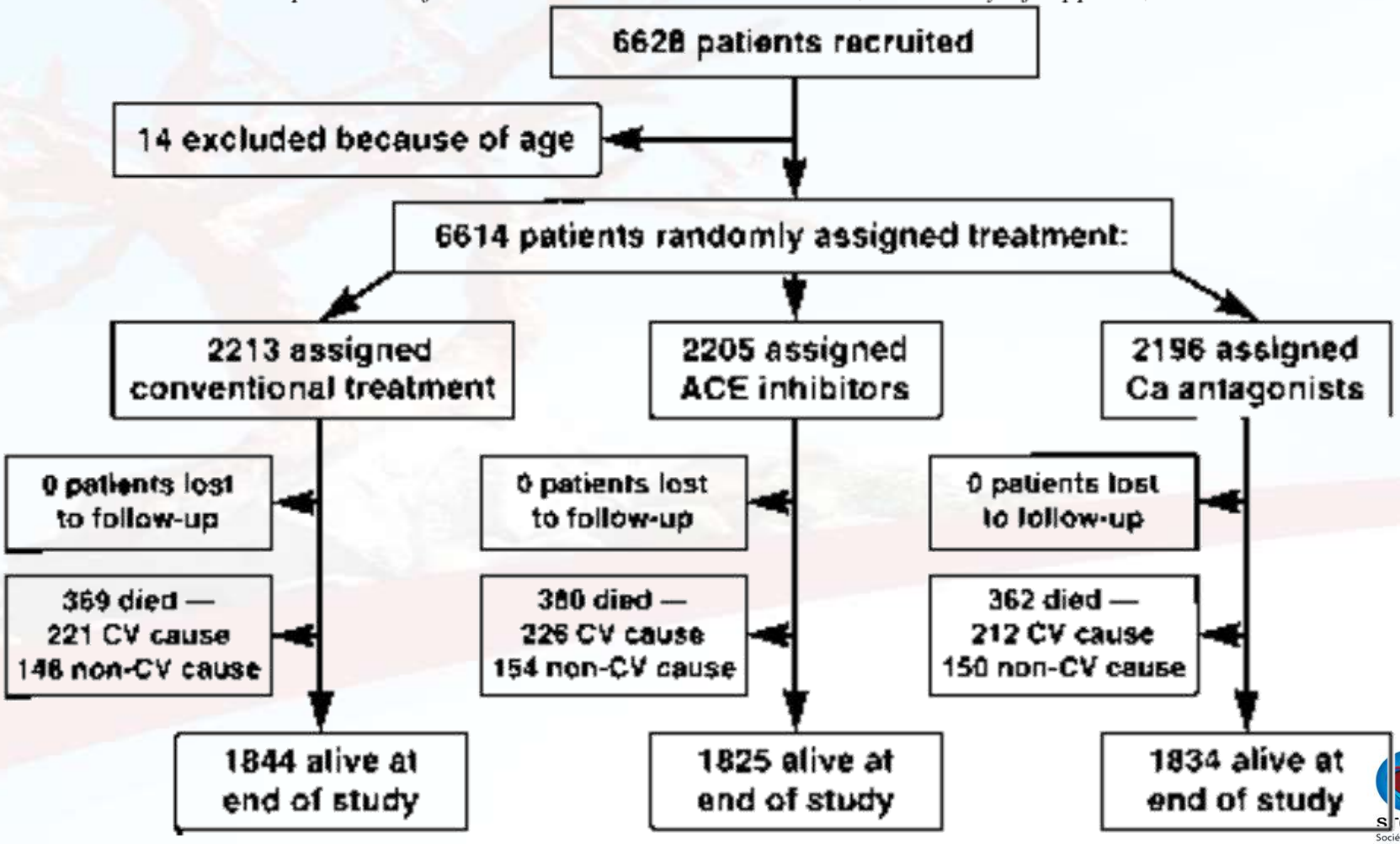
BLOOD PRESSURE 2000; 9 (Suppl 2): 17–20

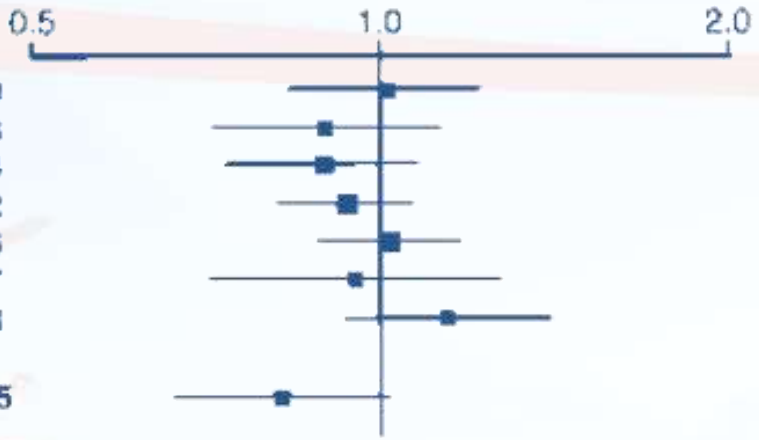
# Results of the STOP-Hypertension-2 Trial

LENNART HANSSON

*From the Department of Public Health and Social Services, University of Uppsala, Sweden*

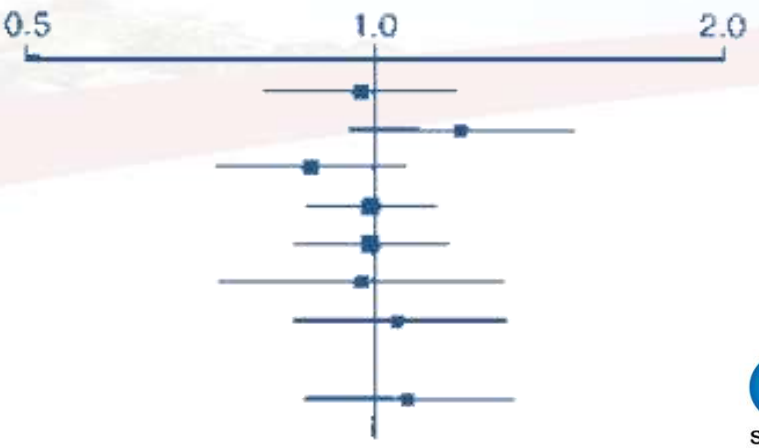


| | Relative risk* (95% CI) | | p |
|---|---|---|---|
| Cardiovascular Mortality | 1.01 | (0.84-1.22) | 0.89 |
| All Myocardial Infarction | 0.90 | (0.72-1.13) | 0.38 |
| All Stroke | 0.90 | (0.74-1.08) | 0.24 |
| All Major CV Events | 0.94 | (0.82-1.07) | 0.32 |
| Total Mortality | 1.02 | (0.89-1.18) | 0.76 |
| Incidence of Diabetes Mellitus | 0.96 | (0.72-1.27) | 0.77 |
| Incidence of Atrial Fibrillation | 1.15 | (0.94-1.41) | 0.18 |
| Incidence of Congestive Heart Failure | 0.83 | (0.67-1.03) | 0.095 |




*Adjusted for age, sex, diabetes, diastolic blood pressure and smoking

| | Relative risk* (95% CI) | | p |
|---|---|---|---|
| Cardiovascular Mortality | 0.97 | (0.80-1.17) | 0.72 |
| All Myocardial Infarction | 1.18 | (0.95-1.47) | 0.13 |
| All Stroke | 0.88 | (0.73-1.06) | 0.16 |
| All Major CV Events | 0.99 | (0.87-1.12) | 0.85 |
| Total Mortality | 0.99 | (0.86-1.15) | 0.90 |
| Incidence of Diabetes Mellitus | 0.97 | (0.73-1.29) | 0.83 |
| Incidence of Atrial Fibrillation | 1.04 | (0.85-1.29) | 0.68 |
| Incidence of Congestive Heart Failure | 1.06 | (0.87-1.31) | 0.56 |

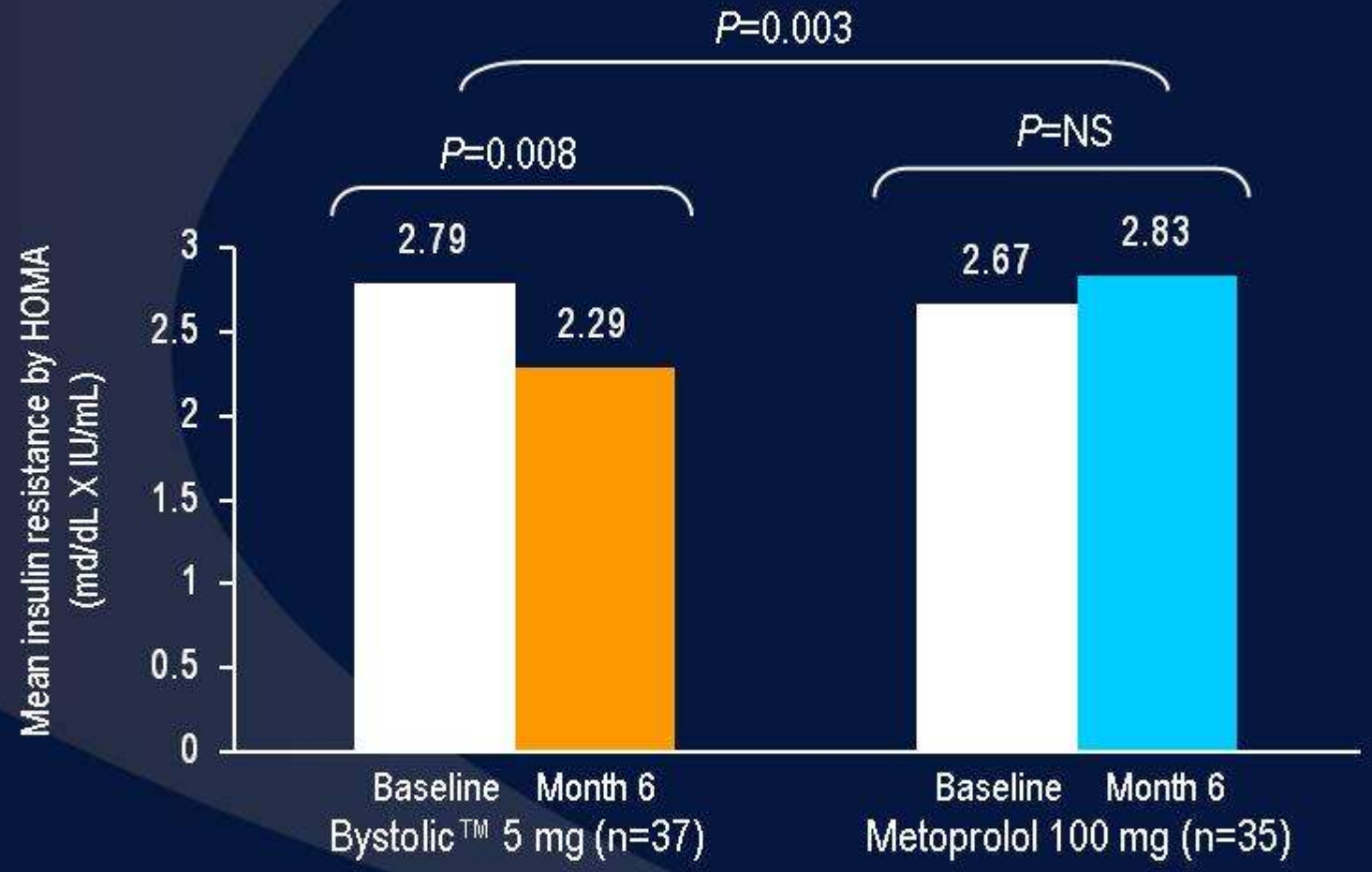


# GEMINI: Relative to metoprolol, treatment with carvedilol stabilized hemoglobin A1c (HbA1c), a measure of glycemic control; improved insulin resistance; and slowed the development of microalbuminuria

| End point | Metoprolol | p | Carvedilol | p |
|---|---|---|---|---|
| Mean HbA1c change with treatment, % (SD) | 0.15 (0.04) | <0.001 | 0.02 (0.04) | 0.65 |
| Insulin sensitivity (%) | -2.0 | 0.48 | -9.1 | 0.004 |
| Progression to microalbuminuria (%) | 10.3 | 6.4 | 0.60 | 0.04 |

Bakris GL. American Heart Association Scientific Sessions 2004. Nov 7-10, 2004; New Orleans, LA.

# Effect of Bystolic™ (nebivolol) and Metoprolol on Insulin Resistance

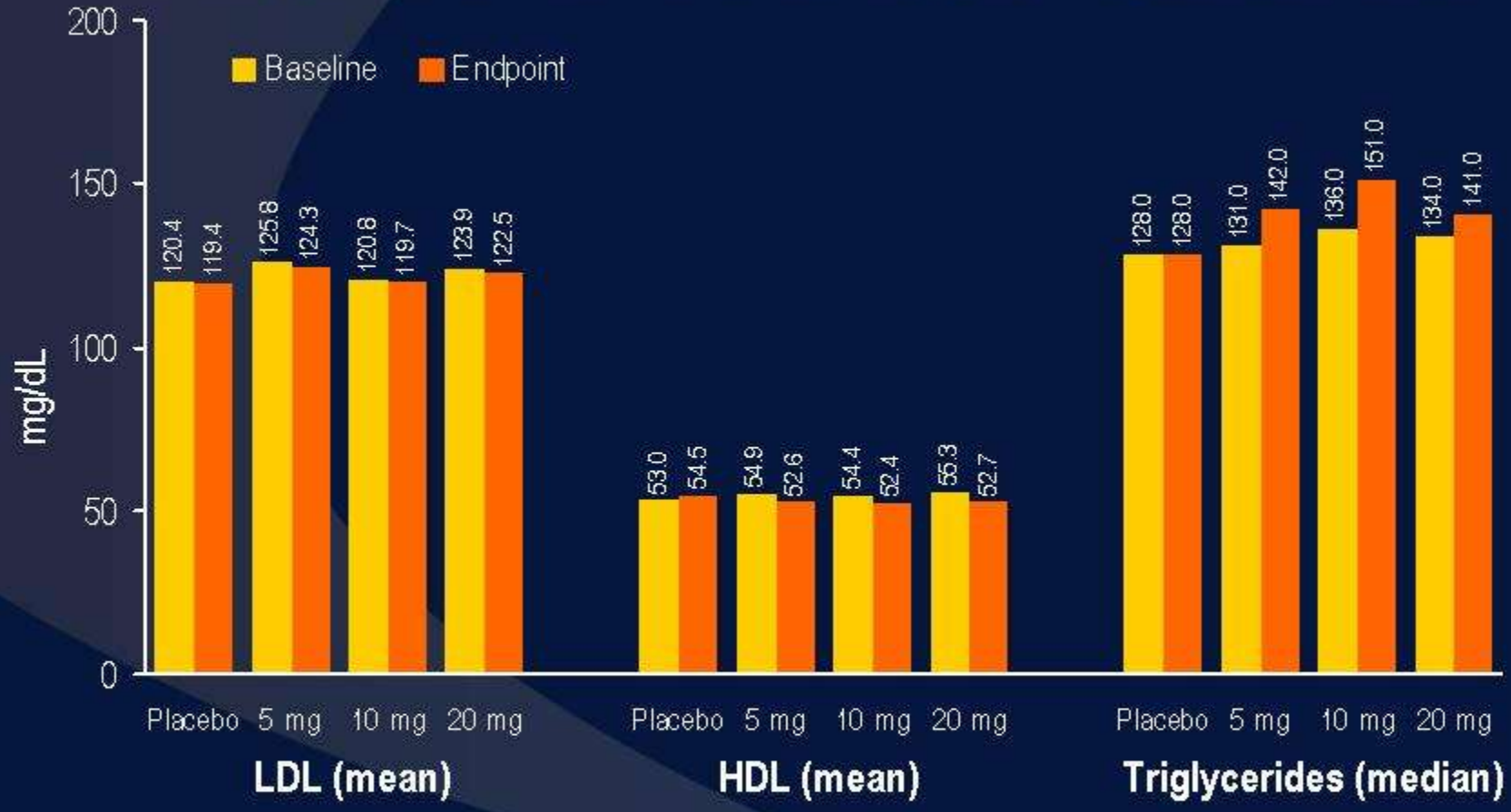



**Bystolic™ is not indicated for glucose control. Bystolic™ is indicated for the treatment of hypertension.**

Baseline SBP/DBP was 153/92 mm Hg and 155/95 mm Hg in the Bystolic™ and metoprolol groups, respectively. Following 6 months of therapy, BP was 131/79 mm Hg and 129/82 mm Hg in the Bystolic™ and metoprolol groups, respectively.
HOMA=homeostasis model assessment: insulin resistance.
Celik T et al. *J Hypertens*. 2006;24:591-596.

# Bystolic™ (nebivolol): Effect on Lipid Levels

## *Pooled Analysis of the Three Monotherapy US Registration Trials*

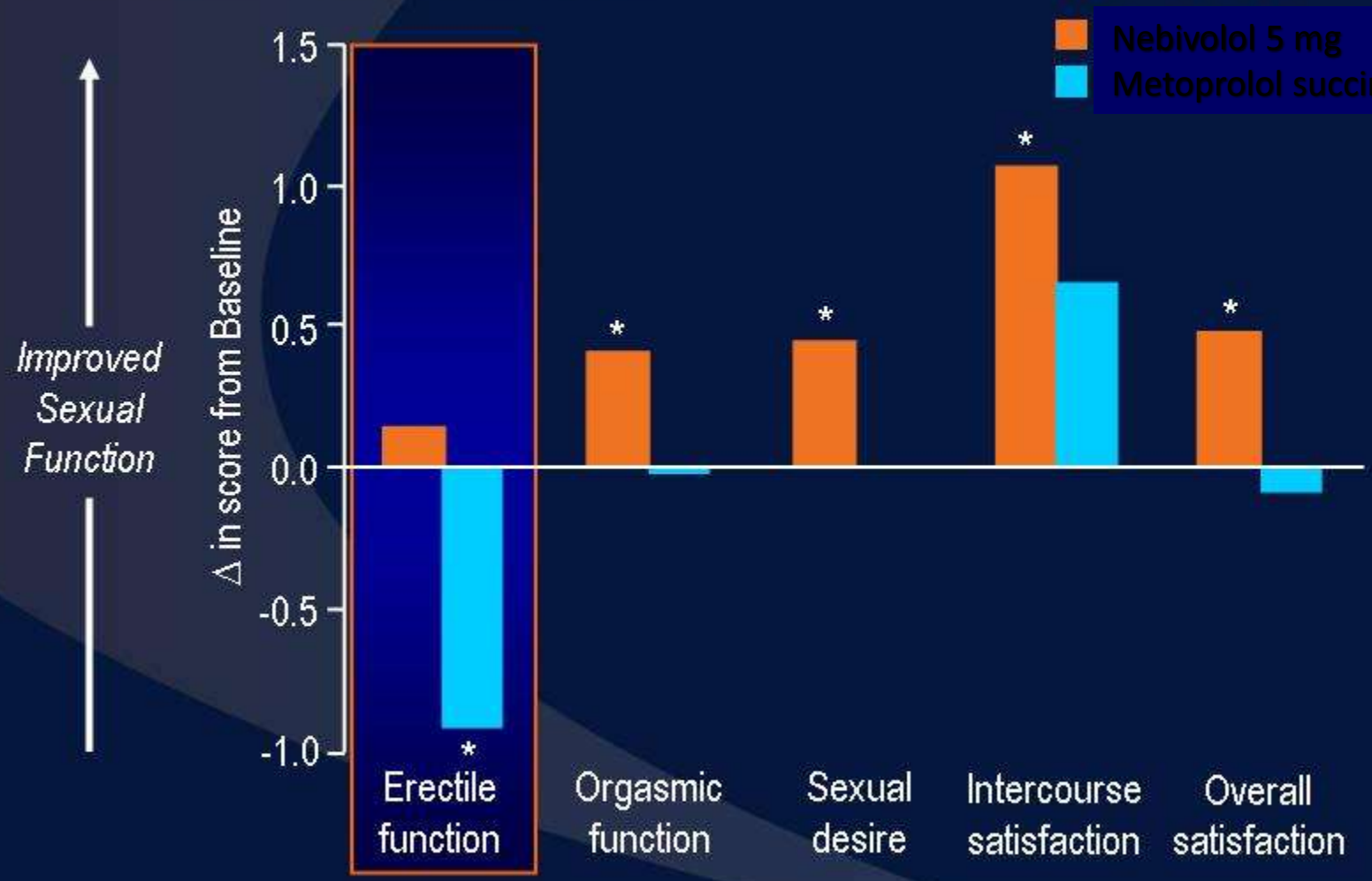



These laboratory parameters are among the 51 standard laboratory values that were collected from patients with mild to moderate hypertension in three U.S. phase III, 3-month, placebo-controlled studies of Bystolic™ monotherapy.

Bystolic™ is not indicated for cholesterol lowering. Bystolic™ is indicated for the treatment of hypertension.


1. Registration trials. Data on file, Forest Laboratories, Inc. New York, NY.
2. Bystolic™ (nebivolol) package insert. New York, NY: Forest Laboratories, Inc; 2007.

# Effect of Nebivolol and Metroprolol on Sexual Function: IIEF




*P<0.05. †Equivalent to metoprolol 100 mg.
IIEF=International Index of Erectile Function.
Brixius K et al. *Clin Exper Pharmacother*. 2007;34:327-331.

*Table 2.* Studies comparing persistence rates of different antihypertensive drugs [20, 29, 30]

| Sstudy | n | Outcome (persistence) | AT-II blockers | ACE-inhibitors | Calcium antagonists | Beta-blockers | Diuretics |
|---|---|---|---|---|---|---|---|
| Jones, 1995 | 10,222 | 6-month persistence | ne | 45% | 41% | 49% | 41% |
| Blooms, 1998 | 21,723 | 1-year persistence | 64% | 58% | 50% | 43% | 38% |
| Caro, 1999 | 22,918 | 4.5-year persistence | ne | 53% | 47% | 49% | 40% |
| Morgan, 2004 | 82,824 | 1-year persistence | 56% | 56% | 52% | 54% | 49% |
| Perreault, 2005 | 21,011 | 3-year persistence | 59% | 58% | 58% | 57% | 48% |
| Polluzzi, 2005 | 6,043 | 3-year persistence | 52% | 43% | 39% | 47% | 23% |
| Simons, 2008 | 48,690 | 33-month persistence | 84% | 84% | 72% | ne | ne |

ne — not evaluated

CME Available



# Differential Effects of Nebivolol and Metoprolol on Central Aortic Pressure and Left Ventricular Wall Thickness

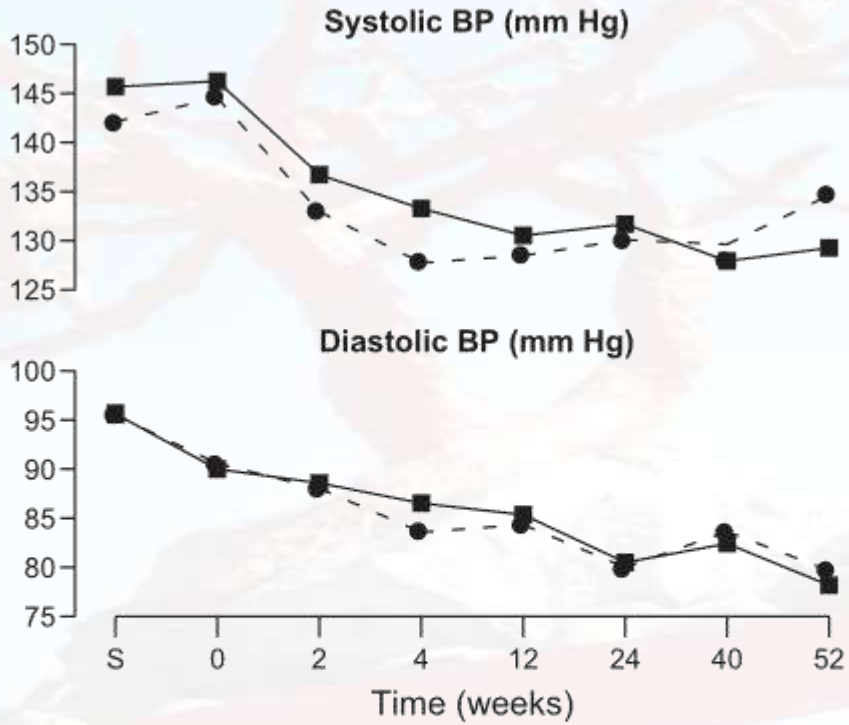



**Figure 1.** Mean reduction in brachial systolic and diastolic blood pressures measured during the study period. Both treatment groups display significantly reduced brachial systolic and dia- blood pressures ($P<0.001$) during 52 weeks of treatment, t difference between the treatment arms. ■ indicates olol; -●-, metoprolol; S, screening period; BP, blood re

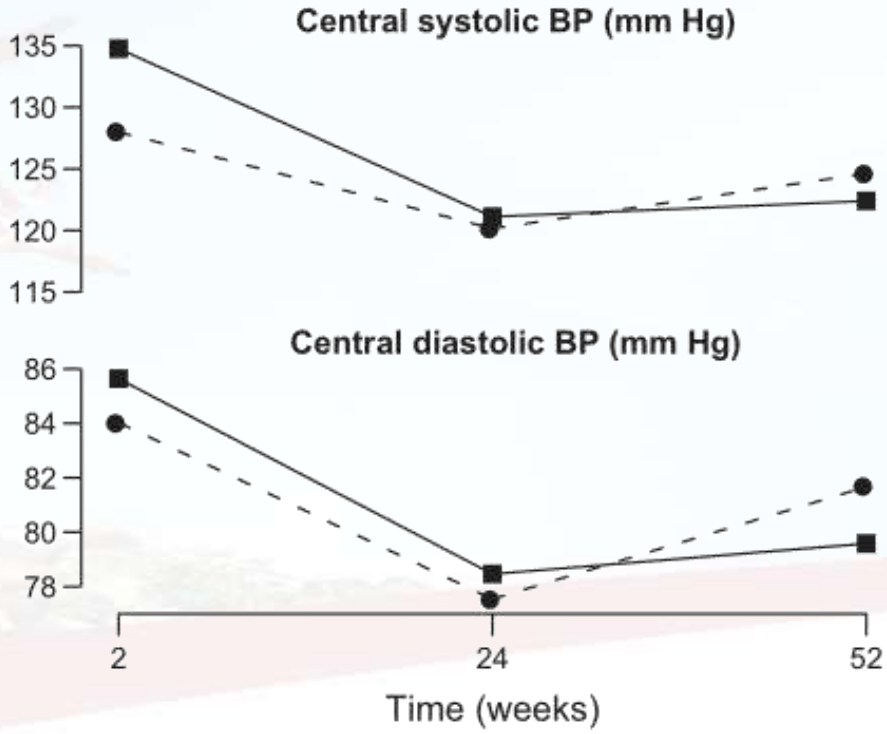



**Figure 2.** Mean reduction in central systolic and diastolic blood pressures measured at baseline and at weeks 24 and 52. Only the nebivolol group displays significantly reduced central systolic ($P<0.001$) and diastolic blood pressures ($P=0.01$) after 52 weeks of treatment compared with baseline values. nebivolol; -●-, metoprolol; BP, blood pressure.

Hypertension 2011;57:1122-112

CoSAC Le congrès des Sociétés Africaines de Cardiologie

STCCCV Société Tunisienne de Cardiologie & de Chirurgie Cardio-Vasculaire

19 March 2015

# Digital capillaroscopy as important tool for early diagnostics of arterial hypertension

Yu. I. Gurfinkel; M. L. Sasonko; A. V. Priezzhev

Author Affiliations +

Proceedings Volume 9448, Saratov Fall Meeting 2014: Optical Technologies in Biophy
XVI; Laser Physics and Photonics XVI; and Computational Biophysics; 944804 (2015);

Hypertension

American Heart Association.

**Hypertension: A Disease of the Microcirculation?**
François Feihl, Lucas Liaudet, Bernard Waeber and Bernard I. Levy

## Effects of Antihypertensive Drugs on Capillary Rarefaction in Spontaneously Hypertensive Rats: Intravital Microscopy and Histologic Analysis

Sabino, Bruno MSc*; Lessa, Marcos A MD, PhD*; Nascimento, Alessandro R MSc*; Rodrigues, Carlos AB MSc†; Henriques, Maria das Graças PhD†; Garzoni, Luciana R PhD*; Levy, Bernard I MD, PhD‡; Tibiriçá, Eduardo MD, PhD*

Journal of Cardiovascular Pharmacology: April 2008 - Volume 51 - Issue 4 - p 402-409
doi: 10.1097/FJC.0b013e3181673bc5
Original Article

# Hypertension
## A Disease of the Microcirculation?

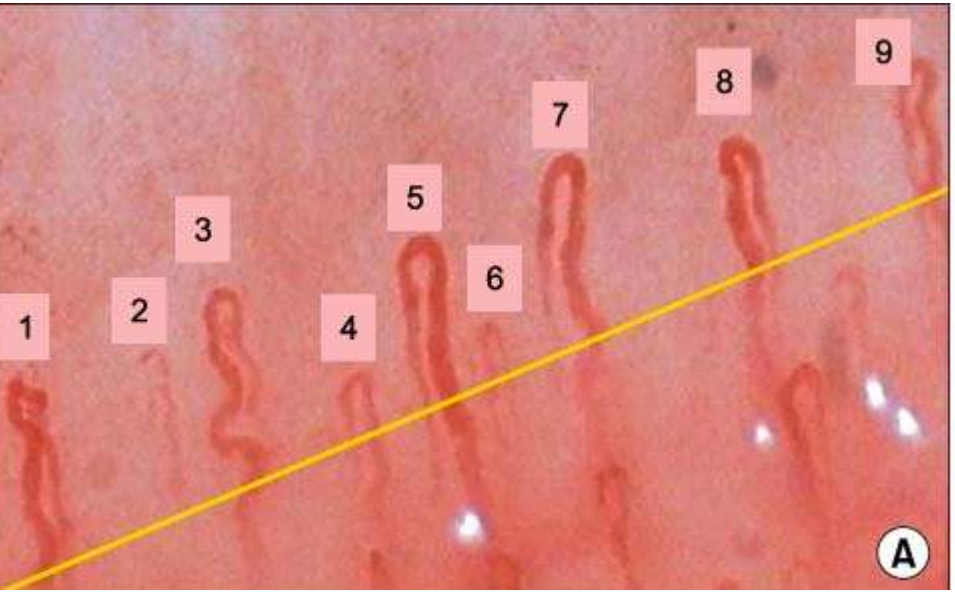
François Feihl, Lucas Liaudet, Bernard Waeber, Bernard I. Levy

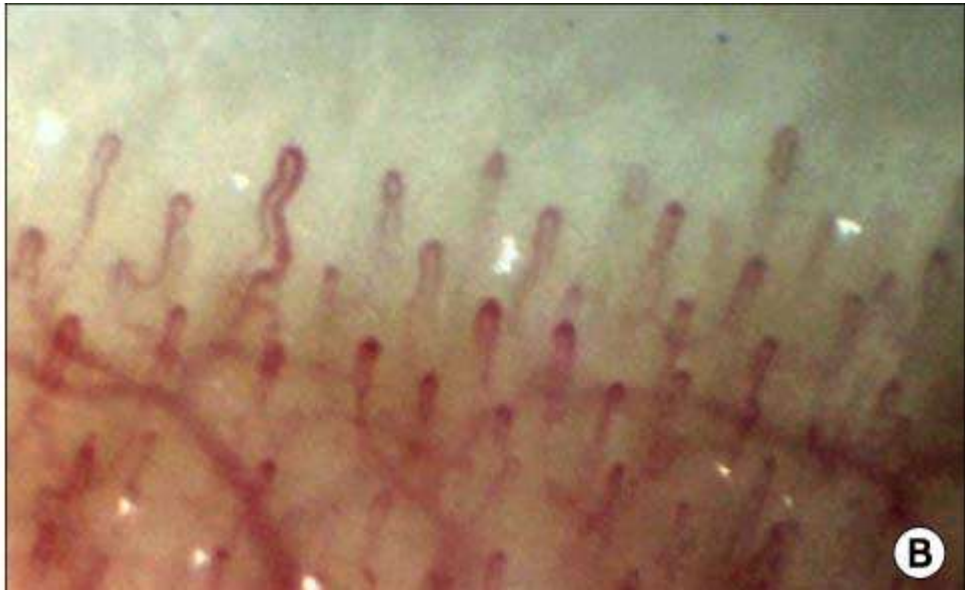
AJH 2006; 19:477–483

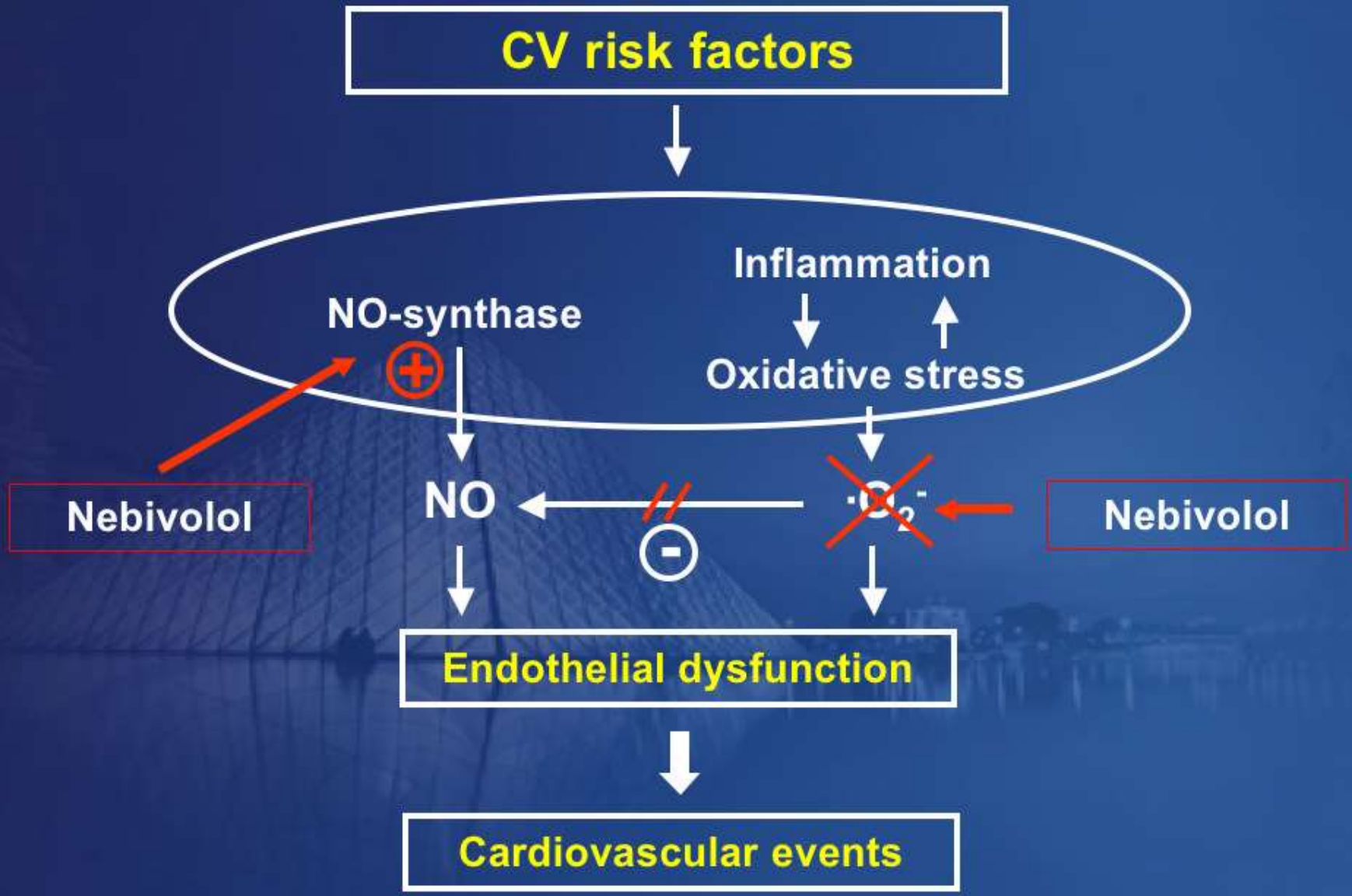
Blood Vessels

## Increased Skin Capillary Density in Treated Essential Hypertensive Patients

Haythem Debbabi, Laurent Uzan,
Jean Jacques Mourad, Michel Safar, Bernard I. Levy, and Eduardo Tibiriçà




CV risk factors
Inflammation
NO-synthase
Oxidative stress
Nebivolol
NO
$\cdot O_2^-$
Nebivolol
Endothelial dysfunction
Cardiovascular events

# Nobel Prize in Medicine 1998


Robert F Furchgott  Louis J Ignarro  Murad Ferid

## Prize motivation: "for their discoveries concerning NITRIC OXIDE as a signalling molecule in the cardiovascular system"

# Les contre-vérités

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STCCCV
Société Tunisienne de Cardiologie & de Chirurgie Cardio-Vasculaire

# ALLHAT Hypertension Trial

42,418 high-risk hypertensive patients

**90% previously treated**
**10% untreated**

**STEP 1 AGENTS**

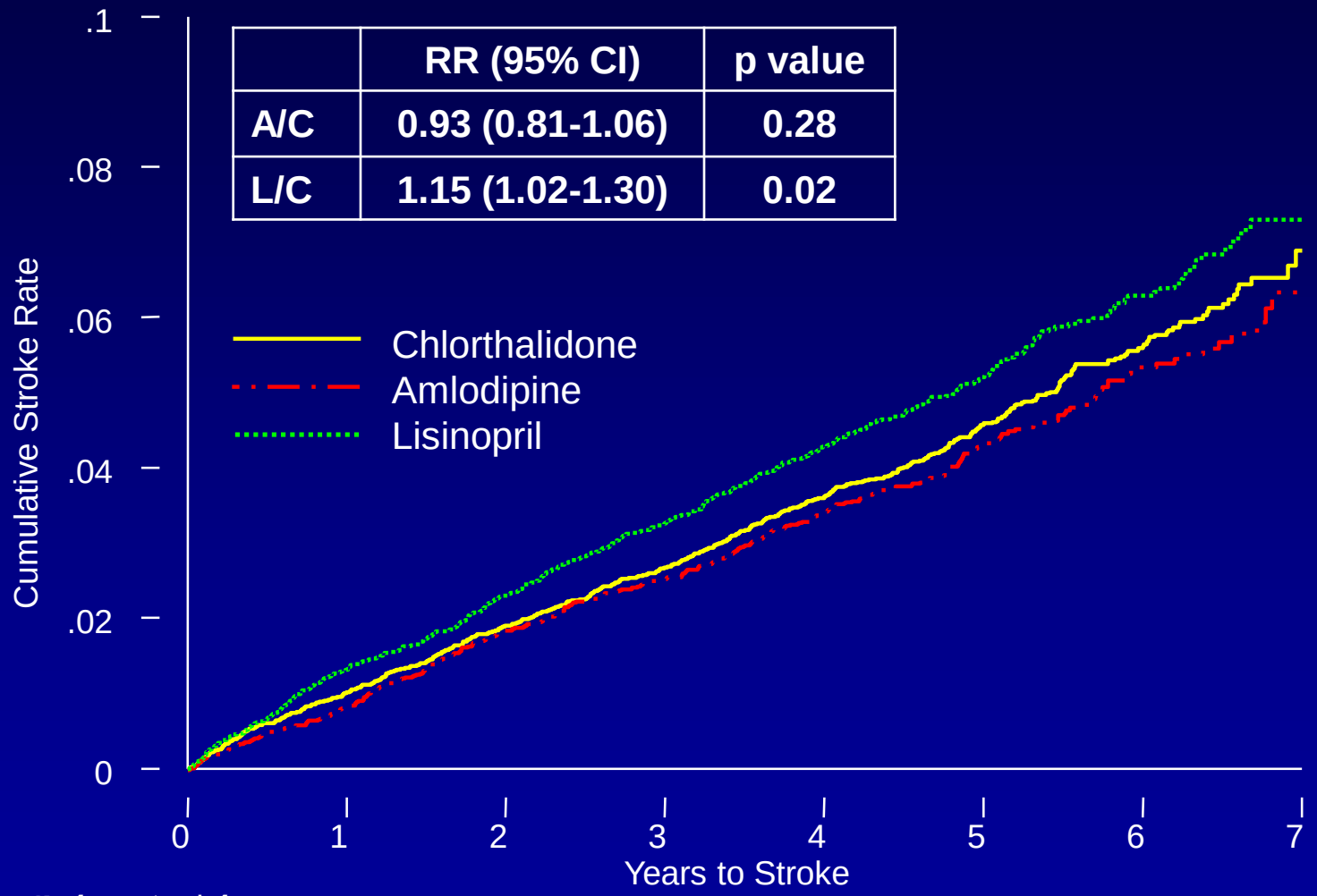
| Chlorthalidone 12.5-25 mg | Amlodipine 2.5-10 mg | Lisinopril 10-40 mg | Doxazosin 1-8 mg |
|---|---|---|---|
| N=15,255 | N=9,048 | N=9,054 | N=9,061 |

**STEP 2 AND 3 AGENTS (5 years)**

| Atenolol | Clonidine | Reserpine | Hydralazine |
|---|---|---|---|
| 28.0% | 10.6% | 4.3% | 10.9% |

# Cumulative Event Rates for Stroke by ALLHAT Treatment Group

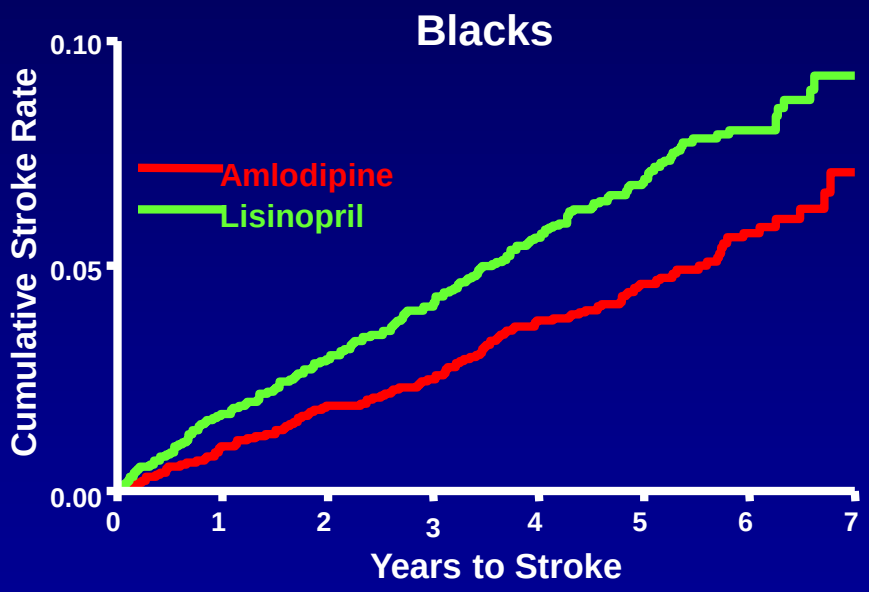
| | RR (95% CI) | p value |
|---|---|---|
| A/C | 0.93 (0.81-1.06) | 0.28 |
| L/C | 1.15 (1.02-1.30) | 0.02 |



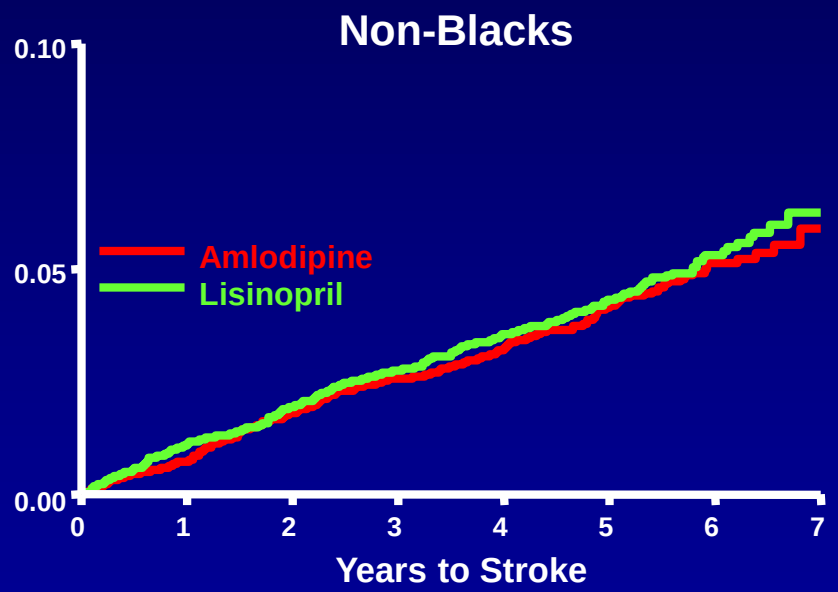

Number at risk:

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Chlor | 15,255 | 14,515 | 13,934 | 13,309 | 11,570 | 6,385 | 3,217 | 567 |
| Amlo | 9,048 | 8,617 | 8,271 | 7,949 | 6,937 | 3,845 | 1,813 | 506 |
| Lisin | 9,054 | 8,543 | 8,172 | 7,784 | 6,765 | 3,891 | 1,828 | 949 |

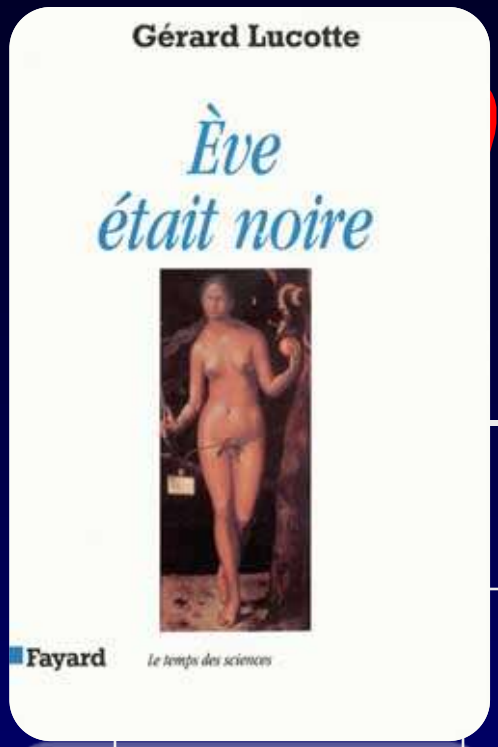
# Cumulative Event Rates for Stroke by Race and Treatment Group




| | RR (95%CI) | P value |
|---|---|---|
| L/A | 1.51 (1.22-1.86) | <0.001 |




| | RR (95%CI) | P value |
|---|---|---|
| L/A | 1.07 (0.89-1.28) | 0.47 |




# Stroke Interaction by Gender and Race

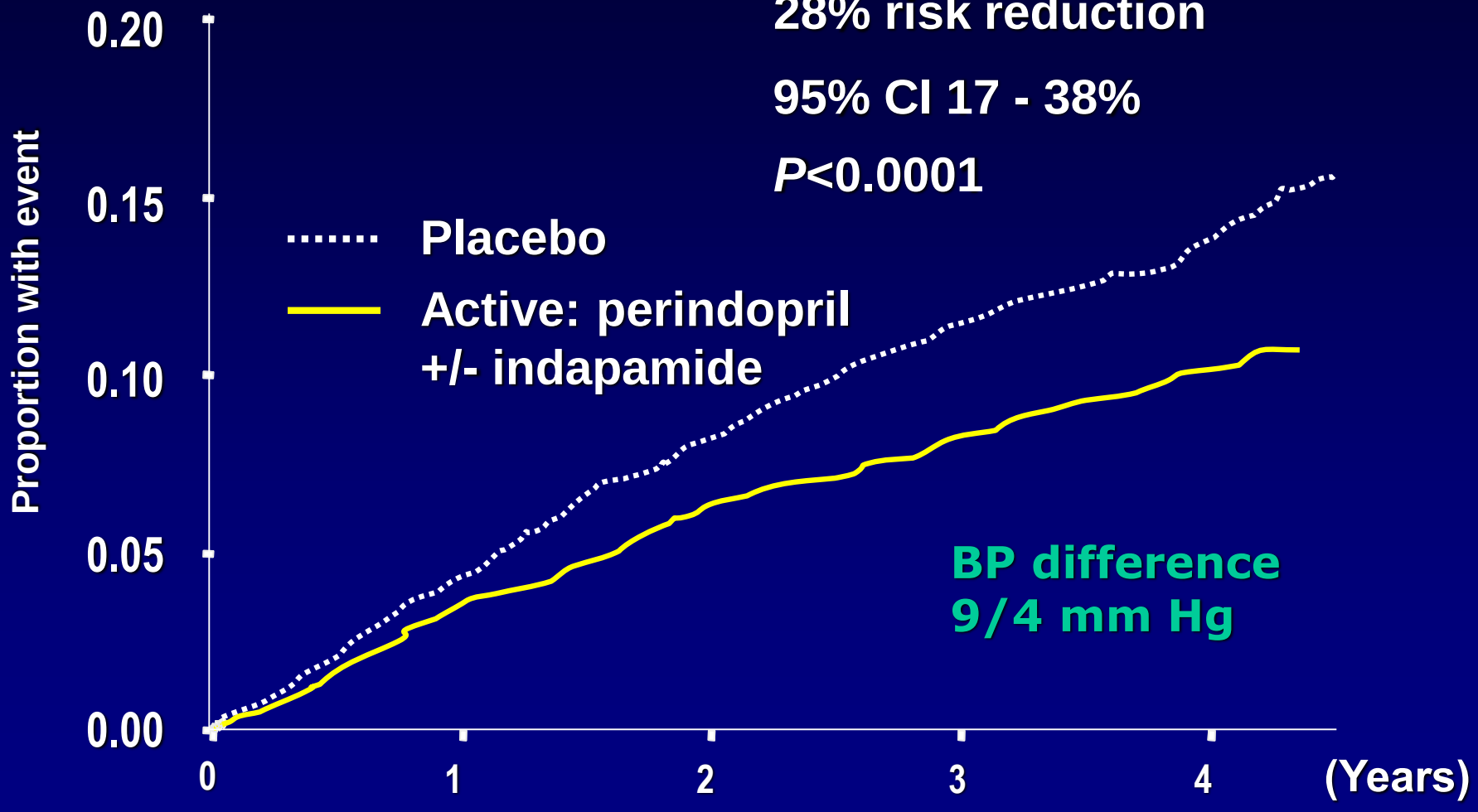
Lisinopril versus Amlodipine

| | Blacks | | Non-Blacks | |
|---|---|---|---|---|
| | Males | Females | Males | Females |
| 6 Yr Event Rate per 100 Pts | 9.2 vs 6.7 | 7.0 vs 4.9 | 5.2 vs 5.9 | 5.3 vs 3.7 |
| Δ | + 37 % | + 45 % | - 11 % | + 46 % |

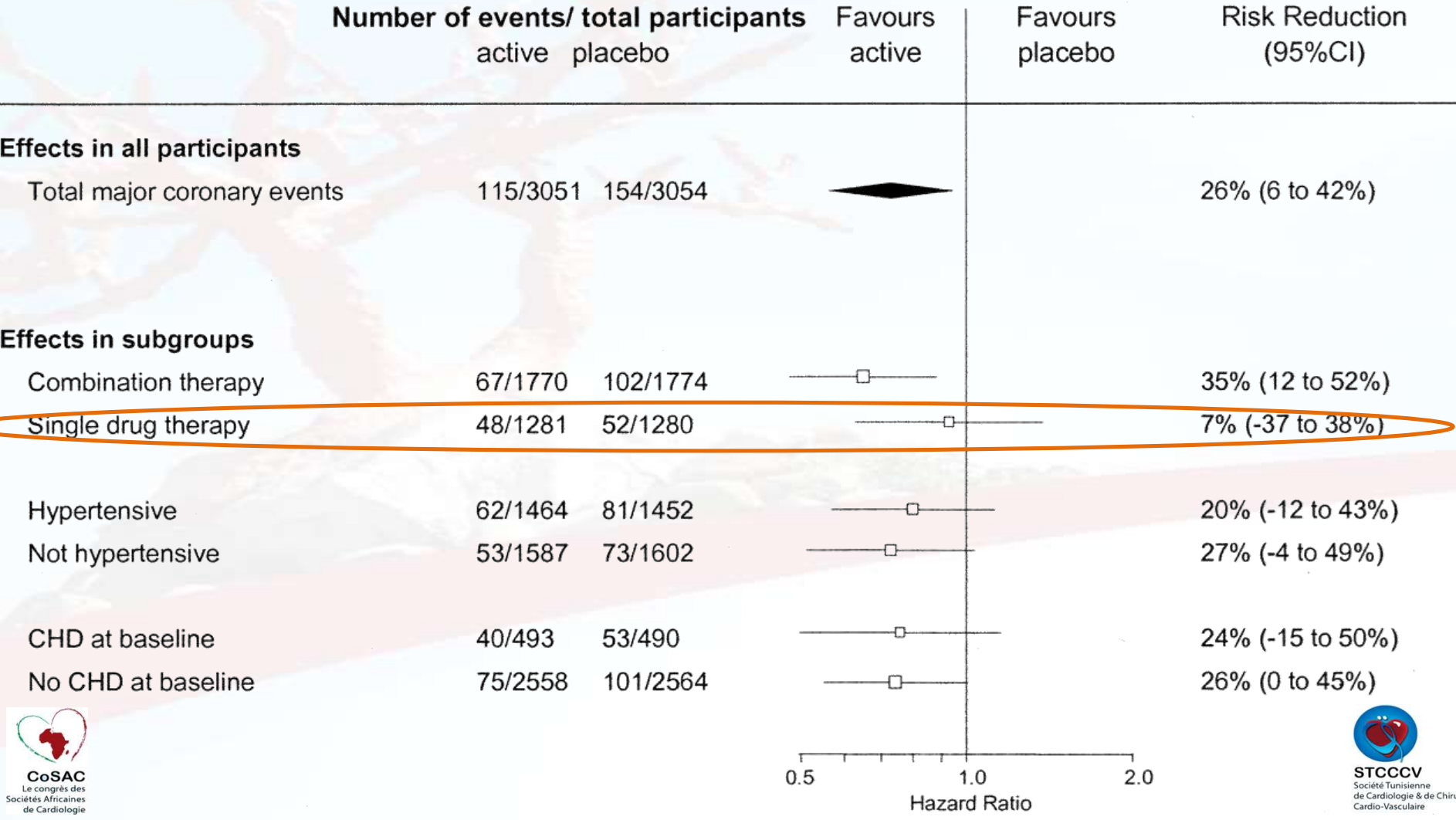
+ favors amlodipine
- favors lisinopril

p=0.02 for interaction of gender within non-blacks

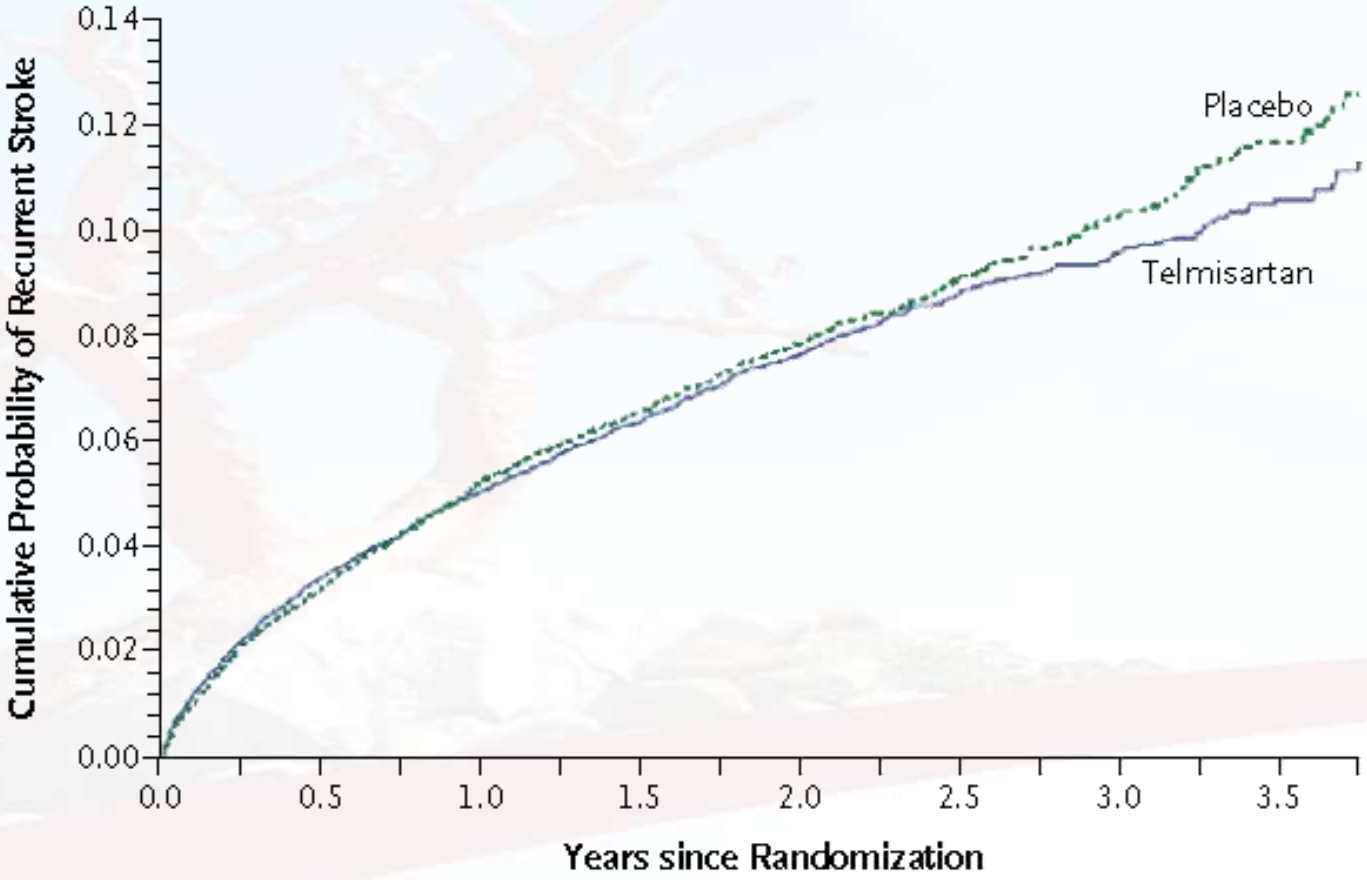
# Stroke Risk Reduction in PROGRESS
## *All participants*




PROGRESS Collaborative Group. *Lancet* 2001;358:1033-41



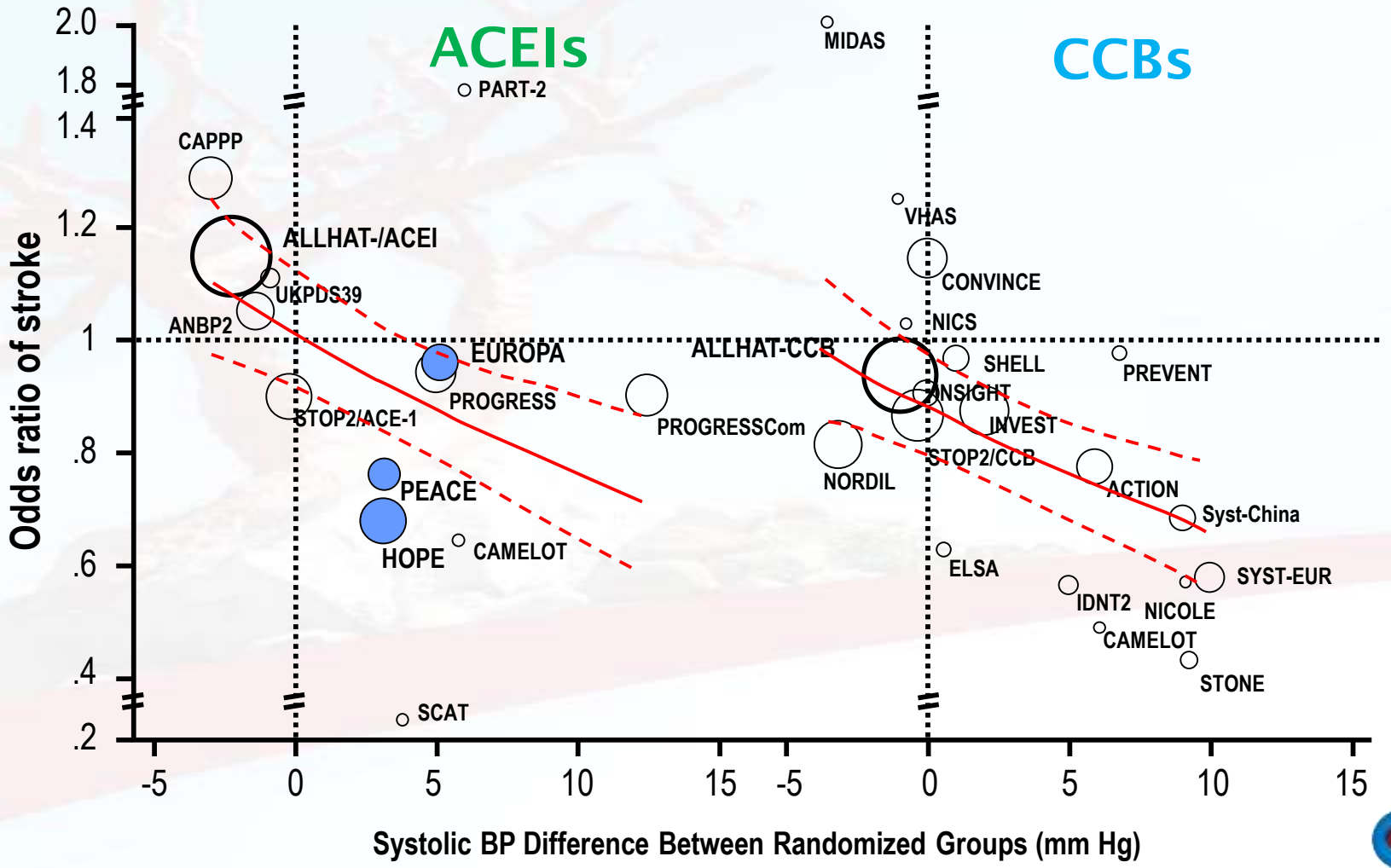
# Telmisartan to Prevent Recurrent Stroke and Cardiovascular Events (PRoFESS Study)




**p = 0.23**

Profess Investigators, N Engl J Med 2008

# STROKE




Verdecchia P et al. *Hypertension*. 2005;46:386-392 (A).

*Pflugers Arch*. 2014 April ; 466(4): 757–765. doi:10.1007/s00424-014-1454-x.

# T-type Calcium Channel Blockers as Neuroprotective Agents

**Benjamin J. Kopecky**, **Ruqiang Liang**, and **Jianxin Bao***
Department of Otolaryngology, Center for Aging, Washington University School of Medicine, St. Louis, MO 63110

Clinically Used Drugs with Possible Neuroprotective Effects

| Drug | Pathways Inhibited | MW (g/mole) | Clinical Dose/mM | IC50 (mM)-T channel | Neuroprotective? |
|---|---|---|---|---|---|
| Anti-Epileptics | | | | | |
| Ethosuximide | T-Type (CaV3.1, CaV3.2); Na | 141.17 | 250-750mg PO BID/**3.5-10** | 0.3-1.0 | Y |
| Trimethadione | T-Type (CaV3.2) | 143.14 | 300-600mg TID-QID/**6-16.7** | ? | Y |
| Zonisamide | T-Type; Oxidative; Carbonic Anhydrase Inhibitor | 212.23 | 400-600mg qD/**1.89-2.83** | 0.05-0.5 | Y |
| Anti-Hypertensives/Angina | | | | | |
| Amlodipine* | T-Type (CaV3.2>CaV3.1 or CaV3.3) and L-Type; Na; K | 408.88 | 5-10mg qD/**0.12-0.24** | 0.031 | Y |
| Aranidipine*J | T-Type and L-Type | 388.37 | 5-20mg qD/**0.012-0.051** | 0.03-0.04 | ? |
| Azelnidipine*CJ | T-Type and L-Type | 582.65 | 8-16mg qD/**0.014-0.028** | 0.04-0.07 | Y |
| Barnidipine*SJO | T-Type and L-Type | 528 | 10-15mg qD/**0.019-0.028** | 0.005-0.02 | ? |
| Benidipine*IJCO | T-Type and L-Type | 542.02 | 2-4mg qD/**0.0037-0.0074** | 0.003-0.2 | ? |
| Efonidipine*J | T-Type and L-Type | 631.66 | 40mg qD/**0.63** | 0.0029 | ? |
| Mibefradil*O | T-Type and L-Type; Na; K | 568.55 | 400mg qD/**0.70** | 0.00017-0.00029 | Y |
| Nicardipine | T-Type and L-Type | 515.99 | 20mg TID-120mg qD/**0.11-0.23** | 0.0028 | Y |
| Nimodipine | T-Type and L-Type | 418.44 | 60mg q4h/**0.86** | 0.0056 | Y |
| Other | | | | | |
| Lomerizine*J | T-Type and L-Type | 541.46 | 5-20mg qD/**0.0009-0.0036** | 0.00000046 | Y |
| Pimozide | T-Type; Dopamine | 461.55 | 2-10mg BID/**0.0089-0.043** | 0.000036-0.000054 | Y |

*Not currently FDA approved; J= Japan, C= China, I= India, S= Spain, O= Other; MW = Molecular Weight

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**Journal of the American College of Cardiology**

Volume 71, Issue 13, April 2018

DOI: 10.1016/j.jacc.2018.01.058

# Angiotensin-Converting Enzyme Inhibitors in Hypertension

## To Use or Not to Use?

Franz H. Messerli, Sripal Bangalore, Chirag Bavishi and Stefano F. Rimoldi

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Société Tunisienne de Cardiologie & de Chirurgie Cardio-Vasculaire


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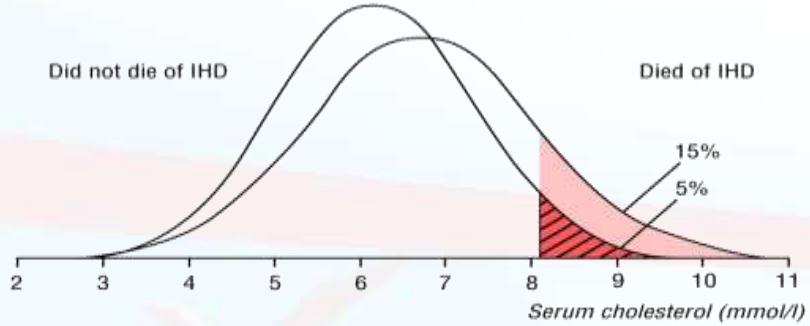
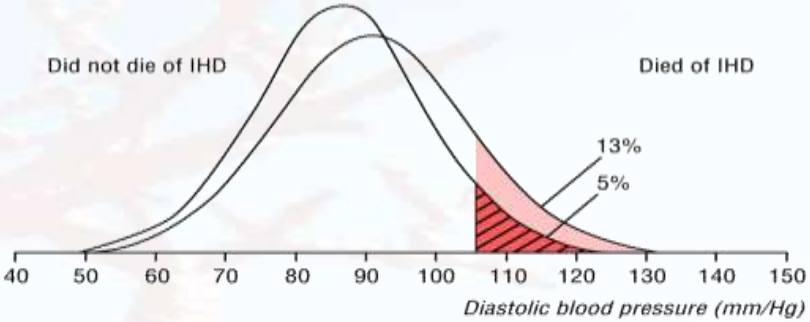
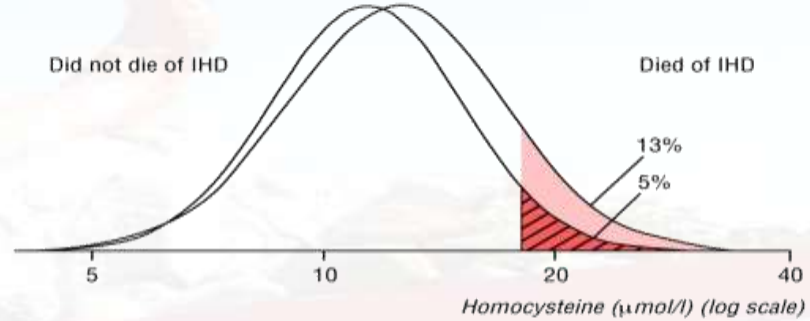
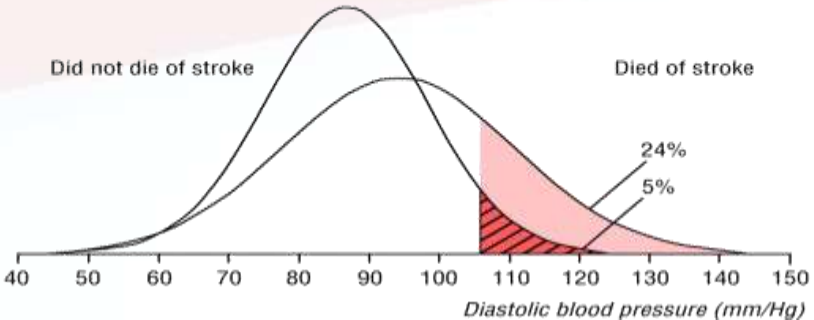
EU



# 2018 ESC/ESH Guidelines for the management of arterial hypertension

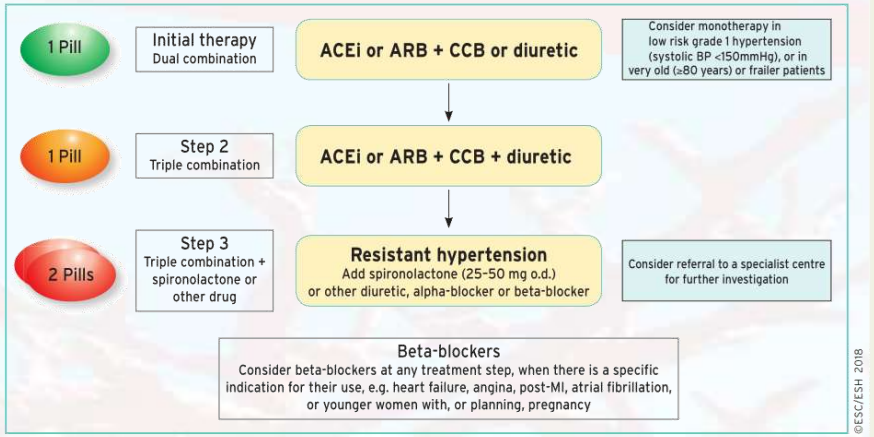



**Figure 4 Core drug treatment strategy for uncomplicated hypertension.** The core algorithm is also appropriate for most patients with HMOD, cerebrovascular disease, diabetes, or PAD. ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; HMOD = hypertension-mediated organ damage; MI = myocardial infarction; o.d. = omni die (every day); PAD = peripheral artery disease.

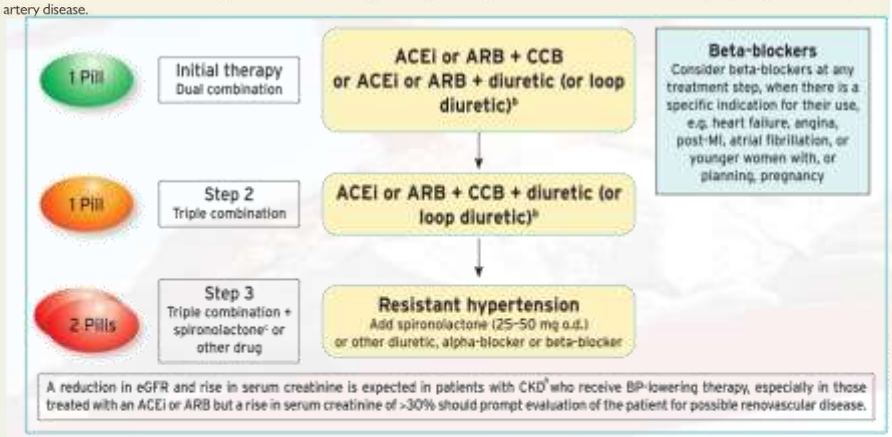



**Figure 6 Drug treatment strategy for hypertension and chronic kidney disease.** ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BP = blood pressure; CCB = calcium channel blocker; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; MI = myocardial infarction; o.d. = omni die (every day).
[a]CKD is defined as an eGFR <60 mL/min/1.72 m$^2$ with or without proteinuria.
[b]Use loop diuretics when eGFR is <30 mL/min/1.72 m$^2$, because thiazide/thiazide-like diuretics are much less effective/ineffective when eGFR is reduced to this level.
[c]Caution: risk of hyperkalaemia with spironolactone, especially when eGFR is <45 mL/min/1.72 m$^2$ or baseline K$^+$ ≥4.5 mmol/L.

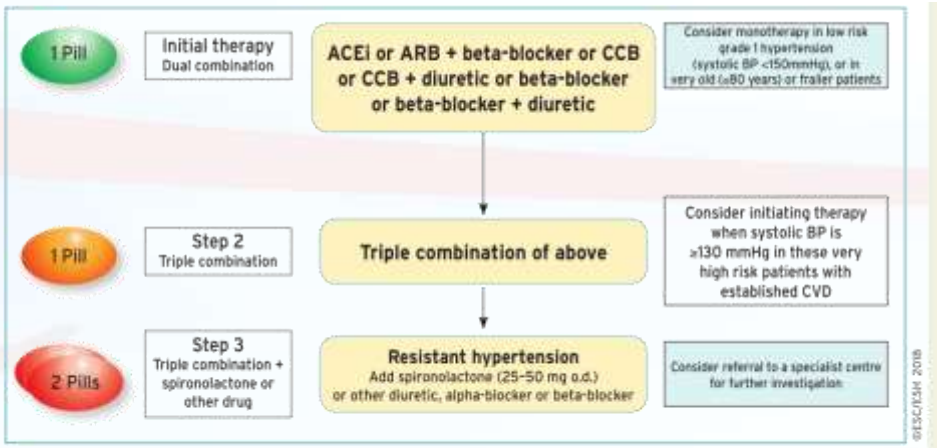



**Figure 5 Drug treatment strategy for hypertension and coronary artery disease.** ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BP = blood pressure; CCB = calcium channel blocker; CVD = cardiovascular disease; o.d. = omni die (every day).

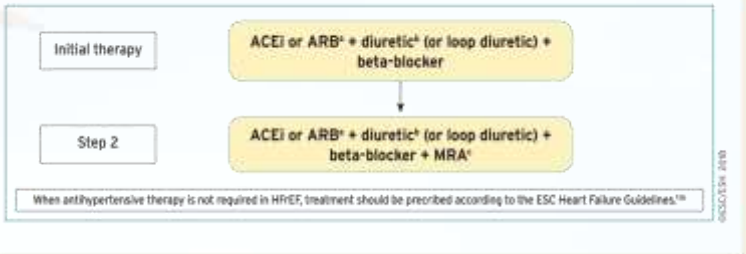



**Figure 7 Drug treatment strategy for hypertension and heart failure with reduced ejection fraction.** Do not use non-dihydropyridine CCBs (e.g. verapamil or diltiazem). ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CCB = calcium channel
[a]Consider an angiotensin receptor/neprilysin inhibitor instead of ACEi or ARB per ESC Heart Failure Guidelines.[136]
[b]Diuretic refers to thiazide/thiazide-like di… oedema.
[c]MRA (… eplerenone).

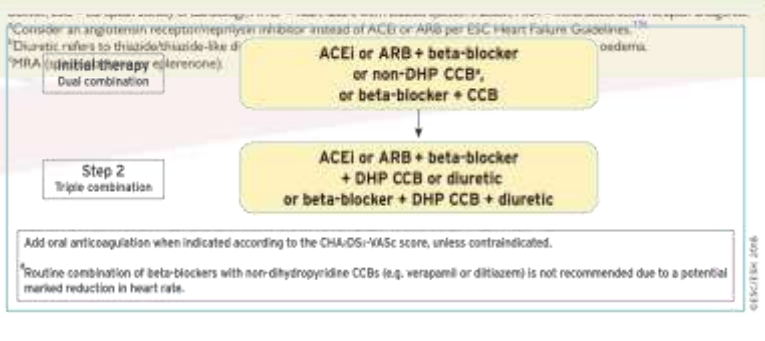



**Figure 8 Drug treatment strategy for hypertension and atrial fibrillation.** ACEi = angiotensin-converting enzyme inhibitor; … fibrillation; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; $CHA_2DS_2$-VASc = $CHA_2DS_2$-VASc = Ca… Hypertension, Age ≥75 (Doubled), Diabetes, Stroke (Doubled) – Vascular disease, Age 65–74 and Sex category (Female); DHP = dihydr…
[a]Non-DHP CCB (non-DHP CCB, e.g. verapamil or diltiazem).

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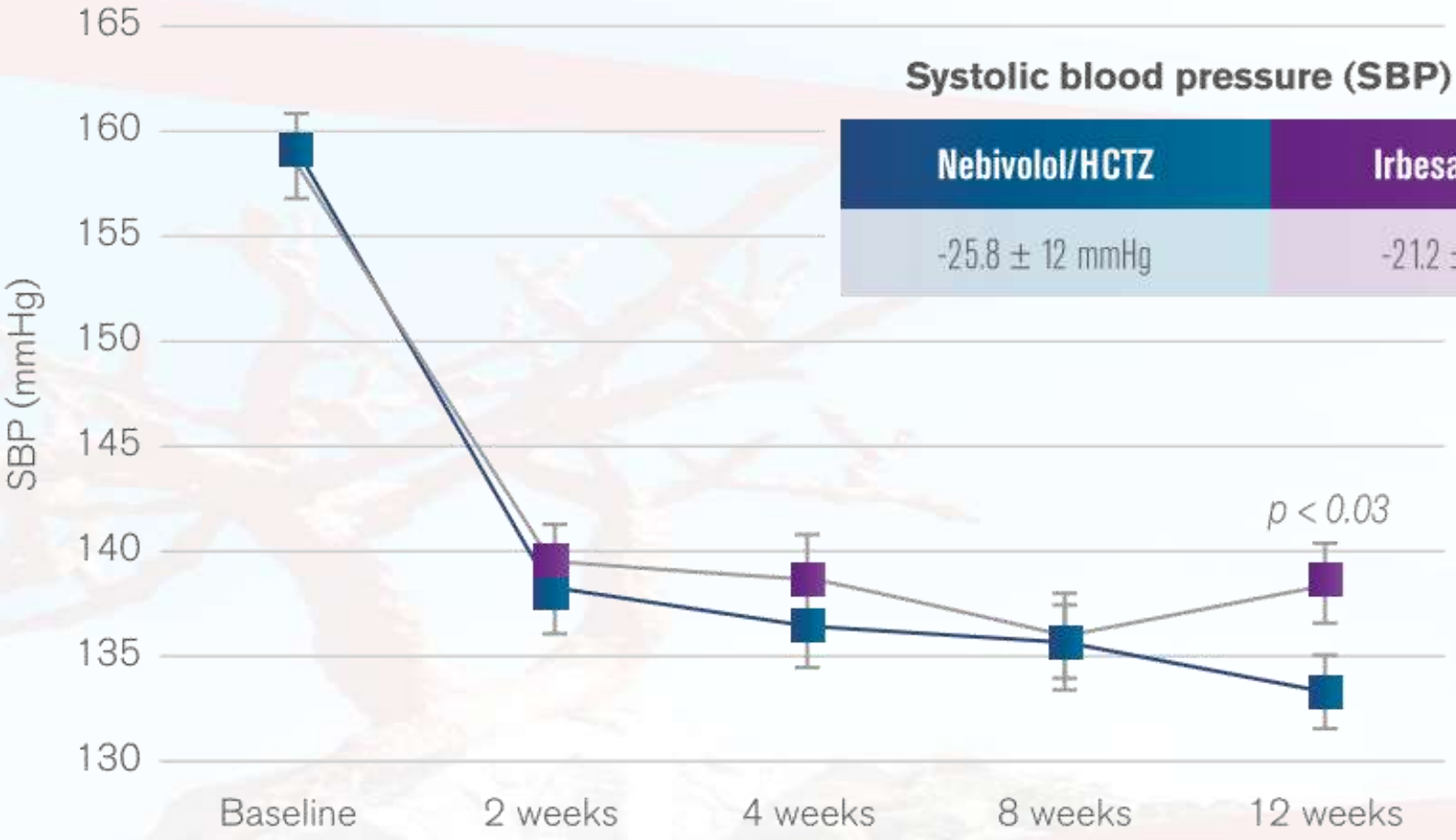


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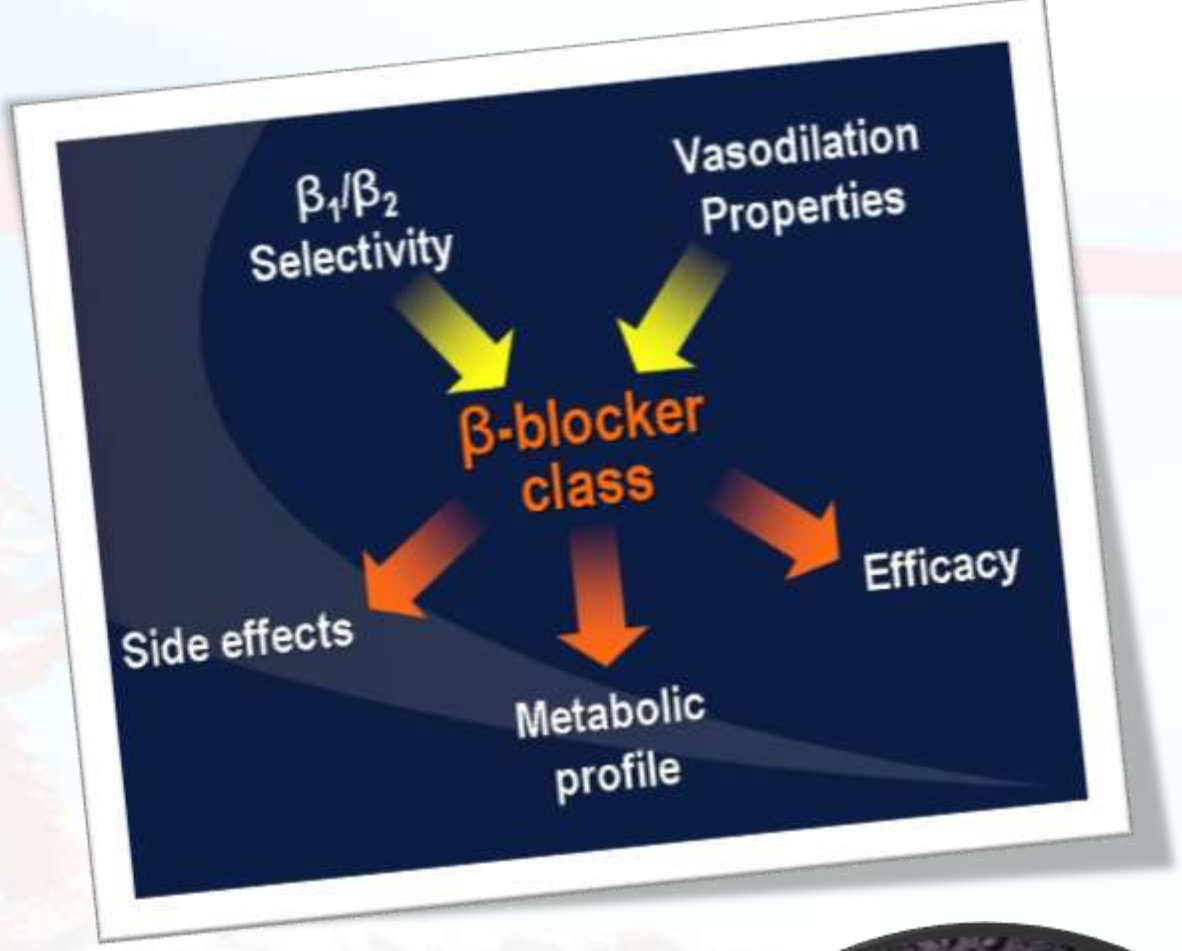



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Merci pour
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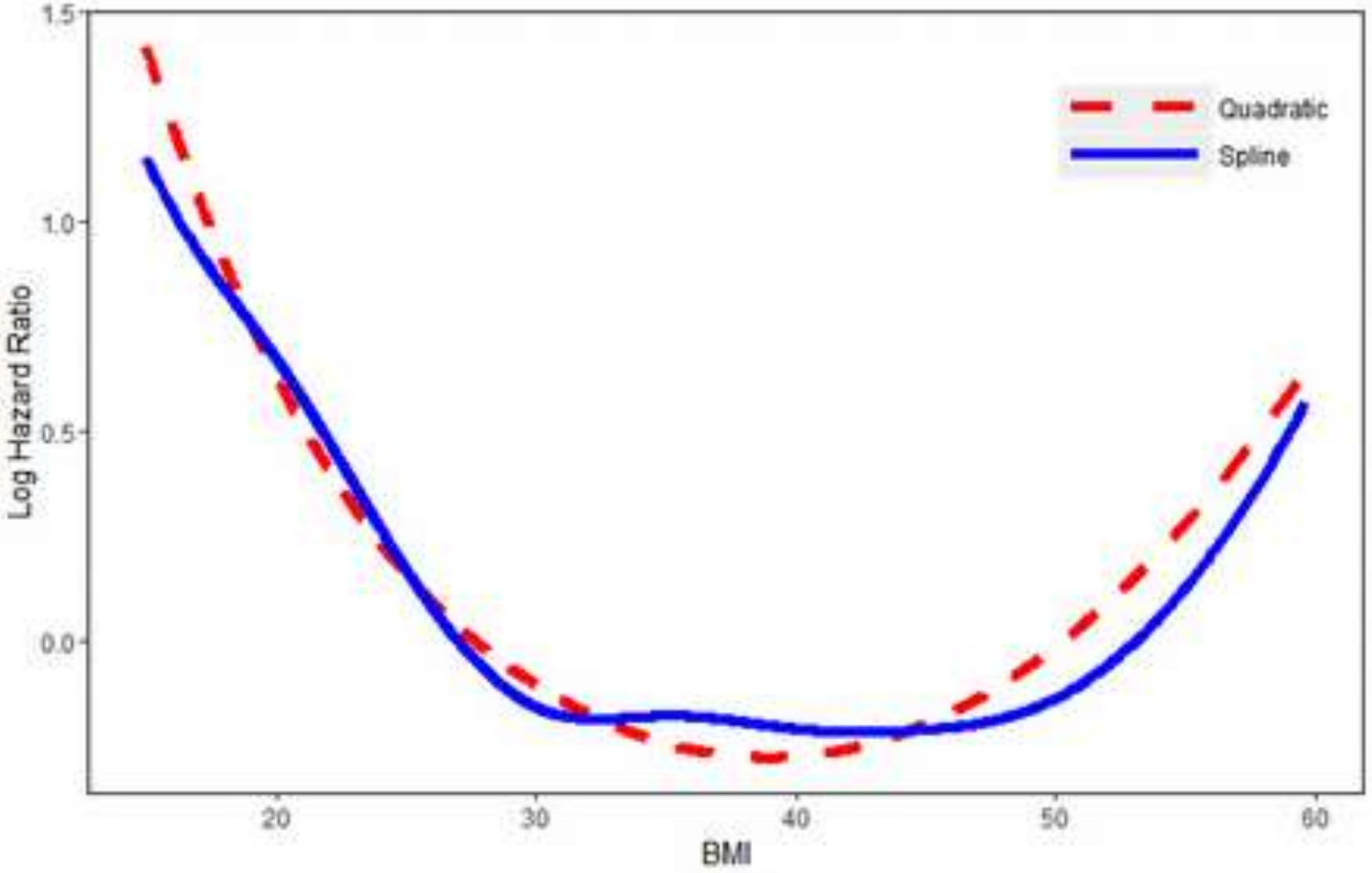
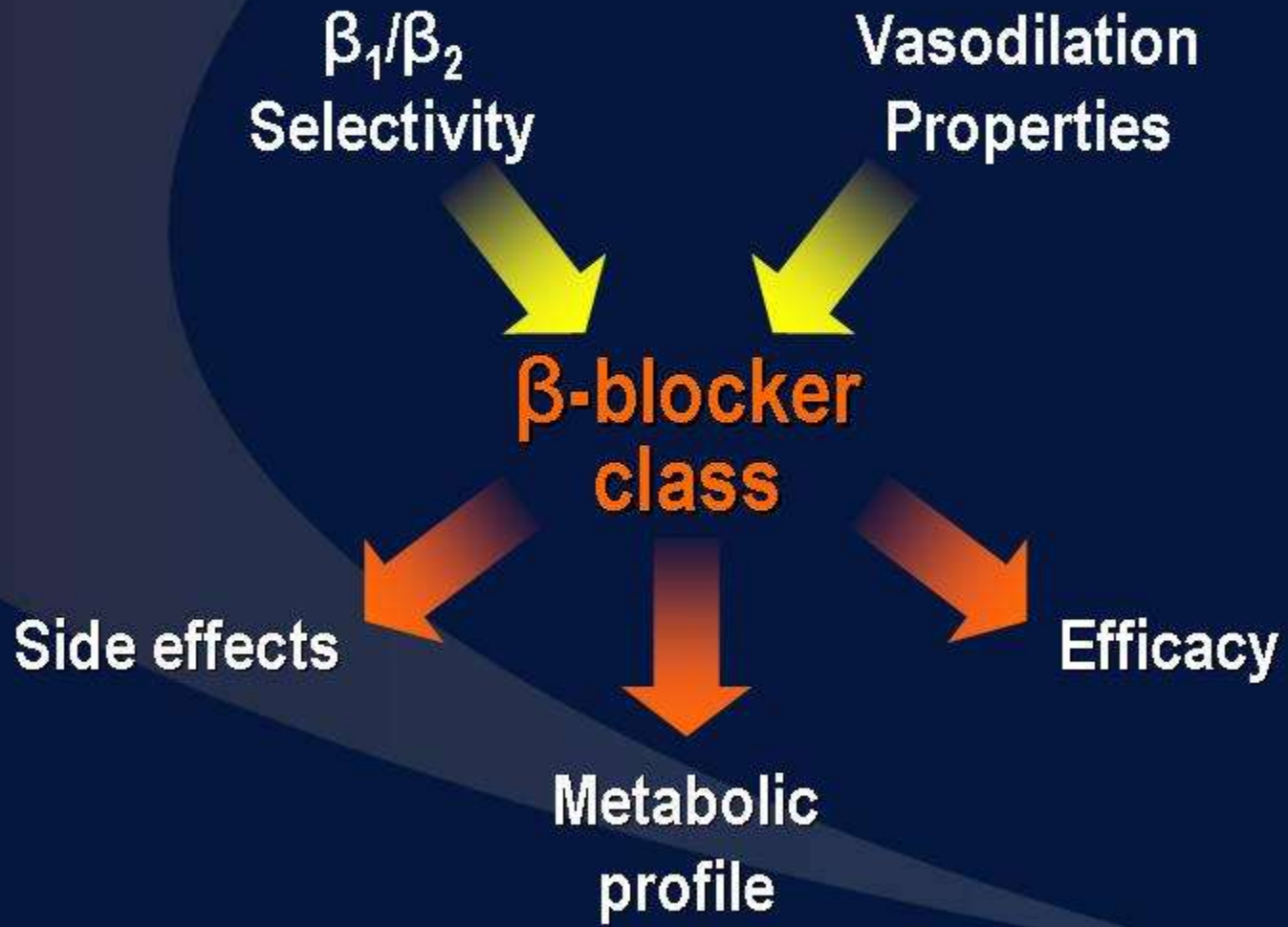
Cardio-Vasculaire

# The Relationship of Body Mass Index to All-Cause Mortality at 8 Years of Follow-Up in ALLHAT



# Main Factors Contributing to Heterogeneity Within the β-blocker Class



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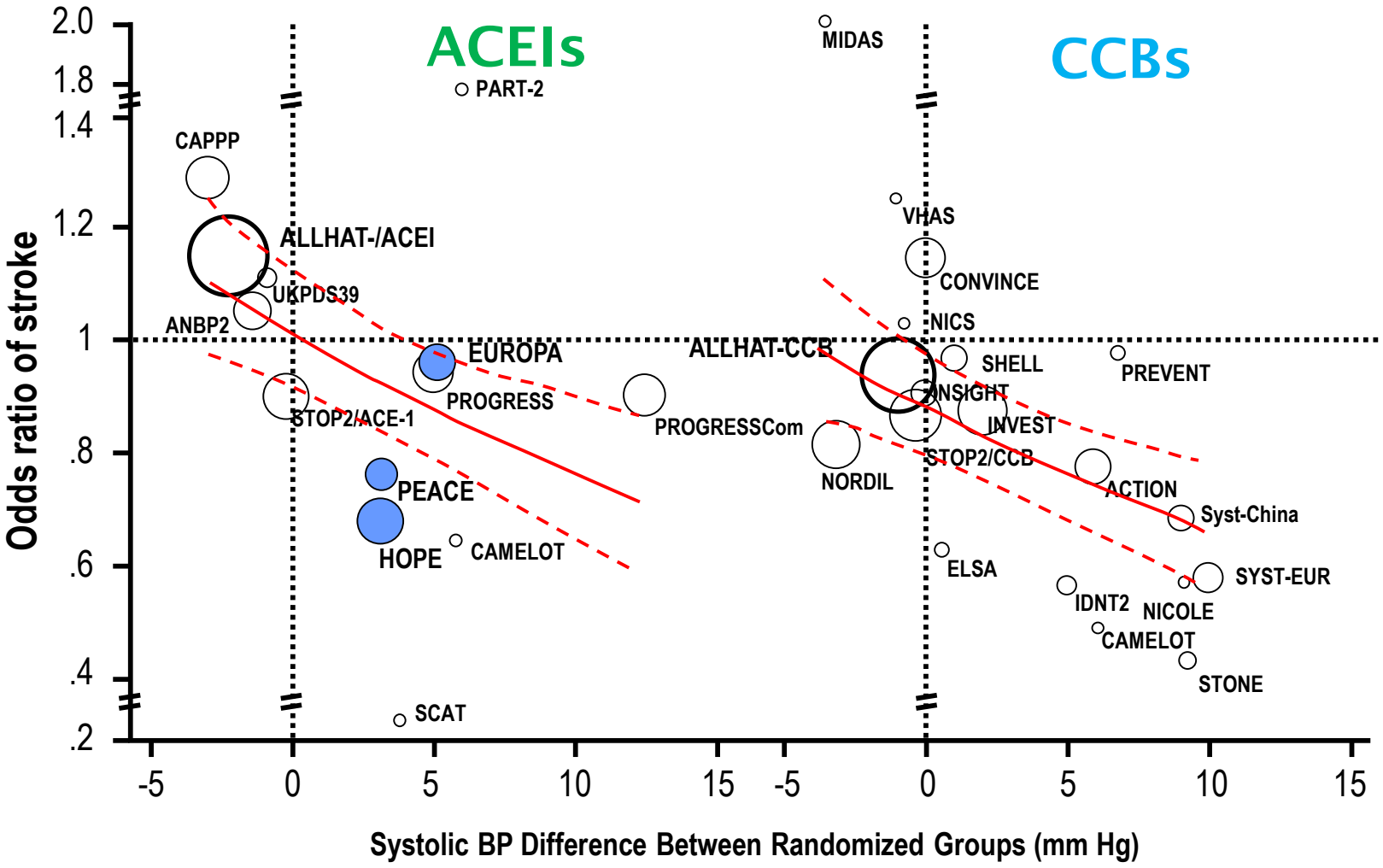
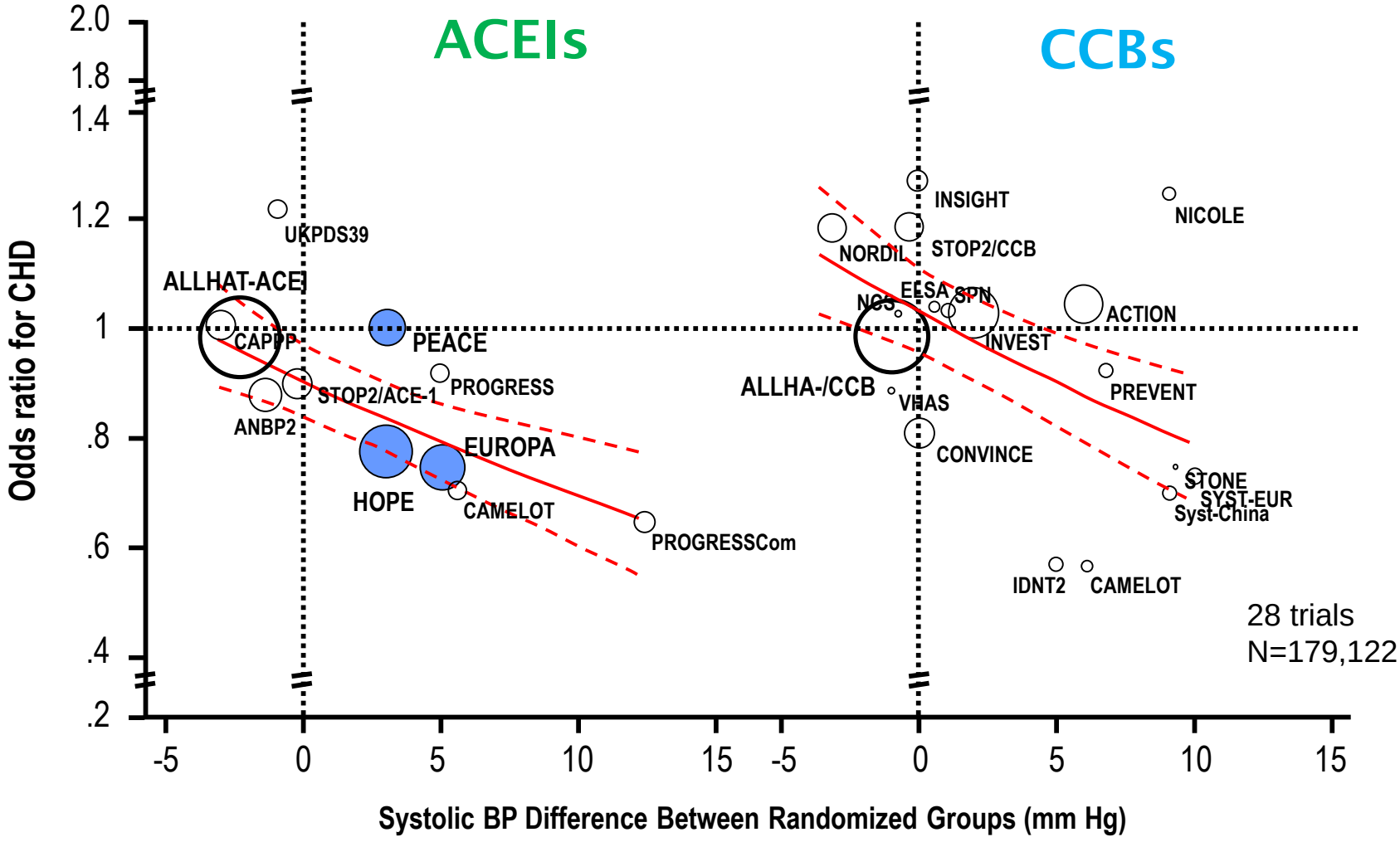



Verdecchia P et al. *Hypertension*. 2005;46:386-392 (A).

# CHD




Verdecchia P et al. *Hypertension.* 2005;46:386-392 (A).

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