# Qu’apportent les grands essais cliniques de l’HTA dans la vie réelle?

Jean-Jacques Mourad,

**Médecine interne & HTA**

**Hotline SOS HTA : 06 HTA 140 90**

**CHU Avicenne,AP-HP et Université Paris 13, Bobigny**

Nice, février 2010

# Usual versus tight control of systolic blood pressure in non-diabetic patients with hypertension (Cardio-Sis): an open-label randomised trial

*Paolo Verdecchia, Jan A Staessen, Fabio Angeli, Giovanni de Simone, Augusto Achilli, Antonello Ganau, Gianfrancesco Mureddu, Sergio Pede, Aldo P Maggioni, Donata Lucci, Gianpaolo Reboldi, on behalf of the Cardio-Sis investigators**

| | Usual control (n=553) | Tight control (n=558) |
|---|---|---|
| Age (years) | 67 (7) | 67 (7) |
| Body-mass index (kg/m²) | 27·8 (4·0) | 27·8 (4·3) |
| Waist circumference (cm) | 98·5 (11·6) | 98·6 (12·2) |
| Systolic pressure (mm Hg) | 163·3 (11·1) | 163·3 (11·3) |
| Diastolic pressure (mm Hg) | 89·7 (8·8) | 89·6 (8·8) |
| Heart rate (beats per min) | 70·4 (10·7) | 71·2 (10·2) |
| Serum creatinine (μmol/L) | 83·8 (18·6) | 83·2 (19·4) |
| Glucose (mmol/L) | 5·43 (0·63) | 5·46 (0·71) |
| Total cholesterol (mmol/L) | 5·63 (1·14) | 5·57 (1·0) |
| HDL cholesterol (mmol/L) | 1·50 (0·51) | 1·50 (0·50) |
| LDL cholesterol (mmol/L) | 3·40 (0·98) | 3·38 (0·94) |
| Women | 324 (59%) | 329 (59%) |
| Current cigarette smoking | 115 (21%) | 120 (22%) |
| Dyslipidaemia* | 425 (77%) | 418 (75%) |
| Coronary artery disease | 69 (13%) | 59 (11%) |
| Stroke or transient ischaemic attack | 49 (9%) | 42 (8%) |
| Occlusive arterial disease | 11 (2%) | 19 (3%) |
| Drugs | | |
| Diuretics | 259 (47%) | 226 (41%) |
| β blockers | 212 (38%) | 180 (32%) |
| ACE inhibitors | 243 (44%) | 245 (44%) |
| Angiotensin-receptor blockers | 159 (29%) | 193 (35%) |
| Calcium-channel blockers | 196 (35%) | 184 (33%) |
| α1 blockers | 52 (9%) | 50 (9%) |
| Centrally acting drugs | 13 (2%) | 13 (2%) |
| Statins | 128 (23%) | 125 (22%) |
| Aspirin | 104 (19%) | 107 (19%) |

Data are mean (SD) or number (%). ACE=angiotensin-converting enzyme.
*Dyslipidaemia is a total cholesterol of 5·2 mmol/L or more, an HDL cholesterol of less than 1·0 mmol/L, or an LDL cholesterol of 3·4 mmol/L or more at randomisation.

| At 2 years | *Usual control* | *Tight control* | *p* |
|---|---|---|---|
| *BP decrease (mmHg)* | ***27.7 / 10.8*** | ***31.3 / 12.3*** | ***0.0001*** |
| *Final BP (mmHg)* | ***136 / 79*** | ***132 / 77*** | ***0.0001 /0.04*** |
| *% < 140 mmHg* | ***66.9*** | ***78.7*** | ***0.0001*** |
| *% < 130 mmHg* | ***27.3*** | ***72.2*** | ***0.0001*** |

Lancet 2009;374:525

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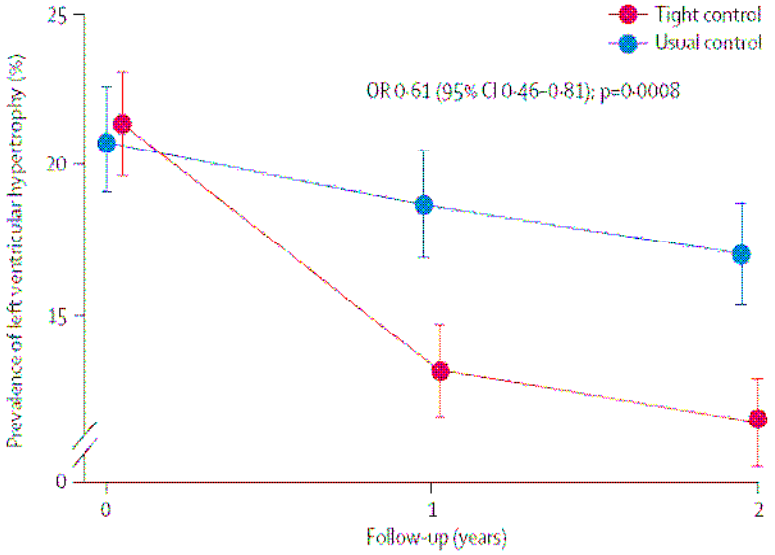


| | Usual control (n=553) | Tight control (n=557) | HR (95% CI) | p value |
|---|---|---|---|---|
| Death from any cause, MI, stroke, TIA, atrial fibrillation, admission for heart failure, angina, or coronary revascularisation* | 52 (9·4%) | 27 (4·8%) | 0·50 (0·31–0·79) | 0·003 |
| Death from any cause, MI, stroke, admission for heart failure, angina, or coronary revascularisation† | 32 (5·8%) | 17 (3·0%) | 0·51 (0·29–0·93) | 0·027 |
| Single components of composite outcomes | | | | |
| Coronary revascularisation | 15 (2·7%) | 5 (0·9%) | 0·33 (0·12–0·91) | 0·032 |
| New-onset atrial fibrillation | 21 (3·8%) | 10 (1·8%) | 0·46 (0·22–0·98) | 0·044 |
| MI | 6 (1·1%) | 4 (0·7%) | 0·66 (0·19–2·34) | 0·52 |
| Admission for heart failure | 7 (1·3%) | 3 (0·5%) | 0·42 (0·11–1·63) | 0·21 |
| Stroke or TIA | 9 (1·6%) | 4 (0·7%) | 0·44 (0·13–1·42) | 0·16 |
| Death from any cause | 5 (0·9%) | 4 (0·7%) | 0·77 (0·21–2·88) | 0·70 |

Data are number of incident events (%). HR=hazard ratio. MI=myocardial infarction. TIA=transient ischaemic attack. *Pre-defined secondary outcome. †Post-hoc defined composite outcome, which does not include transient ischaemic attack and atrial fibrillation.

*Table 2:* Incidence of the secondary outcome, its components, and death from any cause by randomisation group

Lancet 2009;374:525

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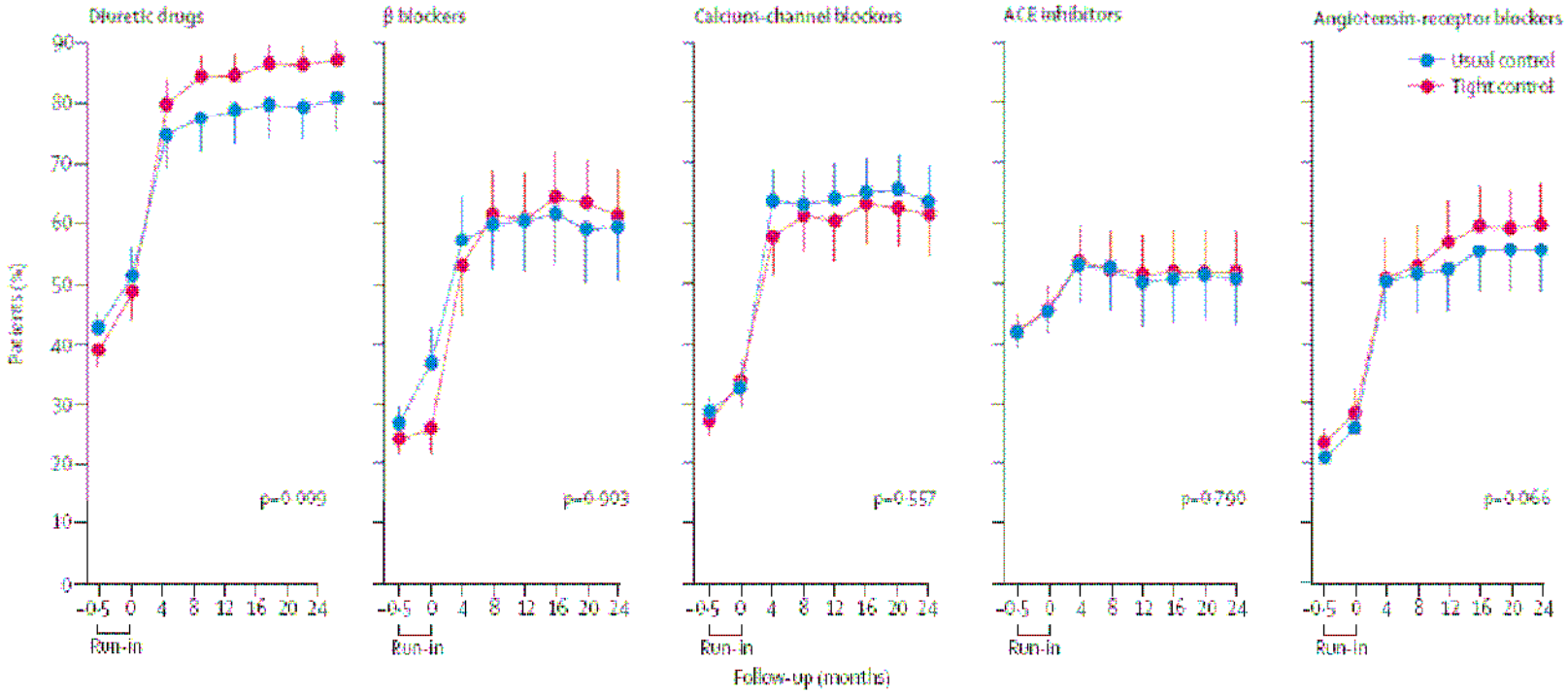


Lancet 2009;374:525

- Le duel des associations (LIFE-ASCOT-ACCOMPLISH)

- Le risque résiduel (ASCOT LLA, JUPITER)

- La courbe en J chez les coronariens ? (INVEST)

- Des « nouvelles » recommandations européennes

- Des injonctions fortes des tutelles

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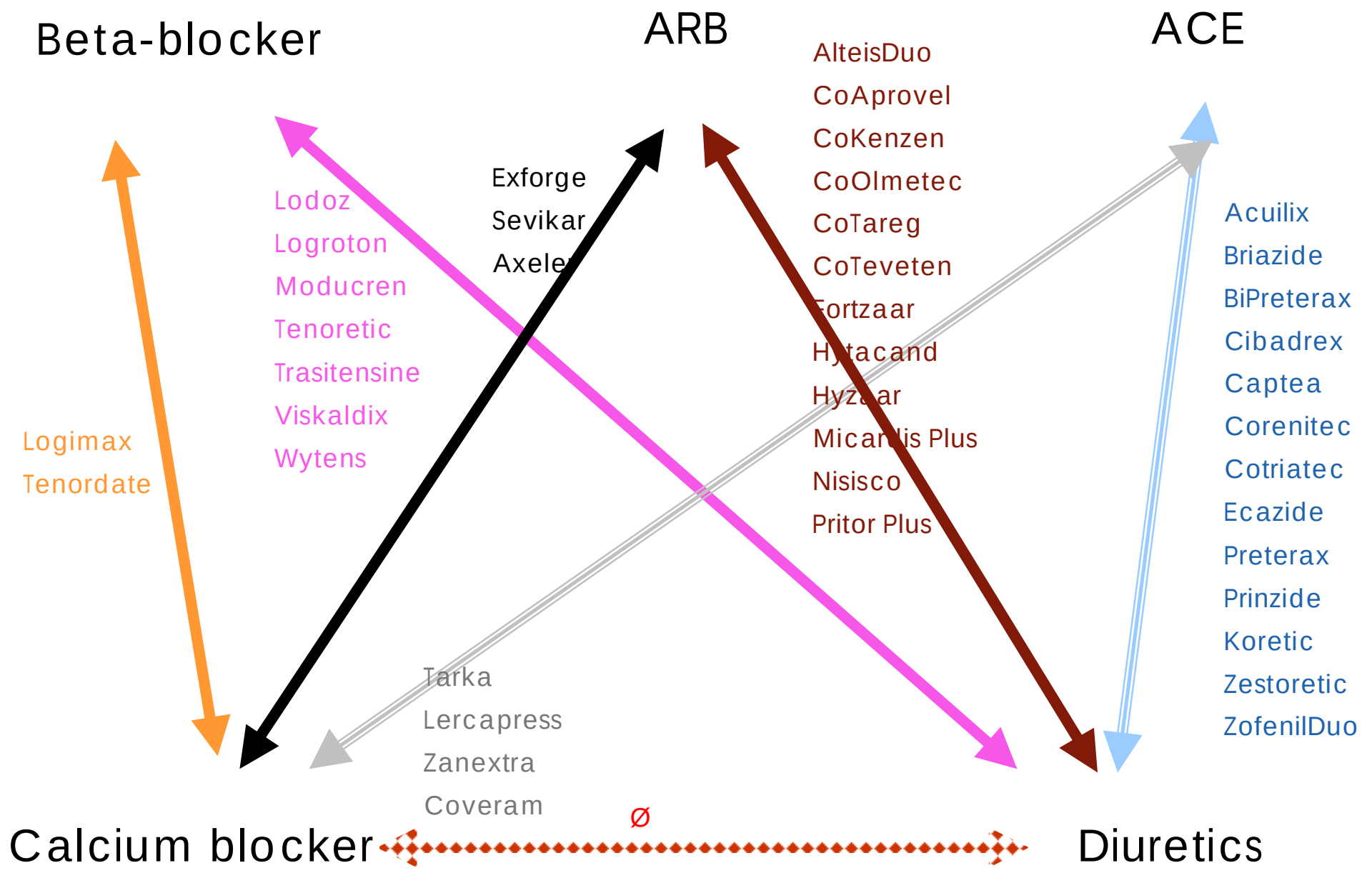

Beta-blocker
ARB
ACE
Logimax
Tenordate
Lodoz
Logroton
Moducren
Tenoretic
Trasitensine
Viskaldix
Wytens
Exforge
Sevikar
Axele
AlteisDuo
CoAprovel
CoKenzen
CoOlmetec
CoTareg
CoTeveten
Fortzaar
Hytacand
Hyzaar
Micardis Plus
Nisisco
Pritor Plus
Acuilix
Briazide
BiPreterax
Cibadrex
Captea
Corenitec
Cotriatec
Ecazide
Preterax
Prinzide
Koretic
Zestoretic
ZofenilDuo
Tarka
Lercapress
Zanextra
Coveram
Ø
Calcium blocker
Diuretics

# LIFE Study Endpoints*

## Primary Endpoint

- Composite of cardiovascular mortality, fatal and non-fatal myocardial infarction, and fatal and non-fatal stroke

## Other predefined endpoints

- total mortality
- angina pectoris†
- heart failure†
- coronary or peripheral revascularization procedures
- resuscitated cardiac arrest
- new-onset diabetes mellitus

*Each endpoint includes only first event; patients could appear in more than one category.
†Requiring hospital admission

Dahlof B, et al. Lancet. 2002;359:995-1003.

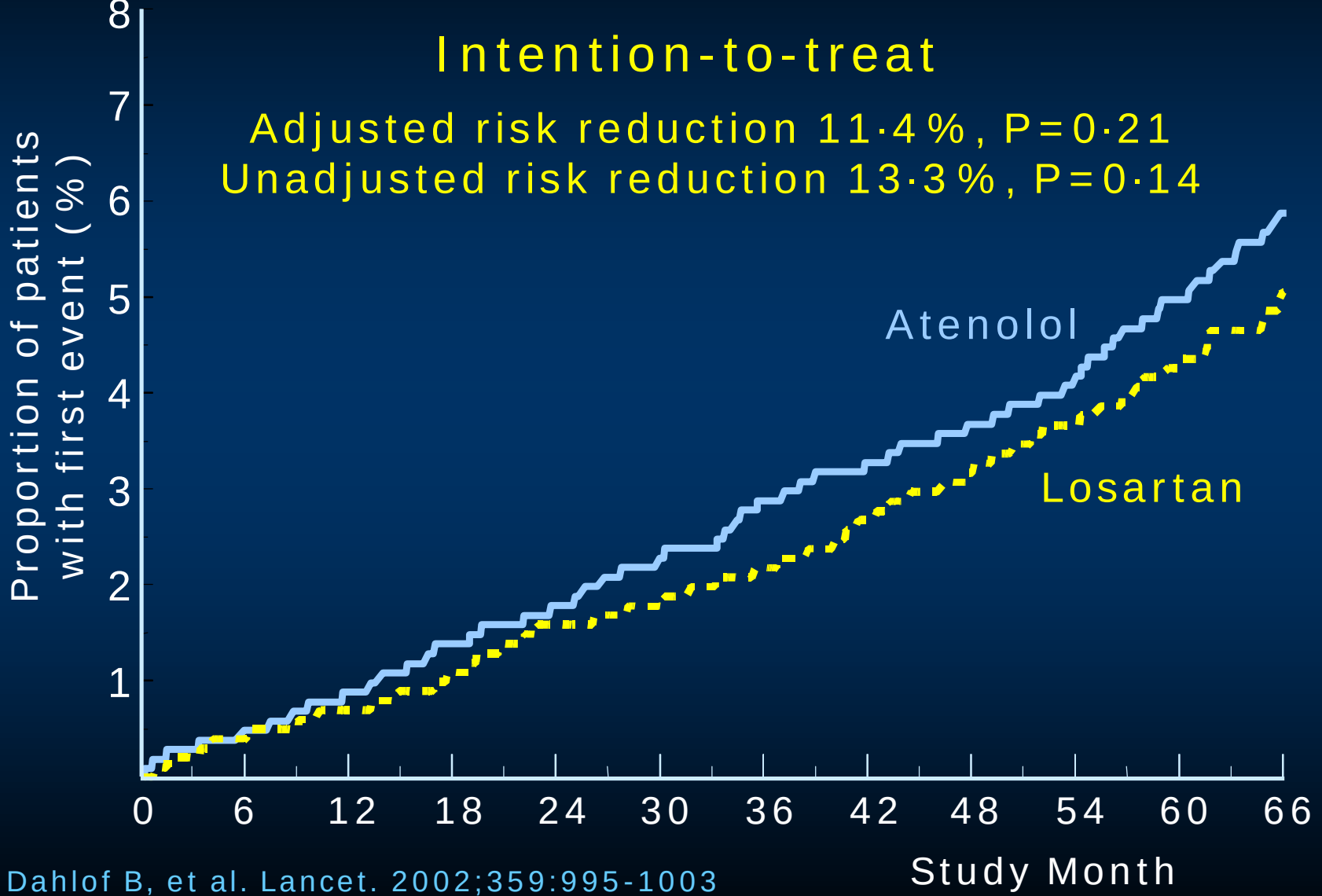
# LIFE Study Blood Pressure and Heart Rate Results

| | Losartan (n=4,605) | Atenolol (n=4,588) |
|---|---|---|
| SBP last visit (mmHg) | 144.1 | 145.4 |
| Change in SBP* | -30.2 | -29.1 |
| DBP last visit (mmHg) | 81.3 | 80.9 |
| Change in DBP | -16.6 | -16.8 |
| MAP last visit (mmHg) | 102.2 | 102.4 |
| BP ≤140/≤90 (%) | 48 | 45 |
| SBP ≤140 mmHg (%) | 49 | 46 |
| DBP ≤ 90 mmHg (%) | 87 | 89 |
| Change in HR (bpm)† | -1.8 | -7.7 |

*P=0.017
†P<0.0001

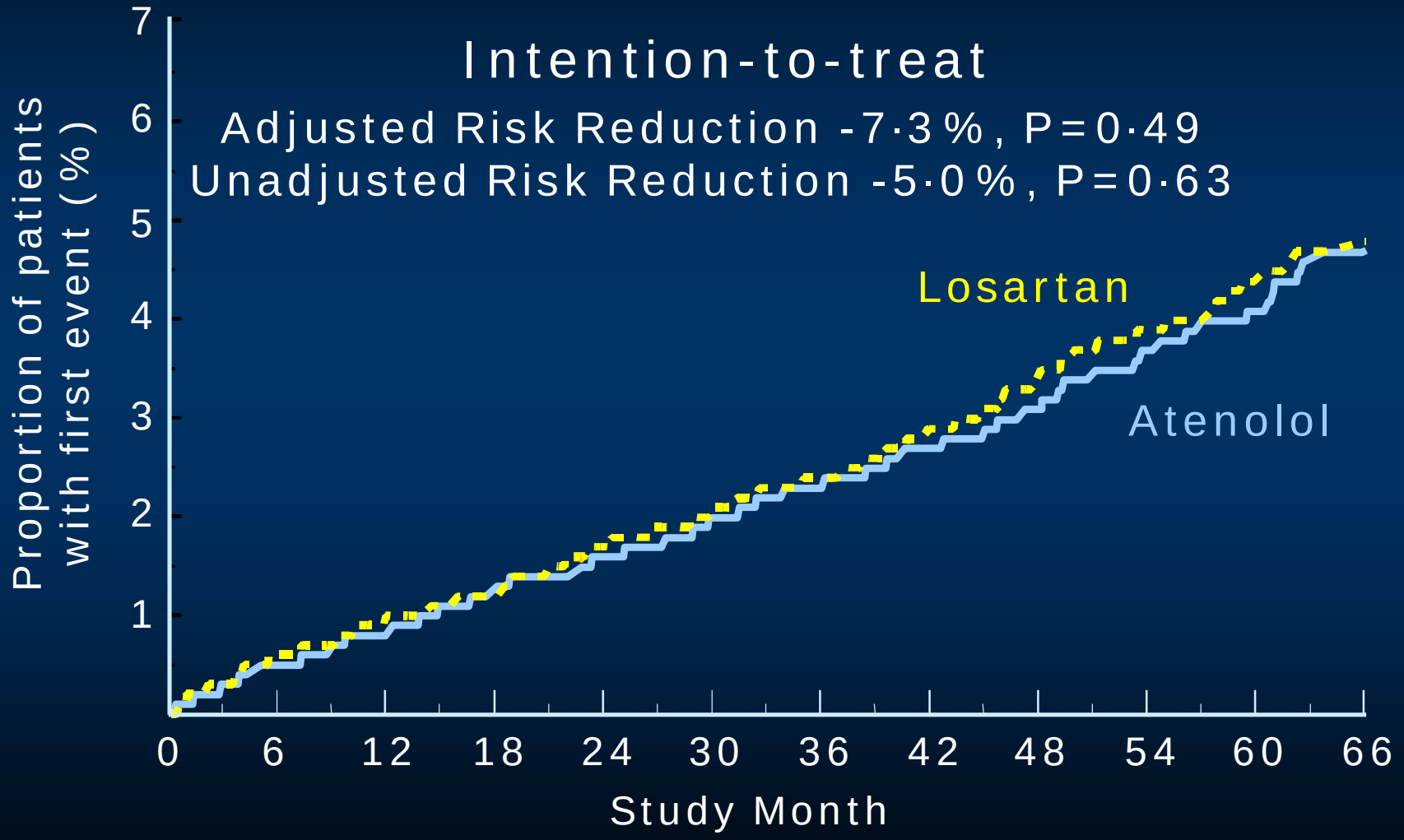
Dahlof B, et al. Lancet. 2002;359:995-1003.

# LIFE Study Cardiovascular Mortality



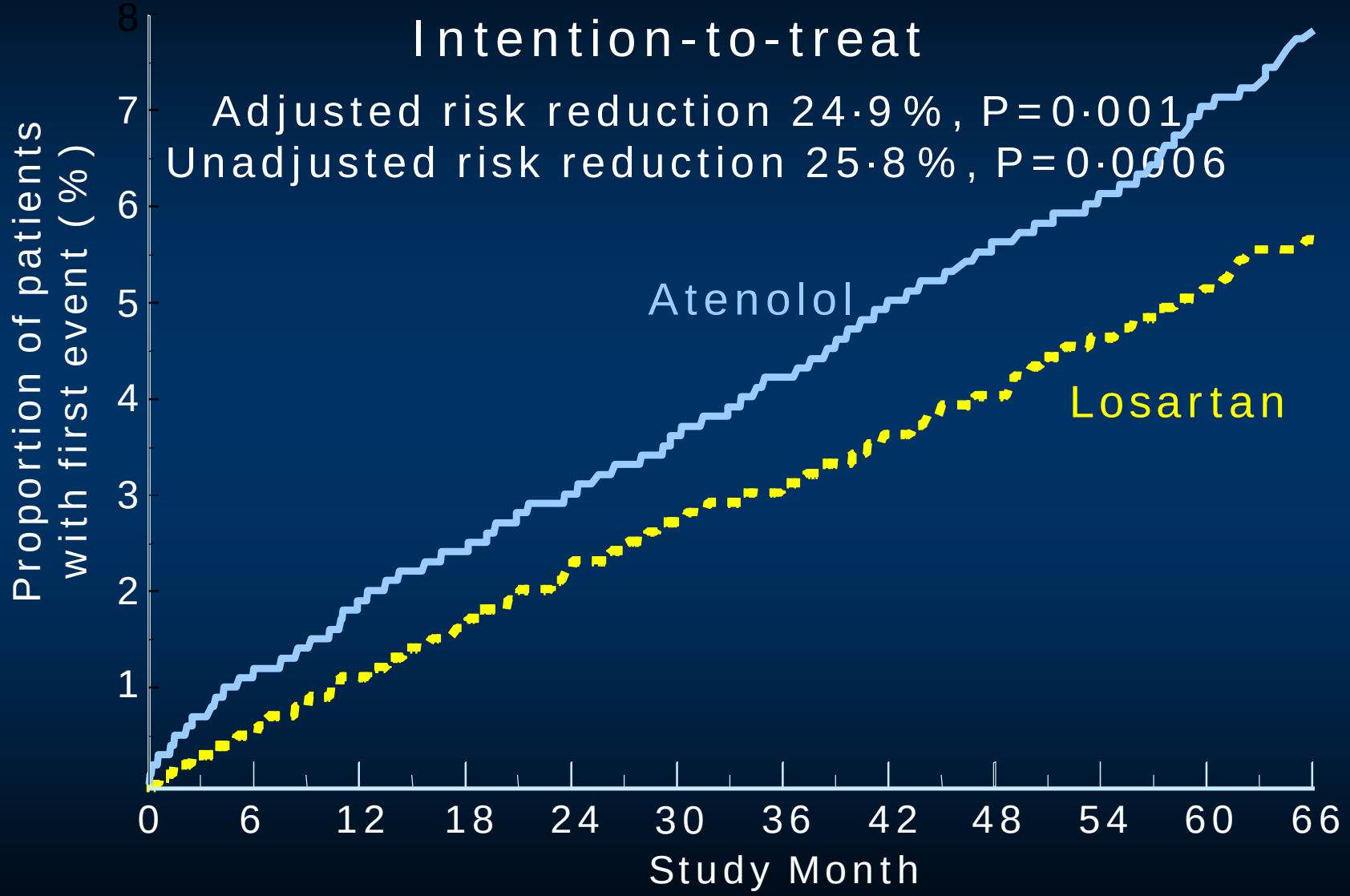

Dahlof B, et al. Lancet. 2002;359:995-1003

# LIFE Study Fatal and Non-Fatal Myocardial Infarction




Dahlof B, et al. Lancet. 2002;359:995-1003

# LIFE Study Fatal and Non-Fatal Stroke

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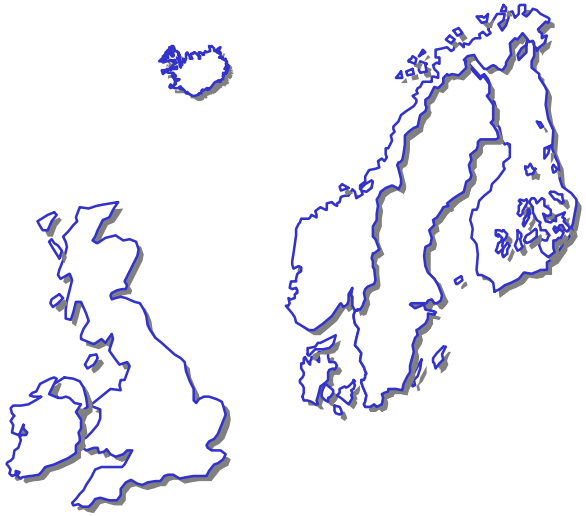
Anglo-Scandinavian ascot Cardiac Outcomes Trial



# Prévention des événements cardiovasculaires par une association amlodipine-périndopril versus une association aténolol-thiazide : l'étude ASCOT-HTA

B.Dahlof (Co-chair), P.Sever (Co-chair), N. Poulter (Secretary)
et al, on behalf of the ASCOT Investigators

Anglo-Scandinavian ascot Cardiac Outcomes Trial

# Objectifs

Ø **Objectif principal :** **comparer l'effet de l'association amlodipine-périndopril avec celui de l'association aténolol-thiazide sur l'infarctus du myocarde non fatal et la mortalité coronaire**

Ø **Objectifs secondaires :**

- **la mortalité toutes causes**
- **la mortalité cardiovasculaire**
- **tous les évènements coronaires**
- **les AVC totaux**
- **le développement d'un diabète…**

*Dahlöf B, Sever PS, Poulter NR et al; for the ASCOT Investigators. Lancet. 2005;366:895-906.*

Anglo-Scandinavian ascot Cardiac Outcomes Trial

# Des hypertendus de tous les jours

Ø **Pression artérielle au dépistage et à l'inclusion :**

- ³ **160/100 mm Hg non traité**
- ³ **140/90 mm Hg traité par un ou plusieurs médicaments**

Ø **âgés de 40 à 79 ans**

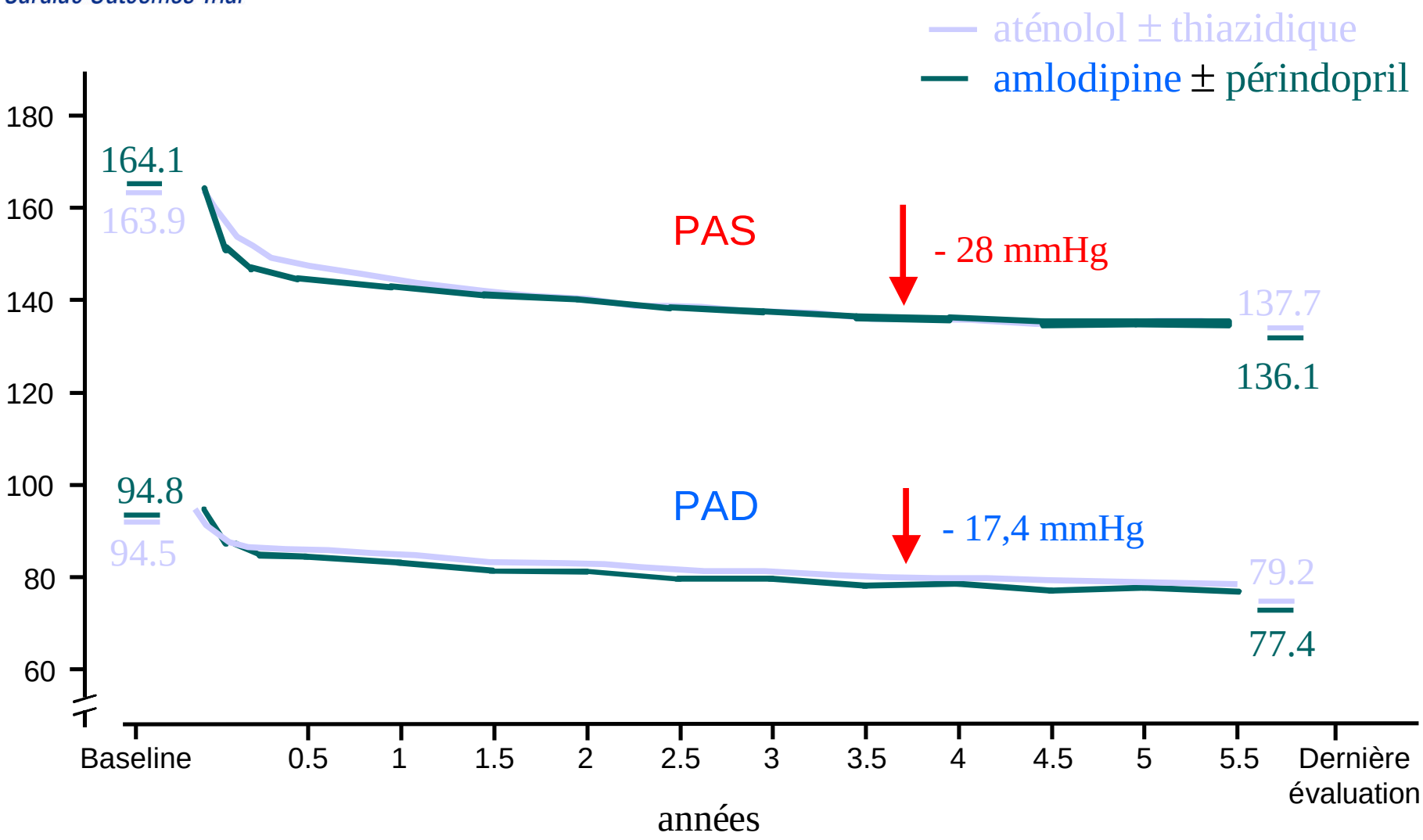
Ø **pas d'antécédent d'IDM et absence de manifestations cliniques de maladie coronaire**

Ø **3 autres facteurs de risque cardiovasculaire ou plus**

*Dahlöf B, Sever PS, Poulter NR et al; for the ASCOT Investigators. Lancet. 2005;366:895-906.*

Anglo-Scandinavian ascot Cardiac Outcomes Trial

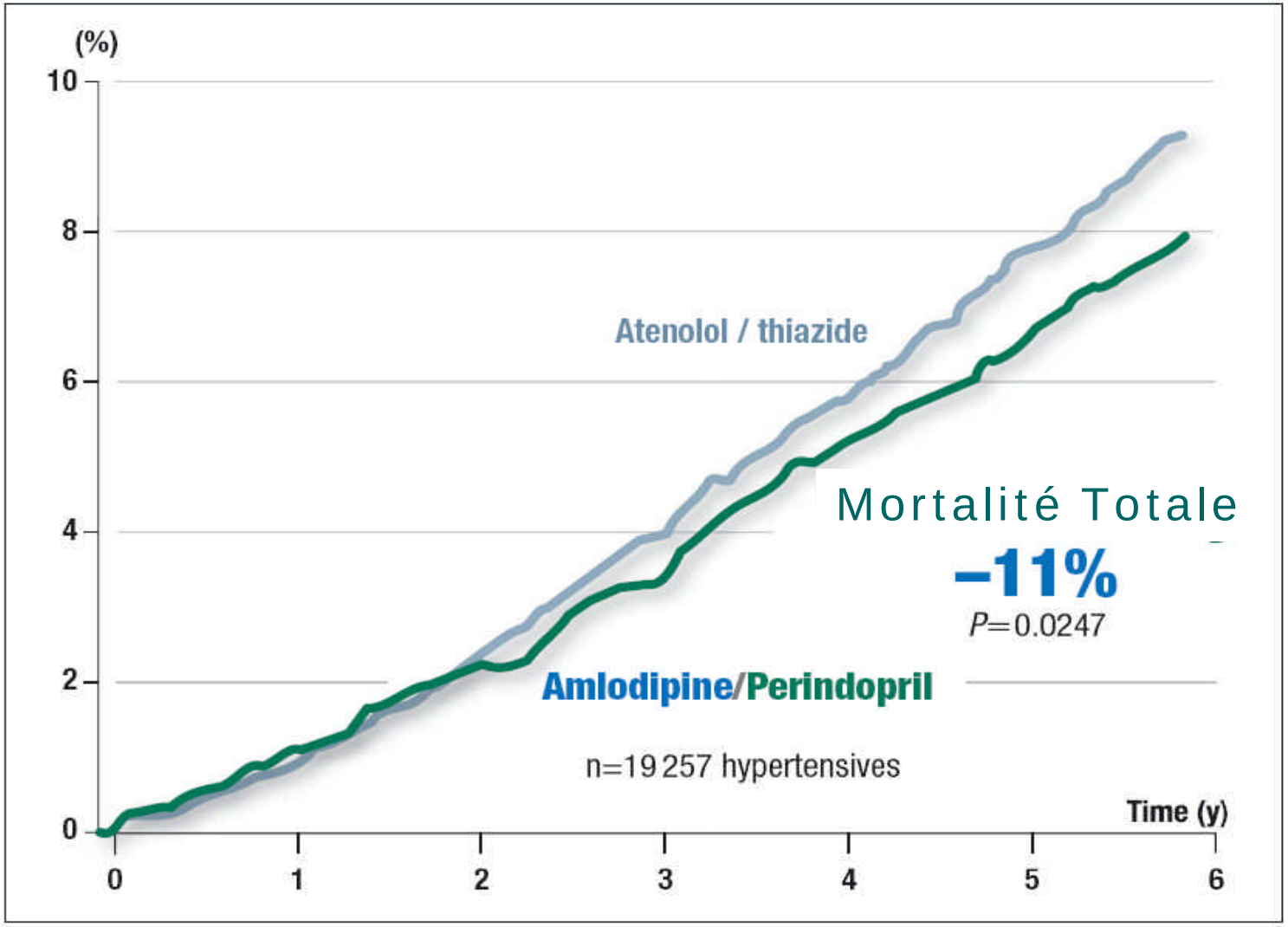
# Effets sur la pression artérielle




*Dahlöf B, Sever PS, Poulter NR et al; for the ASCOT Investigators. Lancet. 2005;366:895-906.*

Anglo-Scandinavian ascot Cardiac Outcomes Trial

# Une réduction de la mortalité totale à 5 ans

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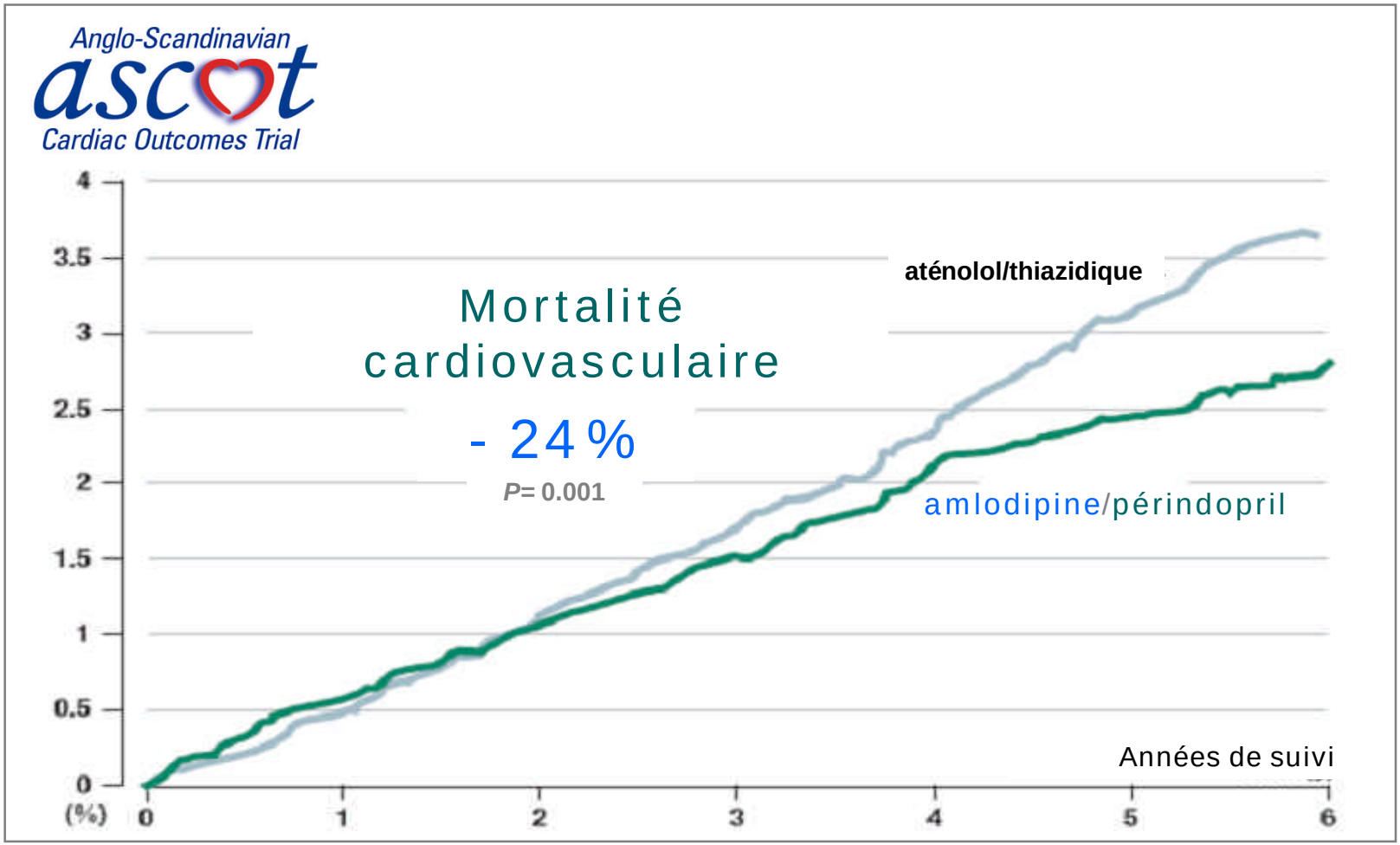
# Une réduction de la mortalité cardiovasculaire

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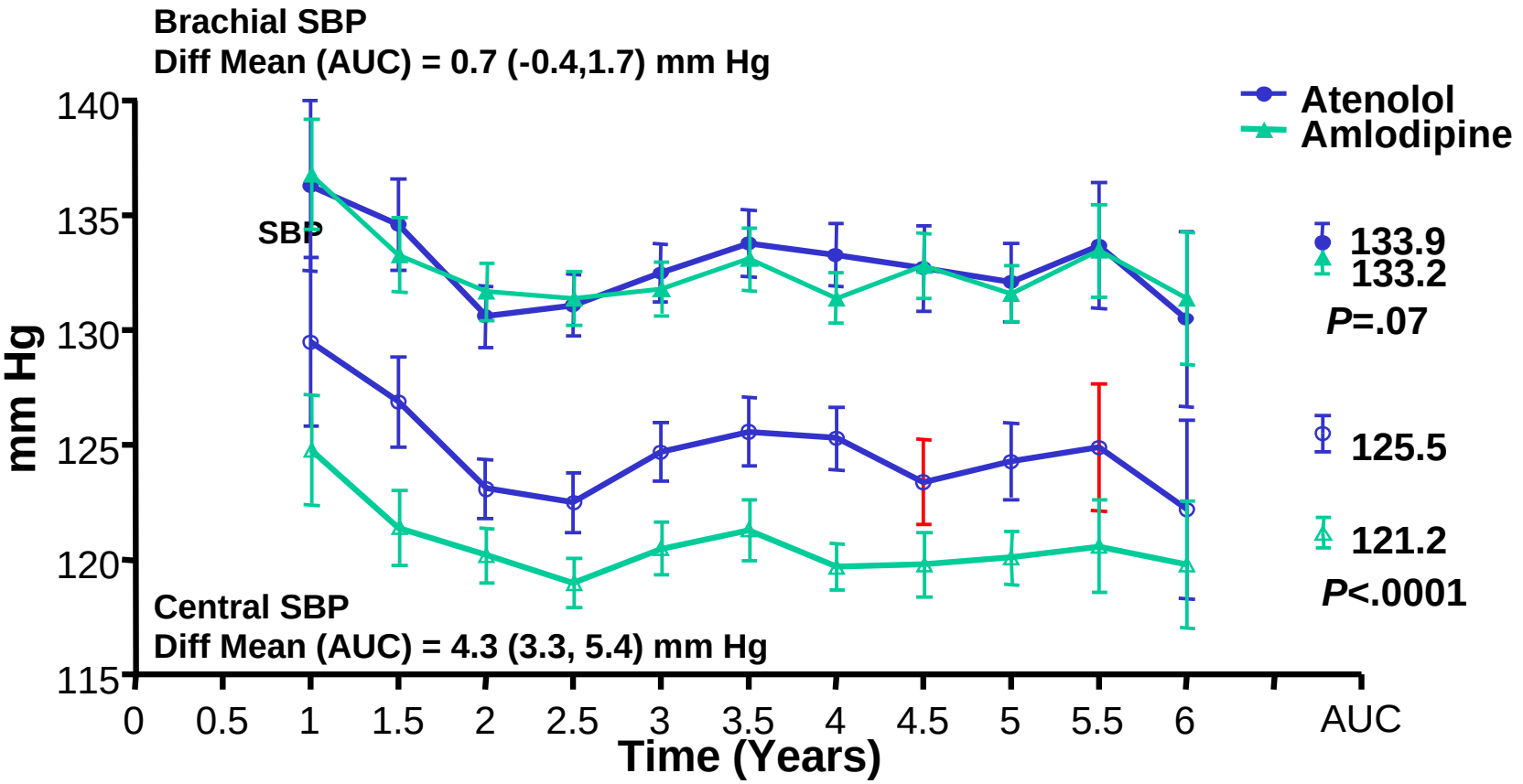
# The Conduit Artery Functional Evaluation (CAFE) Study in ASCOT

## Peripheral And Central SBP on Amlodipine and Atenolol-based Therapy




The CAFE investigators; Circulation 2005 in press

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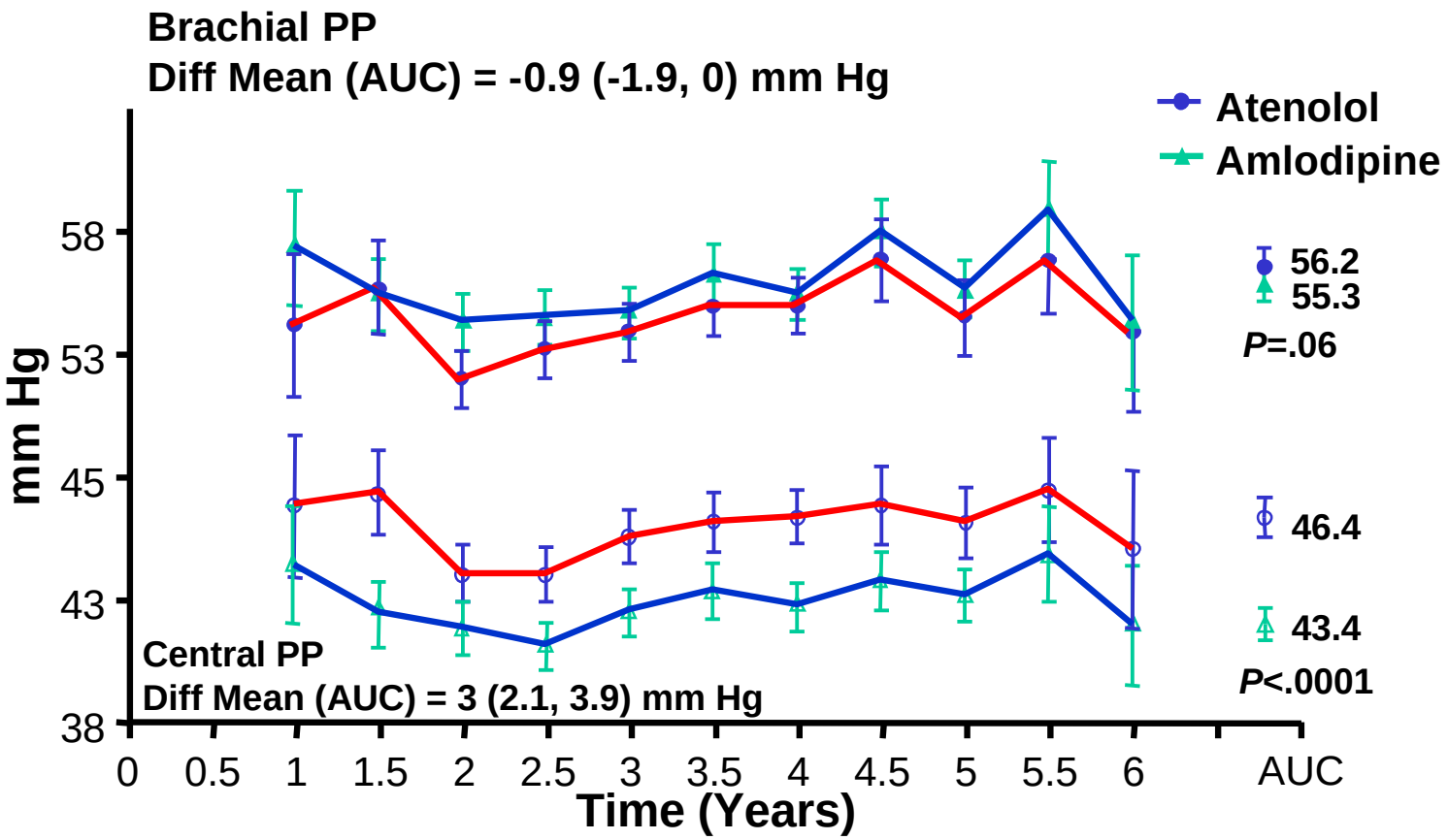
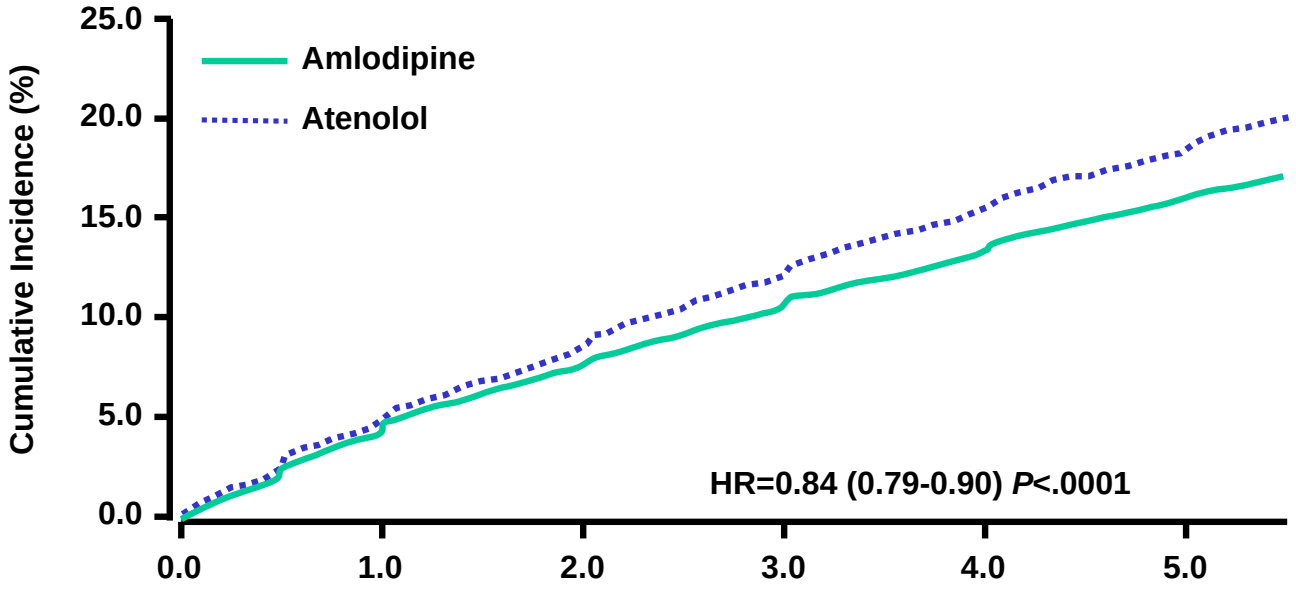
Peripheral And Central Pulse Pressure (PP) on Amlodipine and Atenolol-based Therapy




The CAFE investigators; Circulation 2005 in press

# The Conduit Artery Functional Evaluation (CAFE) Study in ASCOT

**Total CV Events and Procedures + Development of Renal Impairment**




| Number at risk | | | | | | |
|---|---|---|---|---|---|---|
| Amlodipine | 9639 | 9166 | 8808 | 8455 | 8118 | 6965 |
| Atenolol | 9618 | 9115 | 8692 | 8259 | 7872 | 6710 |

The CAFE investigators; Circulation 2005 in press

# Impact of Blood Pressure and Central Aortic Hemodynamics on Clinical Outcomes in the CAFE Study (Hazard/10 mm Hg)

**Updated Cox proportional hazard model for the composite endpoint, unadjusted**

| Factor | $X^2$ | *P* | HR | CI |
|---|---|---|---|---|
| Peripheral PP | 21.0 | <.0001 | 1.21 | 1.12-1.30 |
| Central PP | 17.8 | <.0001 | 1.20 | 1.11-1.30 |
| Augmentation | 7.10 | .008 | 1.22 | 1.06-1.40 |
| $P_1$ height | 19.0 | <.0001 | 1.37 | 1.20-1.54 |

**Updated Cox proportional hazard model for the composite endpoint, adjusted for baseline variables**

| Factor | $X^2$ | *P* | HR | CI |
|---|---|---|---|---|
| Central PP | 3.91 | .048 | 1.11 | 1.00-1.21 |

# Les évènements cliniques corrélés à la pression centrale

## Evènements cardiovasculaires et développement d'une dysfonction rénale

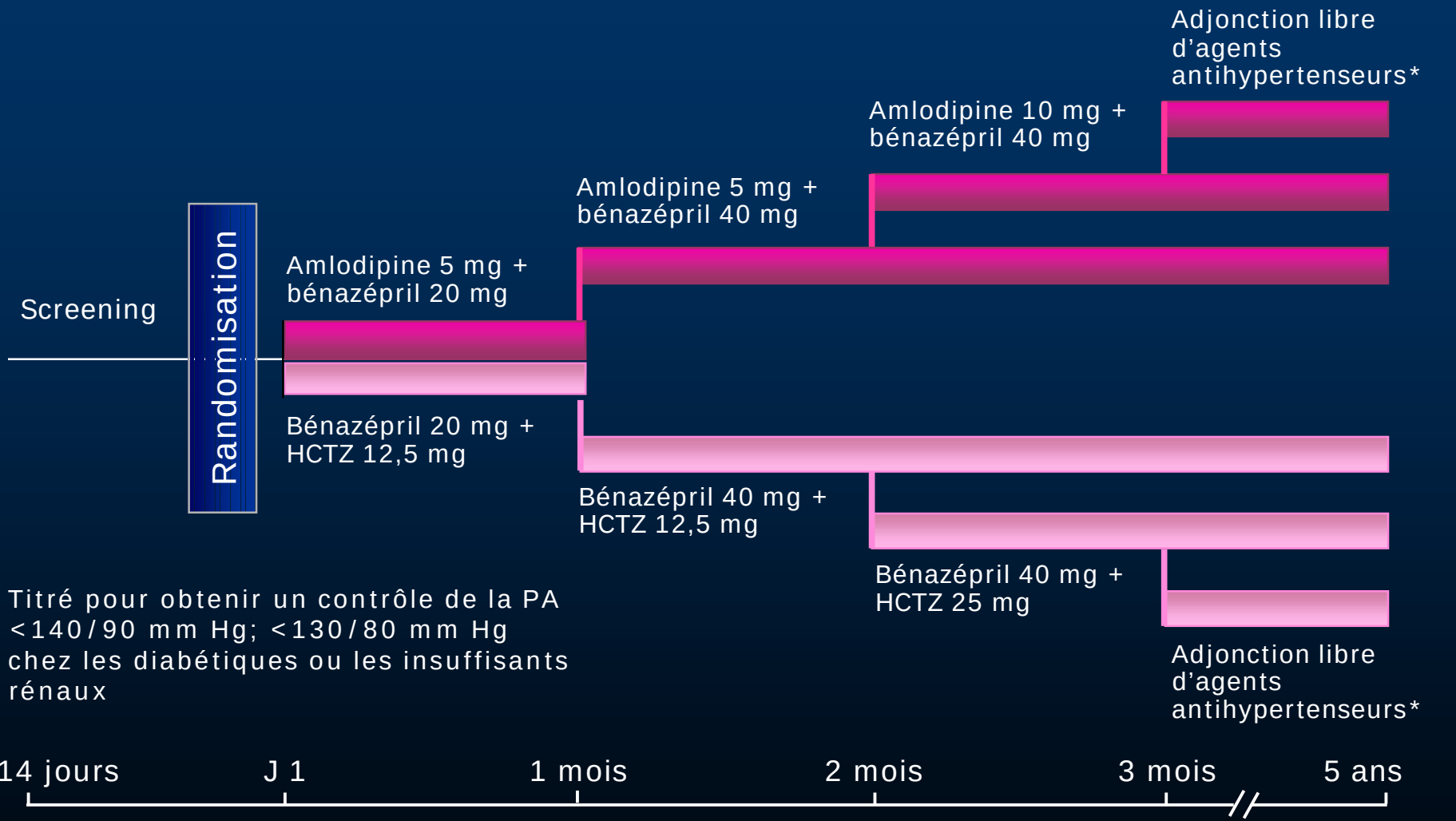
| | | $X^2$ | p | RR | IC à 95% |
|---|---|---|---|---|---|
| Modèle 1 (305 évènements) | PP périphérique | 3.83 | 0.05 | 1.10 | 1.00-1.22 |
| | PP centrale | 3.91 | 0.048 | 1.11 | 1.00-1.23 |
| Modèle 2 (245 évènements) | PP périphérique | 4.5 | 0.034 | 1.12 | 1.01-1.24 |
| | PP centrale | 5.0 | 0.026 | 1.13 | 1.02-1.26 |
| Modèle 3 (225 évènements) | PP périphérique | 4.1 | 0.044 | 1.12 | 1.00-1.25 |
| | PP centrale | 4.1 | 0.043 | 1.13 | 1.00-1.26 |

*The CAFE investigators. Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFÉ) study. Circulation. 2006;113:1213-1225.*

ASCOT BPLA amlodipine/perindopril vs atenolol/HCTZ

ACCOMPLISH benazepril/amlodipine vs benazepril/hctz

# Schéma de l'étude ACCOMPLISH




*Bêtabloquants, alphabloquants, clonidine, diurétiques de l'anse

Jamerson KA et coll. Am J Hypertens. 2004;17:793–801.

# 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*

NEJM 2008;359:2417

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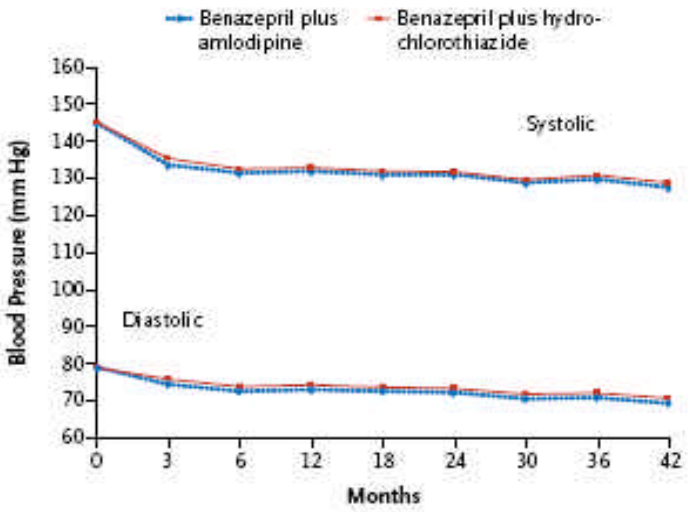


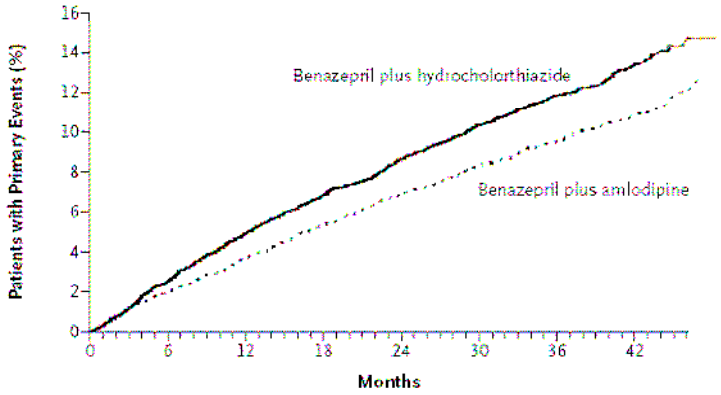


**No. at Risk**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 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).

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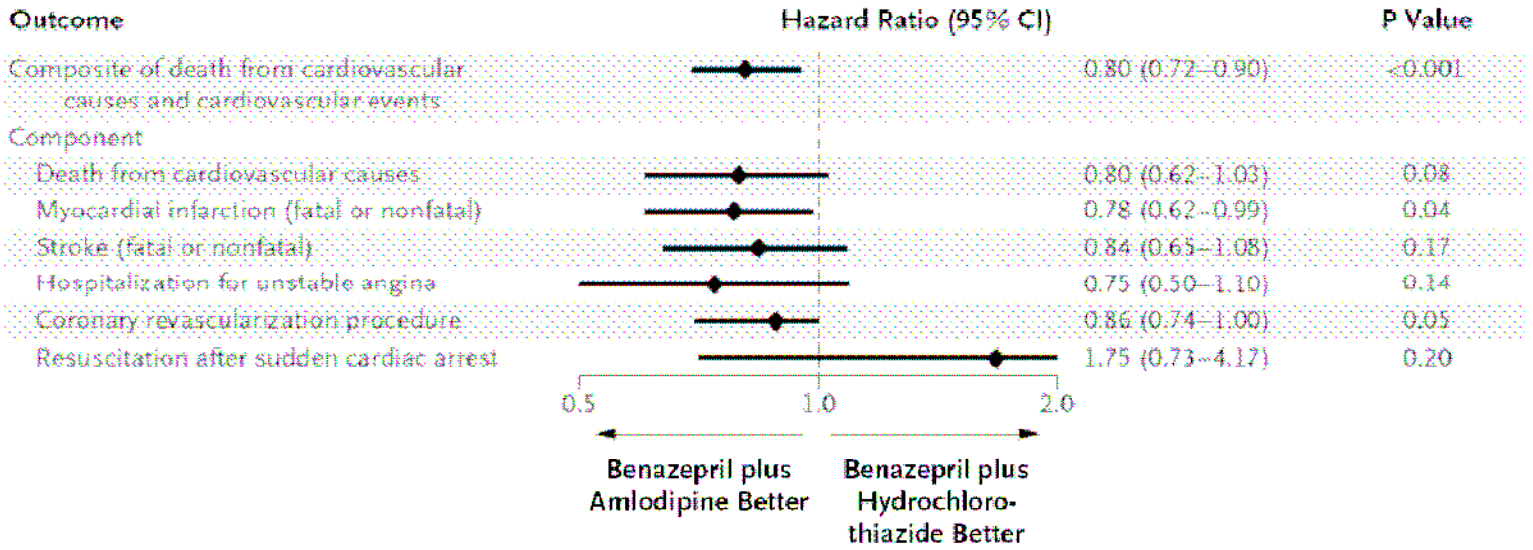


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**Table 1. Demographic and Baseline Characteristics of the Study Patients.***

| Characteristic | Benazepril–Amlodipine Group (N=5744) | Benazepril–Hydrochlorothiazide Group (N=5762) |
|---|---|---|
| Sex — no. (%) | | |
| Male | 3448 (60.0) | 3515 (61.0) |
| Female | 2296 (40.0) | 2246 (39.0) |
| Age — yr | 68.4±6.86 | 68.3±6.86 |
| ≥65 yr — no. (%) | 3813 (66.4) | 3827 (66.4) |
| ≥70 yr — no. (%) | 2363 (41.1) | 2340 (40.6) |
| Weight — kg | 88.7±19.0 | 88.5±18.9 |
| Waist circumference — cm | 103.9±15.2 | 103.8±15.4 |
| Body-mass index‡ | 31.0±6.2 | 31.0±6.2 |
| Blood pressure — mm Hg | | |
| Systolic | 145.3±18.4 | 145.4±18.1 |
| Diastolic | 80.1±10.8 | 80.0±10.7 |
| Pulse — beats/min | 70.5±10.9 | 70.3±11.1 |
| Estimated glomerular filtration rate — ml/min/1.73 m² of body-surface area§ | 78.9±21.2 | 79.0±21.5 |
| Serum values¶ | | |
| Creatinine — mg/dl | 1.0±0.3 | 1.0±0.3 |
| Glucose — mg/dl | 127.9±47.4 | 127.0±45.8 |
| Potassium — mmol/liter | 4.3±0.4 | 4.3±0.4 |
| Total cholesterol — mg/dl | 184.9±40.5 | 184.1±39.3 |
| High-density lipoprotein cholesterol — mg/dl | 49.6±14.1 | 49.5±14.1 |
| Previous antihypertensive treatment — no. (%) | | |
| No. of agents | | |
| 0 | 169 (2.9) | 153 (2.7) |
| 1 | 1312 (22.8) | 1279 (22.2) |
| 2 | 2116 (36.8) | 2047 (35.5) |
| ≥3 | 2147 (37.4) | 2283 (39.6) |
| Lipid-lowering agents | 3851 (67.0) | 3971 (68.9) |
| Beta-blockers | 2675 (46.6) | 2807 (48.7) |
| Antiplatelets agents | 3710 (64.6) | 3735 (64.8) |

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| 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) |

NEJM 2008;359:2417

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## PROCEDURES

The first patient was assigned to a study group on October 29, 2003. Immediately on entering the study (without a washout period), patients were randomly assigned in a global one-to-one ratio to either of the two treatment groups, with assignments made centrally by telephone. Patients began treatment with either a combination of 20 mg of benazepril and 5 mg of amlodipine or a combination of 20 mg of benazepril and 12.5 mg of hydrochlorothiazide, once daily. As dictated by the protocol, the benazepril component in both groups was increased to 40 mg daily 1 month after randomization. Thereafter, investigators could increase the amlodipine dose to 10 mg daily and increase the hydrochlorothiazide dose to 25 mg daily, if necessary, to attain a target blood pressure of less than 140/90 mm Hg (or a recommended target of 130/80 mm Hg for patients with diabetes or kidney disease).

The addition of other antihypertensive agents was permitted (excluding any calcium-channel blockers, any ACE inhibitors, any angiotensin II–receptor blockers, and any thiazide diuretics but including beta-blockers, alpha-blockers, clonidine, and spironolactone). Loop diuretics taken once daily were permitted for volume management. After the initial 3-month dose-adjustment period, patients returned at 6 months and then at 6-month intervals until the end of the trial. Blood pressures were recorded as the average of three readings

## BLOOD PRESSURE

At the time of enrollment in the trial, most patients (97.2%) were being treated for hypertension, and 74.7% were taking two or more classes of antihypertensive medications, though only 37.3% had blood pressure below 140/90 mm Hg at baseline (Table 1).

The baseline blood pressures were similar between the two groups, and the reduction in blood pressure from baseline was similar over the course of the trial (Fig. 1). Mean blood pressure after dose adjustment was 131.6/73.3 mm Hg in the benazepril–amlodipine group (5463 patients) and 132.5/74.4 mm Hg in the benazepril–hydrochlorothiazide group (5474 patients). 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 systolic and diastolic pressures). Blood pressure control, which was defined as a blood pressure of less than 140/90 mm Hg, was attained in an average of 75.4% of patients in the benazepril–amlodipine group and 72.4% in the benazepril–hydrochlorothiazide group.

daily dose was 39.4 mg and 22.1 mg, respectively. By the end of the 6-month dose-adjustment period, 60.9% of the patients in the benazepril–amlodipine group were receiving the maximum dose of 40 mg of benazepril and 10 mg of amlodipine, and 60.3% of the patients in the benazepril–hydrochlorothiazide group received the maximum dose of 40 mg of benazepril and 25 mg of hydrochlorothiazide. In each group, 32.3% of the patients received approved antihypertensive agents in addition to the highest dose of study medication after 1 year in the study. At the completion of the trial, 143 par-

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48% des patients à l'inclusion avaient des béta-bloquants

dont 23% avaient un ATCD authentifié d'IDM

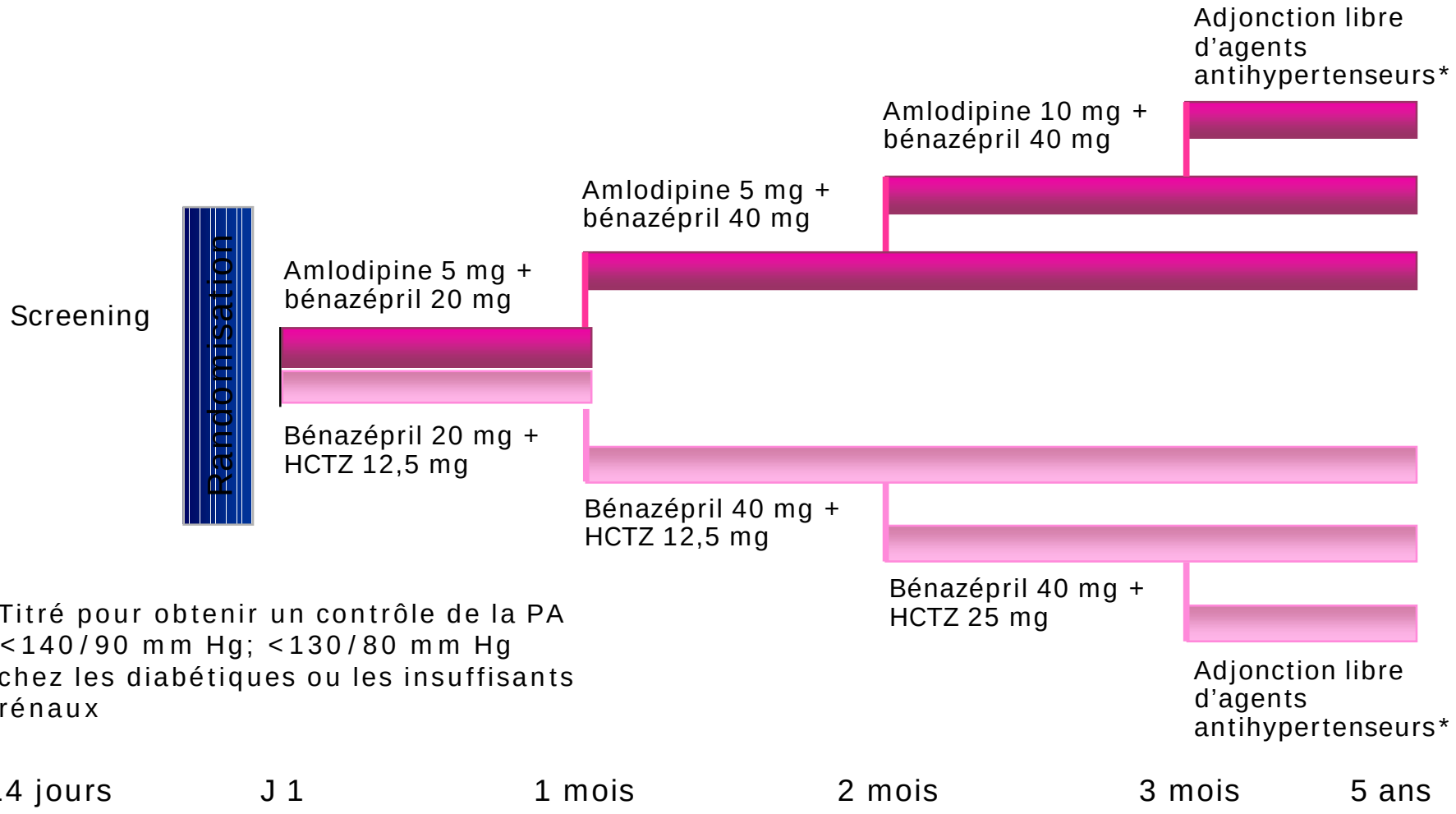
et 36 % avaient une revascularisation coronaire

1ere action des investigateurs:

Sevrage des béta-bloquants....

NEJM 2008;359:2417

# Schéma de l'étude ACCOMPLISH




*Bêtabloquants, alphabloquants, clonidine, diurétiques de l'anse

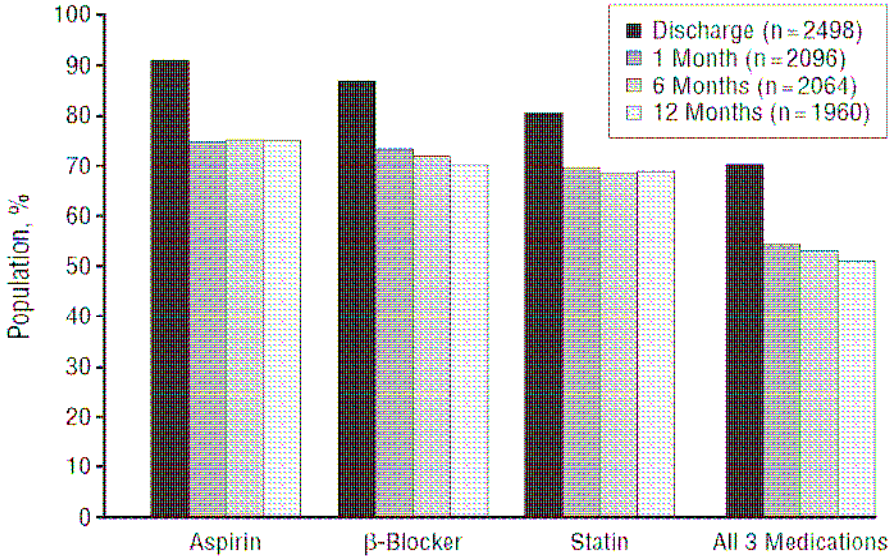
Jamerson KA et coll. Am J Hypertens. 2004;17:793–801.

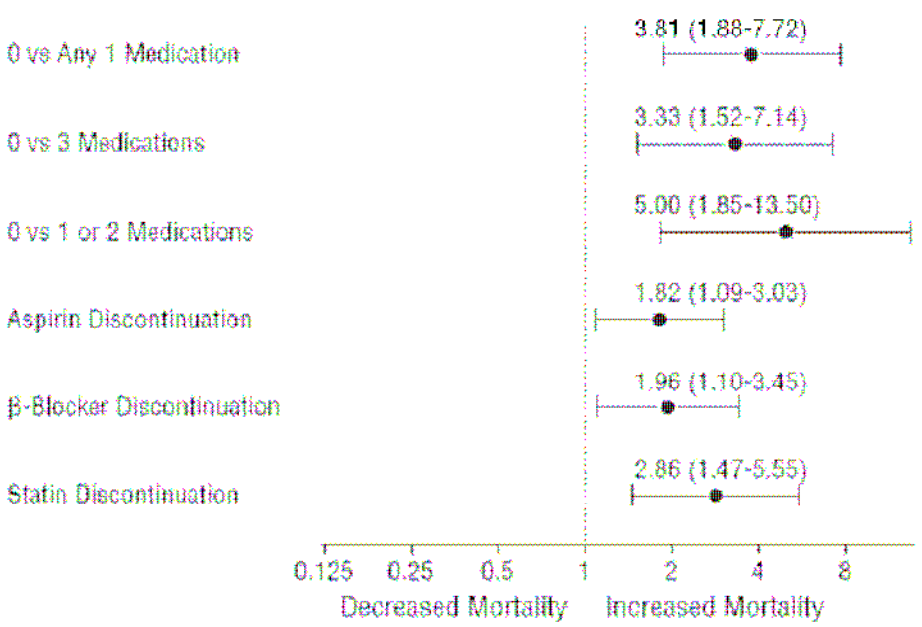
# 2007 Chronic Angina Focused Update of the ACC/AHA 2002 Guidelines for the Management of Patients With Chronic Stable Angina

| | | | |
|---|---|---|---|
| **Blood Pressure Control** | | | |
| Initiate lifestyle modification (weight control, physical activity, alcohol moderation, moderate sodium restriction, and emphasis on fruits, vegetables, and low-fat dairy products) in all patients with blood pressure greater than or equal to 130 mm Hg systolic or 80 mm Hg diastolic. Add blood pressure medication, individualized to other patient requirements and characteristics (i.e., age, race, need for drugs with specific benefits) if blood pressure is not less than 140 mm Hg systolic or 90 mm Hg diastolic, or if blood pressure is not less than 130 mm Hg systolic or 85 mm Hg diastolic for individuals with heart failure or renal insufficiency (less than 80 mm Hg diastolic for individuals with diabetes). | Patients should initiate and/or maintain lifestyle modifications—weight control; increased physical activity; moderation of alcohol consumption; limited sodium intake; and maintenance of a diet high in fresh fruits, vegetables, and low-fat dairy products. | *I (B)* | Modified recommendation (changed text and COR LOE added) |
| | Blood pressure control according to Joint National Conference VII guidelines is recommended (i.e., blood pressure less than 140/90 mm Hg or less than 130/80 mm Hg for patients with diabetes or chronic kidney disease) (11). | *I (A)* | New recommendation |
| | For hypertensive patients with well established coronary artery disease, it is useful to add blood pressure medication as tolerated, treating initially with beta blockers and/or ACE inhibitors, with addition of other drugs as needed to achieve target blood pressure. | *I (C)* | New recommendation |
| **Beta Blockers** | | | |
| Start in all post-MI and acute patients (arrhythmia, LV dysfunction, inducible ischemia) at 5 to 28 days. Continue 6 months minimum. Observe usual contraindications. Use as needed to manage angina, rhythm, or blood pressure in all other patients. | It is beneficial to start and continue beta-blocker therapy indefinitely in all patients who have had MI, acute coronary syndrome, or left ventricular dysfunction with or without heart failure symptoms, unless contraindicated. | *I (A)* | Modified recommendation (changed text and COR LOE added) |

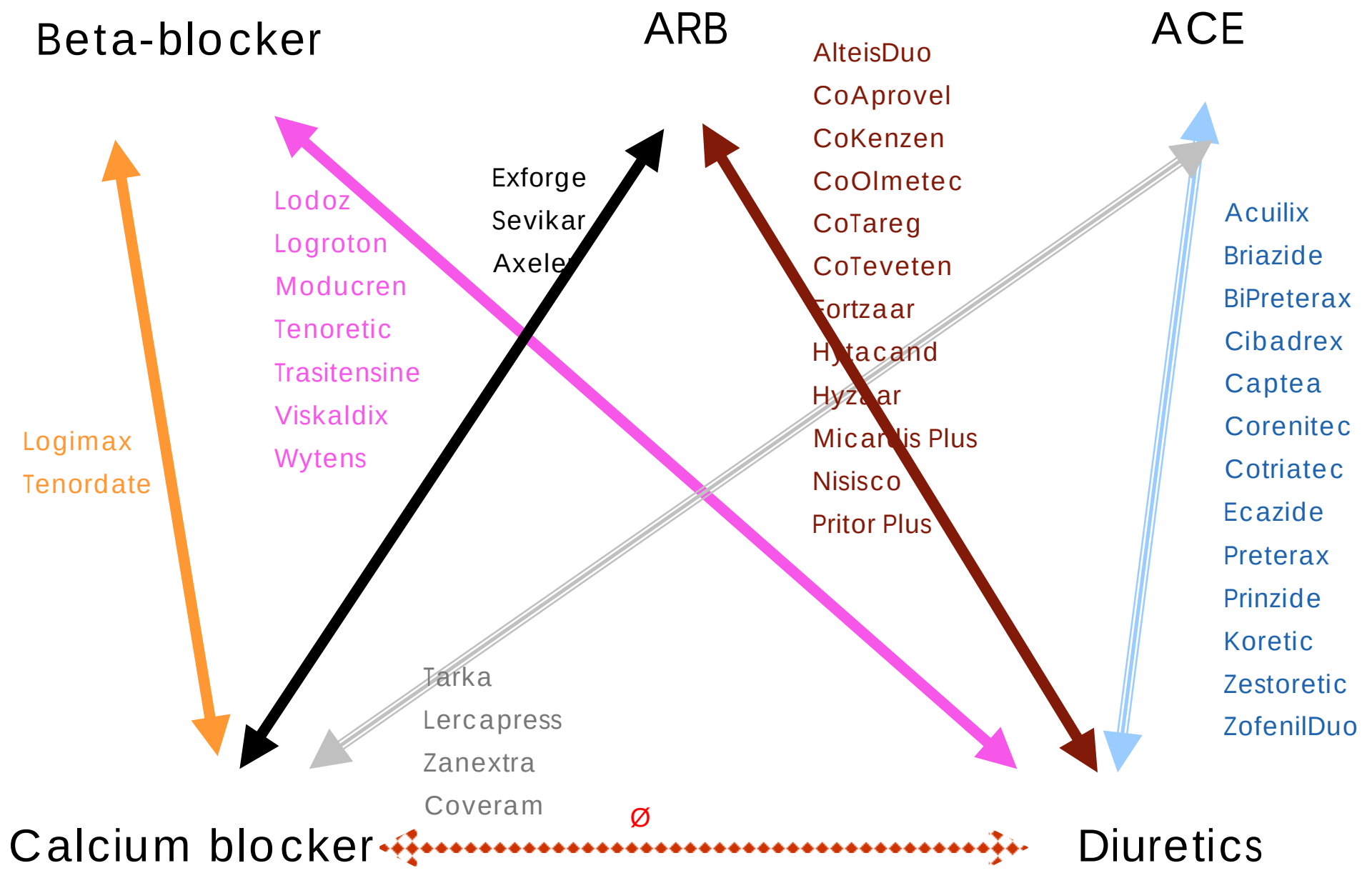
# Impact of Medication Therapy Discontinuation on Mortality After Myocardial Infarction

*P. Michael Ho, MD, PhD; John A. Spertus, MD, MPH; Frederick A. Masoudi, MD, MSPH; Kimberly J. Reid, MS; Eric D. Peterson, MD, MPH; David J. Magid, MD, MPH; Harlan M. Krumholz, MD, SM; John S. Rumsfeld, MD, PhD*




Arch Int Med 2006;166:1842


Beta-blocker
ARB
ACE
Logimax
Tenordate
Lodoz
Logroton
Moducren
Tenoretic
Trasitensine
Viskaldix
Wytens
Exforge
Sevikar
Axele
AlteisDuo
CoAprovel
CoKenzen
CoOlmetec
CoTareg
CoTeveten
Fortzaar
Hytacand
Hyzaar
Micardis Plus
Nisisco
Pritor Plus
Acuilix
Briazide
BiPreterax
Cibadrex
Captea
Corenitec
Cotriatec
Ecazide
Preterax
Prinzide
Koretic
Zestoretic
ZofenilDuo
Tarka
Lercapress
Zanextra
Coveram
Ø
Calcium blocker
Diuretics

- Le duel des associations (LIFE-ASCOT-ACCOMPLISH)

- Le risque résiduel (ASCOT LLA, JUPITER)

- La courbe en J chez les coronariens ? (INVEST)

- Des « nouvelles » recommandations européennes

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# Caractéristiques initiales des patients inclus

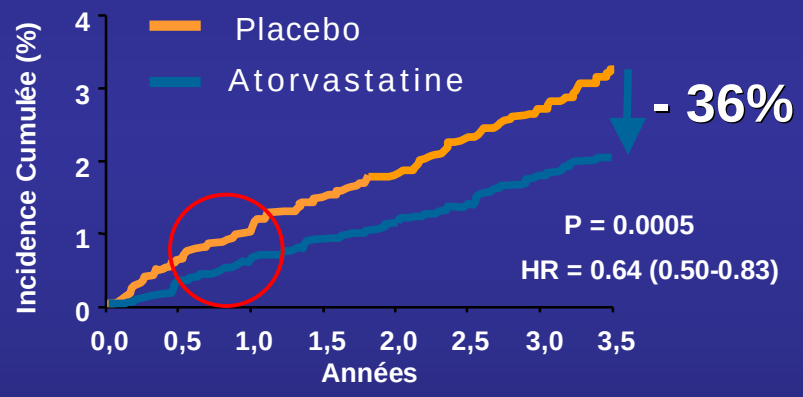
| Caractéristiques | Atorvastatine (n = 5 168) | Placebo (n = 5 137) |
|---|---|---|
| Age* (années) | 63.1 ± 8.5 | 63.2 ± 8.6 |
| Sexe masculin (%) | 81.1 | 81.3 |
| Caucasien (%) | 94.6 | 94.7 |
| PAS* (mm Hg) | 164.2 ± 17.7 | 164.2 ± 18.0 |
| PAD* (mm Hg) | 95.0 ± 10.3 | 95.0 ± 10.3 |
| CT* ( g/l) | 2,12 ± 0,31 | 2,12 ± 0,31 |
| LDL-C* (g/l) | 1,33 ± 0,27 | 1,33 ± 0,27 |
| TG* (g/l) | 1,50 ± 0,80 | 1,42 ± 0,80 |
| HDL-C* (g/l) | 0,51 ± 0,15 | 0,51 ± 0,15 |
| Nb de facteurs de risque* | 3.7 ± 0.9 | 3.7 ± 0.9 |

* Moyenne ± Ecart type

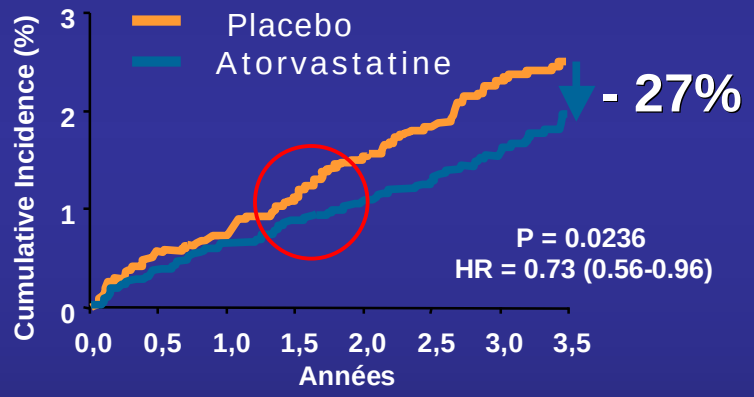
*Sever PS, Dahlöf B, Poulter N, Wedel H, et al, for the ASCOT Investigators. Lancet. 2003;361:1149-58*

# Bénéfices cliniques de l'atorvastatine

CRITÈRE PRIMAIRE
IDM non fatal et évènement coronaire fatal




CRITÈRE SECONDAIRE
AVC fatal et non fatal




Un bénéfice rapide démontré dès 3 ans dans une étude prévue sur 5 ans

*__ASCOT - A__nglo __S__candinavian __C__ardiac __O__utcomes __T__rial. THE LANCET. Vol 361. April 5, 2003.*

# Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein

| Characteristic | Rosuvastatin (N=8901) | Placebo (N=8901) |
|---|---|---|
| Age — yr | | |
| Median | 66.0 | 66.0 |
| Interquartile range | 60.0–71.0 | 60.0–71.0 |
| Female sex — no. (%) | 3426 (38.5) | 3375 (37.9) |
| Race or ethnic group — no. (%)† | | |
| White | 6358 (71.4) | 6325 (71.1) |
| Black | 1100 (12.4) | 1124 (12.6) |
| Hispanic | 1121 (12.6) | 1140 (12.8) |
| Other or unknown | 322 (3.6) | 312 (3.5) |
| Body-mass index‡ | | |
| Median | 28.3 | 28.4 |
| Interquartile range | 25.3–32.0 | 25.3–32.0 |
| Blood pressure — mm Hg | | |
| Systolic | | |
| Median | 134 | 134 |
| Interquartile range | 124–145 | 124–145 |
| Diastolic | | |
| Median | 80 | 80 |
| Interquartile range | 75–87 | 75–87 |
| Current smoker — no. (%) | 1400 (15.7) | 1420 (16.0) |
| Family history of premature CHD — no. (%)§ | 997 (11.2) | 1048 (11.8) |
| Metabolic syndrome — no. (%)¶ | 3652 (41.0) | 3723 (41.8) |
| Aspirin use — no. (%) | 1481 (16.6) | 1477 (16.6) |
| High-sensitivity C-reactive protein — mg/liter‖ | | |
| Median | 4.2 | 4.3 |
| Interquartile range | 2.8–7.1 | 2.8–7.2 |
| LDL cholesterol — mg/dl | | |
| Median | 108 | 108 |

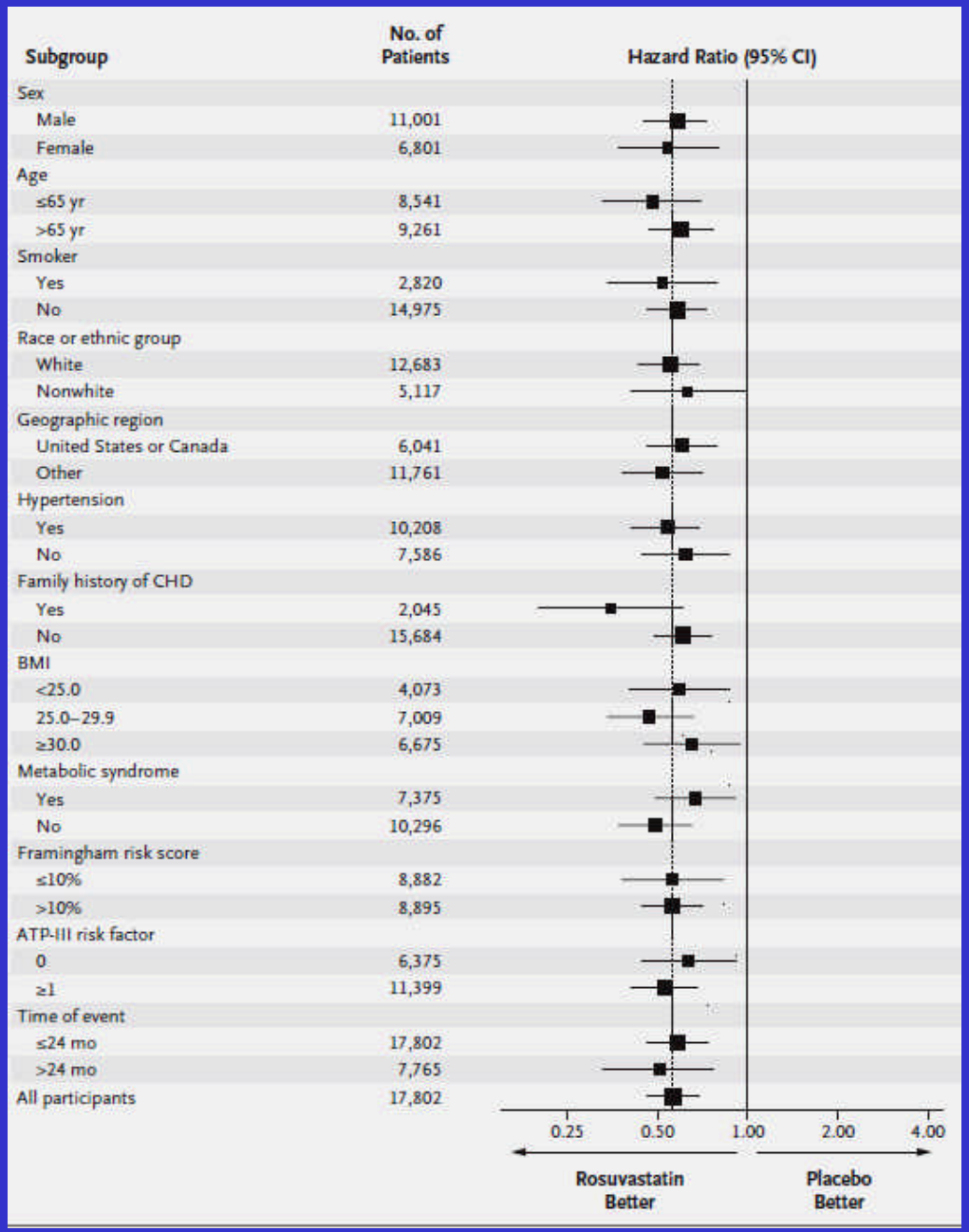
NEJM 2008;359:2195

# Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein

**Table 3. Outcomes According to Study Group.**

| End Point | Rosuvastatin (N=8901) | | Placebo (N=8901) | | Hazard Ratio (95% CI) | P Value |
|---|---|---|---|---|---|---|
| | No. of Patients | Rate per 100 person-yr | No. of Patients | Rate per 100 person-yr | | |
| Primary end point | 142 | 0.77 | 251 | 1.36 | 0.56 (0.46–0.69) | <0.00001 |
| Nonfatal myocardial infarction | 22 | 0.12 | 62 | 0.33 | 0.35 (0.22–0.58) | <0.00001 |
| Any myocardial infarction | 31 | 0.17 | 68 | 0.37 | 0.46 (0.30–0.70) | 0.0002 |
| Nonfatal stroke | 30 | 0.16 | 58 | 0.31 | 0.52 (0.33–0.80) | 0.003 |
| Any stroke | 33 | 0.18 | 64 | 0.34 | 0.52 (0.34–0.79) | 0.002 |
| Arterial revascularization | 71 | 0.38 | 131 | 0.71 | 0.54 (0.41–0.72) | <0.0001 |
| Hospitalization for unstable angina | 16 | 0.09 | 27 | 0.14 | 0.59 (0.32–1.10) | 0.09 |
| Arterial revascularization or hospitalization for unstable angina | 76 | 0.41 | 143 | 0.77 | 0.53 (0.40–0.70) | <0.00001 |
| Myocardial infarction, stroke, or confirmed death from cardiovascular causes | 83 | 0.45 | 157 | 0.85 | 0.53 (0.40–0.69) | <0.00001 |
| Death from any cause | | | | | | |
| Death on known date | 190 | 0.96 | 235 | 1.19 | 0.81 (0.67–0.98) | 0.03 |
| Any death | 198 | 1.00 | 247 | 1.25 | 0.80 (0.67-0.97) | 0.02 |

# Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein




NEJM 2008;359:2195

# SCORE CALCULATION - MEN

| Points | Age, y | HDL | Total Cholesterol | SBP Not Treated | SBP Treated | Smoker | Diabetic |
|---|---|---|---|---|---|---|---|
| −2 | | 60+ | | <120 | | | |
| −1 | | 50–59 | | | | | |
| 0 | 30–34 | 45–49 | <160 | 120–129 | <120 | No | No |
| 1 | | 35–44 | 160–199 | 130–139 | | | |
| 2 | 35–39 | <35 | 200–239 | 140–159 | 120–129 | | |
| 3 | | | 240–279 | 160+ | 130–139 | | Yes |
| 4 | | | 280+ | | 140–159 | Yes | |
| 5 | 40–44 | | | | 160+ | | |
| 6 | 45–49 | | | | | | |
| 7 | | | | | | | |
| 8 | 50–54 | | | | | | |
| 9 | | | | | | | |
| 10 | 55–59 | | | | | | |
| 11 | 60–64 | | | | | | |
| 12 | 65–69 | | | | | | |
| 13 | | | | | | | |
| 14 | 70–74 | | | | | | |
| 15 | 75+ | | | | | | |
| Points allotted | | | | | | | |

D'Agostino R et al. Circulation 2008

- Le duel des associations (LIFE-ASCOT-ACCOMPLISH)

- Le risque résiduel (ASCOT LLA, JUPITER)

- La courbe en J chez les coronariens ? (INVEST)

- Des « nouvelles » recommandations européennes

- Des injonctions fortes des tutelles

Annals of Internal Medicine | ARTICLE

# Dogma Disputed: Can Aggressively Lowering Blood Pressure in Hypertensive Patients with Coronary Artery Disease Be Dangerous?

Franz H. Messerli, MD; Giuseppe Mancia, MD; C. Richard Conti, MD; Ann C. Hewkin, MSc; Stuart Kupfer, MD; Annette Champion, MBA; Rainer Kolloch, MD; Athanase Benetos, MD; and Carl J. Pepine, MD

**Background:** Because coronary perfusion occurs mainly during diastole, patients with coronary artery disease (CAD) could be at increased risk for coronary events if diastolic pressure falls below critical levels.

**Objective:** To determine whether low blood pressure could be associated with excess mortality and morbidity in this population.

**Design:** A secondary analysis of data from the International Verapamil-Trandolapril Study (INVEST), which was conducted from September 1997 to February 2003.

**Setting:** 862 sites in 14 countries.

**Patients:** 22 576 patients with hypertension and CAD.

**Interventions:** Patients from INVEST were randomly assigned to a verapamil sustained-release– or atenolol-based strategy; blood pressure control and outcomes were equivalent.

**Measurements:** An unadjusted quadratic proportional hazards model was used to evaluate the relationship between average on-treatment blood pressure and risk for the primary outcome (all-cause death, nonfatal stroke, and nonfatal myocardial infarction [MI]), all-cause death, total MI, and total stroke. A second model adjusted for differences in baseline covariates.

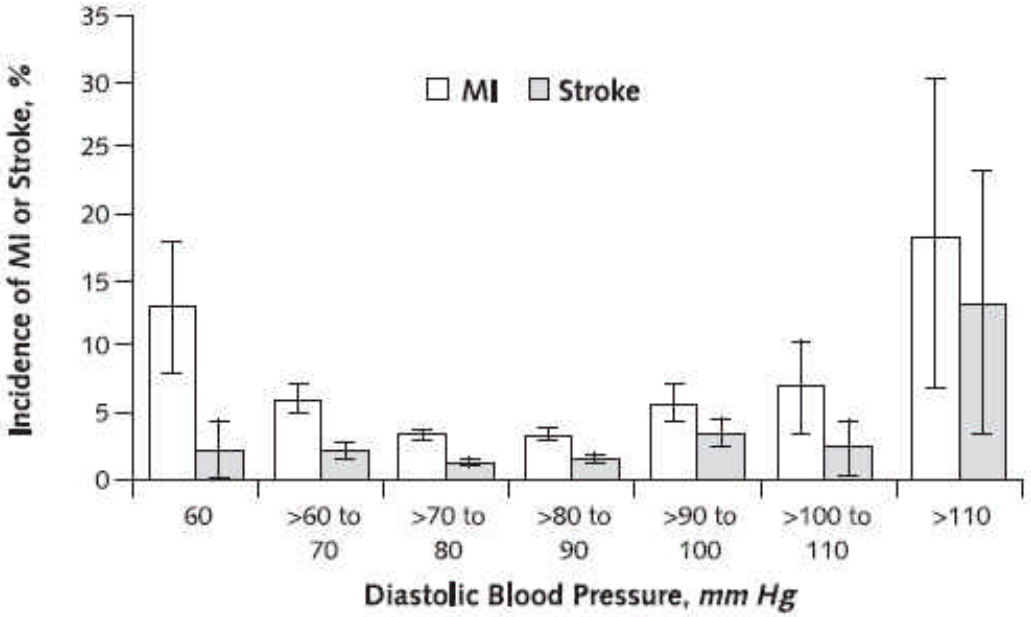
**Results:** The relationship between blood pressure and the primary outcome, all-cause death, and total MI was J-shaped, particularly for diastolic pressure, with a nadir at 119/84 mm Hg. After adjustment, the J-shaped relationship persisted between diastolic pressure and primary outcome. The MI–stroke ratio remained constant over a wide blood pressure range, but at a lower diastolic blood pressure, there were substantially more MIs than strokes. An interaction between decreased diastolic pressure and history of revascularization was observed; low diastolic pressure was associated with a relatively lower risk for the primary outcome in patients with revascularization than in those without revascularization.

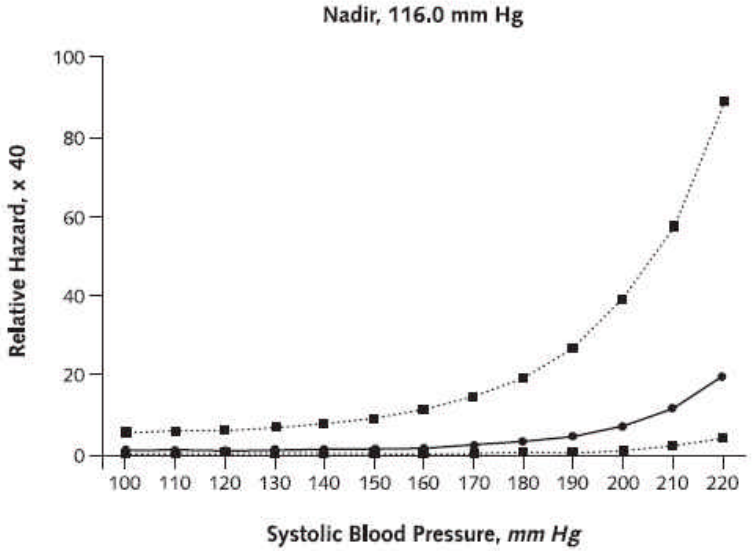
**Limitations:** This is a post hoc analysis of hypertensive patients with CAD.

**Conclusions:** The risk for the primary outcome, all-cause death, and MI, but not stroke, progressively increased with low diastolic blood pressure. Excessive reduction in diastolic pressure should be avoided in patients with CAD who are being treated for hypertension.

*Ann Intern Med.* 2006;144:884-893. www.annals.org
For author affiliations, see end of text.
ClinicalTrial.gov identifier: NCT00133692.

## Incidence of total myocardial infarction (*MI*) and total stroke by diastolic blood pressure strata.




Messerli FH et al. Ann Int Med 2006

- Le duel des associations (LIFE-ASCOT-ACCOMPLISH)

- Le risque résiduel (ASCOT LLA, JUPITER)

- La courbe en J chez les coronariens ? (INVEST)

- Des « nouvelles » recommandations européennes

- Des injonctions fortes des tutelles

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

**Box 4. Blood pressure goals of treatment**

(1) On the whole, there is sufficient evidence to recommend that SBP be lowered below 140 mmHg (and DBP below 90 mmHg) in all hypertensive patients, both those at low moderate risk and those at high risk. Evidence is only missing in the elderly hypertensive patients, in whom the benefit of lowering SBP below 140 mmHg has never been tested in randomized trials.

(2) The recommendation of previous guidelines to aim at a lower goal SBP (<130 mmHg) in diabetic patients and in patients at very high cardiovascular risk (previous cardiovascular events) may be wise, but it is not consistently supported by trial evidence. In no randomized trial in diabetic patients has SBP been brought down to below 130 mmHg with proven benefits, and trials in which SBP was lowered to below 130 mmHg in patients with previous cardiovascular events have given controversial results.

(3) Despite their obvious limitations and a lower strength of evidence, *post hoc* analyses of trial data indicate a progressive reduction of cardiovascular events incidence with progressive lowering of SBP down to about 120 mmHg and DBP down to about 75 mmHg, although the additional benefit at low BP values becomes rather small. At these low BP values also beneficial effects on organ damage have sometimes been observed. A J-curve phenomenon is unlikely to occur until lower values are reached, except perhaps in patients with advanced atherosclerotic artery diseases.

(4) On the basis of current data, it may be prudent to recommend lowering SBP/DBP to values within the range 130–139/80–85 mmHg, and possibly close to lower values in this range, in all hypertensive patients. More critical evidence from specific randomized trials is desirable, however.

J Hypertens 2009;27:2121

- Le duel des associations (LIFE-ASCOT-ACCOMPLISH)

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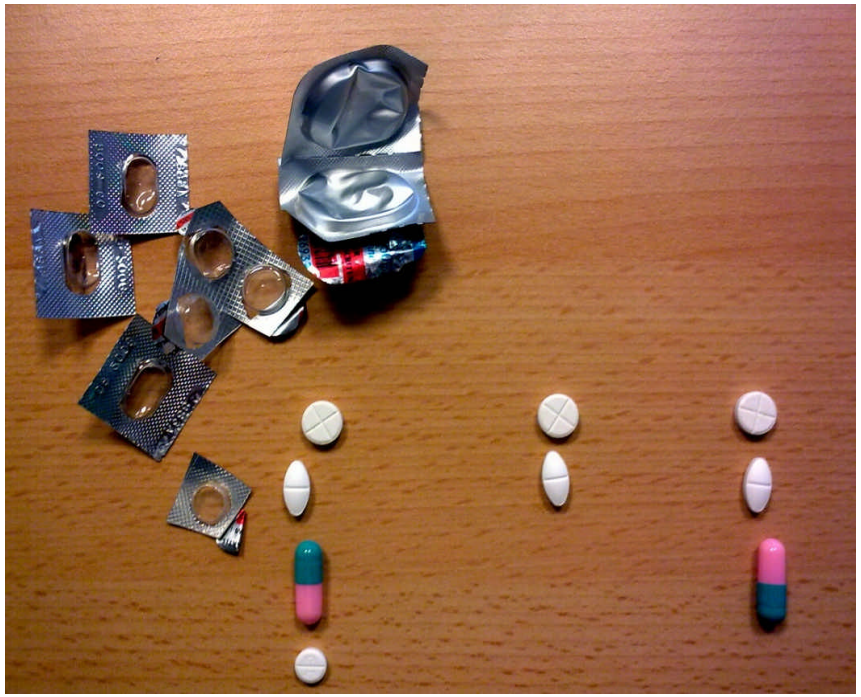
# CAPI

Part des patients traités par anti-hypertenseurs ayant normalisé leurs chiffres tensionnels (< 140/90), objectif cible 50 %

Prescription d'IEC (en nombre de boîtes) /prescription /IEC + sartans (en nombre de boîtes) : objectif cible 65 %

Prescription en nombre de boîtes dans le répertoire pour les antihypertenseurs/prescription d'antihypertenseurs en nombre de boîtes. Objectif cible de 65 %.

# Une révolution au quotidien pour les hypertendus



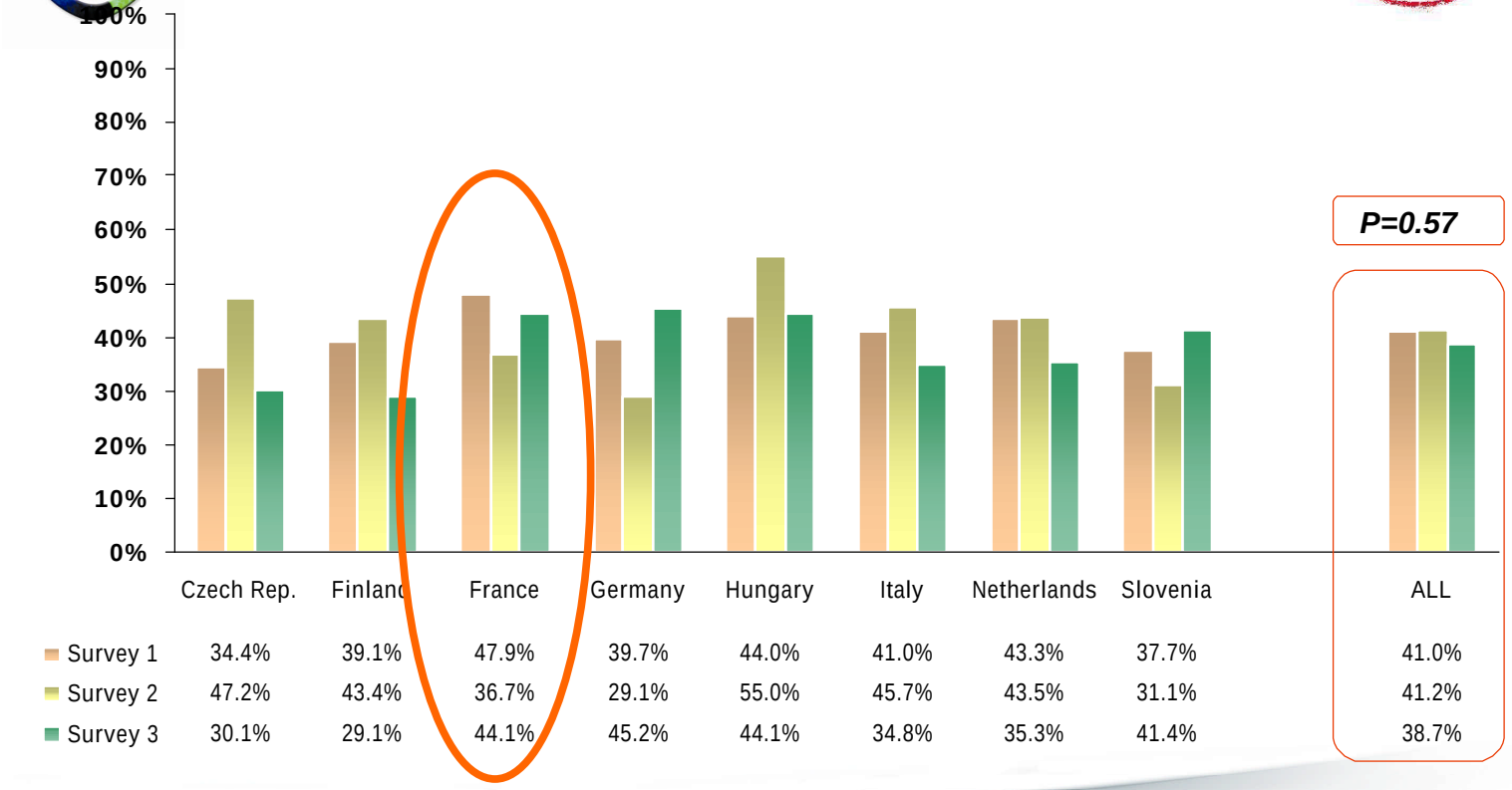
1980

2010

# BONUS

# EUROASPIRE

## Therapeutic Control of Blood Pressure*



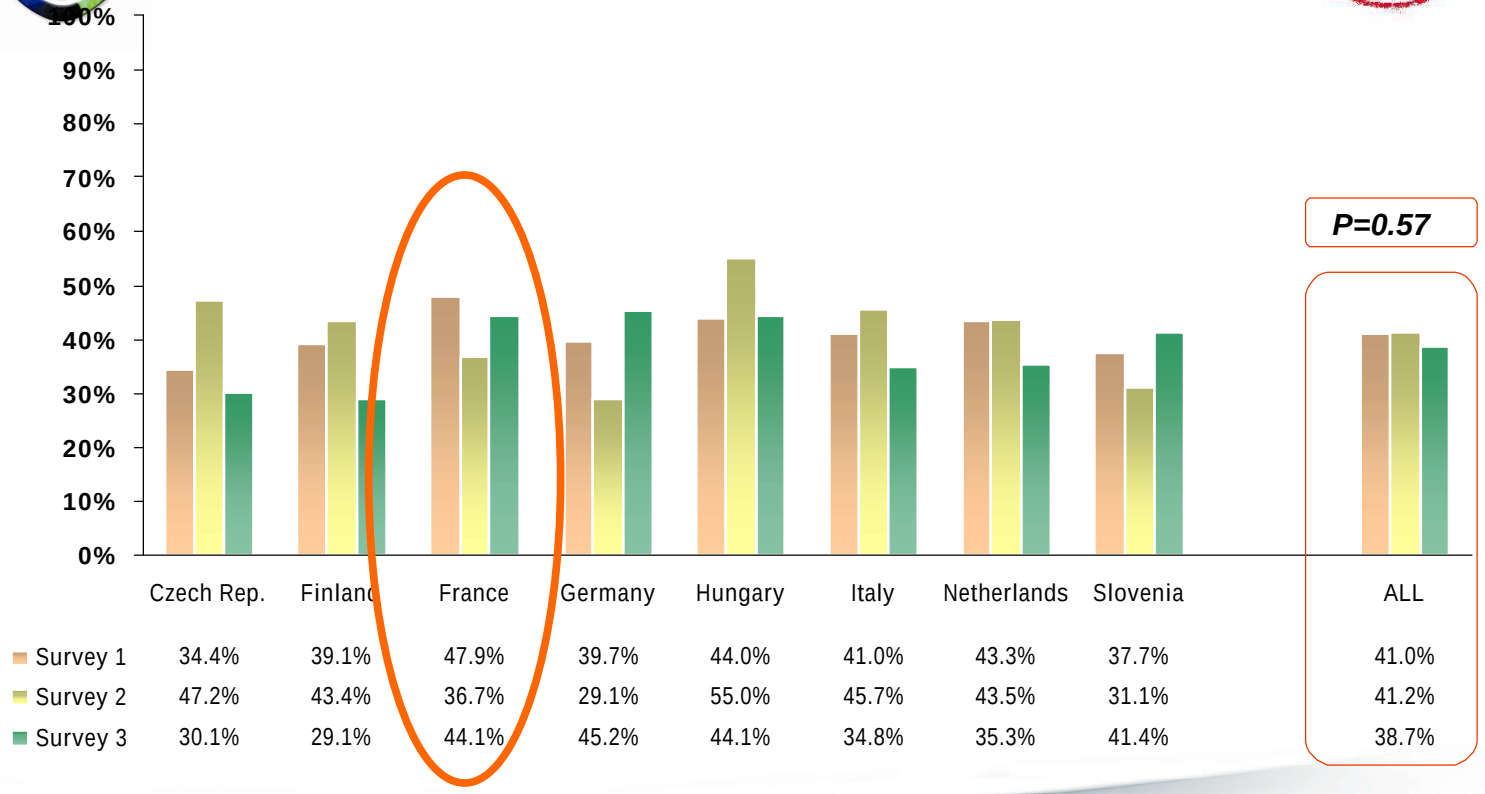

* SBP/DBP < 140/90 mmHg for non-diabetics or < 130/80 mmHg for diabetics

S2 vs. S1 : P=0.98
S3 vs. S2 : P=0.36
S3 vs. S1 : P=0.37

# EUROASPIRE

# OU LE SYNDROME « BASIC INSTINCT »

## Therapeutic Control of Blood Pressure*




* SBP/DBP < 140/90 mmHg for non-diabetics or < 130/80 mmHg for diabetics

S2 vs. S1 : P=0.98
S3 vs. S2 : P=0.36
S3 vs. S1 : P=0.37

# EUROASPIRE

# OU LE SYNDROME « BASIC INSTINCT »