# Comment diminuer la mortalité des diabétiques? Enseignements pour la pratique

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ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

# Associations of Diabetes Mellitus With Total Life Expectancy and Life Expectancy With and Without Cardiovascular Disease

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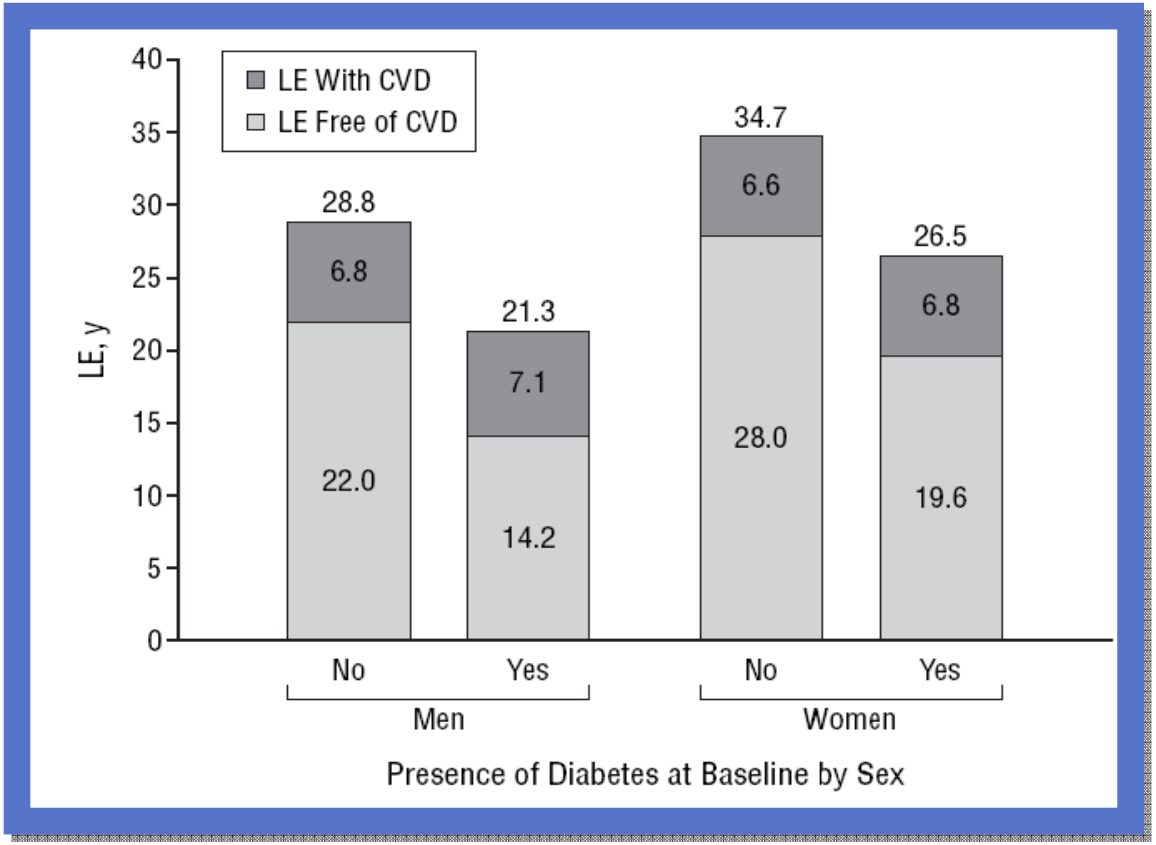



***« Diabetic men and women 50y and older lived on average 7.5 & 8.2 years less than their nondiabetic equivalents. »***

**Arch Int Med 2007;167:1145.**

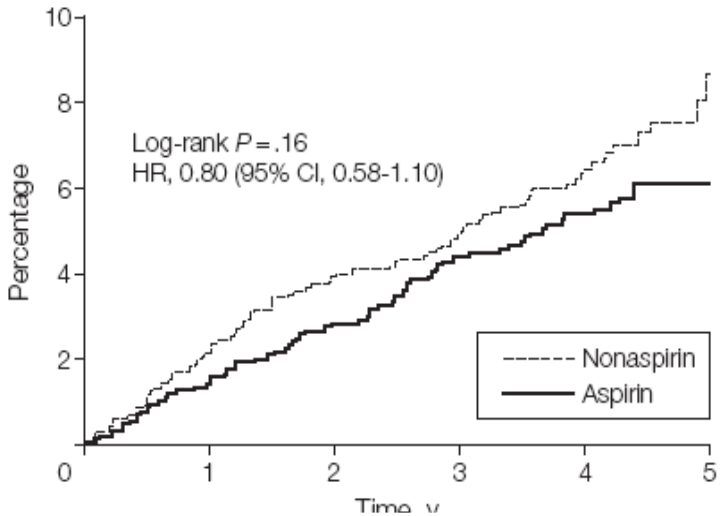
# Low-Dose Aspirin for Primary Prevention of Atherosclerotic Events in Patients With Type 2 Diabetes

## A Randomized Controlled Trial

| | Aspirin Group | | Nonaspirin Group | | | |
|---|---|---|---|---|---|---|
| | No. (%) | No. per 1000 Person-Years | No. (%) | No. per 1000 Person-Years | Hazard Ratio (95% CI) | *P* Value |
| Primary end point: all atherosclerotic events | 68 (5.4) | 13.6 | 86 (6.7) | 17.0 | 0.80 (0.58-1.10) | .16 |
| Coronary and cerebrovascular mortality | 1 (0.08) | 0.2 | 10 (0.8) | 2.0 | 0.10 (0.01-0.79) | .0037 |
| CHD events (fatal + nonfatal) | 28 (2.2) | 5.6 | 35 (2.7) | 6.9 | 0.81 (0.49-1.33) | .40 |
| Fatal MI | 0 | 0 | 5 (0.4) | 1.0 | | |
| Nonfatal MI | 12 (1.0) | 2.4 | 9 (0.7) | 1.8 | 1.34 (0.57-3.19) | .50 |
| Unstable angina | 4 (0.3) | 0.8 | 10 (0.8) | 2.0 | 0.40 (0.13-1.29) | .13 |
| Stable angina | 12 (1.0) | 2.4 | 11 (0.9) | 2.2 | 1.10 (0.49-2.50) | .82 |
| Cerebrovascular disease (fatal + nonfatal) | 28 (2.2) | 5.6 | 32 (2.5) | 6.3 | 0.84 (0.53-1.32) | .44 |
| Fatal stroke | 1 (0.08) | 0.2 | 5 (0.4) | 1.0 | 0.20 (0.024-1.74) | .15 |
| Nonfatal stroke | | | | | | |
| Ischemic | 22 (1.7) | 4.4 | 24 (1.9) | 4.6 | 0.93 (0.52-1.66) | .80 |
| Hemorrhagic | 5 (0.4) | 1.0 | 3 (0.2) | 0.6 | 1.68 (0.40-7.04) | .48 |
| Transient ischemic attack | 5 (0.4) | 1.0 | 8 (0.6) | 1.6 | 0.63 (0.21-1.93) | .42 |
| Peripheral artery disease[a] | 7 (0.6) | 1.4 | 11 (0.9) | 2.2 | 0.64 (0.25-1.65) | .35 |

Abbreviations: CHD, coronary heart disease; CI, confidence interval; MI, myocardial infarction.
[a]Arteriosclerosis obliterans (5 in aspirin group and 8 in nonaspirin group); aortic dissection (2 fatal in the aspirin group and 1 nonfatal in the nonaspirin group); mesenteric artery thrombosis (1 in the nonaspirin group), and retinal artery thrombosis (1 in the nonaspirin group).

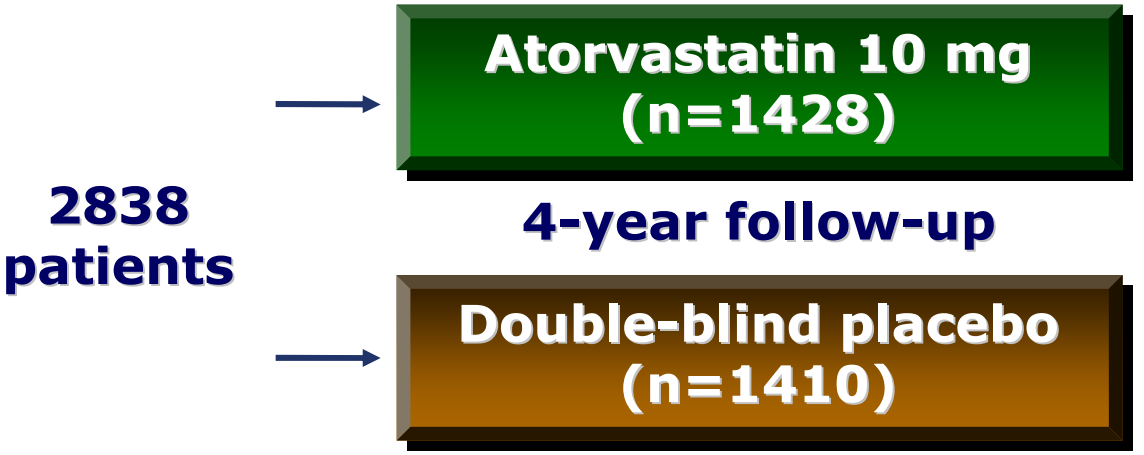
Total Percentage of Atherosclerotic Events According to Treatment Group




**Ogawa H; JAMA Nov 2008 ; on line**

# Collaborative Atorvastatin Diabetes Study (CARDS)

- **Patient Population**
  - *Type 2 diabetes mellitus*
  - *Men and women 40–75 years of age*
  - *Primary CHD and stroke prevention*
  - *LDL-C ≤160 mg/dL (≤4.14 mmol/L)*
  - *TG ≤600 mg/dL (≤6.78 mmol/L)*
  - *≥1 additional RF*
  - *HTN (or on HTN treatment)*
  - *Retinopathy*
  - *Albuminuria*
  - *Current smoking*

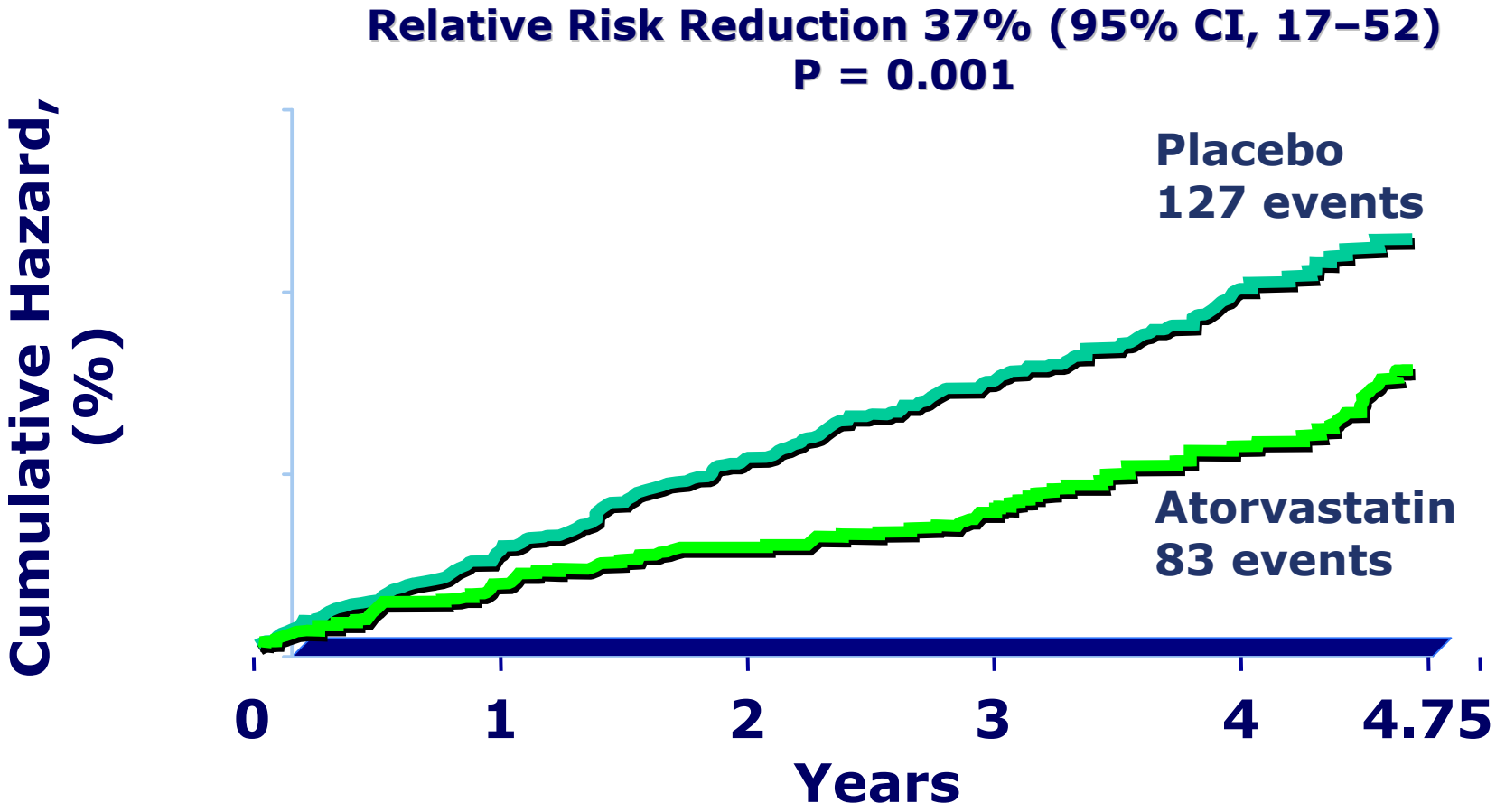



**Primary endpoint:** time to first major CV event (CHD death, nonfatal MI, unstable angina, resuscitated cardiac arrest, coronary revascularization, stroke

**Secondary endpoints:** total mortality, any CV endpoint, lipids, and lipoproteins

Colhoun HM et al. *Lancet* 2004;364:685-6

# CARDS: Effect of Atorvastatin on the Primary Endpoint: Major CV Events Including Stroke



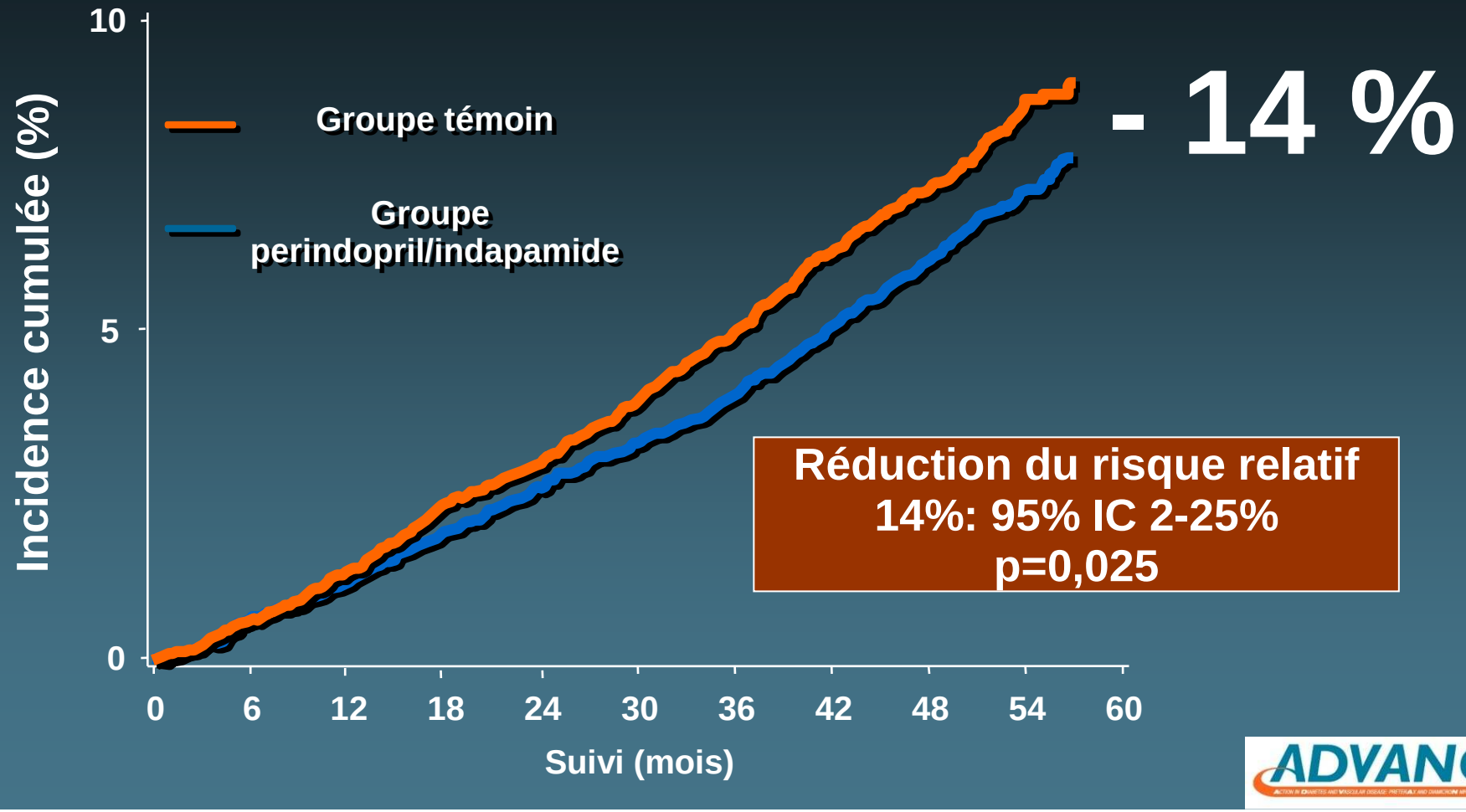

| | | | | | | |
|---|---|---|---|---|---|---|
| Placebo | 1410 | 1351 | 1306 | 1022 | 651 | 305 |
| Atorvastatin | 1428 | 1392 | 1361 | 1074 | 694 | 328 |

Risque absolu : 9.0 vs 5.8%

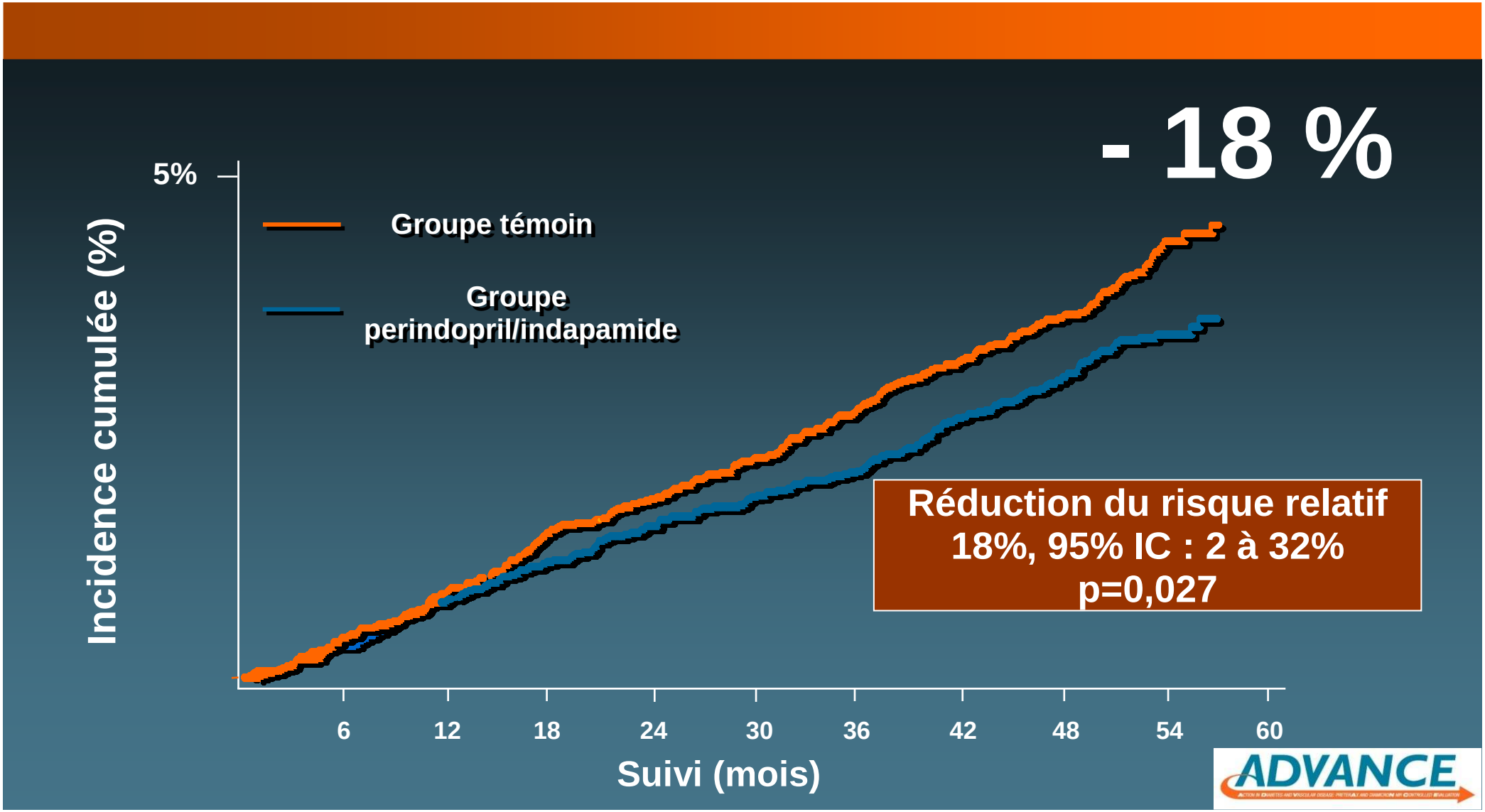
Colhoun HM et al. *Lancet* 2004;364:685-696.

# Réduction de la mortalité totale

*« Traiter 79 patients par perindopril/indapamide pendant 5 ans permet d'éviter un décès»*



# Réduction de la mortalité cardiovasculaire



# Des bénéfices absolus importants

***Une stratégie par perindopril/indapamide***

***permet d'éviter en 5 ans :***

- **1 événement macro ou microvasculaire pour 66 patients traités**
- **1 décès pour 79 patients traités**
- **1 événement coronaire pour 75 patients traités**
- **1 événement rénal pour 20 patients traités**

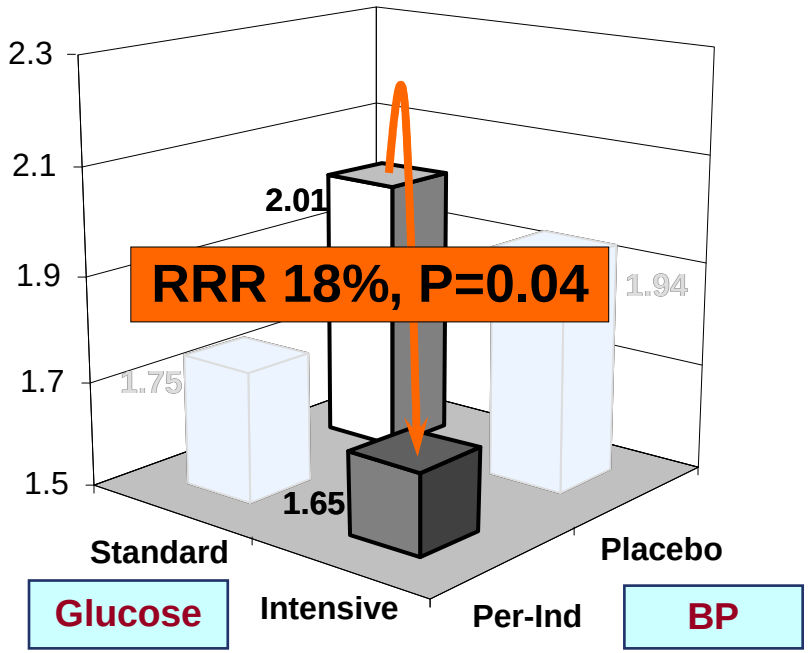
**Ces bénéfices sont similaires dans tous les sous-groupes, quels que soient les traitements associés, le niveau de pression artérielle ou le profil des patients. De plus, le traitement a été très bien toléré.**

ADVANCE


# Résultats
# “Double protection”
# EASD 2008

# Double protection et mortalité totale

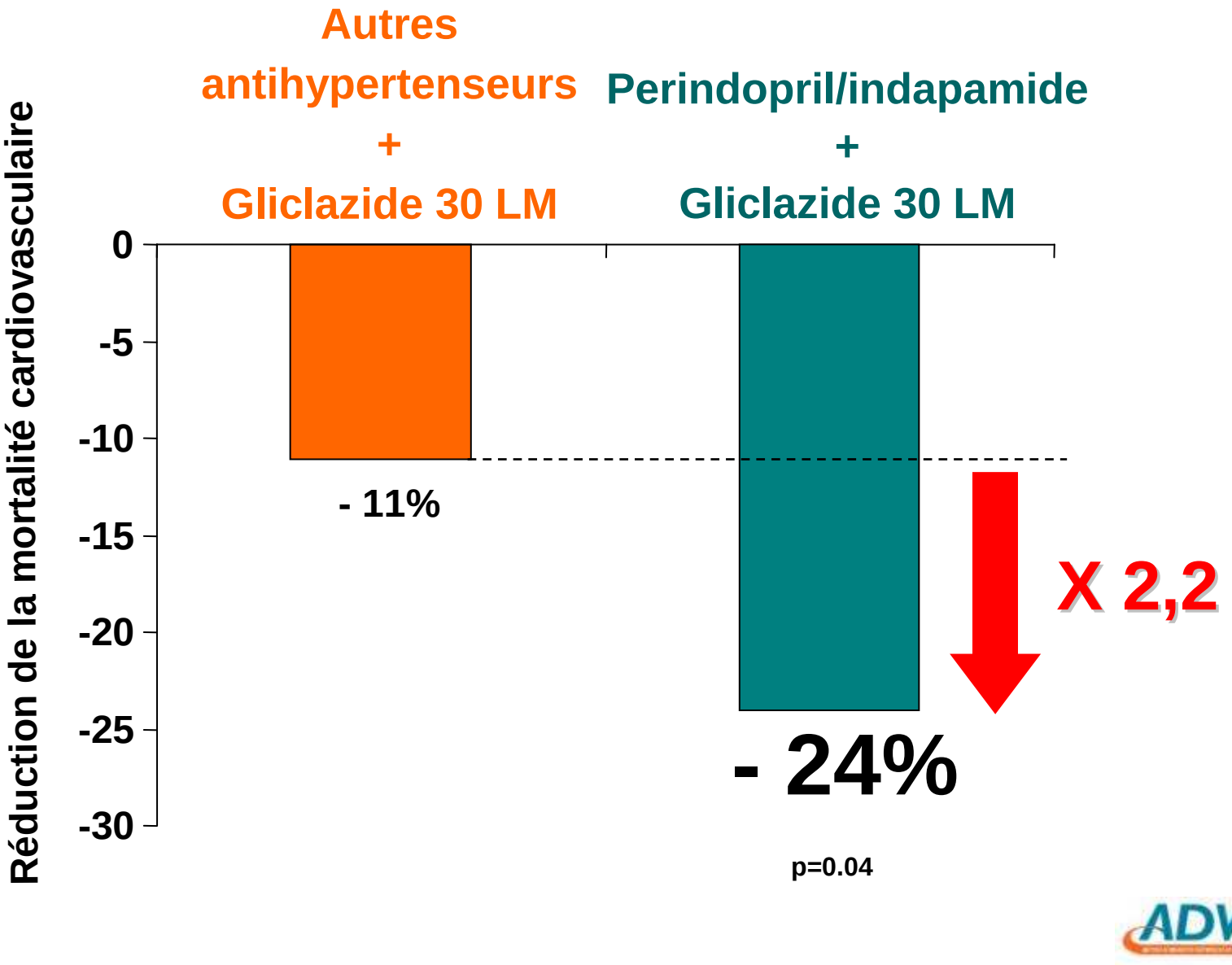
***% d'événements annuel***




**P for interaction=0.90**

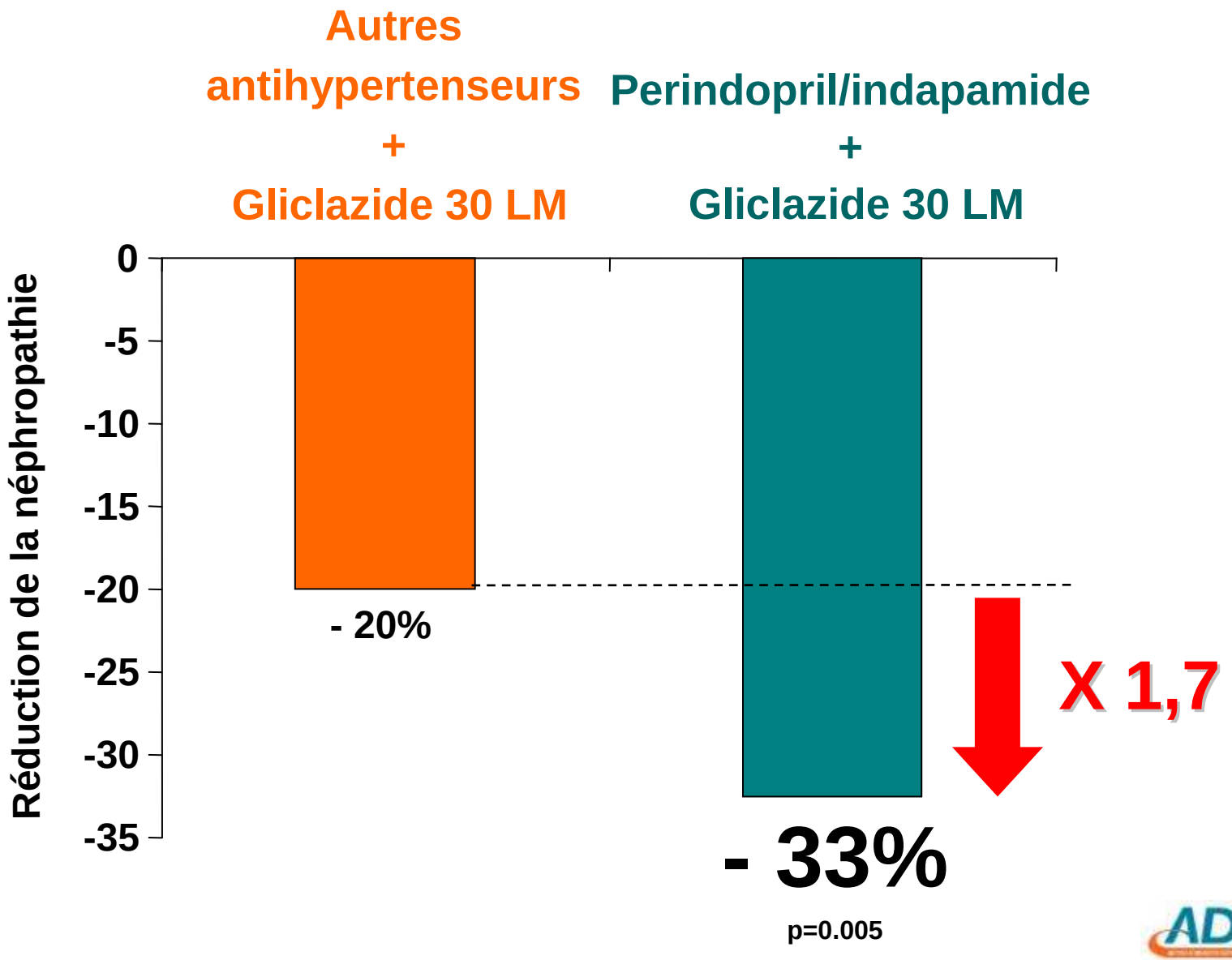
**Les effets sur la PA (Preterax) et sur la glycémie (Diamicron 30) sont indépendants pour tous les événements (pas d'interaction). L'additivité des 2 traitements entraîne des bénéfices importants.**

# Double protection et mortalité cardiovasculaire




ADVANCE

# Double protection et néphropathie



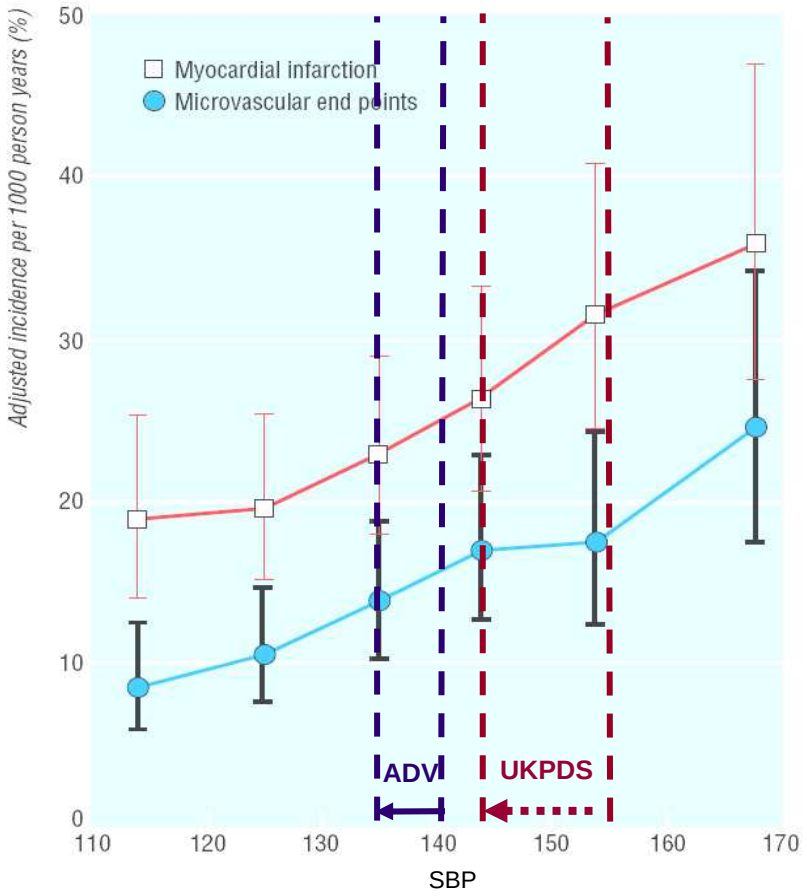
# Bénéfices de la double protection

**L’utilisation conjointe d’une stratégie associant la combinaison fixe perindopril/indapamide au gliclazide 30 LM permet de réduire :**

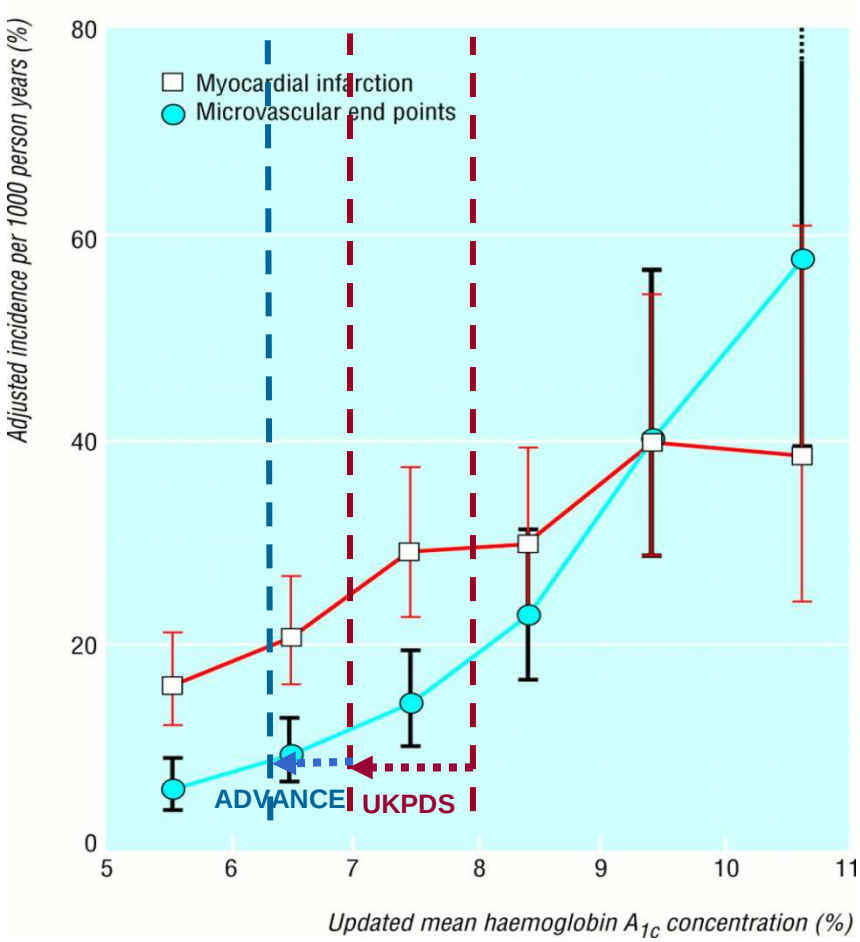
- **de 18% la mortalité totale *(p=0,04)***
- **de 24% la mortalité cardiovasculaire *(p=0,04)***
- **de 33% la néphropathie *(p=0,005)***

# Des résultats qui vont au-delà d'UKPDS

***Pour le contrôle de la pression artérielle***



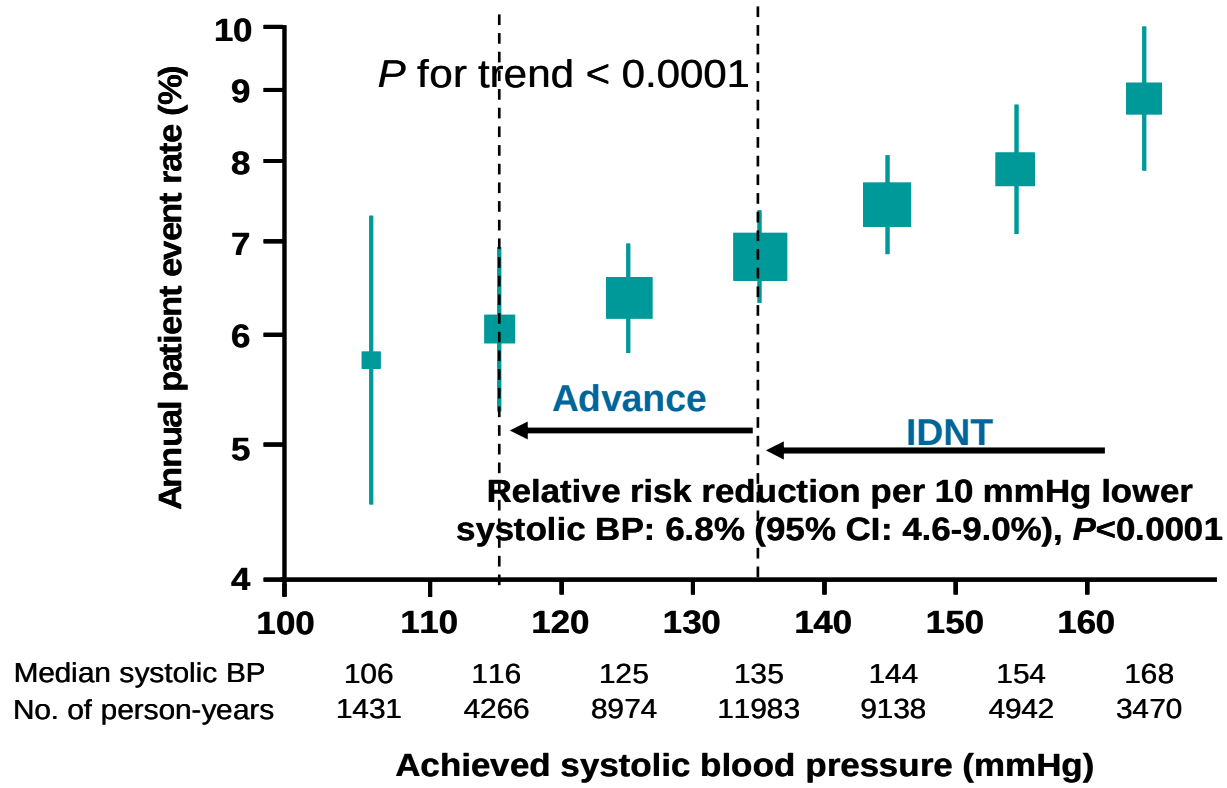

***Pour le contrôle de l'HbA1C***




**UK Prospective Diabetes Study**

# La pression artérielle : un rôle clé dans la prévention des complications rénales

## Renal events by systolic blood pressure achieved during follow-up*




**Adjusted for age, sex, HbA1c, serum lipids, BMI, eGFR, smoking, alcohol use, and study drug*

**B.E. de Galan, J. Chalmers, V. Perkovic, T. Ninomiya, A. Pillai, A. Patel, A. Cass, S. MacMahon, B. Neal, C-E Mogensen, M. Marre,S. Harrap, N. Poulter, M. Cooper,G. Mancia, on behalf of the ADVANCE Collaborative Group ESH 2008**

# Néphroprotection du patient diabétique : 10 ans de progrès

**5. Mortalité**

IEC vs non ISRA : MICROHOPE : + *(2000)*
AA2 vs non ISRA : IDNT : - *(2001)*
AA2 vs non ISRA : RENAAL : - *(2001)*
AA2 vs IEC : ON TARGET : = *(2008)*

**4. Insuffisance rénale**

AA2 vs non ISRA : IDNT : + *(2001)*
AA2 vs non ISRA : RENAAL : + *(2001)*

**3. Protéinurie**

Preterax vs IEC : PREMIER : + *(2003)*
AA2 vs IEC : DETAIL : = *(2004)*

**2. Microalbuminurie**

AA2 vs non ISRA : IRMA 2 : + *(2001)*
AA2 vs non ISRA : MARVAL : + *(2002)*
AA2 vs IEC : ns Lacourciere : ns

**1. Prévention primaire**

IEC vs non ISRA : MICROHOPE : *ns (2000)*
IEC vs non ISRA : BENEDICT : + *(2004)*
AA2 : DIRECT : – *(2008)*
AA2 : ROAD MAP : ? *(2010)*

# Cardiovascular Outcomes in the Irbesartan Diabetic Nephropathy Trial of Patients with Type 2 Diabetes and Overt Nephropathy

Tomas Berl, MD; Lawrence G. Hunsicker, MD; Julia B. Lewis, MD; Marc A. Pfeffer, MD, PhD; Jerome G. Porush, MD; Jean-Lucien Rouleau, MD; Paul L. Drury, MD, FRACP; Enric Esmatjes, MD; Donald Hricik, MD; Chirag R. Parikh, MD; Itamar Raz, MD; Philippe Vanhille, MD; Thomas B. Wiegmann, MD; Bernard M. Wolfe, MD, FRCPC; Francesco Locatelli, MD; Samuel Z. Goldhaber, MD; and Edmund J. Lewis, MD, for the Collaborative Study Group*

Background: Patients with diabetes have increased risk for adverse cardiovascular events. Angiotensin-converting enzyme inhibitors are protective in type 1 diabetes. However, no definitive studies have examined the use of angiotensin-receptor blockers in patients with type 2 diabetes and overt nephropathy. The primary outcomes of the Irbesartan Diabetic Nephropathy Trial were doubling of serum creatinine levels, end-stage renal disease, and death from any cause.

Objective: To compare rates of cardiovascular events among patients with type 2 diabetic nephropathy who received conventional antihypertensive therapy with an angiotensin-receptor blocker (irbesartan) or a calcium-channel blocker (amlodipine), or placebo.

Design: Randomized double-blind, placebo-controlled trial with a median follow-up of 2.6 years. A time event analysis was used.

Setting: 209 centers in the Americas, Europe, Israel, and Australasia.

Participants: 1715 adults with type 2 diabetic nephropathy and hypertension; serum creatinine levels of 89 μmol/L (1.0 mg/dL) to 266 μmol/L (3.0 mg/dL) in women and 106 μmol/L (1.2 mg/dL) to 266 μmol/L (3.0 mg/dL) in men; and urinary protein excretion

Measurements: Time to cardiovascular death, myocardial infarction, congestive heart failure, strokes, and coronary revascularization.

Results: The three groups were not statistically different in the composite of cardiovascular events. Among the components of the composite, there was a trend toward a decrease in strokes in patients receiving amlodipine versus those receiving placebo (hazard ratio, 0.65 [95% CI, 0.35 to 1.22]; $P = 0.18$). Likewise, patients receiving amlodipine had a significantly lower rate of myocardial infarction when compared with placebo recipients (hazard ratio, 0.58 [CI, 0.37 to 0.92]; $P = 0.02$). In contrast, patients receiving irbesartan had a significantly lower incidence of congestive heart failure when compared with placebo recipients (hazard ratio, 0.72 [CI, 0.52 to 1.00]; $P = 0.048$) or amlodipine recipients (hazard ratio, 0.65 [CI, 0.48 to 0.87]; $P = 0.004$).

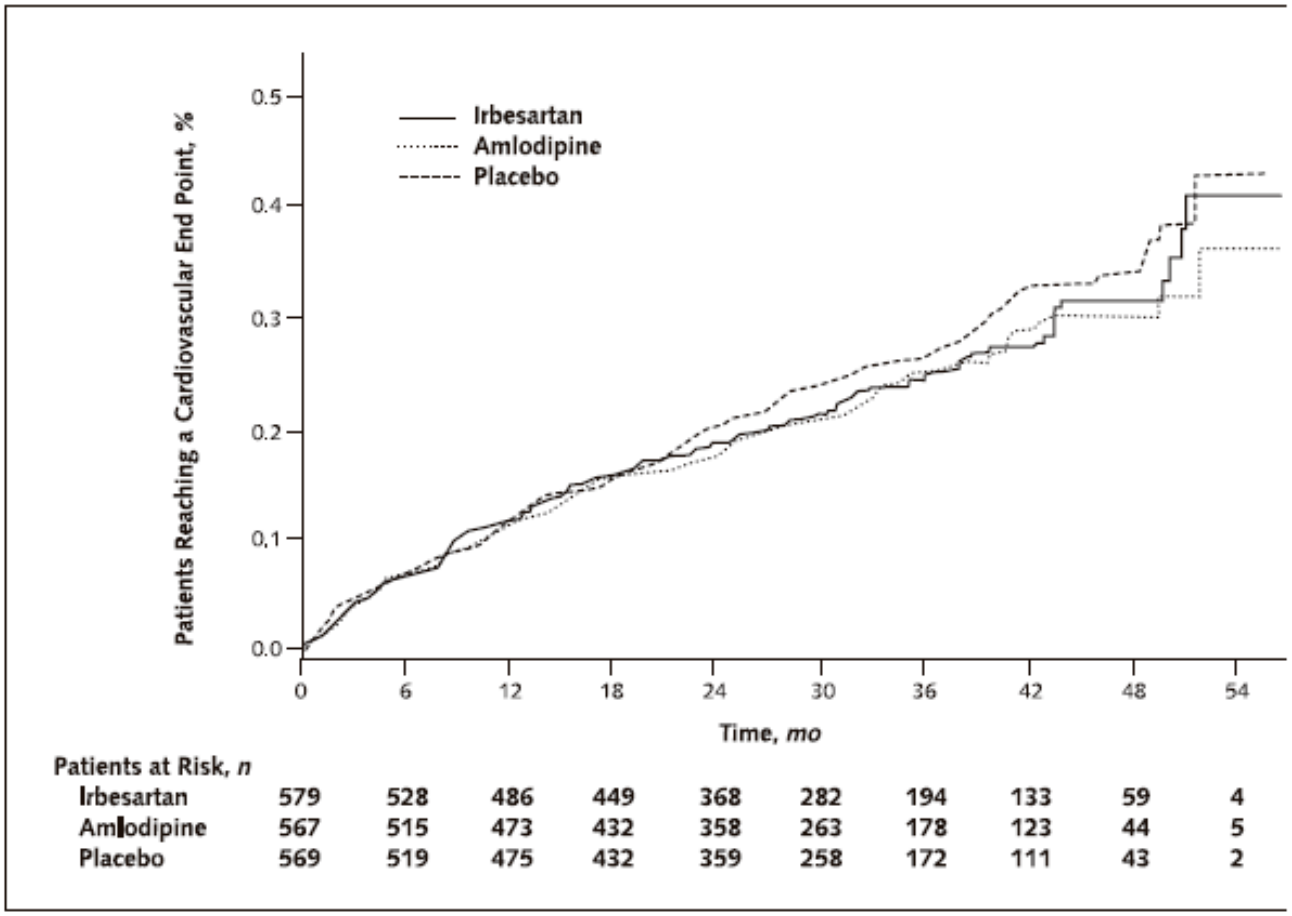
Conclusion: The composite cardiovascular event rate did not differ in patients with type 2 diabetes and overt nephropathy treated with irbesartan, amlodipine, or placebo in addition to conventional antihypertensive therapy.

*Ann Intern Med.* 2003;138:542-549. www.annals.org

**Berl T, Ann Int Med 2003**

# Cardiovascular Outcomes in the Irbesartan Diabetic Nephropathy Trial of Patients with Type 2 Diabetes and Overt Nephropathy

*Figure.* Time to first cardiovascular composite event as a function of treatment assignment.




The numbers of patients at risk in each treatment group at 6-month intervals are shown on the x-axis. There was no statistically significant overall difference among treatment groups ($P > 0.05$) or for any specific pairwise comparison.

**Berl T, Ann Int Med 2003**

*Table 3.* **Risk for Cardiovascular Outcomes by Treatment Group***

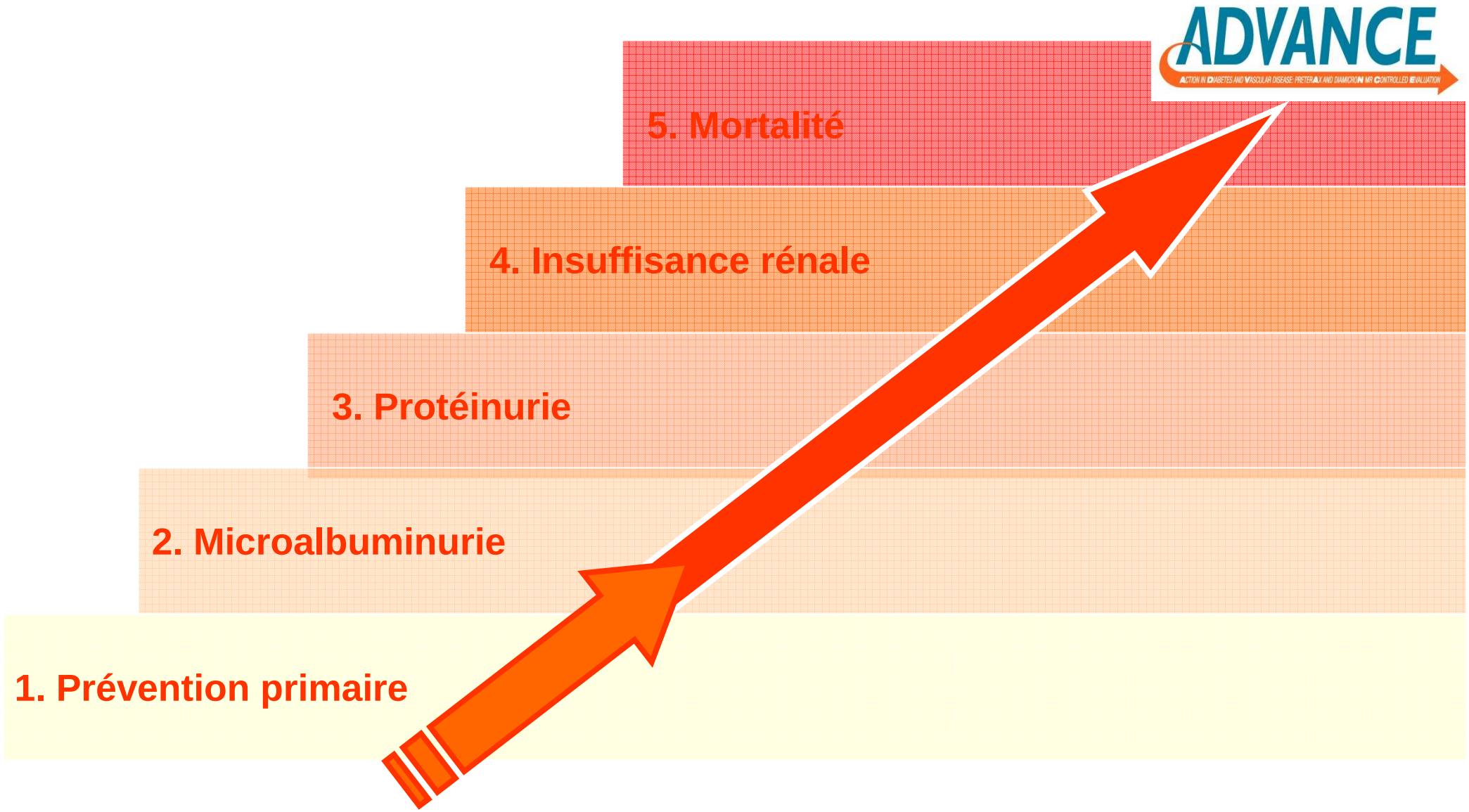
| Cardiovascular Event | Events/Patients | | | Hazard Ratio (95% CI)† | *P* Value |
|---|---|---|---|---|---|
| | Irbesartan Group (*n* = 579) | Amlodipine Group (*n* = 567) | Placebo Group (*n* = 569) | | |
| | ← *n/n* → | | | | |
| Cardiovascular composite | 259/172 | 278/161 | 284/185 | | |
| Irbesartan vs. placebo | | | | 0.90 (0.74–1.10) | >0.2 |
| Amlodipine vs. placebo | | | | 1.21) | >0.2 |
| Irbesartan vs. amlodipine | | | | 0.90 (0.74–1.10) | >0.2 |
| Cardiovascular death | 52/52 | 37/37 | 46/46 | | |
| Irbesartan vs. placebo | | | | 1.08 (0.72–1.60) | >0.2 |
| Amlodipine vs. placebo | | | | 0.79 (0.51–1.22) | >0.2 |
| Irbesartan vs. amlodipine | | | | 1.36 (0.89–2.07) | 0.155 |
| Congestive heart failure | 69 | 143/93 | 113/72 | | |
| Irbesartan vs. placebo | | | | 0.72 (0.52–1.00) | 0.048 |
| Amlodipine vs. placebo | | | | 1.11 (0.83–1.50) | >0.2 |
| Irbesartan vs. amlodipine | | | | 0.65 (0.48–0.87) | 0.004 |
| Myocardial infarction | 48/44 | 29/27 | 51/46 | | |
| Irbesartan vs. placebo | | | | 0.90 (0.60–1.33) | >0.2 |
| Amlodipine vs. placebo | | | | 0.58 (0.37–0.92) | 0.021 |
| Irbesartan vs. amlodipine | | | | 1.54 (0.97–2.45) | 0.068 |
| Cerebrovascular accident | 30/28 | 18/15 | 28/26 | | |
| Irbesartan vs. placebo | | | | 1.01 (0.61–1.67) | >0.2 |
| Amlodipine vs. placebo | | | | 0.65 (0.35–1.22) | 0.18 |
| Irbesartan vs. amlodipine | | | | 1.55 (0.84–2.87) | 0.165 |
| Cardiac revascularization | 31/27 | 32/28 | 39/36 | | |
| Irbesartan vs. placebo | | | | 0.80 (0.49–1.30) | >0.2 |
| Amlodipine vs. placebo | | | | 0.86 (0.54–1.38) | >0.2 |
| Irbesartan vs. amlodipine | | | | 0.93 (0.55–1.55) | >0.2 |

* All patients received conventional antihypertensive therapy that was initiated with irbesartan, amlodipine, or placebo.
† Hazard ratio for cardiovascular death (single end point) was estimated by using proportional hazards (Cox) regression modeling. Risk for subsequent events was estimated by using the counting process method of Anderson and Gill as modified by Lee et al. (18) to account for possible correlation of risk for events within patients.

**Berl T, Ann Int Med 2003**

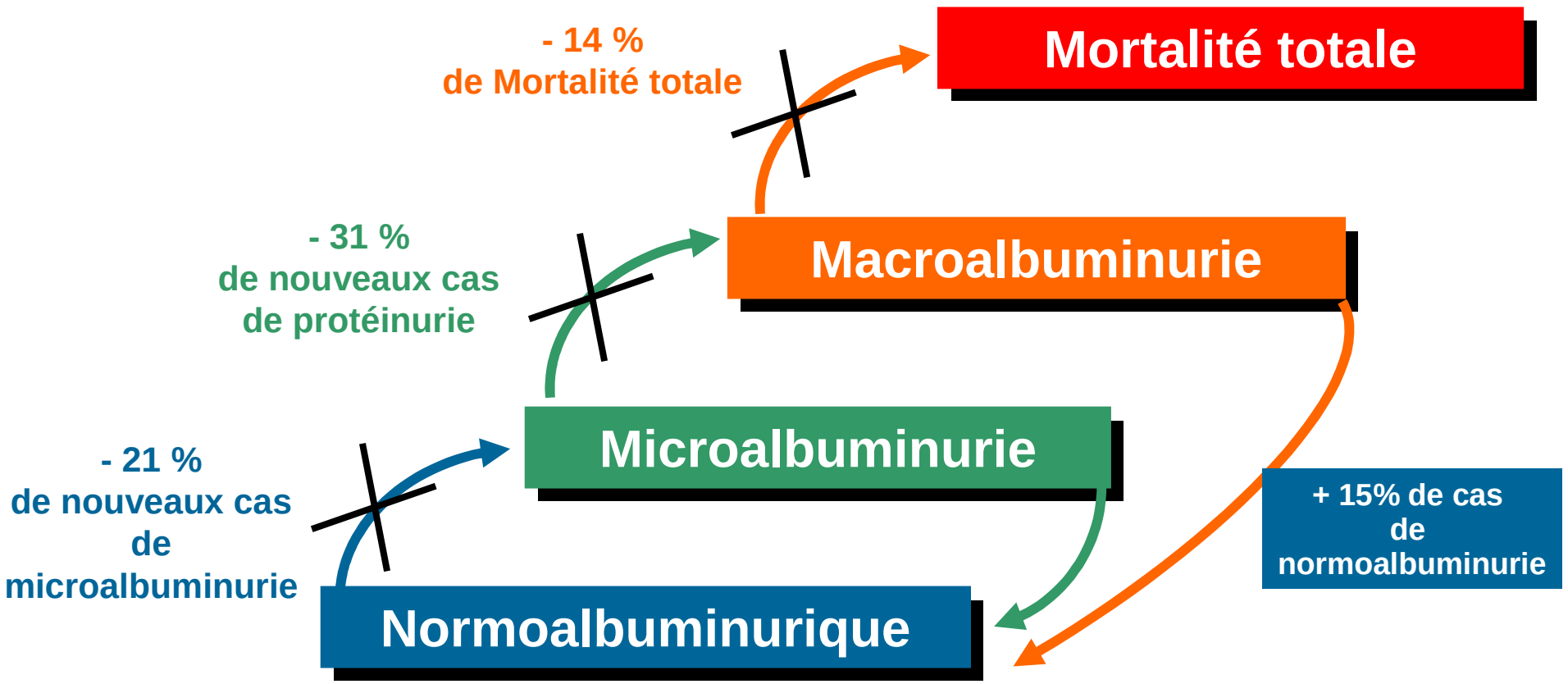
# Peut-on faire mieux ?

## De la prévention primaire rénale à la réduction de la mortalité

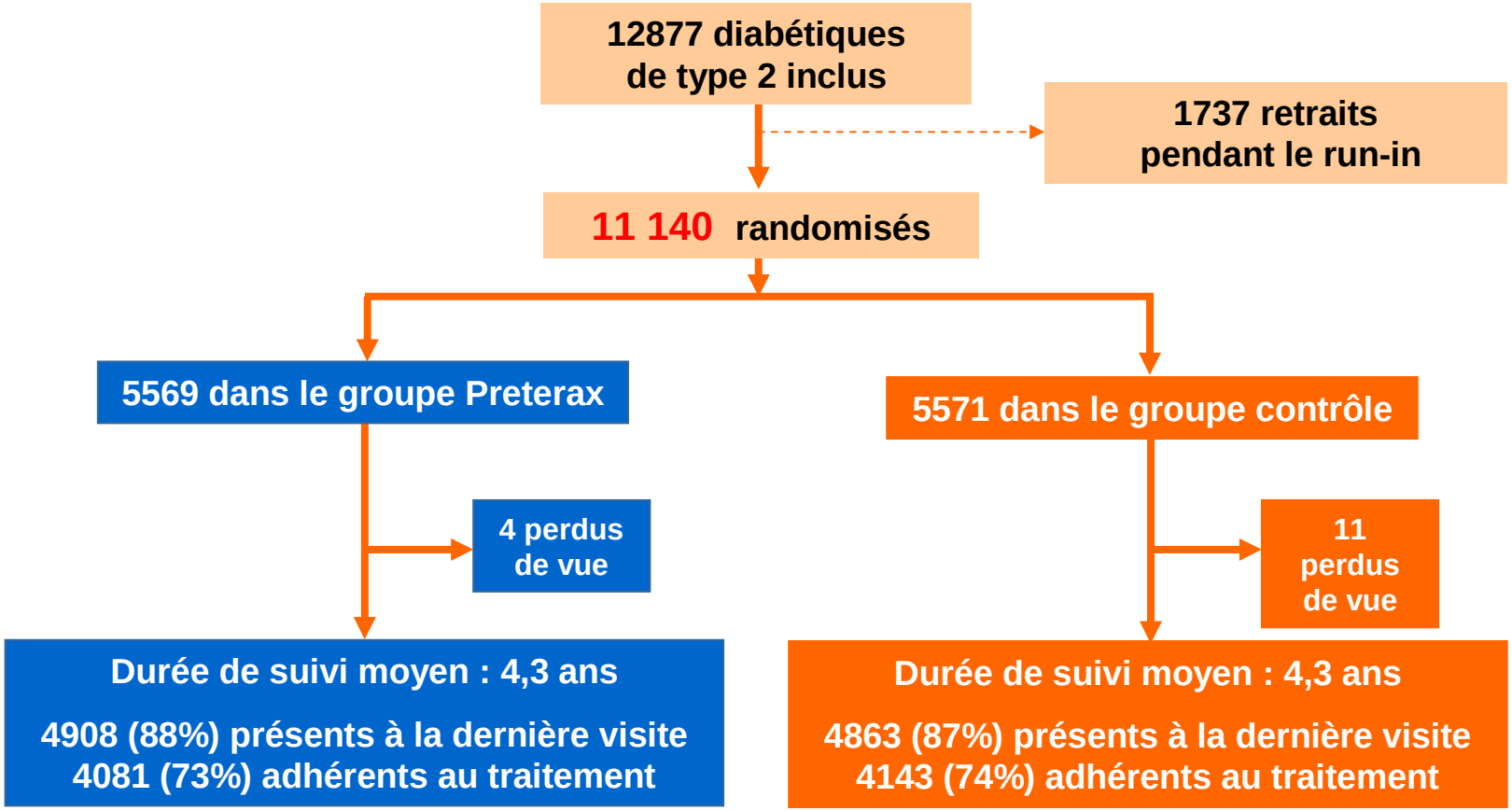


# Pronostic vital et protection rénale

**Groupe Preterax**



# Des résultats fiables et rigoureux




**73 / 74 % d'observance à la fin de l'étude**

# Des résultats transposables aux diabétiques français

| | ***ADVANCE***<br>*A l'inclusion* | ***Étude ENTRED ****<br>*France* |
|---|---|---|
| ***Age*** | ***66 ans*** | ***65 ans*** |
| ***$HbA_{1c}$*** | ***7.5%*** | ***7.5%*** |
| ***IMC*** | ***28 kg/m²*** | ***29 kg/m²*** |
| ***PAS*** | ***145 mm Hg*** | ***144 mm Hg*** |
| ***Durée du diabète*** | ***8 ans*** | ***8 ans*** |
| ***Antécédents*** | | |
| ***macrovasculaires*** | ***32%*** | ***30%*** |
| ***microvasculaires*** | ***10%*** | ***20%*** |
| | ***Fin de suivi*** | |
| ***Antithrombotiques*** | ***61%*** | ***39%*** |
| ***Hypolipidémiants (statines)*** | ***52% (45%)*** | ***55% (44%)*** |
| ***IEC et/ou ARA 2*** | ***73%*** | ***57%*** |

* **Registre représentatif de la population française.Adapté de Fagot-Campagna A. *Diabetes & Metab.* 2008**

# Ma proposition pour un diabétique hypertendu sans ATCD d'infarctus.

DNID + HTA

| Preterax + Tahor 10 +ASA | Bi- Preterax + Tahor 10 +ASA | Bi- Preterax + Caduet 5/10 +ASA | Bi- Preterax + Caduet10/10 +ASA |
|---|---|---|---|

Si toléré Si toléré Si toléré

Je réfléchis à une alternative en cas d'intolérance, ou de contrôle imparfait de la PA ou du LDL au terme de la titration

# Ma proposition pour un diabétique hypertendu sans ATCD d'infarctus.

| Preterax + Tahor 10 +ASA | Bi- Preterax + Tahor 10 +ASA | Bi- Preterax + Caduet 5/10 +ASA | Bi- Preterax + Caduet10/10 +ASA |
|---|---|---|---|

Si toléré Si toléré Si toléré

J'applique l'EBM tout en respectant l'AMM des produits

Je confère au patient une prévention optimale

HOT trial, CARDS trial, ASCOT trial, ADVANCE trial

70 à 80% des patients seront aux objectifs thérapeutiques au terme de la dernière étape.

# Ma proposition pour un diabétique hypertendu sans ATCD d'infarctus.

| Preterax + Tahor 10 +ASA | Bi- Preterax + Tahor 10 +ASA | Bi- Preterax + Caduet 5/10 +ASA | Bi- Preterax + Caduet10/10 +ASA |
|---|---|---|---|
| CTJ 1.46€ | CTJ 1.46€ | CTJ 1.53€ | CTJ 1.53€ |
| | Si toléré | Si toléré | Si toléré |

J'applique l'EBM tout en respectant l'AMM des produits

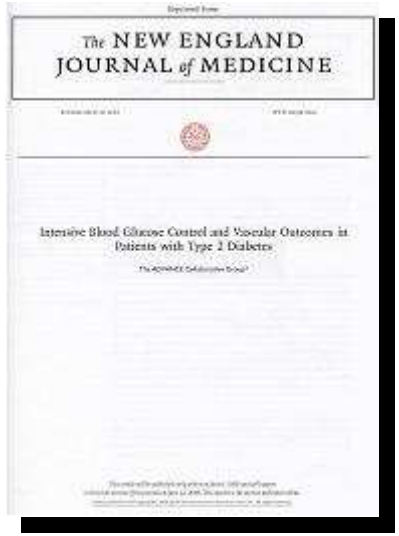
Je confère au patient une prévention optimale

Je tiens compte des problématiques de l'observance

Je n'induis pas de surcoût

J'admets les limites de mon raisonnement individuel

# Conclusion

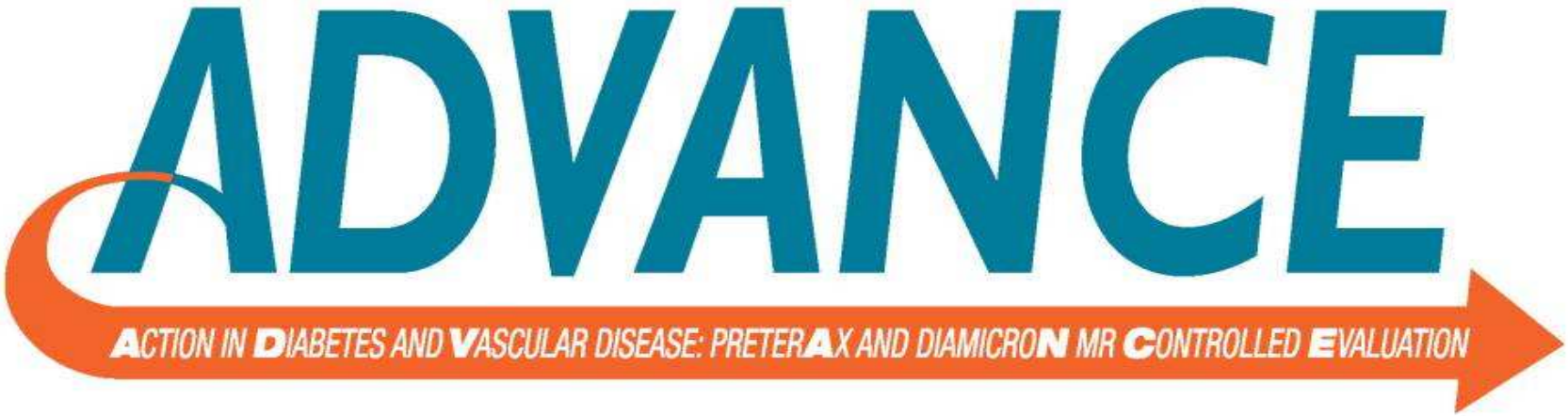

**« L'administration systématique de la combinaison fixe perindopril/indapamide chez les patients diabétiques diminue la mortalité et les complications cardiovasculaires et rénales de ces patients quel que soit leur niveau de PA ou les traitements associés.**

**Le traitement a été bien toléré. »**

**L'ajout de la combinaison fixe perindopril/indapamide au gliclazide 30 LM permet de doubler le niveau de protection cardiovasculaire et rénale.**

**« Ce traitement peut désormais être envisagé de manière systématique. »**

**ADVANCE Collaborative Group. The Lancet. 08 septembre 2007.**


ADVANCE
ACTION IN DIABETES AND VASCULAR DISEASE: PRETERAX AND DIAMICRON MR CONTROLLED EVALUATION

# Perindopril / Indapamide : Une stratégie bien tolérée

| *Raisons majeures de l'arrêt* | *Traitement randomisé* | |
|---|---|---|
| | *Preterax (n=5569)* | *Controle (n=5571)* |
| *Patient incapable de/ ne voulant pas/ suivre les visites* | *521 (9.4%)* | *635 (11.4%)* |
| *Toux* | *184 (3.3%)* | *72 (1.3%)* |
| *Hypotension, vertiges* | *69 (1.2%)* | *22 (0.4%)* |
| *Effets secondaires  importants* | *67 (1.2%)* | *66 (1.2%)* |
| *Autres* | *172 (3.1%)* | *195 (3.5%)* |