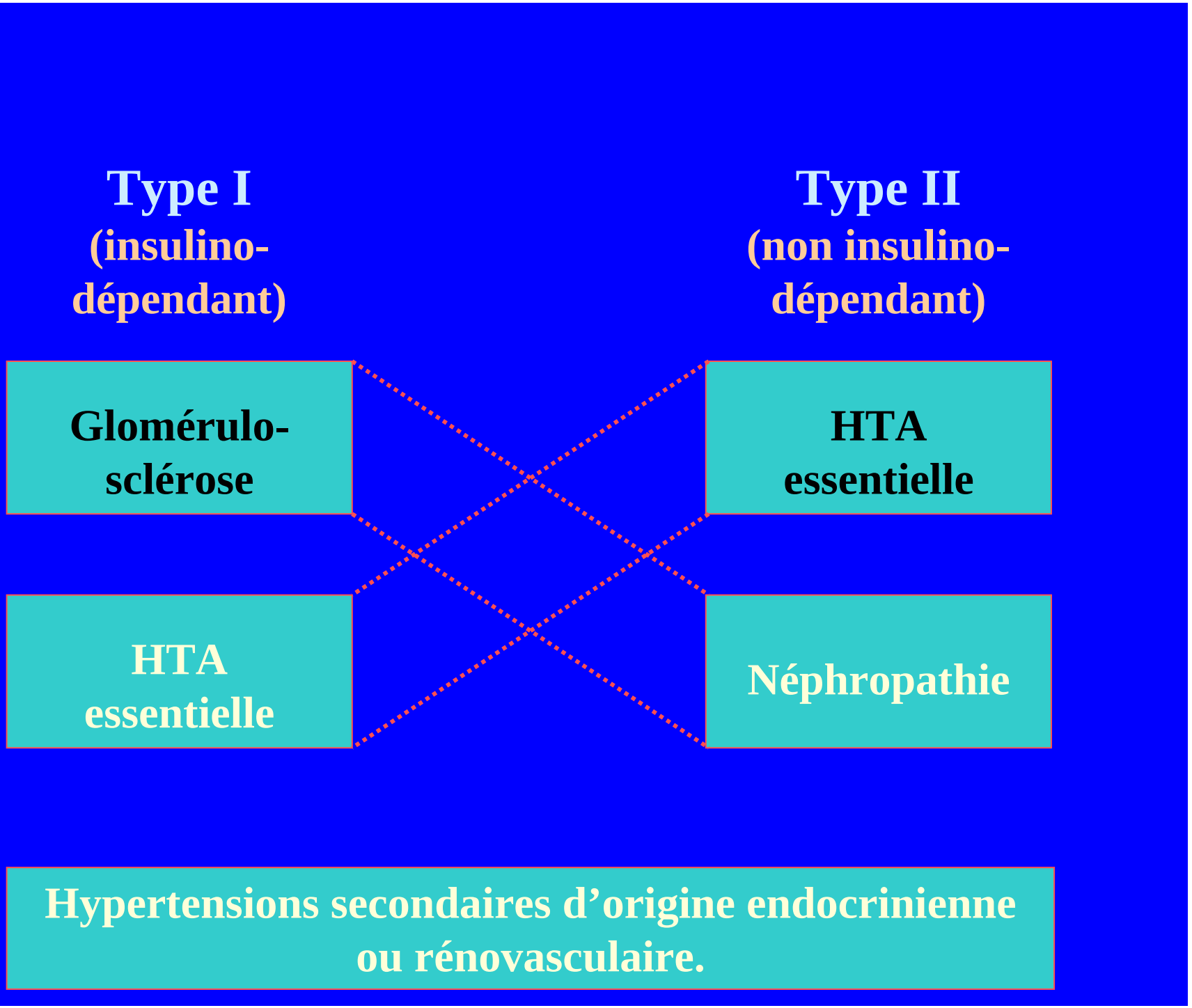
Prise en charge de l'hypertension artérielle chez le diabétique

JM KRZESINSKI
Professeur de Néphrologie et HTA
CHU Liège


Type I
(insulino-dépendant)
Type II
(non insulino-dépendant)
Glomérulo-sclérose
HTA essentielle
HTA essentielle
Néphropathie
Hypertensions secondaires d'origine endocrinienne ou rénovasculaire.

Cardiovascular Outcomes in Framingham Participants With Diabetes

The Importance of Blood Pressure

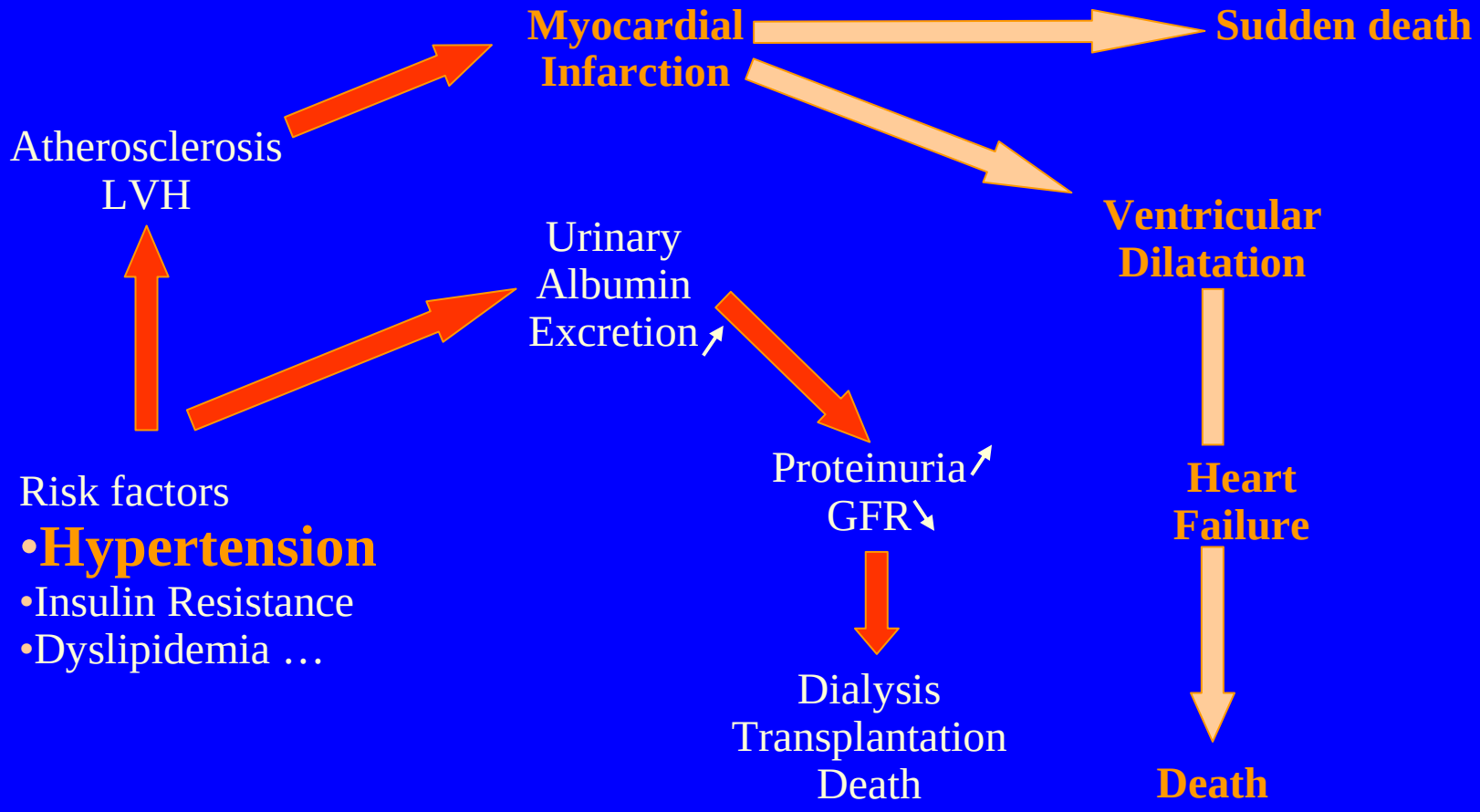
Guanmin Chen, Finlay A. McAlister, Robin L. Walker, Brenda R. Hemmelgarn, Norm R.C. Campbell

Hypertension. 2011

Of the 1145 Framingham subjects newly diagnosed with diabetes mellitus who did not have a previous history of cardiovascular events, 663 (58%) had hypertension at the time that diabetes mellitus was diagnosed.

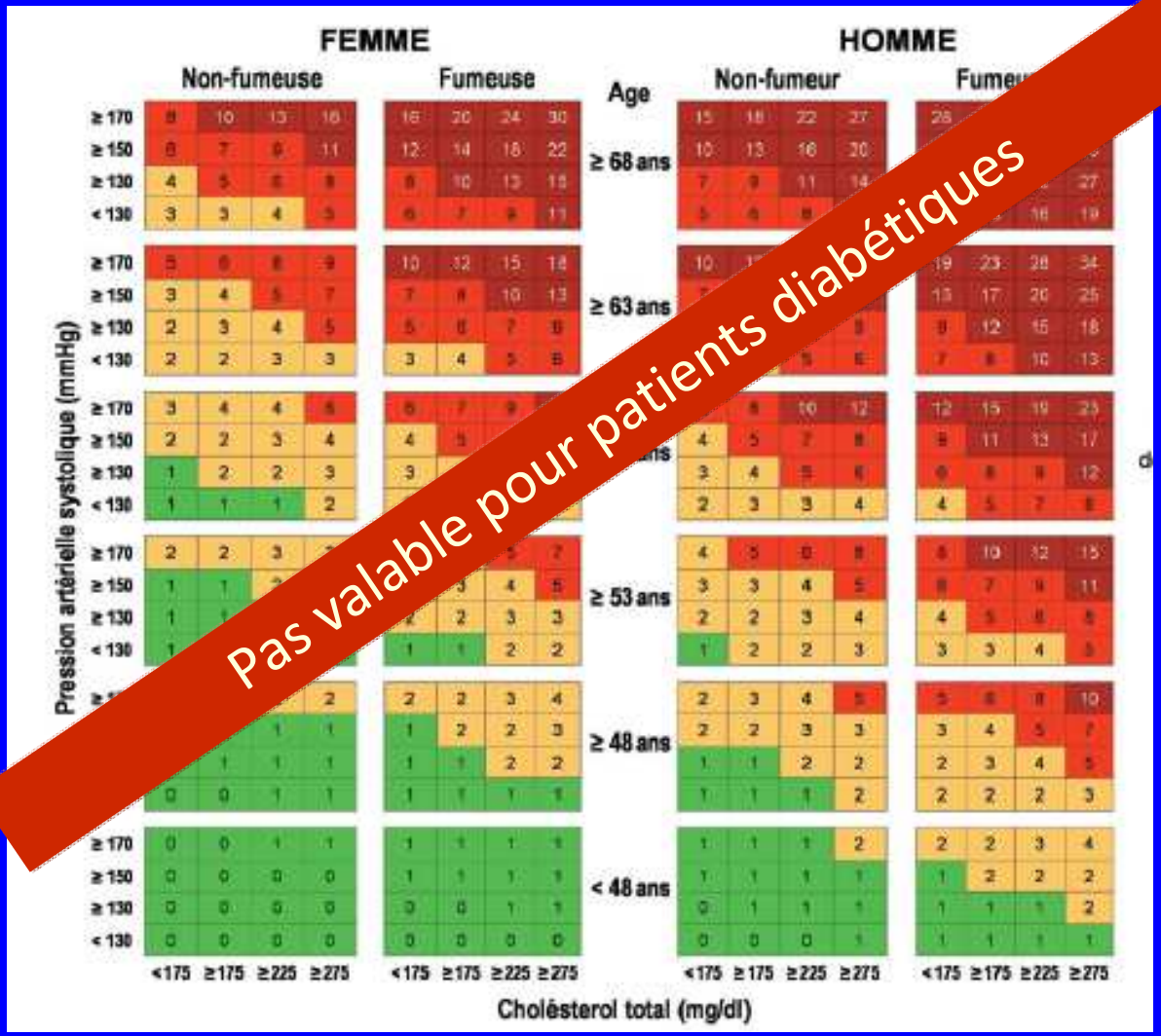
hypertension was associated with a 72% increase in the risk of all-cause death and a 57% increase in the risk of any cardiovascular event in individuals with diabetes mellitus. The population-attributable risk from hypertension in individuals with diabetes mellitus was 30% for all-cause death and 25% for any cardiovascular event (increasing to 44% and 41%, respectively, if the 110 normotensive subjects who developed hypertension during follow-up were excluded

CARDIOVASCULAR AND RENAL MECHANISMS OF MORBIDITY AND MORTALITY



Adapted from Dzau, V. AM Heart J. 1991; 121 : 1244-1263 and Nelson R.G., NEJM 1996; 28 : 1636-1642.

Risque d'événement CV fatal à 10 ans SCORE belge

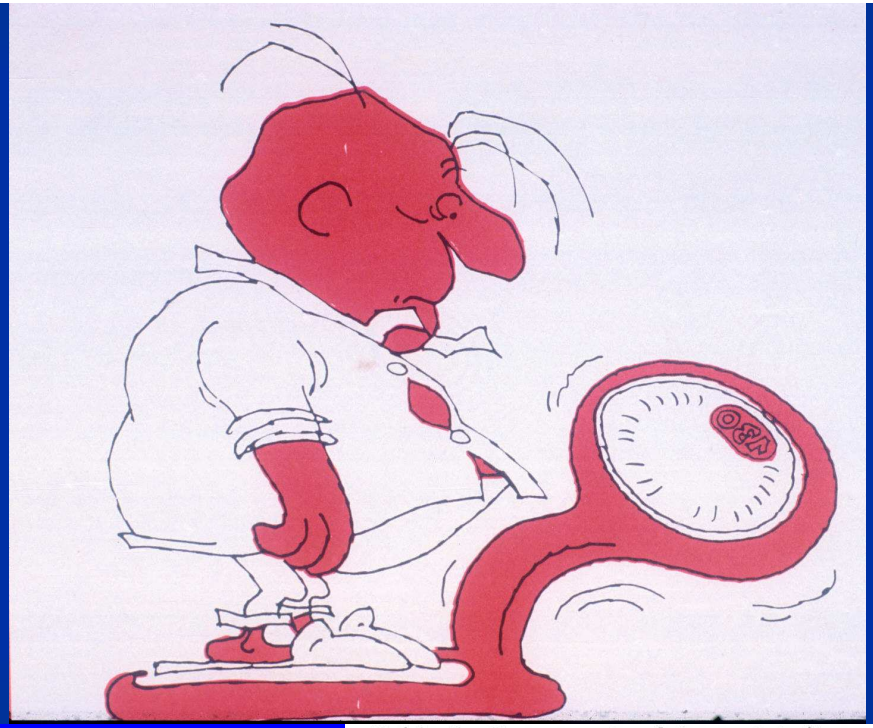


SCORE BELGIUM
© 2004 ESC

- 15 % et plus
- 10 % – 14 %
- 5 % - 9 %
- 3 % - 4 %
- 2 %
- 1 %
- <1 %

Risque à 10 ans de MCV fatales dans des populations à **risque moyen de maladies cardiovasculaires**

Adapté d'après De Backer et coll. Eur Heart J. 2003;24. 1601-1610



Diagnostic Criteria for Metabolic Syndrome (NCEP ATP III)

Diagnosis is made when 3 or more of these risk criteria are met

- ↑ Glucose
- Abdominal Obesity
- ↓ HDL-C
- ↑ BP
- ↑ TG

Glucose ≥ 6.1mmol/L
Waist Circumference
- ♂ ≥ 102cm
- ♀ ≥ 88cm

HDL-C
- ♂ ≤ 1.0 mmol/L
- ♀ ≤ 1.3 mmol/L

BP ≥130/≥85 mmHg
Triglycerides ≥ 1.7mmol/L

NCEP - ATP III Guidelines

JAMA 2001, 285, 2486 & *Circulation* 2004, 109, 4

Table 3 Components of the metabolic syndrome in relation to IMT, decreased ABPI and the prevalence of albuminuria

Metabolic syndrome components (*n*)	IMT (mm) mean±se	*P*-value[b]	Decreased ABPI[a] (%)	*P*-value[b]	Albuminuria (%)	*P*-valu
0	0.85±0.04		2		13	
1	0.90±0.02		10		13	
2	0.94±0.02		12		16	
3	0.95±0.02		11		18	
4	0.97±0.03		18		21	
5	1.07±0.04	<0.001	22	<0.01	24	<0.01

IMT: Intima Media Thickness in common carotid arteries (age- and sex adjusted).
Decreased ABPI: Ankle Brachial Pressure Index ≤0.90 in at least one leg (age- and sex adjusted).
Albuminuria: albumin/creatine ratio >3 mg/mmol (urine portion) (age-adjusted).
se: standard error.

[a]Patients with PAD excluded from analyses

Olijhoek J. et al.
Eur Heart J, 2004.

STRATIFICATION OF THE GLOBAL CV RISK (ESH 2007)

BLOOD PRESSURE (mmHg)					
RISK FACTORS (FR)	**NORMAL** 120 – 129 or 80– 84	**HIGH NORMAL** 130 – 139 or 85– 89	**GRADE 1** 140 – 159 or 90– 99	**GRADE 2** 160– 179 or 100 – 109	**GRADE 3** ≥ 180 or ≥ 110
NO OTHER RF	AVERAGE RISK	AVERAGE RISK	LOW ADDED GROUP	MEDIUM ADDED GROUP	HIGH ADDED GROUP
1-2 RF	LOW ADDED GROUP	LOW ADDED GROUP	MEDIUM ADDED GROUP	MEDIUM ADDED GROUP	VERY HIGH ADDED RISK
3 RF, TOD ,MS DIABETES	MEDIUM ADDED GROUP	HIGH ADDED GROUP	HIGH ADDED GROUP	HIGH ADDED GROUP	VERY HIGH ADDED RISK
ACC	HIGH ADDED GROUP	VERY HIGH ADDED RISK	VERY HIGH ADDED RISK	VERY HIGH ADDED RISK	VERY HIGH ADDED RISK

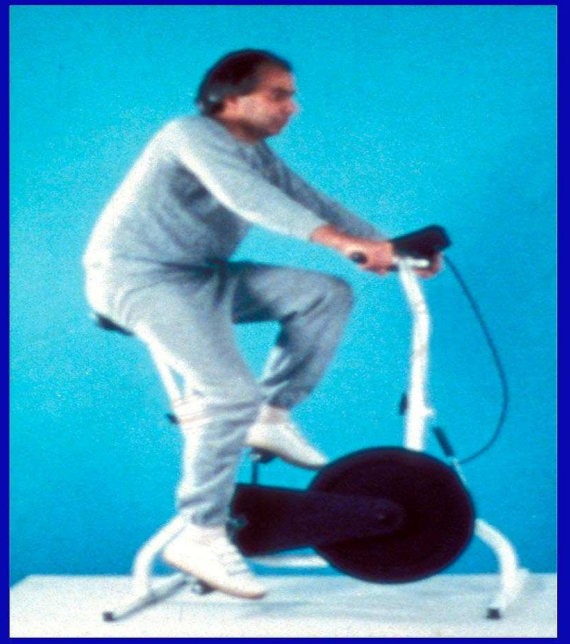
NON-DRUG THERAPY

Weight reduction

Salt restriction

Abstinence from smoking

Exercise



BP-lowering trials in diabetes & HT and vascular disease

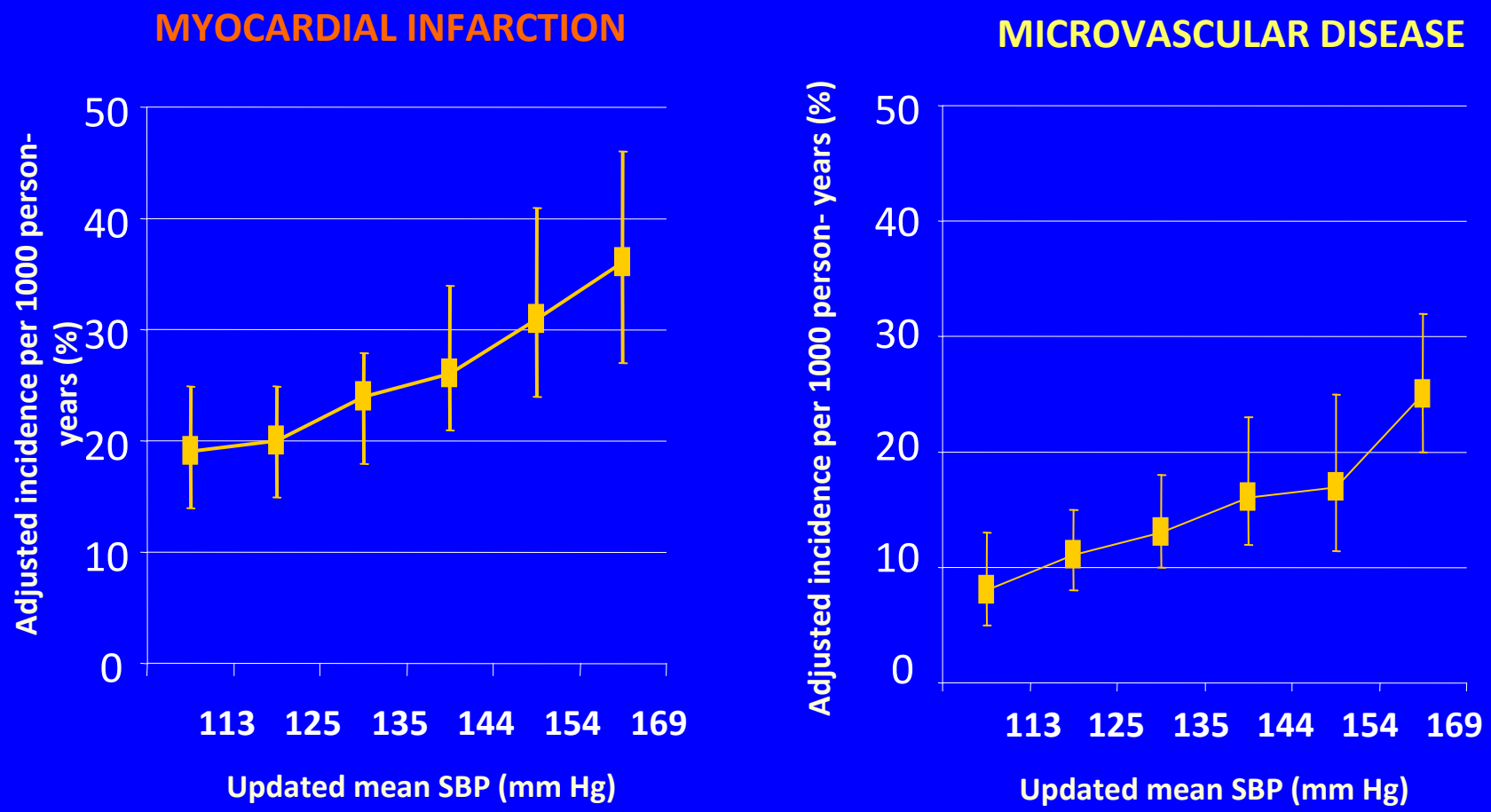
- UKPDS
- HOT
- ABCD
- Syst-Eur
- BP TRIALISTS
- ADVANCE

1. Convincing evidence that BP-lowering reduces macro- and microvascular disease in HT

and

2. That tighter BP control is better

Relation PA et complications



Adler A, Stratton IM, Neil H, et al. *BMJ*. 1998;321:412-419

ACCORD BP Study: Primary and Secondary Outcomes

- Patients with T2D (GFR N, no µAlb) and hypertension (N = 4733)
- Random assignment
  - Intensive therapy: target SBP < 120 mm Hg
  - Standard therapy: target SBP < 140 mm Hg
- 1°outcome: nonfatal MI, nonfatal stroke, death fro m CV causes

Outcome	Intensive	Standard	HR	*P*-value
SBP after 1 year (mmHg)	119.3	133.5	NR	NR
1° outcome (annual rate)	1.87	2.09	0.88	.20
Death from any cause (annual rate)	1.28	1.19	1.07	.55
Stroke (annual rate)	0.32	0.53	0.59	.01
AEs (rate)	3.3	1.3	NR	<.001

The ACCORD Study Group. *N Engl J Med*. 2010 March 14. [Epub ahead of print].

ACCORD: Significant Differences in AEs and Laboratory Measures

Outcome	Intensive	Standard	*P*-value
Event due to BP medications (%)[a]	***3.3***	1.27	< .001
Hypotension (%)	0.7	0.04	< .001
Hyperkalemia (%)	0.4	0.04	.01
eGFR < 30 mL/min/1.73m^2 (%)	4.2	2.2	< .001
eGFR (mL/min/1.73m^2)	74.8	80.6	< .001
Urinary albumin: Cr (mg/g)	12.6	14.9	< .001
Macroalbuminuria (%)	6.6	8.7	.009

[a] Lower BP in intensive group associated with greater exposure to drugs from every class.

The ACCORD Study Group. *N Engl J Med*. 2010 March 14. [Epub ahead of print].

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

The ACCORD Study Group*

ABSTRACT

BACKGROUND

There is no evidence from randomized trials to support a strategy of lowering systolic blood pressure below 135 to 140 mm Hg in persons with type 2 diabetes mellitus. We investigated whether therapy targeting normal systolic pressure (i.e., <120 mm Hg) reduces major cardiovascular events in participants with type 2 diabetes at high risk for cardiovascular events.

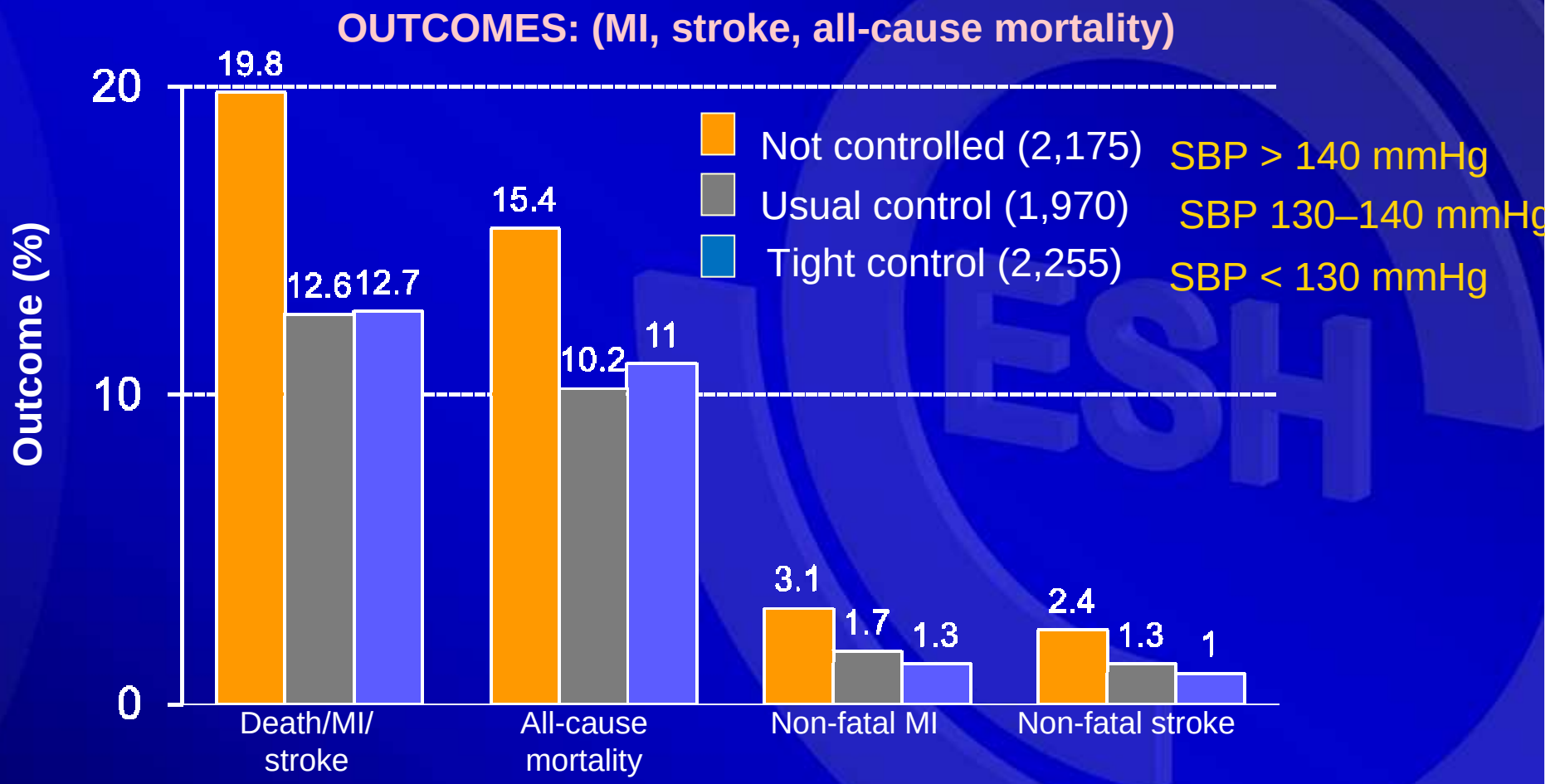
CONCLUSIONS

In patients with type 2 diabetes at high risk for cardiovascular events, targeting a systolic blood pressure of less than 120 mm Hg, as compared with less than 140 mm Hg, did not reduce the rate of a composite outcome of fatal and nonfatal major cardiovascular events. (ClinicalTrials.gov number, NCT00000620.)

This article (10.1056/NEJMoa1001286) was published on March 14, 2010, at NEJM.org.

N Engl J Med 2010.

CV outcomes from the Diabetes Subgroup of INVEST trial



DeHoff-Cooper R et.al. JAMA 2010;304:61-68.

ACCOMPLISH Study
Baseline Patient Characteristics

Patient Characteristic	No Diabetes	All Diabetes	High Risk Diabetes**
Number of Patients	4559	6946	2842
Male	3,009 (66%)*	3,954 (57%)	1,830 (64%)*
Female	1,550 (34%)*	2,992 (43%)	1,012 (36%)*
Age	69.8 (7.0)*	67.5 (6.6)	66.9 (7.2)*
Age ≥ 65 yrs	3,344 (73)*	4,296 (62)	1,668 (59)*
Caucasian	4,075 (89%)*	5,537 (80%)	2,277 (80%)
Black	374 (8%)*	1042 (15%)	429 (15%)

* Significant differences from *"All Diabetes"* cohort

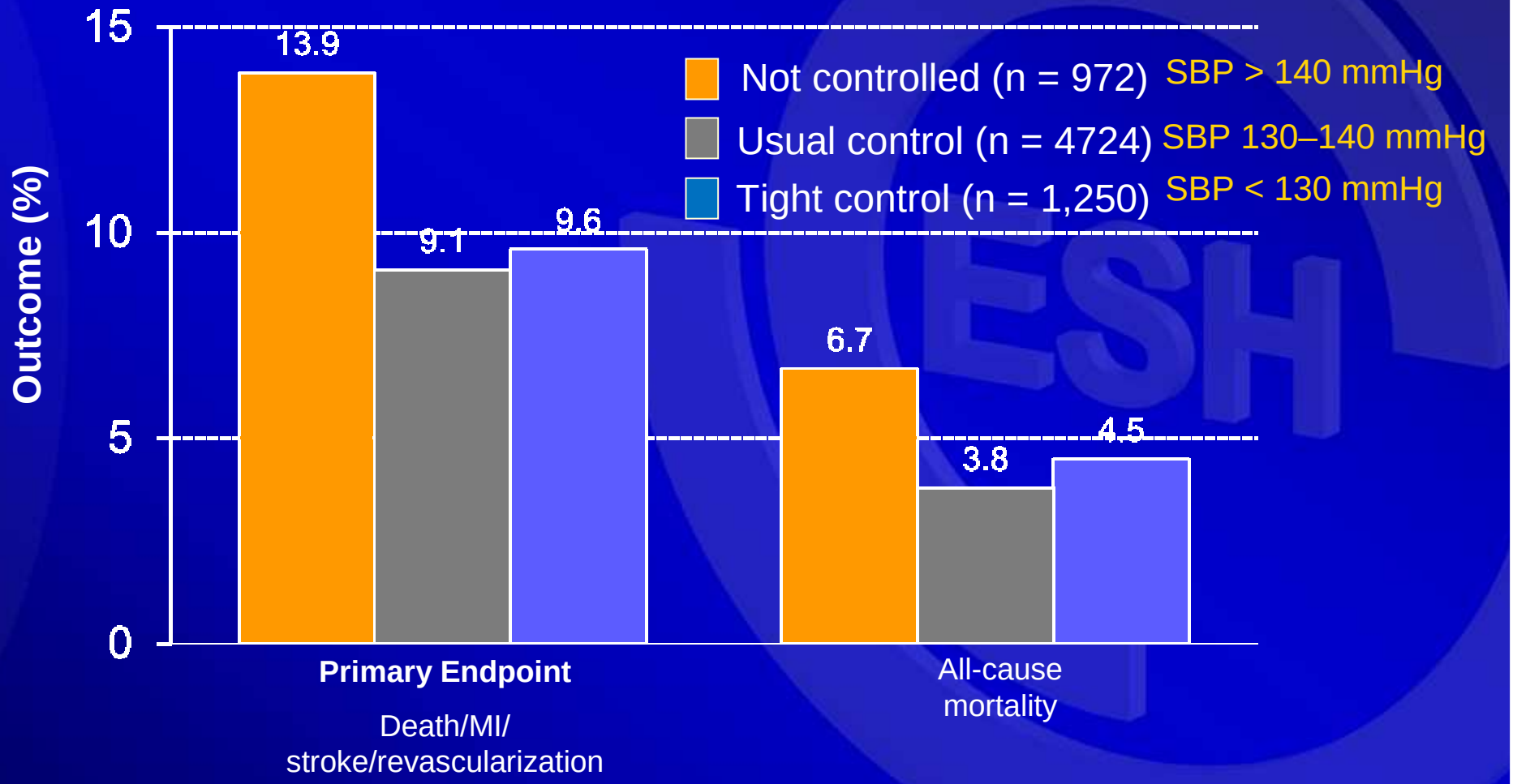
** Patients with diabetes and history of cardiac events, stroke, or renal disease

Values are absolute numbers (%) or mean (SD)

Adapted from: Weber MA, et al. *J Am Coll Cardiol*. 2010;56:77-85.

CV outcomes from the Diabetes Subgroup of ACCOMPLISH trial

OUTCOMES: (MI, stroke, revascularization, all-cause mortality)



Bakris G et.al. in preparation.

JACC Vol. 56, No. 1, 2010
June 29, 2010:77–85

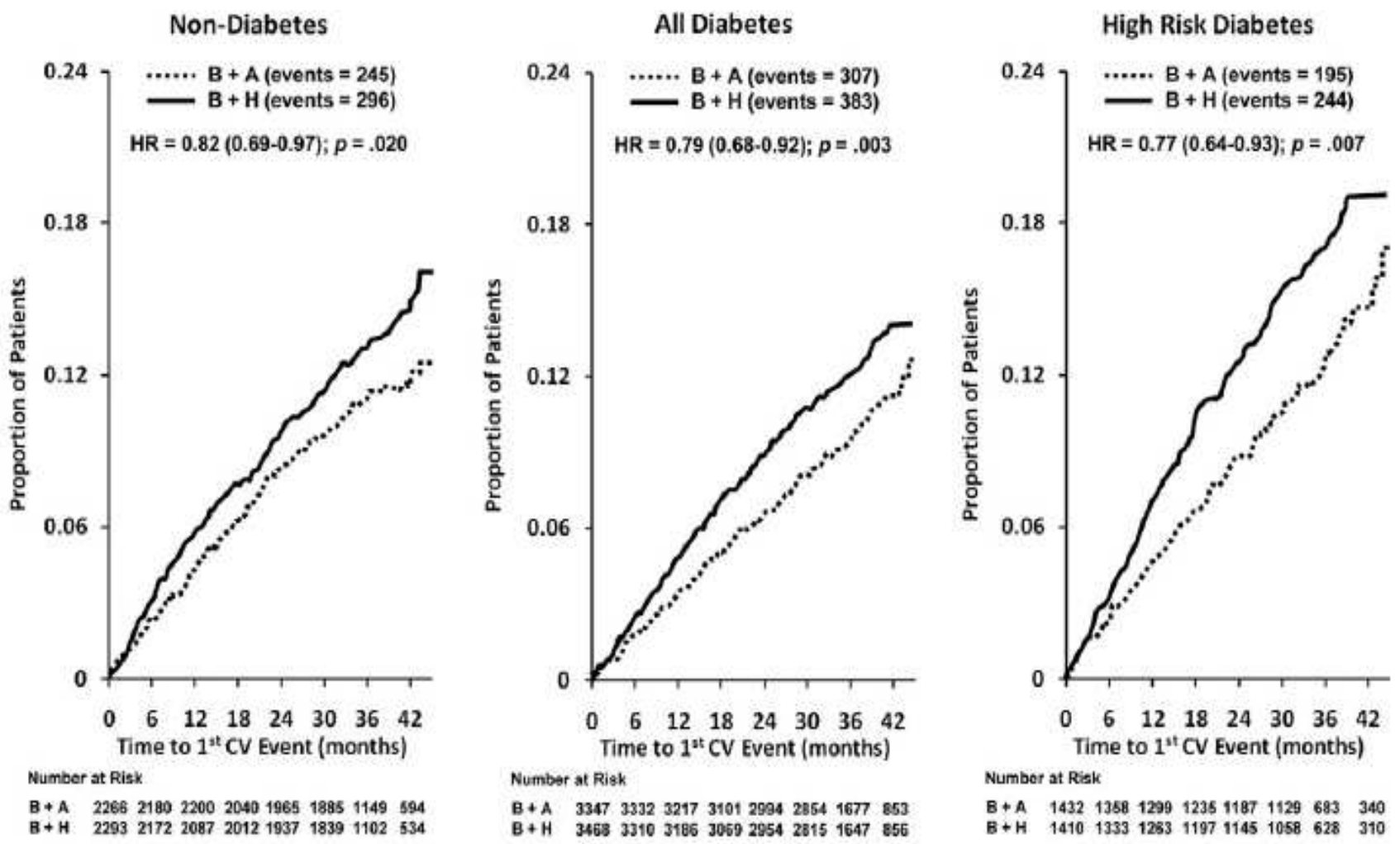


Figure 2 **Time to First Events in Major Patient Subgroups**

Kaplan-Meier curves for time to the first primary composite end point in patients without diabetes, with diabetes,

Valeurs cibles de la PAS chez les patients diabétiques

Lignes directrices ESC/ESH 2007

< 140/90 mmHg pour tous les patients hypertendus

< 130/80 mmHg pour les patients diabétiques et ceux avec risque CV élévé à très élevé

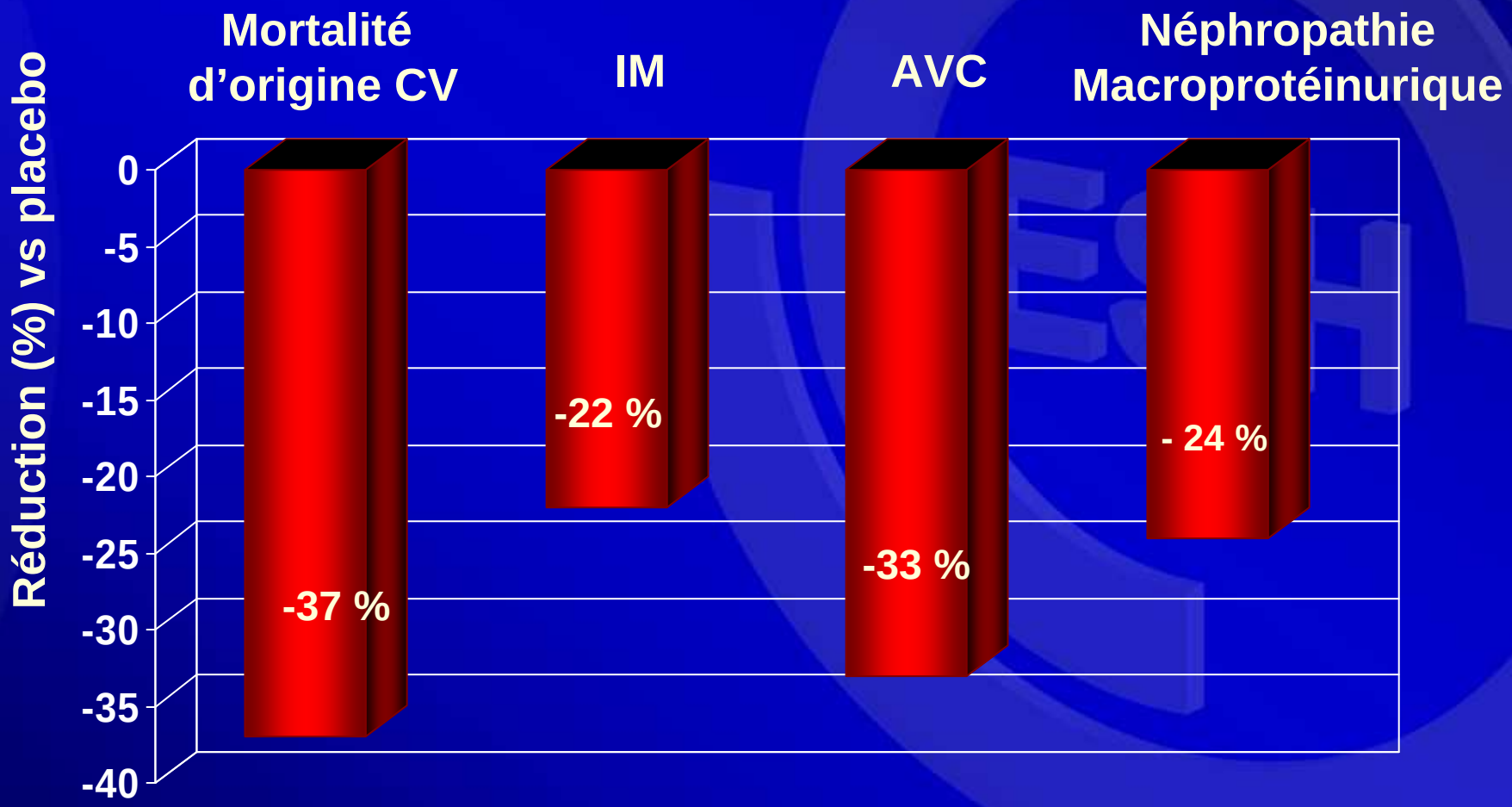
Lignes directrices ESH 2009

< 140/90 mm Hg pour tous les patients hypertendus

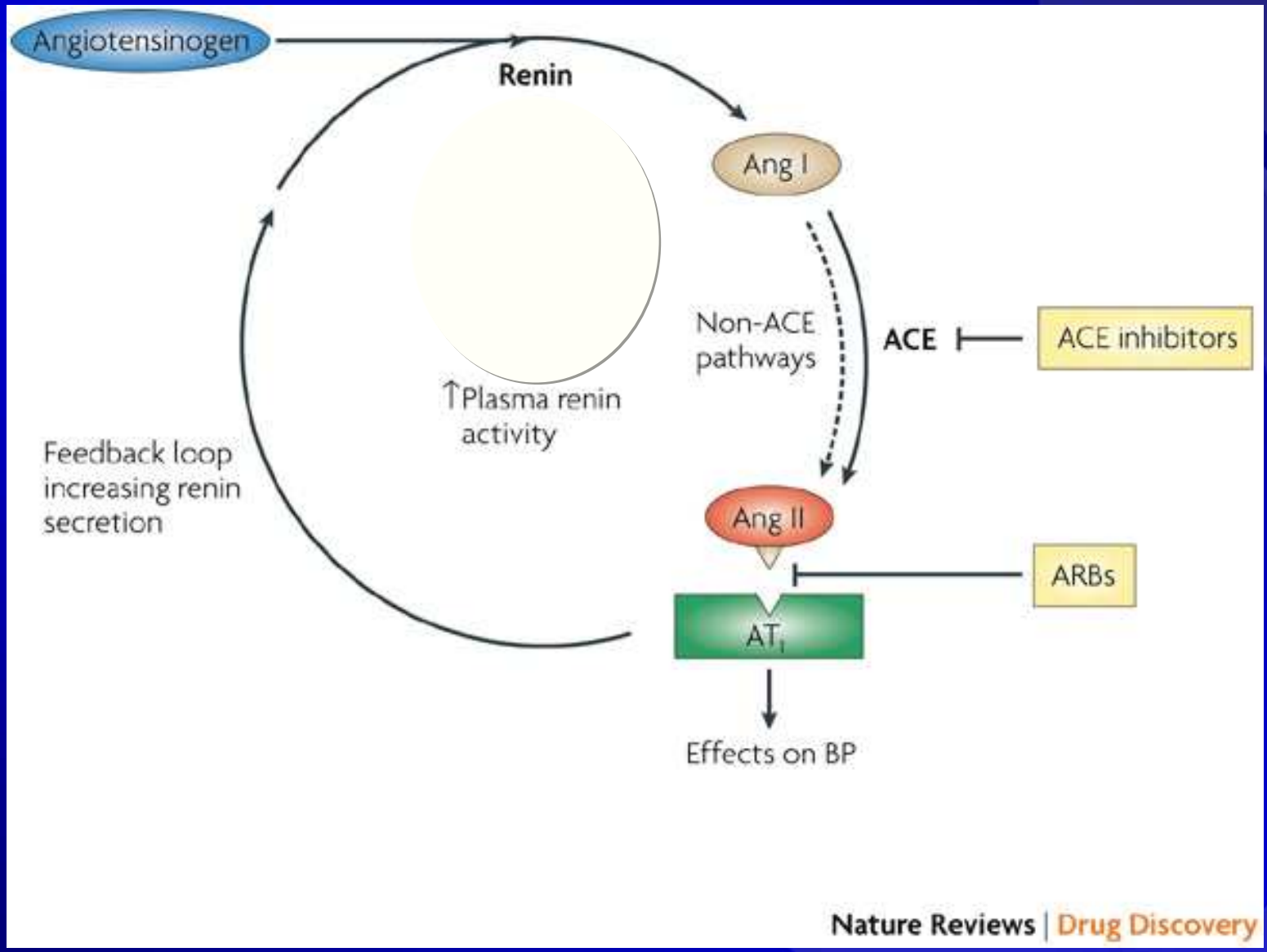
ESC ESH Guidelines for the management of arterial hypertension, Journal of Hypertension 2007, 25:1105–1187
ESH Updated guidelines, J Hypertension 2009

2000 : Apport majeur des IEC sur le plan CV et rénal en prévention secondaire

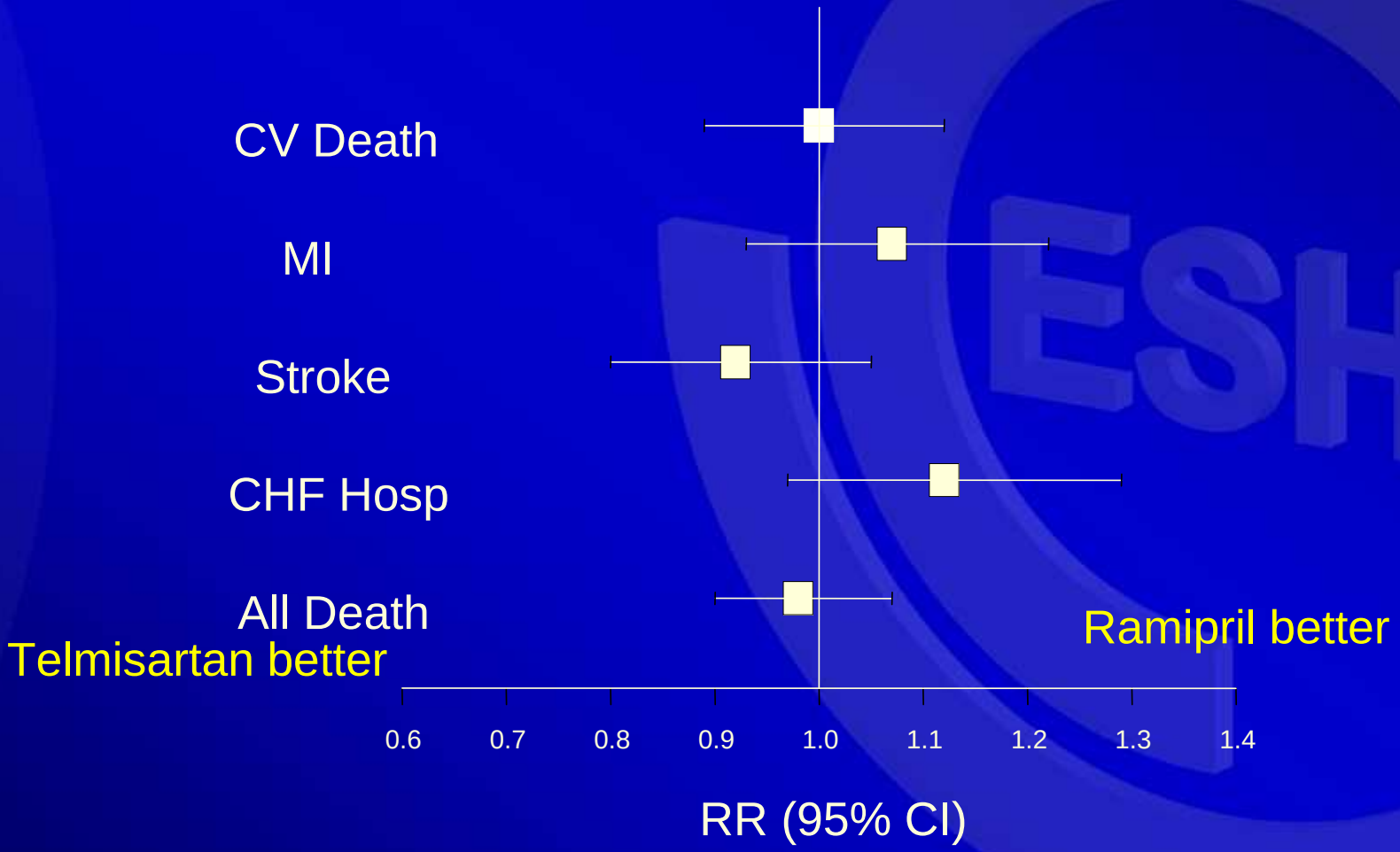
Etude Micro- HOPE (n = 3577 diabétiques)



Heart Outcomes Prevention Evaluation, *Lancet*, 2000.

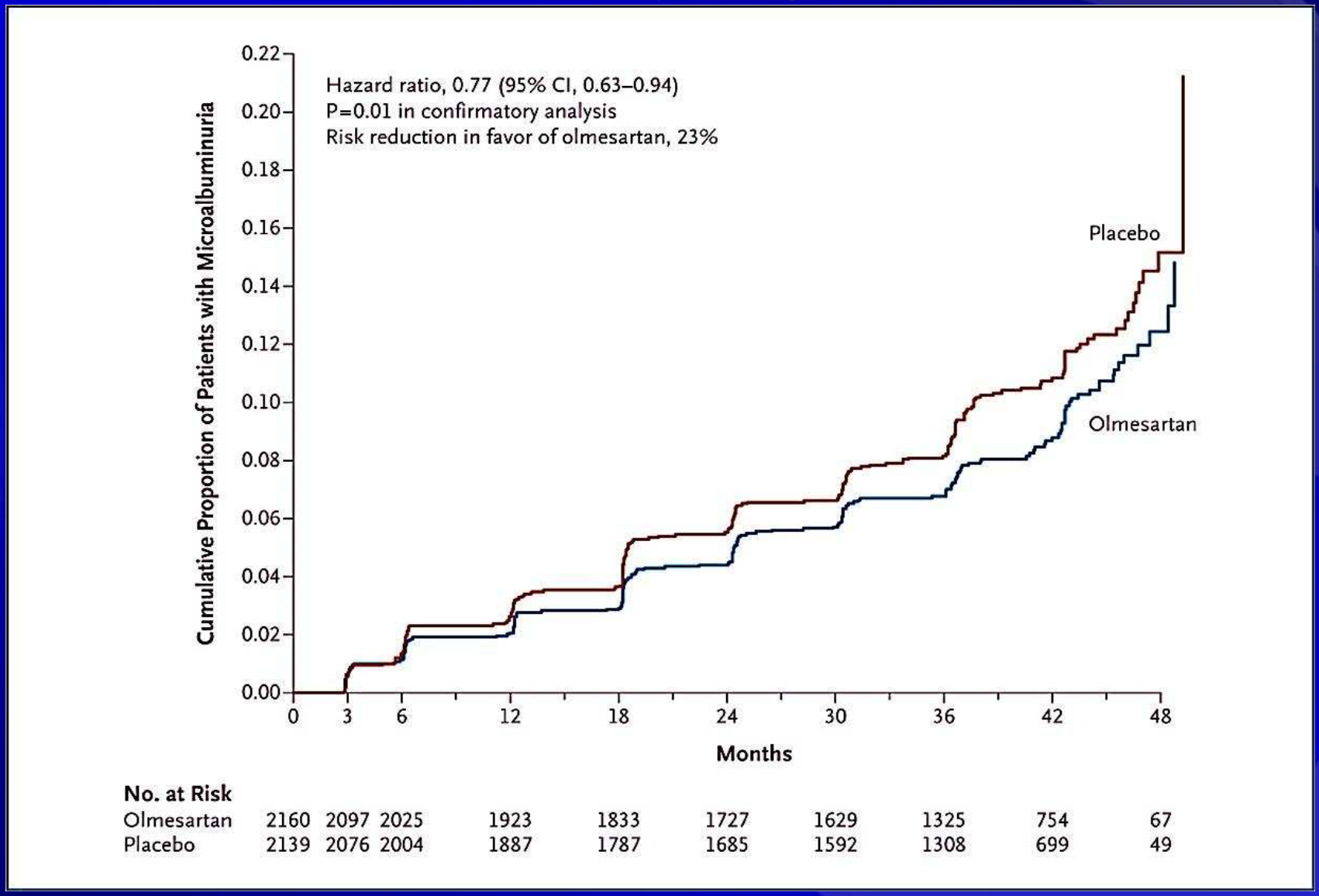

Angiotensinogen
Renin
Ang I
Non-ACE pathways
ACE
ACE inhibitors
↑Plasma renin activity
Feedback loop increasing renin secretion
Ang II
ARBs
AT1
Effects on BP
Nature Reviews | Drug Discovery

ONTARGET Non-Inferiority Comparison



Note that the outcomes are presented as point estimates with confidence intervals. The solid line is the 95% CI representing 1.96 SD for each outcome

Occurrence of Microalbuminuria during the 48-Month Follow-up Period in the Two Study Groups. ROADMAP



Haller H et al. N Engl J Med 2011;364:907-917.

Secondary Efficacy End Points during the Double-Blind Treatment Period. ROADMAP

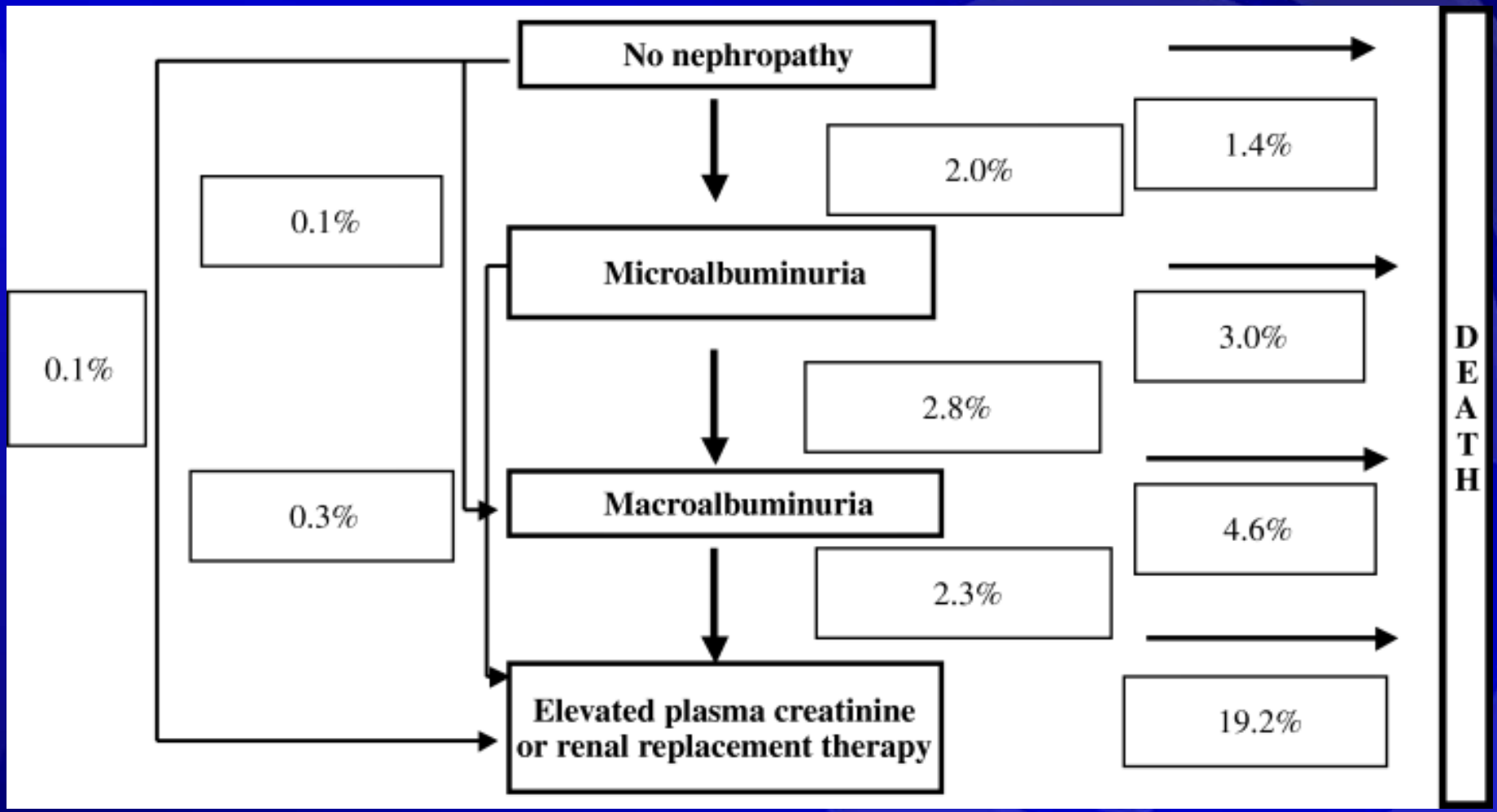
Table 2. Secondary Efficacy End Points during the Double-Blind Treatment Period.*

End Point	Olmesartan (N=2232)	Placebo (N=2215)	Hazard Ratio (95% CI)	P Value
	no. of patients (%)			
Composite of cardiovascular complications or death from cardiovascular causes	96 (4.3)	94 (4.2)	1.00 (0.75–1.33)	0.99
Composite of death from any cause	26 (1.2)	15 (0.7)	1.70 (0.90–3.22)	0.10
Death from cardiovascular causes	15 (0.7)	3 (0.1)		
Death not related to cardiovascular causes	8 (0.4)	10 (0.5)		
Death from unknown cause	3 (0.1)	2 (0.1)		
Composite of death from cardiovascular causes	15 (0.7)	3 (0.1)	4.94 (1.43–17.06)	0.01
Sudden cardiac death	7 (0.3)	1 (<0.1)		
Death due to fatal myocardial infarction	5 (0.2)	0		
Evidence of recent myocardial infarction on autopsy	0	0		
Death due to congestive heart failure	0	0		
Death during or after percutaneous transluminal coronary angioplasty or CABG	1 (<0.1)	0		
Death due to fatal stroke	2 (0.1)	2 (0.1)		
Composite of cardiovascular complications, excluding new-onset atrial fibrillation and transient ischemic attack	63 (2.8)	71 (3.2)	0.87 (0.62–1.22)	0.42
Composite of new-onset atrial fibrillation or transient ischemic attack	19 (0.9)	28 (1.3)	0.67 (0.37–1.19)	0.17
Composite of all cardiovascular complications	81 (3.6)	91 (4.1)	0.87 (0.65–1.18)	0.37

* All results were based on adjudicated end points. The composite secondary efficacy end points were analyzed with the use of a Cox proportional-hazards regression model with study treatment as the fixed effect. For composite end points, the time to the onset of an event was defined as the time from randomization (date of visit 1) to the first occurrence of any component of the composite end point. CABG denotes coronary-artery bypass grafting.

Haller H et al. N Engl J Med 2011;364:907-917.

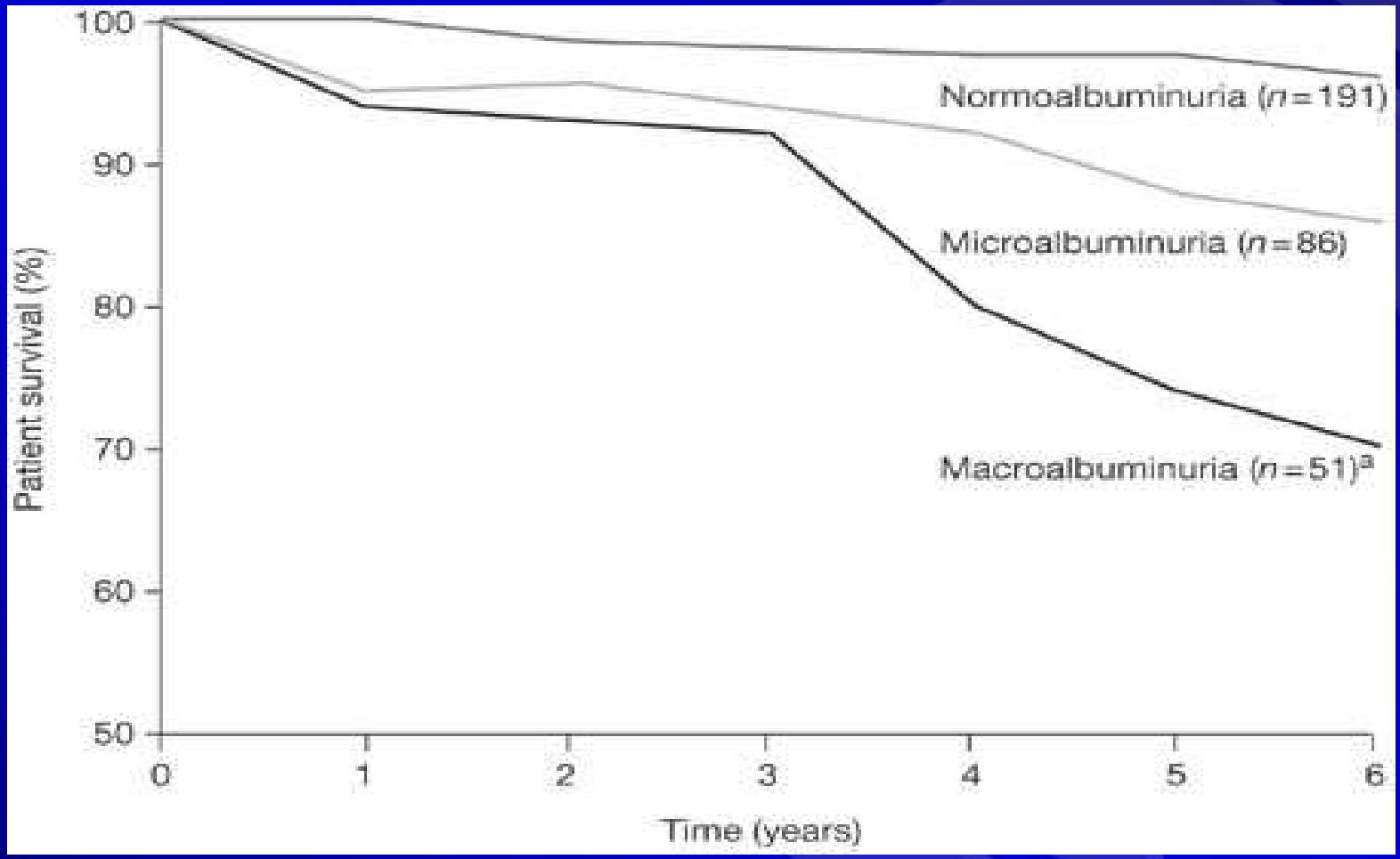
NATURAL HISTORY OF DIABETIC NEPHROPATHY IN TYPE 2 DIABETES



2 goals : Prevent 1) End-stage renal disease 2) Death (cardiovascular)

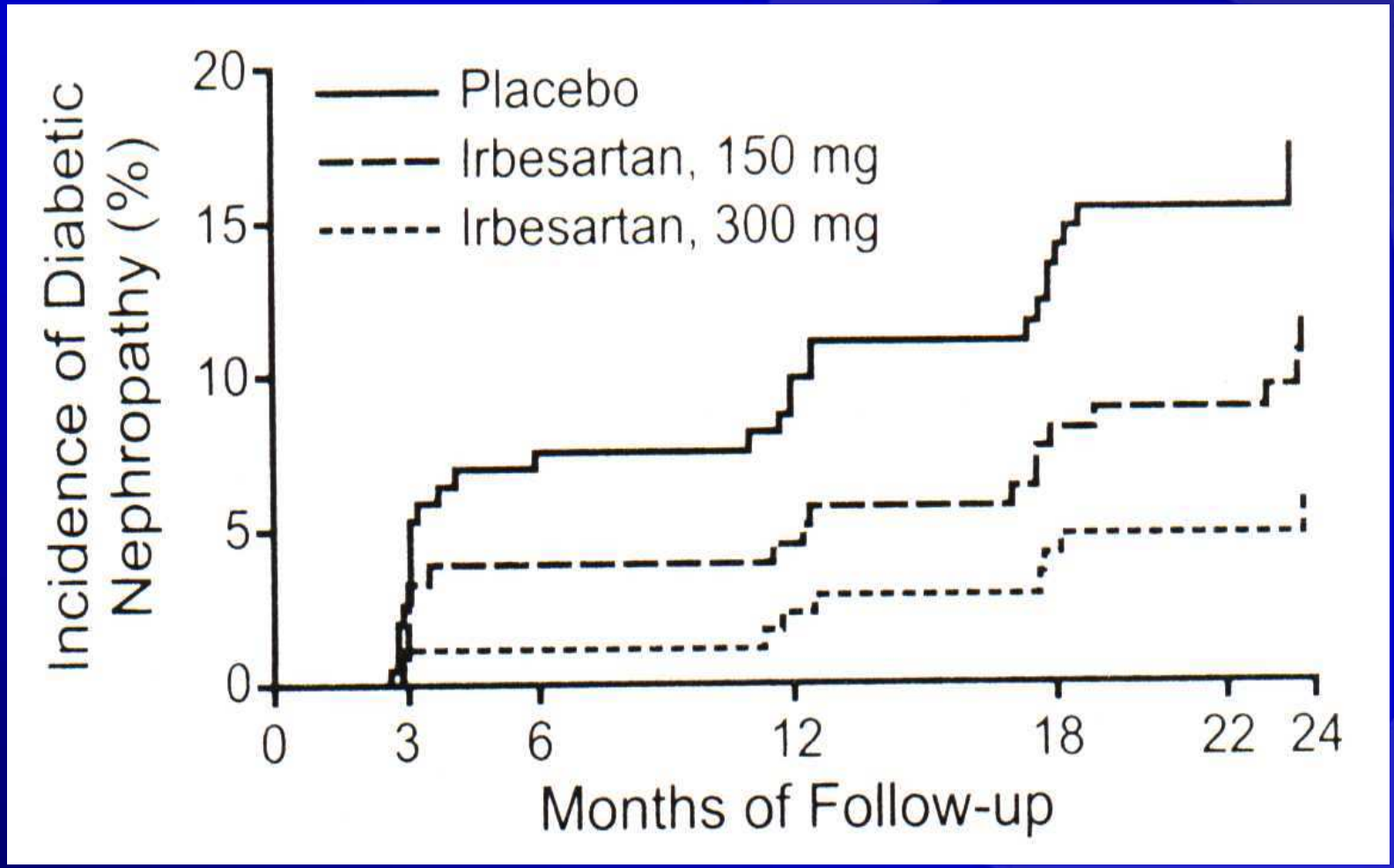
Adler et al (UKPDS Group). Kidney Int 2003, 63, 225-32.

Progressive increases in urinary albumin excretion rate are associated with decreased survival in patients with type 2 diabetes

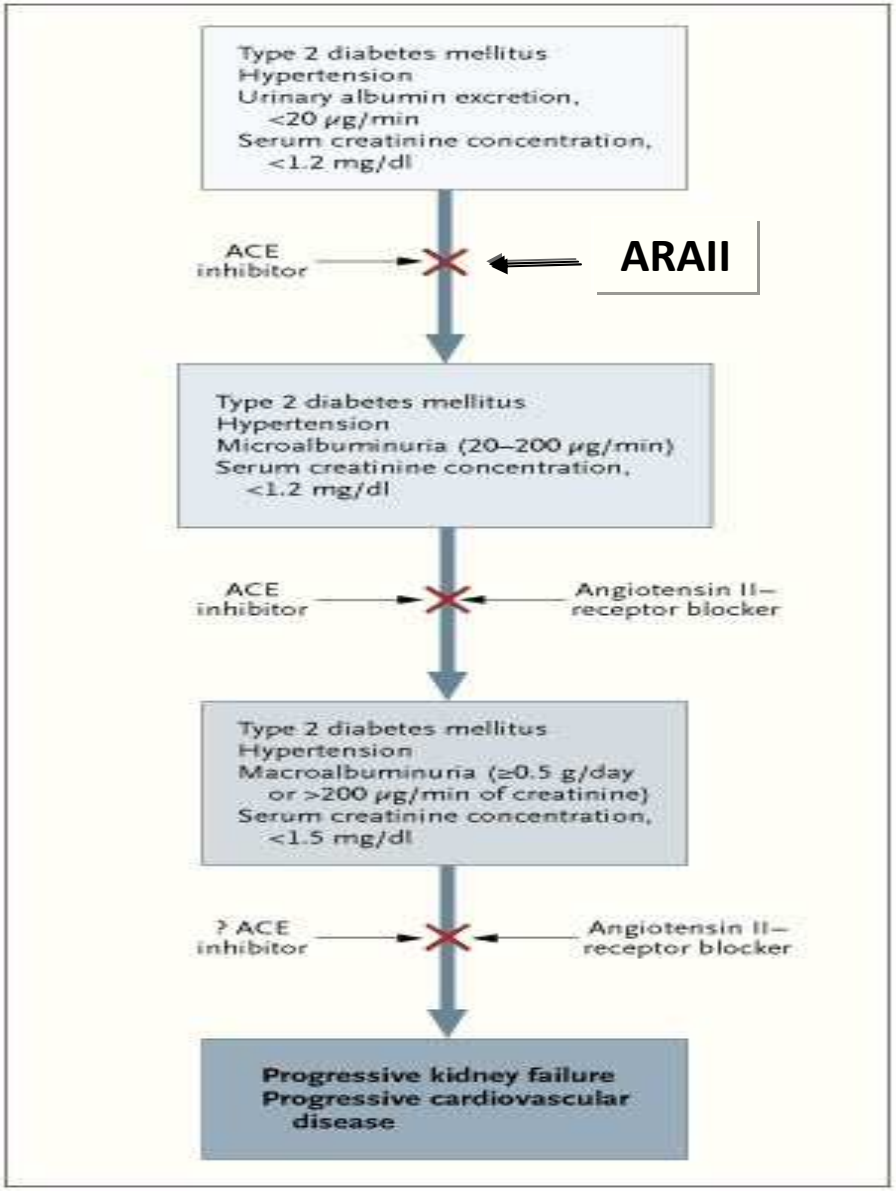


Schrier RW *et al.* (2007) Appropriate blood pressure control in hypertensive and normotensive type 2 diabetes mellitus: a summary of the ABCD trial *Nat Clin Pract Nephrol* **3:** 428–438

Progression of diabetic nephropathy in IRMA 2 study of hypertensive patients with type 2 diabetes and microproteinuria



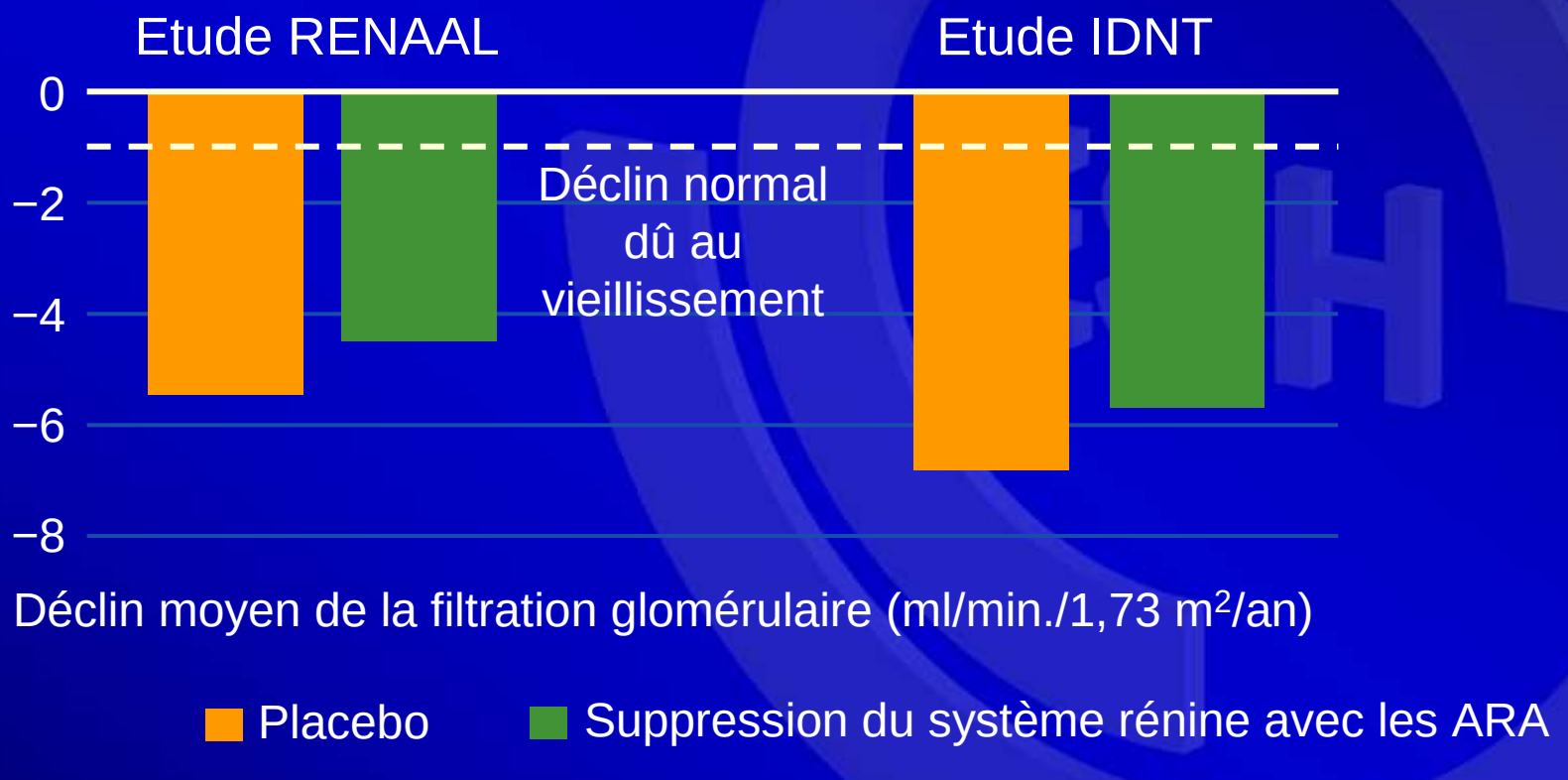
ACE Inhibition versus Angiotensin-Receptor Blockade in Nephropathy Associated with Type 2 Diabetes



Mitch, W. E. N Engl J Med 2004;351:1934-1936

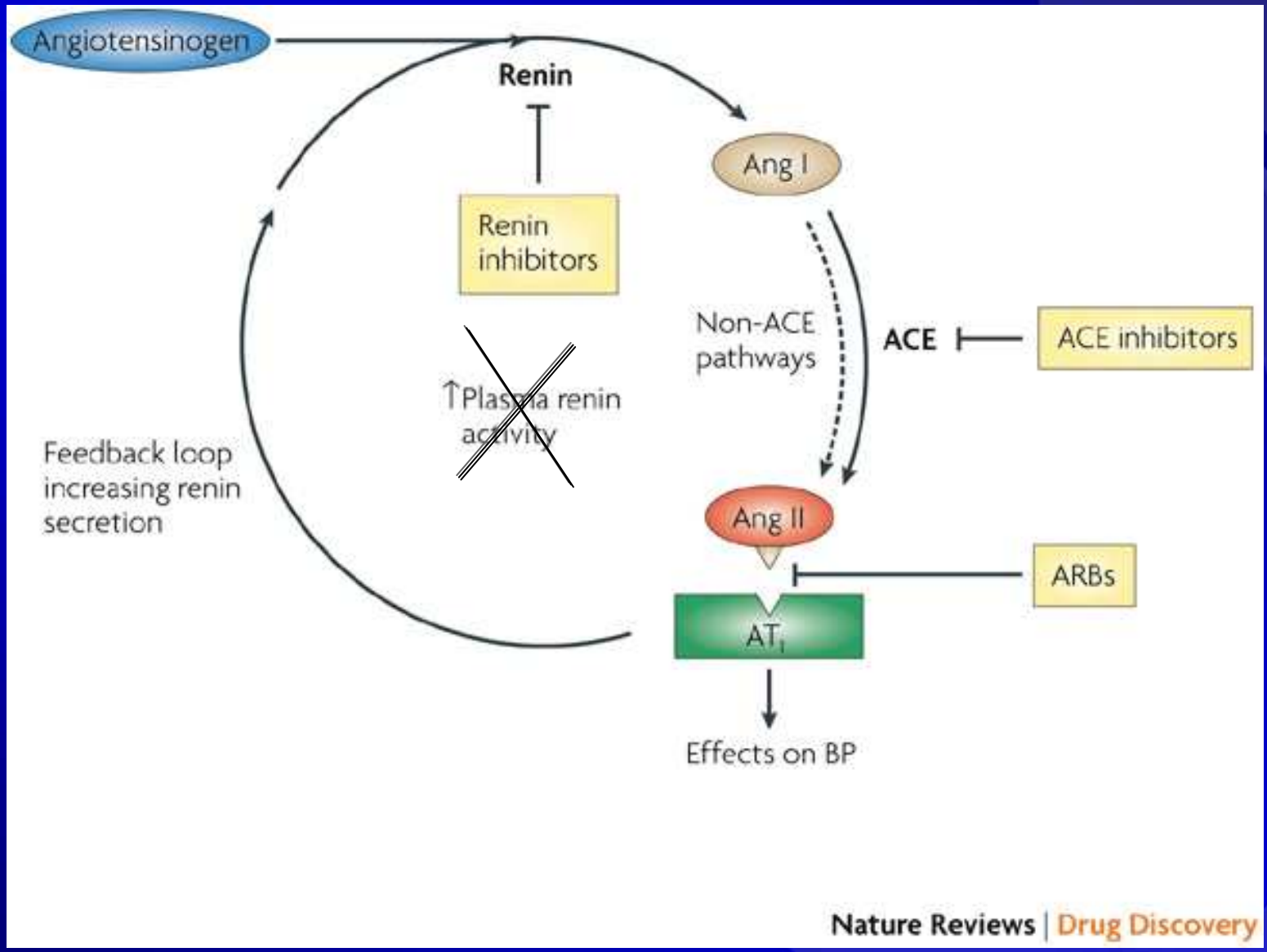
The NEW ENGLAND JOURNAL of MEDICINE

Diabète type 2, néphropathie, utilisation des ARA



ARA = antagonistes des récepteurs de l'angiotensine; PA = pression artérielle; FG = filtration glomérulaire

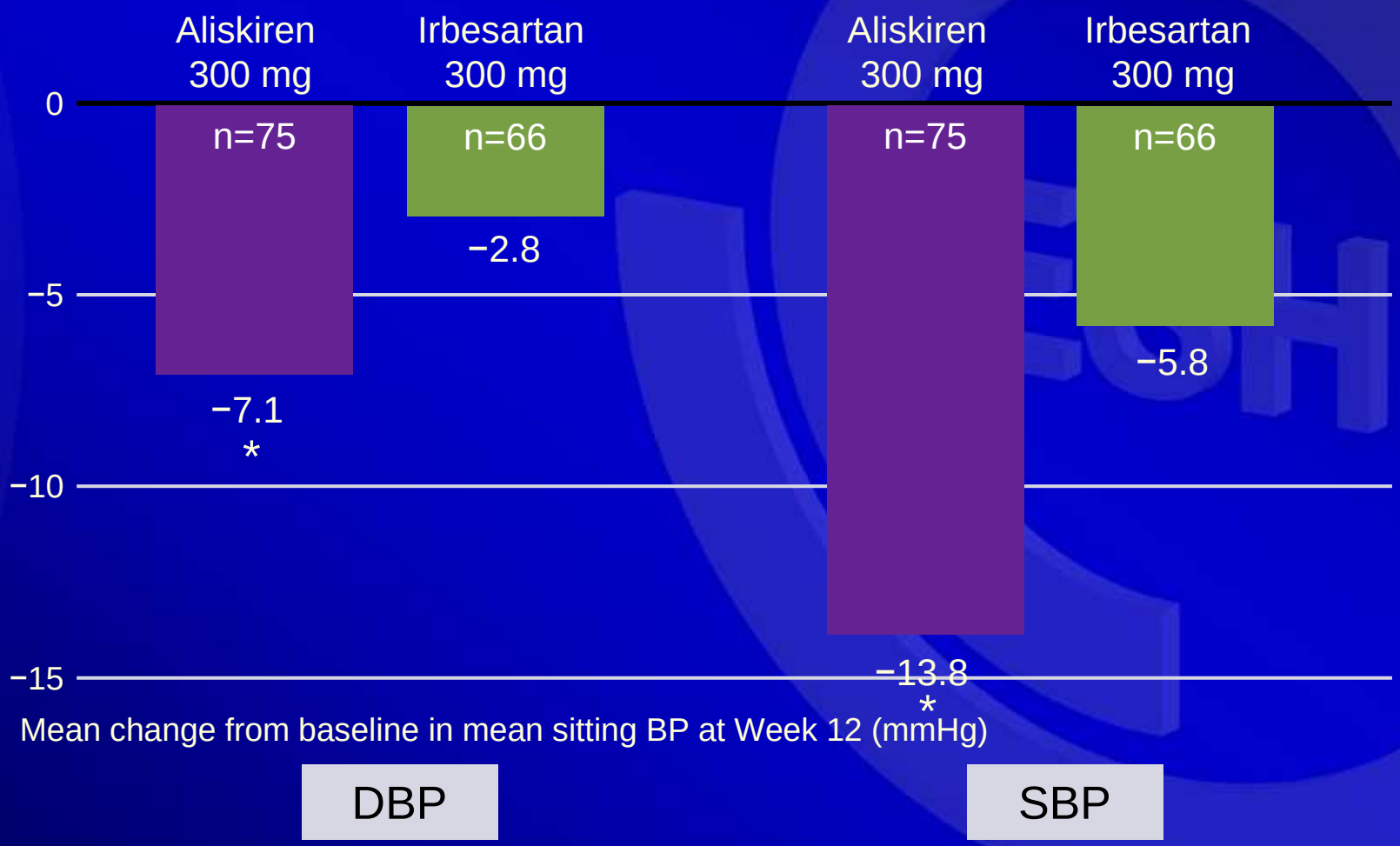
[1] Weber & Giles. 2006


Angiotensinogen
Renin
Ang I
Renin inhibitors
Non-ACE pathways
ACE
ACE inhibitors
↑Plasma renin activity
Feedback loop increasing renin secretion
Ang II
ARBs
AT1
Effects on BP
Nature Reviews | Drug Discovery

Comparative efficacy and safety of aliskiren and irbesartan in patients with hypertension and metabolic syndrome

W Krone[1], M Hanefeld[2], H-F Meyer[3], T Jung[4], M Bartlett[5], C-M Yeh[6], I Rajman[5], MF Prescott[6] and WP Dole[7]

Metabolic Syndrome Patients

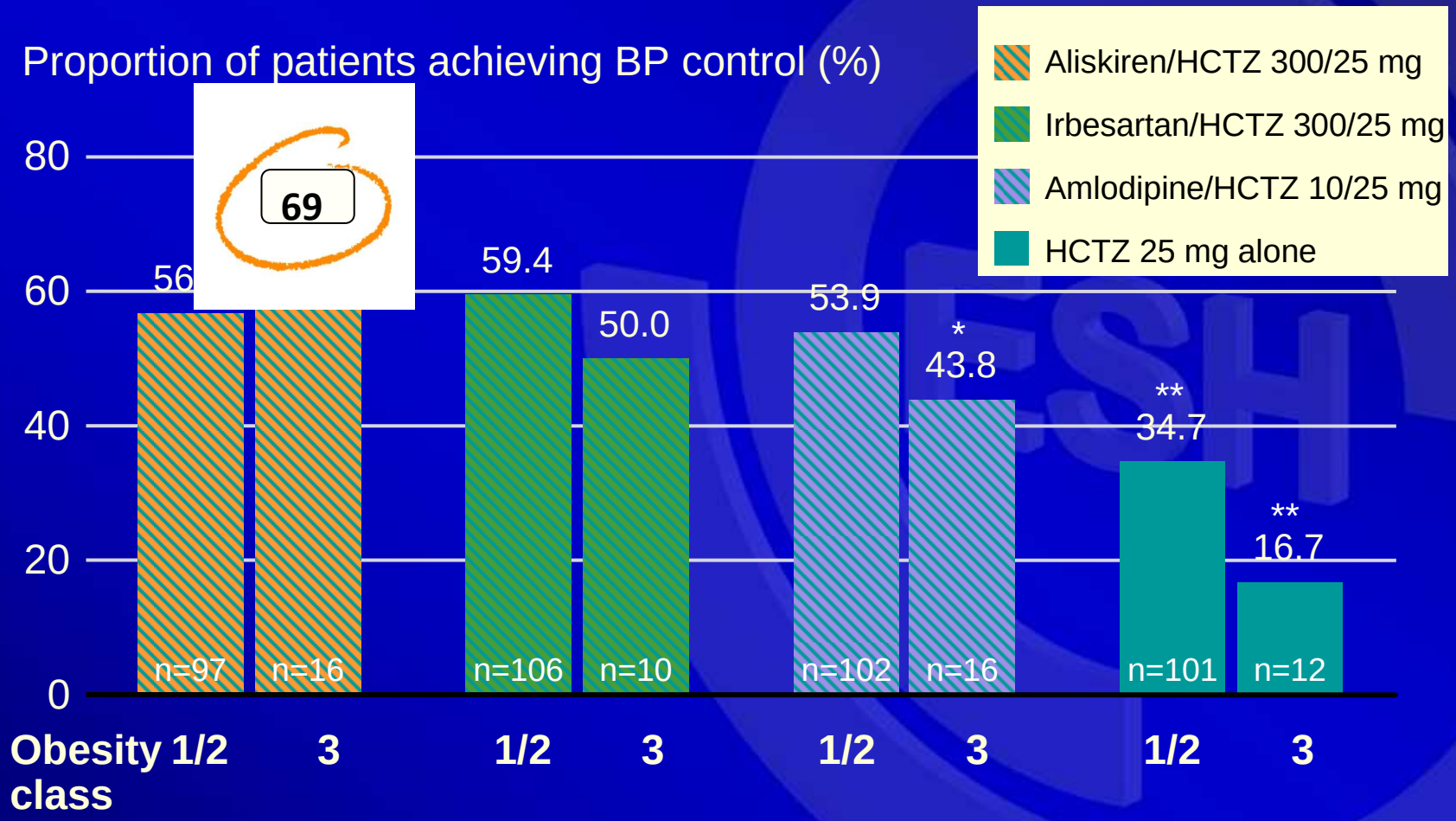


Mean change from baseline in mean sitting BP at Week 12 (mmHg)

* p≤0.001 vs Irbesartan

Krone W, *et al.*JHHTA2010

More Obese Patients Achieve BP Control with Aliskiren/HCTZ vs Other Combinations or HCTZ



BP control defined as BP <140/90 mmHg
* p<0.05, ** p<0.01 vs aliskiren/HCTZ
Class 1/2 obesity: BMI of 30–39.9 kg/m2; class 3 obesity: BMI ≥40 kg/m^2

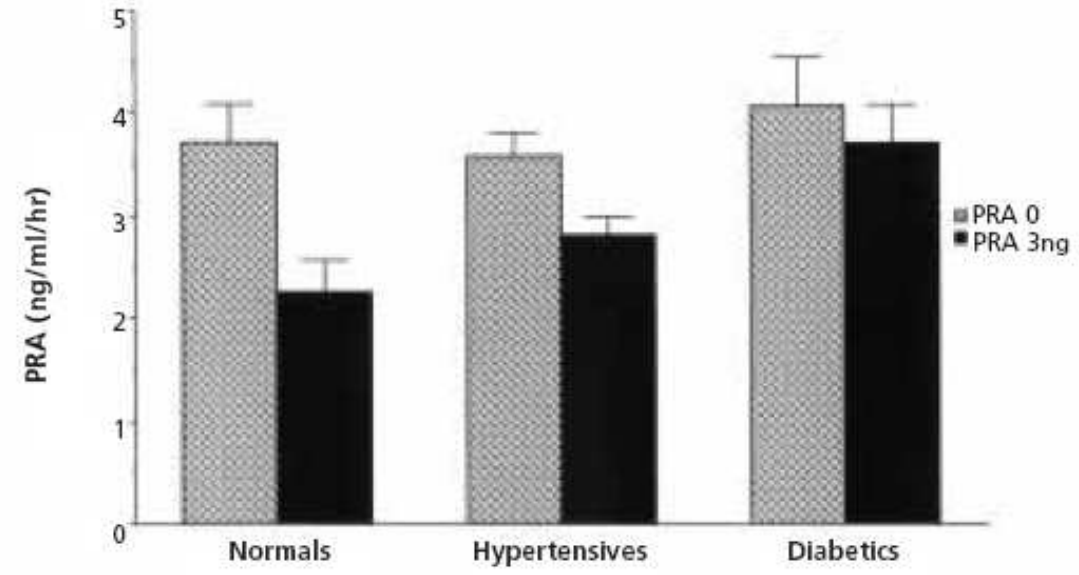
Prescott MF, *et al*. 2007

Blunted suppression of plasma renin activity in diabetes

Michael S Gordon, Deborah A Price and Norman K Hollenberg

Journal of Renin-Angiotensin-Aldosterone System 2000 1: 252

Figure 1b Age-adjusted plasma renin activity (PRA) response to infusion of Ang II (3 ng/kg/min) for 45 minutes. The PRA after Ang II (PRA 3) was significantly lower than basal PRA (PRA 0) in the normal and hypertensive groups ($p<.015$) but unchanged in the diabetic group (p=NS). Means are depicted ± SEM.



Intracellular Angiotensin II Production in Diabetic Rats Is Correlated With Cardiomyocyte Apoptosis, Oxidative Stress, and Cardiac Fibrosis

Vivek P. Singh,[1,2] Bao Le,[2] Renu Khode,[3] Kenneth M. Baker,[1,2] and Rajesh Kumar[1,2]

Diabetes 57:3297–3306, 2008

Aliskiren Inhibits Intracellular Angiotensin II Levels Without Affecting (Pro)renin Receptor Signals in Human Podocytes

AMERICAN JOURNAL OF HYPERTENSION | VOLUME 23 NUMBER 5 | 575-580 | MAY 2010

Mariyo Sakoda[1,2], Atsuhiro Ichihara[1,3], Asako Kurauchi-Mito[1], Tatsuya Narita[1], Kenichiro Kinouchi[1], Kanako Murohashi-Bokuda[1], Moin A. Saleem[4], Akira Nishiyama[5], Fumiaki Suzuki[6] and Hiroshi Itoh[1]

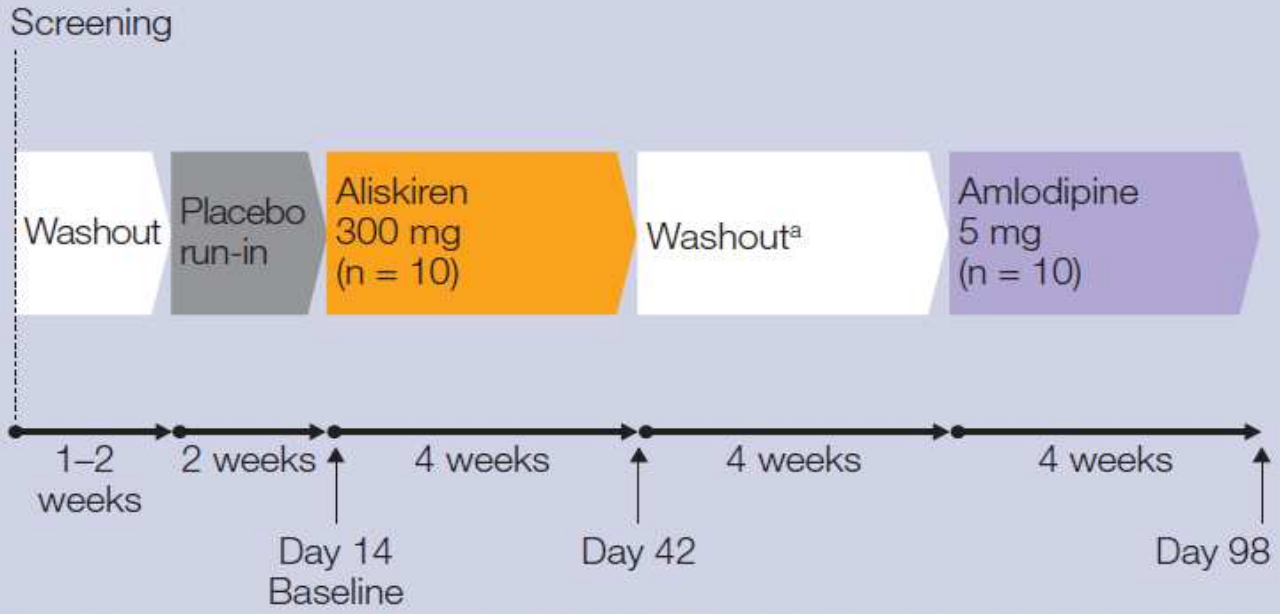
Aliskiren improves insulin resistance and ameliorates diabetic vascular complications in *db/db* mice

Nephrol Dial Transplant (2011) 26: 1194–1204

Aliskiren penetrates adipose & skeletal muscle tissue

- Activation of the RAAS in adipose tissue and skeletal muscles of obese patients may be a contributory factor in the development of hypertension and metabolic abnormalities

Figure 1. An open-label study of aliskiren tissue penetration in obese patients with hypertension



[a]If blood pressure exceeded 140/90 mmHg during this washout period, amlodipine treatment was started early and continued until 8 weeks after the end of the aliskiren treatment period.

Aliskiren penetrates adipose & skeletal muscle tissue

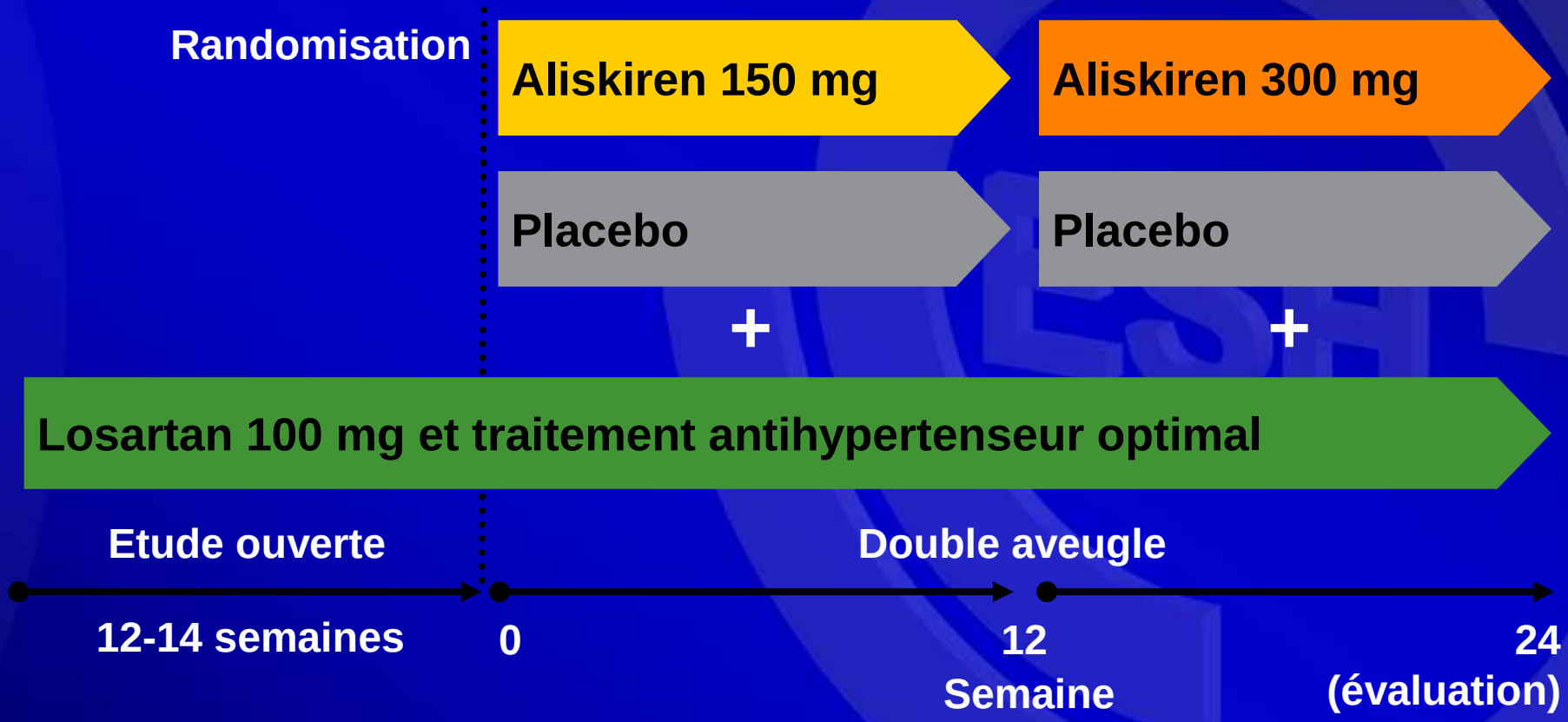
- Interstital fluid, tissue biopsy and blood samples were taken for drug and RAS biomarker assessment on the last day of the placebo run-in period and of the aliskiren and amlodipine treatments periods (days 42 and 98 respectively)
- Mean and median [aliskiren] in the interstitial fluid of sleletal muscle and adipose tissue were above the in vitro IC_{50} for renin (0.33ng/ml) and of similar order of magnitude to plasma aliskiren concentrations. Aliskiren remained detectable 8 weeks after the last dose

Table 2. Aliskiren was detectable in interstitial fluid, s.c. adipose tissue, skeletal muscle and plasma after 4 weeks

	Interstitial fluid (microdialysate) (ng/mL)[a]		Solid tissue (biopsy) (ng/g)		Plasma (ng/mL)
	Adipose tissue	Skeletal muscle	Adipose tissue	Skeletal muscle	
	n = 10	n = 10	n = 6	n = 9	n = 10
Mean ± SD	2.4 ± 2.1	7.1 ± 4.2	29.0 ± 16.7	107.3 ± 68.6	8.4 ± 4.4
Median	1.8	6.5	31.0	78.4	7.6
Range	0.3–7.3	1.9–14.2	7.3–53.4	65.9–284.0	3.5–18.6

[a]Concentrations of aliskiren in microdialysates were derived by the zero flow method using linear regression; thus, the results represent tissue concentrations at zero flow.
s.c., subcutaneous.

Aliskiren in the eValuation of prOteinuria In Diabetes (AVOID)



Étude randomisée en double aveugle avec contrôle par placebo chez des patients hypertendus atteints de diabète de type 2 et de néphropathie

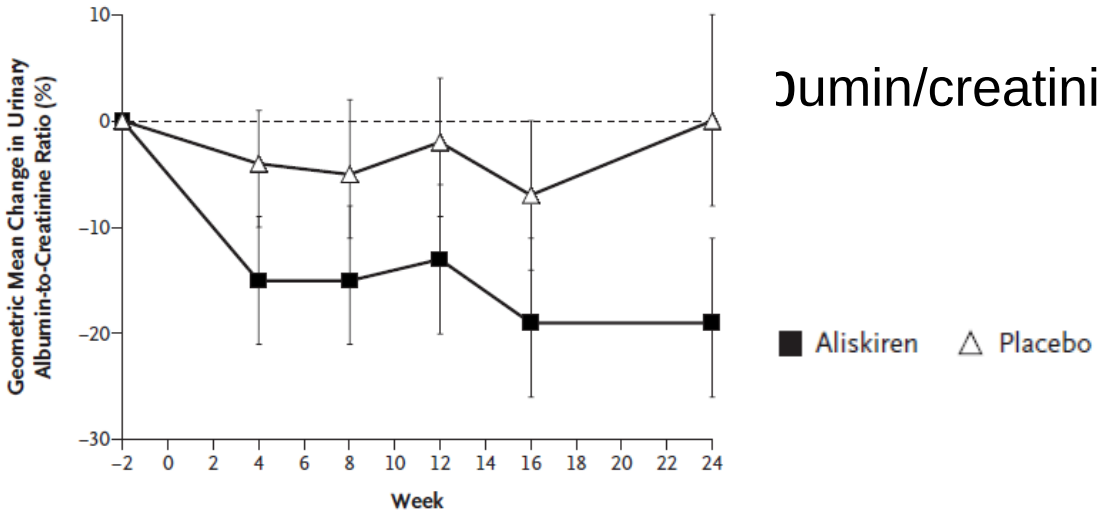
Titration forcée à la semaine 12; toutes les doses ont été administrées une fois par jour

Parving *et al*. N Engl J Med 2008

Dual blockade of the renin-angiotensin system : *In Diabetic nephropathy*

✓**AVOID Study** : mean GFR 67 ml/min , Losartan +Aliskiren vs +Placebo

- Hypertensive patients with diabetes type II & nephropathy (n=599)
- Follow-up : 6 months
- Primary out[illegible] Albumin/creatinine ratio



➔ **combination of aliskiren with losartan provides an additional reduction in UACR of 20% compared with losartan alone.**

N Eng J Med 2008; 358: 2433-2446

CONCLUSION :
Objectifs pour le SM et/ou le DT2

- Arrêt du tabac
- Exercice physique quotidien
- Réduction du NaCl alimentaire
- BMI <25 Kg/m²
- HbA1c <6,5%
- PA < 140/90 mmHg (plus bas si pas coronarien): IEC en premier choix, mais association souvent nécessaire (débat AC vs D).
- Place de l'aliskiren (Rasilez®) à définir, mais pers pectives encourageantes)
- LDL-chol <1g/l (même plus bas stt DT à haut risque CV)
- MA <30 mg/24h
- Aspirine faible dose