Microalbuminuria, Proteinuria, Endothelial Damage – from Bench to the Bedside

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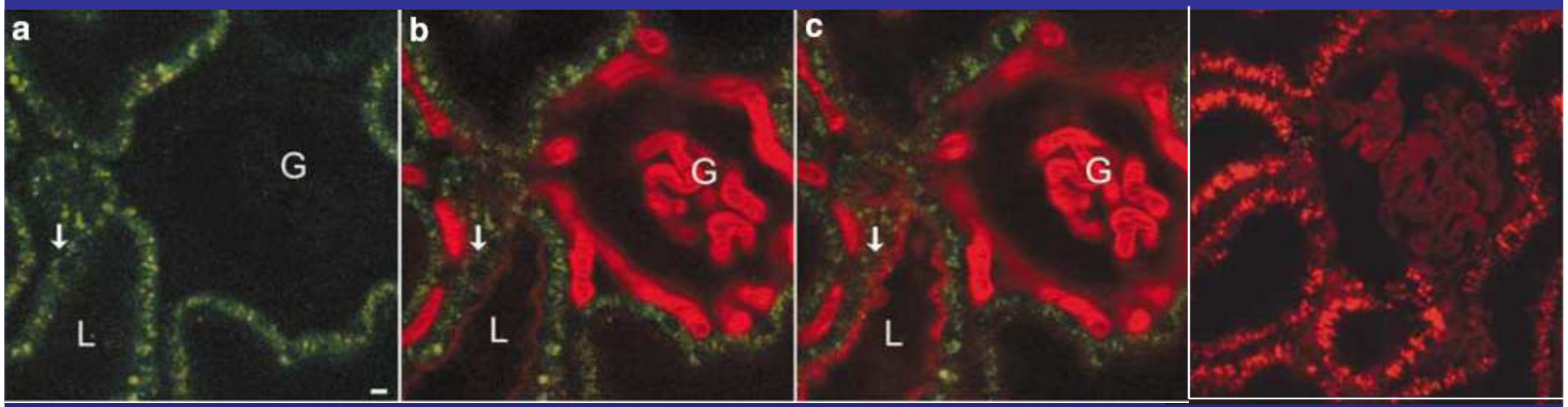
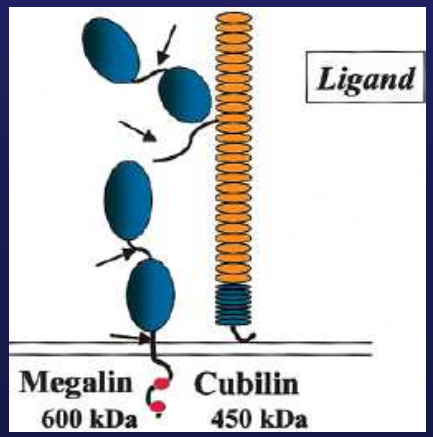
The fate of albumin in the nephron



0 sec — 40 sec — 14 min — 24 h

Filtration → Binding to brush border of PTC → Endocytosis

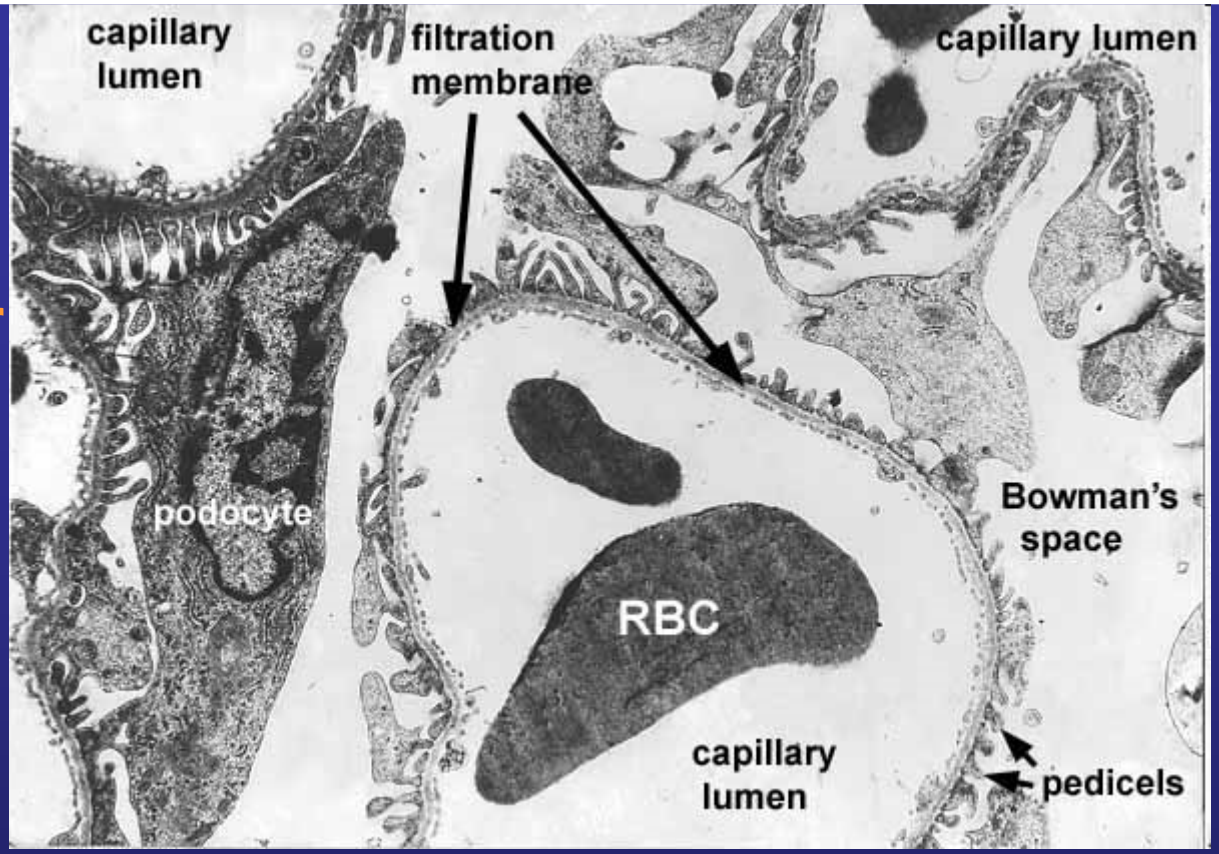
Megalin-cubilin receptors

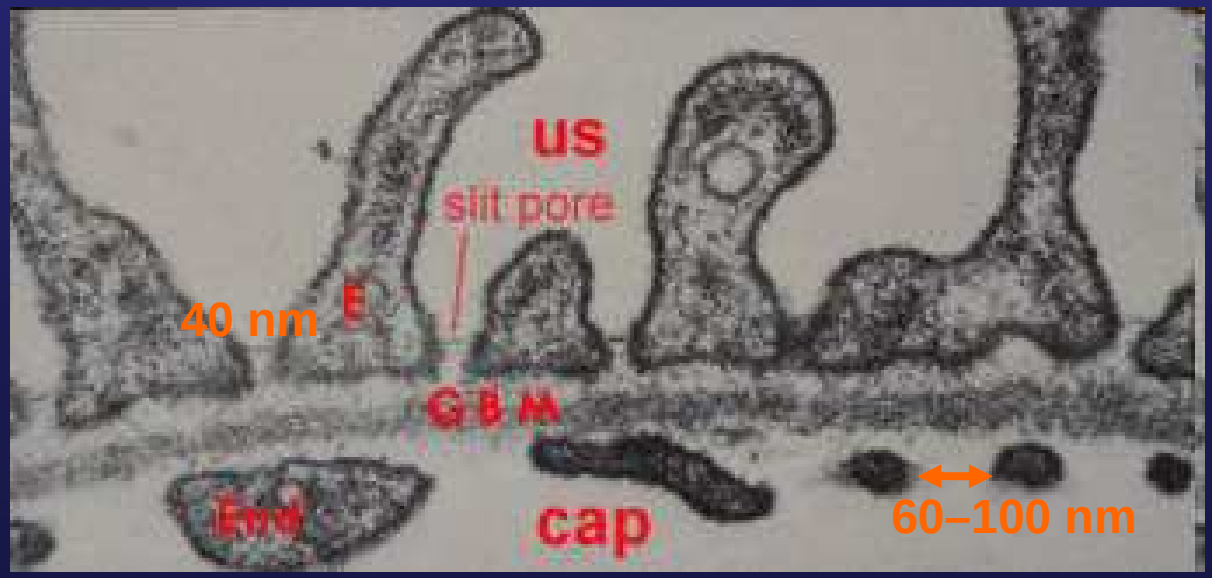


- Lysosomal degradation
- <u>Transcytosis, reabsorption</u>

Russo L. Kidney Int 2007;71:504.

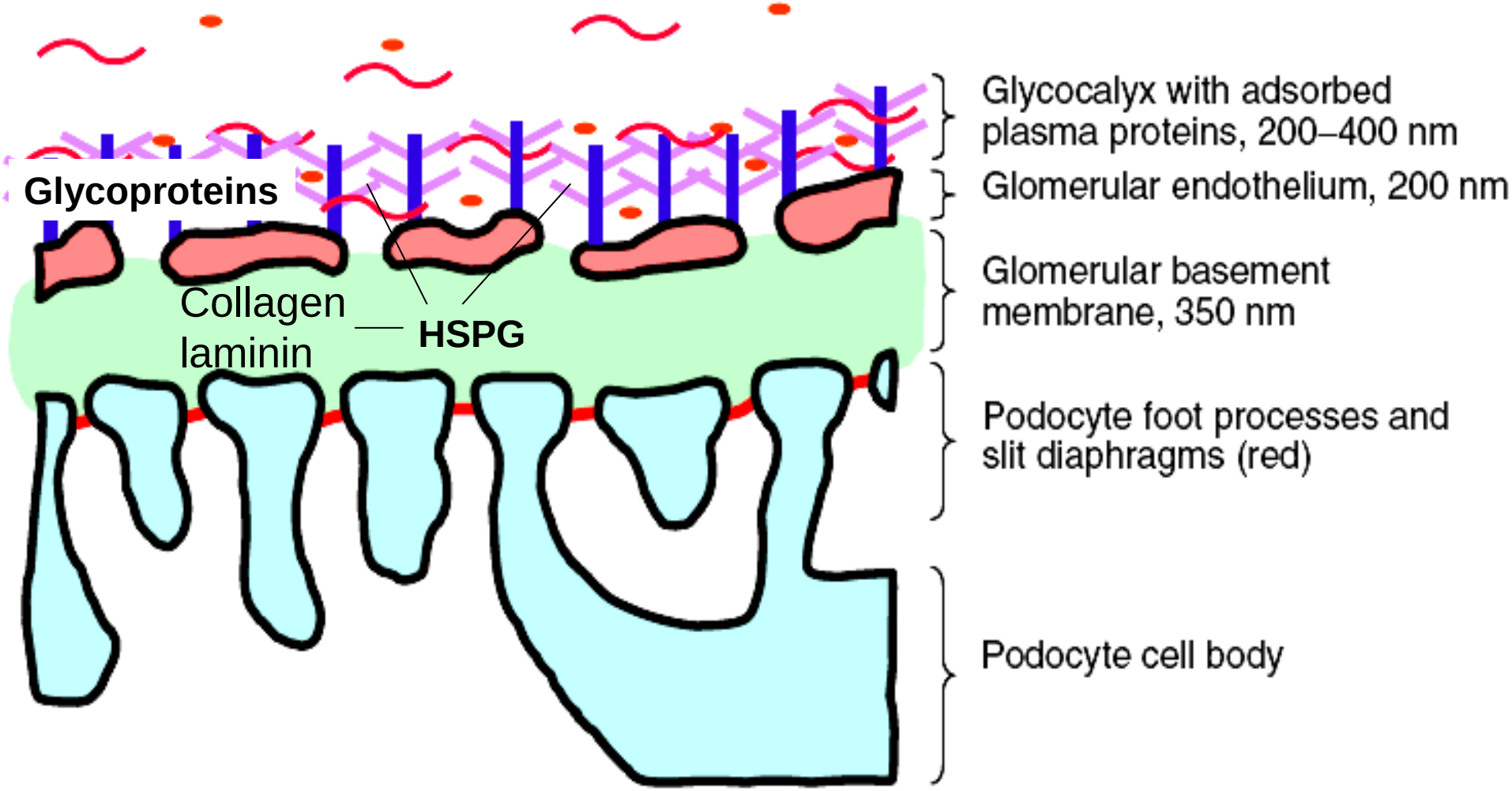
glomerular filtration barrier



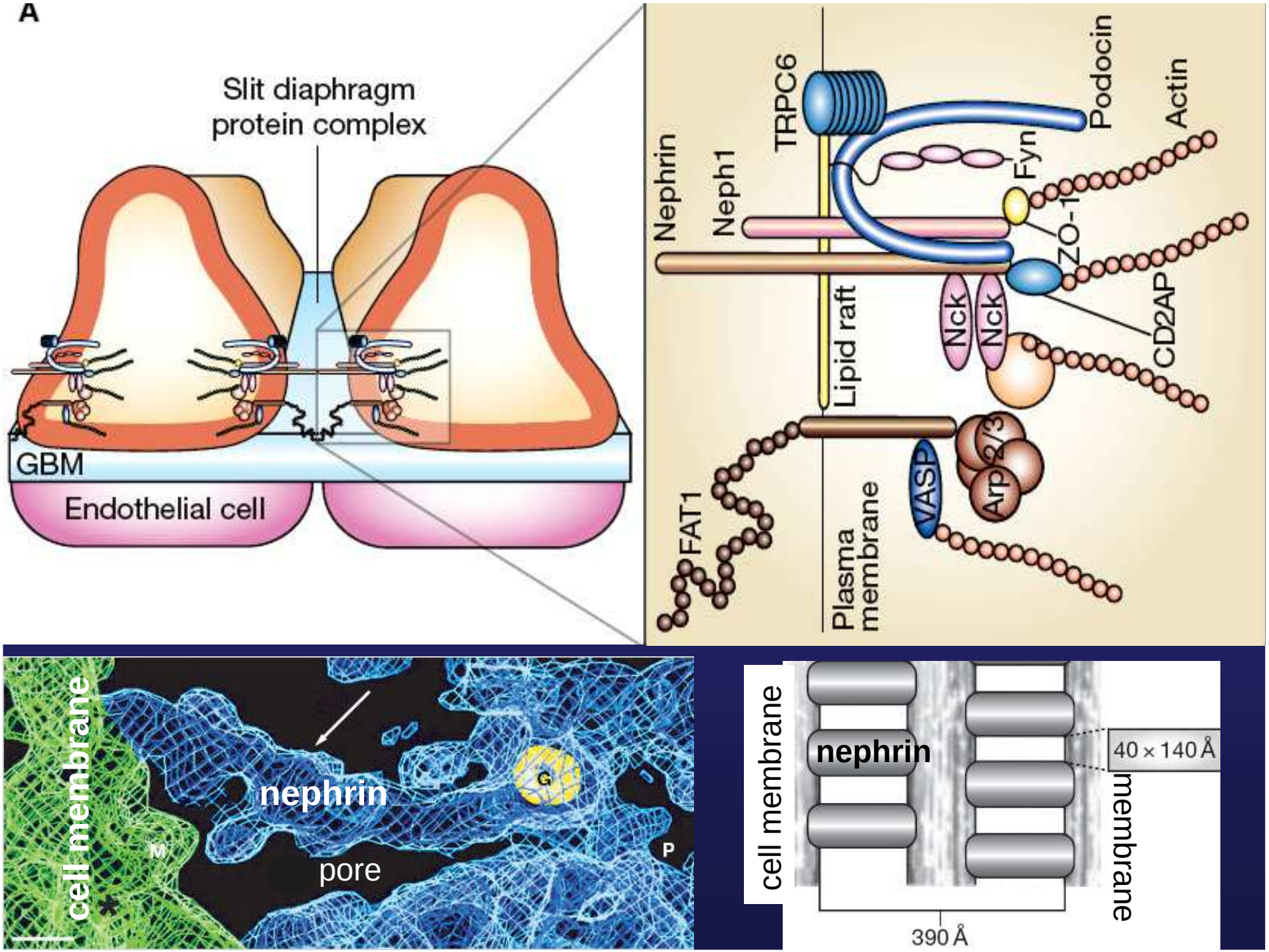


Glomerular filtration barrier

Endothelial glycocalyx forms a barrier to proteins



Satchell S. Diabetologia (2008) 51:714–725


A
Slit diaphragm
protein complex
GBM
Endothelial cell
Nephrin
Neph1
TRPC6
Podocin
Actin
Fyn
ZO-1
CD2AP
Nck
Nck
Lipid raft
FAT1
VASP
Arp2/3
Plasma
membrane
cell membrane
nephrin
pore
M
G
P
cell membrane
nephrin
40 × 140 Å
membrane
390 Å

Glomerular sieving coefficient of albumin

$$GSC = \frac{\text{concentration in filtrate}}{\text{concentration in plasma}}$$

GSC = 0,0006: micropuncture studies , filtrate albumin: 20 mg/l

GSC = 0,03: measurement based on intensity of fluorescence

filtrate albumin: 1000 mg/l

Tojo A. Am J Physiol 1992; 263: F601

Russo L. Kidney Int 2007; 71: 504

History of albuminuria

1969:	**Increased urinary albumin excretion in newly detected hyperglycemics**
1981-1982:	**Term "microalbuminuria" introduced:** UAE below the detection limit of a standard dipstick
1984-1985:	**Range of MAU defined as 30-300 mg /day**
1989:	**Steno hypothesis:** common process underlies both MAU and generalised endothelial dysfunction in diabetes. This process was suggested to be the dysregulation of enzymes involved in metabolism of extracellular matrix.
2000:	**High normal albuminuria**
2004-2005:	**New definition of microalbuminuria was suggested**
2006:	**Time to abandon microalbuminuria?** **Albuminuria - Proteinuria**

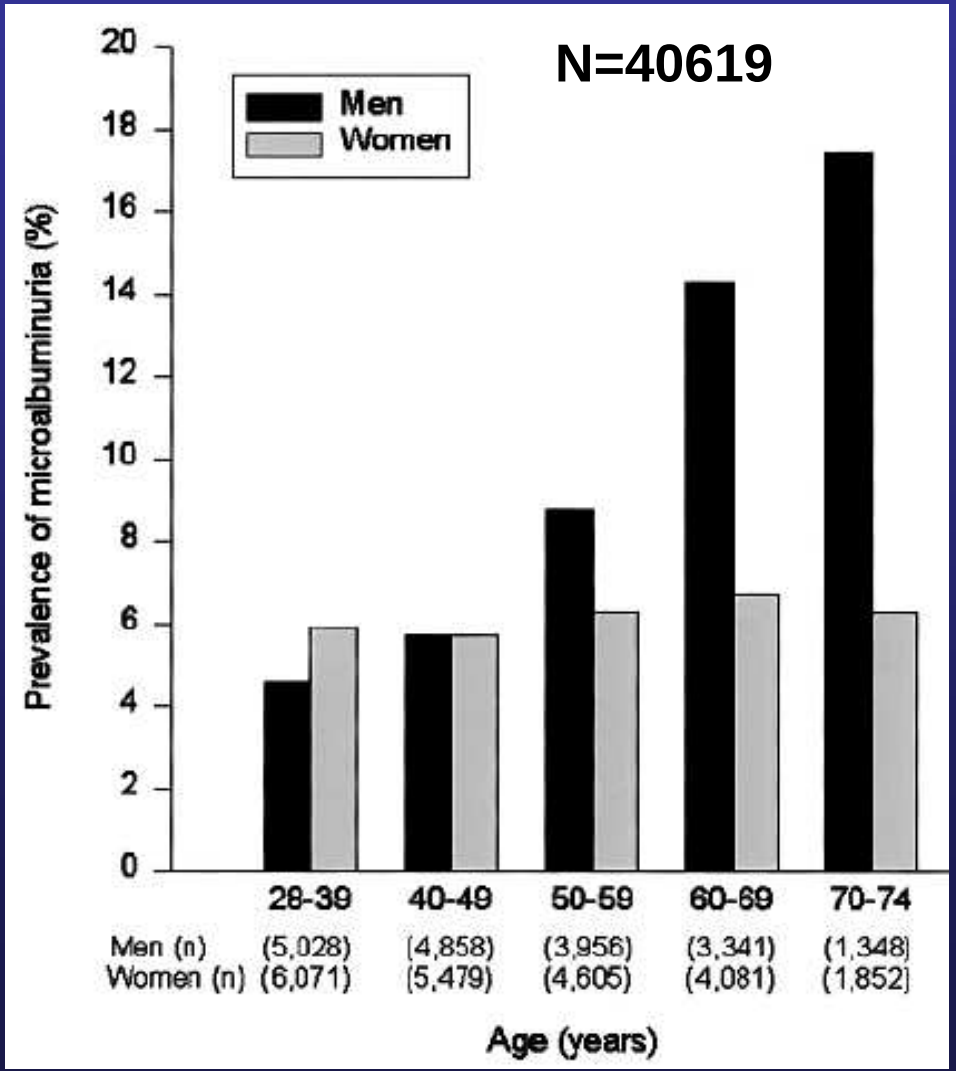
Keen H. Guy's Hosp Rep 1969; 118: 247.
Svendsen P. Acta Endocrinol Suppl 1981; 242:53., Viberti G, Lancet 1982;1: 1430.
Mogensen C. NEJM 1984;310:356., Uremia Invest 1985–86;9:85.
Deckert T, Diabetologia 1989;32:219.
Pinto-Siesma S-J. J Am Soc Nephrol 2000;11:1882., Klausen K. *Circulation* 2004;110;32
Forman J, Brenner B. Kidney Int 2006; 69: 22., Ruggenenti P, Remuzzi G. Kidney Int 2006; 70:1214.

Definition(s) of (micro)albuminuria

	Dipstick	24 h albumin (mg)	Timely coll. (µg/min)	Random alb/creat mg/mmol	24 h protein (mg)
Normal	–	< 30	< 20	< 2,5	< 150
Micro-albuminuria	–	30 - 300	20 - 200	2,5-25	< 500
Proteinuria	+	> 300	> 200	> 25	> 500
High-norm. albuminuria	–	15 - 29	10 - 19		
New definition	–	8 - 300	5 - 200	0,7 - 25	
New concept	Any albuminuria is abnormal (HOPE, LIFE, Framingham, HUNT II)				

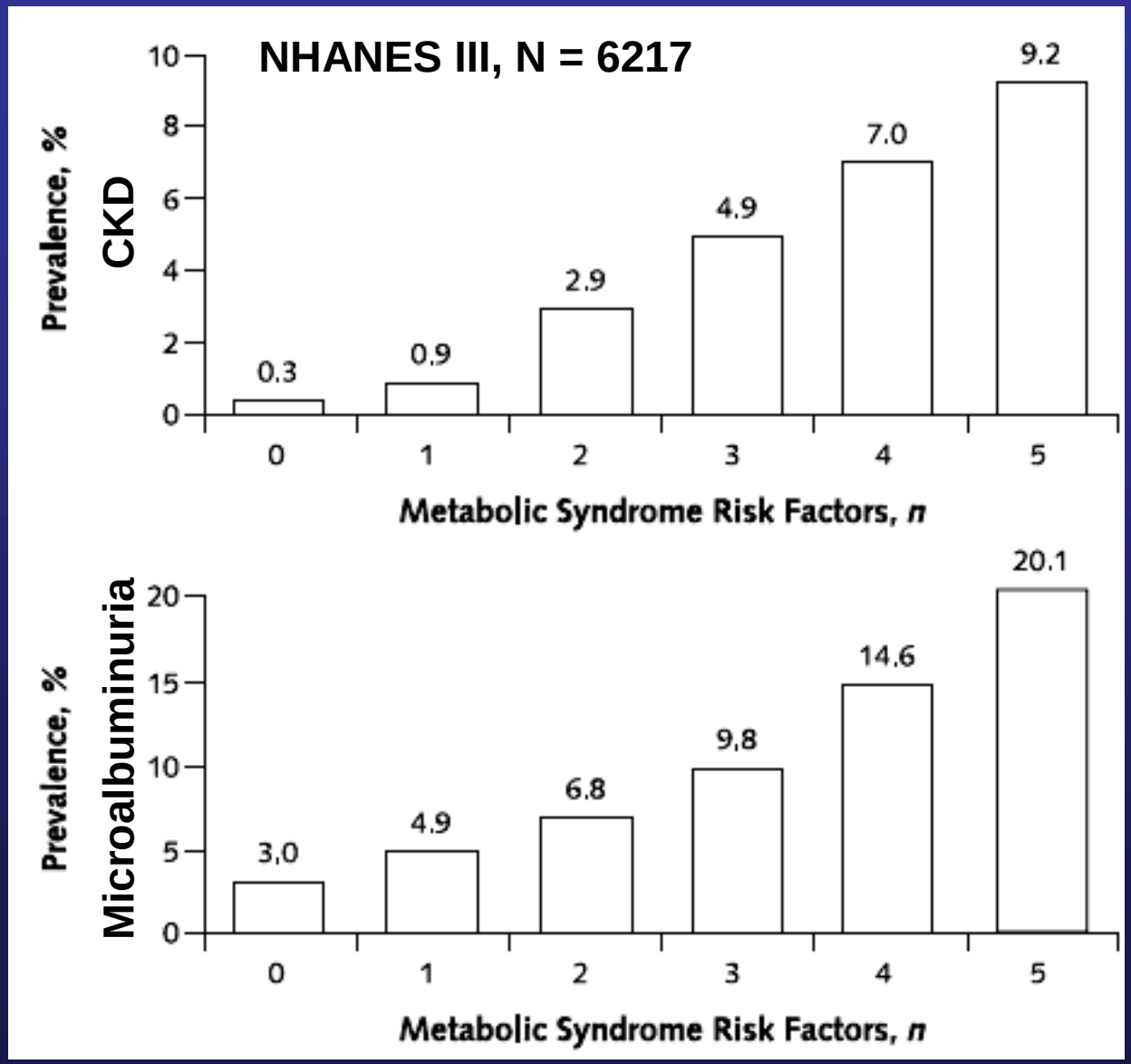
Klausen K. *Circulation* 2004;110;32, Ruggenenti P, Remuzzi G. KI, 2006;70:1214.

Prevention of REnal and Vascular ENd stage Disease (PREVEND) study



de Jong P. NDT 2003,18: 10.

Metabolic syndrome, CKD and MAU



Metabolic syndrome

- Hypertension
- Low HDL
- High TG
- High glucose
- Abdominal obesity

Chen J. *Ann Intern Med.* 2004;140:167

Predictors of MAU in the non-diabetic population

- Age
- Male gender
- Smoking
- Obesitiy
- Insulin resistance
- Hyperlipidemia
- Hypertension
- Natriuresis
- Glomerular hyperfiltration
- Low birth weight

Prevalence of MAU

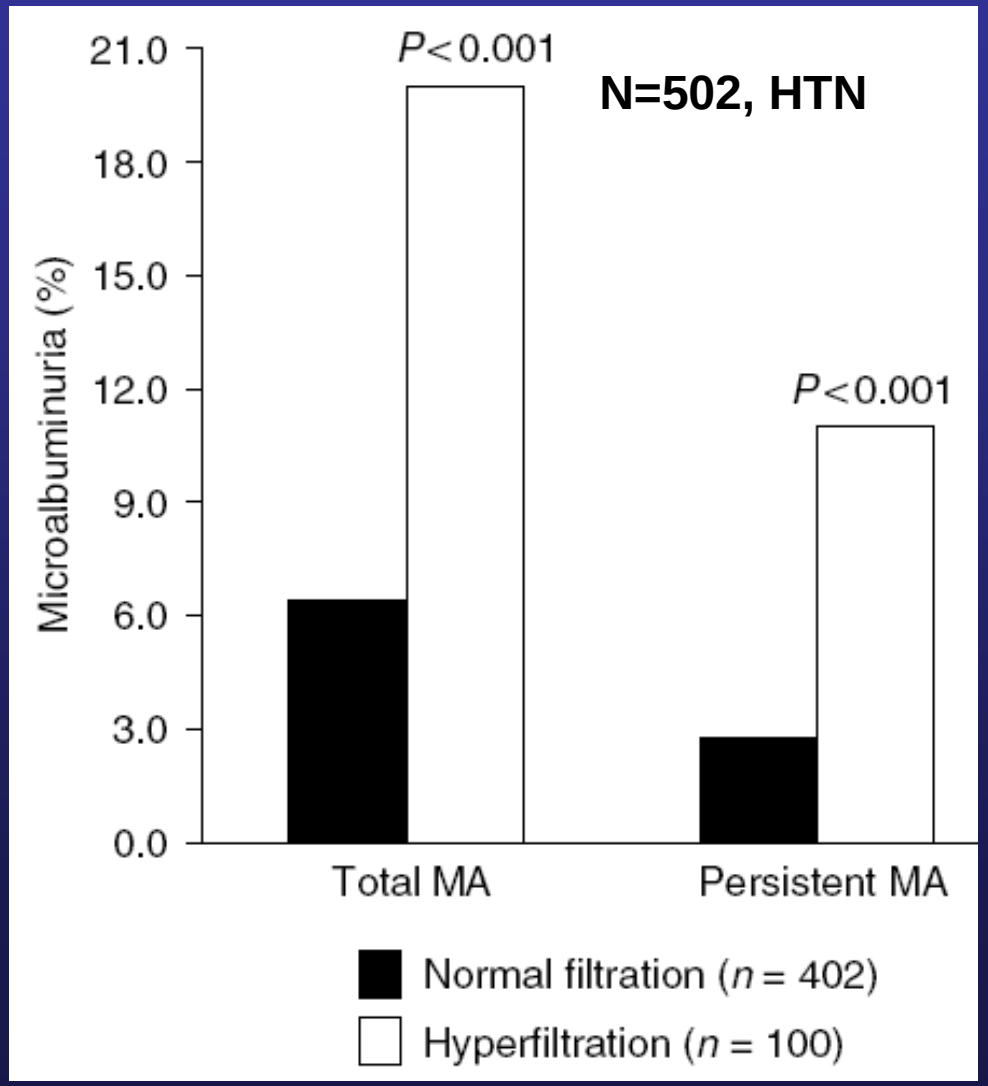
General population: (No DM, no HTN)	5 - 6 %
Hypertensive population:	15 - 40 %
Diabetic population:	20 - 40 %

Mechanisms of albuminuria

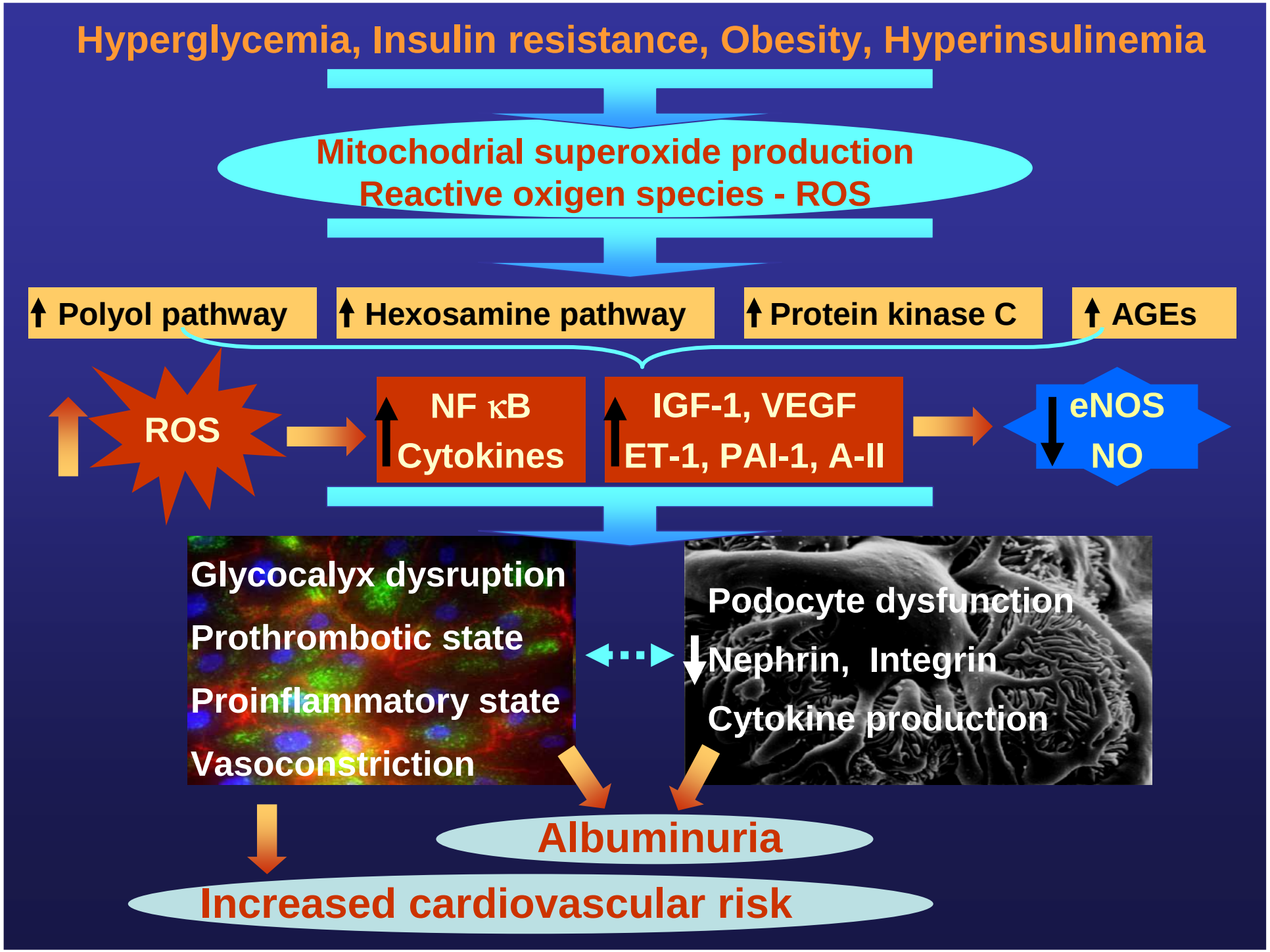
- **Hemodinamic**
  - **Hyperfiltration**
    - Diabetes, hypertension, insulin resistance, obesity
- **Non-hemodinamic**
  - **Endothelial glycocalyx dysruption**
    - Endothelial dysfunction precedes albuminuria
    - Glycocalyx volume correlates with albuminuria
  - **Abnormal structure of slit diaphragm, reduction of nephrin**
  - **Reduced tubular reuptake**
    - Insulin resistance decreases albumin endocytosis

MAU and glomerular hyperfiltration

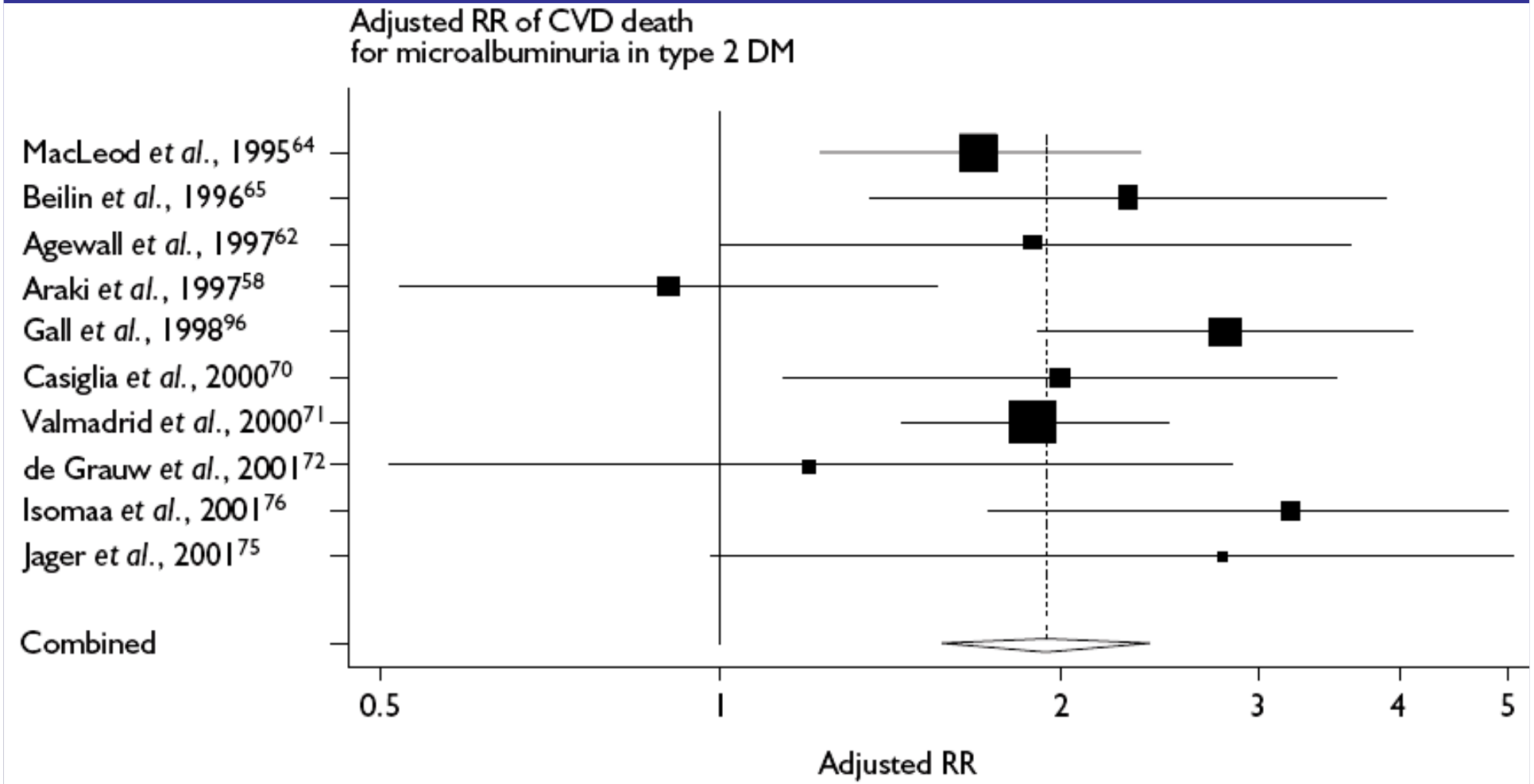
HARVEST



Palatini P. Kidney Int 2006,70:578.

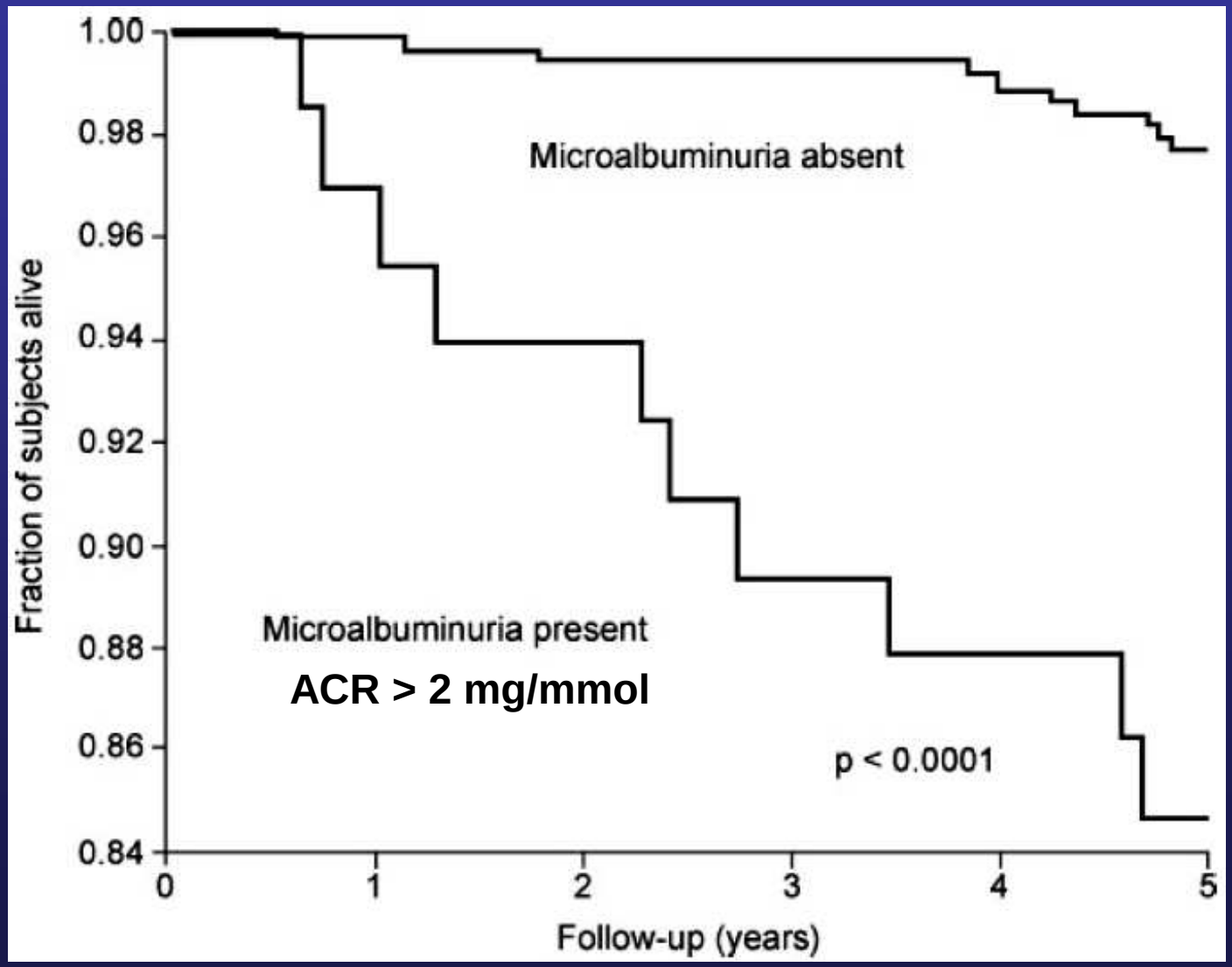

Hyperglycemia, Insulin resistance, Obesity, Hyperinsulinemia
Mitochodrial superoxide production
Reactive oxigen species - ROS
Polyol pathway
Hexosamine pathway
Protein kinase C
AGEs
ROS
NF κB
Cytokines
IGF-1, VEGF
ET-1, PAI-1, A-II
eNOS
NO
Glycocalyx dysruption
Prothrombotic state
Proinflammatory state
Vasoconstriction
Podocyte dysfunction
Nephrin, Integrin
Cytokine production
Albuminuria
Increased cardiovascular risk

MAU and CV mortality



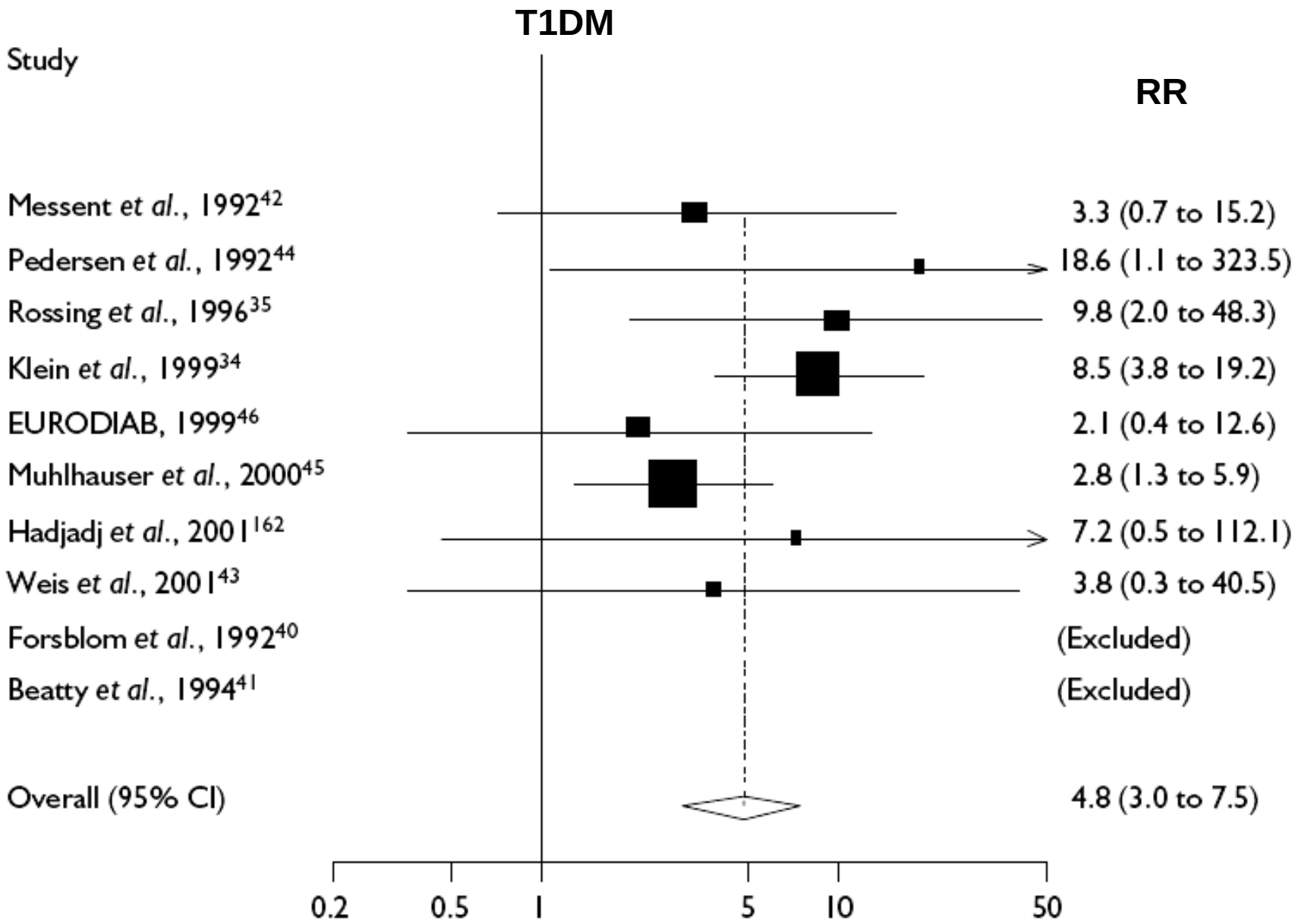
Newman D. Health Technology Assessment 2005; Vol. 9

The HOORN study - population based



Jager A. Arterioscler Thromb Vasc Biol 1999;19: 617.

MAU and risk of end stage renal failure



Newman D. Health Technology Assessment 2005; Vol. 9

Microalbuminuria: independent predictor of renal function loss and CV events in hypertension

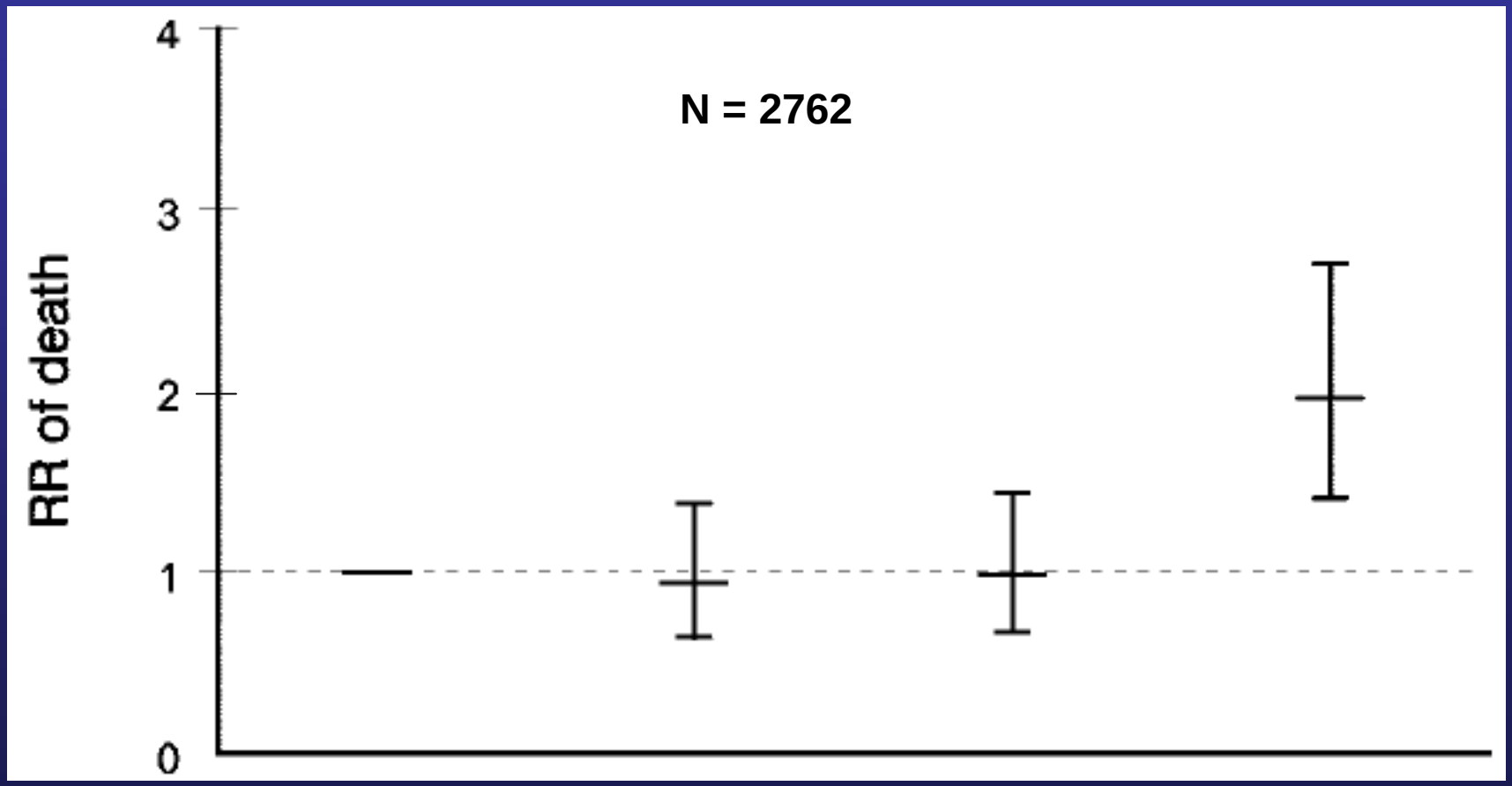
N		Δ C-creat	CV events
141	MAU	- 12 ml/min / 7 yr	21 %
	Normal	- 7 ml/min / 7 yr*	2 %**

* $p < 0,03$

** $p < 0,001$

Bigazzi R. J Hypertens. 1998;16:1325

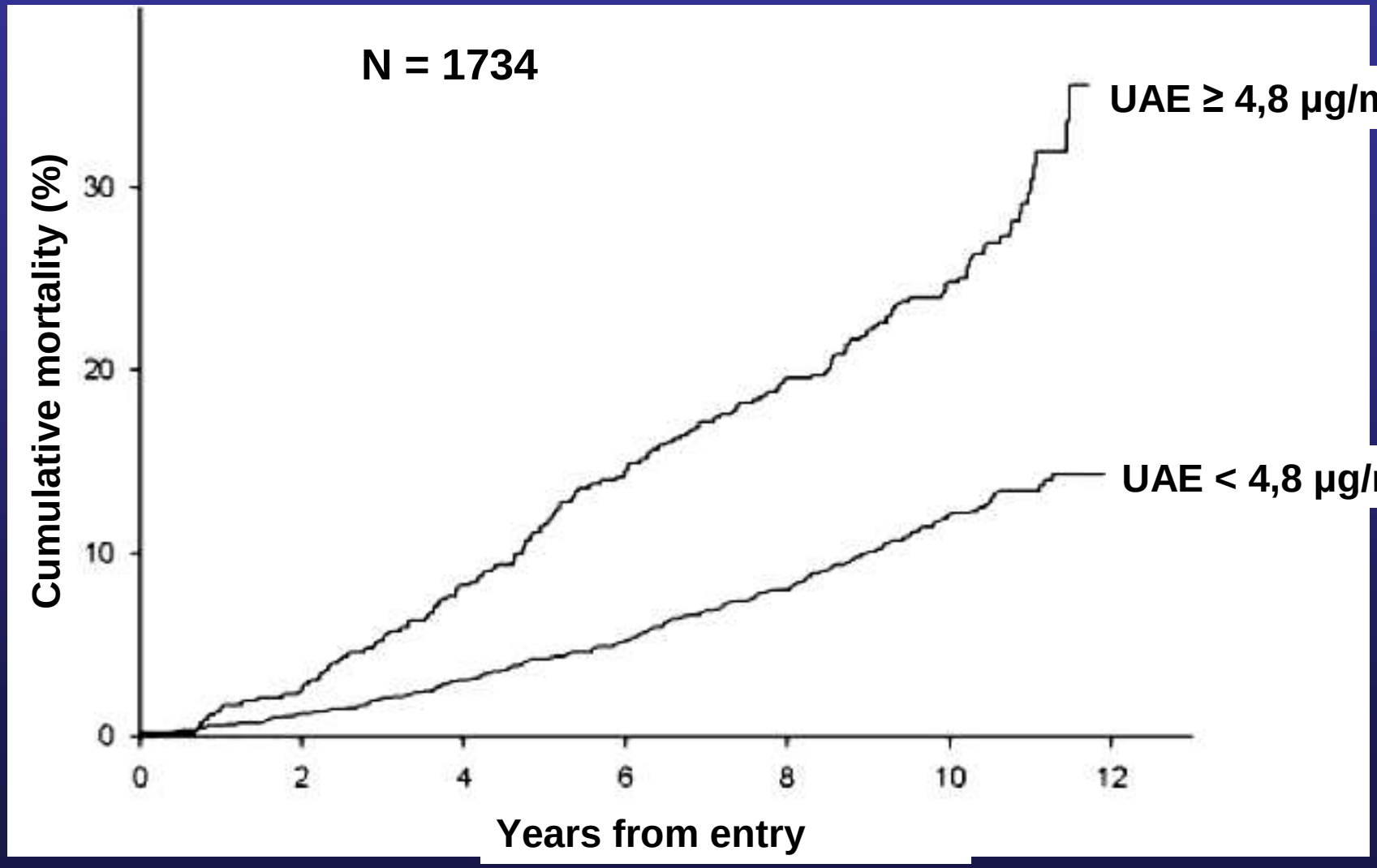
Albuminuria and risk of death in the general population



Albuminuria	< 2,1	2,1-3,0	3,0-4,8	> 4,8	µg/min

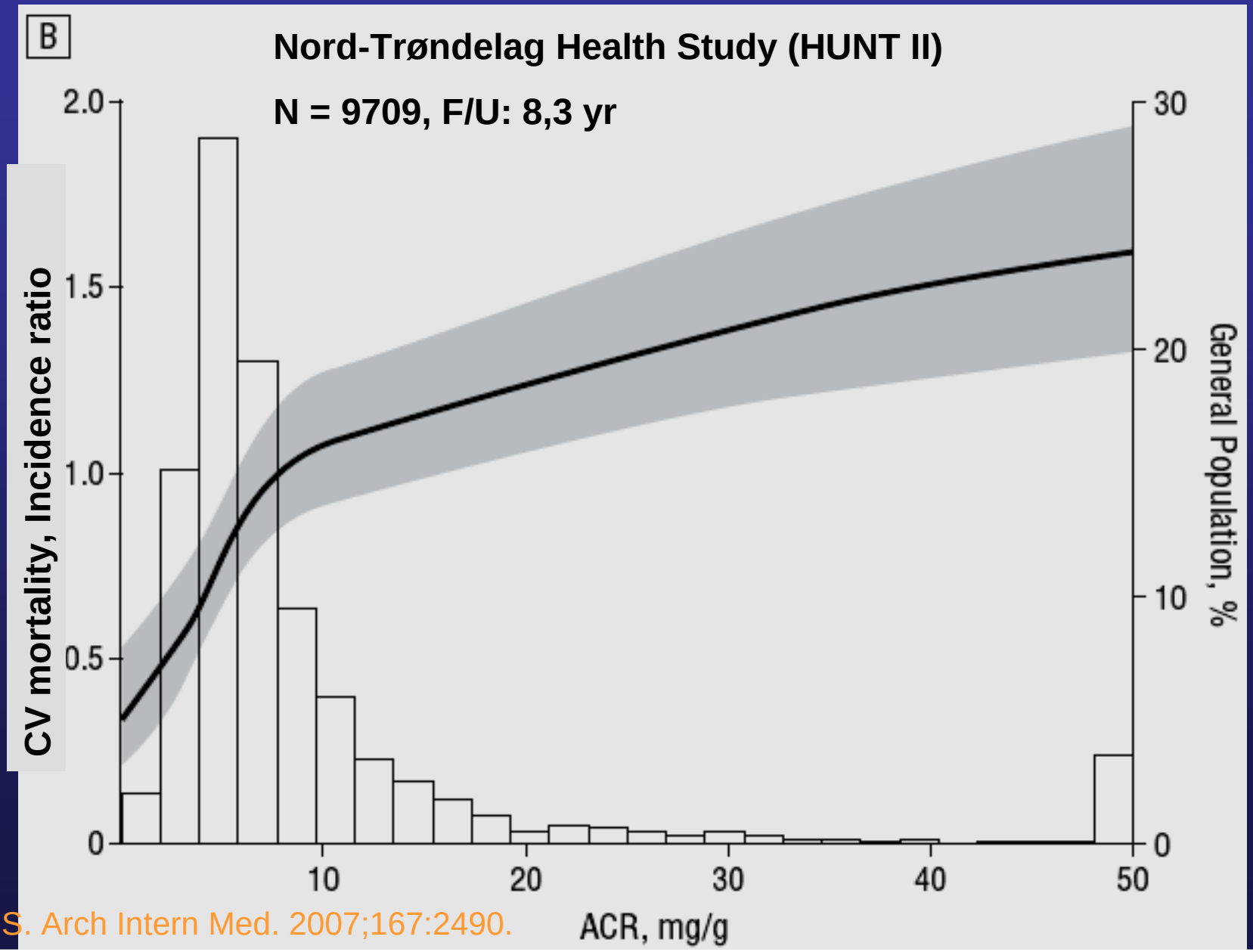
Klausen K. *Circulation* 2004;110;32

Albuminuria and mortality in hypertensive subjects



Klausen K. *Hypertension* 2005;46;33

Albuminuria and cardiovascular mortality



Hallan S. Arch Intern Med. 2007;167:2490.

The significance of albuminuria

Sign of endothelial dysfunction

Sign of insulin resistance

Sign of nephropathy

DIAGNOSIS

Albuminuria

PROGNOSIS

Renal failure

CV morbidity, mortality, total mortality

Albuminuria is a risk factor

Normotensive population

Hypertension

Non-diabetic population

Diabetes mellitus

Loss of renal function

CV morbidity and mortality

All cause mortality

Diabetic population

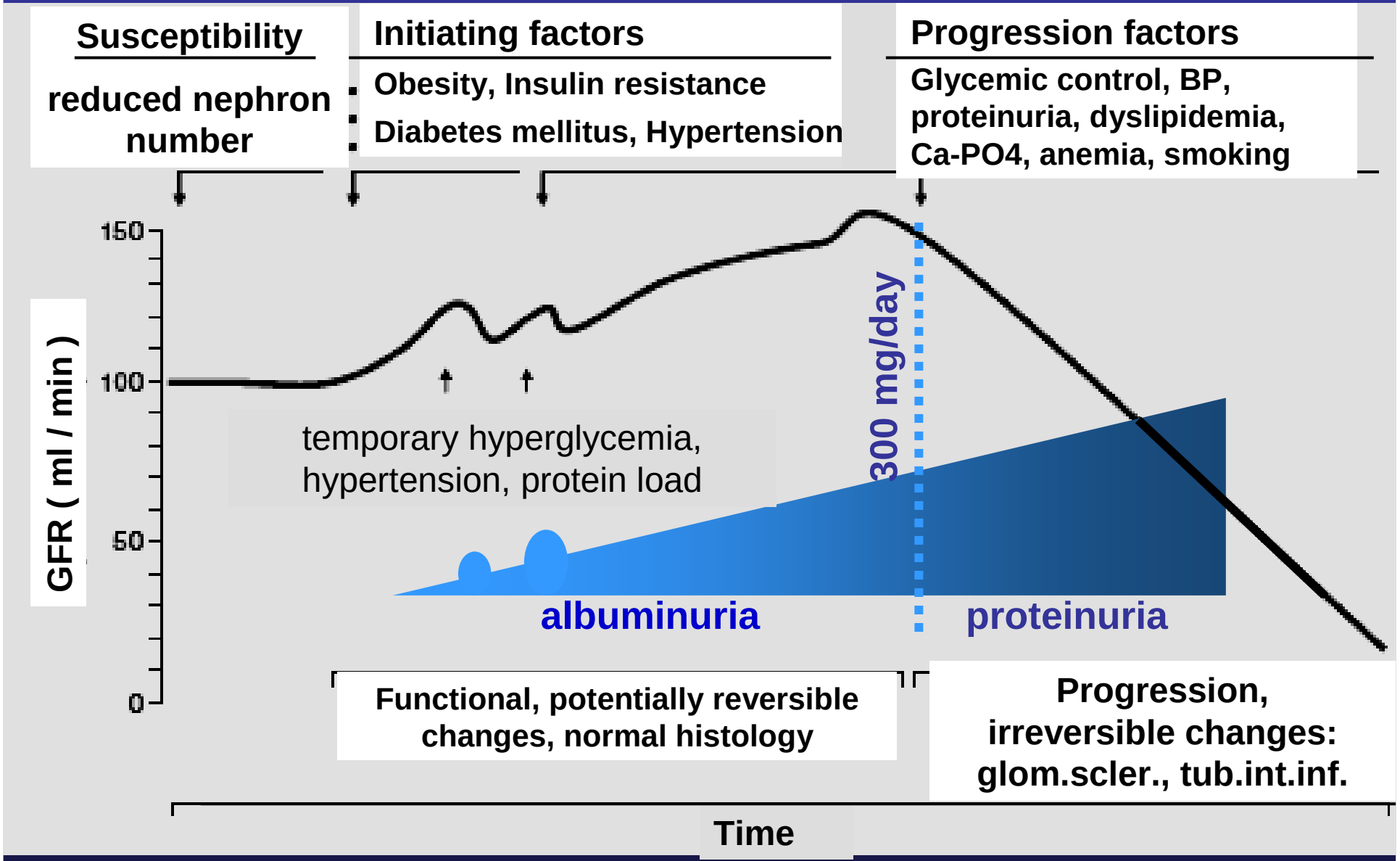
Proteinuria

Loss of renal function

CV morbidity and mortality

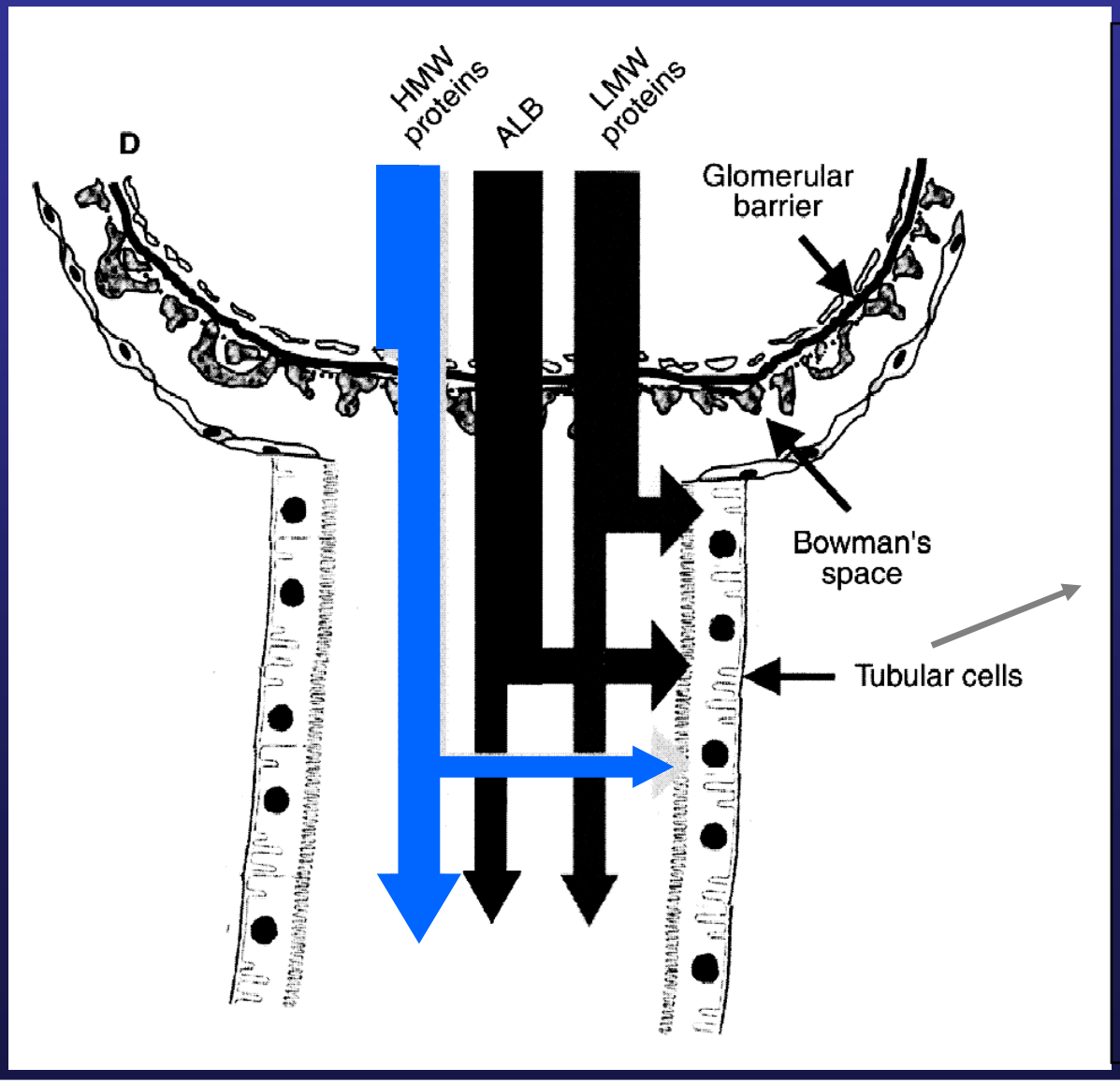
All cause mortality

Albuminuria and progression of kidney disease



Ruggenenti P, Remuzzi G. KI, 2006;70:1214.

Proteinuria causes progression of CKD



Saturation of transport
Toxic cell damage

Chemokines
Macrophage infiltration

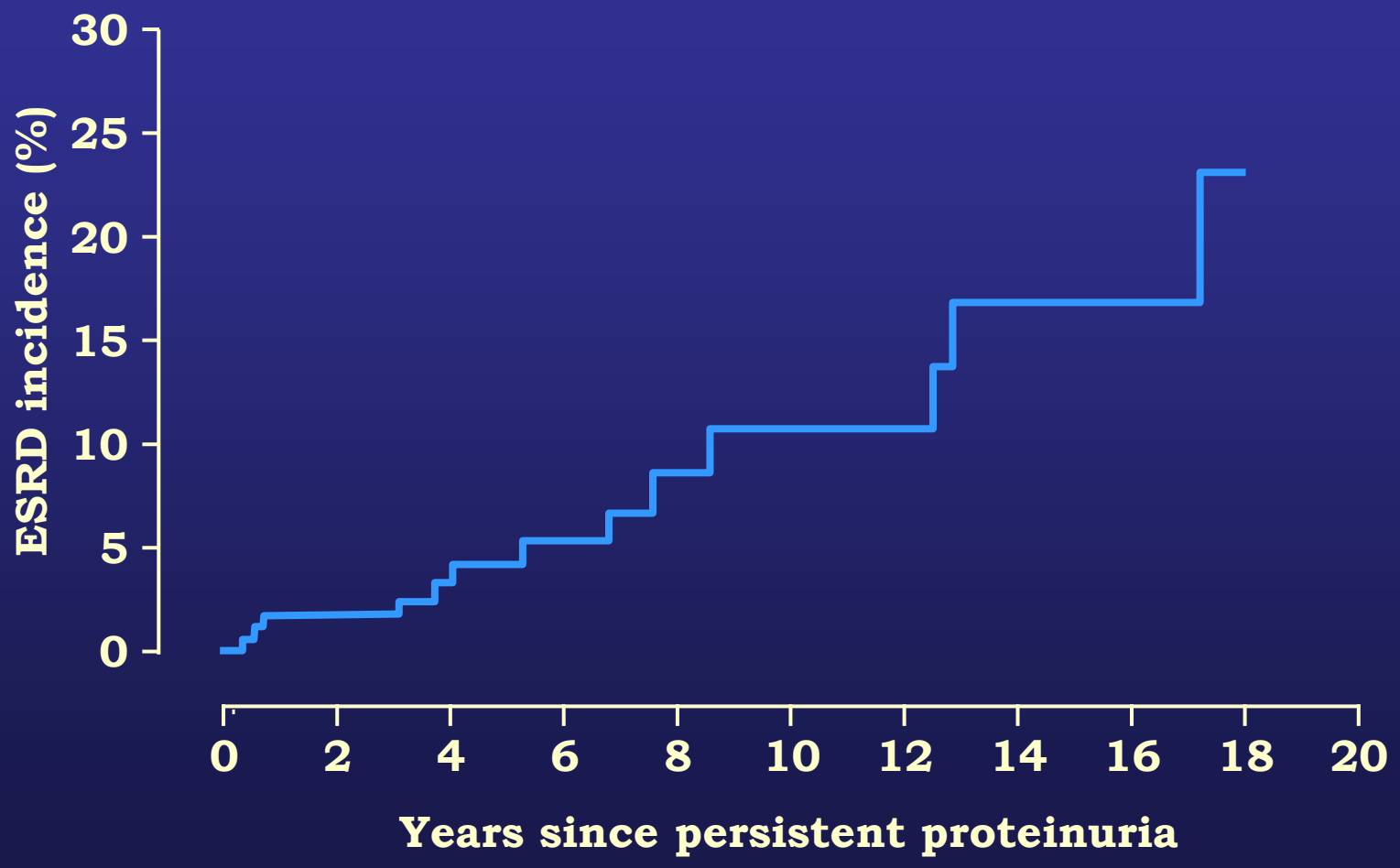
PDGF
ANGII, TGF-β, NF-κB
Cytokines

Phenotype change into fibroblast:epithelial to mesenchymal transition

Apoptosis

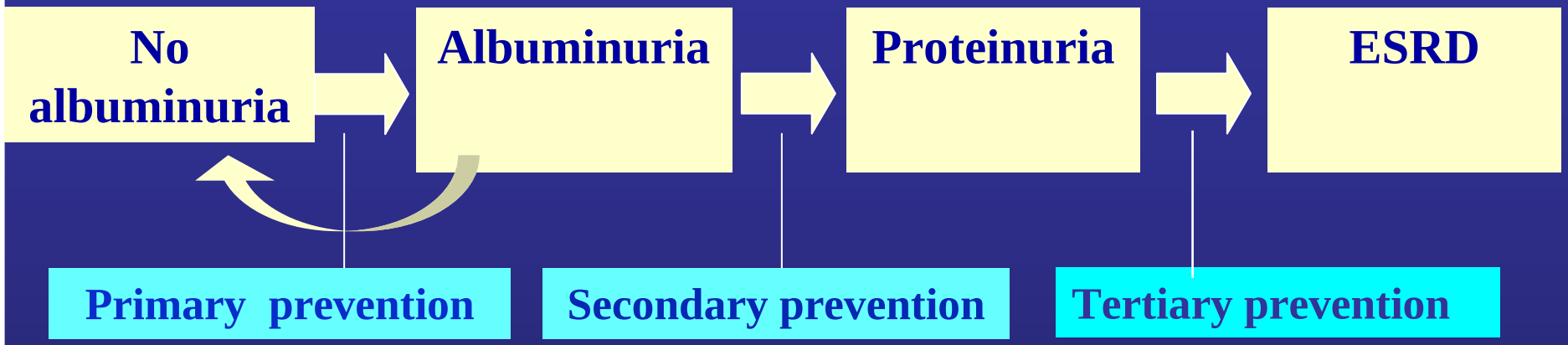
Fibrosis, tubular atrophy

Development of ESRD following appearance of proteinuria



Humphrey et al. *Ann Int Med* 1989;111:788-796.

Therapeutic strategy



Therapeutic targets

- Intraglomerular hypertension
- Systemic hypertension
- Albuminuria
- Hyperlipidemia, Glycemic control
- Oxidative stress, inflammation, fibrosis

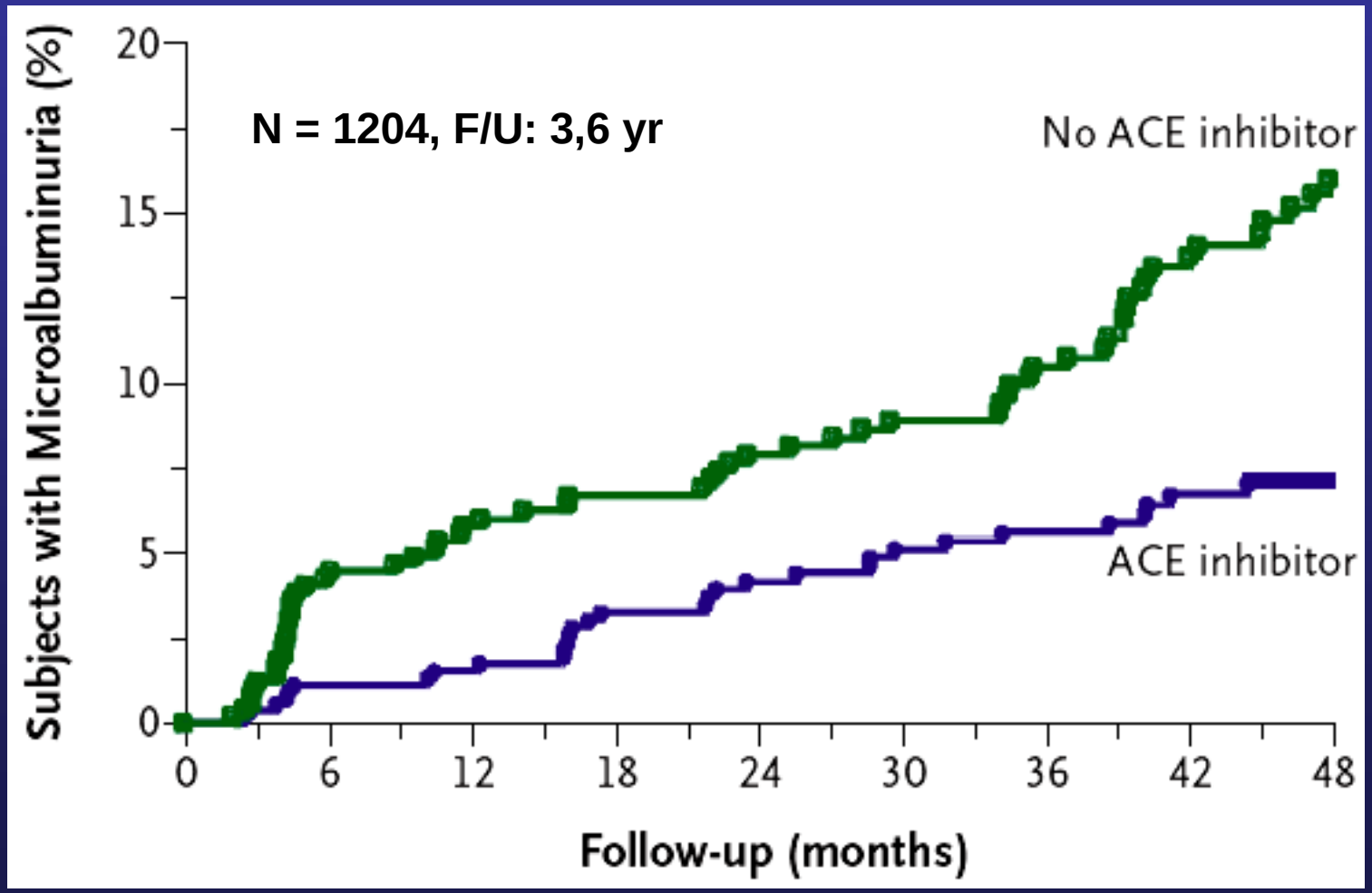
- Progression of CKD
- Cardiovascular morbidity, mortality

Effets of Angiotensin II

- **Hemodinamic**
  - ⇧ gl. capillary pressure
  - ⇧ gl. capillary permeability

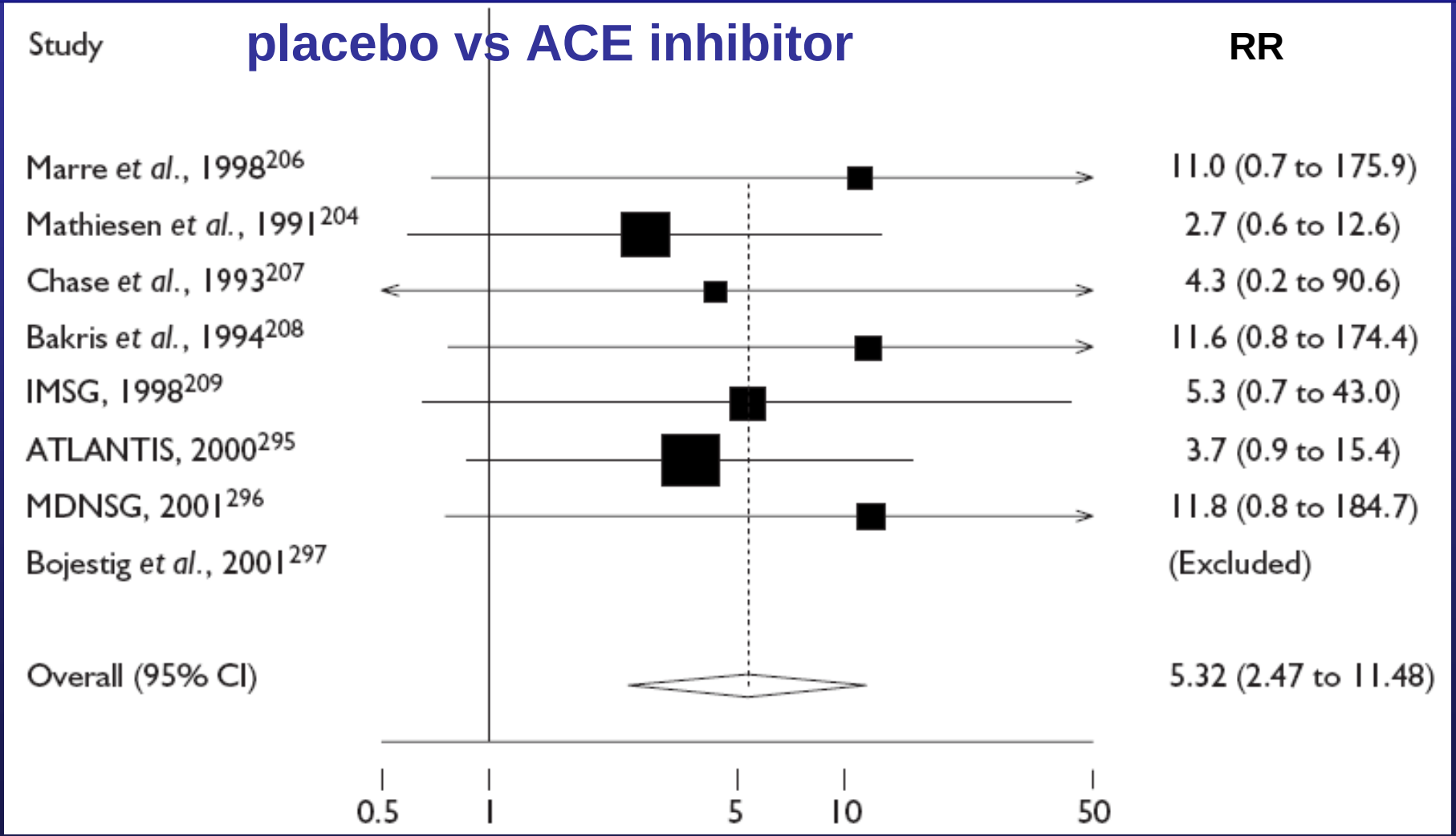
- **Non-hemodinamic**
  - ⇧ NF κB
  - PKC
  - TGFβ, PDGF
  - VCAM
  - ECM proteins
  - ⇩ proteinases
  - ⇩ eNOS
  - ⇧ macrophage / monocyte infiltration

Preventing MAU in normoalbuminuric patients with T2DM: BENEDICT



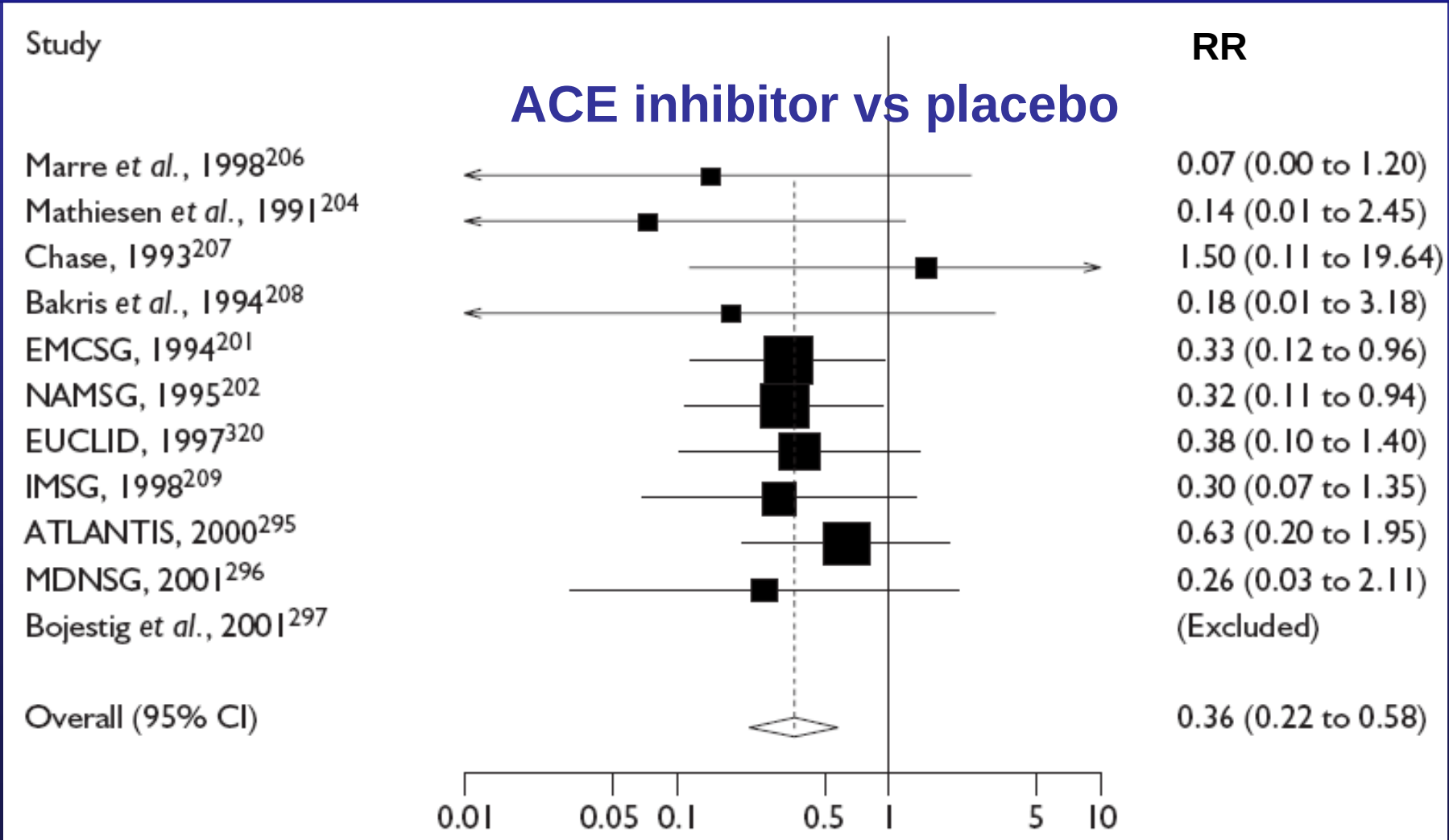
Ruggenenti P. N Engl J Med 2004;351:1941

Regression of MAU in normotensive T1DM patients with MAU



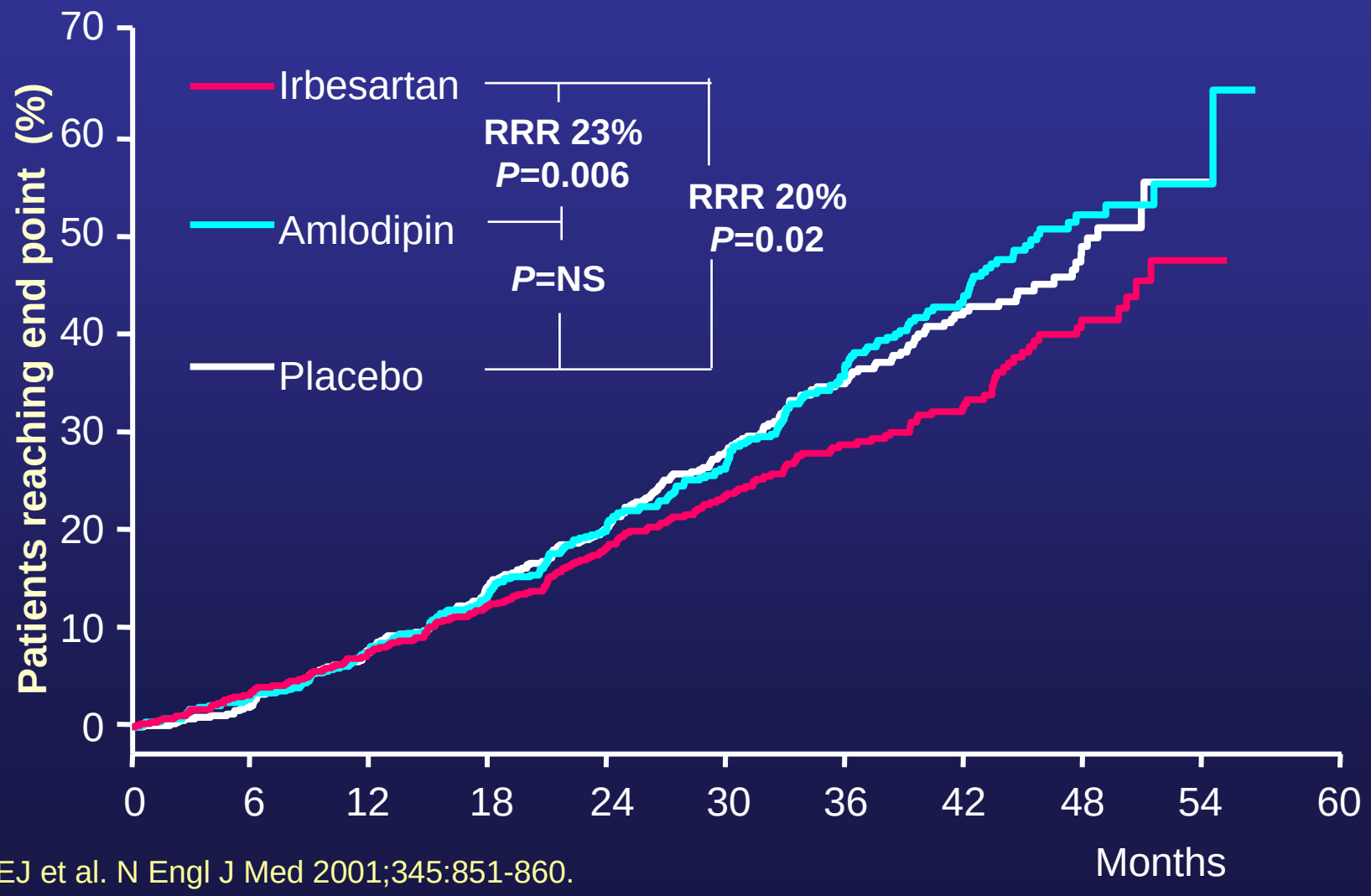
Newman D. Health Technology Assessment 2005; Vol. 9

Secondary prevention of proteinuria in normotensive T1DM patients with MAU



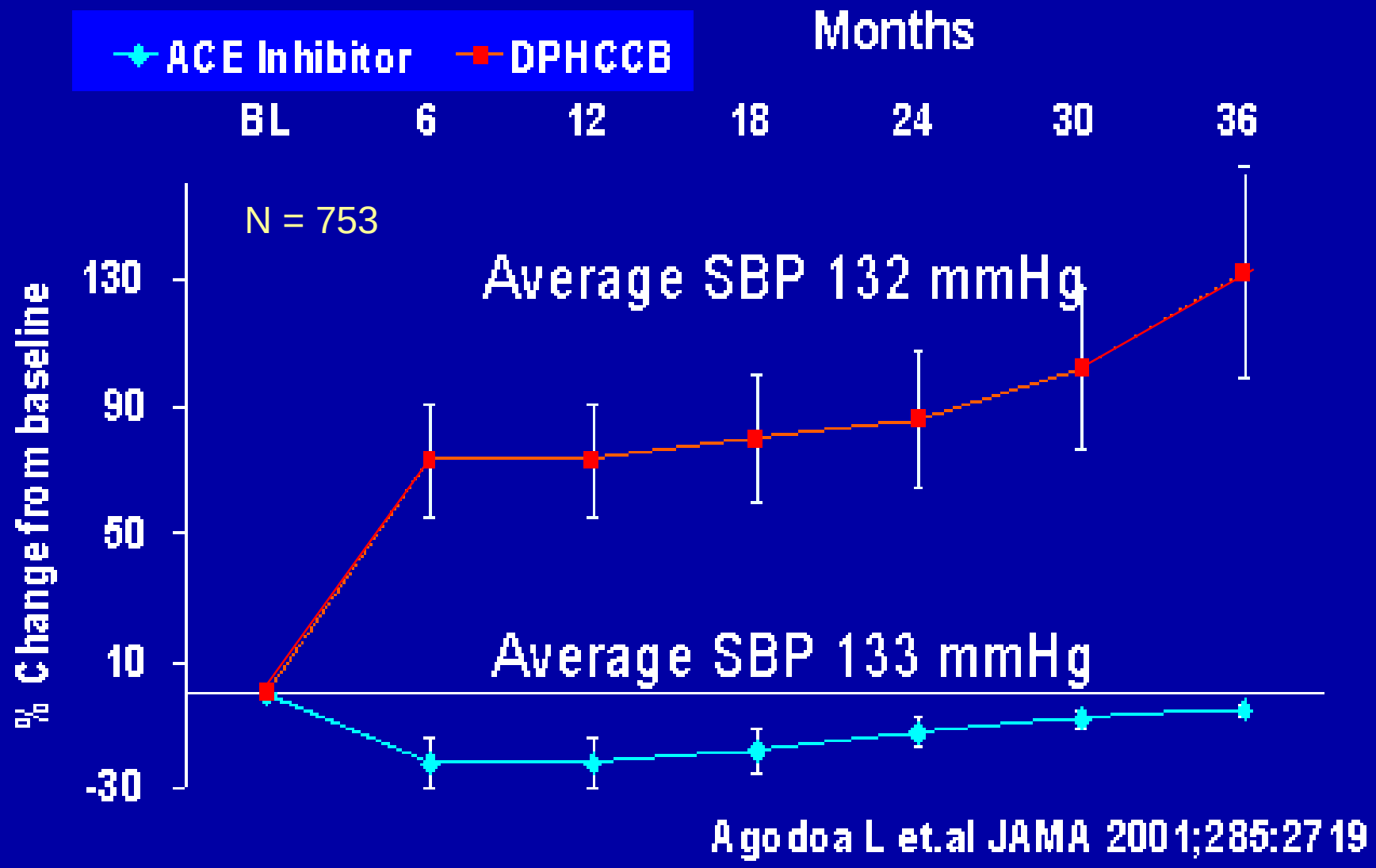
Newman D. Health Technology Assessment 2005; Vol. 9

IDNT : time to doubling of creatinin, ESRD or mortality



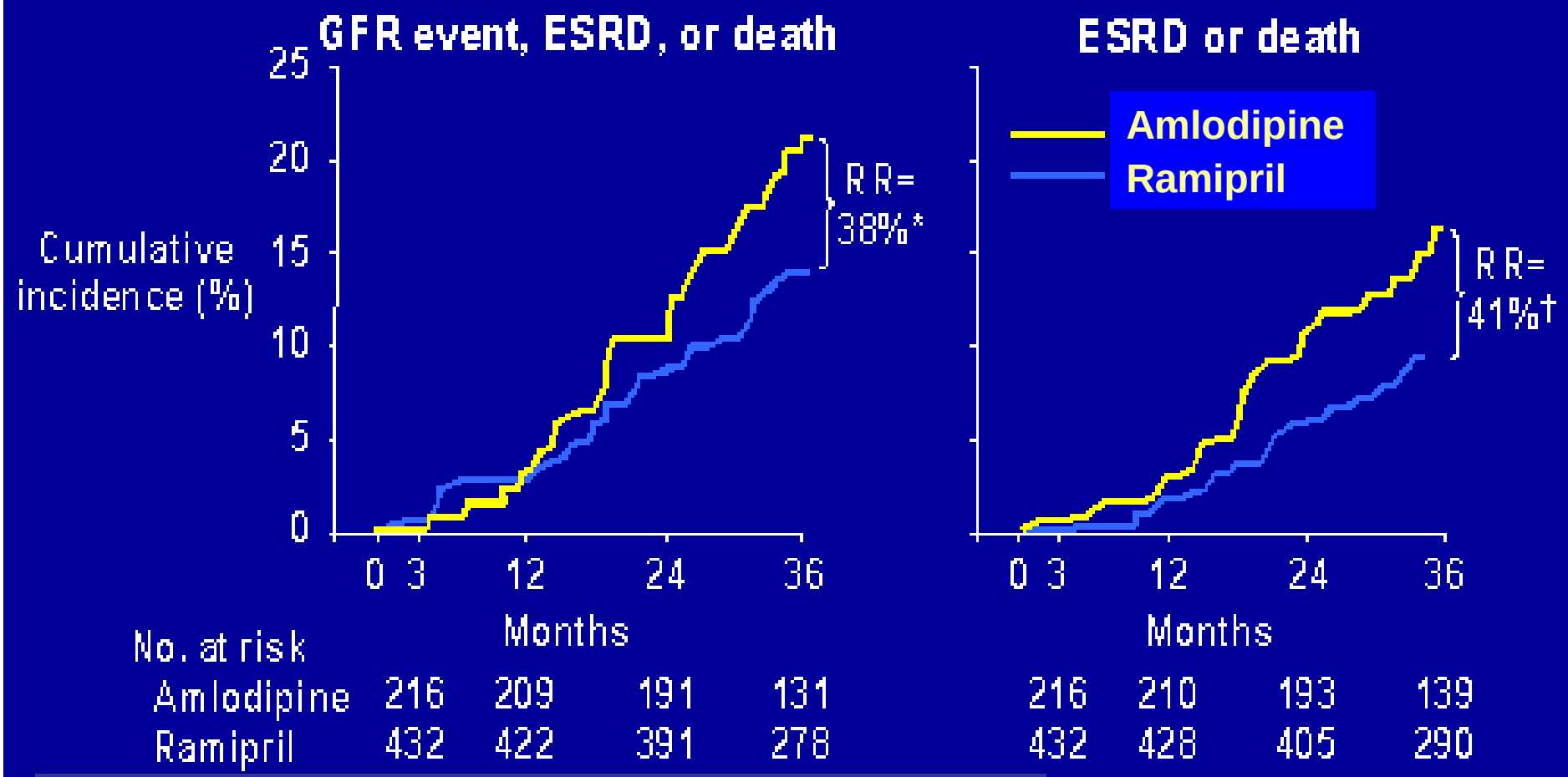
Lewis EJ et al. N Engl J Med 2001;345:851-860.

AASK study:
Change of protein to creatinin ratio



Agodoa L et.al JAMA 2001;285:2719

AASK Study: Incidence of renal events and death

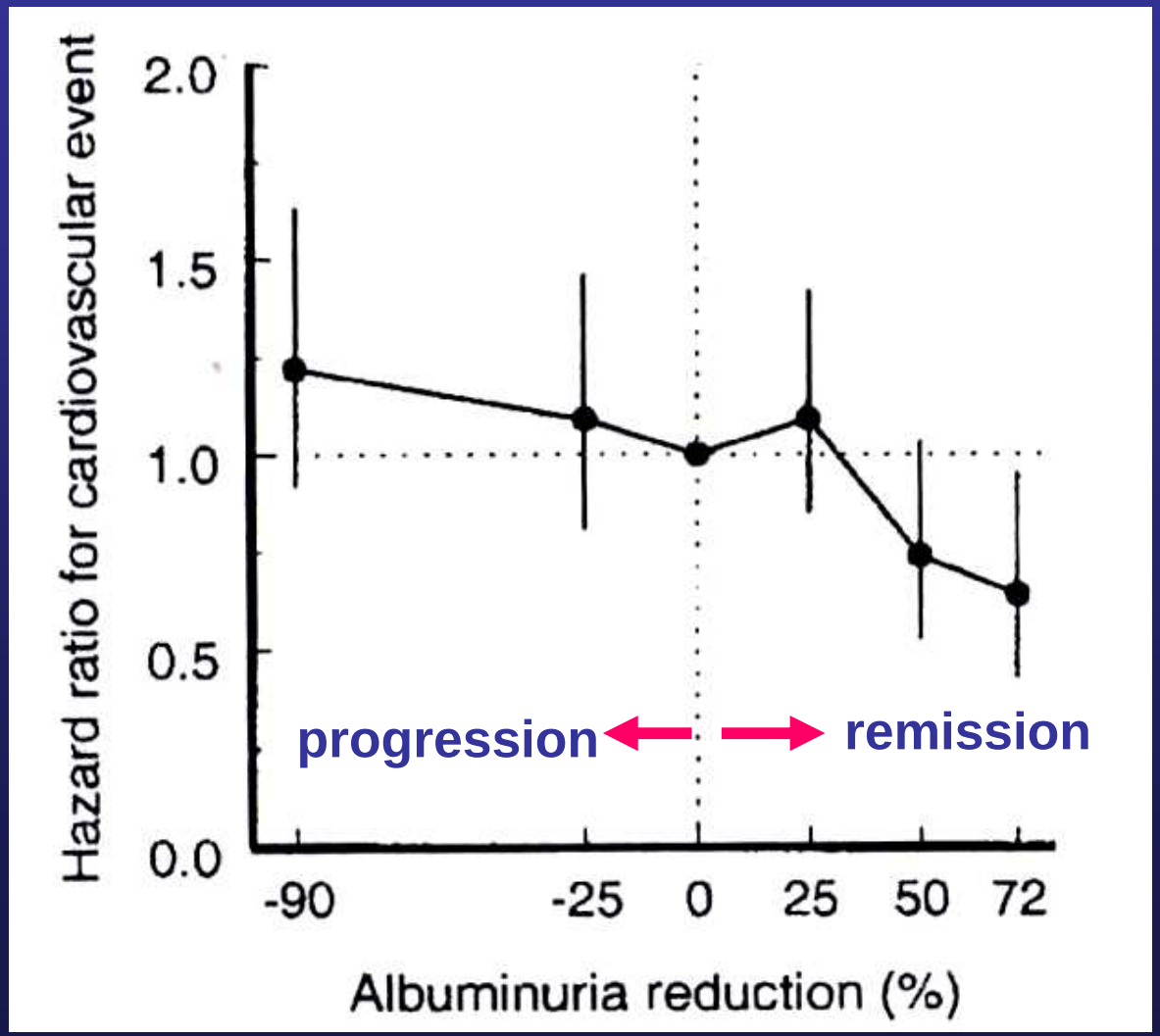


RR: adjusted risk reduction

*** p = 0,005, † p = 0,007**

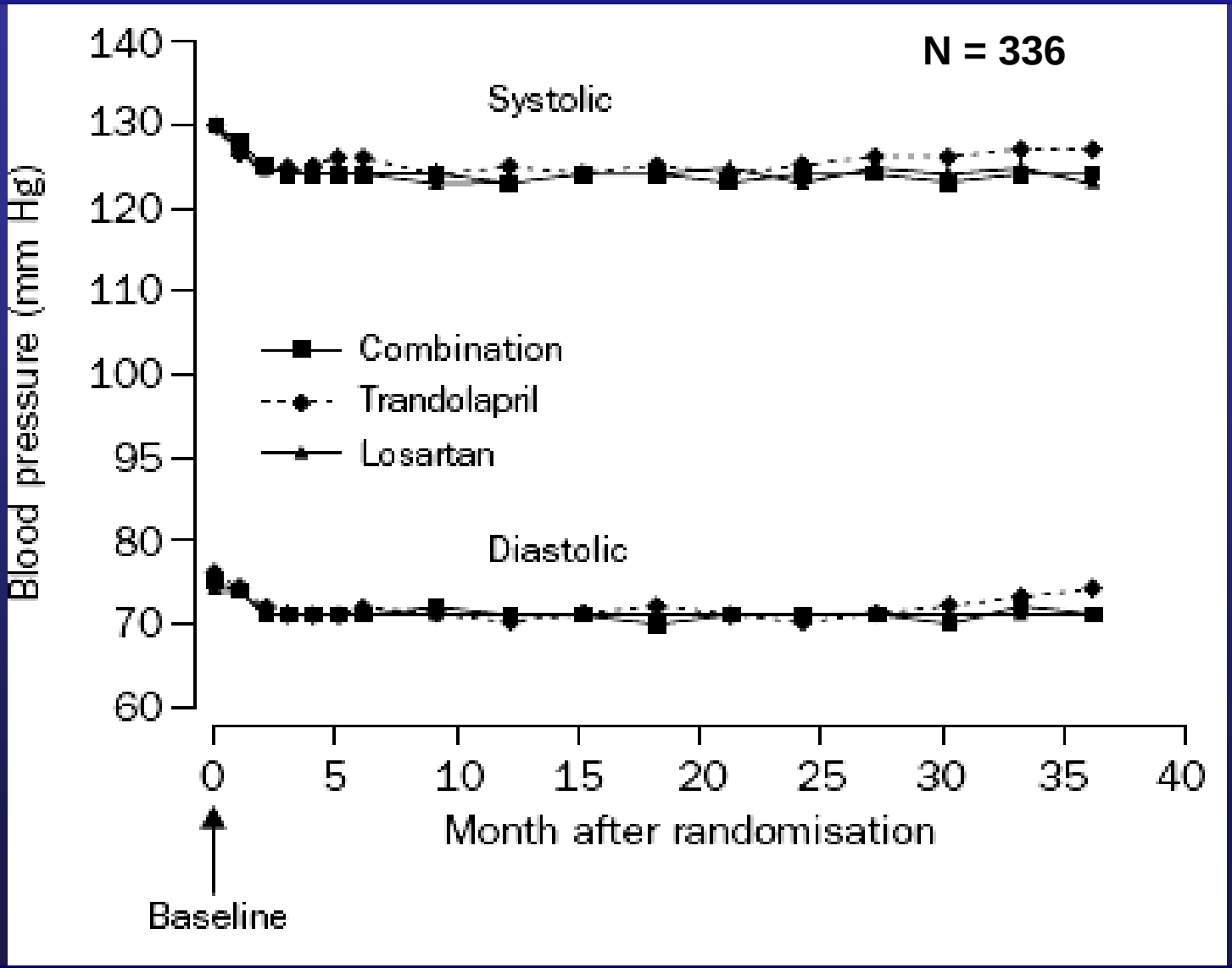
AASK Study Group. *JAMA*. 2001;285:2719–2728.

Reduction in albuminuria translates to reduction in cardiovascular events: RENAAL



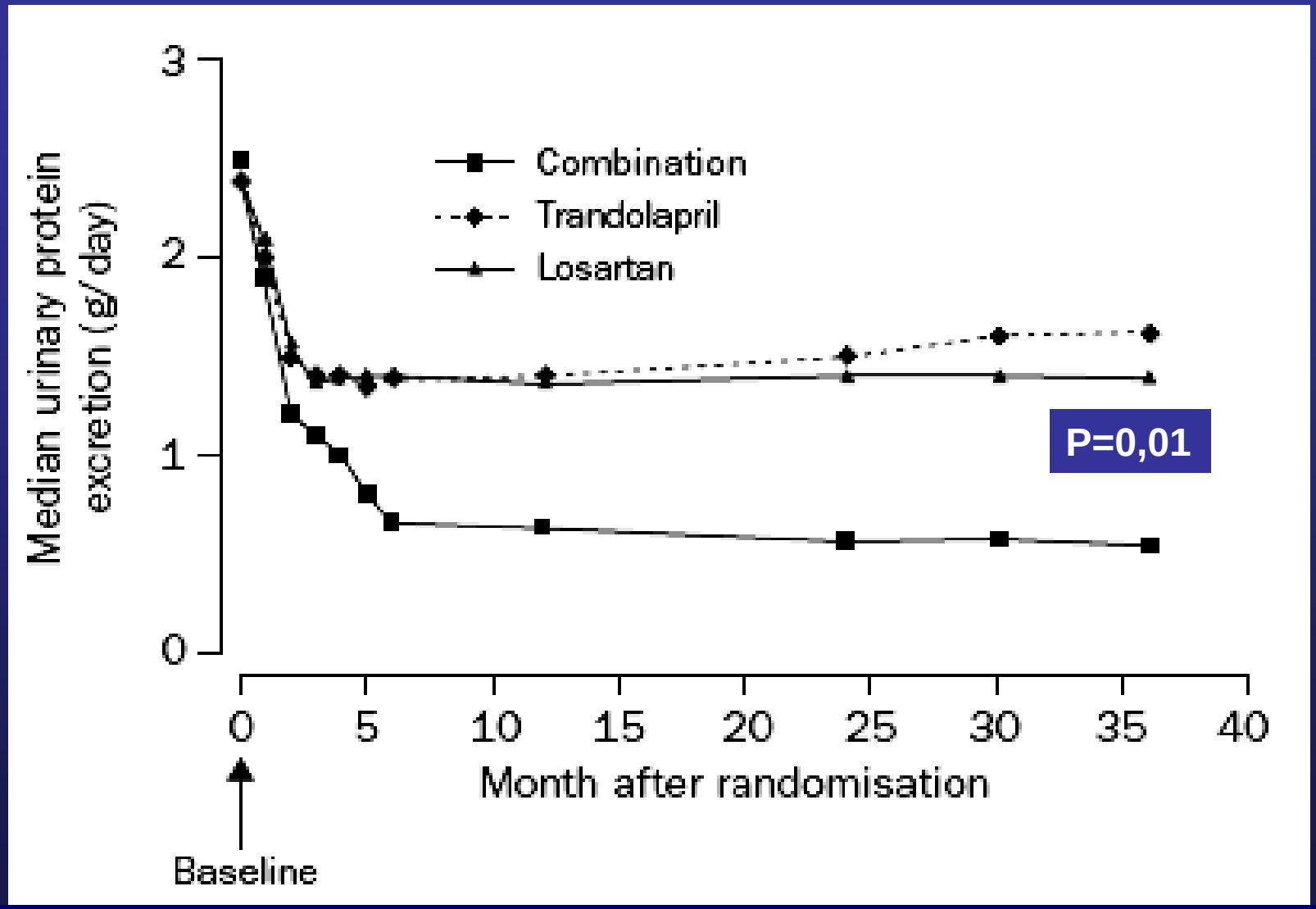
n=1513, Circulation 2004;110:921

Combined ACEi and ARB therapy in non-diabetic renal disease with proteinuria: Cooperate



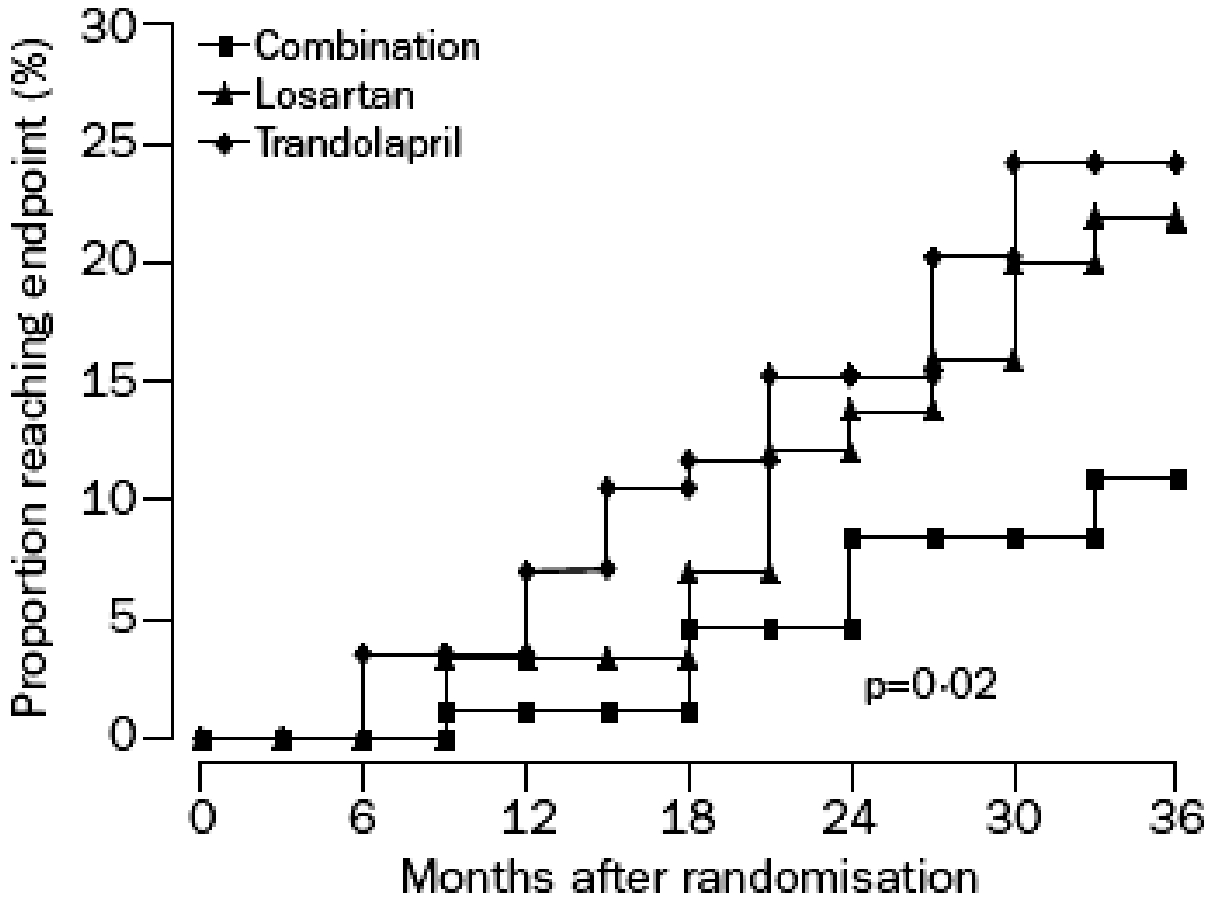
Nakao N. The Lancet 2003; 361:117

Cooperate: proteinuria



Nakao N. The Lancet 2003; 361:117

Cooperate: renal function



Number at risk

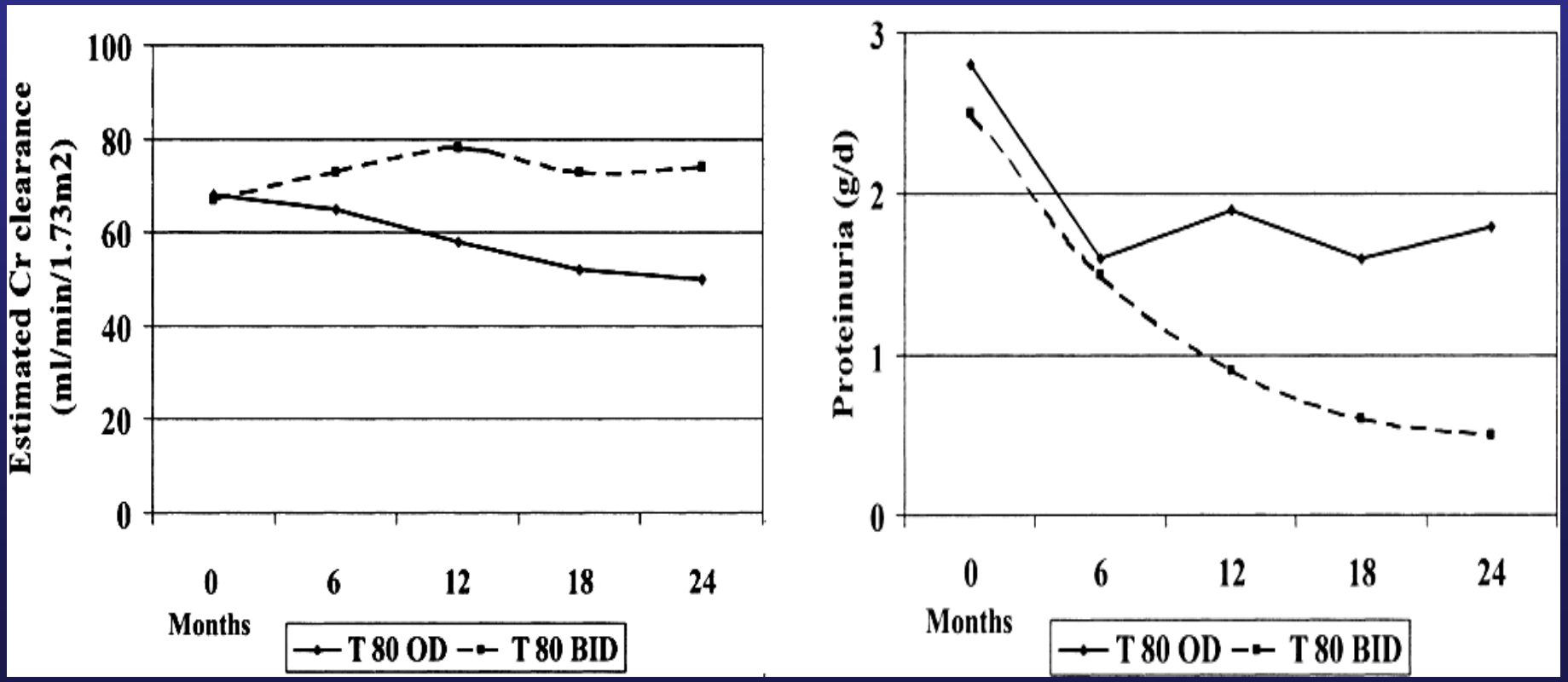
Losartan	89	88	84	79	65	59	47
Trandolapril	86	85	83	75	72	63	58
Combination	88	87	86	83	76	73	67

Nakao N. The Lancet 2003; 361:117

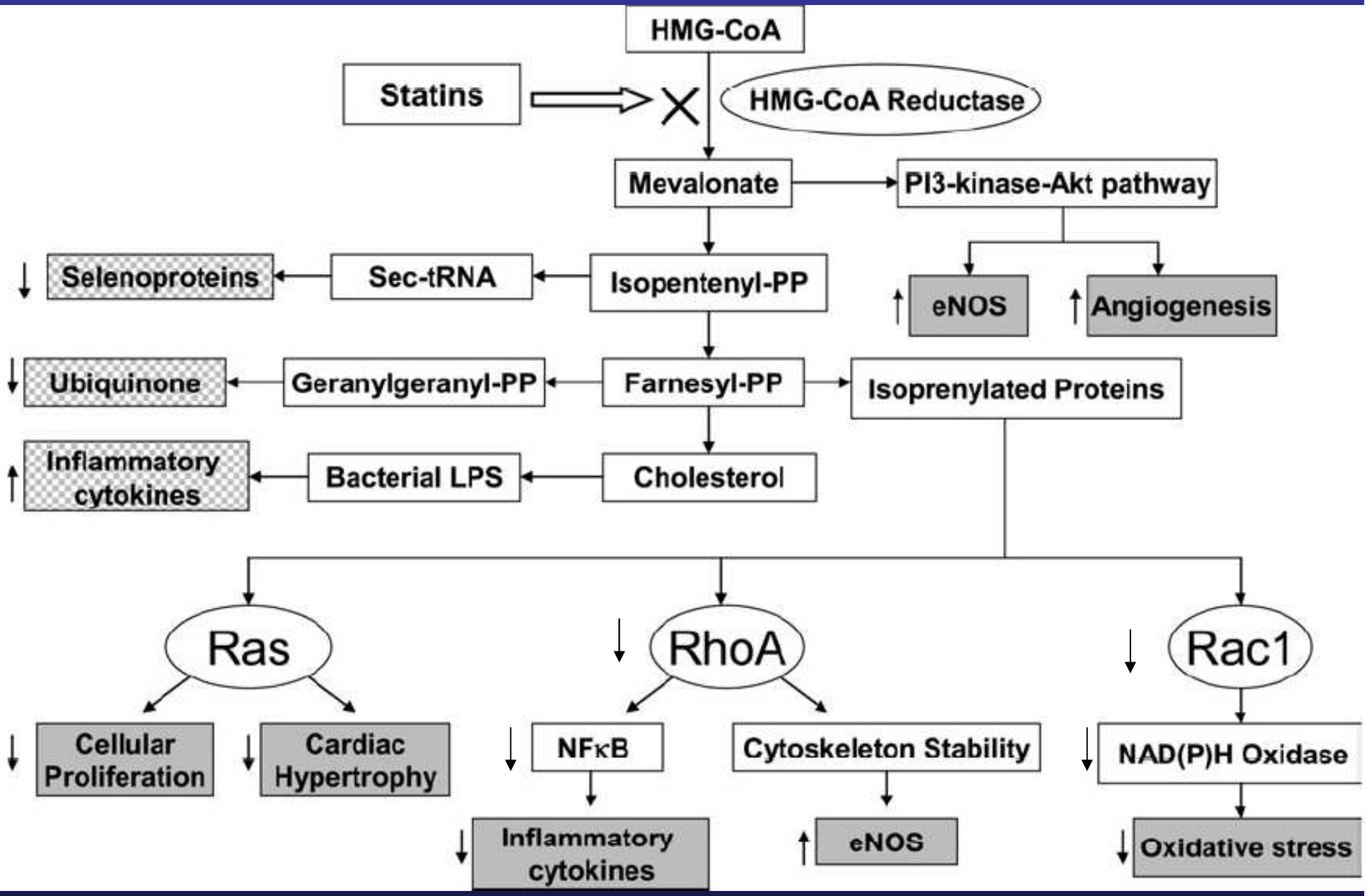
Supramaximal ARB dosing

Non-diabetic renal disease with proteinuria,
n=78, F/U: 2 yrs, Telmisartan 80 mg/d vs 160 mg/d

P< 0,01 **P< 0,01**



AJKD 2005;46:1074


HMG-CoA
Statins
HMG-CoA Reductase
Mevalonate
PI3-kinase-Akt pathway
Selenoproteins
Sec-tRNA
Isopentenyl-PP
eNOS
Angiogenesis
Ubiquinone
Geranylgeranyl-PP
Farnesyl-PP
Isoprenylated Proteins
Inflammatory cytokines
Bacterial LPS
Cholesterol
Ras
RhoA
Rac1
Cellular Proliferation
Cardiac Hypertrophy
NFκB
Cytoskeleton Stability
NAD(P)H Oxidase
Inflammatory cytokines
eNOS
Oxidative stress

Simvastatin maintains steady patterns of GFR and improves AER in type II diabetes

N = 86, MAU, HT

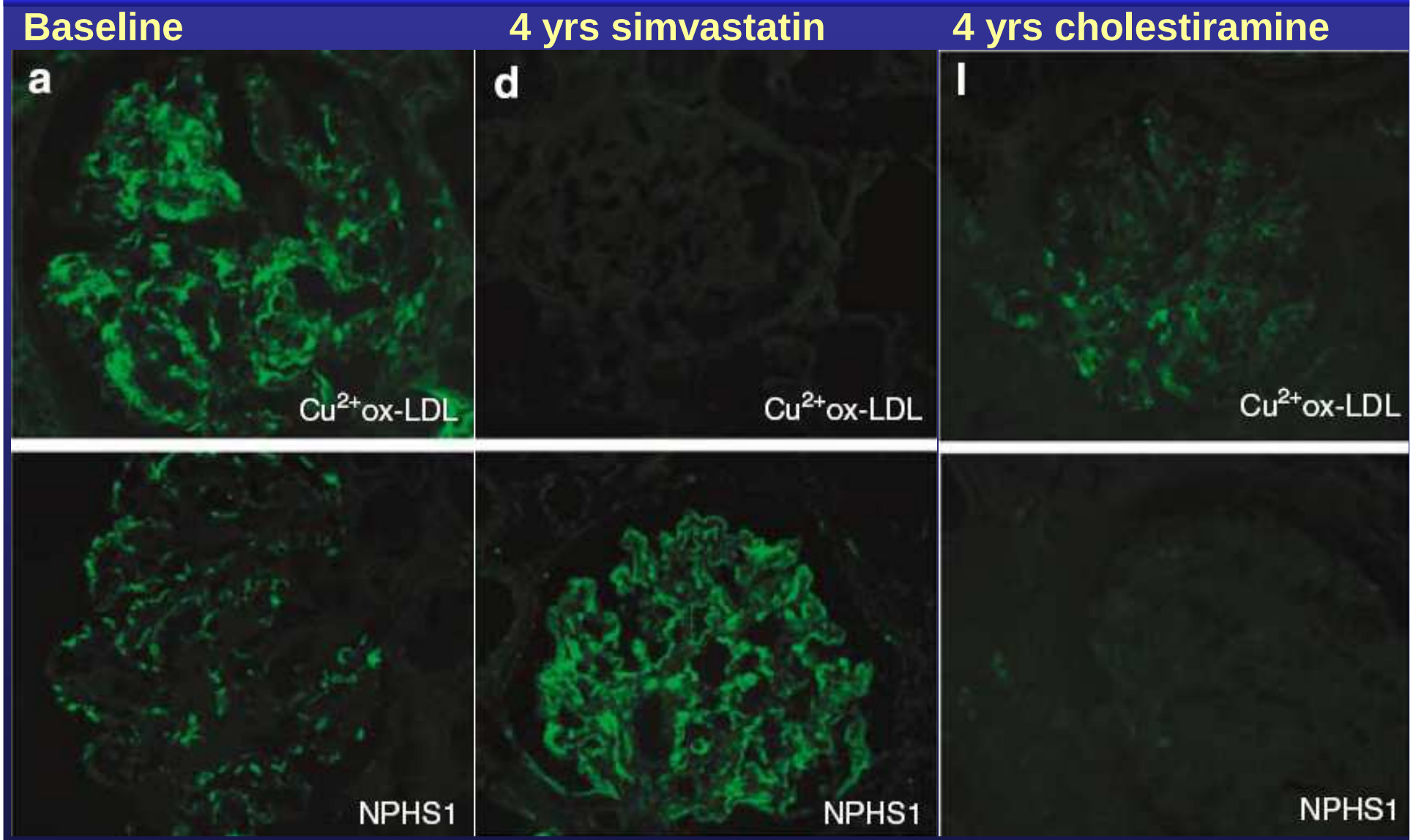
ACE, BB, thiazide + simvastatin vs cholestiramin

F/U: 4 yrs

	GFR (ml/min/1.73m^2)	AER (μg/mg)	Normo	Prot.
Simvastatin				
B	91 ± 8	77 (31–259)	—	—
4 years	90 ± 7	40* (10–319)	29%	4%
Cholestyramine				
B	90 ± 7	88 (34–261)	—	—
4 years	79 ± 8*,**	81 (17–399)	8%**	15%**

Tonolo G. Kidney Int 2006;70:177.

Simvastatin improves expression of slit diaphragm proteins in type II diabetes



Tonolo G. Kidney Int 2006;70:177.

Thiazolidindiones

Rosiglitazon, pioglitazon

Systemic effects

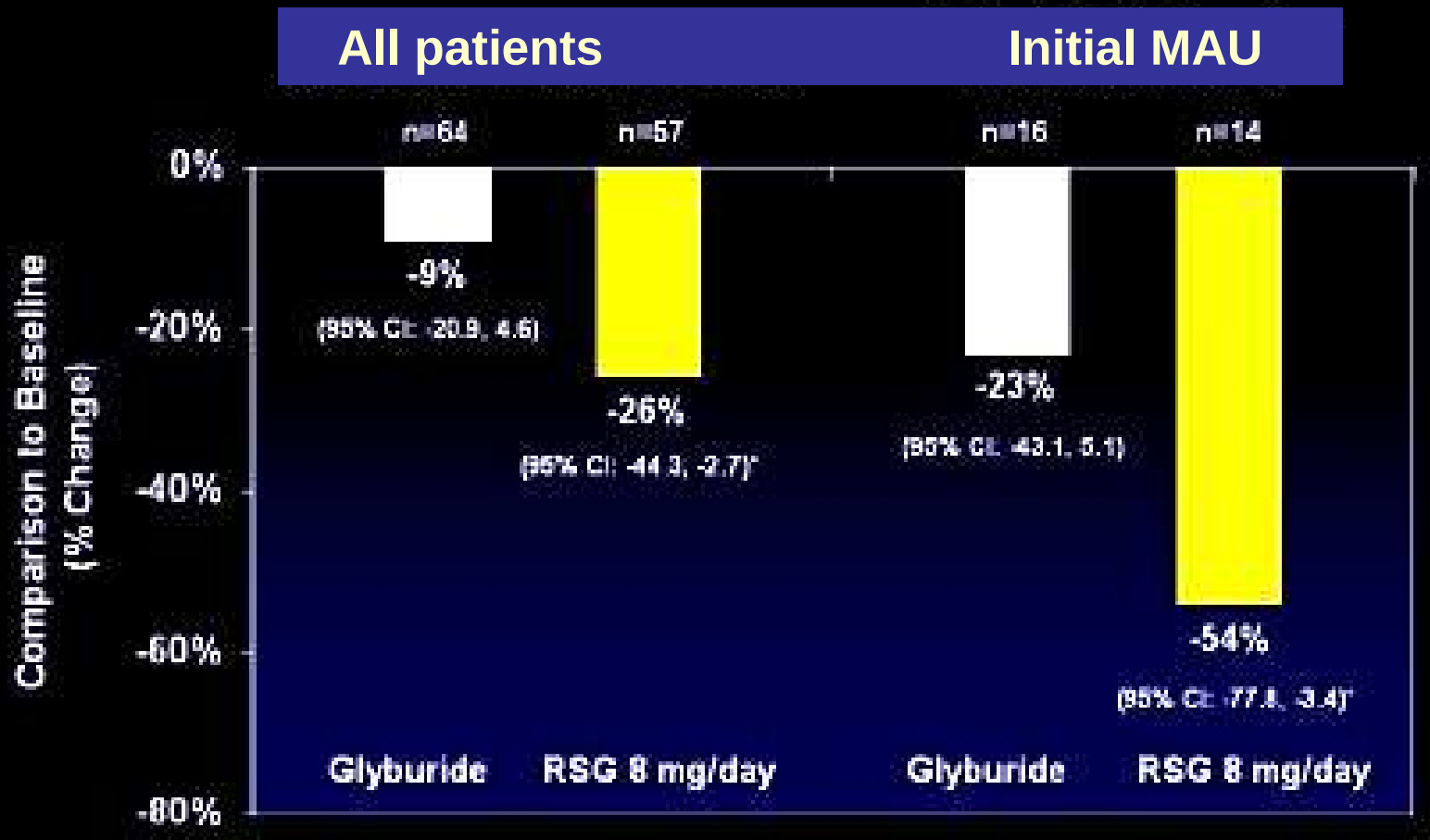
- Hyperinzulinemia
- Hyperglycemia
- Blood pressure
- Endothel dysfunction
- TNF-alfa
- Free fatty acids

Renal effects

- Inflammation
- PAI-1 expression
- RAS and ET-1 effects
- TGF-β expression
- Extracellular matrix
- Lipid toxicity
- Renal cell proliferation

Albuminuria, fibrosis

Rosiglitazon and albuminuria



*p<0.05 vs. glyburide

Bakris et al. Diabetologia 1999;42(Suppl 1):A229, Abs 865

Multifactorial therapeutic intervention

Lifestile

- Stop smoking
- Attain normal body mass index (BMI < 25 kg/m^2)
- Reduce sodium intake (24 h urine Na < 80 mmol)

Blood pressure

- Goal: < 130/80 Hgmm
  < 125/75 Hgmm in case of > 1g/day proteinuria
- ACE inhibitor or Angiotensin Receptor Blocker
  (in combination with Diuretic, CaCB, vasodilating beta blocker)
- Combine ACEi AND ARB in case of > 1g/day proteinuria
  (or use supramaximal ACEi or ARB doses)

Statins

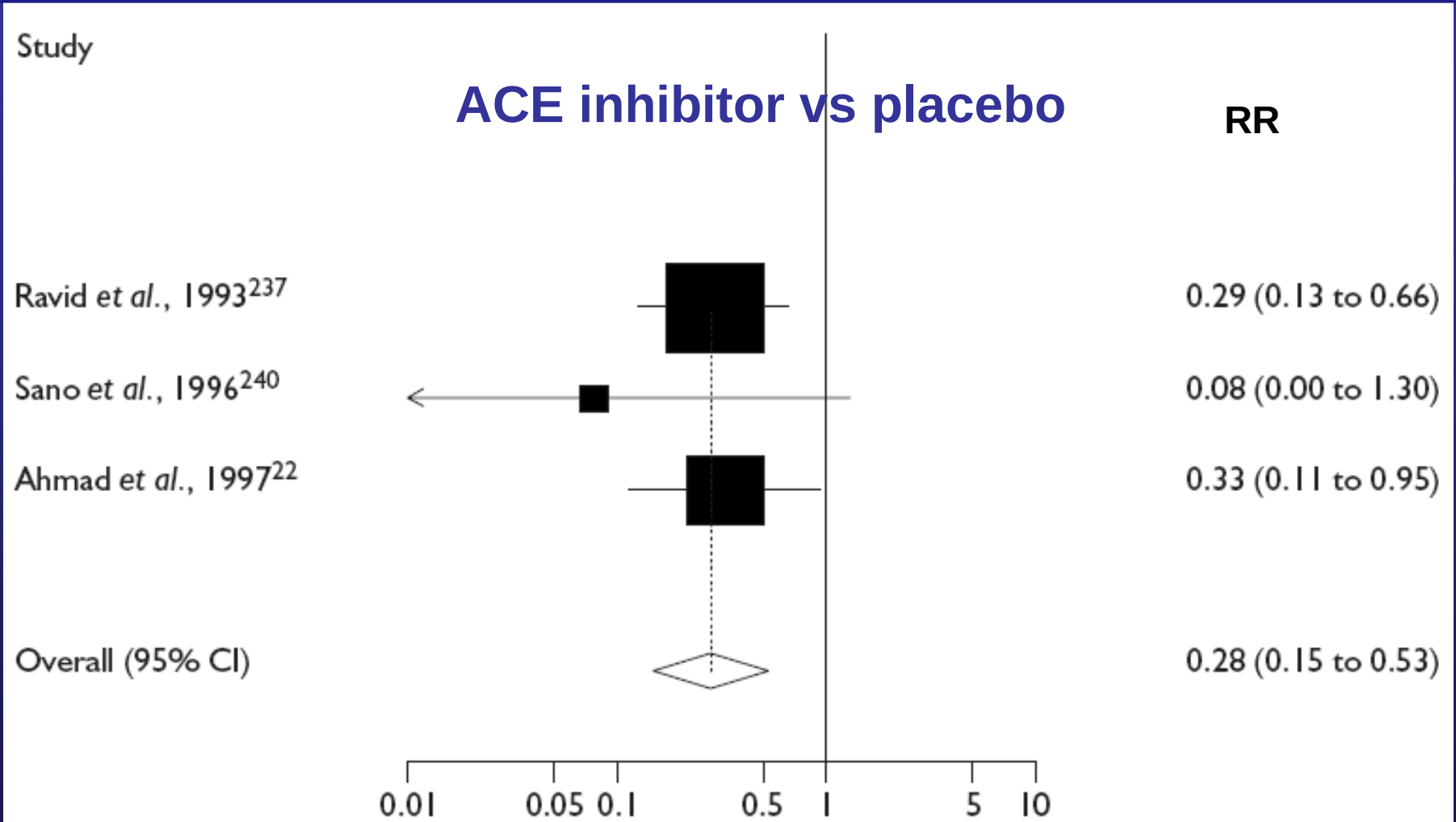
- LDL goal < 2,6 mmol/l, very high risk patients: < 1,8 mmol/l

Strict glycemic control

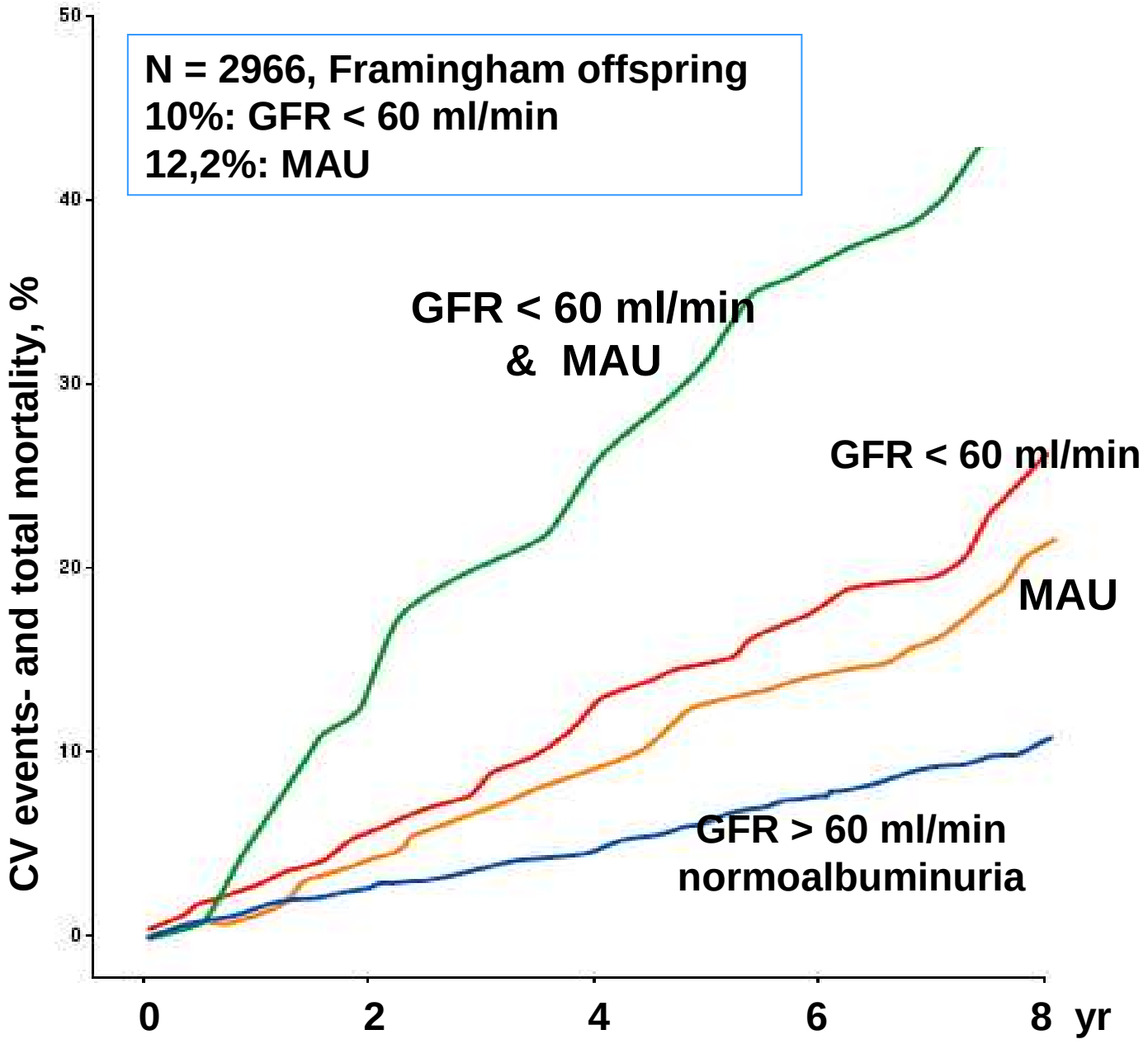
- HBA1c goal < 7 % (T2DM); HBA1c < 6,5 % (T1DM)
- Isulin sensitizers, thiazolidinedions

Aspirin

Secondary prevention of proteinuria in normotensive T2DM patients with MAU



Newman D. Health Technology Assessment 2005; Vol. 9



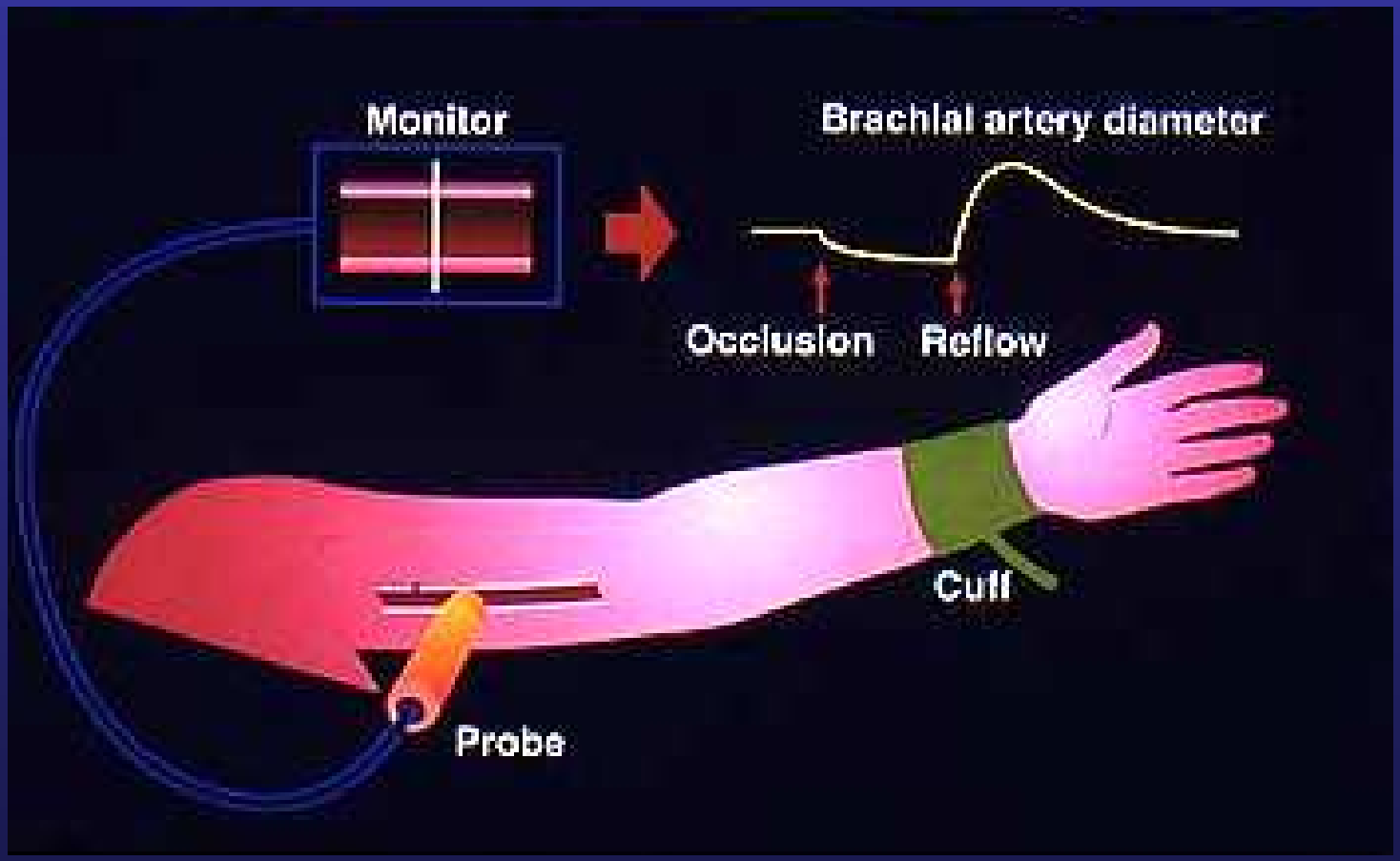
Levey A, Kidney Int, 2005;67:2089

Effect of therapy with ACE inhibitors/ARBs vs other antihypertensive drugs on renal disease progression

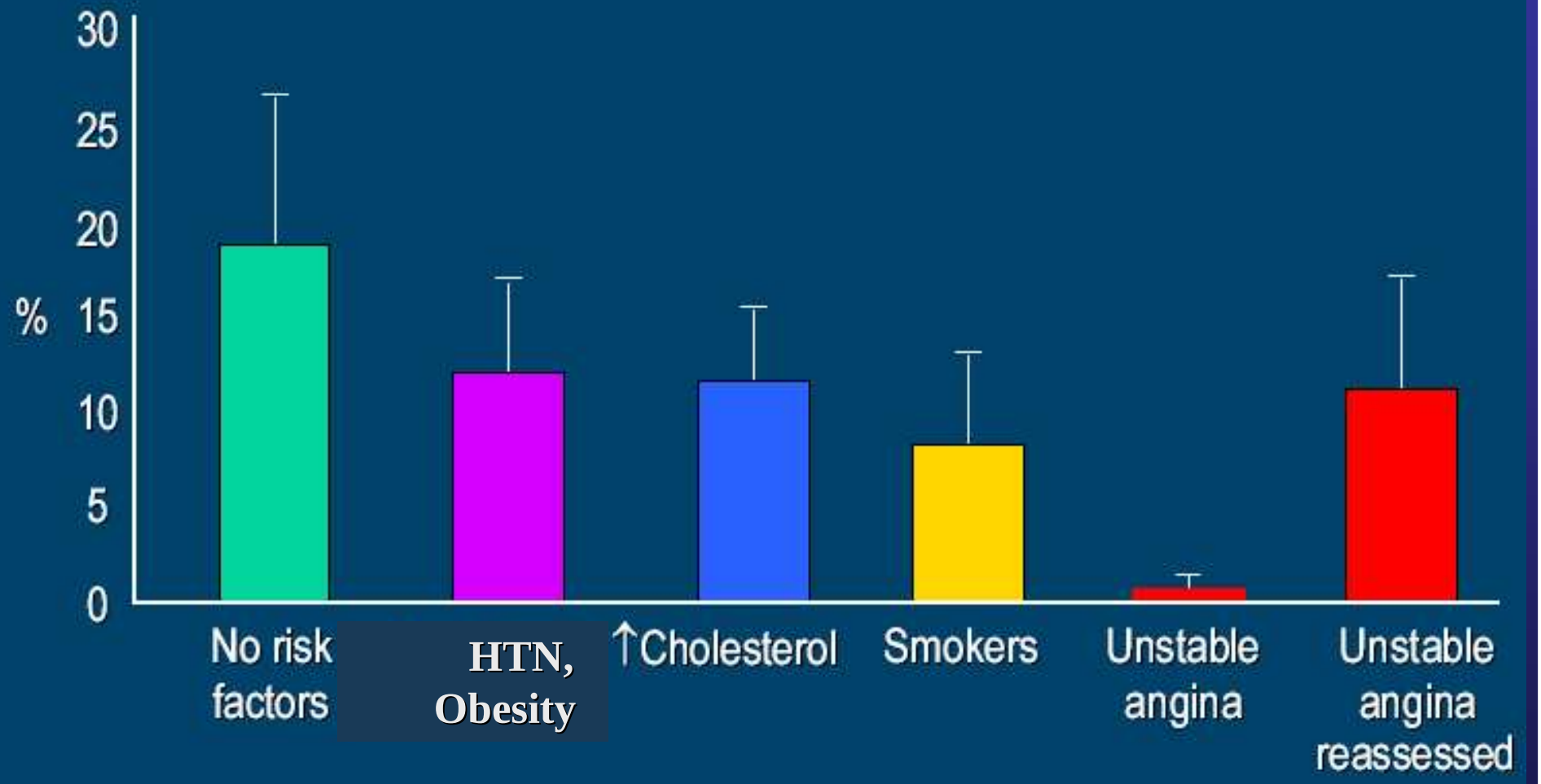
End point	Relative risk (95% CI)	p
Doubling of creatinine 11 studies N = 3376	0.71 (0.49-1.04)	0.07
End-stage renal disease 13 studies N = 37089	0.87 (0.75-0.99)	0.04

Casas JP et al. *Lancet* 2005; 366: 2026-2033

Flow-mediated endothelium-dependent relaxation

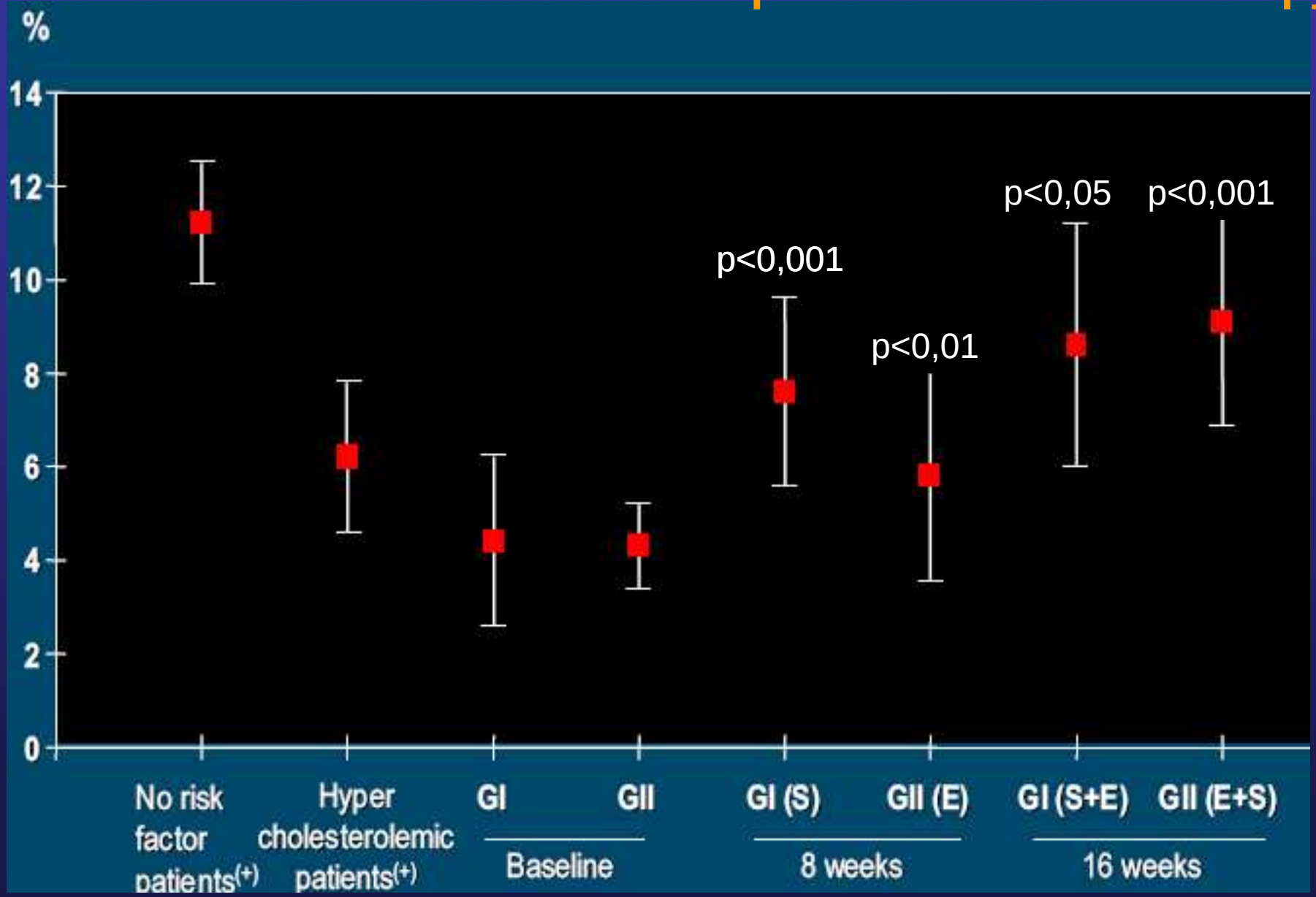


Impaired endothelial function in unstable angina



Esper RJ, et al.Clin Cardiol 1999, **22:**699-703.

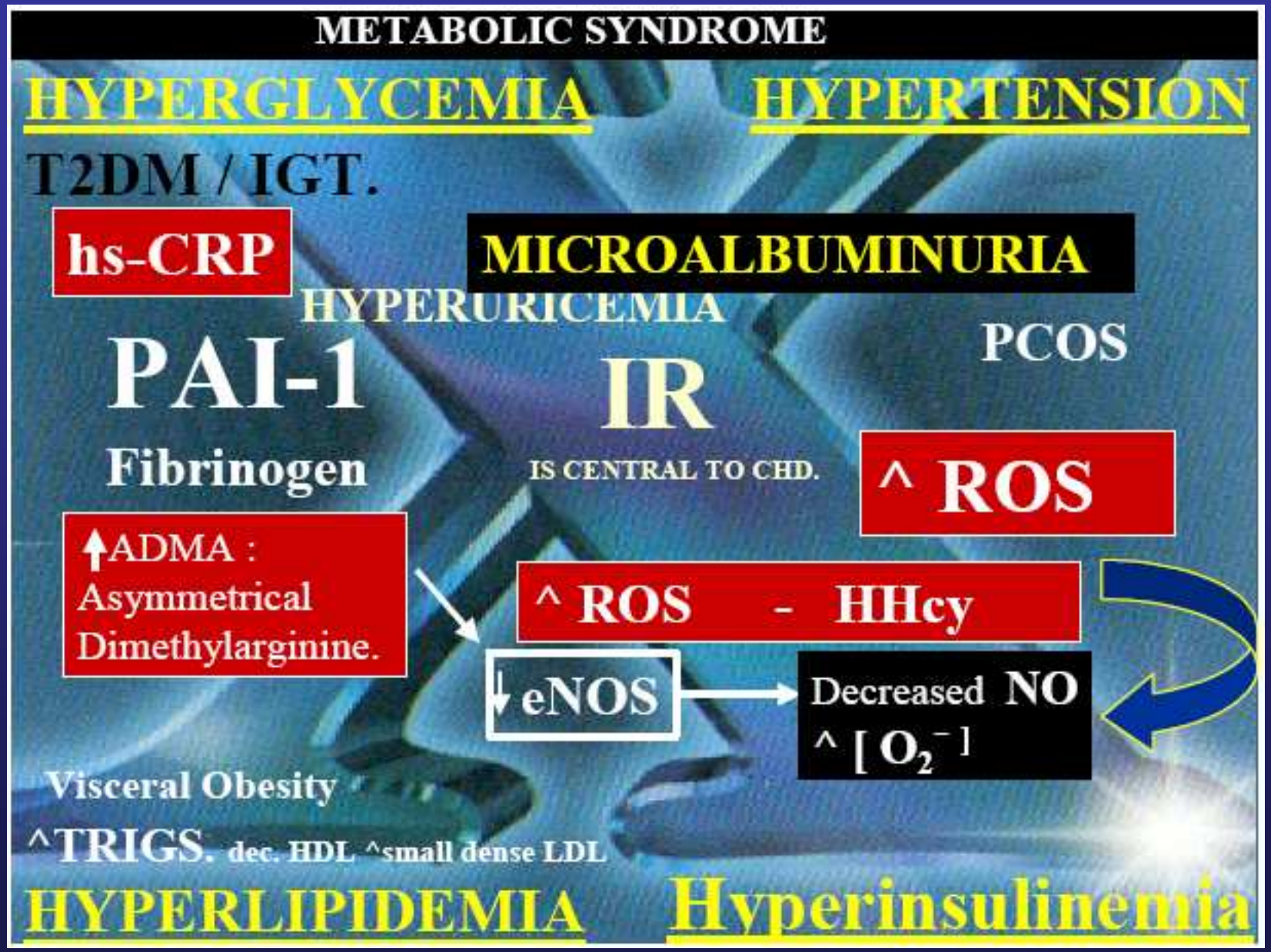
Endothelium dependent vasodilation in hypercholesterolemic patients with CAD: effects of enalapril or simvastatin therapy



Esper RJ,et al. *Am Heart J* 2000,140:684-689.

Table 9: THE RAAS ACRONYM: GLOBAL RISK REDUCTION

R	**Reductase inhibitors** (HMG-CoA). Decreasing modified LDL-cholesterol, i.e. oxidized, acetylated LDL-cholesterol. Decreasing triglycerides and increasing HDL-cholesterol Improving endothelial cell dysfunction. **Restoring** the abnormal Lipoprotein fractions. Thus, decreasing the redox and oxidative stress to the arterial vessel wall and myocardium. **Redox stress reduction.**
A	**AngII inhibition or blockade: ACEi**-prils. **ARBS**-sartans. Both inhibiting the effect of angiotensin-II locally as well as systemically. Affecting hemodynamic stress through their antihypertensive effect as well as the deleterious effects of angiotensin II on cells at the local level – injurious stimuli -decreasing the stimulus for $O_2^{\bullet}$ production. Decreasing the **A-FLIGHT** toxicities. Plus the direct-indirect antioxidant effect within the arterial vessel wall and capillary. **Antioxidant** effects. **Aspirin** antiplatelet, anti-inflammatory effect. **Adrenergic** (non-selective blockade) in addition to its blockade of Prorenin → Renin **Amlodipine** with its calcium channel blocking antihypertensive effect, in addition to its direct antioxidant effects. **Redox stress reduction.**
A	**Aggressive** control of diabetes to HbA_{1c} of less than 7. (This usually requires combination therapy with the use of: Insulin secretagogues, insulin sensitizers (thiazolidinediones), biguanides, alpha-glucosidase inhibitors, and ultimately exogenous insulin.) [36-38] Decreasing modified LDL cholesterol, i.e. glycated – glycoxidated LDL cholesterol. Improving endothelial cell dysfunction. Also decreasing glucotoxicity and the oxidative – redox stress to the intima and pancreatic islet. **Aggressive** control of blood pressure, which usually requires combination therapy, including thiazide diuretics to attain JNC 7 guidelines. **Aggressive** control of Hcy with folic acid and its associated pleiotropic positive effect on re-coupling the eNOS reaction by restoring the activity of the BH4 cofactor to run the eNOS reaction and once again produce eNO, as well as, its direct antioxidant effects: BH4 and eNOS stabilization **Redox stress reduction.**
S	**Statins**. Improving plaque stability (pleiotropic effects) independent of cholesterol lowering. Improving endothelial cell dysfunction. Plus, the direct – indirect antioxidant anti-inflammatory effects within the islet and the arterial vessel wall promoting stabilization of the unstable, vulnerable islet and the arterial vessel wall. **Style**: Lifestyle modification: lose weight, exercise, and change eating habits. **S**top **S**moking **Redox stress reduction**



Hayden M. Nutrition Journal 2004, **3**:4

THE ROS - INFLAMMATORY CYCLE

$O_2^{\bullet}$
-OH•
H2O2
HCLO

A-FLIGHT →

Oxidative Stress (upstream from inflammation)

Redox Stress: A-FLIGHT

Reactive **O**xygen Species

↓

NF kappa B - redox sensitive

hs-CRP ← Cytokines → TNF alpha IL-6, IL-8
Selectins
CAMs, MCP-1

hs-CRP

Inflammation

HCLO

Macrophage derived.

eNO is an inflammatory cycle breaking – chain breaking -- antiinflammatory antioxidant – wondrous gas !

ACE i ,Statins, Folic Acid and PPARS break the inflammatory cycle

Hcy a competitive inhibitor of PPAR alpha agonist: ciprofibrate and PPAR gamma agonist: 15d-PGJ_2

PPAR
Alpha
Gamma

Hcy
Hcy

TZDs:

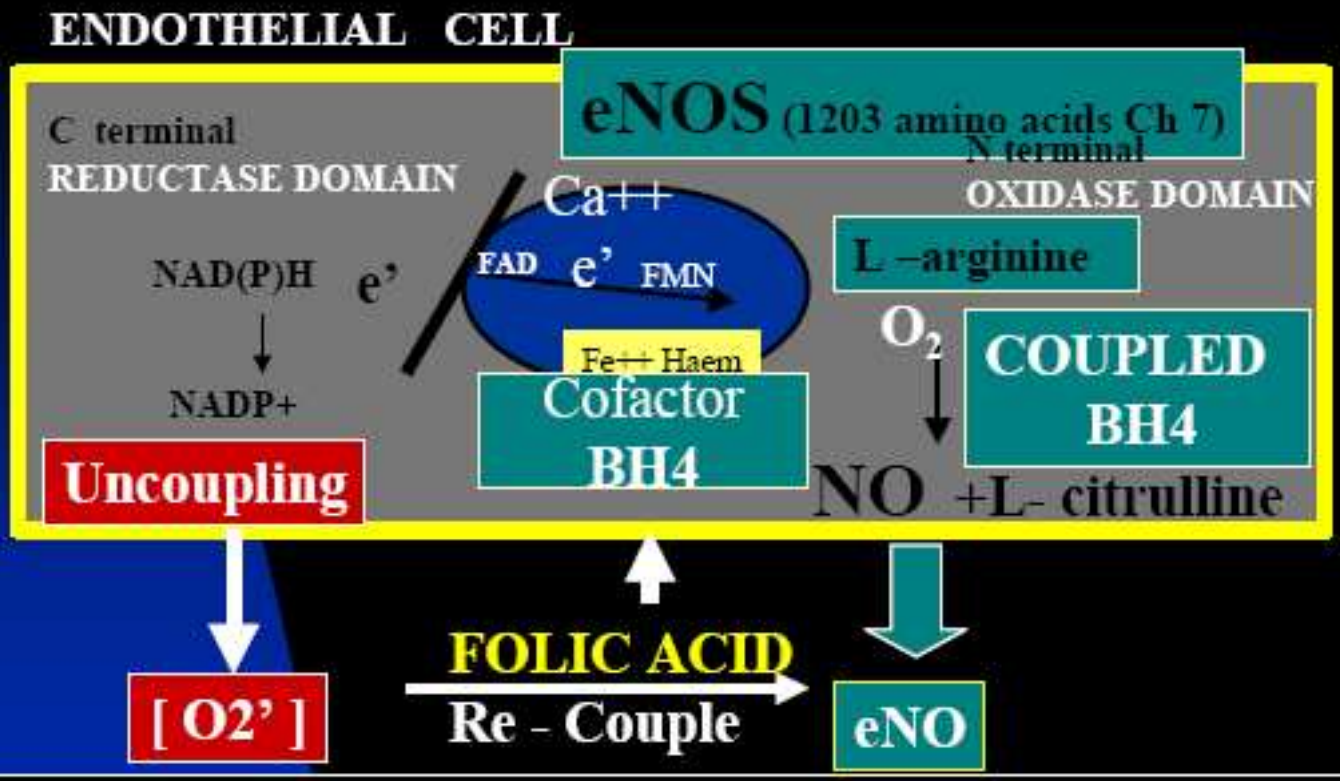
Decreased effect of PPAR alpha and gamma.

ROS

All contributing to Endothelial Cell Dysfunction

No CBS enzyme in Vascular cells.
Relative Ecnothelial Folate Deficiency.
ROS increasing Hcy.

Diabetes a net producer of: [O2'] Due to an uncoupling of the eNOS enzyme

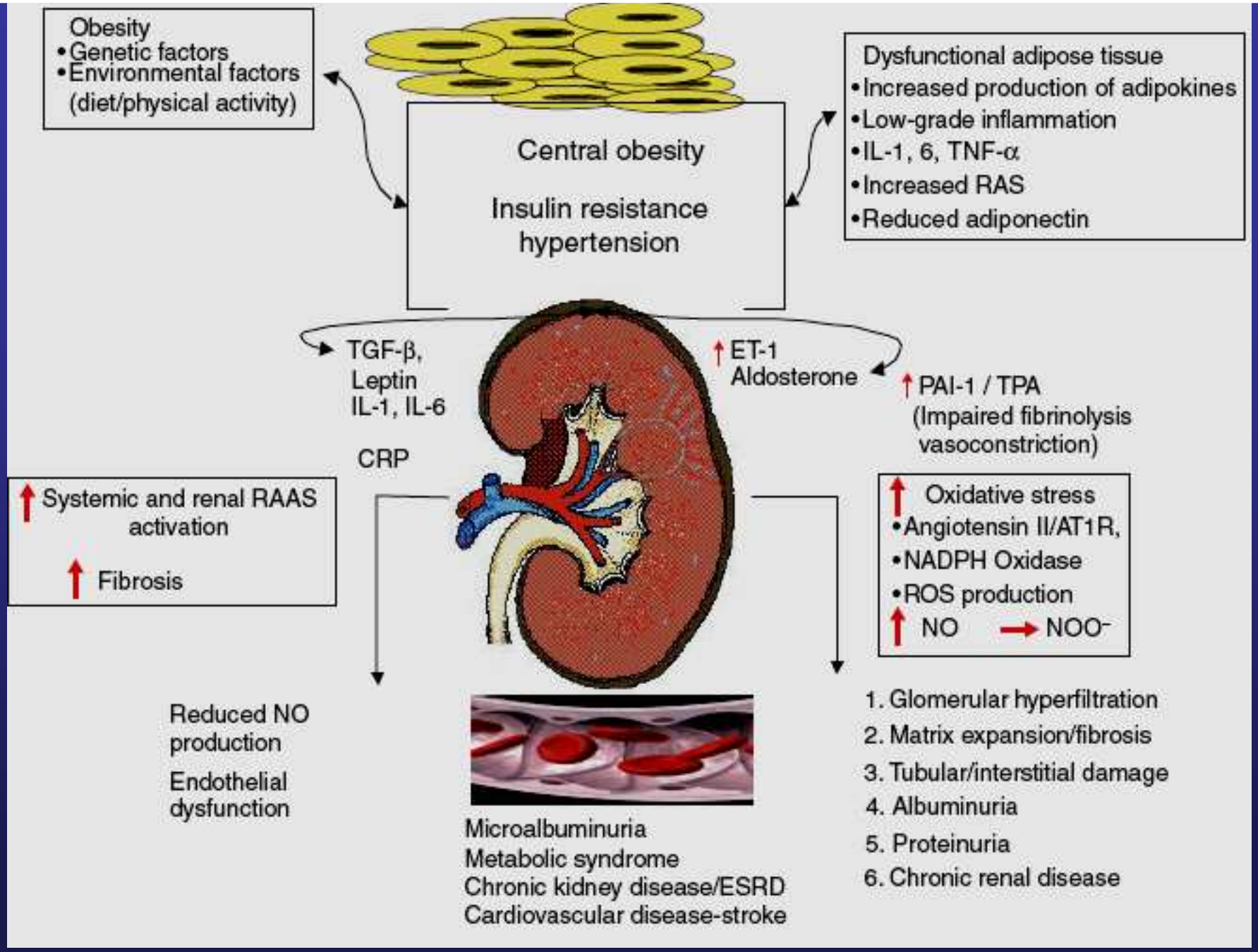


O2 NAD(P)H

ADMA (2) eNOS *Gene Polymorphism or Uncoupling*

(1)L-arginine ——————————→ NO + L-citrulline + NADP+

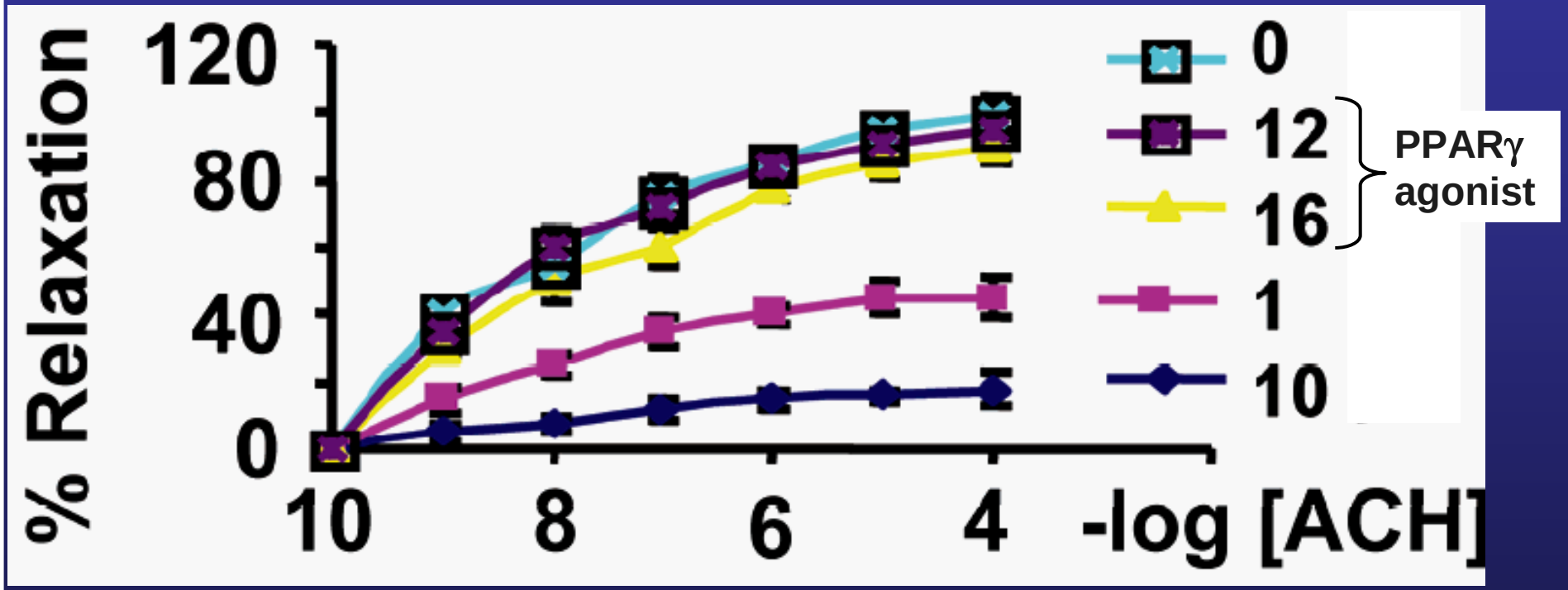
(3) BH4 *Oxidative Stress BH2, BH3*



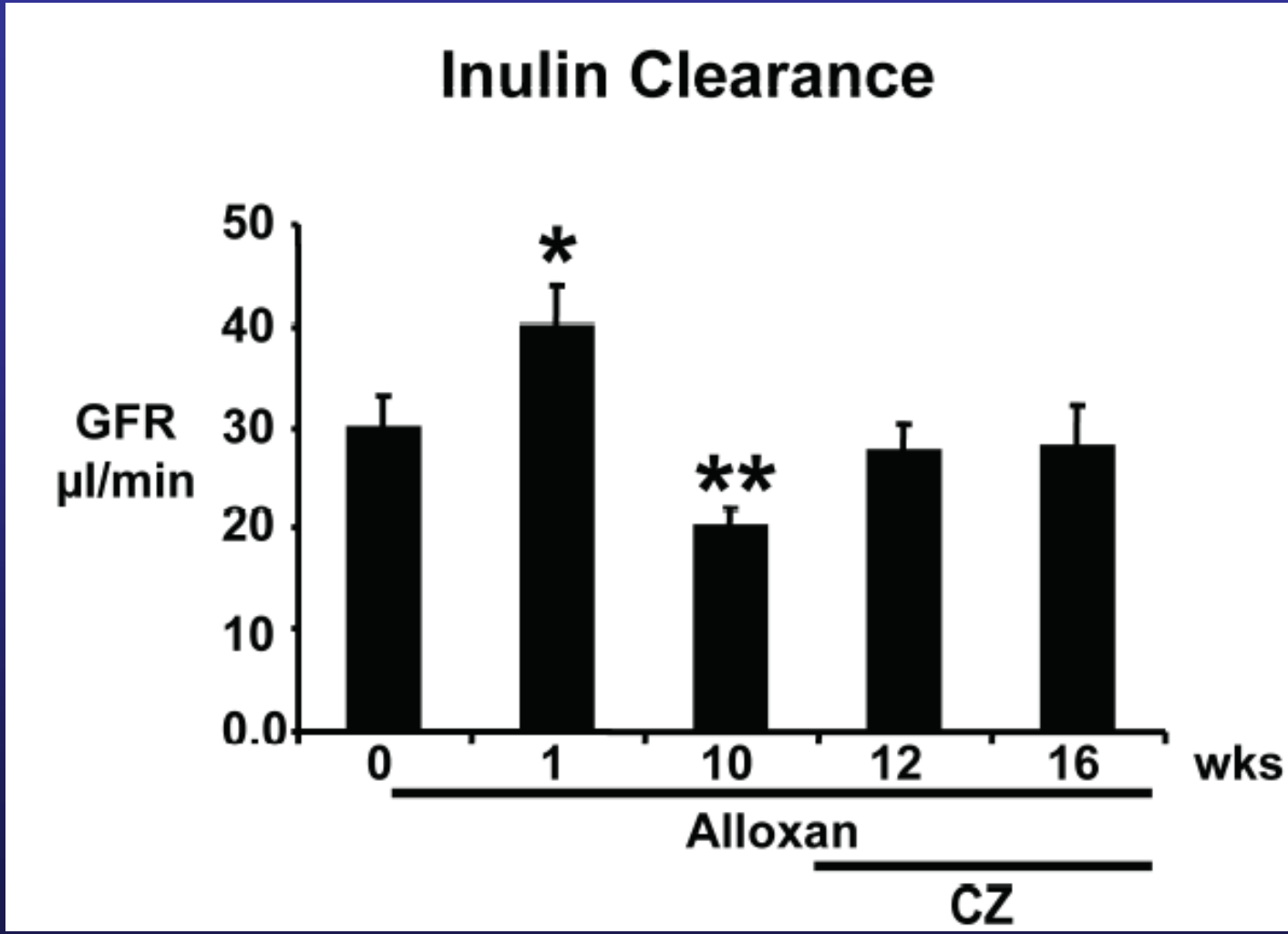
Sowers J. *Kidney International* (2007) **71**, 719–720.

tHCY in micromol/liter	Relative risk of all cause death.	Relative risk of CAD death
< 9	1.0	1.0
9 – 14.9	1.9 (0.7 – 5.1)	2.3 (0.7 – 7.7)
15 – 19.9	2.8 (0.9 – 9.0)	2.5 (0.6 – 10.5)
> 20	4.5 (1.2 – 16.6)	7.8 (1.7 – 35.1)

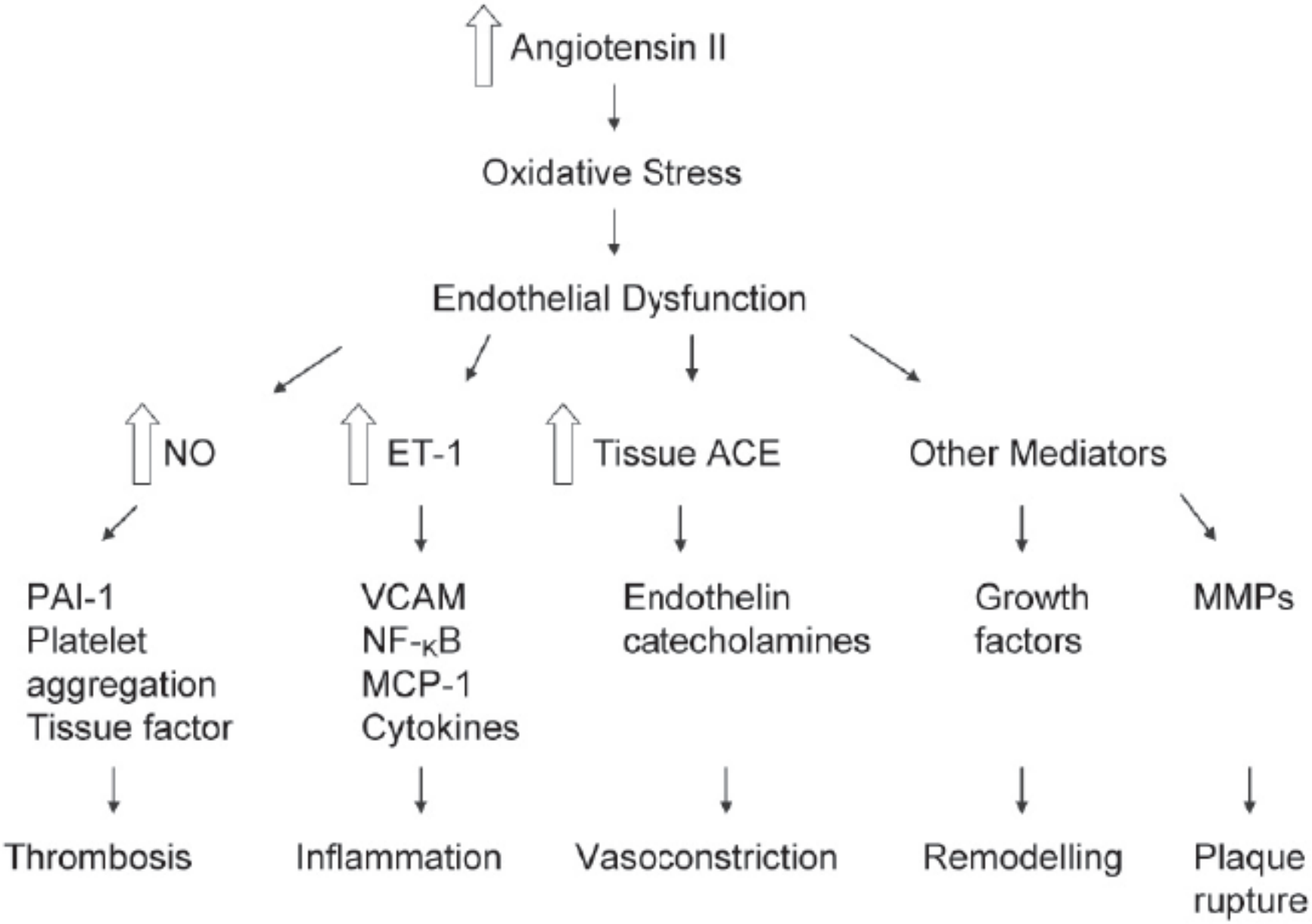
Ridker PM, Morrow DA: *Cardiol Clin* 2003, **21(3):**315-325.

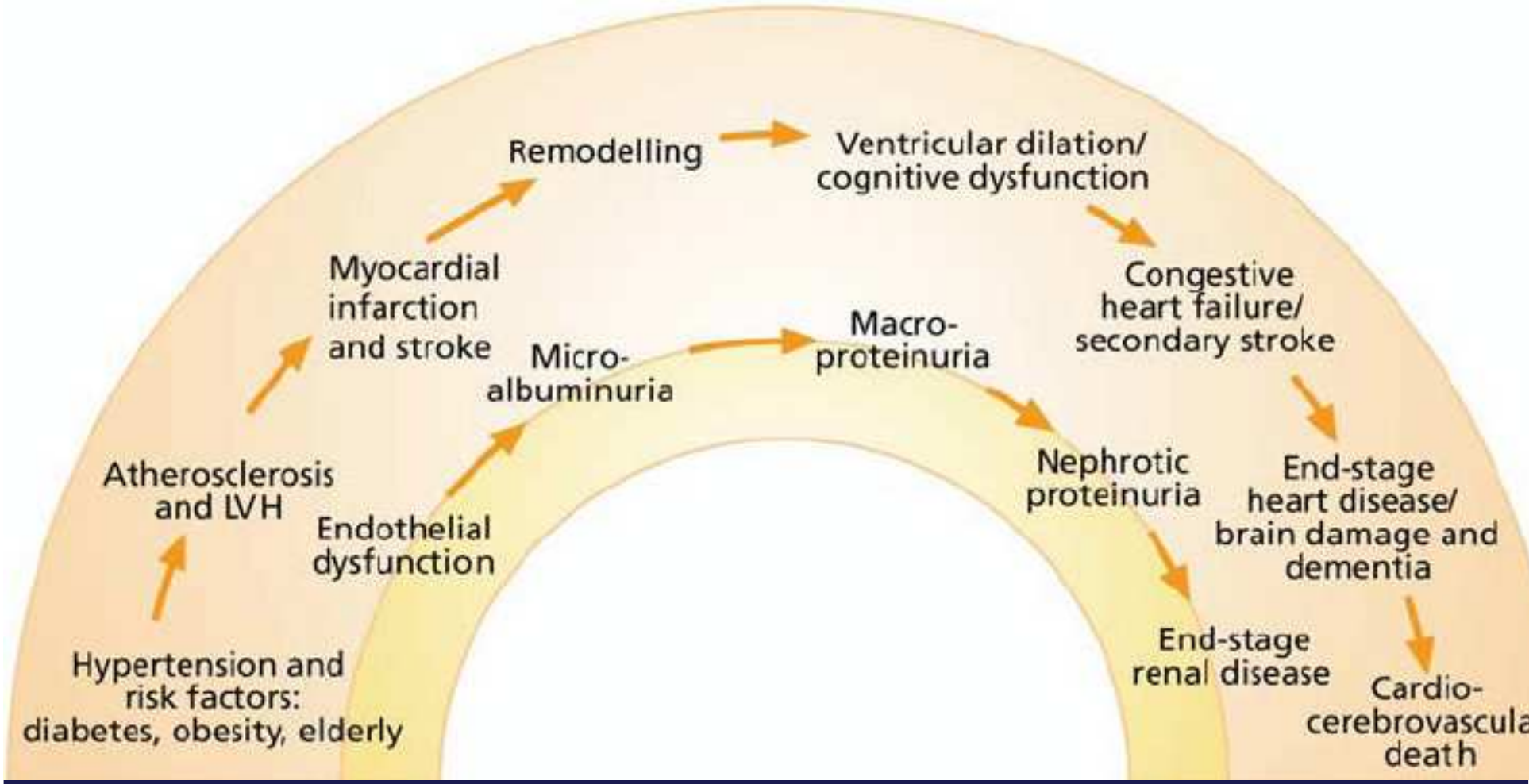


Rodriguez W. Int. J. Biol. Sci. 2008, 4:236.



Rodriguez W. Int. J. Biol. Sci. 2008, 4:236.

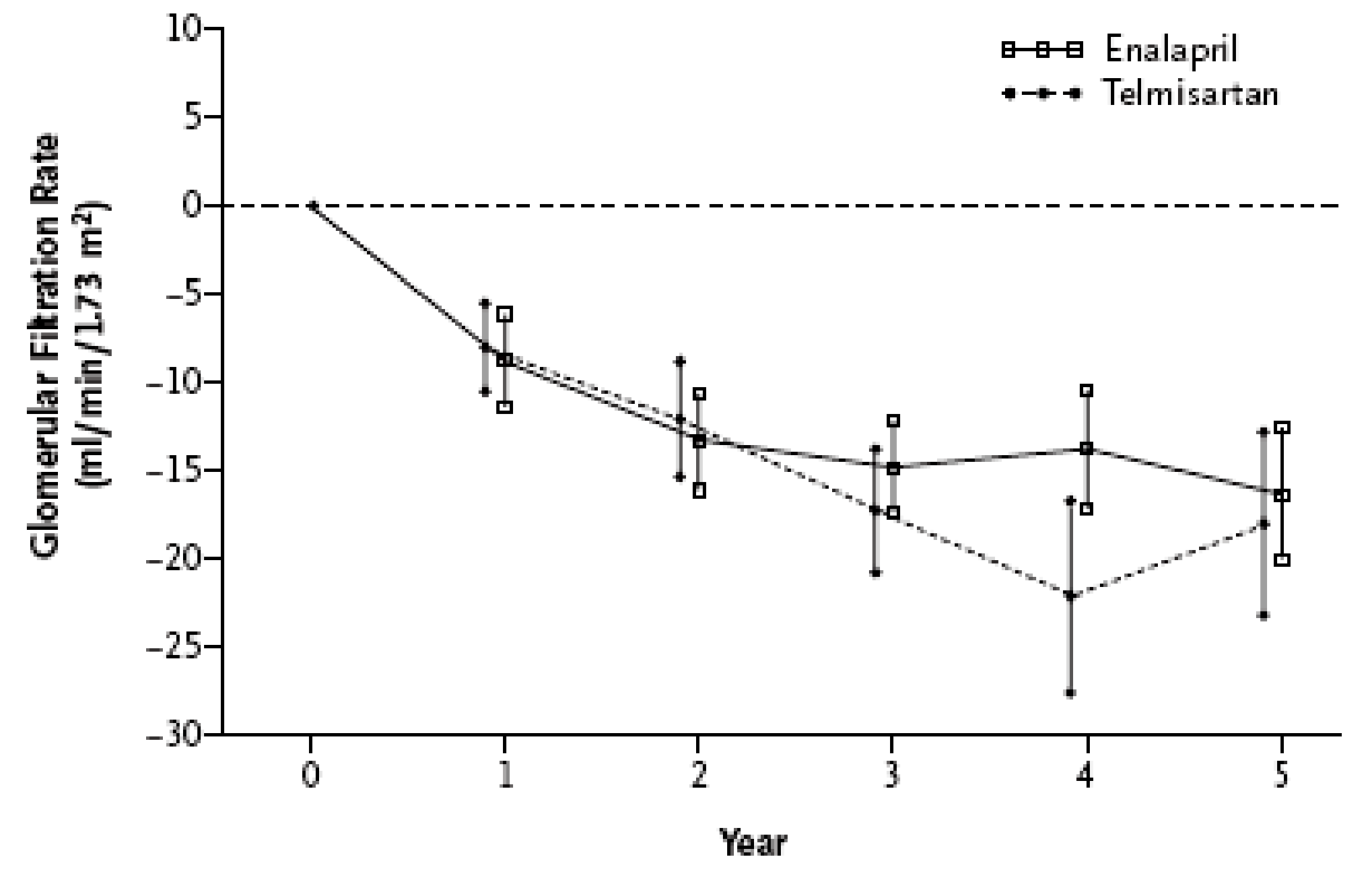

Angiotensin II
Oxidative Stress
Endothelial Dysfunction
NO
ET-1
Tissue ACE
Other Mediators
PAI-1
Platelet
aggregation
Tissue factor
VCAM
NF-κB
MCP-1
Cytokines
Endothelin
catecholamines
Growth
factors
MMPs
Thrombosis
Inflammation
Vasoconstriction
Remodelling
Plaque
rupture

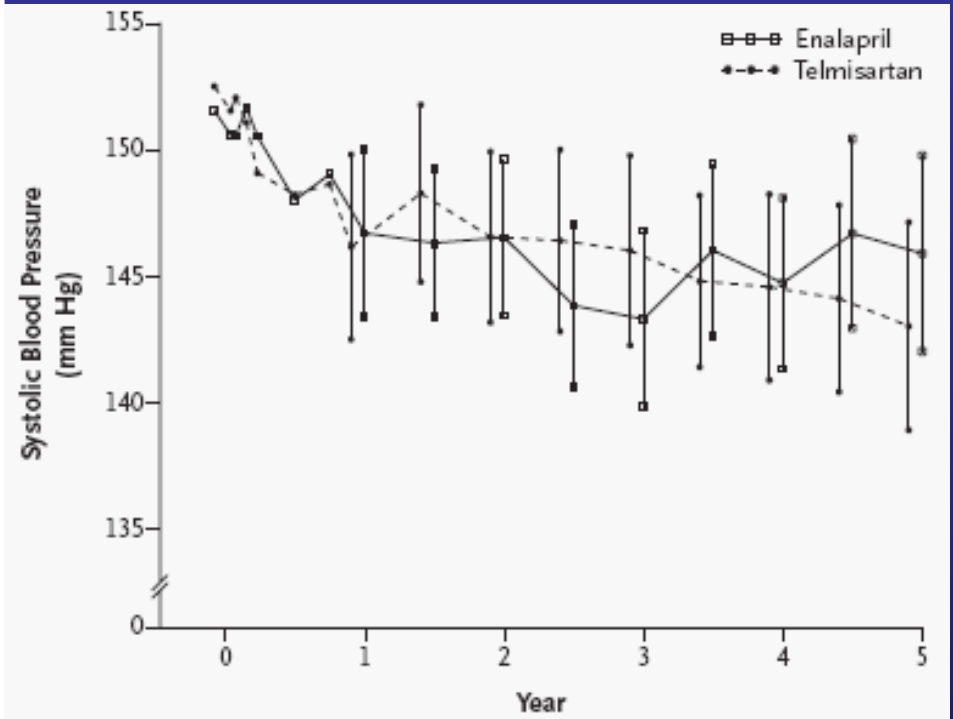

Remodelling
Ventricular dilation/
cognitive dysfunction
Myocardial
infarction
and stroke
Congestive
heart failure/
secondary stroke
Macro-
proteinuria
Micro-
albuminuria
Atherosclerosis
and LVH
Nephrotic
proteinuria
End-stage
heart disease/
brain damage and
dementia
Endothelial
dysfunction
End-stage
renal disease
Hypertension and
risk factors:
diabetes, obesity, elderly
Cardio-
cerebrovascula
death

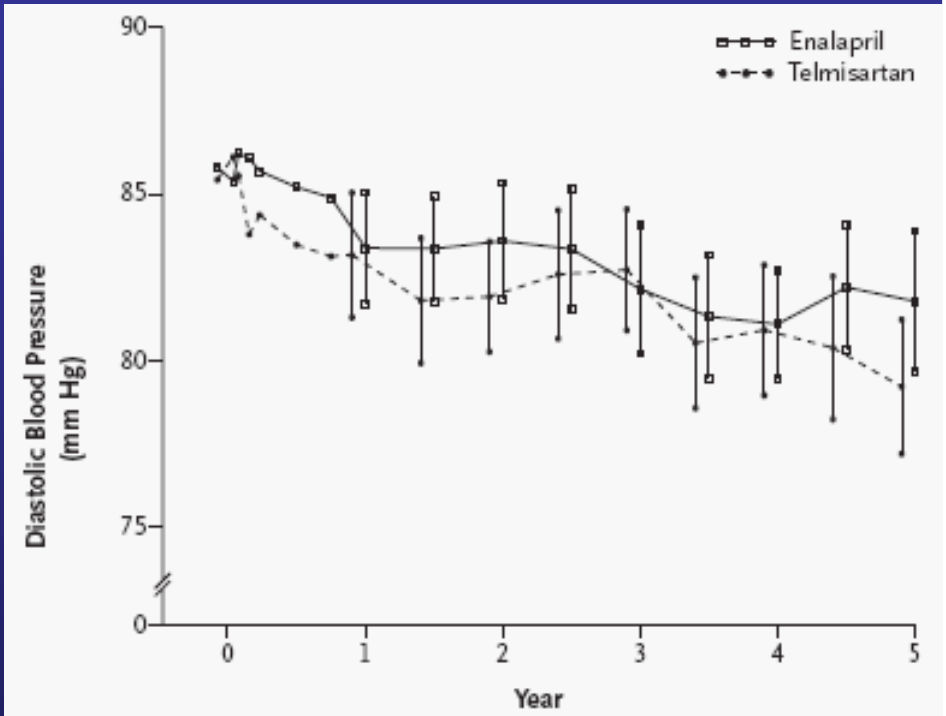
Data from the HOPE, LIFE, RENAAL, IDNT, and AASK studies have demonstrated that a reduction in albuminuria correlated, in a wide range of hypertensive patients with a decrease in the risk of end-stage renal disease, CV events, and death.

ACE gátló vagy ARB?

N = 250, DM2T, GFR > 70 ml/min, MAU: 81 %, MAC: 18%




Enalapril
Telmisartan
Systolic Blood Pressure (mm Hg)
155
150
145
140
135
0
0
1
2
3
4
5
Year


Enalapril
Telmisartan
Diastolic Blood Pressure (mm Hg)
90
85
80
75
0
0
1
2
3
4
5
Year

Maximális adagú ACE gátló vagy ARB mellett a proteinuria > 1g /nap !

- ACE gátló ÉS ARB
- Szupramaximális adagú ACE gátló vagy ARB

Fél adag ACE gátló és angiotensin receptor blokkoló kombinálása diabeteses nephropathiában

Vizelet protein/creatinin

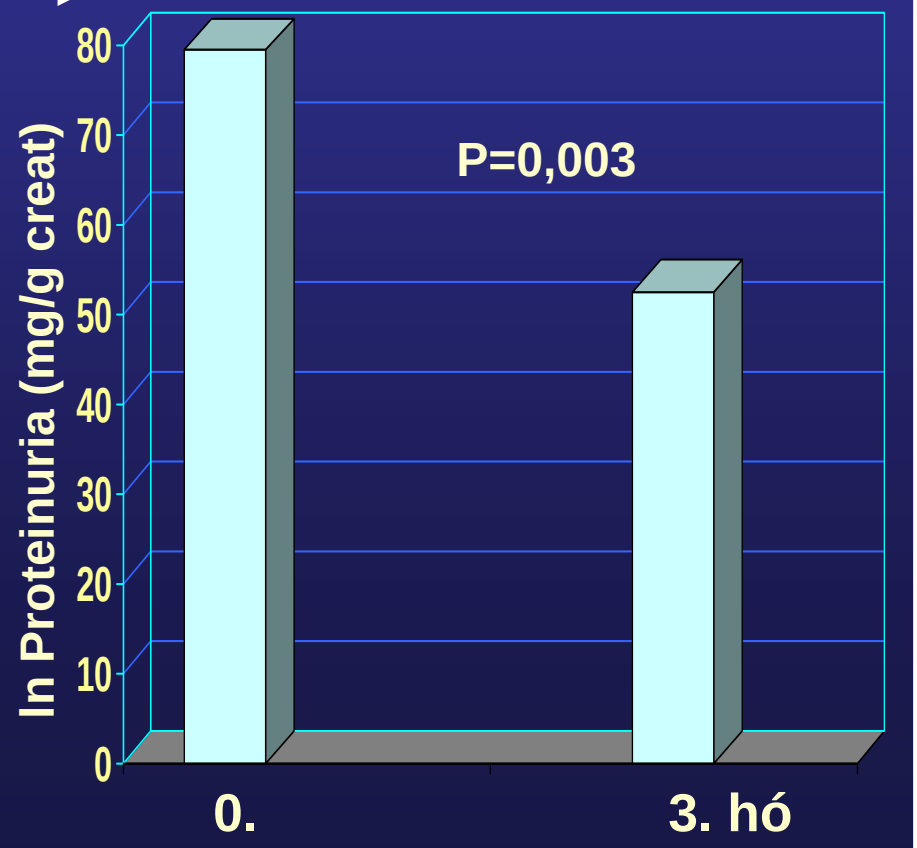
ACE gátló: N= 18
(10 mg/d imidapril)

Kombináció: N=27

ARB: N=9
(8 mg/d candesartan)

3 hónap

> 3 hónap ($\bar{X}$=8 hó)

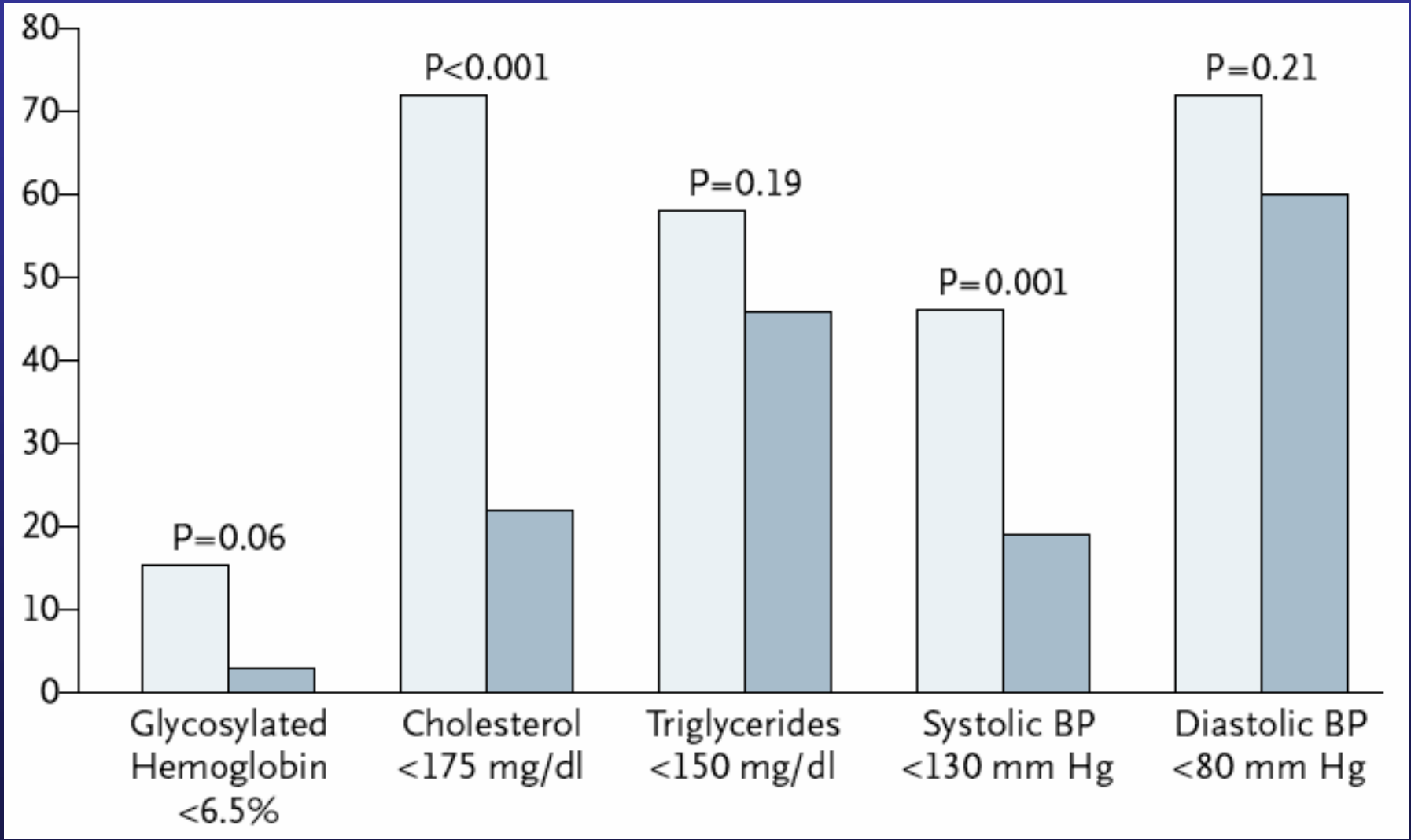


A kombináció mellett a vérnyomás változatlan.

	Before	After	*P* value
HbA_{1c} (%)	7.7 ± 1.5	7.8 ± 1.6	NS
SBP (mm Hg)	140 ± 11	142 ± 15	NS
DBP (mm Hg)	84 ± 9	85 ± 9	NS

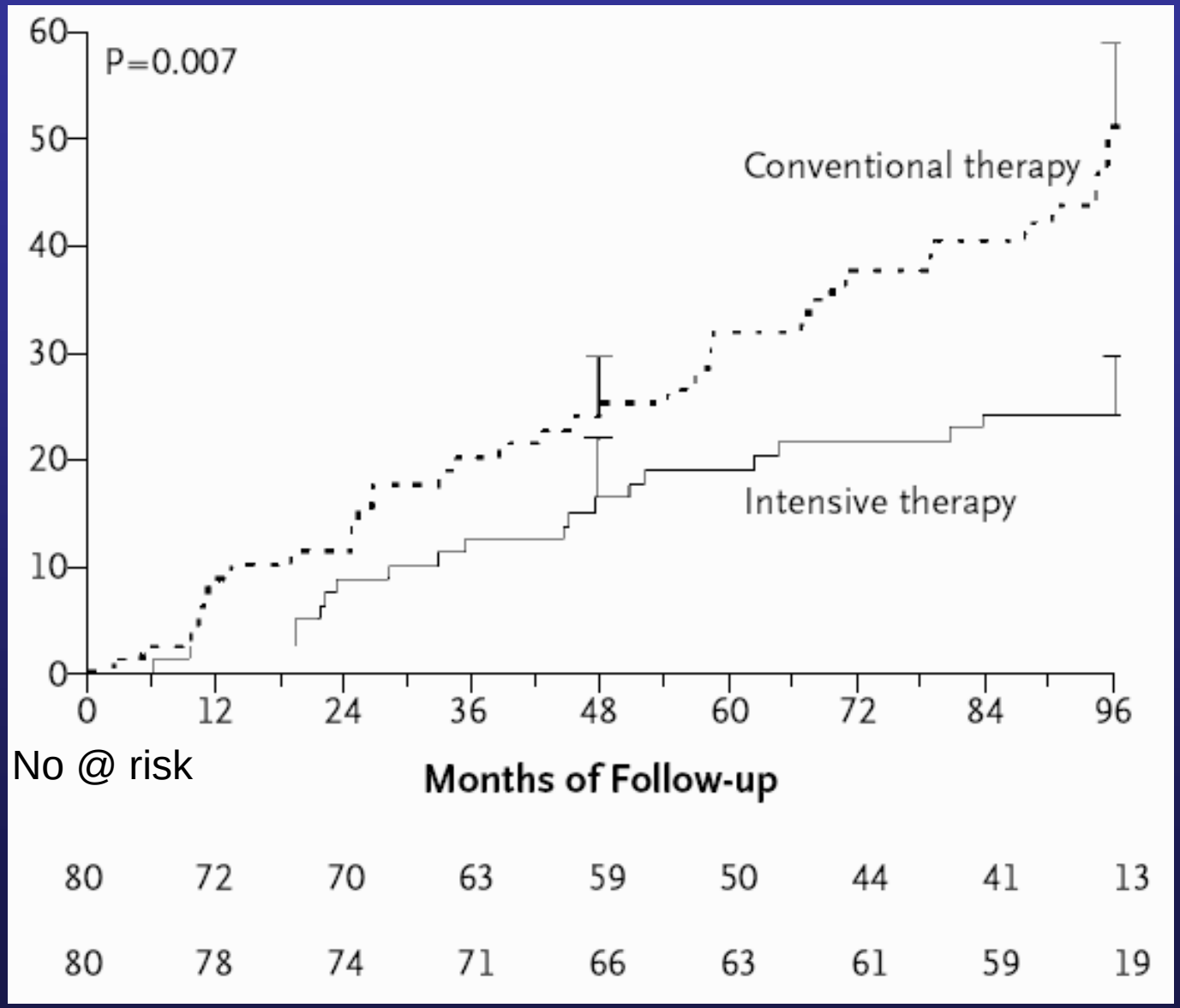
Fujisawa T et al. Am J Hypertens, 2005;18:13

Multifaktoriális intervenció



Gaede P, N Engl J Med 2003;348:383-93.

Multifaktoriális intervenció

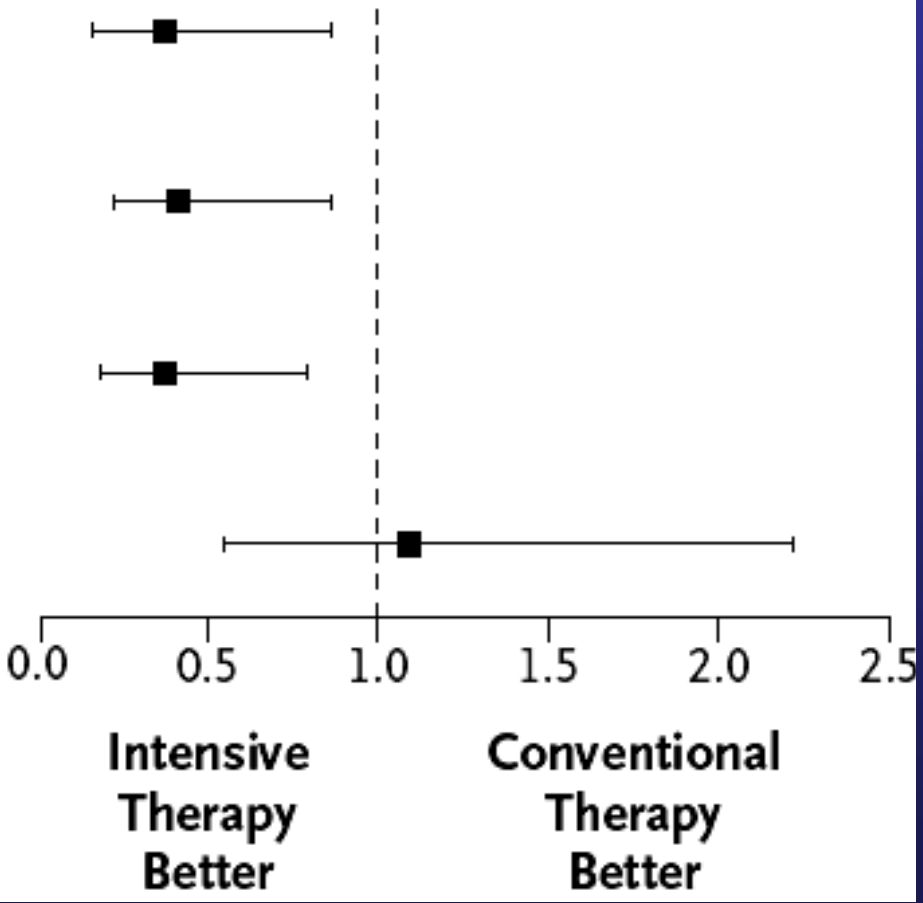


összetett KV végpont %

Gaede P, N Engl J Med 2003;348:383-93.

Multifaktoriális intervenció

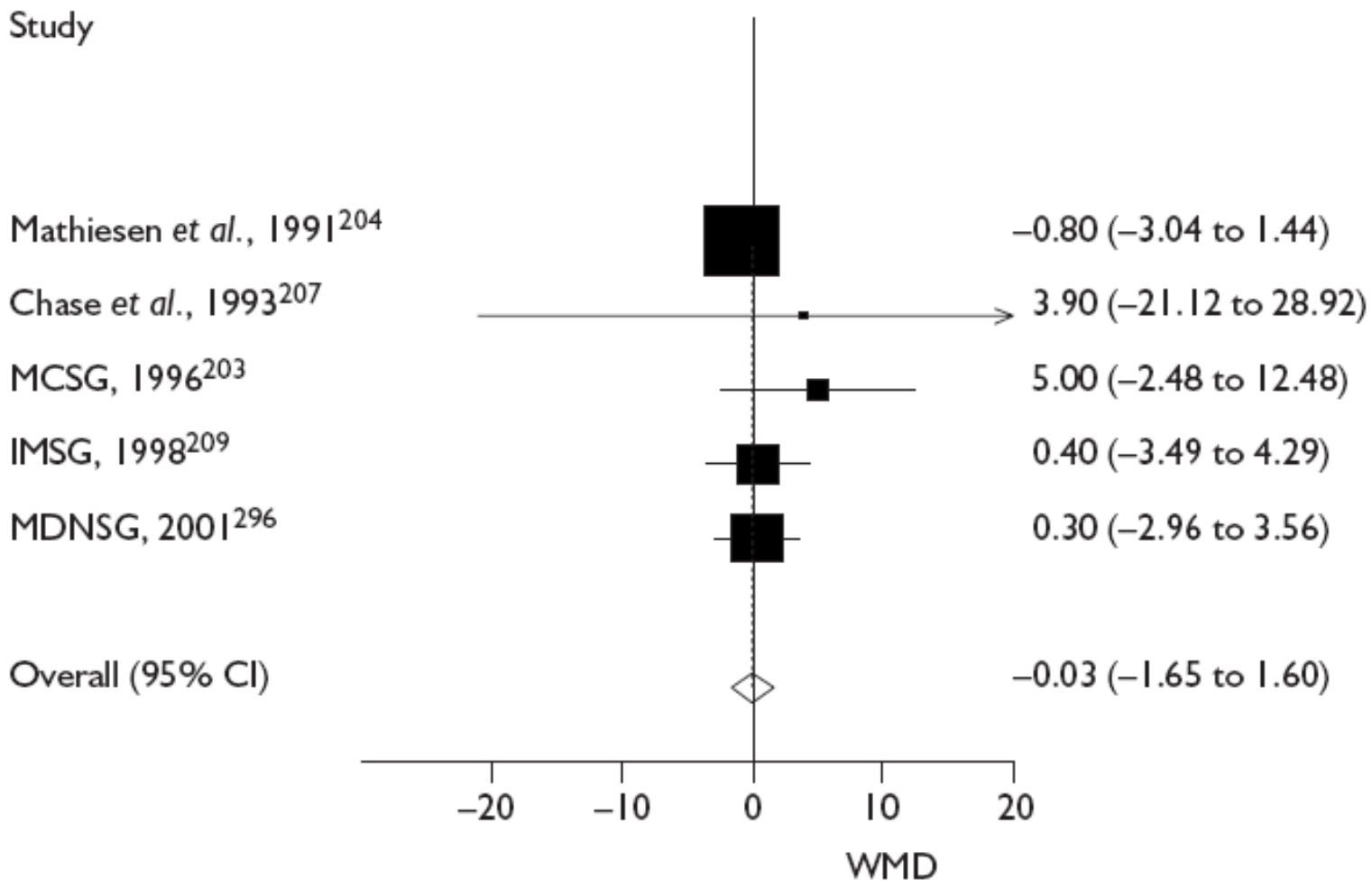
Variable	Relative Risk (95% CI)	P Value
Nephropathy	0.39 (0.17–0.87)	0.003
Retinopathy	0.42 (0.21–0.86)	0.02
Autonomic neuropathy	0.37 (0.18–0.79)	0.002
Peripheral neuropathy	1.09 (0.54–2.22)	0.66



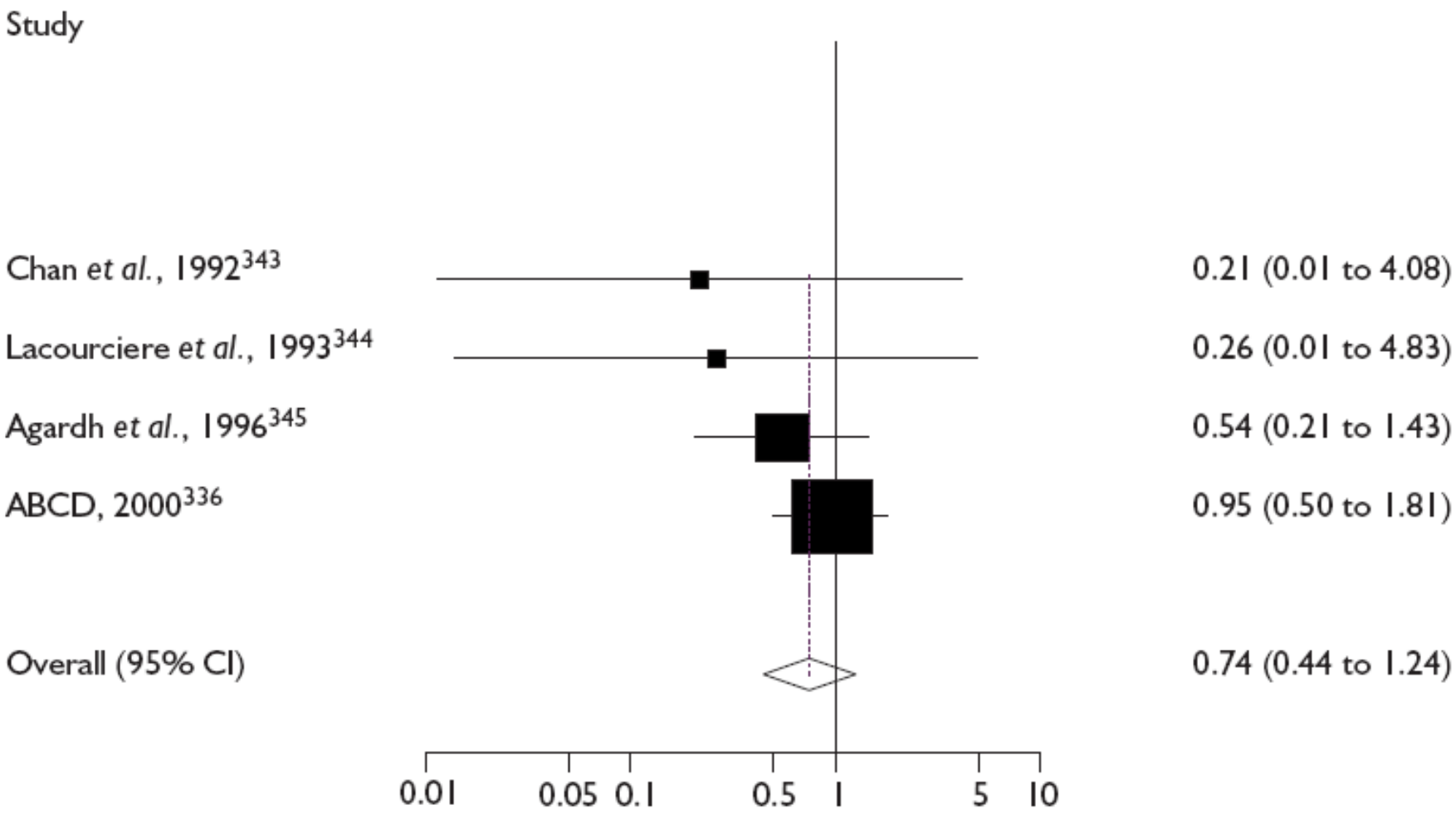
Gaede P, N Engl J Med 2003;348:383-93.

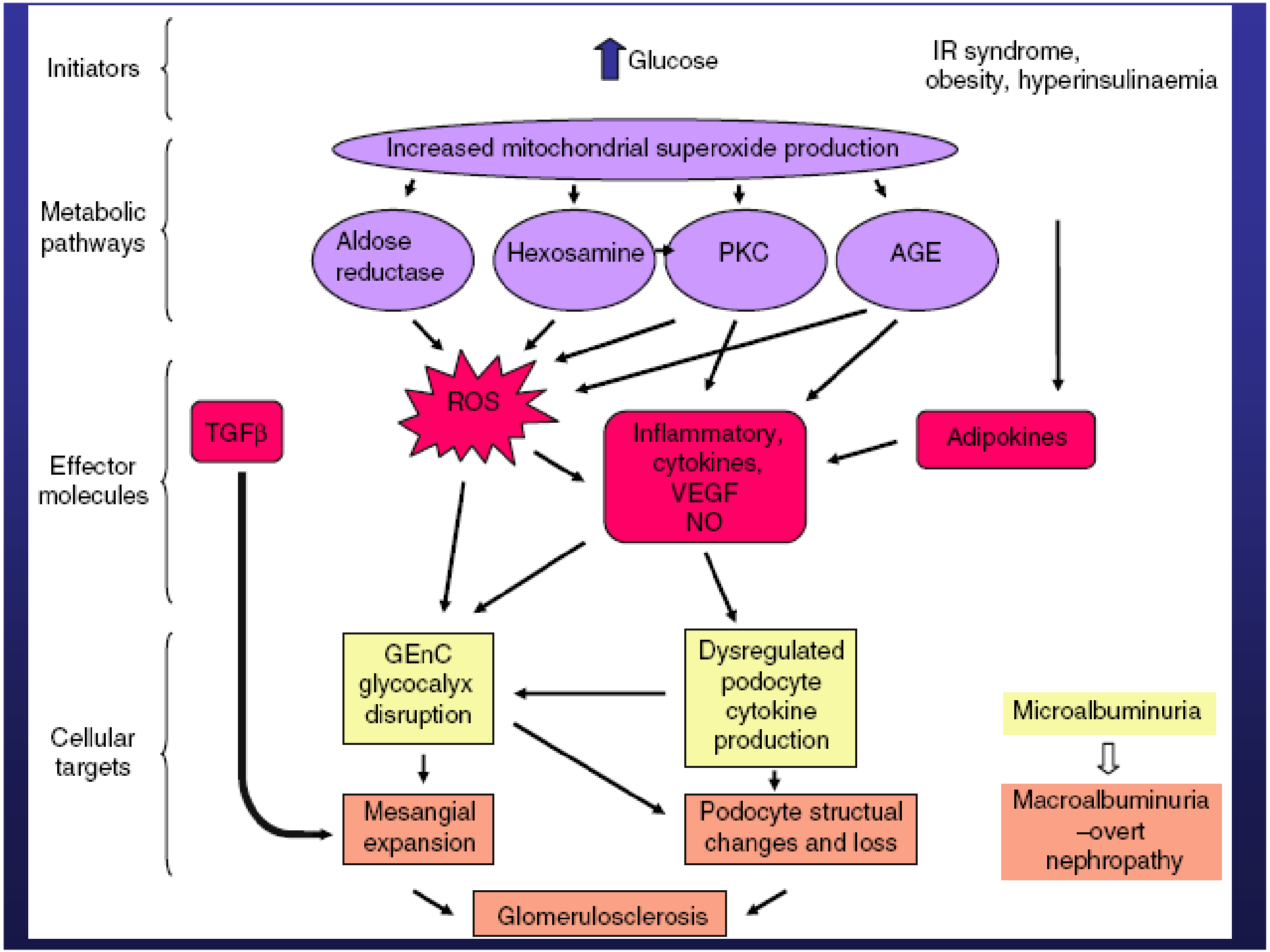
Szekunder prevenció, GFR: Normotonia, MAU, DM1T

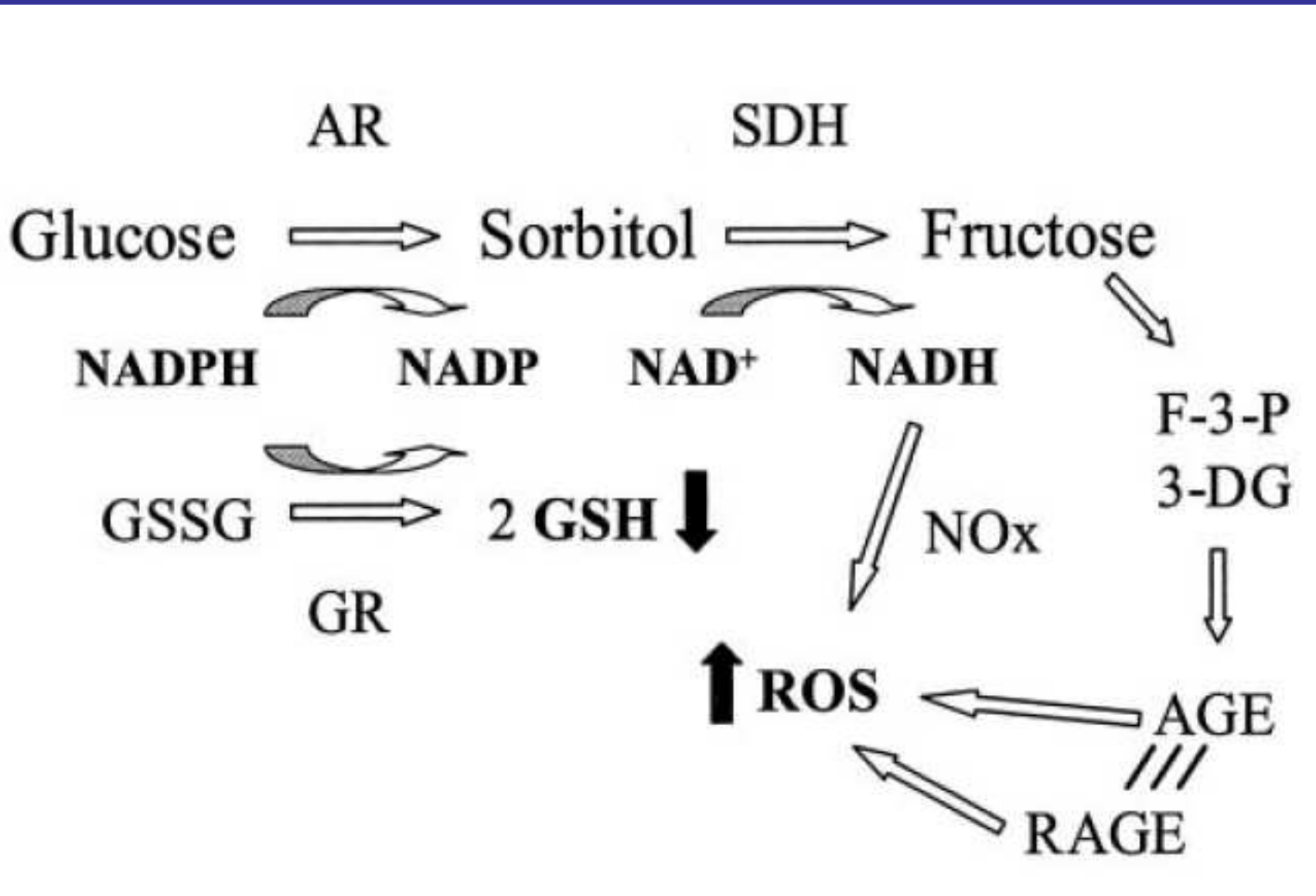
ACE gátló vs placebo

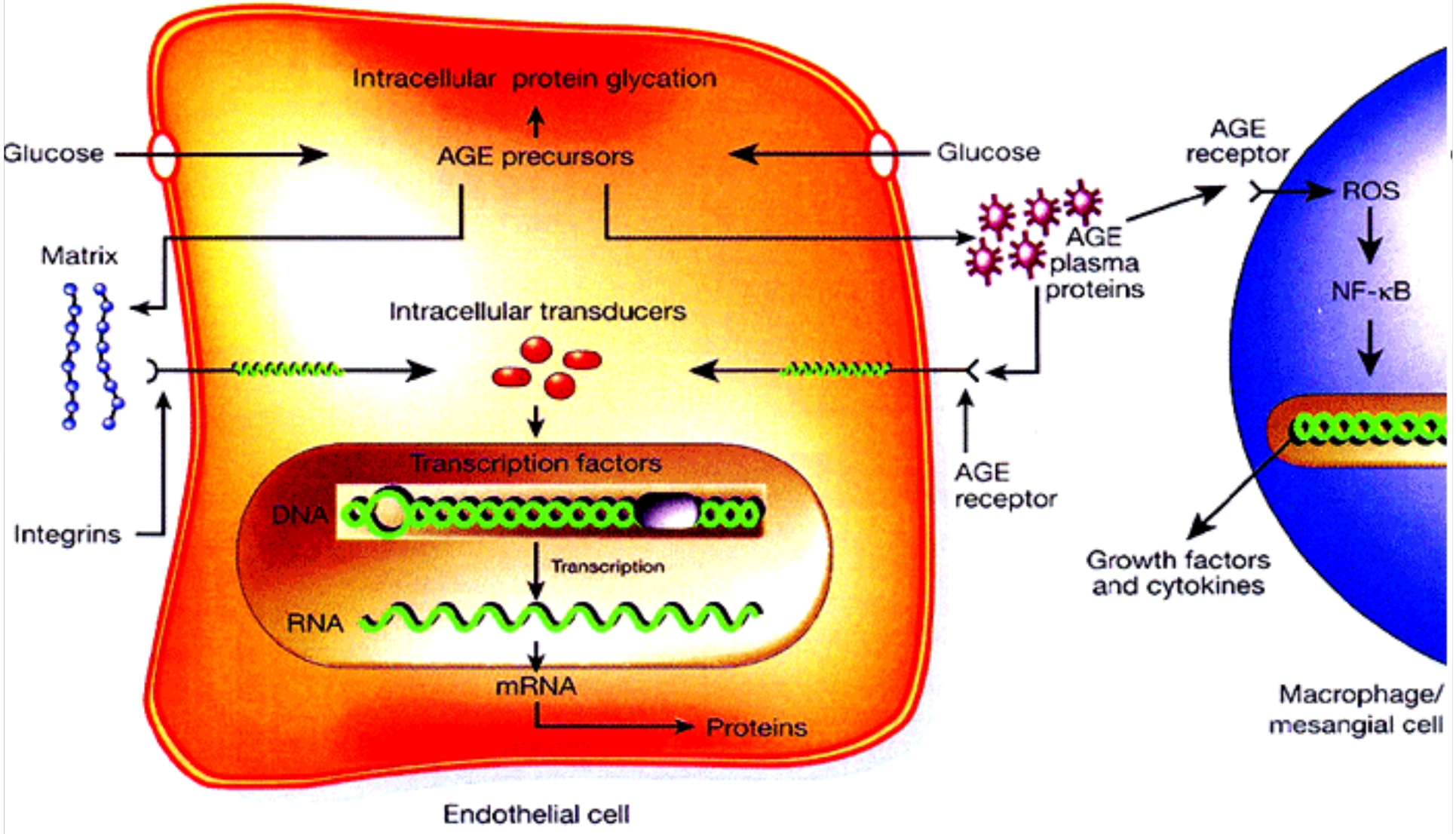


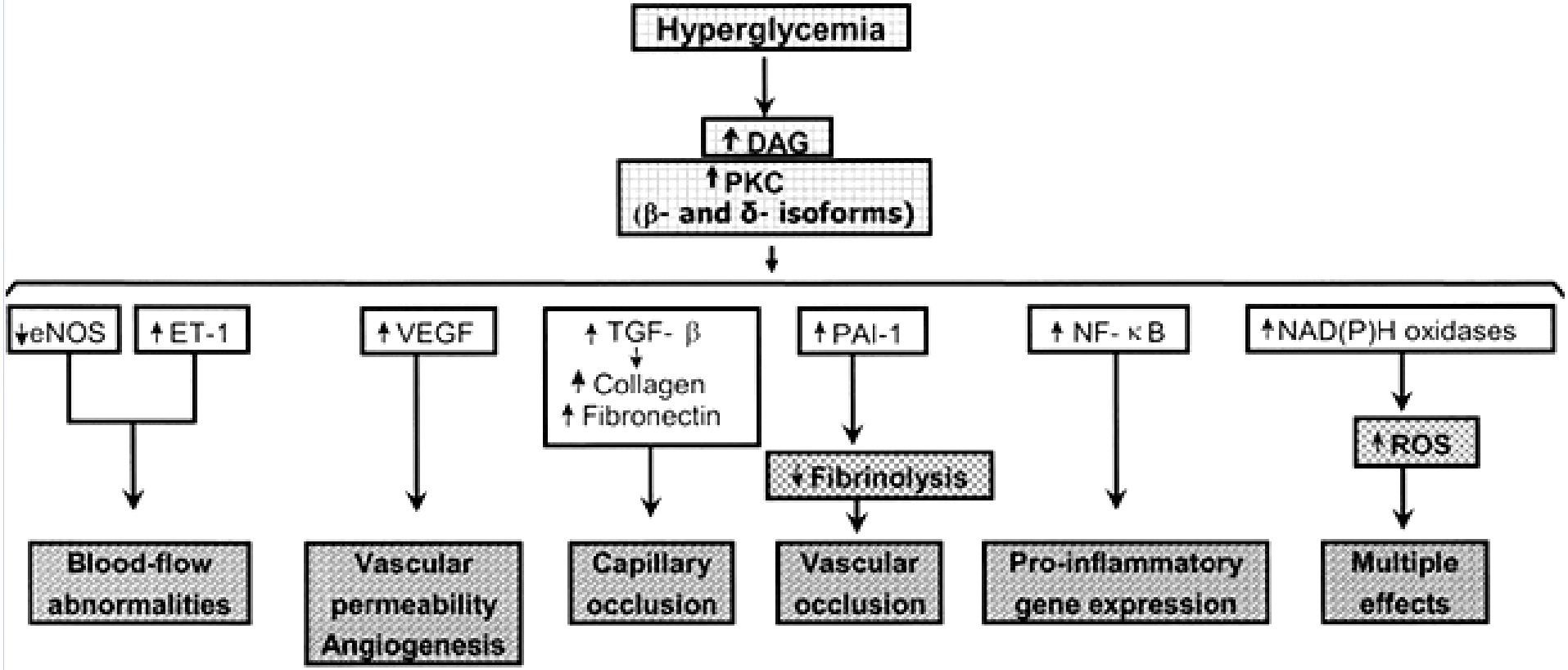
Szekunder prevenció, proteinuria: Normotonia, MAU, DM2T
ACE gátló vs egyéb antihypertensivum

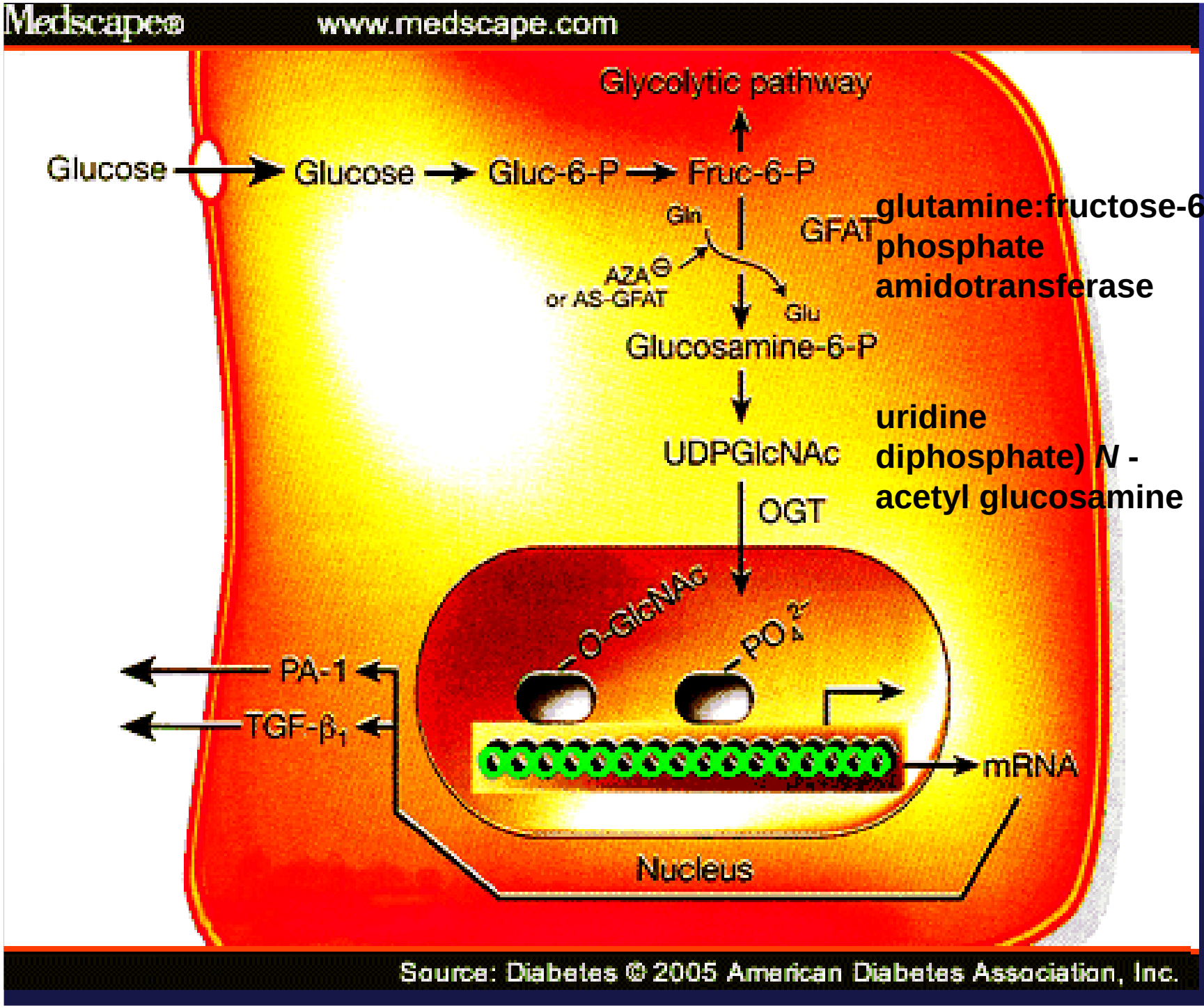



Initiators
Glucose
IR syndrome,
obesity, hyperinsulinaemia
Metabolic pathways
Increased mitochondrial superoxide production
Aldose reductase
Hexosamine
PKC
AGE
Effector molecules
ROS
TGFβ
Inflammatory, cytokines, VEGF NO
Adipokines
Cellular targets
GEnC glycocalyx disruption
Dysregulated podocyte cytokine production
Mesangial expansion
Podocyte structual changes and loss
Glomerulosclerosis
Microalbuminuria
Macroalbuminuria –overt nephropathy


AR
SDH
Glucose
Sorbitol
Fructose
NADPH
NADP
NAD+
NADH
F-3-P
3-DG
GSSG
2 GSH
NOx
GR
ROS
AGE
RAGE

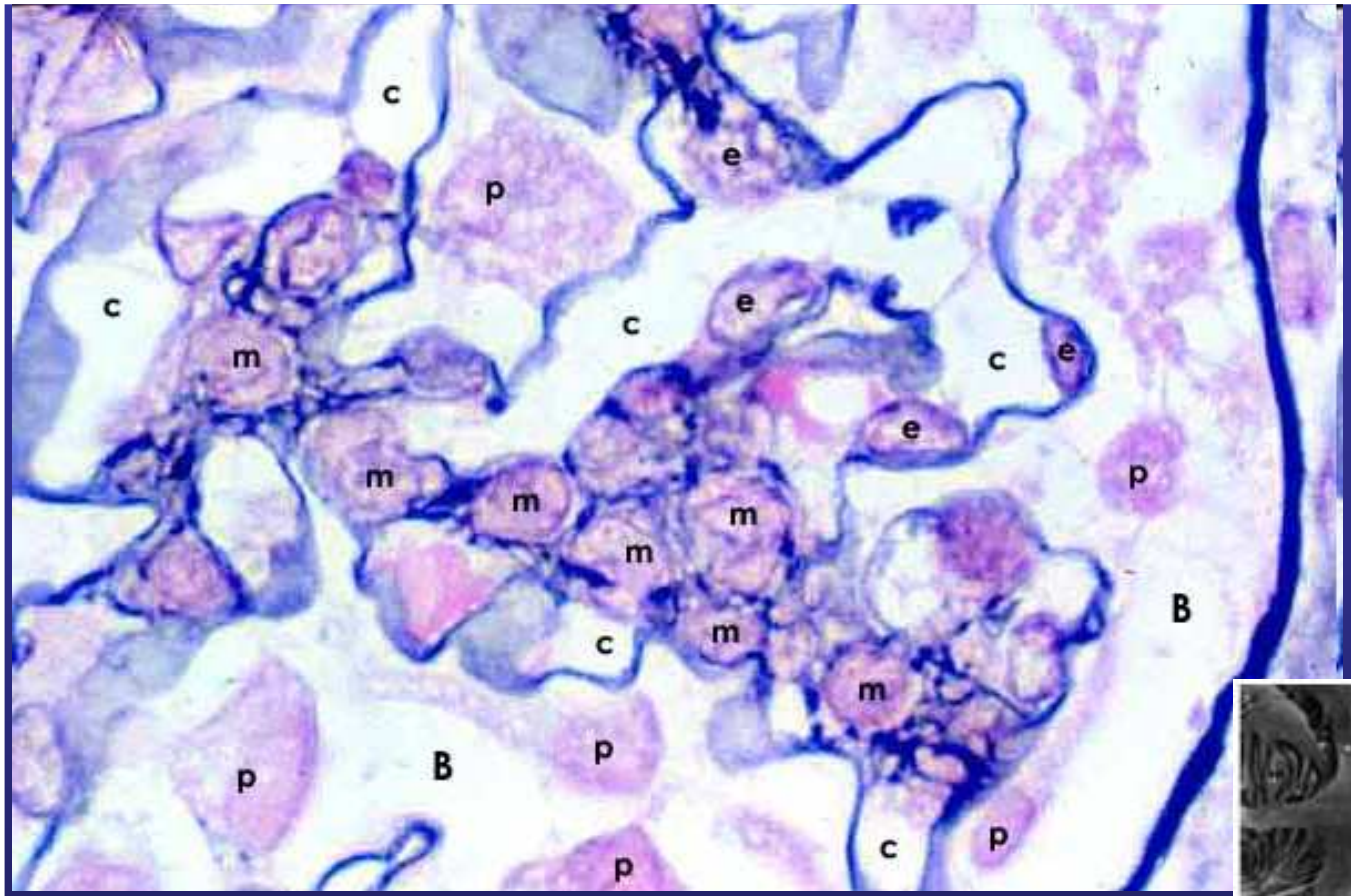


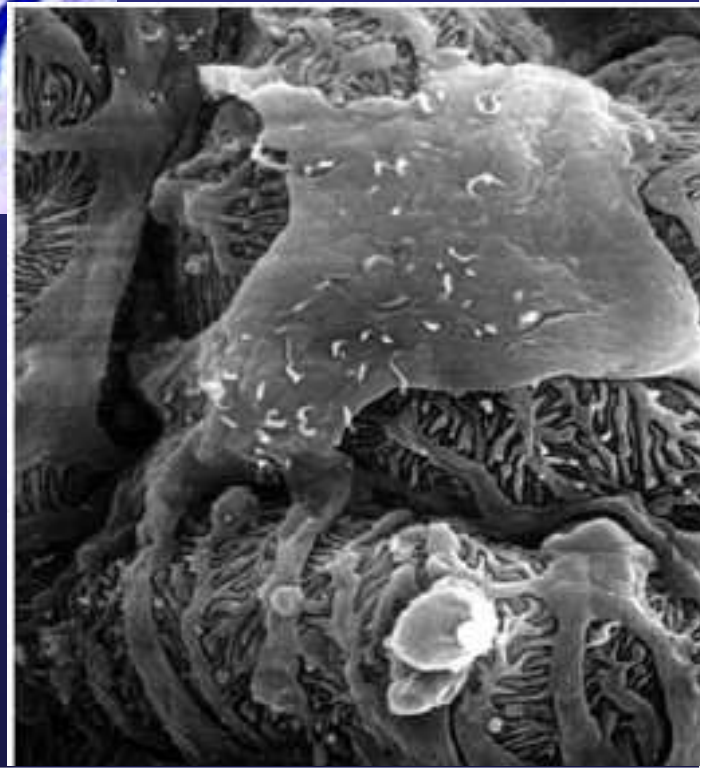


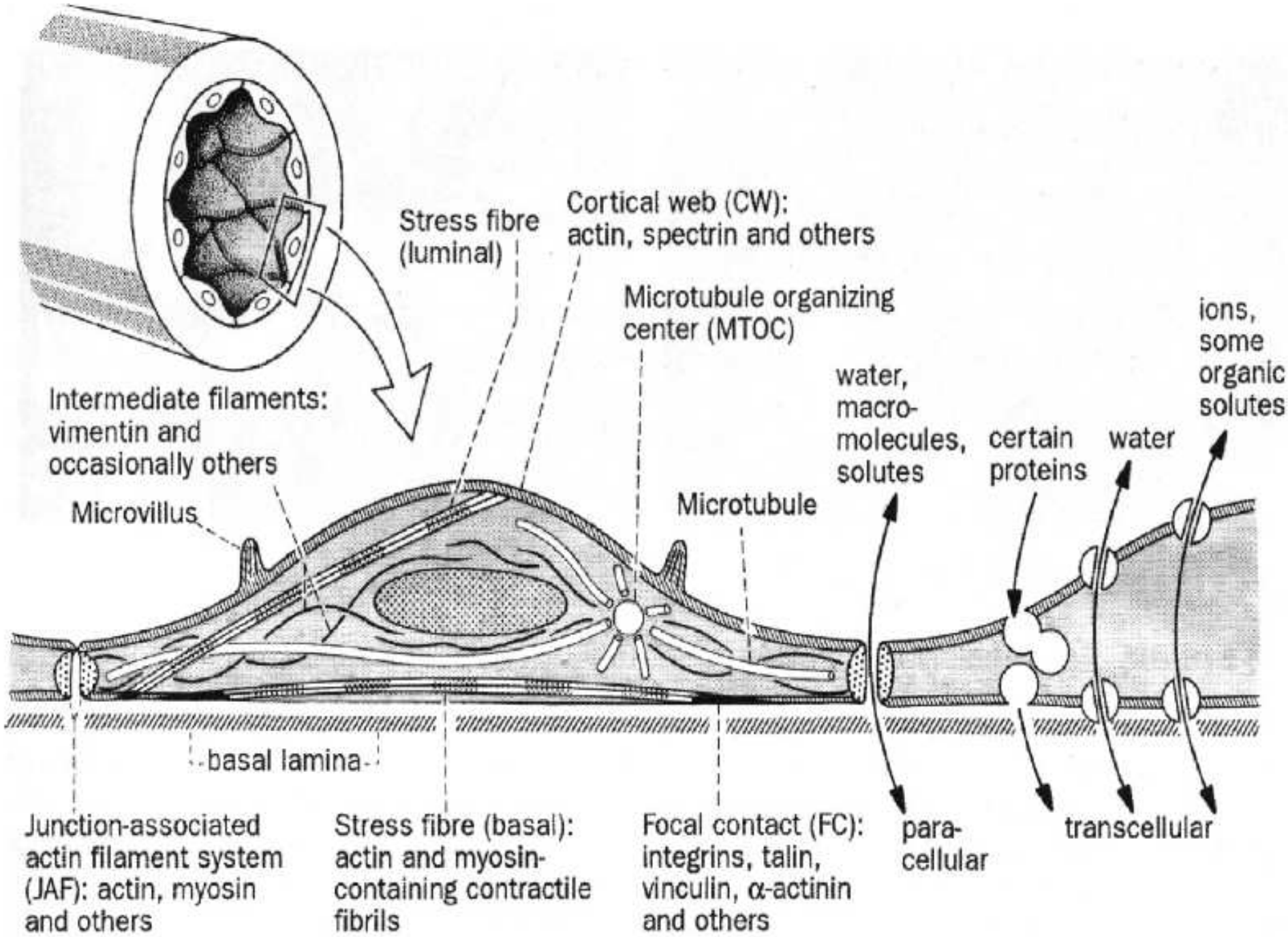


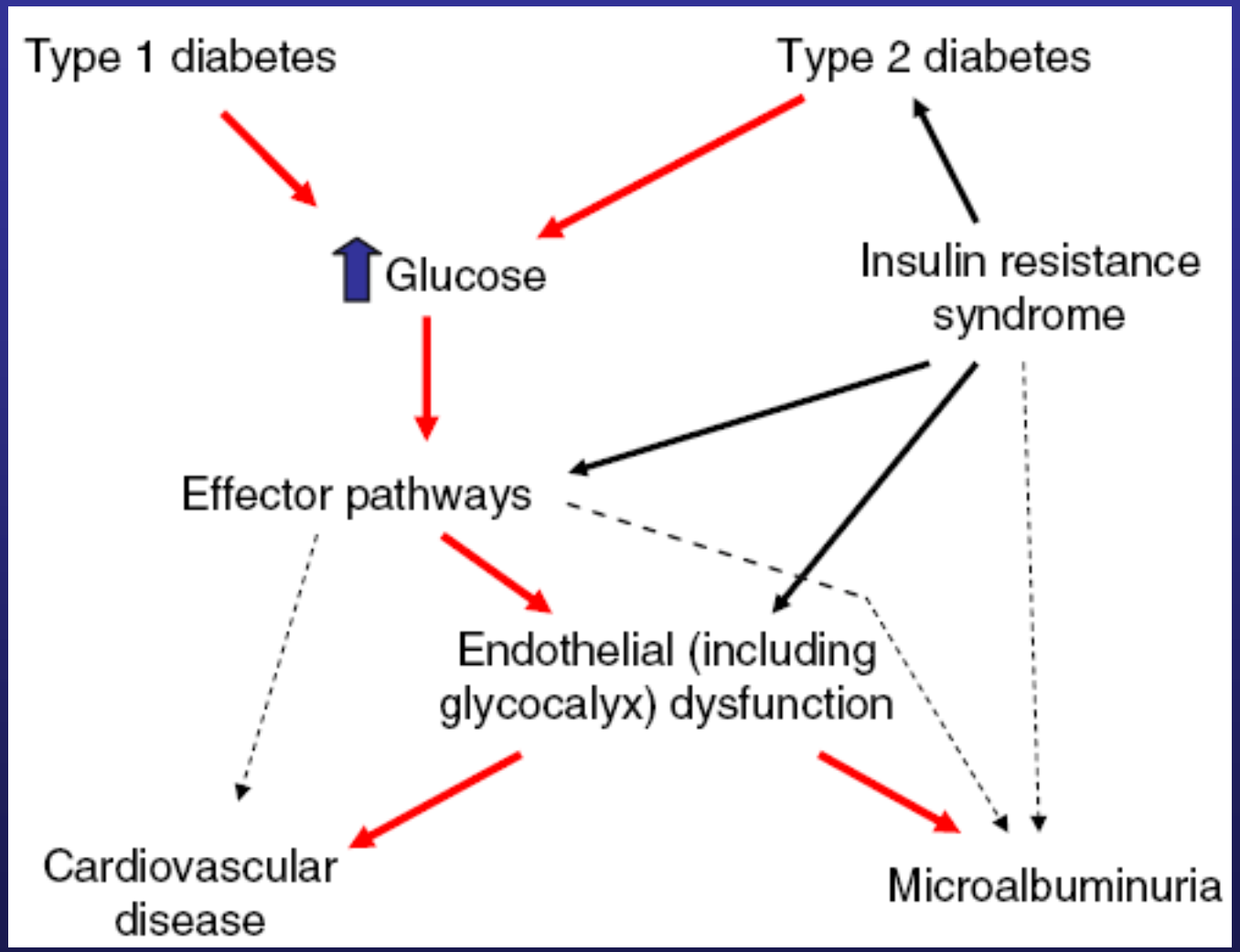
glutamine:fructose-6 phosphate amidotransferase

uridine diphosphate) *N* - acetyl glucosamine

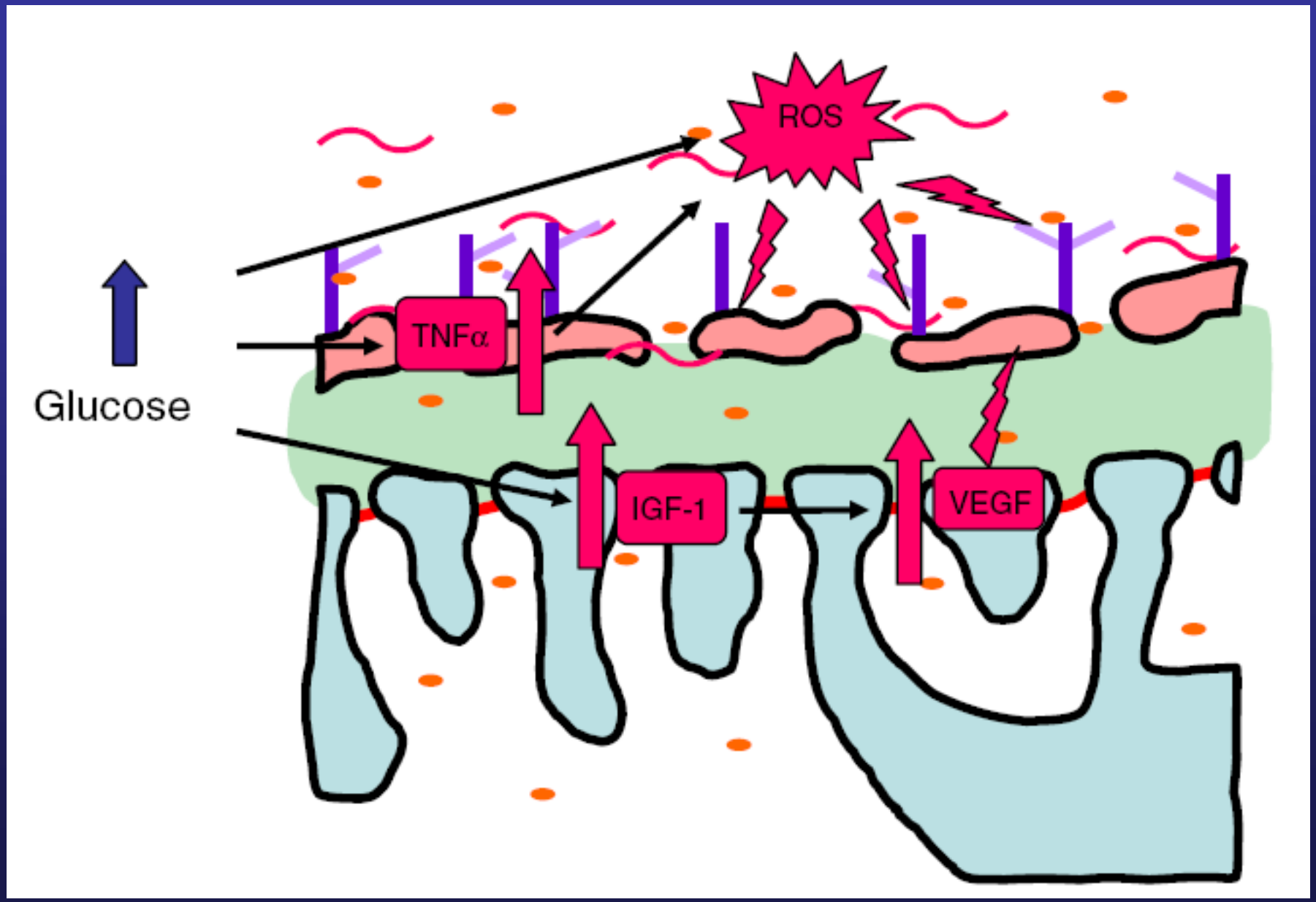

c
e
p
c
e
c
m
c
e
e
p
m
m
m
m
B
c
m
m
p
B
p
c
p
p




Stress fibre (luminal)
Cortical web (CW): actin, spectrin and others
Microtubule organizing center (MTOC)
Intermediate filaments: vimentin and occasionally others
Microvillus
Microtubule
water, macro-molecules, solutes
certain proteins
water
ions, some organic solutes
basal lamina
Junction-associated actin filament system (JAF): actin, myosin and others
Stress fibre (basal): actin and myosin-containing contractile fibrils
Focal contact (FC): integrins, talin, vinculin, α-actinin and others
para-cellular
transcellular



Satchell S. Diabetologia (2008) 51:714–725



Satchell S. Diabetologia (2008) 51:714–725

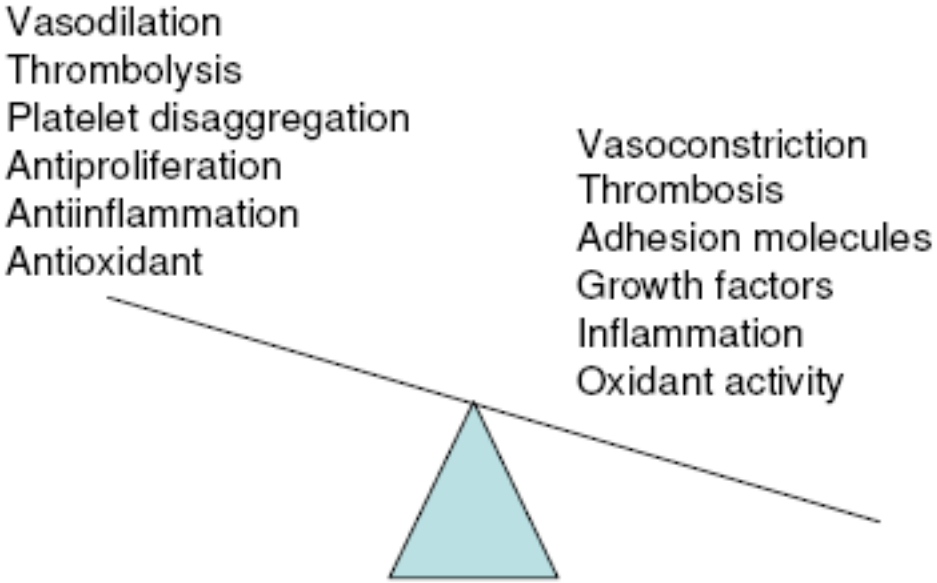
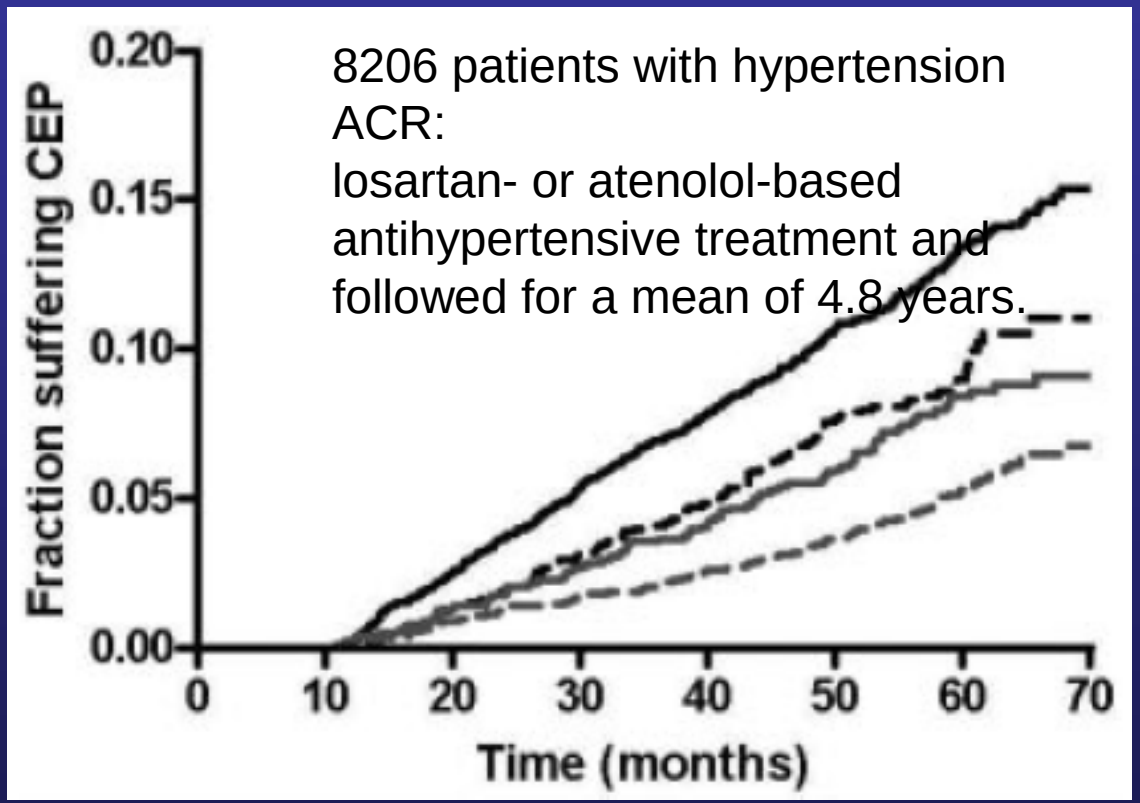


Figure 3
Regulatory functions of the endothelium. Normal or anti-atherogenic vs dysfunction or atherogenic propierties. Fro
Esper RJ, et al.[5]

Reduction in Albuminuria Translates to Reduction in Cardiovascular Events in Hypertensive Patients: Losartan Intervention for Endpoint Reduction in Hypertension Study

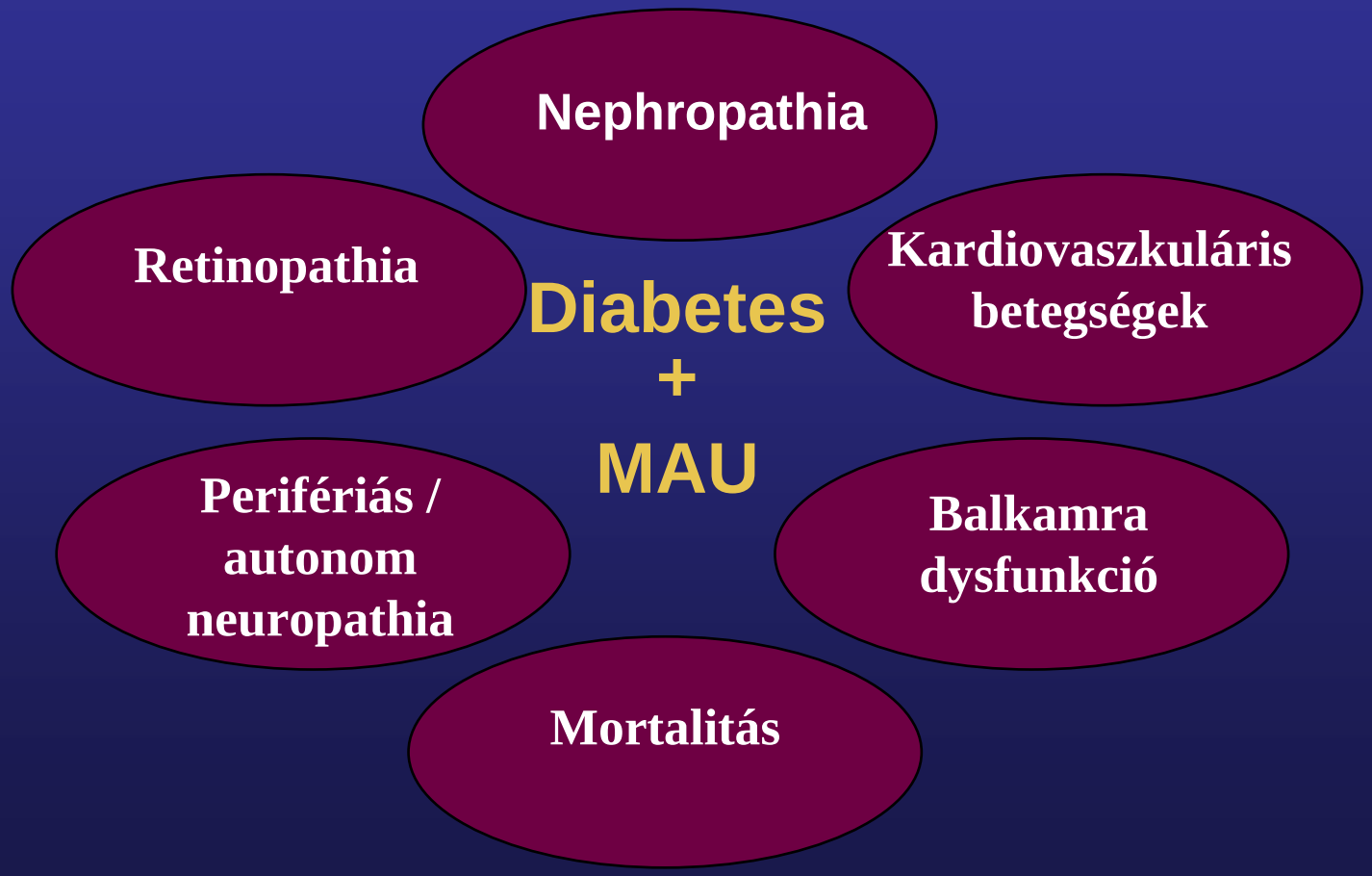


Ibsen H. Hypertension. 2005;45:198

STUDY	Population	Albuminuria	Risk
PREVEND	28 to 75 yr (n=40,548)	UAE 20 to 200 mg/L	CV death: RR 1.29
EPIC-Norfolk	40 to 79 yr (n=20,911)	ACR 2.5 to 25 mg/mmol	Fatal stroke: HR 1.58 CAD death: HR 2.01
Danish MONICA	No CAD, No DM, No CKD (n=2085)	ACR > 0,65 mg/mmol	CAD: RR 2.3
HUNT	No DM No HT (n=2089)	ACR > 0,75 mg/mmol	All-cause mortality: RR 2.3

Weir M. Clin J Am Soc Nephrol 2007;2: 581.

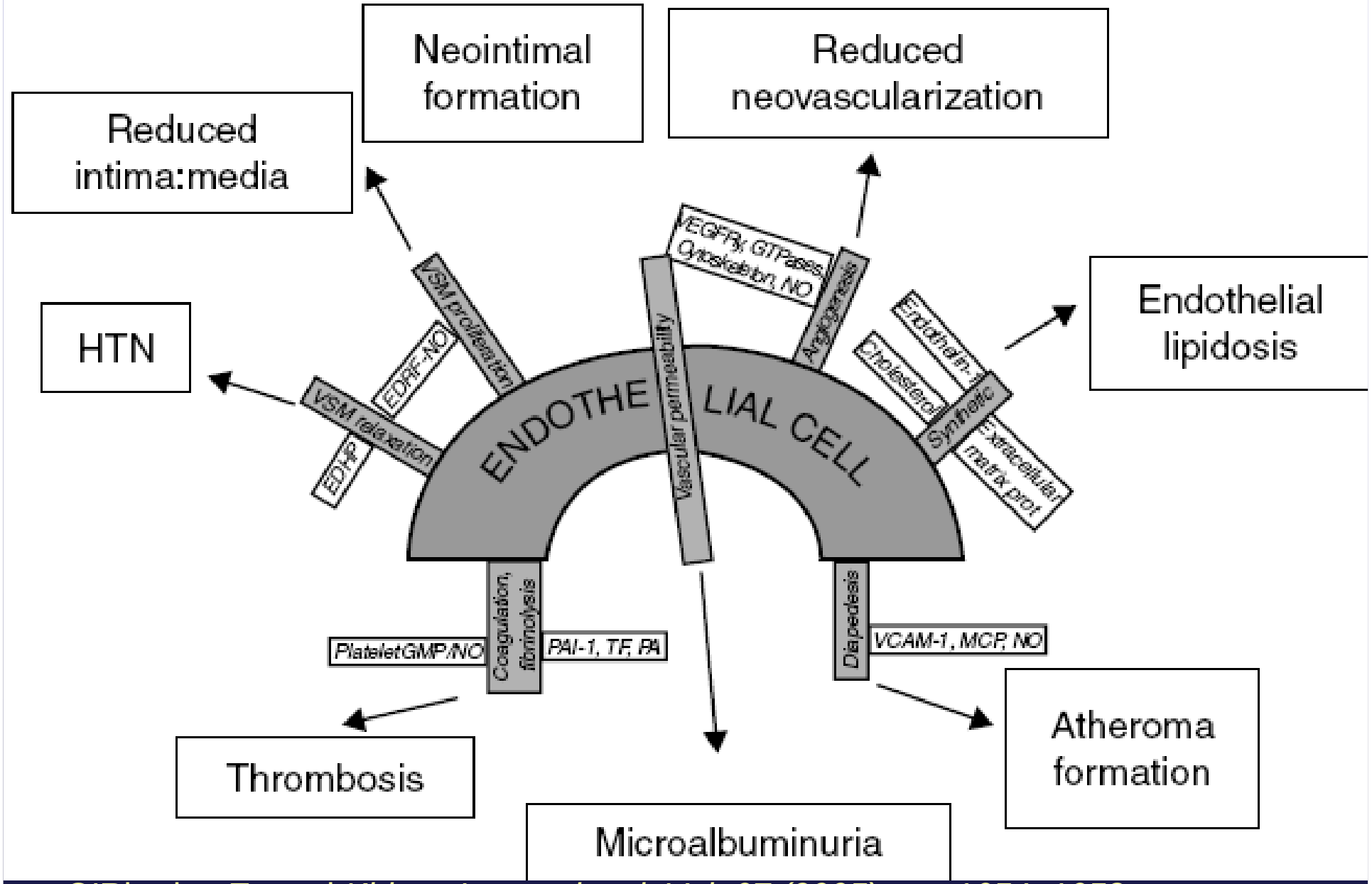
A mikroalbuminuria a morbiditás és mortalitás prediktora



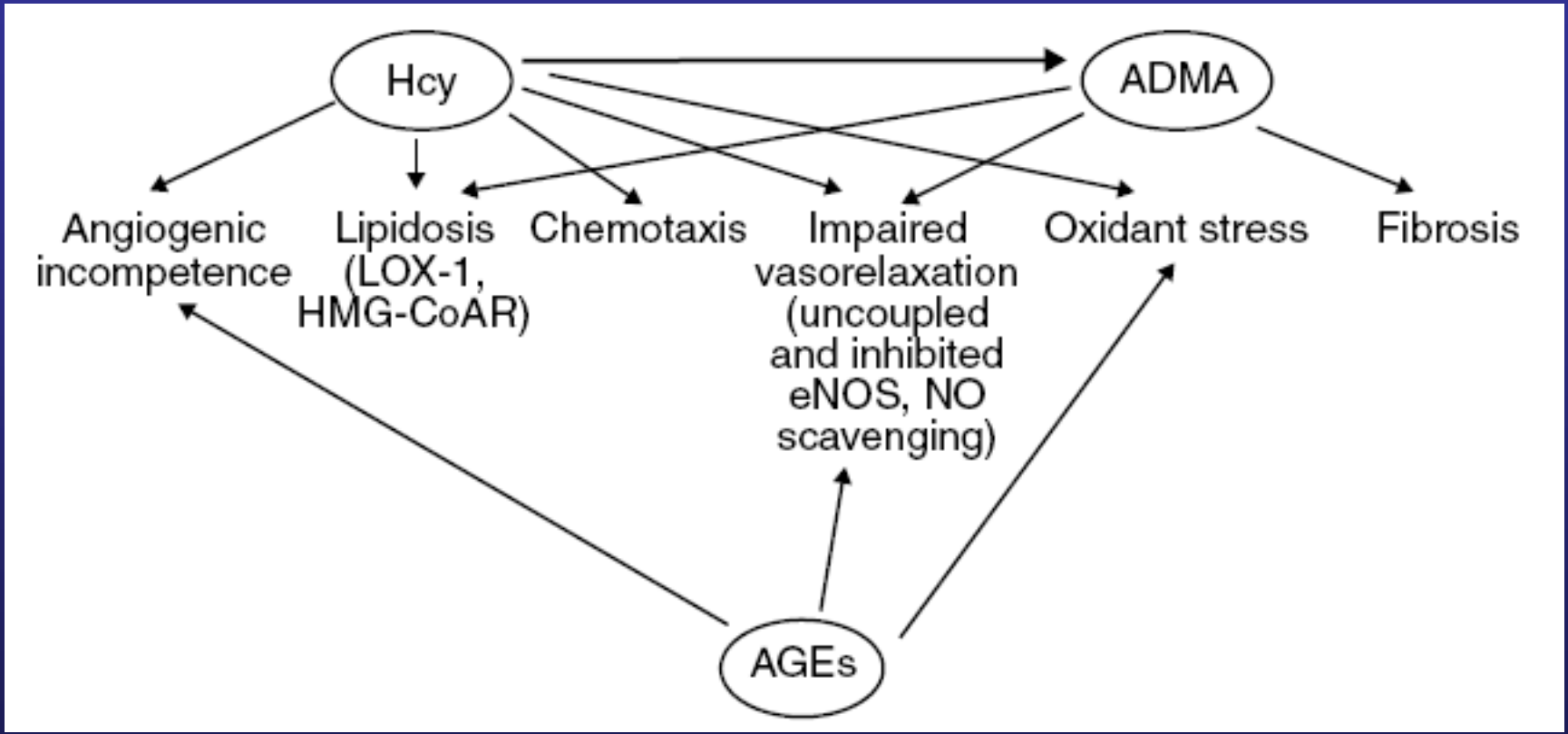
Parving H-H. *J Hypertens* 1996;14(suppl 2):S89-S94.

Therapeutic agents (examples)	Molecules targeted	Phases of endothelial activation affected	Clinical indications
Non-steroidal anti-inflammatory agents (ibuprofen, ASA, celecoxib*)	COX1 and COX2	Type I and II (reduces local blood flow)	Pain, fever and inflammation
Anti-histamines (diphenhydramine, fexofenadine‡)	H1-histamine receptors	Type I (reduces local blood flow and local vascular permeability)	Allergic rhinitis and others
TNF-specific antibodies or soluble TNF receptor (etanercept§)	TNF	Type II (all aspects) and chronic (reduces inflammatory angiogenesis)	Arthritis, psoriasis and inflammatory bowel disease
VEGF-specific antibodies or VEGF receptor antagonists (bevacizumab‖)	VEGFA	Type I and II (reduces vascular permeability and blood flow), and chronic (reduces angiogenesis)	Cancer and macular degeneration (wet)
Statins (simvastatin¶, atorvastatin#)	HMG-CoA reductase and protein prenylation	Type II; decreases IFNγ induced MHC class II expression and adhesion molecules	Hyperlipidaemia and atherosclerosis
IL-1RA (anakinra**)	IL-1	Type II (all aspects)	systemic-onset juvenile idiopathic arthritis and autoinflammatory disorders
Rapamycin (sirolimus‡‡)	mTOR	Angiogenesis	Immunosuppression in transplantation

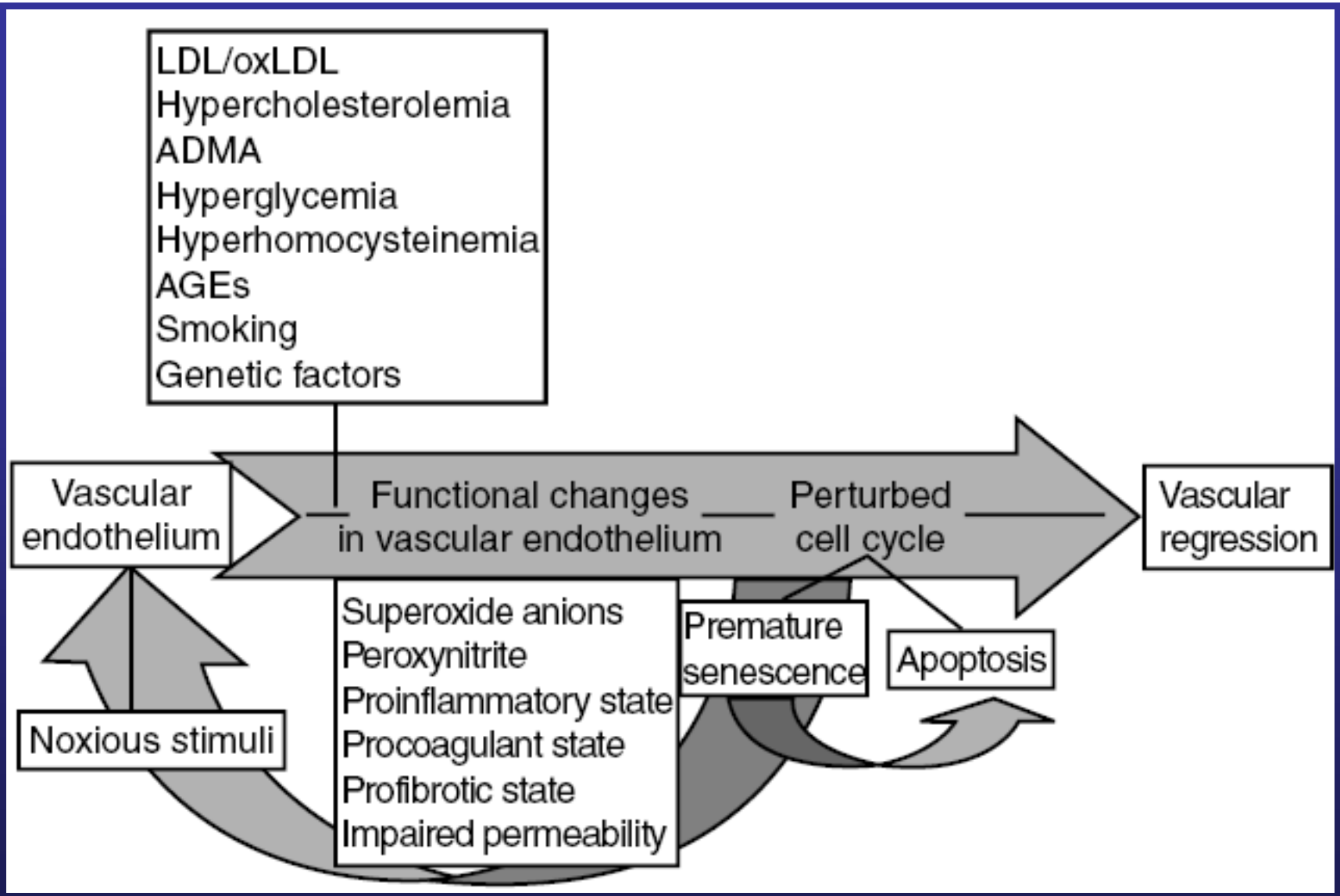
*Celebrex; Pfizer. ‡Allegra; Aventis. § Enbrel; Amgen, Wyeth. ‖ Avastin; Genentech. ¶ Zocor; Merck. # Lipitor; Pfizer. **Kineret; Amgen. ‡‡ Rapamune; Wyeth.
ASA, acetylsalicylic acid; COX, cyclooxygenase; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; IFNγ, interferon-γ; IL-1, interleukin-1; IL-1RA, IL-1 receptor antagonist; mTOR, mammalian target of rapamycin; TNF, tumour-necrosis factor; VEGF, vascular endothelial growth factor.



O'Riordan E. et al.*Kidney International, Vol. 67 (2005), pp. 1654–1658*



O'Riordan E. et al.*Kidney International, Vol. 67 (2005), pp. 1654–1658*



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Thus, the HOPE study suggested that a 0.4-mg/mmol increase in the ratio of urinary albumin to creatinine concentration led to a 5.9% higher age- and sex-adjusted risk of CHD. :Gerstein HC, Mann JF, Yi Q, et al. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. *JAMA*. 2001;286:421–426.

The Irbesartan in Patients
with type II Diabetes and Microalbuminuria showed that inhibition of the RAS by the angiotensin II receptor blocker irbesartan slowed the progression to overt nephropathy and was associated with a reduced number of cardiovascular events as compared to non-RAS inhibitor antihypertensive therapy.9

ACR	RR of CV events
0,4 mg/mmol	5,9%

IRMA: An improvement of the normalization rate to approximately 33% occurred when the full dosage (300 mg) of the renin-angiotensin system blocking drug irbesartan (an angiotensin II receptor blocker) was used as part of the Bplowering regimen to 140/90 mmHg.

Cost-effectiveness of screening for albuminuria with subsequent fosinopril treatment to prevent cardiovascular events: A pharmacoeconomic analysis linked to the Prevention of Renal and Vascular Endstage Disease (PREVEND) study and the Prevention of Renal and Vascular Endstage Disease Intervention Trial (PREVEND IT). *Clin Ther* 28: 432–444, 2006

IMPROVE trial: HTN and increased CV risk: ACE or ARB monother enough: Bakris