STRATEGIES TO SLOW PROGRESSION OF CHRONIC KIDNEY DISEASE

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School of Medicine

GE KDI F CKD

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Part I Chronic Kidney Disease: Basics and Clinical Assessment

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kid
INTERNA

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NKF-KDI

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‘To study the phenomena of disease without books is to sail an uncharted sea, while to study books without patients is not to go to sea at all’
William Osler

SOME DEFINITIONS

Table 1. Definitions of progression, remission and regression of proteinuric chronic nephropathy

Variable	Progression	Remission	Regression
Proteinuria	≥1 g/24 h	<1 g/24 h	<0.3 g/24 h
GFR	Declining*	Stable	Increasing
Renal structural changes	Worsening	Stable	Improving

* Faster than physiological decline associated with aging (0.1 ml/min/1.73 m^2 per month).

Cortinovis Nephron 134:20–24, 2016

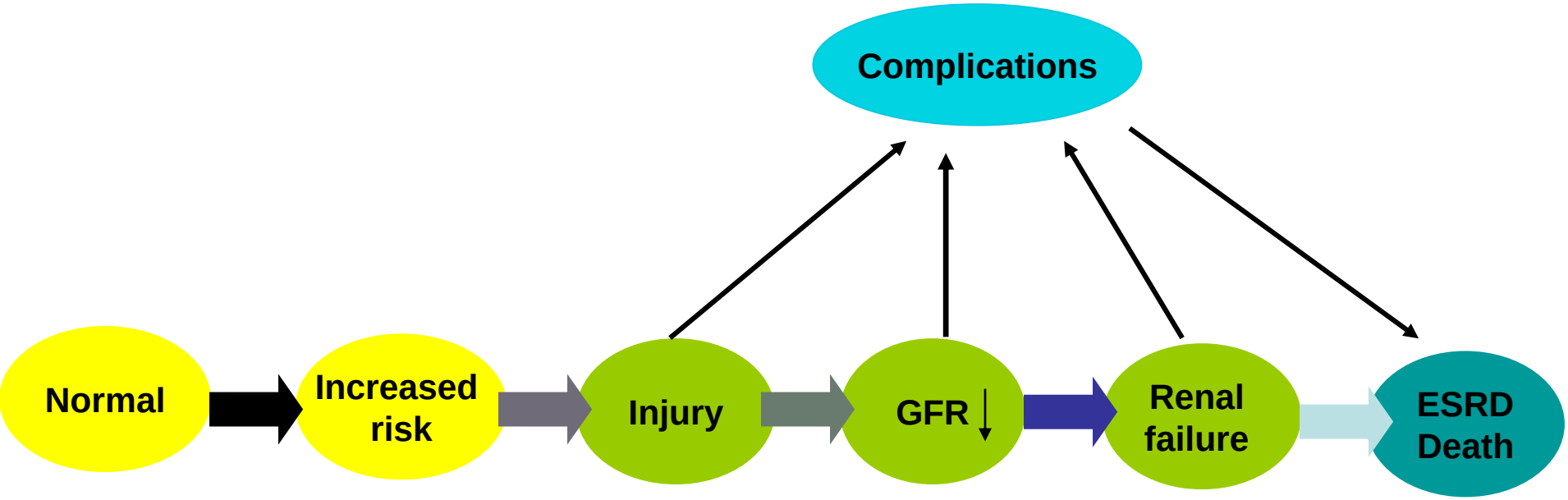
GENERAL PRINCIPLES OF CKD TREATMENT

- **Diagnosis and treatment for primary kidney disease**
- **Determining reversible causes of failure**
- **Slowing down the progression of disease**
- **Management of CKD complications**
- **Preparing for RRT**

POSSIBLE REVERSIBLE CAUSES

- **Acute kidney injury**
- **Primary kidney disease**
- **Collagen tissue disorders**
- **Vasculitis**
- **Early stages of diabetic nephropathy**
- **Renovascular hypertension**
- **Urinary tract obstruction**

CKD PROGRESSES...



Screening for CKD risk factors

CKD risk reduction

Screening for CKD

Diagnosis

Treatment (comorbidities)

Slow progression

Estimate progression

Treat complications

Prepare for RRT

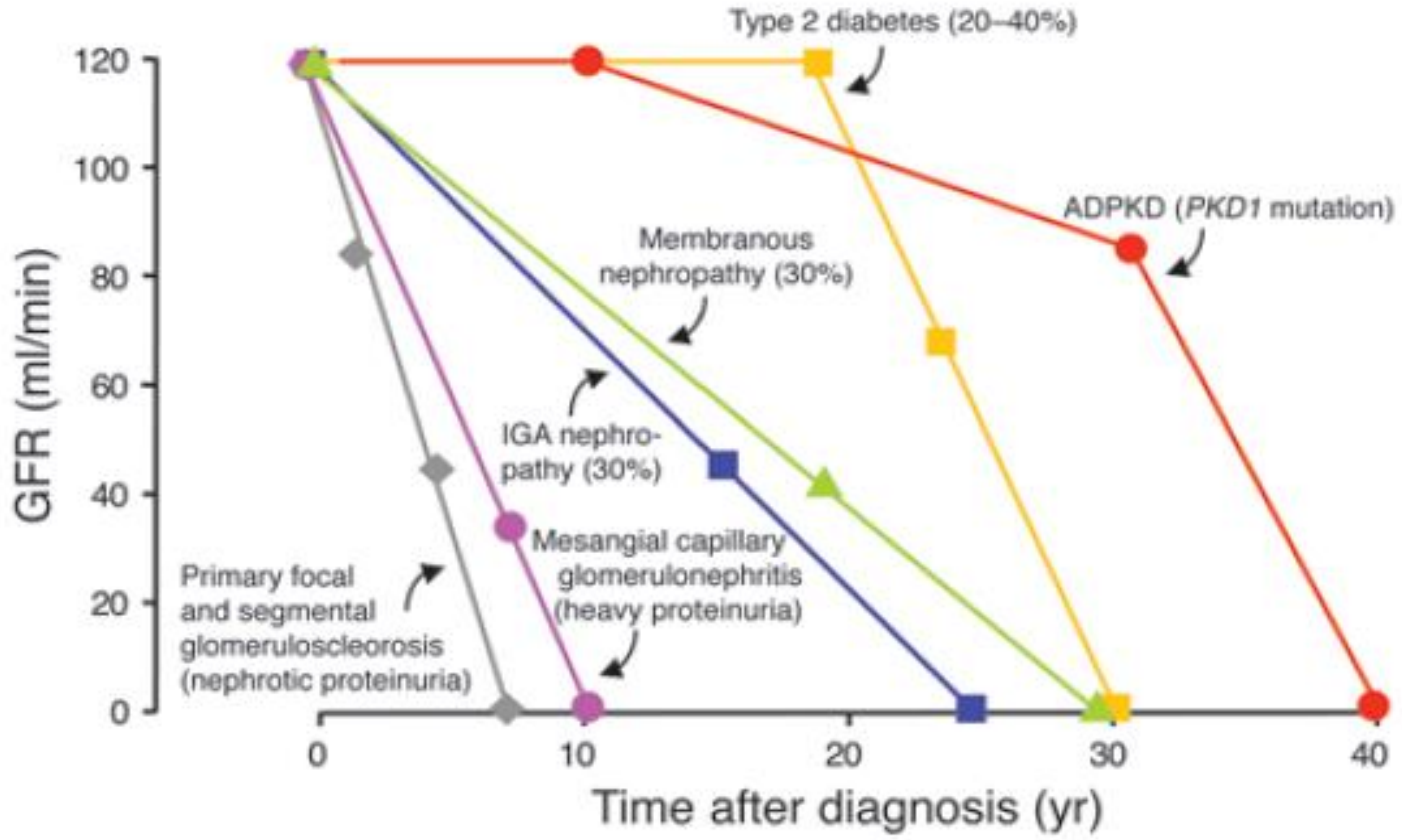
RRT

ASYMPTOMATIC

SYMPTOMATIC

NKF/DOQI 2000 Update. Am J Kidney Dis 37 (Suppl 1), 2001

CKD PROGRESSES...

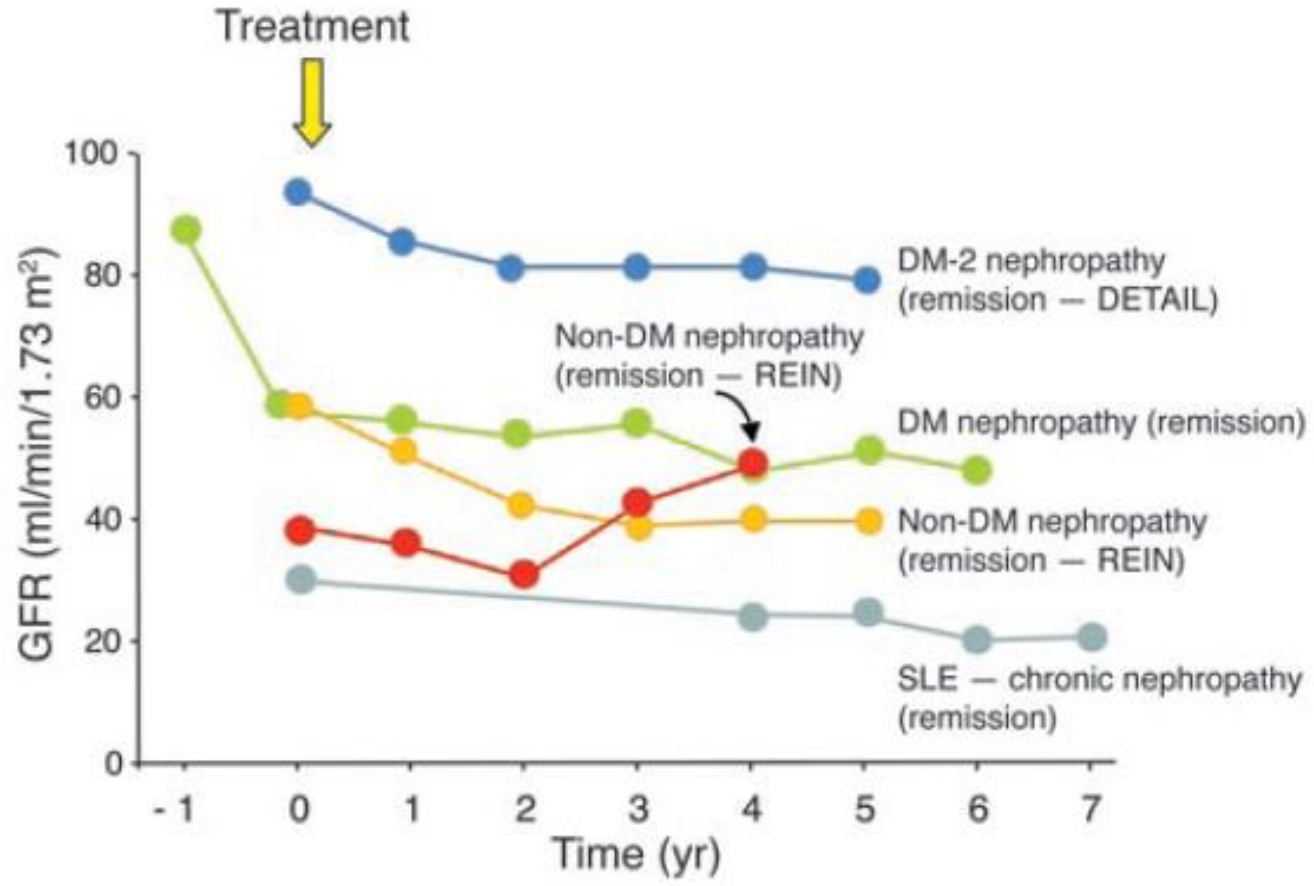


J Clin Invest 116, 2006

SLOW PROGRESSION

- **Treatment of primary kidney disease**
- **Strict control of blood pressure, blockade of RAS**
- **Strict control of blood glucose level**
- **Reduce proteinuria**
- **Protein restriction in diet**
- **Treatment of hyperlipidemia and metabolic acidosis**
- **Quit smoking**
- **Reduce weight**

...CAN BE CONTROLLED !!!



J Clin Invest 116, 2006

BLOOD PRESSURE CONTROL

- **80 - 85% CKD population is hypertensive**
- **Blood presure regulation controls both CKD progression and cardiovascular risks**
- **Combination therapies are preferred (ACEi or ARB or diuretic)**
- **Hypervolemia is crucial (loop diuretics and thiazides)**
- **Life style modification is important, too**

IDEAL ANTIHYPERTENSIVE

1. Adequate control of blood pressure
2. Reduction in proteinuria
3. Slowing down the renal injury
4. Positive effect on serum lipid levels
5. Contribution to extra-renal disorders

ANTIHYPERTENSIVE DRUGS

Preventing Progression of Chronic Kidney Disease: Renin–Angiotensin–Aldosterone System Blockade Beyond Blood Pressure

10

Merlin C. Thomas

Before You Start: Facts You Need to Know

- Activation of the renin–angiotensin–aldosterone system (RAAS) contributes to the development of hypertension in patients with chronic kidney disease.
- Blockade of the RAAS is the most widely used strategy to prevent progression of chronic kidney disease, both in the presence and absence of diabetes.
- Blockade of the RAAS has also been suggested to have pleiotropic effects in the kidney beyond blood pressure lowering, consistent with the role of the RAAS in renal pathophysiology.
- Clinical trials have demonstrated reduction in proteinuria in patients with chronic kidney disease, beyond that seen with other antihypertensive classes despite comparable efficacy with respect to blood pressure lowering.

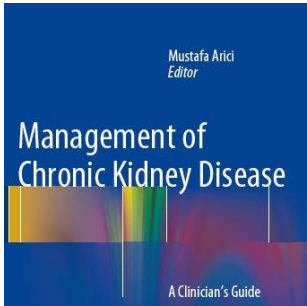
M.C. Thomas, MBChB, PhD, FRACP
Department of Biochemistry of Diabetes Complications, Baker IDI Heart and Diabetes

10.1 The Renin–Angiotensin–Aldosterone System (RAAS)

The renin–angiotensin–aldosterone system (RAAS) is a fundamental regulator of vascular homeostasis, mediated directly through its myriad effects on vascular structure and function and indirectly through its effects in the kidney, including sodium and water handling, glomerular filtration pressure, renal blood flow and tubular growth (Box 10.1). The RAAS is a complex multienzymatic hormonal cascade (Fig. 10.1) whose activity is regulated on many levels, with both positive and negative feedback pathways that ensure optimal responsiveness to both physiological and pathogenic stimuli. At its most simplistic, angiotensinogen, the major

Box 10.1. Some of the Non-haemodynamic Actions of Angiotensin II in the Kidney

Increased sodium retention
Tubular hypertrophy and atrophy
Epithelial to mesenchymal transition
Myofibroblast accumulation
Mesangial contraction
Foot process effacement (dedifferentiation)
Fibrogenesis
Renal tubular acidosis
NADPH-dependent generation of reactive oxygen species
Mitochondrial dysfunction

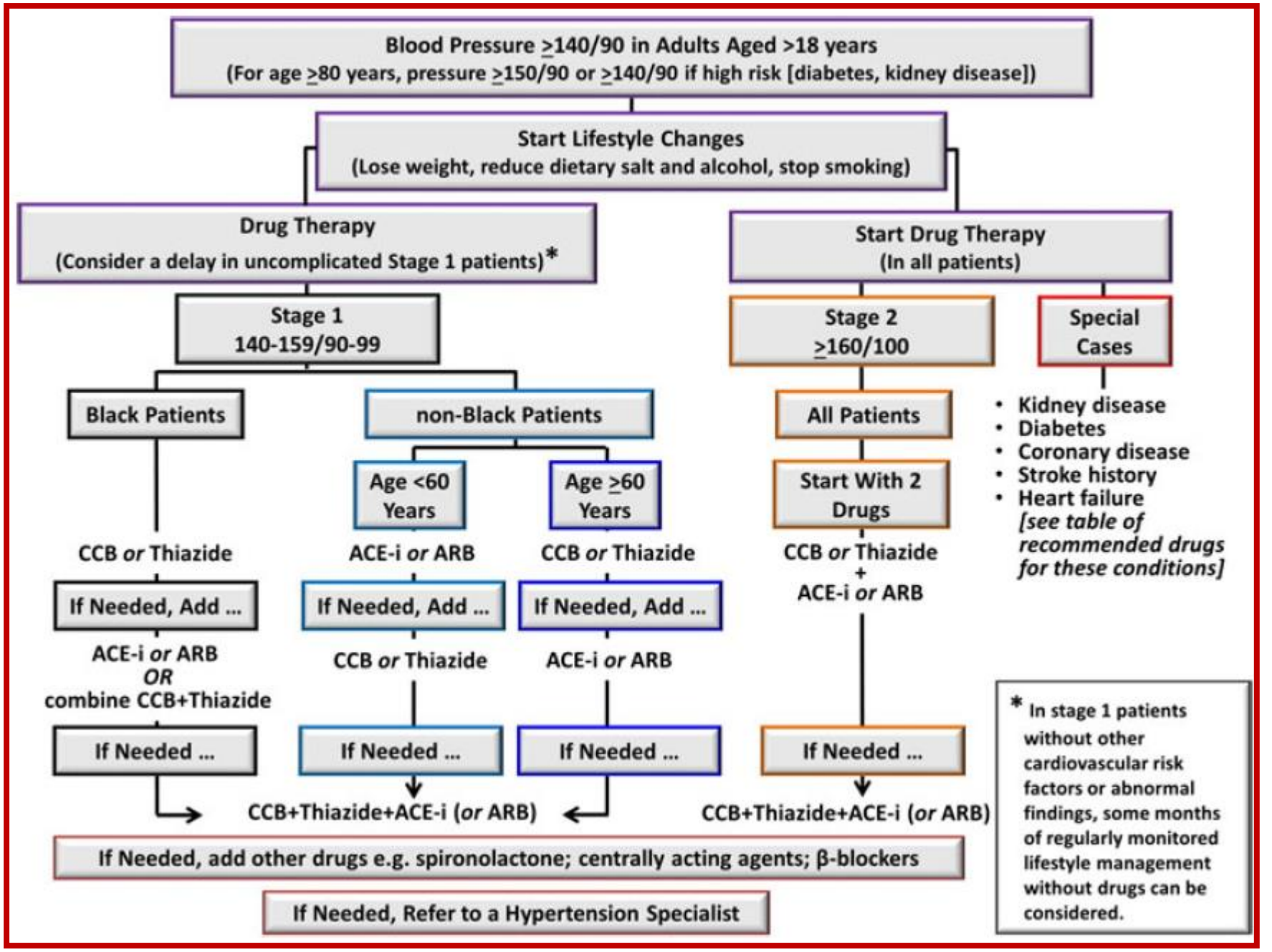


RENAL EFFECTS OF ANTIHYPERTENSIVE DRUGS

	GFR	Proteinuria	Lipid
• ACE inhibitors	☺	☺	☺
• AT-1 receptor antagonists			
• Beta blockers	☺	☺	(?)
• Dihydropiridines	😐	😐	☹
• Diltiazem-Verapamil	😐 ☺	😐	😐
• Alfa blockers	☺	☺	😐
• Central alfa agonists	😐	😐	☺
• Direct vasodilators	😐	😐	☹ (?)
• Diuretics (spirinolacton??)	😐	😐	☺
	😐	😐	☹

TREATMENT OF HYPERTENSION

	Target blood pressure	Non-pharmacologic	Pharmacologic
General population	<140/90 mmHg	Salt restriction Excersize	Personalized
CKD, Stage 1-4, Proteinuria >1g/day	<125/75 mmHg	Salt restriction	ACEi / ARB Diuretics CCB
CKD, Stage 1-4, Proteinuria <1g/day	<130/80 mmHg	Salt restriction	ACEi / ARB Diuretics CCB
CKD, Stage 5	<140/90 mmHg	Salt restriction Fluid restriction UF	All drusgs (except diuretics)


Blood Pressure ≥140/90 in Adults Aged >18 years
(For age ≥80 years, pressure ≥150/90 or ≥140/90 if high risk [diabetes, kidney disease])
Start Lifestyle Changes
(Lose weight, reduce dietary salt and alcohol, stop smoking)
Drug Therapy
(Consider a delay in uncomplicated Stage 1 patients)*
Start Drug Therapy
(In all patients)
Stage 1
140-159/90-99
Stage 2
≥160/100
Special Cases
Black Patients
non-Black Patients
All Patients
Kidney disease
Diabetes
Coronary disease
Stroke history
Heart failure
[see table of recommended drugs for these conditions]
Age <60 Years
Age ≥60 Years
Start With 2 Drugs
CCB or Thiazide
ACE-i or ARB
CCB or Thiazide
CCB or Thiazide
+
ACE-i or ARB
If Needed, Add ...
If Needed, Add ...
If Needed, Add ...
ACE-i or ARB
OR
combine CCB+Thiazide
CCB or Thiazide
ACE-i or ARB
If Needed ...
If Needed ...
If Needed ...
If Needed ...
CCB+Thiazide+ACE-i (or ARB)
CCB+Thiazide+ACE-i (or ARB)
If Needed, add other drugs e.g. spironolactone; centrally acting agents; β-blockers
If Needed, Refer to a Hypertension Specialist
* In stage 1 patients without other cardiovascular risk factors or abnormal findings, some months of regularly monitored lifestyle management without drugs can be considered.

2013 ESH/ESC Guidelines for the Management of Arterial Hypertension

Blood pressure targets in CKD patients

Suggestions	Category	Evidence
Systolic blood pressure should be < 140 mmHg	IIa	B
Systolic blood pressure should be < 130 mmHg if overt proteinuria	IIb	B
If overt proteinuria or microalbuminuria then RAS blockade is better than any other antihypertensive	I	A
To reach target blood pressure at least one drug should be a RAS blocker	I	A
Double blockade of RAS is not recommended for treatment proteinuria	III	A
Combination of aldosteron antagonists with RAS blockers can deteriorate kidney function and cause hyperkalemia	III	C

Clinical Practice: Mini-Review

nephron
Clinical
Practice

Nephron 2016;134:20–24
DOI: 10.1159/000445844

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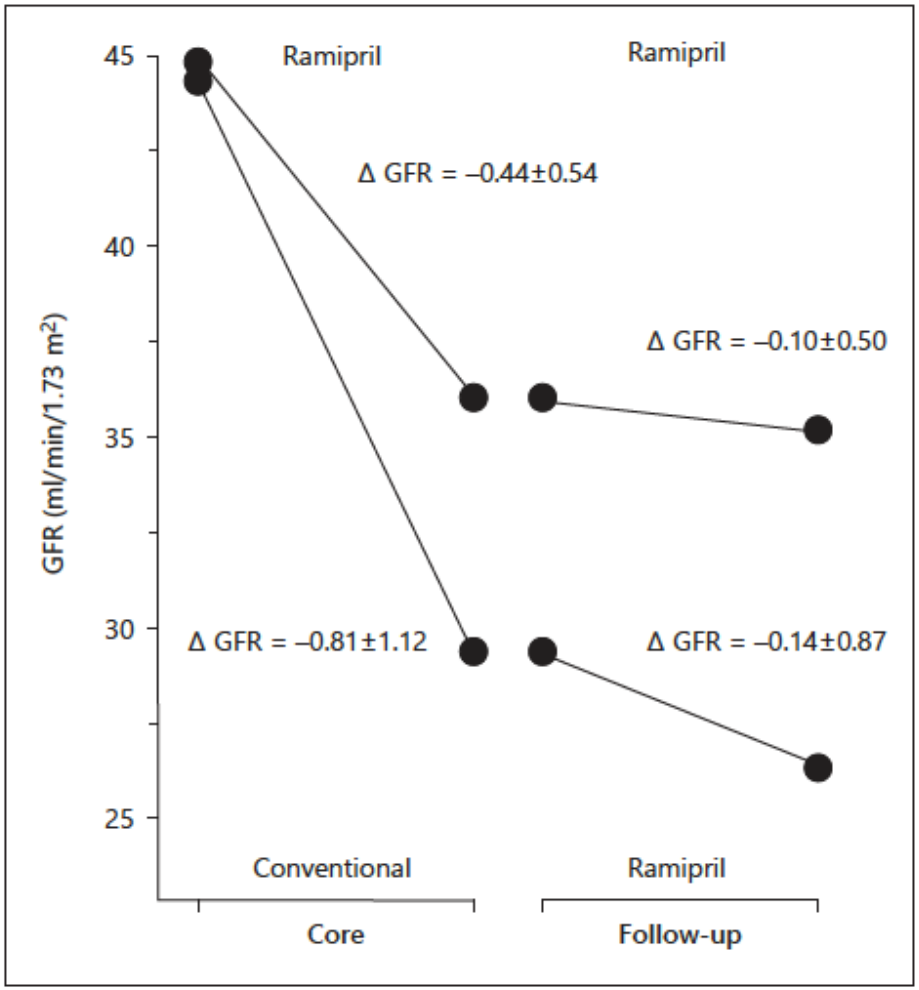
Progression, Remission and Regression of Chronic Renal Diseases

Monica Cortinovis[a] Piero Ruggenenti[a, b] Giuseppe Remuzzi[a–c]

PROTEINURIA TREATMENT



Cortinovis Nephron 134:20–24, 2016

PROTEINURIA TREATMENT

nephron
Clinical
Practice

Nephron 2015;129:39–41
DOI: 10.1159/000368331

Dual Renin-Angiotensin System Blockade for Nephroprotection: Still under Scrutiny

Giorgio Gentile[a, b] Giuseppe Remuzzi[a, b] Piero Ruggenenti[a, b]

[a]IRCCS – Istituto di Ricerche Farmacologiche Mario Negri, Clinical Research Center for Rare D
Daccò, Ranica, Bergamo, and [b]Unit of Nephrology and Dialysis, Azienda Ospedaliera Papa Gi
Italy

PROTEINURIA TREATMENT

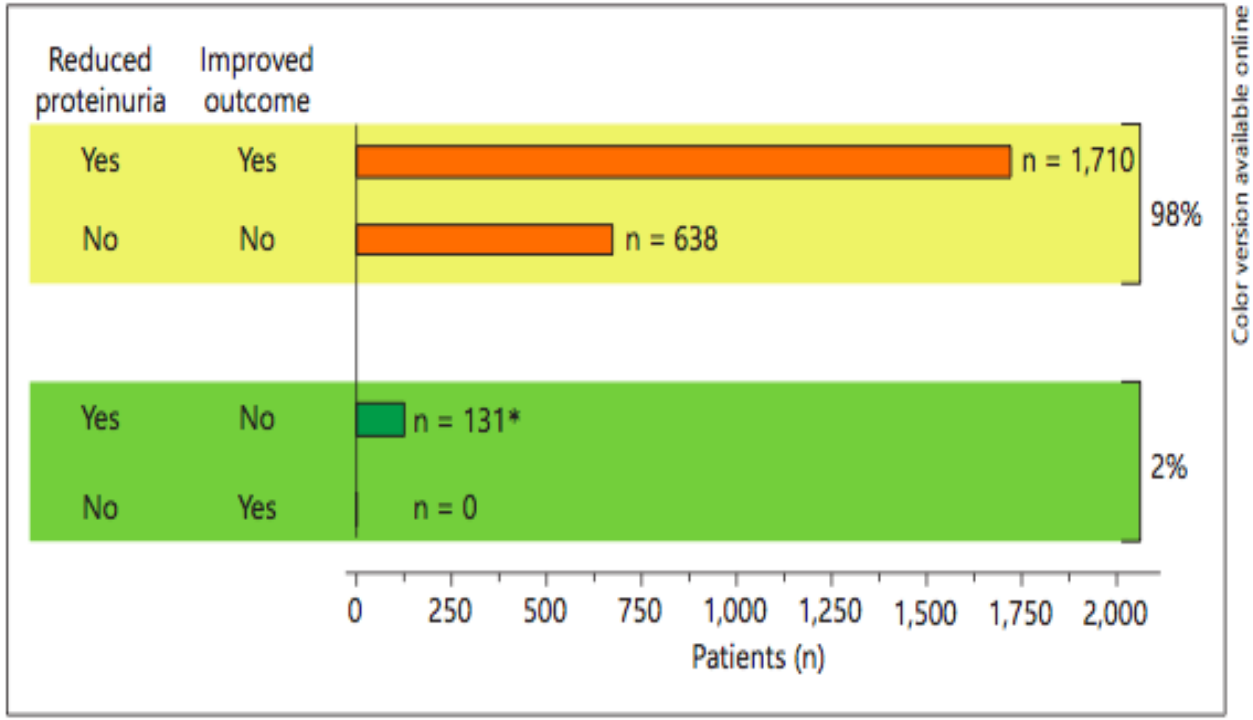


Fig. 1. Change in proteinuria from baseline and renal disease outcome in 2,387 patients with proteinuric CKD included in 11 randomized clinical trials. The asterisk indicates patients who were included in 2 studies that were too small and too short to detect a long-term treatment effect on GFR decline or ESRD events. Modified from Ruggenenti et al. [11].

Gentile et al. Nephron 129:39-41,2015

PROTEINURIA TREATMENT

- ✓ **ONTARGET**
  - **Telmisartan + ramipril / plasebo + telmisartan**
  - **High vascular risk**
  - **Diabetic patients**
  - **Worse outcomes with combination therapy**
- ✓ **ALTITUDE**
  - **Nephro-cardioprotective effect**
  - **Aliskiren + ACE inh/ARB / placebo + ACE inh/ARB**
  - **1515 type 2 diabetic nephropathy patients**
  - **Increased stroke**
  - **Early stop**
  - **Forbidden by FDA**

Gentile et al. Nephron 129:39-41,2015

PROTEINURIA TREATMENT

- ✓ **VA NEPHRON D**

A randomised trial

Lisinopril + Losartan / Losartan

1,448 type 2 diabetes patients with overt nephropathy

Dual RAS inhibition reduced ESRD events by 34%

(p= 0.07)

Significantly higher proteinuria reduction in 2.2 years

Gentile et al. Nephron 129:39-41,2015

PROTEINURIA TREATMENT

- **VALID (ClinicalTrials.gov: NCT00494715)**

(A Prospective, Randomized, Probe Trial to Evaluate Whether,at Comparable Blood Pressure Control,Combined Therapy With ACEI BEN and ARB VAL Reduces Progression to ESRD More Effectively Than BEN or VAL Alone in High Risk Patients With Type 2 Diabetes and Overt Nephropathy)

102 type 2 diabetic patients

Half dose ACE inh (benazepril) and half dose ARB (valsartan)

Gentile et al. Nephron 129:39-41,2015

Modifiable lifestyle and social factors affect chronic kidney disease in high-risk individuals with type 2 diabetes mellitus

Daniela Dunkler[1,2,3], Maria Kohl[1,2,3], Georg Heinze[3], Koon K. Teo[1], Annika Rosengren[4], Janice Pogue[1], Peggy Gao[1], Hertzel Gerstein[1], Salim Yusuf[1], Rainer Oberbauer[3,5] and Johannes F.E. Mann[1,2,6] for the ONTARGET Investigators

[1]Population Health Research Institute, Hamilton Health Sciences/McMaster University, Hamilton, ON, Canada; [2]University of Erlangen-Nürnberg, Department of Nephrology, Erlangen, Germany; [3]Section for Clinical Biometrics, Center for Medical Statistics, Informatics and Intelligent Systems, Medical University of Vienna, Vienna, Austria; [4]Sahlgrenska University Hospital/Östra Hospital, Göteborg, Sweden; [5]KH Elisabethinen Linz and Department of Internal Medicine III, Medical University of Vienna, Vienna, Austria and [6]Schwabing General Hospital, and KfH Kidney Center, Munich, Germany

6972 diabetic patient without macroalbuminuria

CKD progression

- yearly >5% GFR decrease
- ESRD
- microalbuminuria
- macroalbuminuria

} **5.5 years**

Life style/ social factors

- smoking, drinking
- excersize
- financial issues
- education
- social network

Kidney Int 87:784–791,2015

Modifiable lifestyle and social factors affect chronic kidney disease in high-risk individuals with type 2 diabetes mellitus

Daniela Dunkler[1,2,3], Maria Kohl[1,2,3], Georg Heinze[3], Koon K. Teo[1], Annika Rosengren[4], Janice Pogue[1], Peggy Gao[1], Hertzel Gerstein[1], Salim Yusuf[1], Rainer Oberbauer[3,5] and Johannes F.E. Mann[1,2,6] for the ONTARGET Investigators

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31% CKD, 15% death

Social network score risk for CKD and death risk factor

Education is related to CKD

Stress and financial anxiety are not effective

Regular excersize reduces CKD risk

Kidney Int 87:784–791,2015

GLUCOSE CONTROL

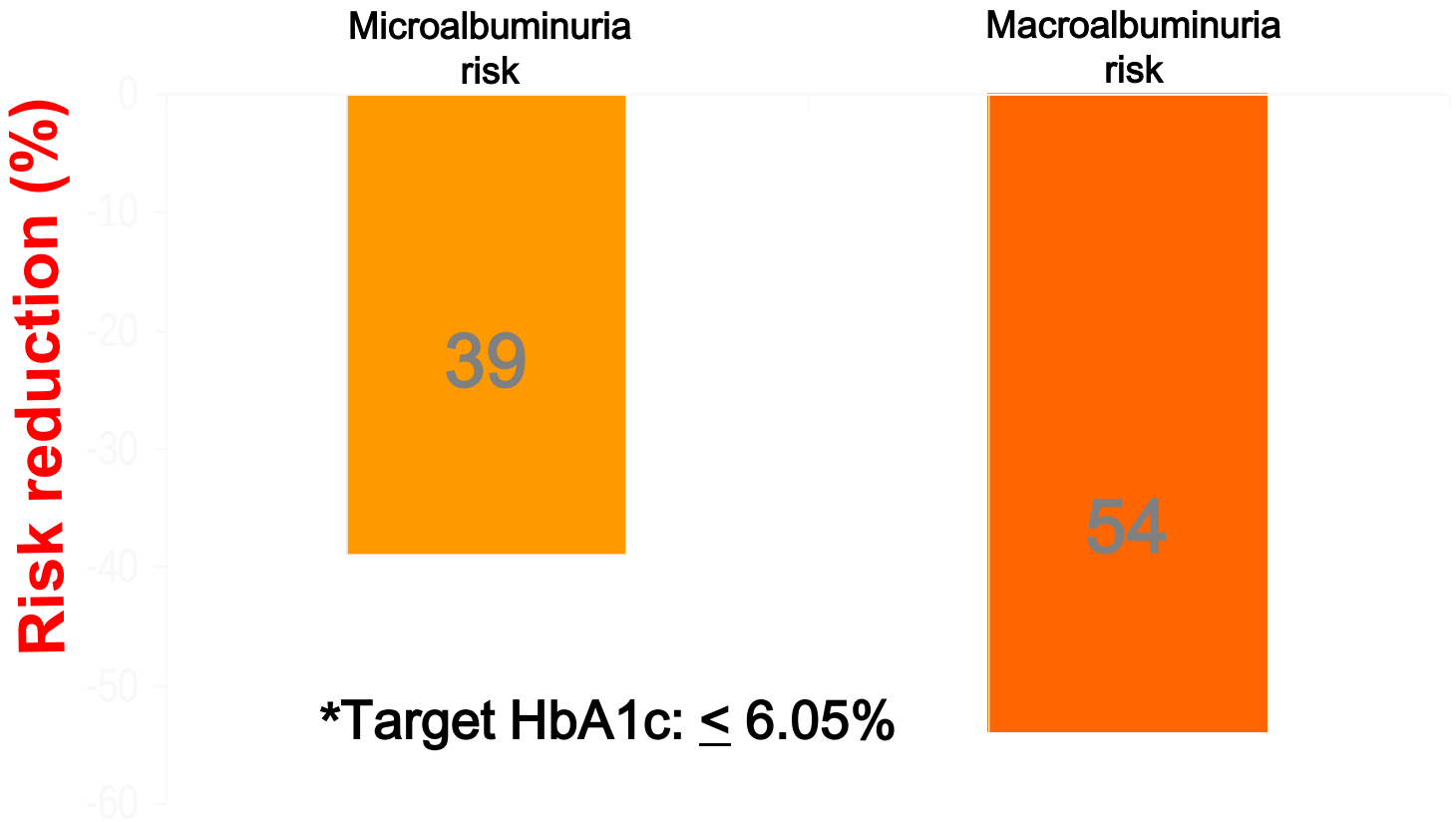
Control of blood sugar has been clearly demonstrated to stop microalbuminuria with two studies

UKPDS GROUP; Lancet 1998

DCCT RESEARCH GROUP; Kidney Int 1995

DCCT
(Diabetes Control and Complications Trial)

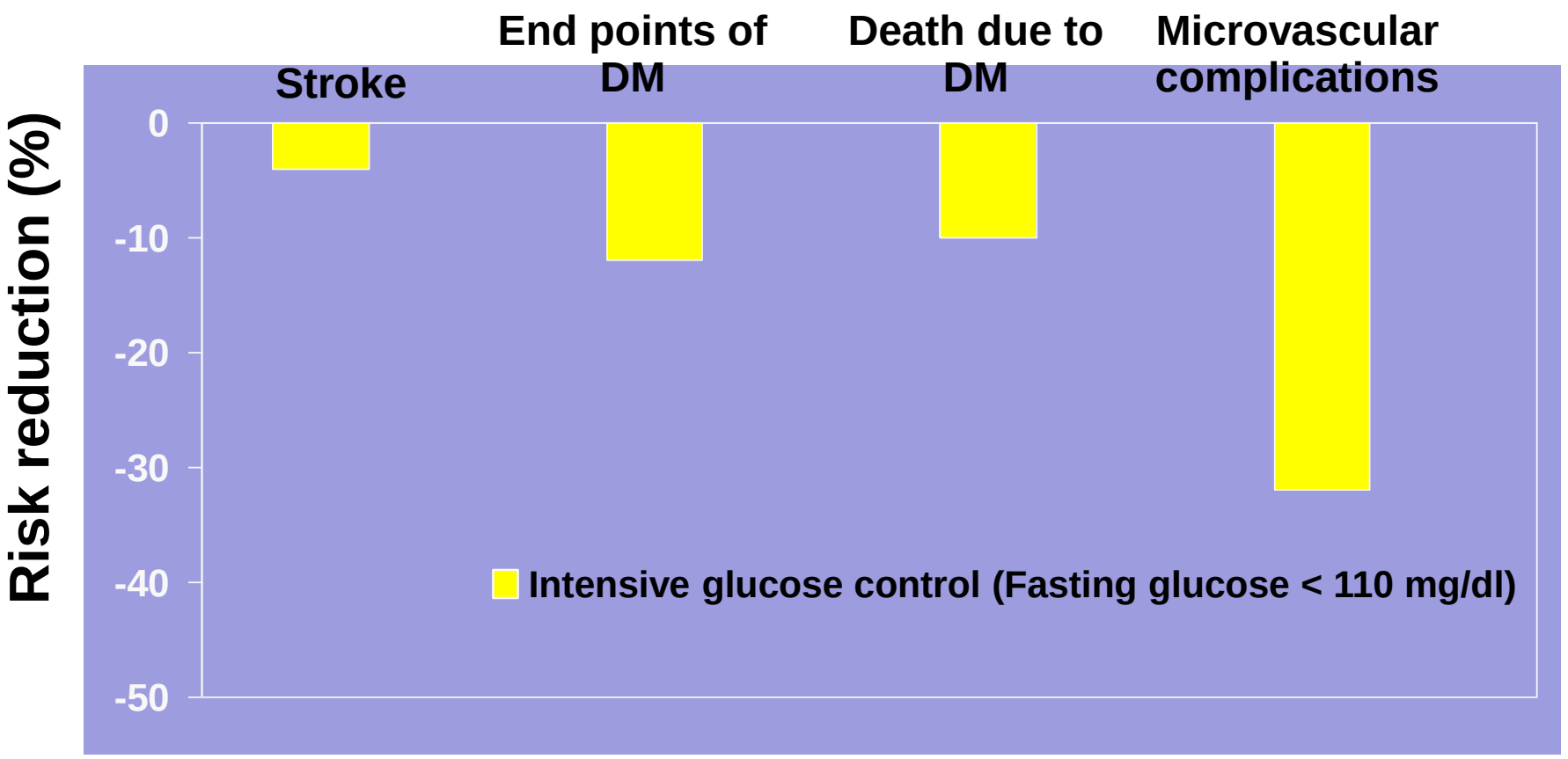
Intensive insulin treatment* in type I diabetes mellitus for nephropathy protection



*Target HbA1c: ≤ 6.05%

DCCT Research Group. N Engl J Med 329:977-986, 1993

UKPDS
(UK Prospective Diabetes Study)



Tip II Diabetes Mellitus
5100 hypertensive patients

UK Prospective Diabetes Study Group. Lancet 352: 837-853, 1998

BLOOD SUGAR CONTROL

	DCCT	Kumamoto	UKPDS
HbA1c	%9 → %7	%9 → %7	%8 → %7
Nephropathy	% 54 ↓	% 70 ↓	% 24-33 ↓
Retinopathy	% 63 ↓	% 69 ↓	% 17-21 ↓
Neuropathy	% 60 ↓	-	-
Macrovascular disease	-	-	% 16 ↓

DCCT Research Group. N Engl J Med 329:977–986, 1993
Ohkubo Y et al. Diabetes Res Clin Pract. 28:103–117, 1995
UKPDS 33. Lancet. 1998;352:837–853, 1998

BLOOD SUGAR CONTROL

DIABETES

Risks of strict glycaemic control in diabetic nephropathy

Martin H. de Borst and Gerjan Navis

A 6-year follow-up study of the ADVANCE trial participants reports that intensive glycaemic control is renoprotective—but does not reduce mortality—in patients with type 2 diabetes mellitus. By contrast, a *post hoc* analysis of the ACCORD trial suggests that intensive glycaemic control might increase mortality in patients with diabetic nephropathy.

De Borst, M. H. & Navis, G. *Nat. Rev. Nephrol.* **11**, 5–6 (2015); published online 4 November 2014; doi:10.1038/nrneph.2014.209

BLOOD SUGAR CONTROL

Table 1 | Trials comparing intensive versus standard glycaemic control in T2DM

	ADVANCE[1]	ADVANCE-ON[3]	ACCORD[2]	Papademetriou *et al.*[4]
Number of patients	11,140	8,494	10,251	10,136
Follow-up (years)	5.0	5.4 (post-trial)	3.4	3.4
Comparison	Intensive versus standard glucose control	Intensive versus standard glucose control	Intensive versus standard glucose control	Intensive versus standard glucose control in CKD and non-CKD subgroups*
HbA_{1c} at study end (%)	6.5 versus 7.3	7.2 versus 7.4	6.3 versus 7.3	CKD: 6.3 versus 7.4 Non-CKD: 6.3 versus 7.5
Primary end point(s) (HR [95% CI])	Major macrovascular or microvascular events (0.90 [0.82–0.98])‡	All-cause mortality (1.00 [0.92–1.08]) Major macrovascular events (1.00 [0.92–1.08])	Nonfatal myocardial infarction, stroke or cardiovascular mortality (0.90 [0.78–1.04])	Cardiovascular or all-cause mortality in CKD versus non-CKD subgroups (1.86 [1.65–2.11])‡
Renal end point (HR [95% CI])	ESRD (0.35 [0.15–0.83])‡	ESRD (0.54 [0.34–0.85])‡	ESRD[5] (0.95 [0.73–1.24])	NA
Cardiovascular mortality (HR [95% CI])	0.88 [0.74–1.04]	0.97 [0.86–1.10]	1.35 [1.04–1.76]‡	CKD: 1.41 [1.05–1.89]‡ Non-CKD: 1.14 [0.82–1.58]
All-cause mortality (HR [95% CI])	0.93 [0.83–1.06]	1.00 [0.92–1.08]	1.22 [1.01-1.46]‡	CKD: 1.31 [1.07–1.60]‡ Non-CKD: 1.08 [0.87–1.34]

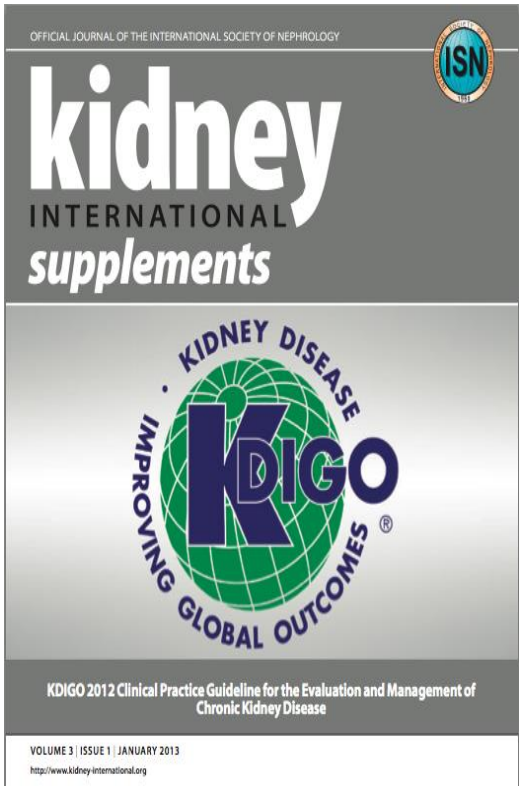
HRs indicate the risk to reach an end point for intensive versus standard glucose control. *ACCORD participants with CKD (n = 3,636) versus those without CKD (n = 6,506). ‡Significant HR. [5]This end point was analysed in a separate publication.[10] Abbreviations: ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation; ADVANCE-ON, ADVANCE-observational study; CKD, chronic kidney disease; ESRD, end-stage renal disease; HR, hazard ratio; NA, not available; T2DM, type 2 diabetes mellitus.

De Borst MH & Navis G. Nat Rev Nephrol 11: 5–6, 2015

BLOOD SUGAR CONTROL

De Borst MH & Navis G. Nat Rev Nephrol 11: 5–6, 2015

BLOOD SUGAR CONTROL



3.1.15: We recommend a target hemoglobin A_{1c} (HbA_{1c}) of ~7.0% (53 mmol/mol) to prevent or delay progression of the microvascular complications of diabetes, including diabetic kidney disease. (*1A*)

3.1.16: We recommend not treating to an HbA_{1c} target of <7.0% (<53 mmol/mol) in patients at risk of hypoglycemia. (*1B*)

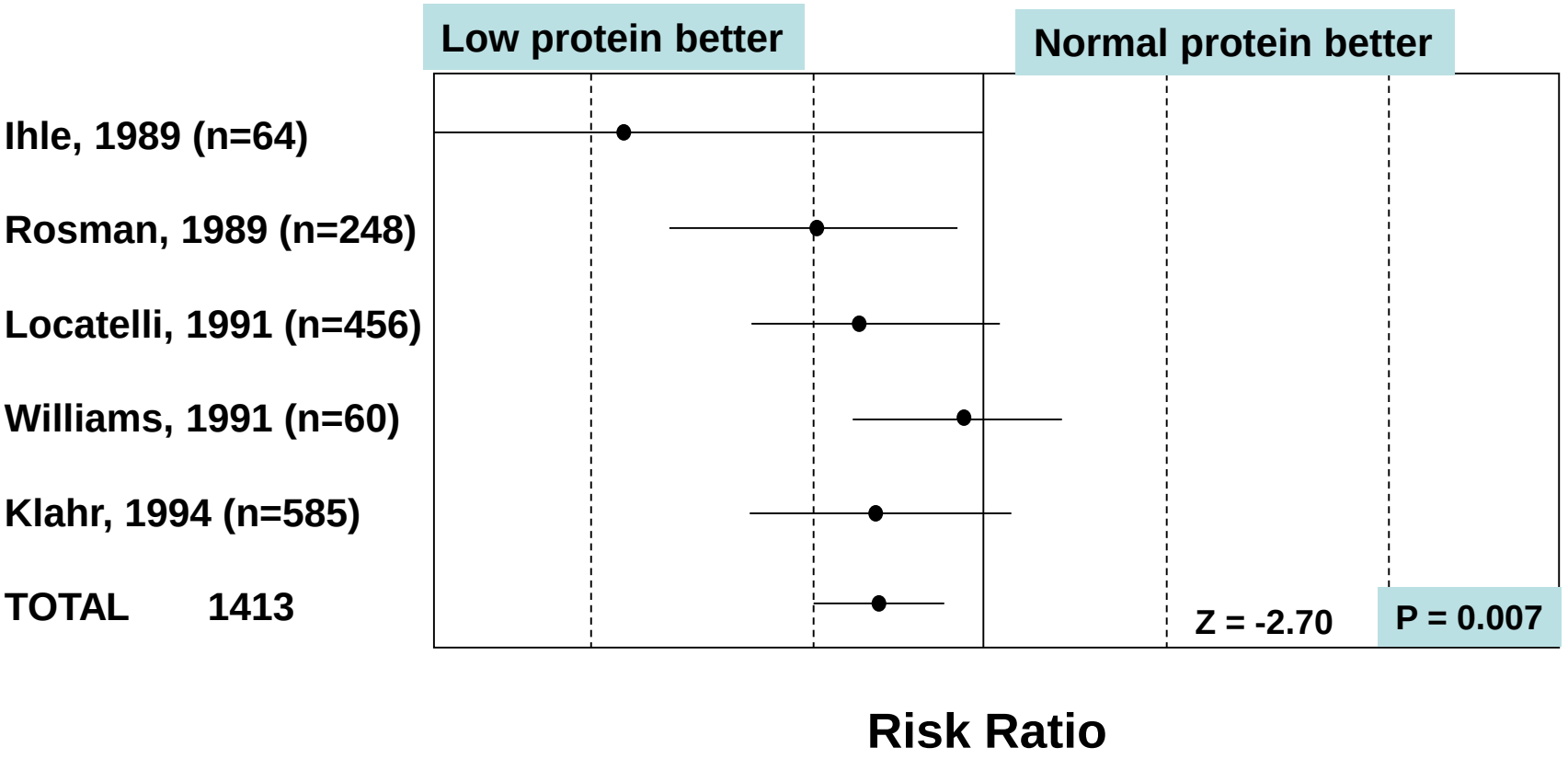
3.1.17: We suggest that target HbA_{1c} be extended above 7.0% (53 mmol/mol) in individuals with comorbidities or limited life expectancy and risk of hypoglycemia. (*2C*)

3.1.18: In people with CKD and diabetes, glycemic control should be part of a multifactorial intervention strategy addressing blood pressure control and cardiovascular risk, promoting the use of angiotensin-converting enzyme inhibition or angiotensin receptor blockade, statins, and antiplatelet therapy where clinically indicated. (*Not Graded*)

THE ROLE OF DIET

- ✓ **Better nutritional status**
- ✓ **Improving uremic toxicity and metabolic disorders of CKD**
- ✓ **Reducing cardiovascular, serebrovascular and peripheral vascular disease**
- ✓ **Slowing the progression of renal failure**

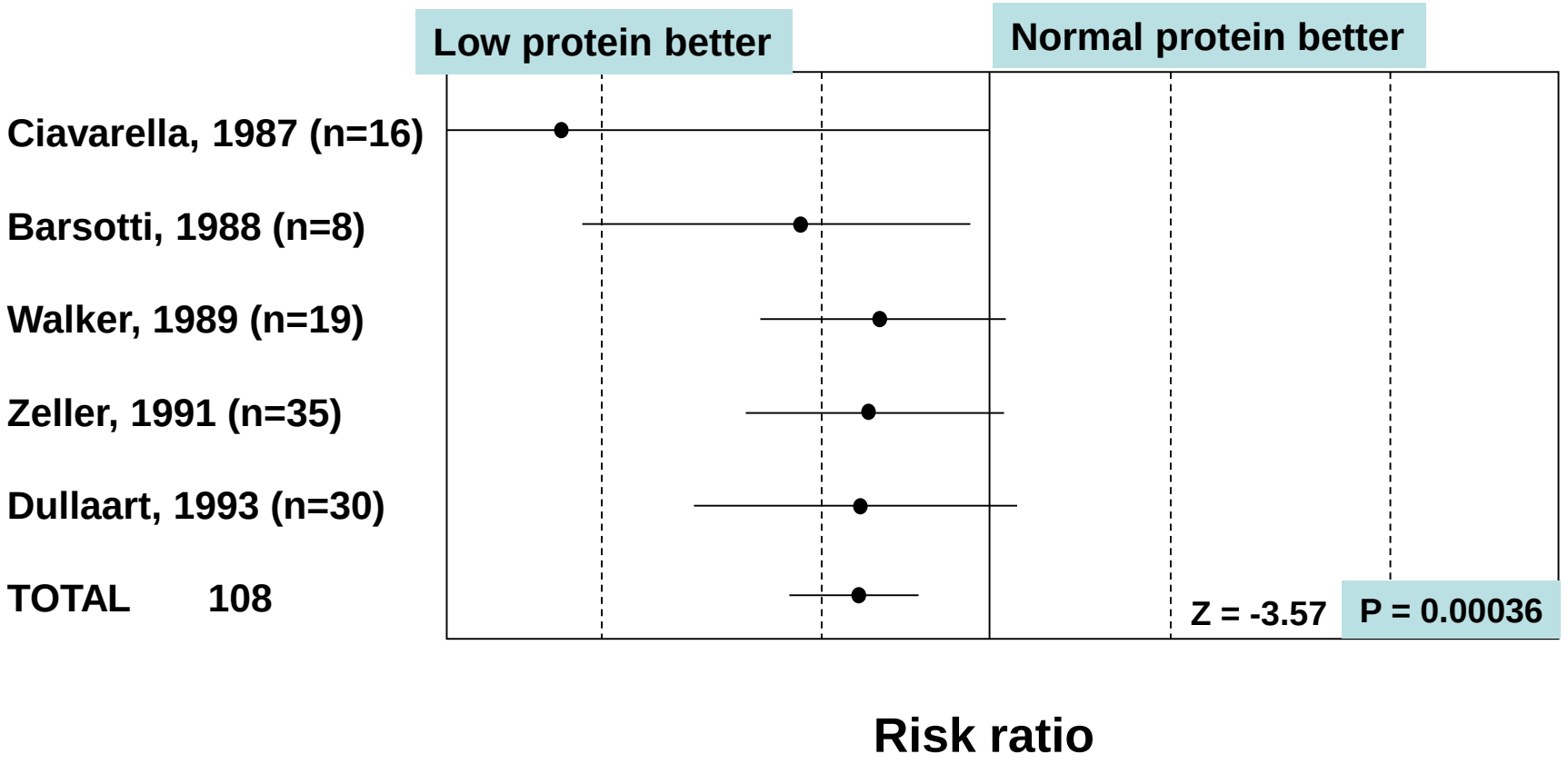
RENOPROTECTIVE EFFECT OF DIET



ESRD or death risk decreased by 33%

Pedrini et al: Ann Intern Med 124: 627-632, 1996

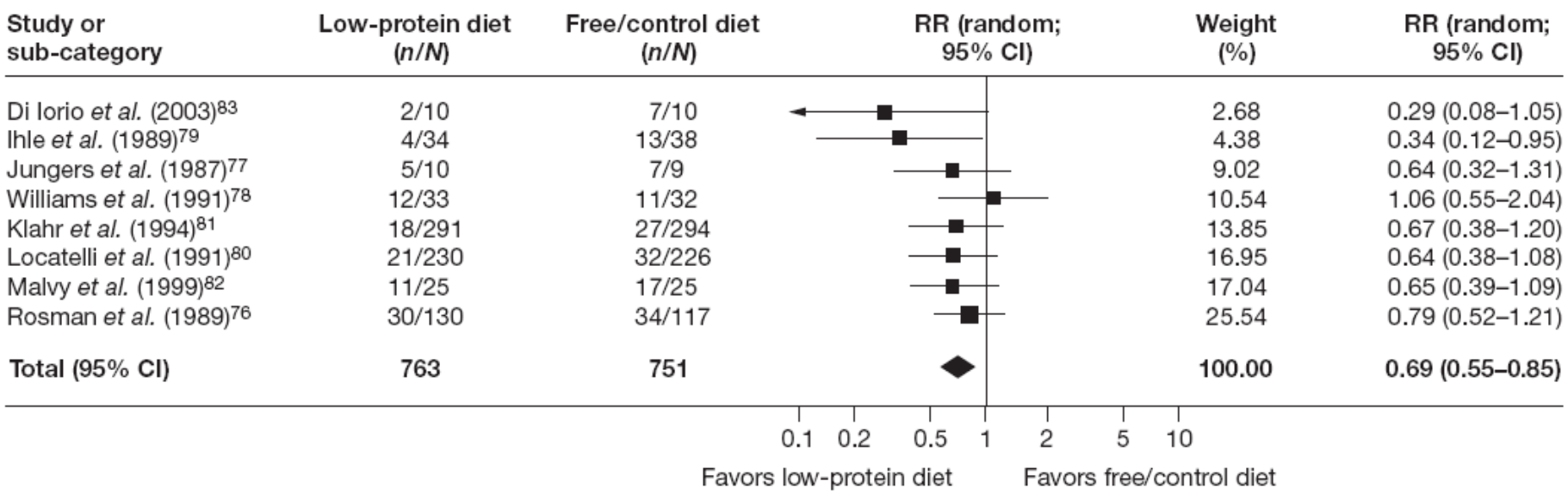
RENOPROTECTIVE EFFECT OF DIET



Reduction in renal function is reduced by 44%

Pedrini et al: Ann Intern Med 124: 627-632, 1996

RENOPROTECTIVE EFFECT OF DIET



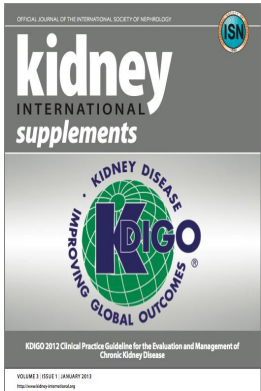
Total events: 103 (low-protein diet), 148 (free/control diet)
Test for heterogeneity: $\chi^2 = 5.78$, df = 7 ($P = 0.57$), $F = 0\%$
Test for overall effect: $Z = 3.45$ ($P = 0.0006$)

***Renal death*: Initiating dialysis, transplantation or death**

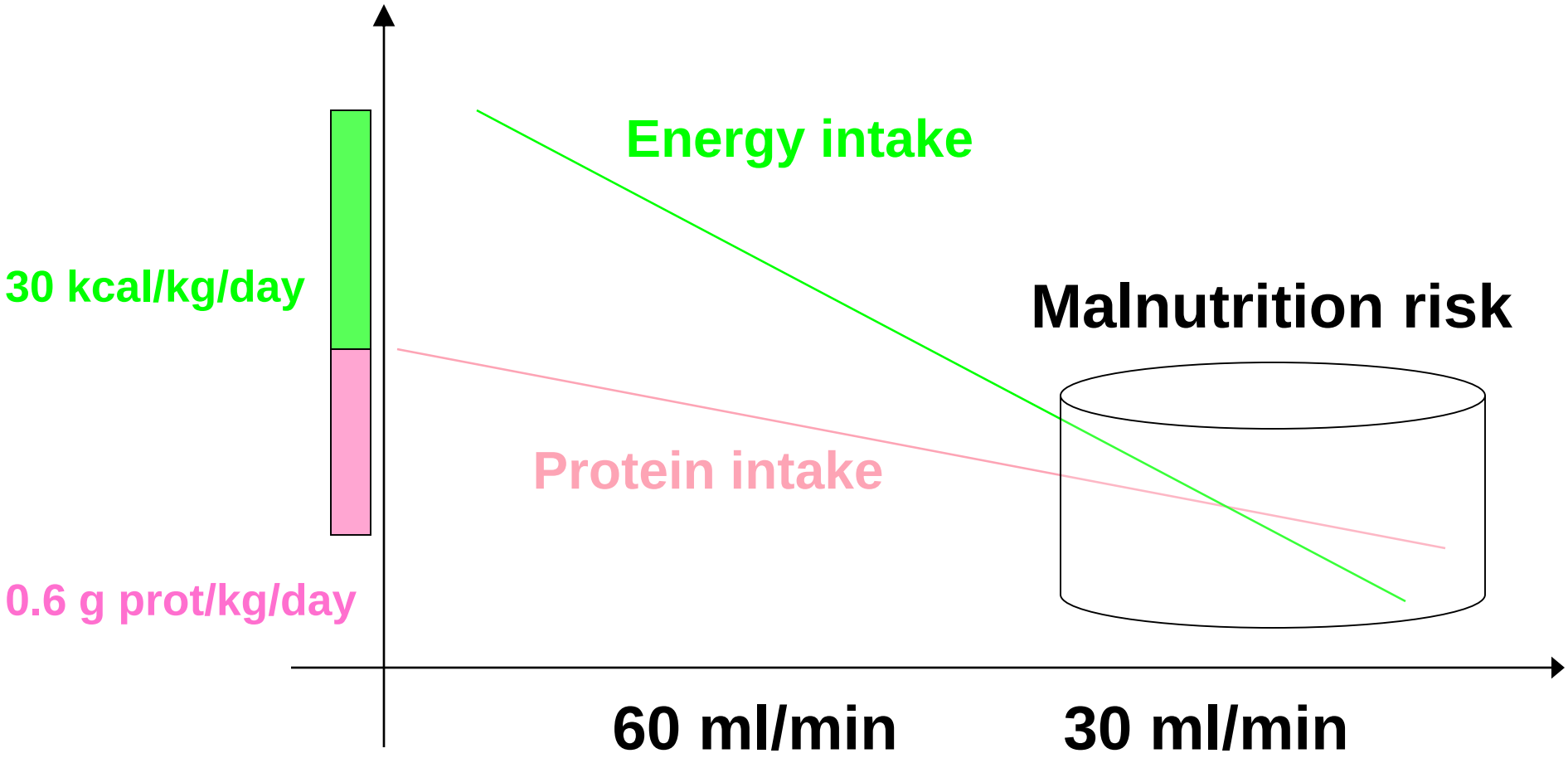
Cochrane Database Systematic Reviews 2006

DIET SUGGESTIONS

- **Fluid** — **1.5-3 liter/day**
- **Protein** — **0.8-1.0 gr/kg/day**
- **Calorie** — **> 30 kcal/kg/day**
- **Lipid** — **30-40% of calories**
- **Polyansaturated/saturated 1 / 1**
- **Carbohydrate** — **Rest of calories**
- **Total fiber** — **20-25 gr/day**



DIET SUGGESTIONS



MALNUTRITION

Protein in take decreases as GFR reduces

> 50 ml/min	**1.10 gr/kg/day**
25-50 ml/min	**0.85 gr/kg/day**
10-25 ml/min	**0.70 gr/kg/day**
< 10 ml/min	**0.54 gr/kg/day**

MALNUTRITION

- **Infection**
- **Cardiovascular event**
- **Others**

Increased morbidity

Increased mortality

Sezer S, et al. J. Turkish Neph. Assoc 3:125-129,2000
Lowrie EG, Lew NL. Am J Kidney Dis XV: 458-482, 1990

MALNUTRITION

- Anorexia
- Continous weight loss
- Body mass index less than 80%
- Decrease in anthropometric measurements
- Growth retardation
- Increased infection risk

- Albumin < 3.5 gr/dl
- Cholesterol < 150 mg/dl
- Transferrin < 150 mg/dl
- Prealbumin < 30 mg/dl
- IGF-1 < 300 µg/L
- Decrease in C and Ig levels
- Decrease in delayed hypersensitivity reactions

LIPID METABOLISM DISORDERS

Hypercholesterolemia is a predictor factor in both diabetic and non-diabetic patients for renal function decrease

Ravid et al. Arch Intern Med 158:998-1004, 1998

Krolewski et al. Kidney Int 45:125-131, 1994

LIPID METABOLISM DISORDERS

ROLE

Accelerated atherosclerosis

Accelerated progression

Intraglomerular hypertension

Mesangial cell activation

Proliferation

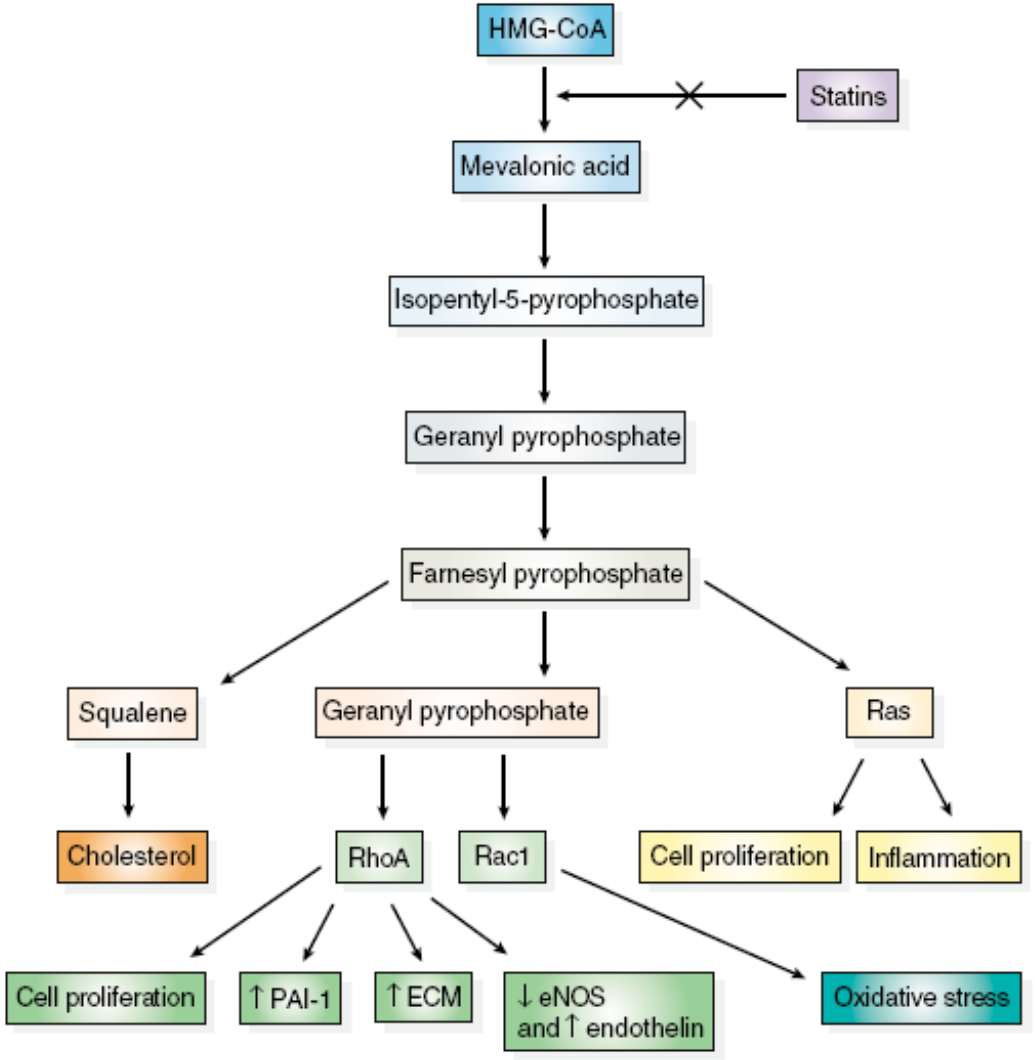
Chemotactic factor production

Fibronectin production

Free oxygen radicals

www.uptodate.com 4 Mart 2015

HYPERLIPIDEMIA TREATMENT



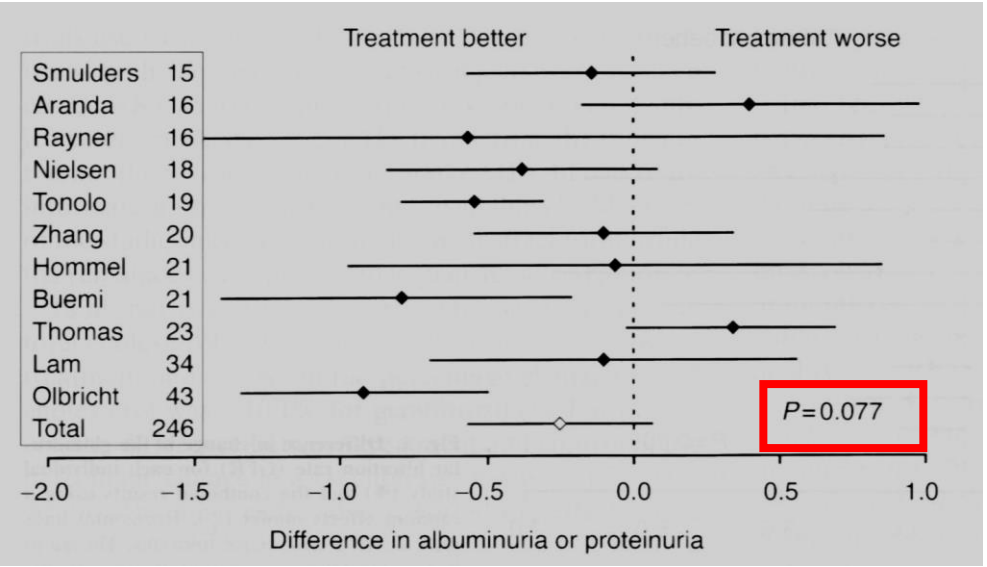
Fried et al Kidney Int 74: 571-576, 2008

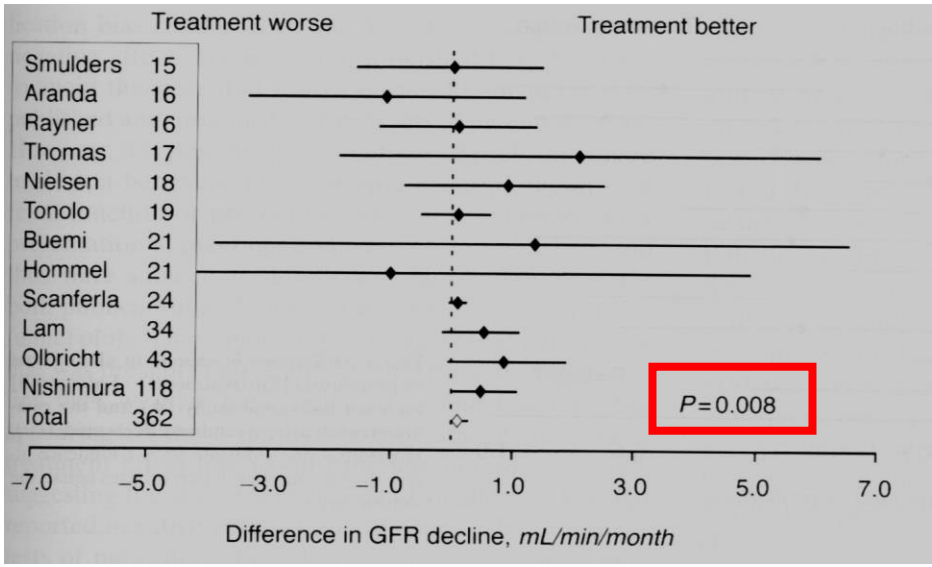
Kidney International, Vol. 59 (2001), pp. 260–269

CLINICAL NEPHROLOGY – EPIDEMIOLOGY – CLINICAL TRIALS

Effect of lipid reduction on the progression of renal disease: A meta-analysis

LINDA F. FRIED, TREVOR J. ORCHARD, and BERTRAM L. KASISKE, for the LIPIDS AND RENAL DISEASE PROGRESSION META-ANALYSIS STUDY GROUP





K/DOQI
(Kidney Disease Outcomes Quality Initiative)

There is not sufficient data for lipid lowering therapy in slowing down the progression of CKD

Fried, 2001
K/DOQI, 2002

HYPERLIPIDEMIA TREATMENT

***The Cholesterol and Recurrent Events* (CARE)**

4159 acute myocardial infarction

Hyperlipidemia

5 years of pravastatin or placebo

Multiple regression analysis

690 proteinuria

proteinuria + GFH <40 ml/min/1.73 m^2

2.5 ml/min/1.73 m^2/year

***www.uptodate.com* 4 Mart 2015**

HYPERLIPIDEMIA TREATMENT

***Treating to New Targets* (TNT) study**

Subgroup 80 mg / 10 mg atorvastatin

10001 coronary artery disease patients

At the beginning mean eGFR 65 ml/min/1.73 m^2

5 year follow-up

Mean eGFR increase

80 mg group 5.2 ml/min/1.73 m^2

10 mg group 3.5 ml/min/1.73 m^2

***www.uptodate.com* 4 Mart 2015**

HYPERLIPIDEMIA TREATMENT

- ***The Prospective Pravastatin Pooling Project***
- **5 year long 3 studies data**

  CARE, WOSCOPS, LIPID
- **3400 CKD patients**
- **GFR 30-60 ml/min/1.73 m^2**
- **Pravastatin or placebo groups**

  Baseline BP and ACE inh usage is same
- **Mean GFR reduction 0.7 ml/min/year**
- **Progression was 34% slower in Pravastatin group (0.2 ml/min/year)**

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HYPERLIPIDEMIA TREATMENT

PREVEND-IT secondary analysis

- **864 patients with albuminuria and stable GFR**
- **After 4 years**
- **Pravastatin and placebo groups GFR**
- **No difference in change**

ALLHAT-LLT study multi-regression analysis

- **pravastatin and placebo groups**
- **ESRD rate for next 6 years**
- **No difference in GFR reduction**

2009 meta-analysis of 11 studies

- **548 patients**
- **No significant improvement in Ccr**

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HYPERLIPIDEMIA TREATMENT

Effects of Lowering LDL Cholesterol on Progression of Kidney Disease

Richard Haynes,* David Lewis,* Jonathan Emberson,* Christina Reith,* Lawrence Agodoa,† Alan Cass,‡ Jonathan C. Craig,§ Dick de Zeeuw,‖ Bo Feldt-Rasmussen,¶ Bengt Fellström,** Adeera Levin,†† David C. Wheeler,‡‡ Rob Walker,§§ William G. Herrington,* Colin Baigent,* Martin J. Landray,* for the SHARP Collaborative Group

*Clinical Trial Service Unit and Epidemiological Studies Unit, Nuffield Department of Population Health, University of Oxford, Oxford, United Kingdom; †National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland; ‡Menzies School of Health Research, Charles Darwin University, Darwin, Northern Territory, Australia; §Sydney School of Public Health, Children's Hospital at Westmead, University of Sydney, Sydney, New South Wales, Australia; ‖Department of Clinical Pharmacy and Pharmacology, University of Groningen, University Medical Centre Groningen, Groningen, The Netherlands; ¶Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; **University Hospital, Uppsala, Sweden; ††University of British Columbia, Vancouver, British Columbia, Canada; ‡‡University College London, London, United Kingdom; and §§Dunedin School of Medicine, University of Otago, Otago, New Zealand

Secondary analysis

Haynes R, et al. Am Soc Nephrol 25: 1825–1833, 2014

HYPERLIPIDEMIA TREATMENT

During randomization

6245 predialysis CKD patients

Simvastatin + ezetimib / placebo

No difference in ESRD risk (33.9% / 34.6%)

Decrease in LDL- cholesterol of 1 mmol/L

caused no change in CKD progression

It is still early to recommend anti-lipemic agents to all CKD patients other than those with atherosclerotic disease

Haynes R, et al. Am Soc Nephrol 25: 1825–1833, 2014

METABOLIC ACIDOSIS

http://www.kidney-international.org

mini review

Bicarbonate therapy for prevention of chronic kidney disease progression

Igor Łoniewski[1] and Donald E. Wesson[2,3]

[1]Sanum Polska Sp. z o.o. ul. Kurza Stopka 5/c, Szczecin, Poland; [2]Department of Internal Medicine, Scott and White Healthcare, Temple, Texas, USA and [3]Texas A&M Health Sciences Center College of Medicine, Temple, Texas, USA

BRIEF REVIEW

www.jasn.org

Current Status of Bicarbonate in CKD

Mirela Dobre, Mahboob Rahman, and Thomas H. Hostetter

Division of Nephrology and Hypertension, Case Western Reserve University, University Hospital Case Medical Center, Cleveland, Ohio

METABOLIC ACIDOSIS

Renal Effects of Metabolic Acidosis:

- **renal hypertrophy and hyperplasia in animal models**
- **activation of the alternative complement pathway**
- **progressive tubular injury**
- **increased endothelin production**
- **tubular interstitial injury**
- **decline in GFR**
- **calcium precipitation in the kidney**

Hostetter TH et al JASN 26:515-523, 2015

METABOLIC ACIDOSIS

Non-Renal Effects of Metabolic Acidosis:

Causes increased bone resorption and decreased bone formation

Causes insulin resistance

Early cardiac fibrosis and impaired diastolic function, which progresses to more global left ventricular remodeling and dysfunction

Reduced myocardial contractility and congestive heart failure

Inflammation, atherosclerosis, elevated endothelin and aldosterone levels

Hostetter TH et al JASN 26:515-523, 2015

METABOLIC ACIDOSIS

Table 1 | Favorable effect of $NaHCO_3$ and alkali supplementation in different CKD animal models

Study	Model	Result
Nath *et al.*[12]	$1\frac{3}{4}$ Nephrectomized rats	↓Impairment of tubular function, ↓histological evidence of tubulo interstitial damage, ↓deposition of the complement components C3 and C5b-9, ↓renal vein total ammonia concentration
Phisitkul *et al.*[2]	5/6 Nx rats and protein acidification	$NaHCO_3$ in combination with anti-hypertensive therapy ameliorated metabolic acidosis and delayed GFR decline
Wesson *et al.*[11]	2/3 Nx rats	$CaHCO_3$ caused ↓H^+ retention, ↓distal nephron acidification, ↓plasma and kidney levels of AII, ET-1, and aldosterone

Abbreviations: AII, angiotensin II; CKD, chronic kidney disease; ET-1, endothelin-1; GFR, glomerular filtration rate.

Łoniewski, Wesson. Kidney Int 85: 529-35, 2014

METABOLIC ACIDOSIS

Table 3. Interventional trials of alkali supplementation aimed to slow progression of kidney disease

First Author (Year)	Population	Treatment Groups	Outcomes	Results	*P* Value
de Brito-Ashurst (2009)[13]	CKD stages 4 and 5	134 patients randomized to sodium bicarbonate versus standard care (24-mo follow-up)	Rate of CrCl decline	Slower (1.88 [−0.39 to 4.15] versus 5.93 [4.19 to 7.76] ml/min per 1.73 m^2	<0.001
			Fall in CrCl>3ml/min per year	Less likely (9% versus 45%)	<0.001
			Development of ESRD requiring dialysis (CrCl<10 ml/min)	Less likely (6.5% versus 33%)	<0.001
Mahajan (2010)[15]	CKD stage 2 hypertensive nephropathy	120 patients randomized to sodium bicarbonate versus placebo versus sodium chloride (5-yr follow-up)	Rate of eGFR decline	Slower decline in eGFR in sodium bicarbonate group of −1.47± 0.19 ml/min per yr versus	
				−2.13±0.19 ml/min per yr versus	0.01
				−2.05±0.19 ml/min per yr	0.03

CrCl, creatinine clearance.

Hostetter TH et al JASN 26:515-523, 2015

METABOLIC ACIDOSIS

Table 2. Ongoing clinical trials of sodium bicarbonate supplementation in CKD

Title (Study Identifier)	Principal Investigators	Study Design	Estimated Enrollment (N)	Eligibility Criteria	Assigned Intervention	Primary Outcomes (Time Frame)
Placebo-Controlled Randomized Clinical Trial of Alkali Therapy in Patients with Chronic Kidney Disease (NCT01452412)	T. Hostetter and M. Melamed	Randomized double-blind placebo controlled trial	150	Adult patients with CKD stages 3B and 4	Sodium bicarbonate versus placebo	Sit to stand to sit speed; HOMA-IR; DEXA of wrist; urinary NGAL and KIM-1 (1 yr)
Effect of Treatment of Metabolic Acidosis on Vascular Function in Patients with Chronic Kidney Disease: A Pilot Study (NCT02031770)	Jessica B. Kendrick	Randomized open-label crossover trial	20	Patients aged 40–70 yr with CKD stage 4	Sodium bicarbonate versus control (no treatment)	Brachial artery flow mediated dilation (14 wk)
A Prospective, Controlled, Randomized, Multicentric Study: Correction of Metabolic Acidosis with Use of Bicarbonate in Chronic Renal Insufficiency (CKD3b-4) (NCT01640119)	Biagio Di Iorio	Randomized open-label trial	600	Adult patients with CKD stage 3B and 4	Sodium bicarbonate versus usual treatment (no bicarbonate)	Doubling of creatinine (3 yr)
Effect of Oral Sodium Bicarbonate Supplementation on Progression of Chronic Kidney Disease in Patients with Chronic Metabolic Acidosis: Study Protocol for a Randomized Controlled Trial (SoBic-Study) (EUDRACT no. 2012-001824-36)	Martina Gaggl	Randomized, controlled, open-label clinical phase IV study	200	CKD stage 3 or 4	High-dose versus low-dose sodium bicarbonate	MDRD eGFR (2 yr)
Investigations of the Optimum Serum Bicarbonate Level in Renal Disease (NCT01574157)	Kalani L. Raphael	Randomized double-blind placebo controlled trial	74	Adult patients with diabetes, proteinuria, and CKD stages 2–4	Sodium bicarbonate versus placebo	Change in urinary TGF-β1 (3 and 6 mo)
Alkali Therapy in Subjects with Sickle Cell Disease (SCD)–Evaluation of Efficacy, Safety, and Beneficial Effects (NCT01894594)	Jane Little	Nonrandomized open-label single group assignment	20	Sickle cell adults patients with eGFR<90 ml/min per 1.73 m^2	Sodium bicarbonate	Serum bicarbonate and potassium levels (12 wk)

HOMA-IR, homeostasis model assessment–estimated insulin resistance; DEXA, dual-energy X-ray absorptiometry; NGAL, neutrophil gelatinase-associated lipocalin; KIM-1, kidney injury molecule-1; MDRD, Modification of Diet in Renal Disease study equation.

Hostetter TH et al JASN 26:515-523, 2015

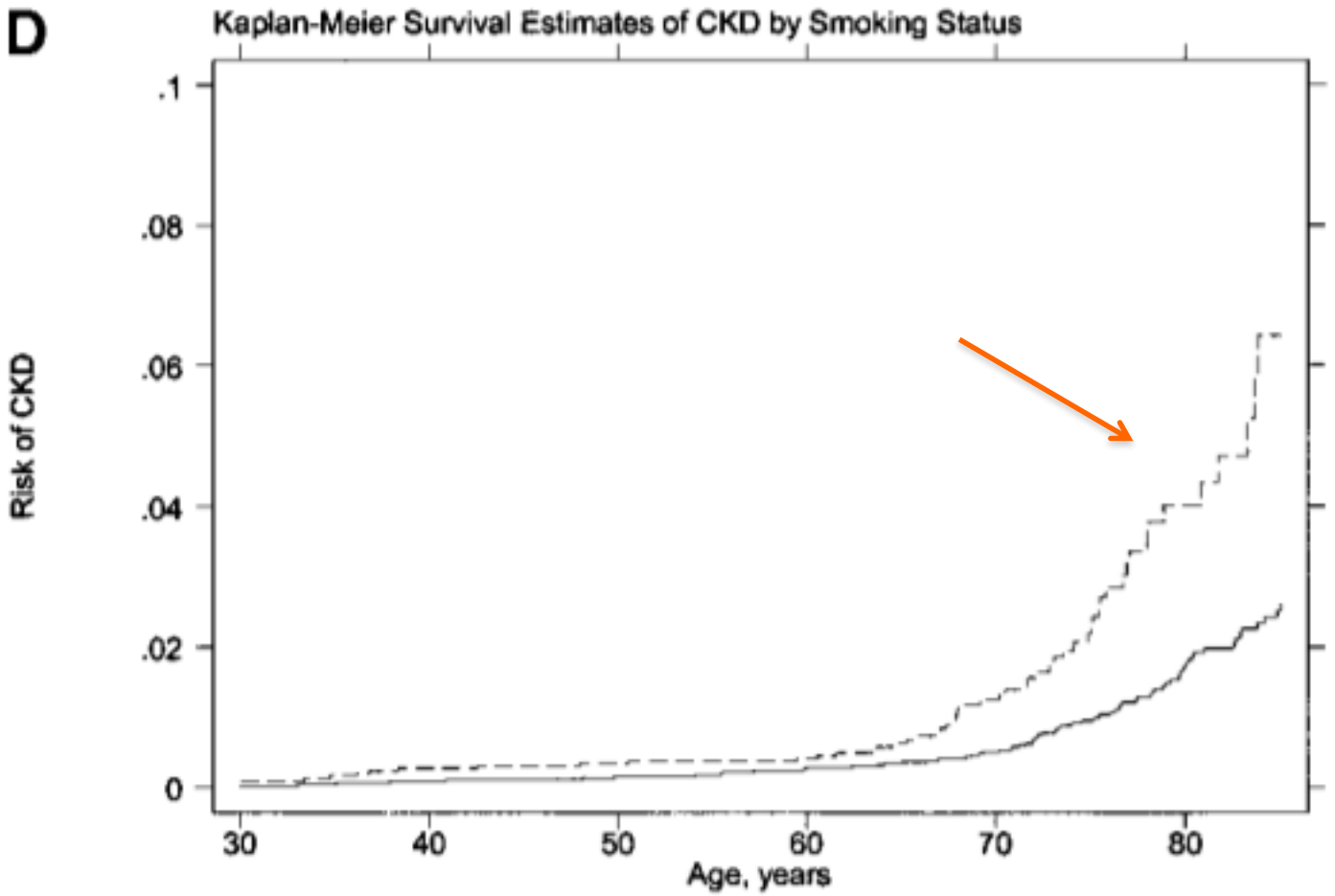
SMOKING

J Am Soc Nephrol 14: 2934–2941, 2003

Risk Factors for Chronic Kidney Disease: A Prospective Study of 23,534 Men and Women in Washington County, Maryland

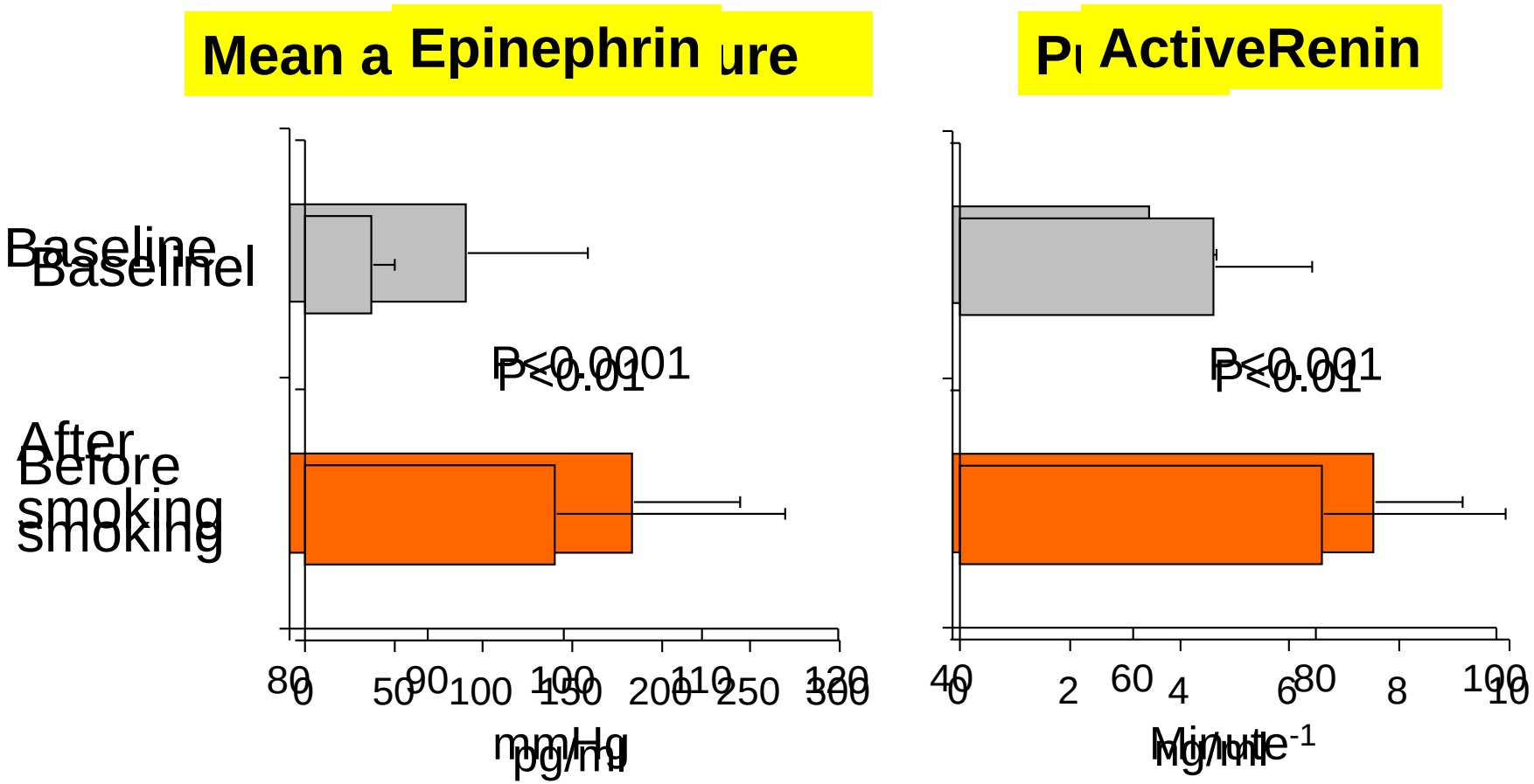
MELANIE K. HAROUN,* BERNARD G. JAAR,* SANDRA C. HOFFMAN,†
GEORGE W. COMSTOCK,† MICHAEL J. KLAG,*†‡ and JOSEF CORESH*†‡§
**Department of Medicine, The Johns Hopkins University School of Medicine, Baltimore, Maryland; †Department of Epidemiology, The Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland; ‡Welch Center for Prevention, Epidemiology, and Clinical Research, The Johns Hopkins University, Baltimore, Maryland; §Department of Biostatistics, The Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland.*

SMOKING



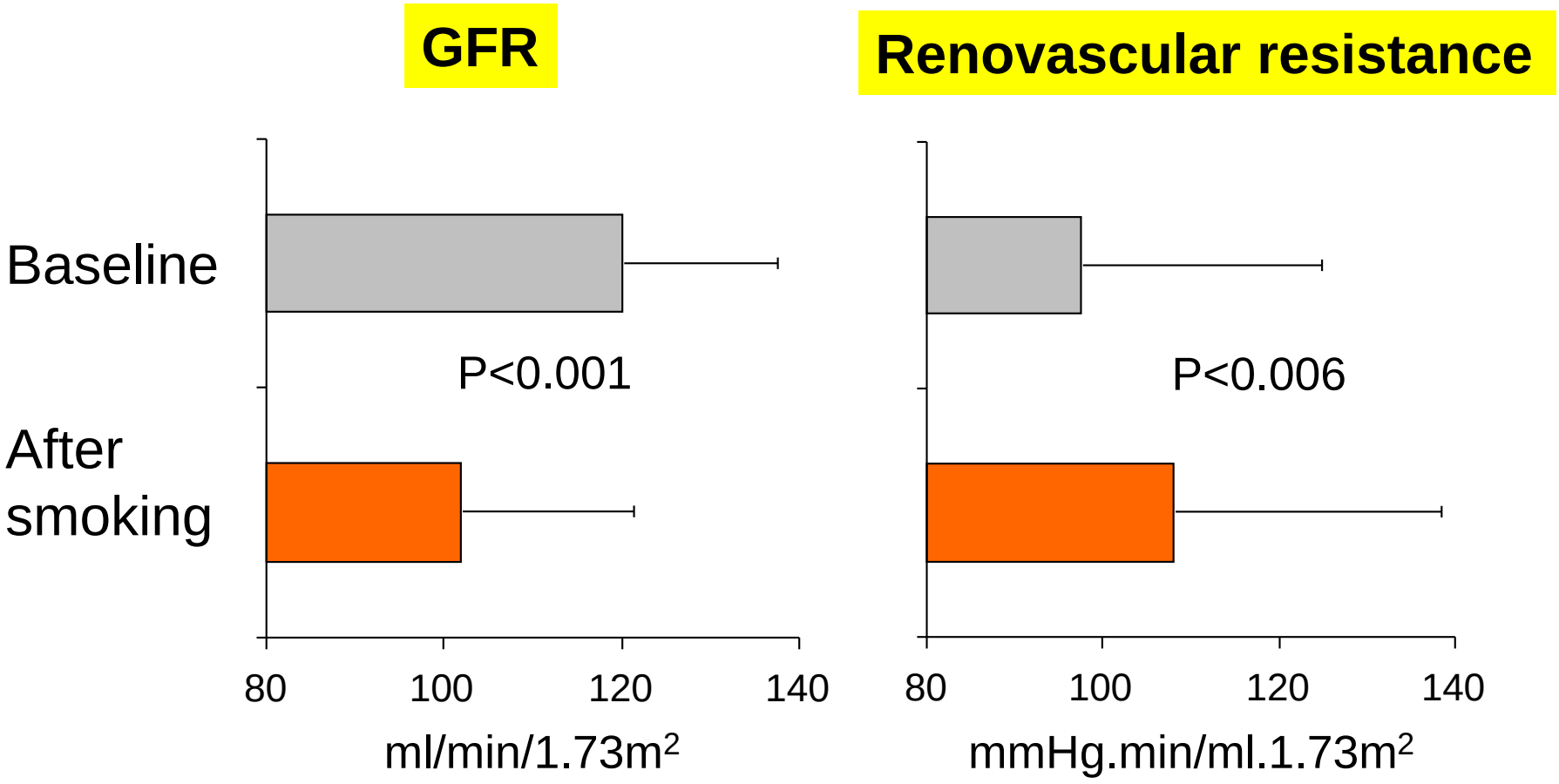
Haroun MK, et al. J Am Soc Nephrol 14: 2934–2941, 2003

SMOKING



Ritz et al.: JASN 9:1798-1804, 1998

SMOKING



Ritz et al.: JASN 9:1798-1804, 1998

SMOKING

Smoking: A Risk Factor for Progression of Chronic Kidney Disease and for Cardiovascular Morbidity and Mortality in Renal Patients—Absence of Evidence or Evidence of Absence?

Stephan R. Orth*

*Dialysis Center Bad
Regensburg, Germany
University of Science
Hospital, Trondheim,

Although it is beyond any
an independent progressi
This is because informati
function in healthy indiv
substantial number of cli
including large, prospecti
experimental studies clear
function deterioration. Th
increased cardiovascular r
an important renal risk fa

Kidney International, Vol. 61 (2002), pp. 2090–2098

Cigarette smoke condensate aggravates renal injury in the renal ablation model

GIULIO ODONI, HIROAKI OGATA, CHRISTIANE VIEDT, KERSTIN AMANN, EBERHARD RITZ, and STEPHAN R. ORTI

*Department of Internal
Erlangen-Nürnberg, Er
(Inselspital), Berne, Sw*

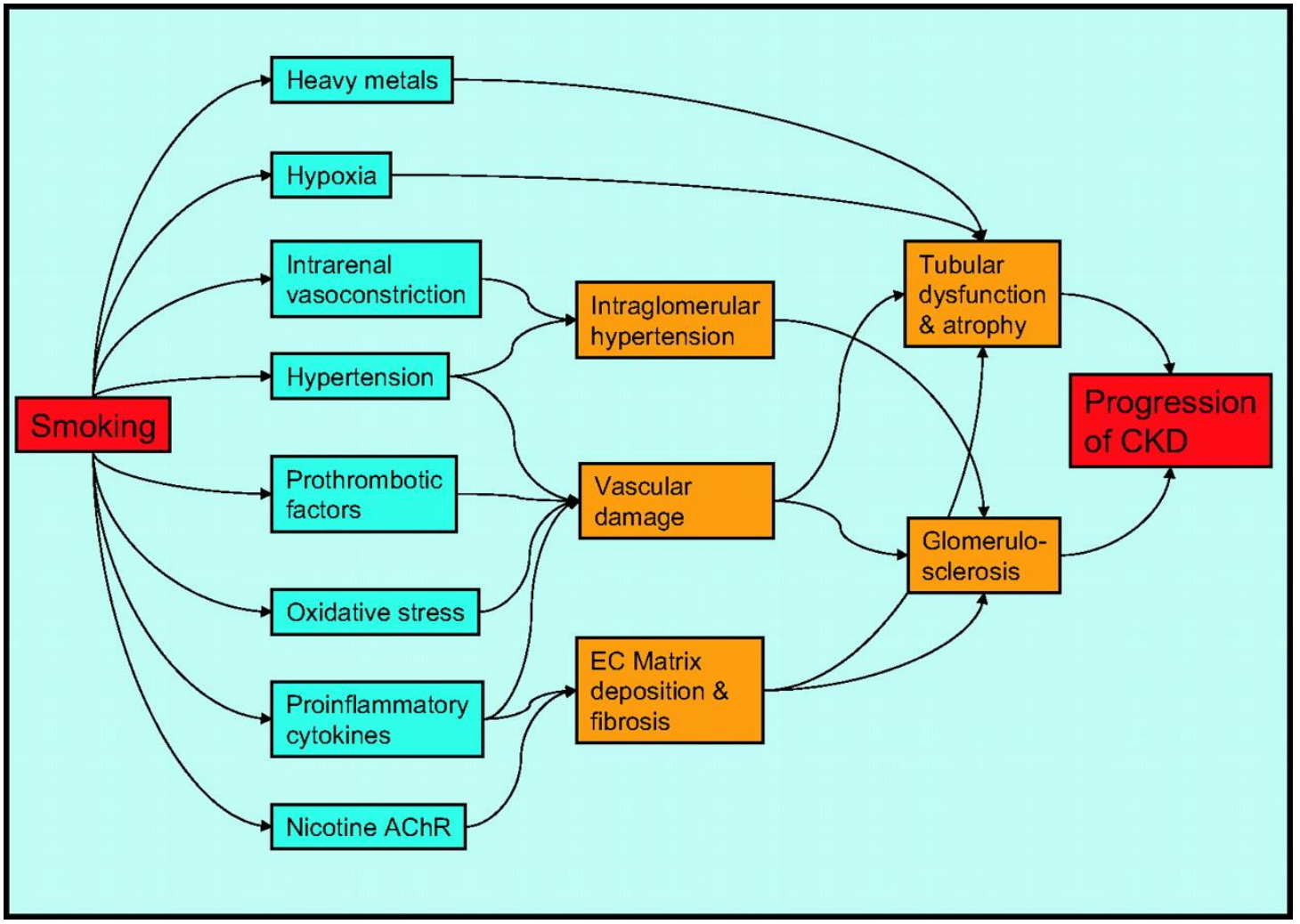
J Am Soc Nephrol 15: 2178–2185, 2004

Association between Smoking and Chronic Renal Failure in a Nationwide Population-Based Case-Control Study

ELISABETH EJERBLAD,* C. MICHAEL FORED,† PER LINDBLAD,* JON FRYZEK,‡ PAUL W. DICKMAN,* CARL-GUSTAF ELINDER,*§ JOSEPH K. MCLAUGHLIN,‡ and OLOF NYRÉN*

**Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden; †Karolinska Institutet, Clinical Epidemiology Unit, Department of Medicine, Karolinska University Hospital, Stockholm, Sweden; ‡The International Epidemiology Institute, Rockville, Maryland, and Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee; and §Department of Renal Medicine, Huddinge University Hospital, Huddinge, Sweden*

SMOKING



Stephan R. Orth, Stein I. Hallan CJASN 3:226-236,2008
Elihimas Júnior et al. J Bras Nefrol 36(4):519-528,2014

SMOKING

PATHOPHYSIOLOGY of the RENAL BIOPSY www.jasn.org

Nodular Glomerulosclerosis in the Nondiabetic Smoker

J Am Soc Nephrol 18: 2032–2036, 2007

Samih H. Nasr and Vivette D. D'Agati

Department of Pathology, Columbia University, College of Physicians & Surgeons, New York, New York

SMOKING

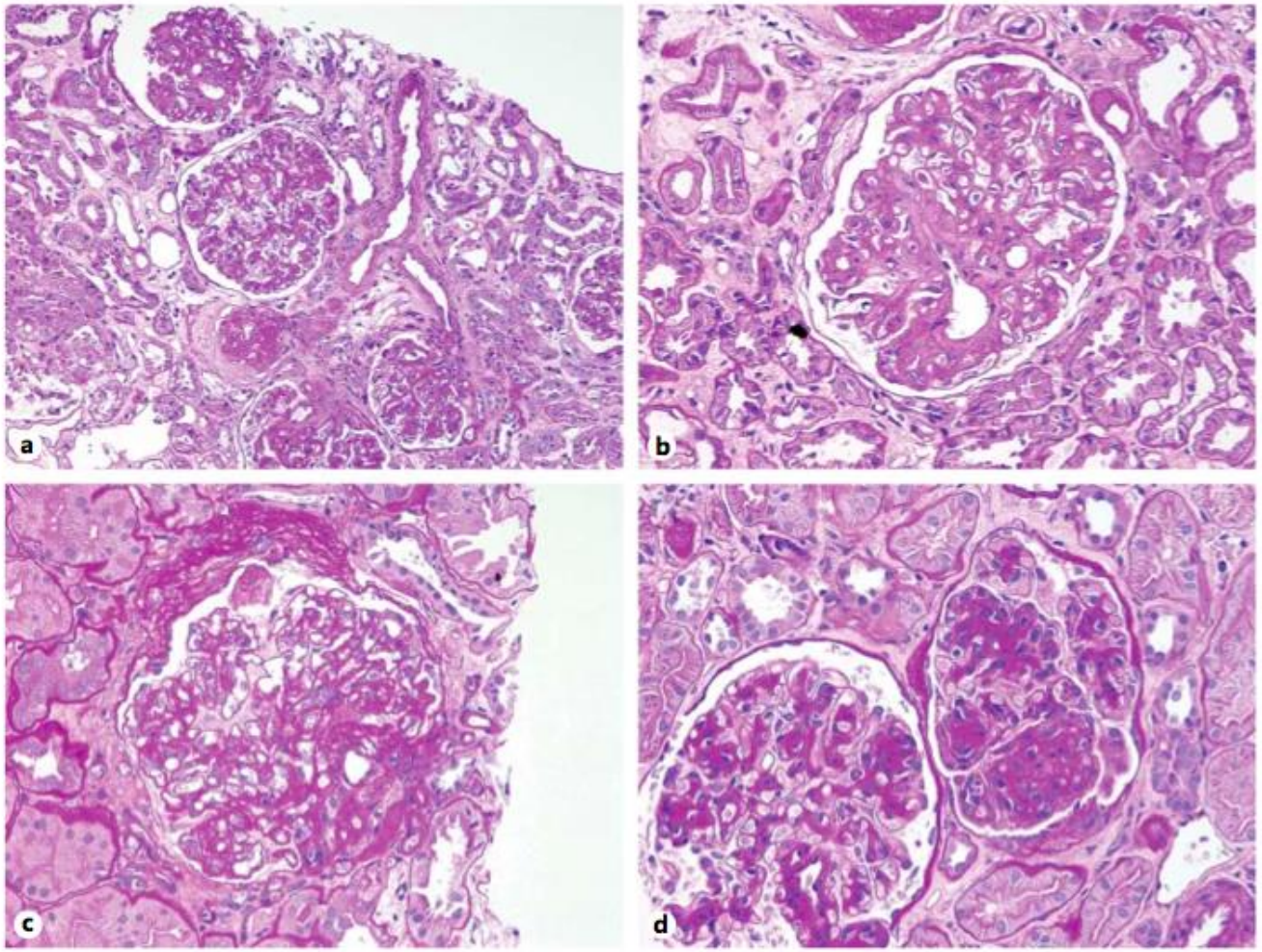


Fig. 1. Light microscopic changes in smoking related glomerulopathy. Diffuse (**a–c**) and nodular (**d**) mesangial glomerulosclerosis. Hilar neovascularization was commonly observed as was capillary wall double contour formation (**c**). Mesangial neovascularization was also present (**d**). Periodic acid Schiff, original magnification ×20 (**a**), ×40 (**b–d**).

SMOKING

Nephrol Dial Transplant (2013) 28: 1329–1331
doi: 10.1093/ndt/gft019
Advance Access publication 28 February 2013

Chronic nicotine exposure and acute kidney injury: new concepts and experimental evidence

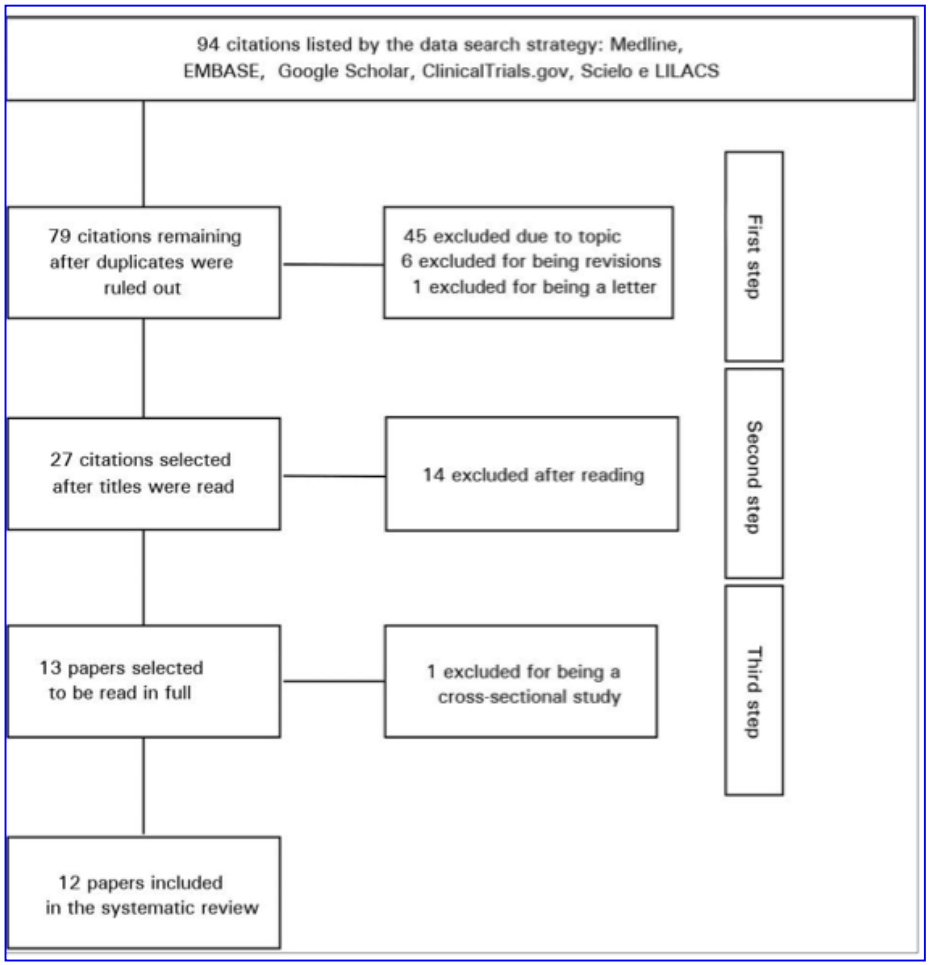
Marijn M. Speeckaert[1],
Joris R. Delanghe[2]
and Raymond C. Vanholder[1]

[1]Department of Nephrology, Ghent University Hospital, 9000 Gent, Belgium and
[2]Department of Clinical Chemistry, Ghent University Hospital, Gent, Belgium

Non-hemodynamic and hemodynamic effects
RAS activation
Mitochondrial depolarization due to oxidative stress
Proximal tubule injury

SMOKING

Smoking as risk factor for chronic kidney disease: systematic review



Elihimas Júnior et al. J Bras Nefrol 36(4):519-528,2014

SMOKING

Most studies have shown that smoking more than 15 packs a year increases the risk of renal disorder progression.[16-18,21,27] This finding appears to be similar to what has been reported for other diseases such as lung cancer in relation to the cumulative effects of smoking.[40] A statistically significant correlation between the cumulative effects of smoking and renal function decline[15-18,21,27] has also been observed when patients with other comorbidities such as HIV[24] and lung transplant recipients were assessed, even more than six months after smoking cessation.[20]

Smoking cessation was assessed in ten studies included in this review and was shown to have been statistically correlated with renal function improvement. However, particularly among heavy smokers - defined as individuals who smoke more than 15 packs of cigarettes a year - the risk of progression persisted, with a relative risk of 8.84.[41]

ol 36(4):519-528,2014

OBESITY

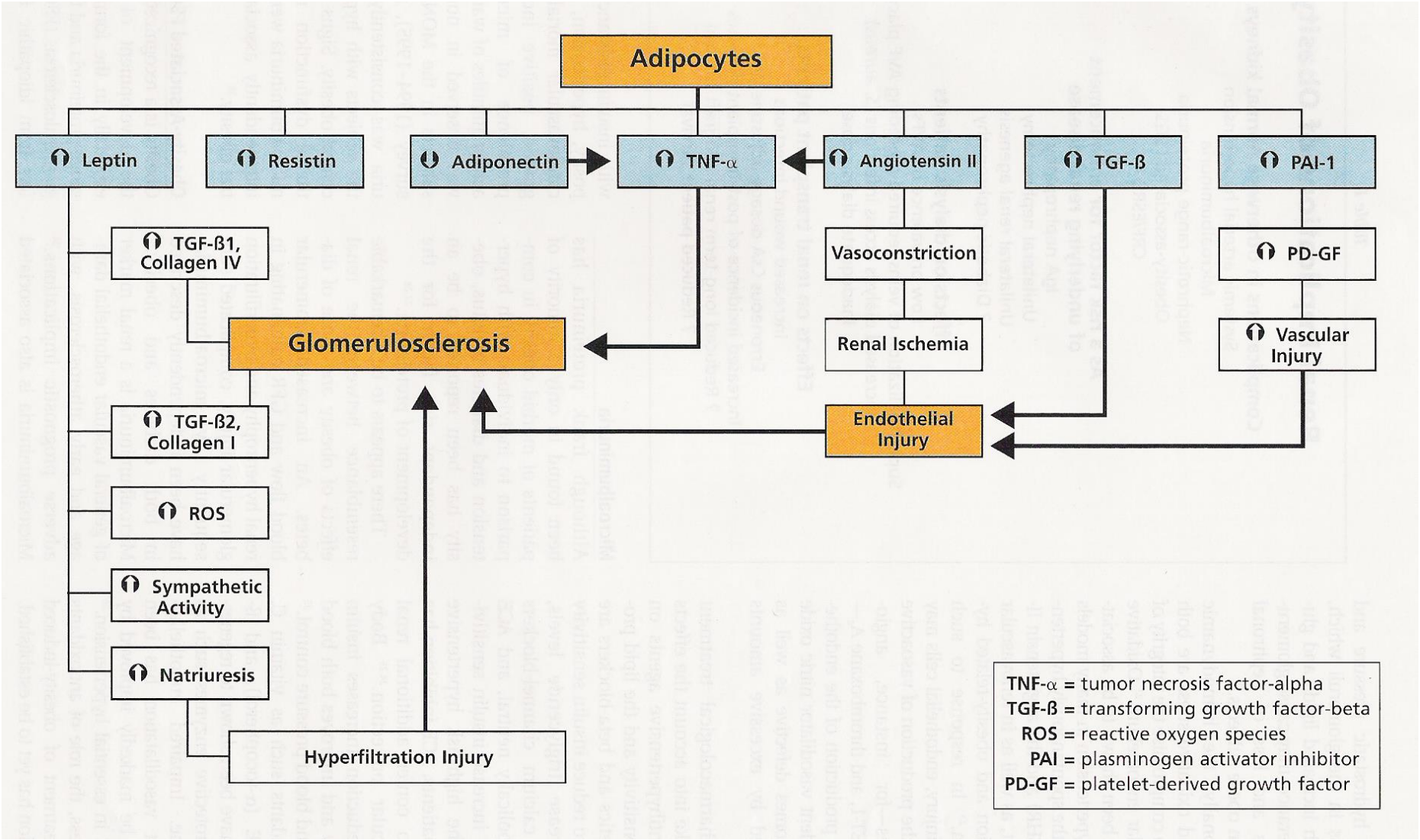
Kidney International, Vol. 59 (2001), pp. 1498–1509

Obesity-related glomerulopathy: An emerging epidemic

NEERAJA KAMBHAM, GLEN S. MARKOWITZ, ANTHONY M. VALERI, JULIE LIN, and VIVETTE D. D'AGATI

Departments of Pathology and Medicine, Columbia University, College of Physicians and Surgeons, New York, New York USA

OBESITY AND THE KIDNEY



OBESITY AND CKD

The Metabolic Syndrome and Chronic Kidney Disease in U.S. Adults

Jing Chen, MD, MSc; Paul Muntner, PhD; L. Lee Hamm, MD; Daniel W. Jones, MD; Vecihi Batuman, MD; Vivian Fonseca, MD; Paul K. Whelton, MD, MSc; and Jiang He, MD, PhD

Background: The metabolic syndrome is a common risk factor for cardiovascular disease.

Objective: To examine the association between the metabolic syndrome and risk for chronic kidney disease and microalbuminuria.

Design: Cross-sectional study.

Setting: The Third National Health and Nutrition Examination Survey.

Patients: Participants 20 years of age or older were studied in the chronic kidney disease ($n = 6217$) and microalbuminuria ($n = 6125$) analyses.

Measurements: The metabolic syndrome was defined as the presence of 3 or more of the following risk factors: elevated blood pressure, low high-density lipoprotein cholesterol level, high triglyceride level, elevated glucose level, and abdominal obesity. Chronic kidney disease was defined as a glomerular filtration rate less than 60 mL/min per 1.73 m^2, and microalbuminuria was defined as a urinary albumin–creatinine ratio of 30 to 300 mg/g.

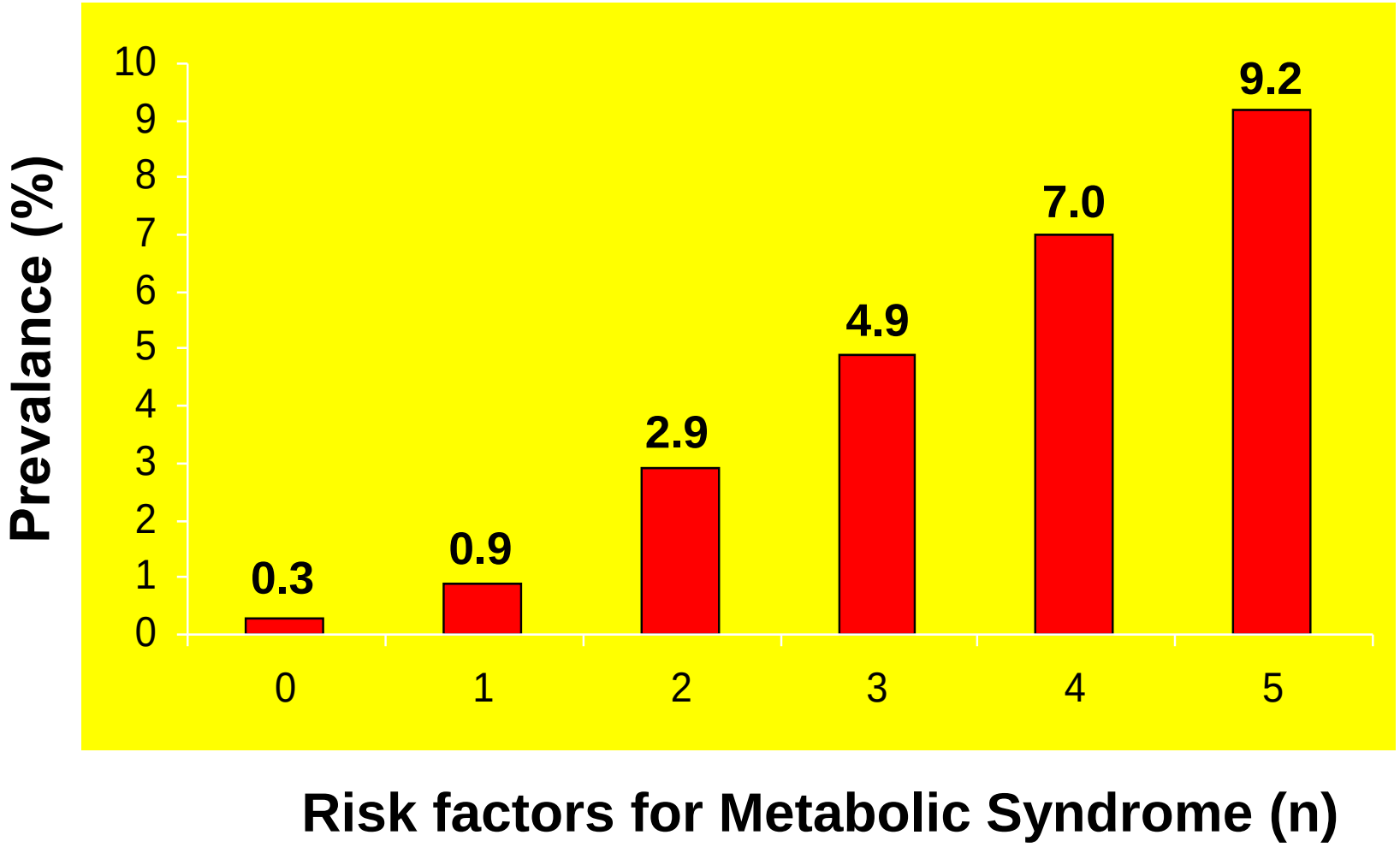
Results: The multivariate-adjusted odds ratios of chronic kidney disease and microalbuminuria in participants with the metabolic syndrome compared with participants without the metabolic syndrome were 2.60 (95% CI, 1.68 to 4.03) and 1.89 (CI, 1.34 to 2.67), respectively. Compared with participants with 0 or 1 component of the metabolic syndrome, participants with 2, 3, 4, and 5 components of chronic kidney disease had multivariate-adjusted odds ratios of 2.21 (CI, 1.16 to 4.24), 3.38 (CI, 1.48 to 7.69), 4.23 (CI, 2.06 to 8.63), and 5.85 (CI, 3.11 to 11.0), respectively. The corresponding multivariate-adjusted odds ratios of microalbuminuria for participants with 3, 4, and 5 components were 1.62 (CI, 1.10 to 2.38), 2.45 (CI, 1.55 to 3.85), and 3.19 (CI, 1.96 to 5.19), respectively.

Conclusions: These findings suggest that the metabolic syndrome might be an important factor in the cause of chronic kidney disease.

Ann Intern Med. 2004;140:167-174. www.annals.org

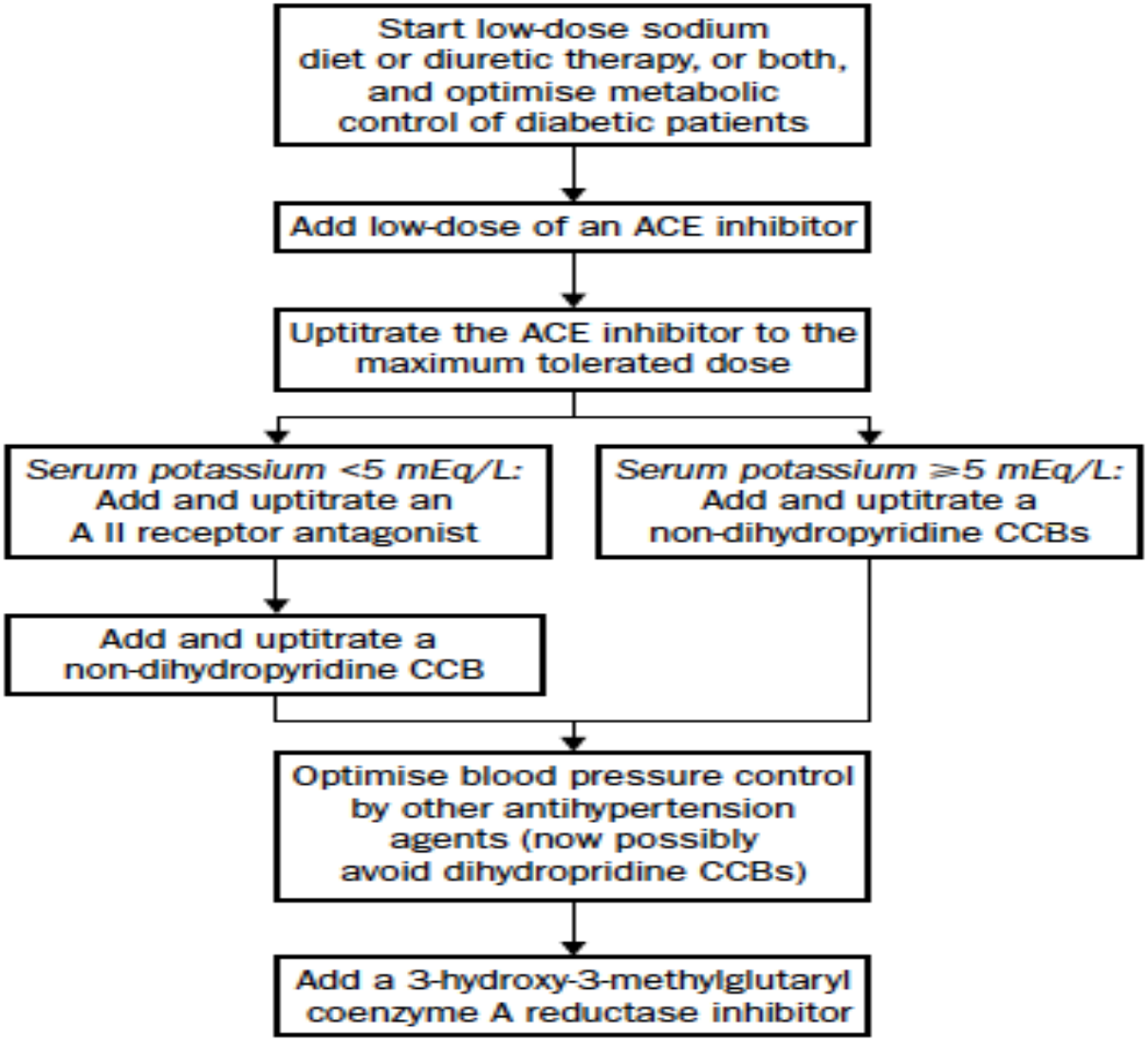
For author affiliations, see end of text.

OBESITY AND CKD



Chen et al.: Ann Intern Med 140: 167-174, 2004

CONCLUSION
REMISSION CLINIC



Ruggenenti et al: Lancet 357: 1601-1608, 2001

CONCLUSION II

Causes	Target	Therapy
HT	130/80 mmHg	Diet, ACEi-ARB
Proteinuria	<1 gr/day	ACEi-ARB
Hyperlipidemia	LDL <130 mg/dl	Diet, statin
Obesity	Waist: < 94 cm (M) < 80 cm (F)	Diet, physical activity
Smoking	0/day	Quit smoking
Hyperglycemia	HbA1c <7%	Ideal weight, excersize, drug
Hyperphosphatemia	P <3.7 mg/dl	Diet, drug
Hyperuricemia	UA <6 mg/dl	Diet, drugs

Harris et al . Naturereviews Nephrology 2009

CONCLUSION III

Friends, social networks, and progressive chronic kidney disease

William M. McClellan[1,2] and John J. Doran[2]

A report by Dunkler *et al.* reminds us that social factors are relevant for today's clinical scientist and practitioner. They report that an increasing number of friends reduces the incidence and progression of chronic kidney disease in type 2 diabetes. The observation that 'friends don't let friends' develop kidney disease suggests that social factors, as well as biomarkers, may be relevant in developing 'personalized renal medicine' and may identify areas for future nephrology research and education.

Kidney International (2015) **87,** 682–684. doi:10.1038/ki.2015.23

THANK YOU FOR YOUR ATTENTION