Anticorpi Monoclonali nella Nefropatia Diabetica

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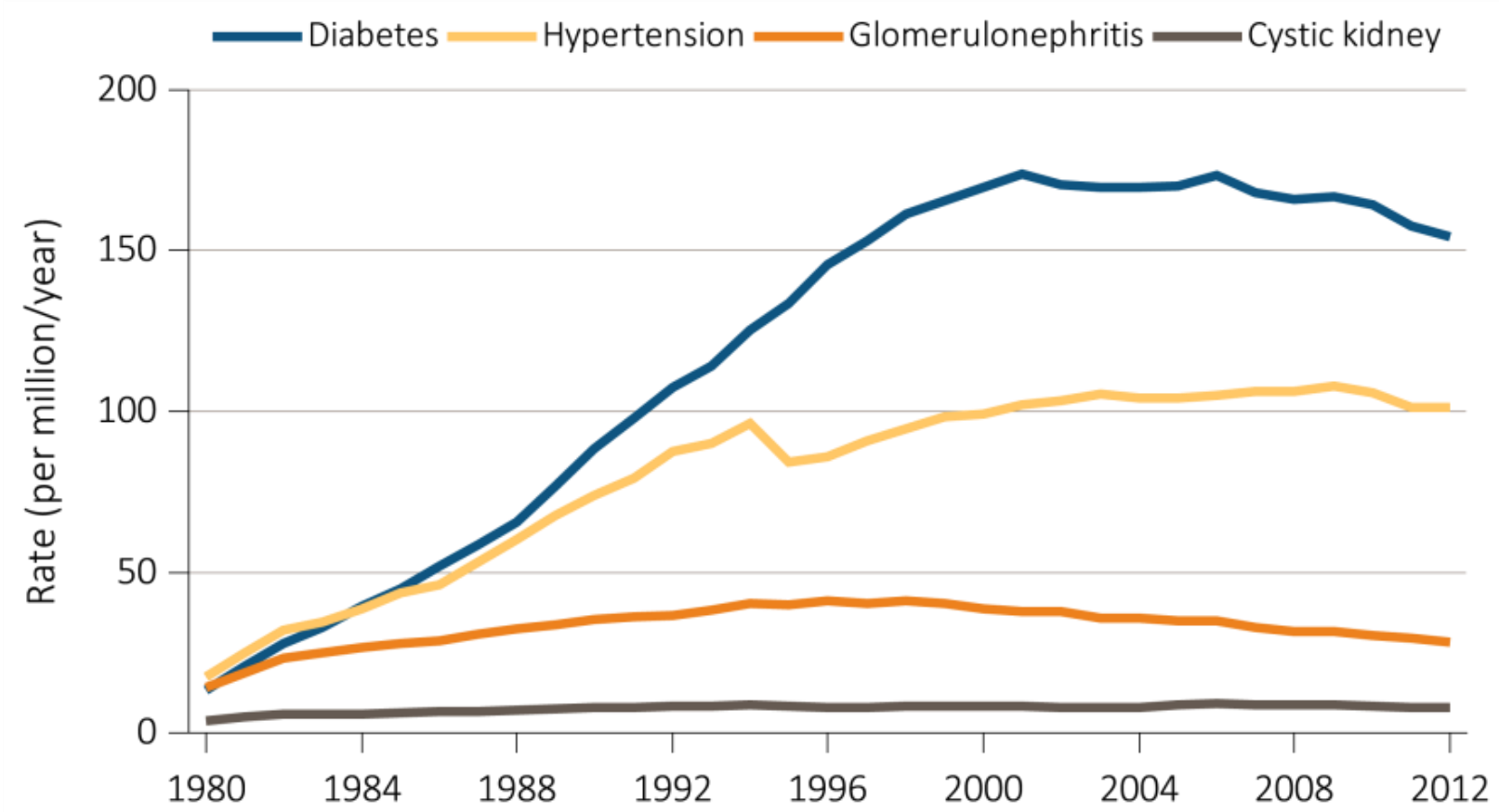
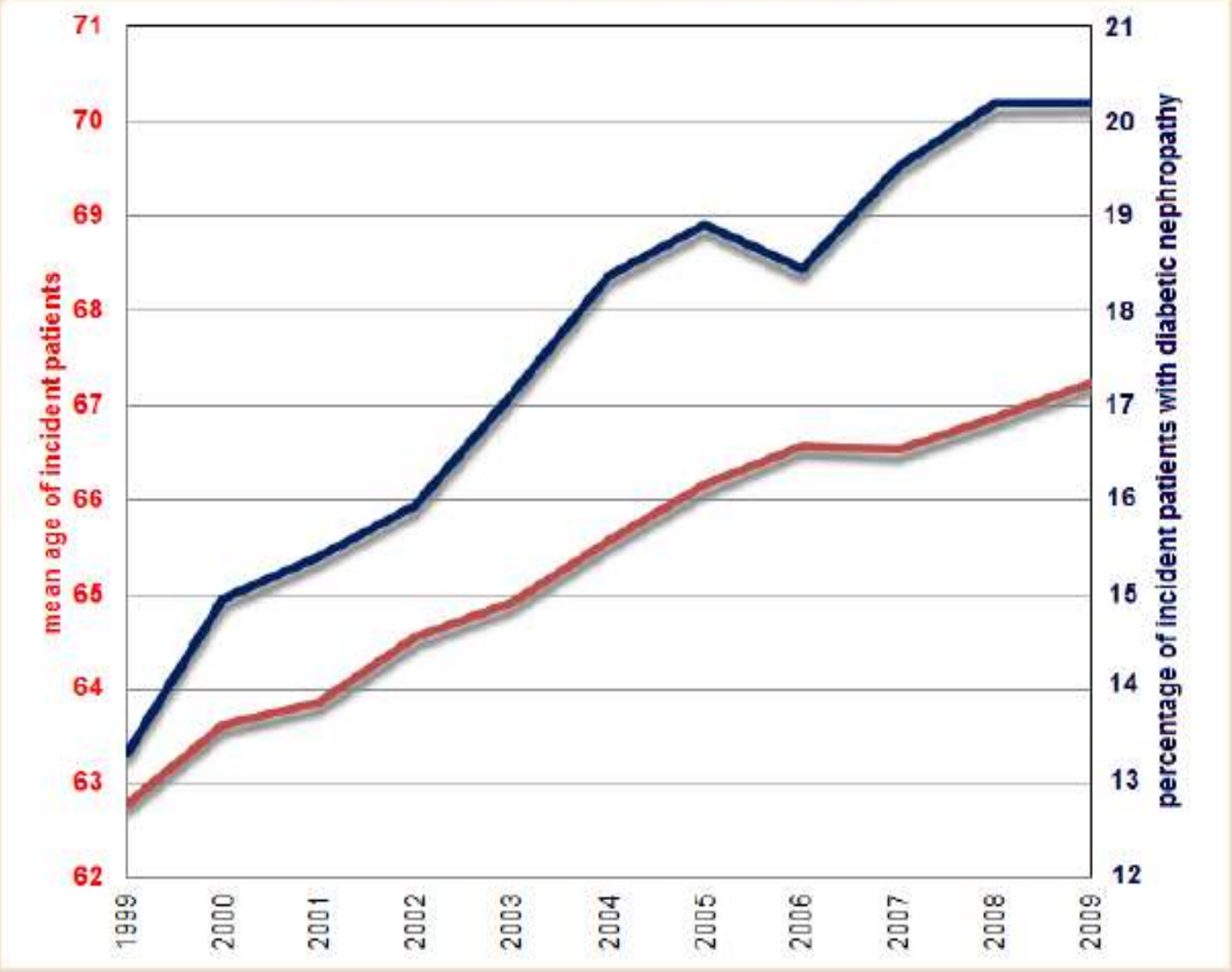
Dimensions of the DN problem

ESRD incidence rate by primary cause in U.S. 1980-2012



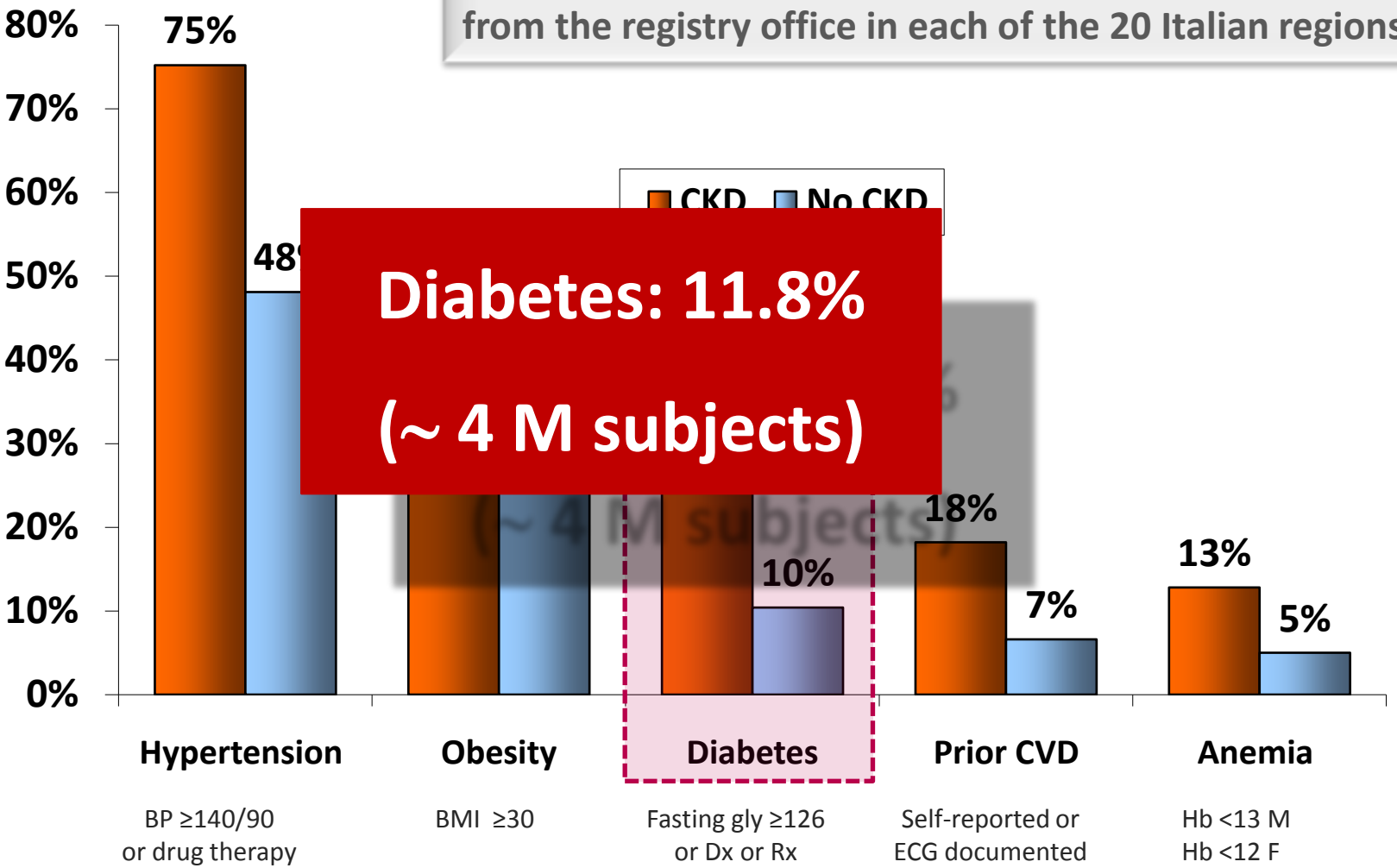
**Adjusted for age, sex, and race. The standard population was the U.S. population in 2011.*

MEAN AGE (years) AND DIABETIC NEPHROPATHY (%) IN INCIDENT PATIENTS



Prevalence and cardiovascular risk profile of chronic kidney disease in Italy: results of the 2008–12 National Health Examination Survey

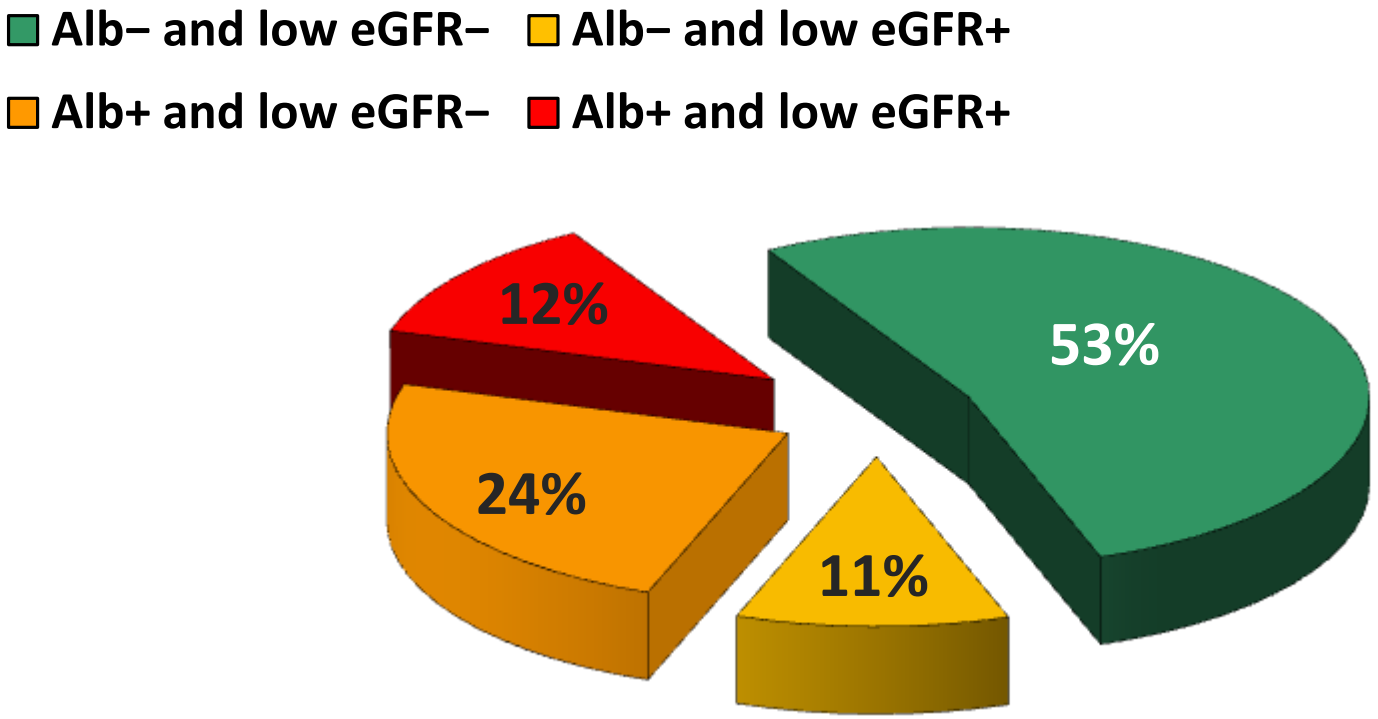
Sample (7.552) representative of general population aged 35-79 years, stratified by age and gender, randomly selected from the registry office in each of the 20 Italian regions



De Nicola for ANMCO-SIN-ISS, NDT 2015

Kidney dysfunction and related cardiovascular risk factors among patients with type 2 diabetes

Large cohort of patients (120.903) with type 2 diabetes mellitus attending 236 Italian Diabetes Clinics in 2009



De Cosmo (RIACE) for AMD-Annals Study Group, NDT 2014

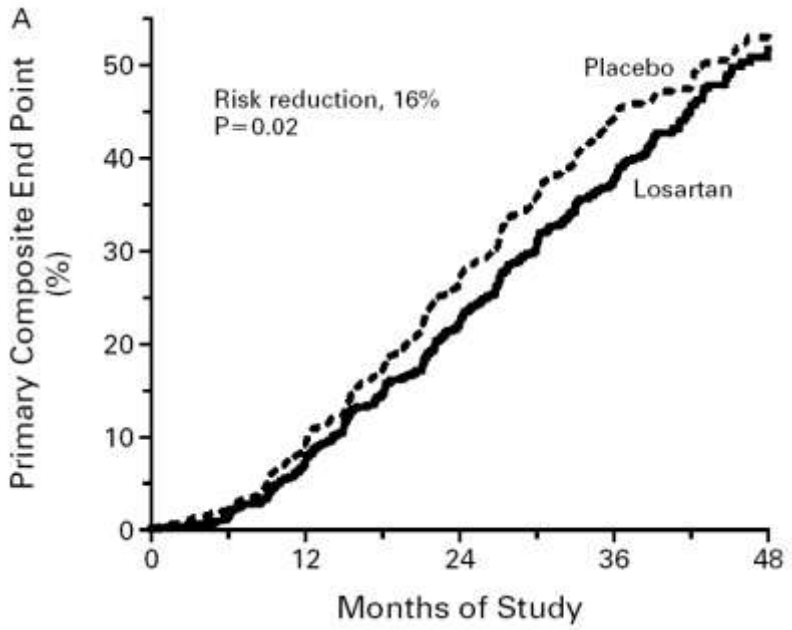
Therapy: *unmet needs*

Residual renal risk in DM-CKD patients under optimal anti-RAS therapy

VOLUME 345 SEPTEMBER 20, 2001 NUMBER 12

EFFECTS OF LOSARTAN ON RENAL AND CARDIOVASCULAR OUTCOMES IN PATIENTS WITH TYPE 2 DIABETES AND NEPHROPATHY

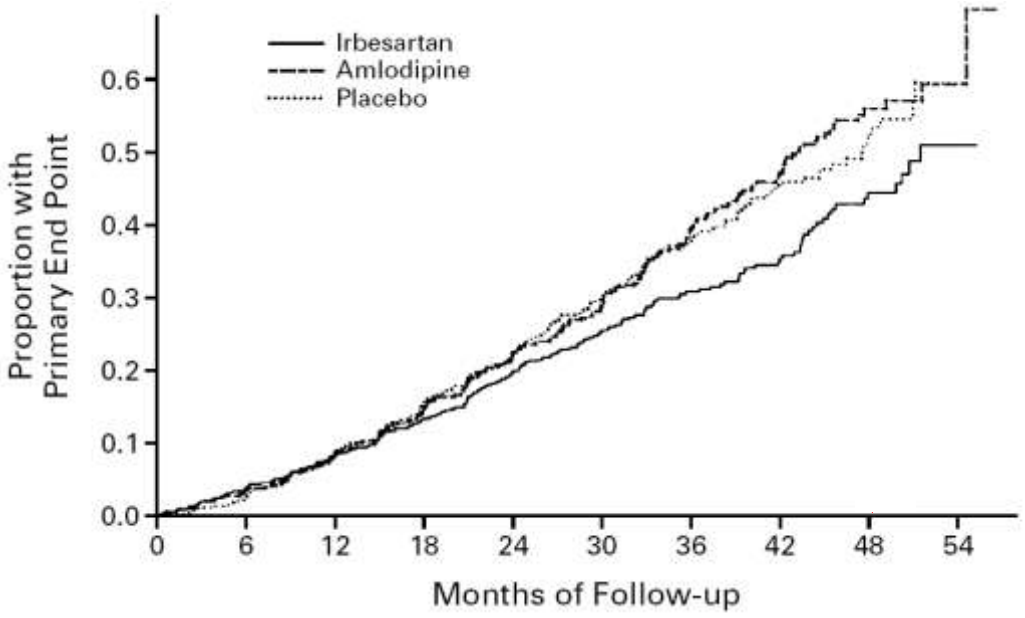
BARRY M. BRENNER, M.D., MARK E. COOPER, M.D., PH.D., DICK DE ZEEUW, M.D., PH.D., WILLIAM F. KEANE, M.D., WILLIAM E. MITCH, M.D., HANS-HENRIK PARVING, M.D., GIUSEPPE REMUZZI, M.D., STEVEN M. SNAPINN, PH.D., ZHONXIN ZHANG, PH.D., AND SHAHNAZ SHAHINFAR, M.D., FOR THE RENAAL STUDY INVESTIGATORS*



RENAAL Study NEJM 2001

RENOPROTECTIVE EFFECT OF THE ANGIOTENSIN-RECEPTOR ANTAGONIST IRBESARTAN IN PATIENTS WITH NEPHROPATHY DUE TO TYPE 2 DIABETES

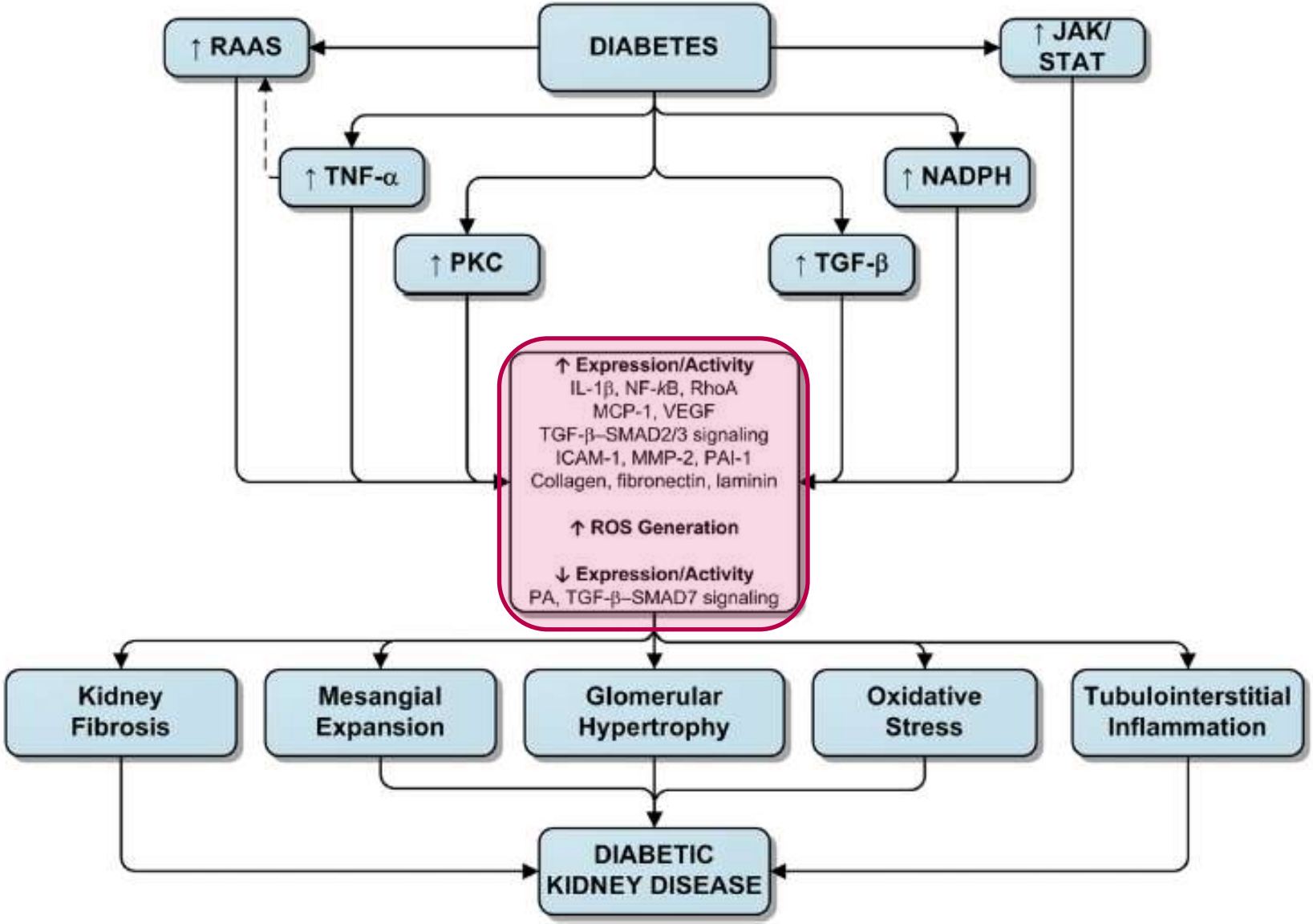
EDMUND J. LEWIS, M.D., LAWRENCE G. HUNSICKER, M.D., WILLIAM R. CLARKE, PH.D., TOMAS BERL, M.D., MARC A. POHL, M.D., JULIA B. LEWIS, M.D., EBERHARD RITZ, M.D., ROBERT C. ATKINS, M.D., RICHARD ROHDE, B.S., AND ITAMAR RAZ, M.D., FOR THE COLLABORATIVE STUDY GROUP*



IDNT Study NEJM 2001

Monoclonal Antibodies

Pathogenesis of Diabetic Nephropathy



Alicic & Tuttle, ACKD 2014

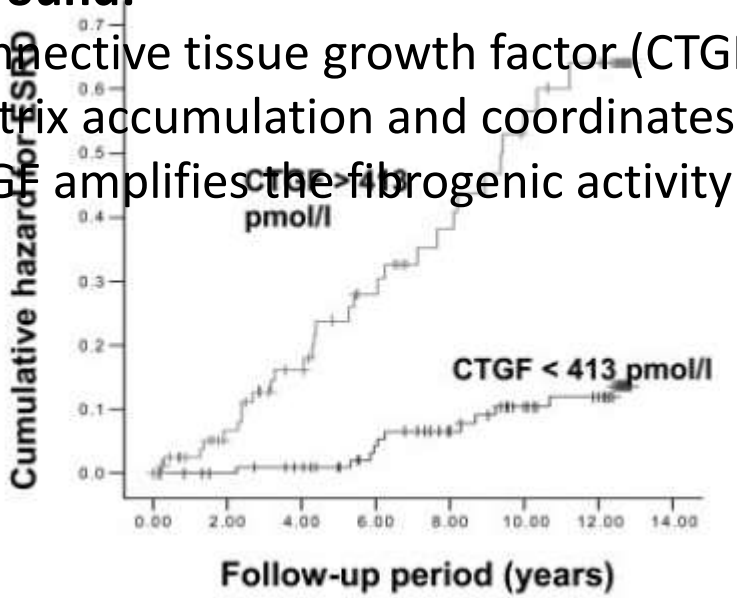
Plasma Connective Tissue Growth Factor Is an Independent Predictor of End-Stage Renal Disease and Mortality in Type 1 Diabetic Nephropathy

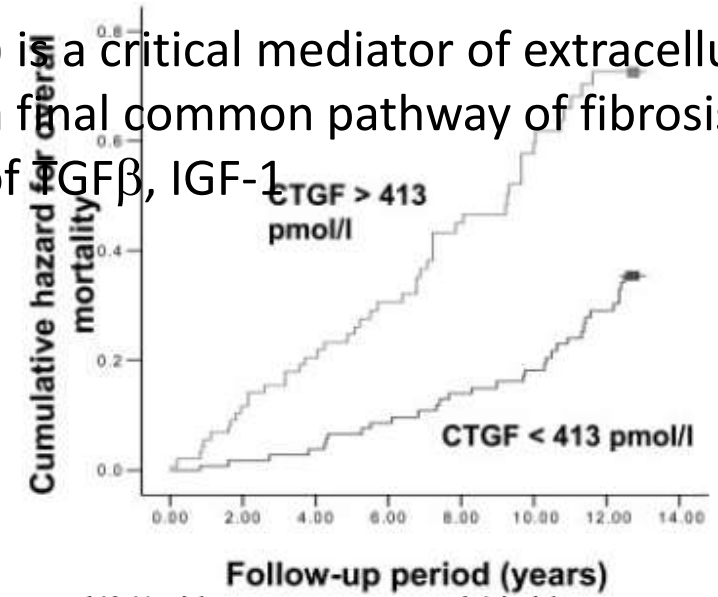
- 198 type 1 DM pts with diabetic nephropathy
- 188 type 1 DM pts with normoalbuminuria
- Follow-up 12.8 years

Cardiorenal risk in patients with diabetic nepropathy by CTGF level

Background:

- Connective tissue growth factor (CTGF) is a critical mediator of extracellular matrix accumulation and coordinates a final common pathway of fibrosis
- CTGF amplifies the fibrogenic activity of TGFβ, IGF-1





History of myocardial infarction	10 (5.1)	2 (1.1)
History of stroke	14 (7.1)	1 (0.5)
CTGF levels		
Plasma CTGF (pmol/l)	381 (270–630)	235 (168–353)

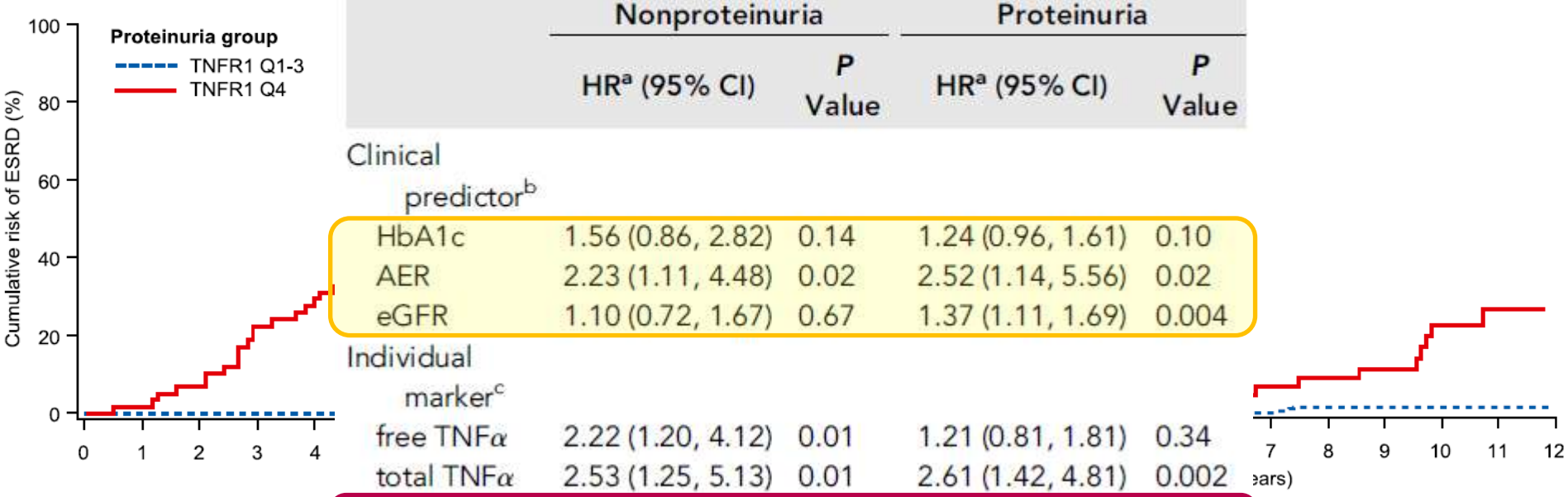
Nguyen, Diabetes Care 2008

Circulating TNF Receptors 1 and 2 Predict ESRD in Type 2 Diabetes

- 410 patients with type 2 diabetes enrolled in 1990 w/h and w/o Uprot *(complications)*
-

Multivariate Cox proportional hazard models of the risk of ESRD in patients with T2D with clinical predictors and the plasma concentration of a TNF marker stratified according to the presence of proteinuria

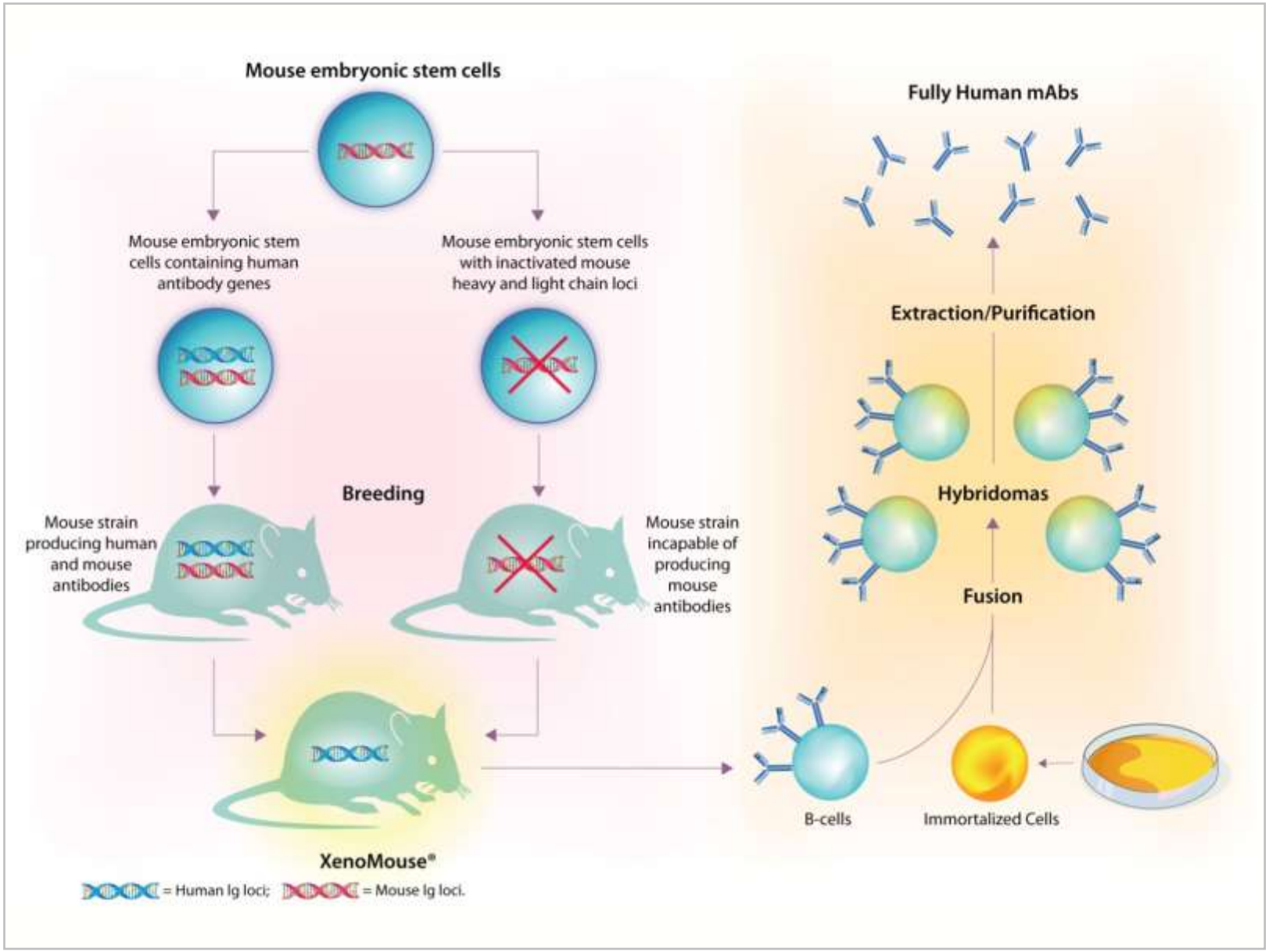
	Nonproteinuria		Proteinuria	
	HR[a] (95% CI)	*P* Value	HR[a] (95% CI)	*P* Value
Clinical predictor[b]				
HbA1c	1.56 (0.86, 2.82)	0.14	1.24 (0.96, 1.61)	0.10
AER	2.23 (1.11, 4.48)	0.02	2.52 (1.14, 5.56)	0.02
eGFR	1.10 (0.72, 1.67)	0.67	1.37 (1.11, 1.69)	0.004
Individual marker[c]				
free TNFα	2.22 (1.20, 4.12)	0.01	1.21 (0.81, 1.81)	0.34
total TNFα	2.53 (1.25, 5.13)	0.01	2.61 (1.42, 4.81)	0.002
TNFR1	7.11 (2.13, 23.69)	0.0004	7.05 (2.23, 22.30)	0.0018
TNFR2	3.82 (1.59, 9.20)	0.0008	5.88 (2.10, 16.43)	0.0013



Niewczas, JASN 2012

From Observation To Intervention…

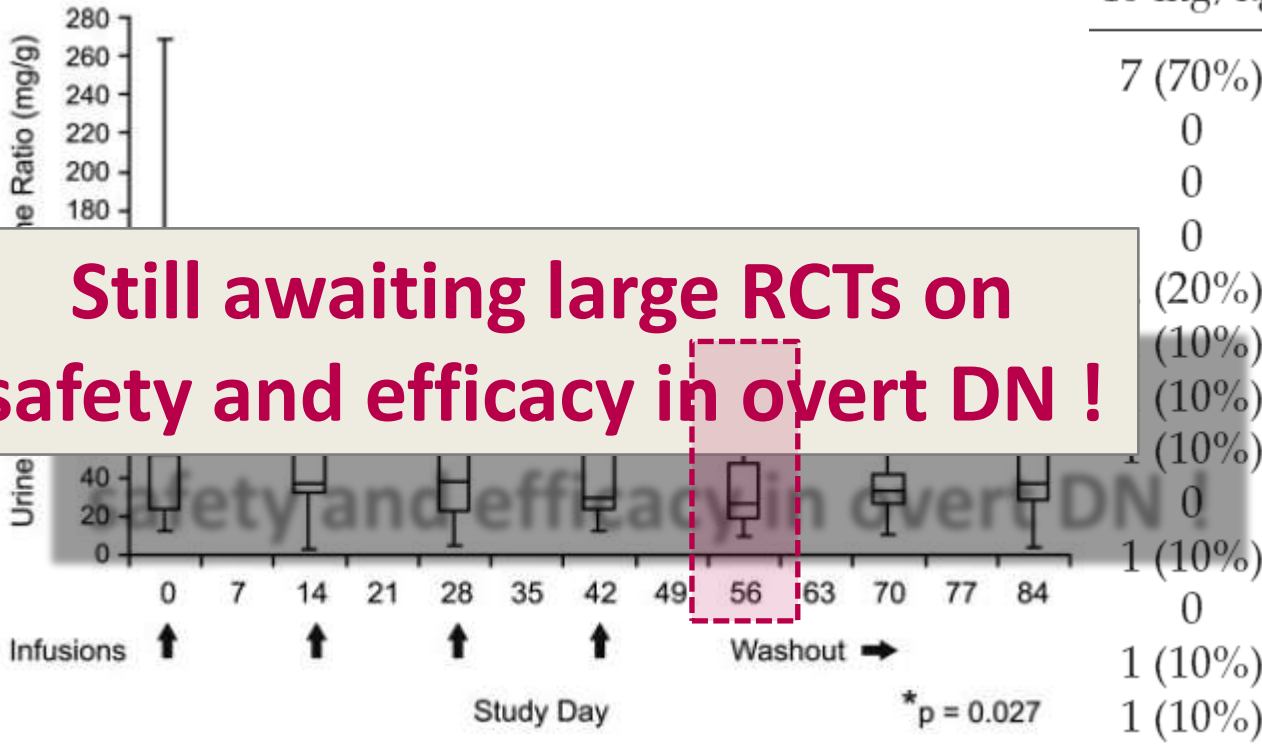
Synthesis of Monoclonal Antibodies



Phase 1 Study of Anti-CTGF Monoclonal Antibody in Patients with Diabetes and Microalbuminuria

- Microalbuminuric subjects (n=24) with type 2 (79%) or type 1 (21%) DM
- Age 58 y, 16 yrs of DM, eGFR 82 mL/min, ACR 61 mg/g

Adverse Event	FG-3019 3 mg/kg (n = 14)	FG-3019 10 mg/kg (n = 10)
Overall		7 (70%)
Headache		0
AST increase		0
LDH incre		0
Herpes sin		(20%)
Fatigue		(10%)
Edema		(10%)
Excoriation		(10%)
Laceration		0
Pain in extre		1 (10%)
Hyperglycem		0
Anemia		1 (10%)
Anxiety		1 (10%)



Still awaiting large RCTs on safety and efficacy in overt DN !

Adler, cJASN 2010

Renal Efficacy and Safety of Anti-TGF-β1 Therapy in Patients with Diabetic Nephropathy

Eli Lilly, Indianapolis; Vanderbilt Univ, Nashville; Univ of Utah, Salt Lake City; Clinique Universitaire de Néphrologie, Grenoble. US and France.

Methods:

- 416 pts ≥25 years of age with T1 (n= 44) or T2 (n=370) diabetes, eGFR 20 to 60 and 2
- rando
- prima

RCTs on LY 2382770 in DN…

…now discontinued !!!

Mean SCr ±				
Baseline				
12-mo Endpoint		2.48±0.96	2.49±0.84	2.49±1.12	2.50±1.01
LS* mean change from baseline (SE)	0.38±0.08	0.48±0.08	0.48±0.08	0.55±0.08

Results:

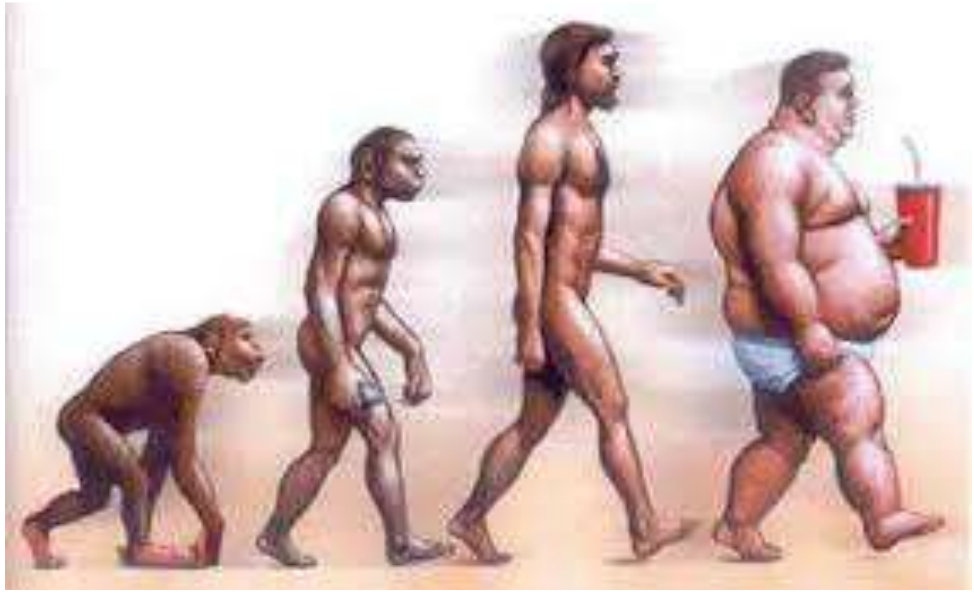
Pt demographics were balanced across groups, including age 62 yrs, 77% men, SCr 2.1 mg/dL, eGFR 35 mL/min/1.73m^2, urine PCR 3.3 g/g, BMI 34, HbA1c 7.9 % and SBP 138 mmHg.

The trial was terminated 4 mo early for efficacy futility !!!

Translational research…Validity in DN?

om basic science

health

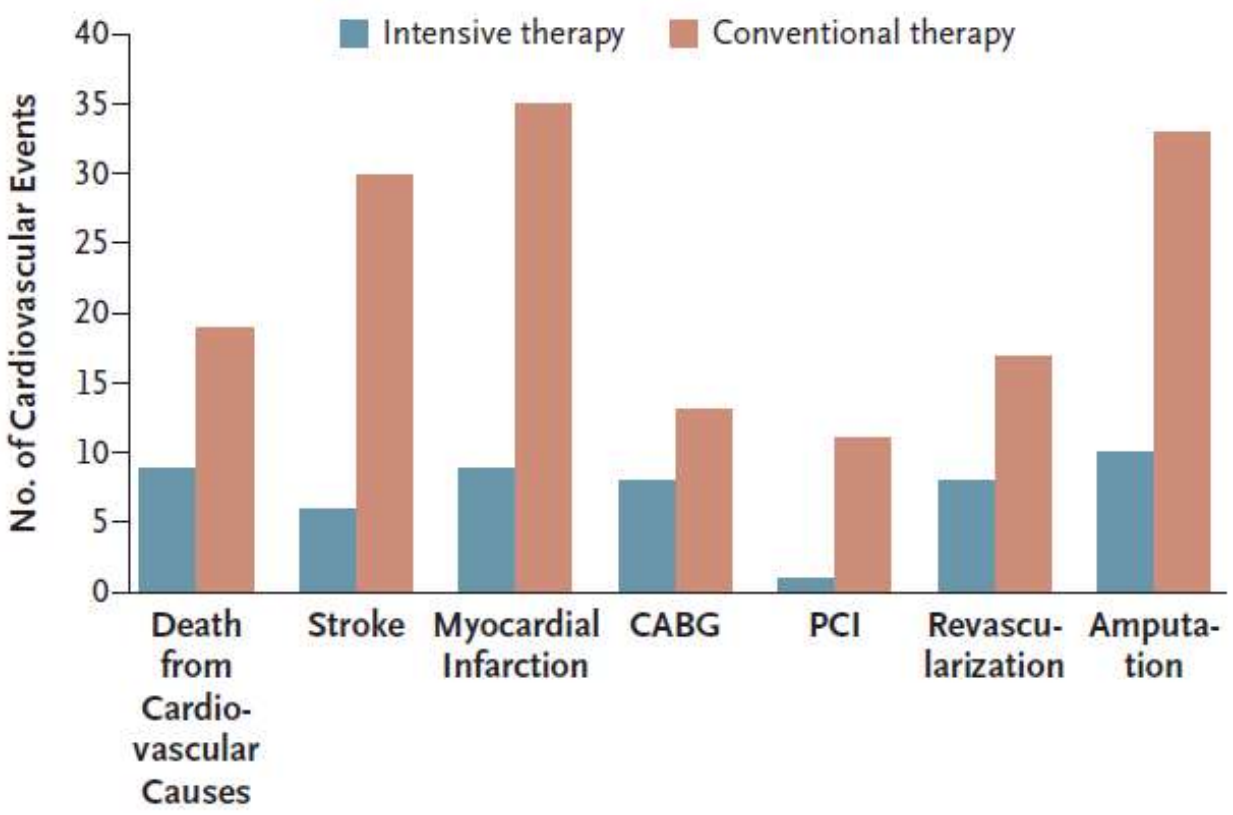


How can I make it… without monoclonal antibodies ?

Effect of a Multifactorial Intervention on Mortality in Type 2 Diabetes

Peter Gæde, M.D., D.M.Sc., Henrik Lund-Andersen, M.D., D.M.Sc.,
Hans-Henrik Parving, M.D., D.M.Sc., and Oluf Pedersen, M.D., D.M.Sc.

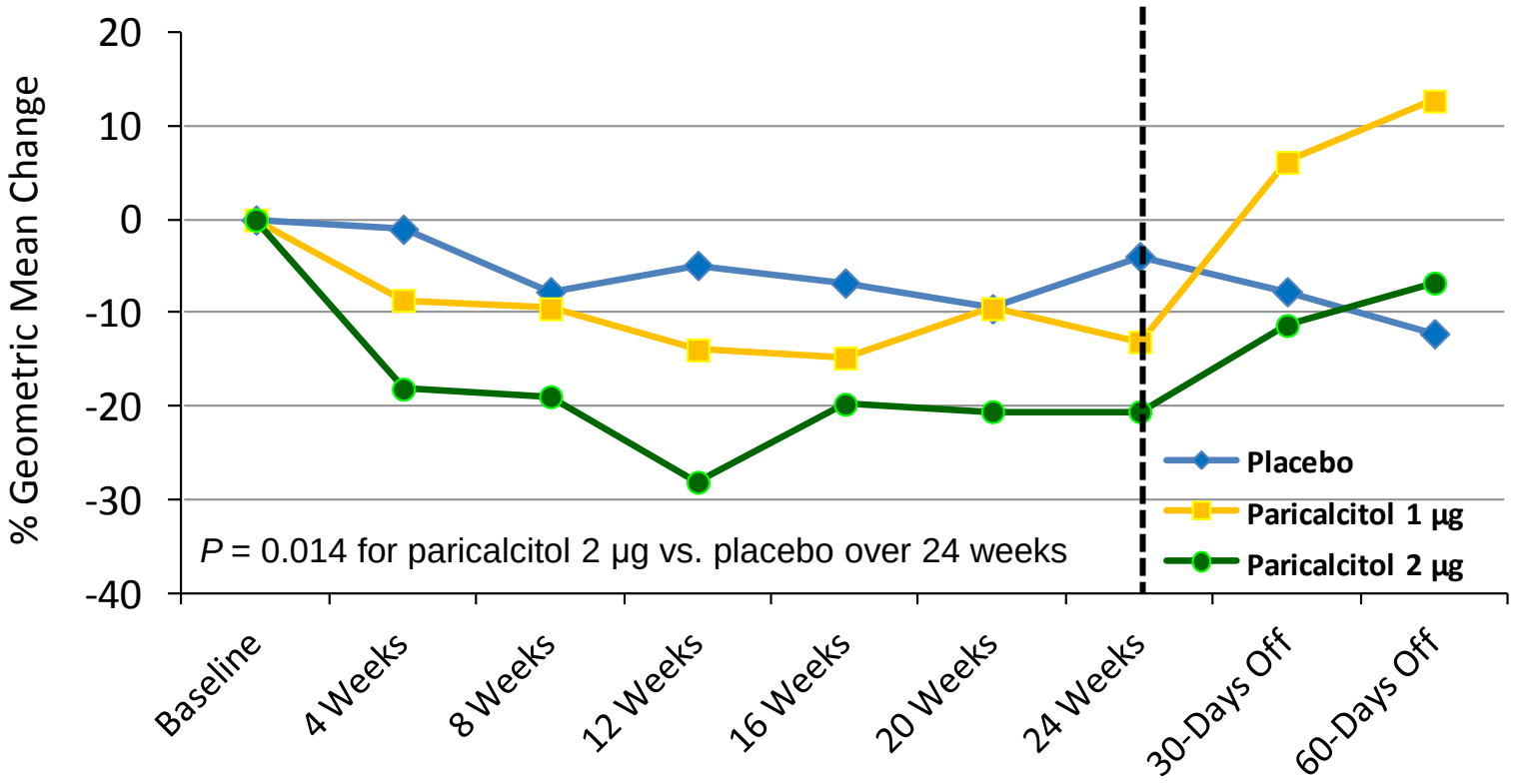
Steno Diabetes Center, Copenhagen
160 pts DM2+Ualb; FU: 13 yrs



BP,mmHg	**146/78**	**132/73**
HbA_{1c},%	**9.0**	**7.9**
LDL-C, mg/dl	**118**	**81**
ASP+STAT,%	**45**	**86**
ACE±ARB,%	**70**	**97**

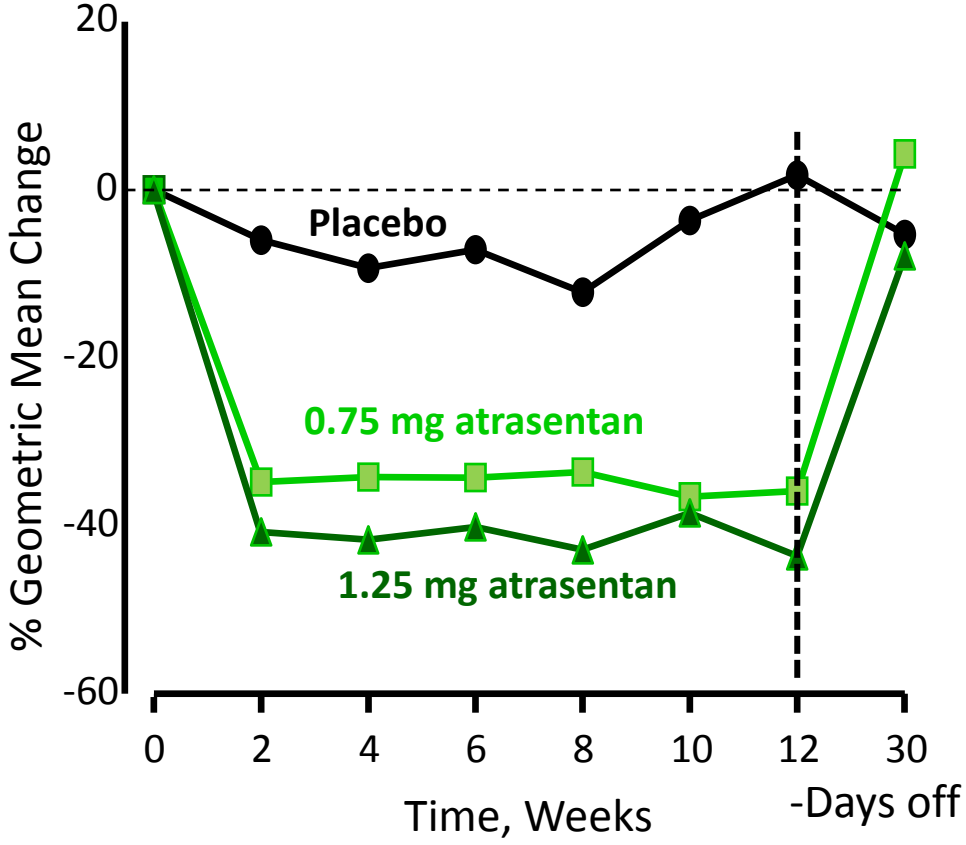
N Engl J Med 2008;358:580-91

VITAL: VDRA (Paricalcitol 2 µg/d) reversibly reduces UACR



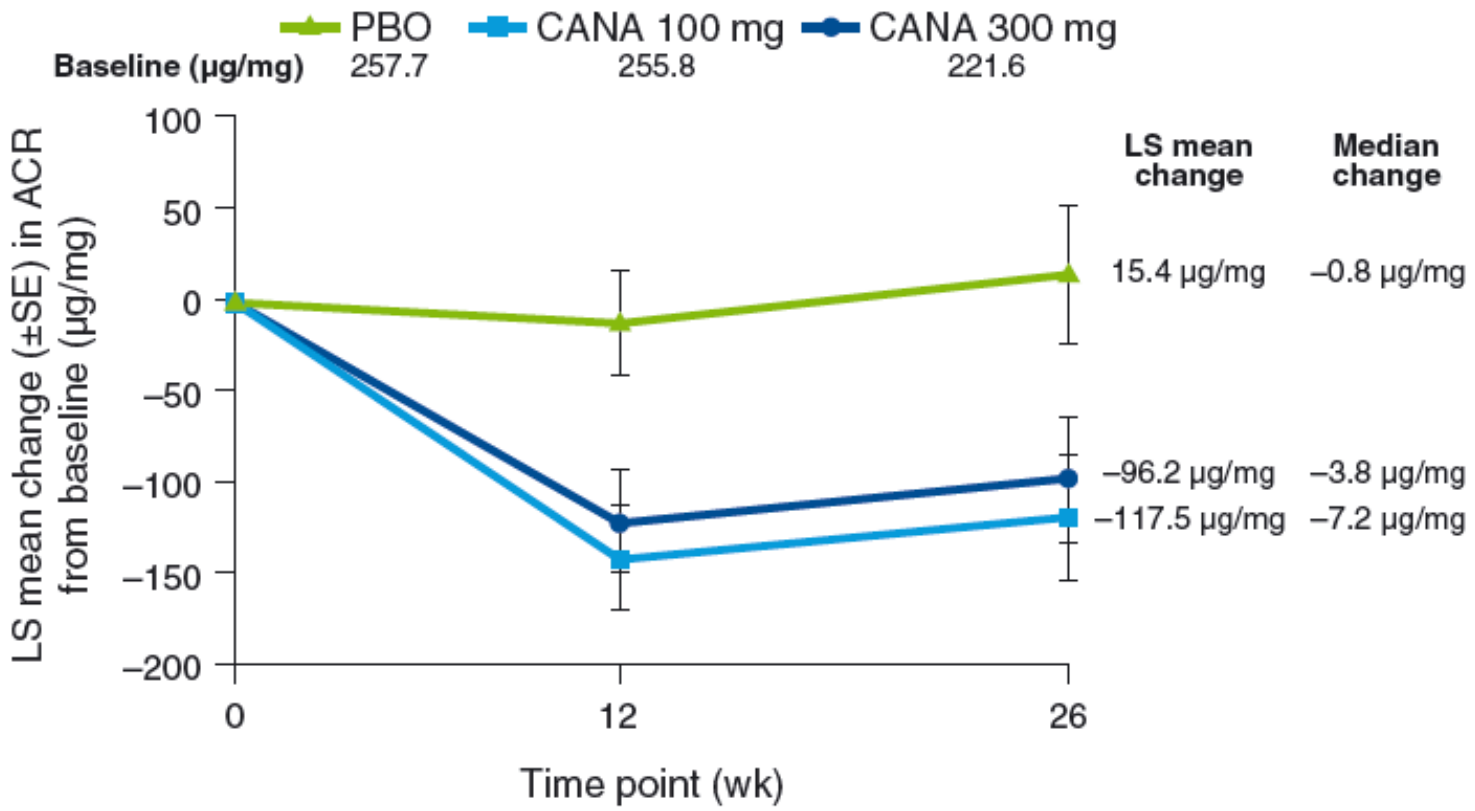
De Zeeuw, Lancet 2010

RADAR: Endothelin A receptor antagonist reduces albuminuria in type 2 DM on top of Anti-RAS



De Zeeuw, JASN 2014

Sodium glucose transport-2 inhibitor decreases albuminuria in type 2 diabetes

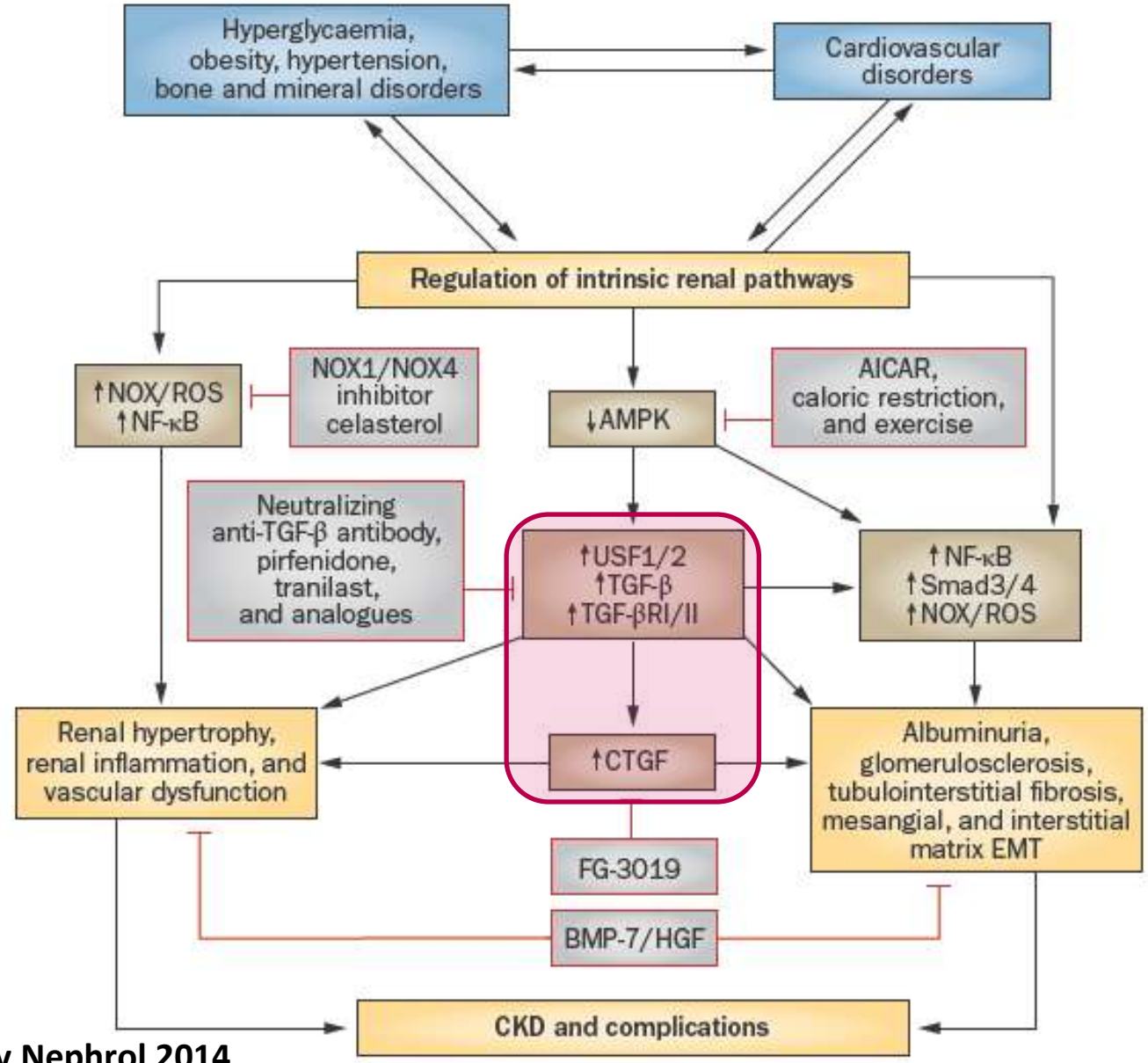


Yale, Diabetes, Obesity and Metabolism 2013

CONCLUSIONS

- In Italy, DM affects about 12% adult population (~ 4 M) and about 50% of type 2 diabetics develop CKD
- Pathogenesis of DM-CKD is complex and involves multiple derangements including inflammation
- Residual very high risk of CKD progression despite anti-RAS
- **Monoclonal antibodies target different molecular mechanisms of inflammation...but the *"Jury is not out"***
- **Meanwhile…intensify global approach and add VDRA**
- **Next Future…SGLT2-Inhibitors and ET_{RA}-antagonists**

Specific targets and potential therapeutic strategies to inhibit or slow CKD progression



Declèves, Nat Rev Nephrol 2014

Trend in the number of prevalent cases of ESRD in U.S. 1980-2012