IMPACT OF DIABETES DRUGS ON CARDIOVASCULAR AND RENAL DISEASE IN TYPE 2 DIABETES
Roma, 2 – 3 febbraio 2018

Quale approccio alla nefropatia diabetica oggi ?

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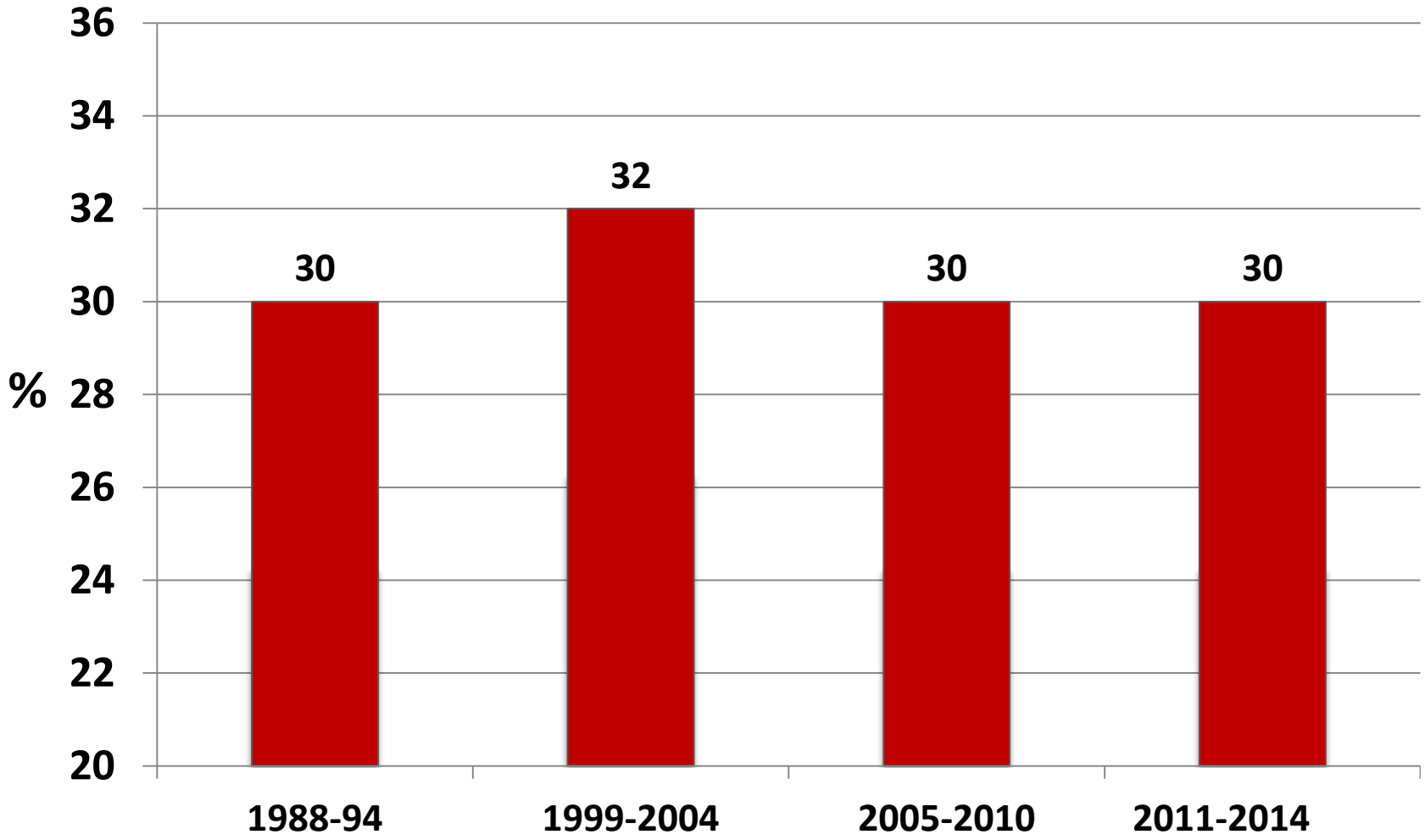
DM-CKD in U.S. adults aged ≥ 18 years
Trend over NHANES 1988 to 2014 surveys



Ali…Gregg, Lancet Diabetes & Endocrinology 2018, in press

Residual renal risk in patients with overt DM2-CKD under anti-RAS therapy

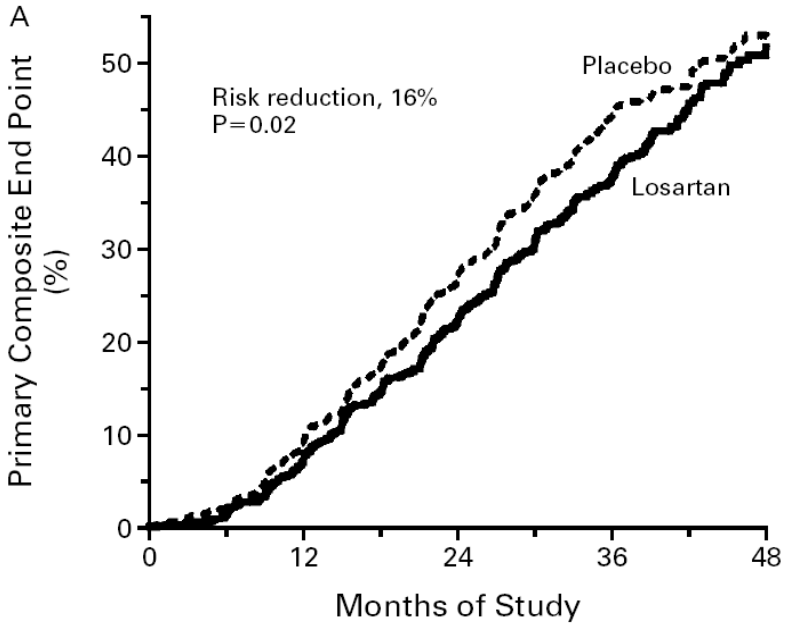
VOLUME 345 SEPTEMBER 20, 2001 NUMBER 12

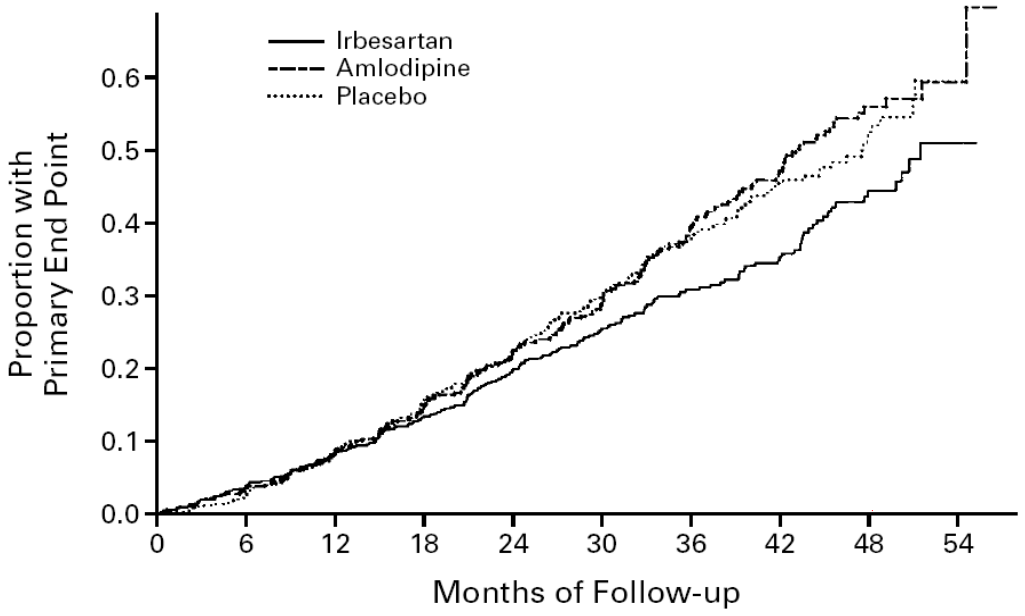
EFFECTS OF LOSARTAN ON RENAL AND CARDIOVASCULAR OUTCOMES IN PATIENTS WITH TYPE 2 DIABETES AND NEPHROPATHY

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*

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*





Main RCTs testing new nephroprotectve interventions in DM-CKD on top of ACEi or ARB

- Aldosterone-antagonists (prot reduction, **NO HARD ENDPOINT**)
- Renin-inhibitors (⇩alb, hard endpoints, ALTITUDE; CV/renal, **STOPPED**)
- Combination ACEi/ARB (⇩alb, hard endpoints, NEPHRON-VA; **STOPPED**)
- Erythropoietin (Hb rise; hard endpoint trial; TREAT; CV/renal; **NO EFFECT**)
- Sulodexide (⇩prot; hard endpoint trial; SUN-Overt**; STOPPED**)
- Sulodexide (⇩alb; surrogate endpoint; SUN-Micro**; NO EFFECT**)
- Statins (hard endpoint trial; SHARP; CV/renal; CV but **NO RENAL EFFECT**)
- VDRA-Paricalcitol (⇩prot, VITAL, **NO HARD ENDPOINT**)
- Monoclonal Ab>TGFß1 (GFR change, **STOPPED FOR FUTILITY**)
- **Atrasentan (⇩alb; hard endpoint, SONAR; STOPPED FOR LOW EVENT RATE)**
- **Dapaglifozin (Efficacy and Renal Safety; DERIVE, CLOSED)**
- **Canaglifozin (ESRD, sCreat double, CREDENCE; ONGOING)**

…We already have something new

Beneficial renal effects of hypogly drugs

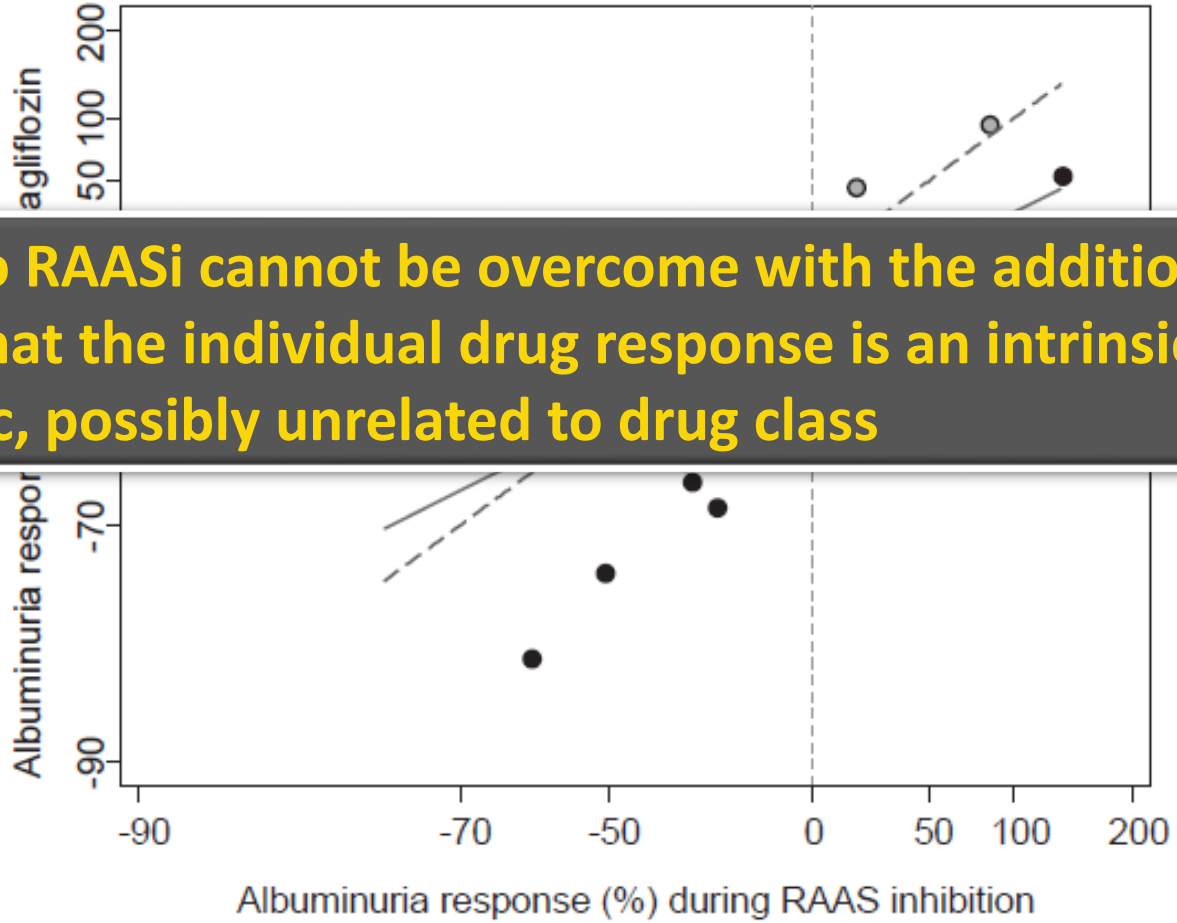
(*prespecified secondary endpoint of RCTs*)

- **EMPAGLIFOZIN (*EMPAREG*)**, NEJM 2016
- **CANAGLIFOZIN (*CANVAS*)**, NEJM 2017
- **LIRAGLUTIDE (*LEADER*)**, NEJM 2017

…but implementation of these new drugs is currently low in diabetology clinical practice !!!

Does SGLT2 inhibition with dapagliflozin overcome individual therapy resistance to RAAS inhibition?

Post-hoc analysis of cross-over trial evaluating albuminuria-lowering effect of dapagliflozin in anti-RAAS treated patients with DM-CKD



Resistance to RAASi cannot be overcome with the addition of SGLT2i, suggesting that the individual drug response is an intrinsic individual characteristic, possibly unrelated to drug class

Petrykiv…Heerspink, Diabetes Obes Metab. 2018

…Use what you have !!!

…possibly better than in the past

AMERICAN DIABETES ASSOCIATION

STANDARDS OF MEDICAL CARE IN DIABETES—2018

Hypertension control

- ✓ All hypertensive patients should have home blood pressure monitored to identify white-coat hypertension (B)
- ✓ Target <130/80 mmHg, may be appropriate for individuals at high risk of CV Disease (B)
- ✓ Anti-RAS , at the maximum tolerated dose as recommended first-line treatment for hypertension in patients with diabetes and ACR >300 mg/g (A), or 30-299 mg/g (B)
- ✓ Lifestyle intervention consists of weight loss if overweight, reduced sodium and increased potassium intake (B)

Diabetes Care, January 2018

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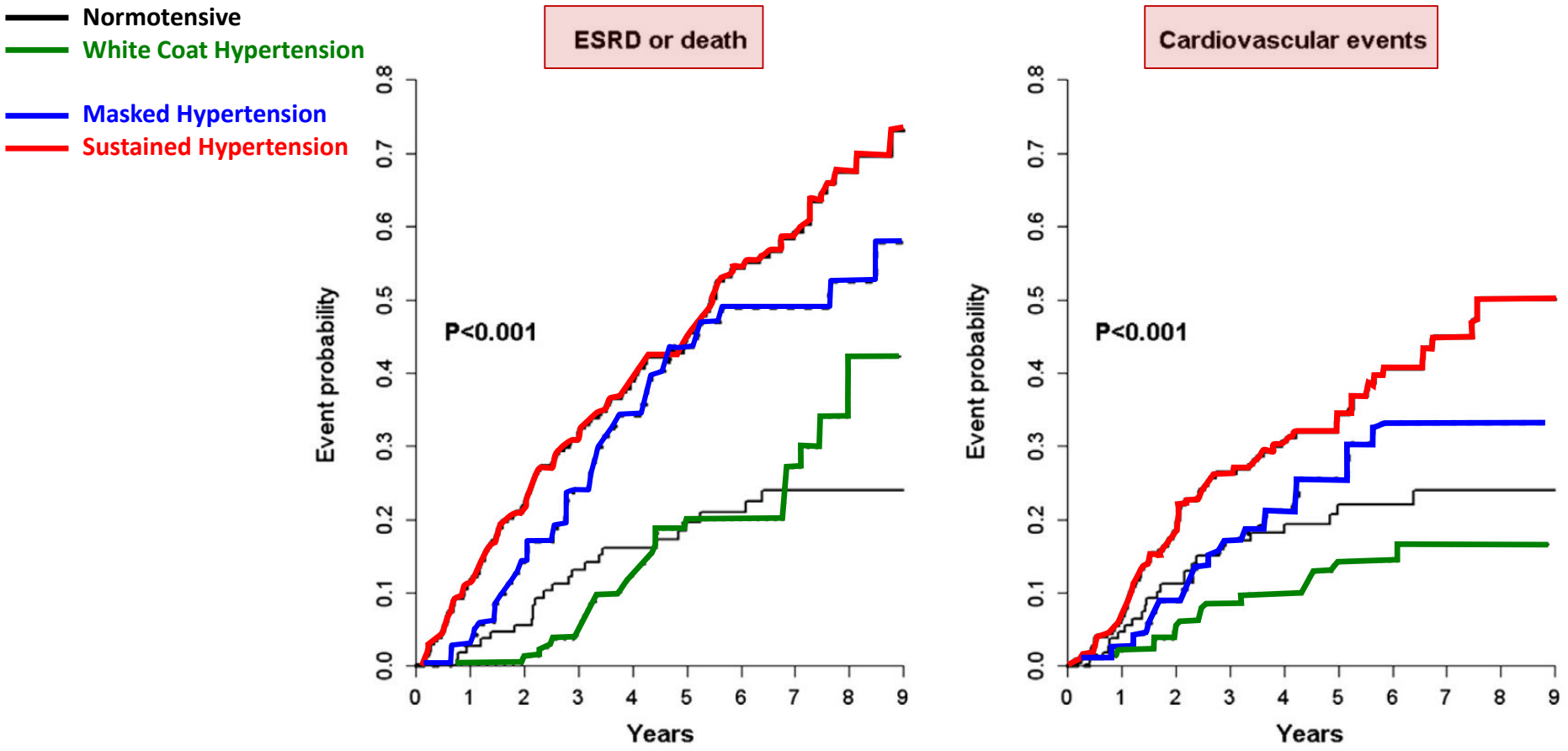
Diabetes Care, January 2018

Assessment of Achieved Clinic and Ambulatory Blood Pressure Recordings and Outcomes During Treatment in Hypertensive Patients With CKD: A Multicenter Prospective Cohort Study

489 consecutive hypertensive pts (DM in 36%) with CKD 1-5 stratified in 4 groups by office (<140/90) and day- (<135/85) and night-time (<120/70) BP goals



Minutolo...De Nicola, AJKD 2014

Nephrol Dial Transplant (2007) 22: 2217–2223
doi:10.1093/ndt/gfm164
Advance Access publication 9 April 2007

NDT
Nephrology Dialysis Transplantation

Original Article

Prevalence and clinical correlates of white coat hypertension in chronic kidney disease

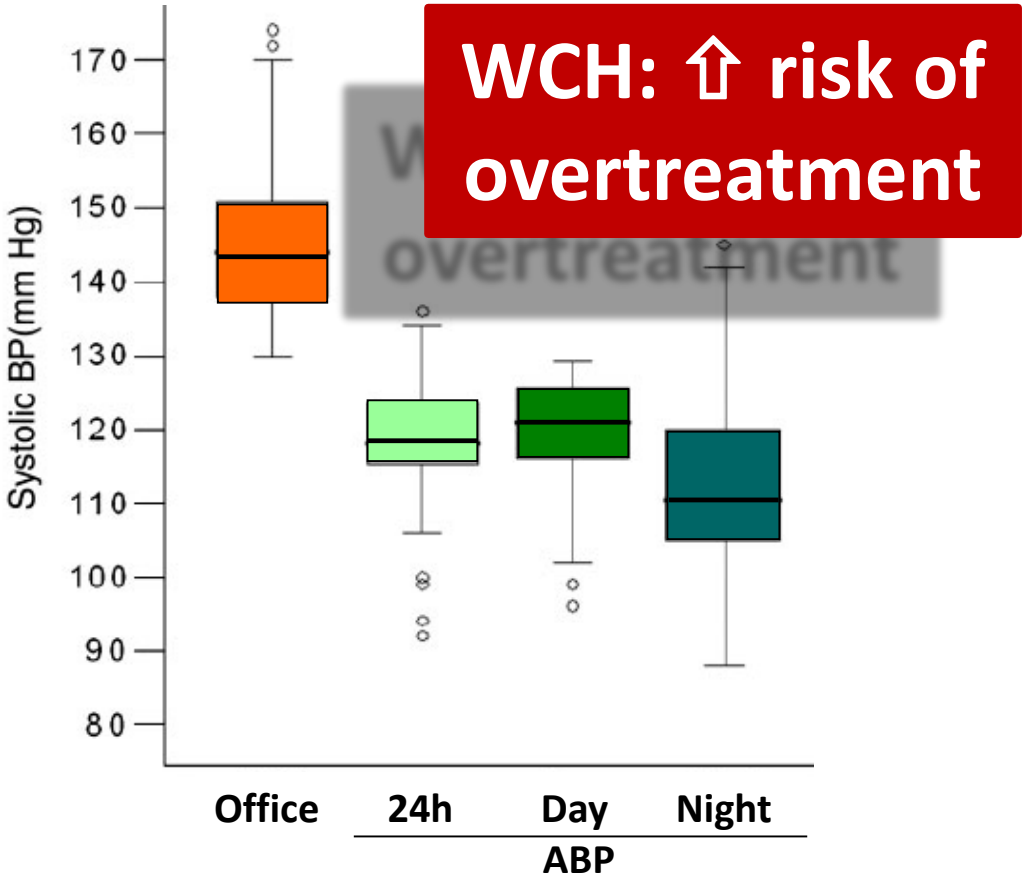
Roberto Minutolo[1], Silvio Borrelli[1], Raffaele Scigliano[1], Vincenzo Bellizzi[2], Paolo Chiodini[3], Bruno Cianciaruso[4], Felice Nappi[5], Pasquale Zamboli[1], Giuseppe Conte[1] and Luca De Nicola[1]

CKD pts with GFR<60

32% WCH

(31% with DM)

In-office BP and 24h ABP in 92 CKD patients with WCH



WCH: ⇧ risk of overtreatment

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Diabetes Care, January 2018

Treat to goal but…
…J effect on CV risk

Trial	Setting	Low SBP thresholds for ⇧ CV risk
IDNT *(JASN '05)*	**DM-2 + CKD**	**120**
ONTARGET *(J Hyp '09)*	**CVD/DM-2**	**130**
INVEST *(JAMA '10)*	**DM-2 + CAD**	**115**
ROADMAP *(NEJM '11)*	**DM-2 + CAD**	**120**

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Diabetes Care, January 2018

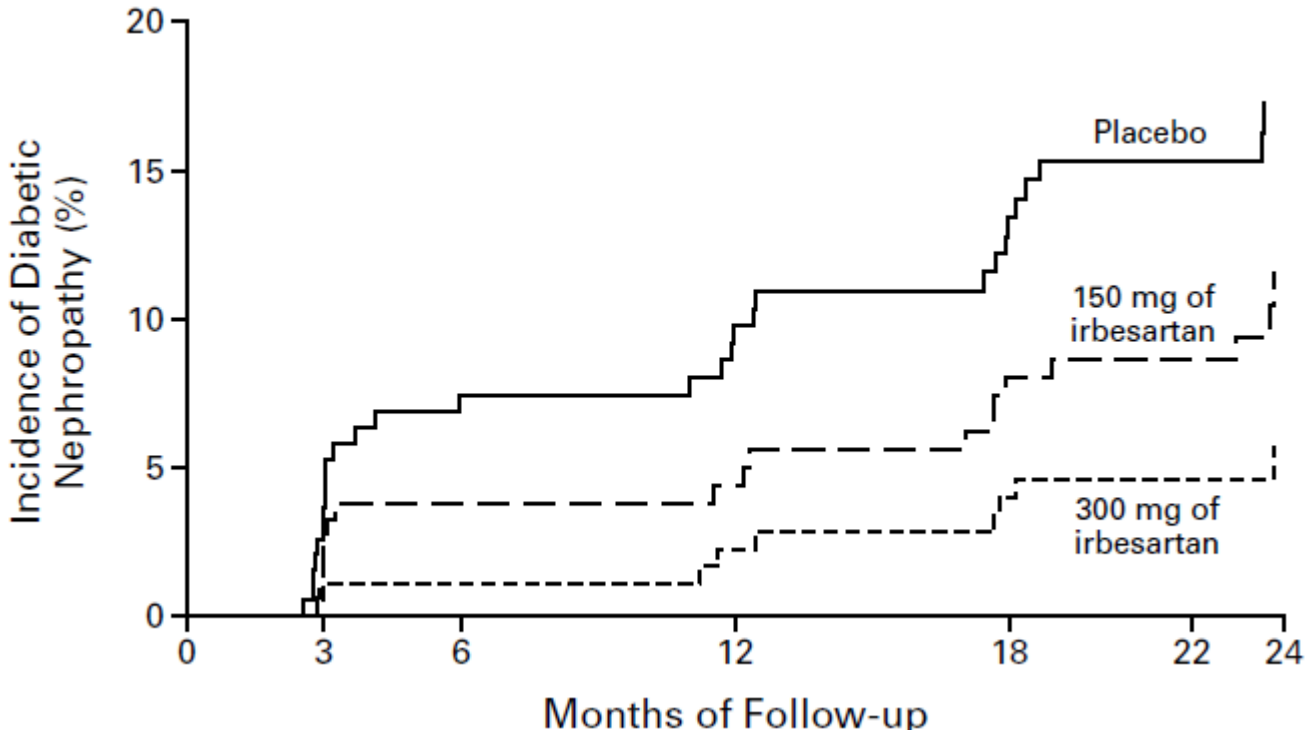
Early antialbuminuric intervention

VOLUME 345 SEPTEMBER 20, 2001 NUMBER 12

THE EFFECT OF IRBESARTAN ON THE DEVELOPMENT OF DIABETIC NEPHROPATHY IN PATIENTS WITH TYPE 2 DIABETES

HANS-HENRIK PARVING, M.D., D.M.Sc., HENDRIK LEHNERT, M.D., JENS BRÖCHNER-MORTENSEN, M.D., D.M.Sc.
RAMON GOMIS, M.D., STEEN ANDERSEN, M.D., AND PETER ARNER, M.D., D.M.Sc.,
FOR THE IRBESARTAN IN PATIENTS WITH TYPE 2 DIABETES AND MICROALBUMINURIA STUDY GROUP*

590 hypertensive patients with DM2 and MAU



Early renin–angiotensin system intervention is more beneficial than late intervention in delaying end-stage renal disease in patients with type 2 diabetes

- BENEDICT, IRMA-2, RENAAL and IDNT trials on RAS intervention in DM2-CKD
- Effect of anti-RAS on delaying ESRD in early*, intermediate* and advanced CKD

Age at which RAS treatment is initiated (years)	Delay in ESRD (years) compared with placebo Disease stage at which RAS treatment is initiated		
	GFR >60 and ACR<30	GFR 30-60 or ACR 30-300	GFR<30 or ACR>300
35	7.4	4.1	0.8
40	6.9	4.0	0.9
45	5.9	4.0	1.1
50	5.7	3.6	1.2
55	5.1	3.5	1.2
60	4.2	3.6	1.4
65	3.5	3.4	1.6

Diabetes, Obesity and Metabolism 18: 64–71, 2016.

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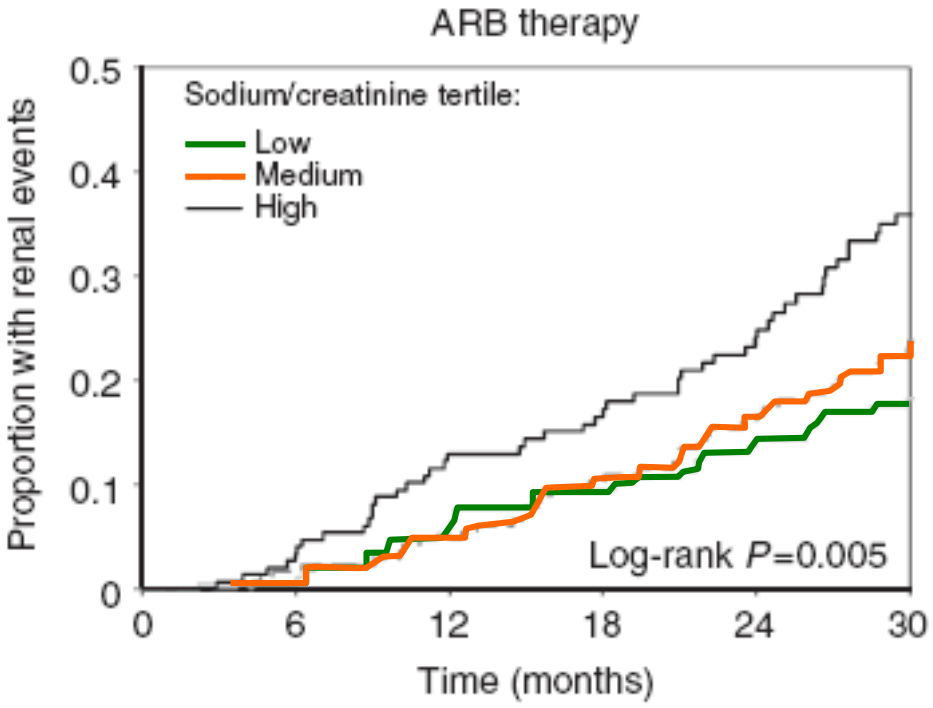
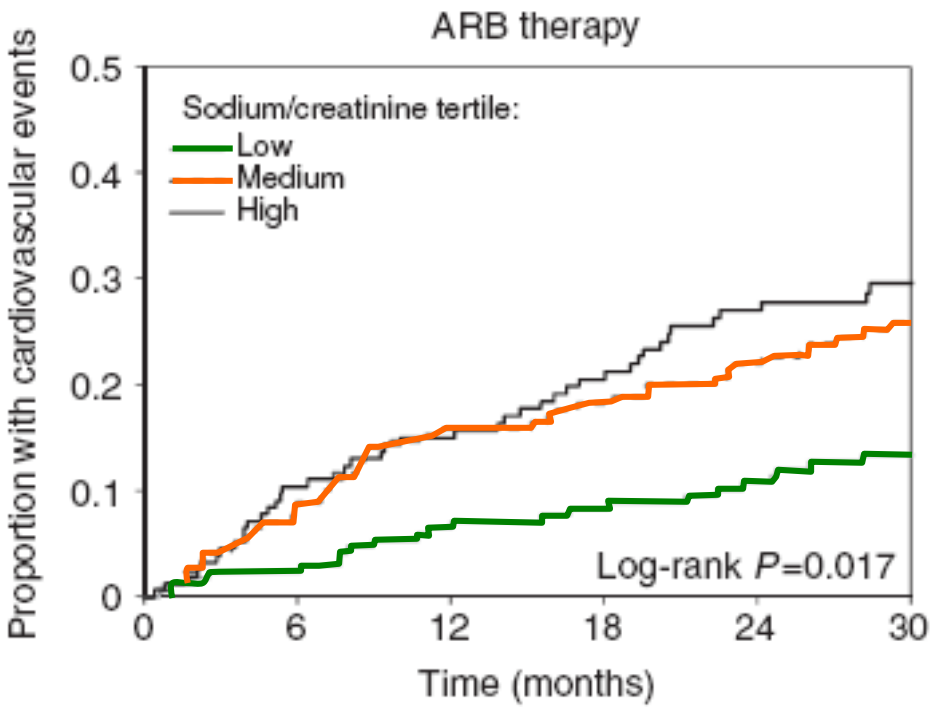
Diabetes Care, January 2018

Moderation of dietary sodium potentiates the renal and cardiovascular protective effects of angiotensin receptor blockers

Hiddo J. Lambers Heerspink[1,7], Frank A. Holtkamp[1,7], Hans-Henrik Parving[2,3], Gerjan J. Navis[4], Julia B. Lewis[5], Eberhard Ritz[6], Pieter A. de Graeff[1] and Dick de Zeeuw[1]

Post-hoc RENAAL-IDNT: 1,177 patients with diabetic nephropathy stratified by UNaV and use of ARBs (losartan o irbesartan) vs non anti-RAS therapy





Kidney International (2012) **82,** 330–337

Poor Glycemic Control in Diabetes and the Risk of Incident Chronic Kidney Disease Even in the Absence of Albuminuria and Retinopathy

Atherosclerosis Risk in Communities (ARIC) Study

Lori D. Bash, MPH; Elizabeth Selvin, PhD, MPH; Michael Steffes, MD, PhD; Josef Coresh, MD, PhD, MHS; Brad C. Astor, PhD, MPH, MS

1871 adults with diabetes mellitus followed up for 11 years

Incident CKD was defined as eGFR <60 mL/min/1.73 m^2 or kidney-related hospitalization

Variable	Total Sample	HbA_{1c} Concentration Category, %			
		<6	6-7	7-8	>8
Albuminuria (93 of 251[b])					
No. of events	103 of 270	15 of 61	14 of 58	13 of 31	61 of 120
Incidence per 1000 person-years	34.53	20.81	30.32	40.49	48.73
Adjusted HR[c] (95% CI)	1.27 (1.14-1.41)[d]	1 [Reference]	0.83 (0.38-1.84)	2.19 (0.96-5.00)	2.54 (1.35-4.79)
No albuminuria (116 of 972[b])					
No. of events	129 of 1035	49 of 504	32 of 239	16 of 100	32 of 192
Incidence per 1000 person-years	9.78	7.55	10.47	12.66	13.46
Adjusted HR[c] (95% CI)	1.20 (1.08-1.32)[d]	1 [Reference]	1.34 (0.83-2.15)	1.75 (0.94-3.27)	2.21 (1.32-3.70)

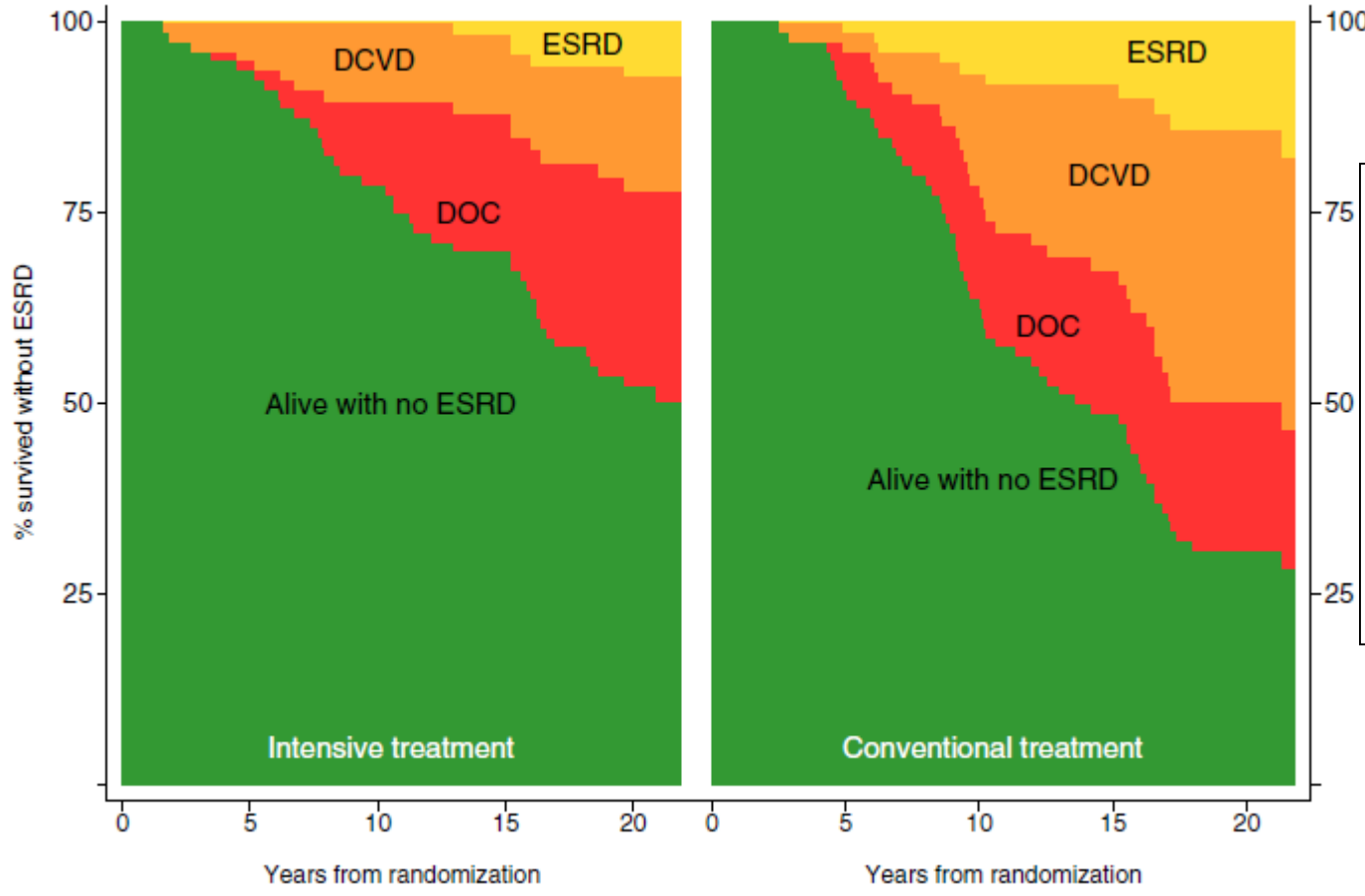
Arch Intern Med. 2008

But don’t forget the STENO-2 …

Multifactorial intervention leads to long-term renal benefits

The Steno-2 experience

- 160 pts DM2+Ualb
- Intensive versus Standard treatment for 7.8 yrs
- Subsequent observation for up to 21 yrs in all patients under intensive treatment



EFFECTS OF TREATMENT at 7.8 yrs

	STD	INT
BP,mmHg	146/78	132/73
A_{1c},%	9.0	7.9
L-C, mg/dl	118	81
P+STAT,%	45	86
E±ARB,%	70	97

Probability of being in the specified state at a given time point.
DCVD: CV death
DOC: other death cause
Adjusted P value for difference in survival estimates = 0.003

Steno-2 study group, KI 2017

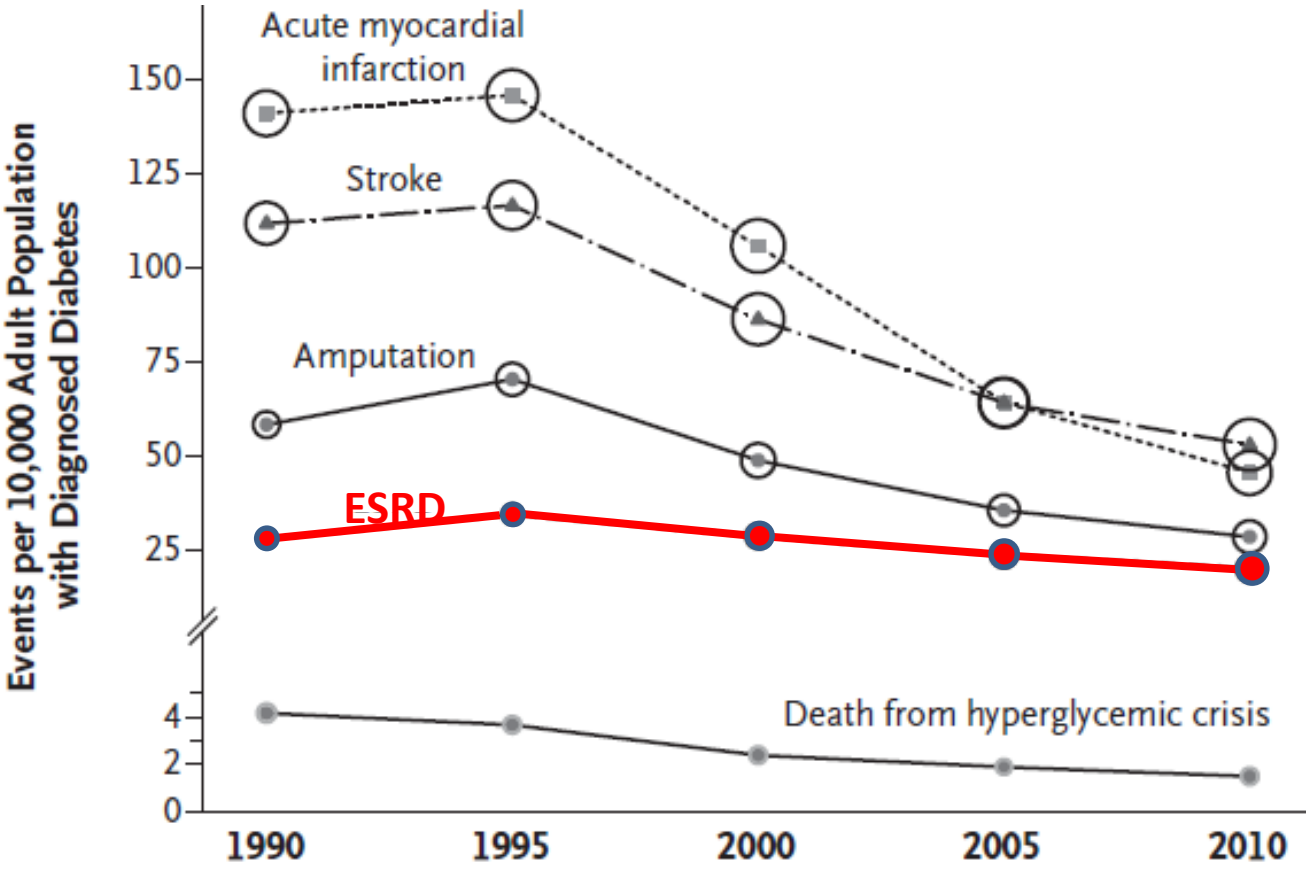
Optimal Management of Diabetic CKD ?

(…while awaiting for new drugs)

- ✓ **BP level ?**
- ✓ **Antihypertensive intervention ?**
- ✓ **Glucose level ?**
- ✓ **Strategy ?**

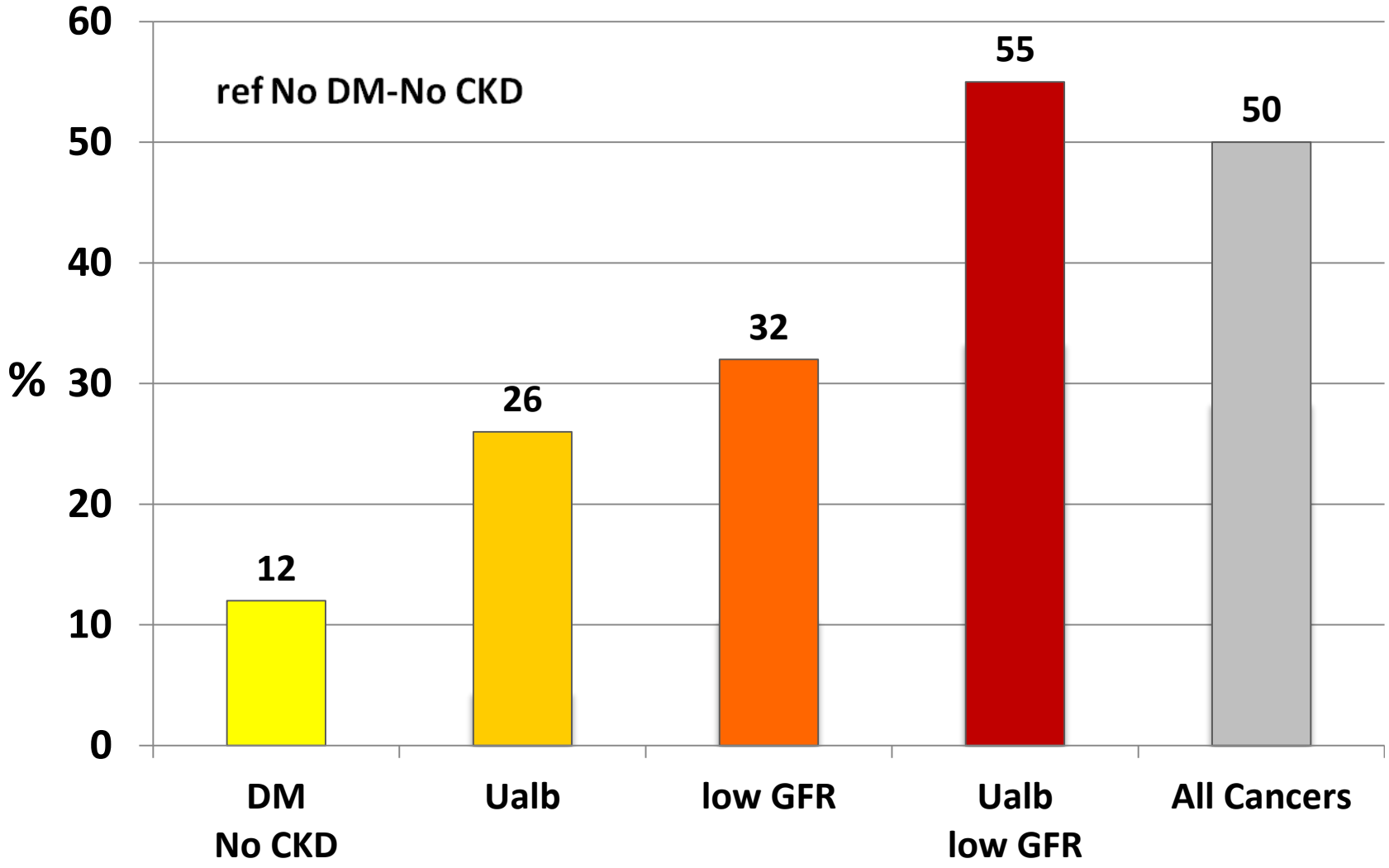
Changes in Diabetes-Related Complications in the United States, 1990–2010

Data from the National Health Interview Survey, the National Hospital Discharge Survey, the U.S. Renal Data System, and the U.S. National Vital Statistics System



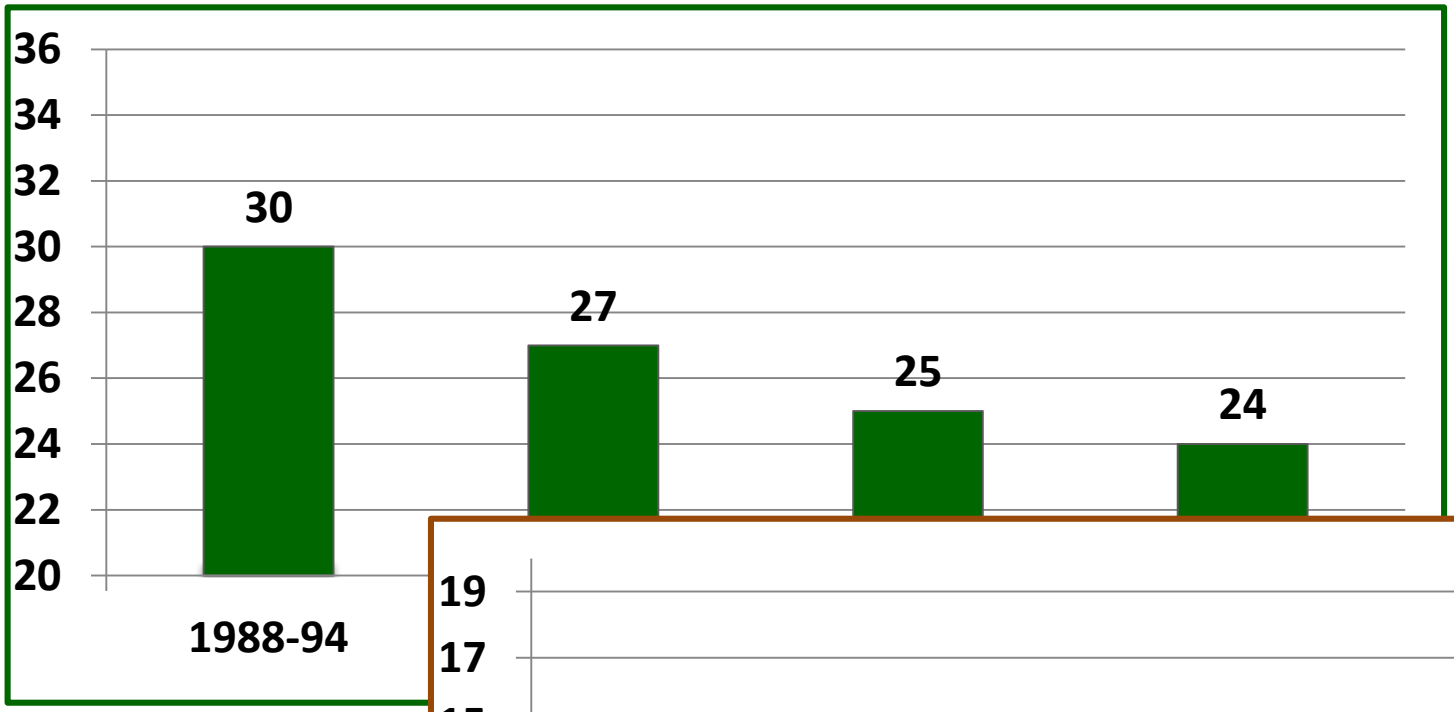
Gregg, NEJM 2014

Excess 10-year standardized cumulative mortality by DM2 and CKD status



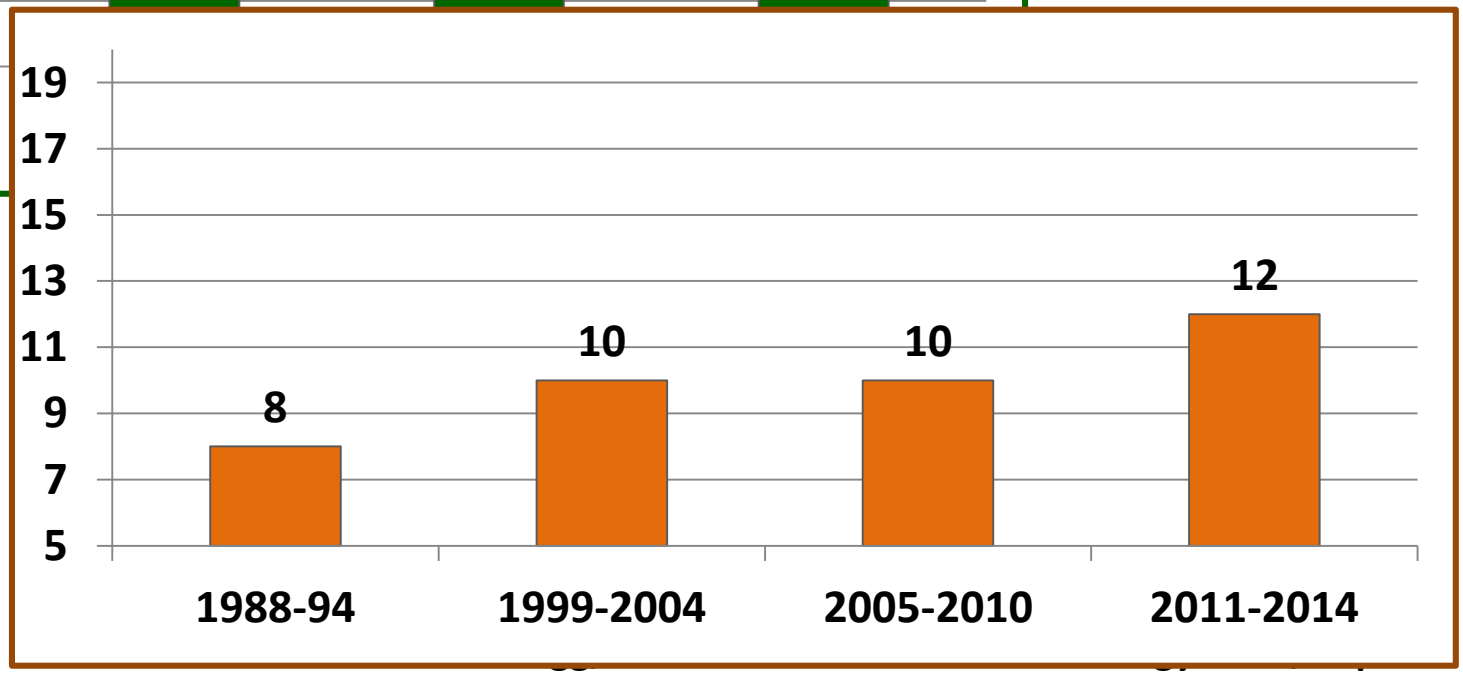
JASN 2013, Lancet 2014

CKD components in U.S. adults aged ≥ 18 years
Trend over NHANES 1988 to 2014 surveys



UAlb >30

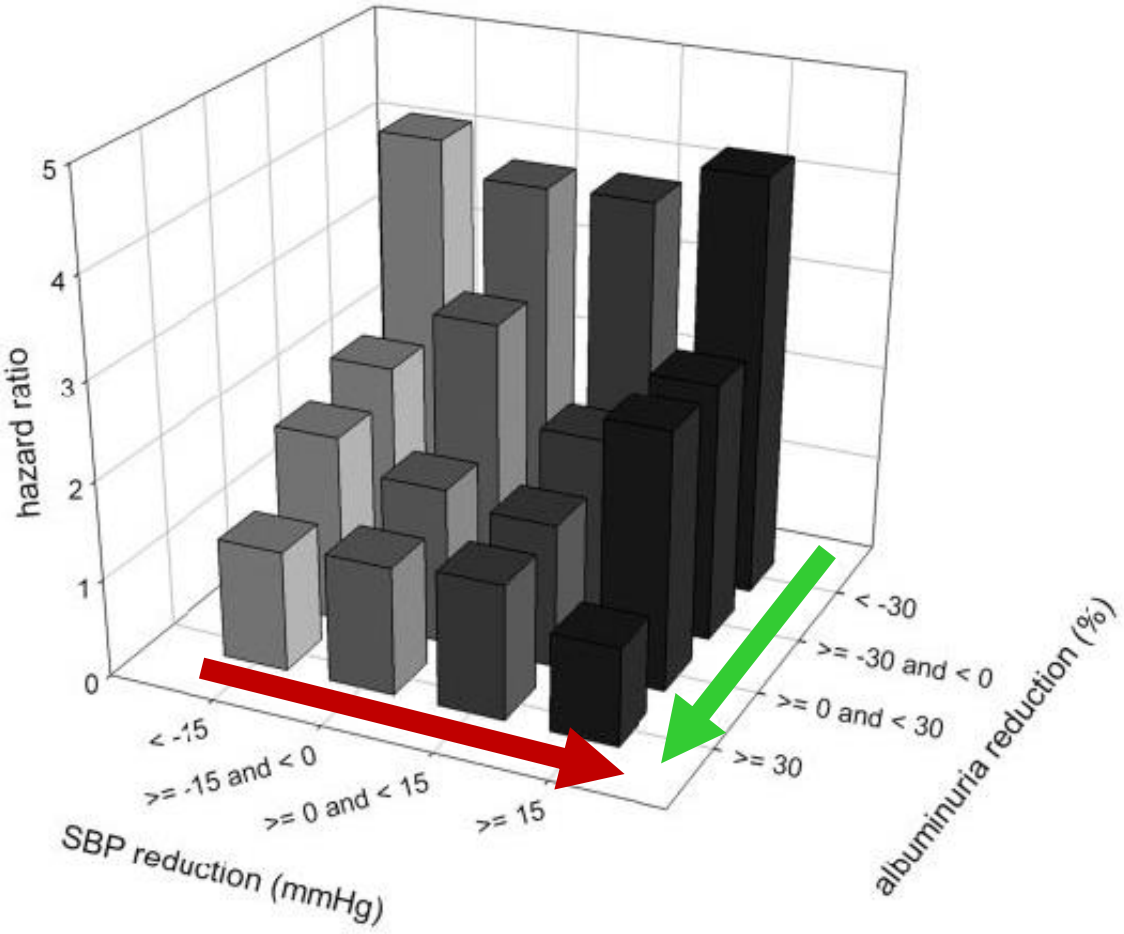
eGFR <60



⇩ UAlb more important than ⇩ SBP in lowering risk of CKD progression

RENAAL: 1513 patients with overt DM2 nephropathy

Renal risk by first 6-month changes of SBP and Ualb



Eijkelkamp JASN 2007