La storia naturale della Nefropatia Diabetica

Luca Di Lullo
UOC Nefrologia - Dialisi
Ospedale L. Parodi – Delfino
Colleferro

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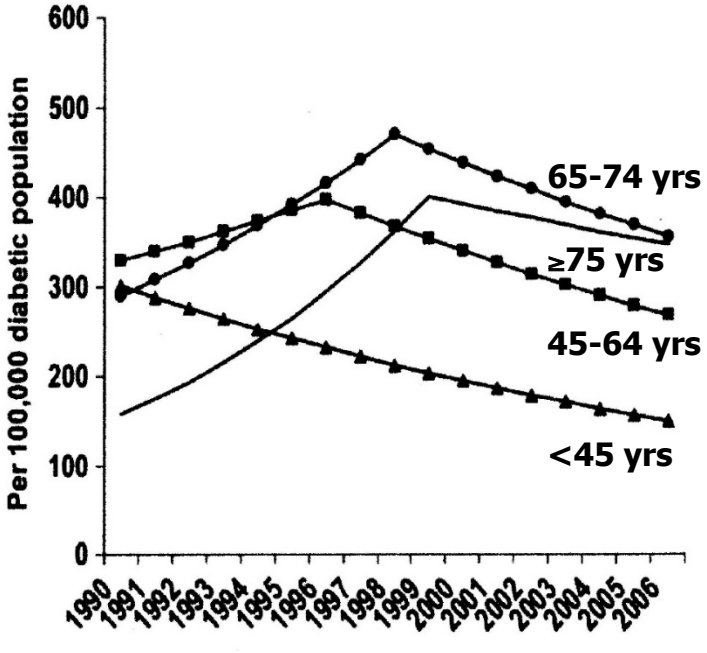
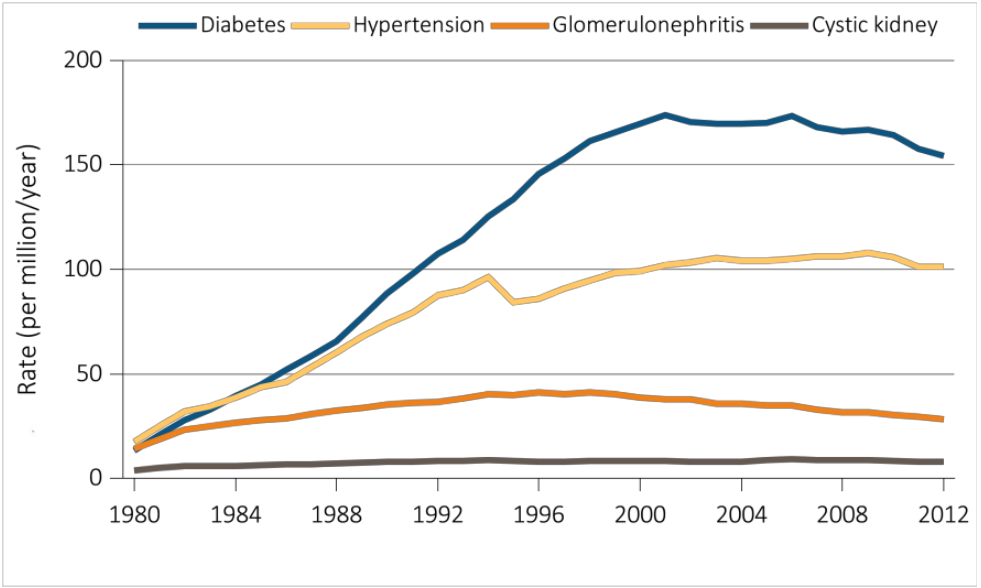
glossario

- UACR - Dosaggio dell'escrezione urinaria di albumina in rapporto a quella della creatinina.
  Nei diabetici, l'esame viene richiesto per monitorare la comparsa di malattia renale (nefropatia diabetica), una complicanza del diabete non ben controllato; valori compresi tra 30 e 300 mg/g (3.4-34 mg/mmol) corrispondono alla diagnosi di microalbuminuria, indice di uno stadio precoce di nefropatia e di un rischio aumentato di complicanze cardiovascolari, mentre valori > 300 mg/g (> 34 mg/mmol) corrispondono a un'albuminuria manifesta e a una malattia renale vera e propria, della quale indicano il rischio di progressione verso l'insufficienza renale. Supera la famosa raccolta delle urine di 24 ore.
- eGFR - Estimated Glomerular Filtration Rate (Stima della velocità di filtrazione glomerulare).
  Questo test misura la concentrazione di creatinina nel sangue e usa il risultato in una formula per calcolare un numero che rifletta la qualità del funzionamento renale, chiamato GFR stimato o eGFR.
- CKD – EPI Creatinina - Formula di Levey per il calcolo del filtrato prescinde dal peso, e tiene conto di creatinina, età, sesso e etnia.

1. **Nefropatia diabetica: epidemiologia**
2. **Nefropatia diabetica: rischio renale**
3. **Nefropatia diabetica: rischio CV**
4. **Implicazioni terapeutiche: reno- e cardio-protezione**

Incidence of treatment for ESRD in diabetic patients in the U.S



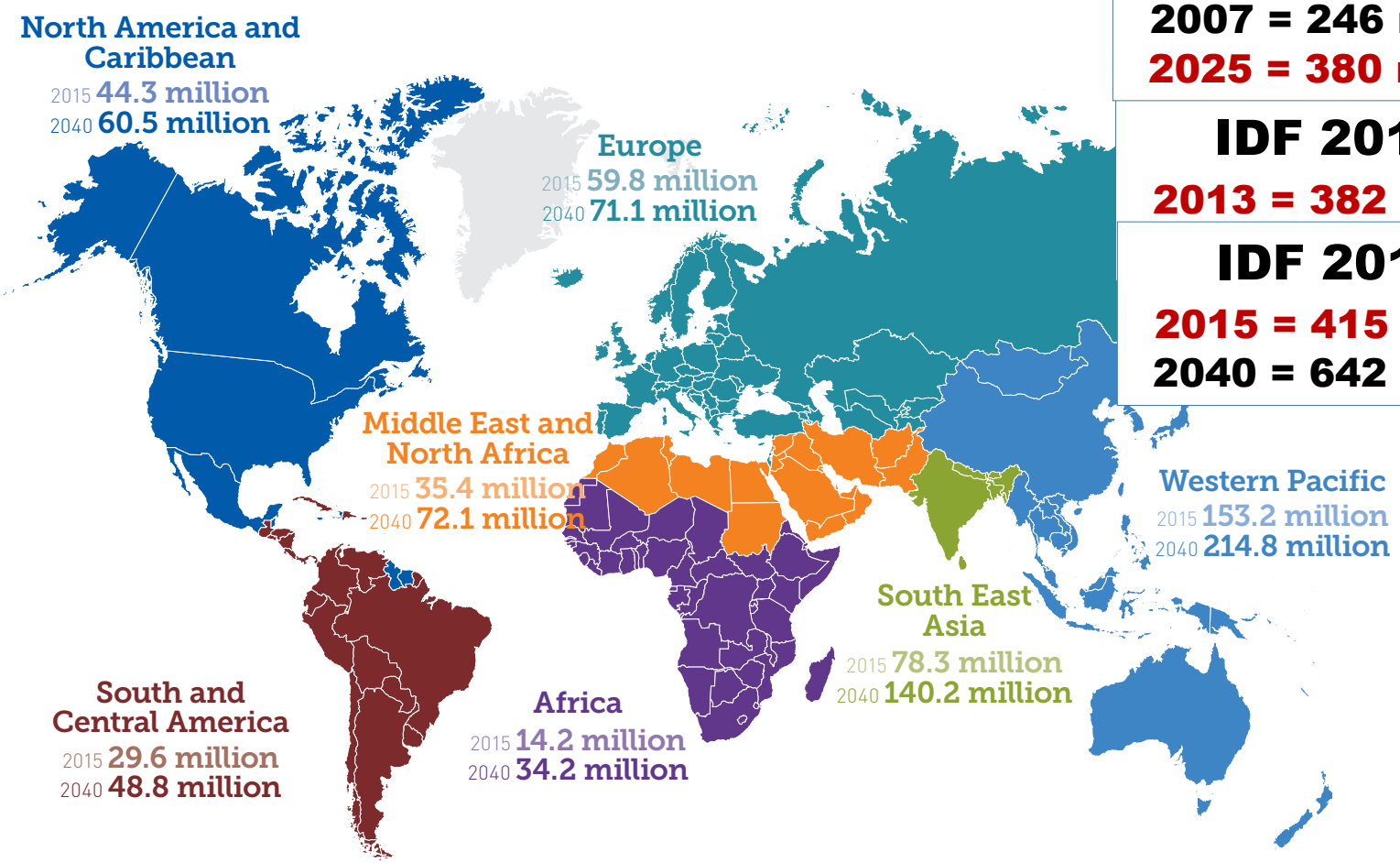


Burrows NR, Diabetes Care 2010

USRDS 2015

Diabetes: A global emergency

Estimated number of people with diabetes worldwide and per region in 2015 and 2040 (20-79 years)



IDF 2007:

2007 = 246 million

2025 = 380 million

IDF 2013:

2013 = 382 million

IDF 2015:

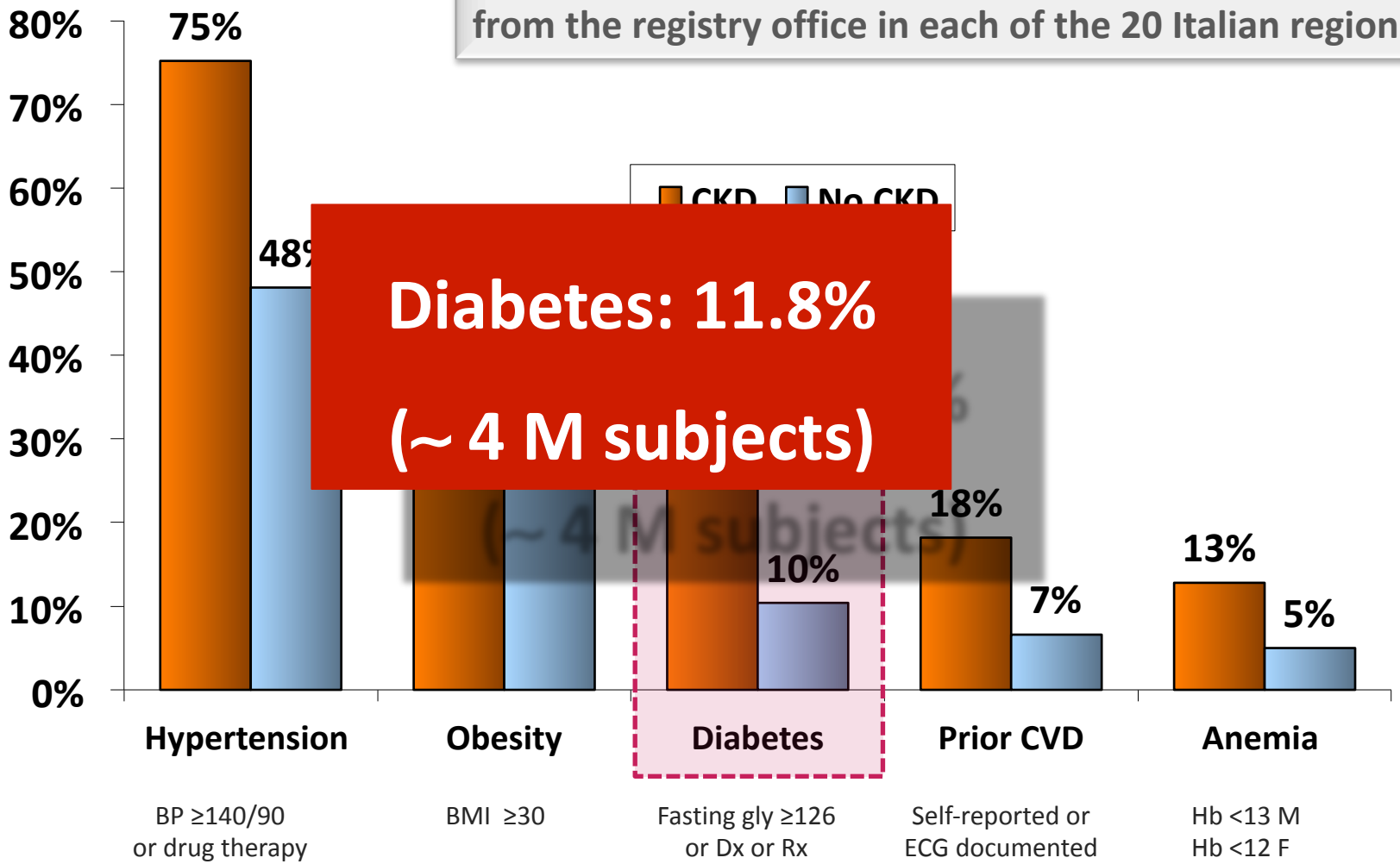
2015 = 415 million

2040 = 642 million

IDF diabetes atlas - 7th edition

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

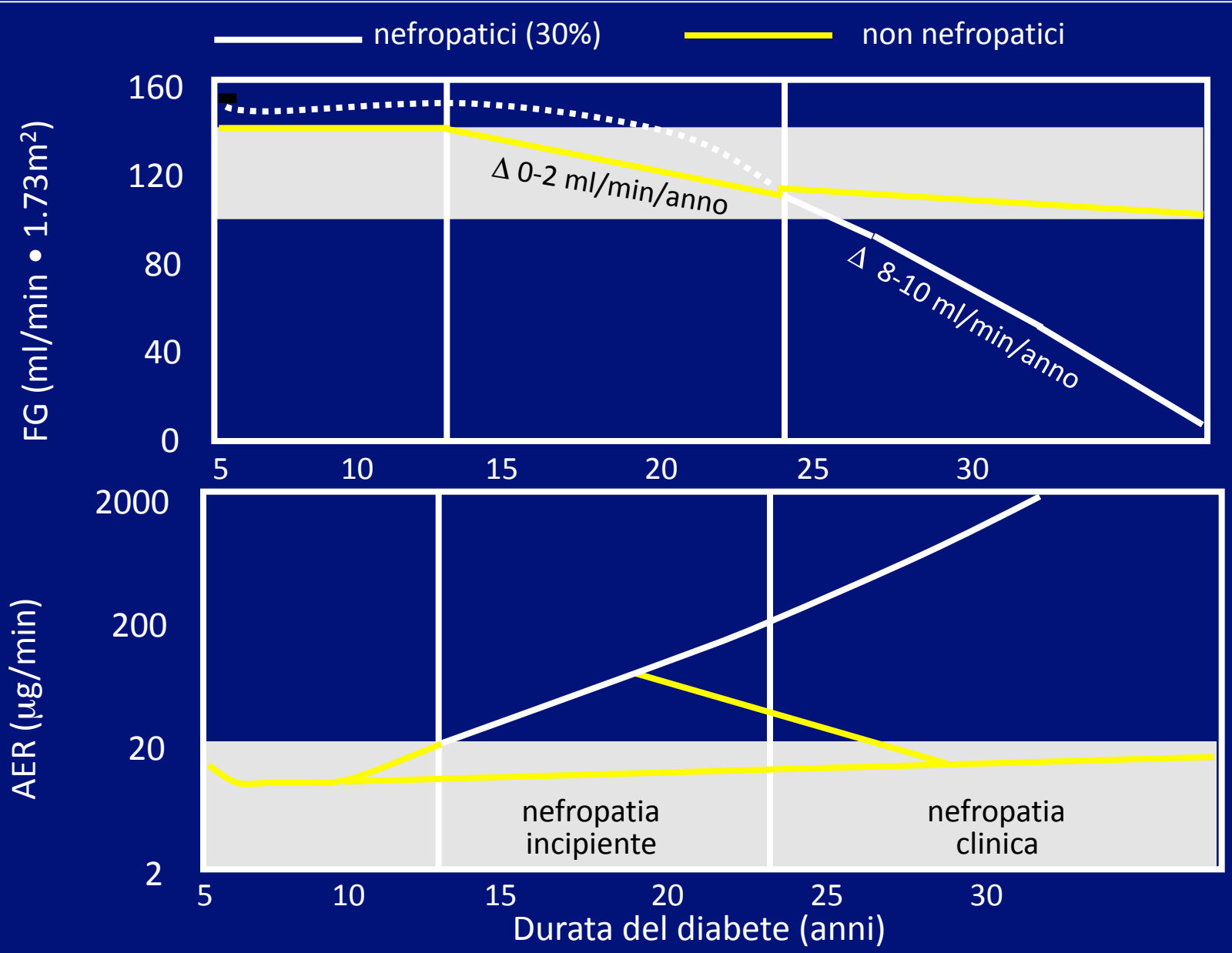
Prevalence and cardiovascular risk profile of chronic kidney disease in Italy: results of the 2008–12 National Health Examination Survey

Multivariate logistic regression analysis estimating clinical correlates of CKD

	CKD	
	OR	95% CI
Age (year)	**1.06**	**1.05–1.07**
Males	1.07	0.87–1.31
High cholesterol	1.09	0.88–1.34
Obesity	**1.42**	**1.17–1.73**
Hypertension	**1.55**	**1.23–1.94**
Diabetes	**1.98**	**1.59–2.46**
High education	0.95	0.78–1.17
CV disease	**1.90**	**1.47–2.42**
Smoking	**1.34**	**1.05–1.72**
Alcohol habit	0.94	0.77–1.15

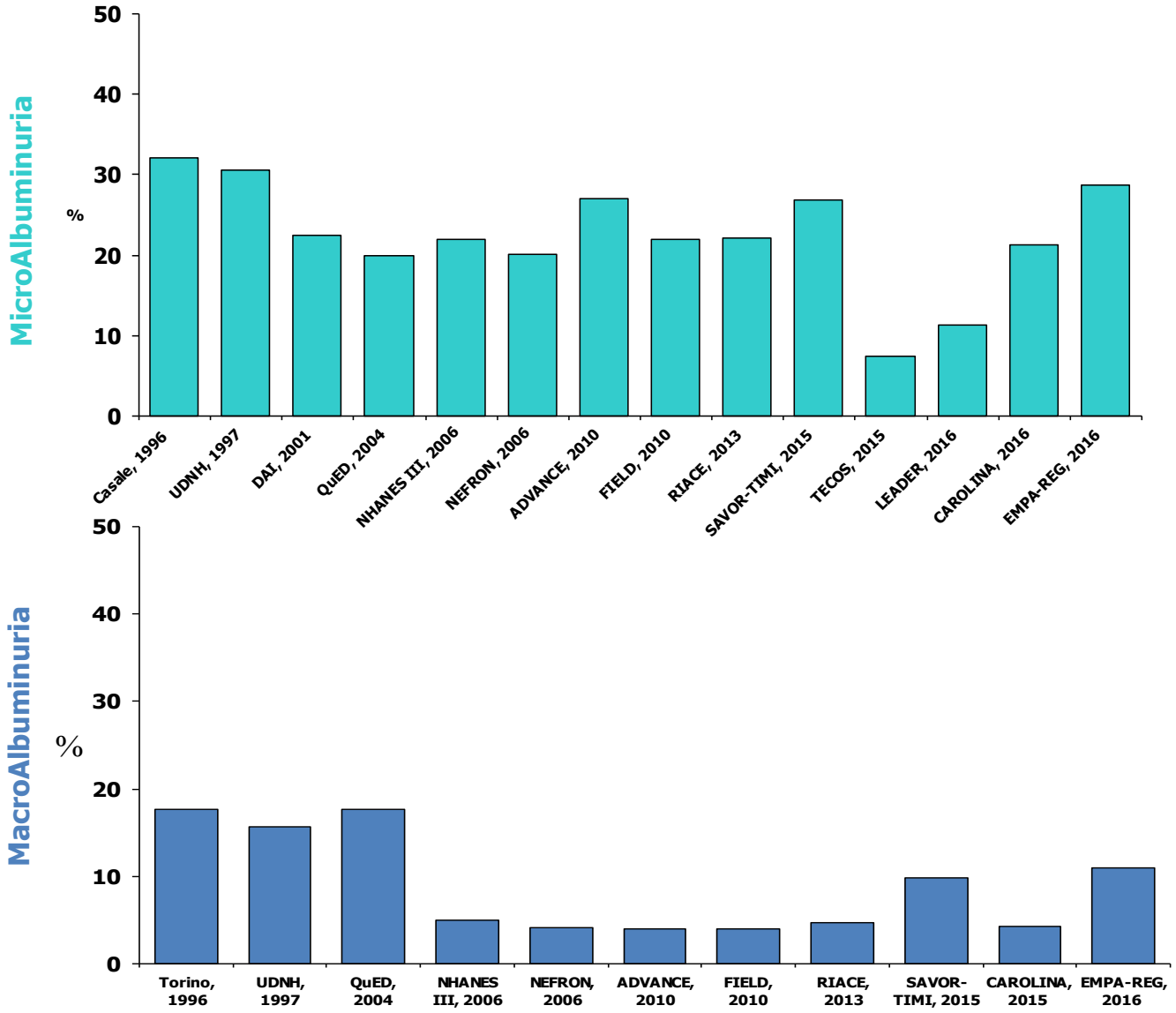
De Nicola for ANMCO-SIN-ISS, NDT 2015

Storia naturale della nefropatia nel diabete tipo 1

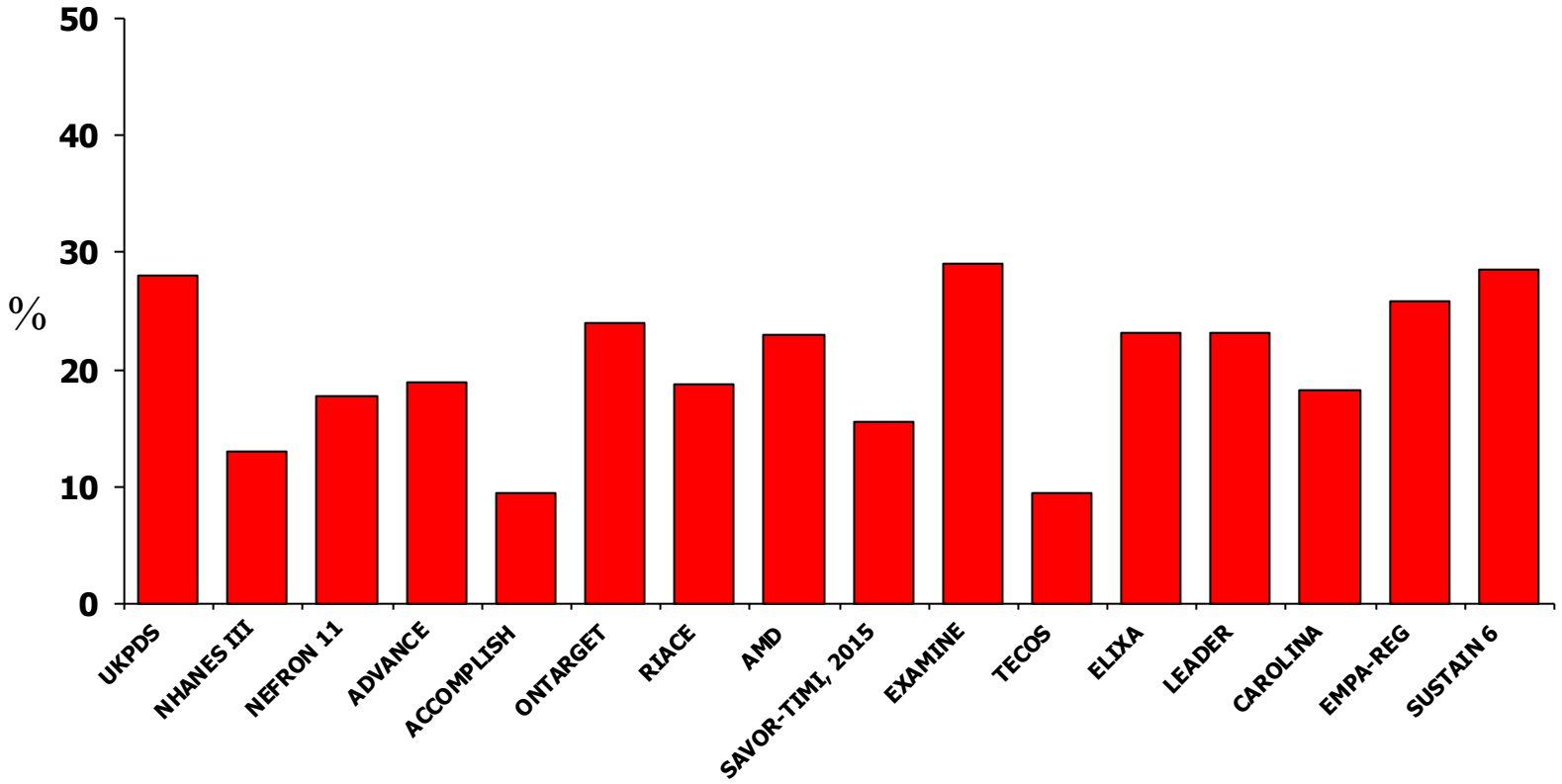


Mogensen et al., 83, 86, 89, 90

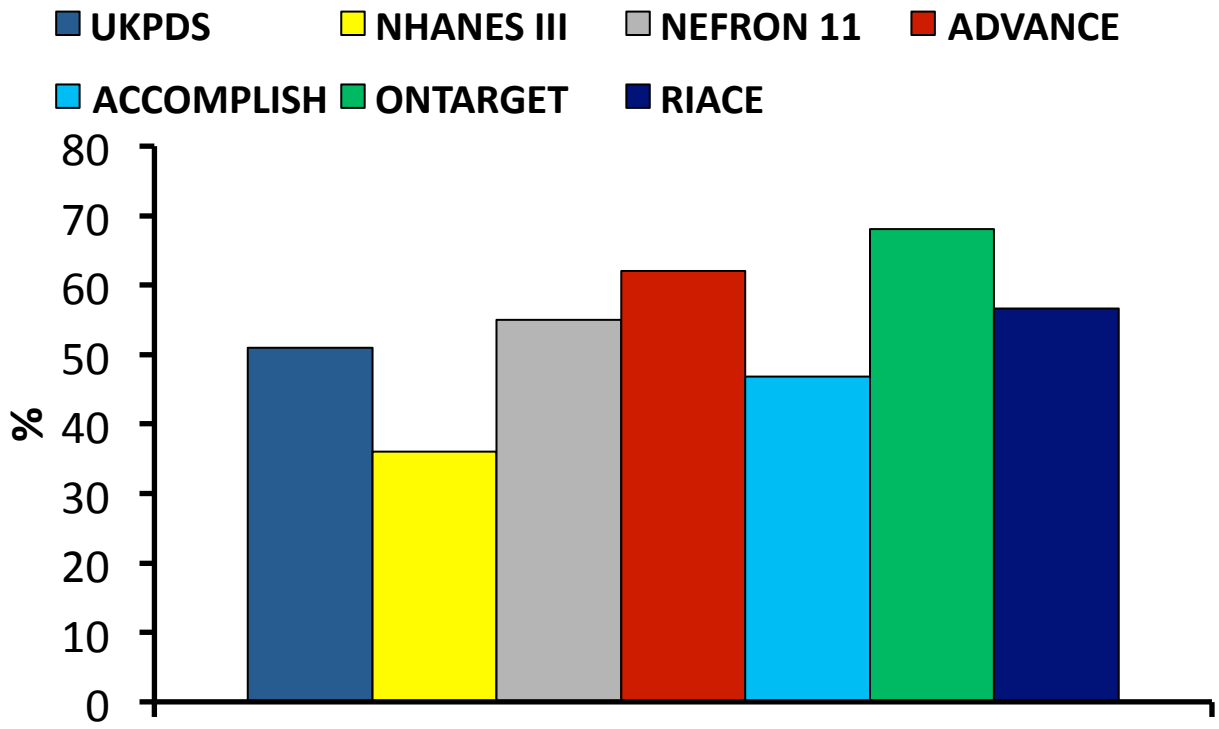
Prevalence of Micro- and Macro-Albuminuria in type 2 DM



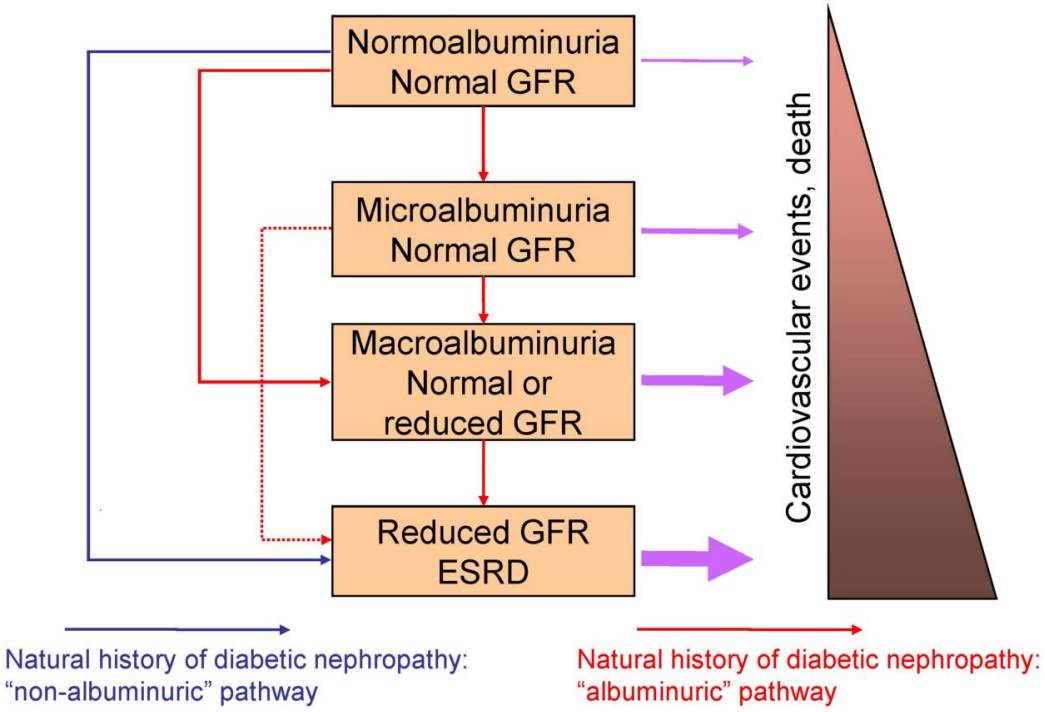
Prevalence of reduced renal function in type 2 DM



Prevalence of reduced renal function with normoalbuminuria in type 2 DM

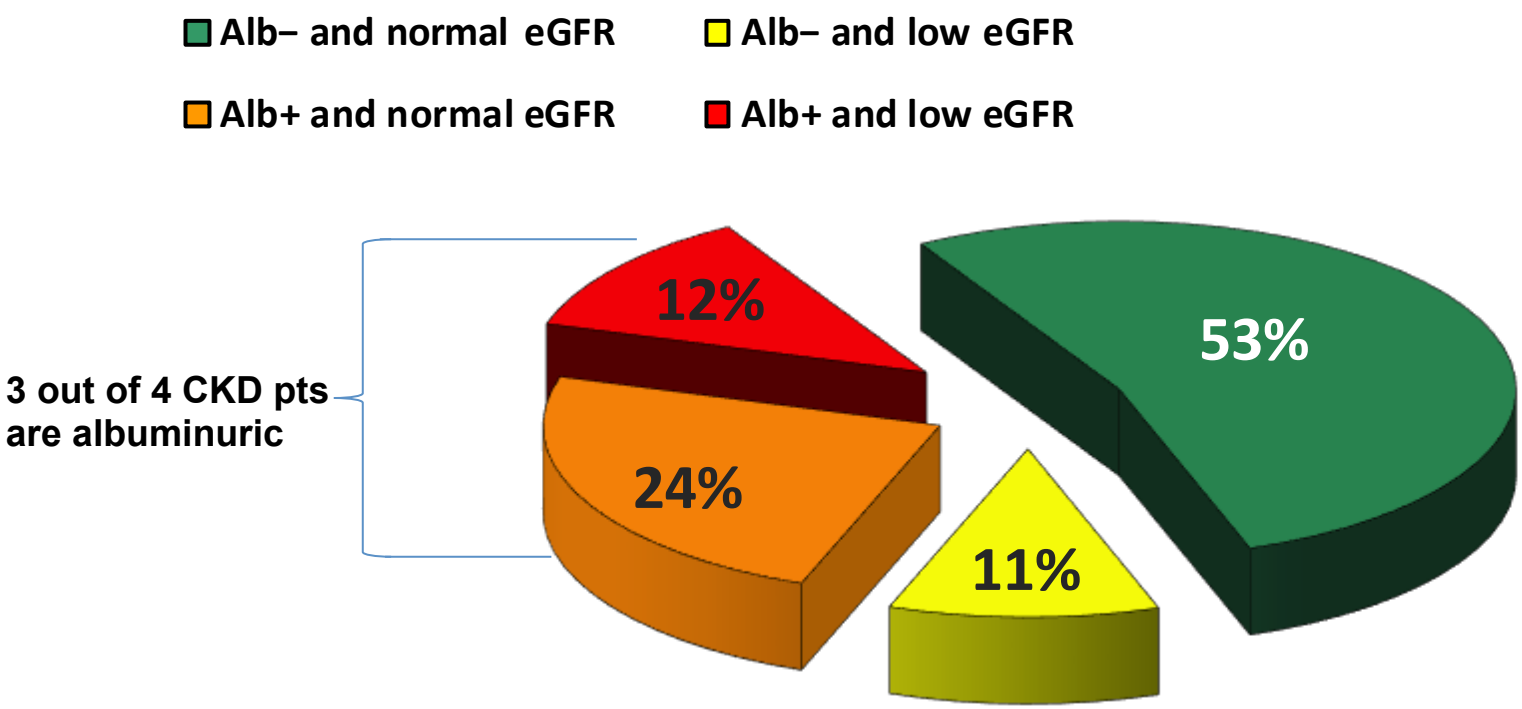


In the last years progression of AER as an obligatory predictor/step of DKD has been challenged.



Penno G, 2016

Prevalence of CKD in a large cohort of patients (120.903) with type 2 diabetes mellitus attending 236 Italian Diabetes Clinics in 2009



De Cosmo, AMD-Annals Study Group, NDT 2014

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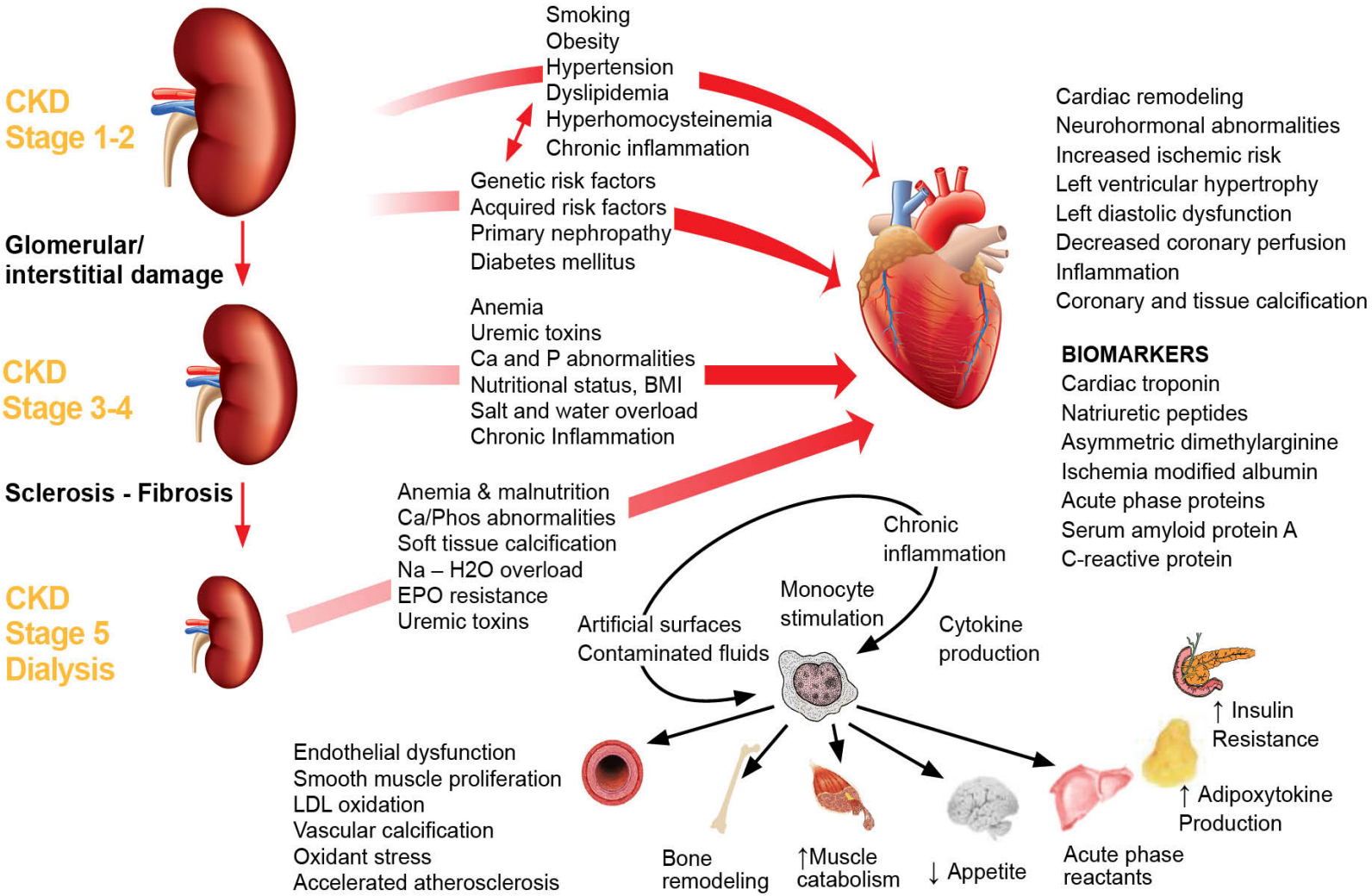
Cardio-Renal Syndrome Type 4

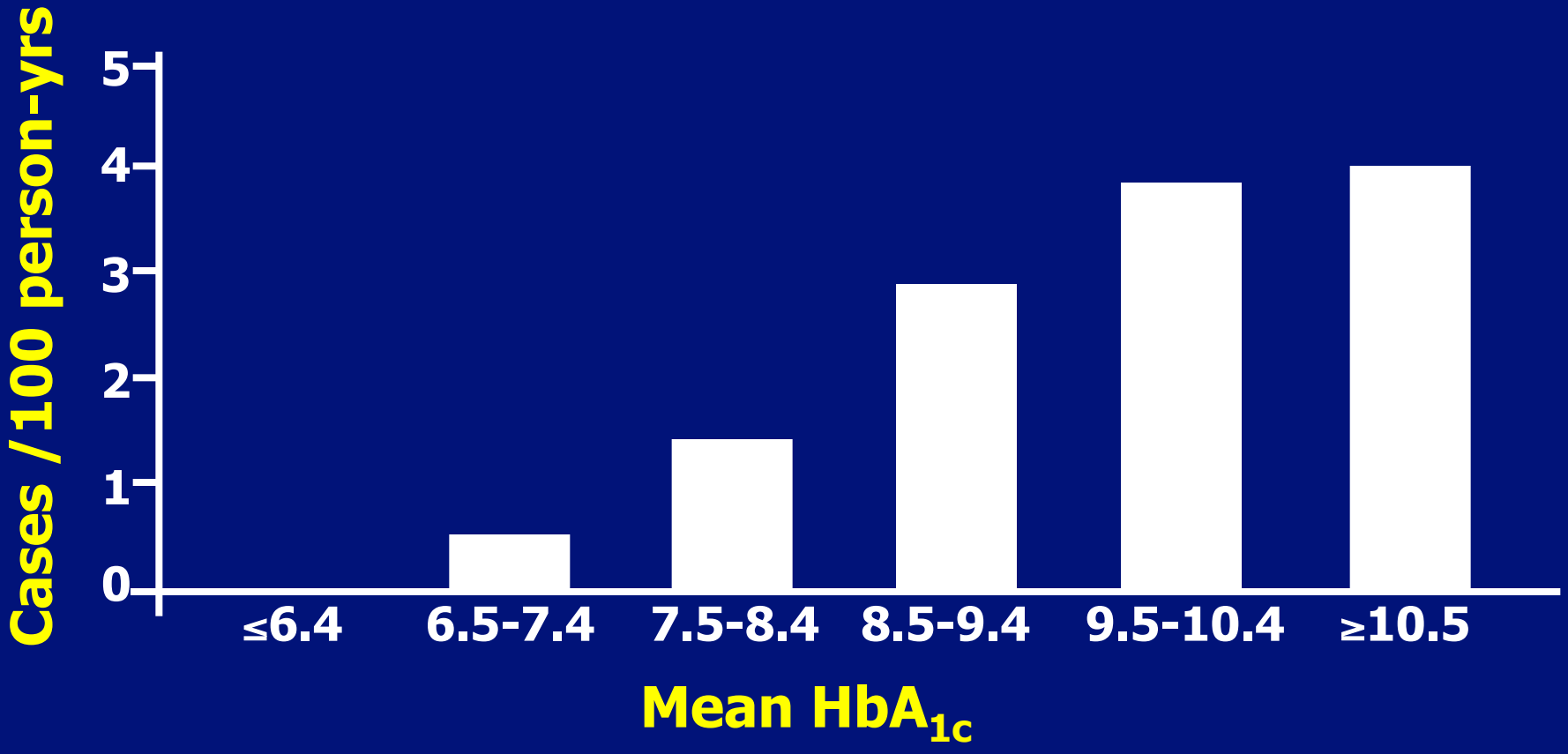


Di Lullo L, Bellasi A, Ronco C. Cardiorenal syndrome: an overview. Adv Chronic Kidney Dis. 2018 Sep;25(5):382-390

Major risk factors and markers for development and progression of renal damage in diabetes

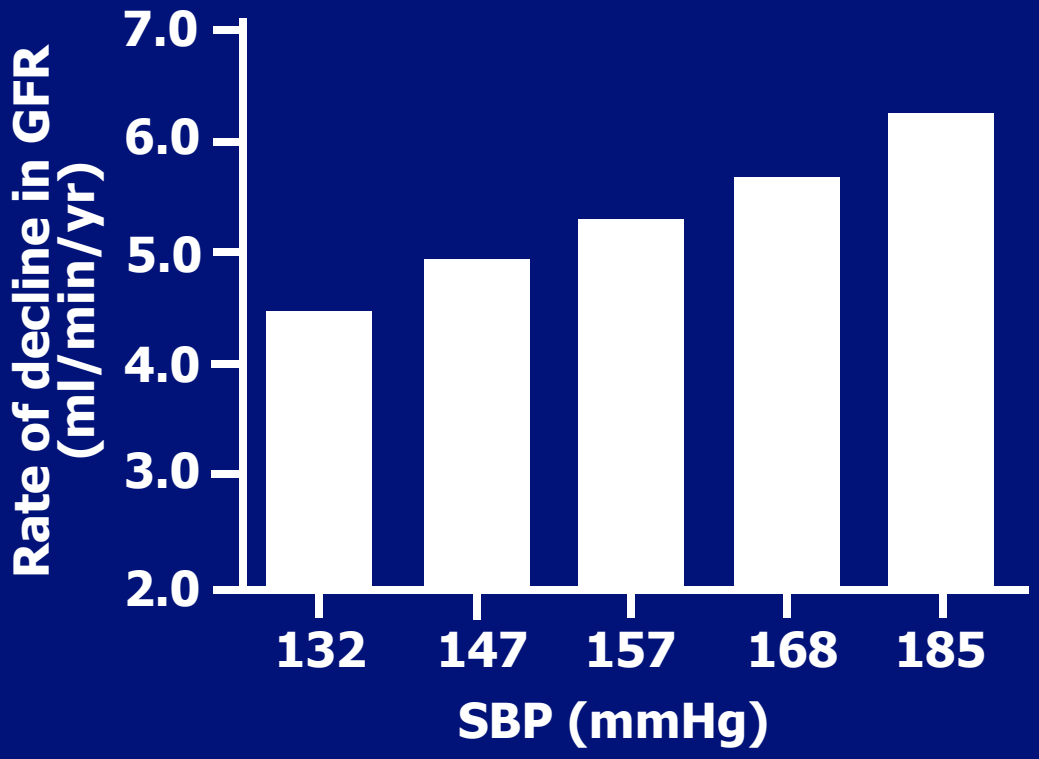
- poor glycemic control
- systemic hypertension
- microalbuminuria (or normoalb. above median) or proteinuria
- lipid abnormalities
- smoking
- high duration of diabetes
- genetic factors
  - male sex
  - family predisposition to hypertension, nephropathies and CV disease
  - ethnic predisposition
  - mutations in specific candidates genes
- early hyperfiltration and hypertrophy (?)
- oligonephropathy (?)

The 7 year incidence density of nephropathy in type 2 diabetes according to HbA_{1c}

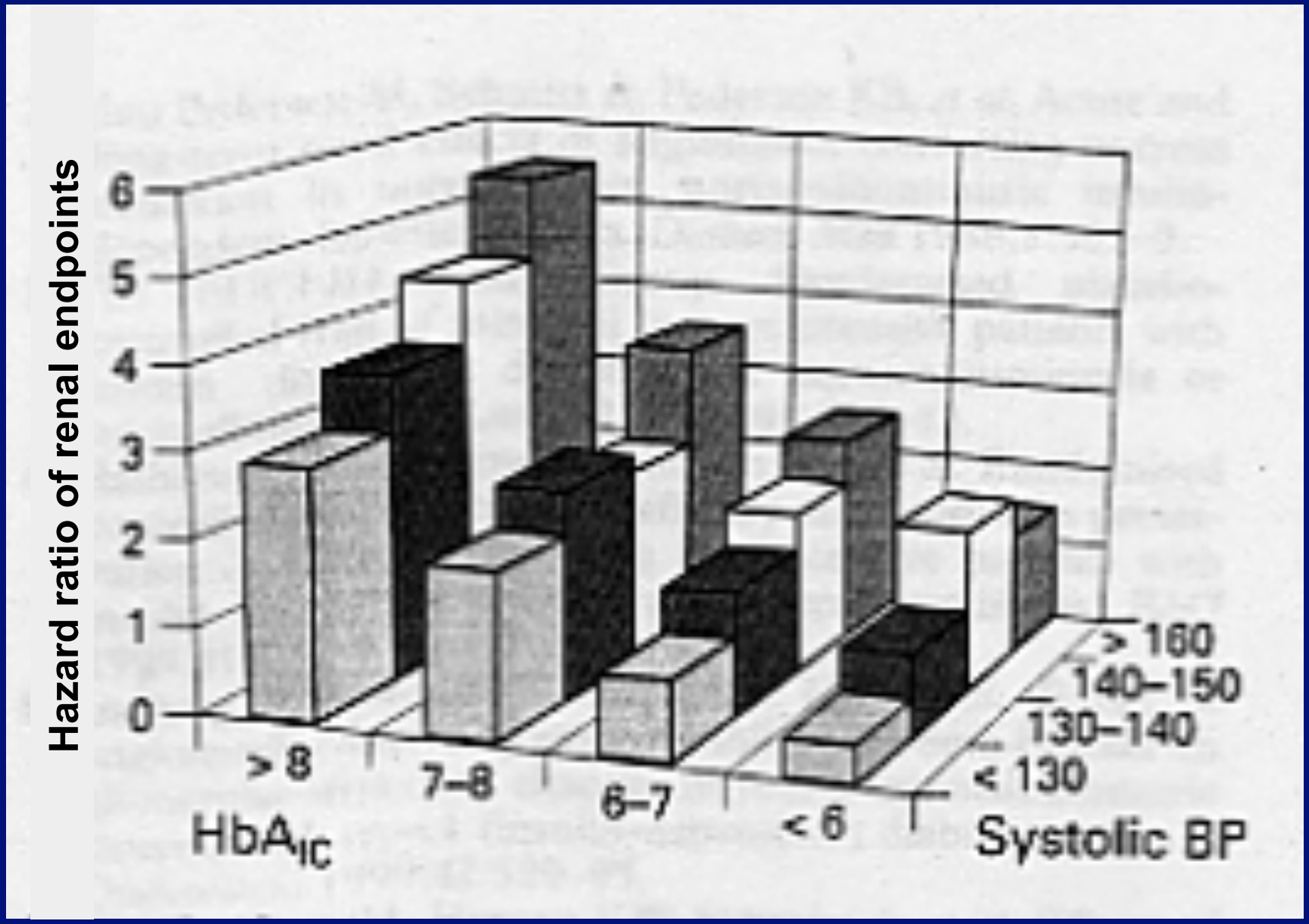


Yokoyama et al., 1998

Impact of SBP on the decline in GFR in 227 pts with type 2 DM and nephropathy (follow-up 6.5 yrs)

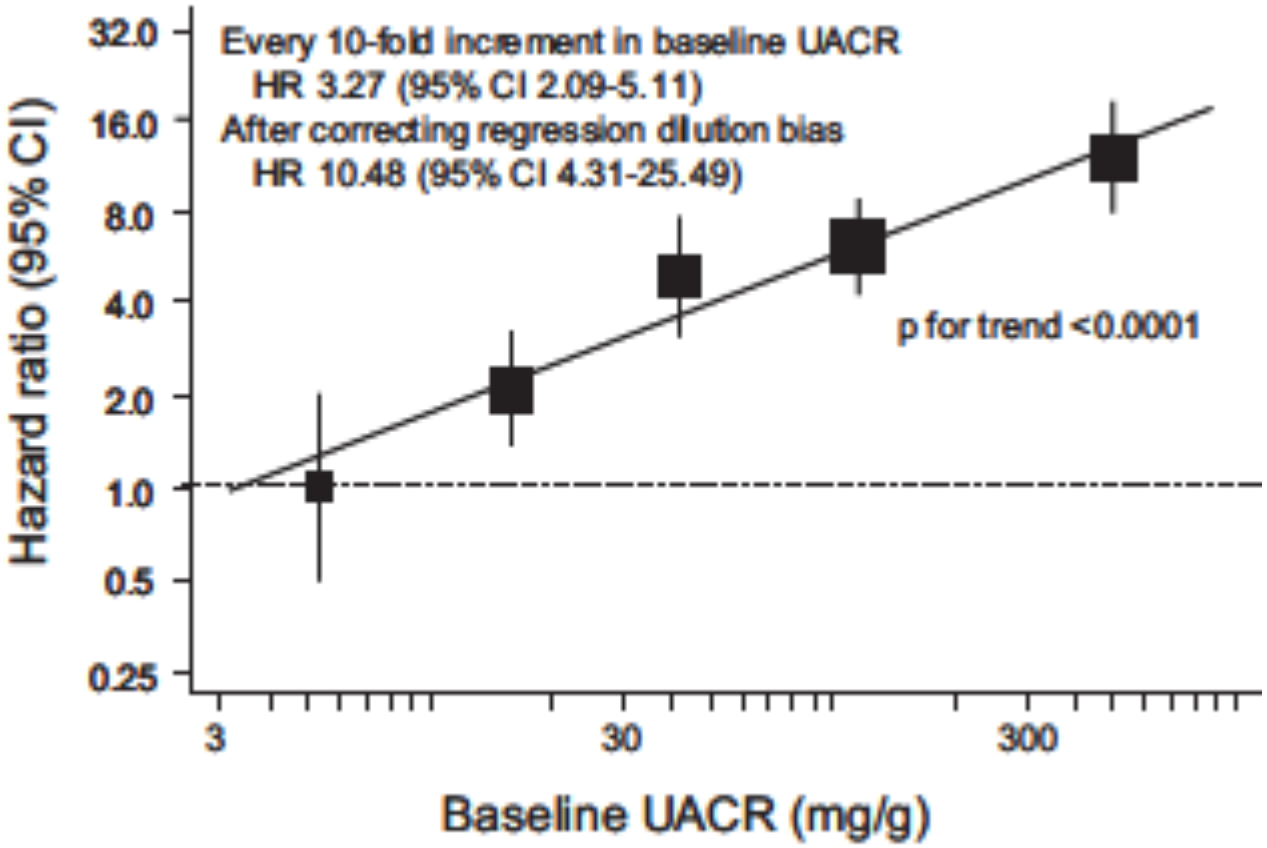


from Rossing et al., KI, 2005



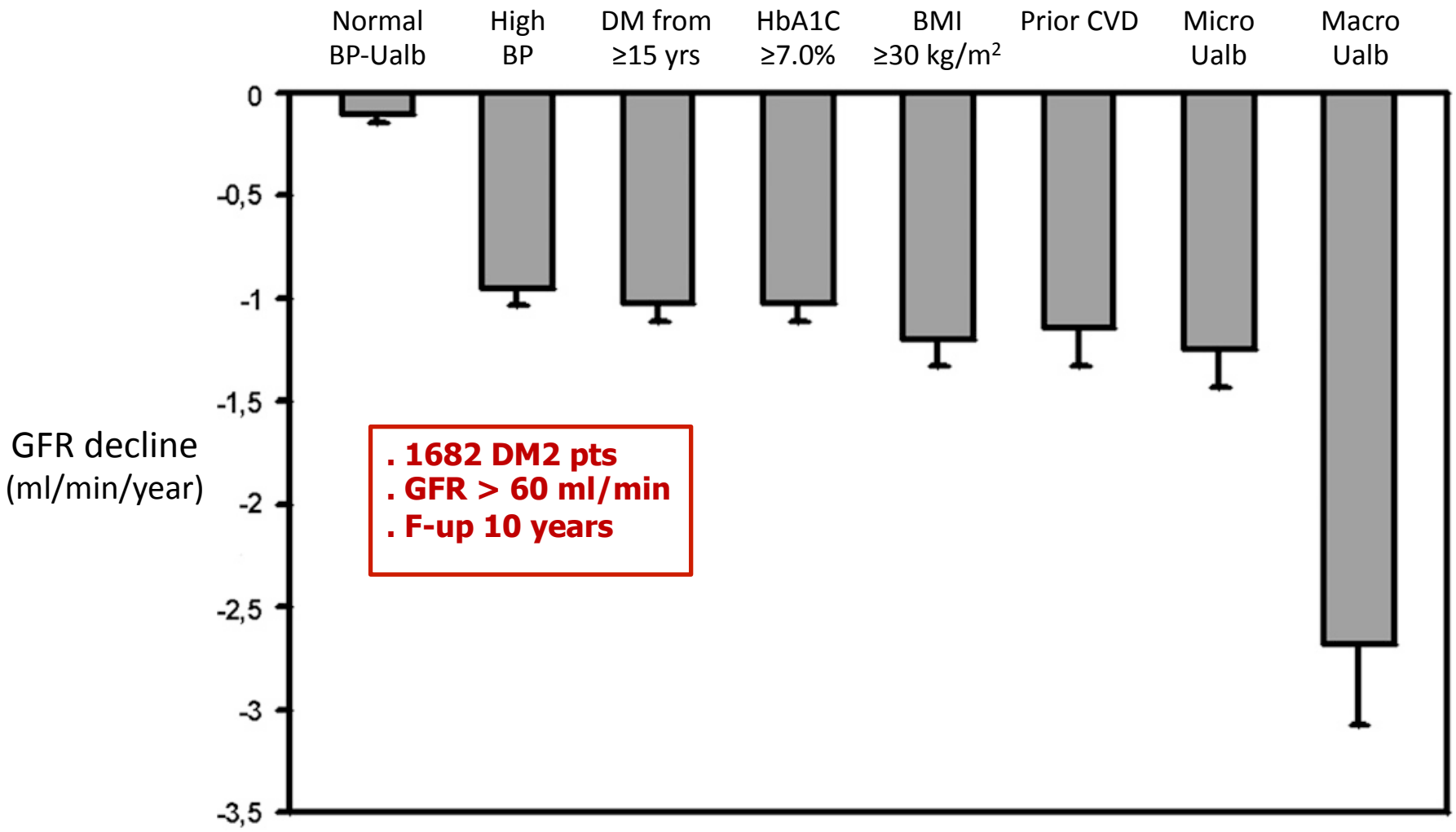
Modified from UKPDS 75, 1998

Association of albuminuria at baseline with the risk for adverse renal outcomes: the ADVANCE trial, 10640 pts, 19% GFR < 60 ml/min, 27% microalb, 4% prot, f-up 4.3 yrs



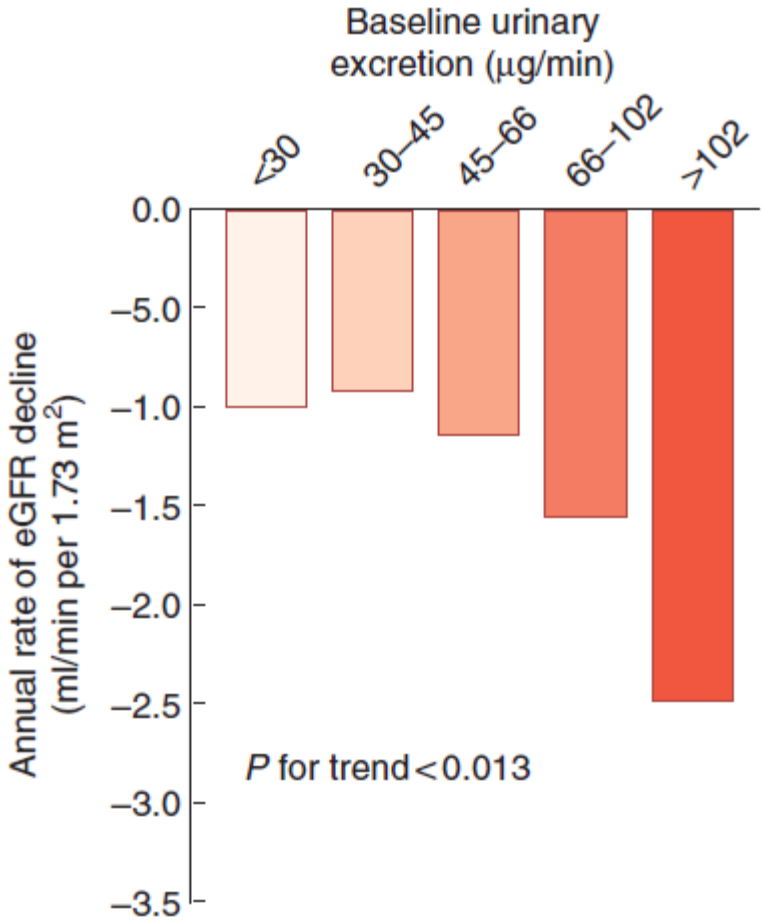
Ninomiya T, JASN, 2009

Predictors of Estimated GFR Decline in Patients with Type 2 Diabetes and Preserved Kidney Function



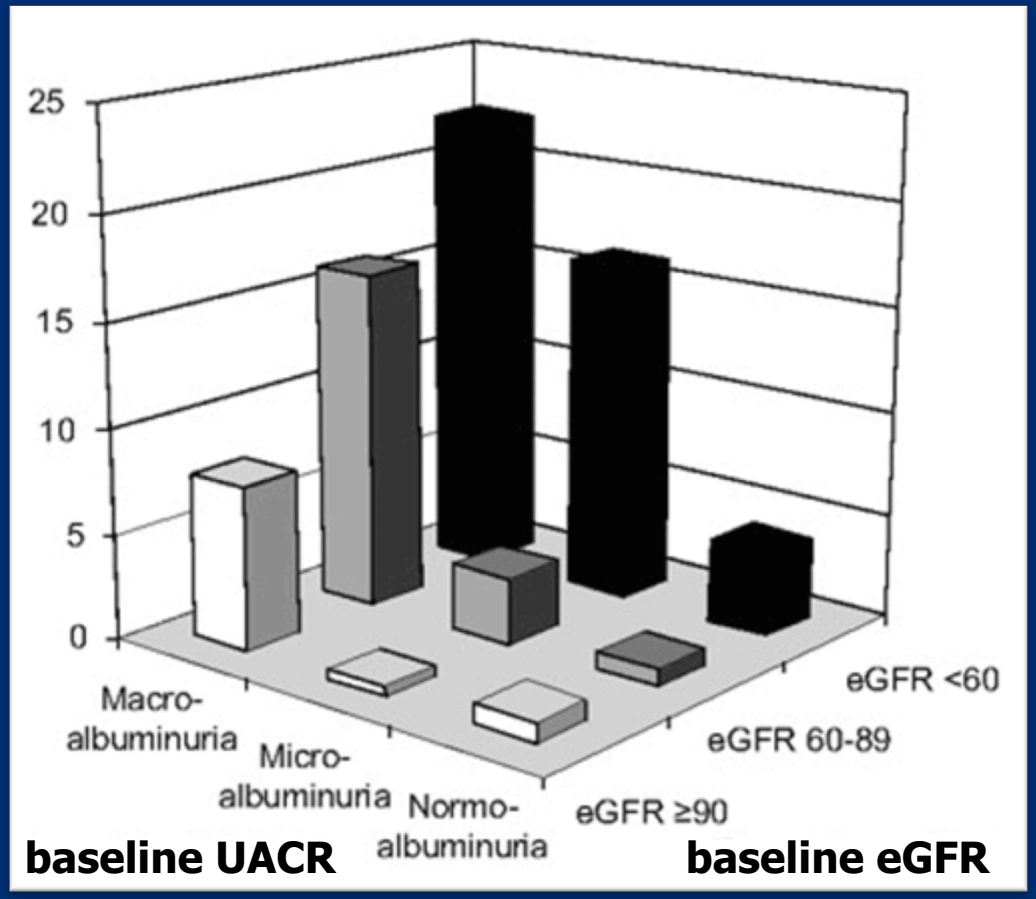
Zoppini, CJASN 2012

Higher albuminuria associates with faster decline in renal function in type 2 diabetes: a post-hoc analysis of the IRMA-2 trial



Hellemons et al, Diabetes Care 2011
Roscioni et al, KI 2014

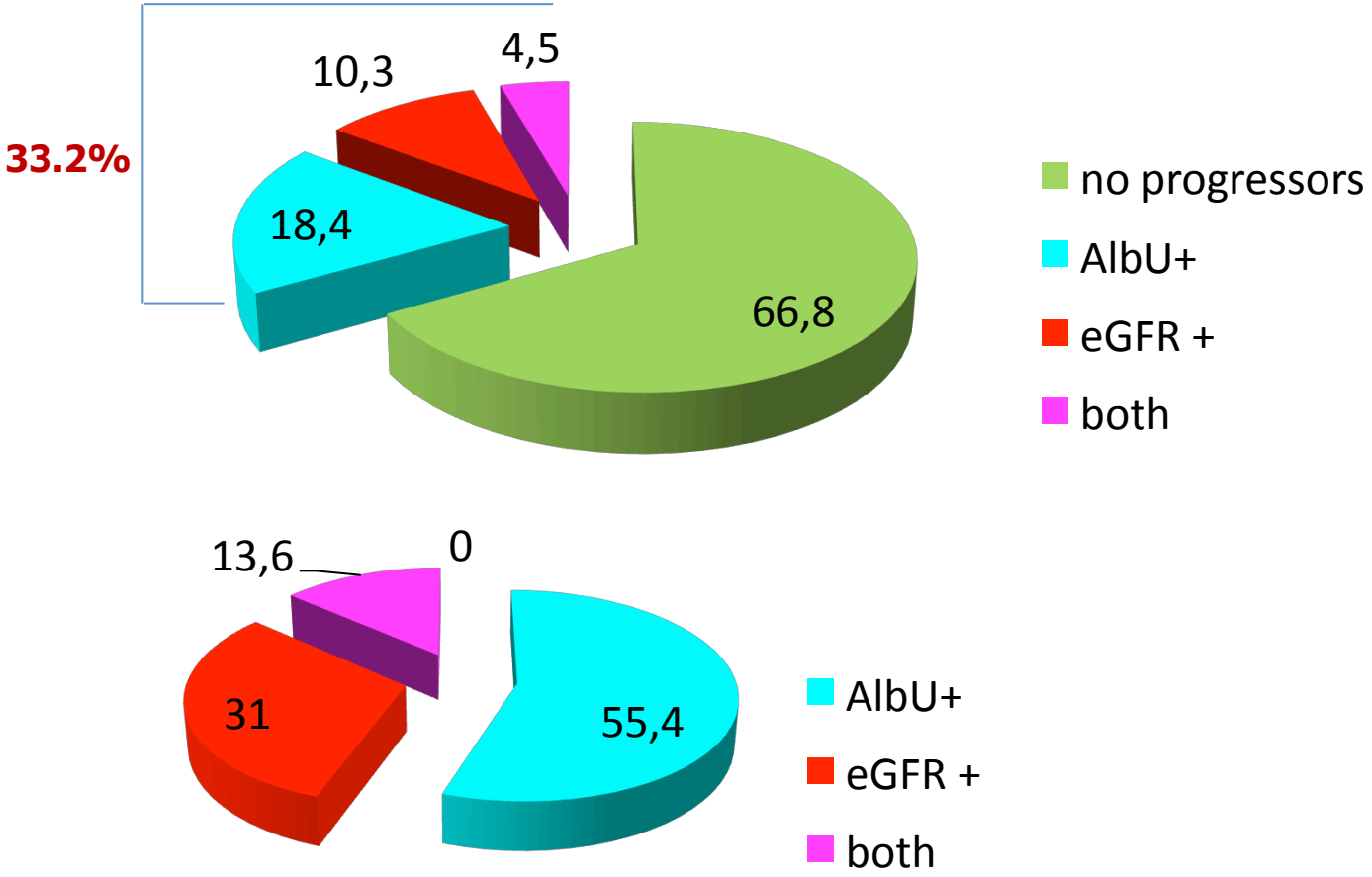
Effect of baseline albuminuria and GFR on renal events in DM (ADVANCE Study, 10640 pts, f.up 4.3 yr, 19% GFR < 60 ml/min, 27% microalb, 4% prot)



Ninomiya T, JASN, 2009

Proportion of patients with eGFR <60mL/min/1.73 m^2, albuminuria, or both at the 4 post-baseline assessments

27,909 DM2 with normoalbuminuria and GFR >60 ml/min from 118 Italian Diabetes Clinics



De Cosmo, AMD-Annals Study Group, Medicine (Baltimore) 2016

Relative risk ratios (RRRs) with (95% CIs) to develop 1. estimated glomerular filtration rate <60 mL/min/1.73m^2 (Alb -/ eGFR+); 2. albuminuria (Alb+/eGFR); or 3. both (Alb+/eGFR+) 27,909 type 2 diabetes from 118 Italian Diabetes Clinics

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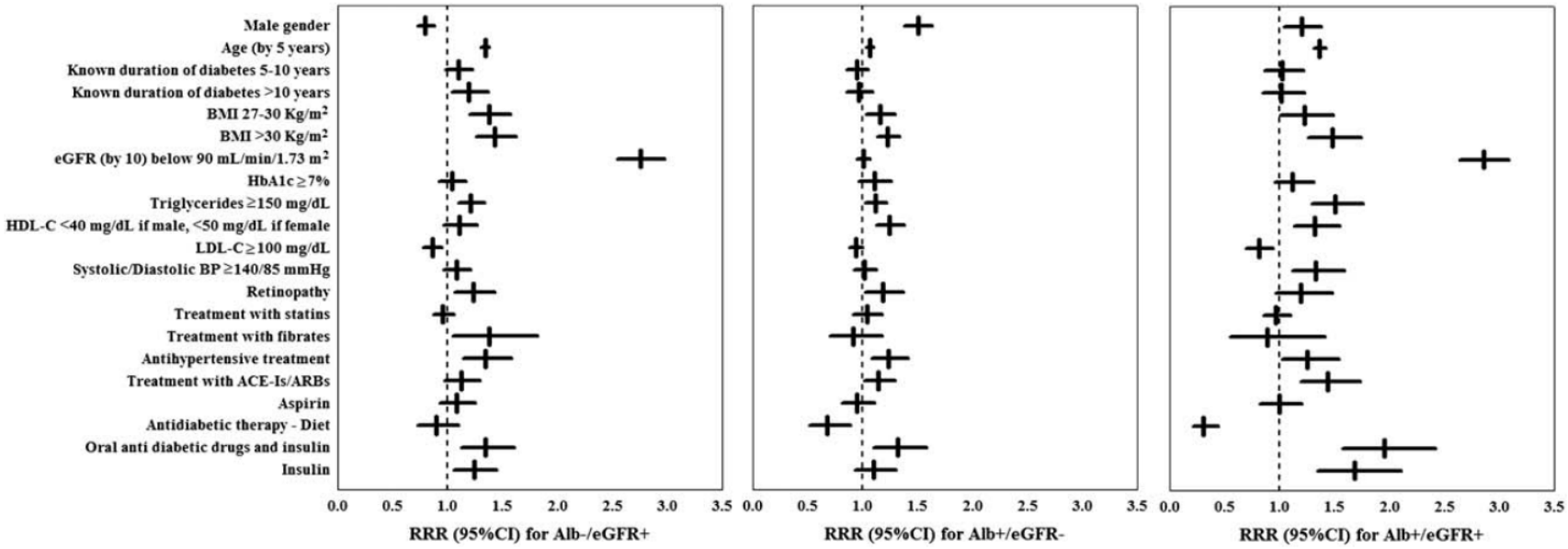

Reduction in eGFR and albuminuria showed distinct sets of risk factors, suggesting that different mechanisms are involved in the development of these 2 components of diabetic kidney disease

De Cosmo, AMD-Annals Study Group, Medicine (Baltimore) 2016

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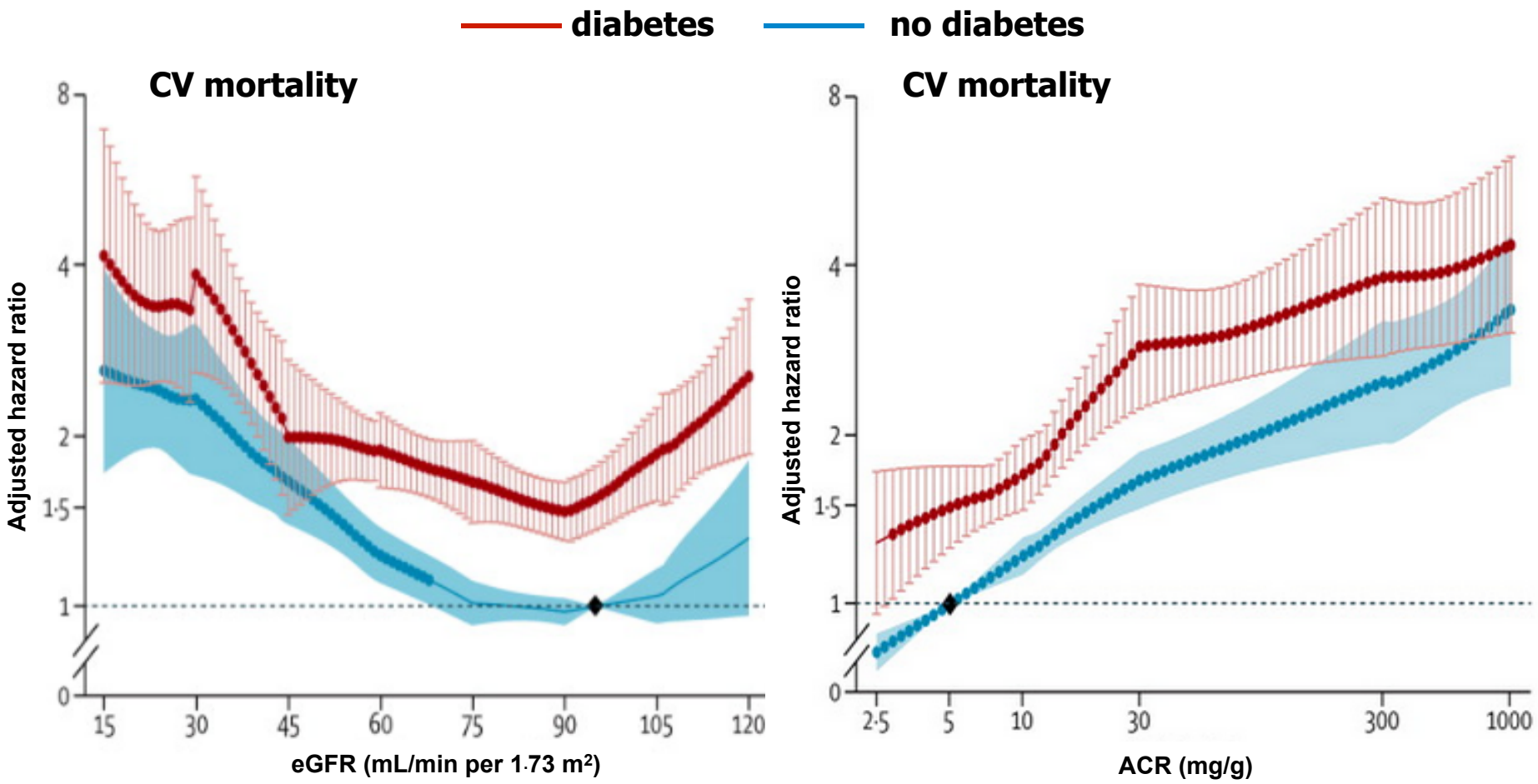
Hazard ratio for CV mortality in the combined general and high-risk populations according to eGFR (CKD-EPI) and albuminuria in pts with and without diabetes (1.024.977 pts)



HR, according to eGFR and ACR, adjusted for each other, age, ethnic origin, race, CV disease, smoking, cholesterol, BMI.

from Fox CS et al for the CKD Prognosis Consortium, Lancet, 2012

Excess Mortality among Persons with Type 2 Diabetes

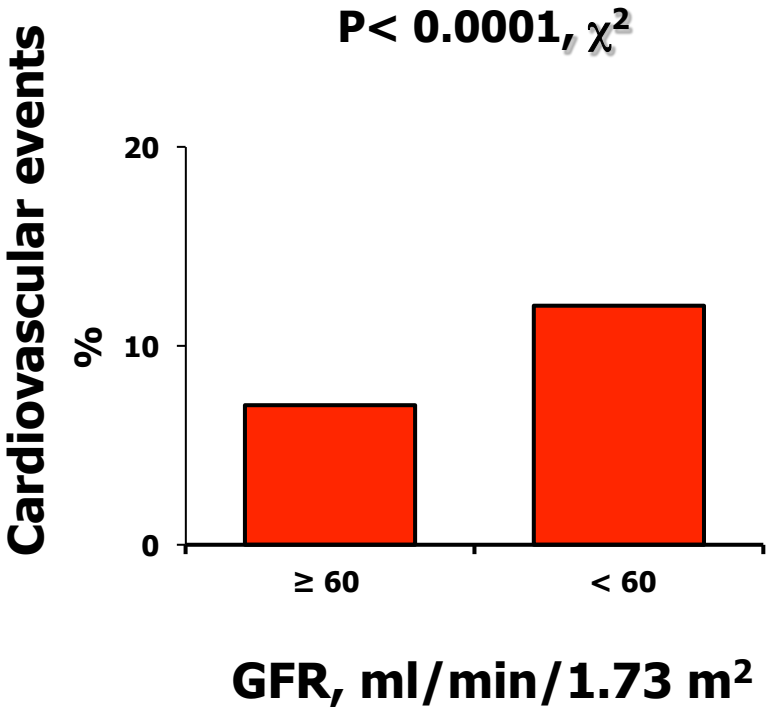
>400.000 pts from Swedish National Diabetes Register followed for a mean of 4.6 yrs

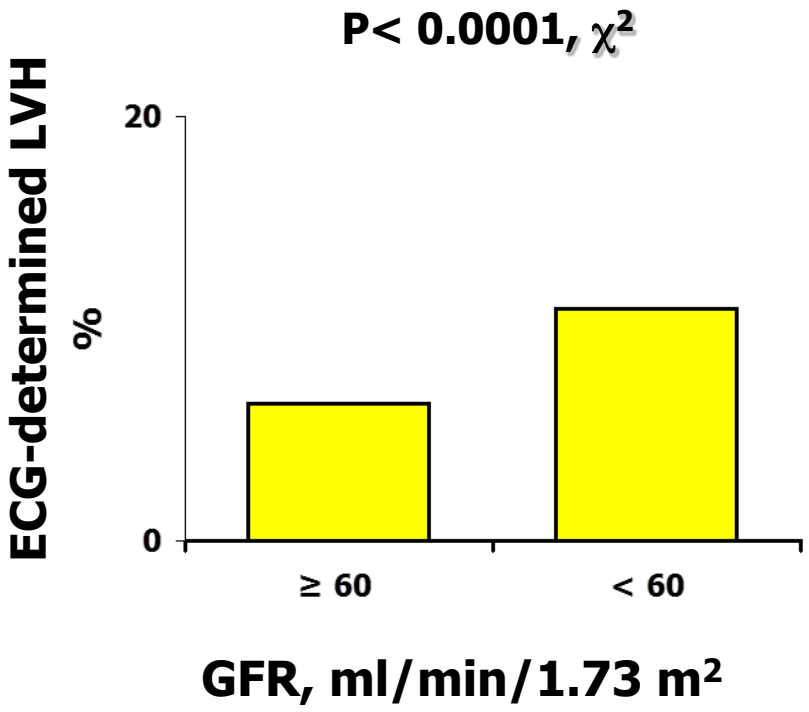
The excess risks of all-cause and cardiovascular death increased with younger age, worse glycemic control, and greater severity of renal complications…

Variable	Death from Any Cause				Death from Cardiovascular Causes			
	<55 Yr	55–64 Yr	65–74 Yr	≥75 Yr	<55 Yr	55–64 Yr	65–74 Yr	≥75 Yr
Reference	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Normoalbuminuria	1.87 (1.70–2.04)	1.27 (1.22–1.32)	0.96 (0.94–0.99)	0.83 (0.82–0.84)	2.19 (1.82–2.62)	1.43 (1.33–1.55)	0.95 (0.91–1.00)	0.79 (0.78–0.81)
Microalbuminuria	2.61 (2.19–3.10)	1.88 (1.75–2.02)	1.44 (1.38–1.50)	1.04 (1.02–1.07)	4.26 (3.19–5.70)	2.38 (2.11–2.69)	1.55 (1.44–1.66)	1.01 (0.97–1.04)
Macroalbuminuria	3.78 (3.03–4.71)	2.88 (2.65–3.13)	2.14 (2.04–2.24)	1.40 (1.37–1.44)	5.58 (3.79–8.20)	3.81 (3.33–4.35)	2.62 (2.44–2.81)	1.37 (1.32–1.42)
Stage 5 chronic kidney disease	14.63 (9.53–22.48)	7.19 (5.75–8.98)	5.97 (5.29–6.73)	3.31 (3.02–3.62)	30.03 (16.08–56.10)	9.22 (6.40–13.29)	5.45 (4.43–6.70)	2.45 (2.11–2.86)
Reference	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
>90 ml/min	2.07 (1.90–2.26)	1.47 (1.41–1.54)	1.17 (1.13–1.21)	0.88 (0.86–0.91)	2.47 (2.08–2.94)	1.56 (1.43–1.69)	1.02 (0.96–1.09)	0.72 (0.69–0.76)
>60–90 ml/min	1.92 (1.69–2.17)	1.30 (1.24–1.36)	0.96 (0.93–0.99)	0.81 (0.80–0.82)	2.59 (2.05–3.27)	1.60 (1.47–1.74)	1.04 (1.00–1.10)	0.77 (0.75–0.78)
>45–60 ml/min	3.84 (2.68–5.50)	2.60 (2.35–2.88)	1.48 (1.41–1.55)	1.02 (1.00–1.04)	5.56 (2.98–10.38)	3.83 (3.29–4.45)	1.75 (1.63–1.89)	1.02 (1.00–1.05)
>30–45 ml/min	5.52 (3.05–9.97)	4.00 (3.44–4.64)	2.42 (2.26–2.58)	1.37 (1.34–1.41)	8.59 (3.21–22.97)	4.72 (3.69–6.04)	2.94 (2.68–3.24)	1.39 (1.35–1.44)
15–30 ml/min	18.79 (11.50–30.72)	6.98 (5.75–8.48)	4.21 (3.84–4.62)	2.21 (2.12–2.30)	35.03 (16.63–73.79)	8.96 (6.59–12.19)	4.58 (3.97–5.28)	2.13 (2.01–2.25)
Stage 5 chronic kidney disease	14.70 (9.57–22.59)	7.23 (5.79–9.04)	6.09 (5.40–6.87)	3.33 (3.04–3.64)	30.26 (16.20–56.52)	9.30 (6.45–13.40)	5.57 (4.53–6.86)	2.48 (2.13–2.89)

Tancredi, NEJM 2015

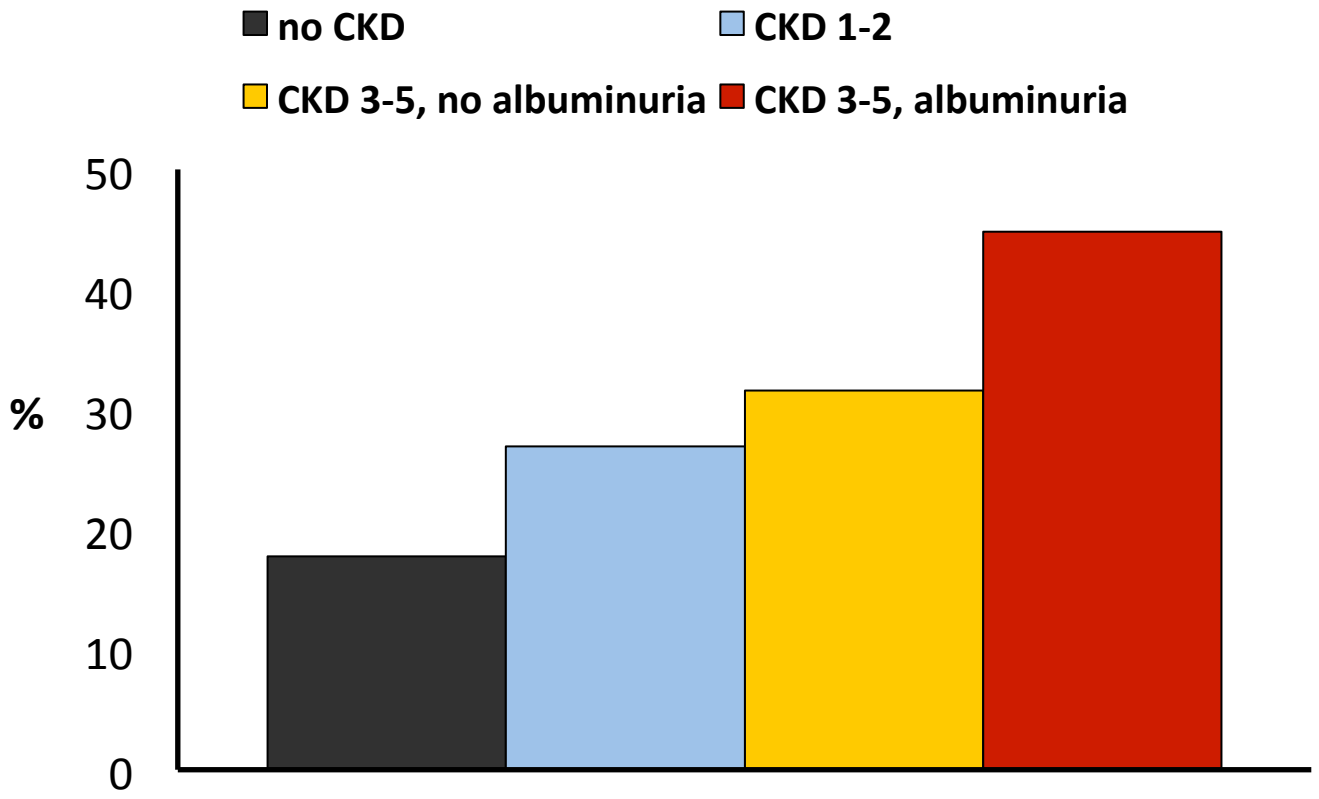
Prevalenza di eventi CV maggiori e di IVS in base al GFR in 7.582 diabetici ipertesi: il Progetto Genoa





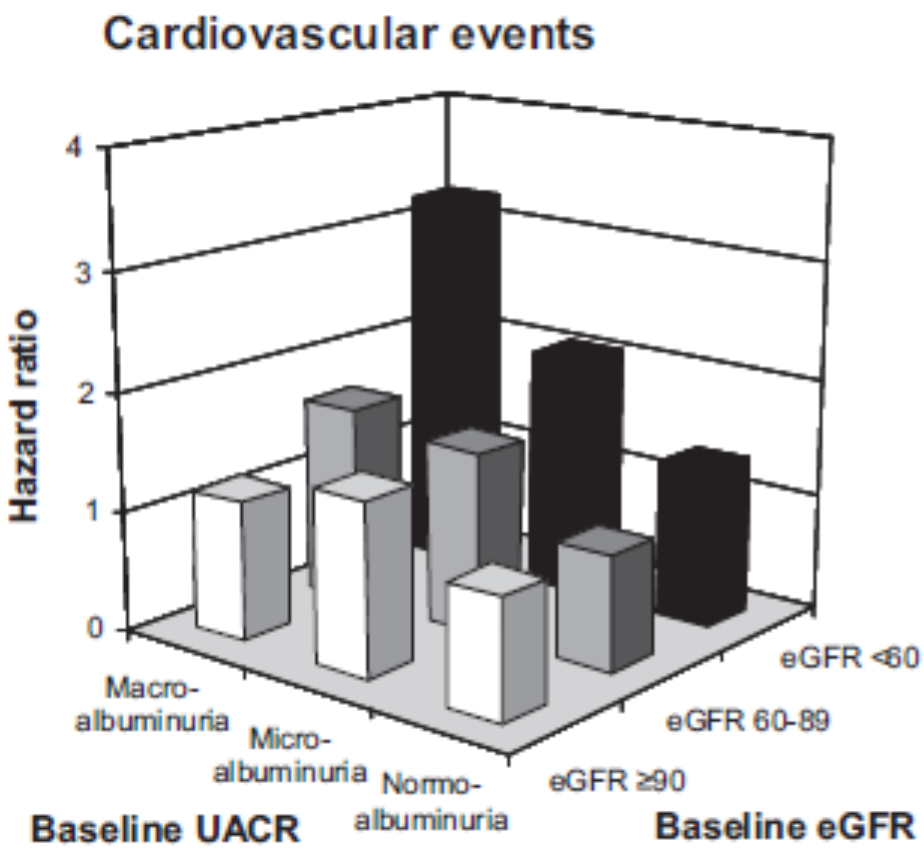
Ravera et al, NDT 2009

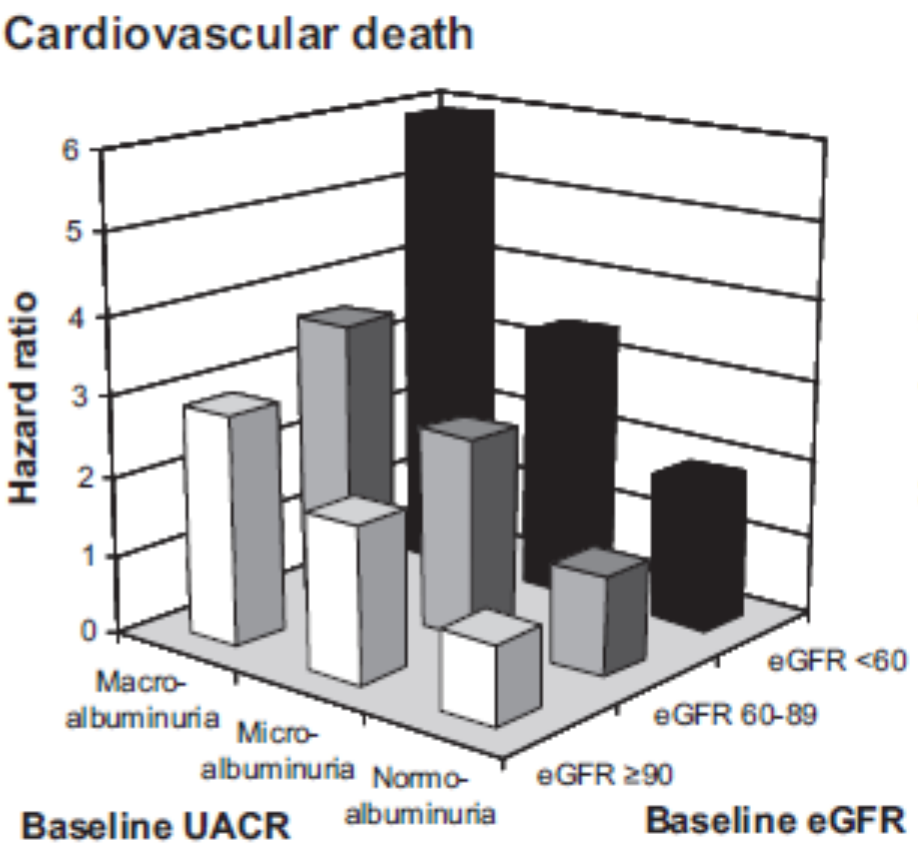
Prevalence of MACE on the basis of the presence and stage of CKD and of albuminuria in 15,773 type 2 DM: the RIACE Study



Penno G, J Hypertens 2011

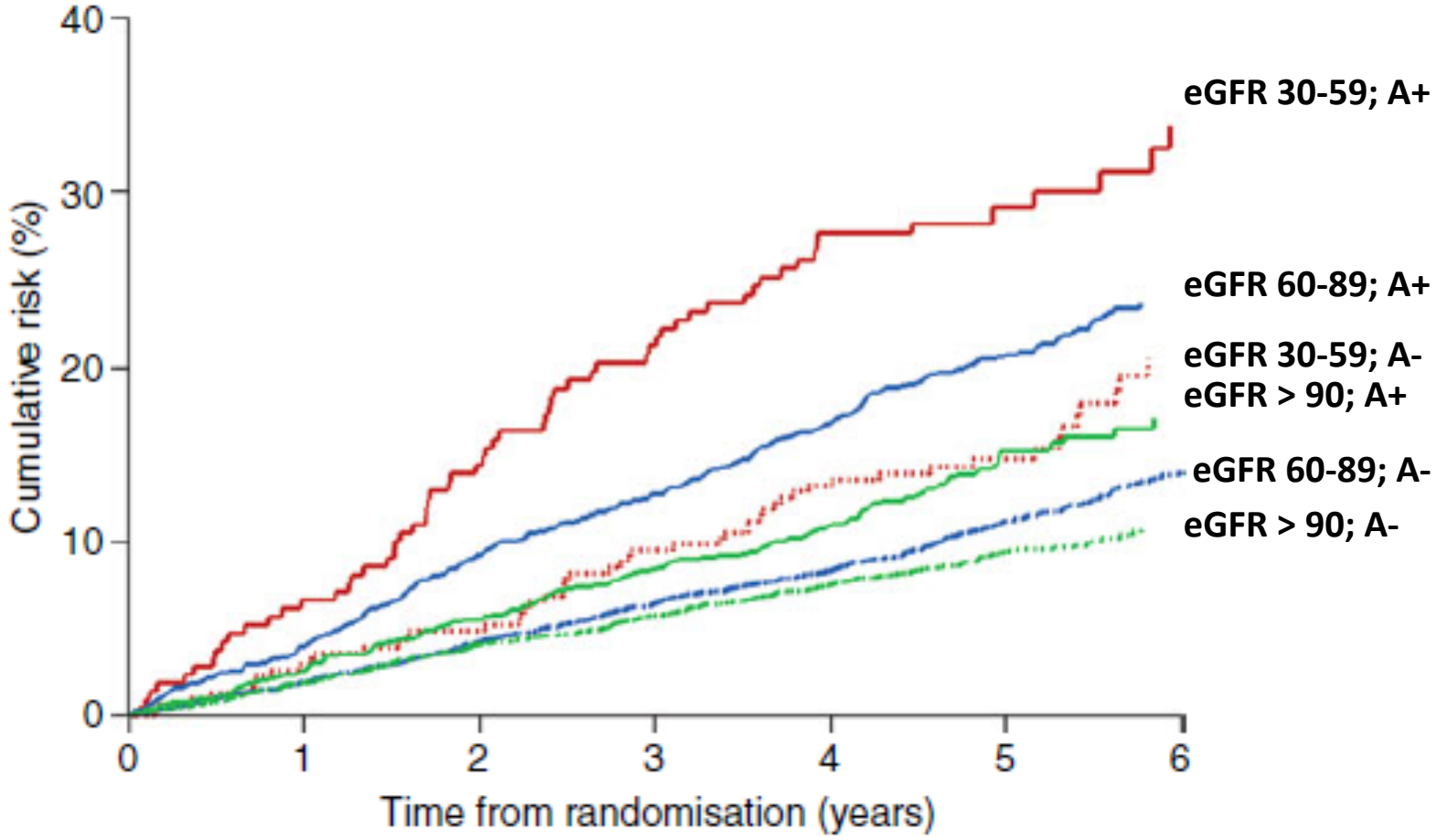
Combined effects of albuminuria and eGFR levels at baseline on the risk for adverse CV outcomes in 10,640 DM 2 patients: ADVANCE study (f-up 4,3 yrs).





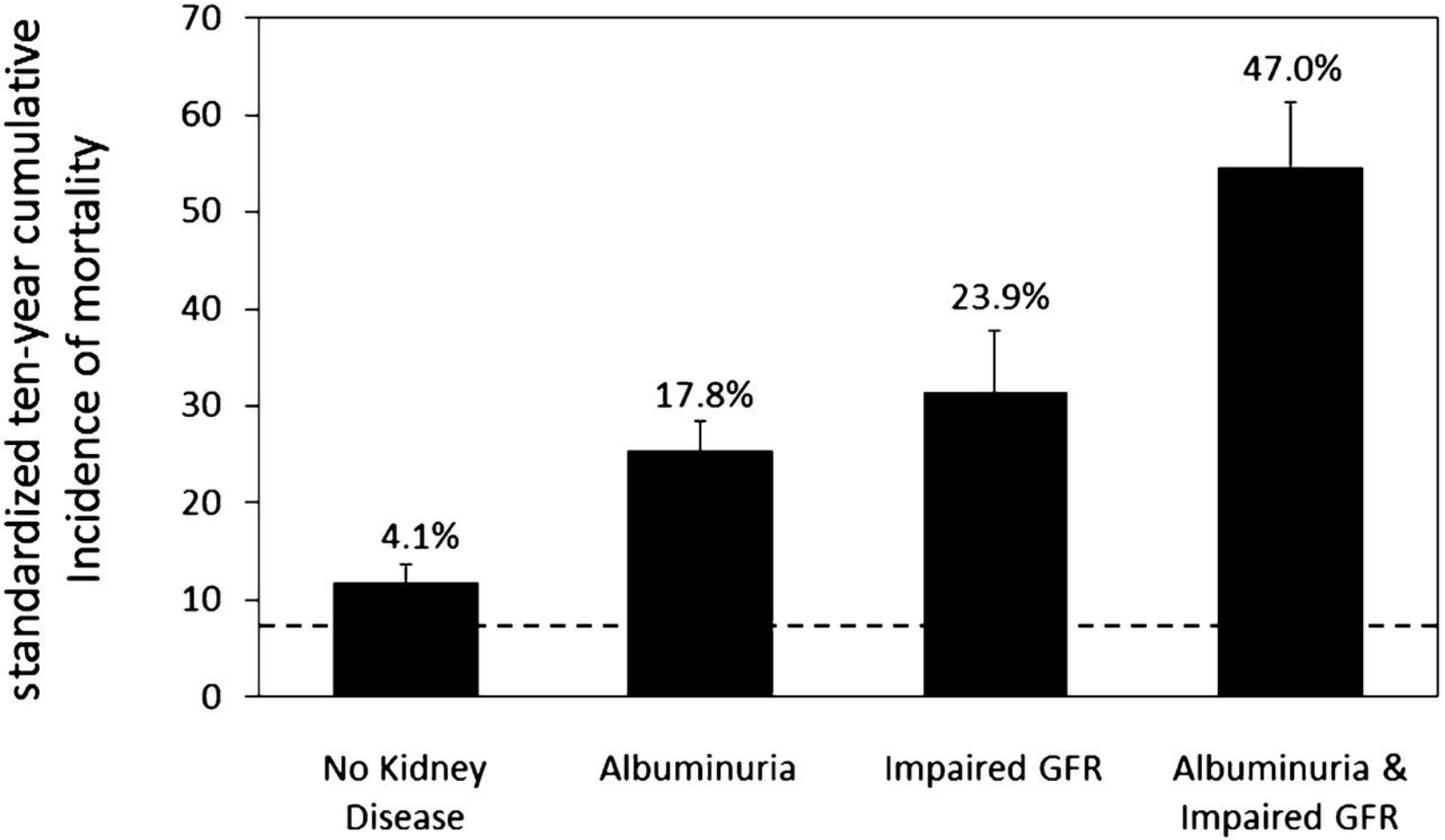
from Ninomiya et al., JASN, 2009

Cardiovascular risk for eGFR groups according to presence of baseline albuminuria:the FIELD study (9,795 DM2 pts, f-up 5yrs)



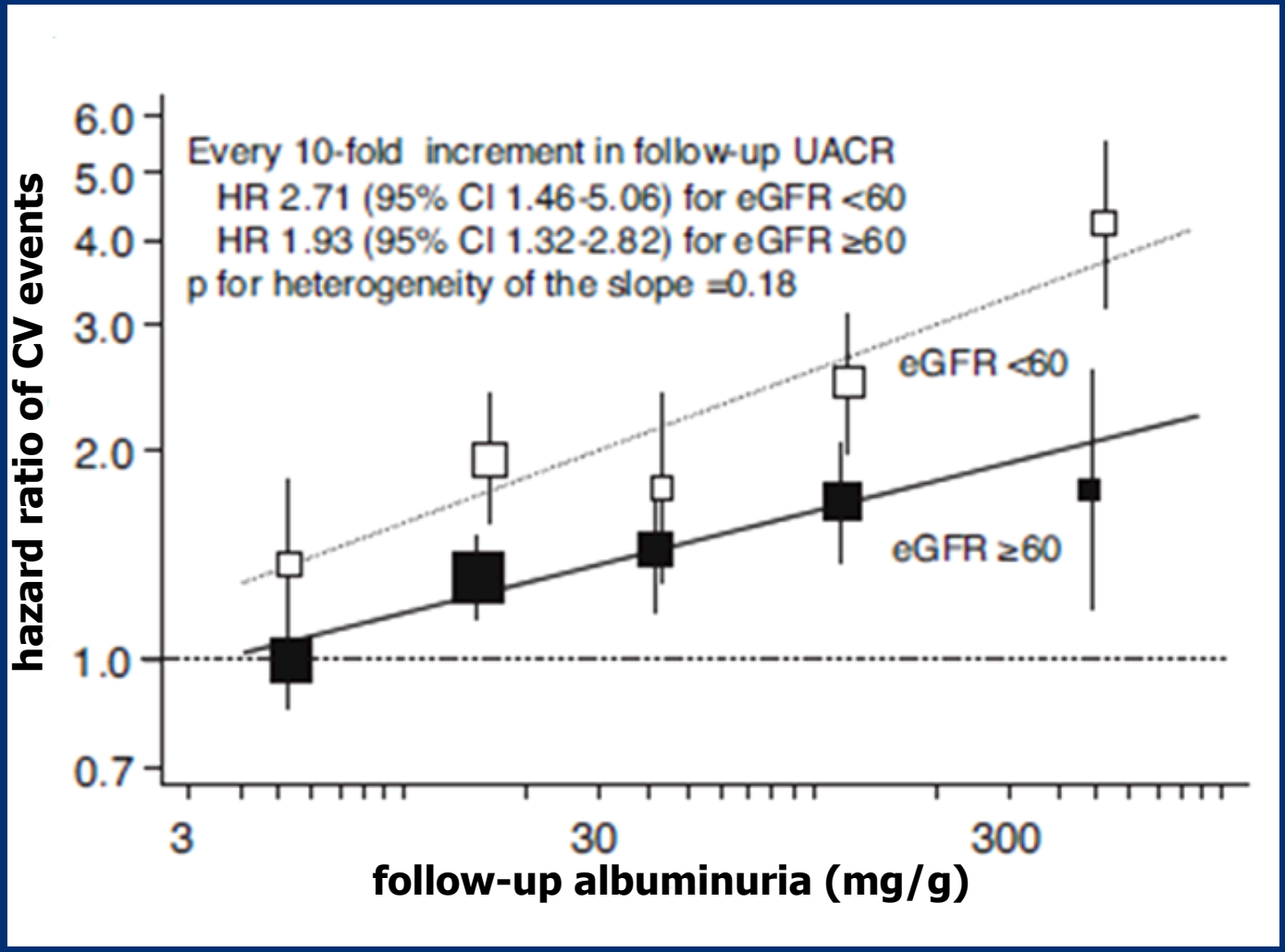
Drury PL et al., Diabetologia, 2011

Ten-year mortality in 15,046 type 2 diabetes by kidney disease manifestation: NHANES III.



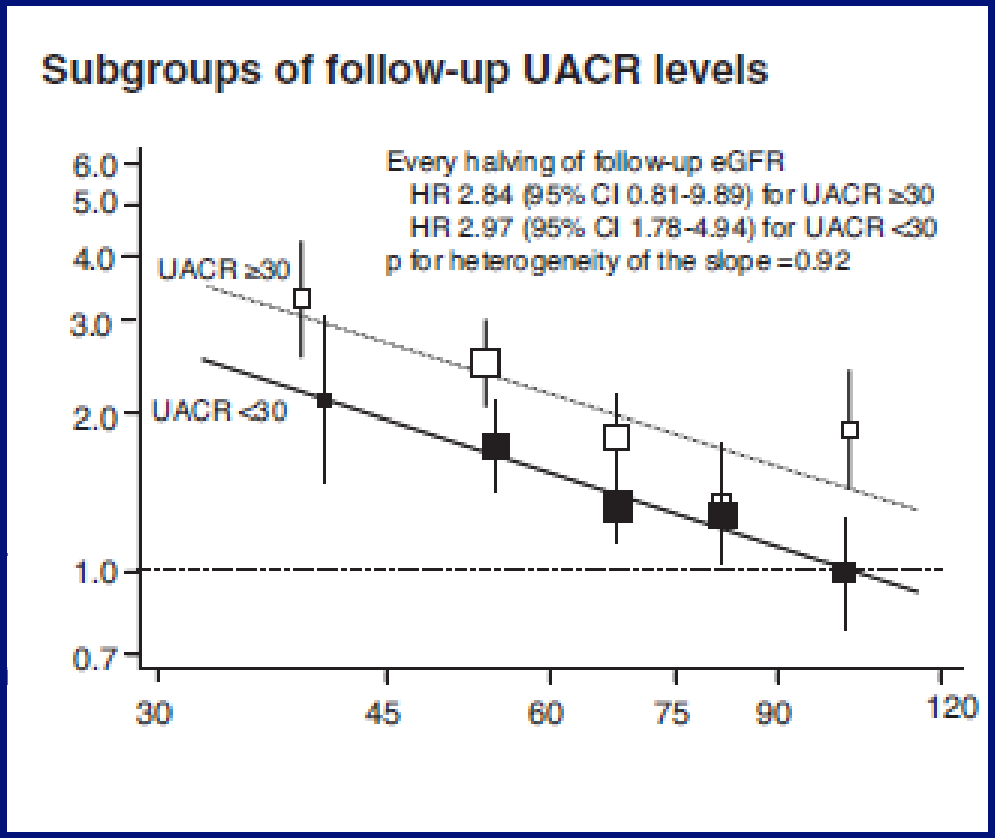
Maryam Afkarian et al. JASN 2013;24:302-308

Follow-up albuminuria predicts CV events in low risk pts with type 2 DM (ADVANCE Study, 10.640 pts)



from Ninomiya et al., JASN, 2009

Follow-up eGFR predicts CV events in low risk pts with type 2 DM (ADVANCE Study, 10.640 pts)



Ninomiya et al., JASN, 2009

Relative incidence of ESRD vs CV mortality in type 2 DM with microalbuminuria (UKPDS, 2003) or with proteinuria (IDNT+RENAAL, 3228 pts)

	ESRD rate /100 pt • yr	CV death rate /100 pt • yr	rate ratios
microalb	0.3	3.0	0.10
alb ≤ 1 g	1.9	2.5	0.77
GFR > 45	1.8	2.9	0.71
alb 1-2 g	4.6	2.3	2.0
alb > 2 g	16	4.0	4.0
GFR 30-45	6.8	2.5	2.7
GFR < 30	21.2	3.8	5.7

from Adler AI, KI, 2003 and Packham DK, AJKD, 2012

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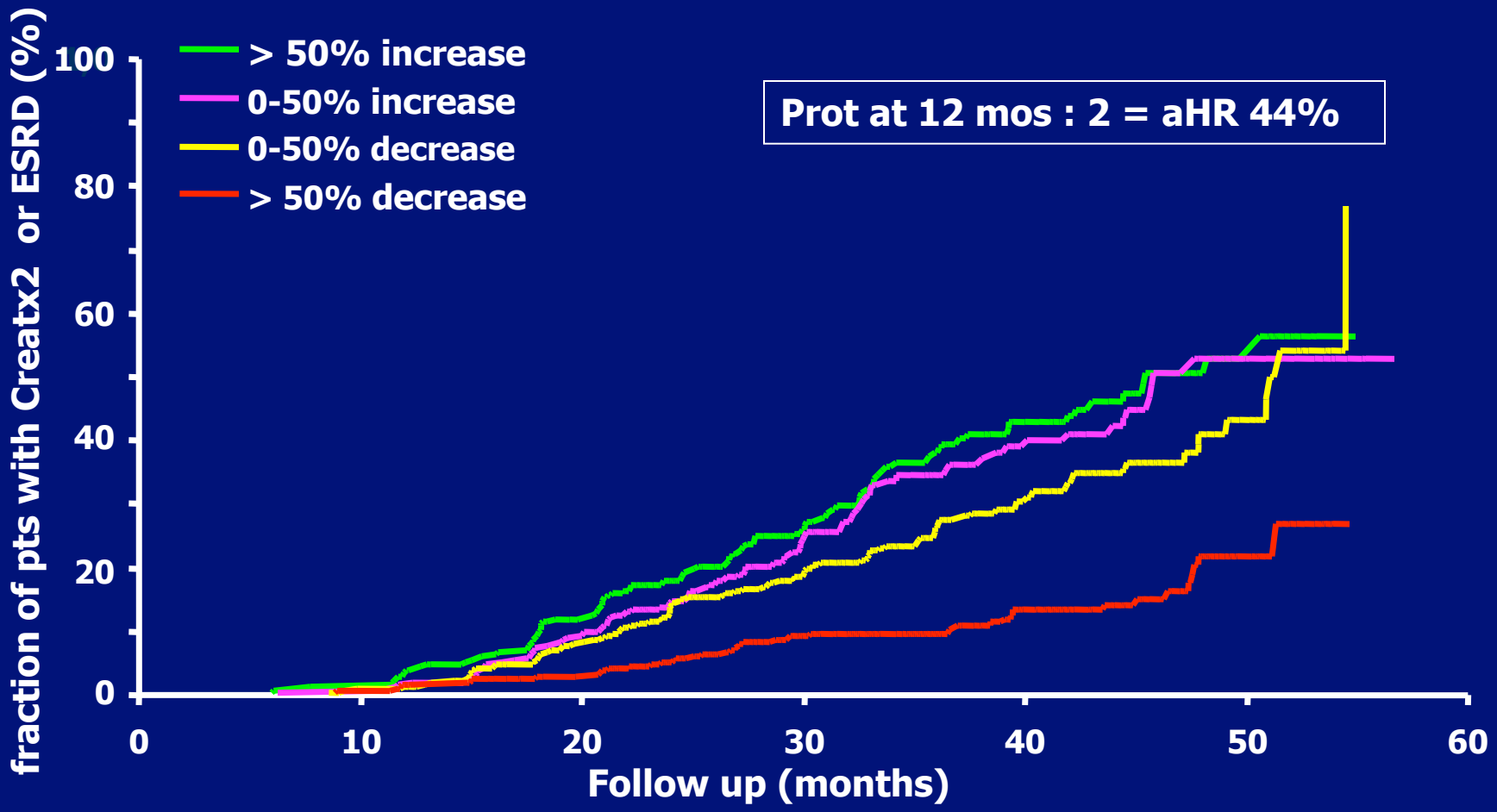
Therapeutic strategies for DN

Evidence based Strategies

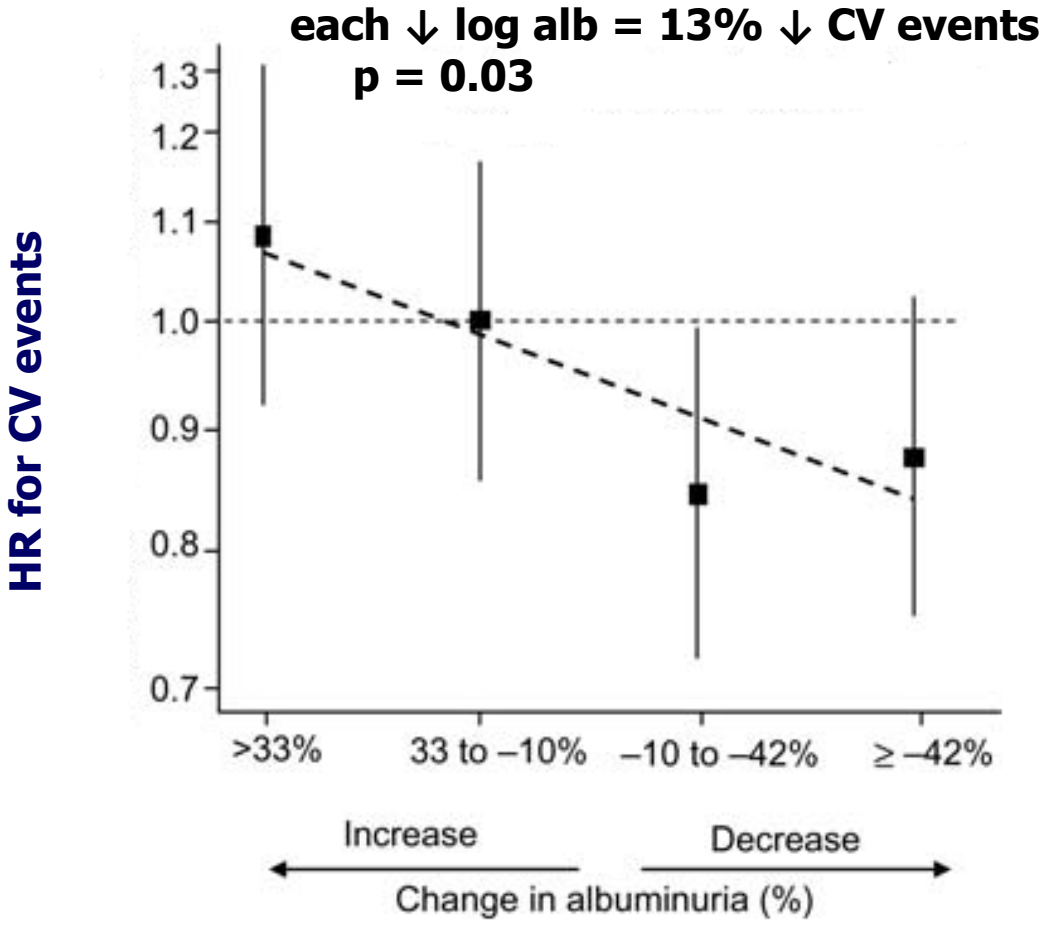
Primary prevention	- Metabolic control - BP control
Secondary prevention	- Metabolic control - BP control - ACE-I or ARB
Tertiary prevention	- BP control - ACE-I in type 1 DM - ARB in type 2 DM

Renoprotective effect of proteinuria reduction in diabetic pts with nephropathy and hypertension (IDNT, 1715 pts, follow-up 2.6 yrs)



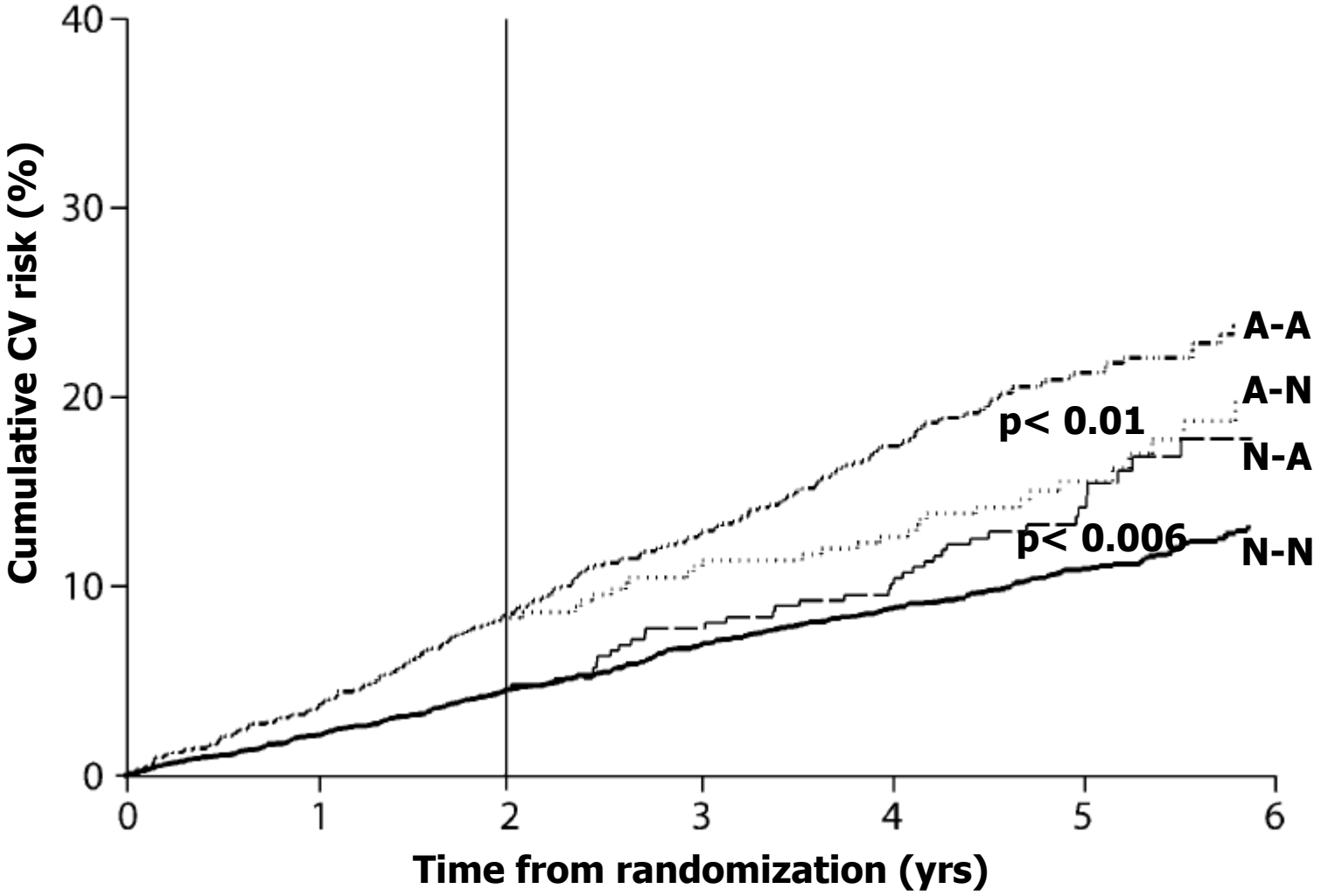
From Atkins et al., AJKD, 2005

Cardioprotective effect of proteinuria reduction at 6 months in diabetic nephropathy (RENAAL+ IDNT, 3228 pts)



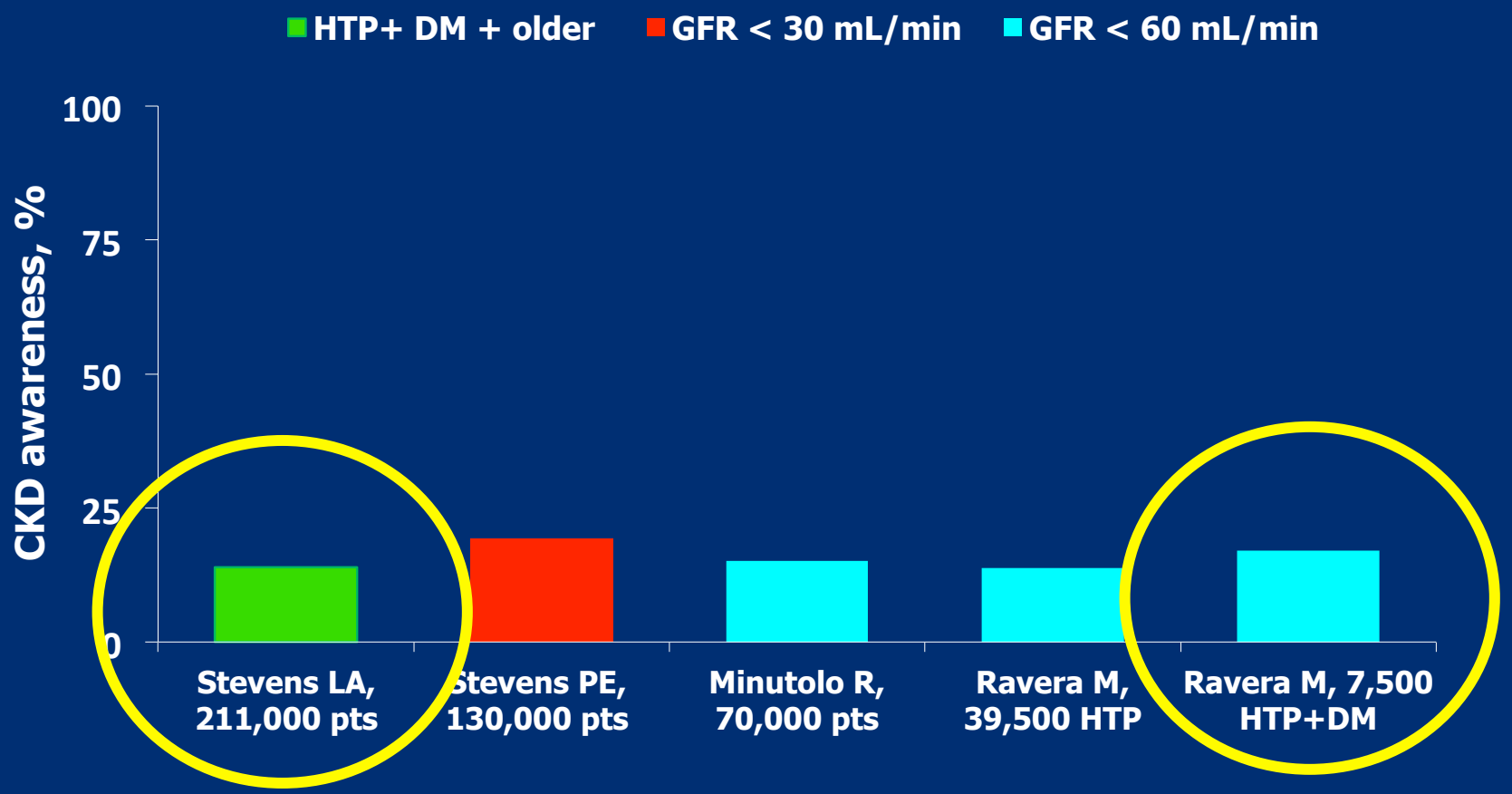
from Holtkamp et al., Eur Heart J, 2011

Effects of changes in albuminuria (2 yrs) on CV events in 4751 low risk pts with type 2 DM (Field Study, f-up 5 yrs)



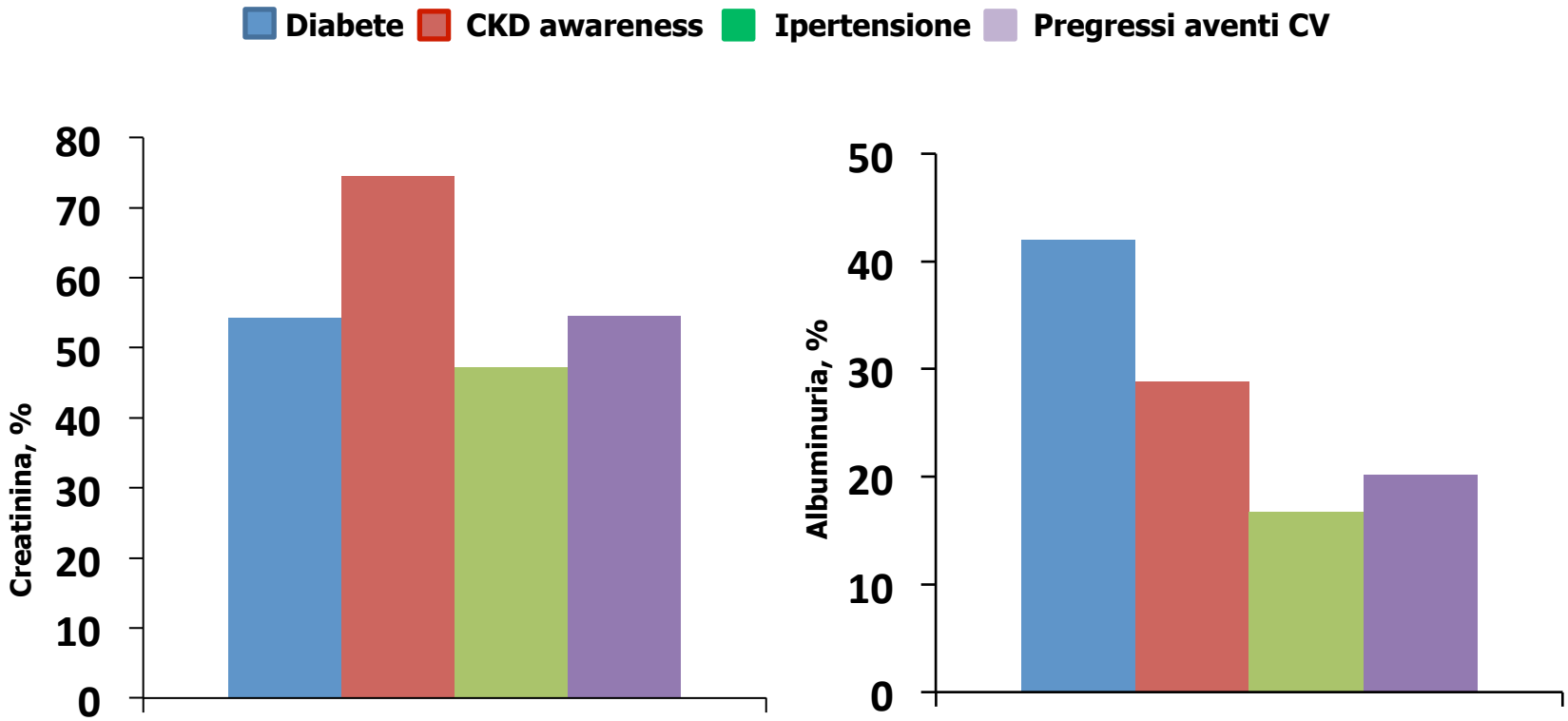
from Drury PL et al., Diabetologia, 2011

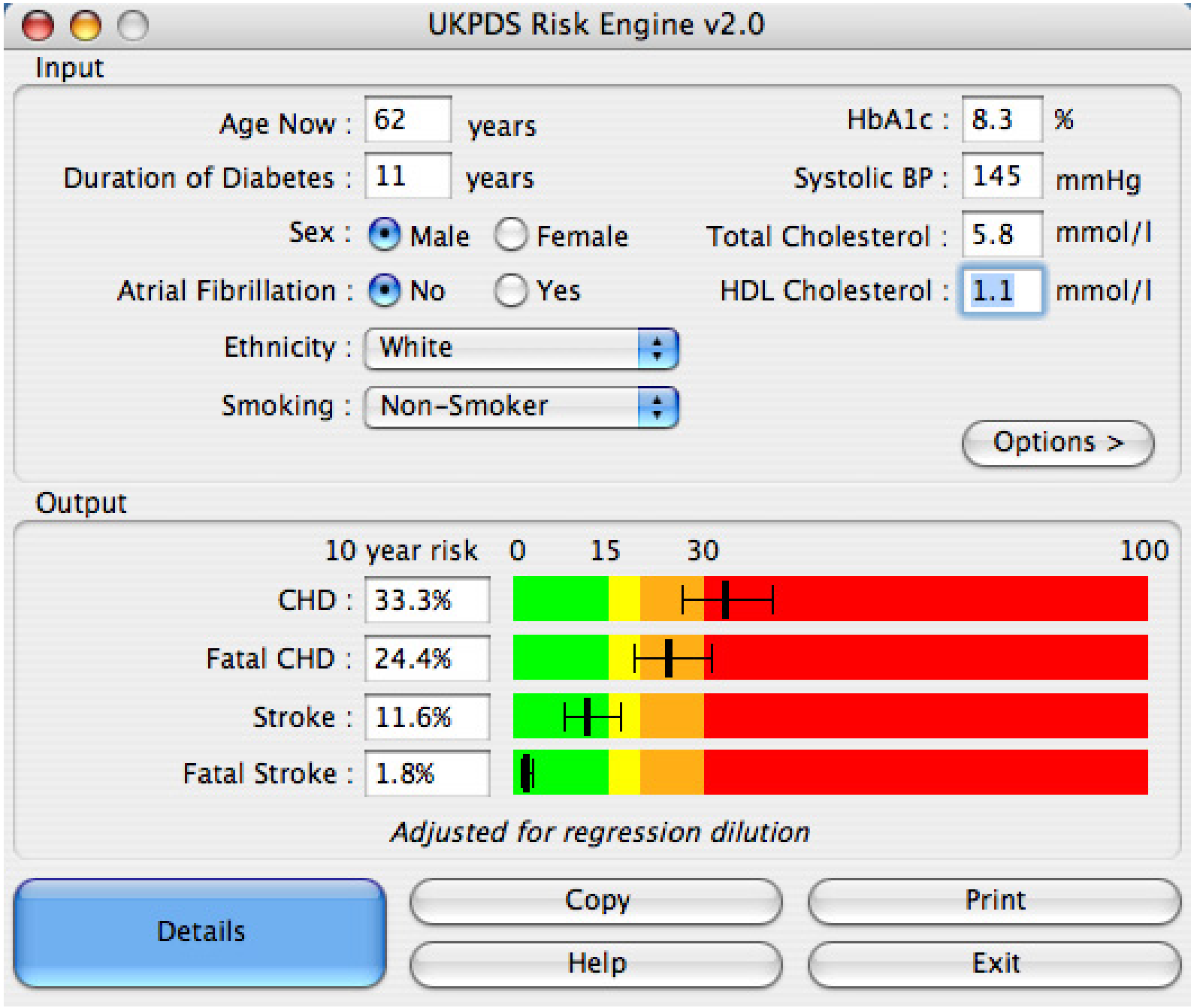
GPs' awareness of CKD



data from: Stevens LA, JASN 2005; Stevens PE, KI 2007; Minutolo R, AJKD 2008; Ravera M, AJKD 2010; Ravera M, NDT 2009.

Percentuale di valutazione di creatininemia in 128.650 pazienti arruolati nel Progetto GENOA



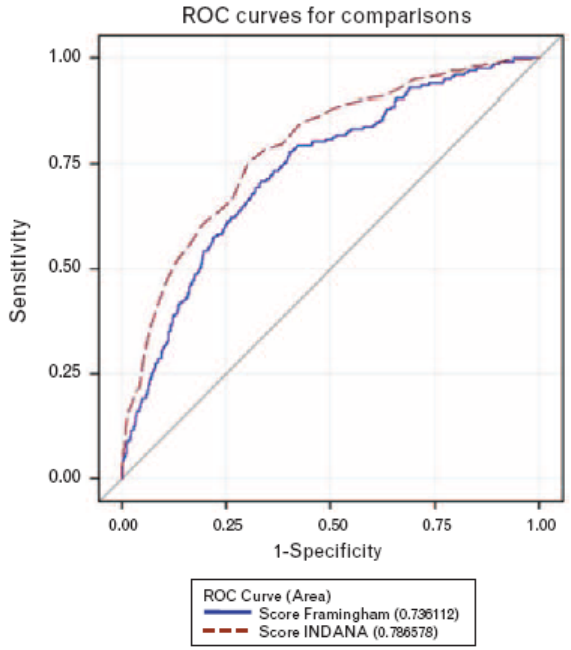


da Standard italiani per la cura del diabete mellito 2016 http://www.dtu.ox.ac.uk/riskengine/

High performance of a risk calculator that includes renal function in predicting mortality of hypertensive patients in clinical application

Maura Ravera[a], Rossella Cannavò[a], Giuseppe Noberasco[b], Alessandro Guasconi[c], Ursula Cabib[a], Laura Pieracci[a], Valeria Pegoraro[c], Ovidio Brignoli[b], Claudio Cricelli[b], Giacomo Deferrari[a], and Ernesto Paoletti[a]

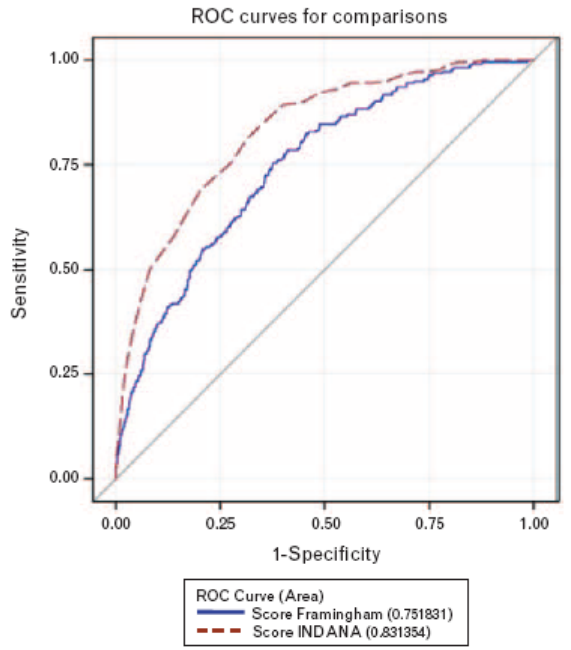
(a)



ROC table for cardiovascular death in UK

Parameter	Estimate	Std Error	95% Confidence limits		t	Pr>|t|
Framingham	0.736112	0.017578	0.701657	0.770567	13.43	<0.0001
INDANA	0.786578	0.016124	0.754975	0.818180	17.77	<0.0001
Difference in AUC	0.050465	0.011765	0.027400	0.073531	4.29	<0.0001

(b)

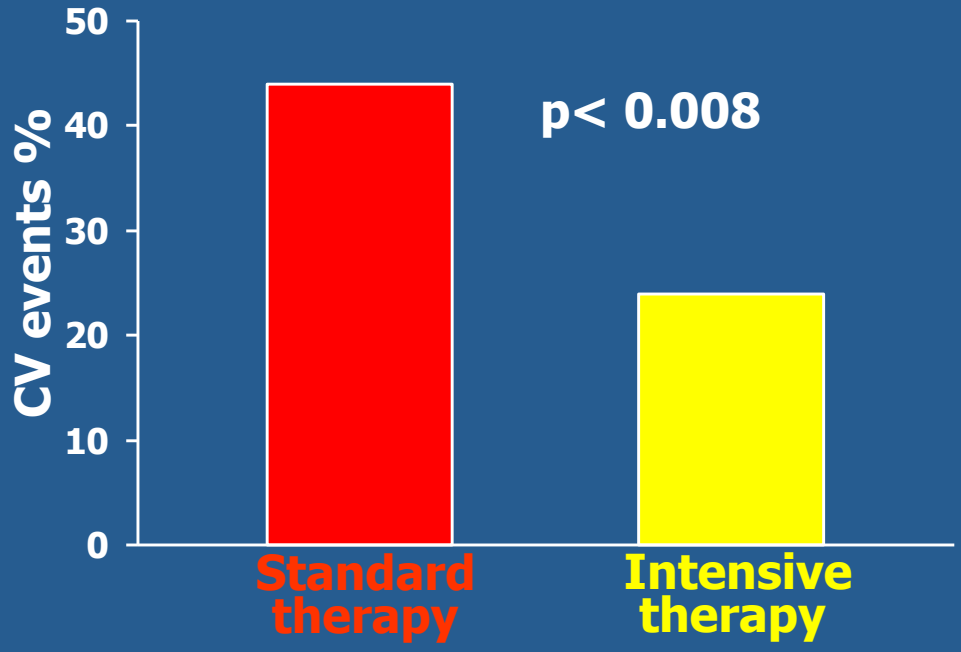


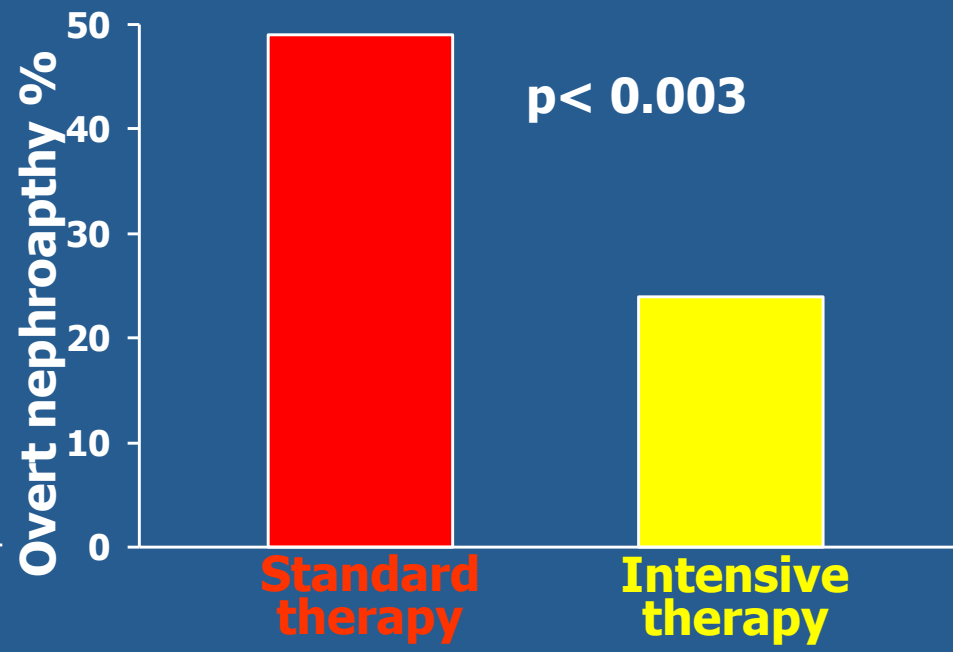
ROC table for cardiovascular death in Italy

Parameter	Estimate	Std Error	95% Confidence limits		t	Pr>|t|
Framingham	0.751831	0.015673	0.721110	0.782552	16.07	<0.0001
INDANA	0.831354	0.013303	0.805278	0.857430	24.91	<0.0001
Difference in AUC	0.079523	0.011053	0.057850	0.101196	7.19	<0.0001

J Hypertens 2014; 32: 1245-54

Reno-and cardioprotective effect of multifactorial intervention in DM with microalbuminuria (160 pts, follow-up: 8 yrs)



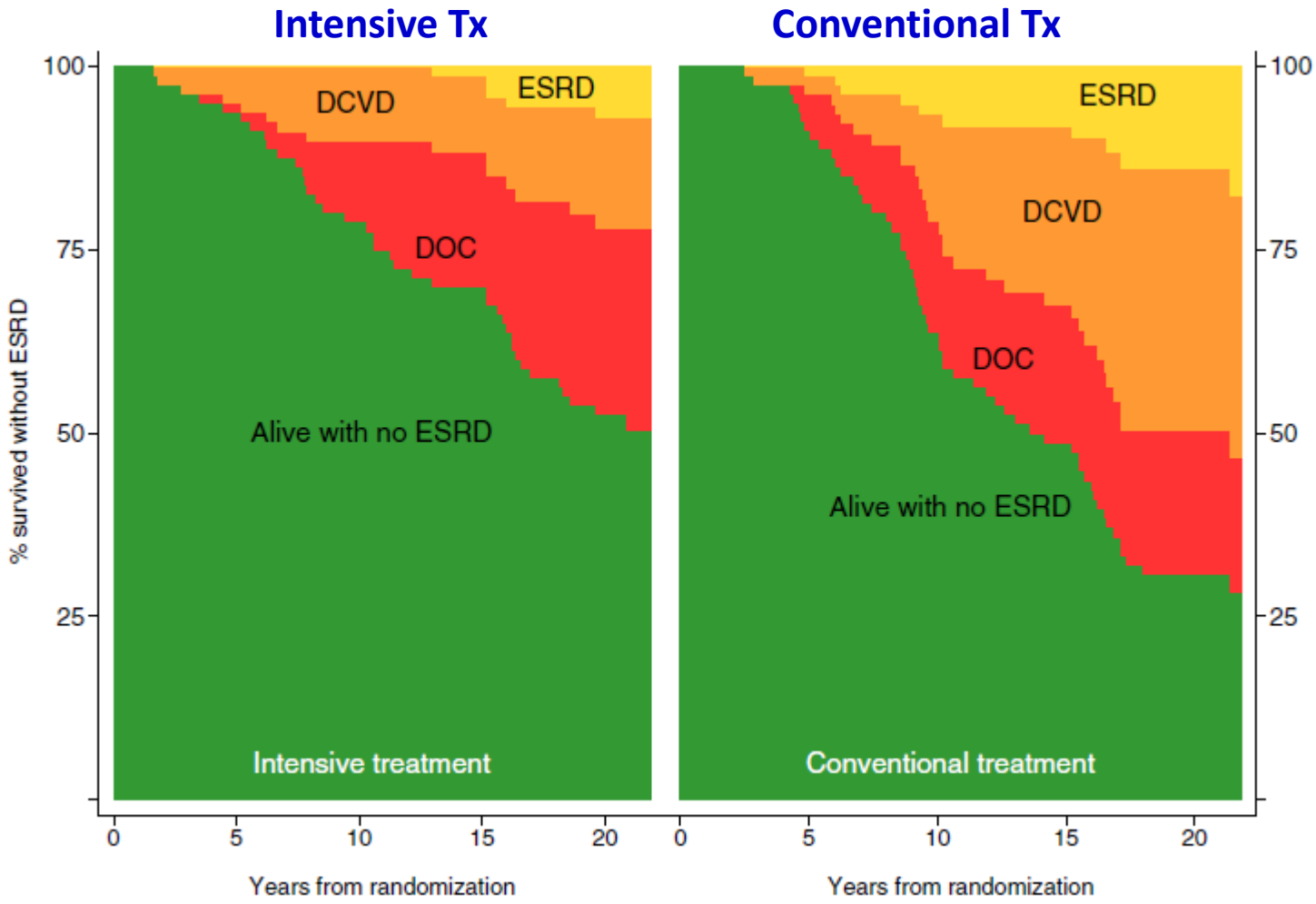


BP, mmHg	146/78	132/73	ASP+STAT, %	45	86
HbA_{1c}, %	9.0	7.9	ACE±ARB, %	70	97
LDL-C, mg/dl	118	81			

From Steno 2 Study, N Engl J Med, 2003

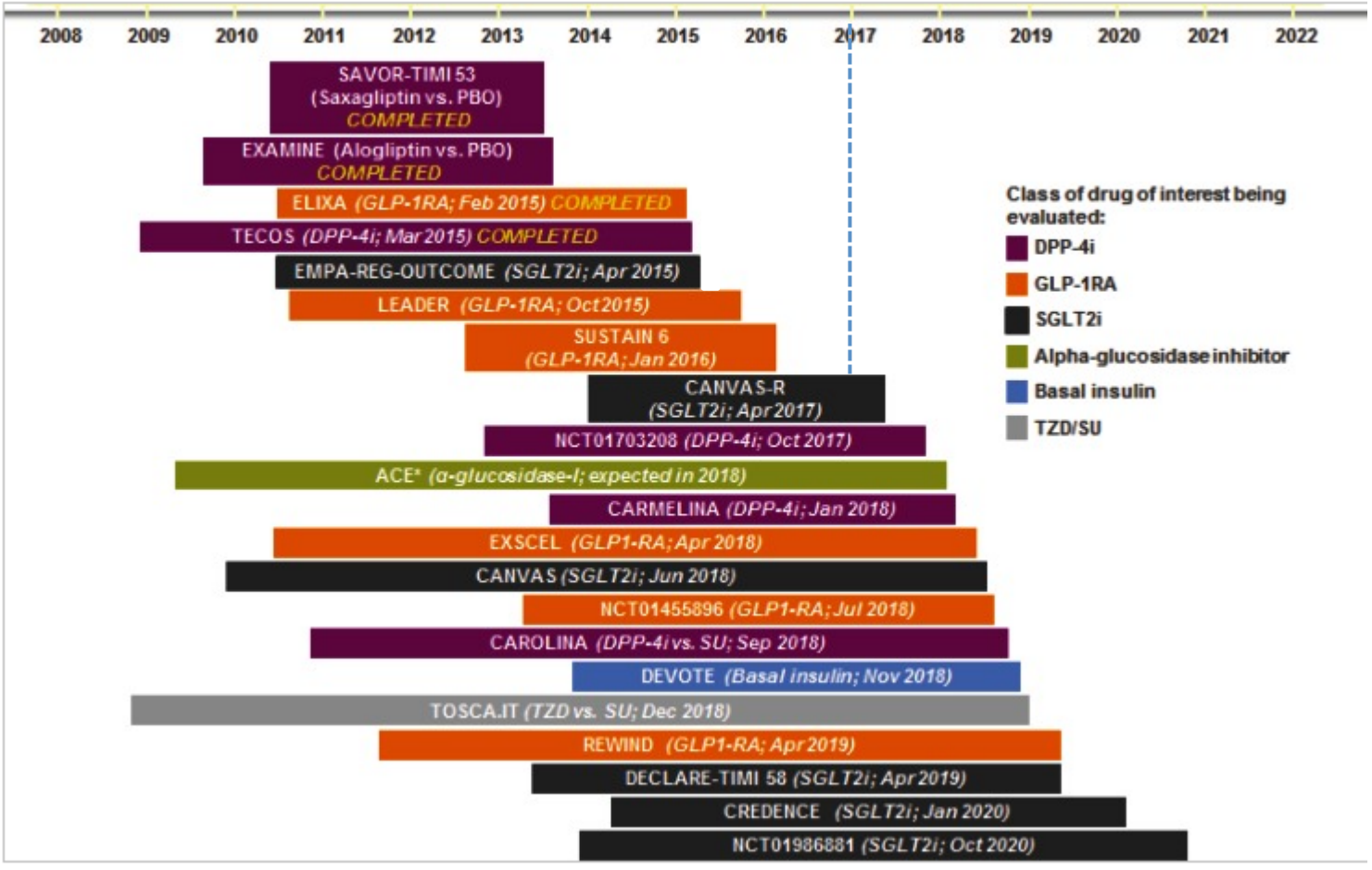
Progression to ESRD and mortality by treatment allocation: The Steno 2 Study

160 DM2 microalbuminurics assigned to conventional or intensified therapy for 7,8 yrs
Follow-up 21 years



Oellgaard J et al KI 2017

CV outcome studies in patients with T2DM



CV outcome studies in patients with T2DM: chronology of completion dates. (https://clinicaltrials.gov/ct2/home; last accessed May 29, 2015) (SAVOR-TIMI 53, NCT01107886; EXAMINE, NCT00968708; ELIXA, NCT01147250; TECOS, NCT00790205; EMPA-REG-OUTCOME, NCT01131676; LEADER, NCT01179048; SUSTAIN 6, NCT01720446; CANVAS-R, NCT01989754; ACE, NCT00829660 (*https://www.dtu.ox.ac.uk/ace/; last accessed May 29, 2015); CARMELINA, NCT01897532; EXSCEL, NCT01144338; CANVAS, NCT01032629; CAROLINA, NCT01243424; DEVOTE, NCT01959529; TOSCA.IT, NCT00700856; REWIND, NCT01394952; DECLARE-TIMI 58, NCT01730534; CREDENCE, NCT02065791; NCT01986881)

Grazie per l'attenzione