SID Società Italiana di Diabetologia

AMD ASSOCIAZIONE MEDICI DIABETOLOGI

7° CONGRESSO CONGIUNTO SID - AMD SICILIA 2022

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11 - 12 NOVEMBRE 2022

Nefropatia diabetica o malattia renale diabetica? Alla ricerca di un fenotipo

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UOC Medicina Interna-Endocrinologia
IRCCS «CSS», San Giovanni Rotondo (FG)

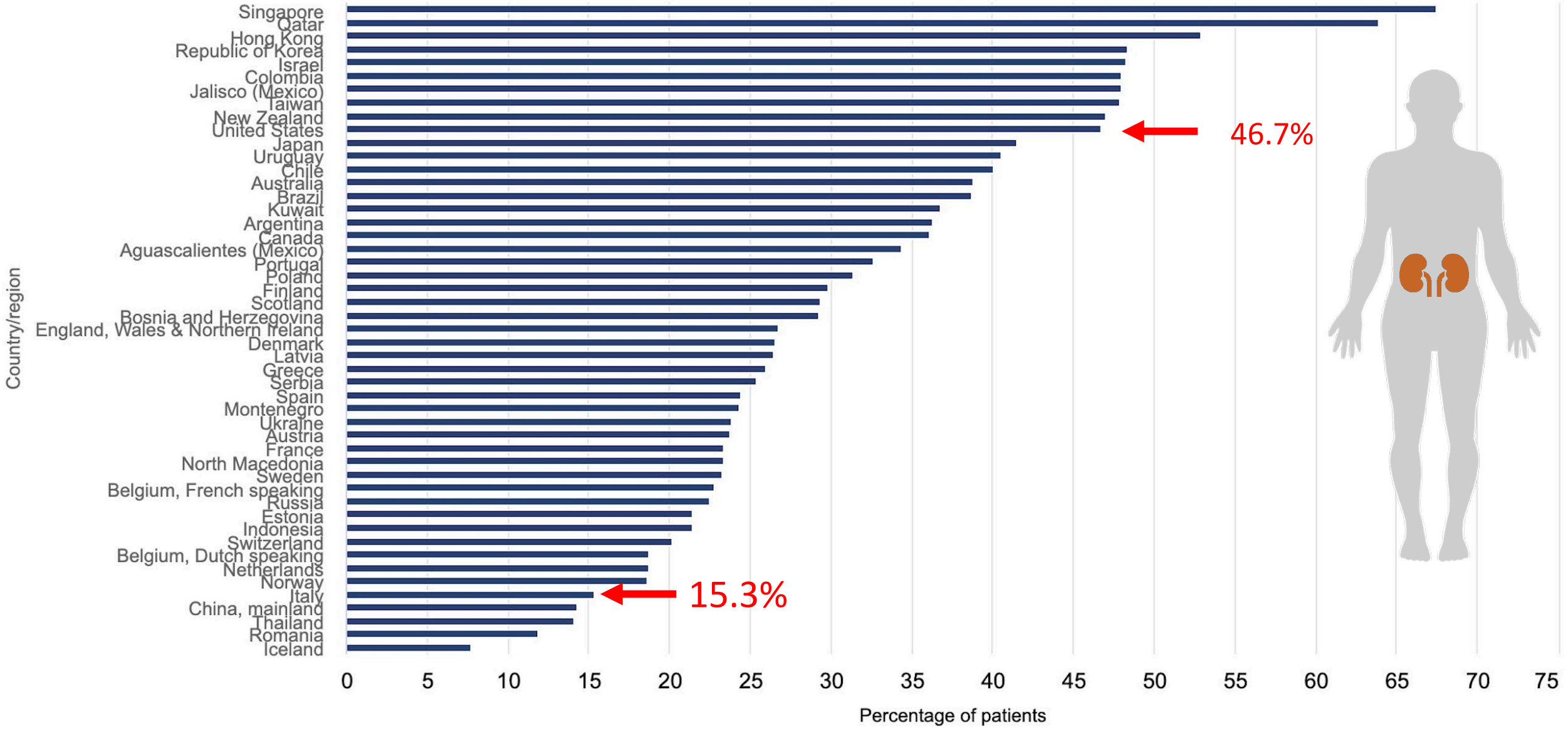
Conflitto di Interessi

Il dott. Salvatore De Cosmo dichiara di aver ricevuto negli ultimi due anni compensi per letture o partecipazione ad Advisory Board dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

Eli Lilly, Boheringer, Astra-Zeneca, MundiPharma, MSD, Sanofi, Novo-Nordisk, Daiichi Sankyo, Bayer.

Percentage of incident cases of treated ESRD attributed to diabetes, by country or region, 2019

Sort by Percentage

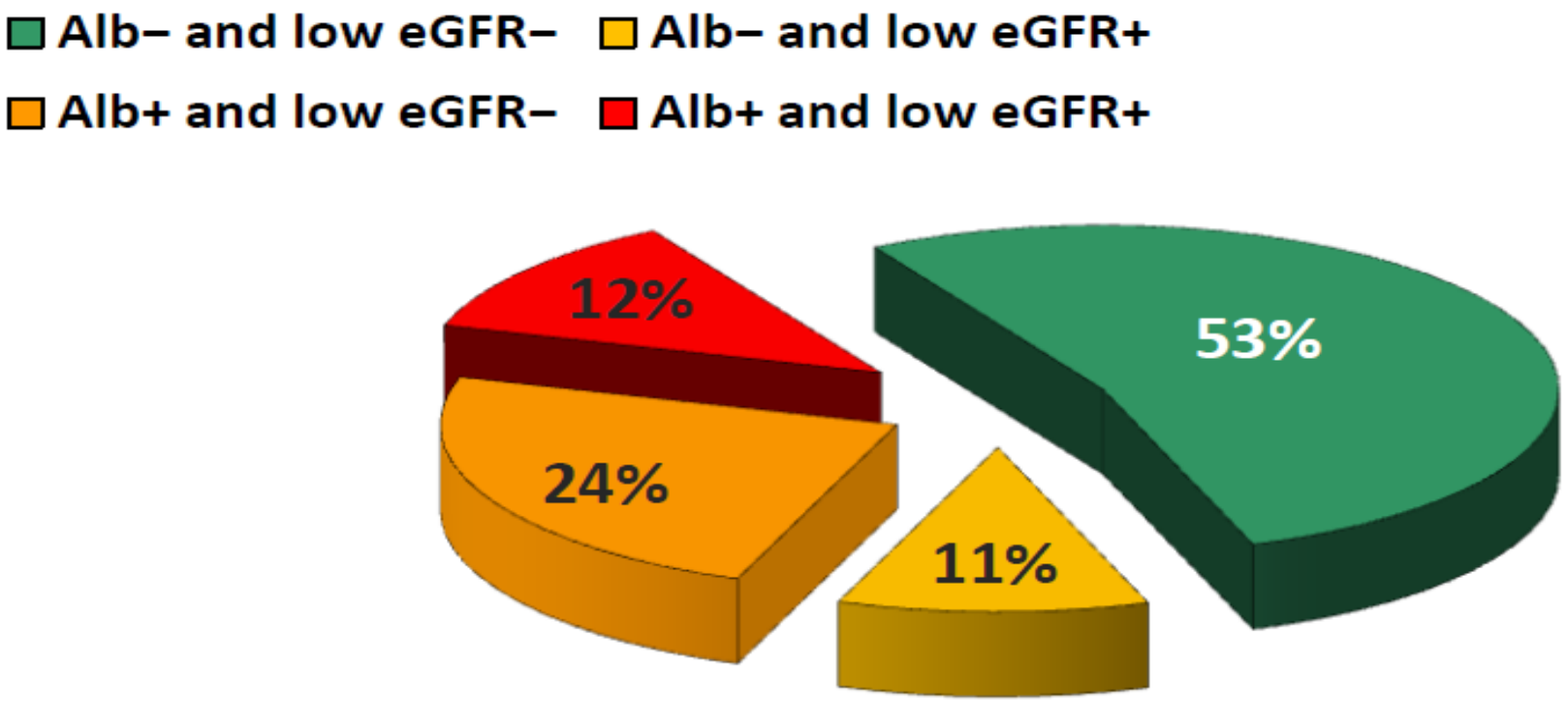


Data Source: 2021 United States Renal Data System Annual Data Report

USRDS

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



S. De Cosmo et al. for AMD-Annals Study Group, *NDT* 2014

Stages of **CKD** are defined according to eGFR and degree of albuminuria

GFR categories, description and range (ml/min/1.73 m²)				Albuminuria stages, description and range (mg/g)		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30	30–300	>300
	G1	Normal or high	≥90			
	G2	Mildly decreased	60–89			
	G3a	Mildly to moderately decreased	45–59			
	G3b	Moderately to severely decreased	30–44			
	G4	Severely decreased	15–29			
	G5	Kidney failure	<15			

Low risk* Moderately increased risk High risk Very high risk

*Defined as low risk for developing mineral and bone disorders and cardiovascular complications if there are no other markers of kidney disease or CKD

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate

Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. *Kidney Int Suppl* 2017;7:1

Diabetic Kidney Disease vs Diabetic Nephropathy

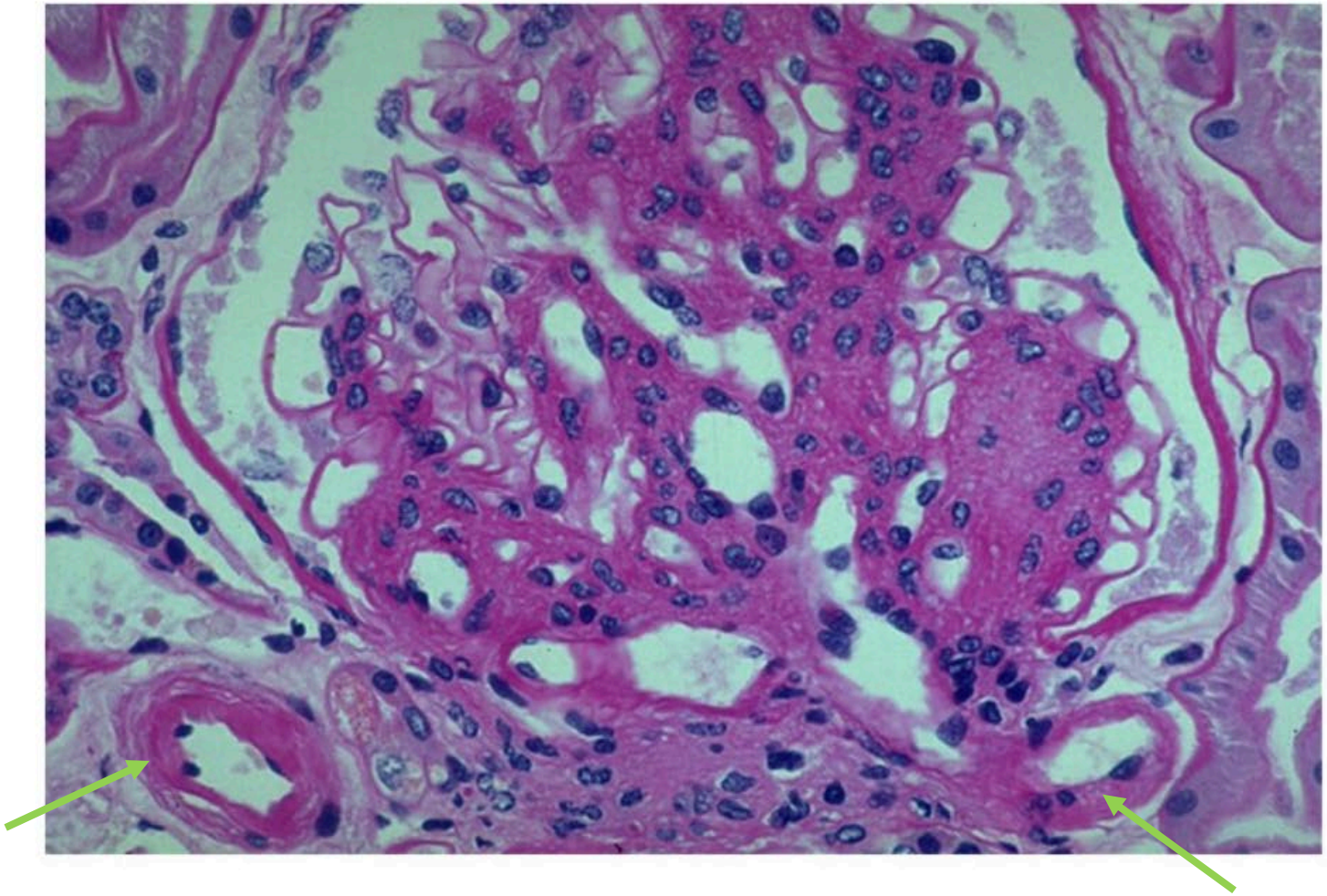
CKD is a clinical diagnosis based upon increased UACR, low eGFR or both

DKD is **chronic kidney disease in diabetes**, not a pathological phenotype

Diabetic Nephropathy is used to specify classic glomerular lesions in diabetes:

- glomerular basement membrane thickening, mesangial expansion and nodules, podocyte loss, endothelial lesions

Classic Diabetic Glomerulopathy



Fioretto P et al, Diabetologia, 2007

Diabetic Kidney Disease vs Diabetic Nephropathy

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DKD is **chronic kidney disease in diabetes**, not a pathological phenotype

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KDIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease

kidney INTERNATIONAL October 2020

Antihyperglycemic therapies in patients with type 2 diabetes (T2D) and CKD

Diagnostically, CKD occurring among people with diabetes is usually attributed to diabetes, unless other causes are readily evident. Certainly, cases of CKD occurring among people with diabetes are actually heterogeneous, and some are caused by other processes. More work is needed to develop granular approaches to CKD diagnosis and classification in diabetes and to determine the roles of kidney biopsy and biomarkers in this evaluation. Here, we adopt the current clinical approach of treating most presentations of diabetes and CKD similarly, modifying the approach as appropriate according to albuminuria or eGFR category. We avoid the term "diabetic kidney disease" to avoid the connotation that CKD is caused by traditional diabetes pathophysiology in all cases, although this term is entirely appropriate when this limitation is recognized. We also avoid the term "diabetic nephropathy," an outdated term for which there is currently no consensus definition. Prevention, screening, and diagnosis of new-onset diabetes after transplantation are also important topics that were considered out of scope for this guideline.

CJASN Clinical Journal of the American Society of Nephrology

The Modern Spectrum of Renal Biopsy Findings in Patients with Diabetes

Vol 8 October, 2013

Shree G. Sharma, Andrew S. Bomback,† Jai Radhakrishnan,† Leal C. Herlitz,‡ Michael B. Stokes,‡ Glen S. Markowitz,‡ and Vivette D. D'Agati‡*

620 pazienti con Diabete M. Tipo 2→ Biopsie renali afferenti ad un Singolo Centro (2011)

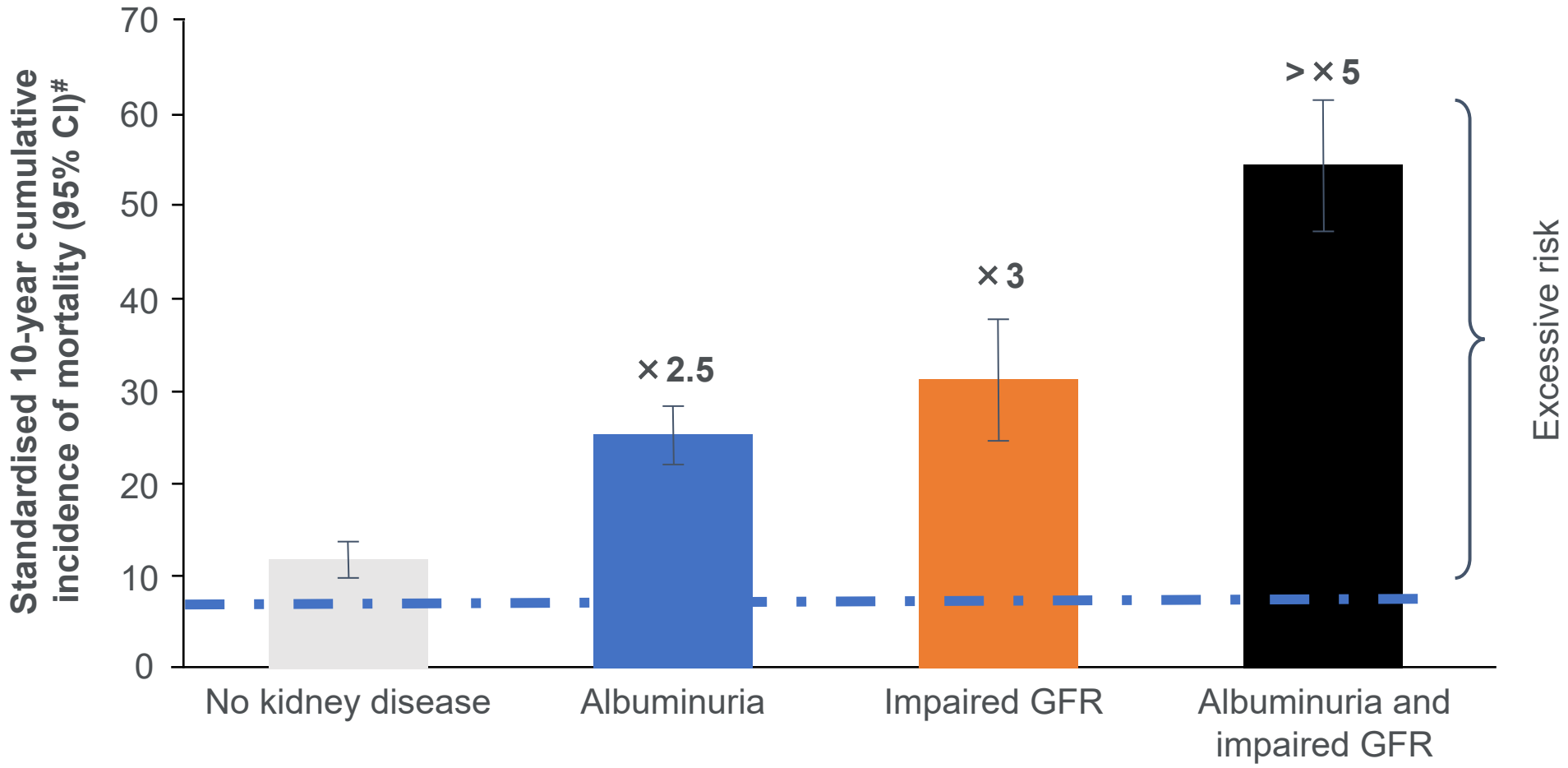
Indicazioni alla Biopsia

- AKI con o senza CKD
- Severità della proteinuria
- Positività test sierologici
- Sedimento urinario attivo

RISULTATI

- **227 (37%) Nefropatia Diabetica (DN) da sola**
- **220 (36%) Nefropatie non Diabetiche (NDRD) da sole**
- **164 (27%) DN + NDRD**

Standardised 10-year cumulative incidence of all-cause mortality by diabetes and kidney disease status in 15,046 participants*



Afkarian M, *et al*. *J Am Soc Nephrol* 2013;24:302–308

Journal of Diabetes and Its Complications xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: WWW.JDCJOURNAL.COM

Association of kidney disease measures with risk of renal function worsening in patients with hypertension and type 2 diabetes

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[e] Department of Cardiovascular and Metabolic Diseases, IRCCS Gruppo Multimedica, San Io San Giovanni, Milano, Italy
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ARTICLE INFO

Article history:
Received 1 September 2016
Received in revised form 11 October 2016
Accepted 26 October 2016
Available online xxxx

Keywords:
Risk factors
Type 2 diabetes
Albuminuria
Glomerular filtration rate
Chronic kidney disease

ABSTRACT

Aims: To assess the role of kidney disease measures on the development of chronic kidney disease (CKD) in patients with type 2 diabetes (T2D) and hypertension (HT).

Methods: Clinical records from a total of 17,160 patients with T2D and HT, a baseline estimated glomerular filtration rate (eGFR) values ≥60 mL/min/1.73 m², evaluation for albuminuria and regular visit during a four-year follow-up were retrieved and analyzed. The incidence of eGFR <60 mL/min/1.73 m² and/or a reduction >30% from baseline was evaluated.

Results: At baseline 23% of patients (n = 3873) had albuminuria. Over the 4-year follow-up 20% (n = 3480) developed a renal endpoint 28% (n = 1074) of those with albuminuria and 17% (n = 2406) of those without albuminuria. The presence of baseline albuminuria entailed a 1.8 independent, greater risk of reaching stage 3 CKD. Patients with normal albuminuria showed a 1.54 ($p < 0.001$) greater risk for each 5 mL reduction (below 90 mL/min) in baseline GFR.

Conclusions: In T2D patients with HT, eGFR reduction and albuminuria are independently associated with a greater risk of developing stage 3 CKD. While baseline albuminuria entails a greater renal risk, due to a larger occurrence of the non-albuminuric phenotype, renal function worsening is more likely to be observed in patients without albuminuria.

1. Introduction

The prevalence of chronic kidney disease (CKD) has been steadily growing in recent years mainly as a consequence of improvements in the prevention and management of cardiovascular complications and the subsequent increase in life expectancy of patients with type 2 diabetes (T2D) (Gregg, Williams, & Geiss, 2014). Yet, the development of renal disease carries an unfavorable impact on patients' quality of life and greatly reduces their life expectancy mainly by raising the incidence of cardiovascular events (Tancredi et al., 2015). Due to its direct and indirect costs, diabetic kidney disease (DKD) is rapidly becoming a major concern for public health systems worldwide.

Albuminuria and glomerular filtration rate (GFR) reduction are well known independent predictors of cardiovascular and renal events (Fox et al., 2012). At variance with the traditional clinical presentation of renal disease in type 1 diabetes, wherein the development of albuminuria is known to precede and predict renal function worsening, in patients with T2D the presence of increased albuminuria carries a somewhat less specific predictive power with respect to renal function deterioration (Penno et al., 2011). Furthermore, it has recently been reported that a significant portion of diabetic patients progressing to ESRD do not show albuminuria or proteinuria (Soetal, 2006).

Hypertension (HT) is an exceedingly common feature of patients with T2D (Hypertension in Diabetes Study, 1993). While an increase in blood pressure (BP) may results from diabetes itself or accompany the development of diabetic renal impairment, it more often precedes the onset of diabetes (Ritz, 2013) and represents a well known risk factor for the development of albuminuria as well as for progression

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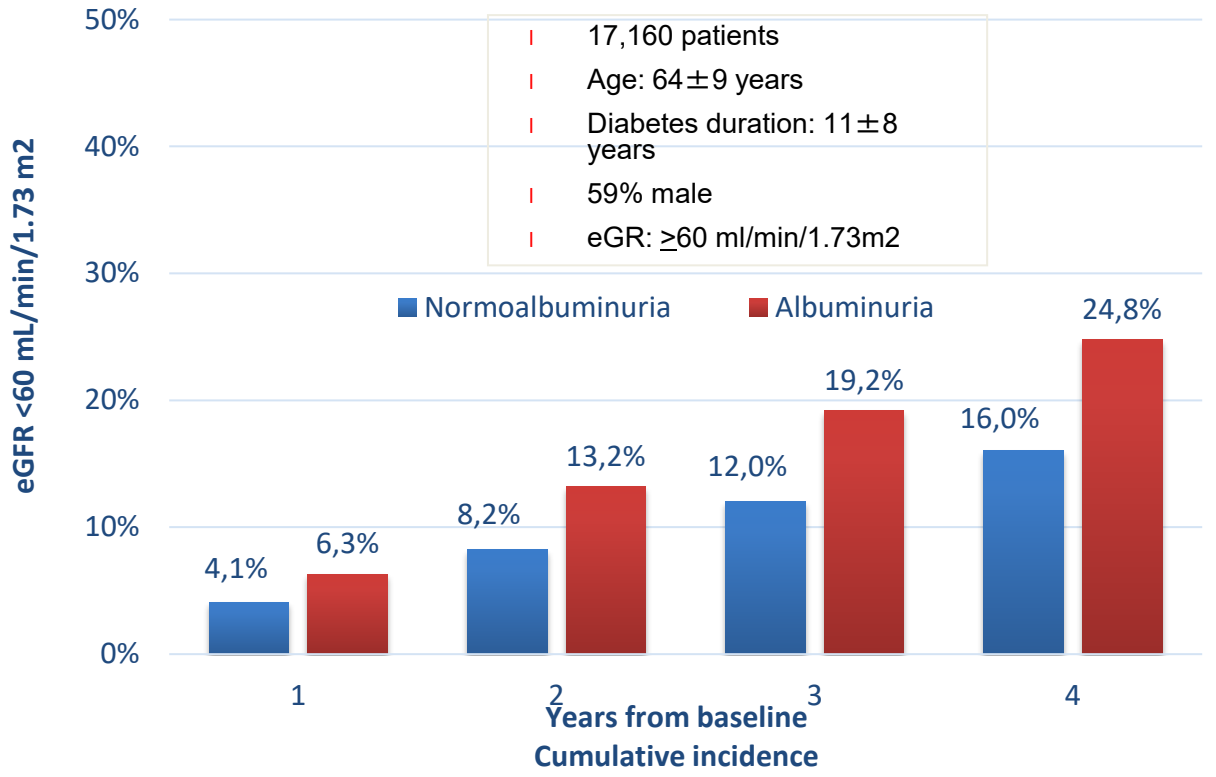
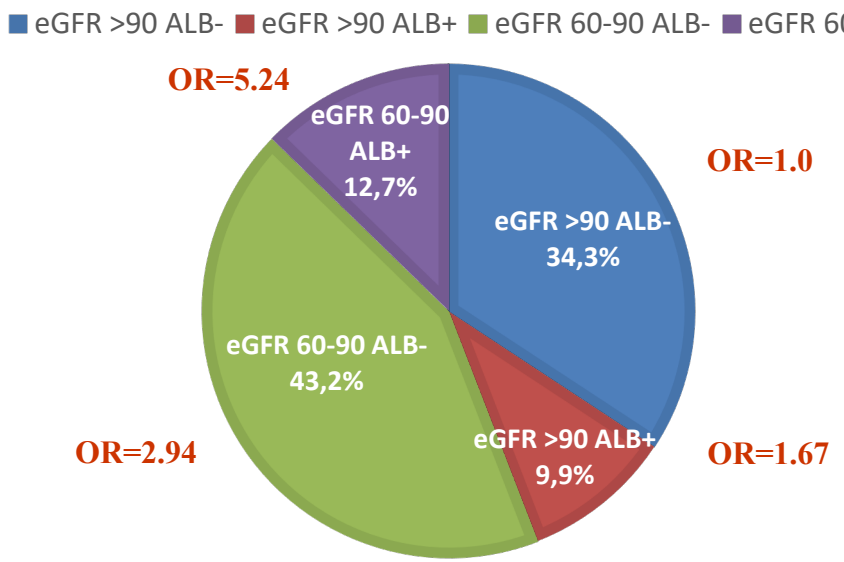
http://dx.doi.org/10.1016/j.jdiacomp.2016.10.030
1056-8727/

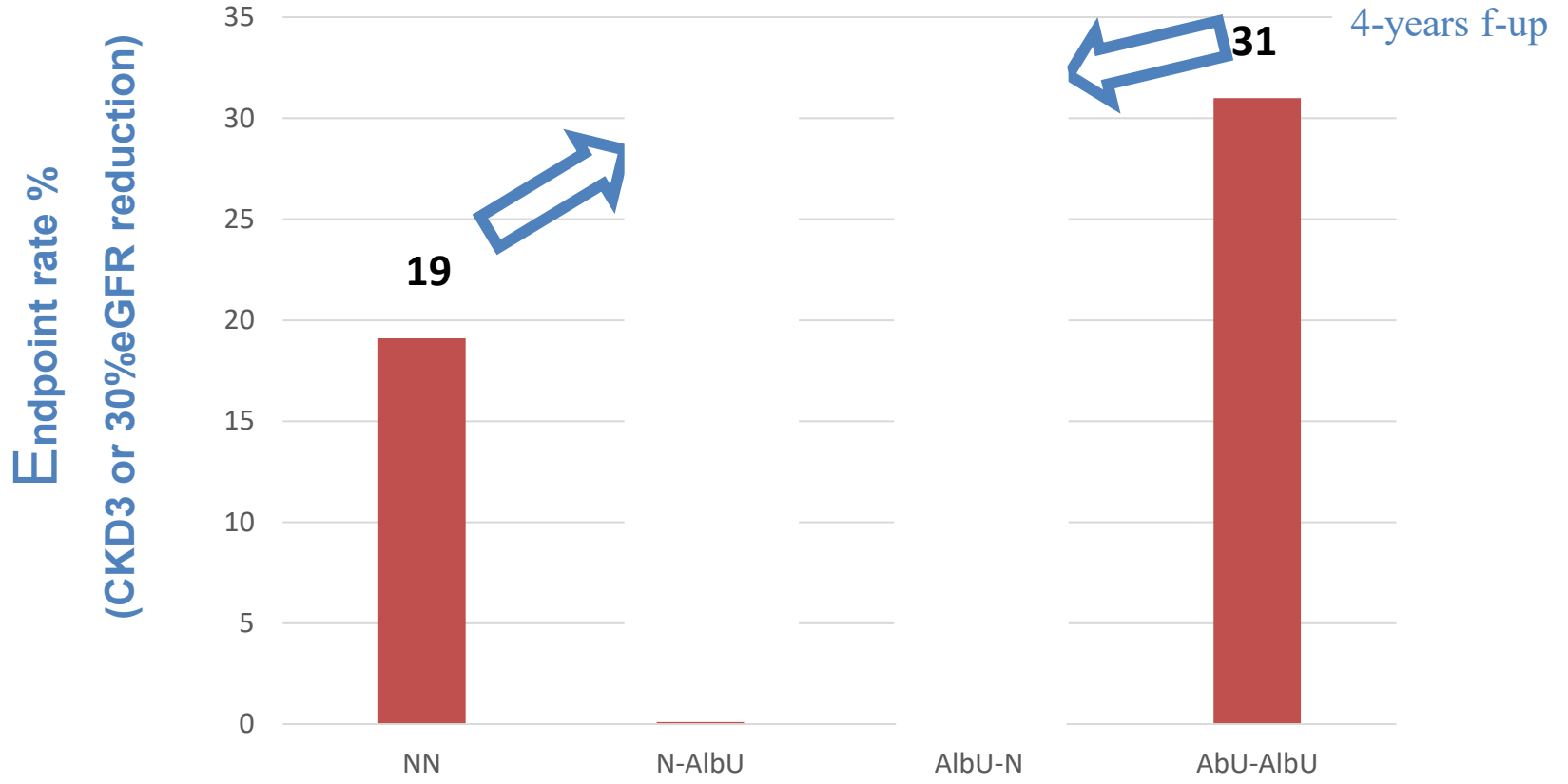
The presence of albuminuria entails a greater renal risk at any given GFR value. However, due to a greater occurrence of the non-albuminuric phenotype at baseline, progression to CKD stage 3 is more likely to be observed in patients without albuminuria.





Changes in albuminuria and renal outcome in patients with hypertension and T2D

12,611 ptz with T2D and HT
eGFR >60 ml/min independently by albuminuria
4-years f-up



“ […] changes in albuminuria translate to changes in risk.”

Viazzi F, Pontremoli R et al. J Hypertens 2018

Table 3

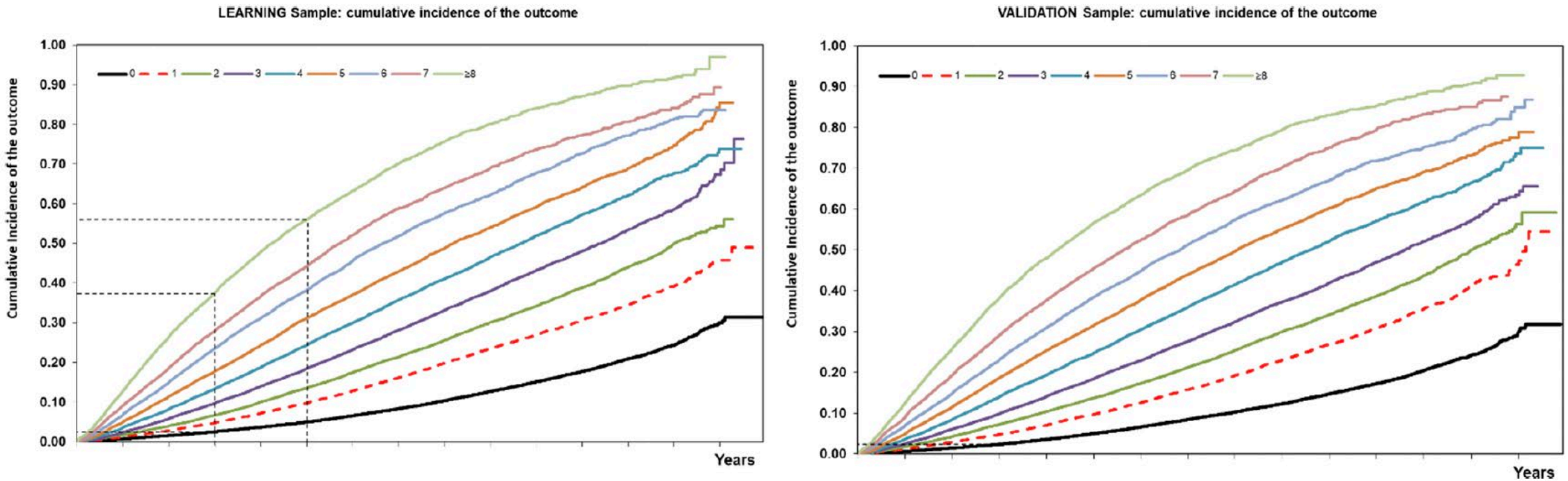


Fig. 2. Survival Curves derived from Learning (left) and Validation (right) sample. 3-years and 5-years risk of developing the primary renal outcome according to eGFR loss score (LEARNING Sample).

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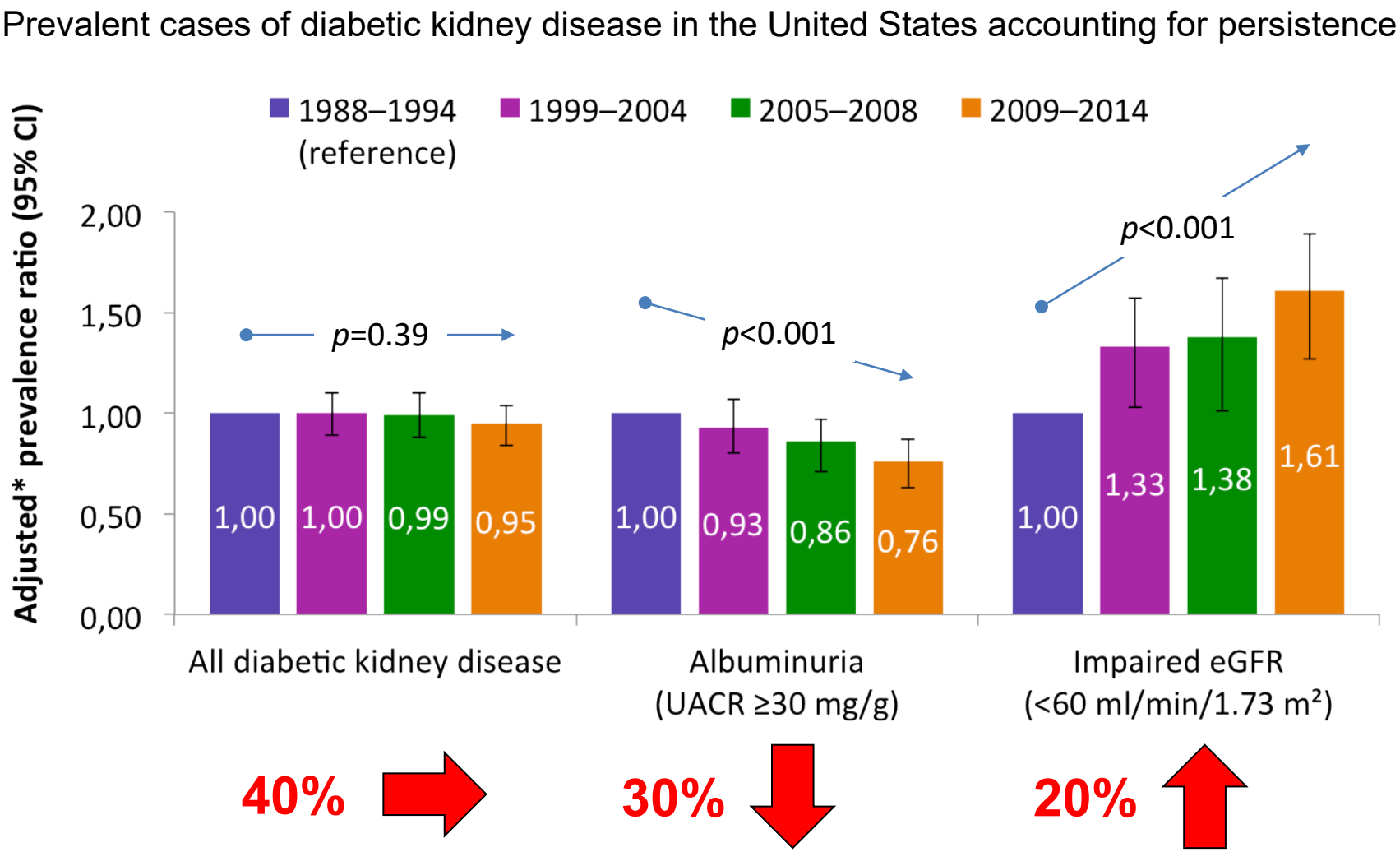
Clinical manifestations of Kidney Disease among US Adults with DM 1988-2014

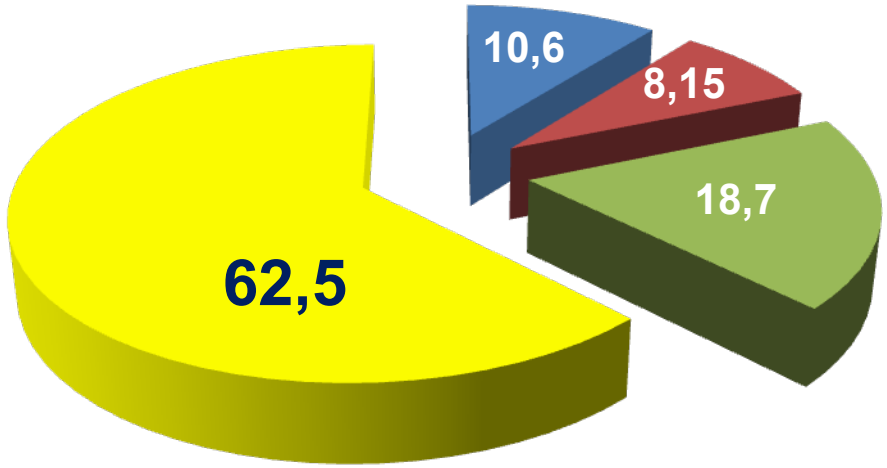


*Adjusted for age, sex, and race/ethnicity. p-values are for trend
UACR, urine albumin-to-creatinine ratio

Afkarian M et al., JAMA, 2016 *USRDS*

DMT2 e FUNZIONE RENALE

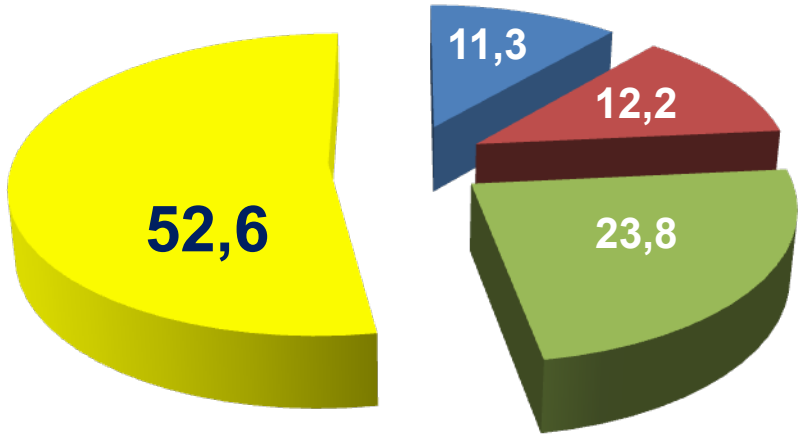
N=15.773



Studio RIACE

(Penno G, J Hypertens 2011)

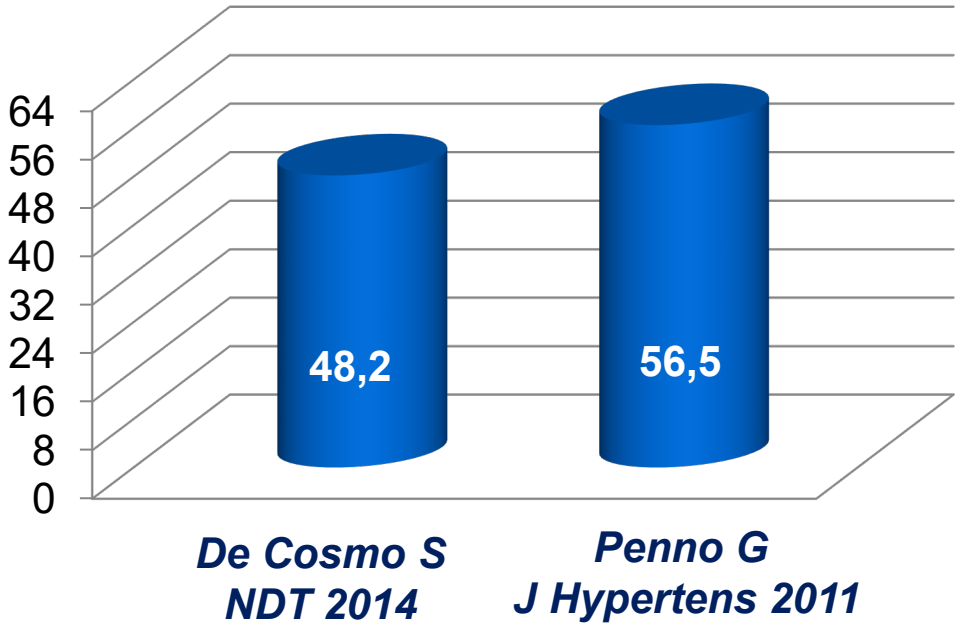
N=120.903



De Cosmo S, NDT 2014

- eGFR>60 ml/min. Normoalb.
- eGFR<60 ml/min. Normoalb.
- eGFR<60 ml/min. Alb.
- eGFR>60 ml/min. Alb.

Pazienti con CKD Normoalbuminurica (%)

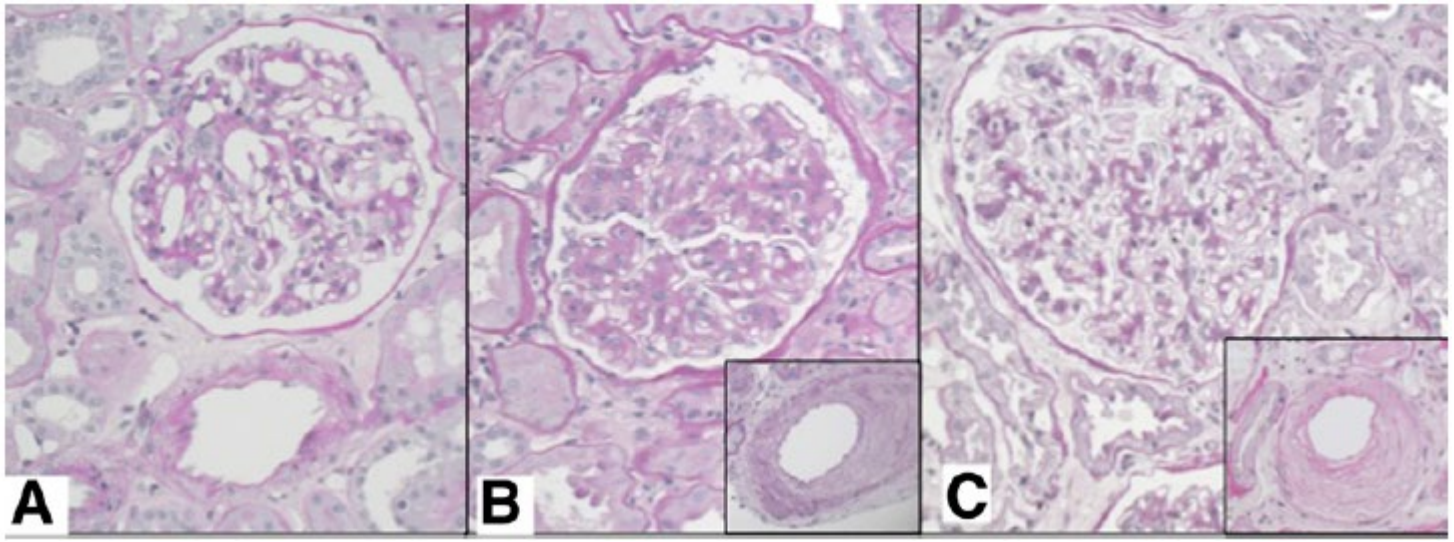


Albuminuria is not a prerequisite for DKD

	Patients n.	DM %	Follow-up years	Renal impairment	Non-albuminuric renal impairment
UKPDS *Diabetes 55: 1832-1839, 2006*	4,006	100	15	28%	67% (51%)
DCCT/EDIC *Diabetes Care 33: 1536-1543, 2010*	1,439	100 (T1DM)	19	6.2%	24%
AMD Annals **Diabetes Metab Res Rev 2017**	**20,464**	100 (T1DM)	19	23.5%	**49%**

MacIsaac RJ et al., *Diabetes Care 27: 195-200, 2004*	301	100	---	36%	39%
Kramer HJ et al., NHANES III *JAMA 289: 3273-3277, 2003*	1,197	100	---	13%	36%
Thomas MC et al., NEFRON *Diabetes Care 32: 1497-1502, 2009*	3,893	100	---	23%	55%
Ninomiya T et al., ADVANCE *J Am Soc Nephrol 20: 1813-1821, 2009*	10,640	100	---	19%	62%
Bakris GL et al., ACCOMPLISH *Lancet 375: 1173-1181, 2010*	11,482	60	---	9.5%	47%
Tube SW et al., ONTARGET/ TRASCEND *Circulation 123: 1098-1107, 2011*	23,422	37	---	24%	68%
Drury PL et al., FIELD *Diabetologia 54: 32-43, 2011*	9,765	100	---	5.3%	59%
RIACE Study Group, RIACE *J Hypertens 29: 1802-1809, 2011*	15,773	100	---	18.8%	57%
AMD ANNALS **NDT 2015**	**116,777**	**100**	**---**	**21%**	**48%**

Danno renale in T2DM con CKD Normoalbuminurica



Normale (paz. 1) | **GS e arteriosclerosi (Paz.3)** | **Arteriosclerosi severa (Paz.8)**

Patient study number	Fioretto category	GS score (0–3)	Mesangial expansion (0–3)	TA/IF (0–3)	Arteriolar hyalinosis (0–3)	Arterioscleros (0–3)	Summary
1	C1	1	0	0	0	0	Not DN, mild IgA nephropathy, no cause for renal impairment found
2	C1	2	0	1	1	1	Mild nonspecific changes, not DN
3	C2	1	3	2	3	2	Typical advanced DN
4	C2	1	1	1	1	1	Typical early DN
5	C2	1	1	0	1	2	Typical early DN
6	C3	1	0	1	2	1	Renovascular, not DN
7	C3	1	0	1	0	2	Renovascular, not DN
8	C3	3	1	3	1	3	Atypical DN, mild glomerular changes + severe vascular and tubulointerstitial disease

Ekinci EI, Diabetes Care 2013

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OBSERVATIONAL STUDY
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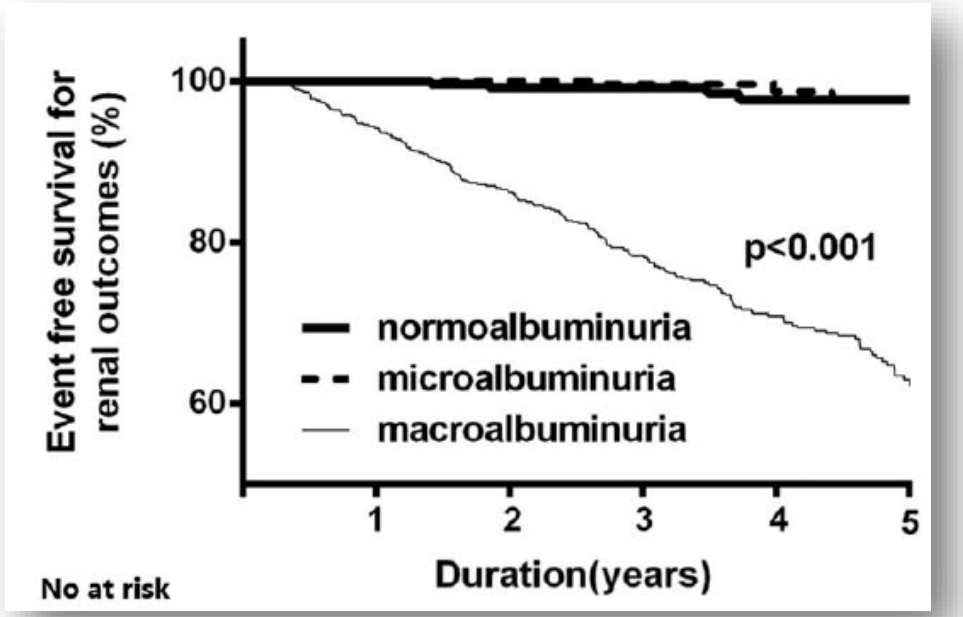
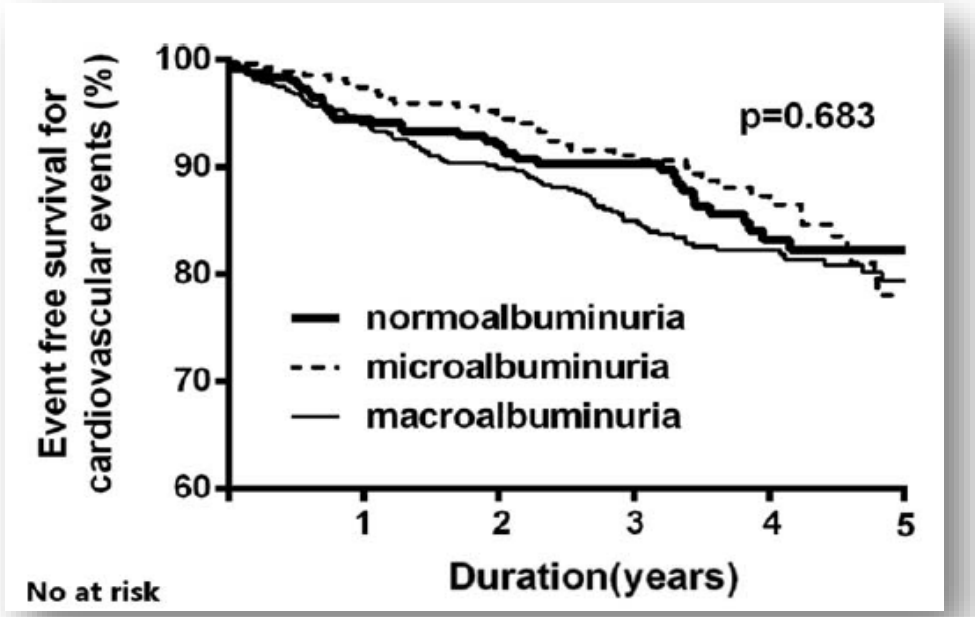
The Incidence of Cardiovascular Events Is Comparable Between Normoalbuminuric and Albuminuric Diabetic Patients With Chronic Kidney Disease

Eunyoung Lee, MD, Hyung Jung Oh, MD, Jung Tak Park, MD, PhD, Seung Hyeok Han, MD, PhD, Dong-Ryeol Ryu, MD, PhD, Shin-Wook Kang, MD, PhD, and Tae-Hyun Yoo, MD, PhD

Medicine 95(15):e3175



Renal events



CV events

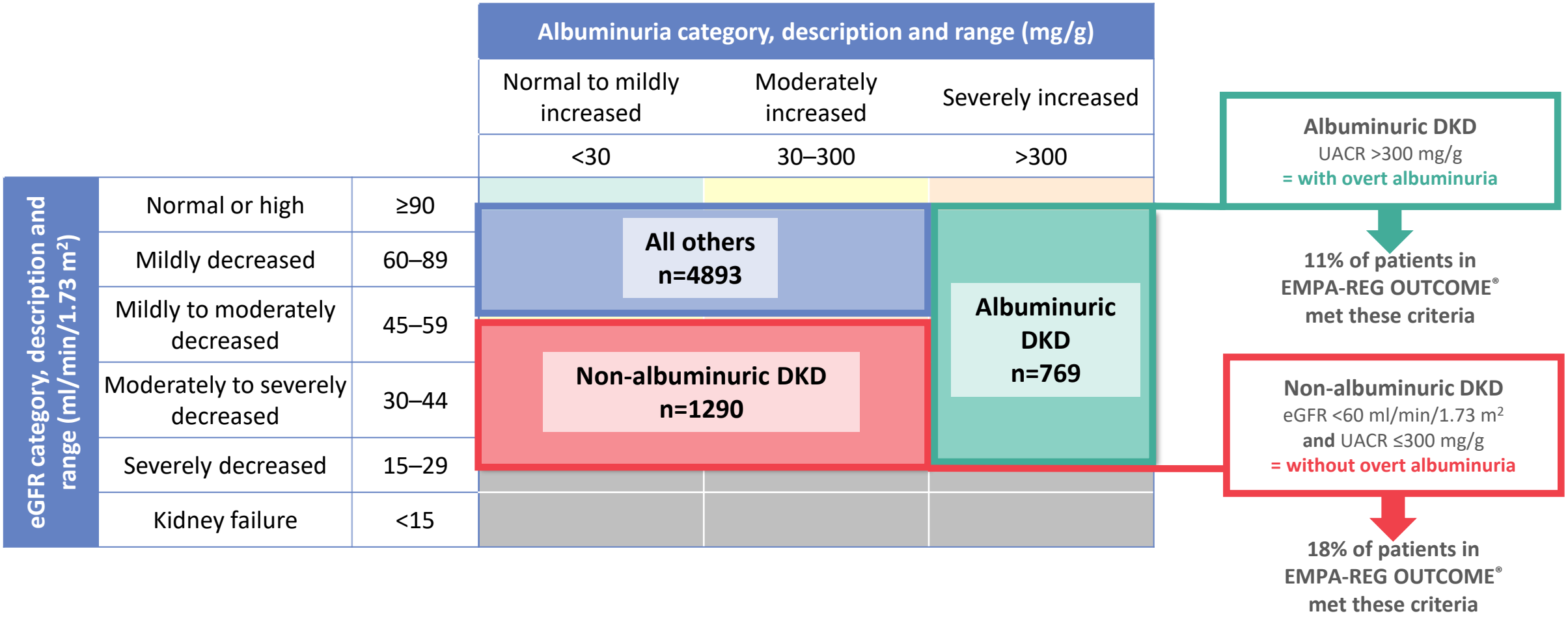
SGLT2 Inhibitors: CV Outcomes Summary

	Kidney composite outcomes	HR (95% CI)
EMPA-REG OUTCOME[1]	**Doubling of the serum creatinine** accompanied by an eGFR of ≤45 mL/min /1.73 m^2, initiation of **renal-replacement** therapy or **death** from renal disease	**0.54** (0.40–0.75)
CANVAS Programme[2]	**Sustained ≥40% reduction in eGFR**, **renal-replacement** therapy (dialysis or transplantation), or **death** from renal causes	**0.60** (0.47–0.77)
DECLARE-TIMI 58[3]	**Sustained ≥40% decrease in eGFR** to <60 mL/min /1.73 m^2, **ESKD**, or **death** from renal causes	**0.53** (0.43–0.66)
VERTIS CV[4]	**Doubling of serum creatinine** from baseline, **dialysis/transplant**, or renal **death**	**0.81** (0.63–1.04)

1. Zinman B, et al. NEJM 2015; 373:2117-2128
2. Neal B, et al. NEJM 2017;377:644-657
3. Wiviott SD, et al. NEJM 2019;380:347-357
4. Cannon CP, et al. NEJM 2020 Oct 8;383(15):1425-1435

EMPA-REG OUTCOME®: Exploratory analysis

Different clinical phenotypes of DKD vs all others

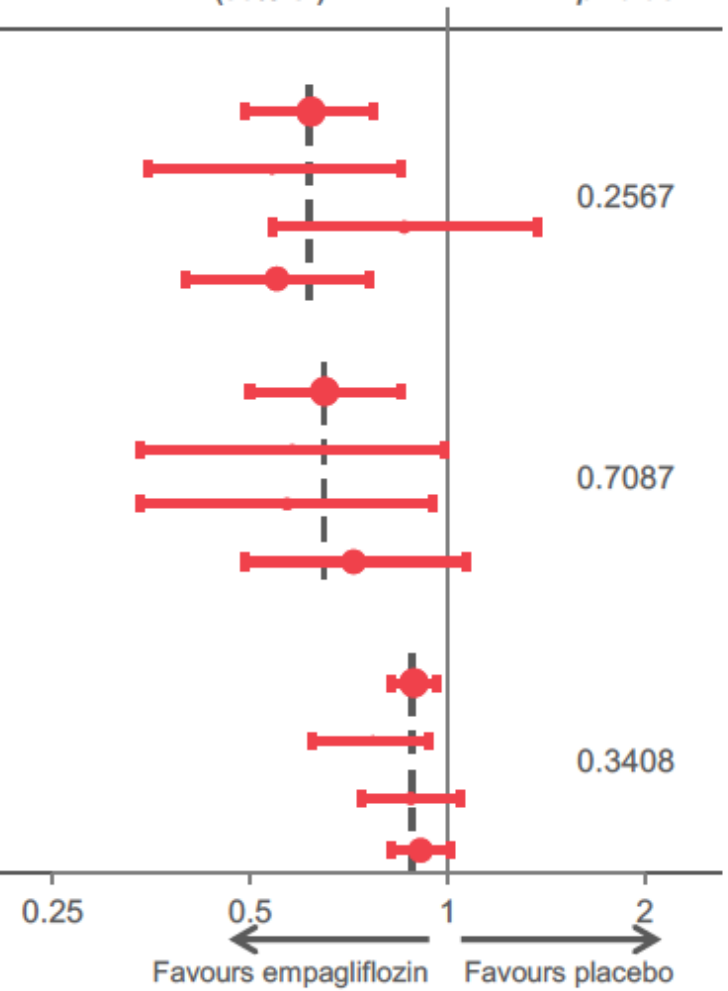


DKD, Diabetic Kidney Disease

Adapted from: Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. *Kidney Int Suppl* 2013;3:1 - Wanner *et al Diabetes Obes Metab*. 2020;1–13.

CV outcomes in patients with albuminuric vs non-albuminuric DKD vs all others

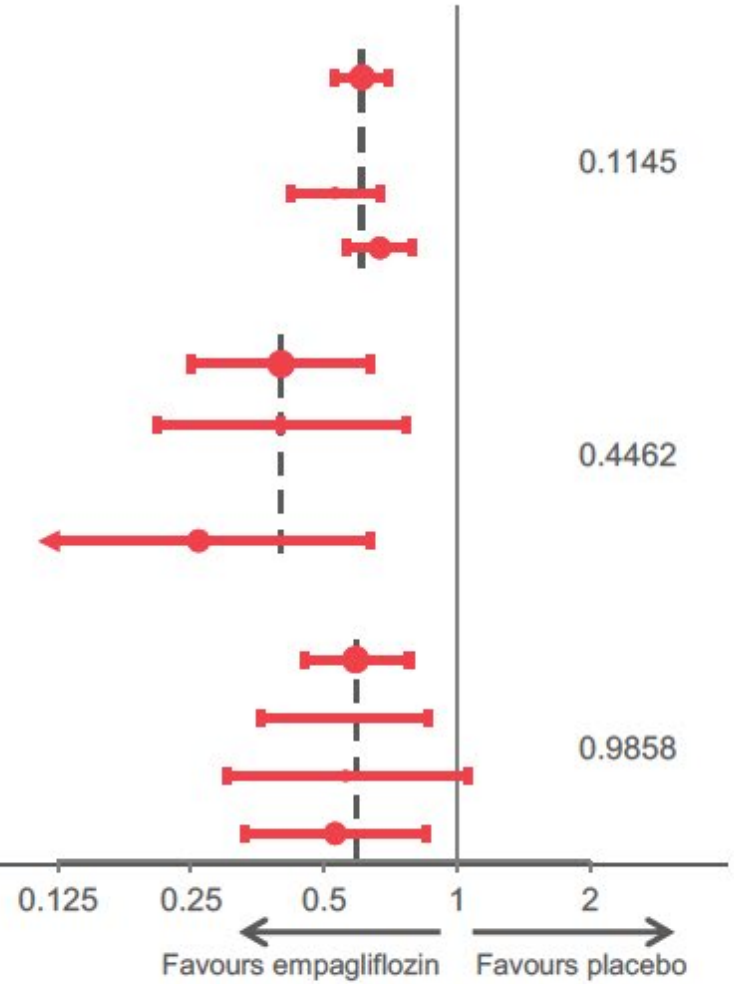
	Empagliflozin		Placebo		Hazard ratio (95% CI)	Interaction *p*-value
	n event/N	%	n event/N	%		
CV death						
All patients	172/4687	3.7	137/2333	5.9	0.62 (0.49, 0.77)	
Albuminuric DKD	42/509	8.3	36/260	13.8	0.54 (0.35, 0.85)	0.2567
Non-albuminuric DKD	47/850	5.5	29/440	6.6	0.86 (0.54, 1.37)	
All others	82/3276	2.5	72/1617	4.5	0.55 (0.40, 0.76)	
HHF						
All patients	126/4687	2.7	95/2333	4.1	0.65 (0.50, 0.85)	
Albuminuric DKD	32/509	6.3	24/260	9.2	0.58 (0.34, 0.99)	0.7087
Non-albuminuric DKD	31/850	3.6	29/440	6.6	0.57 (0.34, 0.95)	
All others	62/3276	1.9	42/1617	2.6	0.72 (0.49, 1.07)	
All-cause hospitalisation						
All patients	1725/4687	36.8	925/2333	39.6	0.89 (0.82, 0.96)	
Albuminuric DKD	237/509	46.6	139/260	53.5	0.77 (0.62, 0.94)	0.3408
Non-albuminuric DKD	373/850	43.9	208/440	47.3	0.88 (0.74, 1.05)	
All others	1093/3276	33.4	575/1617	35.6	0.91 (0.82, 1.01)	



Albuminuric DKD defined as UACR >300 mg/g with any eGFR [CKD-EPI]; non-albuminuric DKD group defined as eGFR <60 ml/min/1.73 m² and UACR ≤300 mg/g; all others group defined as eGFR ≥60 ml/min/1.73 m² or UACR ≤300 mg/g. CV, cardiovascular; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; HHF, hospitalisation for heart failure; UACR; urinary albumin-to-creatinine ratio; Wanner *et al Diabetes Obes Metab*. 2020;1–13

Kidney outcomes in patients with albuminuric vs non-albuminuric DKD vs all others

	Empagliflozin		Placebo		Hazard ratio (95% CI)	Interaction *p*-value
	n event/N	%	n event/N	%		
Incident or worsening nephropathy*						
All patients	525/4124	12.7	388/2061	18.8	0.61 (0.53, 0.70)	
Albuminuric DKD	n/a	n/a	n/a	n/a	NC	0.1145
Non-albuminuric DKD	150/829	18.1	128/431	29.7	0.53 (0.42, 0.67)	
All others	332/3219	10.3	228/1589	14.3	0.67 (0.56, 0.79)	
ESKD, sustained doubling of creatinine, or renal death†						
All patients	31/4645	0.7	37/2323	1.6	0.40 (0.25, 0.64)	
Albuminuric DKD	17/504	3.4	19/260	7.3	0.40 (0.21, 0.77)	0.4462
Non-albuminuric DKD	6/838	0.7	5/438	1.1	NC	
All others	7/3253	0.2	13/1609	0.8	0.26 (0.10, 0.64)	
ESKD, sustained 40% eGFR decline, or renal death‡						
All patients	108/4645	2.3	87/2323	3.7	0.59 (0.45, 0.78)	
Albuminuric DKD	49/504	9.7	36/260	13.8	0.56 (0.36, 0.86)	0.9858
Non-albuminuric DKD	21/838	2.5	18/438	4.1	0.56 (0.30, 1.06)	
All others	36/3253	1.1	33/1609	2.1	0.53 (0.33, 0.85)	



*Defined as progression to macroalbuminuria (UACR >300 mg/g); a doubling of serum creatinine, accompanied by an eGFR of ≤45 ml/min/1.73 m² (MDRD formula); initiation of RRT; or renal death (patients with albuminuric DKD were excluded from this analysis).

†ESKD defined as initiation of RRT or sustained eGFR <15 ml/min/1.73 m². ‡ESKD defined as initiation of RRT or sustained eGFR <10 ml/min/1.73 m². Albuminuric DKD defined as UACR >300 mg/g with any eGFR [CKD-EPI]; non-albuminuric DKD group defined as eGFR <60 ml/min/1.73 m² and UACR ≤300 mg/g; all others group defined as eGFR ≥60 ml/min/1.73 m² or UACR ≤300 mg/g. DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; n/a, not applicable; NC, not calculated; RRT, renal replacement therapy; UACR; urinary albumin-to-creatinine ratio;

Wanner *et al Diabetes Obes Metab*. 2020;1–13

Conclusioni

- La complicanza renale è altamente prevalente nei pazienti con DMT2 che DMT1.
- E’ stato recentemente descritto un nuovo fenotipo di malattia renale, i.e. GFR ridotto in pazienti normoalbuminurici, sia nel DMT2 che nel DMT1.
- E’ sotteso un aspetto istologico differente dalla forma albuminurica
- L’analisi degli ANNALI-AMD ha permesso di approfondire sia le conoscenze epidemiologiche che i fattori predittivi di questo fenotipo di danno renale, costruendo anche un modello di predizione per la perdita di GFR.
- La MRC normalbuminurica ha una più lenta progressione verso la IRT rispetto alla forma albuminurica ma è associata ad un elevato rischio di mortalità soprattutto per cause cardiovascolari.
- E’ indispensabile nella valutazione e nel follow-up dei pazienti con diabete di tipo 2 e di tipo 1 monitorizzare sia la escrezione urinaria di albumina che il filtrato glomerulare.
- Gli SGLT2I (Empagliflozin) appiano essere efficaci nel ridurre il rischio di progressione del danno renale e degli aventi CV nei pazienti con MRC normoalbuminurica.