

Con il patrocinio di



UNIVERSITÀ
CATTOLICA
del Sacro Cuore

Gemelli



Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore



Società Italiana di Cardiologia



LA SOCIETÀ DELLE TRE ANIME



Società Italiana
di Diabetologia



Società Italiana
Nefrologia

Terzo
 **Meta**
Open Forum



"Al CUORE del DIABETE"

Roma | 8.9 Marzo 2024

Aula Brasca, Policlinico Gemelli

Evento Congiunto di

Quando chiedere una biopsia renale

Antonello Pani

Università degli Studi di Cagliari, Dipartimento di
Scienze Mediche e Sanità Pubblica

ARNAS «G. Brotzu» SCU Nefrologia, Dialisi e
Trapianto Renale

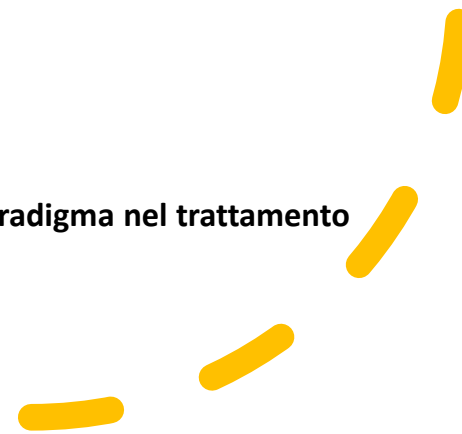
C.N.R. Cagliari

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DISCLOSURES

- **GLAXO SMITH KLINE**
- **Advisory Board**
- **Training Medical Staff**
- **GSK European Anaemia of CKD ALLIANCE meeting**
- **ALEXION**
- **Expert** on SEUa
- **Chairman** on SEUa
- **GENZYME**
- **P.R.I.M.E. Project**
- **NOVARTIS**
- **Chairman Lunch Symposium NOVARTIS – SITO**
- **VIFOR PHARMA ITALIA**
- **Advisory Board** «Sparsentan»
- **OTSUKA**
- **Advisory Board** «Voclosporina»
- **ASTELLAS**
- **Advisory Board DHIFFERENT by NATURE. Roxadustat, il cambio di paradigma nel trattamento dell'anemia da CKD".**

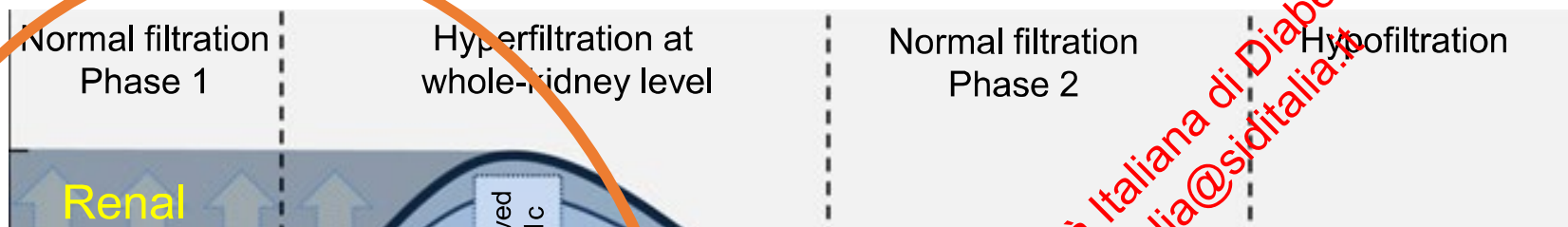
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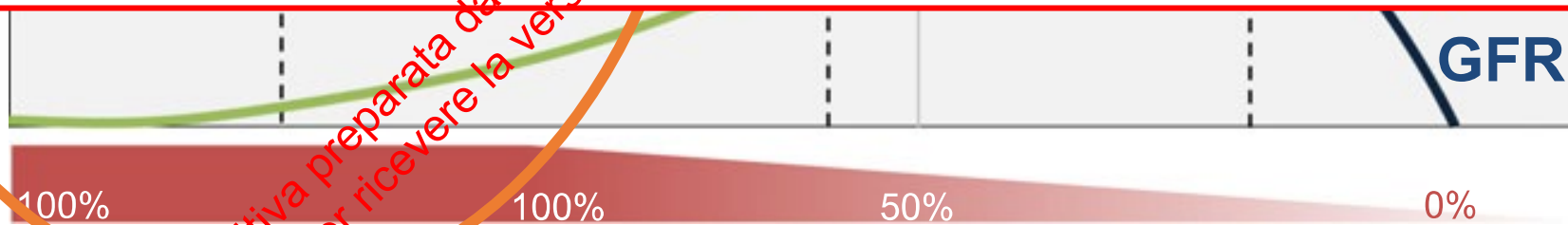
Agenda

1. Definizione e Storia Naturale della DKD
2. Recenti «Concetti» Patogenetici della DKD
3. Diabetic kidney disease vs Non Diabetic kidney disease
4. Attuali Indicazioni alla Biopsia Renale e quali dati di letteratura ci hanno portato a tali indicazioni
5. Eterogeneità delle Lesioni Renali della DKD e Diversi Fenotipi
6. Indicazioni per la Pratica Clinica e Indicazioni per la Ricerca e i RCT
7. Conclusioni

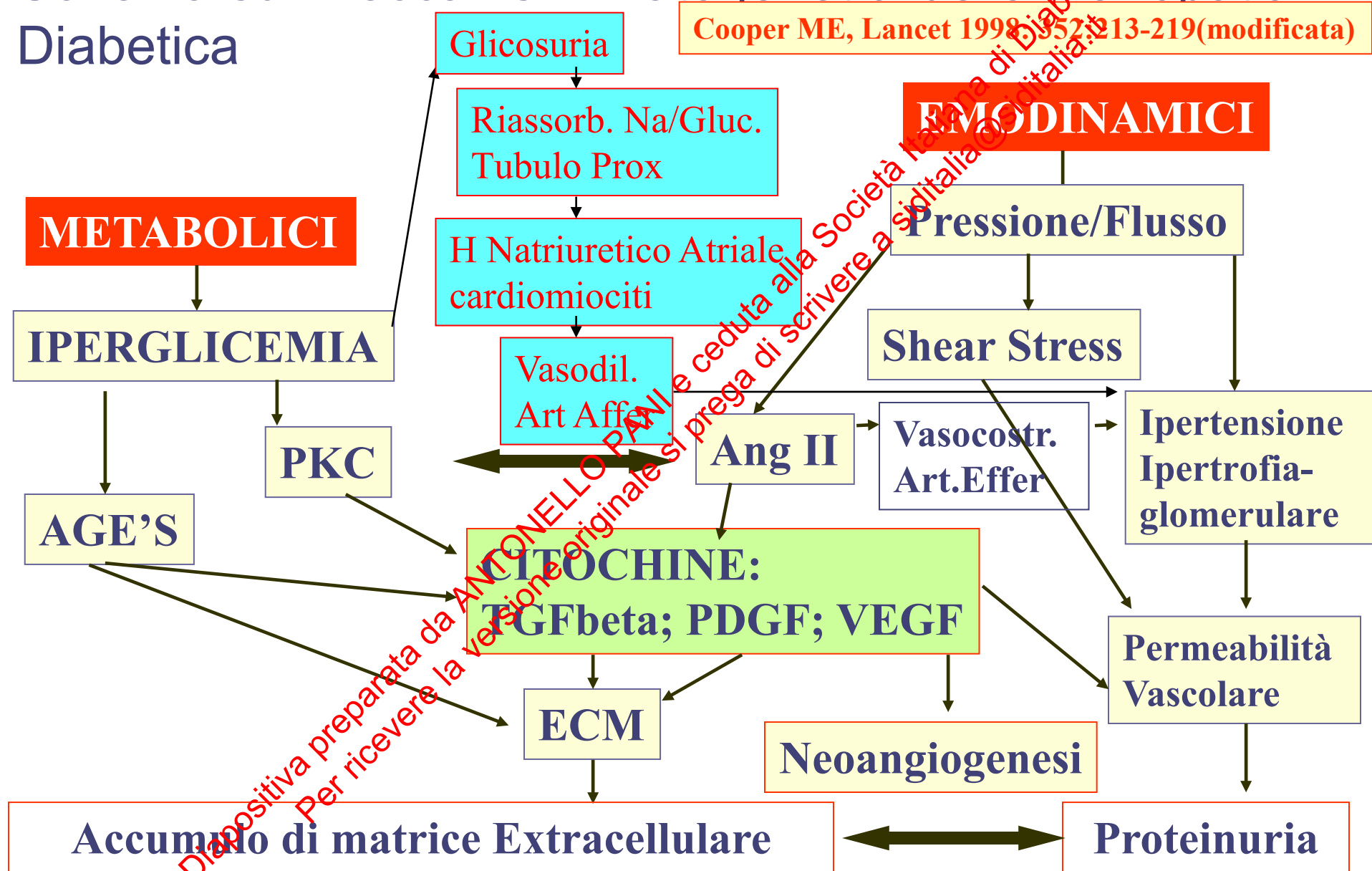
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NELLE FASI PRECOCI DELLA NEFROPATIA
DIABETICA SI OSSERVA UNA PROGRESSIVA
COMPROMISSIONE DELLA RISERVA
FUNZIONALE DEL RENE



Schema sui Meccanismi Patogenetici della Nefropatia Diabetica



Schematic (net) effect of factors implicated in the pathogenesis of glomerular hyperfiltration in diabetes.

Factors causing a net reduction of afferent arteriolar resistance

Vascular factors

Nitric oxide bioavailability

COX-2 prostanoids

Kalikrein-kinins

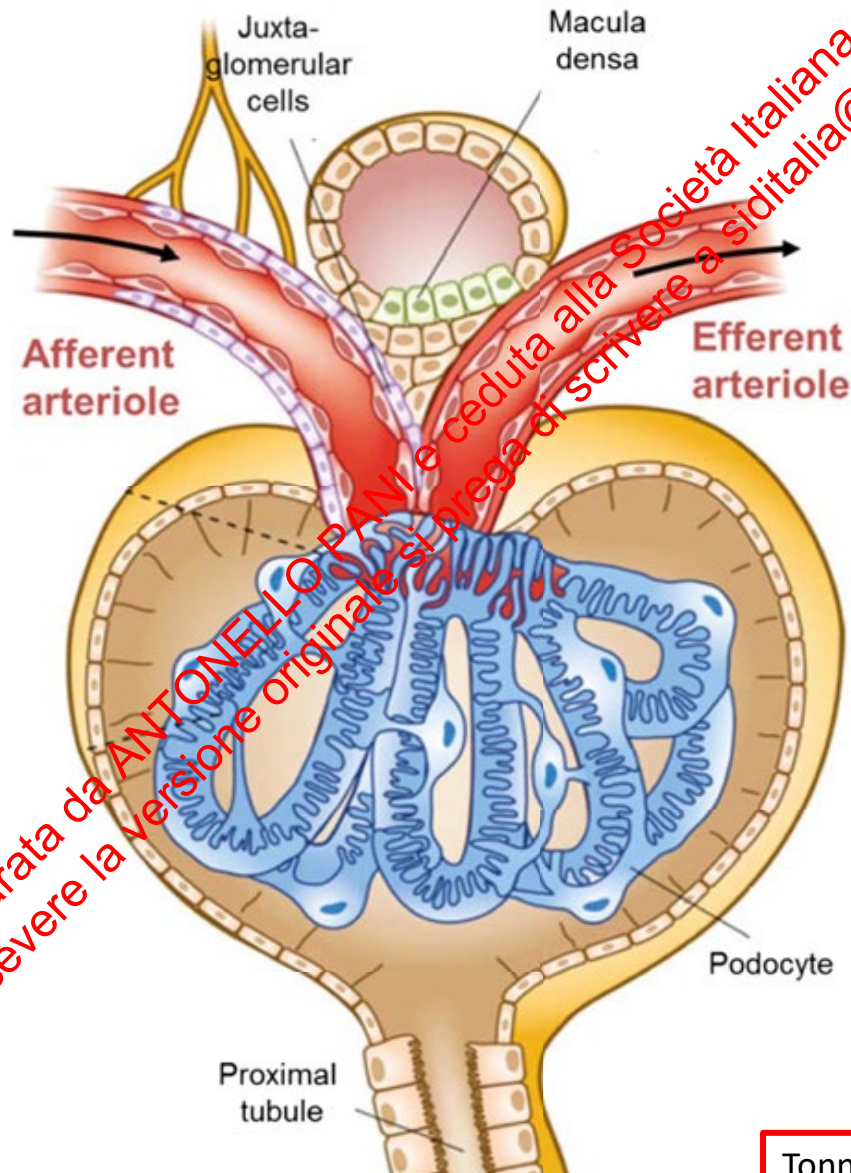
Atrial natriuretic peptide

Angiotensin(1-7)

Hyperinsulinemia *per se*

Tubular signals

Inhibition of tubuloglomerular feedback
(macula densa signals)



Factors causing a net increase of efferent arteriolar resistance

Vascular factors

Angiotensin-II

Thromboxane A2

Endothelin-1 (ETA receptor)

Reactive oxygen species

The pathogenesis of DKD

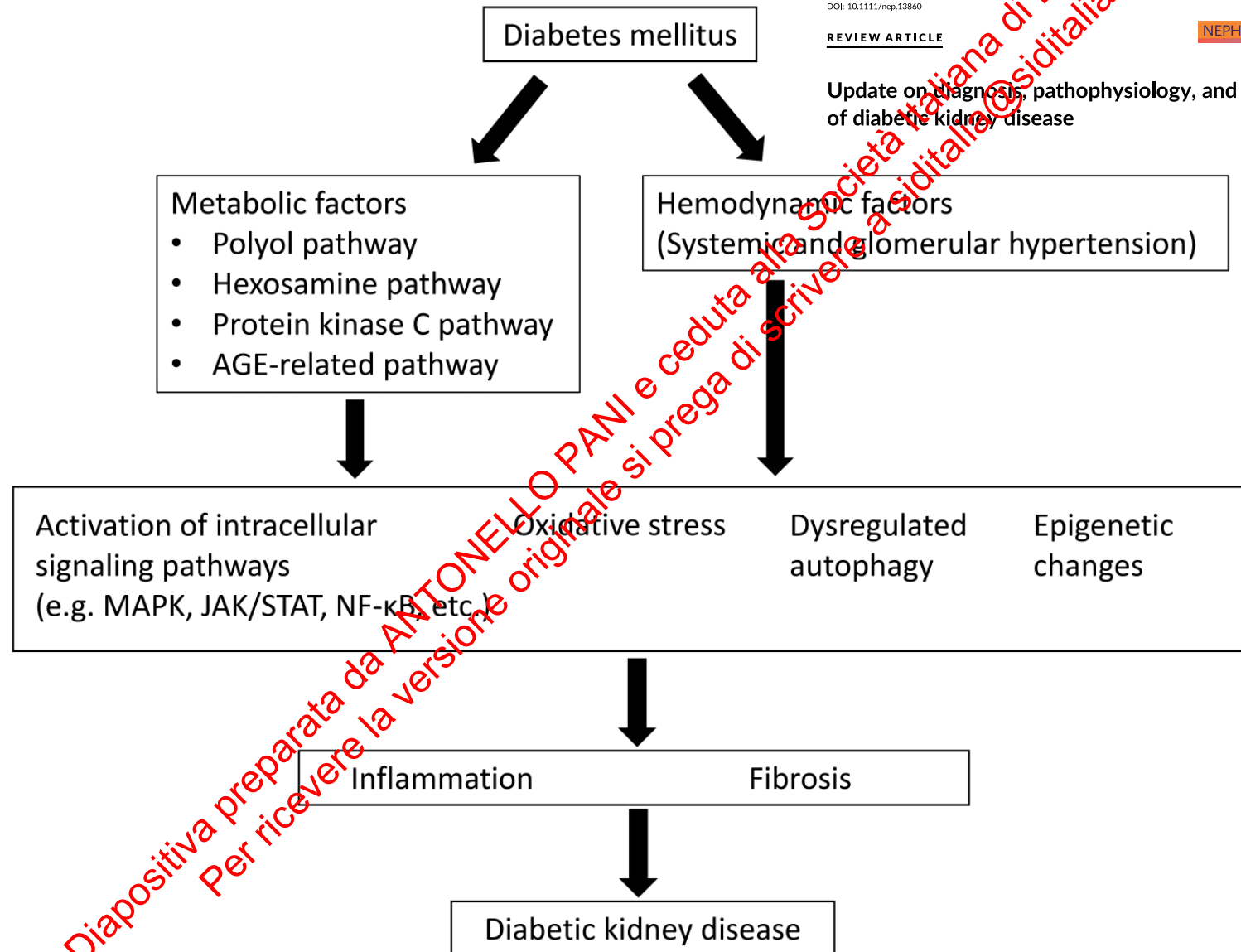
Received: 4 January 2021 | Accepted: 2 February 2021
DOI: 10.1111/nep.13860

REVIEW ARTICLE

NEPHROLOGY  WILEY

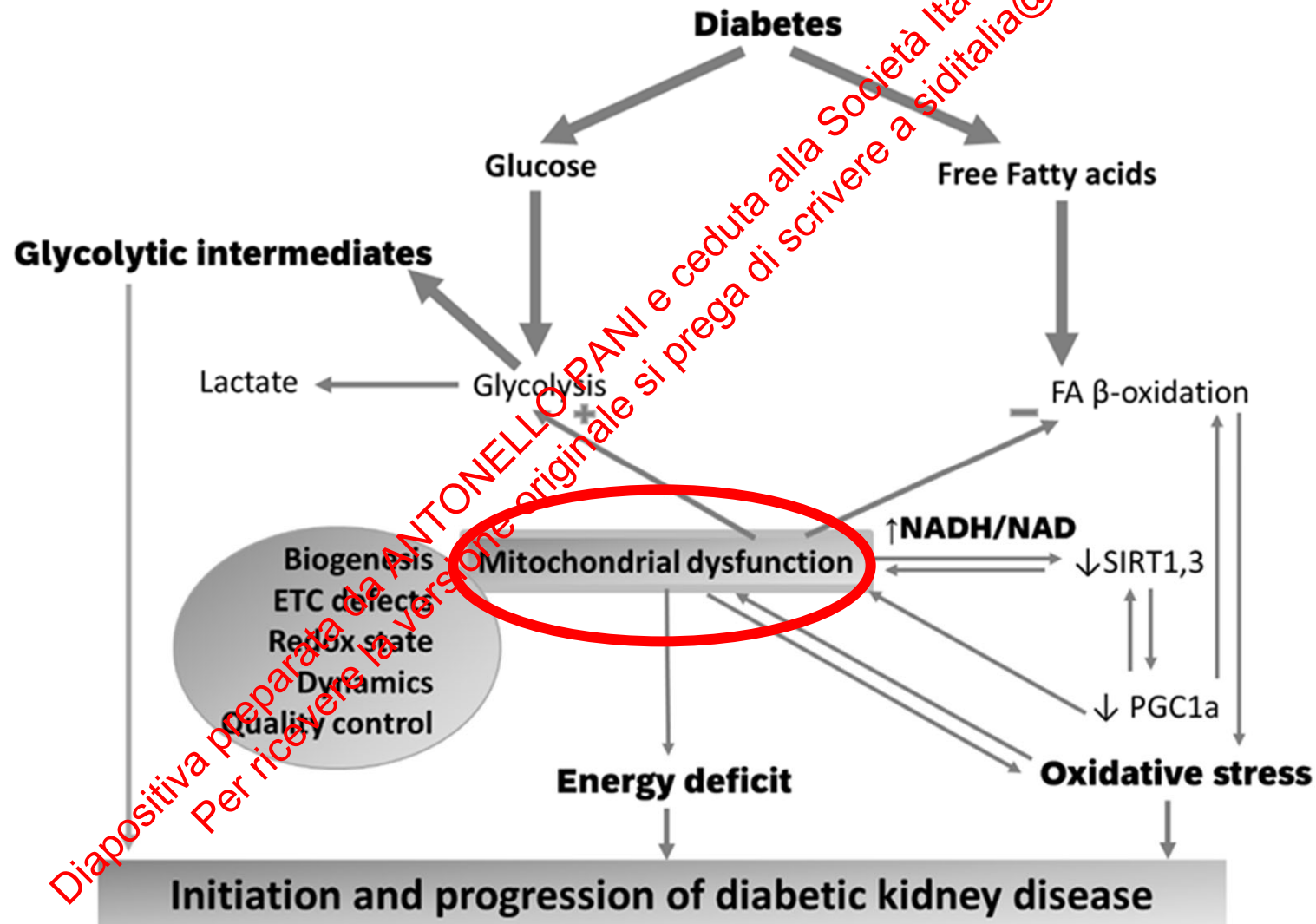
Update on diagnosis, pathophysiology, and management
of diabetic kidney disease

2021



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Excessive energetic substrates in diabetes leads to mitochondrial defects that cause reductive stress, oxidative stress, and energy deficit.



Innate immunity in diabetic kidney disease

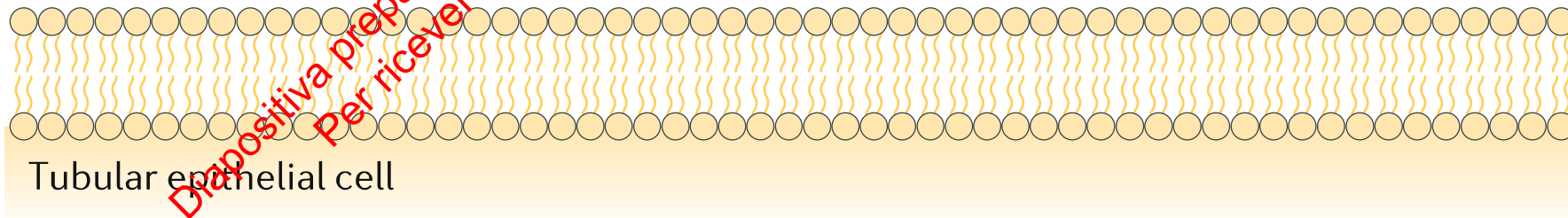
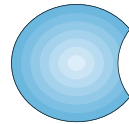
Sydney C. W. Tang * and Wai Han Yiu

The role of inflammation in the pathogenesis of diabetic kidney disease



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Potential mechanisms of complement activation in diabetic kidney disease.



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Domanda 1:

Quali sono i fattori determinanti la progressione del danno renale nella DKD?

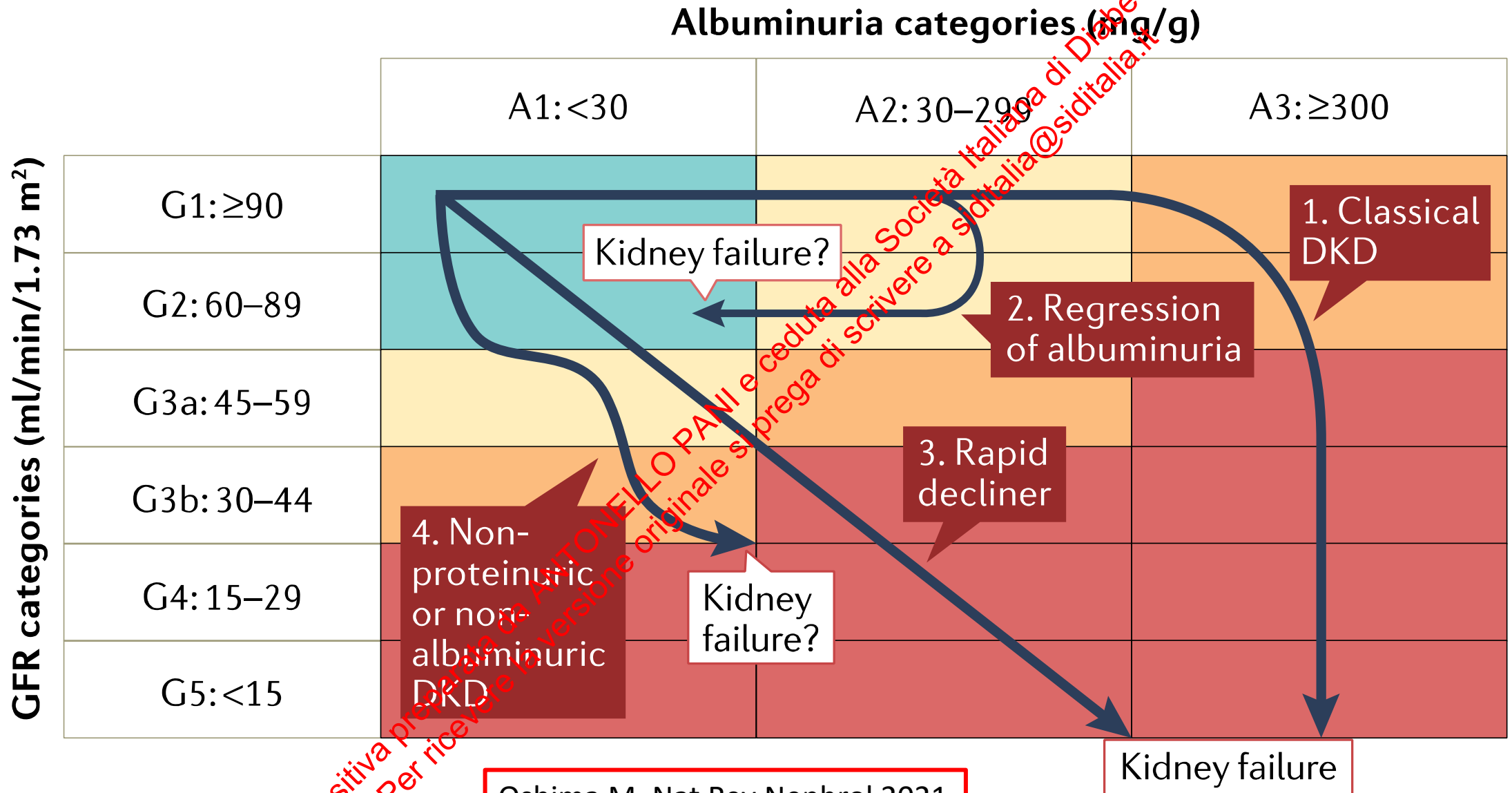
- a) Immunologici
- b) Metabolici ed emodinamici
- c) «Meccanici» (ipertensione glomerulare)
- d) Tutti

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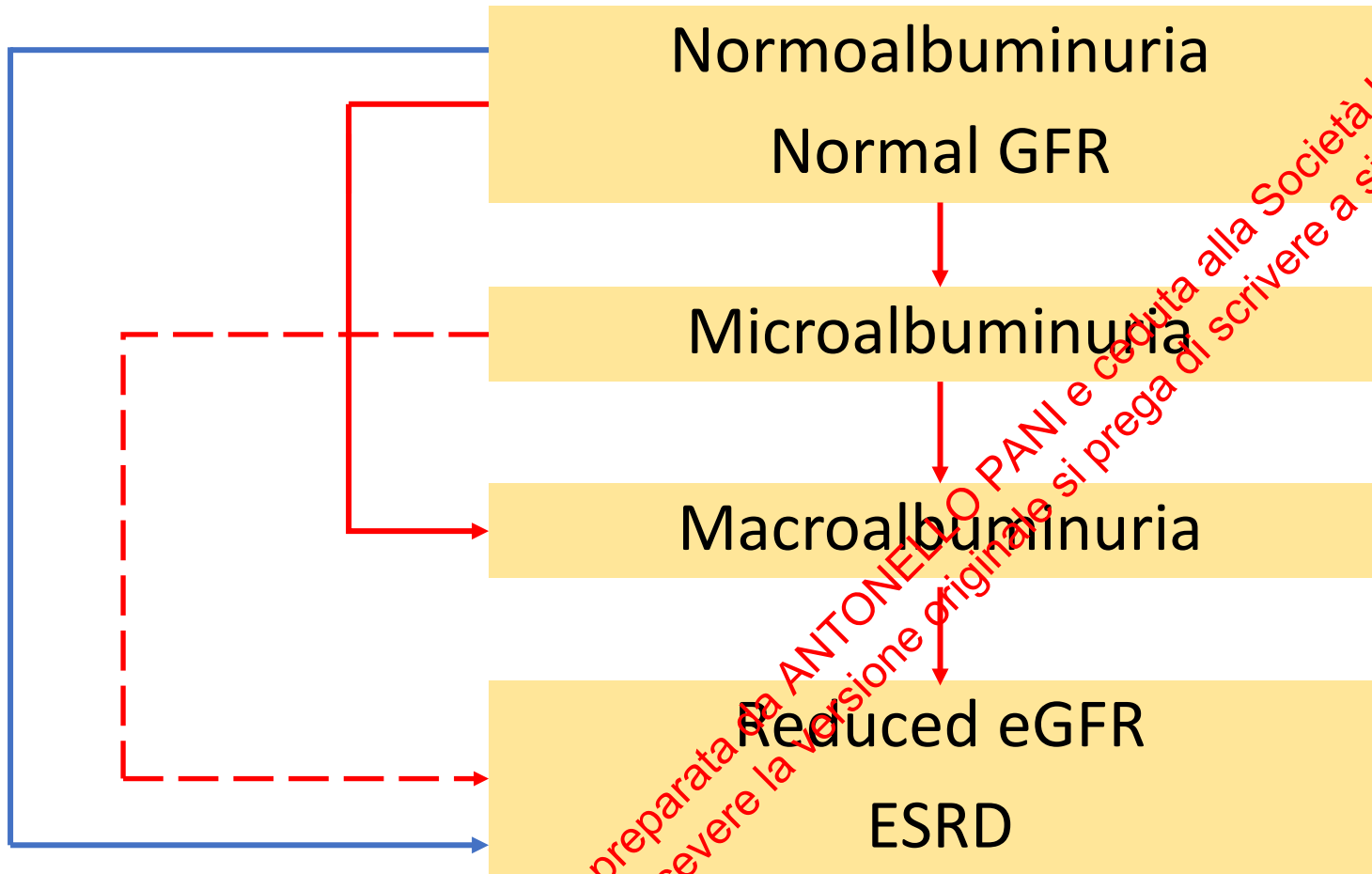
LE PIU' RECENTI EVIDENZE ARRICCHISCONO
LE CONOSCENZE CIRCA LA PATOGENESI
DELLA NEFROPATIA DIABETICA
SOTTOLINEANDO IL RUOLO
DELL'INFIAMMAZIONE, DELLA DISFUNZIONE
MITOCONDRIALE, DEL SISTEMA DEL
COMPLEMENTO E LA CENTRALITA' DEL
DANNO TUBULARE

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Trajectories of kidney function in DKD.



Clinical diagnosis of DKD



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CARDIOVASCULAR EVENTS, DEATH

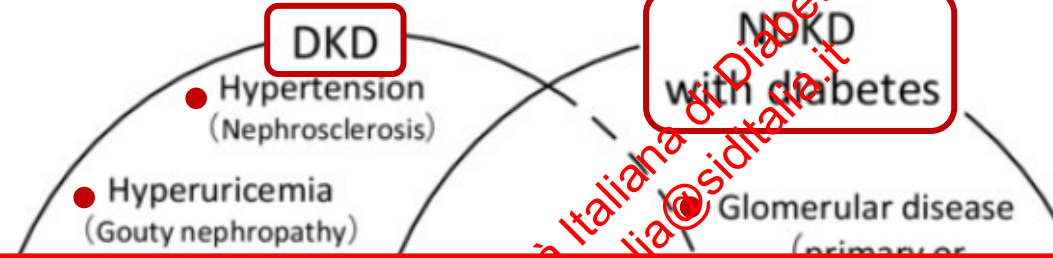
Natural history of DKD «non albuminuric» pattern

Natural history of DKD «albuminuric» pattern

DMT2

~4 million (Italy)

CKD $\approx$ 30% (at least)



**LA MALATTIA RENALE NEL PAZIENTE
DIABETICO SOTTENDE UN PANORAMA
ESTREMAMENTE ETEROGENEO IN TERMINI
DI PRESENTAZIONE CLINICA E STORIA
NATURALE**

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etc.

Multifactorial treatment
against metabolic disorders

Treatment against
each renal disease that cause

Perché effettuare una biopsia renale in un paziente diabetico?

- Finalità esclusivamente diagnostica?
- Finalità diagnostica + finalità prognostica
+ finalità terapeutica?

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Potential indications for renal biopsy in patients with diabetes

Biopsy not indicated when

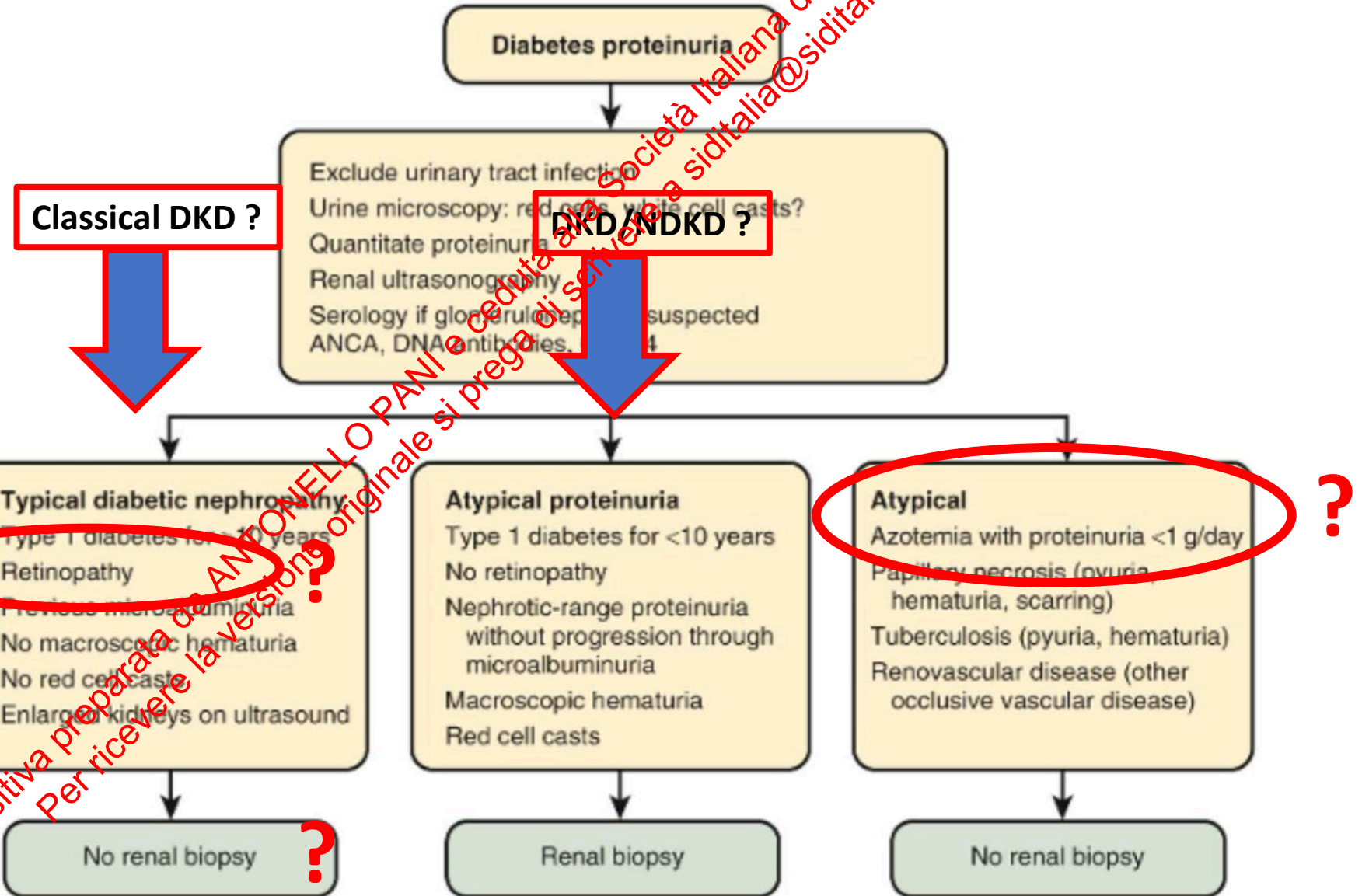
- Typical evolution of renal disease
- Concomitant retinopathy

Biopsy should be considered when

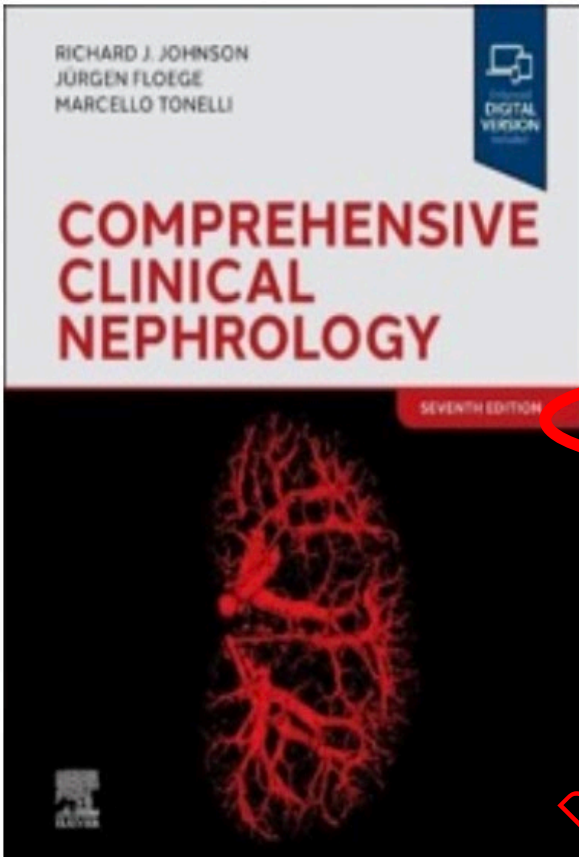
- Renal manifestations are seen atypically (≤ 10 years) early in type 1 diabetes
- Dysmorphic erythrocytes/casts are found (nephritic sediment)
- Rapid deterioration of renal function of unknown cause is noted
- Elevated serum creatinine without urine abnormalities
- Heavy proteinuria ($>5-8$ g/day) persists despite lowering of blood pressure

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Clinical Evaluation of Diabetic Nephropathy



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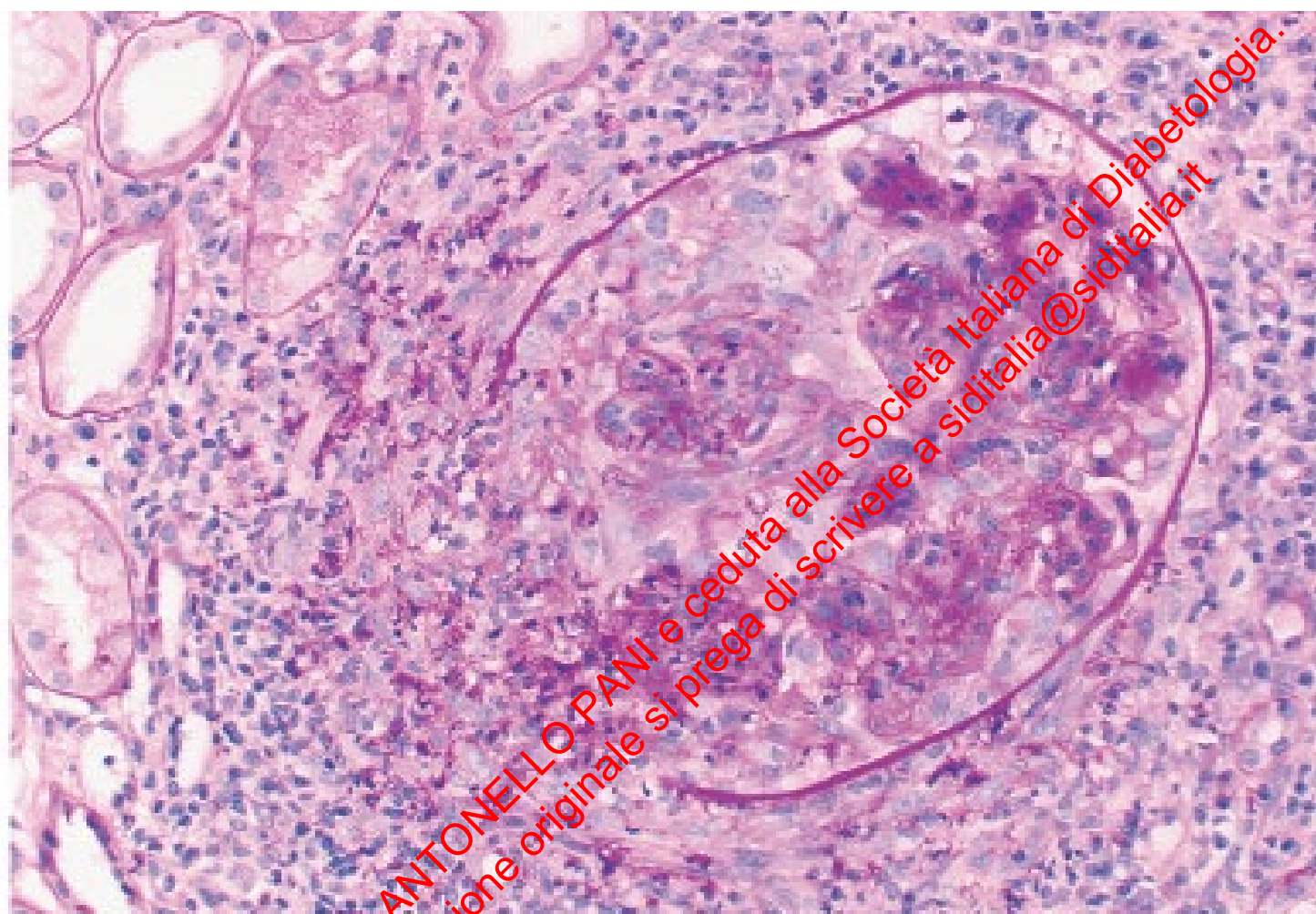


Figure 29.15 Glomerulonephritis superimposed on diabetic nephropathy. A glomerulus showing a cellular crescent with rupture of Bowman's capsule superimposed on nodular diabetic nephropathy. The patient, known to have diabetic nephropathy, presented with rapidly deteriorating renal function and red-cell casts in the urine.

Perché effettuare una biopsia renale in un paziente diabetico?

1) Identificare pazienti affetti da diabete mellito con lesioni renali NON secondarie alla patologia di base (non-diabetic kidney disease: **NDKD**)

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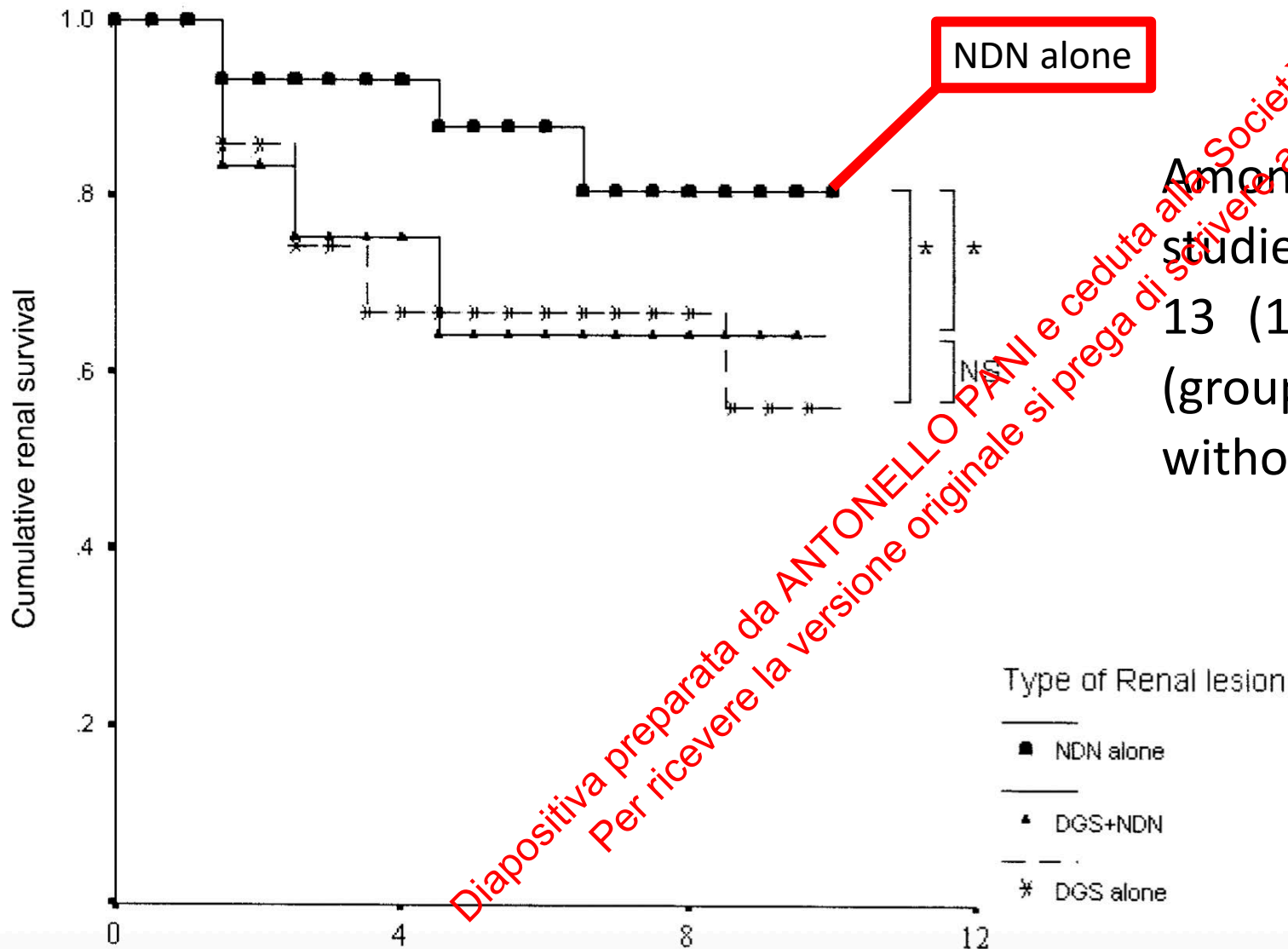
Indications for renal biopsy in patients with diabetes joint position statement of the Italian Society of Nephrology and the Italian Diabetes Society

Dati del Registro Italiano delle Biopsie Renali (RIBR) riguardanti 784 pazienti con diabete mellito tipo 2

Histology	N. Patients	%
Kimmeisteil Wilson DN	312	39.8
Idiopathic membranous nephropathy	85	10.8
IgA nephropathy	44	5.6
Nefroangiosclerosis	39	5.0
Tubule-interstitial nephritis	37	4.7
Primary FSGS	31	4.0
Minimal change GN	27	3.5
ESKD	18	2.3
Micropolyangitis	17	2.2
FSGS secondary to obesity	16	2.0
AA (secondary) amyloidosis	12	1.5
AL (secondary to multiple myeloma) amyloidosis	11	1.4
Focal segmental proliferative GN	11	1.4
Cast Nephropathy in multiple mieloma	11	1.4
Type 1 MPGN	9	1.1
Mesangial proliferative GN	8	1.0
Light chains disease	7	0.9
Granulomatosis with polyangitis	6	0.8
Rapidly progressive GN with crescents	6	0.8
Ischaemic nephropathy	6	0.8
Various diagnosis (less than 5)	66	8.4
Not diagnostic	5	0.6

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Renal Outcome in Type 2 Diabetic Patients With or Without Coexisting Nondiabetic Nephropathies



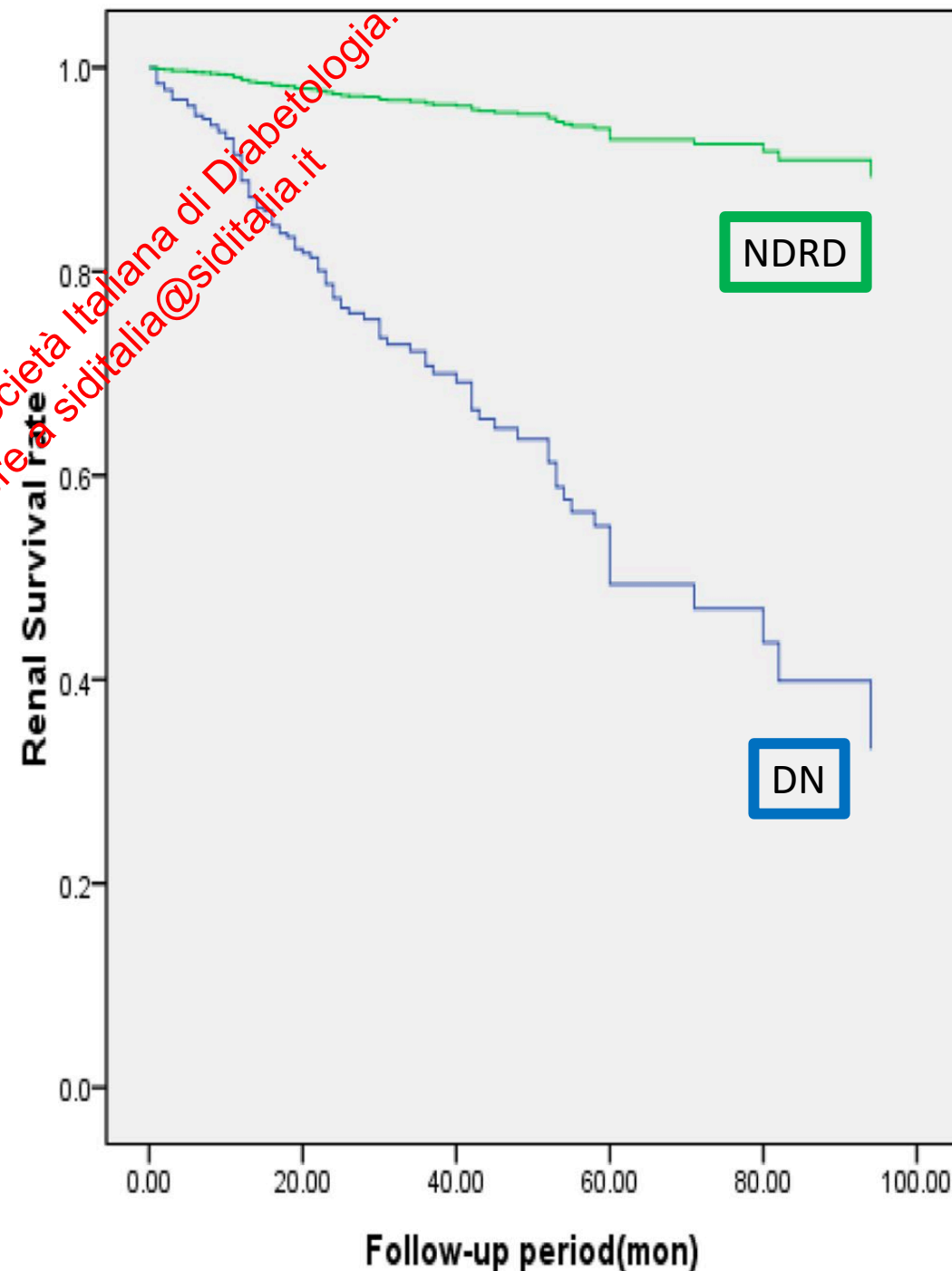
Among the 68 type 2 diabetic patients studied, 24 (35%) had DGS alone (group I), 13 (19%) had DGS coexisting with NDN (group II), and 31 (46%) had NDN alone without DGS (group III).

Identification of clinical predictors of diabetic nephropathy and non-diabetic renal disease in Chinese patients with type 2 diabetes, with reference to disease course and outcome

Jiali Wang^{1,2} · Qianqian Han¹ · Lijun Zhao¹ · Junlin Zhang¹ · Yiting Wang¹ · Yucheng Wu¹ · Tingli Wang¹ · Rui Zhang¹ · Premesh Grung¹ · Huan Xu³ · Fang Liu¹

A total of 505 T2DM patients with renal disease were eligible and enrolled in the present study. Renal biopsy revealed that:

- 302 patients (59.8%) had DN,
- 174 (34.5%) had NDRD, and
- 29 (5.7%) had NDRD superimposed on DN.



Renal biopsy in patients with diabetes: a pooled meta-analysis of 48 studies

Marco Fiorentino¹, Davide Bolignano^{2,3}, Vladimir Tesar⁴, Anna Pisano², Wim Van Biesen³, Giovanni Tripepi², Graziella D'Arrigo² and Loreto Gesualdo¹ on behalf of the ERA-EDTA Immunonephrology Working Group

The prevalence of DN, NDRD and mixed forms ranged from 6.5 to 94% (mean 50.1), 3 to 82.9% (mean 36.9) and 4 to 45.5% (mean 19.7) of the overall diagnoses, respectively. IgA nephropathy was the most common NDRD

Conclusions. NDRD are highly prevalent in patients with diabetes. Clinical judgment alone can lead to wrong diagnoses and delay the establishment of adequate therapies.

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(a) Study

Single study PPV

Event rate Lower limit Upper limit Z-Value p-Value

Zhuo et al.	0,065	0,039	0,107	-9,660	0,000
Sharma et al.	0,370	0,333	0,409	-6,398	0,000
Harada et al.	0,515	0,449	0,634	6,667	0,000
Zajari					
Yaqub					
Oh et al.					
Chong					
Zhang					
Haider					
Chang					
Biesen					
Mou et al.					
Bi et al.					
Lin et al.					
Ghani					
Arif et al.					
Zhou et al.					
Akimoto					
Pham et al.					
Prakas					
Kharra					
Huang					
Soni et al.					
Tone et al.					
Moger					
Rychlik					
Wong et al.					
Serra et al.					
Premaratne					
Mazzuca					
Castelli					
Suzuki					
Izzedine					
Nzerue					
Christie					
Lee et al.					
Condon					

(b) Study

Single study PPV

Event rate Lower limit Upper limit Z-Value p-Value

Zhuo et al.	0,065	0,039	0,107	-9,660	0,000
Sharma et al.	0,370	0,333	0,409	-6,398	0,000
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Castelli					
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Izzedine					
Nzerue					
Christie					
Lee et al.					
Condon					

(c) Study

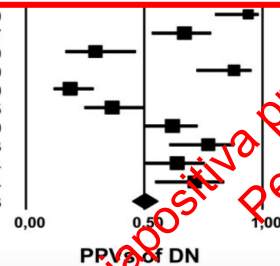
Single study PPV

Event rate Lower limit Upper limit Z-Value p-Value

Olsen et al.	0,090	0,029	0,246	-3,804	0,000
John et al.	0,213	0,137	0,316	-4,786	0,000
Gambara et al.	0,305	0,196	0,442	-2,734	0,006
Richards et al.	0,040	0,012	0,123	-5,135	0,000
Parving et al.	0,029	0,004	0,177	-3,486	0,000
Hironaka et al.	0,143	0,061	0,301	-3,708	0,000
	0,197	0,163	0,236	-11,943	0,000

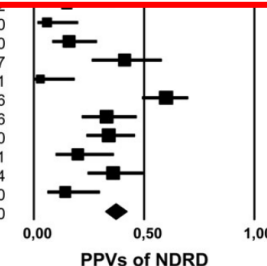
LA SOLA VALUTAZIONE CLINICA HA UNO SCARSO VALORE PREDITTIVO CIRCA IL QUADRO ISTOLOGICO RENALE NEL PAZIENTE DIABETICO

Schwartz et al.	0,940	0,798	0,984	3,921	0,000
Mak et al.	0,670	0,531	0,784	2,378	0,017
Fioretto et al.	0,294	0,166	0,465	-2,327	0,020
Olsen et al.	0,880	0,720	0,954	3,719	0,000
John et al.	0,187	0,116	0,287	-5,125	0,000
Gambara et al.	0,365	0,246	0,503	-1,922	0,055
Richards et al.	0,620	0,500	0,727	1,959	0,050
Parving et al.	0,771	0,605	0,881	3,018	0,003
Kleinknecht et al.	0,640	0,504	0,757	2,011	0,044
Hironaka et al.	0,714	0,545	0,839	2,446	0,014
	0,501	0,449	0,553	0,034	0,973

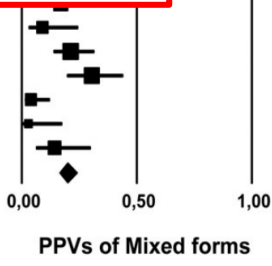


PPVs of DN

Schwartz et al.	0,100	0,067	0,141	-3,921	0,000
Mak et al.	0,160	0,083	0,287	-4,341	0,000
Fioretto et al.	0,412	0,261	0,581	-1,021	0,307
Olsen et al.	0,030	0,004	0,186	-3,406	0,001
John et al.	0,600	0,490	0,701	1,777	0,076
Gambara et al.	0,330	0,216	0,468	-2,401	0,016
Richards et al.	0,340	0,238	0,460	-2,591	0,010
Parving et al.	0,200	0,098	0,364	-3,281	0,001
Kleinknecht et al.	0,360	0,243	0,496	-2,011	0,044
Hironaka et al.	0,143	0,061	0,301	-3,708	0,000
	0,369	0,323	0,418	-5,149	0,000



PPVs of NDRD



PPVs of Mixed forms

RENAL DISEASE IN DIABETICS — WHICH PATIENTS HAVE DIABETIC NEPHROPATHY AND WHAT IS THEIR OUTCOME?*

Indicazioni alla biopsia

Indicazione	N di pazienti
Sindrome nefrosica	24
Proteinuria	23
Insufficienza renale	5 (2 AKI)
Ematuria	1

Lesioni istologiche

Lesione istologica	N. di pazienti
Nefropatia diabetica	39 (73%)
Glomerulonefriti	4
Pielonefrite acuta	1
Necrosi papillare	1
Inadeguata per diagnosi	2
Altro (non DM)	6

RENAL DISEASE IN DIABETICS — WHICH PATIENTS HAVE DIABETIC NEPHROPATHY AND WHAT IS THEIR OUTCOME?*

Fattori di rischio per nefropatia diabetica vs nefropatia non diabetica

	Nefropatia diabetica	Nefropatia non diabetica	P-value
Durata del diabete (anni)	13.1 (8.3)	9.2 (11)	> 0.1
Età di esordio del diabete (anni)	29.9 (17.7)	41.6 (23.4)	> 0.1
Età alla biopsia renale (anni)	42,8 (13.1)	50.4 (17.7)	> 0.1
Insulino-dipendenza	28 (72%)	3 (25%)	< 0.05
Ipertensione	23 (85%)	9 (75%)	> 0.1
Retinopatia diabetica	24 (87%)	3 (75%)	< 0.001
Sindrome nefrosica	20 (39%)	4 (33%)	> 0.1

Different Patterns of Renal Damage in Type 2 Diabetes Mellitus: A Multicentric Study on 393 Biopsies

Gianna Mazzucco, MD, Tullio Bertani, MD, Mirella Fortunato, MD, Monica Bernardi, MD,
Monica Leutner, MD, Renzo Boldorini, MD, and Guido Monga, MD

1997-2000 -> Biopsia renale in 393 pazienti affetti da diabete mellito tipo 2 in
3 Centri Italiani: Torino, Novara (restricted policy, CRPs) e Bergamo
(unrestricted policy, CUP)

Restricted policy (CRPs)

- Ematuria
- Sindrome nefrosica
- Proteinuria > 2 g/d senza retinopatia diabetica
- Insufficienza renale rapidamente evolutiva
- Insufficienza renale di nda

Unrestricted policy (CUP)

- Proteinuria > 0.5 g/d
- Ematuria
- Riduzione della funzione renale

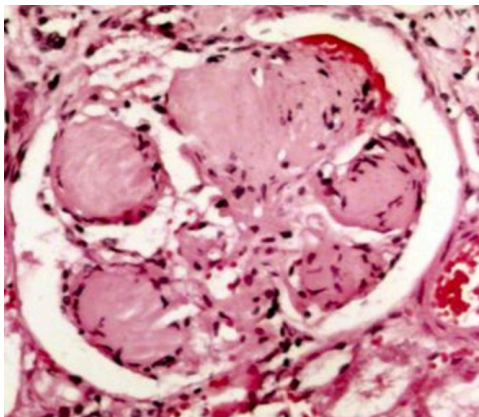
Pazienti con lunga storia di DM e segni di severo danno d'organo microangiopatico non venivano sottoposti a biopsia renale (diagnosi clinica di ND)

Different Patterns of Renal Damage in Type 2 Diabetes Mellitus: A Multicentric Study on 393 Biopsies

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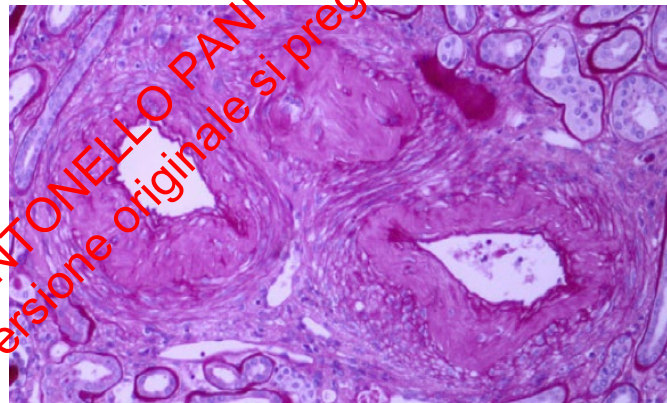
3 CLASSI SULLA BASE DEL DATO ISTOLOGICO

Classe 1



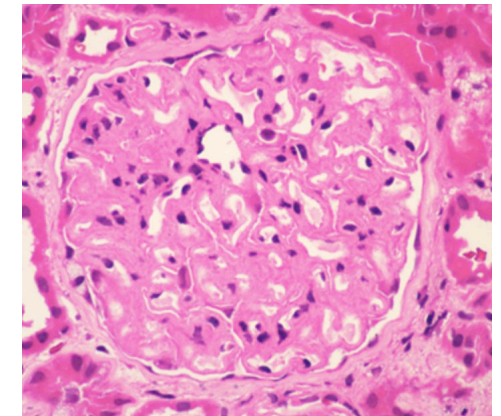
Glomerulosclerosi diabetica

Classe 2



Lesioni vascolari

Classe 3



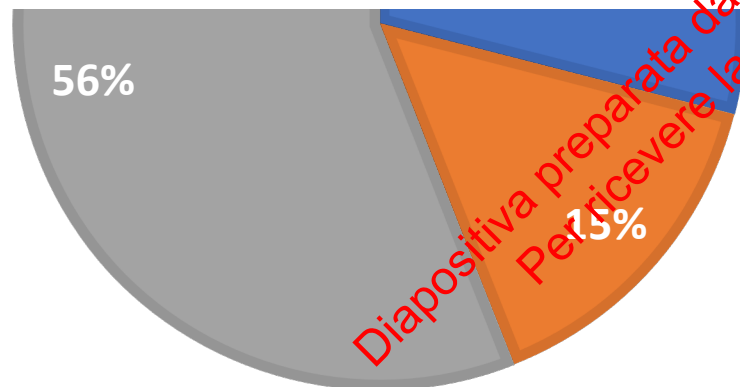
Nefropatia non-diabetica
associata a nefropatia
diabetica (3a) o non
associata (3b)

Diapositiva preparata da ANTONELLO PANI e ceduta alla Società Italiana di Diabetologia.
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Different Patterns of Renal Damage in Type 2 Diabetes Mellitus: A Multicentric Study on 393 Biopsies

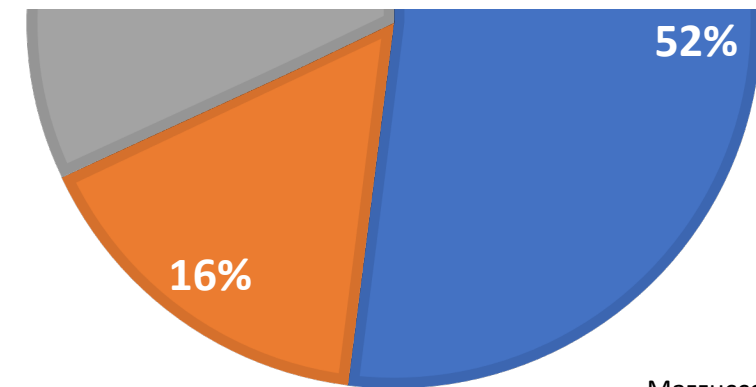
Gianna Mazzucco, MD, Tullio Bertani, MD, Mirella Fortunato, MD, Monica Bernardi, MD,
Monica Leutner, MD, Renzo Boldorini, MD, and Guido Monga, MD

DIFFERENTI INDICAZIONI ALLA BIOPSIA
RENALE DETERMINANO UNA SIGNIFICATIVA
DIFFERENZA IN TERMINI DI LESIONI RENALI
OSSERVATE ALL'ESAME ISTOLOGICO



Classe 2: N.S.

Classe 3: $P < 0.0001$



Nefropatia Diabetica, Non Diabetica, forme miste

The Modern Spectrum of Renal Biopsy Findings in Patients with Diabetes

Shree G. Sharma,^{*} Andrew S. Bomback,[†] Jai Radhakrishnan,[‡] Leal C. Herlitz,[‡] Michael B. Stokes,[‡] Glenn Markowitz,[‡] and Vivette D. D'Agati[‡]

CJASN 2013

Analisi di 2642 biopsie: 620 erano pazienti diabetici

LA DIAGNOSI ISTOLOGICA HA PERMESSO DI
MODIFICARE L'APPROCCIO TERAPEUTICO IN
CIRCA UN PAZIENTE DIABETICO SU TRE

186 (30%) pz avevano lesioni che hanno richiesto terapie particolari

Nefropatia Diabetica, Non Diabetica, forme miste



Characteristics	DN Alone	DN Plus NDRD	NDRD Alone
Participants (n)	227	164	220
Age (yr)	59 (49–65)	63 (55–70) ^a	63 (54–70) ^b
Male sex	129 (56.8)	90 (61.6)	142 (64.6)
Race			
Unknown	108 (47.6)	51 (34.8) ^a	104 (47.3) ^c
White	62 (27.3)	63 (38.4) ^a	70 (31.8)
African American	39 (17.2)	33 (20.1)	29 (13.2)
Hispanic	12 (5.3)	7 (4.3)	8 (3.6)
Asian	4 (1.8)	4 (2.4)	7 (3.2)
Other	2 (0.9)	0 (0.0)	2 (0.9)
DM type 1	9 (4.0)	5 (3.1)	2 (0.9) ^b
Duration of DM (yr)	13 (8–17)	10 (7–18)	5 (3–10) ^{b,c}
Serum creatinine (mg/dl)	2.3 (1.5–3.8)	3.1 (1.7–5.2) ^a	2.3 (1.5–4.4) ^c
eGFR (ml/min per 1.73 m ²)	31.2 (17.5–35.2)	21.4 (12.5–46.6) ^a	32.5 (14.3–60.0) ^c
Proteinuria (g/d)	5.0 (2.8–8.8)	5.0 (2.0–8.0)	2.9 (1.4–7.1) ^{b,c}

Of 620 patients with diabetes who underwent biopsy, 611 had adequate tissue for diagnosis. Categorical variables are expressed as n (%); continuous variables are expressed as median (interquartile range). DN, diabetic nephropathy; NDRD, nondiabetic renal disease; DM, diabetes mellitus; eGFR, estimated GFR.

^aP<0.05 for comparison of DN plus NDRD versus DN alone subgroups.

^bP<0.05 for comparison of NDRD alone versus DN alone subgroups.

^cP<0.05 for comparison of NDRD alone versus DN plus NDRD subgroups.

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Tipo di Nefropatia Non Diabetica



Table 2. Summary of NDRD, with and without DN, found on biopsies of patients with diabetes

Types of NDRD (n)	NDRD Alone (n=220)	DN Plus NDRD (n=164)	P Value ^a
Acute tubular necrosis (109)	38 (17.3)	70 (43.3)	<0.001
FSGS (69)	48 (21.8)	21 (12.8)	0.02
Primary FSGS (6)	6 (2.7)	0 (0.0)	0.03
Secondary FSGS (63) ^b			
HTN related	19 (8.6)	10 (6.1)	0.35
HTN plus obesity related	16 (7.3)	10 (6.1)	0.65
Obesity related	4 (1.8)	1 (0.6)	0.30
Other ^c	3 (1.4)	0 (0.0)	0.13
Hypertensive nephrosclerosis (70) ^b	39 (17.7)	31 (18.9)	0.77
IgA nephropathy (35)	23 (10.5)	12 (7.3)	0.29
Membranous GN (23)	18 (8.2)	5 (3.0)	0.04
Pauci-immune crescentic GN (19)	15 (6.8)	4 (2.4)	0.05
Acute interstitial nephritis (18)	11 (5.0)	7 (4.3)	0.73
Amyloidosis (10)	4 (1.8)	0 (0)	0.01
Myeloma cast nephropathy (10)	8 (3.6)	2 (1.2)	0.14
Acute postinfectious GN (6)	3 (1.4)	3 (1.8)	0.72
Atheroembolic disease (5)	2 (0.9)	3 (1.8)	0.43
Others (10)	5 (2.3)	5 (3.0)	0.64

Values are expressed as n (%). NDRD, nondiabetic renal disease; DN, diabetic nephropathy; HTN, hypertension.

^aP value is from a two-sample test of proportions

^bThirteen cases of secondary FSGS in the NDRD alone subgroup and 16 cases of secondary FSGS in the DN plus NDRD subgroup also showed features of hypertensive nephrosclerosis.

^cIncludes increased muscle mass (n=1), solitary kidney (n=1), and familial FSGS (n=1)

Durata del diabete e altro.....



- **5.9 anni nefropatia non diabetica vs 10.6 anni nefropatia diabetica (p <0.001 - Chang, 2011)**

“Whereas AKI, low complements, and positive M-spike suggest an increased likelihood of finding NDRD on biopsy, long duration of DM emerged as the strongest predictor of finding DN alone”.

Approximately one-quarter of all renal biopsies are performed in patients with DM. Judicious use of renal biopsy has uncovered NDRD alone or superimposed on DN in the majority of such biopsies. ATN is emerging as an important category of NDRD, which has not been reported previously.

Identifying Parameters to Distinguish Non-Diabetic

48.1.31

Akimoto

Bi H 201

Chang 1

Study or Subgroup	diabetic retinopathy(+)		diabetic retinopathy(-)		Weight	Odds Ratio M-H, Random, 95% CI	Odds Ratio M-H, Random, 95% CI
	Events	Total	Events	Total			
42.1.1 all							
Akimoto T 2008	7	28	9	22	5.6%	0.49 [0.14, 1.61]	
Bi H 2011	10	102	90	118	6.7%	0.03 [0.02, 0.07]	
Chang TI 2011	17	51	59	68	6.3%	0.08 [0.03, 0.19]	
Chong YB 2012	17	67	17	22	5.7%	0.10 [0.03, 0.31]	
Fu SX 2007	0	11	26	42	2.3%	0.03 [0.00, 0.49]	
Ghani AA 2009	3	14	11	17	1.5%	0.15 [0.03, 0.75]	
Huang FX 2005	3	17	17	35	5.0%	0.23 [0.06, 0.93]	
Kanauchi M 2001	3	14	7	9	3.7%	0.08 [0.01, 0.59]	
Lee FX 2008	1	6	12	16	2.0%	0.05 [0.00, 0.56]	

Conclusions: We identified that the absence of DR, shorter duration of DM, lower HbA1C, and lower BP may help to distinguish NDRD from DN in patients with diabetes. This could assist clinicians in making a safe and sound diagnosis and lead to more effective treatments.

Heterog

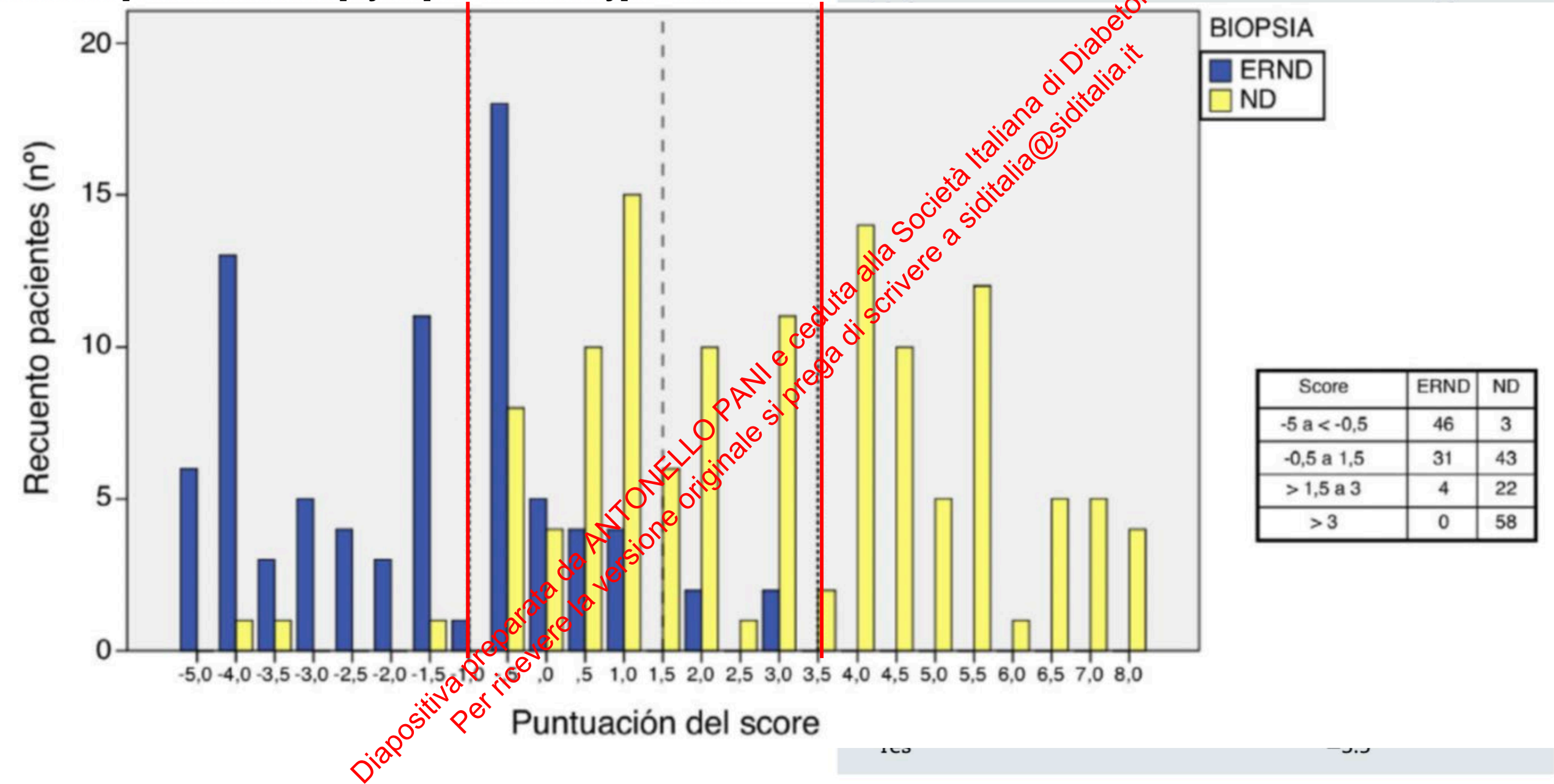
Test for

Suzuki D 2001	8	54	20	44	6.2%	0.21 [0.08, 0.54]	
Tone A 2005	4	24	54	57	4.6%	0.01 [0.00, 0.05]	
Wong TY 2002	8	25	36	43	5.7%	0.09 [0.03, 0.29]	
Zhou JH 2005	5	51	14	59	5.8%	0.35 [0.12, 1.05]	
Subtotal (95% CI)		702		908	100.0%	0.15 [0.09, 0.26]	
Total events	203		638				
Heterogeneity: $\tau^2 = 0.94$; $\chi^2 = 68.08$, $df = 18$ ($P < 0.00001$); $I^2 = 74\%$							
Test for overall effect: $Z = 6.95$ ($P < 0.00001$)							

0.002 0.1 1 10 500
Favours DR(+) Favours DR(-)

When to perform renal biopsy in patients with type 2

Table 5 – Score of points according to risk factor of diabetic nephropathy.



Design and validation of a scoring model for differential diagnosis of diabetic nephropathy and nondiabetic renal diseases in type 2 diabetic patients

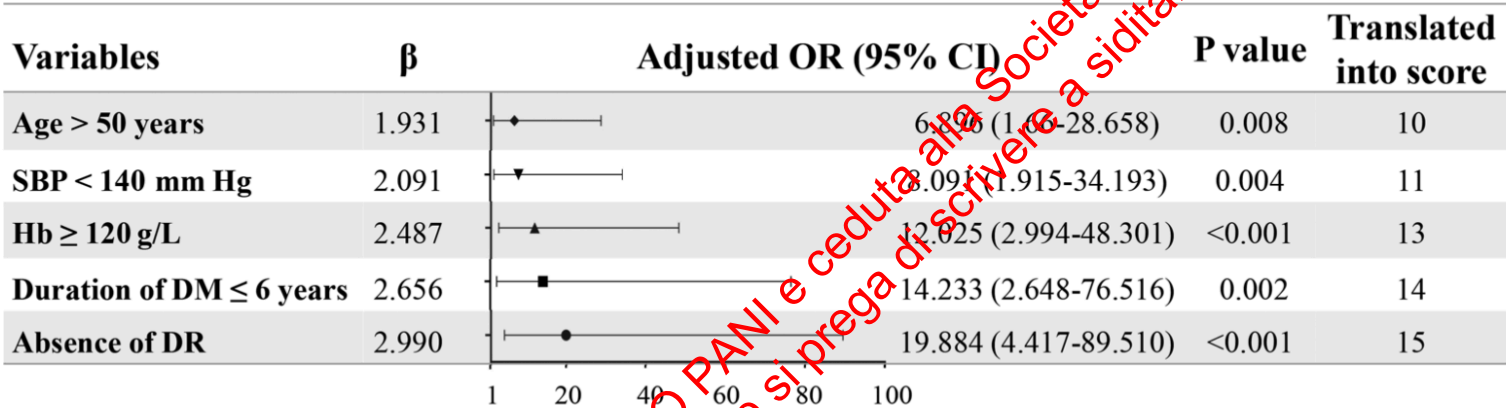
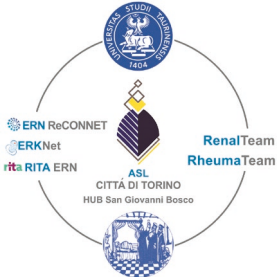


FIGURE 2 Logistic regression model and score derived from it for prediction of NDRD vs DN. The different symbols and horizontal lines represent the diagnostic OR and corresponding 95% CI, respectively. DM, diabetes mellitus; DN, diabetic nephropathy; DR, diabetic retinopathy; Hb, hemoglobin; NDRD, nondiabetic renal disease; OR, odds ratio; SBP, systolic blood pressure

Cutoff points	Sensitivity (%)	95% CI	Specificity (%)	95% CI	Yoden index
>24	100	95-100	63	48-77	0.63
>29	97	90-100	85	71-94	0.82
>37	91	82-97	87	74-95	0.78
>39	80	69-89	96	85-100	0.76
>52	41	30-54	98	89-100	0.39

TABLE 5 Performance of the score model at different cutoff points



The Giovanni Bosco Hub Hospital experience on 300 renal biopsies in diabetic patients



DM patients who underwent renal biopsy over a period of approximately 10 years



MONOCENTRIC RETROSPECTIVE COHORT STUDY

University Department of Nephrology-Dialysis & CMID (Center of Immuno-Rheumatology and Rare Diseases) of San Giovanni Bosco Hospital in Turin

INCLUSION CRITERIA



PATIENTS WITH DIABETES MELLITUS (TYPE 1 AND 2)



KIDNEY BIOPSY FOR ALL REASONS

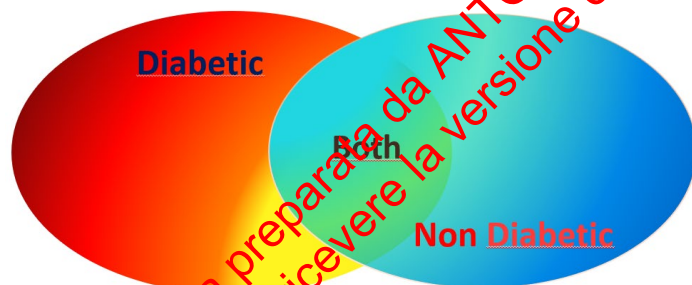
1 January 2014

31 July 2023

9 years and months

BIOPSY INDICATIONS

- Proteinuria
- Worsening of GFR
- Low GFR + proteinuria



1990 biopsies performed

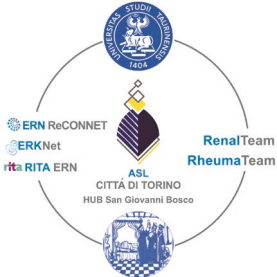
Baseline

297 patients with diabetes included (14.9%)

Characteristics	Total (n° 297)	DN alone (n° 112)	DN + NDRD (n° 56)	NDRD alone (n° 129)
Sex (m/f)	214/83	90/22	42/14	82/47
Age (years)	66.1 ± 11.2	63.6 ± 11.4	67.6 ± 9.6	67.6 ± 11.4
BMI	28.7 ± 5.5	28.7 ± 5.5	30.2 ± 5.2	28 ± 5.6
Smoke (no/yes/ex/not available)	111/75/81/30	36/43/28/5	18/11/18/9	57/21/35/16
Statin (no/yes)	150/147	50/62	26/30	74/55
Hypertension (no/yes)	32/265	7/105	5/51	20/109
ACEi - ARB therapy (no/yes)	113/184	39/73	18/38	56/73
Lower limb vasculopathy (no/yes/not available)	196/82/19	69/37/6	38/13/5	89/32/8
Retinopathy (no/yes/not available)	174/76/47	47/51/14	30/16/10	97/9/23

NO differences:

- Proteinuria
- Serum creatinine
- eGFR (CKD-EPI)
- Lower limb vasculopathy
- Biopsy indication



The Giovanni Bosco Hub Hospital experience on 300 renal biopsies in diabetic patients



Characteristics	Total (n° 297)	DN alone (n° 112)	DN + NDRD (n° 56)	NDRD alone (n° 129)
Diabetes duration (years)	12.7 ± 8.9	14.6 ± 8.8	14.9 ± 8.4	9.9 ± 8.5
Diabetes therapy:				
- Insulin	133 (45%)	63 (56%)	28 (50%)	42 (33%)
- HA	105 (35%)	28 (25%)	18 (32%)	59 (46%)
- Insulin + HA	27 (9%)	11 (10%)	8 (14%)	8 (6%)
- Diet	32 (11%)	10 (9%)	2 (4%)	20 (15%)
Serum creatinine (mg/dl)	3 ± 2.5	2.98 ± 2.5	3.4 ± 2.7	3.0 ± 2.3
eGFR (ml/min per 1.73 m ²)	37.5 ± 28.5	38 ± 28.4	34 ± 26.1	38 ± 29.7
CKD classes				
- Class I	22 (7%)	11 (10%)	5 (9%)	9 (7%)
- Class II	41 (14%)	11 (10%)	5 (9%)	22 (17%)
- Class III	83 (28%)	35 (31%)	17 (30%)	31 (24%)
- Class IV	77 (26%)	27 (24%)	16 (29%)	34 (26%)
- Class V	74 (25%)	28 (25%)	13 (23%)	33 (26%)
Hematuria (n/y)	198/99	82/30	39/17	77/3
Proteinuria (g/day)	3.4 ± 3.4	3.2 ± 2.6	4.3 ± 4.8	3.2 ± 3.4
Albuminuria (mg/l)	1420.4 ± 1732	1317.1 ± 1489	1685 ± 1746	1400 ± 1907
Indication for biopsy				
- Proteinuria	113 (38.1%)	42 (37%)	25 (45%)	46 (36%)
- WRF	43 (14.5%)	13 (12%)	5 (9%)	25 (19%)
- Proteinuria + WRF	140 (47.1%)	56 (50%)	26 (46%)	58 (45%)
- Nephrectomy	1 (0.3%)	1 (1%)	0 (0%)	0 (0%)

- **Group 1 – 112 pts (38%): Diabetic Nephropathy (DN): alone**
- **Group 2 – 56 pts (19%): DN + Non Diabetic Renal Disease (NDRD)**
- **Group 3 – 129 pts (43%): NDRD**

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The Giovanni Bosco Hub Hospital experience on 300 renal biopsies in diabetic patients



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- Insulin + HA	27 (9%)	11 (10%)	8 (14%)	8 (6%)
- Diet	32 (11%)	10 (9%)	2 (4%)	20 (15%)
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- Nephrectomy	1 (0.3%)	1 (1%)	0 (0%)	0 (0%)

DIFFERENCES BETWEEN GROUPS

Mean BMI > in group 2 than group 3 (p=0.01)

HISTORY OF DIABETES: longer in groups 1 (DN alone) and 2 (DN + NDRD) than in group 3 (NDRD) (p=0.00008 and 0.0004).

RETINOPATHY: 45% in group 1, 29% in group 2, 7% in group 3. Difference when comparing group 1 and group 2 with group 3 (p=0.00001 and 0.00005).

INSULIN THERAPY: higher number of patients in group 1 and 2 than in group 3 (p=0.0002 and 0.02).

LOGISTIC REGRESSION

to determine predictors for histopathological diagnosis of DKD

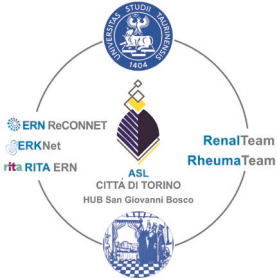
Covariates: duration of diabetes, presence of retinopathy, hypertension, serum creatinine values, eGFR values and 24-hour urinary protein excretion



None of them was found to be statistically significant.

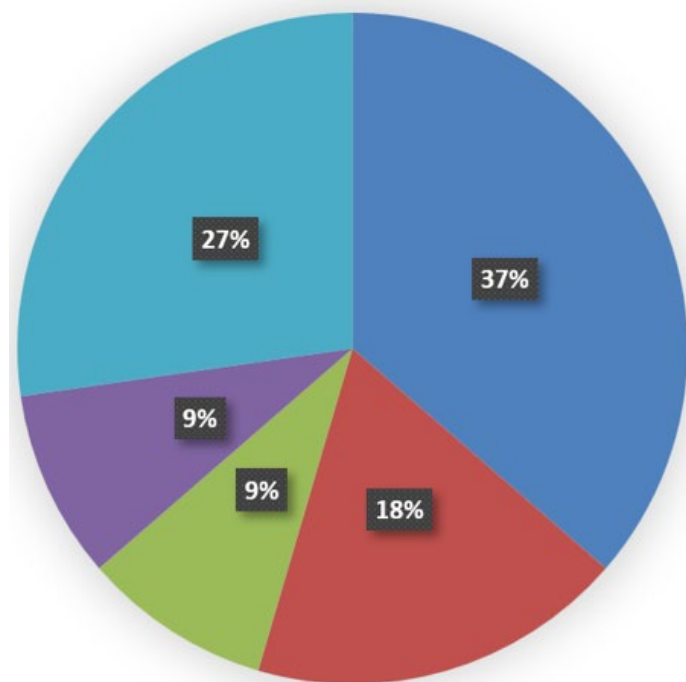
Duration of T2DM not always reliable and easy to establish.

42% of patients with DN had no retinopathy.
7% of patients with NDRD had retinopathy.

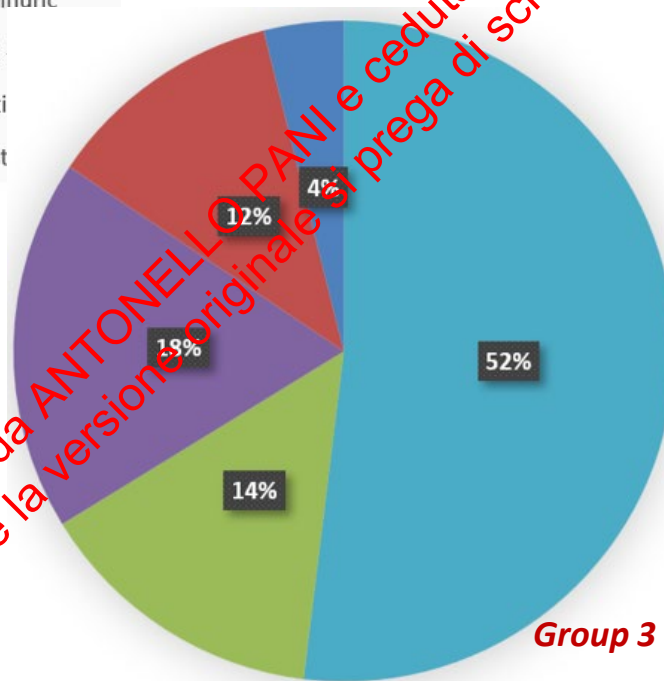
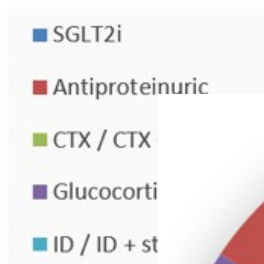


Group 2

The Giovanni Bosco Hub Hospital experience on 300 renal biopsies in diabetic patients

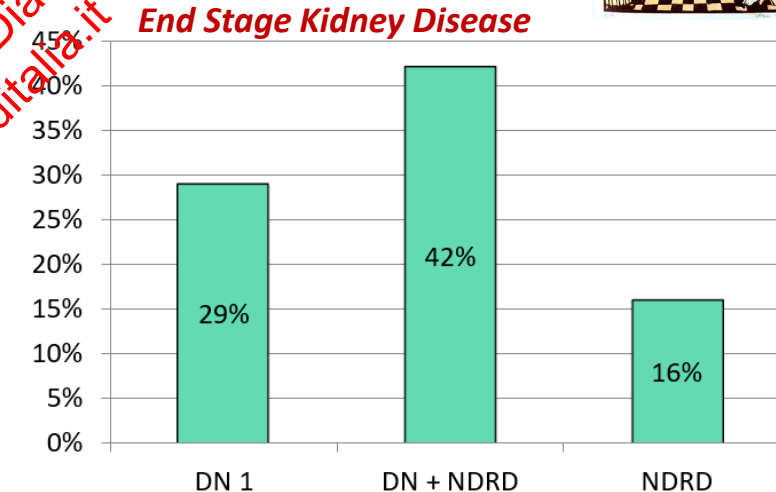


- 22 of 56 patients (39%) changed their therapy
- 10 of these patients received a SPECIFIC treatment

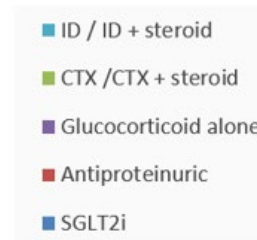


Group 3

- 77 of 129 patients (60%) changed their therapy
- 65 of these patients received a SPECIFIC treatment



Patients in G1 and G2 were more likely to develop ESRD than those in G3 (p=0.03 and 0.002)



Diapositiva preparata da ANTONELLO PANI e ceduta alla Società Italiana di Diabetologia.
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Our experience (1994-2012)

From 1374 renal biopsies performed in our division (S.C.D.U. Nefrologia, Dialisi e Trapianto, ARNAS Brotzu) from January 1994 to February 2012

Patient profile: mean age (yrs): 61.7 ± 13.9 ; M/F: 1.59; Type I Diabetes (%): 8; onset of diabetes (yrs): 11.9 ± 9.5 ; onset of microalbuminuria (yrs): 5.3 ± 5.4 .

Renal Biopsy Clinical Criteria:

1. Rapid onset of: nephrotic syndrome, hematuria, proteinuria ≥ 0.5 to 1 g/24h, proteinuria ≥ 1 to < 3 g/24h; proteinuria > 3 g,
2. Nephritic Syndrome;
3. Acute Kidney Injury;
4. RPGN

Histological diagnosis	n	%	%ap
ACUTE TUBULAR NECROSIS	4	7.0	4.5
AMYLOIDOSIS	1	2.0	1.1
CAST NEPHROPATHY	2	3.9	2.3
PAUCIIMMUNE G.N.	4	7.0	4.5
CRYOGLOBULINEMIA	3	5.9	3.4
FSGS SECONDARY	3	5.9	3.4
ITUN	5	9.8	5.7
INTERSTITIAL NEPHRITIS	6	11.8	6.8
MEMBRANOUS G.N.	8	16	9.1
MESANGIOPROLIFERATIVE G.N.	1	2.0	1.1
MINIMAL CHANGE DISEASE	3	5.9	3.4
MPGN TYPE 1	1	2.0	1.1
NEPHROANGIOSCLEROSIS	6	12	6.8
NON HODGKIN LYMPHOMA	1	2.0	1.1
NORMAL KIDNEY	1	2.0	1.1
POSTINFECTIOUS G.N.	1	2.0	1.1
THROMBOTIC MICROANGIOPATHY	1	2.0	1.1
TOTAL (EXCLUDED DGS)	51	100	58
NDRD	39		44.3
NDRD + DGS	12		13.7
DIABETIC GLOMERULOSCLEROSIS	37		42.0
TOTAL BIOPSIES	88		100

Figure 1: Histological diagnosis in selected patients and prevalence of NDRD, NDRD & DGS, AND DGS alone. Number of cases (n); relative percentages in patients affected with NDRD (%); percentages obtained considering DGS patients

Criteria of Kidney biopsy in Diabetes, suspecting a NDKD

LA PRESENZA DI UNA DI QUESTE
CONDIZIONI RAPPRESENTA
UN'INDICAZIONE ASSOLUTA
ALL'ESECUZIONE DI BIOPSIA RENALE NEL
PAZIENTE DIABETICO (personal opinion del relatore)

complement factors (cryoglobulinemia).

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Domanda 2:

Qual è il motivo principale che giustifica l'esecuzione di una biopsia renale in un paziente diabetico con una sindrome clinica nefrologica?

- A. Per identificare esclusivamente lesioni renali di origine diabetica
- B. Per distinguere tra nefropatia diabetica (DKD) e malattia renale non diabetica (NDKD)
- C. La biopsia non è mai indicata nei pazienti diabetici
- D. Solo per scopi di ricerca

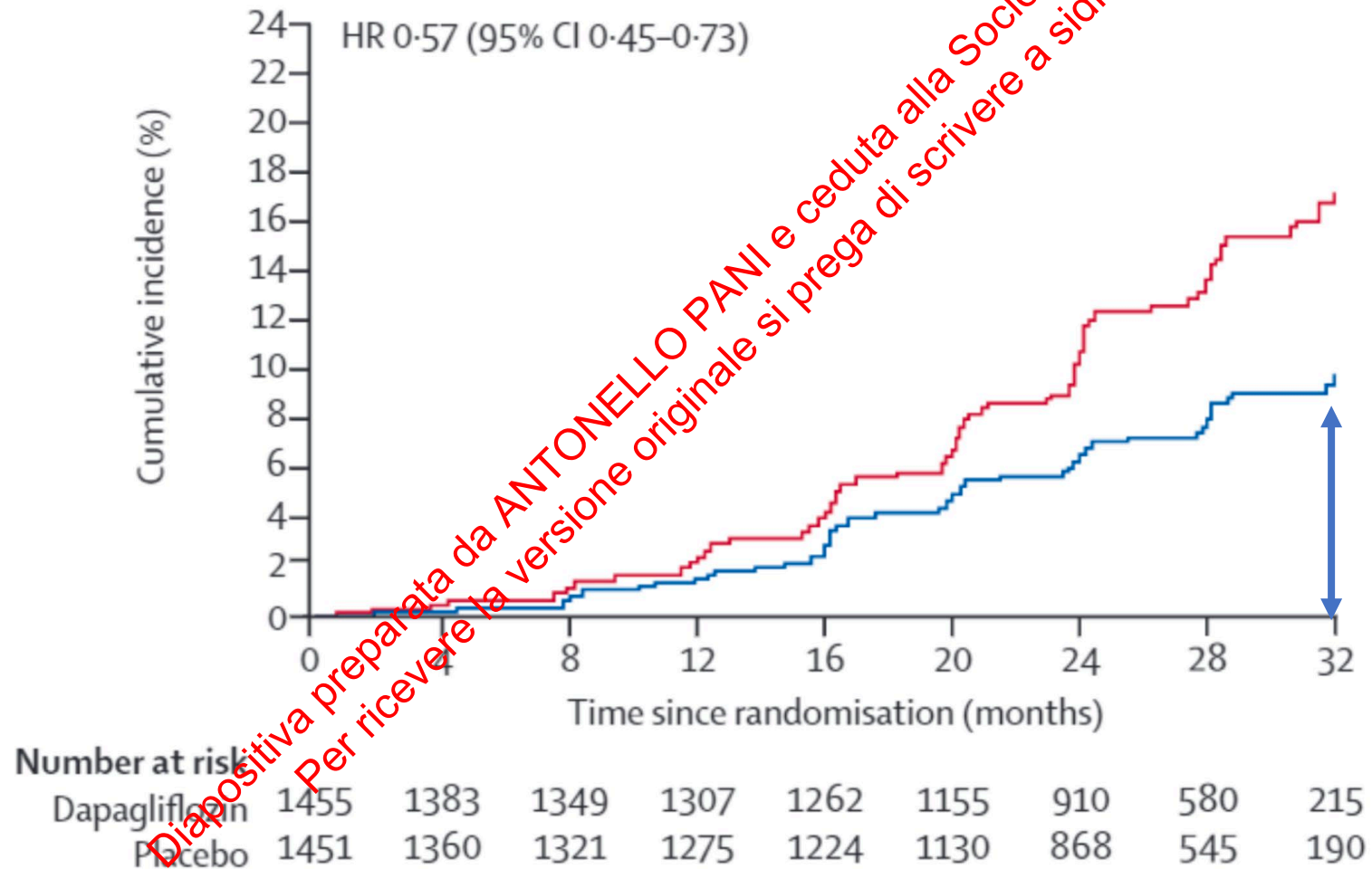
Perché effettuare una biopsia renale in un paziente diabetico?

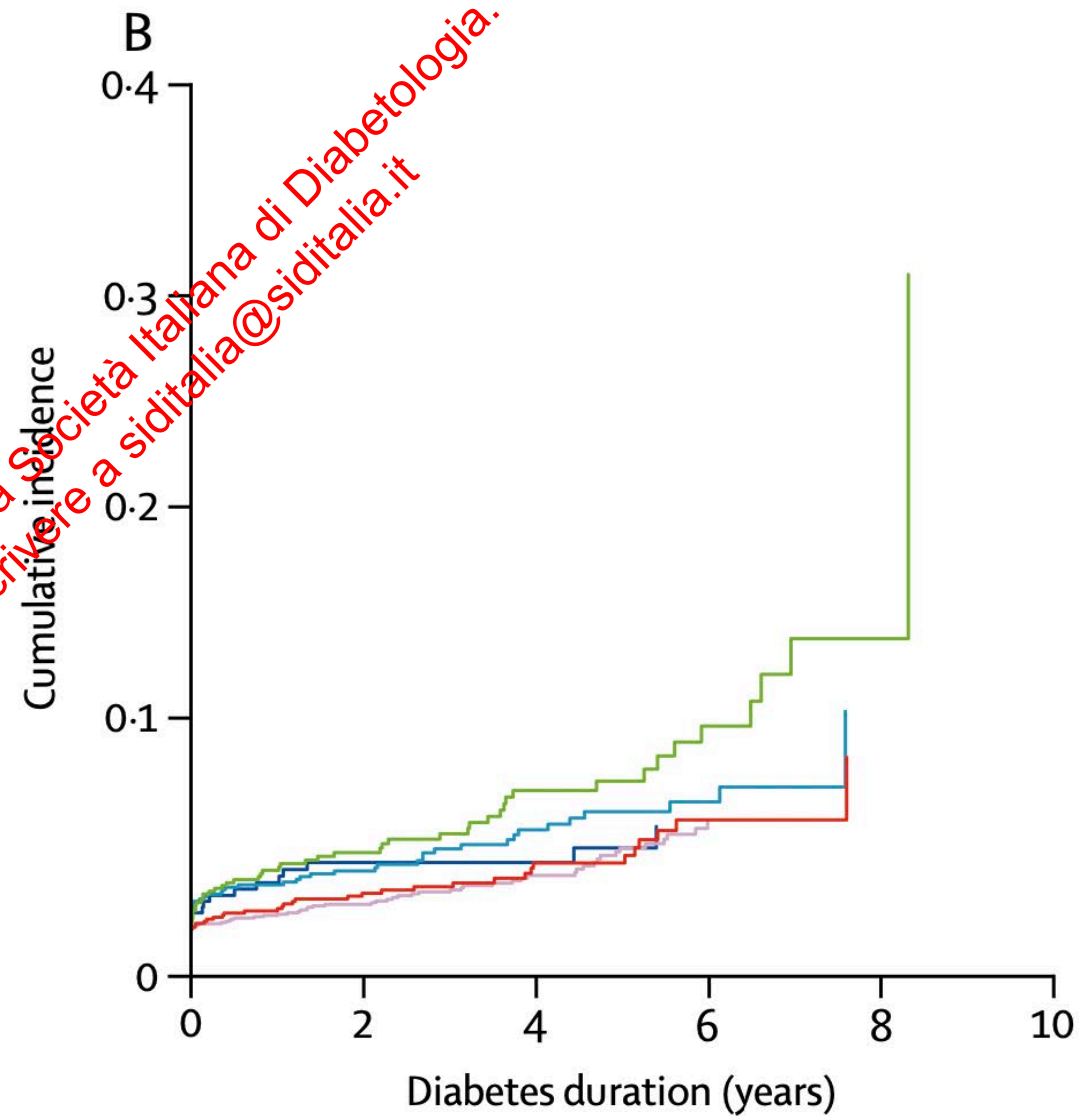
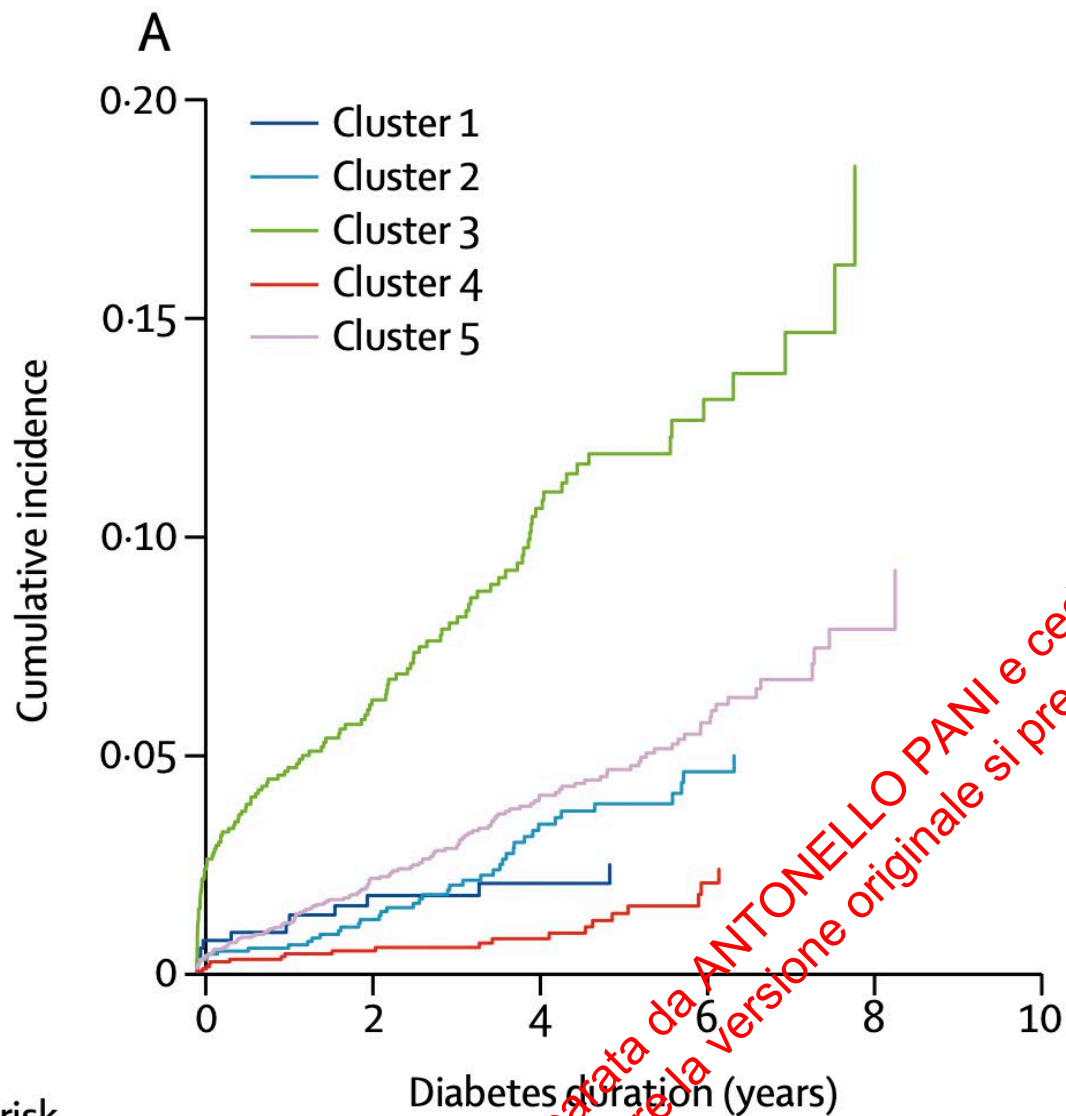
2) Identificare il fenotipo del paziente con DKD
(diabetic kidney disease) e personalizzare
l'approccio terapeutico

Diapositiva preparata da ANTONELLO PANI e ceduta alla Società Italiana di Diabetologia.
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Effects of dapagliflozin on major adverse kidney and cardiovascular events in patients with diabetic and non-diabetic chronic kidney disease: a prespecified analysis from the DAPA-CKD trial

David C Wheeler, Bergur V Stefánsson, Niels Jongs, Glenn M Chertow, Tom Greene, Fan Fan Hou, John J V McMurray, Ricardo Correa-Rotter, Peter Rossing, Robert D Toto, C David Sjöström, Anna Maria Langkilde, Hidde J L Heerspink, for the DAPA-CKD Trial Committees and Investigators*



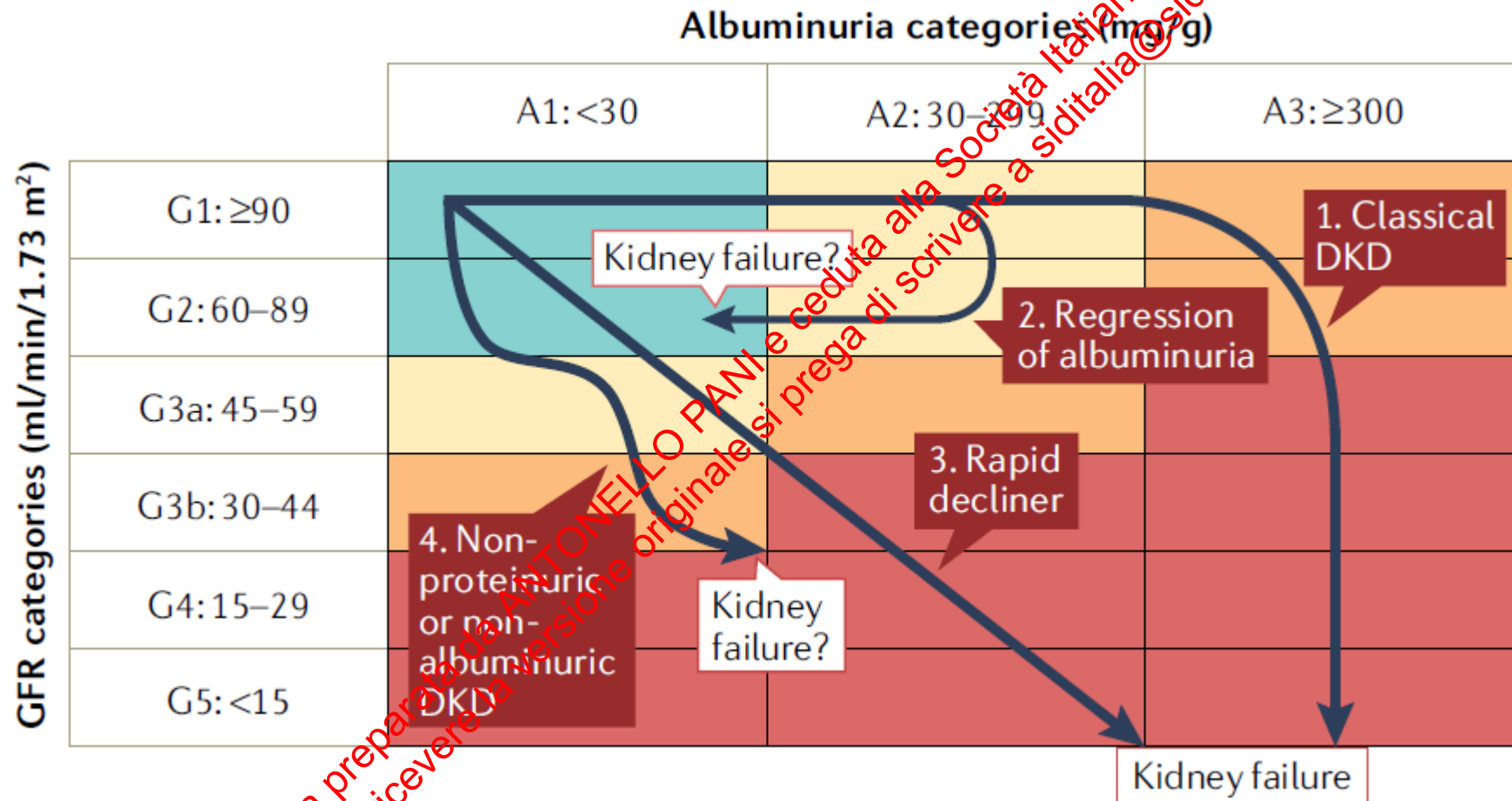


Number at risk

Cluster 1	496	362	220	82	11
Cluster 2	1325	912	511	180	17
Cluster 3	1061	669	337	105	13
Cluster 4	1607	1082	596	206	27
Cluster 5	2880	1968	1128	414	55

	333	213	117	39	5
	388	513	266	81	5
	664	384	193	62	7
	922	546	268	79	7
	1665	1034	541	172	16

Can the progression to ESKD be prevented before it is too late?



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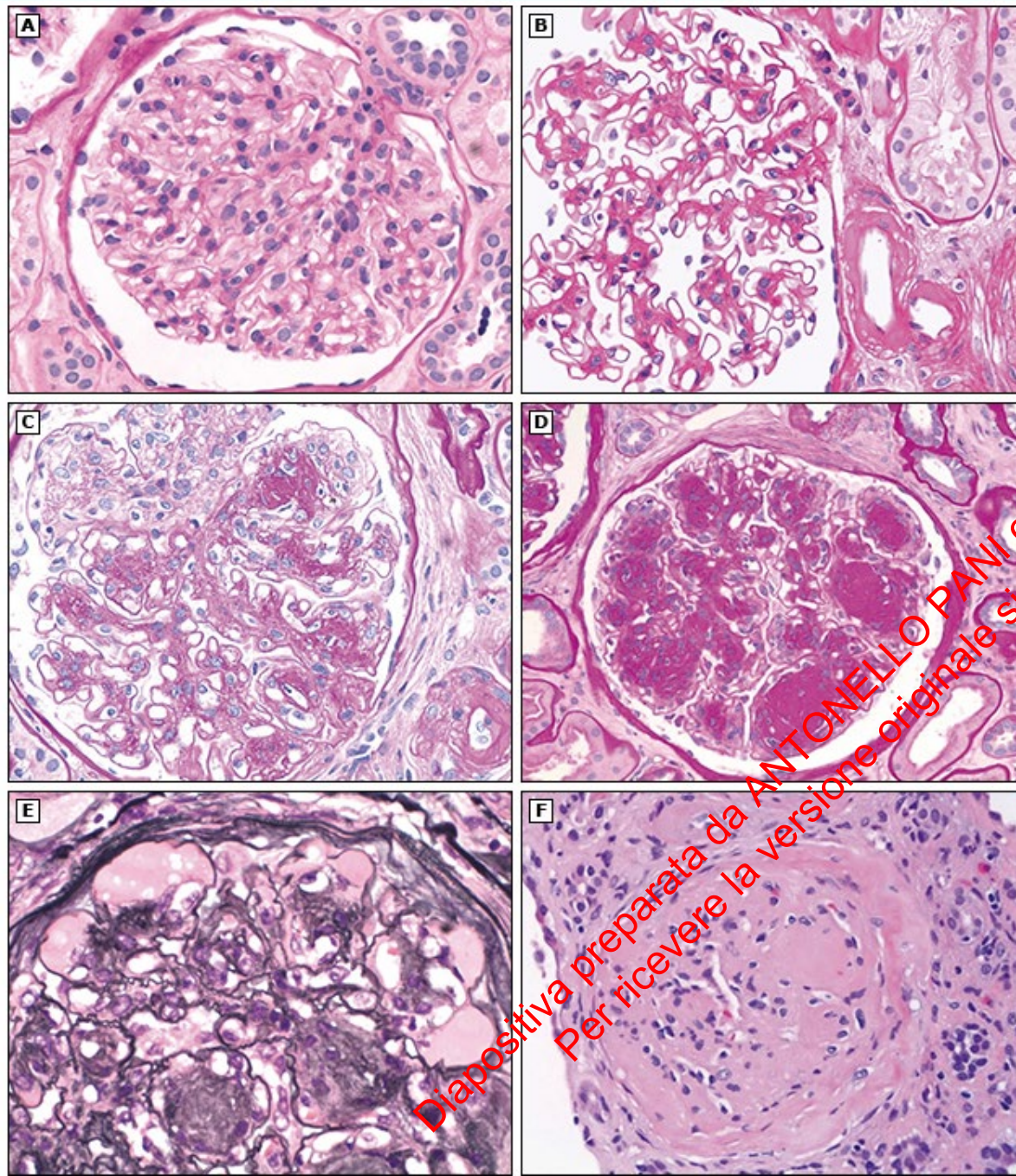
New Classification of DN Renal Pathology Society 2010



Class	Description	Inclusion Criteria
I	Mild or nonspecific LM changes and EM-proven GBM thickening	Biopsy does not meet any of the criteria mentioned below for class II, III, or IV GBM > 395 nm in female and >430 nm in male individuals 9 years of age and older ^a
IIa	Mild mesangial expansion	Biopsy does not meet criteria for class III or IV Mild mesangial expansion in >25% of the observed mesangium
IIb	Severe mesangial expansion	Biopsy does not meet criteria for class III or IV Severe mesangial expansion in >25% of the observed mesangium
III	Nodular sclerosis (Kimmelstiel–Wilson lesion)	Biopsy does not meet criteria for class IV At least one convincing Kimmelstiel–Wilson lesion
IV	Advanced diabetic glomerulosclerosis	Global glomerular sclerosis in >50% of glomeruli Lesions from classes I through III

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Diabetic glomerulopathy

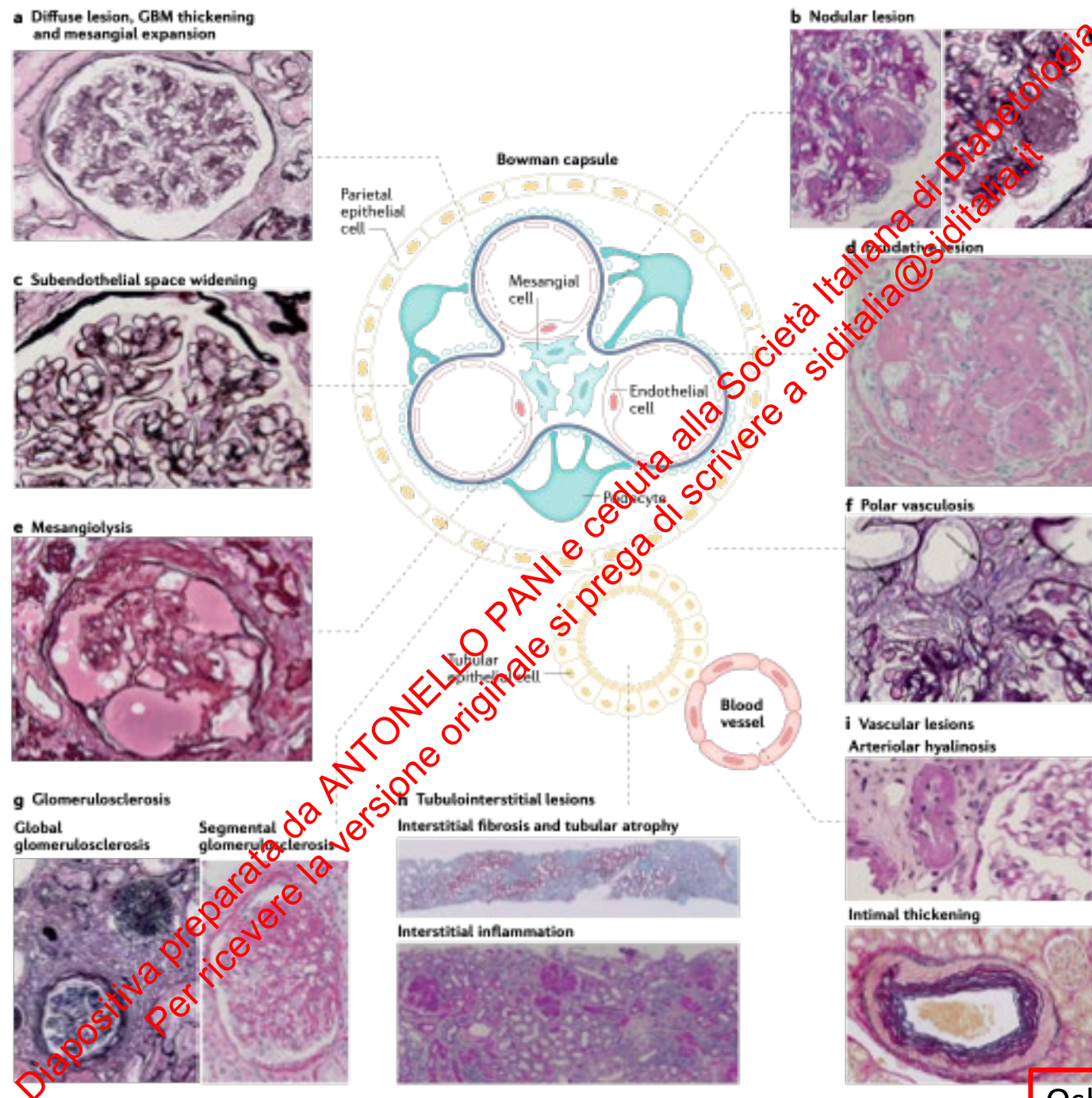


Changes in glomerular histology in diabetic glomerulopathy. (A–D) and (F) were stained with periodic acid-Schiff stain, and (E) was stained with Jones stain. Original magnification, $\times 400$.

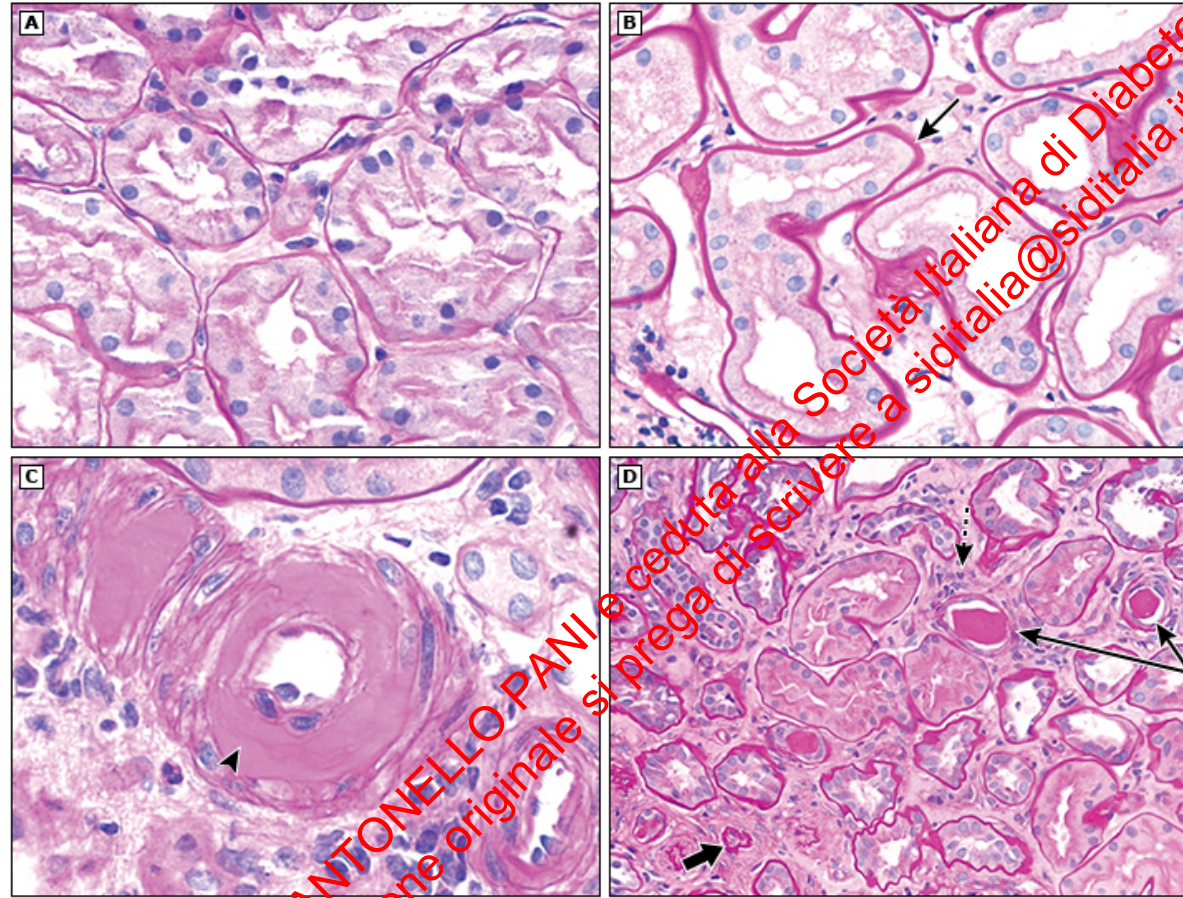
- (A) Normal glomerulus.
- (B) Diffuse mesangial expansion with mesangial cell proliferation.
- (C) Prominent mesangial expansion with early nodularity and mesangiolysis.
- (D) Accumulation of mesangial matrix forming Kimmelstiel–Wilson nodules.
- (E) Dilation of capillaries forming microaneurysms, with subintimal hyaline (plasmatic insudation).
- (F) Obsolescent glomerulus.

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Pathological features of diabetic nephropathy.



Tubulointerstitial changes and arteriolar hyalinosis in diabetic kidney disease



Tubulointerstitial changes in diabetic kidney disease.

(A) Normal renal cortex.

(B) Thickened tubular basement membranes and interstitial widening (arrow).

(C) Arteriole with an intimal accumulation of hyaline material with significant luminal compromise (arrowhead).

(D) Renal tubules and interstitium in advancing diabetic kidney disease, with thickening and wrinkled tubular basement membranes (double arrow), atrophic tubules (thick arrow), some containing casts, and interstitial widening with fibrosis and inflammatory cells (dashed arrow). All sections were stained with period acid-Schiff stain. Original magnification, x200.

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UpToDate®

Spiccata eterogeneità delle lesioni istopatologiche nei pazienti T2DM con Microalbuminuria e Proteinuria

Categoria C I: Struttura renale normale o quasi normale

Istologia normale, o lievi lesioni glomerulari, tubulo-interstiziali e/o vascolari

35% con Microalbuminuria e 15% con proteinuria

Categoria C II: Lesioni istopatologiche tipiche

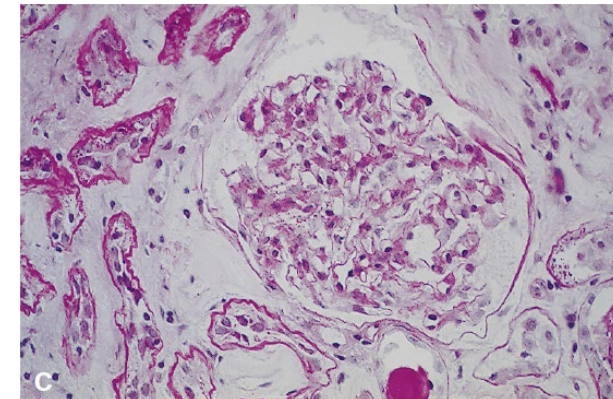
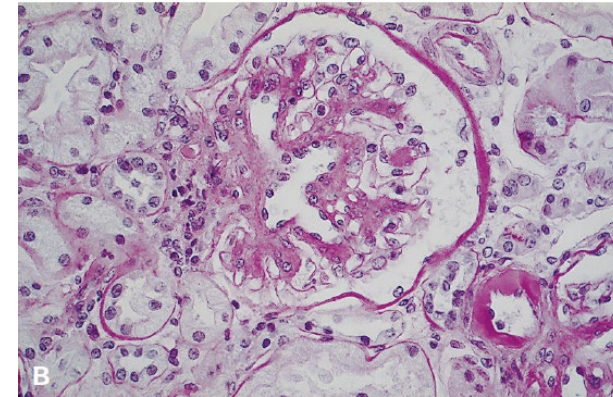
Lesioni diabetiche tipiche, diffuse alle strutture glomerulari », tubulo-interstiziali e vascolari

30% con Microalbuminuria e 50% con proteinuria

Categoria C III: Pattern atipici di danno renale

Lesioni glomerulari relativamente modeste, associate a :
a) marcate alterazioni tubulo-interstiziali (b) lalinosi severa delle arteriole glomerulari, e aterosclerosi dei vasi di maggiore calibro: c) sclerosi glomerulare globale.

35% con Microalbuminuria, 35% con proteinuria



Is the progression to ESKD due to multiple factors?

The rise of clinical and histological patterns

Table 3. Prevalence of Albuminuria and Reduced Estimated Glomerular Filtration Rate Among US Adults With Diabetes by Age, 1988 Through 2014

NHANES Period	No. With Diabetes	Unadjusted Prevalence, % (95% CI)		Adjusted Prevalence Ratio (95% CI) ^b	P Value for Trend
		Based on a Single Laboratory Value	Accounting for Persistence ^a		
Albuminuria (ACR ≥30 mg/g) ^c					
Adults aged <65 y					
1988-1994	256	33.5 (28.3-39.1)	19.5 (13.5-25.4)	1 [Reference]	.001
1999-2004	244	30.0 (25.9-34.4)	17.6 (12.9-22.3)	0.89 (0.72-1.11)	
2005-2008	224	26.6 (22.9-30.7)	15.7 (10.5-20.8)	0.80 (0.64-0.99)	
2009-2014	327	23.9 (20.6-27.6)	14.0 (10.1-18.0)	0.70 (0.57-0.87)	
Adults aged ≥65 y					
1988-1994	278	37.7 (31.7-44.2)	22.1 (15.9-28.4)	1 [Reference]	.15
1999-2004	287	35.7 (31.6-39.9)	20.7 (15.9-25.5)	0.94 (0.77-1.15)	
2005-2008	223	36.8 (33.6-40.2)	21.9 (17.0-26.8)	0.96 (0.80-1.16)	
2009-2014	318	32.3 (28.2-36.7)	19.2 (14.9-23.4)	0.84 (0.68-1.03)	
Reduced Estimated Glomerular Filtration Rate (eGFR <60 mL/min/1.73 m ²) ^d					
Adults aged <65 y					
1988-1994	40	4.0 (2.4-6.5)	2.9 (0-5.9)	1 [Reference]	.15
1999-2004	43	5.3 (3.8-7.4)	3.9 (1.3-6.5)	1.45 (0.80-2.61)	
2005-2008	53	6.0 (4.3-8.3)	4.3 (1.8-6.9)	1.62 (0.89-2.94)	
2009-2014	95	7.6 (5.9-9.9)	5.5 (2.9-8.2)	1.95 (1.12-3.39)	
Adults aged ≥65 y					
1988-1994	174	27.3 (23.3-31.8)	19.3 (13.4-25.3)	1 [Reference]	<.001
1999-2004	230	34.3 (30.1-38.8)	24.6 (18.4-30.9)	1.26 (1.04-1.54)	
2005-2008	189	34.6 (28.6-41.3)	24.4 (18.0-30.9)	1.28 (0.99-1.66)	
2009-2014	355	40.6 (36.5-44.8)	28.9 (22.9-34.9)	1.35 (1.27-1.45)	

OBJECTIVE To characterize the clinical manifestations of kidney disease among US adults with diabetes over time.

DESIGN, SETTING, AND PARTICIPANTS Serial cross-sectional studies of adults aged 20 years or older with diabetes mellitus participating in National Health and Nutrition Examination Surveys from 1988 through 2014.

“Classical” Pattern

(DECLINING)

Therapies are controlling diabetes

Glucose-lowering medications, RAAS inhibitors, and statins

“GFR” Pattern

(RISING)

Therapies are controlling diabetes

- It is possible that the hemodynamic effects of RAAS inhibitors and improved blood pressure control could contribute
- An increasing duration of diabetes may be contributing to kidney damage.

Is the progression to ESKD due to multiple factors?

The rise of clinical and histological patterns

Diffuse					MesLy					ICell				
Score	G & Y	Orange	Red	Total	Score	G & Y	Orange	Red	Total	Score	G & Y	Orange	Red	Total
0	18.4	6.0	3.9	7.0	0	87.4	68.0	52.3	62.5	0	40.8	20.8	5.9	15.7
1	46.6	28.2	14.3	23.5	1	12.6	32.0	47.7	37.5	1	44.7	59.7	51.3	52.3
2	23.3	26.8	25.0	25.2		100.0	100.0	100.0	100.0	2	13.6	12.8	27.0	21.1
3	11.7	38.9	56.8	44.4						3	1.0	6.7	15.8	11.0
	100.0	100.0	100.0	100.0							100.0	100.0	100.0	100.0
Nodular					PVas					Hyalin				
Score	G & Y	Orange	Red	Total	Score	G & Y	Orange	Red	Total	Score	G & Y	Orange	Red	Total
0	84.2	67.6	46.4	58.3	0	57.4	33.3	23.4	31.8	0	24.3	6.8	3.3	8.8
1	15.8	32.4	53.6	41.7	1	42.6	66.7	76.6	68.2	1	30.1	27.7	13.4	21.1
	100.0	100.0	100.0	100.0		100.0	100.0	100.0	100.0	2	17.5	19.6	23.1	21.6
SubendW					GMeg					Arterio				
Score	G & Y	Orange	Red	Total	Score	G & Y	Orange	Red	Total	Score	G & Y	Orange	Red	Total
0	64.9	48.6	23.8	37.2	0	78.0	69.4	59.7	65.3	0	37.1	23.4	8.3	16.9
1	25.8	32.6	40.4	35.9	1	22.0	30.6	40.3	34.7	1	38.9	46.8	46.9	45.6
2	4.1	13.2	21.0	16.1		100.0	100.0	100.0	100.0	2	24.2	27.7	42.9	35.9
3	5.2	5.6	14.8	10.8						3	0.0	2.1	1.8	1.6
	100.0	100.0	100.0	100.0							100.0	100.0	100.0	100.0
Exudative					IFTA									
Score	G & Y	Orange	Red	Total	Score	G & Y	Orange	Red	Total					
0	84.5	64.4	40.4	54.2	0	35.9	13.4	2.3	10.9					
1	15.5	35.6	59.6	45.8	1	42.7	44.3	20.5	30.3					
	100.0	100.0	100.0	100.0	2	18.4	28.9	35.4	27.9					
					3	2.9	13.4	41.8	27.9					
						100.0	100.0	100.0	100.0					

G & Y, green and yellow; Diffuse, diffuse lesion (mesangial expansion); Nodular, nodular lesion (nodular sclerosis); SubendW, subendothelial space widening (double contour of basement membrane); Exudative, exudative lesion; MesLy, mesangiolysis; Microangiopathy, PVas, peri-hilar neo-vascularization (polar vasculosis); GMeg, glomerulomegaly; IFTA, interstitial fibrosis and tubular atrophy; ICell, interstitial cell infiltration; Hyalin, arteriolar hyalinosis; Arterio, arteriosclerosis with intimal thickening.

Kidney biopsies and clinical data of **600 patients** with type 2 diabetes were collected retrospectively from 13 centers across Japan. Thirteen pathologic findings (nine glomerular lesions, two interstitial lesions, and two vascular lesions) were clearly defined and scored.

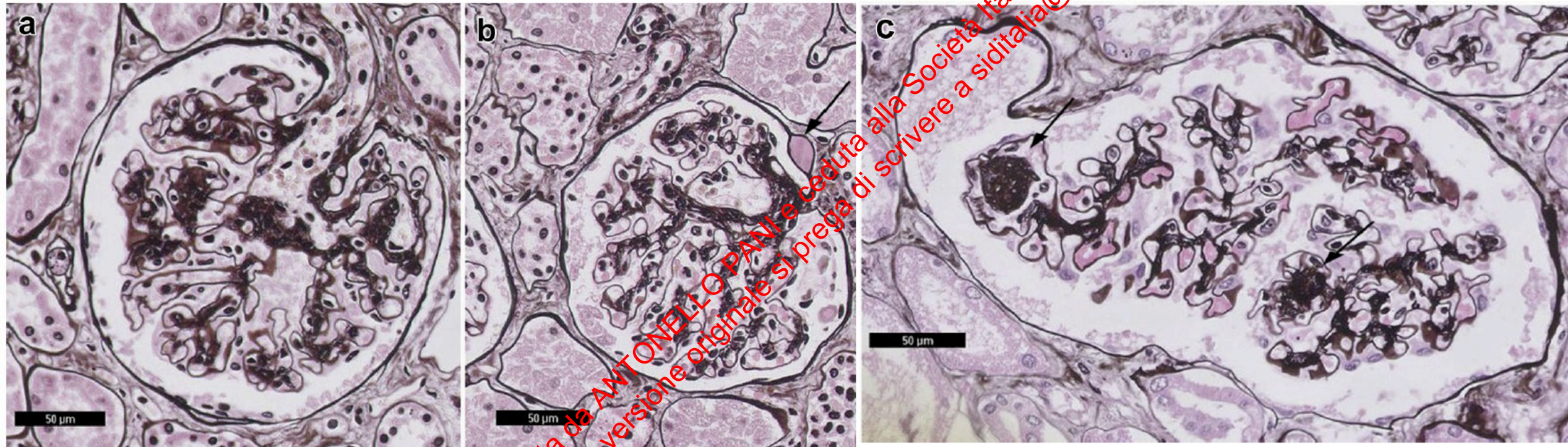
G&Y, Orange, and Red refer to the KDIGO 2012 CKD heatmap.

Some histological patterns are observed since the first degree of CKD, the green and yellow zones in CKD heatmaps (G&Y), rising interest of an early intervention in diabetes control.

- Nodular
- Mesangiolysis
- Exudation

Are clinical patterns in DKD sufficiently sensible and specific?

Based on autopsy studies, when clinical manifestations appear DKD is too “late”



Mesangial expansion
(stage II)

Capsular drops

KW nodules
(stage III)

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Is the progression to ESKD due to multiple factors? The rise of clinical and histological patterns

LA PRESENZA DI LESIONI GLOMERULARI
IDENTIFICA UN GRUPPO DI PAZIENTI CON
ELEVATO RISCHIO DI ESRD ANCHE IN
ASSENZA DI ALBUMINURIA E CON
FUNZIONE RENALE NORMALE O
MINIMAMENTE RIDOTTA

Diapositiva preparata da ANTONELLO PAM e ceduta alla Società Italiana di Diabetologia.
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Domanda 3:

La biopsia renale può fornire precocemente un profilo prognostico renale e generale del paziente diabetico?

- VERO
- FALSO

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Nonalbuminuric DKD and Risk of All-Cause Mortality, Cardiovascular, and Kidney Outcomes in Type 2 Diabetes

Settings & Participants	Analysis	Results																
 HONG KONG DIABETES BIOBANK 香港糖尿病生物庫  Multicenter, prospective, cohort study  N = 19,025  Follow-up: 3.1 years	Exposures No diabetic kidney disease (DKD)  Decreased eGFR only  Albuminuria only  Decreased eGFR + albuminuria Statistical Analysis • Competing risk models • Multiple imputation to create 5 datasets • No DKD as reference group	 Mortality  CVD  HHF*  CKD Progression	HR (95% CI) <table><tr><td> 1.59 (1.04-2.44)</td><td> 1.14 (0.88-1.48)</td><td> 3.08 (1.82-5.21)</td><td> 2.37 (1.63-3.43)</td></tr><tr><td> 2.00 (1.52-2.63)</td><td> 1.19 (1.02-1.40)</td><td> 3.14 (2.09-4.73)</td><td> 3.77 (3.05-4.66)</td></tr><tr><td> 3.26 (2.43-4.38)</td><td> 1.47 (1.23-1.76)</td><td> 5.50 (3.63-8.34)</td><td> 14.01 (11.31-17.36)</td></tr></table>				 1.59 (1.04-2.44)	 1.14 (0.88-1.48)	 3.08 (1.82-5.21)	 2.37 (1.63-3.43)	 2.00 (1.52-2.63)	 1.19 (1.02-1.40)	 3.14 (2.09-4.73)	 3.77 (3.05-4.66)	 3.26 (2.43-4.38)	 1.47 (1.23-1.76)	 5.50 (3.63-8.34)	 14.01 (11.31-17.36)
 1.59 (1.04-2.44)	 1.14 (0.88-1.48)	 3.08 (1.82-5.21)	 2.37 (1.63-3.43)															
 2.00 (1.52-2.63)	 1.19 (1.02-1.40)	 3.14 (2.09-4.73)	 3.77 (3.05-4.66)															
 3.26 (2.43-4.38)	 1.47 (1.23-1.76)	 5.50 (3.63-8.34)	 14.01 (11.31-17.36)															

CONCLUSION: Nonalbuminuric DKD is associated with higher risks of HHF and CKD progression compared with no DKD, regardless of baseline eGFR.

*HHF: Hospitalization for heart failure

Qiao Jin, Andrea O. Luk, Eric SH Lau, et al (2022)

@AJKDonline | DOI: 10.1053/j.ajkd.2022.11.010

AJKD
AMERICAN JOURNAL OF KIDNEY DISEASES

La DKD si esprime con fenotipi diversi, con profili di rischio differenti, e verso similmente con caratteristiche istopatologiche differenti.

Nonproteinuric Versus Proteinuric Phenotypes in Diabetic Kidney Disease: A Propensity Score-Matched Analysis of a Nationwide, Biopsy-Based Cohort Study

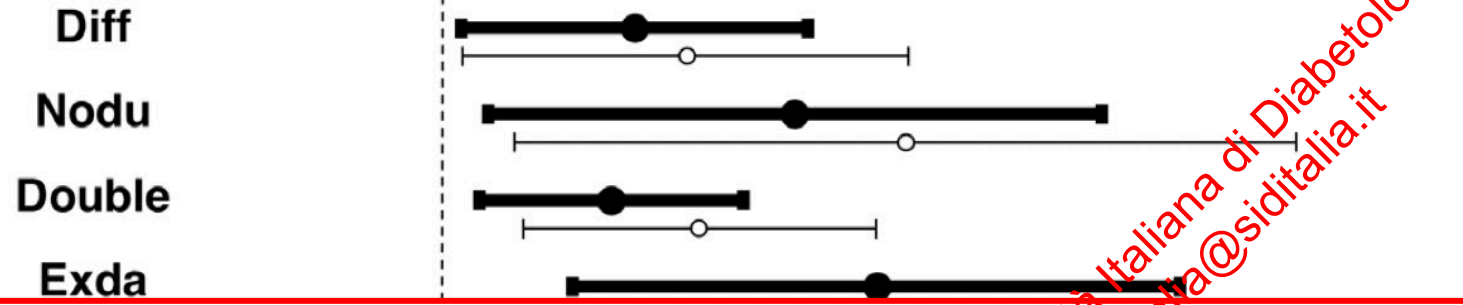
526 pazienti con DM Tipo 2 e funzione renale ridotta (eGFR <60 mL/min/1.73 m²), sottoposti ad agobiopsia renale



IL FENOTIPO DKD NON ALBUMINURICO IDENTIFICA UNA POPOLAZIONE CON RISCHIO DI PROGRESSIONE VERSO L'ESRD INTERMEDIO TRA DKD ALBUMINURICA E DIABETICI NON NEFROPATICI

Number at risk					Number at risk				
Non proteinurics	88	35	15	11	Non proteinurics	82	34	15	11
Proteinurics	438	61	12	4	Proteinurics	164	31	7	2

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**FIBROSI INTERSTIZIALE, ATROFIA TUBULARE
E INFILTRATO INFIAMMATORIO
INTERSTIZIALE CORRELANO CON IL RISCHIO
DI RAPIDO DECLINO DELLA FUNZIONE
RENALE**

≥5 mL/min/1.73

0.5

1

2

4

8

8

3

1

0

1

0

HR (95% CI)

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Patterns of renal injury in NIDDM patients with microalbuminuria



P. Fioretto¹, M. Mauer², E. Brocco¹, M. Velussi³, F. Frigato³, B. Muollo³, M. Sambataro³, C. Abaterusso¹, B. Baggio¹, G. Crepaldi¹, R. Nosadini^{1,4}

¹ Department of Internal Medicine and Center for the Study of Aging of the National Research Council, University of Padova Medical School, Padova, Italy

² Pediatric Nephrology, University of Minnesota Medical School, Minneapolis, Minnesota, USA

³ Diabetes Centers of Monfalcone, Mestre, Este and Contarina, Italy

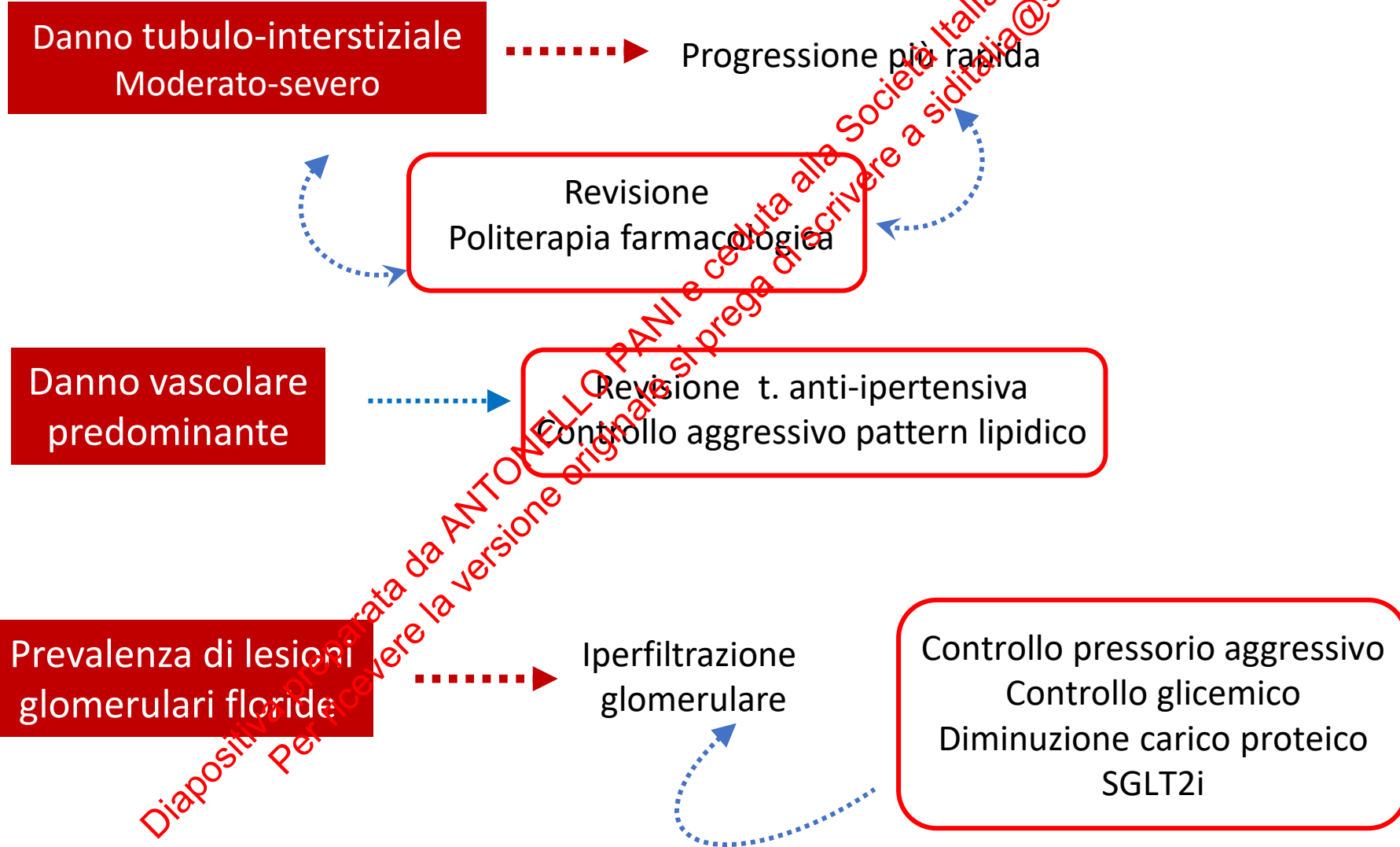
⁴ Division of Endocrinology, University of Sassari Medical School, Sassari, Italy

Table 3. Diabetic retinopathy in relation to patterns of renal injury

Category	Diabetic retinopathy		
	Absent	Background	Proliferative
C I	5	5	0
C II	0	5	5
C III	6	8	0

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Quale potenziale valore prognostico-terapeutico dei riscontri bioptici?



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Razionale per biopsia renale in paziente con sospetta DKD



PRO

- Le lesioni istologiche della DKD sono eterogenee e presentano un impatto prognostico significativo circa la progressione verso ESRD e il rischio CV
- La diagnosi clinica di DKD è talora fallace e spesso può giungere in maniera tardiva nella storia naturale della malattia
- Il profilo di DKD "non albuminurico" assume un peso crescente nell'ambito dei pazienti diabetici
- Il profilo fenotipico evidenziato dall'istologia renale potrebbe permettere un approccio personalizzato alla terapia

CON

- Difficoltà nella pratica clinica ad estendere l'indicazione bioptica a pazienti non albuminurici con funzione renale normale o lievemente ridotta (fasi precoci della DKD "non albuminurica")
- Perplessità circa l'impatto reale sulla modifica dell'approccio terapeutico (in considerazione dell'attuale standard of care)

Diapositive preparata da ANTONELLO PANFILI ceduta alla Società Italiana di Diabetologia.
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Prognostic imaging biomarkers for diabetic kidney disease (iBEat): study protocol

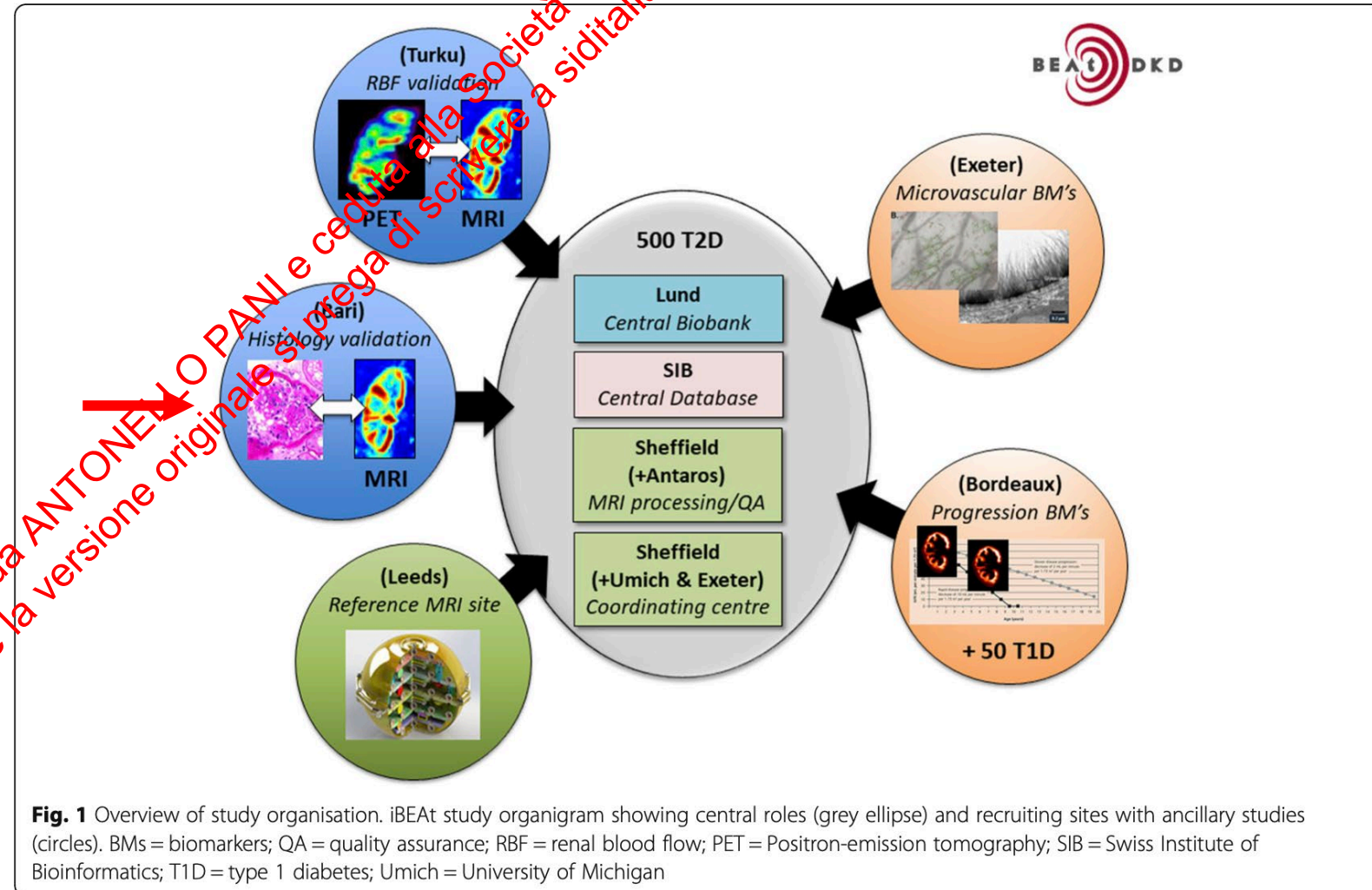


Kim M. Gooding^{1,2*}, Chrysta Lienczewski³, Massimo Papale⁴, Niina Koivuviita^{5,6}, Marlena Maziarz⁷, Anna-Maria Dutius Andersson⁷, Kanishka Sharma⁸, Paola Pontrelli⁴, Alberto Garcia Hernandez⁹, Julie Bailey¹⁰, Kay Tobin¹¹, Virva Saunavaara¹², Anna Zetterqvist⁷, David Shelley^{10,13}, Irvin Teh¹⁴, Claire Ball², Sapna Puppala¹⁰, Mark Ibberson¹⁵, Anil Karihaloo¹⁶, Kaj Metsärinne⁵, Rosamonde E. Banks¹⁷, Peter S. Gilmour¹⁸, Michael Mansfield¹⁰, Mark Gilchrist¹, Dick de Zeeuw^{19,20}, Hiddo J. L. Heerspink^{19,20}, Pirjo Nuutila^{5,6}, Matthias Kretzler^{3,21}, Matthew Welberry Smith¹¹, Loreto Gesualdo⁴, Dennis Andress²², Nicolas Grenier²³, Angela C. Shore^{1,2}, Maria F. Gomez^{7†}, Steven Sourbron^{8†} and for the BEAT-DKD consortium

Biopsy in DKD: research

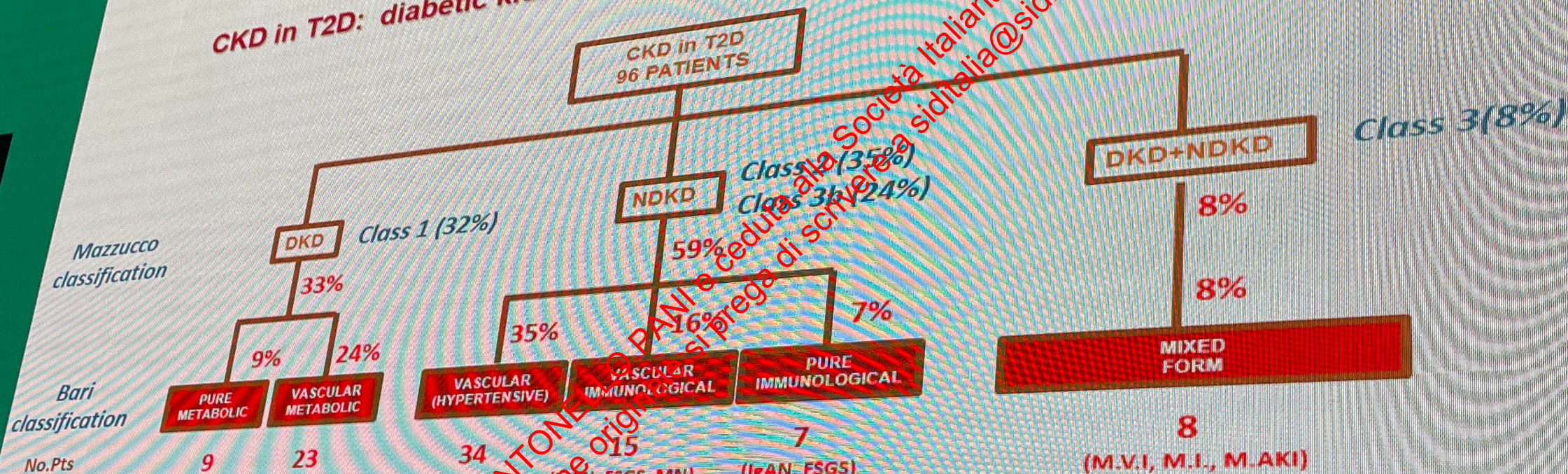
Patient's Phenotyping

Histopathological
Clinical
Imaging
Omics



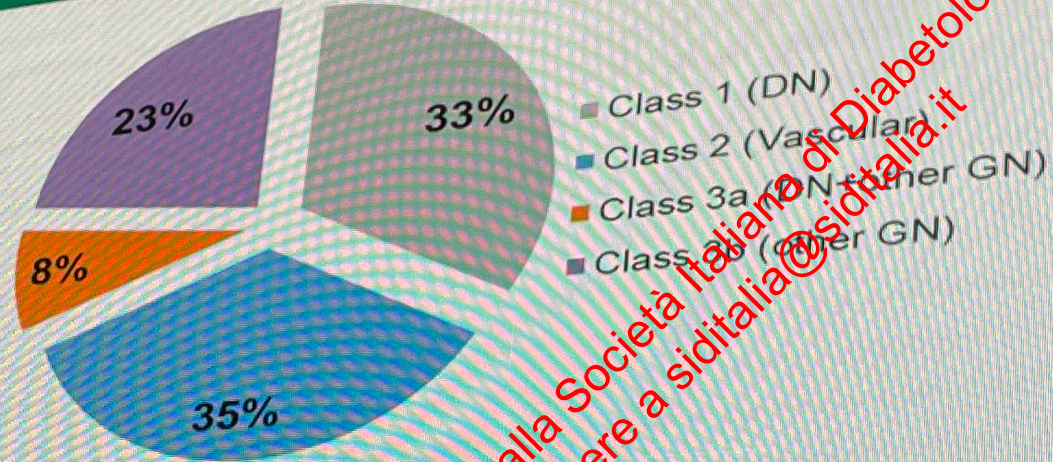
BARI CLASSIFICATION

CKD in T2D: diabetic kidney disease versus nondiabetic kidney disease



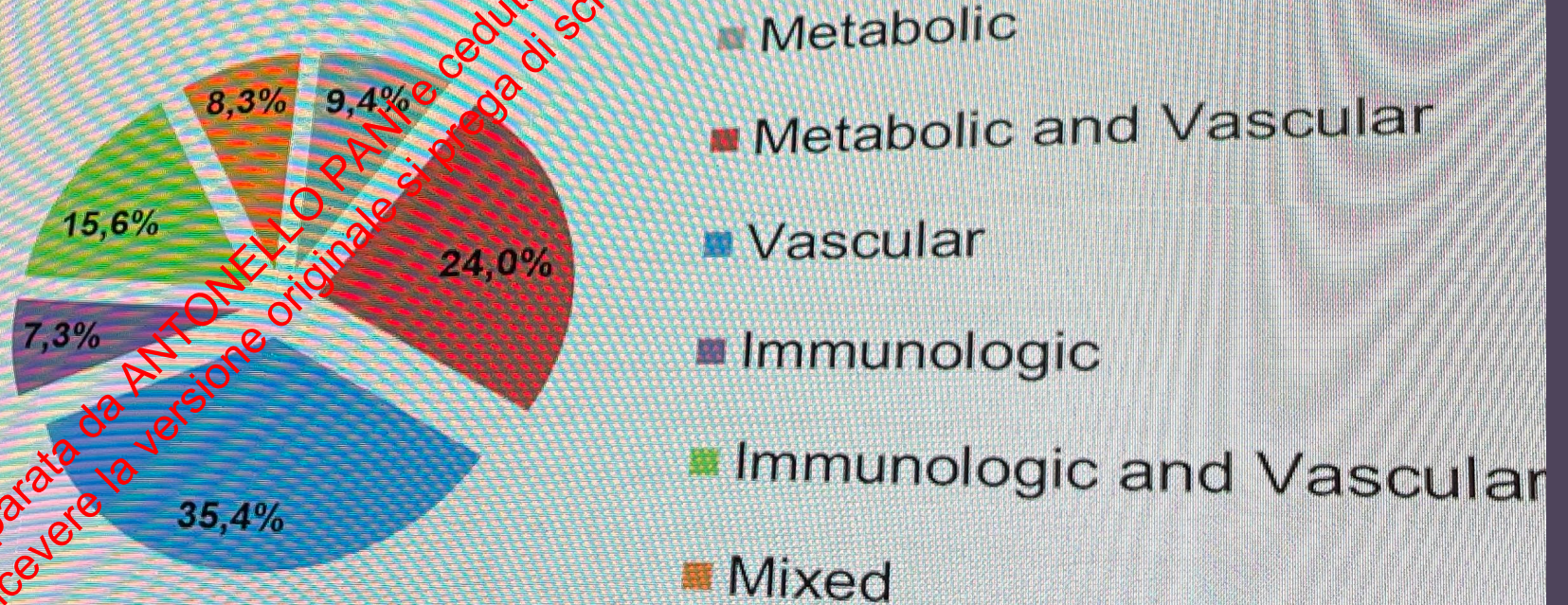
Mazzucco Classification

	n of cases	% of cases
Class 1 (DN)	32	33%
Class 2 (Vascular)	34	35%
Class 3a (DN+other GN)	8	8%
Class 3b (other GN)	22	23%
TOT	96	



Bari Classification

	n of cases	% of cases
Metabolic	9	9%
Metabolic and Vascular	23	24%
Vascular	34	35%
Immunologic	7	7%
Immunologic and Vascular	15	16%
Mixed	8	8%
TOT	96	



TAKE HOME MESSAGES



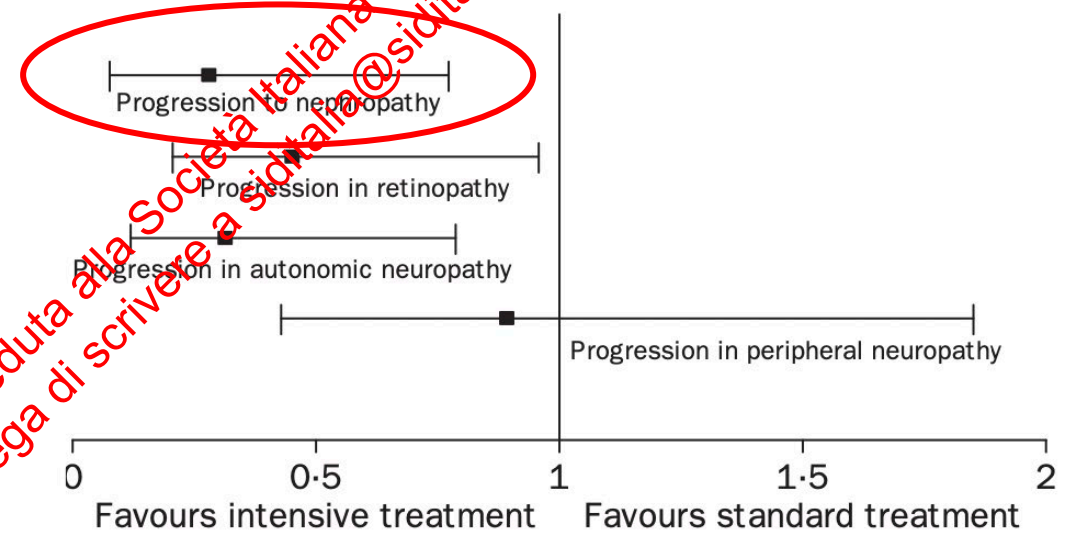
- La malattia renale nel paziente diabetico comprende un ampio spettro di condizioni sia conseguenti alla patologia diabetica (DKD) sia indipendenti da essa (NDKD)
- I pazienti con NDKD presentano una prognosi renale migliore rispetto ai pazienti con DKD
- La probabilità clinica di una condizione di NDKD aumenta in assenza di retinopatia diabetica e con storia di diabete mellito < 5 anni
- La diagnosi della NDKD è una diagnosi istologica
- Il fenotipo della DKD è eterogeneo sia clinicamente sia istologicamente
- Le lesioni vascolari sono un elemento precoce nella storia naturale della DKD non albuminurica
- L'estensione delle indicazioni biotiche nei pazienti con verosimile DKD in ambito di ricerca rappresenta un passaggio necessario per una miglior comprensione dei fenotipi di DKD e per la validazione di nuovi biomarkers

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TAKE HOME MESSAGES: NO DKD WITHOUT DIABETES!

Intensified multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: the Steno type 2 randomised study

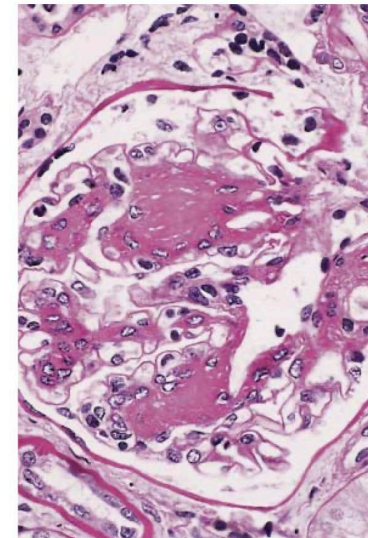
Peter Gæde, Pernille Vedel, Hans-Henrik Parving, Oluf Pedersen



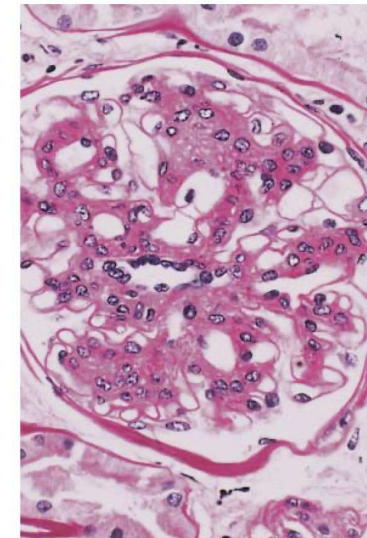
REVERSAL OF LESIONS OF DIABETIC NEPHROPATHY AFTER PANCREAS TRANSPLANTATION

REVERSAL OF LESIONS OF DIABETIC NEPHROPATHY AFTER PANCREAS TRANSPLANTATION

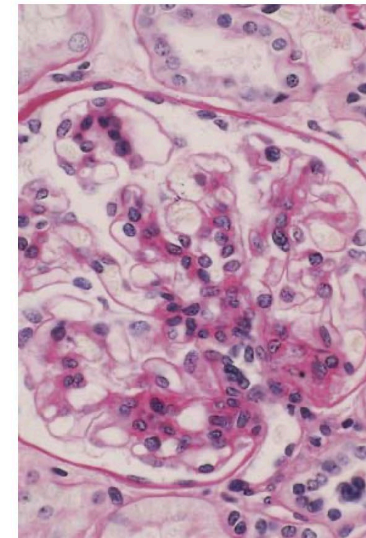
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Grazie G1G1 Per Sempre

**«Il suo non fu un no alla Juve o all'Inter
ma fu un SI per SEMPRE alla Sardegna»**