

**CATANIA**  
29 febbraio 2020

Hotel Mercure Catania Excelsior



# SGLT2

## INIBITORI

e progressione della malattia renale  
nel diabete tipo 2

## Epidemiologia della malattia renale cronica nel diabete

Ferdinando Carlo Sasso, MD-PhD

Dipartimento di Scienze Medico Chirurgiche Avanzate



Università  
degli Studi  
della Campania  
*Luigi Vanvitelli*

Diapositiva preparata da FERDINANDO SASSO e ceduta alla Società Italiana di Diabetologia.  
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**Dichiarazione esplicita di trasparenza delle fonti di finanziamento  
e dei rapporti con soggetti portatori di interessi commerciali**

*Il sottoscritto* **Prof. Ferdinando Carlo Sasso**

*in qualità di Relatore*

*ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 17 del Reg.  
Applicativo dell'Accordo Stato-Regioni del 5 novembre 2009, dichiara  
che negli ultimi due anni ha avuto i seguenti rapporti anche di  
finanziamento con soggetti portatori di interessi commerciali in campo  
sanitario:*

*Eli Lilly, Mundipharma,  
Roche Diagnostics,  
Novo Nordisk, MSD*

*29 febbraio 2020*

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# Inquadramento Diagnostico

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# Chronic Kidney Disease Diagnosis and Management

CKD is defined as the presence of an abnormality in kidney structure or function **persisting for more than 3 months**. This includes **1 or more** of the following:

- (1) GFR <60 mL/min/1.73 m<sup>2</sup>,
- (2) Albuminuria (ie, urine albumin 30 mg/24h or urine albumin-to-creatinine ratio [ACR] 30 mg/g)
- (3) Abnormalities in urine sediment, histology
- (4) Imaging suggestive of kidney damage
- (5) History of kidney transplantation

# Identificare i soggetti a rischio è semplice, economico e... *cost-effective*

**Prognosis of CKD by GFR  
and Albuminuria Categories:  
KDIGO 2012**

|                                                                      |     |                                  |       | Persistent albuminuria categories |                             |                          |
|----------------------------------------------------------------------|-----|----------------------------------|-------|-----------------------------------|-----------------------------|--------------------------|
|                                                                      |     |                                  |       | Description and range             |                             |                          |
| GFR categories (ml/min/1.73m <sup>2</sup> )<br>Description and range |     |                                  |       | A1                                | A2                          | A3                       |
|                                                                      |     |                                  |       | Normal to mildly increased        | Moderately increased        | Severely increased       |
|                                                                      |     |                                  |       | <30 mg/g<br><3 mg/mmol            | 30-300 mg/g<br>3-30 mg/mmol | >300 mg/g<br>>30 mg/mmol |
|                                                                      | 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   |                                   |                             |                          |

**sCreat**  
(costo 1.13 €)

**Es. urine**  
(costo 1.14 €)



## Mai basarsi sulla sola creatininemia negli anziani....

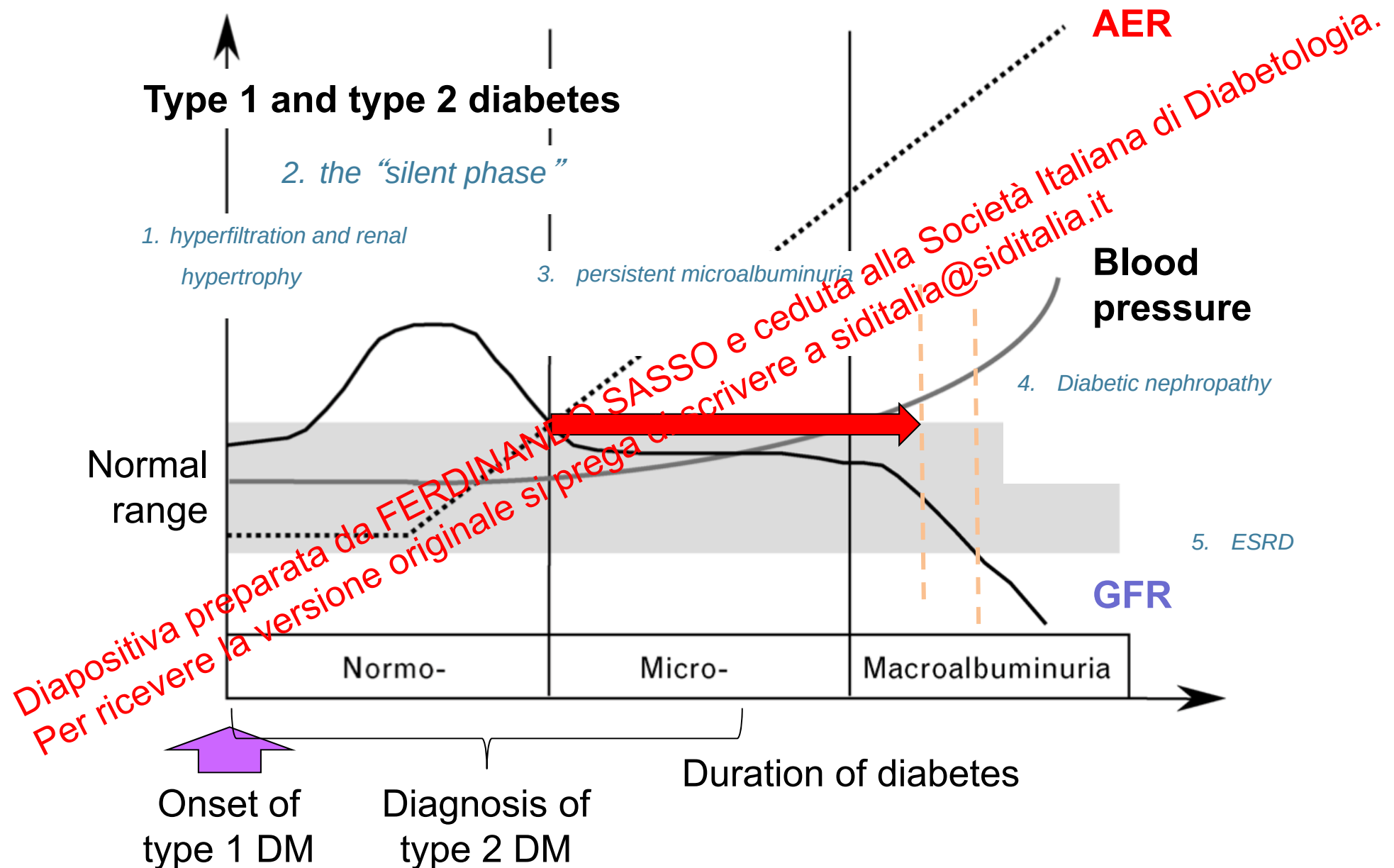
Serum creatinine concentrations corresponding to eGFR levels of 60 mL/min/1.73 m<sup>2</sup> by the abbreviated MDRD equation or 60 mL/min by the Cockcroft–Gault equation

| Age<br>(yrs) | MDRD Equation     |       |                  |       | Cockcroft–Gault |       |
|--------------|-------------------|-------|------------------|-------|-----------------|-------|
|              | European-American |       | African-American |       | Men             | Women |
|              | Men               | Women | Men              | Women |                 |       |
| 50           | 1.34              | 1.05  | 1.58             | 1.22  | 1.50            | 1.28  |
| 60           | 1.30              | 1.00  | 1.53             | 1.18  | 1.33            | 1.13  |
| 70           | 1.26              | 0.97  | 1.49             | 1.15  | 1.17            | 0.99  |
| 80           | 1.23              | 0.95  | 1.46             | 1.12  | 1.00            | 0.85  |

Calculations assume weight of 72 kg and body surface area of 1.73 m<sup>2</sup>. Creatinine in mg/dL.

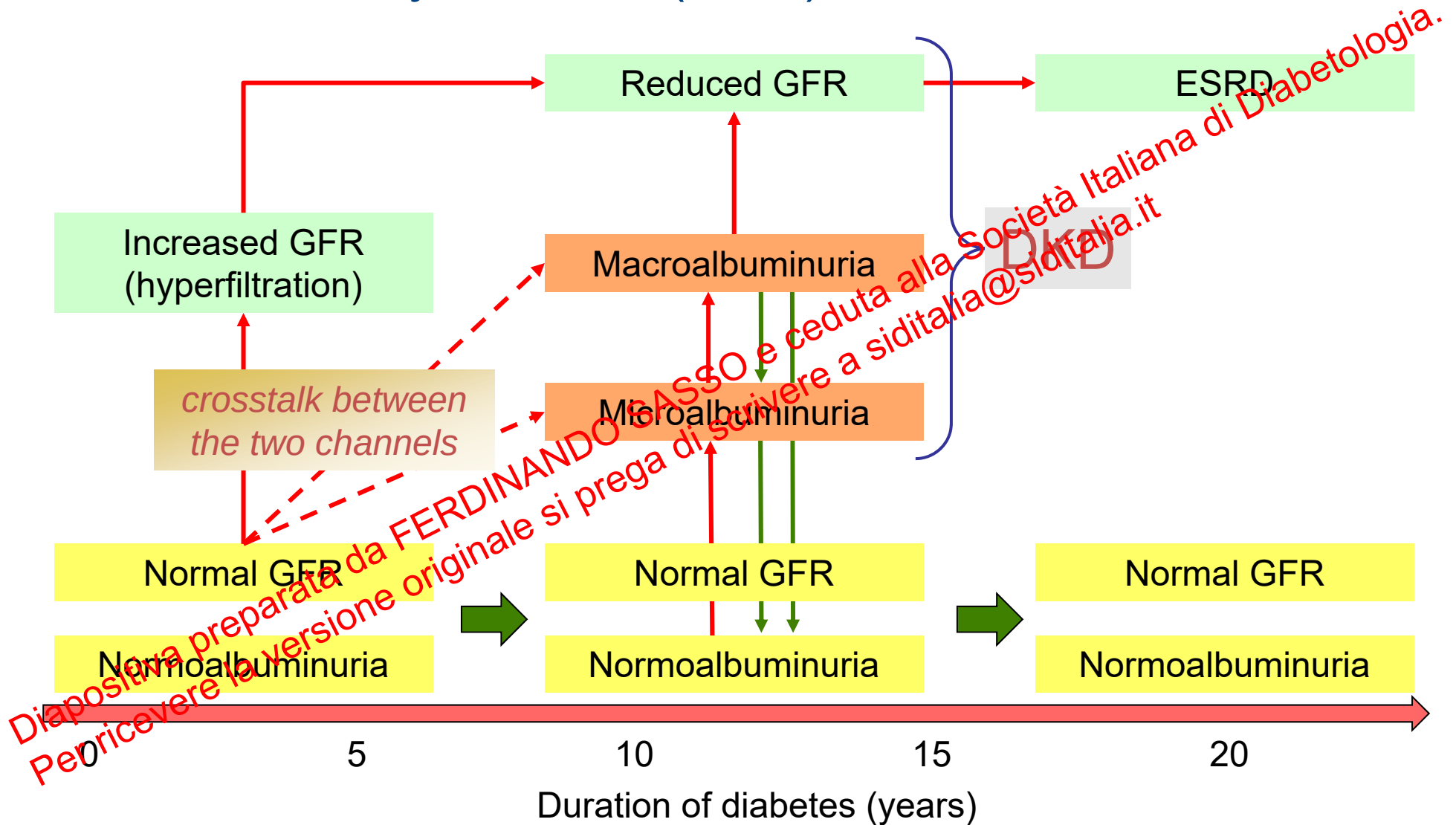
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Historically, for people at risk of developing DKD, an initial increase in AER has been linked to a subsequent decline in GFR



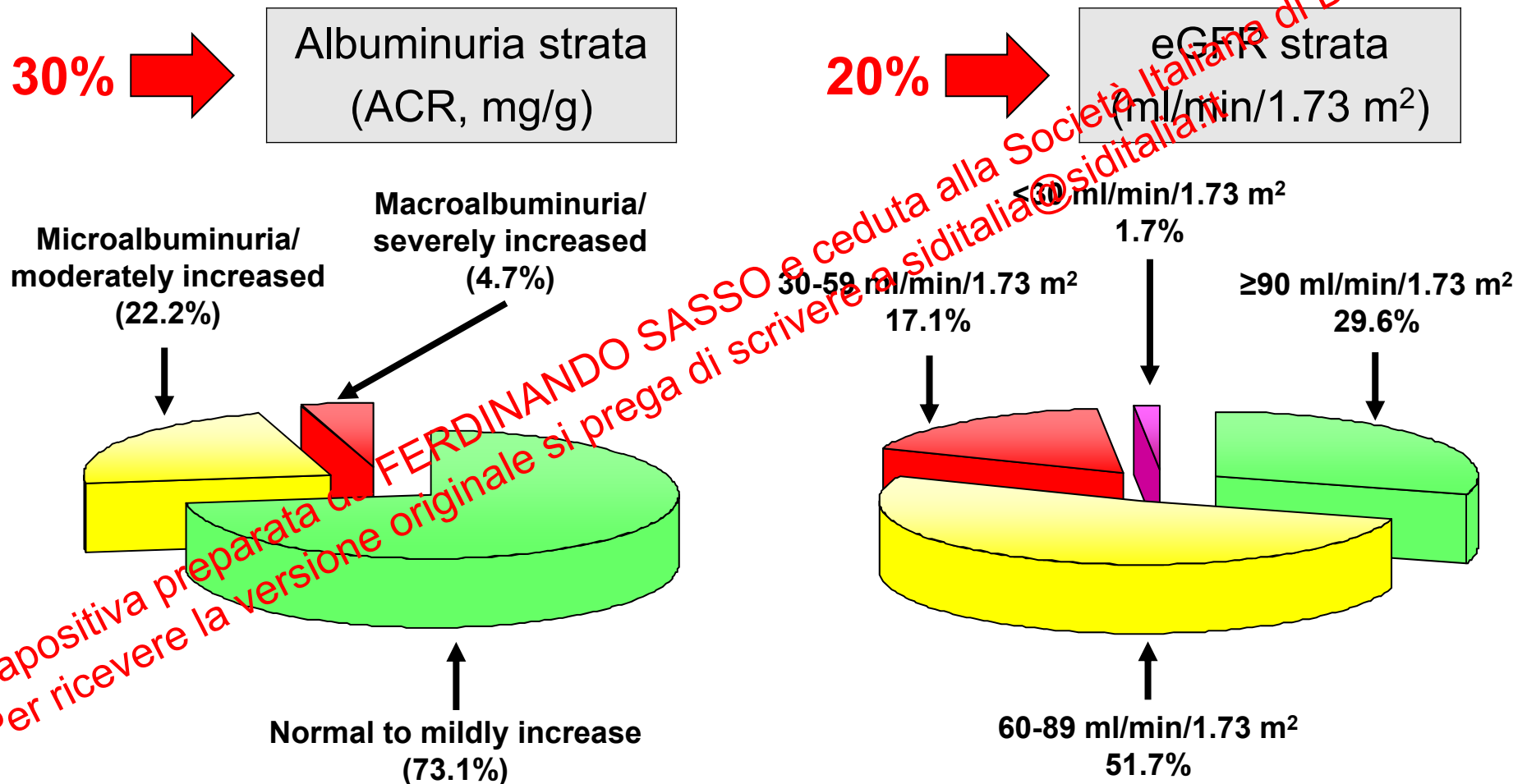


# Schematic presentation of variable clinical courses of Diabetic Kidney Disease (DKD)



# Renal dysfunction is common in patients with T2DM

The RIACE Study: 15,773 patients with T2DM



# Renal dysfunction is common in patients with T2DM

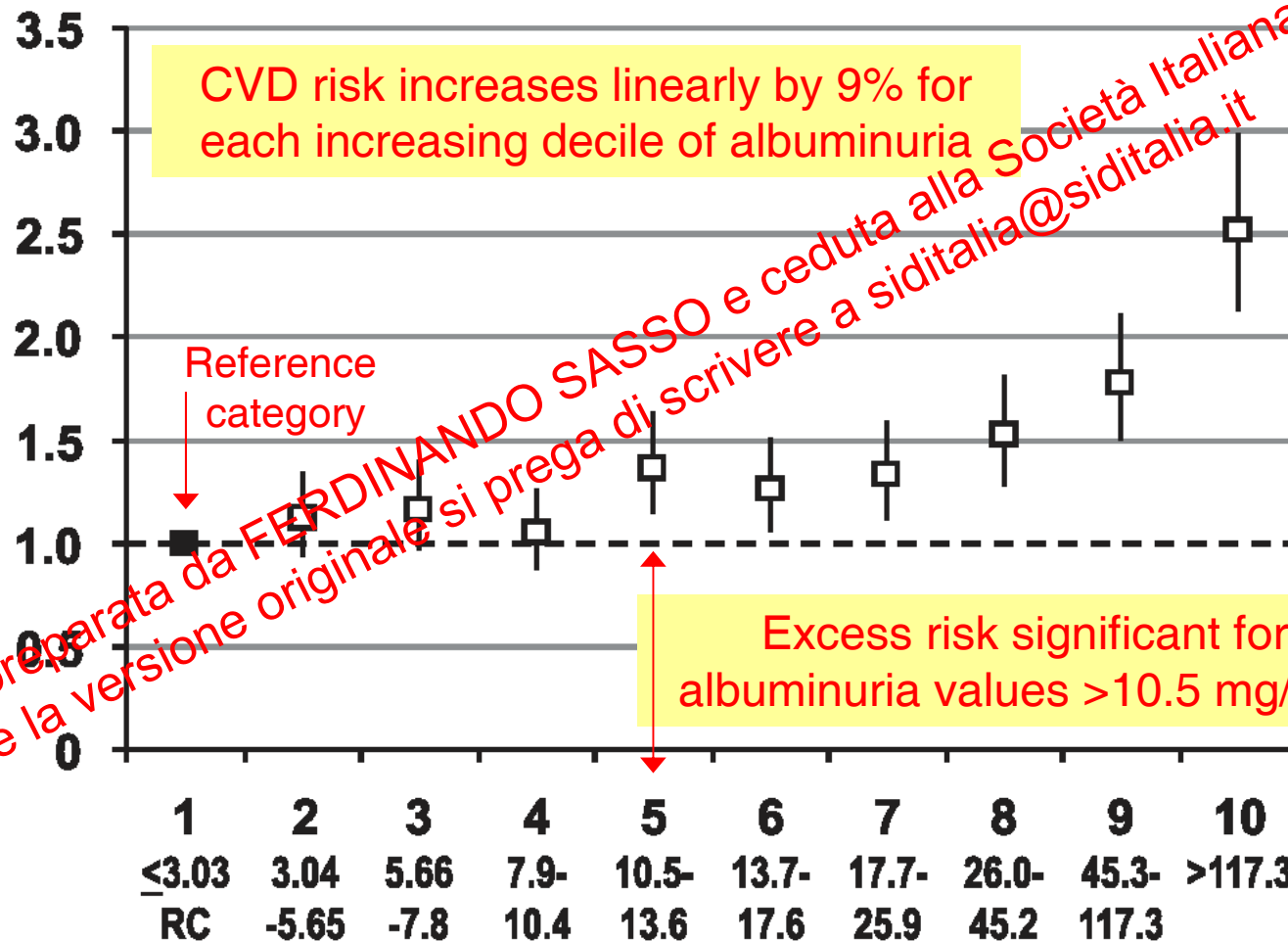
The RIACE Study:  
15,773 patients with  
T2DM

|                                        |     |       | Albuminuria                                                         |                                                                  |                |
|----------------------------------------|-----|-------|---------------------------------------------------------------------|------------------------------------------------------------------|----------------|
|                                        |     |       | Normal<br>(A1)                                                      | Mild<br>(A2)                                                     | Severe<br>(A3) |
| eGFR<br>ml/min/<br>1.73 m <sup>2</sup> | G1  | >90   | Stage 0<br>(no CKD)<br><b>62.5%</b>                                 | Stage 1-2<br>albuminuric phenotype<br><b>18.7%</b>               |                |
|                                        | G2  | 60-89 |                                                                     |                                                                  |                |
|                                        | G3a | 45-59 | Stage 3-5<br>Non<br>albuminuric<br>CKD<br>Phenotype<br><b>10.6%</b> | Stages 3-5<br><br>Albuminuric<br>CKD<br>Phenotype<br><b>8.2%</b> |                |
|                                        | G3b | 30-44 |                                                                     |                                                                  |                |
|                                        | G4  | 15-29 |                                                                     |                                                                  |                |
|                                        | G5  | <15   |                                                                     |                                                                  |                |

# The RIACE (Renal Insufficiency and Cardiovascular Events) study



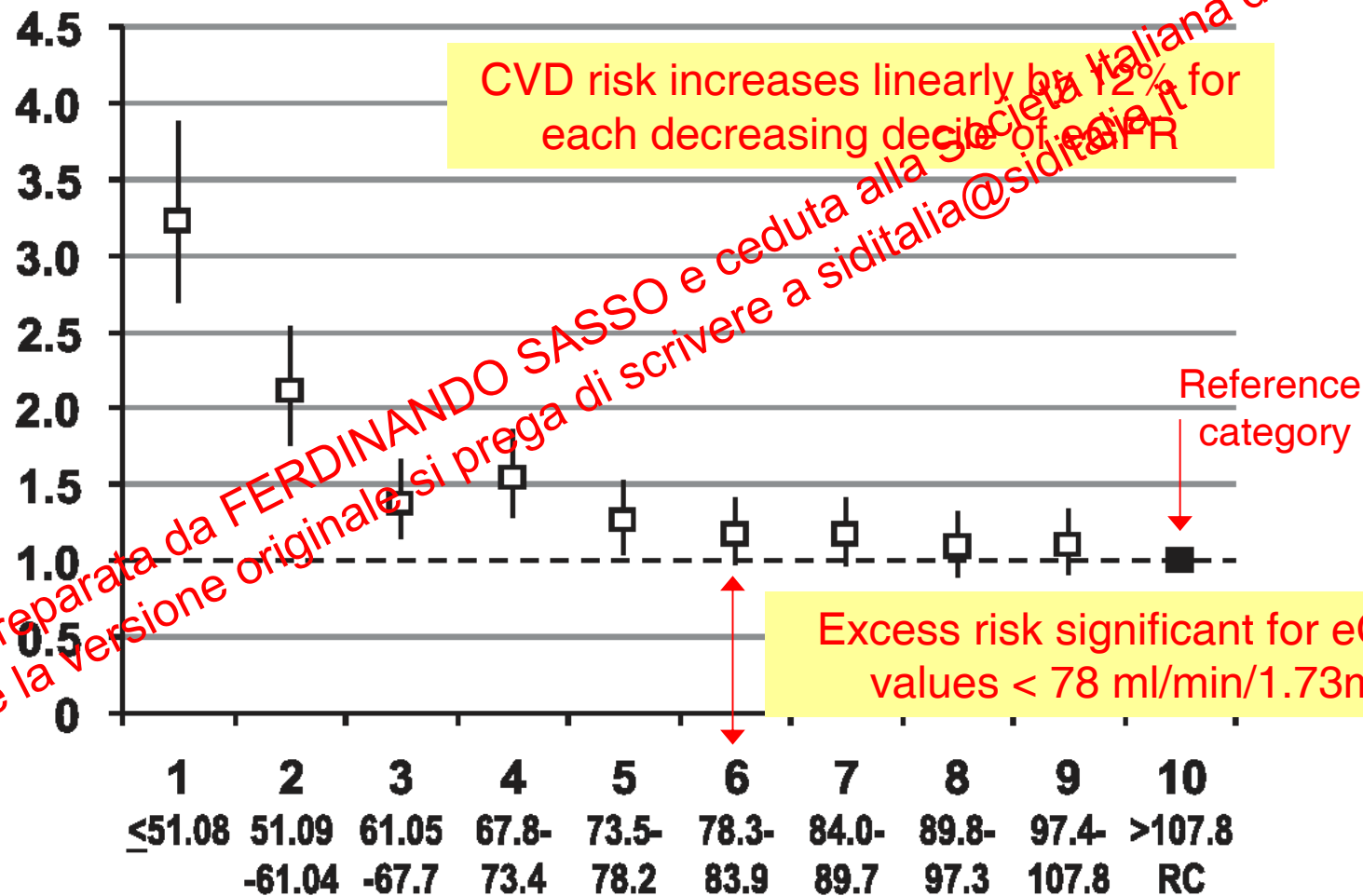
Age and sex-adjusted risk of major CVD events according to albuminuria deciles (mg/24h)



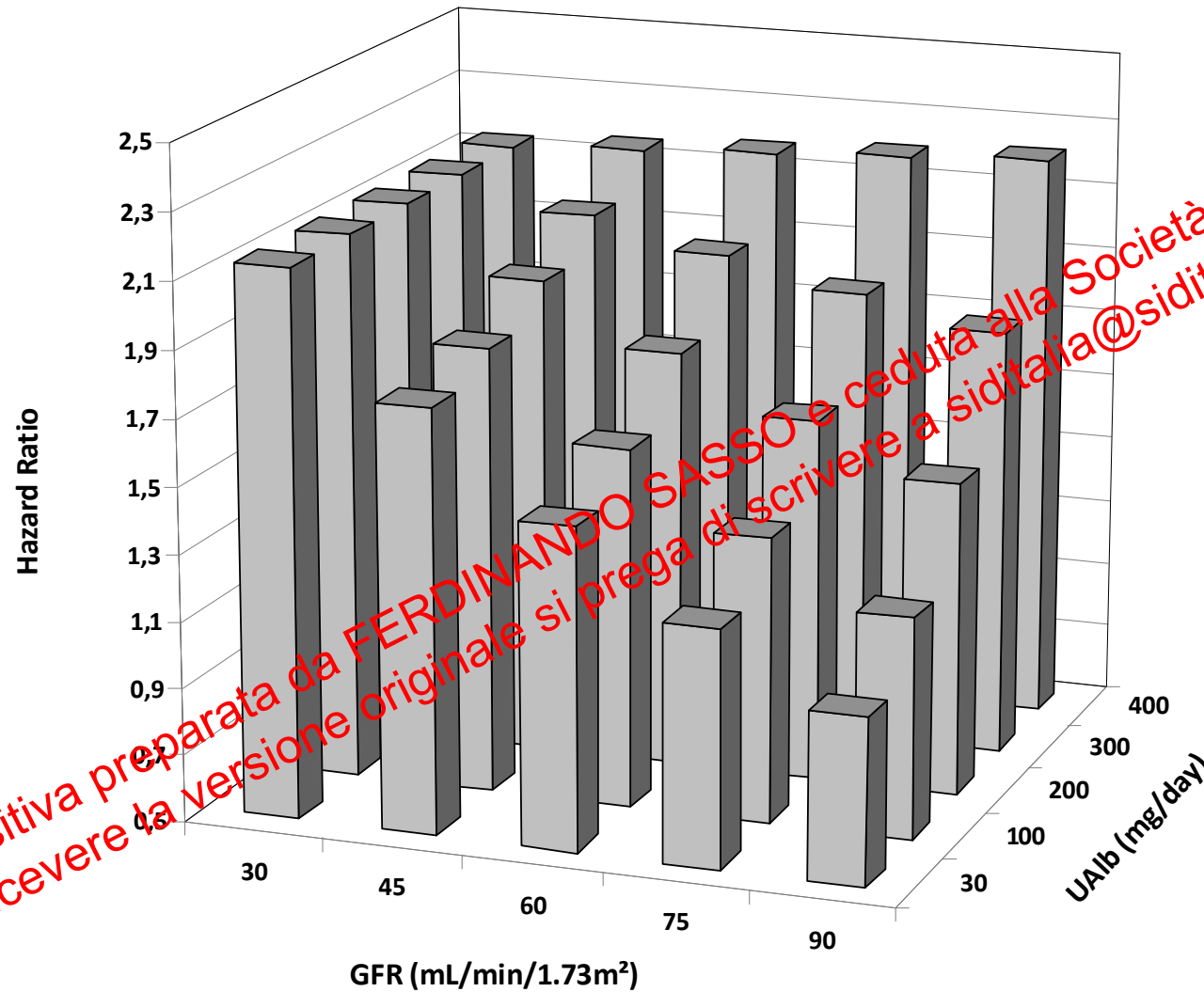
# The RIACE (Renal Insufficiency and Cardiovascular Events) study



Age and sex-adjusted risk of major CVD events according to eGFR deciles (mg/24h)



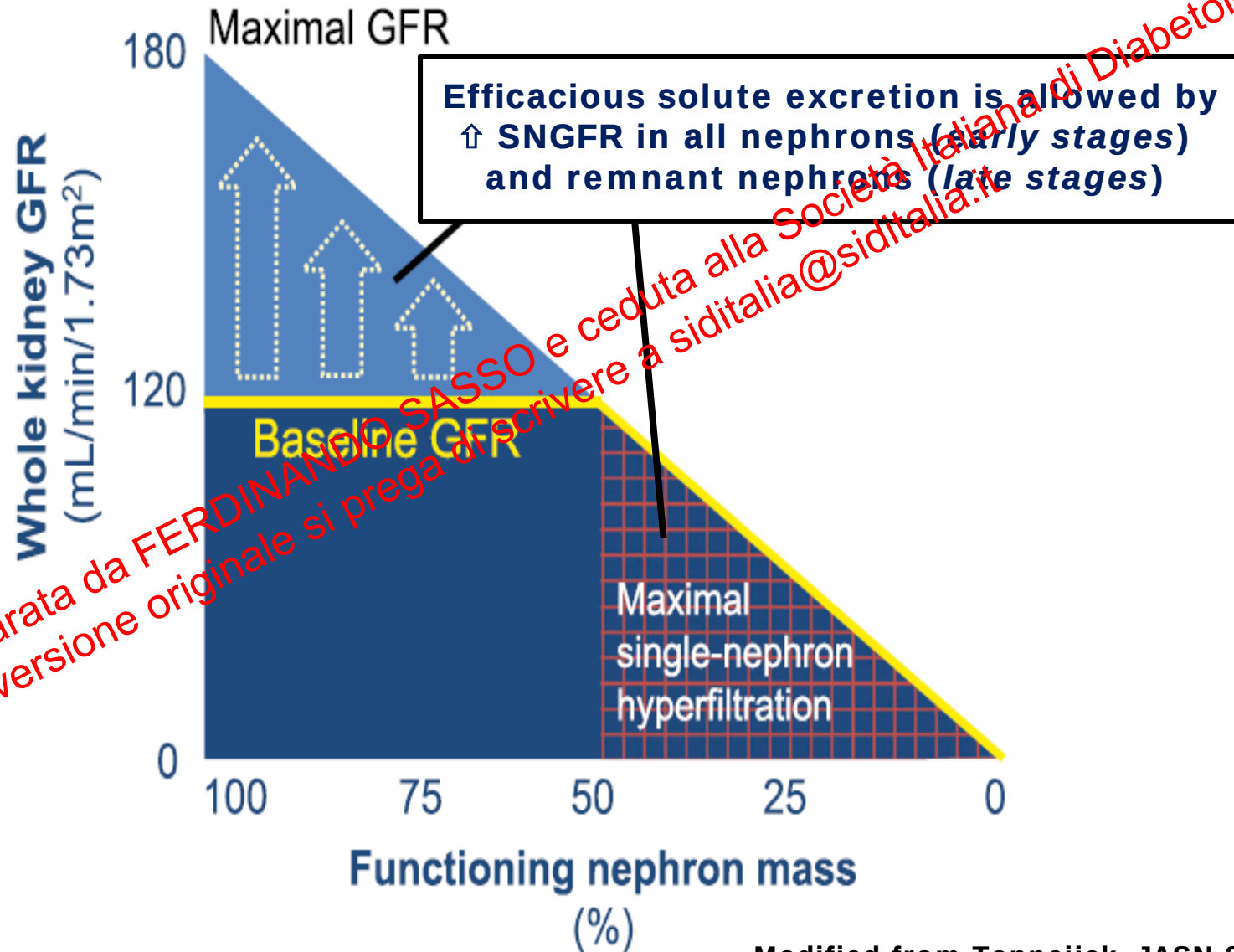
# NID-2 Study: Rischio CV e funzione renale



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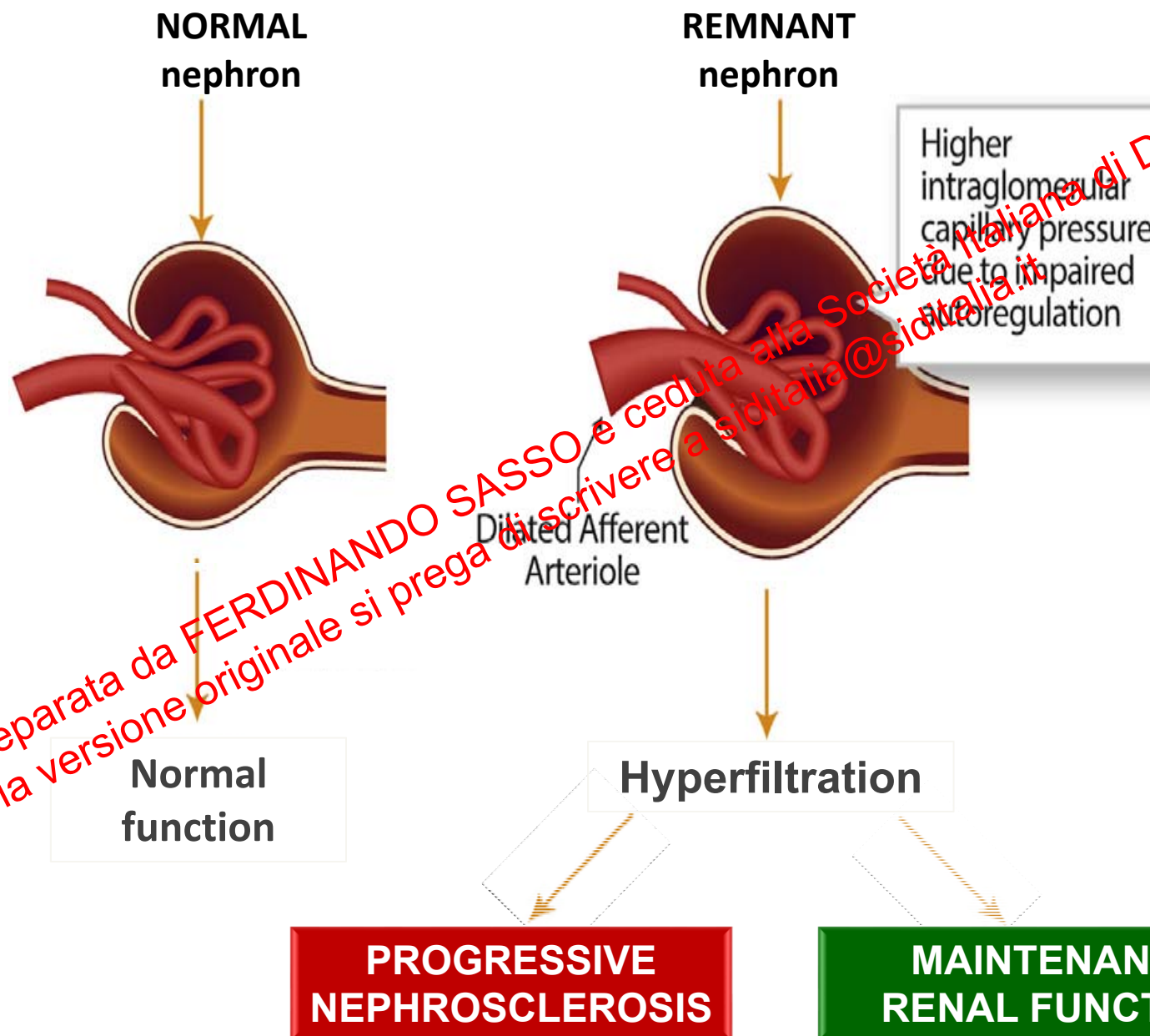


# Hyperfiltration: early and persistent compensatory mechanism to maintain adequate solute excretion in CKD



Modified from Tonneijck, JASN 2017

# Hyperfiltration: the two sides of the coin...



# Epidemiologia della CKD

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850,000,000+

People world wide have kidney diseases

10.4% men and 11.8% women



Mark D. Okusa,  
President ASN 2018



Oct 2018

Jager, Kidney Int, 30 Sept 2019

# Analysis of the Global Burden of Disease study highlights the global, regional, and national trends of chronic kidney disease epidemiology from 1990 to 2016

Yan Xie<sup>1</sup>, Benjamin Bowe<sup>1</sup>, Ali H. Mokdad<sup>2</sup>, Hong Xian<sup>1,3</sup>, Yan Yan<sup>1,4</sup>, Tingting Li<sup>1,5</sup>, Geetha Maddukuri<sup>1,6</sup>, Cheng-You Tsai<sup>1,3</sup>, Tasheia Floyd<sup>1,6</sup> and Ziyad Al-Aly<sup>1,5,7,8</sup>

Kidney International (2018) 94, 567–581;

**The significant increase of global burden of CKD is primarily driven by demographic expansion and aging**

|                   | Change in the last 25 years (1990-2016) |                           |                                           |
|-------------------|-----------------------------------------|---------------------------|-------------------------------------------|
|                   | Absolute<br>(100,000 persons)           | Rate<br>(100,000 persons) | Age-standardized rate<br>(100,000 person) |
| Incidence of CKD  | +89%                                    | +34%                      | +4%                                       |
| Prevalence of CKD | +87%                                    | +33%                      | +0.4%                                     |
| Death due to CKD  | +98%                                    | +41%                      | +8%                                       |
| DALYs* due to CKD | +62%                                    | +16%                      | -4%                                       |

\*DALYs: *Disability-Adjusted Life-Years* = (years lost due to premature death + years living with disability due to CKD)



Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017

GBD 2017 Causes of Death Collaborators\*

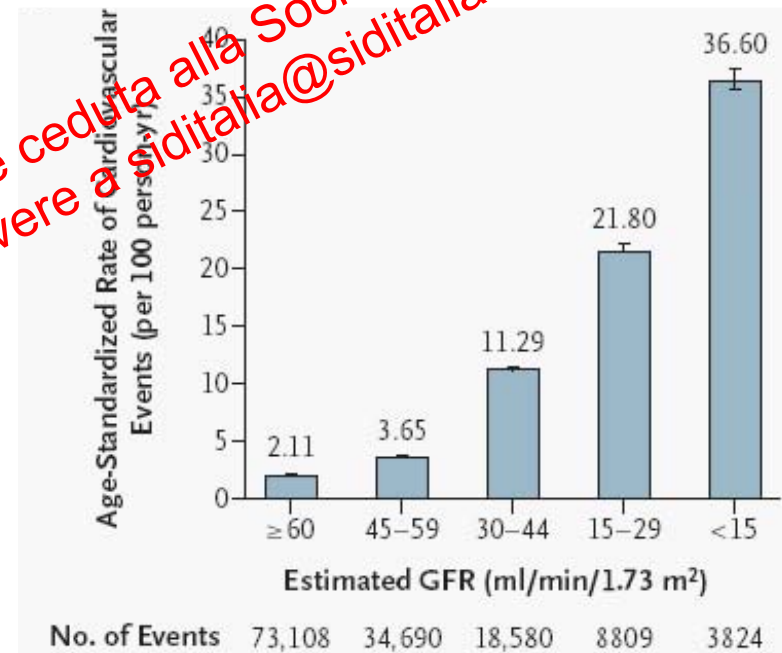
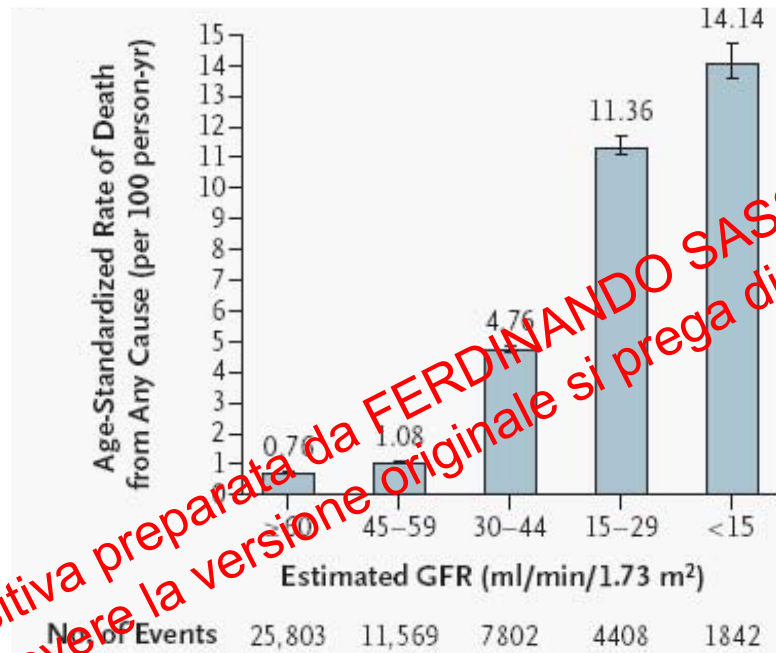
Lancet 2018; 392: 1736–88

## Ten-year change in mortality rate by CKD cause

|                                                            | All-age deaths (thousands)   |                            | Age-standardised death rate (per 100 000) |                            | All-age YLL (thousands)            |                            | Age-standardised YLL rate (per 100 000) |                            |
|------------------------------------------------------------|------------------------------|----------------------------|-------------------------------------------|----------------------------|------------------------------------|----------------------------|-----------------------------------------|----------------------------|
|                                                            | 2017                         | Percentage change, 2007–17 | 2017                                      | Percentage change, 2007–17 | 2017                               | Percentage change, 2007–17 | 2017                                    | Percentage change, 2007–17 |
| Chronic kidney disease                                     | 1230.2<br>(1195.1 to 1258.8) | 33.7%<br>(30.5 to 36.1)*   | 13.1<br>(12.5 to 13.7)                    | 1.5%<br>(–0.9 to 3.2)      | 28 508.5<br>(27 610.2 to 29 314.0) | 21.0%<br>(18.2 to 23.5)*   | 359.4<br>(348.2 to 369.6)               | –2.5%<br>(–4.7 to –0.6)*   |
| Chronic kidney disease due to type 1 diabetes mellitus     | 77.3<br>(62.4 to 95.2)       | 23.2%<br>(19.0 to 27.4)*   | 0.9<br>(0.8 to 1.2)                       | –1.2%<br>(–4.0 to 1.2)     | 2622.0<br>(2121.7 to 3205.5)       | 17.8%<br>(13.6 to 22.3)*   | 31.9<br>(25.9 to 38.9)                  | –2.9%<br>(–5.6 to –0.3)*   |
| Chronic kidney disease due to type 2 diabetes mellitus     | 349.0<br>(321.8 to 395.8)    | 41.1%<br>(36.4 to 43.6)*   | 4.5<br>(4.0 to 5.1)                       | 4.2%<br>(1.4 to 6.2)*      | 6671.9<br>(5825.5 to 7625.9)       | 35.4%<br>(31.0 to 38.7)*   | 82.8<br>(72.4 to 94.5)                  | 2.9%<br>(–0.2 to 5.2)      |
| Chronic kidney disease due to hypertension                 | 365.7<br>(346.6 to 391.5)    | 41.4%<br>(37.4 to 44.2)*   | 4.6<br>(4.0 to 5.2)                       | 3.2%<br>(0.4 to 5.2)*      | 5954.8<br>(5175.1 to 6741.9)       | 33.4%<br>(29.3 to 36.5)*   | 75.2<br>(65.4 to 84.9)                  | 2.3%<br>(–0.7 to 4.5)      |
| Chronic kidney disease due to glomerulonephritis           | 189.7<br>(165.2 to 217.3)    | 25.5%<br>(22.1 to 28.8)*   | 2.4<br>(2.1 to 2.8)                       | –1.3%<br>(–3.2 to 0.7)     | 5554.9<br>(4929.1 to 6250.8)       | 12.7%<br>(9.6 to 16.1)*    | 70.6<br>(62.8 to 79.4)                  | –5.5%<br>(–7.5 to –3.3)*   |
| Chronic kidney disease due to other and unspecified causes | 266.8<br>(232.8 to 304.0)    | 25.9%<br>(22.4 to 29.4)*   | 3.4<br>(3.0 to 3.9)                       | –1.4%<br>(–3.7 to 0.6)     | 7704.8<br>(6794.9 to 8614.8)       | 10.0%<br>(6.8 to 13.4)*    | 98.9<br>(87.4 to 110.0)                 | –7.7%<br>(–9.9 to –5.4)*   |

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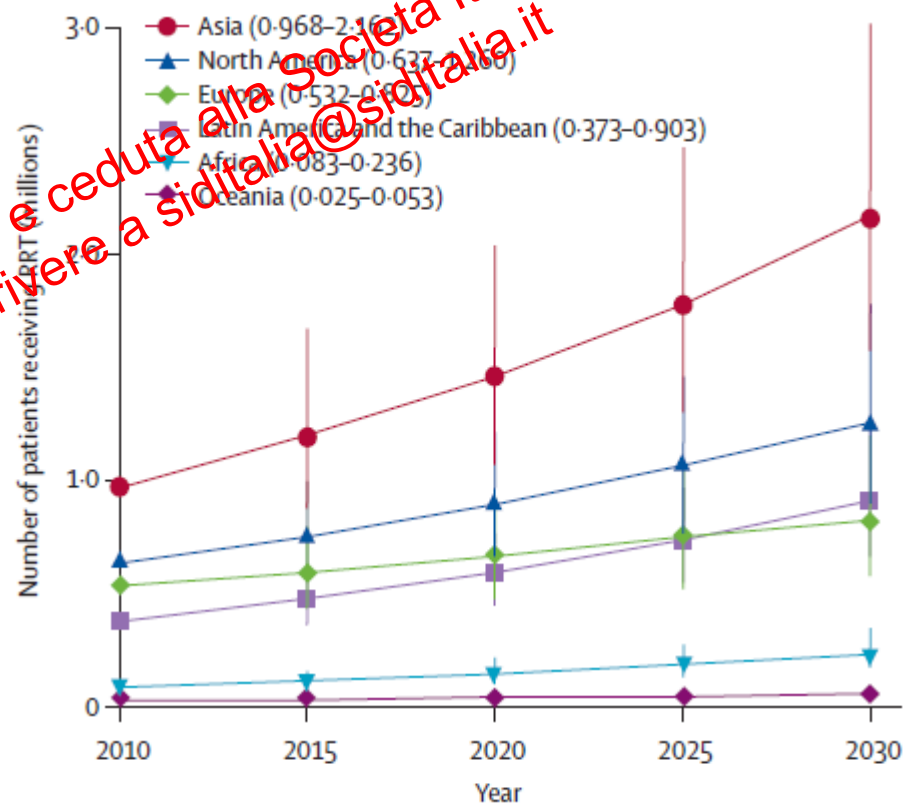
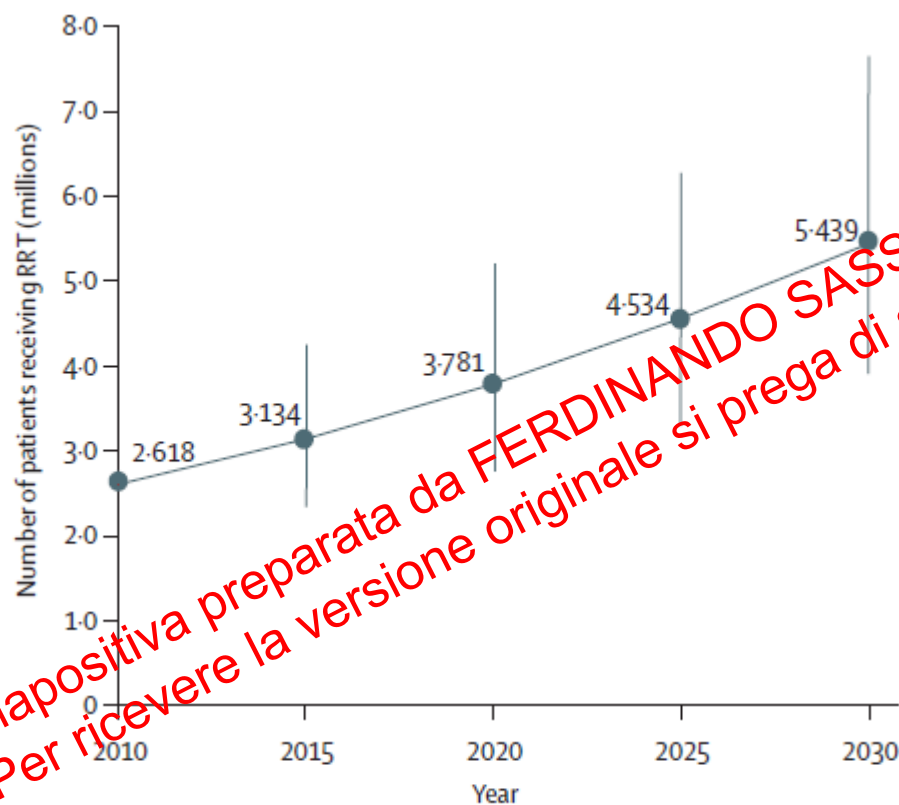
# Il rischio CV aumenta sin dalle fasi iniziali della CKD



Go, NEJM 2004

Se non riusciamo a rallentare/fermare  
la progressione della CKD...

...nel 2030 (vs 2010) avremo il doppio dei pazienti in dialisi





# Chronic kidney disease prevalence in the general population: heterogeneity and concerns

Luca De Nicola<sup>1</sup> and Carmine Zoccali<sup>2</sup>

Nephrol Dial Transplant (2016) 31: 331–335

| Country      | Period         | N            | eGFR           | CKD, %     |
|--------------|----------------|--------------|----------------|------------|
| Poland       | 2011           | 2,413        | CKD-EPI        | 5.8        |
| Tanzania     | 2014           | 481          | MDRD           | 7.0        |
| <b>Italy</b> | <b>2008-12</b> | <b>7,552</b> | <b>CKD-EPI</b> | <b>7.1</b> |
| India        | 2010-11        | 9,797        | CKD-EPI        | 7.5        |
| Spain        | 2004-08        | 2,746        | MDRD           | 9.1        |
| Malaysia     | 2011           | 878          | CKD-EPI        | 9.1        |
| Sweden       | 1990-94        | 2,489        | MDRD           | 10.4       |
| Netherlands  | 1997-98        | 2,489        | MDRD           | 10.4       |
| China        | 2007-10        | 47,204       | MDRD           | 10.8       |
| Australia    | 1999-00        | 10,949       | CKD-EPI        | 11.5       |
| England      | 2009-10        | 5,799        | CKD-EPI        | 11.9       |
| Canada       | 2007-09        | 3,689        | CKD-EPI        | 12.5       |
| USA          | 1999-04        | 13,233       | MDRD           | 13.1       |

- CKD Stage 1-5 : 10.4% (95%CI 11.7-15.1%)
- CKD Stage 3-5 : 3.8% (95%CI 9.2–12.2%)

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# Epidemiology of Diabetic CKD



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# Osservatorio ARNO Diabete

*Il profilo assistenziale della popolazione con diabete*



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Rapporto 2019  
Volume XXXI  
Collana Rapporti Arno

Grafico 23<sup>15</sup>

Le 10 più frequenti diagnosi principali nei ricoveri ordinari in soggetti con e senza diabete  
(tassi per 1000 soggetti)

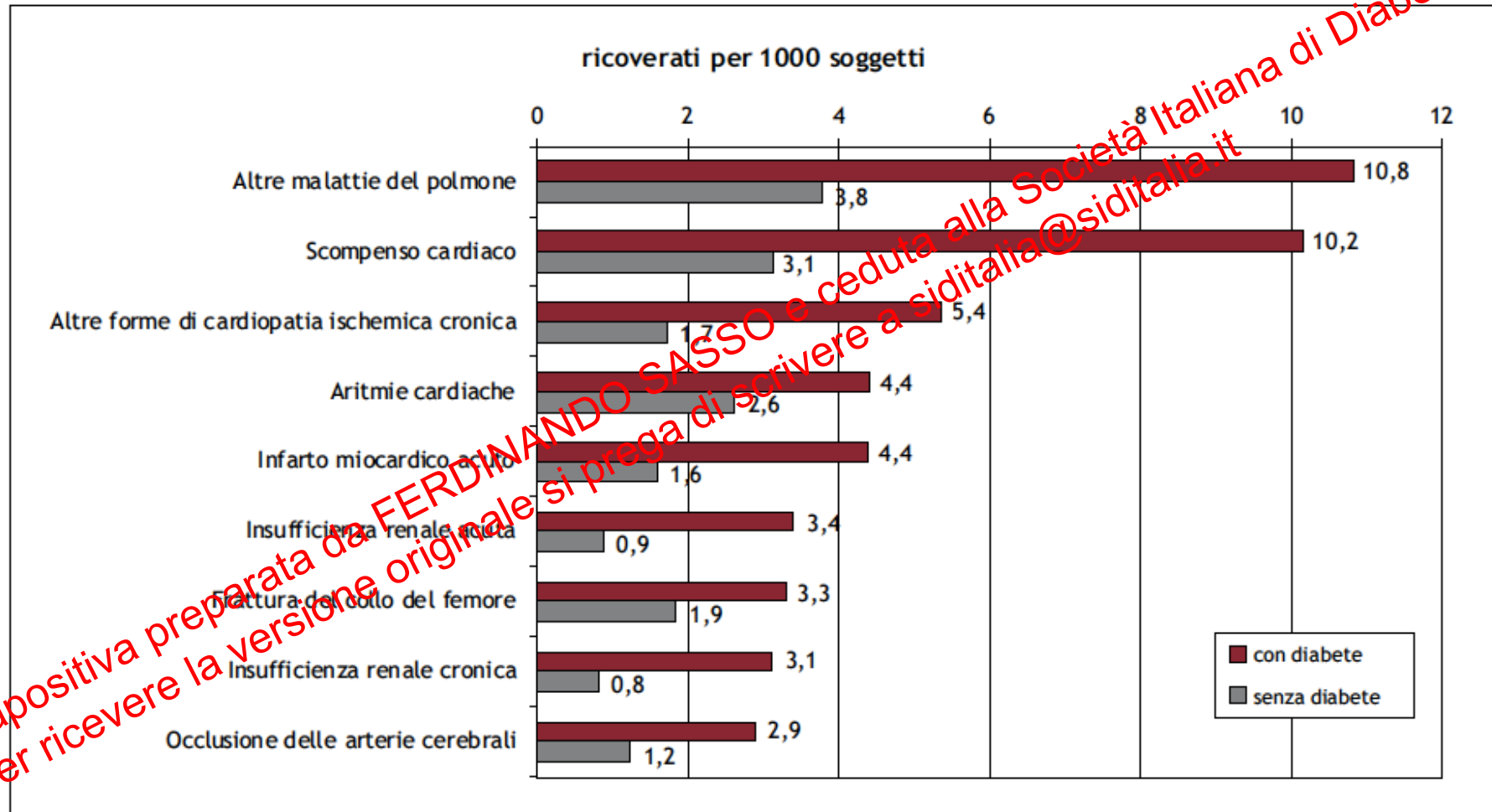
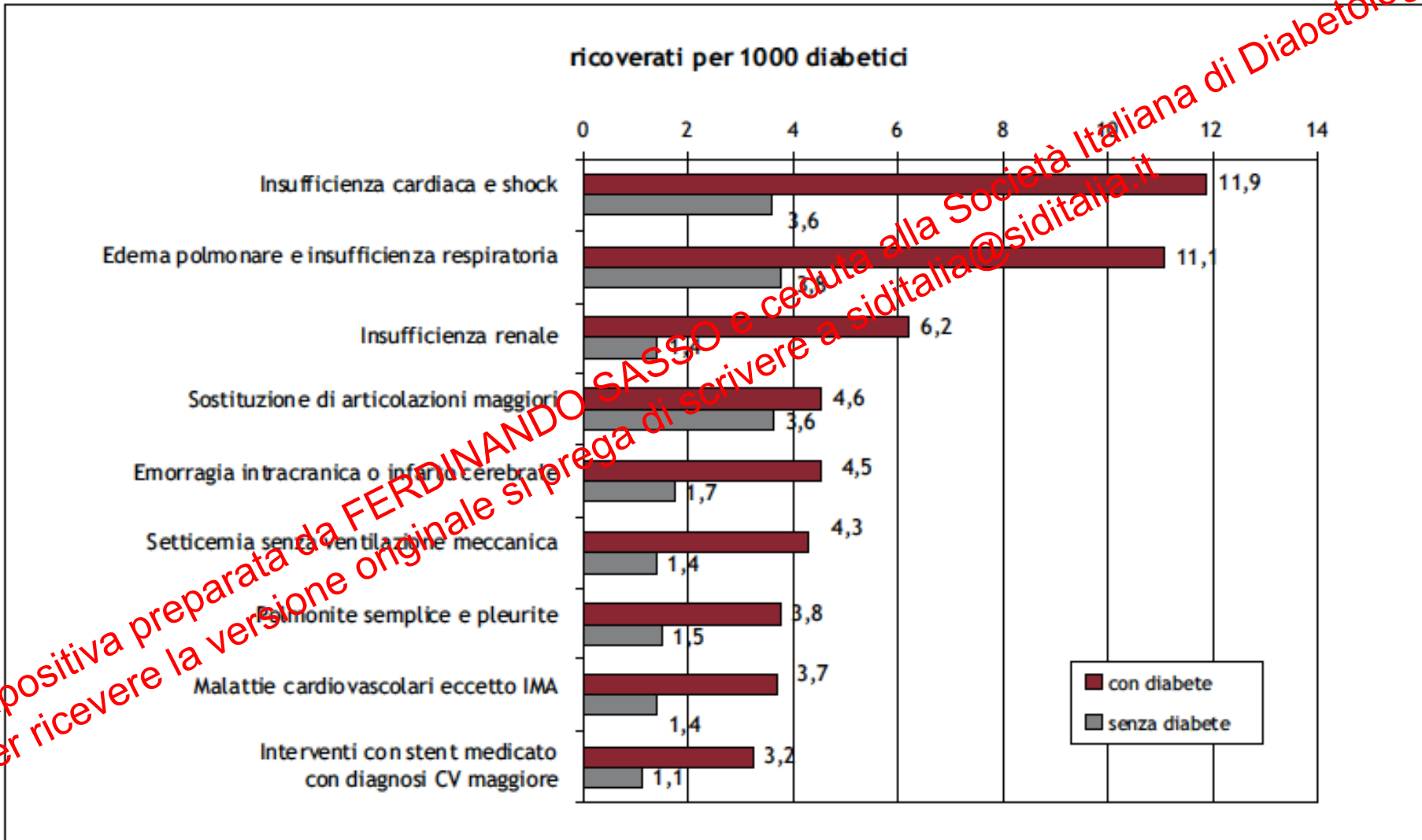


Grafico 28<sup>17</sup>

I 10 più frequenti DRG in caso di ricovero ordinario nei soggetti con e senza diabete  
(tassi per 1000 soggetti)





Frequenza di alcuni indicatori di esito in ambito diabetologico (ricoveri e procedure)

| Indicatore                                           | N. pazienti | % (N=697.208) | Δ% Casi vs Controlli | % Femmine (N=341.269) | % Maschi (N=355.939) |
|------------------------------------------------------|-------------|---------------|----------------------|-----------------------|----------------------|
| Malattie apparato circolatorio (ICD-IX: 390-459)     | 29.302      | 4,2           | 105%                 | 3,4                   | 4,9                  |
| Cardiopatia ischemica (ICD-IX: 410-414)              | 7.421       | 1,1           | 188%                 | 0,6                   | 1,5                  |
| Diabete (ICD-IX: 250)                                | 7.113       | 1,0           | -                    | 0,8                   | 1,2                  |
| Vasculopatia cerebrale (ICD-IX: 430-434;436;437-438) | 5.664       | 0,8           | 92%                  | 0,8                   | 0,8                  |
| Infarto miocardico acuto (ICD-IX: 410)               | 2.293       | 0,3           | 161%                 | 0,2                   | 0,4                  |
| Insufficienza renale (ICD-IX: 585-586)               | 1.767       | 0,3           | 329%                 | 0,2                   | 0,3                  |
| Emodialisi (Spec. 39.95.1 - 39.95.9)                 | 1.693       | 0,2           | 275%                 | 0,2                   | 0,3                  |
| Rivascolarizzazione coronarica (Intervento : 36.0X)  | 1.435       | 0,2           | 221%                 | 0,1                   | 0,3                  |
| Obterioopatia arti inferiori (ICD-IX: 440.2X)        | 1.400       | 0,2           | 286%                 | 0,1                   | 0,3                  |
| Fotocoagulazione retinica (Spec. 14.33-14.34)        | 1.395       | 0,2           | 353%                 | 0,2                   | 0,2                  |

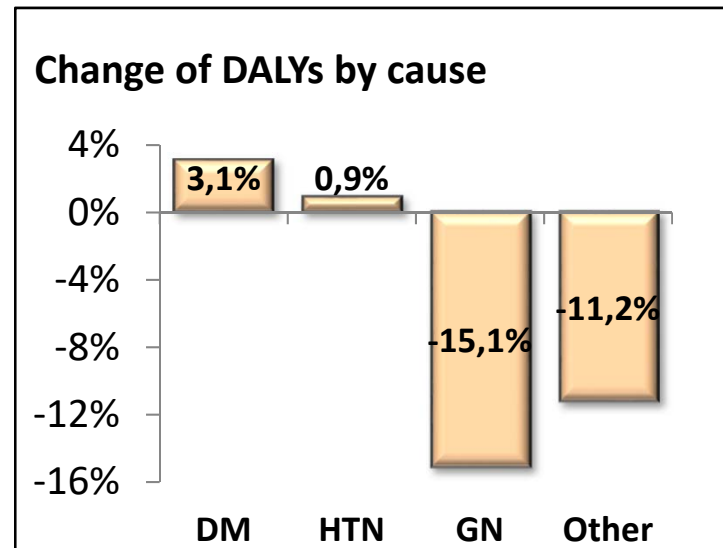
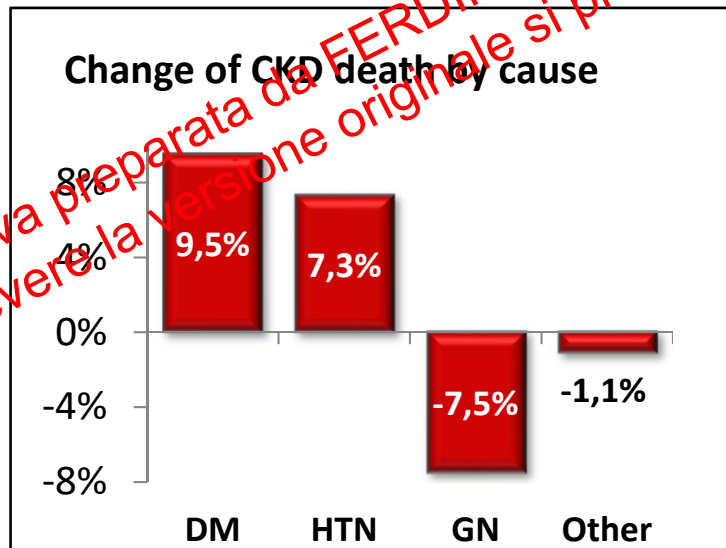
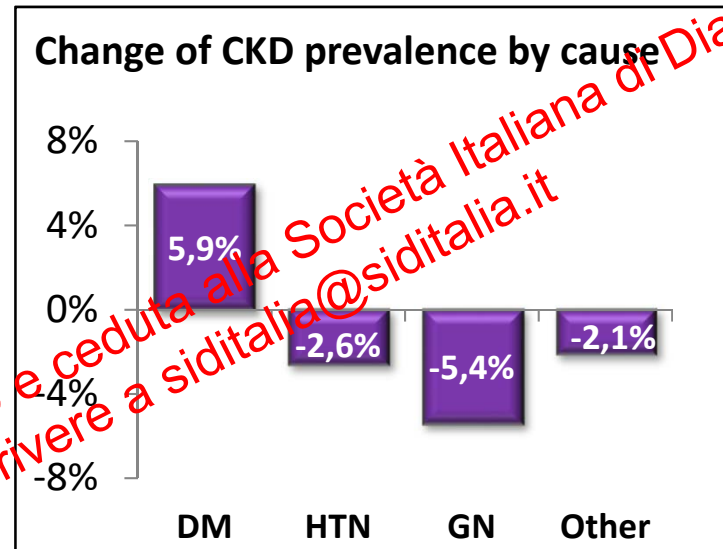
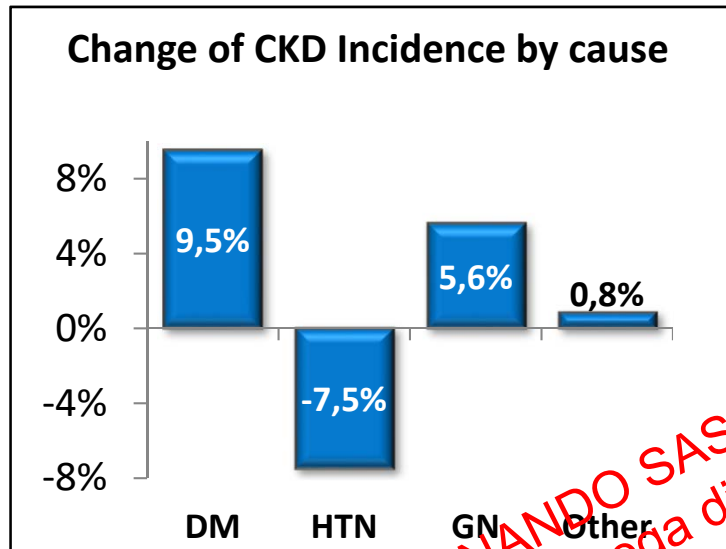
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# Analysis of the Global Burden of Disease study highlights the global, regional, and national trends of chronic kidney disease epidemiology from 1990 to 2016

*Kidney International* (2018) **94**, 567–581

Changes of Age-standardized rate (100,000 person)



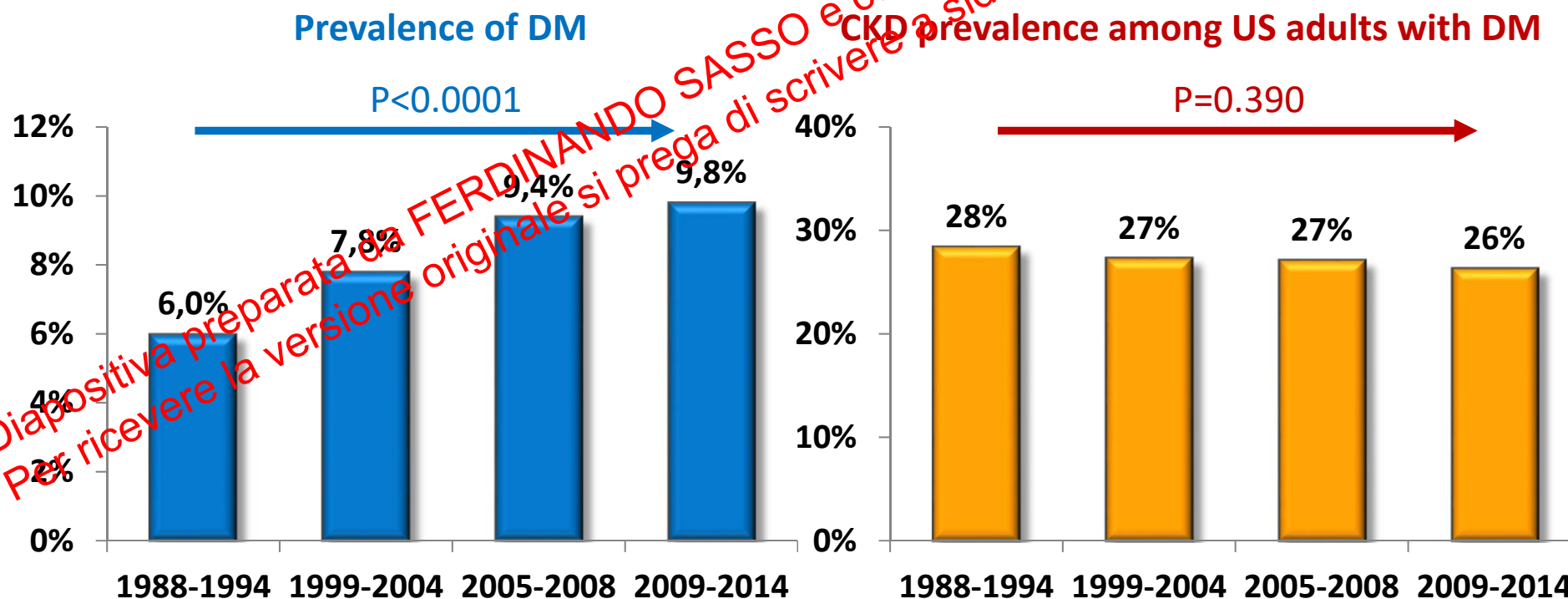
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# Clinical Manifestations of Kidney Disease Among US Adults With Diabetes, 1988-2014

Maryam Afkarian, MD, PhD; Leila R. Zelnick, PhD; Yoshio N. Hall, MD; Patrick J. Heagerty, PhD;  
Katherine Tuttle, MD, FASN, FACP; Noel S. Weiss, MD, DrPH; Ian H. de Boer, MD, MS

JAMA. 2016;316(17):602-610.

**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.



**Come si sta modificando negli ultimi decenni la prevalenza dei markers di CKD nel DM2?**

- a) La prevalenza di ACR  $>30\text{mg/g}$  sta aumentando
- b) La prevalenza di GFR  $<60\text{ ml/min/1.73m}^2$  sta riducendosi
- c) La prevalenza di ACR  $>30\text{mg/g}$  sta riducendosi e di GFR  $<60\text{ ml/min/1.73m}^2$  sta aumentando
- d) La prevalenza di ACR  $>30\text{mg/g}$  sta aumentando e di GFR  $<60\text{ ml/min/1.73m}^2$  sta riducendosi

Diapositiva preparata da FERDINANDO SASO e ceduta alla Società Italiana di Diabetologia.  
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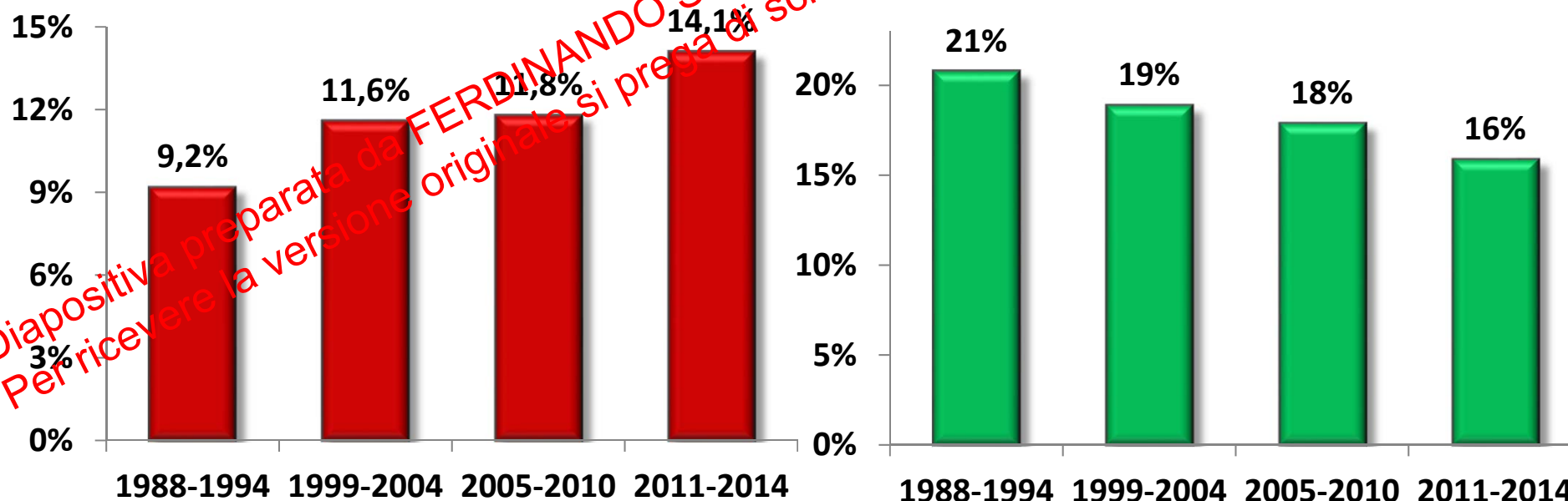
## Prevalence of CKD markers among US adults with DM

GFR<60 mL/min/1.73m<sup>2</sup>

P<0.0001

ACR≥30 mg/g

P<0.0001

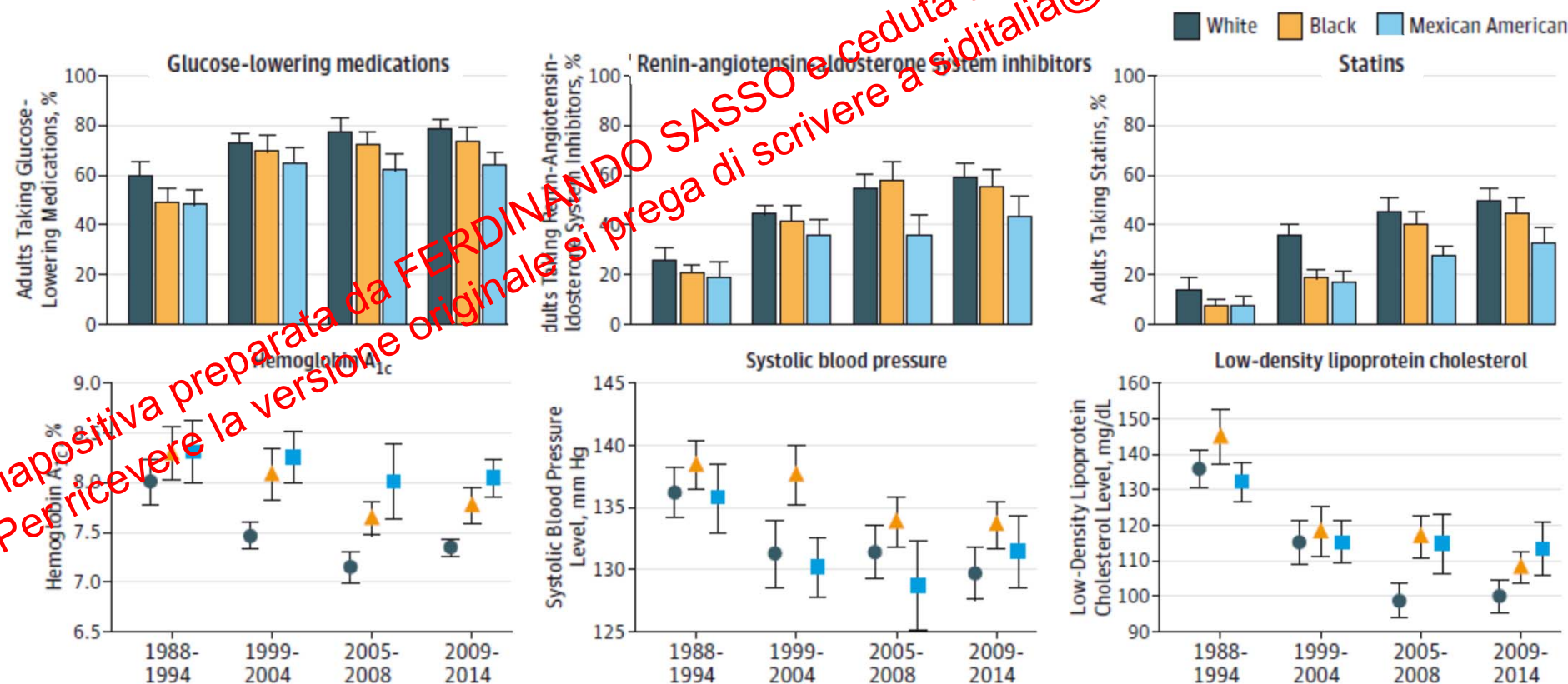


# Clinical Manifestations of Kidney Disease Among US Adults With Diabetes, 1988-2014

Maryam Afkarian, MD, PhD; Leila R. Zelnick, PhD; Yoshio N. Hall, MD; Patrick J. Heagerty, PhD;  
Katherine Tuttle, MD, FASN, FACP; Noel S. Weiss, MD, DrPH; Ian H. de Boer, MD, MS

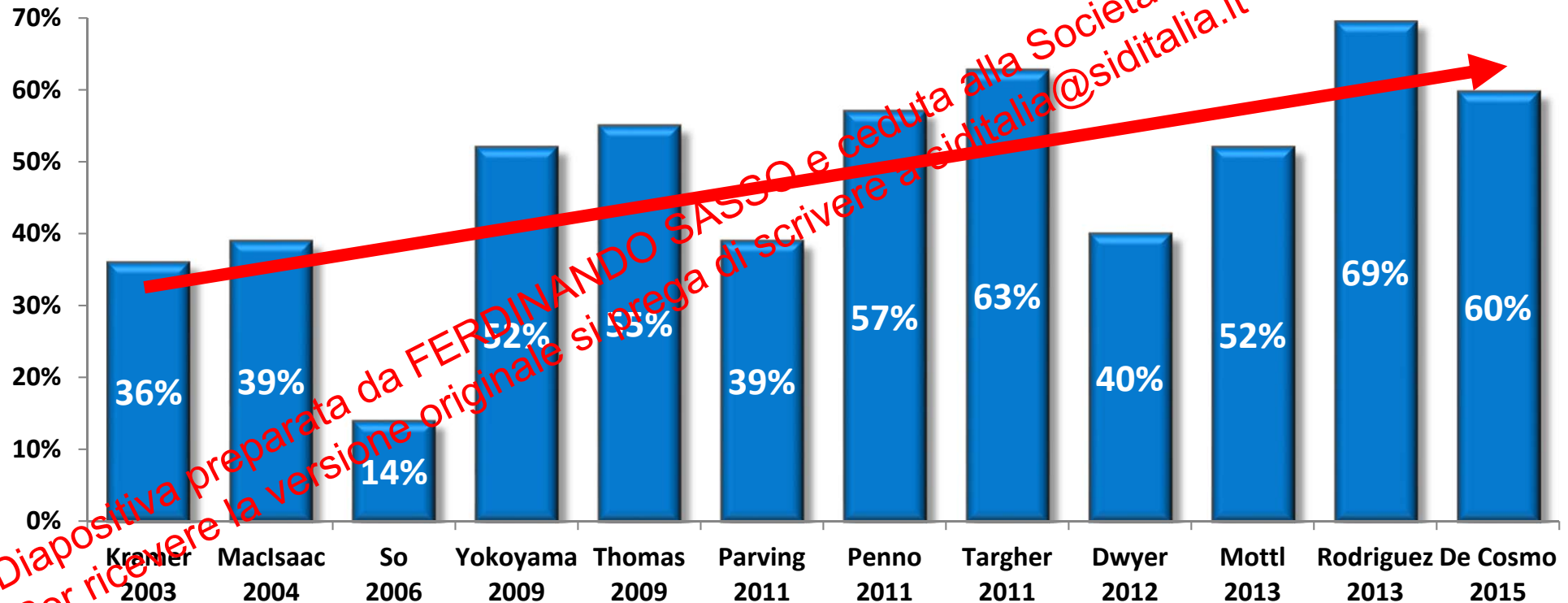
JAMA. 2016;316(19):602-610.

The lower prevalence of albuminuria observed over time may be attributable to a higher rate of glucose-lowering drugs, RAAS inhibitors, and statins with a consequent lower HbA1c, SBP and LDL





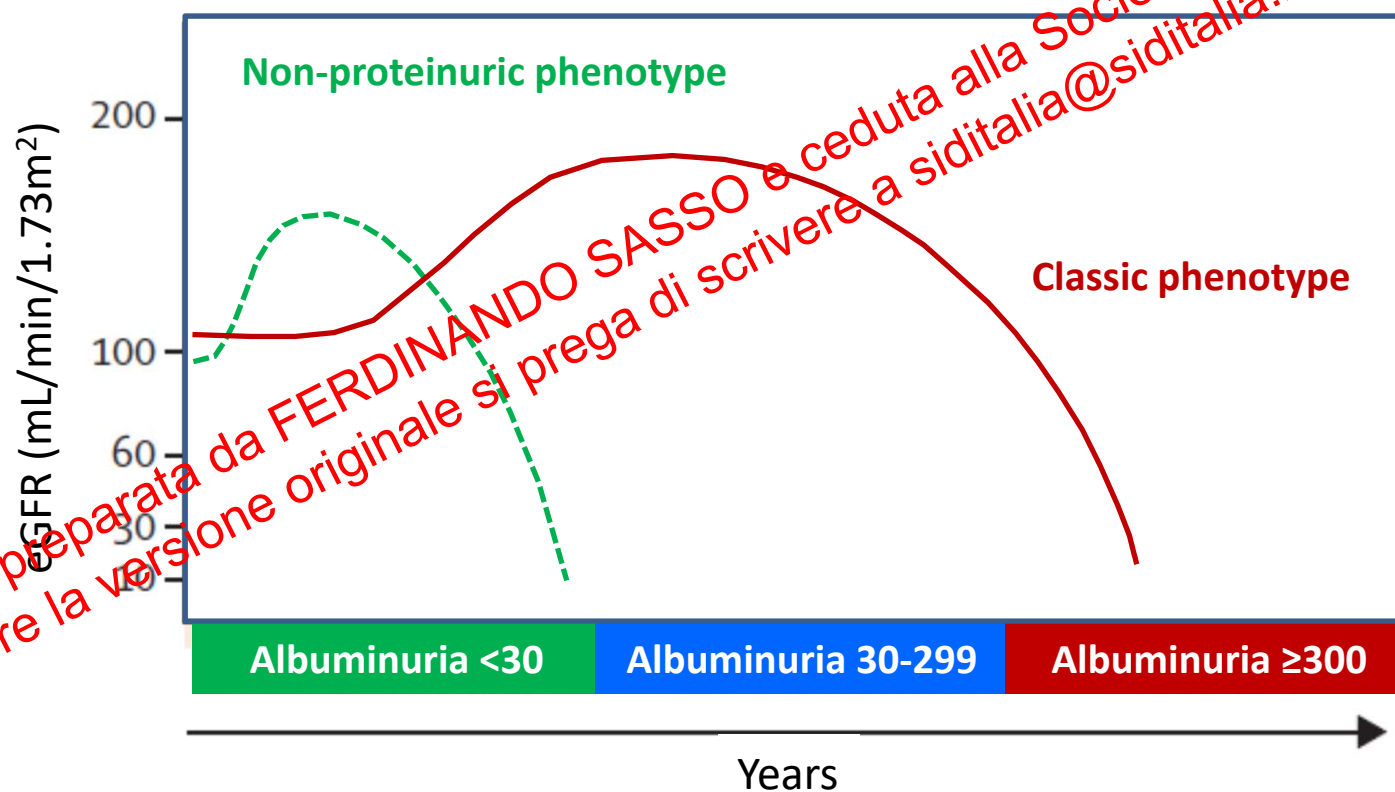
# Increasing prevalence of the non-proteinuric phenotype of renal disease in cross-sectional studies in type 2 diabetes



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# Evolution of renal function in the classic versus non-proteinuric phenotype of diabetic kidney disease



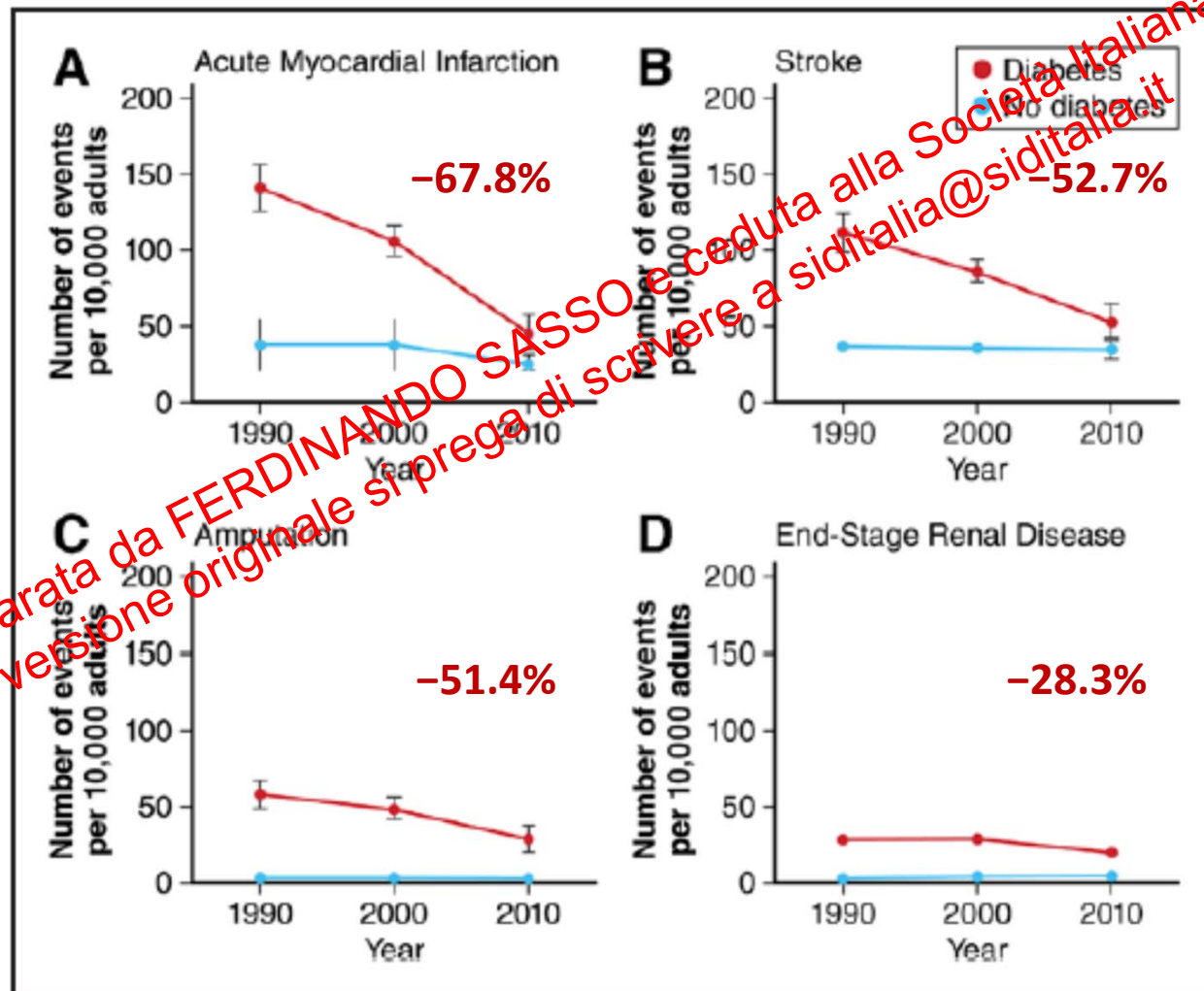
# Prognosis of Diabetic CKD



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

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



**Il fenotipo non albuminurico della DKD nel DM2 si associa a:**

- a) Minor mortalità**
- b) Minor rischio CV**
- c) Minor rischio renale**
- d) a+b+c**

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# Increasing Mortality in Adults With Diabetes and Low Estimated Glomerular Filtration Rate in the Absence of Albuminuria

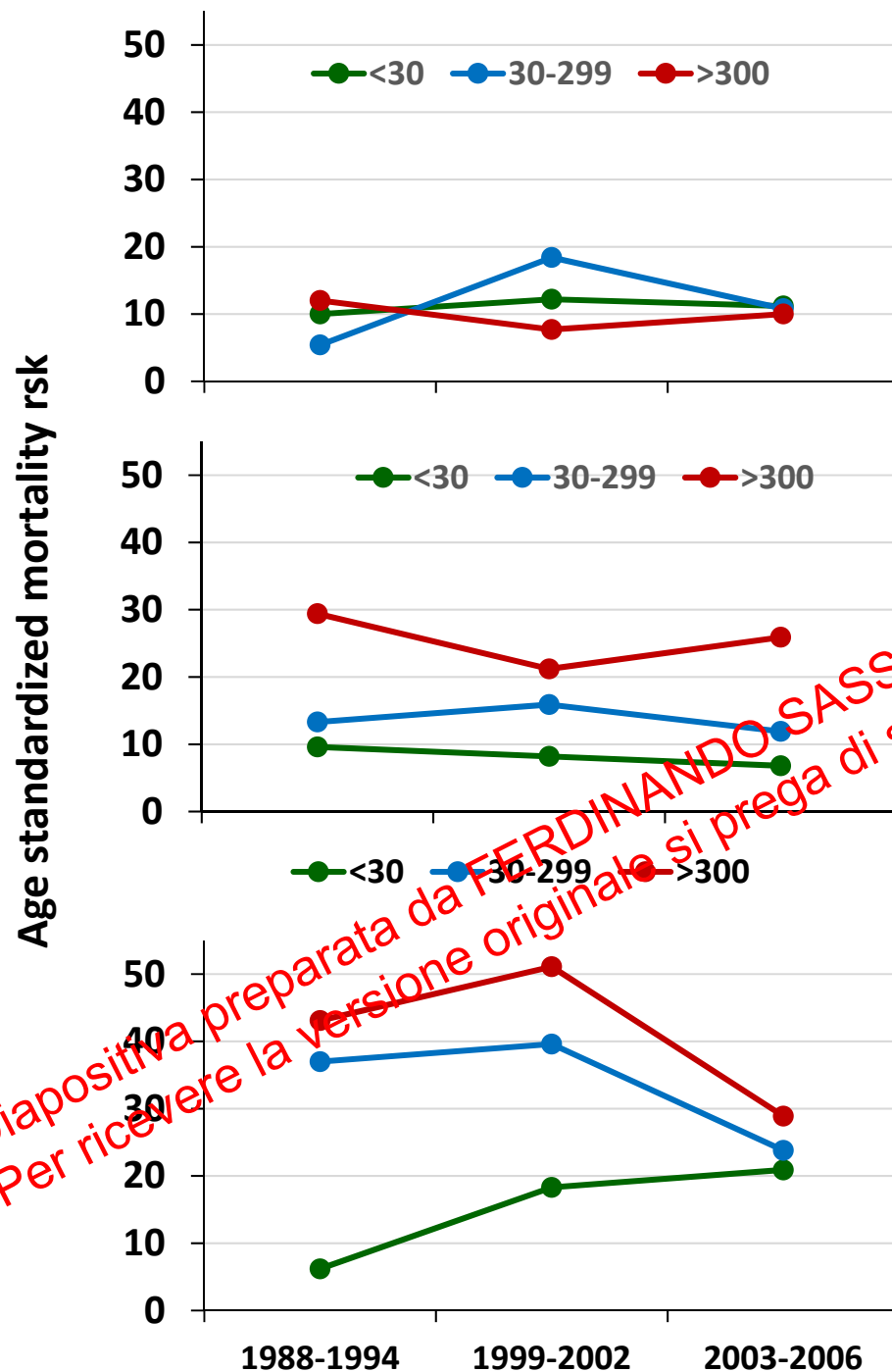
Holly Kramer,<sup>1,2,3</sup> Robert E. Boucher,<sup>4</sup>  
David Leehey,<sup>2,3</sup> Linda Fried,<sup>5</sup> Guo Wei,<sup>4</sup>  
Tom Greene,<sup>4</sup> Sylvia E. Rosas,<sup>6</sup>  
Richard Cooper,<sup>1</sup> Guichan Cao,<sup>1</sup>  
and Srinivasan Beddhu<sup>4,7</sup>

Diabetes Care Publish Ahead of Print, published online February 7, 2018

## RESEARCH DESIGN AND METHODS

Data from the National Health and Nutrition Examination Surveys (NHANES) 1988–2006 were used to examine mortality trends in adults with diabetes, defined as physician diagnosis, fasting glucose  $\geq 126$  mg/dL, hemoglobin A<sub>1c</sub>  $>6.5\%$  (48 mmol/mol), or use of glucose-lowering medications. Mortality trends by CKD phenotype (estimated glomerular filtration rate [eGFR] and urine albumin-to-creatinine ratio [ACR] level)

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GFR  $\geq 90$  mL/min/1.73m<sup>2</sup>

GFR 60-89 mL/min/1.73m<sup>2</sup>

GFR  $< 60$  mL/min/1.73m<sup>2</sup>

Diapositiva preparata da FERDINANDO SASSO e ceduta alla Società Italiana di Diabetologia.  
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# Non-albuminuric renal impairment is a strong predictor of mortality in individuals with type 2 diabetes: the Renal Insufficiency And Cardiovascular Events (RIACE) Italian multicentre study

Giuseppe Penno<sup>1</sup> • Anna Solini<sup>2</sup> • Emanuela Orsi<sup>3</sup> • Enzo Bonora<sup>4</sup> • Cecilia Fondelli<sup>5</sup> • Roberto Trevisan<sup>6</sup> • Monica Vedovato<sup>7</sup> • Franco Cavalot<sup>8</sup> • Olga Lamacchia<sup>9</sup> • Marco Scardapane<sup>10</sup> • Antonio Nicolucci<sup>10</sup> • Giuseppe Pugliese<sup>11</sup>  • for the Renal Insufficiency And Cardiovascular Events (RIACE) Study Group

- Prospective cohort of 15,656 individuals with DM2 enrolled in 2006-2008
- Outcome: all-cause mortality (mean follow-up 7.4 years) in patients stratified by albuminuria (AER>30 mg/d) and/or low GFR (<60 mL/min/1.73m<sup>2</sup>)

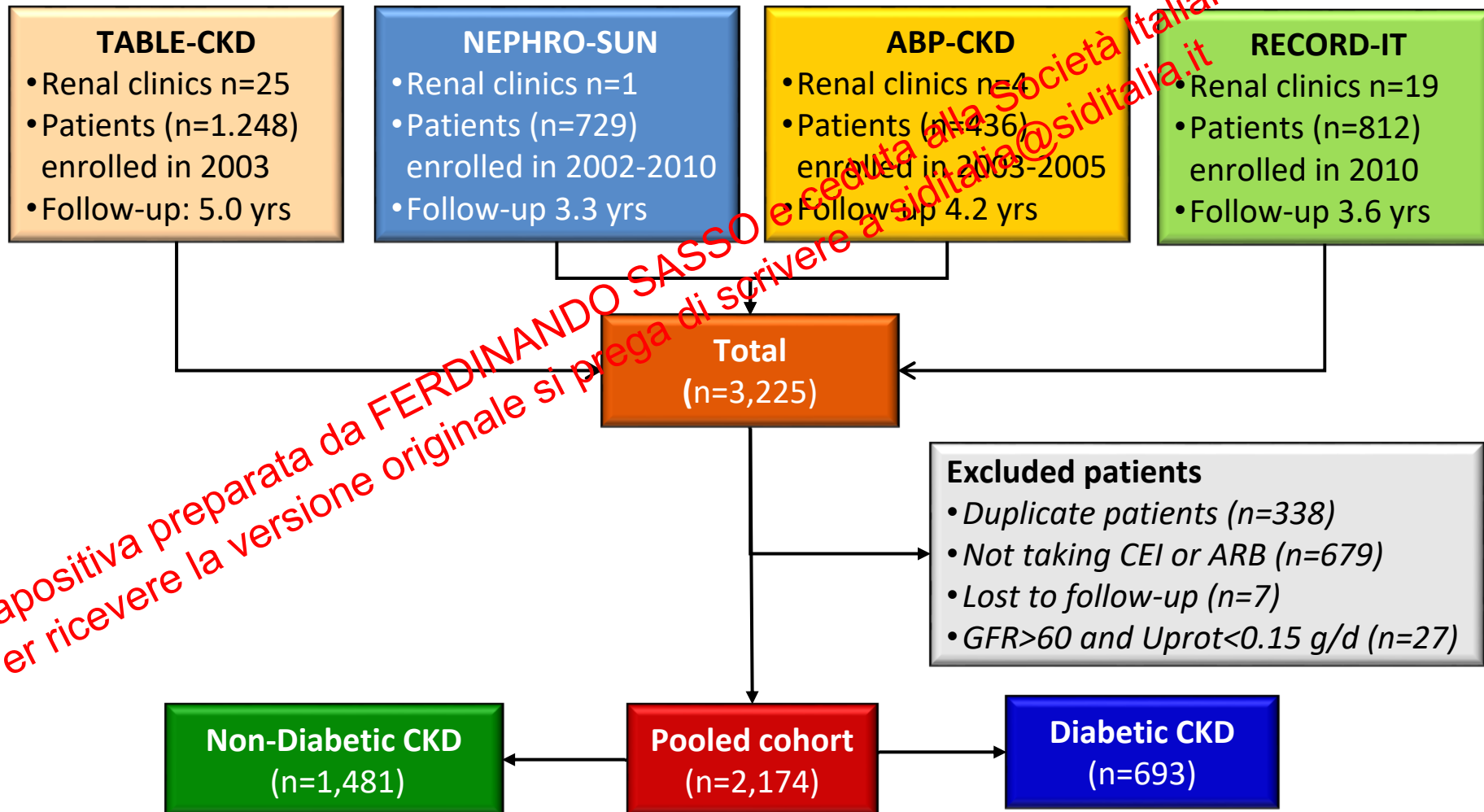
| DKD phenotype                    | Description                | Prevalence<br>[N (%)] |
|----------------------------------|----------------------------|-----------------------|
| No DKD                           | <i>AER&lt;30/GFR≥60</i>    | 9984 (63.8)           |
| Albuminuric with preserved GFR   | <i>AER≥30/GFR≥60</i>       | 2966 (18.9)           |
| Non-albuminuric DKD              | <i>AER&lt;30/GFR&lt;60</i> | 1476 (9.4)            |
| Albuminuric DKD with reduced GFR | <i>AER≥30/GFR&lt;60</i>    | 1230 (7.9)            |

\* Adjusted for: age, sex, smoking, diabetes duration, HbA1c, BMI, eWC, triacylglycerols, cholesterol, HDL, lipid lowering treatment, SBP, DBP, antihypertensive treatment, diabetic retinopathy grade, any CVD and any cancer

# Cardiorenal prognosis by residual proteinuria level in diabetic chronic kidney disease: pooled analysis of four cohort studies

Roberto Minutolo<sup>1</sup>, Francis B. Gabbai<sup>2</sup>, Michele Provenzano<sup>1</sup>, Paolo Chiodini<sup>3</sup>, Silvio Borrelli<sup>1</sup>, Carlo Garofalo<sup>1</sup>, Ferdinando C. Sasso<sup>4</sup>, Domenico Santoro<sup>5</sup>, Vincenzo Bellizzi<sup>6</sup>, Giuseppe Conte<sup>1</sup>, Luca De Nicola<sup>1</sup>

Nephrol Dial Transplant (2018) 1–8

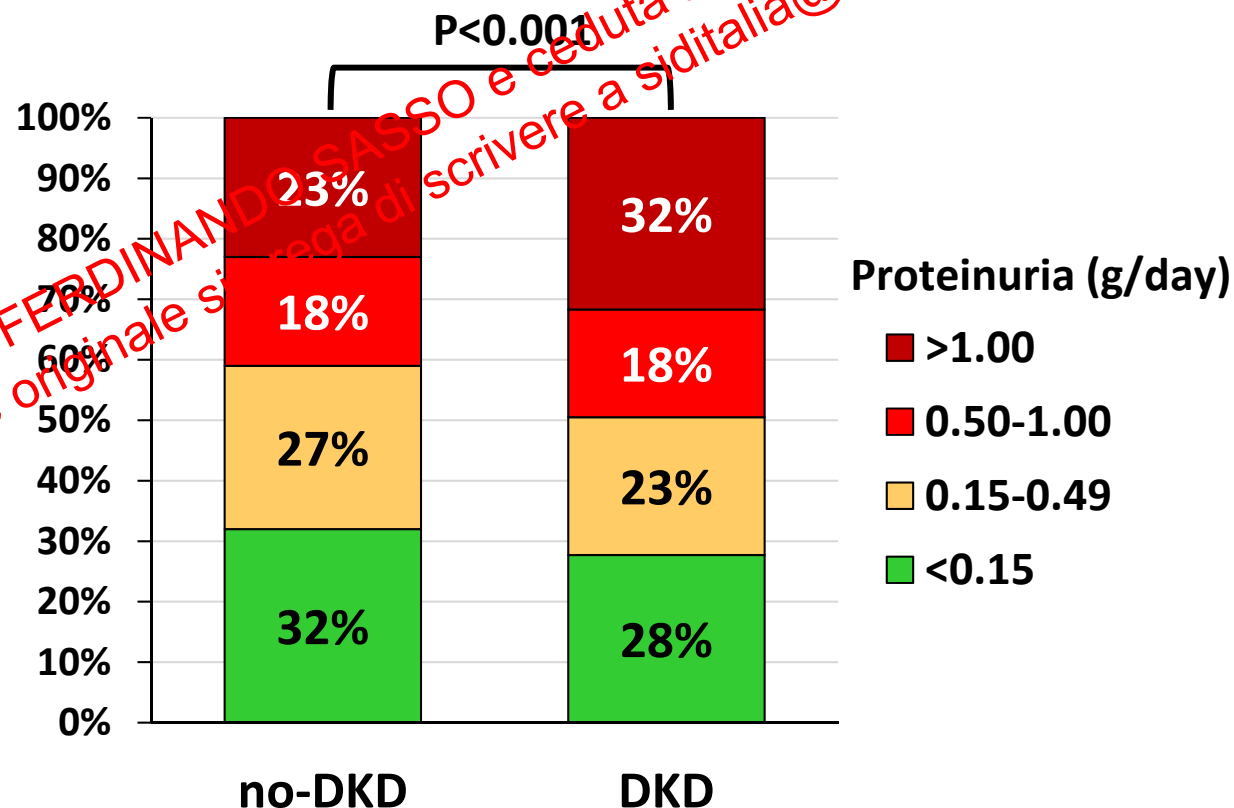


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Nephrol Dial Transplant (2018) 1–8

| Proteinuria categories | 24h Proteinuria (g/day) |           |           |       |
|------------------------|-------------------------|-----------|-----------|-------|
|                        | <0.15                   | 0.15-0.49 | 0.50-1.00 | >1.00 |



# Cardiorenal prognosis by residual proteinuria level in diabetic chronic kidney disease: pooled analysis of four cohort studies

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Nephrol Dial Transplant (2018) 1–8

Demographic and clinical characteristics of DKD and non-DKD patients stratified according to proteinuria category

|                          | No DM-CKD (N=1481)                    |           |          |          |                  | DM-CKD (N=693)                        |           |         |         |                  |
|--------------------------|---------------------------------------|-----------|----------|----------|------------------|---------------------------------------|-----------|---------|---------|------------------|
|                          | <i>Proteinuria categories (g/day)</i> |           |          |          | <i>P</i>         | <i>Proteinuria categories (g/day)</i> |           |         |         | <i>P</i>         |
|                          | <0.15                                 | 0.15-0.49 | 0.5-1    | >1       | <i>for trend</i> | <0.15                                 | 0.15-0.49 | 0.5-1   | >1      | <i>for trend</i> |
| Number                   | 471                                   | 401       | 266      | 343      |                  | 191                                   | 159       | 124     | 219     |                  |
| Age (years)              | 69±14                                 | 66±14     | 64±15    | 60±16    | <0.001           | 72±8*                                 | 69±11*    | 68±11*  | 66±11*  | <0.001           |
| Males (%)                | 49.9                                  | 57.4      | 63.5     | 65.9     | <0.001           | 56.0                                  | 54.7      | 54.0    | 64.4    | 0.140            |
| BMI (kg/m <sup>2</sup> ) | 27.8±4.7                              | 27.2±4.7  | 27.1±4.8 | 27.6±4.9 | 0.099            | 30±5*                                 | 30±6*     | 29±6*   | 29±5*   | 0.132            |
| CKD (%)                  | 33.8                                  | 27.9      | 27.1     | 24.5     | 0.026            | 52.9*                                 | 48.4*     | 42.7*   | 47.9*   | 0.371            |
| SBP (mmHg)               | 136±19                                | 135±18    | 137±19   | 139±18   | 0.006            | 141±17*                               | 141±19*   | 141±20* | 147±20* | 0.001            |
| DBP (mmHg)               | 78±11                                 | 79±11     | 80±11    | 82±10    | <0.001           | 76±11*                                | 78±11     | 78±11   | 80±12*  | 0.001            |

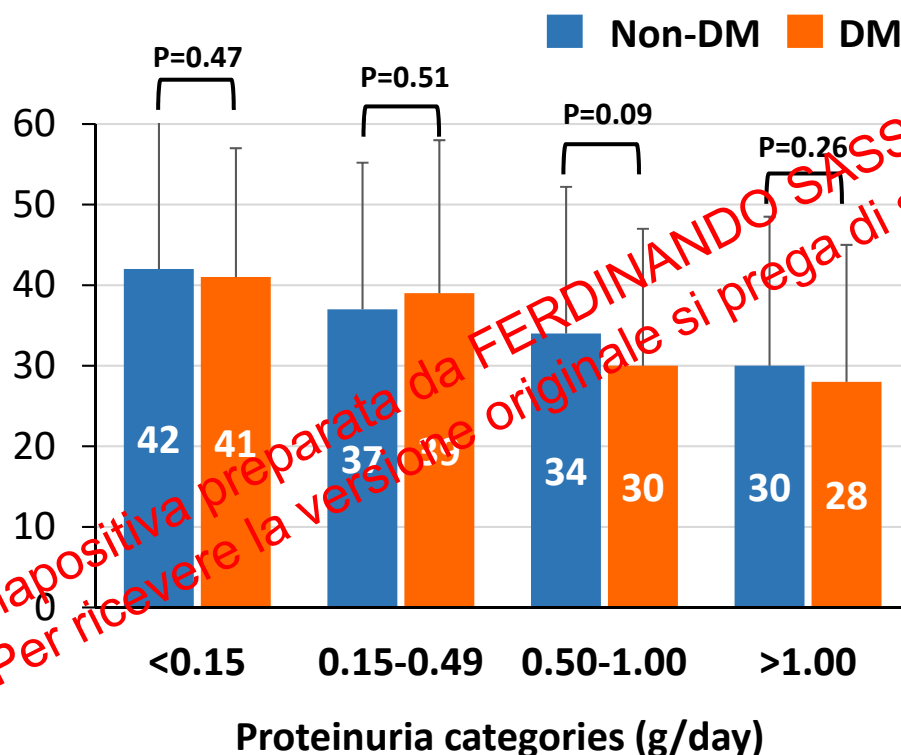


# Cardiorenal prognosis by residual proteinuria level in diabetic chronic kidney disease: pooled analysis of four cohort studies

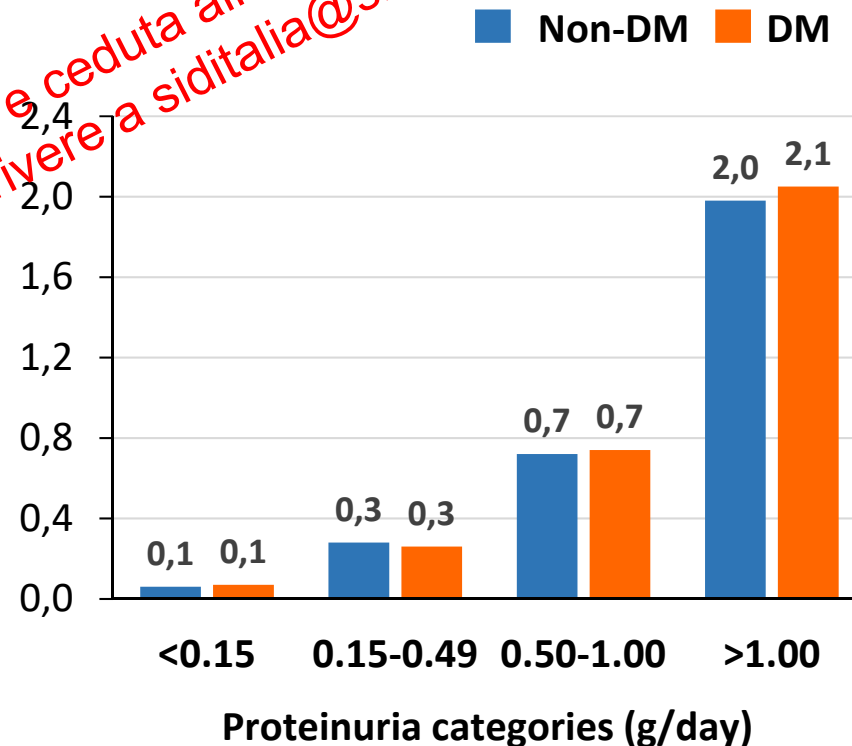
Roberto Minutolo<sup>1</sup>, Francis B. Gabbai<sup>2</sup>, Michele Provenzano<sup>1</sup>, Paolo Chiodini<sup>3</sup>, Silvio Borrelli<sup>1</sup>, Carlo Garofalo<sup>1</sup>, Ferdinando C. Sasso<sup>4</sup>, Domenico Santoro<sup>5</sup>, Vincenzo Bellizzi<sup>6</sup>, Giuseppe Conte<sup>1</sup>, Luca De Nicola<sup>1</sup>

Nephrol Dial Transplant (2018) 1–8

### GFR-EPI (mL/min/1.73m<sup>2</sup>)



### Median proteinuria (g/day)



# Cardiorenal prognosis by residual proteinuria level in diabetic chronic kidney disease: pooled analysis of four cohort studies

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Nephrol Dial Transplant (2018) 1–8

|                     | Proteinuria categories (g/day) |                      |                     |                     |
|---------------------|--------------------------------|----------------------|---------------------|---------------------|
|                     | <0.15                          | 0.15–0.49            | 0.50–1.49           | ≥1.50               |
|                     | HR<br>(95% CI)                 | HR<br>(95% CI)       | HR<br>(95% CI)      | HR<br>(95% CI)      |
| All-cause mortality |                                |                      |                     |                     |
| Non-diabetic CKD    | Reference                      | 1.15<br>(0.79–1.71)  | 1.60<br>(1.07–2.40) | 1.69<br>(1.20–2.55) |
| Diabetic CKD        | 0.81<br>(0.65–1.32)            | 1.92*<br>(1.25–2.95) | 1.99<br>(1.26–3.15) | 1.98<br>(1.28–3.06) |

Cox models were stratified by cohort and adjusted for baseline covariates: age, gender, BMI, smoking, CVD, LVH, calcium, phosphate, albumin, Hb, GFR, SBP, LDL-C, tryglicerides, RAS inhibitors, statin

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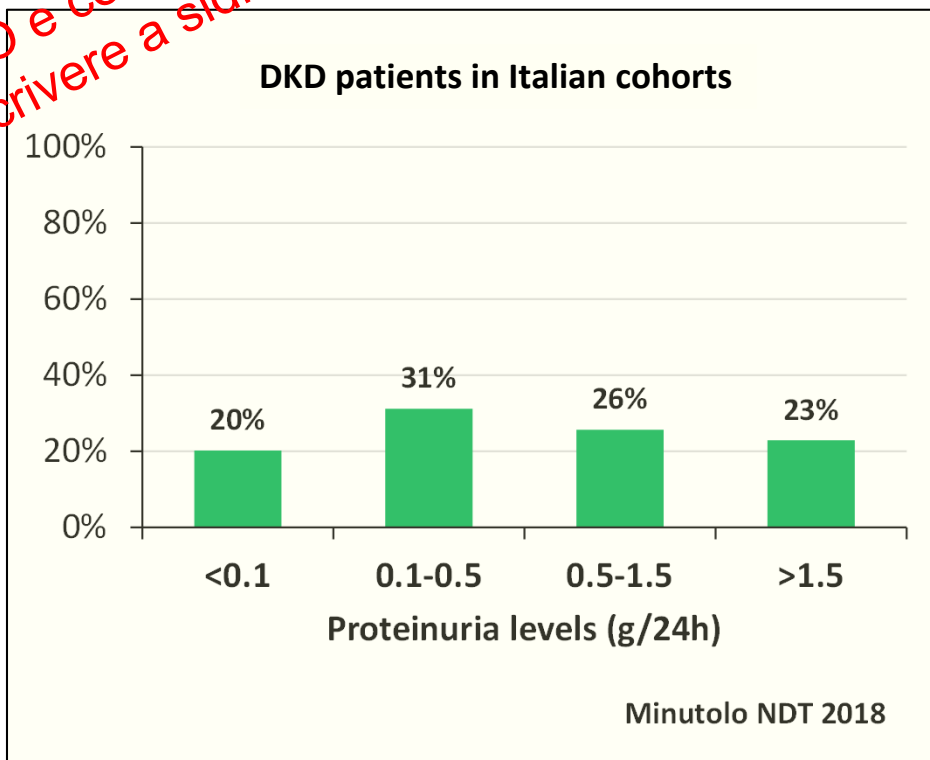
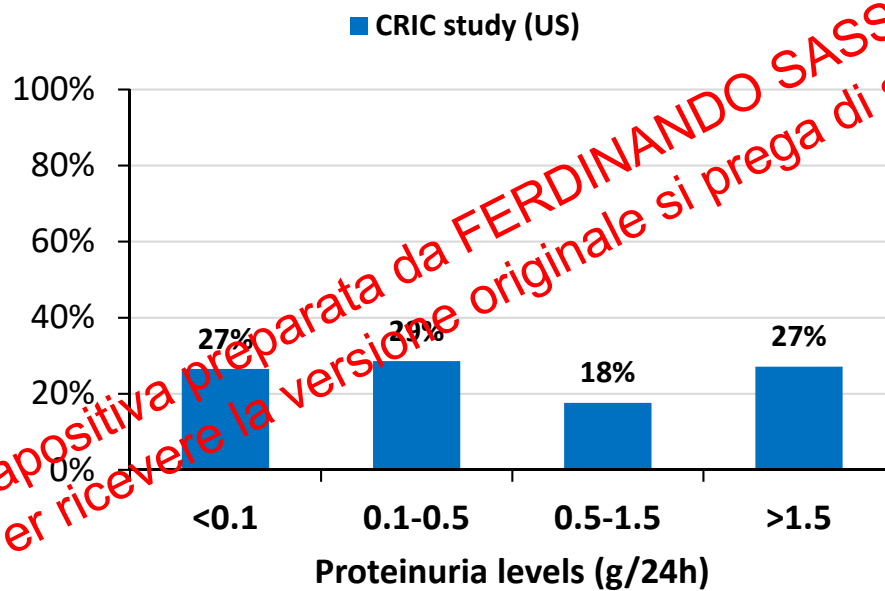


# Risk of Progression of Nonalbuminuric CKD to End-Stage Kidney Disease in People With Diabetes: The CRIC (Chronic Renal Insufficiency Cohort) Study

Digsum N. Koye, Dianna J. Magliano, Christopher M. Reid, Christopher Jepson, Harold I. Feldman, William H. Herman, and Jonathan E. Shaw

AJKD XXXX | Iss XX | Month 2018

CRIC participants with diabetes and reduced GFR (n=1,813) stratified by proteinuria

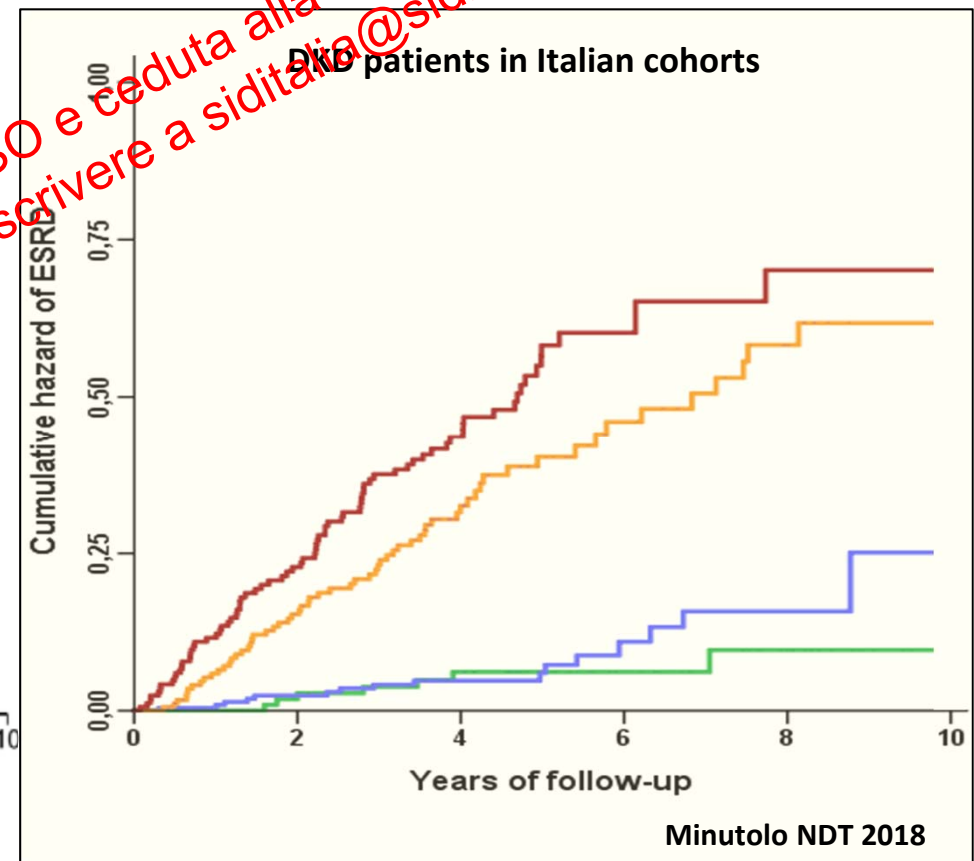
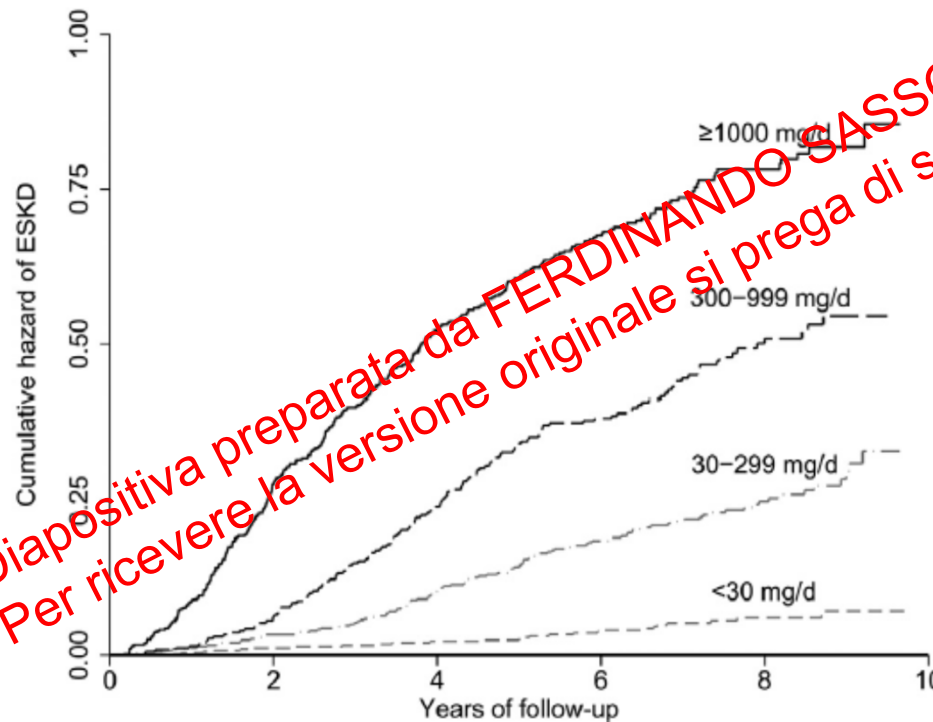


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CRIC participants with diabetes and reduced GFR (n=1,813) stratified by proteinuria



# Take home message

1. Prevalence of non-proteinuric phenotype of DKD is increasing in the last years likely due to a wider use of RAS inhibitors and better glycemic control
2. Non-proteinuric phenotype of DKD is associated with lower mortality, CV and renal risk, similarly to non-diabetic CKD.
3. In proteinuric patients ( $>0.5$  g/day), cardiorenal risk similarly increases regardless of diabetic status.
4. The effect of diabetic status *per se* only emerges in the presence of moderate proteinuria (0.15–0.49 g/day), where diabetes heralds a higher risk of CV morbidity and mortality

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# US approach to CKD: Old and New

**1943**

artificial kidney

**1960**

shunt for dialysis

**2016**

**13**

**90,000**

**120,000**

die each day waiting for a transplant  
are waiting for a kidney transplant  
annually began dialysis

*Scientific Registry of Transplant Recipient: 2015 Annual Data Report*



**Advancing American Kidney Health**



**Reduce risk of kidney failure**

By 2030, new ESKD pts by 25%

**Improve access to and quality of person-centered treatments for kidney failure**

By 2025, 80% new pts with home dialysis or transplant

**Increase access to kidney transplants**

By 2030, double number of kidneys available for transplant

***The time has come for dialysis to take its place in a museum among the most revolutionary, lifesaving, and soon to be historical medical devices***

US Department of Health and Human Services – cJASN 5 November 2019

**OLD view**

# Is There a “Point of No Return” in Progressive Renal Disease?<sup>1</sup>

Giuseppe Maschio,<sup>2</sup> Lamberto Oldrizzi, and Carlo Ruggi

*The protective effects of both dietary and pharmacological intervention in CKD becomes less effective when sCreat is only slightly increased (1.5-2.0 mg/dL)*

NEW view

Perspective

CJASN ePress. Published on October 8, 2019 as doi:10.2215/CJN.07820719

## Preserving Kidney Function Instead of Replacing It

Alan S. Kliger,<sup>1</sup> and Frank C. Brosius on behalf of the Diabetic Kidney Disease Task Force of the American Society of Nephrology\*

It is time for nephrology to embrace a change in paradigm: returning to our traditional focus on pathophysiology and kidney preservation.







**12 March  
2020**

World Kidney Day  
is a joint initiative of

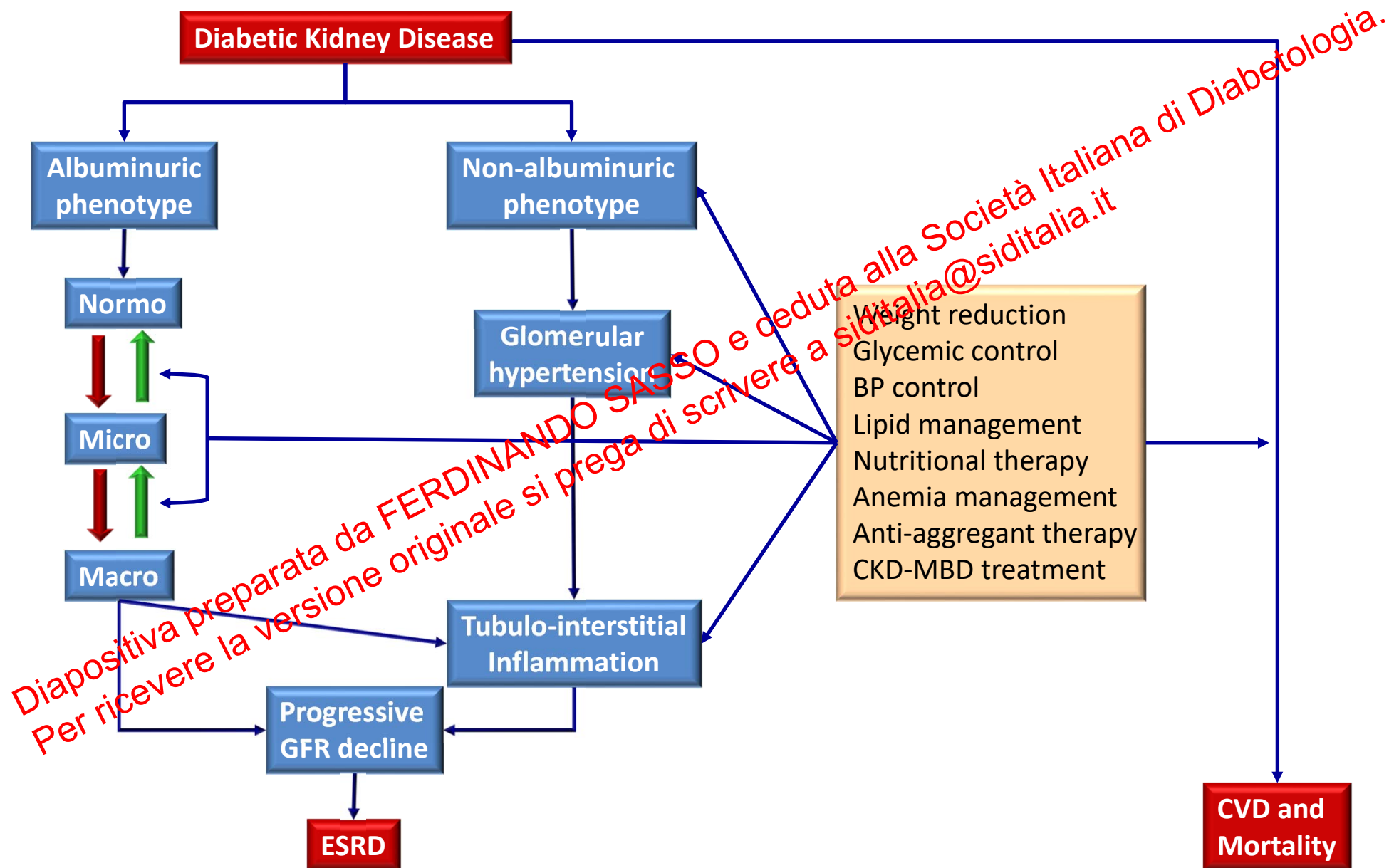


© World Kidney Day 2006 - 2020

Kidney Health for Everyone Everywhere – from Prevention to Detection and Equitable Access to Care

| Approach             | Main goal              | Additional targets                                                       | Alarming signs                                    | Risk factors to target                                                              | Interventions                                                                                                                                                                                                                                                                               |
|----------------------|------------------------|--------------------------------------------------------------------------|---------------------------------------------------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Primary prevention   | Avert kidney disease   | Manage risk factors for kidney disease; educate on primordial prevention | Glomerular hyperfiltration                        | Diabetes; hypertension; obesity; solitary kidney; genetic risks; other risk factors | Support lifestyle modifications with moderate physical activity; provide dietary advice including avoidance of high sodium and excessive protein intake; prevent and manage obesity; improve glycaemic and blood pressure control; identify genetic risk factors; ensure adequate hydration |
| Secondary prevention | Identify early disease | Slow CKD progression; prolong kidney health                              | Emerging or worsening albuminuria; declining eGFR | Proteinuria; uncontrolled hypertension; poor glycaemic control; high protein intake | Manage proteinuria; encourage low-sodium and low-protein diet; encourage more plant-based sources for dietary protein; identify and offer effective pharmacotherapy; individualize therapy; identify and manage additional CKD risk factors; explore integrative and alternative approaches |
| Tertiary prevention  | Avoid kidney failure   | Delay dialysis transition; preserve the remaining kidney function        | Worsening uraemic signs and symptoms              | AKI events and AKI risk factors; worsening cardiac function (cardiorenal syndrome)  | Manage uraemic symptoms and comorbidities; manage fluid and sodium retention; manage cardiovascular risk factors; explore novel kidney preservative and supportive therapies                                                                                                                |

# What to do next.....



## Prospettive Future ?

**MULTIDISCIPLINARIETÀ**

**Riferimento in  
tempo della CKD**

**Maggiore  
efficacia della  
terapia**

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**RIMINI, 2 OTTOBRE 2019**

**1° CONVEGNO NAZIONALE CONGIUNTO SIN - SID**

**La Malattia Renale Diabetica (DKD):  
Presente e Futuro dell'Approccio  
Integrato Nefro-Diabetologico**

**TEAM WORK FOR WORK SUCCESS**

**Società Italiana di Diabetologia (SID)**  
**Società Italiana di Nefrologia (SIN)**

**Documento congiunto su “Storia naturale della malattia renale nel diabete e trattamento dell’iperglicemia nei pazienti con diabete di tipo 2 e ridotta funzione renale”**

**A cura del Gruppo di Lavoro Intersocietario SID-SIN sulla Nefropatia Diabetica**

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