



# IL CROSS-TALK cuore *rene*

FISIOPATOLOGIA  
ED ASPETTI CLINICI

ROMA 15 MAGGIO 2019



Dipartimento di Medicina Clinica e Molecolare  
Università "La Sapienza", Roma  
UOC Medicina Specialistica Endocrino-metabolica  
Azienda Ospedaliero-Universitaria Sant'Andrea, Roma

Cross-talk rene-cuore  
effetti della CKD  
sull'apparato cardiovascolare

Diapositiva preparata da GIUSEPPE PUGLIESE e ceduta alla Società Italiana di Diabetologia.  
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- ✓ **Relazioni/moderazioni/partecipazioni a board retribuite:** Astra-Zeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Mundipharma, Novartis, Sigma-Tau, Takeda.

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In fede

*Giuseppe Pugliese*

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❖ Impact of CKD on cardiovascular system

❖ CKD and cardiovascular risk

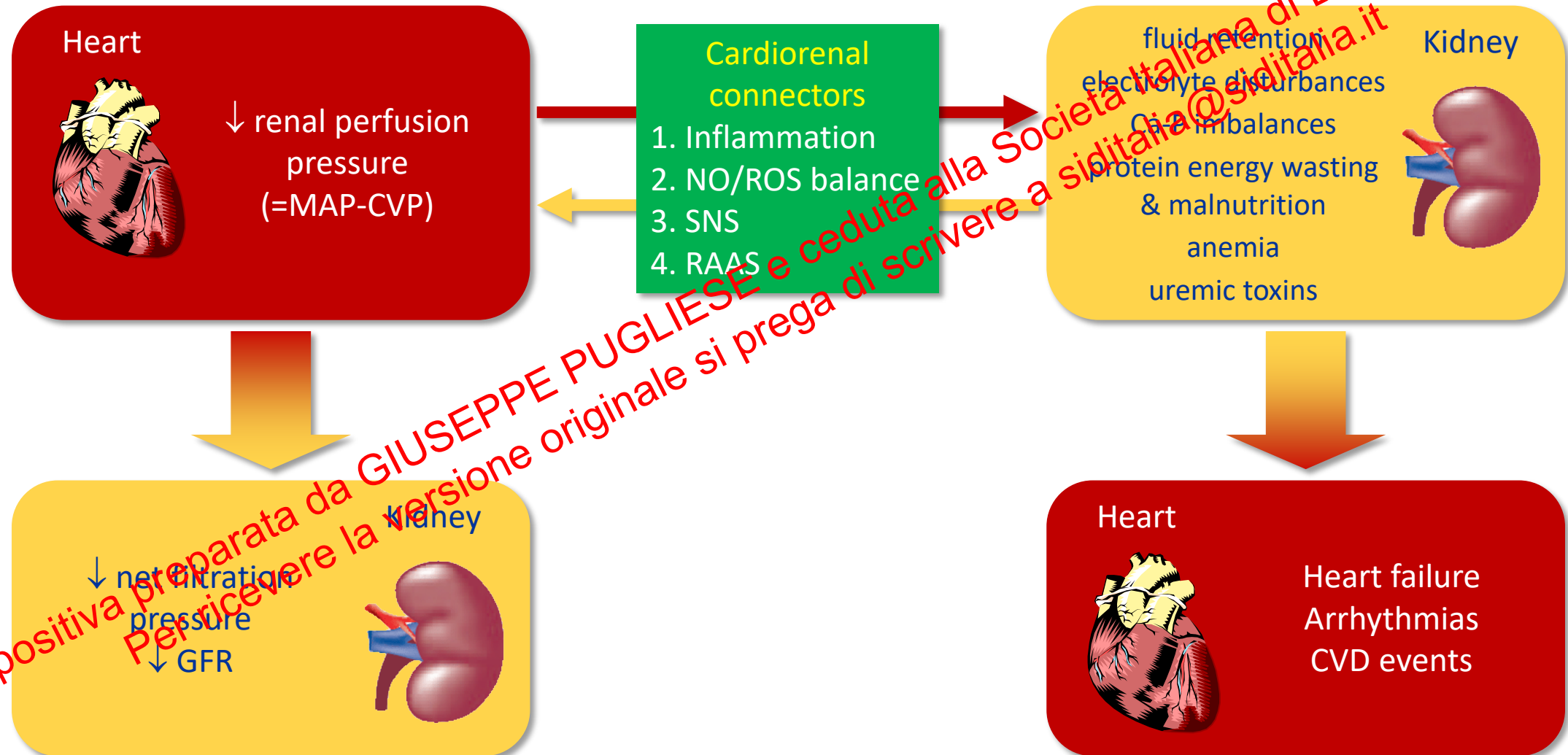
❖ Renal protection and cardiovascular risk

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# Heart-kidney interactions

## Cardiorenal syndromes





# Classification of cardio-renal syndromes

1

Acute kidney injury (AKI) secondary to acute heart failure (HF)

2

Progressive chronic kidney disease (CKD) secondary to chronic HF

3

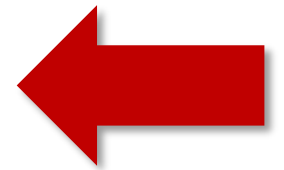
Acute HF secondary to primary AKI

4

Chronic cardiac dysfunction secondary to primary CKD

5

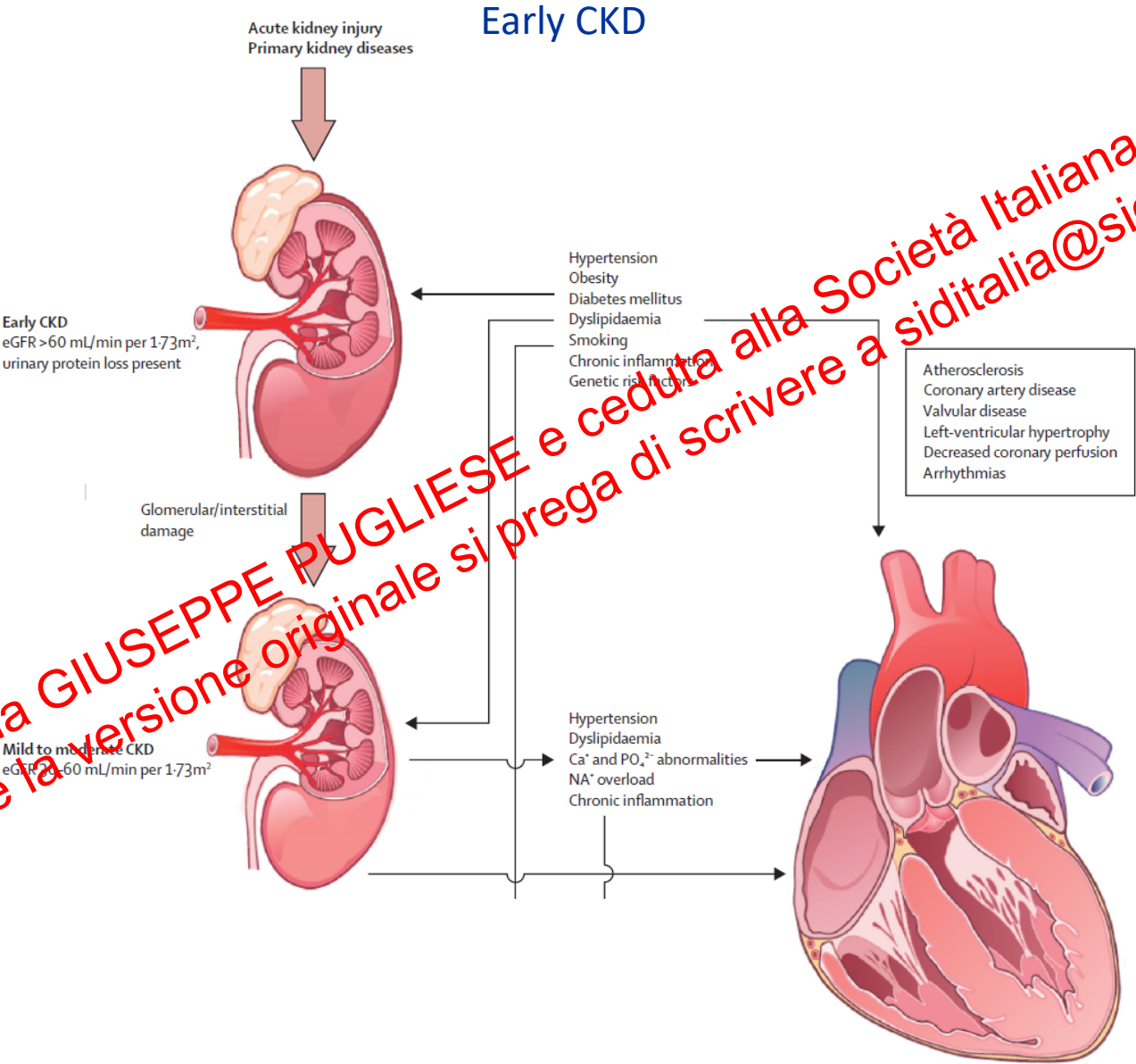
Combined cardiac and renal dysfunction due to acute or chronic systemic disorders



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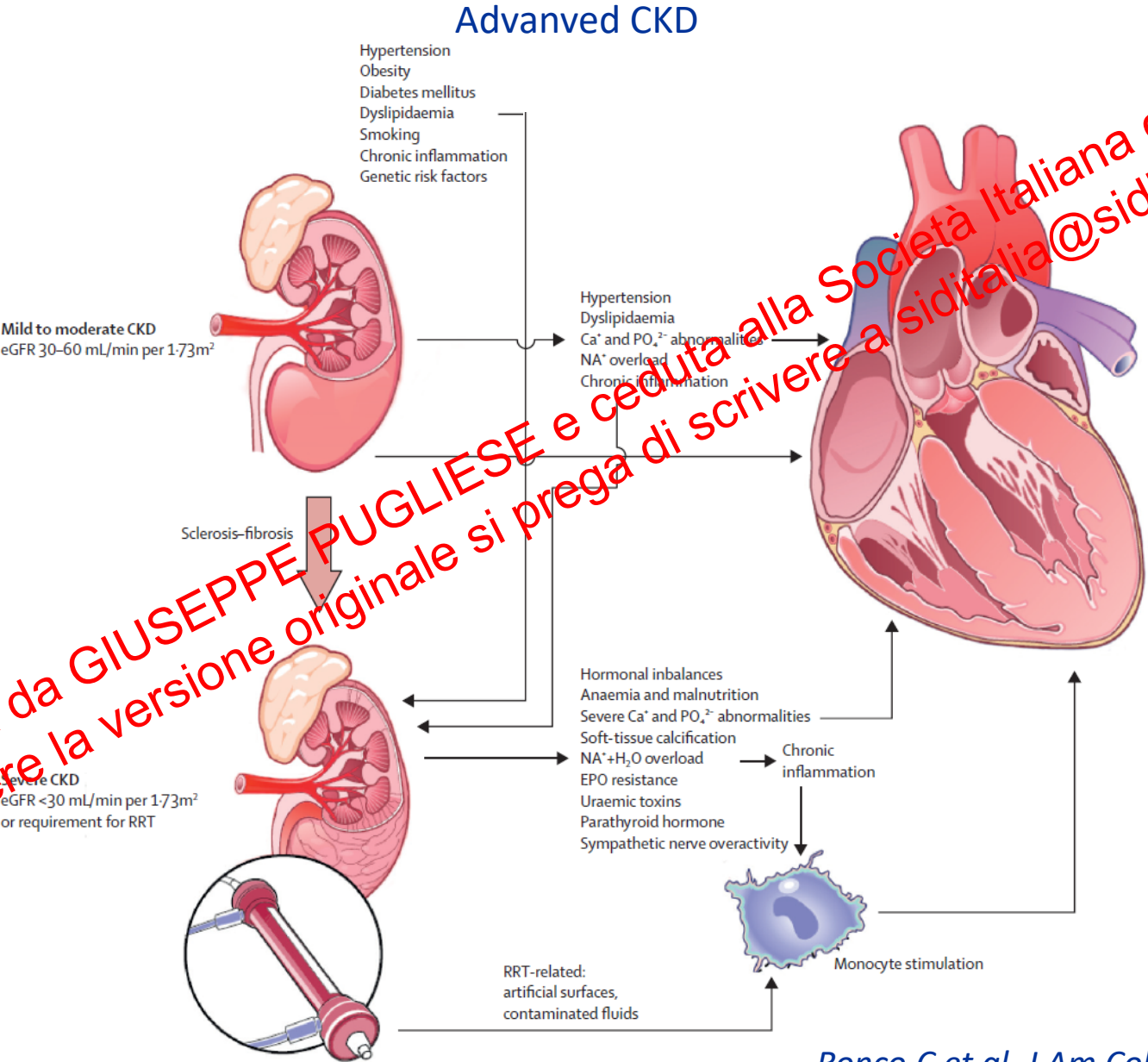
# Mechanisms of cardio-renal syndrome type 4





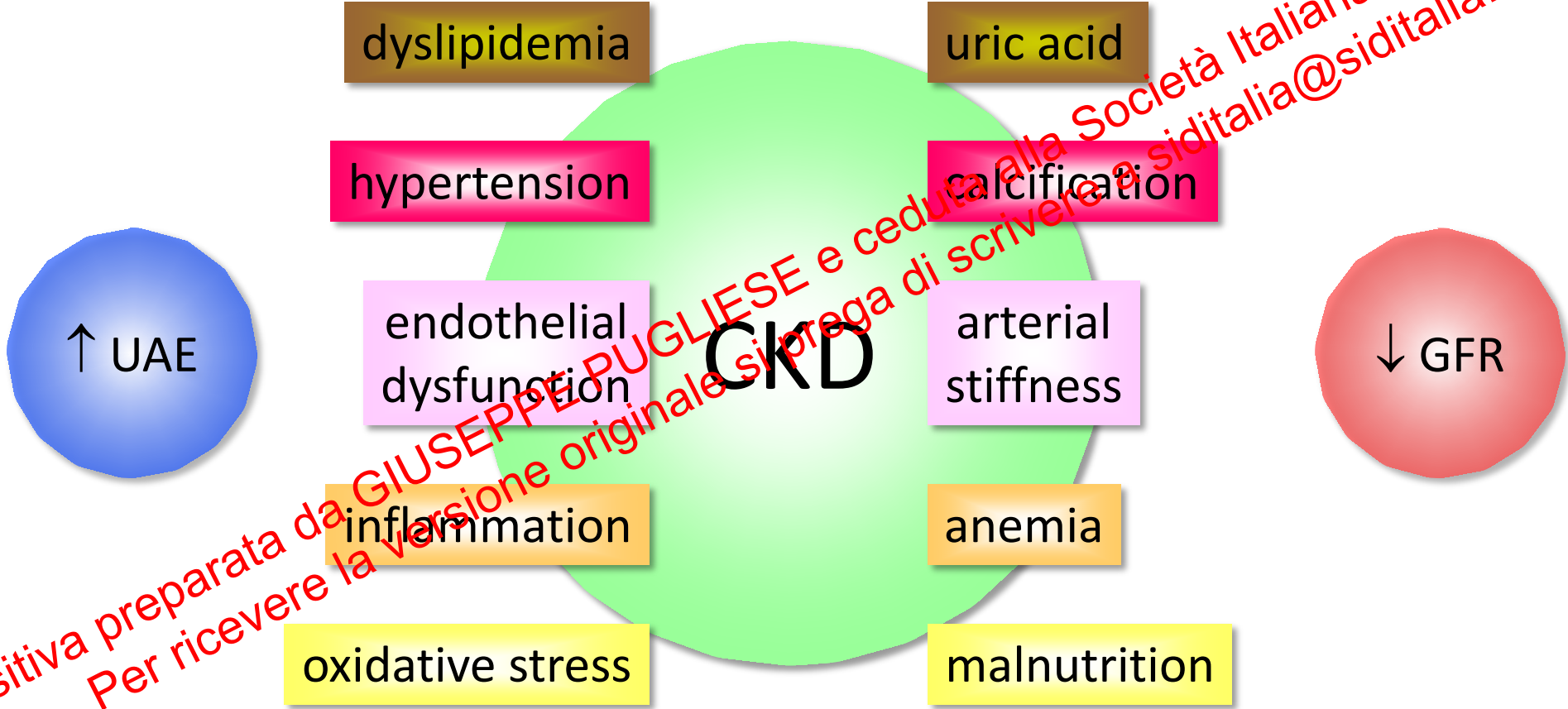


# Mechanisms of cardio-renal syndrome type 4





# Mechanisms of cardio-renal syndrome type 4

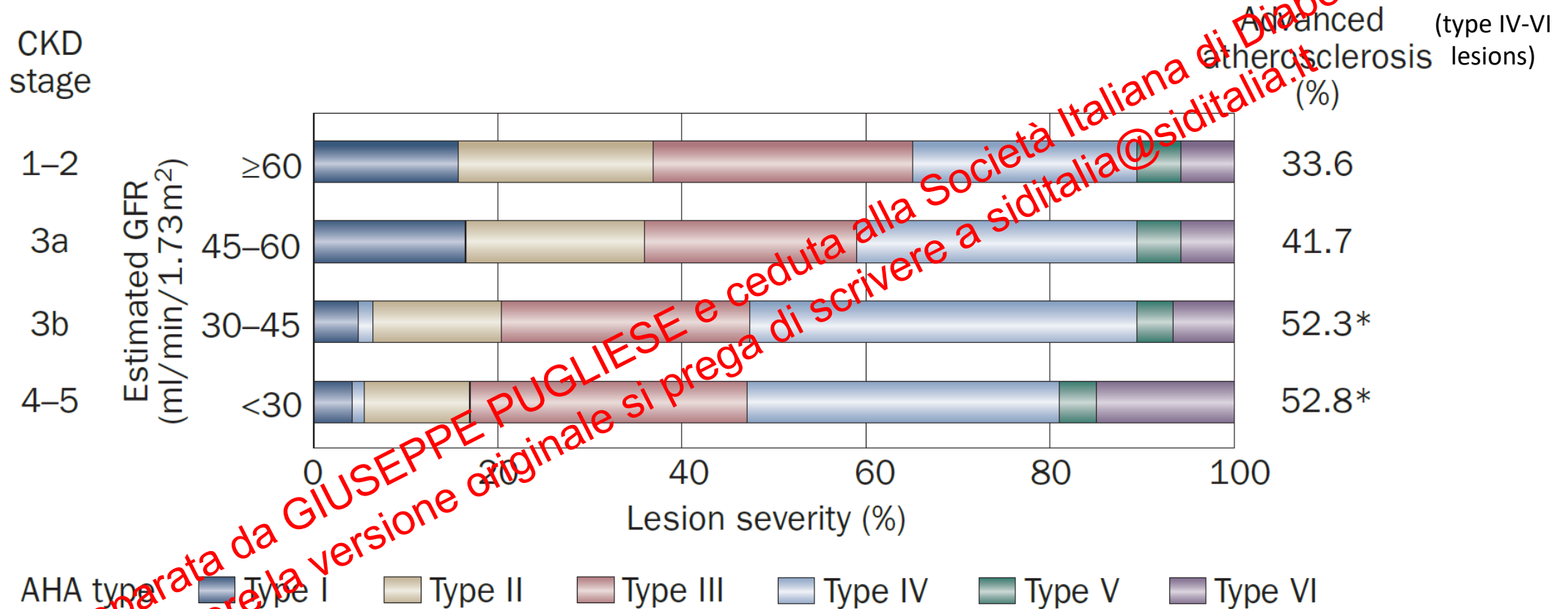






# Mechanisms of cardio-renal syndrome type 4

## Atherosclerotic lesion types of coronary arteries as a function of CKD stage



Type I (initial lesion), intimal thickening with isolated foam cells;

Type II (fatty-streak lesion), intimal thickening with intracellular lipid accumulation;

Type III (intermediate lesion): type II changes and small extracellular lipid pools;

Type IV (atheroma), type II changes and core of extracellular lipid;

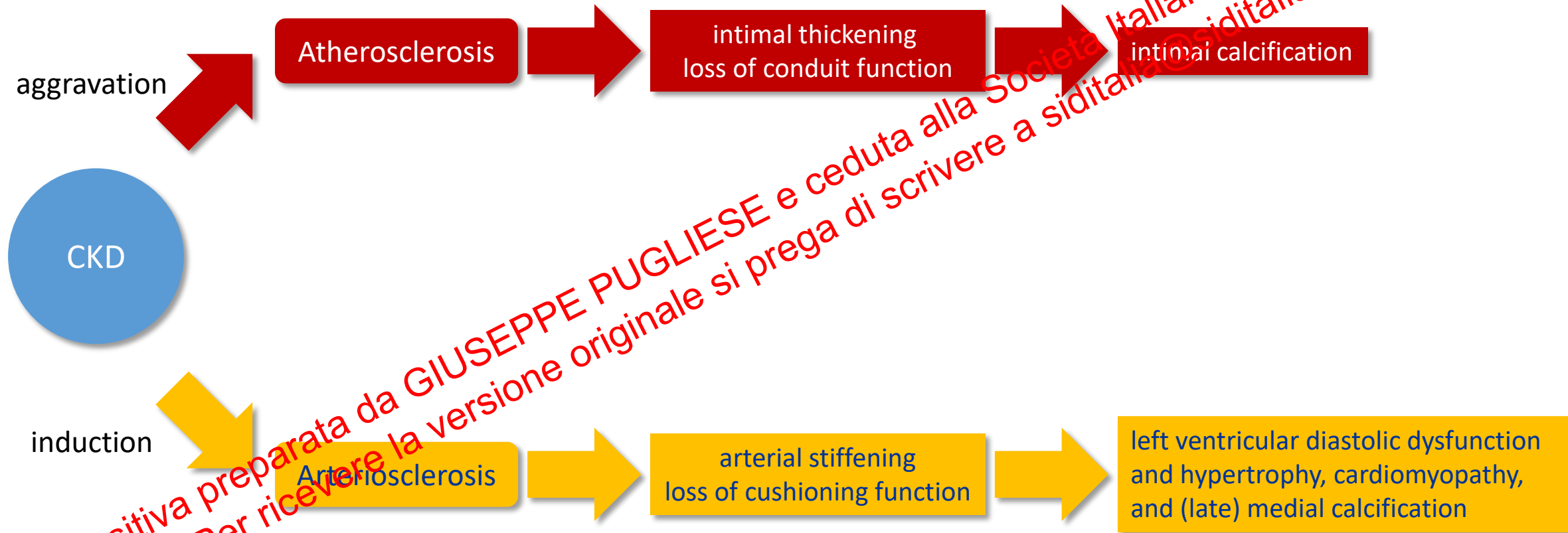
Type V (fibroatheroma), lipid core and fibrotic layer to lesions, or mainly calcified, or mainly fibrotic;

Type VI (complicated lesion), disrupted lesion with hematoma or hemorrhage or thrombotic deposits.



## Mechanisms of cardio-renal syndrome type 4

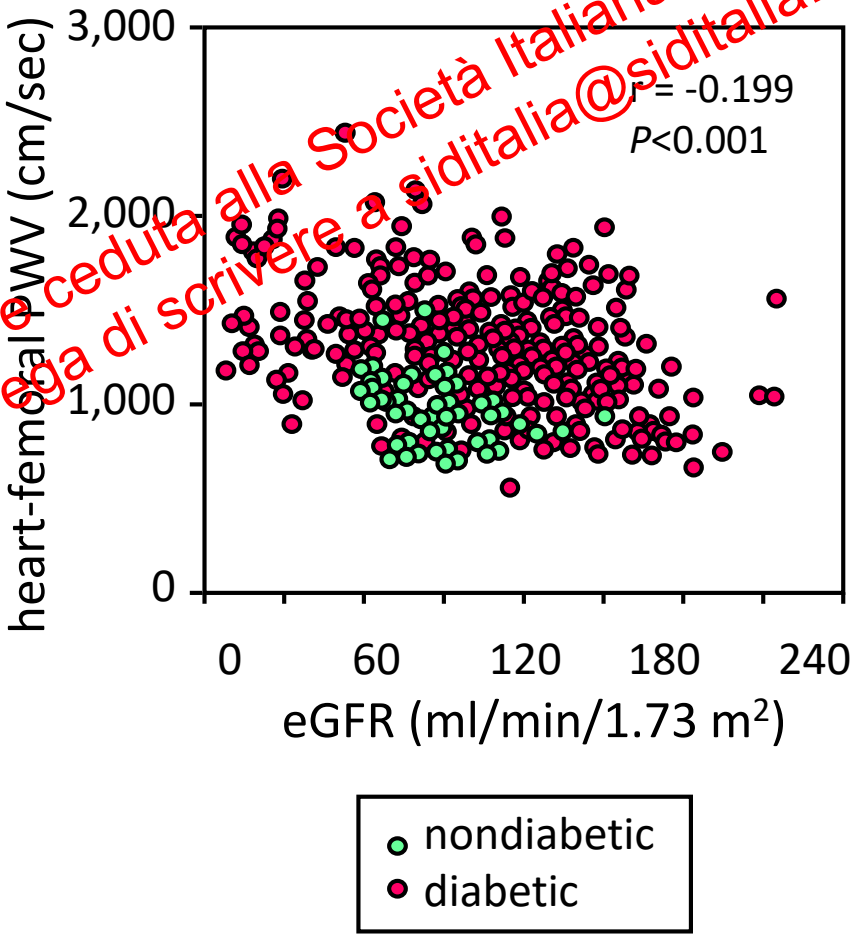
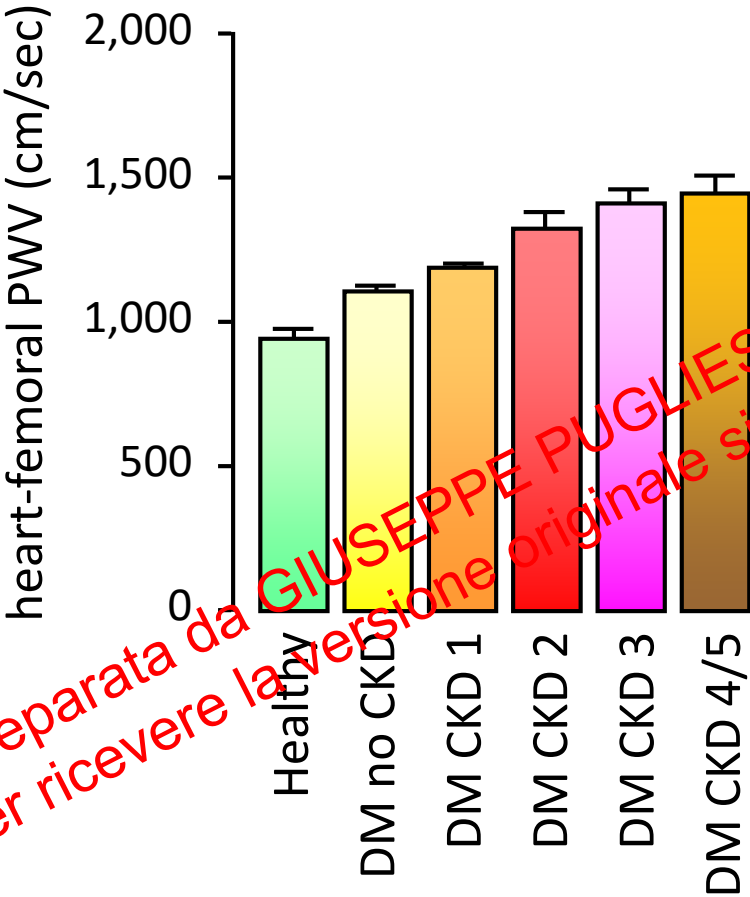
### Atherosclerotic versus arteriosclerosis in CKD





# Mechanisms of cardio-renal syndrome type 4

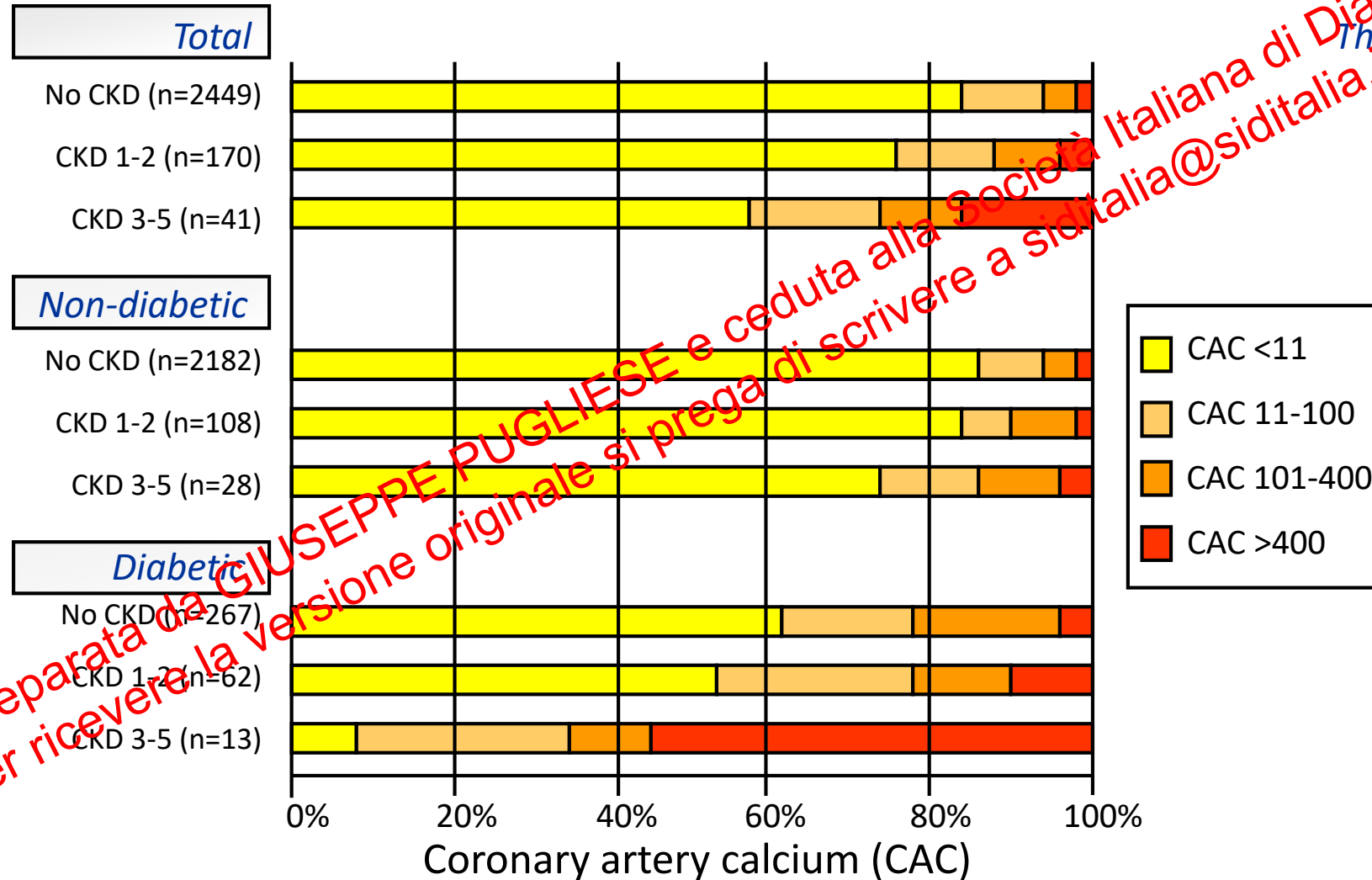
Arterial stiffness in CKD





# Mechanisms of cardio-renal syndrome type 4

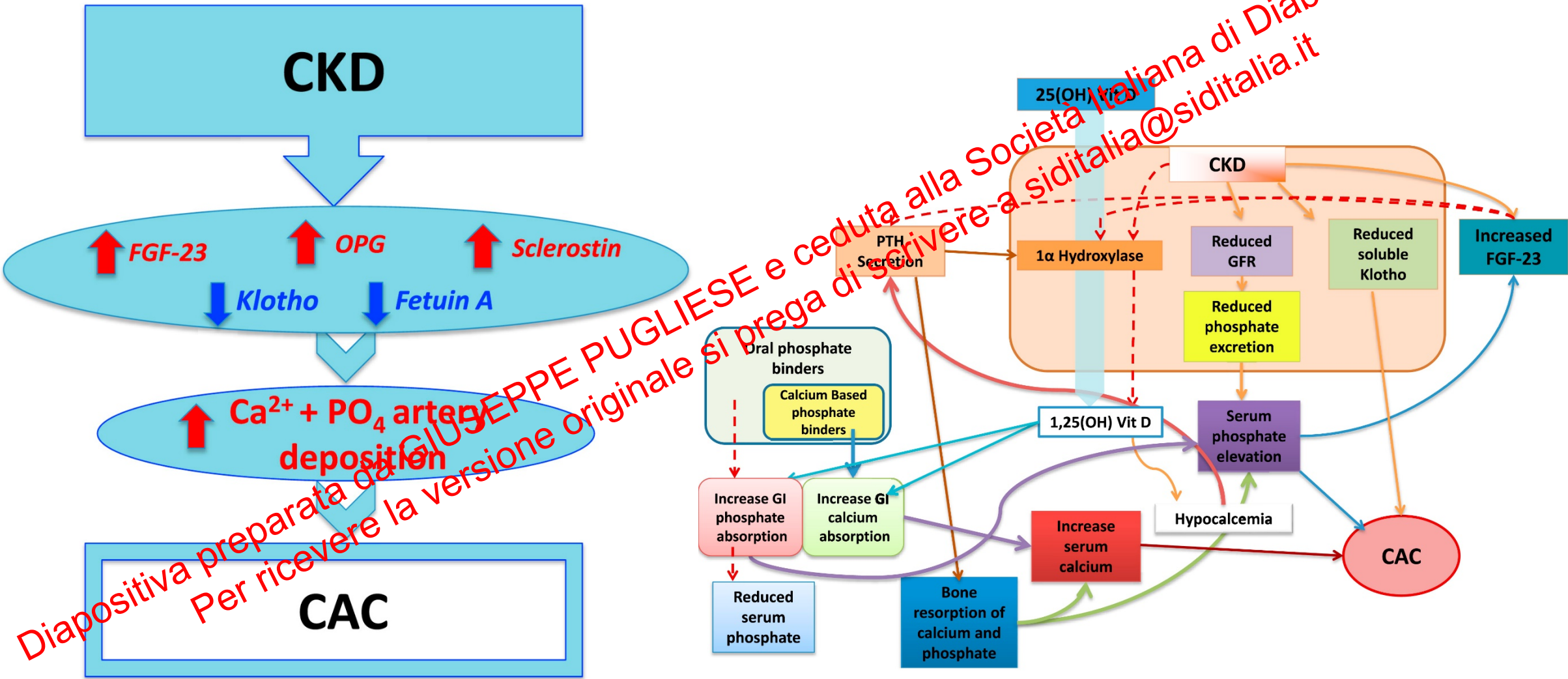
## Vascular calcification in CKD





# Mechanisms of cardio-renal syndrome type 4

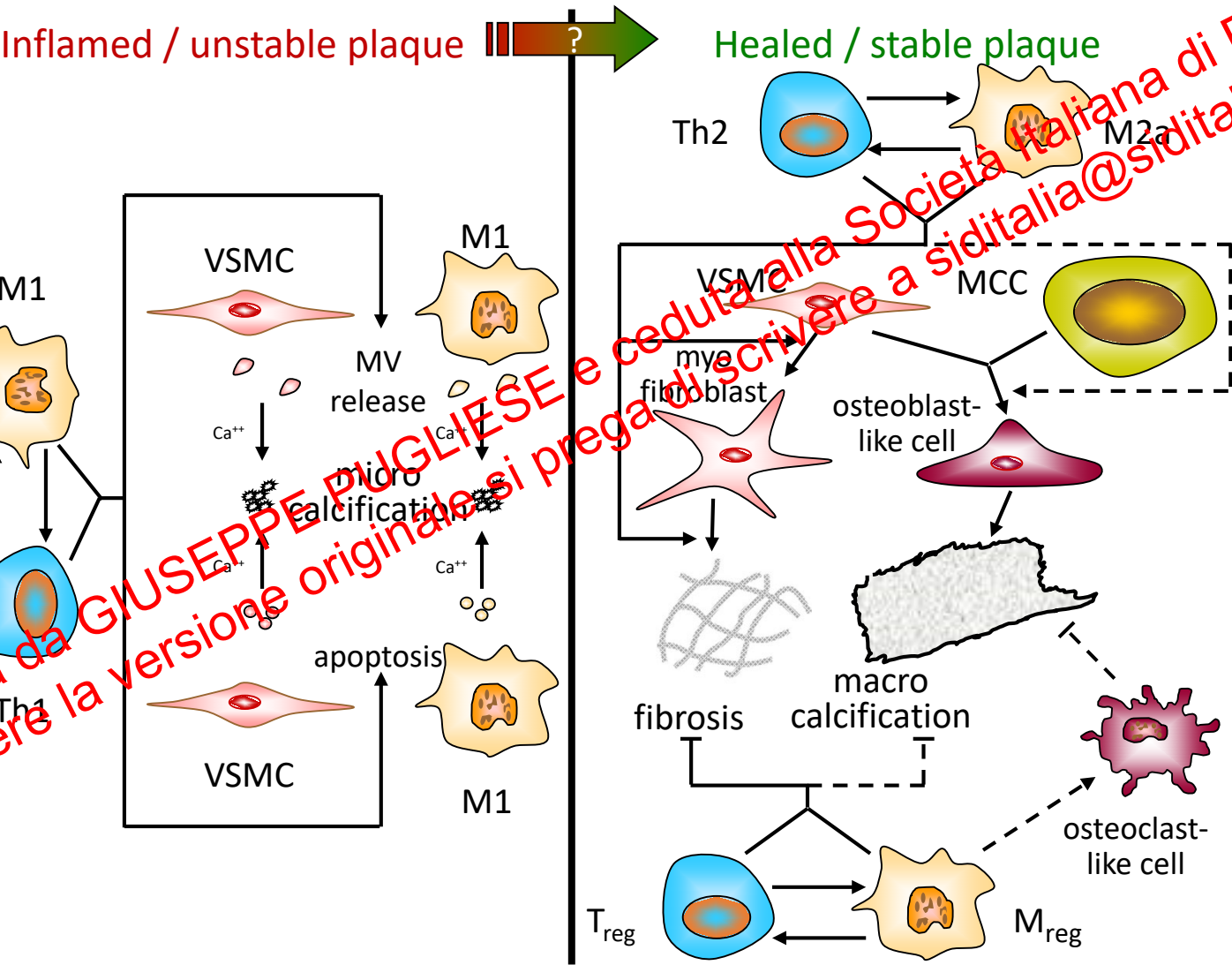
## Mechanisms of vascular calcification in CKD





# Mechanisms of cardio-renal syndrome type 4

## Effect of calcification on plaque stability in CKD

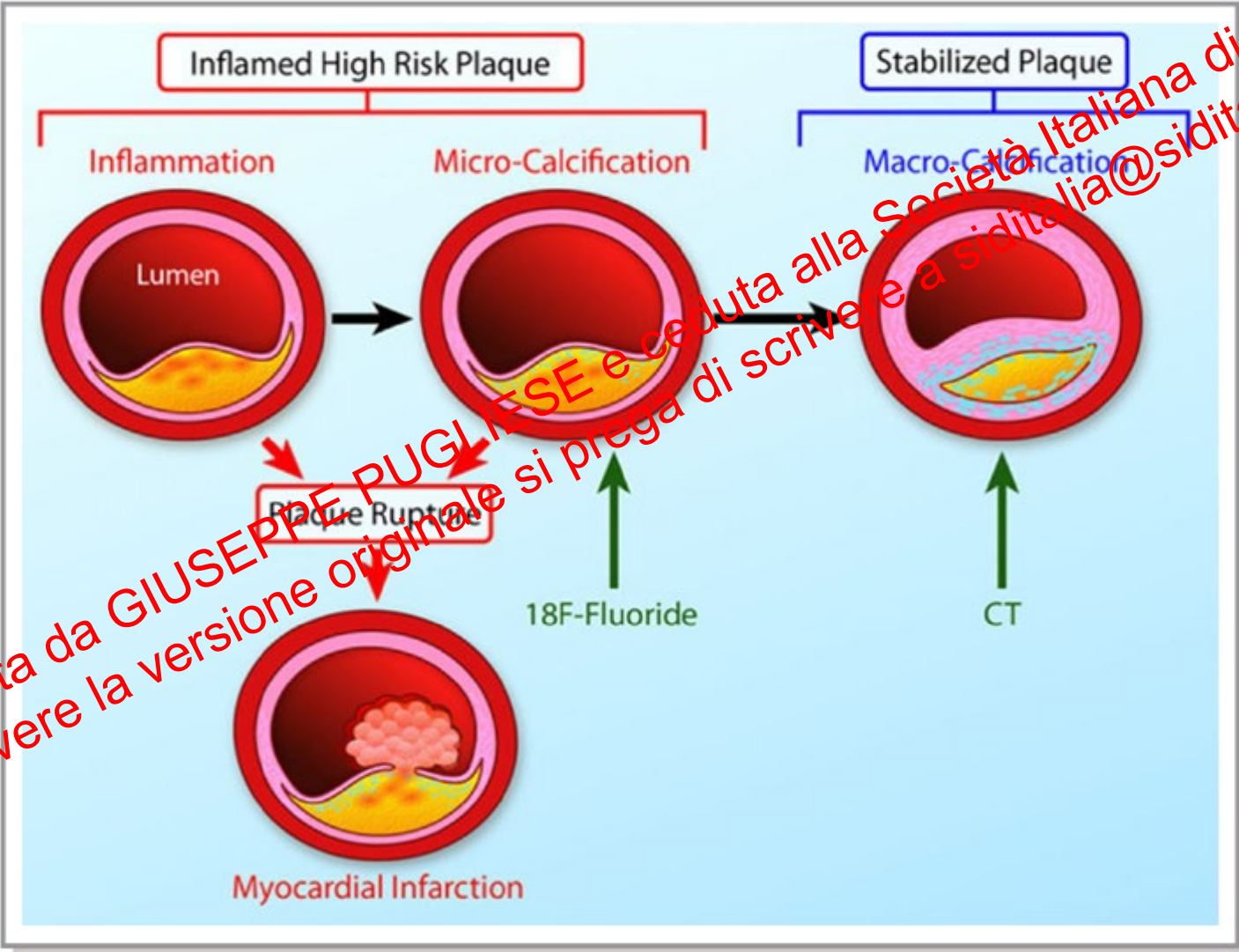






# Mechanisms of cardio-renal syndrome type 4

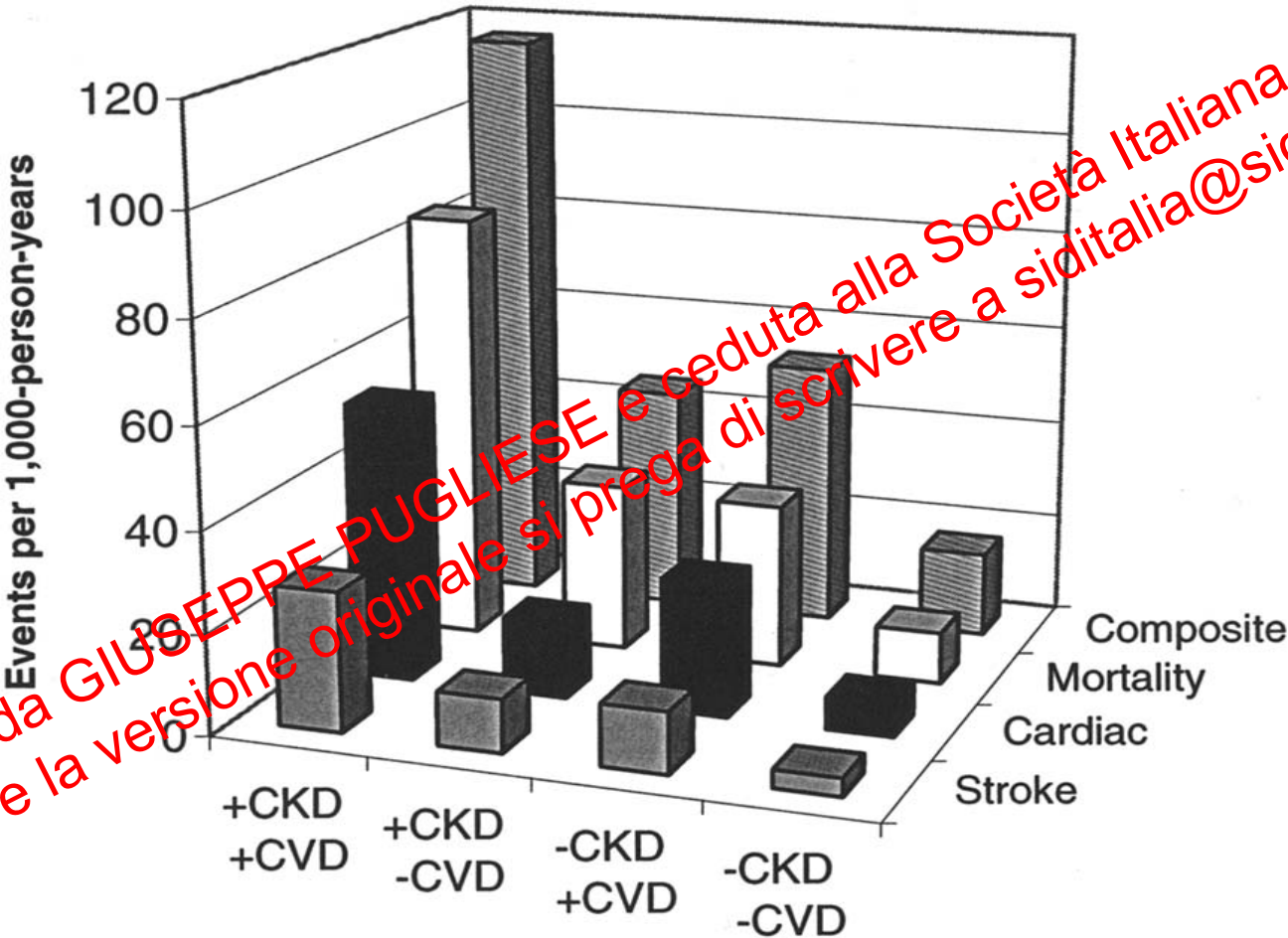
Effect of calcification on plaque stability in CKD





# Cardiovascular risk in CKD

CVD morbidity and mortality in individuals with and without CKD and CVD

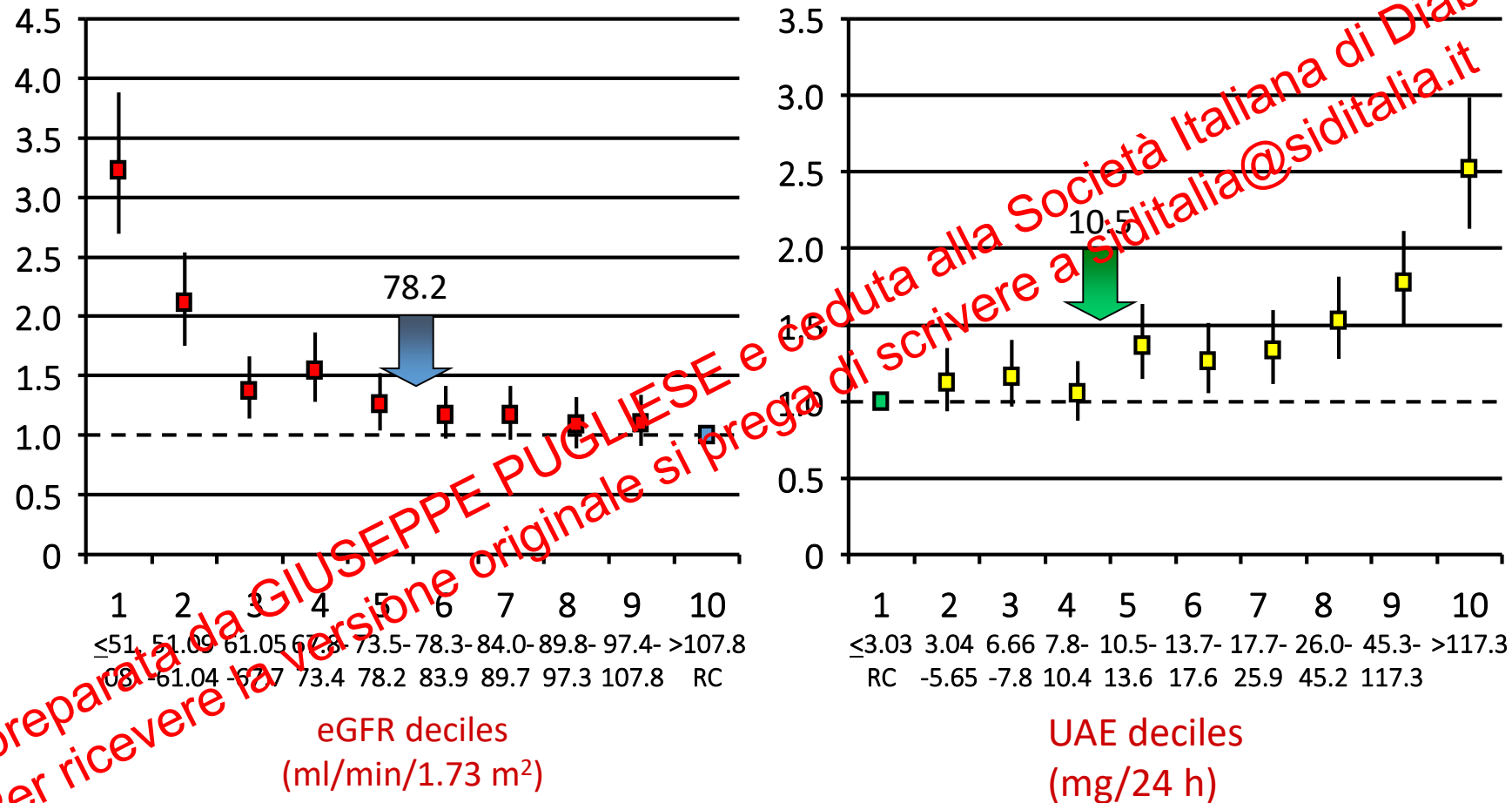


Pooled analysis of 4 community-based studies: Atherosclerosis Risk in Communities, Framingham Heart, Framingham Offspring, and Cardiovascular Health Study



# Relation of albuminuria and eGFR to CVD events

## Albuminuria and eGFR thresholds for CVD events

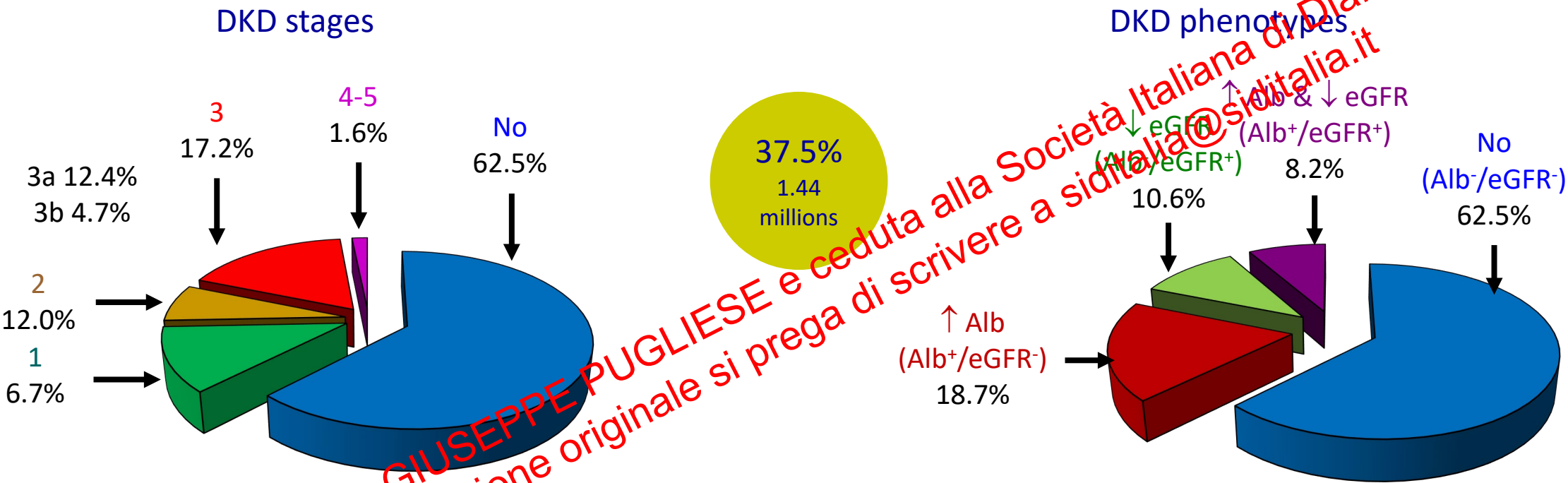


Analysis of 15,773 patients with type 2 diabetes from the Renal Insufficiency And Cardiovascular Events (RIACE) Study



# Prevalence of DKD in people with type 2 diabetes

Crude prevalence of DKD in patients with type 2 diabetes from Italy



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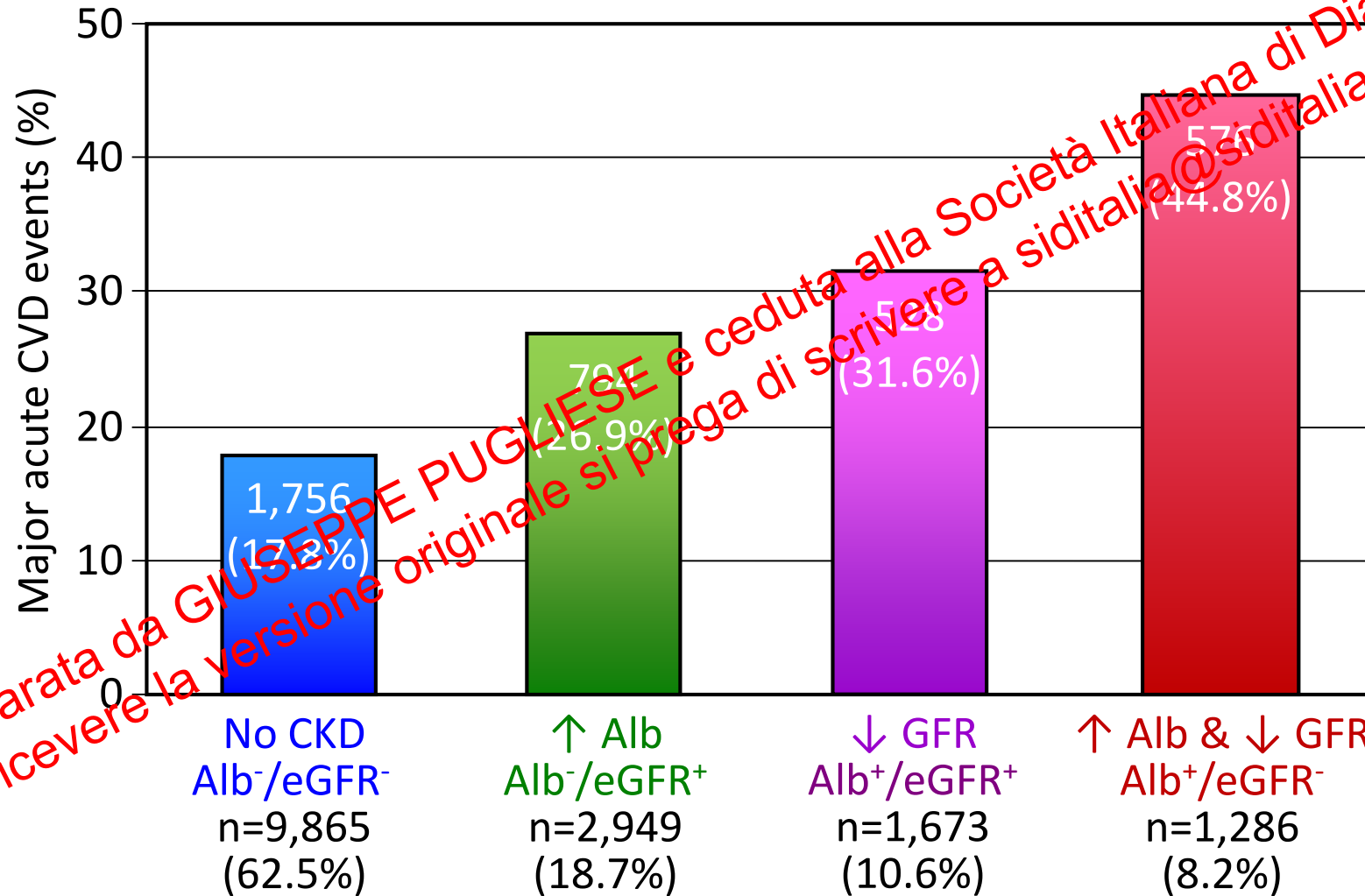
| DKD phenotype  | DKD stahe | Albuminuria | eGFR |
|----------------|-----------|-------------|------|
| No             | 0         | -           | -    |
| ↑ Alb          | 1-2       | +           | -    |
| ↓ eGFR         | 3-5       | -           | +    |
| ↑ Alb & ↓ eGFR | 3-5       | +           | +    |

Analysis of 15,773 patients with type 2 diabetes from the Renal Insufficiency And Cardiovascular Events (RIACE) Italian multicentre study



# Prevalence of CVD in people with type 2 diabetes

Crude prevalence of any CVD according to DKD phenotype



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Analysis of 15,773 patients with type 2 diabetes from the Renal Insufficiency And Cardiovascular Events (RIACE) Italian multicentre study



# Prevalence of CVD in people with type 2 diabetes

## Crude prevalence of CVD by vascular bed according to DKD phenotype

| Event                           | All             | No CKD<br>Alb <sup>-</sup> /eGFR <sup>-</sup> | ↑ Alb<br>Alb <sup>+</sup> /eGFR <sup>-</sup> | ↓ GFR<br>Alb <sup>-</sup> /eGFR <sup>+</sup> | ↑ Alb & ↓ GFR<br>Alb <sup>+</sup> /eGFR <sup>+</sup> | P       |
|---------------------------------|-----------------|-----------------------------------------------|----------------------------------------------|----------------------------------------------|------------------------------------------------------|---------|
| N (%)                           | 15,773<br>(100) | 9,865<br>(62.5)                               | 2,949<br>(18.7)                              | 1,673<br>(10.6)                              | 1,286<br>(8.2)                                       |         |
| Any major acute<br>CVD event    | 3,564<br>(23.2) | 1,756<br>(17.8)                               | 794<br>(26.9)                                | 528<br>(31.6)                                | 576<br>(44.8)                                        | <0.0001 |
| AMI                             | 1,758<br>(11.2) | 874<br>(8.9)                                  | 346<br>(11.7)                                | 271<br>(16.2)                                | 267<br>(20.8)                                        | <0.0001 |
| Coronary<br>revascularization   | 1,584<br>(10.0) | 794<br>(8.0)                                  | 301<br>(10.7)                                | 246<br>(14.7)                                | 228<br>(17.7)                                        | <0.0001 |
| Stroke                          | 515<br>(3.27)   | 226<br>(2.3)                                  | 123<br>(4.2)                                 | 75<br>(4.5)                                  | 91<br>(7.1)                                          | <0.0001 |
| Carotid<br>revascularization    | 867<br>(5.5)    | 372<br>(3.8)                                  | 193<br>(6.5)                                 | 132<br>(7.9)                                 | 170<br>(13.2)                                        | <0.0001 |
| Foot<br>ulcer/gangrene          | 532<br>(3.4)    | 183<br>(1.9)                                  | 150<br>(5.1)                                 | 72<br>(4.3)                                  | 127<br>(9.9)                                         | <0.0001 |
| Lower limb<br>revascularization | 456<br>(2.9)    | 182<br>(1.8)                                  | 102<br>(3.5)                                 | 68<br>(4.1)                                  | 104<br>(8.1)                                         | <0.0001 |

Analysis of 15,773 patients with type 2 diabetes from the Renal Insufficiency And Cardiovascular Events (RIACE) Italian multicentre study





# Risk of CVD in people with type 2 diabetes

## Risk of CVD by vascular bed according to DKD phenotype

|                        | ↑ Alb<br>Alb <sup>+</sup> /eGFR <sup>-</sup> |           | ↓ GFR<br>Alb <sup>-</sup> /eGFR <sup>+</sup> |           | ↑ Alb & ↓ GFR<br>Alb <sup>+</sup> /eGFR <sup>+</sup> |           |
|------------------------|----------------------------------------------|-----------|----------------------------------------------|-----------|------------------------------------------------------|-----------|
|                        | OR                                           | 95% CI    | OR                                           | 95% CI    | OR                                                   | 95% CI    |
| Total CVD events       | 1.20                                         | 1.08-1.33 | 1.52                                         | 1.34-1.73 | 1.90                                                 | 1.66-2.19 |
| Coronary events        | 0.90                                         | 0.79-1.02 | 1.51                                         | 1.30-1.76 | 1.27                                                 | 1.08-1.49 |
| Cerebrovascular events | 1.41                                         | 1.20-1.65 | 1.22                                         | 1.01-1.48 | 1.69                                                 | 1.40-2.00 |
| Peripheral events      | 1.51                                         | 1.25-1.82 | 1.40                                         | 1.11-1.76 | 1.88                                                 | 1.52-2.34 |

Logistic regression analysis with stepwise variable selection

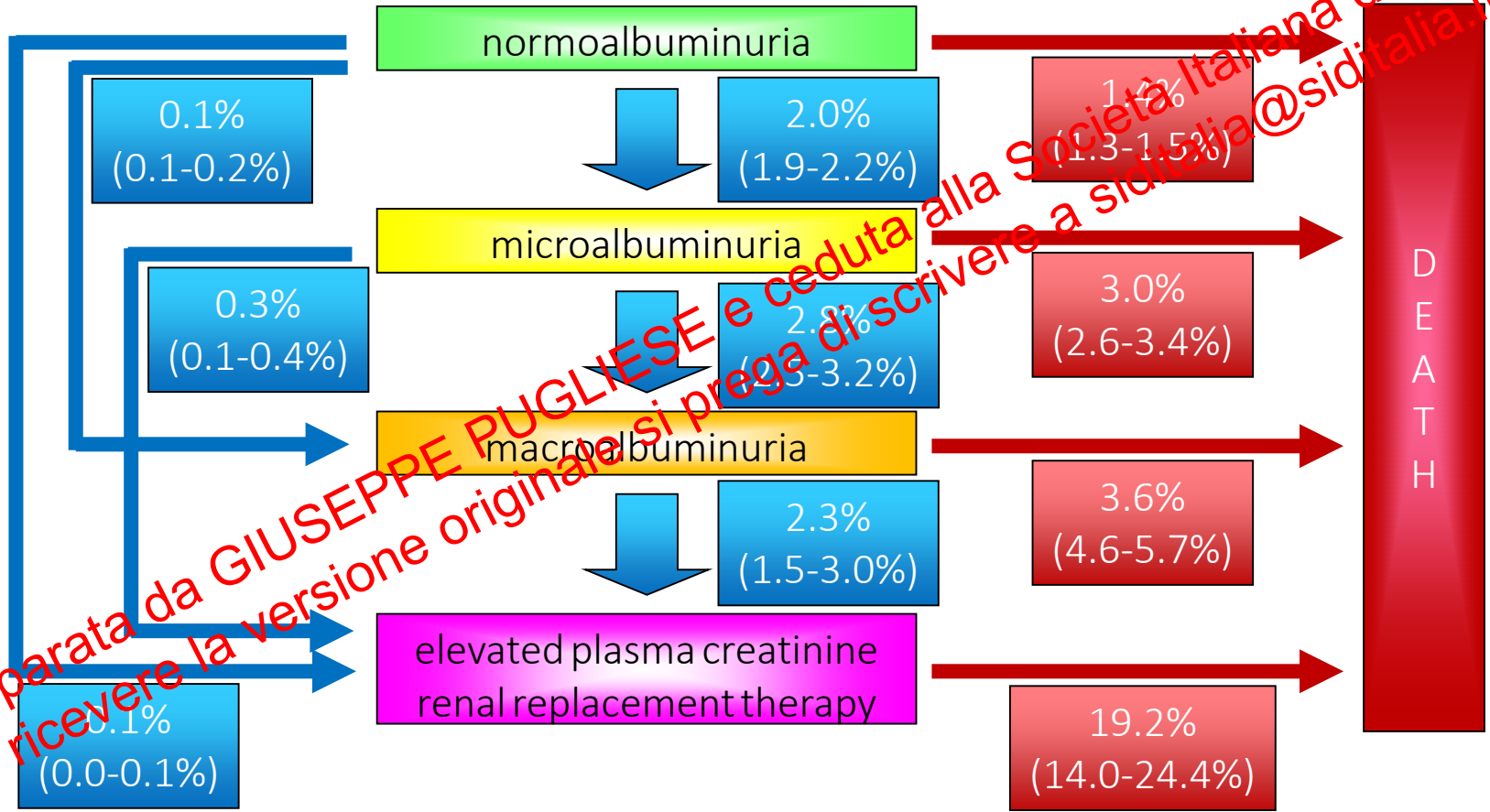
Analysis of 15,773 patients with type 2 diabetes from the Renal Insufficiency And Cardiovascular Events (RIACE) Italian multicentre study

*Solini A et al, Diabetes Care 2012; 35:143-149*



# Progression to ESRD versus death from CVD

Annual transition rates through the stages of nephropathy and to death from any cause.



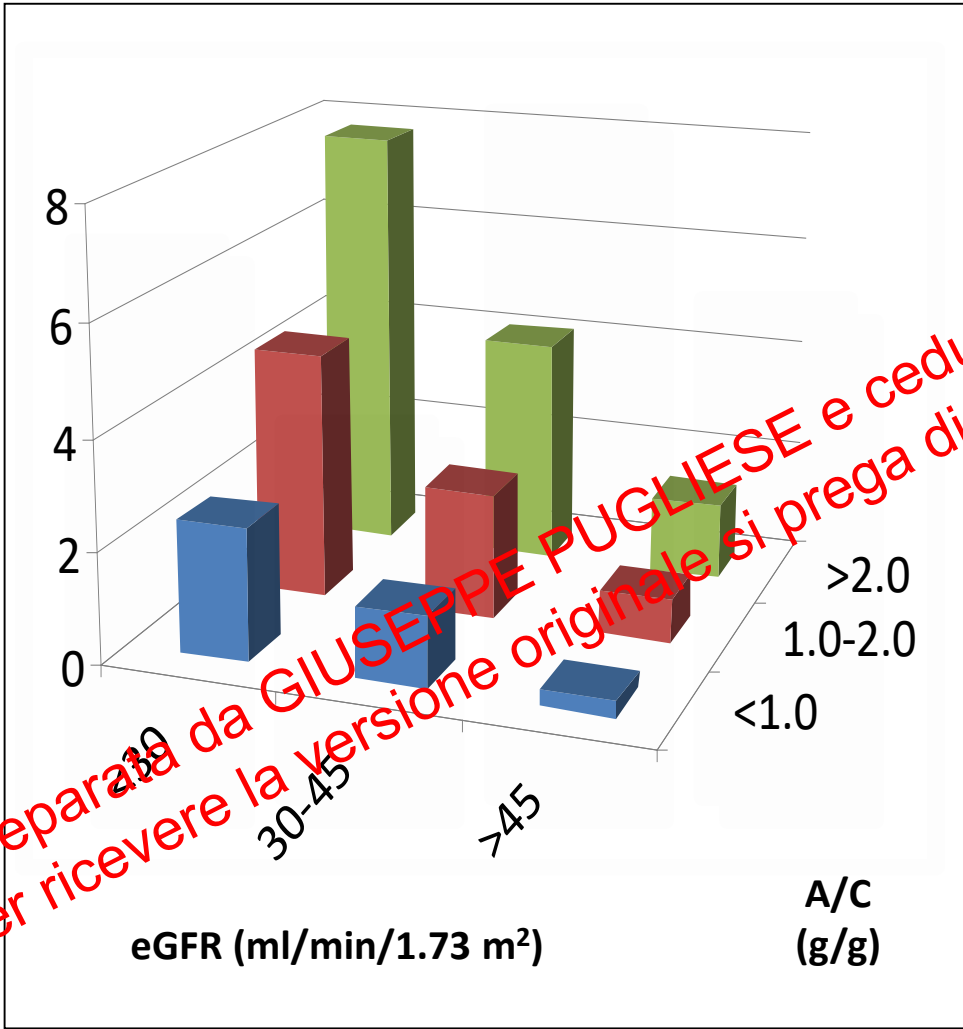
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Post-hoc analysis of the United Kingdom Prospective Diabetes Study (UKPDS) 64



# Progression to ESRD versus death from CVD

## Risk of ESRD for each albuminuria and eGFR category



- 3,228 adult patients from 2 prospective randomized controlled clinical trials:
1. Irbesartan Diabetic Nephropathy Trial (IDNT);
  2. Reduction of Endpoints in Non-Insulin-Dependent Diabetes With the Angiotensin II Antagonist Losartan (RENAAL).

| A/C (g/g) | eGFR (ml/min/1.73 m²) |                      |                      |
|-----------|-----------------------|----------------------|----------------------|
|           | <30                   | 30-45                | >45                  |
| >2.0      | 12.87<br>(5.97-27.74) | 7.46<br>(3.63-15.33) | 7.40<br>(3.32-16.47) |
| 1.0-2.0   | 7.12<br>(3.16-16.04)  | 3.47<br>(1.63-7.40)  | 2.80<br>(1.18-6.64)  |
| <1.0      | 3.61<br>(1.49-8.73)   | 1.49<br>(0.64-3.48)  | 1.00<br>(Ref)        |

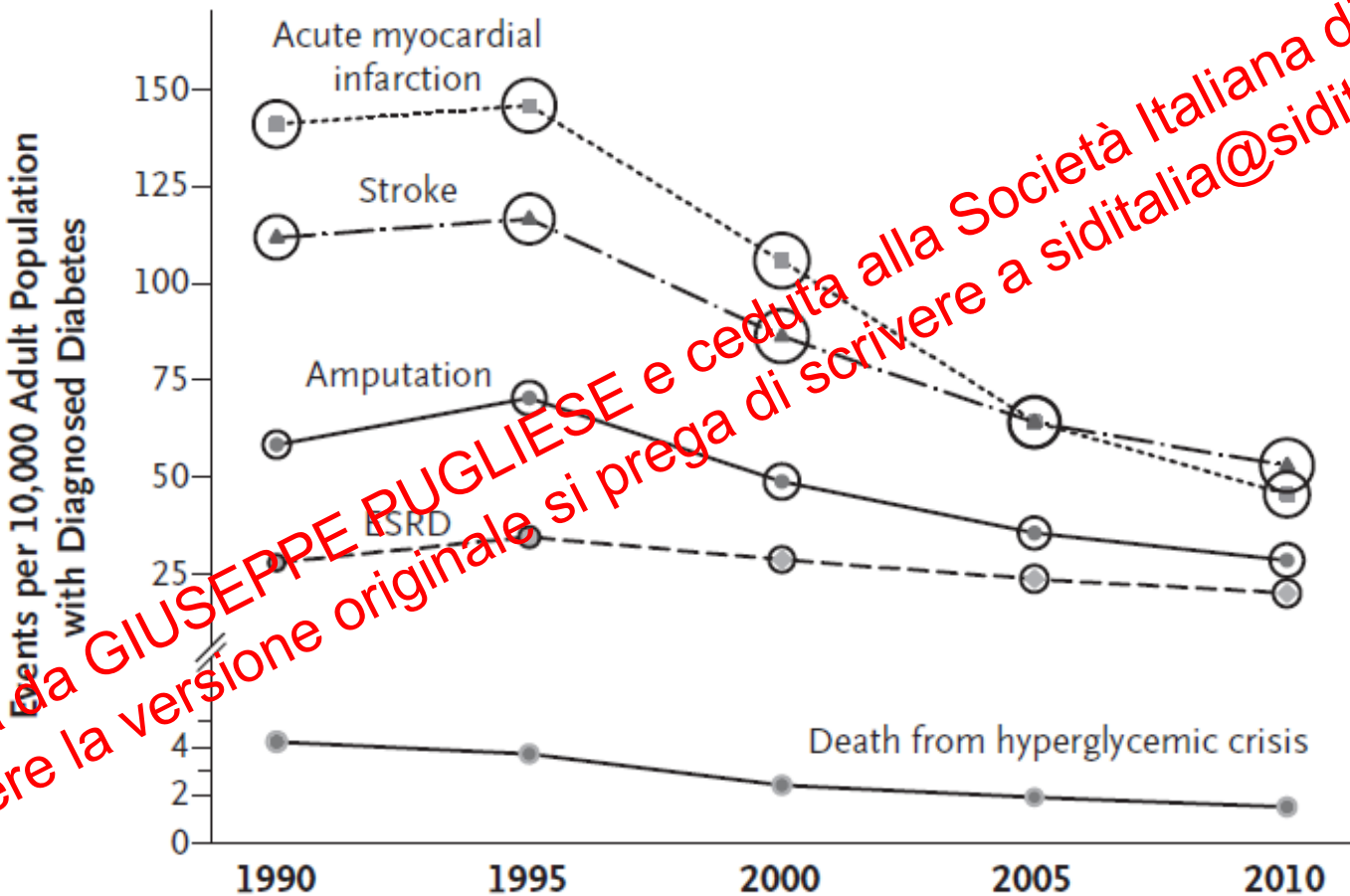
Multivariate adjusted risk of ESRD for each albuminuria and eGFR category, accounting for the possibility of competing events between ESRD and CV death

The Diabetes Mellitus Treatment for Renal Insufficiency Consortium (DIAMETRIC) Database



# Trend in diabetic complications in people with type 2 diabetes

Trends in age-standardized rates of diabetes-related complications among US adults with diagnosed diabetes, 1990–2010

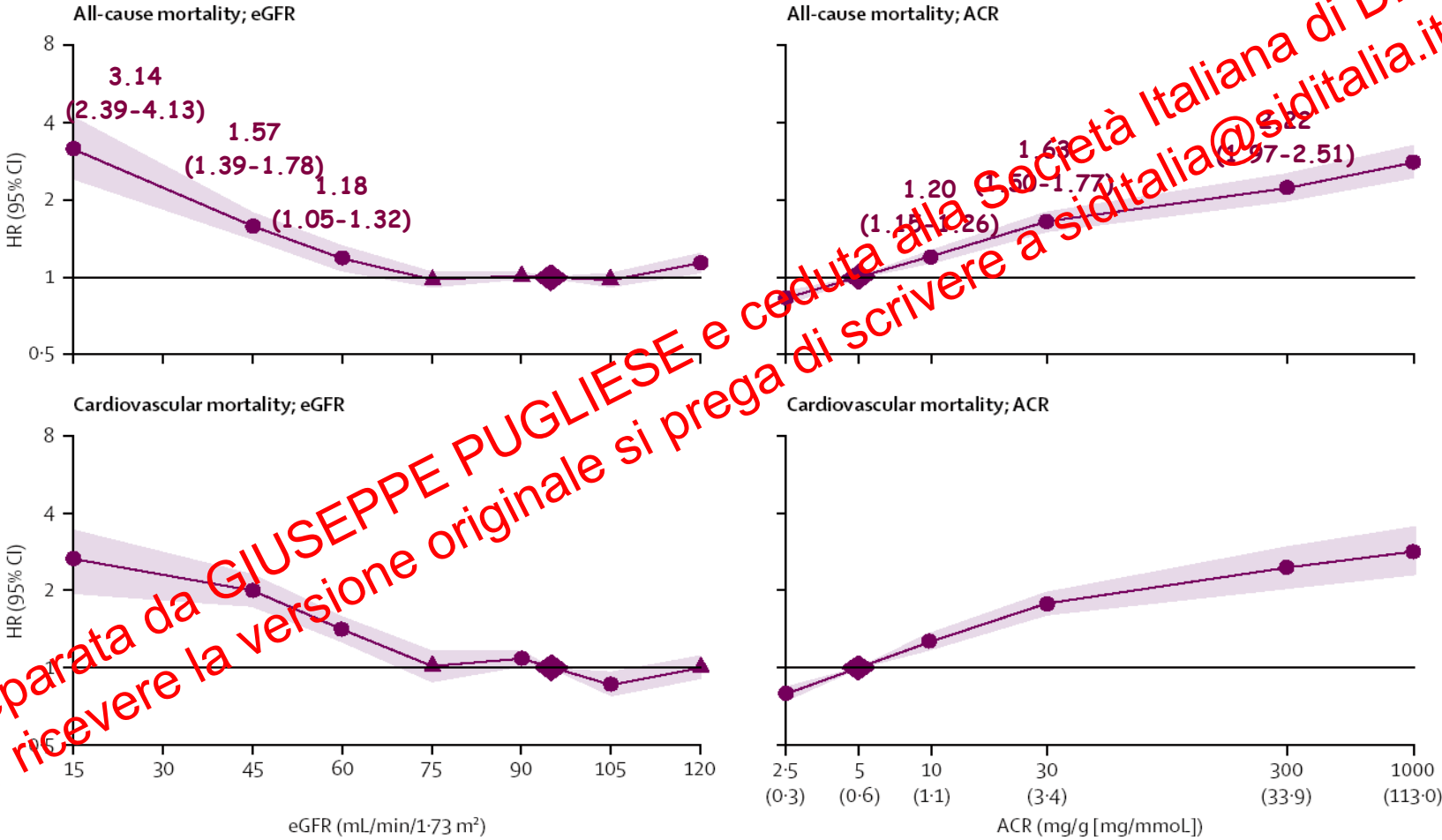


Analysis of data from the National Health Interview Survey, the National Hospital Discharge Survey, the U.S. Renal Data System, and the U.S. National Vital Statistics System



# Relation of albuminuria and eGFR to all-cause and CVD mortality

## Risk of death by albuminuria and eGFR

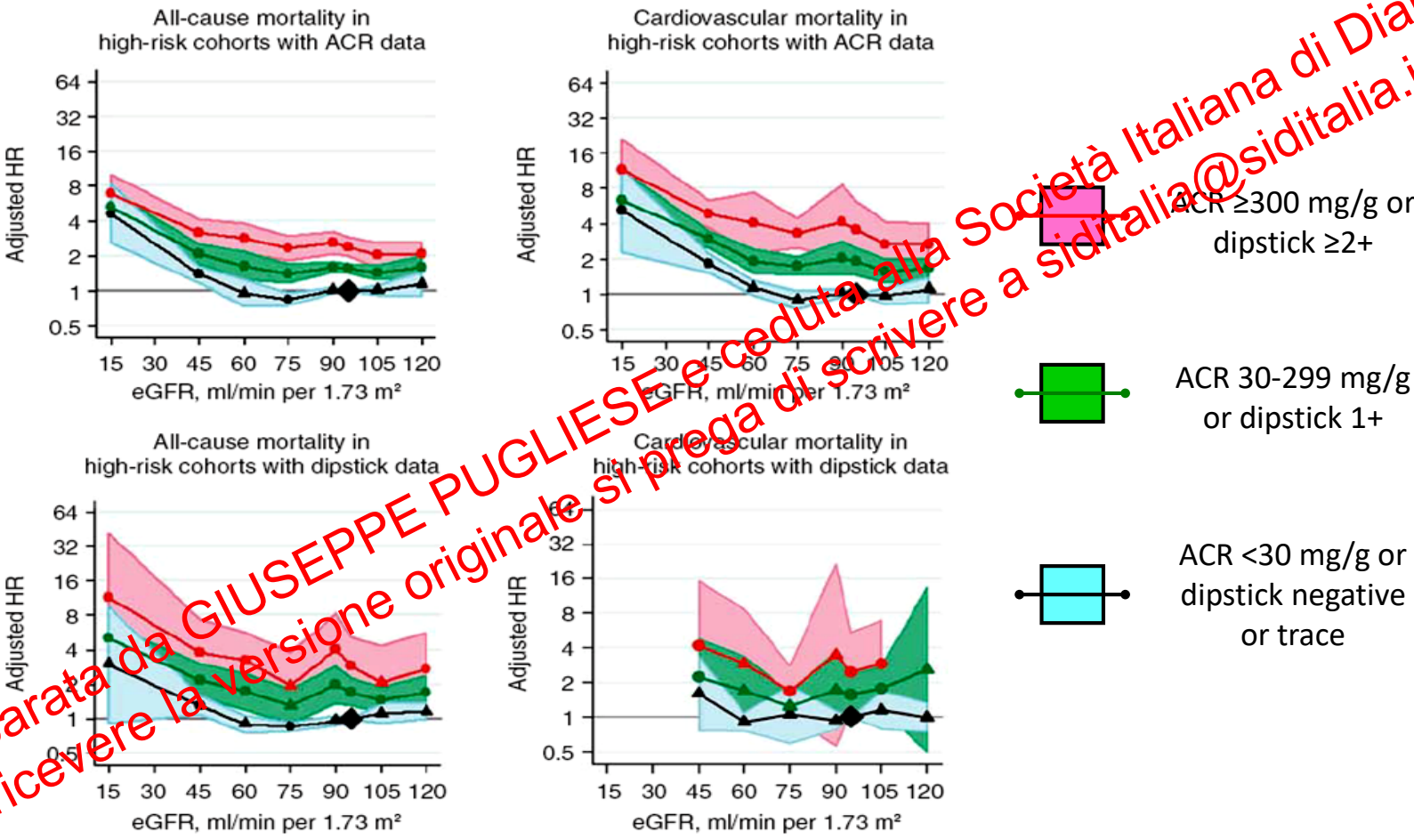


Meta-analysis of data of 105,872 participants with ACR measurements from the general population



# Relation of albuminuria and eGFR to all-cause and CVD mortality

## Risk of death by albuminuria and eGFR



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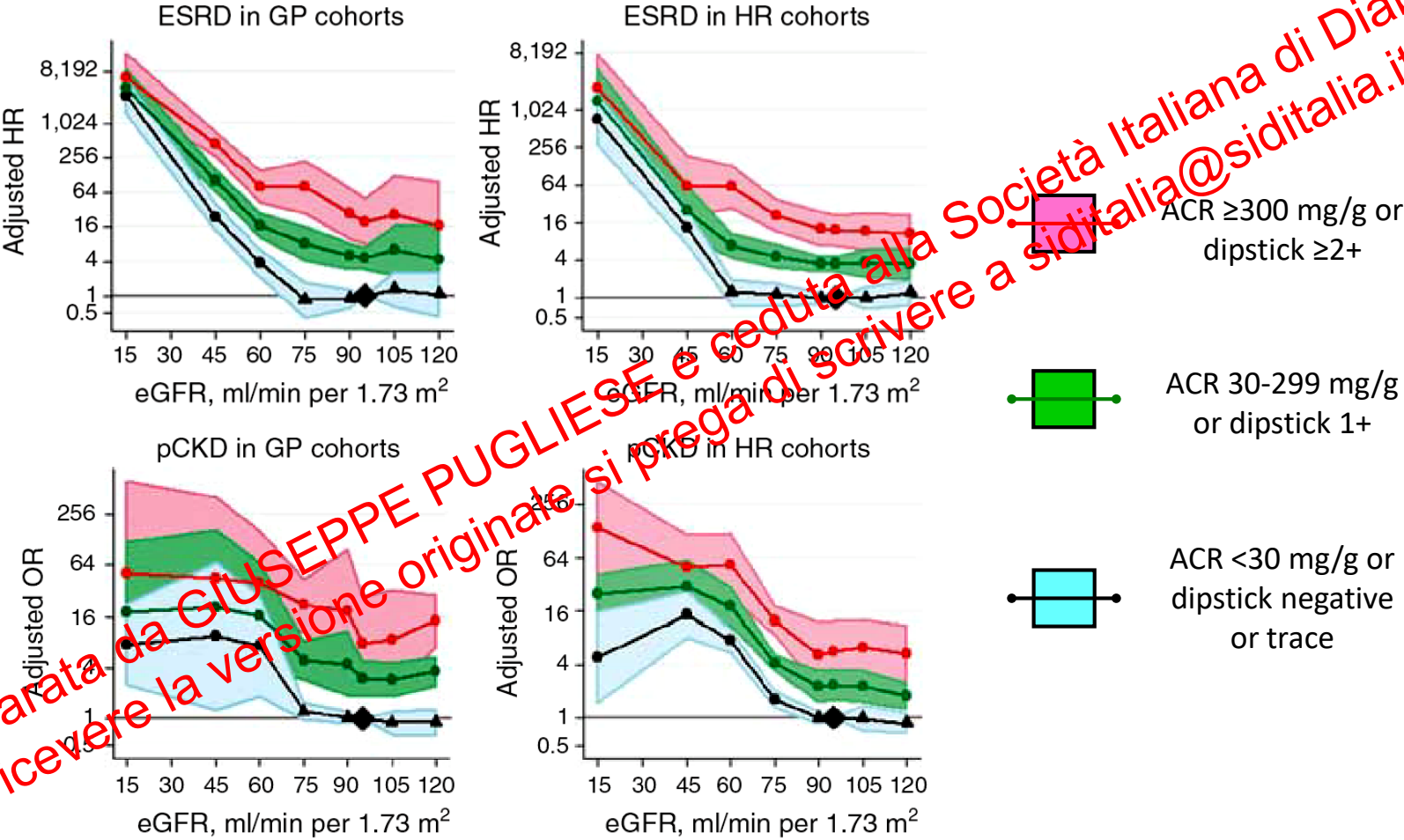
Meta-analysis of data of 105,872 participants from 10 cohorts with diabetes (49.6%), hypertension or CVD and ACR measurements or with diabetes (32.4%), hypertension or CVD and dipstick measurements





# Relation of albuminuria and eGFR to adverse renal outcomes

## Risk of adverse renal outcomes by albuminuria and eGFR

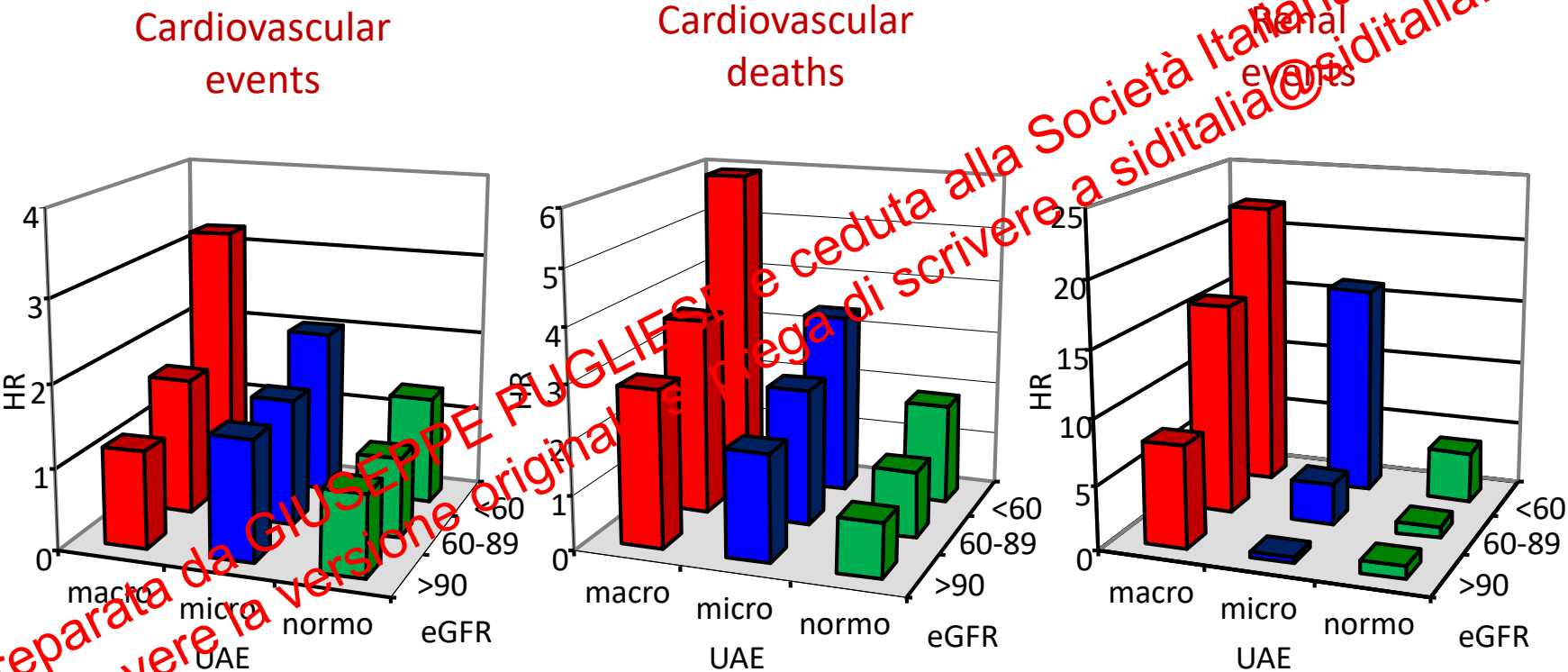


Meta-analysis of data of 845,125 participants from 9 nine general population cohorts and 173,892 patients from 8 cohorts at high risk for CKD



# Relation of albuminuria and eGFR to adverse renal outcomes

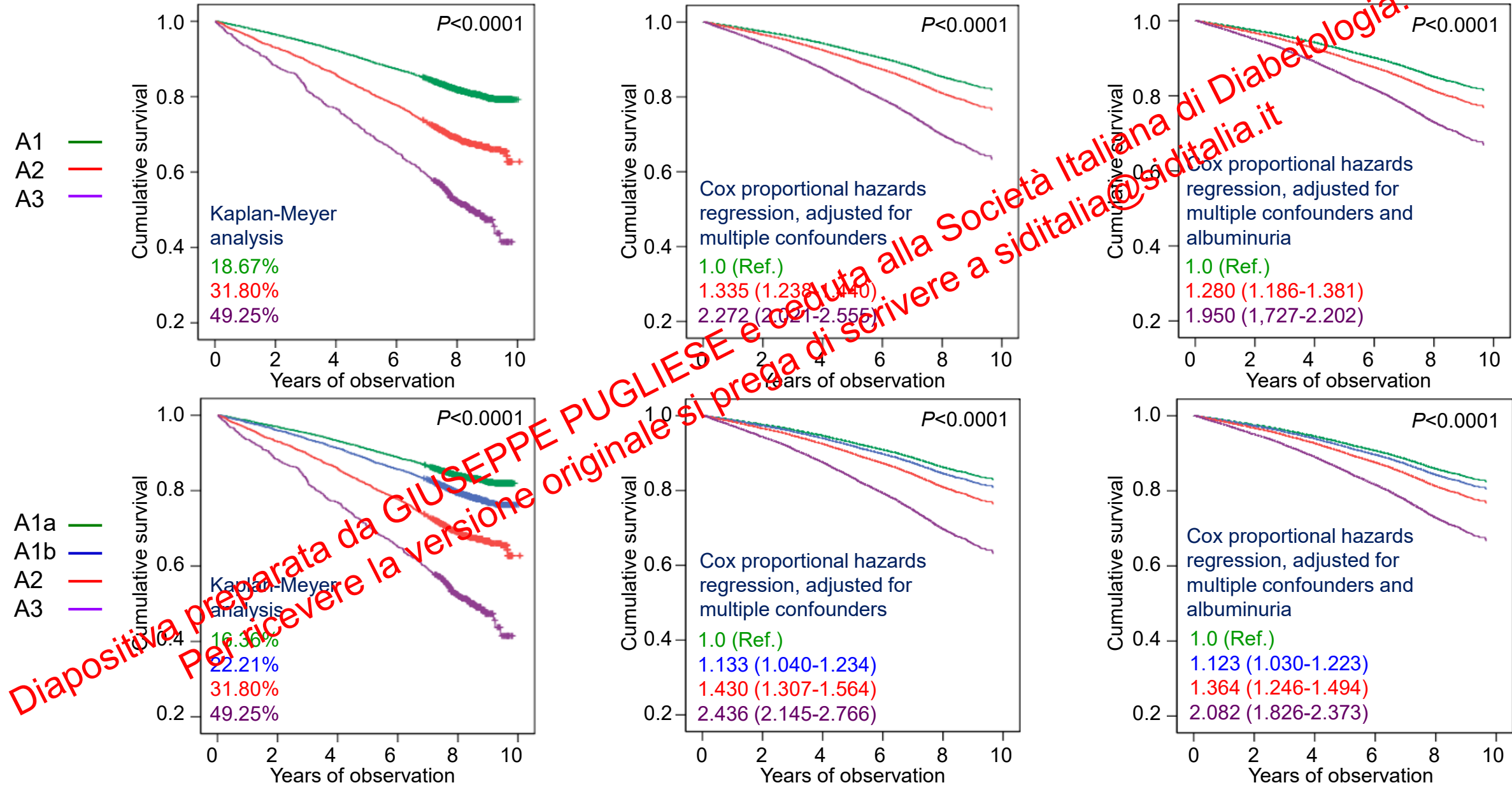
Risk of all-cause & CVD mortality and adverse renal outcomes by albuminuria and eGFR



Analysis of data of 10,640 patients with type 2 diabetes from the the Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation (ADVANCE) Study over a median follow-up of 4.3 years

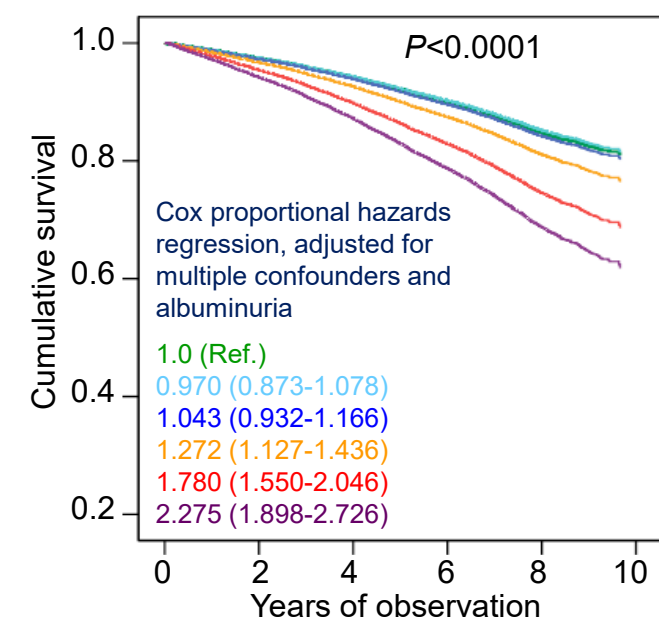
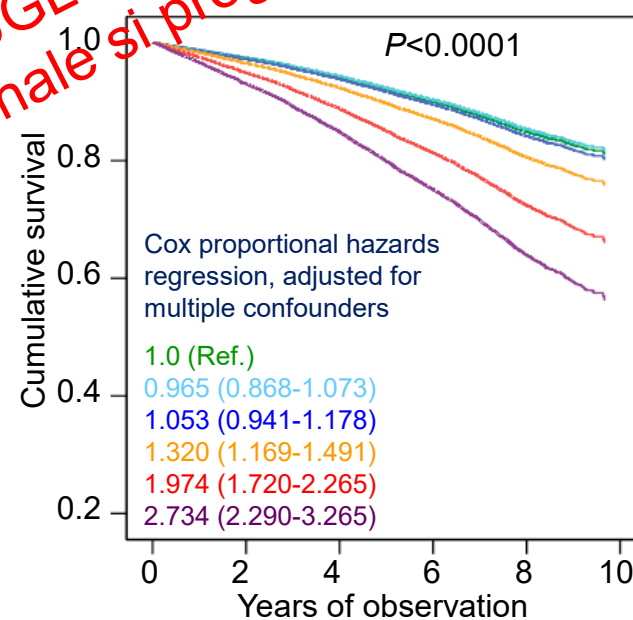
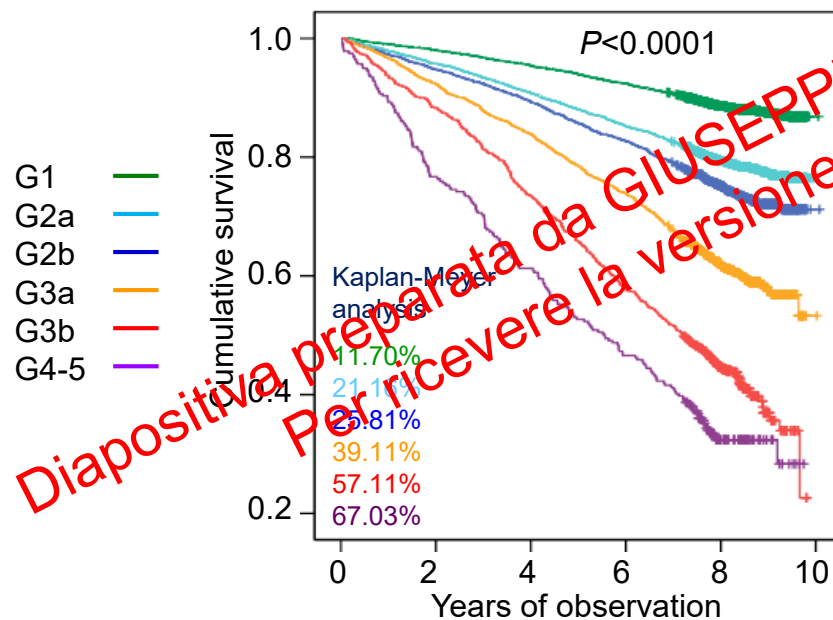
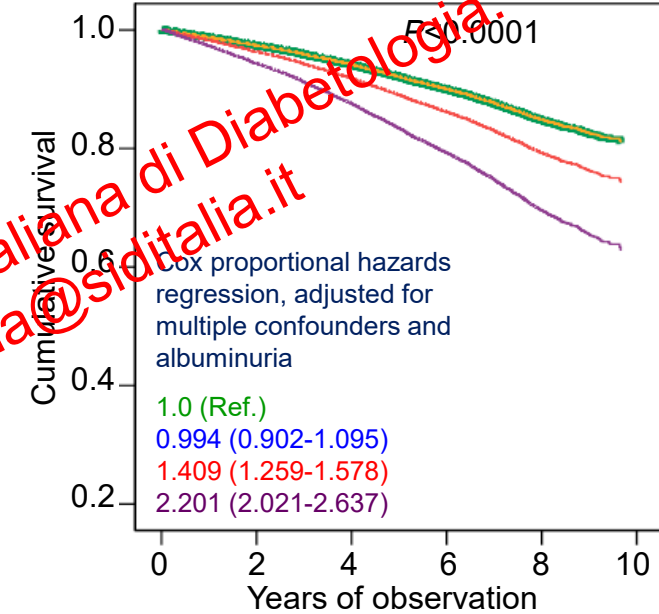
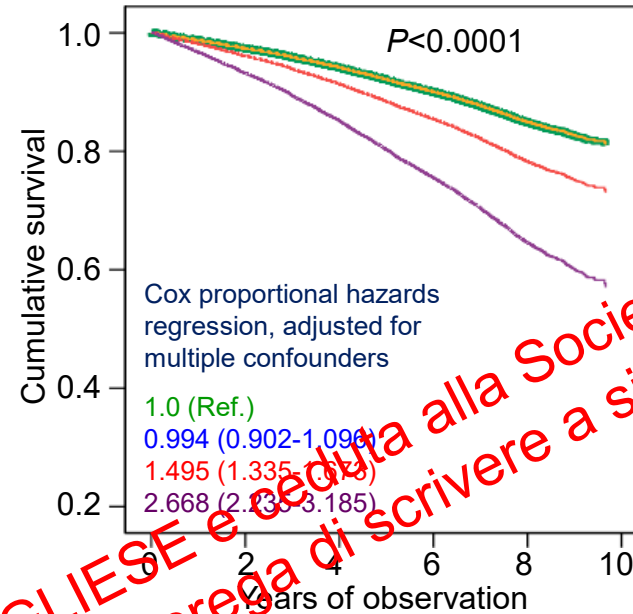
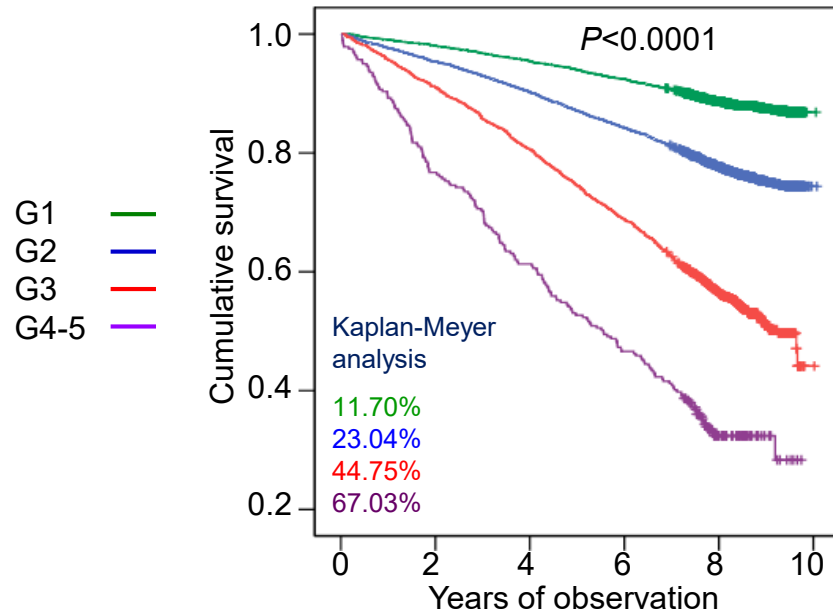


# Relation of albuminuria categories to all-cause mortality



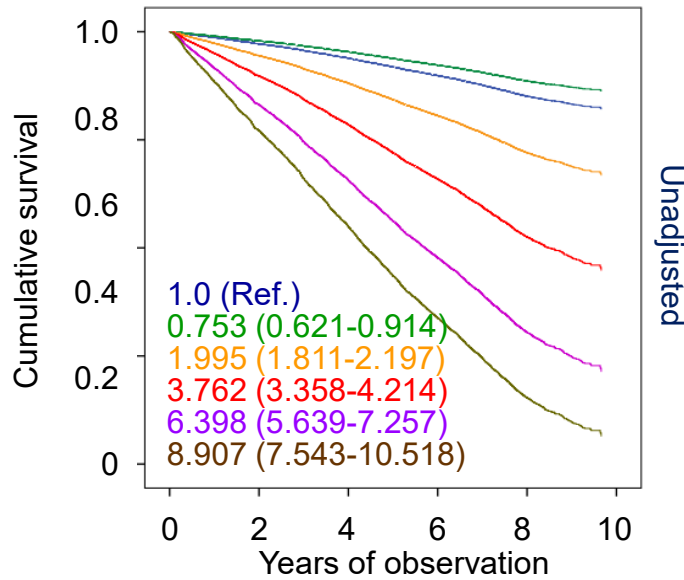


# Relation of eGFR categories to all-cause mortality

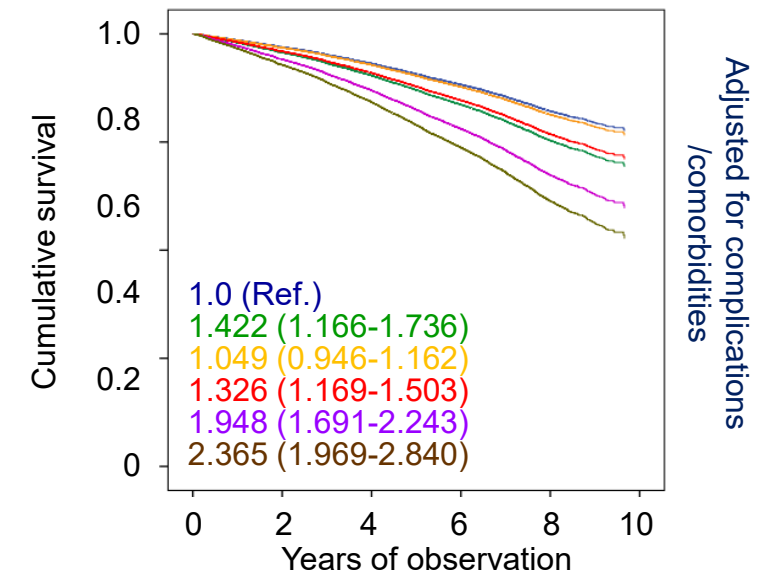
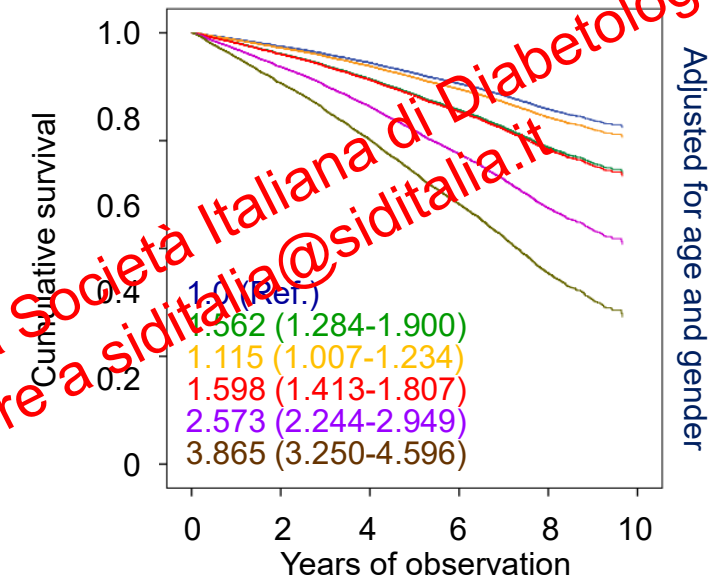
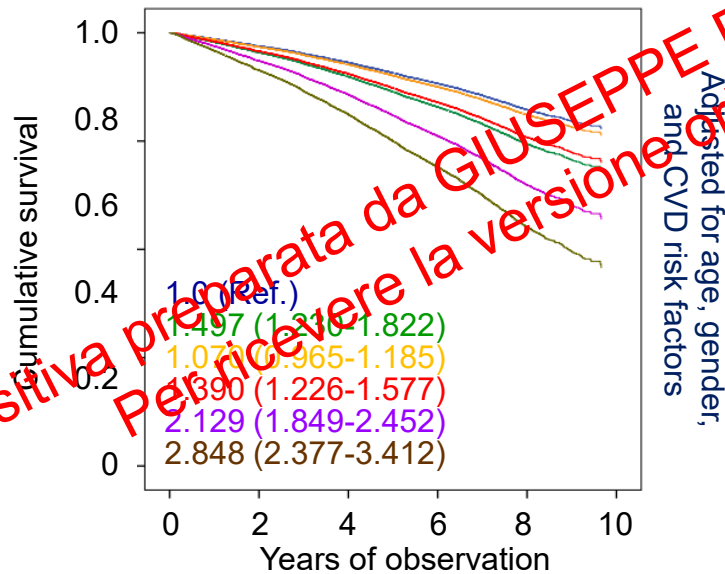




# Relation of eGFR categories to all-cause mortality



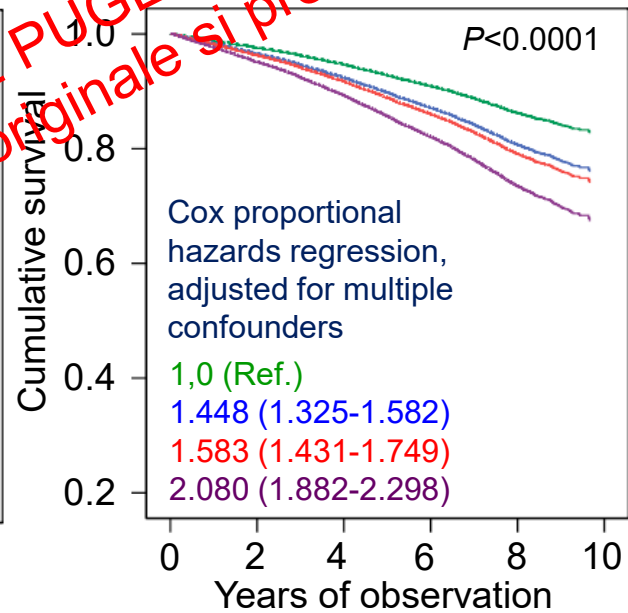
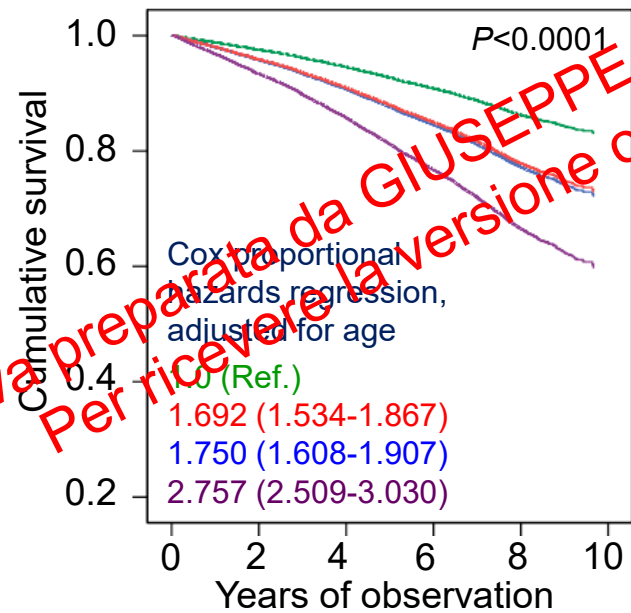
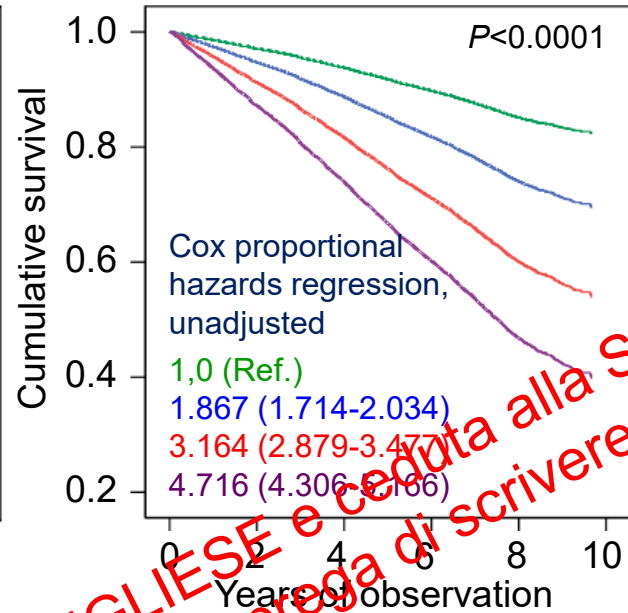
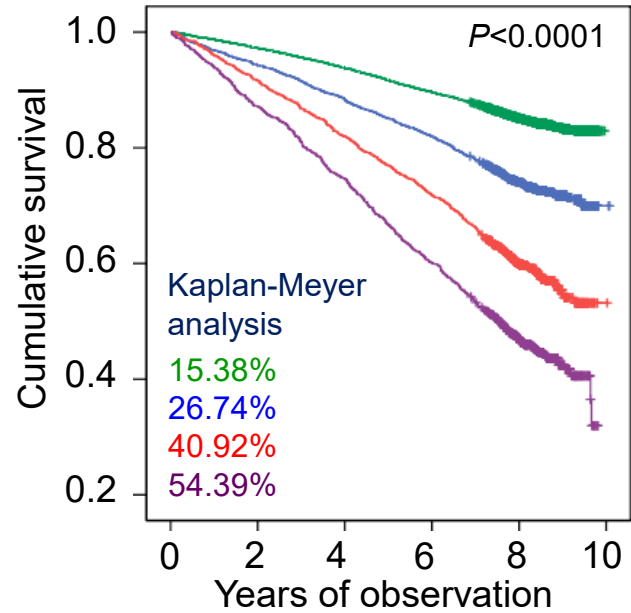
G1a  
G1b  
G2  
G3a  
G3b  
G4-5







# Relation of DKD phenotypes to all-cause mortality



Alb-/eGFR- — Alb+/eGFR- —  
Alb-/eGFR+ — Alb+/eGFR+ —





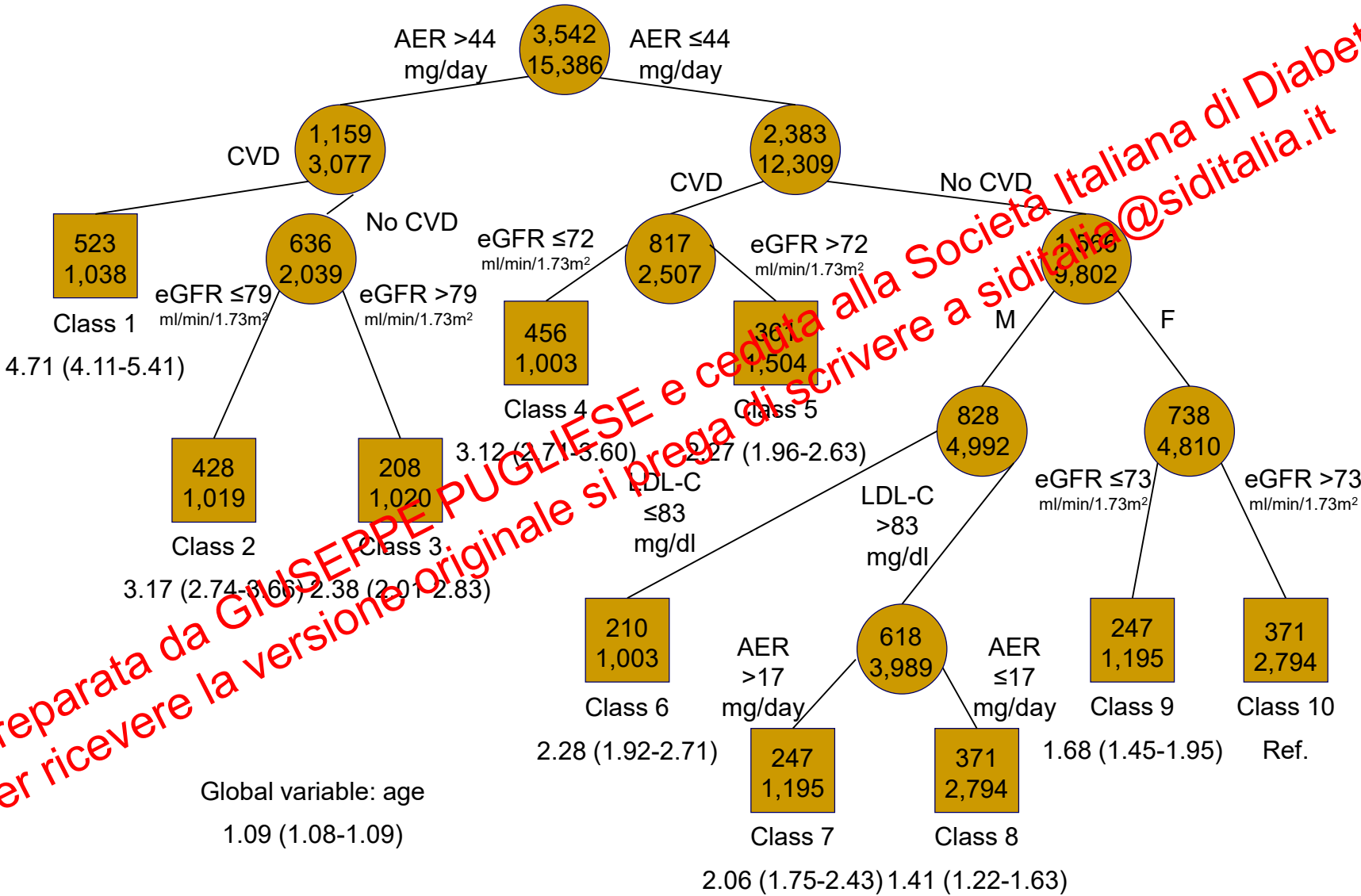
## Relation of KDIGO categories to all-cause mortality

| KDIGO categories | A1a                 | A1b                 | A2                  | A3                  |
|------------------|---------------------|---------------------|---------------------|---------------------|
| G1               | 1 (Ref.)            | 0.936 (0.780-1.124) | 1.313 (1.079-1.599) | 2.192 (1.546-3.108) |
| G2a              | 0.798 (0.667-0.956) | 1.050 (0.885-1.246) | 1.310 (1.089-1.575) | 2.477 (1.816-3.379) |
| G2b              | 1.104 (0.833-1.120) | 1.057 (0.878-1.273) | 1.388 (1.148-1.678) | 1.706 (1.232-2.362) |
| G3a              | 1.316 (1.071-1.617) | 1.389 (1.138-1.694) | 1.482 (1.218-1.804) | 2.263 (1.708-3.000) |
| G3b              | 1.847 (1.400-2.438) | 2.248 (1.791-2.821) | 2.089 (1.686-2.590) | 2.784 (2.136-3.629) |
| G4-5             | 1.613 (0.876-2.968) | 2.245 (1.494-3.374) | 2.785 (2.094-3.703) | 4.662 (3.590-6.054) |

Cox proportional hazards regression, adjusted for multiple confounders



# Determinants of all-cause mortality

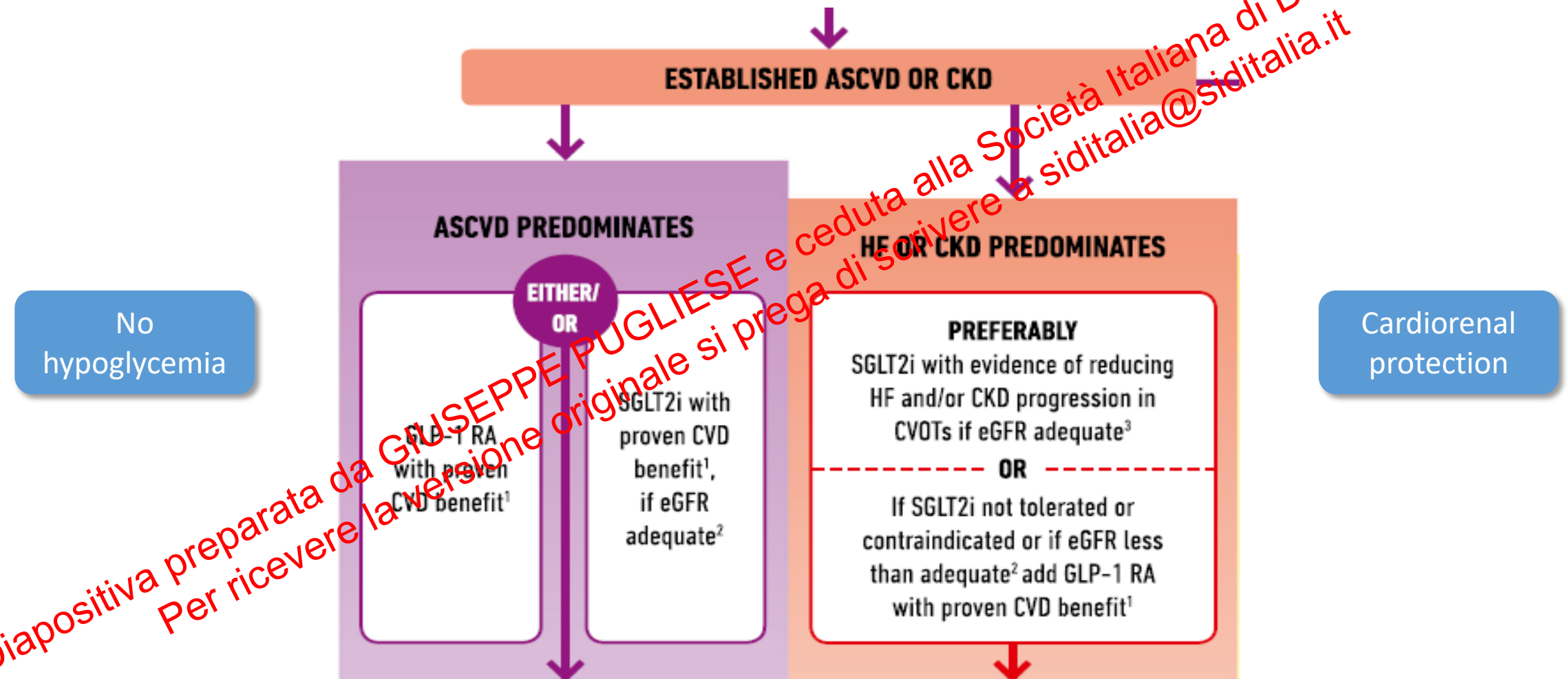


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# Cardiorenal protection with anti-hyperglycemic agents

American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) Consensus Report





# Cardiovascular protection with GLP-1 receptor agonists

|                                                                       |  (1) |  (2) |  (3) |  (4) |  (5) |
|-----------------------------------------------------------------------|----------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| Drug                                                                  | Lixisenatide                                                                           | Liraglutide                                                                             | Semaglutide                                                                             | Exenatide LAR                                                                           | Albiglutide                                                                             |
| N                                                                     | 6,068                                                                                  | 9,340                                                                                   | 3,297                                                                                   | 14,752                                                                                  | 9,463                                                                                   |
| Follow-up (years)                                                     | 2.1                                                                                    | 3.8                                                                                     | 2.1                                                                                     | 3.2                                                                                     | 1.6                                                                                     |
| History of CVD (%)                                                    | 100                                                                                    | 81                                                                                      | 83                                                                                      | 73.1                                                                                    | 100                                                                                     |
| Primary endpoint (MACE)                                               | 1.02 (0.89–1.17)*<br>P=NS                                                              | 0.87 (0.78–0.97)<br>P=0.001                                                             | 0.74 (0.58–0.95)<br>P=0.02                                                              | 0.91 (0.83–1.00)<br>P=0.06                                                              | 0.78 (0.68–0.90)<br>P=0.0006                                                            |
| Fatal or nonfatal myocardial infarction                               | 1.03 (0.87–1.22)<br>P=NS                                                               | 0.86 (0.73–1.00)<br>P=0.046                                                             | 0.74 (0.51–1.08)<br>P=NS†                                                               | 0.97 (0.85–1.10)<br>P=NS                                                                | 0.75 (0.61–0.90)<br>P=0.003                                                             |
| Fatal or nonfatal stroke                                              | 1.12 (0.79–1.58)<br>P=NS                                                               | 0.86 (0.71–1.06)<br>P=NS                                                                | 0.61 (0.38–0.99)<br>P=0.04†                                                             | 0.85 (0.70–1.03)<br>P=NS                                                                | 0.86 (0.66–1.14)                                                                        |
| Death from cardiovascular causes                                      | 0.98 (0.78–1.22)<br>P=NS                                                               | 0.78 (0.66–0.93)<br>P=0.007                                                             | 0.98 (0.65–1.48)<br>P=NS                                                                | 0.88 (0.76–1.02)<br>P=NS                                                                | 0.93 (0.73–1.19)                                                                        |
| Death from any cause                                                  | 0.94 (0.78–1.13)<br>P=NS                                                               | 0.85 (0.74–0.97)<br>P=0.02                                                              | 1.05 (0.74–1.50)<br>P=NS                                                                | 0.86 (0.77–0.97)<br>P<0.05                                                              | 0.95 (0.79–1.16)                                                                        |
| Hospitalization for heart failure                                     | 0.96 (0.75–1.23)<br>P=NS                                                               | 0.87 (0.73–1.05)<br>P=NS                                                                | 1.11 (0.77–1.61)<br>P=NS                                                                | 0.94 (0.78–1.13)<br>P=NS                                                                | NA                                                                                      |
| Death from cardiovascular causes or hospitalization for heart failure | NA                                                                                     | NA                                                                                      | NA                                                                                      | 0.85 (0.70–1.04)<br>P=NS                                                                | NA                                                                                      |

\*4-point MACE;

† only nonfatal.

1. Pfeffer MA et al. *N Engl J Med.* 2015;373;2247-2257; 2. Marso SP et al. *N Engl J Med.* 2016;375;311-322; 3. Marso SP et al. *N Engl J Med.* 2016;375;1834-1844; 4. Holman RR et al. *N Engl J Med.* 2017;377;1228-1239; 5. Hernandez HF et al. *Lancet.* 2018;392:1519–1529



# Cardiovascular protection with SGLT2 inhibitors

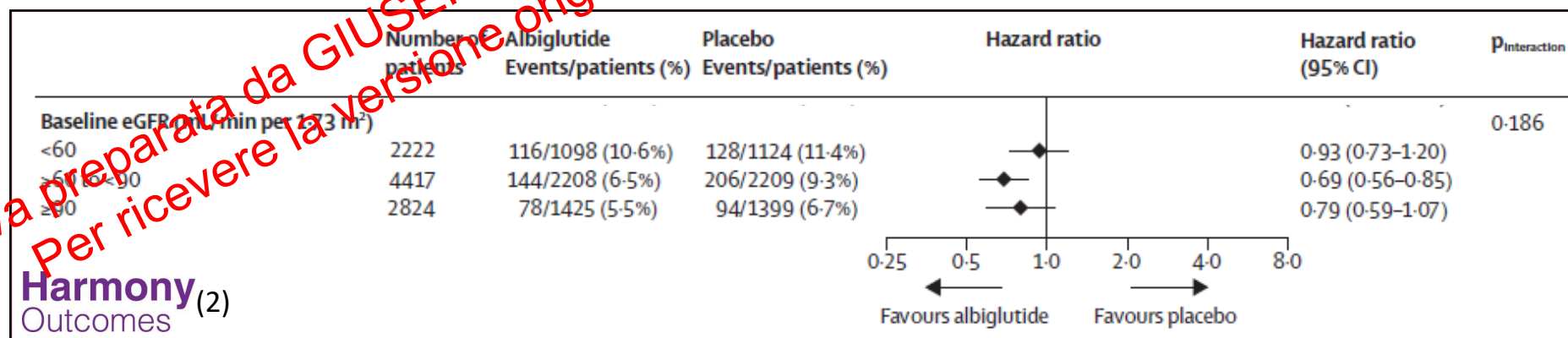
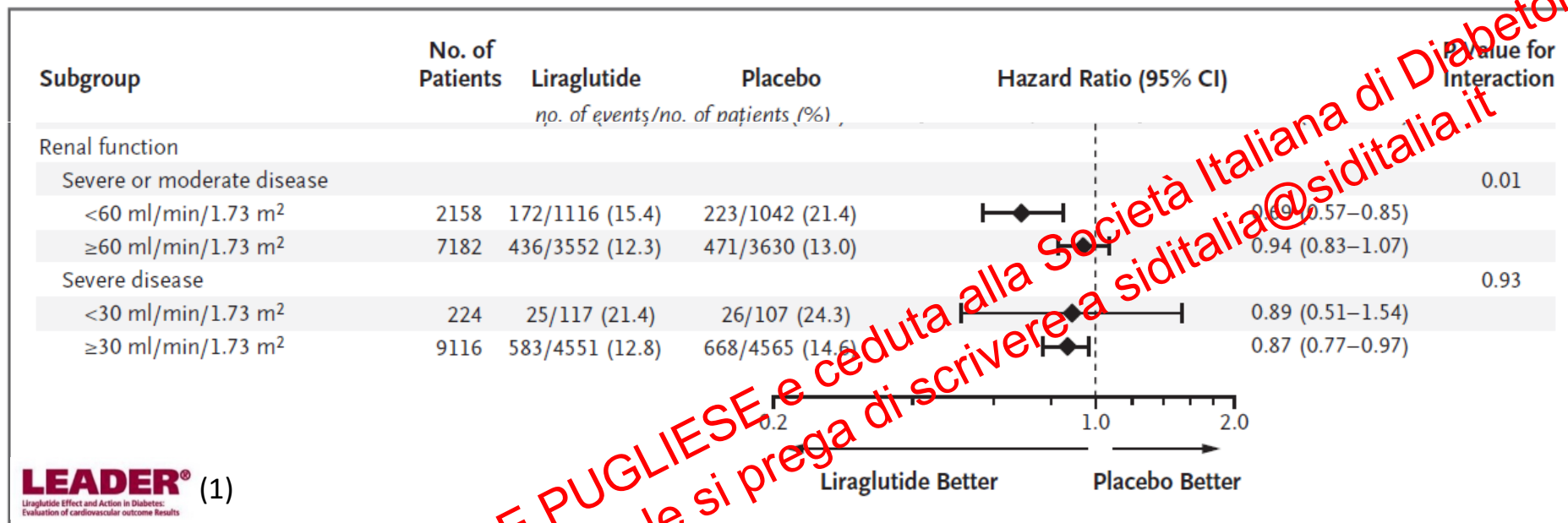
|                                                                       |  EMPA-REG OUTCOME® (1) |  CANVAS Program (2) |  DECLARE TIM-5B (3) |  CREDENCE (4) |
|-----------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|
| Drug                                                                  | Empagliflozin                                                                                           | Canagliflozin                                                                                          | Dapagliflozin                                                                                          | Canagliflozin                                                                                    |
| N                                                                     | 7,020                                                                                                   | 10,142                                                                                                 | 11,160                                                                                                 | 4,401                                                                                            |
| Follow-up (years)                                                     | 3.1                                                                                                     | 2.4                                                                                                    | 2.4                                                                                                    | 2,6                                                                                              |
| History of CVD (%)                                                    | 100                                                                                                     | 65.6                                                                                                   | 40.6                                                                                                   | 50,4                                                                                             |
| Primary endpoint (MACE)                                               | 0.86 (0.74–0.99) P=0.04                                                                                 | 0.86 (0.75–0.97) P=0.02                                                                                | 0.93 (0.84–1.03) P=NS                                                                                  | 0.80 (0.67–0.95) P=0.01†                                                                         |
| Fatal or nonfatal myocardial infarction                               | 0.87 (0.70–1.09) P=NS                                                                                   | 0.89 (0.75–1.09) P=NS                                                                                  | 0.89 (0.77–1.01) P=NS                                                                                  | NA                                                                                               |
| Fatal or nonfatal stroke                                              | 1.18 (0.89–1.56) P=NS                                                                                   | 0.87 (0.69–1.09) P=NS                                                                                  | 1.01 (0.84–1.21) P=NS                                                                                  | NA                                                                                               |
| Death from cardiovascular causes                                      | 0.68 (0.49–0.77) P<0.001                                                                                | 0.87 (0.72–1.06) P=NS                                                                                  | 0.98 (0.82–1.17) P=NS                                                                                  | 0.78 (0.61–1.00) P=0.05                                                                          |
| Death from any cause                                                  | 0.68 (0.57–0.82) P<0.001                                                                                | 0.87 (0.74–1.01) P=NS                                                                                  | 0.93 (0.82–1.04) P=NS                                                                                  | 0.83 (0.68–1.02) P=NS                                                                            |
| Hospitalization for heart failure                                     | 0.65 (0.50–0.85) P=0.002                                                                                | 0.67 (0.52–0.87) P<0.05                                                                                | 0.73 (0.61–0.88) P<0.05                                                                                | 0.61 (0.47–0.80) P<0.001                                                                         |
| Death from cardiovascular causes or hospitalization for heart failure | 0.66 (0.55–0.79) P<0.001*                                                                               | 0.78 (0.67–0.91) P<0.05                                                                                | 0.83 (0.73–0.95) P=0.005                                                                               | 0.69 (0.57–0.83) P<0.001                                                                         |

\*excluding fatal stroke; † MACE as secondary endpoint.

1. Zinman B et al. *N Engl J Med.* 2015; 373:2117-2128
2. Neal B et al. *N Engl J Med.* 2017;377:644-657
3. Wiviott SD et al. *N Engl J Med.* 2019;380:347-357
4. Perkovic V et al. *N Engl J Med.* 2019; April 14



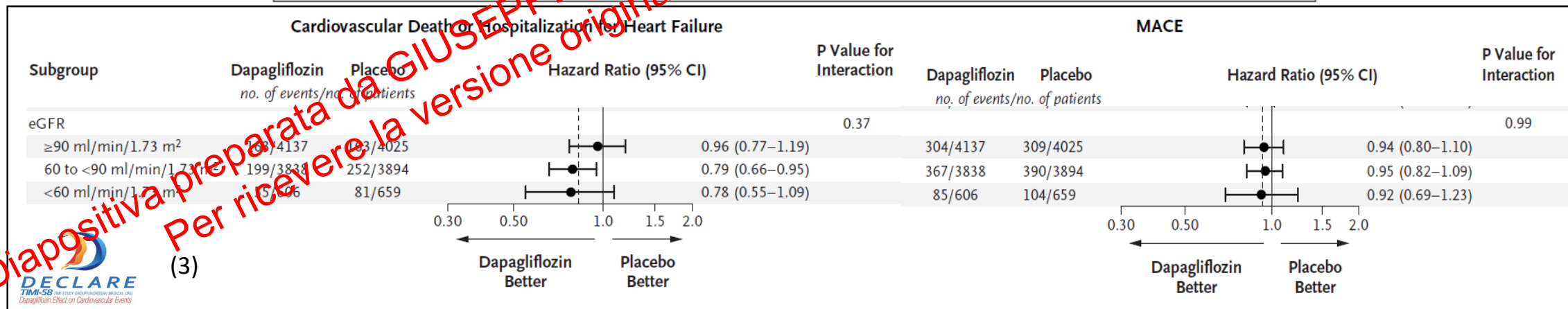
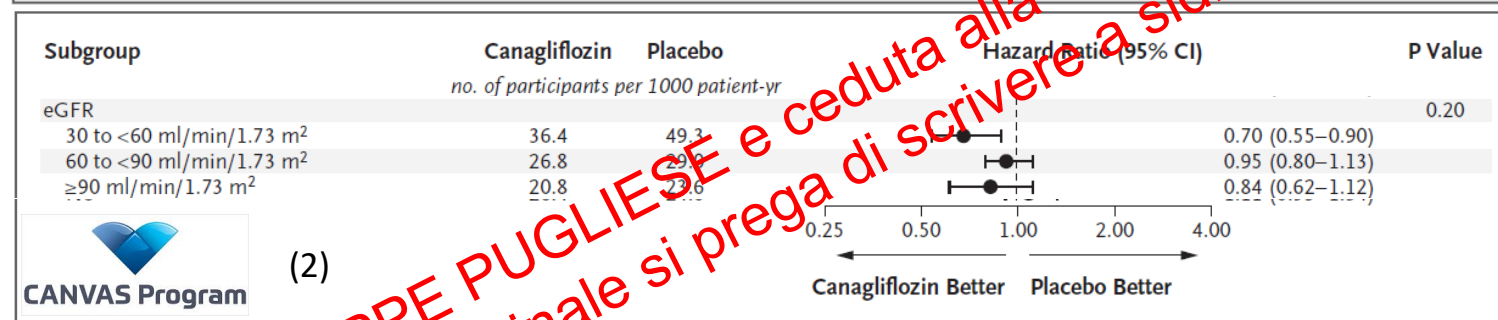
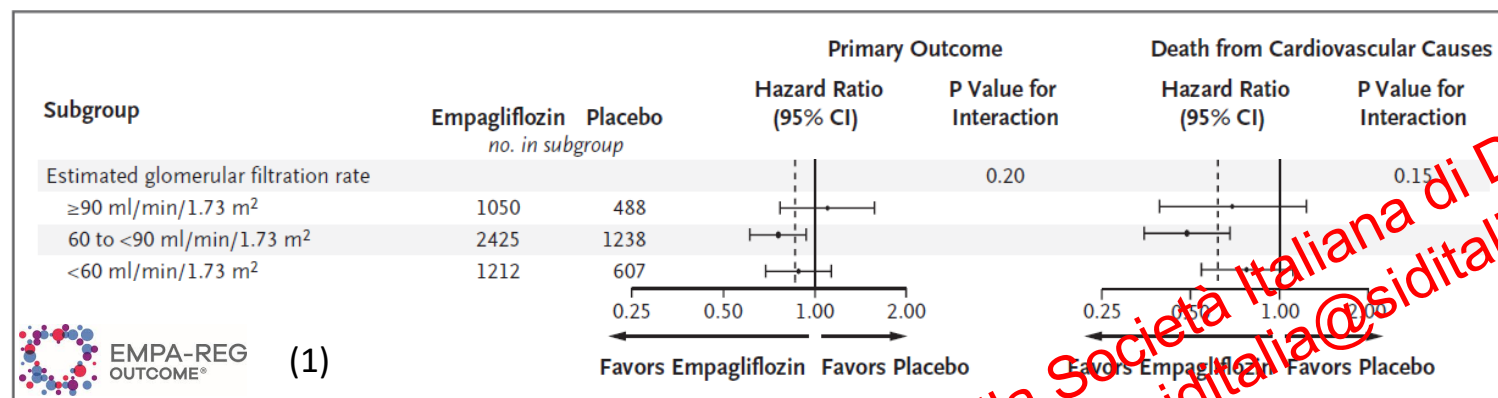
# Cardiovascular protection with GLP-1 receptor agonists by eGFR







# Cardiovascular protection with SGLT2 inhibitors by eGFR



1. Zinman B et al. *N Engl J Med.* 2015; 373:2117-2128;
2. Neal B et al. *N Engl J Med.* 2017;377:644-657;
3. Wiviott SD et al. *N Engl J Med.* 2019;380:347-357



# Cardiovascular protection with SGLT2 inhibitors in DKD patients



| Primary                                                                                            | Hazard ratio (95% CI) | P value |
|----------------------------------------------------------------------------------------------------|-----------------------|---------|
| 1. ESKD, doubling of serum creatinine, or renal or CV death                                        | 0.70 (0.59–0.82)      | 0.00001 |
| Secondary                                                                                          |                       |         |
| 2. CV death or hospitalization for heart failure                                                   | 0.69 (0.57–0.83)      | <0.001  |
| 3. CV death, MI, or stroke                                                                         | 0.80 (0.67–0.95)      | 0.01    |
| 4. Hospitalization for heart failure                                                               | 0.61 (0.47–0.80)      | <0.001  |
| 5. ESKD, doubling of serum creatinine, or renal death                                              | 0.66 (0.53–0.81)      | <0.001  |
| 6. CV death                                                                                        | 0.78 (0.61–1.00)      | 0.0502  |
| 7. All-cause mortality                                                                             | 0.83 (0.68–1.02)      | NA      |
| 8. CV death, MI, stroke, hospitalization for heart failure, or hospitalization for unstable angina | 0.74 (0.63–0.86)      | NA      |



### ❖ Impact of CKD on cardiovascular system

CVD and CKD influence each other in the context of the cardio-renal syndromes

CKD favors CVD via several mechanisms, including increased calcification

### ❖ CKD and cardiovascular risk

CKD is associated with an increased CVD risk since its early phase

Both increased albuminuria and reduced eGFR are associated with an increased risk for total and CVD mortality and morbidity independent of each other and of other CVD risk factors

### ❖ Renal protection and cardiovascular risk

Renal protection may be associated with improved CVD outcomes

Diapositiva preparata da GIUSEPPE PUGLIESE e ceduta alla Società Italiana di Diabetologia.  
Per ricevere la versione originale si prega di scrivere a [siditalia@siditalia.it](mailto:siditalia@siditalia.it)