IL CROSS-TALK

cuore-rene

FISIOPATOLOGIA
ED ASPETTI CLINICI

CATANIA 4 NOVEMBRE 2019

DIPARTIMENTO DI MEDICINA CLINICA
E SPERIMENTALE
UNIVERSITA' DEGLI STUDI DI MESSINA

La malattia renale cronica ed il rischio cardiovascolare

Giuseppina T. Russo

DICHIARAZIONE
CONFLITTO D'INTERESSE DOCENTI

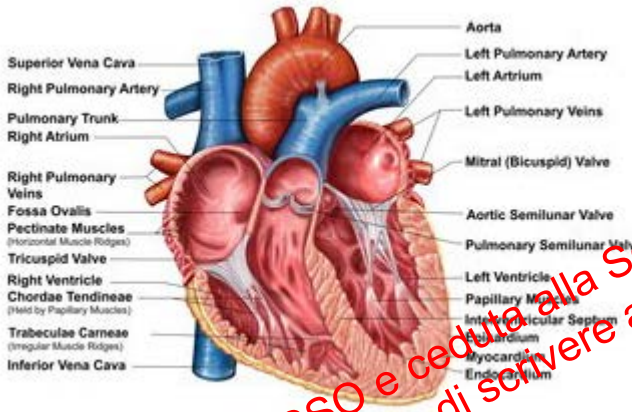
In ottemperanza alla normativa ECM ed al principio trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario, il *docente deve "rilasciare al provider o all'organizzatore la dichiarazione di conflitto d'interessi (ultimi 2 anni rapporti diretti con aziende) e che successivamente* debba informare l'aula all'atto della sua presentazione o comunque prima della lezione/relazione dichiarandolo ai discenti".*

Lecturer , Scientific consultant for:

Boehringer Ingelheim- Eli-Lilly, Novo-Nordisk- Astra Zeneca – Sanofi

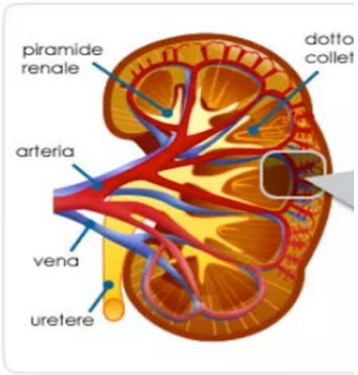
I rapporti tra *diabete*, *cuore* e *rene* sono complessi ed in continua evoluzione

Epidemilogia



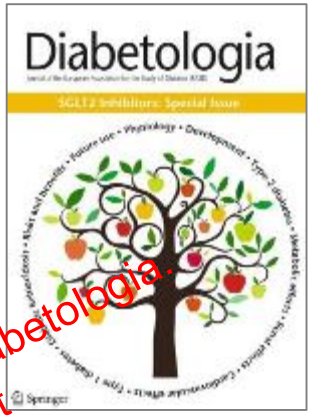
Diagnosi

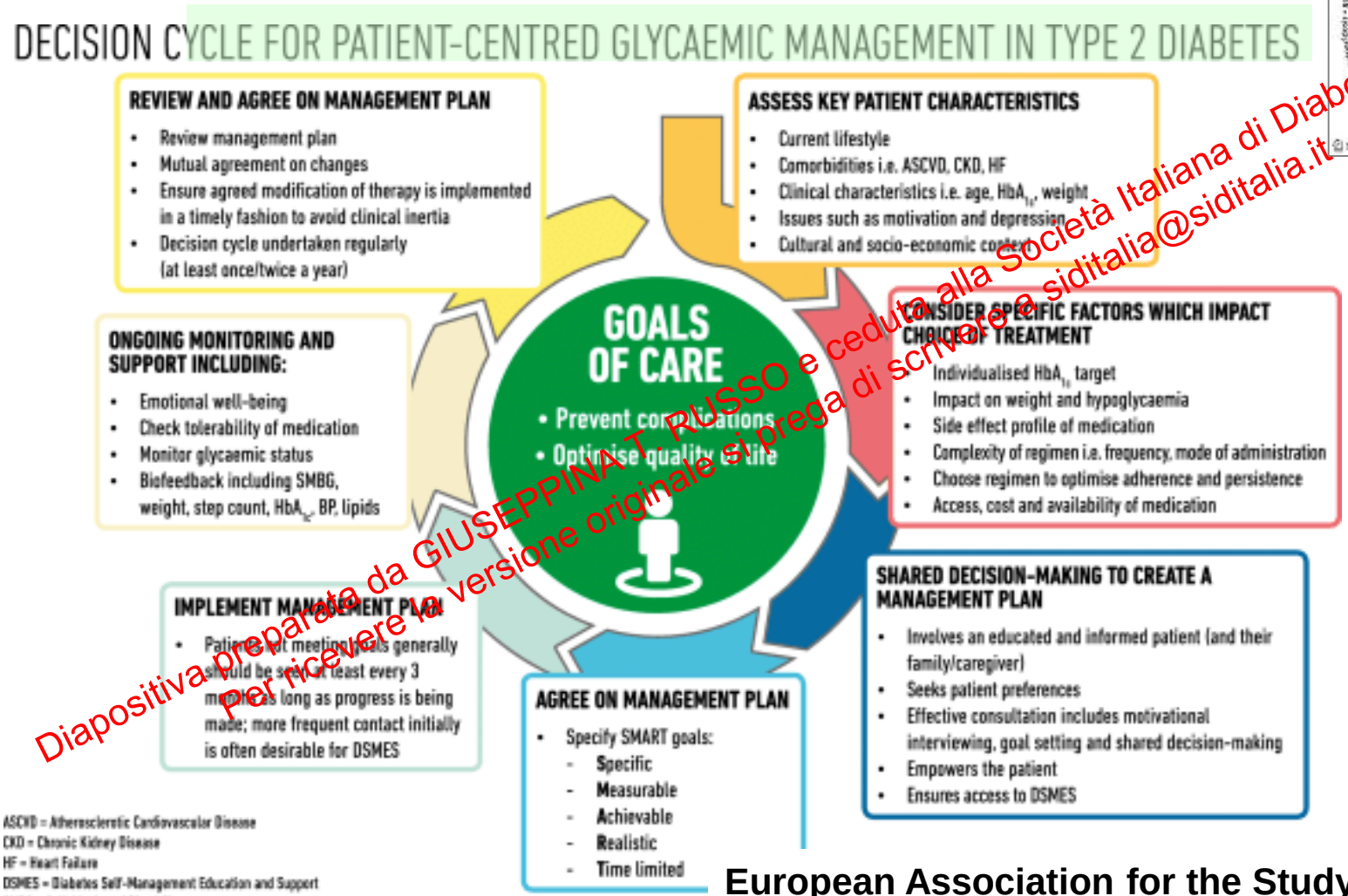
Fisiopatologia



Trattamento

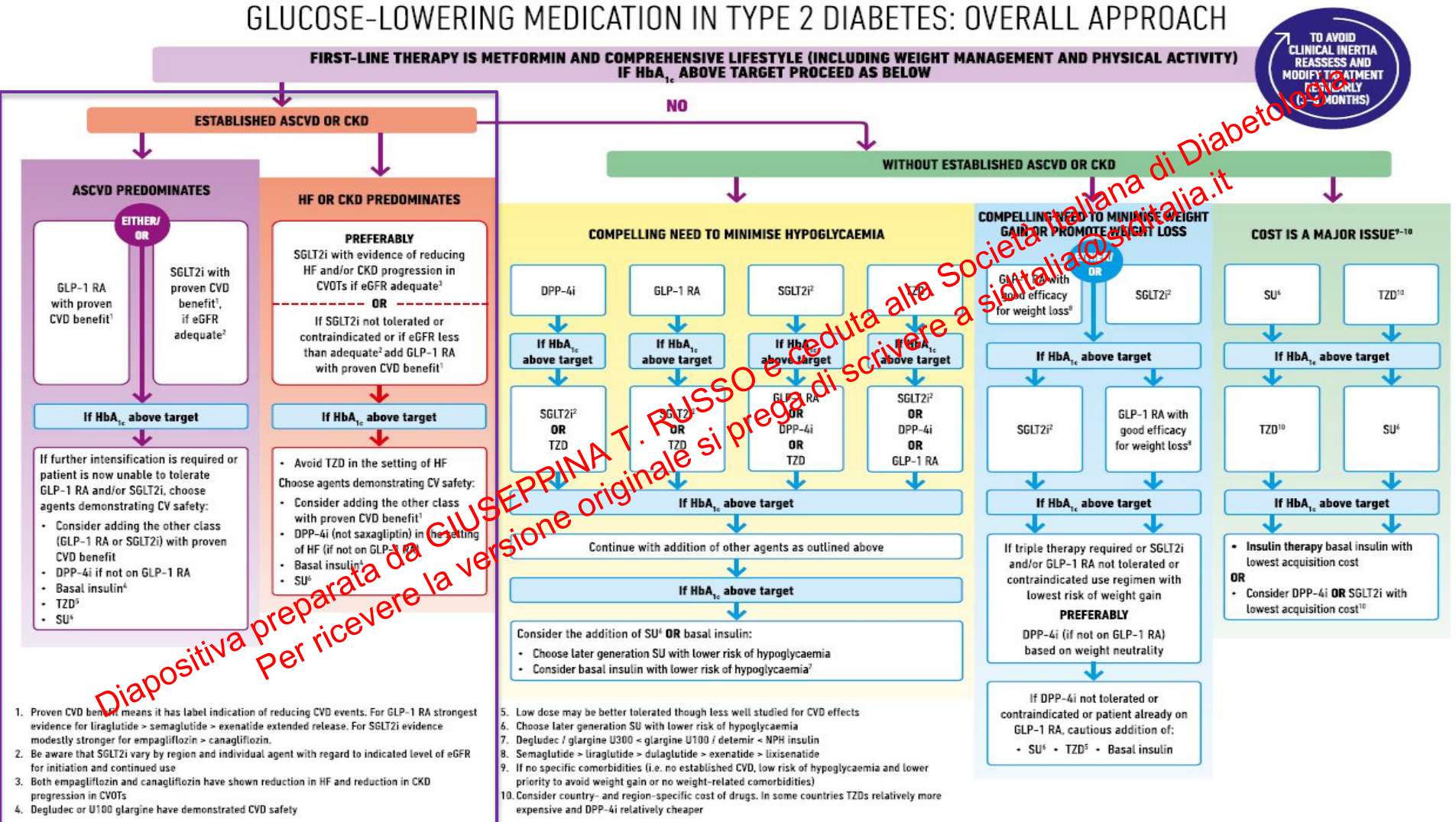
Il diabete: *un nuovo paradigma*





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

Cuore e Rene sono al centro del nuovo paradigma



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

Il diabete è un equivalente di rischio cardiovascolare

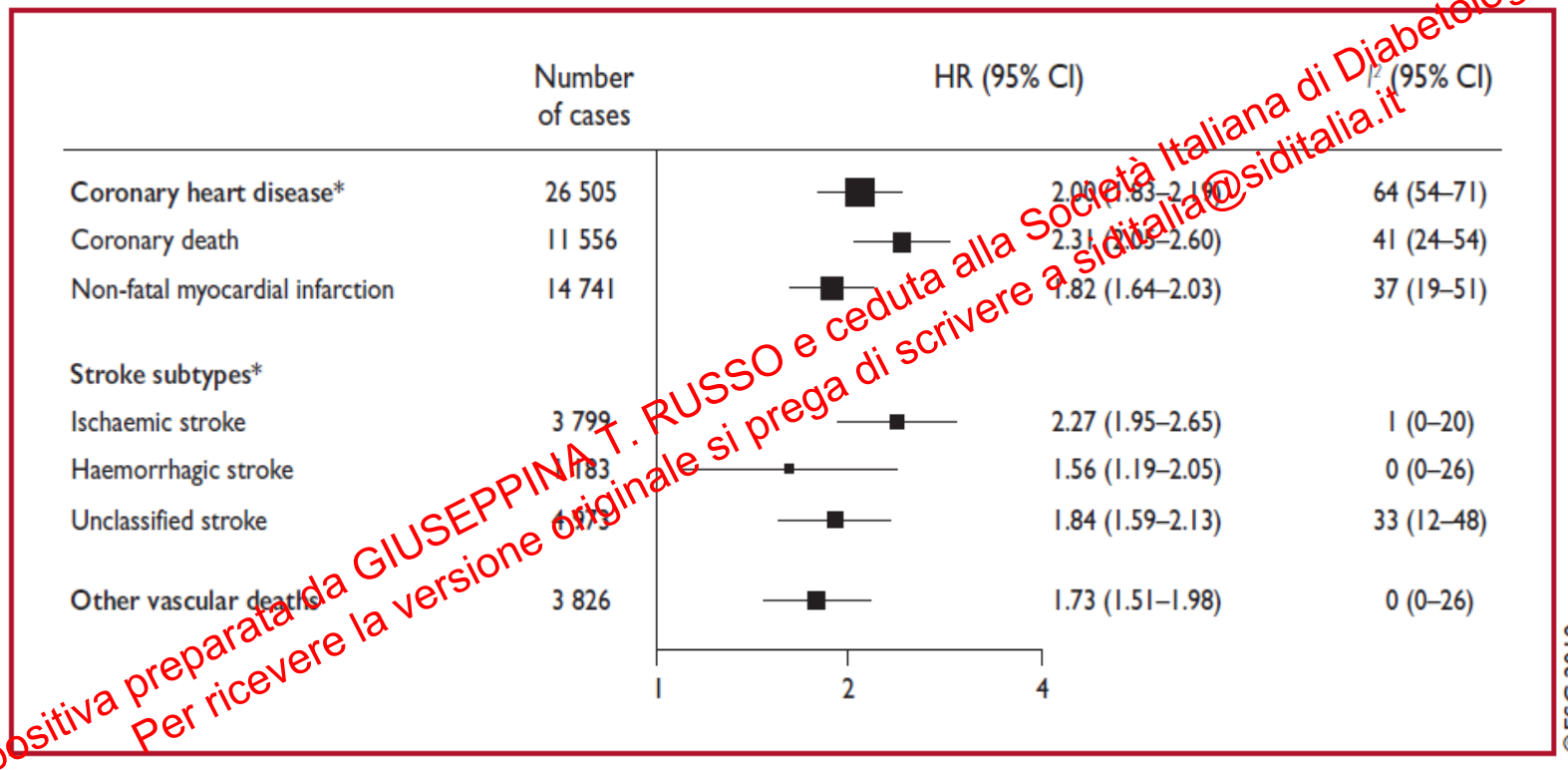


Figure 1 Hazard ratios for vascular outcomes in people with vs. without diabetes mellitus at baseline, based on analyses of 530 083 patients. Reproduced with permission.[23] Hazard ratios were adjusted for age, smoking status, body mass index, and systolic blood pressure, and—where appropriate—stratified by sex and trial arm. The 208 coronary heart disease outcomes that contributed to the grand total could not contribute to the subtotals of coronary death or non-fatal myocardial infarction because there were <11 cases of these coronary disease subtypes in some studies. CI = confidence interval; HR = hazard ratio. [a]Includes fatal and non-fatal events.

Diabetes is a potent CVD risk factor in both men and women

Hindawi Publishing Corporation
International Journal of Endocrinology
Volume 2015, Article ID 832484, 2 pages
http://dx.doi.org/10.1155/2015/832484

Editorial

Type 2 Diabetes and Cardiovascular Risk in Women

Giuseppina T. Russo,[1] Giovannella Baggio,[2] Maria Chiara Rossi,[3] and Alexandra Kautzky-Willer[4]

[1]*Dipartimento di Medicina Clinica e Sperimentale, Policlinico Universitario "G. Martino", Via C. Valeria, 98121 Messina, Italy*
[2]*Chair of the Gender Medicine, University of Padua, Via Giustiniani 2, 35128 Padua, Italy*
[3]*Laboratory of Clinical Epidemiology of Diabetes and Chronic Diseases, Fondazione Mario Negri Sud, Via Nazionale 8/A, 66030 Santa Maria Imbaro, Italy*
[4]*Gender Medicine Unit, Division of Endocrinology and Metabolism, Department of Internal Medicine III, Medical University of Vienna, Währinger Gürtel 18-20, 1090 Vienna, Austria*

Correspondence should be addressed to Giuseppina T. Russo; giuseppina.russo@unime.it

Received 18 January 2015; Accepted 18 January 2015

Cardiovascular diseases (CVD) are the leading cause of death, also in diabetic women. Since 1998, when Haffner et al. [1] stated that subjects with type 2 diabetes mellitus (T2DM) had a CVD risk "equivalent" to previous myocardial infarction, a large number of studies have shown that this relative risk for CVD due to diabetes is greater in women than in men [2].

CVD in diabetic subjects is not entirely related to chronic hyperglycaemia and a number of other factors such as dyslipidemia, hypertension, hormonal, genetic, and environmental factors, as well as low-grade systemic inflammation and endothelial damage, lifestyle behaviours, adherence to therapies, and/or psychosocial factors may contribute to the worst outcomes observed in diabetic women. Notably, it is increasingly recognized that many risk factors show gender differences in their prevalence and association with CVD events, and this aspect must be specifically targeted when aiming at primary and secondary CVD prevention in diabetic subjects.

In this special issue, we looked at CVD in women with diabetes from different perspectives, giving a great contribution to this topic, in terms of mortality, management of risk factors, and therapies.

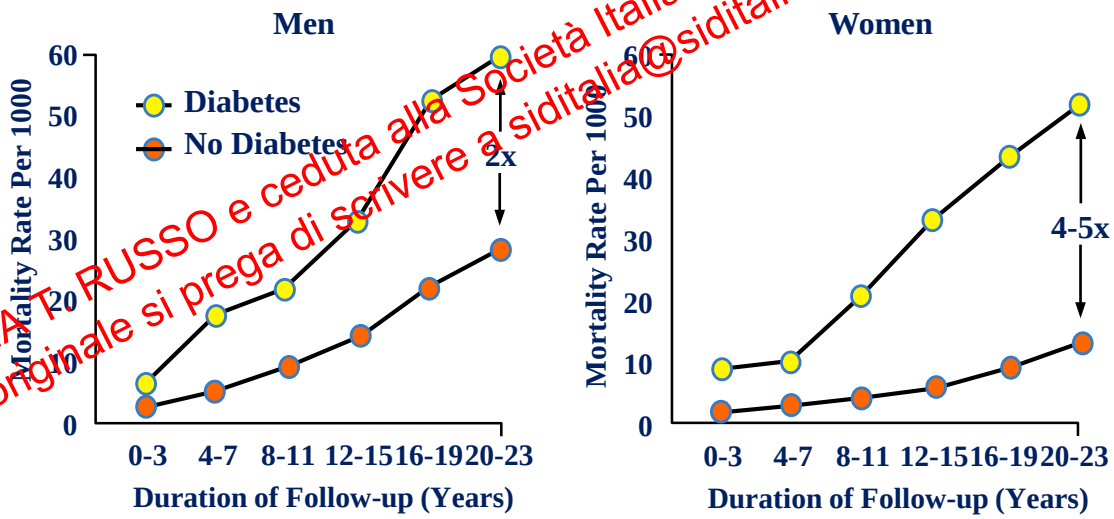
Two papers of this special issue looked at sex differences in CVD mortality associated with diabetes. One conducted on a large population-based sample from Italy demonstrated an excess of mortality in diabetic subjects as compared to nondiabetic ones and a greater impact of diabetes in females than in males for mortality for all causes, for CVD and for myocardial infarction and renal causes. In another study, G. Luo et al. showed in a retrospective analysis that fasting plasma glucose was an independent predictor of in-hospital mortality for nondiabetic coronary patients.

Gender-specific prevalence and management of major and emerging CVD risk factors in different populations were also the main purpose of several papers of this special issue.

The paper by S. Chen et al., with a very interesting experimental protocol, showed the relationships of albuminuria, a well-recognized CVD risk factor, with circulating levels of angiopoietin-1 (Ang-1), Ang-2, and vascular endothelial growth factor (VEGF) in serum and urine.

Potential gender differences in the distribution and control of major CVD risk factors were investigated in another three very large high-risk populations. Thus, in the eControl Study, a study on 286,791 patients with T2DM in Catalonia, Spain, J. Franch-Nadal et al. found that cardiometabolic control was worse in subjects with prior CVD; but control of several risk factors showed gender differences, favouring women with prior CVD only for smoking and BP, whereas LDL-cholesterol (LDL-C) levels were remarkably uncontrolled in women both with and without CVD.

The results of an overall bad control of LDL-C in women were also demonstrated in a very large Italian diabetic outpatient population from the Annals Study Initiative. This study, conducted on 415.294 patients (45.3% women) from



Krolewski AS, et al. Evolving natural history of coronary disease in diabetes mellitus.

***Am J Med* 1991;90(Supp 2A):56S-61S.**

Life Expectancy and Cause-Specific Mortality in Type 2 Diabetes: A Population-Based Cohort Study Quantifying Relationships in Ethnic Subgroups

Alison K. Wright,[1,2] Evangelos Kontopantelis,[3] Richard Emsley,[4] Iain Buchan,[3] Naveed Sattar,[5] Martin K. Rutter,[2,6] and Darren M. Ashcroft[1]

Diabetes Care 2017;40:338–345 | DOI: 10.2337/dc16-1616

Le malattie CVD principale cause di morte nel DM2

OBJECTIVES

This study *1*) investigated life expectancy and cause-specific mortality rates associated with type 2 diabetes and *2*) quantified these relationships in ethnic subgroups.

RESEARCH DESIGN AND METHODS

This was a cohort study using Clinical Practice Research Datalink data from 383 general practices in England with linked hospitalization and mortality records. A total of 187,968 patients with incident type 2 diabetes from 1998 to 2015 were matched to 908,016 control subjects. Abridged life tables estimated years of life lost, and a competing risk survival model quantified cause-specific hazard ratios (HRs).

RESULTS

A total of 40,286 deaths occurred in patients with type 2 diabetes. At age 40, white men with diabetes lost 5 years of life and white women lost 8 years compared with those without diabetes. A loss of between 1 and 2 years was observed for South Asians and blacks with diabetes. At age older than 65 years, South Asians with diabetes had up to 1.1 years' longer life expectancy than South Asians without diabetes. Compared with whites with diabetes, South Asians with diabetes had lower adjusted risks for mortality from cardiovascular (HR 0.82; 95% CI 0.75, 0.89), cancer (HR 0.43; 95% CI 0.36, 0.51), and respiratory diseases (HR 0.60; 95% CI 0.48, 0.76). A similar pattern was observed in blacks with diabetes compared with whites with diabetes.

CONCLUSIONS

Type 2 diabetes was associated with more years of life lost among whites than among South Asians or blacks, with older South Asians experiencing longer life expectancy compared with South Asians without diabetes. The findings support optimized cardiovascular disease risk factor management, especially in whites with type 2 diabetes.

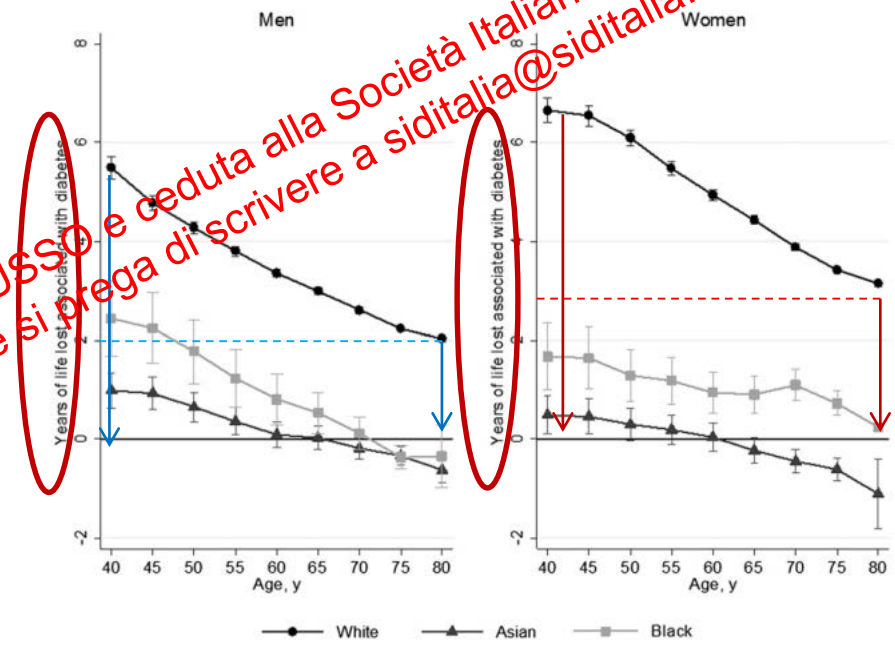


Figure 1—Difference in life expectancy between patients with and without type 2 diabetes at different ages in groups stratified by sex and ethnicity. For example, the line representing white men indicates that at the age of 40 years, white men with type 2 diabetes are predicted to die approximately 6 years earlier than white men without diabetes.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

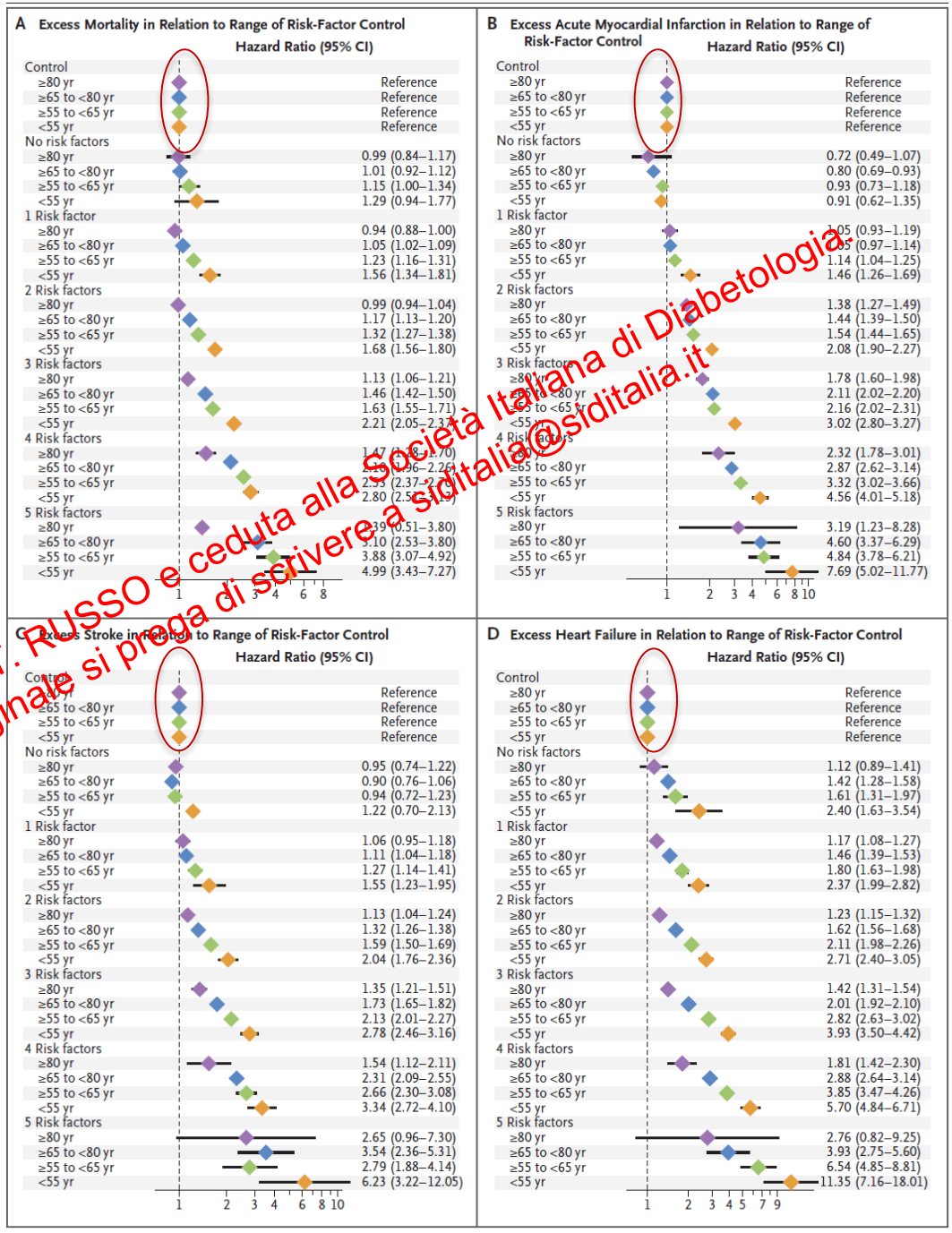
Risk Factors, Mortality, and Cardiovascular Outcomes in Patients with Type 2 Diabetes

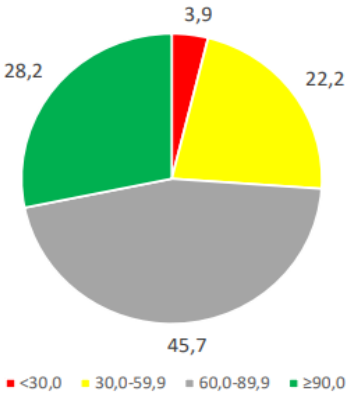
Aidin Rawshani, M.D., Araz Rawshani, M.D., Ph.D., Stefan Franzén, Ph.D.,

Swedish National Diabetes Register

Figure 1 (facing page). Adjusted Hazard Ratios for Outcomes, According to Age Category and Number of Risk-Factor Variables outside Target Ranges, among Patients with Type 2 Diabetes, as Compared with Matched Controls.

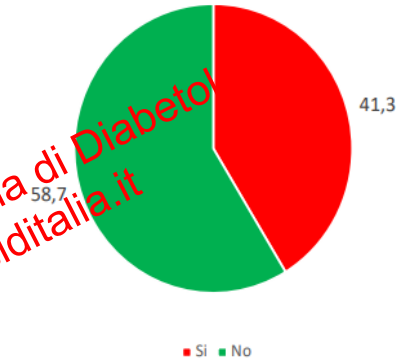
Hazard ratios show the excess risk of each outcome among patients with type 2 diabetes, as compared with matched controls from the general population, according to age categories and to the number of risk-factor variables (scale, none to five) that were outside target ranges currently recommended in guidelines. The analysis included patients with type 2 diabetes and controls matched for age, sex, and county in Sweden. We constructed a Cox hazards model for each age category, and these models were adjusted for the covariable "category"; this covariable denotes the number of risk-factor variables that were within target ranges. These Cox model analyses were performed on five imputed data sets for each age category, and hazard ratios were pooled from all the data sets with the use of Rubin's rule.





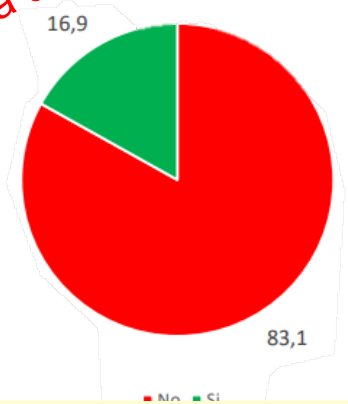
Andamento per 4 classi del filtrato glomerulare (%)

Soggetti con HbA1c ≤7%

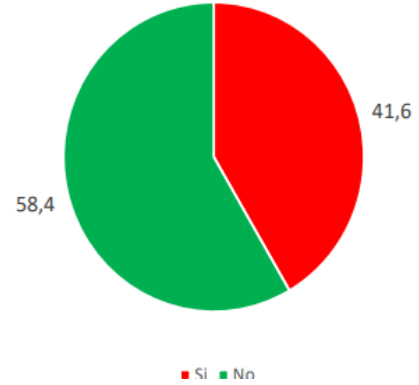


Soggetti con BMI ≥30 kg/m² (%)

Soggetti con microalbuminuria (%)



Soggetti con HbA1c ≤7%, con colesterolo LDL <100 mg/dl e pressione arteriosa <140/90 mmHg



Soggetti con colesterolo LDL <100 mg/dl

Nuova definizione del rischio CVD nel diabete

ESC European Society of Cardiology
European Heart Journal (2019) 00, 1–69
doi:10.1093/eurheartj/ehz486
ESC GUIDELINES

2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD

The Task Force for diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD)

Table 7 Cardiovascular risk categories in patients with diabetes[a]

Very high risk	Patients with DM **and** established CVD **or** other target organ damage **or** three or more major risk factors[c] **or** early onset T1DM of long duration (>20 years)
High risk	Patients with DM duration ≥10 years without target organ damage plus any other additional risk factor
Moderate risk	Young patients (T1DM aged <35 years or T2DM aged <50 years) with DM duration <10 years, without other risk factors

© ESC 2019

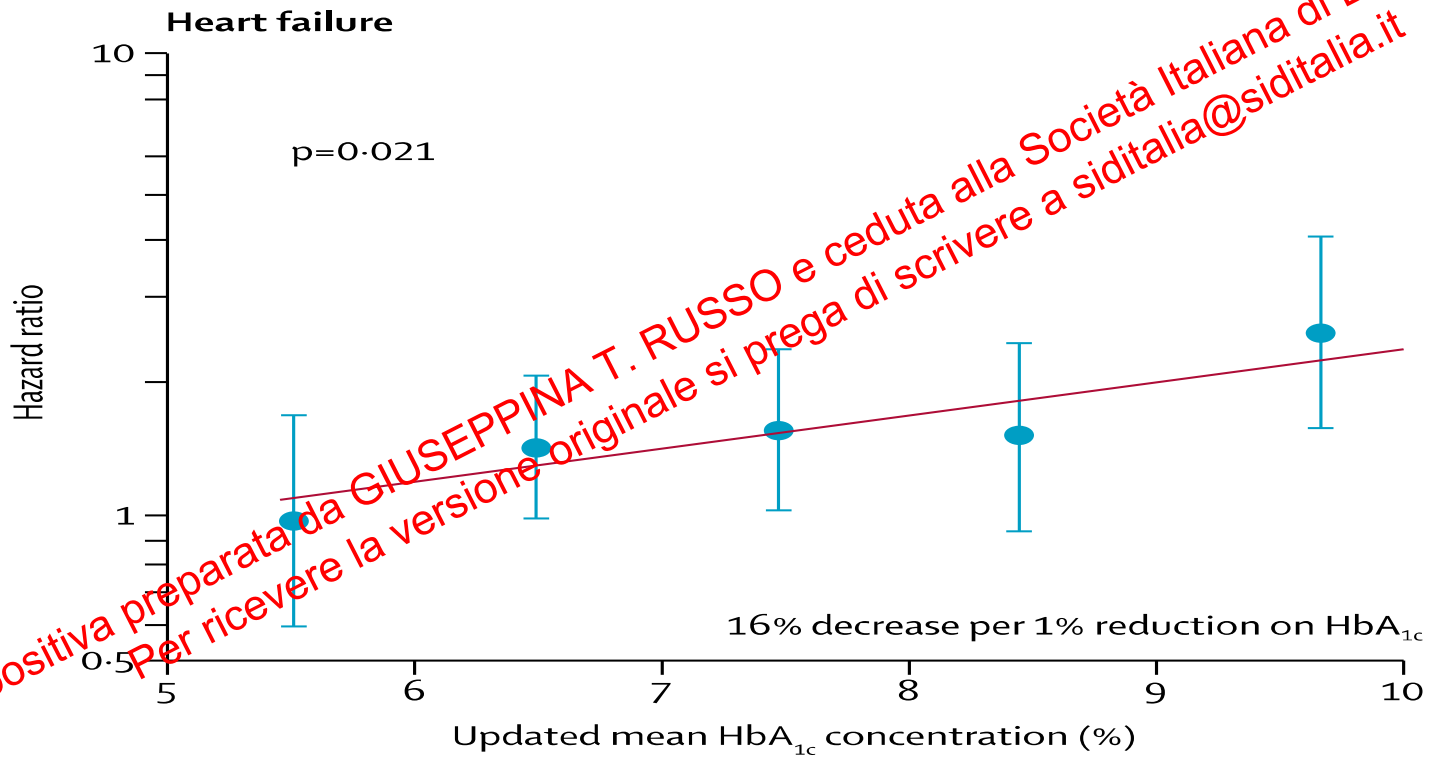
CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

[a]Modified from the 2016 European Guidelines on cardiovascular disease prevention in clinical practice.[27]

[b]Proteinuria, renal impairment defined as eGFR ≥30 mL/min/1.73 m^2, left ventricular hypertrophy, or retinopathy.

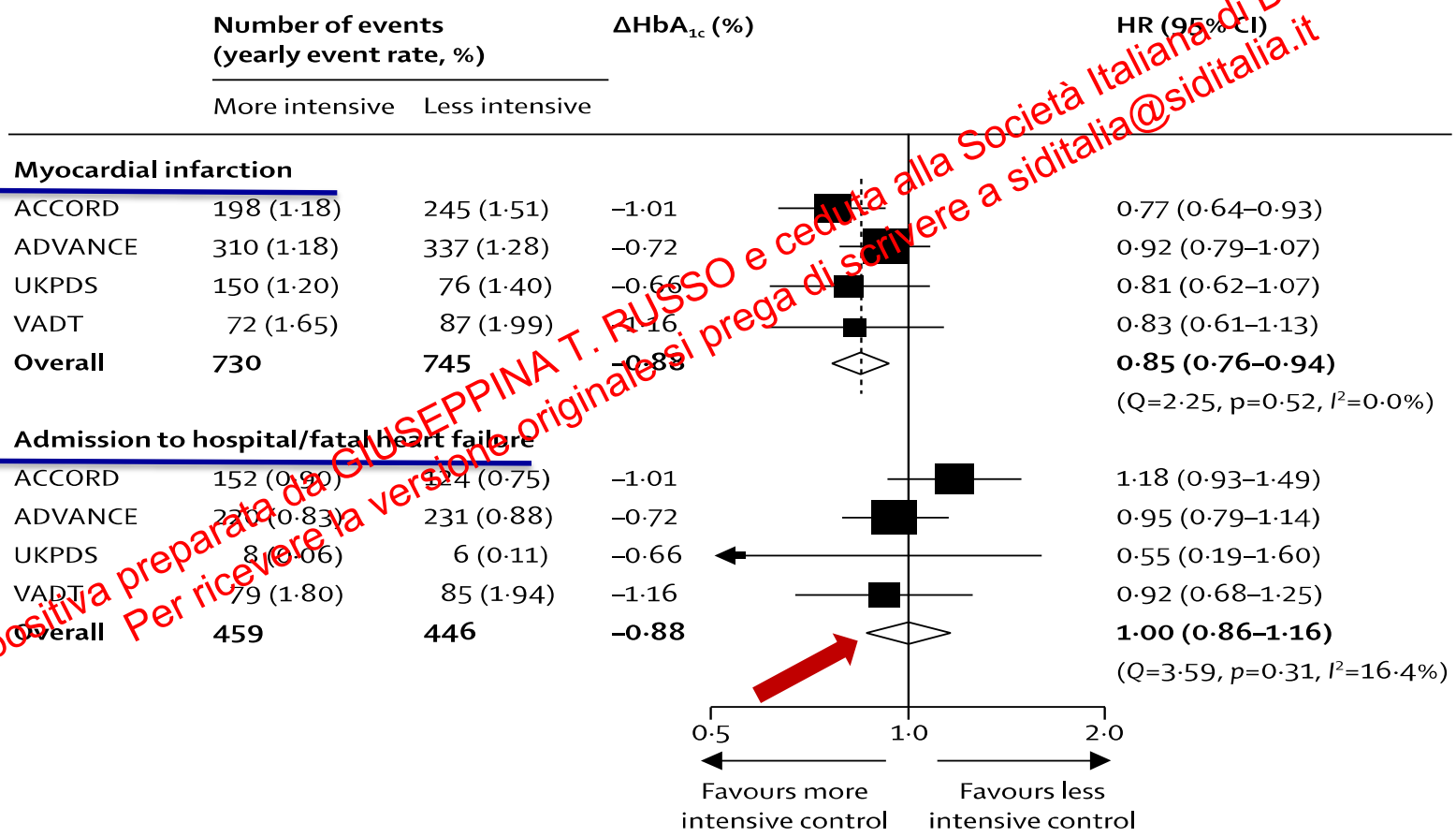
[c]Age, hypertension, dyslipidemia, smoking, obesity.

Hazard ratios (HRs), with 95% CIs as floating absolute risks, as an estimate of association between category of updated mean haemoglobin A1c (HbA1c) concentration and *heart failure*



Stratton IM et al. BMJ 2000; 321: 405–12.

Effects in trials of more versus less intensive glycaemic control on myocardial infarction (fatal or non-fatal) and heart failure resulting in admission to hospital or death



Turnbull FM et al. Diabetologia 2009; 52: 2288–98

Prime 10 diagnosi in caso di ricovero ordinario

Osservatorio ARNO Diabete CINECA-SID – Report 2015, dati 2014

Diagnosi principale nella SDO	Tassi per 1000 diabetici	Tassi per 1000 non diabetici	Differenza rispetto ai non diabetici (%)
Scompenso cardiaco	17.0	5.9	288
Insufficienza respiratoria	12.1	5.5	220
Infarto del miocardio	7.1	3.1	229
Artrosi	5.2	4.6	130
Altre forme di cardiopatia ischemica	5.1	2.1	242
Fratture del collo del femore	5.0	3.1	161
Occlusione arterie cerebrali	4.8	2.4	200
Aritmie cardiache	4.4	3.0	146
Aterosclerosi	4.4	1.1	400
Colelitiasi	4.1	3.1	132

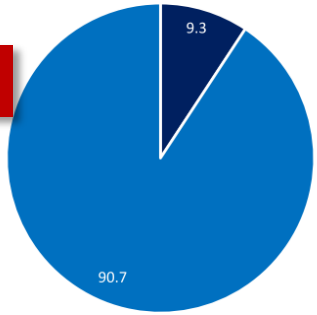
Circa 4 diabetici su 100 in un anno si ricoverano per CVD

INDICATORI DI ESITO FINALE

Annali AMD – Full Data Circle

Soggetti con storia di infarto del miocardio (%)

IMA: 9.3%



L'elevata qualità dei dati del Full Data Circle è confermata anche da questo indicatore, in cui risulta una prevalenza di storia d'infarto del miocardio pari al 9.3%. Questo dato è in linea con i dati epidemiologici disponibili e si traduce, in termini assoluti, in 4440 pazienti con infarto pregresso assistiti nell'anno 2015.

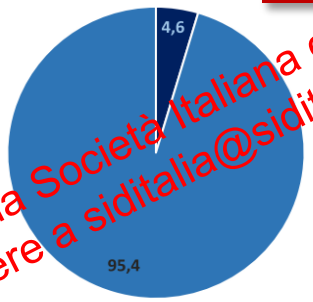
Soggetti con storia di rivascolarizzazione coronarica (%)

Rivascolarizzazione coronarica: 7.7%

In aggiunta al dato sulla storia d'infarto del miocardio, questo indicatore suggerisce che un 7.7% dei pazienti ha subito un intervento pregresso di rivascolarizzazione coronarica, per un totale di 3682 soggetti.

Soggetti con storia di ictus (%)

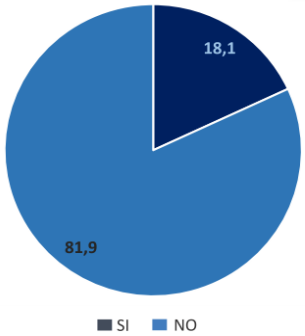
ICTUS: 4.6%



Anche questo dato è in linea con l'atteso in base ai dati epidemiologici, con una prevalenza di storia di ictus tra i pazienti con DM2 pari al 4.6% (2217 soggetti).

Soggetti con storia di malattia cardiovascolare (%)

CVD: 18.1%



Complessivamente, i soggetti con storia di infarto/ictus/rivascolarizzazione coronarica o periferica / by pass coronarico o periferico) costituivano il 18.1% dei casi visti nel 2015.

Malattia cardiovascolare nel diabete in Italia

RIACE Study-SID, Pugliese et al – Cardiovasc Diabetol 2014; 13: 59

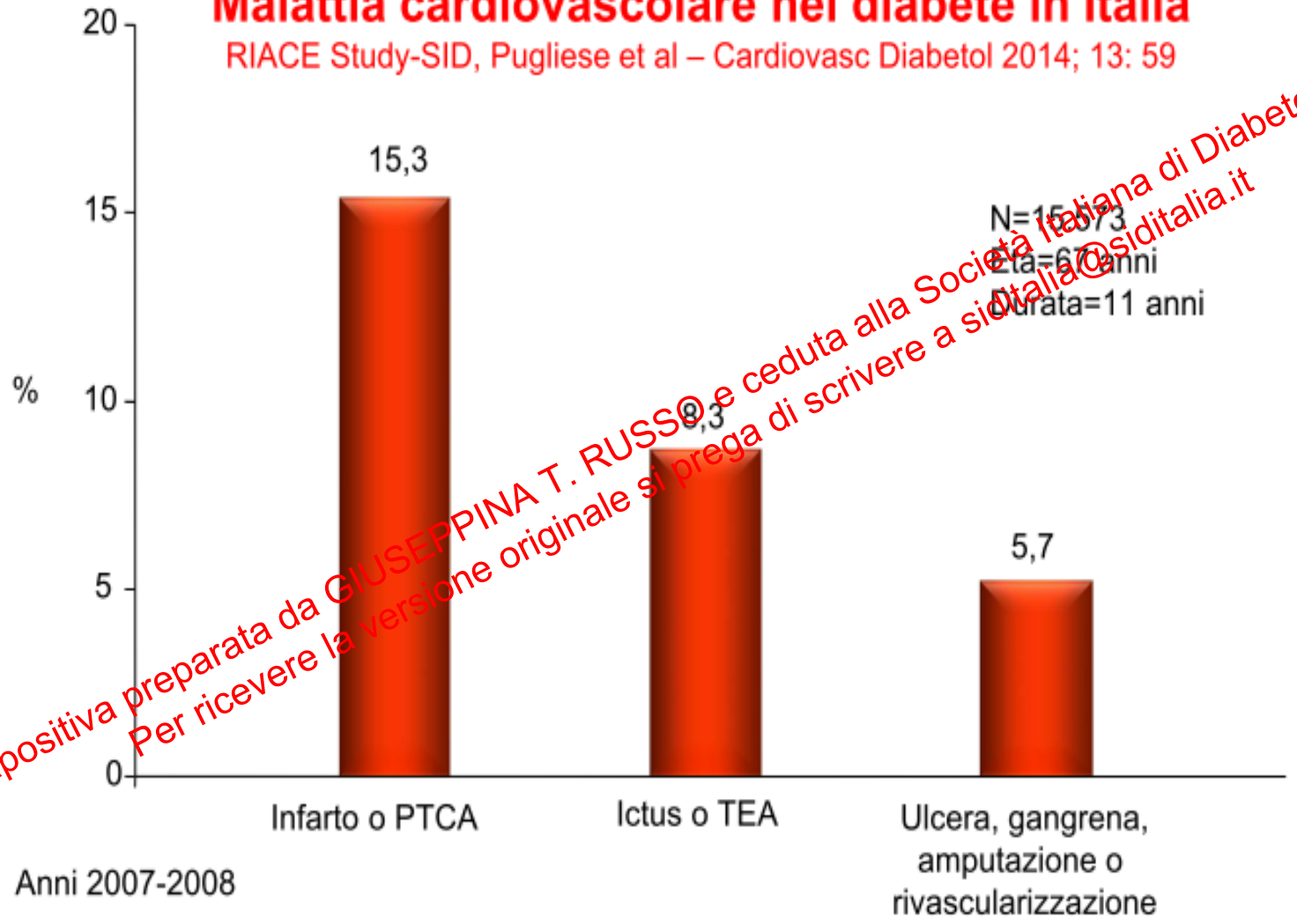
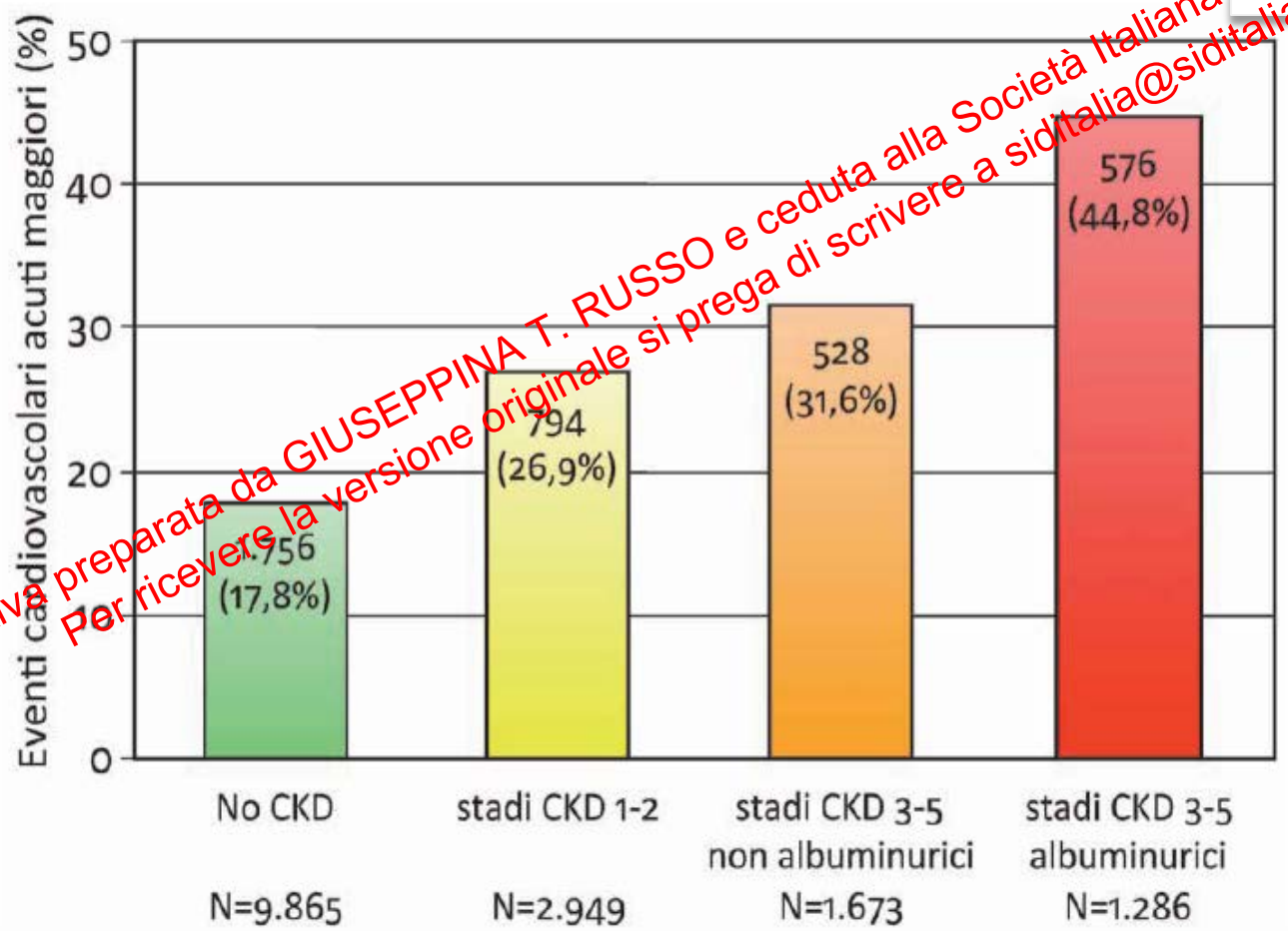


Figura 2 ◆ Prevalenza di eventi cardiovascolari acuti maggiori in base al fenotipo di CKD nella coorte di pazie
diabete di tipo 2 dello studio RIACE [modificato da 5].



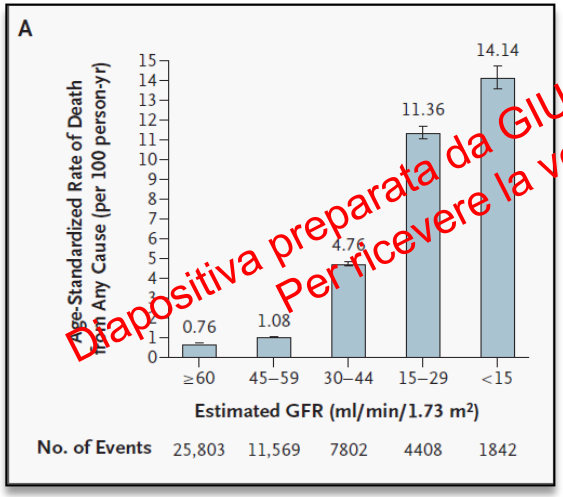
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

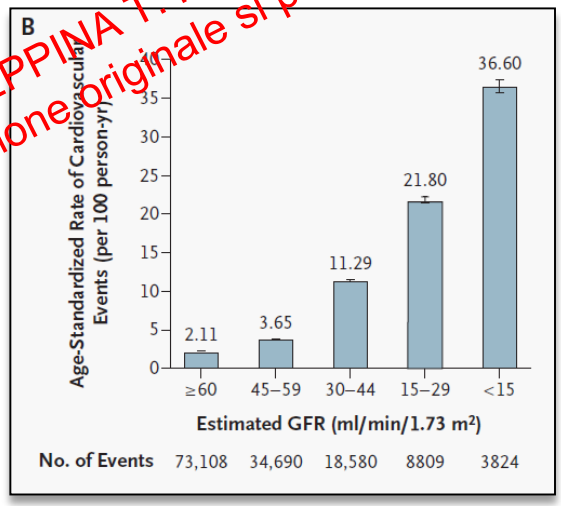
Chronic Kidney Disease and the Risks of Death, Cardiovascular Events, and Hospitalization

Alan S. Go, M.D., Glenn M. Chertow, M.D., M.P.H., Dongjie Fan, M.S., M.H., Charles E. McCulloch, Ph.D., and Chi-yuan Hsu, M.D.

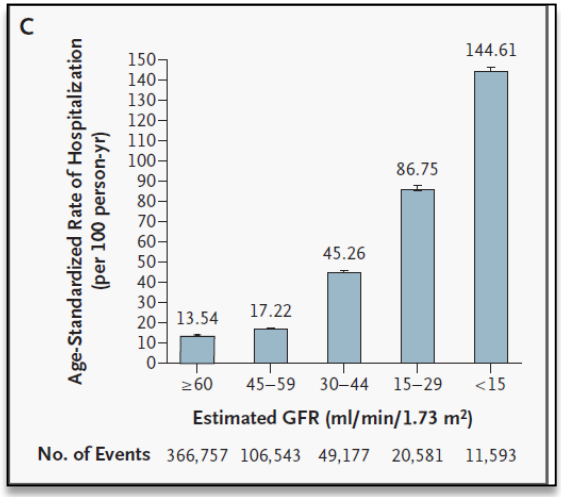
CKD nella popolazione generale è associata ad un elevato rischio CVD



Morte



Eventi CVD



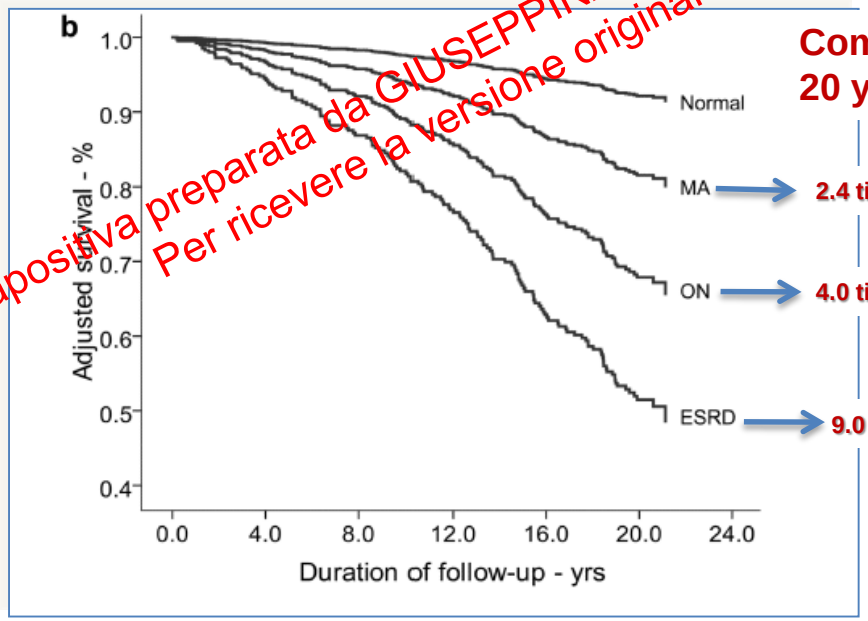
Ospedalizzazioni

Published in final edited form as:
Diabetologia. 2010 November ; 53(11): 2312–2319. doi:10.1007/s00125-010-1860-3.

Nel DM1 la DKD è associata ad un elevata mortalità

In the absence of renal disease 20-year mortality risk in type 1 diabetes is comparable to that of the general population: a report from the Pittsburgh Epidemiology of Diabetes Complications Study

T. J. Orchard[1], A. M. Secrest[1], R. G. Miller[1], and T. Costacou[1]
[1] Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania



Compared to normal subjects 20 years Mortality risk was higher

- MA → **2.4 times (95%CI 1.4-4-3)**
- ON → **4.0 times (95%CI 2.3-7.0)**
- ESRD → **9.0 times (95%CI 4.3-18.7)**

Altri predittori di mortalità nel DM1 erano sesso maschile, durata diabete, WHR, HbA1c, SBP, smoking, GFR<60, macrovascular disease.

CLINICAL EPIDEMIOLOGY www.jasn.org

Kidney Disease and Increased Mortality Risk in Type 2 Diabetes

Maryam Afkarian,* Michael C. Sachs,* Bryan Kestenbaum,* Irl B. Hirsch,† Katherine R. Tuttle,‡§ Jonathan Himmelfarb,* and Ian H. de Boer*

Nel DM2 la DKD è associata ad un elevata mortalità

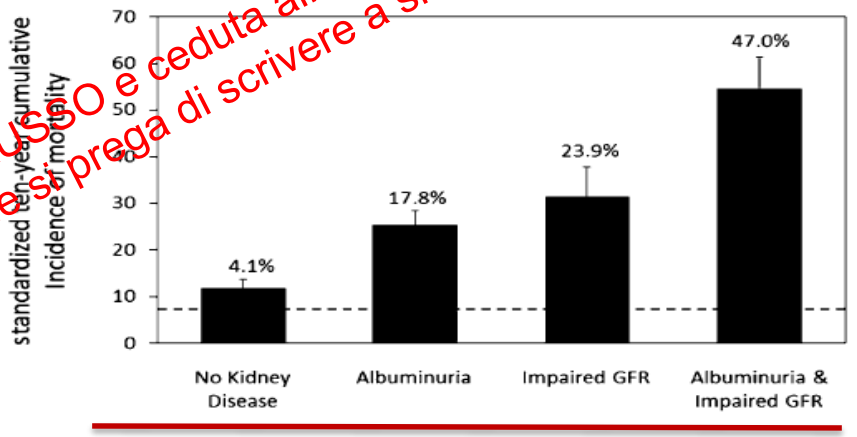
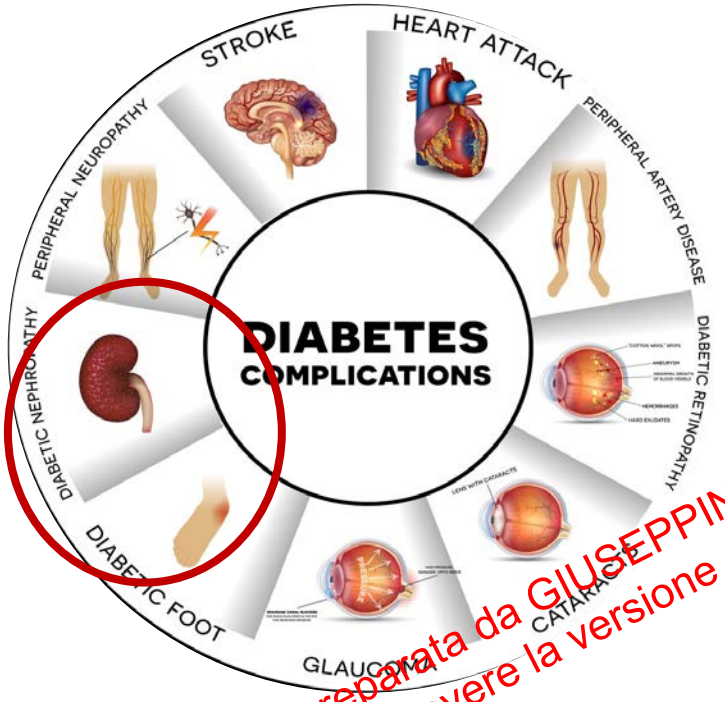


Figure 2. Ten-year mortality in type 2 diabetes by kidney disease manifestation. Absolute differences in mortality risk were estimated using linear regression and were adjusted for age, sex, and race. Standardized 10-year all-cause cumulative incidences were estimated for the mean levels of the covariates in the study population. The dashed line indicates mortality in persons without diabetes or kidney disease (the reference group). The numbers above bars indicate excess mortality above the reference group. Error bars indicate 95% CIs.

www.jasn.org 2013

✓ **Diabetes is expected to double within the next 20 years, with a significant increase in cardiovascular disease and in all the diabetes-related complications that are a major cause of disability, reduced quality of life and premature death**



Diabetic kidney disease (DKD) prevalence:
30% DM1
40% DM2

Health Related Quality of Life

Complication	Mean
Mild stroke	0.70
Diabetic neuropathy	0.66
Angina	0.64
DIABETIC NEPHROPATHY	0.64
Amputation	0.55
Diabetic retinopathy	0.53
Blindness	0.38
End-stage renal disease	0.35
Major stroke	0.31

0 = death, 1 = life in perfect health

Huang S et al. Diabetes Care 2007

***La nefropatia diabetica** è tra le più gravi complicanze del diabete per il rischio di progressione verso l'uremia terminale e l'elevata mortalità.*

Original Contribution

FREE

July 25, 2001

Albuminuria and Risk of Cardiovascular Events, Death, and Heart Failure in Diabetic and Nondiabetic Individuals

Hertzel C. Gerstein, MD, MSc; Johannes F. E. Mann, MD; Qilong Yi, PhD; et al

» Author Affiliations

JAMA. 2001;286(4):421-426. doi:10.1001/jama.286.4.421

Table 2. Incidence and Risk of Cardiovascular Events in HOPE Study Participants With and Without Baseline Microalbuminuria by Randomized Group*

Variables	Placebo % With MA	Placebo % Without MA	Placebo Crude Risk (95% CI)	Placebo P Value	Placebo Adjusted Risk (95% CI)†	Placebo P Value	Ramipril % With MA	Ramipril % Without MA	Ramipril Crude Risk (95% CI)	Ramipril P Value	Ramipril Adjusted Risk (95% CI)†	Ramipril P Value
All participants												
MI, stroke, or CV death	26.4	15.2	1.73 (1.52-1.98)	<.01	1.75 (1.49-2.05)	<.001	19.6	12.4	1.58 (1.35-1.85)	<.01	1.42 (1.18-1.71)	<.001
All-cause mortality	20.3	9.8	2.07 (1.77-2.42)	<.01	1.92 (1.59-2.31)	<.001	15.7	8.9	1.77 (1.48-2.12)	<.01	1.52 (1.23-1.88)	<.001
CHF hospitalization	6.9	2.5	2.77 (2.06-3.73)	<.01	2.42 (1.70-3.45)	<.001	6.9	2.0	3.47 (2.54-4.73)	<.01	2.59 (1.78-3.77)	<.001
Diabetes history												
MI, stroke, or CV death	28.1	15.3	1.87 (1.55-2.25)	<.01	1.84 (1.46-2.31)	<.001	21.1	12.6	1.68 (1.35-2.10)	<.01	1.44 (1.11-1.86)	.006
All-cause mortality	20.8	10.6	1.96 (1.56-2.46)	<.01	1.85 (1.41-2.43)	<.001	16.3	7.9	2.05 (1.57-2.68)	<.01	1.64 (1.21-2.22)	.002
CHF hospitalization	8.2	2.5	3.24 (2.11-4.96)	<.01	4.51 (2.55-7.96)	<.001	8.9	2.6	3.46 (2.29-5.23)	<.01	2.91 (1.79-4.73)	<.001
No diabetes history												
MI, stroke, or CV death	23.3	15.2	1.53 (1.25-1.88)	<.01	1.60 (1.27-2.02)	<.001	17.4	12.3	1.41 (1.11-1.80)	.005	1.31 (0.99-1.73)	.06
All-cause mortality	19.7	9.5	2.09 (1.65-2.63)	<.01	1.86 (1.42-2.43)	<.001	14.9	9.4	1.60 (1.22-2.09)	<.01	1.36 (1.01-1.85)	.04
CHF hospitalization	5.0	2.5	2.04 (1.26-3.30)	.004	1.41 (0.81-2.45)	.2	4.2	1.7	2.49 (1.45-4.28)	<.01	1.94 (1.03-3.64)	.04

Kidney International, Vol. 63 (2003), pp. 225–232

Development and progression of nephropathy in type 2 diabetes: The United Kingdom Prospective Diabetes Study (UKPDS 64)

AMANDA I. ADLER, RICHARD J. STEVENS, SUE E. MANLEY, RUDY W. BILOUS, CAROLE A. CULL, and RURY R. HOLMAN, on behalf of the UKPDS GROUP

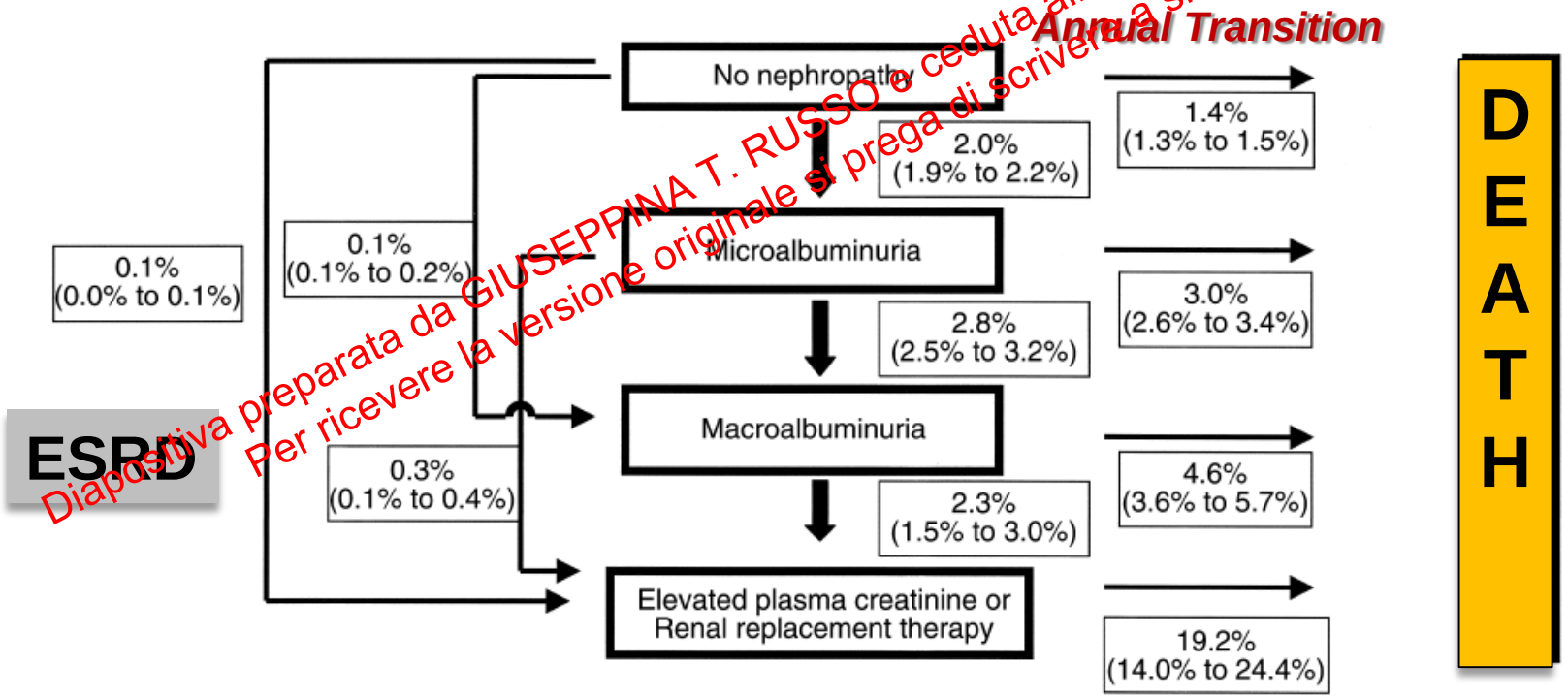


Fig. 1. Annual transition rates with 95% confidence intervals through the stages of nephropathy and to death from any cause.

Kidney Int, 2003

Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis

Caroline S Fox, Kunihiro Matsushita, Mark Woodward, Henk J G Bilo, John Chalmers, Hiddo J Lambers Heerspink, Brian J Lee, Robert M Perkins, Peter Rossing, Toshimi Sairenchi, Marcello Tonelli, Joseph A Vassalotti, Kazumasa Yamagishi, Josef Coresh, Paul E de Jong, Chi-Pang Wen, Robert G Nelson, for the Chronic Kidney Disease Prognosis Consortium

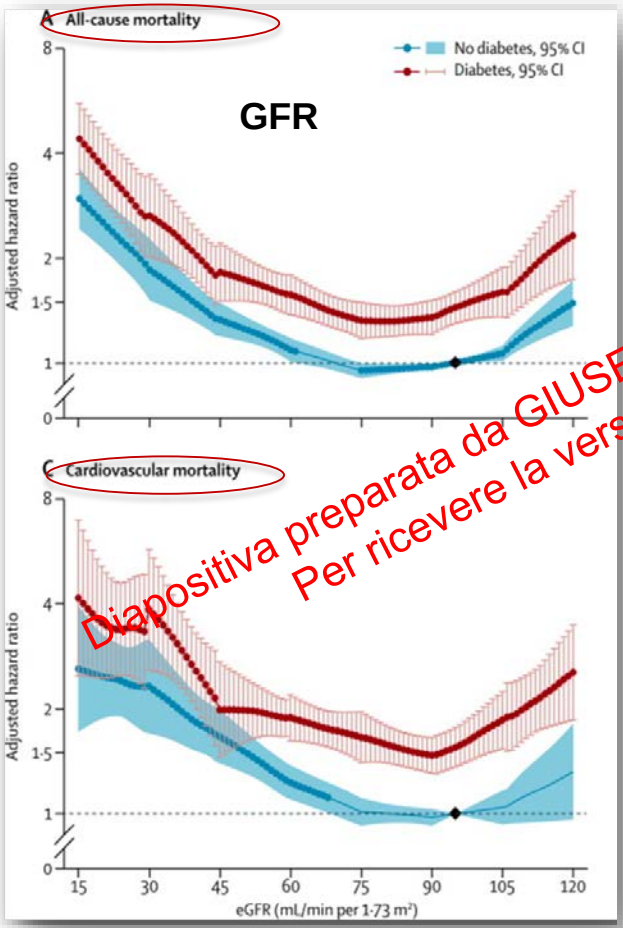
Lancet 2012; 380: 1662–73
Published Online September 24, 2012

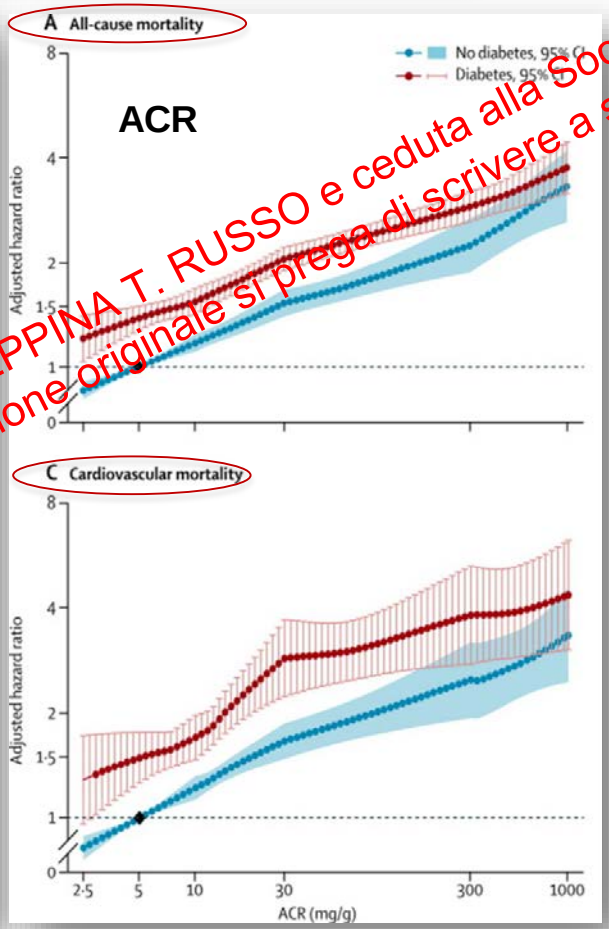
Summary

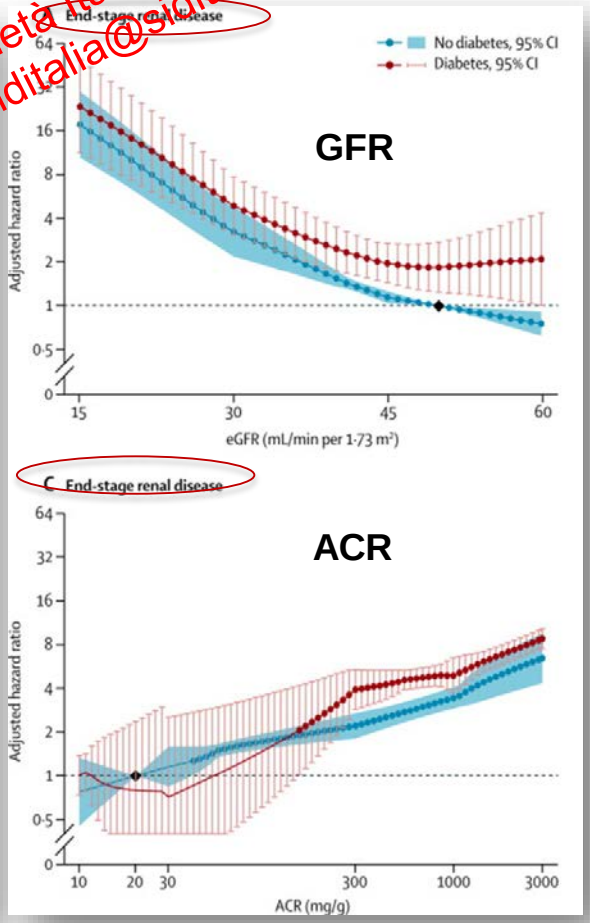
Background Chronic kidney disease is characterised by low estimated glomerular filtration rate (eGFR) and high albuminuria, and is associated with adverse outcomes. Whether these risks are modified by diabetes is unknown.

- Data for *1,024,977 participants (128,505 with diabetes)* from 30 general population and high-risk cardiovascular cohorts and 13 chronic kidney disease cohorts.

- In the general and high-risk cohorts, *mortality risks were 1,2 - 1,9 times higher for* participants with *diabetes* than for those without diabetes across the ranges of eGFR and albumin-to-creatinine ratio (ACR).







La DKD ha due componenti: MAU e low EGFR,

- **Sono espressione della stessa "malattia"?**

Albuminuria e creatinina sono entrambe necessarie per la diagnosi di DKD

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012

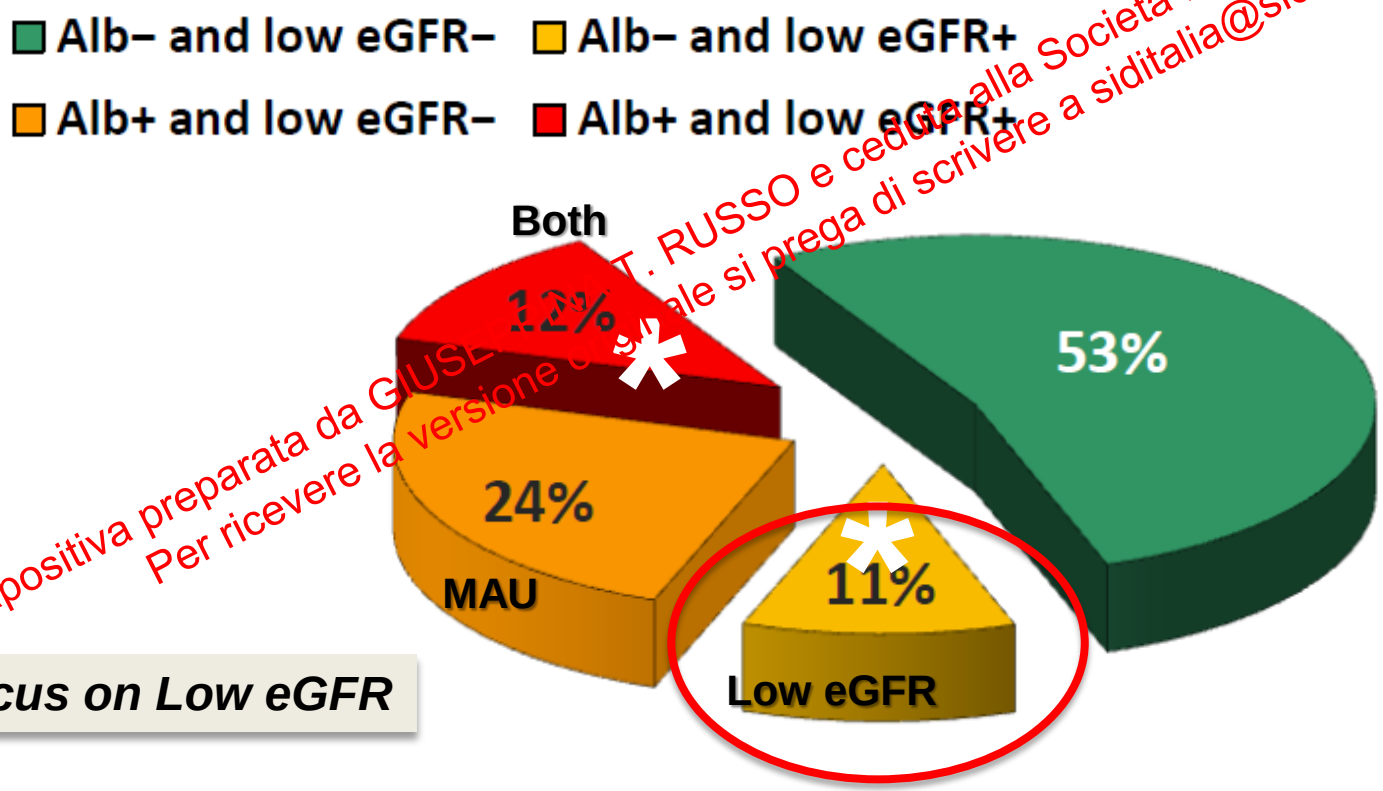
GFR categories (ml/min/ 1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90			
	G2	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			

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.

Figure 1 | Staging of CKD.[15] Green: low risk (if no other markers of kidney disease, no CKD); yellow: moderately increased risk; orange: high risk; red: very high risk. Reprinted with permission from Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl.* 2013;3:1–150. Copyright © 2013 KDIGO. CKD, chronic kidney disease; GFR, glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes.

Kidney dysfunction and related cardiovascular risk factors among patients with type 2 diabetes

Large cohort of patients (120.903) with type 2 diabetes mellitus attending 236 Italian Diabetes Clinics in 2009



Focus on Low eGFR

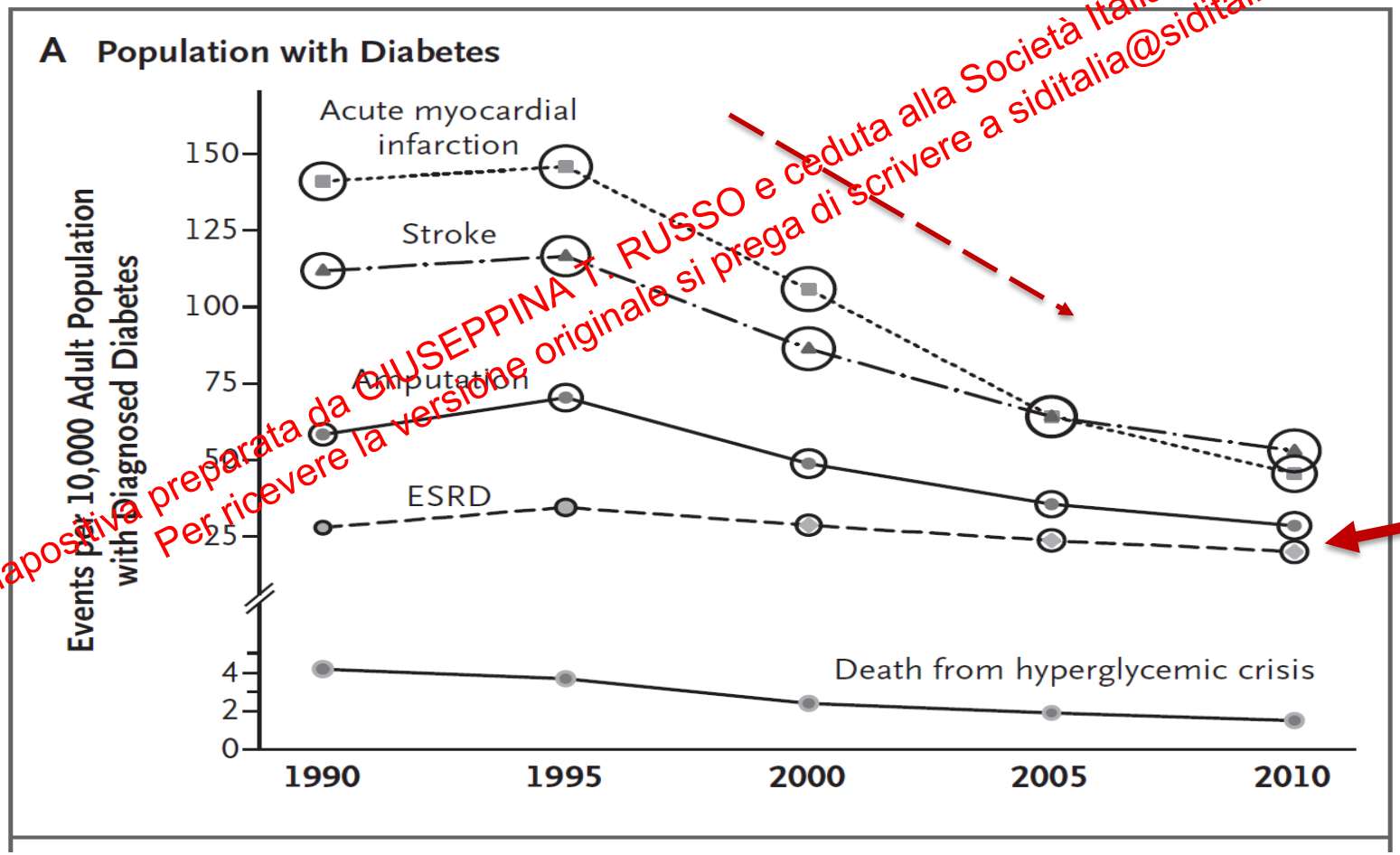
S. De Cosmo, Russo GT et al. for AMD-Annals Study Group, *NDT* 2014

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

Edward W. Gregg, Ph.D., Yanfeng Li, M.D., Jing Wang, M.D.,
Nilka Rios Burrows, M.P.H., Mohammed K. Ali, M.B., Ch.B., Deborah Rolka, M.S.,
Desmond E. Williams, M.D., Ph.D., and Linda Geiss, M.A.



Epidemiologia DKD nell'ultimo ventennio

RAAS inibitori

Invecchiamento

Low eGFR↑ + MAU ↓ = ↔ DKD

Ridotta mortalità totale e CVD

Box 1. *During the last decades, prevalence of DKD has not decreased and incidence of ESKD has decreased only slightly, with major changes in the two main DKD manifestations, i.e., albuminuria, the prevalence of which has decreased (with macroalbuminuria remaining stable), and reduced eGFR, the prevalence of which has increased (especially for eGFR <30 ml/min/1.73 m²).*

Please cite this article as: Pugliese G et al., Diabetic kidney disease: New clinical and therapeutic issues. Joint position statement of the Italian Diabetes Society and the Italian Society of Nephrology on "The natural history of diabetic kidney disease and treatment of hyperglycemia in patients with..., Nutrition, Metabolism & Cardiovascular Diseases, https://doi.org/10.1016/j.numecd.2019.07.017

Progressive Decline in Estimated Glomerular Filtration Rate in Patients With Diabetes After Moderate Loss in Kidney Function—Even Without Albuminuria

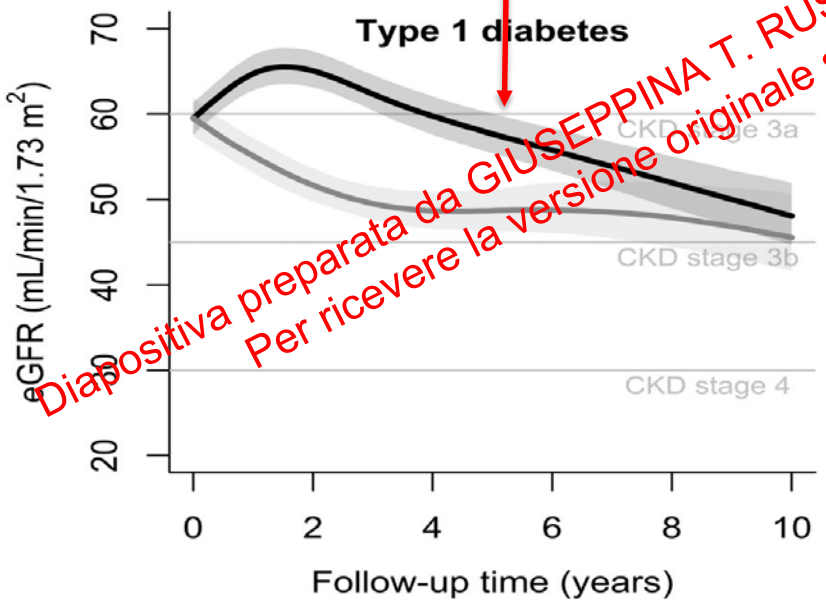
Dorte Vistisen,[1] Gregers Stig Andersen,[1] Adam Hulman,[2,3,4] Frederik Persson,[1] Peter Rossing,[1,5] and Marit Eika Jørgensen[1,6]

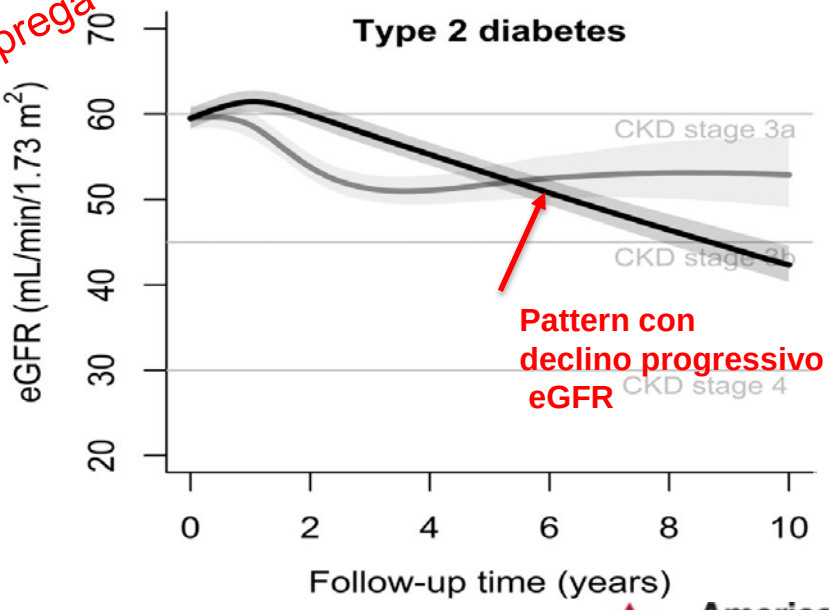
Diabetes Care 2019;42:1886–1894 | https://doi.org/10.2337/dc19-0349

Estimated eGFR trajectories for the subset of persons with normoalbuminuria who were also without albuminuria at baseline for those with a first recorded low eGFR just below 60 mL/min/1.73 m2. (CKD3)

STUDY DESIGN AND PARTICIPANTS
The study is based on 3,543 adults with type 1 diabetes or type 2 diabetes treated at **Steno Diabetes Center Copenhagen followed up to 16 years of follow-up**

Pattern con declino progressivo eGFR





Pattern con declino progressivo eGFR

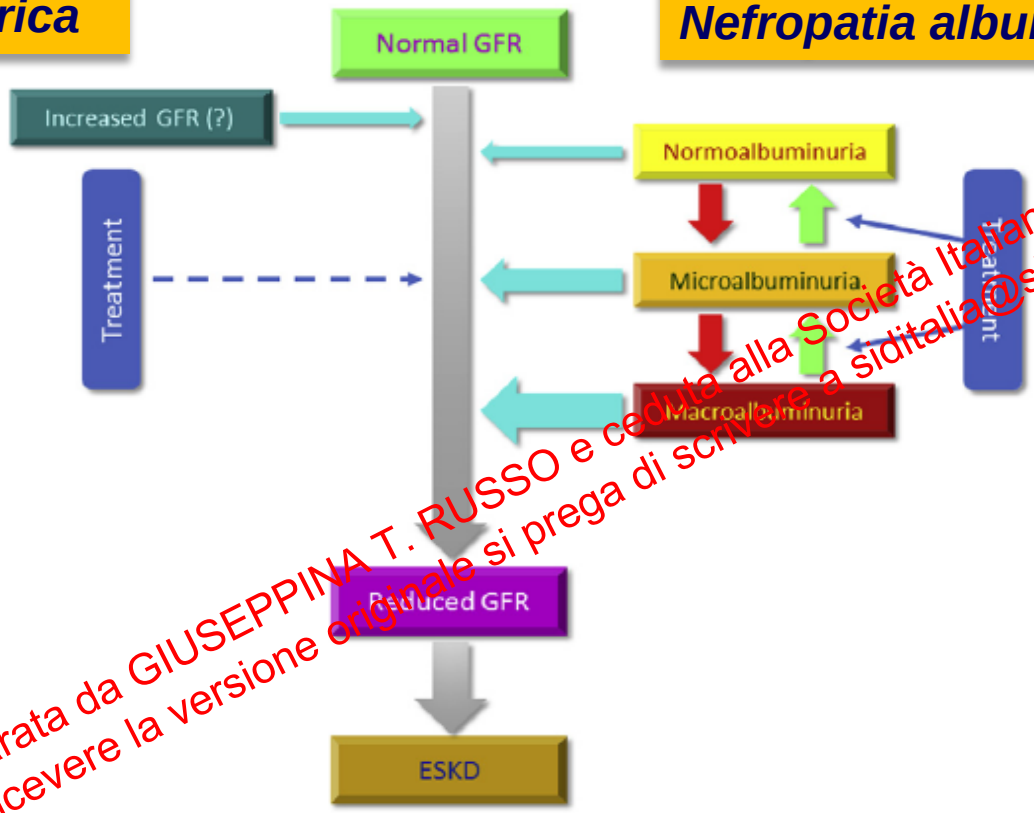
Dorte Vistisen et al. Dia Care 2019;42:1886-1894

American Diabetes Association.

Nuova definizione della malattia renale nel diabete

Insufficienza renale NON albuminurica

Nefropatia albuminurica



Declino renale progressivo

Figure 1 Albuminuric and nonalbuminuric pathways of DKD progression. DKD = diabetic kidney disease; GFR = glomerular filtration rate; ESKD = end-stage kidney disease.

Please cite this article as: Pugliese G et al., Diabetic kidney disease: New clinical and therapeutic issues. Joint position statement of the Italian Diabetes Society and the Italian Society of Nephrology on "The natural history of diabetic kidney disease and treatment of hyperglycemia in patients with..., Nutrition, Metabolism & Cardiovascular Diseases, https://doi.org/10.1016/j.numecd.2019.07.017

Low eGFR without albuminuria: *a distinct entity or a DKD variant*?

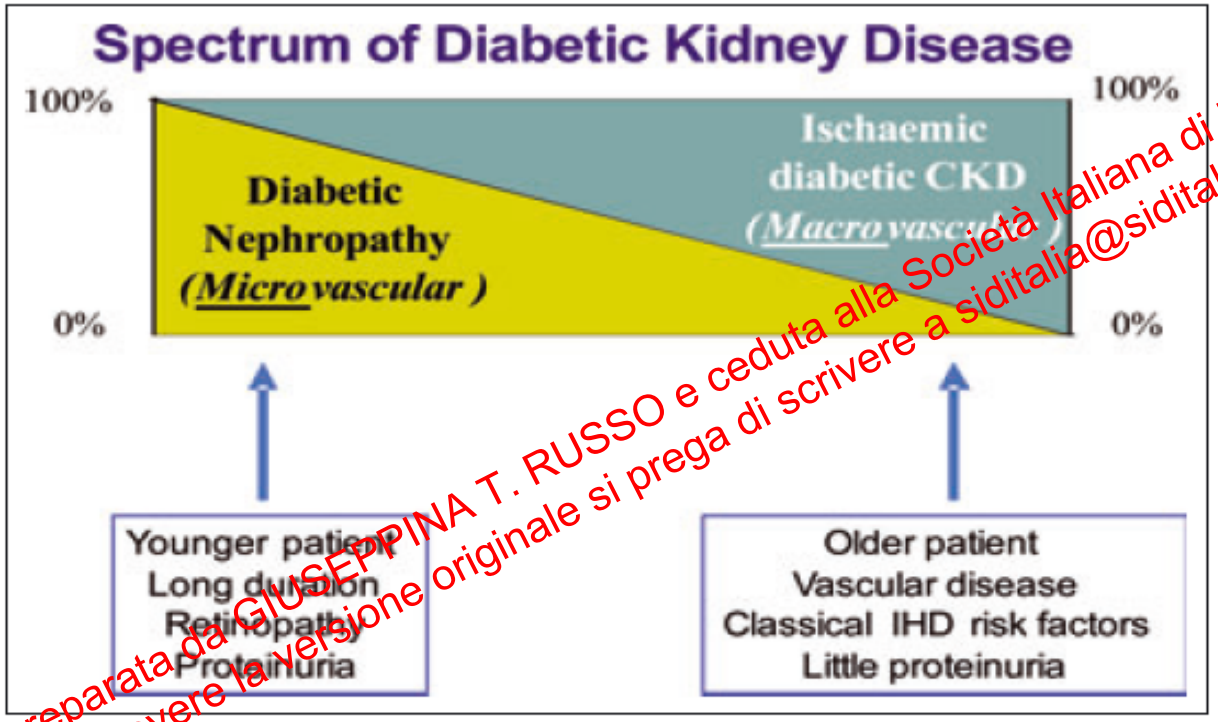


Figure 1. Spectrum of diabetic kidney disease with classical diabetic nephropathy as exemplified with proteinuria and other micro-vascular complications on the left and a macro-vascular CKD variant on the right.

Hill, Fogarty. J Renal Care 2012

Diabetes & Metabolic Syndrome: Clinical Research & Reviews 13 (2019) 474–479

Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

journal homepage: www.elsevier.com/locate/dsx

Review

Albuminuric and non-albuminuric patterns of chronic kidney disease in type 2 diabetes

Vadim V. Klimontov*, Anton I. Korbut

Table 1
The prevalence of CKD clinical manifestations in patients with diabetes.

Study, population	Years	N	Prevalence		
			Elevated AER, %	eGFR<60 mL/min × 1.73 m², %	NA-CKD, %
National Health and Nutrition Examination Surveys (NHANES), USA	1988–1994	1431	20.8	9.2	7.6[a]
	2009–2014	2097	15.9	14.1	10.3[a]
The study of CKD in diabetic Pima Indians, USA	1982–1988	837	47.4[a]	6.5	0.6
	2001–2006	1310	42.4[a]	6.6	1.1
Chronic Renal Insufficiency Cohort (CRIC) Study, USA	2003–2008	1908	71.6	N/D	28.4
U.K. Prospective Diabetes Study (UKPDS), UK	1977–1997	4006	52.2[a]	42.2[a]	14.4[a]
Action in Diabetes and Vascular disease: Preterax and Diamicron-MR Controlled Evaluation study (ADVANCE), Australasia, Asia, Europe and North America	2001–2008	10640	30.7[a]	19.1[a]	11.8
The Renal Insufficiency and Cardiovascular Events (RIACE), Italy	2007–2008	15773	26.9[a]	17.1	9.4[a]
Study of NA-CKD in type 2 diabetic patients, Sweden	2003–2006	66065	23.9[a]	17.2[a]	10.2[a]
CKD in the type 2 diabetic patients: of a Mediterranean area, GEDAPS 2007 Evaluation, Spain	2007	2642	19.5 (among 1478 patients)	22.9	14.7
National evaluation of the frequency of renal impairment cO-existing with NIDDM (NEFRON), Australia	2005	3893	34.6	23.6	12.7
Study of CKD in diabetic patients in Japan	2008–2009	1197	43.7[a]	41.9	18.6

Russo *et al. BMC Geriatrics* (2018) 18:38
DOI 10.1186/s12877-018-0732-4

BMC Geriatrics

RESEARCH ARTICLE Open Access

Diabetic kidney disease in the elderly: prevalence and clinical correlates

Giuseppina T. Russo[1,9*], Salvatore De Cosmo[2], Francesca Viazzi[3], Antonio Mirijello[2], Antonio Ceriello[4,5], Pietro Guida[6], Carlo Giorda[7], Domenico Cucinotta[1], Roberto Pontremoli[3], Paola Fioretto[8] and the AMD-Annals Study Group

La prevalenza della DKD aumenta all'aumentare dell'età

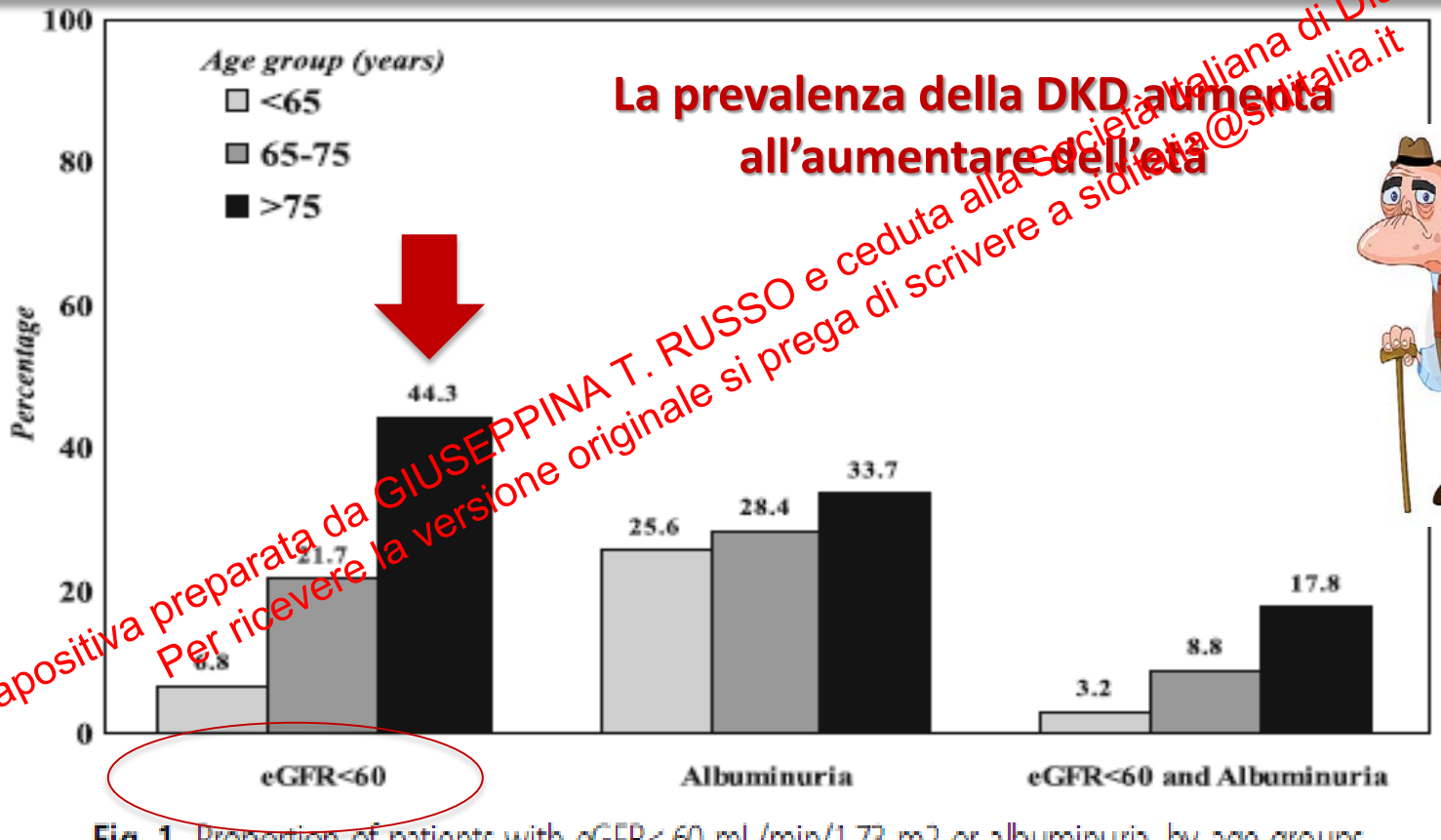
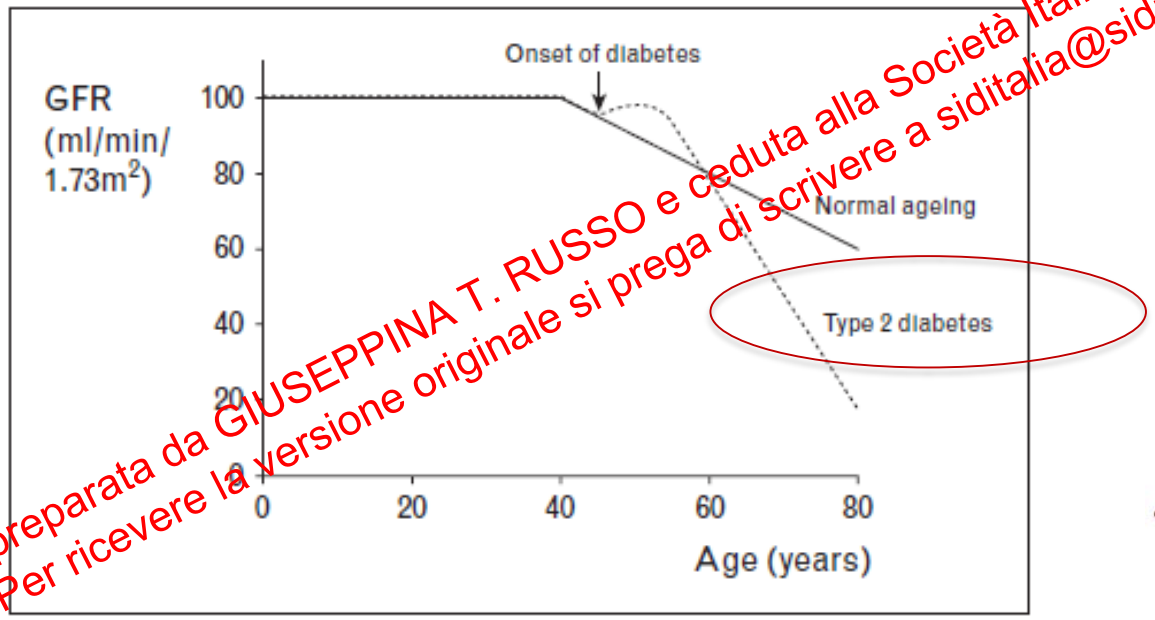


Fig. 1 Proportion of patients with eGFR< 60 mL/min/1.73 m2 or albuminuria, by age groups

Il declino del GFR nel DM2 non è *solo* legato all'età….

Figure 6 Schematic representation of the expected decline in GFR with age and a proposed accelerated decline in GFR that is not accompanied by a significant increase in AER that occurs after the onset of type 2 diabetes over and above that expected with age alone



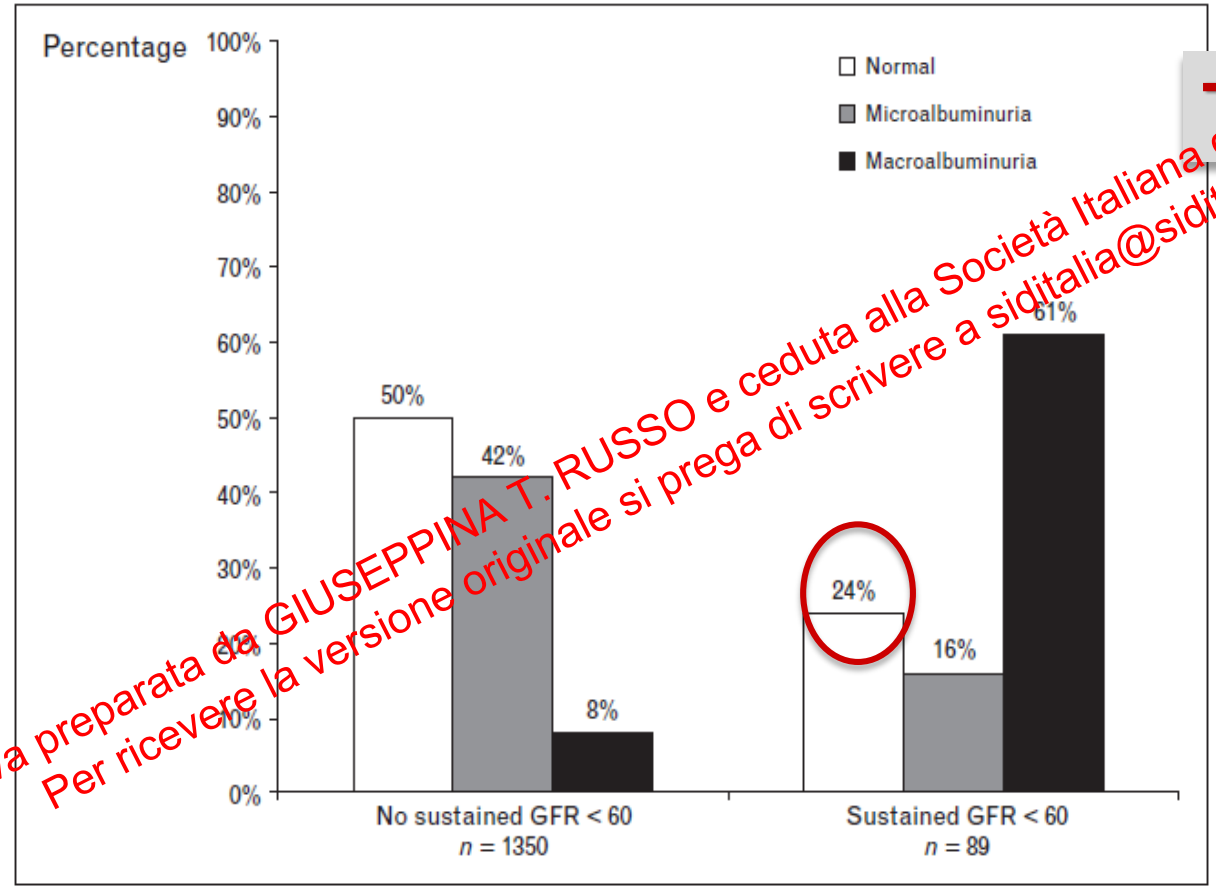
AER, albumin excretion rate; GFR, glomerular filtration rate.

Diabetic chronic kidney disease MacIsaac and Jerums

Current Opinion in Nephrology and Hypertension 2011, 20:246–257

Prevalenza di Low GFR senza MAU nel DCCT/EDIC

Figure 4 The proportion of patients with type 1 diabetes with normalbuminuria, microalbuminuria or macroalbuminuria and a sustained eGFR less than 60 ml/min/1.73 m^2 in the DCCT and EDIC study



DCCT, Diabetes Control and Complications Trial; EDIC, Epidemiology of Diabetes Interventions and Complications; eGFR, estimated glomerular filtration rate. Reproduced with permission from [37••].

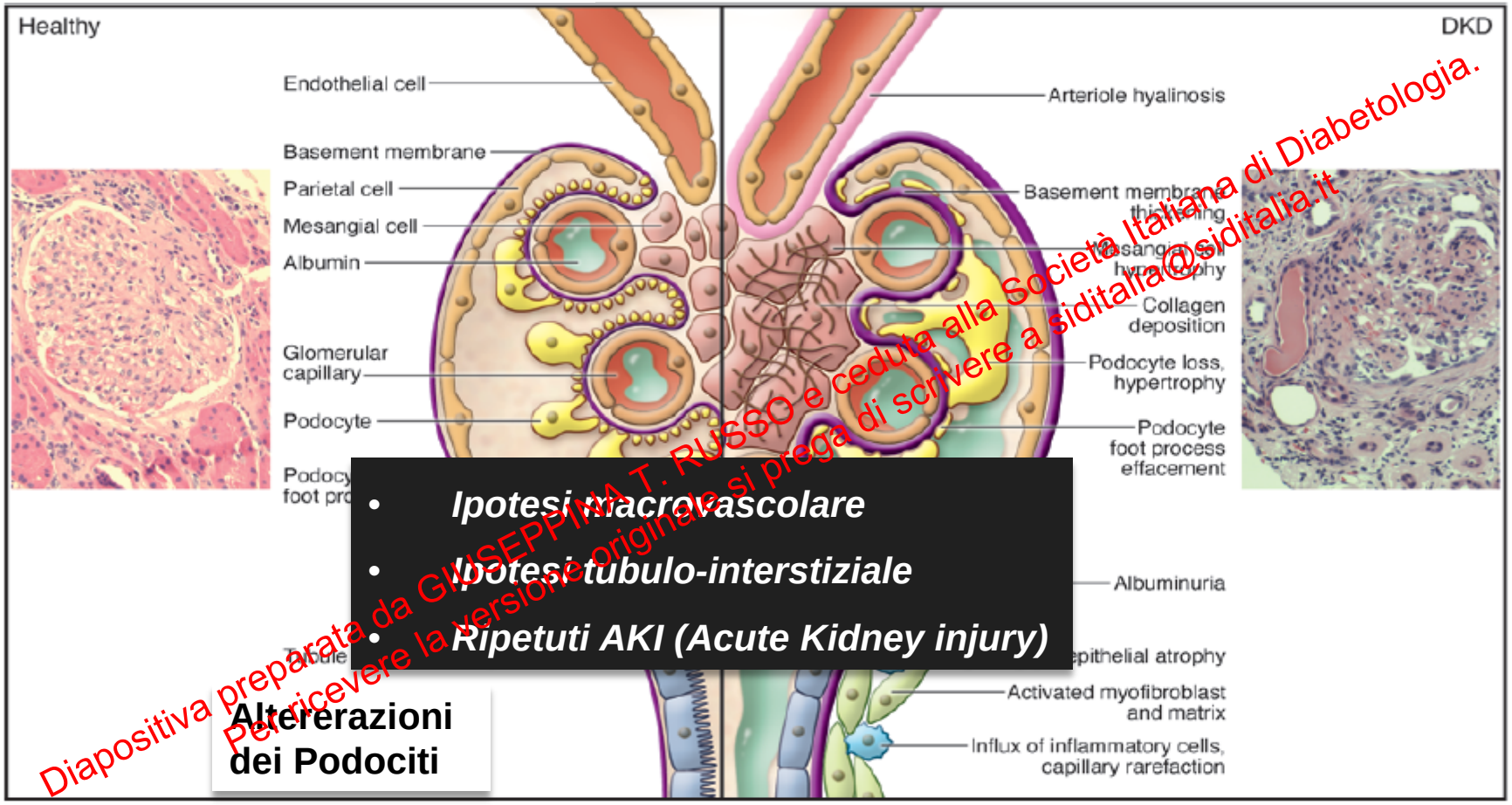
Molitch ME, Steffes M, Sun W, *et al.* Development and progression of renal insufficiency with and without albuminuria in adults with type 1 diabetes in the diabetes control and complications trial and the epidemiology of diabetes interventions and complications study. Diabetes Care 2010; 33: 1536–1543.

Current Opinion in Nephrology and Hypertension 2011, 20:246–257

Molecular mechanisms of diabetic kidney disease

Kimberly Reidy,[1,2] Hyun Mi Kang,[1] Thomas Hostetter,[3] and Katalin Susztak[1]

[1]Renal Electrolyte and Hypertension Division, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA. [2]Department of Pediatrics, Albert Einstein College of Medicine, Yeshiva University, New York, New York, USA. [3]Division of Nephrology, Department of Medicine, Case Western Reserve University, Cleveland, Ohio, USA.



- *Ipotesi macrovascolare*
- *Ipotesi tubulo-interstiziale*
- *Ripetuti AKI (Acute Kidney injury)*

Alterazioni dei Podociti

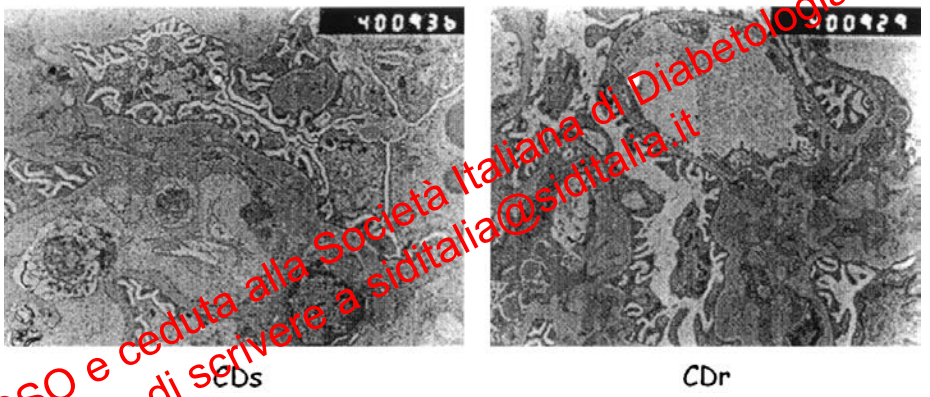
Figure 1

Pathological lesions of DKD. The normal healthy glomerulus includes afferent arterioles, capillary loops, endothelial cells, basement membrane, podocytes, parietal epithelial cells, and tubule epithelial cells and is impermeable to albumin. In contrast, the diabetic glomerulus displays arterial hyalinosis, mesangial expansion, collagen deposition, basement membrane thickening, podocyte loss and hypertrophy, albuminuria, tubular epithelial atrophy, accumulation of activated myofibroblasts and matrix, influx of inflammatory cells, and capillary rarefaction. Also shown are a normal healthy human glomerular section and a kidney section from a sample with DKD (PAS stained). Original magnification, ×400.

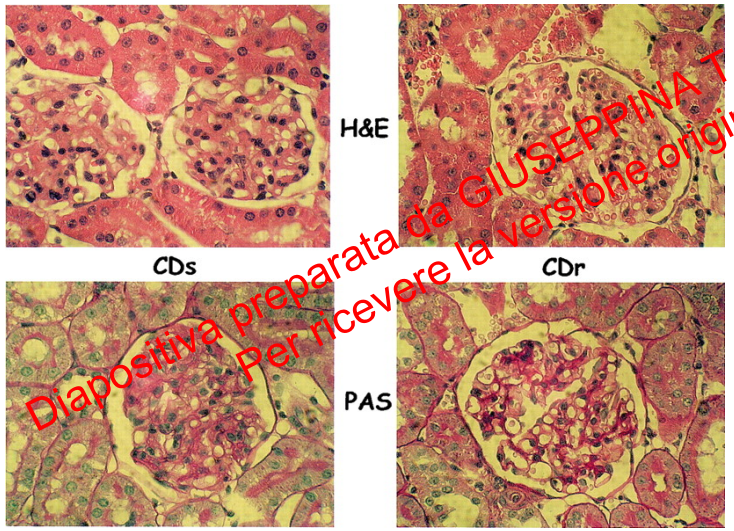
Nonproteinuric Diabetes-Associated Nephropathy in the Cohen Rat Model of Type 2 Diabetes

Chana Yagil,[1] Adiel Barak,[2] David Ben-Dor,[3] Eliezer Rosenmann,[1] Joel Bernheim,[4] Mordechai Rosner,[5] Yael Segev,[6] Sarah Weksler-Zangen,[7] Itamar Raz,[8] and Yoram Yagil[1]

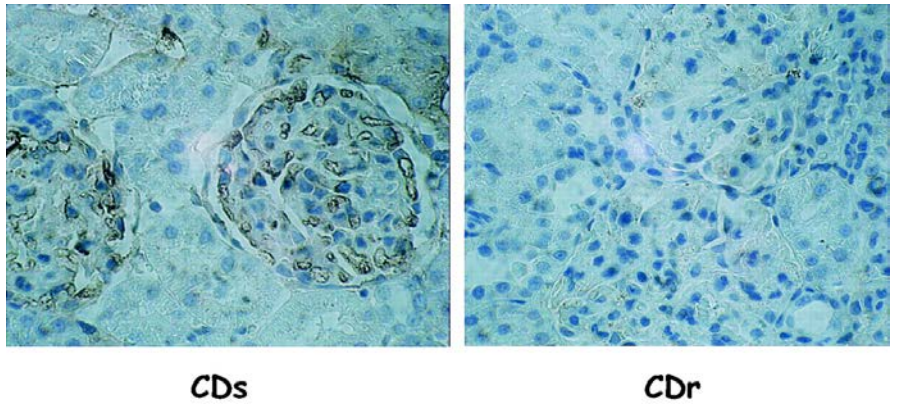
***The Cohen diabetic rat* is known to develop progressive impairment in renal function with morphological changes that are typical of *diabetic glomerulosclerosis* but *without proteinuria*.**



Electron micrographs (×4,000) of representative kidney sections of CDs and CDr fed diabetogenic diet for 3 months.



Hematoxylin and eosin (H&E) and PAS stains of 2- to 3-μm sections of kidneys (×400) from CDs and CDr fed diabetogenic diet for 3 months.



Immunocytochemical staining for type IV collagen (in brown) in sections of kidneys of CDs and CDr fed diabetogenic diet for 3 months.

Diabetes 2005; 54:1487–1496

Diabetologia (1996) 39: 1569–1576

Diabetologia

Patterns of renal injury in NIDDM patients with microalbuminuria

P. Fiorette[1], M. Mauer[2], E. Brocco[1], M. Velussi[3], F. Frigato[3], B. Muollo[3], M. Sambataro[3], C. Abaterusso[1], B. Baggio[1], G. Crepaldi[1], 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

summary, microalbuminuric NIDDM patients are structurally heterogeneous with less than one third having "typical" diabetic nephropathology. The presence of both "typical" and "atypical" patterns of renal pathology was associated with worse metabolic control, suggesting that hyperglycaemia may cause different patterns of renal injury in older NIDDM compared to younger IDDM patients. [Diabetologia (1996) 39: 1569–1576]

34 Pazienti DM2 con MAU hanno diverse lesioni istologiche

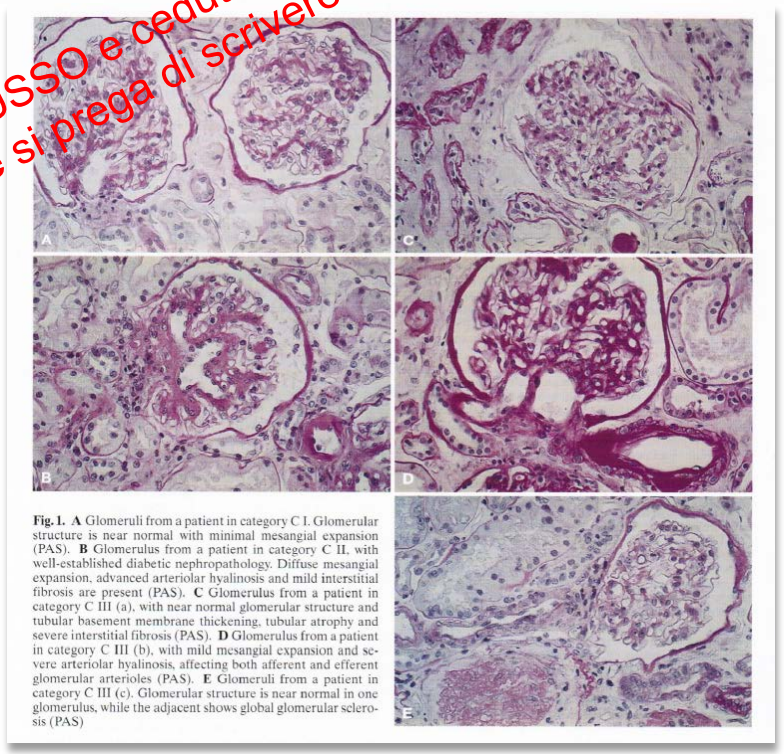


Fig. 1. **A** Glomeruli from a patient in category C I. Glomerular structure is near normal with minimal mesangial expansion (PAS). **B** Glomerulus from a patient in category C II, with well-established diabetic nephropathology. Diffuse mesangial expansion, advanced arteriolar hyalinosis and mild interstitial fibrosis are present (PAS). **C** Glomerulus from a patient in category C III (a), with near normal glomerular structure and tubular basement membrane thickening, tubular atrophy and severe interstitial fibrosis (PAS). **D** Glomerulus from a patient in category C III (b), with mild mesangial expansion and severe arteriolar hyalinosis, affecting both afferent and efferent glomerular arterioles (PAS). **E** Glomeruli from a patient in category C III (c). Glomerular structure is near normal in one glomerulus, while the adjacent shows global glomerular sclerosis (PAS)

CKD in diabetes: diabetic kidney disease versus nondiabetic kidney disease

Hans-Joachim Anders[1], Tobias B. Huber[2], Berend Isermann[3] and Mario Schiffer[4]*

<10%

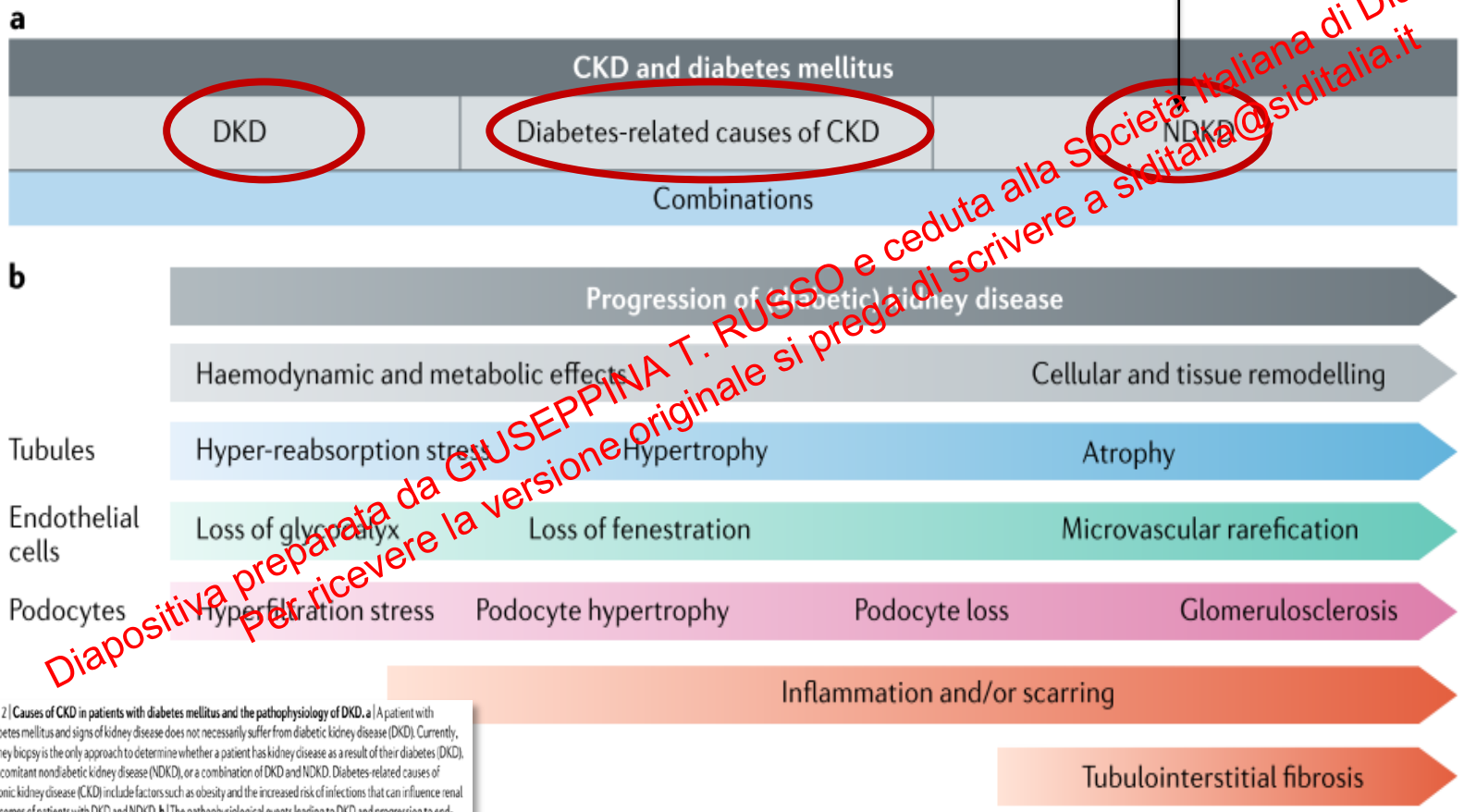


Fig. 2 | **Causes of CKD in patients with diabetes mellitus and the pathophysiology of DKD. a** | A patient with diabetes mellitus and signs of kidney disease does not necessarily suffer from diabetic kidney disease (DKD). Currently, kidney biopsy is the only approach to determine whether a patient has kidney disease as a result of their diabetes (DKD), concomitant nondiabetic kidney disease (NDKD), or a combination of DKD and NDKD. Diabetes-related causes of chronic kidney disease (CKD) include factors such as obesity and the increased risk of infections that can influence renal outcomes of patients with DKD and NDKD. **b** | The pathophysiological events leading to DKD and progression to end-stage renal disease can be separated into early (haemodynamic and metabolic) and late (cellular and tissue remodelling) events. In the early phase, massive glucose filtration and glomerular hyperfiltration induce tubular hyper-reabsorption of glucose and sodium, leading to glomerular and tubular hypertrophy and, eventually, to glomerulosclerosis and tubule atrophy. In endothelial cells, early loss of glycocalyx and fenestration leads first to proteinuria and later to microvascular rarefication, promoting atrophy and scaring. Sterile inflammation (that is, the local induction of cytokines, chemokines, and immune cell recruitment) accompanies and promotes tissue remodelling, contributing to atrophy and scarring.

review www.kisupplements.org

Diagnosis of diabetic kidney disease: state of the art and future perspective

Frederik Persson[1] and Peter Rossing[1,2]

[1]Steno Diabetes Center Copenhagen, Gentofte, Denmark; and [2]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

Creatinina e albuminuria sono i marcatori giusti di danno renale nel diabete?

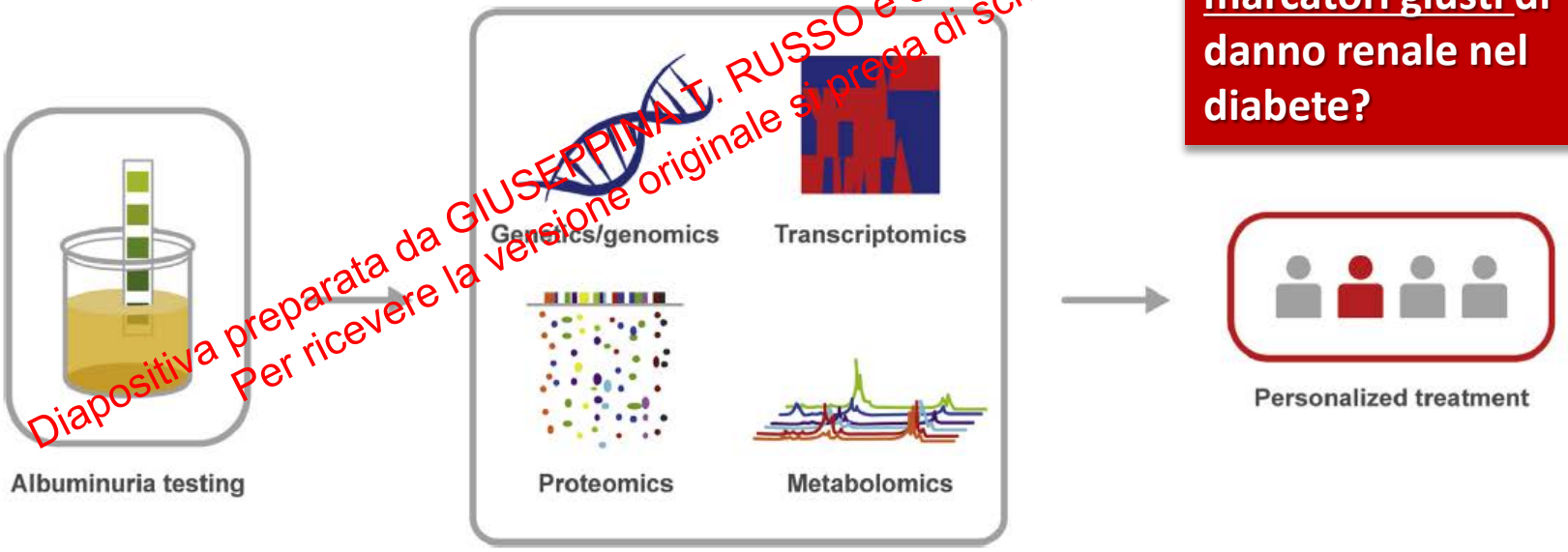


Figure 2| From albuminuria to personalized treatment.

Acta Diabetologica (2018) 55:1093–1104
https://doi.org/10.1007/s00592-018-1193-0

REVIEW ARTICLE

Advances in understanding the genetic basis of diabetic kidney disease

Man Li[1,2] · Marcus G. Pezzolesi[1,3,4]

Diverse varianti genetiche associate con DKD, tuttavia isolated low *eGFR poco studiato*

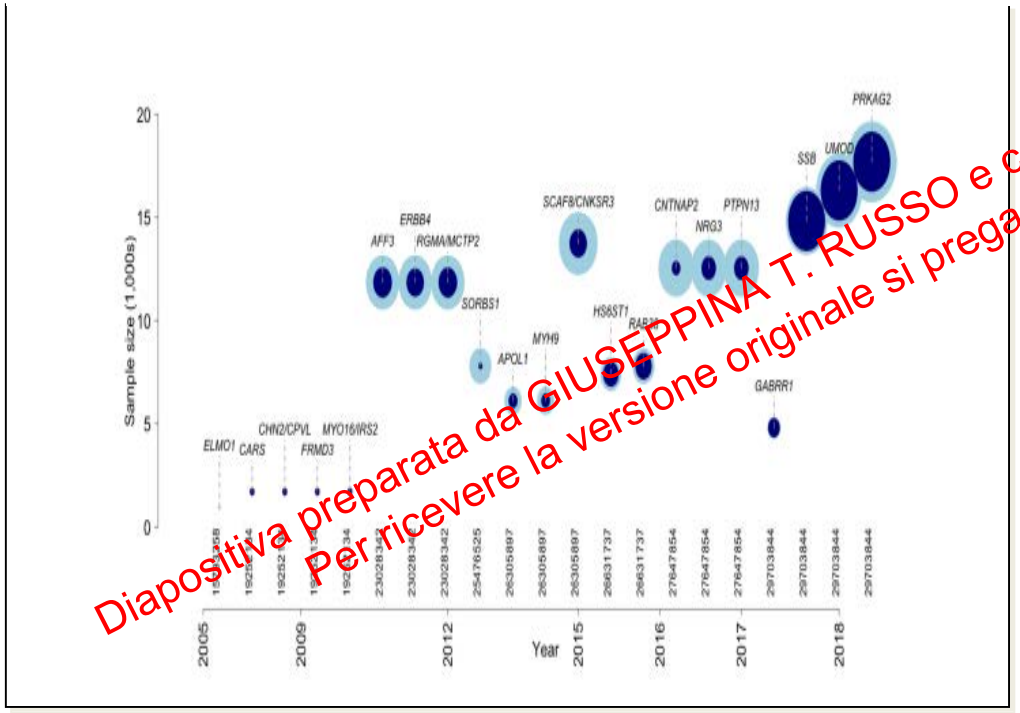
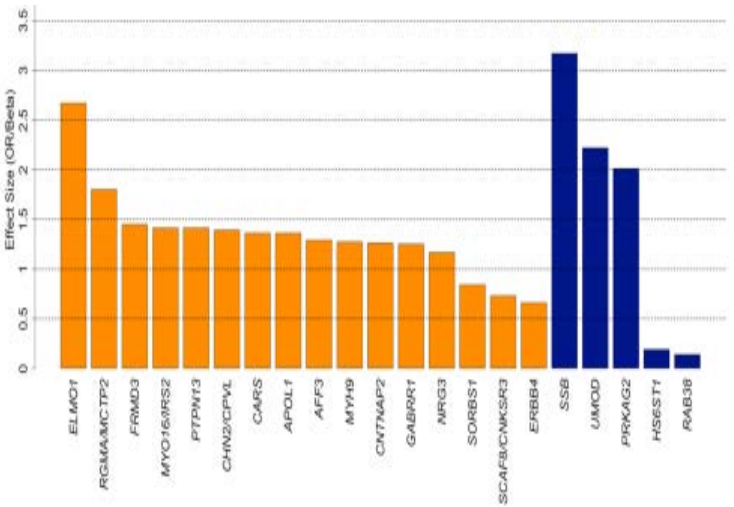


Fig. 3 Effect sizes for DKD loci identified through GWAS. Odds ratios (OR) and beta estimates for dichotomous (orange) and quantitative DKD traits (blue), respectively, are presented for all DKD GWAS loci with p value $< 1.0 \times 10^{-5}$. Of note, the effect sizes for the *SSB*, *UMOD*, and *PRKAG2* loci are from associations with eGFR while those for *HS6ST1* and *RAB38* are from associations with uACR

Nessun *locus* definitivamente associato con la DKD

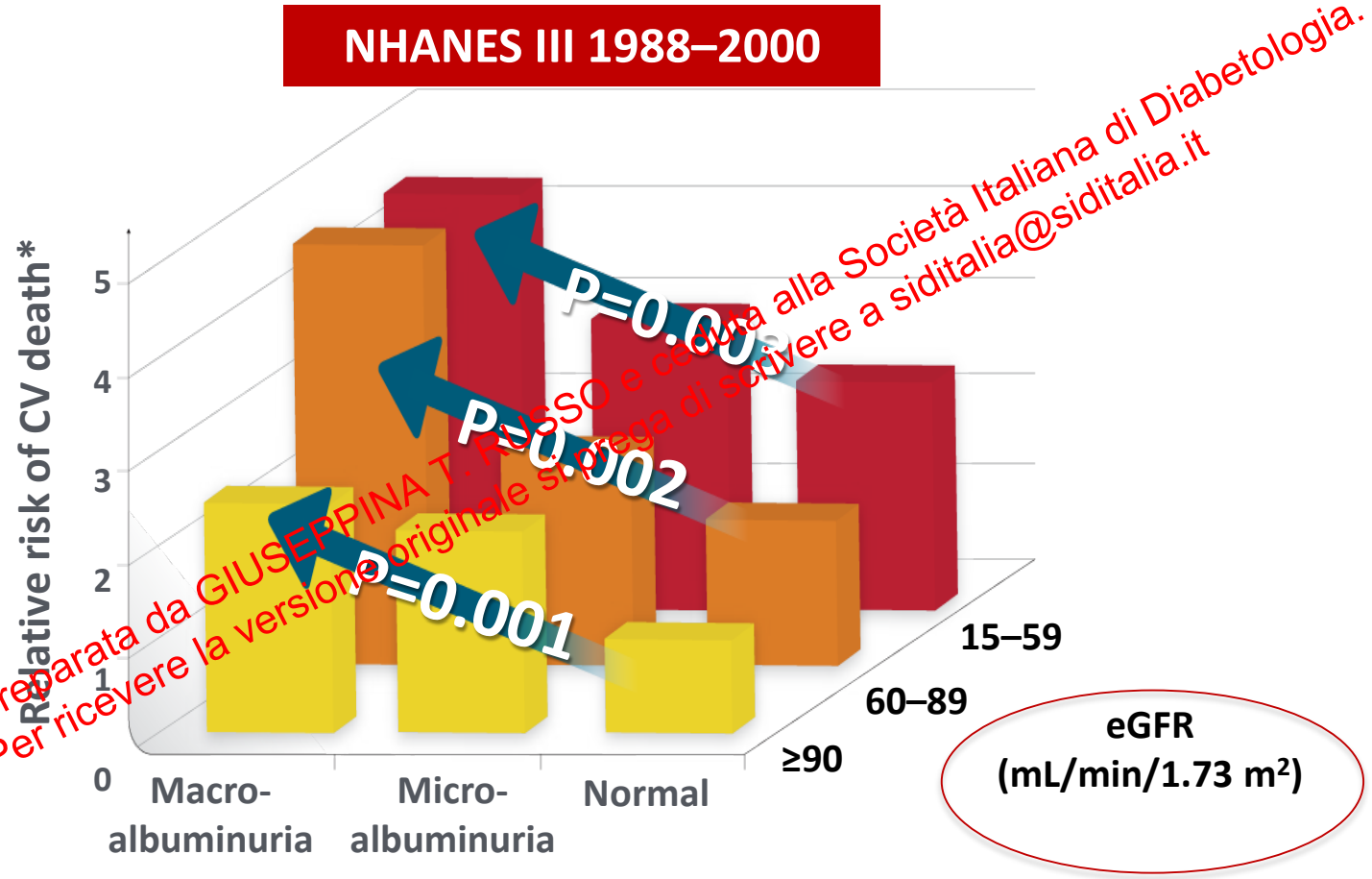


Overall, small Effect size

La DKD ha due componenti: MAU e low EGFR,

- **Sono entrambi fattori di rischio *indipendenti* per gli eventi CVD?**

Cardiovascular (CV) mortality risk increases with declining renal function



*Adjusted for age, sex, race/ethnicity, previous CV disease, blood pressure category, use of antihypertensive medication, diabetes mellitus, smoking status, body mass index, physical activity level, low density lipoprotein and high density lipoprotein cholesterol, log triglyceride level, and C-reactive protein category.

Astor BC, *et al*. *Am J Epidemiol* 2008;167:1226–34.

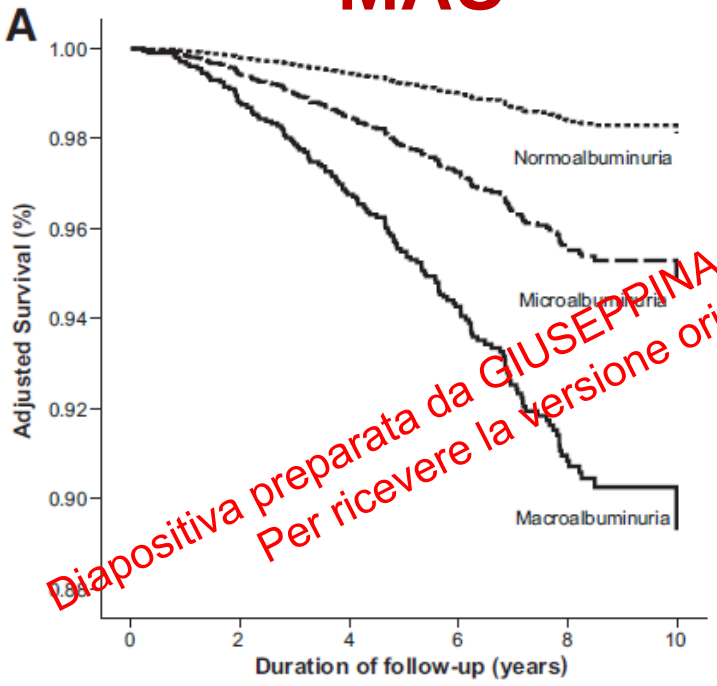
MAU e lowGFR sono associati in modo INDIPENDENTE all'incidenza di eventi CVD nel DM1

ORIGINAL ARTICLE

The Presence and Severity of Chronic Kidney Disease Predicts All-Cause Mortality in Type 1 Diabetes

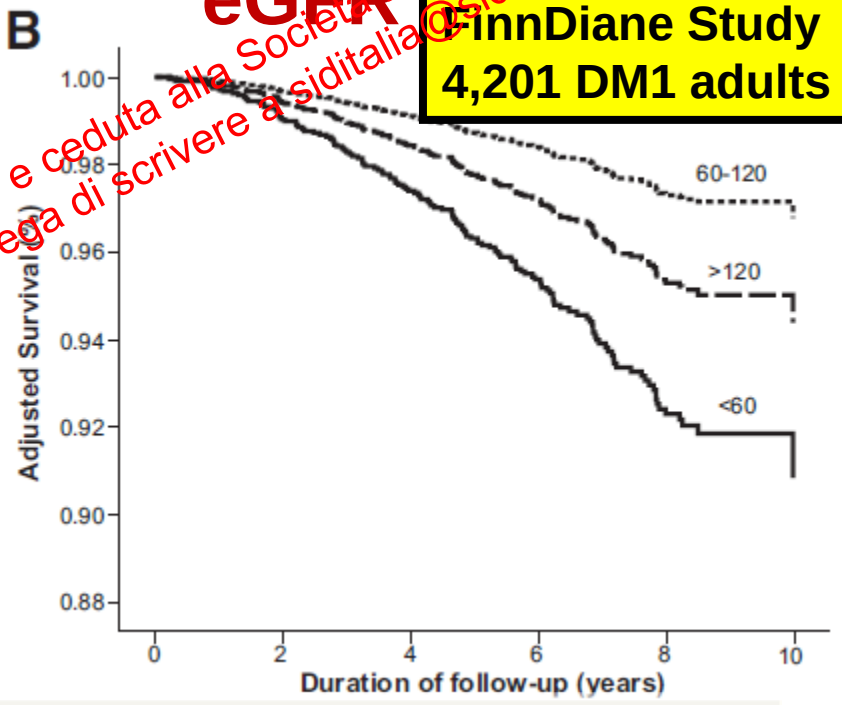
Per-Henrik Groop,[1,2] Merlin C. Thomas,[3] John L. Moran,[4] Johan Wadèn,[1,2] Lena M. Thorn,[1,2] Ville-Petteri Mäkinen,[1,2] Milla Rosengård-Bärlund,[1,2] Markku Saraheimo,[1,2] Kustaa Hietala,[1,2,5] Outi Heikkilä,[1,2] and Carol Forsblom[1,2] on behalf of the FinnDiane Study Group

MAU



eGFR

FinnDiane Study
4,201 DM1 adults



CONCLUSIONS—An independent graded association was observed between the presence and severity of kidney disease and mortality in a large contemporary cohort of individuals with type 1 diabetes. These findings highlight the clinical and public health importance of chronic kidney disease and its prevention in the management of type 1 diabetes. *Diabetes* 58:1651–1658, 2009

FIG. 1. Survival plots showing Cox-adjusted survival of individuals with type 1 diabetes from the FinnDiane study, stratified for the presence and severity of albuminuria (*A*), estimated GFR (*B*), and the presence and severity of retinopathy (*C*) at baseline. All figures are adjusted for age; sex; duration of diabetes; body habitus; the presence and extent of macro- and microvascular complications; glycemic, lipid, and blood pressure control; and drug management. The latter figure (*C*) is not adjusted for the presence and severity of nephropathy, as discussed in the text.

Regression of albuminuria and its association with incident cardiovascular outcomes and mortality in type 1 diabetes: the FinnDiane

Jansson FJ, Forsblom C, Harjutsalo V, Thorn LM, Wadén J, Elonen N, Ahola AJ, Saraheimo M, Groop PH; FinnDiane Study Group. Study.

FinnDiane

Strati di albuminuria	HR (95% CI)		
	Eventi cardiovascolari	Mortalità per tutte le cause	Mortalità per cause cardiovascolari
Normoalbuminuria	1 (Reference)	1 (Reference)	1 (Reference)
Microalbuminuria			
"Regressors"	1.42 (0.75-2.68)	1.32 (0.65-2.69)	1.41 (0.51-3.87)
"Persistent"	2.62 (1.95-3.54) *	2.87 (2.11-3.91) **	3.21 (2.09-4.93)
Macroalbuminuria			
"Regressors"	3.15 (2.02-4.92)	3.86 (2.55-5.83)	4.31 (2.41-7.68)
"Persistent"	5.49 (4.31-7.00) **	7.22 (5.69-9.14) **	9.90 (7.14-13.7) **

Diabetologia. 2018

CLINICAL EPIDEMIOLOGY www.jasn.org

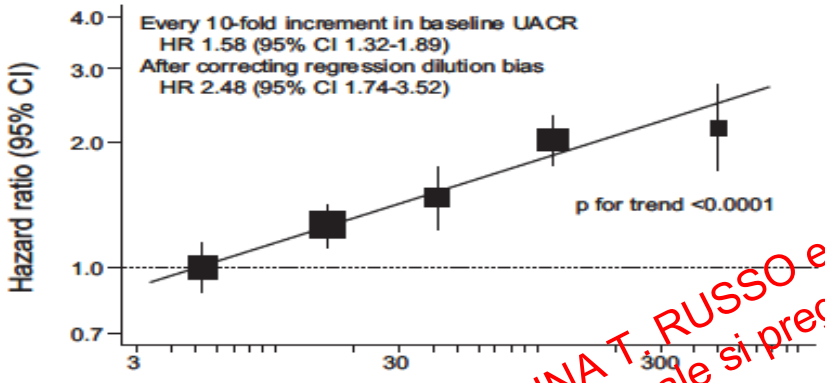
Albuminuria and Kidney Function Independently Predict Cardiovascular and Renal Outcomes in Diabetes

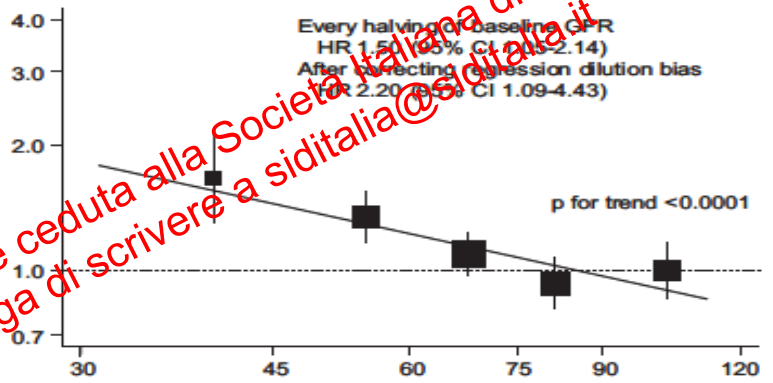
Toshiharu Ninomiya,* Vlado Perkovic,* Bastiaan E. de Galan,*† Sophia Zoungas,* Avinesh Pillai,* Meg Jardine,* Anushka Patel,* Alan Cass,* Bruce Neal,* Neil Poulter,‡ Carl-Erik Mogensen,§ Mark Cooper,‖ Michel Marre,¶ Bryan Williams,** Pavel Hamet,†† Giuseppe Mancia,‡‡ Mark Woodward,*§§ Stephen MacMahon,* and John Chalmers,* on behalf of the ADVANCE Collaborative Group

ADVANCE STUDY

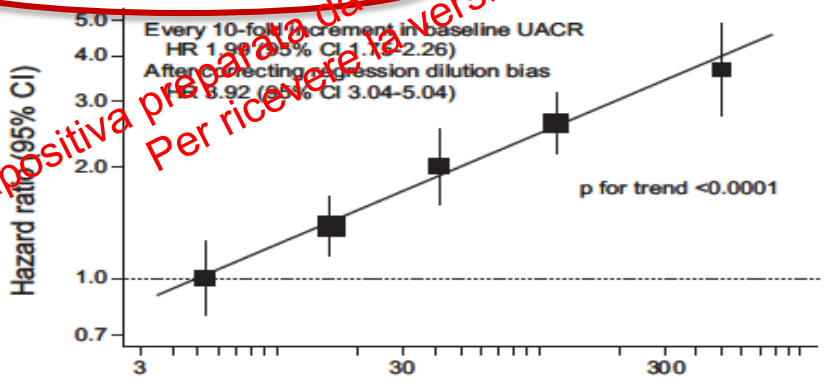
MAU e lowGFR sono associati in modo INDIPENDENTE all'incidenza di eventi CVD nel DM2

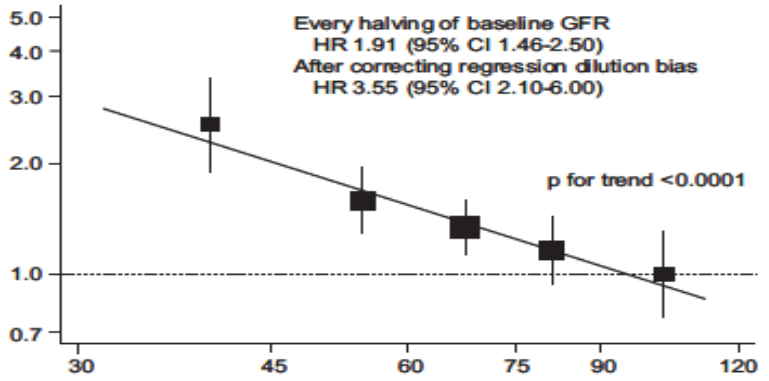
Cardiovascular events





Cardiovascular death





J Am Soc Nephrol 20: 1813–1821, 2009

European Heart Journal (2003) 24, 381–383

ELSEVIER

Editorial

Looking for people at high cardiovascular risk? Look at serum-creatinine

J.F.E. Mann[a*], I. Dulau-Florea[b], J. Franke[b]

Comparison of Two Creatinine-Based Estimating Equations in Predicting All-Cause and Cardiovascular Mortality in Patients With Type 2 Diabetes

GIOVANNI TARGHER, MD[1]
GIACOMO ZOPPINI, MD[1]
WILLIAM MANTOVANI, MD[2]
MICHEL CHONCHOL, MD[3]
CARLO NEGRI, MD[1]
VINCENZO STOICO, MD[1]
ALESSANDRO MANTOVANI, MD[1]
FRANCESCA DE SANTI, MD[1]
ENZO BONORA, MD[1]

Quale formula usare?

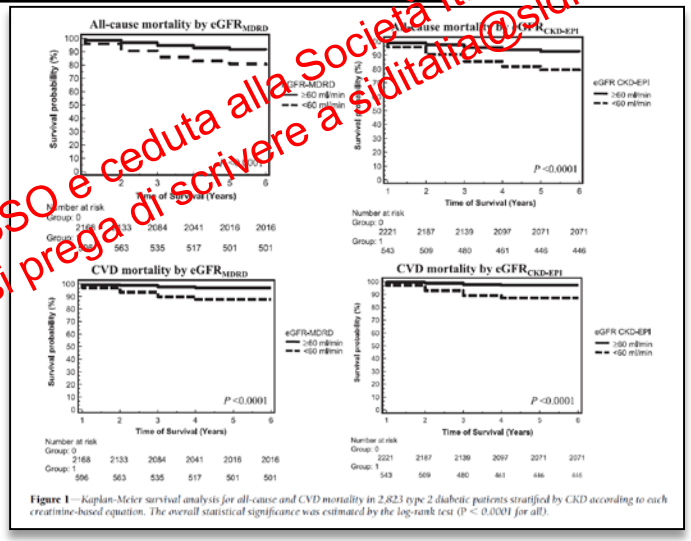


Figure 1—*Kaplan-Meier survival analysis for all-cause and CVD mortality in 2,823 type 2 diabetic patients stratified by CKD according to each creatinine-based equation. The overall statistical significance was estimated by the log-rank test (P < 0.0001 for all).*

CONCLUSIONS—Our findings suggest that the estimation of GFR using the CKD-EPI equation more appropriately stratifies patients with type 2 diabetes according to the risk of all-cause and cardiovascular mortality compared with the MDRD study equation.

Diabetes Care 35:2347–2353, 2012

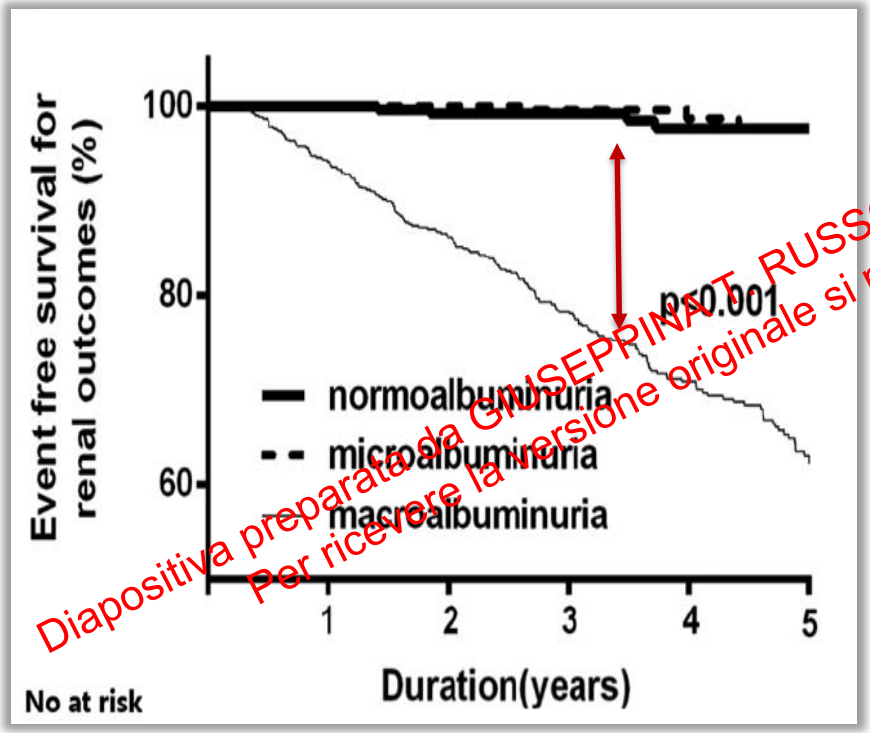
Medicine
OBSERVATIONAL STUDY
OPEN

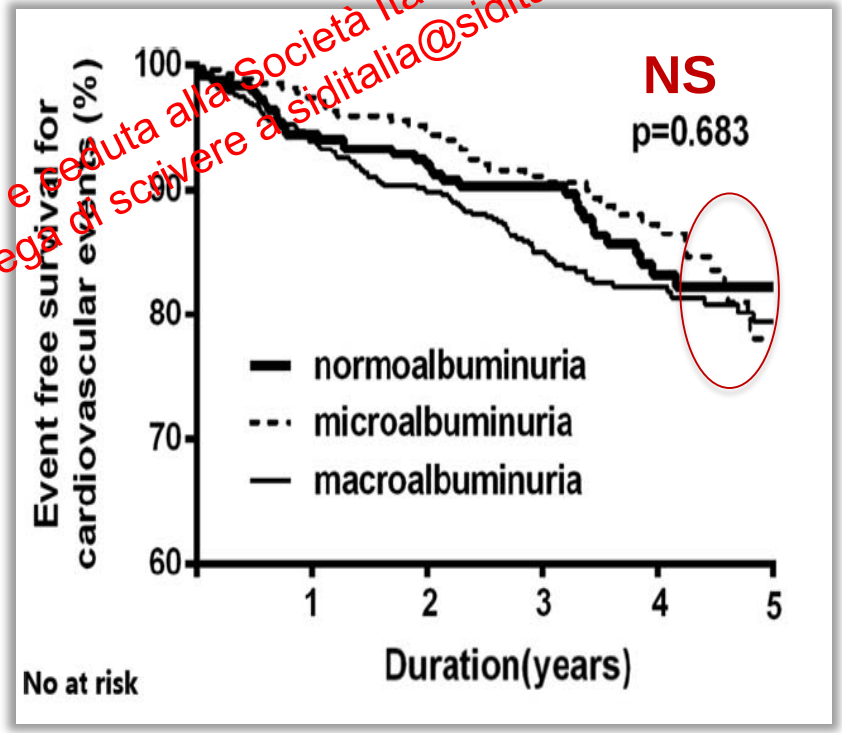
The Incidence of Cardiovascular Events Is Comparable Between Normoalbuminuric and Albuminuric Diabetic Patients With Chronic Kidney Disease

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

Medicine 95(15):e3175

CKD DM patients with and without MAU





Renal events

CV events

Diverging Association of Reduced Glomerular Filtration Rate and Albuminuria With Coronary and Noncoronary Events in Patients With Type 2 Diabetes

RIACE

The Renal Insufficiency And Cardiovascular Events (RIACE) Italian Multicenter Study

ANNA SOLINI, MD[1]
GIUSEPPE PENNO, MD[2]
ENZO BONORA, MD[3]
CECILIA FONDELLI, MD[4]
EMANUELA ORSI, MD[5]
MAURA AROSIO, MD[6]
ROBERTO TREVISAN, MD[7]
MONICA VEDOVATO, MD[8]
MAURO CIGNARELLI, MD[9]
FRANCESCO ANDREOZZI, MD[10]
ANTONIO NICOLUCCI, MD
GIUSEPPE PUGLIESE, MD
FOR THE RENAL INSUFFICIENCY AND CARDIOVASCULAR EVENTS (RIACE) STUDY GROUP

- **Coronary events, *N* = 2,405,**
- **Cerebrovascular, *N* = 1,298,**
- **Peripheral, *N* = 894**

Table 3—*Logistic regression analysis of coronary (N = 2,405), cerebrovascular (N = 1,298), or peripheral (N = 894) events with CKD phenotypes as covariates*

Variable	Coronary events	Cerebrovascular events	Peripheral events
Age (1 year)	1.020 (1.014–1.026)	1.030 (1.022–1.038)	1.013 (1.004–1.021)
Male sex	2.129 (1.906–2.379)	1.16 (1.02–1.33)	1.23 (1.04–1.45)
CKD phenotype			
No CKD	1.0	1.0	1.0
Stages 1–2 CKD	0.901 (0.794–1.022)	1.41 (1.20–1.65)	1.51 (1.25–1.82)
Nonalbuminuric stage ≥3 CKD	1.514 (1.304–1.757)	1.22 (1.01–1.48)	1.40 (1.11–1.76)
Albuminuric stage ≥3 CKD	1.270 (1.083–1.490)	1.69 (1.40–2.00)	1.88 (1.52–2.34)
Cerebrovascular events	2.472 (2.156–2.834)	2.51 (2.19–2.87)	2.77 (2.37–3.23)
Peripheral events	2.702 (2.306–3.167)	3.75 (3.17–4.44)	3.81 (3.21–4.51)

Results are presented as OR (95% CI). Variables excluded: HbA_{1c}, BMI. OHA, oral hypoglycemic agent.

La DKD ha due componenti: MAU e low EGFR,

- ***Sono associati a diversi fattori di rischio CVD?***

I Fattori di rischio *CVD sono associati alla DKD*


Documento di consenso
e raccomandazioni per la prevenzione
cardiovascolare in Italia
2018

Tabella 1. Fattori di rischio.

Modificabili		Non modificabili
Maggiori	**Minori o non convenzionali**	
• Pressione arteriosa sistolica • Colesterolo totale • Diabete mellito • Fumo di sigaretta	• Pressione arteriosa diastolica • Colesterolo HDL • Trigliceridi • Sindrome metabolica • Obesità addominale • Sedentarietà • Stresso emotivo e/o fisico • Iperuricemia • Indici di flogosi	• Età • Sesso • Etnia • Familiarità per malattie cardiovascolari

Kidney dysfunction and related cardiovascular risk factors among patients with type 2 diabetes

Salvatore De Cosmo[1], Maria Chiara Rossi[2], Fabio Pellegrini[2], Giuseppe Lucisano[2], Simonetta Ba
Sandro Gentile[3], Antonio Ceriello[4], Giuseppina Russo[5], Antonio Nicolucci[2], Carlo Giorda[6],
Francesca Viazzi[7], Roberto Pontremoli[7] and the AMD-Annals Study Group

Low eGFR e MAU differente *set* di fattori di rischio CVD

Table 3. Results of multivariate logistic regression analysis (backward models) showing the relationship between traits of DKD and traditional diabetic and cardiovascular risk factors. Reference category for all were patients with normoalbuminuria and eGFR ≥ 60 mL/min/1.73 m².

	Dependent variables					
	Low eGFR normal albuminuria		Albuminuria normal eGFR		Low eGFR and albuminuria	
Independent variables	OR	95%CI	OR	95% CI	OR	95% CI
Age (by 1 year)	1.12	1.10–1.12	1.01	1.01–1.01	1.12	1.12–1.13
DBP (by 5 mmHg)	0.97	0.95–0.98	1.04	1.03–1.05	NS	NS
SBP (by 5 mmHg)	0.98	0.97–0.99	1.03	1.02–1.03	1.04	1.04–1.05
Total cholesterol (by 10 mg/dL)	1.04	1.02–1.07	1.05	1.04–1.06	1.07	1.04–1.10
HDL-C (by 5 mg/dL)	0.93	0.92–0.95	0.95	0.94–0.96	0.88	0.86–0.89
LDL-C (by 10 mg/dL)	0.96	0.93–0.98	0.95	0.94–0.96	0.94	0.91–0.96
Triglycerides (by 10 mg/dL)	1.02				1.03	1.02–1.03
BMI (by 1 kg/m²)	0.95				1.05	1.04–1.05
Duration of diabetes (by 1 year)	1.01				1.02	1.01–1.02
HbA1c (by 1%)	0.96				0.97	0.95–1.00
Males versus females	0.69				1.52	1.42–1.63
Smokers (yes versus no)	0.84				1.22	1.11–1.34
Oral agents versus diet	0.88				1.14	0.98–1.32
Oral agents + insulin versus diet	1.09				2.01	1.70–2.39
Insulin versus diet	2.06				5.59	4.74–6.59
Use of antihypertensive drugs	1.60				2.67	2.34–3.05
Use of ACE inhibitors and/or ARBs	1.24	1.13–1.37	1.33	1.23–1.42	1.24	1.12–1.36
Use of statins	1.10	1.03–1.17	NS	NS	1.17	1.09–1.25
Retinopathy	NS	NS	1.41	1.33–1.49	1.64	1.52–1.77

OR, odds ratio; 95% CI, 95% confidence of intervals; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; BMI, body mass index; HbA1c, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; ACE, angiotensin converting enzyme; ARBs, angiotensin receptor blockers.

Fenotipo Low eGFR associato con:

Sesso femminile, non fumatore, anziano, lunga durata malattia, debole o nessuna associazione con retinopatia e HbA1c

De Cosmo, Russo, et al, Nephrol Dial Transplant 2014

Observational Study

Medicine®

OPEN

Predictors of chronic kidney disease in type 2 diabetes

A longitudinal study from the AMD Annals initiative

Salvatore De Cosmo (MD)[a,*], Francesca Viazzi (MD)[b], Antonio Pacilli (MD)[a], Carlo Giorda (MD)[c], Antonio Ceriello (MD)[d], Sandro Gentile (MD)[e], Giuseppina Russo (MD)[f], Maria C. Rossi (MD)[g], Antonio Nicolucci (MD)[h], Pietro Guida (MSC)[h], Roberto Pontremoli (MD, PhD)[b], and the AMD-Annals Study Group

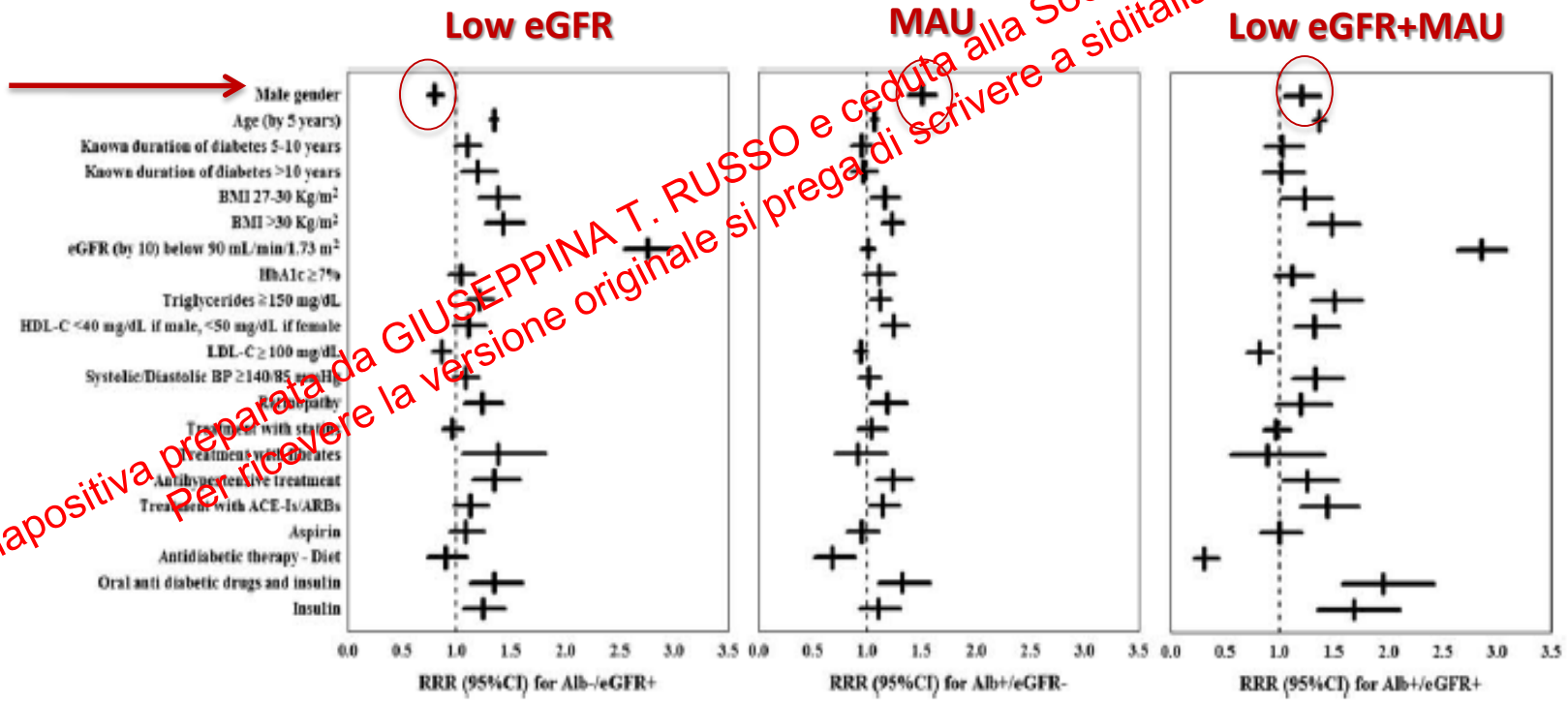
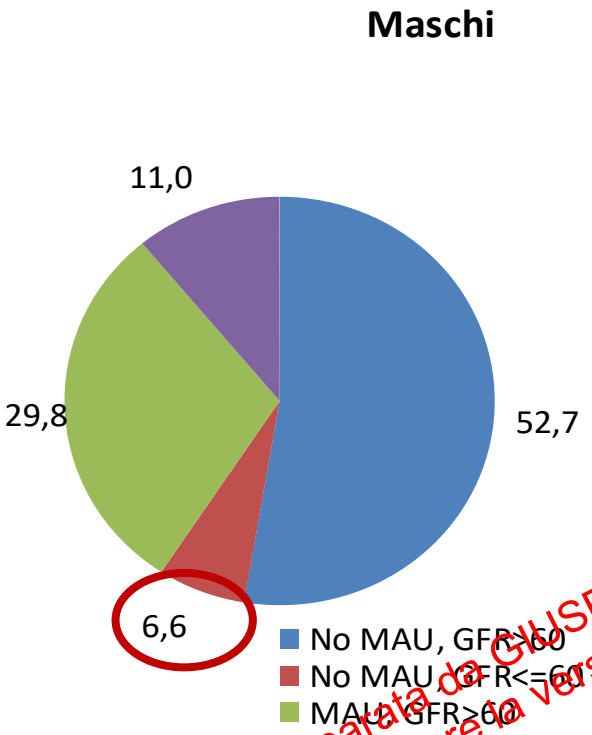
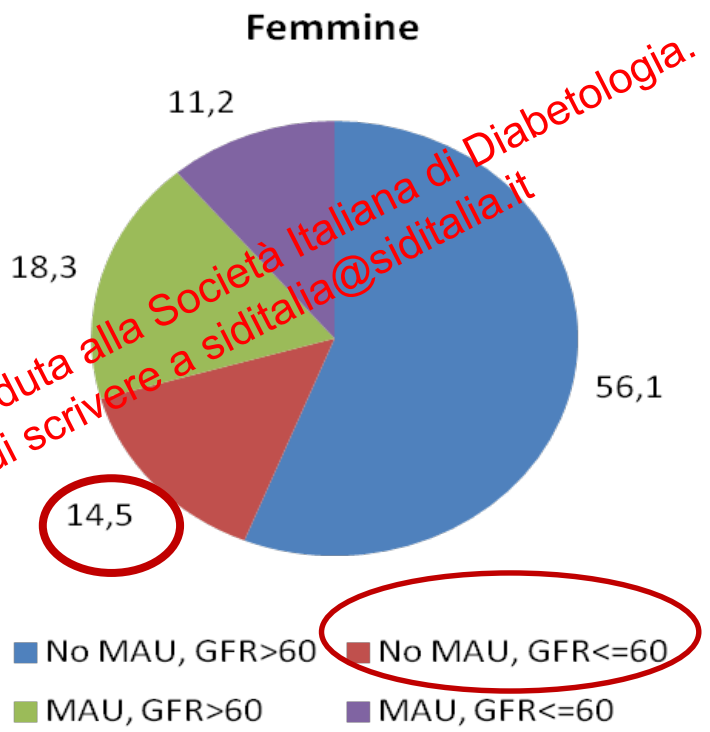


Figure 1. Multivariate relative risk ratios (RRRs) with their 95% confidence intervals (95% CIs) to develop estimated glomerular filtration rate <60 mL/min/1.73 m^2 (Alb−/eGFR+) = albuminuria (Alb+/eGFR−) = or both (Alb+/eGFR+). Antidiabetic therapy was analyzed by using oral antidiabetic drugs as reference category. Analysis performed by using a multinomial logistic regression model with the missing indicator method for each incomplete variable.

De Cosmo, Russo, et al, 2016

Distribuzione della popolazione divisa per *sesso* in relazione alla presenza di MAU e di riduzione del GFR (%)






Nephrol Dial Transplant (2014) 29: 65[illegible]
doi: 10.1093/ndt/gft506
Advance Access [illegible] January 2014

Kidney dysfunction and related cardiovascular risk factors among patients with type 2 diabetes

Salvatore De Cosmo[1], Maria Chiara Rossi[2], Fabio Pellegrini[3], Giuseppe Lucisano[3], Simonetta Bacci[1], Sandro Gentile[3], Antonio Ceriello[4], Giuseppina Russo[5], Antonio Nicolucci[2], Carlo Giorda[6], Francesca Viazzi[7], Roberto Pontremoli[7] and the AMD-Annals Study Group

I dati raccolti nel corso della normale pratica clinica da 251 Servizi di Diabetologia diffusi sull'intero territorio nazionale

415.346 soggetti con diagnosi di diabete di tipo 2 (DM2) sono stati visti nel corso dell'anno 2009.

I dati raccolti mediante cartella clinica informatizzata e costituzione del File Dati AMD.

Risk of coronary artery disease and stroke according to *sex* and presence of diabetic nephropathy in type 1 diabetes

Valma Harjutsalo PhD ,Merlin C Thomas PhD ,,Carol Forsblom DMSc ,Per-Henrik Groop DMSc, On Behalf of the FinnDiane Study Group

FinnDiane

Materials and Methods
The study included 4410 people with T1D from the Finnish Diabetic Nephropathy Study (FinnDiane), divided by DN status, and a control population of 12 434 people without diabetes. CVD events were identified from the Finnish nationwide health registries. Cumulative incidences for CAD and stroke were calculated and standardized incidence ratios (SIRs) were estimated between participants with T1D and the control group, stratified by DN status and sex.

Results

The cumulative incidence rates of CAD and stroke were similar in men and women within different nephropathy groups. The standardized incidence ratios for CAD was 7.5 (95% confidence interval [CI] 6.9-8.2), 17.2 (95% CI 14.9-19.5) in women and 5.3 (95% CI 4.7-5.9) in men.
The SIR for stroke was 5.0 (95% CI 4.3-5.5), similar in men and women.

Conclusions

Although the excess CVD risk is several-fold greater in women compared to men, the absolute CVD risk in men and women was equal when nephropathy was taken into account

DIABETES, OBESITY AND METABOLISM
A JOURNAL OF PHARMACOLOGY AND THERAPEUTICS

Journal of Diabetes and Its Complications 30 (2016) 227–236

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: WWW.JDCJOURNAL.COM

Cardiovascular and all-cause mortality in patients with type 2 diabetes mellitus in the MADIABETES Cohort Study: Association with chronic kidney disease

o-Fort [a,b,c,*], Francisco Javier San Andrés-Rebollo [d], Carmen de Burgos-Lunar [b,c,e], s-Herranz [a,b], Enrique Carrillo-de-Santa-Pau [f], Rosa María Chico-Moraleja [g], cía [h], Ana López-de-Andrés [h], belo [b,i], On behalf of MADIABETES Group

DM2

MAU e lowGFR sono associati in modo INDIPENDENTE all'incidenza di eventi CVD nel DM2, con un peso diverso in uomini e donne

Aims: To determine the effect of CKD and CKD stage according to eGFR and albuminuria categories on all-cause and cardiovascular mortality after a **5-year follow-up.**

Methods: Prospective cohort study of **3443 outpatients with type 2 diabetes mellitus.**

Table 4
Hazard ratios for all-cause mortality for CKD at baseline and albuminuria (Model 1) and CKD risk (Model 2).

A. For the overall sample (n = 3407).

	Variables		aHR[a] (95% CI)	p value
Model 1	**CKD at baseline**, *Yes*	*With LDL C =114 mg/dl (p50)*	1.72 (1.39–2.13)	<0.01
		With LDL C =135 mg/dl (p75)	2.11 (1.61–2.76)	<0.01
		With LDL C =153 mg/dl (p90)	3.59 (2.03–6.36)	<0.01
	Albuminuria, *Yes (ref. no)*		1.23 (0.94–1.61)	0.13

B. Stratified by gender (men, n = 1713; women, n = 1694).

Model 1		**Men**		
	CKD at baseline, *Yes (ref. no)*		1.44 (1.07–1.93)	0.02
	Albuminuria, *Yes (ref. no)*		1.28 (0.91–1.81)	0.16
		Women		
	CKD at baseline, *Yes (ref. no)*		1.95 (1.43–2.67)	<0.01
	Albuminuria, *Yes (ref. no)*		1.14 (0.73–1.80)	0.56

Conclusions: CKD at baseline is an independent risk factor for all-cause and cardiovascular mortality in the overall cohort, men and women, or in primary and secondary prevention of coronary heart disease. Albuminuria is an independent risk factor for all-cause and cardiovascular mortality only in primary prevention.

Clin J Am Soc Nephrol 10: 1921–1929, November, 2015

Article

Serum Uric Acid and Risk of CKD in Type 2 Diabetes

Salvatore De Cosmo, Francesca Viazzi, Antonio Pacilli, Carlo Giorda, Antonio Ceriello, Sandro Gentile, Giuseppina Russo, Maria C. Rossi, Antonio Nicolucci, Pietro Guida, Daniel Feig, Richard J. Johnson, Roberto Pontremoli, and the AMD-Annals Study Group

ORs for developing DKD by quintiles of sex-specific uric acid levels

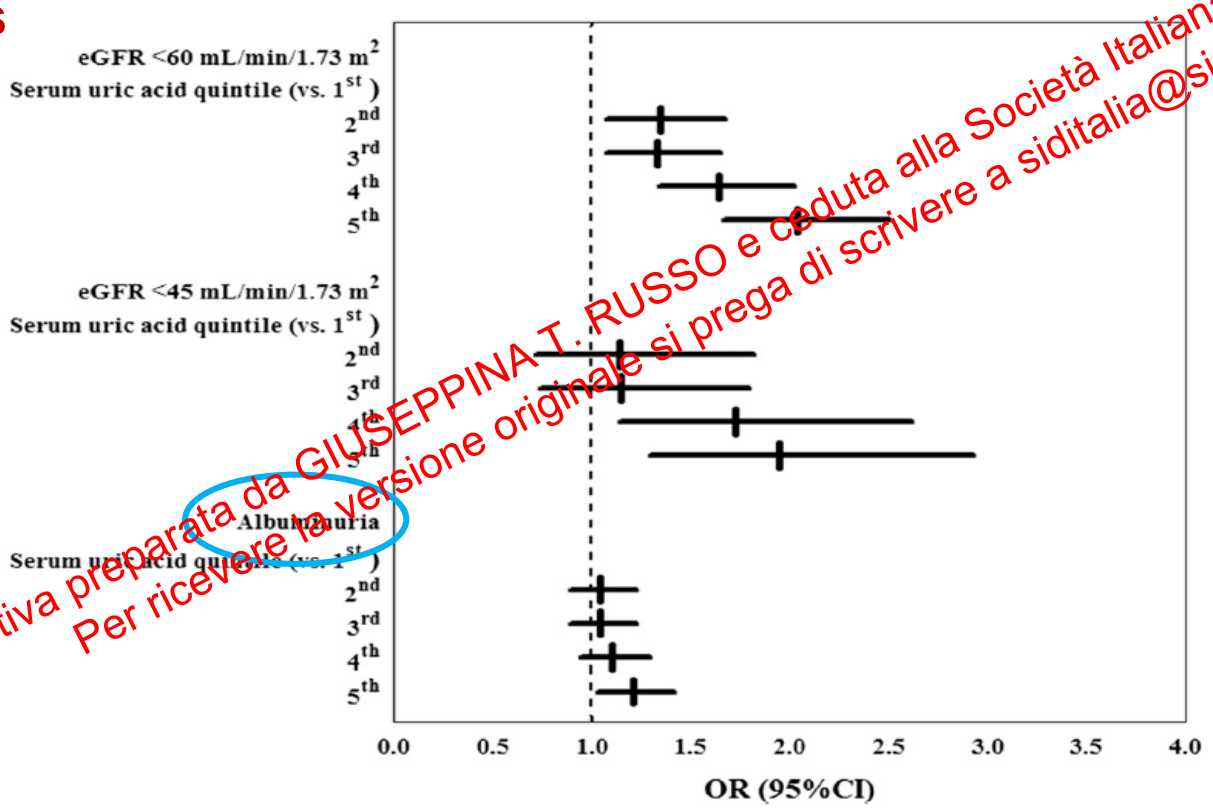


Figure 1. | The graded relationship of serum uric acid (SUA) with the development of incident low eGFR and albuminuria in type 2 diabetes. Odds ratios (ORs) with their 95% confidence intervals (95% CIs) for eGFR <60 or <45 ml/min per 1.73 m^2 and albuminuria onset by sex-specific quintile of serum uric acid adjusted for baseline eGFR. The first serum uric acid quintile was considered as reference category.

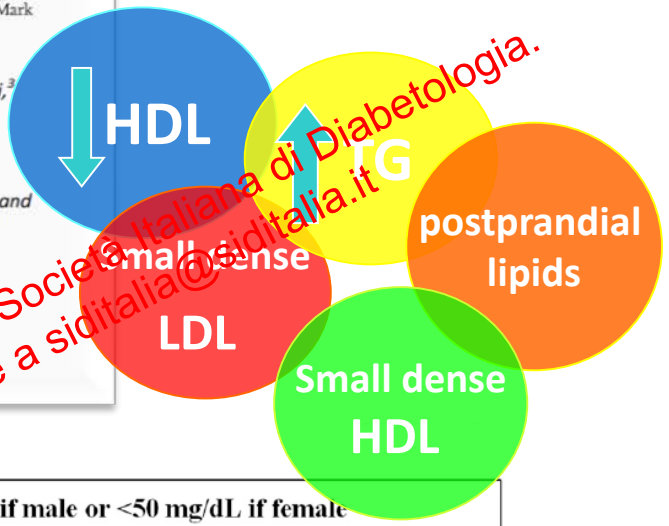
De Cosmo, Russo,et al, CJASN 2015

Diabetes Care Volume 39, December 2016 1

Plasma Triglycerides and HDL-C Levels Predict the Development of Diabetic Kidney Disease in Subjects With Type 2 Diabetes: The AMD Annals Initiative

Giuseppina T. Russo,[1] Salvatore De Cosmo,[2] Francesca Viazzi,[3] Antonio Pacilli,[2] Antonio Ceriello,[4,5] Stefano Genovese,[5] Pietro Guida,[6] Carlo Giorda,[7] Domenico Cucinotta,[1] Roberto Pontremoli,[3] Paola Fioretto,[8] and the AMD-Annals Study Group

Diabetes Care 2016;39:1–10 | DOI: 10.2337/dc16-1246



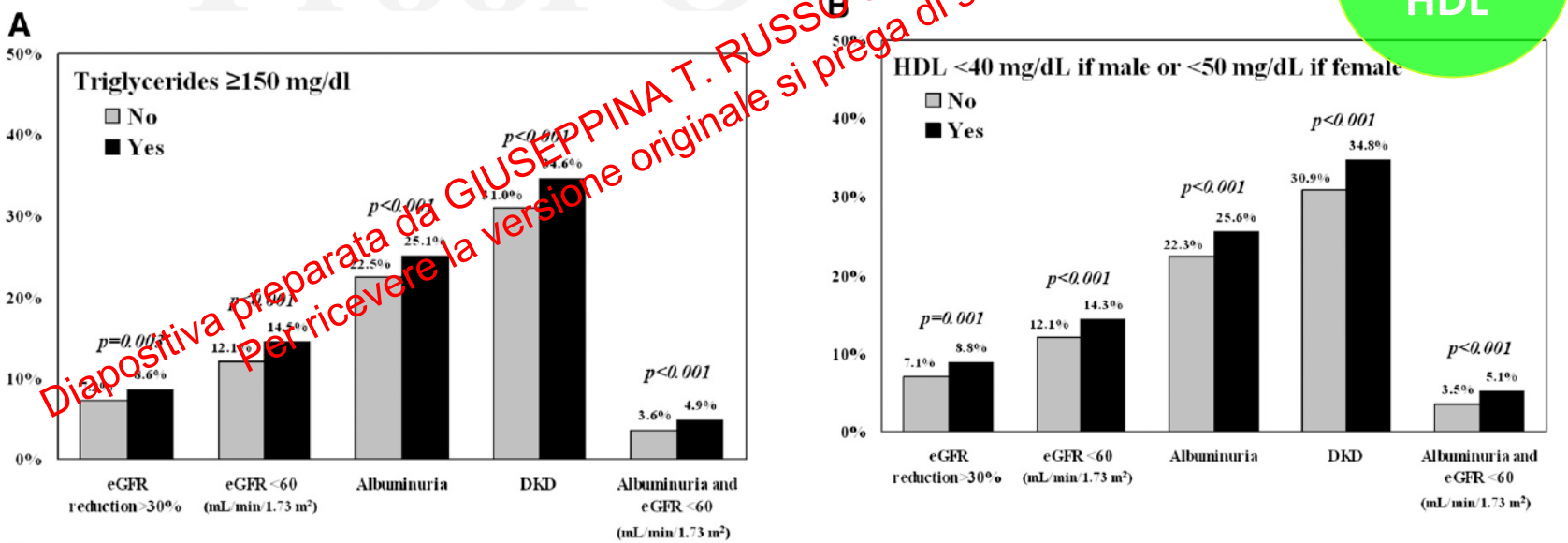


Figure 1—*A*: DKD incidence according to baseline TG ≥150 mg/dL. *B*: DKD incidence according to baseline HDL-C (<40 mg/dL in men; <50 mg/dL in women).

Russo GT, Pontremoli R, Cucinotta D, De Cosmo et al, *Diabetes Care 2016*

RESEARCH ARTICLE

Hypertriglyceridemia Is Independently Associated with Renal, but Not Retinal Complications in Subjects with Type 2 Diabetes: A Cross-Sectional Analysis of the Renal Insufficiency And Cardiovascular Events (RIACE) Italian Multicenter Study

Giuseppe Penno[1], Anna Solini[1], Giacomo Zoppini[2], Cecilia Fondelli[3], Roberto Trevisan[4], Monica Vedovato[5], Gabriella Gruden[6], Olga Lamacchia[7], Antonio E. Pontiroli[8], Maura Arosio[9], Emanuela Orsi[10], Giuseppe Pugliese[11]*, for the Renal Insufficiency And Cardiovascular Events (RIACE) Study Group[¶]

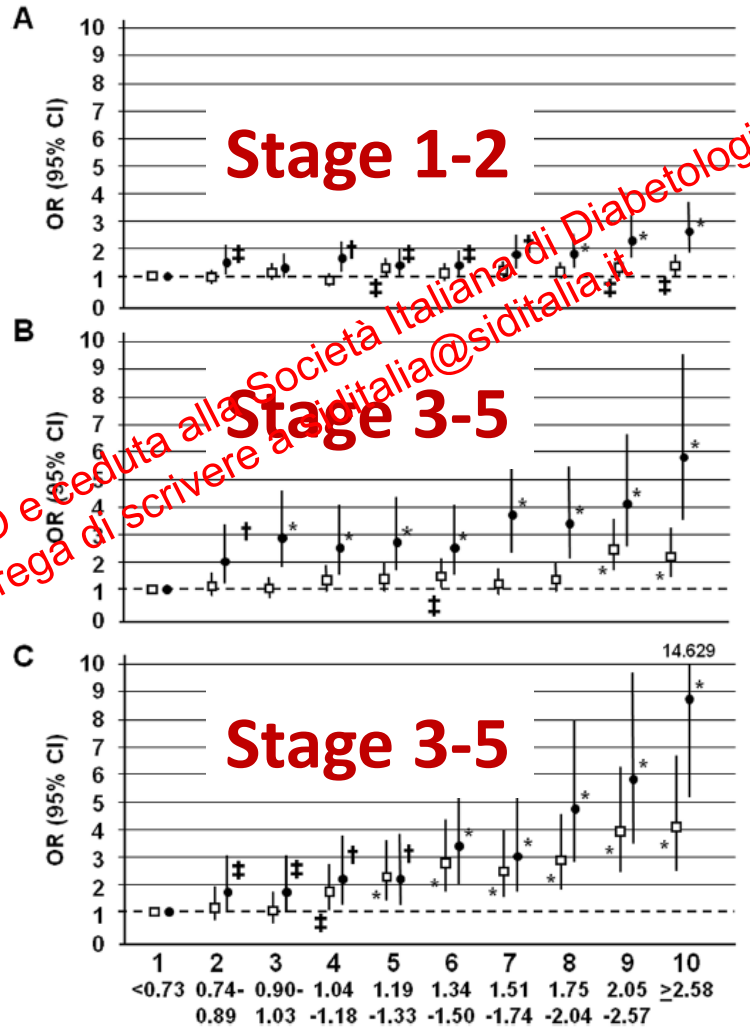
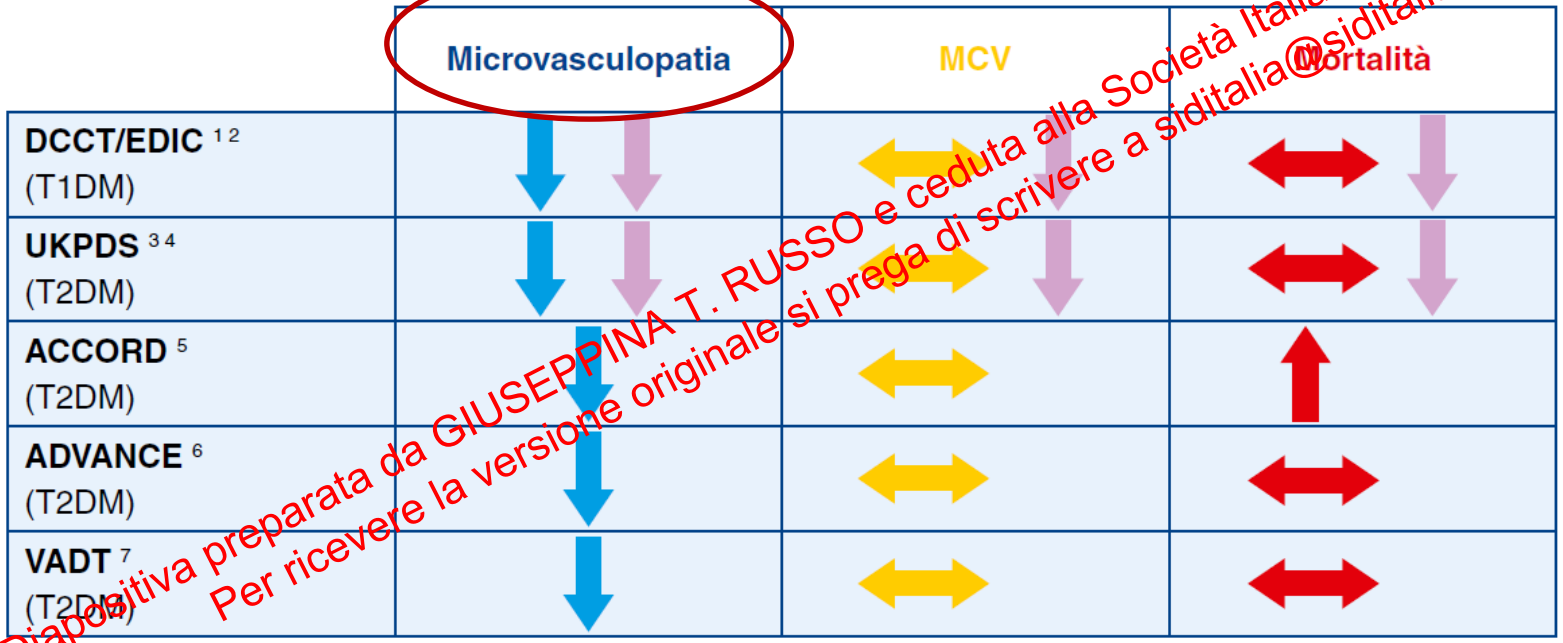


Fig 1. Adjusted risk of CKD Stages 1–2 (Panel A), CKD Stages 3–5 nonalbuminuric (Panel B) and CKD Stages 3–5 albuminuric (Panel C) (OR [95% CI]) according to deciles of triglyceride levels in subjects without (□) and with (•) statin treatment. ORs are adjusted for age, male gender, smoking status, diabetes duration, HbA_{1c}, BMI, HDL and LDL cholesterol, hypertension, and blockade of the renin-angiotensin system. Significant at * $P<0.0001$, † P at least <0.01, ‡ P at least <0.05.

doi:10.1371/journal.pone.0125512.g001

DKD : Quale è il Ruolo dell'iperglicemia?

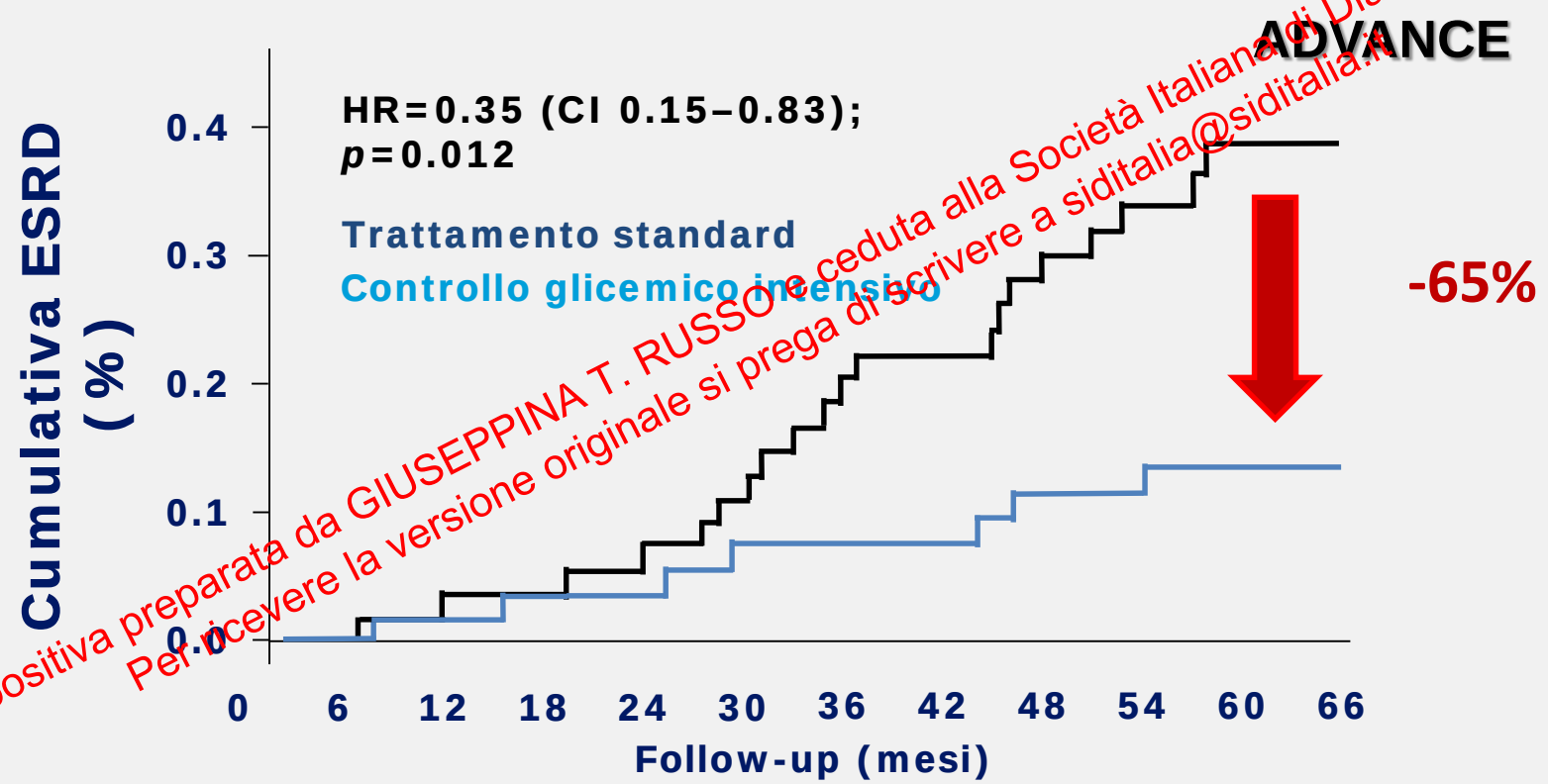
FIGURA 5. Impatto del trattamento intensivo della glicemia sulle complicanze: sintesi dei grandi trial.



[1] N Engl J Med 1993;329:977-86.
[2] N Engl J Med 2005;353:2643-53.
[3] Lancet 1998;352:837-53.
[4] N Engl J Med 2008;359:1577-89.
[5] N Engl J Med 2008;358:2545-59.
[6] N Engl J Med 2008;358:2560-72.
[7] N Engl J Med 2009;360:129-39.

T1DM: diabete mellito tipo 1; T2DM: diabete mellito tipo 2.

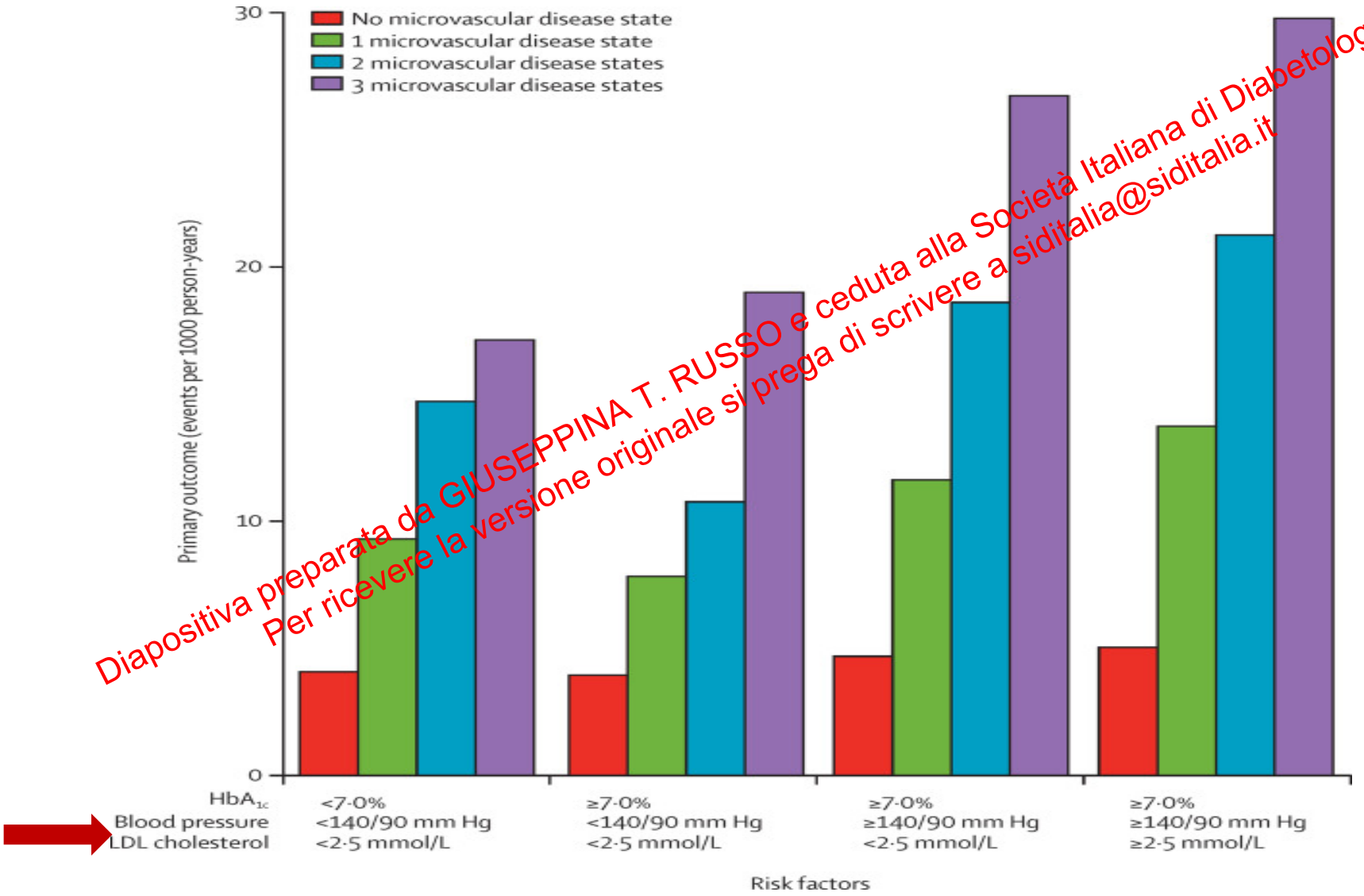
Un controllo glicemico intensivo riduce il rischio *di malattia renale terminale* nei pazienti diabetici



Perkovic V et al. *Kidney Int* 2013;83:517–523

CI: intervallo di confidenza; ESRD: malattia renale allo stadio terminale; HR: hazard ratio.

Adjusted event rates for the primary outcome by cumulative burden of microvascular disease and established risk factor goals



The Lancet Diabetes & Endocrinology, Volume 4, Issue 7, 2016, 588–597

Prevalence and progression of *subclinical atherosclerosis* in patients with chronic kidney disease and diabetes

Ana Palanca, Per-Henrik Groop et al.

ABSTRACT

Background and aims

This study aims to analyze the prevalence and progression of subclinical atherosclerosis in CKD patients with and without diabetes.

Methods

We included data from CKD patients with and without diabetes free from previous cardiovascular events from the **NEFRONA cohort.** Patients underwent **baseline and 24-month follow-up carotid and femoral ultrasound examinations.** Multivariable models were used to assess the contribution of diabetes to the **presence and plaque progression.**

Results

A total of 419 patients with diabetes and 1120 without diabetes were included.

At baseline, the proportion of patients with plaque was higher among diabetic patients (81.4% *vs.* 64.1%, $p < 0.001$).

Diabetic patients more frequently had more than two vascular territories with plaque (64.4% *vs.* 48.4%, $p < 0.001$).

ultivariable analysis indicated that plaque at baseline was significantly associated with age, gender, smoking and renal replacement therapy (RRT) in the non-diabetic patients,

but only with age and male gender in diabetic patients. Plaque progression was significantly associated with age, number of territories with basal plaque, smoking and RRT in both groups.

Conclusions

Subclinical atherosclerosis is more prevalent, carries a higher plaque burden and is more rapidly progressive in renal patients with diabetes. In these patients, diabetes outweighs other described risk factors associated with the presence of subclinical atherosclerosis.

Nutrition, Metabolism & Cardiovascular Diseases (2011) 21, 286–293

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/nmcd

Nutrition, Metabolism & Cardiovascular Diseases

ELSEVIER

DM2

Microangiopathy is independently associated with presence, severity and composition of carotid atherosclerosis in type 2 diabetes

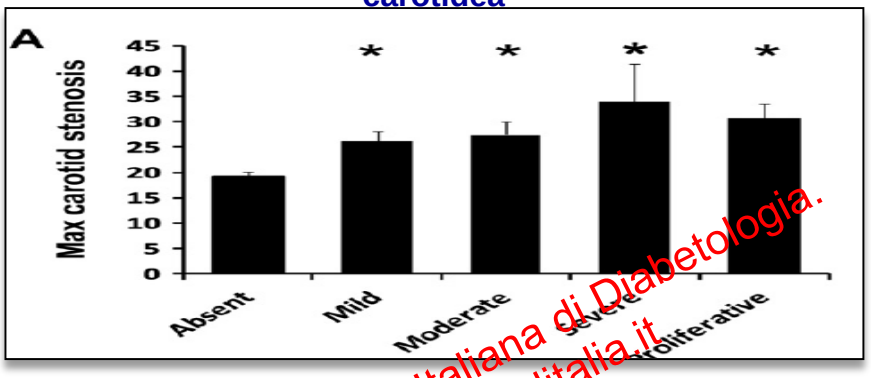
S. Vigili de Kreutzenberg [a,*], A. Coracina [a], A. Volpi [b], G.P. Fadini [a], A.C. Frigo [c], G. Guarneri [a], A. Tiengo [a], A. Avogaro [a]

Abstract *Background and aims:* Common mechanisms for the development of micro- and macroangiopathic diabetic complications have been suggested. We aimed to cross-sectionally investigate strength and characteristics of the association between carotid atherosclerosis and microangiopathy in type 2 diabetic patients.

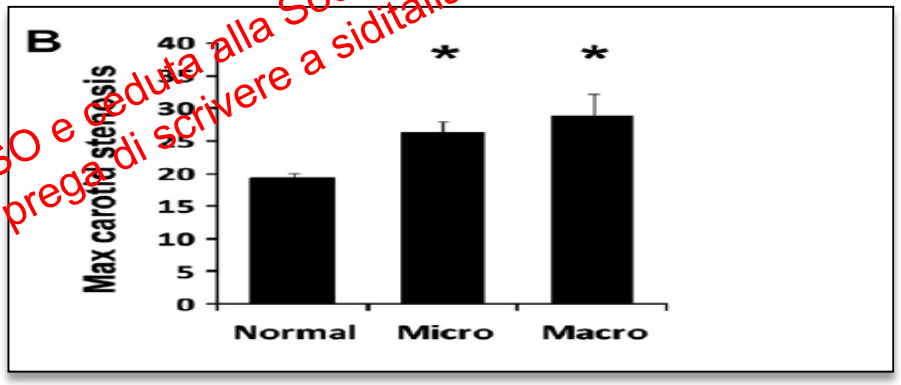
Methods and results: Common carotid artery intima–media thickness (cIMT), carotid plaque (CP) type and degree of stenosis were evaluated by ultrasound, along with the determination of anthropometric parameters, HbA1c, lipid profile, assessment of diabetic retinopathy and nephropathy, in 662 consecutive patients with type 2 diabetes mellitus (T2DM). Patients were divided according to high/low cIMT, presence/absence of CP and of retinopathy and nephropathy. Patients with CP were older, more prevalently males, past smokers, had longer diabetes duration, significantly lower HDL cholesterol and more prevalent ischemic heart disease (all $p < 0.05$) as compared to those with cIMT < 1 mm. Microangiopathies were more prevalent in patients with CP than in those without. At multivariate logistic regression, factors independently associated with the presence of CP were age, past smoke, HDL cholesterol, retinopathy and retinopathy plus nephropathy. A significant independent correlation of CP stenosis with stage of retinopathy and nephropathy was found. Finally, echolucent CPs were associated with a lower prevalence of proliferative retinopathy than CP containing calcium deposits.

Conclusion: In T2DM, retinopathy, alone or in combination with nephropathy, is independently associated to CP and severity of microangiopathy correlates with severity of carotid atherosclerosis. These observations, together with the different prevalence of proliferative retinopathy according to CP types, point to possible common pathogenic mechanisms in micro- and macrovascular complications.

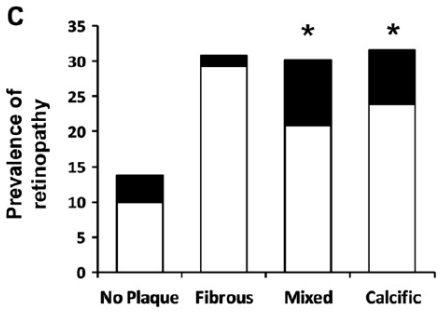
Correlazione tra stadio *RETINOPATIA* e stenosi carotidea

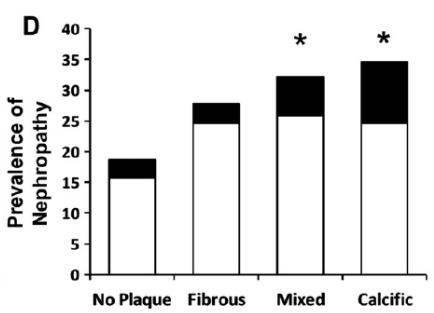


Correlazione tra stadio *NEFROPATIA* e stenosi carotidea



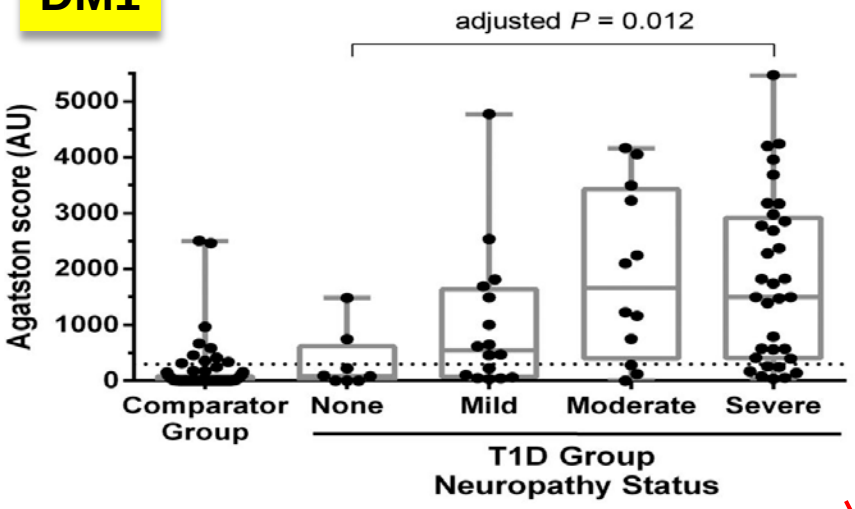
Composizione placca carotidea e RETINOPATIA (C) e NEFROPATIA (D)

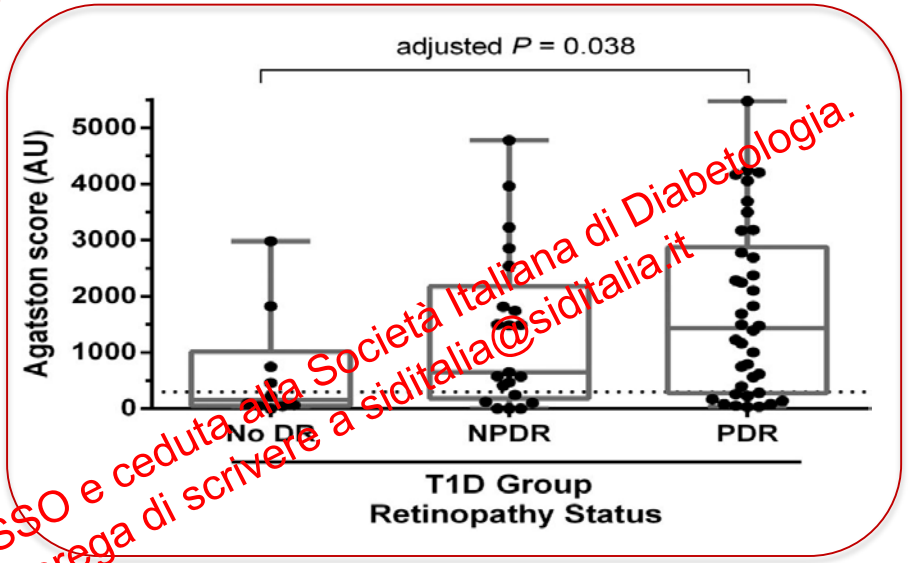


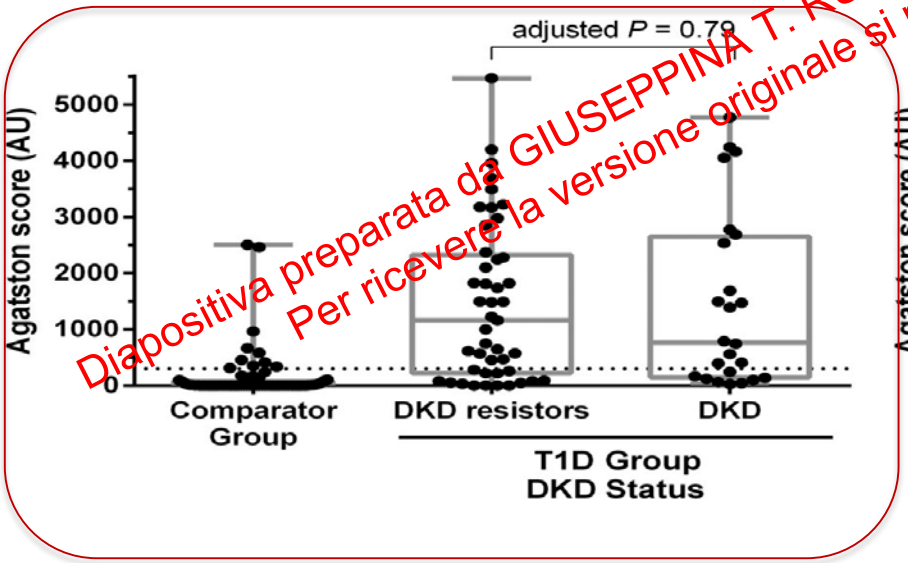


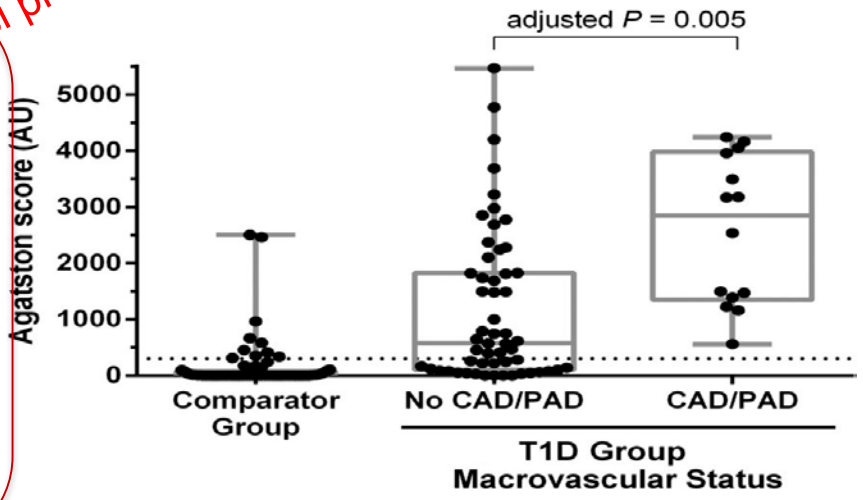
The distribution of Agatston scores stratified by the presence and severity of complication.

DM1







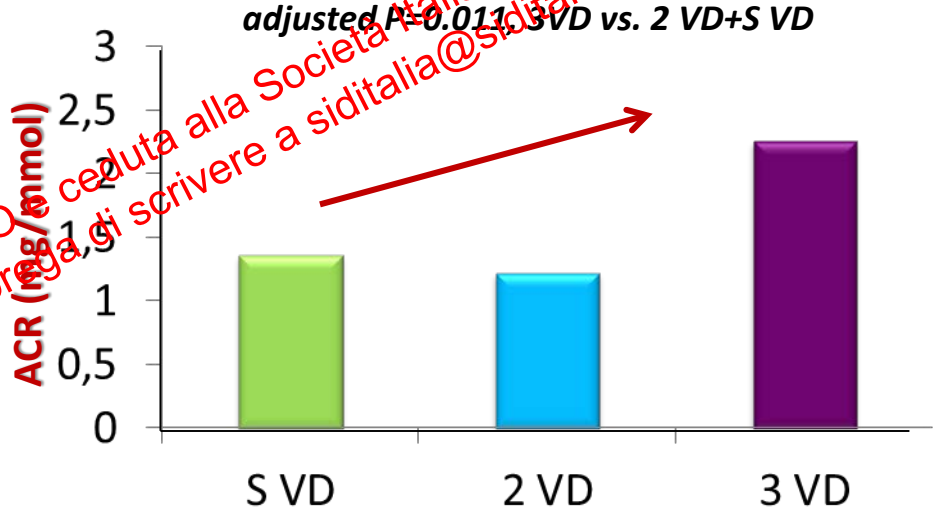


Julie A. Lovshin, D. Cherney et al. **Atherosclerosis and Microvascular Complications: Results From the Canadian Study of Longevity in Type 1 Diabetes.** Dia Care 2018;41:2570-2578

American Diabetes Association.

EGFR and ACR values according to the burden of coronary atherosclerosis.

N=208 patients, 69.3±11 yrs, N=97 T2DM



Atherosclerotic burden

M. D'Errico et al., Acta Diabetol. 2017

Diabetologia (2017) 60:2129–2138
DOI 10.1007/s00125-017-4360-x

REVIEW

La fisiopatologia delle complicanze, complessa in evoluzione

Vascular complications in diabetes: old messages, new thoughts

Josephine M. Forbes[1,2,3] · Amelia K. Fotheringham[1,4]

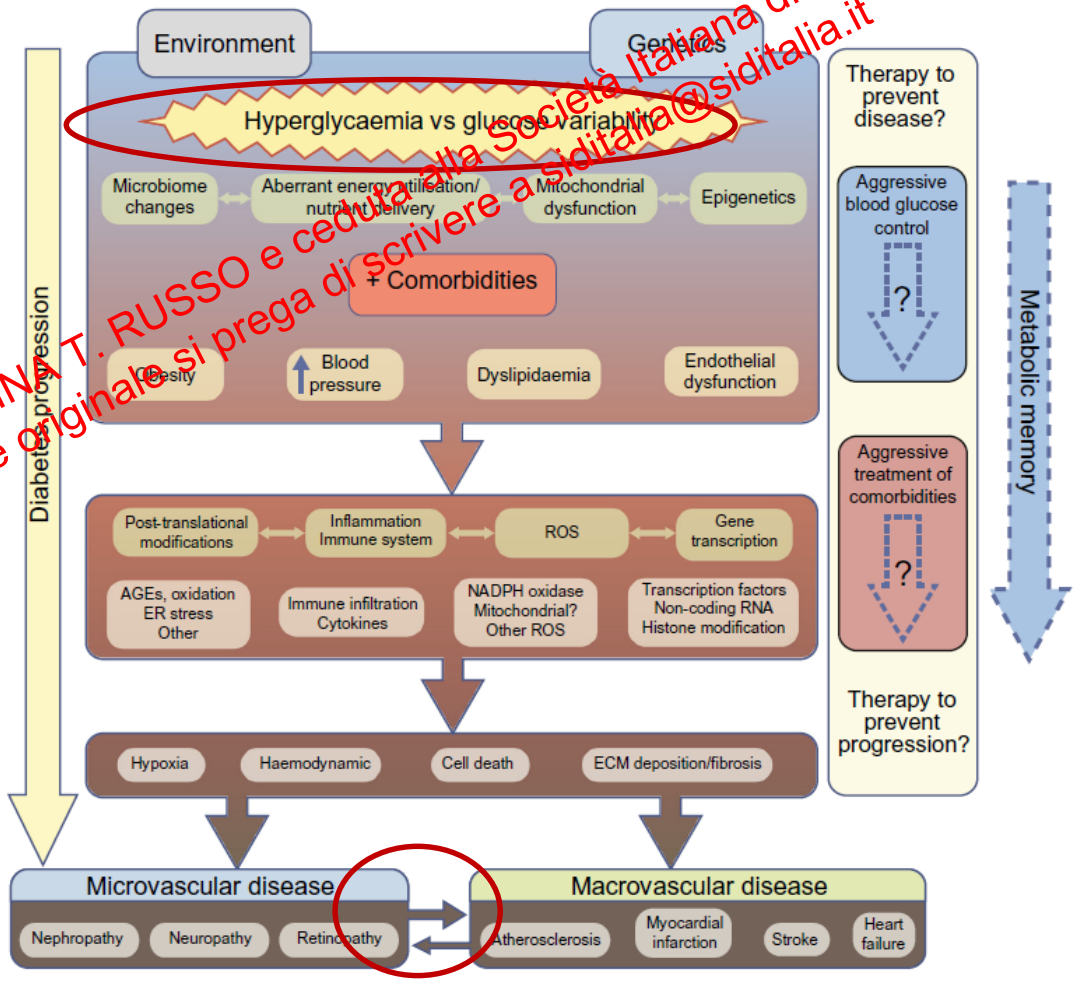
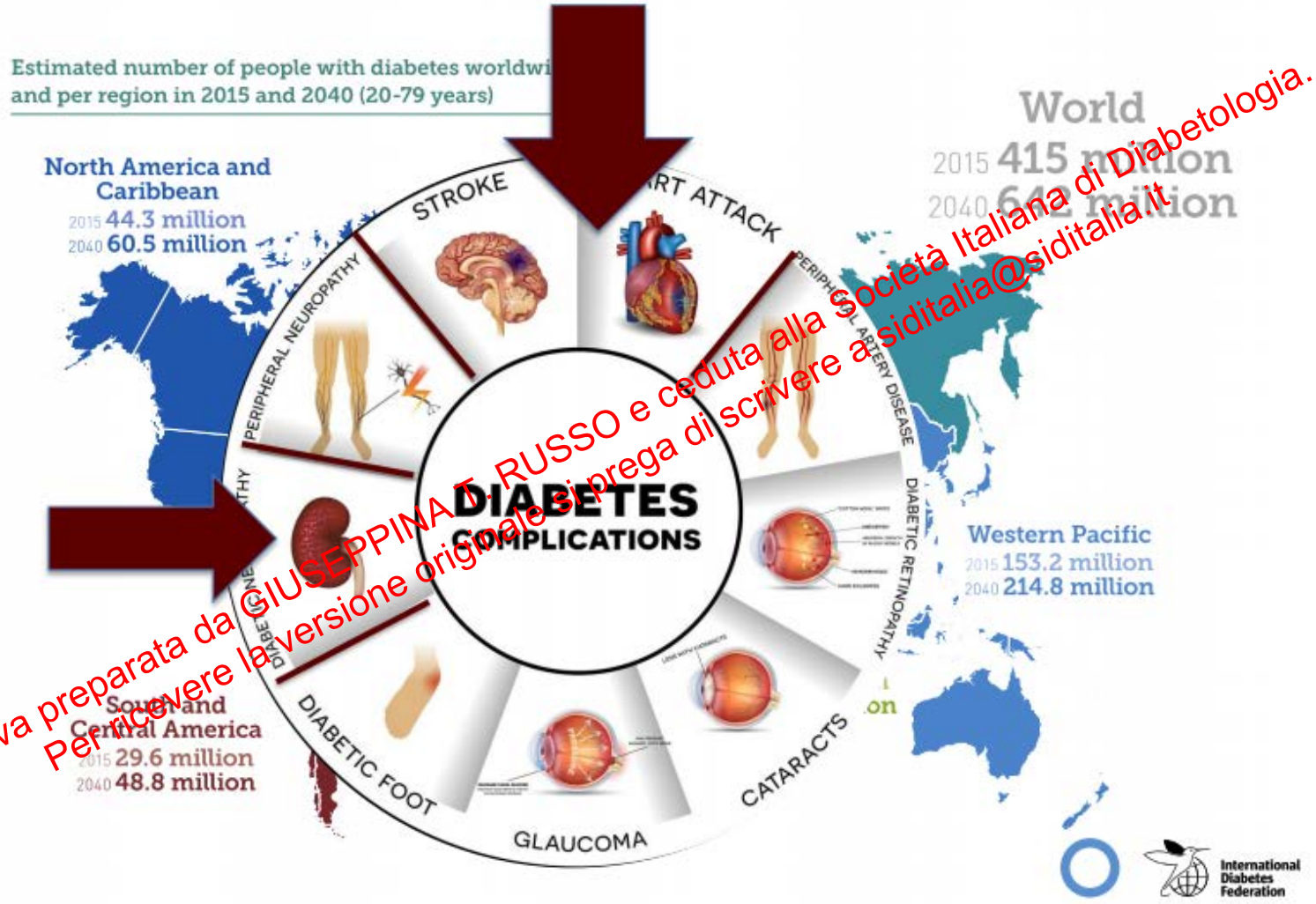


Fig. 1 Schematic representation of the pathways to diabetes complications discussed in this review and how they fit into current paradigms. Susceptibility to diabetes complications is driven by a combination of environmental factors (e.g. diet, lifestyle, microbiota, pathogen exposure) and genetic programming. With diabetes onset, many changes occur that are thought to be pathological, including involvement of pathways that have been explored recently and are highlighted in this review. These include the following: changes to the microbiome, potentially affecting substrate delivery and utilisation, gastrointestinal inflammation and permeability, release of intestinal toxins, neuroendocrine signalling and the immune system; aberrant energy utilisation, substrate delivery and nutrient flux, which can alter the metabolic pathways utilised by tissues affected by complications; mitochondrial dysfunction in the form of mitochondrial fission and fusion, decreased biogenesis, aberrant energy utilisation and delivery and, potentially, ROS generation; epigenetic changes, which alter the regulation of genes associated with pathological pathways. All these factors are likely to be exacerbated by the presence of comorbidities (obesity, raised blood pressure, dyslipidaemia, endothelial dysfunction), initiating a downstream cascade of interacting pathways, ultimately resulting in microvascular and macrovascular complications. These pathways include post-translational modifications (AGE formation, oxidation of proteins and lipids and ER stress), inflammation and immune dysregulation (increases in inflammatory cytokines, chemoattractant molecules and ultimately immune cell infiltration), ROS production, and gene expression and transcription. Current therapeutic strategies include intensive blood glucose control and treatment of comorbidities, with the former appearing to be more effective early in disease development. The paucity of therapies that actually prevent or reverse complications once they are established remains one of the major challenges posed by the global diabetes pandemic. ECM, extracellular matrix; ER, endoplasmic reticulum

Per prevenire l'insorgenza e la progressione di CVD e DKD serve un vero cambiamento…



Nuova definzione del *team* che assiste il paziente con DM

DOCTORS TEAM

Nefrologi + Diabetologi + Cardiologi

Grazie per l'attenzione

Importance of risk factors in CVD in Diabetes

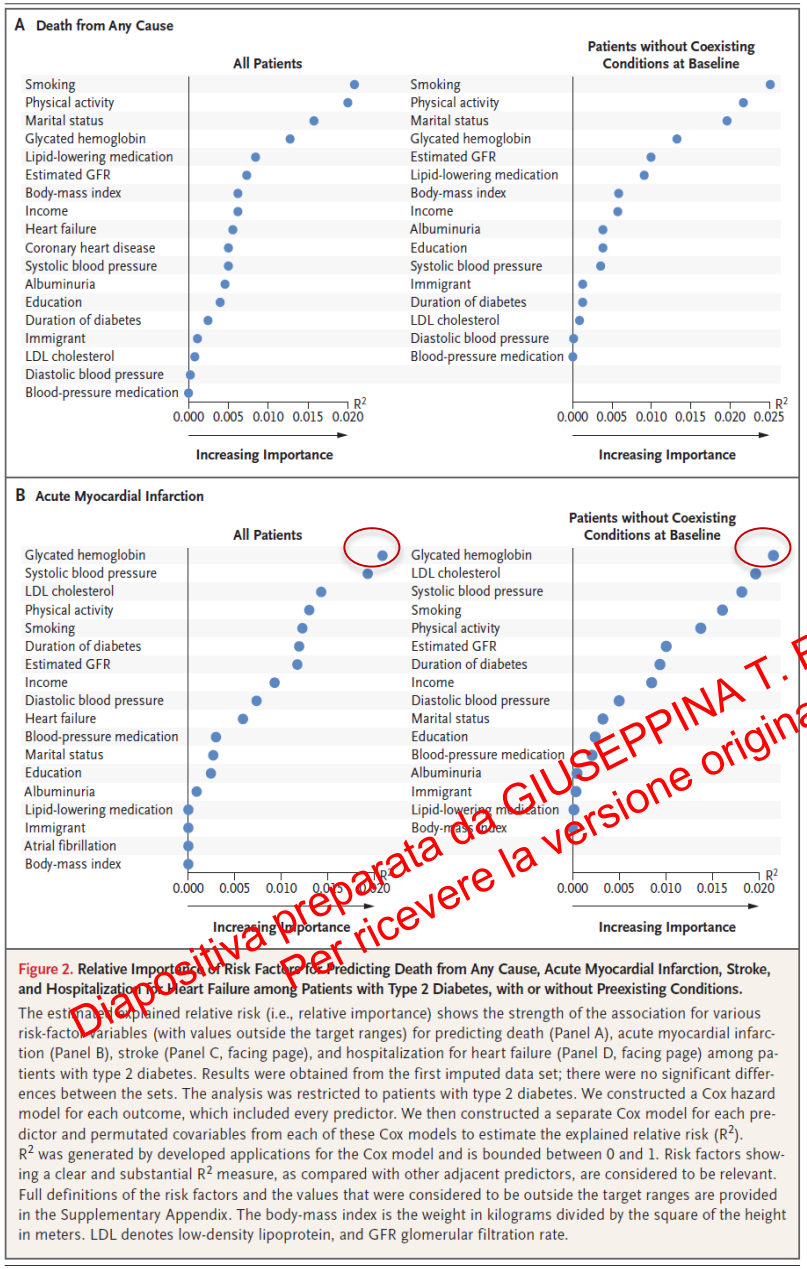


Figure 2. Relative Importance of Risk Factors for Predicting Death from Any Cause, Acute Myocardial Infarction, Stroke, and Hospitalization for Heart Failure among Patients with Type 2 Diabetes, with or without Preexisting Conditions.

The estimated explained relative risk (i.e., relative importance) shows the strength of the association for various risk-factor variables (with values outside the target ranges) for predicting death (Panel A), acute myocardial infarction (Panel B), stroke (Panel C, facing page), and hospitalization for heart failure (Panel D, facing page) among patients with type 2 diabetes. Results were obtained from the first imputed data set; there were no significant differences between the sets. The analysis was restricted to patients with type 2 diabetes. We constructed a Cox hazard model for each outcome, which included every predictor. We then constructed a separate Cox model for each predictor and permutated covariables from each of these Cox models to estimate the explained relative risk (R^2). R^2 was generated by developed applications for the Cox model and is bounded between 0 and 1. Risk factors showing a clear and substantial R^2 measure, as compared with other adjacent predictors, are considered to be relevant. Full definitions of the risk factors and the values that were considered to be outside the target ranges are provided in the Supplementary Appendix. The body-mass index is the weight in kilograms divided by the square of the height in meters. LDL denotes low-density lipoprotein, and GFR glomerular filtration rate.