Il dr. ROBERTO TREVISAN dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- NOVO
- SANOFI
- LILLY
- NOVARTIS
- ASTRA ZENECA
- MEDTRONIC
- MERCK
- TAKEDA
- BOEHRINGER

Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).

Riduzione delle complicanze croniche nel diabete di tipo 1: a che punto siamo?

Roberto Trevisan

Direttore UOC Malattie Endocrine – Diabetologia

ASST – Papa Giovanni XXIII, Bergamo

Sistema Socio Sanitario
Ospedale Papa Giovanni XXIII
Regione Lombardia
ASST Papa Giovanni XXIII

Agenda

- A che punto siamo?
- Il ruolo dell'inibizione del RAS
- Il controllo della glicemia
- Non solo microangiopatia
- La terapia con microinfusori
- Prospettive future

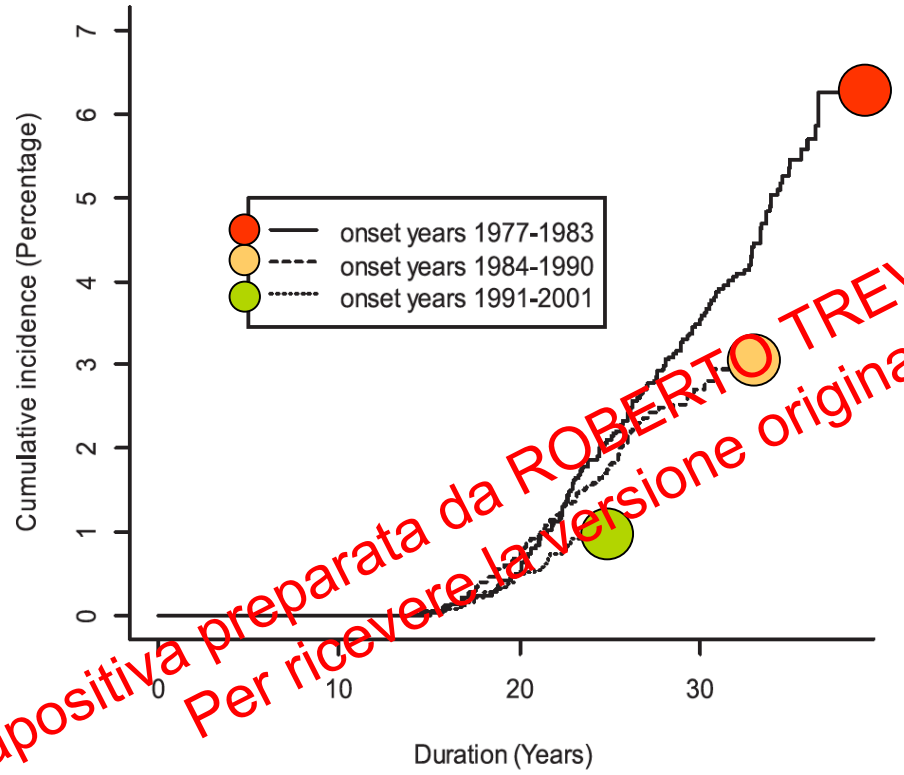
Large-scale studies on prediction and prevention of complications associated with type 1 diabetes

	Complications assessed	Main findings
Diabetes Control and Complications Trial (DCCT)/Pittsburgh Epidemiology of Diabetes Complications study (2009)[112]	Cardiovascular disease, nephropathy, retinopathy	The frequencies of serious complications in patients with type 1 diabetes, especially when treated intensively, are lower than those reported historically
Finnish Diabetic Nephropathy (FinnDiane) Study (2009)[113]	Cardiovascular disease, nephropathy	In patients with type 1 diabetes, variations in glycated haemoglobin concentration predicted the incidence of microalbuminuria and progression to renal disease, and incidence of cardiovascular disease
DCCT/ Epidemiology of Diabetes Interventions and Complications (EDIC) study (2011)[114]	Nephropathy	In patients with type 1 diabetes and persistent microalbuminuria, intensive glycaemic control, blood pressure control, and favourable lipid panels lead to fewer long-term renal complications
FinnDiane (2009)[115]	Nephropathy	An independent and graded association exists between the presence and severity of kidney disease and premature mortality in type 1 diabetes
Genetics of Diabetes in Kidney Collection (2009)[116]	Nephropathy	Identified genes associated with susceptibility to diabetic nephropathy, near the *FRMD3* and *CARS* loci
Swedish Renal Registry (2010)[117]	Nephropathy	Substantial differences in risk for nephropathy in male versus female patients with type 1 diabetes, with age at diagnosis an important factor (early diagnosis lowers risk)
DCCT/EDIC (2009)[118]	Autonomic neuropathy	Patients given intensive insulin therapy had less cardiac autonomic neuropathy than those who received conventional treatment
Acetyl-L-carnitine Clinical Trials (2009)[119]	Neuropathy	Raised triglycerides correlate with progression of diabetic neuropathy
DCCT/EDIC (2008)[120]	Retinopathy	Intensive insulin therapy (*vs* conventional therapy) reduces development and progression of diabetic retinopathy, with a treatment-related difference (metabolic memory) continuing for at least 10 years
Diabetic REtinopathy Candesartan Trials (DIRECT; 2008)[121]	Retinopathy	The angiotensin receptor blocker, candesartan, reduces retinopathy development but does not stop retinopathy progression

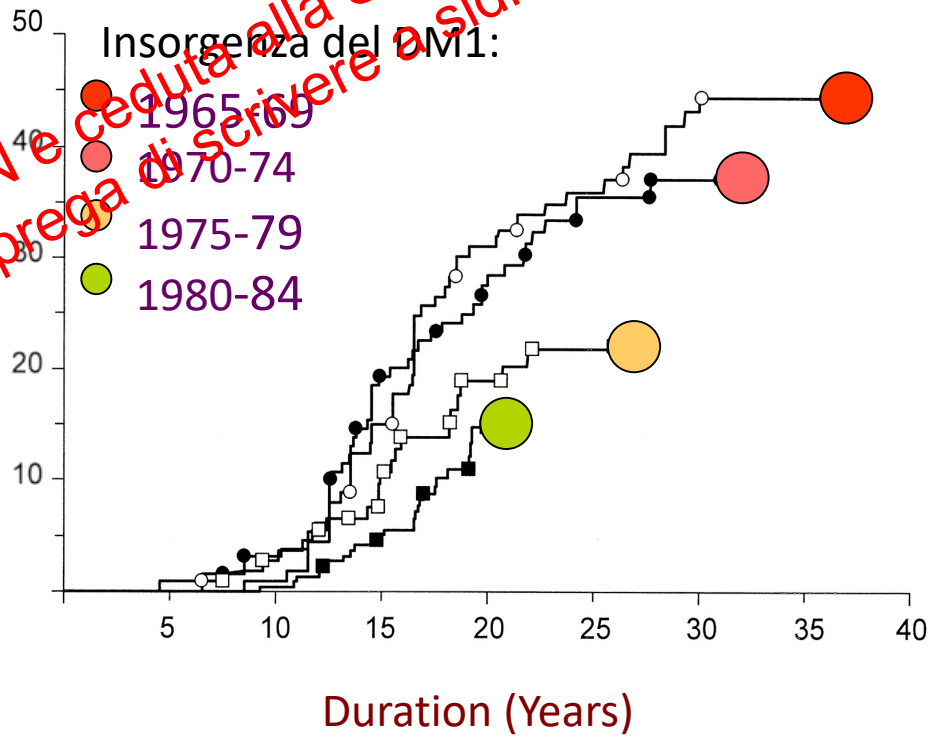
The Lancet 2015

Epidemiologia della nefropatia nel diabete di tipo 1

Cumulative incidence of **ESRD** due to type 1 diabetes (%)



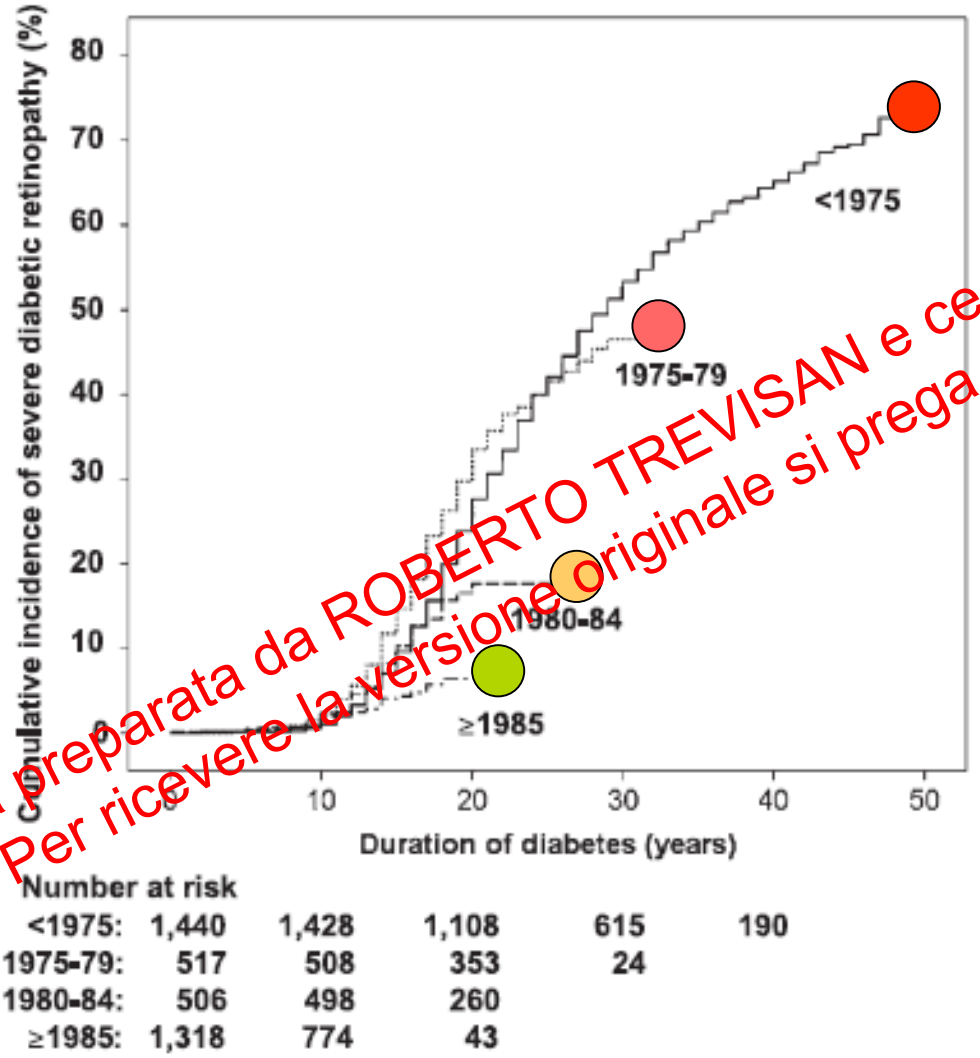
Cumulative incidence of **Diabetic Nephropathy** due to type 1 diabetes (%)



Toppe C et al. Diabetes Care 2019;42:27–31

Hovind P et al. Diabetes Care 2003; 26:1258-1264

Epidemiologia di retinopatia nel diabete di tipo 1: The FinnDiane Study

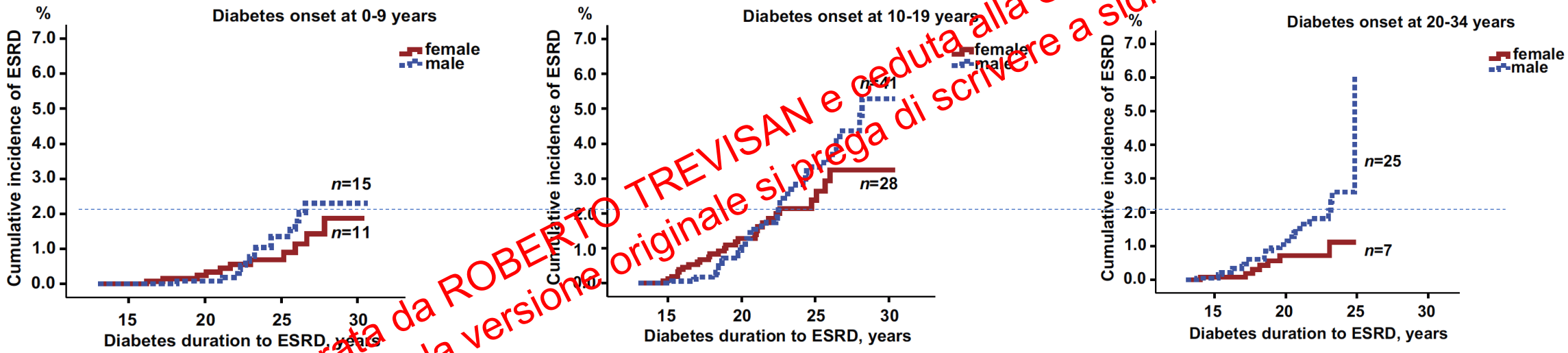


Incidenza cumulativa della retinopatia diabetica avanzata ("sight-threatening") in pazienti con DM1 per durata di diabete e periodo di diagnosi

Kyto JP et al. Diabetes Care 2011; 2005-2007

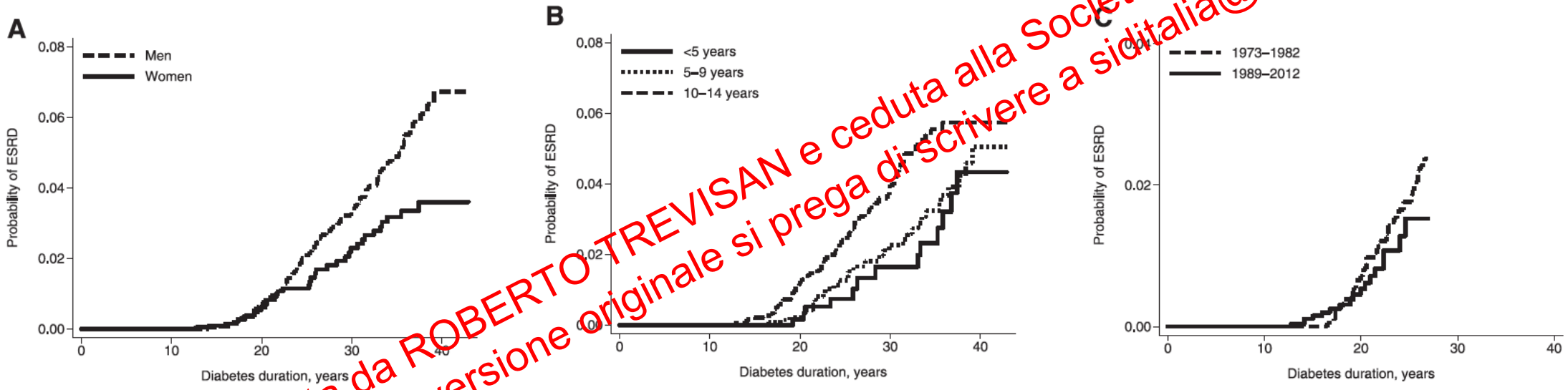
A Nationwide Population-Based Cohort Study

Cumulative incidences of developing ESRD in male and female patients with type 1 diabetes onset at 0–9, 10–19, and 20–34 years



Diabetes 59: 1803–1808, 2010

Low Incidence of End-Stage Renal Disease in Childhood-Onset Type 1 Diabetes Followed for Up to 42 Years

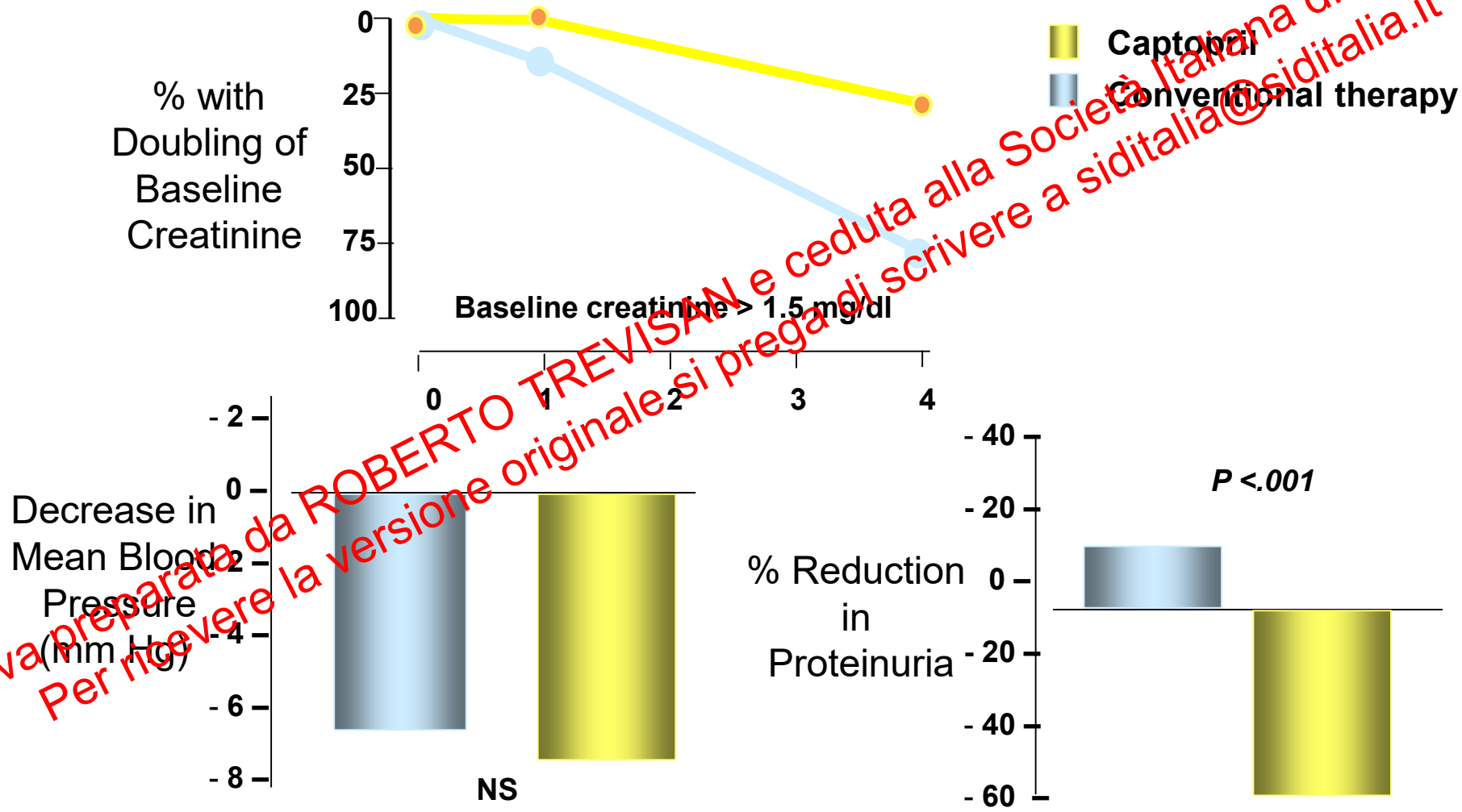


We report a very low incidence of ESRD among patients with childhood-onset diabetes in Norway. The risk was lower in women compared with men and in individuals in whom diabetes was diagnosed at a younger age.

Gagnum V et al., Diabetes Care 2018;41:420–425

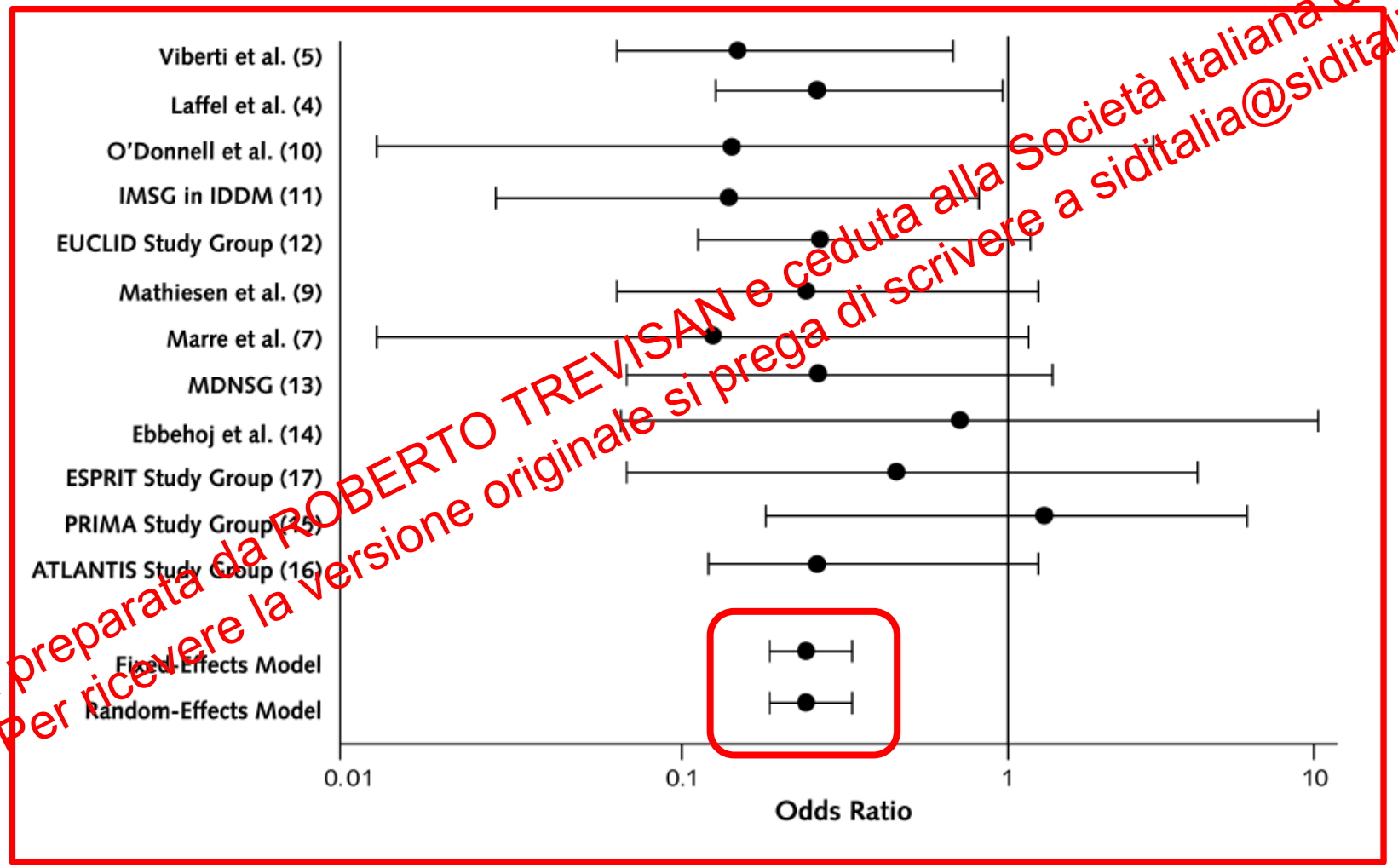
Il RUOLO DELL'INIBIZIONE DEL SISTEMA RENINA-ANGIOTENSINA

ACE-I IS BETTER THAN CONVENTIONAL THERAPY IN TYPE 1 DIABETES



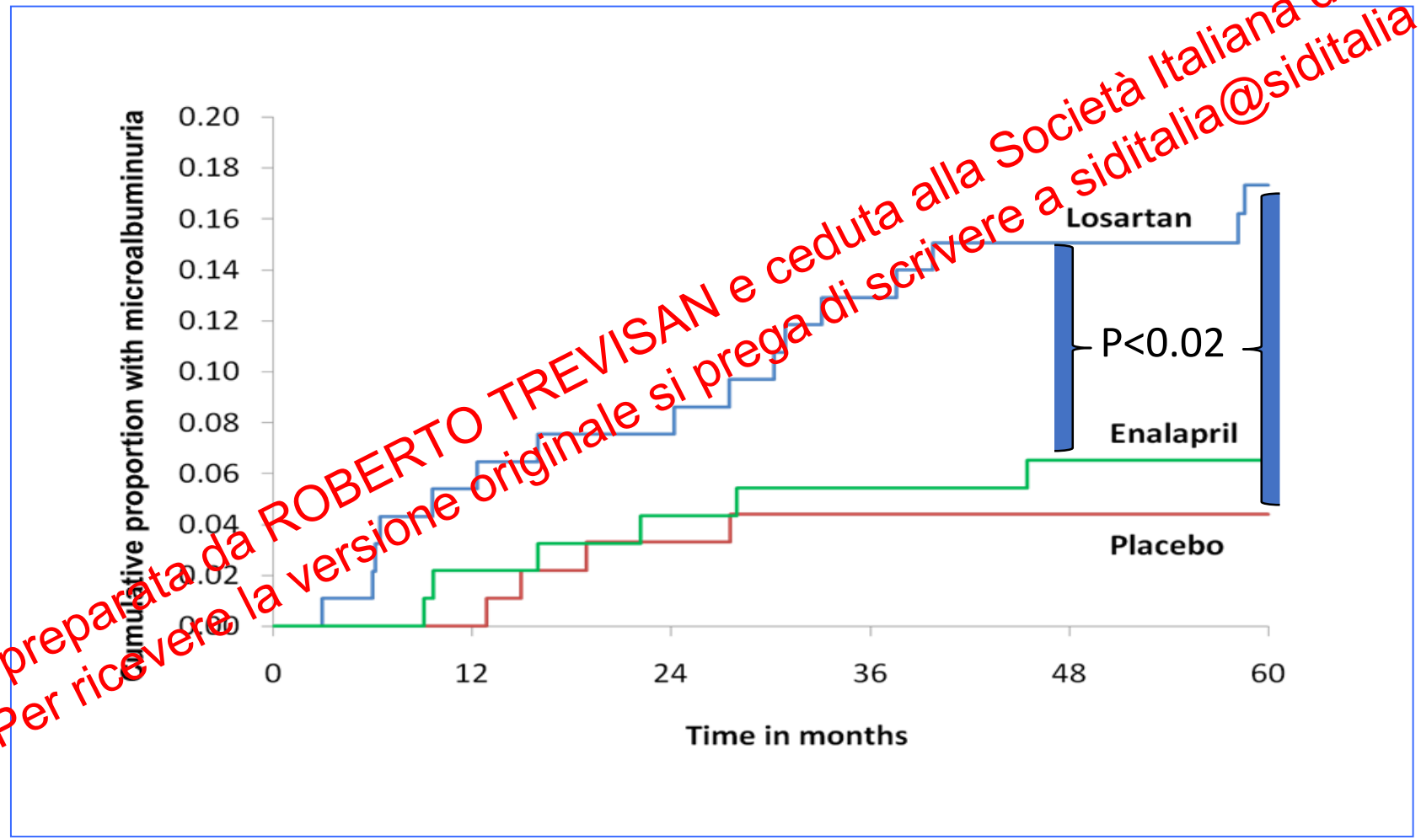
Lewis et al. N Engl J Med. 1993;329:1456-1462.

ACEI in Type 1 Diabetes and risk of progression from Microalbuminuria to Macroalbuminuria



ACEI in Nephropathy Study Group, Ann Intern Med, 2001

Cumulative proportion of Subjects Developing Microalbuminuria

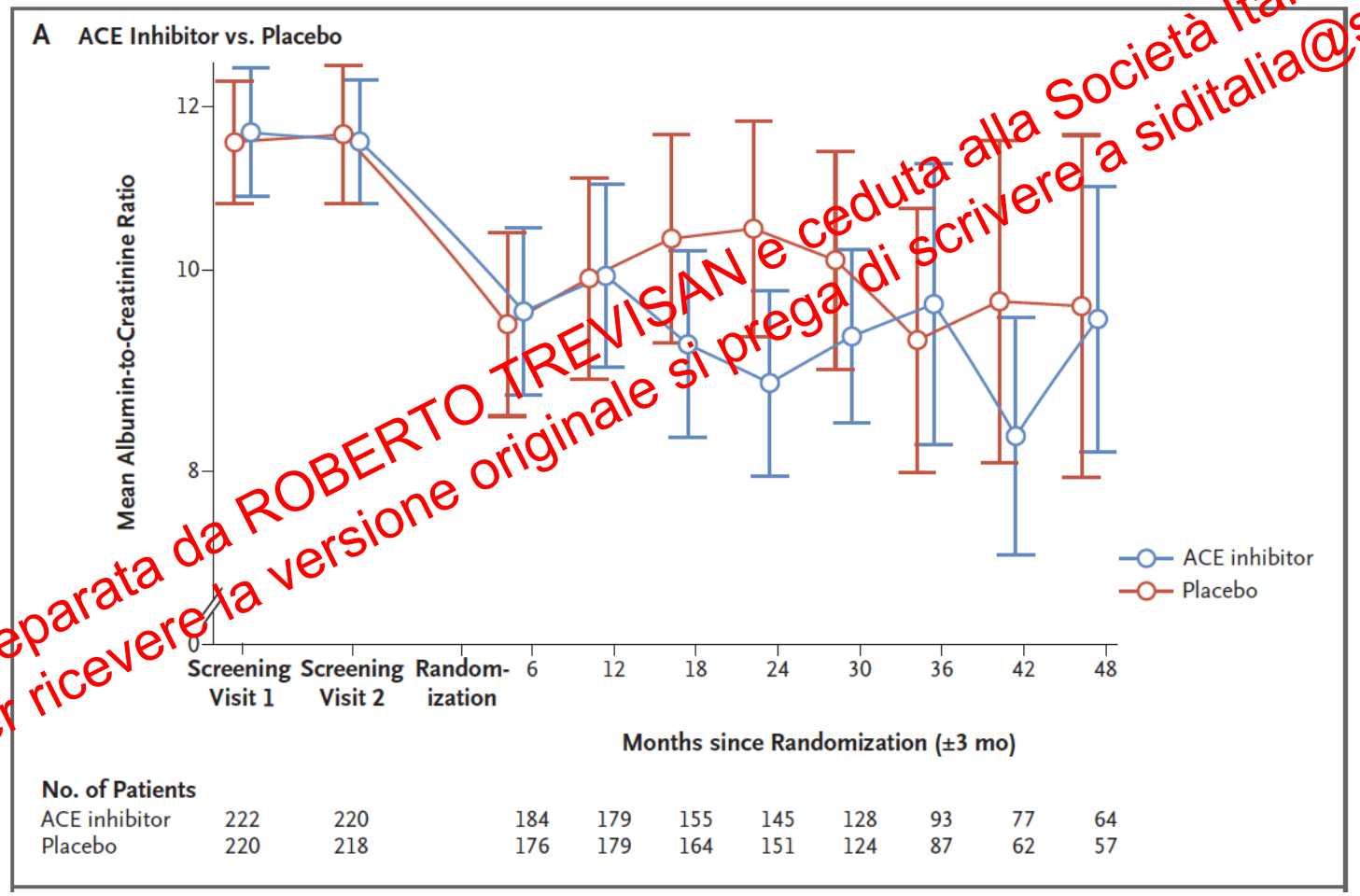


RASS Group

Mauer M, NEJM, 2009

Albumin-to-Creatinine Ratios and Cumulative Probability of Microalbuminuria during the Trial

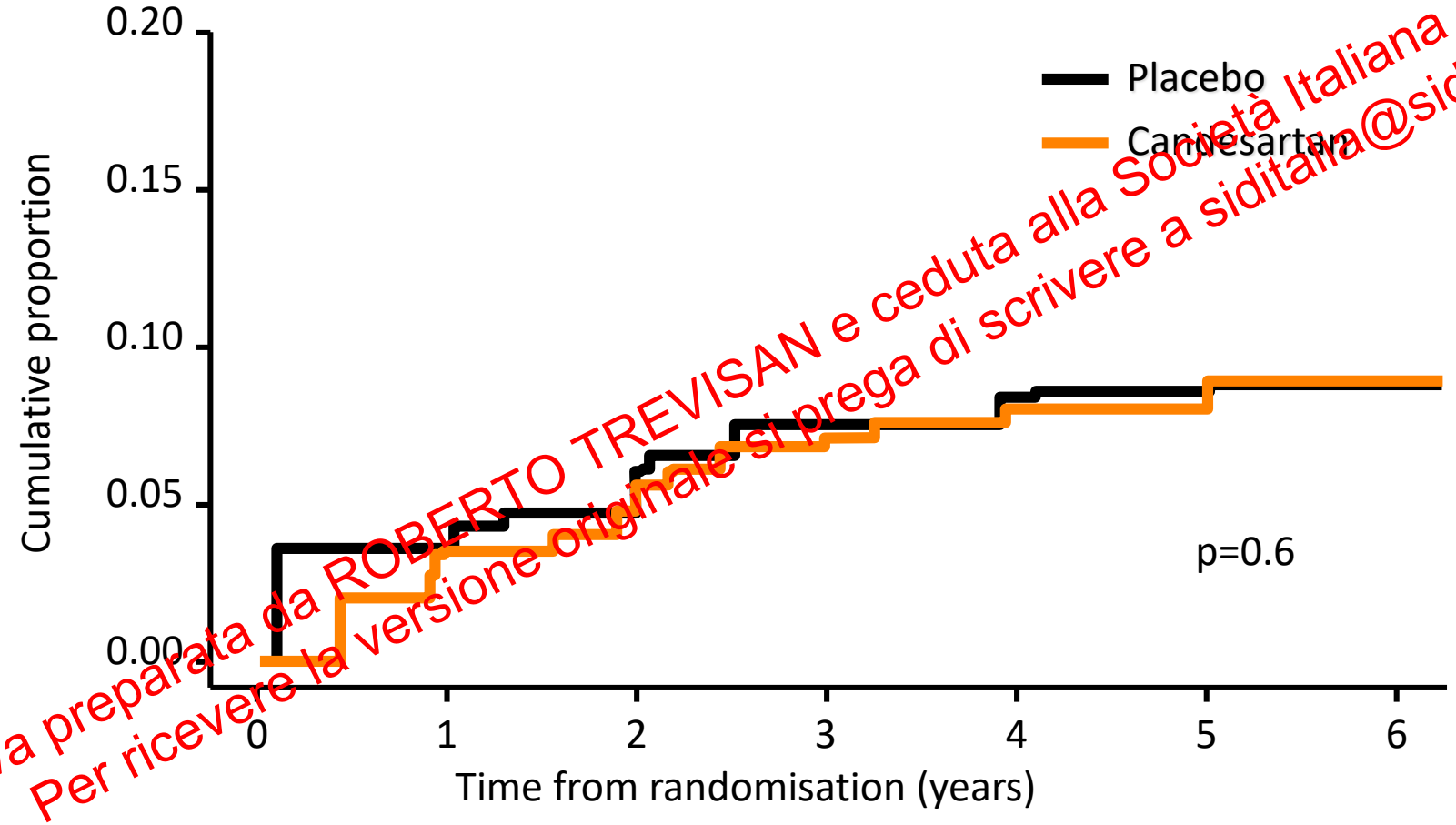
Primary outcome: the change in repeated-measures analysis of the albumin-to-creatinine ratio, assessed according to the area under the curve of the log10 albumin-to-creatinine ratio



N Engl J Med 2017;377:1733-45

DIRECT-Renal: Microalbuminuria incidence

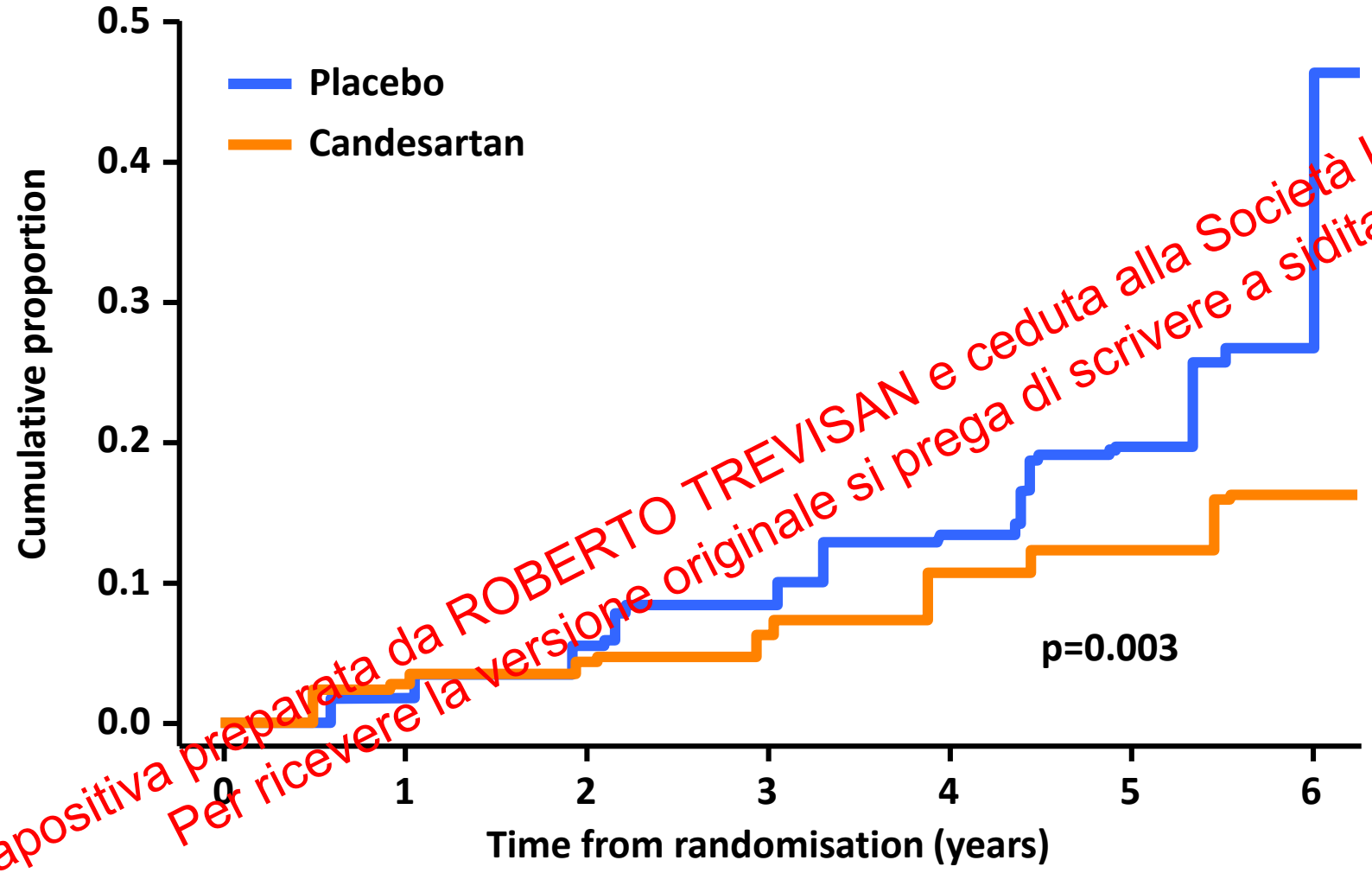
Candesartan has no effect on microalbuminuria incidence in Diabetes



Number at risk							
Placebo	2618	2410	2247	2092	1754	526	15
Candesartan	2613	2426	2278	2150	1793	540	13

Ann Intern Med. 2009 Jul 7;151(1):11-20

DIRECT-Prevent 1: Retinopathy incidence 3-step change



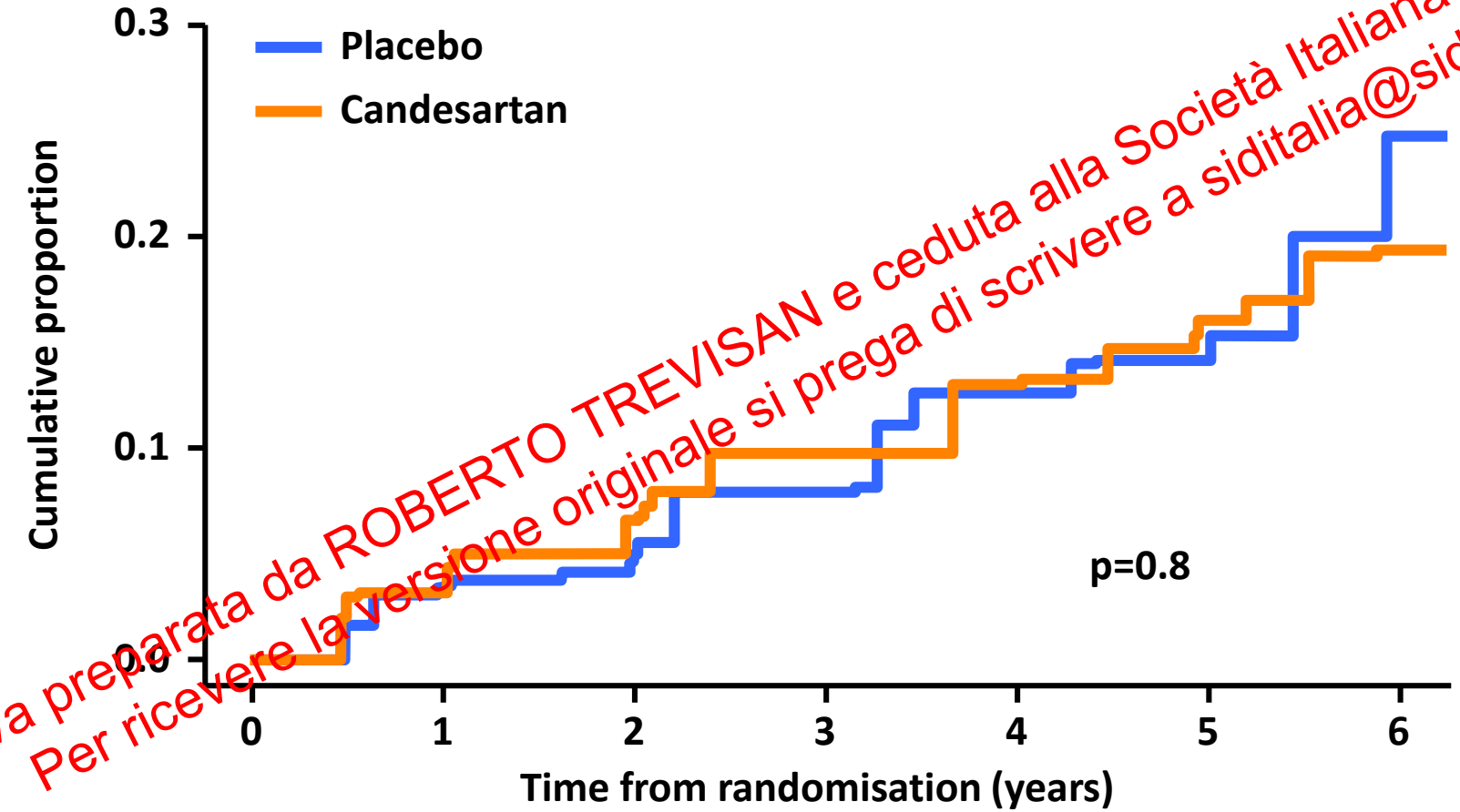
No at risk							
Placebo	710	663	630	587	419	109	1
Candesartan	711	651	615	587	422	108	1

Candesartan reduced incidence of retinopathy in normoalbuminuric normotensive type 1 diabetes

By 18% (p=0.0508) 2-step change, primary endpoint
35% (p=0.003) 3-step change, post hoc analysis

Lancet. 2008 Oct 18;372(9647):1394-402.

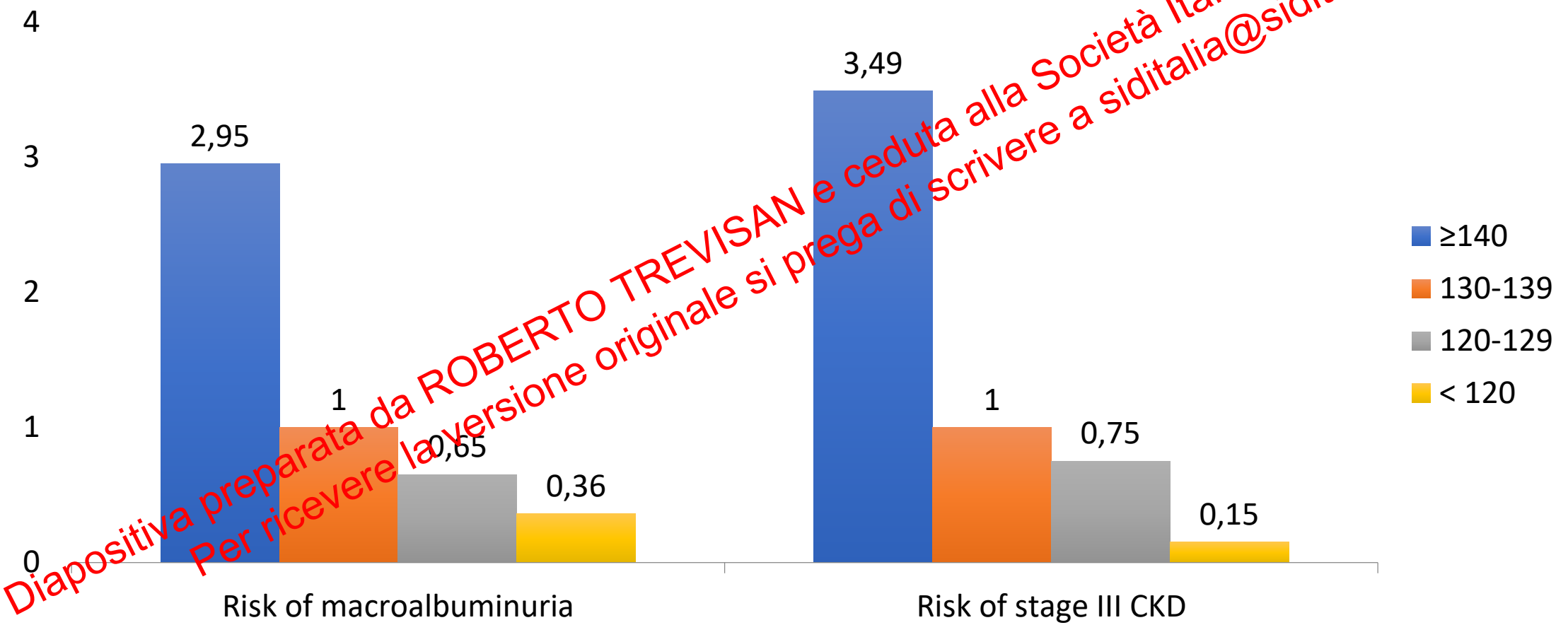
DIRECT-Protect 1: Retinopathy progression 3-step change



No at risk							
Placebo	954	875	820	770	612	188	4
Candesartan	951	863	814	767	626	195	5

Lancet. 2008 Oct 18;372(9647):1394-402.

Association Between Blood Pressure and Adverse Renal Events in Type 1 Diabetes during a median follow-up time of 24 years (DCCT-EDIC)



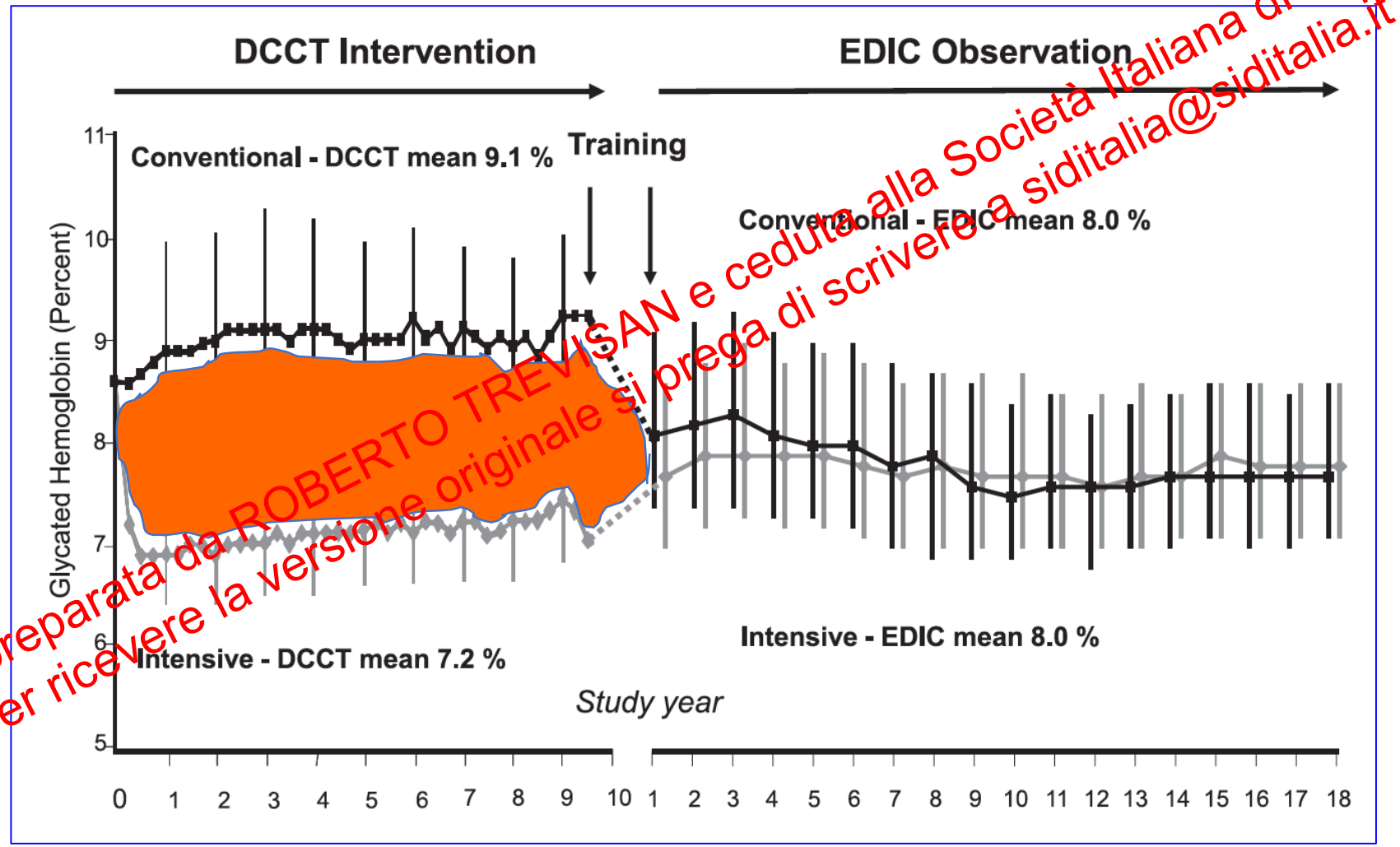
Diabetes Care 2016;39:2218–2224

IL CONTROLLO DELLA GLICEMIA

DOPO 30 ANNI IL DCCT CONTINUA A DARE INCREDIBILI INFORMAZIONI

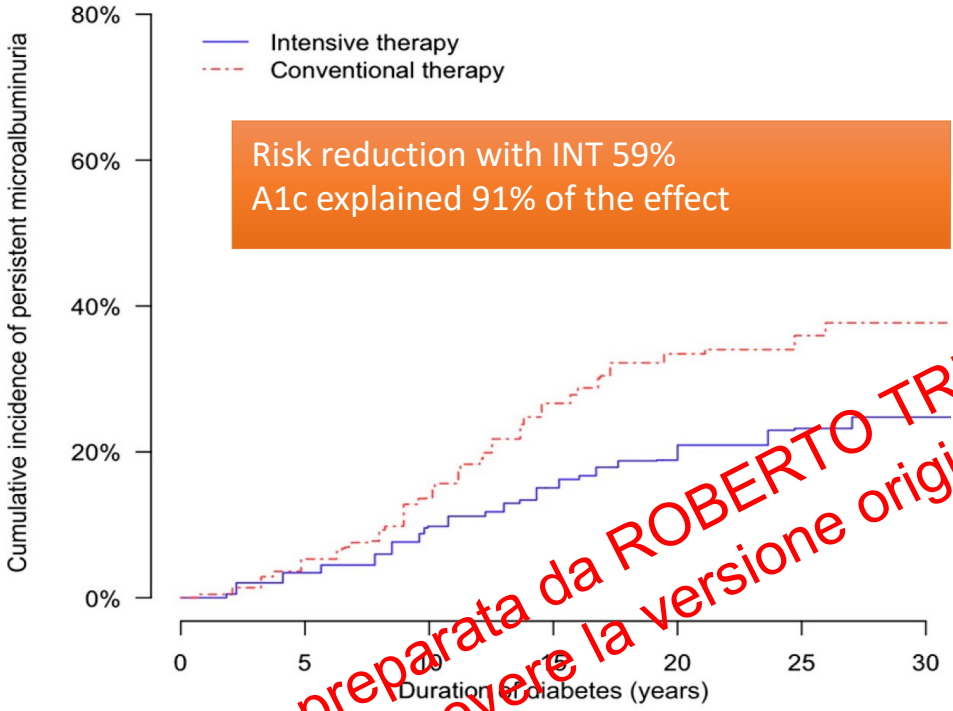
DCCT-EDIC: Overview at 30 yrs

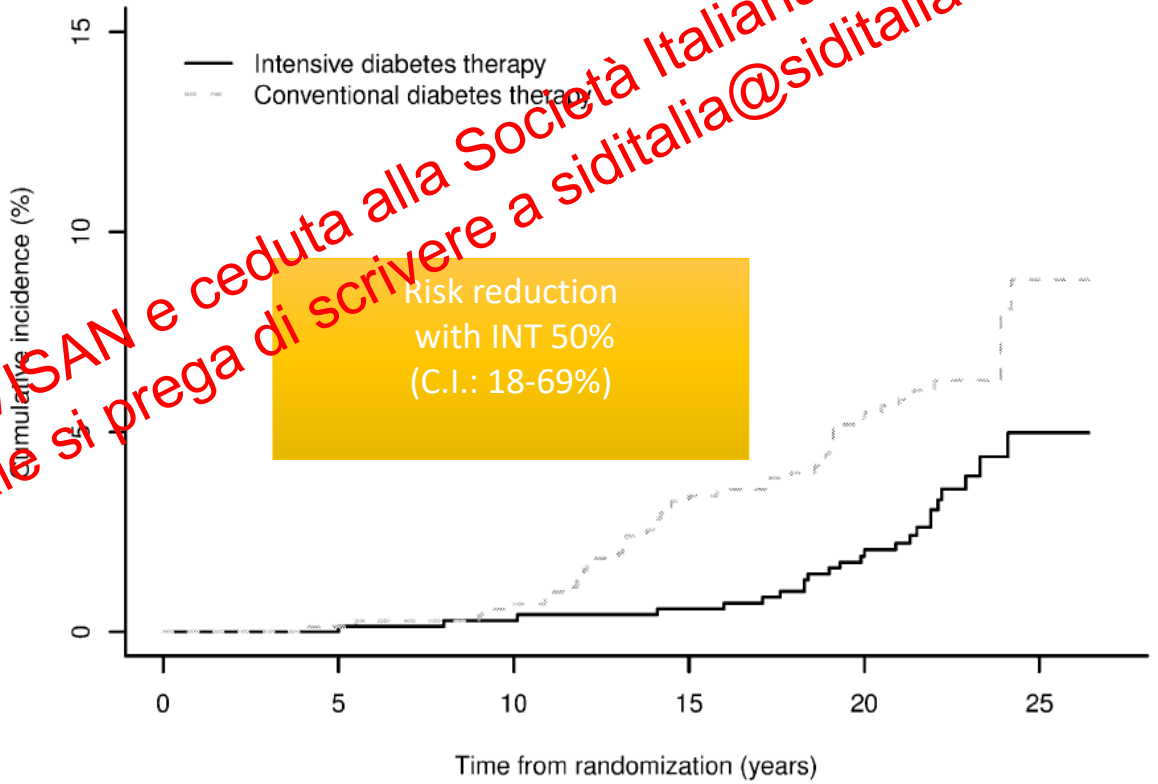
Median HbA1c concentrations during DCCT, the “training” period between DCCT and EDIC, and EDIC



Diabetes 2013;62:3976–3986

Kidney Disease in the Diabetes Control and Complications Trial/ Epidemiology of Diabetes Interventions and Complications Study (DCCT-EDIC)

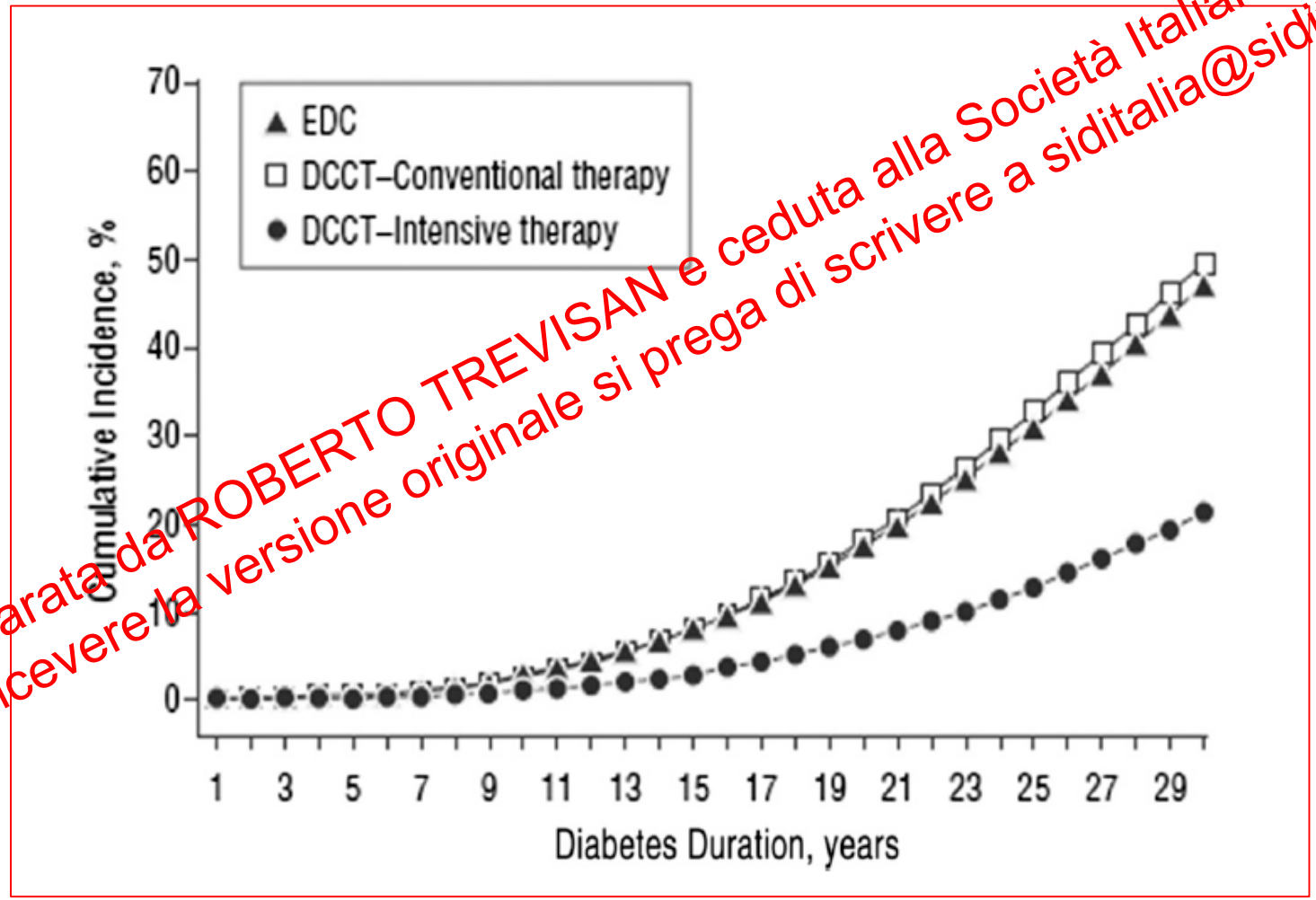




Diabetes Care 2014;37:24–30

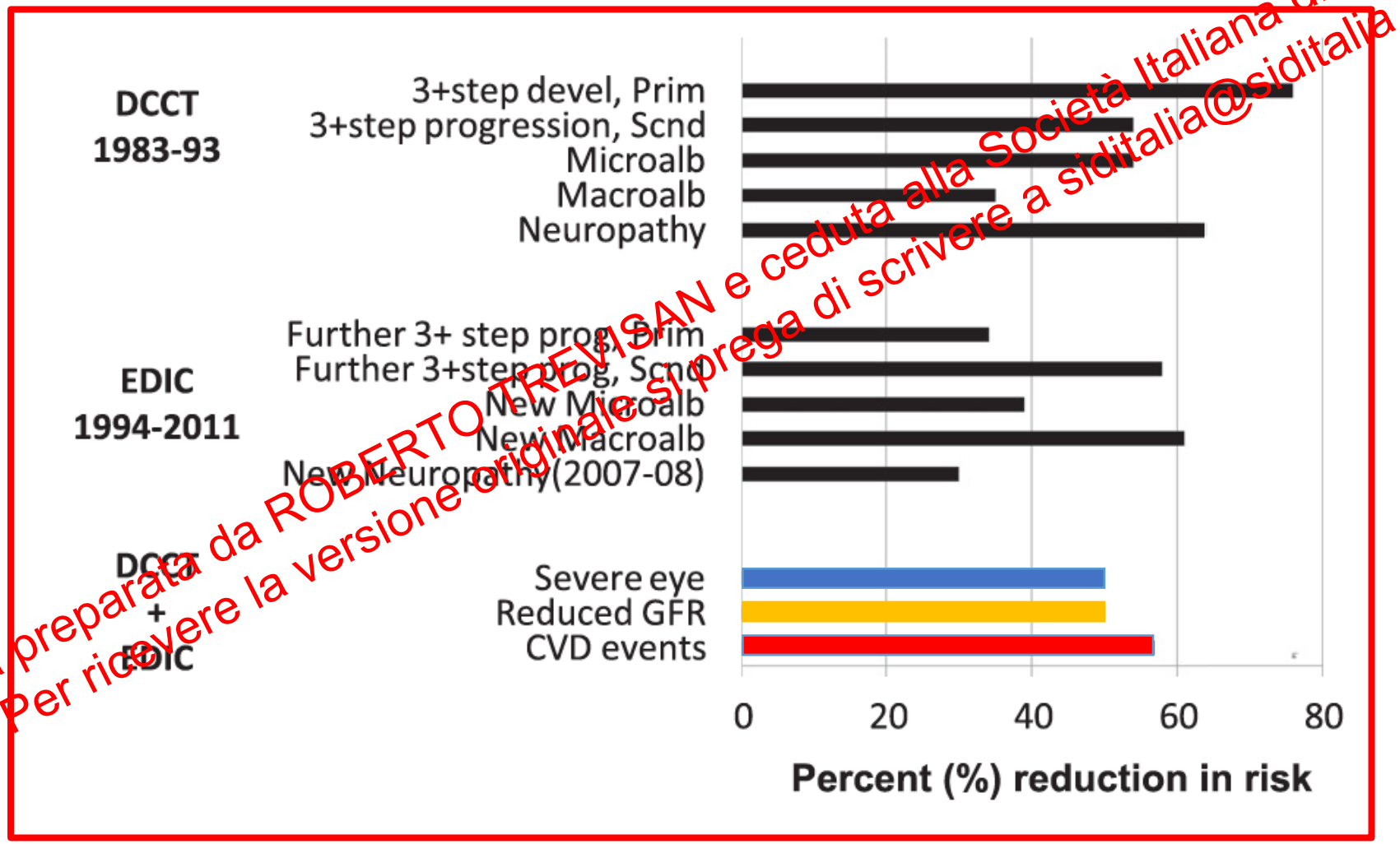
The cumulative incidence of any **major eye disease end point** (PDR, CSME, application of laser, or development of blindness) in relation to diabetes duration

DCCT CON (open squares) and INT (solid circles) groups are presented. Also presented is the cumulative incidence of these major eye disease end points observed in the observational Pittsburgh Epidemiology of Diabetes Complications (EDC) study (solid triangles).



Diabetes Care 2014;37:17–23

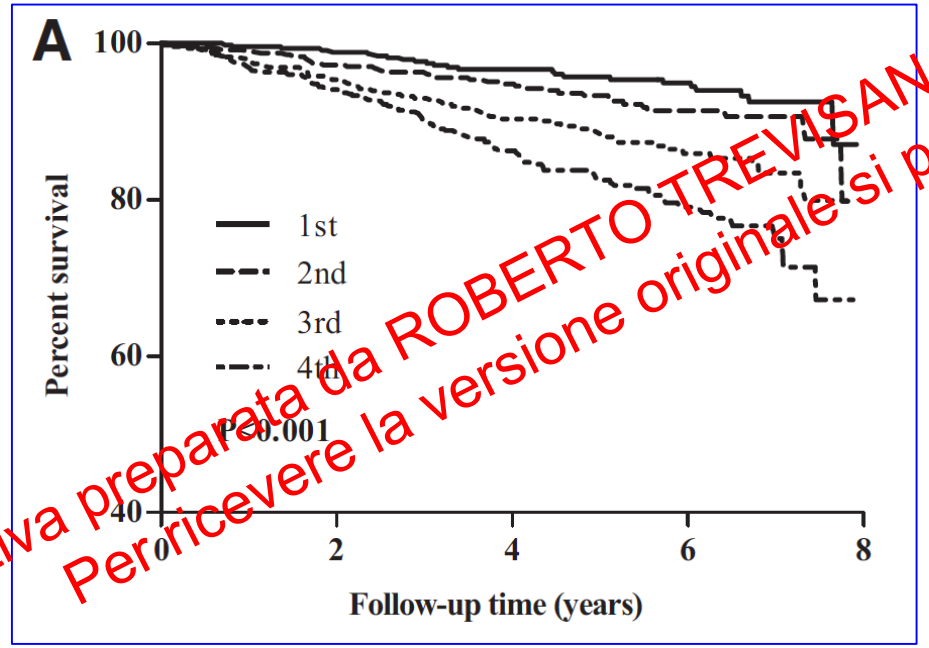
Summary of reduction in major complications with INT compared with CON during DCCT, EDIC, and combined study periods



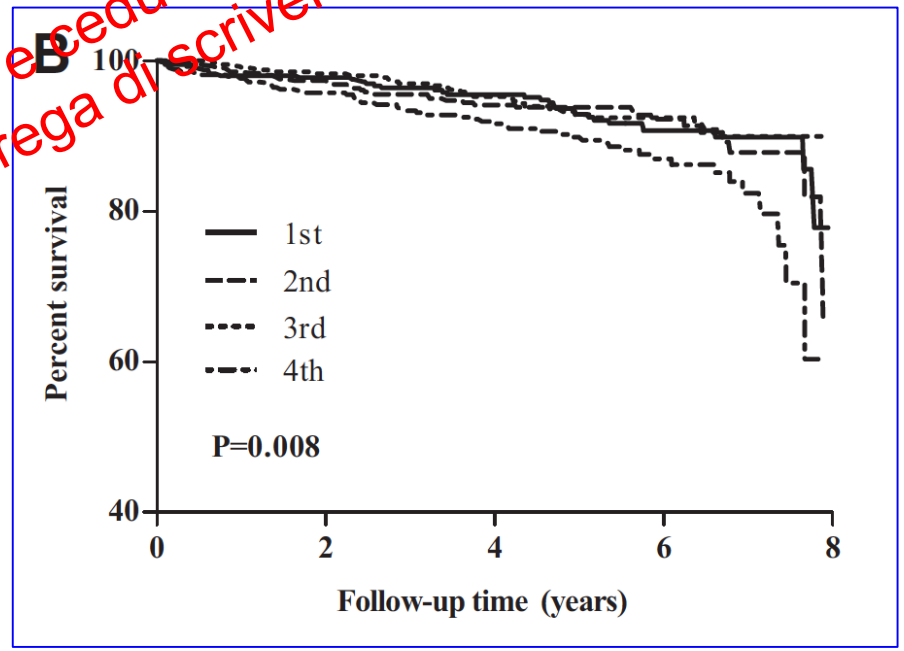
Diabetes Care 2014;37:9–16

A1C Variability Predicts Incident Cardiovascular Events, Microalbuminuria, and Overt Diabetic Nephropathy inPatients With Type 1 Diabetes

Survival curves for any progression in renal status (defined as any increase in albuminuria level or progression to ESRD) by quartiles of SD of serially measured A1C values



Survival curves for a CVD event (coronary event, stroke, peripheral vascular event) by quartiles of SD of serially measured A1C values.



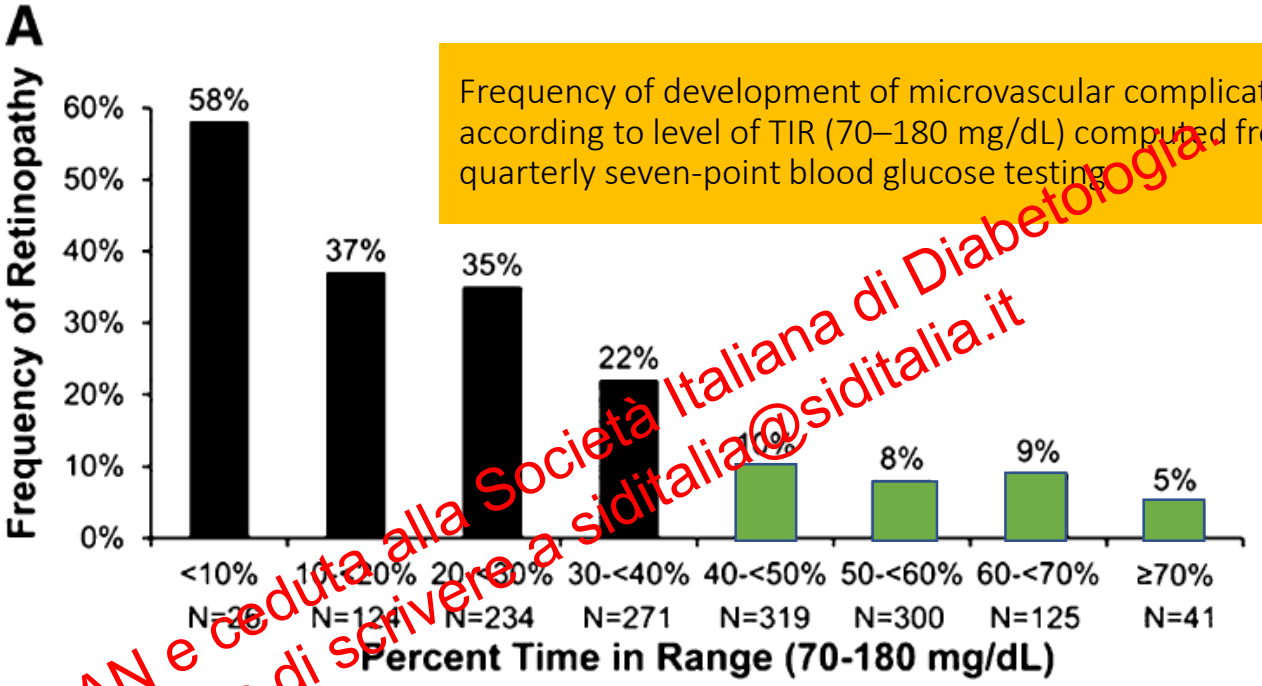
Diabetes 58:2649–2655, 2009

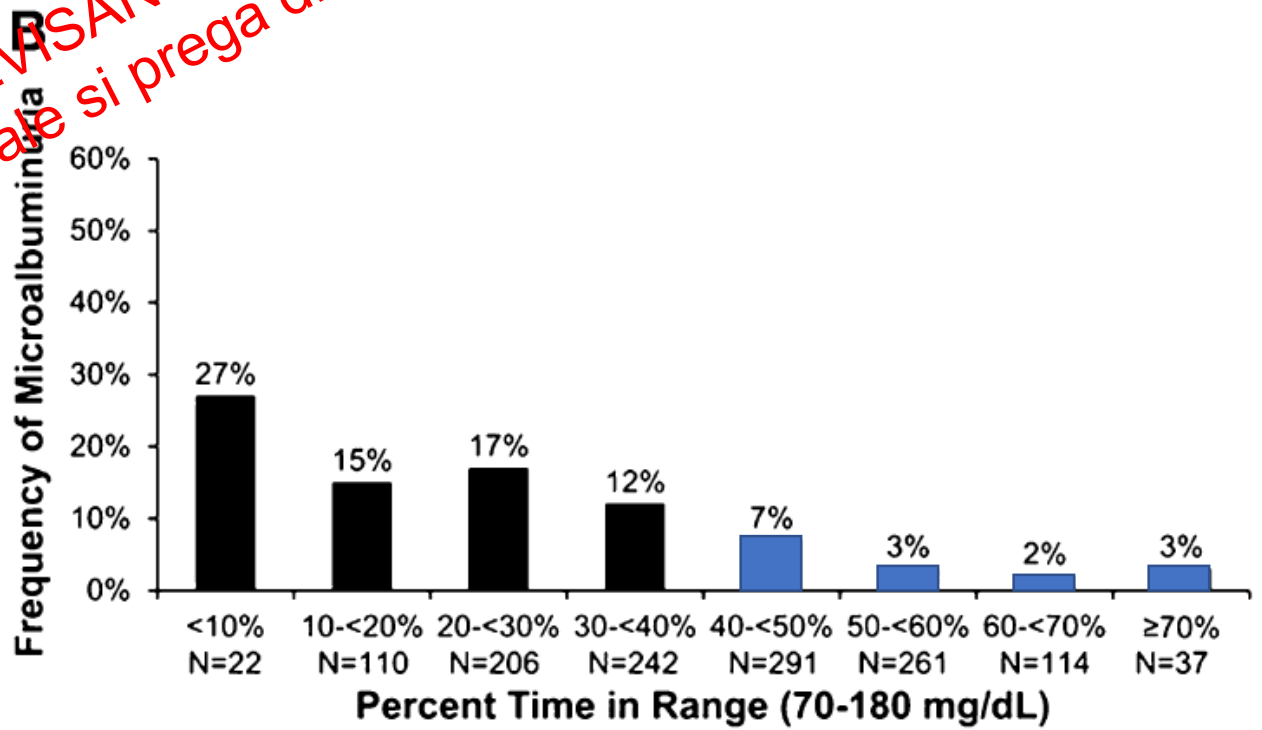
Validation of Time in Range as an Outcome Measure for Diabetes Clinical Trials

Roy W. Beck,[1] Richard M. Bergenstal,[2] Tonya D. Riddlesworth,[1] Craig Kollman,[1] Zhaomian Li,[1] Adam S. Brown,[3] and Kelly L. Close[4]

https://doi.org/10.2337/dc18-1444

Frequency of development of microvascular complication according to level of TIR (70–180 mg/dL) computed from quarterly seven-point blood glucose testing

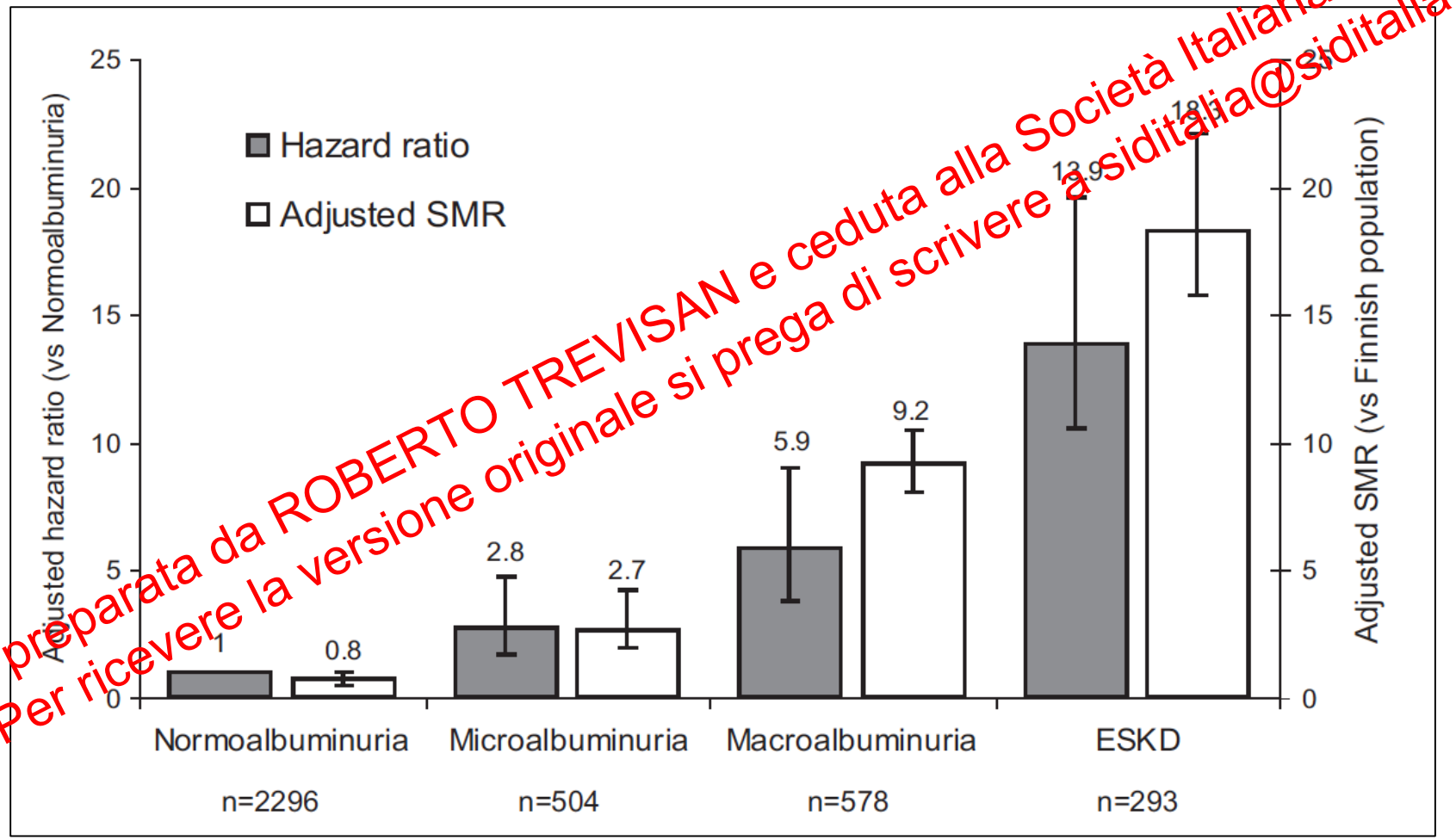




NON SOLO MICROANGIOPATIA

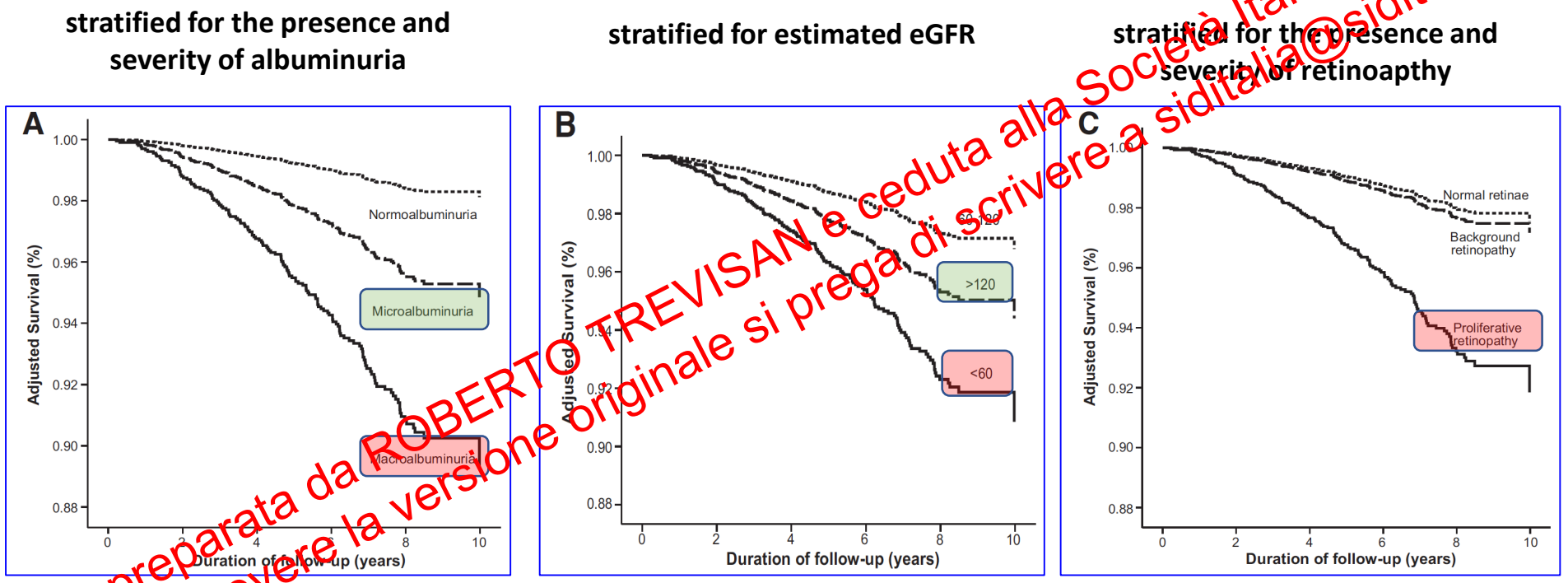
LA MORTALITA' NEL DIABETE DI TIPO 1

Risk of mortality in individuals with type 1 diabetes from the FinnDiane study associated each level of albuminuria and end-stage kidney disease (ESKD)



Diabetes 58:1651–1658, 2009

Survival plots showing Cox-adjusted survival of individuals with type 1 diabetes from the FinnDiane study

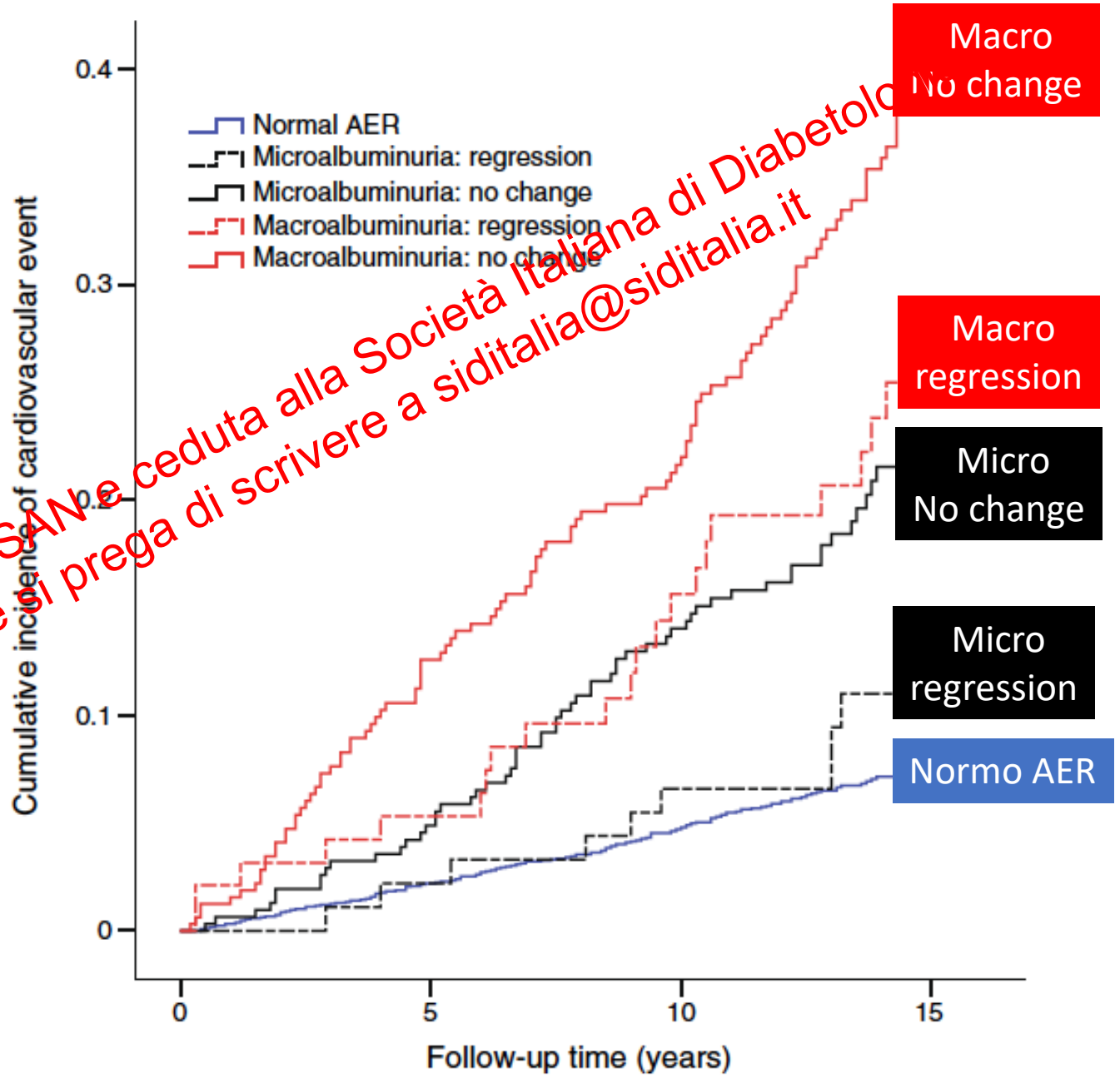


All figures are adjusted for age; sex; duration of diabetes; body habitus; the presence and extent of macro and microvascular complications; glycemic, lipid, and blood pressure control; and drug management.

Diabetes 58:1651–1658, 2009

Kaplan–Meier cumulative incidence curves for **cardiovascular events** over a follow-up of 15 years stratified by status of albuminuria at baseline

3642 participants from the Finnish Diabetic Nephropathy (FinnDiane) Study



Diabetologia 2018

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Glycemic Control and Excess Mortality in Type 1 Diabetes

Marcus Lind, M.D., Ph.D., Ann-Marie Svensson, Ph.D., Mikhail Kosiborod, M.D., Soffia Gudbjörnsdottir, M.D., Ph.D., Aldina Pivodic, M.Sc., Hans Wedel, Ph.D., Sofia Dahlqvist, Mark Clements, M.D., Ph.D., and Annika Rosengren, M.D., Ph.D.

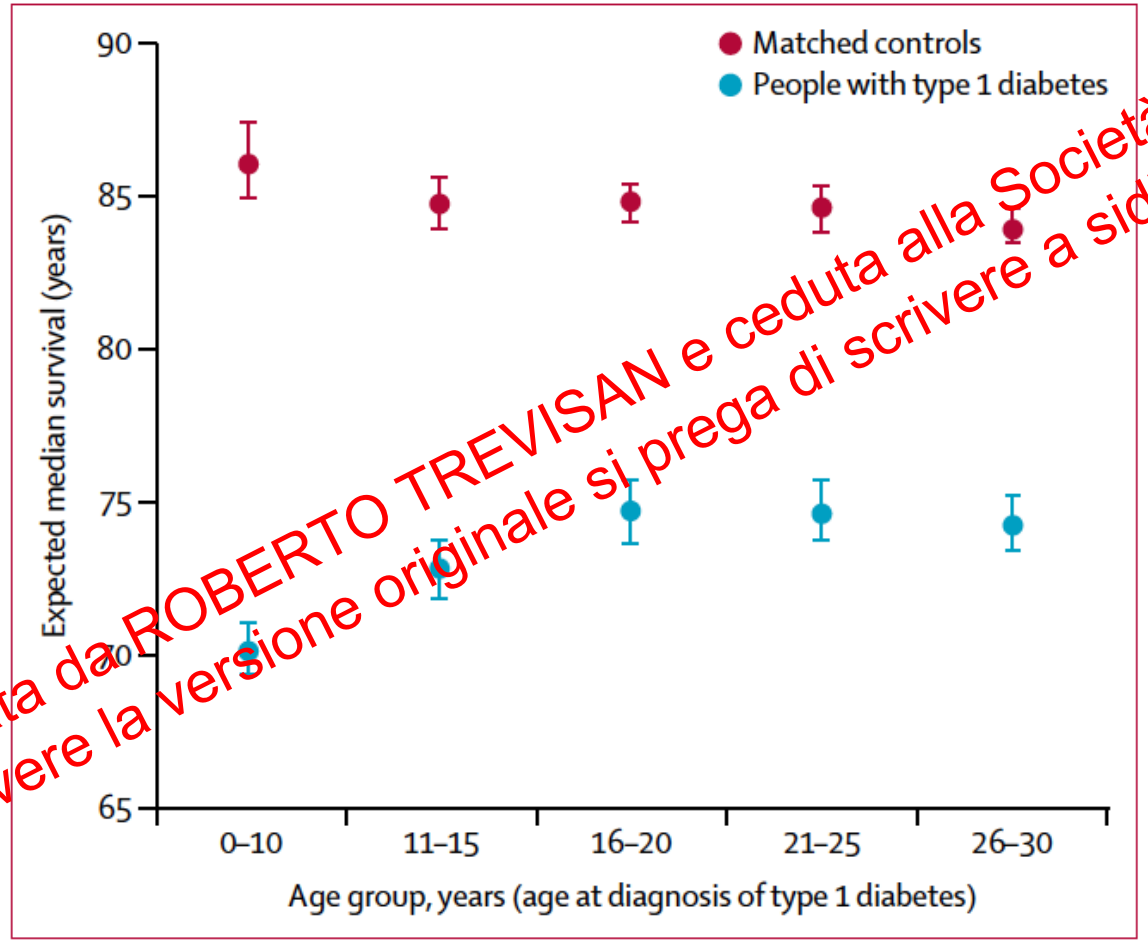
N Engl J Med 2014;371:1972-82.

Adjusted Hazard Ratios for Death from Any Cause and Death from Cardiovascular Causes among Patients with Type 1 Diabetes versus Controls, According to Time-Updated Mean Glycated Hemoglobin Level

Variable	Hazard Ratio	
	Death from Any Cause	Death from Cardiovascular Disease
Time-updated mean glycated hemoglobin level — no. of events/total no.	7386/200,539	2326/200,539
Reference group (controls)	1.00	1.00
≤6.9%	2.36 (1.97–2.83)	2.92 (2.07–4.13)
7.0–7.8%	2.38 (2.02–2.80)	3.39 (2.49–4.61)
7.9–8.7%	3.11 (2.66–3.62)	4.44 (3.32–5.96)
8.8–9.6%	3.65 (3.11–4.30)	5.35 (3.94–7.26)
≥9.7%	8.51 (7.24–10.01)	10.46 (7.62–14.37)

N Engl J Med 2014;371:1972-82.

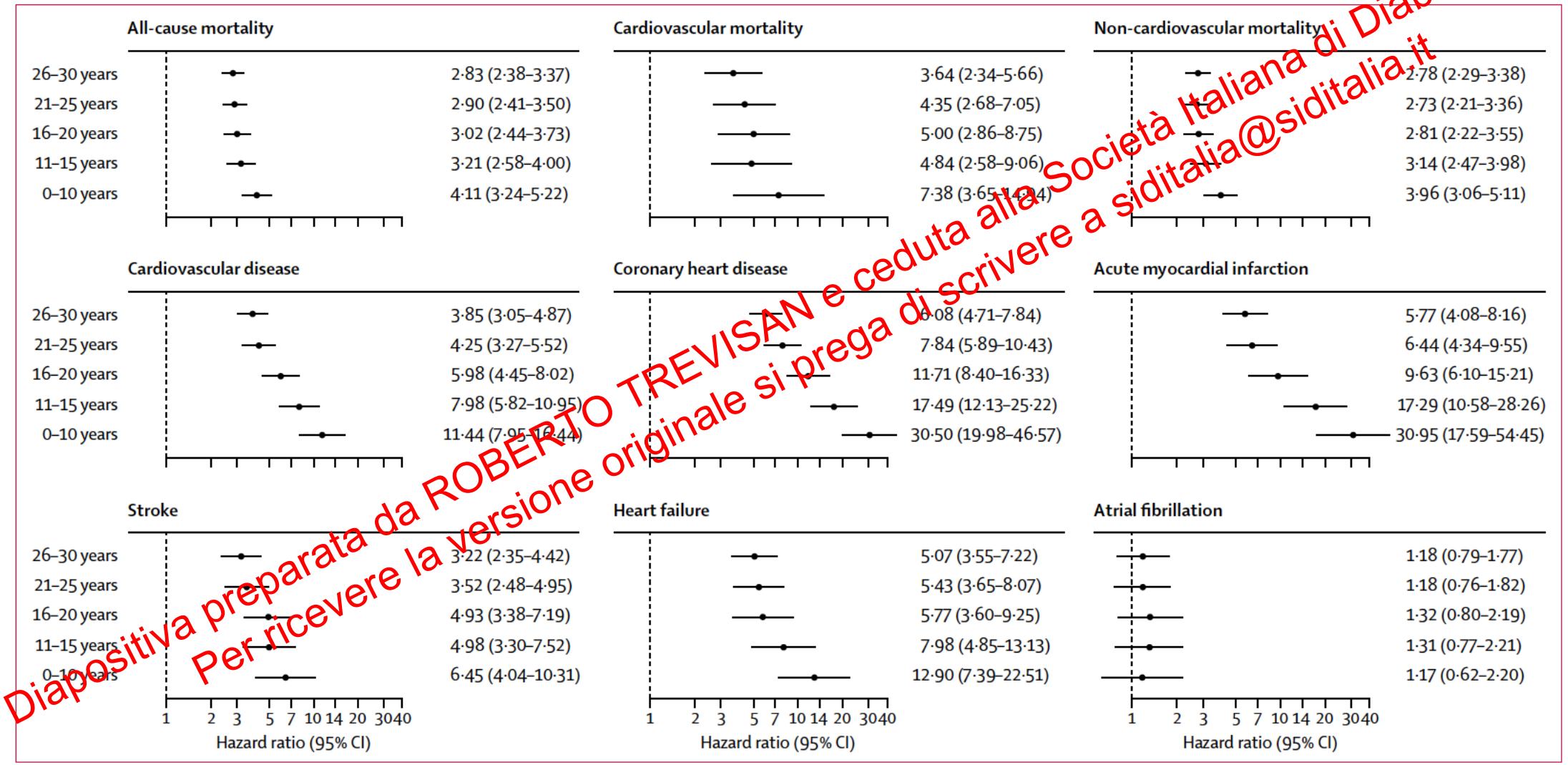
Life-years lost in relation to age at onset of type 1 diabetes



Lancet 2018; 392: 477–86

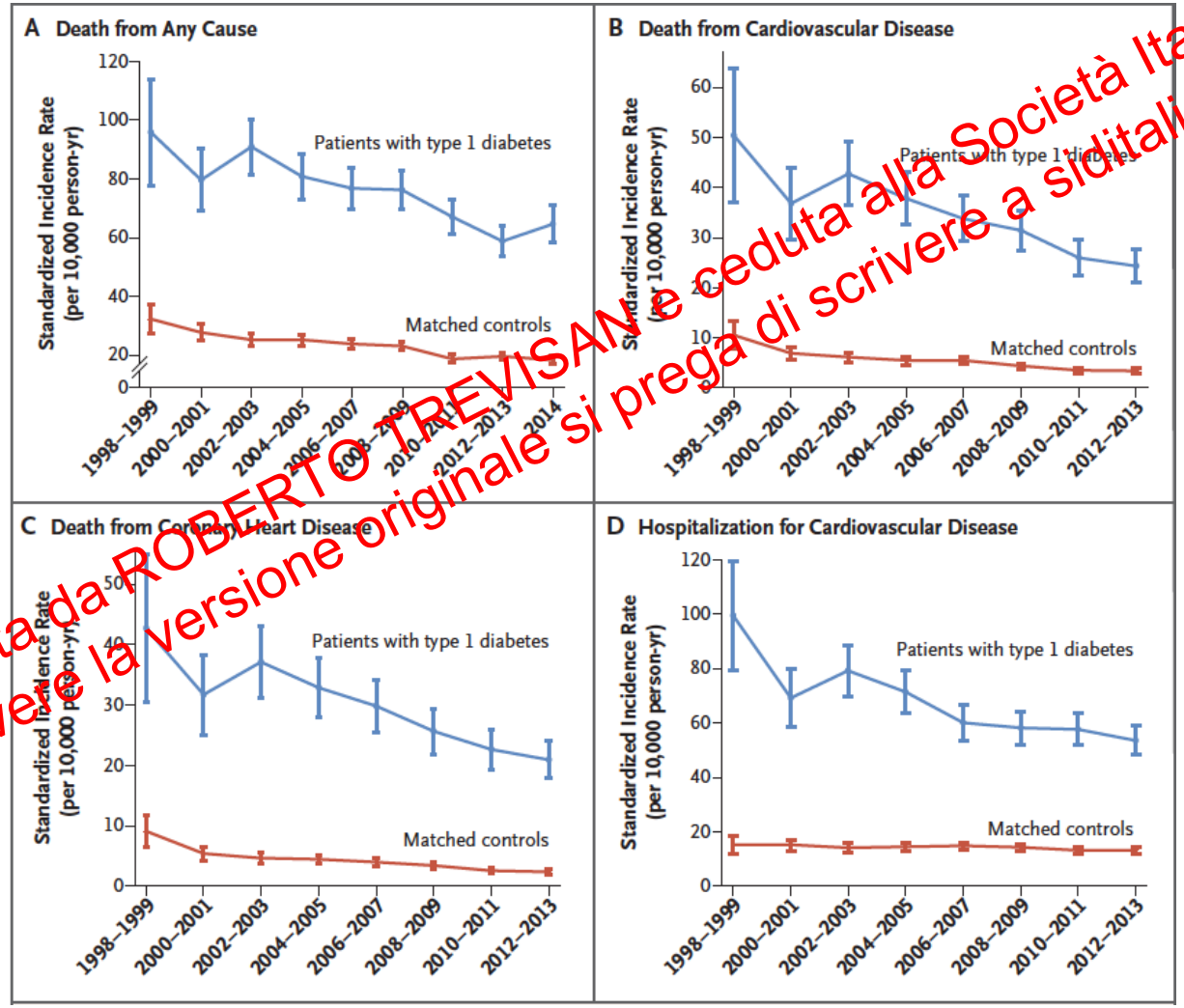
Adjusted hazard ratios for all outcomes, according to age at type 1 diabetes diagnosis

Matched controls served as a reference group



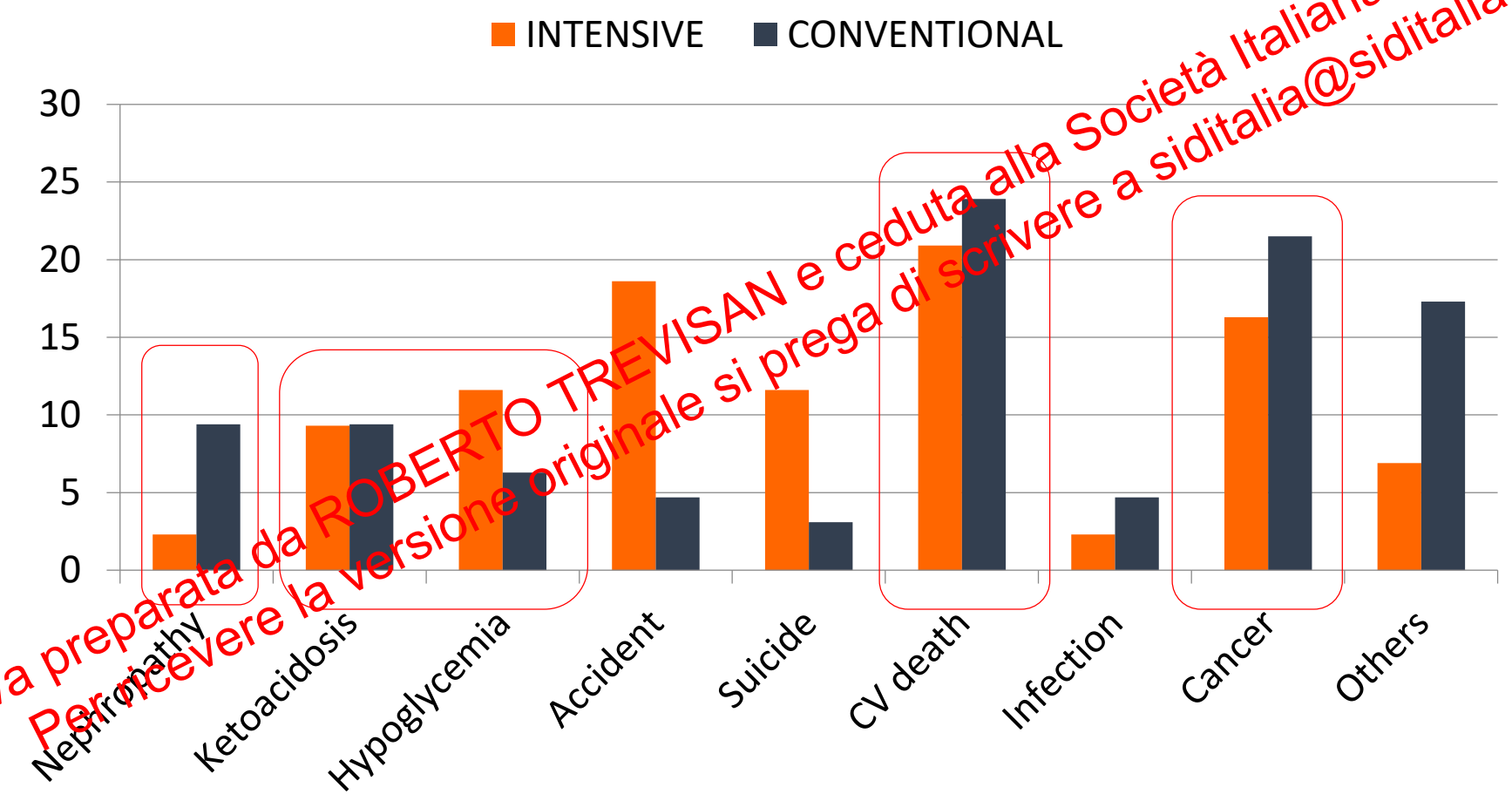
Lancet 2018; 392: 477–86

Major Cardiovascular Outcomes in Patients with Type 1 Diabetes and Matched Controls



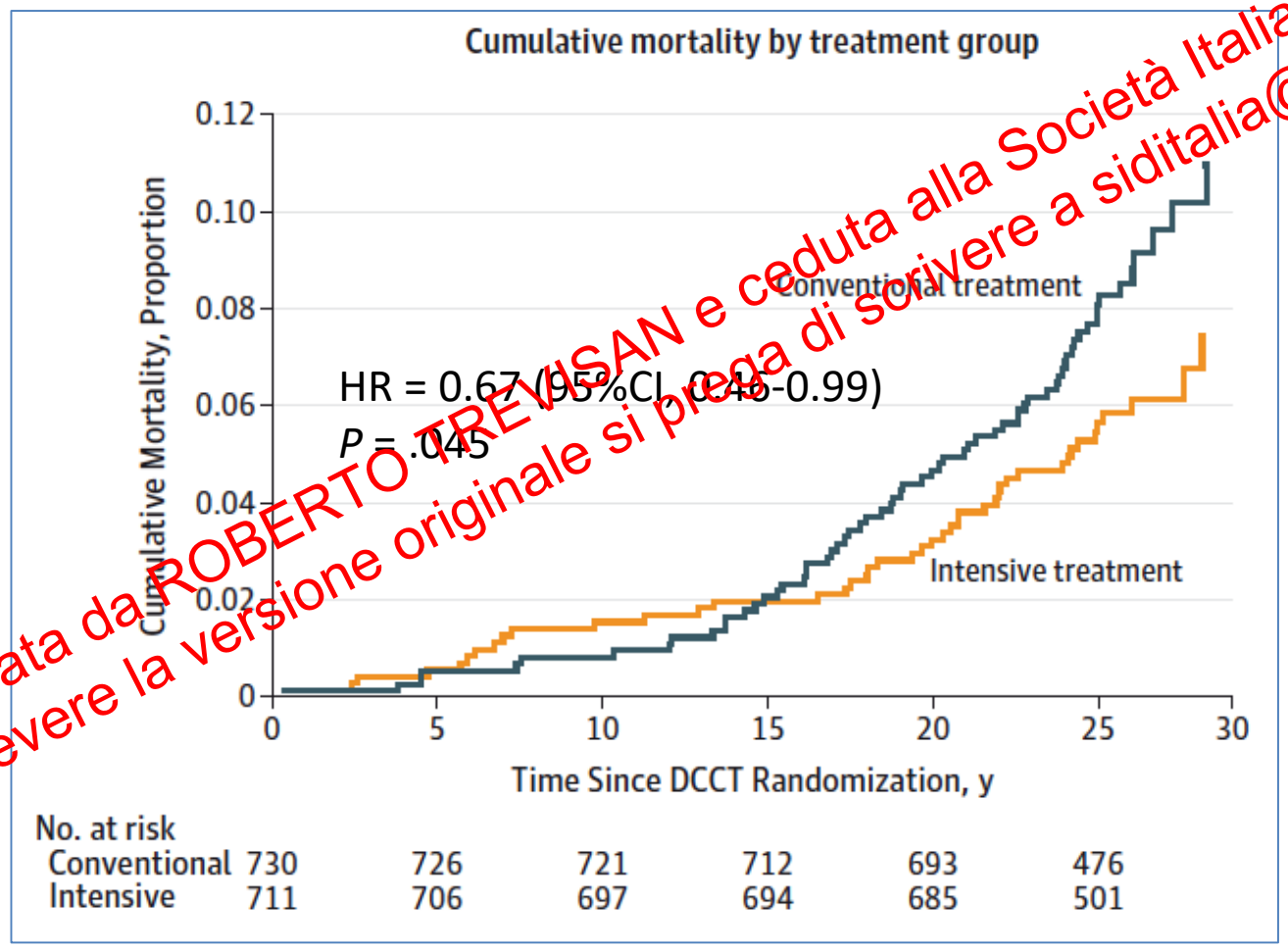
N Engl J Med 2017;376:1407-18.

Distribution of the Causes of Death in the DCCT



JAMA. 2015;313(1):45-53

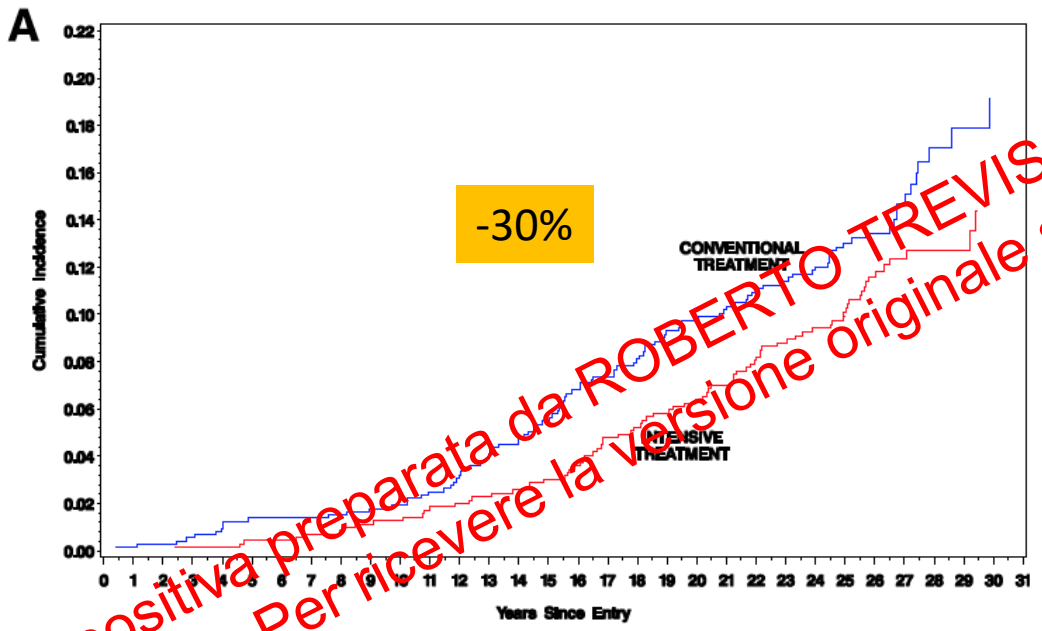
Cumulative Incidence of Mortality in the Diabetes Control and Complications Trial



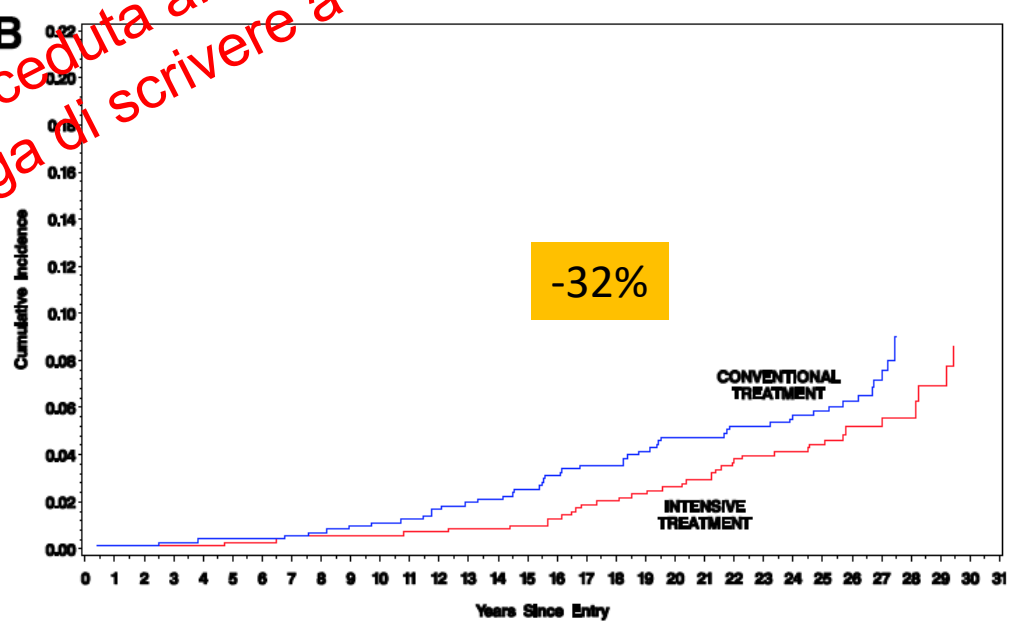
JAMA. 2015;313(1):45-53

Cumulative incidence of cardiovascular outcomes in the conventional treatment and intensive treatment groups during up to 30 years of DCCT/EDIC treatment and follow-up

The first of any of the predefined CVD outcomes

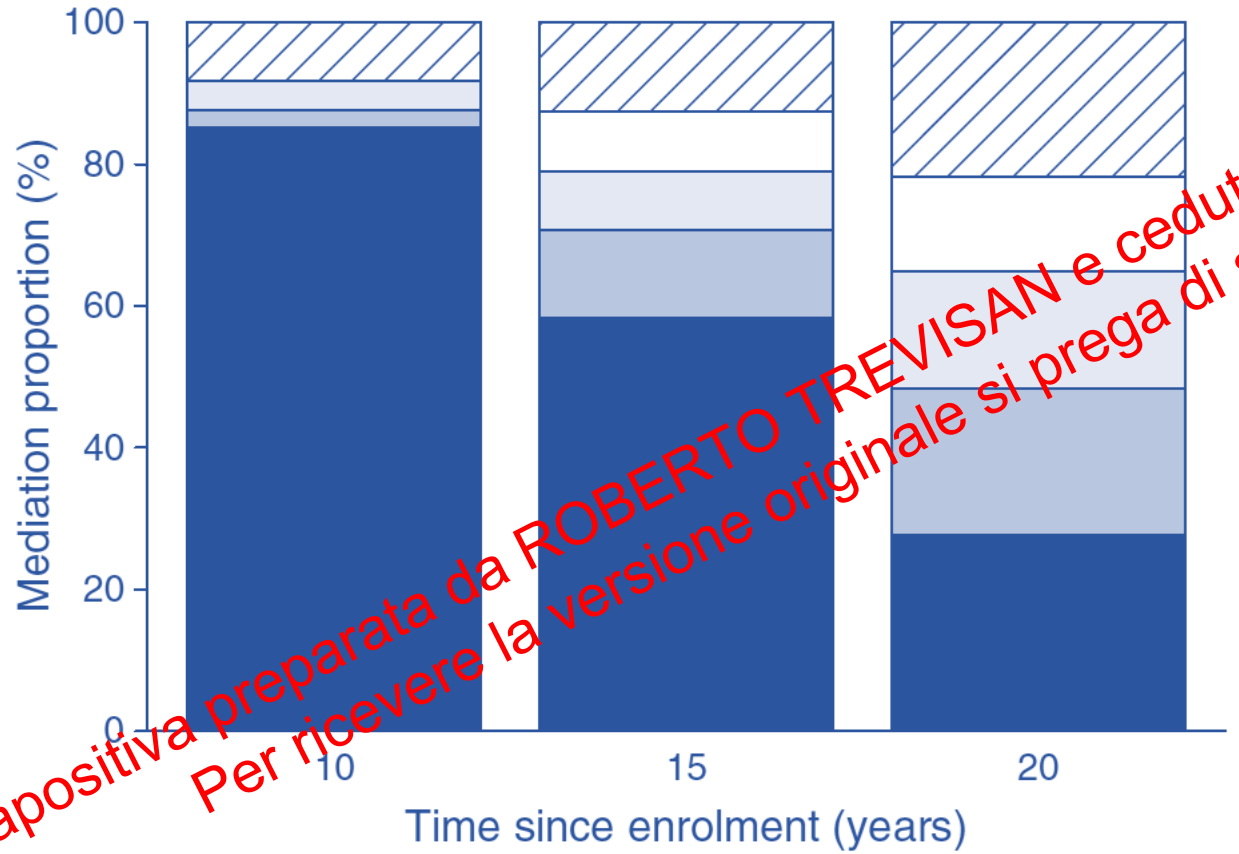


The first occurrence of MACE



Dia Care 2016;39:686-693

The relationship of blood glucose with cardiovascular disease is mediated over time by traditional risk factors in type 1 diabetes: the DCCT/EDIC study



indirect effects through LDLc

indirect effects through TG

indirect effects through pulse rate

indirect effects through SBP

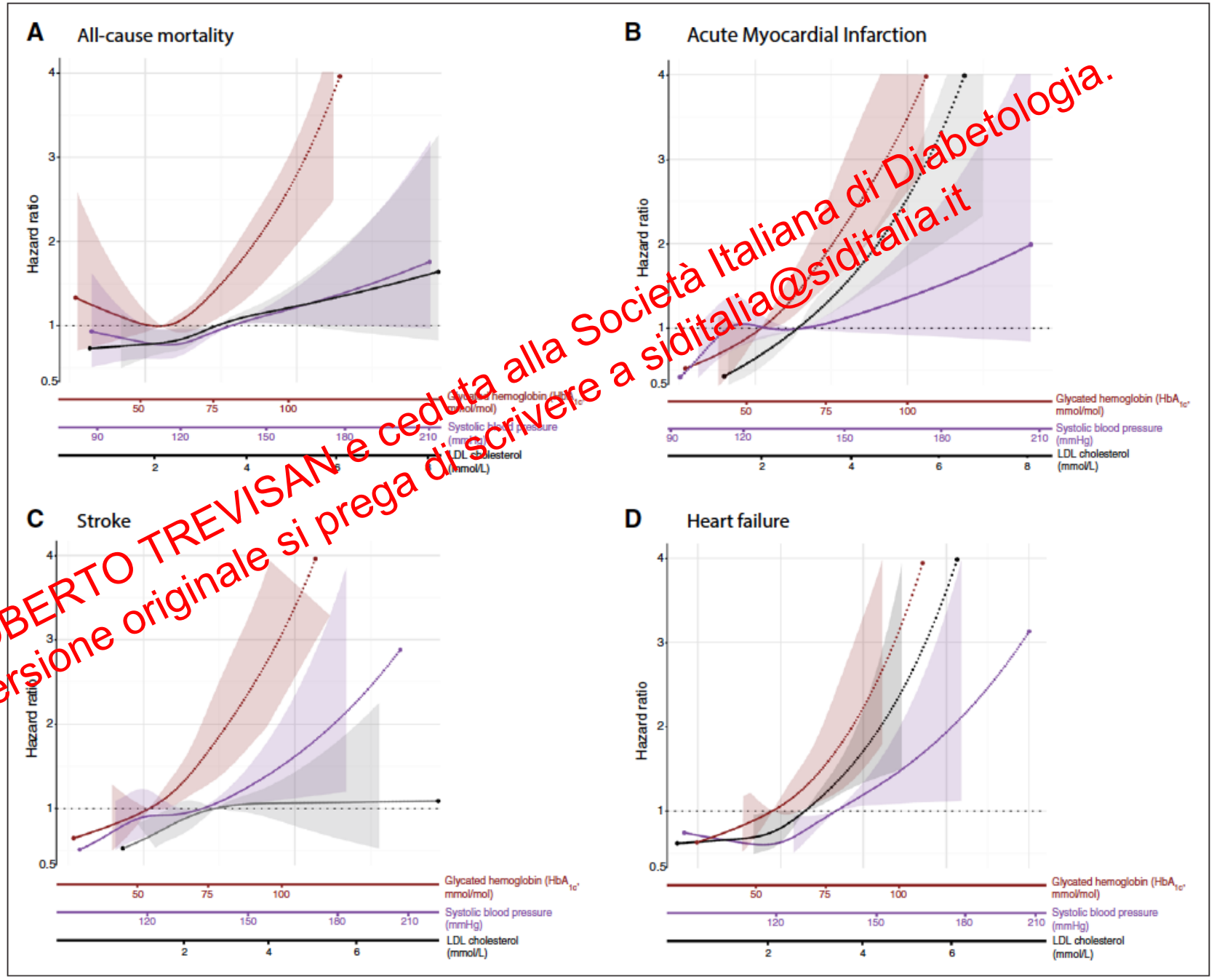
direct effect of HbA1c on CVD risk

Diabetologia (2017) 60:2084–2091

Association between HbA1c, systolic blood pressure (SBP), and lLDL-C and all-cause mortality, acute myocardial infarction, stroke, and hospitalization for heart failure in T1DM.

- HbA1c is a strong predictor for all outcomes, and its association is likely integrated with albuminuria and duration of diabetes mellitus
- LDL-C and SBP display independent predictability.
- LDL-C appears to be a more important prognostic factor than previously appreciated.

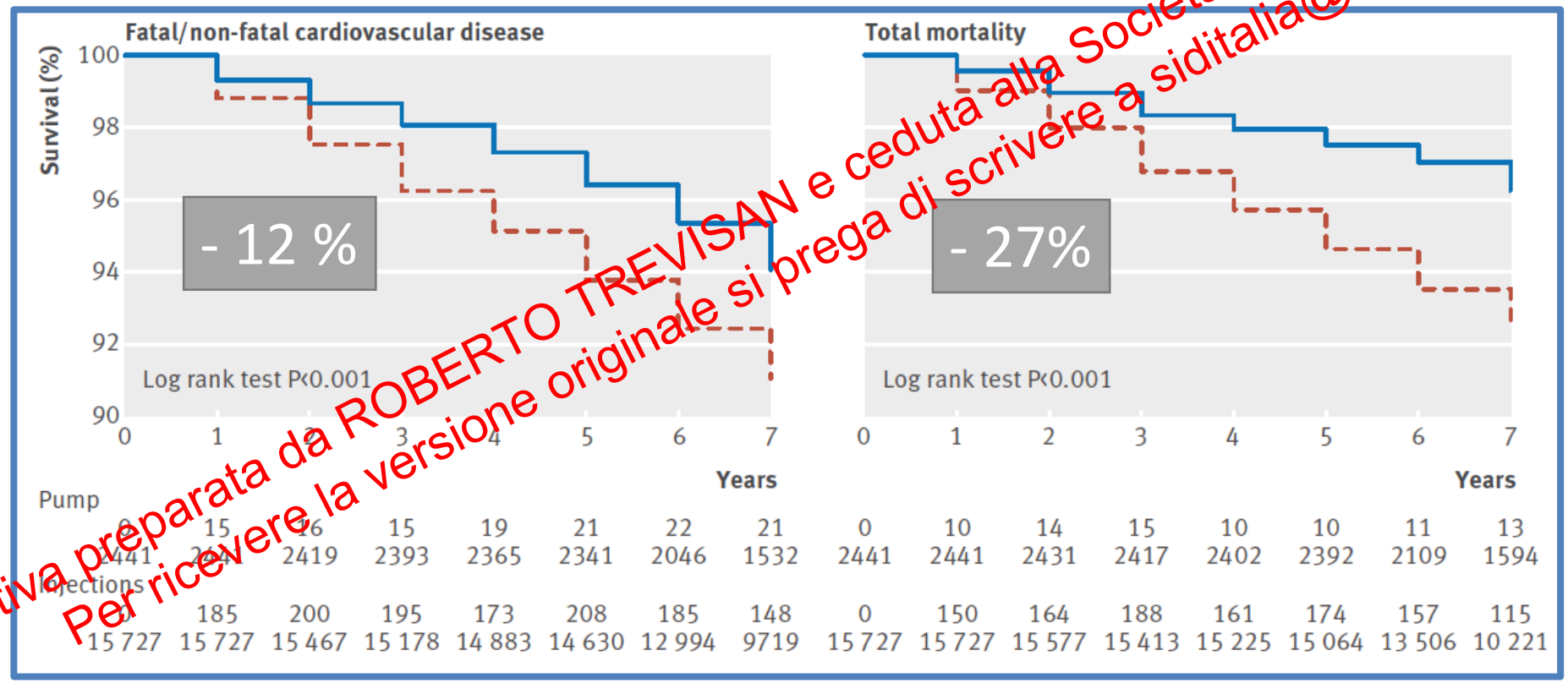
Circulation. 2019;139:1900–1912.



La terapia con microinfusore

Kaplan-Meier crude survival curves in 18 168 individuals with type 1 diabetes according to treatment with insulin pump therapy or multiple daily injections

The Swedish National Diabetes Register



BMJ 2015;350:h3234

DIABETICMedicine

DOI: 10.1111/j.1464-5491.2009.02736.x

Original Article: Complications

Continuous subcutaneous insulin infusion is more effective than multiple daily insulin injections in preventing albumin excretion rate increase in Type 1 diabetic patients

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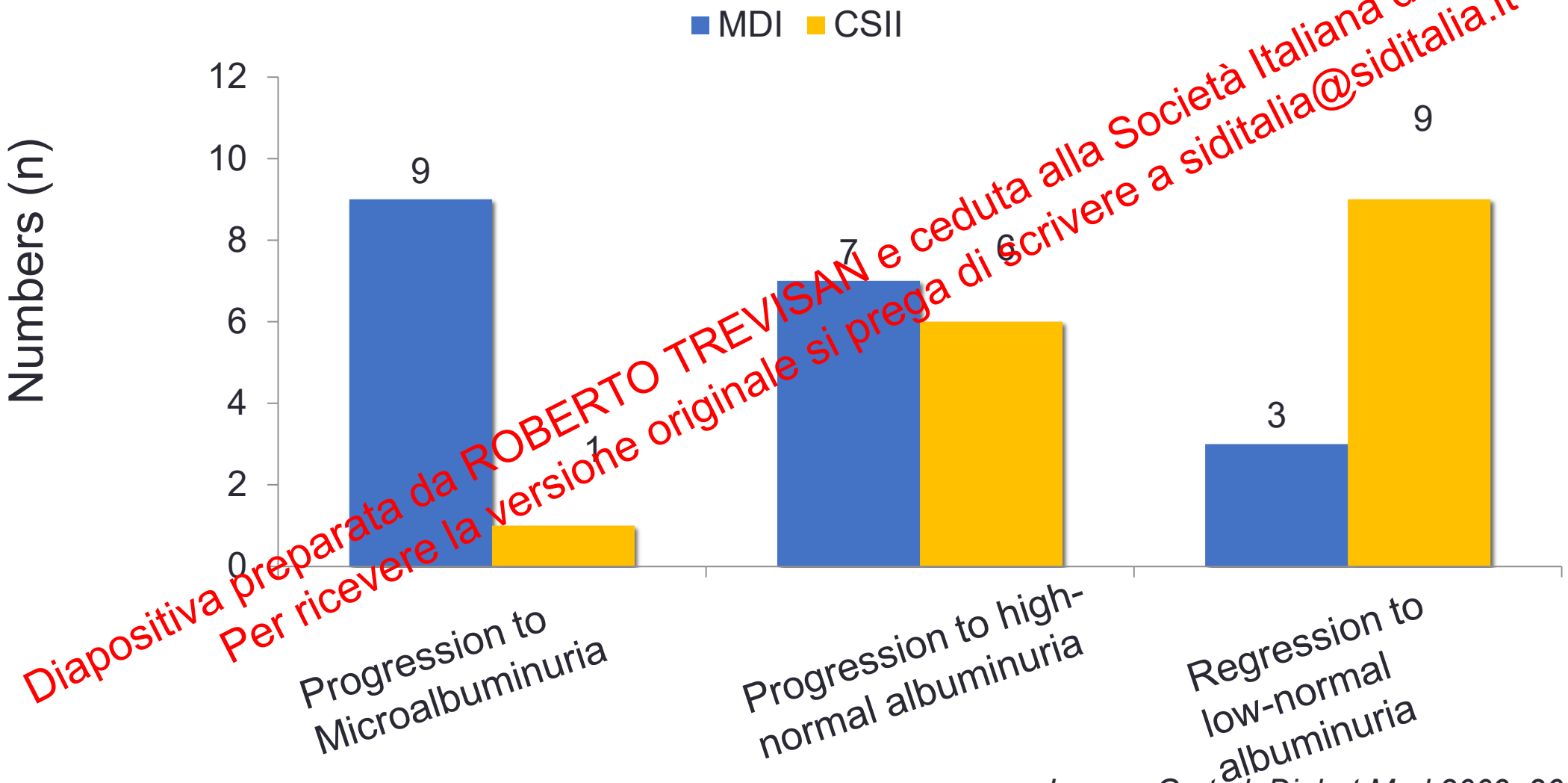
Accepted 10 April 2009

A 3-year multicenter retrospective observational CASE-CONTROL study

Progression/Regression of AER

110 T1 pts on CSII vs 110 on MDI



Lepore G et al. Diabet Med 2009; 26 (6): 602-8.

DIABETIC Medicine
DOI: 10.1111/dme.12950

Research: Complications

Effect of 4 years subcutaneous insulin infusion treatment on albuminuria, kidney function and HbA_{1c} compared with multiple daily injections: a longitudinal follow-up study

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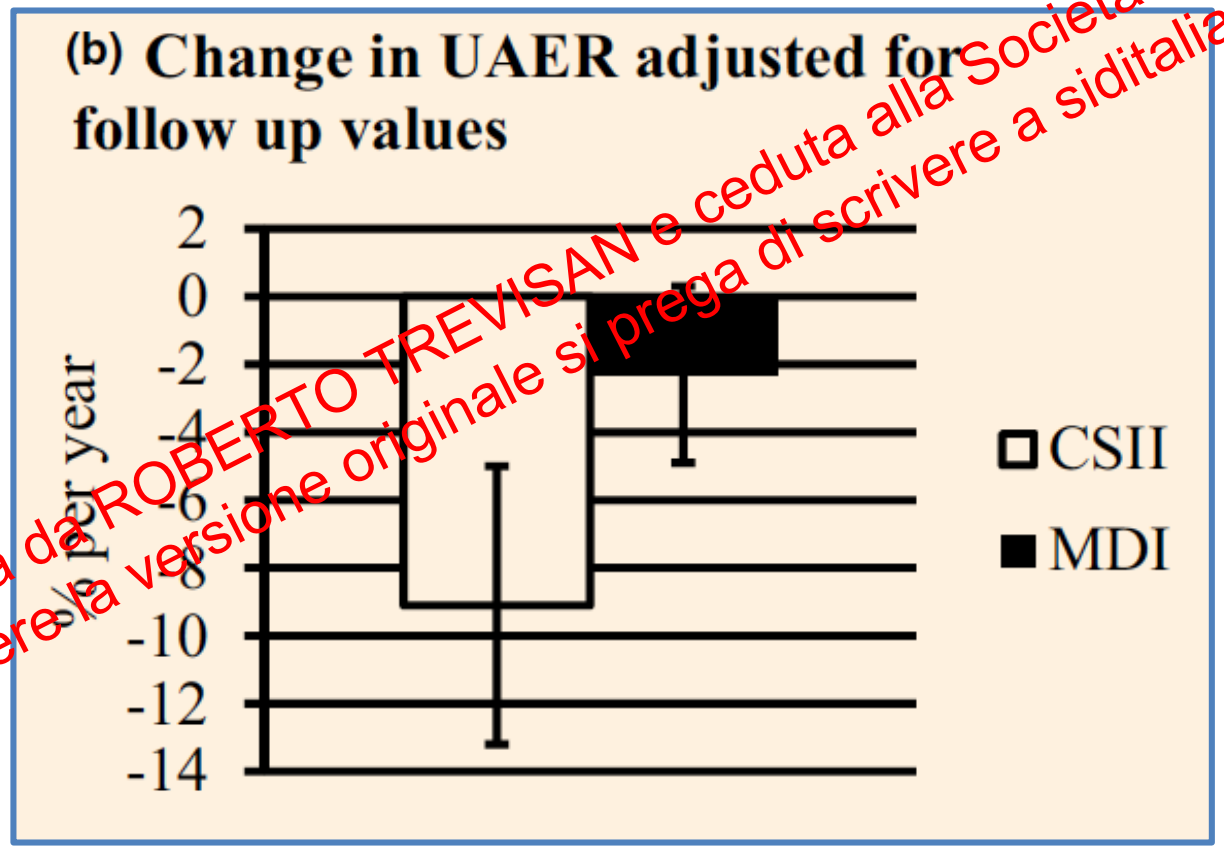
Accepted 28 August 2013

Annual change in urine albumin/creatinine ratio adjusted for follow-up values

Diabet. Med. 32, 1445–1452 (2015)



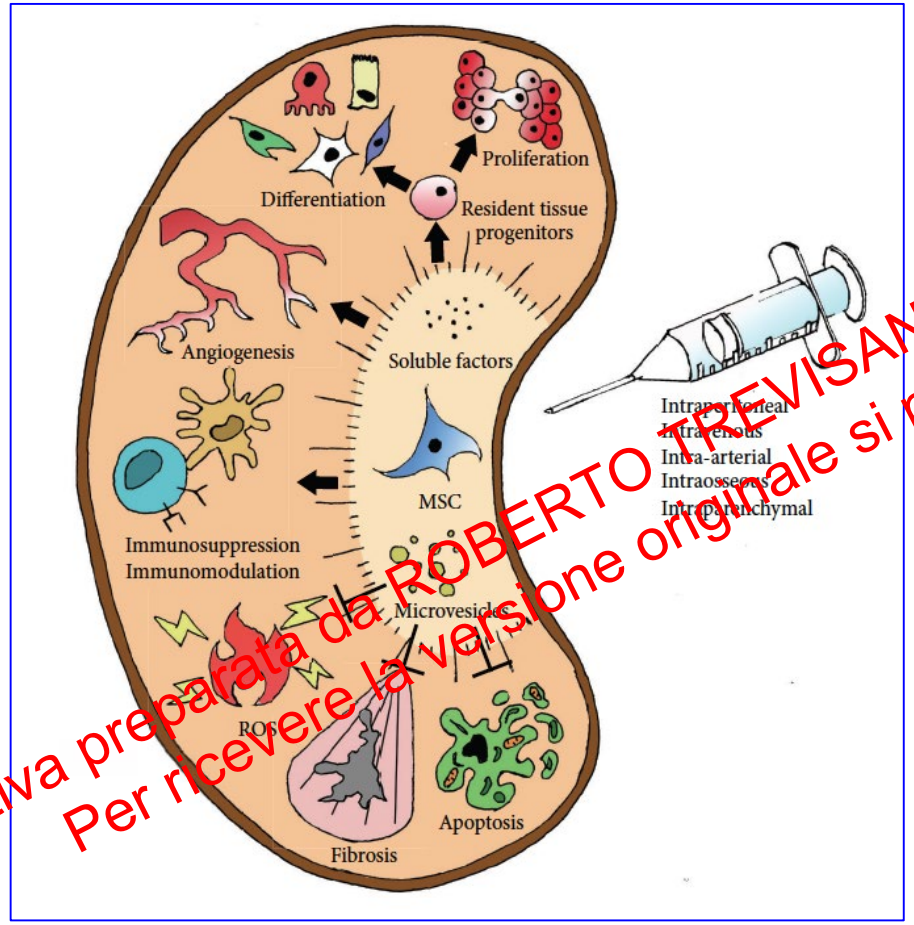
Adjustment includes sex, age, diabetes duration and baseline or follow-up values, respectively, of HbA1c, eGFR, urine albumin/creatinine ratio, mean arterial pressure, total cholesterol, renin–angiotensin–aldosterone system inhibition, antihypertensive treatment, smoking and CSII vs. MDI treatment.

PROSPETTIVE FUTURE

- Il ruolo degli SGLT2i
  - Riduzione Iperfiltrazione
  - Riduzione Ipertensione glomerulare
  - Riduzione rischio cardiovascoalre come nel diabete 2?
- La terapia cellulare

Review Article

Mesenchymal Stem Cell-Based Therapy for Kidney Disease: A Review of Clinical Evidence



Diabetic kidney disease					
NCT02[illegible]682		Novel stromal cell therapy for diabetic kidney disease (NEPHSTROM)	Galway, Ireland; Bergamo, Italy; Belfast, United Kingdom; Birmingham, United Kingdom	I/II	Diabetic kidney disease
24 months	48	Allogeneic bmMSC	Experimental: MSC i.v. infusion 3 doses 80, 160, 240×10^6 MSC Placebo comparator: only vehicle		Randomized, parallel assignment, double-blind, placebo-controlled

Stem Cells International, Vol 2016, Article ID 4798639

Conclusioni

- La incidenza di microangiopatia si è ridotta negli ultimi decenni.
- L'inibizione del RAS rimane centrale nella riduzione della progressione del danno renale.
- Il buon controllo glicemico rimane fondamentale per la prevenzione della macroangiopatia.
- La malattia cardiovascolare è la causa principale di mortalità nel diabete di tipo 1.
- La terapia con microinfusore sembra garantire una migliore prognosi cardio-renale, almeno in parte indipendente dall'effetto su gicemia e A1c.
- La inibizione di SGLT2 potrebbe migliorare la prognosi cardiorenale.
- Terapie con cellule staminali potrebbero presto offrire nuove strade per il trattamento delle complicanze del diabete.

Grazie

per la vostra attenzione