Gli endpoint micro-vascolari nei trial di outcome cardiovascolare

Giorgio Sesti

University "Magna Graecia" of Catanzaro
ITALY

Potenziali conflitti di interesse

Il Prof Giorgio Sesti dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

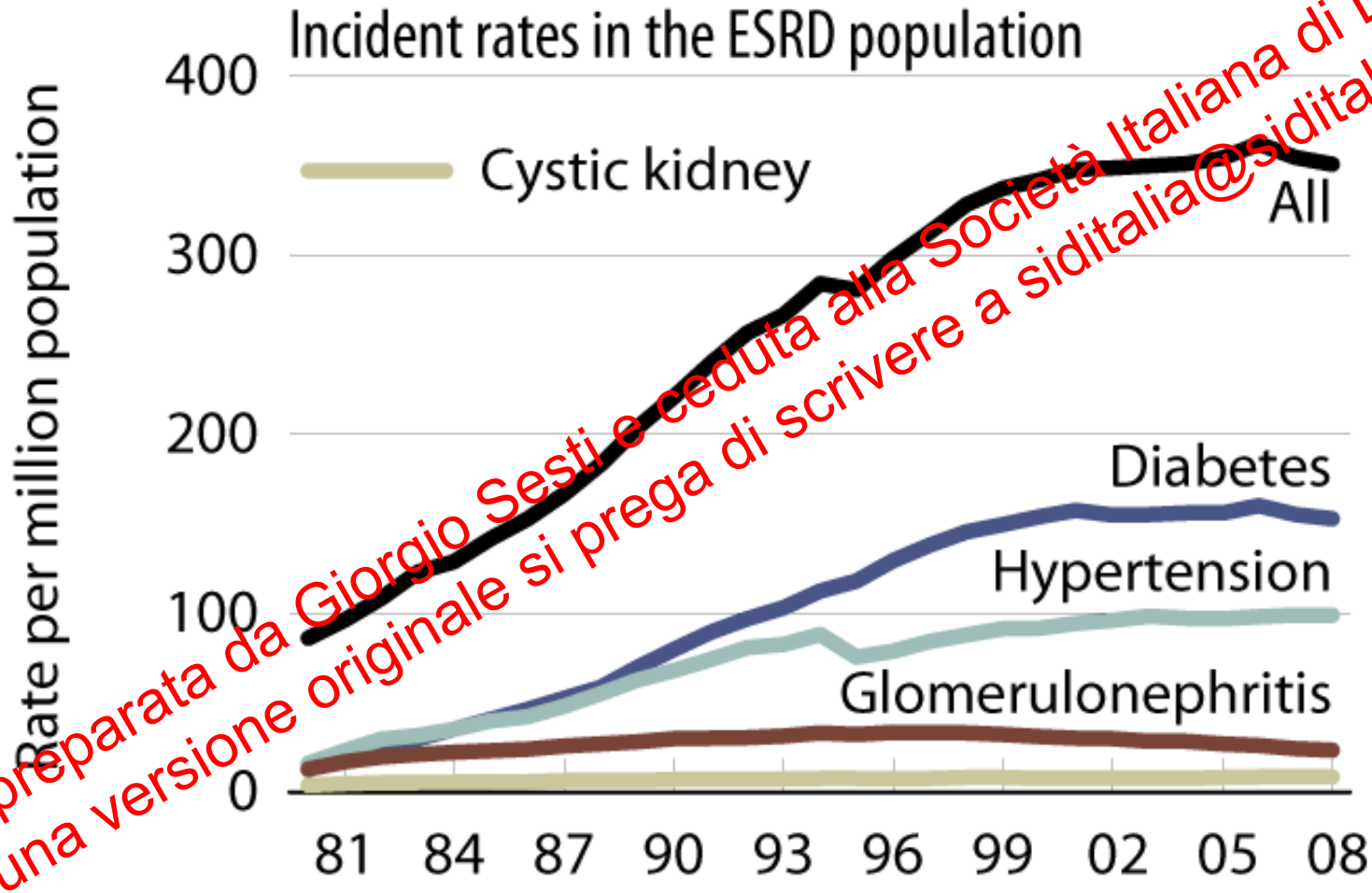
Novo Nordisk, MSD, Boehringer-Ingelheim, Lilly, Janssen, AstraZeneca, Novartis e Takeda per attività di Relatore ad eventi.

Novo Nordisk, Intarcia, Boehringer-Ingelheim, Lilly, MSD, Servier, AstraZeneca e Janssen per attività di Consulenza.

Ringrazio caldamente la SID per lo straordinario contributo alla mia formazione culturale, scientifica e clinica.

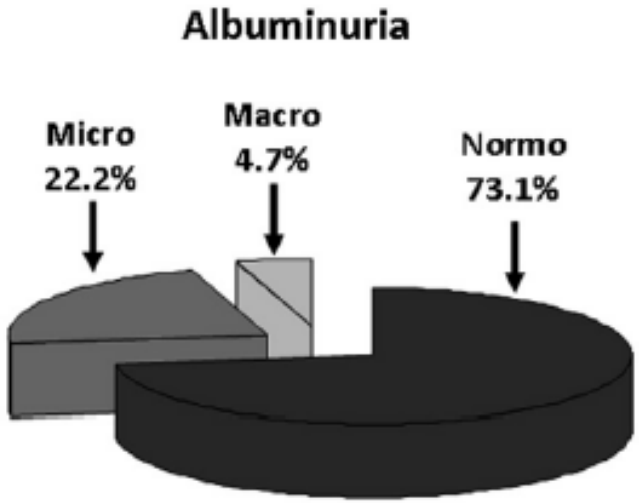
Senza il fondamentale sostegno della SID non sarei oggi qui a presentare questa mia relazione.

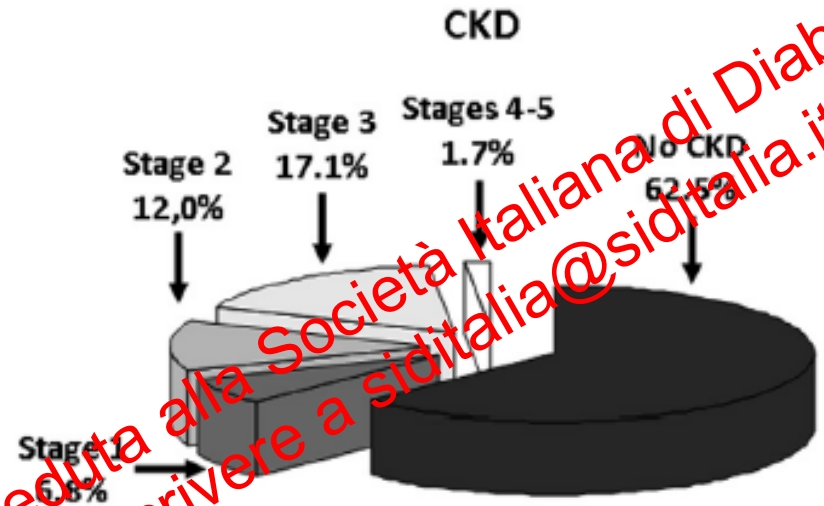
Adjusted ESRD incident rates, by primary diagnosis, & diabetes in the general population

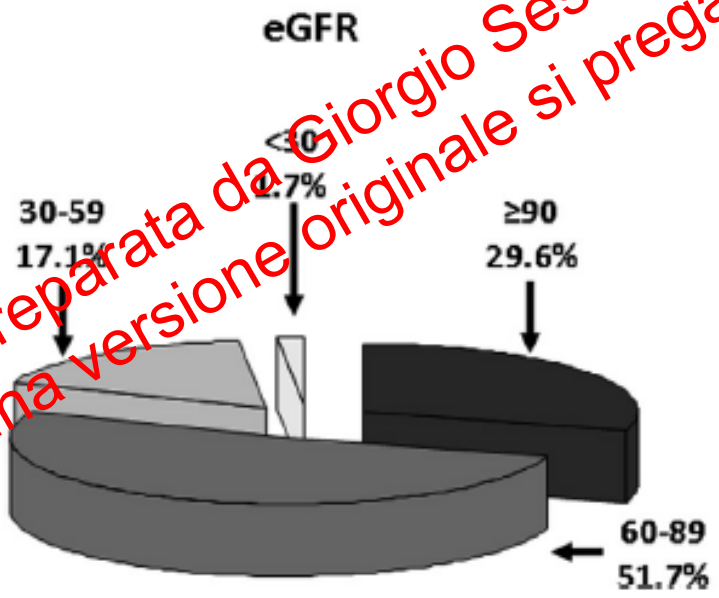


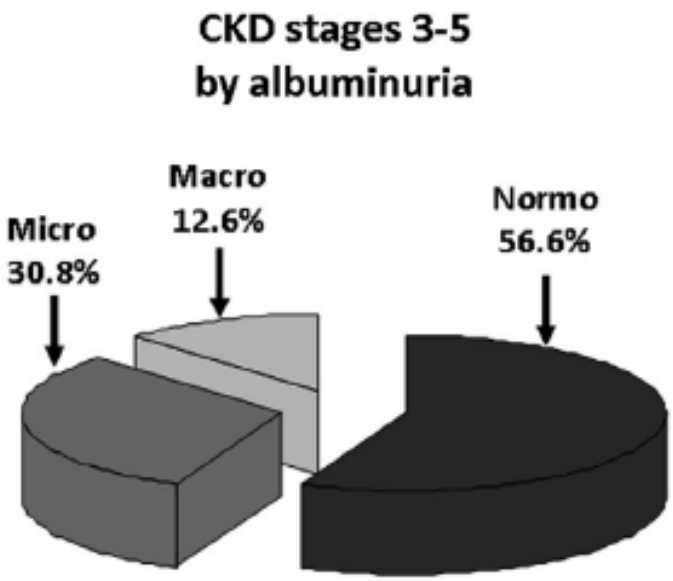
Incident ESRD patients; rates adjusted for age, gender, & race. Data on the prevalence of diabetes in the general population obtained from the CDC's Behavioral Risk Factor Surveillance System, at www.cdc.gov/brfss.

Prevalence of albuminuria and eGFR categoried and CKD stages (with stratification of subjects with Stages 3-5 CKD by albuminuria) in the RIACE cohort



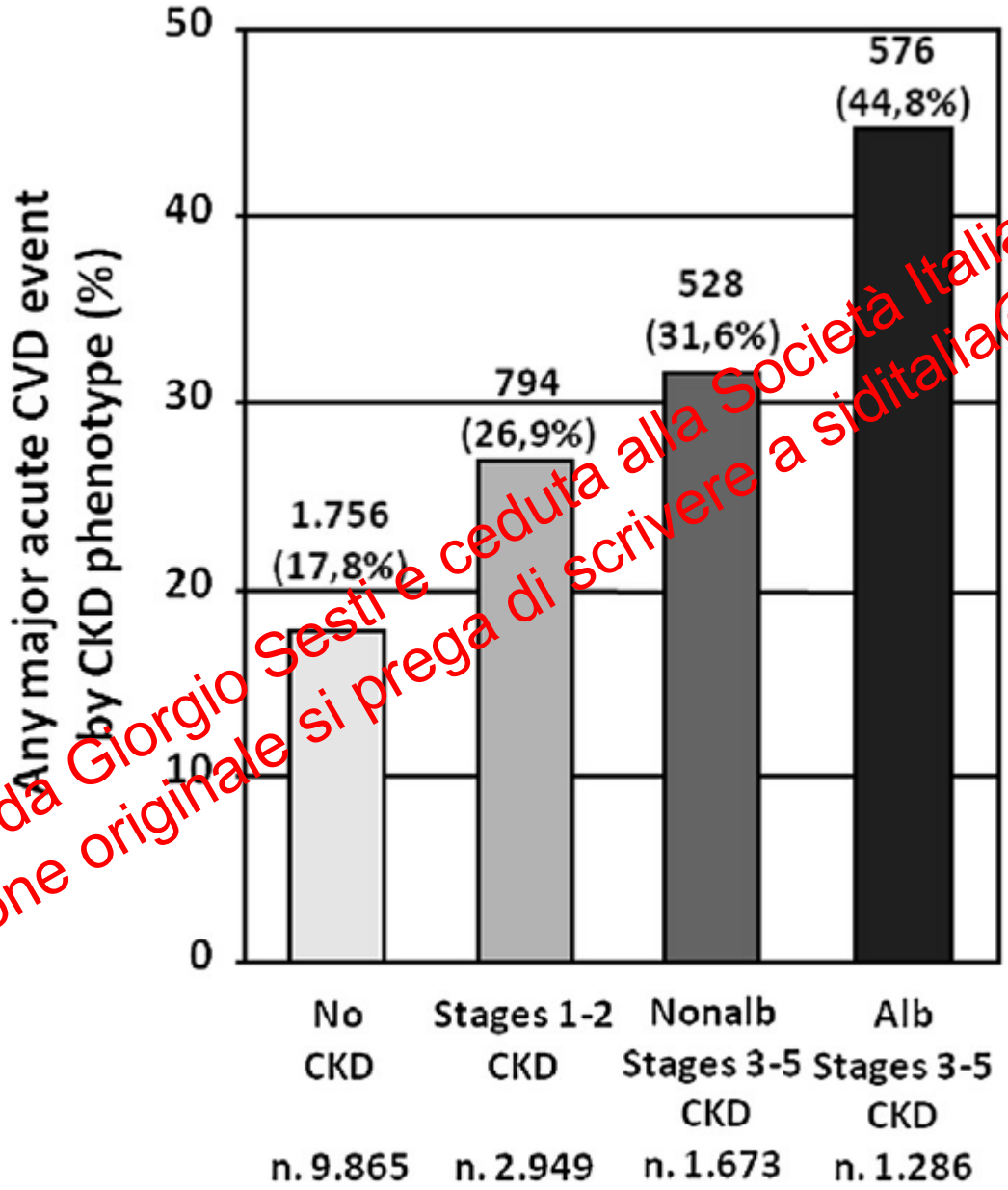






Pugliese G et at. Nutr Metab Cardiovasc Dis 24: 815-822, 2014

Prevalence of major acute CVD events by CKD phenotype in the RIACE cohort



Publiese G et at. Nutr Metab Cardiovasc Dis 24: 815-822, 2014

Landmark CV outcomes studies in type 2 diabetes

1. Intensive glucose control vs. standard-therapy on CV outcome:

- **UKPDS**
- **ACCORD**
- **ADVANCE**
- **VADT**

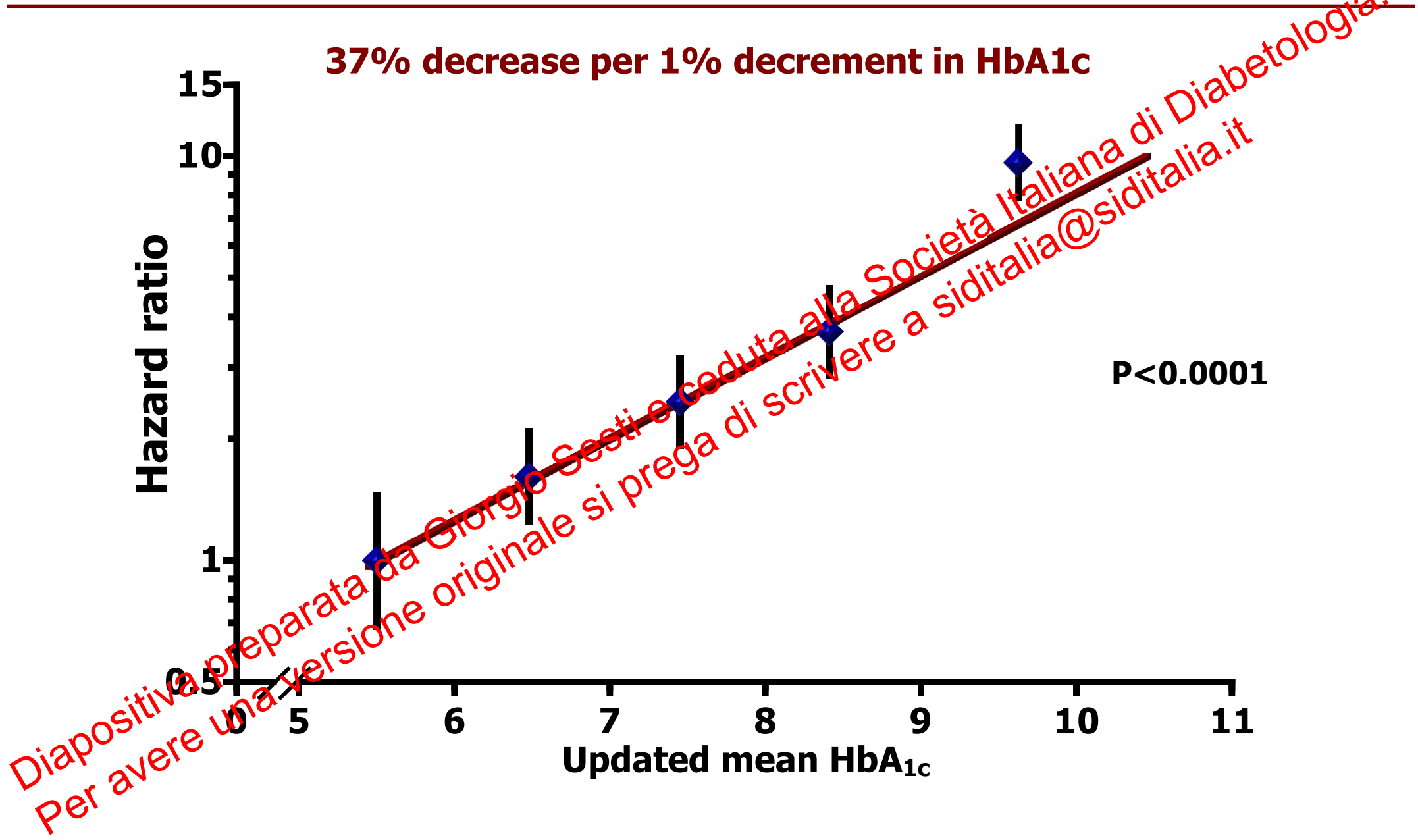
2. Glucose-lowering drugs vs. placebo on CV outcome:

- **HOME (metformin add on to insulin)**
- **Origin (insulin glargine)**

3. New glucose-lowering drugs vs. placebo on CV outcome after 2008 FDA guidance:

- **SAVOR-TIMI 53 (saxagliptin)**
- **EXAMINE (alogliptin)**
- **TECOS (sitagliptin)**
- **ELIXA (lixisenatide)**
- **EMPA-REG OUTCOME (empagliflozin)**
- **LEADER (liraglutide)**
- **SUSTAIN-6 (semaglutide)**

Microvascular Endpoints



UKPDS 35. BMJ 2000; 321: 405-12

UKPDS, ACCORD, ADVANCE, and VADT Study Characteristics

	UKPDS 33	UKPDS 34	ACCORD	ADVANCE	VADT
Protocol Characteristics					
A1C goals, % (I vs S)[a]	FPG <108 mg/dL vs. best achievable FPG with diet alone	FPG <108 mg/dL vs. best achievable FPG with diet alone	<6.0 vs 7.0-7.9	≤6.5 vs based on local guidelines	<6.0 (action if >6.5) vs planned separation of 1.5
Protocol for glycemic control (I vs. S)[a]	Sulfonylurea or insulin vs. diet alone	Metformin vs. diet alone	Multiple drugs in both arms	Multiple drugs added to gliclazide vs multiple drugs with no gliclazide	Multiple drugs in both arms
Management of other risk factors	Embedded blood pressure trial	Embedded blood pressure trial	Embedded blood pressure and lipid trials	Embedded blood pressure trial	Protocol for intensive treatment in both arms

[a]Medication rates for ACCORD are for any use during the study.

I = intensive glycemic control; S = standard glycemic control.

Turnbull FR, et al. Diabetologia 52:2288–2298, 2009

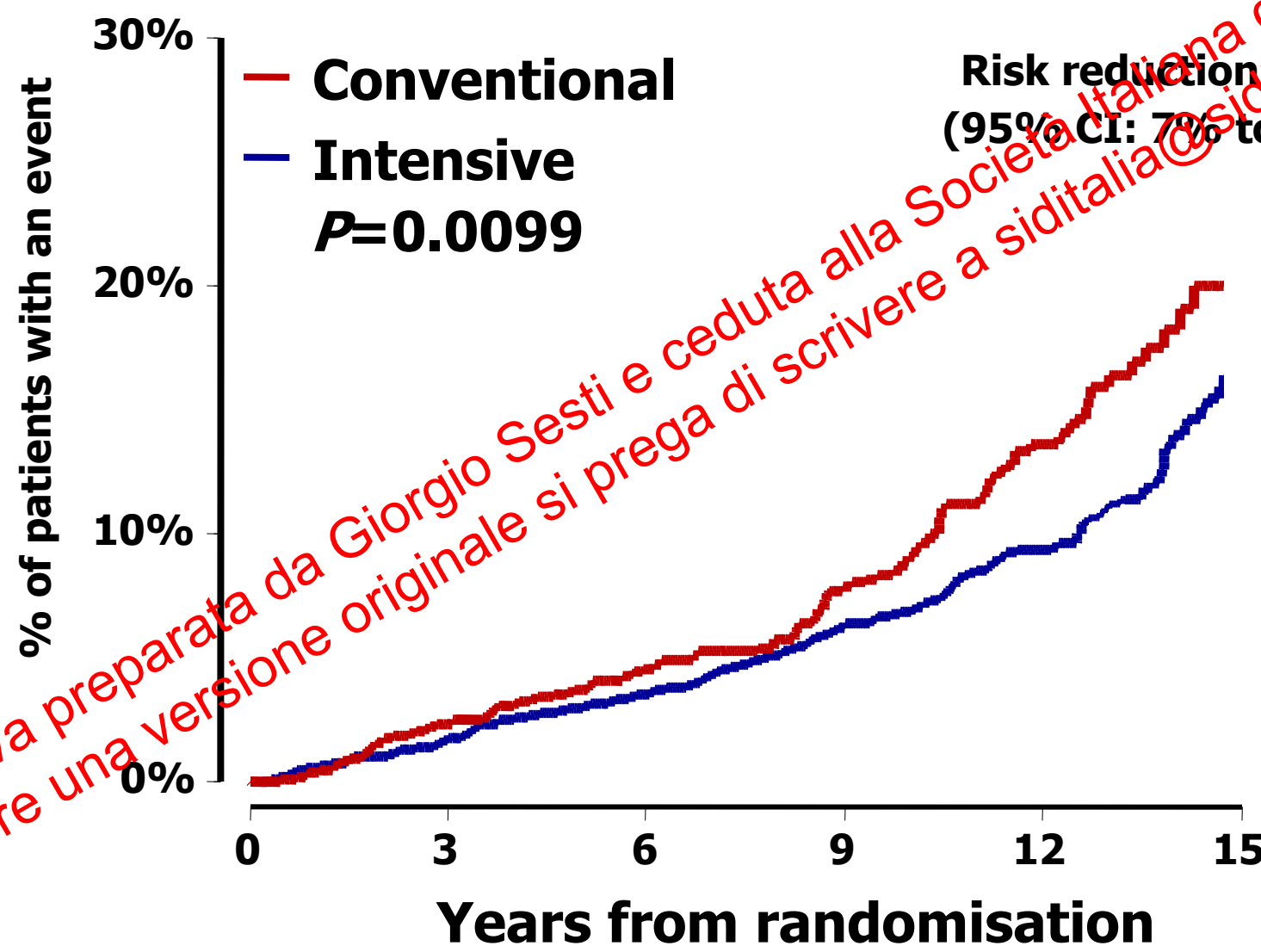
UKPDS, ACCORD, ADVANCE, and VADT Results

	UKPDS 33	UKPDS 34	ACCORD	ADVANCE	VADT
Outcomes					
HbA1c (Intensive vs. Standard)	7.0 vs. 7.9%	7.4 vs. 8.0	6.5 vs. 7.3%	6.4 vs. 7.5%	6.9 vs. 8.4%
Definition of outcome	21 clinical endpoints	21 clinical endpoints	Nonfatal MI, nonfatal stroke, CVD death	Microvascular plus macrovascular (nonfatal MI, nonfatal stroke, CVD death) outcomes	Nonfatal MI, nonfatal stroke, CVD death, hospitalization for heart failure, revascularization
RR for microalbu-minuria	0.88 (0.75-1.04)	1.00 (0.77-1.30)	**0.88 (0.80-0.96)**	**0.92 (0.86-0.98)**	0.74 (0.51-1.07)
RR for End Stage Renal Disease	0.74 (0.33-1.67)	1.20 (0.17-8.49)	0.91 (0.73-1.15)	**0.35 (0.18-0.70)**	0.64 (0.25-1.64)

Coca SG et al. Arch Intern Med 172(10):761-769, 2012

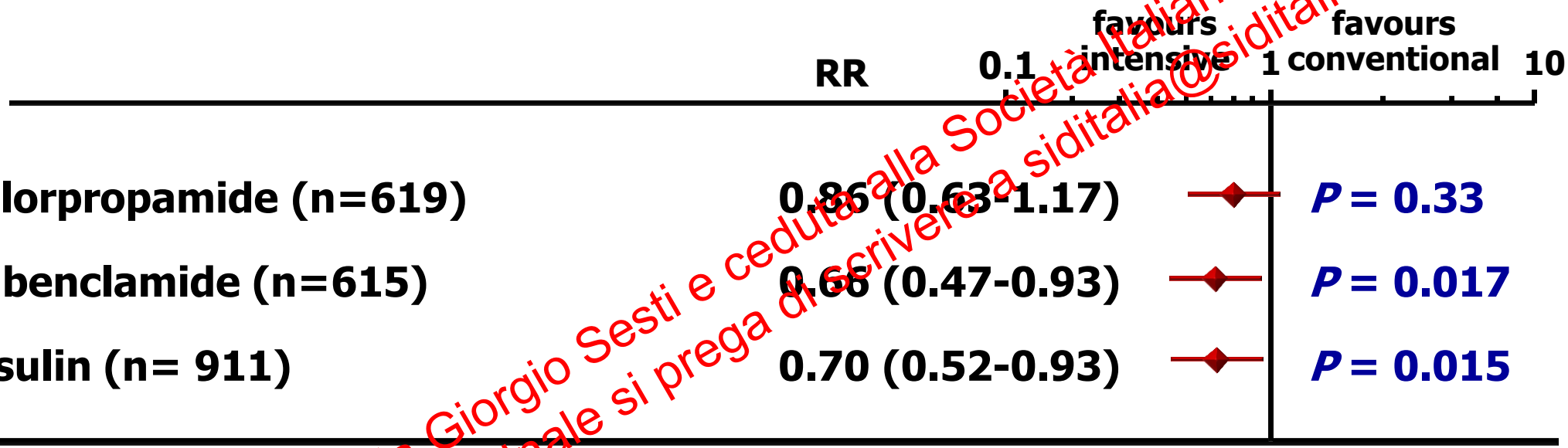
UKPDS - Microvascular Endpoints (cumulative)

renal failure or death, vitreous haemorrhage or photocoagulation 346 of 3867 patients (9%)



Lancet 352:837-853, 1998

UKPDS 33: Microvascular events (Retinopathy and nephropathy)

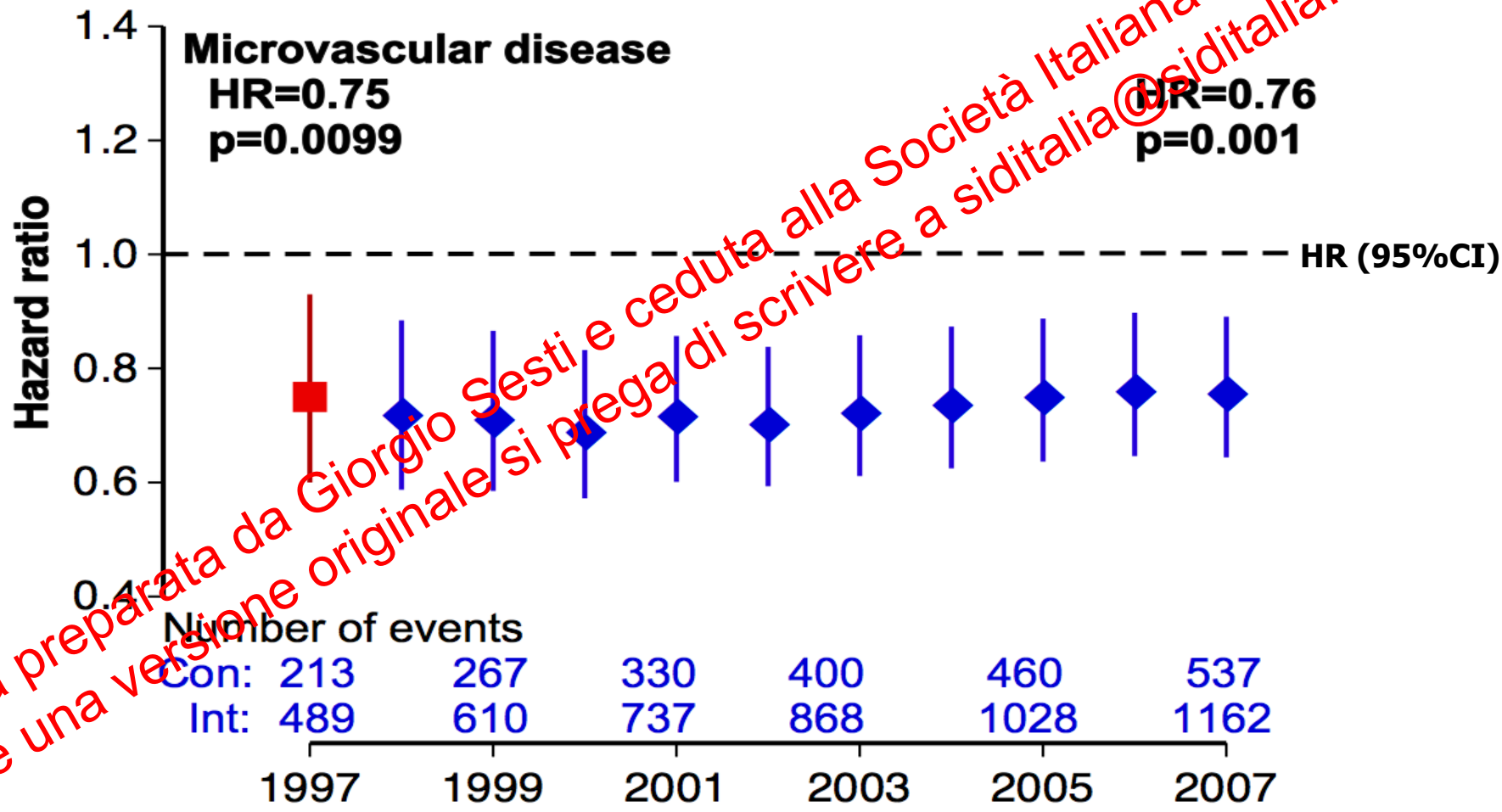


UKPDS 33 Lancet 352:837-853, 1998

UKPDS 80: Extended effects of improved glycemic control in patients with newly diagnosed type 2 diabetes- Microvascular disease Hazard Ratio

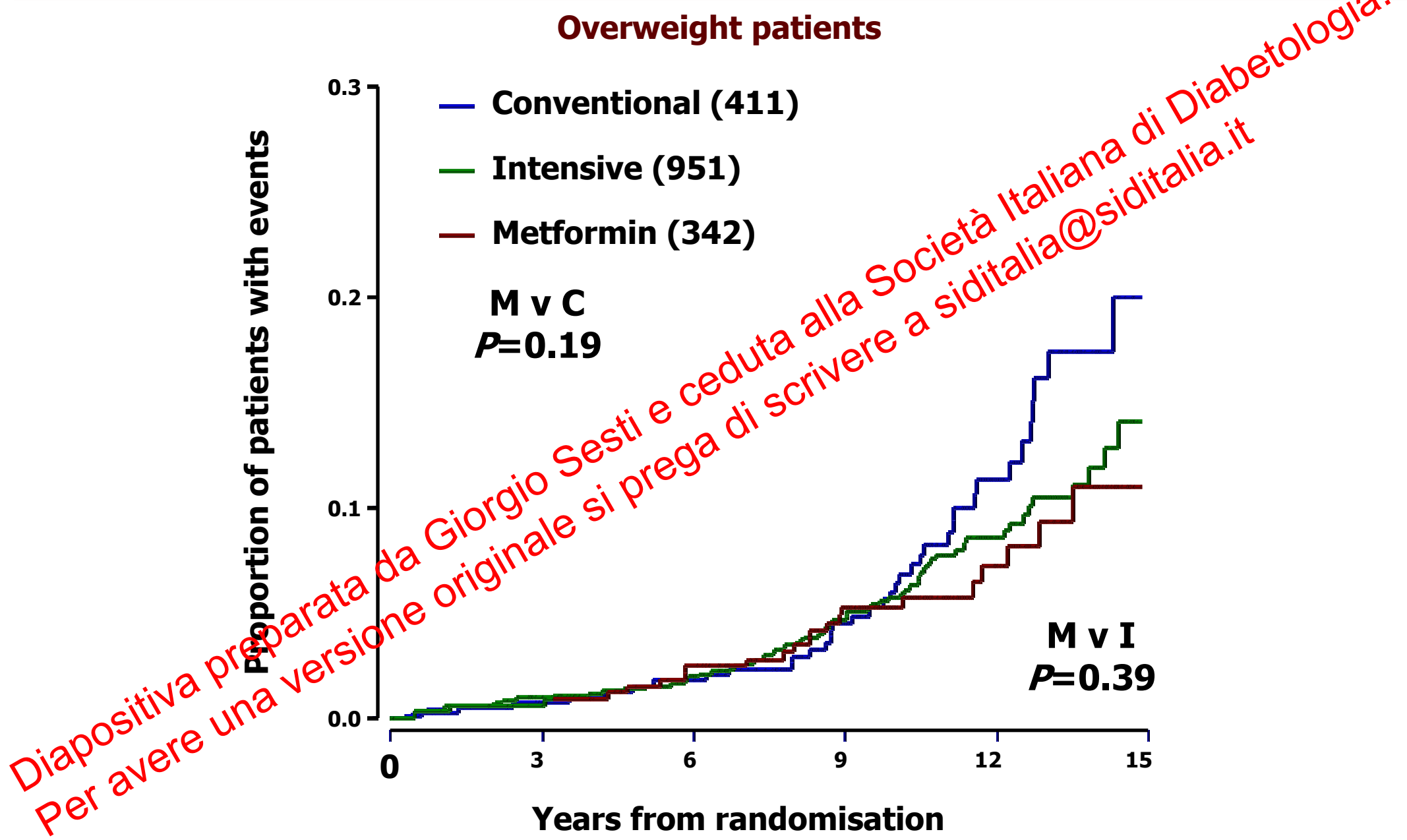
(photocoagulation, vitreous haemorrhage, renal failure)

Intensive (SU/Ins) *vs.* Conventional glucose control



Holman R.R. et al. N Engl J Med 359:1577-1589, 2008

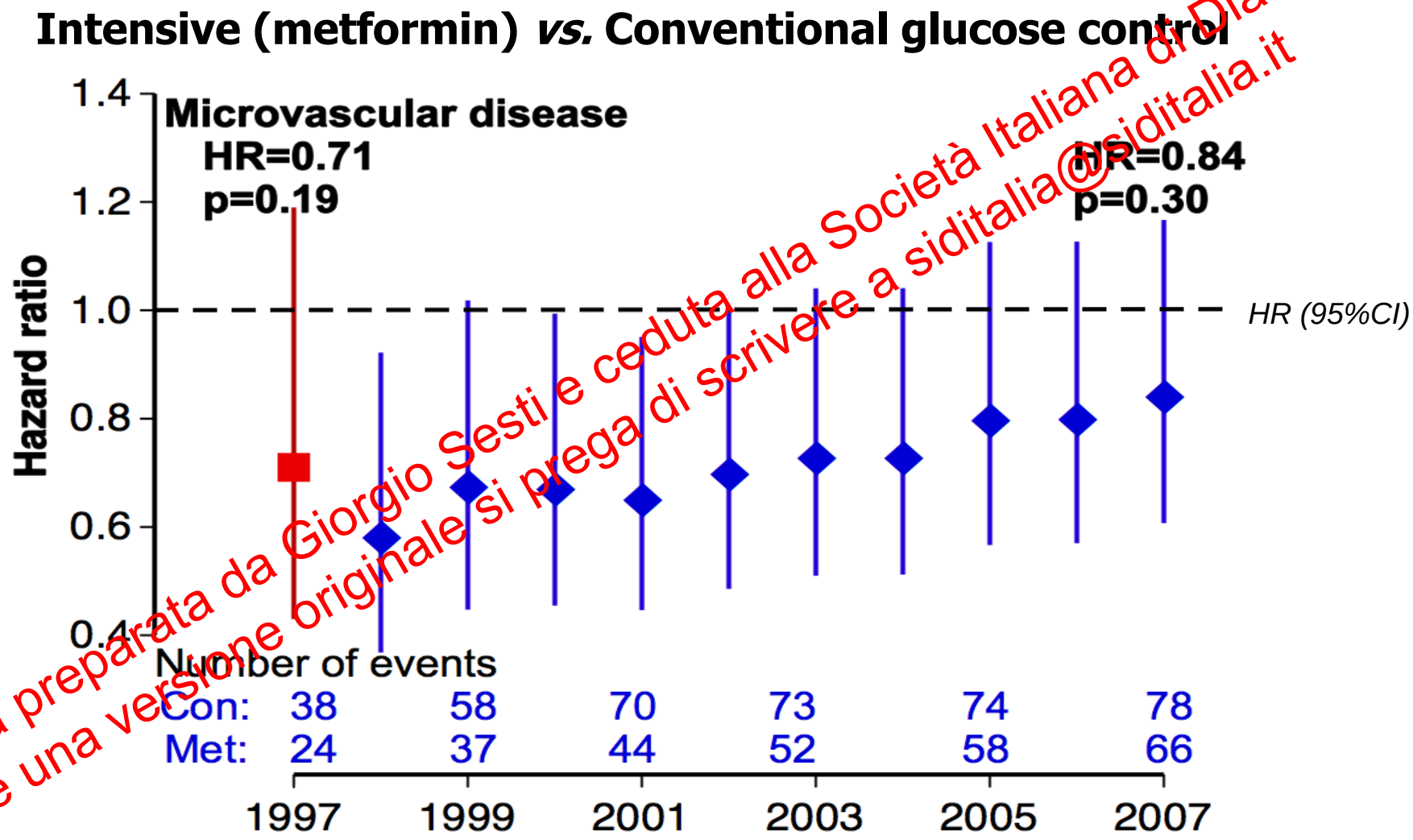
UKPDS 34 Metformin substudy: Microvascular endpoints



UKPDS 34. Lancet 352:854-865, 1998

UKPDS 80: Extended effects of improved glycemic control in patients with newly diagnosed type 2 diabetes- Microvascular disease Hazard Ratio

(Photocoagulation, vitreous haemorrhage, renal failure)



Holman R.R. et al. N Engl J Med 359:1577-1589, 2008

Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial

*Faramarz Ismail-Beigi, Timothy Craven, Mary Ann Banerji, Jan Basile, Jorge Calles, Robert M Cohen, Robert Cuddihy, William C Cushman, Saul Genuth, Richard H Grimm Jr, Bruce P Hamilton, Byron Hoogwerf, Kuane Karl, Lois Katz, Armand Krikorian, Patrick O'Connor, Rodica Pop-Busui, Ulrich Schubart, Debra Simmons, Harris Taylor, Abraham Thomas, Daniel Weiss, Irene Hramiak, for the ACCORD trial group**

Ismail-Beigi F et al. Lancet 76:419-430, 2010

Composite Microvascular Outcomes

1st Composite Outcome:

Development of renal failure *or* diabetic eye complications

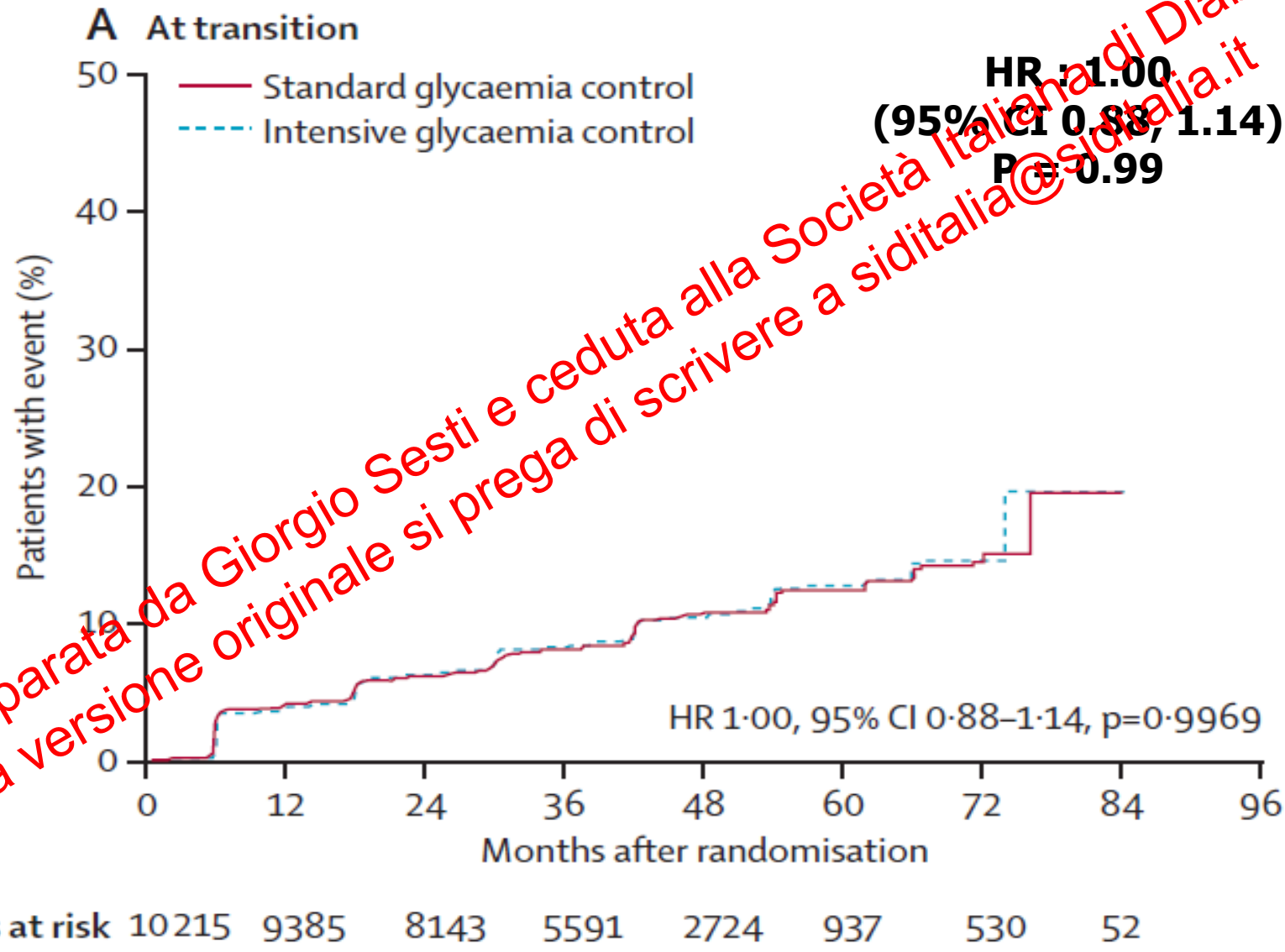
Renal failure: initiation of dialysis or ESRD, renal transplantation, or irreversible rise of serum creatinine above 3.3 mg/dL

Eye complications: retinal photocoagulation or vitrectomy to treat diabetic retinopathy

Essentially replicates UKPDS composite micro-vascular outcome

Ismail-Beigi F et al. Lancet 76:419-430, 2010

Kaplan-Meier plots of the micro-vascular primary composite outcome
Data until transition of intensive glycemia group to standard therapy



Ismail-Beigi F et al. Lancet 76:419-430, 2010

Nephropathy Outcomes

1. **Development of microalbuminuria**

   (albumin:creatinine ratio ≥30 and <300 mg/g)

2. **Development of macroalbuminuria**

   (albumin:creatinine ratio ≥ 300 mg/g)

3. **Development of renal failure**

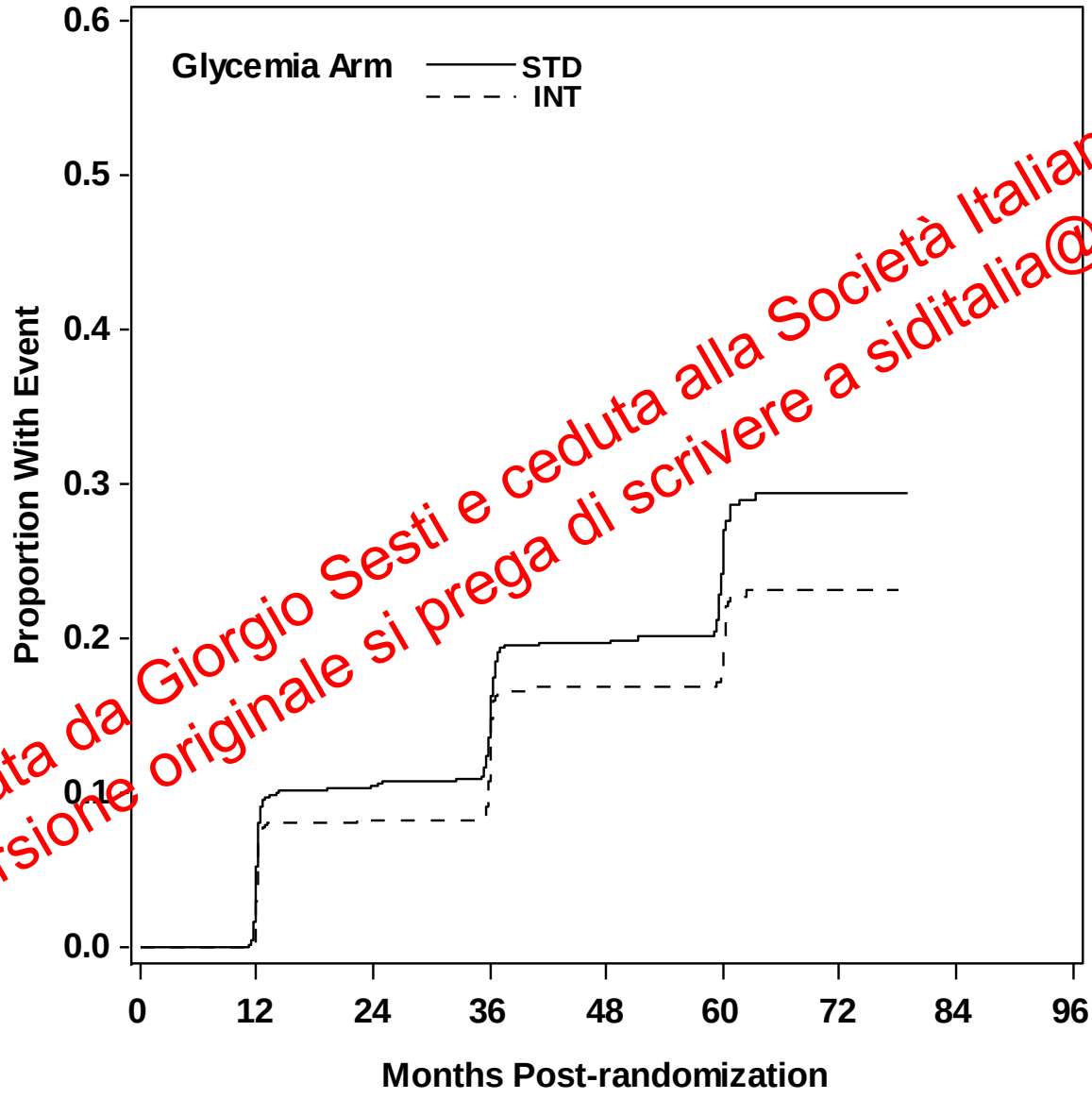
   (initiation of dialysis or ESRD, or renal transplantation, or irreversible rise of serum creatinine above 3.3 mg/dL)

4. **Development of any of outcomes 1 to 3, above**

5. **Doubling of baseline serum creatinine *or* more than 20 mL/min/1.73 m^2 decrease in estimated GFR**

Ismail-Beigi F et al. Lancet 76:419-430, 2010

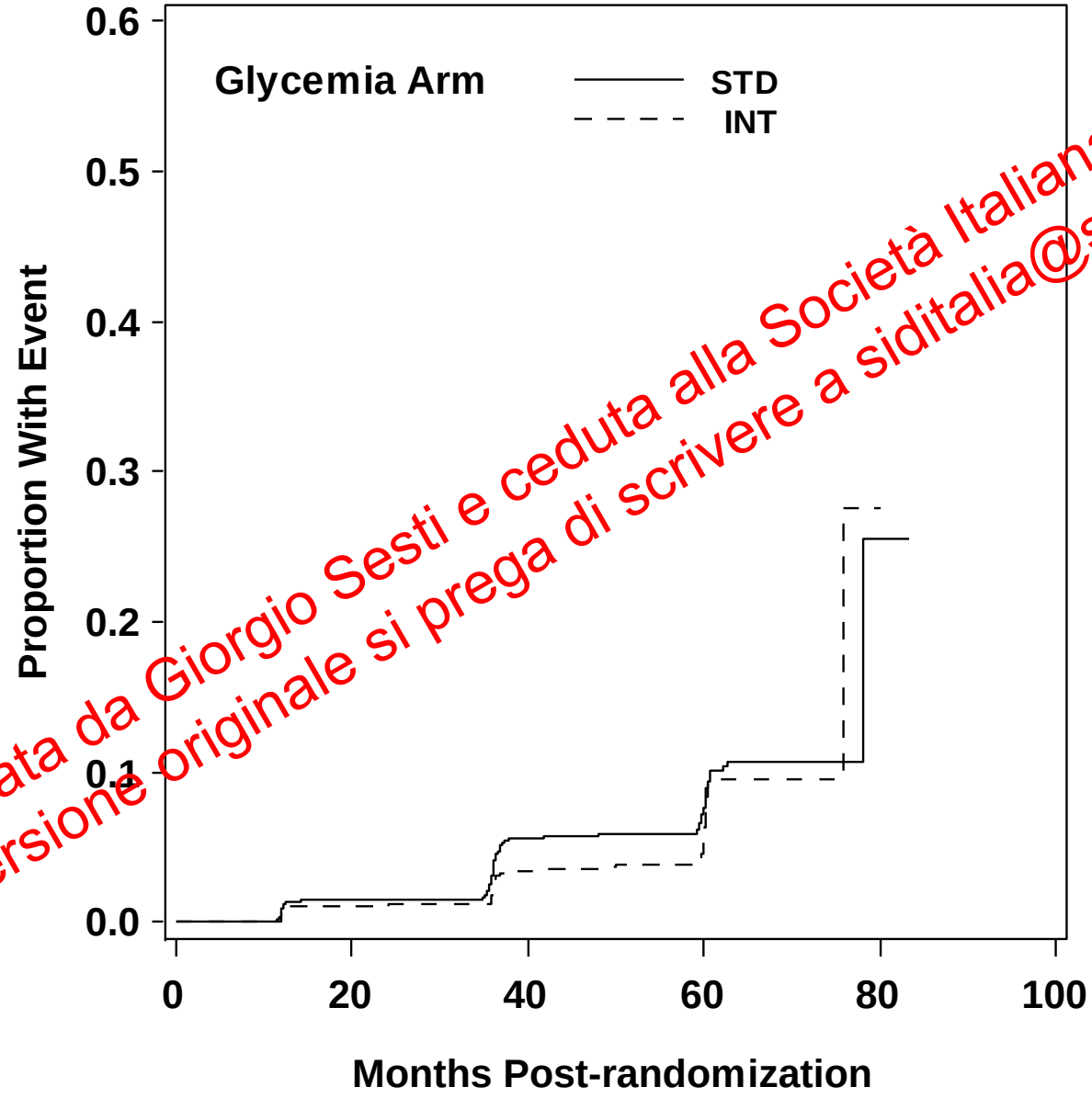
Comparison of intensive and standard glycaemic therapy for development of microalbuminuria, until transition



HR (95% CI):
0.79 (0.69, 0.90)
***P*= 0.0005**

Ismail-Beigi F et al. Lancet 76:419-430, 2010

Comparison of intensive and standard glycemic therapy for development of macroalbuminuria, until transition



HR (95% CI):
0.68 (0.54, 0.86)
P = 0.0013

Ismail-Beigi F et al. Lancet 76:419-430, 2010

The NEW ENGLAND JOURNAL of MEDICINE

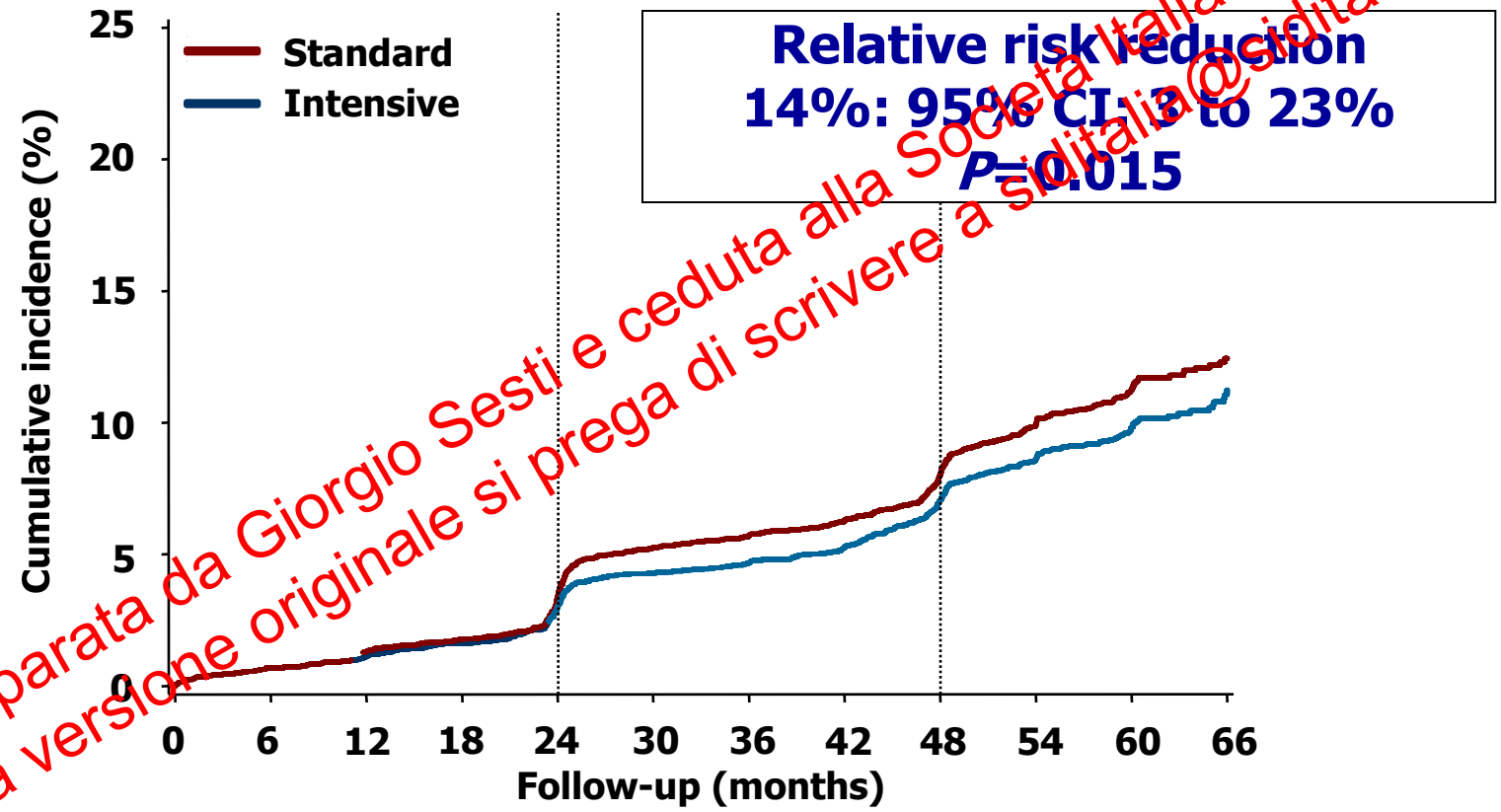
ORIGINAL ARTICLE

Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes

The ADVANCE Collaborative Group*

N Engl J Med 358:2560-2572, 2008

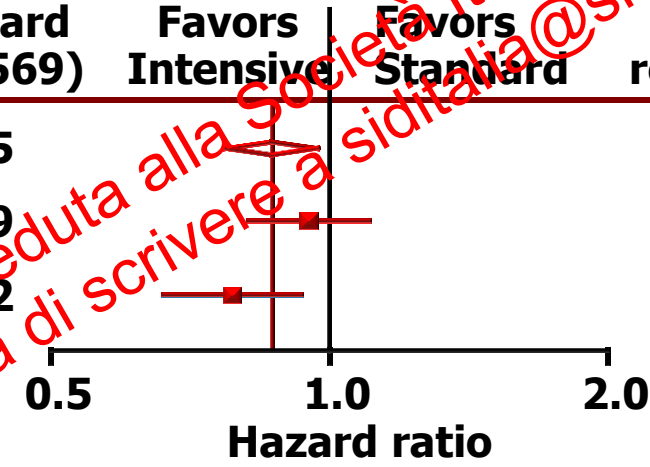
Major microvascular events



N Engl J Med 358:2560-2572, 2008

ADANCE: Major microvascular events

	Number of patients with event			Relative risk reduction (95% CI)
	Intensive (n=5,571)	Standard (n=5,569)	Favors Intensive / Favors Standard	
Microvascular	526	605		14% (3 to 23) †
New or worsening retinopathy	332	349		5% (-10 to 18)
New or worsening nephropathy	230	292		21% (7 to 34) ‡



†*P*=0.01

‡*P*=0.006

N Engl J Med 358:2560-2572, 2008

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Glucose Control and Vascular Complications in Veterans with Type 2 Diabetes

William Duckworth, M.D., Carlos Abraira, M.D., Thomas Moritz, M.S., Domenic Reda, Ph.D., Nicholas Emanuele, M.D., Peter D. Reaven, M.D., Franklin J. Zieve, M.D., Ph.D., Jennifer Marks, M.D., Stephen N. Davis, M.D., Rodney Hayward, M.D., Stuart R. Warren, J.D., Pharm.D., Steven Goldman, M.D., Madeline McCarren, Ph.D., M.P.H., Mary Ellen Vitek, William G. Henderson, Ph.D., and Grant D. Huang, M.P.H., Ph.D., for the VADT Investigators*

VADT = Veterans Affairs Diabetes Trial

Duckworth, W et al. N Engl J Med 360:129-139, 2009

VADT: Microvascular Outcomes

Outcome, n/N (%)	Standard (n=899)	Intensive (n=892)	*P*
Retinopathy			
Progression to proliferative disease	16/399 (4.0%)	23/406 (5.7%)	0.27
Progression to macular edema	17/361 (4.7)	12/371 (3.2)	0.31
Increase of 2 steps in disease severity	88/399 (22.1)	69/406 (17.0)	0.07
New onset	66/135 (48.9)	54/128 (42.2)	0.27
Nephropathy			
Serum creatinine >3 mg/dL	16/884 (1.8)	18/882 (2.0)	0.72
Glomerular filtration rate <15 mL/min	11/884 (1.2)	7/882 (0.8)	0.35
Any increase in albuminuria	48/731 (6.6)	30/728 (4.1)	0.05
New Neuropathy			
Any	218/498 (43.8)	202/464 (43.5)	0.94
Mononeuropathy	20/498 (4.0)	22/464 (4.7)	0.58
Peripheral	199/498 (40.0)	178/464 (38.4)	0.61
Autonomic	26/498 (5.2)	38/464 (8.2)	0.07

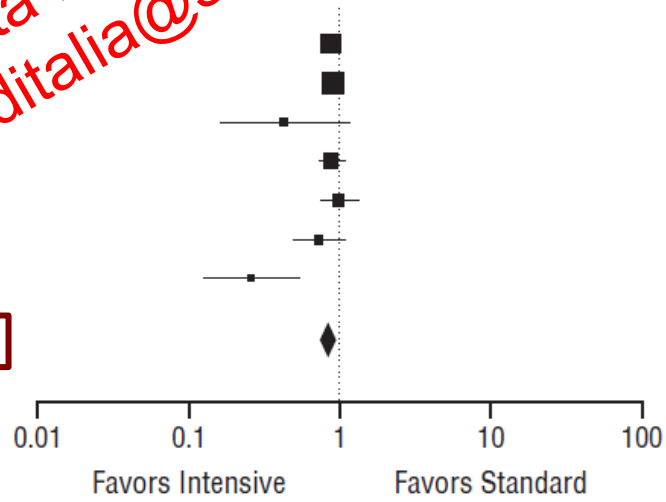
Duckworth W et al; the VADT Study Investigators. N Engl J Med 360(2):129-139, 2009

Role of intensive glucose control in development of renal endpoints in type 2 diabetes mellitus: Microalbuminuria

Study or Subgroup	Intensive Therapy Events	Intensive Therapy Total	Standard Therapy Events	Standard Therapy Total	Weight, %	Risk Ratio M-H, Random (95% CI)
ACCORD[8,14]	720	3250	828	3273	27.3	0.88 (0.80-0.96)
ADVANCE[12]	1318	5571	1434	5569	29.3	0.92 (0.86-0.98)
Kumamoto[4,15]	5	52	11	50	1.3	0.44 (0.16-1.17)
UKPDS 33[16]	368	2277	172	938	19.6	0.88 (0.76-1.04)
UKPDS 34[17]	79	342	95	411	12.2	1.00 (0.77-1.30)
VADT[11]	43	442	61	463	7.6	0.74 (0.51-1.07)
VA Feasibility Trial[5]	7	42	30	46	2.5	0.26 (0.13-0.52)
Total (95% CI)		**11976**		**10750**	**100.0**	**0.86 (0.76-0.96)**
Total events	**2540**		**2631**			

Heterogeneity: $\tau^2 = 0.01$; $\chi^2_6 = 16.71$; $P = .01$; $I^2 = 64\%$

Test for overall effect: $z = 2.60$; $P = .009$



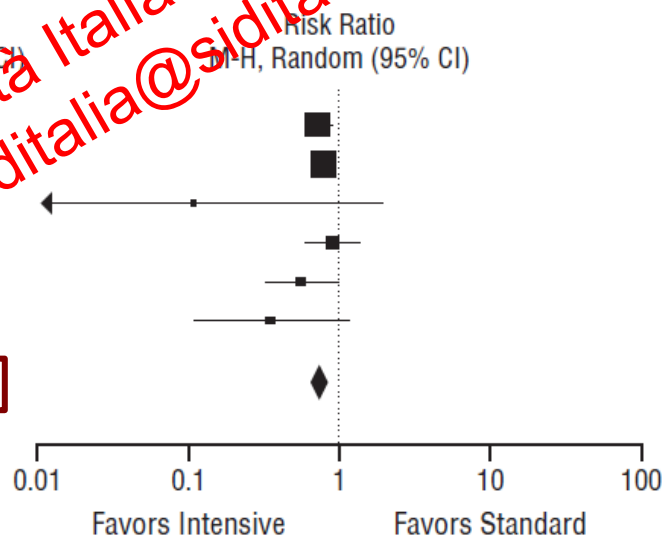
Coca SG et al. Arch Intern Med 172(10):761-769, 2012

Role of intensive glucose control in development of renal endpoints in type 2 diabetes mellitus: Macroalbuminuria

Study or Subgroup	Intensive Therapy Events	Intensive Therapy Total	Standard Therapy Events	Standard Therapy Total	Weight, %	Risk Ratio M-H, Random (95% CI)
ACCORD[8,14]	195	4397	272	4424	39.3	0.72 (0.60-0.86)
ADVANCE[12]	230	5571	292	5569	42.5	0.79 (0.67-0.93)
Kumamoto[4,15]	0	52	4	50	0.2	0.11 (0.01-1.94)
UKPDS 33[16]	72	2277	33	938	10.4	0.90 (0.60-1.35)
VADT[11]	20	693	36	703	6.2	0.56 (0.33-0.96)
VA Feasibility Trial[5]	3	24	10	28	1.4	0.35 (0.11-1.13)
Total (95% CI)		**13014**		**11712**	**100.0**	**0.74 (0.65-0.85)**
Total events	**520**		**647**			

Heterogeneity: $\tau^2 = 0.00$; $\chi^2_5 = 5.73$; $P = .33$; $I^2 = 13\%$

Test for overall effect: $z = 4.24$; $P = .001$



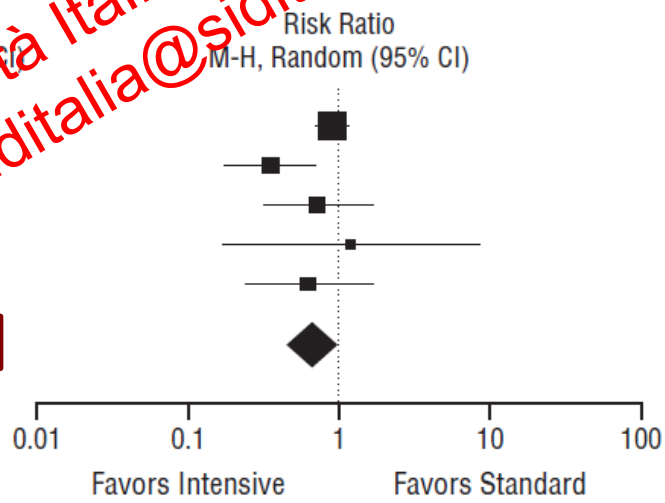
Coca SG et al. Arch Intern Med 172(10):761-769, 2012

Role of intensive glucose control in development of renal endpoints in type 2 diabetes mellitus: end-stage renal disease

Study or Subgroup	Intensive Therapy Events	Intensive Therapy Total	Standard Therapy Events	Standard Therapy Total	Weight, %	Risk Ratio M-H, Random (95% CI)
ACCORD[8,14]	138	5119	151	5115	43.2	0.91 (0.73-1.15)
ADVANCE[12]	11	5571	31	5569	21.2	0.35 (0.18-0.70)
UKPDS 33[16]	16	2729	9	1138	17.3	0.74 (0.33-1.67)
UKPDS 34[17]	2	342	2	411	4.2	1.20 (0.17-8.49)
VADT[11]	7	882	11	884	14.1	0.64 (0.25-1.64)
Total (95% CI)		**14 643**		**13 117**	**100.0**	**0.69 (0.46-1.05)**
Total events	**174**		**204**			

Heterogeneity: $\tau^2 = 0.09$; $\chi^2_4 = 7.08$; $P = .13$; $I^2 = 43\%$

Test for overall effect: $z = 1.72$; $P = .09$



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   - EMPA-REG OUTCOME (empagliflozin)
   - LEADER (liraglutide)
   - SUSTAIN-6 (semaglutide)

Long-term Effects of Metformin on Metabolism and Microvascular and Macrovascular Disease in Patients With Type 2 Diabetes Mellitus

Hyperinsulinemia: the Outcome of its Metabolic Effects (HOME)

The HR for the primary end point, an aggregate of microvascular and macrovascular morbidity and mortality, was 0.92 (95% CI, 0.72-1.18; *P*=0.33).

The HR for the secondary, microvascular endpoint was 1.04 (95% CI, 0.75-1.44; *P*=0.43).

Kooy A et al. Arch Intern Med 169:616-625, 2009

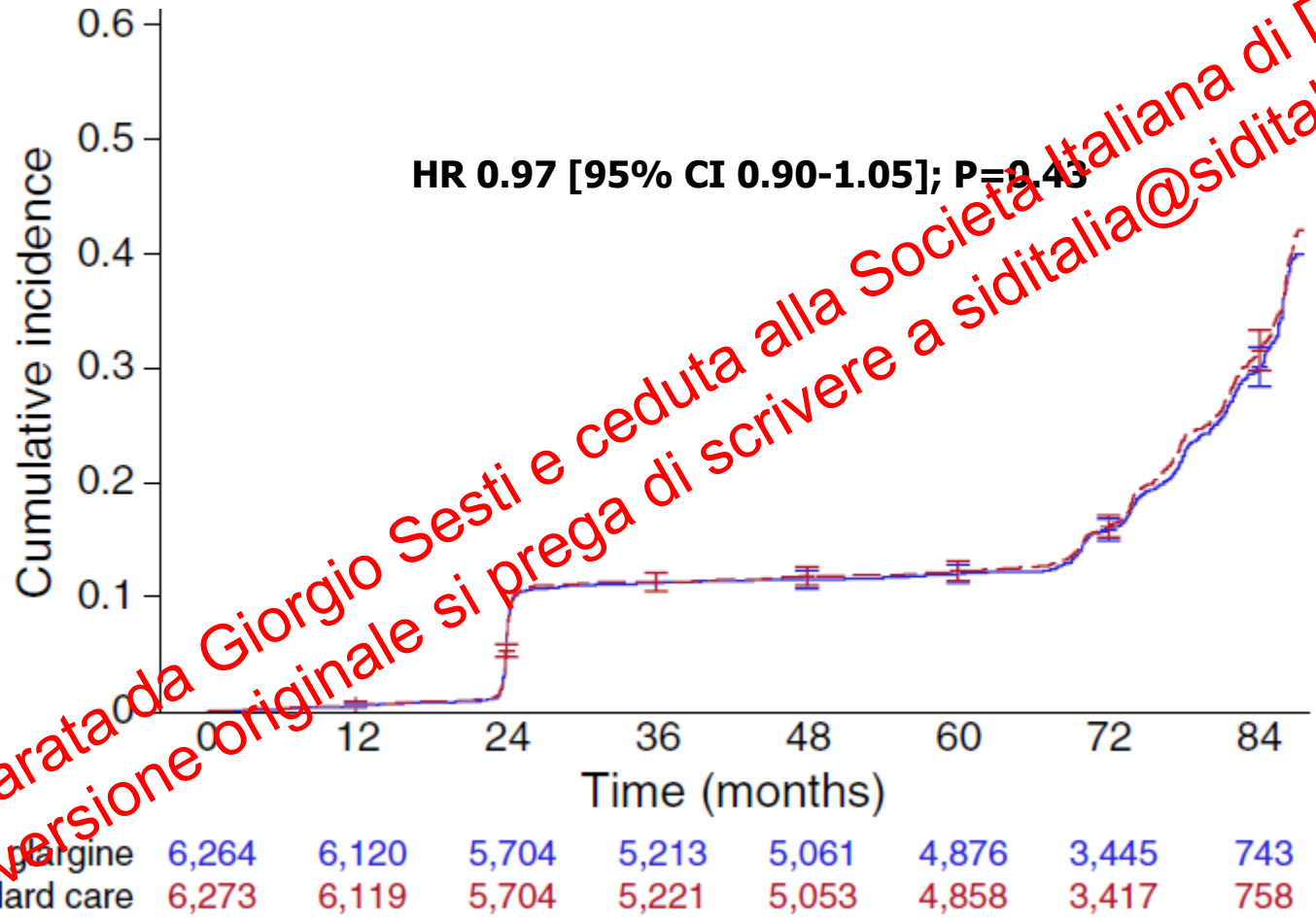
Basal insulin glargine and microvascular outcomes in dysglycaemic individuals: results of the Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial

The ORIGIN trial investigators · Richard E. Gilbert · Johannes F. E. Mann · Markolf Hanefeld · Giatgen Spinas · Jackie Bosch · Salim Yusuf · Hertzel C. Gerstein

The ORIGIN trial investigators. Diabetologia 57:1325–1331, 2014

Incidence of the primary micro-vascular composite outcome in participants to ORIGIN trial

Time-to-event curves for the composite microvascular outcome*



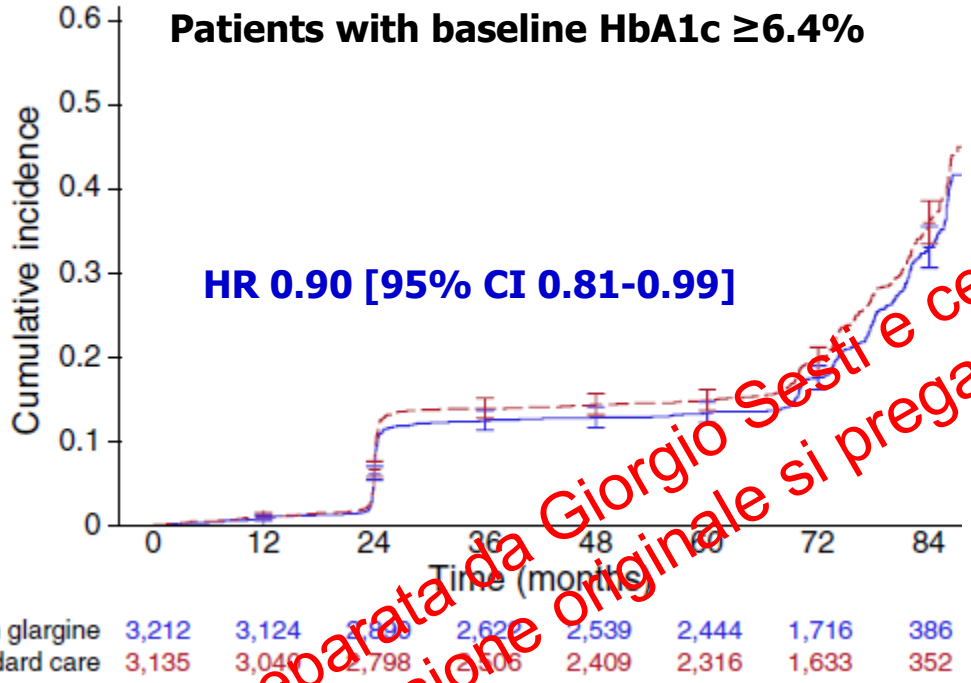
Median follow-up of 6.2 years.

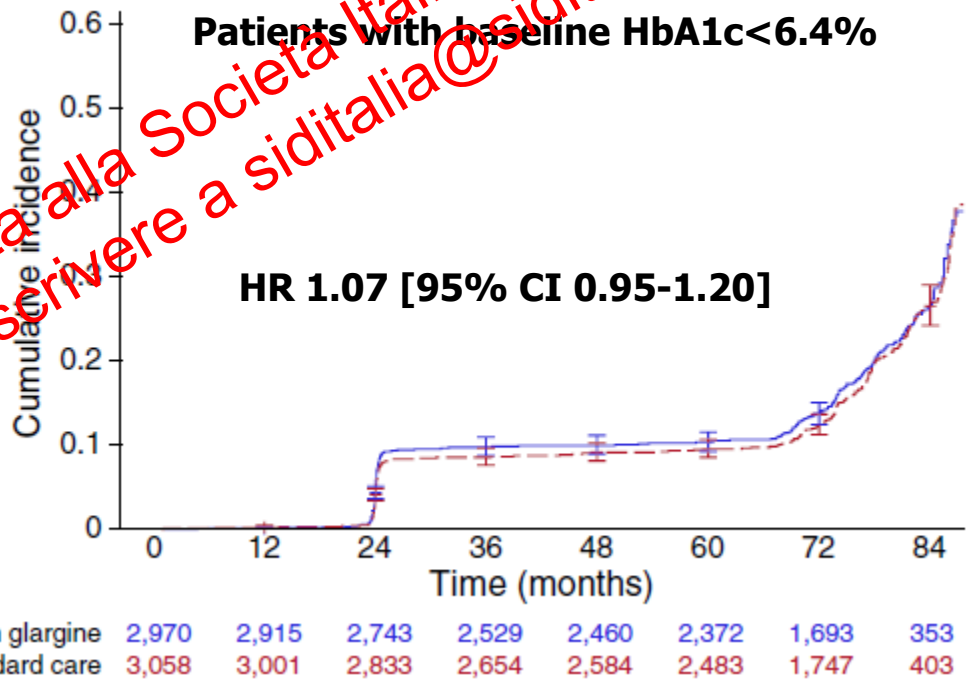
***Doubling of serum creatinine, worsening of albuminuria, renal replacement therapy or death due to renal failure, or diabetic retinopathy requiring retinal photocoagulation or vitrectomy.**

The ORIGIN trial investigators. Diabetologia 57:1325–1331, 2014

Insulin glargine reduced the incidence of the primary micro-vascular composite outcome in participants whose baseline HbA1c was ≥6.4%: ORIGIN

Time-to-event curves for the composite micro-vascular outcome*





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2. Glucose-lowering drugs vs. placebo on CV outcome:
   - HOME (metformin add on to insulin)
   - Origin (insulin glargine)
3. New glucose-lowering drugs vs. placebo on CV outcome after 2008 FDA guidance:
   - SAVOR-TIMI 53 (saxagliptin)
   - EXAMINE (alogliptin)
   - TECOS (sitagliptin)
   - ELIXA (lixisenatide)
   - EMPA-REG OUTCOME (empagliflozin)
   - LEADER (liraglutide)
   - SUSTAIN-6 (semaglutide)

The NEW ENGLAND JOURNAL of MEDICINE

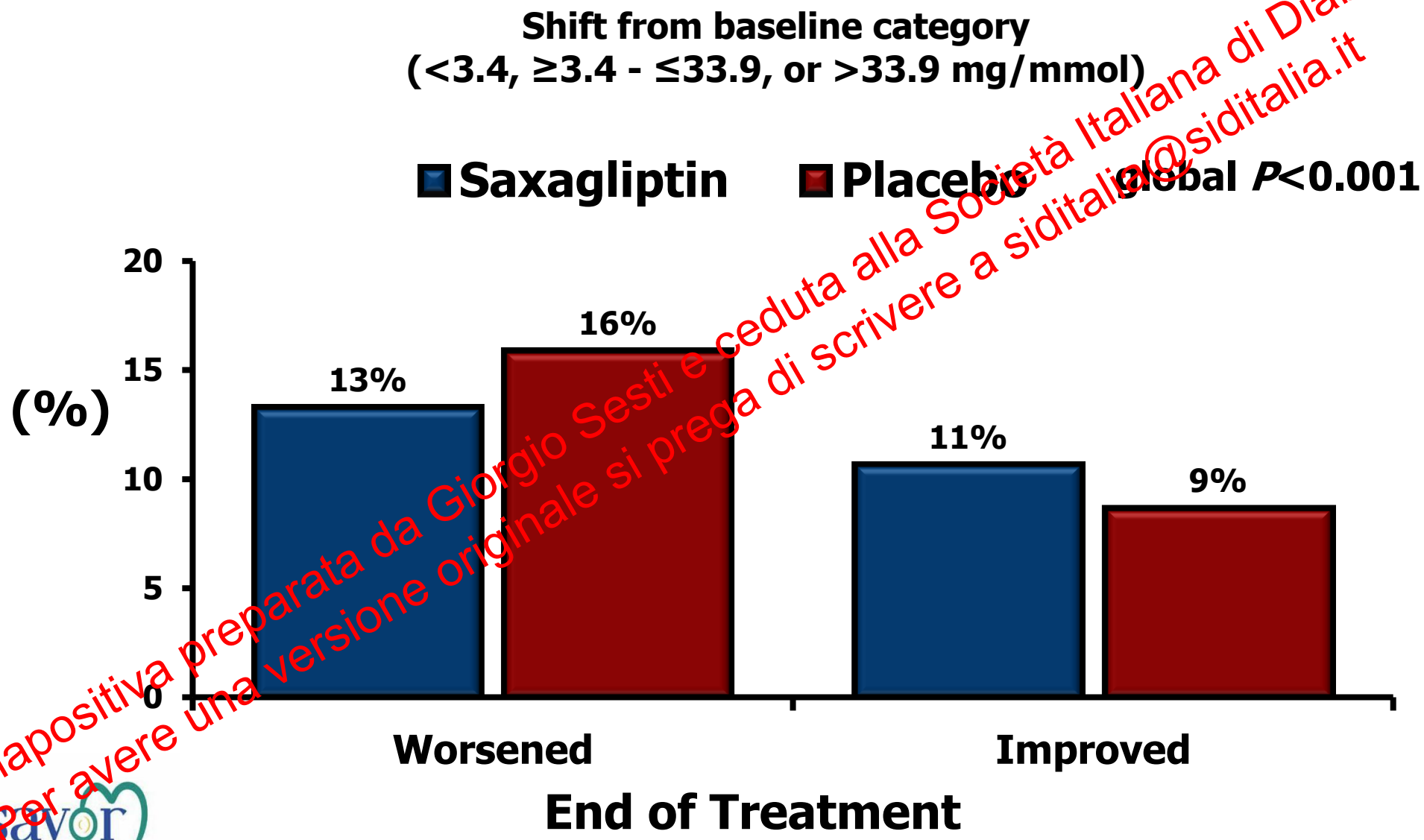
ORIGINAL ARTICLE

Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus

Benjamin M. Scirica, M.D., M.P.H., Deepak L. Bhatt, M.D., M.P.H., Eugene Braunwald, M.D., P. Gabriel Steg, M.D., Jaime Davidson, M.D., Boaz Hirshberg, M.D., Peter Ohman, M.D., Robert Frederich, M.D., Ph.D., Stephen D. Wiviott, M.D., Elaine B. Hoffman, Ph.D., Matthew A. Cavender, M.D., M.P.H., Jacob A. Udell, M.D., M.P.H., Nihar R. Desai, M.D., M.P.H., Ofri Mozenson, M.D., Darren K. McGuire, M.D., Kausik K. Ray, M.D., Lawrence A. Leiter, M.D., and Itamar Raz, M.D., for the SAVOR-TIMI 53 Steering Committee and Investigators*

Scirica BM et al. N Engl J Med 2013

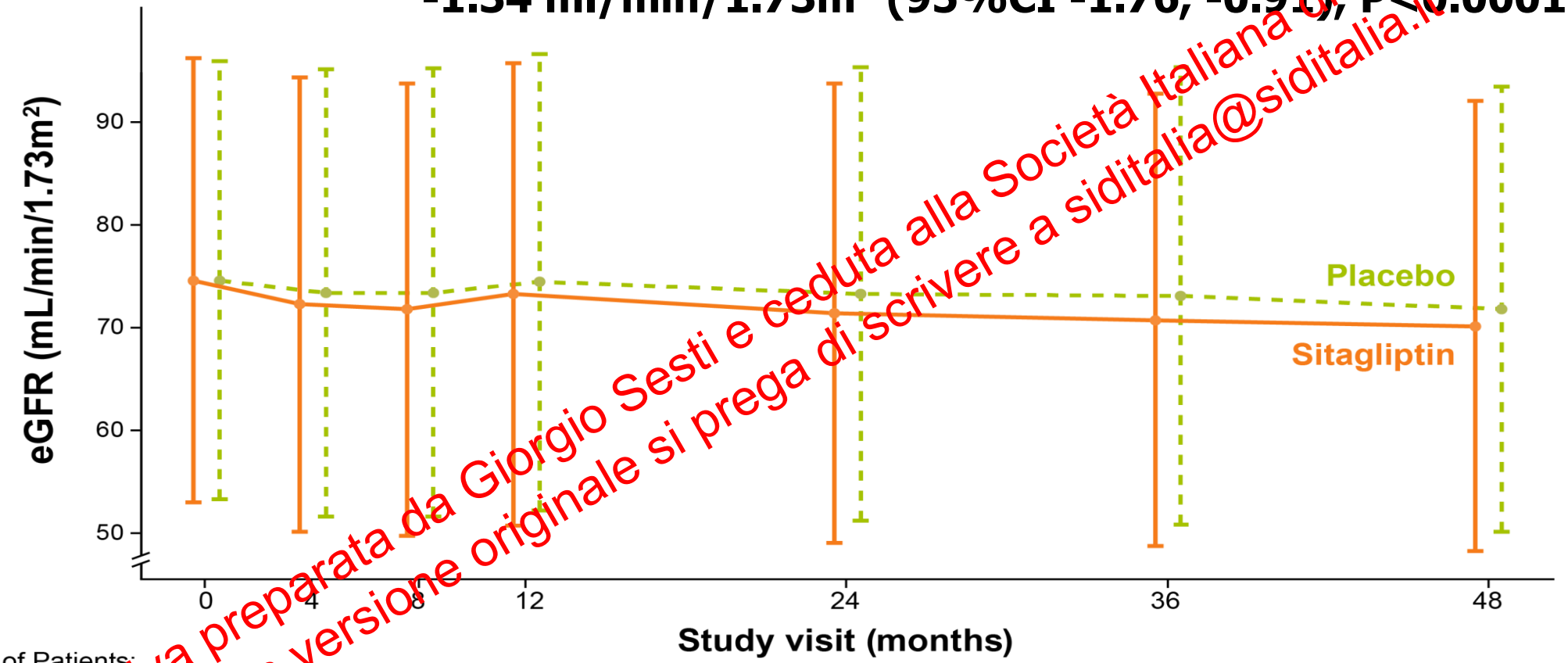
Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with DM - TIMI 53- Changes in Microalbuminuria



Scirica BM et al. N Engl J Med 2013

Estimated Glomerular Filtration Rate (eGFR)

Estimated overall mean difference*:
-1.34 ml/min/1.73m² (95%CI -1.76, -0.91), P<0.0001



# of Patients:							
Sitagliptin	7,254	3,984	3,722	5,135	5,209	3,068	1,248
Placebo	7,274	4,005	3,674	5,053	5,108	2,957	1,213

*Mixed model with random intercept & slope, adjusted for baseline value and region

TECOS
TRIAL EVALUATING CARDIOVASCULAR OUTCOMES WITH SITAGLIPTIN

Gren JB et al. N Engl J Med 373:232-42, 2015

The NEW ENGLAND JOURNAL of MEDICINE

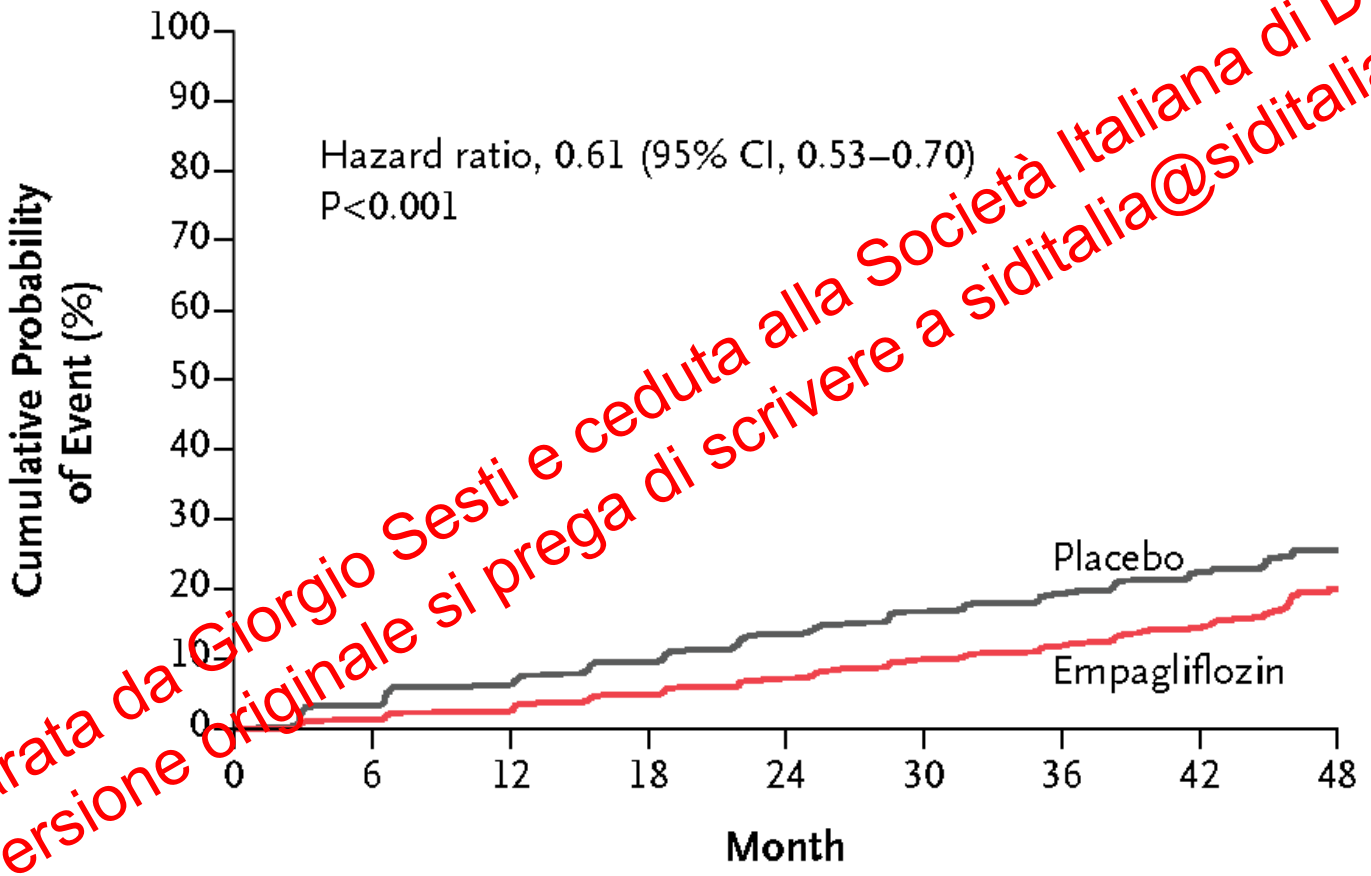
ORIGINAL ARTICLE

Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes

Christoph Wanner, M.D., Silvio E. Inzucchi, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Maximilian von Eynatten, M.D., Michaela Mattheus, Dipl. Biomath., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Bernard Zinman, M.D., for the EMPA-REG OUTCOME Investigators*

N Engl J Med 373:2117-2128, 2015

Kaplan–Meier analysis of incident or worsening nephropathy, defined as progression to macroalbuminuria (urinary albumin to-creatinine ratio, >300 mg/g); a doubling of the serum creatinine level, accompanied by an eGFR of ≤45 ml per minute per 1.73 m², the initiation of renal-replacement therapy; or death from renal disease



No. at Risk									
Empagliflozin	4124	3994	3848	3669	3171	2279	1887	1219	290
Placebo	2061	1946	1836	1703	1433	1016	833	521	106

Wanner C et al. N Engl J Med 375(4):323-34, 2016

Risk Comparison for Renal Outcomes in the EMPA-REG OUTCOME Trial

Renal Outcome Measure	Patients (%)		HR (95% CI)
	Empagliflozin	Placebo	
Incident or worsening nephropathy or CV death	16.2	23.6	0.61 (0.55 to 0.69)
Incident or worsening nephropathy	12.7	18.8	0.61 (0.53 to 0.70)
Progression to macroalbuminuria	11.2	16.2	0.62 (0.54 to 0.72)
Doubling of serum creatinine level accompanied by eGFR of ≤45 mL/min/1.73 m^2	1.5	2.6	0.56 (0.39 to 0.79)
Initiation of renal replacement therapy	0.3	0.6	0.45 (0.21 to 0.97)
Incident albuminuria in patients with a normal albumin level at baseline	51.5	51.2	0.95 (0.87 to 1.04)

Wanner C et al. N Engl J Med 375(4):323-34, 2016

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

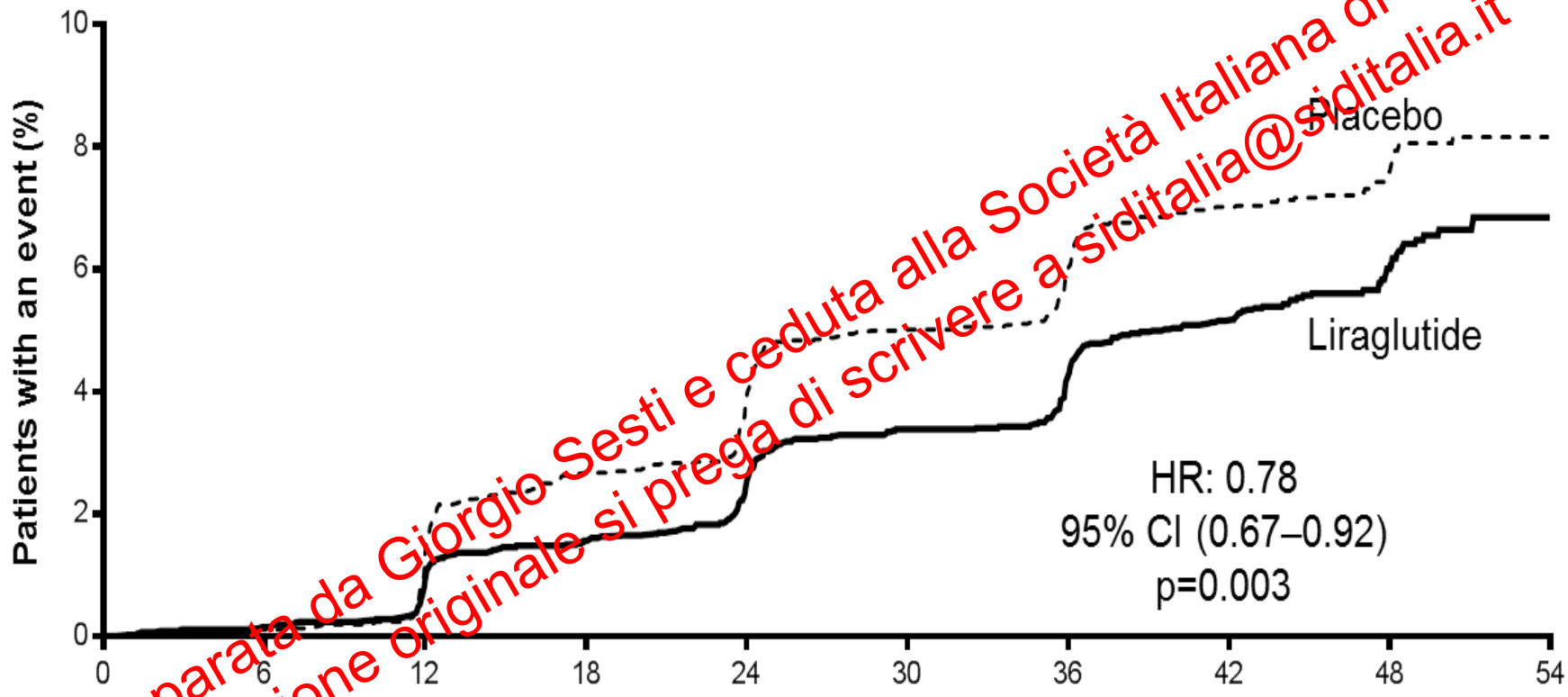
Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

Steven P. Marso, M.D., Gilbert H. Daniels, M.D., Kirstine Brown-Frandsen, M.D., Peter Kristensen, M.D., E.M.B.A., Johannes F.E. Mann, M.D., Michaela A. Nauck, M.D., Steven E. Nissen, M.D., Stuart Pocock, Ph.D., Neil R. Poulter, F.Med.Sci., Lasse S. Ravn, M.D., Ph.D., William M. Steinberg, M.D., Mette Stockner, M.D., Bernard Zinman, M.D., Richard M. Bergenstal, M.D., and John B. Buse, M.D., Ph.D., for the LEADER Steering Committee on behalf of the LEADER Trial Investigators*

Marso SP et al. N Engl J Med 2016

LEADER - Time to first renal event

Macroalbuminuria, doubling of serum creatinine, ESRD, renal death



Patients at risk

Liraglutide	4668	4635	4561	4492	4400	4304	4210	4114	1632	454
Placebo	4672	4643	4540	4428	4316	4196	4094	3990	1613	433

LEADER® Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results

The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months, because less than 10% of the patients had an observation time beyond 54 months. CI: confidence interval; ESRD: end-stage renal disease; HR: hazard ratio.

Marso SP et al. N Engl J Med 2016

ORIGINAL ARTICLE

Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

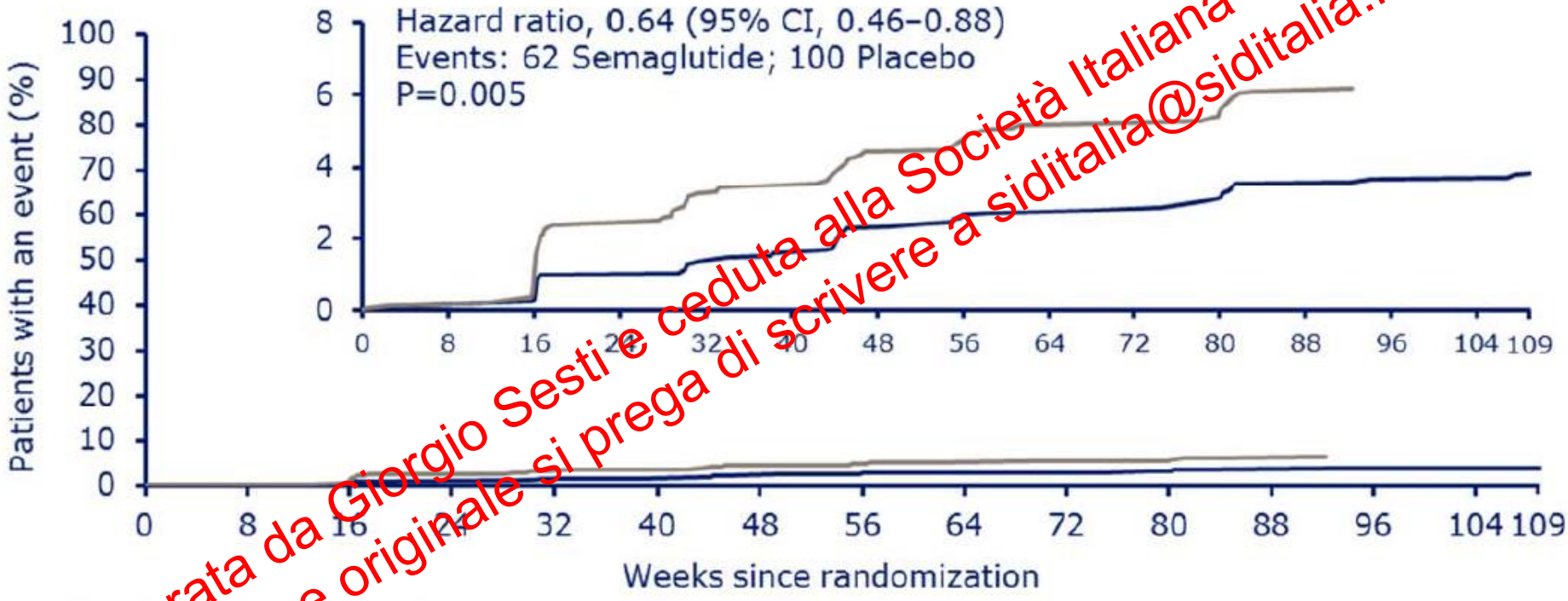
Steven P. Marso, M.D., Stephen C. Bain, M.D., Agostino Consoli, M.D., Freddy G. Eliaschewitz, M.D., Esteban Jódar, M.D., Lawrence A. Leiter, M.D., Ildiko Lingvay, M.D., M.P.H., M.S.C.S., Julio Rosenstock, M.D., Jochen Seufert, M.D., Ph.D., Mark L. Warren, M.D., Vincent Woo, M.D., Oluf Hansen, M.Sc., Anders G. Holst, M.D., Ph.D., Jonas Pettersson, M.D., Ph.D., and Tina Vilsbøll, M.D., D.M.Sc., for the SUSTAIN-6 Investigators*

Marso SP et al. N Engl J Med 2016

SUSTAIN-6 Study: Time to first renal event

Macroalbuminuria, doubling of serum creatinine, ESRD, renal death

New or worsening nephropathy



Marso SP et al. N Engl J Med 2016

Tabella 16. Terapia non insulinica nel diabete tipo 2 con insufficienza renale cronica

Stadio IRC	LIEVE	MODERATA	GRAVE	DIALISI
eGFR	>60 ml/min	30-60 ml/min	15-30 ml/min	<15 ml/min
Metformina	≥2 g/die	Non indicato (utilizzabile)	NO	NO
Acarbosio	Da titolare	Da titolare	NO	NO
Gliptine				
Sitagliptin	100 mg/die	50 mg/die	25 mg/die	25 mg/die
Vildagliptin	100 mg/die	50 mg/die	50 mg/die	50 mg/die
Saxagliptin	5 mg/die	2,5 mg/die	2,5 mg/die	NO
Linagliptin	5 mg/die	5 mg/die	5 mg/die	5 mg/die
Alogliptin	25 mg/die	12,5 mg/die[a]	6,25 mg/die	6,25 mg/die
GLP-1 agonisti				
Exenatide	20 µg/die	Cautela[b]	NO	NO
Exenatide LAR	2 mg/die	NO[c]	NO	NO
Liraglutide	Dosi usuali	Dosi usuali	NO	NO
Lixisenatide	Dosi usuali	Cautela[b]	NO	NO
Sulfoniluree	Da titolare	Da titolare[d]	NO	NO
Repaglinide	Da titolare	Non indicato (utilizzato)	NO	NO
Pioglitazone	Dosi usuali	Dosi usuali	Dosi usuali	NO[e]
Gliflozine				
Dapagliflozin	Dosi usuali	NO	NO	NO
Empagliflozin	Dosi usuali	NO	NO	NO
Canagliflozin	Dosi usuali	NO	NO	NO

[a] La riduzione della dose da 25 a 12,5 mg/die è prevista quando eGFR scende sotto 50 ml/min.
[b] Cautela necessaria quando eGFR è inferiore a 50 ml/min
[c] Farmaco non indicato quando eGFR è inferiore a 50 ml/min
[d] Alcune sulfoniluree (gliquidione, glimepiride) hanno metabolismo prevalentemente epatico, ma non sono state comunque studiate in modo esteso in pazienti con insufficienza renale; una accurata titolazione della dose è comunque raccomandabile, almeno per eGFR inferiore a 60 ml/min.
[e] Il pioglitazone è controindicato per eGFR inferiore a 5 ml/min.