SID
Società Italiana di Diabetologia

PARMA DIABETE 2017

Parma, 19/21 ottobre 2017

Nuovi farmaci e rischio cardiovascolare

Giorgio Sesti

Università “Magna Graecia” di Catanzaro

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, Astra Zeneca, Theras Lifetech, Abbott e Novartis per attività di Relatore ad eventi.

Servier, Mylan, Novo Nordisk, Boehringer Ingelheim, Lilly, Astra Zeneca, MSD Italy, Sanofi, Pfizer e Abbott 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.

Landmark CV outcomes studies in type 2 diabetes

1. **Intensive glucose control vs. standard-therapy on CV outcome:**
   - **UKPDS 33 and 34**
   - **ACCORD**
   - **ADVANCE**
   - **VADT**
2. **Glucose-lowering drugs vs. placebo on CV outcome:**
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   - **EXAMINE (alogliptin)**
   - **TECOS (sitagliptin)**
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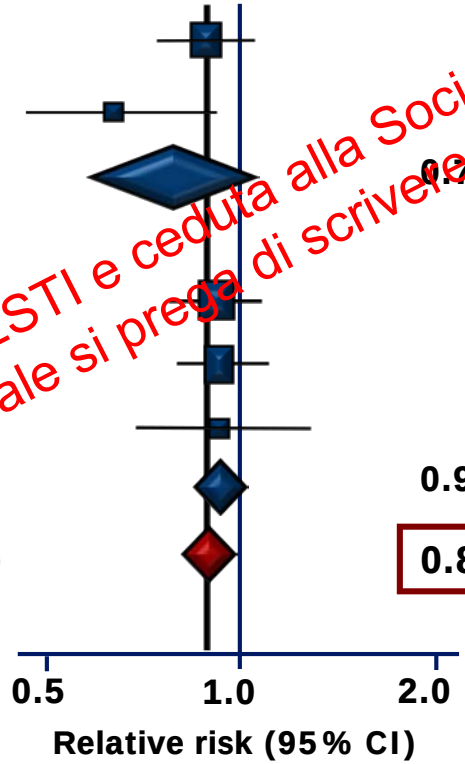
   - **SUSTAIN-6 (semaglutide)**
   - **EMPA-REG OUTCOME (empagliflozin)**
   - **CANVAS (canagliflozin)**
   - **DEVOTE (insulin degludec)**
   - **EXSCEL (exenatide OW)**

Meta-analysis of ACCORD, ADVANCE, VADT and UKPDS suggests intensive glucose control reduces the risk of CVD by 11 %

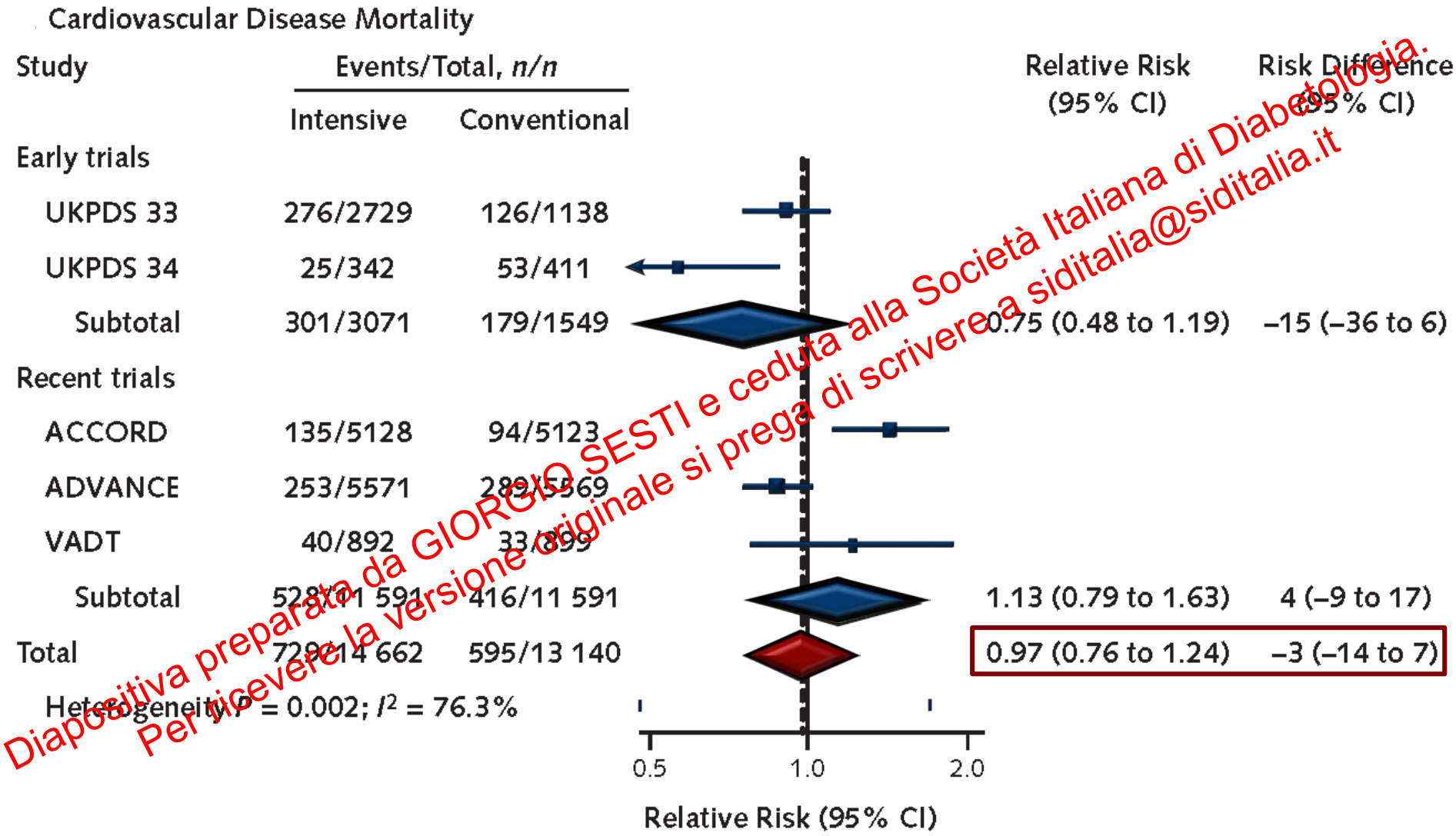
	Events/total, n/n		Relative risk (95% CI)	Risk difference (95% CI)
	Intensive	Conventional		
Early trials				
UKPDS 33	387/2729	186/1138		
UKPDS 34	39/342	73/411		
Subtotal	426/3071	259/1549	0.78 (0.59–1.04)	–20 (–38 to –1)
Recent trials				
ACCORD	295/5128	325/5123		
ADVANCE	310/5571	337/5569		
VADT	75/892	82/899		
Subtotal	680/11,591	744/11,591	0.91 (0.83–1.01)	–6 (–9 to –3)
Total	1106/14,662	1003/13,140	0.89 (0.81–0.96)	–11 (–17 to –5)
Heterogeneity $p = 0.48$; $I^2 = 0.0\%$				



ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADVANCE, Action in Diabetes and Vascular Disease; CI, confidence interval; VADT, Veterans Affairs Diabetes Trial

Kelly et al. Ann Intern Med 2009;151:394–403

Meta-analysis of ACCORD, ADVANCE, VADT and UKPDS suggests no significant difference in CV mortality



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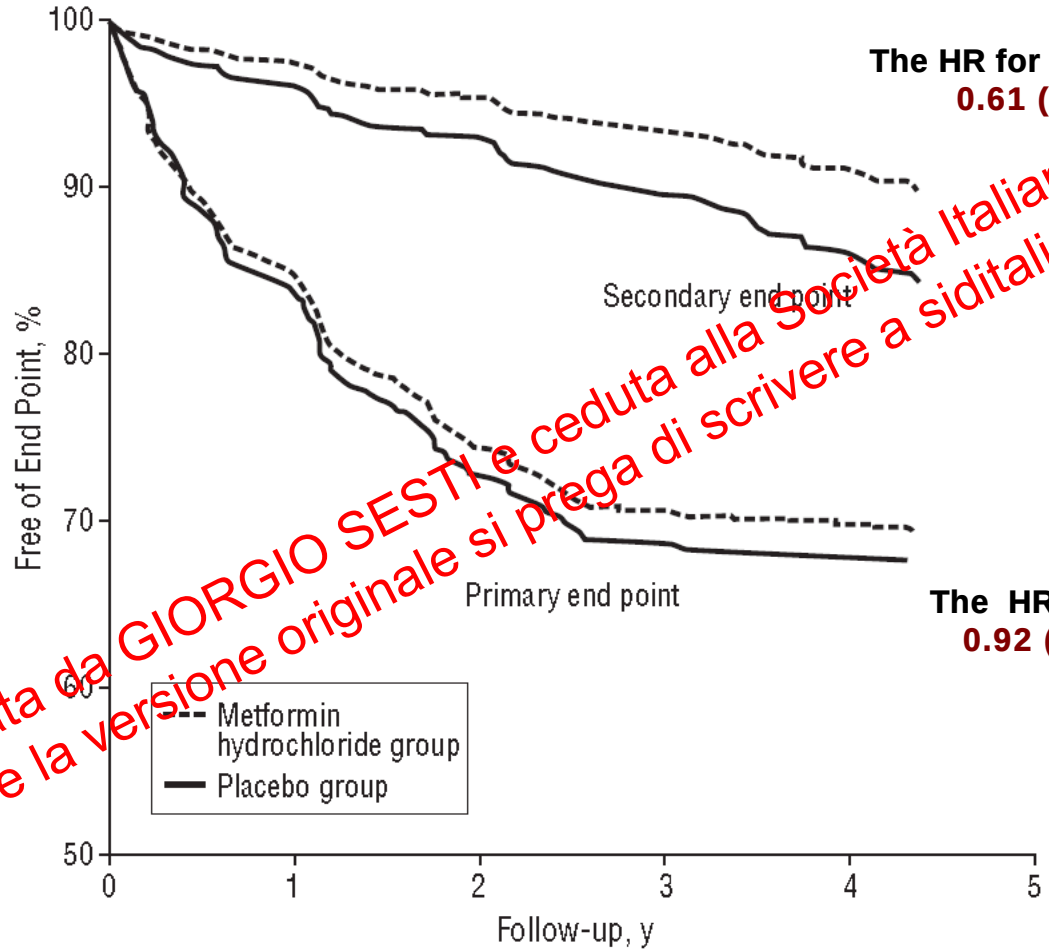
Long-term Effects of Metformin on Metabolism and Microvascular and Macrovascular Disease in Patients With Type 2 Diabetes Mellitus

Hyperinsulinemia: the Outcome of its Metabolic Effects (HOME)

Characteristic	Placebo Group (n=194)	Metformin Hydrochloride Group (n=196)
Demography		
Men/women	97/97	81/115
Age, mean (SD), y	59 (11)	64 (10)
Currently smoking	59 (30)	38 (19)
Duration of type 2 diabetes mellitus, y	12 (8)	14 (9)
Prior macrovascular and microvascular disease		
Cardiovascular history	0.92 (1.3)	1.17 (1.4)
Diabetic polyneuropathy score	7.51 (5.4)	8.36 (6.3)

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

Metformin treatment was not associated with an improvement in the primary aggregate microvascular and macrovascular endpoint, but it was associated with a decreased risk of the secondary macrovascular endpoint



The HR for the macrovascular end point was 0.61 (95% CI, 0.40-0.94; *P*=0.02)

The HR for the primary end point was 0.92 (95% CI, 0.72-1.18; *P*=0.33)

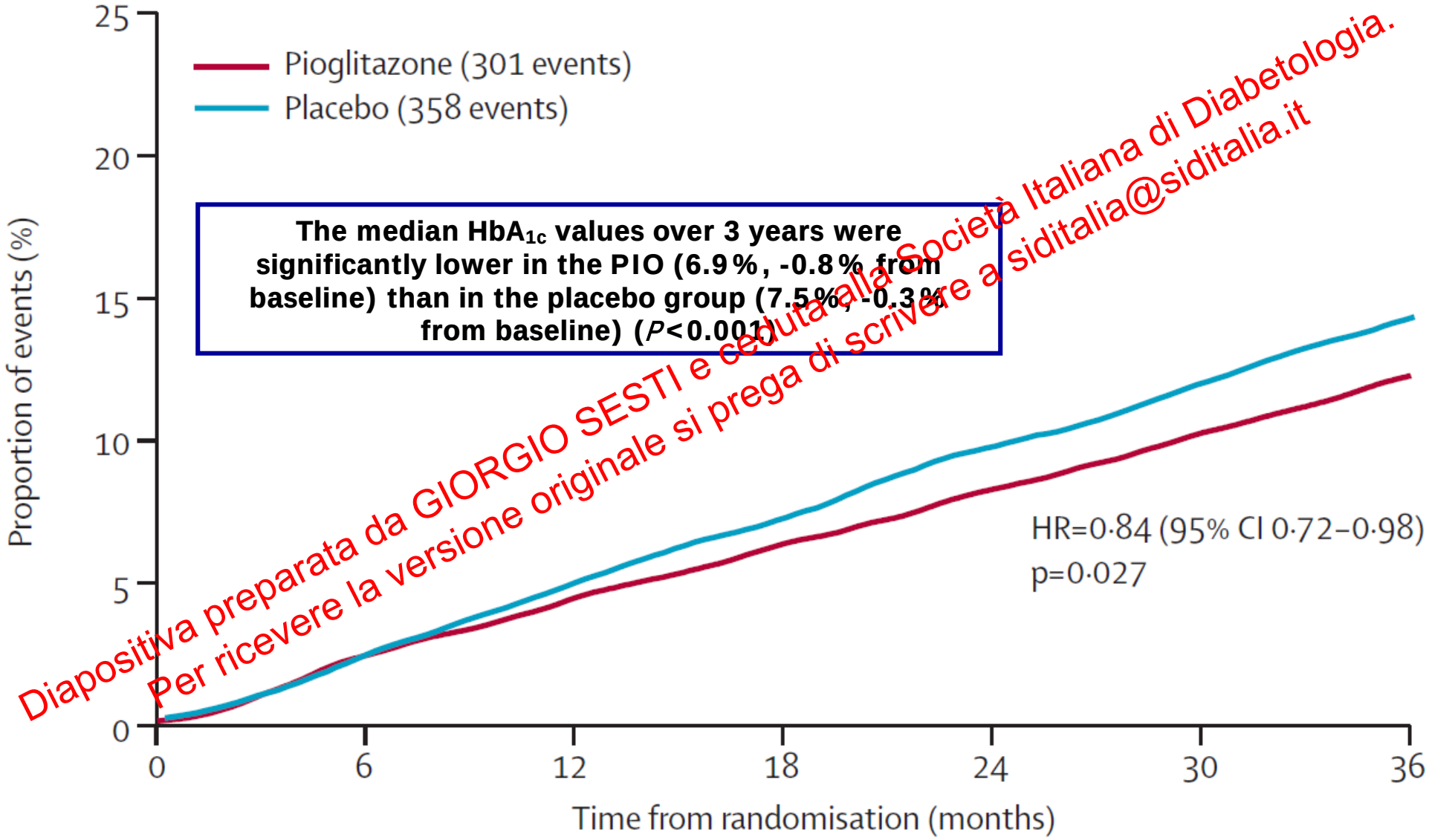
Kooy A et al. Arch Intern Med 169:616-625, 2009

Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial

John A Dormandy, Bernard Charbonnel, David J A Eckland, Erland Erdmann, Massimo Massi-Benedetti, Ian K Moules, Allan M Skene, Meng H Tan, Pierre J Lefèbvre, Gordon D Murray, Eberhard Standl, Robert G Wilcox, Lars Wilhelmsen, John Betteridge, Kåre Birkeland, Alain Golay, Robert J Heine, László Korányi, Markku Laakso, Marián Mokáň, Antonis Norkus, Zaiga Pirags, Toomas Podar, André Scheen, Werner Scherbaum, Guntram Schernthaner, Ole Schmitz, Jan Škrha, Ulf Smith, Jan Tatoň, on behalf of the PROactive investigators*

Dormandy JA et al. Lancet 2005; 366: 1279–89

PROactive: Time to Secondary Composite Endpoint (Death from any cause, non-fatal myocardial infarction, or stroke)



Lancet 366: 1279–1289, 2005

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Basal Insulin and Cardiovascular and Other Outcomes in Dysglycemia

The ORIGIN Trial Investigators*

ORIGIN Trial Investigators, N Engl J Med 367: 319-28, 2012

ORIGIN - Participants (Key Inclusion Criteria)

- **Age ≥ 50 yrs** *AND*
- **Dysglycemia** *AND*

  EITHER **IFG or IGT or new type 2 DM by OGTT**

  [i.e. FPG ≥ 110 (6.1); or 2 Hr PG ≥ 140 (7.8)]

  OR **prior type 2 DM @ stable dose ≥ 10 wks & …**

  on no OADs … + HbA1c < 9.0%

  < half-max 1 OAD + HbA1c < 8.5%

  ≥ half-max 1 OAD + HbA1c < 8.0%

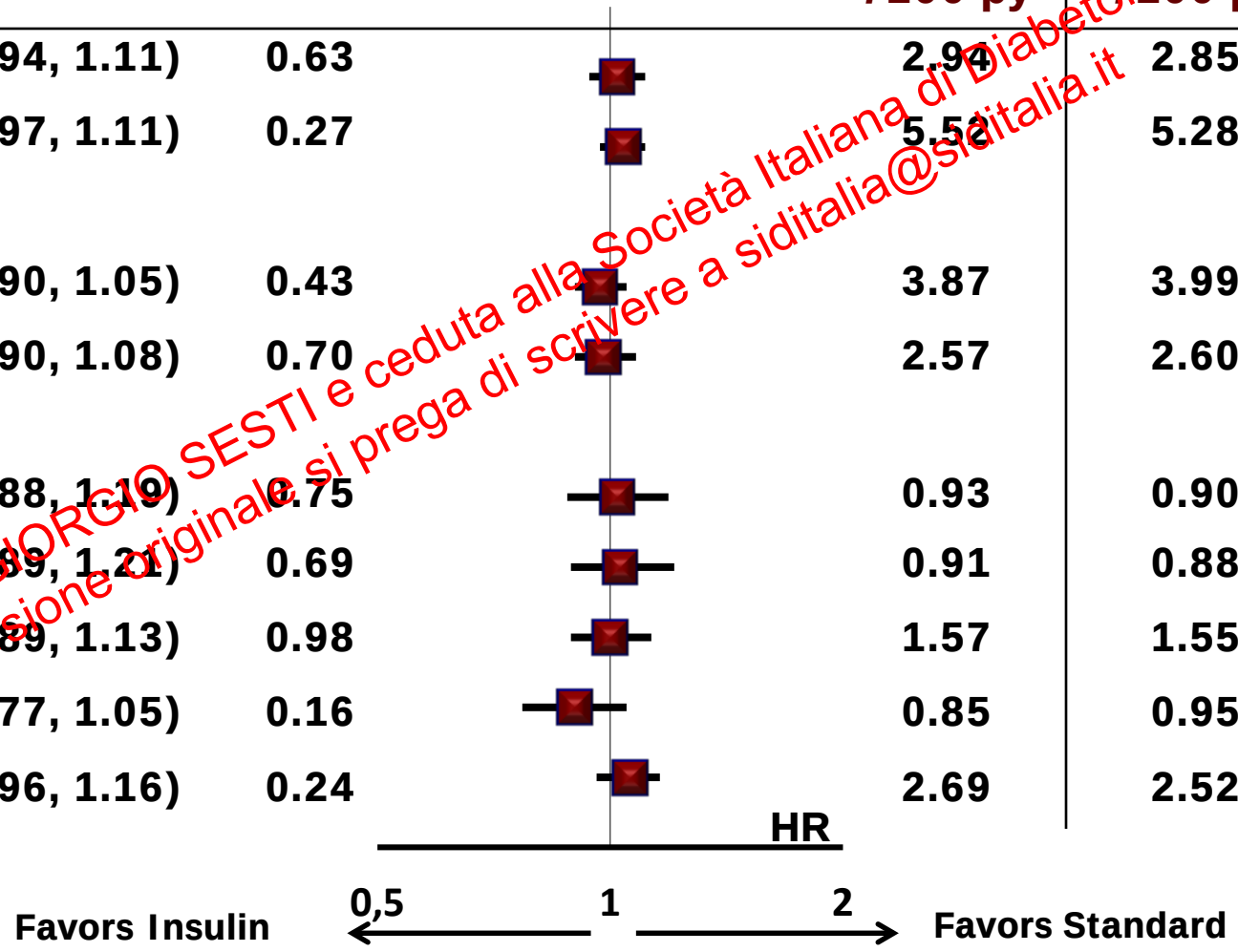
- **High CV Risk**

  EITHER **Prior MI, stroke, revasc, angina + doc. ischemia**

  OR **MA, proteinuria, LVH, 50% art. stenosis, ABI < 0.9**

Primary & Secondary Outcomes & their Components

	HR (95% CI)	P	Insulin /100 py	Standard /100 py
1st Coprimary	1.02 (0.94, 1.11)	0.63	2.94	2.85
2nd Coprimary	1.04 (0.97, 1.11)	0.27	5.52	5.28
Microvascular	0.97 (0.90, 1.05)	0.43	3.87	3.99
Death	0.98 (0.90, 1.08)	0.70	2.57	2.60
MI	1.02 (0.88, 1.19)	0.75	0.93	0.90
Stroke	1.03 (0.89, 1.21)	0.69	0.91	0.88
CV Death	1.00 (0.89, 1.13)	0.98	1.57	1.55
CHF Hospital	0.90 (0.77, 1.05)	0.16	0.85	0.95
Revascularized	1.06 (0.96, 1.16)	0.24	2.69	2.52



1st Co-primary: MI, Stroke, or CV Death
2nd Co-primary CV death, MI, stroke , revasc or CHF hospitalization

ORIGIN Trial Investigators, N Engl J Med 367: 319-28, 2012

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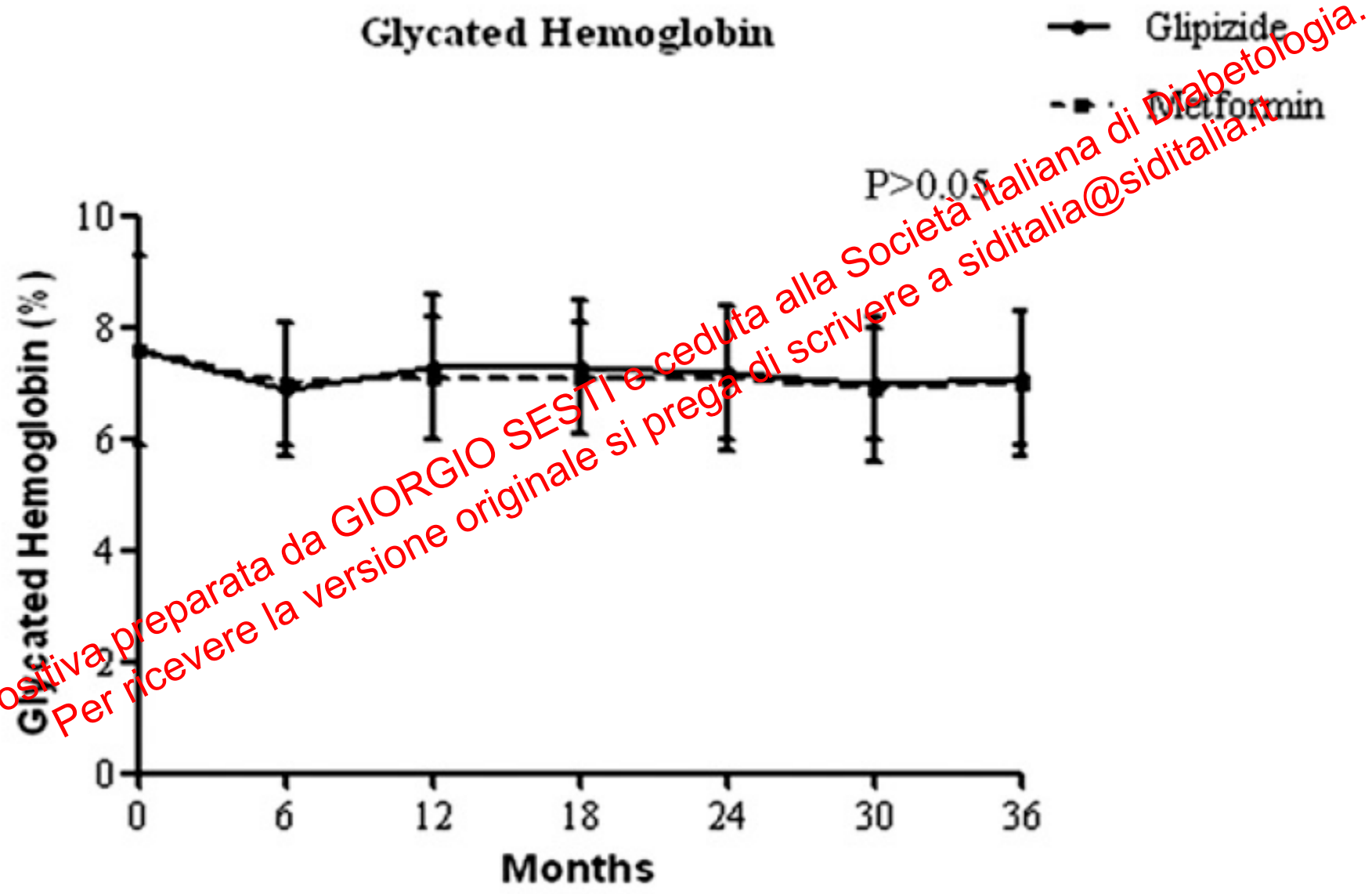
Effects of Metformin Versus Glipizide on Cardiovascular Outcomes in Patients With Type 2 Diabetes and Coronary Artery Disease

Jie Hong, MD[1]
Yifei Zhang, MD[1]
Shenghan Lai, MD[2]
Ankang Lv, MD[1]
Qing Su, MD[3]
Yan Dong, MD[3]
Zhiguang Zhou, MD[4]
Weili Tang, MD[4]
Jiajun Zhao, MD[5]
Lianqun Cui, MD[5]
Dajin Zou, MD[6]
Dawang Wang, MD[7]
Hong Li, MD[8]
Chao Liu, MD[9]
Guoting Wu, MD[10]
Jie Shen, MD[11]
Dalong Zhu, MD[12]
Weiqing Wang, MD[1]
Weipeng Shen, MD[1]
Guang Ning, MD, PhD[1]
on behalf of the SPREAD-DIMCAD Investigators*

Hong CJ et al. Diabetes Care 36:1304–1311, 2013

Effects of metformin versus glipizide on cardiovascular outcomes in patients with type 2 diabetes and coronary artery disease



Hong CJ et al. Diabetes Care 36:1304–1311, 2013

Effects of metformin versus glipizide on cardiovascular outcomes in patients with type 2 diabetes and coronary artery disease

The composite primary study end points were cardiovascular events, including nonfatal myocardial infarction, nonfatal stroke or arterial revascularization by percutaneous transluminal coronary angioplasty (PTCA) or by coronary artery bypass graft, death from a cardiovascular cause, and death from any cause.

Variable	Hazard Ratio	95% Confidence Interval
Medications		
Glipizide	1.00	
Metformin	0.54	0.30 – 0.90
Age	1.03	1.00 – 1.06
Male	0.73	0.27 – 1.93
Duration of diabetes	0.98	0.86 – 1.08
Duration of CAD	0.98	0.92 – 1.05
Smoking history	1.07	0.81 – 1.40

Hong CJ et al. Diabetes Care 36:1304–1311, 2013

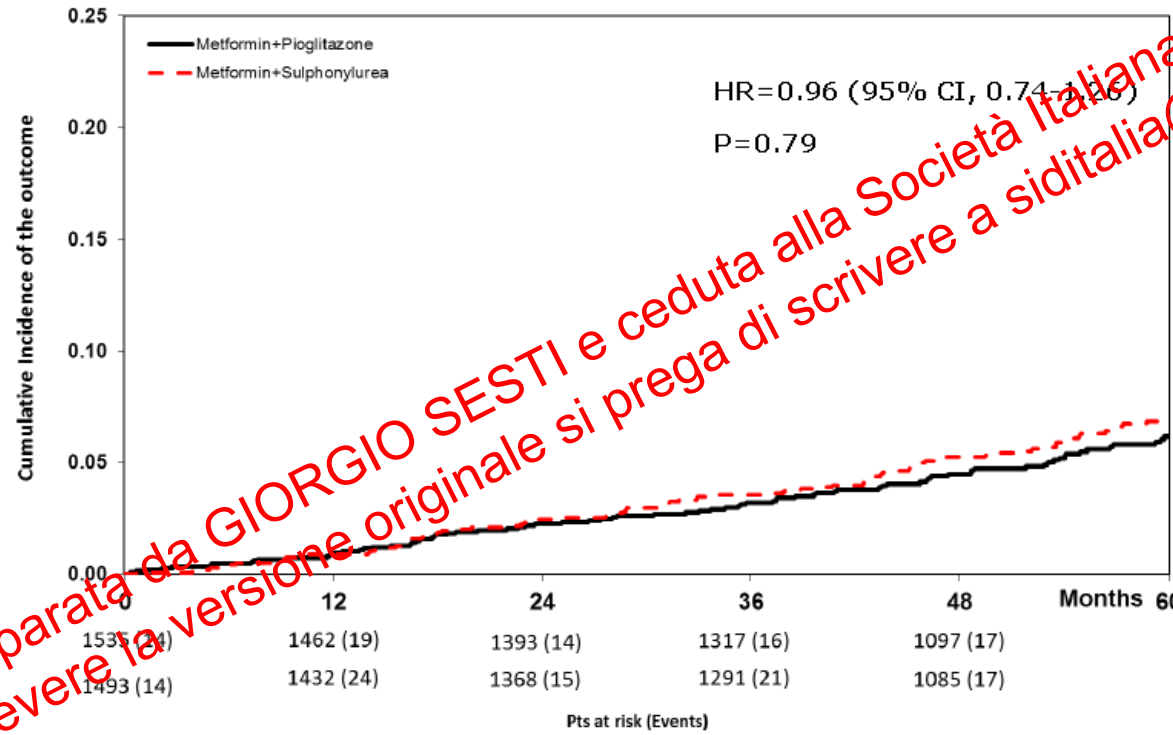
Effects on the incidence of cardiovascular events of the addition of pioglitazone versus sulfonylureas in patients with type 2 diabetes inadequately controlled with metformin (TOSCA.IT): a randomised, multicentre trial

Olga Vaccaro*, Maria Masulli*, Antonio Nicolucci, Enzo Bonora, Stefano Del Prato, Aldo P Maggioni, Angela A Rivellese, Sebastiano Squatrito, Carlo B Giorda , Giorgio Sesti, Paolo Mocarelli, Giuseppe Lucisano, Michele Sacco, Stefano Signorini, Fabrizio Cappellini, Gabriele Perriello, Anna Carla Babini, Annunziata Lapolla, Giovanna Gregori, Guido Giordano, Laura Corsi, Raffaella Buzzetti, Gennaro Clemente, Graziano Di Cianni, Rossella Iannarelli, Renza Cordera, Olga La Macchia, Chiara Zamboni, Cristiana Scaranna, Massimo Boemi, Ciro Iovine, Davide Lauro, Sergio Leotta, Elisabetta Dall'Aglio, Emanuela Cannarsa, Laura Tonutti, Giuseppe Pugliese, Antonio C Bossi, Roberto Anichini, Francesco Dotta, Antonino Di Benedetto, Giuseppe Citro, Daniela Antenucci, Lucia Ricci, Francesco Giorgino, Costanza Santini, Agostino Gnasso, Salvatore De Cosmo, Donatella Zavaroni, Monica Vedovato, Agostino Consoli, Maria Calabrese, Paolo di Bartolo, Paolo Fornengo, Gabriele Riccardi for the Thiazolidinediones Or Sulfonylureas Cardiovascular Accidents Intervention Trial (TOSCA.IT) study group† under the mandate of the Italian Diabetes Society

Vaccaro O et al. Lancet Diabetes Endocrinol 2017

Primary outcome

All-cause death, non-fatal MI - including silent MI, non-fatal stroke, urgent coronary revascularization



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. CI: confidence interval; HR: hazard ratio.

Vaccaro O et al. Lancet Diabetes Endocrinol 2017

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The NEW ENGLAND JOURNAL of MEDICINE

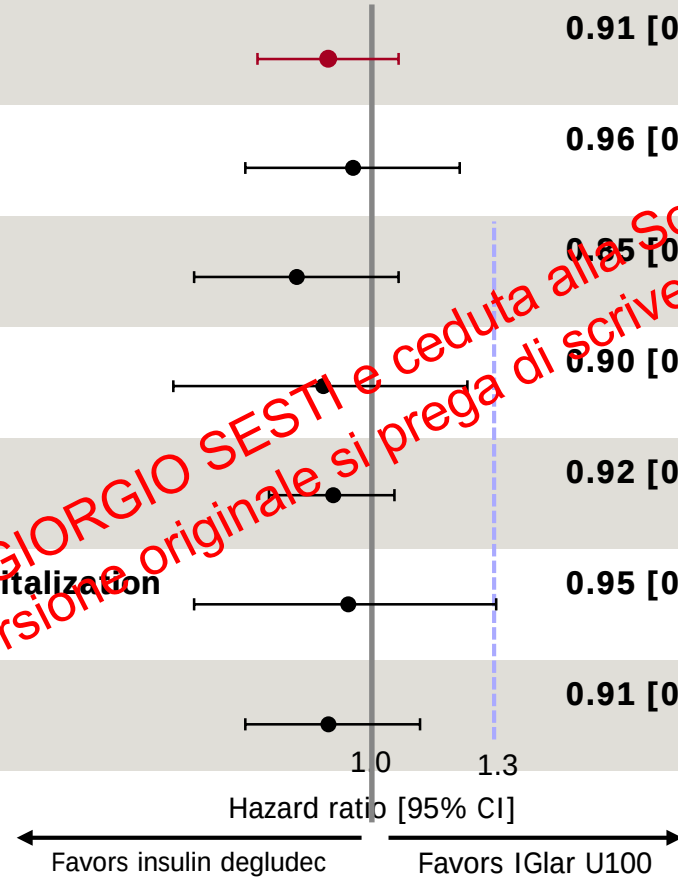
ORIGINAL ARTICLE

Efficacy and Safety of Degludec versus Glargine in Type 2 Diabetes

Steven P. Marso, M.D., Warren K. McGuire, M.D., Bernard Zinman, M.D., Neil R. Poulter, F.Med.Sci., Scott S. Emerson, M.D., Ph.D., Thomas R. Pieber, M.D., Richard E. Pratley, M.D., Poul-Martin Haahr, M.D., Martin Lange, M.D., Ph.D., Kirstine Brown-Frandsen, M.D., Alan Moses, M.D., Simon Skibsted, M.D., Ph.D., Kajsa Kvist, Ph.D., and John B. Buse, M.D., Ph.D., for the DEVOTE Study Group*

3-point MACE, 4-point MACE and all-cause death

	Hazard ratio [95% CI]	Insulin degludec		IGlar U100	
		N	%	N	%
3-point MACE	0.91 [0.78; 1.06]	325	8.5	356	9.3
CV death*	0.96 [0.76; 1.21]	136	3.6	142	3.7
Non-fatal MI	0.85 [0.68; 1.06]	144	3.8	169	4.4
Non-fatal stroke	0.90 [0.65; 1.23]	71	1.9	79	2.1
4-point MACE†	0.92 [0.80; 1.05]	386	10.1	419	11.0
Unstable angina requiring hospitalization	0.95 [0.68; 1.31]	71	1.9	74	1.9
All-cause death	0.91 [0.76; 1.11]	202	5.3	221	5.8



CV death includes undetermined cause of death; †4-point MACE defined as cardiovascular death, non-fatal myocardial infarction, non-fatal stroke or unstable angina requiring hospitalization

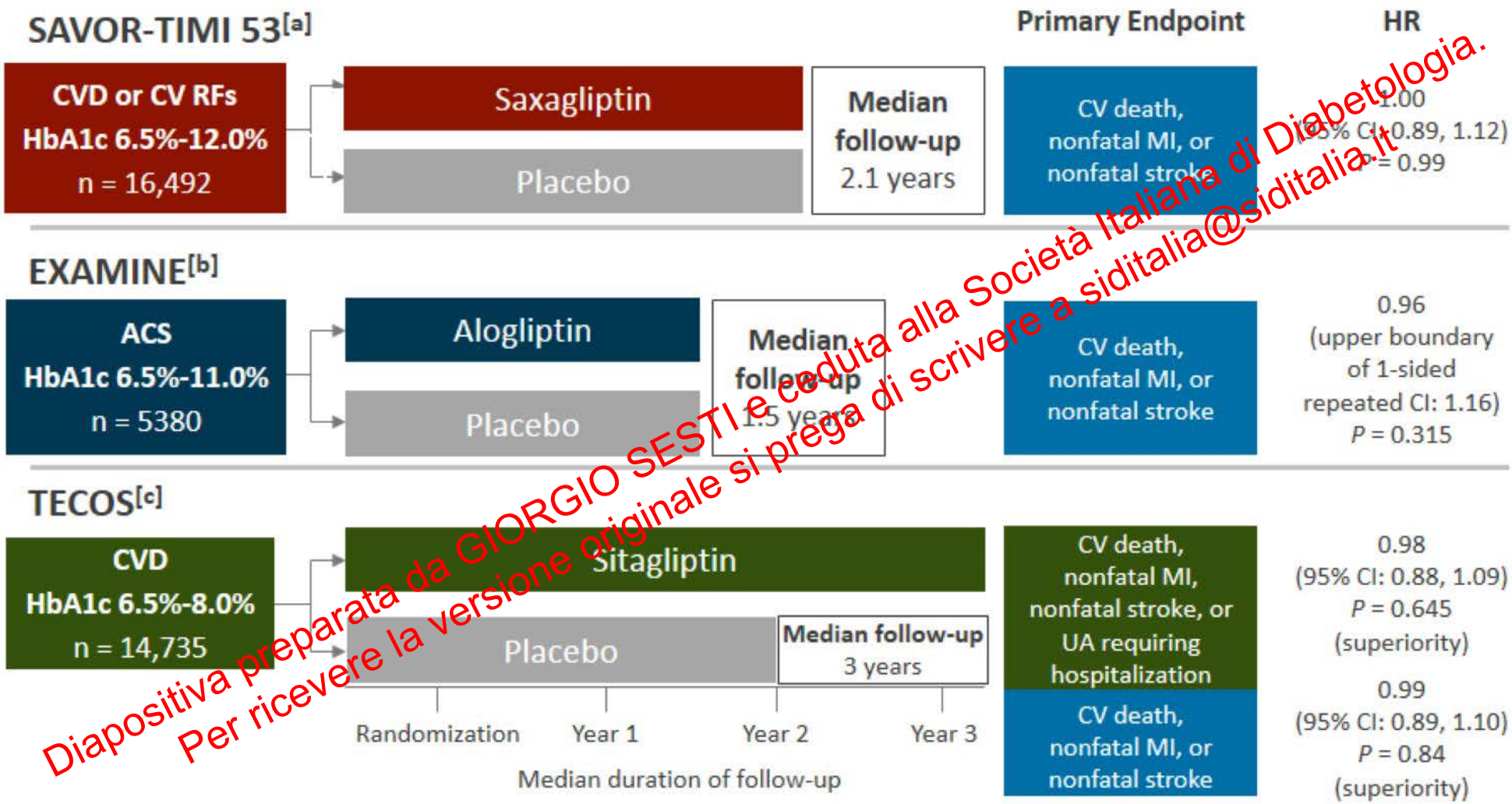
Marso SP et al. N Engl J Med 377(8):723-732, 2017

Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus

Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes

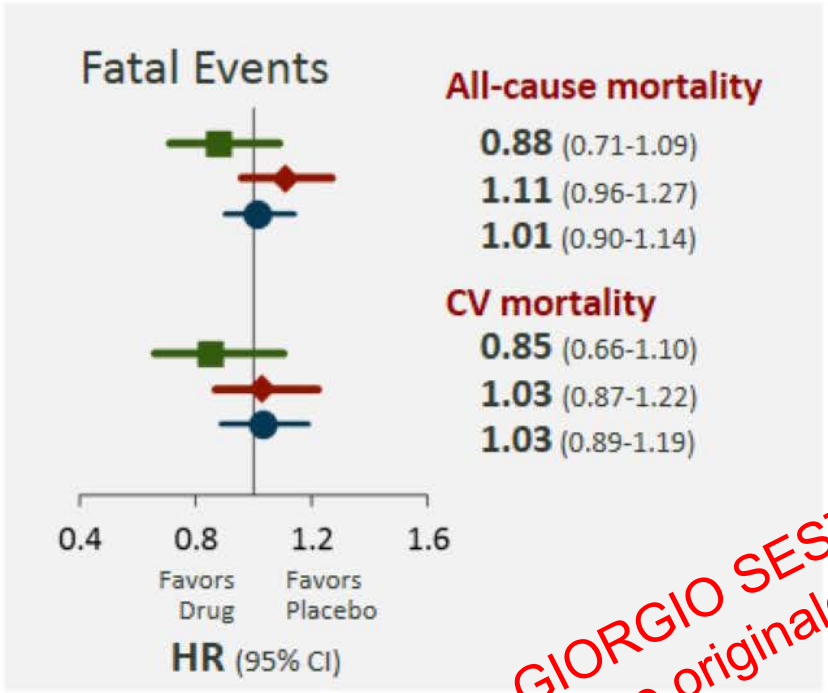
Alogliptin after acute coronary syndrome in patients with type 2 diabetes

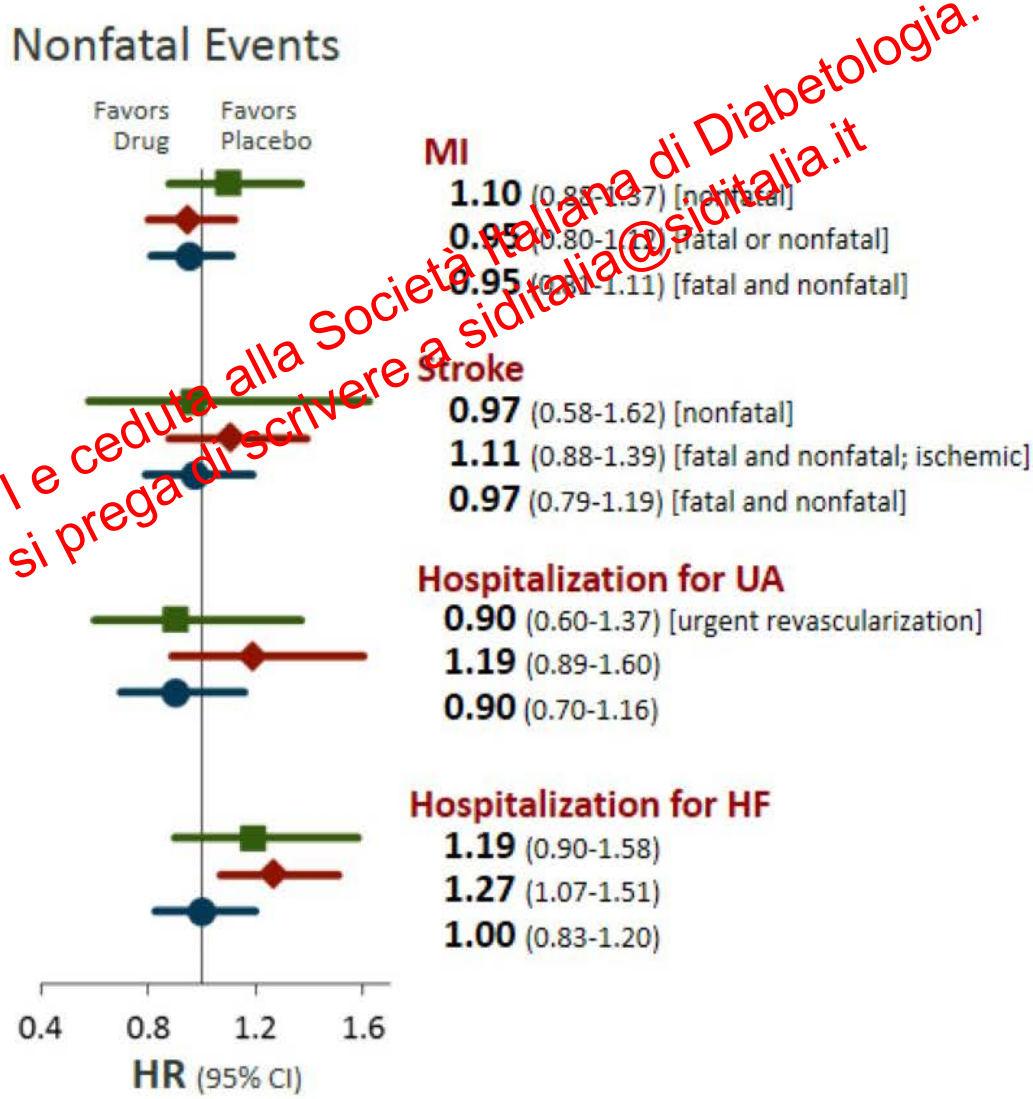
CV outcomes for DPP-4 inhibitors



a. Scirica BM, et al. *N Engl J Med*. 2013;369:1317-1326; b. White W, et al. *N Engl J Med*. 2013;369:1327-1335; c. Green JB, et al. *N Engl J Med*. 2015;373:232-242.

SAVOR-TIMI 53, EXAMINE, and TECOS: Adjudicated Endpoints

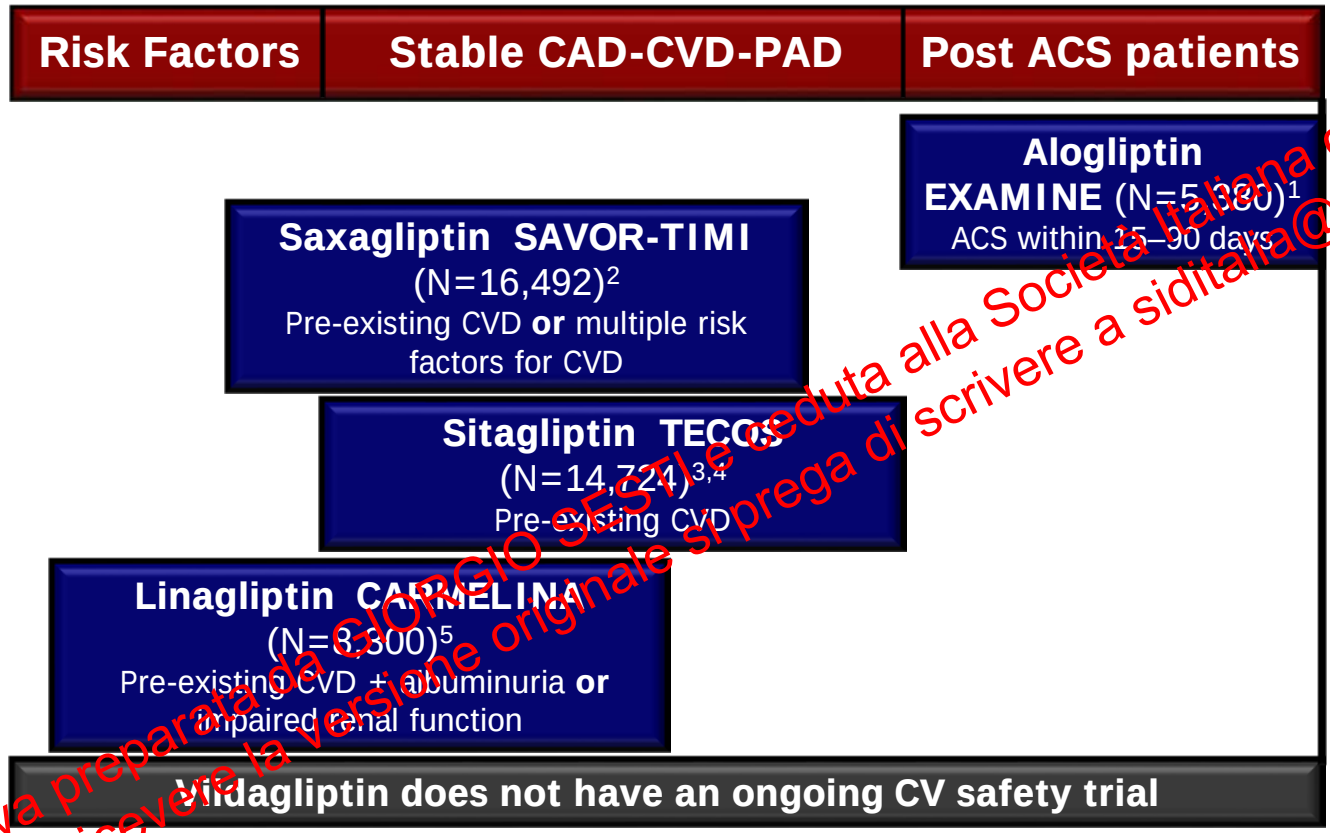




EXAMINE[a]
SAVOR[b]
TECOS[c]

a. White WB, et al. *N Engl J Med*. 2013;369:1327-1335.
b. Scirica BM, et al. *N Engl J Med*. 2013;369:1317-1326.
c. Green JB, et al. *N Engl J Med*. 2015;373:232-242.

Baseline risk of patient populations enrolled in CV safety trials of DPP-4 inhibitors



CV = cardiovascular; DPP-4 = dipeptidyl peptidase-4; CAD = coronary artery disease; CVD = cardiovascular disease; PAD = peripheral artery disease; ACS = acute coronary syndrome; EXAMINE = Examination of Cardiovascular Outcomes: Alogliptin vs Standard of Care in Patients With Type 2 Diabetes Mellitus and Acute Coronary Syndrome; SAVOR-TIMI = Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus Trial-Thrombolysis in Myocardial Infarction; TECOS = Trial Evaluating Cardiovascular Outcomes With Sitagliptin; CARMELINA = Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus at High Vascular Risk.

1. White W et al. N Engl J Med. 2013;369:1327–1335. **2.** Scirica BM et al. N Engl J Med. 2013;369:1317–1326. **3.** Bethel MA et al. Diabetes Obes Metab. 2015; 10.1111/dom.12441. **4.** TECOS: Trial Evaluating Cardiovascular Outcomes with Sitagliptin ClinicalTrials.gov web site. https://clinicaltrials.gov/ct2/show/NCT00790205. Accessed: January 30, 2015; **5.** CARMELINA: Cardiovascular and renal microvascular outcome study with linagliptin in patients with type 2 diabetes mellitus at high vascular risk. ClinicalTrials.gov web site. http://clinicaltrials.gov/ct2/show/ NCT01703298. Accessed September 12, 2014.

DPP-4 inhibitors and CVOT

- Among patients with T2D and established CVD, the rates of MACE were not increased or decreased with the DPP-4 inhibitors alogliptin, saxagliptin, or sitagliptin as compared with placebo[a-c]
- Although established CVD was present in the vast majority of patients in these studies, some other characteristics of the patient populations were heterogeneous in the 3 trials

DPP-4 inhibitors are simple to take; they are oral agents with few associated adverse events.

a. Scirica BM, et al. *N Engl J Med*. 2013;369:1317-1326; b. White WB, et al. *N Engl J Med*. 2013;369:1327-1335; c. Green JB, et al. *N Engl J Med*. 2015;373:232-242.

Lixisenatide in acute coronary syndrome, a long-term cardiovascular end point trial of lixisenatide vs placebo

LEADER®

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

Liraglutide and cardiovascular outcomes in type 2 diabetes

SUSTAIN

SEMAGLUTIDE UNABATED SUSTAINABILITY
IN TREATMENT OF TYPE 2 DIABETES

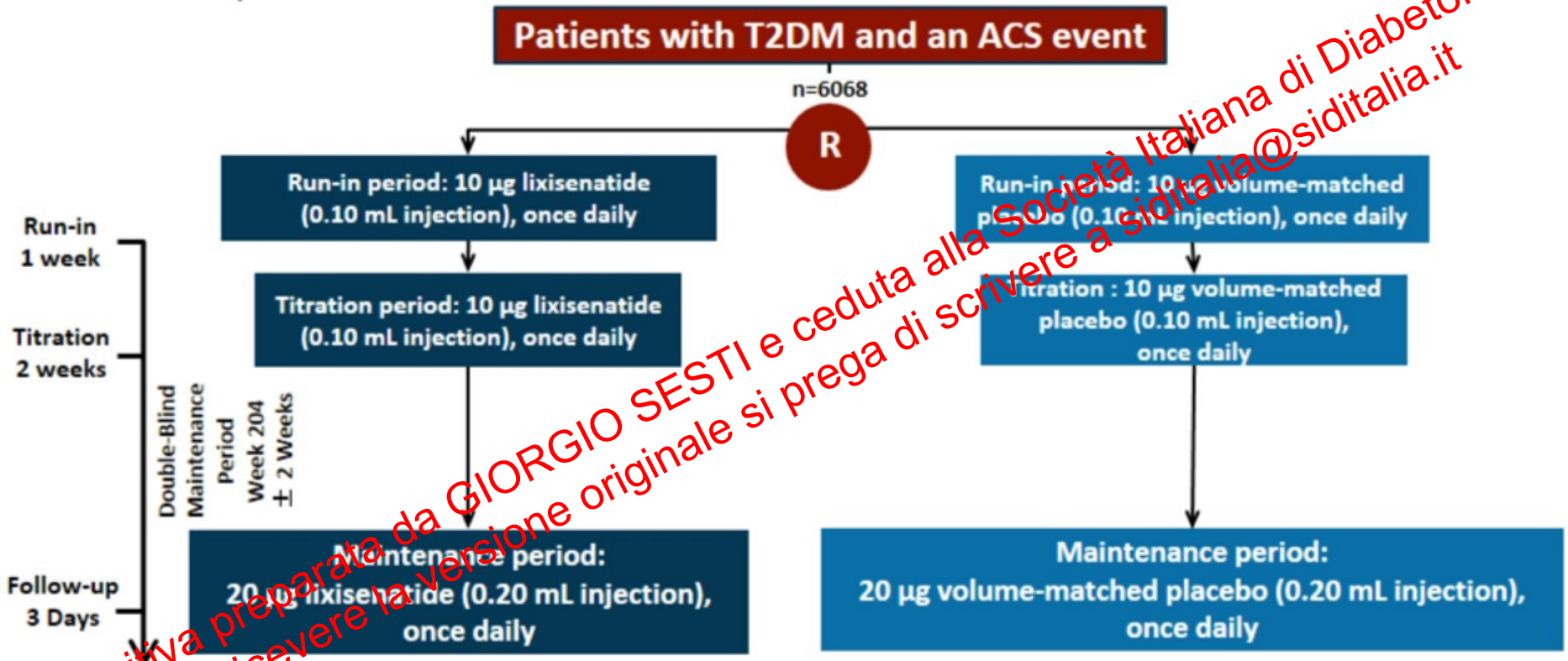
SUSTAIN 6: cardiovascular and other long-term outcomes with semaglutide in subjects with type 2 diabetes

EXSCEL®

Exenatide Study of Cardiovascular Event Lowering

ELIXA: Study Design

- A randomized, double-blind, placebo-controlled, parallel-group, multicenter, Phase 3, event-driven trial



Primary Endpoints

Time to first occurrence of the primary CV event: CV death, nonfatal MI, nonfatal stroke, or hospitalization for UA

Secondary Endpoints

Primary endpoints or hospitalization for HF

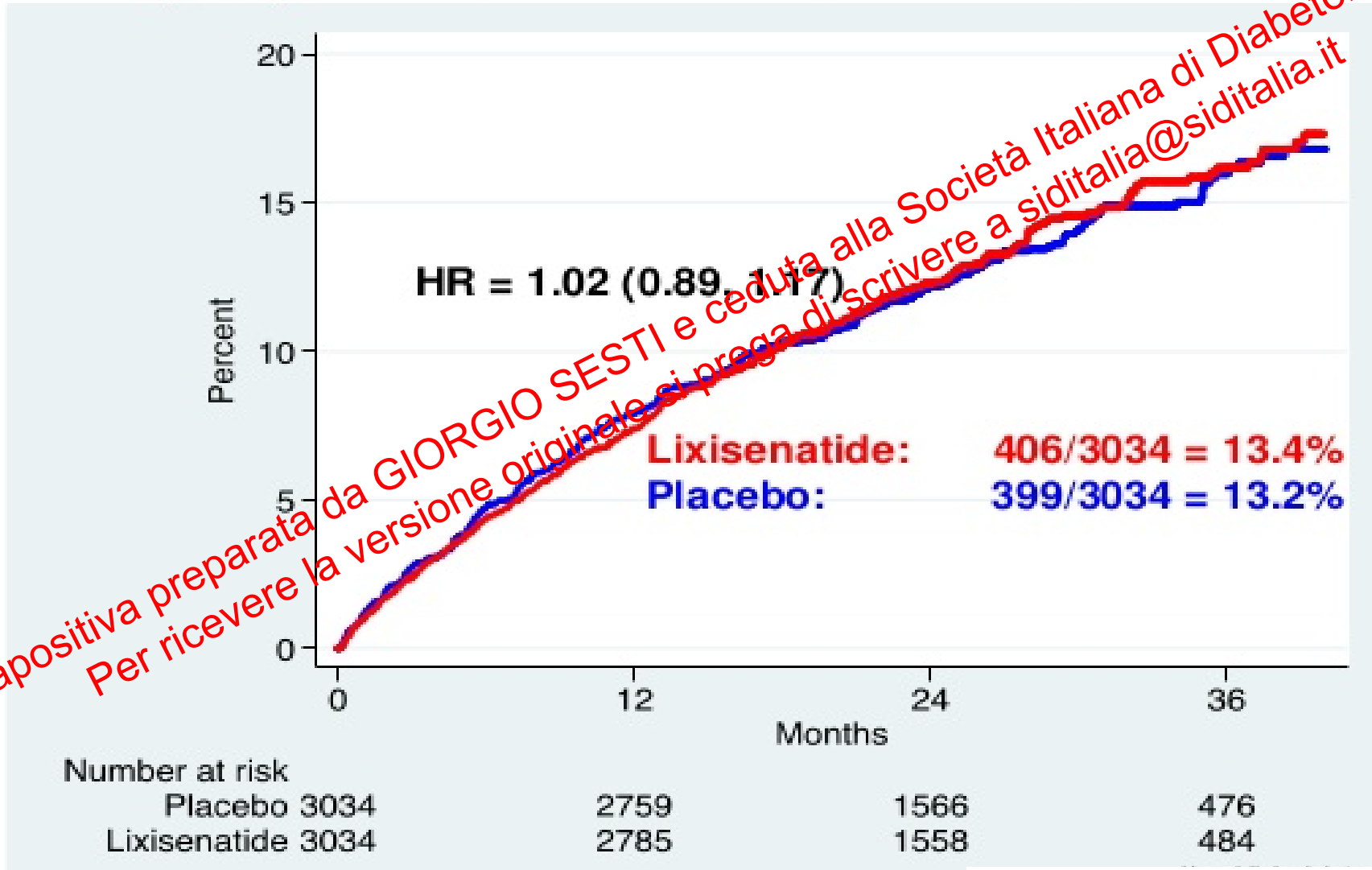
Primary endpoints or hospitalization for HF or coronary revascularization procedure

Percent change in the UACR from baseline to 108 weeks

Bentley-Lewis R, et al. *Am Heart J.* 2015:69:631-638.

Primary Outcome

CV Death, MI, Stroke or UA



Pfeffer MA et al. N Engl J Med 373:2247-57, 2015

Individual Components of Primary

Outcome	# and % of Subjects with Event, and Event Rate		
	Placebo (N = 3034)	Lixisenatide (N = 3034)	Hazard Ratio (95% CI)
CV Mortality	158 (5.2%) 2.4/100pt-yr	156 (5.1%) 2.3/100pt-yr	0.98 (0.78, 1.22)
MI (fatal / non-fatal)	261 (8.6%) 4.1/100pt-yr	270 (8.9%) 4.2/100pt-yr	1.03 (0.87, 1.22)
Stroke (fatal / non-fatal)	60 (2.0%) 0.9/100pt-yr	67 (2.2%) 1.0/100pt-yr	1.12 (0.79, 1.58)
Unstable Angina	10 (0.3%) 0.1/100pt-yr	11 (0.4%) 0.2/100pt-yr	1.11 (0.47, 2.62)

Pfeffer MA et al. N Engl J Med 373:2247-57, 2015

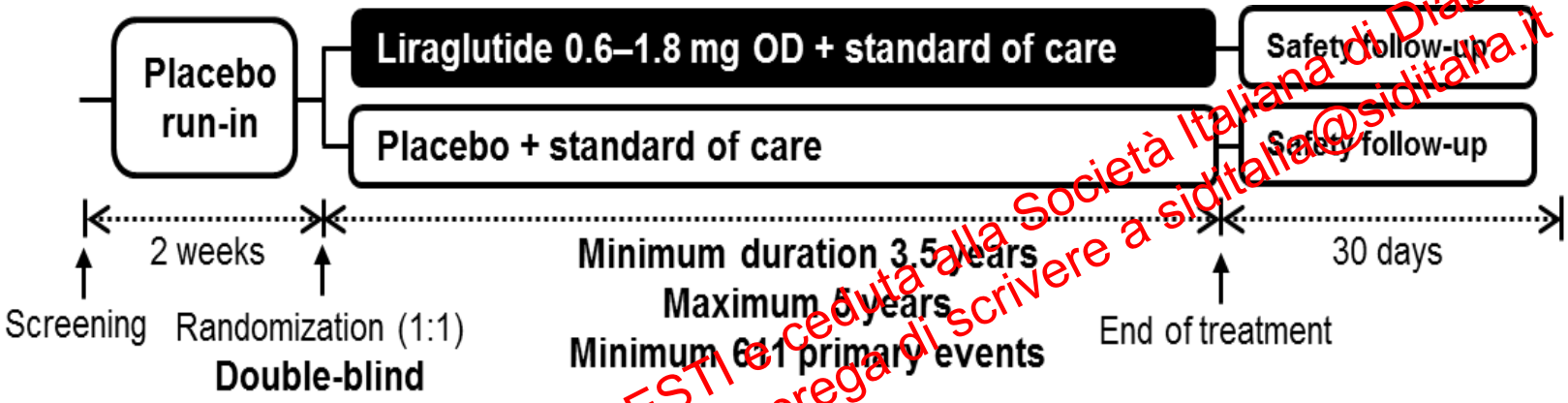
The NEW ENGLAND JOURNAL of MEDICINE

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., Michael 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*

LEADER: Study design



Key inclusion criteria

- T2DM, HbA_{1c} ≥7.0%
- Antidiabetic drug naïve; OADs and/or basal/premix insulin
- Age ≥50 years and established CV disease or chronic renal failure

  or
- Age ≥60 years and risk factors for CV disease

Key exclusion criteria

- T1DM
- Use of GLP-1RAs, DPP-4i, pramlintide, or rapid-acting insulin
- Familial or personal history of MEN-2 or MTC

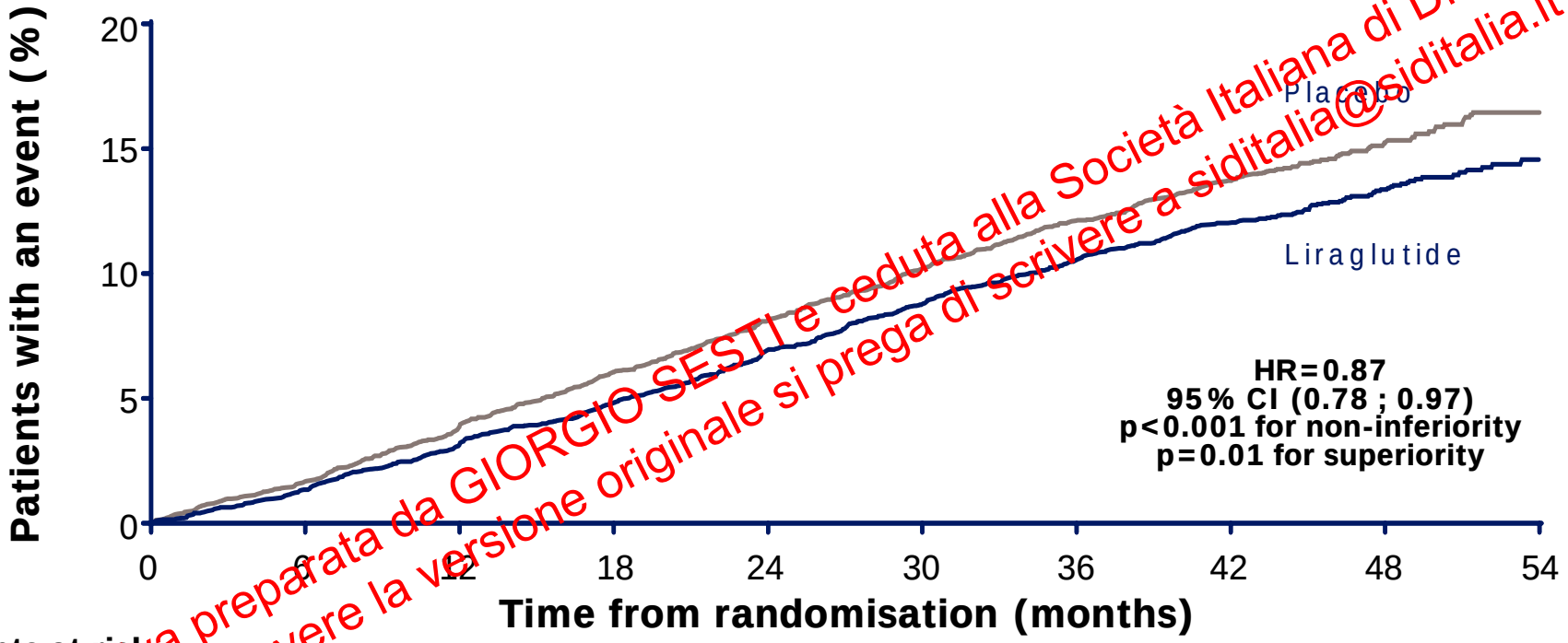
LEADER®
Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results

CV: cardiovascular; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA: glucagon-like peptide-1 receptor agonist; HbA_{1c}: glycated hemoglobin; MEN-2: multiple endocrine neoplasia type 2; MTC: medullary thyroid cancer; OAD: oral antidiabetic drug; OD: once daily; T2DM: type 2 diabetes mellitus.

Marso SP et al. N Engl J Med 375(4):311-22, 2016

Primary outcome

CV death, non-fatal myocardial infarction, or non-fatal stroke



Patients at risk

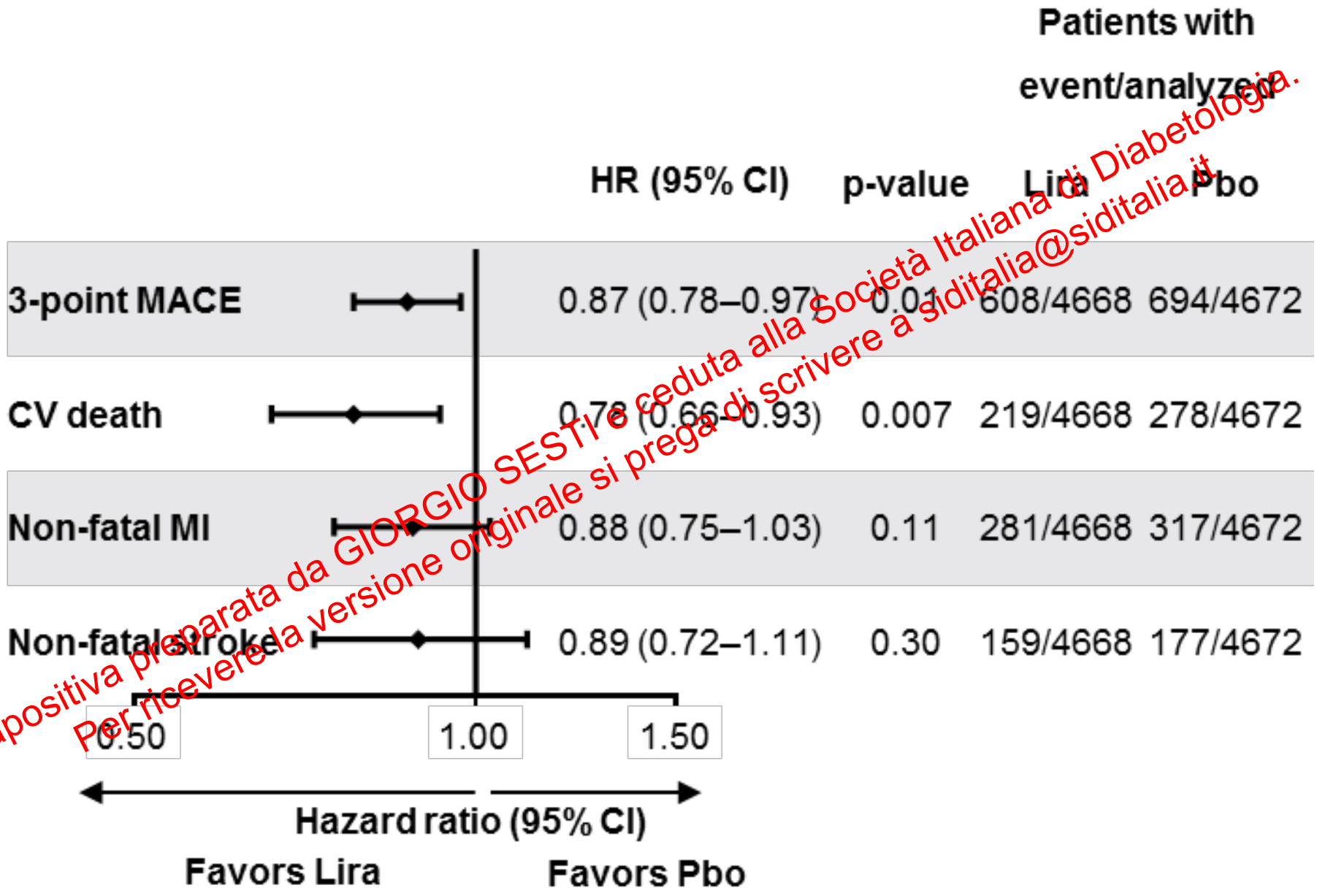
Liraglutide	4668	4593	4496	4400	4280	4172	4072	3982	1562	424
Placebo	4672	4588	4473	4352	4237	4123	4010	3914	1543	407

The primary composite outcome in the time-to-event analysis was the first occurrence of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke. 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; CV: cardiovascular; HR: hazard ratio.

Marso SP et al. N Engl J Med 375(4):311-22, 2016

LEADER - Individual components of the primary endpoint



Marso SP et al. N Engl J Med 375(4):311-22, 2016

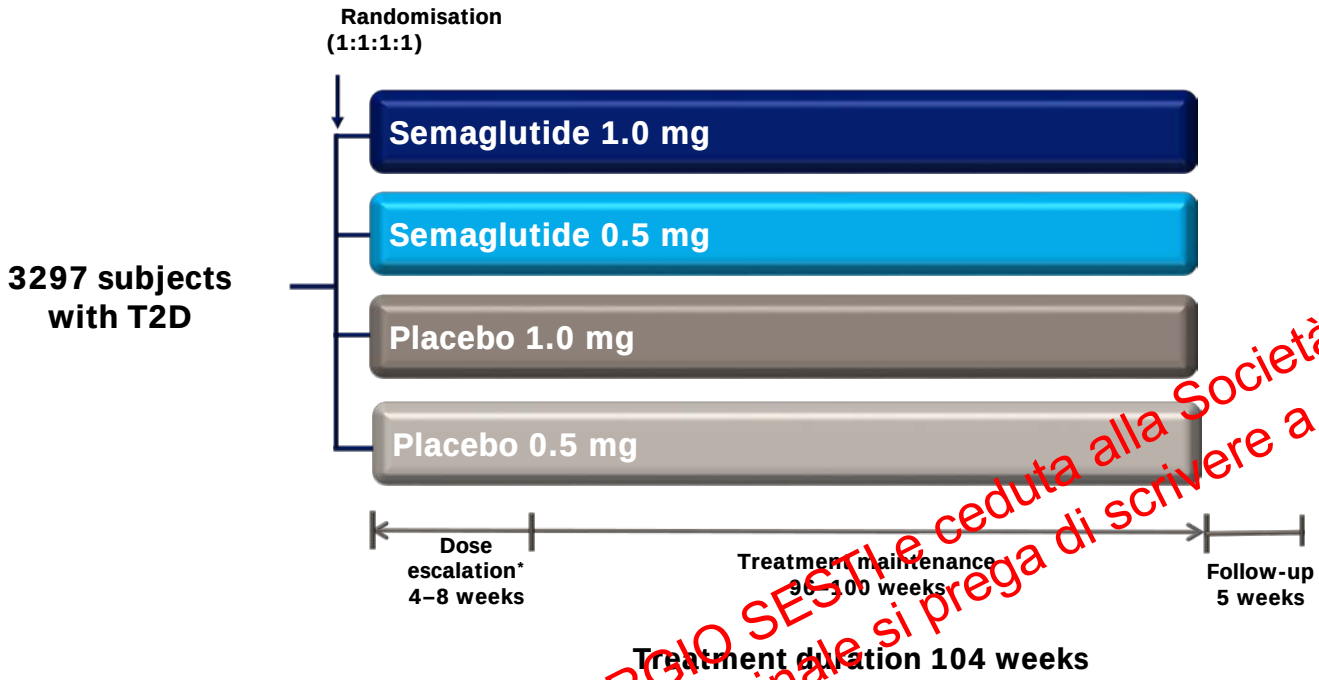
The NEW ENGLAND JOURNAL of MEDICINE

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., Olufunmilayo 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*

Trial design



Trial information

- Randomised, double-blind, placebo-controlled, four-armed parallel-group trial
- Additional glucose-lowering medication could be added to achieve glycaemic control at the discretion of investigator

Inclusion criteria

- HbA_{1c} ≥7.0%
- Previously on 0–2 OADs, basal or pre-mix insulin ± 0–2 OADs
- Age ≥50 years with established CVD (prior cardio-, cerebro- or peripheral vascular disease, chronic heart failure [NYHA class II–III]), or CKD stage 3 or worse

or

- Age ≥60 years with at least one cardiovascular risk factor

Key endpoints

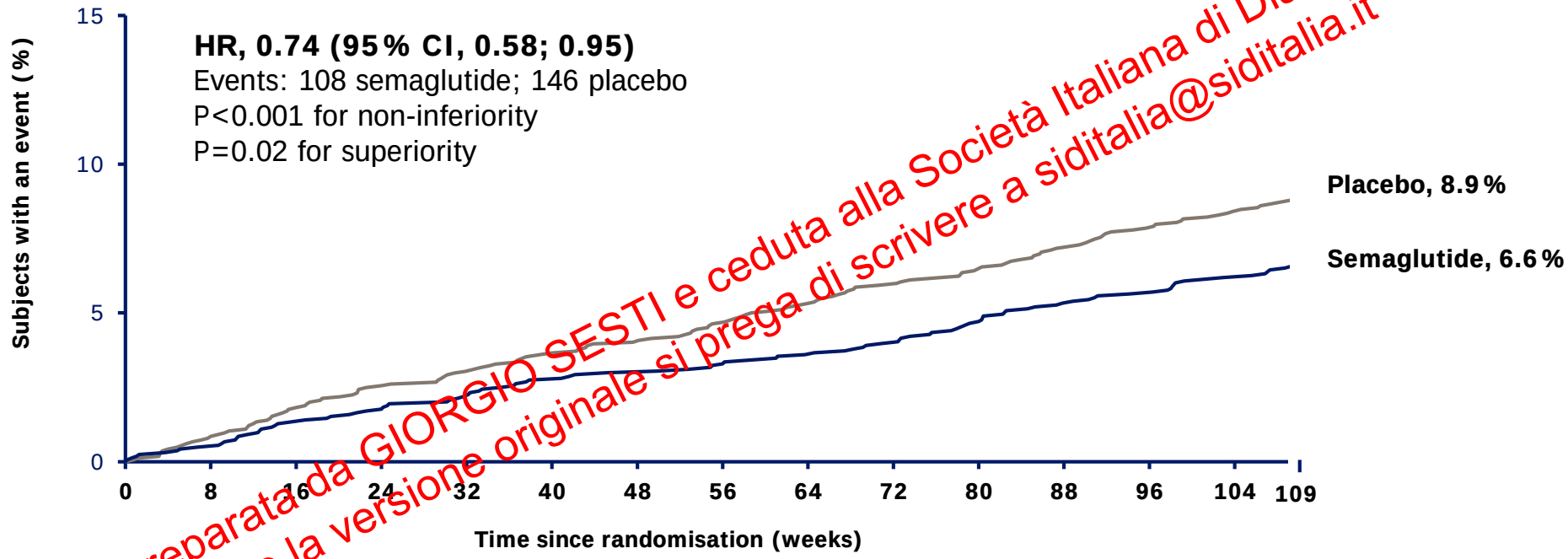
- Primary: time to first occurrence of death from cardiovascular causes, non-fatal myocardial infarction or non-fatal stroke
- Secondary: time to first occurrence of revascularisation, unstable angina requiring hospitalisation, hospitalisation for heart failure, all-cause death,
non-fatal MI or non-fatal stroke; time to each individual component

*Dose escalation from a starting dose of 0.25 mg, dose doubled each step until trial dose achieved. www.ClinicalTrials.gov (NCT01720446). Novo Nordisk, Data on file.
CKD, chronic kidney disease; CVD, cardiovascular disease; MI, myocardial infarction; NYHA, New York Heart Association; OAD, oral antidiabetic drug.

Marso SP et al. N Engl J Med 375:1834-44, 2016

Primary outcome

Time to First Occurrence of CV Death or Non-fatal MI or Non-fatal Stroke

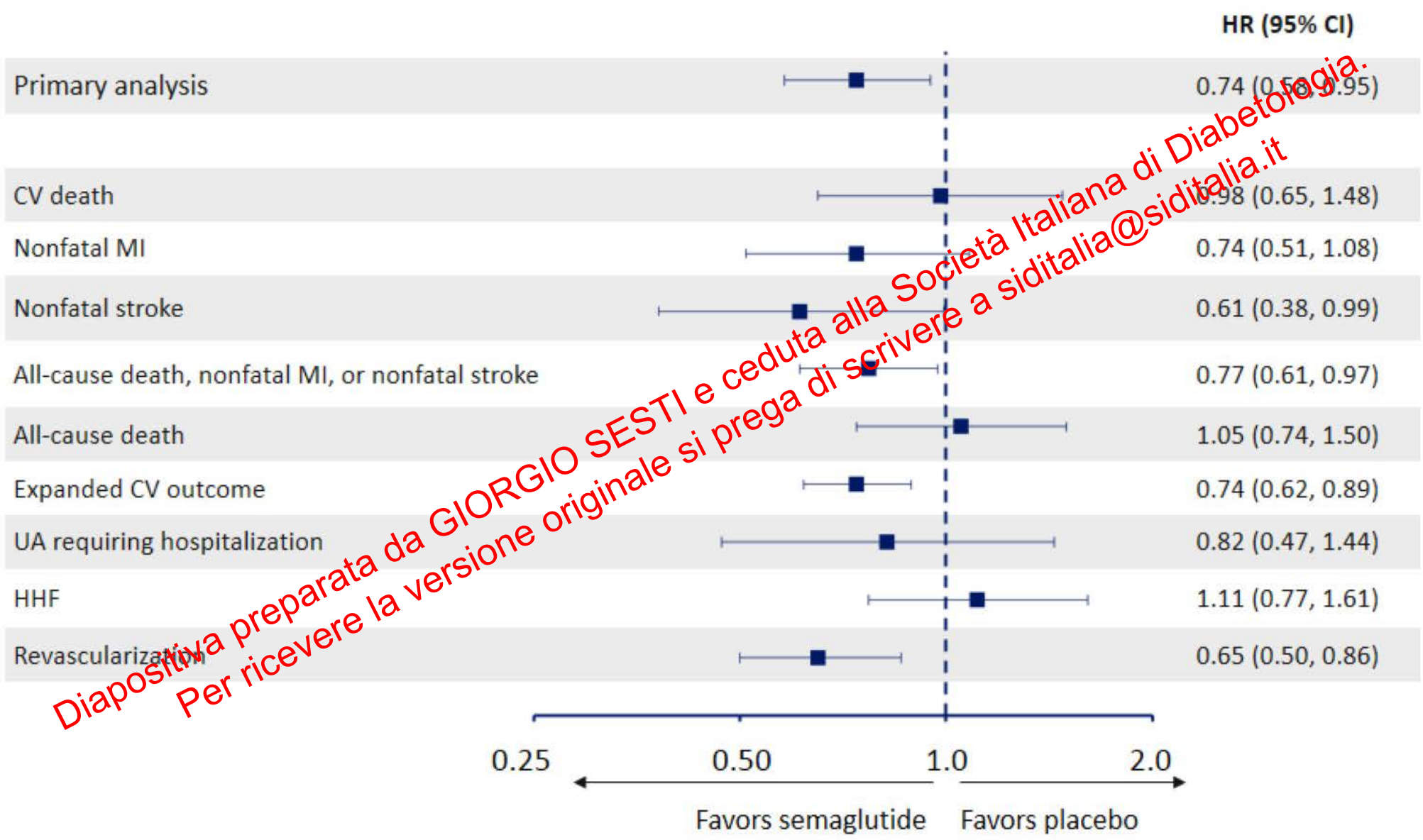


Number of subjects at risk

Semaglutide	1648	1619	1601	1584	1568	1543	1524	1513
Placebo	1649	1616	1586	1567	1534	1508	1479	1466

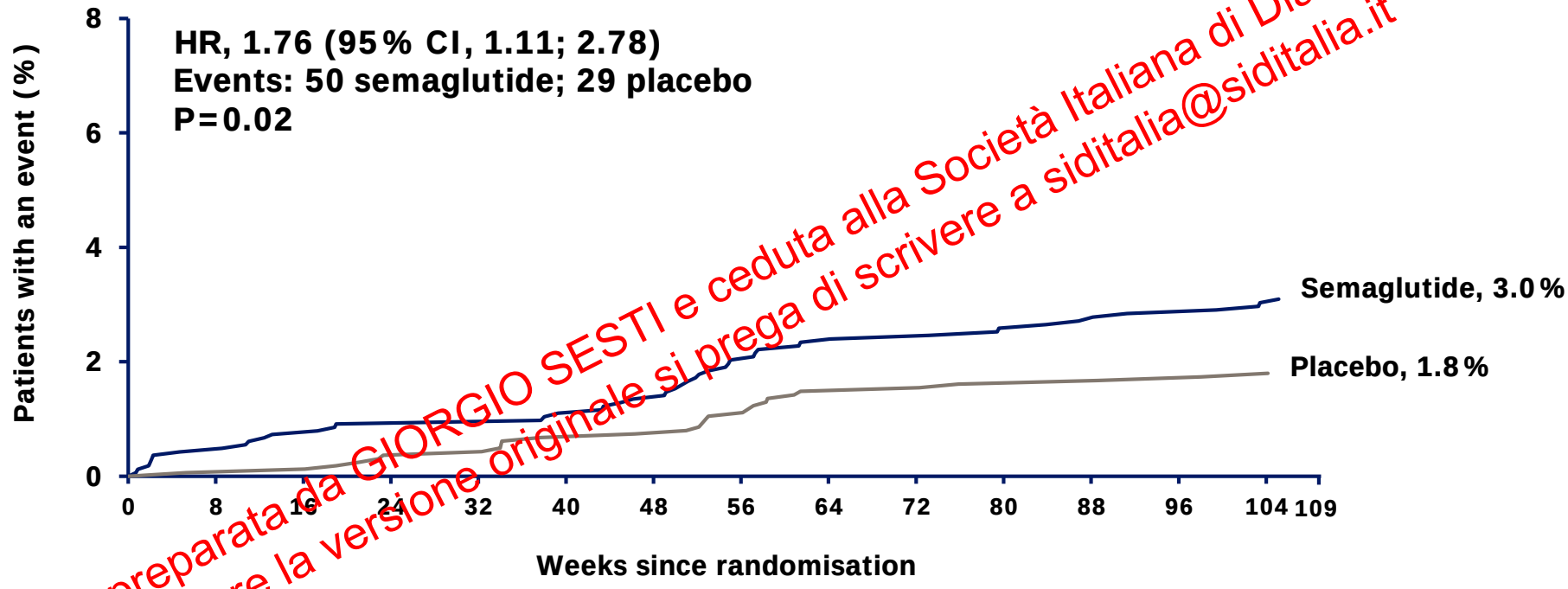
Marso SP et al. N Engl J Med 375:1834-44, 2016

SUSTAIN-6 Study: CV endpoints



Marso SP et al. N Engl J Med 375:1834-44, 2016

Diabetic retinopathy complications



Number of patients at risk

Semaglutide	1648	1622	1612	1595	1570	1548	1535	1525
Placebo	1649	1636	1617	1605	1576	1558	1539	1530

Marso SP et al. N Engl J Med 375:1834-44, 2016

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes

Rury R. Holman, F.Med.Sci., M. Angelyn Bethel, M.D., Robert J. Mentz, M.D., Vivian P. Thompson, M.P.H., Yuliya Lokhnygina, Ph.D., John B. Buse, M.D., Ph.D., Juliana C. Chan, M.D., Jasmine Choi, M.S., Stephanie M. Gustavson, Ph.D., Wayyan Iqbal, M.D., Aldo P. Maggioni, M.D., Steven P. Marso, M.D., Peter Öhman, M.D., Ph.D., Neha J. Pagidipati, M.D., M.P.H., Neil Poulter, F.Med.Sci., Ambady Ramachandran, M.D., Bernard Zinman, M.D., and Adrian F. Hernandez, M.D., M.H.S., for the EXSCEL Study Group*

EXSCEL: Study Design

Aim is for glycaemic equipoise

Key Inclusion Criteria

- T2DM, HbA1c 6.5-10% (inclusive)
- Anti-DM drug naïve, oral agents and/or insulin
- ≥18 years old
- Any level of CV risk
- **~70% with prior CV event**
  - **Prior coronary, cerebrovascular or peripheral vascular event or stenosis**

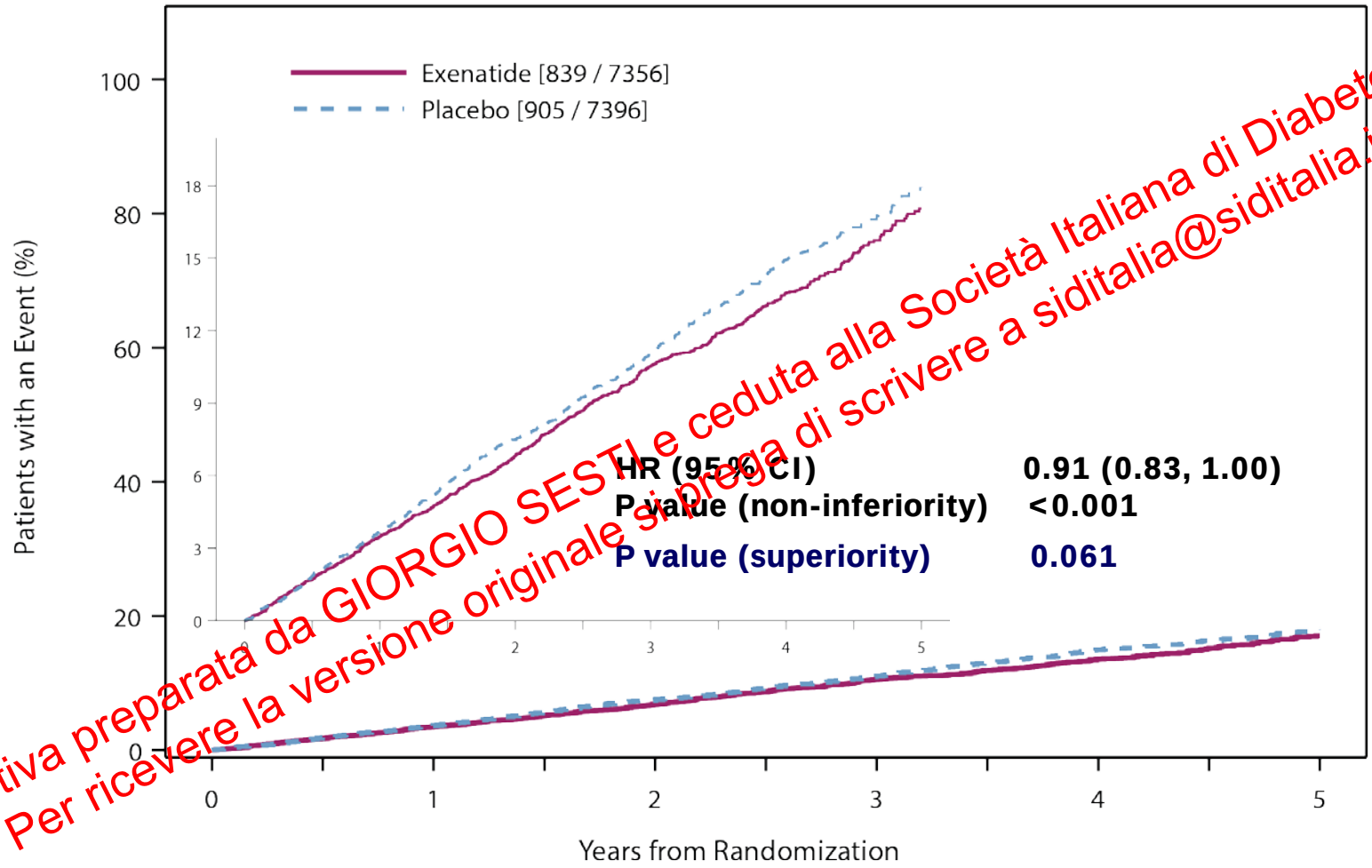
Key Exclusion Criteria

- T1DM
- ≥2 episodes of severe hypoglycaemia within 12 months
- Current or prior GLP1-RA
- eGFR <30mL/min/1.73m^2
- Prior pancreatitis
- Personal or familial history of MEN-2
- Baseline calcitonin >40ng/L

Holman RR et al. N Engl J Med 2017

Primary Composite Cardiovascular Outcome

Intention-to-Treat Analysis for Non-inferiority & Superiority

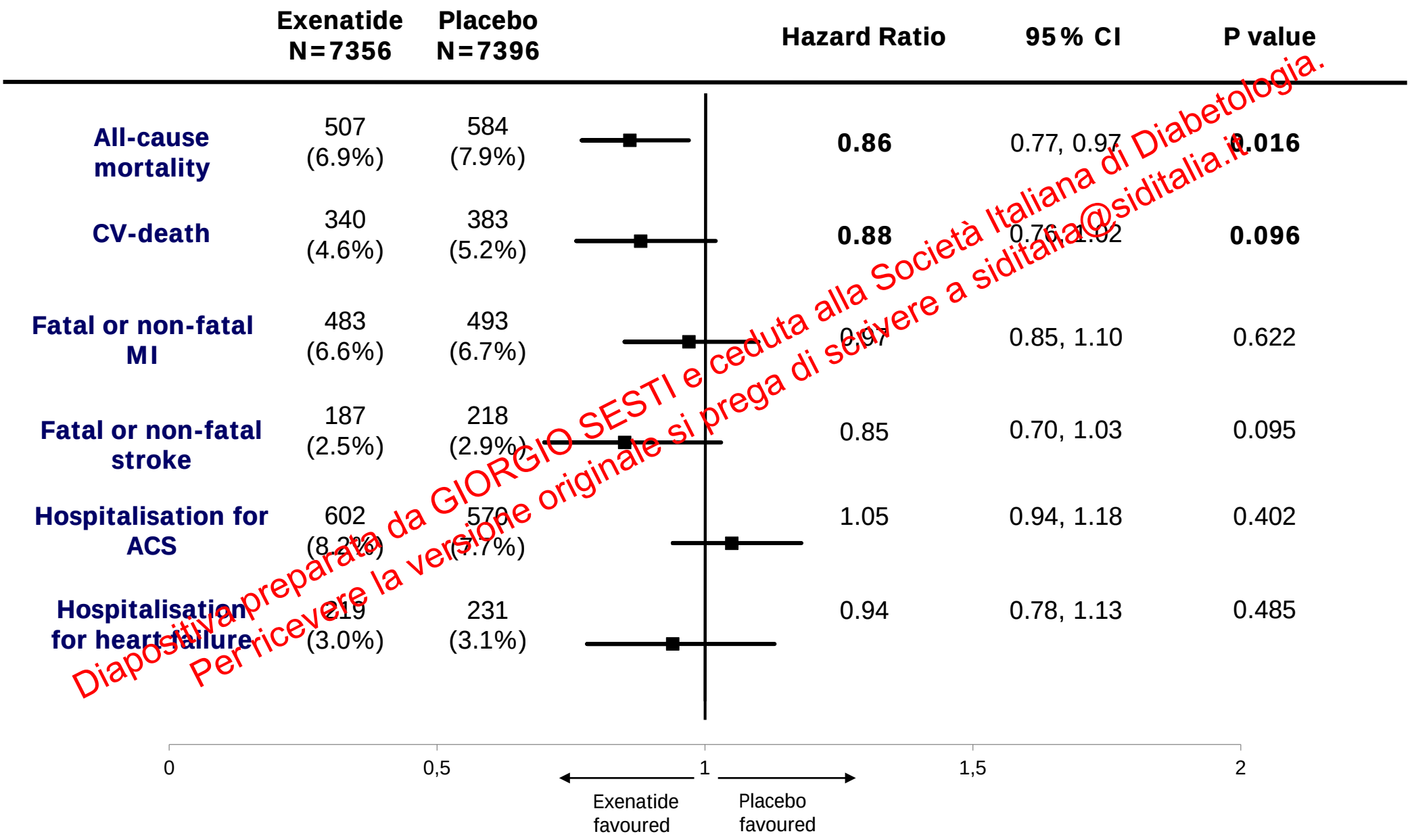


No at Risk

Exenatide	7356	7101	6893	6580	5912	4475	3595	3053	2281	1417	727
Placebo	7396	7120	6897	6565	5908	4468	3565	2961	2209	1366	687

Holman RR et al. N Engl J Med 2017

Forest Plot of Secondary Endpoints (Intention-to-Treat Analysis)



Holman RR et al. N Engl J Med 2017

ELIXA, LEADER, SUSTAIN-6 and EXSCEL: Results

	ELIXA[1] N=6.068	LEADER[2] N=9.340	SUSTAIN-6[3] N=3.297	EXSCEL[4] N=14.752
Outcomes	**Lixisenatide vs Placebo Hazard Ratio (95% CI)**	**Liragludite vs Placebo Hazard Ratio (95% CI)**	**Semaglutide vs Placebo Hazard Ratio (95% CI)**	**Extended-release exenatide vs Placebo Hazard Ratio (95% CI)**
3-point MACE	1.02 (0.89 - 1.17)	**0.87 (0.78 - 0.97)**	**0.74 (0.58 - 0.95)**	0.91 (0.83-1.00)
CV death	0.98 (0.78 - 1.22)	**0.78 (0.66 - 0.93)**	0.98 (0.65 - 1.48)	0.88 (0.76-1.02)
Non-fatal MI	1.03 (0.87 - 1.22)	0.88 (0.75 - 1.03)	0.74 (0.51 - 1.08)	0.95 (0.84 -1.09)
Non-fatal stroke	1.12 (0.79 - 1.58)	0.89 (0.72 - 1.11)	**0.61 (0.38 - 0.99)**	0.86 (0.70-1.07)
Death from any cause	0.94 (0.78 - 1.13)	**0.85 (0.74 – 0.97)**	1.05 (0.74 - 1.50)	**0.86* (0.77 – 0.97)**

***This difference was not considered to be statistically significant on the basis of the hierarchical testing plan**

1 Pfeffer MA et al. N Engl J Med 373:2247-57, 2015; 2 Marso SP et al. N Engl J Med 375(4):311-22, 2016; 3 Marso SP et al. N Engl J Med 375:1834-44, 2016; 4 Holman R et al. N Engl J Med 2017

Potential explaination for differences in GLP-1 RA CVOT

Differences in the study populations

- ELIXA was performed in patients with T2DM who had had a recent ACS[a]

a. Pfeffer MA, et al. *N Engl J Med*. 2015;33:2247-2257.

ELIXA, LEADER, SUSTAIN-6 and EXSCEL: Results

	ELIXA[1] N=6.068	LEADER[2] N=9.340	SUSTAIN-6[3] N=3.297	EXSCEL[4] N=14.752
	Lixisenatide vs Placebo Hazard Ratio (95% CI)	Liragludite vs Placebo Hazard Ratio (95% CI)	Semaglutide vs Placebo Hazard Ratio (95% CI)	Extended-release exenatide vs Placebo Hazard Ratio (95% CI)
CV risk	Patients with a spontaneous ACS within 180 days following the hospital admission for the ACS but after discharge.	Age >50 years with one CVD (CHD, cerebrovascular disease, PAD, CKD, HF of NYHA class II or III) or age >60 years with one CV risk factor (microalbuminuria or proteinuria, hypertension and LVH, left ventricular systolic or diastolic dysfunction, or an ankle–brachial index of less than 0.9)	Age >50 years with one CVD (CHD, cerebrovascular disease, PAD, CKD, HF of NYHA class II or III) or age >60 years with one CV risk factor (microalbuminuria or proteinuria, hypertension and LVH, left ventricular systolic or diastolic dysfunction, or an ankle–brachial index of less than 0.9)	The trial was designed such that approximately 70% of enrolled patients would have had previous cardiovascular events and 30% would not have had previous cardiovascular events.
Diabete duration (years)	9.3	12.9	13.9	12.0
HbA1c%	7.7	8.7	8.7	8.0

1 Pfeffer MA et al. N Engl J Med 373:2247-57, 2015; 2 Marso SP et al. N Engl J Med 375(4):311-22, 2016; 3 Marso SP et al. N Engl J Med 375:1834-44, 2016; 4 Holman R et al. N Engl J Med 2017

Potential explaination for differences in GLP-1 RA CVOT

Differences in the study populations

- ELIXA was performed in patients with T2DM who had had a recent ACS[a]

Duration of action of GLP-1 RA[b]

a. Pfeffer MA, et al. *N Engl J Med*. 2015;33:2247-2257.
b. Dalsgaard NB, et al. *Expert Opin Drug Saf*. 2017;16:351-363.

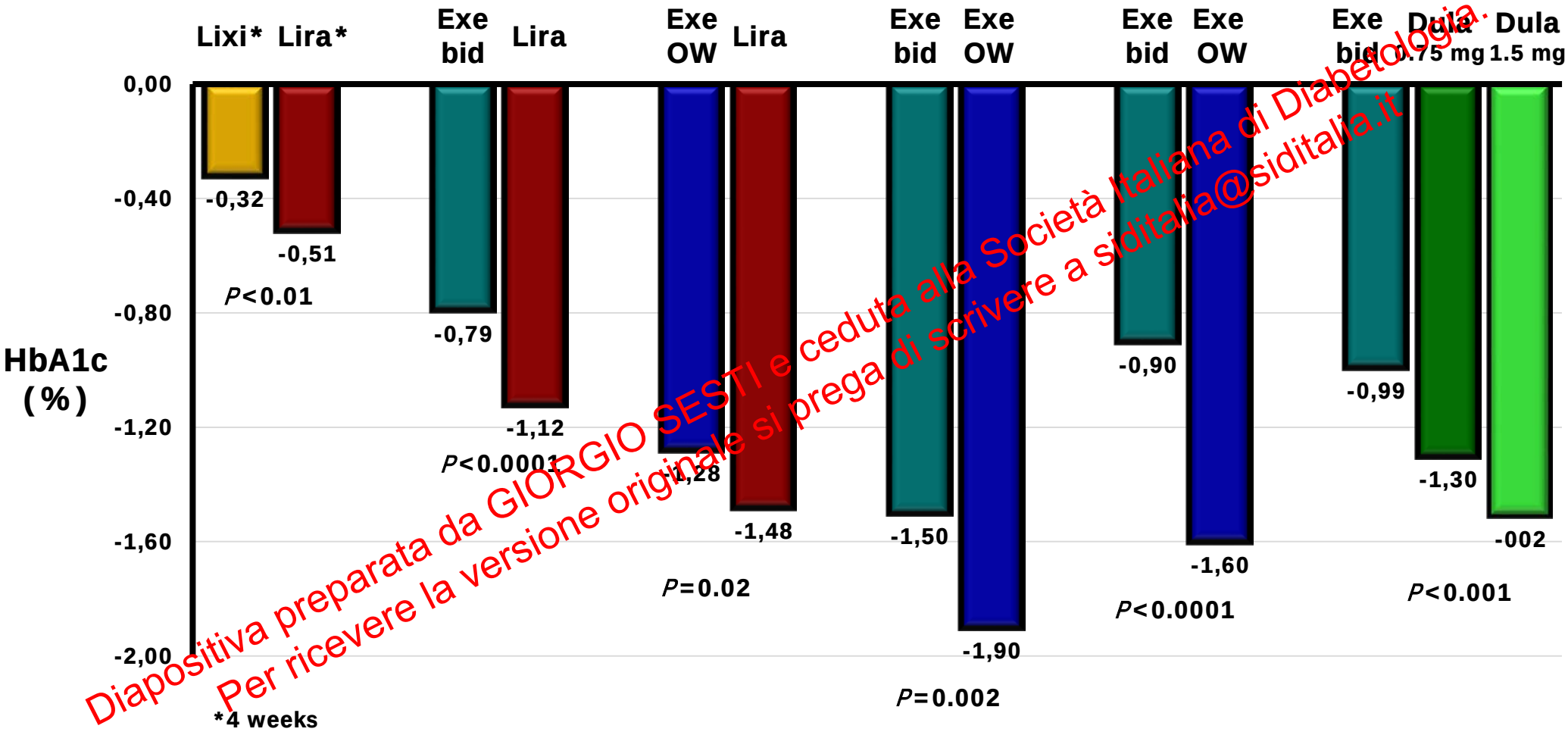
Pharmacokinetic properties: Short versus long-acting GLP-1RAs

Category	Agent	Half-life	T_{max}
Short-acting <24 hours	Exenatide BID[1]	2.4 hours	2 hours
	Lixisenatide OD[2]	2.7–4.3 hours	1.25–2.25 hours
Long-acting ≥24 hours	Liraglutide OD[3]	13 hours	8–12 hours
	Dulaglutide OW[4]	90 hours	24–48 hours
	Albiglutide OW[5,6]	6–7 days	3–5 days
	Semaglutide OW[7]	6.5–7 days	36 hours
	Exenatide OW[8]	7–14 days	6–7 weeks

BID, twice daily; OD, once daily; OW, once weekly; T_{max}, time to reach maximum concentration

1. Byetta® SmPC. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000698/WC500051845.pdf; 2. Lyxumia® SmPC. Available from: http://www.medicines.org.uk/emc/medicine/27405/SPC/; 3. Victoza® SmPC. Available from: http://www.medicines.org.uk/emc/medicine/21986/SPC/; 4. Barrington et al. Diabetes Obes Metab 2011;13:434–8; 5. Bush et al. Diabetes Obes Metab 2009;11:498–505; 6. Matthews et al. J Clin Endo Metab 2008;93:4810–7;
7. Novo Nordisk Data on file; 8. Fineman et al. Clin Pharmacokinet 2011;50:65–74

Comparison of short-acting versus long-acting GLP-1RA: HbA1c



GLP-1 RA, glucagon-like peptide 1 receptor agonist; bid, twice daily; Lixi, lixisenatide; Lira, liraglutide; Exe, exenatide; Dula, dulaglutide

Kapitza C et al. Diabetes Obes Metab 2013; 15: 642–649; Buse J et al. Lancet 2009; 374, 39-47; Drucker et al. Lancet 2008; 372: 1240-50; Blevins T et al J. Clin. Endocrinol. Metab 2011; 96:1301-1310; Wysham C et al. Diabetes Care 2014; 37:2159-2167

ELIXA, LEADER, SUSTAIN-6 and EXSCEL: Results

	ELIXA[1] N=6.068	LEADER[2] N=9.340	SUSTAIN-6[3] N=3.297	EXSCEL[4] N=14.752
	Lixisenatide vs. Placebo	Liragludite vs. Placebo	Semaglutide vs. Placebo	Extended-release exenatide vs Placebo Hazard Ratio (95% CI)
Median follow-up (years)	2.1	3.8	2.1	3.2
HbA1c mean difference for GLP-1 vs. placebo	-0.27% (95% CI, -0.31, -0.22)	-0.4% 95% CI, -0.45,-0.34)	-0.7% (*P*<0.0001)	–0.53% (95% CI, –0.57 to –0.50)
Body weight mean difference for GLP-1 vs. placebo	-0.7 Kg (*P*<0.001)	-2.3 Kg (*P*<0.001)	-4.4 Kg (*P*<0.0001)	–1.27 kg (P<0.001)
Systolic blood pressure mean difference for GLP-1 vs. placebo	–0.8 mmHg (95% CI, -1.3,-0.3)	–1.2 mmHg (95% CI, -0.5,-1.9)	–2.6 mmHg (95% CI, -4,1,-1.1)	–1.57 mm Hg (95% CI, -1.92 to-1.21)

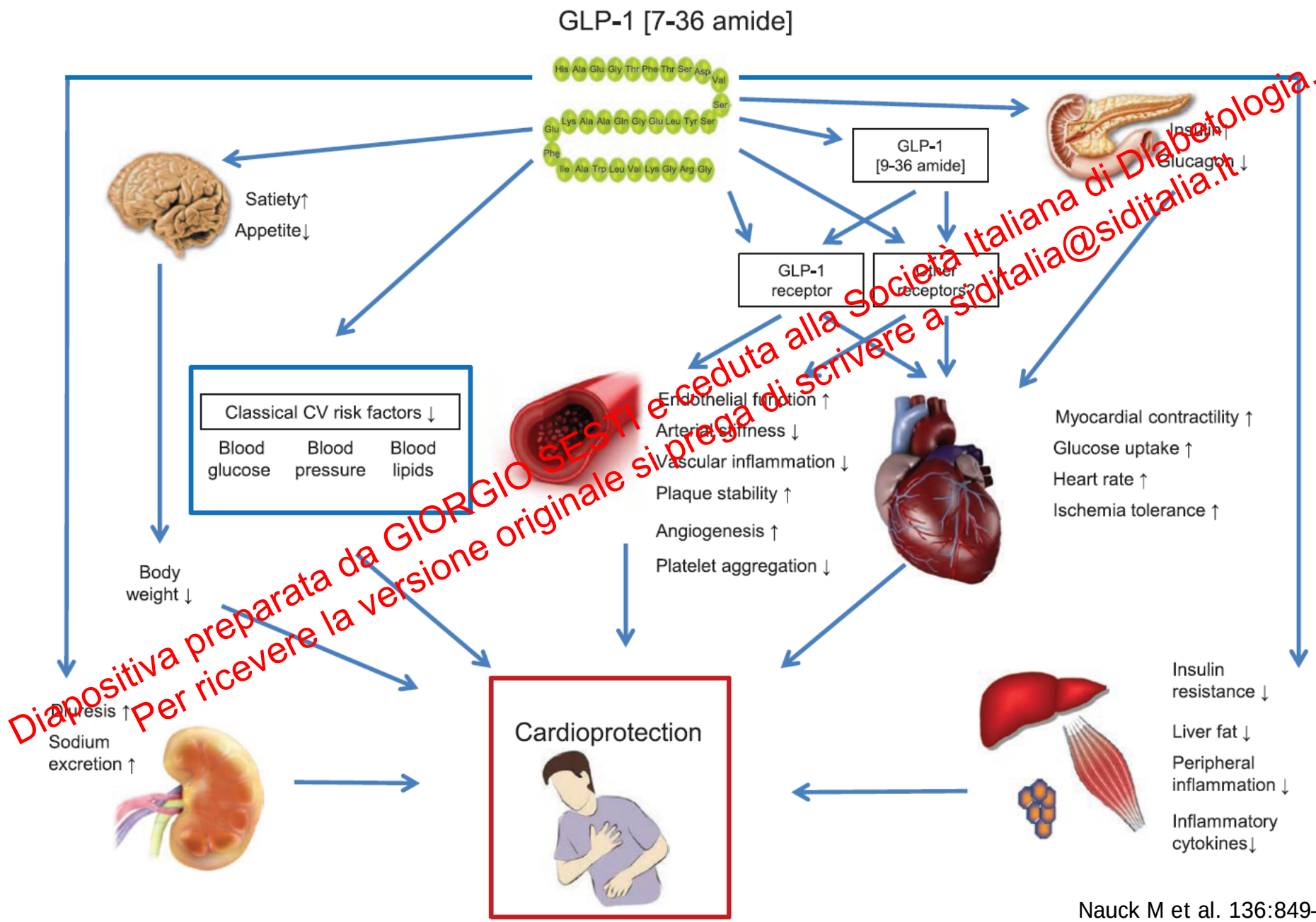
1 Pfeffer MA et al. N Engl J Med 373:2247-57, 2015; 2 Marso SP et al. N Engl J Med 375(4):311-22, 2016; 3 Marso SP et al. N Engl J Med 375:1834-44, 2016; 4 Holman R et al. N Engl J Med 2017

Effects of native GLP-1 or GLP-1 RAs in human studies, which lead to a modified CV function

Effect(s) on	GLP-1 [7–36 Amide]	Exenatide	Liraglutide
Cardioprotection against ischemia	• Intravenous GLP-1 LVEF↑, regional contractility ↑; • Coronary balloon occlusion: preserved left ventricular function; • 72 h after acute MI: LVEF↑, regional wall motility ↑	• STEMI: intravenous exenatide: salvage index (non-necrosed roportion of area at risk) ↑; • Subcutaneous exenatide: infarct size ↓	• Liraglutide preserved LVEF after PCI; • Non–STEMI: liraglutide-preserved LVEF after PCI
Endothelium-derived vasodilation	• Endothelial nitric oxide synthase ↑ in HUVECs; • Intravenous GLP-1: acetyl choline–induced vasodilation ↑ in healthy e in T2DM subjects with stable CAD.	• Endothelial nitric oxide synthase in HUVECs ↑; postprandial endothelial function ↑	• Endoplasmic reticulum Stress ↓, and TNFα-induced oxidative stress ↓ and inflammation ↓ in HUVECs; • eNOS ↑, endothelin-1 expression↓; • Acetyl choline–mediated forearm blood flow (↑)
Inflammatory/ anti-inflammatory factors	• No immediate effects reported	• CRP ↓ by 61% • Adiponectin ↑ by 12%	• CRP ↓ by 23% • Adiponectin↑ by 40%

Modified from Nauck M et al. 136:849–870, 2017

Potential mechanisms mediating a beneficial effect of GLP-1 RAs on reducing CV events



Nauck M et al. 136:849–870, 2017

Potential explaination for differences in GLP-1 RA CVOT

Differences in the study populations

- ELIXA was performed in patients with T2DM who had had a recent ACS[a]

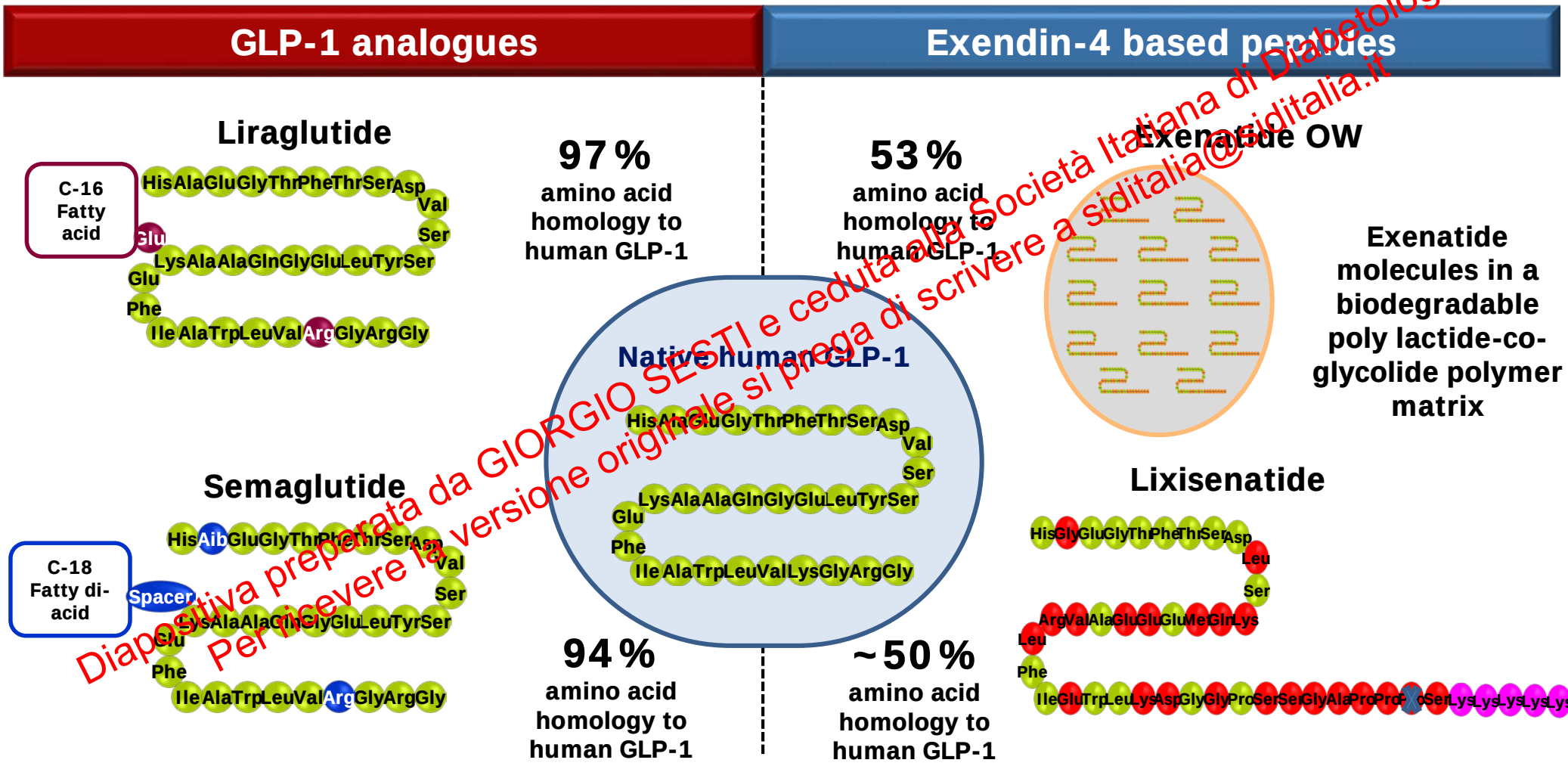
Duration of action of GLP-1 RA[b]

GLP-1 RA backbone[b]

- Exendin-4 vs GLP-1

a. Pfeffer MA, et al. *N Engl J Med*. 2015;33:2247-2257.
b. Dalsgaard NB, et al. *Expert Opin Drug Saf*. 2017;16:351-363.

Composition of small GLP-1RAs: GLP-1 analogues versus exendin-based peptides



Victoza® SmPC. Available from: http://www.medicines.org.uk/emc/medicine/21986/SPC/; Nauck et al. Diabetologia 2012;55(Suppl.1):S7;2-OP; Byetta® SmPC. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000698/WC500051845.pdf; Lyxumia® SmPC. Available from: http://www.medicines.org.uk/emc/medicine/27405/SPC/; Christensen et al. IDrugs 2009;12:503–13; Ratner et al. Diabet Med 2010;27:1024–32; Fineman et al. Clin Pharmacokinet 2011;50:65–74; DeYoung et al. Diab Technol Ther 2011;13: 1145–54

Potential explaination for differences in GLP-1 RA CVOT

Differences in the study populations

- ELIXA was performed in patients with T2DM who had had a recent ACS[a]

Duration of action of GLP-1 RA[b]

GLP-1 RA backbone[b]

- Exendin-4 vs GLP-1

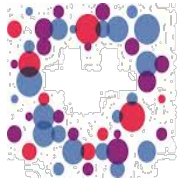
Differences in the use of nonstudy medications

a. Pfeffer MA, et al. *N Engl J Med*. 2015;33:2247-2257.
b. Dalsgaard NB, et al. *Expert Opin Drug Saf*. 2017;16:351-363.

ELIXA, LEADER, SUSTAIN-6 and EXSCEL: Introduction of antihyperglycemic medication during the trial

	ELIXA[1] N=6.068	LEADER[2] N=9.340	SUSTAIN-6[3] N=3.297	EXSCEL[4] N=14.752
	Lixisenatide vs. Placebo	Liragludite vs. Placebo	Semaglutide (0.5/1 mg) vs. Placebo	Extended-release exenatide vs Placebo Hazard Ratio (95% CI)
Insulin	Not reported	28.6 vs 43.2%**	10.3/8.5 vs 24.8/23.2%**	9.4 vs 13.8%
Metformin	Not reported	5.4 vs 6.4%*	3.9/2.6 vs 5.6/3.5%	4.9 vs 6.1%
DPP-4 inhibitors	Not reported	3.2 vs 3.6%	1.7/2.7 vs 3.9/2.5%*	7.5 vs 10.6%
SGLT-2 inhibitors	Not reported	2.1 vs 2.8%*	2.5/2.8 vs 4.9/6.4%**	6.5 vs 9.4%
Glinides	Not reported	1.8 vs 2.9%**	0.8/0.5 vs 1.7/1.6%*	0.7 vs 1.0%
Sulfonylureas	Not reported	7.6 vs 10.8%**	3.5/3.9 vs 7.3/8.1%**	6.9 vs 8.8%
TZDs	Not reported	2.1 vs 3.4%**	0.8/0.9 vs 3.6/3.4%**	2.0 vs 2.3%

1 Pfeffer MA et al. N Engl J Med 373:2247-57, 2015; 2 Marso SP et al. N Engl J Med 375(4):311-22, 2016; 3 Marso SP et al. N Engl J Med 375:1834-44, 2016; 4 Holman R et al. N Engl J Med 2017



EMPA-REG OUTCOME®

Empagliflozin, cardiovascular outcomes and mortality in type 2 diabetes

CANVAS Program

Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

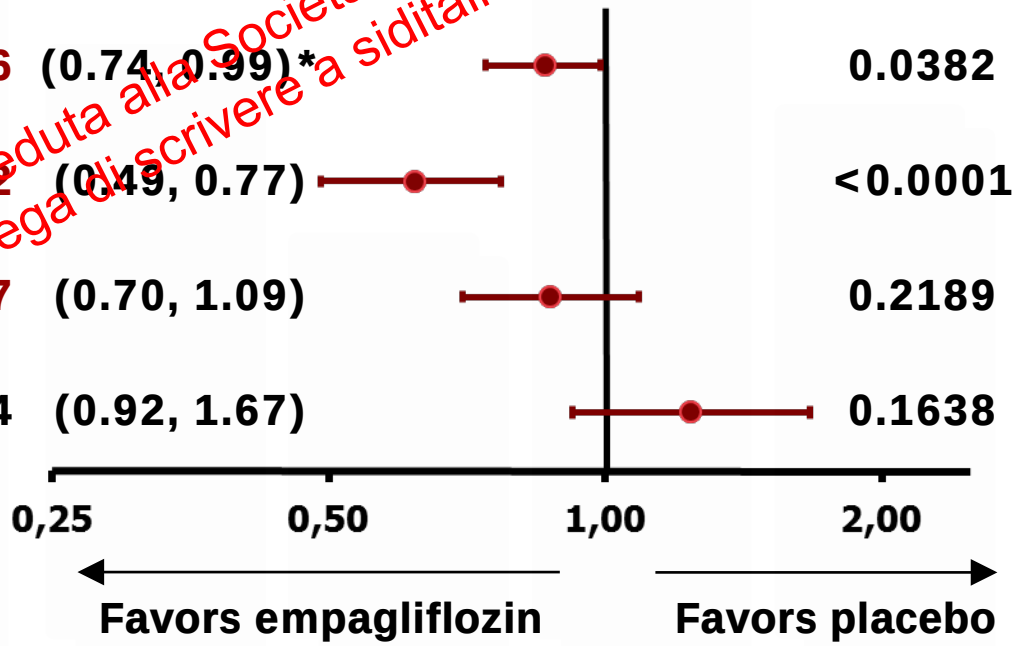
Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

Zinman B et al. N Engl J Med 373:2117-2128, 2015

Primary outcome

	Patients with event / analysed				
	Empagliflozin	Placebo	HR	(95% CI)	*p*-value
Primary outcome:					
3-point MACE	490/4687	282/2333	0.86	(0.74, 0.99)*	0.0382
CV death	172/4687	137/2333	0.62	(0.49, 0.77)	<0.0001
Non-fatal MI	213/4687	121/2333	0.87	(0.70, 1.09)	0.2189
Non-fatal stroke	158/4687	60/2333	1.24	(0.92, 1.67)	0.1638



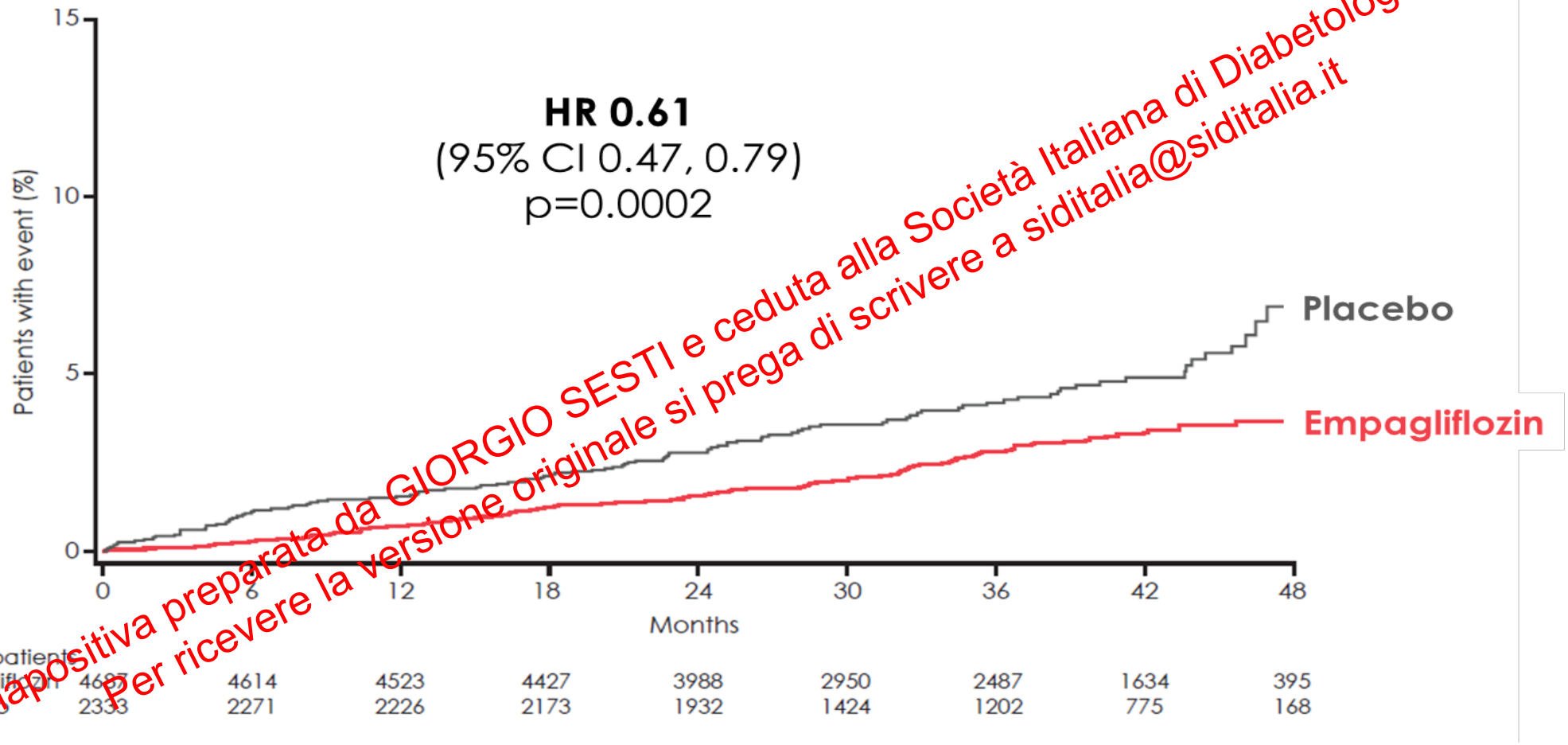
Cox regression analysis. 3-point MACE: Time to first occurrence of CV death, non-fatal MI or non-fatal stroke.

MACE, Major Adverse Cardiovascular Event; HR, hazard ratio; CI, confidence interval; CV, cardiovascular; MI, myocardial infarction.
*95.02% CI

Zinman B et al. N Engl J Med 373:2117-2128, 2015

EMPA-REG OUTCOME®

Hospitalization for or death from heart failure



Cumulative incidence function. HR, hazard ratio; CI, confidence interval.

EMPA-REG OUTCOME®

Fitchett D et al. European Heart Journal 37, 1526–1534, 2016

The NEW ENGLAND JOURNAL of MEDICINE

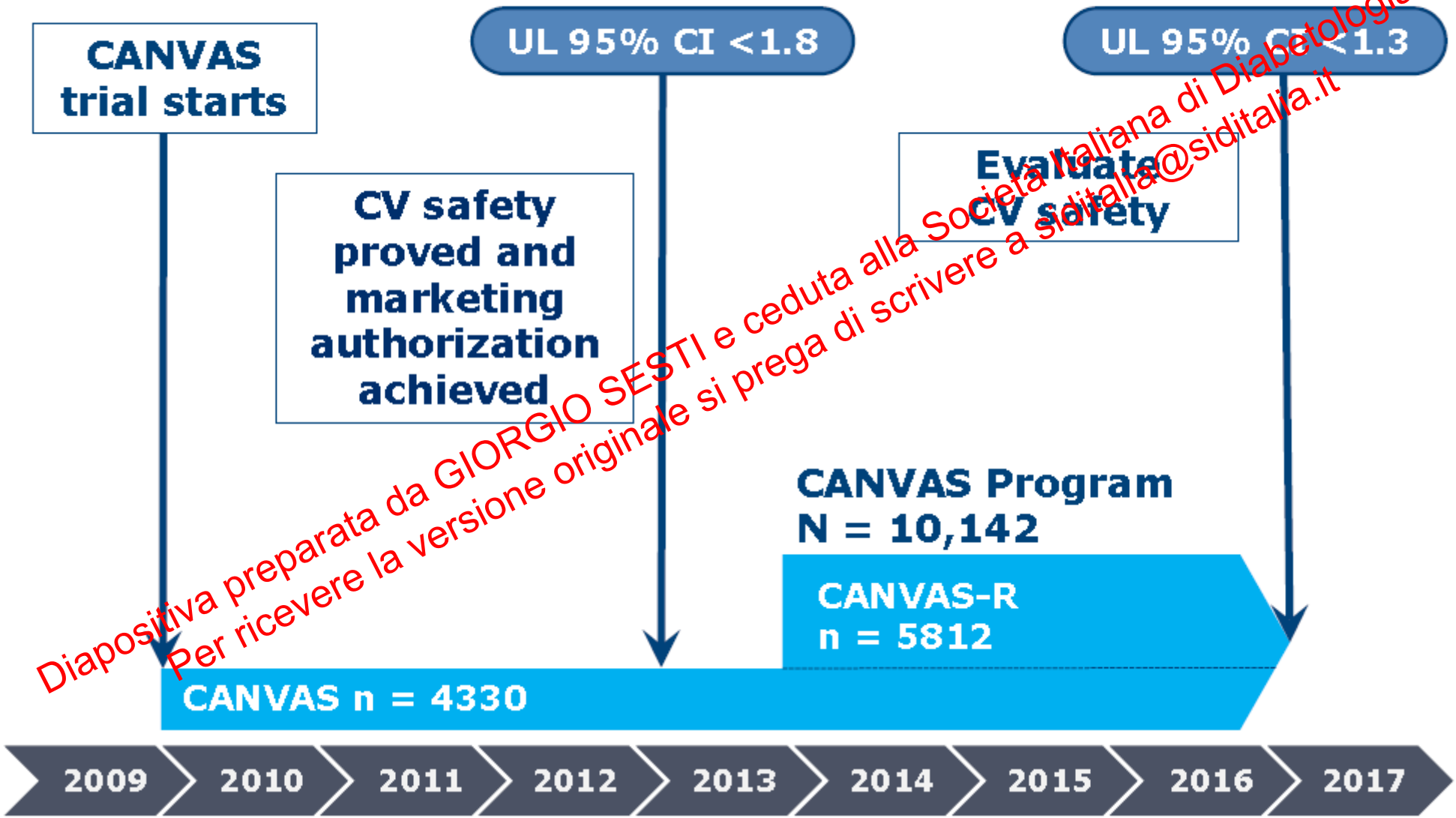
ORIGINAL ARTICLE

Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes

Bruce Neal, M.B., Ch.B., Ph.D., Vlado Perkovic, M.B., B.S., Ph.D., Kenneth W. Mahaffey, M.D., Dick de Zeeuw, M.D., Ph.D., Greg Fulcher, M.D., Ngozi Erondu, M.D., Ph.D., Wayne Shaw, D.S.L., Gordon Law, Ph.D., Mehul Desai, M.D., and David R. Matthews, D.Phil., B.M., B.Ch., for the CANVAS Program Collaborative Group*

Neal B et al. N Engl J Med 377:644-657, 2017

Final Design



Neal B et al. N Engl J Med 377:644-657, 2017

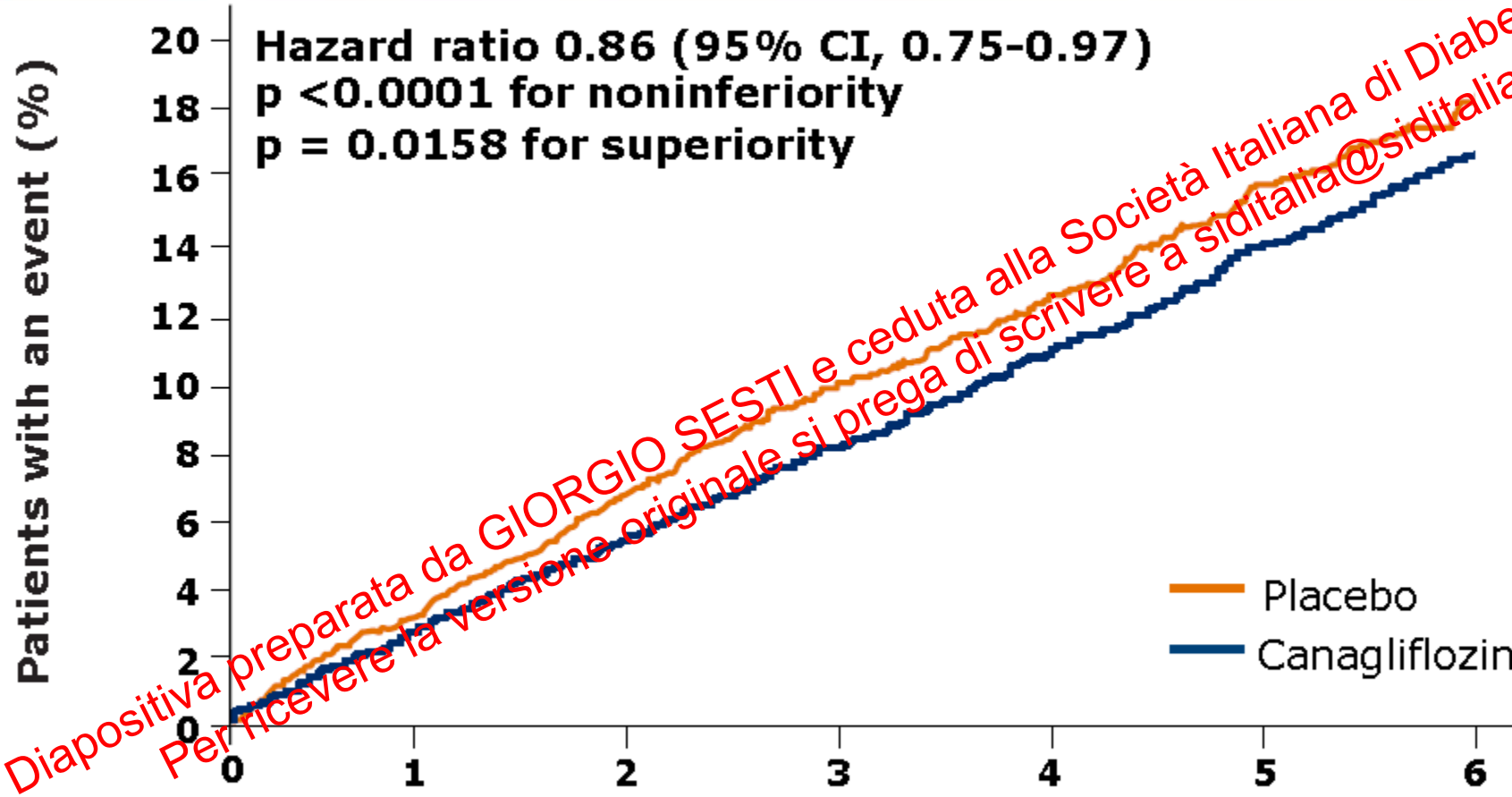
What Was the Population Studied?

- T2DM ~14 years
- High CV risk
- Hypertensive
- Overweight
- Multiple comorbidities
- 2/3 with prior CV disease
- 1/3 primary prevention

Neal B et al. N Engl J Med 2017 in press

Primary MACE Outcome

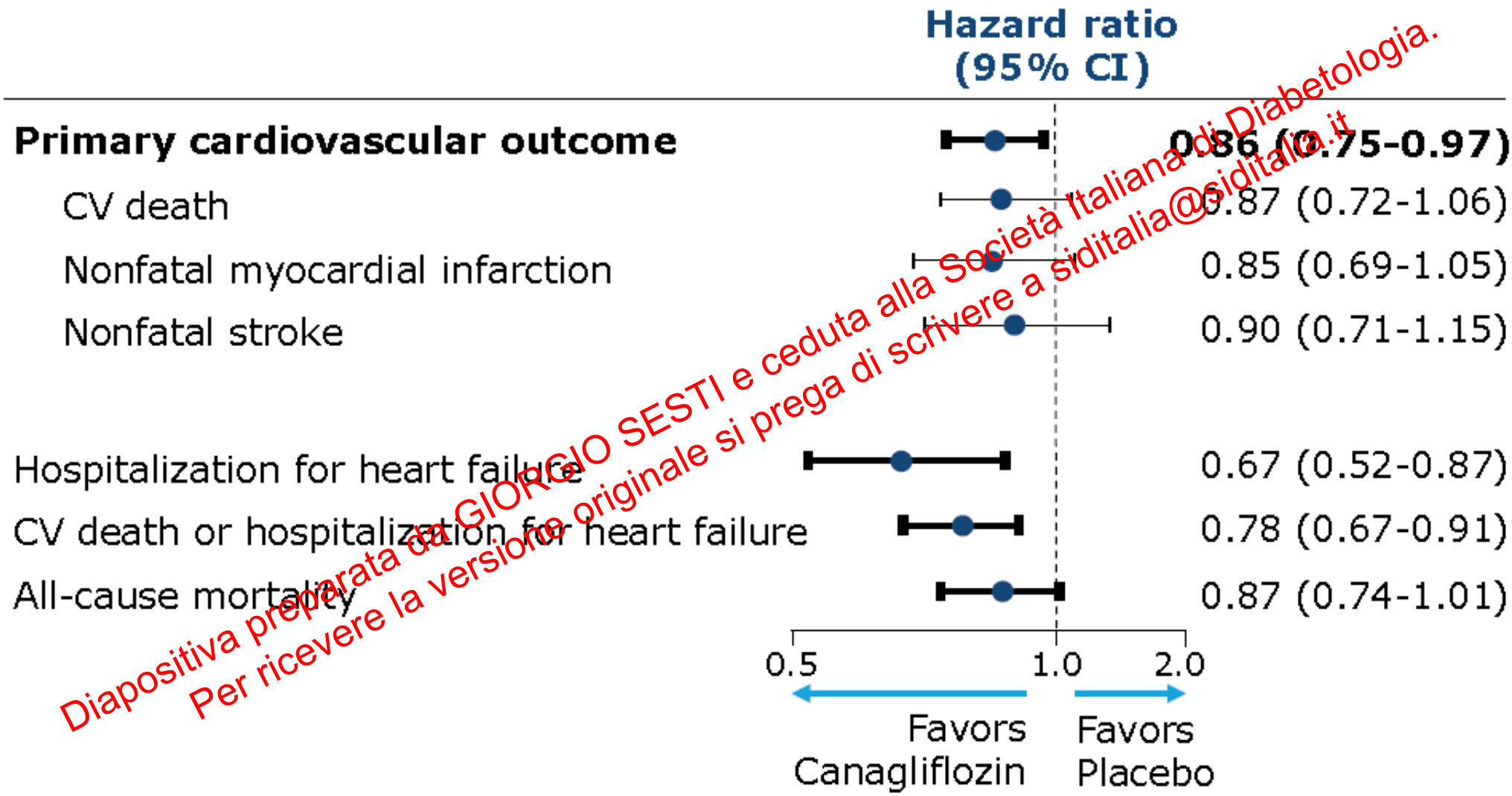
CV Death, Nonfatal Myocardial Infarction or Nonfatal Stroke



No. of patients							
Placebo	4347	4153	2942	1240	1187	1120	789
Canagliflozin	5795	5566	4343	2555	2460	2363	1661

Neal B et al. N Engl J Med 377:644-657, 2017

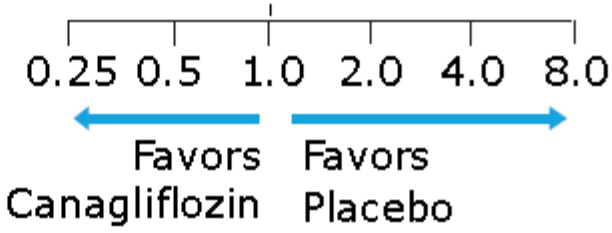
CANVAS - Cardiovascular Outcome



Neal B et al. N Engl J Med 377:644-657, 2017

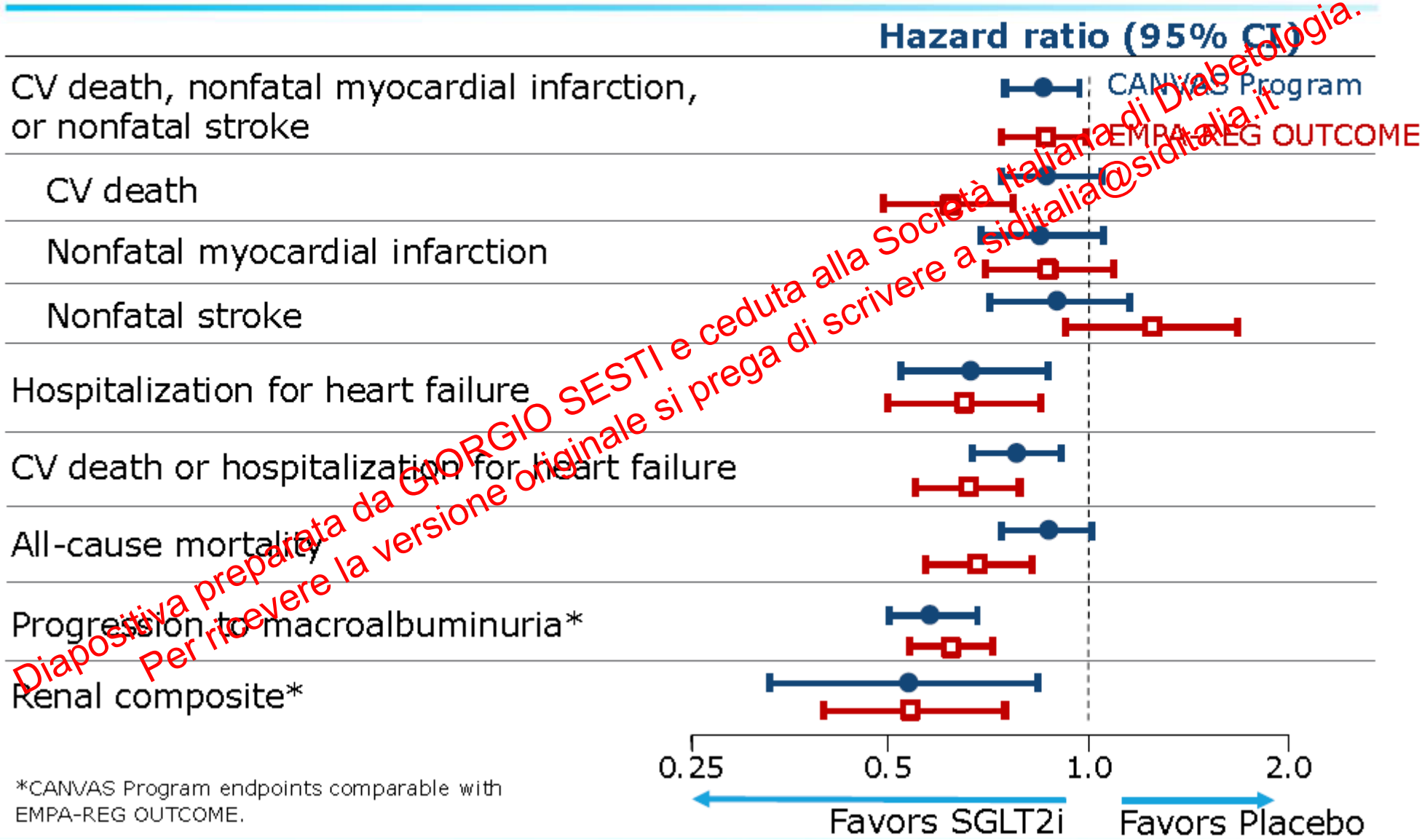
Highest Level of Amputation

	Event rate per 1000 patient-years		Hazard ratio (95% CI)
	Canagliflozin	Placebo	
All amputations (n = 187)	6.3	3.4	1.97 (1.41-2.75)
Minor amputation (71%)	4.5	2.4	1.94 (1.31-2.88)
Toe	3.4	2.2	
Transmetatarsal	1.0	0.3	
Major amputation (29%)	1.8	0.9	2.03 (1.08-3.82)
Ankle	0.04	0.07	
Below-knee	1.2	0.6	
Above-knee	0.6	0.2	



Neal B et al. N Engl J Med 2017 in press

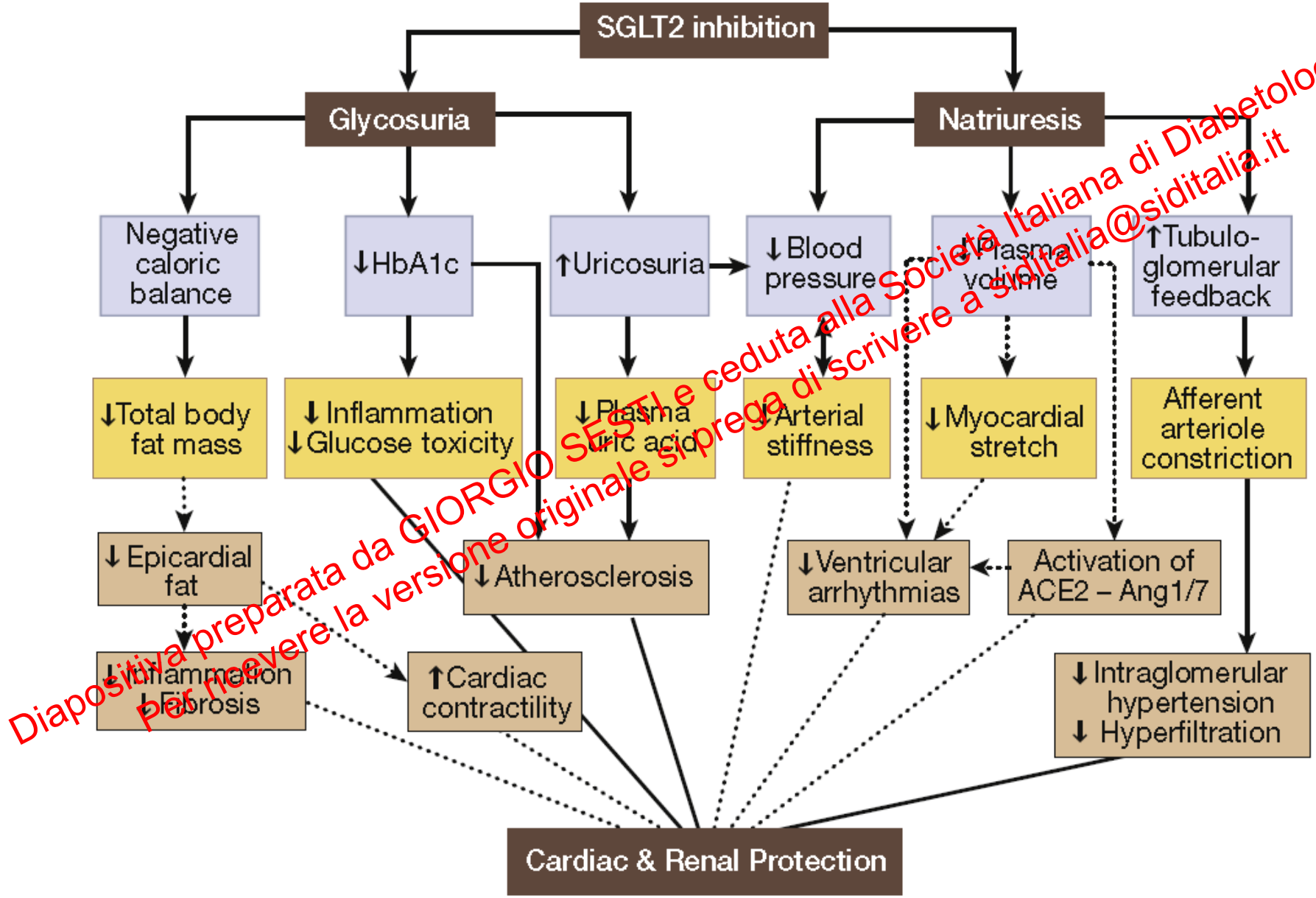
Key Outcomes in the CANVAS Program and EMPA-REG OUTCOME



*CANVAS Program endpoints comparable with EMPA-REG OUTCOME.

Neal B et al. N Engl J Med 2017 in press

Possible mechanisms responsible for cardiovascular and renal protection with SGLT2 inhibition



Rajasekera H et al. Kidney International 89, 524–526, 2016

CONCLUSIONS

- **All safety CVOTs were designed to proof cardiovascular *SAFETY* of new drugs for diabetes.**

- **As such, they all succeeded.**

Glycemic and Extraglycemic Effects of New Therapeutic Classes for T2D

DPP-4 Inhibitors	GLP-1 Receptor Agonists	SGLT-2 Inhibitors
➢ Approximate HbA1c lowering: 0.5% to 0.7%	➢ Approximate HbA1c lowering: 1% to 1.5%	➢ Approximate HbA1c lowering: 0.5% to 1%
➢ Weight neutral	➢ Weight loss	➢ Weight loss
➢ Low risk of hypoglycemia	➢ Low risk of hypoglycemia	➢ Low risk of hypoglycemia
➢ Proved CV safety	➢ Blood pressure lowering	➢ Blood pressure lowering
	➢ Proved CV benefit for liraglutide and semaglutide (exenatide for total mortality)	➢ Proved CV benefit

2017 ADA Standard of Medical Care in Diabetes

"In patients with long-standing suboptimally controlled type 2 diabetes and established atherosclerotic cardiovascular disease, **empagliflozin** or **liraglutide** should be considered as they have been shown to reduce cardiovascular and all-cause mortality when added to standard care."

- Level of evidence B

ADA. *Diabetes Care*. 2017;40(Suppl 1):S64-S74.

fondata nel 1964

SID

Società Italiana
di Diabetologia

POSITION STATEMENT

Farmaci ipoglicemizzanti, malattie cardiovascolari e renali

Enzo Bonora, Antonio Bossi, Daniela Bruttomesso, Angelo De Pascale, Gabriella Gruden, Davide Lauro, Frida Leonetti, Edoardo Mannucci, Roberto Miccoli, Annalisa Natalicchio, Gianluca Perseghin, Francesco Purrello, Giorgio Sesti

Questo documento rappresenta la posizione ufficiale della Società Italiana di Diabetologia (SID) ma non può essere visto come prescrittivo per il singolo paziente e non può sostituire, in ogni caso, il giudizio clinico. E' stato fatto ogni sforzo per raggiungere un consenso tra tutti gli autori.

1. Quali farmaci ipoglicemizzanti introdotti sul mercato negli ultimi anni hanno mostrato benefici su outcome cardiovascolari e in quali categorie di pazienti?

2016

Al momento attuale i farmaci ipoglicemizzanti che posseggono documentati benefici cardiovascolari sono metformina (prevenzione primaria), empagliflozin, liraglutide e pioglitazone (prevenzione secondaria).

2017

Al momento attuale i farmaci ipoglicemizzanti che sulla base di RCTs posseggono documentati benefici cardiovascolari sono metformina (prevenzione primaria e secondaria), empagliflozin, canaglifozin, liraglutide e pioglitazone (prevenzione secondaria).

2. I farmaci che hanno mostrato benefici cardiovascolari potrebbero eventualmente essere usati contemporaneamente e, in caso affermativo, in quali situazioni?

2016

L'associazione di empagliflozin e liraglutide potrebbe essere un'eccellente opzione terapeutica per i pazienti con pregressa malattia cardiovascolare, ma sono necessarie ulteriori evidenze al riguardo.

2017

L'associazione di inibitori di SGLT2, in particolare empaglfozin e canaglifozin, e liraglutide potrebbe essere una opzione terapeutica per i pazienti con pregressa malattia cardiovascolare

3. Nei pazienti con malattia cardiovascolare ben controllati dal punto di vista metabolico la terapia ipoglicemizzante dovrebbe essere modificata alla luce dei risultati dei più recenti trial?

2016

In pazienti con pregressa malattia cardiovascolare la terapia ipoglicemizzante dovrebbe includere empagliflozin oppure liraglutide anche in persone in buon controllo glicemico con la terapia in corso.

2017

In pazienti con pregressa malattia cardiovascolare la terapia ipoglicemizzante dovrebbe includere inibitori di SGLT2, in particolare empaglifozin, canaglifozin e liraglutide anche in presenza di buon controllo glicemico con la terapia in corso.

6. I benefici osservati nei pazienti con malattia cardiovascolare nota (prevenzione secondaria) possono essere estesi ai pazienti senza malattia cardiovascolare (prevenzione primaria)?

2016

Sulla base delle evidenze disponibili sembra prematuro considerare che i benefici raggiunti con questi farmaci nei pazienti con pregressa malattia cardiovascolare possano essere estesi ai pazienti in prevenzione primaria.

2017

Sulla base delle evidenze disponibili sembra prematuro considerare che i benefici raggiunti con questi farmaci nei pazienti con pregressa malattia cardiovascolare possano essere estesi ai pazienti in prevenzione primaria.

7. Alcune indicazioni/raccomandazioni di uso o non uso di empagliflozin e/o liraglutide dovrebbero essere cambiate alla luce dei risultati di questi recenti trial?

2016

Sembrano assai solide le evidenze che dovrebbero condurre ad una specifica indicazione d'uso di empagliflozin e liraglutide nei soggetti con pregressa malattia cardiovascolare. Inoltre, per empagliflozin dovrebbe essere rimossa la raccomandazione a non usare in caso di insufficienza renale moderata, quanto meno nei soggetti con eGFR compreso fra 30 e 60 ml/min x 1.73m^2.

2017

L'EMA ha recepito in RCP i benefici cardiovascolari di empagliflozin e liraglutide nei soggetti con pregressa malattia cardiovascolare. Per empagliflozin e per gli altri inibitori di SGLT-2 è auspicabile che venga rimossa la raccomandazione che non permette il loro impiego in caso di insufficienza renale moderata, quanto meno nei soggetti con eGFR compreso fra 30 e 60 ml/min x 1.73m^2.

THANK YOU !

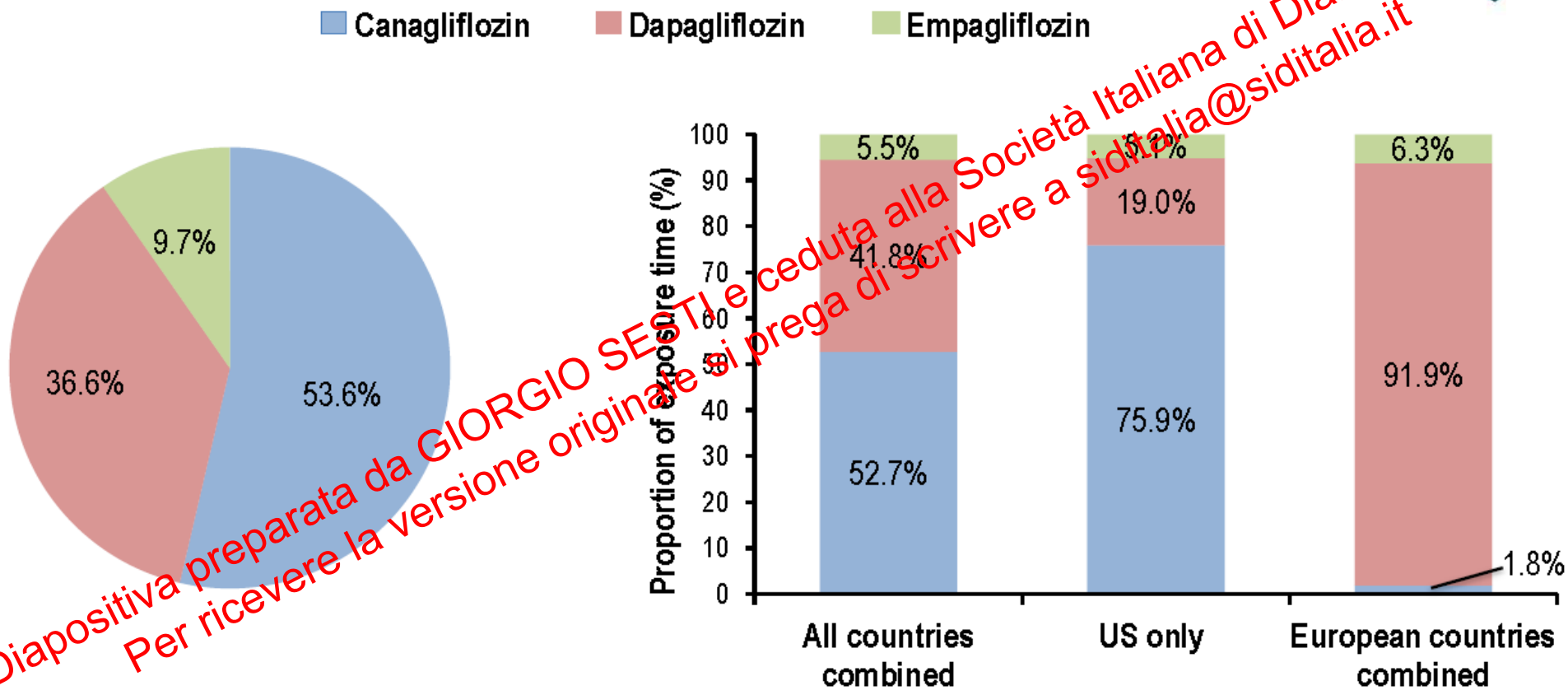
Now it’s time for discussion.

CVDREAL

ACC.17

Contribution of SGLT-2 inhibitor Class as a Proportion of Exposure Time in Propensity-Match Cohorts

Cohort 1: HHF Analysis (N=309,046)

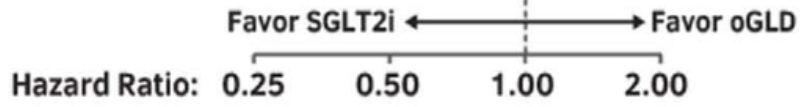


CVDREAL

All-Cause Death Primary Analysis

ACC.17

Database	N	# of events	HR (95% CI)
US	143,264	250	0.38 (0.29, 0.50)
Norway	25,050	364	0.55 (0.44, 0.68)
Denmark	18,468	323	0.46 (0.37, 0.57)
Sweden	18,378	317	0.47 (0.37, 0.60)
UK	10,462	80	0.73 (0.47, 1.15)
Total	215,622	1384	0.49 (0.41, 0.57)



P-value for SGLT2i vs oGLD: <0.001

Heterogeneity p-value: 0.089

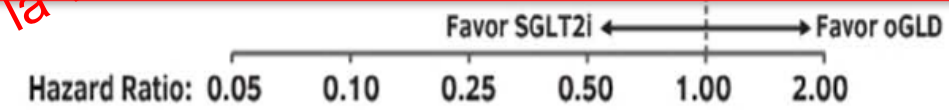
Data are on treatment, unadjusted; oGLD=other glucose-lowering drug; HR=hazard ratio

CVDREAL

ACC.17

HHF Primary Analysis

Database	N	# of events	HR (95% CI)
US	233,798	298	0.55 (0.44, 0.69)
Norway	25,050	278	0.62 (0.49, 0.79)
Denmark	18,468	167	0.77 (0.59, 1.01)
Sweden	18,378	191	0.61 (0.45, 0.82)
UK	10,462	16	0.36 (0.12, 1.13)
Germany	2900	11	0.14 (0.03, 0.68)
Total	309,056	961	0.61 (0.51, 0.73)



P-value for SGLT2i vs oGLD: <0.001

Heterogeneity p-value: 0.169

Data are on treatment, unadjusted; oGLD=other glucose-lowering drug; HR=hazard ratio

5. I benefici cardiovascolari si accompagnano a benefici renali e, se sì, quali?

2016

Empagliflozin e liraglutide oltre a benefici cardiovascolari, hanno determinato, indipendentemente dagli effetti sulla glicemia, importanti benefici renali. In virtù di ciò, quanto meno in soggetti con pregressa malattia cardiovascolare, empagliflozin o liraglutide dovrebbero essere considerate utili nella nefroprotezione. E' possibile che i benefici di empagliflozin si estendano anche agli altri inibitori di SGLT-2, e che quelli di liraglutide siano condivisi anche da altri agonisti del recettore di GLP-1 ma ciò deve essere ancora verificato con studi clinici di outcome renale attualmente in corso.

2017

Empagliflozin, canagliflozin e liraglutide oltre a benefici cardiovascolari, hanno determinato, indipendentemente dagli effetti sulla glicemia, importanti benefici renali. In virtù di ciò, quanto meno in soggetti con pregressa malattia cardiovascolare, empagliflozin, canagliflozin o liraglutide dovrebbero essere considerate utili nella nefroprotezione. E' possibile che i benefici di empagliflozin e canagliflozin si estendano anche agli altri inibitori di SGLT-2, e che quelli di liraglutide siano condivisi anche da altri agonisti del recettore di GLP-1 ma ciò deve essere ancora verificato con studi clinici di outcome renale attualmente in corso.

6. I benefici osservati nei pazienti con malattia cardiovascolare nota (prevenzione secondaria) possono essere estesi ai pazienti senza malattia cardiovascolare (prevenzione primaria)?

2016

Sulla base delle evidenze disponibili sembra prematuro considerare che i benefici raggiunti con questi farmaci nei pazienti con pregressa malattia cardiovascolare possano essere estesi ai pazienti in prevenzione primaria.

2017

Sulla base delle evidenze disponibili sembra prematuro considerare che i benefici raggiunti con questi farmaci nei pazienti con pregressa malattia cardiovascolare possano essere estesi ai pazienti in prevenzione primaria

Trial design and demographics

Variable	EMPA-REG OUTCOME (N = 7,020)	LEADER (N = 9,340)	SUSTAIN-6 (N = 3,297)
Treatment intervention	Empagliflozin 10 and 25 mg vs. placebo	Liraglutide 0.6–1.8 mg vs. placebo	Semaglutide 0.5–1.0 mg vs. placebo
Main inclusion criteria	Preexisting CVD	≥50 years + preexisting CVD, CKD, HF; ≥60 years + CVD risk factors	≥50 years + preexisting CVD; ≥60 years + CVD risk factors
HbA1c inclusion criteria	7.0–10.0	>7.0	>7.0
Mean age (years)	63.1	64.3	64.6
Female	28	36	39
Mean BMI (kg/m2)	30.6	32.5	32.8
Mean baseline HbA1c, %	8.1	8.7	8.7
Diabetes duration >10 years	57	Mean 12.8 years	Mean 13.9 years
Current cigarette smoker	13	12	55 (smoking history)
History of hypertension	94	90	93
History of CVD	99	81	83
Prior MI/stroke or TIA	47/23	31/16	33/15
Statin use	77	72	73
History of cardiac failure	10	18	24
eGFR <60 mL/min/1.73 m2	26	25	28
Completed study	97	96.8	98
Vital status known	99.2	99.7	99.6

Impact on cardiometabolic factors

	EMPA-REG OUTCOME			LEADER			SUSTAIN-6				
								AD		P value	
End point	Baseline	AD	P	Baseline	AD	P	Baseline	0.5 mg	1.0 mg	0.5 mg	1.0 mg
HbA1c, %	8.1	−0.3	NR	8.7	−0.4	<0.001	8.7	−0.66	−1.05	<0.0001	<0.0001
SBP, mmHg	135	−4.0	NR	136	−1.2	<0.001	135.6	−1.3	−2.6	NS	<0.001
DBP, mmHg	77	−1.0	NR	77	+0.6	0.004	77	−0.04	+0.14	NS	NS
Weight, kg	86	−2.0	NR	92	−2.3	<0.001	92.1	−2.9	−4.4	<0.0001	<0.0001
LDL cholesterol, mg/dL	86	+5.3	NR	89.5	−1.6	0.02	82.3	−3.3	−0.8	<0.05	NS
HDL cholesterol, mg/dL	44.5	+2.0	NR	45.5	+0.3	0.07	43.7	0	+1.7	NS	<0.001
Heart rate, bpm	71	0.0	NR	72	+3.0	<0.001	72	+2.0	+2.5	<0.0001	<0.0001

AD, absolute difference relative to baseline (– implying lower and + implying higher values with active treatment); NR, not reported; NS, not significant.

CV outcomes

Variable	EMPA-REG OUTCOME		LEADER		SUSTAIN-6	
	Empagliflozin	Placebo	Liraglutide	Placebo	Semaglutide	Placebo
n	4,687	2,333	4,668	4,672	1,648	1,649
Follow-up (median, years)	3.2	3.1	3.8	3.8	2.1	2.1
Primary outcome (3-point MACE)	HR 0.86 (95% CI 0.74, 0.99) P = 0.04		HR 0.87 (95% CI 0.78, 0.97) P = 0.01		HR 0.74 (95% CI 0.58, 0.95) P = 0.02	
CV death	HR 0.62 (95% CI 0.49, 0.77)		HR 0.78 (95% CI 0.66, 0.93)		HR 0.98 (95% CI 0.65, 1.48)	
Nonfatal MI*	HR 0.87 (95% CI 0.70, 1.09)		HR 0.86 (95% CI 0.73, 1.00)		HR 0.74 (95% CI 0.51, 1.08)	
*Silent MIs were screened and adjudicated in LEADER and SUSTAIN-6 but not in EMPA-REG OUTCOME						
Nonfatal stroke	HR 1.18 (95% CI 0.89, 1.56)		HR 0.86 (95% CI 0.71, 1.06)		HR 0.61 (95% CI 0.38, 0.99)	

CV outcomes

Variable	EMPA-REG OUTCOME		LEADER		SUSTAIN-6	
	Empagliflozin	Placebo	Liraglutide	Placebo	Semaglutide	Placebo
n	4,687	2,333	4,668	4,672	1,648	1,649
Key secondary outcome (4-point or expanded MACE)	HR 0.89 (95% CI 0.78, 1.01)		HR 0.88 (95% CI 0.81, 0.96)		HR 0.74 (95% CI 0.62, 0.89)	
Hospitalization for heart failure	HR 0.65 (95% CI 0.50, 0.85)		HR 0.87 (95% CI 0.73, 1.05)		HR 1.11 (95% CI 0.77, 1.61)	
All-cause death	HR 0.68 (95% CI 0.57, 0.82)		HR 0.85 (95% CI 0.74, 0.97)		HR 1.05 (95% CI 0.74, 1.50)	
Hospitalization for unstable angina	HR 0.99 (95% CI 0.74, 1.34)		HR 0.98 (95% CI 0.76, 1.26)		HR 0.82 (95% CI 0.47, 1.44)	

Evaluating strength of evidence of CV outcomes using NNT

End point	Trial	Effect size		
		HR	NNT	P value (z score)
3-point MACE	EMPA-REG OUTCOME	0.86	63	0.038 (2.02)
	LEADER	0.87	66	0.01 (2.55)
All-cause deaths	EMPA-REG OUTCOME	0.68	39	0.0001 (3.94)
	LEADER	0.85	98	0.017 (2.39)
CV deaths	EMPA-REG OUTCOME	0.62	45	0.0001 (3.87)
	LEADER	0.78	104	0.007 (2.71)
Hospitalization for heart failure	EMPA-REG OUTCOME	0.65	71	0.0017 (2.93)
	LEADER	0.87	NE	0.15 (1.42)

Microvascular outcomes

End point	EMPA-REG OUTCOME		LEADER		SUSTAIN-6	
	Empagliflozin	Placebo	Liraglutide	Placebo	Semaglutide	Placebo
Composite microvascular outcome (renal plus retinal events)	HR 0.62 (95% CI 0.54, 0.70)		HR 0.84 (95% CI 0.73, 0.97)		NA	
	P < 0.001		P = 0.02			
New or worsening nephropathy (composite renal outcome)	HR 0.61 (95% CI 0.53, 0.70)		HR 0.78 (95% CI 0.67, 0.92)		HR 0.64 (95% CI 0.46, 0.88)	
	P < 0.0001		P = 0.003		P = 0.005	
New-onset persistent macroalbuminuria	HR 0.62 (95% CI 0.54, 0.72)		HR 0.74 (95% CI 0.60, 0.91)		HR 0.54 (95% CI 0.37, 0.77)	
	P < 0.0001				P = 0.001	
Doubling of serum creatinine	HR 0.56 (95% CI 0.39, 0.79)		HR 0.88 (95% CI 0.66, 1.18)		HR 1.28 (95% CI 0.64, 2.58)	
	P = 0.0009				P = 0.48	
Renal replacement therapy	HR 0.45 (95% CI 0.21, 0.97)		HR 0.87 (95% CI 0.61, 1.24)		HR 0.91 (95% CI 0.40, 2.07)	
	P = 0.041				P = 0.83	
Renal death	NA		HR 1.59 (95% CI 0.52, 4.87)		NA	
Retinopathy (composite outcome)	NR		HR 1.15 (95% CI 0.87, 1.52)		HR 1.76 (95% CI 1.11, 2.78)	
			P = 0.33		P = 0.02	

CV outcomes

Variable	EMPA-REG OUTCOME		LEADER		SUSTAIN-6	
	Empagliflozin	Placebo	Liraglutide	Placebo	Semaglutide	Placebo
n	4,687	2,333	4,668	4,672	1,648	1,649
Follow-up (median, years)	3.2	3.1	3.8	3.8	2.1	2.1
Key secondary outcome (4-point or expanded MACE)	599 (12.8%) 46.4/1,000 PY	333 (14.3%)52.5/1,000 PY	948 (20.3%)53/1,000 PY	1,062 (22.7%)60/1,000 PY	108 (12.1%) 61.7/1,000 PY	264 (16%)83.6/1,000 PY
	HR 0.89 (95% CI 0.78, 1.01)		HR 0.88 (95% CI 0.81, 0.96)		HR 0.74 (95% CI 0.62, 0.89)	
Hospitalization for heart failure	95 (4.1%) 14.5/1,000 PY	126 (2.7%)9.4/1,000 PY	218 (4.7%)12/1,000 PY	248 (5.3%)14/1,000 PY	59 (3.6%) 17.6/1,000 PY	54 (3.3%)16.1/1,000 PY
	HR 0.65 (95% CI 0.50, 0.85)		HR 0.87 (95% CI 0.73, 1.05)		HR 1.11 (95% CI 0.77, 1.61)	
All-cause death	269 (5.7%)19.4/1,000 PY	194 (8.3%)28.6/1,000 PY	381 (8.2%)21/1,000 PY	447 (9.6%)25/1,000 PY	62 (3.8%)18.2/1,000 PY	60 (3.6%)17.6/1,000 PY
	HR 0.68 (95% CI 0.57, 0.82)		HR 0.85 (95% CI 0.74, 0.97)		HR 1.05 (95% CI 0.74, 1.50)	
Hospitalization for unstable angina	133 (2.8%)10/1,000 PY	66 (2.8%)10/1,000 PY	122 (2.6%)7/1,000 PY	124 (2.7%)7/1,000 PY	22 (1.3%)6.5/1,000 PY	27 (1.6%)8/1,000 PY
	HR 0.99 (95% CI 0.74, 1.34)		HR 0.98 (95% CI 0.76, 1.26)		HR 0.82 (95% CI 0.47, 1.44)	

CV outcomes

Variable	EMPA-REG OUTCOME		LEADER		SUSTAIN-6	
	Empagliflozin	Placebo	Liraglutide	Placebo	Semaglutide	Placebo
n	4,687	2,333	4,668	4,672	1,648	1,649
Follow-up (median, years)	3.2	3.1	3.8	3.8	2.1	2.1
Primary outcome (3-point MACE)	490 (10.5%) 37.4/1,000 PY	282 (12.1%) 43.9/1,000 PY	608 (13.0%) 34/1,000 PY	694 (14.9%) 39/1,000 PY	108 (6.6%) 32.4/1,000 PY	146 (8.9%) 44.4/1,000 PY
	HR 0.86 (95% CI 0.74, 0.99)		HR 0.87 (95% CI 0.78, 0.97)		HR 0.74 (95% CI 0.58, 0.95)	
	P = 0.04		P = 0.01		P = 0.02	
CV death	172 (3.7%) 12.4/1,000 PY	137 (5.9%) 20.2/1,000 PY	219 (4.7%) 12/1,000 PY	278 (6.0%) 16/1,000 PY	44 (2.7%) 12.9/1,000 PY	46 (2.8%) 13.5/1,000 PY
	HR 0.62 (95% CI 0.49, 0.77)		HR 0.78 (95% CI 0.66, 0.93)		HR 0.98 (95% CI 0.65, 1.48)	
Nonfatal MI*	213 (4.5%) 16/1,000 PY	121 (5.2%) 18.5/1,000 PY	281 (6.0%) 16/1,000 PY	317 (6.8%) 18/1,000 PY	47 (2.9%) 14.0/1,000 PY	64 (3.9%) 19.2/1,000 PY
	HR 0.87 (95% CI 0.70, 1.09)		HR 0.86 (95% CI 0.73, 1.00)		HR 0.74 (95% CI 0.51, 1.08)	
Nonfatal stroke	150 (3.2%) 11.2/1,000 PY	60 (2.6%) 9.1/1,000 PY	159 (3.4%) 9/1,000 PY	177 (3.8%) 10/1,000 PY	27 (1.6%) 8/1,000 PY	44 (2.7%) 13.1/1,000 PY
	HR 1.18 (95% CI 0.89, 1.56)		HR 0.86 (95% CI 0.71, 1.06)		HR 0.61 (95% CI 0.38, 0.99)	