


# Possiamo puntare ancor di più sulla protezione cardiovascolare?

*Simona Frontoni*

University of Rome "Tor Vergata", Department of Systems Medicine
Division of Endocrinology, Diabetes and Metabolic Diseases
S. Giovanni Calibita Fatebenefratelli Hospital, Rome, Italy

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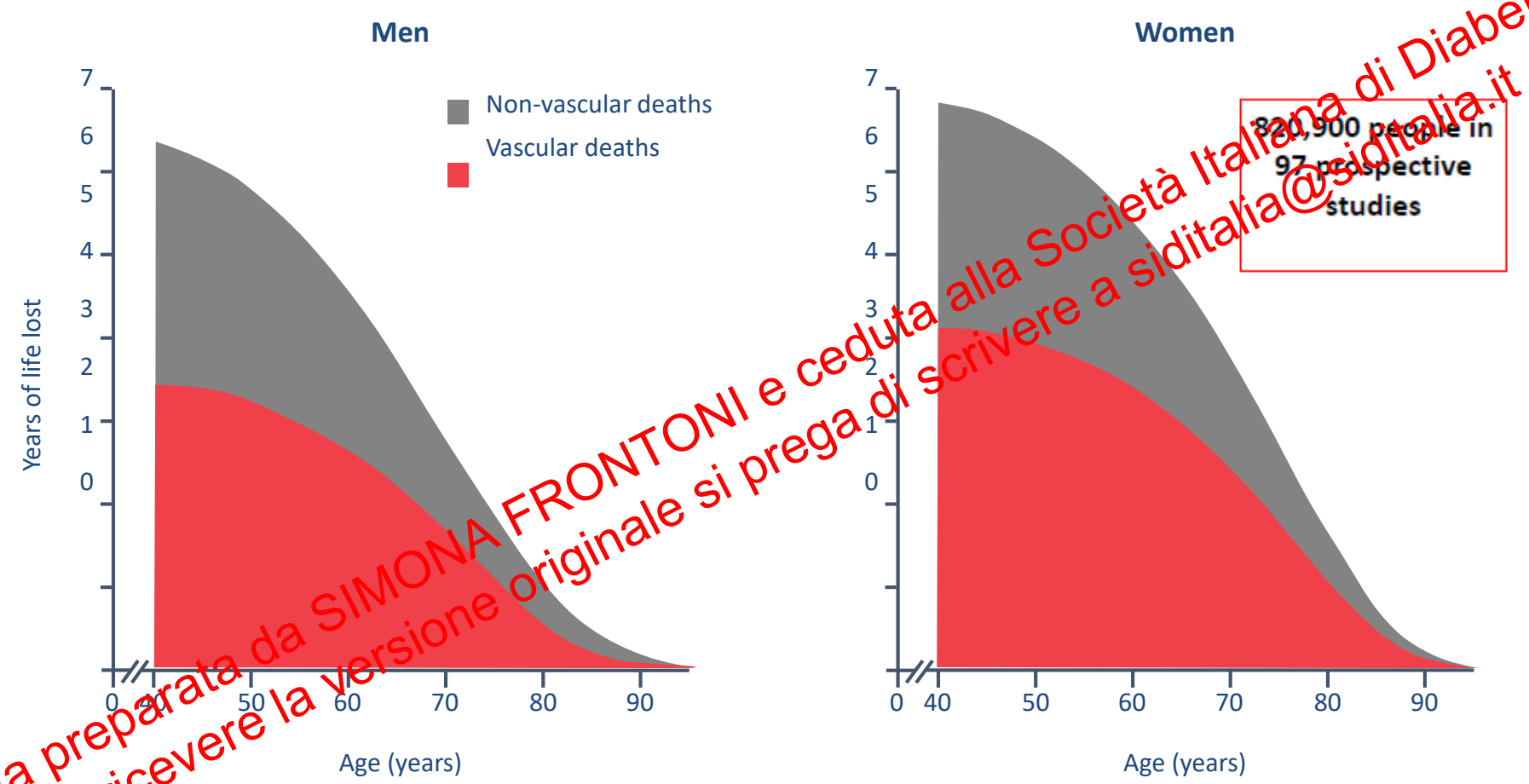
UNIVERSITÀ DEGLI STUDI DI ROMA

# Diabetes is associated with significant loss of life years

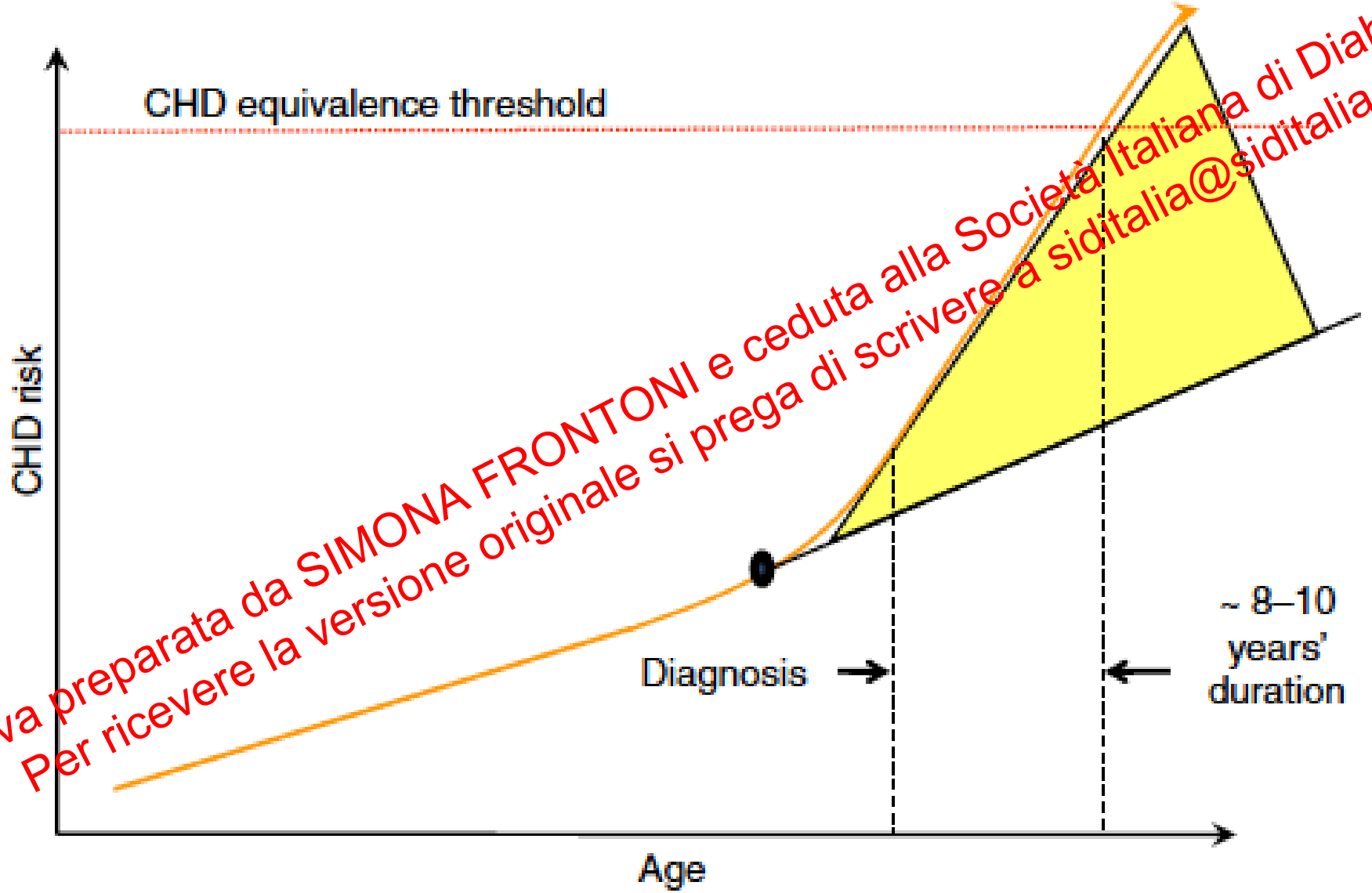





*In media una persona di 50 anni con diabete in assenza di storia di malattia cardio-vascolare ha una aspettativa di vita inferiore di 6 anni rispetto alle persone senza diabete*

*Seshasai et al. N Engl J Med 2011;364:829-41*

# A conceptual look at vascular risk and its determinants before and during the course of type 2 diabetes

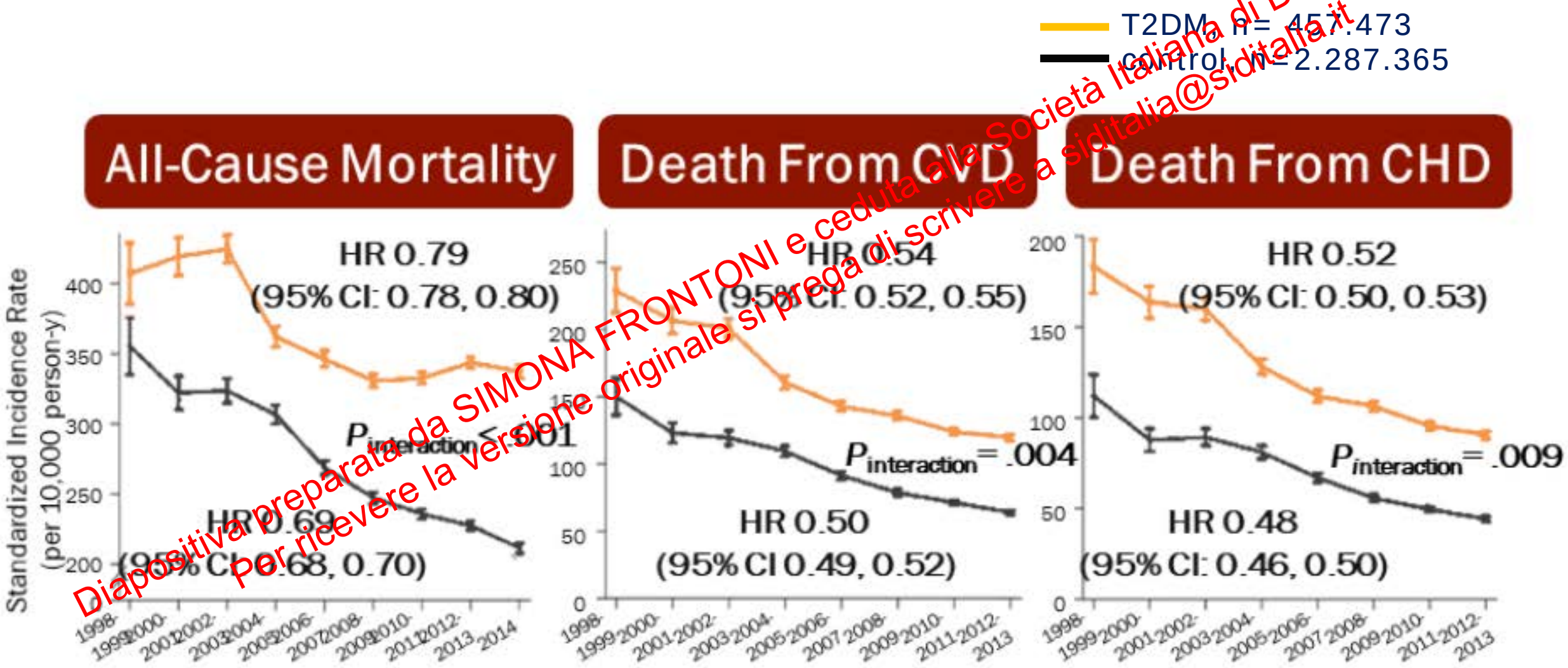





*Sattar N, Diabetologia 2013*

# SWEDISH NATIONAL DIABETES REGISTER

*The gradient of increased risk persists…*






*Rawshani A, NEJM 2017*

# I DOMANDA

Quali sono i principali fattori di rischio per mortalità per tutte le cause, nei pazienti con diabete di tipo 2?

a) Fumo, attività fisica, emoglobina glicata

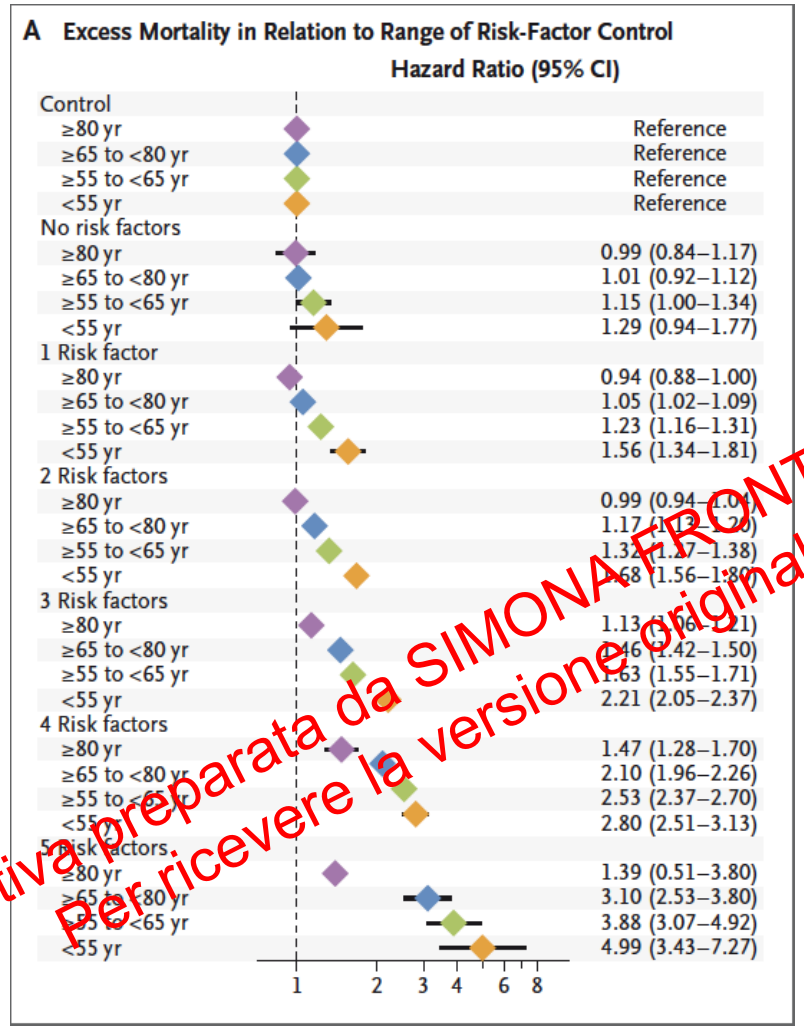
b) Colesterolo LDL, pressione diastolica, albuminuria

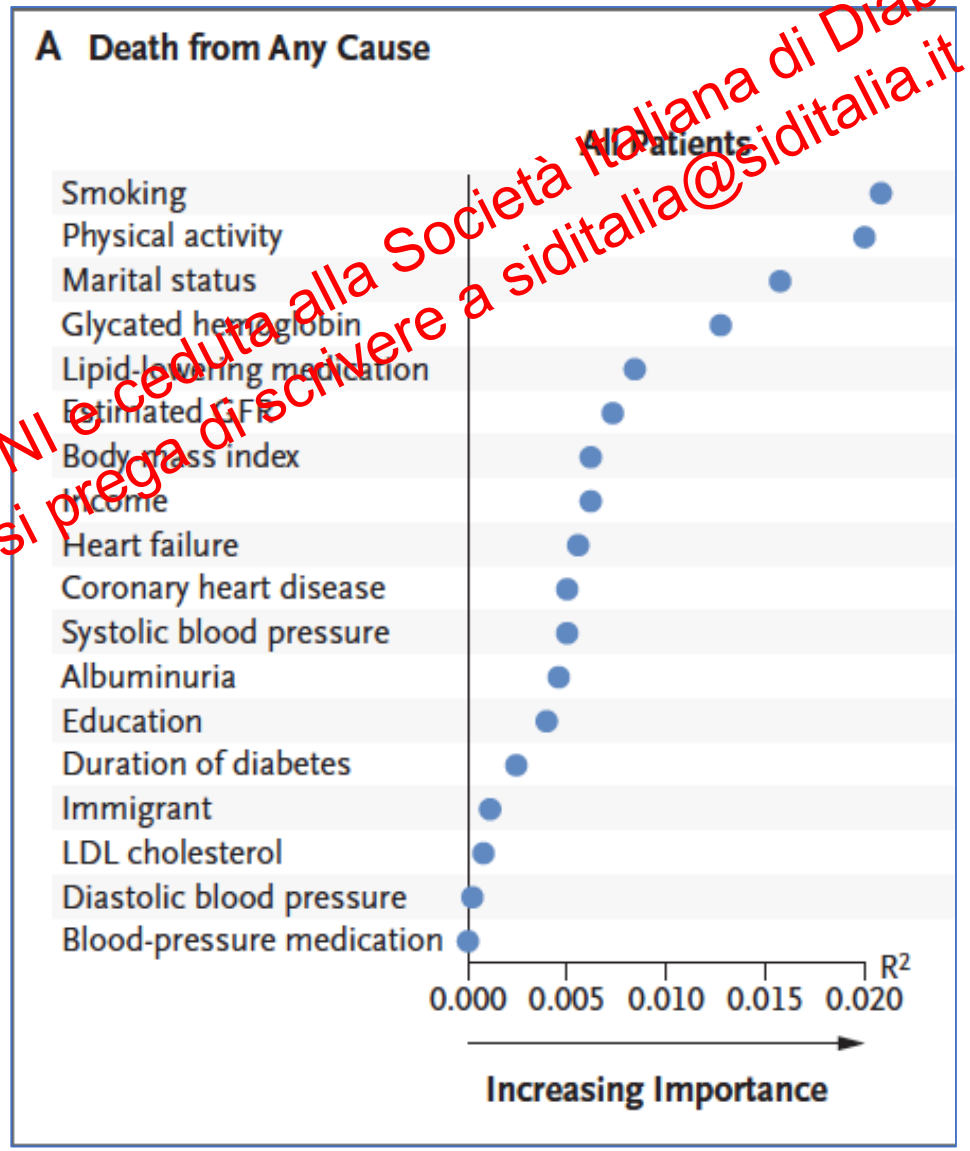
c) Pressione sistolica, durata di malattia, livello di istruzione

d) Pressione sistolica, pressione diastolica, albuminuria

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

HbA1c, LDL-C, UALB, smoking, BP



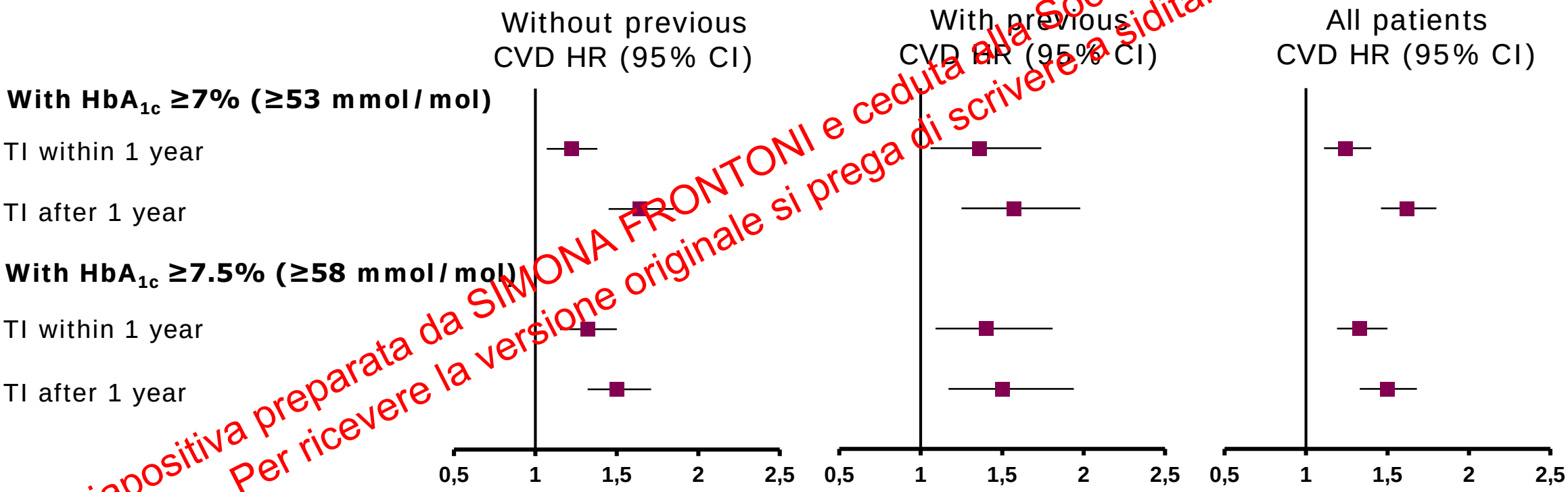






*Rawshani A, NEJM 2018*

# Treatment Intensification (TI) May Decrease the Risks of CV Events in Patients with T2DM

Risks of any CV event associated with delays in treatment intensification in interaction with poor glycaemic control during 1 year post-diagnosis

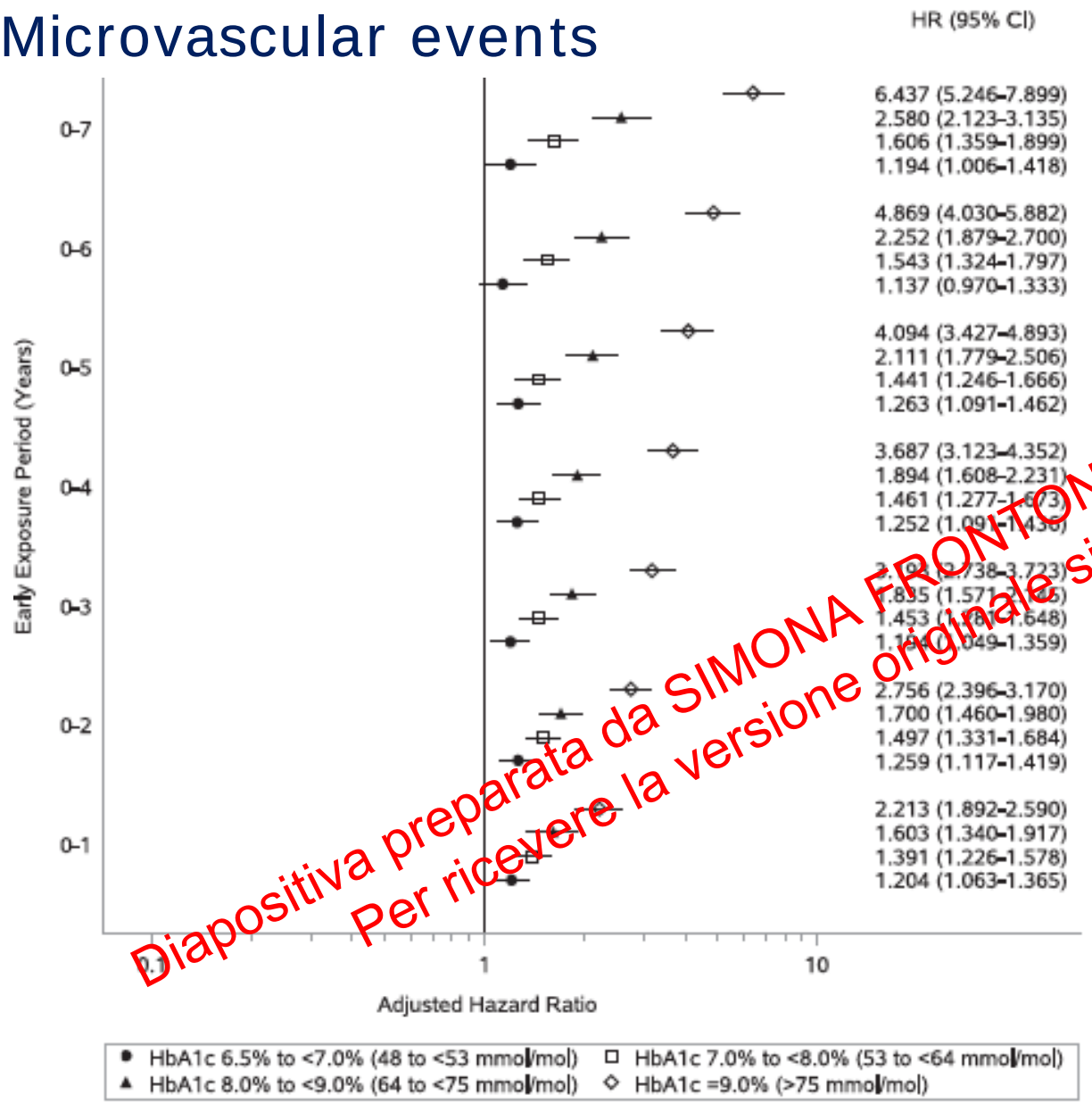




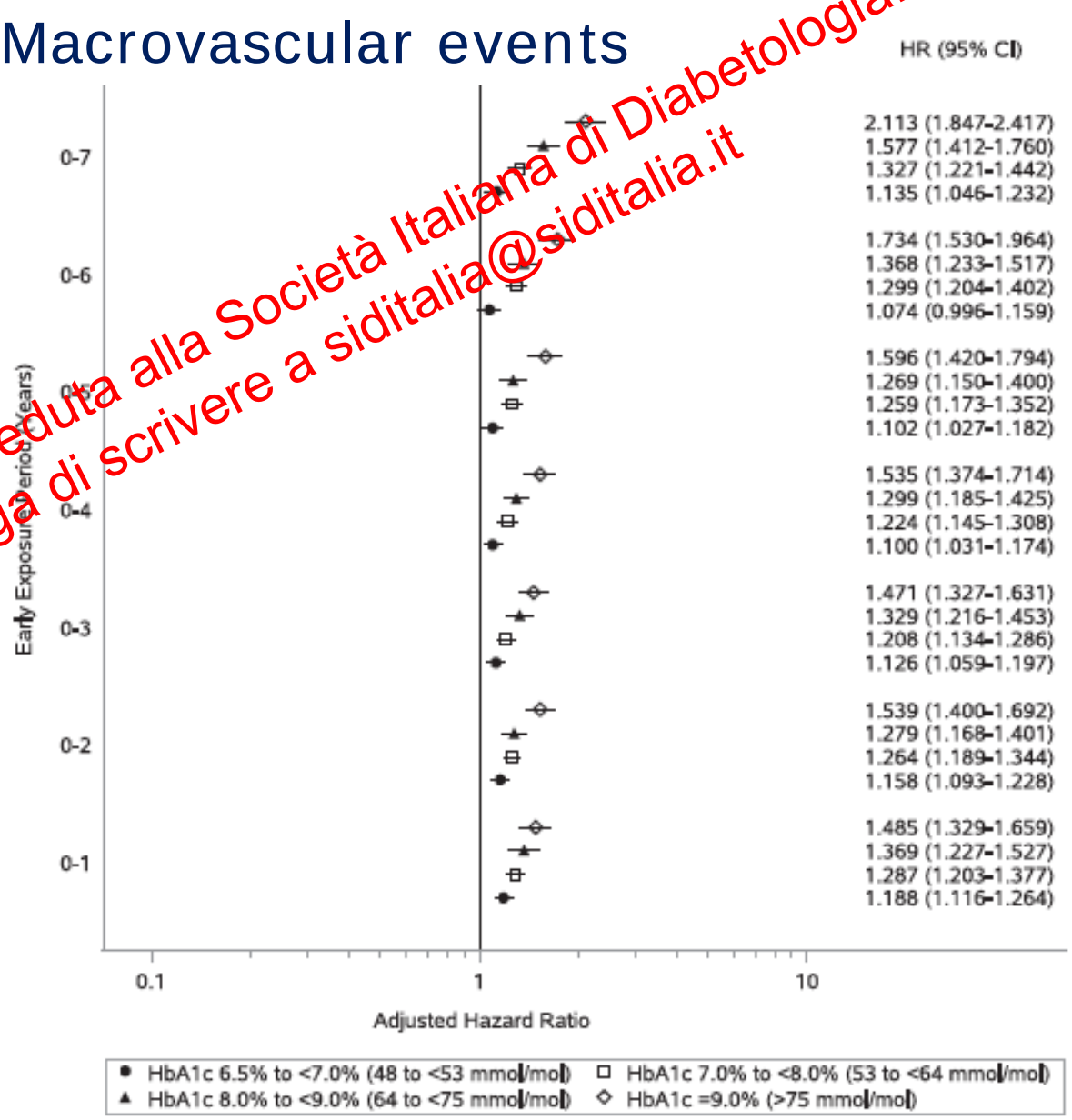

*Paul SK, et al. Cardiovasc Diabetol 2015;14:100*

# The Legacy Effect in Type 2 Diabetes
## Impact of Early Glycemic Control on Future Complications

### Microvascular events




### Macrovascular events



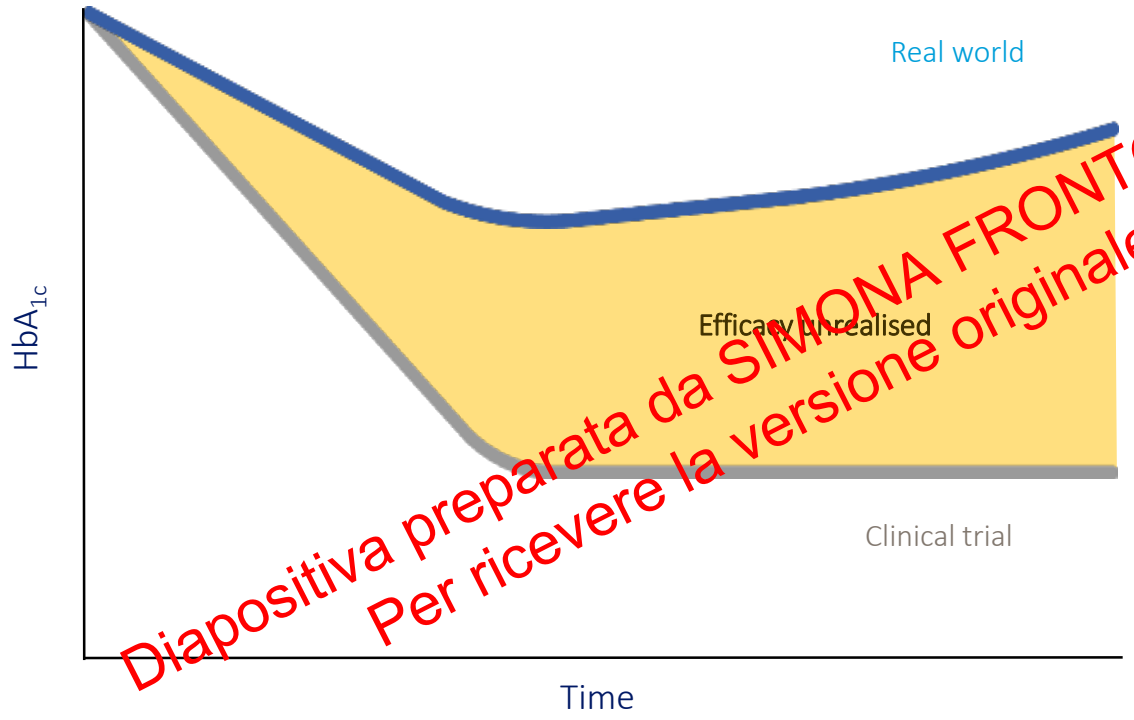



*Laiteerapong et al. Diabetes Care 2019*

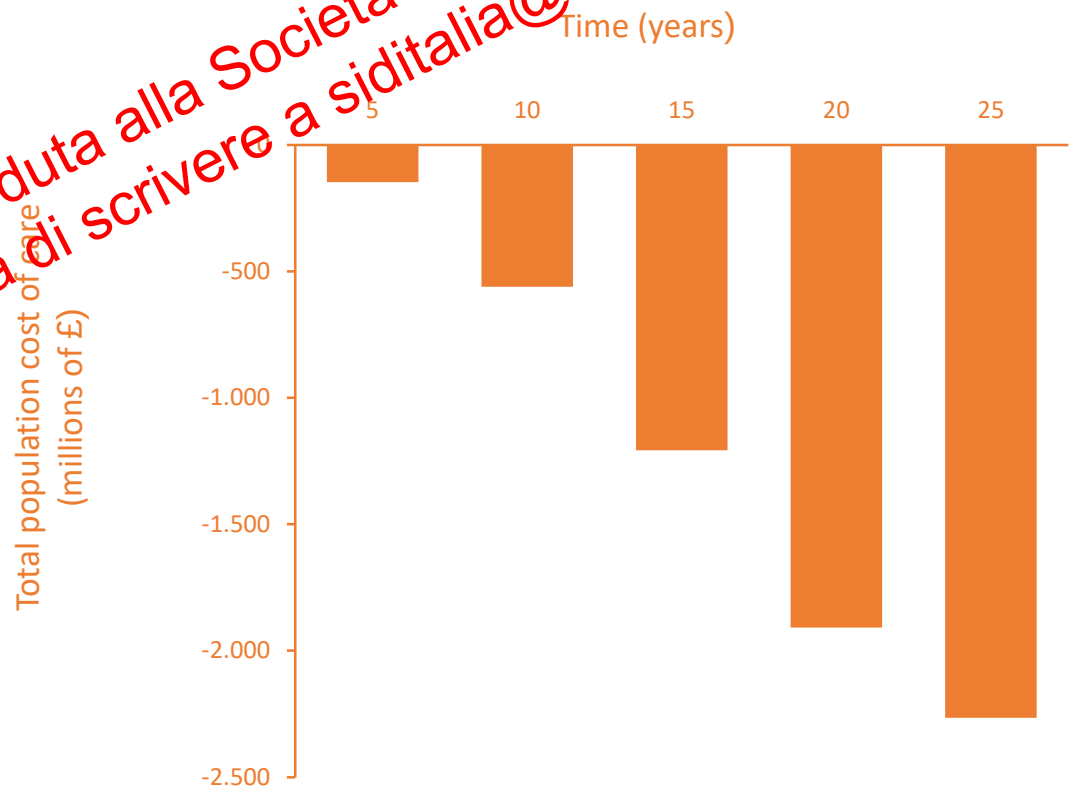
# Avoiding complications reduces cost over time

There may be an efficacy gap between clinical trial results and real-world outcomes in T2D management

Conceptual schematic




Estimated cost reductions over time for the total UK adult population with T2D from **avoided complications** for management of $HbA_{1c}$ at <7.5%



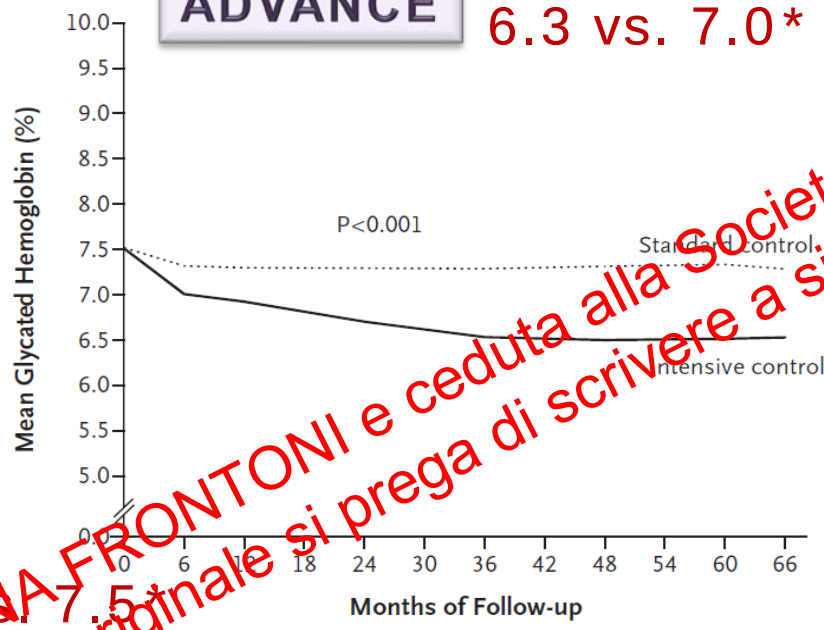



*Baxter M, et al. Diabet Med. 2016;33:1575-1581. Edelman SV, Polonsky WH. Diabetes Care. 2017;40:1425-1432.*

# Treatment Intensification Trials

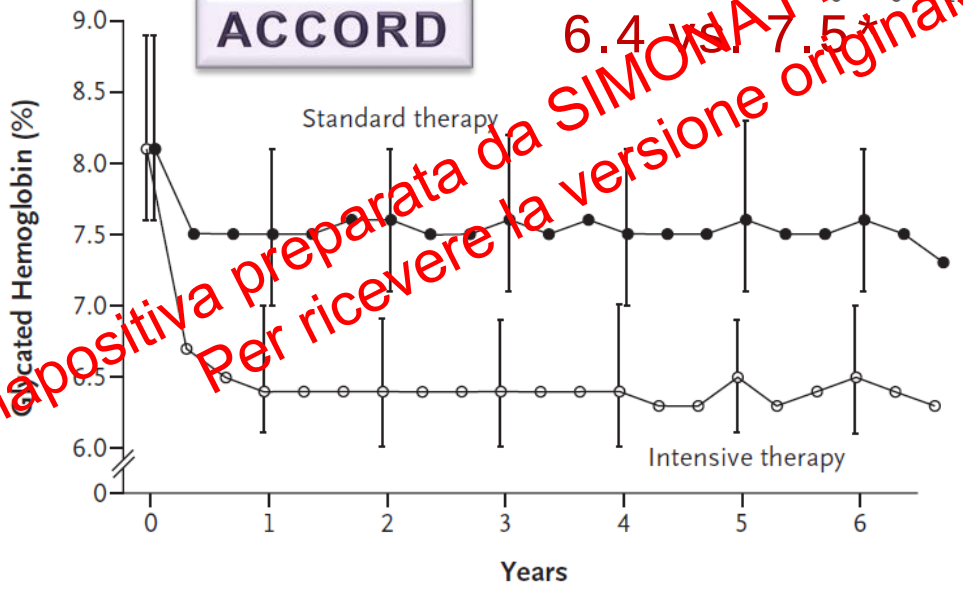
## ADVANCE

6.3 vs. 7.0*



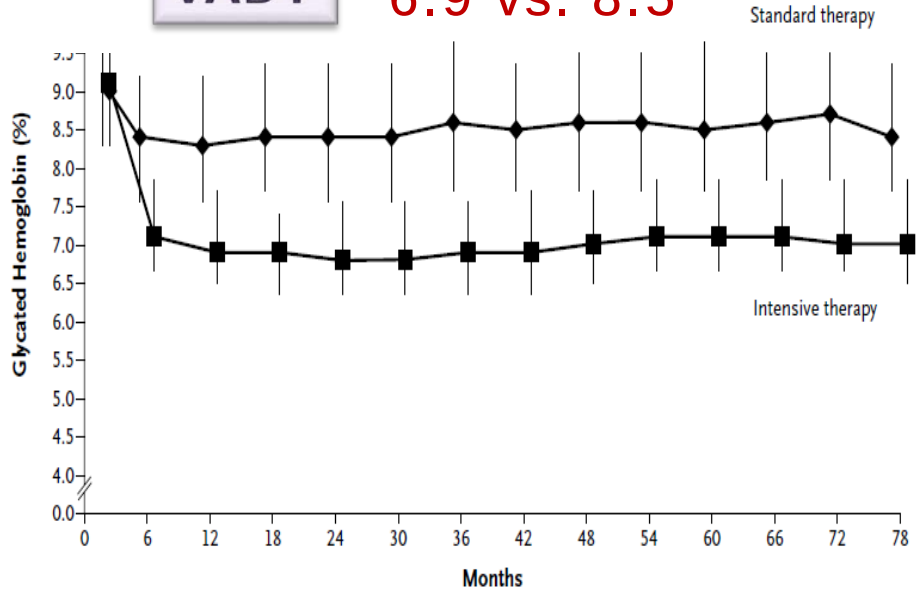

## ACCORD

6.4 vs. 7.5*




## VADT

6.9 vs. 8.5*



# CV Outcome Studies with Intensive Glucose Lowering

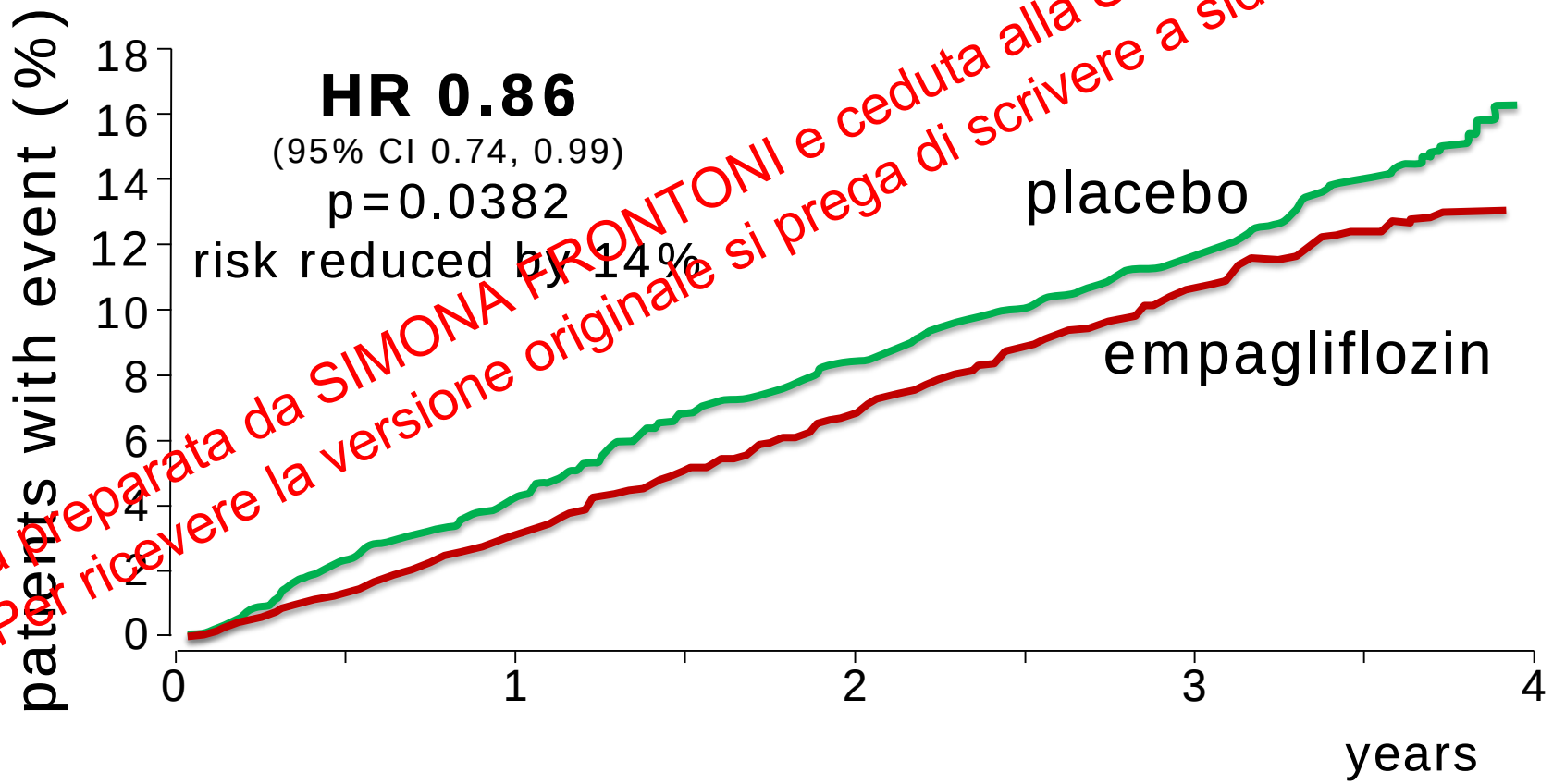
| Study | N | Follow-up (yr) | $HbA_{1c}$ (%) difference between arms | Primary endpoint | Primary endpoint HR (95% CI) | All-cause mortality HR (95% CI) | Weight gain (kg) | Major hypoglycemia (%) |
|---|---|---|---|---|---|---|---|---|
| ACCORD | 10,251 | 3.5 | 1.1 | MACE | 0.90 (0.78-1.04) | 1.22 (1.01-1.46) | 3.5 vs. 0.4 | 16.2 vs. 5.1 |
| ADVANCE | 11,140 | 5.0 | 0.8 | MACE | 0.94 (0.84-1.06) | 0.93 (0.83-1.06) | 0.0 vs. -1.0 | 2.7 vs. 1.5 |
| VADT | 1,791 | 5.6 | 1.5 | MACE + HF, vascular surgery, new, ischemic amputation | 0.88 (0.74-1.05) | 1.07 (0.81-1.42) | 7.8 vs. 3.4 | 21.2 vs. 9.9 |



*Adapted from Giorgino F et al., Diabetes Care 39 Suppl 2:S187-95, 2016*

# EMPAREG: MACE (primary outcome)

## CV Death, Nonfatal Myocardial Infarction or Nonfatal Stroke

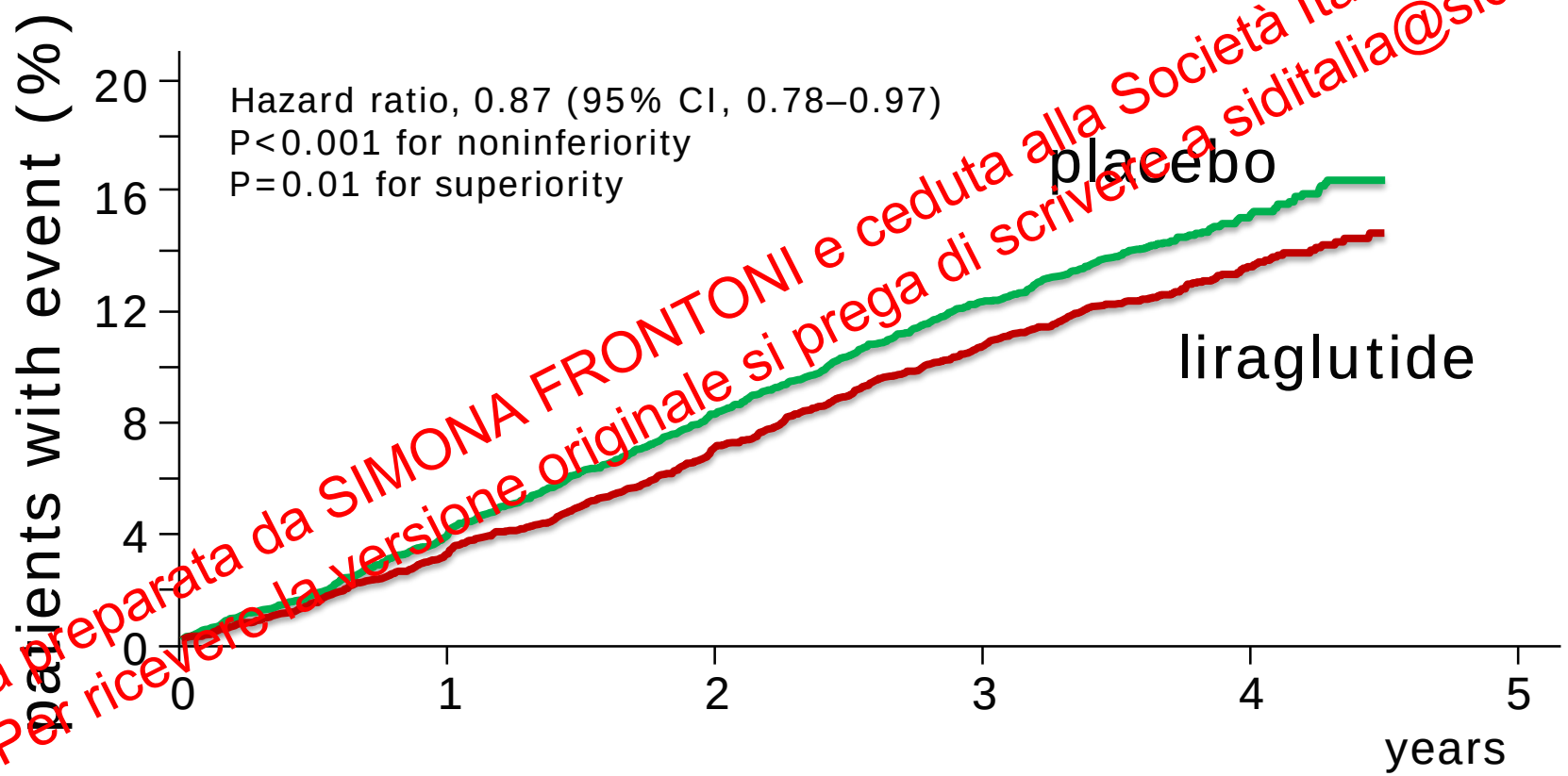





*Zinman B et al.: NEJM 373:2117, 2015*

# LEADER: MACE (primary outcome)

## CV Death, Nonfatal Myocardial Infarction or Nonfatal Stroke

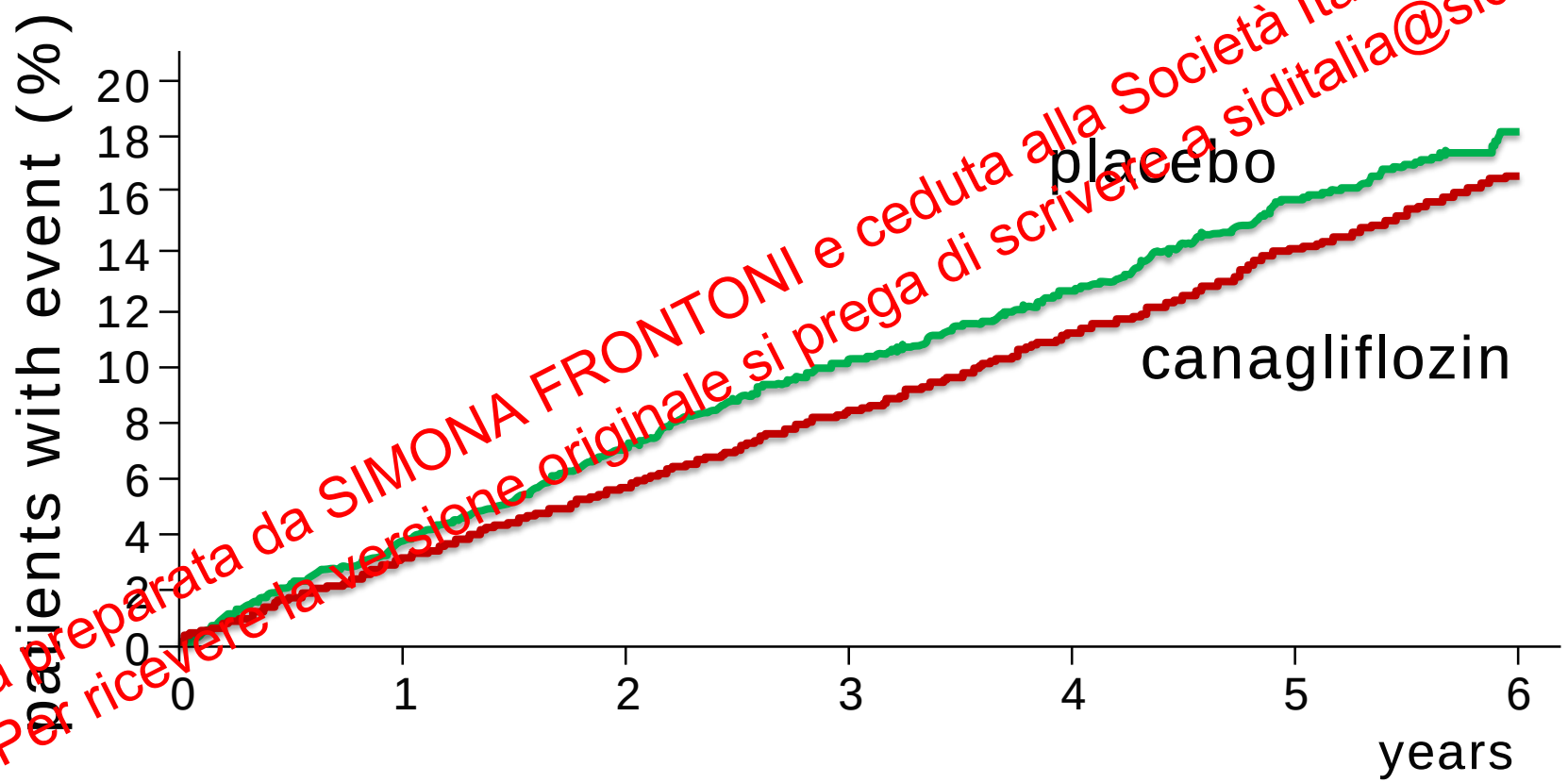





*Marso SP et al.: NEJM 375:311, 2016*

# CANVAS: MACE (primary outcome)

## CV Death, Nonfatal Myocardial Infarction or Nonfatal Stroke

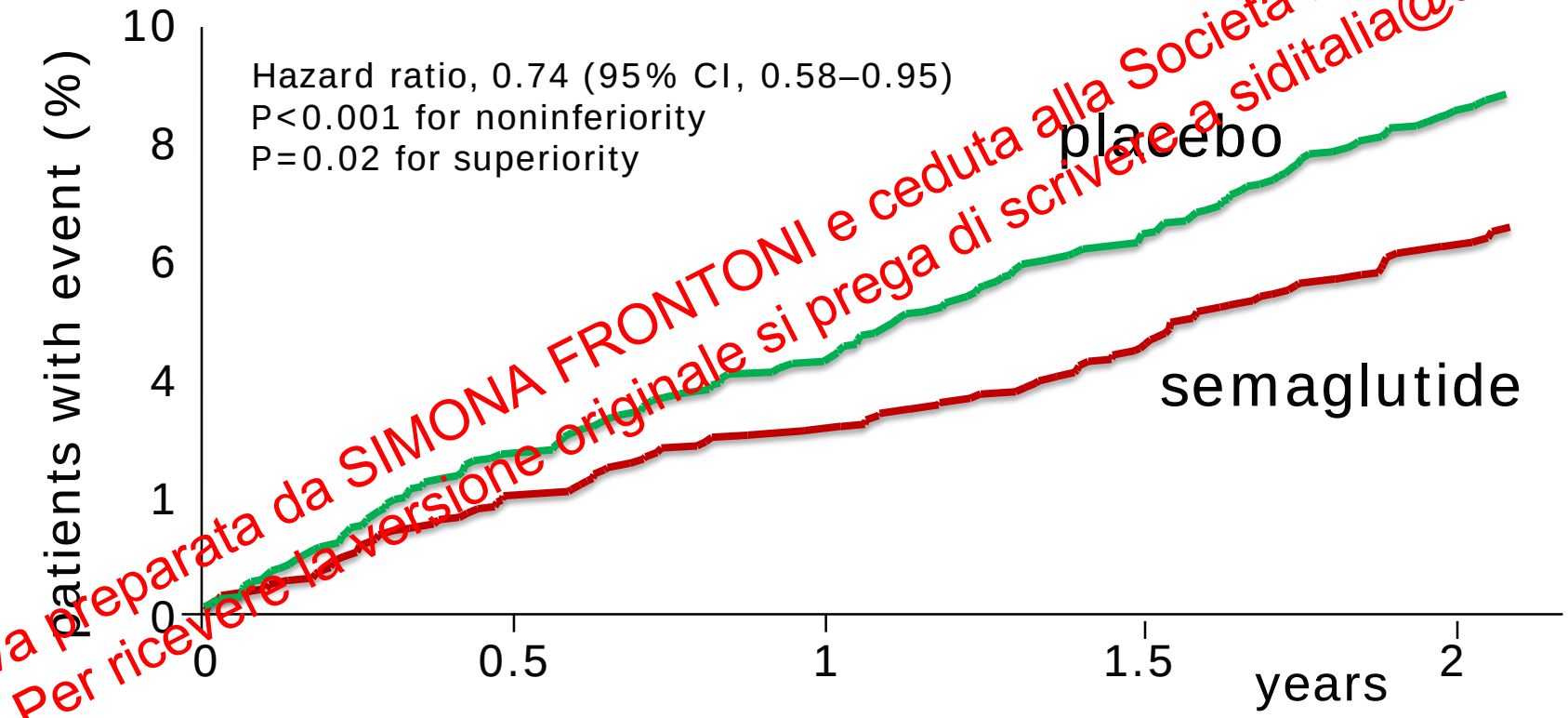





*Neal B et al.: NEJM Jun 12, 2017*

# SUSTAIN6: MACE (primary outcome)

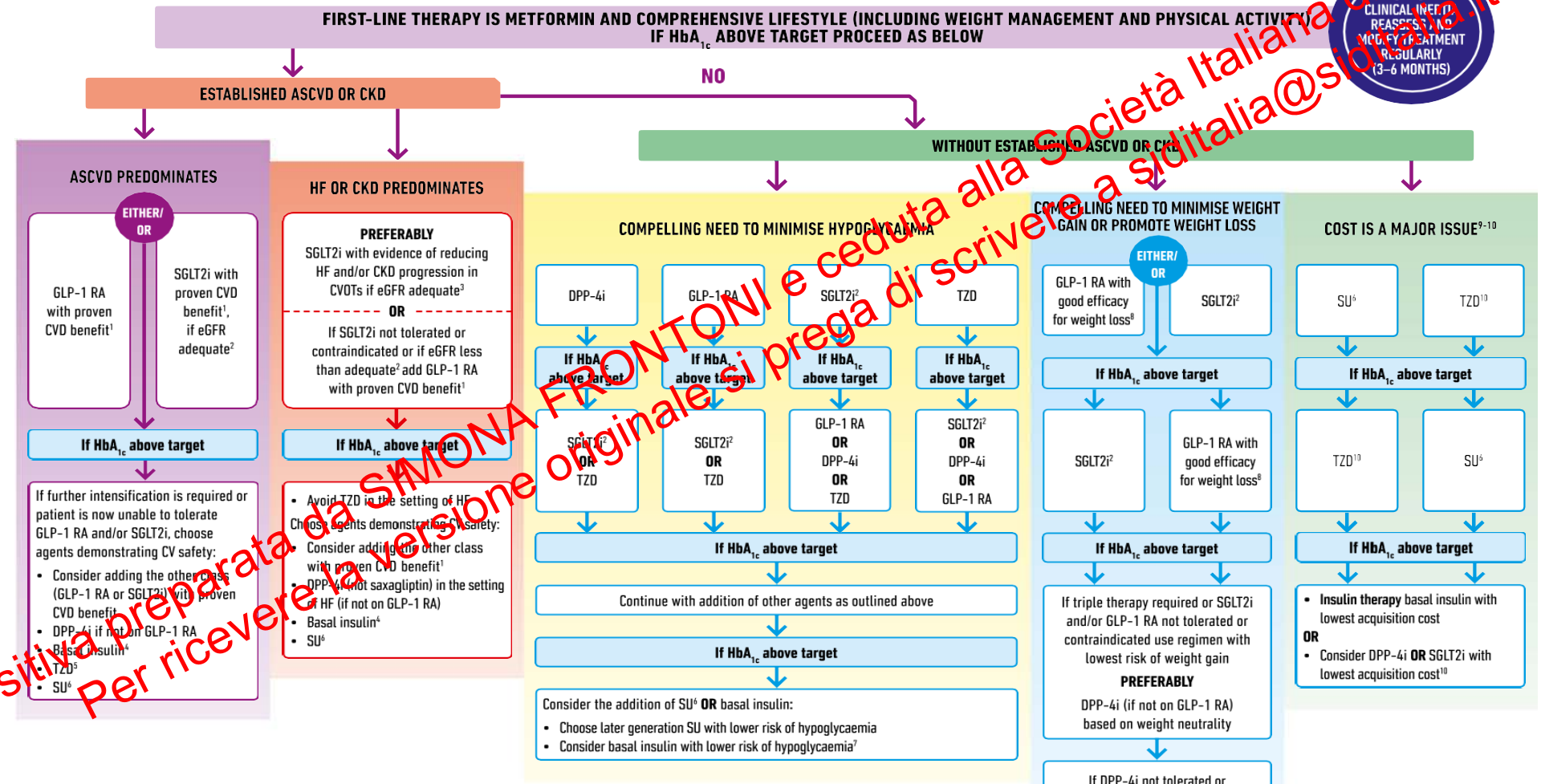
## CV Death, Nonfatal Myocardial Infarction or Nonfatal Stroke





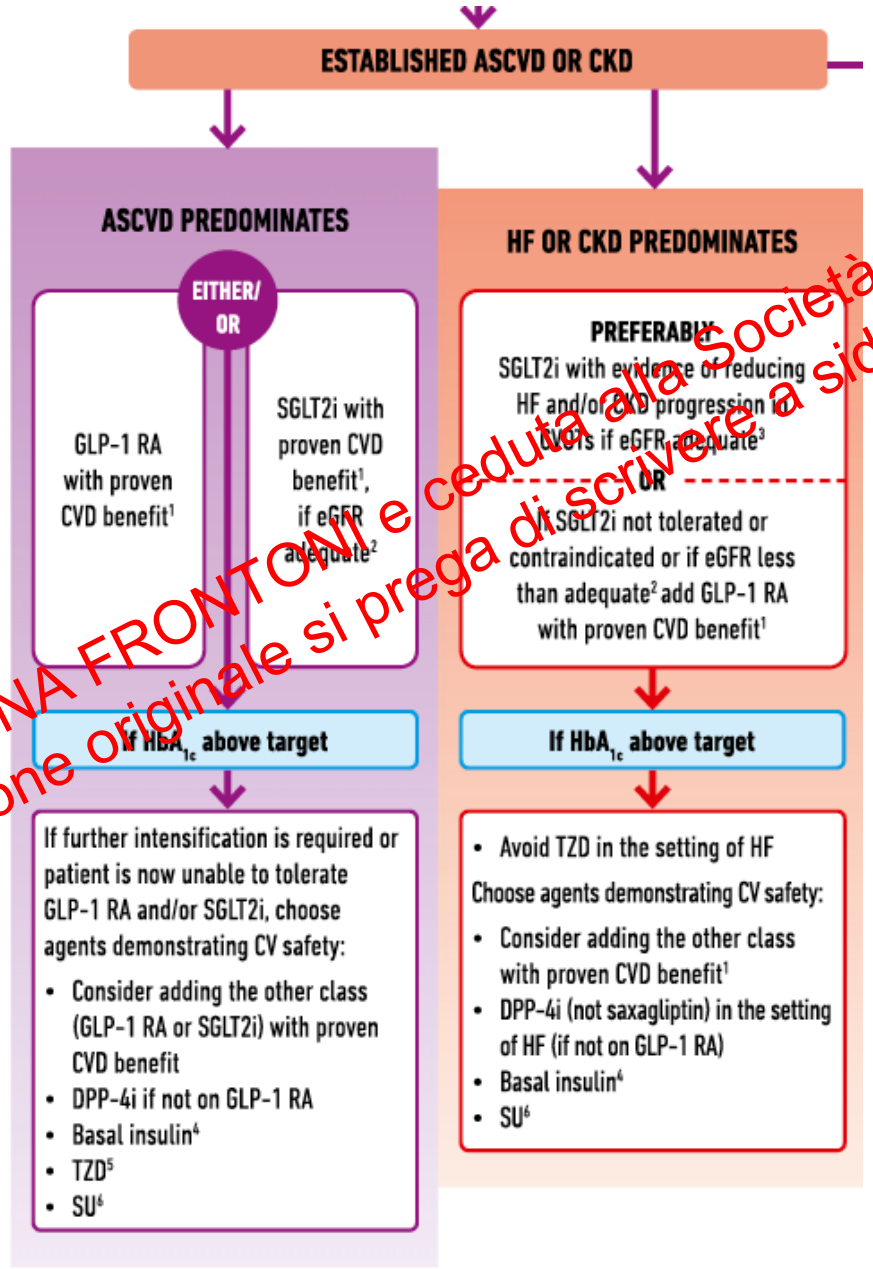

*Marso SP et al.: NEJM 375:1834, 2016*

# ADA/EASD




1.

# ADA/EASD



# II DOMANDA

Qual è il Number needed to treat per prevenire una morte CV, infarto miocardico non-fatale o stroke non-fatale in 2 anni, nel SUSTAIN 6?

a) 32

b) 45

c) 70

d) 65

# SUSTAIN6
## CV outcomes summary

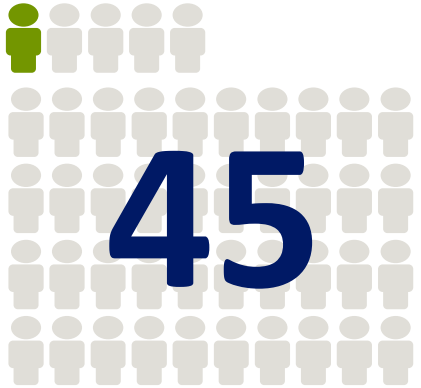
**Primary outcome of CV death, non-fatal MI or non-fatal stroke**

**26%**

**risk reduction**

**vs placebo**

**Number needed to treat to prevent one CV death, non-fatal MI or non-fatal stroke**



**45**

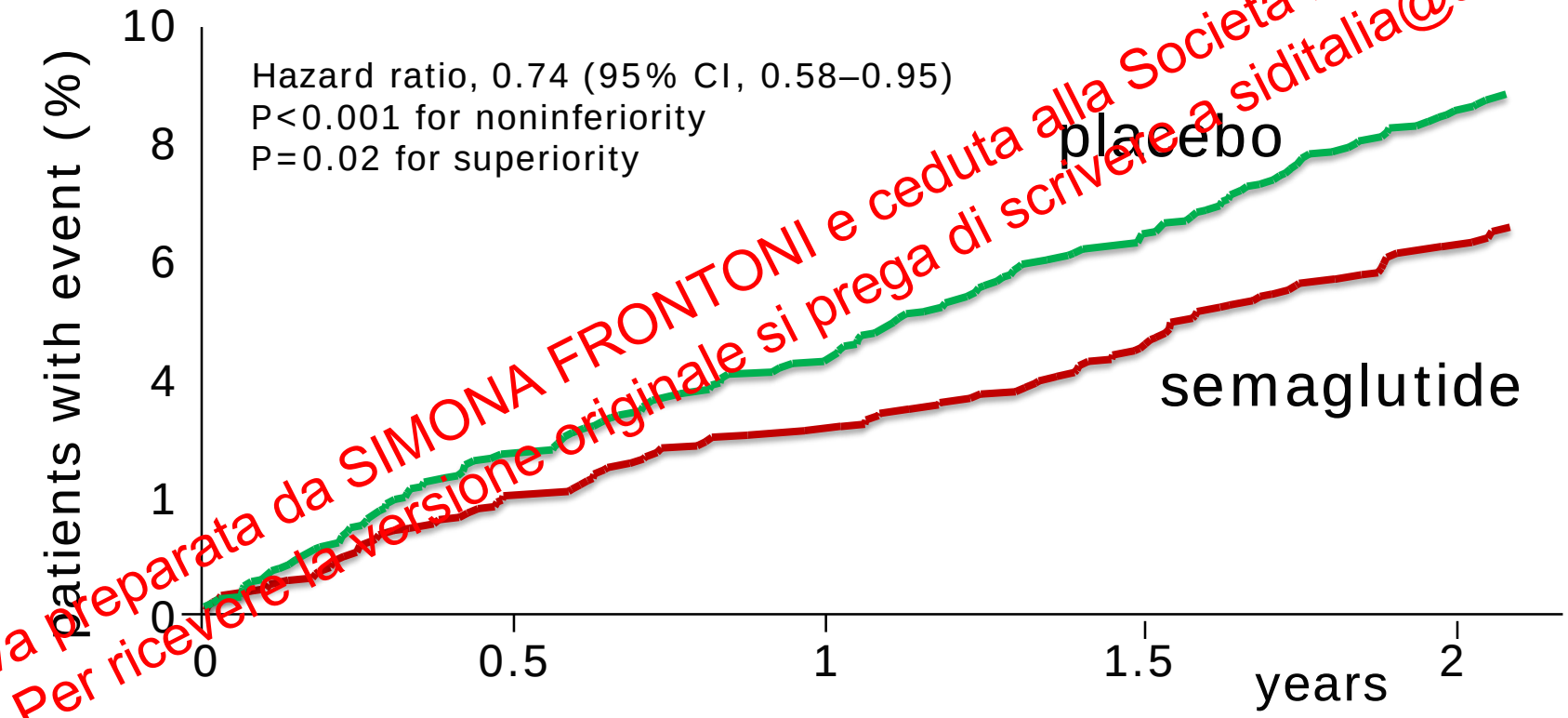
**for 2 years**



*Marso SP, et al. N Engl J Med 2016;375:1834–44.*

# SUSTAIN6: MACE (primary outcome)

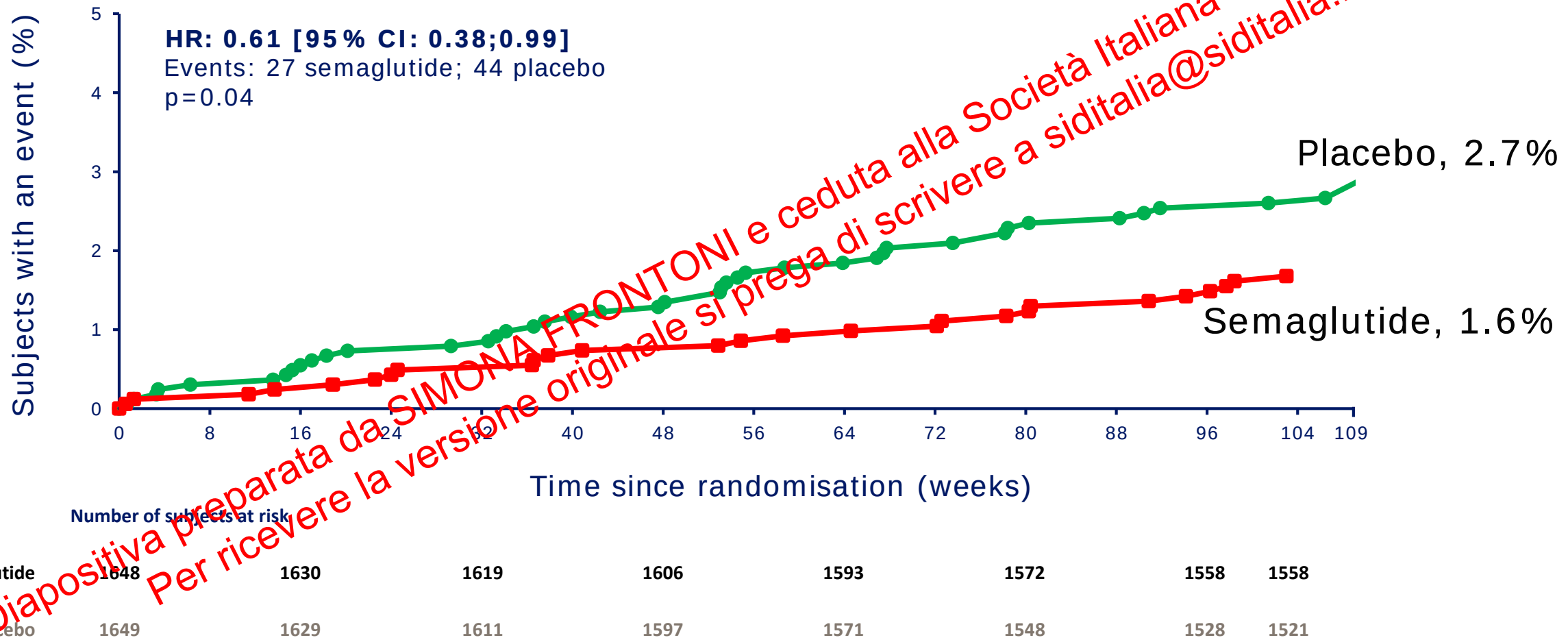
## CV Death, Nonfatal Myocardial Infarction or Nonfatal Stroke






*Marso SP et al.: NEJM 375:1834, 2016*

# SUSTAIN6
## Nonfatal Stroke

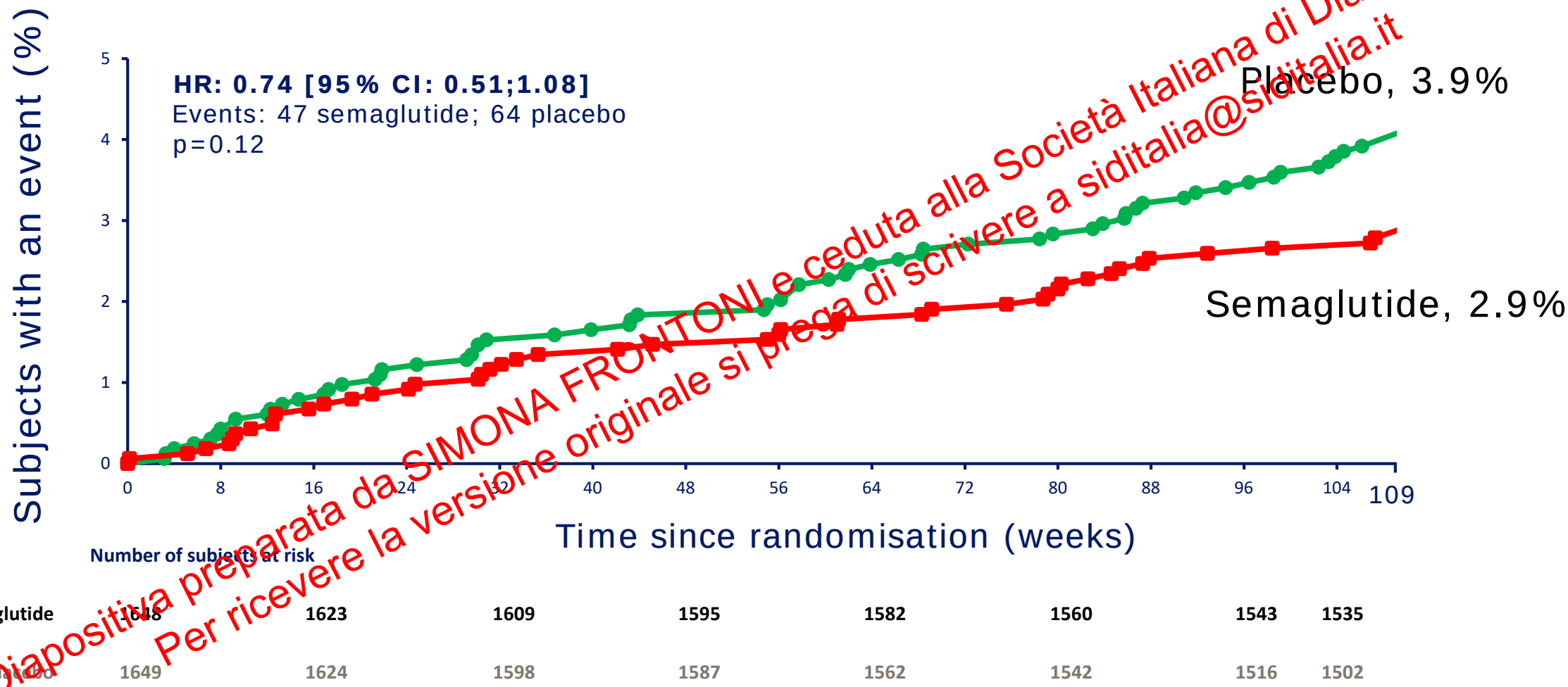





*Kaplan Meier plot for time from randomisation to first event adjudication committee-confirmed non-fatal stroke using 'in-trial' data from subjects in the full analysis set. HR is from a stratified proportional hazard model. CI, confidence interval; HR, hazard ratio.*

*Marso SP, et al. N Engl J Med 2016;375:1834–44.*

# SUSTAIN6
## Nonfatal MI

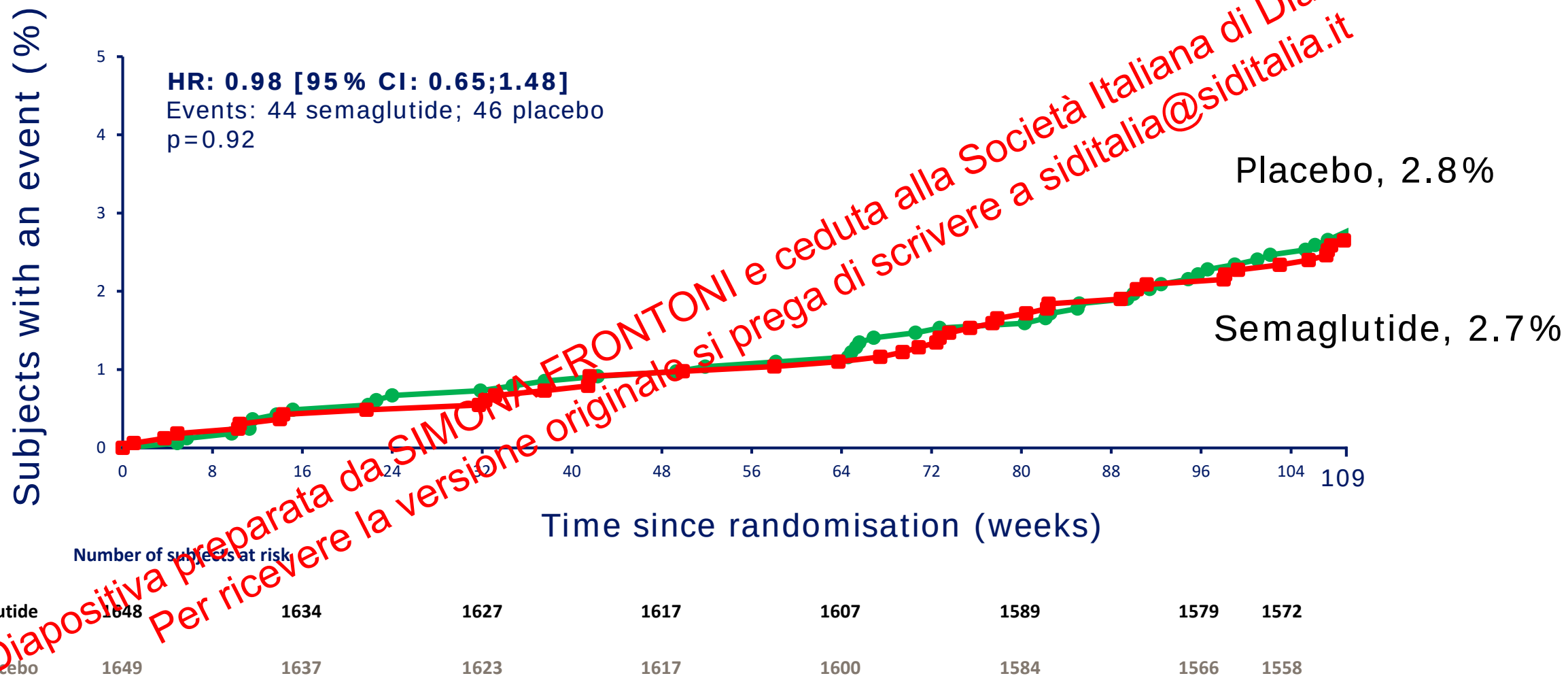





*Kaplan Meier plot for time from randomisation to first event adjudication committee-confirmed non-fatal MI using 'in-trial' data from subjects in the full analysis set. HR is from a stratified proportional hazard model. CI, confidence interval; HR, hazard ratio; MI, myocardial infarction.*

*Marso SP, et al. N Engl J Med 2016;375:1834–44.*

# SUSTAIN6
## CV death






*Kaplan Meier plot for time from randomisation to event adjudication committee-confirmed cardiovascular death using 'in-trial' data from subjects in the full analysis set. HR is from a stratified proportional hazard model. CI, confidence interval; CV, cardiovascular; HR, hazard ratio.*

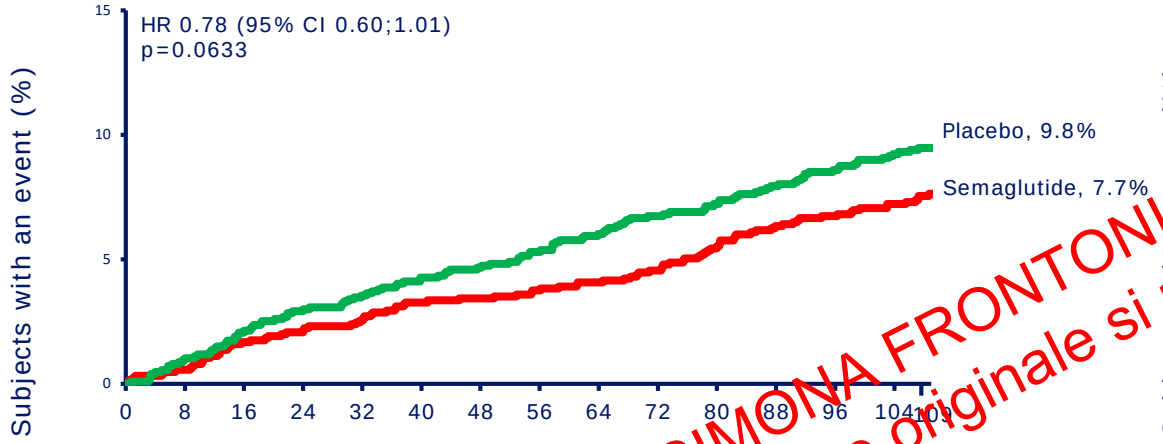
*Marso SP, et al. N Engl J Med 2016;375:1834–44.*

# SUSTAIN6: MACE (primary outcome)

## CV Death, Nonfatal Myocardial Infarction or Nonfatal Stroke

*IN SUBJECTS WITH ESTABLISHED CV DISEASE VS THOSE WITH CV RISK FACTORS ONLY*

### Established CV disease

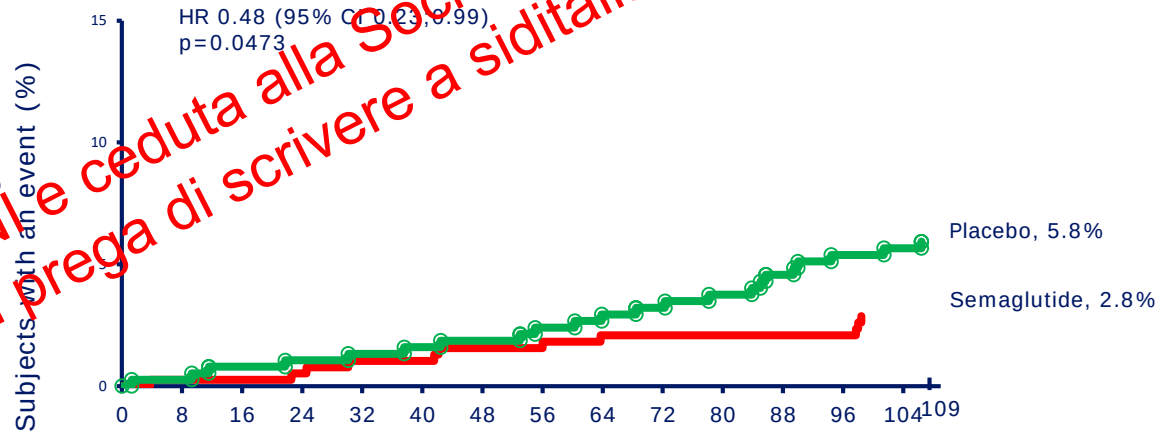



Time since randomisation (weeks)

Number of subjects at risk

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Semaglutide | 1,262 | 1,236 | 1,222 | 1,207 | 1,193 | 1,169 | 1,151 | 1,143 |
| Placebo | 1,271 | 1,242 | 1,217 | 1,201 | 1,176 | 1,154 | 1,131 | 1,120 |

### CV risk factors




Time since randomisation (weeks)

Number of subjects at risk

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Semaglutide | 386 | 383 | 379 | 377 | 375 | 374 | 373 | 370 |
| Placebo | 378 | 374 | 369 | 366 | 358 | 354 | 348 | 346 |



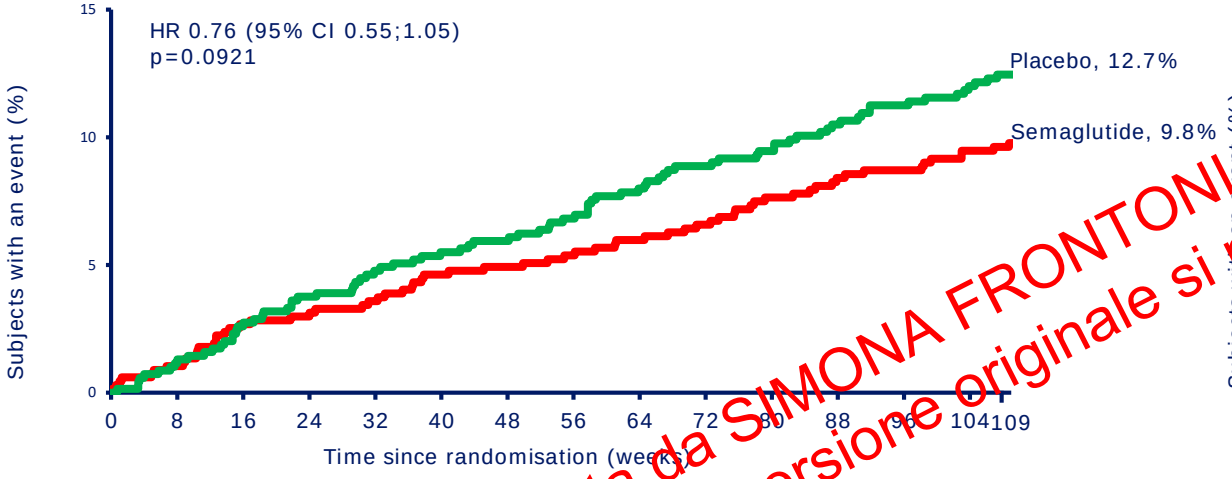
*Kaplan–Meier estimates: Cox proportional hazards models of time from randomisation to first EAC-confirmed MACE in the full analysis set, and treatment by subgroup interaction, if applicable, as fixed factor(s). Data were pooled for semaglutide groups and placebo groups, respectively. CI, confidence interval; CV, cardiovascular; EAC, event adjudication committee; HR, hazard ratio; MACE, major adverse cardiovascular event.*
*Bain SC et al. Presented at the European Society of Cardiology Congress, 25–29 August 2018, Munich, Germany. Poster Presentation P2859.*

# SUSTAIN6: MACE (primary outcome)

## CV Death, Nonfatal Myocardial Infarction or Nonfatal Stroke

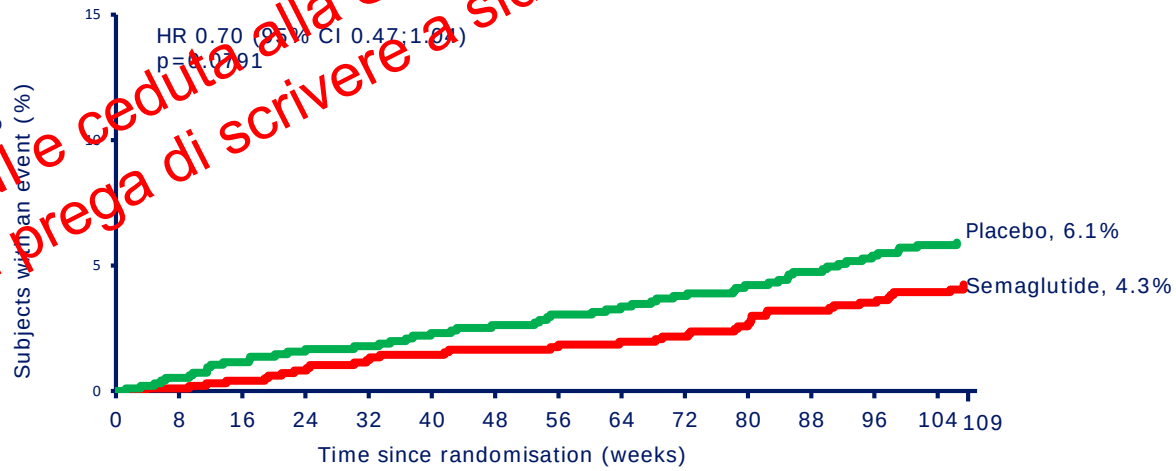
*IN SUBJECTS WITH PRIOR MI/STROKE VS THOSE WITHOUT PRIOR MI/STROKE*

### With prior MI/stroke




| Number of subjects at risk | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Semaglutide | 673 | 652 | 645 | 634 | 625 | 607 | 599 | 593 |
| Placebo | 673 | 653 | 643 | 625 | 610 | 593 | 586 | |

### Without prior MI/stroke




| Number of subjects at risk | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Semaglutide | 975 | 967 | 956 | 950 | 943 | 936 | 925 | 920 |
| Placebo | 955 | 943 | 933 | 924 | 909 | 898 | 886 | 880 |

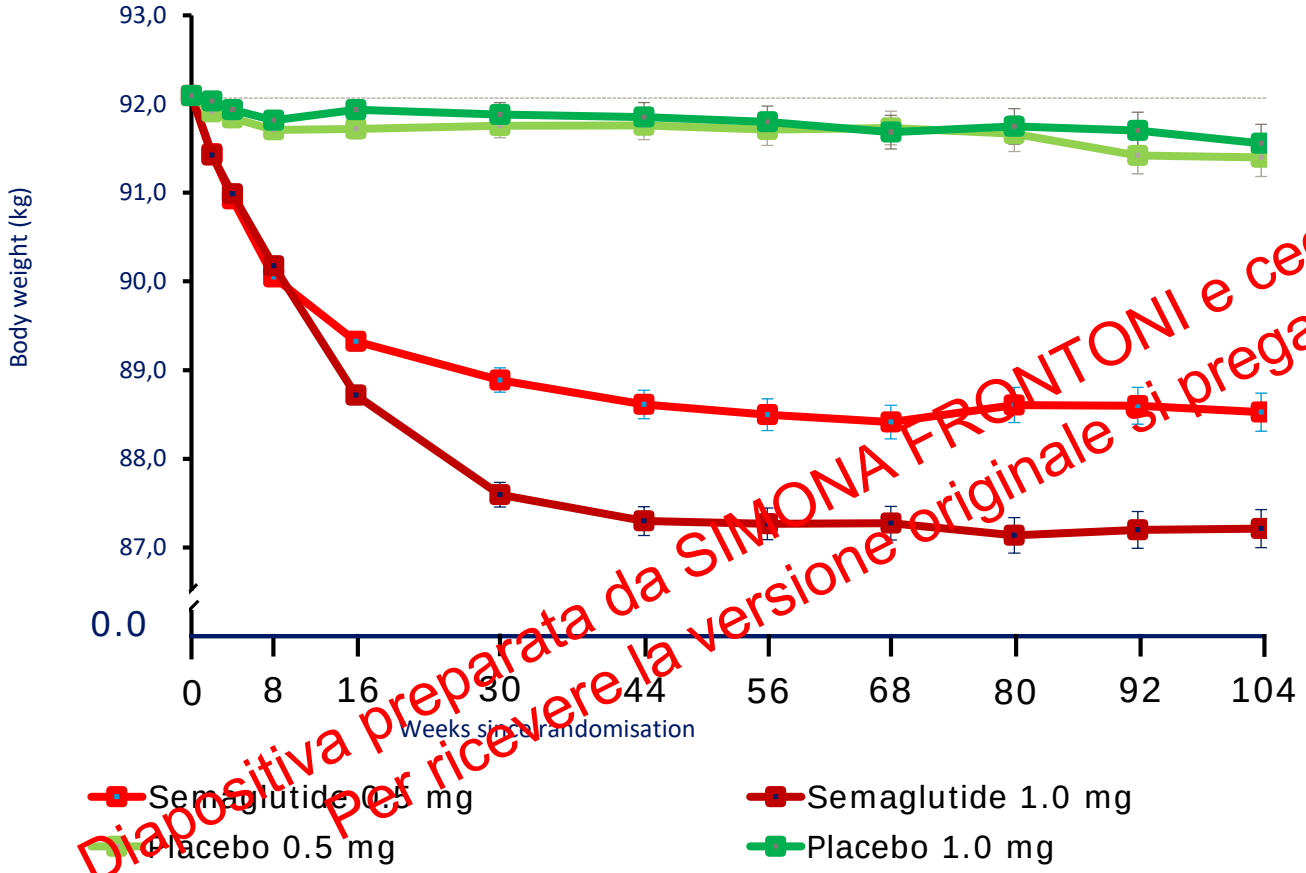


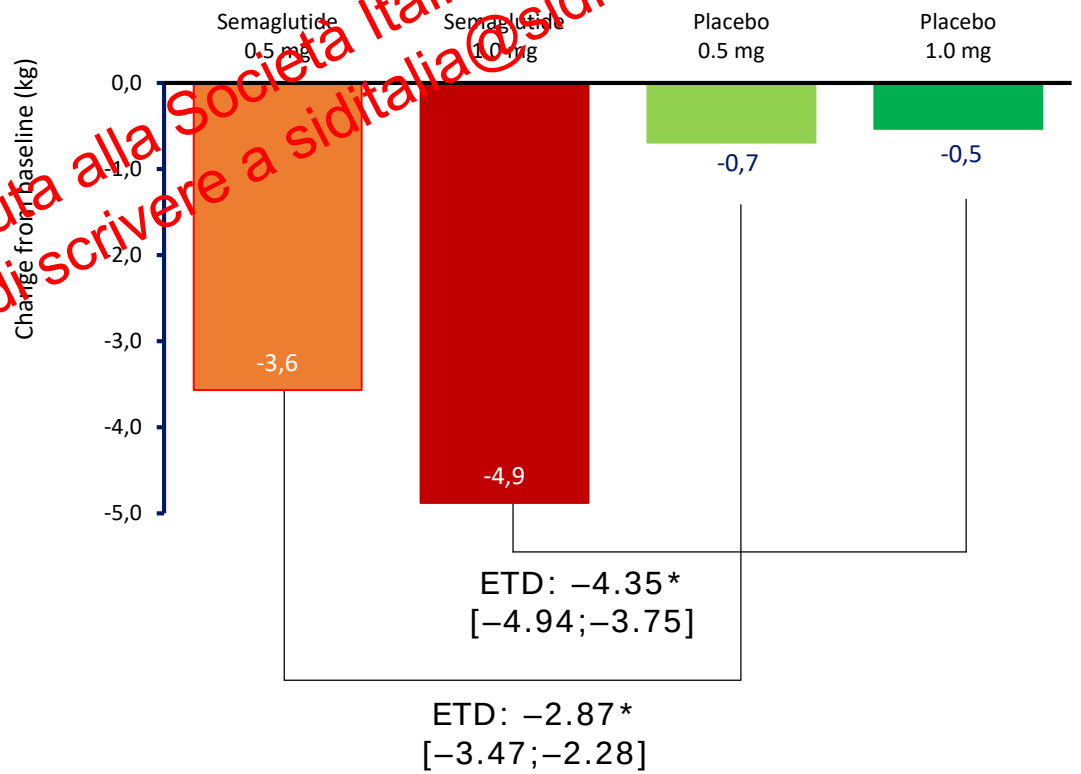
*Kaplan–Meier estimates: Cox proportional hazards models of time from randomisation to first EAC-confirmed MACE in the full analysis set, and treatment by subgroup interaction, if applicable, as fixed factor(s). Data were pooled for semaglutide groups and placebo groups, respectively. CI, confidence interval; EAC, event adjudication committee; HR, hazard ratio; MACE, major adverse cardiovascular event; MI, myocardial infarction. Bain SC et al. Presented at the European Society of Cardiology Congress, 25–29 August 2018, Munich, Germany. Poster Presentation P2859.*

# SUSTAIN6: Body weight

## Estimated mean by week and change from baseline at week 104

*Overall mean at baseline: 92.1 kg*



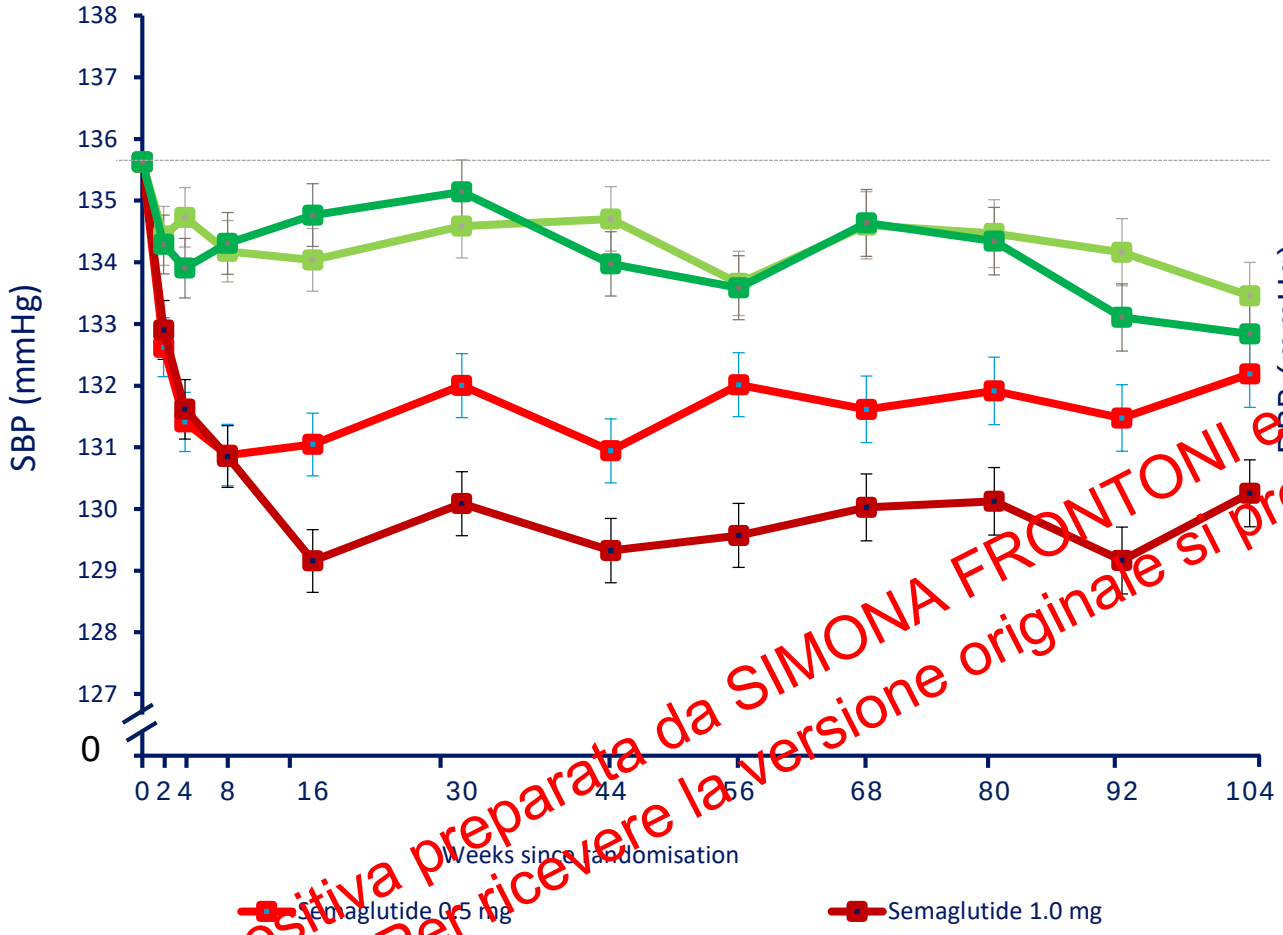



*Marso SP et al. N Engl J Med 2016;375:1834–44.*

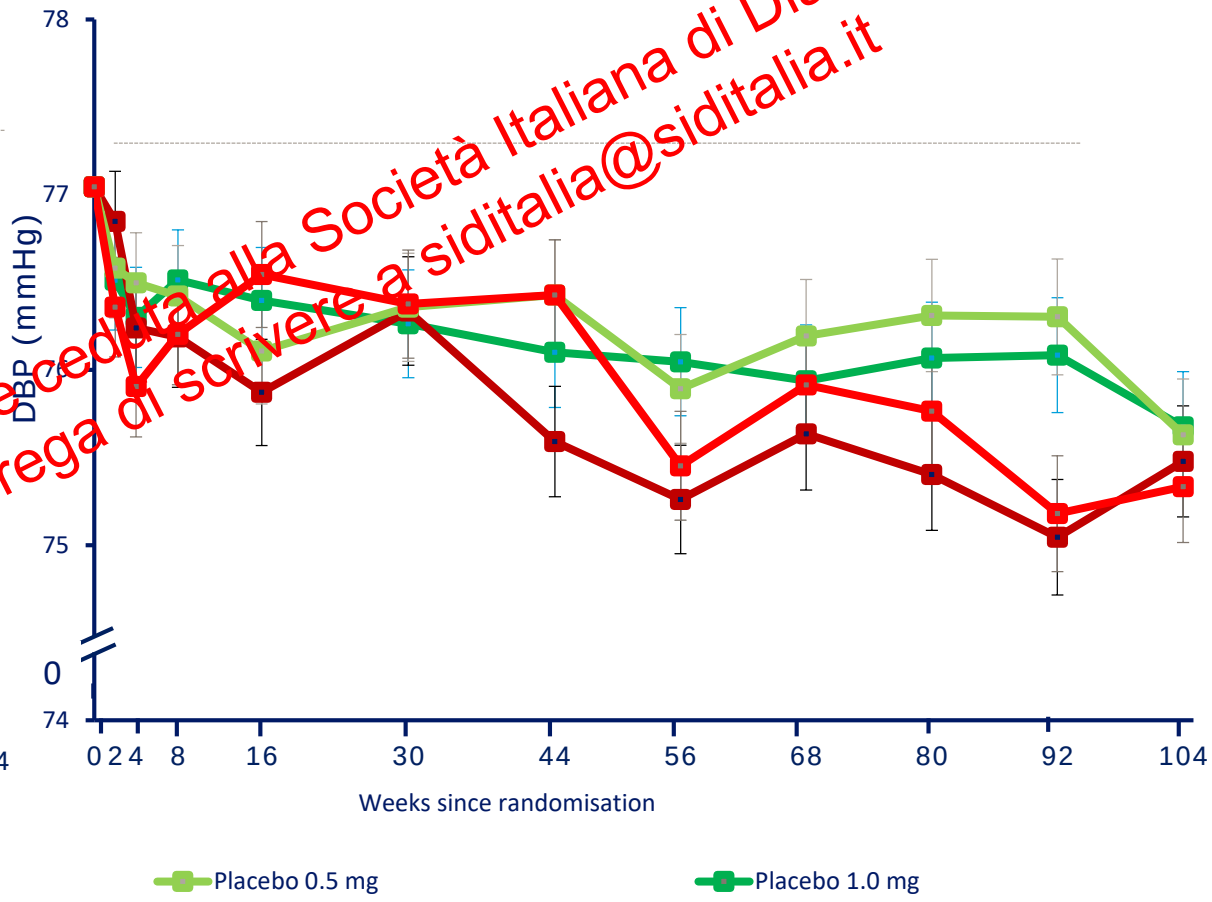
# SUSTAIN6: Blood pressure

## Estimated mean by week and change from baseline at week 104

*Overall mean at baseline: 135.6 mmHg*




*Overall mean at baseline: 77.0 mmHg*



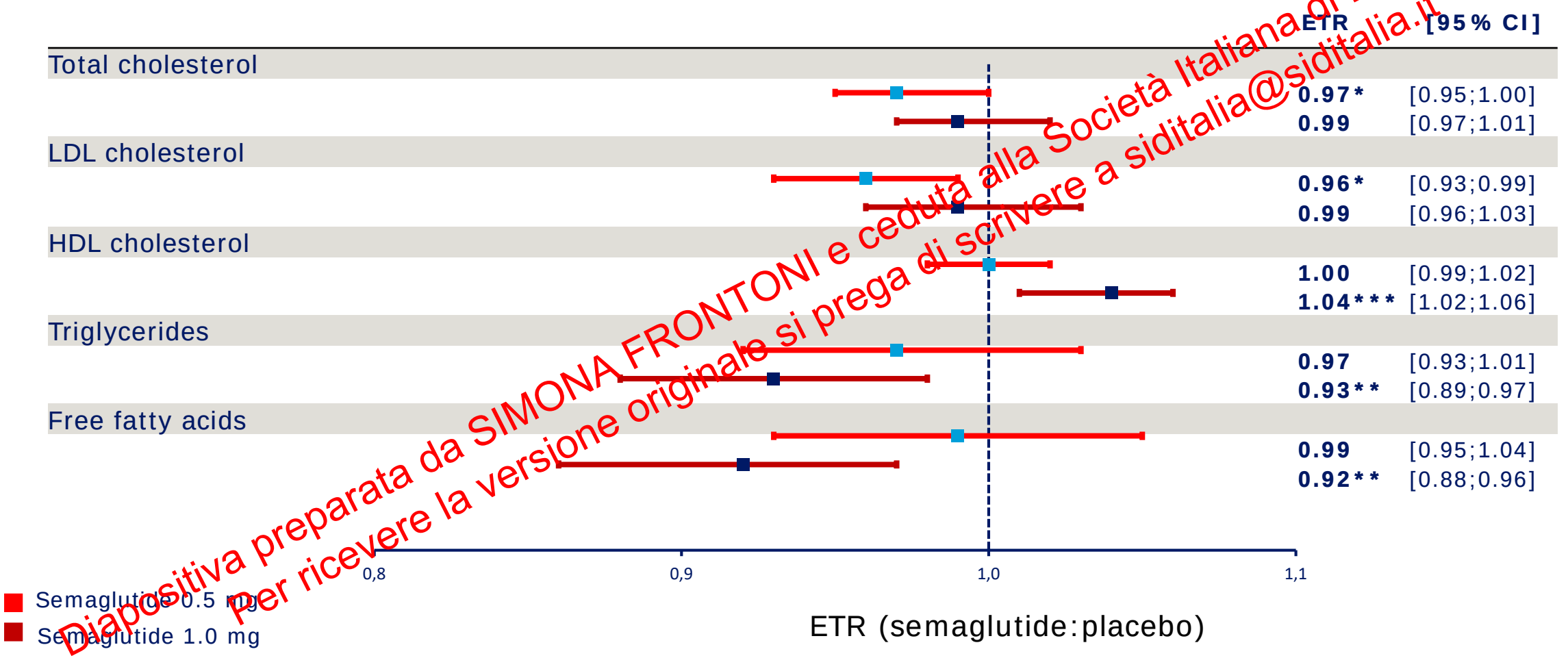

Semaglutide 0.5 mg
Semaglutide 1.0 mg
Placebo 0.5 mg
Placebo 1.0 mg



**Indicates significance (p-value <0.0001).*
*CI, confidence interval; SBP, systolic blood pressure; ETD, estimated treatment difference.*
*Marso SP et al. N Engl J Med 2016;375:1834–44.*

# SUSTAIN6: Lipids

## Ratio to baseline

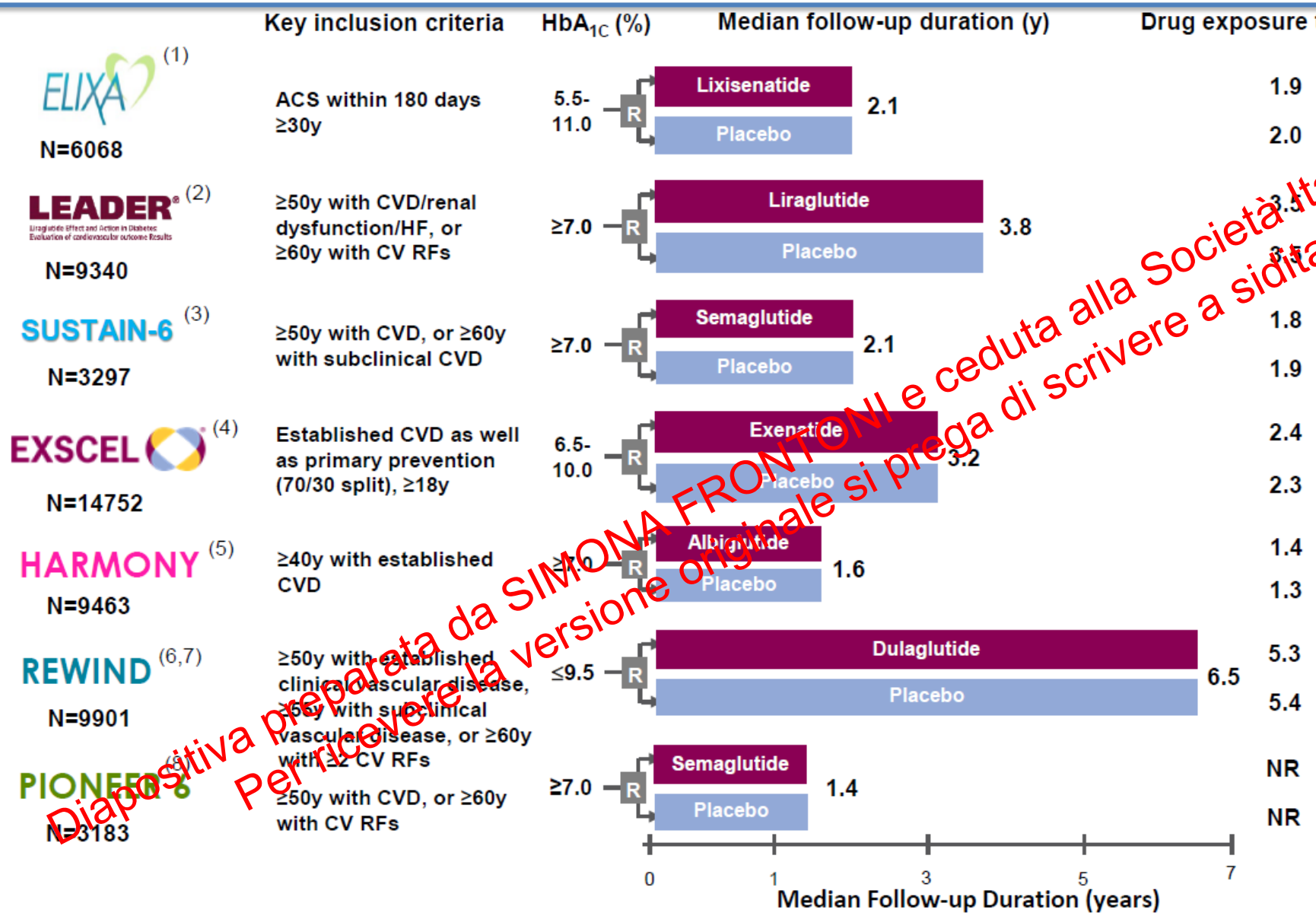





**P<0.05; **P<0.001; ***P<0.0001. Data are ETRs to baseline, and treatment ratios with CI, based on in-trial data for scheduled visits for the full analysis set. Each parameter was analysed by a mixed model for repeated measures with treatment group*

*Marso SP et al. N Engl J Med 2016;375:1834–44.*

# CVOTs: an overview



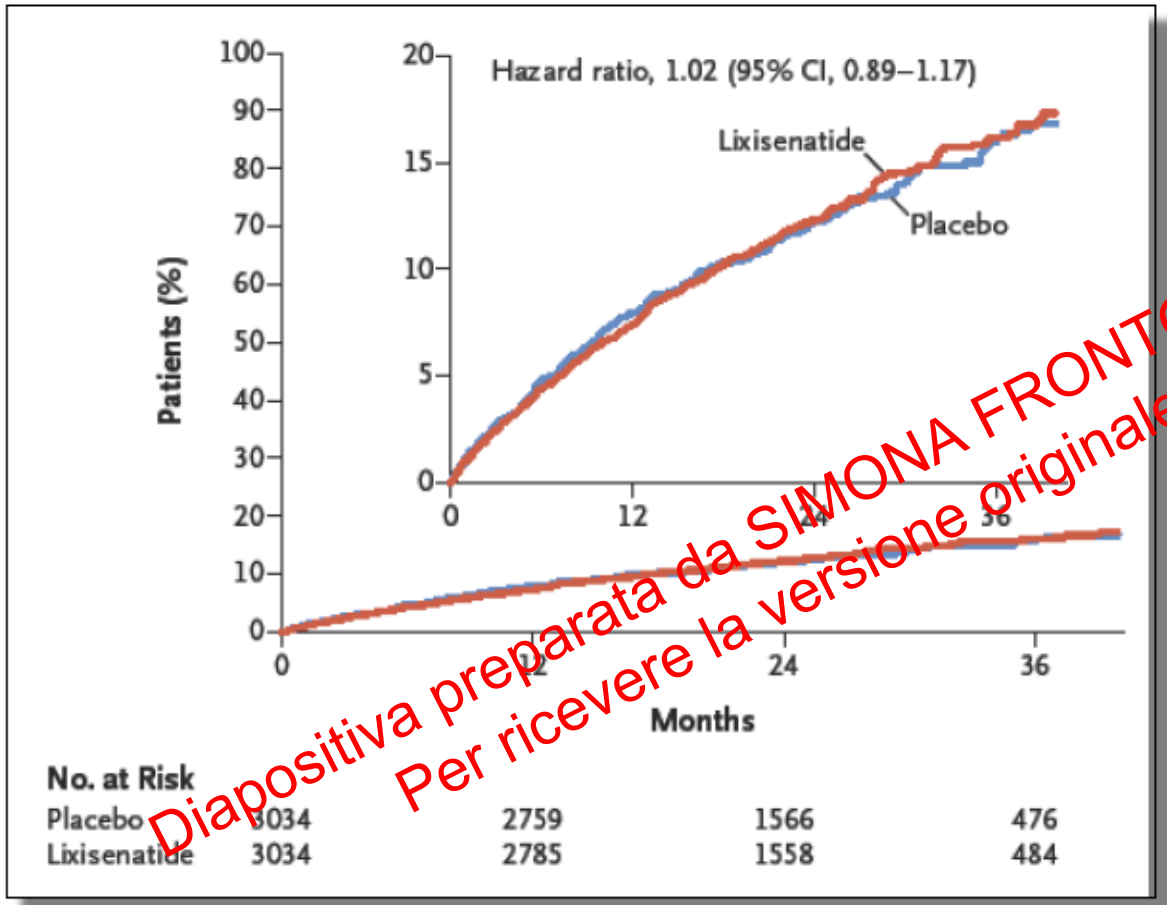

ACS, acute coronary syndrome; CV, cardiovascular; CVD, CV disease; CVOTs, cardiovascular outcomes trials; GLP-1 RA, glucagon-like peptide-1 receptor agonist; $HbA_{1c}$, glycated haemoglobin; HF, heart failure; MACE, major adverse CV events; NR, not reported; R, randomisation; RFs, risk factors; y, years.


[1]Pfeffer MA, et al. *N Engl J Med* 2015;373:2247–2257
[2]Marso SP, et al. *N Engl J Med* 2016;375:311–322
[3]Marso SP, et al. *N Engl J Med* 2016;375:1834–1844
[4]Holman RR, et al., *N Engl J Med* 2017;377:1228–1239
[5]Hernandez AF, et al. *Lancet* 2018;392(10157):1519–1529
[6]Gerstein HC, et al. *Diabetes Obes Metab* 2018;20:42–49
[7]https://clinicaltrials.gov/ct2/show/NCT01394952
[8]Husain M, et al *N Eng J Med* 2019

# CVOTs: ELIXA

## Lixisenatide: effect on major cardiovascular events

Results of the ELIXA trial



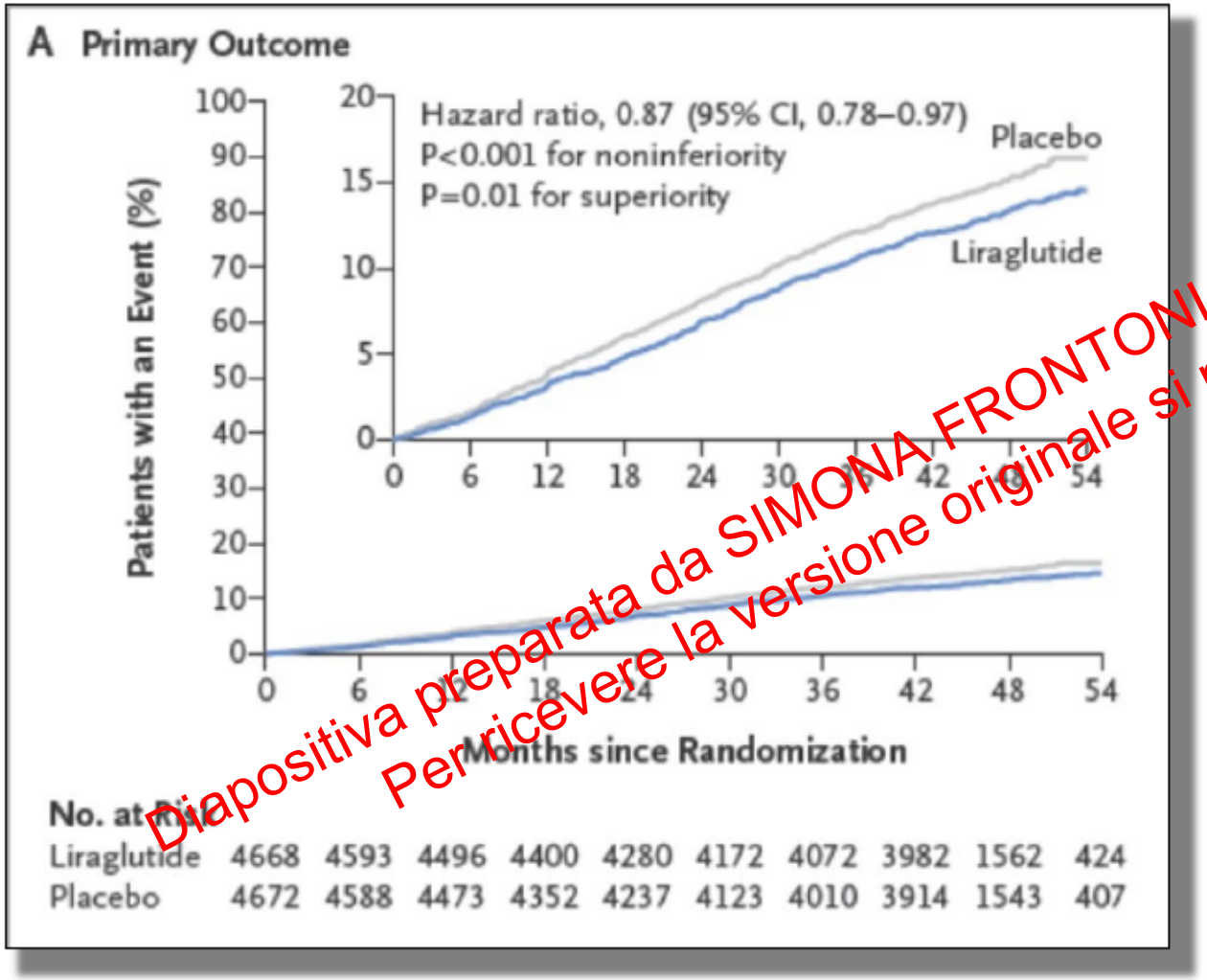

**Principal endpoint:**
4-point MACE
(nonfatal MI, nonfatal stroke, and cardiovascular death, hospitalization for unstable angina)

6068 T2DM patients with recent acute coronary syndrome, lixisenatide vs placebo 1:1.
Follow-up: 2.1 y

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

# Liraglutide: effect on major cardiovascular events

## Results of the LEADER trial




**Principal endpoint:**
3-point MACE
(nonfatal MI, nonfatal stroke, and cardiovascular death)

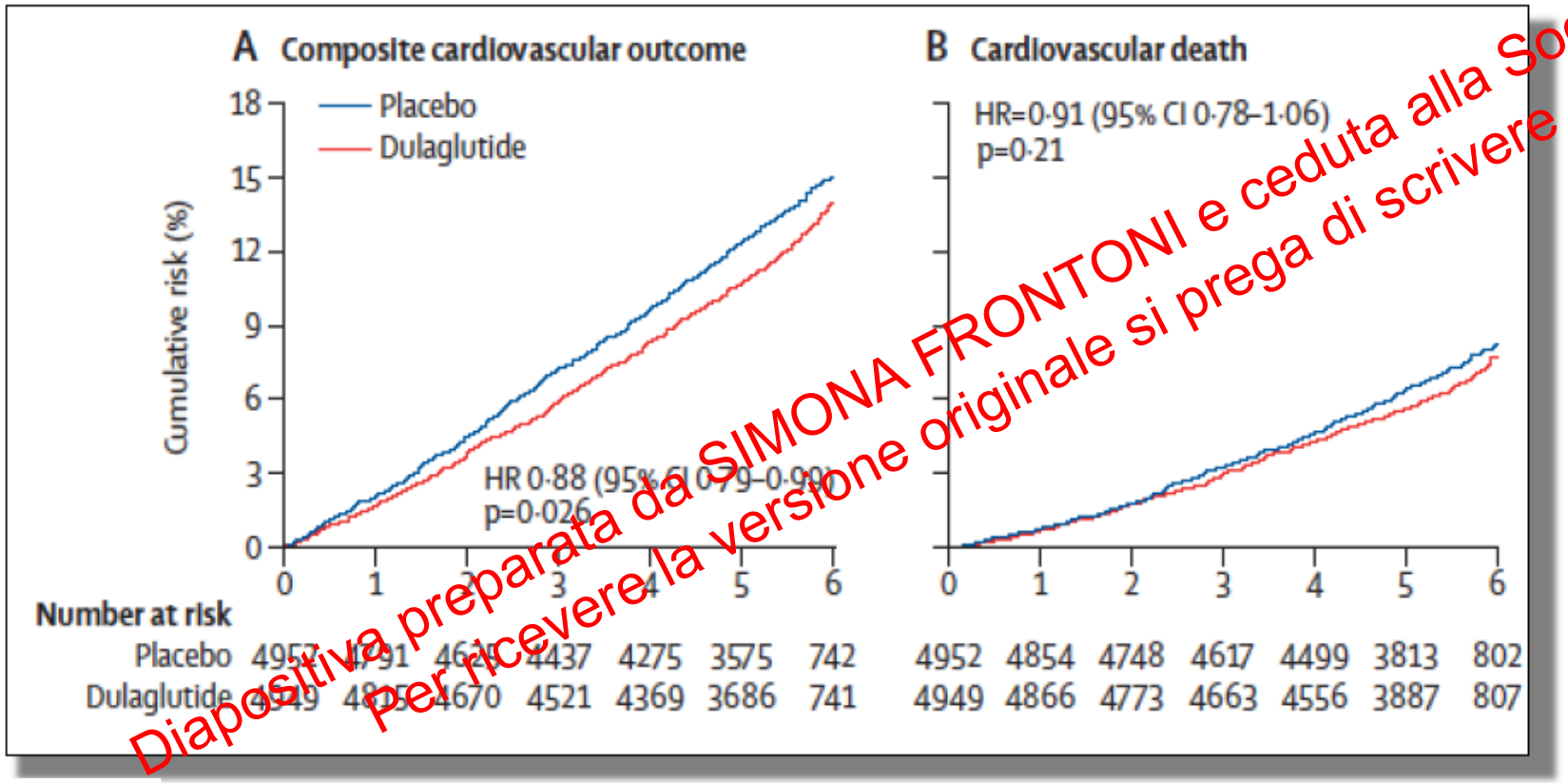
9,340 T2DM patients with prior cardiovascular disease and/or high CV risk, Liraglutide vs placebo 1:1.
Follow-up: 4 y

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

# CVOTs: REWIND

## Dulaglutide: effect on MACE

Results of the REWIND trial




**Principal endpoint:**
3-point MACE
(nonfatal MI, nonfatal stroke, and cardiovascular death)

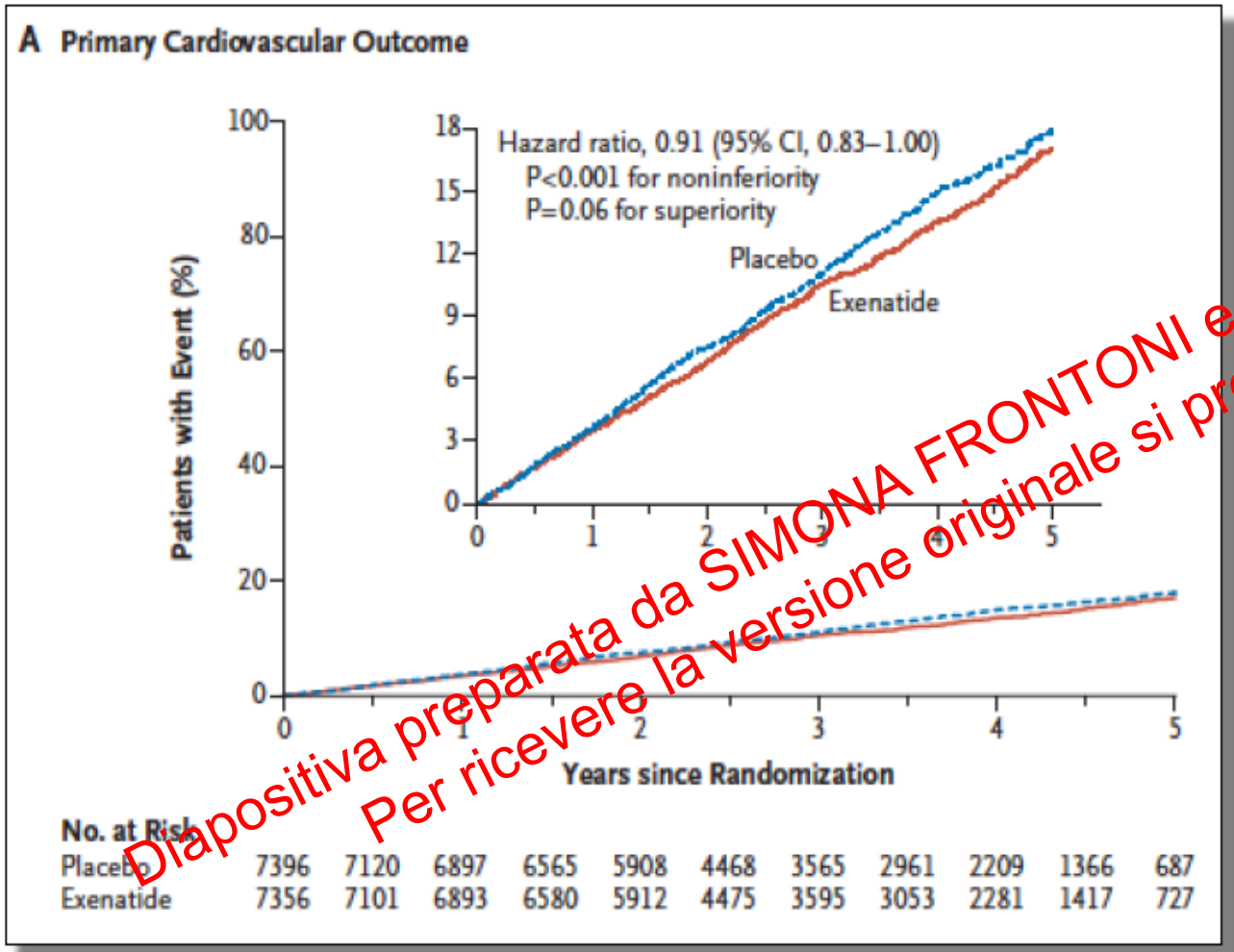
9,901 T2DM patients with prior cardiovascular disease and/or high CV risk, dulaglutide vs placebo 1:1. Follow-up: 5.6 y

Gerstein HC et al. *Lancet* 2019

# CVOTs: EXSCEL

## Exenatide LAR: effect on major cardiovascular events

Results of the EXSCEL trial




**Principal endpoint:**
3-point MACE
(nonfatal MI, nonfatal stroke, and cardiovascular death)

14,752 T2DM patients with prior cardiovascular disease and/or high CV risk, exenatide LAR vs placebo 1:1. Follow-up: 3.2 y

Holman RR et al. *N Engl J Med* 377: 1228-39, 2016

# CVOTs: SUMMARY

| | ELIXA | LEADER | SUSTAIN-6 | EXSCEL | HARMONY | REWIND | PIONEER 6 | |
|---|---|---|---|---|---|---|---|---|
| Diabetes duration (years) | 9.3 | 12.8 | 13.9 | 12 | 14.1 | 10 | 14.9 | Baseline Risk Level |
| Baseline HbA1c (%) | 7.6 | 8.7 | 8.7 | 8.0 | 8.7 | 7.5 | 8.2 | |
| Baseline BMI (kg/m²) | 30.1 | 32.5 | 32.8 | 31.7 | 32.3 | 32.8 | 32.3 | |
| History of CVD (%) | 100 | 81.3 | 83 | 73.1 | 100 | 31.4 | 84.6 | |
| Hypertension (%) | 76.3 | 90 | 92.8 | 90.3 | 88.4 | 93.2 | 95.3 | |
| eGFR <60 (%) | 23.2 | 21.7 | 28.5 | 21.7 | 22.6 | 22.2 | 27 | |
| Mortality rate (events/100 patient-yr) | 3.1; 3.3 | 2.1; 2.5 | 1.8; 1.7 | 2.0; 2.3 | 2.4; 2.5 | 2.1; 2.3 | 1.1; 2.2 | |
| MACE rate (events/100 patient-yr) | 6.4; 6.3 | 3.4; 3.9 | 3.2; 4.4 | 3.7; 4.0 | 4.6; 5.9 | 2.3; 2.6 | 2.9; 3.7 | |
| MACE HR | 1.02 [95% CI 0.89–1.17]) | **0.87 [95% CI 0.78–0.97] p=0.01** | **0.74 [95% CI 0.58–0.95] p=0.02** | 0.91 [95% CI 0.83–1.00] p=0.06 | **0.78 [95% CI 0.68–0.90] p=0.0006** | **0.88 [95% CI 0.79–0.99] p=0.026** | 0.79 [95% CI 0.57-1.11) p=0.17 | Main Outcomes |
| All-cause mortality HR | 0.94 [95% CI 0.78–1.13] | 0.85 [95% CI 0.74–0.97] | 1.05 [95% CI 0.74 –1.50] | 0.86 [95% CI 0.77–0.97] | 0.95 [95% CI 0.79–1.16] | 0.90 [95% CI 0.80–1.01] | 0.51 [95% CI 0.31-0.84) | |



Pfeffer, M.A. *et al.* (2015) *N. Engl. J. Med.* 373, 2247–2257; Marso, S.P. *et al.* (2016) *N. Engl. J. Med.* 375, 311–322; Marso, S.P. *et al.* (2016) *N. Engl. J. Med.* 375, 1834–1844; Holman, R.R. *et al.* (2017) *N. Engl. J. Med.* 377, 1228–1239; Hernandez, A.F. *et al.* (2018) *Lancet* 392, 1519–1529; Gerstein, H.C. *et al.* (2019) *Lancet* DOI: 10.1016/S0140-6736(19)31149-3; Husain, M. *et al.* (2019) *N. Engl. J. Med.* DOI: 10.1056/NEJMoa1901118.

# GLP-1RAs Have Multifactorial Effects

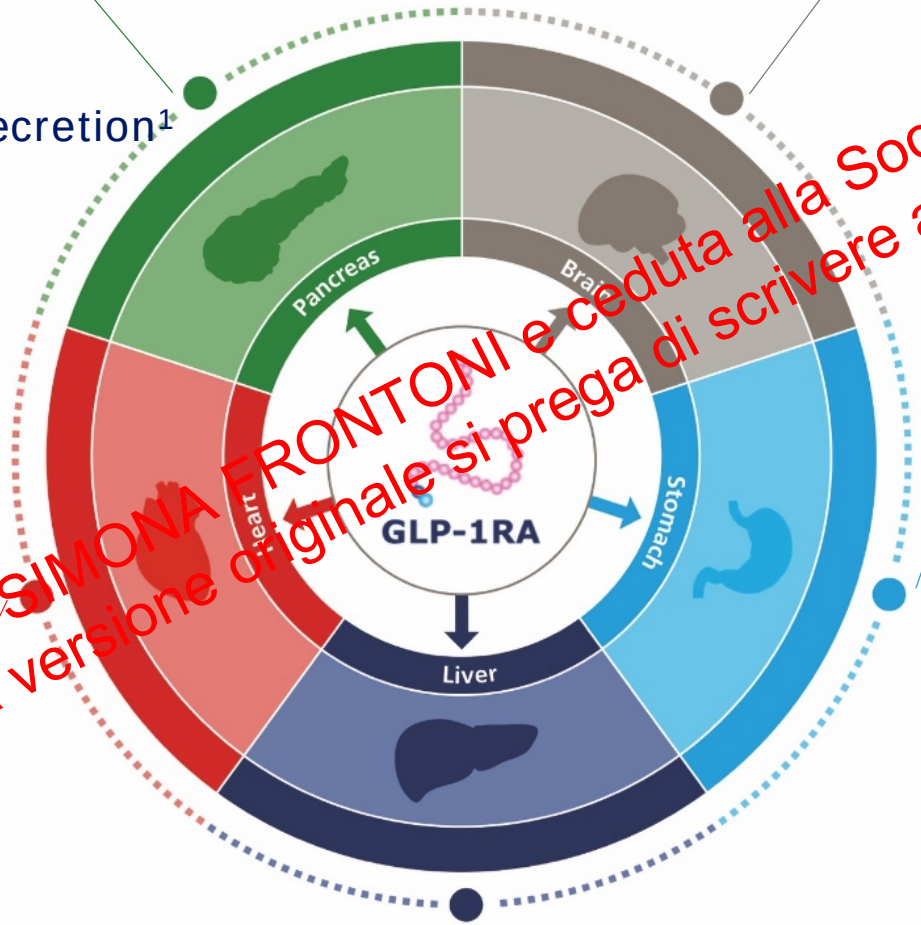
*PHARMACOLOGICAL EFFECTS OF GLP-1RAs*

## Pancreas

- ↑ Beta-cell function[1]
- ↑ Insulin biosynthesis[1]
- ↑ Glucose-dependent insulin secretion[1]
- ↓ Glucose-dependent glucagon secretion[1]

## Brain

- ↓ Body weight[5]
- ↓ Food intake[6]
- ↑ Satiety[7,8]




## Stomach

- ↓ Gastric emptying[9]

## Heart

- ↓ Cardiovascular risk[2]
- ↓ Fatty acid metabolism[3]
- ↑ Cardiac function[3]
- ↓ Systolic blood pressure[3]
- ↓ Inflammation[4]

## Liver

- ↓ Endogenous glucose production[10]
- ↑ Hepatic insulin sensitivity[10]
- ↓ *De novo* lipogenesis[10]
- ↓ Lipotoxicity[10]
- ↓ Steatosis[11]



*Adapted from Campbell JE, Drucker DJ. Cell Metab 2013;17:819–37 and Pratley RE, Gilbert M. Rev Diabet Stud 2008;5:73–94.*

# Conclusioni

- Un controllo glicemico intensivo APPROPRIATO permette di ottenere il mantenimento a lungo termine del controllo metabolico e di prevenire le complicanze micro e macrovascolari del diabete.

- L'uso di farmaci che riducono la glicemia in maniera efficace e sicura e contestualmente sono in grado di migliorare il rischio CV globale, modificando la traiettoria temporale della macroangiopatia, dovrebbe essere anticipato il più possibile.

- Gli analoghi del GLP-1 rappresentano un'opzione terapeutica ESTREMAMENTE efficace, per garantire una protezione cardiovascolare certamente in prevenzione secondaria, ma probabilmente anche in prevenzione primaria.

- Un'appropriata analisi dei costi dei GLP1-Ras dovrebbe considerare i vantaggi in termini di risparmio di ipoglicemie (e quindi anche numero di visite, automonitoraggio della glicemia) e di outcome cardiovascolari