# L'EVOLUZIONE DELLA TERAPIA DEL DIABETE DI TIPO 2

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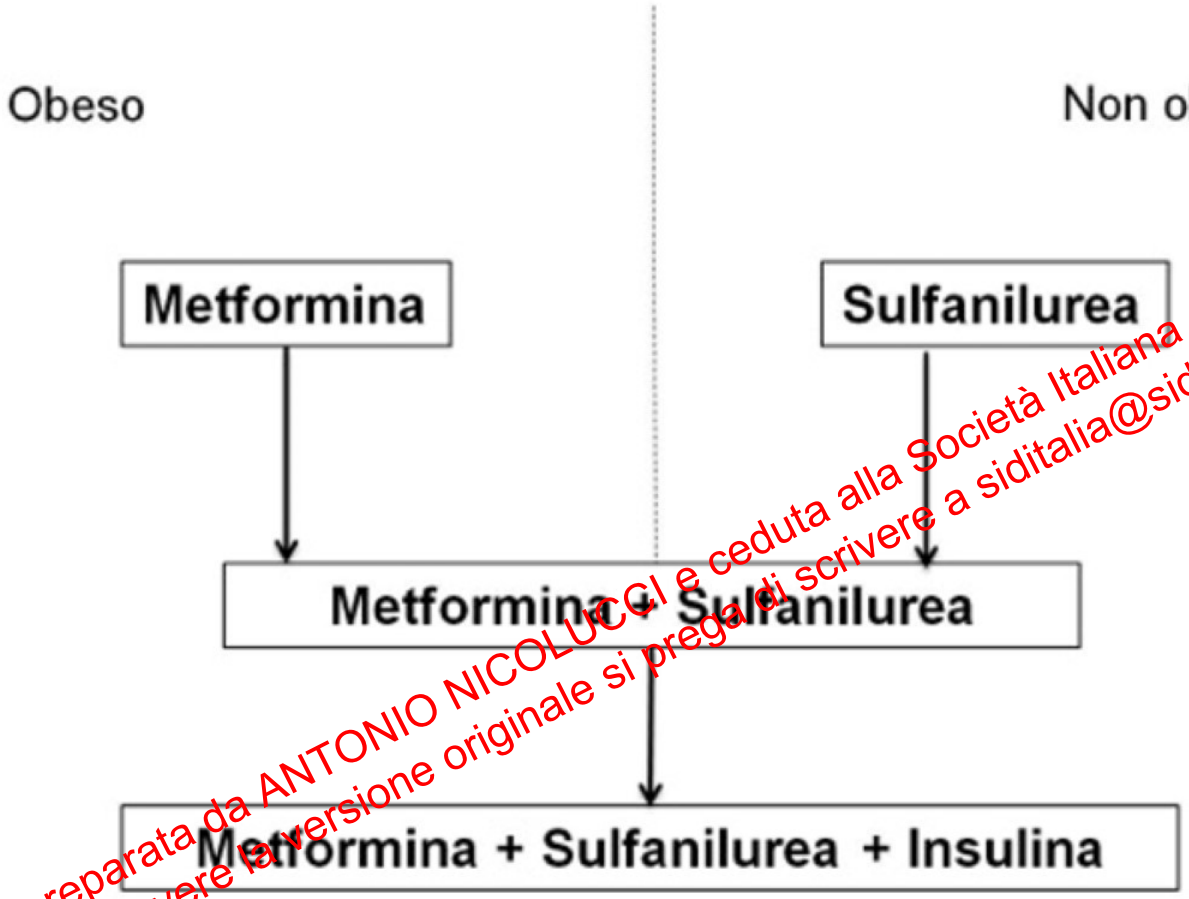
CORESEARCH
Center for Outcomes Research and Clinical Epidemiology

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

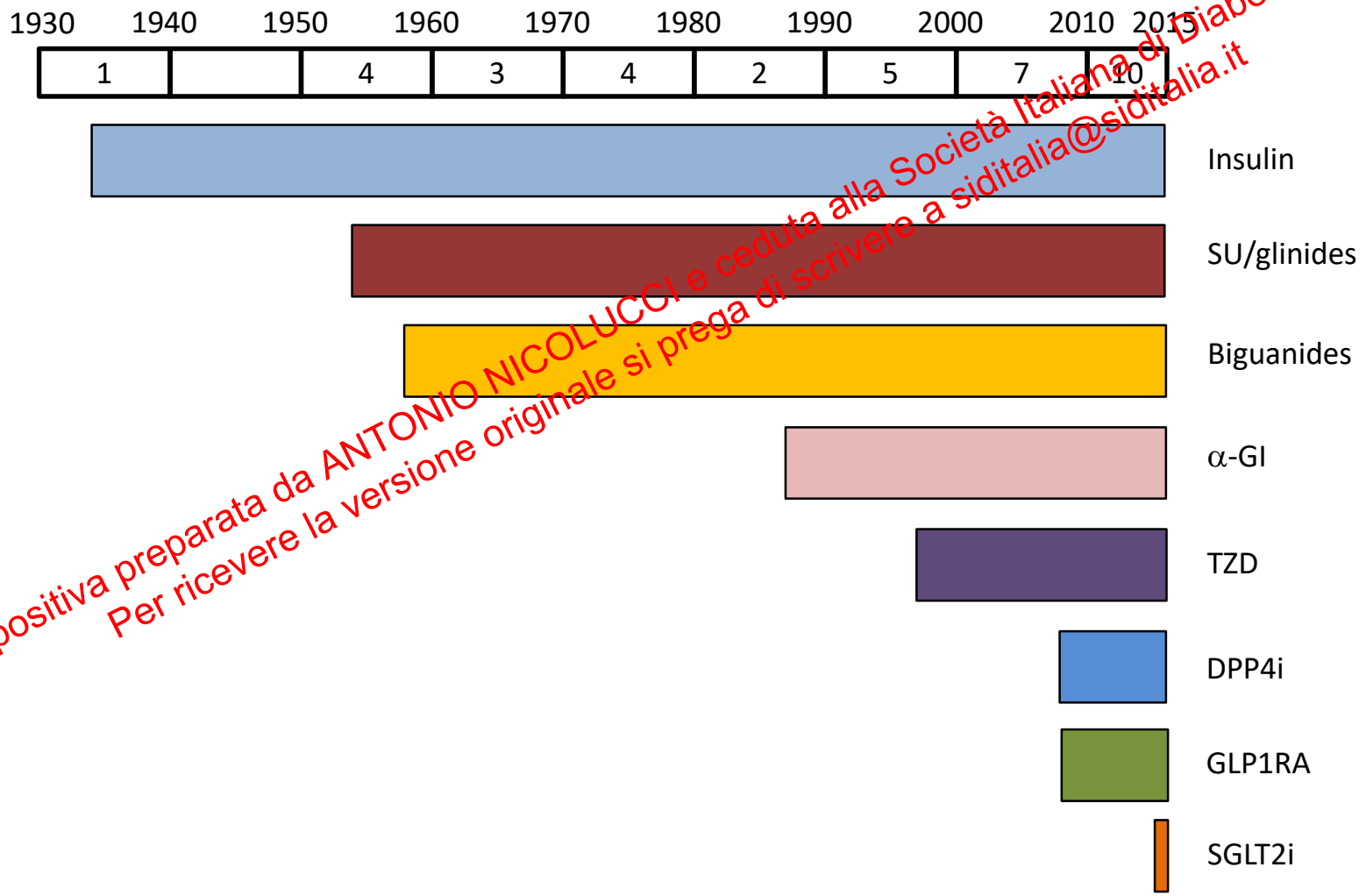
- Novo Nordisk
- Astra Zeneca
- Eli Lilly
- Sigma Tau
- Medtronic
- Dexcom
- Artsana
- Foracare

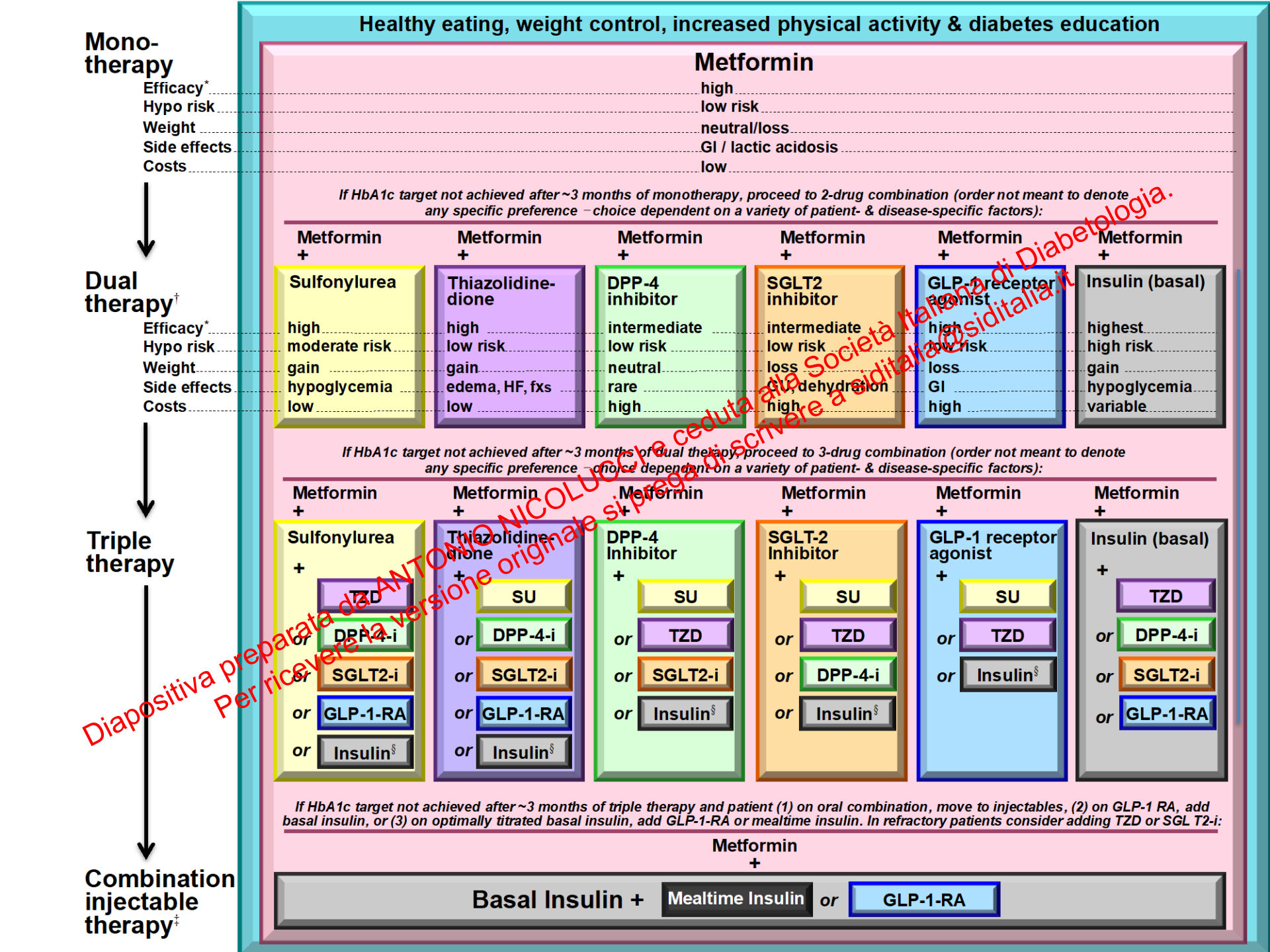





AMD, SID, SIMG, SIMI, SIF, SIGG, FAND, CeRGAS.
Progetto per l'organizzazione dell'assistenza al diabete dell'adulto.
Ed. Health Alliance S.r.L., Milano 1998.

# Drugs for T2DM





# T2DM Trials of More vs. Less Glucose Lowering

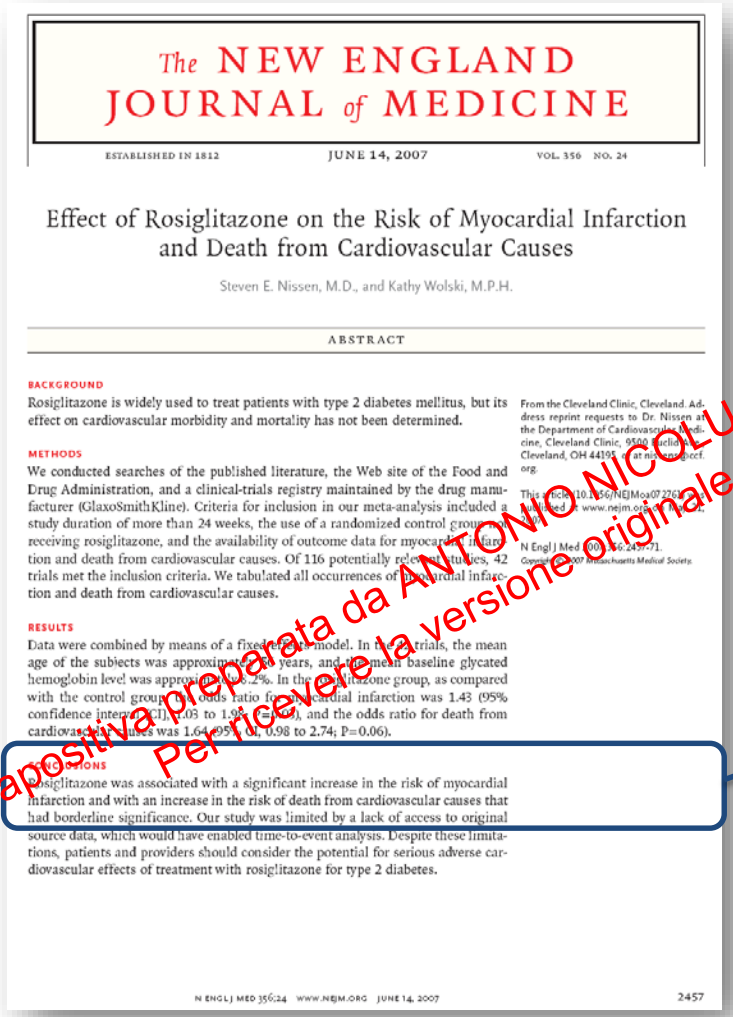
| Study | Duration (years) | N | Glycemia | |
|---|---|---|---|---|
| | | | Target | A1C achieved (%) |
| UKPDS[1] | 10 | 3,867 | FPG < 6 mmol/L | 7.0 vs. 7.9 |
| ACCORD[2] | 3.4 | 10,251 | A1C < 6.0% | 6.4 vs. 7.5 |
| ADVANCE[3] | 5 | 11,140 | A1C ≤ 6.5% | 6.5 vs. 7.3 |
| VADT[4] | 5.6 | 1,791 | A1C < 6.0% | 6.9 vs. 8.4 |



ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADVANCE, Action in Diabetes and Vascular disease: PreterAx and Diamicron MR Controlled Evaluation; UKPDS, UK Prospective Diabetes Study; VADT, Veterans Affairs Diabetes Trial

[1]UKPDS Group *Lancet* 1998;352:837-53; [2]Riddle et al *Diabetes Care* 2010;33:983-90; [3]Woodward et al *Diabetes Care* 2011;34:2491-5; [4]Duckworth et al *N Engl J Med* 2009;360:129-39

# The Rosiglitazone experience



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 14, 2007 VOL. 356 NO. 24

Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

Steven E. Nissen, M.D., and Kathy Wolski, M.P.H.

ABSTRACT

BACKGROUND

Rosiglitazone is widely used to treat patients with type 2 diabetes mellitus, but its effect on cardiovascular morbidity and mortality has not been determined.

METHODS

We conducted searches of the published literature, the Web site of the Food and Drug Administration, and a clinical-trials registry maintained by the drug manufacturer (GlaxoSmithKline). Criteria for inclusion in our meta-analysis included a study duration of more than 24 weeks, the use of a randomized control group receiving rosiglitazone, and the availability of outcome data for myocardial infarction and death from cardiovascular causes. Of 116 potentially relevant studies, 42 trials met the inclusion criteria. We tabulated all occurrences of myocardial infarction and death from cardiovascular causes.

RESULTS

Data were combined by means of a fixed-effects model. In these trials, the mean age of the subjects was approximately 55 years, and the mean baseline glycated hemoglobin level was approximately 8.2%. In the rosiglitazone group, as compared with the control groups, the odds ratio for myocardial infarction was 1.43 (95% confidence interval [CI], 1.03 to 1.98; P=0.03), and the odds ratio for death from cardiovascular causes was 1.64 (95% CI, 0.98 to 2.74; P=0.06).

CONCLUSIONS

Rosiglitazone was associated with a significant increase in the risk of myocardial infarction and with an increase in the risk of death from cardiovascular causes that had borderline significance. Our study was limited by a lack of access to original source data, which would have enabled time-to-event analysis. Despite these limitations, patients and providers should consider the potential for serious adverse cardiovascular effects of treatment with rosiglitazone for type 2 diabetes.

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This article (10.1056/NEJMoa072761) was published at www.nejm.org on May 21, 2007.

N Engl J Med 2007;356:2457-71.

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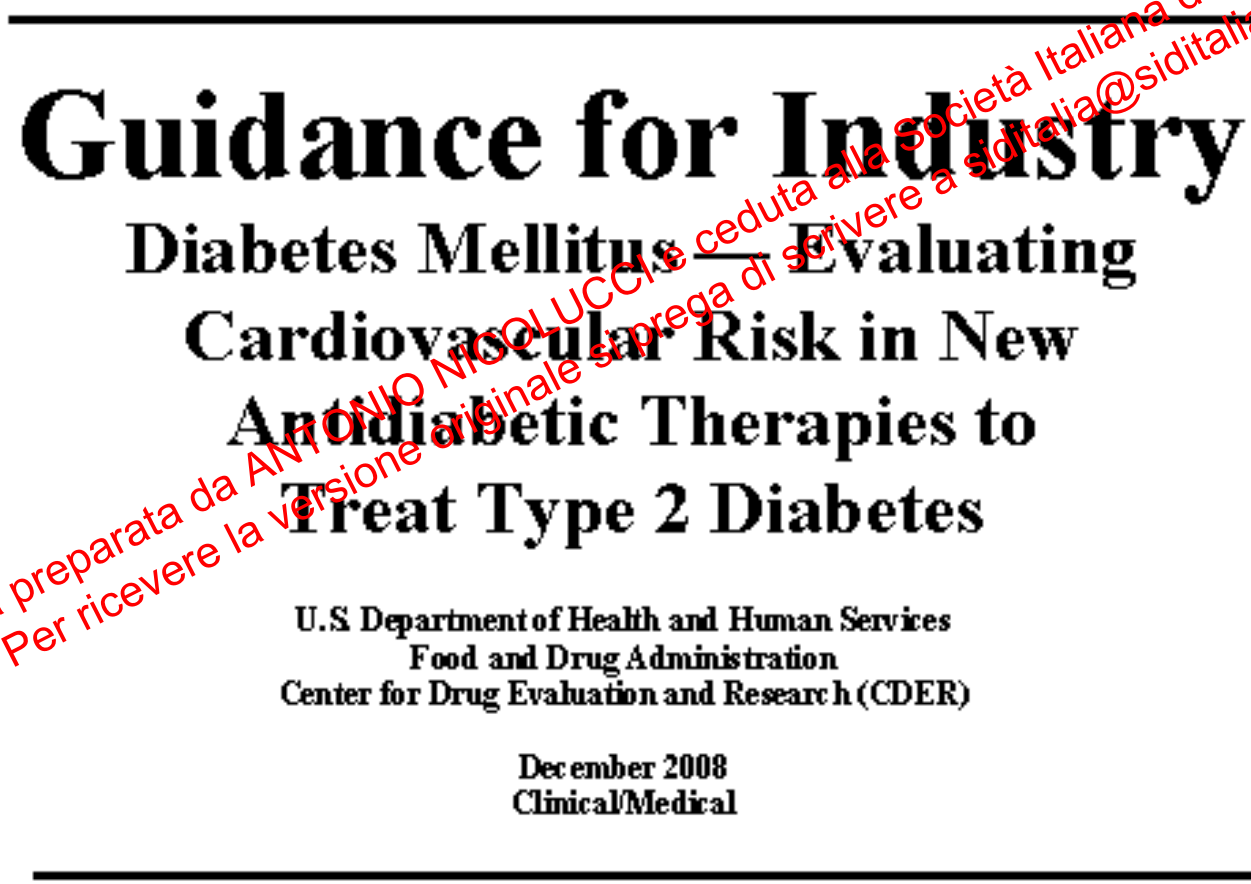
N ENGL J MED 356;24 WWW.NEJM.ORG JUNE 14, 2007 2457

*"Rosiglitazone was associated with a significant increase in the risk of myocardial infarction and with an increase in the risk of death from cardiovascular causes that had borderline significance."*

# 2008: the year of the paradigm shift



# Guidance for Industry

## Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

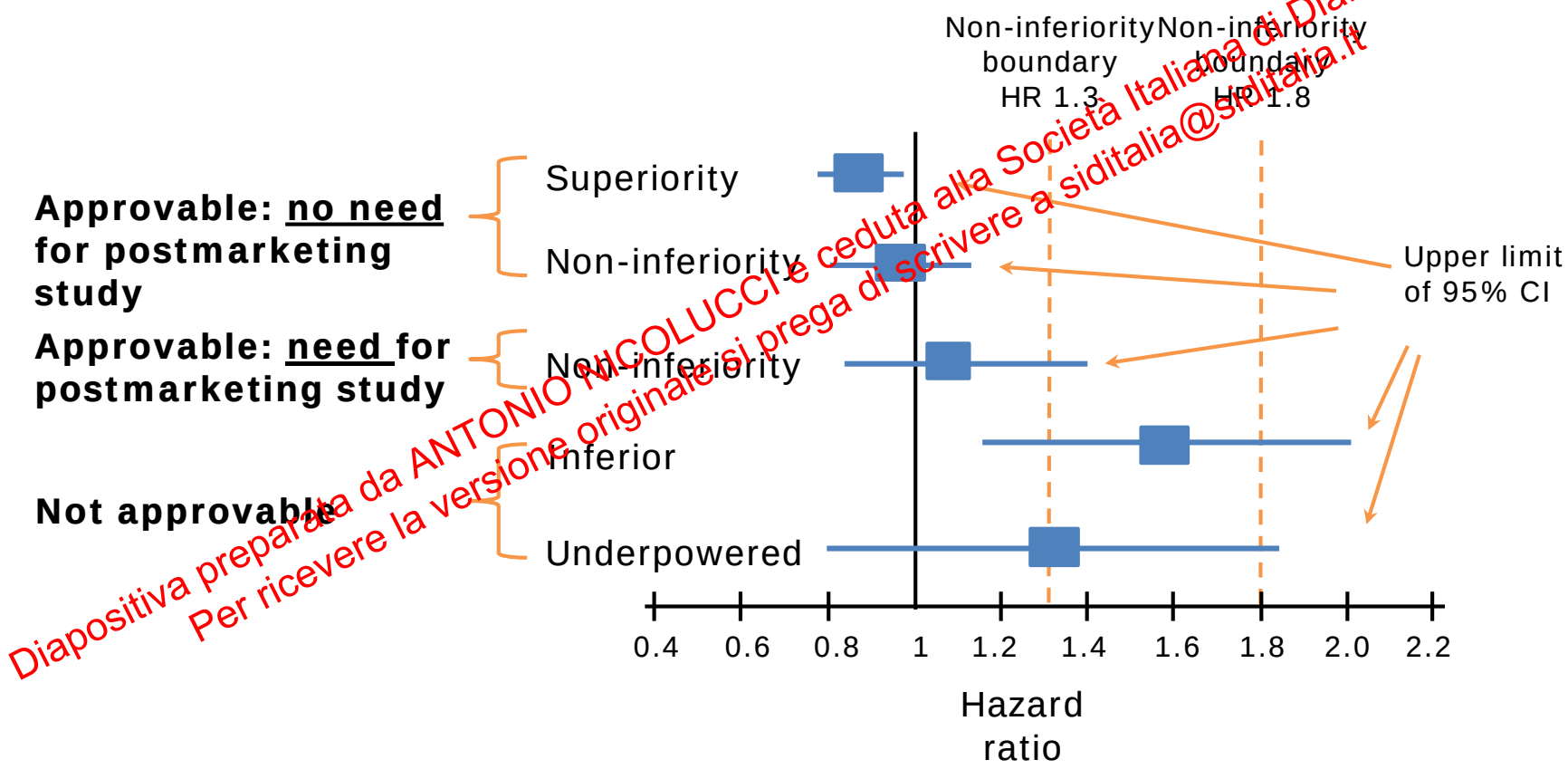
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

December 2008
Clinical/Medical

# Efficacy trials vs. safety trials

| | Efficacy trials | Safety trials |
|---|---|---|
| Aim | Demonstrate CV benefit | Demonstrate CV safety |
| Aim of treatment | Maximize HbA1c difference | Minimize HbA1c difference (equipoise) |
| Comparator | Usually active drug | Usually placebo |
| Study population | High proportion of patients without CVD/CKD | High proportion of patients with CVD/CKD |
| Primary endpoint | Heterogeneous | MACE |
| Study duration | Pre-specified | Event driven |
| Primary analysis | Superiority | Non inferiority |

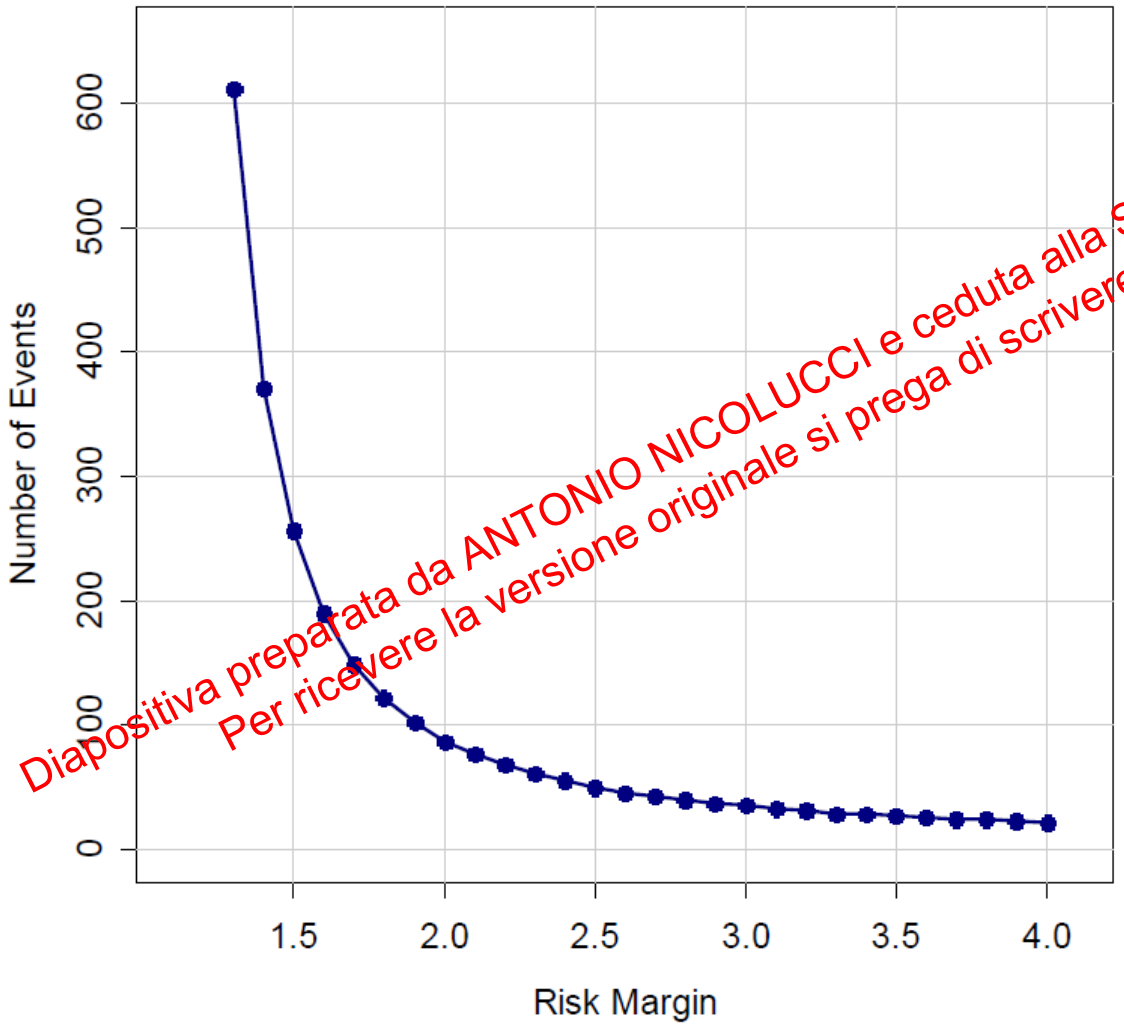
# FDA criteria for requirement of a postmarketing CV outcomes trial






Hirshberg B, Raz I. *Diabetes Obes Metab* 2011;34(Suppl. 2):S101–S106.

# Risk margin (Δ) impact






| Δ | D |
|---|---|
| 1.3 | 611 |
| 1.5 | 256 |
| 1.8 | 122 |
| 2.0 | 88 |
| 3.0 | 35 |
| 4.0 | 22 |

Assume: $\rho=1.0$, $Z_{\beta} = 1.28$,

$Z_{1-\alpha/2} = 1.96$

# Risk margin (Δ) impact

## Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

N Engl J Med 2015;373:2117-28

The primary hypothesis was noninferiority for the primary outcome with empagliflozin (pooled doses of 10 mg and 25 mg) versus placebo with a margin of **1.3** for the hazard ratio.

For the test of noninferiority for the primary outcome with a margin of 1.3 at a one-sided level of 0.0249, at least **691 events** were required to provide a power of at least 90% on the assumption of a true hazard ratio of 1.0.

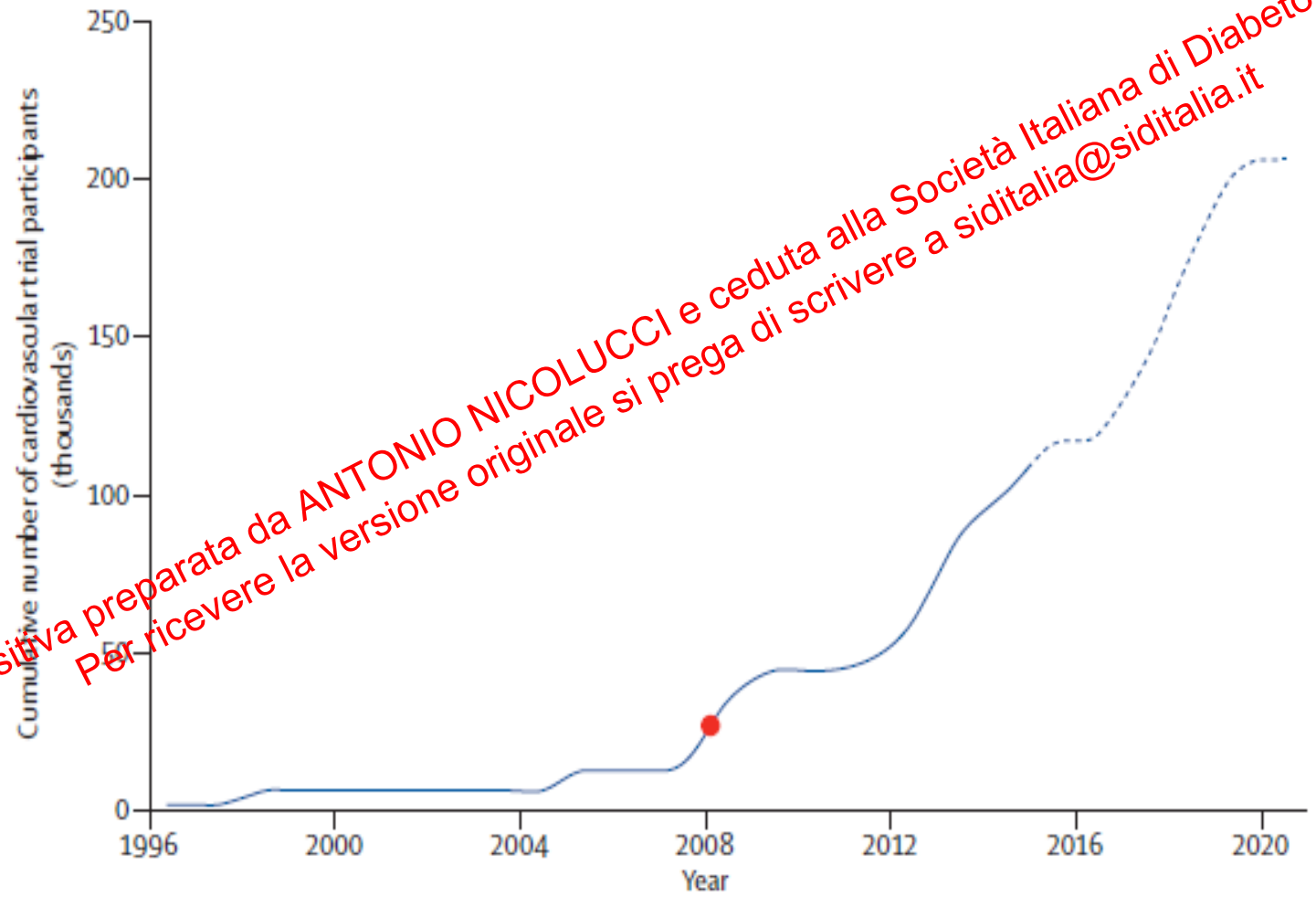
# Risk margin (Δ) impact

Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

The New England Journal of Medicine

We determined that the enrollment of 3260 patients would be required to determine the primary outcome in at least **122** patients and provide a power of 90% to reject a hazard ratio of at least **1.80** at the 0.05 level of significance.

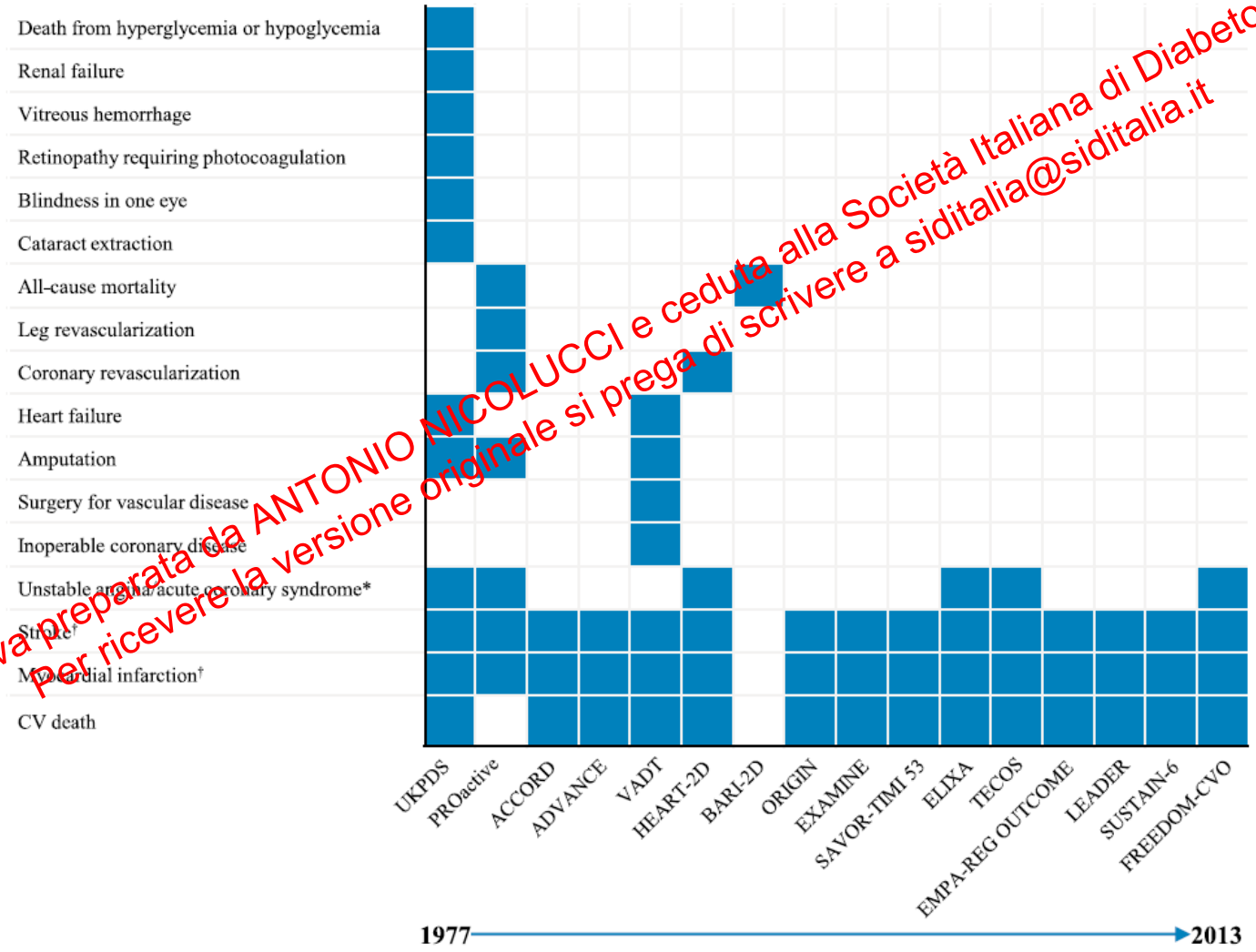
# Cumulative number of participants with diabetes in cardiovascular outcome trials over time






*Holman R et al The Lancet , 2014*

# Evolution of prospectively planned primary end points in completed CVOTs

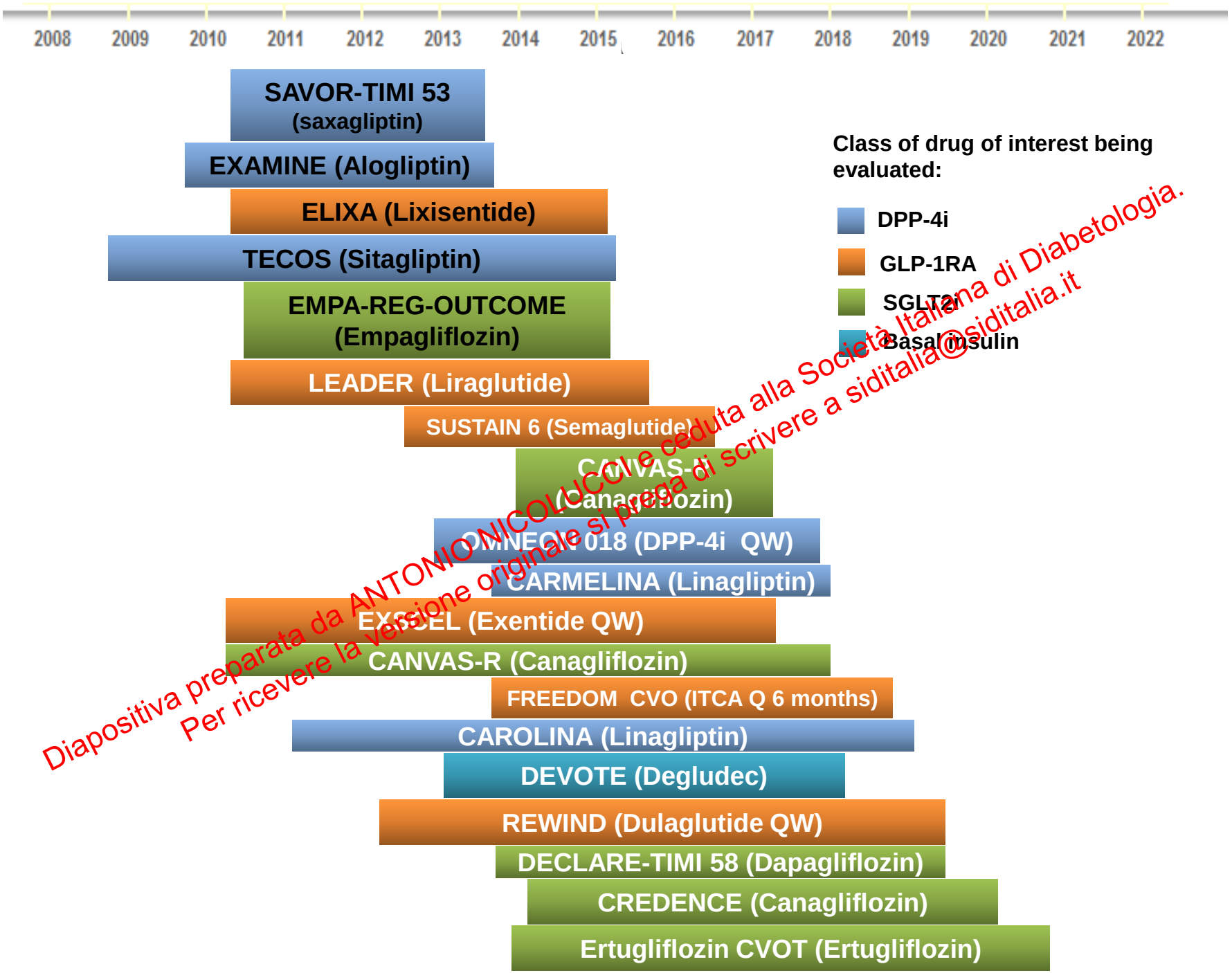




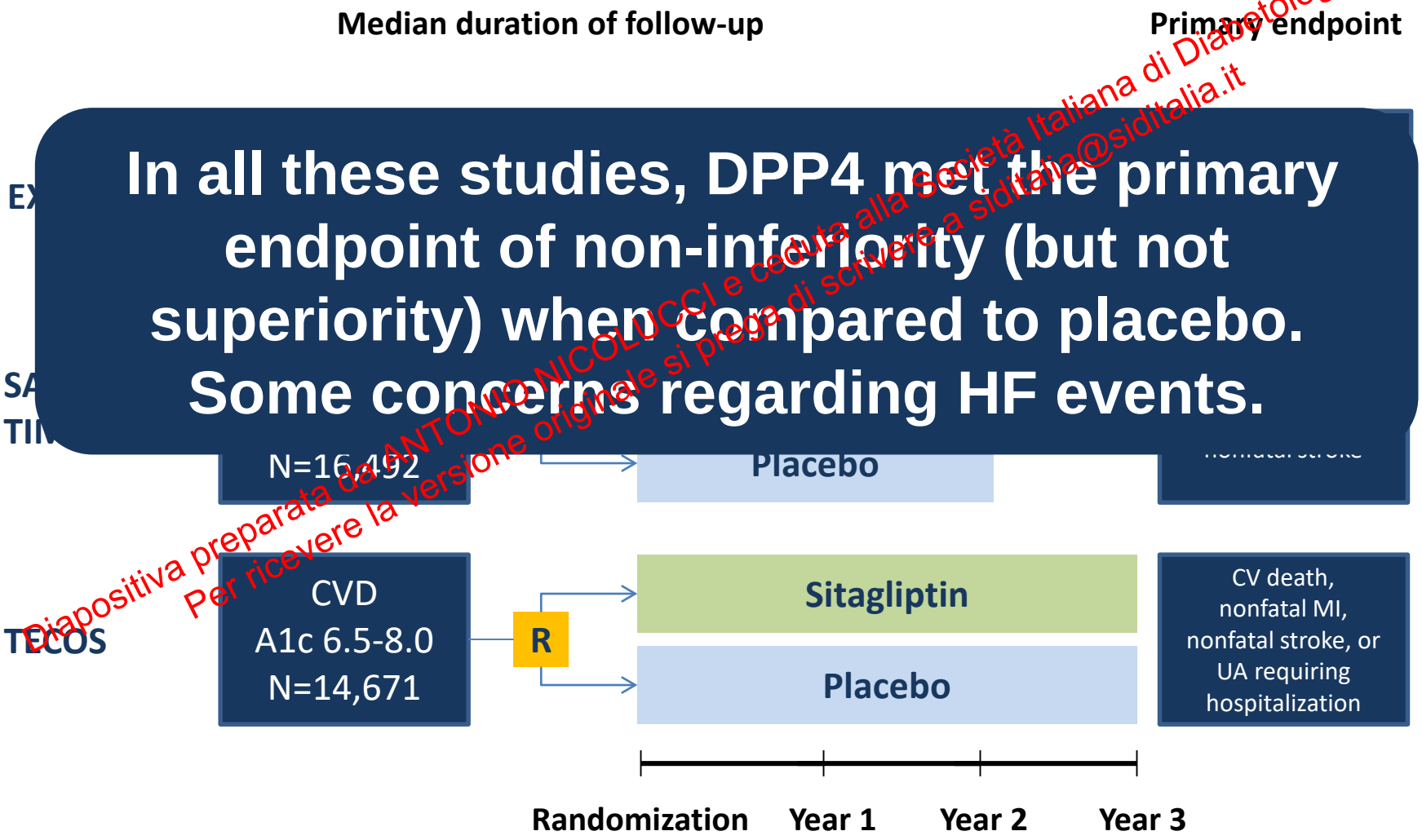

*Marx N et al Diabetes Care 2017*

# Global distribution of participants

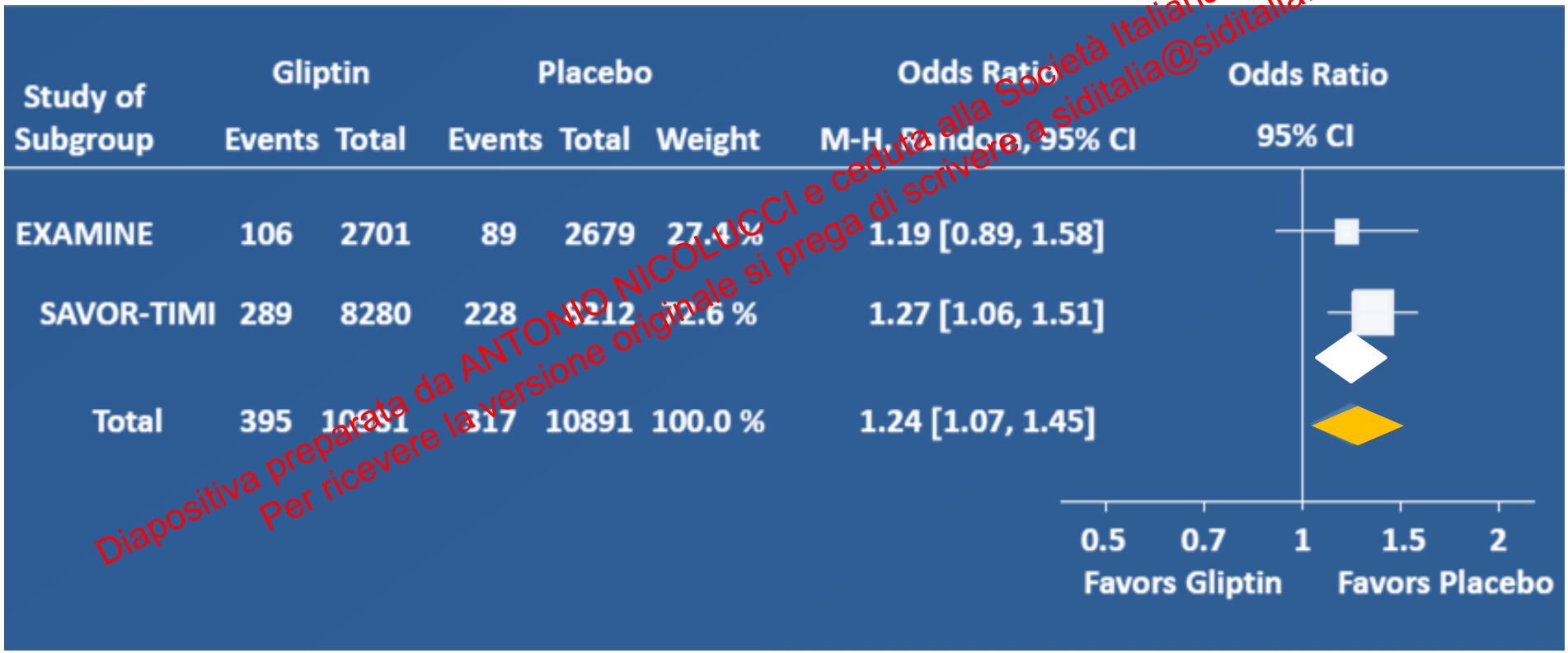
| Study | US/Canada | WE | EE | Middle East | Africa | Australasia | LatinAmerica |
|---|---|---|---|---|---|---|---|
| Pre-FDA Guidance | | | | | | | |
| ADVANCE | X | | X | | | X | |
| Proactive | | X | X | | | | |
| HEART2D | X | X | X | X | X | | |
| SPREADDIMCAD | | | | | | | |
| Aleglitazar(term.) | | | | | | | |
| Acarbose | | | | | | X | |
| Phantom | X | | | | | | |
| RECORD | | X | X | | | X | |
| Post-FDA Guidance | | | | | | | |
| TOSCA-IT | | X | | | | | |
| TECOS | X | X | X | X | X | X | X |
| ACE | | | | | | X | |
| EXAMINE | X | X | X | X | X | X | X |
| TIDE | | X | X | X | X | X | X |
| SAVOR-TIMI53 | X | X | X | X | X | X | X |
| EXSCEL | X | X | X | X | | X | X |
| ELIXA | X | X | X | X | X | X | X |
| LEADER | X | X | X | X | X | X | X |
| CAROLINA | X | X | X | X | X | X | X |
| Taspog | X | X | X | X | X | X | X |
| CANVAS | X | X | X | X | | X | X |
| BI10773 | X | X | X | X | X | X | X |
| AAA | | | | | | X | |
| RASCIN | X | | | | | | |
| ALECARDIO | X | X | X | X | | X | X |



# CVOTs on DPP-4i



# DPP-4 inhibitors: Meta-analysis of HF hospitalizations in SAVOR-TIMI 53 and EXAMINE



# Hospitalization for Heart Failure*
# ITT Population

| Numbers of patients with events | Sitagliptin n=7332 | Placebo n=7339 |
|---|---|---|
| **Hospitalization for heart failure†** | **228 (3.1%)** | **229 (3.1%)** |
| | 1.07 *per* 100 pyrs | 1.09 *per* 100 pyrs |
| | **ITT HR=1.00 (0.83, 1.20), p=0.98** | |
| | | |
| **Hospitalization for heart failure or cardiovascular death†** | **538 (7.3%)** | **525 (7.2%)** |
| | 2.54 *per* 100 pyrs | 2.50 *per* 100 pyrs |
| | **ITT HR=1.02, (0.90, 1.15), p=0.74** | |



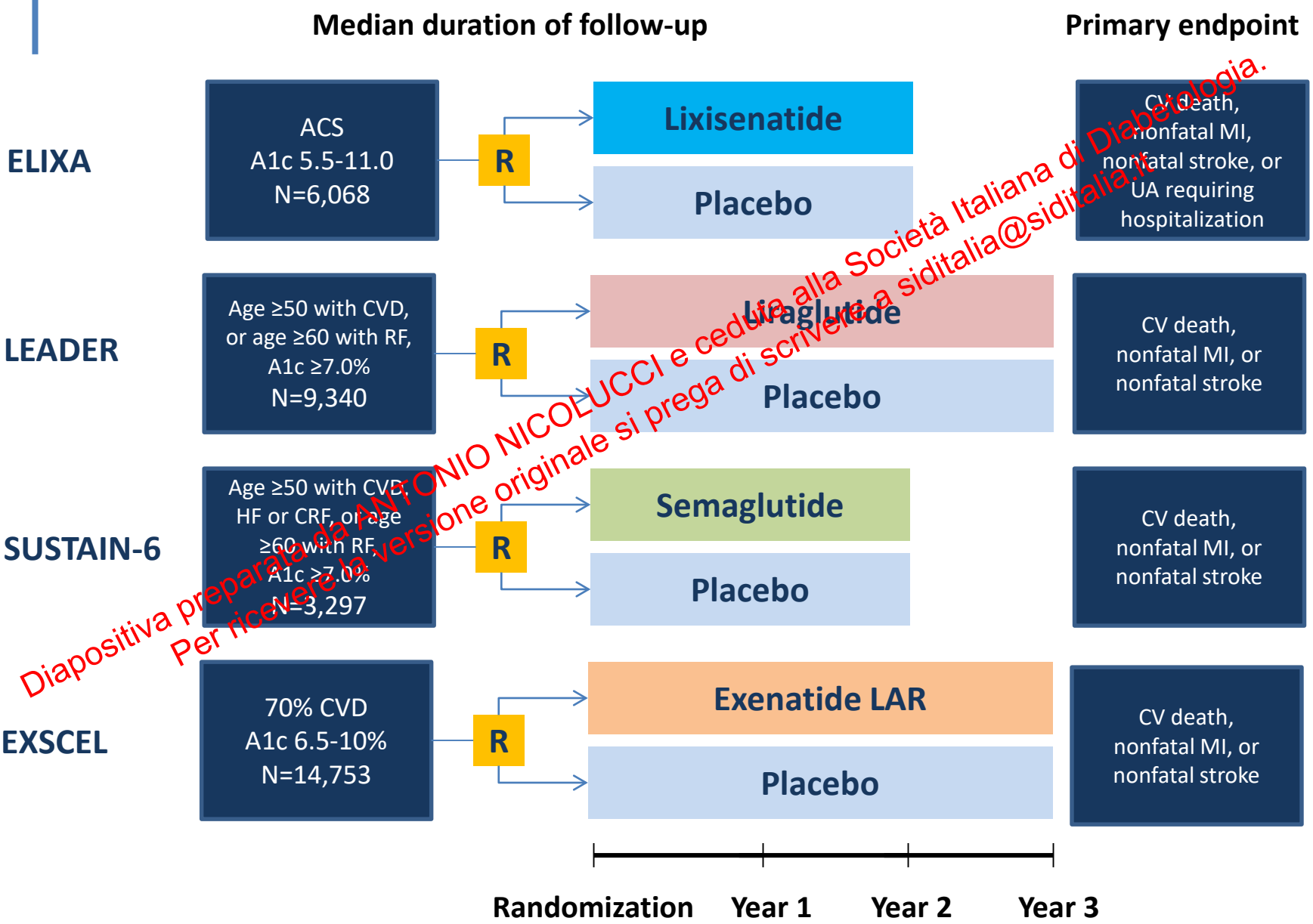
* *Adjusted for history of heart failure at baseline*

† *Prespecified analyses*

*Green JB et al. NEJM 2015*

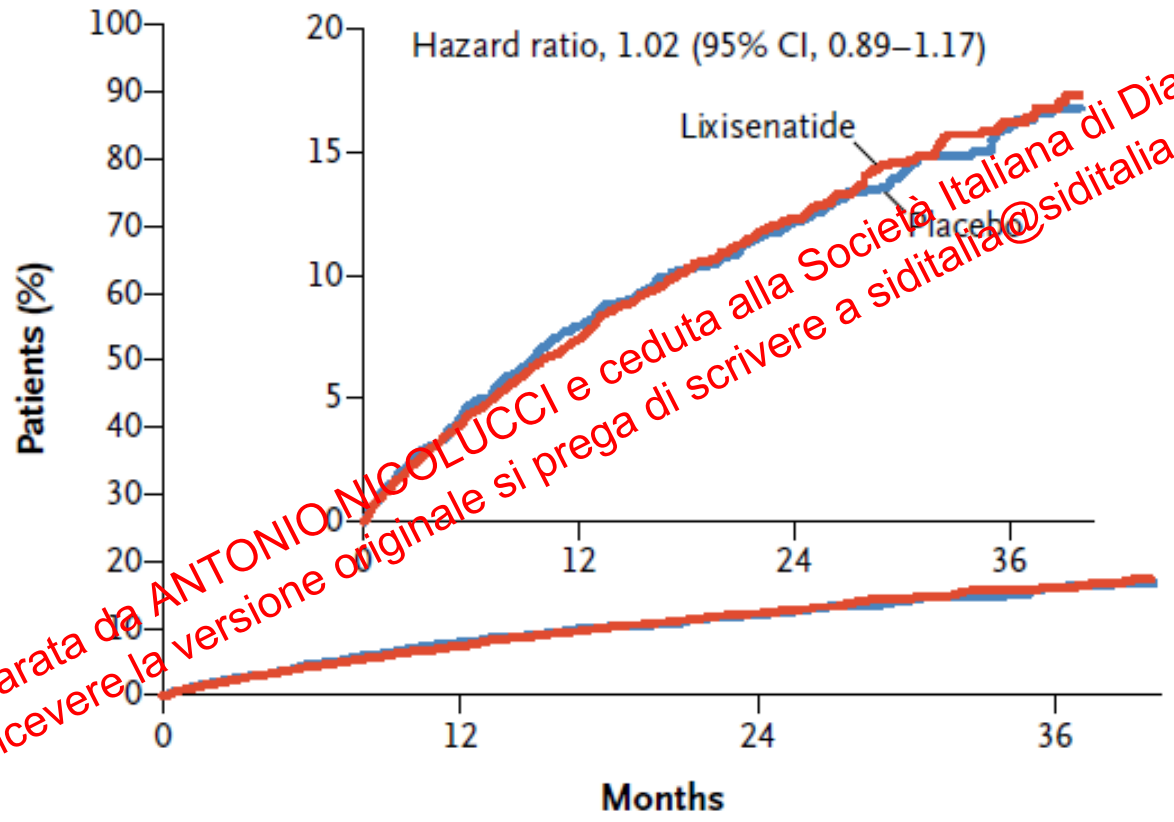
TRIAL EVALUATING CARDIOVASCULAR TECOS OUTCOMES WITH SITAGLIPTIN

# CVOTs on GLP-1 ra



# Primary outcome

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




| No. at Risk | | | | |
|---|---|---|---|---|
| Placebo | 3034 | 2759 | 1566 | 476 |
| Lixisenatide | 3034 | 2785 | 1558 | 484 |

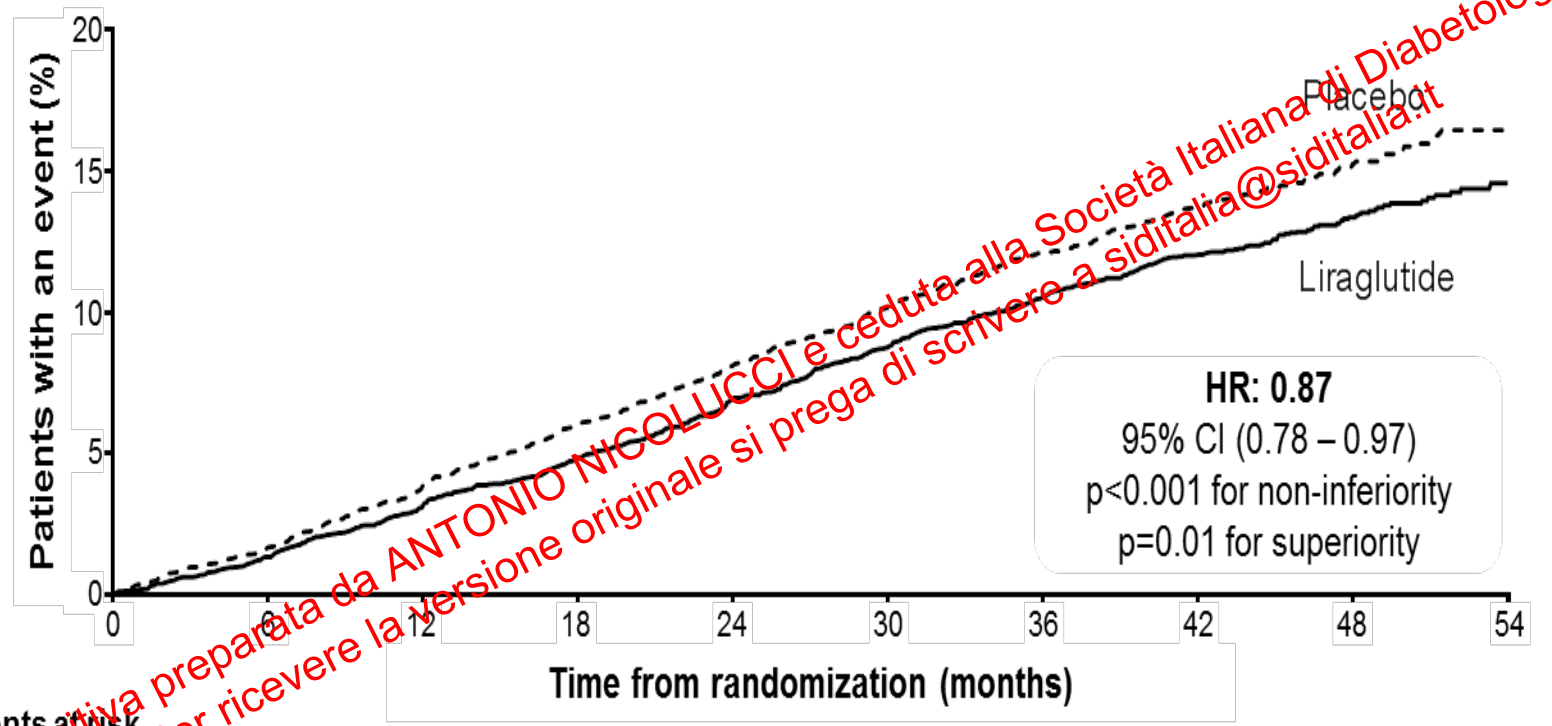


**ELIXA trial**

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

# 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 |

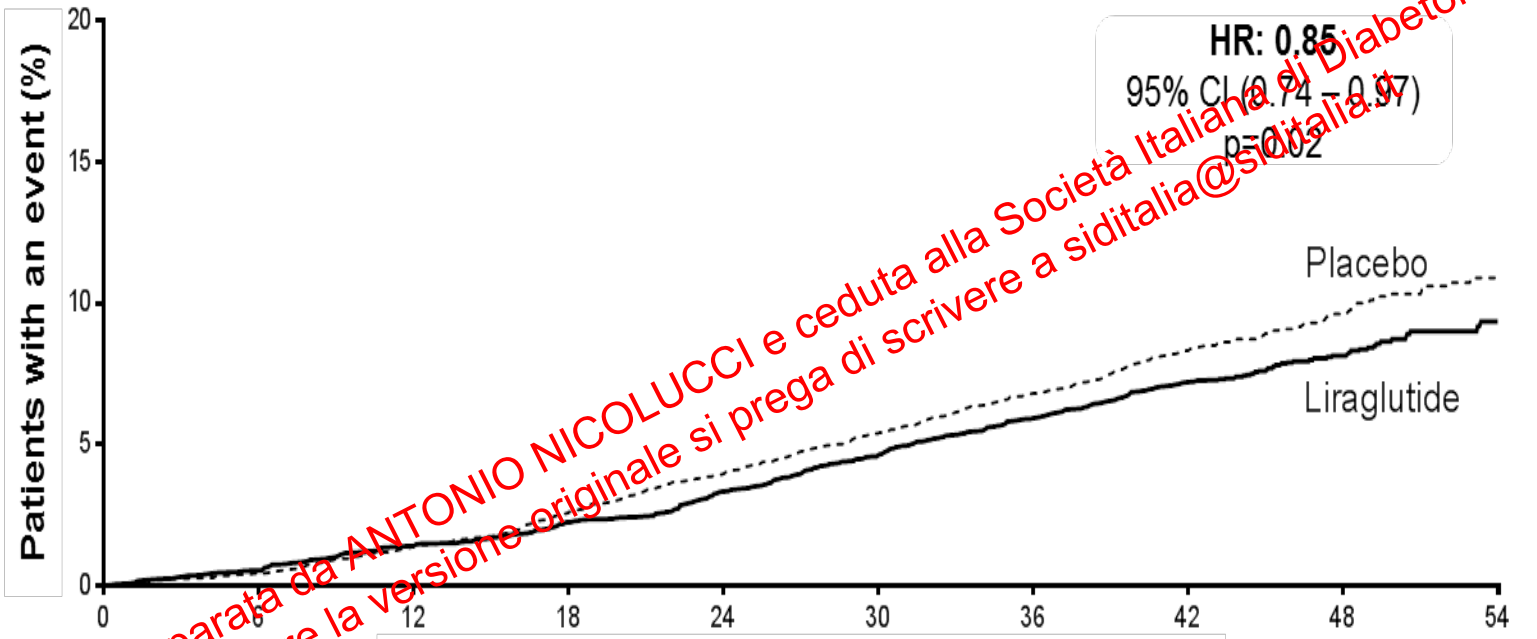


LEADER

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.

Presented at the American Diabetes Association 76th Scientific Sessions, Session 3-CT-SY24. June 13 2016, New Orleans, LA, USA.

# All-cause mortality




| Patients at risk | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Liraglutide | 4668 | 4641 | 4599 | 4558 | 4505 | 4445 | 4382 | 4322 | 1723 | 484 |
| Placebo | 4672 | 4648 | 4601 | 4546 | 4479 | 4407 | 4338 | 4268 | 1709 | 465 |



LEADER

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; HR: hazard ratio.

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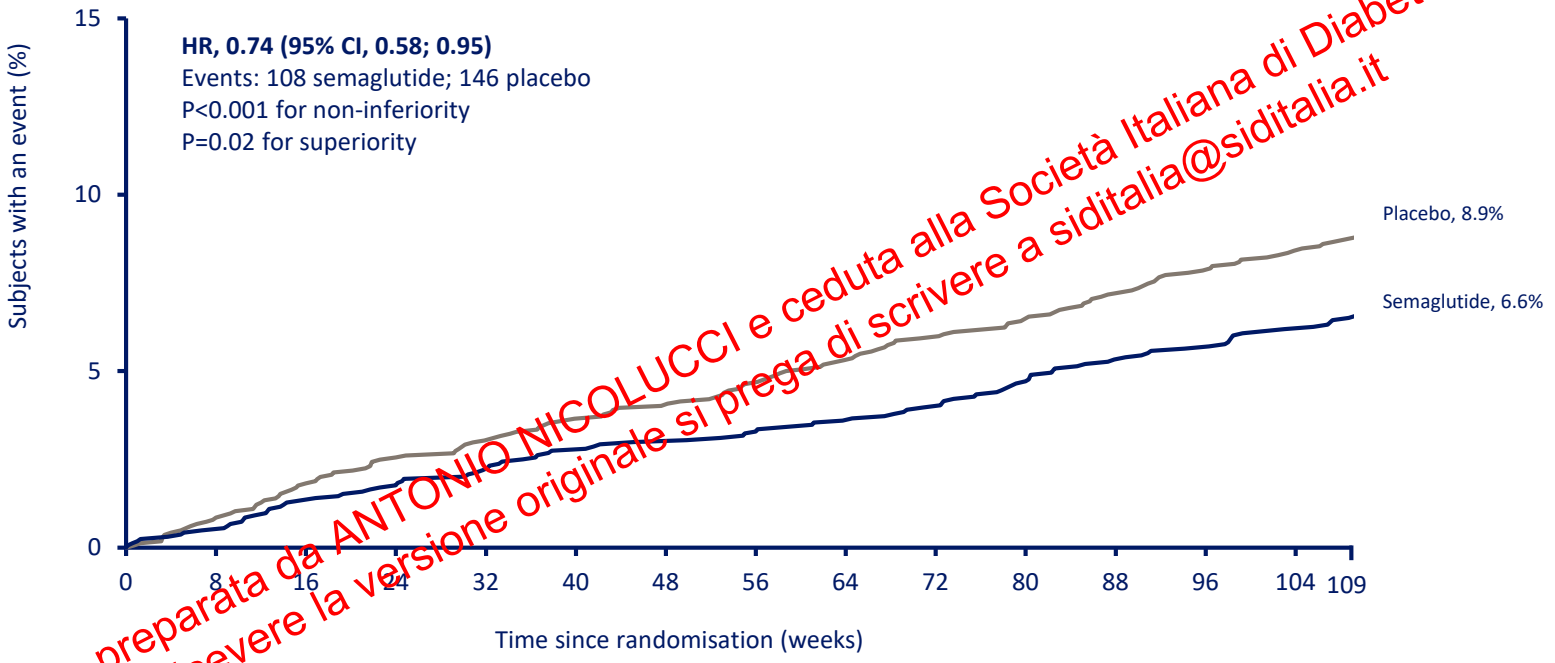
# Primary outcome

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






**Number of subjects at risk**

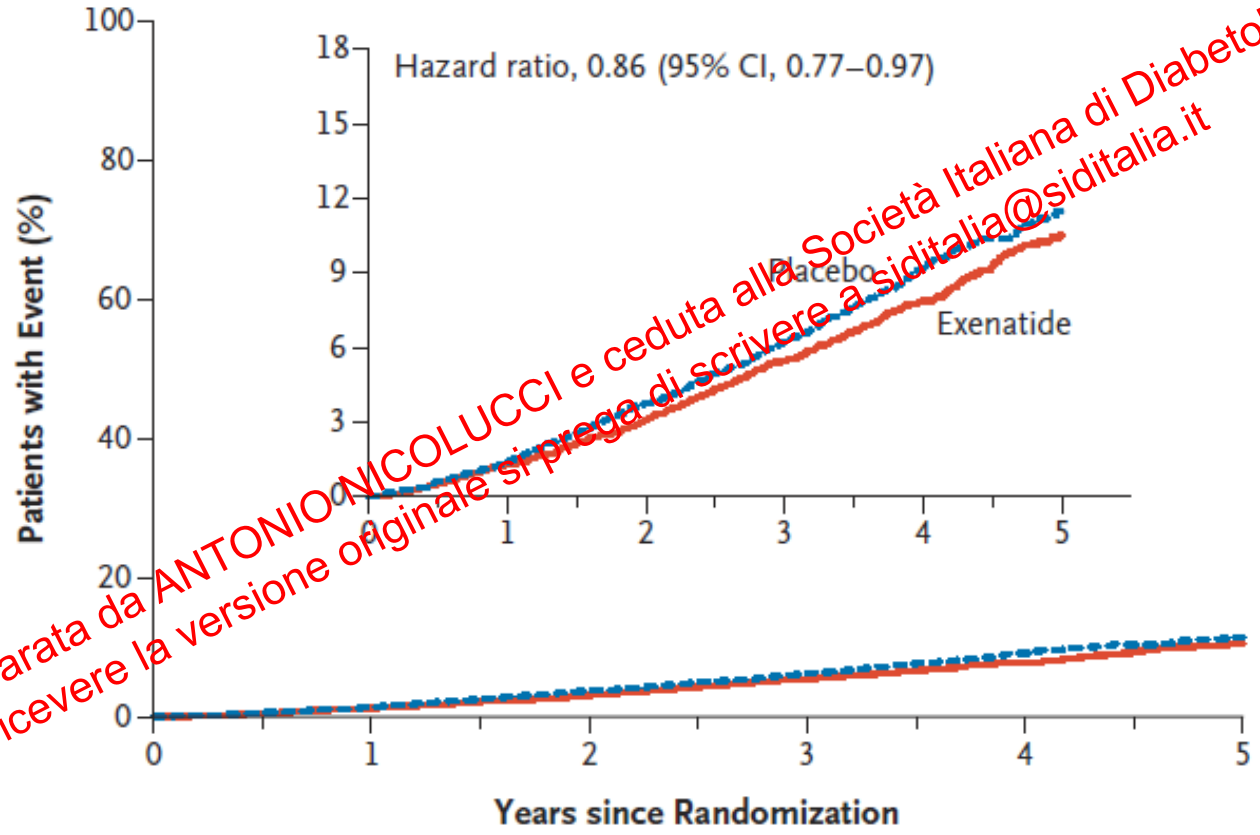
| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Semaglutide** | **1648** | **1619** | **1601** | **1584** | **1568** | **1543** | **1524** | **1513** |
| Placebo | 1649 | 1616 | 1586 | 1567 | 1534 | 1508 | 1479 | 1466 |

**SUSTAIN-6 trial**

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

# All-cause mortality

*ITT analysis*




| No. at Risk | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Placebo | 7396 | 7344 | 7278 | 7058 | 6470 | 5019 | 4091 | 3478 | 2666 | 1695 | 892 |
| Exenatide | 7356 | 7304 | 7234 | 7028 | 6433 | 4991 | 4095 | 3518 | 2698 | 1726 | 907 |

# Meta-analysis on GLP1 RA

## MACE-3

| Study name | Hazard ratio | Lower limit | Upper limit | Z-Value | p-Value |
|---|---|---|---|---|---|
| EXSCEL | 0.91 | 0.83 | 1.00 | -1.87 | 0.061 |
| LEADER | 0.87 | 0.78 | 0.97 | -2.43 | 0.015 |
| SUSTAIN-6 | 0.74 | 0.58 | 0.95 | -2.41 | 0.016 |
| | 0.88 | 0.81 | 0.95 | -3.12 | 0.002 |

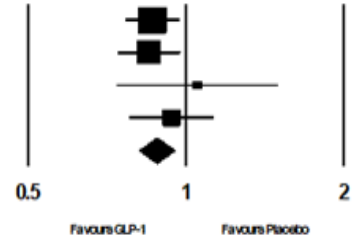

Meta Analysis

$I^2$: 22%, Q-test p value: 0.28



## All Cause Mortality

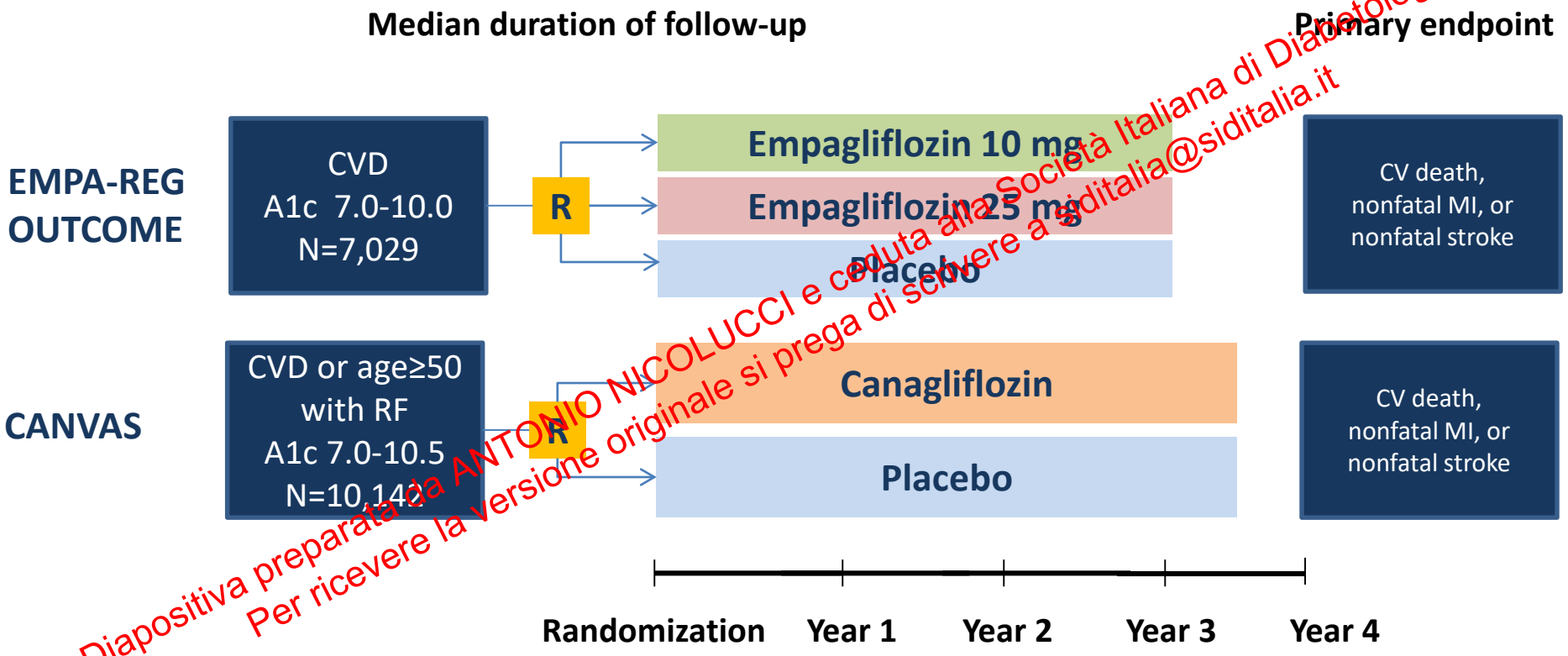
| Study name | Hazard ratio | Lower limit | Upper limit | Z-Value | p-Value |
|---|---|---|---|---|---|
| EXSCEL | 0.86 | 0.77 | 0.97 | -2.42 | 0.016 |
| LEADER | 0.85 | 0.74 | 0.97 | -2.32 | 0.020 |
| SUSTAIN-6 | 1.05 | 0.74 | 1.50 | 0.27 | 0.787 |
| ELIXA | 0.94 | 0.78 | 1.13 | -0.67 | 0.501 |
| | 0.88 | 0.81 | 0.95 | -3.16 | 0.002 |




Meta Analysis

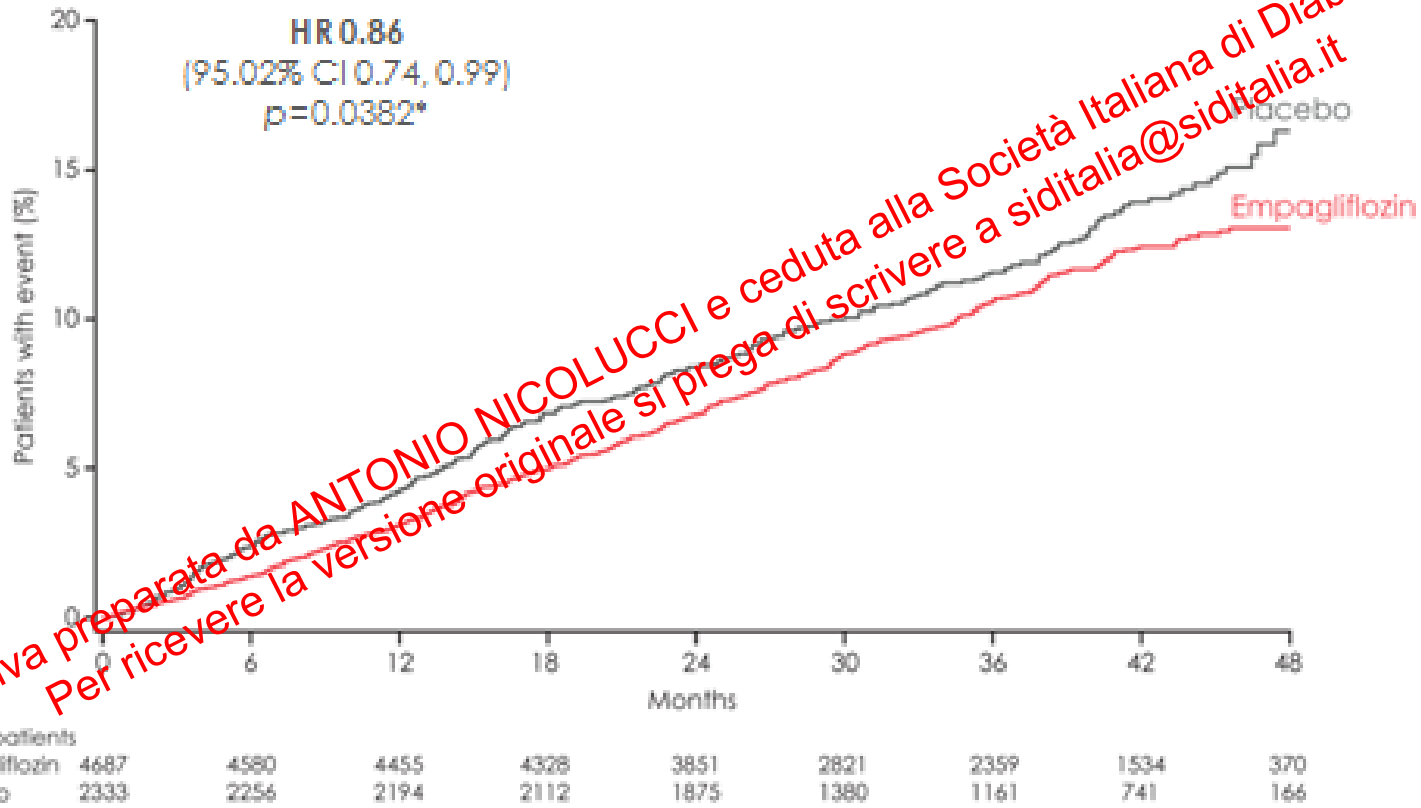
$I^2$: 0%, Q-test p value: 0.63

# CVOTs on SGLT2i



# Primary outcome

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



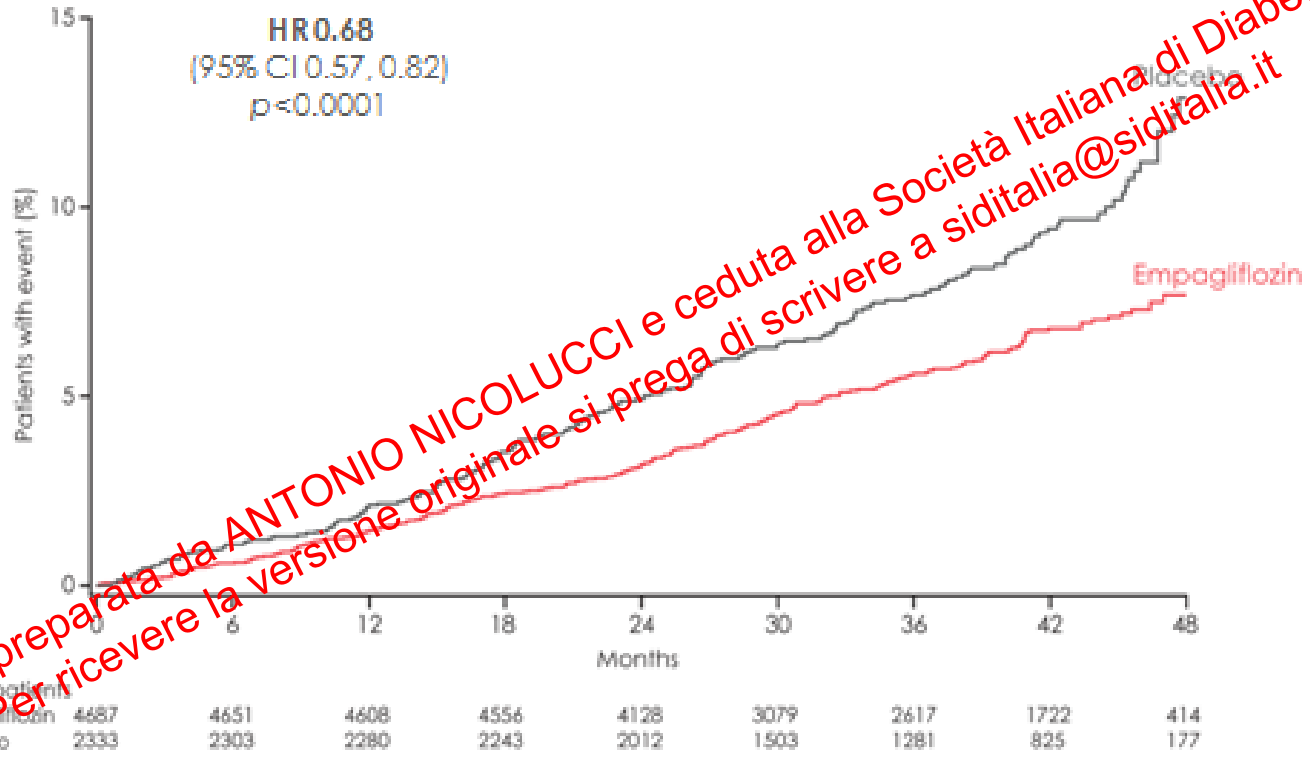



Cumulative incidence function. MACE, Major Adverse Cardiovascular Event; HR, hazard ratio.
* Two-sided tests for superiority were conducted (statistical significance was indicated if p≤0.0498)

*Zinman et al N Engl J Med 2015;Sep 17 [Epub ahead of print]*

EMPA-REG OUTCOME®

# All-cause mortality




Kaplan-Meier estimate. HR, hazard ratio

Zinman et al N Engl J Med 2015;Sep 17 [Epub ahead of print]

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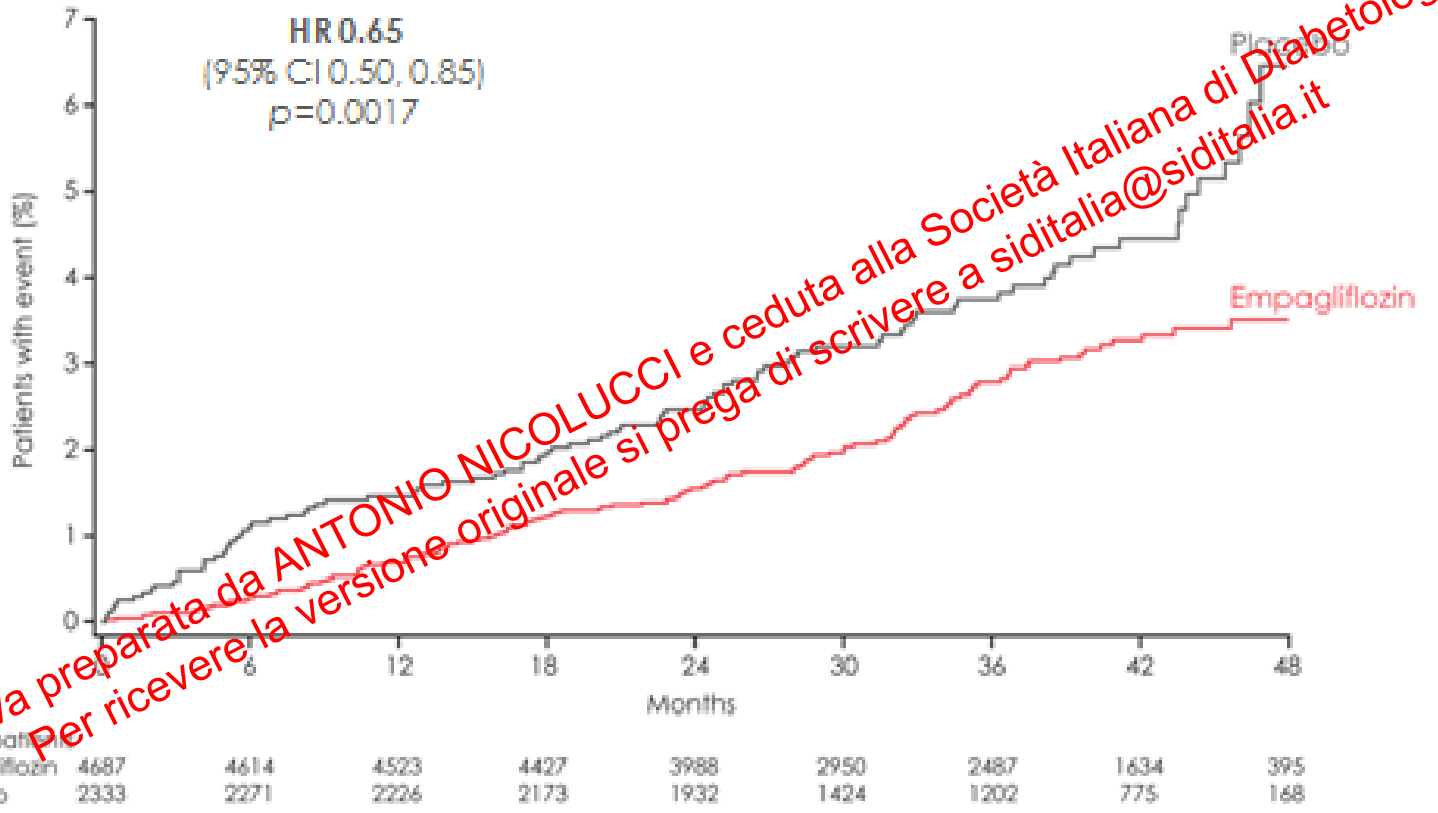
# Hospitalization for heart failure






Cumulative incidence function. HR, hazard ratio

From: https://s3-eu-west-1.amazonaws.com/mevents/easd/empa-reg-slide-kit.pptx

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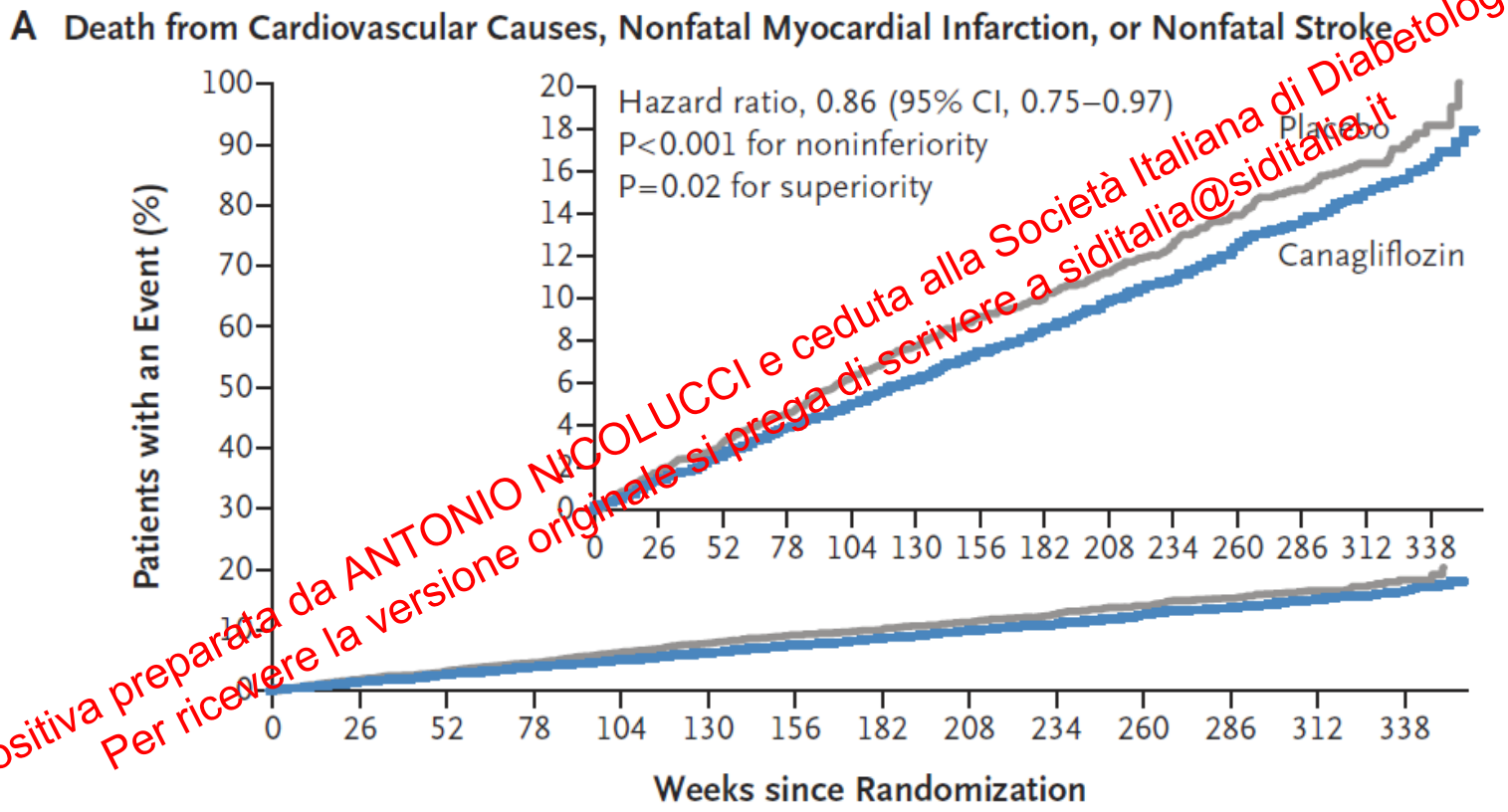
# Primary outcome

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

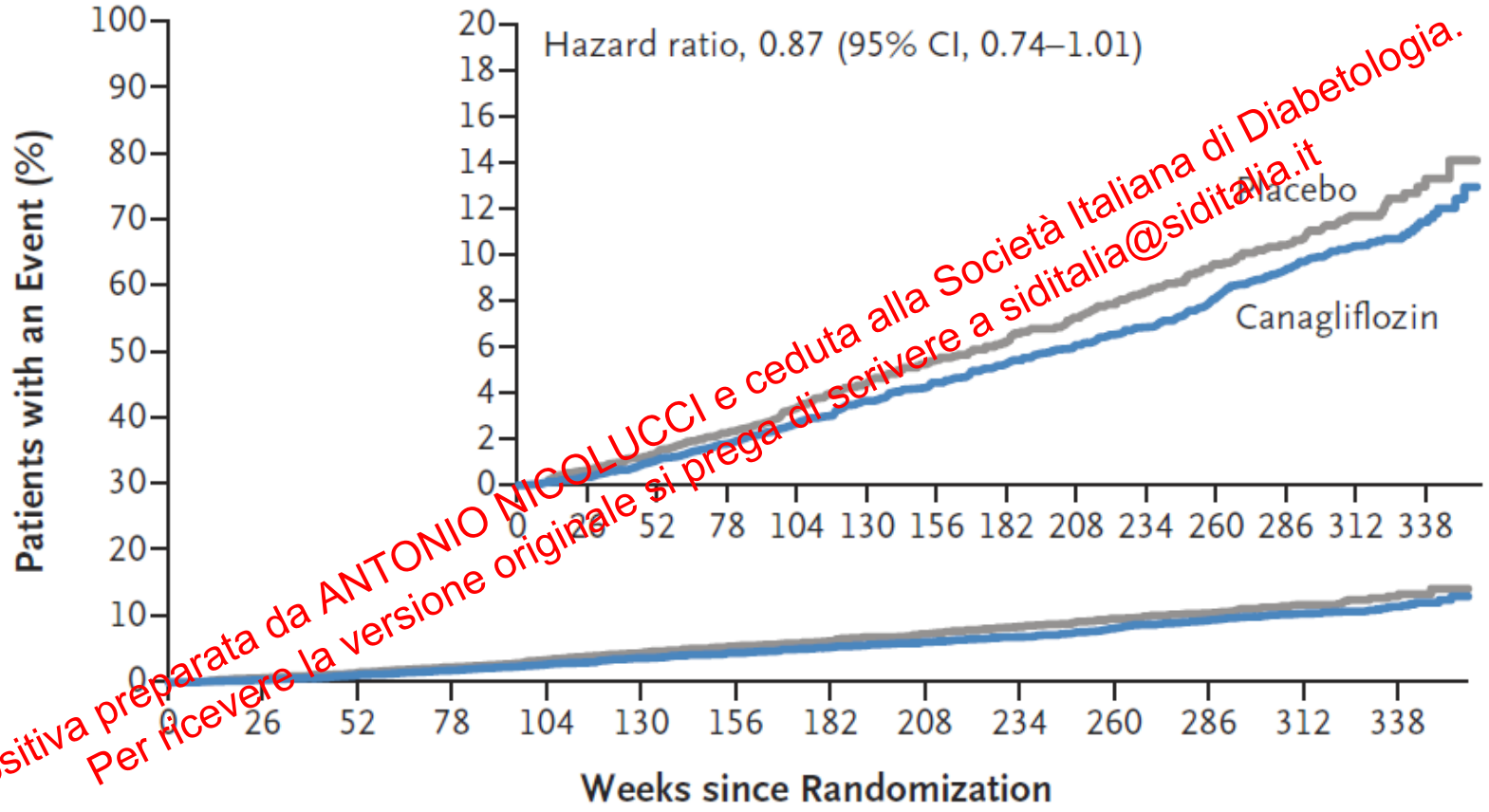





**CANVAS trial**

*N Engl J Med 2017;377:644-57*

# All-cause mortality





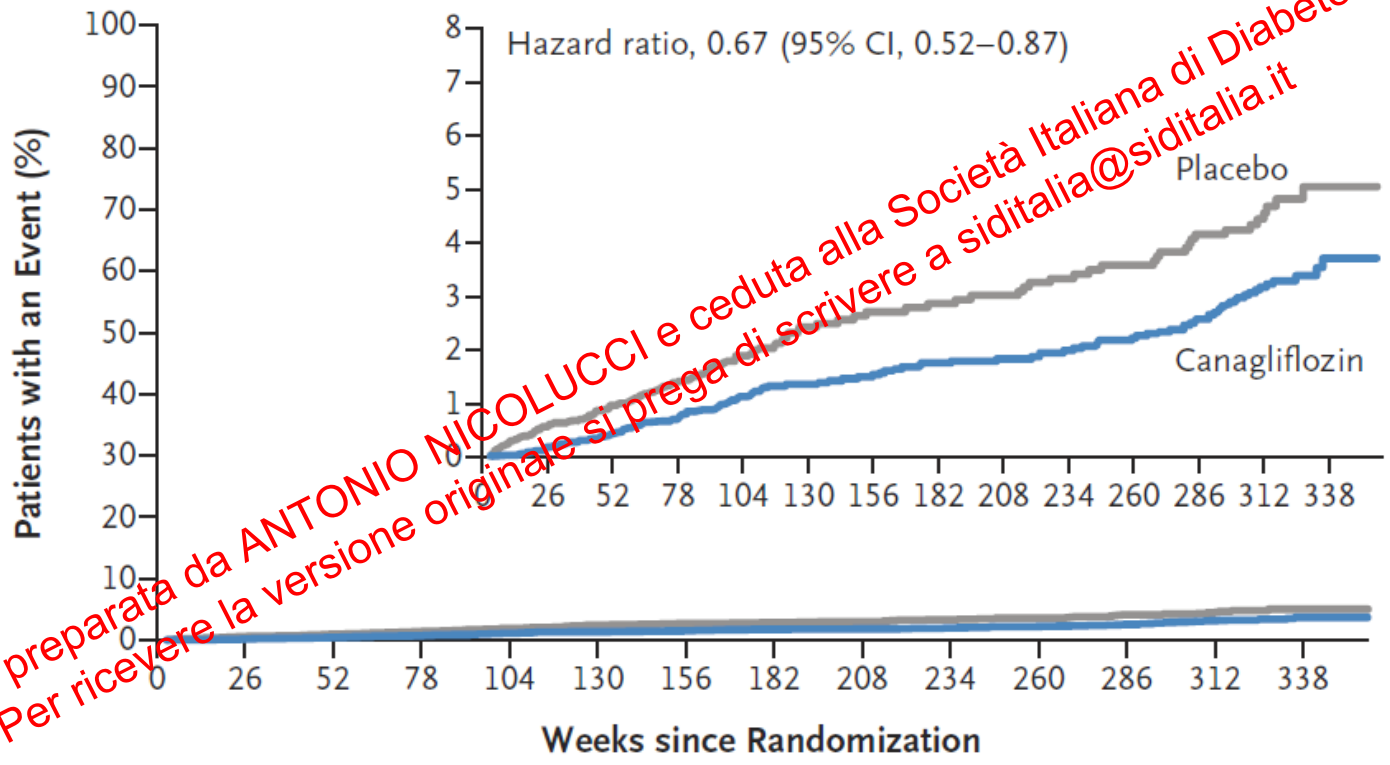

**No. at Risk**

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Placebo | 4347 | 4316 | 4279 | 4236 | 3119 | 1759 | 1356 | 1344 | 1328 | 1310 | 1292 | 1280 | 924 | 258 |
| Canagliflozin | 5795 | 5768 | 5723 | 5679 | 4576 | 3182 | 2761 | 2736 | 2710 | 2687 | 2651 | 2615 | 1904 | 532 |

**CANVAS trial**

*N Engl J Med 2017;377:644-57*

# Hospitalization for hearth failure




**No. at Risk**

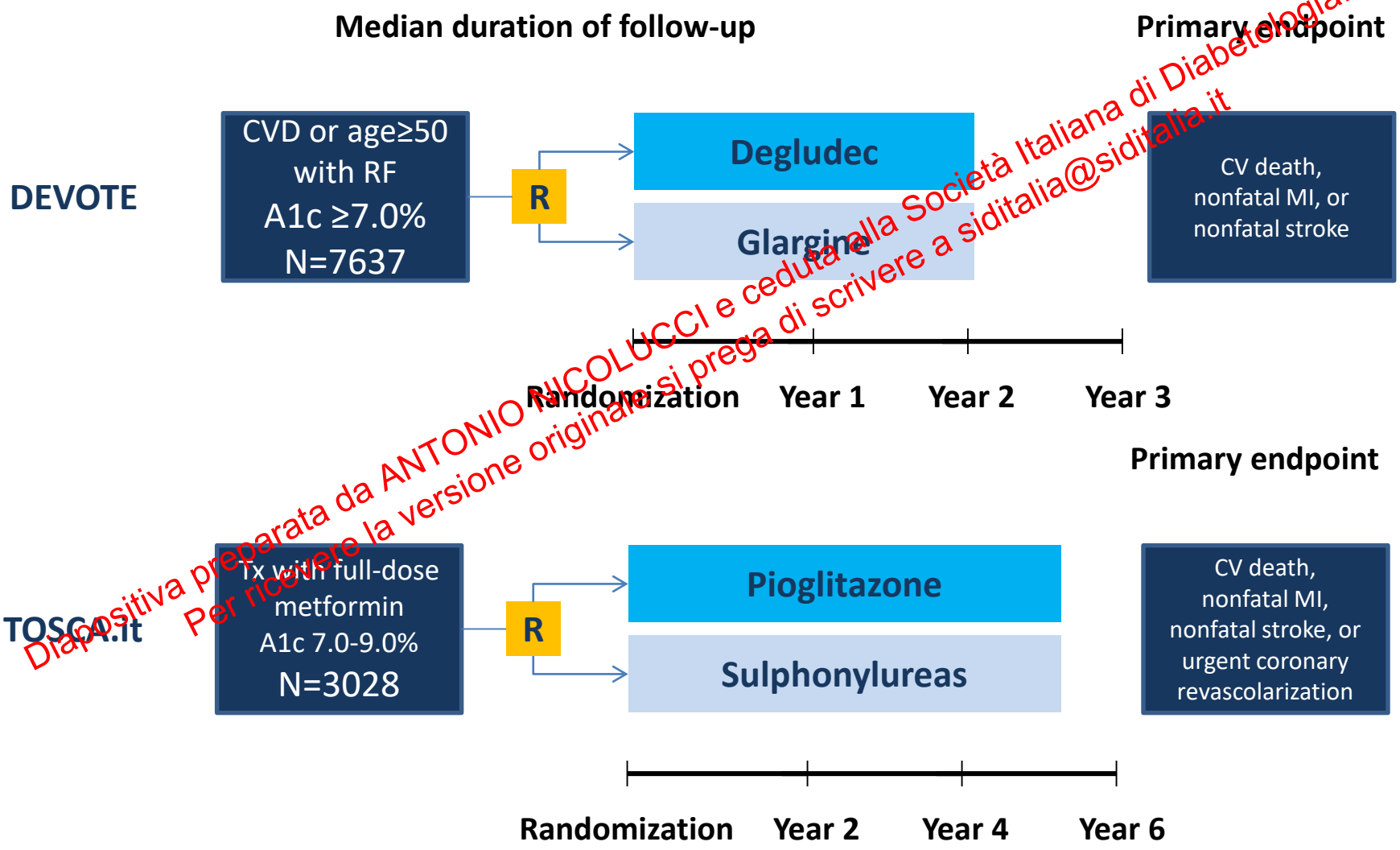
| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Placebo | 4347 | 4267 | 4198 | 4123 | 3011 | 1667 | 1274 | 1256 | 1236 | 1210 | 1180 | 1158 | 829 | 233 |
| Canagliflozin | 5795 | 5732 | 5653 | 5564 | 4437 | 3059 | 2643 | 2610 | 2572 | 2540 | 2498 | 2451 | 1782 | 490 |



**CANVAS trial**

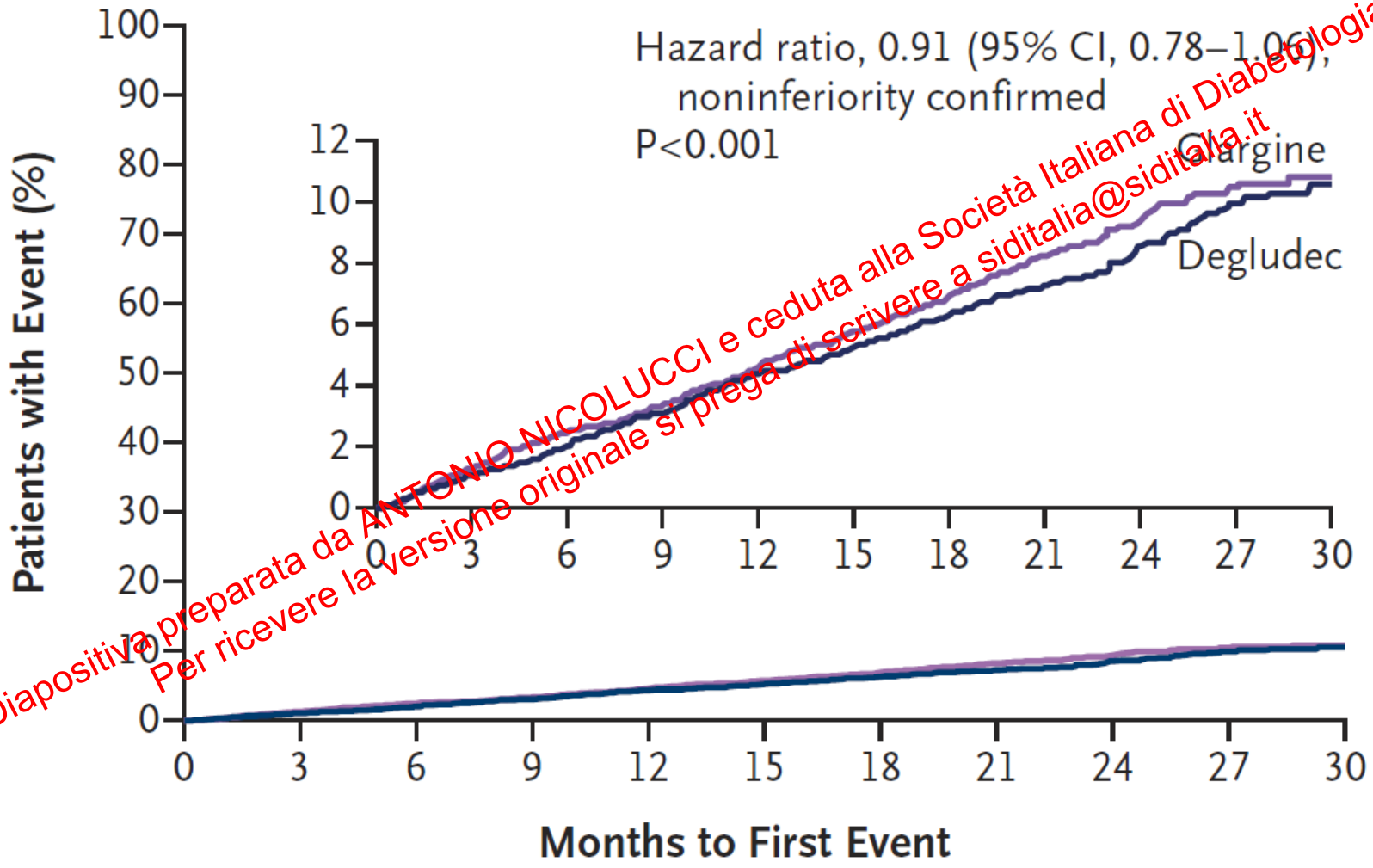
*N Engl J Med 2017;377:644-57*

# CVOTs with head to head comparisons



# Primary outcome

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

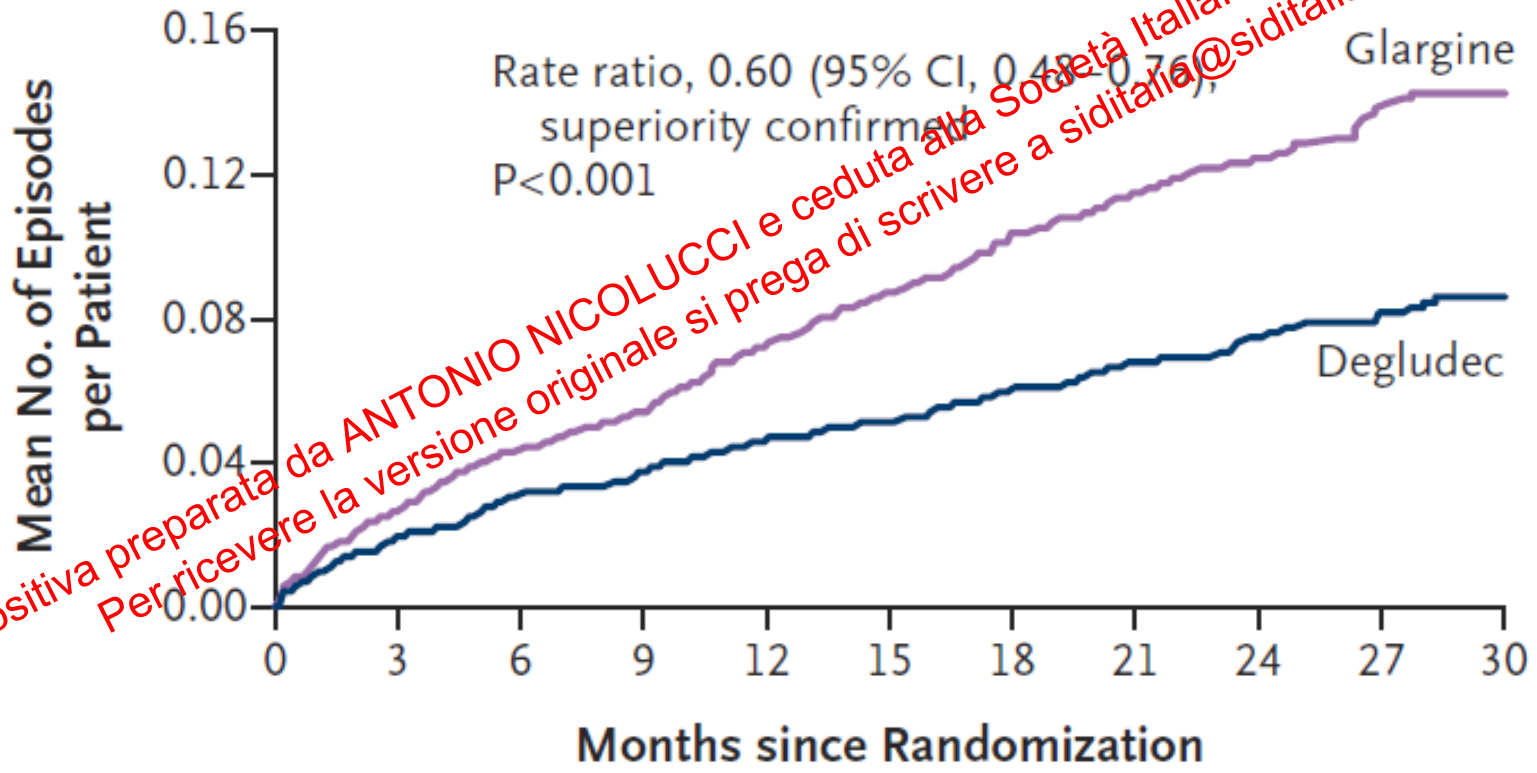





**DEVOTE trial**

*N Engl J Med 2017; June 12*

# Severe hypoglycemia



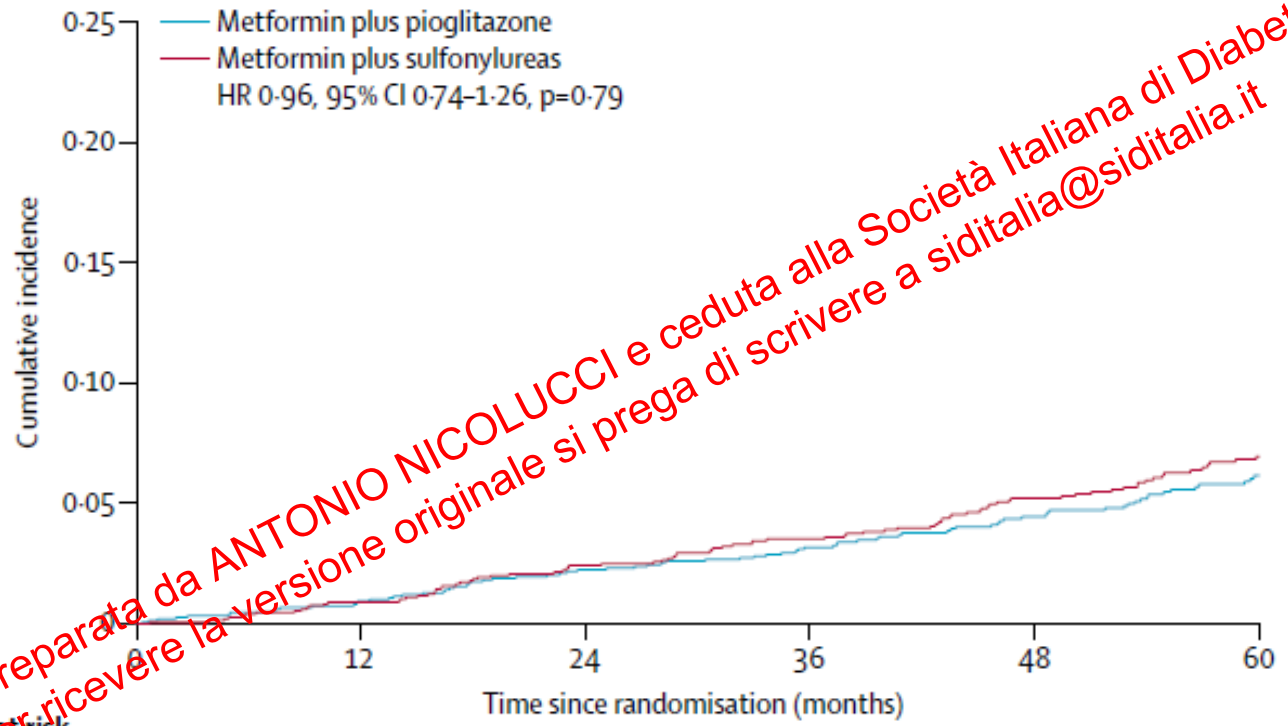



**DEVOTE trial**

*N Engl J Med 2017; June 12*

# Primary outcome

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




| Number at risk (events) | | | | | |
|---|---|---|---|---|---|
| Metformin plus pioglitazone | 1535 (14) | 1462(19) | 1393 (14) | 1317 (16) | 1097 (17) |
| Metformin plus sulfonylureas | 1493 (14) | 1432 (24) | 1368 (15) | 1291 (21) | 1085 (17) |

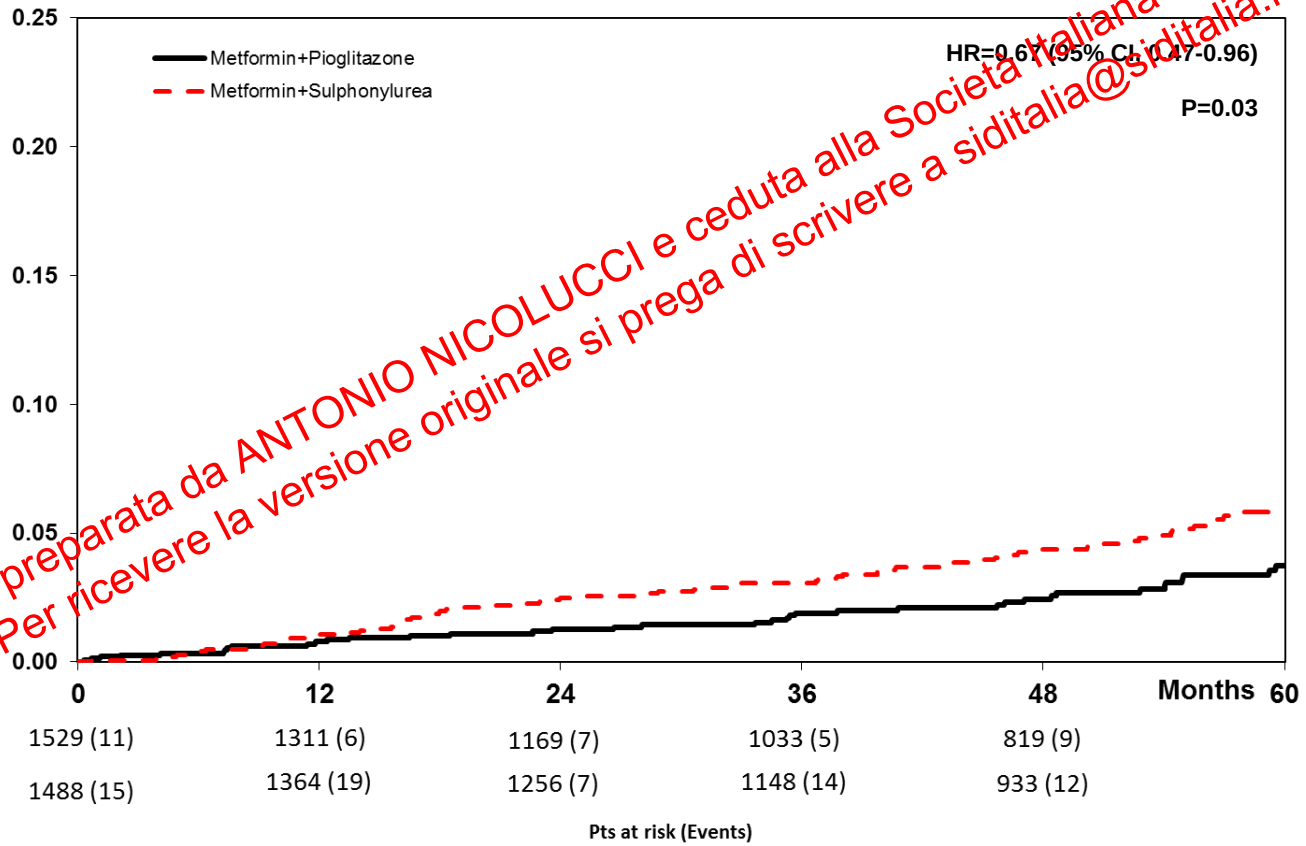


TOSCA·IT

*Lancet Endocrinol 2017; Sept13*

# Key secondary outcome, on treatment population

Sudden death, fatal and non-fatal MI (including silent MI), fatal and non-fatal stroke, major leg amputation (above the ankle), coronary, leg or carotid arteries revascularization

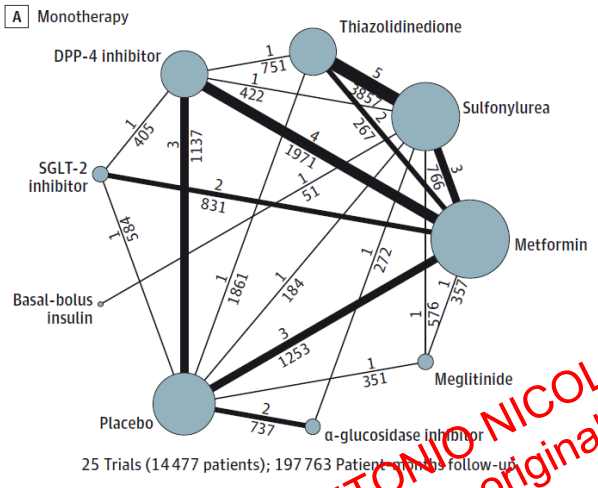


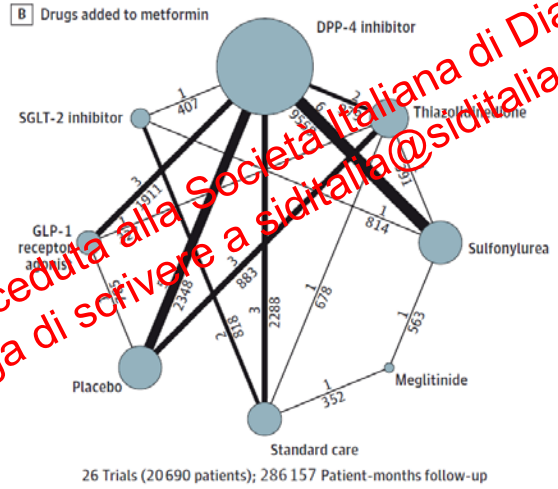


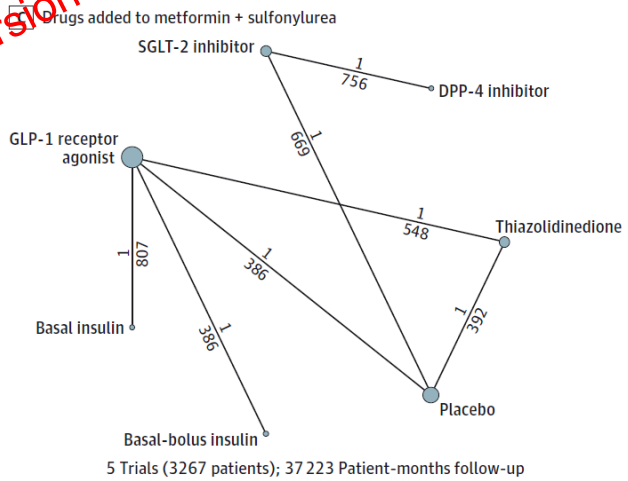

TOSCA·IT

*Lancet Endocrinol 2017; Sept13*

# Available Glucose-Lowering Drugs on Cardiovascular Mortality in Clinical Trials of Type 2 Diabetes






*JAMA. 2016;316(3):313-324*

# From RCTs to RWE

**Lower Risk of Heart Failure and Death in Patients Initiated on Sodium-Glucose Cotransporter-2 Inhibitors Versus Other Glucose-Lowering Drugs**

The CVD-REAL Study (Comparative Effectiveness of Cardiovascular Outcomes in New Users of Sodium-Glucose Cotransporter-2 Inhibitors)

*Circulation.* 2017;136:249–259.

**Cardiovascular Mortality and Morbidity in Patients with Type 2 Diabetes Following Initiation of Sodium-Glucose Co-Transporter-2 Inhibitors Versus Initiation of Other Glucose-Lowering Drugs (CVD-REAL Nordic): a Multinational Observational Analysis**

*Lancet Diabetes Endocrinol.* 2017.

Dapagliflozin Compared to DPP-4 inhibitors is Associated with Lower Risk of Cardiovascular Events and All-cause Mortality in Type 2 Diabetes Patients (CVD-REAL Nordic): a multinational observational study

*DOM 2017*

# Conclusioni

- Negli ultimi anni l’armamentario terapeutico a disposizione del diabetologo si è arricchito in modo sostanziale, con la possibilità di combinare meccanismi d’azione molteplici e di personalizzare la terapia
- Le nuove classi di farmaci si sono mostrate sicure dal punto di vista cardiovascolare, e in alcuni casi è stato documentato un beneficio sugli eventi cardiovascolari, sulla progressione del danno renale e sulla mortalità
- I CVOTs soddisfano a pieno le richieste degli enti regolatori, ma sono meno utili per guidare la pratica clinica (assenza di confronti head to head, confronto vs. placebo con baseline therapy poco chiara, selezione di pazienti ad elevatissimo rischio, spesso focus solo su outcomes CV)
- Le informazioni derivanti dai CVOTs andranno necessariamente affiancate da quelle dei Real World Data, che consentiranno di valutare il profilo di efficacia e sicurezza dei farmaci su popolazioni più rappresentative della normale pratica clinica