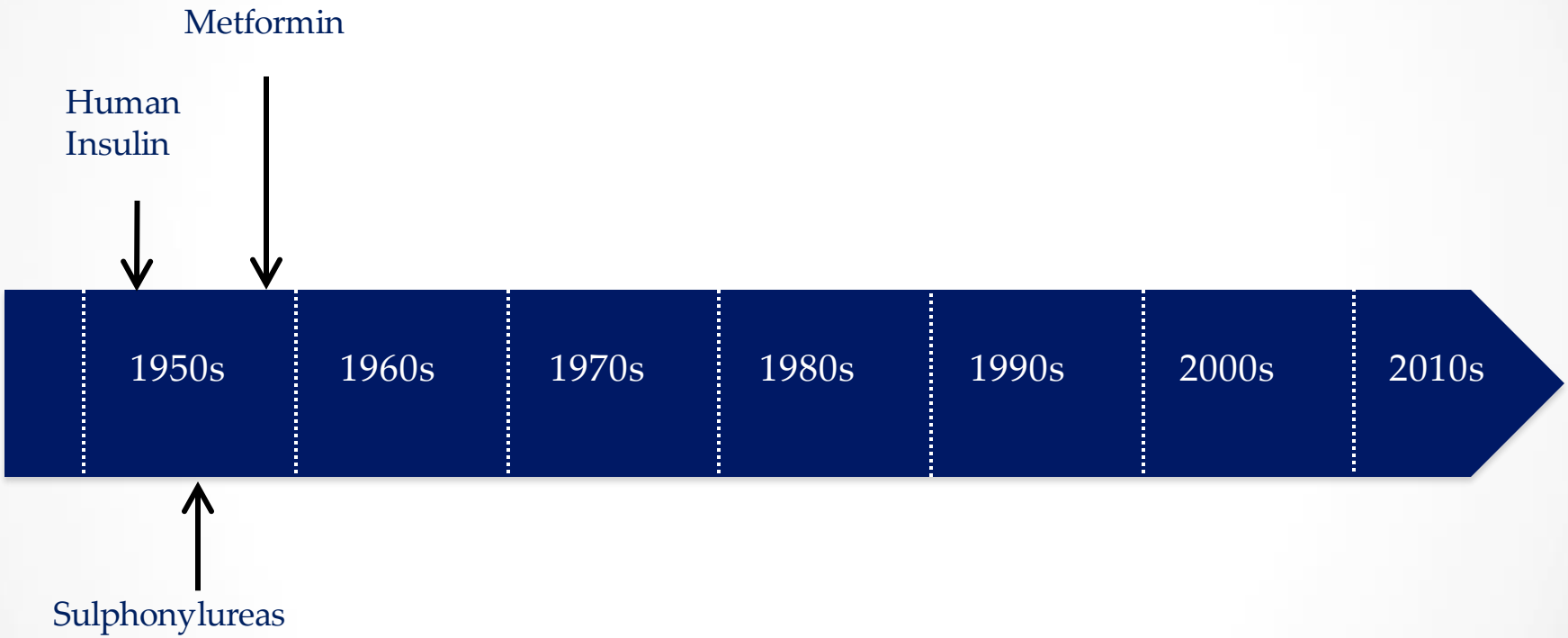
Marcello Monesi
UOC DIABETOLOGIA FERRARA

QUANDO LA METFORMINA FALLISCE: LA LEZIONE DEI GRANDI TRIALS

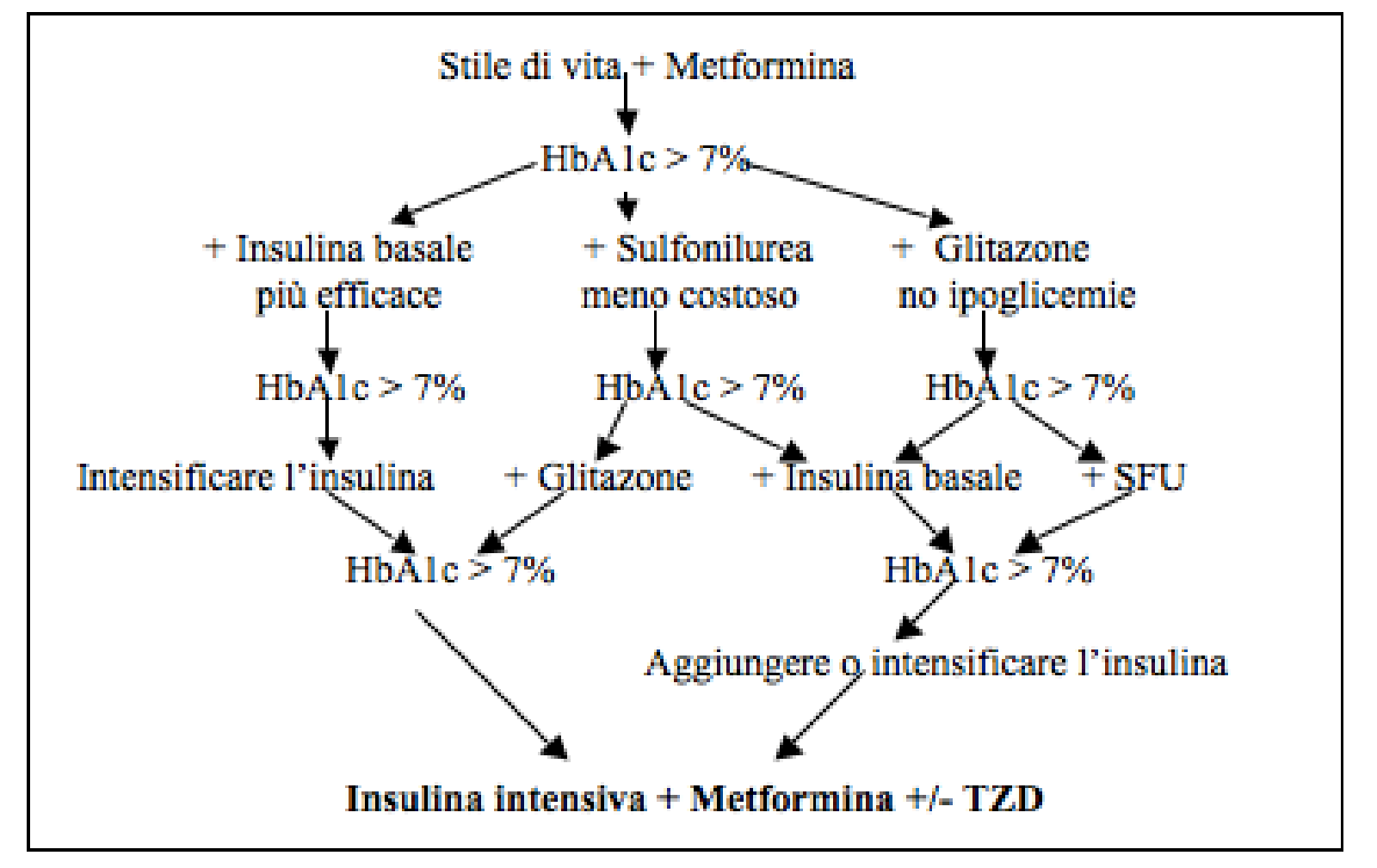
Ferrara, 22 aprile 2017

La terapia del Diabete tipo 2:

una lunga storia… con recenti sviluppi

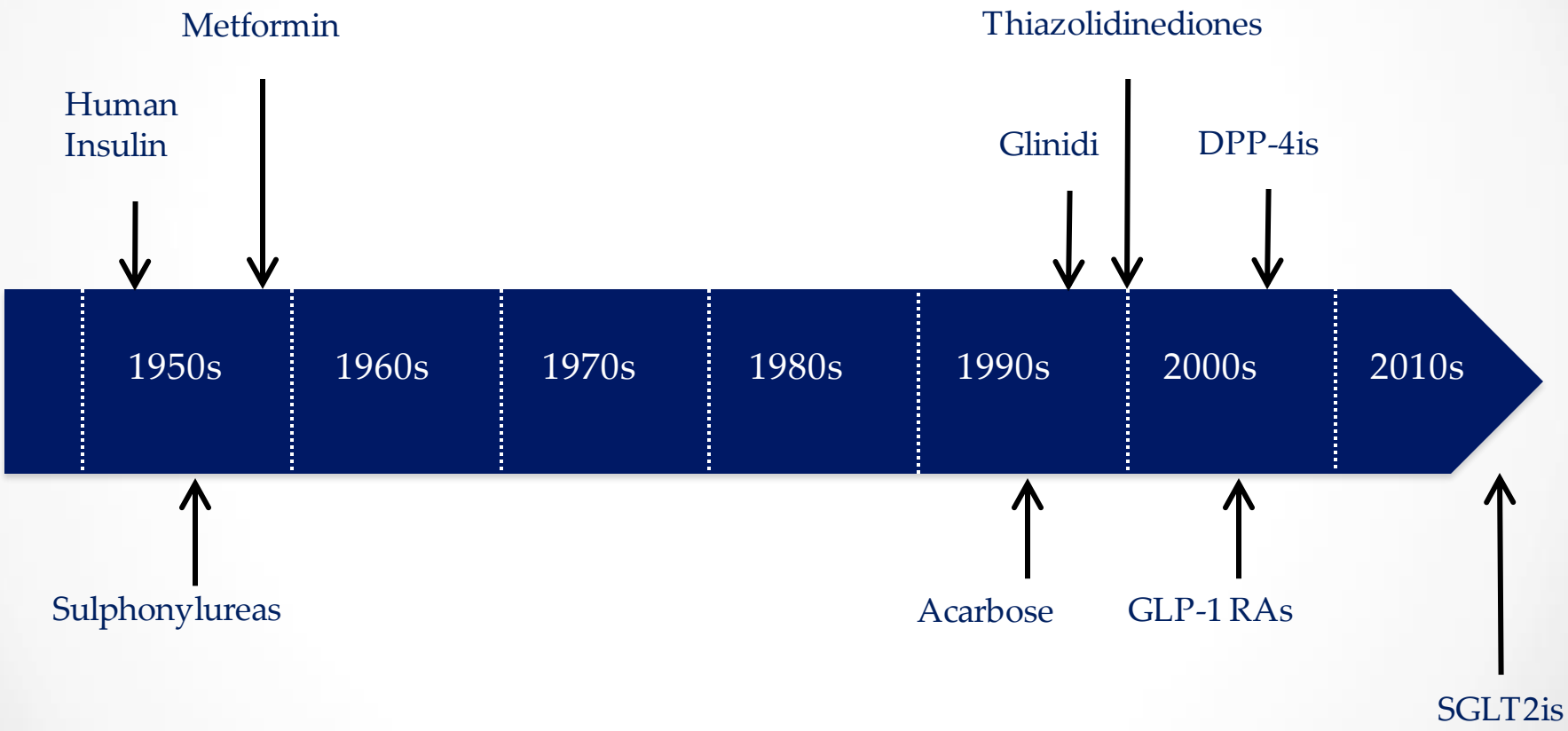


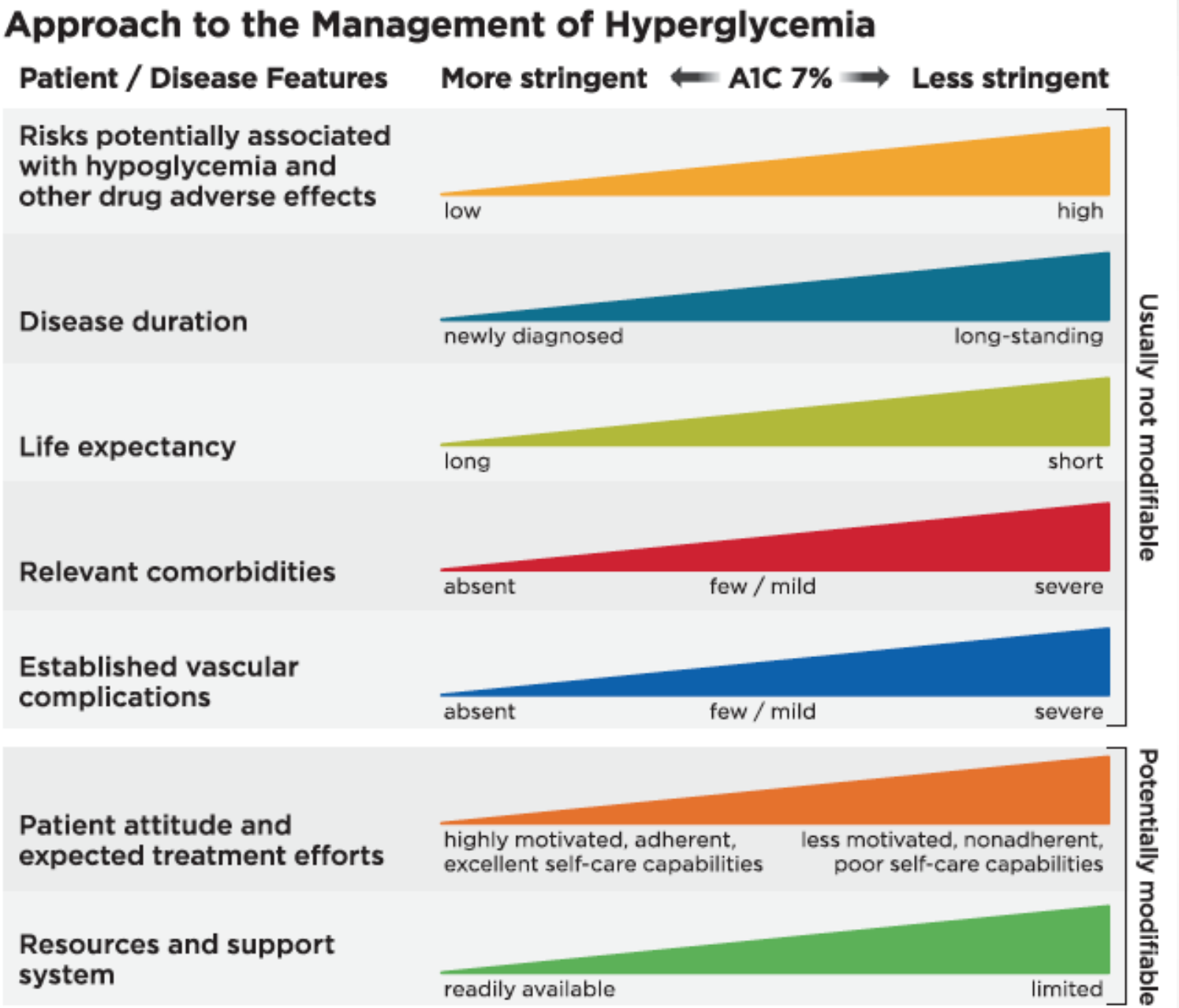
Algoritmi di terapia: dall'approccio centrato sul target glicemico…



La terapia del Diabete tipo 2:

una lunga storia… con recenti sviluppi




Approach to the Management of Hyperglycemia
Patient / Disease Features
More stringent
A1C 7%
Less stringent
Risks potentially associated with hypoglycemia and other drug adverse effects
low
high
Disease duration
newly diagnosed
long-standing
Life expectancy
long
short
Relevant comorbidities
absent
few / mild
severe
Established vascular complications
absent
few / mild
severe
Usually not modifiable
Patient attitude and expected treatment efforts
highly motivated, adherent, excellent self-care capabilities
less motivated, nonadherent, poor self-care capabilities
Resources and support system
readily available
limited
Potentially modifiable

ADA 2017

Start with Monotherapy unless:

A1C is greater than or equal to 9%, **consider Dual Therapy.**

A1C is greater than or equal to 10%, blood glucose is greater than or equal to 300 mg/dL, or patient is markedly symptomatic, **consider Combination Injectable Therapy** (See Figure 8.2).

Monotherapy — Metformin — Lifestyle Management

EFFICACY*	high
HYPO RISK	low risk
WEIGHT	neutral/loss
SIDE EFFECTS	GI/lactic acidosis
COSTS*	low

If A1C target not achieved after approximately 3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

Dual Therapy — Metformin + — Lifestyle Management

	Sulfonylurea	Thiazolidinedione	DPP-4 inhibitor	SGLT2 inhibitor	GLP-1 receptor agonist	Insulin (basal)
EFFICACY*	high	high	intermediate	intermediate	high	highest
HYPO RISK	moderate risk	low risk	low risk	low risk	low risk	high risk
WEIGHT	gain	gain	neutral	loss	loss	gain
SIDE EFFECTS	hypoglycemia	edema, HF, fxs	rare	GU, dehydration, fxs	GI	hypoglycemia
COSTS*	low	low	high	high	high	high

If A1C target not achieved after approximately 3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

Triple Therapy — Metformin + — Lifestyle Management

Sulfonylurea +	Thiazolidinedione +	DPP-4 inhibitor +	SGLT2 inhibitor +	GLP-1 receptor agonist +	Insulin (basal) +
TZD	SU	SU	SU	SU	TZD
or DPP-4-i	or DPP-4-i	or TZD	or TZD	or TZD	or DPP-4-i
or SGLT2-i	or SGLT2-i	or SGLT2-i	or DPP-4-i	or SGLT2-i	or SGLT2-i
or GLP-1-RA	or GLP-1-RA	or Insulin[§]	or GLP-1-RA	or Insulin[§]	or GLP-1-RA
or Insulin[§]	or Insulin[§]		or Insulin[§]		

If A1C target not achieved after approximately 3 months of triple therapy and patient (1) on oral combination, move to basal insulin or GLP-1 RA, (2) on GLP-1 RA, add basal insulin, or (3) on optimally titrated basal insulin, add GLP-1 RA or mealtime insulin. Metformin therapy should be maintained, while other oral agents may be discontinued on an individual basis to avoid unnecessarily complex or costly regimens (i.e., adding a fourth antihyperglycemic agent).

Combination Injectable Therapy (See Figure 8.2)

ADA 2017

EFFICACIA

HBA1C
PESO CORPOREO
PRESSIONE ARTERIOSA, ASSETTO LIPIDICO, FREQUENZA CARDIACA

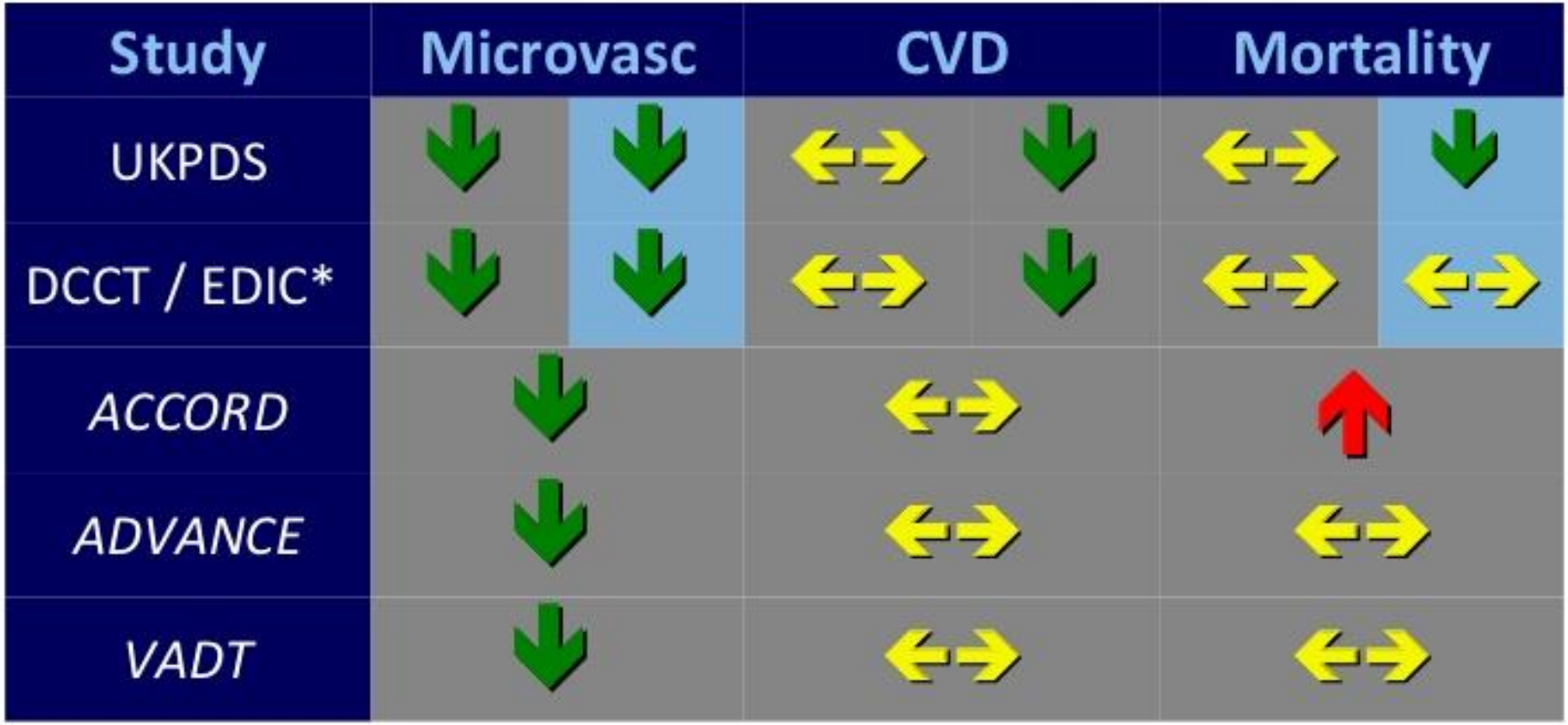
SICUREZZA

RISCHIO IPOGLICEMIA
RISCHIO/BENEFICIO CARDIOVASCOLARE
TOLLERABILITA'
MODALITA' DI SOMMINISTRAZIONE
EFFETTI COLLATERALI

SICUREZZA CARDIOVASCOLARE

2009

Impact of Intensive Therapy for Diabetes: Summary of Major Clinical Trials



Metformina VS Sulfaniluree in monoterapia

REVIEW

Annals of Internal Medicine

Diabetes Medications as Monotherapy or Metformin-Based Combination Therapy for Type 2 Diabetes

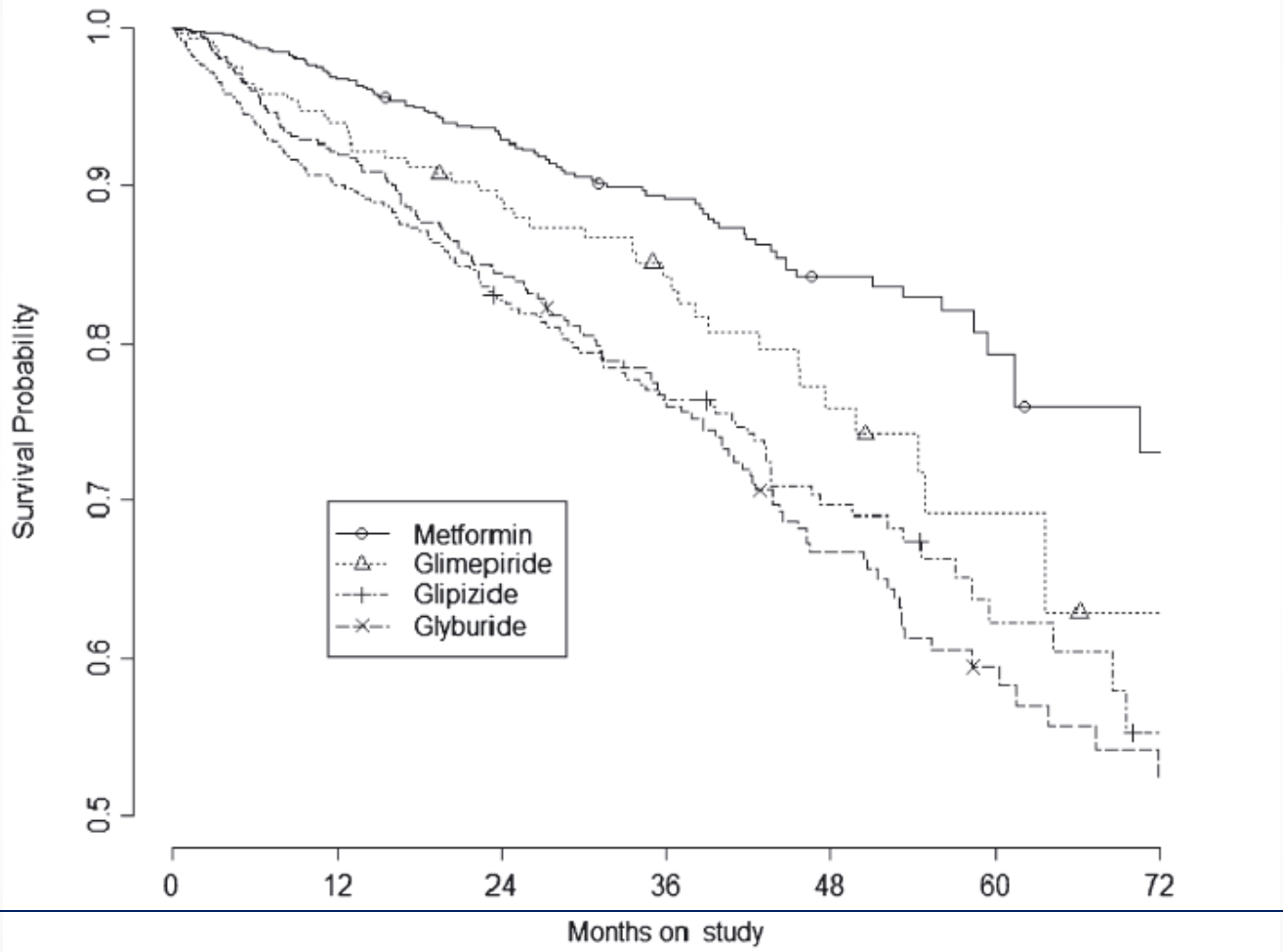
A Systematic Review and Meta-analysis

Nisa M. Maruthur, MD, MHS; Eva Tseng, MD, MPH; Susan Hutfless, PhD; Lisa M. Wilson, ScM; Catalina Suarez-Cuervo, MD; Zackary Berger, MD, PhD; Yue Chu, MSPH; Emmanuel Iyoha, MBChB, MPH; Jodi B. Segal, MD, MPH; and Shari Bolen, MD, MPH

Outcome	Range in RR From RCTs	Range in RD From RCTs	Adjusted HR From Observational Studies	Strength of Evidence
All-cause mortality	0.5 to 1.0 (2 studies [15, 16])	−5.0% to −0.1% (2 studies [15, 16])	0.5 to 0.8 (7 studies* [17–23])	Low
CVD mortality	0.6 to 0.7 (2 studies [15, 16])	−2.9% to −0.1% (2 studies [15, 16])	0.6 to 0.9 (3 studies [19, 21, 24])	Moderate
CVD morbidity	0.7 to 1.6 (2 studies [15, 16])	−0.4% to 10.1% (2 studies [15, 16])	0.3 to 0.9 (5 studies† [19, 20, 22, 25, 26])	Low

CVD = cardiovascular disease; HR = hazard ratio; RCT = randomized, controlled trial; RD = risk difference; RR = relative risk.
* One additional retrospective cohort study reported an odds ratio of 0.9 (27).
† One additional case–control study reported an odds ratio of 0.8 (28).

Monoterapia in pazienti DM2



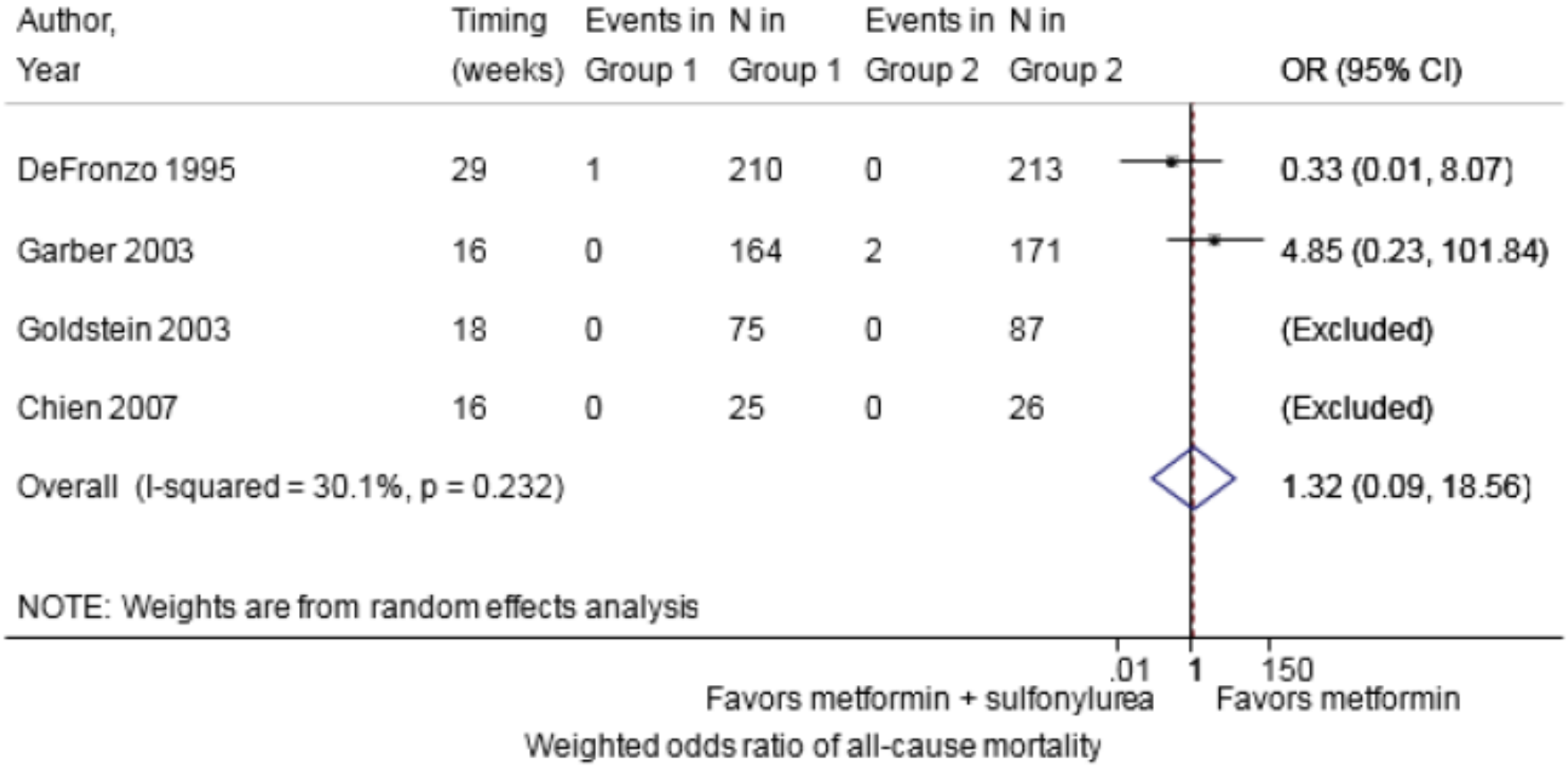
Rischio di mortalità vs metformina in pz con pregresso evento CV:

Glipizide HR 1.41 (1.07-1.87); Glibenclamide HR 1.38 (1.04-1.83)

- Diabetes Obes Metab. 2012 Sep;14(9):803-9

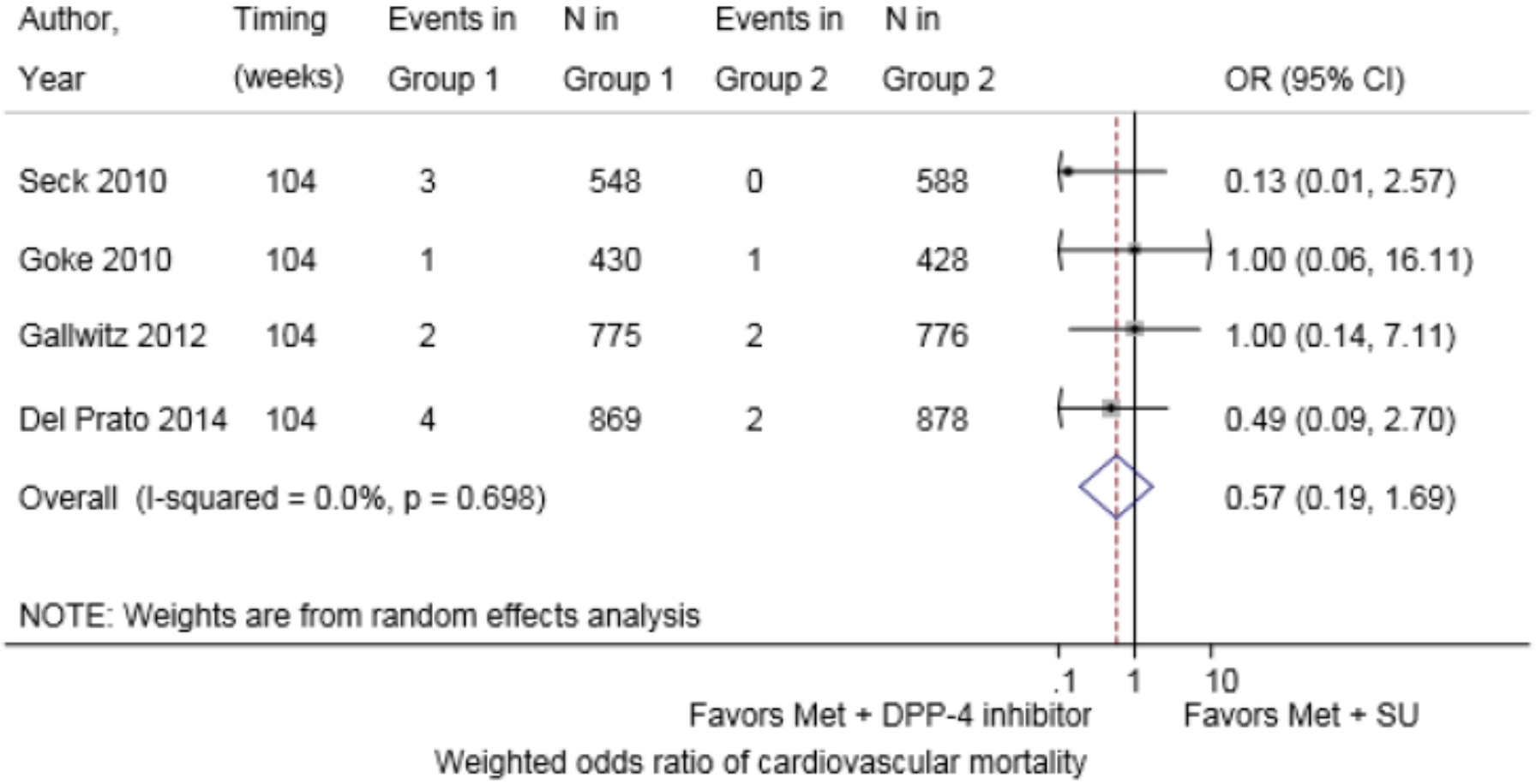
Metformina VS duplice Metformina-Sulfaniluree

Figure 43. Pooled odds ratio of short-term all-cause mortality comparing metformin with a combination of metformin plus a sulfonylurea



Metformina+DPP4 VS Metformina+Sulfaniluree

Figure 50. Pooled odds ratio for long-term cardiovascular mortality comparing combination of metformin plus a sulfonylurea with a combination of metformin plus a DPP-4 inhibitor



Cardiovascular safety of sulfonylureas: a meta-analysis of randomized clinical trials

M. Monami[1], S. Genovese[2] & E. Mannucci[3]

- Metanalisi che confronta SU con agente non SU in DM2 (115 RCT, circa 45000 pz)
- End points: Major cardiovascular events (MACE) e mortalità
- OR for MACE with SU treatment vs comparators was 1.08 (0.86-1.36): no signal for cardiovascular risk
- Use of SU was not associated with any significant difference in the incidence of MI with respect to comparators OR: 0.88 (0.75-1.04)
- The use of sulfonylureas is associated with increased mortality 1.22 (1.01-1.49) and a higher risk of stroke 1.28 (1.03-1.60)

•Diabetes Obes Metab. 2013 Oct;15(10):938-53

American Diabetes Association.
75th ANNIVERSARY scientificsessions
JUNE 5-9, 2015 • BOSTON, MA

•SU does not increase the risk of all-cause or CV mortality: A meta-analysis

- 47 RCTs were included, totalizing 37650 patients
- SU were not associated with total (OR 1.12, 95% C.I. 0.96 to 1.30; I2 = 0%, p = 0.67) or cardiovascular mortality (OR 1.12, 95% C.I. 0.87 to 1.42; I2 = 12%, p = 0.30)
- SU were also not associated with increased risk of myocardial infarction(OR 0.92, 95% CI 0.76 - 1.12; I2 = 3% p = 0.42) or stroke (OR 1.16, 95% CI 0.81 - 1.66; I2 = 30% p = 0.09)

Sulfonylureas are not associated with increased Cardiovascular Mortality

•Rados DV, Pinto LC, Remonti LR, et al. Sulfonylureas are not associated with increased mortality: Meta-analysis and trial sequential analysis of randomized clinical trials. American Diabetes Association 2015 Scientific Sessions; June 6, 2015; Boston, MA. Abstract 16-OR

Contents available at ScienceDirect

Diabetes Research and Clinical Practice

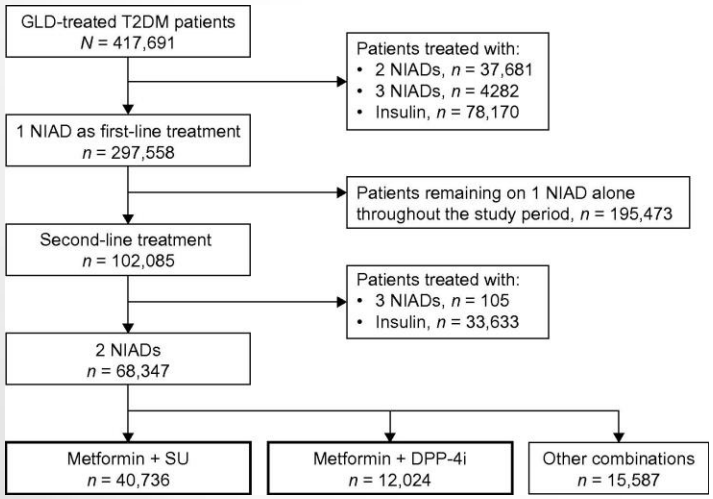
journal homepage: www.elsevier.com/locate/diabres

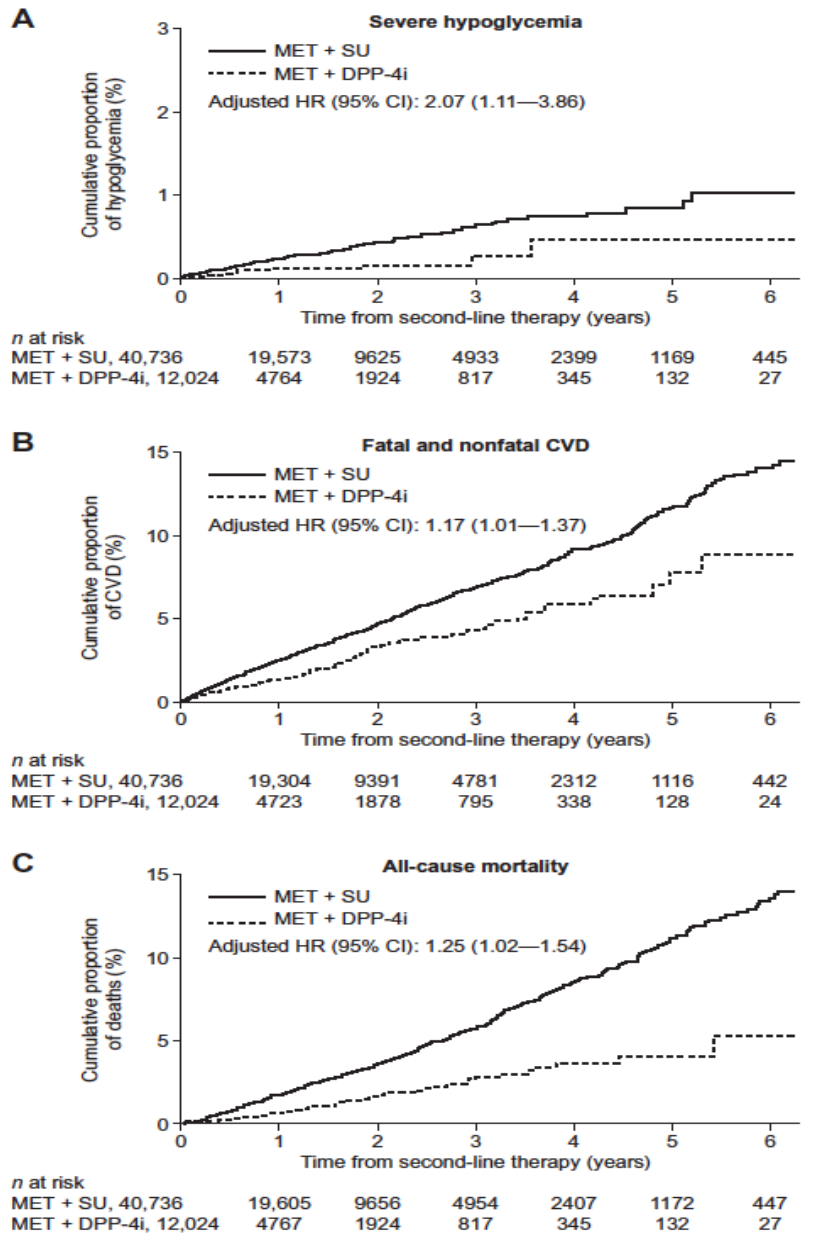
International Diabetes Federation

Sulphonylurea compared to DPP-4 inhibitors in combination with metformin carries increased risk of severe hypoglycemia, cardiovascular events, and all-cause mortality

Jan W. Eriksson [a], *Johan Bodegard* [b,*], *David Nathanson* [c], *Marcus Thuresson* [d], *Thomas Nyström* [c], *Anna Norhammar* [e]

[a] Department of Medical Sciences, Clinical Diabetes and Metabolism, Uppsala University, Uppsala, Sweden
[b] AstraZeneca Nordic-Baltic, Södertälje, Sweden
[c] Department of Clinical Science and Education, Division of Internal Medicine, Unit for Diabetes Research, Karolinska Institute, Södersjukhuset, Stockholm, Sweden
[d] Statisticon AB, Uppsala, Sweden
[e] Cardiology Unit, Department of Medicine, Solna, Karolinska Institute, Stockholm, Sweden





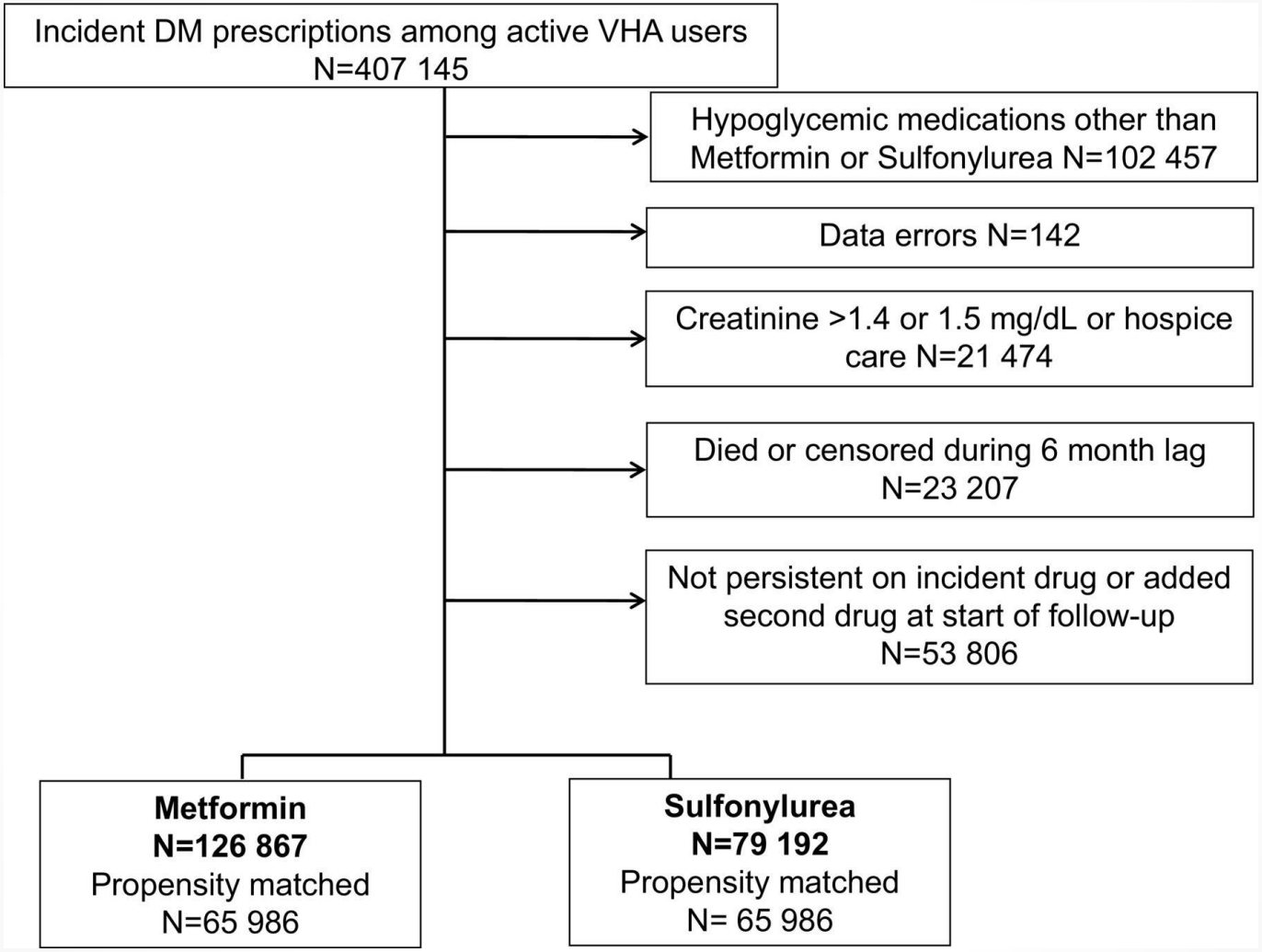
Comparative Safety of Sulfonylurea and Metformin Monotherapy on the Risk of Heart Failure: A Cohort Study

by Christianne L. Roumie, Jea Young Min, Lucy D'Agostino McGowan, Caroline Presley, Carlos G. Grijalva, Amber J. Hackstadt, Adriana M. Hung, Robert A. Greevy, Tom Elasy, and Marie R. Griffin

J Am Heart Assoc
Volume 6(4):e005379
April 19, 2017

American Heart Association | American Stroke Association

Flow of eligible patients included.



Christianne L. Roumie et al. J Am Heart Assoc 2017;6:e005379

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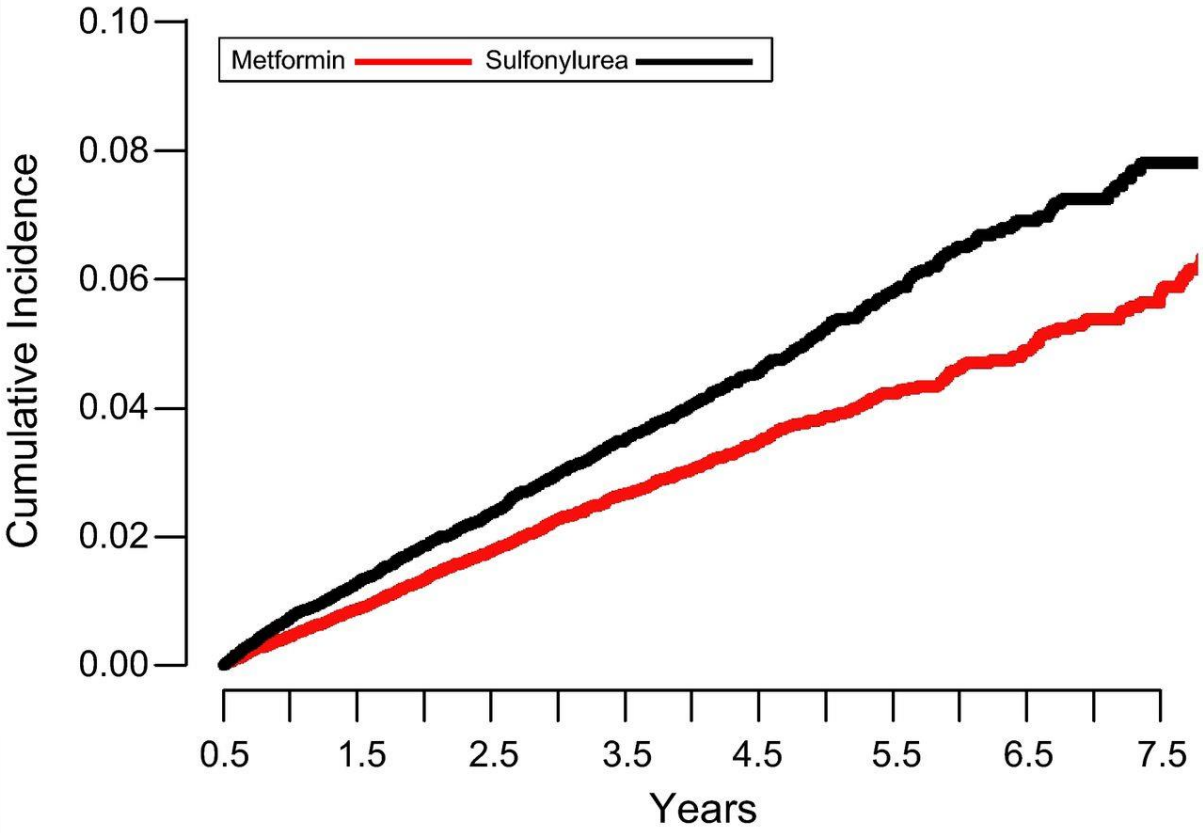
Cumulative incidence of heart failure hospitalization or cardiovascular death over time.



	6 months	1.5 years	2.5 years	3.5 years	4.5 years	5.5 years	6.5 years	7.5 years
Metformin								
N at Risk	65986	35388	22232	14861	9863	5514	2736	1187
N events		436	256	164	103	60	28	17
Sulfonylurea								
N at Risk	65986	31225	17633	10529	6230	3264	1531	665
N events		613	262	164	91	61	28	10

Christianne L. Roumie et al. J Am Heart Assoc 2017;6:e005379

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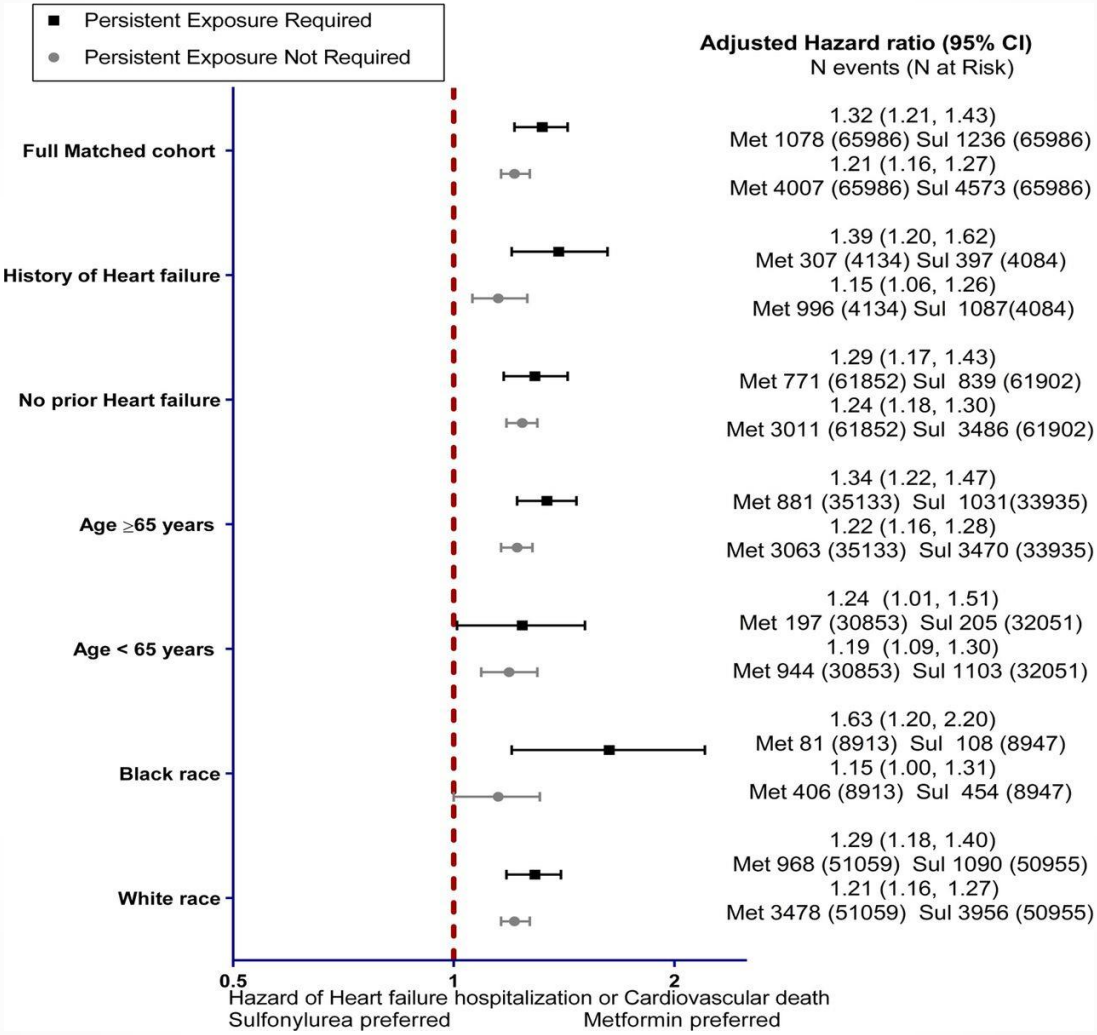
Adjusted hazard ratio and 95%CIs of subgroups.



Christianne L. Roumie et al. J Am Heart Assoc 2017;6:e005379

American Heart Association | American Stroke Association

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2004


[thefacebook]
login register about
Email:
Password:
register
login
Welcome to Thefacebook!
[Welcome to Thefacebook]
Thefacebook is an online directory that connects people through social networks at colleges.
We have opened up Thefacebook for popular consumption at Harvard University.
You can use Thefacebook to:
Search for people at your school
Find out who are in your classes
Look up your friends' friends
See a visualization of your social network
To get started, click below to register. If you have already registered, you can log in.
Register
Login
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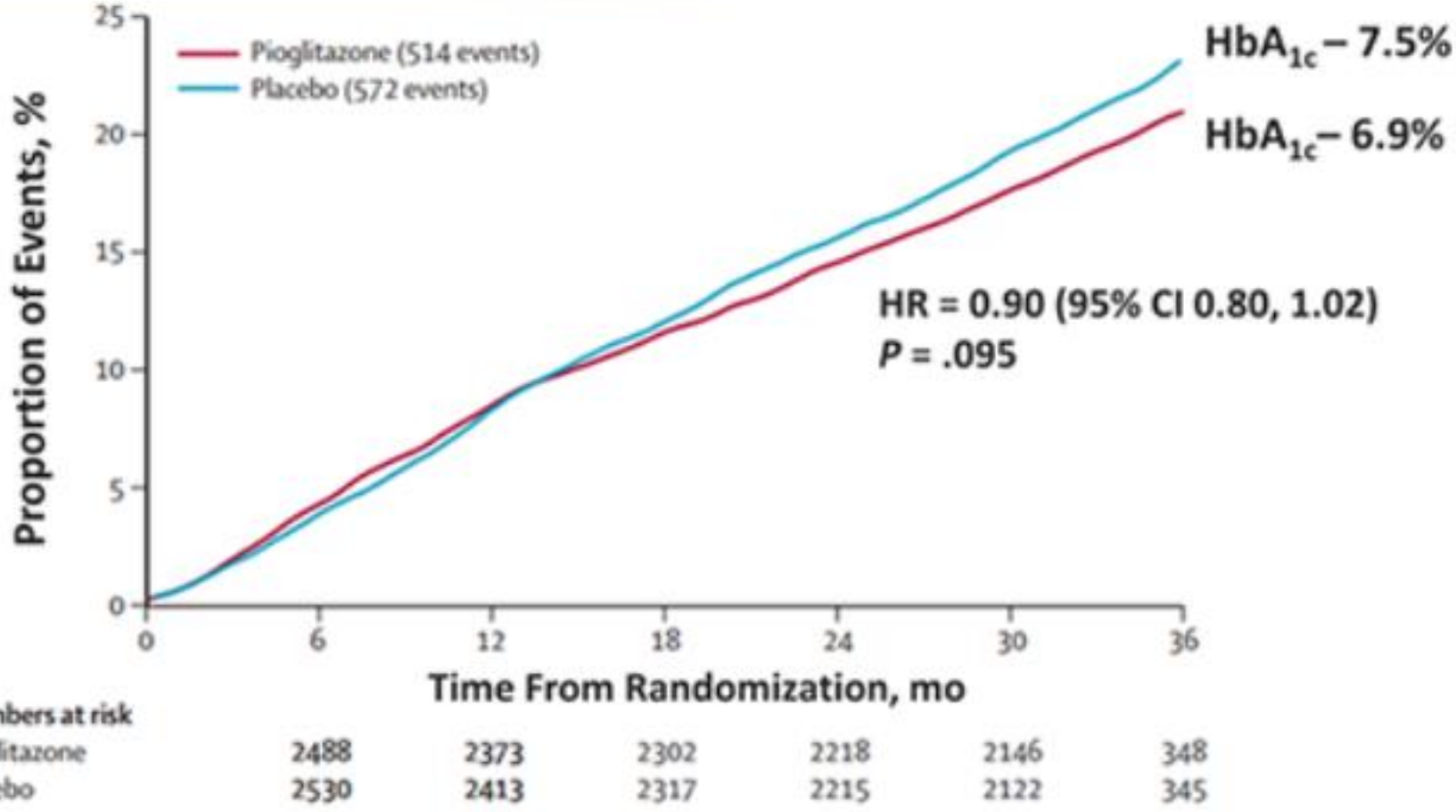
ATHENS 2004
ATHENS 2004

PROactive: Study design

Objective:	Assess the effects of pioglitazone on reducing macrovascular events in type 2 diabetes
Design:	Randomized, double-blind, placebo-controlled
Population:	N = 5238 with type 2 diabetes and history of macrovascular disease
Treatment:	Pioglitazone (up to 45 mg) or placebo
Primary outcome:	Composite of all-cause mortality, MI, ACS, coronary or peripheral revascularization, amputation, stroke
Secondary outcomes:	Individual components of primary outcome, CV mortality
Follow-up:	4 years

Dormandy JA et al. *Lancet*. 2005;366:1279-89.
Charbonnel B et al. *Diabetes Care*. 2004;27:1647-53.

PROactive Primary Endpoint

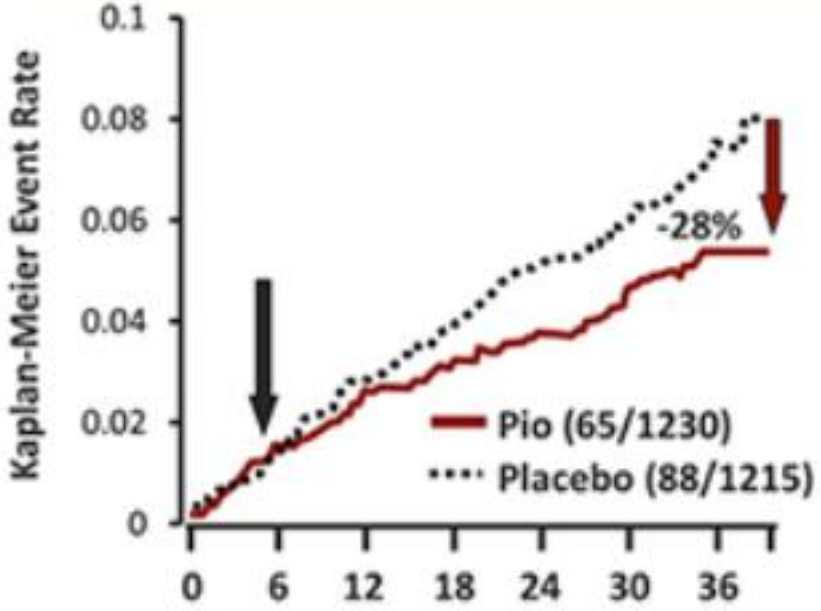


Primary endpoint: death, MI, CVA, ACS, leg revasc/amputation, PCI, or CABG.

PROactive: *Pioglitazone (Pio) Reduces "Hard" Coronary Heart Disease Endpoints*

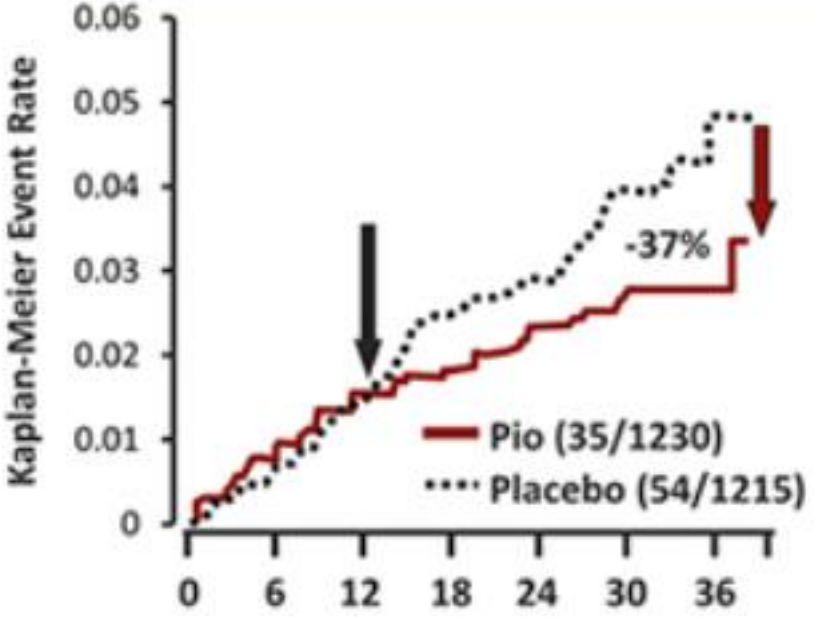
Time to Fatal/Nonfatal MI (Excluding Silent MI)

	HR	95% CI	*P* Value
Pio vs placebo	0.72	0.52, 0.99	.045

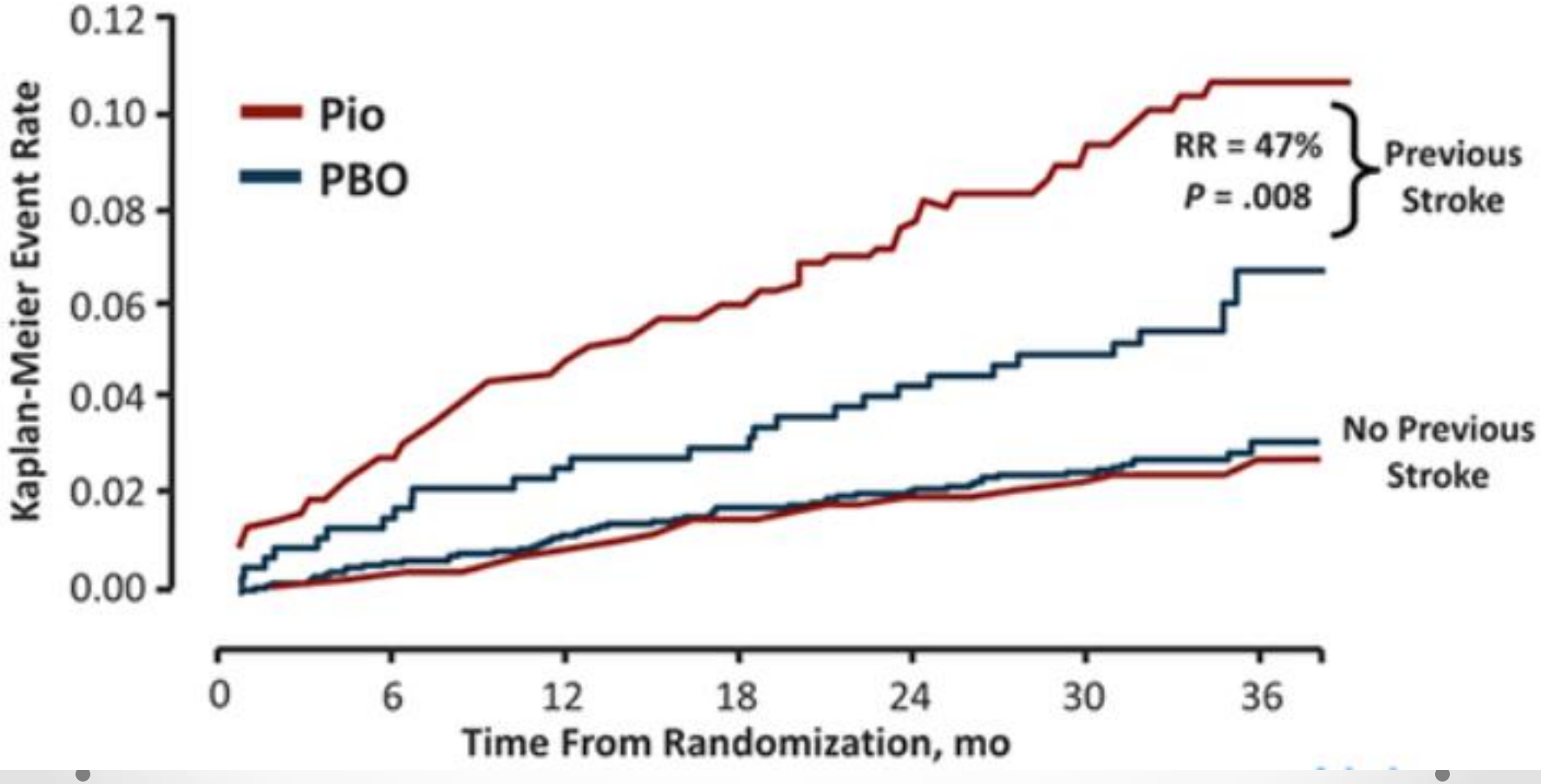


Time to ACS

	HR	95% CI	*P* Value
Pio vs placebo	0.63	0.41, 0.97	.035



PROactive: *Time to Fatal/Nonfatal Stroke in Patients With Previous Stroke*



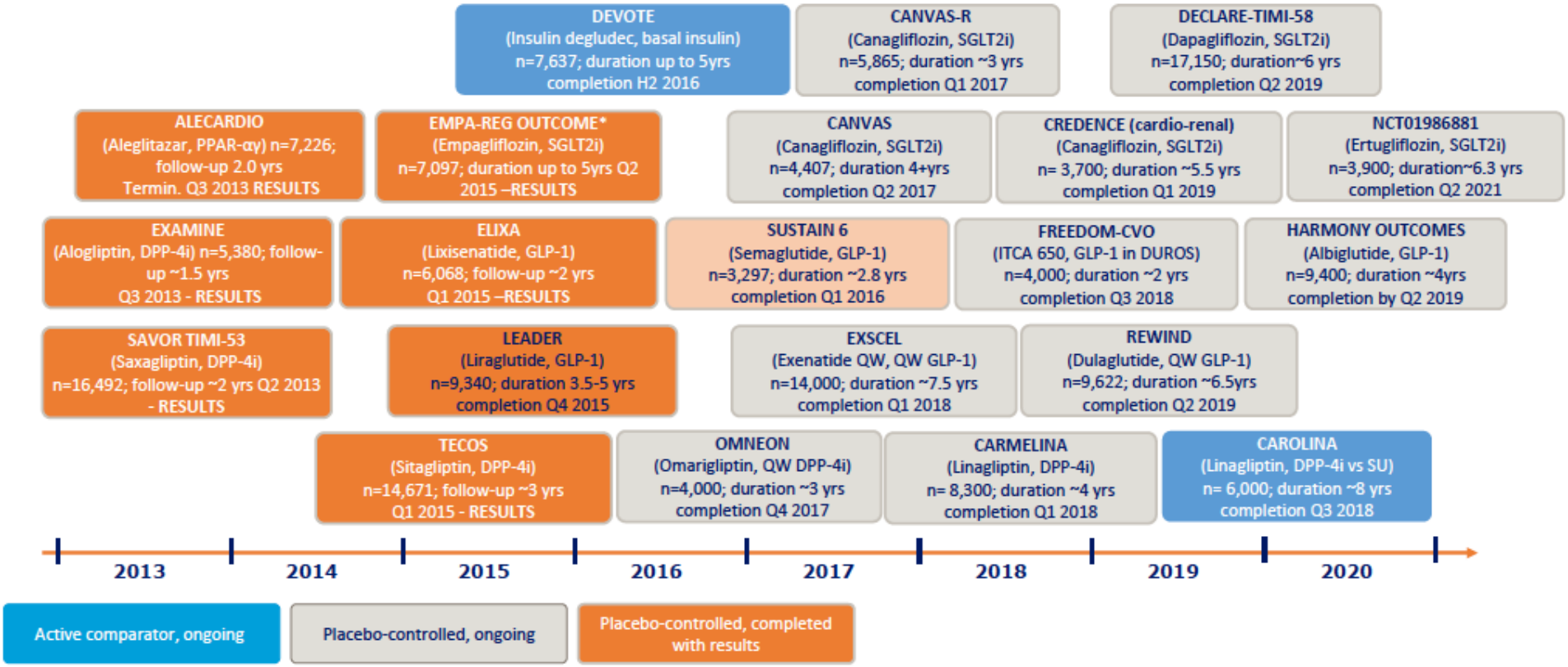
PROactive

HF Hospitalization and Mortality

N = 5238

	Pio, n (%)	PBO, n (%)	*P*
HF leading to hospital admission*	149 (5.7)	108 (4.1)	.007
Fatal HF	25 (0.96)	22 (0.84)	NS

Ongoing and recently completed cardiovascular outcomes trials placebo controlled and active comparators



Source: ClinicalTrials.gov (30 June 2015). 'Completion date' is the estimated completion date for the primary outcomes measure. *Also known as C-SCADE-8.

savor TIMI 53
TIMI STUDY GROUP / HADASSAH MEDICAL ORG

Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus

TECOS
TRIAL EVALUATING CARDIOVASCULAR OUTCOMES WITH SITAGLIPTIN

Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes

Alogliptin after acute coronary syndrome in patients with type 2 diabetes

Empagliflozin, cardiovascular outcomes and mortality in type 2 diabetes

ELIXA

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

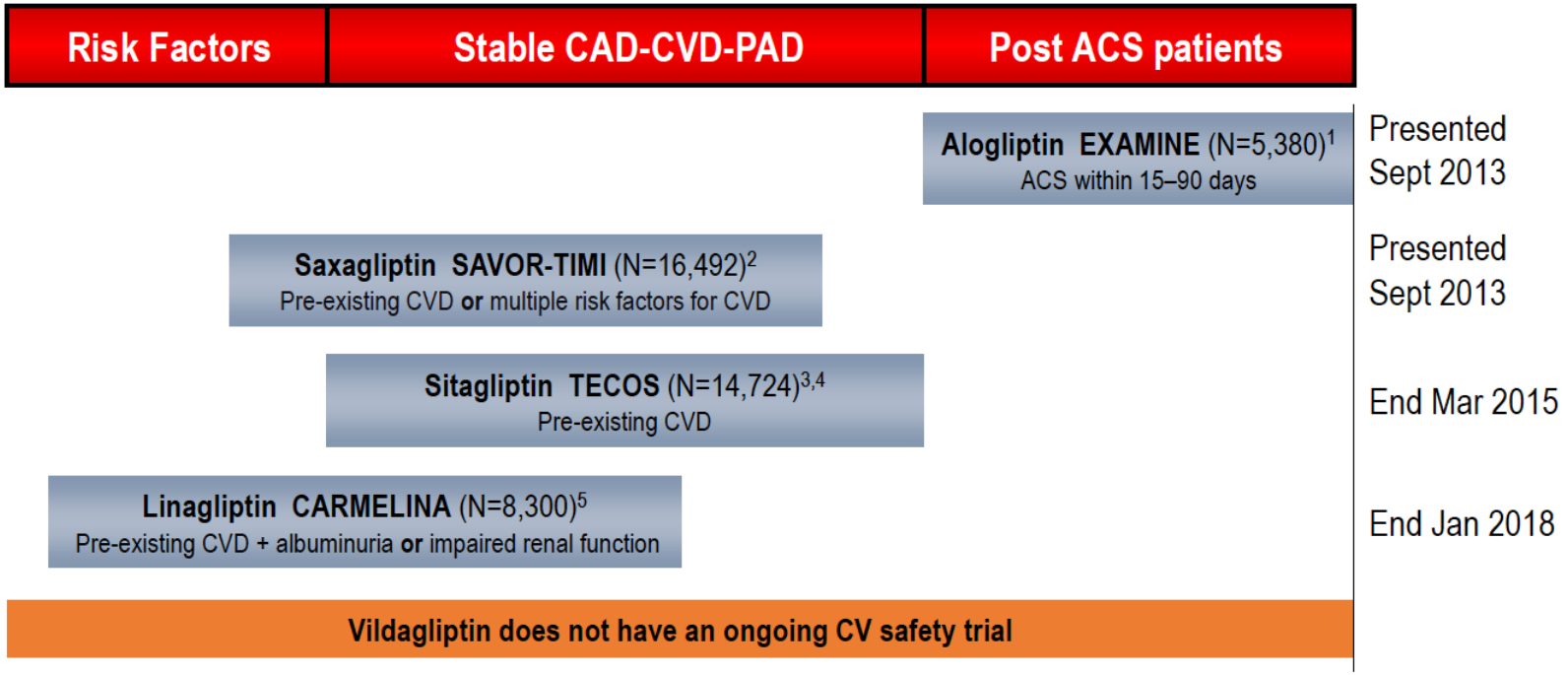
SUSTAIN
SEMAGLUTIDE UNABATED SUSTAINABILITY IN TREATMENT OF TYPE 2 DIABETES

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

SICUREZZA CARDIOVASCOLARE DEI DPP-IV INIBITORI

	EXAMINE	SAVOR-TIMI	TECOS
	Alogliptin vs Placebo	Saxagliptin vs Placebo	Sitagliptin vs Placebo
Popolazione in studio, N	5380	16492	14671
Durata del diabete, anni	7.2	10.3	11.0
HbA1c basale, %	8.0	8.0	7.3
Durata media dell'osservazione, anni	1.5	2.1	3.0
End point primario	morte CV, IMA non fatale o ictus non fatale	morte CV, IMA non fatale o ictus non fatale	morte CV, IMA non fatale, ictus non fatale o ricovero per angina instabile

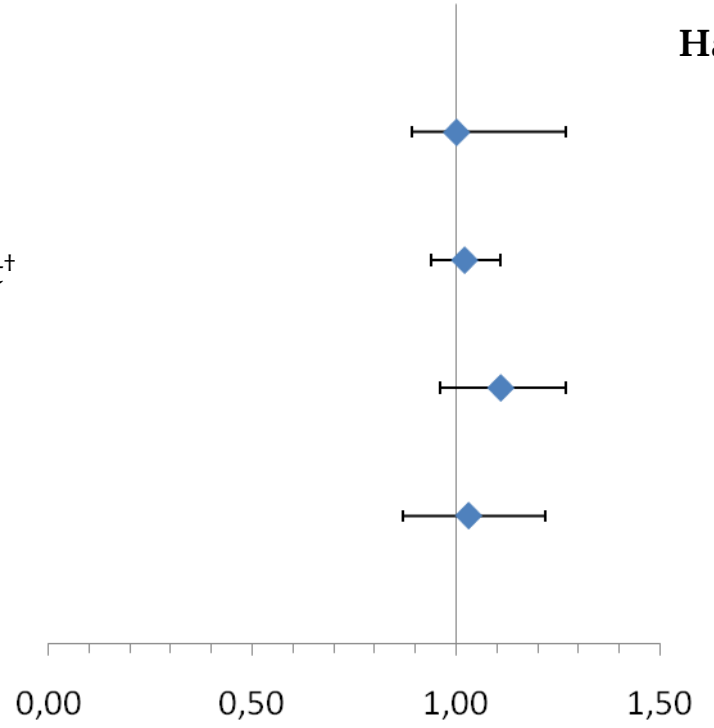
Baseline Risk of Patient Populations Enrolled in CV Safety Trials of DPP-4 Inhibitors



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.

SAVOR-TIMI Prespecified Composite Endpoints and Mortality (n=16,492)
SAXAGLIPTIN

	Hazard ratio (95% CI)	*P* value
Primary composite endpoint*	1.00 (0.89-1.27)	0.99
Secondary composite endpoint†	1.02 (0.94-1.11)	0.66
Death from any cause	1.11 (0.96-1.27)	0.15
CV death	1.03 (0.87-1.22)	0.52

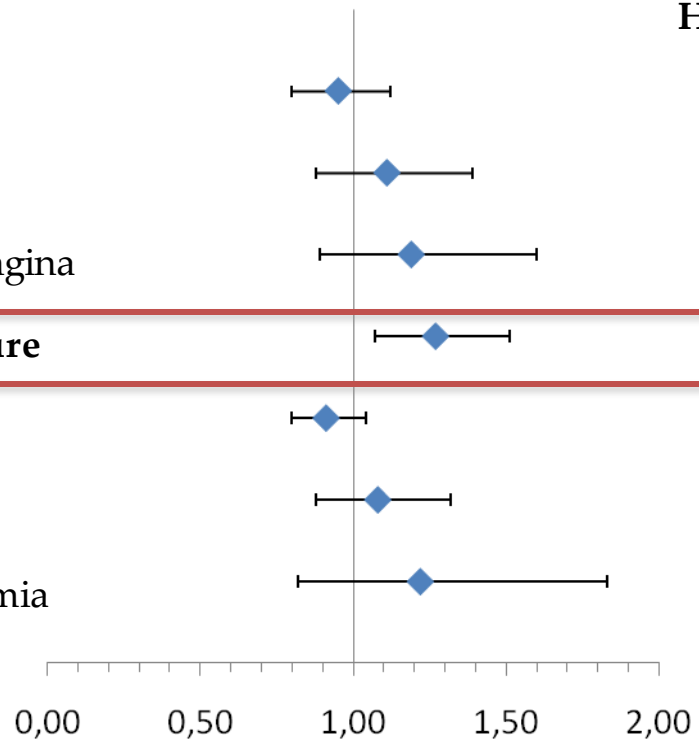


NESSUNA DIFFERENZA RISPETTO A PLACEBO NEGLI ENDPOINT PRIMARI

CI, confidence interval; CV, cardiovascular; SAVOR-TIMI, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction.

Scirica BM, et al. *N Engl J Med.* 2013;369,1317-1326.

SAVOR-TIMI Prespecified Individual Endpoints (n=16,492) SAXAGLIPTIN



	Hazard ratio (95% CI)	*P* value
Myocardial infarction	0.95 (0.80-1.12)	0.52
Ischemic stroke	1.11 (0.80-1.12)	0.38
Hospitalization for unstable angina	1.19 (0.89-1.60)	0.24
Hospitalization for heart failure	**1.27 (1.07-1.51)**	**0.007**
Hospitalization for coronary revascularization	0.91 (0.80-1.04)	0.18
Renal endpoint*	1.08 (0.88-1.32)	0.46
Hospitalization for hypoglycemia	1.22 (0.82-1.83)	0.33

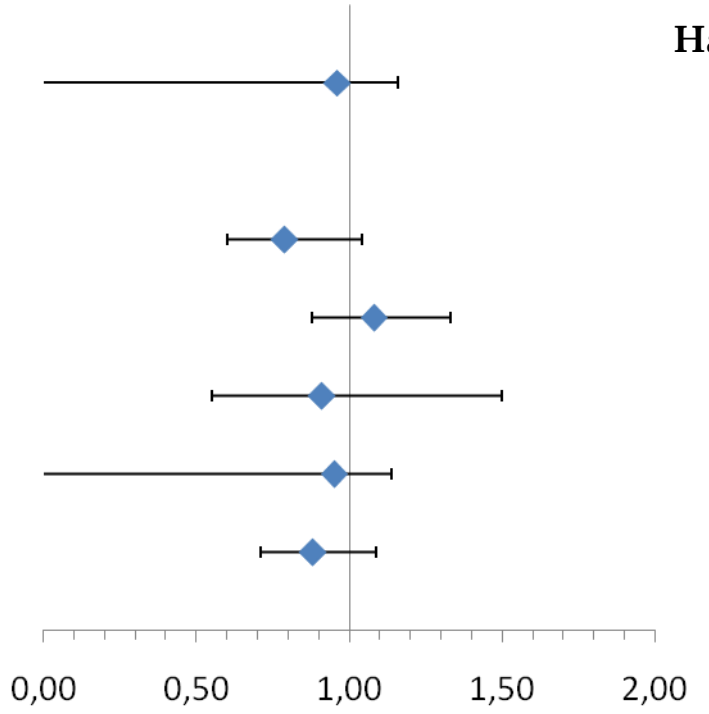
INCREMENTO SIGNIFICATIVO DEI RICOVERI PER SCOMPENSO CARDIACO

*Doubling of creatinine, initiation of dialysis, renal transplantation, or creatinine >6.0 mg/dL

CI, confidence interval; CV, cardiovascular; SAVOR-TIMI, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction.

Scirica BM, et al. *N Engl J Med.* 2013;369,1317-1326.

EXAMINE Safety Endpoints (n=5380) ALOGLIPTIN

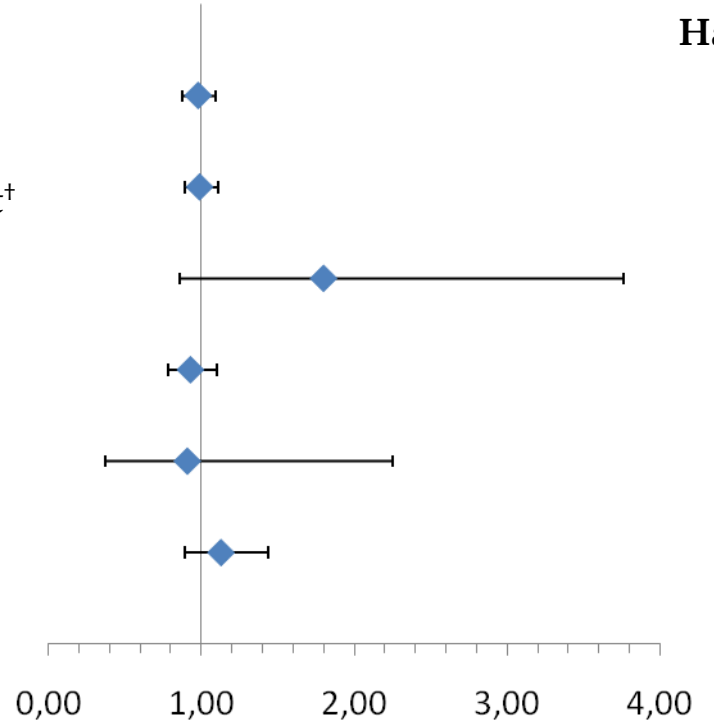


	Hazard ratio (95% CI)	*P* value
Primary composite	0.96 (≤1.16)*	0.32
Primary endpoint components		
CV death	0.79 (0.6-1.04)	0.10
Nonfatal MI	1.08 (0.88-1.33)	0.47
Nonfatal stroke	0.91 (0.55-1.50)	0.71
Primary secondary endpoint†	0.95 (≤1.14)*	0.26
Death from any cause	0.85 (0.66-1.10)	0.21

NESSUNA DIFFERENZA RISPETTO A PLACEBO NEGLI ENDPOINT PRIMARI

TECOS Per Protocol Analysis (n=14,523) SITAGLIPTIN

	Hazard ratio (95% CI)	*P* value
Primary composite endpoint*	0.98 (0.88-1.09)	<0.001 (NF)
Secondary composite endpoint†	0.99 (0.89-1.11)	<0.001 (NF)
Acute pancreatitis	1.80 (0.86-3.76)	0.12
Any cancer (except nonmelanoma skin cancer)	0.93 (0.89-1.44)	0.38
Pancreatic cancer	0.91 (0.37-2.25)	0.85
Severe hypoglycemia	1.13 (0.89-1.44)	0.31



NESSUNA DIFFERENZA RISPETTO A PLACEBO NEGLI OUTCOME PRIMARI

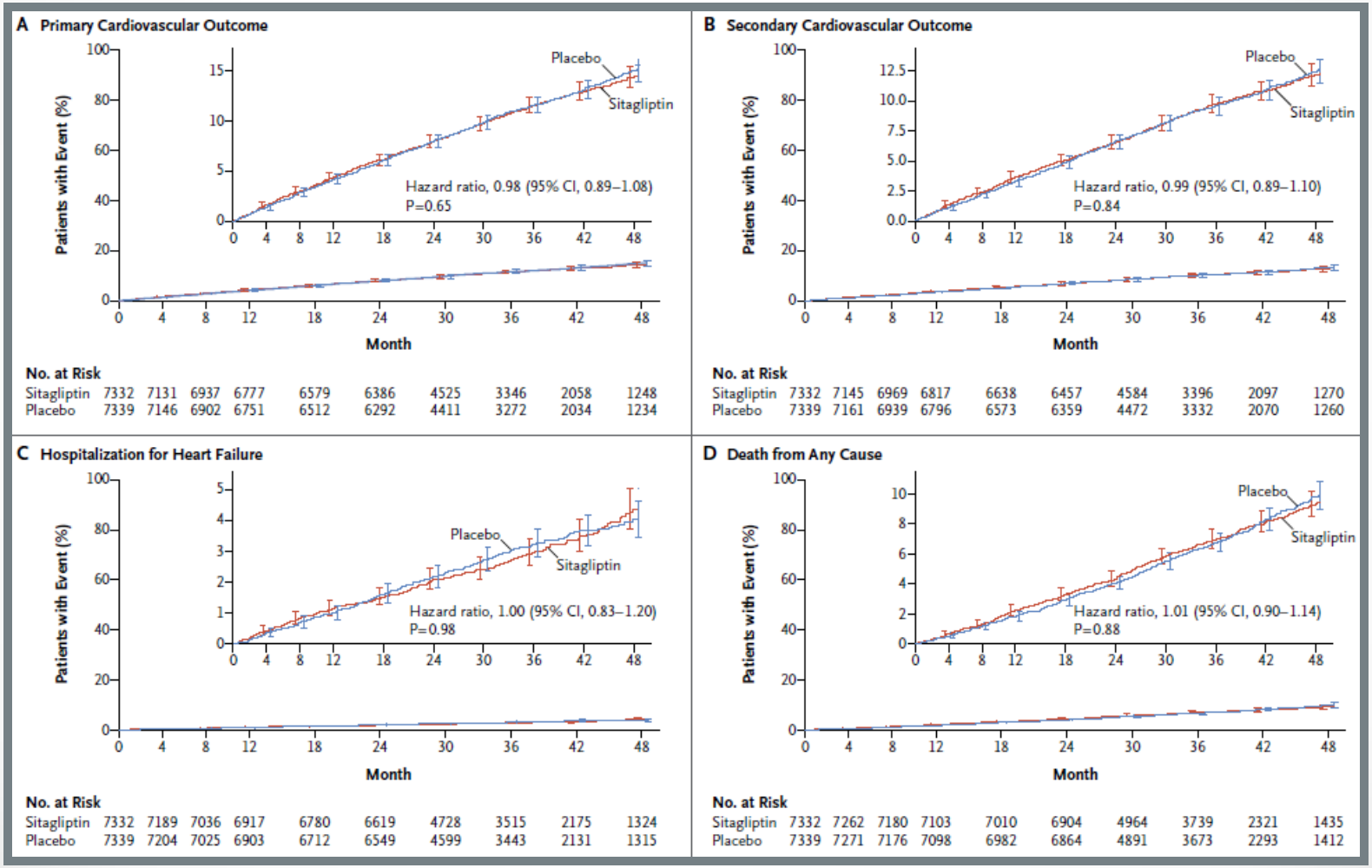
*Cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina.

†Secondary composite: cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke.

NF, noninferiority; TECOS, Trial Evaluating Cardiovascular Outcomes with Sitagliptin.

Green JB, et al. *N Engl J Med*. 2015; Jun 8. [Epub ahead of print]

TECOS
(n=14,671)
SITAGLIPTIN



TECOS, Trial Evaluating Cardiovascular Outcomes with Sitagliptin.

Green JB, et al. *N Engl J Med*. 2015; Jun 8. [Epub ahead of print]

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

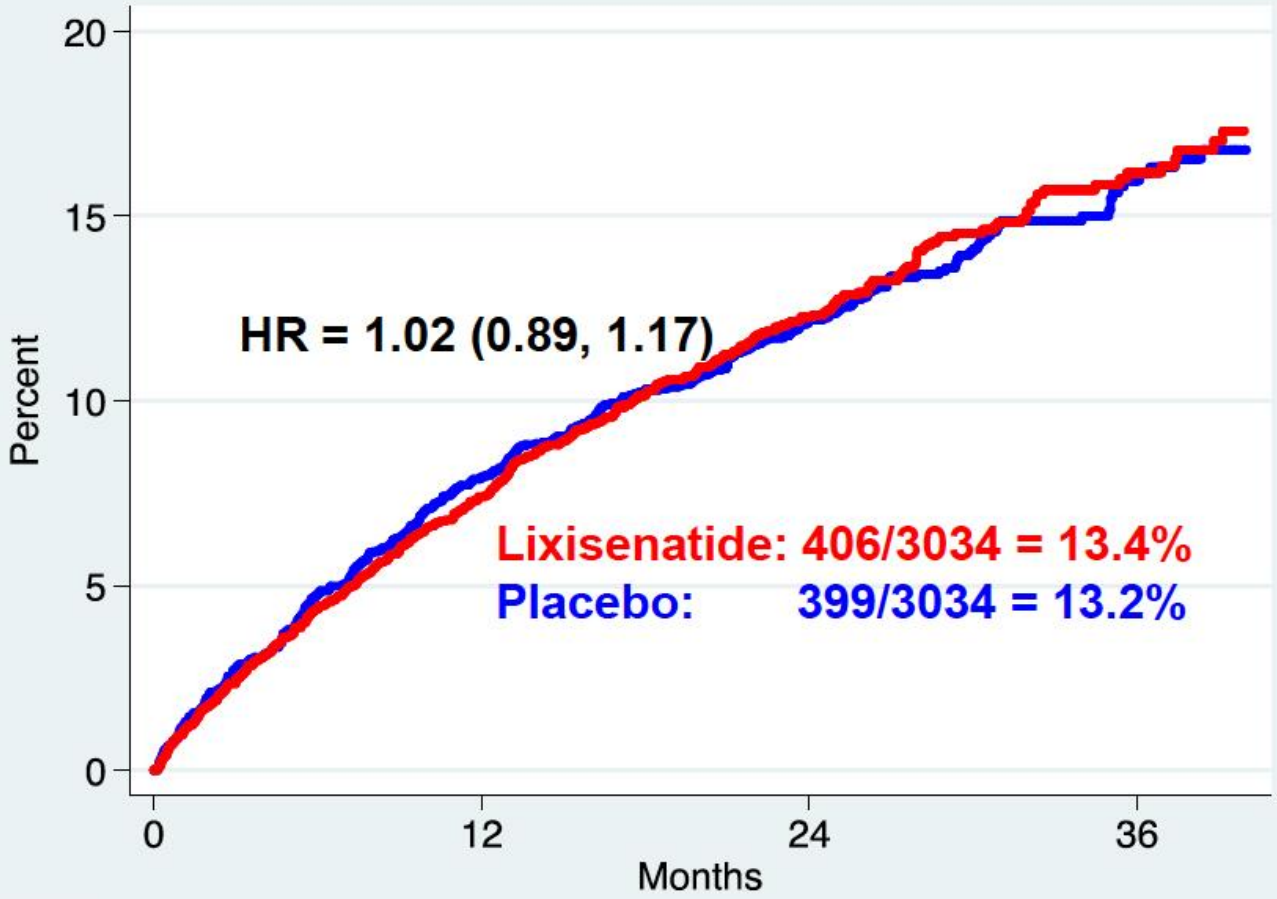
Empagliflozin, cardiovascular outcomes and mortality in type 2 diabetes

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

Liraglutide and cardiovascular outcomes in type 2 diabetes

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

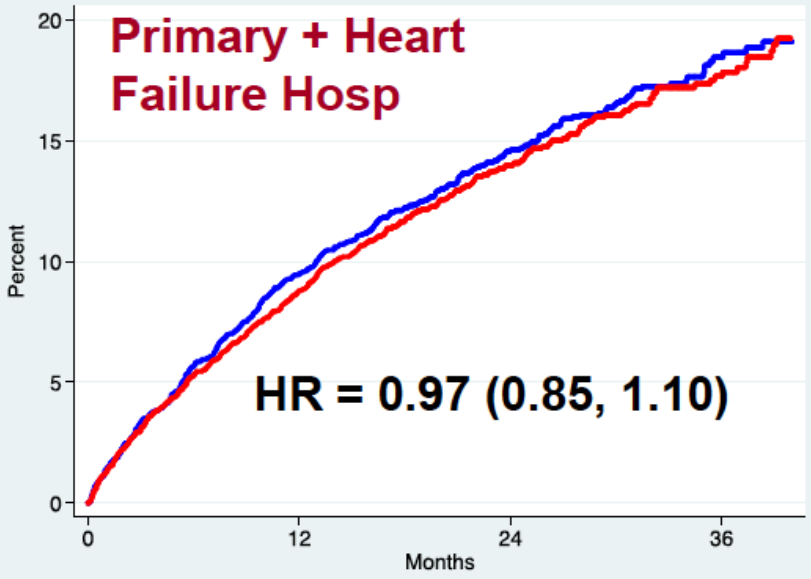
1° Outcome (CV Death, MI, Stroke or UA)

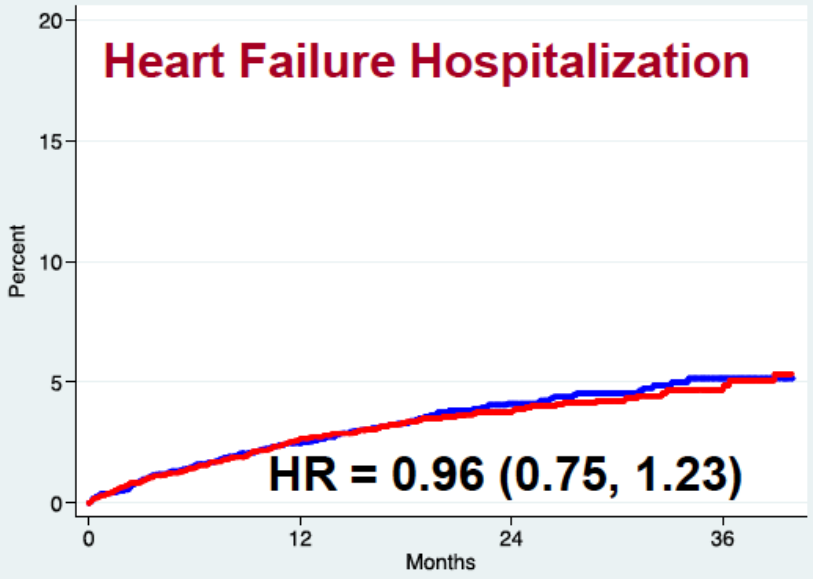


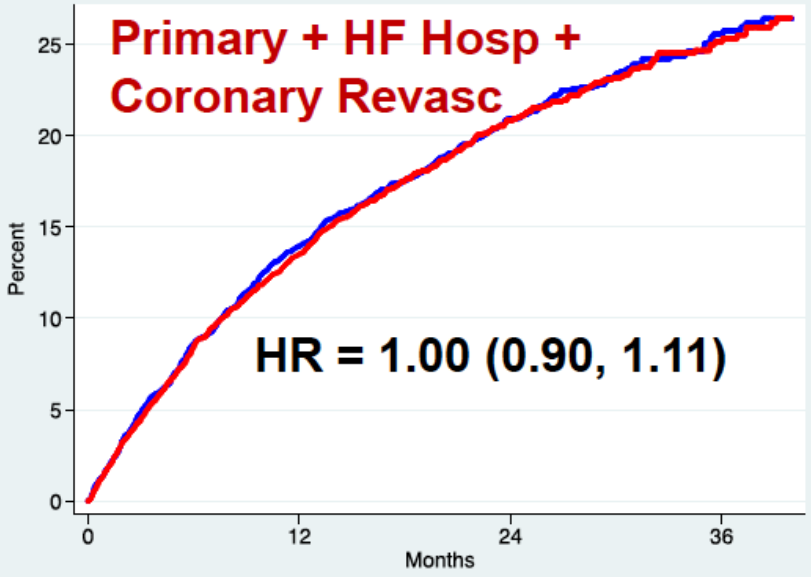
Number at risk				
Placebo	3034	2759	1566	476
Lixisenatide	3034	2785	1558	484

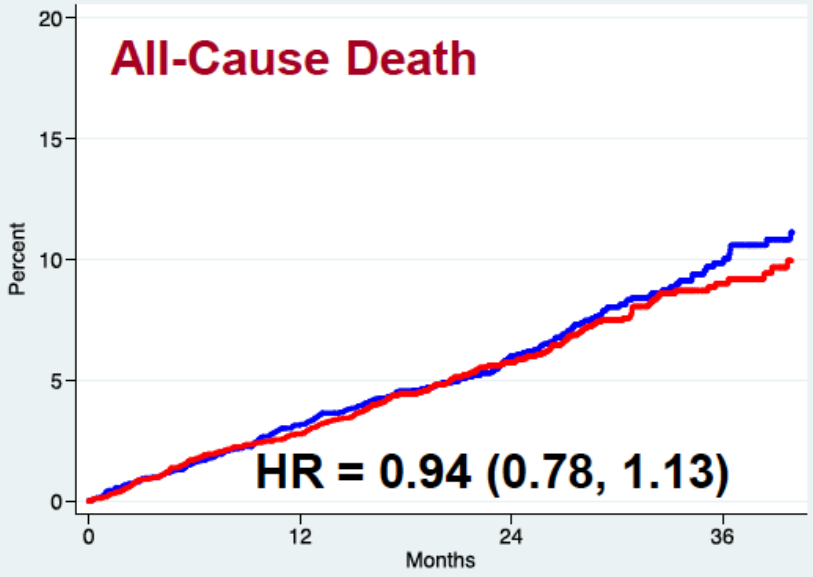
Lixisenatide & CV Outcomes

ELIXA









savor TIMI 53
TIMI STUDY GROUP / HADASSAH MEDICAL ORG

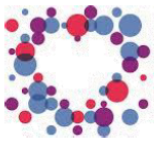
Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus

TECOS
TRIAL EVALUATING CARDIOVASCULAR OUTCOMES WITH SITAGLIPTIN

Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes

EXAMINE

Alogliptin after acute coronary syndrome in patients with type 2 diabetes


EMPA-REG OUTCOME®

Empagliflozin, cardiovascular outcomes and mortality in type 2 diabetes

ELIXA

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

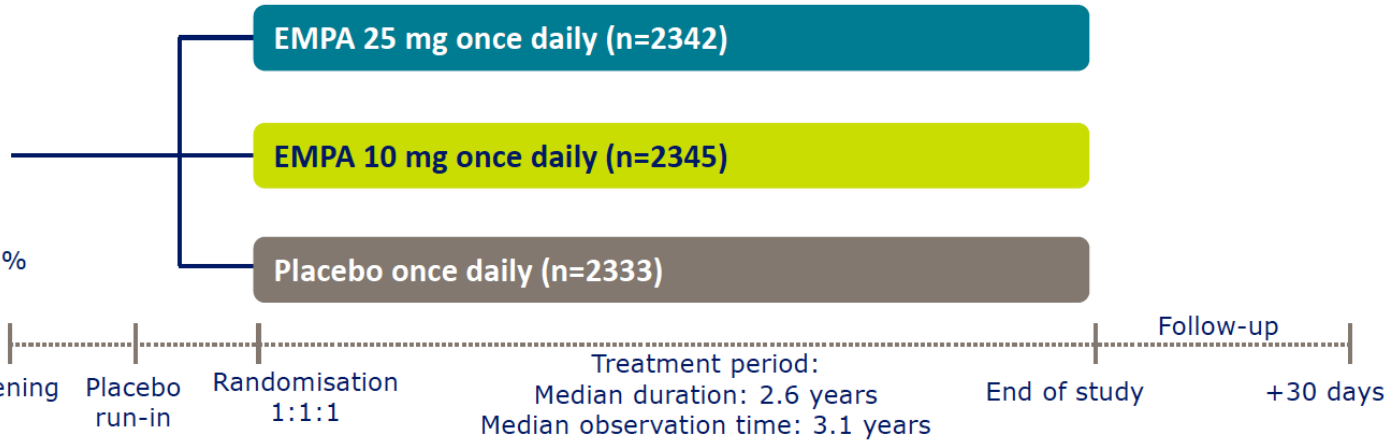
SUSTAIN
SEMAGLUTIDE UNABATED SUSTAINABILITY IN TREATMENT OF TYPE 2 DIABETES

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

EMPA-REG OUTCOME: study design

N=7028

- T2DM
- Age: ≥18 years; ≥20 years in Japan; ≤65 years in India
- Established CV disease
- Drug naïve and HbA_{1c} ≥7.0 to ≤9.0% **or**
  Stable background antidiabetes therapy* and HbA_{1c} ≥7.0 to ≤10.0%
- BMI ≤45.0 kg/m^2
- eGFR ≥30 mL/min/1.73m^2



Primary composite endpoint

- Three-point MACE - time to first occurrence of:
  - CV death,
  - Non-fatal MI†, **or**
  - Non-fatal stroke

Key secondary endpoints

- Four-point MACE - time to first occurrence of:
  - CV death,
  - Non-fatal MI†
  - Non-fatal stroke, **or**
  - Hospitalisation for unstable angina

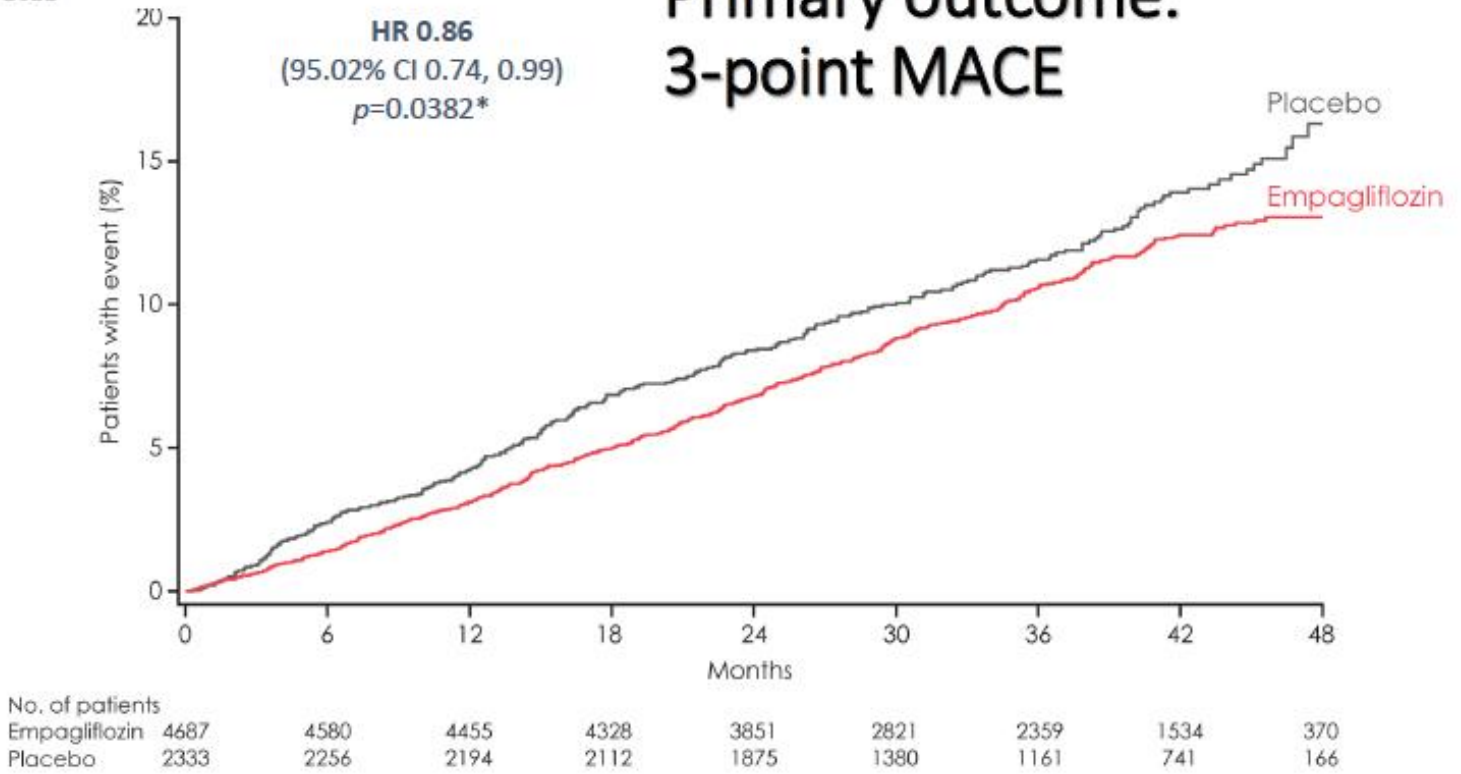
*Except pioglitazone in Japan; †Excluding silent MI.
Background glucose-lowering therapy unchanged in first 12 weeks, then adjusted at the investigator's discretion to achieve desired glycaemic control.
BMI, body mass index; CV, cardiovascular; CVOT, cardiovascular outcome trial; eGFR, estimated glomerular filtration rate; EMPA, empagliflozin; HbA_{1c}, glycosylated haemoglobin; MACE, major adverse cardiovascular event; MI, myocardial infarction; T2DM, type 2 diabetes mellitus.
Zinman B et al. *Cardiovasc Diabetol* 2014;13:102; Zinman B et al. *N Engl J Med* 2015;373(22):2117–28

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

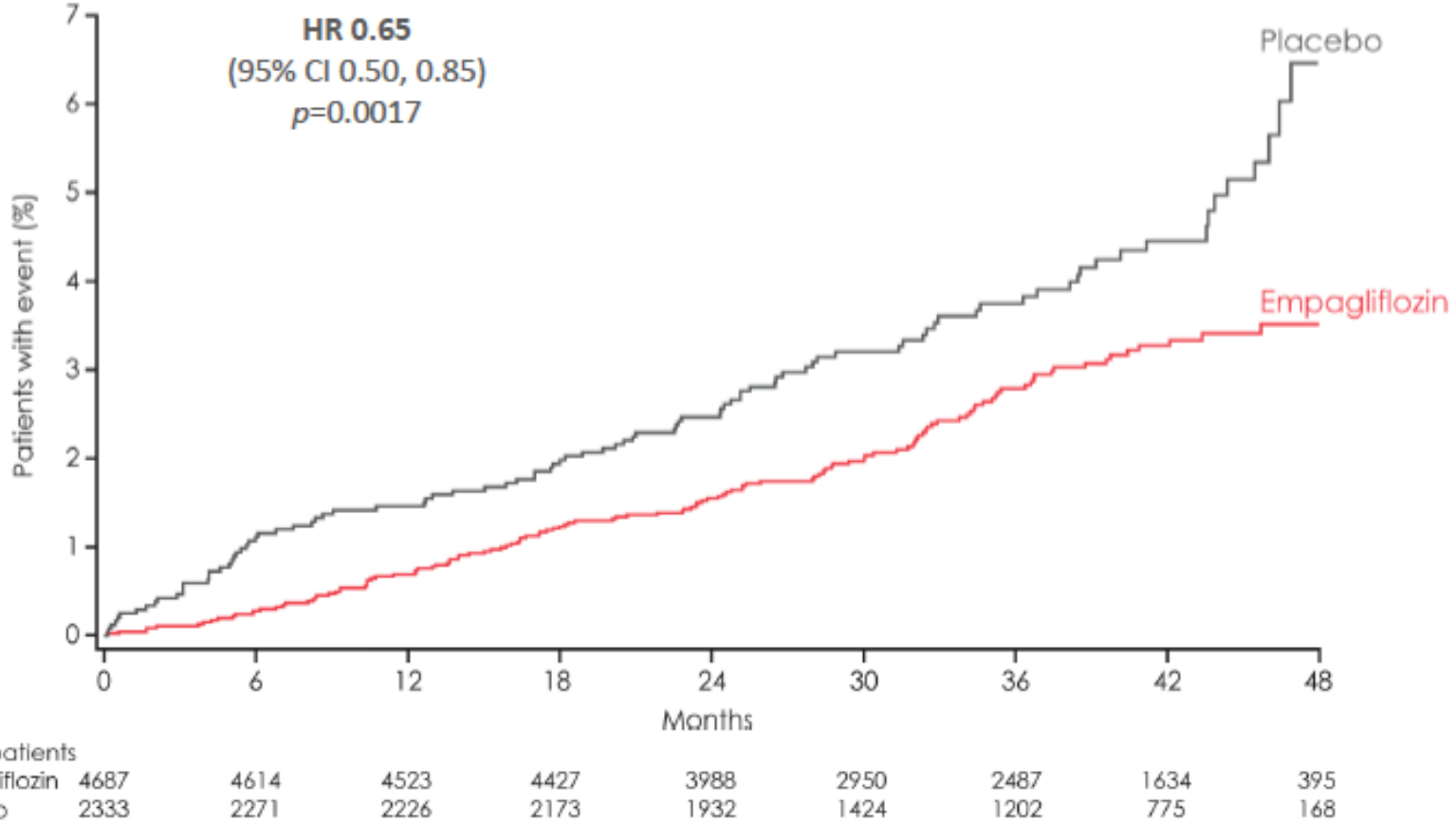
N Engl J Med 2015; 373:2117-2122

Primary outcome: 3-point MACE



EMPAREG-OUTCOME:

Hospitalisation for Heart Failure



Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

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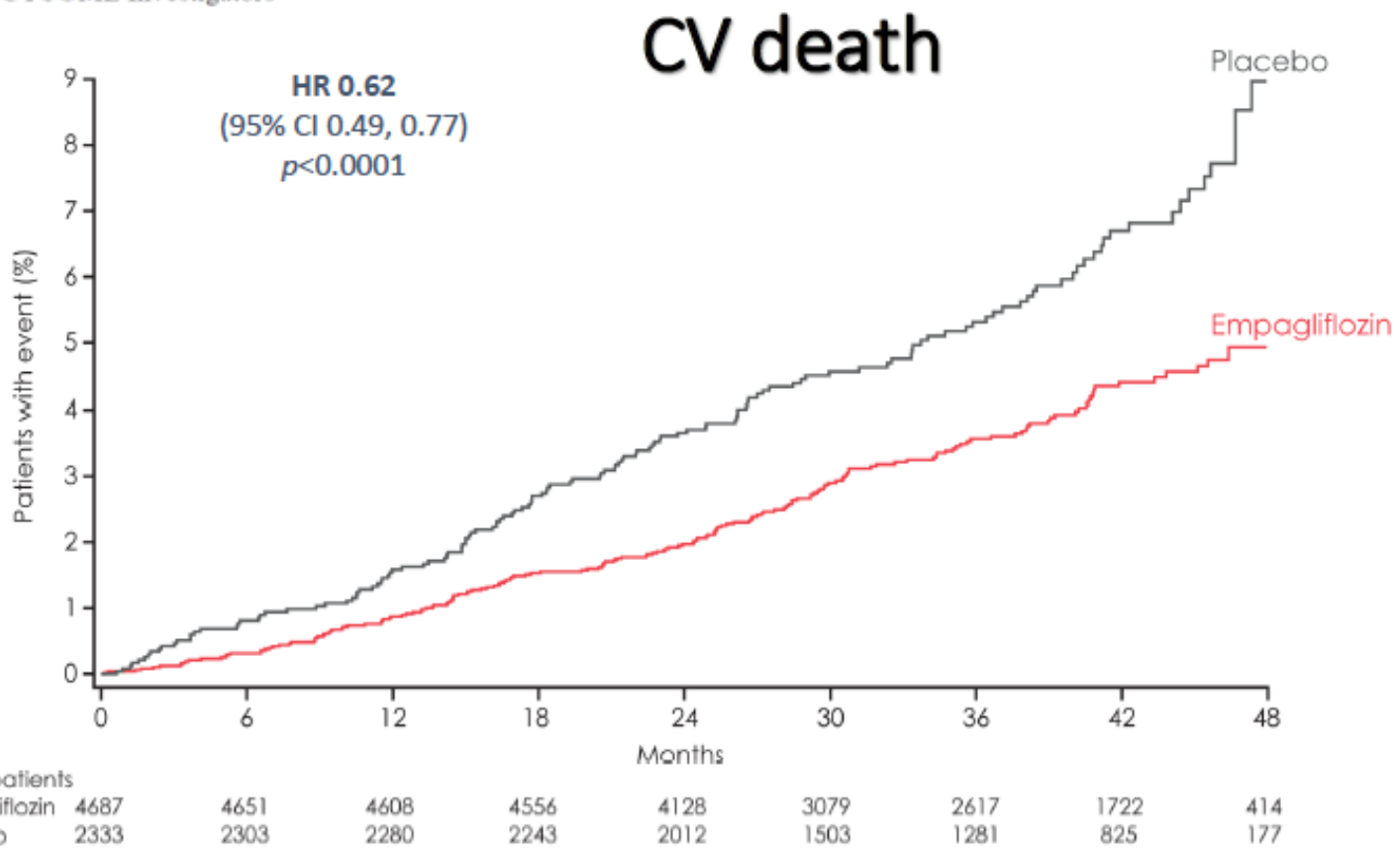
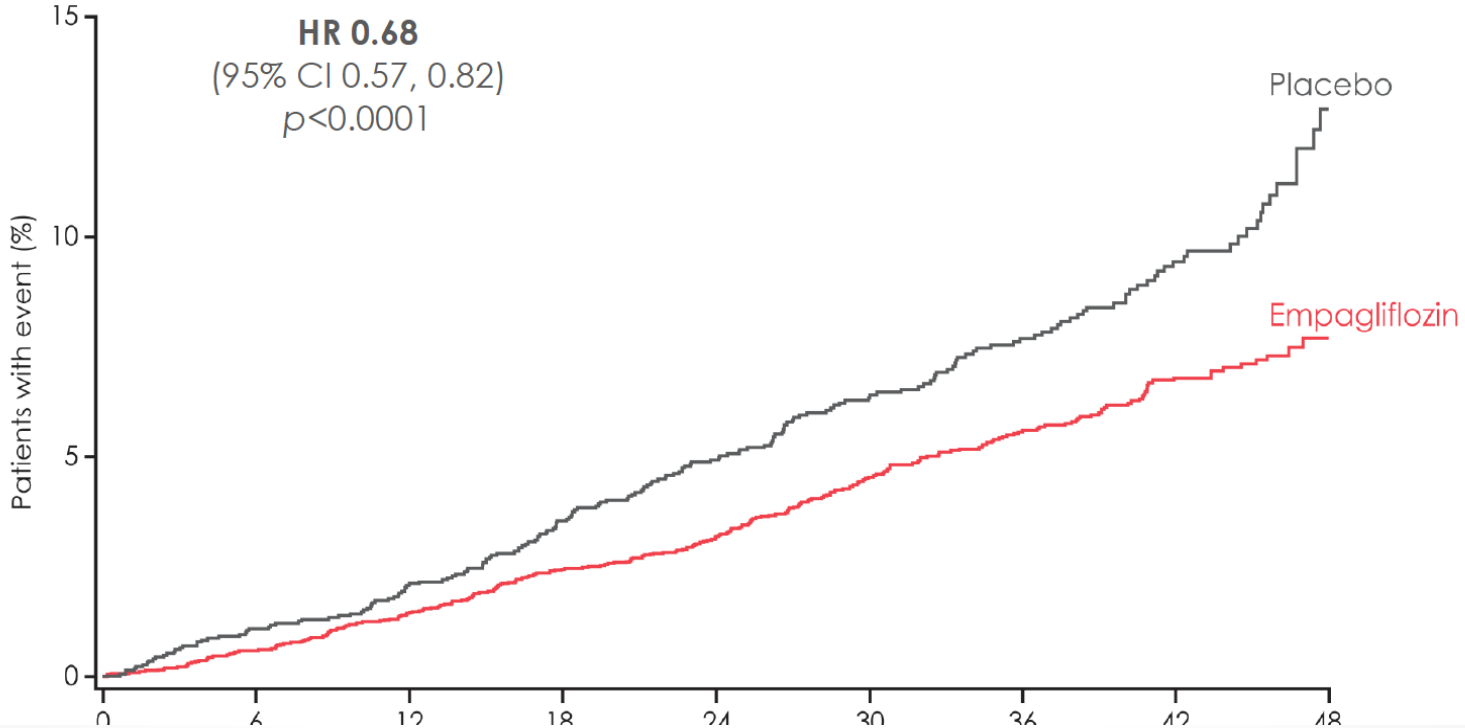


EMPA-REG OUTCOME

All-cause mortality



EMPA-REG OUTCOME

- RIDUZIONE DEI RICOVERI PER SCOMPENSO CARDIACO DEL 35%
- RIDUZIONE DEL RISCHIO DI MORTE CARDIOVASCOLARE DEL 38%
- RIDUZIONE DEL RISCHIO DI MORTE PER TUTTE LE CAUSE DEL 32%
- Non differenze rispetto a placebo per infarto e stroke non fatale

SGLT2: effetto di classe?

Acta Diabetol
DOI 10.1007/s00592-016-0892-7

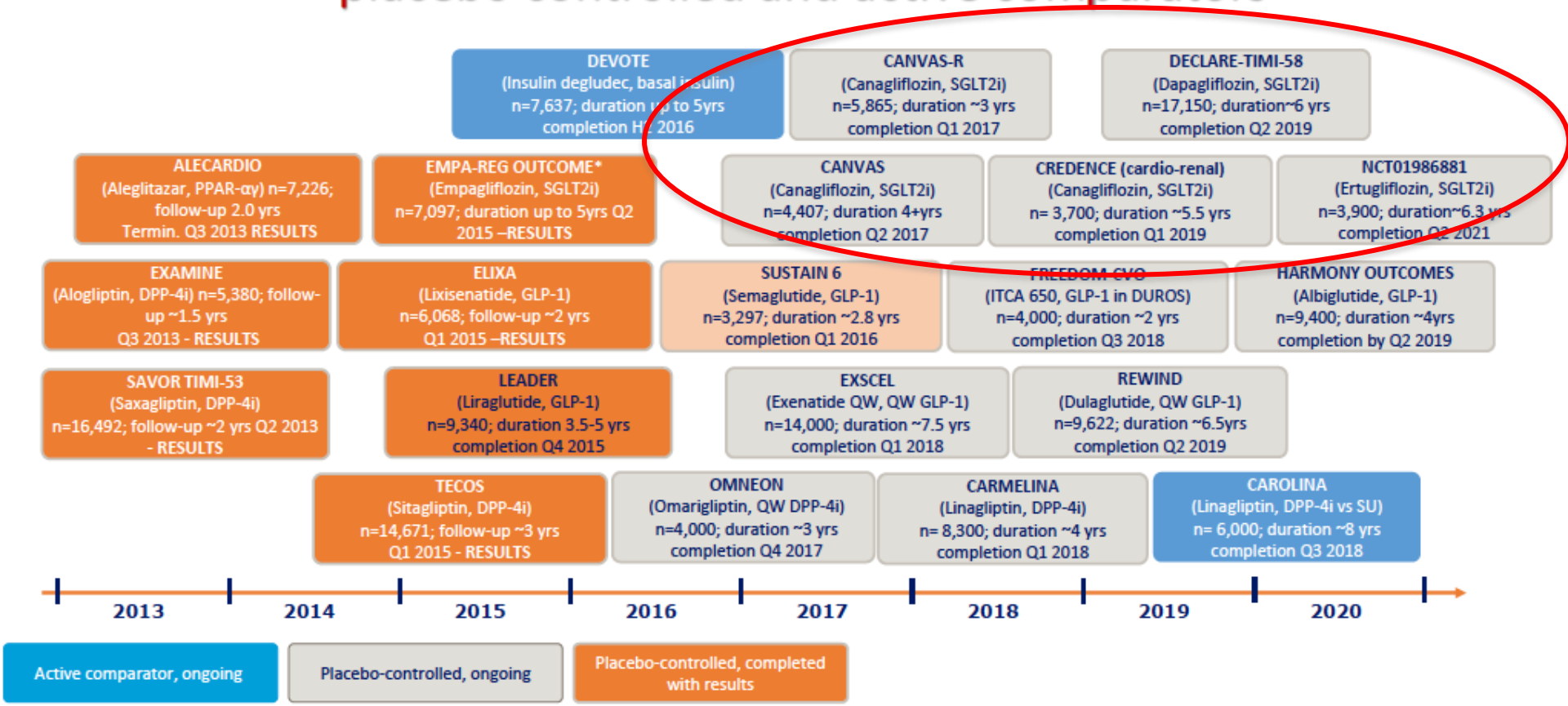
ORIGINAL ARTICLE

Effects of SGLT-2 inhibitors on mortality and cardiovascular events: a comprehensive meta-analysis of randomized controlled trials

Matteo Monami[1] · Ilaria Dicembrini[1] · Edoardo Mannucci[1]

Metanalisi di 71 studi (31199 pz in trattamento SGLT-2i, 16088 nel gruppo comparator)

Ongoing and recently completed cardiovascular outcomes trials placebo controlled and active comparators



Source: ClinicalTrials.gov (30 June 2015). 'Completion date' is the estimated completion date for the primary outcomes measure. *Also known as C-SCADE-8.

All cause mortality

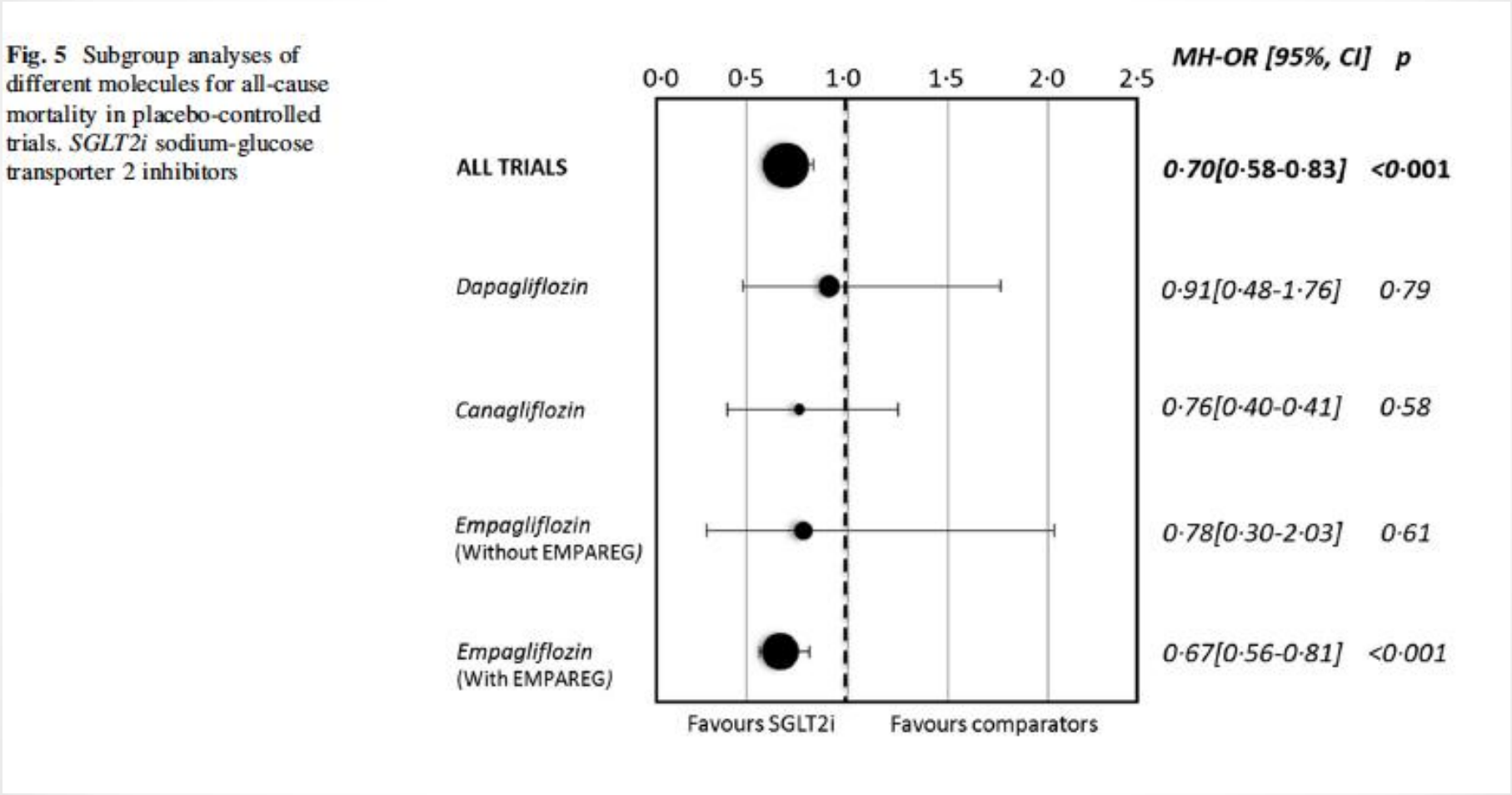
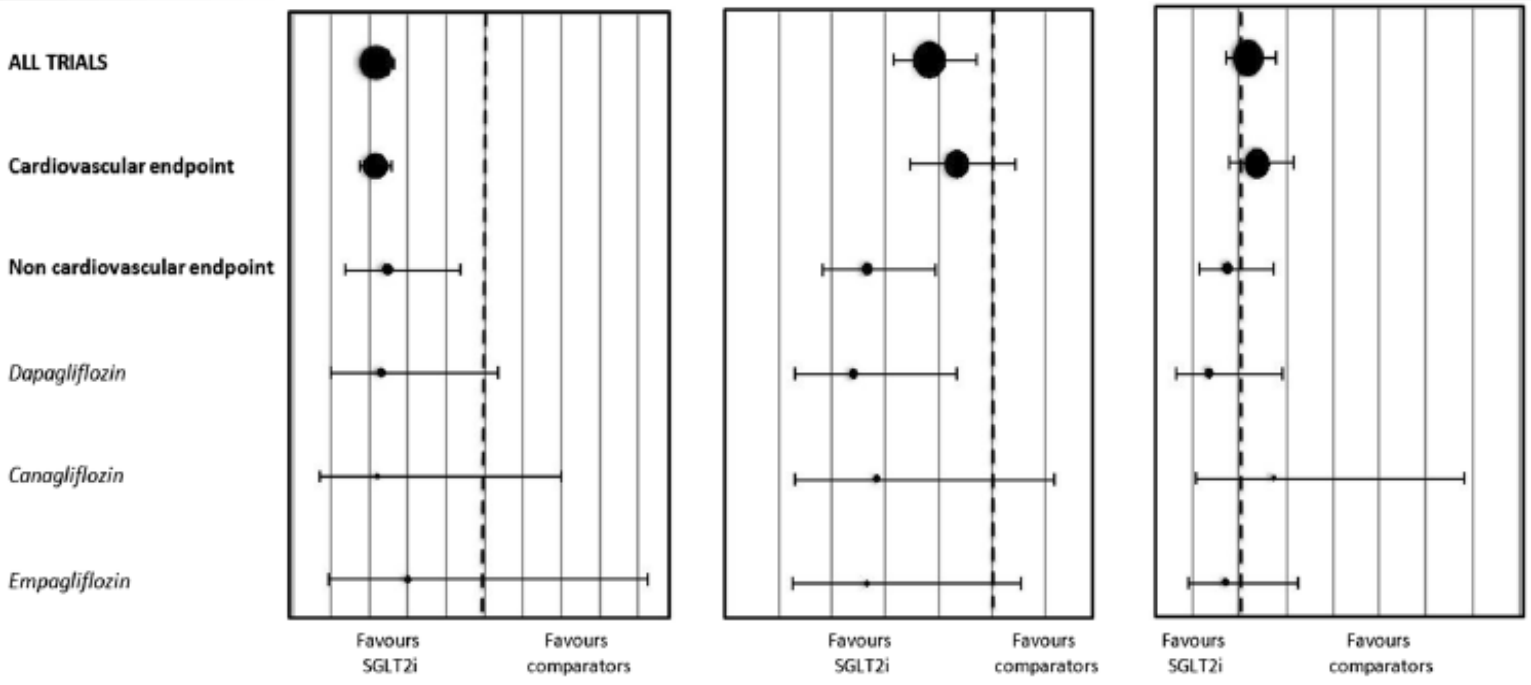


Fig. 5 Subgroup analyses of different molecules for all-cause mortality in placebo-controlled trials. *SGLT2i* sodium-glucose transporter 2 inhibitors

MORTALITA' CV INFARTO MIOCARDICO STROKE

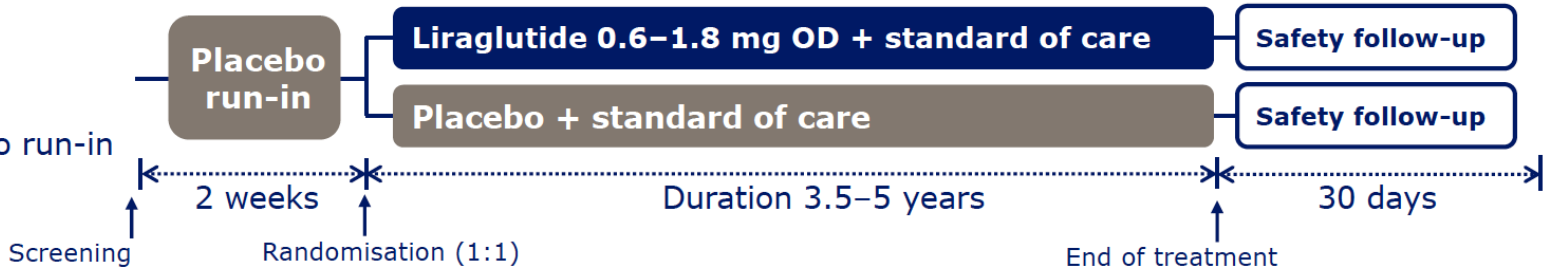


	MH-OR [95%, CI]	p	MH-OR [95%, CI]	p	MH-OR [95%, CI]	p
All trials:	*0·43[0·36-0·53]*	*<0·001*	*0·77[0·63-0·94]*	*0·010*	*1·09[0·86-1·38]*	*0·50*
CV endpoint	*0·43[0·35-0·52]*	*<0·001*	*0·87[0·69-1·09]*	*0·23*	*1·19[0·89-1·58]*	*0·23*
Non CV endpoint	*0·49[0·27-0·87]*	*0·016*	*0·53[0·36-0·79]*	*0·002*	*0·88[0·57-1·36]*	*0·57*
Dapagliflozin	*0·46[0·20-1·07]*	*0·071*	*0·48[0·26-0·87]*	*0·017*	*0·68[0·31-1·46]*	*0·32*
Canagliflozin	*0·44[0·14-1·40]*	*0·16*	*0·57[0·26-1·25]*	*0·15*	*1·36[0·54-3·40]*	*0·51*
Empaglflozin	*0·60[0·19-1·85]*	*0·37*	*0·53[0·25-1·11]*	*0·093*	*0·85[0·45-1·62]*	*0·63*

LEADER: Study design

9340 patients

- Double blinded
- 2-week placebo run-in



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

CV, cardiovascular; HbA_{1c}, glycosylated haemoglobin; OAD, oral antidiabetic drug; OD, once daily; T2DM, type 2 diabetes mellitus.
Marso SP et al. *N Engl J Med* 2016. DOI: 10.1056/NEJMoa1603827.

Primary and key secondary outcomes

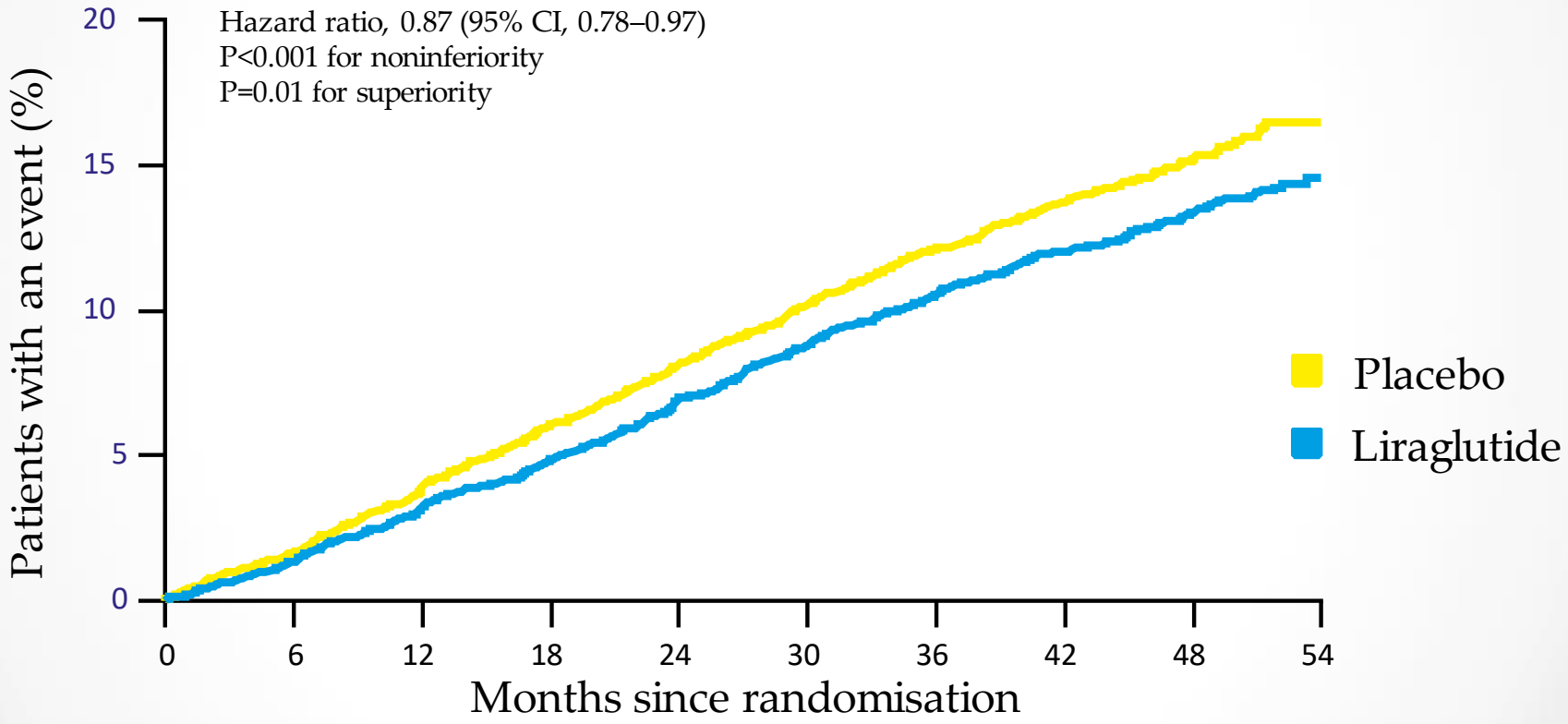
Primary outcome	**Time to first MACE composed of** • CV death • Non-fatal MI • Non-fatal stroke
Key secondary outcomes	**Time to first occurrence of** • Expanded composite CV outcome (CV death, non-fatal MI, non-fatal stroke, coronary revascularisation, unstable angina pectoris requiring hospitalisation, or hospitalisation for heart failure) • All-cause death • Each individual component of expanded composite CV outcome

CV, cardiovascular; MACE, major adverse cardiovascular event; MI, myocardial infarction.

Marso SP et al. *N Engl J Med* 2016. DOI: 10.1056/NEJMoa1603827.

LEADER trial: Primary Outcome

First occurrence of CV death, nonfatal myocardial infarction, or nonfatal stroke in the time-to-event analysis in patients with type 2 diabetes and high CV risk.

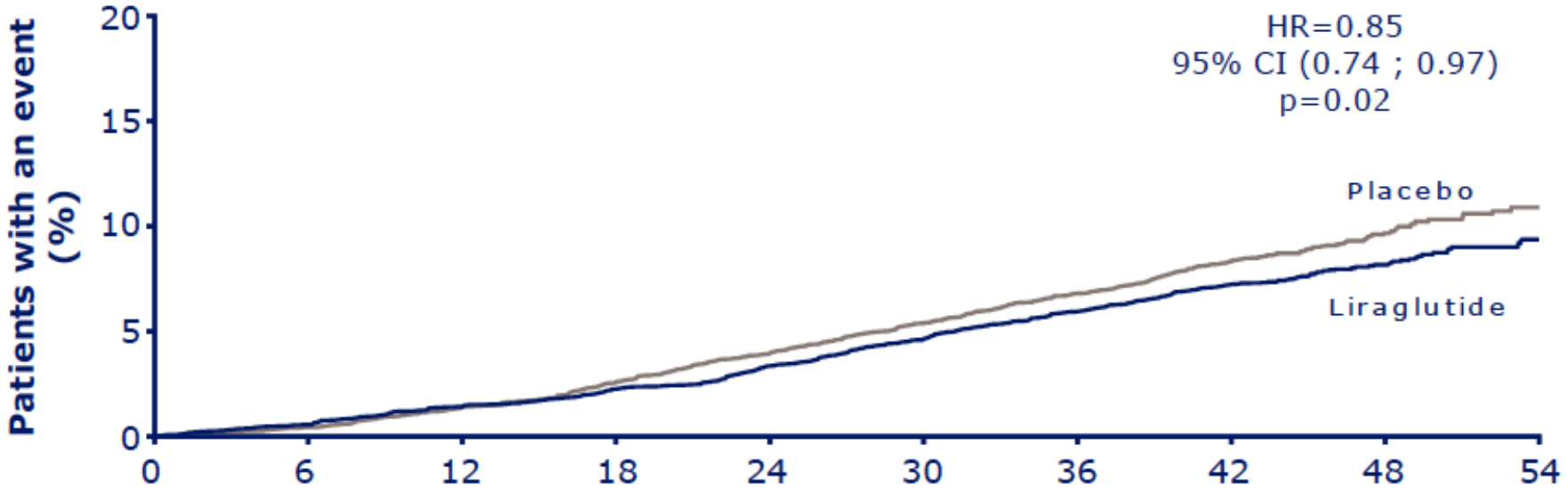


Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results (LEADER) trial

Adapted from: Marso SP *et al*, NEJM 2016

LEADER STUDY

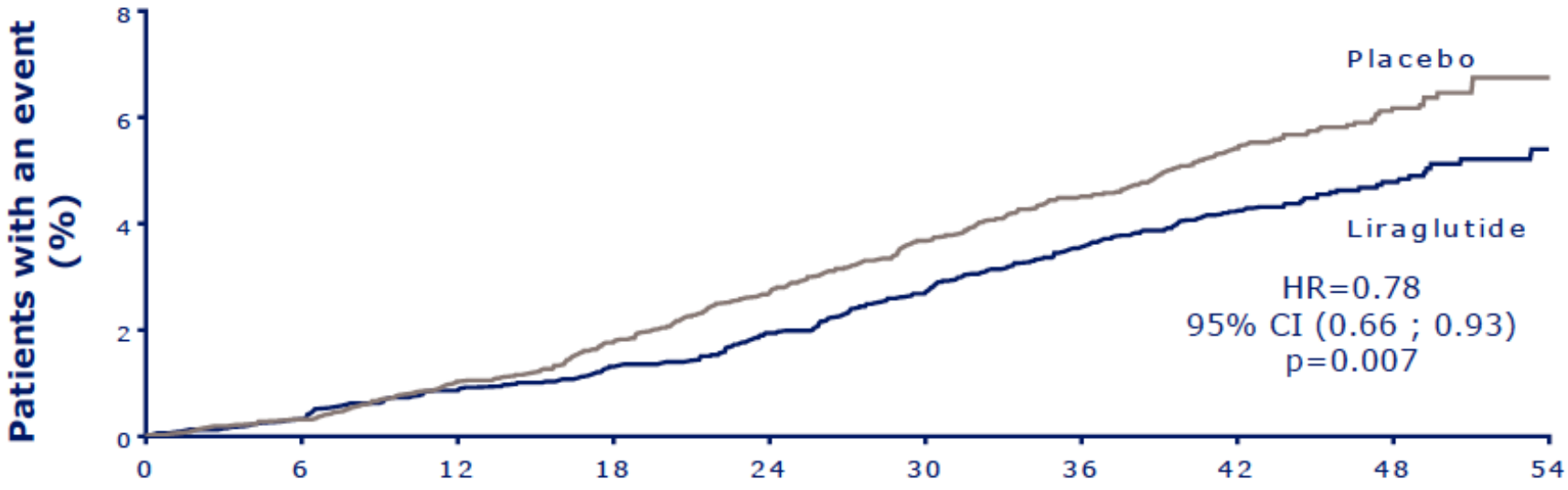
All-cause death



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 STUDY

CV death



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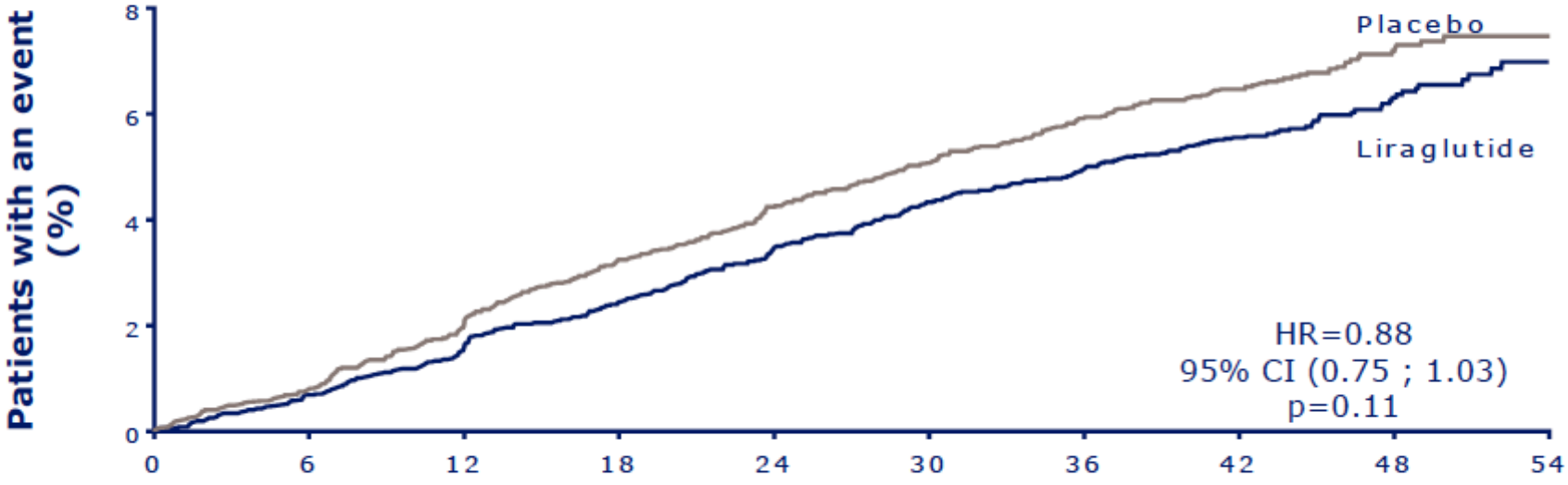
Placebo	4672	4648	4601	4546	4479	4407	4338	4267	1709	465

LEADER STUDY

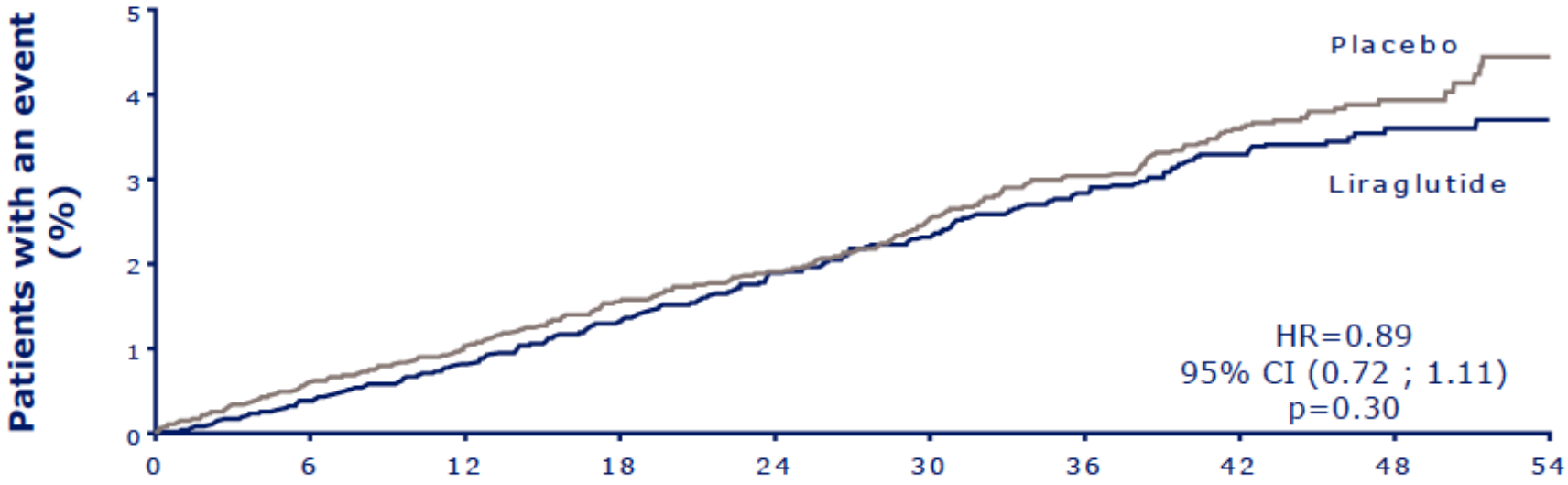
Non-fatal myocardial infarction



Patients at risk										
Liraglutide	4668	4609	4531	4454	4359	4263	4181	4102	1619	440
Placebo	4672	4613	4513	4407	4301	4202	4103	4020	1594	424

LEADER STUDY

Non-fatal stroke



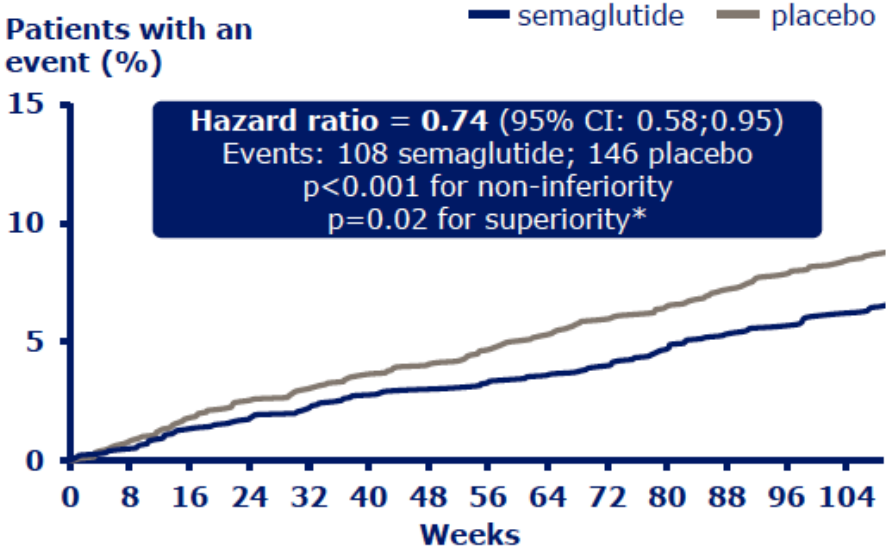
Patients at risk										
Liraglutide	4668	4624	4564	4504	4426	4351	4269	4194	1662	465
Placebo	4672	4622	4558	4484	4405	4314	4228	4141	1648	445

LEADER STUDY

- RIDUZIONE DEL RISCHIO DI MORTE CARDIOVASCOLARE DEL 22%
- RIDUZIONE DEL RISCHIO DI MORTE PER TUTTE LE CAUSE DEL 15%
- Non differenze significative rispetto a placebo per infarto non fatale, stroke non fatale

Semaglutide significantly reduced the risk of major cardiovascular events in the SUSTAIN 6 trial

Semaglutide demonstrated 26% reduction in composite CV outcome compared with placebo



Note: p-value is two-sided, pooled data reported for both semaglutide and placebo
MACE: Major adverse cardiovascular event; 3-point MACE comprises cardiovascular death, non-fatal myocardial infarction and non-fatal stroke; CI: Confidence interval
* No adjustment for multiple tests
Source: Marso SP, Bain SC, Consoli A, *et al.* Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *The New England journal of medicine*. 2016

Key results

- Non-inferiority of semaglutide compared to placebo was confirmed for time to first MACE
- Semaglutide reduced the risk of composite cardiovascular outcome, ie time from randomisation to first occurrence of CV death, non-fatal MI or non-fatal stroke, by 26% compared to placebo
- The result was consistent across sensitivity analyses

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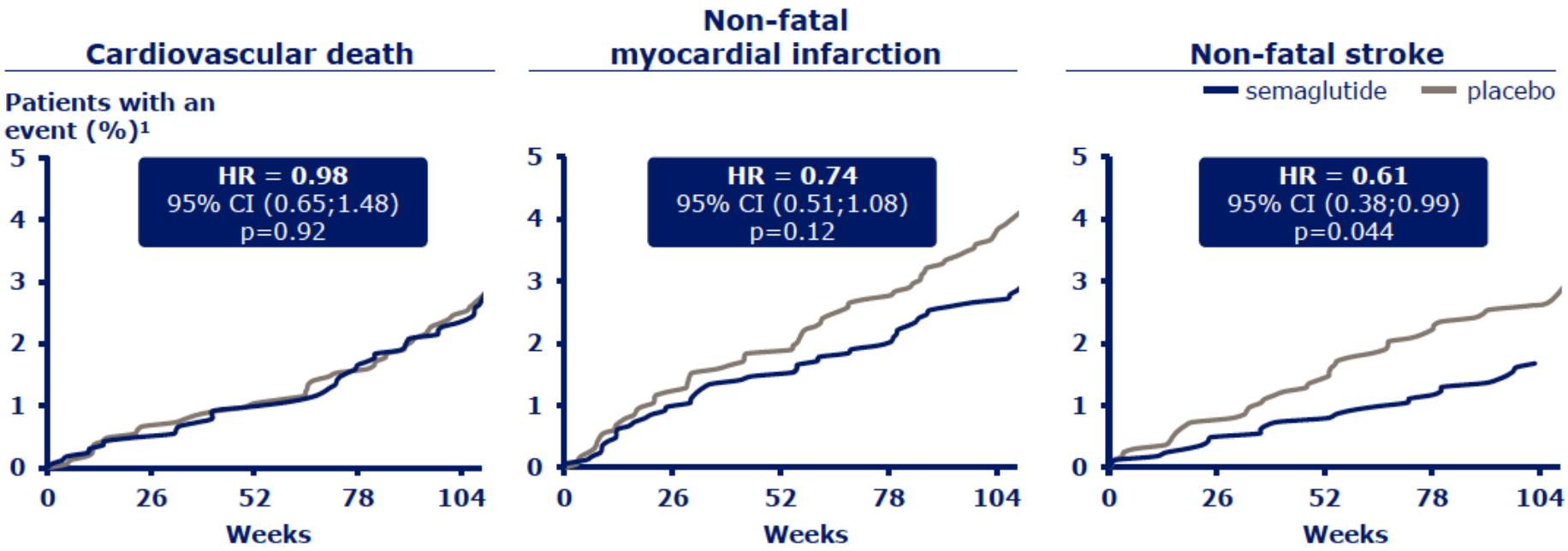
The MACE risk reduction was driven by non-fatal MI and non-fatal stroke in the SUSTAIN 6 trial



Note: All p-values are two-sided, pooled data reported for both semaglutide and placebo
MACE: Major adverse cardiovascular events; MI: Myocardial infarction; HR: Hazard ratio; CI: Confidence interval
[1]The time to event analyses were specified post-hoc
Source: Marso SP, Bain SC, Consoli A, *et al*. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *The New England journal of medicine*. 2016

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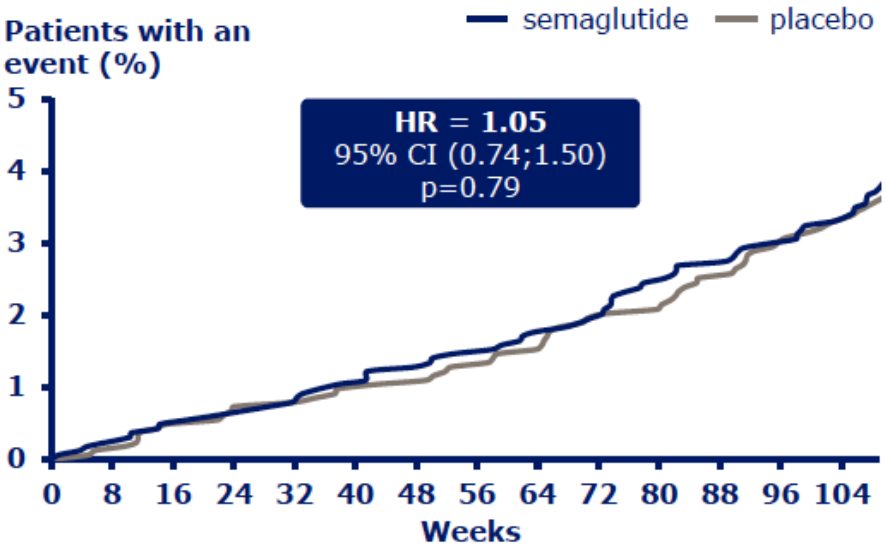
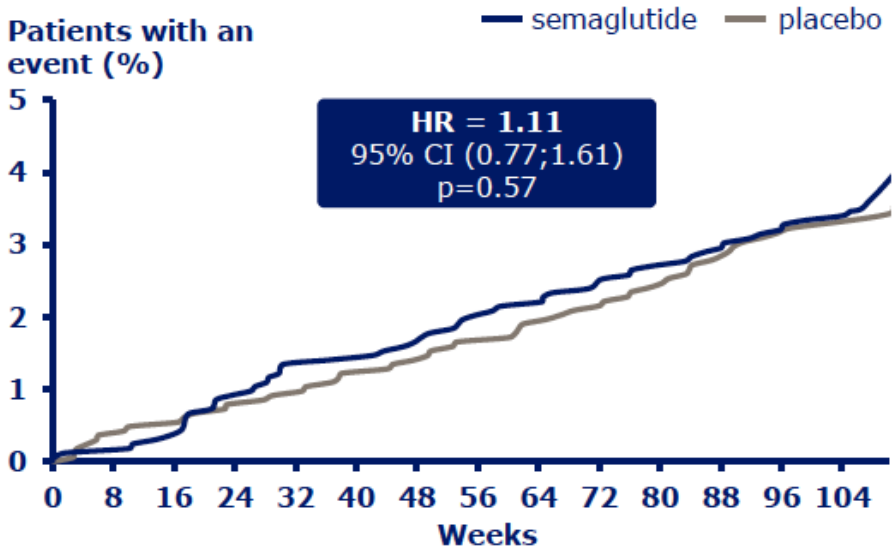
No significant differences in risk of all-cause-death and hospitalisation for heart failure with sema in SUSTAIN 6

No significant difference in the risk of all-cause-death



No significant difference in the risk of patients being hospitalised for heart failure



Note: All p-values are two-sided, pooled data reported for both semaglutide and placebo
Sema: Semaglutide; HR: Hazard ratio; CI: Confidence interval
Source: Marso SP, Bain SC, Consoli A, *et al*. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *The New England journal of medicine*. 2016

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EMPA-REG

End point	HR	95% CI
MACE-3	0,86	0,74-0,99
CV DEATH	0,62	0,49-0,77
MI	0,87	0,70-1,09
STROKE	1,24	0,92-1,67

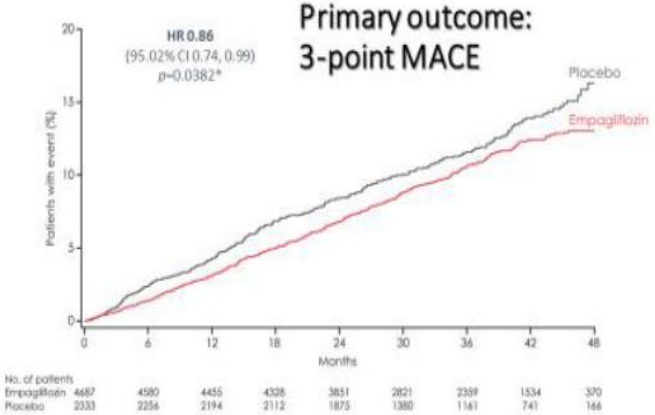
LEADER

End point	HR	95% CI
MACE-3	0,87	0,78-0,97
CV DEATH	0,78	0,66-0,93
MI	0,88	0,75-1,03
STROKE	0,89	0,72-1,11

SUSTAIN-6

End point	HR	95% CI
MACE-3	0,74	0,58-0,95
CV DEATH	0,98	0,65-1,48
MI	0,74	0,51-1,08
STROKE	0,61	0,38-0,99

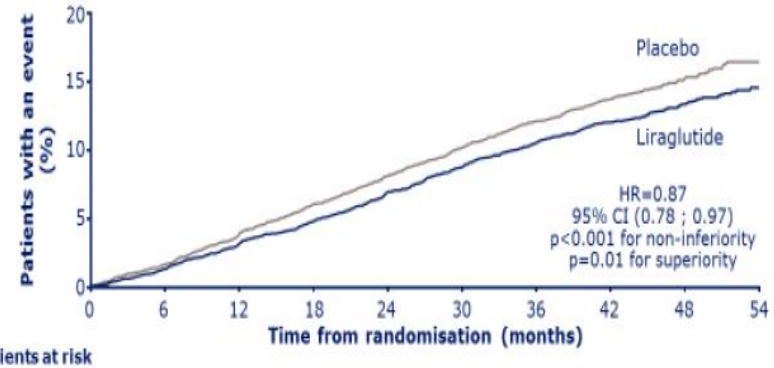
EMPA-REG



LEADER

Primary outcome

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



Patients at risk

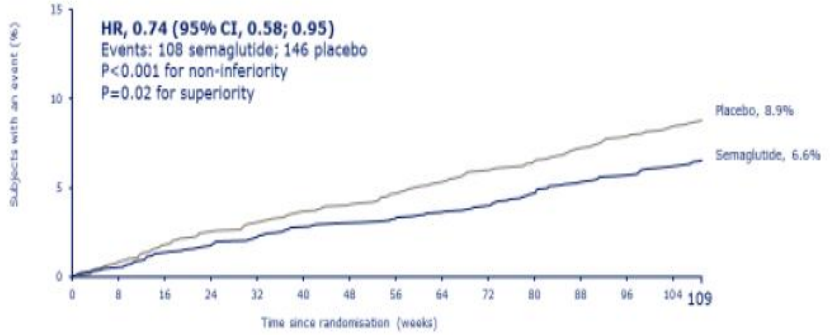
Liraglutide	4668	4593	4496	4400	4280	4172	4072	3982	1562	424
Placebo	4672	4588	4473	4352	4237	4123	4010	3914	1543	407

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* 2016. DOI: 10.1056/NEJMoa1603827.

SUSTAIN-6

Primary outcome

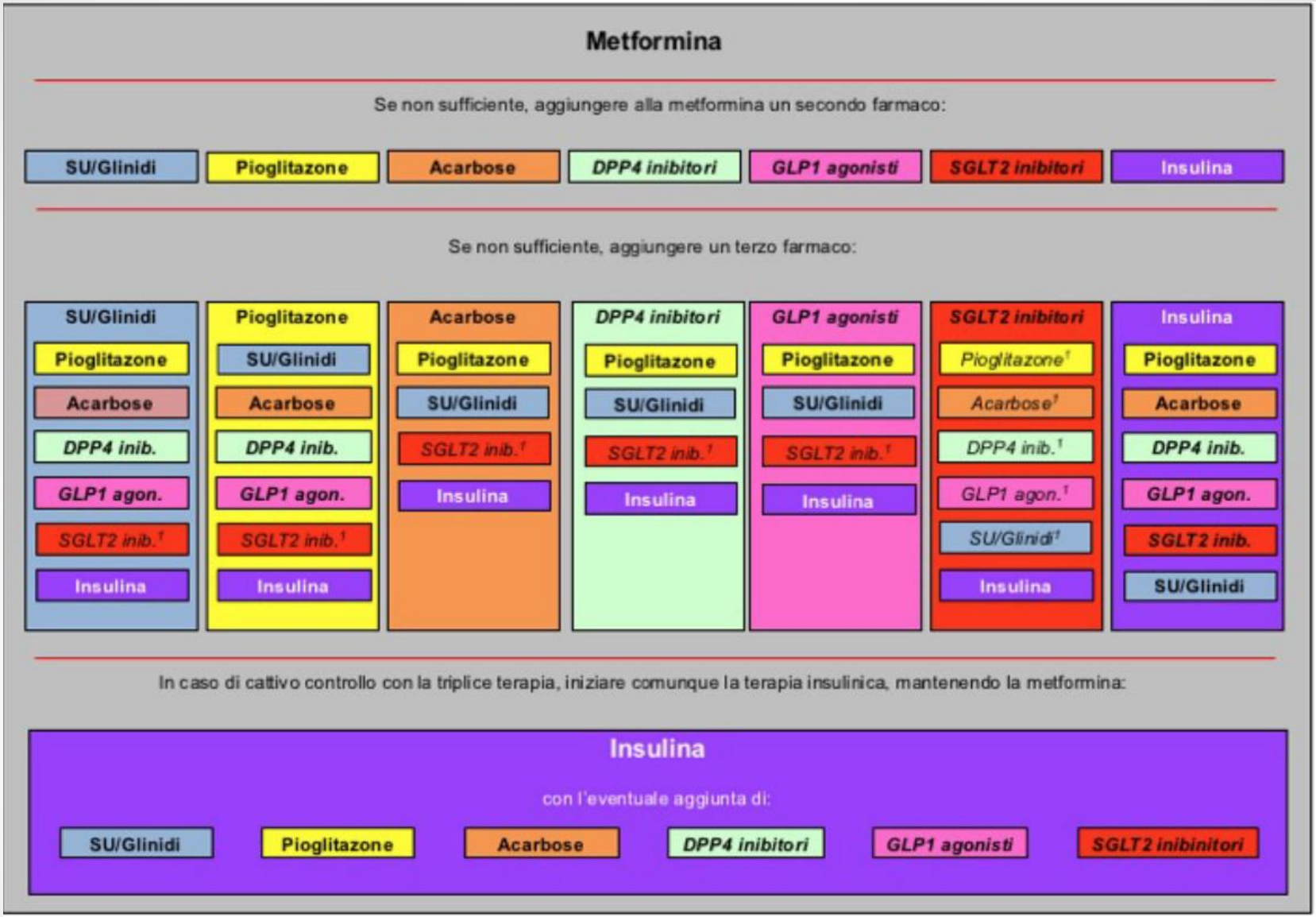
TIME TO FIRST OCCURRENCE OF CV DEATH OR NON-FATAL MI OR NON-FATAL STROKE



Number of subjects at risk

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

Figure 1A. Kaplan Meier plot for first event adjudication committee-confirmed CV death, non-fatal MI and non-fatal stroke using 'in-trial' data from subjects in the full analysis set.
*Not prespecified. CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction.
Marso et al. NEJM [in press]



In **neretto** le combinazioni rimborsate, in ***neretto corsivo*** le combinazioni rimborsate solo con piano terapeutico specialistico, in *corsivo* le combinazioni indicate ma non rimborsate.

[1] Indicazioni approvate da EMA, per le quali AIFA ha deciso di non concedere la rimborsabilità.

STANDARD DI CURA AMD-SID 2016

	Metfor-mina	Acarbosio	GLP-1	Gliflo-zina	Glip-tina	Pioglita-zone	SU/ glinide	Insulina basale	Insulina basal-bolus
Riduzione della HbA_{1c} a breve termine (3-6 mesi)*	+++	+	+++	++	++	+	+++	+++	++++
Riduzione della HbA_{1c} a medio termine (1-2 anni)*	++	+	+++	++	++	++	++	+++	++++
Riduzione della HbA_{1c} a lungo termine (oltre 2 anni)*	++	+	+++	++	ND	+++	+	+++	++++
Riduzione del peso corporeo	+/-	+/-	+++	++	-	-	-	-	-
Riduzione della pressione arteriosa	+/-	-	+	++	-	+	-	-	-
Riduzione della morbilità/mortalità CV**	++	-	-	+++	-	++	-	-	-

STANDARD DI CURA AMD-SID 2016

	Metfor-mina	Acarbosio	Agon-sta GLP-1	Gliflo-zina	Glip-tina	Pioglita-zone	SU/ glinide	Insulina basale	Insulina basal-bolus
Interazioni con altri farmaci	-	-	-	-	-	+	+++	+++	++++
Ipoglicemie	-	-	-	-	-	-	++	+++	++++
Aumento di peso	-	-	-	-	-	++	+	+++	++++
Pancreatiti	-	-	+/-	-	+/-	-	-	-	-
Fratture	-	-	-	-/+[a]	-	+++	-	-	-
Scompenso cardiaco	-	-	-	-	-/+[b]	++	+	-	-
Disturbi gastrointe-stinali	++	+++	++	-/+	-	-	-	-	-
Infezioni genitali	-	-	-	+	-	-	-	-	-

Il pieghevole dell'Appropriatezza Terapeutica

Classe	Molecola	Efficacia su		Durata d'azione (ore)	Rischio ipoglicemico	Effetto sul peso corporeo	Via di eliminazione	Anziano >75 anni in buone condizioni generali
		FPG	PPG					
Inibitori α-glicosidasi	Acarbose	A	M	4	A in monoterapia	↔	I	I
Insulino-sensibilizzanti	Metformina	M	L	7-12	A in monoterapia	↓	R	C se IRC o altre cause di accumulo lattato
	Pioglitazione	M	L	24-30	A in monoterapia	↑	SGE + R minimo	C
Secretagoghi	Glibenclamide	M	M/F	20-24	G	↑	R	S
	Gliclazide	M	M/F	10-15 (24 se RM)	M in assenza di alcuni determinanti	↑	R	C
	Glimepiride	M	M/F	24	G	↑	R + F	C
	Glipizide	M	M	12-14	M in assenza di alcuni determinanti	↑	R	C
	Gliquidone	M	M	8-10	M in assenza di alcuni determinanti	↑	F	C
	Repaglinide	L	F	6-8	M in assenza di alcuni determinanti	↑	F	C per mancanza di evidenza
GLP1-RA	Exenatide BID	M	F	2-4	A in monoterapia	↓	R	C per mancanza di evidenza
	Exrnatide LAR	F	M	4-8 giorni	A in monoterapia	↓	R	C per mancanza di evidenza
	Liraglutide	F	M	10-14	A in monoterapia	↓	R + F + SGE	C per mancanza di evidenza
	Lixisenatide	M	M/F	3-4	A in monoterapia	↓	R	C per mancanza di evidenza
Inibitori DPP-4	Sitagliptin	M	M/F	8-14	A in monoterapia	↔	R	I
	Vildagliptin	M	M/F	2-3	A in monoterapia	↔	R	I
	Saxagliptin	M	M/F	2.2-3.8	A in monoterapia	↔	R	I
	Linagliptin	M	M/F	10-40	A in monoterapia	↔	R	I
	Alogliptin	M	M/F	12-21	A in monoterapia	↔	R	I
SGLT2 inibitori	Canaglifozin	M	M/F	12.9	A in monoterapia	↓	SGE + R	C
	Dapaglifozin	M	L	10.6-13.1	A in monoterapia	↓	R + SGE	S
	Empaglifozin	M	L	13.1	A in monoterapia	↓	R + SGE	C

A (= assente) L (= lieve) M (= moderata) F (= forte)	L (= lieve) M (= moderata) F (= forte)

L (= lieve) M (= moderata) G (= grave)	↑ (= aumento) ↔ (= neutro) ↓ (= riduzione)	F (= fegato) R (= rene) SGE (= sistema gastroenterico)	I (= indicato) S (= sconsigliato) C (= da utilizzare con qualche cautela)

Giudizio incerto perché la letteratura in merito è scarsa

GLP1- RA = agonisti recettoriali del GLP1

Nota: in riferimento alla nota "M in assenza di alcuni determinanti" si intende che il rischio diventa grave in presenza di determinanti quali basso grado di educazione, nefro- o epatopatia o altro fattore che nel caso specifico risulti clinicamente rilevante.

1ª edizione, 15 aprile 2015 Gruppo Appropriatezza

Il pieghevole dell'Appropriatezza Terapeutica

Classe	Molecola	Epatopatia			Nefropatia con GFR mL/min:				Cardiopatia			Altre contro-indicazioni	Effetti collaterali (vedi legenda)
		Child A	Child B	Child C	> 60	60-30	< 30	Dialisi	Assente	CHD	NYHA		
Insulino-sensibilizzanti	Metformina	OK	No	No	Sì	Ridurre dose	No	No	OK	OK	II-IV	IR	GE, S
	Pioglitazione	OK	Attenzione	No	Sì	Sì	Sì	No	OK	OK	No	V	OS, V, C, F, O
Inibitori α-glicosidasi	Acarbose	OK	Attenzione	No	Sì	Sì	No	No	OK	OK	OK	GE	GE
Secretagoghi	Glibenclamide	OK	Attenzione	No	OK	Attenzione	No	No	OK	Attenzione	Attenzione	–	E (deficit G6PD)
	Glicazide	OK	Attenzione	No	OK	Attenzione	No	No	OK	Attenzione	OK	–	E (deficit G6PD)
	Glimepiride	OK	Attenzione	No	OK	Attenzione	No	No	OK	Attenzione	OK	–	E (deficit G6PD)
	Glipizide	OK	Attenzione	No	OK	Ridurre dose, monitorare	No	No	OK	Attenzione	OK	–	Insufficienza surrenalica; E (deficit G6PD)
	Gliquidone	OK	Attenzione	No	OK	Ridurre dose	No	No	OK	Attenzione	OK	–	Insufficienza surrenalica; E (deficit G6PD)
	Repaglinide	OK	Ridurre dose	No	OK	Attenzione	Attenzione	No	OK	Attenzione	OK	–	–
GLP1-RA	Exenatide BID	OK	OK	OK	OK	5 mg	No	No	OK	OK	OK	GE	GE
	Exenatide LAR	OK	OK	OK	OK	No	No	No	OK	OK	OK	GE	GE
	Liraglutide	OK	No	No	OK	OK	No	No	OK	OK	III e IV lim	GE	GE
	Lixisenatide	OK	OK	OK	OK	Attenzione	No	No	OK	OK	OK	GE	GE
Inibitori DPP-4	Sitagliptin	OK	OK	No	100 mg	50 mg	25 mg	25 mg	OK	OK	OK*	–	RF, cefalea
	Vildagliptin	OK	No	No	100 mg	50 mg	50 mg	50 mg c lim	OK	OK	IV No*	–	vertigini
	Saxagliptin	OK	OK	No	5 mg	2.5 mg	2,5 mg c lim	No	OK	OK	III e IV c*	–	D, vertigini
	Linagliptin	OK	OK	OK	5 mg	5 mg	5 mg	5 mg	OK	OK	OK*	–	Rari
	Alogliptin	OK	OK	No	25 mg	12,5 mg	6,25 mg	6,25 mg	OK	OK	OK*	–	RF, cefalea
SGLT2 inibitori	Canagliflozin	OK	OK	No	OK	GFR 60-45 dose max 100 mg	GFR < 45 No	No	OK	OK	OK	–	Infezioni genito-urinarie deplezione di volume
	Dapagliflozin	OK	OK	Ridurre dose	OK	No	No	No	OK	OK	OK	V	Infezioni genito-urinarie deplezione di volume
	Empagliflozin	OK	OK	No	OK	GFR 60-45 dose max 10 mg	GFR < 45 No	No	OK	OK	OK	–	Infezioni genito-urinarie deplezione di volume

LEGENDA	Giudizio incerto perché la letteratura in merito è scarsa
	c lim = occorre cautela perché l'esperienza è limitata; III e IV c = in III e IV classe NYHA occorre cautela; III e IV lim = in III e IV classe NYHA l'esperienza è limitata
	IR (= insufficienza respiratoria); RF (= rinofaringite); F (= fegato). R (= rene), C (= cuore), D (= derma), GE (= gastroenterico), OS (= osso), O (= occhio), S (= sangue), V (= vescica), P (= pancreas)

* Si rimanda al testo per i particolari

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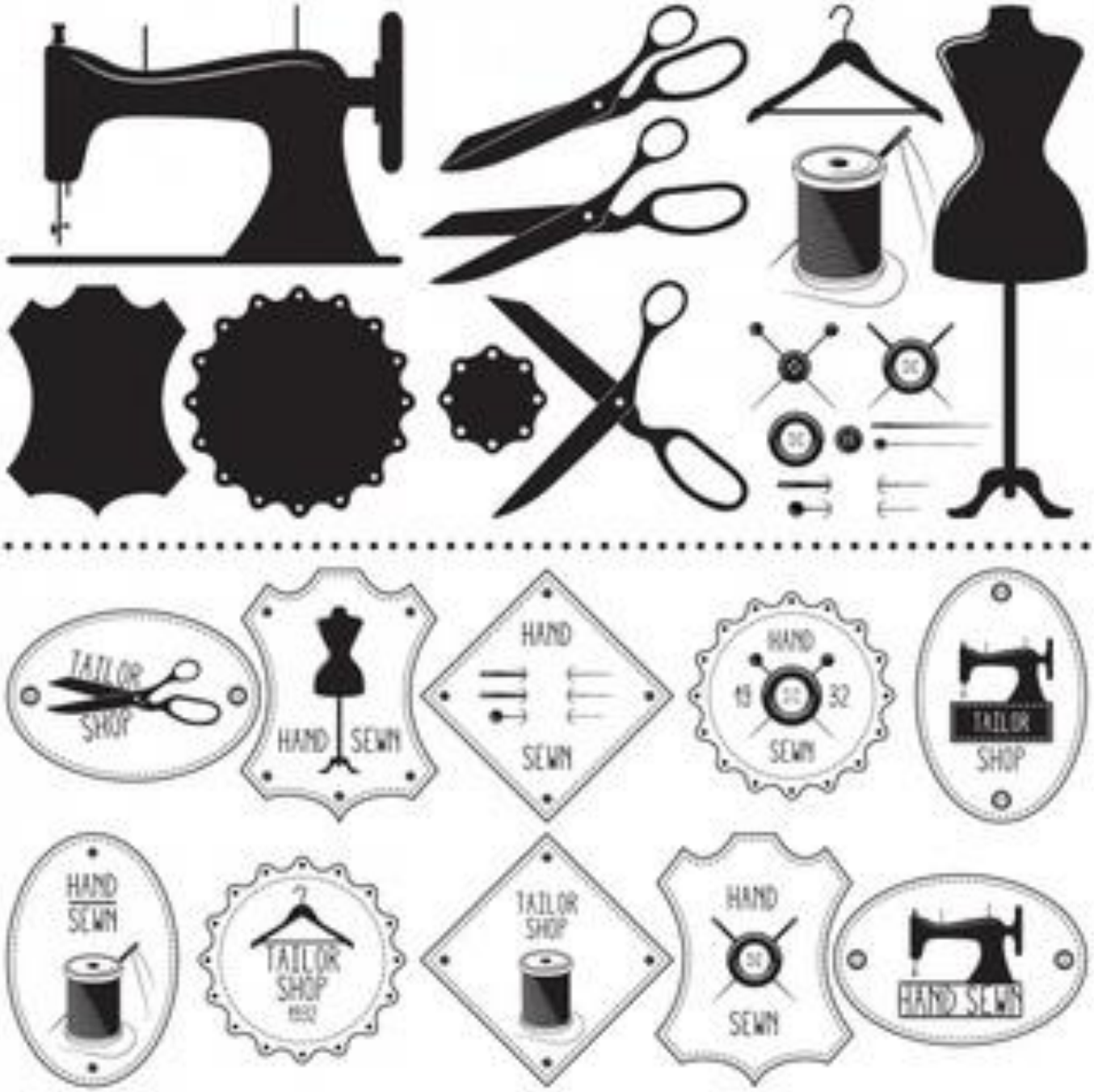
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GRAZIE PER L'ATTENZIONE