ROADSHOW DIABETOLOGIA
DIABETE MELLITO E COMPLICANZE CARDIOVASCOLARI
Milano, 5 dicembre 2018

Diabete mellito e complicanze cardiovascolari: dimensione del problema, bisogni ed evoluzioni terapeutiche

Stefano Genovese

Unità di Diabetologia, Endocrinologia e Malattie Metaboliche

Centro Cardiologico Monzino

Disclosure Statement

- Stefano Genovese, in the last three years, has received speaking and/or consulting fees and research grants from:
  - Abbott Diabetes Care
  - AstraZeneca
  - Boehringer Ingelheim
  - Bristol-Myers Squibb
  - Bruno Farmaceutici
  - Eli Lilly
  - Janssen
  - Lifescan
  - Menarini
  - Merck Sharp & Dohme
  - Mundipharma
  - Novartis
  - Novo Nordisk
  - Sanofi
  - Takeda

Cardiovascular diseases are the leading cause of morbidity and mortality in patients with diabetes mellitus

BEYOND

2×

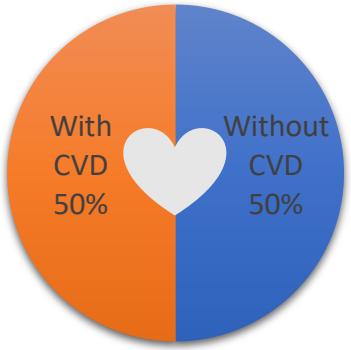
INCREASED RISK OF DEATH

FOR CARDIOVASCULAR CAUSES[1]

UP TO

4×

INCEASED RISK OF MI AND STROKE[2,3]



50-60%

OF DEATHS

DUE TO CVD[4,5]

People with diabetes live up to

6

years

less than people without diabetes in the same risk range[1]

1. Seshasai *et al*. *N Engl J Med* 2011;364:829–841; 2. Folsom *et al*. *Diabetes Care* 1999;22:1077–83; 3. Huxley *et al*. *BMJ* 2006;332:73–8; 4. IDF. Diabetes Atlas. 2015; 5. WHO - Global Atlas on Cardiovascular Diseases Prevention and Control

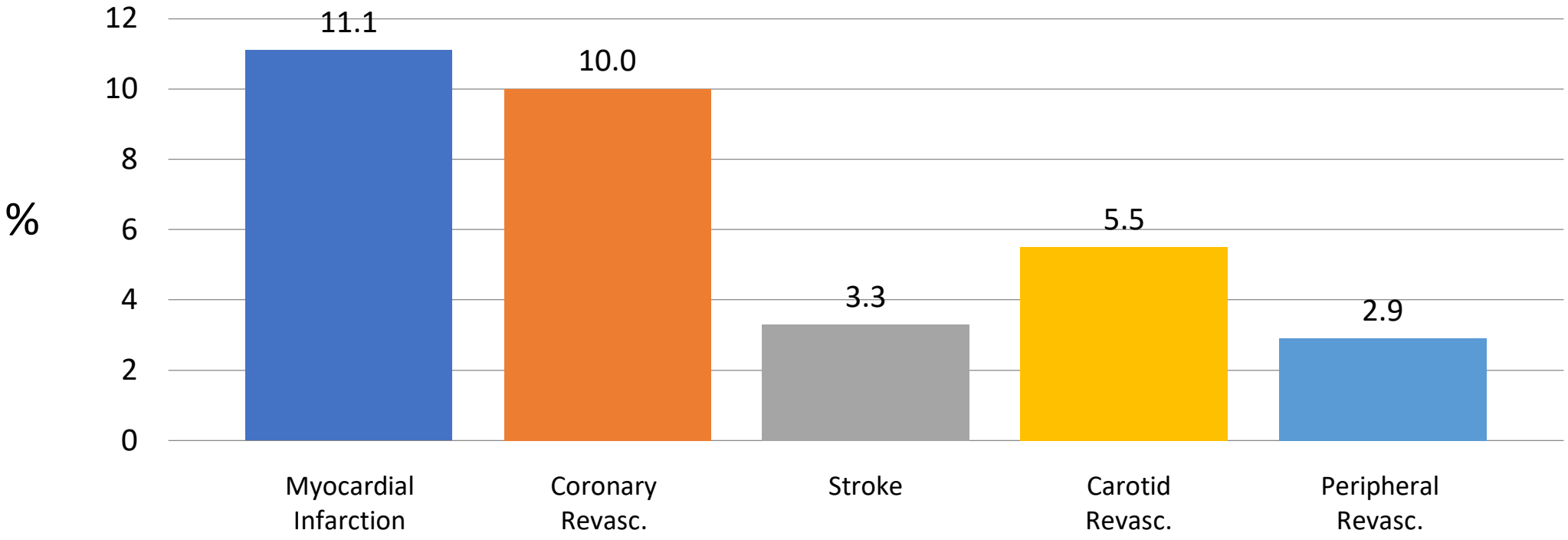
Hyperglycaemia is among the most important causes of death

	1	2	3	4	5	6
Global	Blood pressure	Smoking	BMI	Childhood undernutrition	Fasting plasma glucose	Alcohol use
Developed	Blood pressure	BMI	Smoking	Alcohol use	Fasting plasma glucose	Total cholesterol
Developing	Blood pressure	Childhood undernutrition	Fasting plasma glucose	Smoking	BMI	Household pollution
ITALY	Blood pressure	BMI	Smoking	Fasting plasma glucose	Glomerular filtration	Total cholesterol

Global Burden of Disease *Lancet* 2015;386:2287-323

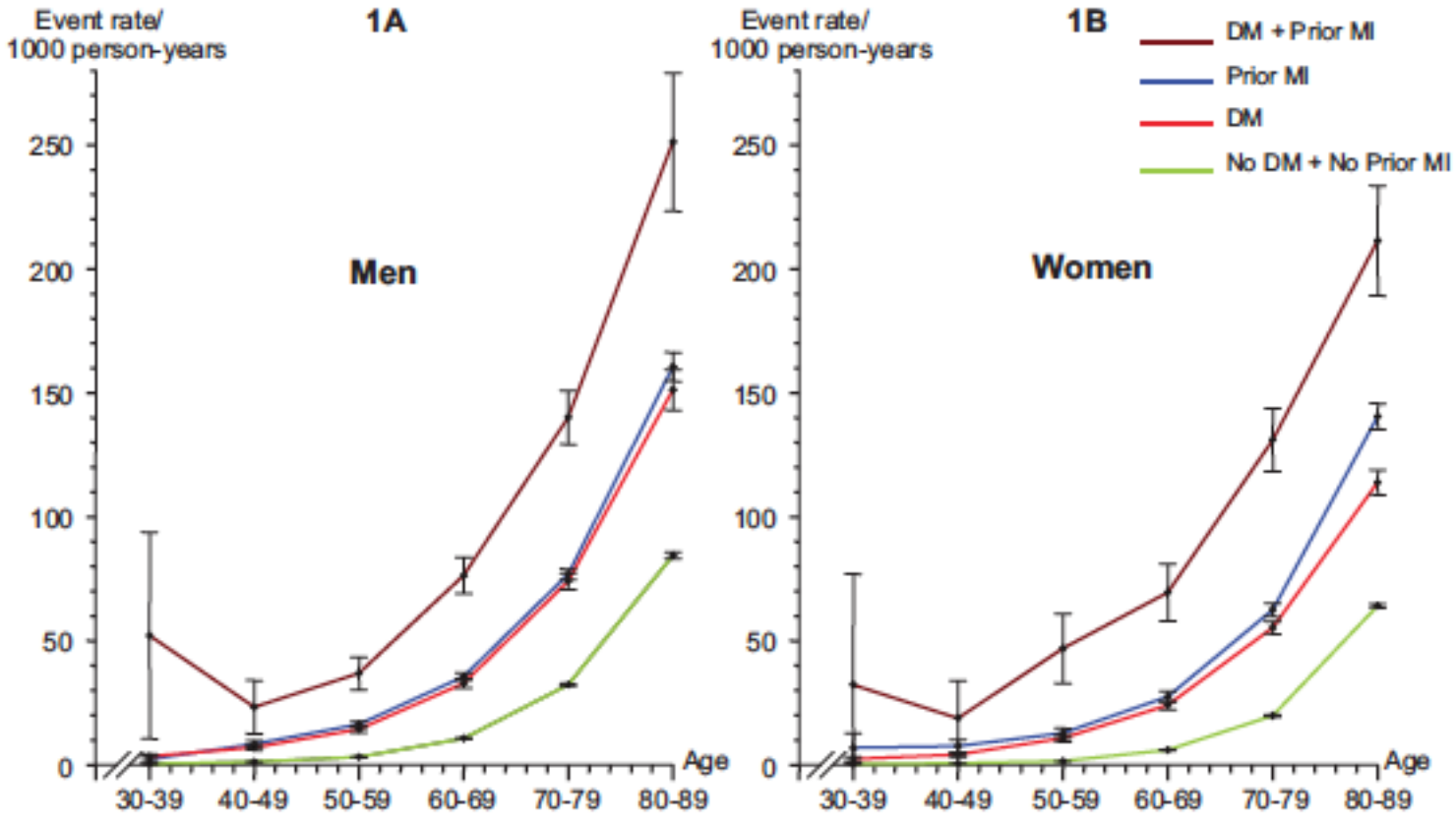
The burden of cardiovascular disease in type 2 diabetes mellitus in Italy

Prevalence of cardiovascular complications in people with type 2 diabetes



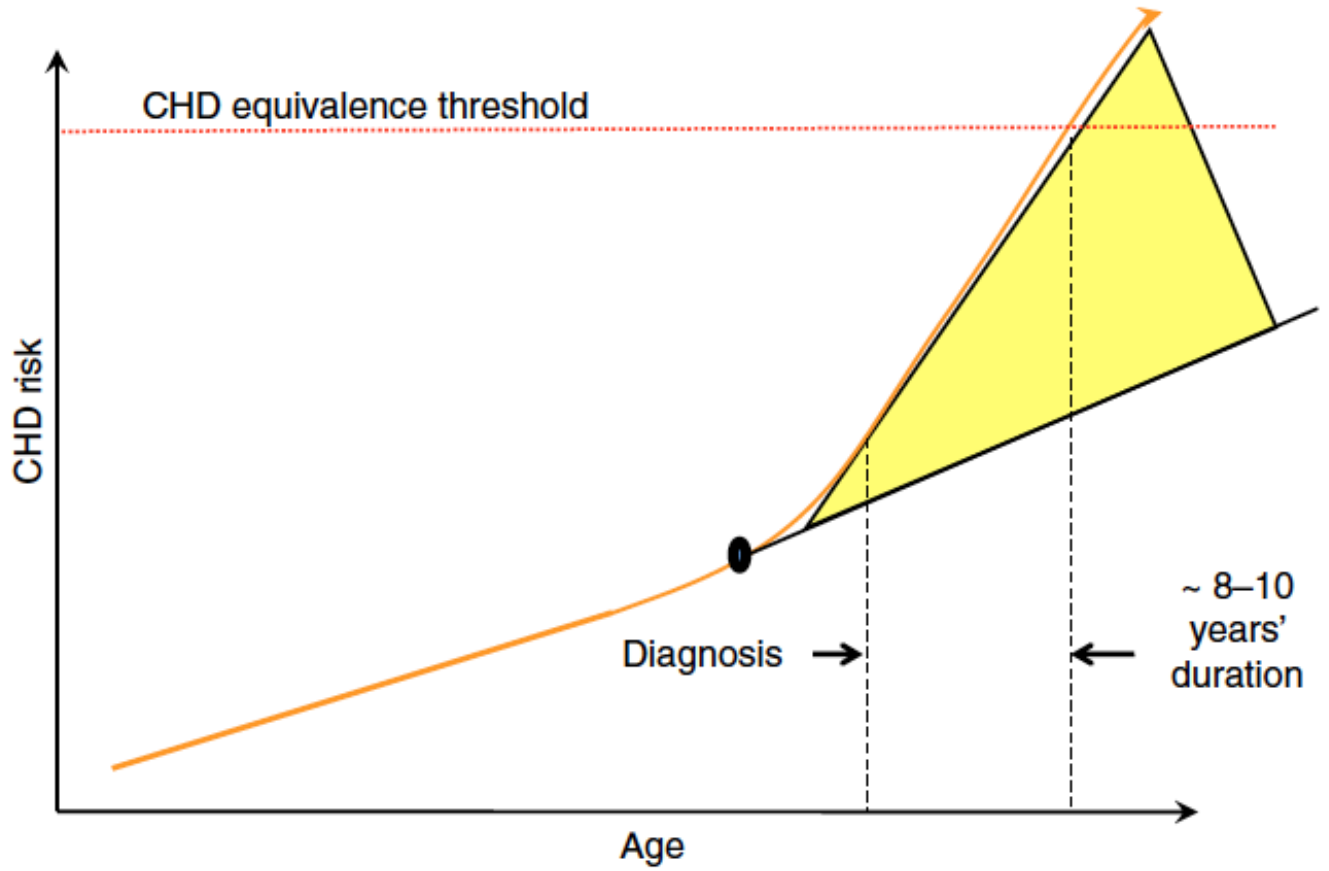
Studio RIACE; Penno et al. *Journal of Internal Medicine*, 2013, 274; 176–191

Diabetes patients requiring glucose-lowering therapy and nondiabetics with a prior MI carry the same cardiovascular risk
A population study of 3.3 mln people



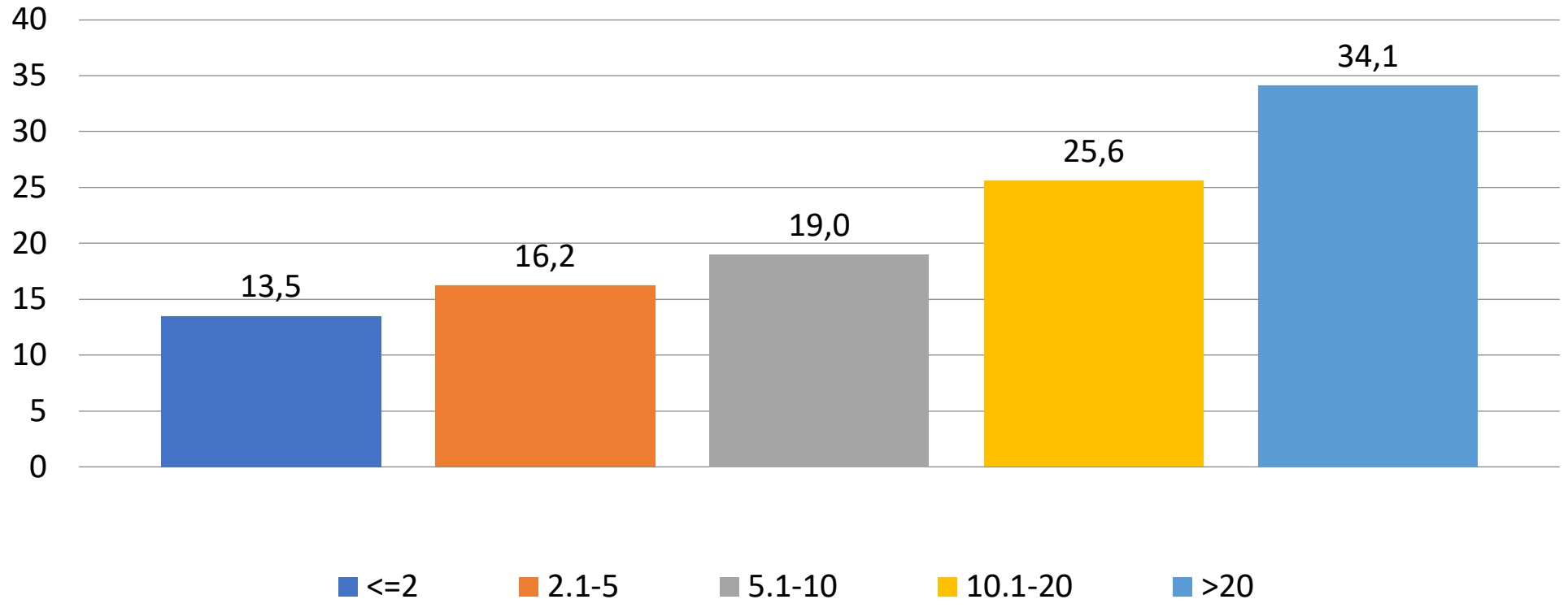
Schramm TK eta al. Circulation. 2008;117:1945-1954

Is diabetes a CHD equivalent?



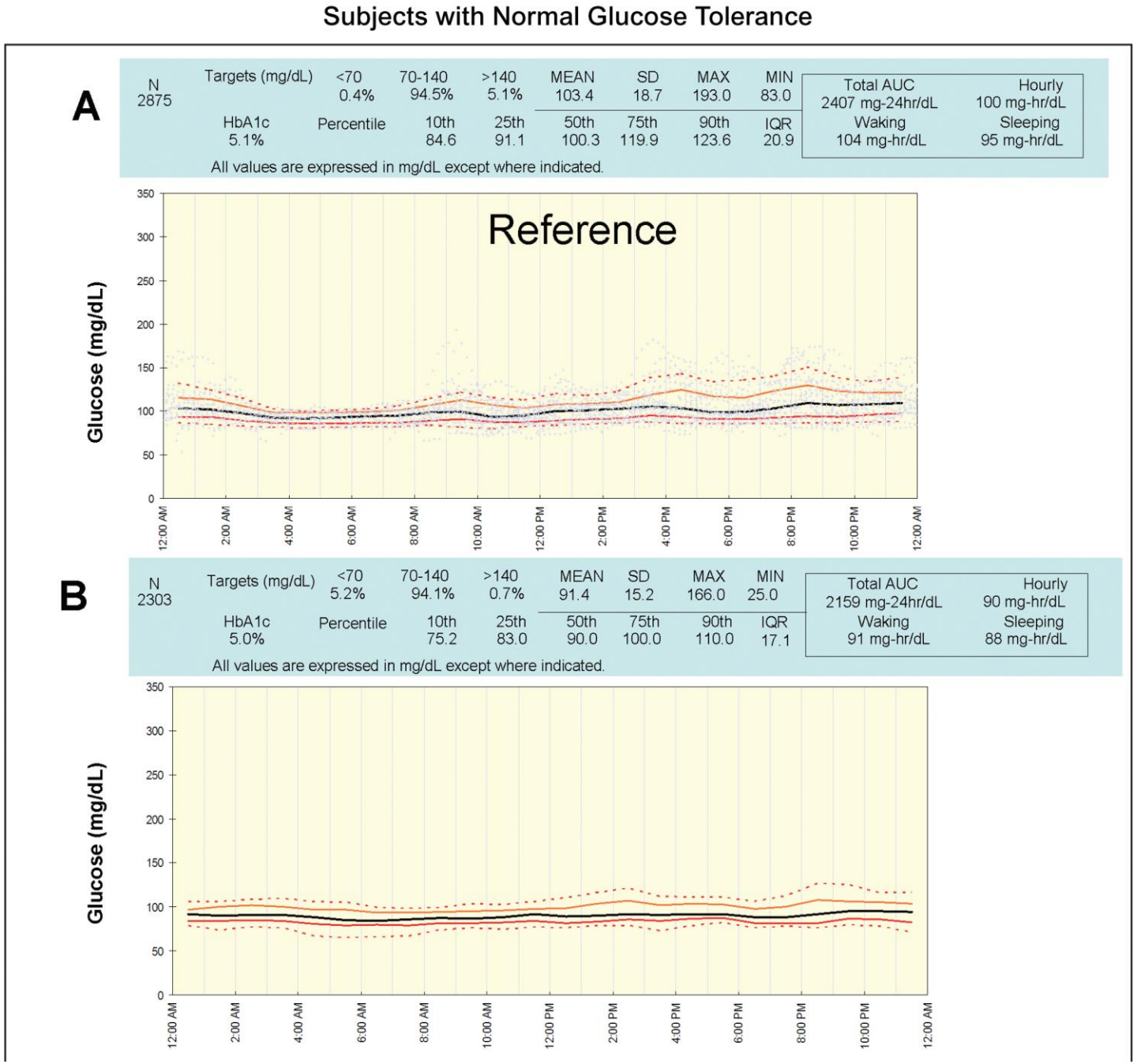
Adapted from Sattar N. Diabetologia. 2013;56:686–95;

Prevalence of cardiovascular complications based on the duration of diabetes



MI, stroke, coronary, carotid and peripheral revascularisation

Studio RIACE; data on file



The modal day and the AGP depict 3,628 continuous glucose readings measured for 30 days

The modal day shows each data point graphed without regard to date

The AGP replaces the individual data points with five smoothed frequency curves, which represent the underlying glycaemic pattern (accounting for outlier values)

The statistical summary (shown separately, but contained in the AGP report) is customisable

AGP, ambulatory glucose profile; IQR, interquartile range

Mazze RS, et al. *Diabetes Technol Ther* 2008;10:149–159

Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus

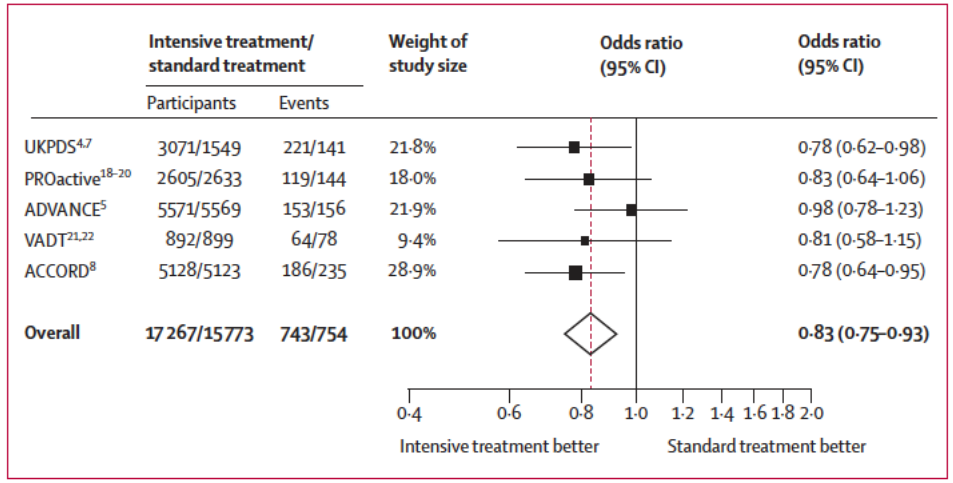


Figure 1: Probability of events of non-fatal myocardial infarction with intensive glucose-lowering versus standard treatment

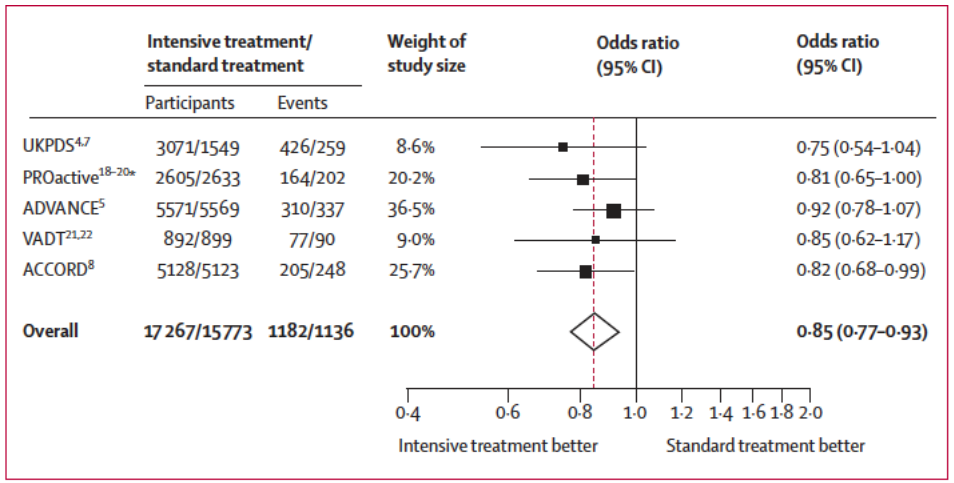


Figure 2: Probability of events of coronary heart disease with intensive glucose-lowering versus standard treatment

*Included non-fatal myocardial infarction and death from all-cardiac mortality.

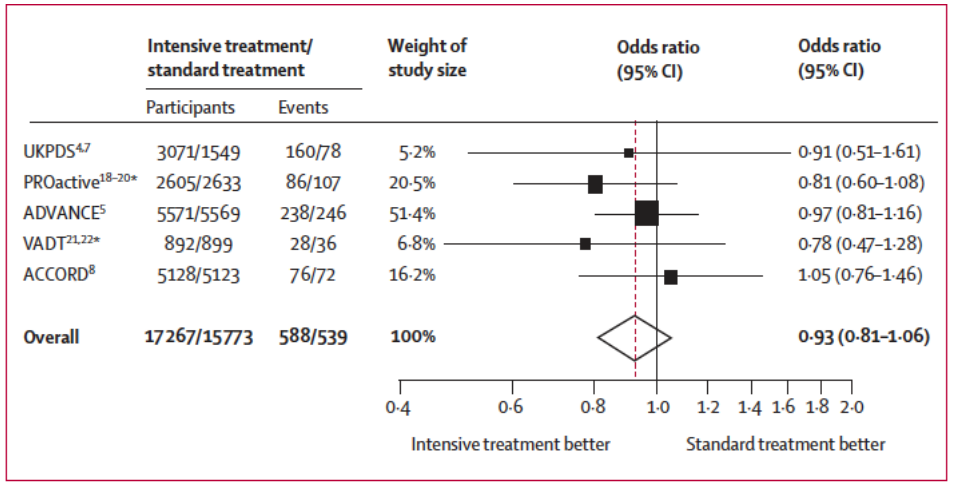


Figure 3: Probability of events of stroke with intensive glucose-lowering versus standard treatment

*Included only non-fatal strokes.

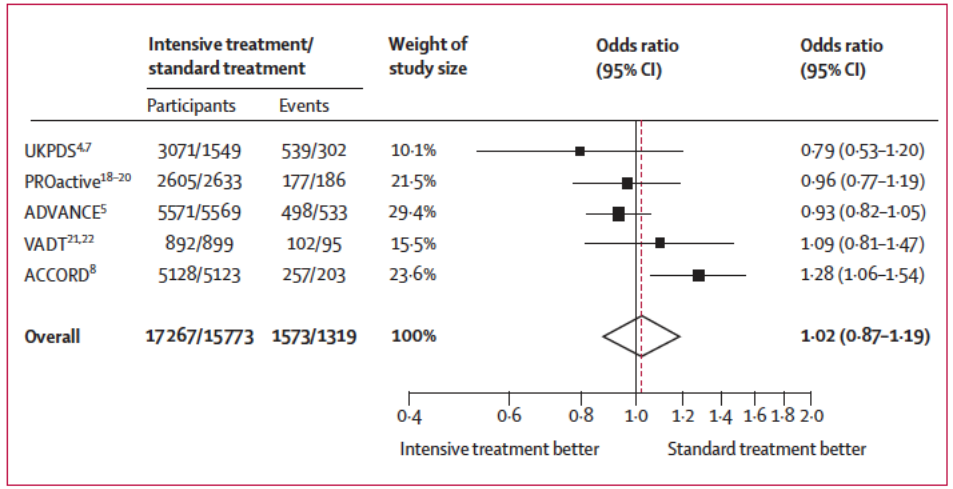


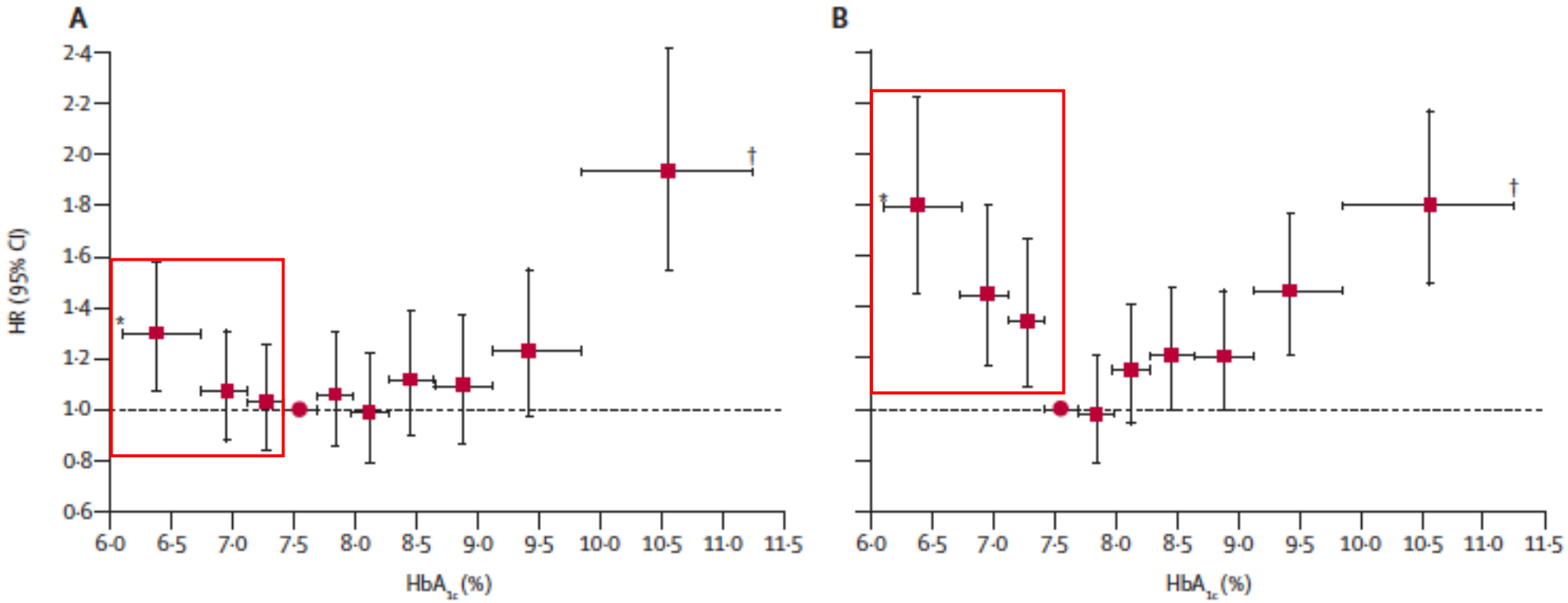
Figure 4: Probability of events of all-cause mortality with intensive glucose-lowering versus standard treatment

Ray KK, et al. *Lancet* 2009;373:1765–1772

Adjusted Hazard Ratios for all-cause mortality by HbA1c deciles in people given oral combination and insulin-based therapies

Non-insulin treated patients (n=27,965)

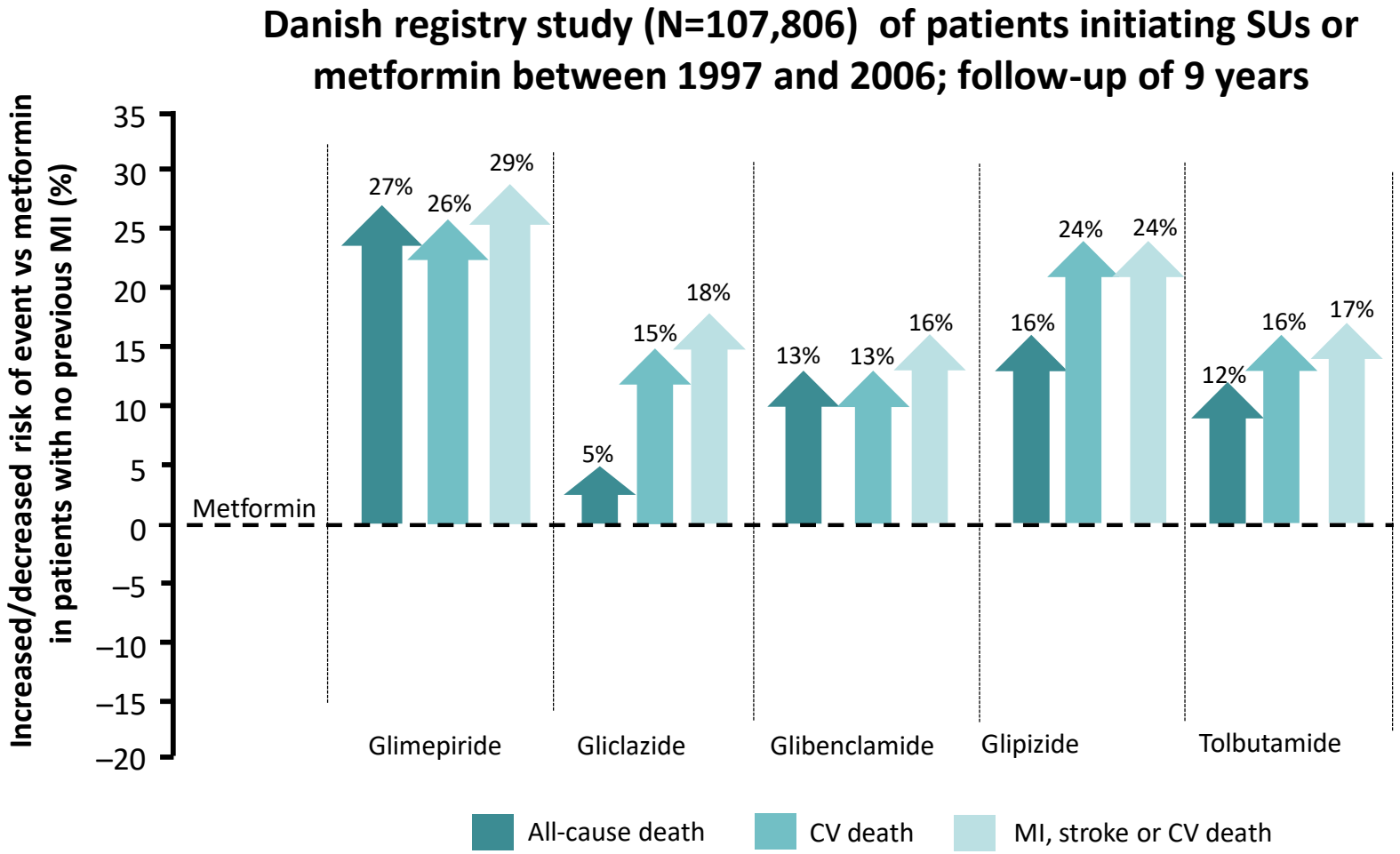
Insulin treated patients (n=20,005)



HbA_{1c}, glycated haemoglobin

Currie CJ, et al. *Lancet* 2010;375:481–489

Monotherapy with many SUs is associated with increased mortality and CV risk when compared with metformin



CV, cardiovascular; MI, myocardial infarction; SU, sulphonylureas

Schramm KT, et al. *Eur Heart J* 2011;32:1900–1908

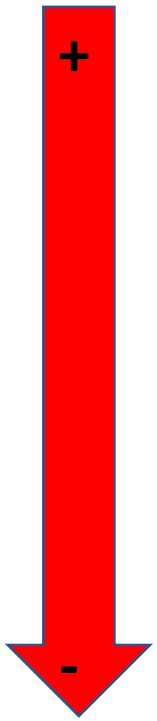
DIABETES/METABOLISM RESEARCH AND REVIEWS
Diabetes Metab Res Rev 2006; **22**: 000–000.
Published online in Wiley InterScience (www.interscience.wiley.com). **DOI:** 10.1002/dmrr.642

RESEARCH ARTICLE

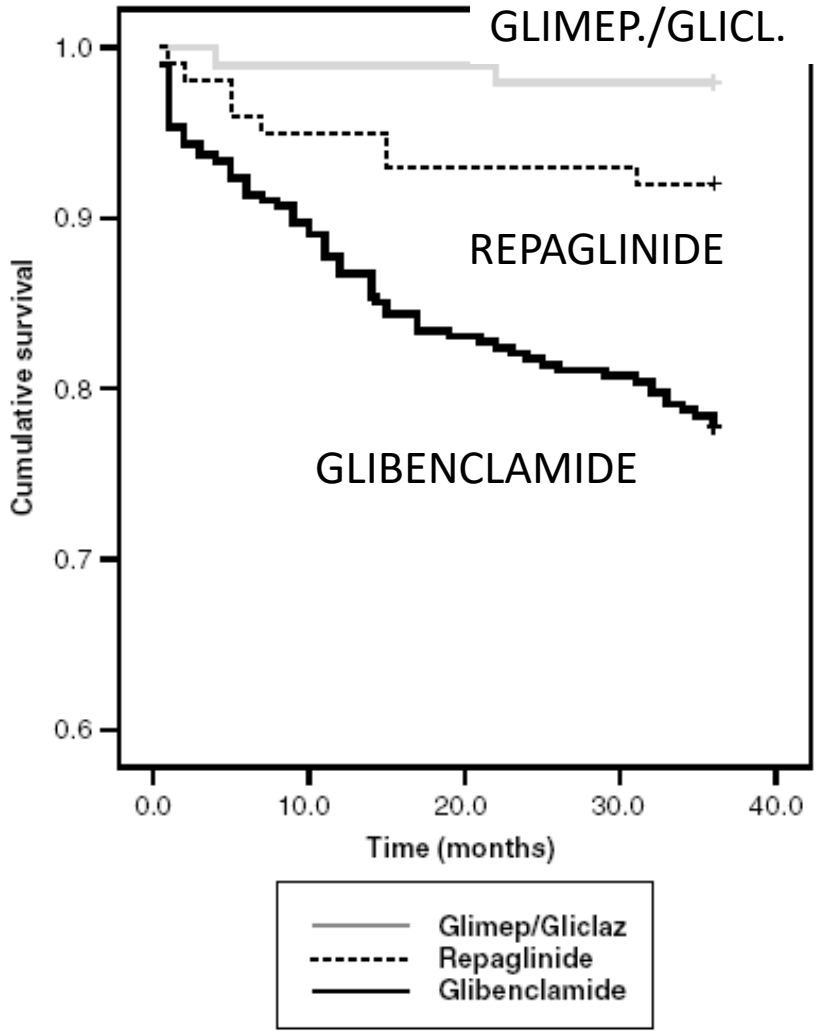
Three-year mortality in diabetic patients treated with different combinations of insulin secretagogues and metformin

Matteo Monami
Chiara Luzzi
Caterina Lamanna
Veronica Chiasserini
Filomena Addante
Carla Maria Desideri
Giulio Masotti
Niccolò Marchionni
Edoardo Mannucci*

ATP-K channel affinity for β-cell

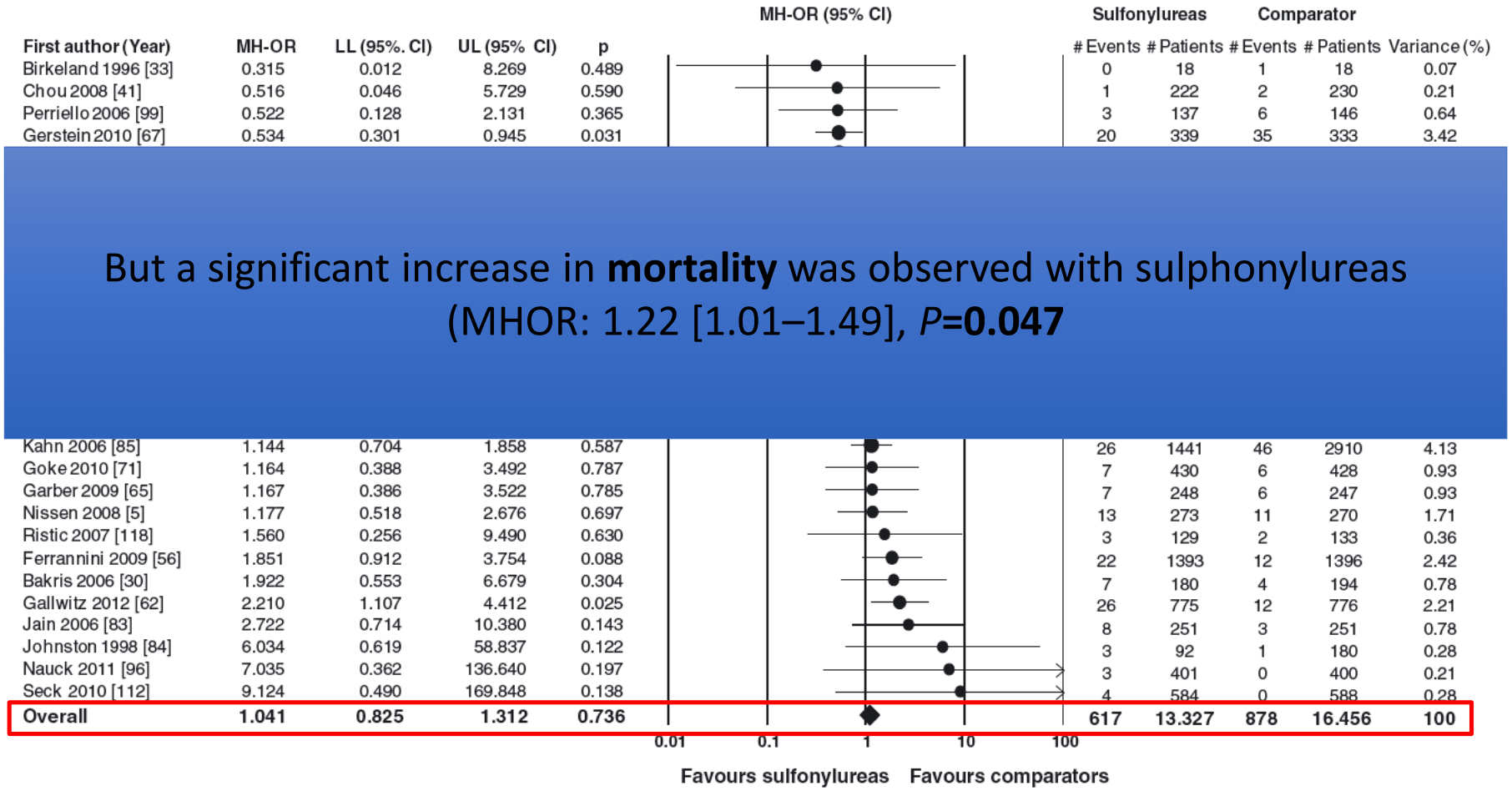


N= 2,002 T2DM patients
Follow up: 3 years



T2DM, Type 2 diabetes mellitus

Cardiovascular safety of sulphonylureas: a meta-analysis of randomised clinical trials



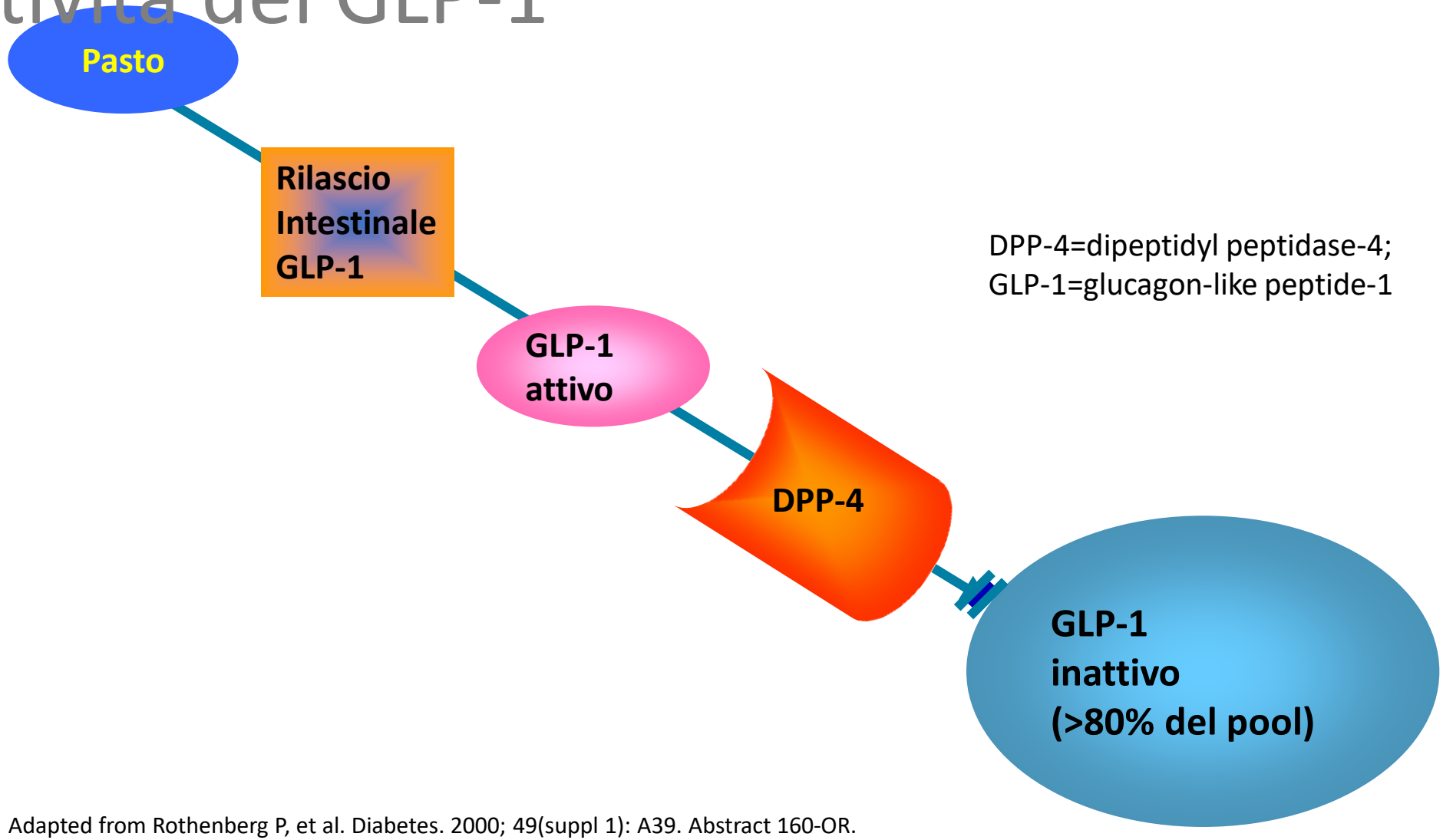
But a significant increase in **mortality** was observed with sulphonylureas (MHOR: 1.22 [1.01–1.49], *P*=**0.047**

MHOR, Mantel-Haenszel odds ratio

Monami M, et al. *Diabetes Obes Metab* 2013;15:938–953

DPP4-I

L’inibizione dell’enzima DPP4 aumenta l’attività del GLP-1

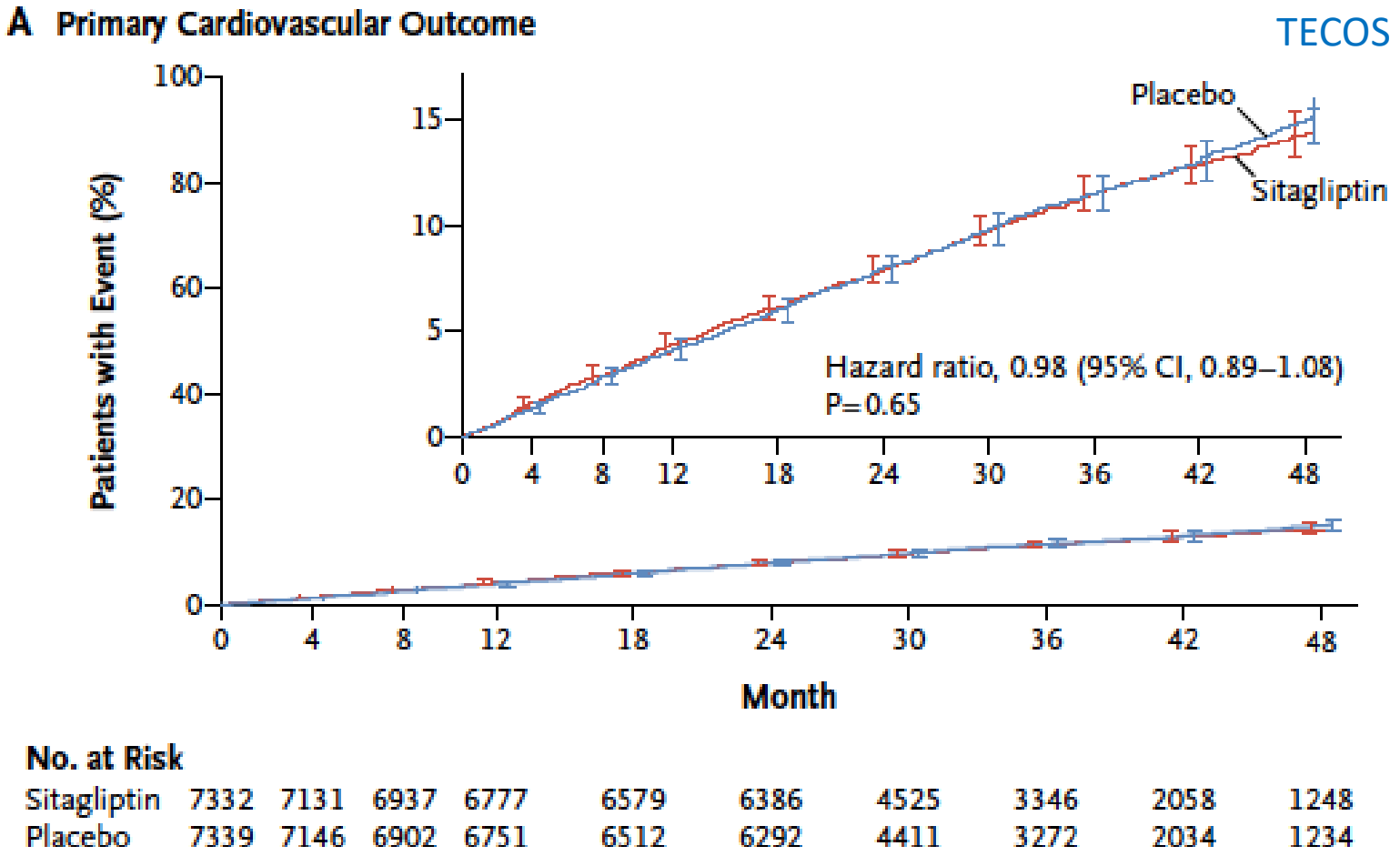


DPP-4=dipeptidyl peptidase-4;
GLP-1=glucagon-like peptide-1

Adapted from Rothenberg P, et al. Diabetes. 2000; 49(suppl 1): A39. Abstract 160-OR.
Adapted from Deacon CF, et al. Diabetes. 1995; 44: 1126-1131.

CV safety of DPP4-I

TECOS



Combination therapy with metformin plus sulphonylureas versus metformin plus DPP-4 inhibitors: association with major adverse cardiovascular events and all-cause mortality

Table 2. Sulphonylurea (SU) and dipeptidyl peptidase-4 inhibitor (DPP-4i) types at cohort entry and exit.

SU	SU generation	First prescription, n (%)		Last prescription, n (%)		DPP-4i	First prescription, n (%)		Last prescription, n (%)	
Gliclazide	2	30 301	(89.2)	30 297	(89.2)	Sitagliptin	5864	(74.6)	5857	(74.5)
Glimepiride	2	2337	(6.9)	2397	(7.1)	Saxagliptin	996	(12.7)	1012	(12.9)
Glipizide	2	896	(2.6)	883	(2.6)	Vildagliptin	730	(9.3)	678	(8.6)
Glibenclamide	2	330	(1.0)	279	(0.8)	Linagliptin	274	(3.5)	317	(4.0)
Tolbutamide	1	119	(0.4)	127	(0.4)					
		33 983	(100.0)	33 983	(100.0)		7864	(100.0)	7864	(100.0)

Table 3. Events, crude rates, risk ratios and adjusted hazard ratios (aHRs) for all-cause mortality in patients treated with metformin plus sulphonylurea (SU) versus metformin plus dipeptidyl peptidase-4 inhibitor (DPP-4i) dual therapy.

Study design	Cohort (in combination with metformin)	n	Events	Crude rates (per 1000 person-years)	Crude risk ratio (95% CI)	aHR (95% CI)	p
All subjects	SU	33 983	1133	16.9	2.327 (1.864–2.904)	1.357 (1.076–1.710)	0.010
	DPP-4i	7864	84	7.3			
Directly matched	SU	5447	96	10.2	2.108 (1.466–3.076)	1.850 (1.245–2.749)	<0.001
	DPP-4i	5447	40	4.9			
Propensity-matched	SU	6901	121	10.7	1.743 (1.289–2.379)	1.497 (1.092–2.052)	0.012
	DPP-4i	6901	63	6.2			

Morgan CL et al Diabetes, Obesity and Metabolism 16: 977–983, 2014

Combination therapy with metformin plus sulphonylureas versus metformin plus DPP-4 inhibitors: association with major adverse cardiovascular events and all-cause mortality

Table 4. Events, crude rates, risk ratios and adjusted hazard ratios (aHRs) for first major adverse cardiovascular events (MACE) in patients treated with metformin plus sulphonylurea (SU) versus metformin plus dipeptidyl peptidase-4 inhibitor (DPP-4i) dual therapy.

Study design	Cohort (in combination with metformin)	n*	Events	Crude rates (per 1000 person-years)	Crude risk ratio (95% CI)	aHR (95% CI)	p
All subjects	SU	29 865	661	11.3	2.145 (1.629–2.824)	1.710 (1.280–2.285)	<0.001
	DPP-4i	7091	55	5.3			
Directly matched	SU	4423	58	7.7	1.469 (0.965–2.234)	1.323 (0.832–2.105)	0.237
	DPP-4i	4423	35	5.2			
Propensity-matched	SU	6175	88	8.8	1.688 (1.191–2.414)	1.547 (1.076–2.225)	0.019
	DPP-4i	6229	48	5.2			

*With no prior MACE.

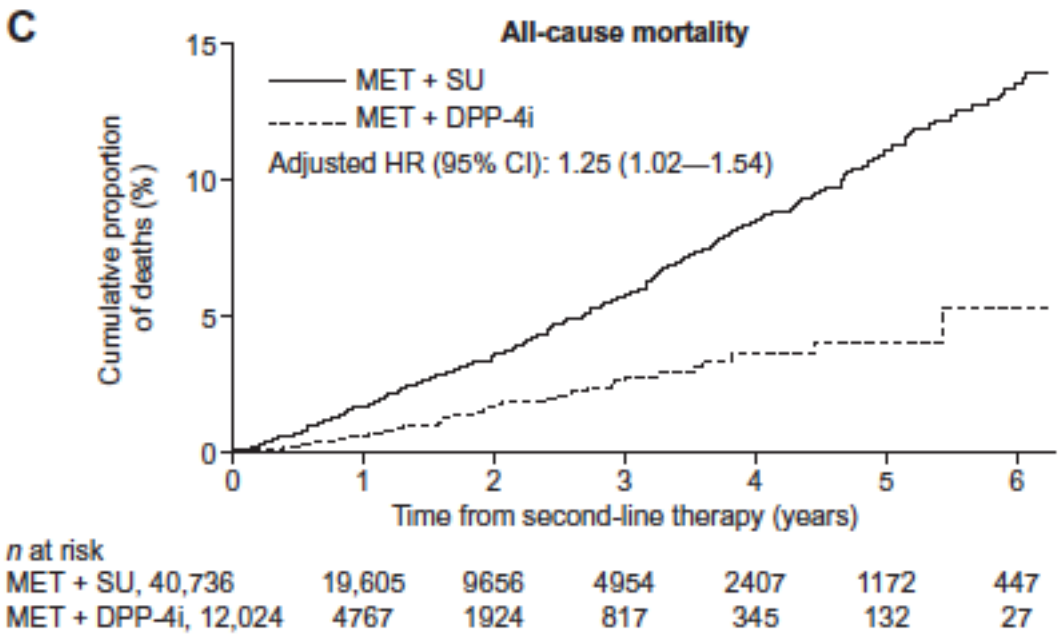
Directly Matched Cohorts: Exposed (metformin plus DPP-4i) patients were matched to non-exposed (metformin plus SU) patients by age (±2 years), gender, year of index exposure, diabetes duration (±1 year), BMI (±3 kg/m2), serum creatinine (±10 µmol/L) and HbA1c [±1% (±11 mmol/mol)].

Propensity-matched Cohorts: Exposed patients were matched to non-exposed patients by propensity score, incorporating age, gender, year of index exposure, diabetes duration, BMI, serum creatinine, total cholesterol, SBP, GP contacts in the 12 months to index date, HbA1c, Charlson index, smoking status and line of therapy.

Morgan CL et al Diabetes, Obesity and Metabolism 16: 977–983, 2014

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

All patients with T2D in Sweden who initiated second-line treatment with metformin + sulphonylurea or metformin + DPP-4i during 2006–2013 (n = 40,736 and 12,024, respectively) were identified in this nationwide study



Eriksson JW et al Diabetes Res Clin Pract. 2016 Jul;117:39-47

Sulphonylureas increase the risk of hospitalisation for heart failure in comparison to DPP4-i

Risk of hospitalization for heart failure in patients with type 2 diabetes newly treated with DPP-4 inhibitors or other oral glucose-lowering medications: a retrospective registry study on 127,555 patients from the Nationwide OsMed Health-DB Database

Gian Paolo Fadini[1], Angelo Avogaro[1]*, Luca Degli Esposti[2], Pierluigi Russo[3], Stefania Saragoni[2], Stefano Buda[2], Giuseppe Rosano[3,4,5], Sergio Pecorelli[3,6], and Luca Pani[3], on behalf of the OsMed Health-DB Network[†]

127,555 patients
2.6 years (mean duration of observation)

127,555 pts

39,465 pts

Table 4 Results of the Cox proportional hazard multiple regression analysis in the whole study population including hospitalization episodes with a primary or secondary HF diagnosis

Variable	Before propensity matching		After propensity matching	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Glucose-lowering medications				
Sulphonylureas (reference)	1.000		1.000	
Glitazones	0.926 (0.807–1.063)	0.277	0.777 (0.635–0.950)	0.014
DPP-4 inhibitors	0.751 (0.630–0.895)	0.001	0.642 (0.510–0.808)	<0.001

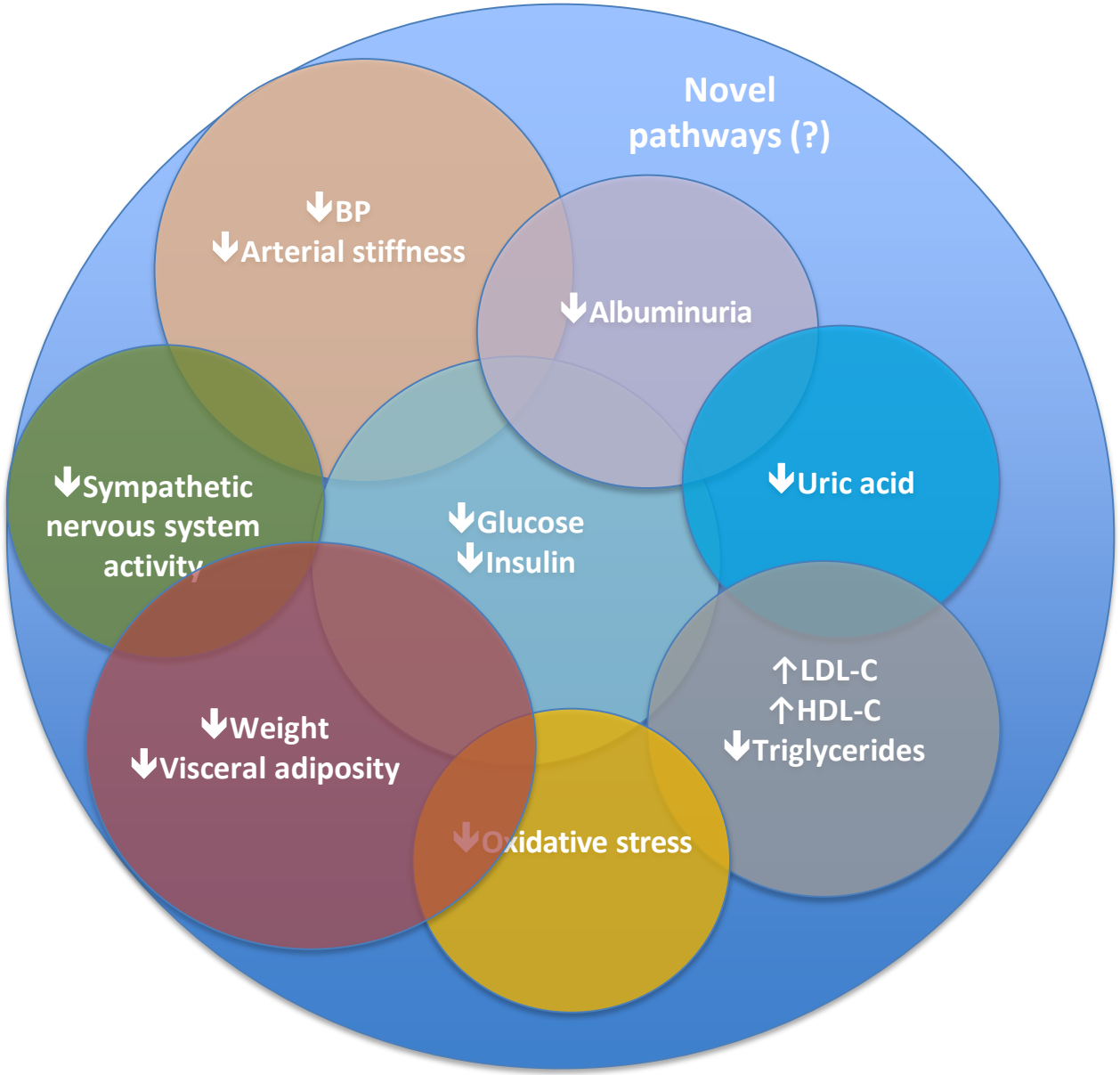
Conclusion: In a very large observational study, the use of DPP-4i was associated with a reduced risk of HHF when compared with sulphonylureas

DPP-4i, dipeptidyl peptidase-4 inhibitor; HHF, hospitalisation for heart failure

Fadini GP, et al. *Eur Heart J* 2015;36:2454–2462

SGLT2-I

SGLT2i Modulates Several Factors Related to CV risk

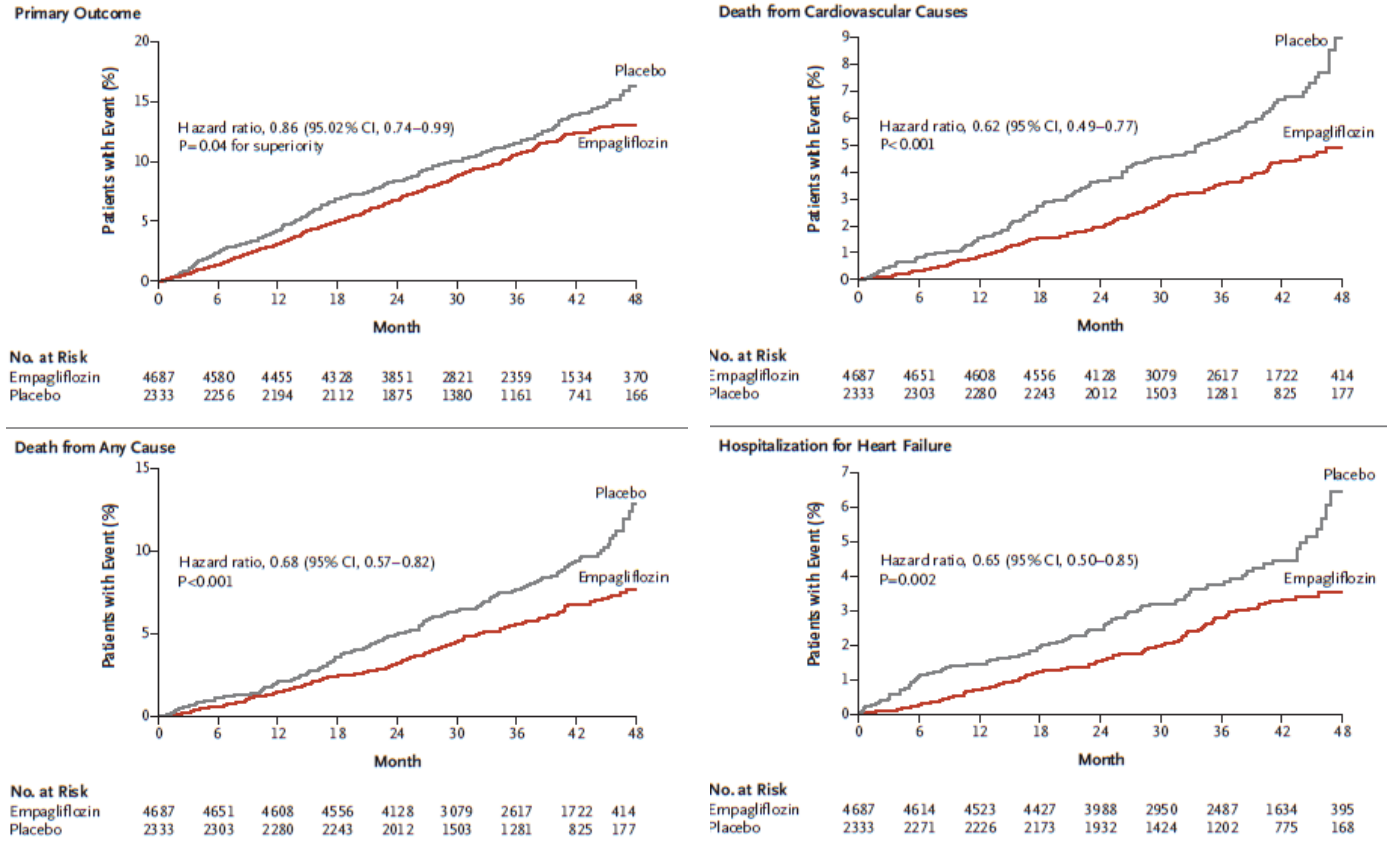


BP, blood pressure; CV, cardiovascular;
HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol;
SGLT2i, sodium–glucose co-transporter 2 inhibitor

Adapted from Inzucchi SE, et al. *Diab Vasc Dis Res* 2015;12:90–100

EMPA-REG: Empagliflozin CV Safety Trial

N=7020, T2DM with CV disease, RDBPC design, Empa 10 or 25 mg/d added to standard care, median 3.1 yrs.
Age 63 yrs, Wt ~86 kg. 1º endpoint = 3pt MACE, composite of CV death, fatal and non-fatal MI and stroke



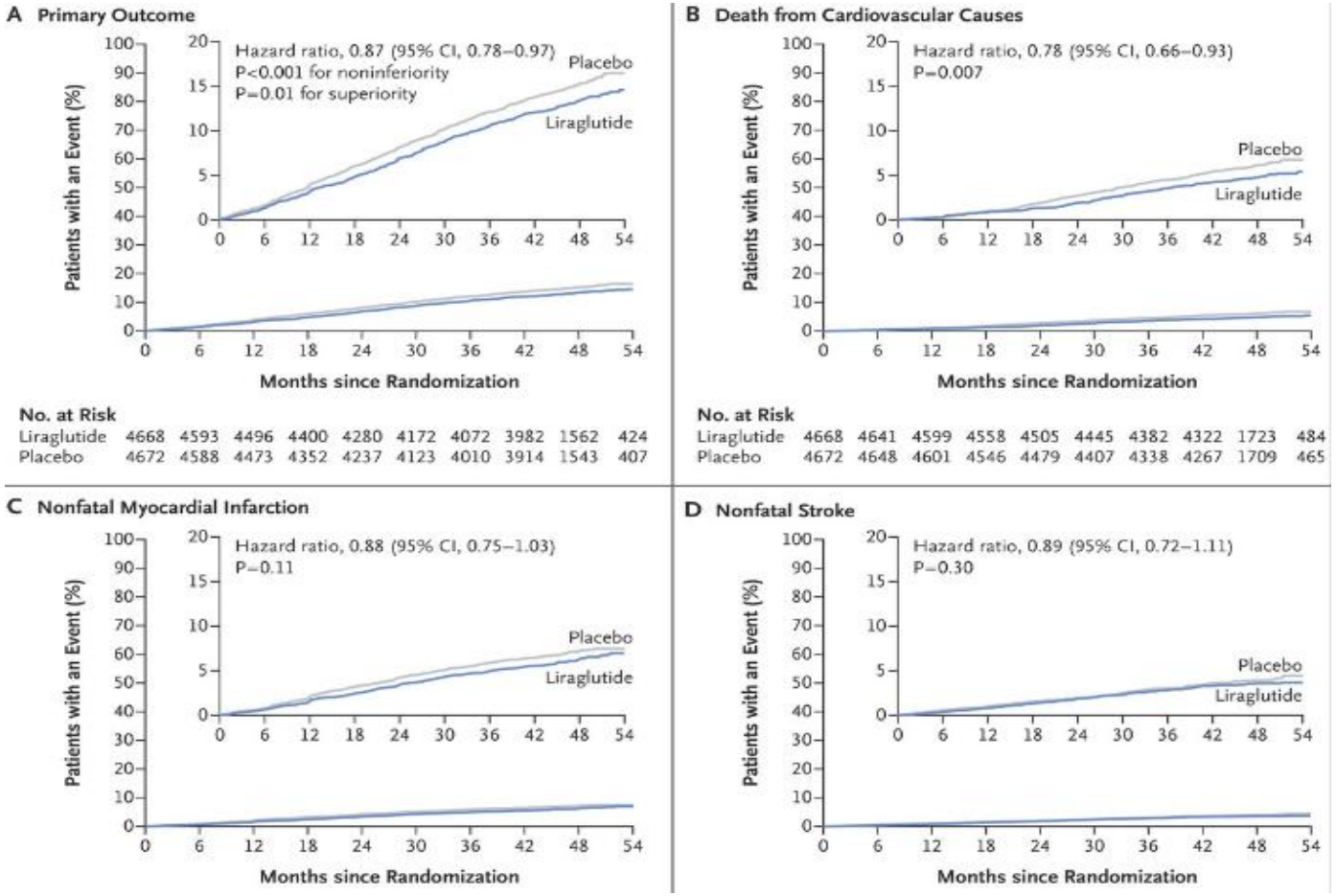
1º in 490/4687 (10.5%) in Empa groups vs 282/2333 (12.1%) in Pbo, HR 0.86; 95% CI 0.74, 0.99; *P*=0.04; N/S differences in MI or stroke, but Empa lowered rates of CV deaths (3.7%, vs 5.9%; RRR 38%), hospitalisation for HF (2.7% vs 4.1%, RRR 35%), and death from any cause (5.7% vs 8.3%, RRR 32%)

CV, cardiovascular; HF, heart failure; HR, hazard ratio; MACE, major adverse cardiac event; MI, myocardial infarction; RRR, relative risk ratio; T2DM, Type 2 diabetes mellitus

Zinman B, et al. *N Engl J Med* 2015;373:2117–2128

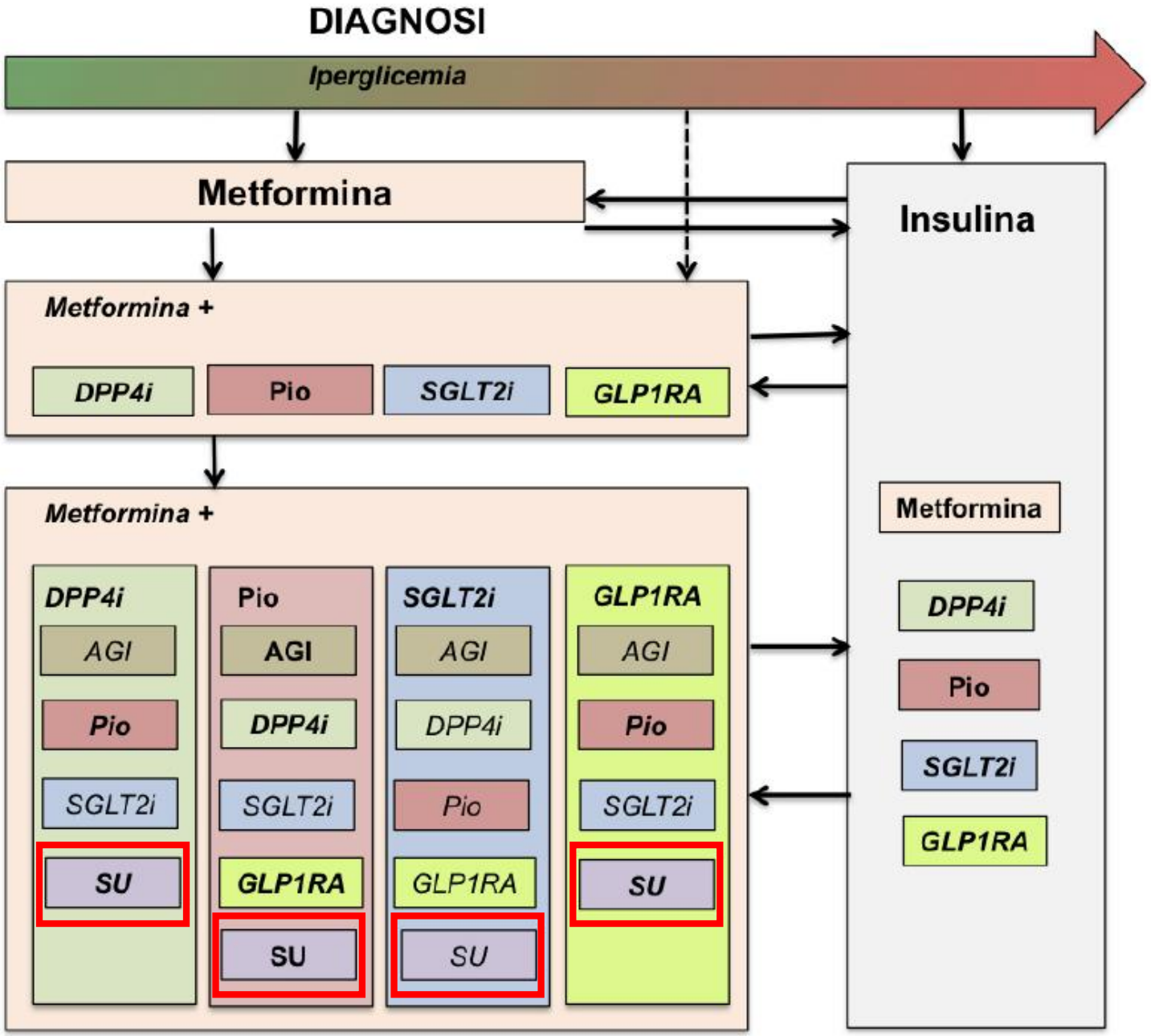
GLP1-RA

LEADER Study: Liraglutide CV Safety Trial



CV, cardiovascular

Marso SP, et al. *N Engl J Med* 2016;375:311–322



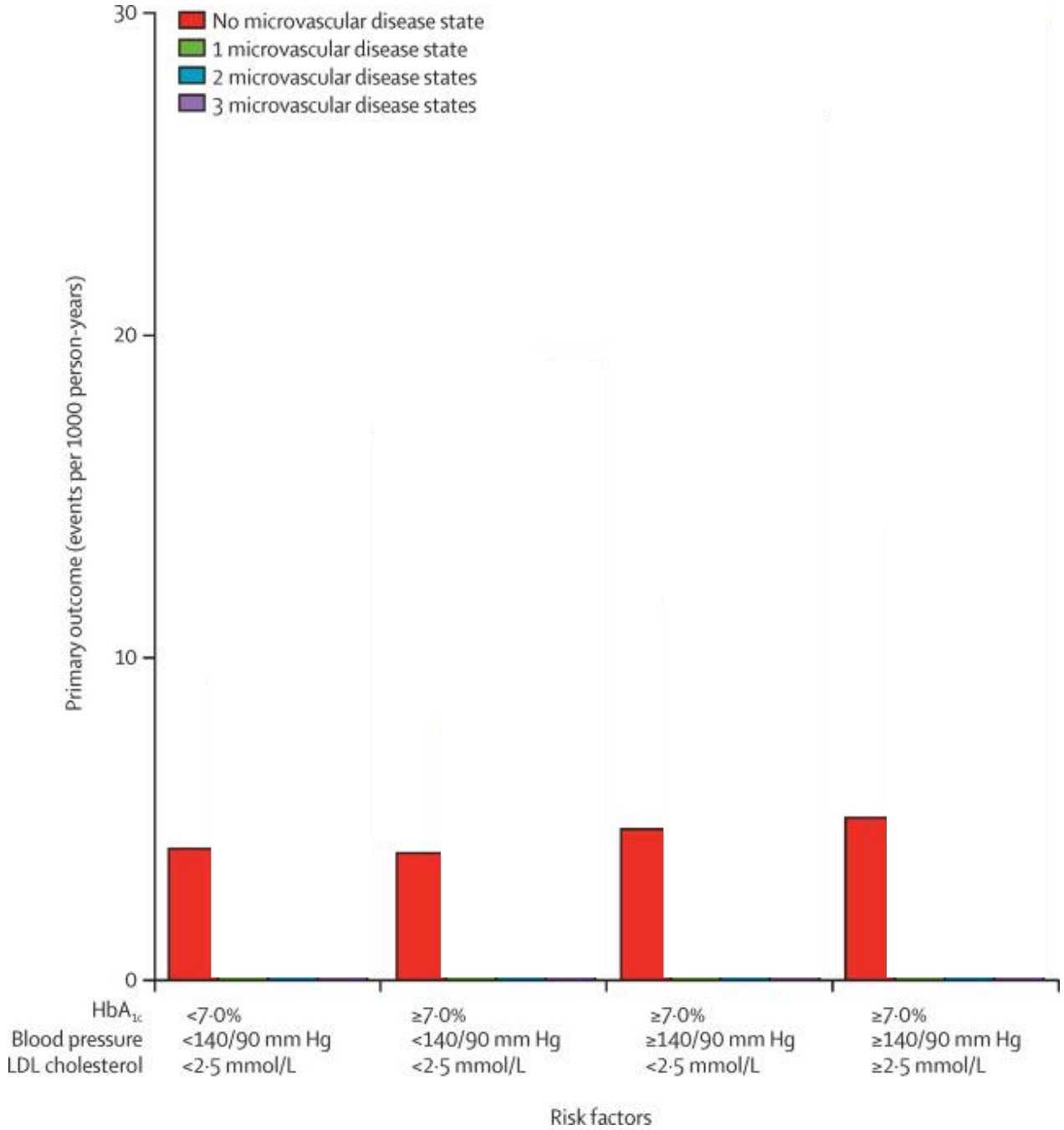
Standard Italiani per la cura del diabete mellito 2018 AMD SID

Standard Italiani per la cura del diabete mellito 2018 AMD SID

In associazione a metformina, sulla base del profilo complessivo di efficacia, tollerabilità e sicurezza, pioglitazone, inibitori DPP4, agonisti GLP1 o inibitori SGLT2 sono preferibili rispetto a acarbose, sulfoniluree o glinidi. *I B*

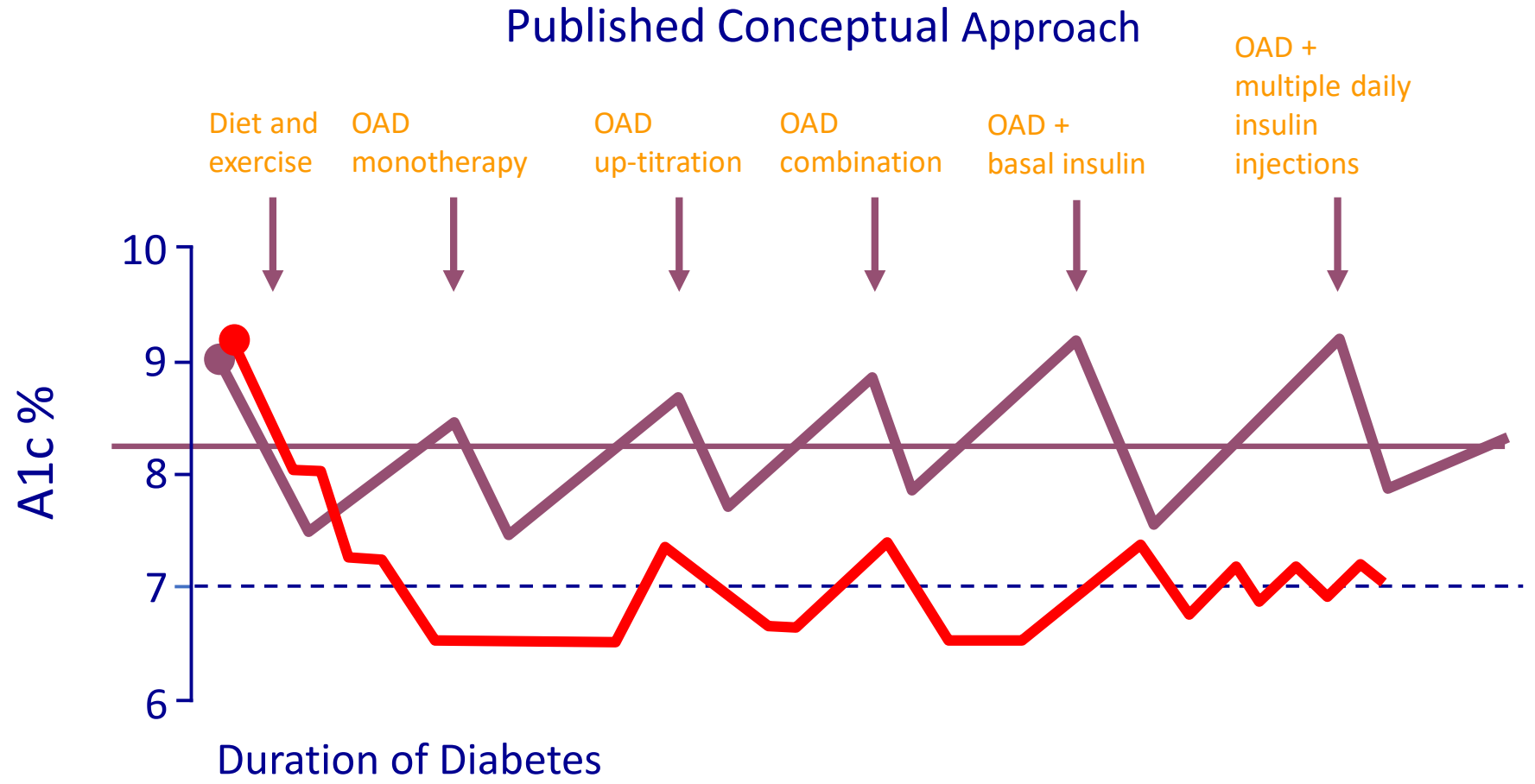
La glibenclamide, che si associa ad un rischio di ipoglicemia maggiore anche rispetto alle altre sulfoniluree, non deve essere mai usata. *I A*

Nei pazienti con pregressi eventi cardiovascolari maggiori SGLT-2 inibitori, GLP-1 agonisti a lunga durata d'azione e pioglitazone devono essere considerati farmaci di prima scelta, salvo controindicazioni. *II A*



The Lancet Diabetes & Endocrinology, Volume 4, Issue 7, 2016, 588–597

Earlier and more aggressive intervention may improve treating to target compared with conventional therapy



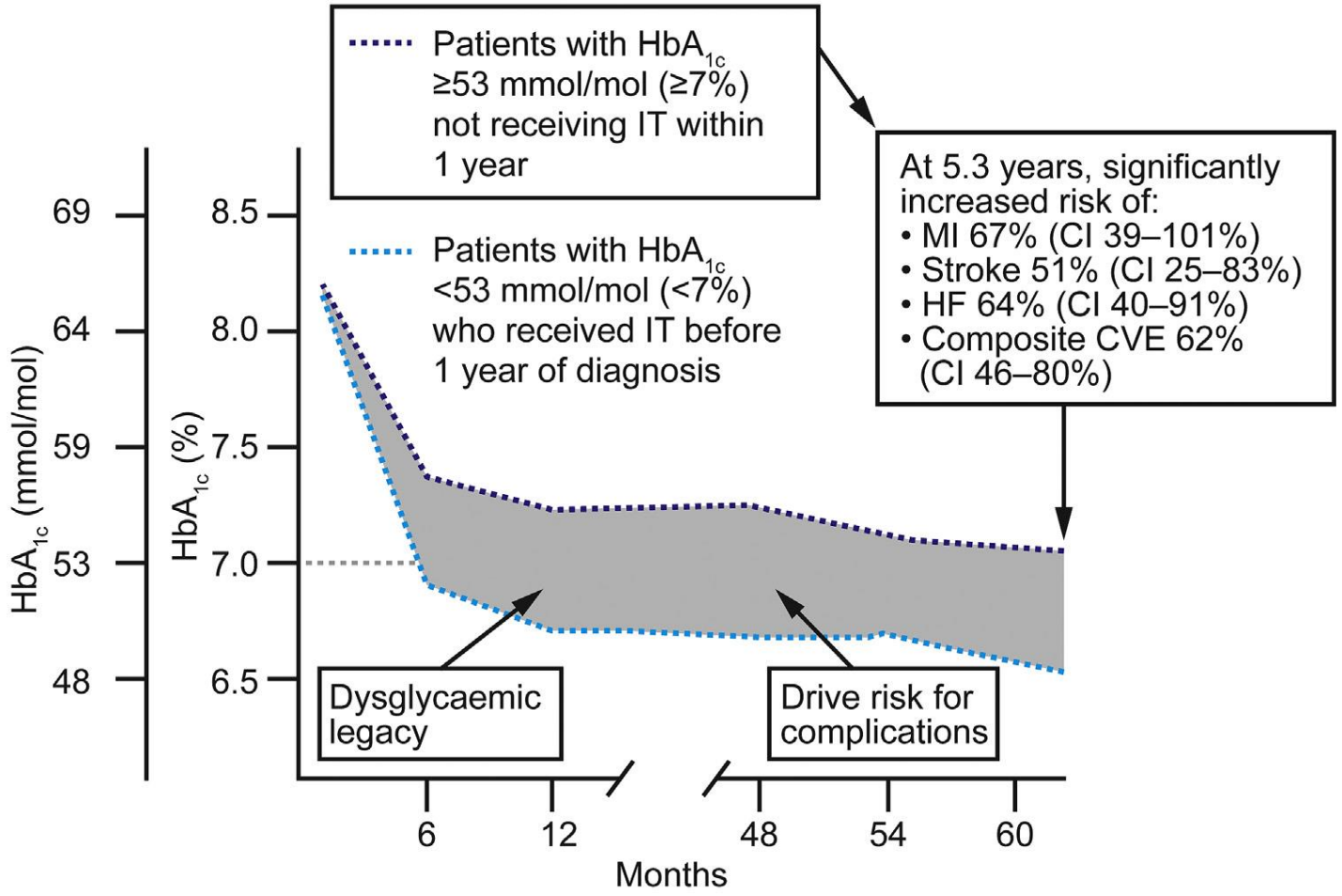
Adapted from Del Prato S et al. Int J Clin Pract. 2005;59:1345–1355.

Clinical inertia

- Is failure of health care providers to initiate or intensify therapy when indicated.
- Clinical inertia is due to at least three problems:
  - overestimation of care provided;
  - use of “soft” reasons to avoid intensification of therapy;
  - and lack of education, training, and practice organization aimed at achieving therapeutic goals.

Phillips LS et al. Ann Intern Med. 2001;135:825-834

Consequences of delayed intervention in patients without previous CVD



Khunti K. et al. Prim Care Diabetes. 2017 Feb; 11 (1): 3-12

Conclusioni

- La prevenzione delle malattie cardiovascolari nasce dalla **prevenzione del diabete**
- Bisogna **aggredire** il diabete cercando di ridurre la glicemia verso valori normali, in sicurezza
- I nuovi farmaci hanno dimostrato di **ridurre** gli eventi cardiovascolari
- I medici di medicina generale **non** possono prescrivere i farmaci innovativi
- Sostenibilità economica

Thank you for your attention

Centro Cardiologico
Monzino