78° Congresso Nazionale FIMMG

Villasimius, 4 ottobre 2021

La valutazione del rischio globale nel paziente diabetico con polipatologie

Stefano Genovese

Unità di Diabetologia, Endocrinologia e Malattie Metaboliche

Centro Cardiologico Monzino

Dichiarazione di conflitti di interesse

Stefano Genovese, negli ultimi tre anni, ha ricevuto onorari per conferenze e/o consulenze e borse di ricerca da:

- Abbott Diabetes Care
- AstraZeneca
- Boehringer Ingelheim
- Eli Lilly
- Hikma Pharmaceuticals
- Janssen
- Menarini
- Merck Sharp & Dohme
- Molteni Farmaceutici
- Mundipharma
- Novartis
- Novo Nordisk
- Sanofi
- Takeda
- Teva
- Zentiva

Le malattie cardiovascolari rappresentano una causa principale di morbilità e mortalità fra le persone con diabete mellito

OLTRE

2×

AUMENTATO RISCHIO DI MORTE

PER CAUSE CARDIOVASCOLARI[1]

FINO A

4×

AUMENTATO RISCHIO DI INFARTO E ICTUS[2,3]

50-60%

DEI DECESSI

ATTRIBUIBILI ALLE MCV[4,5]

Le persone con diabete vivono fino a

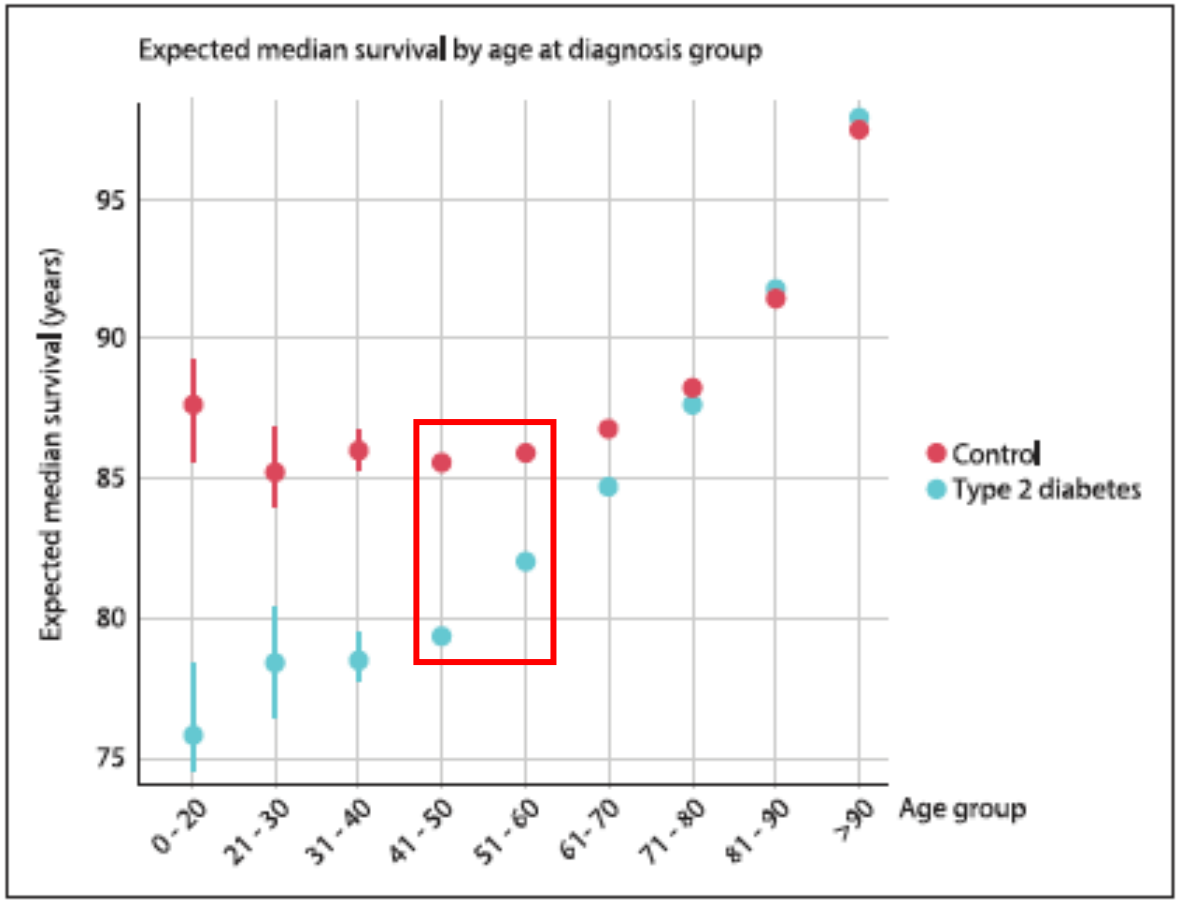
6

anni

di meno rispetto a persone senza diabete nella stessa fascia di rischio[1]

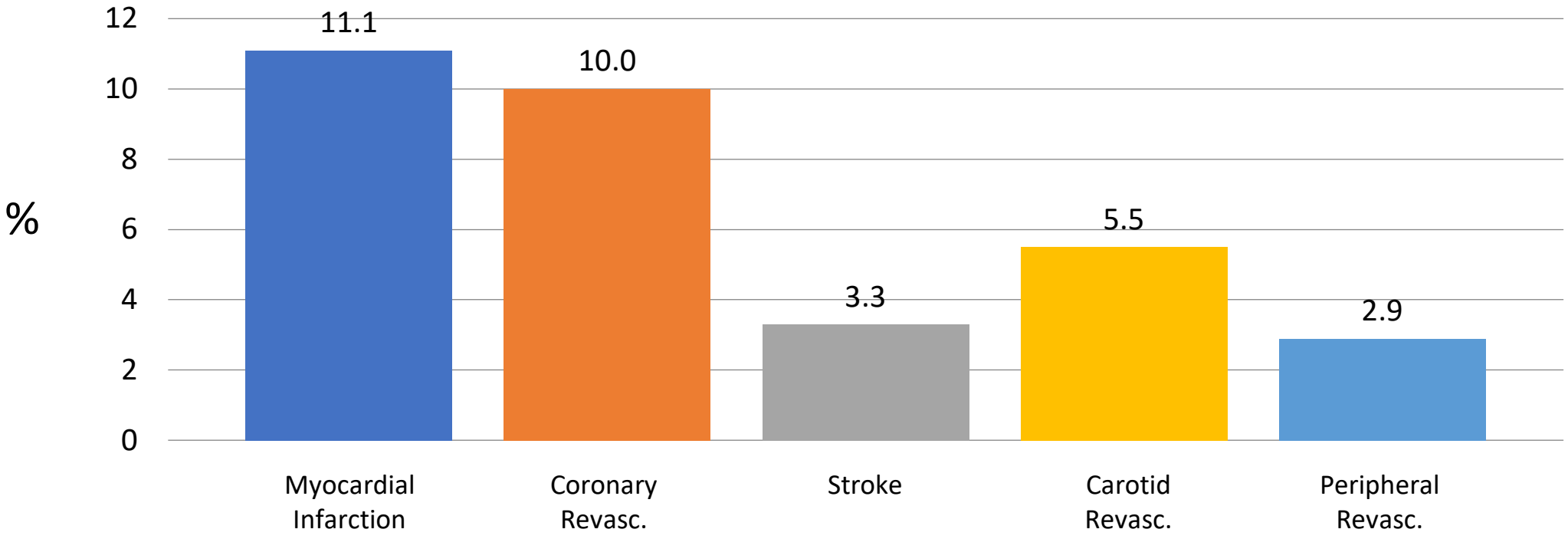
1. Seshasai *et al*. *N Engl J Med* 2011;364:829–841; 2. Folsom *et al*. *Diabetes Care* 1999;22:1077–83; 3. Huxley *et al*. *BMJ* 2006;332:73–8; 4. IDF. Diabetes Atlas. 2015.
5. WHO - Global Atlas on Cardiovascular Diseases Prevention and Control

Età alla diagnosi di T2DM e perdita di anni di vita in persone senza precedenti malattie cardiovascolari



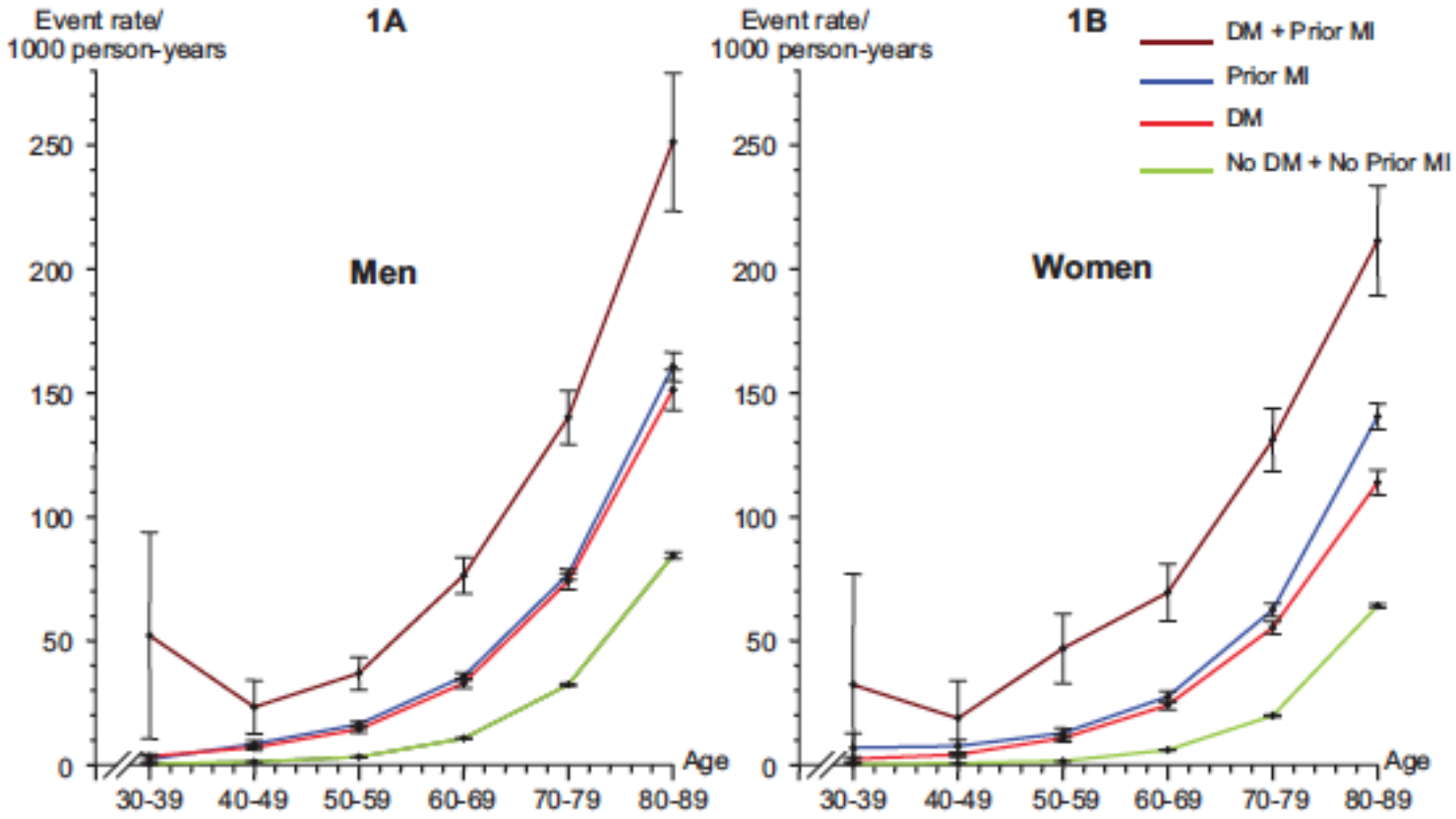
Sattar *et al*. *Circulation 2019 May 7;139(19):2228-2237. doi: 10.1161/CIRCULATIONAHA.118.*

Prevalence of cardiovascular complications in people with type 2 diabetes in Italy



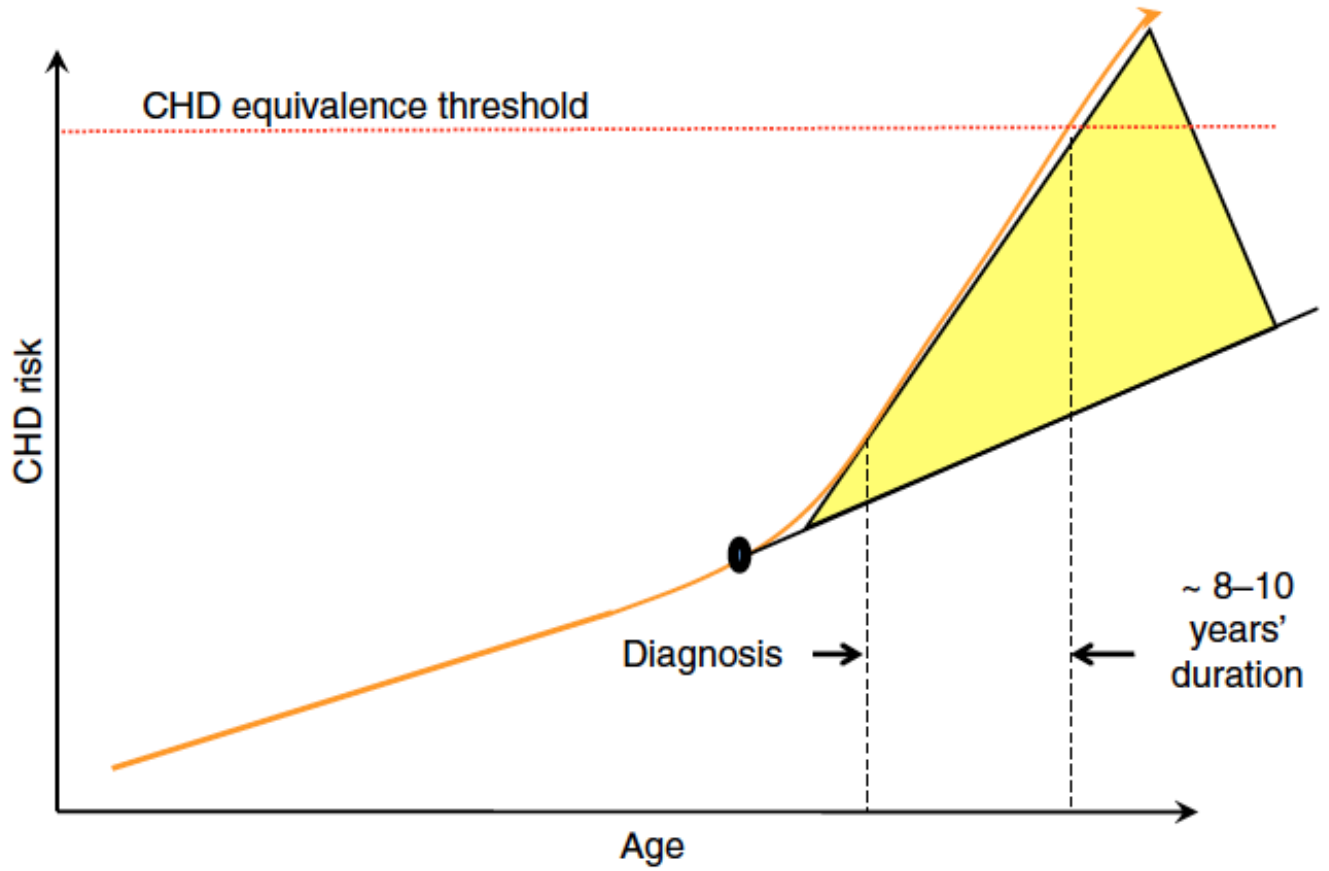
Studio RIACE; Penno et al. *Journal of Internal Medicine*, 2013, 274; 176–191

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



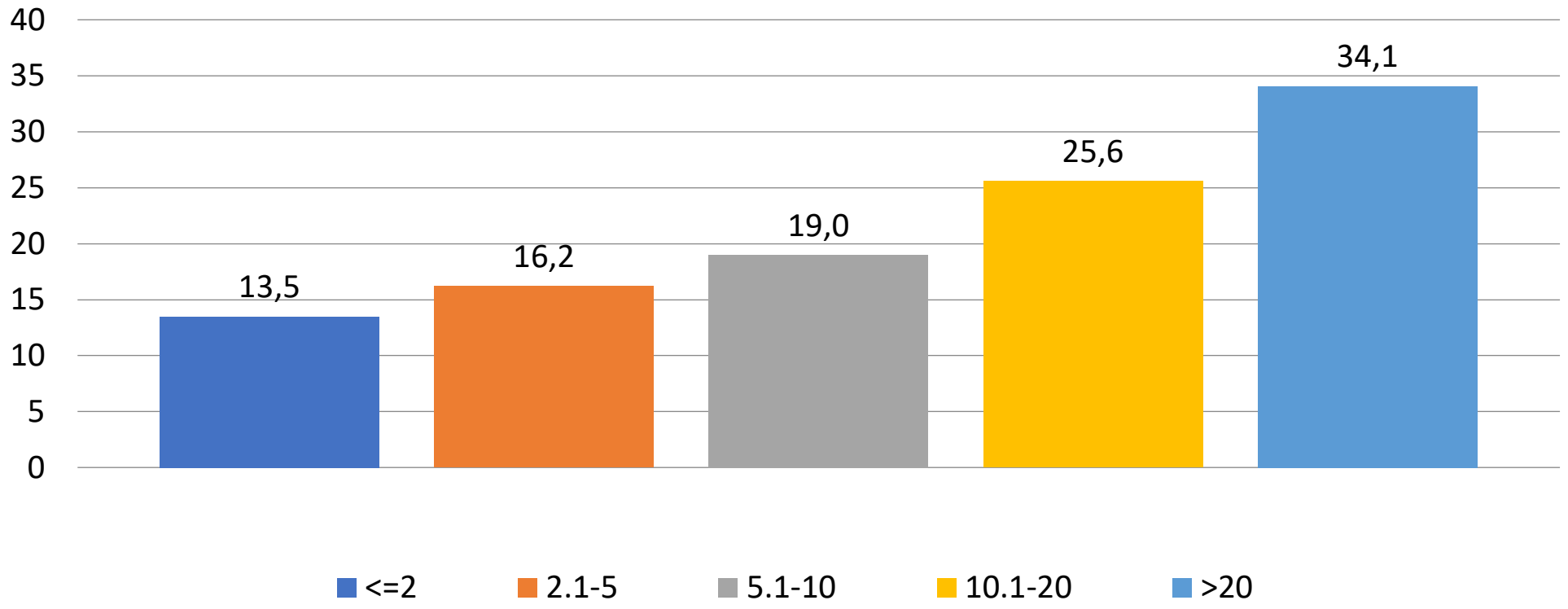
Schramm TK eta al. Circulation. 2008;117:1945-1954

Is diabetes a CHD equivalent?



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

Prevalence of cardiovascular complications based on the duration of diabetes in Italy



MI, stroke, coronary, carotid and peripheral revascularisation

Studio RIACE; data on file

Cardiovascular risk categories in patients with diabetes[a]

Very high risk	Patients with DM **and** established CVD **or** other target organ damage[b] **or** three or more major risk factors[c] **or** early onset T1DM of long duration (>20 years)
High risk	Patients with DM duration ≥10 years without target organ damage plus any other additional risk factor
Moderate risk	Young patients (T1DM aged <35 years or T2DM aged <50 years) with DM duration <10 years, without other risk factors

CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

[a]Modified from the 2016 European Guidelines on cardiovascular disease prevention in clinical practice.

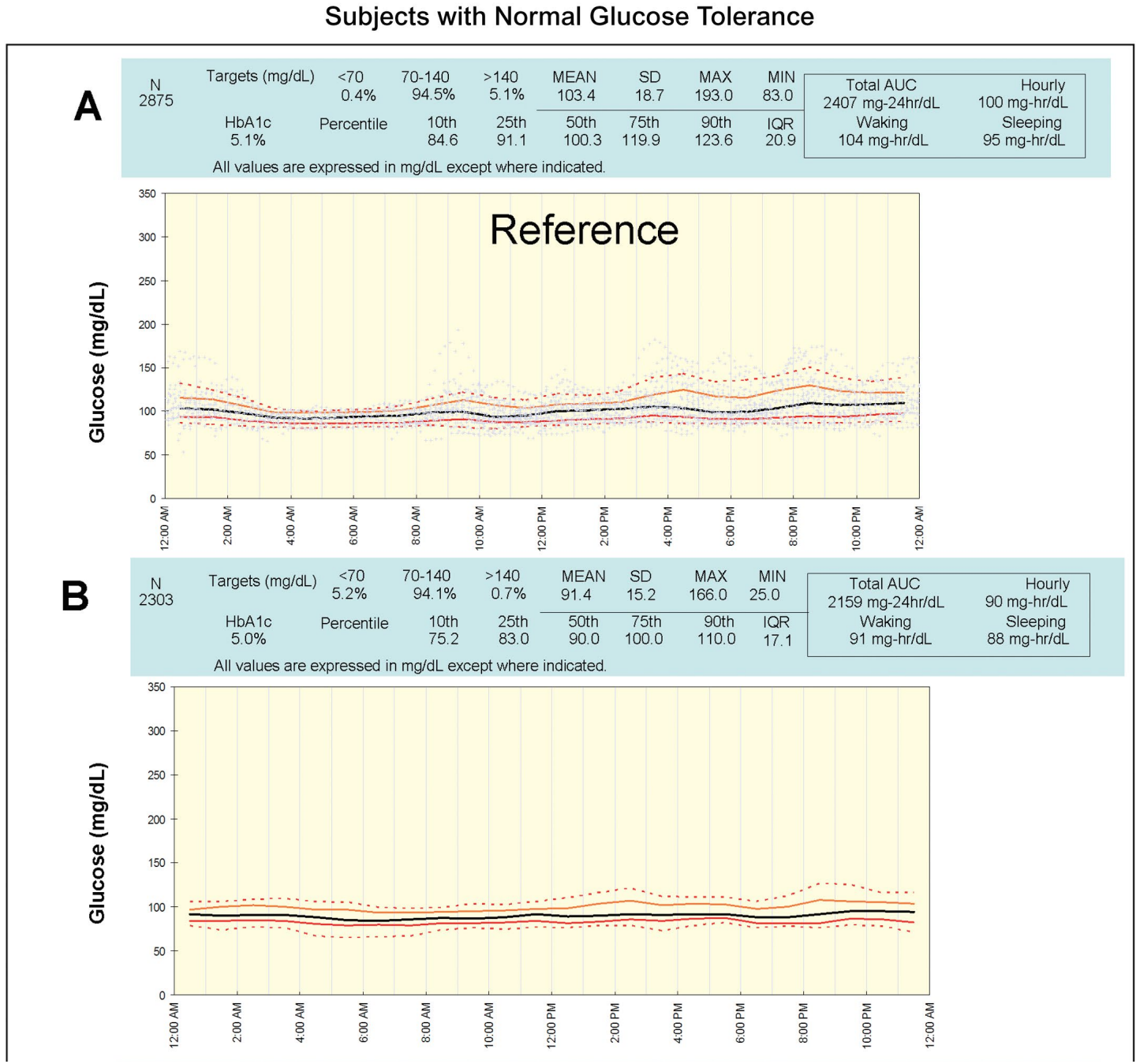
[b]Proteinuria, renal impairment defined as eGFR <30 mL/min/1.73 m2, left ventricular hypertrophy, or retinopathy.

[c]Age, hypertension, dyslipidemia, smoking, obesity.

European Heart Journal (2020) 41, 255 323

Treat to target or Treat to benefit?

La glicemia



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

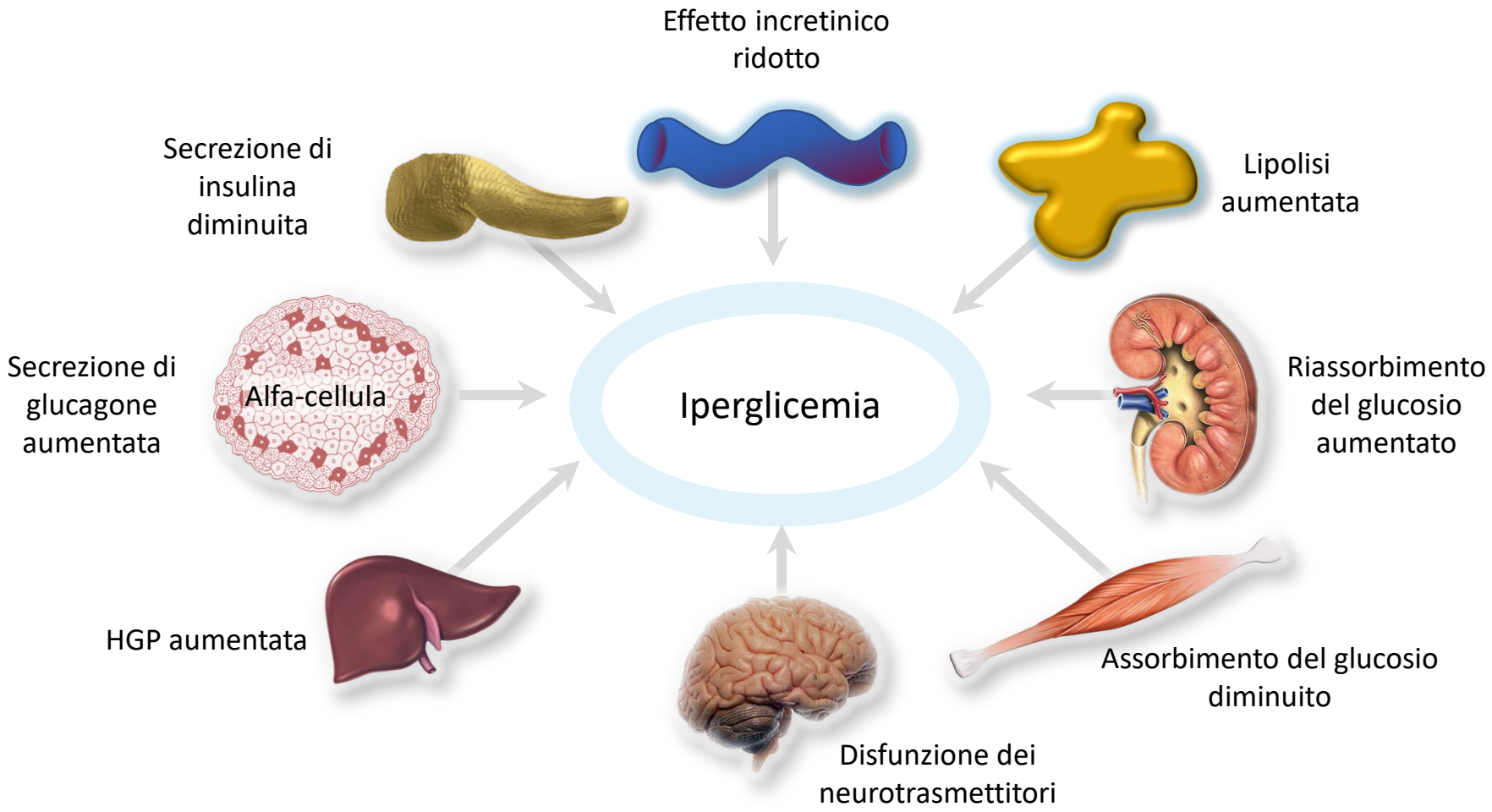
The modal day shows each data point graphed without regard to date

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

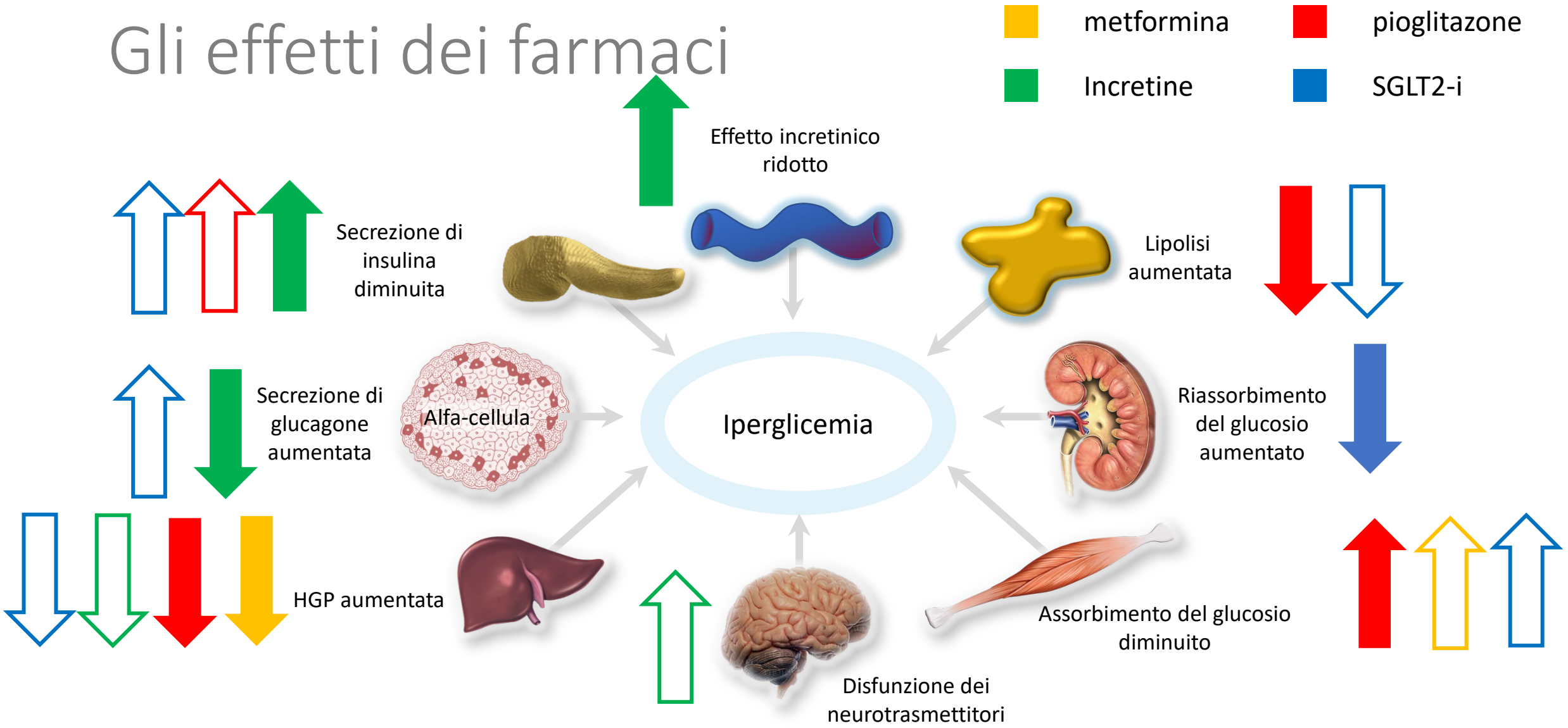
AGP, ambulatory glucose profile; IQR, interquartile range

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

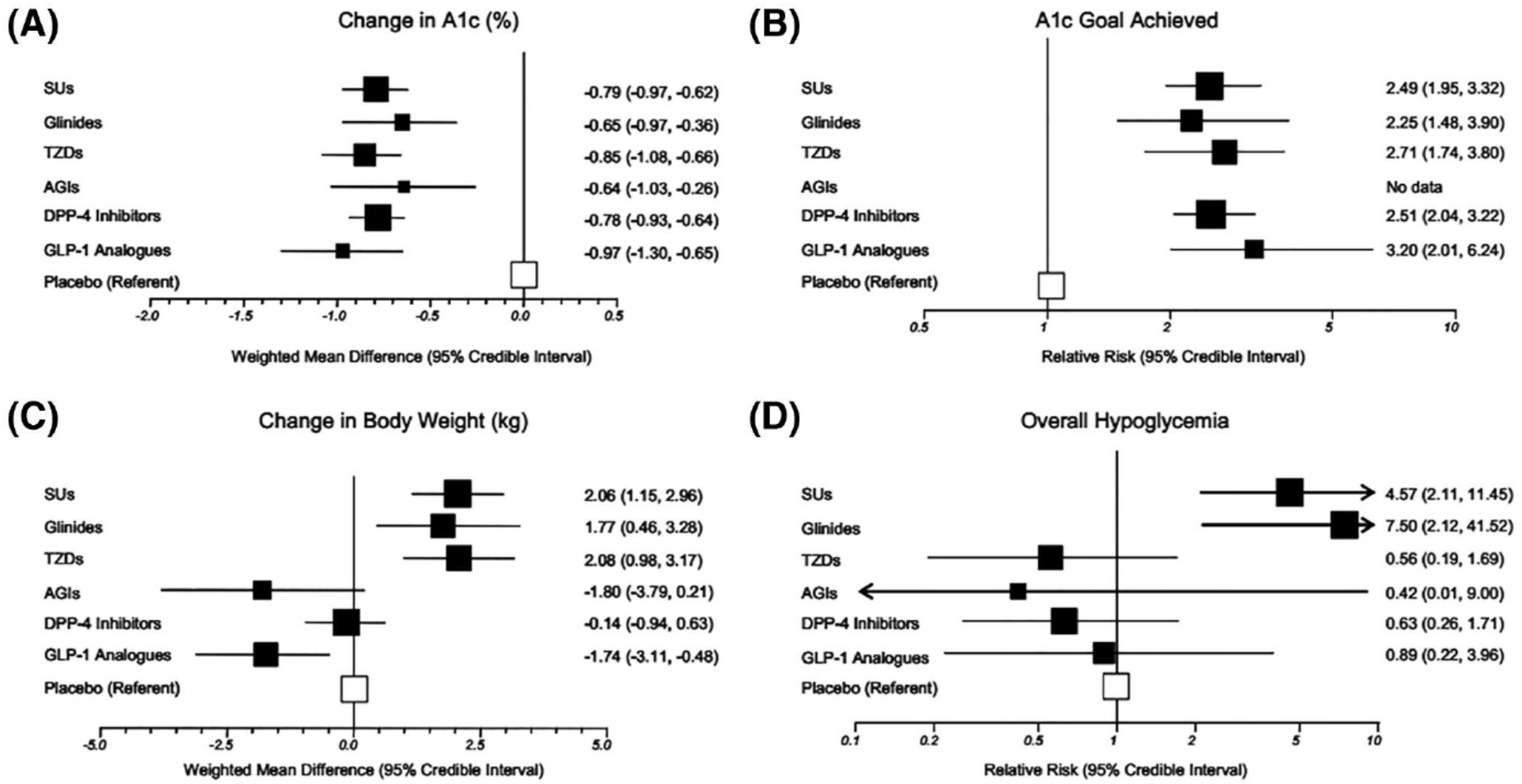


De Fronzo RA. Diabetes 2009;58:773-795

Gli effetti dei farmaci



Modified from De Fronzo RA. Diabetes 2009;58:773-795



*HbA1c goal <7% (53 mmol/mol). The squares represent the pooled effect size for each class of oral glucose-lowering drug. Error bars represent 95% credible intervals. The number of trials included in each mixed-treatment comparison analysis is as follows: A = 26 trials, B = 13 trials, C = 15 trials and D = 24 trials.

Orsini Federici et al. Diabetes Metab Res Rev. 2021;1–18; doi: 10.1002/dmrr.3434

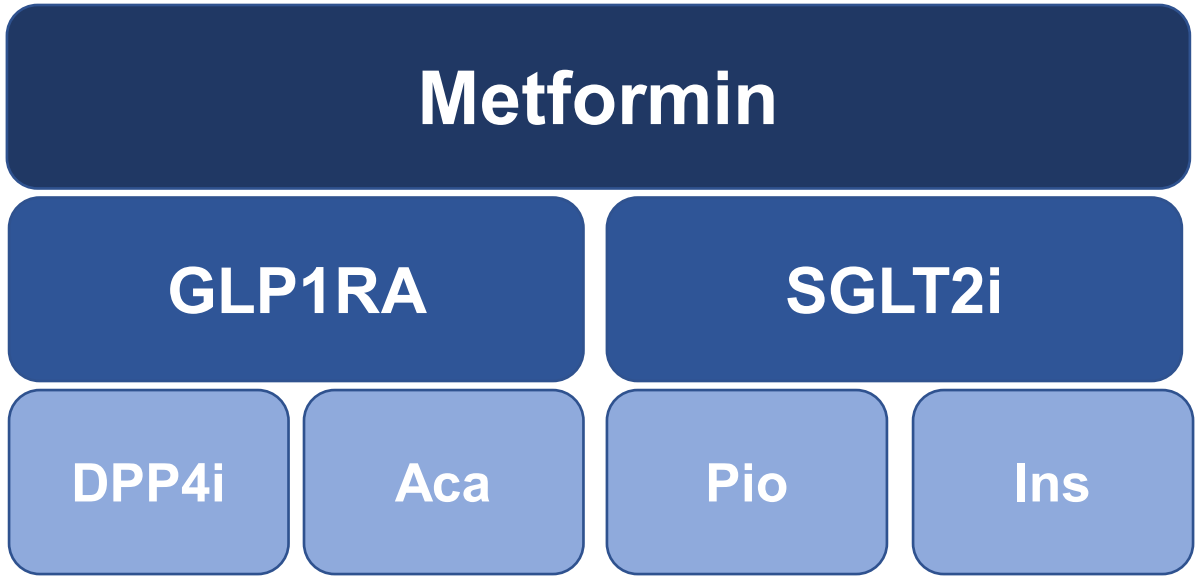
Terapia Farmacologica

Quali sono i farmaci di prima, seconda e terza istanza da impiegare per il controllo della glicemia nei pazienti con diabete di tipo 2 senza pregressi eventi cardiovascolari?

Si raccomanda l'uso di metformina come farmaco di prima scelta per il trattamento a lungo termine in pazienti con diabete di tipo 2 senza pregressi eventi cardiovascolari.

SGLT-2i e GLP-1 RA sono raccomandati come farmaci di seconda scelta.

Pioglitazone, DPP-4i, acarbosio ed insulina dovrebbero essere considerati farmaci di terza scelta.



Forza della raccomandazione: forte. Qualità delle prove: moderata.

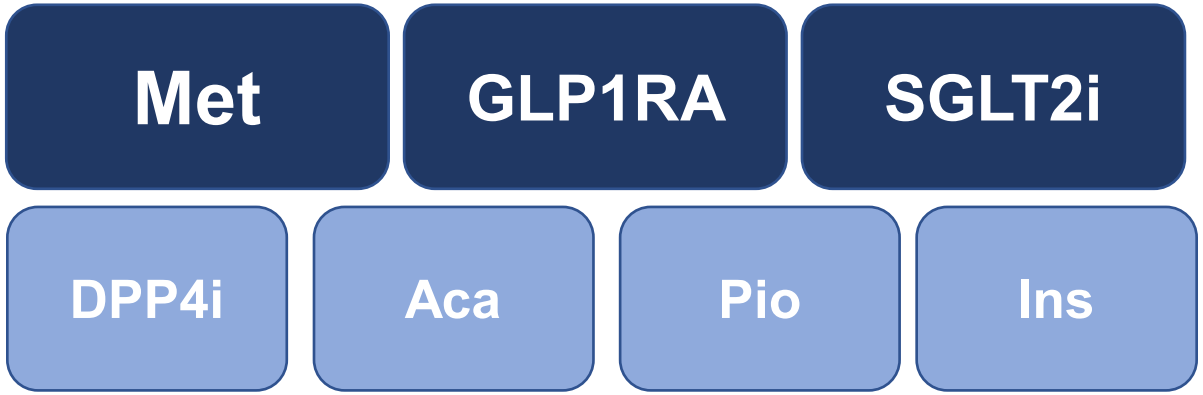
SISTEMA NAZIONALE LINEE GUIDA DELL'ISTITUTO SUPERIORE DI SANITÀ (6 luglio 2021)

Terapia Farmacologica

Quali sono i farmaci di prima, seconda e terza istanza da impiegare per il controllo della glicemia nei pazienti con diabete di tipo 2 con pregressi eventi cardiovascolari?

Si raccomanda l'uso di metformina, SGLT-2i e GLP-1 RA come farmaci di prima scelta per il trattamento a lungo termine in pazienti con diabete di tipo 2 con pregressi eventi cardiovascolari e senza scompenso cardiaco.

Pioglitazone, DPP-4i, acarbosio ed insulina dovrebbero essere considerati farmaci di seconda scelta.



Forza della raccomandazione: forte. Qualità delle prove: moderata.

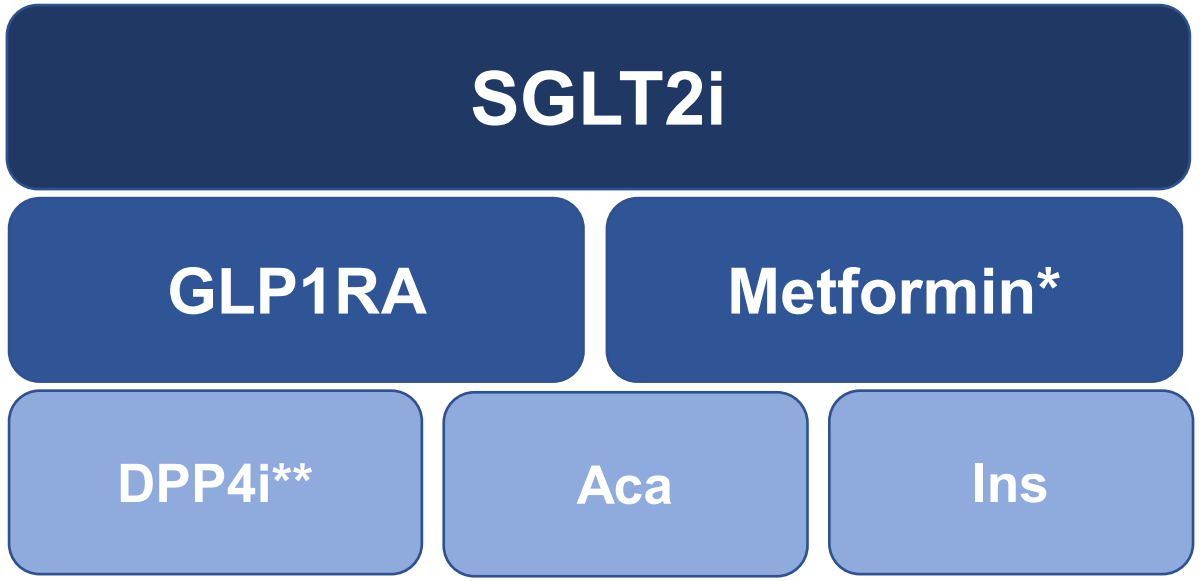
SISTEMA NAZIONALE LINEE GUIDA DELL'ISTITUTO SUPERIORE DI SANITÀ (6 luglio 2021)

Terapia Farmacologica

Quali sono i farmaci di prima, seconda e terza istanza da impiegare per il controllo della glicemia nei pazienti con diabete di tipo 2 con scompenso cardiaco?

Si raccomanda l'uso di SGLT-2i come farmaci di prima scelta per il trattamento a lungo termine di pazienti con diabete di tipo 2 con scompenso cardiaco.

I GLP-1 RA e metformina dovrebbero essere considerati come farmaci di seconda scelta, mentre DPP-4i, acarbosio ed insulina come farmaci di terza scelta.

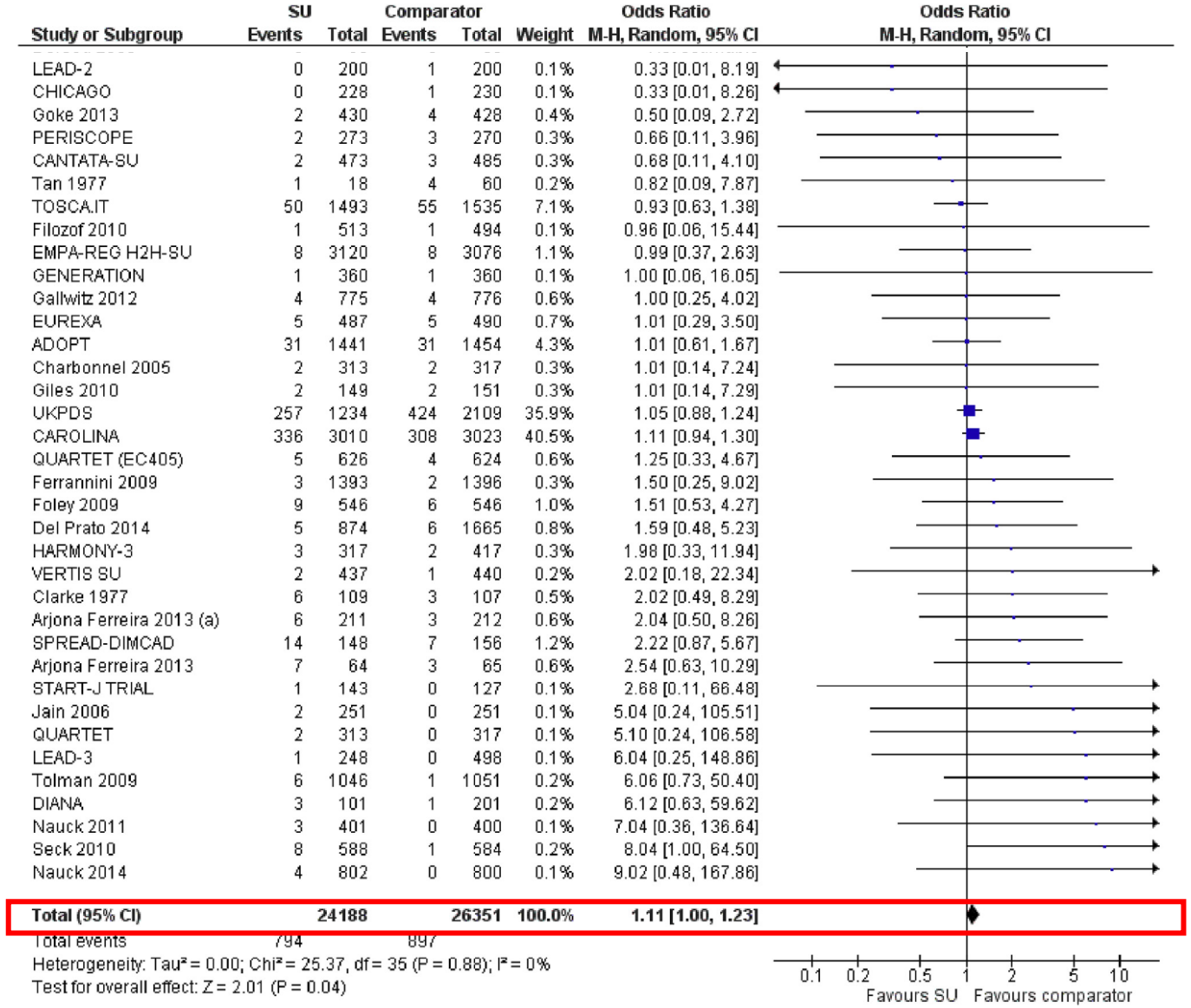


*La metformina è controindicata in classe NYHA III-IV
**Saxagliptin è associato ad un aumento di ricoveri per scompenso cardiaco

Forza della raccomandazione: forte. Qualità delle prove: moderata.

SISTEMA NAZIONALE LINEE GUIDA DELL'ISTITUTO SUPERIORE DI SANITÀ (6 luglio 2021)

Effetto dei secretagoghi dell'insulina sugli eventi CV e sulla mortalità per tutte le cause: una meta-analisi di studi randomizzati controllati



Study or Subgroup	SU Events	SU Total	Comparator Events	Comparator Total	Weight	Odds Ratio M-H, Random, 95% CI
LEAD-2	0	200	1	200	0.1%	0.33 [0.01, 8.19]
CHICAGO	0	228	1	230	0.1%	0.33 [0.01, 8.26]
Goke 2013	2	430	4	428	0.4%	0.50 [0.09, 2.72]
PERISCOPE	2	273	3	270	0.3%	0.66 [0.11, 3.96]
CANTATA-SU	2	473	3	485	0.3%	0.68 [0.11, 4.10]
Tan 1977	1	18	4	60	0.2%	0.82 [0.09, 7.87]
TOSCA.IT	50	1493	55	1535	7.1%	0.93 [0.63, 1.38]
Filozof 2010	1	513	1	494	0.1%	0.96 [0.06, 15.44]
EMPA-REG H2H-SU	8	3120	8	3076	1.1%	0.99 [0.37, 2.63]
GENERATION	1	360	1	360	0.1%	1.00 [0.06, 16.05]
Gallwitz 2012	4	775	4	776	0.6%	1.00 [0.25, 4.02]
EUREXA	5	487	5	490	0.7%	1.01 [0.29, 3.50]
ADOPT	31	1441	31	1454	4.3%	1.01 [0.61, 1.67]
Charbonnel 2005	2	313	2	317	0.3%	1.01 [0.14, 7.24]
Giles 2010	2	149	2	151	0.3%	1.01 [0.14, 7.29]
UKPDS	257	1234	424	2109	35.9%	1.05 [0.88, 1.24]
CAROLINA	336	3010	308	3023	40.5%	1.11 [0.94, 1.30]
QUARTET (EC405)	5	626	4	624	0.6%	1.25 [0.33, 4.67]
Ferrannini 2009	3	1393	2	1396	0.3%	1.50 [0.25, 9.02]
Foley 2009	9	546	6	546	1.0%	1.51 [0.53, 4.27]
Del Prato 2014	5	874	6	1665	0.8%	1.59 [0.48, 5.23]
HARMONY-3	3	317	2	417	0.3%	1.98 [0.33, 11.94]
VERTIS SU	2	437	1	440	0.2%	2.02 [0.18, 22.34]
Clarke 1977	6	109	3	107	0.5%	2.02 [0.49, 8.29]
Arjona Ferreira 2013 (a)	6	211	3	212	0.6%	2.04 [0.50, 8.26]
SPREAD-DIMCAD	14	148	7	156	1.2%	2.22 [0.87, 5.67]
Arjona Ferreira 2013	7	64	3	65	0.6%	2.54 [0.63, 10.29]
START-J TRIAL	1	143	0	127	0.1%	2.68 [0.11, 66.48]
Jain 2006	2	251	0	251	0.1%	5.04 [0.24, 105.51]
QUARTET	2	313	0	317	0.1%	5.10 [0.24, 106.58]
LEAD-3	1	248	0	498	0.1%	6.04 [0.25, 148.86]
Tolman 2009	6	1046	1	1051	0.2%	6.06 [0.73, 50.40]
DIANA	3	101	1	201	0.2%	6.12 [0.63, 59.62]
Nauck 2011	3	401	0	400	0.1%	7.04 [0.36, 136.64]
Seck 2010	8	588	1	584	0.2%	8.04 [1.00, 64.50]
Nauck 2014	4	802	0	800	0.1%	9.02 [0.48, 167.86]
Total (95% CI)		**24188**		**26351**	**100.0%**	**1.11 [1.00, 1.23]**
Total events	794		897			

Heterogeneity: Tau² = 0.00; Chi² = 25.37, df = 35 (P = 0.88); I² = 0%
Test for overall effect: Z = 2.01 (P = 0.04)

- Metanalisi di 46 RCT (24188 nel braccio con SU e 26351 nel braccio di confronto)
- I secretagoghi dell'insulina erano associati a un rischio significativamente aumentato di mortalità per tutte le cause rispetto a placebo/nessuna terapia o altre terapie anti-iperglicemiche **(MH-OR 1.11 [1.00, 1.23], p = 0.04)**

Adapted from Mannucci E et al. Nutrition, Metabolism & Cardiovascular Diseases 2020; 30: 1601-1608

Il Sistema Sanitario Nazionale (SSN)

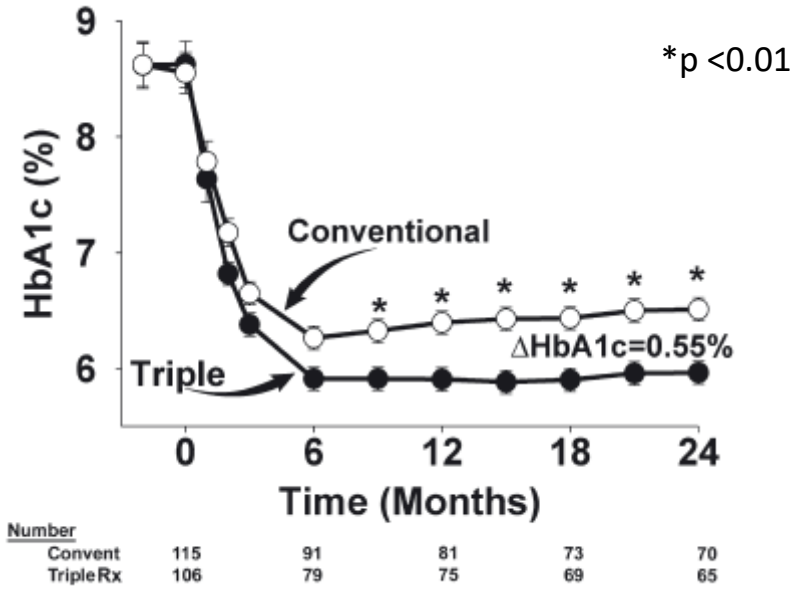
- I principi fondamentali su cui si basa il SSN dalla sua istituzione, avvenuta con la legge n.833 del 1978, sono:
  - Universalità: l'estensione delle prestazioni sanitarie a tutta la popolazione
  - Uguaglianza: i cittadini devono accedere alle prestazioni del SSN senza nessuna distinzione di condizioni individuali, sociali ed economiche
  - Equità: a tutti i cittadini deve essere garantita parità di accesso in rapporto a uguali bisogni di salute

Perché il trattamento ideale è la terapia combinata?

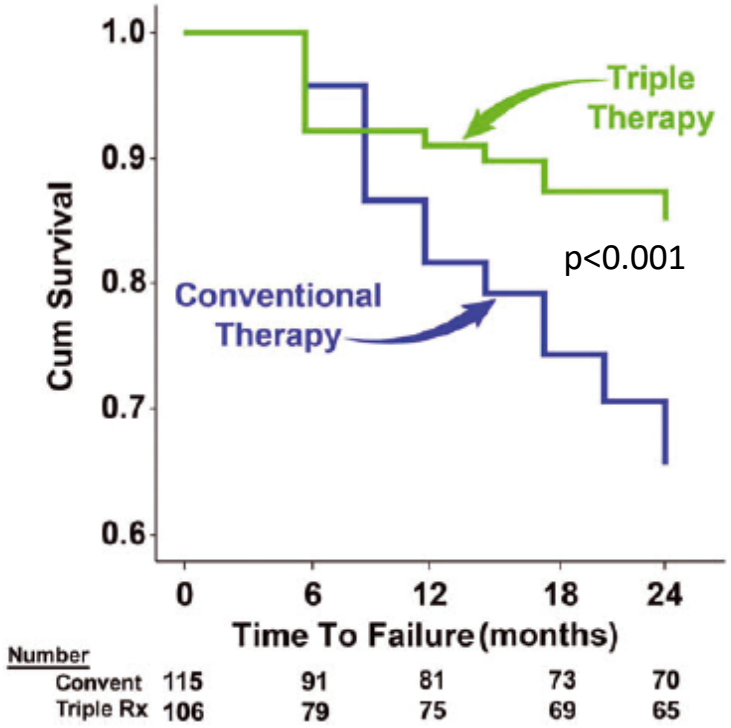
- Base fisiopatologica
- Meccanismo d'azione complementare
- Efficacia e sicurezza
- Effetti extra-glicemici

Initial combination therapy with metformin, pioglitazone and exenatide is more effective than sequential add-on therapy in subjects with new-onset diabetes

Time-related change in HbA1c



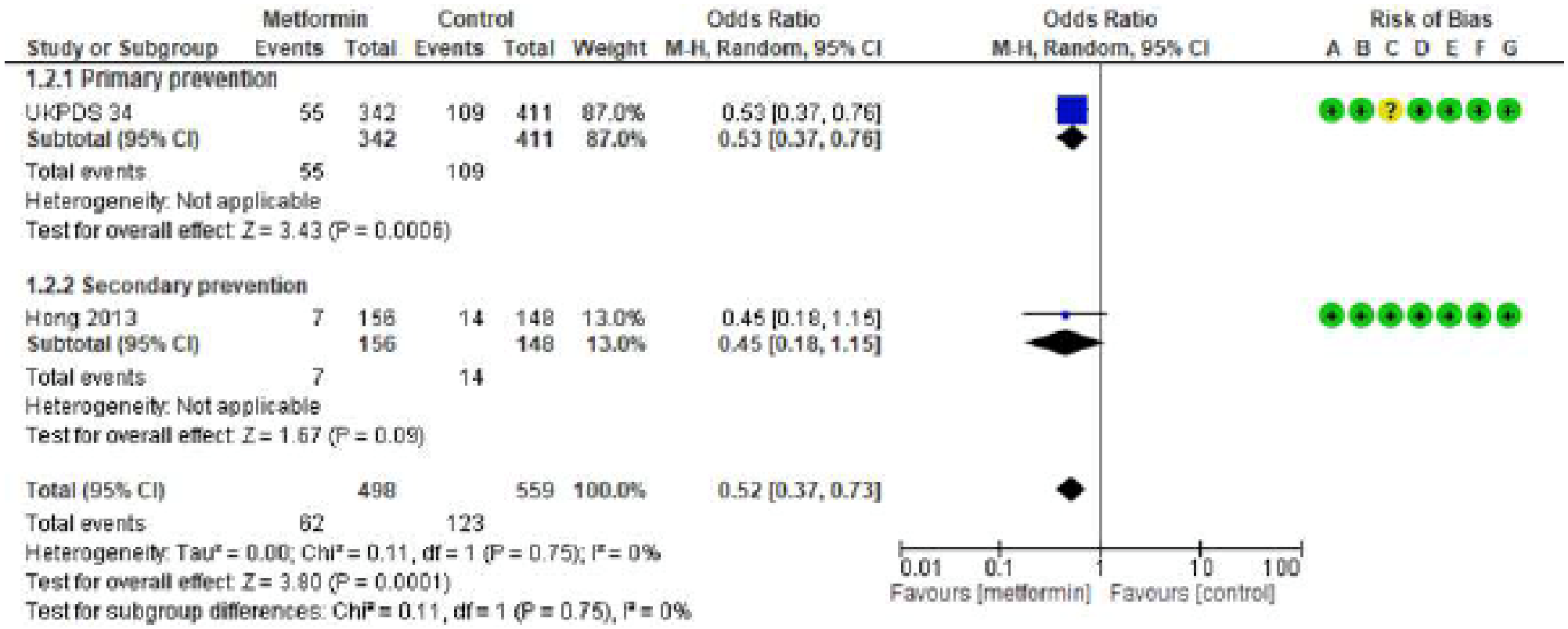
Kaplan–Meier plot of time to treatment failure, defined as HbA1c >6.5%



Abdul-Ghani MA et al Diabetes, Obesity and Metabolism 17: 268–275, 2015

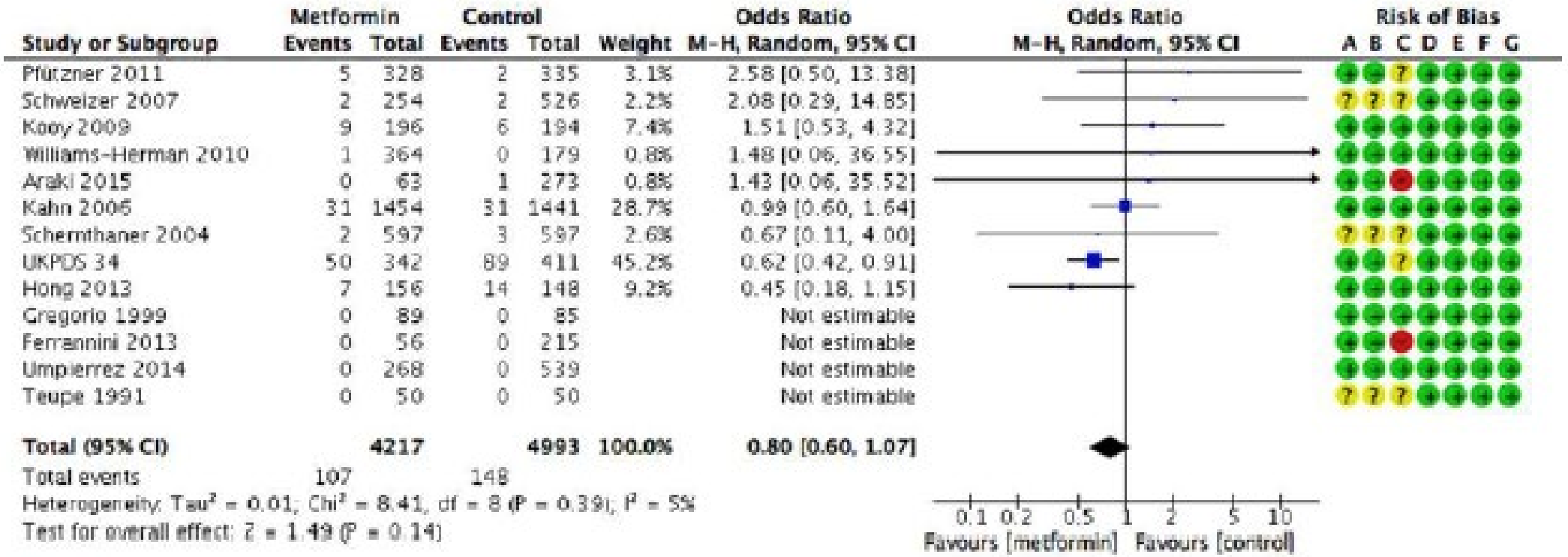
Caso clinico 1

Effetti del trattamento con metformina rispetto a placebo/nessun trattamento o altri farmaci attivi sul rischio di MACE



Monami M. et al. Nutrition, Metabolism & Cardiovascular Diseases 2020

Effetti del trattamento con metformina rispetto aì placebo/nessun trattamento o altri farmaci attivi sul rischio di morte da tutte le cause



Study or Subgroup	Metformin Events	Metformin Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Pfützner 2011	5	328	2	335	3.1%	2.58 [0.50, 13.38]
Schweizer 2007	2	254	2	526	2.2%	2.08 [0.29, 14.85]
Kooy 2009	9	196	6	194	7.4%	1.51 [0.53, 4.32]
Williams-Herman 2010	1	364	0	179	0.8%	1.48 [0.06, 36.55]
Araki 2015	0	63	1	273	0.8%	1.43 [0.06, 35.52]
Kahn 2006	31	1454	31	1441	28.7%	0.99 [0.60, 1.64]
Schernthaner 2004	2	597	3	597	2.6%	0.67 [0.11, 4.00]
UKPDS 34	50	342	89	411	45.2%	0.62 [0.42, 0.91]
Hong 2013	7	156	14	148	9.2%	0.45 [0.18, 1.15]
Gregorio 1999	0	89	0	85		Not estimable
Ferrannini 2013	0	56	0	215		Not estimable
Umpierrez 2014	0	268	0	539		Not estimable
Teupe 1991	0	50	0	50		Not estimable
Total (95% CI)		**4217**		**4993**	**100.0%**	**0.80 [0.60, 1.07]**
Total events	107		148			

Heterogeneity: Tau² = 0.01; Chi² = 8.41, df = 8 (P = 0.39); I² = 5%
Test for overall effect: Z = 1.49 (P = 0.14)

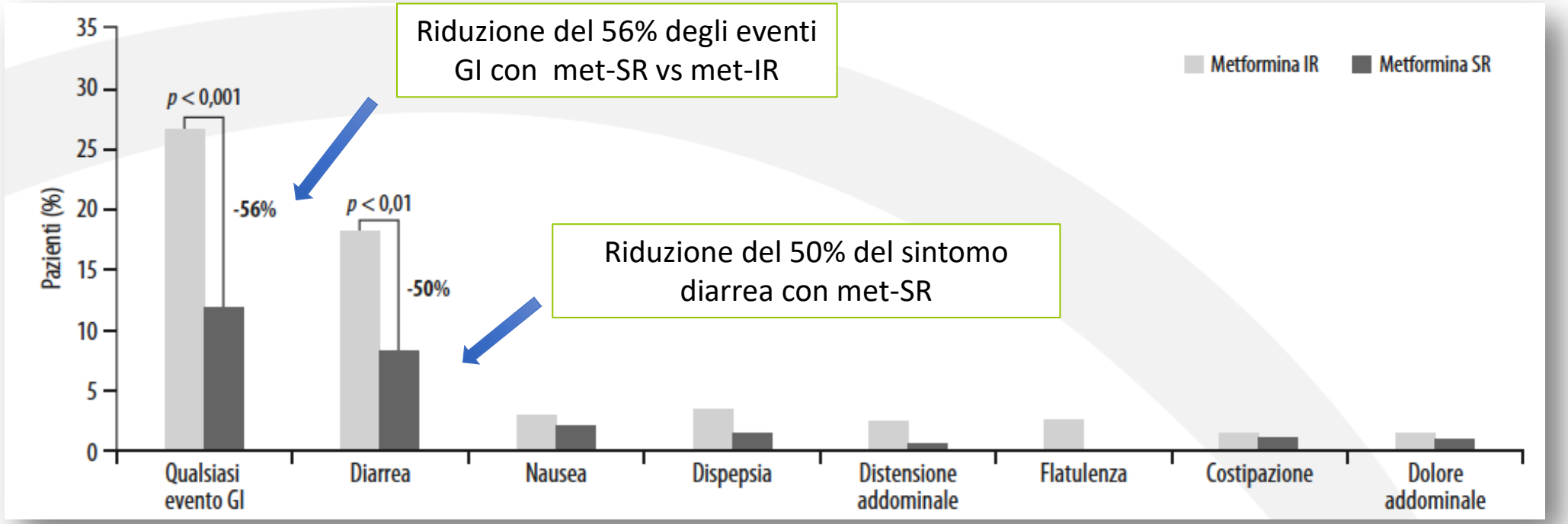
Odds Ratio M-H, Random, 95% CI

0.1 0.2 0.5 1 2 5 10
Favours [metformin] Favours [control]

Risk of Bias A B C D E F G

Monami M. et al. Nutrition, Metabolism & Cardiovascular Diseases 2020

Effetti collaterali GI sostituendo met-IR con met-SR

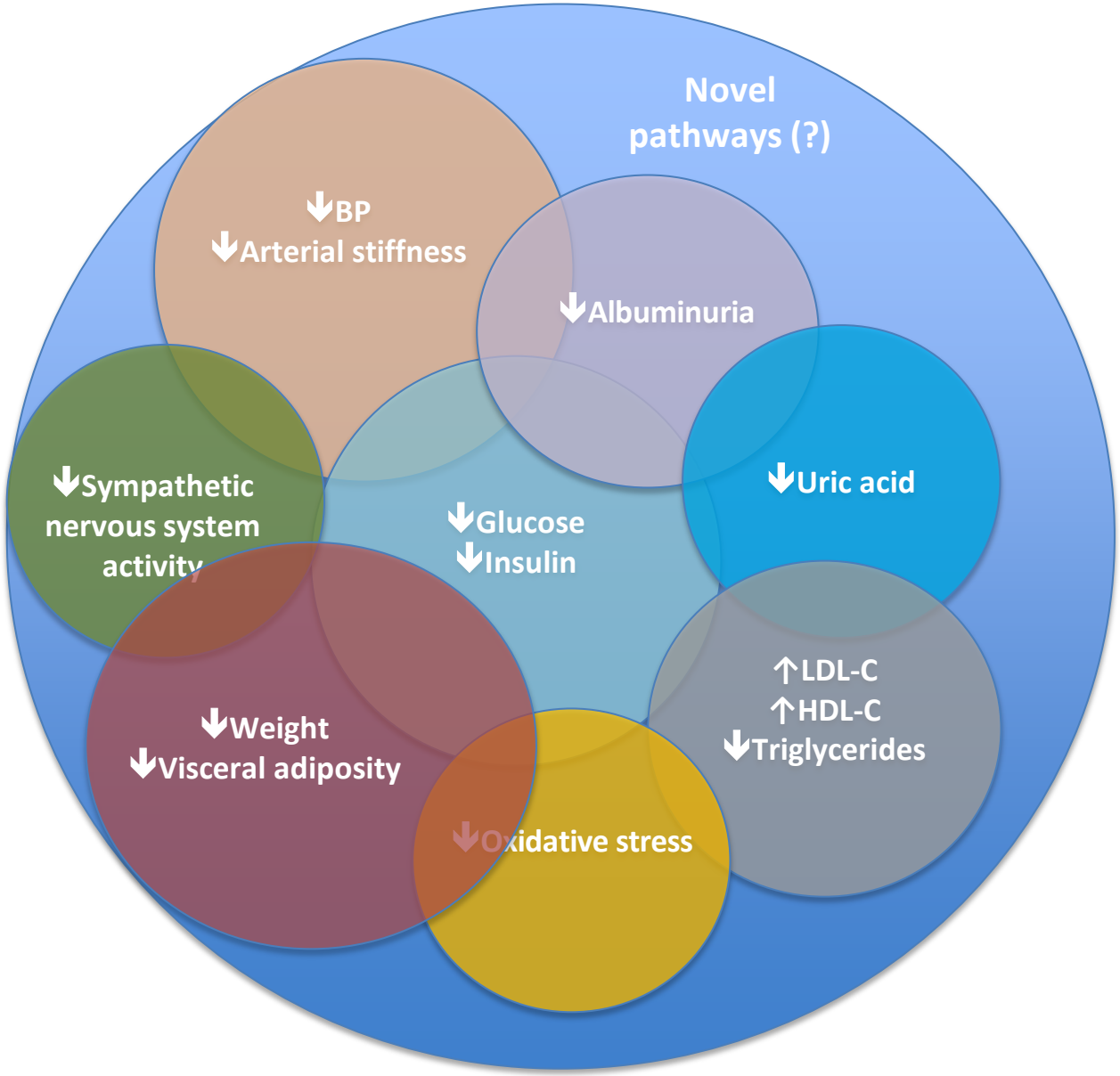


p=0.0006

p=0.0084

Curr Med Res Opin 2004 Apr;20(4):565-72

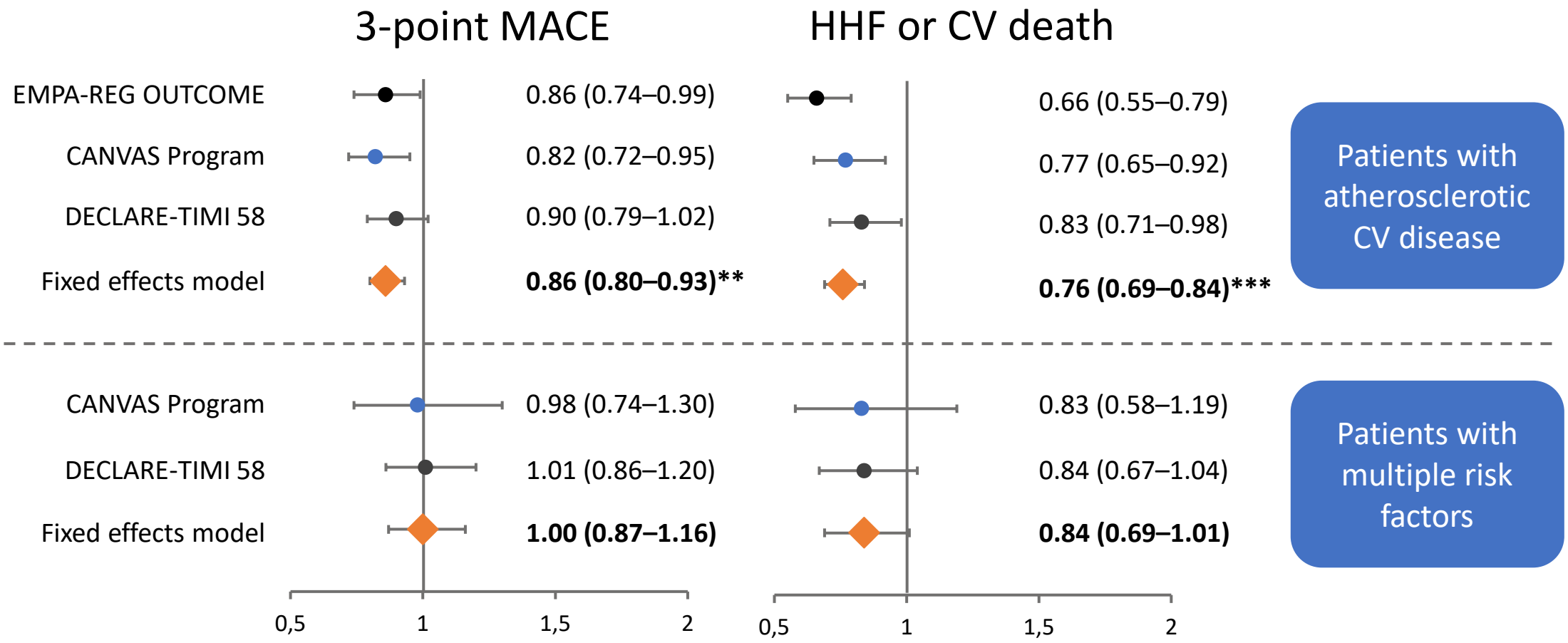
SGLT2i Modulates Several Factors Related to CV risk



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

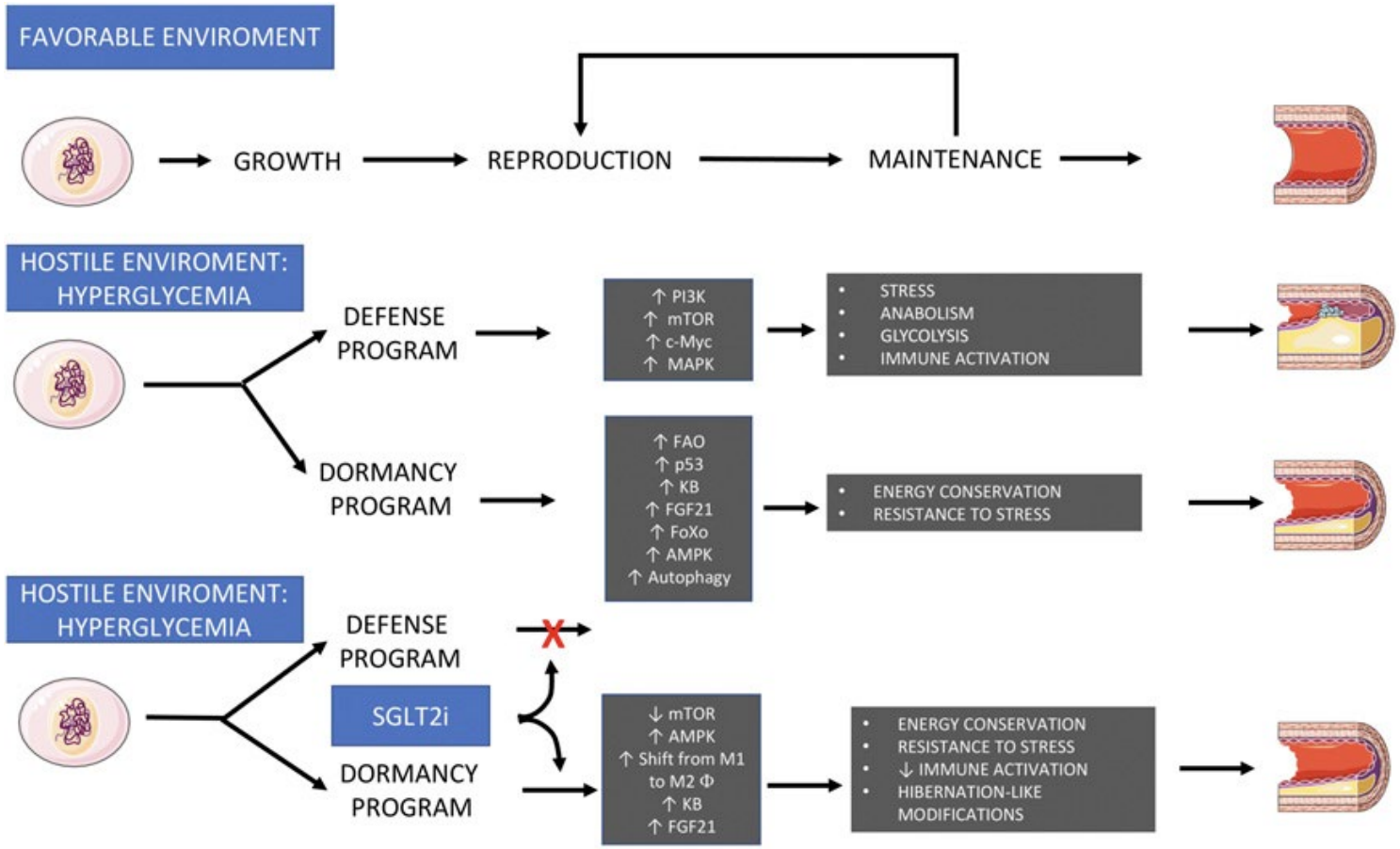
The SGLT2i class offers cardioprotection in a broad range of patients with T2D: network meta-analysis[1]



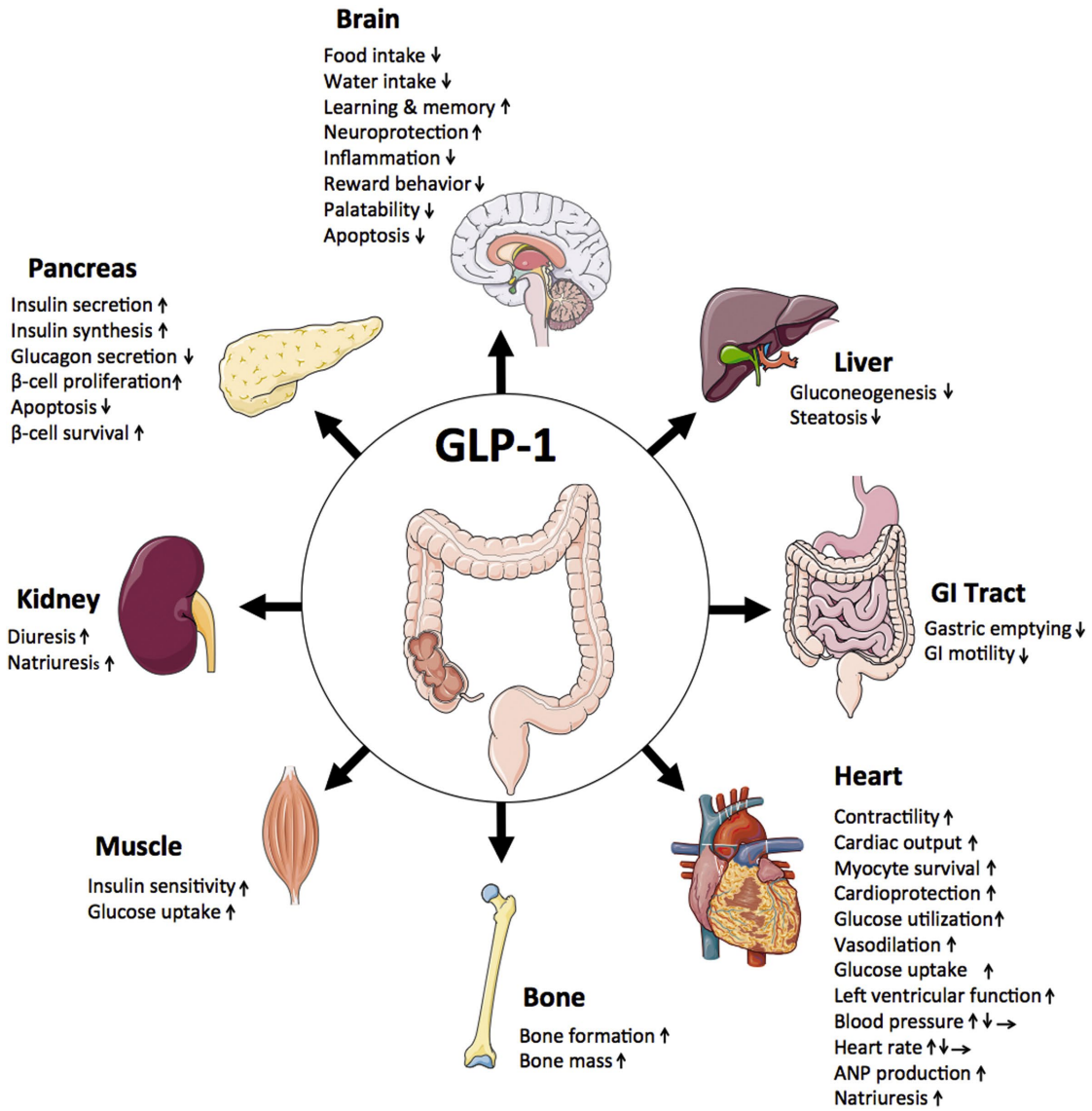
**$p < 0.001$; ***$p < 0.0001$. Values shown are hazard ratio (95% confidence interval)
CV, cardiovascular disease; HHF, hospitalization for heart failure; MACE, major adverse cardiovascular events

Zelniker TA *et al. Lancet* 2019;393:31-9.

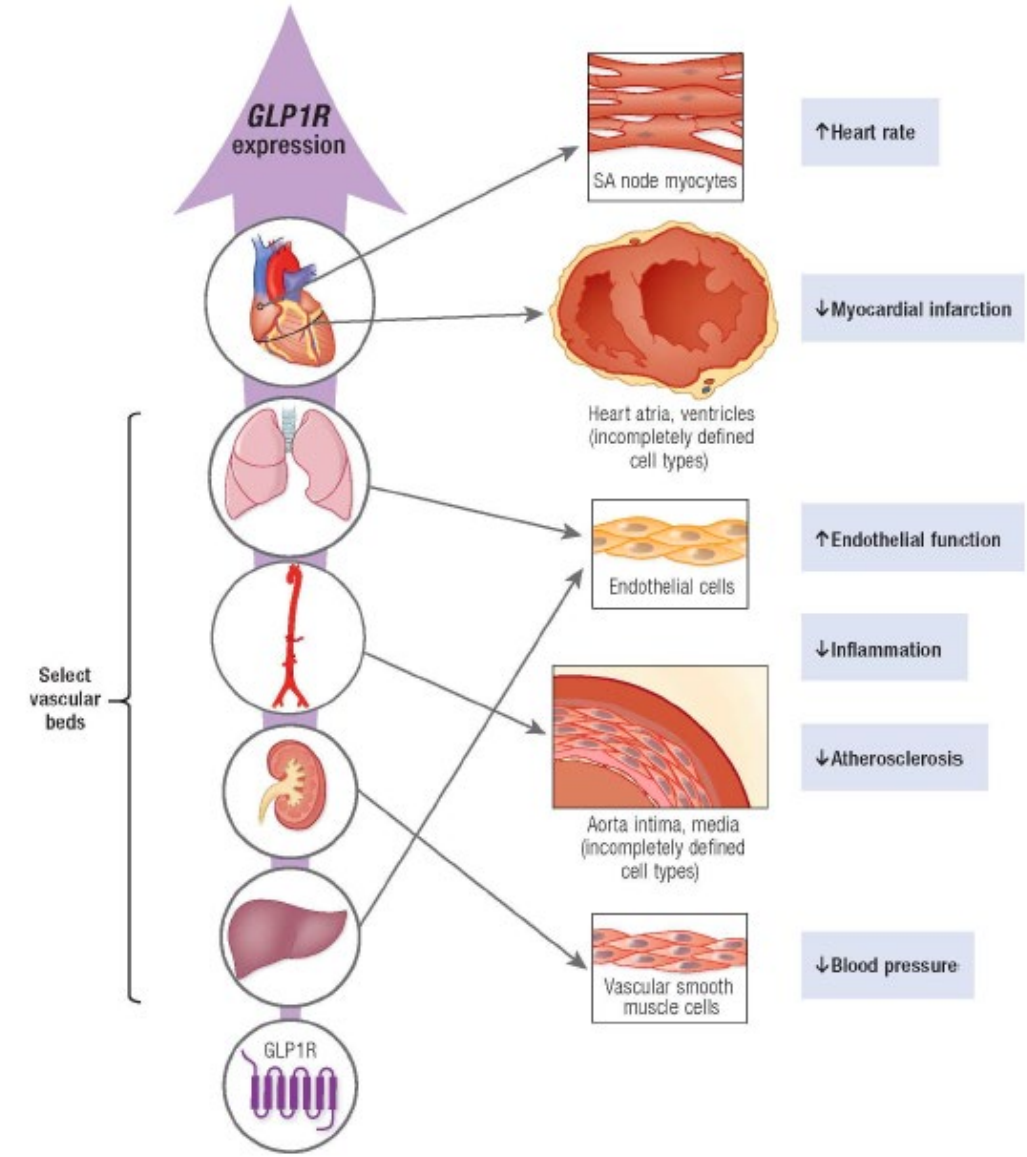
Reinterpreting cardiorenal protection of renal sodium–glucose cotransporter 2 inhibitors via cellular life history programming



Avogaro A et al. Diabetes Care 2020;43:501–507



Muller TD et al. Mol Metab 2019; 30:72-130

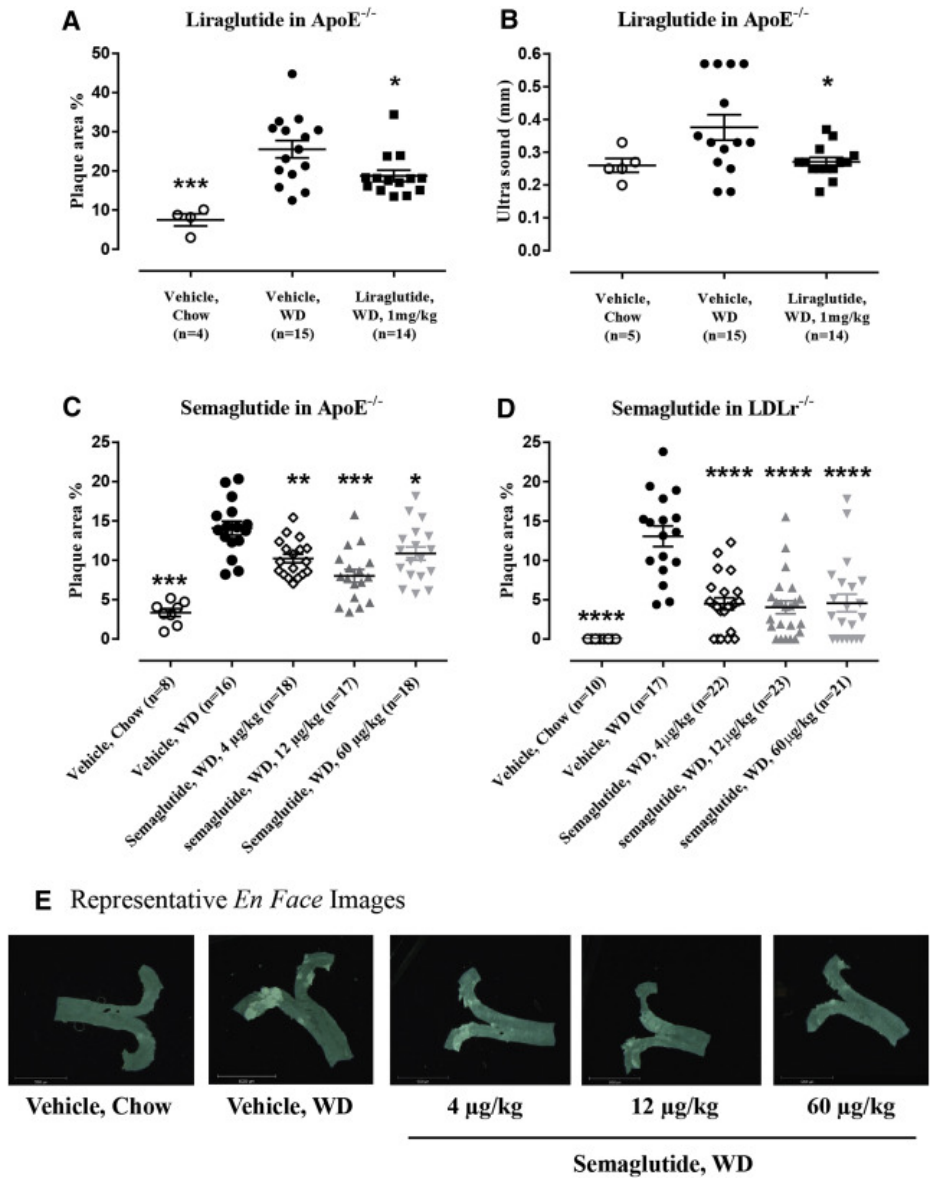


McLean B et al. Endocrine Reviews 2020 Dec 15;bnaa032

- The GLP-1RAs liraglutide and semaglutide reduce cardiovascular risk in type 2 diabetes patients.

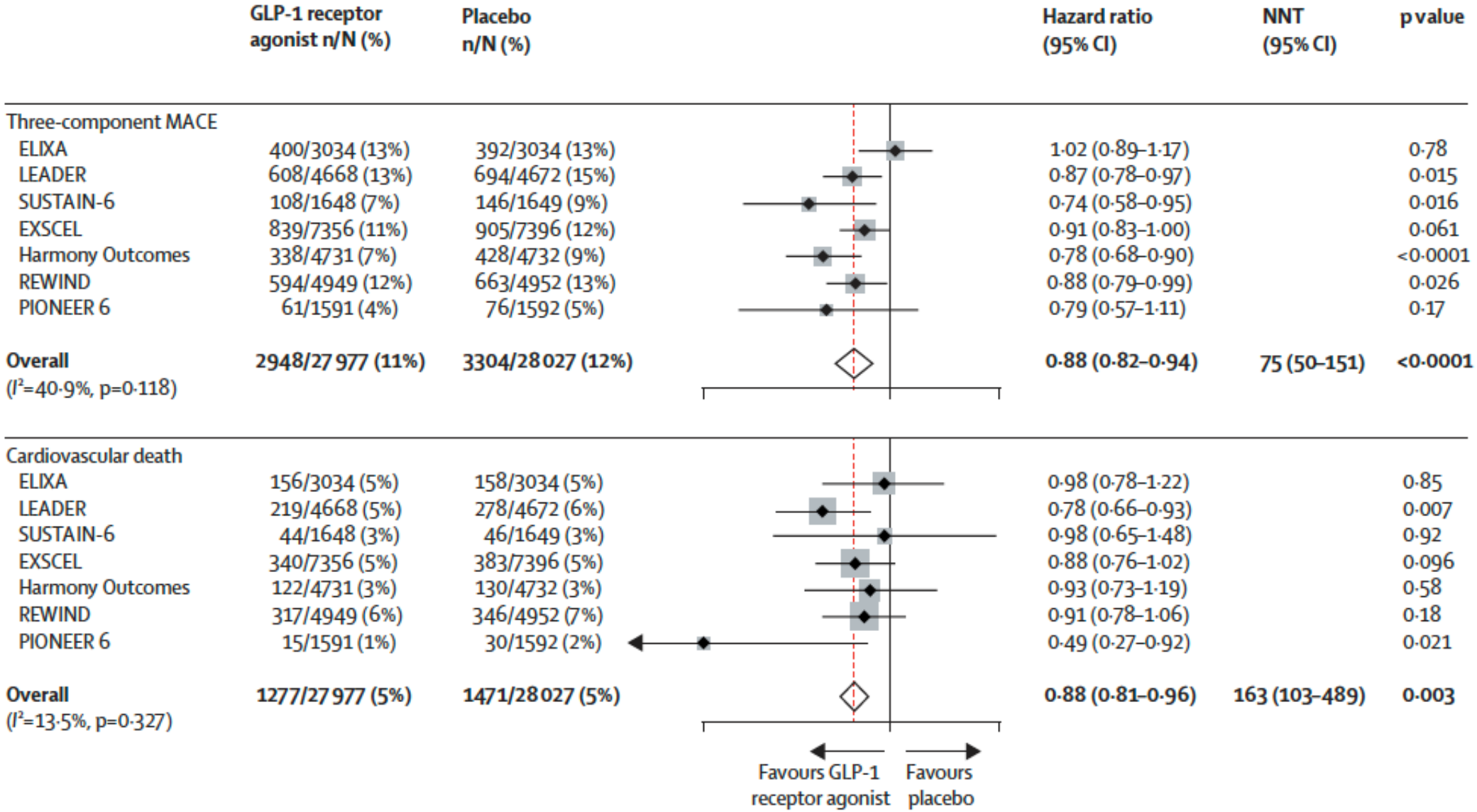
- In ApoE -/- mice and LDLr -/- mice, liraglutide and semaglutide treatment significantly attenuated plaque lesion development, in part independently of body weight and cholesterol lowering.

- Semaglutide decreased levels of plasma markers of systemic inflammation in an acute inflammation model (lipopolysaccharide), and transcriptomic analysis of aortic atherosclerotic tissue revealed that multiple inflammatory pathways were down-regulated by semaglutide.



JACC Basic Transl Sci. 2018 Nov 21;3(6):844-857.

A systematic review and meta-analysis of CVOT with GLP1-RA



Kristensen LS et al.; *Lancet Diabetes Endocrinol* 2019

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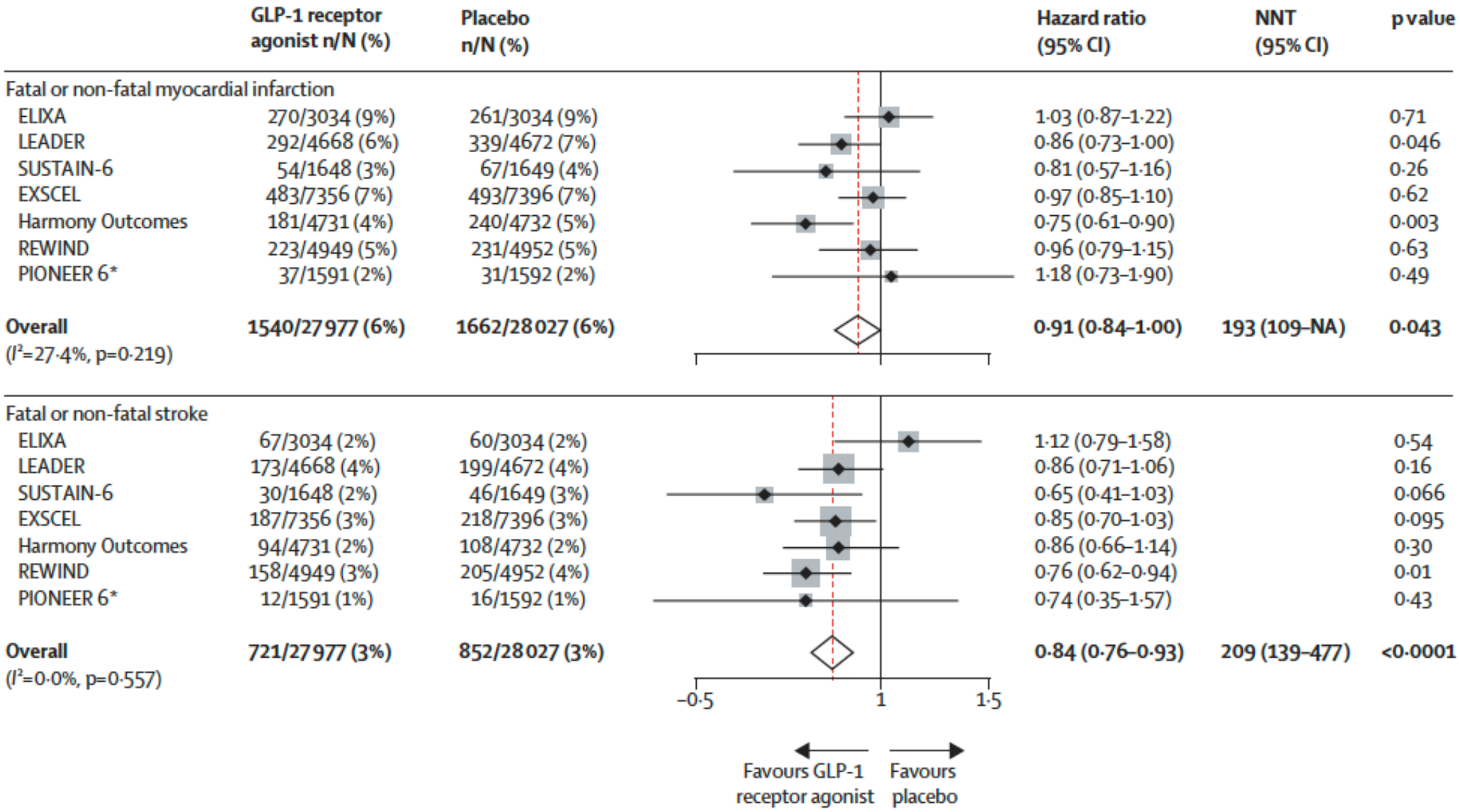
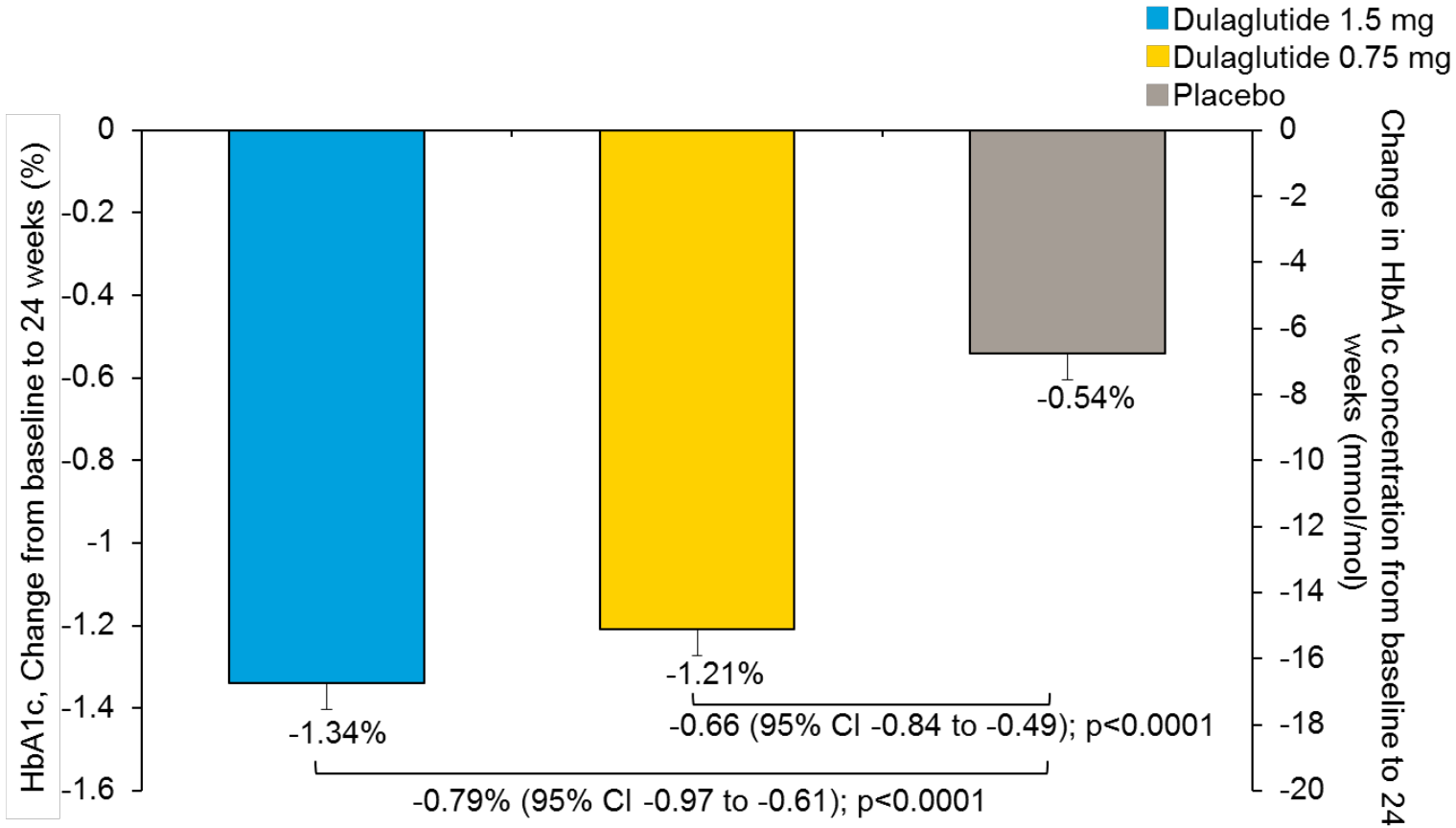


Kristensen LS et al.; *Lancet Diabetes Endocrinol* 2019

Award 10 - HbA1c Change from baseline to 24 weeks in add-on to SGLT2-i



Error bars show SEs; HbA1c=glycated haemoglobin; SE=standard error

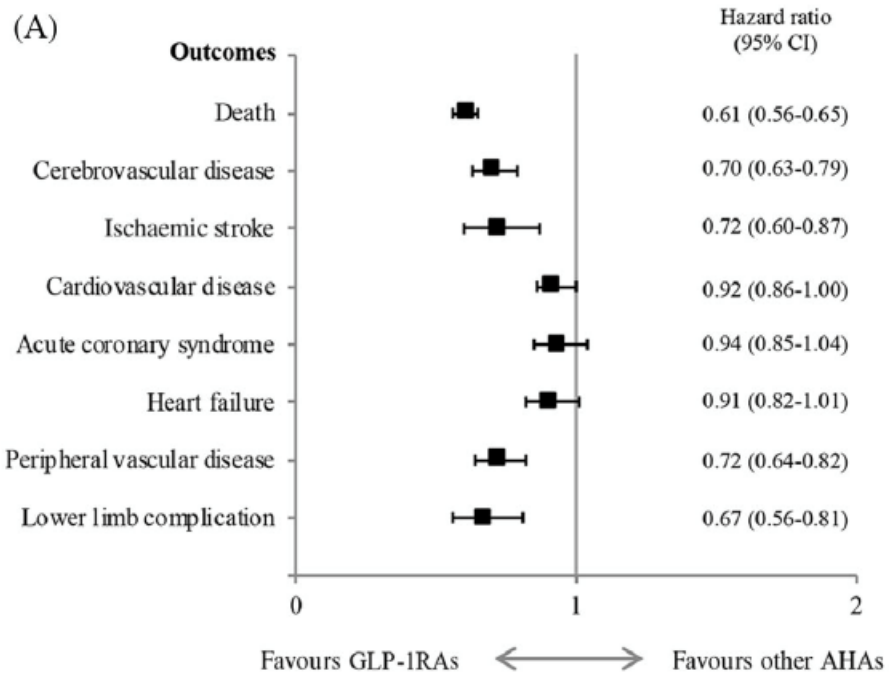
Ludvik et al. *Lancet Diabetes Endocrinol* 2018.

Lower risk of death and cardiovascular events in patients with diabetes initiating glucagon-like peptide-1 receptor agonists or sodium-glucose cotransporter-2 inhibitors: A real-world study in two Italian cohorts

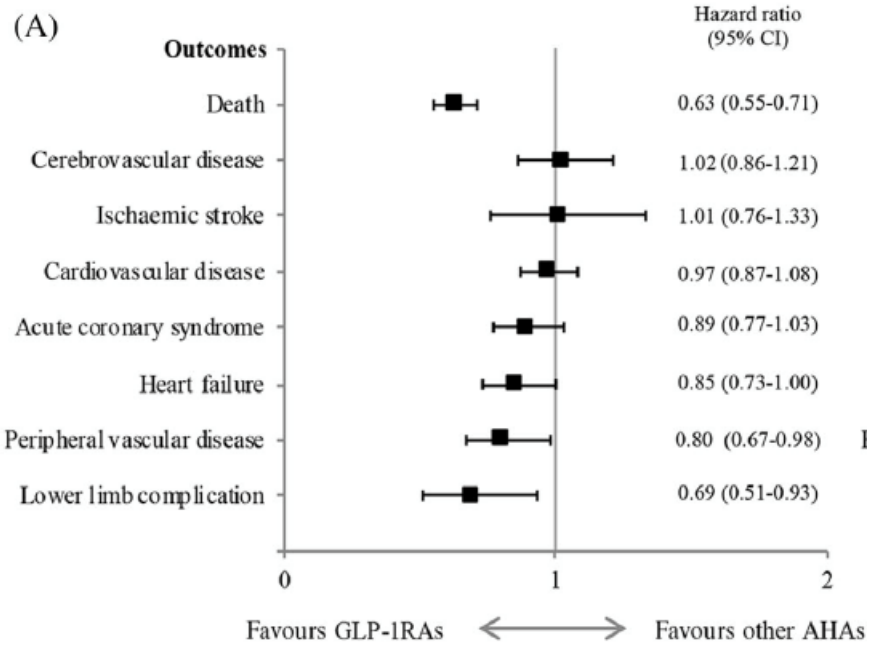
Marta Baviera PharmD[1] | Stefano Genovese MD[2] | Vito Lepore MD[3,4] | Pierluca Colacioppo MSc[1] | Fabio Robusto MD[3] | Mauro Tettamanti MSc[5] | Antonio D'Ettorre MSc[3] | Fausto Avanzini MD[1] | Ida Fortino MSc[6] | Antonio Nicolucci MD[3] | Maria C. Roncaglioni MSc[1] | Francesco Giorgino MD[7]

Dopo propensity-score matching, la coorte lombarda e pugliese includevano rispettivamente 18716 e 9772 soggetti con GLP-1RA (follow-up mediano per GLP-1RAs e altri AHAs: 3.9 e 3.7 anni n Lombardia e 2.8 e 2.9 anni in Puglia)

Lombardia



Puglia



other AHAs including metformin, sulphonylureas, glinides, thiazolidinediones, acarbose, and DPP-4i

Baviera M et al. Diabetes Obes Metab. 2021;1–12.

Lower risk of death and cardiovascular events in patients with diabetes initiating glucagon-like peptide-1 receptor agonists or sodium-glucose cotransporter-2 inhibitors: A real-world study in two Italian cohorts

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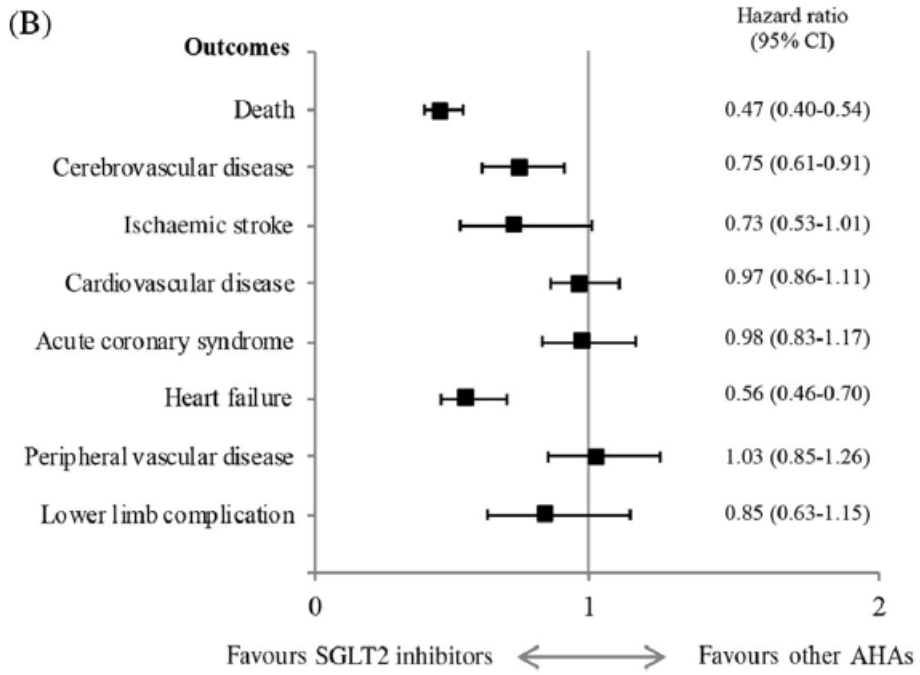
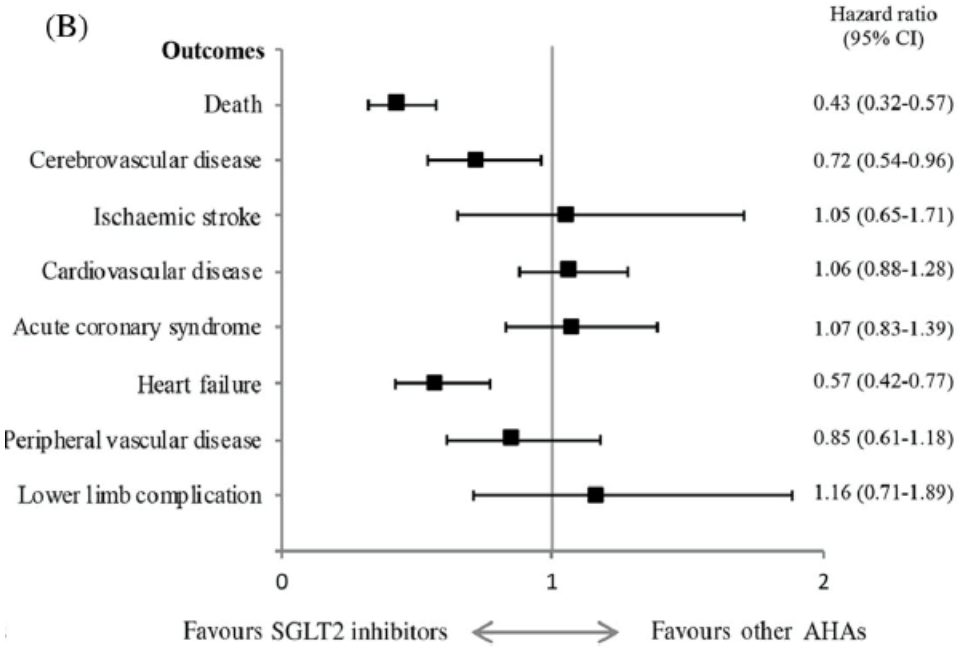
Dopo propensity-score matching, la coorte lombarda e pugliese includevano rispettivamente 11683 e 6046 soggetti con SGLT2-i.
(follow-up mediano per SGLT2-i e altri AHAs: 1.8 e 1.6 anni n Lombardia e 1.6 e 1.5 anni in Puglia)

Lombardia

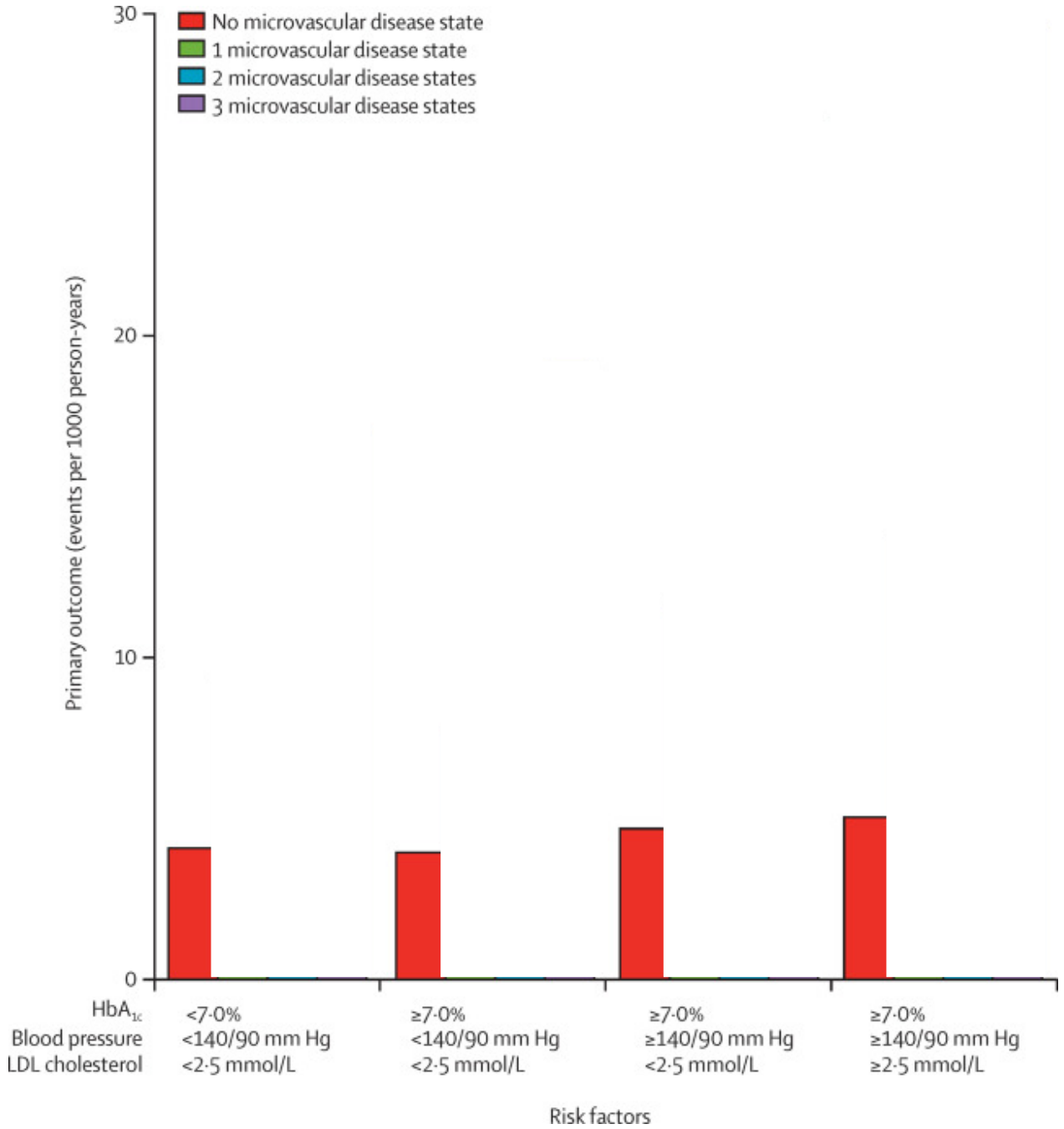


Puglia



other AHAs including metformin, sulphonylureas, glinides, thiazolidinediones, acarbose, and DPP-4i

Baviera M et al. Diabetes Obes Metab. 2021;1–12.



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

Caso clinico 2

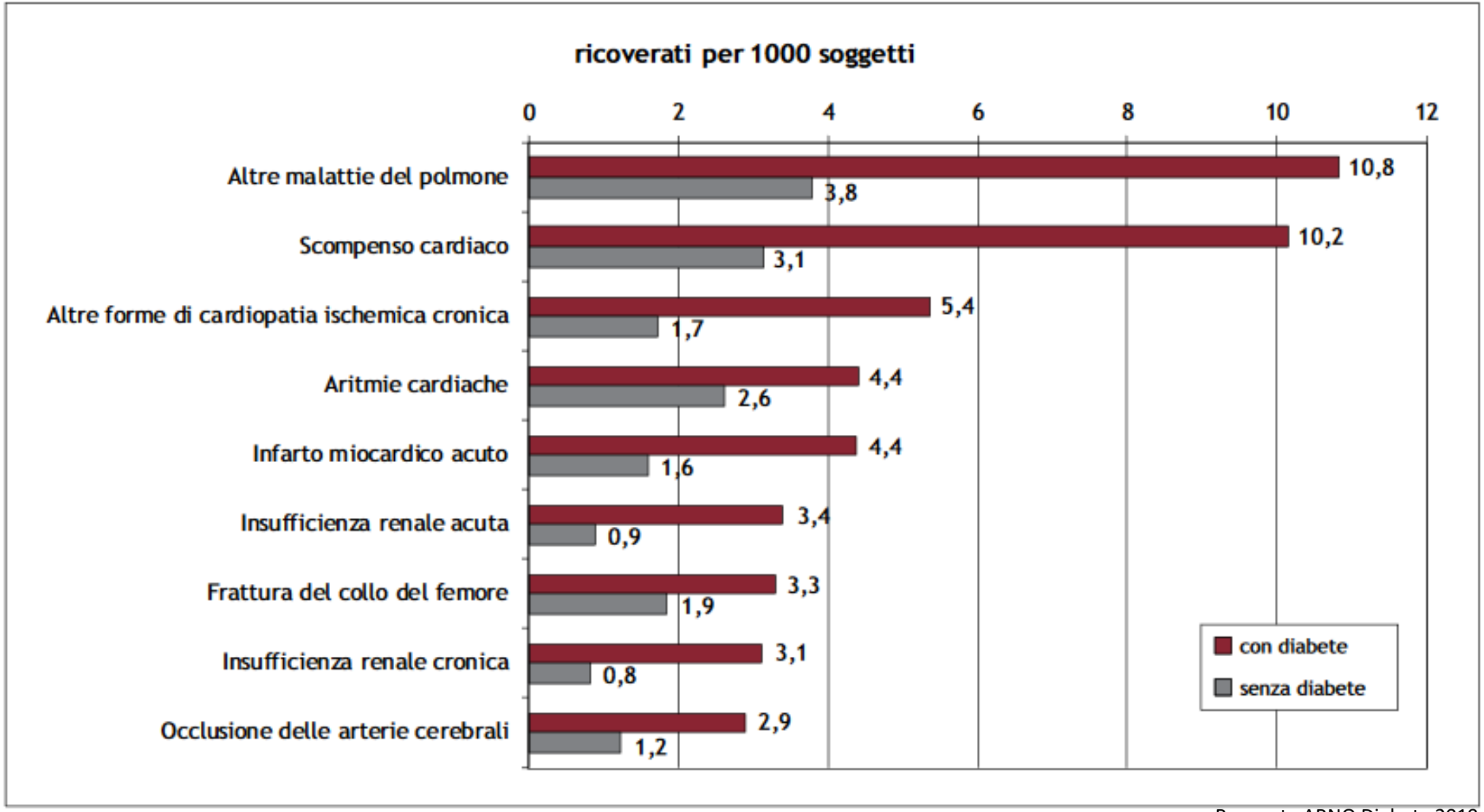
Prevalence Rates of CV Comorbidities in Persons With T2DM: Results of a Systematic Literature Review

Sex	CV Outcome	Studies	N	Rate (%)	95% Confidence Interval (%)
Both	Stroke	39	3,901,505	7.6	6.6, 8.6
	MI	13	3,518,833	10.0	7.5, 12.5
	Angina pectoris	4	354,743	14.6	12.0, 17.3
	Heart failure	14	601,154	14.9	13.0. 16.7
	Atherosclerosis	4	1153	29.1	21.7, 36.4
	Coronary artery disease	42	3,833,200	21.2	20.3, 22.2
	CVD (any)	53	4,289,140	32.2	30.0, 34.4

Globally, more than 30% of persons with T2DM have some form of CV disorder. CVD is a major cause of mortality in patients with T2DM.

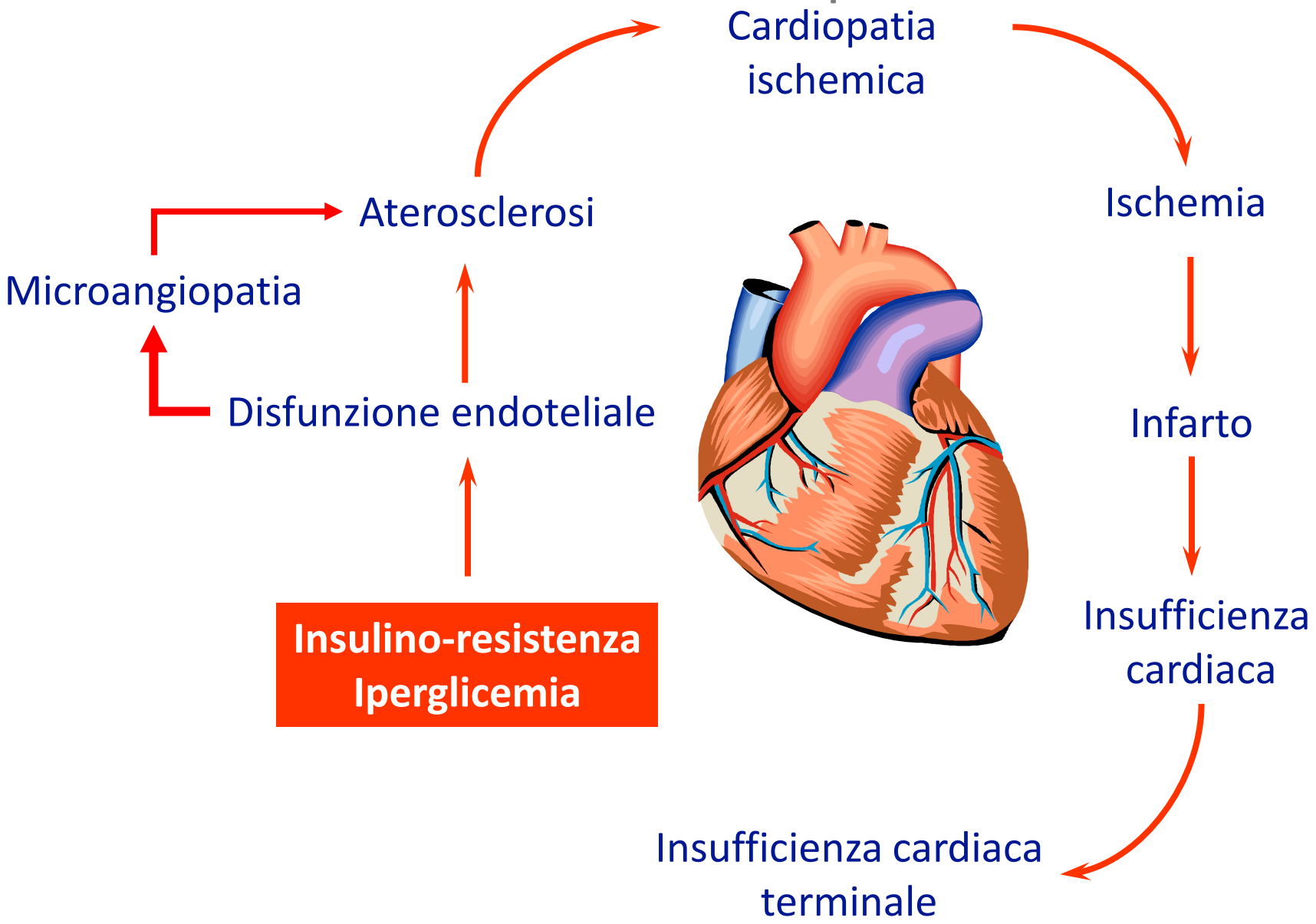
Einarson TR, et al. *Cardiovasc Diabetol*. 2018;17:83.

Le 10 più frequenti diagnosi principali nei ricoveri ordinari in soggetti con e senza diabete (tassi per 1000 soggetti)



Rapporto ARNO Diabete 2019

Storia naturale della cardiopatia nel diabete

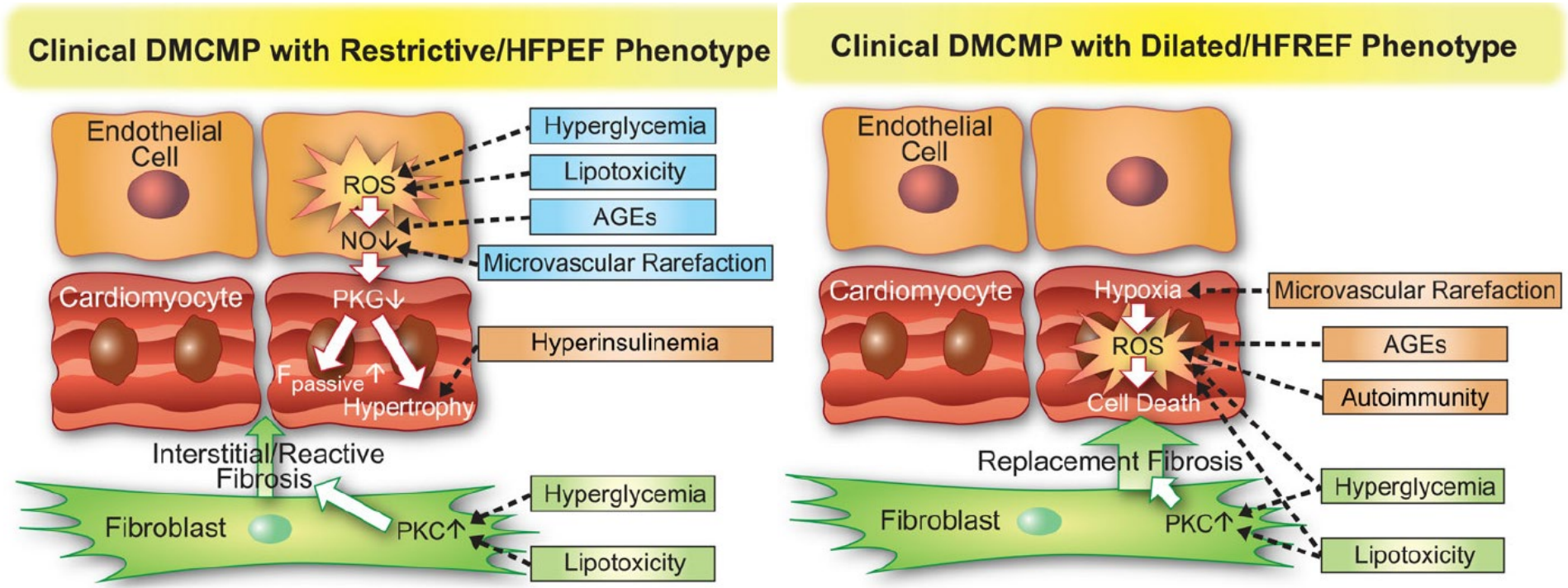


Clinical update

Clinical diabetic cardiomyopathy: a two-faced disease with restrictive and dilated phenotypes

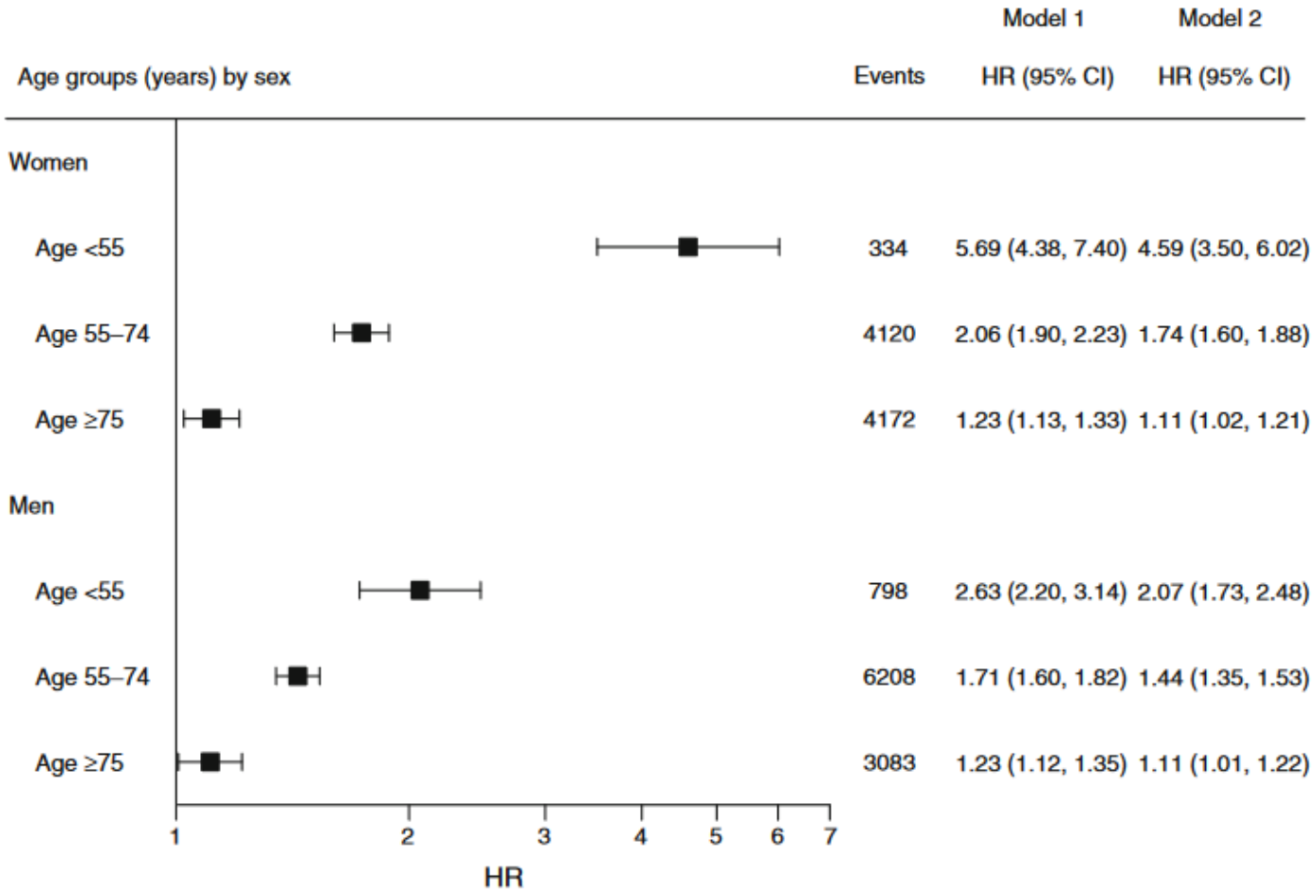
Petar M. Seferović[1] and Walter J. Paulus[2]*

[1]University Medical Center, Belgrade, Serbia; and [2]Institute for Cardiovascular Research VU (ICaR-VU), VU University Medical Center, Van der Boechorststraat 7, 1081 BT Amsterdam, The Netherlands



Eur Heart J 2015 Jul 14;36(27):1718-27, 1727a-1727c.

Excess risk of hospitalization for heart failure among people with T2DM



Rosengren A et al. Diabetologia 2018;61:2300

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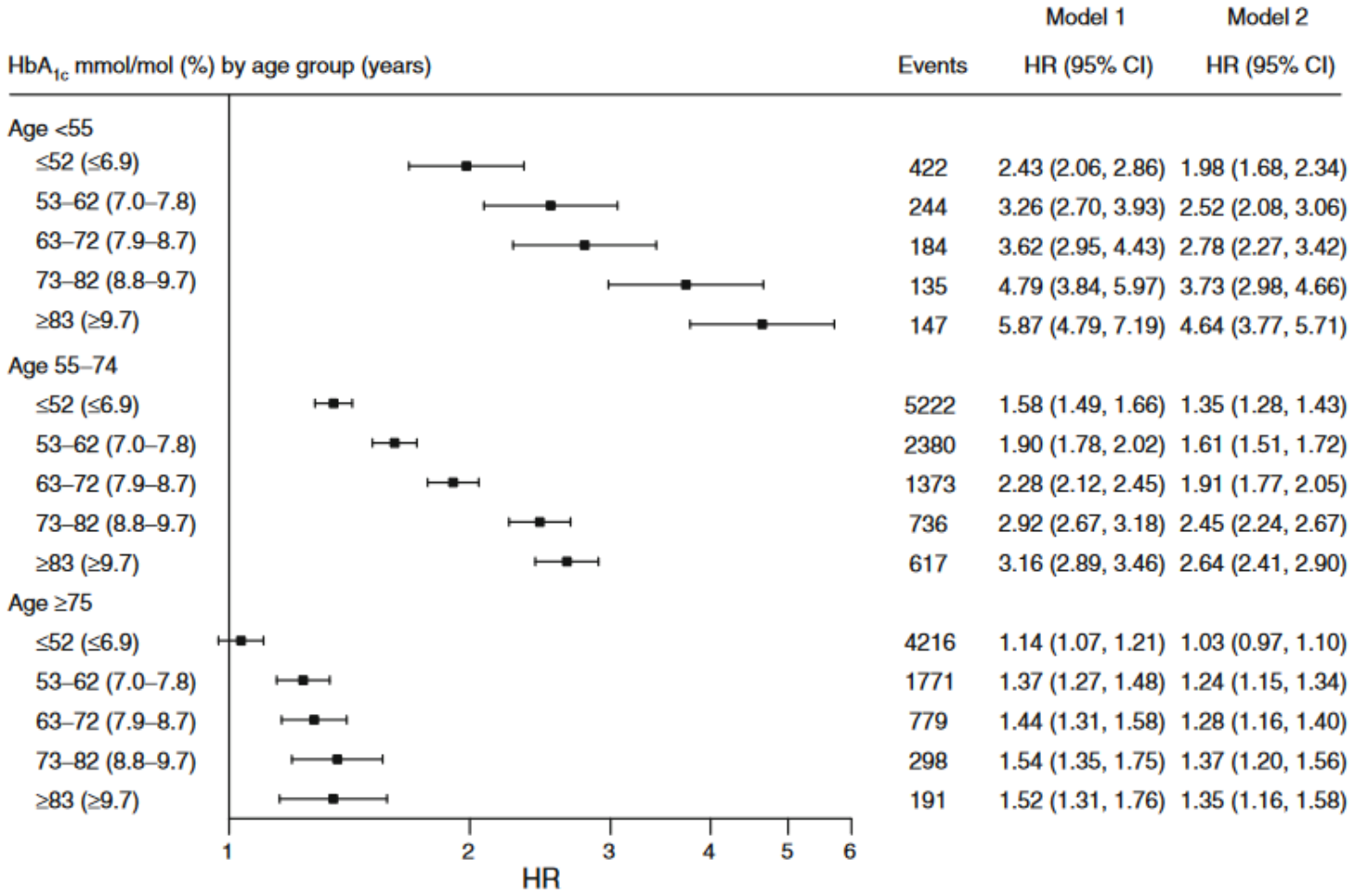
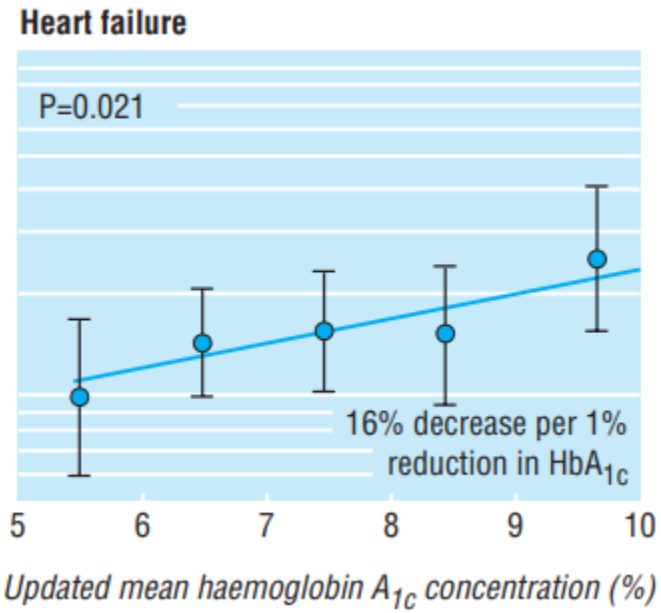


Rosengren A et al. Diabetologia 2018;61:2300

Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study



Relationship of Hemoglobin A1C and Mortality in Heart Failure Patients With Diabetes

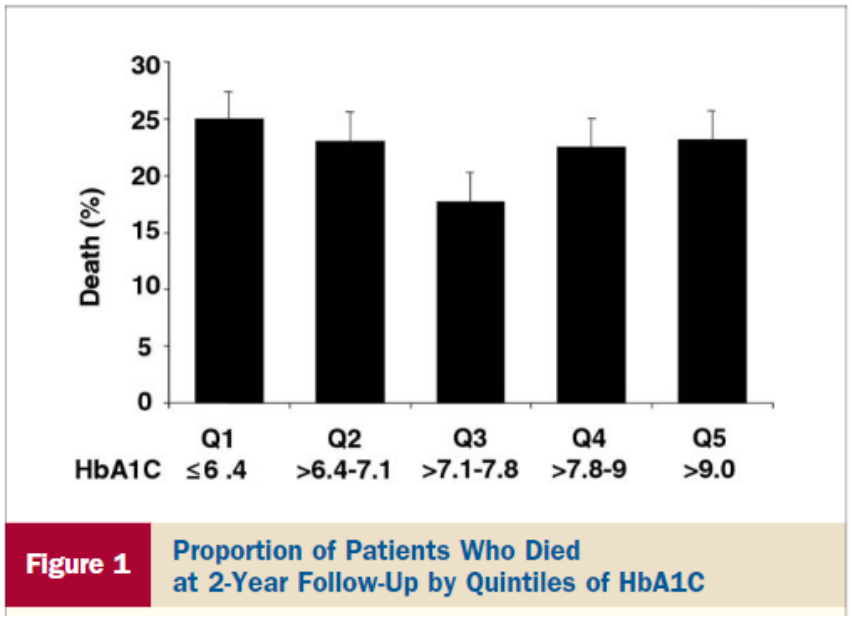
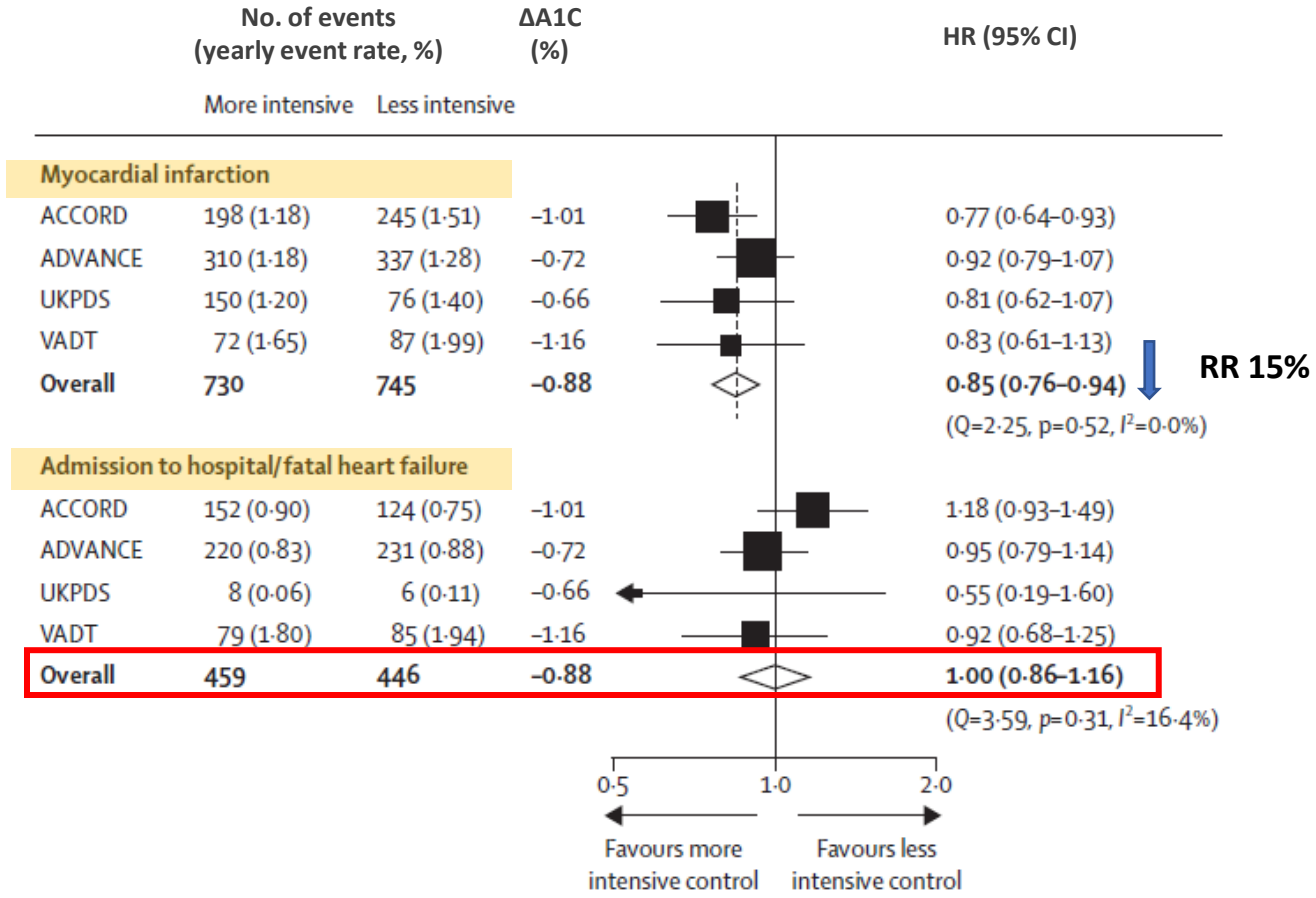


Figure 1 Proportion of Patients Who Died at 2-Year Follow-Up by Quintiles of HbA1C

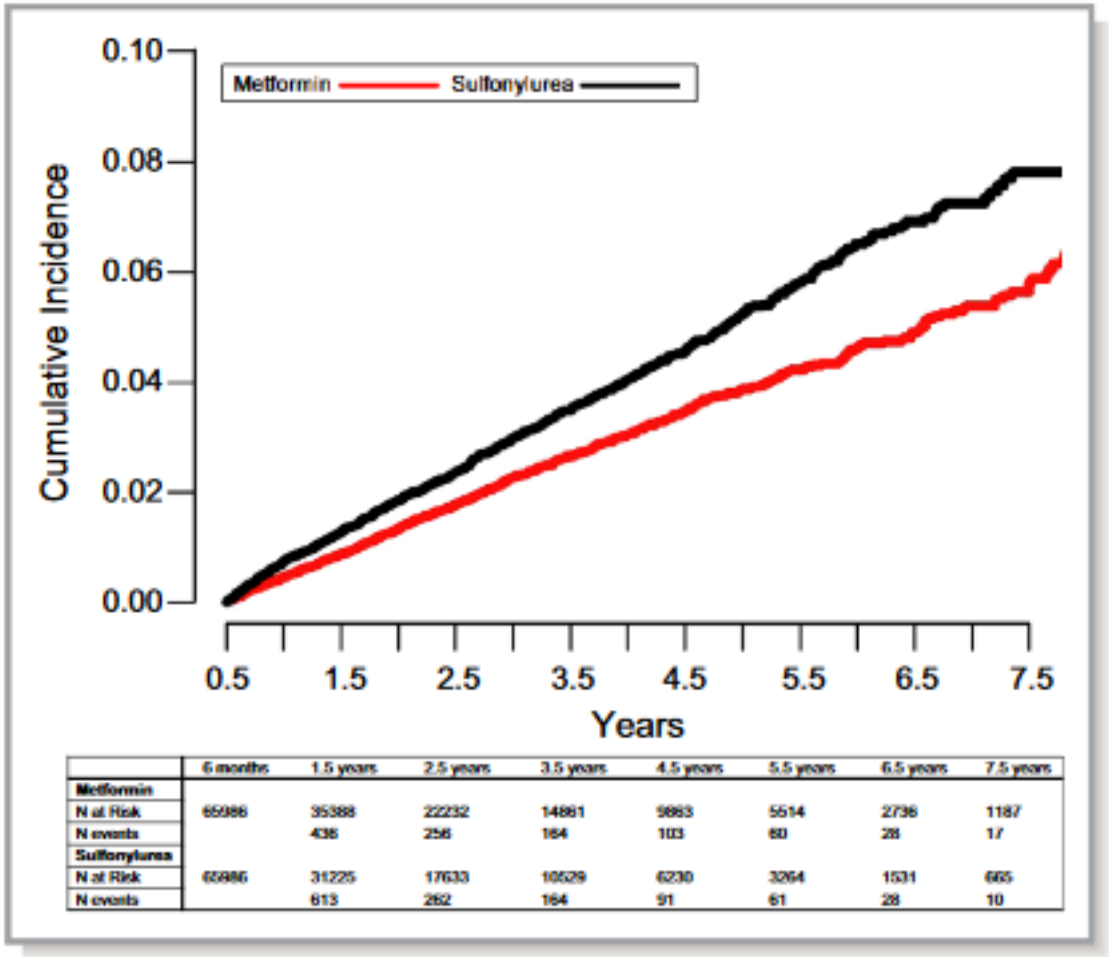
Stratton IM et al. BMJ 2000;321:405-412.
Aguilar D et al. JACC 2009;54:422-428

Effect of More vs Less Intensive Glycemic Control on MI and HF resulting in Hospital Admission or Death



Turnbull FM et al. Diabetologia. 2009;52:2288-98.

Comparative safety of sulfonylurea and metformin monotherapy on the risk of heart failure: a cohort study

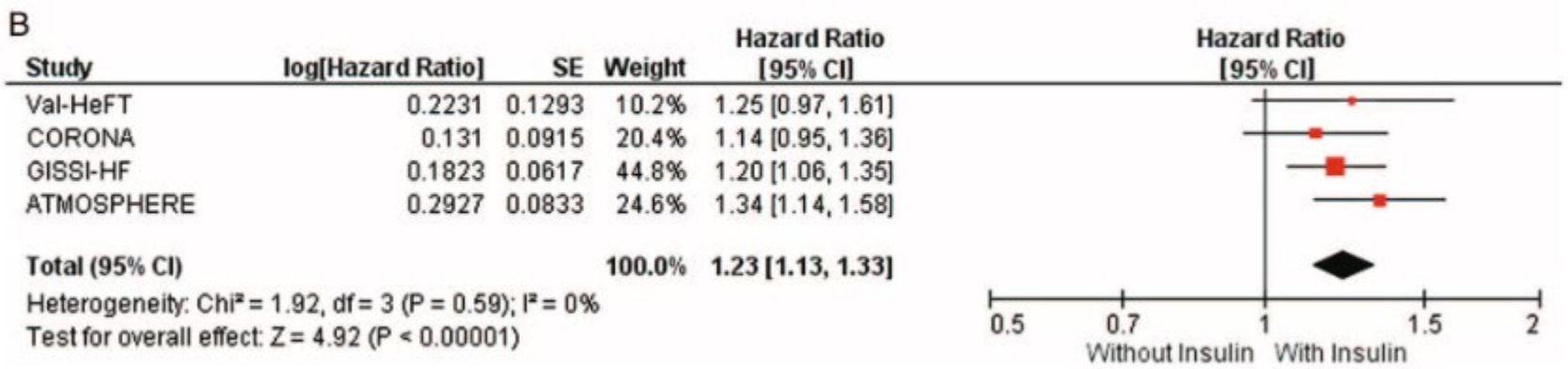


	6 months	1.5 years	2.5 years	3.5 years	4.5 years	5.5 years	6.5 years	7.5 years
Metformin								
N at Risk	65886	35388	22232	14861	9863	5514	2736	1187
N events		438	256	164	103	60	28	17
Sulfonylurea								
N at Risk	65886	31225	17633	10529	6230	3264	1531	665
N events		613	262	164	91	61	28	10

Roumie CL et al. J Am Heart Assoc 2017;6(4)

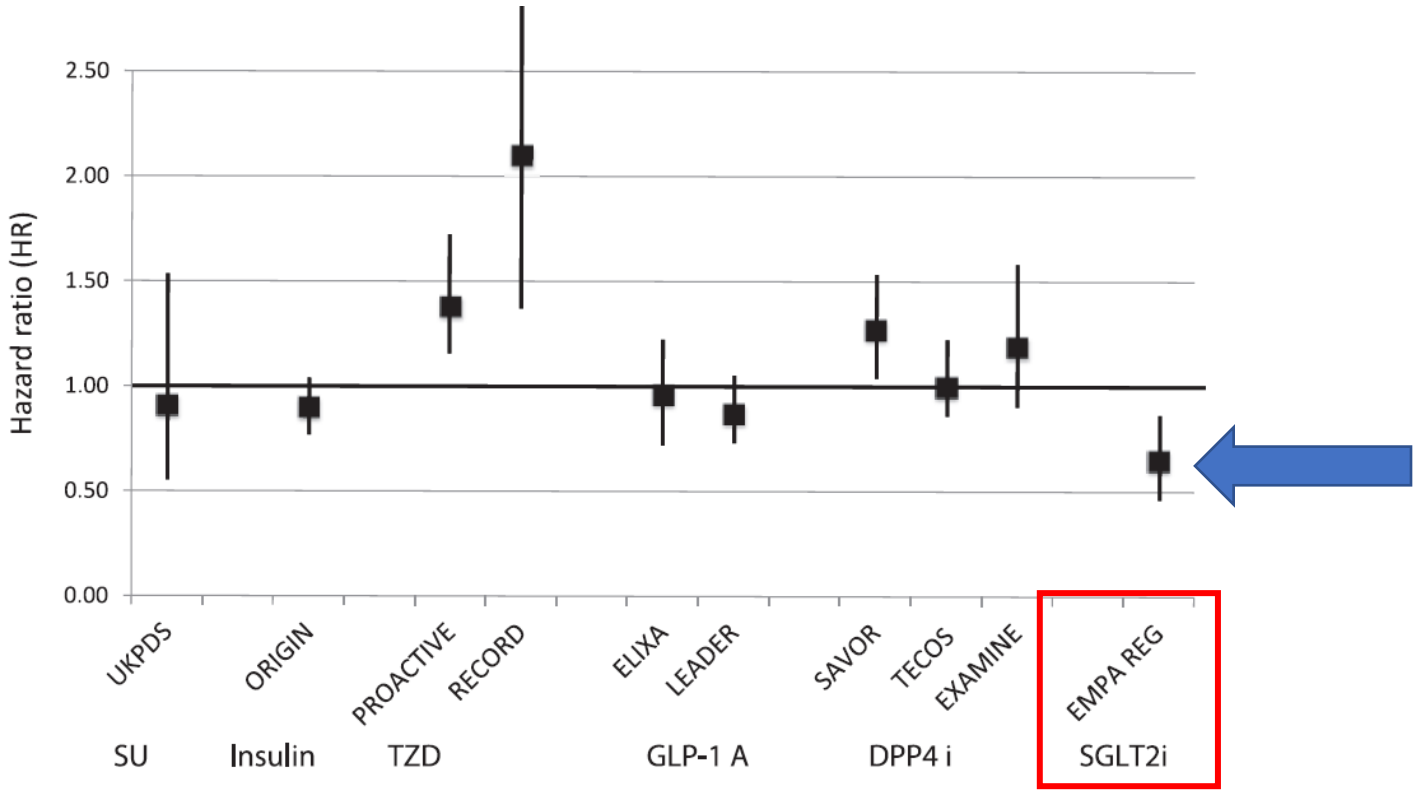
Treatment with insulin is associated with worse outcome in patients with chronic heart failure and diabetes

Study	*n* events/*n* pts	Outcome	Univariate model	Multivariable model	Multivariable model with PS (IPTW)
Val-HeFT	293/1276	All-cause mortality	1.28 [1.01–1.62], $P=0.039$	1.18 [0.93–1.50], $P=0.175$	1.23 [0.98–1.55], $P=0.079$
	284/1276	HF hospitalization[a]	1.34 [1.06–1.71], $P=0.0146$	1.28 [0.96–1.70], $P=0.0888$	1.25 [0.97–1.61], $P=0.0812$
CORONA	496/1477	All-cause mortality	1.27 [1.05–1.53], $P=0.014$	1.28 [1.05–1.56], $P=0.013$	1.27 [1.05–1.53], $P=0.014$
	467/1477	HF hospitalization[a]	1.28 [1.05–1.55], $P=0.014$	1.17 [0.96–1.42], $P=0.129$	1.14 [0.95–1.36], $P=0.159$
GISSI-HF	675/1974	All-cause mortality	1.58 [1.35–1.85], $P<0.0001$	1.54 [1.29–1.83], $P<0.0001$	1.29 [1.10–1.51], $P=0.0014$
	712/1974	HF hospitalization[a]	1.35 [1.18–1.54], $P<0.0001$	1.18 [1.01–1.36], $P=0.0319$	1.20 [1.06–1.35], $P=0.0036$
ATMOSPHERE	743/1944	All-cause mortality	1.27 [1.08–1.49], $P=0.004$	1.25 [1.05–1.47], $P=0.010$	1.26 [1.09–1.45]*, $P=0.001$
	541/1944	HF hospitalization[a]	1.44 [1.20–1.73], $P<0.001$	1.36 [1.12–1.64], $P=0.002$	1.34 [1.14–1.58]**, $P=0.001$



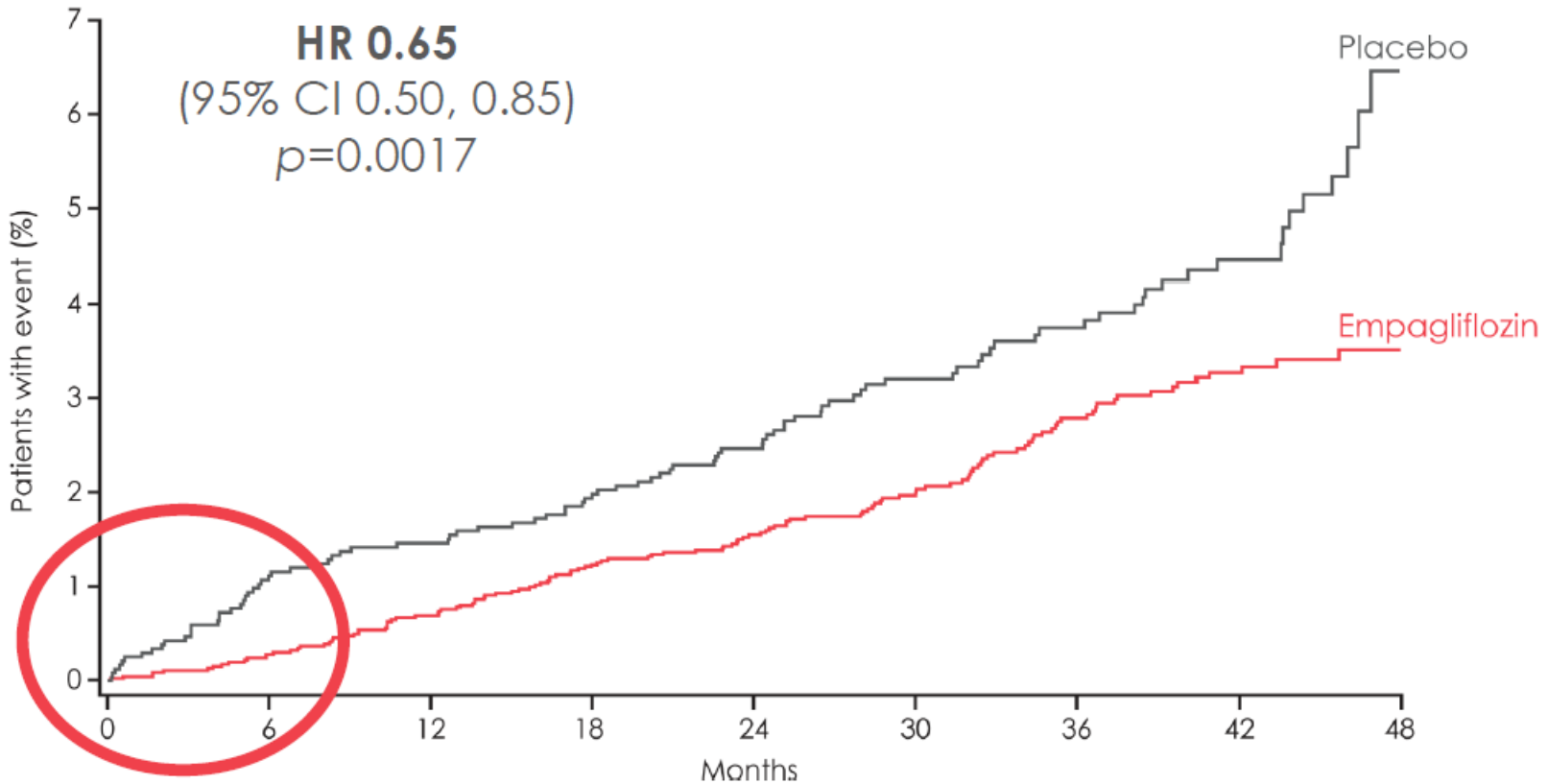
Cosmi F et al. European Journal of Heart Failure 2018;20:888-895

The impact of glucose-lowering drugs on the incidence of hospitalization for heart failure in patients with diabetes



Fitchett DH, EHJ HF 2016;19:43-53

Hospitalisation for heart failure

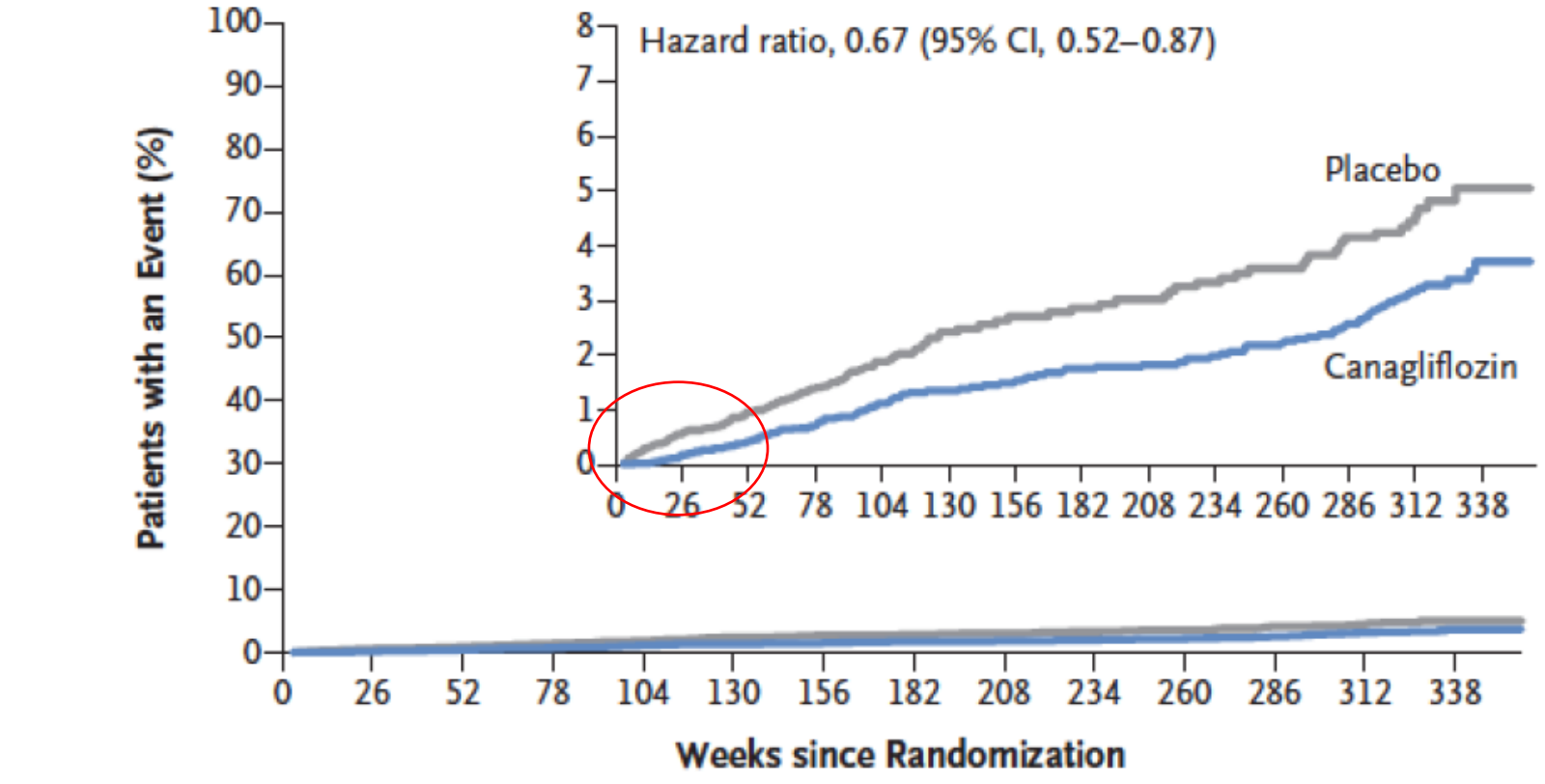


No. of patients									
Empagliflozin	4687	4614	4523	4427	3988	2950	2487	1634	395
Placebo	2333	2271	2226	2173	1932	1424	1202	775	168

Cumulative incidence function. HR, hazard ratio

EMPA-REG OUTCOME®

CANVAS: Canagliflozin and Cardiovascular Events in Type 2 Diabetes

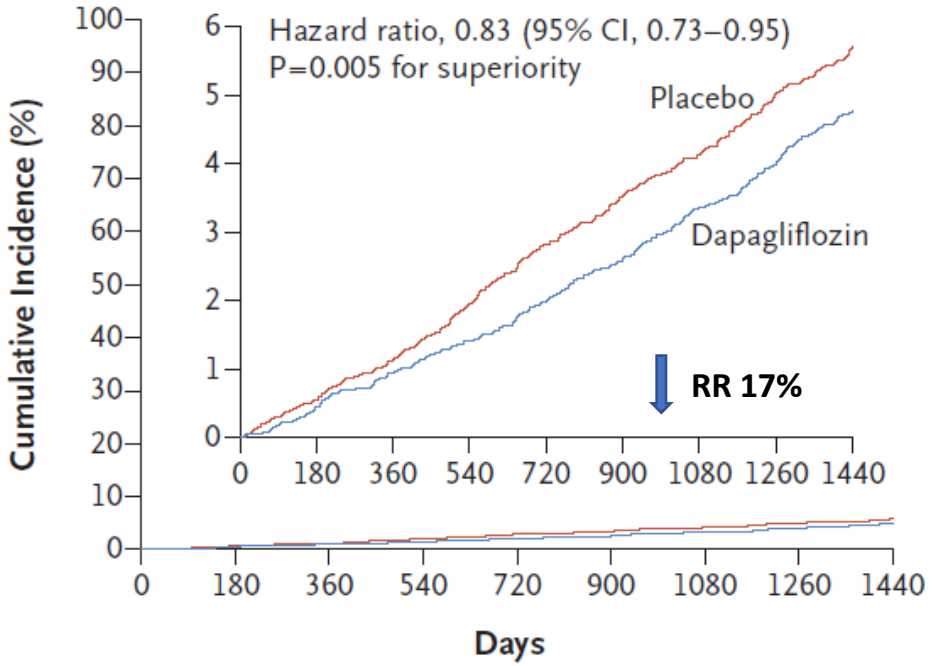


N Engl J Med. 2017 Aug 17;377(7):644-657.

DECLARE TIMI-58: Primary Endpoints

CV death, MI, ischemic stroke

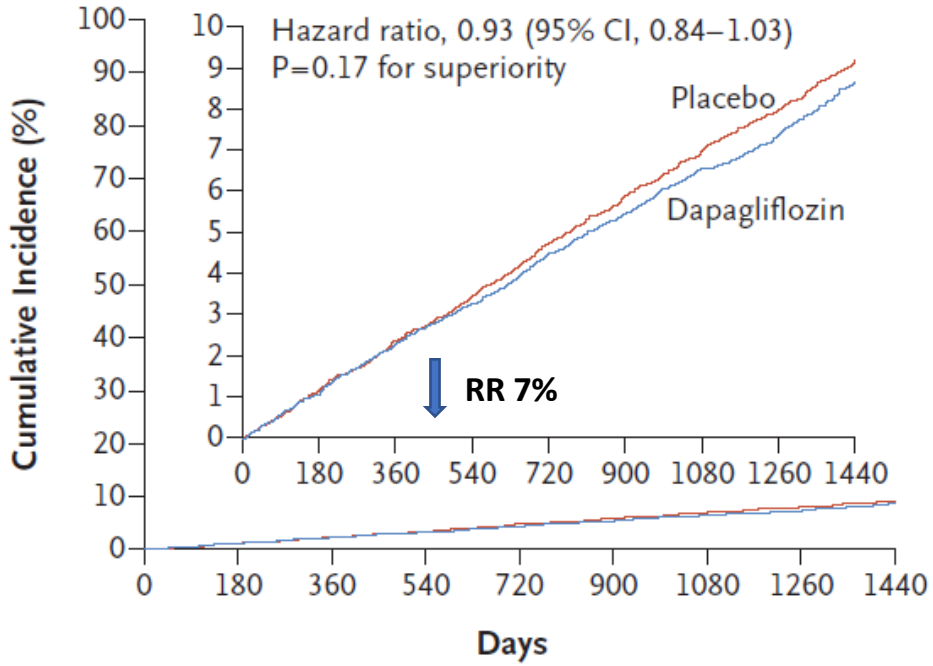
A Cardiovascular Death or Hospitalization for Heart Failure



No. at Risk

Placebo	8578	8485	8387	8259	8127	8003	7880	7367	5362
Dapagliflozin	8582	8517	8415	8322	8224	8110	7970	7497	5445

B MACE

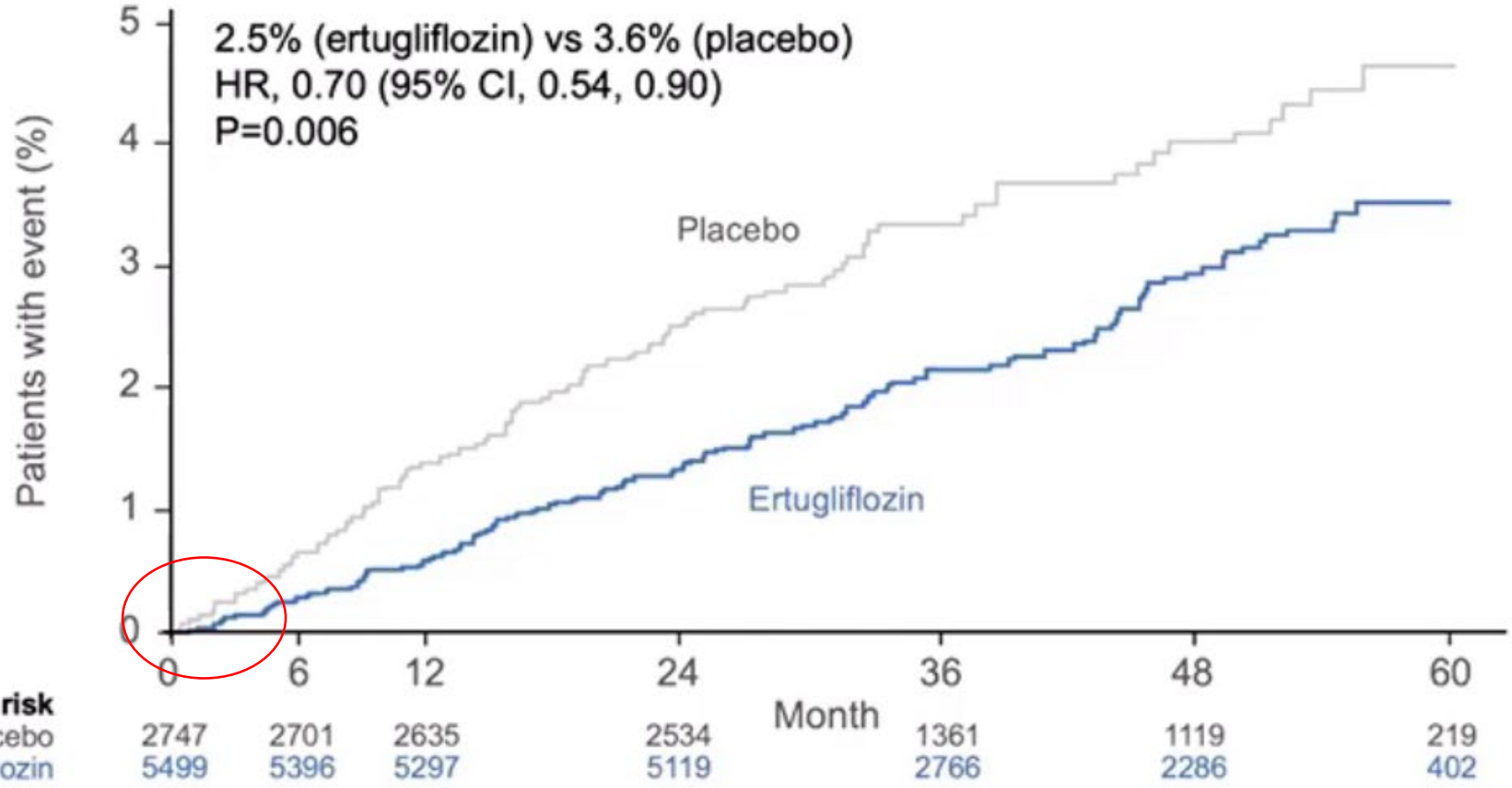


No. at Risk

Placebo	8578	8433	8281	8129	7969	7805	7649	7137	5158
Dapagliflozin	8582	8466	8303	8166	8017	7873	7708	7237	5225

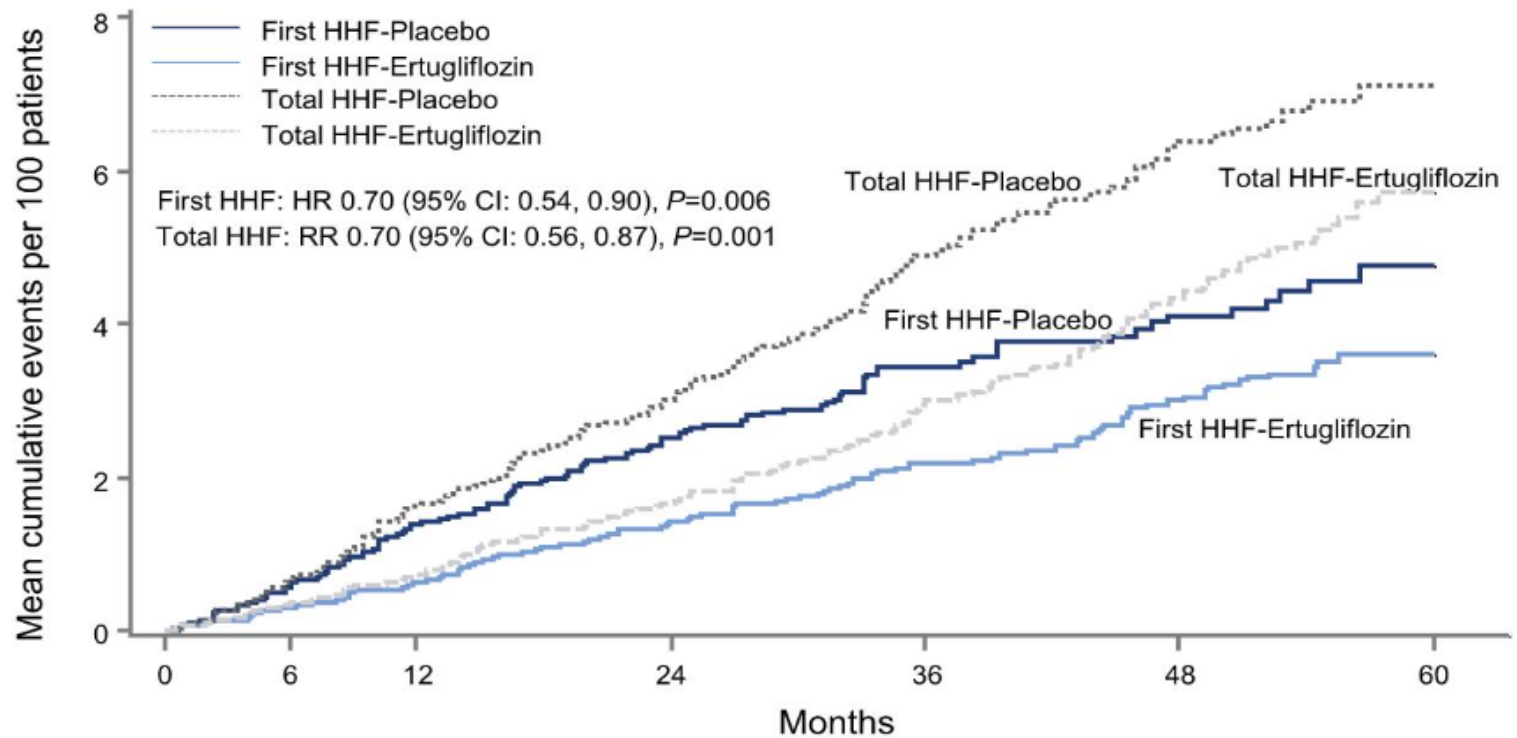
Wiviott SD, NEJM 2018

HHF*



*Intention-to-treat analysis set that included all randomized patients with no upper limit on the ascertainment window for the superiority outcomes (N=5499 for ertugliflozin and N=2747 for placebo).
CI, confidence interval; HHF, hospitalization for heart failure; HR, hazard ratio.

Cumulative incidence of first and total (first + recurrent) HHF events

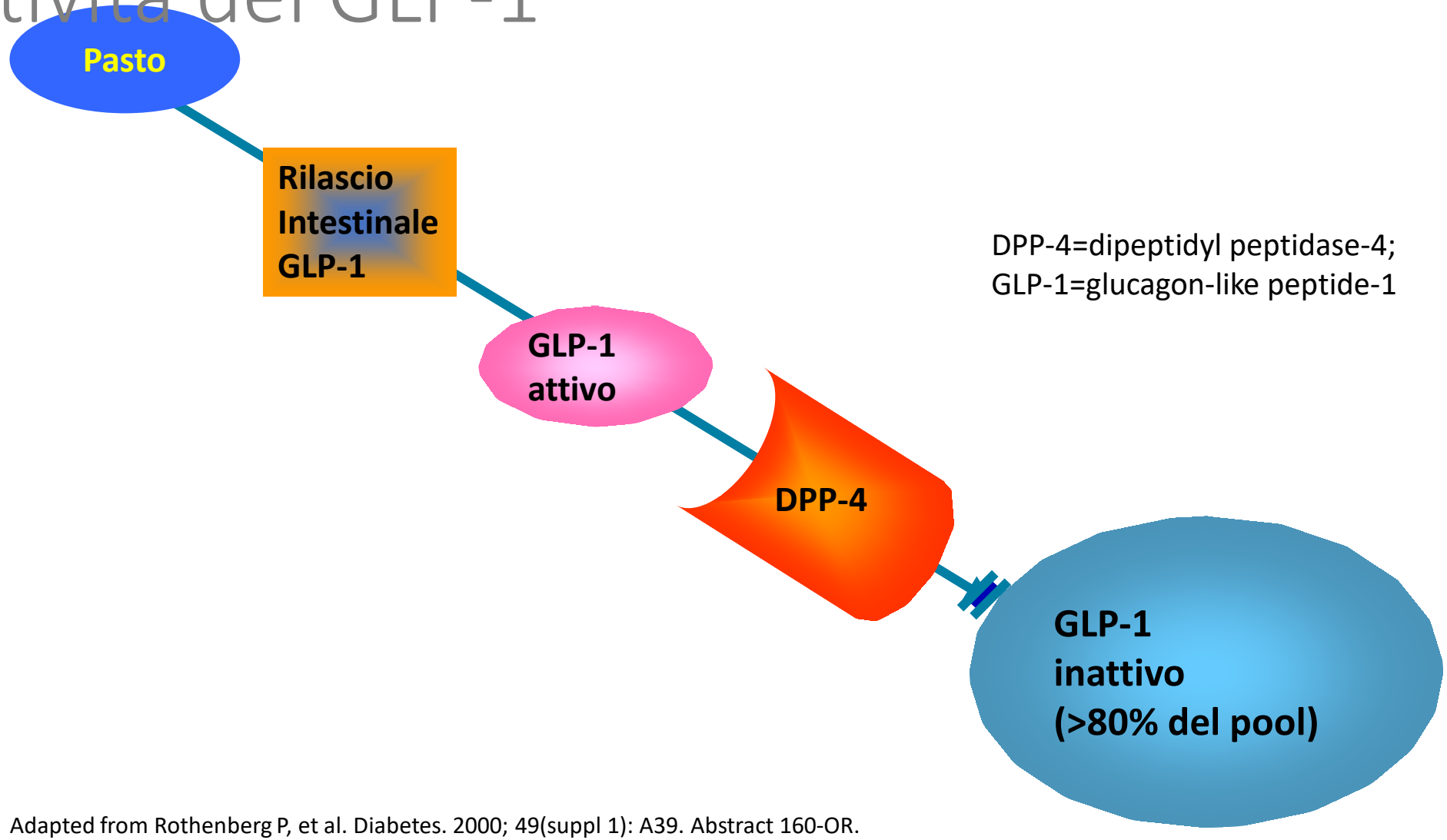


No. at risk							
Total HHF-Placebo	2747	2715	2665	2585	1398	1151	225
Total HHF-Ertugliflozin	5499	5411	5327	5177	2806	2338	416

Ertugliflozin includes 5 mg and 15 mg doses
CI, confidence interval; HHF, hospitalization for heart failure; HR, hazard ratio; RR, rate ratio.

I DPP4-inibitori

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



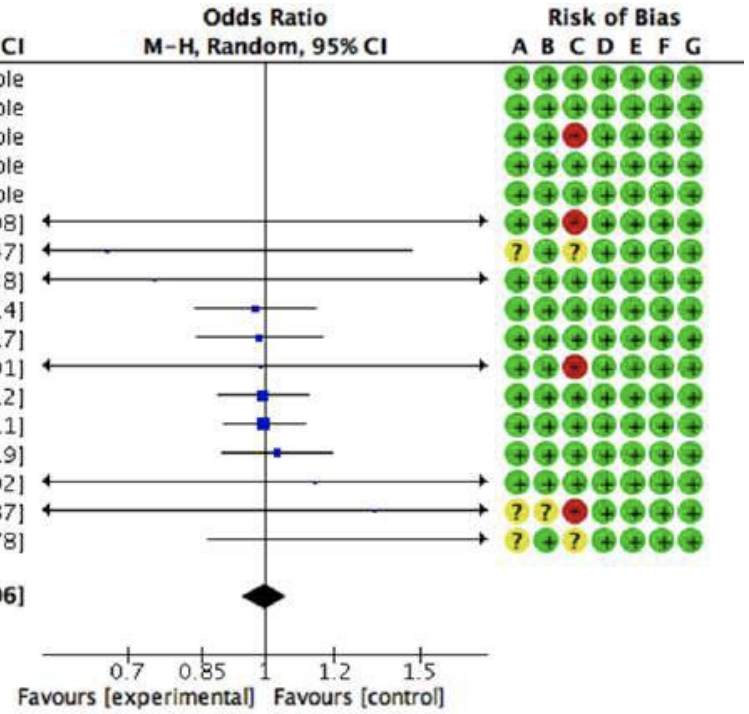
DPP-4=dipeptidyl peptidase-4;
GLP-1=glucagon-like peptide-1

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.

Effetti del trattamento con DPP-4i rispetto a placebo/nessun trattamento o altri farmaci attivi sul rischio di MACE

Study or Subgroup	Dpp4i Events	Dpp4i Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Ahren 2014 (101)	0	302	0	710		Not estimable
McMurray 2018 (39)	0	128	0	126		Not estimable
Mita 2016 (26)	0	83	0	82		Not estimable
Ferrannini 2009 (156)	0	1396	0	1393		Not estimable
Arturi 2017 (37)	0	10	0	10		Not estimable
Mita 2016 (34)	0	172	2	169	0.0%	0.19 [0.01, 4.08]
Del Prato 2014 (41)	14	1665	11	874	0.5%	0.67 [0.30, 1.47]
Goke 2013 (83)	3	428	4	430	0.2%	0.75 [0.17, 3.38]
Rosenstock 2019 (38)	356	3023	362	3010	14.1%	0.98 [0.84, 1.14]
White 2013 (27)	315	2701	316	2679	12.4%	0.99 [0.84, 1.17]
Oyama 2016 (35)	4	222	4	220	0.2%	0.99 [0.24, 4.01]
Scirica 2013 (32)	613	8280	609	8212	25.2%	1.00 [0.89, 1.12]
Green 2015 (33)	745	7332	746	7339	29.8%	1.00 [0.90, 1.11]
Rosenstock 2019 (29)	434	3494	420	3485	16.7%	1.04 [0.90, 1.19]
Rosenstock 2019 (30)	4	467	7	931	0.2%	1.14 [0.33, 3.92]
Yki-Jarvinen 2013 (72)	8	631	6	630	0.3%	1.34 [0.46, 3.87]
Foley 2009	16	546	8	546	0.5%	2.03 [0.86, 4.78]
Total (95% CI)		**30880**		**30846**	**100.0%**	**1.00 [0.94, 1.06]**
Total events	2512		2495			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 5.55$, df = 11 (P = 0.90); $I^2 = 0\%$
Test for overall effect: Z = 0.05 (P = 0.96)



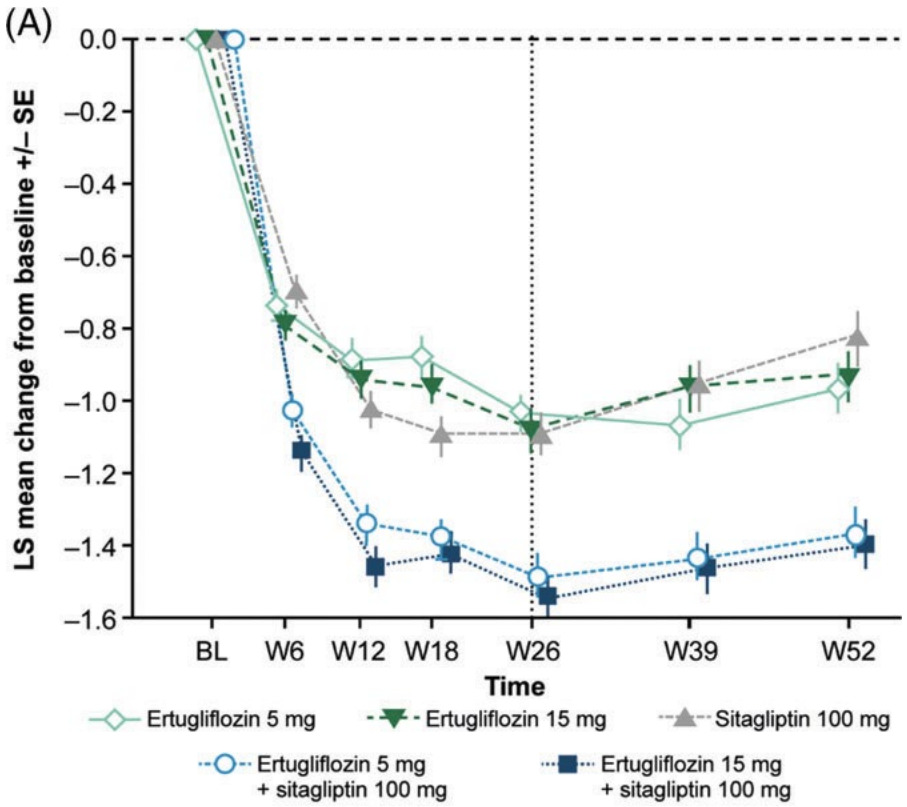
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

DPP-4 inibitori: quale spazio?

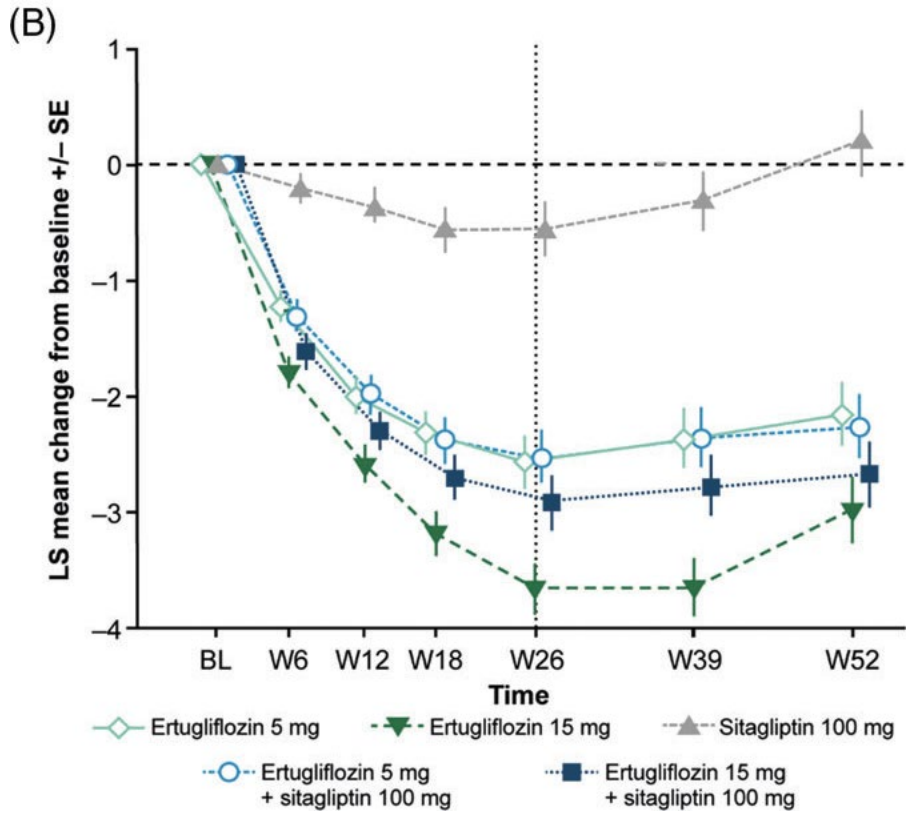
In associazione agli SGLT2-inibitori per migliorare il controllo glicemico

Ertugliflozin plus sitagliptin versus either individual agent over 52 weeks in patients with T2DM inadequately controlled with metformin: The VERTIS FACTORIAL randomized trial

HbA1c



Body weight



Diabetes Obes Metab. 2018;20:1111–1120

DPP-4 inibitori: quale spazio?

Al posto delle sulfoniluree

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.

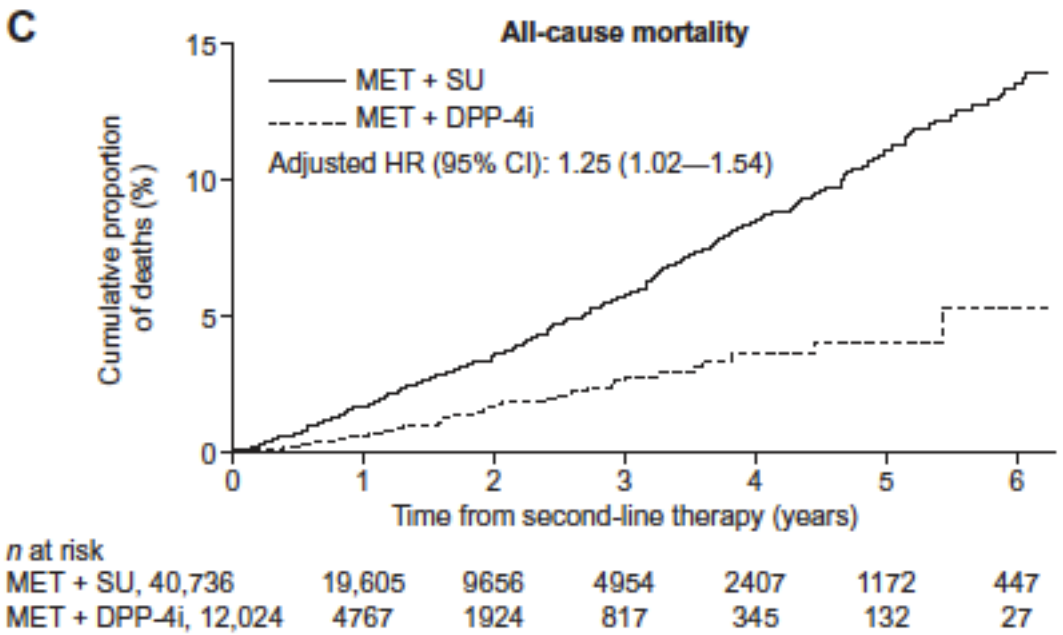
Directly Matched Cohorts: Exposed (metformin plus DPP-4i) patients were matched to non-exposed (metformin plus SU) patients by age (±2 years), gender, year of index exposure, diabetes duration (±1 year), BMI (±3 kg/m2), serum creatinine (±10 µmol/L) and HbA1c [±1% (±11 mmol/mol)].

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

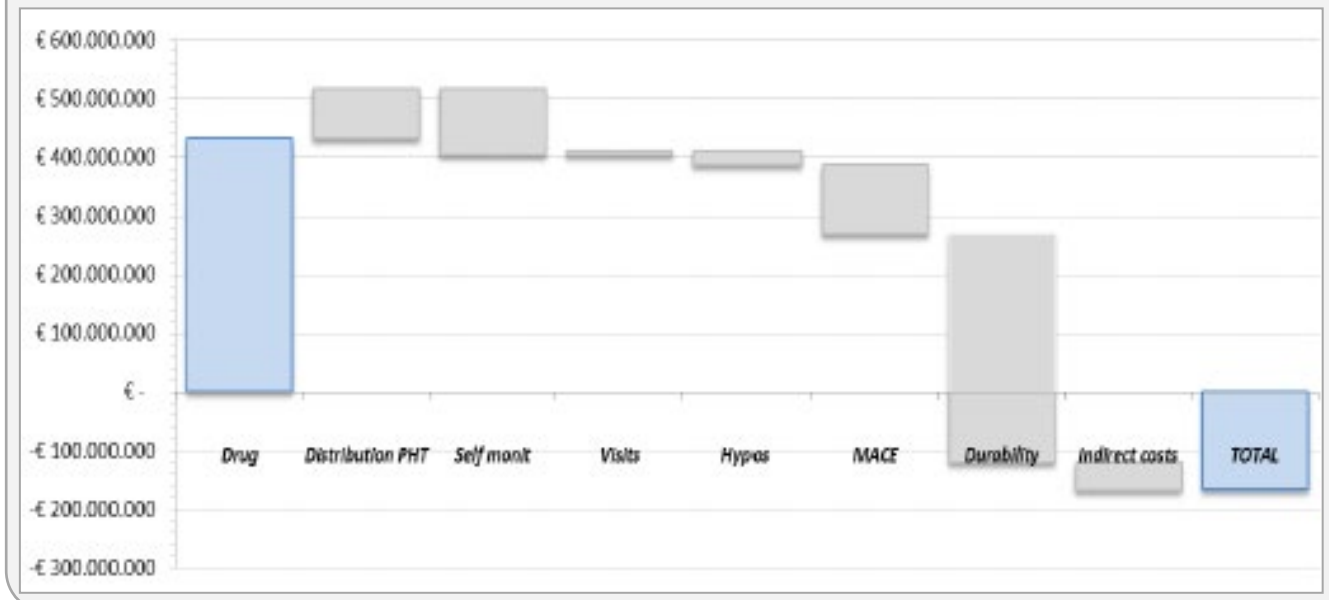
Fadini GP, et al. *Eur Heart J* 2015;36:2454–2462

Il valore di sitagliptin secondo l'approccio HTA

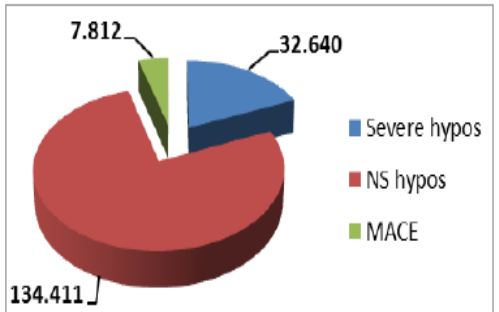
Quattro analisi di cost consequence [1-4] sviluppate su coorti di pazienti non controllate con la sola metformina, evidenziano che **l'impiego di sitagliptin rispetto a sulfaniluree genera vantaggi gestionali associati a:**

- **Minore frequenza di automonitoraggi glicemici**
- **Minore incidenza di eventi avversi** (es. ipoglicemie severe e non severe),
- **Minori complicanze cardiovascolari**
- **Ritardo nel passaggio a terapia insulinica legato alla maggiore durability**
- **Minori costi indiretti** (assenza da lavoro, ore di lavoro perse)

Cost consequence analysis: 500.000 diabetics patients over 36 months [Lorenzoni et al 2016]



Events avoided



Nello scenario Italia, su una coorte ipotetica di **500.000 pazienti non controllati con la sola metformina,** i maggiori costi associati al costo di **sitagliptin** sono compensati da riduzioni in altre voci di costo, generando a **36 mesi un risparmio pari a 166milioni di euro** nel confronto con sulfaniluree.

1.Baccetti et al Cost consequence analysis di sitagliptin vs le terapie tradizionali nel trattamento del diabete mellito di tipo 2 in Regione Toscana. VIII Congresso nazionale SIHTA, Roma 1-3 Ottobre 2015

2.Genovese et al. Economic burden of type 2 diabetes mellitus treatment strategies: a cost consequence analysis of sitagliptin vs sulfonylureas in Lombardy region. ISPOR Conference Milano 2015.

3. Torre et al., Economic evaluation of type 2 diabetes mellitus treatment strategies: a cost consequence analysis of sitagliptin vs conventional treatment in italian regions. AIES Giugno 2015.

4. Lorenzoni et al. ISPOR 2016

DPP-4 inibitori: quale spazio?

Nei pazienti con esordio di diabete in età molto anziana

DPP-4 inibitori: quale spazio?

Nei pazienti che non possono assumere e che non tollerano GLP1-RA e SGLT2-i

Ad esempio, pazienti con:

- incontinenza urinaria
- catetere vescicale a permanenza
- basso peso corporeo
- sarcopenia
- …

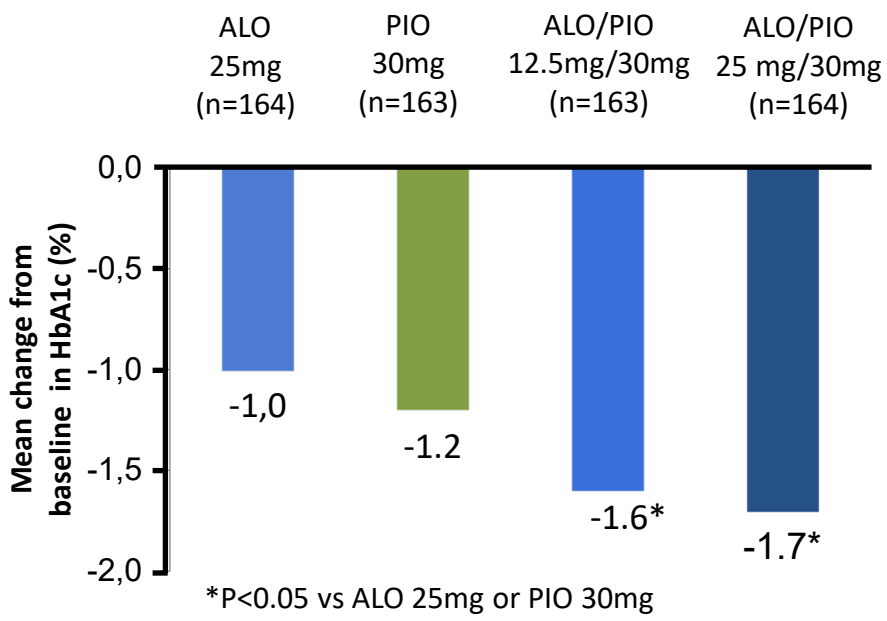
DPP-4 inibitori: quale spazio?

In associazione a pioglitazone in pazienti con marcata insulino-resistenza con o senza CVD che non tollerano GLP1RA

Significantly greater glycaemic control with alogliptin-pioglitazone vs respective monotherapies

26-week, double-blind, parallel-group study in patients with T2DM inadequately controlled on diet and exercise randomised to alogliptin monotherapy, pioglitazone monotherapy, or alogliptin + pioglitazone combination therapy ((N=655)

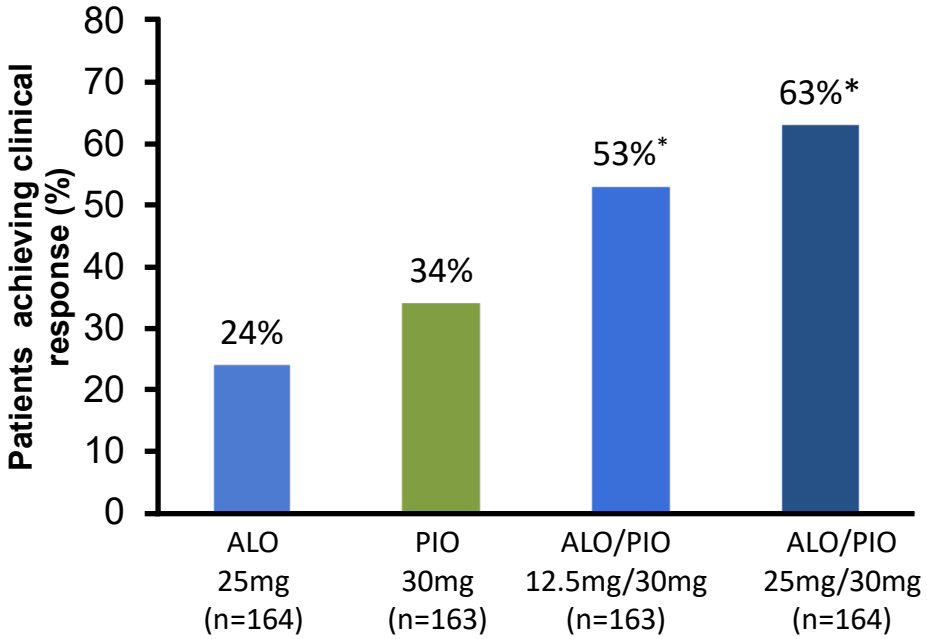
HbA1c change at week 26



*P<0.05 vs ALO 25mg or PIO 30mg

Mean baseline HbA1c: 8.8%

Patients achieving clinical response of HbA1c ≤7.0%



Rosenstock J et al. *Diabetes Care*. 2010;33:2406–2408

DPP-4 inibitori: quale spazio?

In pazienti con IRC in stadio terminale

DPP-4 inibitori: quale spazio?

In pazienti con infezione da SARS-Cov2

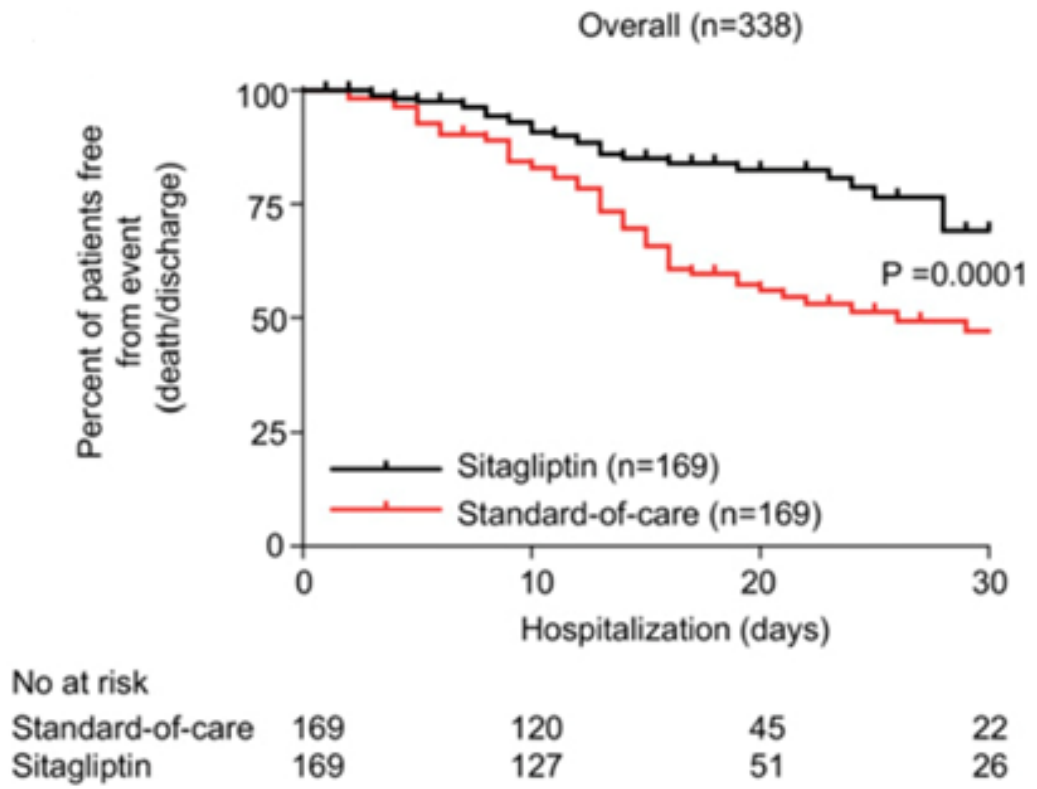
Sitagliptin in T2DM and COVID-19 (388 patients)

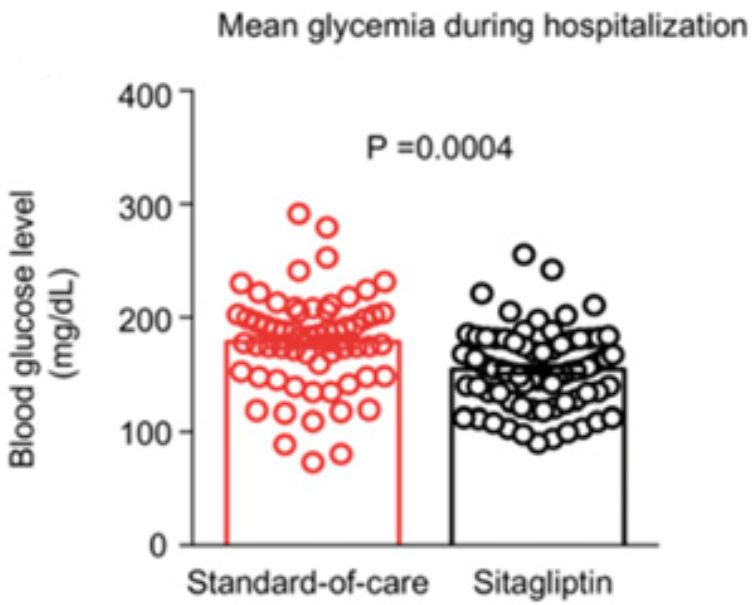
Solerte SB et al, Diabetes Care, 2020

Table 1—Baseline demographic and clinical characteristics of patients

Characteristic	Standard of care	Sitagliptin	*P* value
Age (years)	69 ± 1.0	69 ± 0.9	0.83
Elderly patients ≥70 years of age, *n* (%)	90 (53)	92 (54)	0.91
Male sex, *n* (%)	115 (68)	123 (73)	0.40
Duration of diabetes (years)	8.7 ± 1.2	9.2 ± 0.8	0.73
Coexisting conditions, *n* (%)			
Cardiovascular disease	53 (38)	65 (40)	0.63
Chronic kidney disease	34 (28)	34 (21)	0.26
Hypertension	80 (67)	118 (74)	0.23
Cancer	17 (14)	27 (17)	0.62
Glucose-lowering medications, *n* (%)			
Metformin	63 (39)	79 (44)	0.16
Insulin	48 (30)	39 (22)	0.15
Other oral antidiabetic agents	50 (31)	61 (34)	0.25
Antihypertensive drugs, *n* (%)			
ACE inhibitors	29 (50)	38 (38)	0.13
β-Blockers	34 (56)	32 (33)	0.007
Diuretics	30 (52)	36 (38)	0.13
Antiplatelet drugs	29 (49)	39 (40)	0.32
Anticoagulant drugs	52 (77)	74 (68)	0.17
Respiratory rate (breaths/min)	25.8 ± 0.7	23.7 ± 0.6	0.04
Clinical score (0–7)	4.4 ± 0.1	4.4 ± 0.08	0.88
BMI (kg/m^2)	30 ± 0.6	29 ± 0.4	0.18
HbA_{1c} (%)	7.5 ± 0.1	7.5 ± 0.1	0.66
HbA_{1c} (mmol/mol)	58.6 ± 1.2	58.6 ± 1.3	0.98
Glycemia (mg/dL)	188 ± 6.8	180 ± 6.7	0.38
Serum creatinine (mg/dL)	1.4 ± 0.08	1.2 ± 0.08	0.10
Lymphocyte count ($\times 10^{-9}$/L)	0.9 ± 0.06	1.1 ± 0.17	0.13
CRP (mg/L)	19 ± 2.3	14 ± 0.7	0.01
D-dimer (μg/mL)	6,377 ± 1,928	5,835 ± 1,391	0.82
Interleukin-6 (ng/L)	95 ± 9.7	89 ± 10.7	0.71
LDH (units/L)	423 ± 43	387 ± 16	0.43
Ferritin (μg/mL)	601 ± 48	688 ± 97	0.43
AST (units/L)	42 ± 3.0	43 ± 2.6	0.79
ALT (units/L)	38 ± 2.4	40 ± 2.9	0.74
Procalcitonin (ng/mL)	12.7 ± 4.4	8.3 ± 3.3	0.42
Oxygen saturation (%)	92 ± 0.7	92 ± 0.5	0.31

Sitagliptin improves survival in T2DM and COVID-19 disease

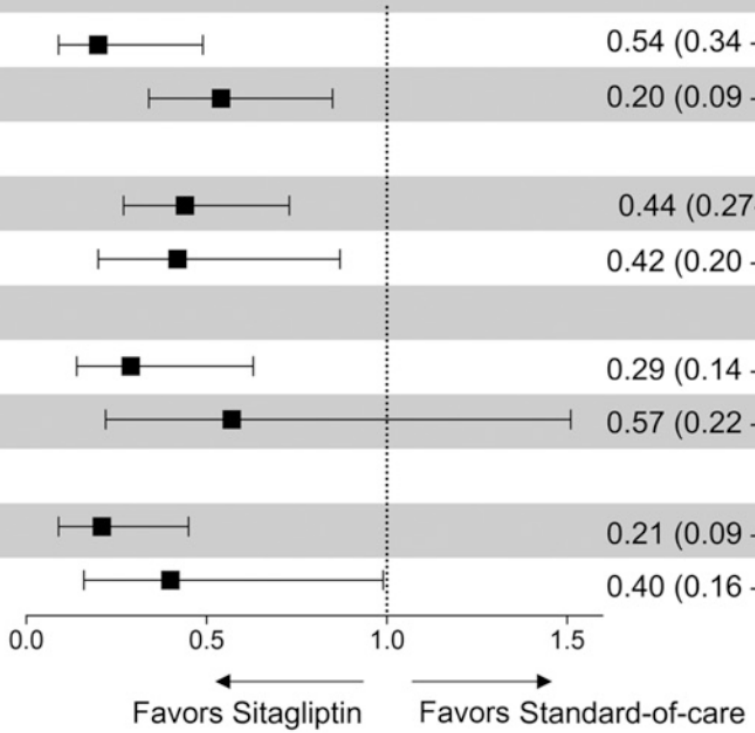




Solerte SB et al, Diabetes Care, 2020

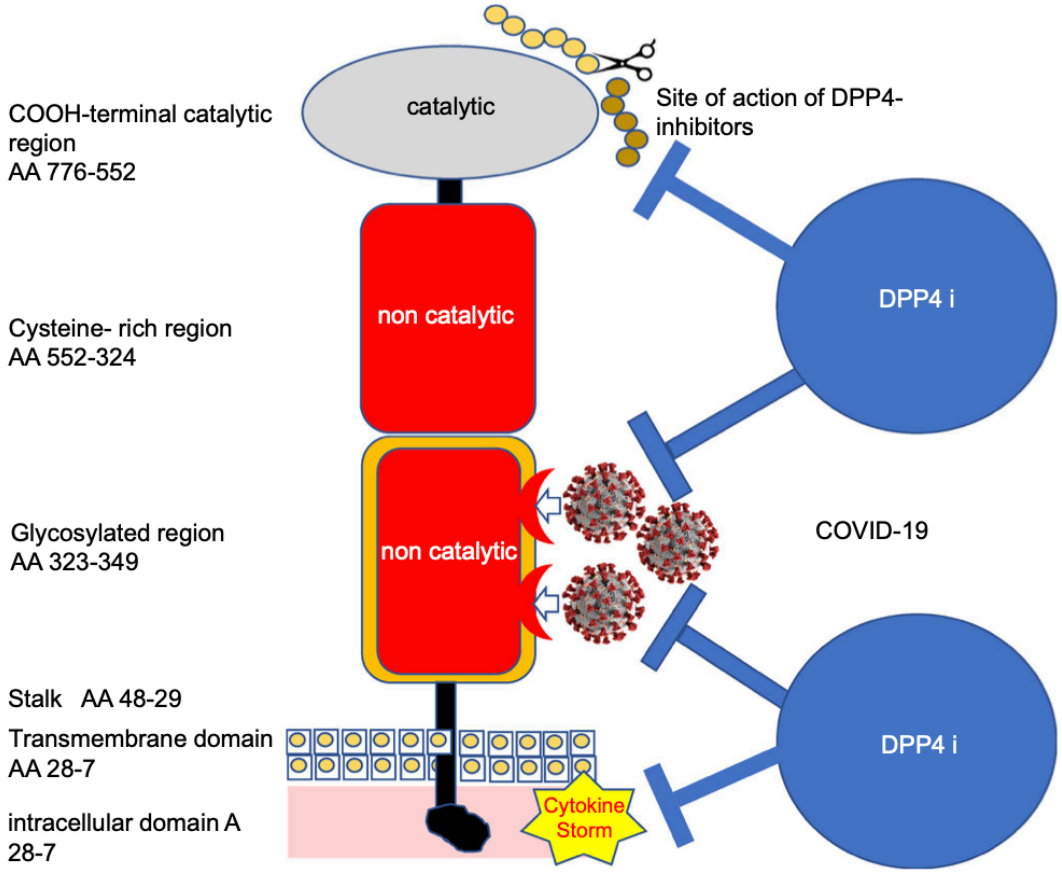
Sitagliptin vs standard of care

Subgroup	Sitagliptin *(n of pts at risk)*	Standard-of-care *(n of pts at risk)*	Hazard Ratio (95% CI)	p value	p interaction
Age					0.12
Age ≥ 70 years	92	90	0.54 (0.34 – 0.85)	0.009	
Age < 70 years	77	79	0.20 (0.09 – 0.49)	0.001	
Sex					0.82
Male	123	115	0.44 (0.27-0.73)	0.001	
Female	46	54	0.42 (0.20 – 0.87)	0.03	
Baseline HbA1c					0.20
> 7.5 %	37	25	0.29 (0.14 – 0.63)	0.0003	
≤ 7.5%	56	32	0.57 (0.22 – 1.51)	0.23	
Baseline BMI					0.33
> 29 kg/m^2	42	36	0.21 (0.09 – 0.45)	0.0002	
≤ 29 kg/m^2	47	36	0.40 (0.16 – 0.99)	0.03	



Solerte SB et al, Diabetes Care, 2020

Hypotetic role of DPP4-i to antagonize COVID-19 virulence and immunopathology



Solerte et al, Acta Diabetol, 2020

Treat to Target or Treat to Benefit?

Both!!

Grazie per la vostra attenzione

Centro Cardiologico
Monzino