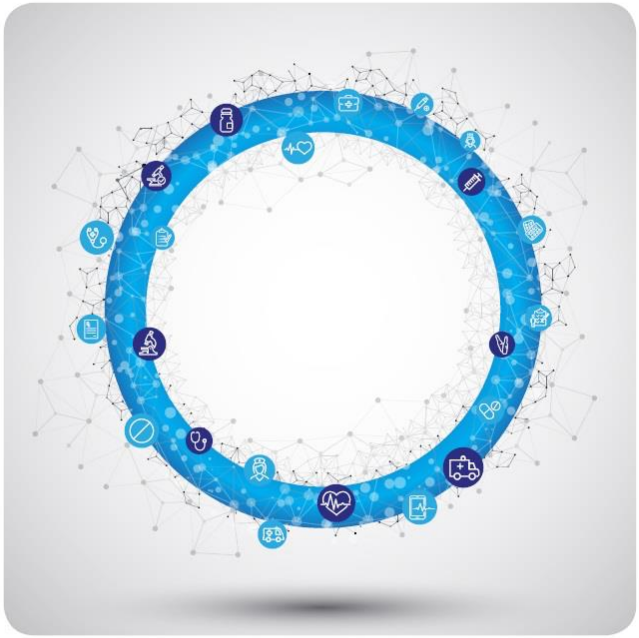
L'innovazione tecnologica (farmaci e device): cosa sta cambiando nel «real world»



Giulio Marchesini

SSD Malattie del Metabolismo e Dietetica Clinica

"Alma Mater Studiorum" Università

Azienda Ospedaliero-Universitaria di Bologna

BOLOGNA

SAVOIA HOTEL REGENCY
Via del Pilastro, 2

7 OTTOBRE 2019

HIGHWAY DIABETES

IL PAZIENTE AL CENTRO?

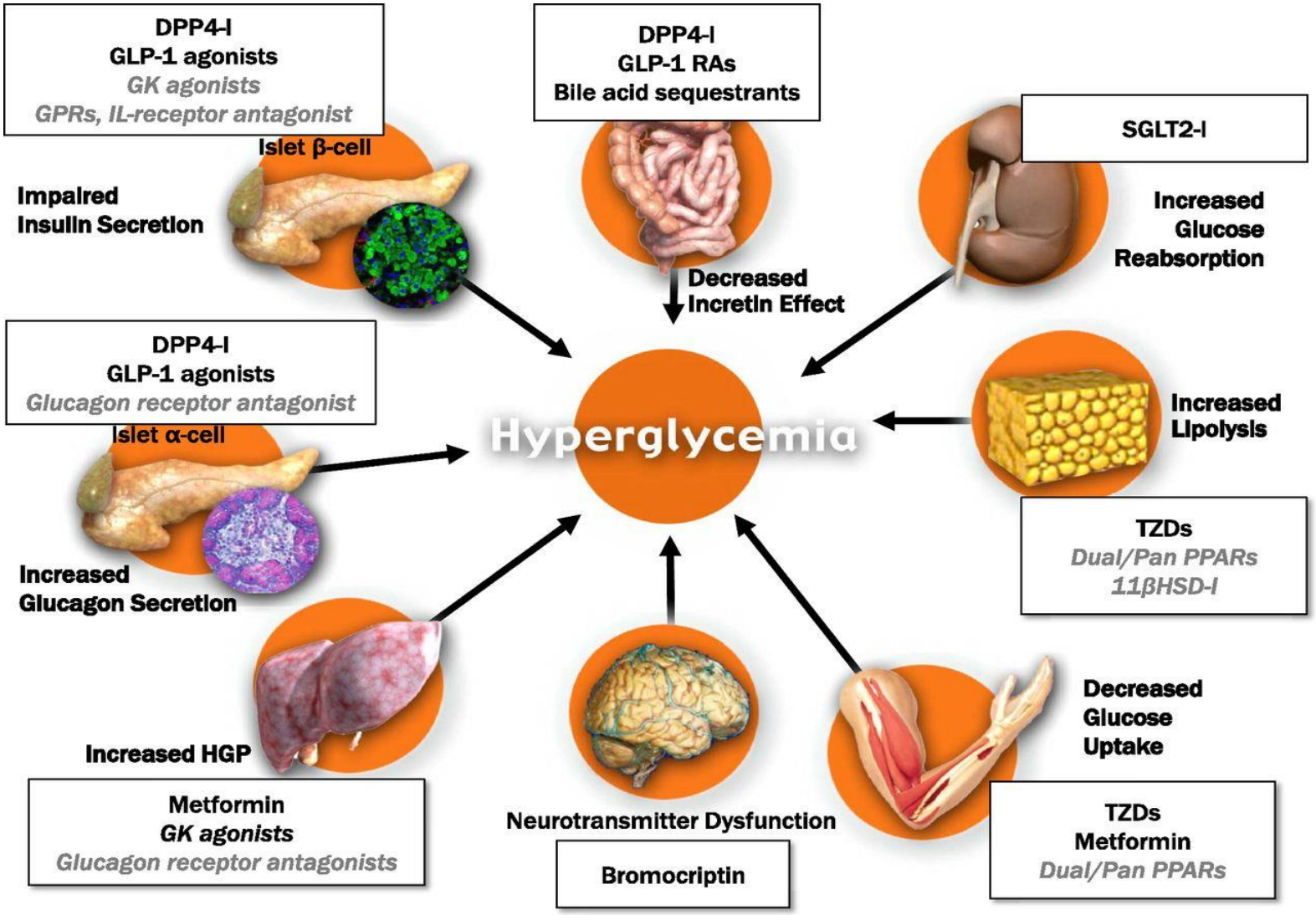
2019 MOTORE SANITÀ
Gestire il Cambiamento

Disclosures

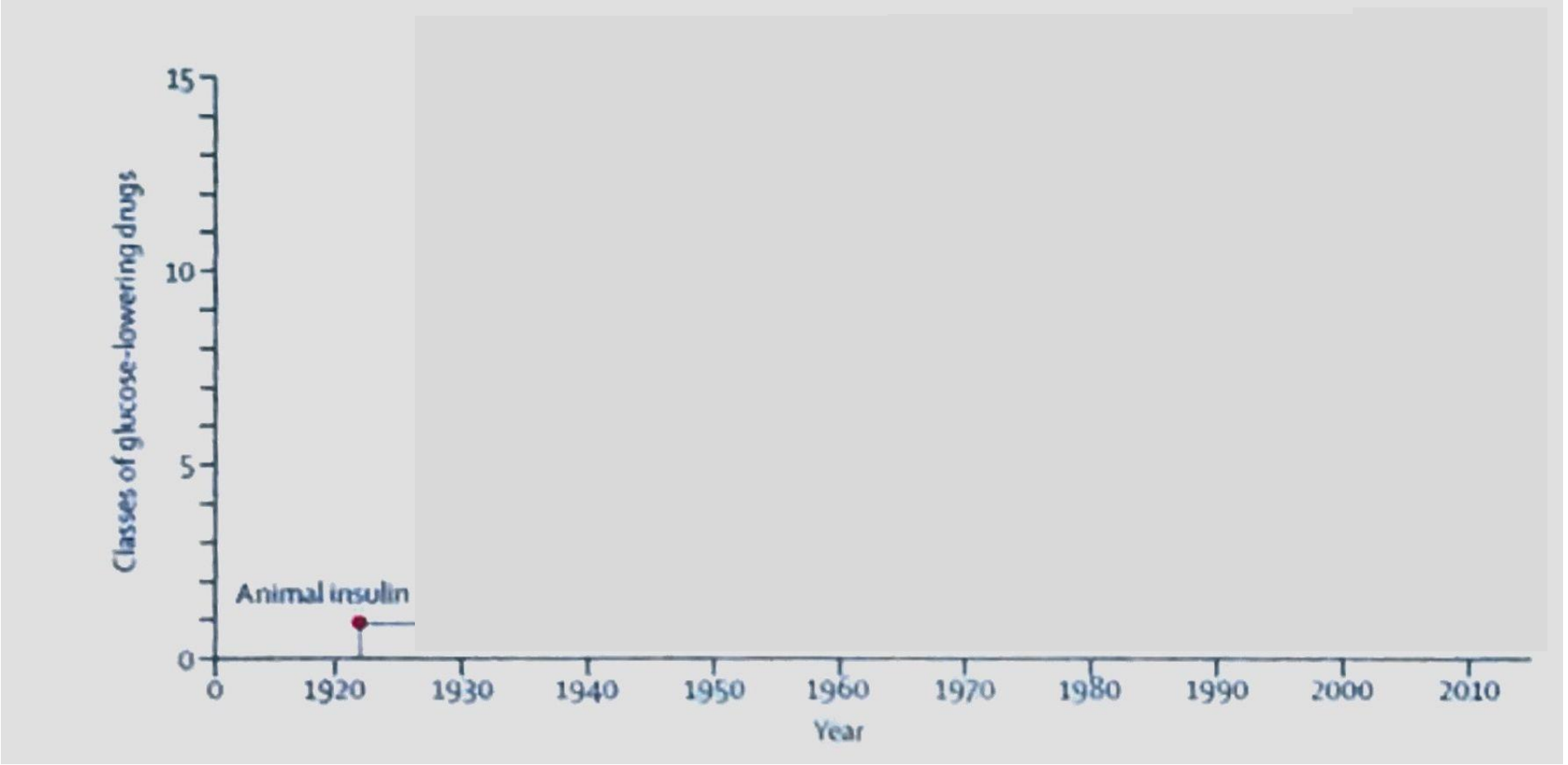
Giulio Marchesini

- **Advisory Board**: Eli Lilly, Gilead, Novartis, Intercept
- **Honoraria**: Astra-Zeneca
- **Clinical Studies**: Janssen Cilag, Sanofi, Eli Lilly, Gilead, GENFIT, Glaxo, Intercept,

Diabetes treatment - 2018



La scala dei farmaci del diabete



Cahn, Lancet Diabetes Endocrinol 2015

Innovazione terapeutica

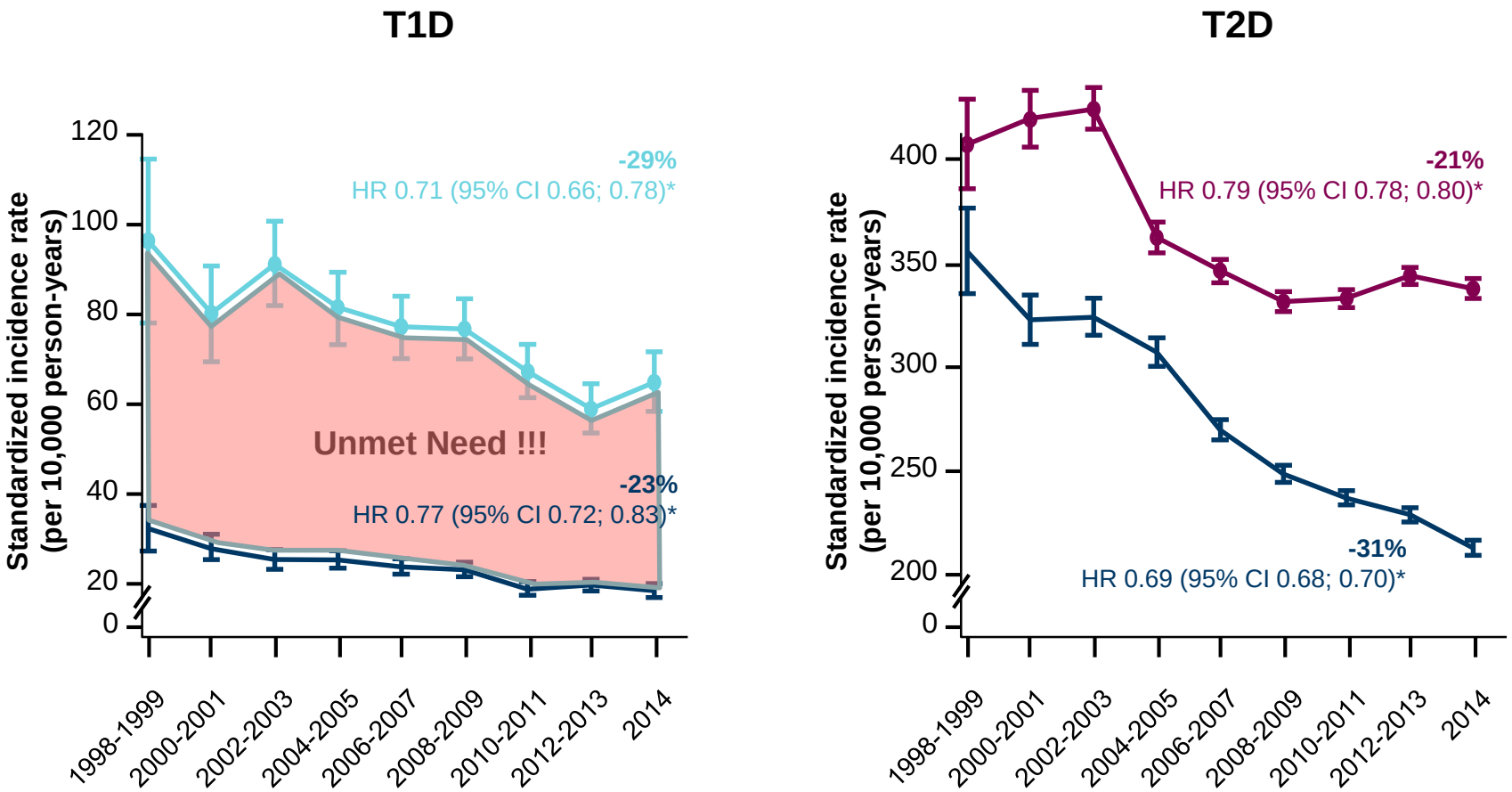
Device

- Continuos glucose monitoring

Farmaci

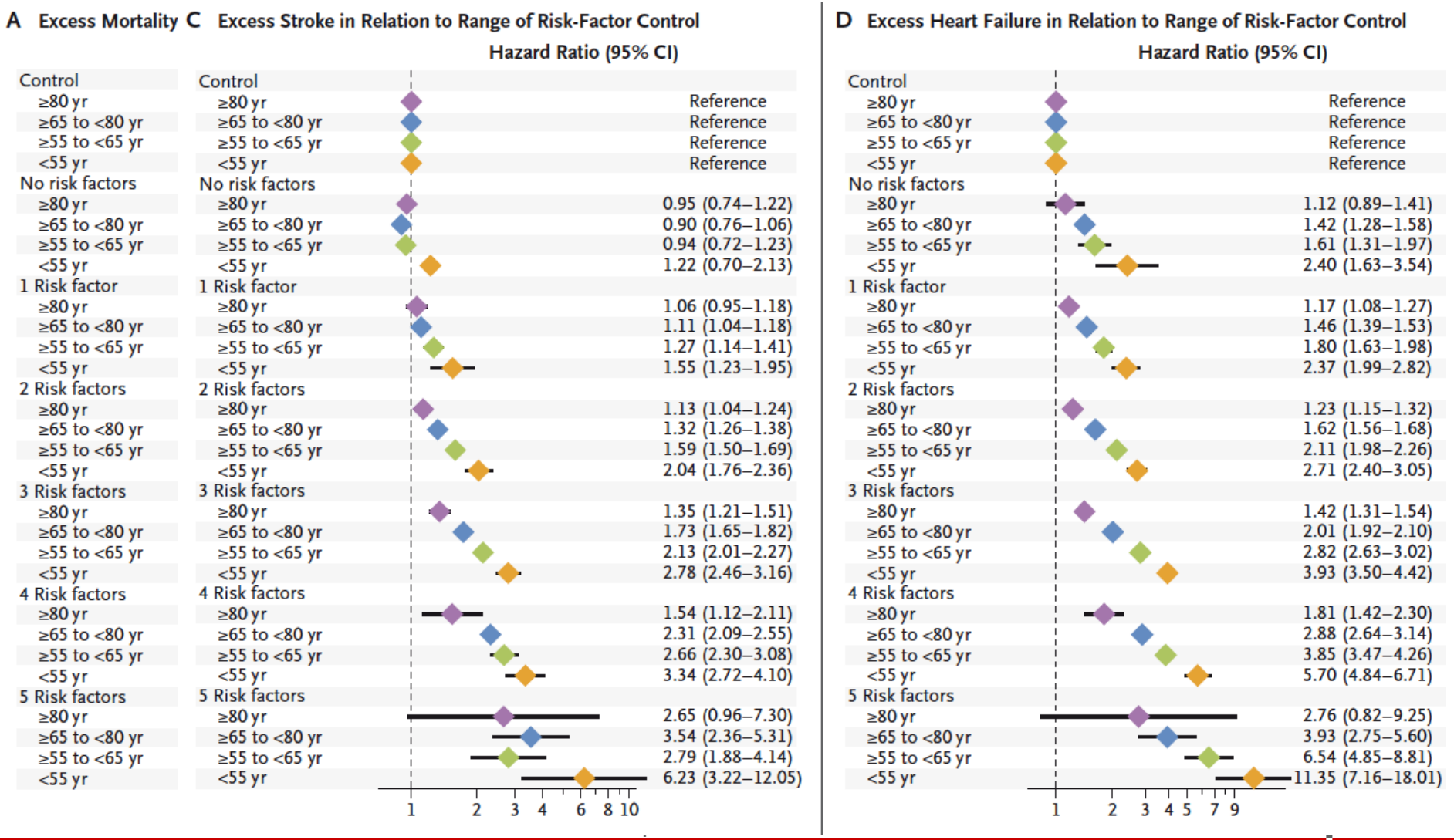
- GLP-1RAs (Peso, rischio CV)
- SGLT-2Is (Scompenso cardiaco, Funzione renale

Comparison of total mortality in T1D and T2D



Relative event-rate reduction.
CI = confidence interval; HR = hazard ratio

Mortality risks in T2D



Ricoveri ospedalieri (ordinari e DH)

Rank	Diagnosi	Diagnosi principale	N. totale ricoveri	% su totale ricoveri	Δ % Casi vs Controlli	N. pazienti ricoverati	Ricoverati /1000	N. ricoveri per ricoverato
1	428	Insufficienza cardiaca (scompenso cardiaco)	12.301	6,8	62%	7.344	11,5	1,7
2	250	Diabete mellito	11.222	6,2	-	5.604	8,7	2,0
3	518	Insufficienza respiratoria e/o edema polm. acuto	6.802	3,8	28%	4.147	6,5	1,6
4	410	Infarto miocardico acuto	4.736	2,6	22%	2.987	4,7	1,6
5	427	Aritmie cardiache	4.189	2,3	49%	2.556	4,0	1,6
6	715	Artrosi	3.891	2,2	-23%	2.536	4,0	1,5
7	V43	Organo o tessuto sostituito con altri mezzi	3.723	2,1	-36%	2.639	4,1	1,4
8	414	Altre forme di Cardiopat. ischemica cronica	3.607	2,0	2%	2.472	3,9	1,5
9	434	Occlusione delle arterie cerebrali	3.246	1,8	-50%	2.530	3,9	1,3
10	491	Bronchite cronica	3.039	1,7	143%	1.669	2,6	1,8

ARNO 2015
Costi diretti del diabete

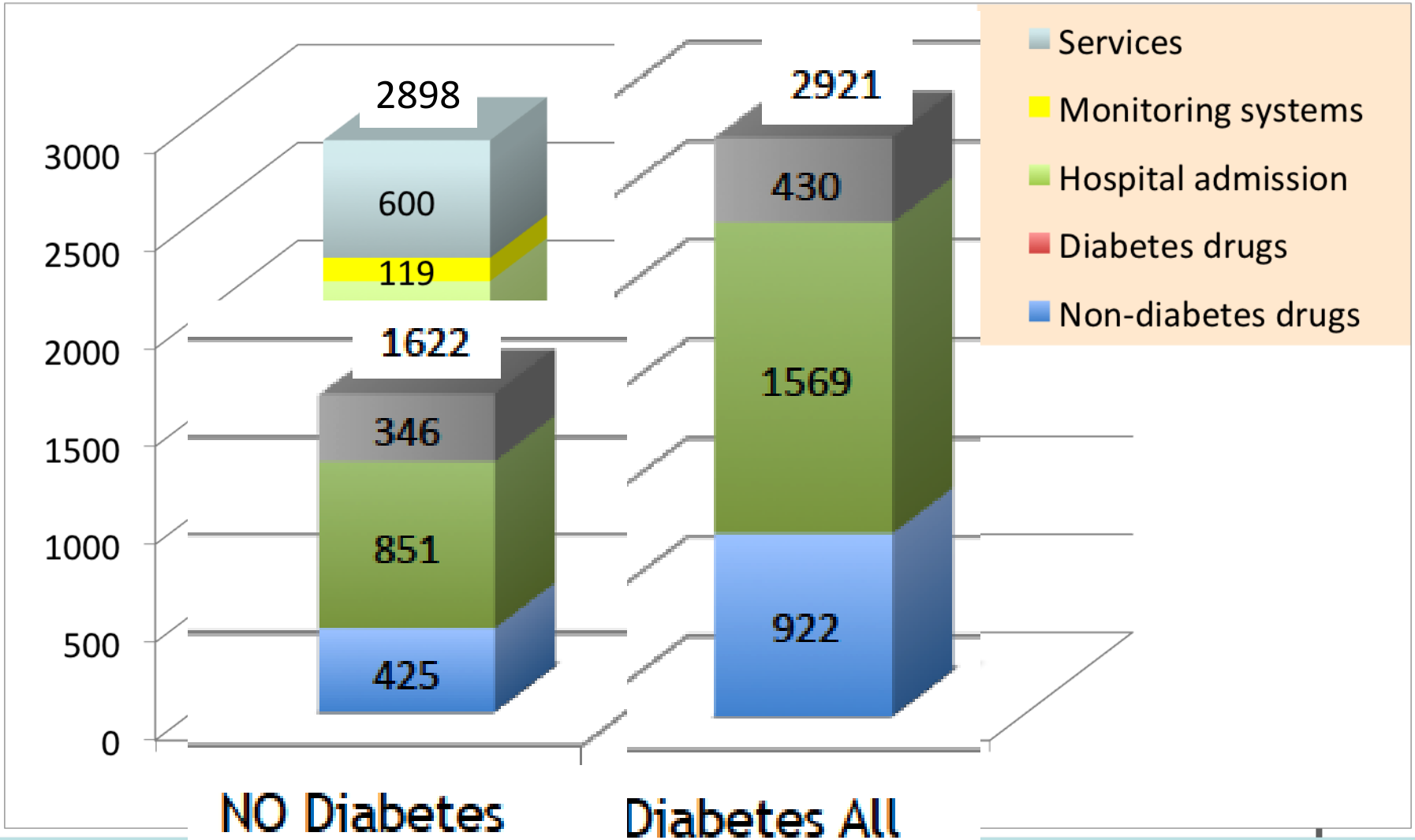


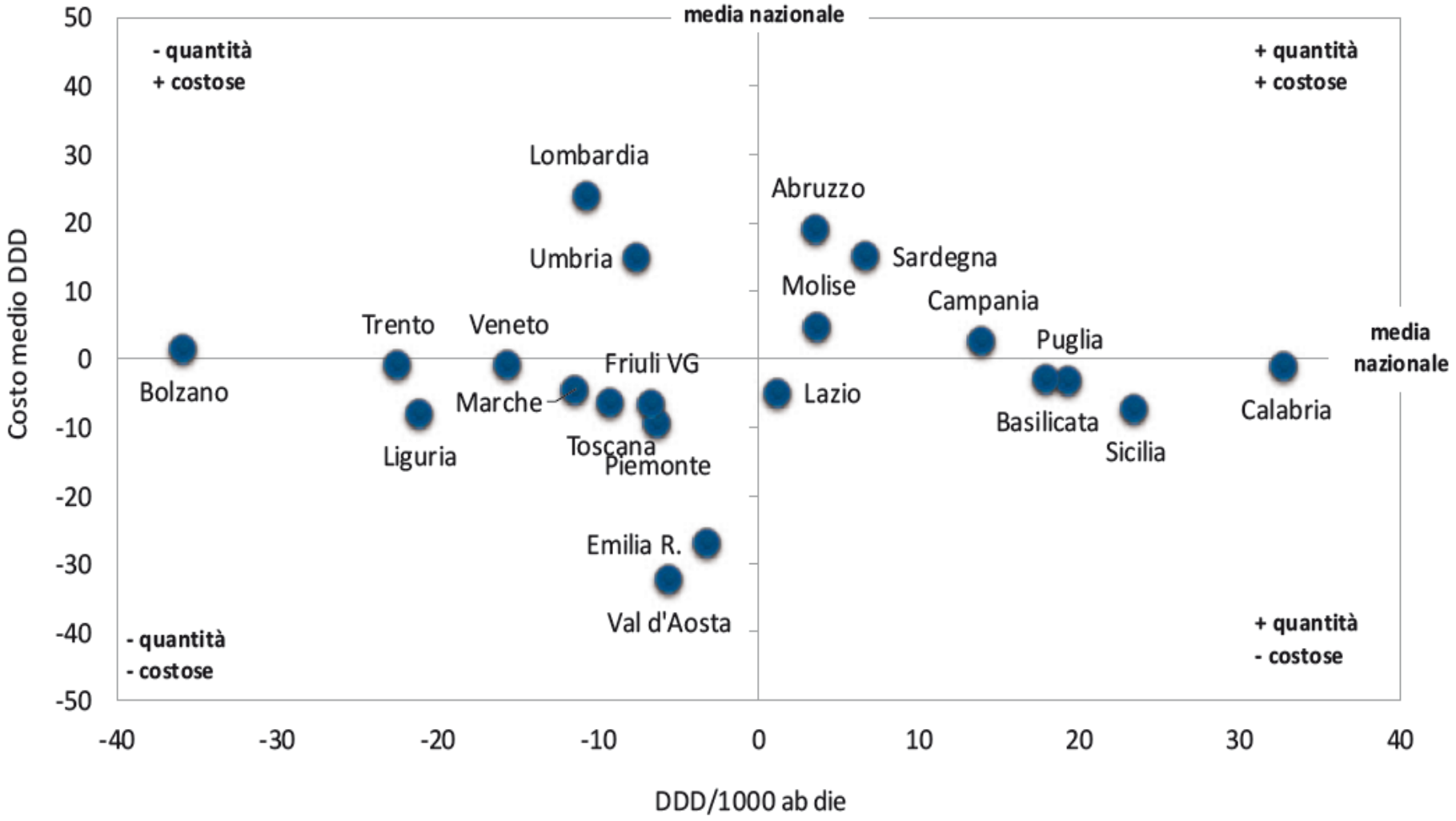
Table 3 Impact of patients demographic and clinical characteristics on annual healthcare costs expressed as cost ratio 95% confidence interval and marginal cost (€) in a cohort of prevalent cases of diabetes (year 2012).

Diabetes related conditions and complications (absence)			
Hypertension	1.43	1.40–1.47	657
Heart disease	2.11	2.06–2.17	1996
Nephropathy/ESRD	3.37	3.16–3.60	4683
Cerebrovascular disease	2.95	2.77–3.14	3861
Amputations	3.49	2.81–4.40	5042
Lower extremity revascularization	3.37	2.72–4.25	4808
Retinopathy	1.78	1.60–1.99	1587
Neuropathy	1.85	1.62–2.13	1723
Acute complications (absence)	1.84	1.61–2.11	1704

Gruppo Sottogruppo	Spesa totale (in mil)	% su spesa SSN	Spesa pro capite	Δ% 18-17	DDD/ 1000 ab die	Δ% 18-17
Antidiabetici	**945,4**	**4,3**	**15,63**	**4,7**	**63,2**	**0,8**
Insuline ed analoghi	424,9	1,9	7,03	-2,3	15,3	-0,4
Gliptine (inibitori della DPP-4) sole o ass.	150,1	0,7	2,48	4,4	5,7	10,1
Analoghi del GLP-1 (glucagon-like peptide 1)	98,3	0,4	1,62	22,6	1,7	28,9
Metformina	91,5	0,4	1,51	3,7	22,1	2,0
Glifozine sole o ass.	62,8	0,3	1,04	42,6	2,1	50,5
Altri ipoglicemizzanti orali	52,7	0,2	0,87	-6,7	11,9	-9,3
Pioglitazone da solo e in ass.	28,7	0,1	0,48	-6,0	1,7	-3,6
Repaglinide	21,7	0,1	0,36	-11,1	2,6	-11,8
Insuline in associazione a GLP-1	14,8	0,1	0,25	>100	0,1	>100

L'uso dei Farmaci in Italia

Sottogruppi e sostanze 2013 2014 2015 2016 2017 2018 Δ %

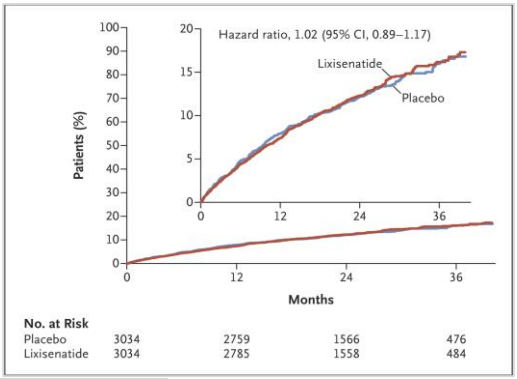


GLP-1RA treatment & CV outcomes (MACE-4)

ELIXA

ORIGINAL ARTICLE

Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome

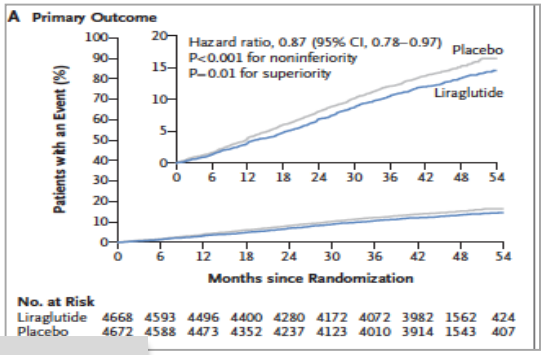


LEADER

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

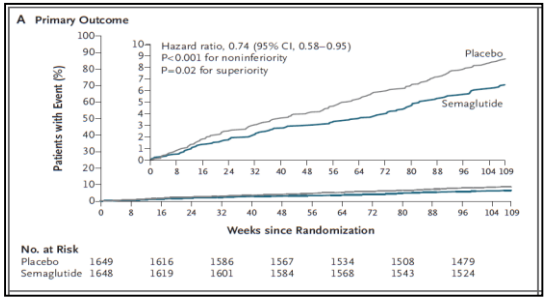


SUSTAIN 6

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

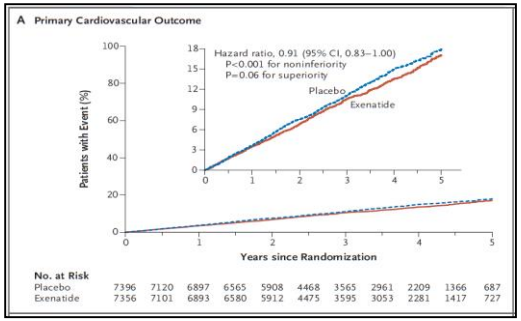
Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes



EXSCEL

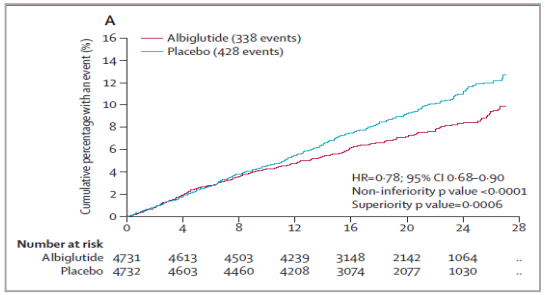
ORIGINAL ARTICLE

Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes



HARMONY

Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial

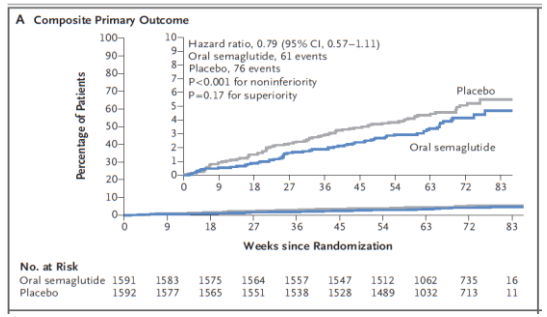


PIONEER 6

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes



GLP-1RA treatment & CV outcomes (MACE-4)

REWIND

Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial

Hertzel C Gerstein, Helen M Colhoun, Gilles R Dagenais, Rafael Diaz, Mark Lakshmanan, Prem Pais, Jeffrey Probst
Matthew C Riddle, Lars Rydén, Denis Xavier, Charles Messan Atisso, Leanne Dyal, Stephanie Hall, Purnima Rao-M
Alvaro Avezum, Jan Basile, Namsik Chung, Ignacio Conget, William C Cushman, Edward Franek, Nicolae Hancu, M
Petr Jansky, Matyas Keltai, Fernando Lanas, Lawrence A Leiter, Patricio Lopez-Jaramillo, Ernesto German Cardona
Nana Pogosova, Peter J Raubenheimer, Jonathan E Shaw, Wayne H-H Sheu, Theodora Temelkova-Kurktschiev, fa

	Dulaglutide (n=4949)		Placebo (n=4952)		Hazard ratio (95% CI)	p value
	Number of patients (%)	Incidence rate (number of events per 100 person-years)	Number of patients (%)	Incidence rate (number of events per 100 person-years)		
Primary composite outcome	594 (12·0%)	2·35	663 (13·4%)	2·66	0·88 (0·79–0·99)*	0·026
Myocardial infarction	223 (4·5%)	0·87	231 (4·7%)	0·91	0·96 (0·79–1·15)	0·63
Non-fatal myocardial infarction	205 (4·1%)	0·80	212 (4·3%)	0·84	0·96 (0·79–1·16)	0·65
Fatal myocardial infarction	26 (0·5%)	0·10	20 (0·4%)	0·08	1·29 (0·72–2·30)	0·40
Stroke	158 (3·2%)	0·61	205 (4·1%)	0·81	0·76 (0·62–0·94)	0·010
Non-fatal stroke	135 (2·7%)	0·52	175 (3·5%)	0·69	0·76 (0·61–0·95)	0·017
Fatal stroke	26 (0·5%)	0·10	33 (0·7%)	0·13	0·78 (0·47–1·30)	0·34
Cardiovascular death†	317 (6·4%)	1·22	346 (7·0%)	1·34	0·91 (0·78–1·06)	0·21
Non-cardiovascular death	219 (4·4%)	0·84	246 (5·0%)	0·95	0·88 (0·73–1·06)	0·18
All-cause death	536 (10·8%)	2·06	592 (12·0%)	2·29	0·90 (0·80–1·01)	0·067
Hospital admission for heart failure or urgent visit	213 (4·3%)	0·83	226 (4·6%)	0·89	0·93 (0·77–1·12)	0·46
Hospital admission for unstable angina	88 (1·8%)	0·34	77 (1·6%)	0·30	1·14 (0·84–1·54)	0·41
Composite microvascular outcome (eye or renal outcome)	910 (18·4%)	3·76	1019 (20·6%)	4·31	0·87 (0·79–0·95)	0·0020
Eye outcome‡	95 (1·9%)	0·37	76 (1·5%)	0·30	1·24 (0·92–1·68)	0·16
Renal outcome§	848 (17·1%)	3·47	970 (19·6%)	4·07	0·85 (0·77–0·93)	0·0004

All hazard ratios (HRs) were estimated with Cox proportional hazards models and p values are two-sided. *After accounting for α=0·009 spent on the primary outcome for the interim analysis, the α for the final analysis is 0·0467, and the HR is 0·88 (95·33% CI 0·79–0·99). †Includes deaths of unknown cause. ‡Photocoagulation, anti-vascular endothelial growth factor therapy, or vitrectomy. §New macroalbuminuria, a sustained decline in estimated glomerular filtration rate of 30% or more from baseline, or chronic renal replacement therapy.

Table 2: Primary and secondary outcomes

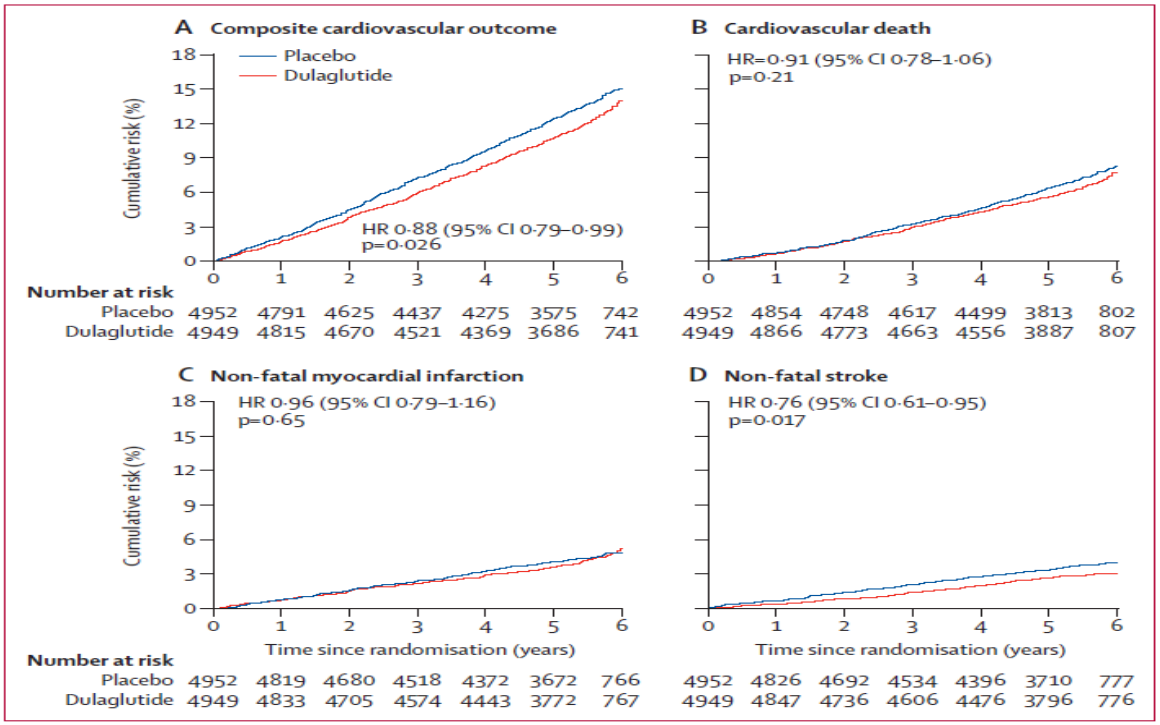
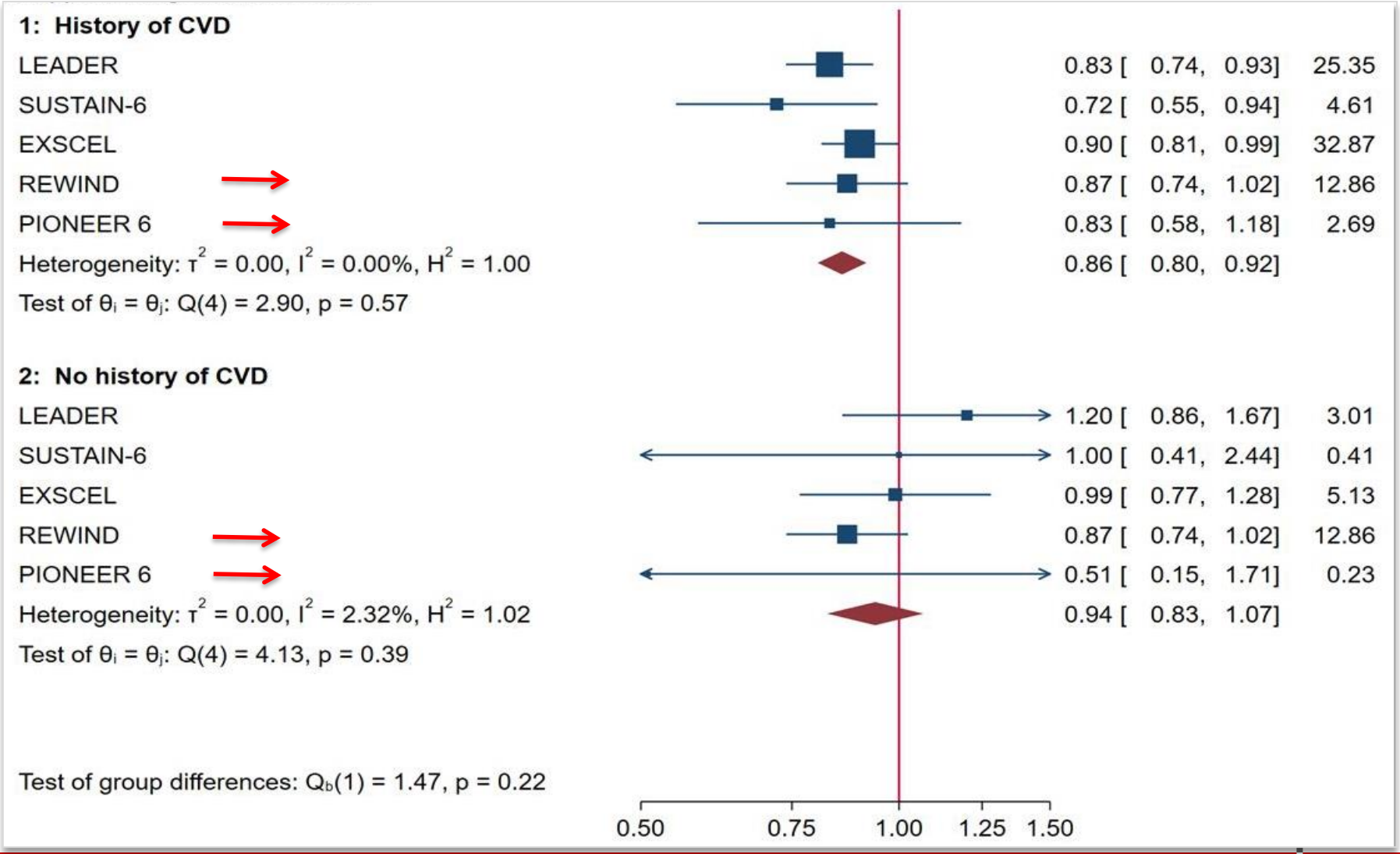


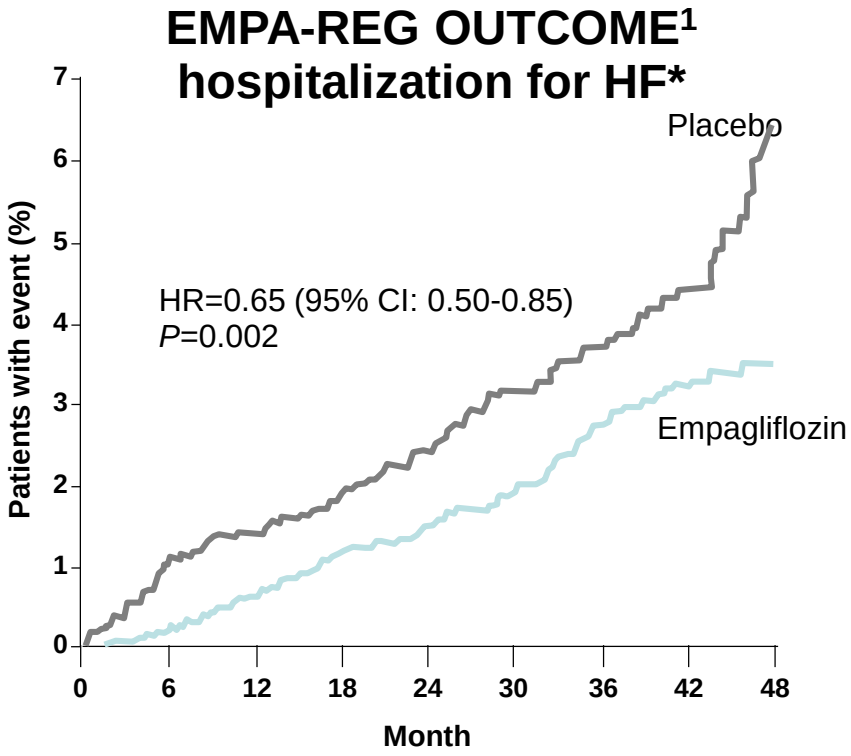
Figure 2: Cumulative incidence of cardiovascular outcomes
HR=hazard ratio. HbA_{1c}=glycated haemoglobin A_{1c}.

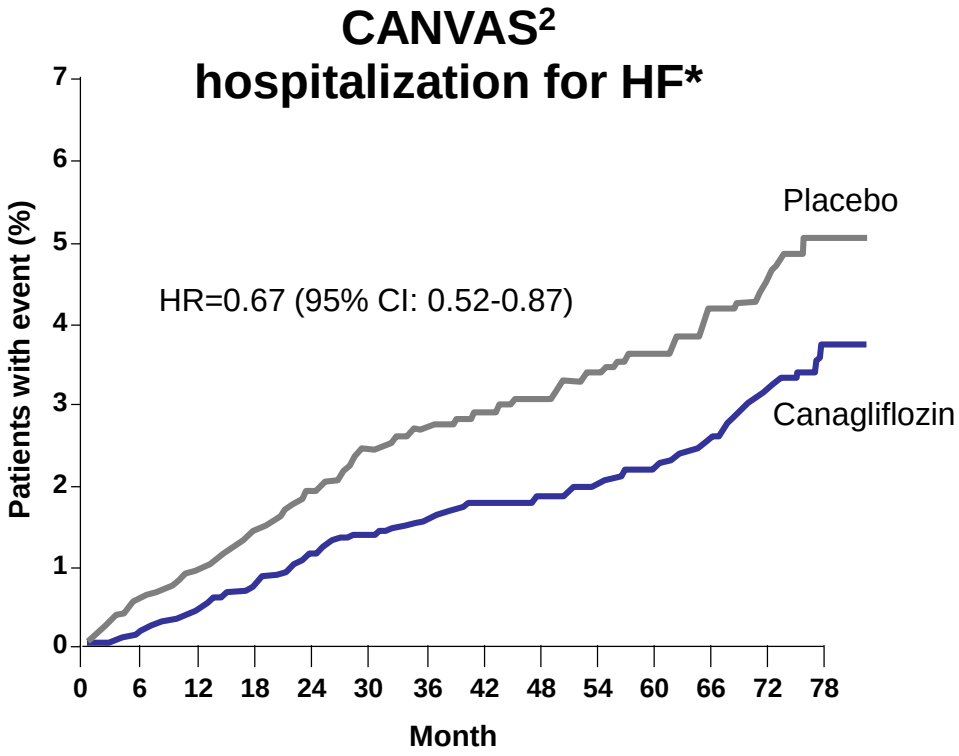
Meta-analysis of all published CVOTs with GLP-1RAs: impact of presence of CVD at baseline on risk reduction



Giugliano, Diabetes Obes Metab. 2019

HF prevention in trials examining SGLT2 inhibitor use in T2D



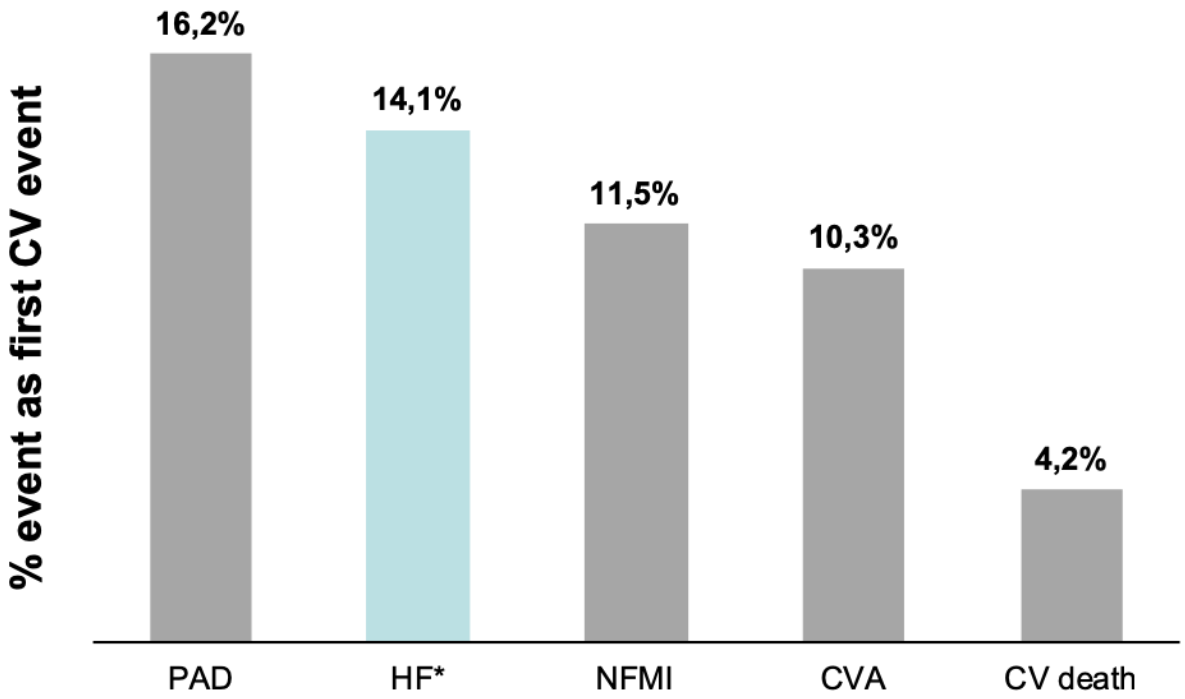


*hHF is an exploratory end point in both studies.

1. Zinman B, et al. *N Engl J Med.* 2015;373:2117–2128.
2. Neal B, et al. *N Engl J Med.* 2017;377:644-657.

HF was the first manifestation of T2D-related CV disease more often than was MI or stroke

Cohort study of patients (n=1.9 million) with T2D and incidence of CV disease



*Heart failure post MI was not included in this definition of HF

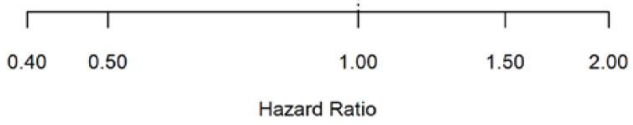
- HF was the second most common presentations of T2D-related CV disease.
- Yet, myocardial infarction and stroke continue to be chosen as primary outcomes of major type 2 diabetes trials, as part of the MACE endpoint.

- CV, cardiovascular; CVA, cerebrovascular accident; HF, heart failure; NFMI, nonfatal myocardial infarction; PAD, peripheral arterial disease; T2D, type 2 diabetes.

Shah AD, et al. *Lancet Diabetes Endocrinol.* 2015;3:105-113

Meta-analysis of GLP-1RA and SGLT2i trials on the composite outcome of new-onset macroalbuminuria, sustained doubling of serum creatinine or a 40% decline in eGFR, ESKD, or renal death

Trials	Patients	Events	Treatment n/N	Placebo n/N	Weights	HR [95% CI]
GLP1-RA						
ELIXA	5286	375	203/2639	172/2647	20.0	0.84 [0.68, 1.02]
LEADER	9340	605	268/4668	337/4672	32.2	0.78 [0.67, 0.92]
SUSTAIN-6	3297	162	62/1648	100/1649	7.7	0.64 [0.46, 0.88]
EXSCEL	14752	773	366/6256	407/6222	40.1	0.88 [0.76, 1.01]
Fixed Effects for GLP1-RA (P-value<0.001)						0.82 [0.75, 0.89]
SGLT2i						
EMPA-REG OUTCOME	6185	913	525/4124	388/2061	24.9	0.61 [0.53, 0.70]
CANVAS Program	10142	847	NA	NA	25.0	0.57 [0.50, 0.66]
DECLARE-TIMI 58	17160	1675	678/8582	997/8578	50.1	0.66 [0.60, 0.73]
Fixed Effects for SGLT2i (P-value<0.001)						0.62 [0.58, 0.67]



Zelniker TA, et al. *Circulation*. 2019;139(17):2022-2031.

Il problema "renale" nel diabete

ORIGINAL ARTICLE

Chronic Kidney Disease and the Risks of Death, Cardiovascular Events, and Hospitalization

Alan S. Go, M.D., Glenn M. Chertow, M.D., M.P.H., Dongjie Fan, M.S.P.H., Charles E. McCulloch, Ph.D., and Chi-yuan Hsu, M.D.

1,120,295 adults within a large, integrated system of health care delivery in whom serum creatinine had been measured between 1996 and 2000 and who had not undergone dialysis or kidney transplantation (9.6% with diabetes). We examined the multivariable association between the estimated GFR and the risks of death, cardiovascular events, and hospitalization, follow-up, 2.8 yrs – over 3 mil patient-years).

Go, N Engl J Med 2012

Il problema "renale" come equivalente cardiovascolare

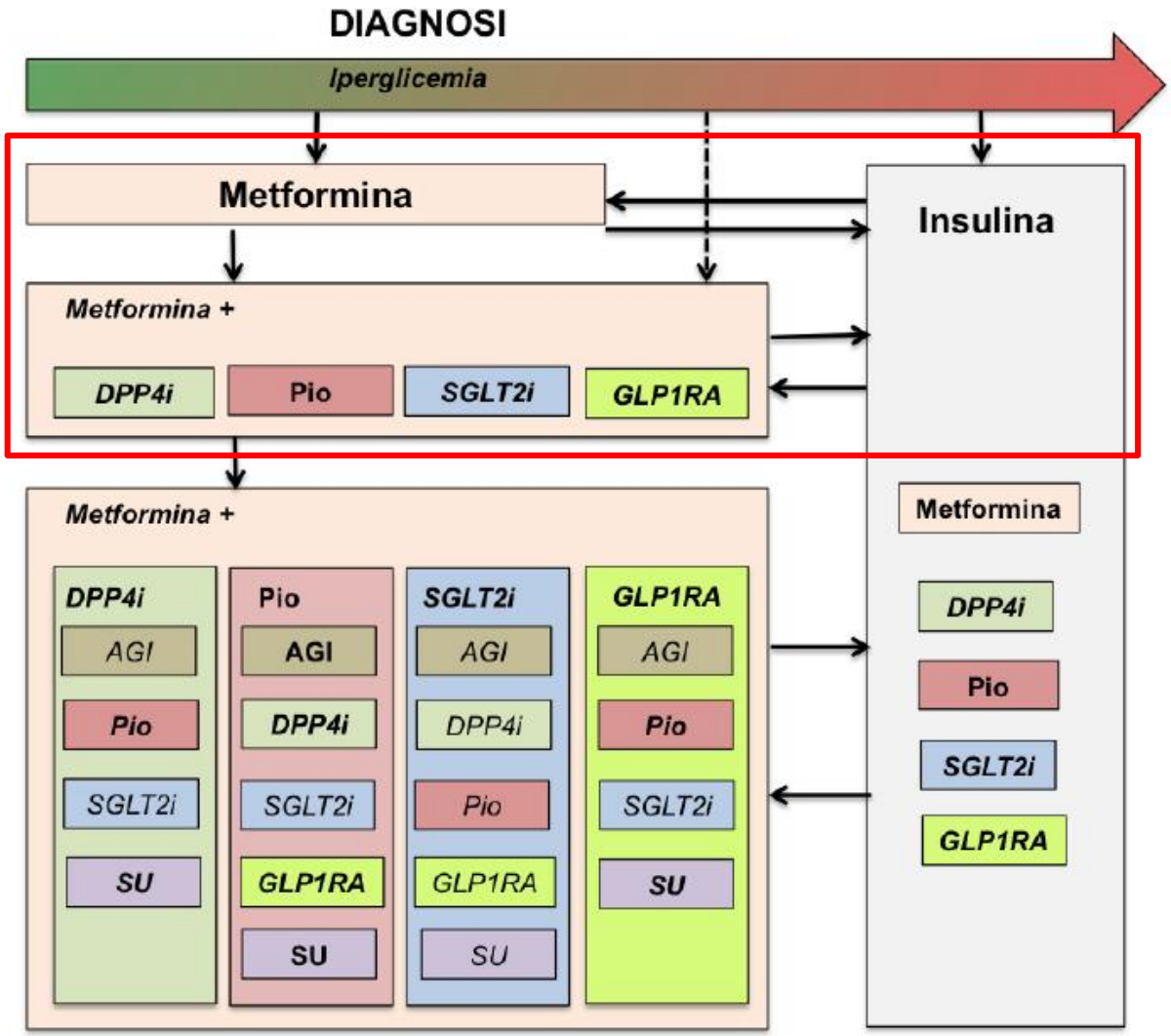
Table 2. Adjusted Hazard Ratio for Death from Any Cause, Cardiovascular Events, and Hospitalization among 1,120,295 Ambulatory Adults, According to the Estimated GFR.*

Estimated GFR	Death from Any Cause	Any Cardiovascular Event	Any Hospitalization
	adjusted hazard ratio (95 percent confidence interval)		
≥60 ml/min/1.73 m²†	1.00	1.00	1.00
45–59 ml/min/1.73 m²	1.2 (1.1–1.2)	1.4 (1.4–1.5)	1.1 (1.1–1.1)
30–44 ml/min/1.73 m²	1.8 (1.7–1.9)	2.0 (1.9–2.1)	1.5 (1.5–1.5)
15–29 ml/min/1.73 m²	3.2 (3.1–3.4)	2.8 (2.6–2.9)	2.1 (2.0–2.2)
<15 ml/min/1.73 m²	5.9 (5.4–6.5)	3.4 (3.1–3.8)	3.1 (3.0–3.3)

The analyses were adjusted for age, sex, income, education, use or nonuse of dialysis, and the presence or absence of prior coronary heart disease, prior chronic heart failure, prior ischemic stroke or transient ischemic attack, prior peripheral arterial disease, diabetes mellitus, hypertension, dyslipidemia, cancer, a serum albumin level of 3.5 g per deciliter or less, dementia, cirrhosis or chronic liver disease, chronic lung disease, documented proteinuria, and prior hospitalizations.

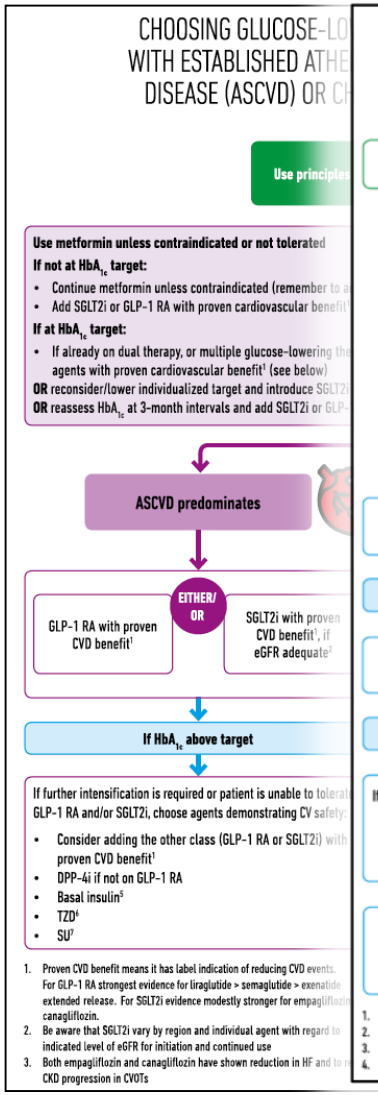
Go, N Engl J Med 2012

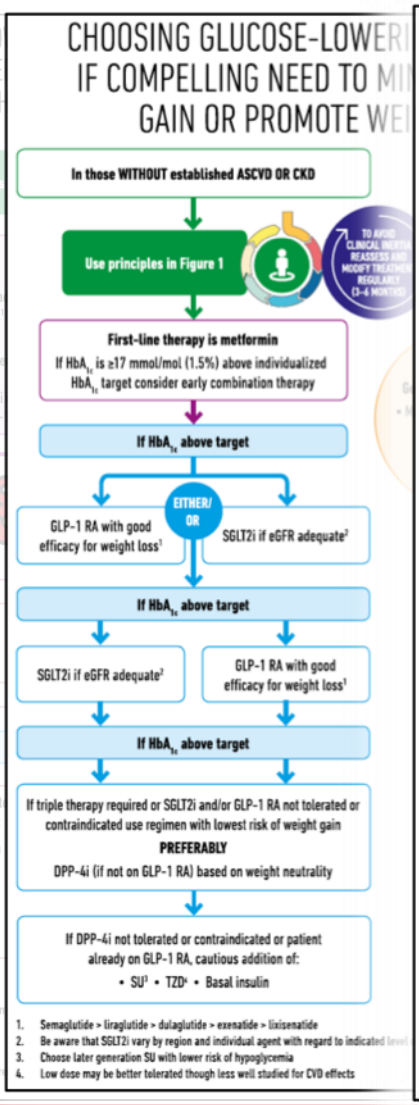
Standard italiani per la cura del diabete mellito 2018

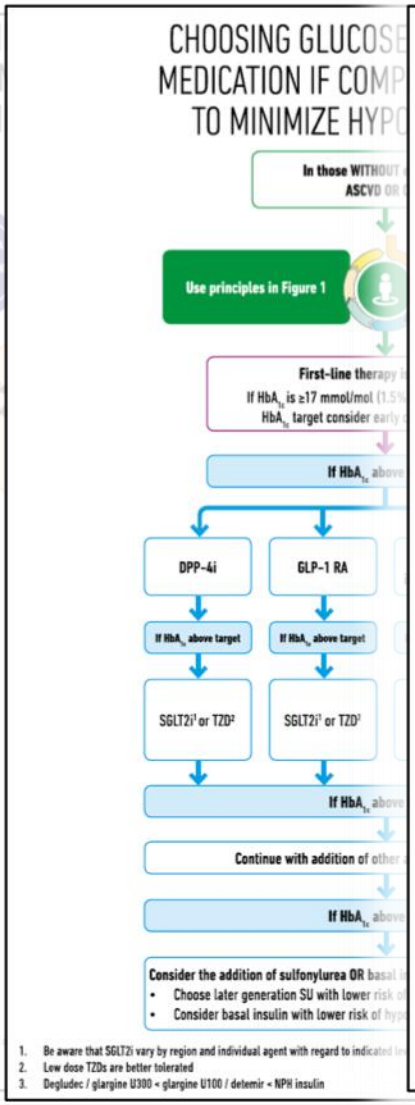


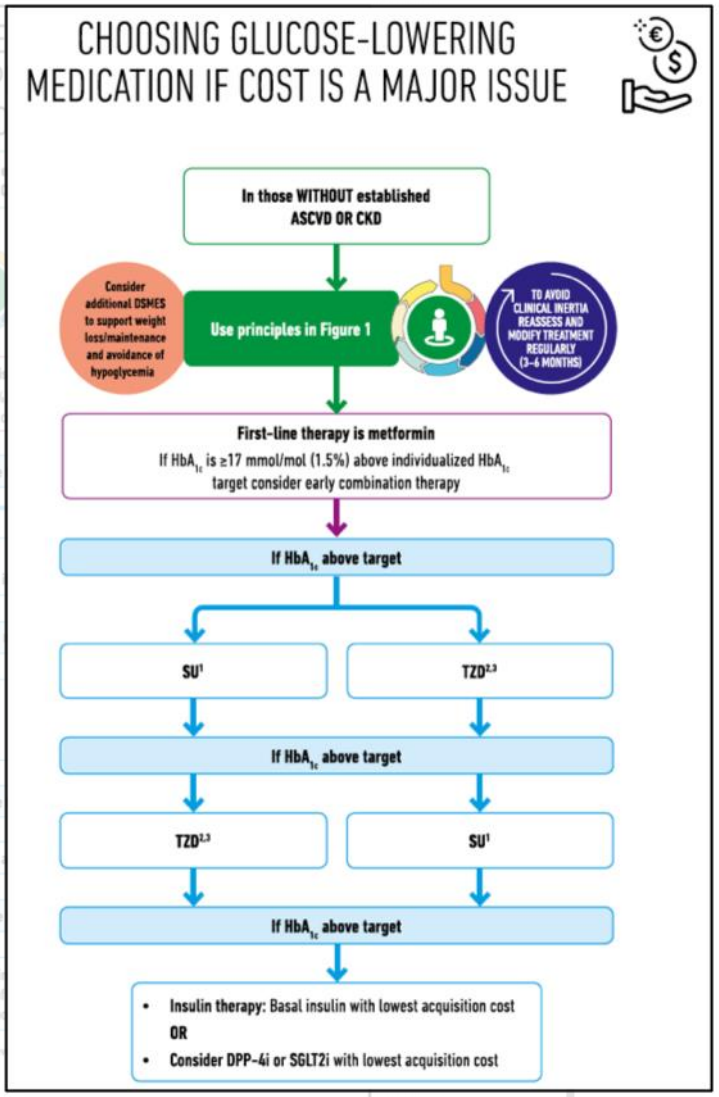
NO Sulfoniluree
(eventualmente Gliclazide)

Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)





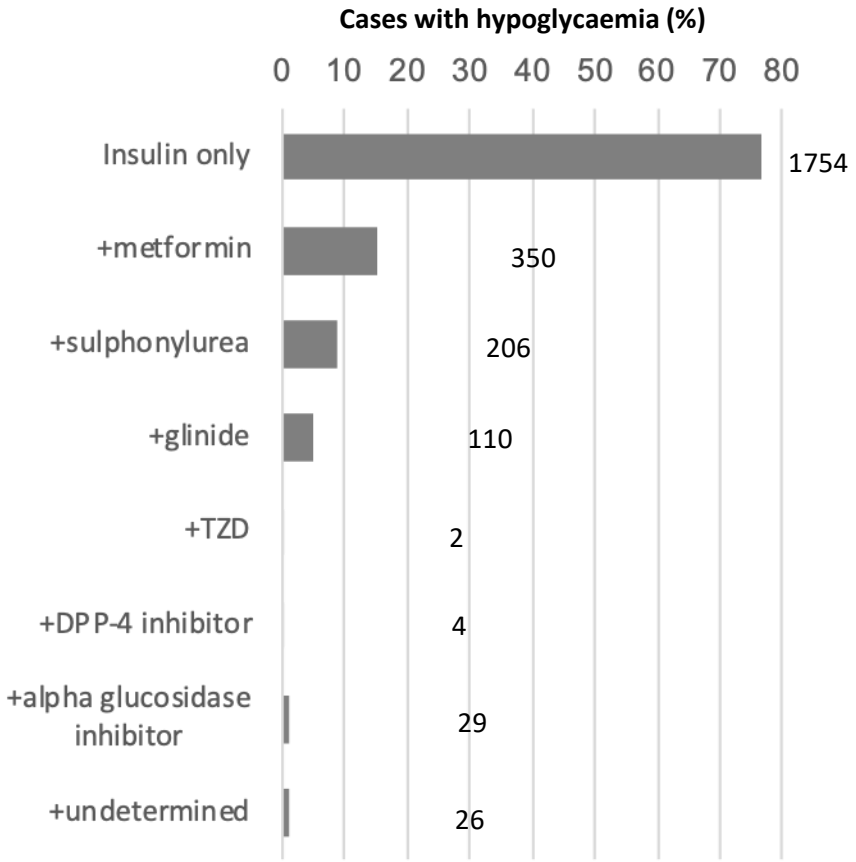




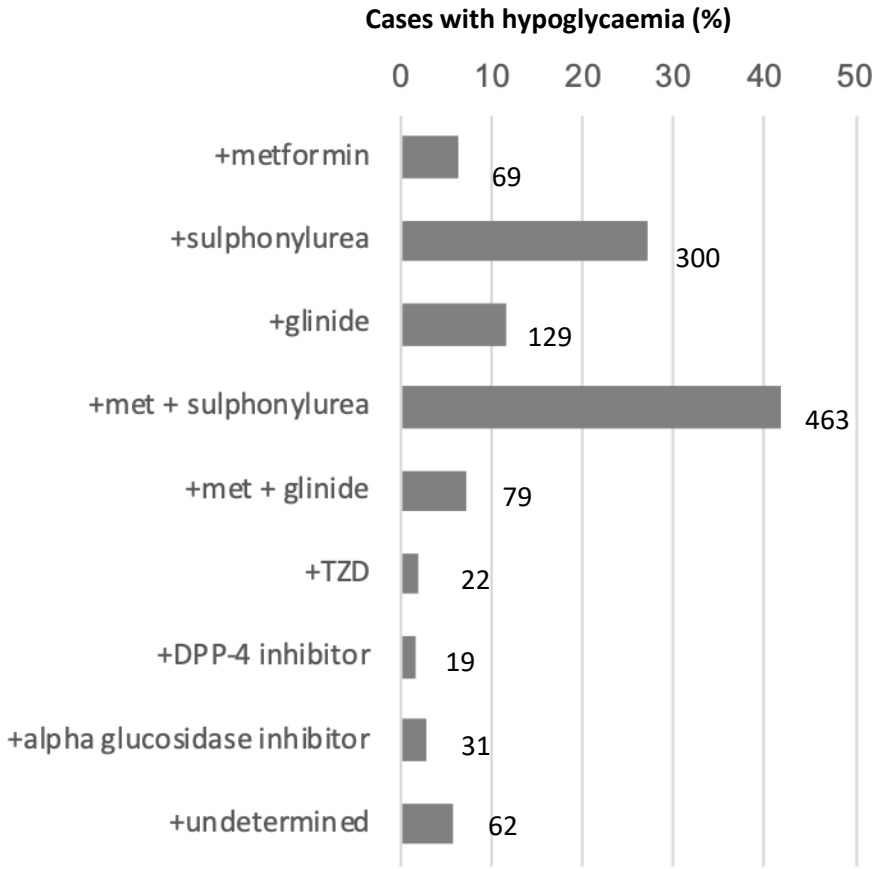
Davies, Diabetologia & Diabetes Care, 2018

HYPOTHESYS: Drug treatment

Insulin cases

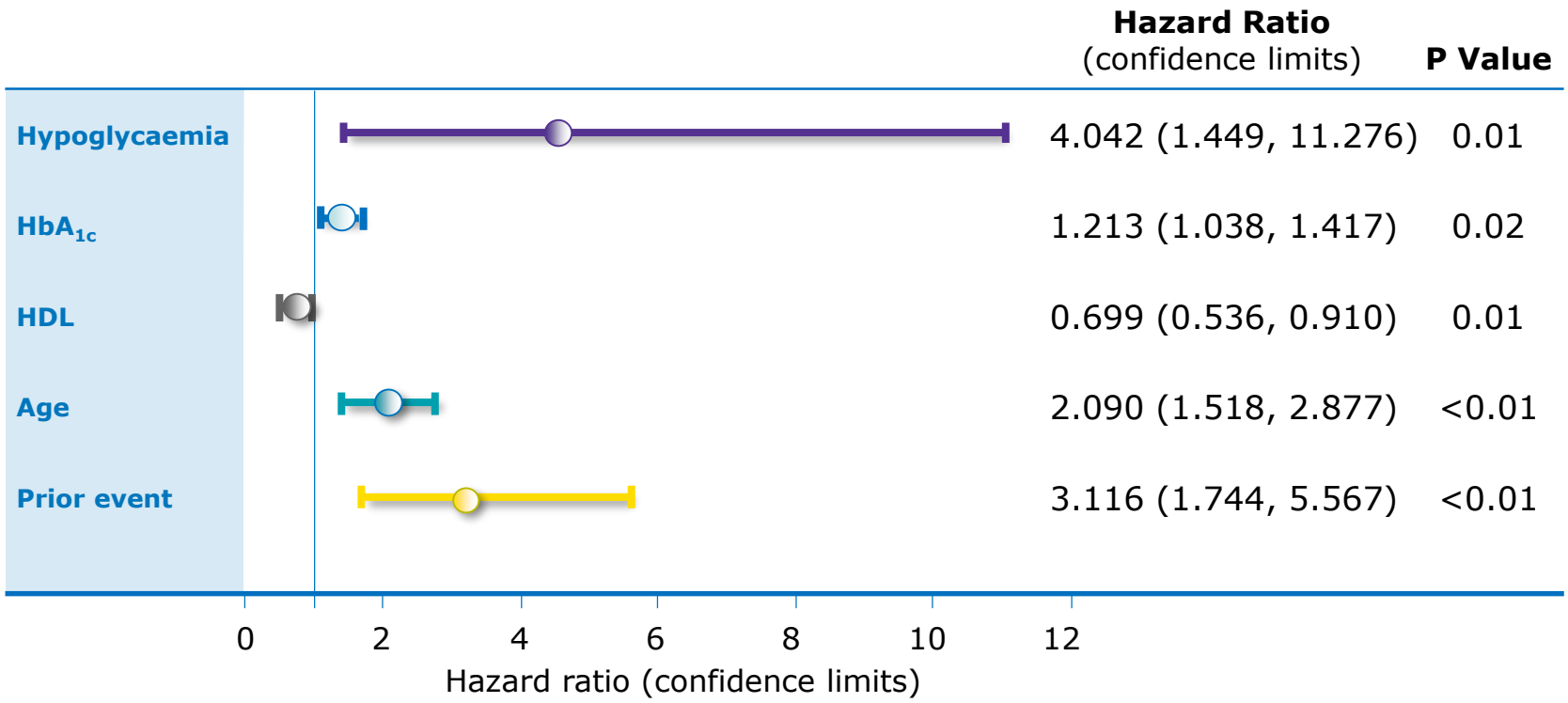


Oral agents



Of note, among the 23 cases where DPP-4 inhibitors were recorded, insulin was present in 4, metformin in 18, sulphonylureas in 11, repaglinide in 4, TZDs in 2, in various combinations

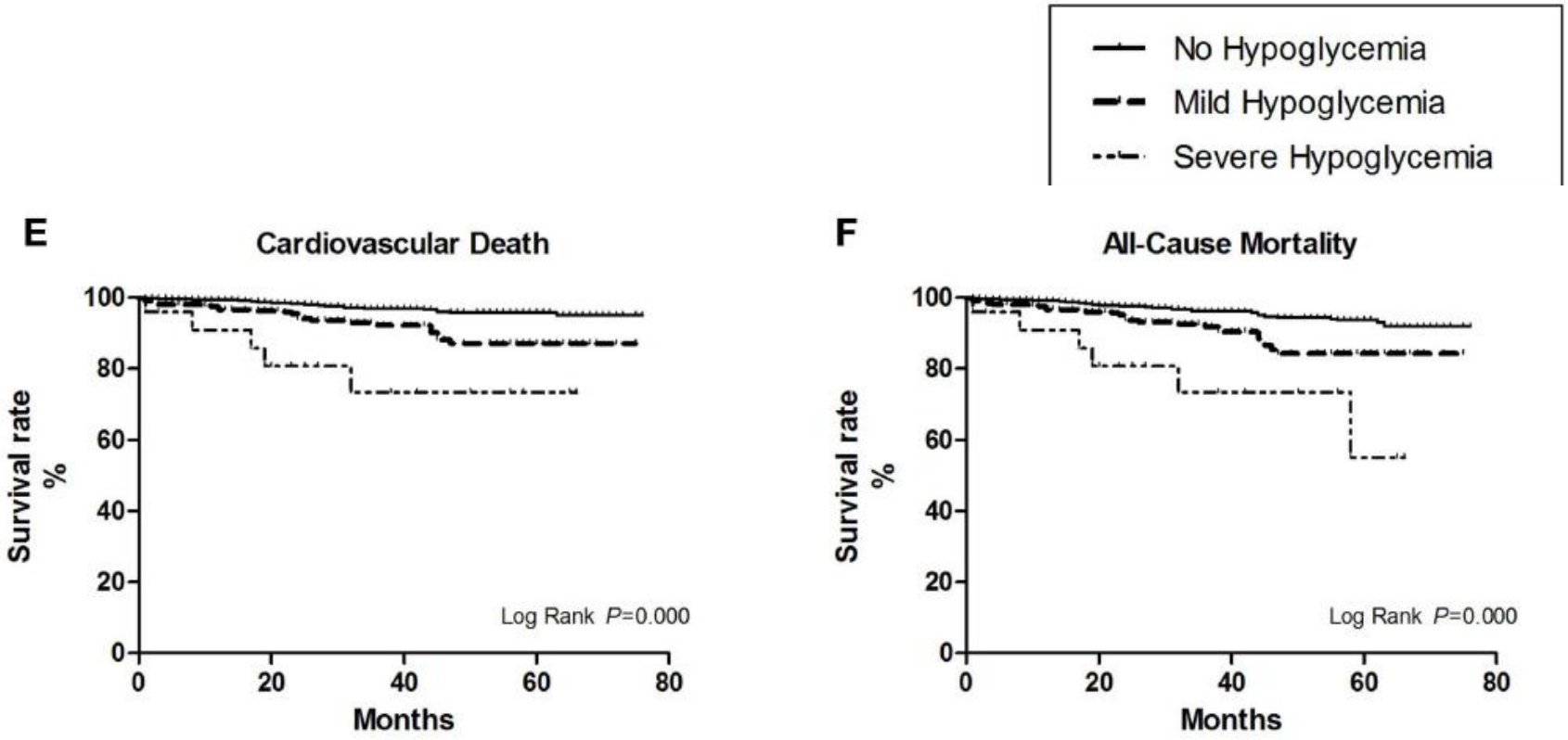
Ipoglicemia come maggiore predittore di morte per eventi cardiovascolari (VADT)



Duckworth, N Engl J Med 2008.

The association of hypoglycemia assessed by CGM with CV outcomes and mortality in type 2 diabetes

A retrospective cohort study was conducted with 1,520 pts with T2DM. The severity of hypoglycemia event was assessed by CGM. 347 participants experienced hypoglycemia (323 mild hypoglycemia, 24 severe hypoglycemia, 72.6% asymptomatic. During a median follow-up of 31 months, 380 participants reached the primary outcome of MACE.



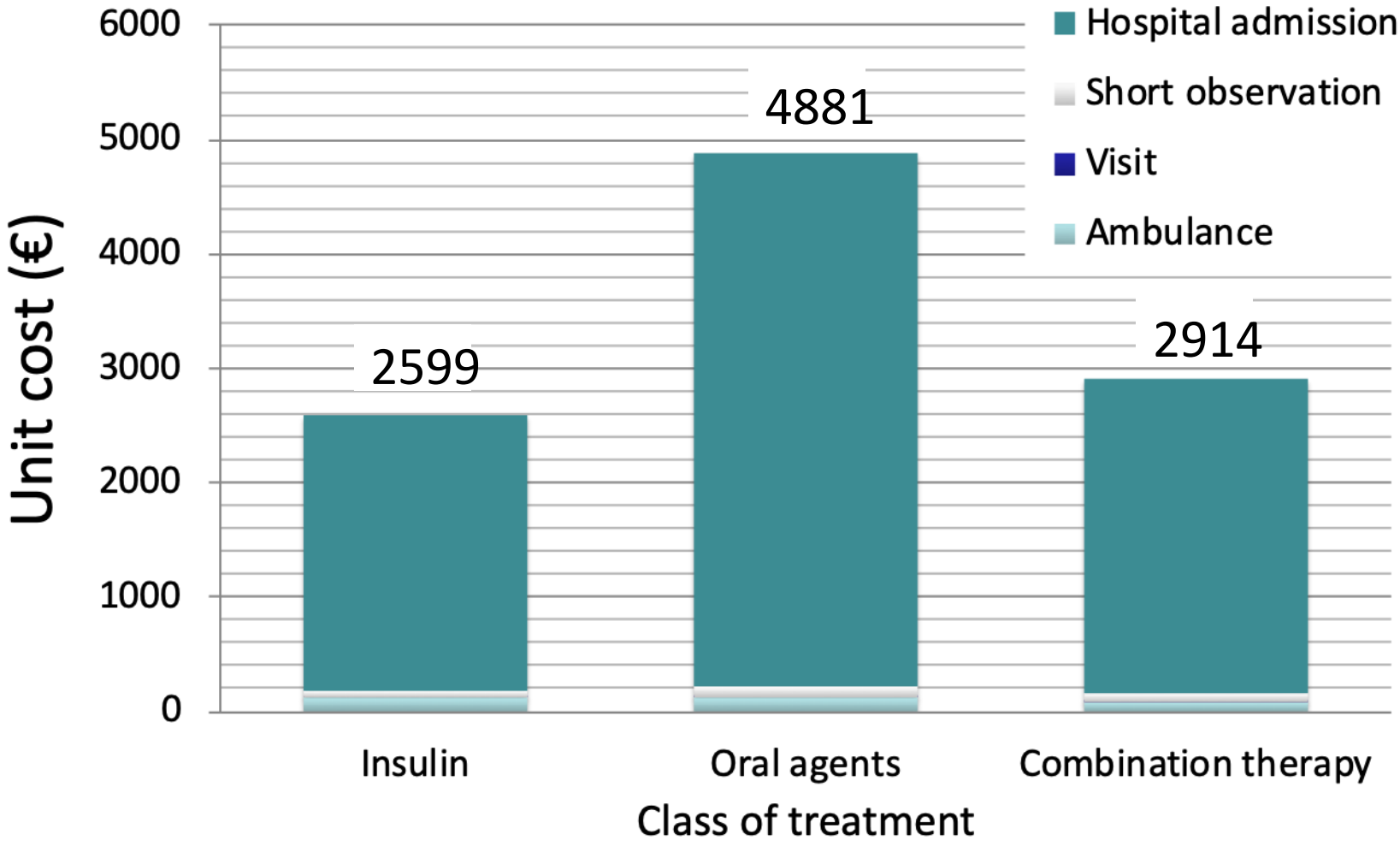
Wei, Front Endocrinol 2019

Table 2 Mean per patient annual healthcare cost (in Euros) by several patient and disease characteristics in a cohort of prevalent cases of diabetes (year 2012).

Variables	N	%	Mean annual costs (SD)			
			Drug	Outpatient	Hospitalizations	Total
Presence of diabetes related conditions and complications						
Hypertension	96 791	74.2	1026 ± 1853	515 ± 2070	1629 ± 4858	3169 ± 6038
Heart disease	21 587	16.5	1350 ± 1988	702 ± 2993	4093 ± 7389	6144 ± 8669
Nephropathy/ESRD	3017	2.3	1948 ± 2288	3212 ± 11 237	9968 ± 10 723	15 128 ± 16 123
Cerebrovascular disease	3196	2.4	1167 ± 1131	661 ± 3413	8347 ± 10 113	10 175 ± 11 049
Amputations	242	0.2	1804 ± 2457	2098 ± 6882	18 831 ± 13 635	22 733 ± 17 011
Lower extremity revascularization	240	0.2	1634 ± 1213	1098 ± 3162	12 781 ± 10 592	15 513 ± 11 814
Retinopathy	1012	0.8	1424 ± 1629	939 ± 2841	4301 ± 7484	6665 ± 8833
Neuropathy	666	0.5	1621 ± 1268	1372 ± 5568	8180 ± 10 033	11 174 ± 12 691
Presence of acute complications						
Hypoglycaemic coma	73	0.1	1658 ± 3300	1305 ± 4576	9040 ± 9929	12 003 ± 12 183
Ketoacidosis	398	0.3	731 ± 1168	650 ± 1891	4655 ± 7871	6036 ± 9123
Other coma	77	0.1	1057 ± 839	452 ± 855	7699 ± 8540	9208 ± 8638
Hyperosmolarity	137	0.1	1285 ± 1331	917 ± 3417	8073 ± 8030	10 275 ± 10 428
Presence of comorbidities						
COPD	11 459	8.8	1575 ± 1673	646 ± 2501	2764 ± 6245	4985 ± 7404
Cancer	5063	3.9	1925 ± 3646	1354 ± 2101	6854 ± 8386	10 132 ± 9940
Depression	19 820	15.2	1252 ± 2016	629 ± 2630	2318 ± 5817	4199 ± 7166
Disease duration						
Incident cases	17 273	13.2	633 ± 1219	495 ± 2138	2023 ± 5545	3151 ± 6613
Prevalent cases	113 229	86.8	925 ± 1745	468 ± 1845	1343 ± 4339	2737 ± 5434

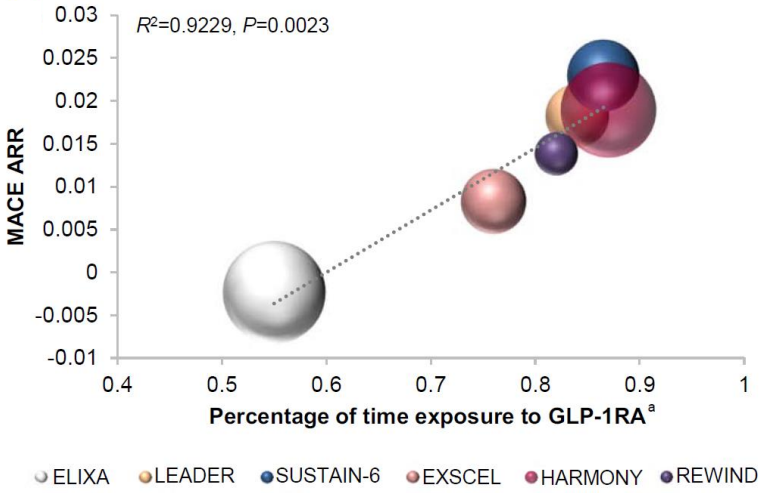
Costs associated with emergency care and hospitalization for severe hypoglycemia

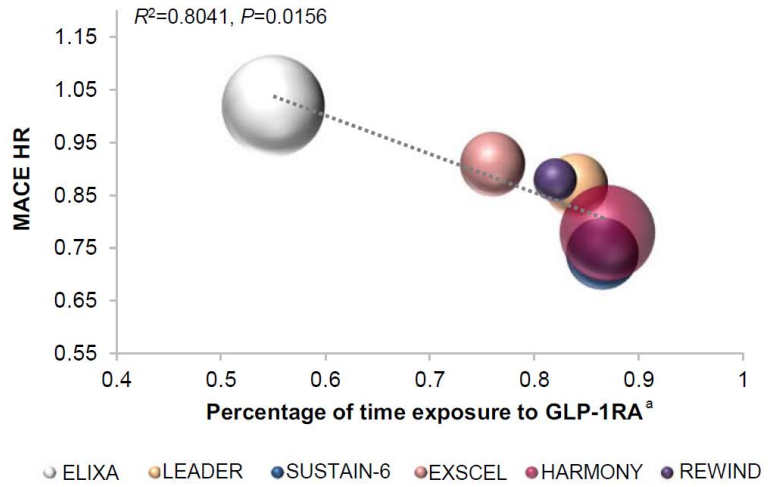
G. Veronese [a,b,*], G. Marchesini [a], G. Forlani [a], S. Saragoni [c], L. Degli Esposti [c], E. Centis [a], A. Fabbri [d], the Italian Society of Emergency Medicine (SIMEU)



Correlation between Percentage of Time Exposure to Study Drug and MACE ARR and HR

- **Time of exposure to the investigational GLP-1 RA is positively correlated with the MACE ARR and, accordingly, negatively correlated with the MACE HR.**
  (Actual exposure to lixisenatide in ELIXA is estimated to be approximately 56%)
- **Baseline CV risk level does not seem to be related to changes in CV outcomes.**
  (Sphere size represents the baseline CV risk of the study population, expressed as MACE incidence rate in the control arm [# events per 100 patient-year])

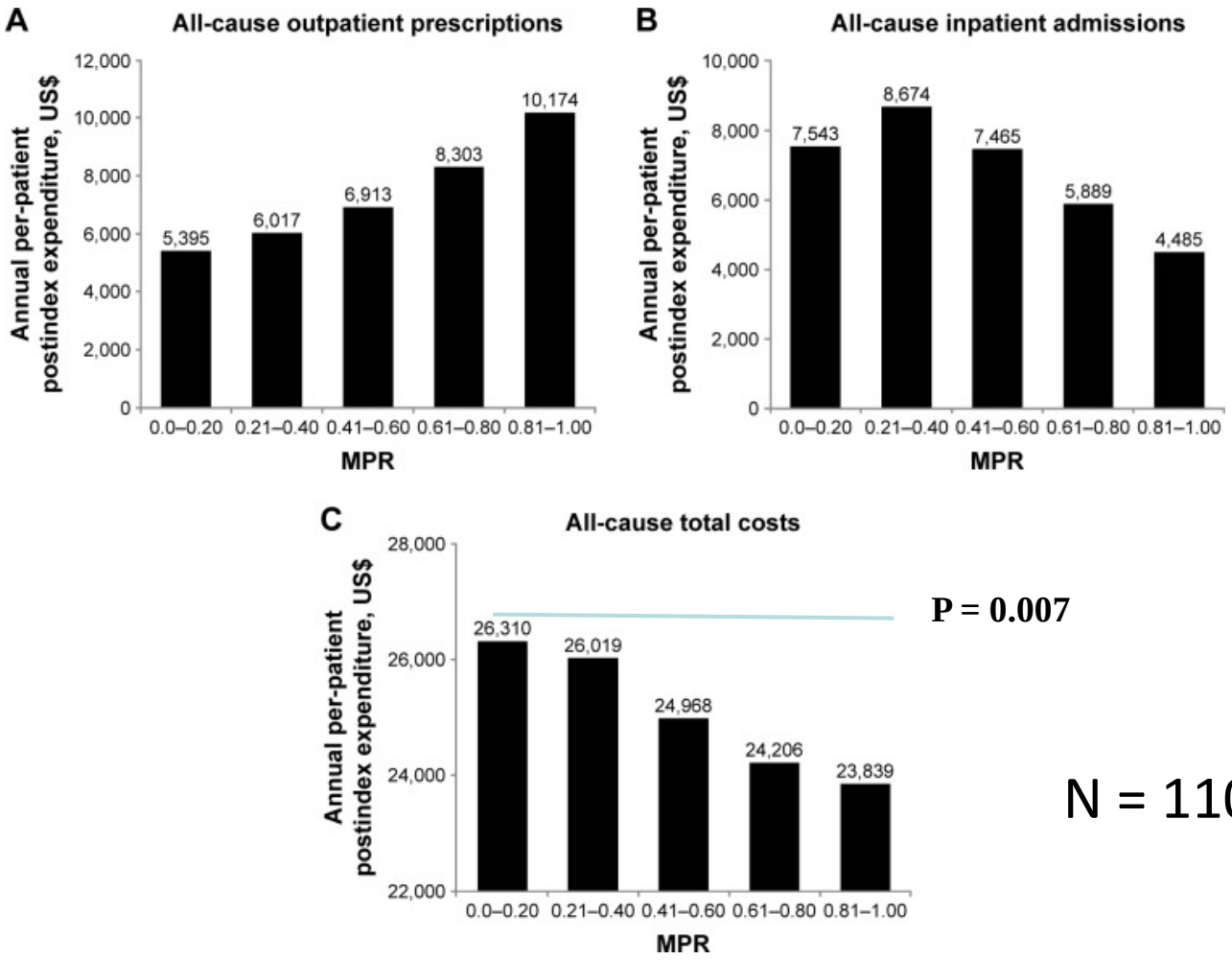




(a) The percentage of time exposure to study drug is expressed as median in ELIXA, HARMONY Outcomes and REWIND, and as mean in LEADER, SUSTAIN–6 and EXSCEL

ARR, absolute risk reduction; CV; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio; MACE, major adverse cardiovascular event.

Correlation between treatment adherence, outcomes and costs in T2DM



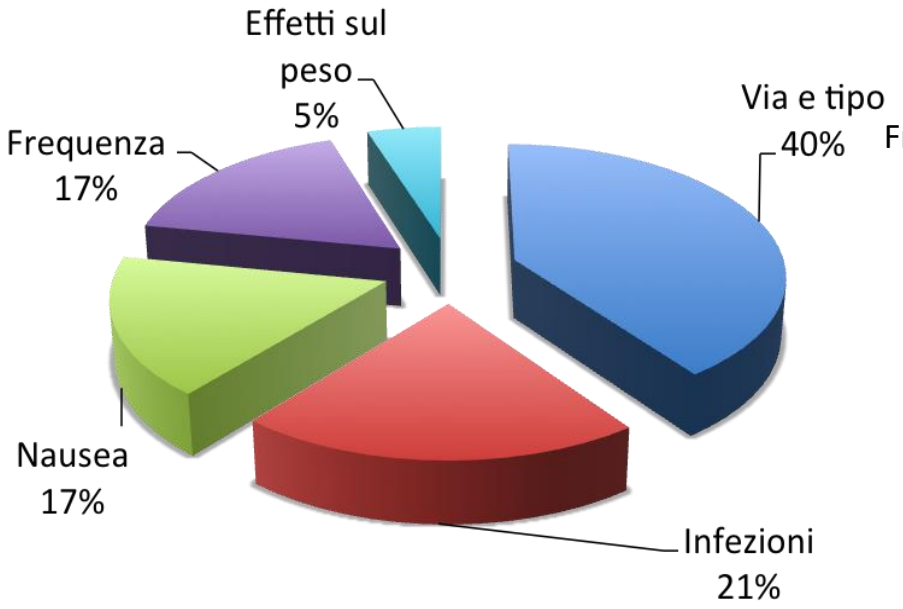
P = 0.007

N = 110 studies

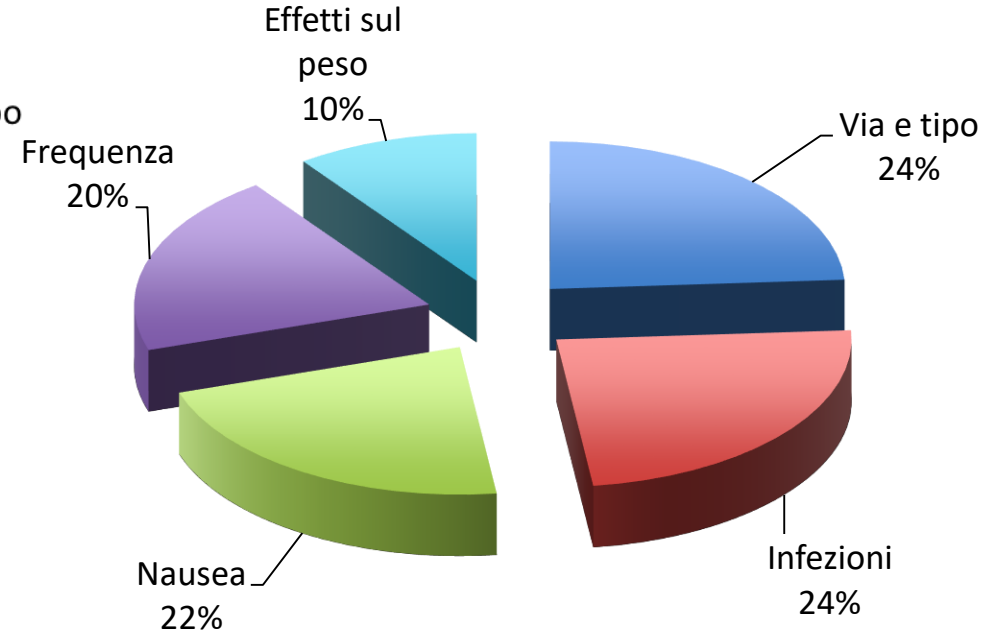
Kennedy-Martin, Patient Prefer Adherence. 2017

Progetto «Imparare dal paziente diabetico»: Importanza relativa delle scelte terapeutiche

Naïve

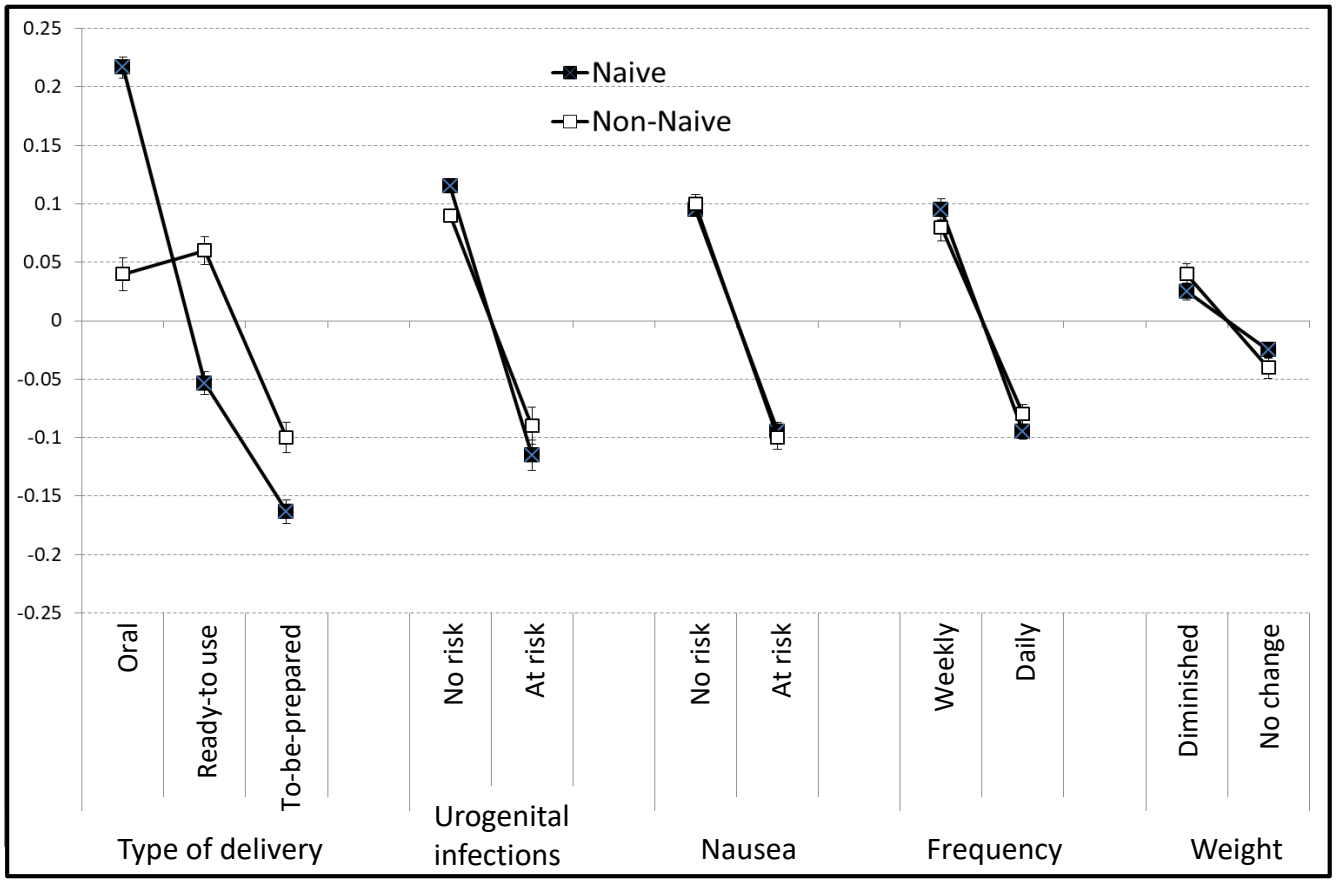


Non-naïve



Marhesini, Acta Diabetologica 2018

Progetto «Imparare dal paziente diabetico»

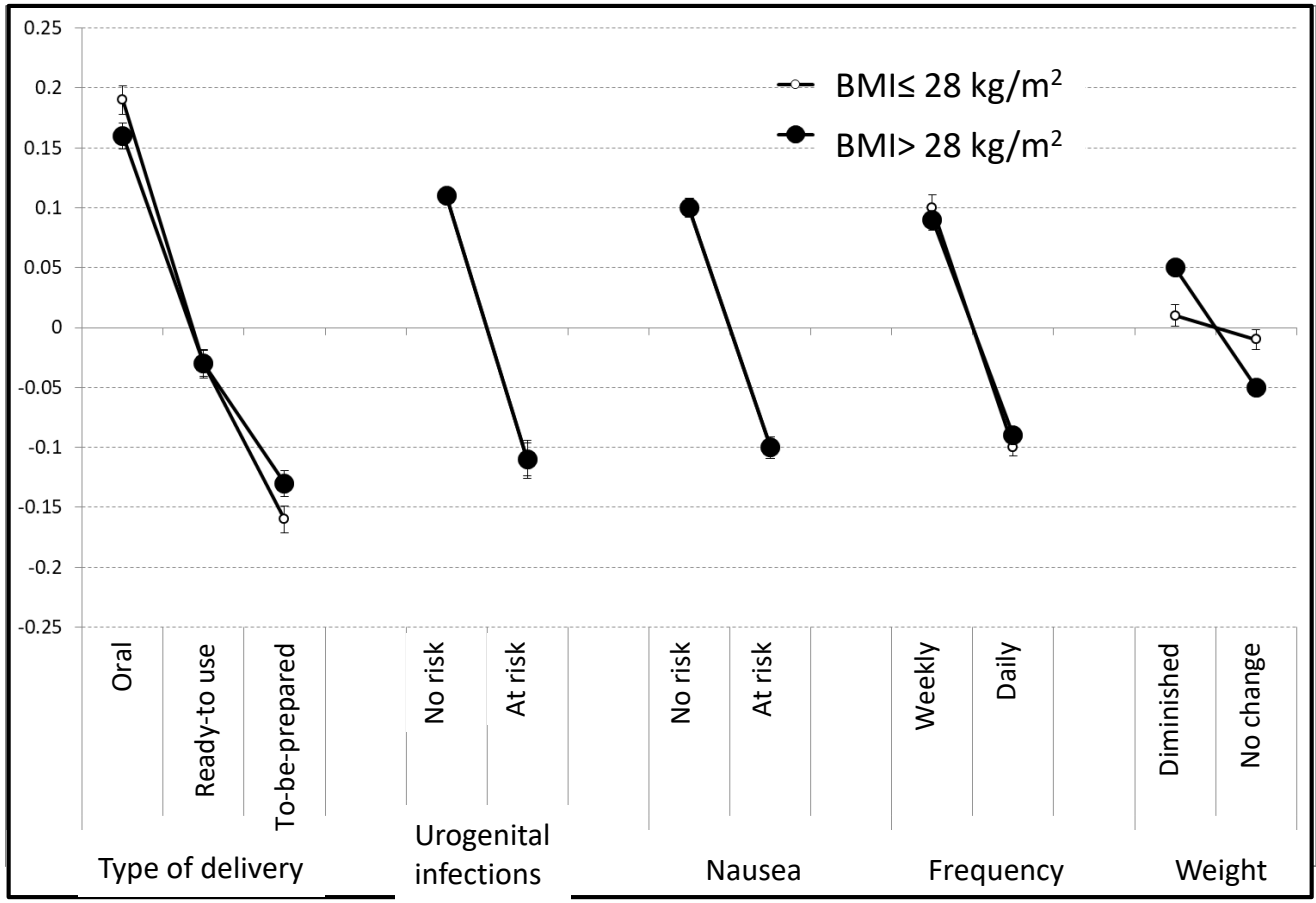


- Nei soggetti naïve si conferma una forte preferenza per la terapia orale;
- Nei non-naïve la terapia iniettiva "pronta e getta" è preferita alla terapia orale.

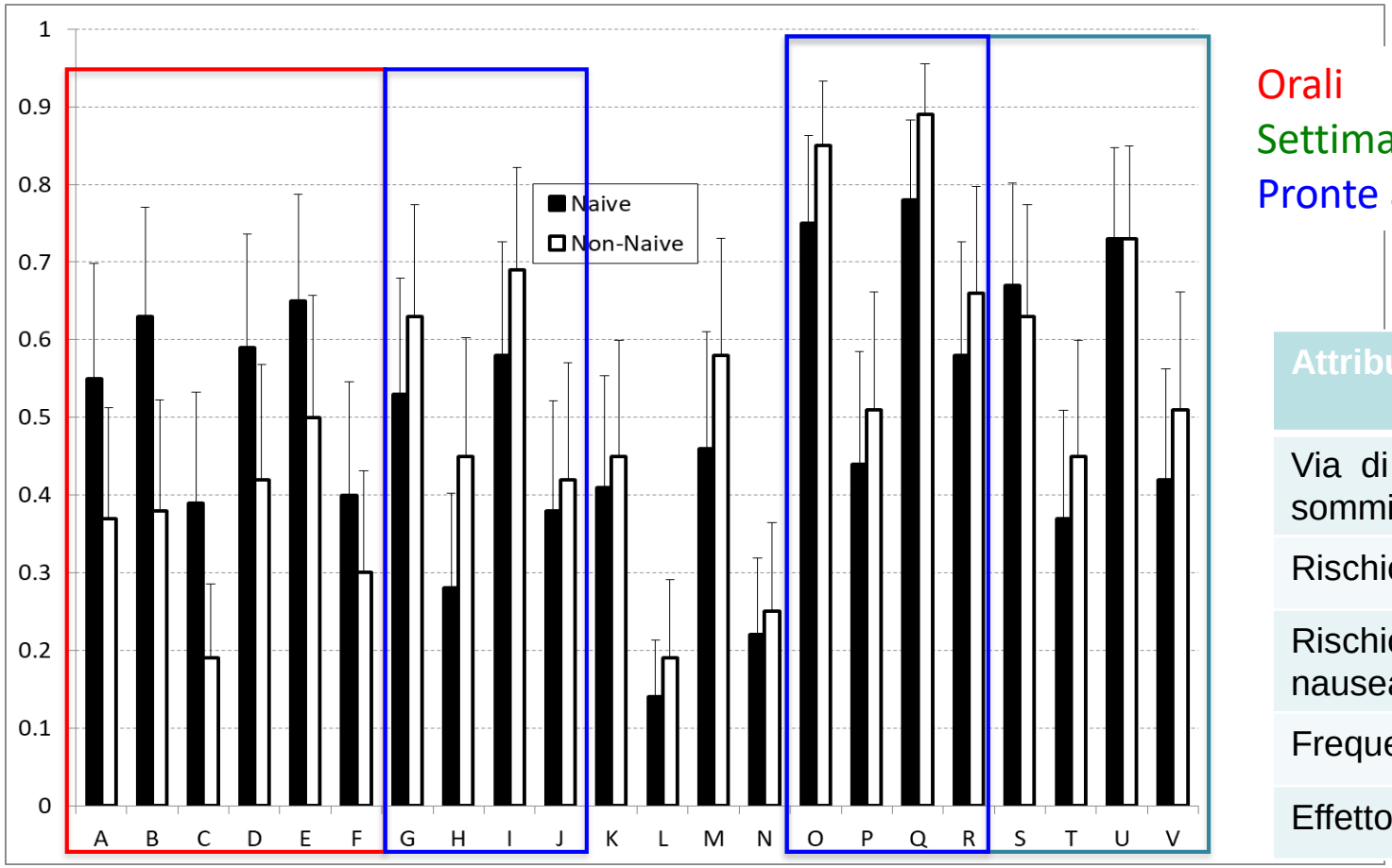
- Il lieve vantaggio per una terapia che aiuti nella perdita di peso nei non-naïve si spiega per il loro maggior BMI

Progetto «Imparare dal paziente diabetico»

- Gli effetti favorevoli sul peso guidano la scelta della terapia solo nella popolazione con BMI elevato, sia usando come cut-off il valore mediano della nostra popolazione (28 kg/m^2), sia considerando il superamento della soglia di obesità (BMI ≥ 30 kg/m^2)



Progetto «Imparare dal paziente diabetico»



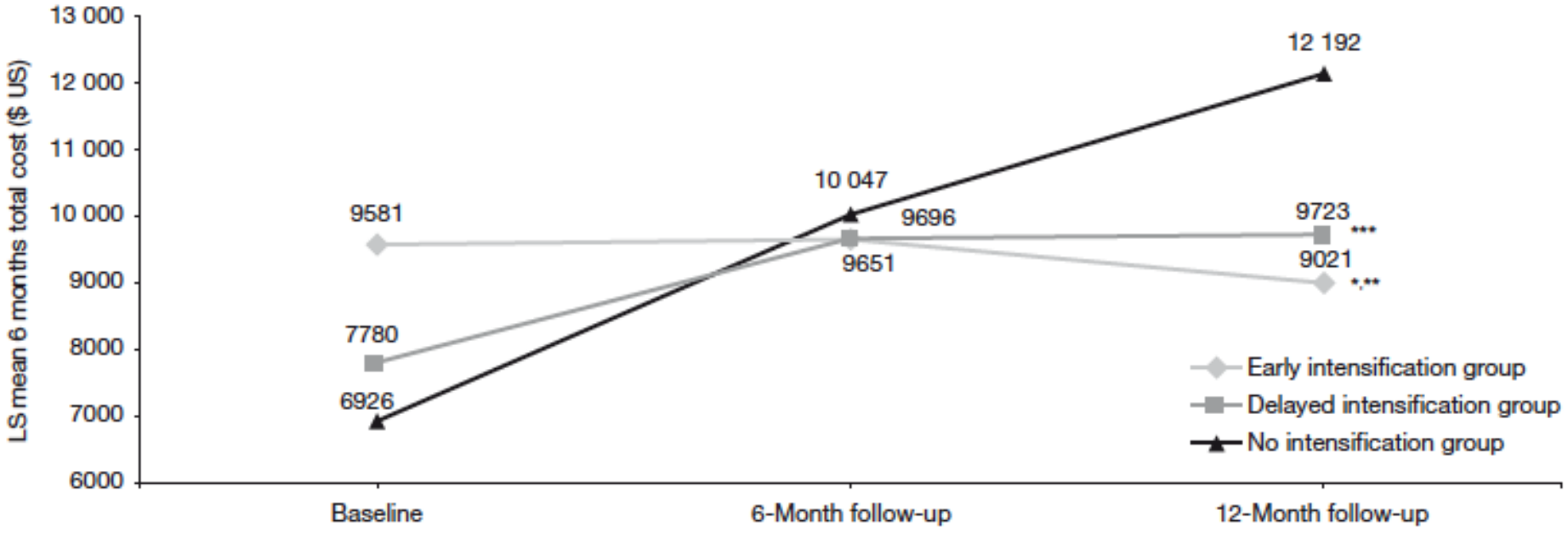
Orali
Settimanali
Pronte all'uso

Attributo	Importanza relativa
Via di somministrazione	34%
Rischio di UTI	22%
Rischio di nausea	20%
Frequenza	19%
Effetto sul peso	6%

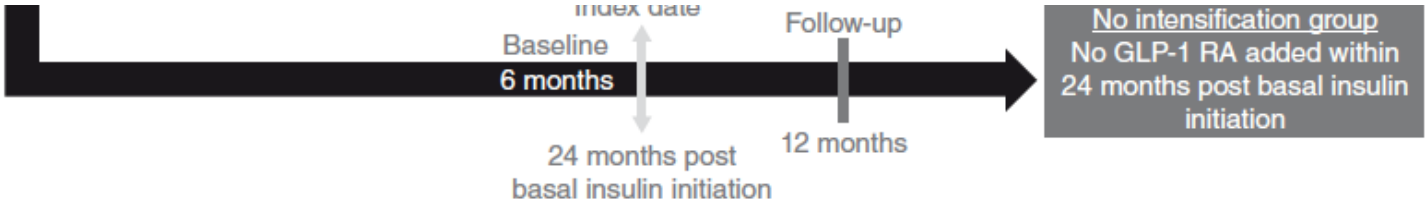
Impact of delaying treatment intensification with a glucagon-like peptide-1 receptor agonist in patients with type 2 diabetes uncontrolled on basal insulin: A longitudinal study of a US administrative claims database

Inclusion criteria:

Baseline:

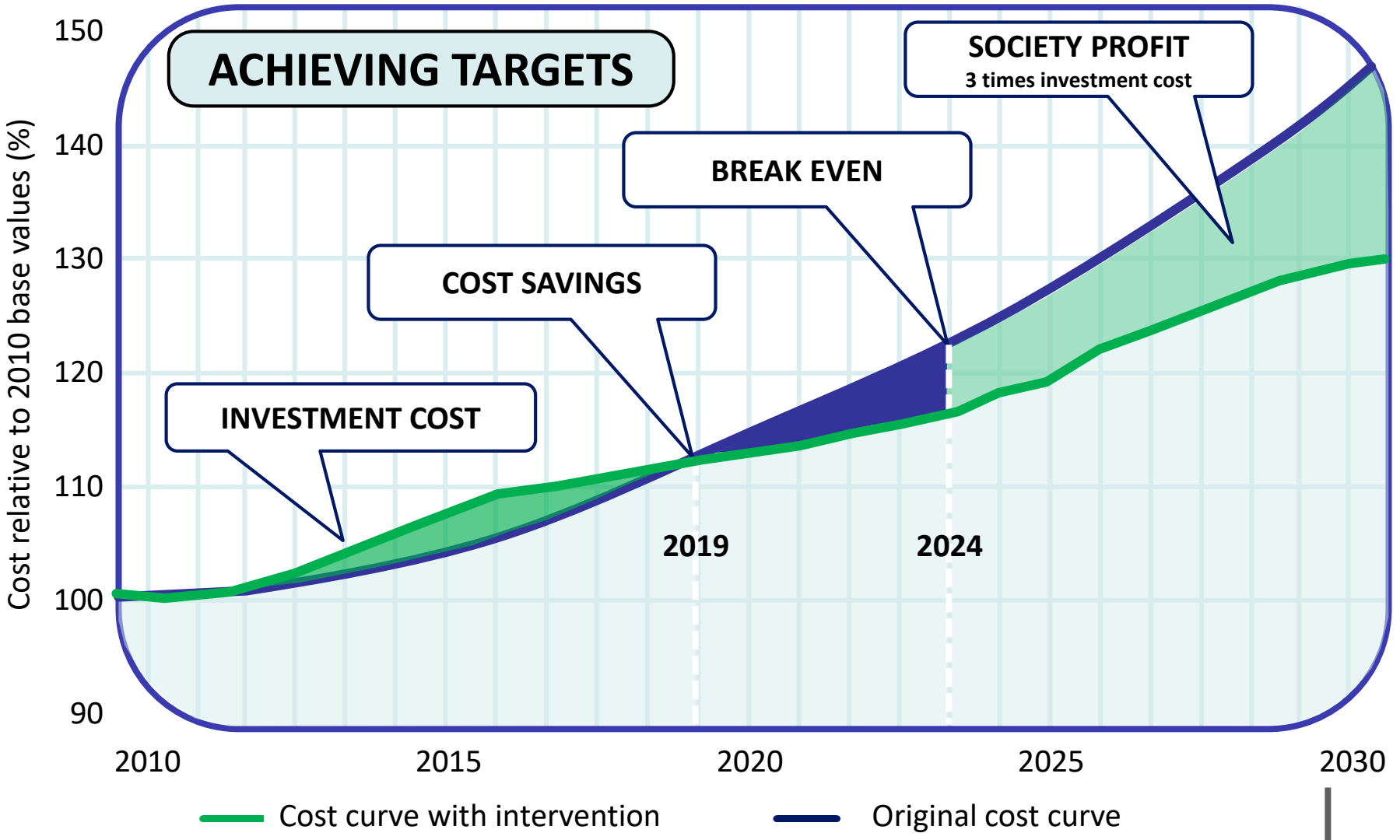


*P = .0557 vs Delayed intensification group; **P < .0001 vs No intensification group; ***P = .001 vs No intensification group.



Tong, DOM 2018

The cost of intensive glucose control: can we afford it?



Simulation from UKPDS and CORE diabetes model