

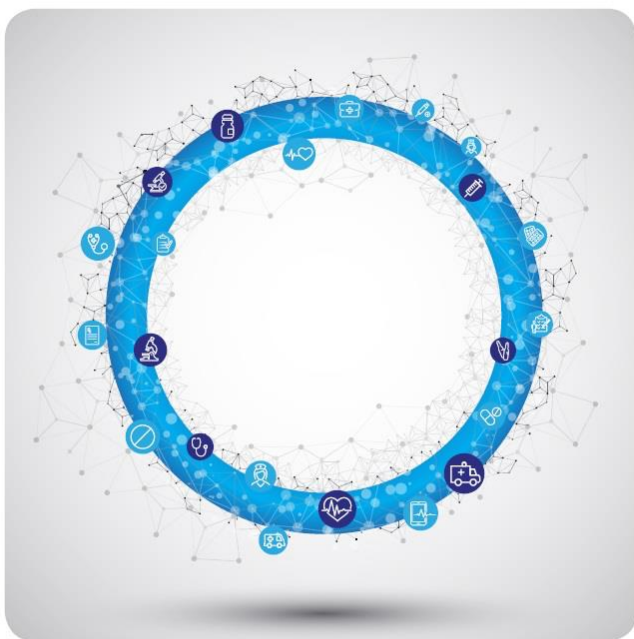
L'innovazione tecnologica (farmaci e device): cosa sta cambiando nel «real world»

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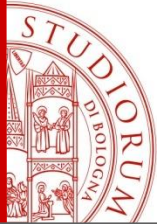
BOLOGNA

SAVOIA HOTEL REGENCY
Via del Pilastro, 2

7 OTTOBRE 2019

HIGHWAY DIABETES
IL PAZIENTE AL CENTRO?

2019 **MOTORE**
SANITÀ
Gestire il Cambiamento

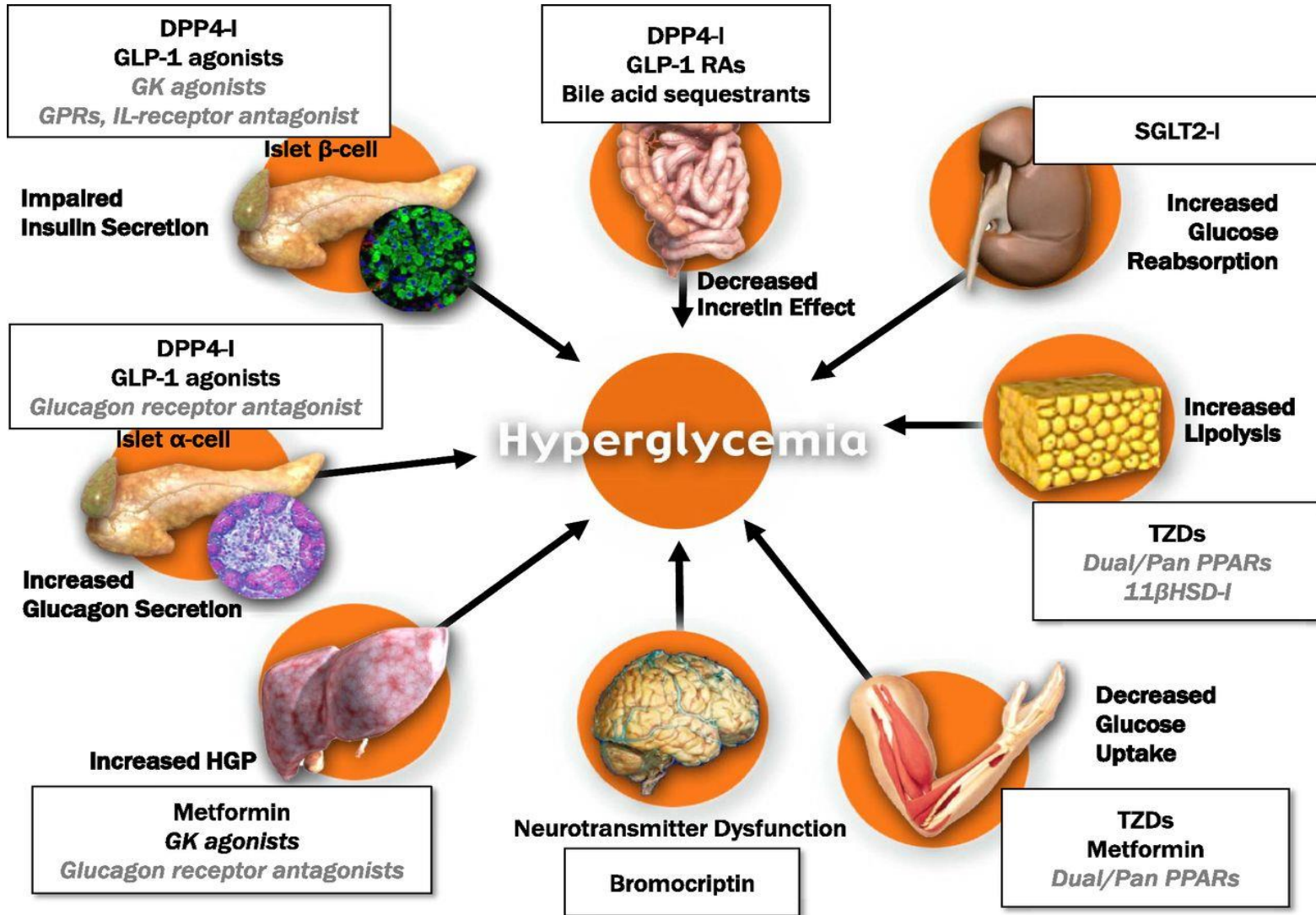


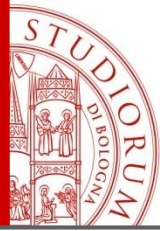
Disclosures

Giulio Marchesini

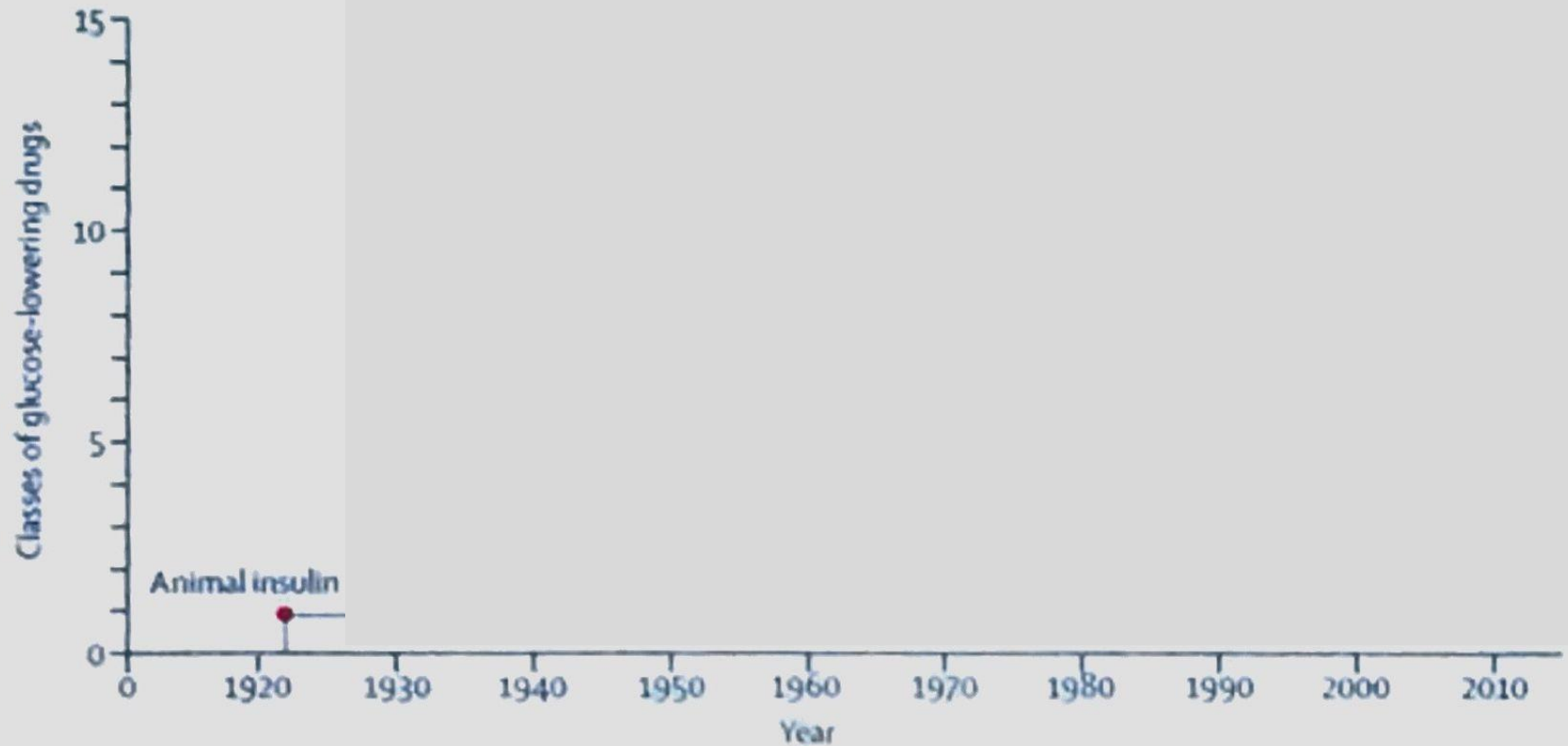
- **Advisory Board:** Eli Lilly, Gilead, Novartis, Intercept
- **Honoraria:** Astra-Zeneca
- **Clinical Studies:** Janssen Cilag, Sanofi, Eli Lilly, Gilead, GENFIT, Glaxo, Intercept,

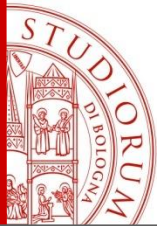
Diabetes treatment - 2018





La scala dei farmaci del diabete





Innovazione terapeutica

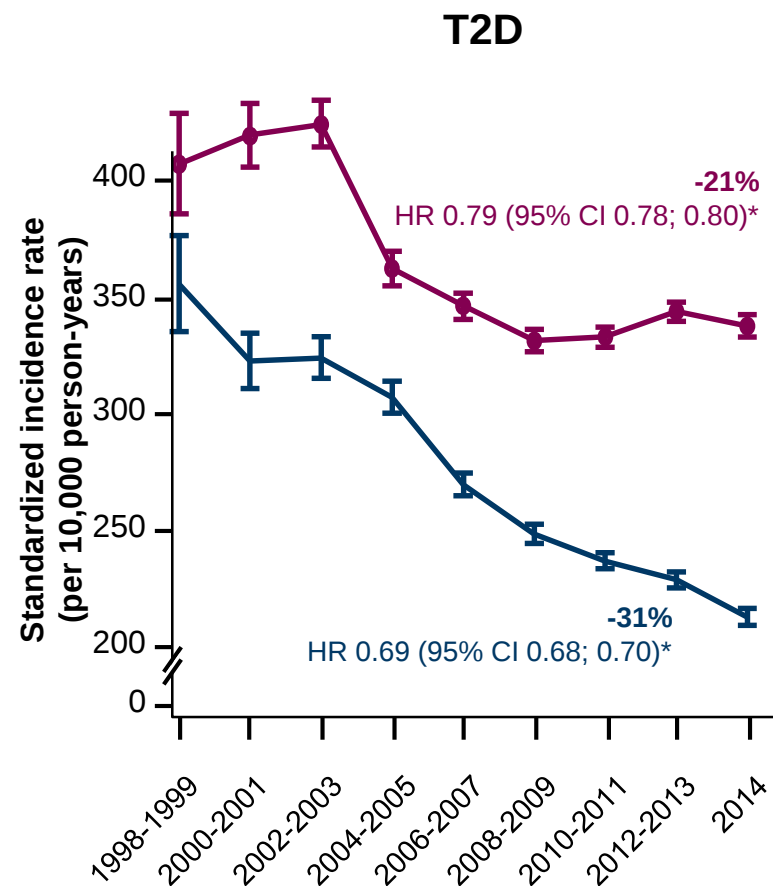
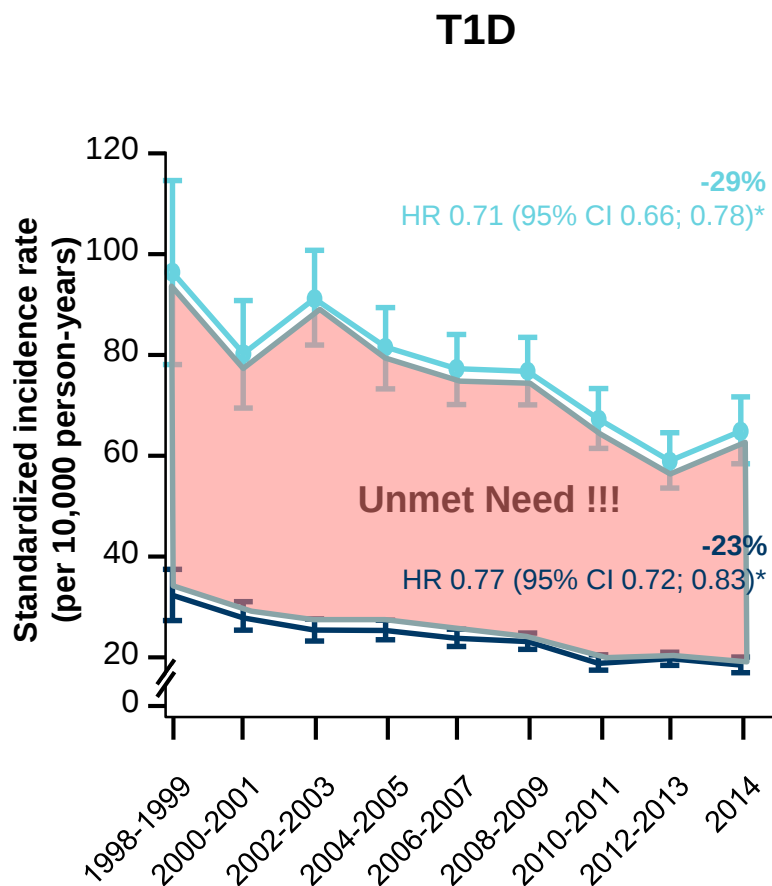
Device

- Continuous 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

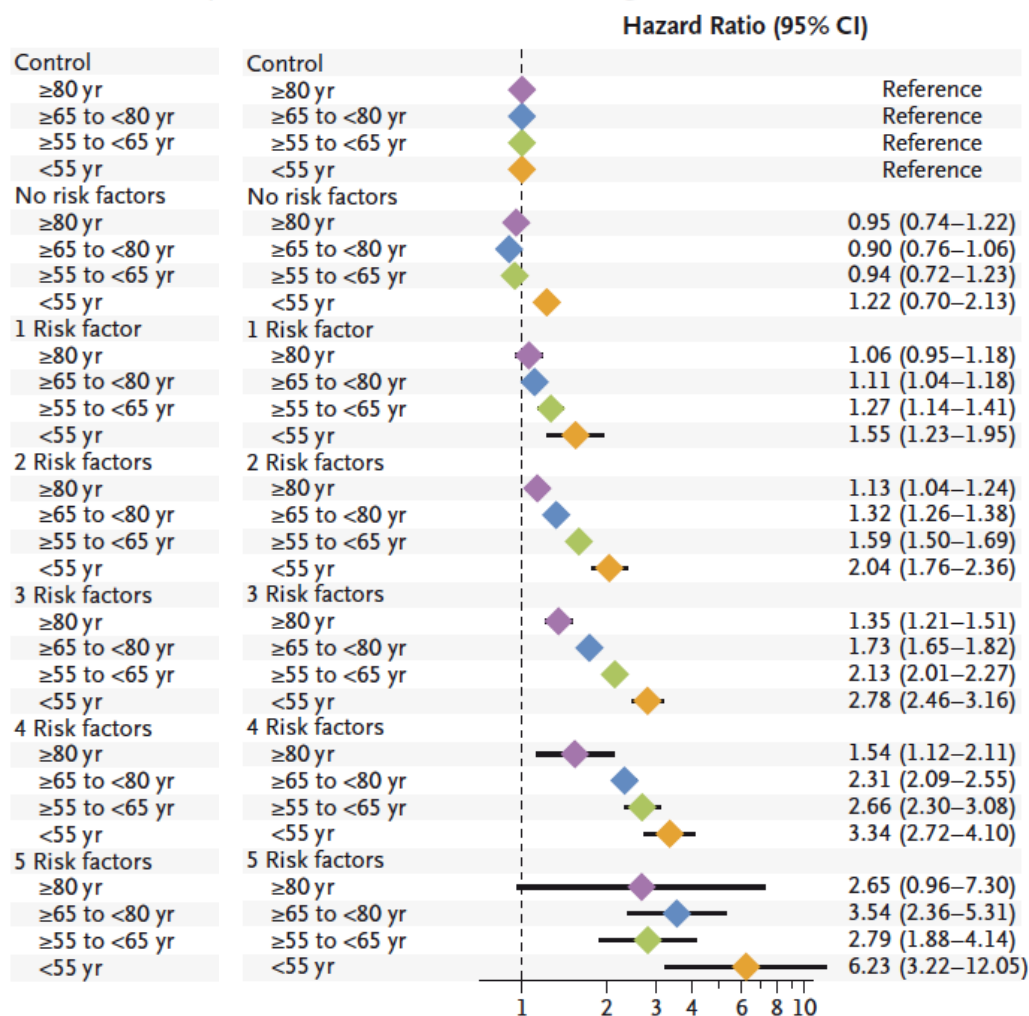
— T1D

— T2D

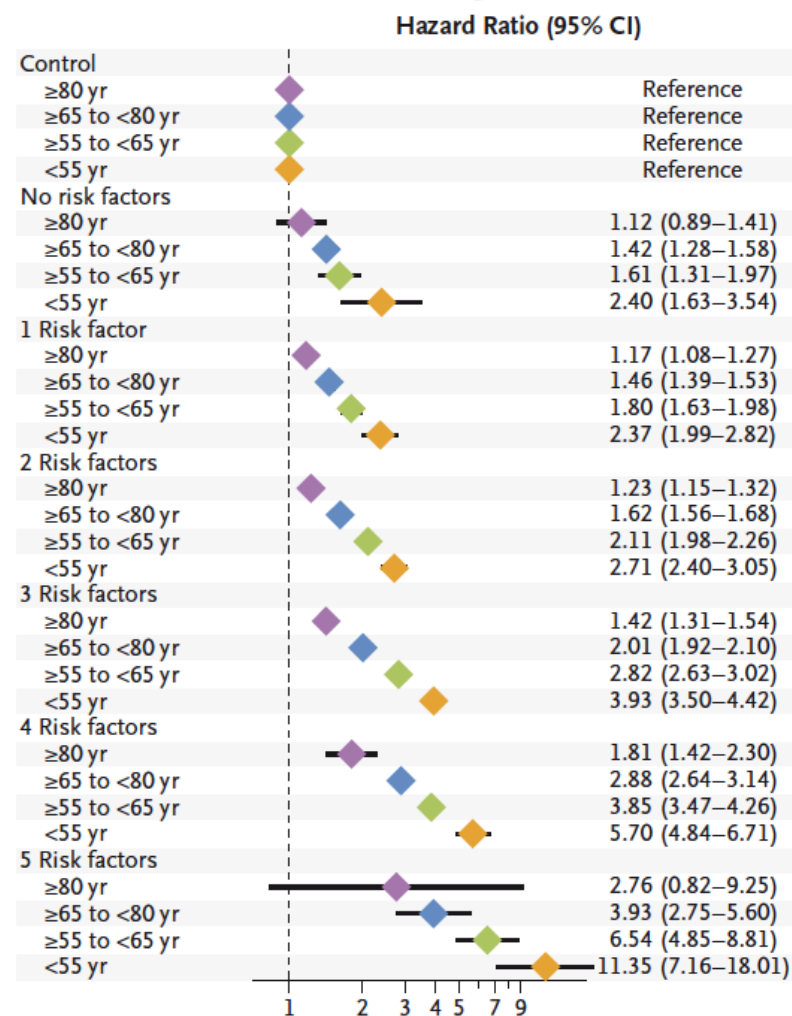
— Matched controls

Mortality risks in T2D

A Excess Mortality C Excess Stroke in Relation to Range of Risk-Factor Control



D Excess Heart Failure in Relation to Range of Risk-Factor Control



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

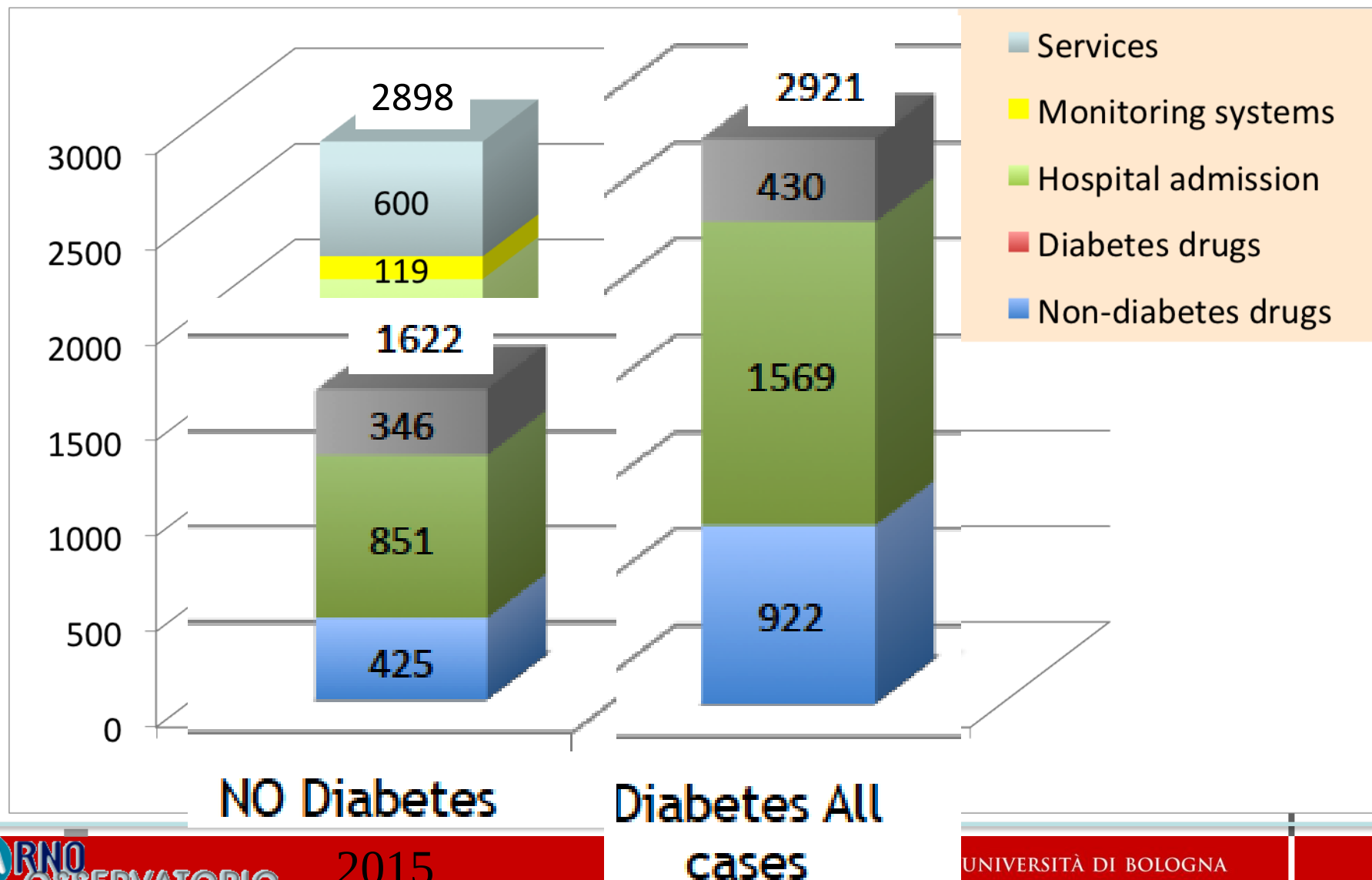
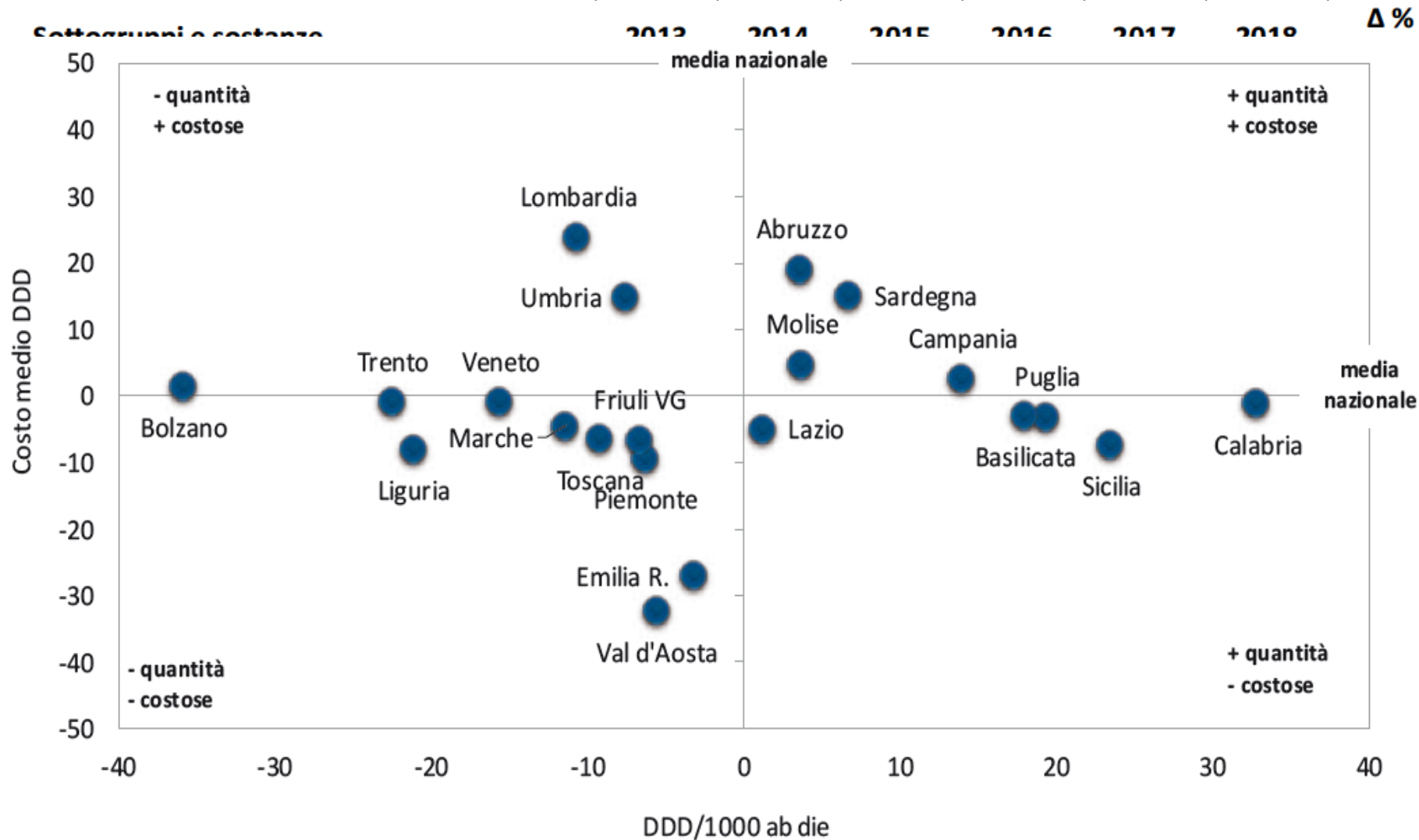


Table 3 Impact of patients demographic and clinical characteristics on annual healthcare costs expressed as cost ratio 95% confidence interval and marginal cost (€) in a cohort of prevalent cases of diabetes (year 2012).

**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

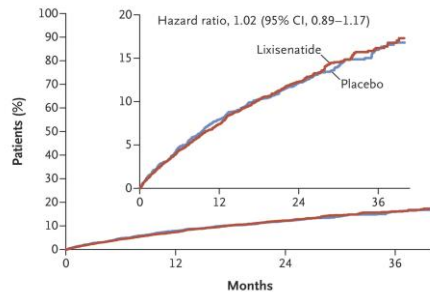


GLP-1RA treatment & CV outcomes (MACE-4)

ELIXA

ORIGINAL ARTICLE

Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome



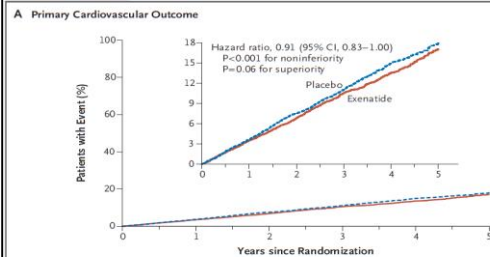
No. at Risk	0	12	24	36
Placebo	3034	2759	1566	476
Lixisenatide	3034	2785	1558	484

EXSCEL

THE NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

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



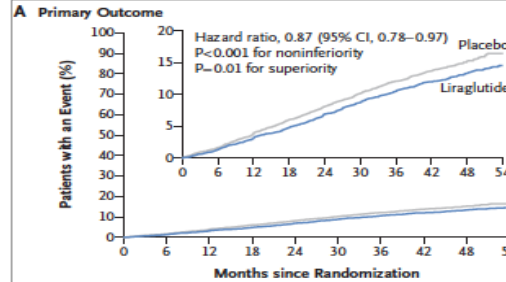
No. at Risk	0	1	2	3	4	5
Placebo	7396	7120	6897	6565	5908	4468
Exenatide	7356	7101	6893	6580	5912	4475

LEADER

THE NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

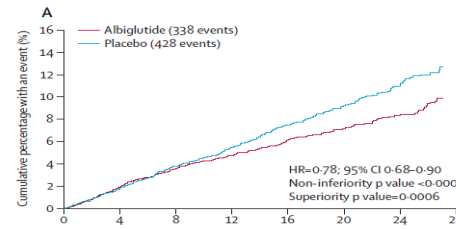


No. at Risk	0	6	12	18	24	30	36	42	48	54
Liraglutide	4668	4593	4496	4400	4280	4172	4072	3982	1562	424
Placebo	4672	4588	4473	4352	4237	4123	4010	3914	1543	407

HARMONY

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

Adrian F Hernandez, Jennifer B Green, Salim Jassam, Ralph B D'Agostino Sr, Christopher B George, Nigel F Jones, Lawrence A Latta, Anne E Rosenberg, Kristina N Sigman, Matthew C Sommadossi, Karl M Thorge, John V Mahoney, Stefano Del Prato, for the Harmony Outcomes committees and investigators*



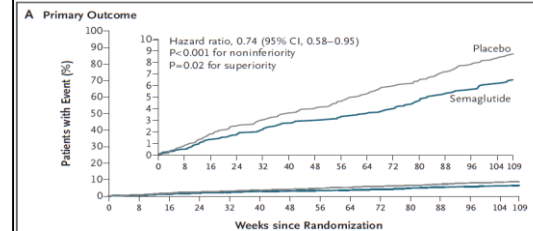
Number at risk	0	4	8	12	16	20	24	28
Albiglutide	4731	4613	4503	4239	3148	2142	1064	..
Placebo	4732	4603	4460	4208	3074	2077	1030	..

SUSTAIN 6

THE NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes



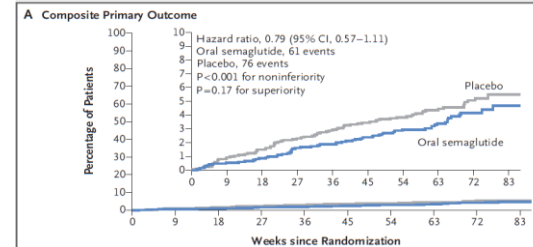
No. at Risk	0	8	16	24	32	40	48	56	64	72	80	88	96	104	109
Placebo	1649	1616	1586	1567	1534	1508	1479	1449	1419	1389	1359	1329	1299	1269	1239
Semaglutide	1648	1619	1601	1584	1568	1543	1524	1499	1479	1459	1439	1419	1399	1379	1359

PIONEER 6

THE NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes



No. at Risk	0	9	18	27	36	45	54	63	72	83
Oral semaglutide	1591	1583	1575	1564	1557	1547	1512	1062	735	16
Placebo	1592	1577	1565	1551	1538	1528	1489	1032	713	11

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

Articles

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 Messian Atisso, Leanne Dyal, Stephanie Hall, Purnima Rao-N Alvaro Avezum, Jan Basile, Namsik Chung, Ignacio Conget, William C Cushman, Edward Franek, Nicolae Hancu, A Petr Jansky, Matyas Koltai, Fernando Lanas, Lawrence A Leiter, Patricia Lopez-Jaramilla, Ernesto German Cardone, Nana Pogossova, 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 $\alpha=0.009$ 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

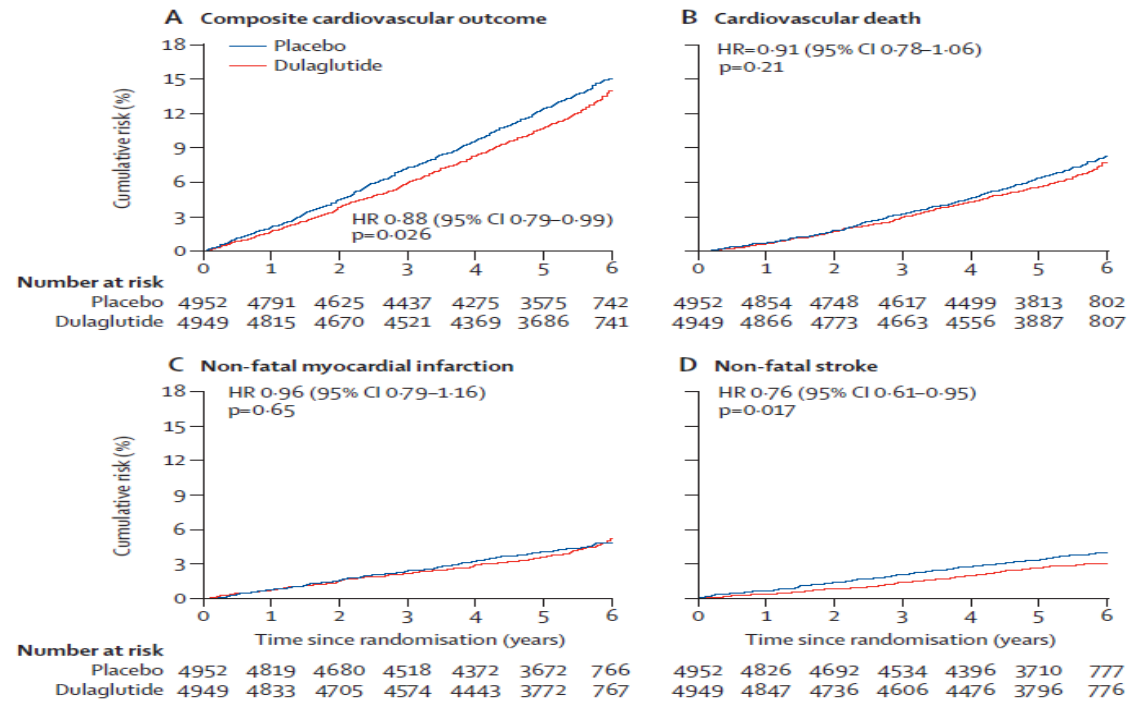
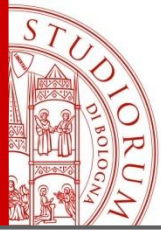


Figure 2: Cumulative incidence of cardiovascular outcomes
HR=hazard ratio. HbA_{1c}=glycated haemoglobin A_{1c}.



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

1: History of CVD

LEADER

SUSTAIN-6

EXSCEL

REWIND

PIONEER 6

Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$

Test of $\theta_i = \theta_j$: $Q(4) = 2.90$, $p = 0.57$

2: No history of CVD

LEADER

SUSTAIN-6

EXSCEL

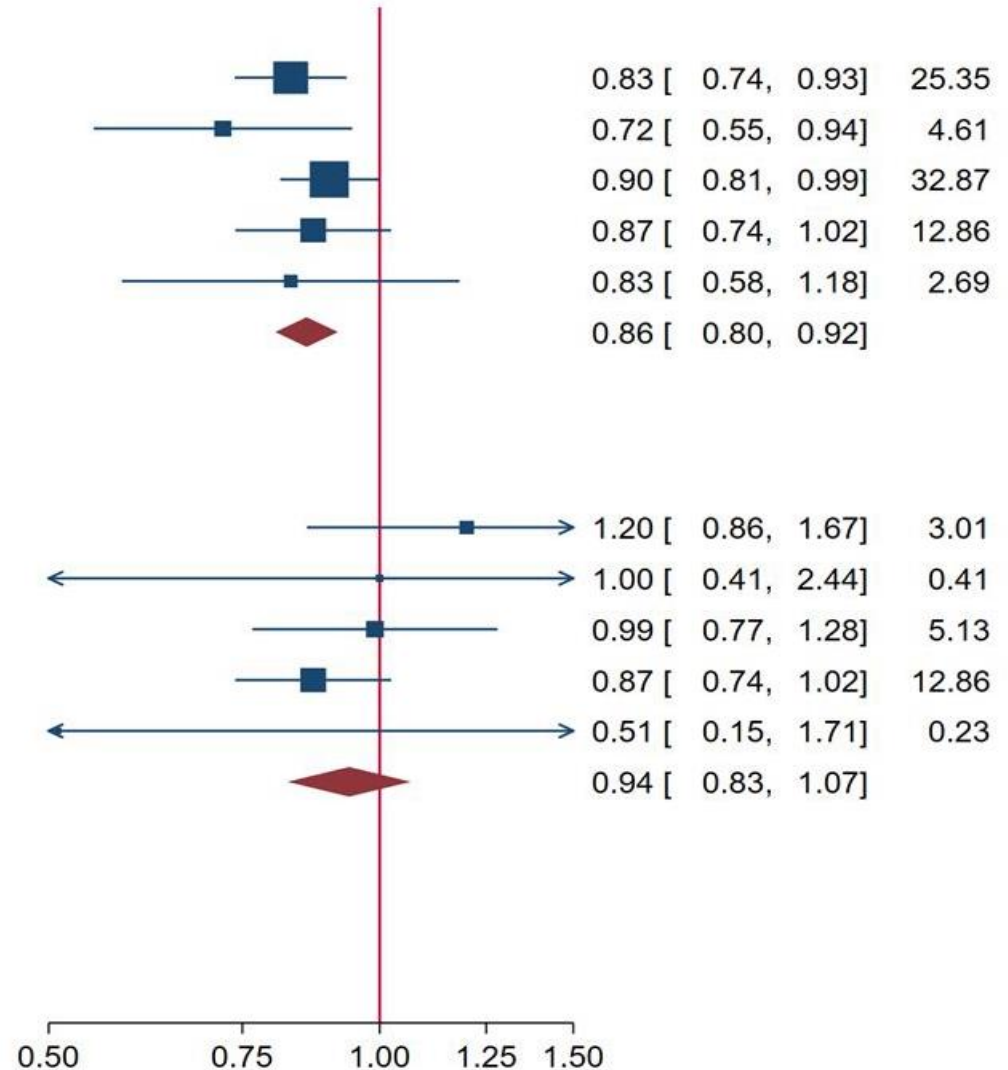
REWIND

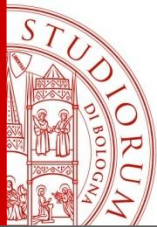
PIONEER 6

Heterogeneity: $\tau^2 = 0.00$, $I^2 = 2.32\%$, $H^2 = 1.02$

Test of $\theta_i = \theta_j$: $Q(4) = 4.13$, $p = 0.39$

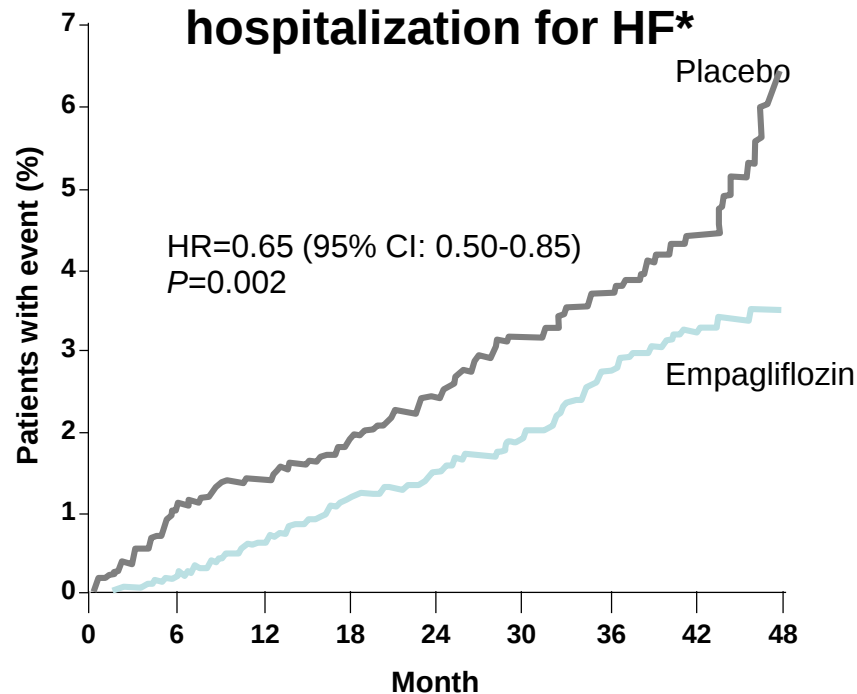
Test of group differences: $Q_b(1) = 1.47$, $p = 0.22$



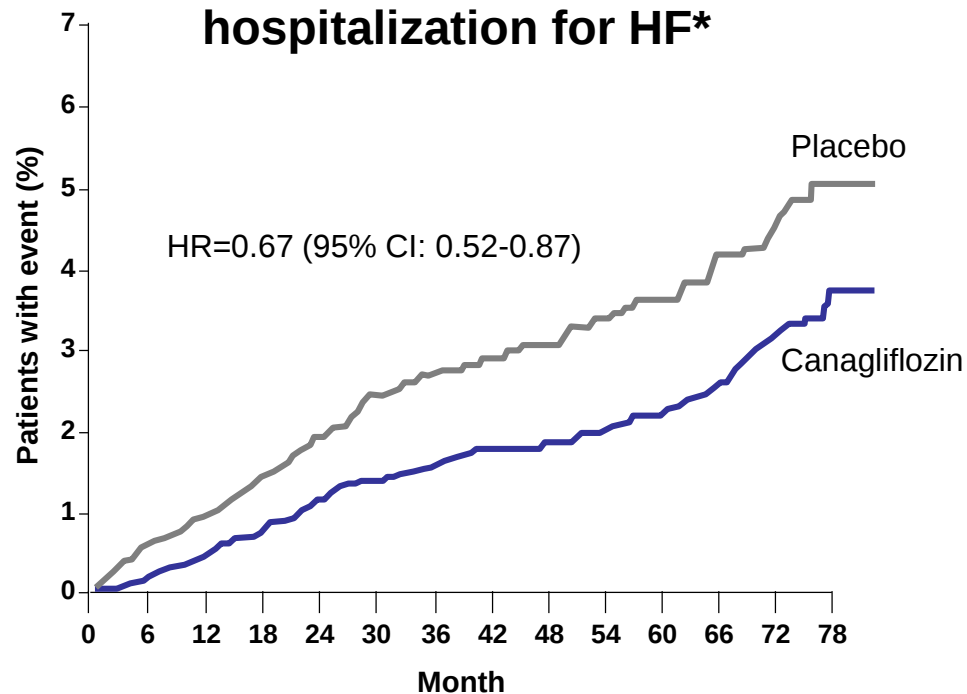


HF prevention in trials examining SGLT2 inhibitor use in T2D

EMPA-REG OUTCOME¹
hospitalization for HF*



CANVAS²
hospitalization for HF*

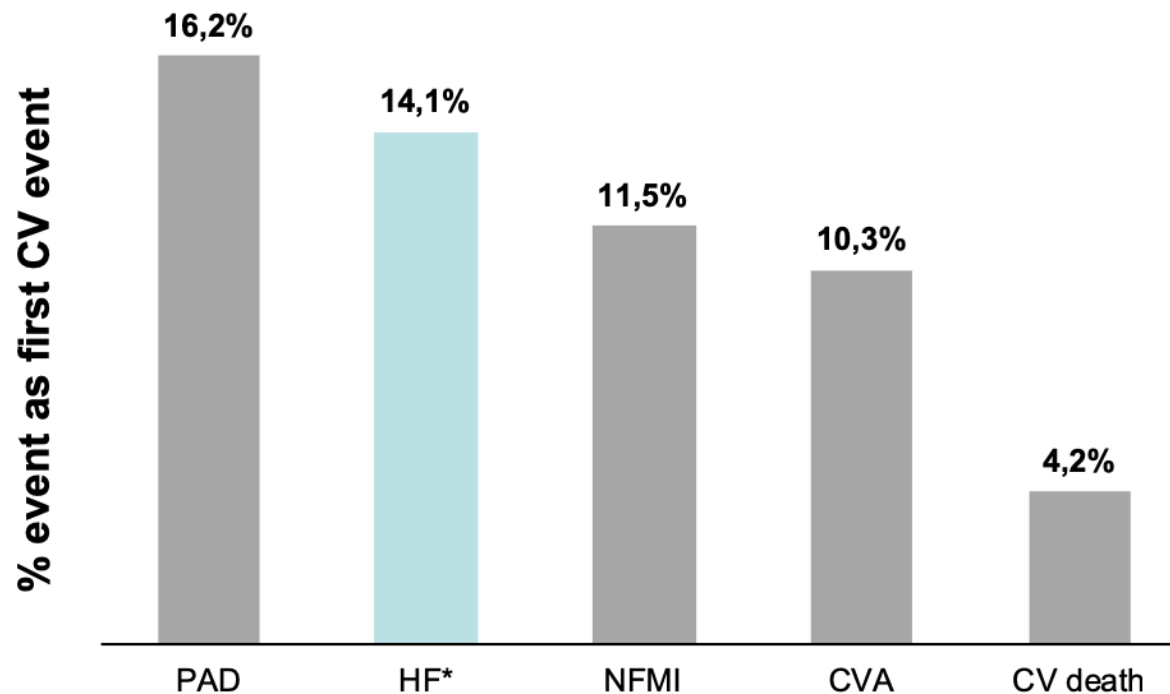


*hHF is an exploratory end point in both studies.

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

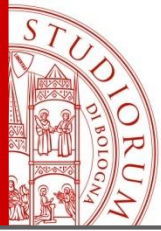
Cohort study of patients (n=1.9 million) with T2D and incidence of CV disease



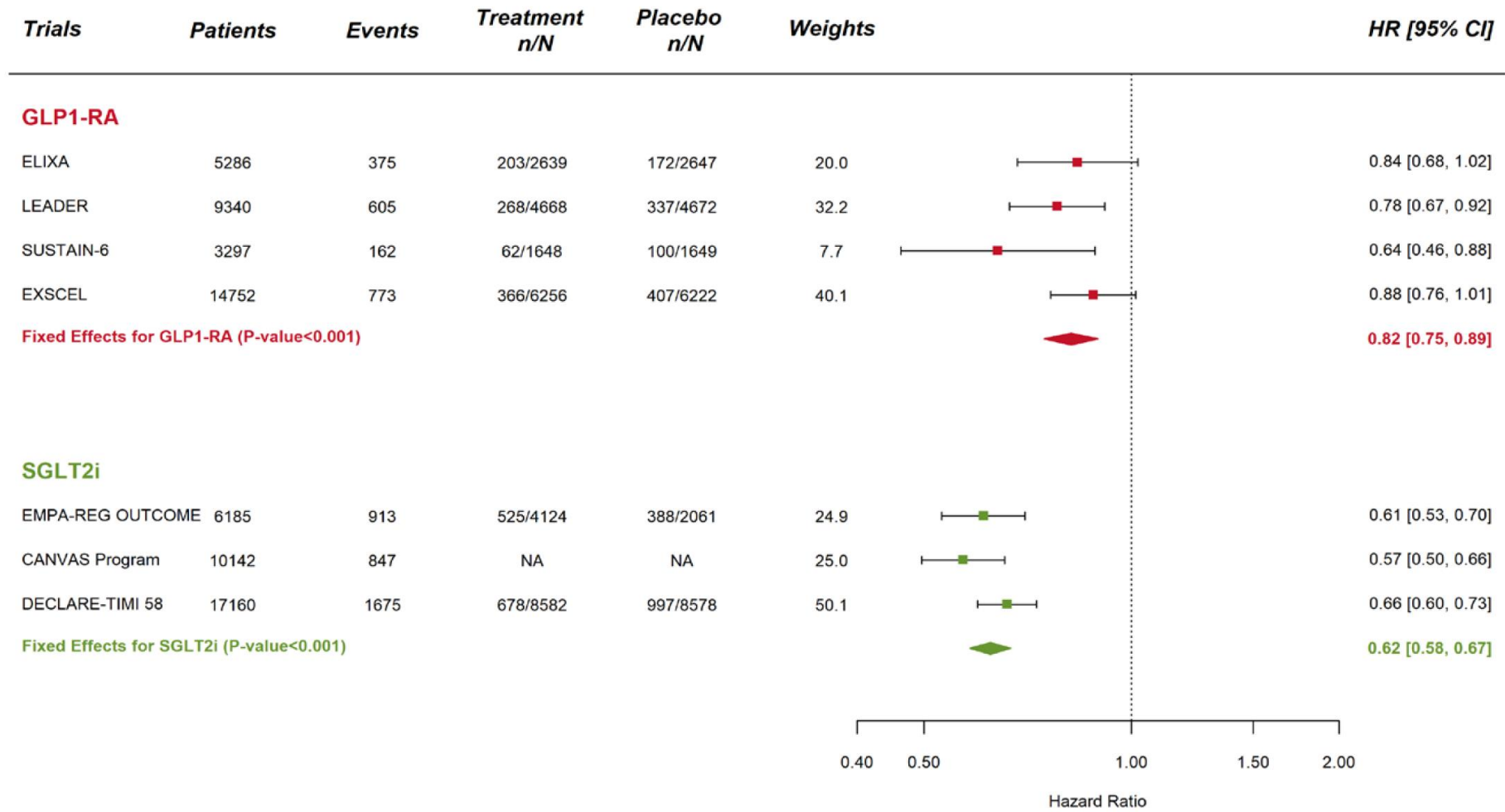
*Heart failure post MI was not included in this definition of HF

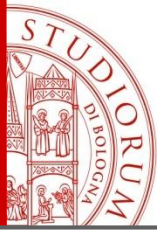
- CV, cardiovascular; CVA, cerebrovascular accident; HF, heart failure; NFMI, nonfatal myocardial infarction; PAD, peripheral arterial disease; T2D, type 2 diabetes.

- 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.



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





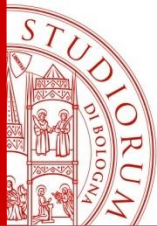
Il problema “renale” nel diabete

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).



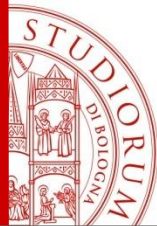
Il problema “renale” come equivalente cardiovascolare

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
	<i>adjusted hazard ratio (95 percent confidence interval)</i>		
≥60 ml/min/1.73 m ² †	1.00	1.00	1.00
45–59 ml/min/1.73 m ²	1.2 (1.1–1.2)	1.4 (1.4–1.5)	1.1 (1.1–1.1)
30–44 ml/min/1.73 m ²	1.8 (1.7–1.9)	2.0 (1.9–2.1)	1.5 (1.5–1.5)
15–29 ml/min/1.73 m ²	3.2 (3.1–3.4)	2.8 (2.6–2.9)	2.1 (2.0–2.2)
<15 ml/min/1.73 m ²	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.

Standard italiani per la cura del diabete mellito 2018



DIAGNOSI

Iperglicemia

Metformina

Insulina

Metformina +

DPP4i

Pio

SGLT2i

GLP1RA

Metformina +

DPP4i

AGI

Pio

SGLT2i

SU

Pio

AGI

DPP4i

SGLT2i

GLP1RA

SU

SGLT2i

AGI

DPP4i

Pio

GLP1RA

SU

GLP1RA

AGI

DPP4i

Pio

SU

Metformina

DPP4i

Pio

SGLT2i

GLP1RA

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)

CHOOSING GLUCOSE-LOWERING MEDICATION IF COMPELLING NEED TO MINIMIZE RISK OF ASCVD OR CHD

Use principles

Use metformin unless contraindicated or not tolerated

If not at HbA_{1c} target:

- Continue metformin unless contraindicated (remember to add SGLT2i or GLP-1 RA with proven cardiovascular benefit)

If at HbA_{1c} target:

- If already on dual therapy, or multiple glucose-lowering agents with proven cardiovascular benefit¹ (see below) OR reconsider/lower individualized target and introduce SGLT2i OR reassess HbA_{1c} at 3-month intervals and add SGLT2i or GLP-1 RA

ASCVD predominates

GLP-1 RA with proven CVD benefit¹ OR SGLT2i with proven CVD benefit¹, if eGFR adequate²

If HbA_{1c} above target

If further intensification is required or patient is unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV safety:

- Consider adding the other class (GLP-1 RA or SGLT2i) with proven CVD benefit¹
- DPP-4i if not on GLP-1 RA
- Basal insulin³
- TZD⁴
- SU⁵

- Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.
- Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
- Both empagliflozin and canagliflozin have shown reduction in HF and in CV mortality in CVOTs

CHOOSING GLUCOSE-LOWERING MEDICATION IF COMPELLING NEED TO MINIMIZE RISK OF WEIGHT GAIN OR PROMOTE WEIGHT LOSS

In those WITHOUT established ASCVD OR CKD

Use principles in Figure 1

First-line therapy is metformin

If HbA_{1c} is ≥17 mmol/mol (1.5%) above individualized HbA_{1c} target consider early combination therapy

If HbA_{1c} above target

GLP-1 RA with good efficacy for weight loss¹ OR SGLT2i if eGFR adequate²

If HbA_{1c} above target

SGLT2i if eGFR adequate² OR GLP-1 RA with good efficacy for weight loss¹

If HbA_{1c} above target

If triple therapy required or SGLT2i and/or GLP-1 RA not tolerated or contraindicated use regimen with lowest risk of weight gain

PREFERABLY

DPP-4i (if not on GLP-1 RA) based on weight neutrality

If DPP-4i not tolerated or contraindicated or patient already on GLP-1 RA, cautious addition of:

- SU⁵ • TZD⁴ • Basal insulin

- Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
- Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
- Choose later generation SU with lower risk of hypoglycemia
- Low dose may be better tolerated though less well studied for CVD effects

CHOOSING GLUCOSE-LOWERING MEDICATION IF COMPELLING NEED TO MINIMIZE RISK OF HYPOTENSION

In those WITHOUT established ASCVD OR CKD

Use principles in Figure 1

First-line therapy is metformin

If HbA_{1c} is ≥17 mmol/mol (1.5%) above individualized HbA_{1c} target consider early combination therapy

If HbA_{1c} above target

DPP-4i

GLP-1 RA

If HbA_{1c} above target

If HbA_{1c} above target

SGLT2i¹ or TZD²

SGLT2i¹ or TZD²

If HbA_{1c} above target

If HbA_{1c} above target

Continue with addition of other agent

Continue with addition of other agent

If HbA_{1c} above target

If HbA_{1c} above target

Consider the addition of sulfonylurea OR basal insulin

- Choose later generation SU with lower risk of hypoglycemia
- Consider basal insulin with lower risk of hypoglycemia

- Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
- Low dose TZDs are better tolerated
- Degludec / glargine U300 > glargine U100 / detemir > NPH insulin

CHOOSING GLUCOSE-LOWERING MEDICATION IF COST IS A MAJOR ISSUE



In those WITHOUT established ASCVD OR CKD

Use principles in Figure 1

First-line therapy is metformin

If HbA_{1c} is ≥17 mmol/mol (1.5%) above individualized HbA_{1c} target consider early combination therapy

If HbA_{1c} above target

SU¹

TZD^{2,3}

If HbA_{1c} above target

TZD^{2,3}

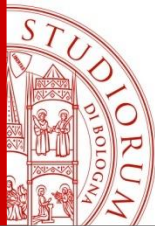
SU¹

If HbA_{1c} above target

- Insulin therapy: Basal insulin with lowest acquisition cost OR
- Consider DPP-4i or SGLT2i with lowest acquisition cost

Consider additional DSMES to support weight loss/maintenance and avoidance of hypoglycemia

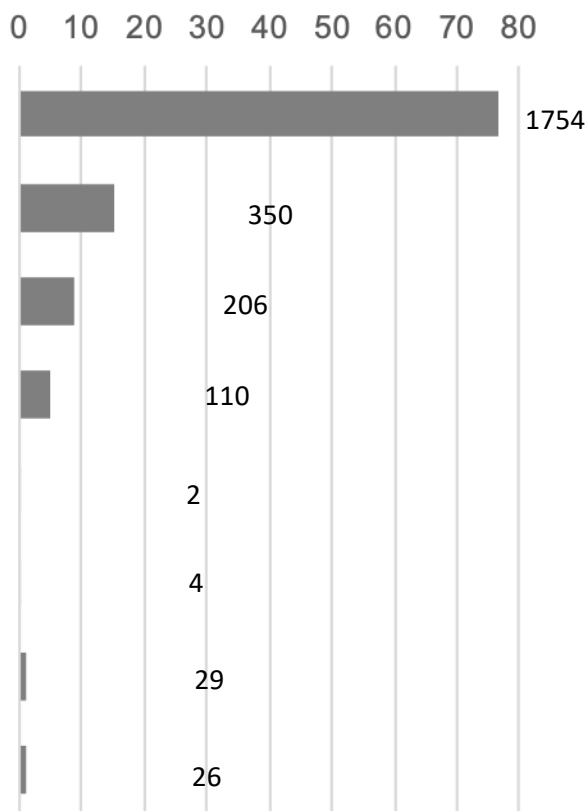
TO AVOID CLINICAL INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3-4 MONTHS)



HYPOTHESIS: Drug treatment

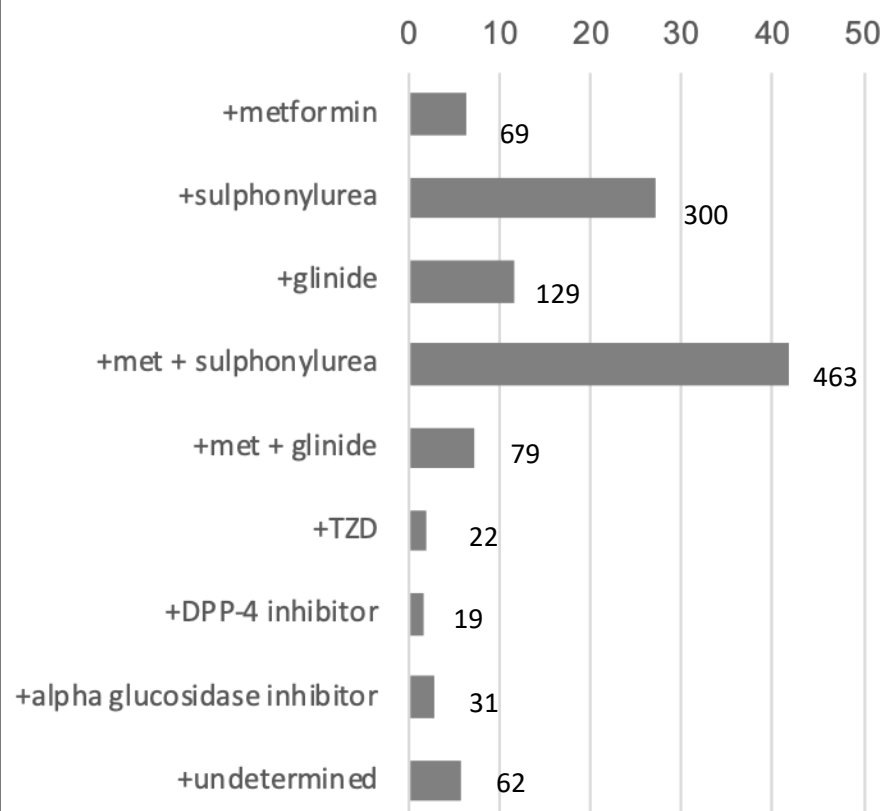
Insulin cases

Cases with hypoglycaemia (%)

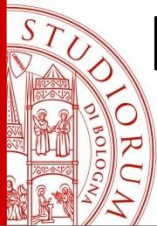


Oral agents

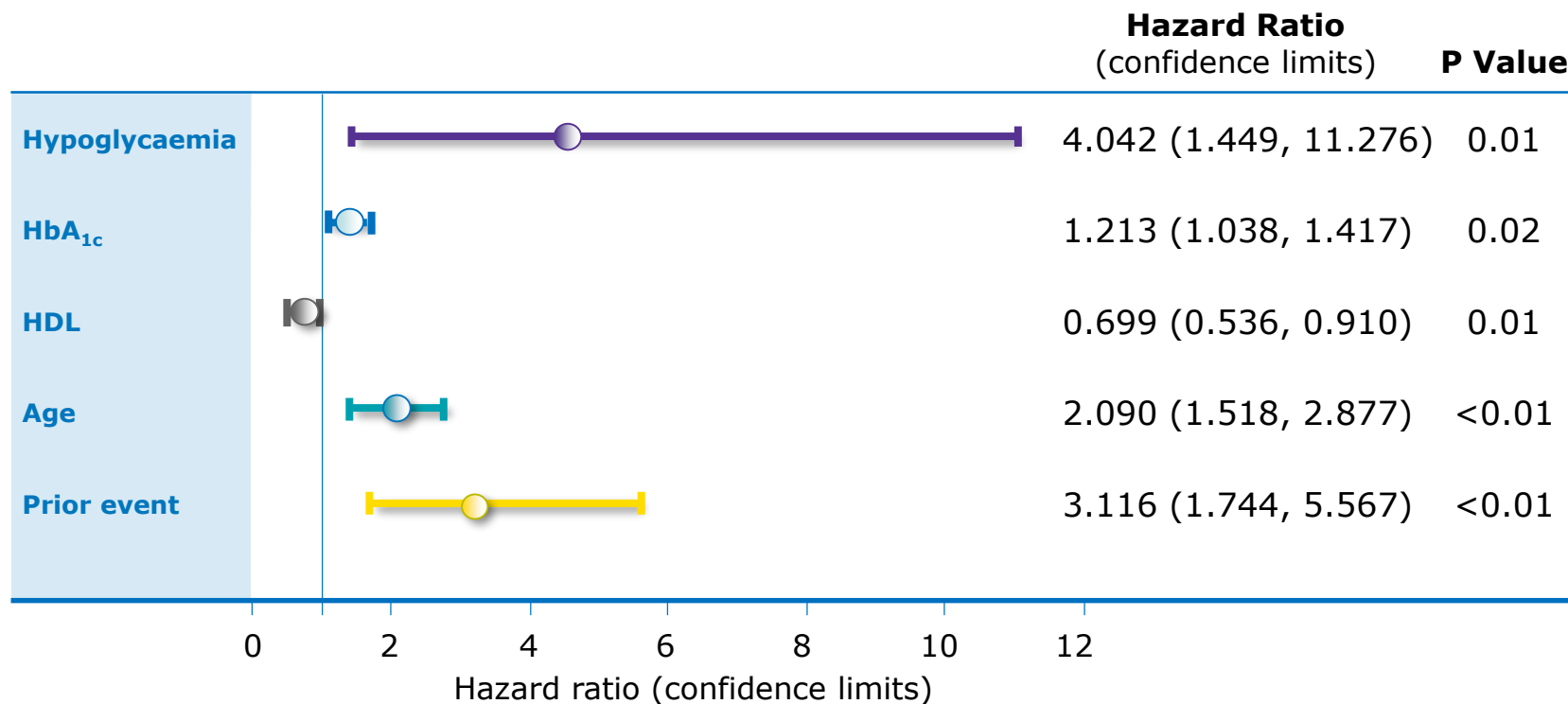
Cases with hypoglycaemia (%)



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)



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.

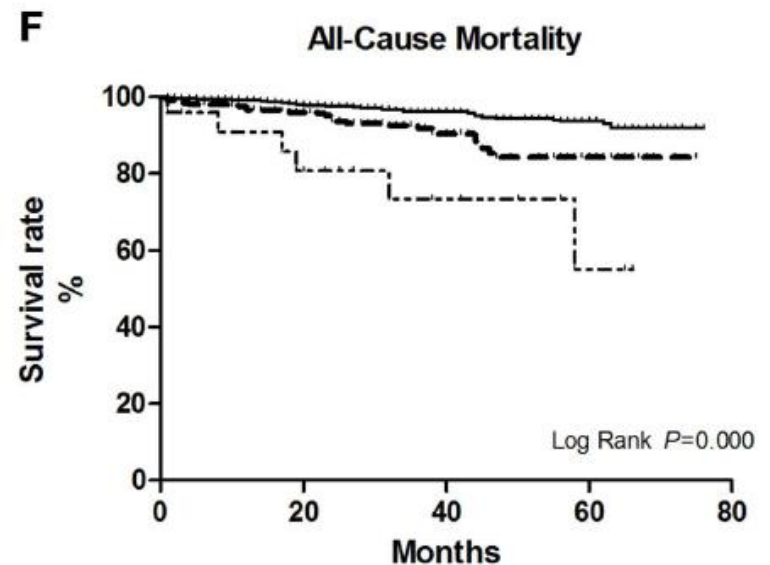
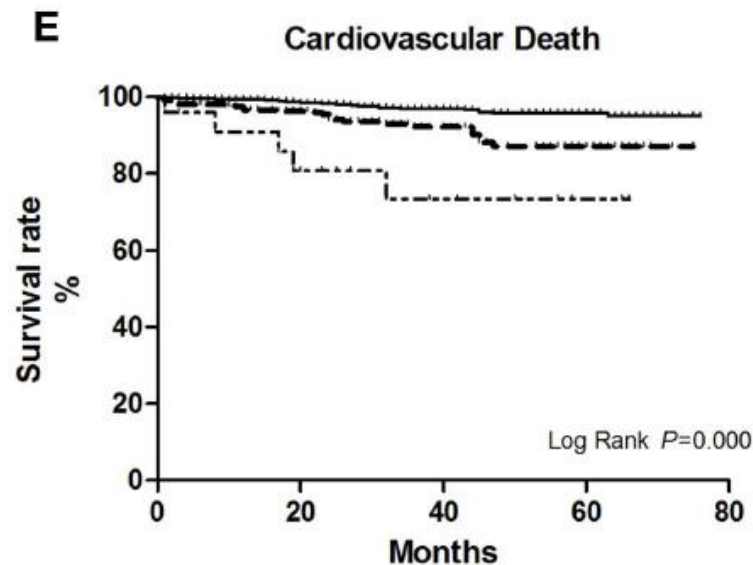
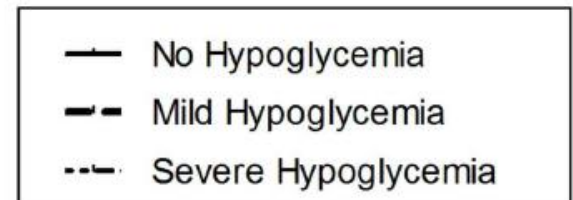
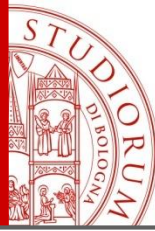


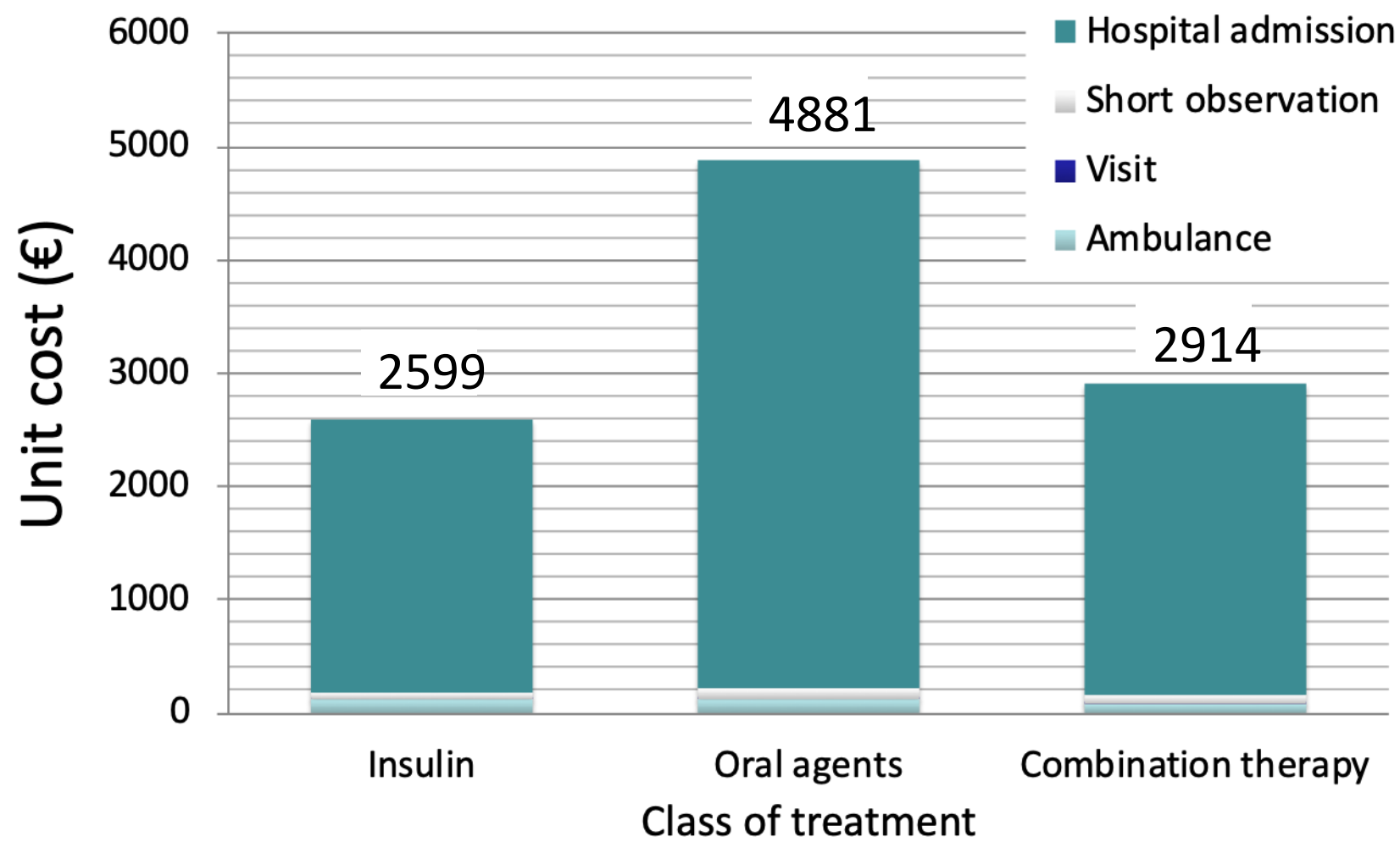
Table 2 Mean per patient annual healthcare cost (in Euros) by several patient and disease characteristics in a cohort of prevalent cases of diabetes (year 2012).

Variables	N	%	Mean annual costs (SD)			
			Drug	Outpatient	Hospitalizations	Total
Presence of diabetes related conditions and complications						
Hypertension	96 791	74.2	1 026 ± 1853	515 ± 2070	1629 ± 4858	3169 ± 6038
Heart disease	21 587	16.5	1 350 ± 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	1 167 ± 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)

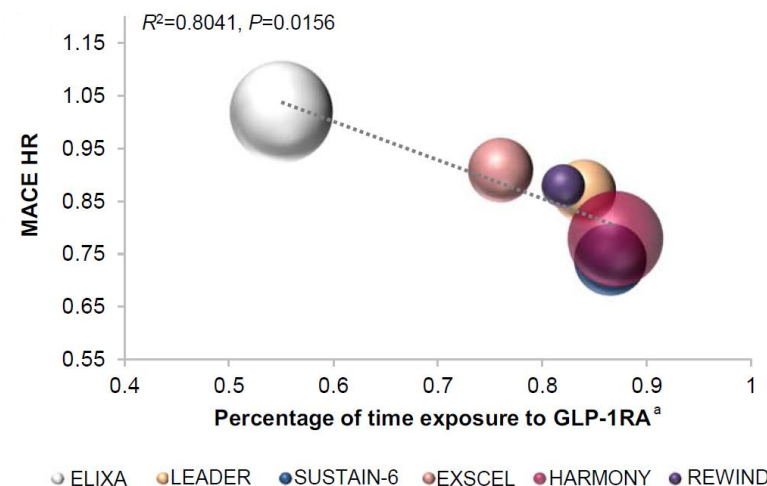
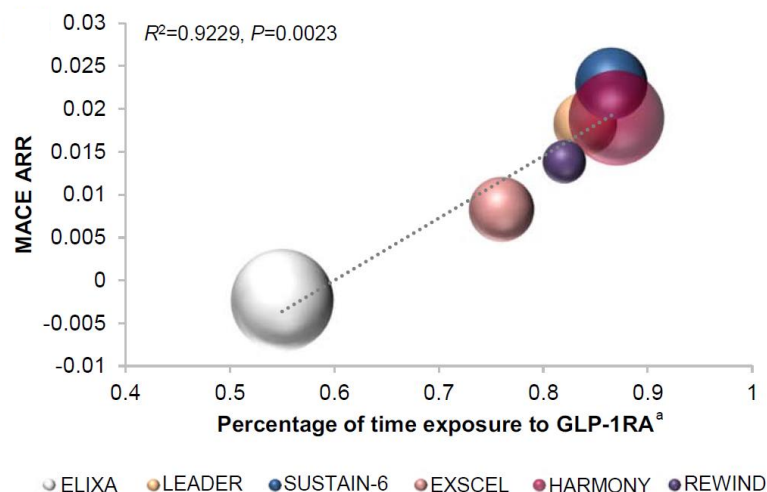


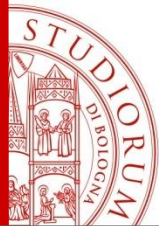
Correlation between Percentage of Time Exposure to Study Drug and MACE ARR and HR

- **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])

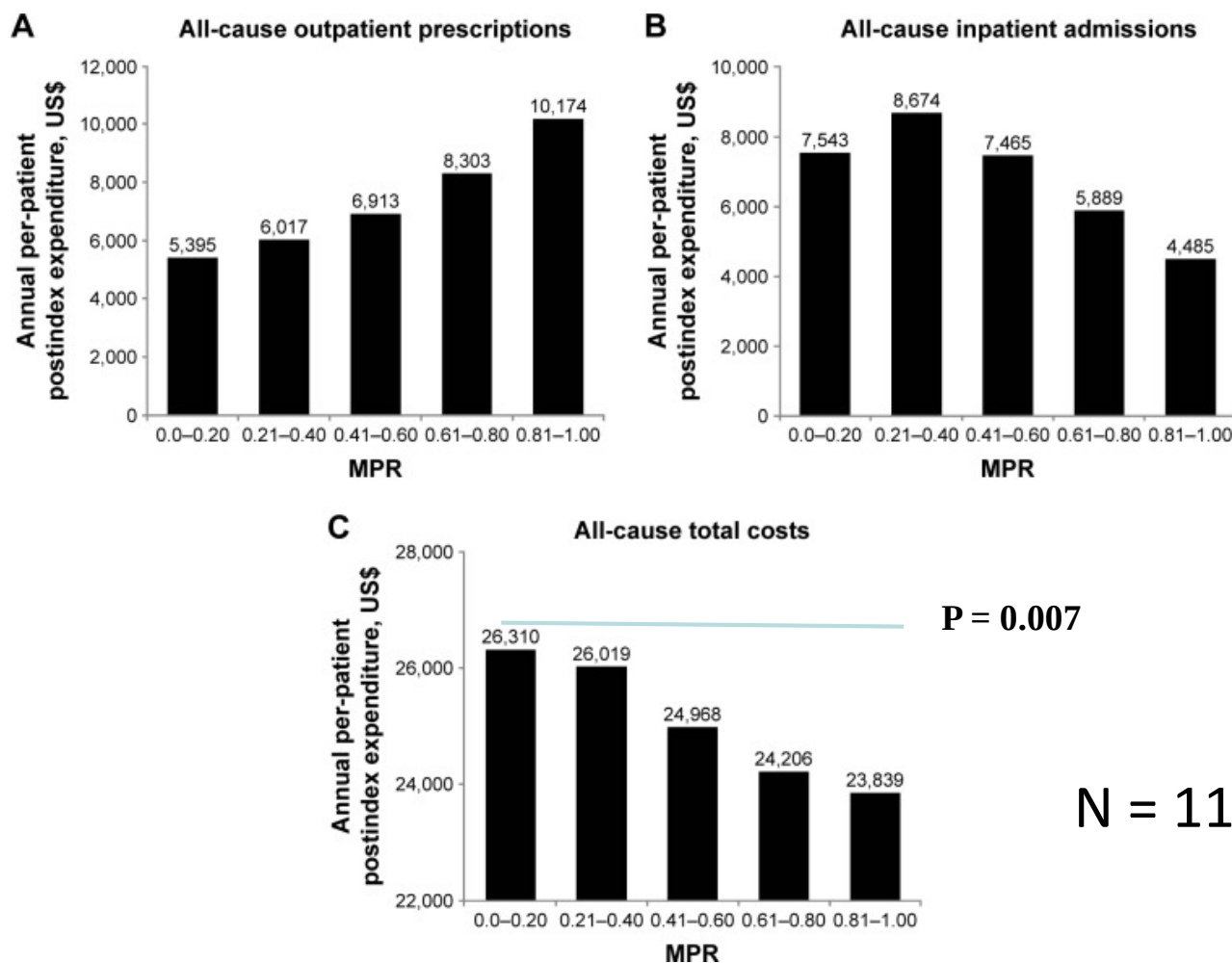
(a) The percentage of time exposure to study drug is expressed as median in ELIXA, HARMONY Outcomes and REWIND, and as mean in LEADER, SUSTAIN-6 and EXSCEL

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



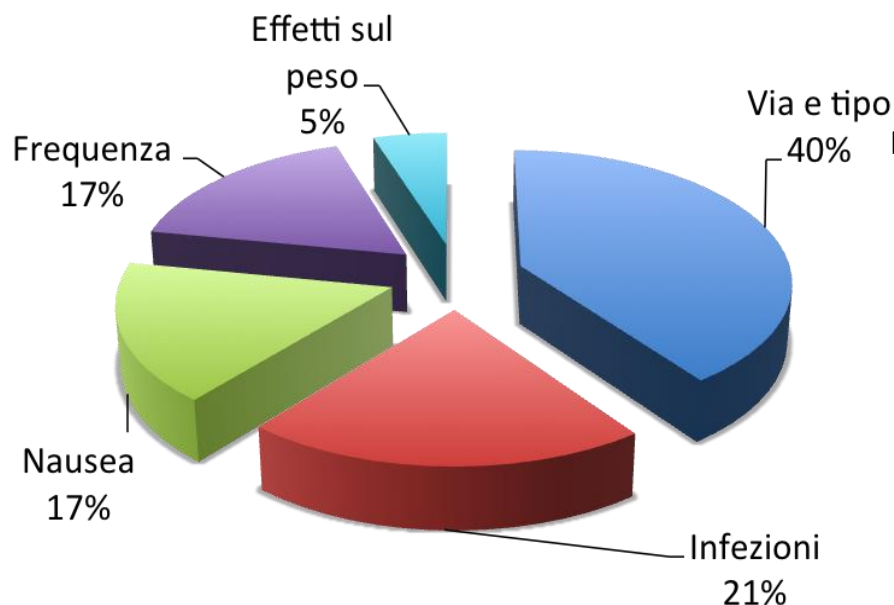


Correlation between treatment adherence, outcomes and costs in T2DM

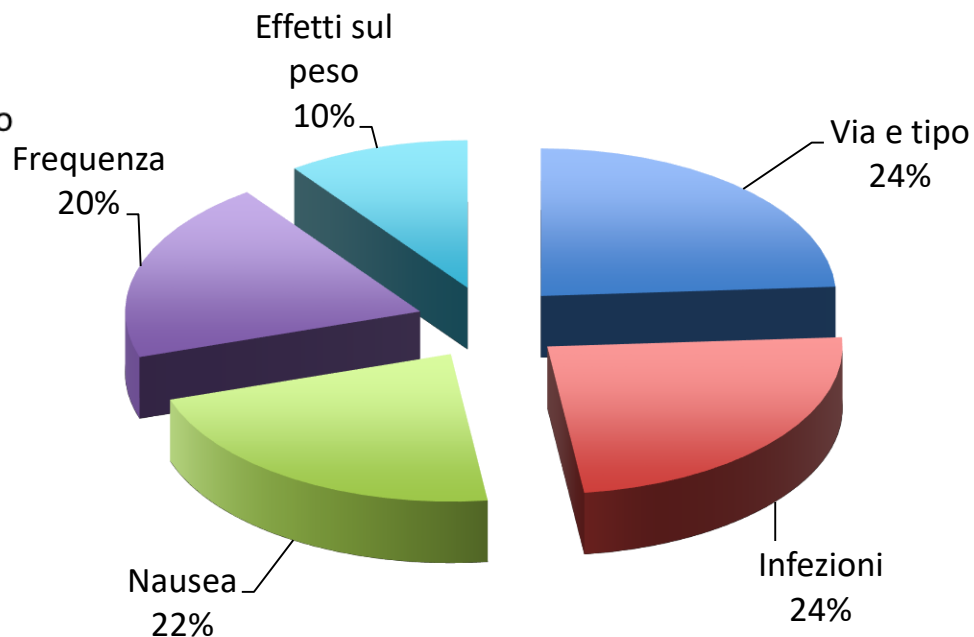


Progetto «Imparare dal paziente diabetico»: Importanza relativa delle scelte terapeutiche

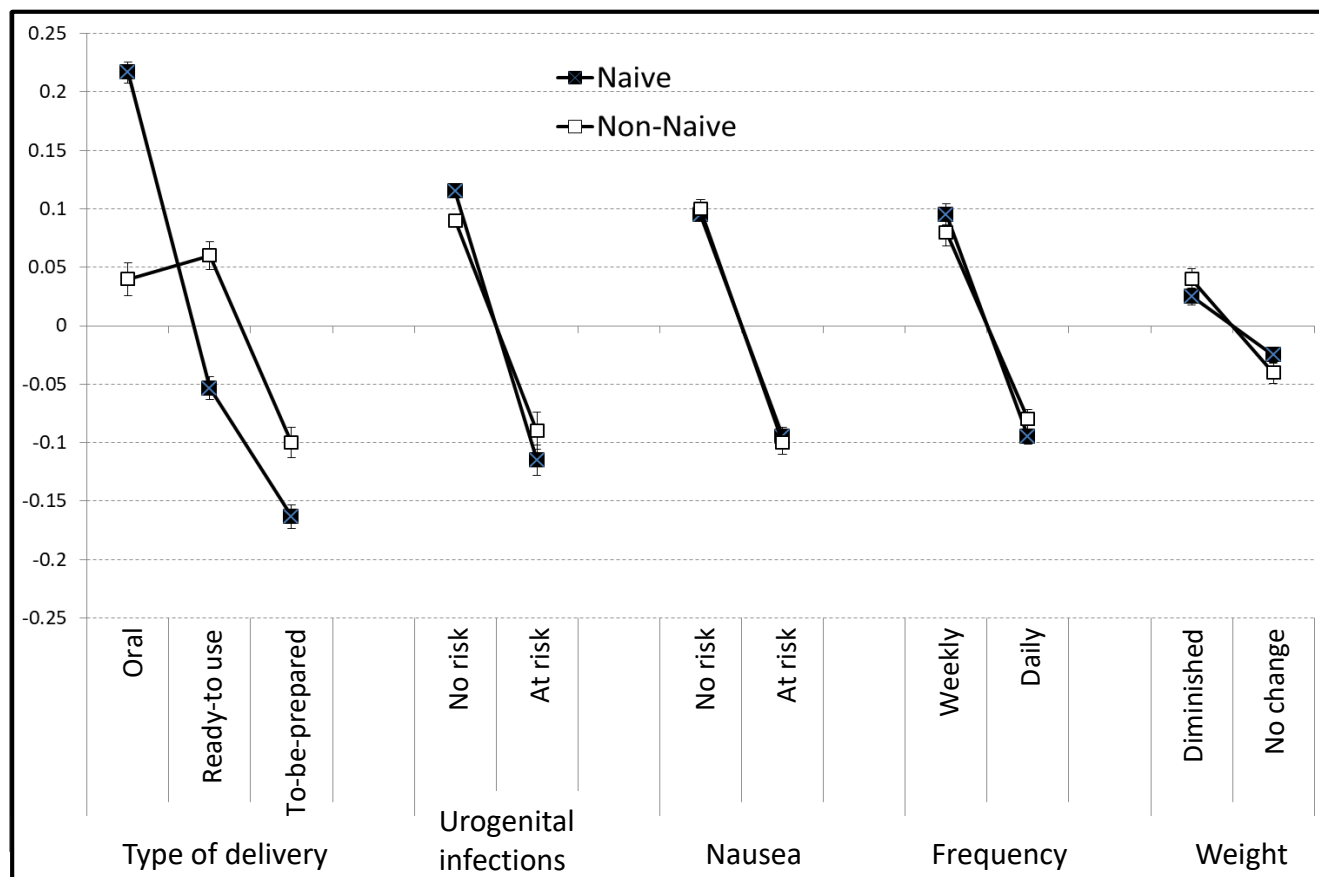
Naïve



Non-naïve



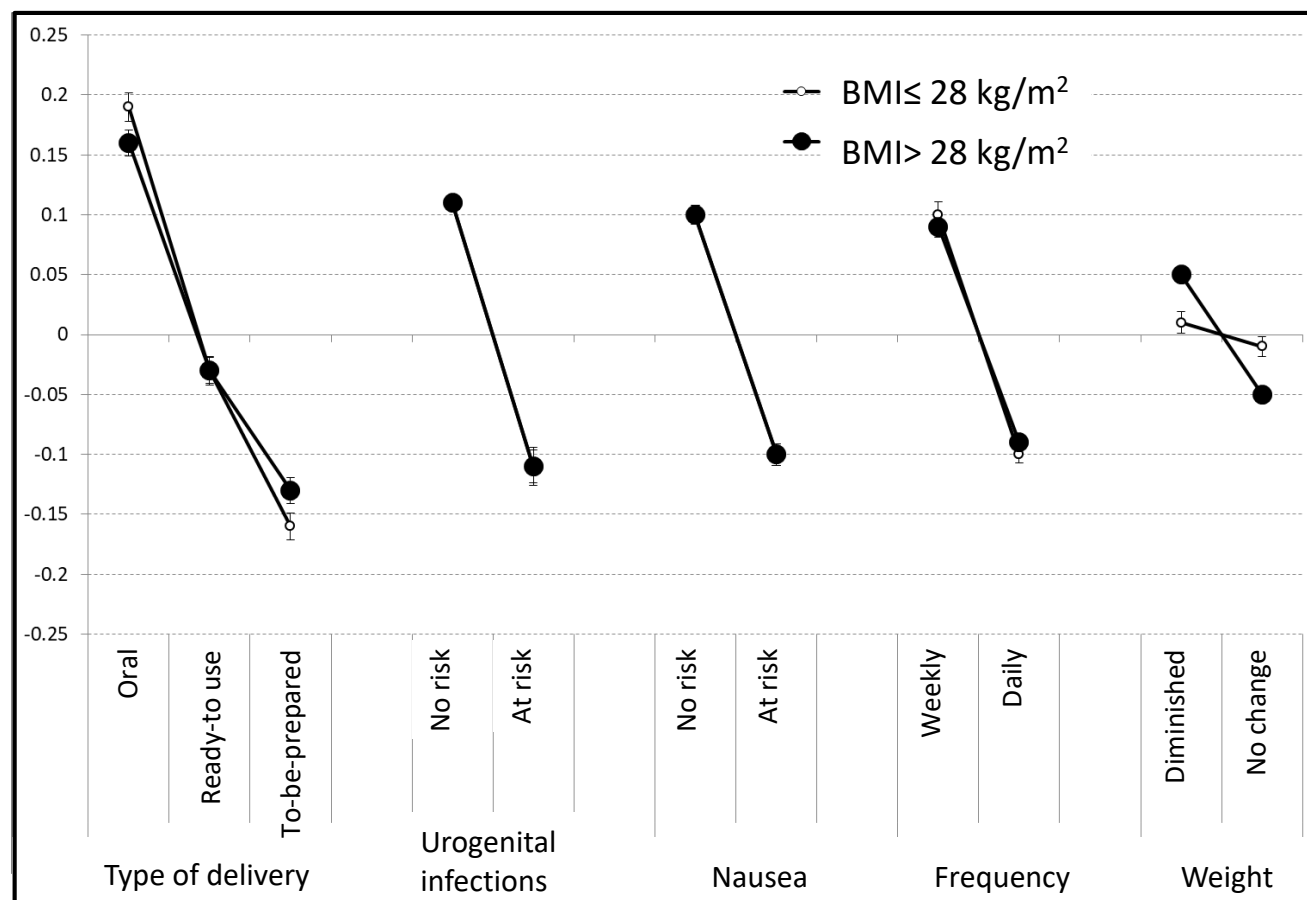
Progetto «Imparare dal paziente diabetico»

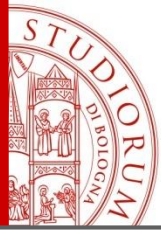


- Nei soggetti naïve si conferma una forte preferenza per la terapia orale;
- Nei non-naïve la terapia iniettiva “pronta e getta” è preferita alla terapia orale.
- Il lieve vantaggio per una terapia che aiuti nella perdita di peso nei non-naïve si spiega per il loro maggior BMI

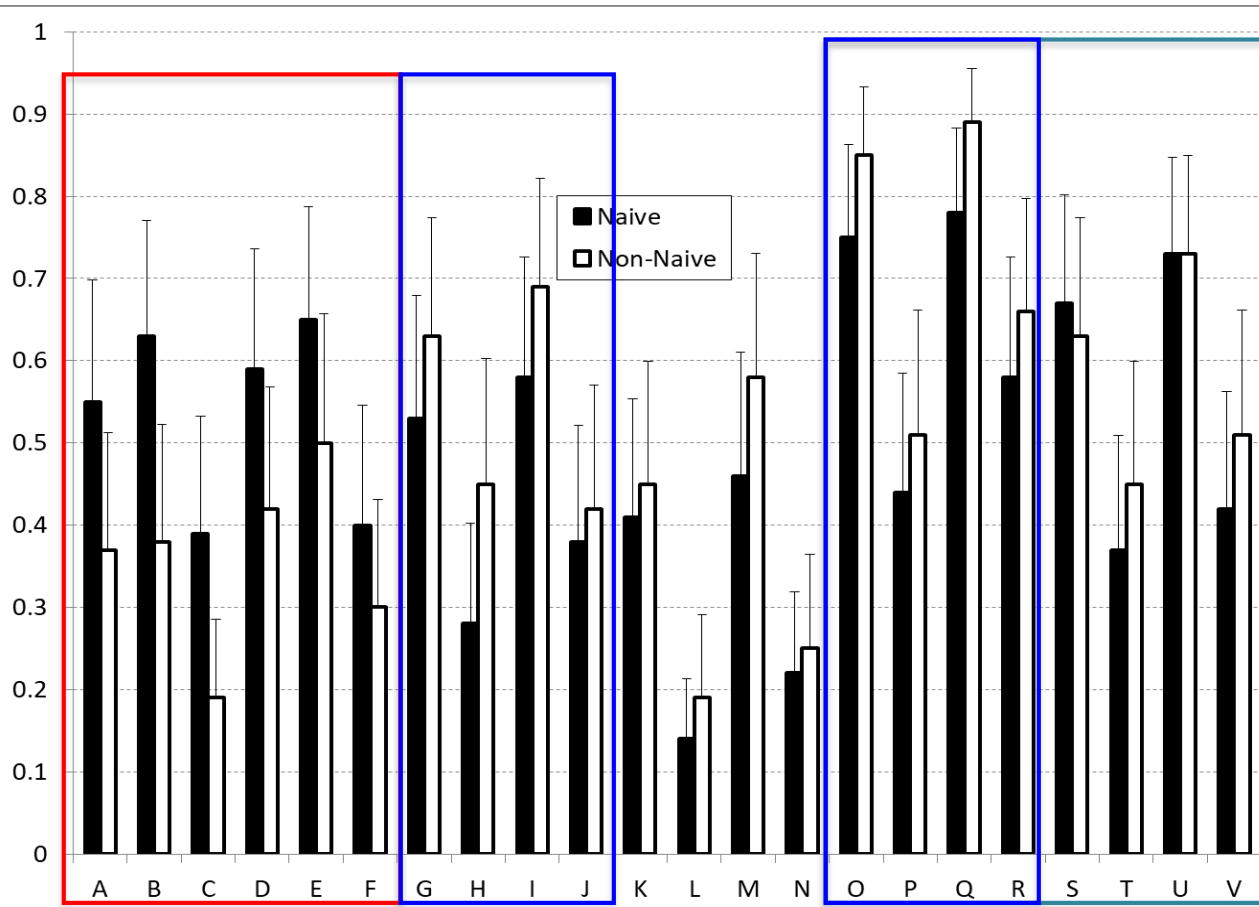
Progetto «Imparare dal paziente diabetico»

- 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 ($\text{BMI} \geq 30 \text{ kg/m}^2$)





Progetto «Imparare dal paziente diabetico»



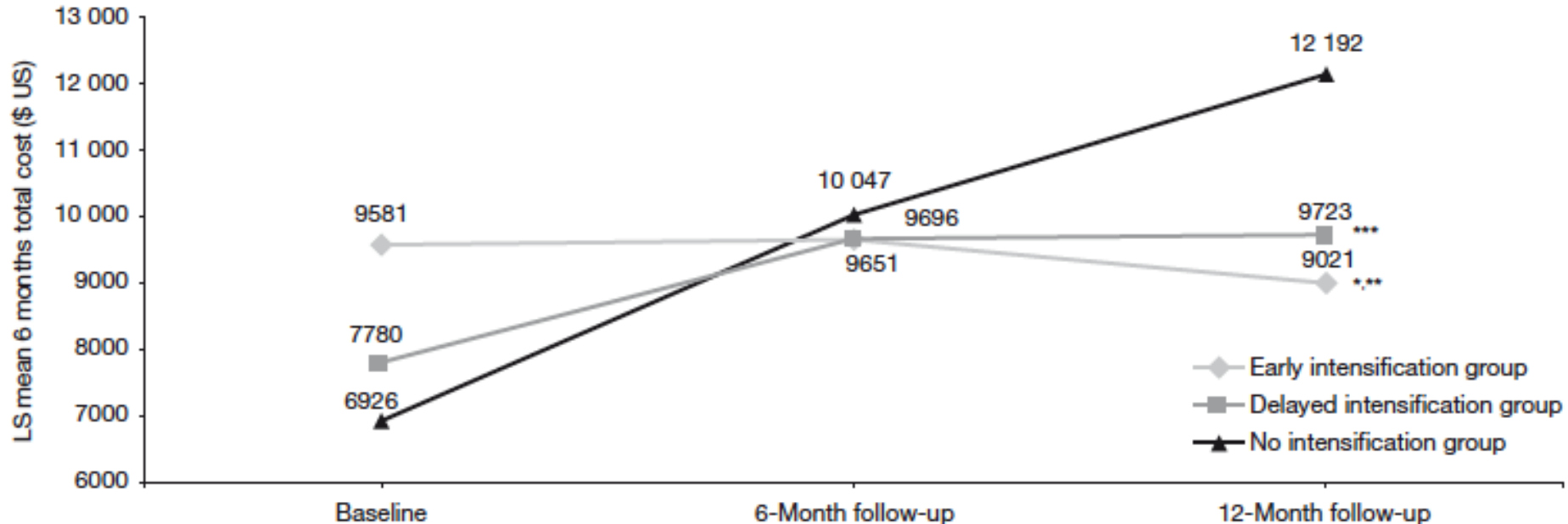
Orali
Settimanali
Pronte all'uso

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

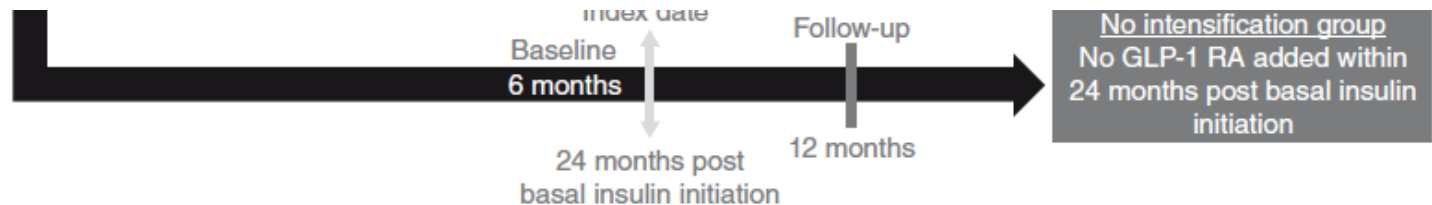
Impact of delaying treatment intensification with a glucagon-like peptide-1 receptor agonist in patients with type 2 diabetes uncontrolled on basal insulin: A longitudinal study of a US administrative claims database

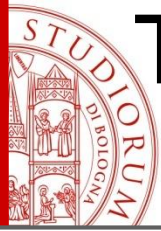
Inclusion criteria:

Baseline:



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





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

