GLP-1 RAS SETTIMANALI NELLA REAL-LIFE

Dott.ssa Chiara Pascucci
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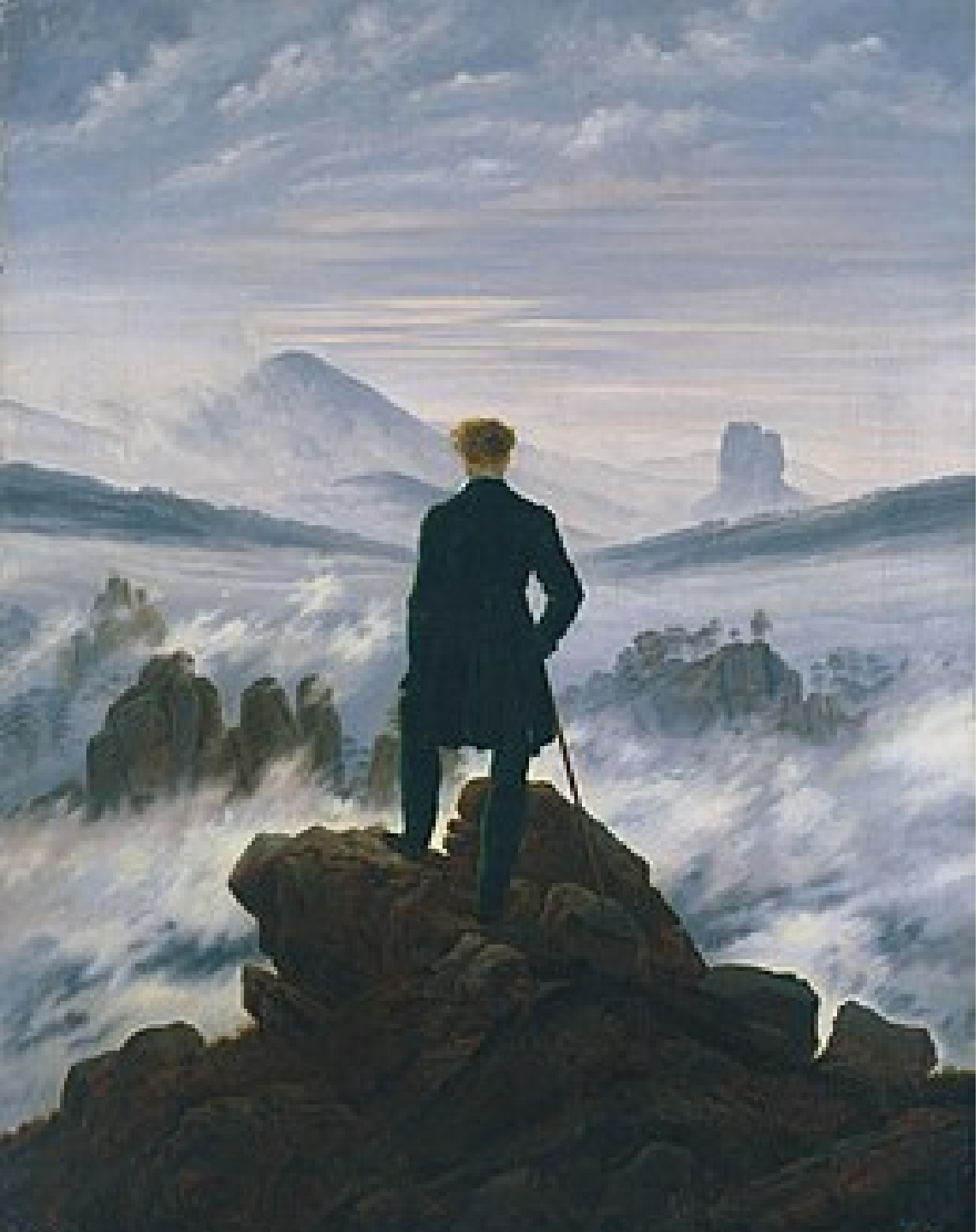
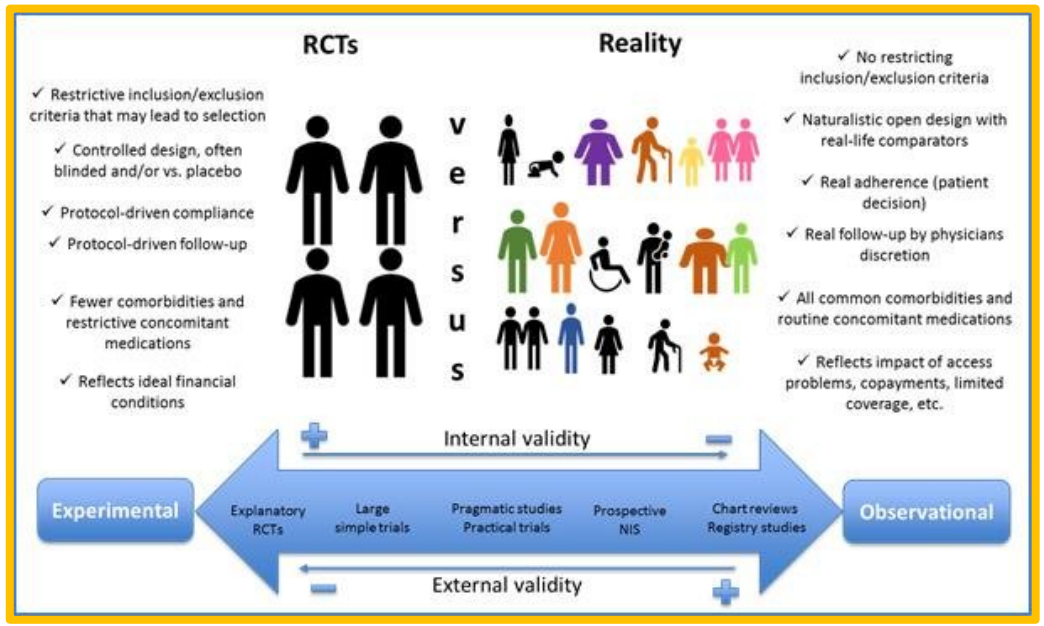


Disclosures

-Boehringer Ingelheim; Novo-Nordisk

From RCTs to **Real World Studies**



Outcomes	RCTs	RWS	Possible Reason Explaining Differences
Hba1c	Lira 1.8 mg and Sema 1.0 mg > ExeOW Dula 1.5 mg = Lira 1.8 mg Dula = ExeOW (from NWMA) Sema (0.5 or 1.0 mg) > Dula 1.5 mg	Lira = ExeOW Dula > Lira Dula > ExeOW No RWS	- Up-titration in RWS is lower than RCTs - Overall Adherence in RWS is lower than RCTs - Adherence specifically influenced by compound/devices (eg, dulaglutide>exeOW) - Different clinical characteristics between patients enrolled in RCTs vs those treated with GLP-1RAs in RWS
Body Weight	Lira 1.8 mg and Sema 1.0 mg > ExeOW Dula 1.5 mg < Lira 1.8 mg Dula = ExeOW (from NWMA) Sema (0.5 or 1.0 mg) > Dula 1.5 mg	Lira = ExeOW Dula = Lira Dula > ExeOW No RWS	

N Justo et al. Technical Report, 2018

ML Morieri et al. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy, *2020*

Opportunities from RWSs on GLP1-RAs

- ✓ Monitor safety and effectiveness, care quality, cost-effectiveness, adherence and persistence
- ✓ Investigate populations under-represented in RCTs (elderly, subjects with CKD and other comorbidities, non obeses)
- ✓ Provide head-to-head comparison between different active compounds
- ✓ Evaluate RCTs-unexplored outcomes

Front Endocrinol (Lausanne). 2022 Jun 17;13:880164. doi: 10.3389/fendo.2022.880164. eCollection 2022.

Tolerability and Effectiveness of Switching to Dulaglutide in Patients With Type 2 Diabetes Inadequately Controlled With Insulin Therapy

Youngsook Kim [1], Ji Hye Huh [2], Minyoung Lee [1], Eun Seok Kang [1], Bong-Soo Cha [1], Byung-Wan Lee [1]

Diabetes Ther (2021) 12:527–536
https://doi.org/10.1007/s13300-020-00984-x

ORIGINAL RESEARCH

Real-World Effectiveness Analysis of Switching From Liraglutide or Dulaglutide to Semaglutide in Patients With Type 2 Diabetes Mellitus: The Retrospective REALISE-DM Study

Akshay B. Jain · Steve Kanters · Reena Khurana · Jagoda Kissock ·

BMJ Open Diabetes Research & Care

Real-world use of once-weekly semaglutide in patients with type 2 diabetes: pooled analysis of data from four SURE studies by baseline characteristic subgroups

Jean-Frar
Sergiu Ca
Patrick H
Bernd Sc

Diabetes Ther
https://doi.org/10.1007/s13300-021-01010-4

ORIGINAL RESEARCH

Outcomes in GLP-1 RA-Experienced Patients Switching to Once-Weekly Semaglutide in a Real-World Setting: The Retrospective, Observational EXPERT Study

Ildiko Lingvay · Andreas R. Kirk · Søren Lophaven · Michael L. Wolden · Jay H. Shubrook

Received: November 18, 2020 / Accepted: January 23, 2021

Emerging technology, pharmacology and Therapetics
Original research

Clinical and economic outcomes among injection-naïve patients with type 2 diabetes initiating dulaglutide compared with basal insulin in a US real-world setting: the DISPEL Study

Reema Mody [1], Qing Huang [2], Maria Yu [3], Hiren Patel [4], Xian Zhang [2], Liya Wang [2], Michael Grabner [2]
Correspondence to Dr Reema Mody; mody_reema@lilly.com

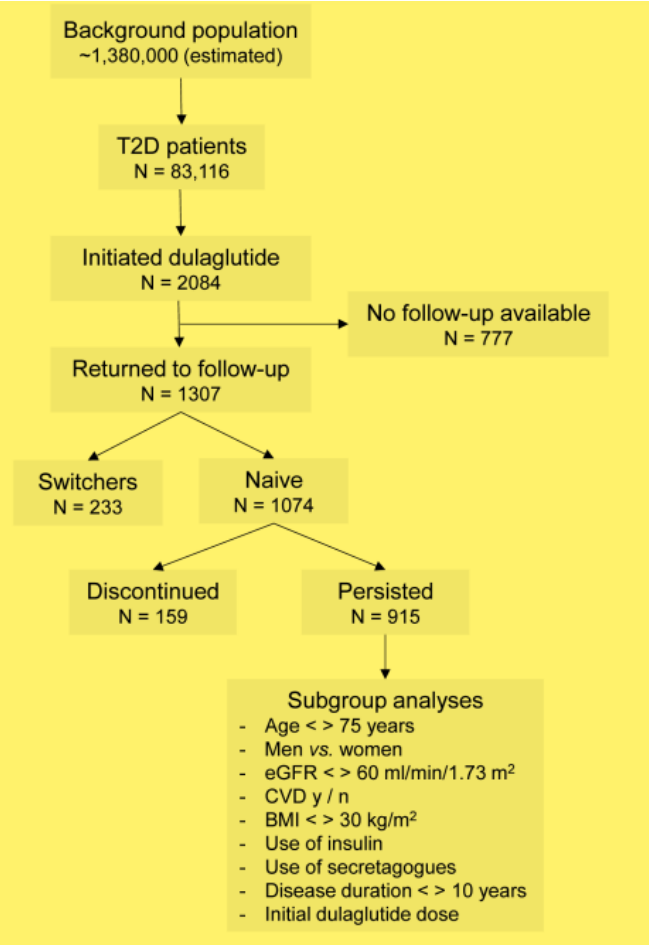
Observational Study · Diabetes Obes Metab. 2019 Apr;21(4):920-929. doi: 10.1111/dom.13603. Epub 2019 Jan 9.

Adherence, persistence, glycaemic control and costs among patients with type 2 diabetes initiating dulaglutide compared with liraglutide or exenatide once weekly at 12-month follow-up in a real-world setting in the United States

Reema Mody [1], Qing Huang [2], Maria Yu [3], Ruizhi Zhao [2], Hiren Patel [4], Michael Grabner [2], Laura Fernández Landó [4]

Effectiveness of **Dulaglutide** in the Real World and in **Special Populations**

(Veneto 2015-2018)



Switchers:

- 52.7% liraglutide
- 40.0% exenatide OW
- 7.3% lixisenatide

Initial weekly dulaglutide dose

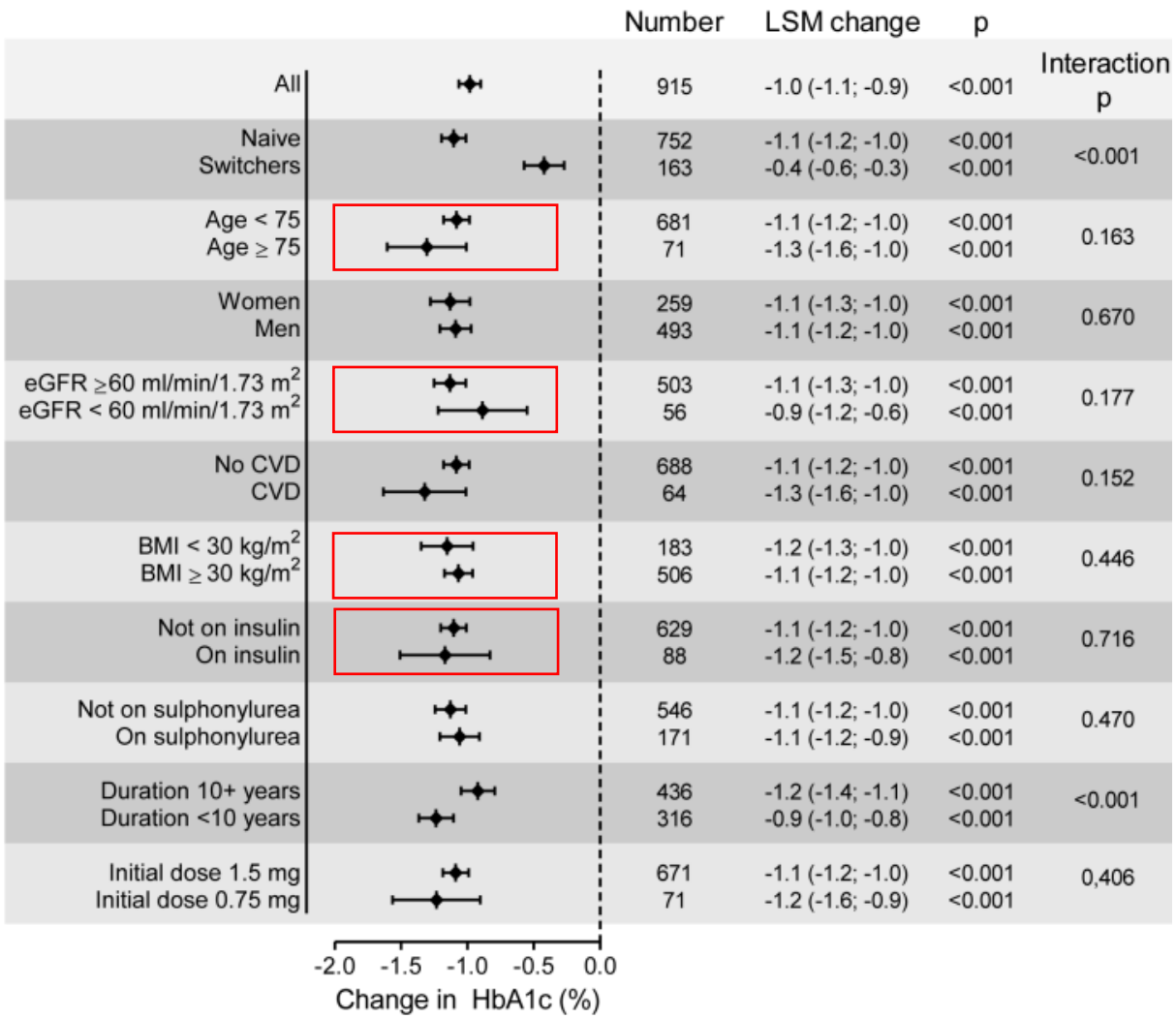
- 90,1% 1,5 mg
- 9,9% 0,75 mg

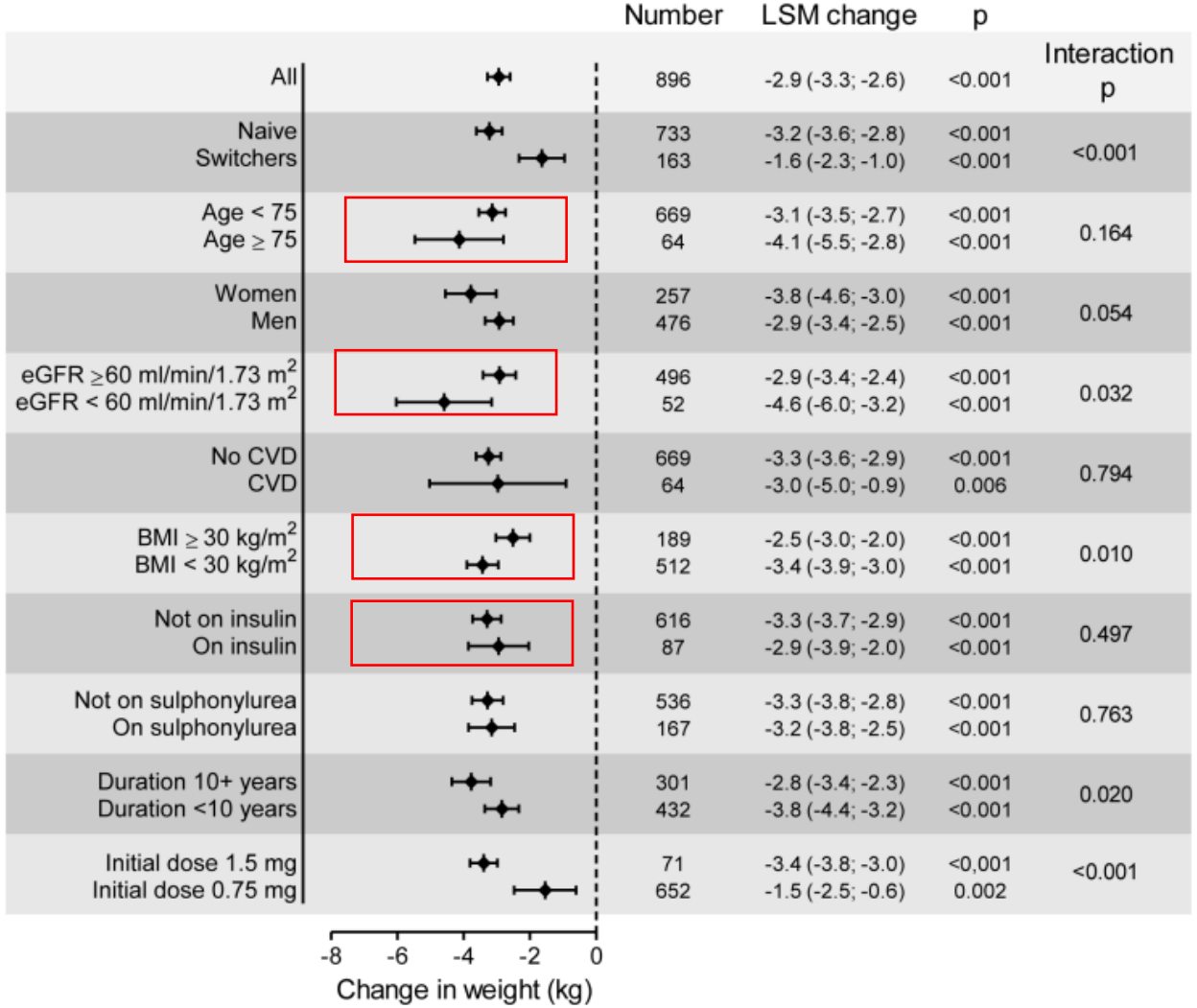
Clinical Differences Naïve vs Switchers:

- Diabetes duration ys (9,8 vs 12)
- HbA1c% (8,2 vs 7,6)

ML Morieri et al. J Clin Endocrinol Metab, 2020

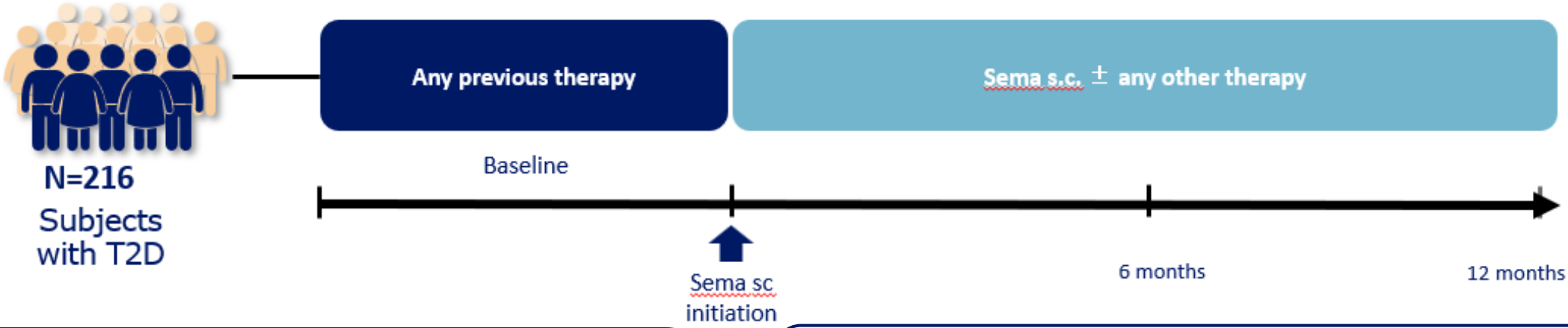
Effectiveness of Dulaglutide according to **patient characteristics**





ML Morieri et al. J Clin Endocrinol Metab, 2020

Effectiveness in Real World of **OW Semaglutide:** Results from a Retrospective Observational Study in Umbria (Perugia, Citta`di Castello, Castiglione del Lago)



Aim

To review the clinical effectiveness of semaglutide s.c. in Italy

- **Co-primary endpoints: changes in HbA1c and weight after 6 months**
- Secondary Endpoints: changes at 12 months; proportion of patients reaching HbA1c <7% and weight loss > 5%

Inclusion criteria

- T2D initiating Semaglutide s.c. therapy between oct 2019 and oct 2020
- Satisfaction of reimbursement criteria

Study population was stratified in:

- **Naïve** (New GLP1 RA users)
- **Switchers** (from another GLP1RAs)

C Di Loreto et al. Diabetes Ther, 2022

Basaline Characteristics

Table 1 Baseline patient characteristics at the first prescription of semaglutide

Variable	Overall (mean ± SD or %)	Naïve (mean ± SD or %)	Switchers (mean ± SD or %)	*p* value*
N	216	135	81	
Age (years)	64.1 ± 10.4	64.1 ± 11.1	64.1 ± 9.2	0.67
Males (%)	65.7	65.2	66.7	0.82
Diabetes duration(years)	12.5 ± 8.3	11.4 ± 8.6	14.4 ± 7.5	**0.004**
Family history of diabetes(%)	59.8	62.5	55.8	0.44
Previous cardiovascular disease	31.0	35.6	23.5	0.06
Stroke	2.8	3.0	2.5	0.38
Myocardial infarction	23.6	26.7	18.5	
Stroke + IMA	1.9	2.2	1.2	
Ischemic heart disease	2.3	3.7	0.0	
Dilated cardiomyopathy	0.5	0.0	1.2	
Years passed from the diagnosis of the first major cardiovascular	5.1 ± 4.7	4.6 ± 4.0	6.5 ± 6.0	0.24
HbA1c (%)	8.4 ± 1.4	8.4 ± 1.6	8.3 ± 1.3	0.79
Obesity indices				
Waist circumference (cm)	113.0 ± 14.1	114.0 ± 12.9	111.2 ± 16.1	0.25
Weight (kg)	94.6 ± 18.7	95.0 ± 17.5	94.0 ± 20.5	0.53
BMI (kg/m^2)	33.5 ± 5.9	33.7 ± 5.7	33.0 ± 6.3	0.21

N=216

Naive 135

- 51.1% OHAs
- 48.9% basal insulin
- 27,4% basal bolus

Switchers 81

- *66.7% liraglutide 1.8 mg*
- *15.4% dulaglutide*
- *9.0% exenatide OW*
- *66,7% basal insulin*

C Di Loreto et al. Diabetes Ther, 2022

Effectiveness Results

Table 2 Effectiveness of semaglutide: results of longitudinal models by treatment group

Change in:	Visit	Naive			Switchers		
		Estimated mean and 95% CI	Estimated mean difference from T0 and 95% CI	Within group *p* value*	Estimatedmean and 95% CI	Estimated mean difference from T0 and 95% CI	Within group *p*value*
HbA1c (%)	T0	8.4 (8.19;8.62)			8.24 (7.95;8.53)		
	T6	7.09 (6.85;7.34)	− 1.31 (− 1.56;− 1.06)	< 0.0001	7.46 (7.14;7.78)	− 0.78 (− 1.11;− 0.45)	< 0.0001
	T12	7.15 (6.81;7.49)	− 1.26 (− 1.6;− 0.91)	< 0.0001	7.42 (6.94;7.9)	− 0.82 (− 1.3;− 0.34)	0.0001
Weight (kg)	T0	95.25 (92.11;98.39)			94.44 (90.37;98.52)		
	T6	91.34 (88.17;94.5)	− 3.92 (− 4.79;-3.05)	< 0.0001	91.8 (87.68;95.92)	− 2.64 (− 3.81;− 1.48)	< 0.0001
	T12	90.03 (86.72;93.34)	− 5.22 (− 6.51;− 3.93)	< 0.0001	91.32 (87.02;95.62)	− 3.13 (− 4.8;-1.45)	0.0003

HbA1c levels < 7%

- **52% in Naïve**
- **31% in Switchers**

Weight loss> 5%

- **46.9% in Naive**
- **25.9% in Switchers**

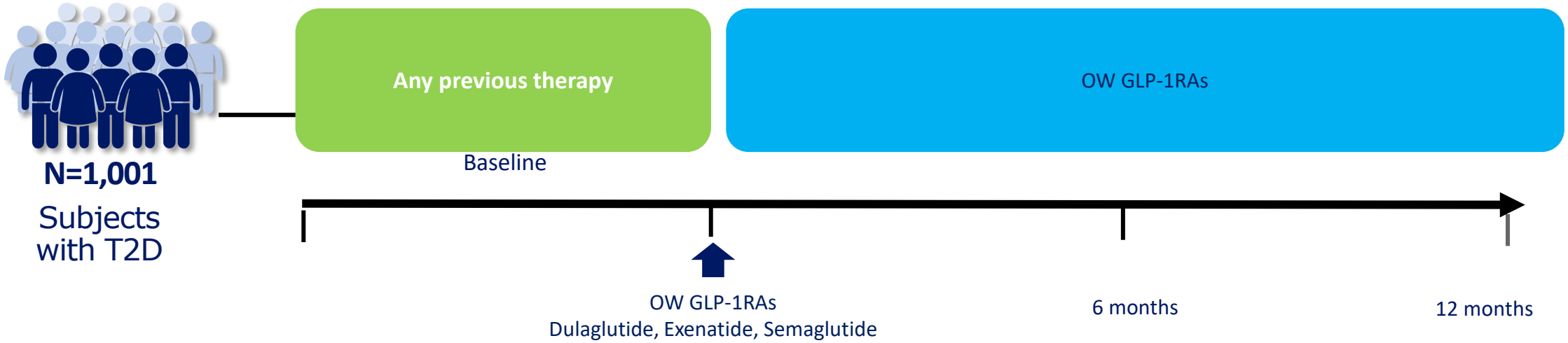
Semaglutide dose

- **0.82 mg/wk T6; 0.86 mg/wk T12 in Naive**
- **0.96/wk T6 and T12 in Switchers**

C Di Loreto et al. Diabetes Ther, 2022

Effectiveness and Tolerability of **Once-Weekly GLP-1 Ras** in Clinical Practice: A Focus on **Switching Between Once-Weekly Molecules**

(Chieti-Pescara 2018-2021)



Aim

- to evaluate the effectiveness and tolerability of OW GLP-1RAs
- to assess the clinical benefits of switching from one GLP-1RA to another in a routine clinical setting
- **Co-primary endpoints: changes in HbA1c and weight after 6 months**

Inclusion criteria

- Aged 18–80 years T2D initiating OW GLP1 Ras therapy between apr 2018 and jan 2021

Study population was stratified in:

- **Naïve** (New GLP1 RA users)
- **Switchers** (from another GLP1RAs)

G Di Dalmazi et al. Front. Endocrinol, 2022

Baseline characteristics overall and by GLP1-RA

	Overall	Dulaglutide	Exenatide	Semaglutide	p-value*
N	1,001	435	187	379	
Age (years)	63.9 ± 9.2	64.9 ± 9.6	63.1 ± 8.9	63.1 ± 8.9	**0.006**
Gender (%)					
Women	43.9	43.0	53.5	40.1	**0.009**
Men	56.1	57.0	46.5	59.9	
Diabetes duration (years)	12.5 ± 7.9	13.4 ± 7.8	10.6 ± 7.2	12.4 ± 8.1	**0.0002**
Body weight (kg)	89.7 ± 18.3	87.4 ± 17.5	91.3 ± 18.4	91.7 ± 18.7	**0.004**
BMI (kg/m^2)	32.8 ± 6.0	31.9 ± 5.5	34.2 ± 6.2	33.2 ± 6.4	**0.0001**
BMI ≥ 30 kg/m^2	63.8	55.4	74.7	67.8	**<0.0001**
Waist circumference (cm)	110.4 ± 12.2	109.6 ± 12.0	111.5 ± 12.3	111.4 ± 12.7	0.20
Systolic blood pressure (mmHg)	140.3 ± 20.1	139.3 ± 18.6	152.0 ± 25.6	134.2 ± 16.0	**0.01**
Diastolic blood pressure (mmHg)	80.9 ± 10.3	79.4 ± 8.8	86.4 ± 14.7	80.2 ± 8.6	0.07
Fasting plasma glucose (mg/dl)	163.8 ± 41.6	164.6 ± 41.4	167.8 ± 35.9	159.1 ± 45.9	0.13
HbA1c (%)	8.1 ± 1.1	8.0 ± 1.0	7.8 ± 0.6	8.2 ± 1.3	**0.03**
Total cholesterol (mg/dl)	176.9 ± 41.1	176.8 ± 41.4	179.9 ± 35.7	175.6 ± 43.1	0.43
HDL Cholesterol (mg/dl)	45.1 ± 12.4	45.7 ± 12.8	47.5 ± 13.3	43.3 ± 11.3	**0.01**
Triglycerides (mg/dl)	180.7 ± 119.1	182.0 ± 129.8	169.1 ± 80.9	184.7 ± 122.2	0.87
LDL Cholesterol (mg/dl)	96.0 ± 34.3	96.2 ± 33.9	98.5 ± 29.7	94.8 ± 36.8	0.55
eGFR (mg/min/1.73 m^2)	77.6 ± 22.7	74.0 ± 23.2	81.3 ± 18.1	79.4 ± 23.4	**0.01**
eGFR < 60 mg/min/1.73 m^2 (%)	25.3	29.6	16.5	24.6	0.0575
Creatinine (mg)	1.0 ± 0.5	1.0 ± 0.4	0.9 ± 0.3	1.0 ± 0.6	0.07
Microalbuminuria (mg/dl)	95.7 ± 286.3	79.0 ± 239.4	98.6 ± 301.6	114.3 ± 327.6	0.55
Microangiopathy** (%)	39.3	36.5	43.1	39.6	0.37
Macroangiopathy*** (%)	22.8	25.0	16.5	24.3	0.07
Background glucose lowering treatments:					
Metformin (%)	82.2	83.2	86.1	79.2	0.10
Sulfonylureas (%)	12.4	16.3	18.7	4.7	**<0.0001**
Pioglitazone (%)	11.0	11.0	13.9	9.5	0.29
DPP4-inhibitors (%)	19.9	28.0	31.6	4.7	**<0.0001**
SGLT2-inhibitors (%)	10.7	12.9	8.6	9.2	0.14
Basal insulin therapy (%)	28.9	23.0	9.6	45.1	**<0.0001**
Antihypertensive treatment (%)	73.9	71.8	76.5	74.2	0.5147
Lipid-lowering treatment (%)	56.0	56.5	50.3	58.4	0.1829
Antiplatelet agents (%)	43.8	43.4	41.7	45.2	0.72
Switch from another GLP-1RA	36.6	25.9	16.0	58.0	**<0.0001**

*Data are mean and standard deviations or proportion. *Student's t-test, Mann–Whitney test, or Chi-square test as appropriate. Statistically significant p-values ($p < 0.05$) are in bold.*
***Retinopathy, nephropathy, and neuropathy ***Ischemic heart disease, stroke, and peripheral arterial disease.*

Clinical Differences Naïve vs Switchers:

- Diabetes duration ys (11,4 vs 14,1)
- HbA1c% (8,2 vs 7,8)
- Background glucose lowering treatment

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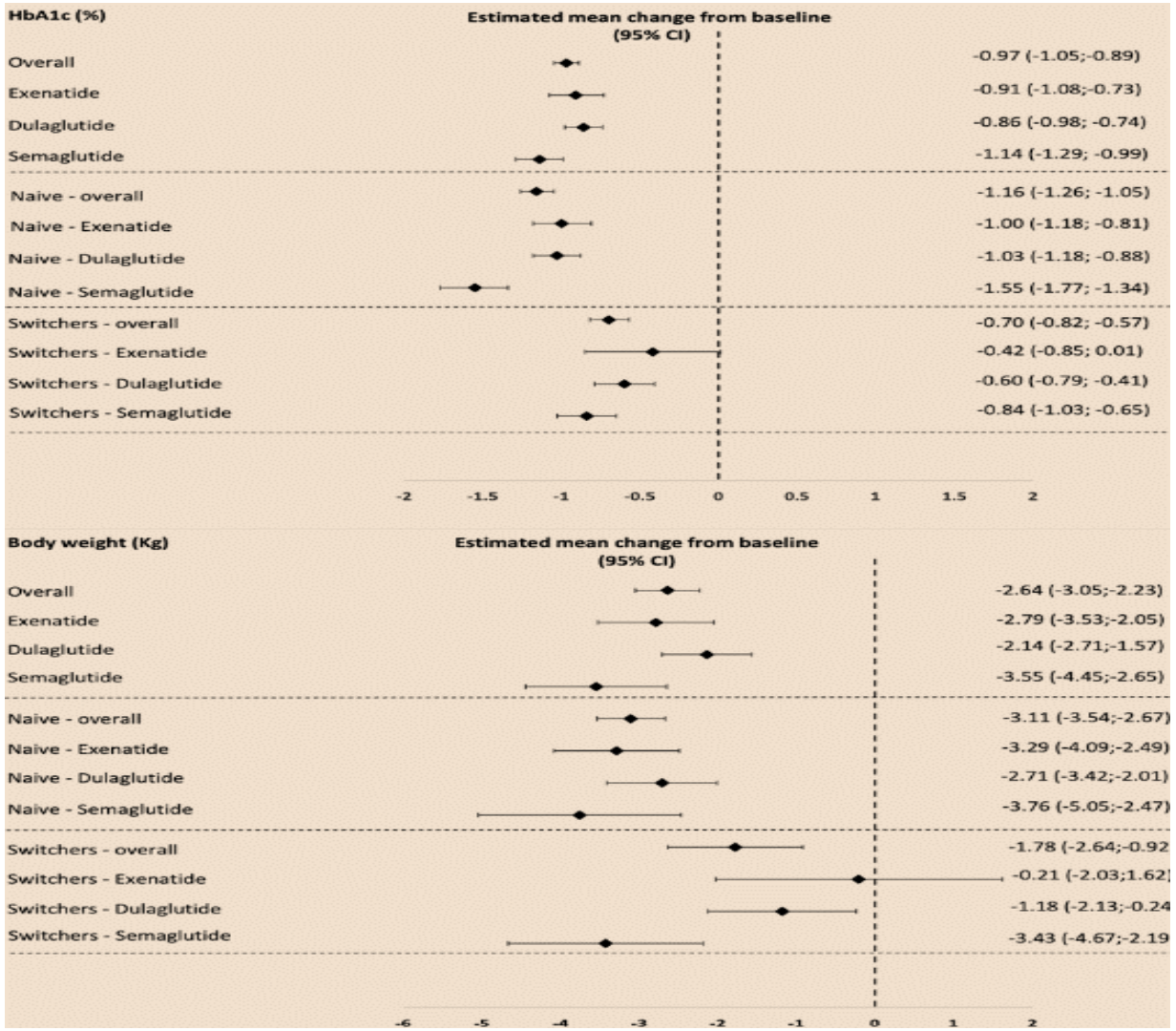
Comparing Effectiveness of OW GLP1RAs Through a Propensity Score Adjustment



Endpoint	GLP-1RA	Visit	NAIVE				SWITCHERS			
			Estimated mean and 95% CI	Estimated mean difference from T0 and 95% CI	Within group p-value*	Between group p-value**	Estimated mean and 95% CI	Estimated mean difference from T0 and 95% CI	Within group p-value*	Between group p-value**
HbA1c	Dulaglutide	T0	8.11 (7.98;8.24)	–	–		7.89 (7.74;8.05)			
		T6	7.08 (6.94;7.22)	−1.03 (−1.18;−0.88)	**<0.0001**	**0.001**	7.29 (7.12;7.47)	−0.60 (−0.79;−0.41)	**<0.0001**	0.09
		T12	7.18 (7.03;7.33)	−0.93 (−1.09;−0.77)	**<0.0001**	**0.0006**	7.4 (7.22;7.59)	−0.49 (−0.69;−0.29)	**<0.0001**	0.06
	Exenatide	T0	7.87 (7.71;8.04)	–	–		7.46 (7.08;7.83)			
		T6	6.88 (6.71;7.05)	−1.00 (−1.18;−0.81)	**<0.0001**		7.04 (6.64;7.44)	−0.42 (−0.85;0.01)	0.05	
		T12	6.94 (6.75;7.12)	−0.94 (−1.14;−0.74)	**<0.0001**		7.05 (6.64;7.46)	−0.41 (−0.84;0.03)	0.07	
	Semaglutide	T0	8.51 (8.34;8.68)	–	–		8.00 (7.87;8.14)			
		T6	6.95 (6.75;7.16)	−1.55 (−1.77;−1.34)	**<0.0001**		7.16 (6.98;7.35)	−0.84 (−1.03;−0.65)	**<0.0001**	
		T12	6.96 (6.7;7.22)	−1.55 (−1.82;−1.28)	**<0.0001**		7.14 (6.91;7.37)	−0.87 (−1.1;−0.63)	**<0.0001**	
Weight	Dulaglutide	T0	89.21 (86.93;91.49)	–	–		85.57 (82.88;88.27)			
		T6	86.5 (84.2;88.79)	−2.71 (−3.42;−2.01)	**<0.0001**	0.15	84.39 (81.64;87.14)	−1.18 (−2.13;−0.24)	**0.01**	**0.0006**
		T12	86.77 (84.46;89.08)	−2.44 (−3.2;−1.68)	**<0.0001**	**0.000**	84.93 (82.17;87.69)	−0.64 (−1.61;0.33)	0.19	0.14
	Exenatide	T0	90.39 (87.48;93.29)	–	–	–	96.24 (89.76;102.72)			
		T6	87.09 (84.18;90.01)	−3.29 (−4.09;−2.49)	**<0.0001**		96.03 (89.52;102.54)	−0.21 (−2.03;1.62)	0.82	
		T12	86.74 (83.81;89.68)	−3.64 (−4.52;−2.77)	**<0.0001**		95.78 (89.24;102.31)	−0.46 (−2.37;1.46)	0.64	
	Semaglutide	T0	91.07 (88.04;94.09)	–	–		90.79 (88.24;93.34)			
		T6	87.31 (84.11;90.5)	−3.76 (−5.05;−2.47)	**<0.0001**		87.36 (84.61;90.11)	−3.43 (−4.67;−2.19)	**<0.0001**	
		T12	84.78 (81.49;88.06)	−6.29 (−7.84;−4.73)	**<0.0001**		87.24 (84.28;90.19)	−3.55 (−5.2;−1.91)	**<0.0001**	

*Within-group and between-group comparisons (T6 vs. T0 and T12 vs. T0). *Paired t-test derived from linear mixed models for repeated measurements. **Unpaired t-test derived from linear mixed models for repeated measurements. Statistically significant p-values (p<0.05) are in bold. *Chi-square test between, OW exenatide, and OW semaglutide. Statistically significant p-values (p < 0.05) are in bold.*

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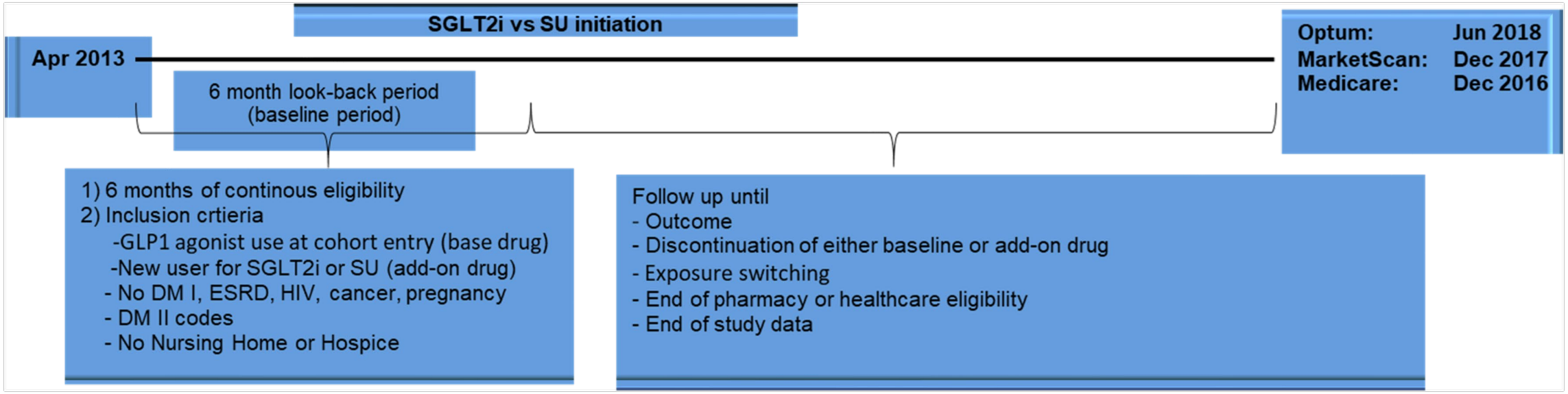
Risk of Cardiovascular Outcomes in T2D Patients Following Addition of **SGLT2-Is Versus Sulfonylureas to** Baseline **GLP-1RA** Therapy

(US 2013-2018)

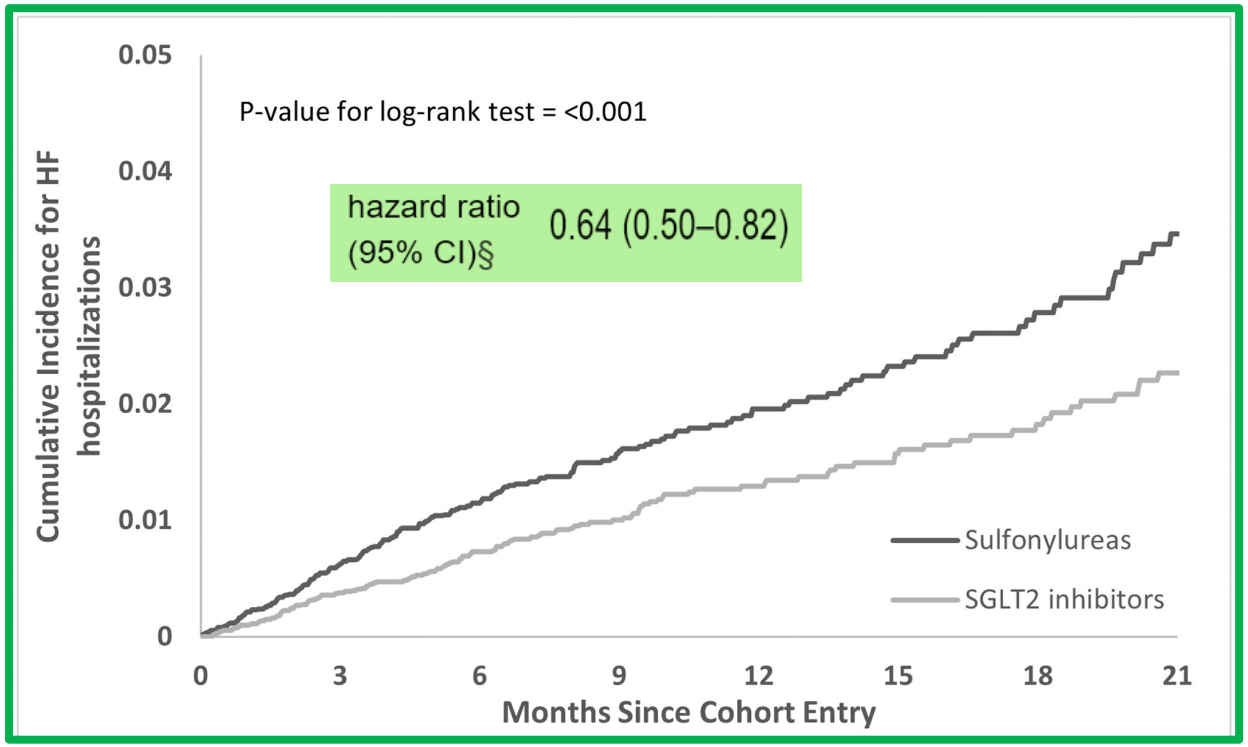


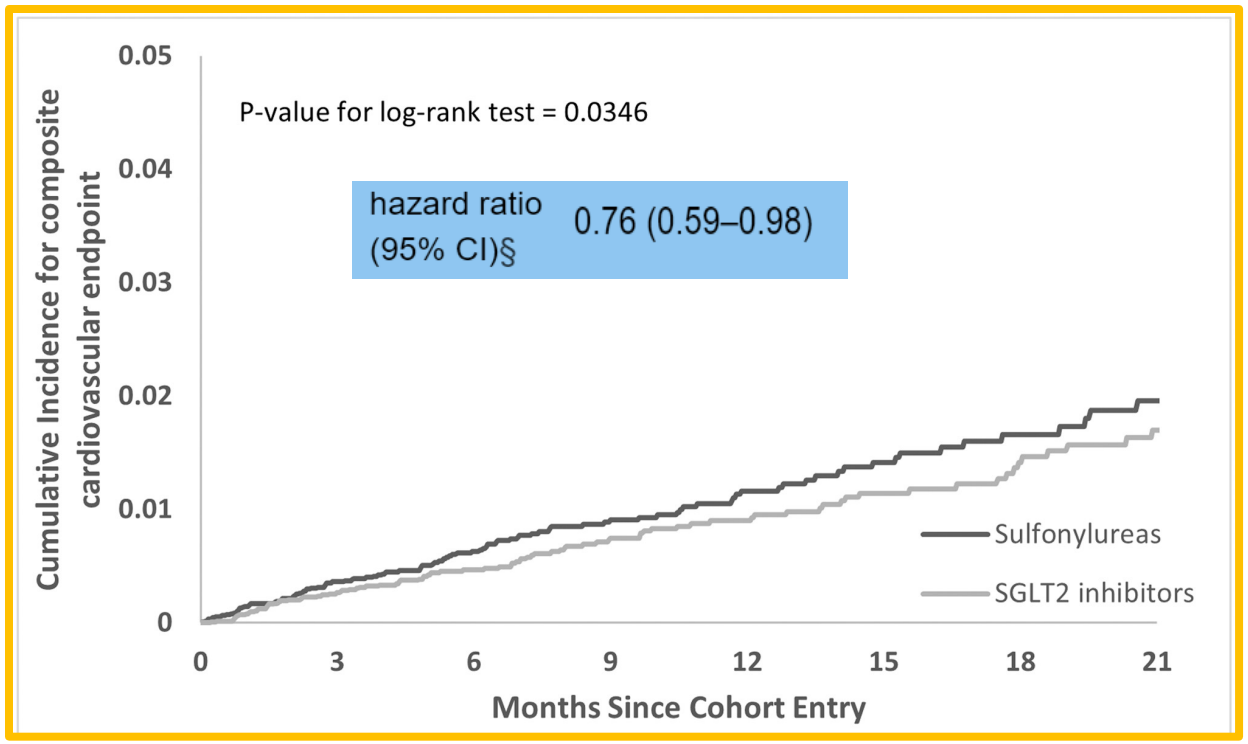
Primary outcomes:

- Composite cardiovascular endpoint (myocardial infarction, stroke, and all-cause mortality)
- Heart failure hospitalization

C Dave et al. Circulation, 2021

- ❑ 1:1 propensity score matched adjusting for >95 baseline covariate
- ❑ 2 cohorts of 12,584 pts (age 58,3 ys; female 48,2%)
- ❑ liraglutide (60,3%); canagliflozin (61,6%); glimepiride (54,9%)





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Conclusions

Real World Studies on OW GLP1-Ras

- Clarify **long term effectiveness** and **safety** of GLP1-RAs in clinical practice even in **underrepresented population**, including those aged ≥ 75 years, nonobese, or with chronic kidney disease

- Suggest that **switching between GLP-1RAs** represents a **possible choice** when the ongoing drug is unable to provide the desired glycemic control and/or weight loss or when gastrointestinal adverse effects occur

- Support for **adding SGLT2i** to existing GLP-1RA therapy **to confer additional cardiovascular benefit** in patients with diabetes in routine clinical care

GRAZIE PER L'ATTENZIONE

GRAZIE PER L'ATTENZIONE