Effetti collaterali di GLP-1RA (vs SGLT2i?): what-is e what-if

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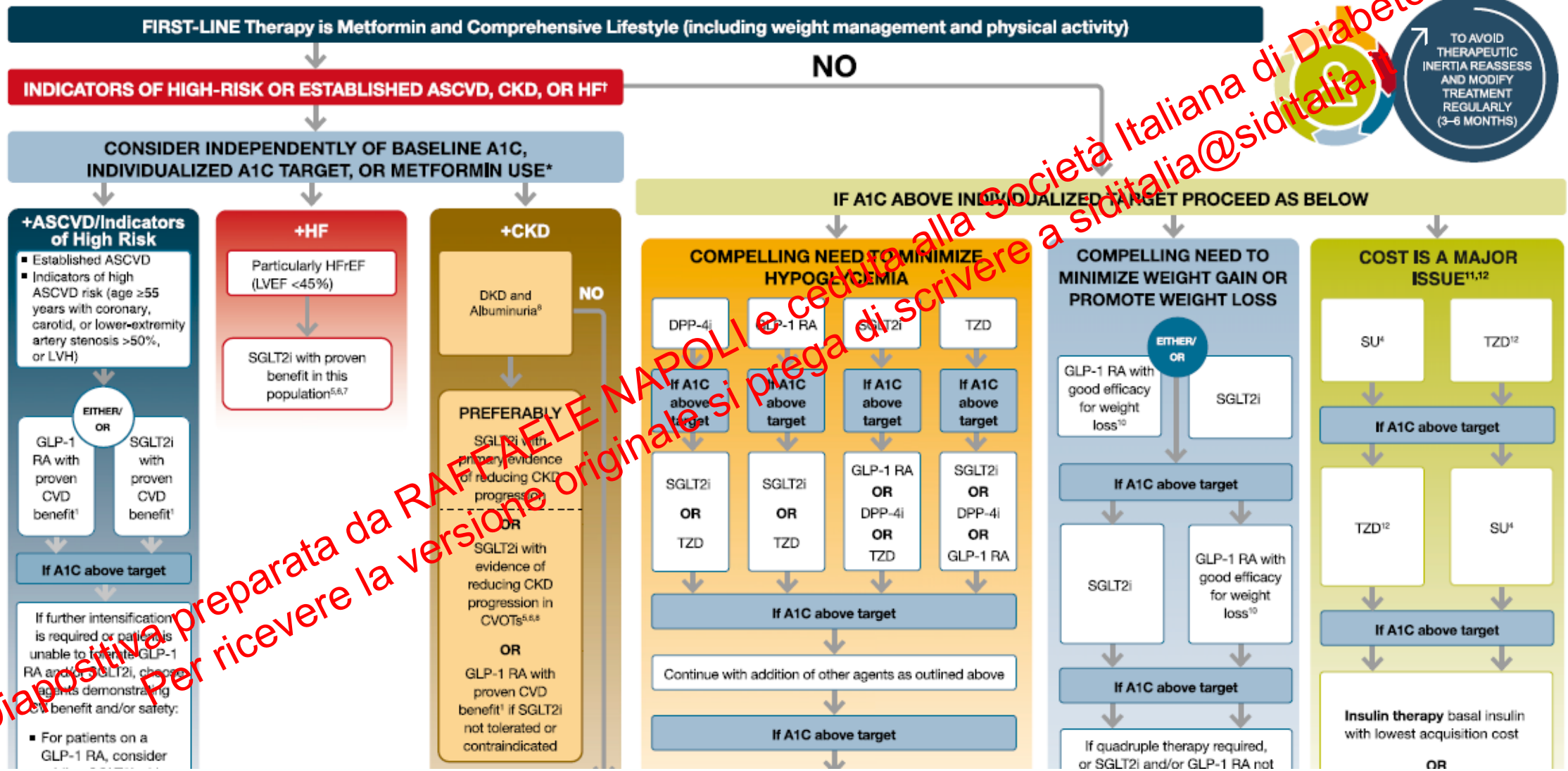
Dichiarazione compensi

Il prof. Raffaele Napoli dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

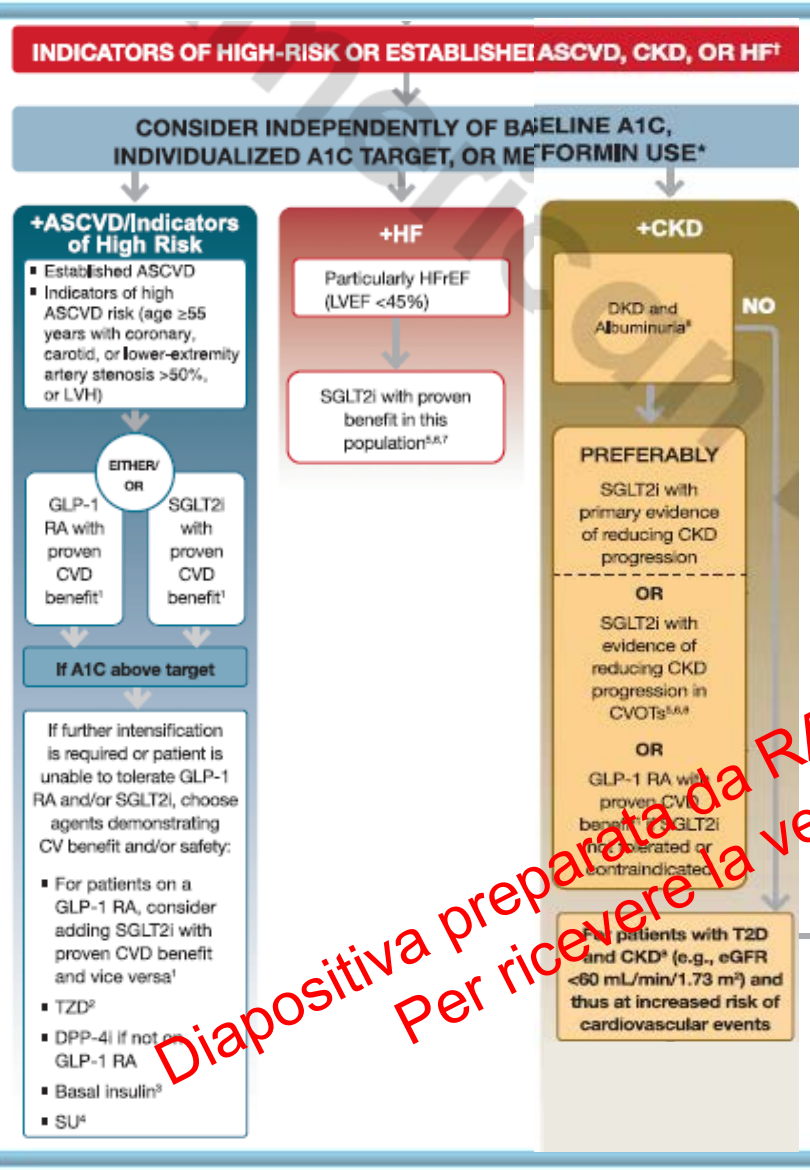
Astra Zeneca, Boehringer Ingelheim, Eli Lilly, MSD, Mundipharma, Novo Nordisk, Sanofi, Servier

Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).

American Diabetes Association

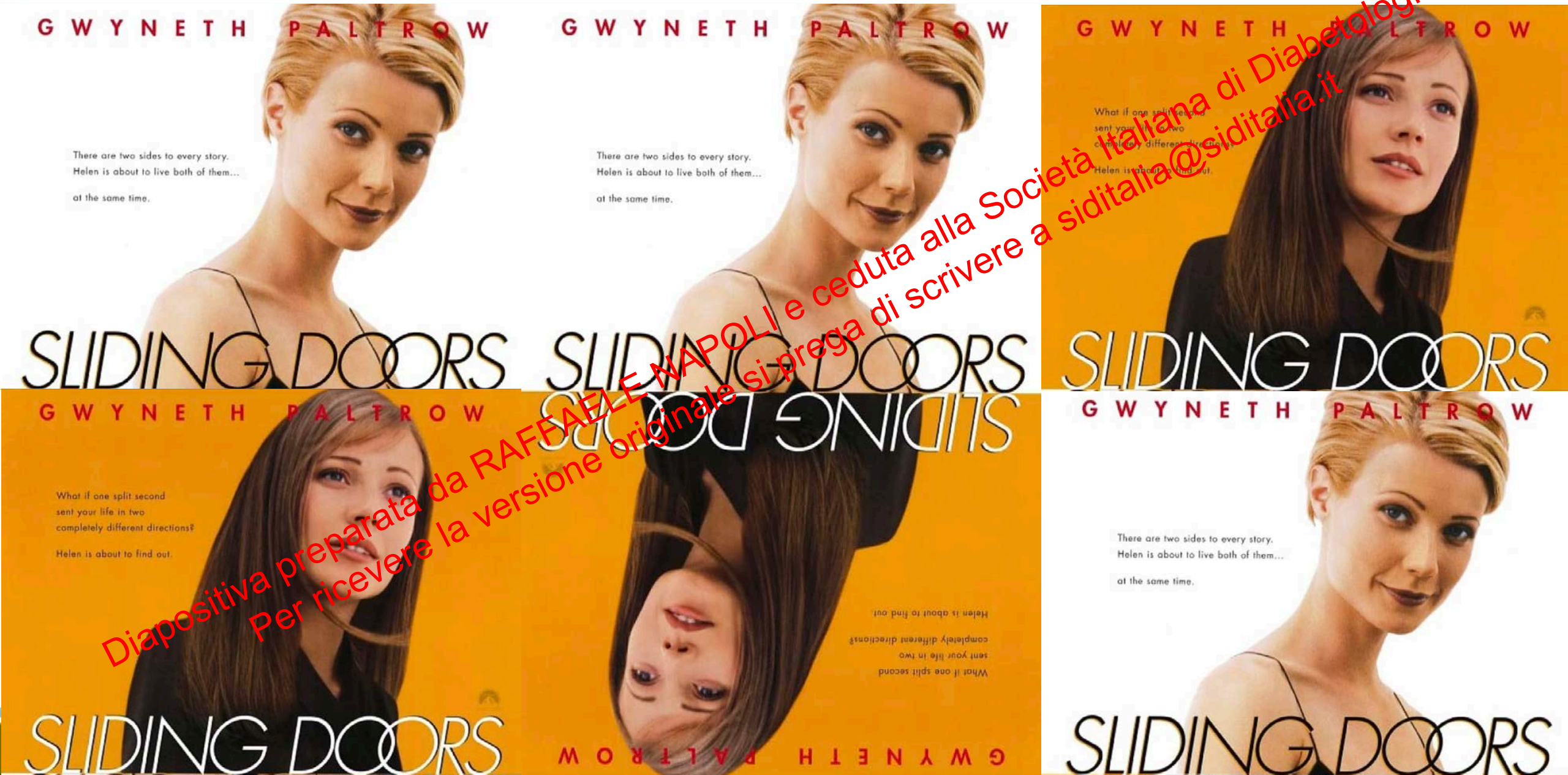


American Diabetes Association

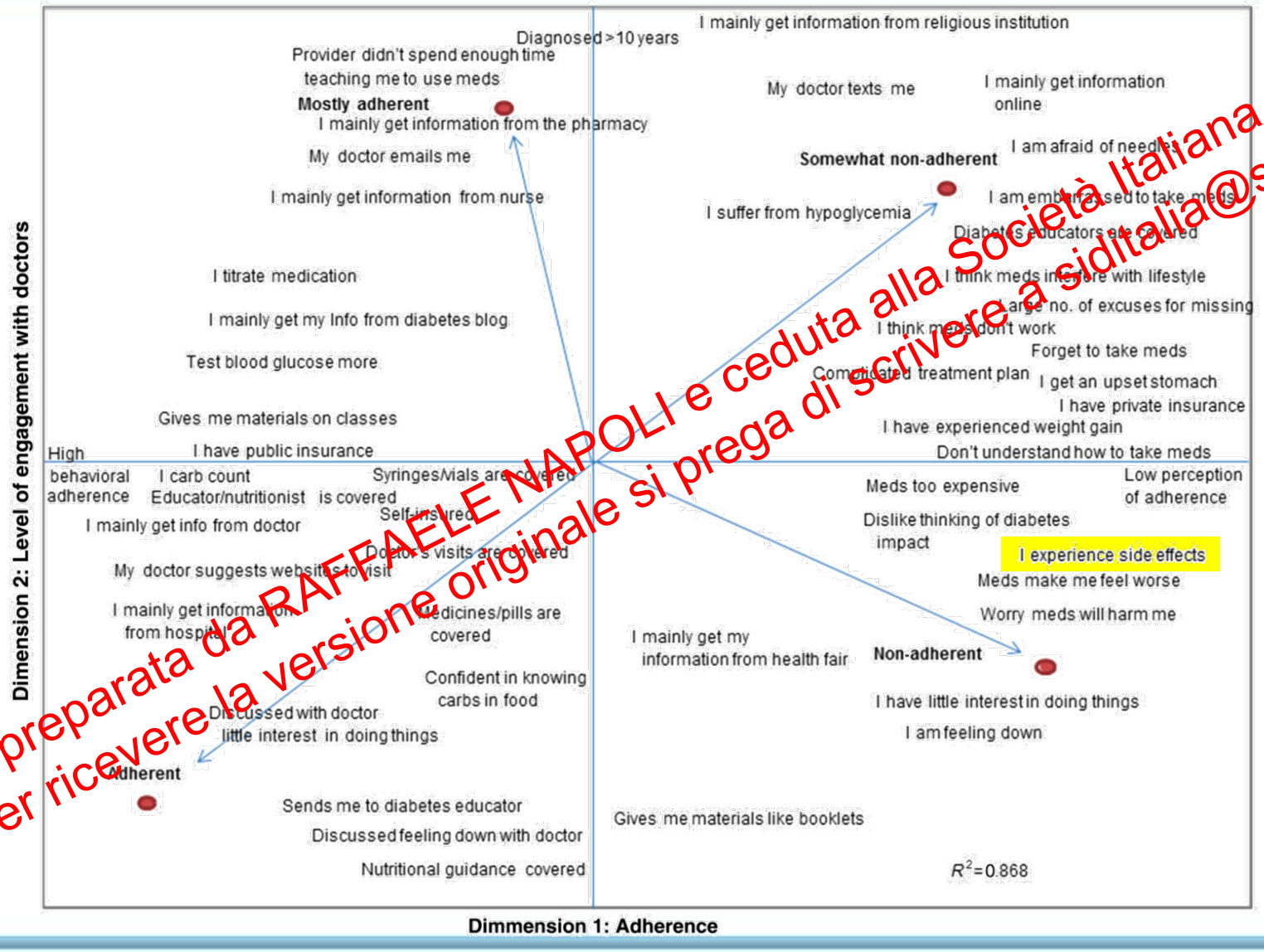


	CV effects		Renal effects	
	ASCVD	HF	Progression of DKD	Dosing/use considerations*
SGLT-2 inhibitors	Benefit: empagliflozin†, canagliflozin	Benefit: empagliflozin†, canagliflozin, dapagliflozin‡	Benefit: canagliflozin§, empagliflozin, dapagliflozin	▪ Renal dose adjustment required (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin)
GLP-1 RAs	Neutral: exenatide once weekly, lixisenatide Benefit: dulaglutide†, liraglutide†, semaglutide†	Neutral	Benefit on renal end points in CVOTs, driven by albuminuria outcomes: liraglutide, semaglutide, dulaglutide	▪ Exenatide, lixisenatide: avoid for eGFR <30 mL/min/1.73 m² ▪ No dose adjustment for dulaglutide, liraglutide, semaglutide ▪ Caution when initiating or increasing dose due to potential risk of nausea, vomiting, diarrhea, or dehydration. Monitor renal function in patients reporting severe adverse GI reactions when initiating or increasing dose of therapy.

Effetti collaterali di GLP-1RA (vs SGLT2i?): what-is e what-if

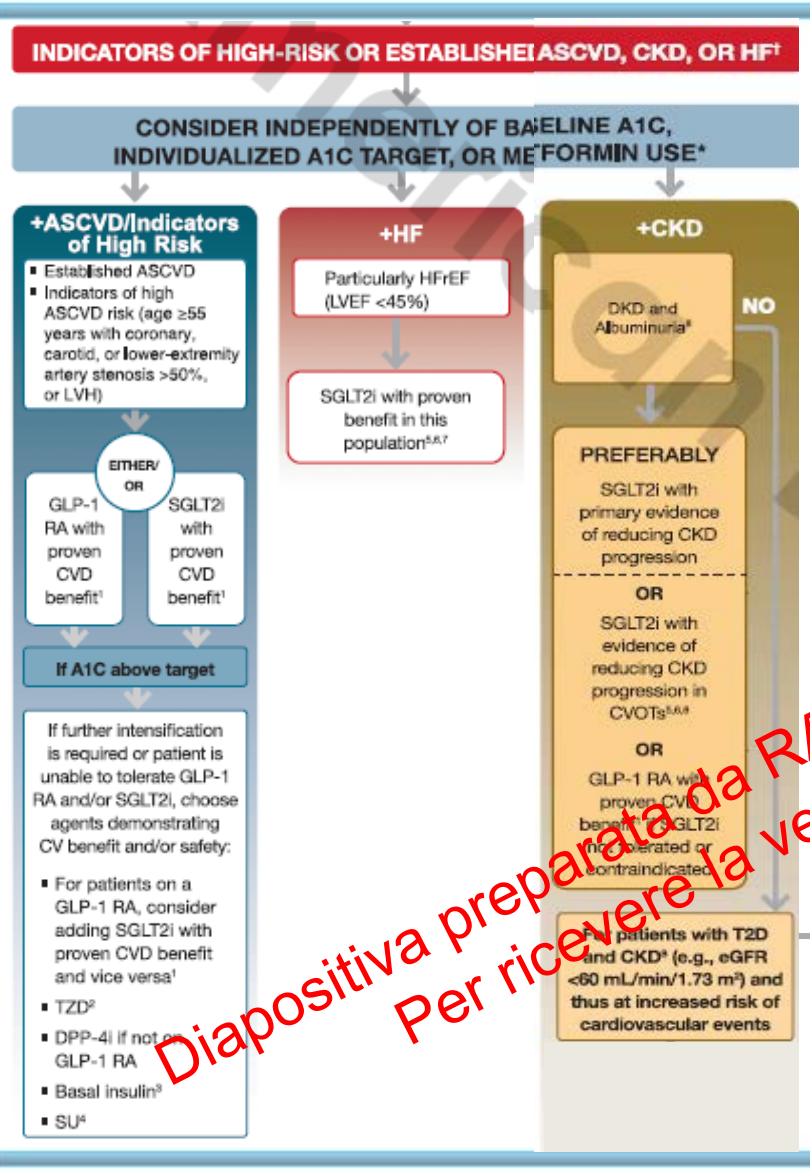


Determinants of adherence to diabetes treatment



Larkin AT et al., J of Diabetes 2015

American Diabetes Association



	CV effects		Renal effects		Additional considerations
	ASCVD	HF	Progression of DKD	Dosing/use considerations*	
SGLT-2 inhibitors	Benefit: empagliflozin†, canagliflozin	Benefit: empagliflozin†, canagliflozin, dapagliflozin‡	Benefit: canagliflozin§, empagliflozin, dapagliflozin	▪ Renal dose adjustment required (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin)	▪ Should be discontinued before any scheduled surgery to avoid potential risk for DKA ▪ DKA risk (all agents, rare in T2D) ▪ Risk of bone fractures (canagliflozin) ▪ Genitourinary infections ▪ Risk of volume depletion, hypotension ▪ ↑LDL cholesterol ▪ Risk of Fournier's gangrene
GLP-1 RAs	Neutral: exenatide once weekly, lixisenatide Benefit: dulaglutide†, liraglutide†, semaglutide†	Neutral	Benefit on renal end points in CVOTs, driven by albuminuria outcomes: liraglutide, semaglutide, dulaglutide	▪ Exenatide, lixisenatide: avoid for eGFR <30 mL/min/1.73 m² ▪ No dose adjustment for dulaglutide, liraglutide, semaglutide ▪ Caution when initiating or increasing dose due to potential risk of nausea, vomiting, diarrhea, or dehydration. Monitor renal function in patients reporting severe adverse GI reactions when initiating or increasing dose of therapy.	▪ **FDA Black Box:** Risk of thyroid C-cell tumors in rodents; human relevance not determined **(liraglutide, albiglutide, dulaglutide, exenatide extended release, semaglutide)** ▪ GI side effects common (nausea, vomiting, diarrhea) ▪ Injection site reactions ▪ Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected.

Adverse effects of GLP-1 RA and SGLT2i

GLP-1 RAs

- **FDA Black Box:** Risk of thyroid C-cell tumors (**liraglutide, albiglutide, dulaglutide, exenatide extended release**)
- Gastrointestinal side effects common (nausea, vomiting, diarrhea)
- Injection site reactions
- ?Acute pancreatitis risk

SGLT-2 inhibitors

- **FDA Black Box:** Risk of amputation (**canagliflozin**)
- Risk of bone fractures (canagliflozin)
- DKA risk (all agents, rare in T2DM)
- Genitourinary infections
- Risk of volume depletion, hypotension
- ↑LDL cholesterol
- Risk of Fournier's gangrene

Adverse effects of GLP-1 RA and SGLT2i

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Adverse effects of GLP-1 receptor agonists

- Gastrointestinal
- Pancreatitis
- C cell proliferation and Thyroid cancer
- Hypoglycemia
- Cardiovascular safety

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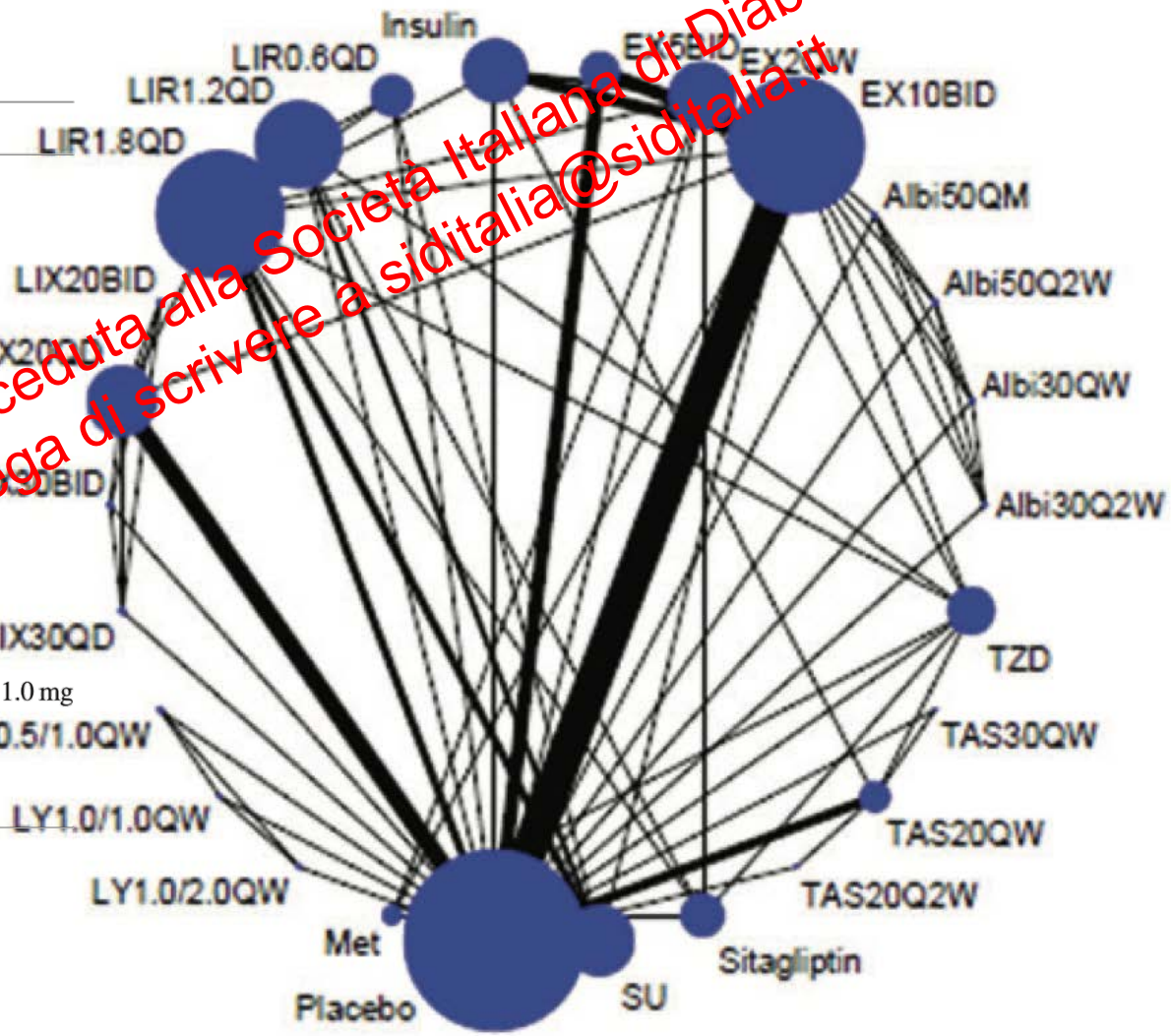
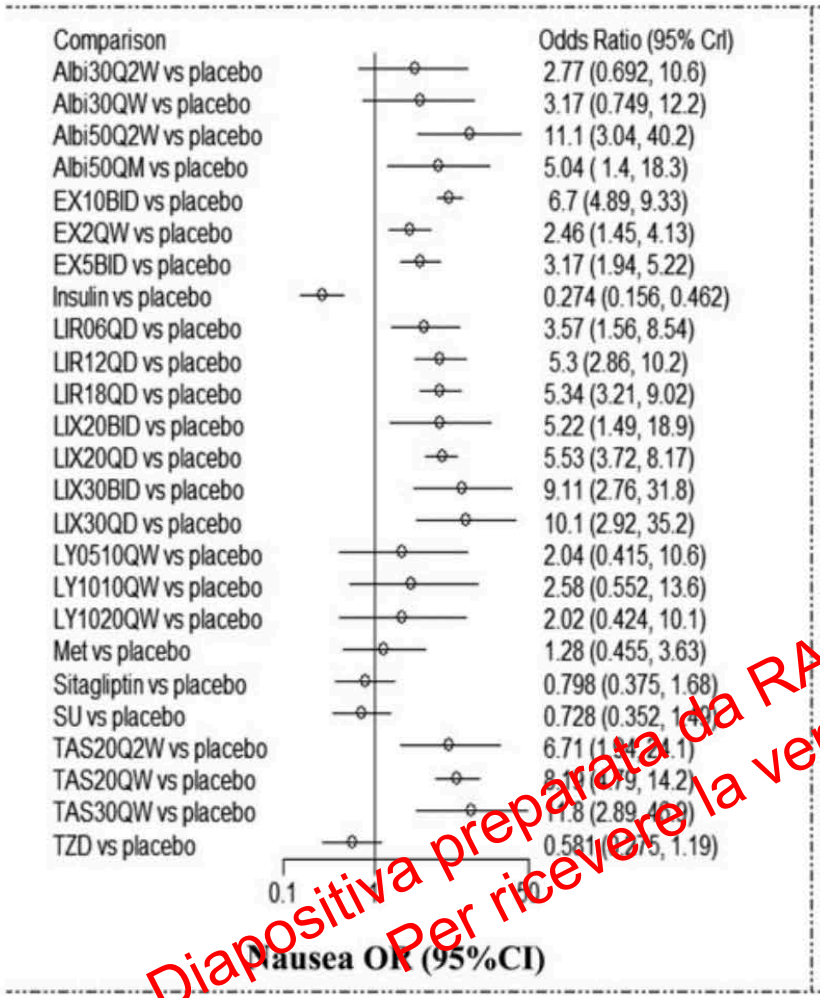
Gastrointestinal Adverse effects of GLP-1 receptor agonists

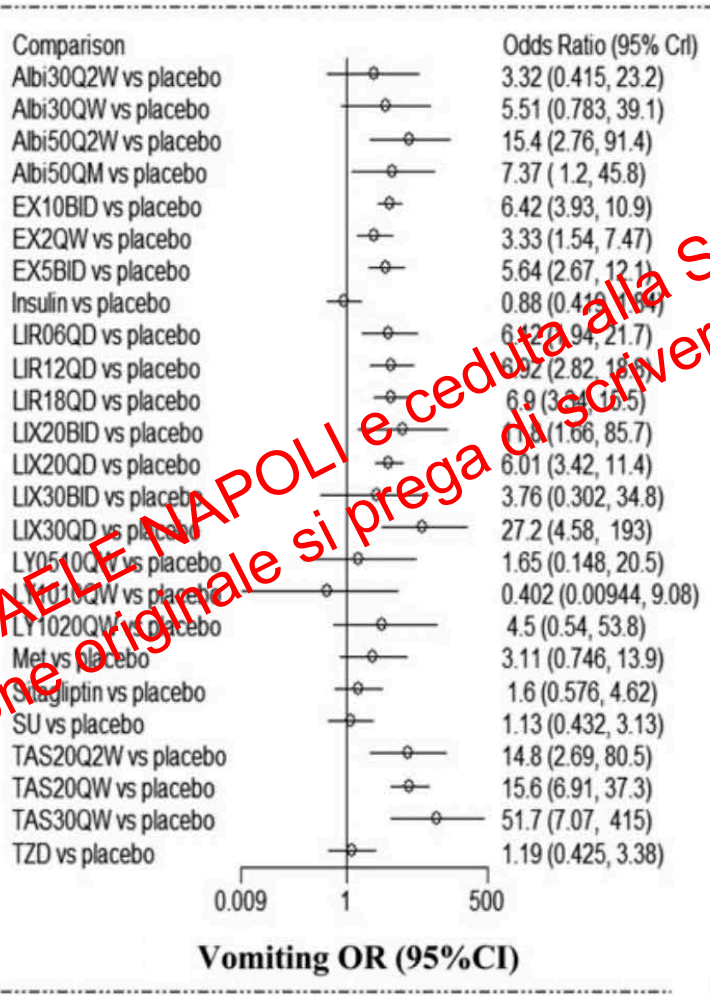
GLP-1 RAs	*Abbreviation*	*Clinical dosage*	*Explanation of dose-arm*
Albiglutide	Albi	Albi30Q2W	30 mg once biweekly
		Albi30QW	30 mg once weekly
		Albi50Q2W	50 mg once biweekly
		Albi50QM	50 mg once monthly
Exenatide	EX	EX5BID	5 μg twice daily
		EX10BID	10 μg twice daily
		EX2QW	2 mg once weekly
Liraglutide	LIR	LIR0.6QD	0.6 mg once daily
		LIR1.2QD	1.2 mg once daily
		LIR1.8QD	1.8 mg once daily
Taspoglutide	TAS	TAS20Q2W	20 mg once weekly
		TAS20QW	20 mg once biweekly
		TAS30QW	30 mg once weekly
Lixisenatide	LIX	LIX20BID	20 μg twice daily
		LIX20QD	20 μg once daily
		LIX30BID	30 μg twice daily
		LIX30QD	30 μg once daily
LY2189265	LY	LY0.5/1.0QW	0.5 mg once weekly for 4 weeks, then 1.0 mg once weekly for 12 weeks
		LY1.0/1.0QW	1.0 mg once weekly for 16 weeks
		LY1.0/2.0QW	1.0 mg once weekly for 4 weeks, then 2.0 mg once weekly for 12 weeks

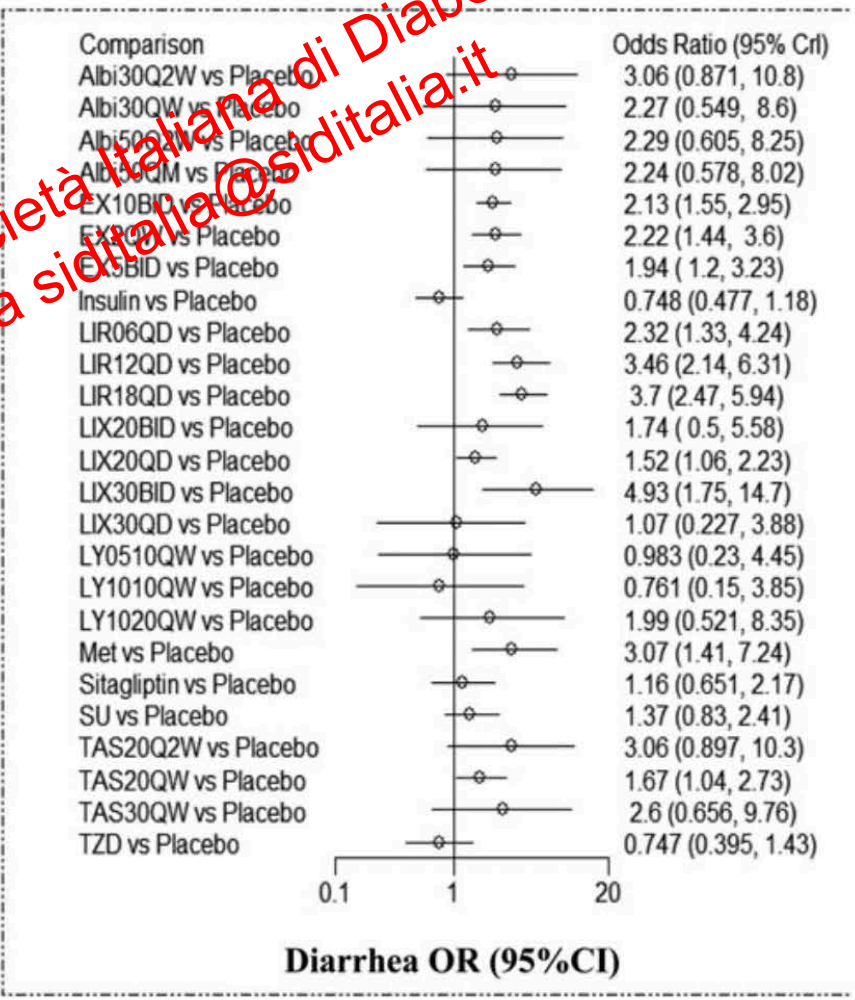


Sun F et al., DIABETES TECHNOLOGY & THERAPEUTICS 2015

Gastrointestinal Adverse effects of GLP-1 receptor agonists







Gastrointestinal Adverse effects of GLP-1 receptor agonists

Treatment	Nausea SUCRA	Nausea Rank	Vomiting SUCRA	Vomiting Rank	Diarrhea SUCRA	Diarrhea Rank
Albi30Q2W	0.3940	17	0.3784	17	0.6488	6
Albi30QW	0.4436	13	0.5072	14	0.4848	14
Albi50Q2W	**0.8188**	**2**	0.7652	4	0.5572	10
Albi50QM	0.5828	11	0.6076	7	0.5484	11
EX10BID	0.7144	6	0.5728	9	0.5316	12
EX2QW	0.3220	18	0.3448	19	0.5732	9
EX5BID	0.3976	16	0.5164	13	0.4712	15
Insulin	0.0004	26	0.0604	25	0.0644	26
LIR0.6QD	0.4420	14	0.5372	11	0.5908	8
LIR1.2QD	0.6132	9	0.5708	10	**0.7828**	**3**
LIR1.8QD	0.5968	10	0.5848	8	**0.8072**	**2**
LIX20BID	0.5800	12	0.6820	6	0.4328	16
LIX20QD	0.6256	8	0.5348	12	0.3480	18
LIX30BID	0.7564	5	0.4120	16	**0.8476**	**1**
LIX30QD	**0.7936**	**3**	**0.8460**	**2**	0.2504	20
LY0.5/1.0	0.3056	20	0.2416	20	0.2228	22
LY1.0/1.0	0.4072	15	0.0312	26	0.1468	23
LY1.0/2.0	0.3184	19	0.4584	15	0.4864	13
Met	0.1808	21	0.3484	18	0.3516	4
SU	0.0744	24	0.1104	23	0.2912	19
Sitagliptin	0.0880	23	0.1808	21	0.2292	21
TAS20Q2W	0.6948	7	0.7352	5	0.6580	5
TAS20QW	0.7088	4	**0.7888**	**3**	0.3900	17
TAS30QW	**0.8320**	**1**	**0.8852**	**1**	0.5952	7
TZD	0.0368	25	0.1216	22	0.0648	25
Placebo	0.1360	22	0.0848	24	0.1428	24

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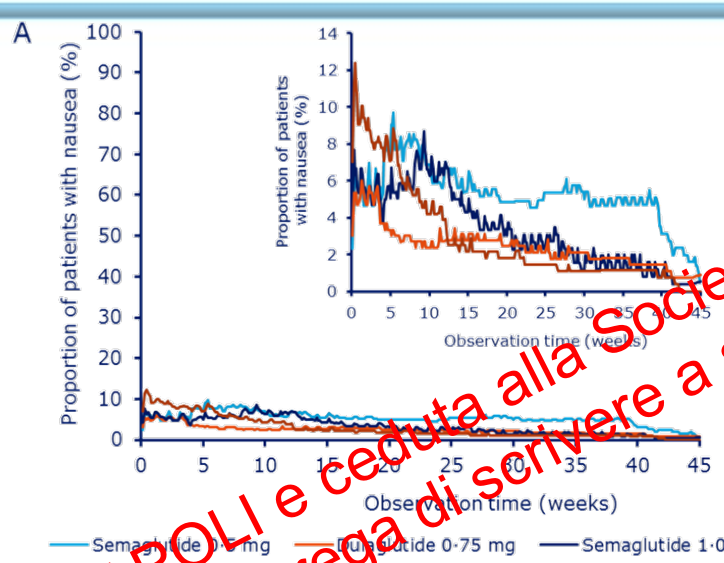
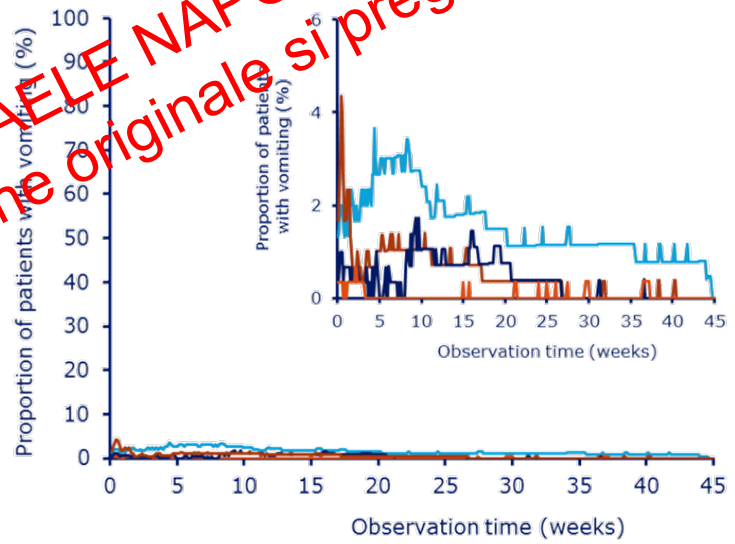


	Semaglutide 0·5 mg (n=301)	Dulaglutide 0·75 mg (n=299)	Semaglutide 1·0 mg (n=300)	Dulaglutide 1·5 mg (n=299)
N° of patients with event [E]	84 [145]	30 [66]	63 [192]	60 [108]

	n	E	(E%)	n	E	(E%)	n	E	(E%)	n	E	(E%)
Mild	60	127	(87·6)	34	60	(90·9)	51	147	(76·6)	48	84	(77·8)
Moderate	11	12	(8·3)	6	6	(9·1)	22	42	(21·9)	16	21	(19·4)
Severe	6	6	(4·1)	0			3	3	(1·6)	3	3	(2·8)



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N° of patients with event [E]	31 [51]	12 [16]	31 [48]	29 [40]

	n	E	(E%)	n	E	(E%)	n	E	(E%)	n	E	(E%)
Mild	25	39	(76·5)	11	15	(93·8)	18	25	(52·1)	18	22	(55·0)
Moderate	6	7	(13·7)	1	1	(6·3)	13	21	(43·8)	11	16	(40·0)
Severe	4	5	(9·8)	0			1	2	(4·2)	2	2	(5·0)

Sun F et al., DIABETES TECHNOLOGY & THERAPEUTICS 2015, & Pratley RA et al., Lancet Diabetes Endocrinology 2018

Gastrointestinal Adverse effects of GLP-1 receptor agonists

	Nausea		*Vomiting*		*Diarrhea*	
Treatment	*SUCRA*	*Rank*	*SUCRA*	*Rank*	*SUCRA*	*Rank*
Albi30Q2W	0.3940	17	0.3784	17	0.6488	6
Albi30QW	0.4436	13	0.5072	14	0.4848	14
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TAS20QW	0.7888	4	**0.7888**	**3**	0.3900	17
TAS30QW	**0.8320**	**1**	**0.8852**	**1**	0.5952	7
TZD	0.0368	25	0.1216	22	0.0648	25
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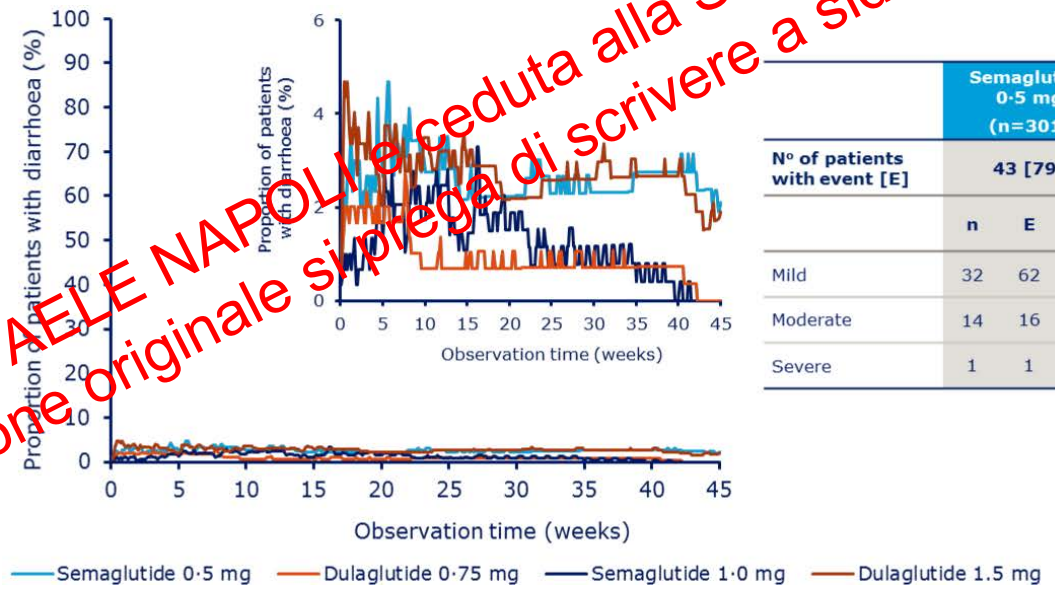

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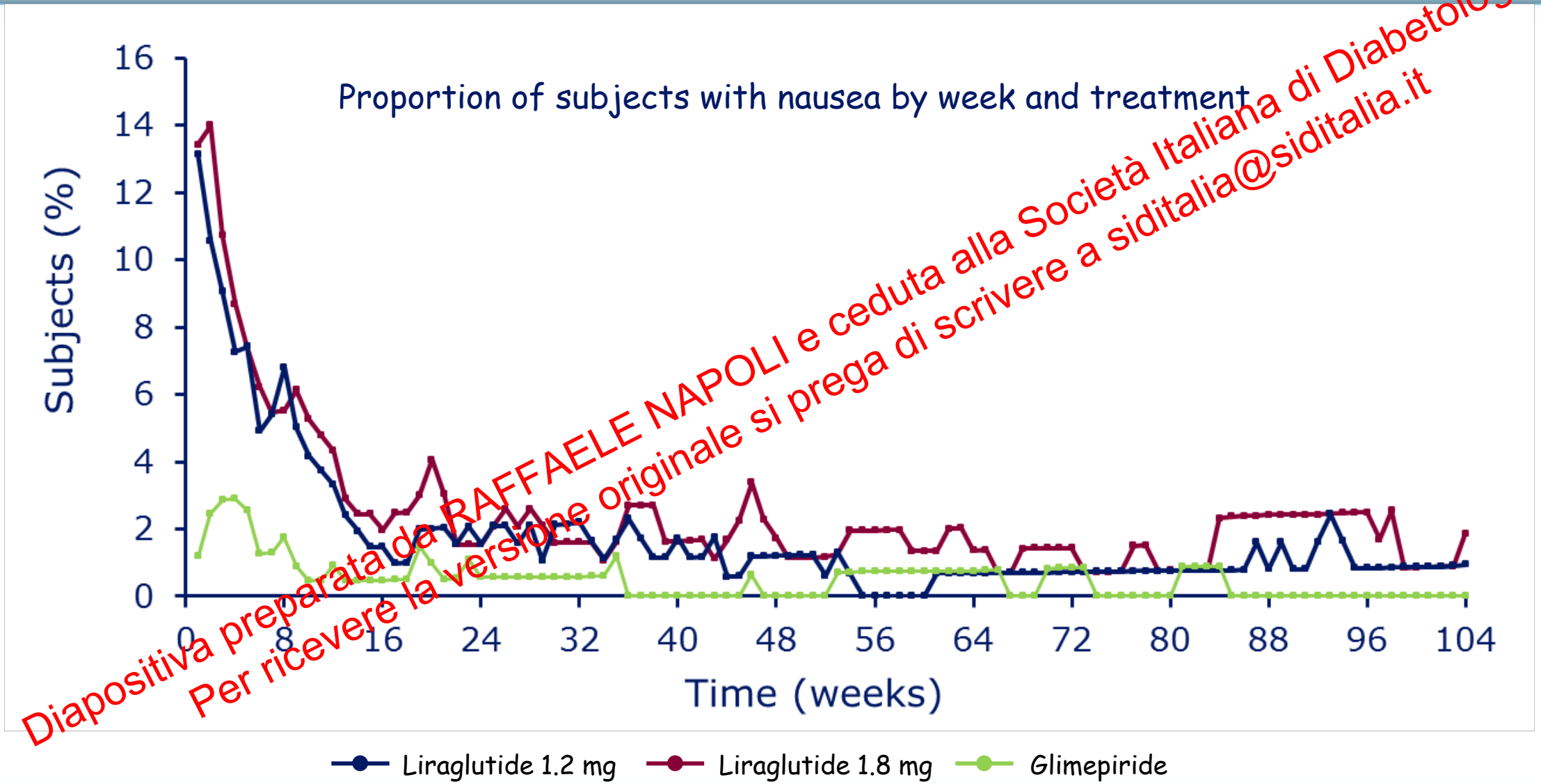
N° of patients with event [E]	43 [79]			23 [42]			41 [96]			53 [75]		
	n	E	(E%)	n	E	(E%)	n	E	(E%)	n	E	(E%)
Mild	32	62	(78·5)	19	33	(78·6)	33	76	(79·2)	41	61	(81·3)
Moderate	14	16	(20·3)	6	8	(19·0)	12	19	(19·8)	11	12	(16·0)
Severe	1	1	(1·3)	1	1	(2·4)	1	1	(1·0)	2	2	(2·7)

Sun F et al., DIABETES TECHNOLOGY & THERAPEUTICS 2015 & Pratley RA et al., Lancet Diabetes Endocrinology 2018

Nausea with liraglutide is transient



Garber et al. Diabetes Obes Metab 2011

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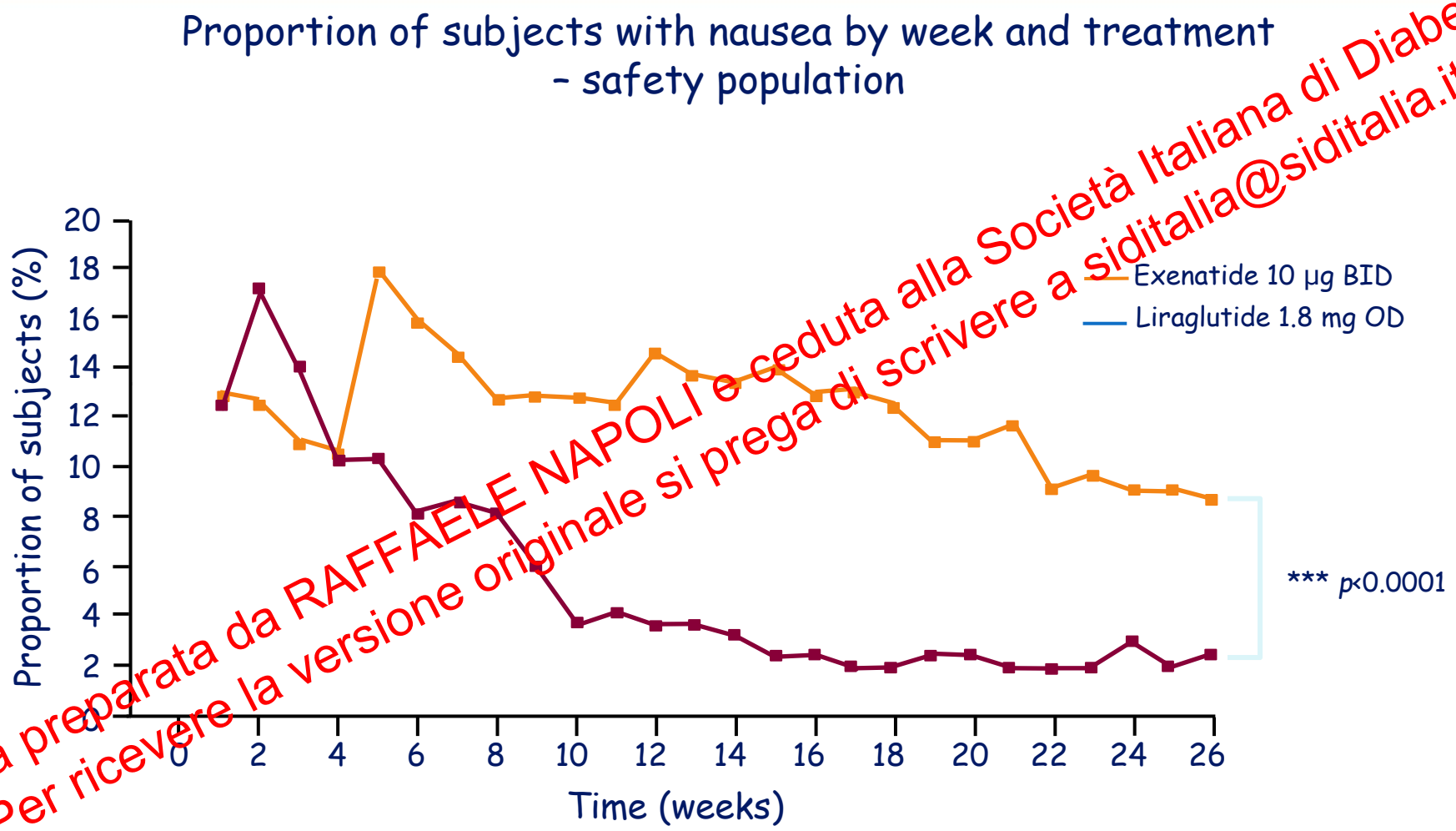
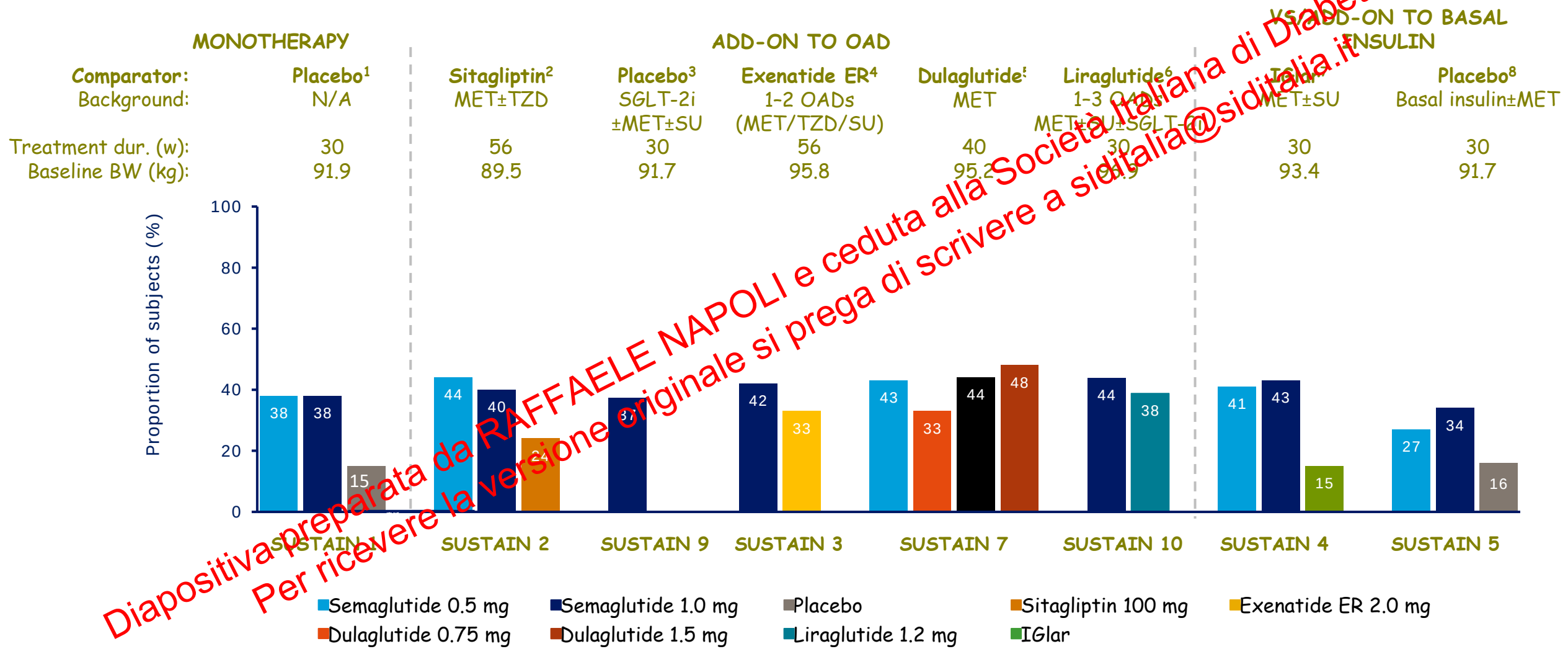


***p<0.0001 for treatment differences (estimated treatment rate ratio for liraglutide vs. exenatide, 0.448)
Data are number (%) of patients exposed to treatment (safety population)

Proportion of subjects reporting GI AEs



1. Sorli C et al. *Lancet Diabetes Endocrinol* 2017; 2. Ahrén B et al. *Lancet Diabetes Endocrinol* 2017; 3. Ahmann AJ et al. *Diabetes Care* 2018; 4. Aroda VR et al. *Lancet Diabetes Endocrinol* 2017; 5; Rodbard HW et al. *J Clin Endocrinol Metab* 2018; 6. Pratley RE et al. *Lancet Diabetes Endocrinol* 2018; 7. Zinman B et al. *Lancet Diabetes*

Gastrointestinal Adverse Events with Semaglutide

Event	Semaglutide		Placebo	
	0.5 mg (N=826)	1.0 mg (N=822)	0.5 mg (N=824)	1.0 mg (N=825)
	number of patients (percent)			
Adverse event leading to treatment discontinuation	95 (11.5)	119 (14.5)	47 (5.7)	63 (7.6)
Nausea	18 (2.2)	38 (4.6)	2 (0.2)	2 (0.2)
Vomiting	14 (1.7)	23 (2.8)	3 (0.4)	2 (0.2)
Diarrhea	15 (1.8)	19 (2.3)	5 (0.6)	2 (0.2)
Gastrointestinal disorder§	419 (50.7)	430 (52.3)	294 (35.7)	290 (35.2)
Diarrhea	148 (17.9)	151 (18.4)	98 (11.9)	87 (10.5)
Nausea	143 (17.3)	180 (21.9)	62 (7.5)	67 (8.1)
Vomiting	87 (10.5)	122 (14.8)	43 (5.2)	34 (4.1)

Marso SP et al., NEJM 2016

Adverse event overview

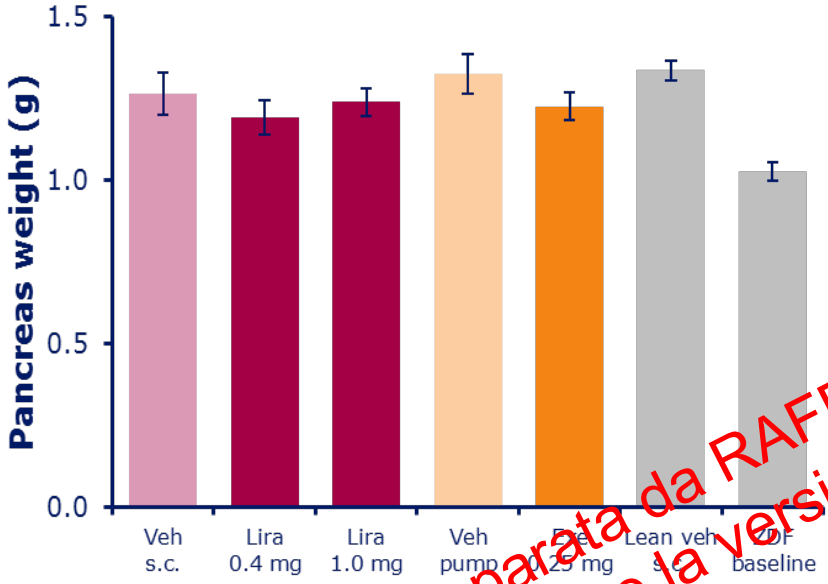
Proportion of subjects (%)	Monotherapy[1] SUSTAIN 1 — 30 weeks			Vs sitagliptin[2] SUSTAIN 2 — 56 weeks*			Vs exenatide ER[3] SUSTAIN 3 — 56 weeks*		Vs IGlar[4] SUSTAIN 4 — 30 weeks			Add-on to basal insulin[5] SUSTAIN 5 — 30 weeks			Vs dulaglutide[6] SUSTAIN 7 — 40 weeks				Add-on to SGLT-2i Vs placebo SUSTAIN 9[7] — 30 weeks		Vs liraglutide SUSTAIN 10[8] — 30 weeks	
	Sema		PBO	Sema		Sita	Sema	Exe	Sema		IGlar	Sema		PBO	Sema		Dula		Sema	PBO	Sema	Lira
	0.5 mg	1.0 mg		0.5 mg	1.0 mg	100 mg	1.0 mg	2.0 mg	0.5 mg	1.0 mg		0.5 mg	1.0 mg		0.5 mg	1.0 mg	0.75 mg	1.5 mg	1.0 mg		1.0 mg	1.2 mg
AEs	64	56	53	75	71	72	75	76	70	73	65	69	64	58	68	69	62	74	69	60	71	66
Serious AEs	5	5	4	7	7	7	9	6	6	5	5	6	9	7	6	8	8	7	5	4	6	8
Discontinuation due to AEs	6	5	2	8	10	3	9	7	6	8	1	5	6	1	8	10	5	7	9	2	11	7
Discontinuation due to GI AEs[9]	4	3	1	7	8	1	6	3	3	5	0	2	5	0	5	6	2	5	7	0	8	4

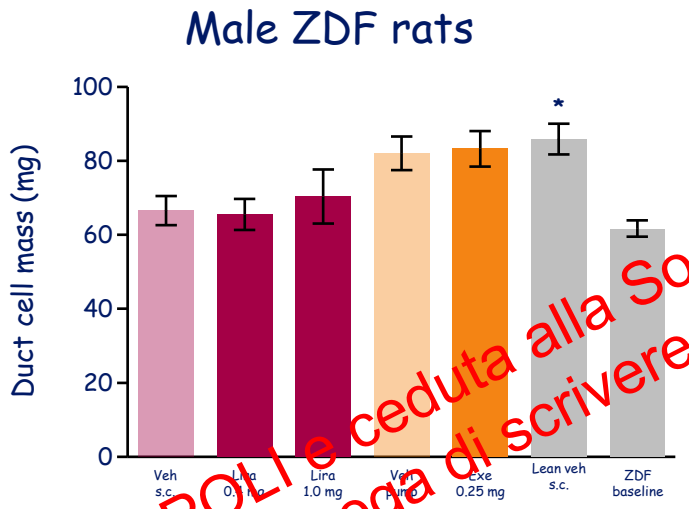
1. Sorli C et al. *Lancet Diabetes Endocrinol* 2017; 2. Ahrén B et al. *Lancet Diabetes Endocrinol* 2017; 3. Ahmann AJ et al. *Diabetes Care* 2018; 4. Aroda VR et al. *Lancet Diabetes Endocrinol* 2017; 5; Rodbard HW et al. *J Clin Endocrinol Metab* 2018; 6. Pratley RE et al. *Lancet Diabetes Endocrinol* 2018; 7. Zinman B et al. *Lancet Diabetes*

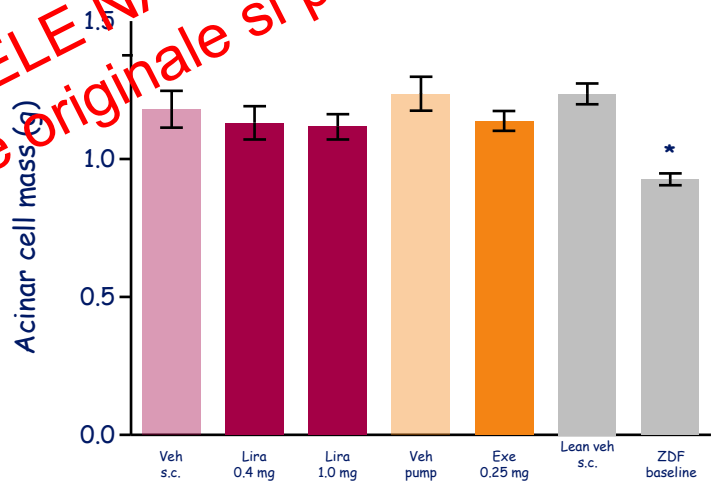
Adverse effects of GLP-1 receptor agonists

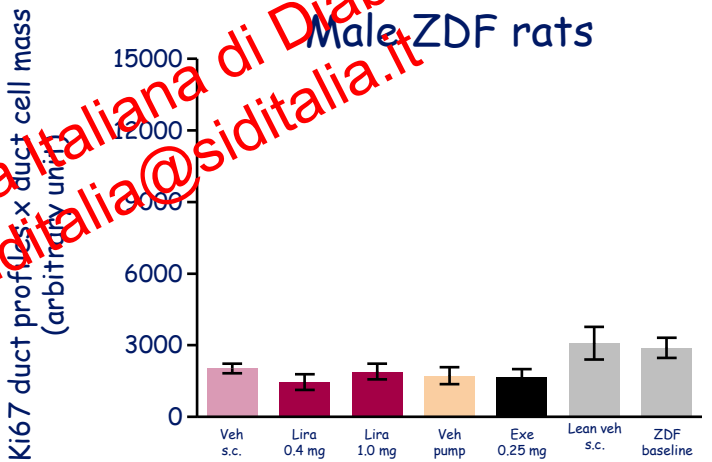
- Gastrointestinal
- Pancreatitis
- C cell proliferation and Thyroid cancer
- Hypoglycemia
- Cardiovascular safety

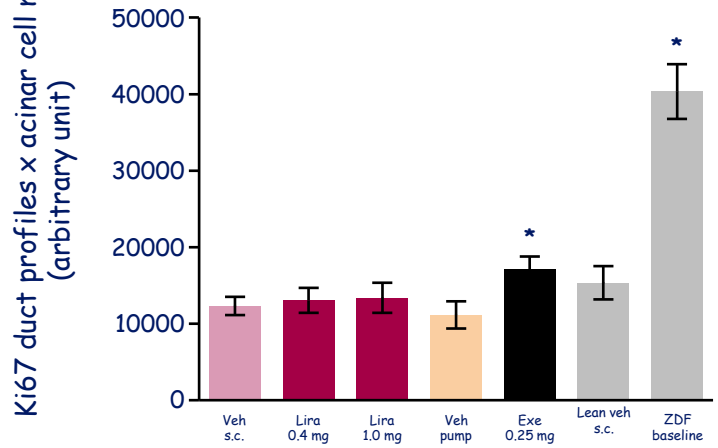
Liraglutide and exenatide had no effect on overall pancreas weight or on acinar or duct cell mass or proliferation



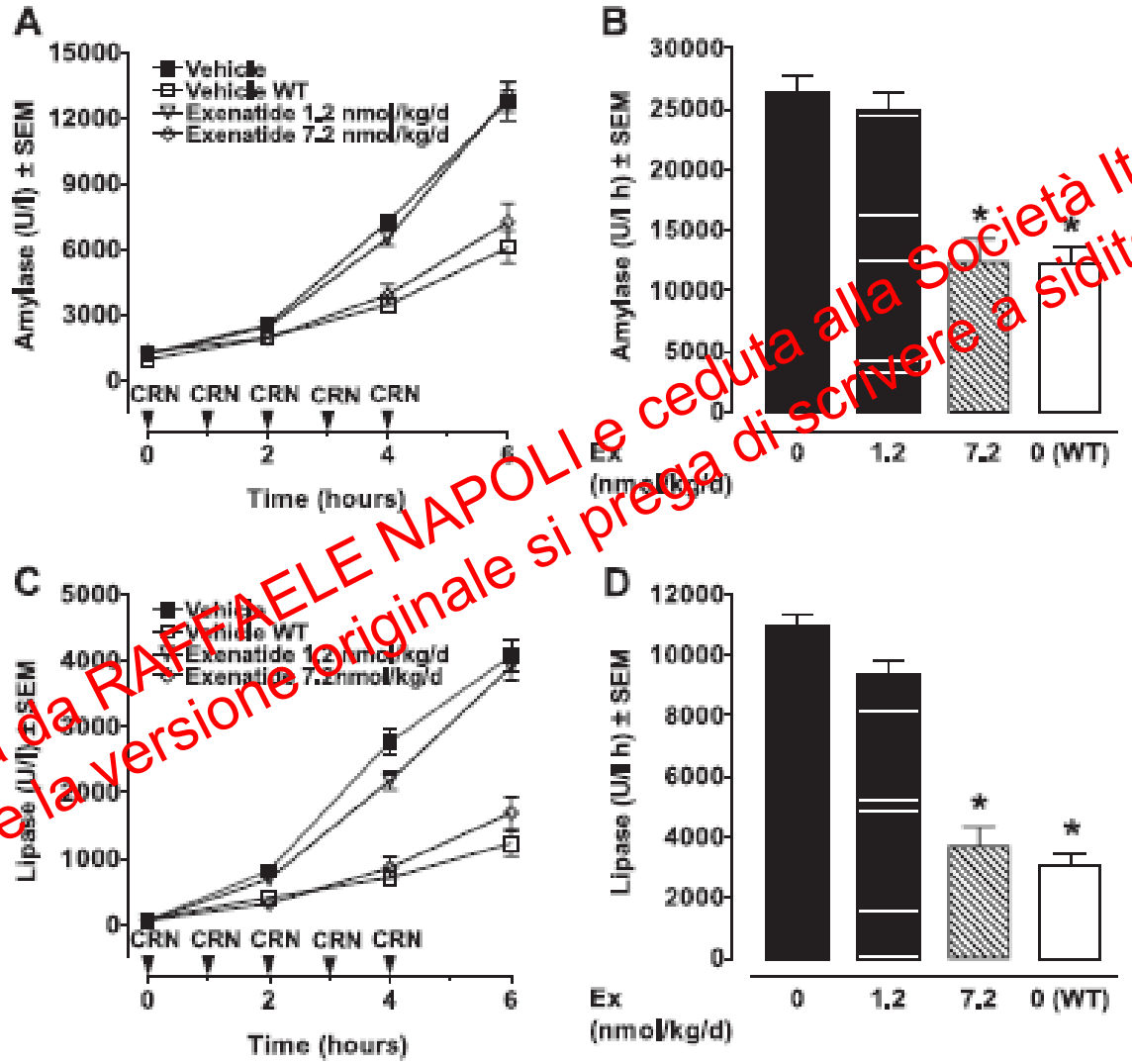








Exenatide does not evoke pancreatitis and attenuates chemically induced pancreatitis in normal and diabetic rodents



Tatarkiewicz K, *Am J Physiol Endocrinol Metab 299: E1076–E1086, 2010*

Rodent and monkey toxicology studies

No evidence of cellular metaplasia or ductal hyperplasia

- Macroscopic: no signs
- Microscopic:
  - No pancreatitis in rats or monkeys
  - Pancreatitis equally distributed across groups in mice and not the cause of death for any animal

MICE (104 weeks)	Male					Female				
Liraglutide (mg/kg/day)	0	0.03 [0.2]	0.2 [1.6]	1.0 [13]	3.0 [36]	0	0.03 [0.2]	0.2 [1.6]	1.0 [13]	3.0 [36]
No. examined	79	67	67	67	79	79	67	66	66	76
No. with microscopic pancreatitis	3	2	1	1	1	0	3	3	3	3

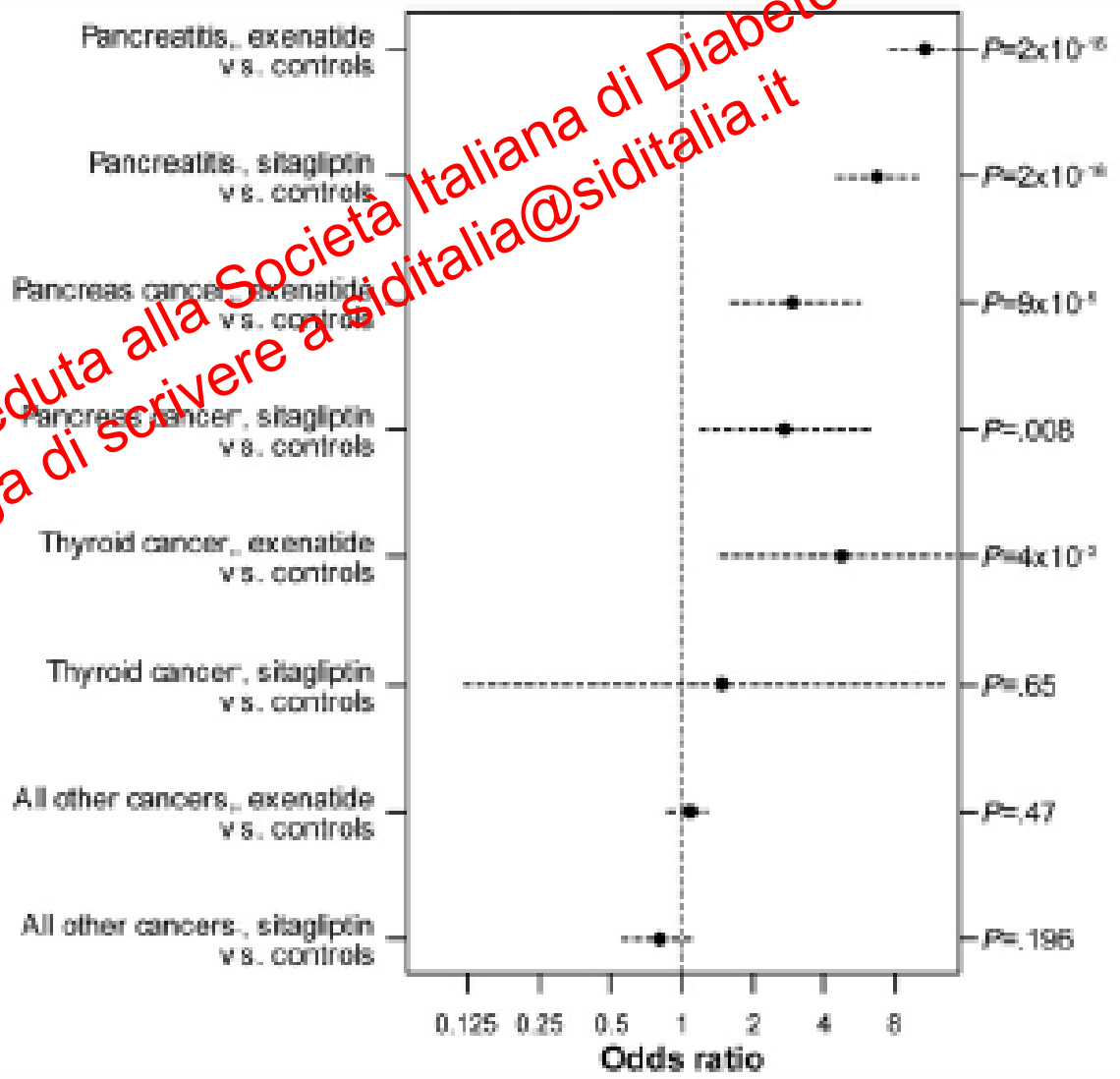
RATS (104 weeks)	Male				Female			
Liraglutide (mg/kg/day)	0	0.075 [0.5]	0.25 [2.4]	0.75 [8.1]	0	0.075 [0.5]	0.25 [2.4]	0.75 [8.1]
No. examined	50	50	49	50	50	50	50	50
No. with microscopic pancreatitis	0	0	0	0	0	0	0	0

MONKEYS (87 weeks)	Male			Female		
Liraglutide (mg/kg/day)	0	0.25 [9]	5 [63]	0	0.25 [9]	5 [63]
No. examined	5	5	5	5	4	5
No. with microscopic pancreatitis	0	0	0	0	0	0

Number in [ ] indicates x fold human exposure of 1.8mg QD

Pancreatitis, Pancreatic, and Thyroid Cancer w/ GLP-1–Based Therapies

Methods: Search of US Food and Drug Administration's database of reported adverse events for those associated with the dipeptidyl peptidase4 inhibitor sitagliptin and exenatide, from 2004-2009



ELASHOFF M, …, and PETER C. BUTLER, Gastroenterology 2011

Marked Expansion of Exocrine and Endocrine Pancreas With Incretin Therapy in Humans With Increased Exocrine Pancreas Dysplasia and the Potential for Glucagon-Producing Neuroendocrine Tumors

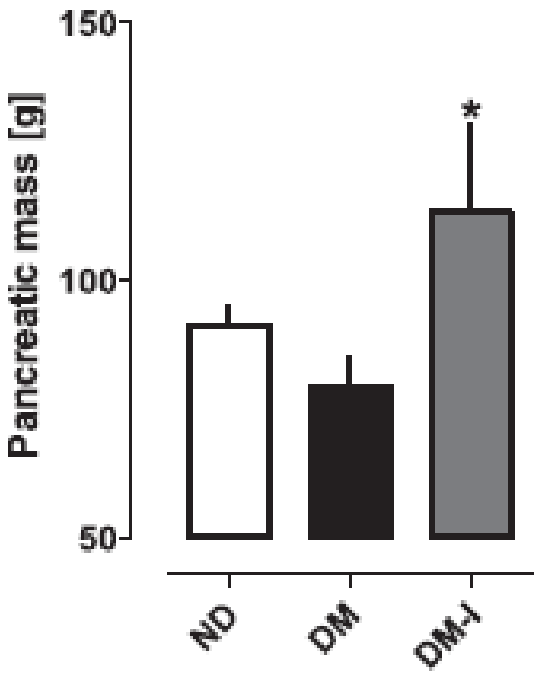
Study subjects. All pancreata were procured from brain-dead organ donors by the JDRF Network for Pancreatic Organ Donors with Diabetes (nPOD) coordinated through the University of Florida in Gainesville, Florida

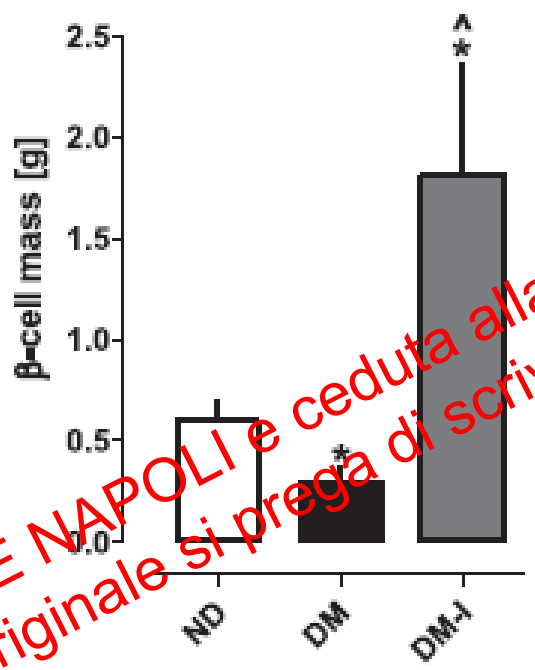
Clinical characteristics of brain-dead organ donors

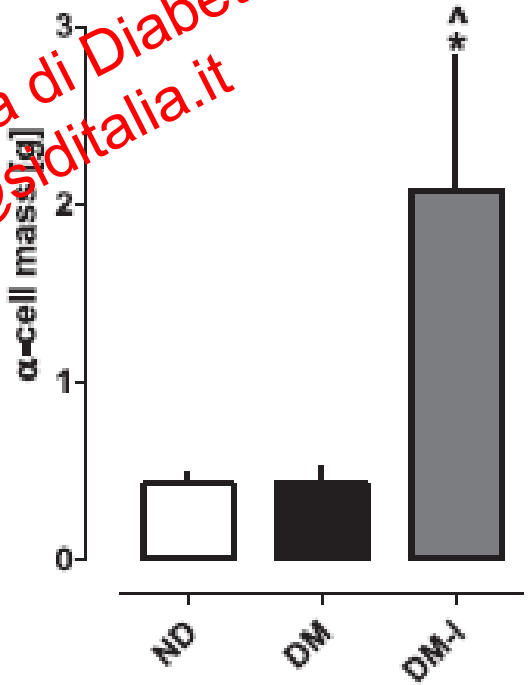
Case	Age (years)	Duration of DM (years)	Sex	BMI (kg/m^2)	Treatments	Cause of death
DM-I						
6157	74	1	F	39	Januvia	ICH/stroke
6185	46	15	M	41	Januvia, metformin	Anoxia
6186	68	5	M	31	Januvia, metformin	ICH/stroke
6189	49	26	F	36	Januvia, metformin, glipizide	Stroke
6199	53	20	M	30	Januvia, insulin pen	ICH/stroke
6194	47	13	M	31	Humulin, NovoLog, Januvia	ICH/stroke
6203	68	5	M	39	Januvia, metformin	Stroke
6206	59	16	M	42	Januvia, metformin	Stroke
Mean (SEM)	58 (4)	12 (3)		33 (3)		
DM						
6028	32	17	M	30	Insulin	Gunshot wound to head
6059	18	6	F	39	None	Cardiovascular
6108	57	2	M	30	Metformin	ICH/stroke
6110	20	0.2	F	40	None	ICH/stroke, DKA
6109	48	—	F	33	None	ICH/stroke, DKA
6114	42	2	M	31	Metformin, noncompliant	Asphyxiation
6124	62	3	M	34	Metformin	ICH/stroke
6130	44	10	F	30	Insulin	ICH/stroke
6133	45	20	F	40	Insulin	Cardiovascular
6139	37	1.5	F	45	None	Seizure
6142	29	14	F	34	None	Bacterial meningitis
6149	39	20	F	29	Insulin	ICH/stroke
Mean (SEM)	40 (4)	8 (3)		35 (2)		
ND						
6009	45		M	31		Anoxia
6015	39		F	32		Anoxia
6012	64		F	31		Cerebrovascular/stroke
6016	42		M	31		Cerebrovascular/stroke
6019	68		F	24		Head trauma
6020	60		M	30		Cerebrovascular/stroke
6022	75		M	31		Cerebrovascular/stroke
6034	32		F	25		Head trauma
6060	24		M	33		Head trauma
6097	43		F	36		Cerebrovascular/stroke
6099	14		M	30		Head trauma
6102	45		F	35		Cerebrovascular/stroke
6158	40		M	30		Head trauma
6165	45		F	25		Cerebrovascular/stroke
Mean (SEM)	45 (5)			30 (1)		

DKA, diabetic ketoacidosis; F, female; ICH, intracerebral hemorrhage; M, male.

Marked Expansion of Exocrine and Endocrine Pancreas With Incretin Therapy in Humans With Increased Exocrine Pancreas Dysplasia and the Potential for Glucagon-Producing Neuroendocrine Tumors







- Endocrine pancreas are markedly enlarged in DM-I individuals,with increased exocrine cell proliferation.

- Alpha-cell hyperplasia and neuroendocrine tumor and microadenoma formation consistent with chronic inhibition of glucagon secretion by GLP-1.

- These findings lend additional weight to concerns regarding the effects of long-term GLP-1–related therapy with respect to unintended proliferative actions on the exocrine pancreas and now also a possible increased risk of neuroendocrine tumors.

The…Butler's Study

Case	Age (years)	Duration of DM (years)	Sex	BMI (kg/m^2)	Treatments	Cause of death
DM-I						
6157	74	1	F	39	Januvia	ICH/stroke
6185	46	15	M	41	Januvia, metformin	Anoxia
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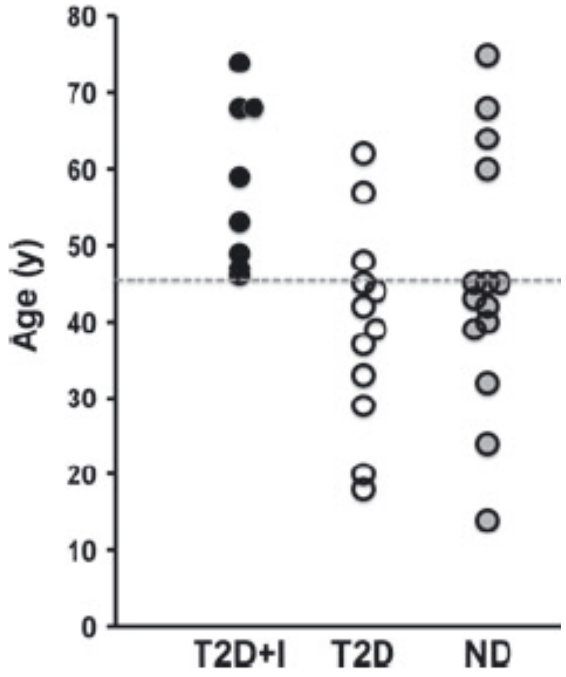
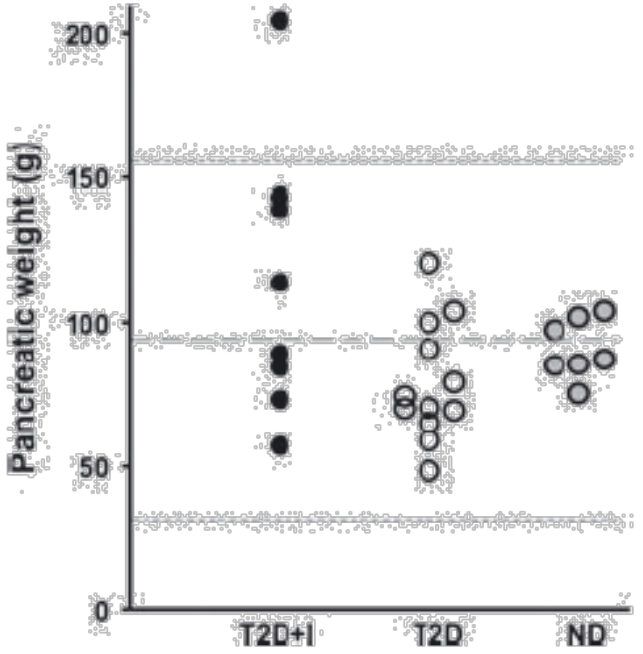
Mean (SEM)	40 (4)	8 (3)		35 (2)		

Butler AE,…, and Peter C. Butler, Diabetes 2013

Reanalysis of study of pancreatic effects of incretin therapy: methodological deficiencies



Conclusions of Butler paper	Our reanalysis
Approximately forty percentage increased pancreatic mass in T2D with incretin therapy compared to T2D controls	One outlier pancreas skewed data; others are within normal range. T2D control group may have included T1D subjects with lower pancreas weight
Increased exocrine proliferation	Proliferation marker Ki67 seen almost exclusively in PanINS, which occur more frequently with increasing age. The treated group was older than controls
Increased pancreatic intraepithelial neoplasia (PanINs)	PanIN occurrence increases with age with few seen under age of 40, and the treated group was older than controls
Alpha cell hyperplasia	• Problematic morphometric measurements due in part to variable intensity of staining • Similar findings in age-matched non-incretin-treated subjects



S. Bonner-Weir & G. C. Weir Diabetes, Obesity and Metabolism 16: 661–666, 2014

Reanalysis of study of pancreatic effects of incretin therapy: methodological deficiencies

Conclusions of Butler paper	Our reanalysis
Occurrence of glucagon-expressing neuroendocrine tumour	Probably an incidental finding since 10% of pancreases from subjects over 60 years have silent endocrine tumours
B cell mass increased sixfold in incretin-treated subjects compared to T2D conventional treatment	• Inappropriate cohort of T2D controls (only 6 agematched T2D) with some subjects probably to be T1D • Problematic morphometric measurements due in part to variable intensity of staining
Increased number of cells coexpressing insulin and glucagon	No reanalysis by us; images of immunofluorescent sections were not in nPOD database

…we find that the data presented in the Butler paper have serious methodological deficiencies that preclude any meaningful conclusions.

S. Bonner-Weir & G. C. Weir. Diabetes, Obesity and Metabolism 16: 661–666, 2014

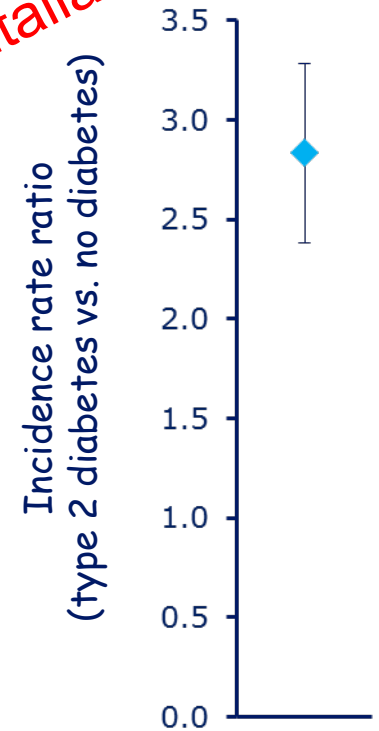
Incidence of pancreatitis

Pancreatitis incidence in the general population

- EU: 0.05–0.5 cases per 1000 healthy person-years[1]
- USA: 0.4–1.9 cases per 1000 healthy person-years[2–5]

Pancreatitis incidence in people with type 2 diabetes

- Patients with type 2 diabetes have a 1.5- to 3-fold higher risk than the general population[2,6,7]
- Up to 5.6 cases per 1000 patient-years[5]



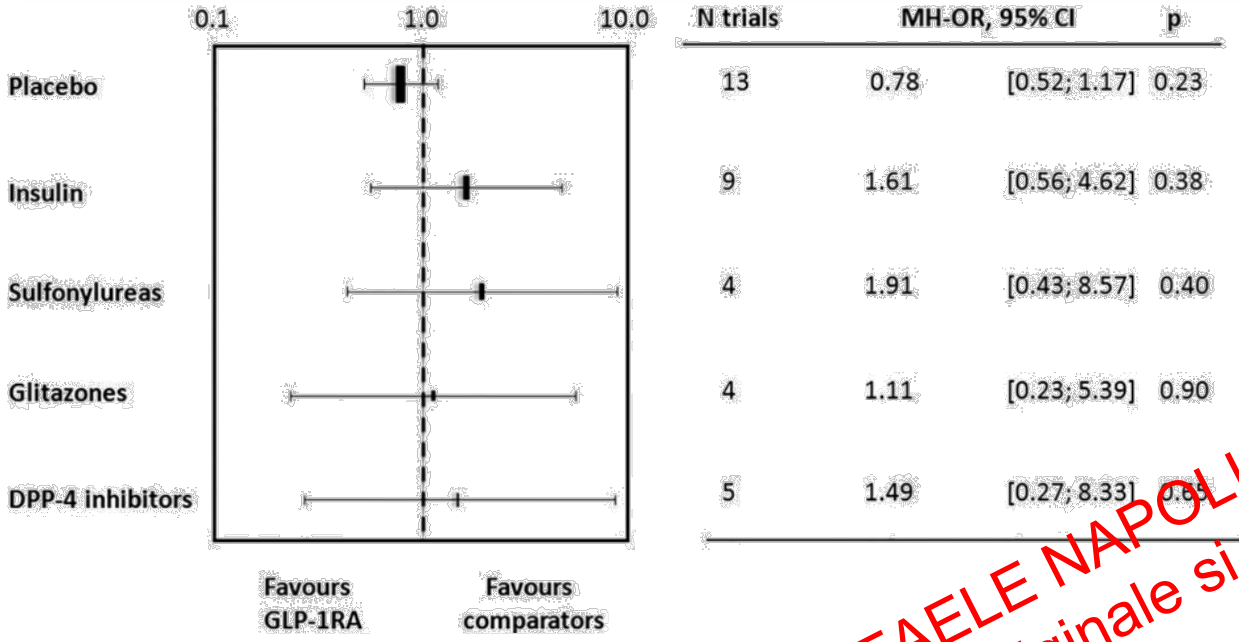
1. Vadav *et al. Pancreas* 2006; 2. Noel *et al. Diabetes Care* 2009; 3. Frey *et al. Pancreas* 2006;4. Fagenholz et al. *Pancreas* 2007; 5. Garg *et al. Diabetes Care* 2010;6. Girman *et al. Diabetes Obes Metab* 2010; 7. Lai *et al. Am J Gastroenterol* 2011

Diagnosis of acute pancreatitis

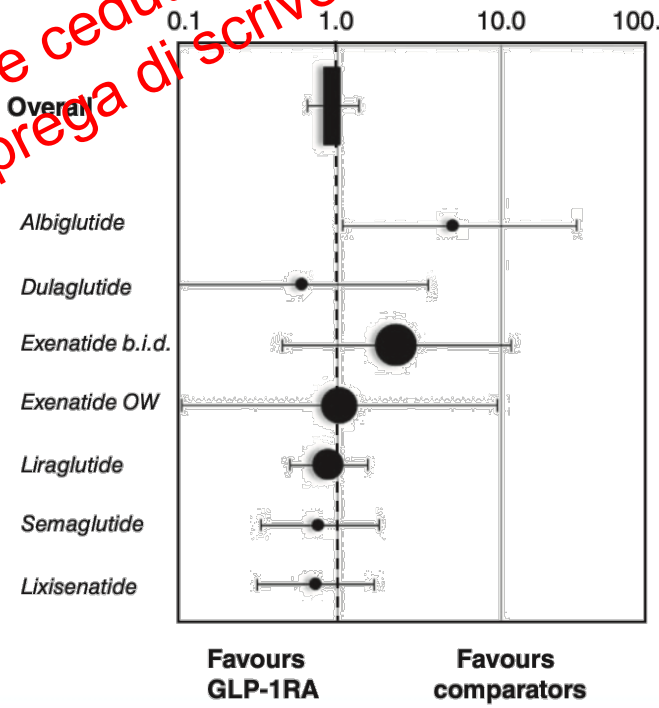
The Atlanta classification 2013

- An algorithm that is frequently used to diagnose acute pancreatitis depends on 2/3 of the following criteria:
  - characteristic abdominal pain
  - ≥3-fold elevation of amylase or lipase
  - positive imaging of the pancreas (CT/MRI scan)

Risk of Pancreatitis with GLP-1 RA



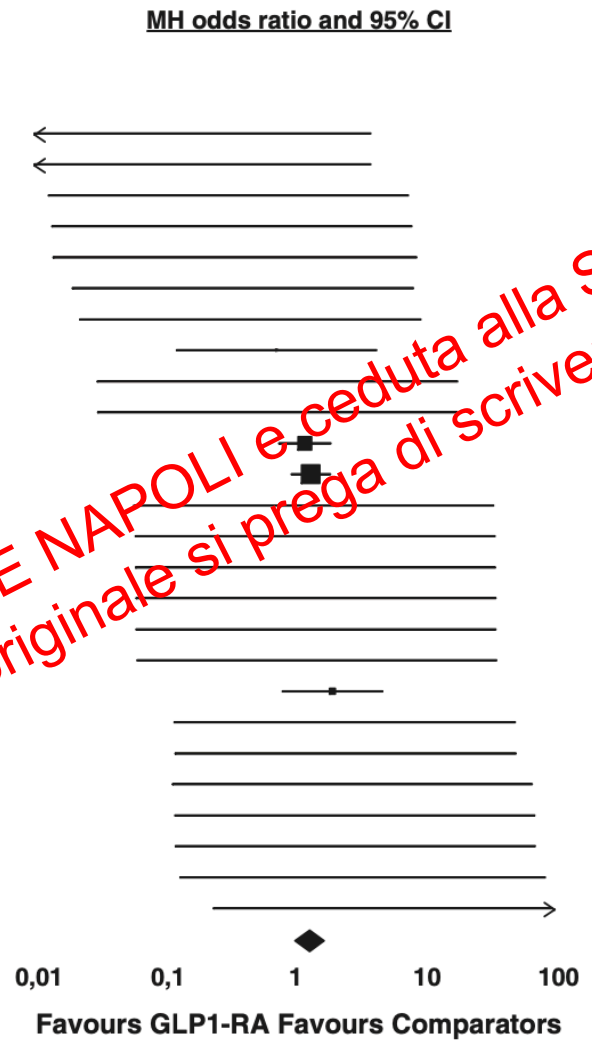
	N trials	MH-OR, 95% CI		p
Placebo	13	0.78	[0.52; 1.17]	0.23
Insulin	9	1.61	[0.56; 4.62]	0.38
Sulfonylureas	4	1.91	[0.43; 8.57]	0.40
Glitazones	4	1.11	[0.23; 5.39]	0.90
DPP-4 inhibitors	5	1.49	[0.27; 8.33]	0.65



	N trials	MH-OR, 95% CI		p
Overall	***25***	***0.93***	***[0.65; 1.34]***	***0.71***
Albiglutide	4	5.01	[1.06; 28.61]	0.040
Dulaglutide	4	0.60	[0.10; 3.57]	0.57
Exenatide b.i.d.	4	2.30	[0.46; 11.52]	0.31
Exenatide OW	2	1.03	[0.11; 9.39]	0.98
Liraglutide	8	0.87	[0.51; 1,51]	0.63
Semaglutide	1	0.75	[0.31; 1.78]	0.51
Lixisenatide	5	0.72	[0.32; 1.66]	0.45

Monami M et al., DOM 2017

Risk of cholelitiasis with GLP-1 RA

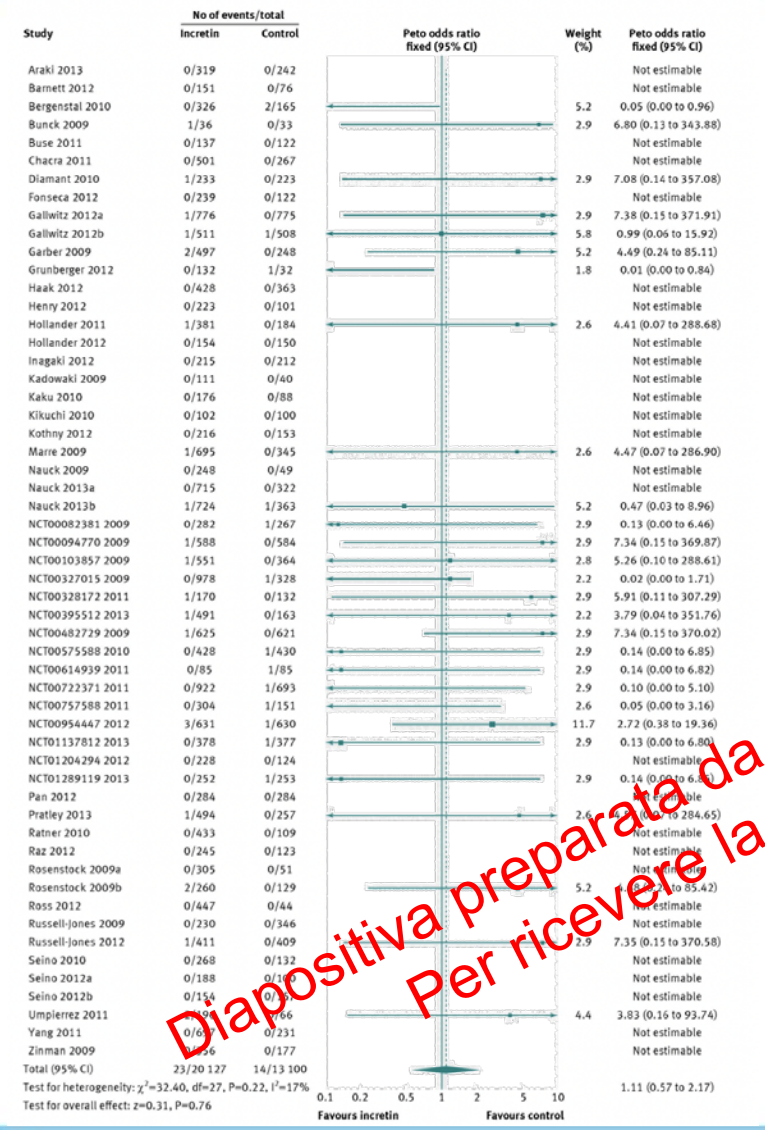


Study name	MH odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Relative weight	GLP-1 RA Events	GLP-1 RA Patients	Comparator Events	Comparator Patients
Seino 2010	0,16	0,01	4,03	-1,11	0,268	0,63	0	268	1	132
Zinman 2009	0,16	0,01	4,04	-1,11	0,268	0,63	0	355	1	175
Diamant 2012	0,32	0,01	7,84	-0,70	0,483	0,63	0	283	1	223
NCT00976937	0,34	0,01	8,35	-0,66	0,507	0,63	0	158	1	161
Grunberger 2012	0,36	0,01	9,09	-0,62	0,532	0,62	0	29	1	32
Bergenstal 2010	0,41	0,02	8,60	-0,57	0,566	0,70	0	160	2	381
Ahrén 2014	0,47	0,02	9,79	-0,49	0,625	0,70	0	302	2	710
Marre 2009	0,75	0,12	4,48	-0,32	0,748	2,01	3	695	2	346
Miyagawa 2015	0,76	0,03	18,77	-0,17	0,865	0,63	1	280	0	70
NCT01064687	0,76	0,03	18,72	-0,17	0,866	0,63	1	280	0	70
Marso 2016 (SUSTAIN-6)	1,23	0,76	1,99	0,85	0,394	28,13	38	1,648	31	1,649
Marso 2016 (LEADER)	1,37	0,95	1,97	1,67	0,096	47,88	68	4,668	50	4,672
Weissman 2014	1,44	0,06	35,45	0,22	0,824	0,63	1	504	0	241
Pratley 2011	1,48	0,06	36,43	0,24	0,811	0,63	1	446	0	219
NCT01648582	1,48	0,06	36,49	0,24	0,810	0,63	1	516	0	254
Umpierrez 2014	1,50	0,06	36,84	0,25	0,805	0,63	1	539	0	268
Garber 2011	1,50	0,06	36,92	0,25	0,805	0,63	1	498	0	248
NCT01644500	1,52	0,06	37,46	0,26	0,798	0,63	1	336	0	271
Pfeffer 2015 (ELIXA)	2,00	0,81	4,97	1,50	0,134	7,83	14	3,034	7	3,034
NCT01149421	2,49	0,12	51,01	0,59	0,557	0,70	2	505	0	250
Blonde 2015	2,53	0,12	52,82	0,60	0,550	0,70	2	588	0	296
Heine 2005	2,85	0,12	70,29	0,64	0,522	0,63	1	282	0	267
Inagaki 2012	3,07	0,12	78,37	0,67	0,506	0,63	1	215	0	212
Araki 2015	3,00	0,12	74,13	0,67	0,502	0,63	1	181	0	180
Jaiswal 2015	3,42	0,13	88,40	0,74	0,459	0,61	1	22	0	24
Gallwitz 2012	4,99	0,24	104,20	1,04	0,300	0,70	2	490	0	487
Overall MH-OR	1,30	1,01	1,68	2,05	0,041	**100,00**	**141**	**17,232**	**99**	**14,872**

I^2<0.001; Kendall's tau: -0.19; p=0.16

Monami M et al., DOM 2017

Risk of Pancreatitis in T2D



Pancreatic Safety of Incretin-Based Drugs — FDA and EMA Assessment

Amy G. Egan, M.D., M.P.H., Eberhard Blind, M.D., Ph.D., Kristina Dunder, M.D., Pieter A. de Graeff, M.D., B. Timothy Hummer, Ph.D., Todd Bourcier, Ph.D., and Curtis Rosebraugh, M.D., M.P.H.

…Both agencies agree that assertions concerning a causal association between incretin-based drugs and pancreatitis or pancreatic cancer, as expressed recently in the scientific literature and in the media, are inconsistent with the current data…

…The FDA and the EMA believe that the current knowledge is adequately reflected in the product information or labeling, and further harmonization among products is planned in Europe.

Adverse effects of GLP-1 receptor agonists

- Gastrointestinal
- Pancreatitis
- C cell proliferation and Thyroid cancer
- Hypoglycemia
- Cardiovascular safety

Thyroid

- The thyroid gland is responsible for producing thyroid hormones that regulate many aspects of metabolic function
- The thyroid is also the site of the C-cells that produce calcitonin.
- Calcitonin has a role in the regulation of calcium levels
- C-cell cancer is a very rare form of thyroid cancer

Concern from animal studies due to C-cell carcinoma in two animal species

- Preclinical studies on **rodents** indicated increased risk from proliferation of C-cells
- For safety, studies investigated doses far higher than would be used by humans

	Mice										Rats							
	Males					Females					Males				Females			
Dose (mg/kg/day)	**0**	**0.03**	**0.2**	**1.0**	**3.0**	**0**	**0.03**	**0.2**	**1.0**	**3.0**	**0**	**0.075**	**0.25**	**0.75**	**0**	**0.075**	**0.25**	**0.75**
Focal C-cell hyperplasia (%)	0	0	1.5	16	38	0	0	10	15	29	22	29	40	48	28	29	55	48
C-cell adenoma (%)	0	0	0	13	19	0	0	0	6	20	12	16	42	46	10	27	33	56
C-cell carcinoma (%)	0	0	0	0	0	0	0	0	0	**3**	**2**	**8**	**6**	**14**	0	0	**4**	**6**

- The incidence of liraglutide-induced medullary thyroid cancer did not affect the overall survival rate among either rats or mice

Rats are predisposed to C-cell changes

Adenoma, benign tumour arising from certain cells, e.g. C-cells; carcinoma, malignant tumour (cancer) arising from certain cells, e.g. C-cells

Rodents have many GLP-1-sensitive C-cells; humans have far fewer C-cells, and no detectable effect from GLP-1

1. Humans have far fewer C-cells than rodents

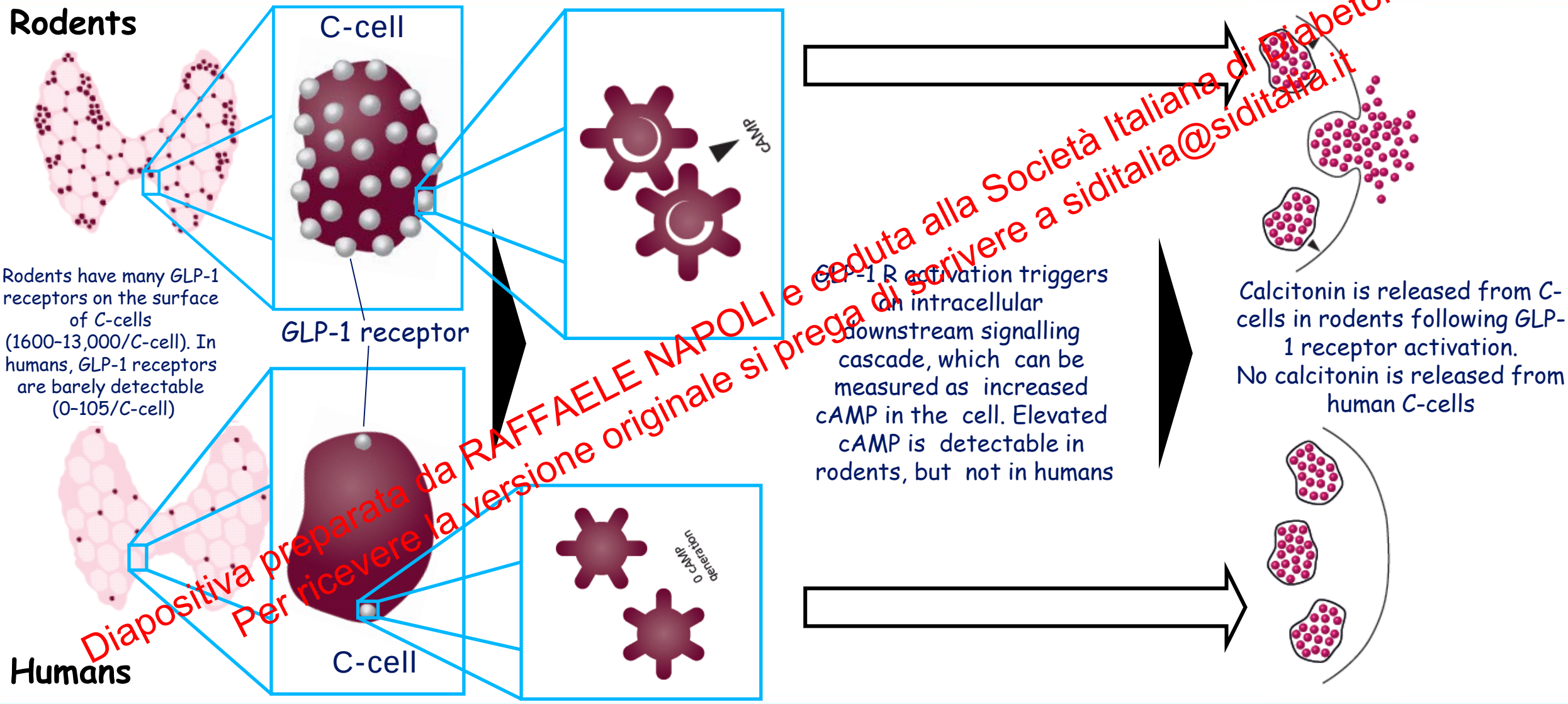
Species	C-cell density (n/mm thyroid)	Difference to humans in fold
Human	10±26	–
Monkey	23±10	2
Mouse	216±62	22
Rat	449±222	45

cAMP, cyclic adenosine monophosphate

2. GLP-1 has effects in rodent, but not human, C-cells

	Rodents	Humans
GLP-1 receptor density (n/cell)	1600–13,000	0–105
cAMP generation (liraglutide EC_{50}, pM)	5800	Not detected
Calcitonin release (liraglutide EC_{50}, pM)	5300	Not detected

The thyroid: rodents *vs.* humans



Bjerre Knudsen *et al. Endocrinology* 2010;151:1473–86

No growth of C-cells seen in monkey studies

- High doses of liraglutide do not stimulate C-cell hyperplasia in primates in an 87-week study

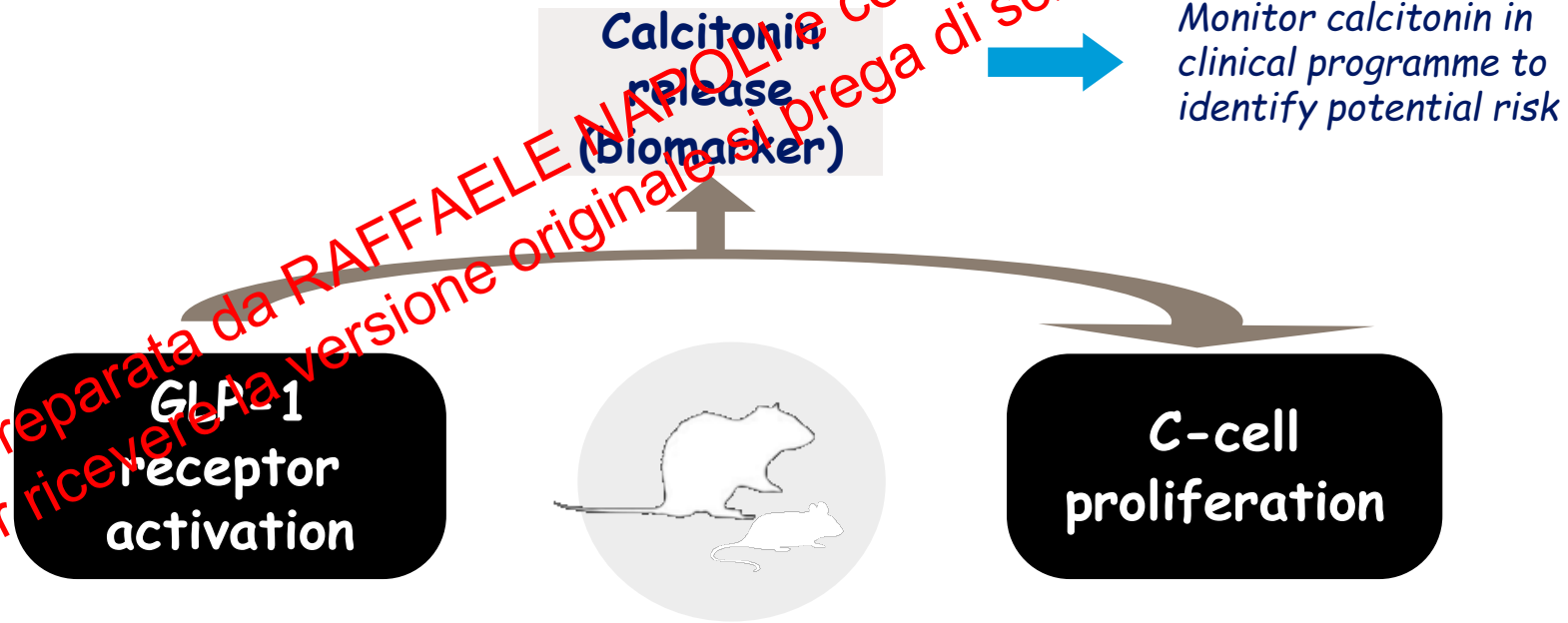
Monkeys

Dose (mg/kg)	0	0.2	5.0
Fold human exposure	N/A	8	64
C-cell hyperplasia incidence	None	None	None

Bjerre Knudsen *et al. Endocrinology* 2010;151:1473-86

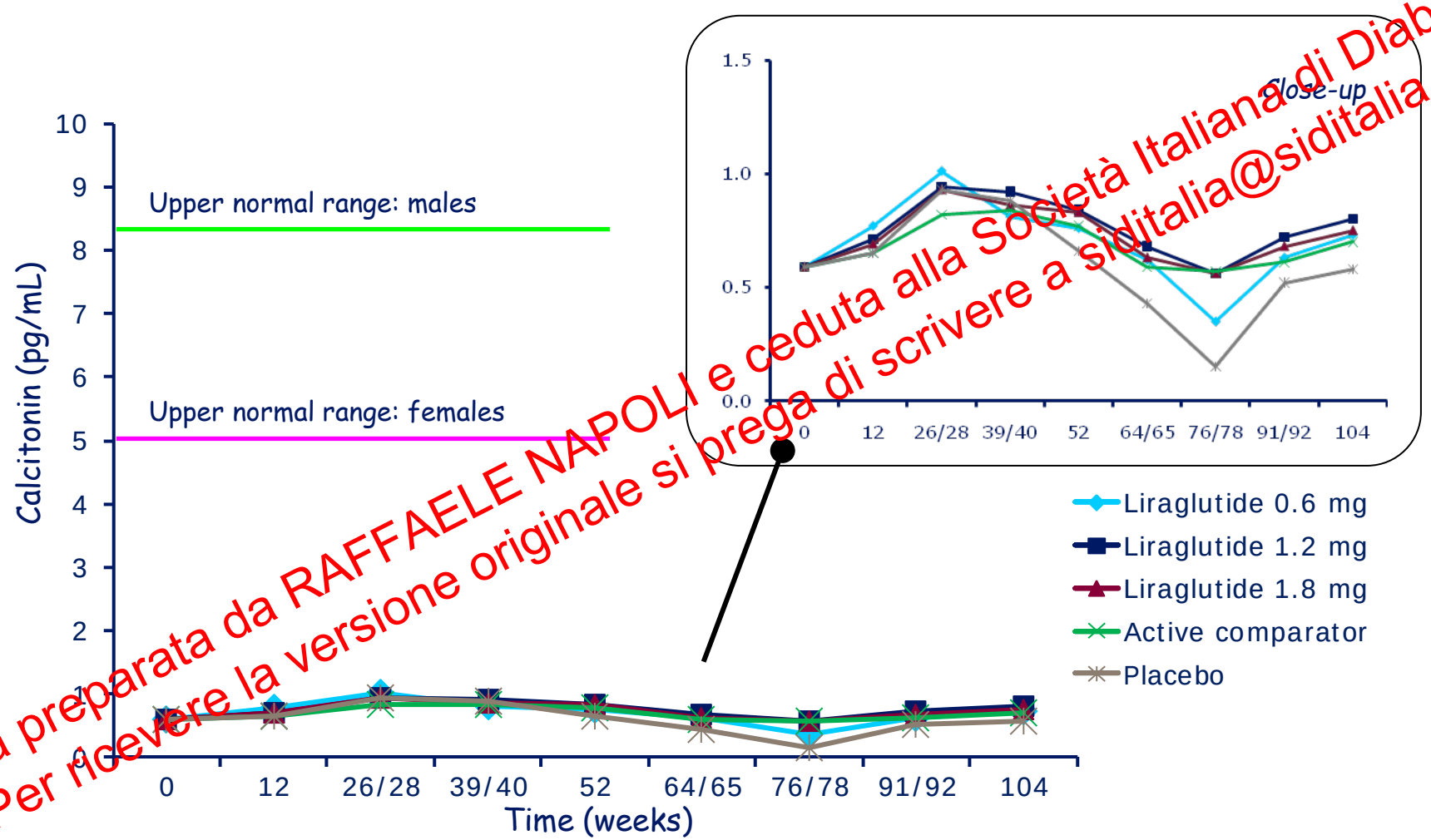
Calcitonin as a marker of C-cell activation in human clinical trials

- GLP-1 receptor activation in rodent C-cells has two effects:
  - increased secretion of calcitonin
  - C-cell proliferation



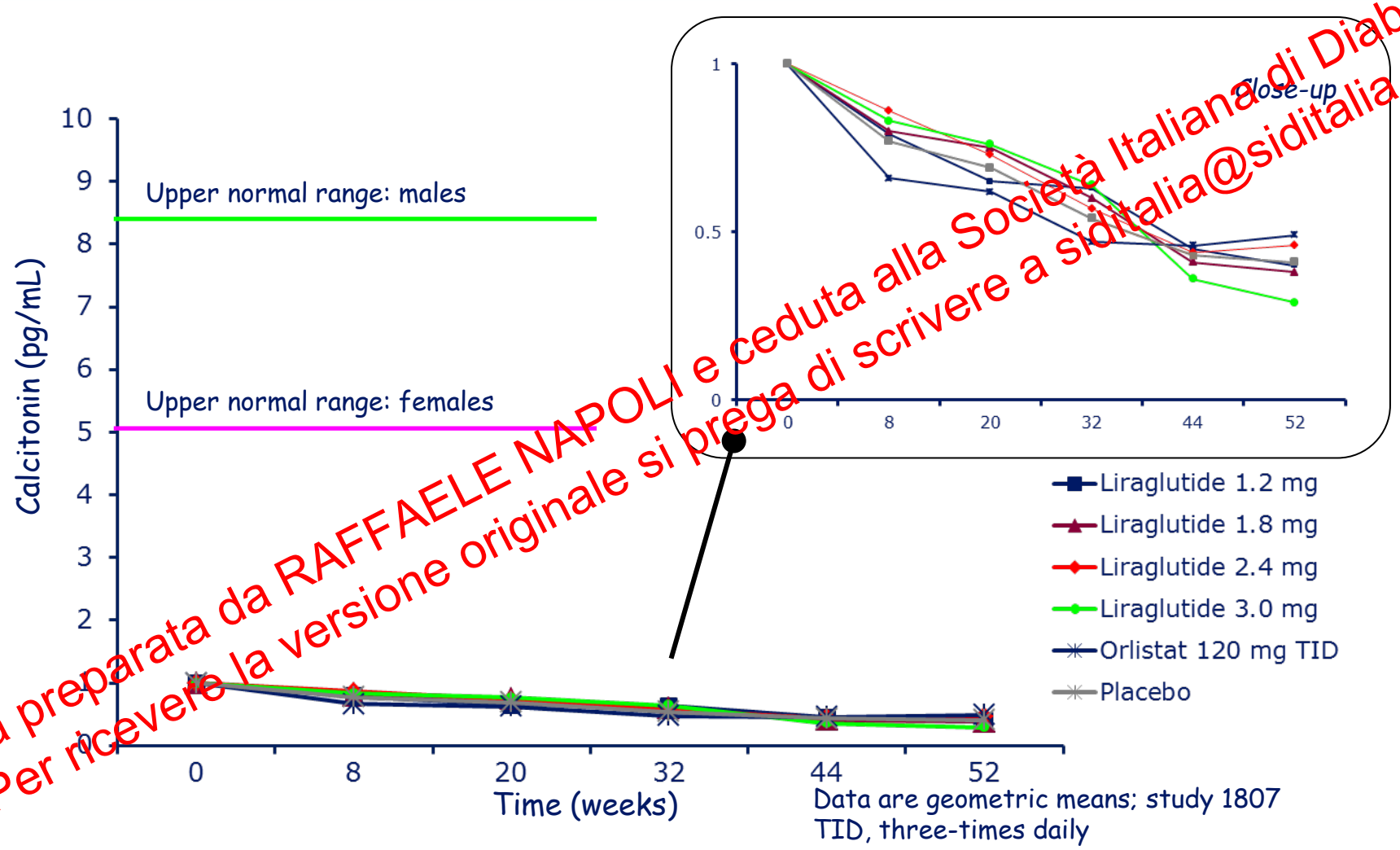
Crespel *et al. Endocrinology* 1996; Lamari *et al. FEBS Lett* 1996;Vertongen *et al. Endocrinology* 1994; Kurosawa *et al. Arch Gerontol Geriatr* 1988

Calcitonin levels observed in LEAD studies



Data are least squares (LS) means (95% CI); studies 1572 and 1573

Calcitonin levels: obese subjects without diabetes

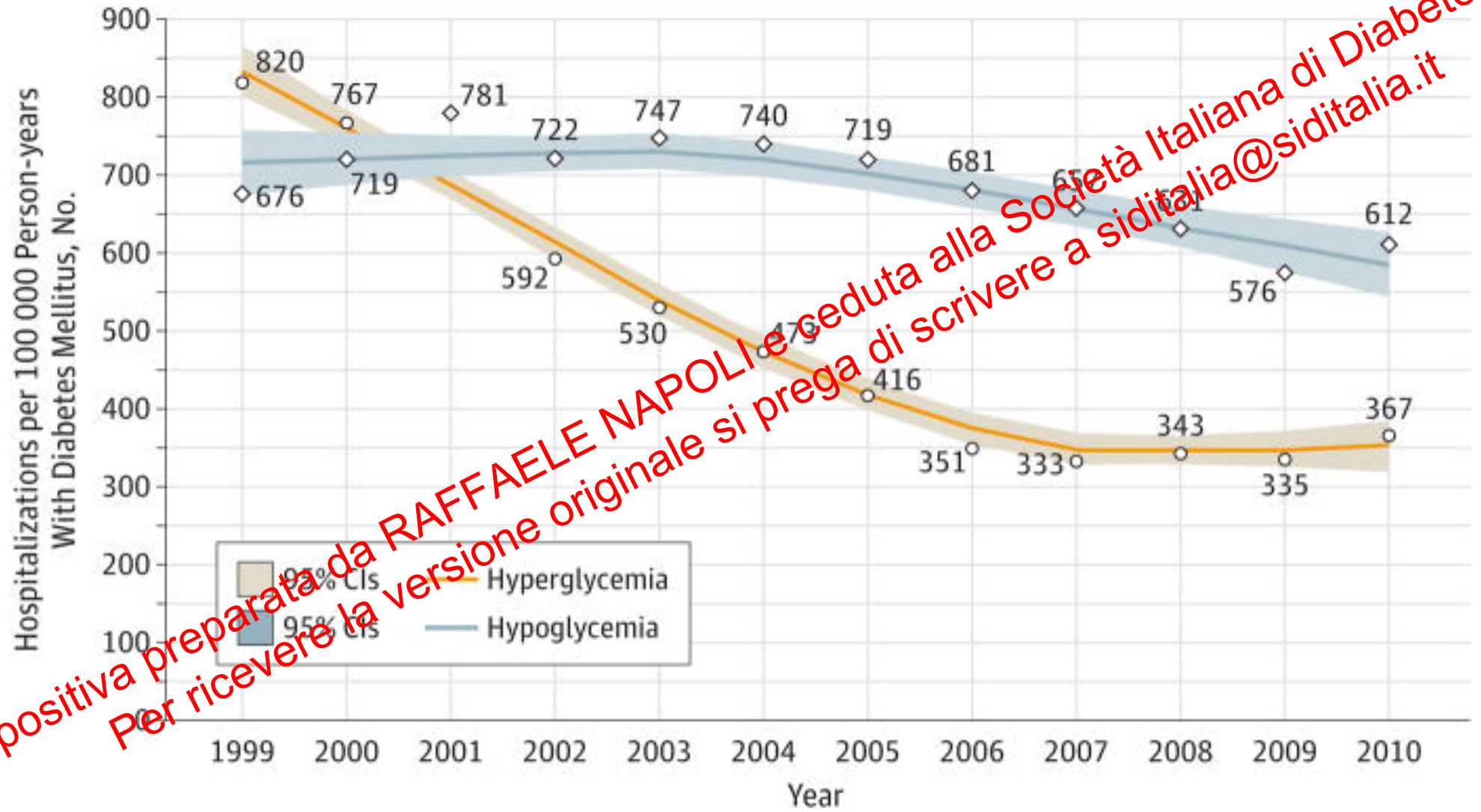


Hegedus *et al. J Clin Endocrin Metab* 2011;96:853-60

Adverse effects of GLP-1 receptor agonists

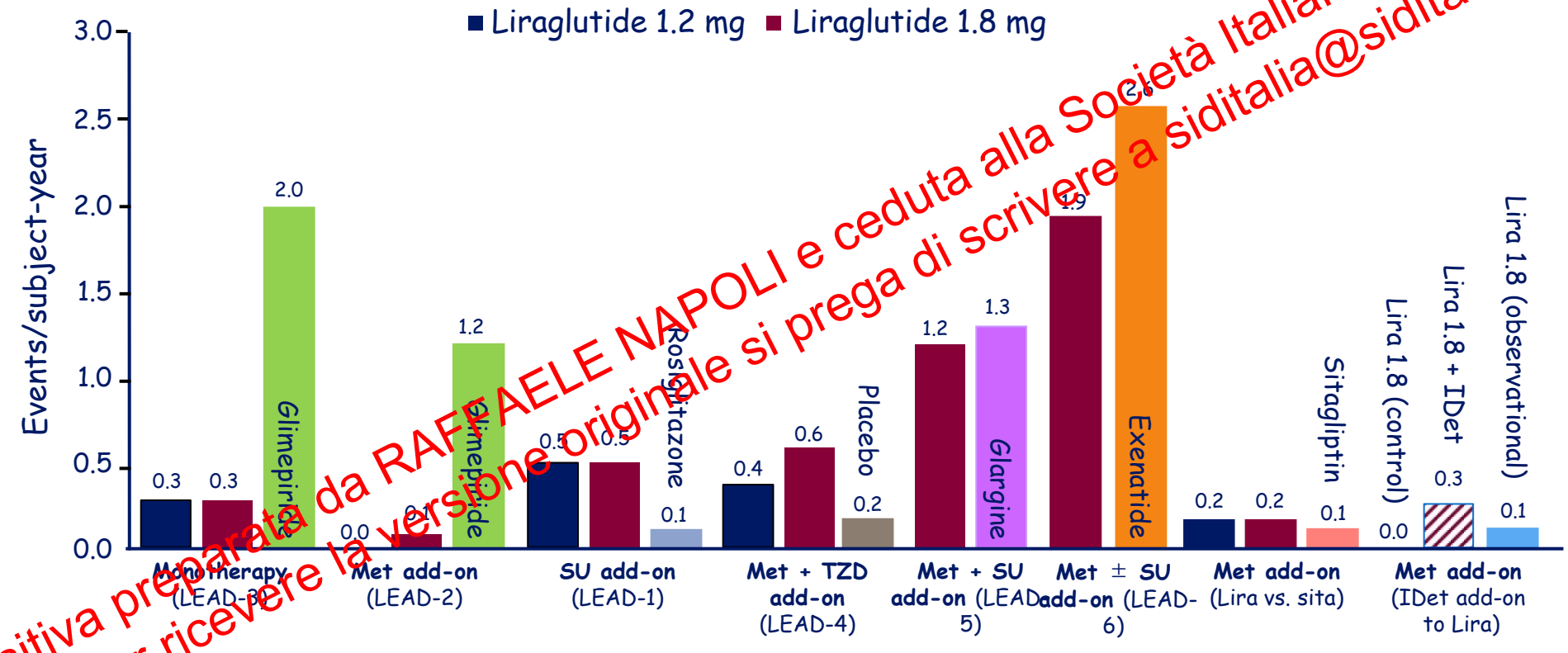
- Gastrointestinal
- Pancreatitis
- C cell proliferation and Thyroid cancer
- Hypoglycemia
- Cardiovascular safety

National trends in US hospital admissions for hyperglycemia and hypoglycemia among Medicare beneficiaries, 1999 to 2011.



Lipska KJ et al JAMA 2014

Rates of minor hypoglycaemia throughout the liraglutide clinical development programme



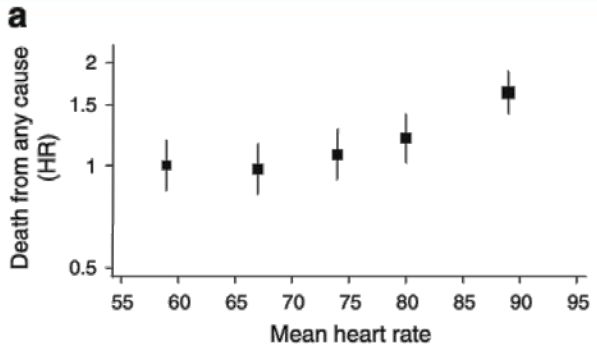
IDet, insulin detemir; lira, liraglutide; met, metformin; SU, sulphonylurea; TZD, thiazolidinedione

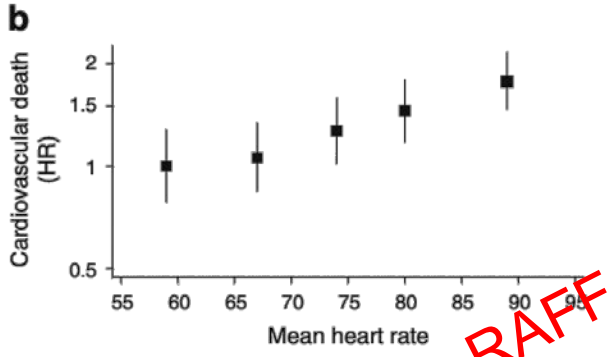
Marre *et al. Diabetic Med* 2009; Nauck *et al. Diabetes Care* 2009; Garber *et al. Lancet* 2009; Zinman *et al. Diabetes Care* 2009; Russell-Jones *et al. Diabetologia* 2009; Buse *et al. Lancet* 2009; Pratley *et al. Lancet* 2010; DeVries *et al. Diabetes Care* 2012

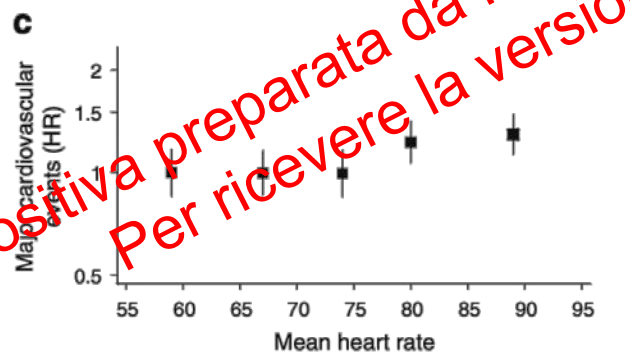
Adverse effects of GLP-1 receptor agonists

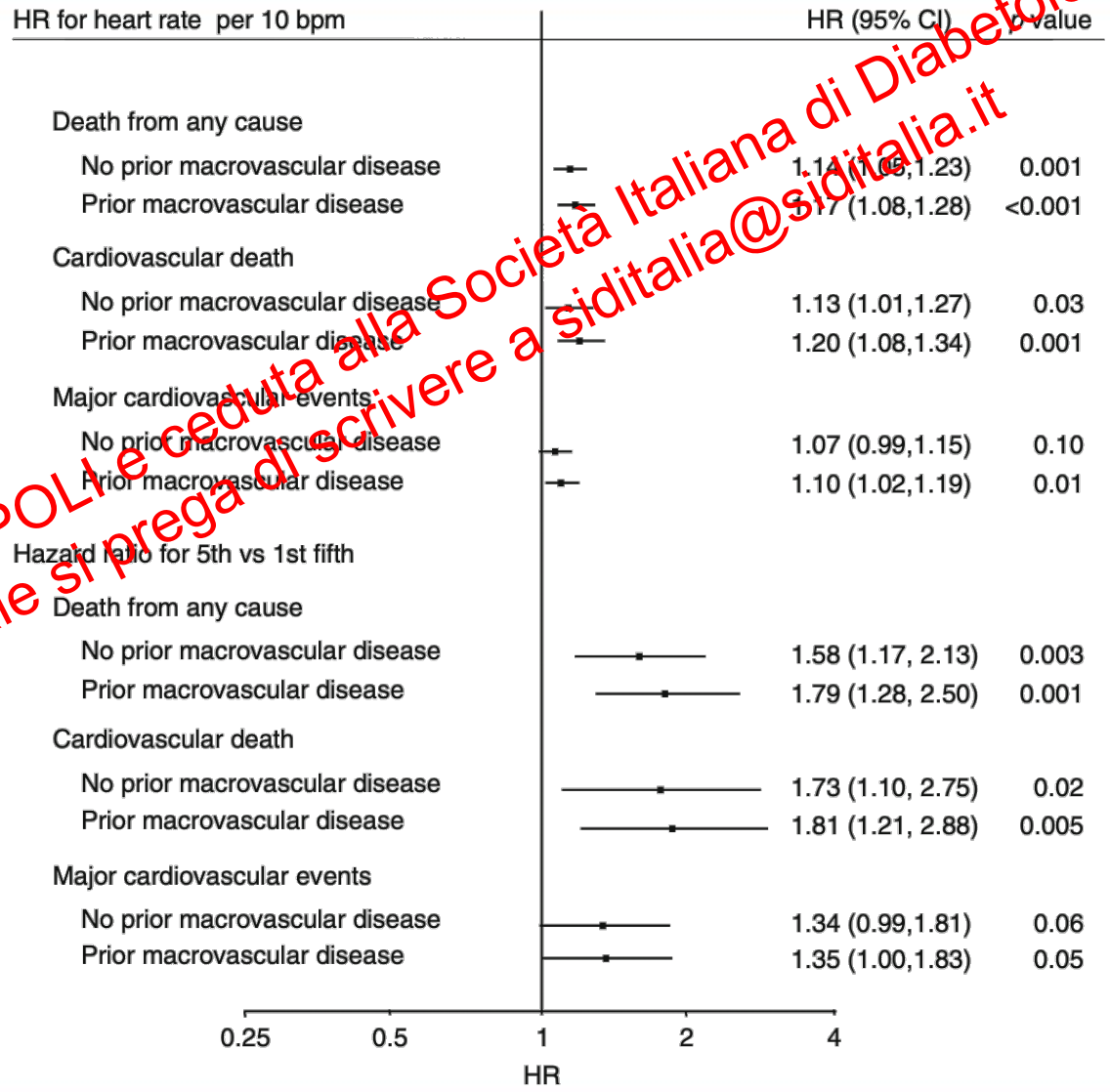
- Gastrointestinal
- Pancreatitis
- C cell proliferation and Thyroid cancer
- Hypoglycemia
- Cardiovascular safety

Baseline resting heart rate and the risk of death





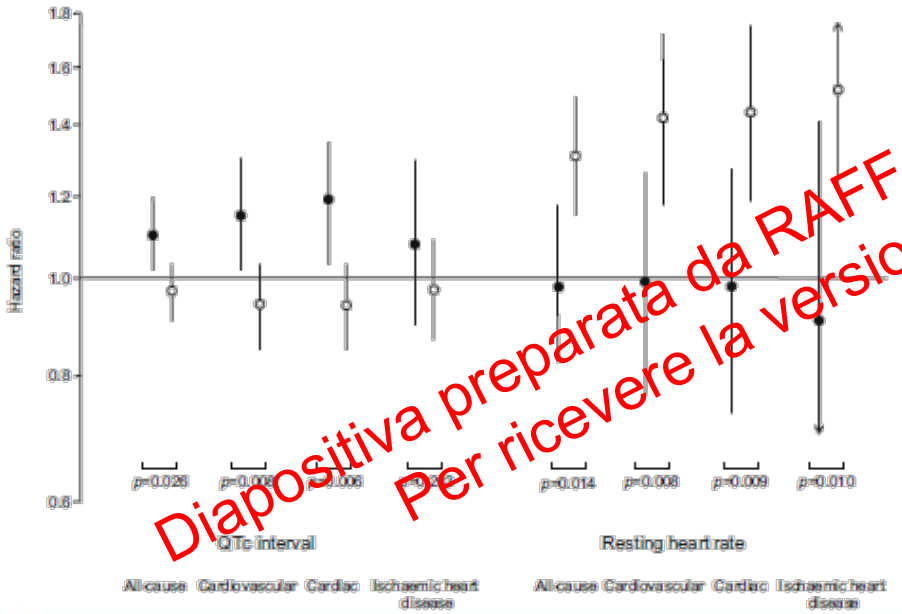




Hillis GS et al., Diabetologia 2012

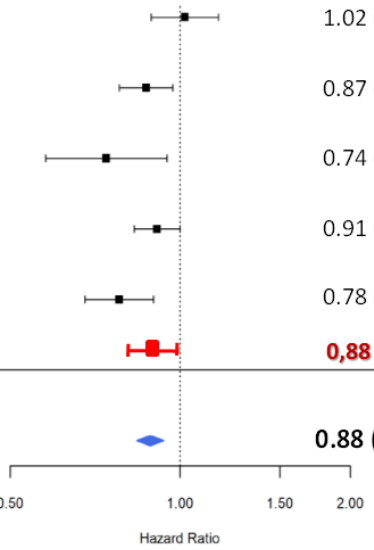
Diabetes and cardiovascular risk

	Overall baseline	Low dose				High dose			
		Semaglutide 0·5 mg (n=301)	Dulaglutide 0·75 mg (n=299)	Estimated treatment difference (95% CI)	p value	Semaglutide 1·0 mg (n=306)	Dulaglutide 1·5 mg (n=299)	Estimated treatment difference (95% CI)	p value
Blood pressure and heart rate									
Mean systolic blood pressure (mm Hg)	133·0 (14·3)	−2·4 (0·76)	−2·2 (0·75)	−0·28 (−2·37 to 1·81)	0·79	−4·9 (0·77)	−2·9 (0·75)	−2·02 (−4·14 to 0·09)	0·0607
Mean diastolic blood pressure (mm Hg)	81·0 (8·9)	−0·6 (0·48)	−0·3 (0·47)	−0·22 (−1·54 to 1·10)	0·74	−2·0 (0·49)	<−0·1 (0·47)	−2·02 (−3·35 to −0·68)	0·0031
Mean heart rate (bpm)	75·0 (10·3)	2·1 (0·51)	1·6 (0·49)	0·53 (−0·84 to 1·91)	0·45	4·0 (0·51)	2·4 (0·50)	1·55 (0·15 to 2·95)	0·0304



Meta-analysis of MACE (GLP-1 RA CVOTs)

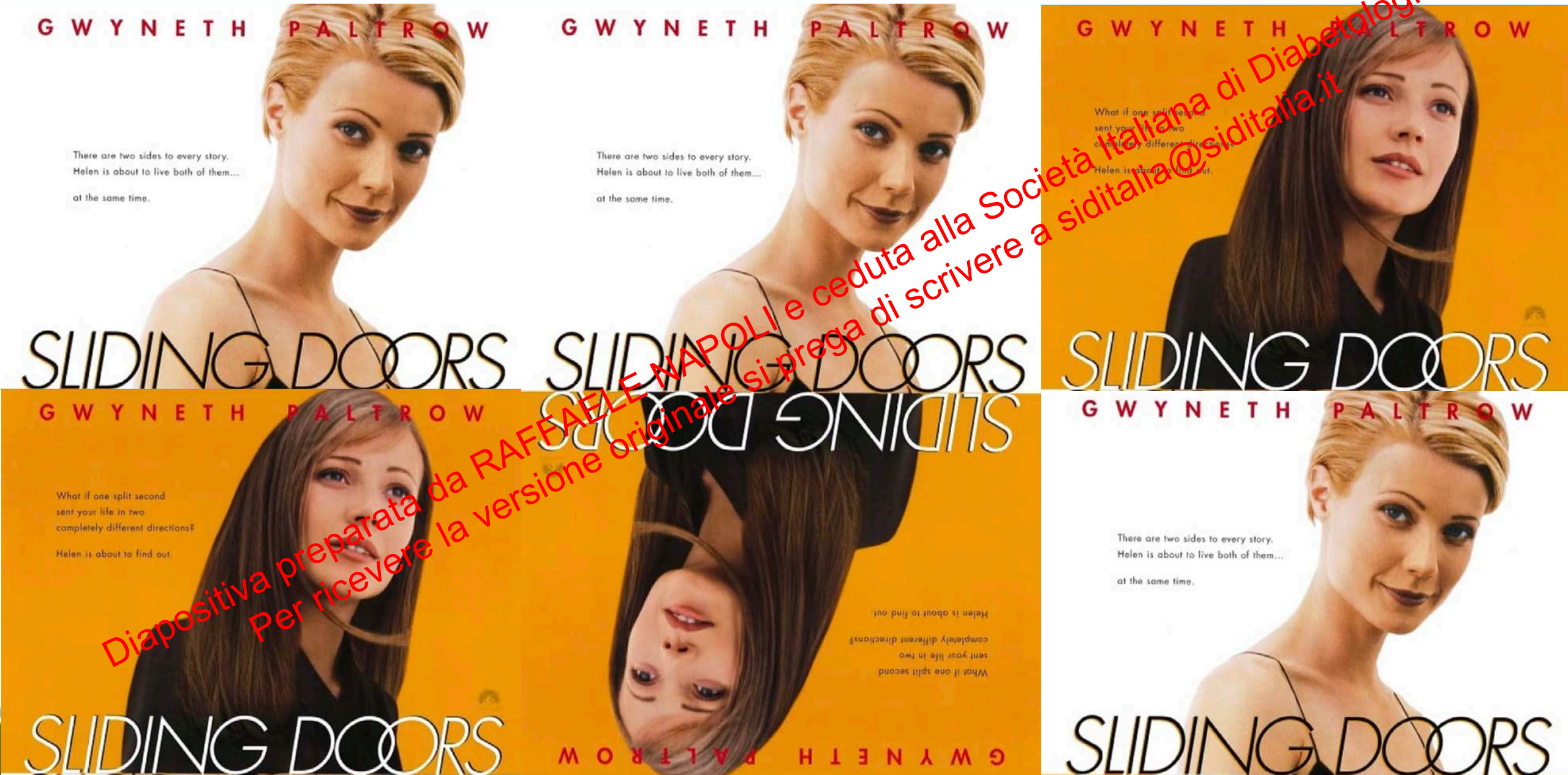
Trials	Patients	Events	Treatment	Placebo	Weights	HR (95% CI)
ELIXA	6068	805	406/3034	399/3034	16.7	1.02 (0.89, 1.17)
LEADER	9340	1302	608/4668	694/4672	26.3	0.87 (0.78, 0.97)
SUSTAIN 6	3297	254	108/1648	146/1649	5.1	0.74 (0.58, 0.95)
EXSCEL	14752	1744	839/7356	905/7396	36.0	0.91 (0.83, 1.00)
HARMONY	9463	766	338/4731	428/4732	15.9	0.78 (0.68, 0.90)
REWIND						**0,88 (0,79, 0,99)**
Fixed Effects for MACE Outcome (P-value < 0.001)						0.88 (0.84, 0.94)



Stettler C et al. Diabetologia 2007

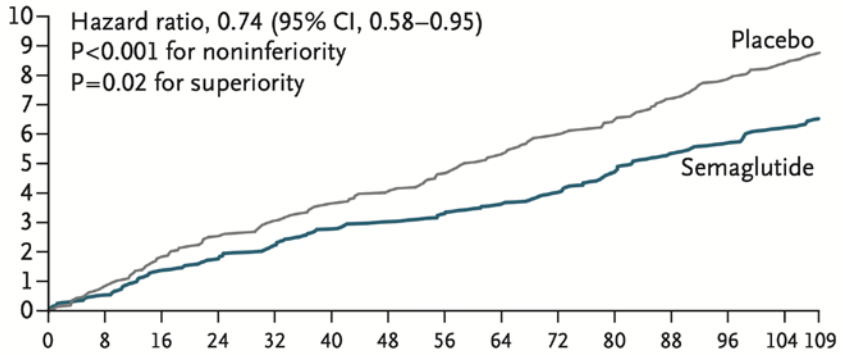
Pratley RA et al., Lancet Diabetes Endocrinology 2018

Effetti collaterali di GLP-1RA (vs SGLT2i?): what-is e what-if



Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

Primary Outcome: 3p MACE



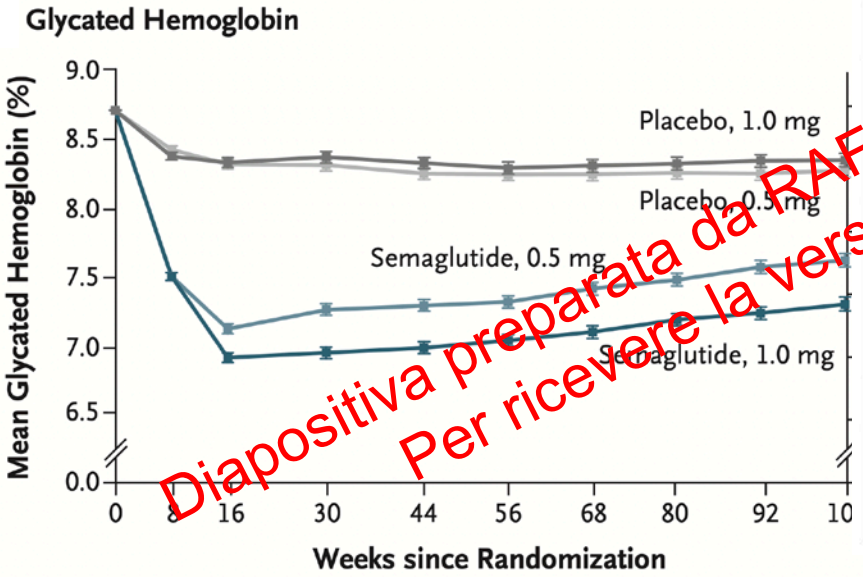


Table 2. Primary and Secondary Cardiovascular and Microvascular Outcomes.

Outcome	Semaglutide (N=1648)		Placebo (N=1649)		Hazard Ratio (95% CI)*	P Value
	no. (%)	*no./100 person-yr*	*no. (%)*	*no./100 person-yr*		
Primary composite outcome†	108 (6.6)	3.24	146 (8.9)	4.44	0.74 (0.58–0.95)	<0.001 for noninferiority; 0.02 for superiority
Expanded composite outcome‡	199 (12.1)	6.17	264 (16.0)	8.36	0.74 (0.62–0.89)	0.002
All-cause death, nonfatal myocardial infarction, or nonfatal stroke	122 (7.4)	3.66	158 (9.6)	4.81	0.77 (0.61–0.97)	0.03
Death						
From any cause	62 (3.8)	1.82	60 (3.6)	1.76	1.05 (0.74–1.50)	0.79
From cardiovascular cause	44 (2.7)	1.29	46 (2.8)	1.35	0.98 (0.65–1.48)	0.92
Nonfatal myocardial infarction	47 (2.9)	1.40	64 (3.9)	1.92	0.74 (0.51–1.08)	0.12
Nonfatal stroke	27 (1.6)	0.80	44 (2.7)	1.31	0.61 (0.38–0.99)	0.04
Hospitalization for unstable angina pectoris	22 (1.3)	0.65	27 (1.6)	0.80	0.82 (0.47–1.44)	0.49
Revascularization	83 (5.0)	2.50	126 (7.6)	3.85	0.65 (0.50–0.86)	0.003
Hospitalization for heart failure	59 (3.6)	1.76	54 (3.3)	1.61	1.11 (0.77–1.61)	0.57
Retinopathy complications§	50 (3.0)	1.49	29 (1.8)	0.86	1.76 (1.11–2.78)	0.02
New or worsening nephropathy¶	62 (3.8)	1.86	100 (6.1)	3.06	0.64 (0.46–0.88)	0.005

Marso SP et al., N Engl J Med 2016

Baseline characteristics across the SUSTAIN clinical trial programme

Mean (SD)	SUSTAIN 1 *N* = 387	SUSTAIN 2 *N* = 1225	SUSTAIN 3 *N* = 809	SUSTAIN 4 *N* = 1082	SUSTAIN 5 *N* = 396	JP SUSTAIN MONO *N* = 308	JP SUSTAIN OAD *N* = 601	SUSTAIN 6 *N* = 3297
Age, years	53.7 (11.3)	55.1 (10.0)	56.6 (10.7)	56.5 (10.4)	56.8 (10.1)	58.3 (10.7)	58.5 (10.3)	64.6 (7.4)
HbA1c, %	8.1 (0.9)	8.1 (0.9)	8.3 (1.0)	8.2 (0.9)	8.4 (0.8)	8.1 (0.9)	8.1 (0.9)	8.7 (1.5)
T2D duration, years	4.2 (5.5)	6.6 (5.1)	9.2 (6.8)	8.6 (6.3)	13.3 (7.8)	8.0 (6.3)	8.8 (6.4)	13.9 (8.1)
Systolic blood pressure, mm Hg	128.8 (13.2)	132.6 (14.9)	133.5 (14.5)	132.1 (15.3)	134.8 (16.0)	129.1 (14.8)	129.2 (13.0)	135.6 (17.1)
Medical history of DR, *n* (%)	15 (3.9)	94 (7.7)	30 (3.7)	50 (4.6)	55 (13.9)	42 (13.6)	87 (14.5)	969 (29.4)

Vilsbøll T et al., DOM 2018

DR adverse events as reported across the SUSTAIN clinical trial programme

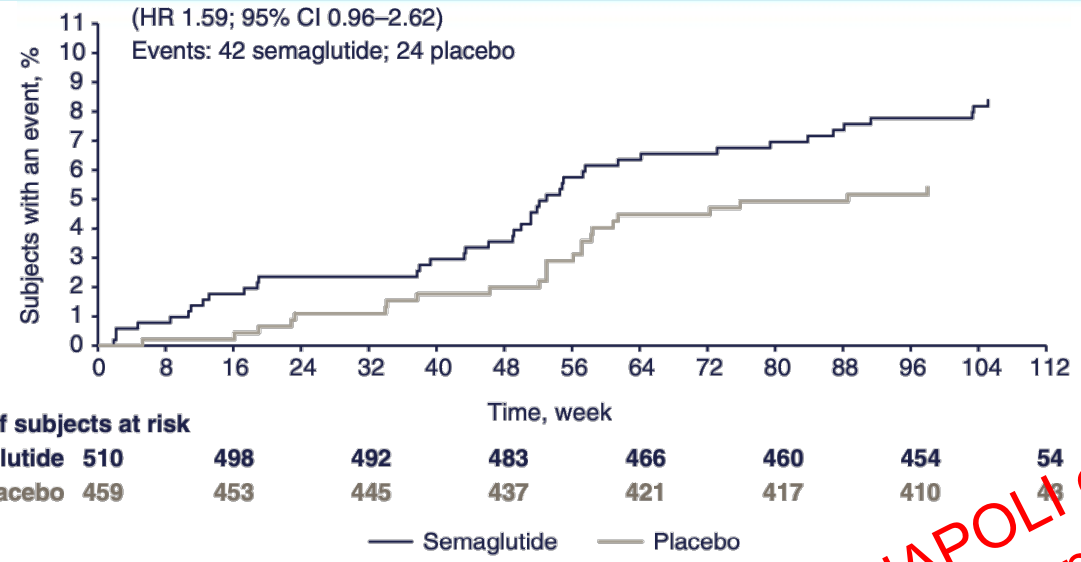
SUSTAIN 1-5 and Japanese SUSTAIN trials												
	Semaglutide 0.5 mg *N* = 1373				Semaglutide 1.0 mg *N* = 1777				Comparators *N* = 2657			
	n	**(%)**	**E**	**R**	***n***	**(%)**	**E**	**R**	***n***	**(%)**	**E**	**R**
All events	32	(2.1)	35	2.6	30	(1.5)	36	1.9	51	(2.0)	31	2.1
Severe	0		0		0		0		0		0	
Moderate	3	(0.2)	4	0.3	3	(0.2)	5	0.3	6	(0.4)	6	0.4
Mild	29	(1.9)	31	2.3	27	(1.3)	31	1.6	25	(1.6)	25	1.7
SAEs	0		0		0		0		0		0	

SUSTAIN 6												
	Semaglutide 0.5 mg *N* = 826				Semaglutide 1.0 mg *N* = 822				Placebo *N* = 1649			
	n	**(%)**	**E**	**R**	**n**	**(%)**	**E**	**R**	**n**	**(%)**	**E**	**R**
All events	74	(9.0)	86	5.0	82	(10.0)	99	5.8	125	(7.6)	145	4.3
Severe	5	(0.6)	6	0.4	5	(0.6)	5	0.3	7	(0.4)	7	0.2
Moderate	27	(3.3)	33	1.9	22	(2.7)	25	1.5	35	(2.1)	37	1.1
Mild	44	(5.3)	47	2.8	57	(6.9)	69	4.1	86	(5.2)	101	3.0
SAEs	6	(0.7)	7	0.4	5	(0.6)	6	0.4	8	(0.5)	8	0.2

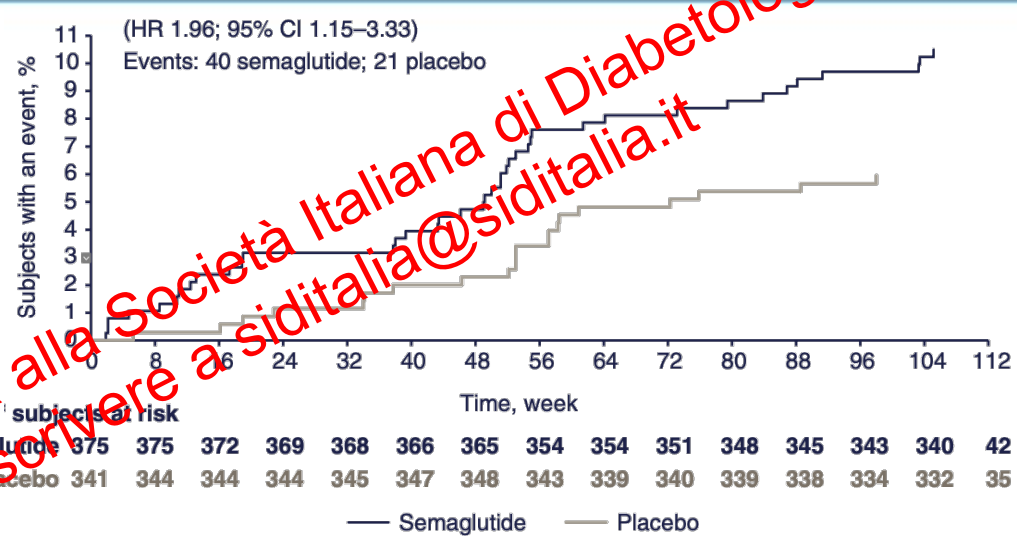
Vilsbøll T et al., DOM 2018

Time to first EAC-DRC in SUSTAIN 6

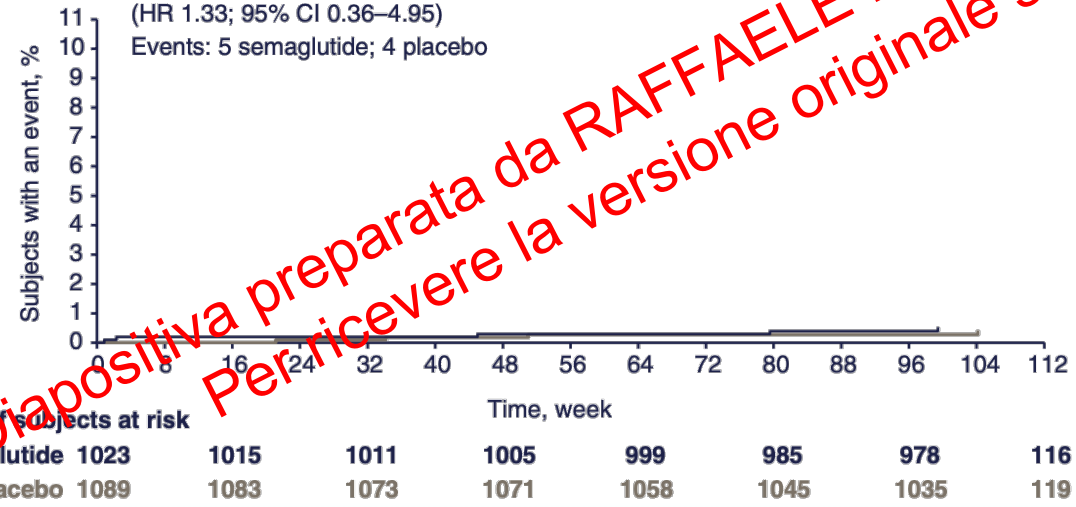
Baseline DR: Yes



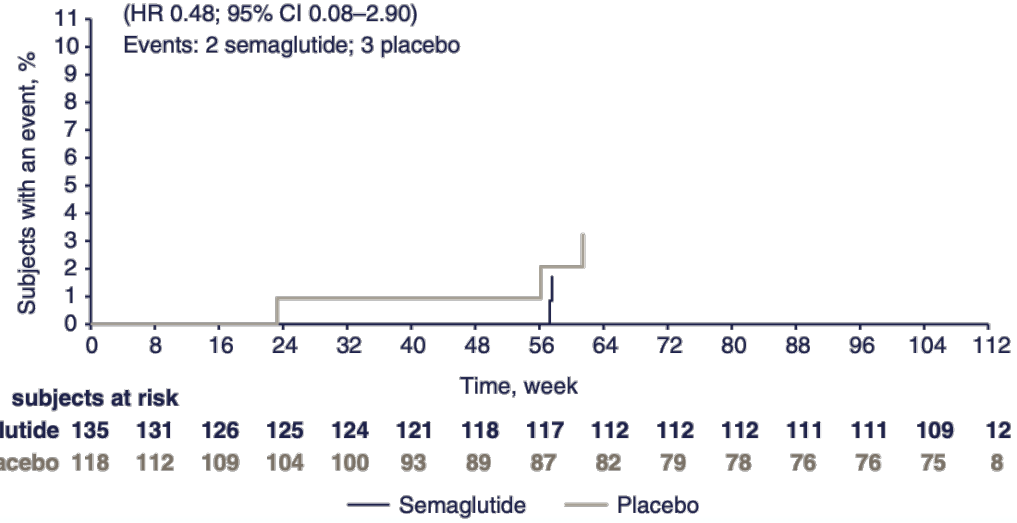
Insulin use before: Yes



Baseline DR: No

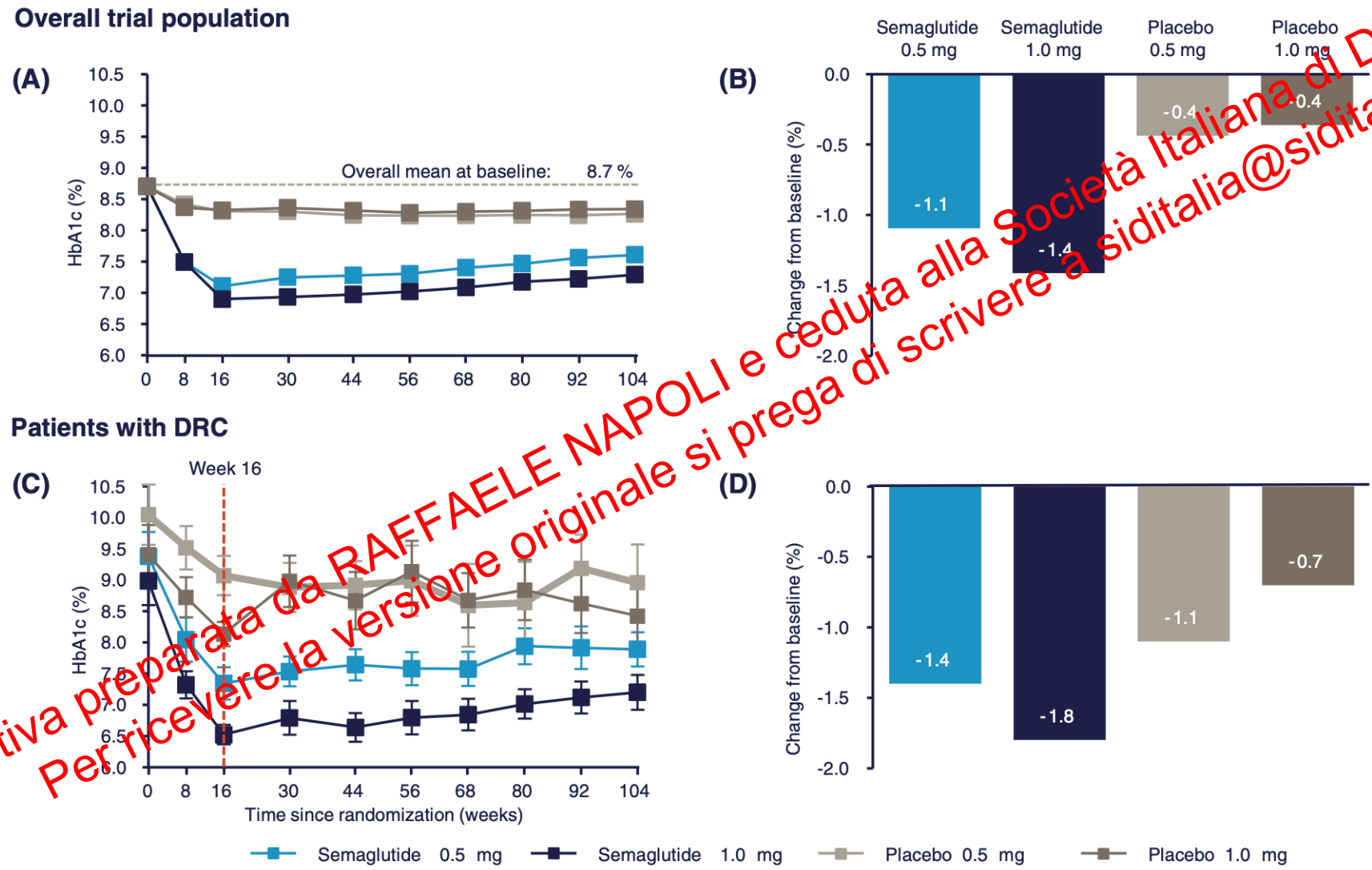


Insulin use before: No



Vilsbøll T et al., DOM 2018

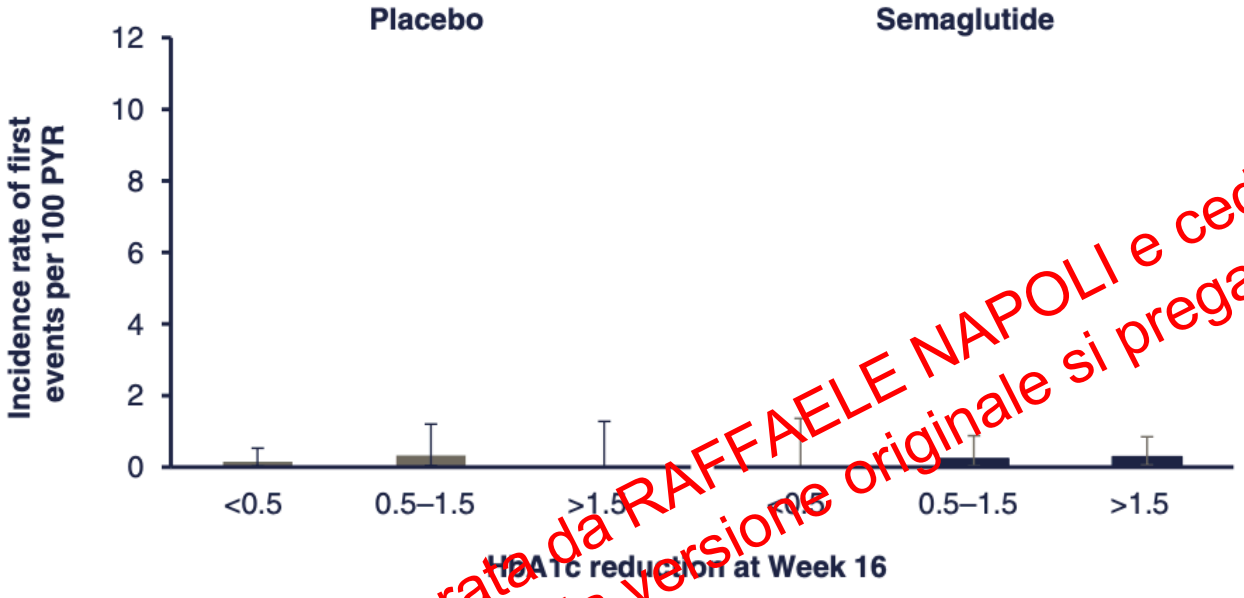
Glycated haemoglobin (HbA1c) in SUSTAIN 6



Vilsbøll T et al., DOM 2018

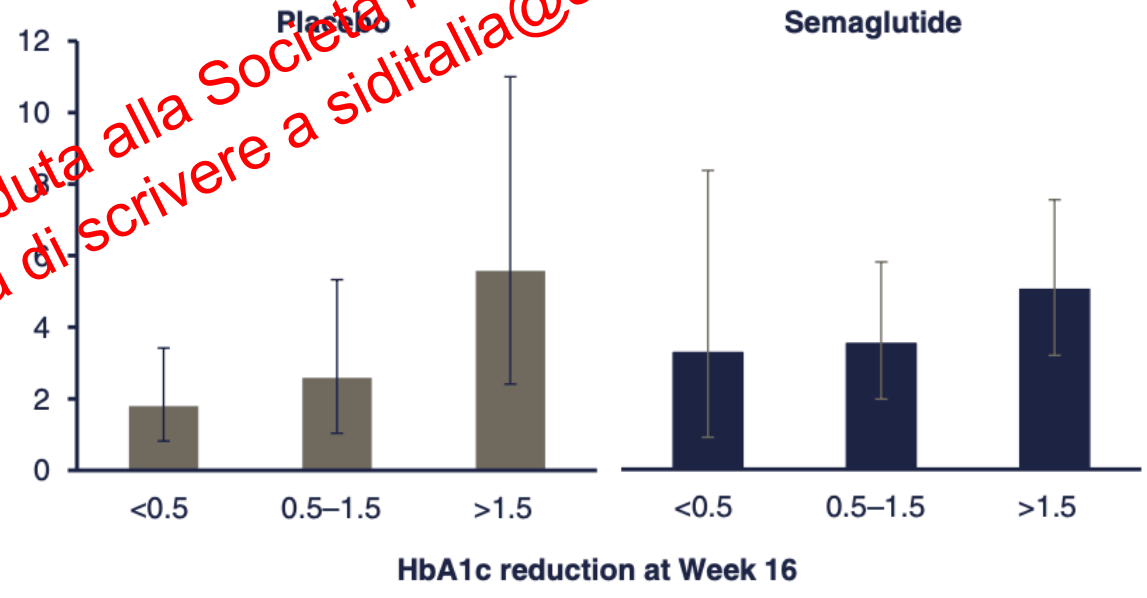
Incidence of DRC in SUSTAIN 6 by baseline DR and HbA1c reduction

No baseline DR



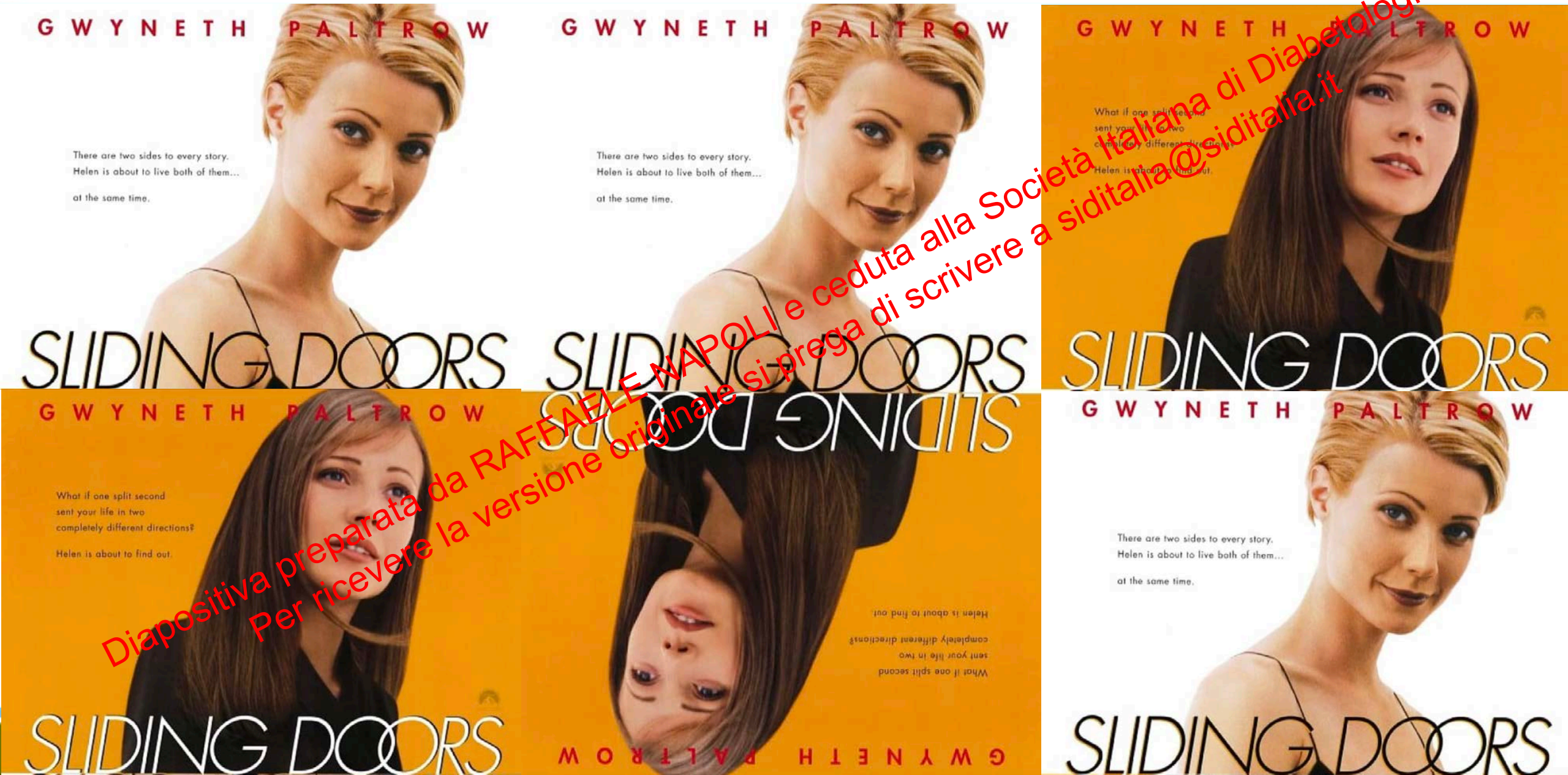
Patients with event/at risk	2/658	2/291	0/140	0/131	2/399	3/493

Baseline DR



	9/245	7/138	8/76	4/61	15/213	23/236

Effetti collaterali di GLP-1RA (vs SGLT2i?): what-is e what-if



Adverse effects of GLP-1 RA and SGLT2i

SGLT-2 inhibitors

- **FDA Black Box:** Risk of amputation (**canagliflozin**)
- Risk of bone fractures (canagliflozin)
- DKA risk (all agents, rare in T2DM)
- Genitourinary infections
- Risk of volume depletion, hypotension
- ↑LDL cholesterol
- Risk of Fournier's gangrene

GLP-1 RAs

- Gastrointestinal side effects common (nausea, vomiting, diarrhea)
- Injection site reactions
- ?Acute pancreatitis risk
- FDA Black Box: Risk of thyroid C-cell tumors (liraglutide, albiglutide, dulaglutide, exenatide extended release)

Adverse effects of SGLT2i

- Risk of amputation and bone fractures
- Diabetic Ketoacidosis
- Genitourinary infections
- Risk of volume depletion and hypotension

Adverse effects of SGLT2i

- Risk of amputation and bone fractures
- Diabetic Ketoacidosis
- Genitourinary infections
- Risk of volume depletion and hypotension

Adverse effects in CANVAS and CREDENCE

IMPORTANT SAFETY INFORMATION

INVOKANA® can cause serious side effects, including:

- **Amputations. INVOKANA® may increase your risk of lower-limb amputations. Amputations mainly involve removal of the toe or part of the foot; however, amputations involving the leg, below and above the knee, have also occurred. Some people had more than one amputation, some on both sides of the body.** You may be at a higher risk of lower-limb amputation if you: have a history of amputation, have heart disease or are at risk for heart disease, have had blocked or narrowed blood vessels (usually in leg), have damage to the nerves (neuropathy) in the leg, or have had diabetic foot ulcers or sores. **Call your doctor right away if you have new pain or tenderness, any sores, ulcers, or infections in your leg or foot.** Your doctor may decide to stop your INVOKANA® for a while if you have any of these signs or symptoms. Talk to your doctor about proper foot care.

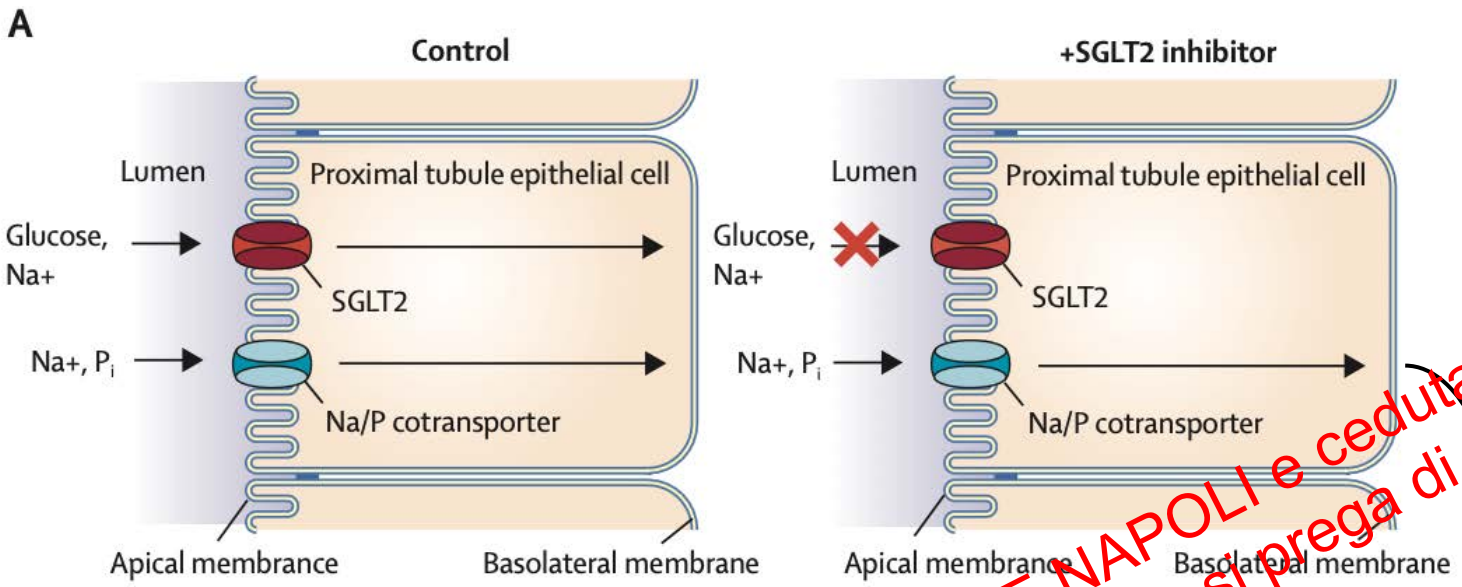
Table 2. Adverse Events.*

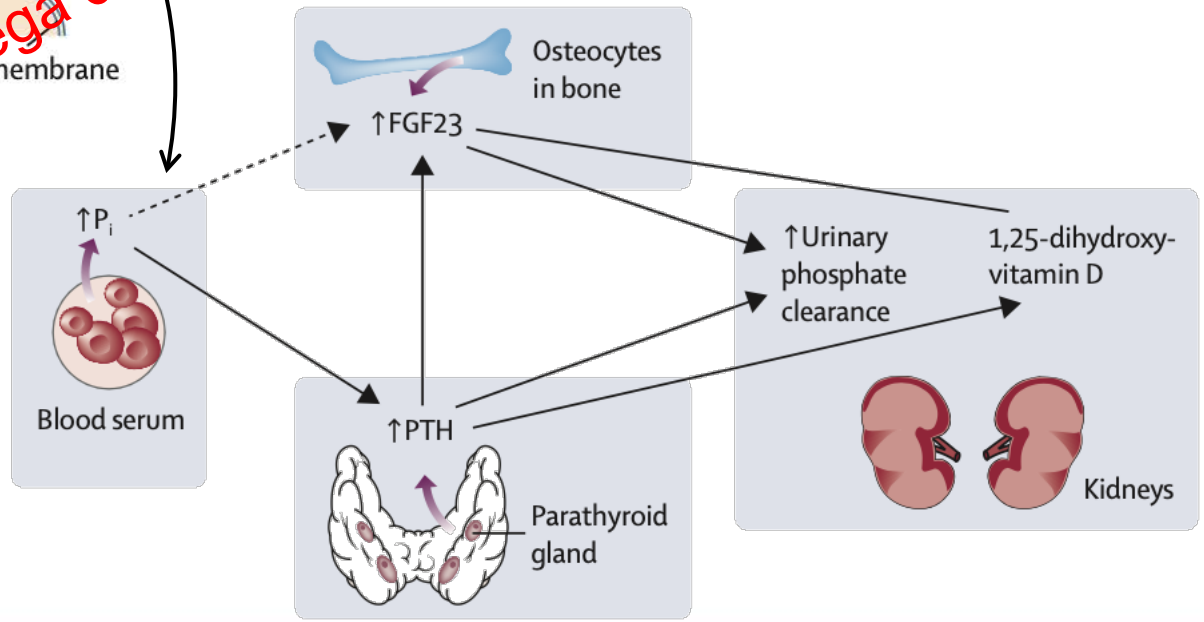
Event	Canagliflozin	Placebo	P Value†
	event rate per 1000 patient-yr		
All serious adverse events	104.3	120.0	0.04
Adverse events leading to discontinuation	35.5	32.8	0.07
Serious and nonserious adverse events of interest recorded in the CANVAS Program			
Acute pancreatitis (adjudicated)	0.5	0.4	0.63
Cancer			
Renal cell	0.6	0.2	0.17
Bladder	1.0	1.1	0.74
Breast	3.1	2.6	0.65
Photosensitivity‡	1.0	0.3	0.07
Diabetic ketoacidosis (adjudicated)	0.6	0.3	0.14
Amputation	6.3	3.4	<0.001
Fracture (adjudicated)‡			
All	15.4	11.9	0.02
Low-trauma	11.6	9.2	0.06
Venous thromboembolic events	1.7	1.7	0.63
Infection of male genitalia§	34.9	10.8	<0.001
Serious and nonserious adverse events of interest collected in CANVAS alone¶			
Osmotic diuresis	34.5	13.3	<0.001
Volume depletion	26.0	18.5	0.009

Safety‡						NA
Any adverse event	1784/2200	1860/2197	351.4	379.3	0.87 (0.82–0.93)	NA
Any serious adverse event	737/2200	806/2197	145.2	164.4	0.87 (0.79–0.97)	NA
Serious adverse event related to trial drug	62/2200	42/2197	12.2	8.6	1.45 (0.98–2.14)	NA
Amputation	70/2200	63/2197	12.3	11.2	1.11 (0.79–1.56)	NA
Fracture	67/2200	68/2197	11.8	12.1	0.98 (0.70–1.37)	NA
Cancer						
Renal-cell carcinoma	1/2200	5/2197	0.2	0.9	NA	NA
Breast cancer§	8/761	3/731	4.1	1.6	2.59 (0.69–9.76)	NA
Bladder cancer	10/2200	9/2197	1.7	1.6	1.10 (0.45–2.72)	NA

Perkovic V et al., NEJM 2019 & Neal B et al., NEJM 2017

Proposed mechanisms of SGTL2i adverse effects on bone





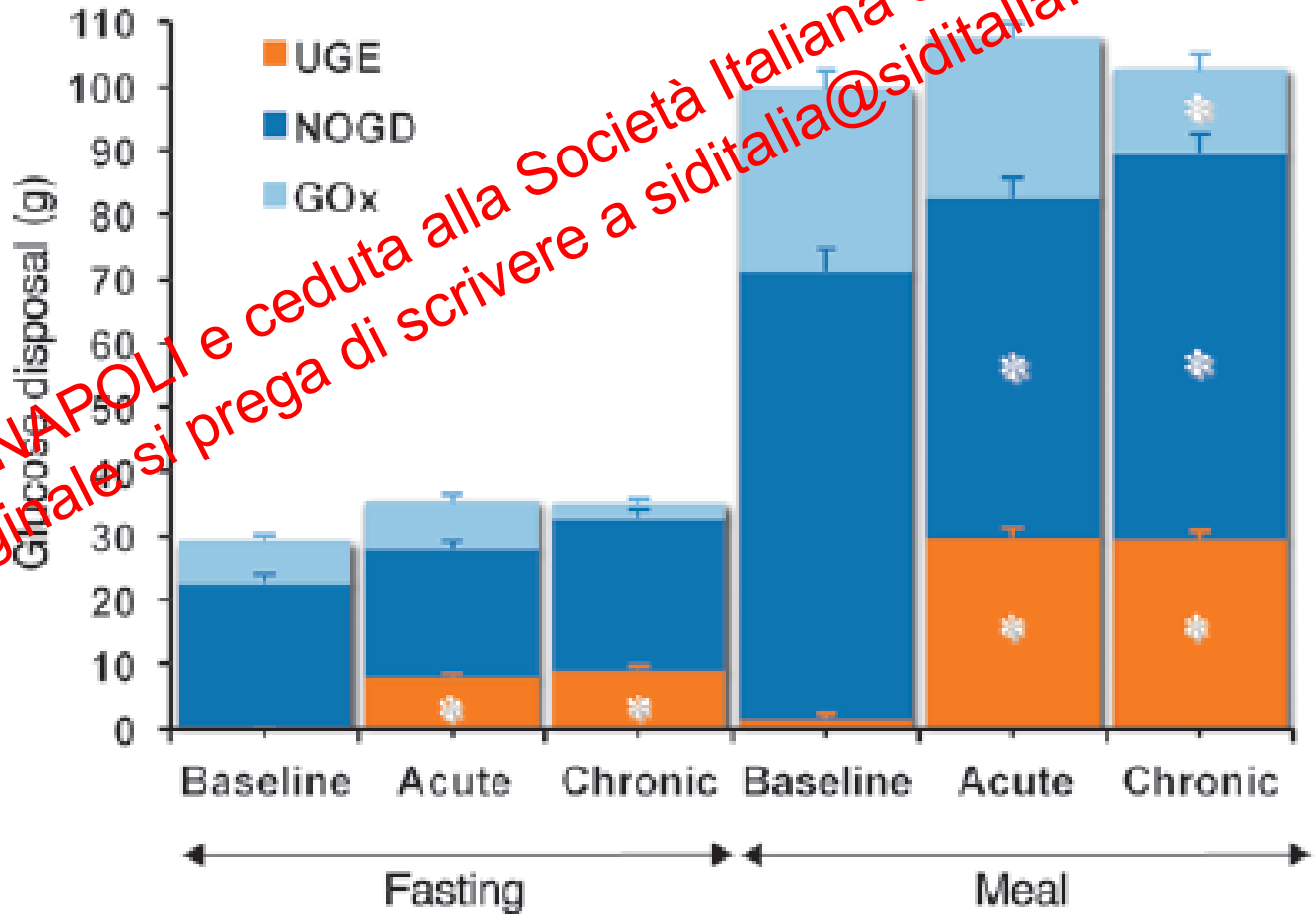
Taylor SA et al., Lancet 2015

Adverse effects of SGLT2i

- Risk of amputation and bone fractures
- Diabetic Ketoacidosis
- Genitourinary infections
- Risk of volume depletion and hypotension

Metabolic Response to SGLT2 Inhibition in T2D

66 T2D pts
BMI 32±5, HbA1c 55±8,
Empagliflozin 25 mg,
Treatment 4 wks



Ferrannini E et al J Clin Invest 2014

Metabolic Response to SGLT2 Inhibition in T2D

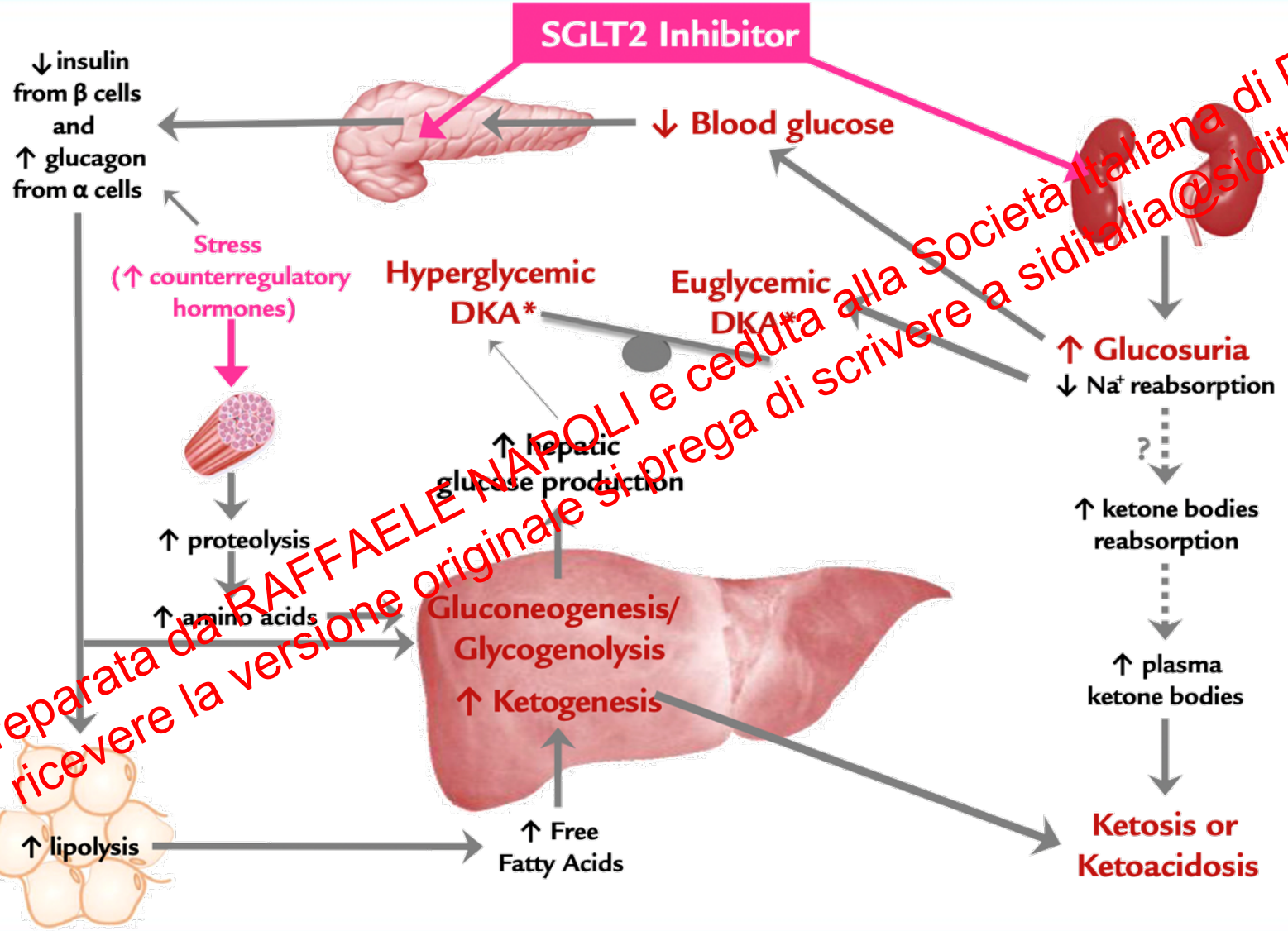
66 T2D pts
BMI 32±5, HbA1c 55±8,
Empagliflozin 25 mg,
Treatment 4 wks

UGE and substrate oxidation rates[A]

	Baseline	Acute	Chronic	P^B	P^C
Fasting urine output (l) [IQR]	0.6 [0.4]	0.7 [0.5]	0.5 [0.4]	0.0002	0.0116
Fasting UGE_{AUC} (g) [IQR]	0.02 [0.03]	7.8 [4.4]	9.2 [5.2]	<0.0001	<0.0001
Meal urine output (l) [IQR]	0.6 [0.5]	0.8 [0.4]	0.8 [0.4]	<0.0001	<0.0001
Meal UGE_{AUC} (g) [IQR]	0.3 [1.6]	29.0 [12.5]	28.2 [15.4]	<0.0001	<0.0001
Meal NPRQ [IQR]	0.79 [0.13]	0.79 [0.10]	0.74 [0.11]	NS	<0.0001
GOx_{AUC} (g) [IQR]	31 [35]	30 [29]	12 [32]	NS	<0.0001
$NOGD_{AUC}$ (g) [IQR]	67 [44]	52 [33]	58 [37]	<0.0001	0.0050
Meal LOx_{AUC} (g) [IQR]	26 [18]	26 [17]	31 [13]	NS	0.0005
Meal POx_{AUC} (g) [IQR]	12 [10]	12 [8]	14 [8]	NS	NS
Fasting EE (kJ/min) [IQR]	4.9 [1.1]	4.8 [0.7]	4.8 [0.8]	0.0113	NS
Meal EE (kJ/min) [IQR]	5.5 [1.2]	5.3 [1.0]	5.3 [1.0]	NS	NS
Meal-stimulated EE (%)	12 [8]	13 [8]	12 [11]	NS	NS

Ferrannini E et al J Clin Invest 2014

Mechanism of SGLT2i-associated DKA

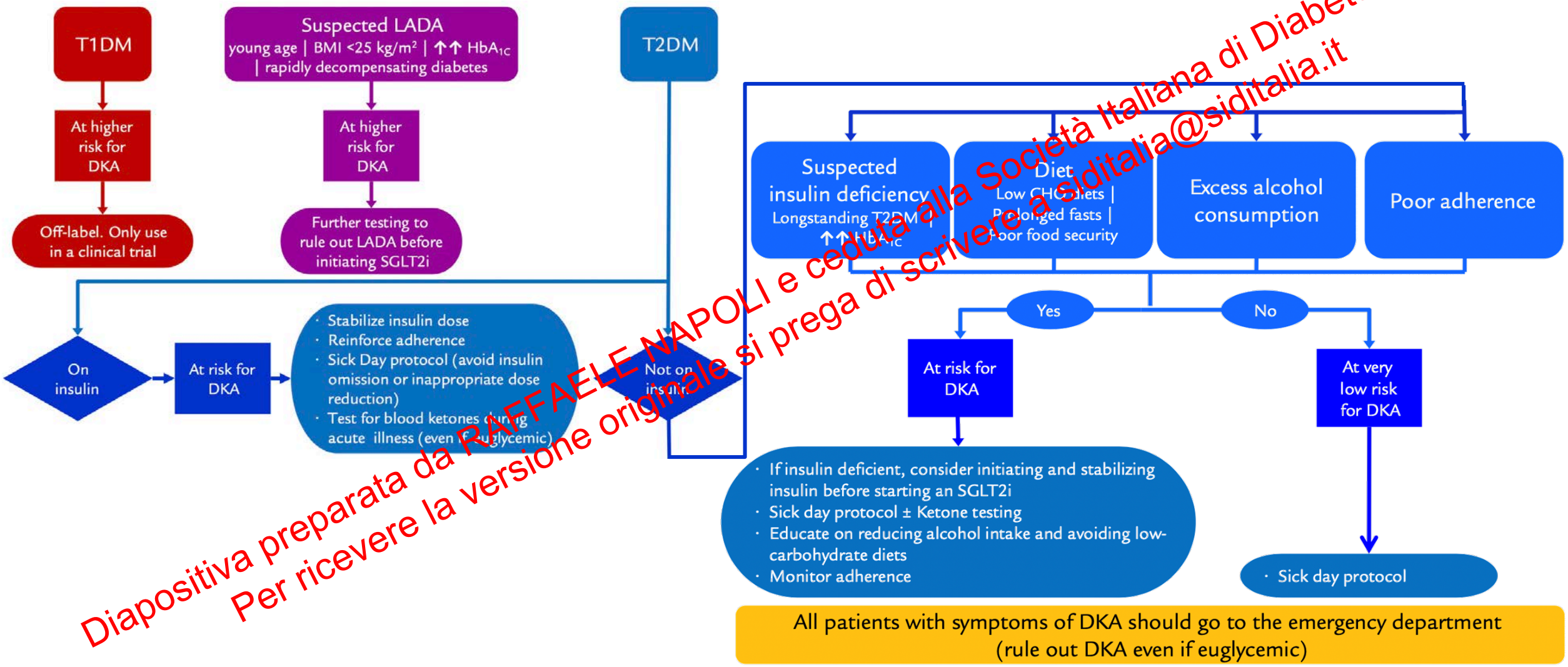


Goldenberg RM et al. , Clin ical Therapeutics 2016

Precipitants for SGLT2i-associated DKA and actions to prevent its occurrence

The insulin dose should be maintained, and supplemental insulin may be necessary	
Precipitant	**Action(s) Regarding SGLT2 Inhibitor**
Acute illness (eg, infection, gastroenteritis, myocardial infarction/stroke)	Hold at onset Restart when feeling well and able to eat and drink
Bariatric surgery	Hold while on preoperative low-carbohydrate diet Revaluate postoperatively
Major surgical procedures	Hold 3 days* before surgery Restart when feeling well and able to eat and drink
Risk of dehydration (eg, extensive exercise, preparing for colonoscopy)	Hold until able to maintain hydration
Low-carbohydrate diet	Hold until normal diet resumes
Excessive alcohol intake	Stop immediately Reassess at a later date

Prescribing sodium-glucose cotransporter 2 inhibitors (SGLT2i) and prevention of DKA



Adapted from Goldenberg RM et al. , Clin ical Therapeutics 2016

EMA confirms recommendations to minimise ketoacidosis risk with SGLT2 inhibitors for diabetes

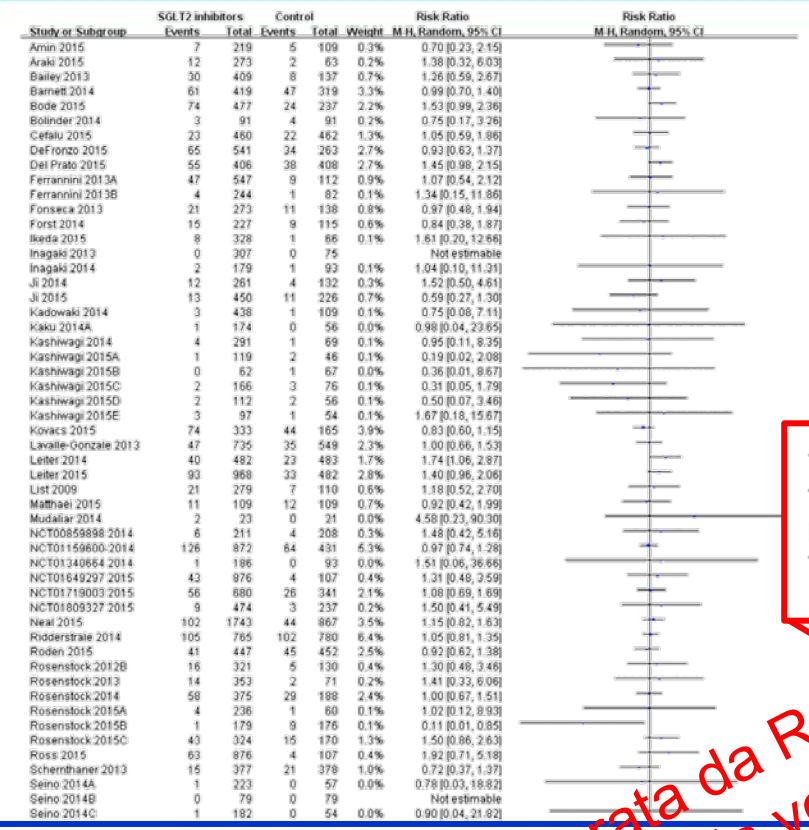
Information for healthcare professionals

- Rare cases of diabetic ketoacidosis …have occurred in patients taking SGLT2i. A number of these cases were atypical with patients having only moderately raised blood sugar levels…
- Always consider the possibility of diabetic ketoacidosis in patients taking SGLT2 inhibitors who have non-specific symptoms such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue or sleepiness…
- Inform patients of the signs and symptoms of diabetic ketoacidosis and advise them to seek medical advice immediately if they develop such signs and symptoms.
- Stop treatment with SGLT2 inhibitors immediately if diabetic ketoacidosis is suspected or confirmed, and do not re-start treatment unless another clear precipitating factor for the condition is identified and resolved.
- Stop treatment with SGLT2 inhibitors temporarily in patients undergoing major surgical procedures or hospitalised due to acute serious medical illnesses. Treatment may be restarted once the patient's condition has stabilised.
- Exercise caution in patients with risk factors for ketoacidosis and inform patients of these factors. These include low reserve of insulin-secreting cells, a sudden reduction in insulin dose, an increased requirement for insulin (due to illness, surgery or alcohol abuse) and conditions that restrict food intake or can lead to severe dehydration.

Adverse effects of SGLT2i

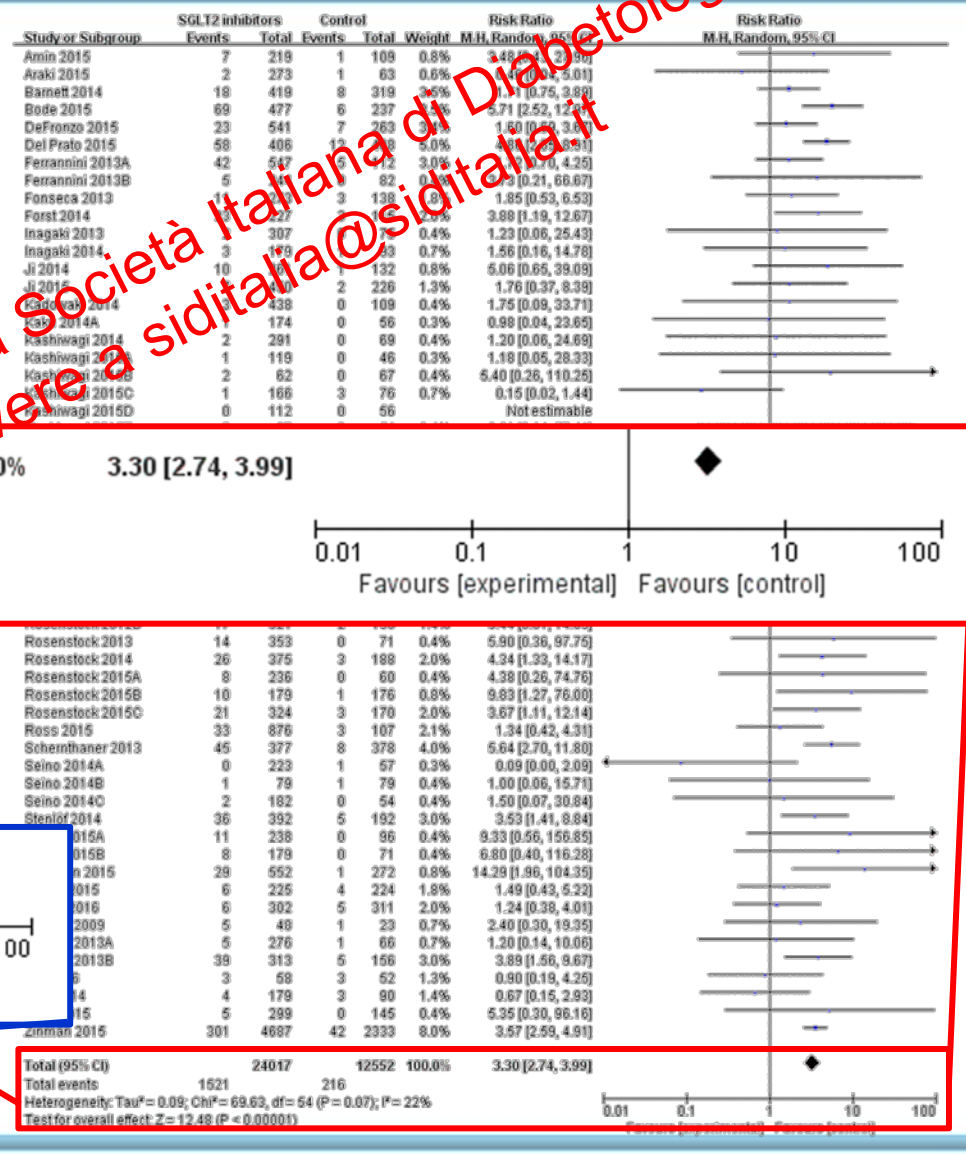
- Risk of amputation and bone fractures
- Diabetic Ketoacidosis
- Genitourinary infections
- Risk of volume depletion and hypotension

UTI and Genital infections in T2D patients receiving SGLT2i versus control in RCT



UTI

Genital Infections



Adverse effects of SGLT2i

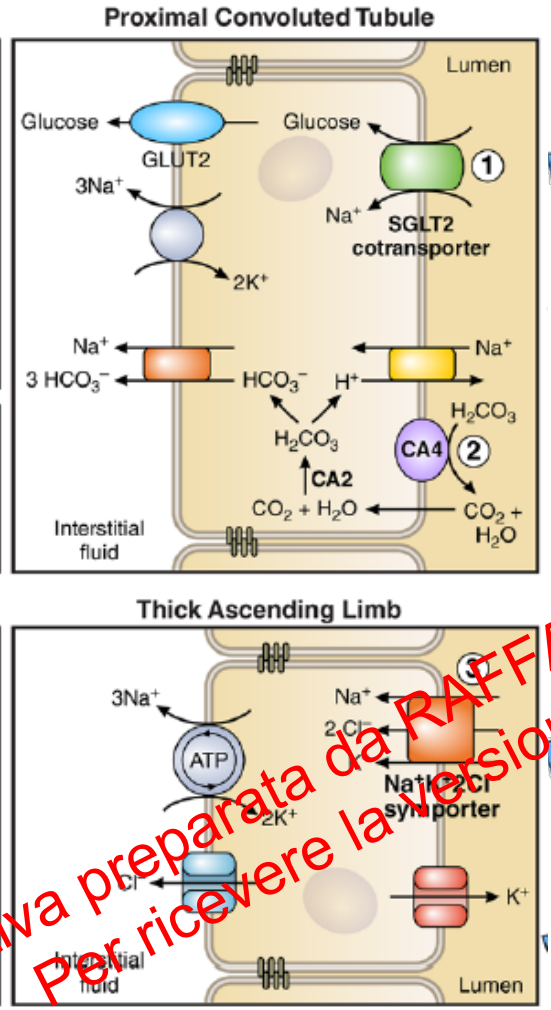
- Risk of amputation and bone fractures
- Diabetic Ketoacidosis
- Genitourinary infections
- Risk of volume depletion and hypotension

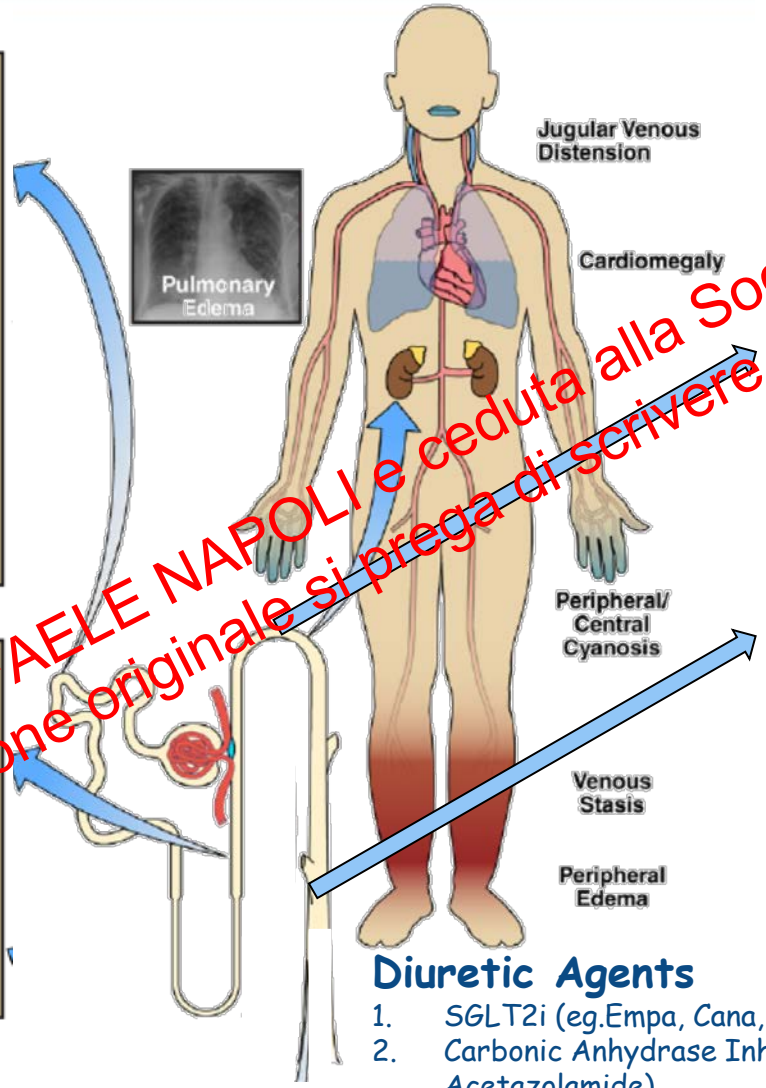
Diuretic agents, their mechanisms of action, and potential impact in HF

SGLT2i
- ↑ Natriuresis
- ↓ PV
- ↓ Blood pressure
- ↓ Nephropathy events
- ↓ CV events (including in HHF)

Carbonic Anhydrase Inhibitors
No known effect(s) on HHF

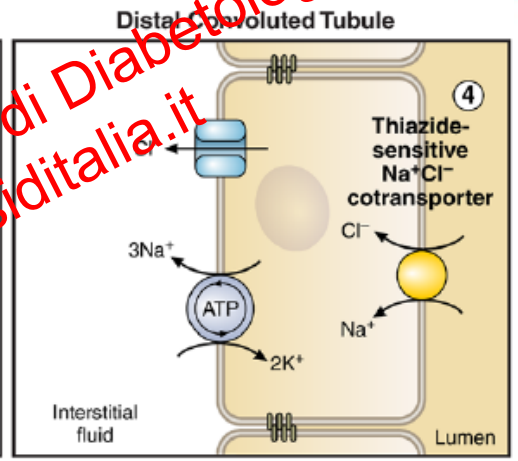
Loop Diuretics
- ↑ Natriuresis
- ↓ PV/volume overload
- ↓ Preload
- ↓ HHF



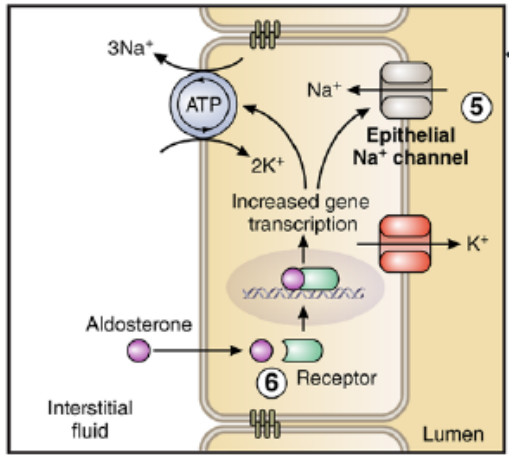


Thiazide Diuretics
- ↑ Natriuresis
- ↓ PV (transient)
- ↓ Blood pressure
- ↓ Loop diuretic augmenting effect

No known effect(s) on HHF



Aldosterone Receptor Antagonists
- ↓ LV remodelling
- ↓ HHF



Diuretic Agents

1. SGLT2i (eg.Empa, Cana, Dapa)
2. Carbonic Anhydrase Inhibitor (eg. Acetazolamide)
3. Loop diuretic (eg. Furosemide)
4. Thiazide diuretic (eg. Hydrochlorothiaz.)
5. Epithelial Na+ Channel inh. (eg. Amiloride)
6. Aldosterone Receptor Blocker (eg. Spironolactone)

Adverse effects in CANVAS and CREDENCE

IMPORTANT SAFETY INFORMATION

INVOKANA® can cause serious side effects, including:

- **Amputations. INVOKANA® may increase your risk of lower-limb amputations. Amputations mainly involve removal of the toe or part of the foot; however, amputations involving the leg, below and above the knee, have also occurred. Some people had more than one amputation, some on both sides of the body.** You may be at a higher risk of lower-limb amputation if you: have a history of amputation, have heart disease or are at risk for heart disease, have had blocked or narrowed blood vessels (usually in leg), have damage to the nerves (neuropathy) in the leg, or have had diabetic foot ulcers or sores. **Call your doctor right away if you have new pain or tenderness, any sores, ulcers, or infections in your leg or foot.** Your doctor may decide to stop your INVOKANA® for a while if you have any of these signs or symptoms. Talk to your doctor about proper foot care.

Table 2. Adverse Events.*

Event	Canagliflozin	Placebo	P Value†
	event rate per 1000 patient-yr		
All serious adverse events	104.3	120.0	0.04
Adverse events leading to discontinuation	35.5	32.8	0.07
Serious and nonserious adverse events of interest recorded in the CANVAS Program			
Acute pancreatitis (adjudicated)	0.5	0.4	0.63
Cancer			
Renal cell	0.6	0.2	0.17
Bladder	1.0	1.1	0.74
Breast	3.1	2.6	0.65
Photosensitivity‡	1.0	0.3	0.07
Diabetic ketoacidosis (adjudicated)	0.6	0.3	0.14
Amputation	6.3	3.4	<0.001
Fracture (adjudicated)‡			
All	15.4	11.9	0.02
Low-trauma	11.6	9.2	0.06
Venous thromboembolic events	1.7	1.7	0.63
Infection of male genitalia§	34.9	10.8	<0.001
Serious and nonserious adverse events of interest collected in CANVAS alone¶			
Osmotic diuresis	34.5	13.3	<0.001
Volume depletion	26.0	18.5	0.009

Safety‡						
Any adverse event	1784/2200	1860/2197	351.4	379.3	0.87 (0.82–0.93)	NA
Any serious adverse event	737/2200	806/2197	145.2	164.4	0.87 (0.79–0.97)	NA
Serious adverse event related to trial drug	62/2200	42/2197	12.2	8.6	1.45 (0.98–2.14)	NA
Amputation	70/2200	63/2197	12.3	11.2	1.11 (0.79–1.56)	NA
Fracture	67/2200	68/2197	11.8	12.1	0.98 (0.70–1.37)	NA
Cancer						
Renal-cell carcinoma	1/2200	5/2197	0.2	0.9	NA	NA
Breast cancer§	8/761	3/731	4.1	1.6	2.59 (0.69–9.76)	NA
Bladder cancer	10/2200	9/2197	1.7	1.6	1.10 (0.45–2.72)	NA

Perkovic V et al., NEJM 2019 & Neal B et al., NEJM 2017

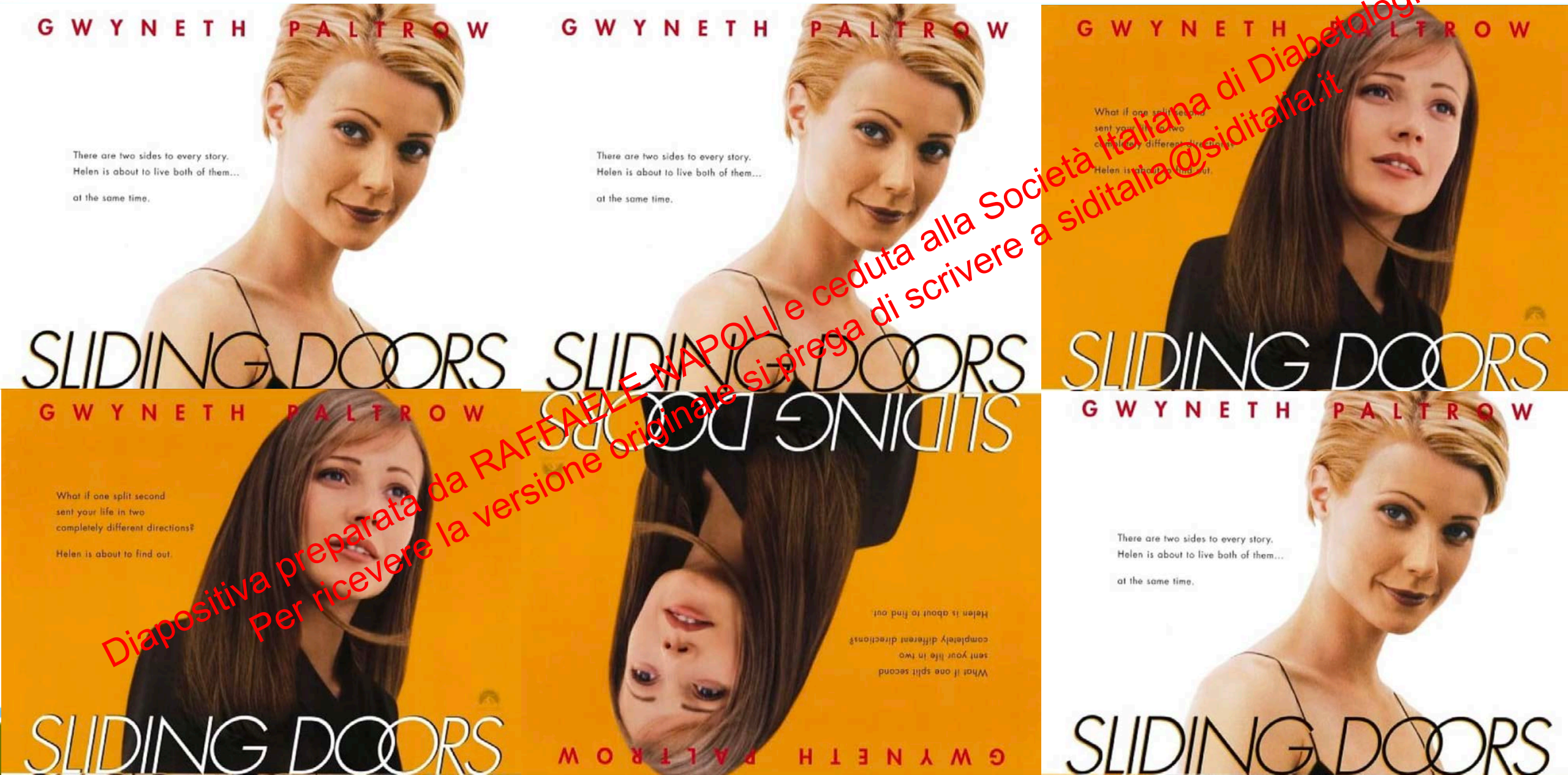
Adverse effects in DAPA-HF & EMPEROR-Reduced

Variable	Dapagliflozin (N=2373)		Plac (N=2
	values	*events/100 patient-yr*	*values*
Safety outcomes			
Discontinuation due to adverse event — no./total no. (%)	111/2368 (4.7)	—	116/2368 (4.9)
Adverse events of interest — no./total no. (%)			
Volume depletion	178/2368 (7.5)	—	162/2368 (6.8)
Renal adverse event	153/2368 (6.5)	—	170/2368 (7.2)
Fracture	49/2368 (2.1)		50/2368 (2.1)
Amputation	13/2368 (0.5)	—	12/2368 (0.5)
Major hypoglycemia**	4/2368 (0.2)		4/2368 (0.2)
Diabetic ketoacidosis††	3/2368 (0.1)	—	0
Fournier's gangrene	0		1/2368 (<0.1)

	Empagliflozin (n=1863) N (%)	Placebo (n=1863) N (%)
Patients with any adverse event	1420 (76.2)	1463 (78.5)
Patients with any serious adverse event	772 (41.4)	896 (48.1)
Selected adverse events of interest		
Hypotension	176 (9.4)	163 (8.7)
Symptomatic hypotension	106 (5.7)	103 (5.5)
Volume depletion	197 (10.6)	184 (9.9)
Ketoacidosis	0 (0.0)	0 (0.0)
Hypoglycemic events*	27 (1.4)	28 (1.5)
In patients with type 2 diabetes	20 (2.2)	22 (2.4)
In patients without type 2 diabetes	7 (0.7)	6 (0.6)
Urinary tract infections	91 (4.9)	83 (4.5)
Complicated urinary tract infections	19 (1.0)	15 (0.8)
Genital infections	31 (1.7)	12 (0.6)
Complicated genital infections	6 (0.3)	5 (0.3)
Bone fractures	45 (2.4)	42 (2.3)
Events leading to lower limb amputation	13 (0.7)	10 (0.5)

McMurray JJV et al., NEJM 2019 & Packer M et al., NEJM 2020

Effetti collaterali di GLP-1RA (vs SGLT2i?): what-is e what-if



On-treatment adverse events during the Pioneer 2 Trial

	Patients, *n* (%)	
	Oral semaglutide 14 mg (*n* = 410)	Empagliflozin 25 mg (*n* = 409)
Adverse events	289 (70.5)	283 (69.2)
Serious adverse events	27 (6.6)	37 (9.0)
Adverse event severity		
Mild	242 (59.0)	240 (58.7)
Moderate	140 (34.1)	118 (28.9)
Severe	24 (5.9)	23 (5.6)
Severe or blood glucose–confirmed symptomatic hypoglycemic episode*†‡	7 (1.7)	8 (2.0)
ADA-classified hypoglycemic episode*	45 (11.0)	39 (9.5)
Severe hypoglycemic episode*†	1 (0.2)	1 (0.2)
Most frequent adverse events ≥5% in either group (preferred term)		
Nausea	81 (19.8)	10 (2.4)
Diarrhea	38 (9.3)	13 (3.2)
Vomiting	30 (7.3)	7 (1.7)
Decreased appetite	21 (5.1)	2 (0.5)
Influenza	8 (2.0)	21 (5.1)
Adverse events resulting in premature trial drug discontinuation	44 (10.7)	18 (4.4)

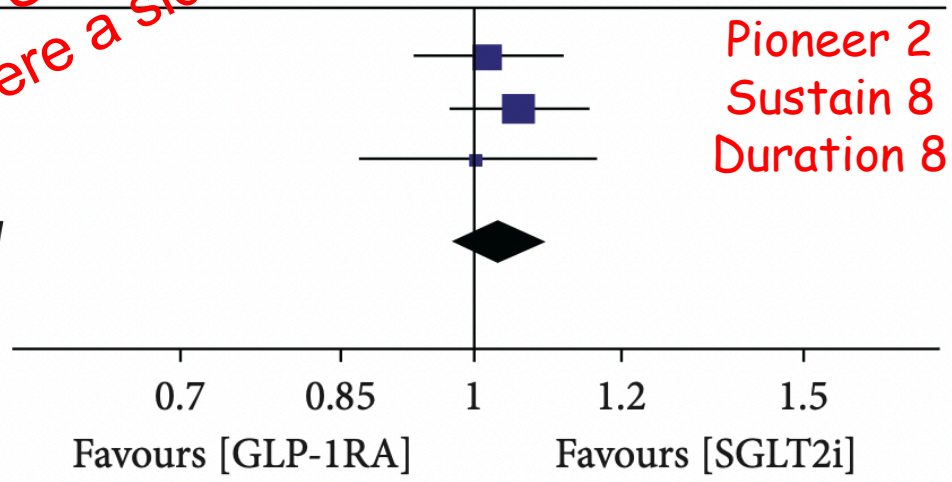
Rodbard HW et al., Diabetes Care 2019

Overall safety of GLP-1RAs with SGLT-2is

Study or subgroup	GLP-1RA Events	GLP-1RA Total	SGLT2i Events	SGLT2i Total	Weight (%)	Risk ratio M-H, random, 95% CI
Rodbard 2019	289	410	283	409	38.9	1.02 [0.93, 1.11]
Lingvay 2019	298	392	283	394	45.6	1.06 [0.97, 1.15]
Jabbour 2018	143	230	144	233	15.5	1.01 [0.87, 1.16]
Total (95% CI)		*1032*		*1036*	*100.00*	*1.03 [0.98, 1.09]*
Total events	730		710			

Heterogeneity: $tau^2 = 0.00$; $chi^2 = 0.56$, $df = 2$ ($p = 0.76$); $I^2 = 0\%$

Test for overall effect: $Z = 1.19$ ($p = 0.24$)



Ding L et al., International Journal of Endocrinology 2020

Strategies to mitigate the adverse effects of SGLT2i and GLP1-RA

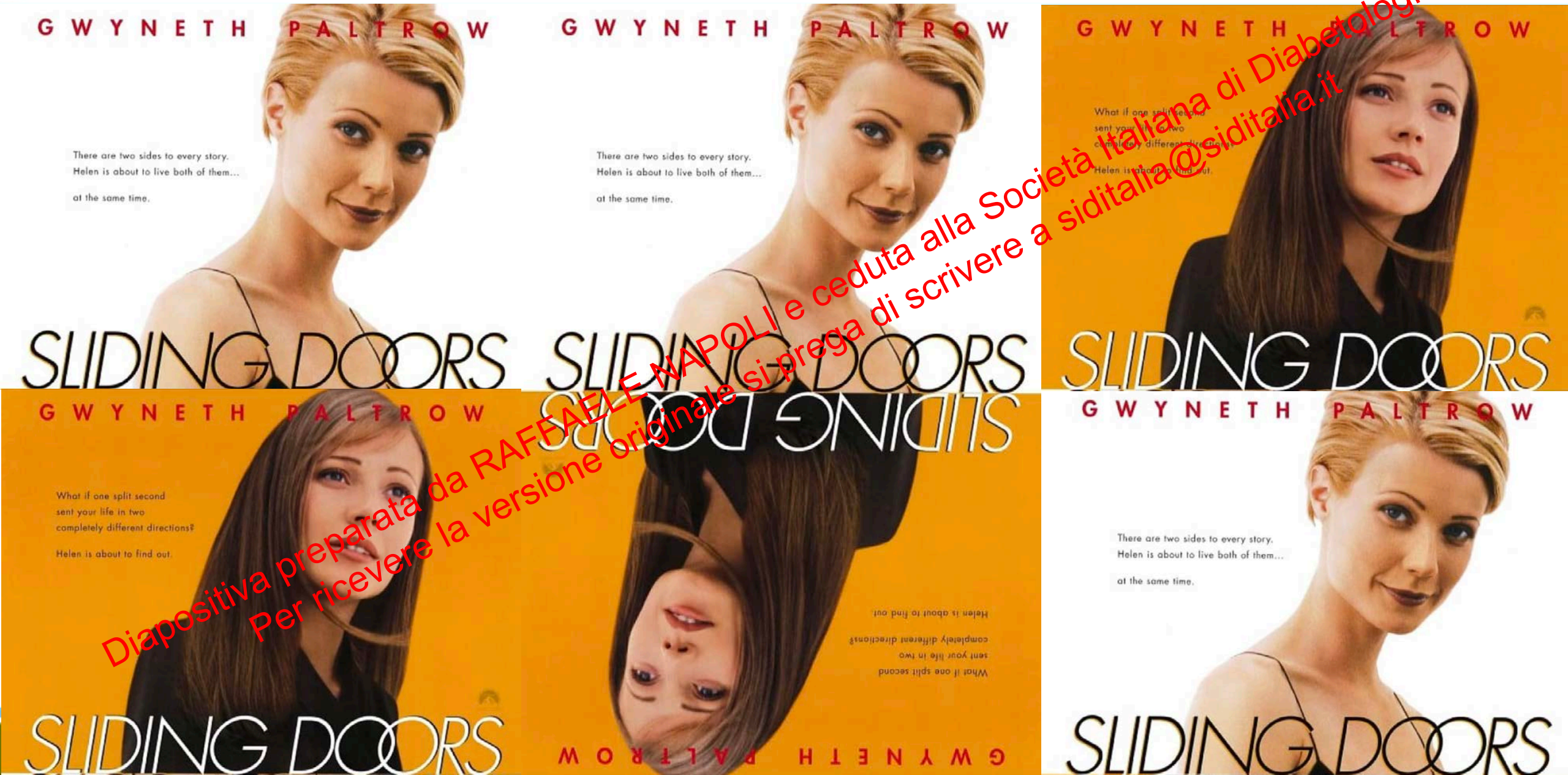
Adverse Effects	Frequency	Severity	Mitigating Strategies
SGLT2i			
Genital fungal infection	[a]	Low	Keep genital area dry and clean. Prophylactic topical treatment for fungal infection in high-risk patients
Volume depletion	[a]	Low	Proactive dose reduction of diuretics in euvolemic patients. Hold SGLT2i when patients have nausea, vomiting, or diarrhea. Implement "Sick day protocol"
UTI	[b]	Low	Use with caution. Avoid in patients at high risk of recurrent UTI (*e.g.*, indwelling foley catheter or self-catheterization)
DKA	[c]	High	Patient education on early recognition and implement "STOP DKA" protocol (stop SGLT2; test for ketones, maintain intake of fluid and carbohydrates, and use maintenance and supplemental insulin)
Amputation	[b]	High	Encourage self-examination by patients or caregivers. Foot examination by health care provider at clinic visits. Temporarily hold SGLT2i when having an open wound or infection of the foot
Bone fracture	[b]	High	Caution in patients with risk of fall. Monitor PTH and vitamin D
GLP-1 RA			
Nausea/vomiting/diarrhea	[a]	Low	Patient education on symptom recognition. Start at low dose and slowly uptitrate over 2–4 wk
Cholelithiasis and cholecystitis	[b]	High	Patient education on recognition of symptoms
Acute pancreatitis	[d]	High	Caution in patients with history of pancreatitis

SGLT2i, sodium glucose co-transporter 2 inhibitor; GLP-1 RA, glucagon-like peptide 1 receptor agonist; UTI, urinary tract infection; DKA, diabetic ketoacidosis; PTH, parathyroid hormone.
[a]Commonly reported in multiple, large clinical trials.
[b]Increased risk reported in a single, large clinical trial.
[c]Increased risk reported in meta-analysis of clinical trials.
[d]Reported in small clinical trials or case series.

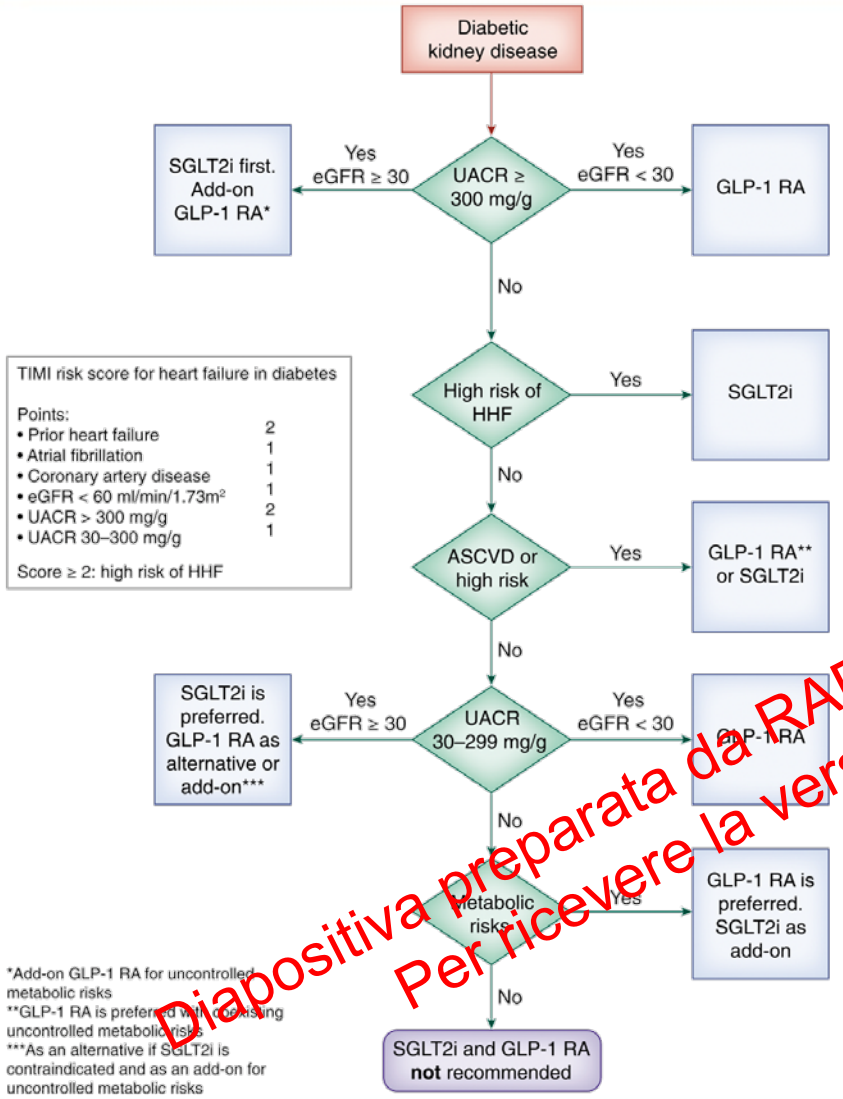
Cox analysis on adverse events, and corresponding event rates (calculated/1000 p-y)

	SGLT2i		GLP-1RA		Total		HR (CI)	p value
	Events	Event rate	Events	Event rate	Events	Event rate	SGLT2i/GLP-1 RA	
GUTI	4	0.76	2	0.39	6	0.57	1.91 (0.35 – 10.41)	0.456
Fournier's gangrene	0	0.00	0	0.00	0	0.00	N/A	N/A
Bone fracture	26	4.92	23	4.44	49	4.68	1.10 (0.63 – 1.93)	0.73
Diabetic ketoacidosis	1	0.19	1	0.19	2	0.19	0.97 (0.06 – 15.56)	0.985
Acute renal disease	13	2.46	23	4.44	36	3.44	0.55 (0.28 – 1.09)	0.086
Amputation	10	1.89	6	1.16	16	1.53	1.59 (0.58 – 4.37)	0.37
Pancreatitis	4	0.76	2	0.39	6	0.57	1.98 (0.36 – 10.81)	0.43
Pancreatic cancer	9	1.7	6	1.16	15	1.43	1.45 (0.52 – 4.08)	0.48

Effetti collaterali di GLP-1RA (vs SGLT2i?): what-is e what-if



Decision Algorithm for Prescribing SGLT2i and GLP-1 RA for DKD



eGFR	UACR <30 mg/g	UACR 30–299 mg/g	UACR ≥300 mg/g
>60 ml/min per 1.73 m²	SGLT2i or GLP-1 RA[a]	SGLT2i is preferred. GLP-1 RA as an alternative if SGLT2i is contraindicated or not tolerated, and as an add-on for uncontrolled metabolic risk[b]	SGLT2i should be initiated. GLP-1 RA as an add-on for uncontrolled metabolic risk[c]
30–60 ml/min per 1.73 m²	SGLT2i is preferred. GLP-1 RA as an alternative if SGLT2i is contraindicated or not tolerated, and as an add-on for uncontrolled metabolic risk[b]		SGLT2i should be initiated. GLP-1 RA as an add-on for uncontrolled metabolic risk[c]
15–29 ml/min per 1.73 m²	GLP-1 RA (dulaglutide) is preferred. Initiation of SGLT2i is currently contraindicated[d]		

Li J et al., CJASN 2020