Nouveautés en diabète: les doubles agonistes GIP/GLP1

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Divulgations

- *Financement de recherche: CIHR, FRQS, Eli Lilly*
- *Consultant/présentations: Janssen, Novartis Pharmaceuticals Canada, NovoNordisk Canada, HLS Therapeutics, Eli Lilly*
- *Les appellations génériques seront employées pour les médicaments cités et les usages expérimentaux non couramment approuvés par Santé Canada seront mentionnées, le cas échéant.*

Objectifs

CENTRE DE RECHERCHE | CHUS

Discuter des mécanismes d'action anti-diabétiques des doubles agonistes GIP/GLP1

Revoir les données cliniques concernant cette nouvelle classe de médicament pour le diabète de type 2

Discuter de la place de cette nouvelle classe dans la prise en charge clinique du diabète de type 2

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GIP vs. GLP1: incretin effect

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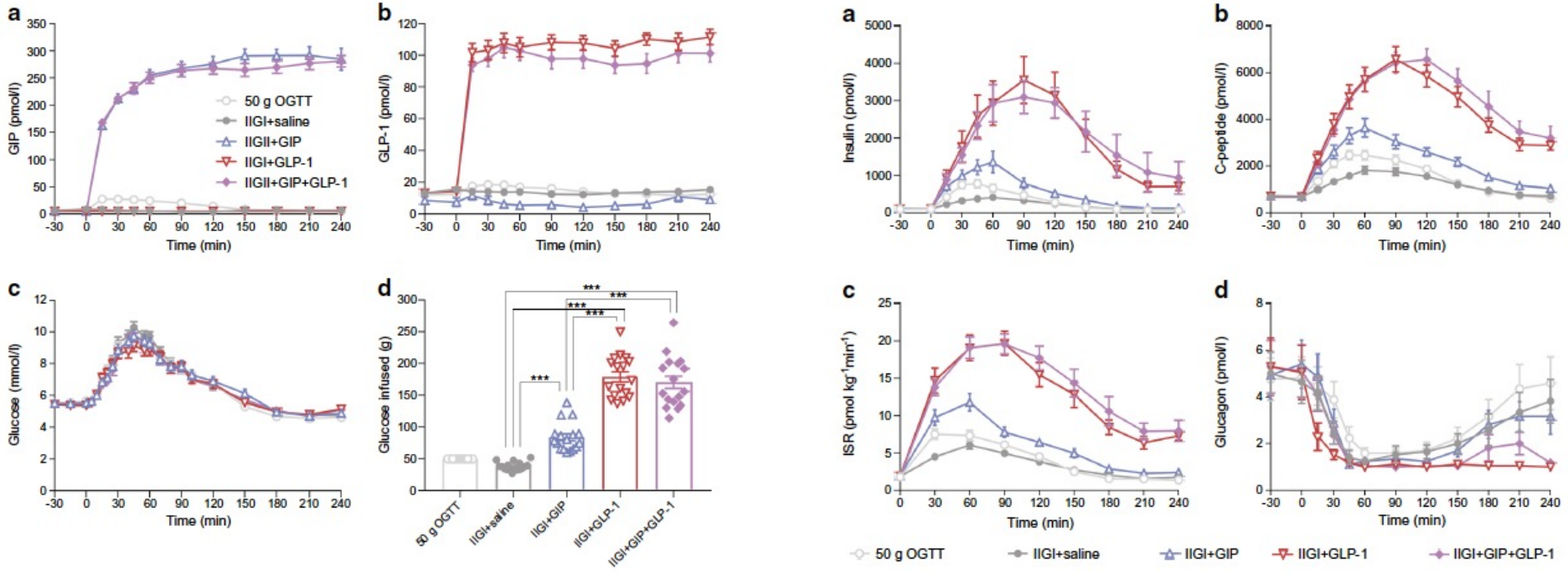
N = 17 overweight/obese men, randomized, crossover study



Bergmann NC et al. Diabetologia 2019;62:665-675

GIP vs. GLP-1

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Glucagon-like Peptide-1 Receptor Agonism

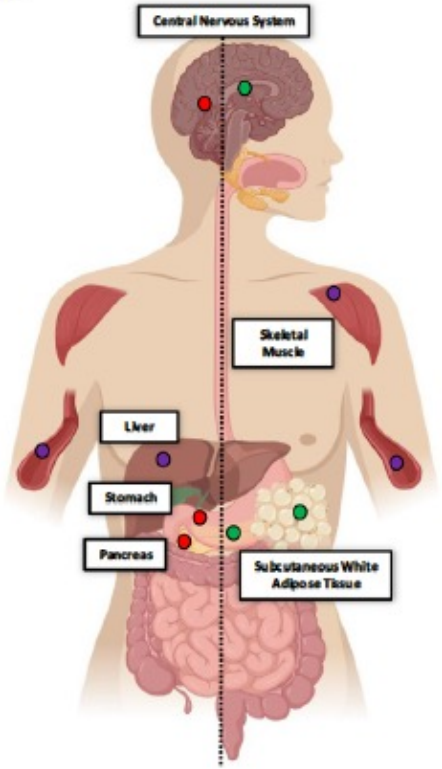
Central Nervous System
- ↑ Satiety
- ↓ Food Intake
- ↑ Nausea
- ↓ Body Weight

Pancreas
- ↑ Insulin
- ↓ Glucagon

Stomach
- ↓ Gastric Emptying

Systemic
- ↓ Hyperglycemia

Liver
- ↑ Insulin Sensitivity
- ↓ Hepatic Glucose Production
- ↓ Ectopic Lipid Accumulation



Glucose-dependent Insulinotropic Polypeptide Receptor Agonism
Glucagon-like Peptide 1 Receptor Agonism
Indirect Action

Glucose-dependent Insulinotropic Polypeptide Receptor Agonism

Central Nervous System
- ↓ Food Intake
- ↓ Nausea
- ↓ Body Weight

Pancreas
- ↑ Insulin
- ↑ Glucagon

Subcutaneous White Adipose Tissue
- ↑ Insulin Sensitivity
- ↑ Lipid Buffering Capacity
- ↑ Blood Flow
- ↑ Storage Capacity
- ↓ Proinflammatory Immune Cell Infiltration

Systemic
- ↓ Hyperglycemia
- ↓ Dietary Triglyceride

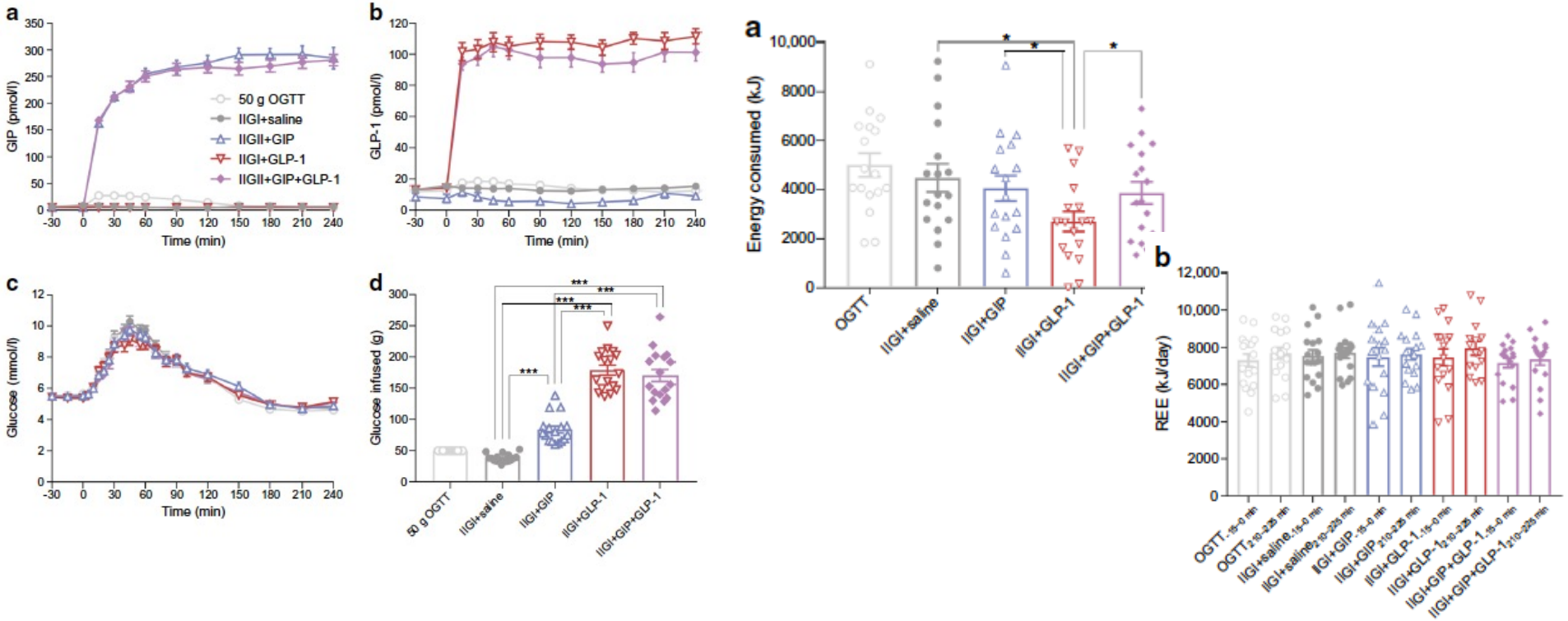
Skeletal Muscle
- ↑ Insulin Sensitivity
- ↑ Metabolic Flexibility
- ↓ Ectopic Lipid Accumulation

Samms RJ et al. Trends Endocrinol Metab 2020;31:410-421

GIP vs. GLP1: acute food intake

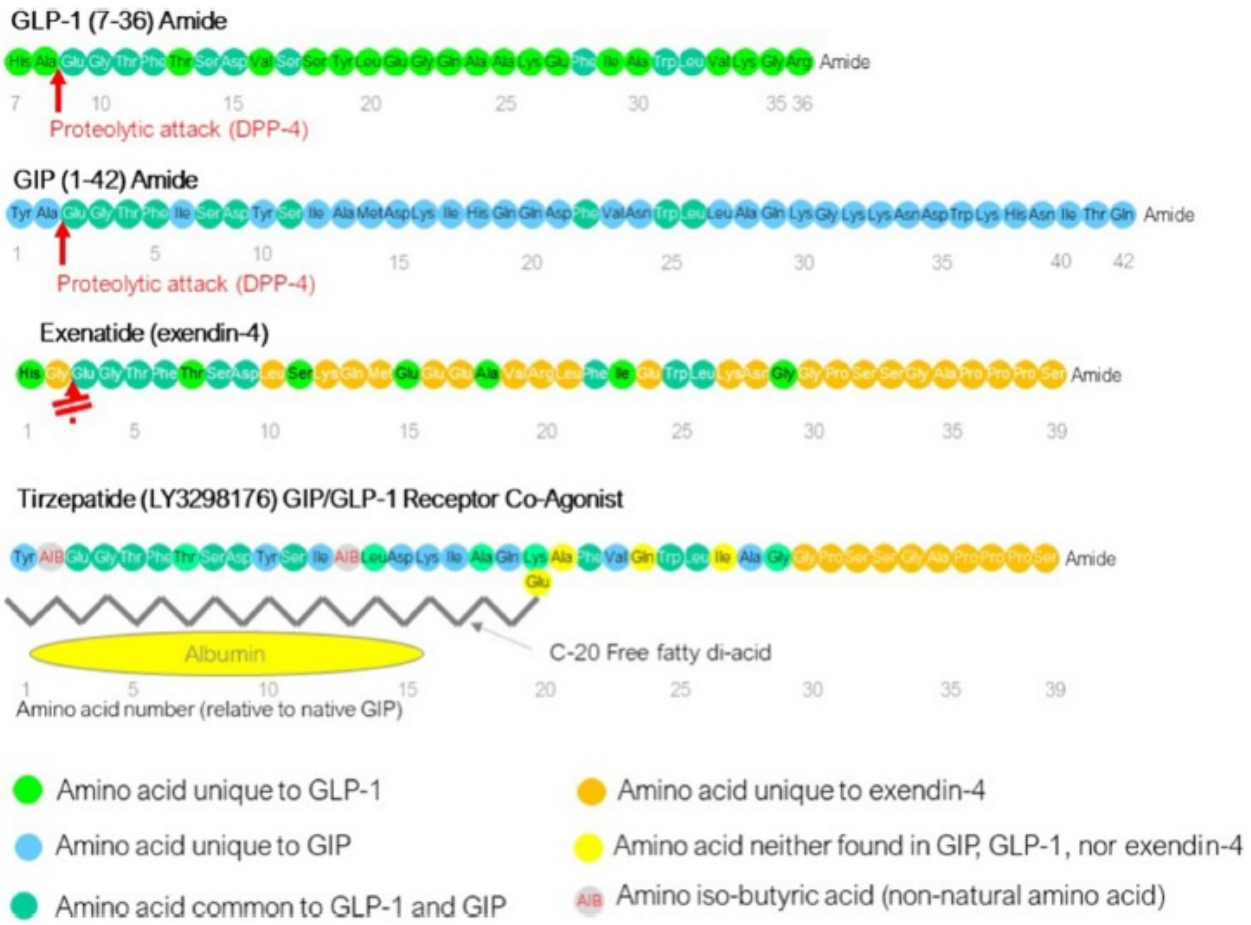
CENTRE DE RECHERCHE | CHUS

N = 17 overweight/obese men, randomized, crossover study



Bergmann NC et al. Diabetologia 2019;62:665-675

Tirzepatide - structure



Nauk MA et D'Alessio DA. Cardiovasc Diabetol 2022;21:169

Tirzepatide - pharmacology

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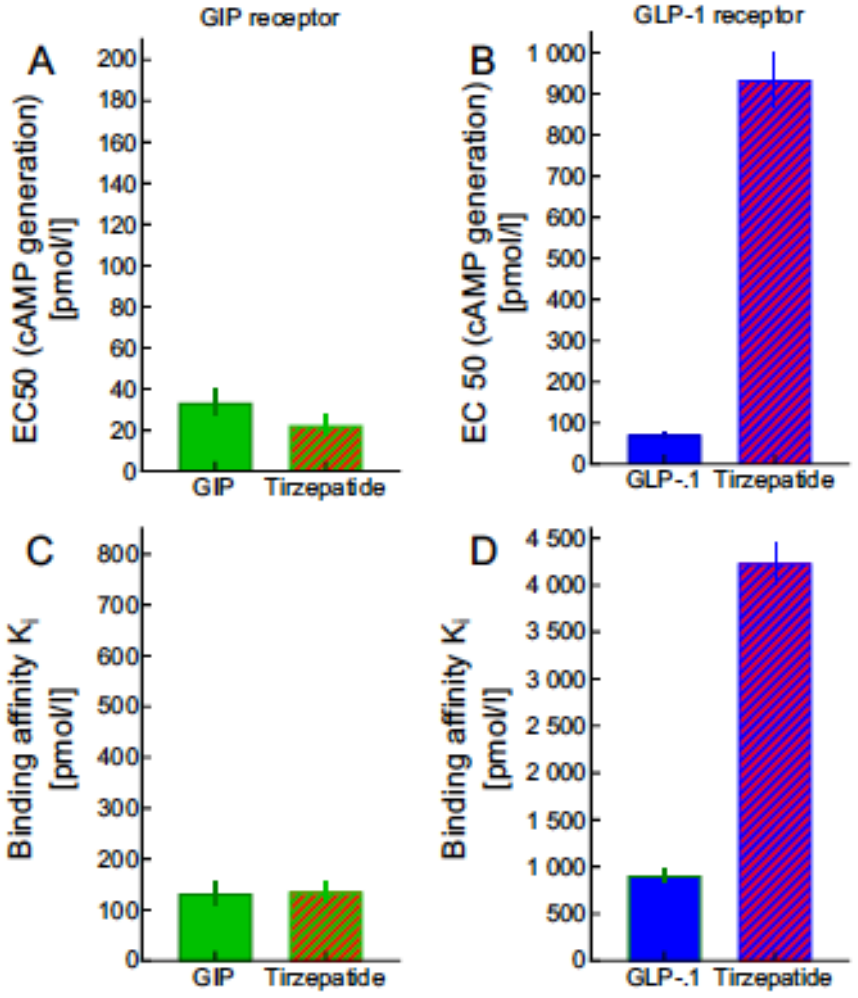
Linear dose – Cmax relationship

Time to Cmax – 24-48 h

Elimination half-life ~ 5 days

No change with impaired renal or liver function

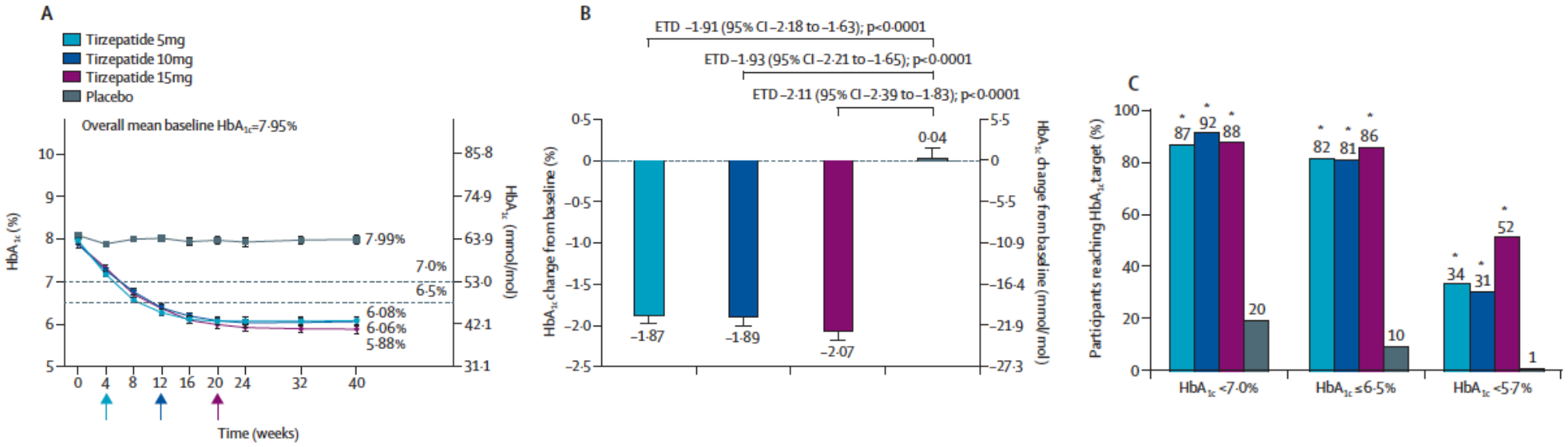
GIP agonist or antagonist?



Nauk MA et D'Alessio DA. Cardiovasc Diabetol 2022;21:169

Tirzepatide vs. placebo SURPASS 1

Randomized, open-label, parallel-group, multicenter phase 3 trial T2D N = 478



Rosenstock J et al. The Lancet 2021;398:143-155

Tirzepatide vs. placebo SURPASS 1

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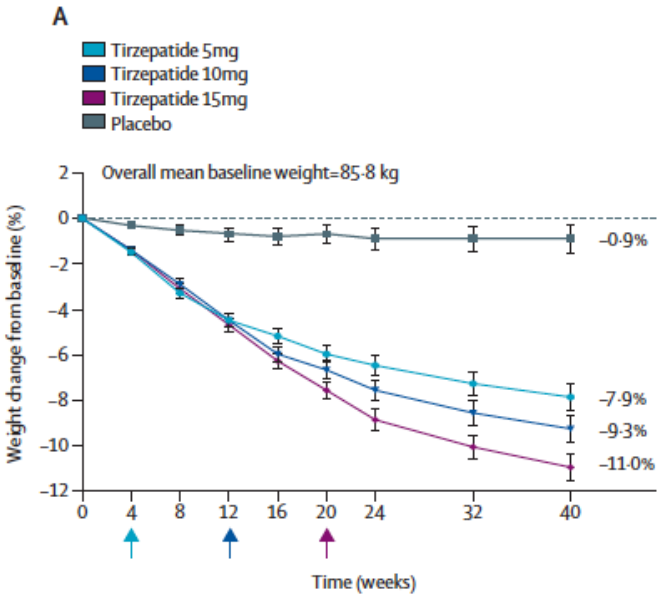

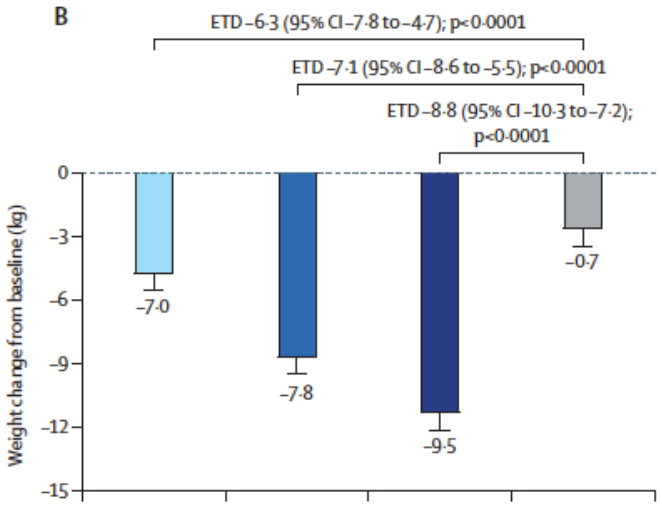

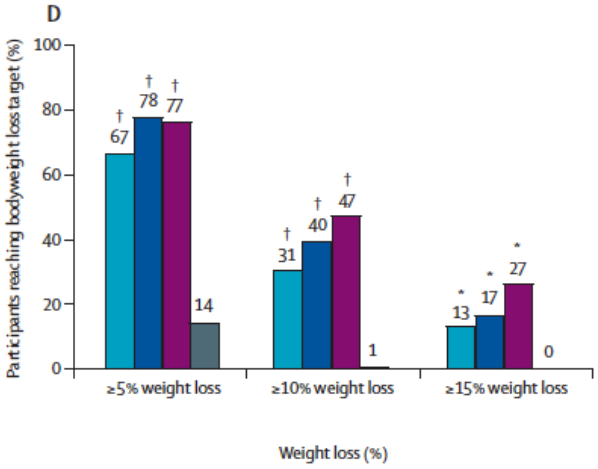

Rosenstock J et al. The Lancet 2021;398:143-155

Tirzepatide vs. placebo SURPASS 1

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	Tirzepatide 5 mg (n=121)	Tirzepatide 10 mg (n=121)	Tirzepatide 15 mg (n=121)	Placebo (n=115)	Total (n=478)
Participants with ≥1 treatment-emergent adverse event	83 (69%)	81 (67%)	77 (64%)	76 (66%)	317 (66%)
Serious adverse events	5 (4%)	2 (2%)	1 (1%)	3 (3%)	11 (2%)
Deaths*	0	0	0	1 (1%)	1 (<1%)
Adverse event leading to study drug discontinuation	4 (3%)	6 (5%)	8 (7%)	3 (3%)	21 (4%)
Gastrointestinal disorder (system order class)	3 (2%)	6 (5%)	8 (7%)	1 (1%)	18 (4%)
Gastrointestinal disorder (preferred term)	1 (1%)	2 (2%)	2 (2%)	0	5 (1%)
Diarrhoea	0	2 (2%)	2 (2%)	0	4 (1%)
Nausea	0	2 (2%)	1 (1%)	1 (1%)	4 (1%)
Abdominal discomfort	0	0	2 (2%)	0	2 (<1%)
Dyspepsia	1 (1%)	0	1 (1%)	0	2 (<1%)
Colitis ischaemic	1 (1%)	0	0	0	1 (<1%)

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Tirzepatide vs. placebo SURPASS 1

CENTRE DE RECHERCHE | CHUS

	Tirzepatide 5 mg (n=121)	Tirzepatide 10 mg (n=121)	Tirzepatide 15 mg (n=121)	Placebo (n=115)	Total (n=478)
Treatment-emergent adverse events occurring in ≥5% of participants in any treatment group (preferred term)					
Nausea	14 (12%; 31)	16 (13%; 82)	22 (18%; 50)	7 (6%; 8)	59 (12%; 171)
Diarrhoea	14 (12%; 21)	17 (14%; 19)	14 (12%; 20)	9 (8%; 15)	54 (11%; 75)
Hyperglycaemia	4 (3%)	5 (4%)	3 (2%)	31 (27%)	43 (9%)
Nasopharyngitis	7 (6%)	8 (7%)	8 (7%)	10 (9%)	33 (7%)
Dyspepsia	11 (9%)	8 (7%)	7 (6%)	4 (3%)	30 (6%)
Decreased appetite	5 (4%)	8 (7%)	10 (8%)	1 (1%)	24 (5%)
Headache	5 (4%)	4 (3%)	5 (4%)	9 (8%)	23 (5%)
Constipation	7 (6%)	6 (5%)	8 (7%)	1 (1%)	22 (5%)
Vomiting	4 (3%; 6)	3 (2%; 3)	7 (6%; 9)	2 (2%; 3)	16 (3%; 21)
Influenza	7 (6%)	3 (2%)	0	2 (2%)	12 (3%)
Gastritis	6 (5%)	0	3 (2%)	0	9 (2%)
All gastrointestinal adverse events	46 (38%)	50 (41%)	50 (41%)	22 (19%)	168 (35%)

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Tirzepatide vs. placebo SURPASS 1

CENTRE DE RECHERCHE | CHUS

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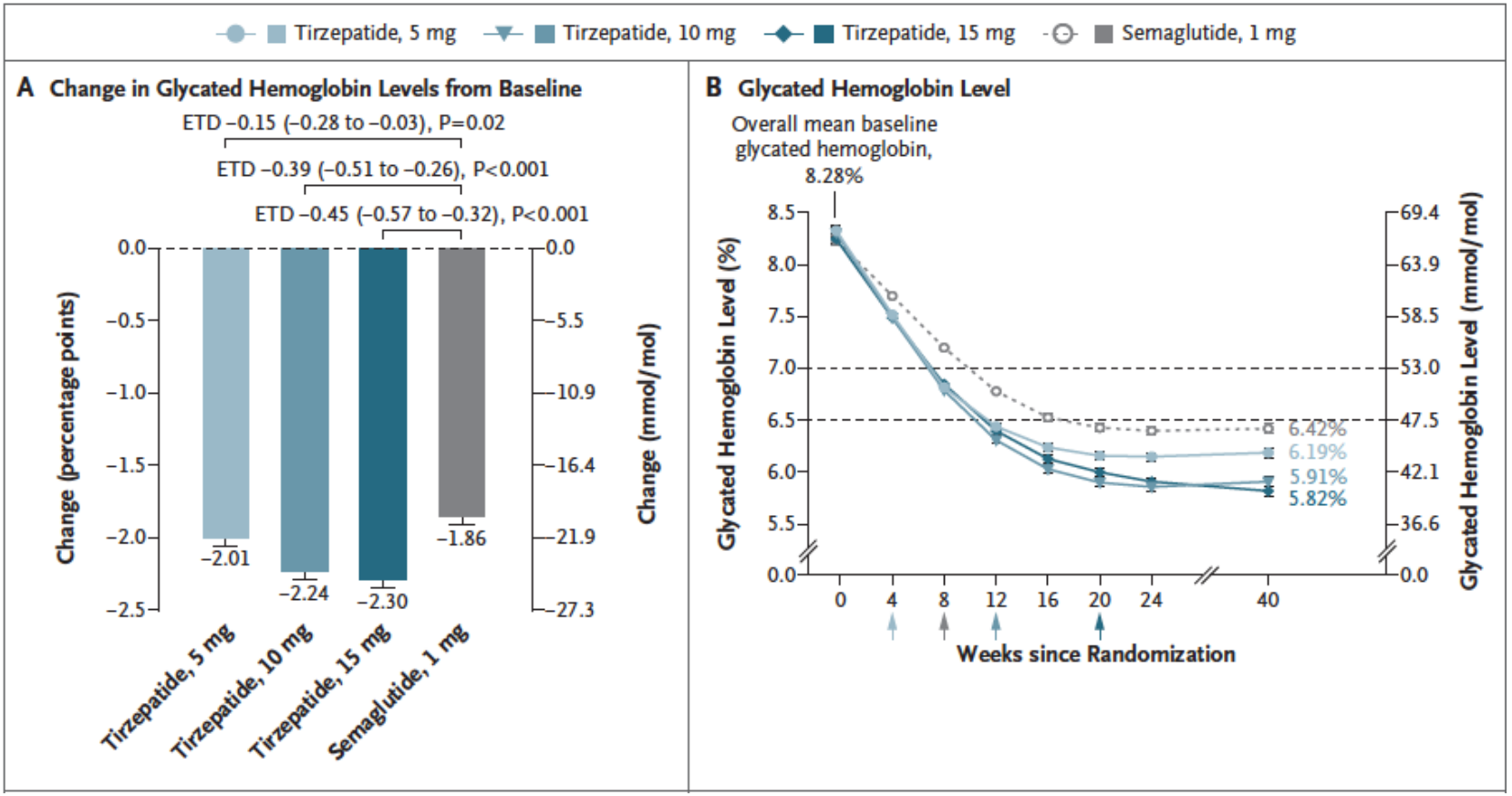
Other adverse events					
Hypoglycaemia (blood glucose <70 mg/dL)	7 (6%; 16)	8 (7%; 19)	8 (7%; 19)	1 (1%; 6)	24 (5%; 60)
Hypoglycaemia (blood glucose <54 mg/dL)	0	0	0	1 (1%; 3)	1 (<1%; 3)
Severe hypoglycaemia	0	0	0	0	0
Injection site reactions	4 (3%; 6)	4 (3%; 31)	3 (2%; 15)	0	11 (2%; 52)
Adjudicated pancreatitis†	0	0	0	0	0
Pancreatic cancer†	1 (1%)	0	0	0	1 (<1%)
Cholelithiasis†	1 (1%)	0	0	0	1 (<1%)
Hypersensitivity‡	3 (2%; 3)	2 (2%; 2)	1 (1%; 1)	1 (1%; 1)	7 (1%; 7)

Rosenstock J et al. The Lancet 2021;398:143-155

Tirzepatide vs. semaglutide SURPASS 2

CENTRE DE RECHERCHE | CHUS

Randomized, open-label, parallel-group, multicenter phase 3 trial T2D N = 1879

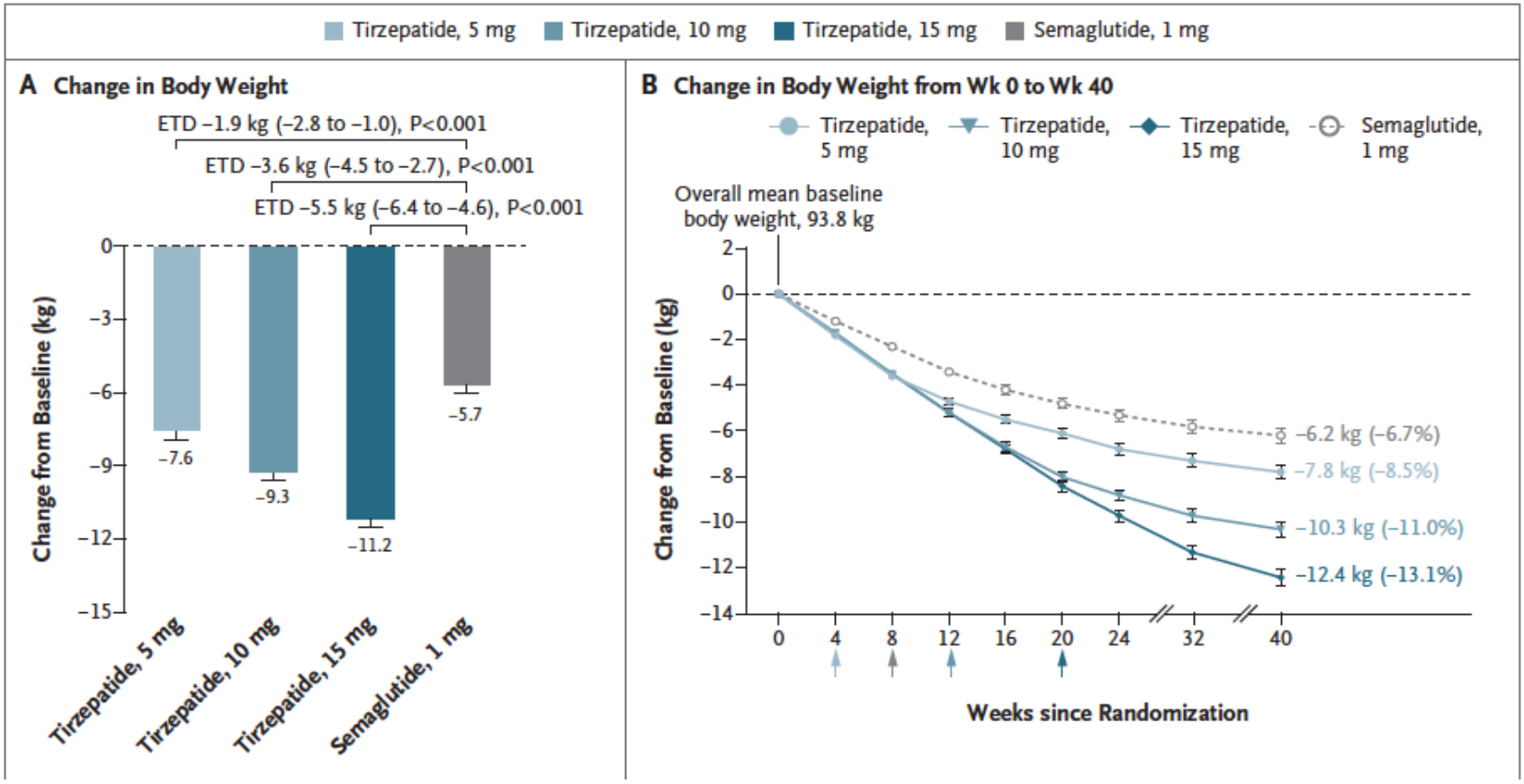


Frias JP et al. N Engl J Med 2021;385:503-515

Tirzepatide vs. semaglutide SURPASS 2

CENTRE DE RECHERCHE | CHUS

Randomized, open-label, parallel-group, multicenter phase 3 trial T2D N = 1879



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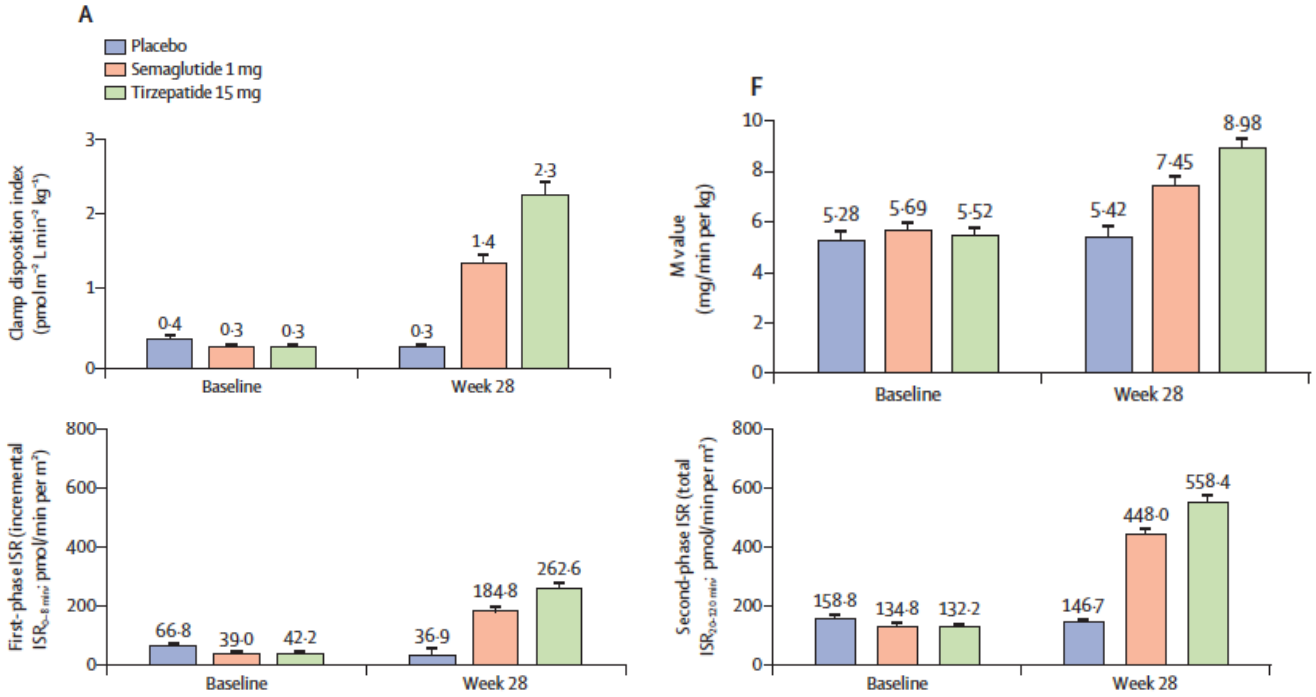
Tirzepatide vs. semaglutide: mechanisms

CENTRE DE RECHERCHE | CHUS

Randomized, open-label, parallel-group, multicenter phase 1 trial T2D N = 117



Heise T et al. Lancet Diabetes Endocrinol 2022;10:418-429

Tirzepatide vs. semaglutide: mechanisms

CENTRE DE RECHERCHE | CHUS

Randomized, open-label, parallel-group, multicenter phase 1 trial T2D N = 117

	Tirzepatide 15 mg	Semaglutide 1 mg	Placebo
(Continued from previous page)			
Mixed meal tolerance test outcomes			
Total glucagon $AUC_{0\text{-}240\ min}$, pmol L^{-1} min			
Baseline	3760·7 (259·4)	3927·5 (262·7)	4640·2 (349·8)
Week 28	2283·6 (136·4)	2835·7 (137·5)	4071·1 (186·0)
Change from baseline	−1733·0 (136·4)	−1181·0 (137·5)	54·5 (186·0)
ETD versus placebo	−1787·5 (−2249·0 to −1325·9); p<0·0001	−1235·4 (−1695·8 to −775·1); p<0·0001	..
Incremental glucagon $AUC_{0\text{-}240\ min}$, pmol L^{-1} min			
Baseline	937·1 (102·9)	972·4 (104·3)	1000·9 (138·8)
Week 28	121·0 (86·3)	462·6 (87·3)	758·7 (116·3)
Change from baseline	−843·6 (86·3)	−502·0 (87·3)	−205·9 (116·3)
ETD versus placebo	−637·7 (−925·2 to −350·2); p<0·0001	−296·1 (−584·8 to −7·5); p=0·045	..
ETD versus semaglutide 1 mg	−341·6 (−585·2 to −97·9); p=0·0065	..	..

Heise T et al. Lancet Diabetes Endocrinol 2022;10:418-429

Tirzepatide vs. semaglutide SURPASS 2

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Table 2. Adverse Events and Safety.*

Event	Tirzepatide						Semaglutide		Total (N=1878)	
	5 mg (N=470)		10 mg (N=469)		15 mg (N=470)		1 mg (N=469)			
	No. of patients (%)	*No. of events*	*No. of patients (%)*	*No. of events*	*No. of patients (%)*	*No. of events*	*No. of patients (%)*	*No. of events*	*No. of patients (%)*	*No. of events*
Patients with ≥1 adverse event	299 (63.6)	—	322 (68.7)	—	324 (68.9)	—	301 (64.2)	—	1246 (66.3)	—
Patients with ≥1 serious adverse event	33 (7.0)	—	25 (5.3)	—	27 (5.7)	—	13 (2.8)	—	98 (5.2)	—
Death†	4 (0.9)	—	4 (0.9)	—	4 (0.9)	—	1 (0.2)	—	13 (0.7)	—
Adverse events leading to discontinuation of tirzepatide or semaglutide	28 (6.0)	—	40 (8.5)	—	40 (8.5)	—	19 (4.1)	—	127 (6.8)	—
Adverse events occurring in ≥0.2% of the overall population (i.e., 3 patients) and leading to discontinuation of tirzepatide or semaglutide										
Nausea	6 (1.3)	—	7 (1.5)	—	4 (0.9)	—	4 (0.9)	—	21 (1.1)	—
Vomiting	1 (0.2)	—	4 (0.9)	—	4 (0.9)	—	3 (0.6)	—	12 (0.6)	—
Diarrhea	1 (0.2)	—	3 (0.6)	—	6 (1.3)	—	1 (0.2)	—	11 (0.6)	—
Abdominal pain	2 (0.4)	—	1 (0.2)	—	2 (0.4)	—	4 (0.9)	—	9 (0.5)	—
Dyspepsia	2 (0.4)	—	1 (0.2)	—	2 (0.4)	—	0	—	5 (0.3)	—
Decreased appetite	1 (0.2)	—	2 (0.4)	—	2 (0.4)	—	0	—	5 (0.3)	—
Fatigue	1 (0.2)	—	1 (0.2)	—	1 (0.2)	—	1 (0.2)	—	4 (0.2)	—
Elevated blood calcitonin level	1 (0.2)	—	1 (0.2)	—	1 (0.2)	—	0	—	3 (0.2)	—
Constipation	0	—	2 (0.4)	—	0	—	1 (0.2)	—	3 (0.2)	—
Covid-19–related pneumonia	1 (0.2)	—	1 (0.2)	—	0	—	1 (0.2)	—	3 (0.2)	—
Injection-site reaction	0	—	2 (0.4)	—	1 (0.2)	—	0	—	3 (0.2)	—

Frias JP et al. N Engl J Med 2021;385:503-515

Tirzepatide vs. semaglutide SURPASS 2

CENTRE DE RECHERCHE | CHUS

Event	Tirzepatide						Semaglutide		Total (N=1878)	
	5 mg (N=470)		10 mg (N=469)		15 mg (N=470)		1 mg (N=469)			
	No. of patients (%)	*No. of events*	*No. of patients (%)*	*No. of events*	*No. of patients (%)*	*No. of events*	*No. of patients (%)*	*No. of events*	*No. of patients (%)*	*No. of events*
Adverse events occurring in ≥5% of patients in any treatment group, according to preferred term										
Nausea	82 (17.4)	111	90 (19.2)	124	104 (22.1)	136	84 (17.9)	126	360 (19.2)	497
Diarrhea	62 (13.2)	120	77 (16.4)	99	65 (13.8)	102	54 (11.5)	68	258 (13.7)	389
Vomiting	27 (5.7)	35	40 (8.5)	56	46 (9.8)	61	39 (8.3)	53	152 (8.1)	205
Dyspepsia	34 (7.2)	—	29 (6.2)	—	43 (9.1)	—	31 (6.6)	—	137 (7.3)	—
Decreased appetite	35 (7.4)	—	34 (7.2)	—	42 (8.9)	—	25 (5.3)	—	136 (7.2)	—
Constipation	32 (6.8)	—	21 (4.5)	—	21 (4.5)	—	27 (5.8)	—	101 (5.4)	—
Abdominal pain	14 (3.0)	—	21 (4.5)	—	24 (5.1)	—	24 (5.1)	—	83 (4.4)	—
All gastrointestinal adverse events	188 (40.0)	—	216 (46.1)	—	211 (44.9)	—	193 (41.2)	—	808 (43.0)	—
Other adverse events										
Hypoglycemia, blood glucose level <54 mg/dl	3 (0.6)	3	1 (0.2)	2	8 (1.7)	10	2 (0.4)	2	14 (0.7)	17
Severe hypoglycemia	1 (0.2)	1	0	0	1 (0.2)‡	1‡	0	0	2 (0.1)	2
Injection-site reaction	9 (1.9)	—	13 (2.8)	—	21 (4.5)	—	1 (0.2)	—	44 (2.3)	—
Adjudicated pancreatitis	0	—	2 (0.4)	—	2 (0.4)	—	3 (0.6)	—	7 (0.4)	—
Cholelithiasis	4 (0.9)	—	4 (0.9)	—	4 (0.9)	—	2 (0.4)	—	14 (0.7)	—
Hypersensitivity§	9 (1.9)	—	13 (2.8)	—	8 (1.7)	—	11 (2.3)	—	41 (2.2)	—
Diabetic retinopathy¶	0	—	2 (0.4)	—	0	—	0	—	2 (0.1)	—

Frias JP et al. N Engl J Med 2021;385:503-515

Tirzepatide vs. insulin degludec SURPASS 3

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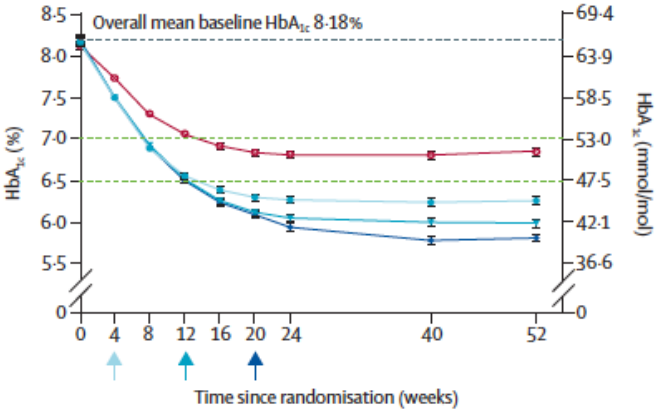
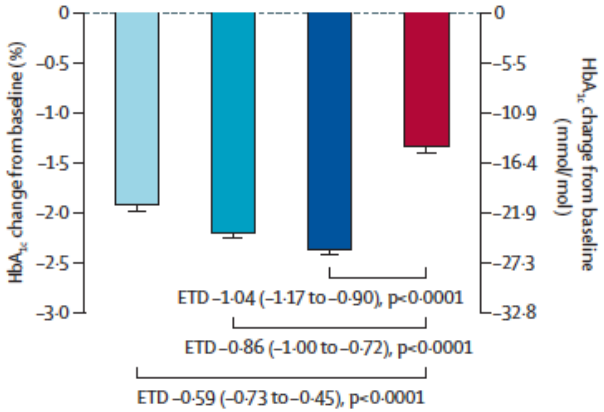
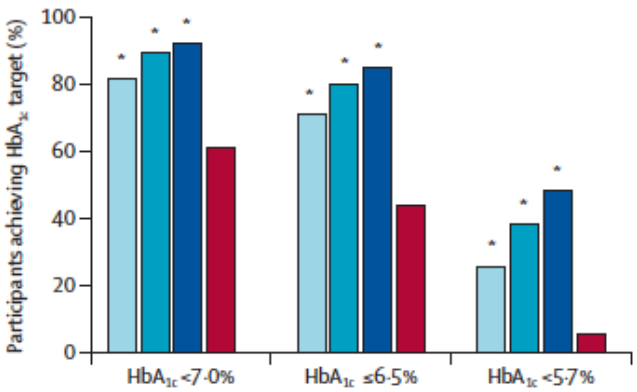
Randomized, open-label, parallel-group, multicenter phase 3 trial T2D N = 1444





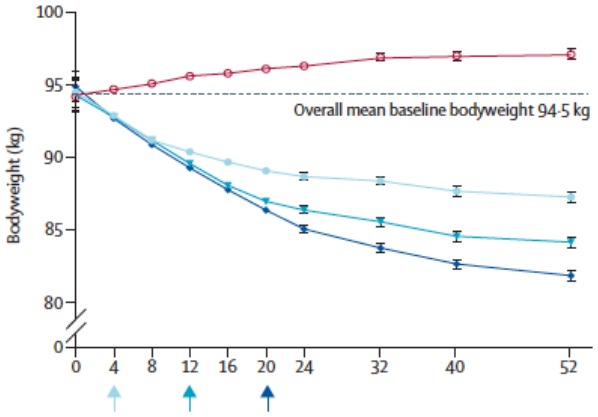


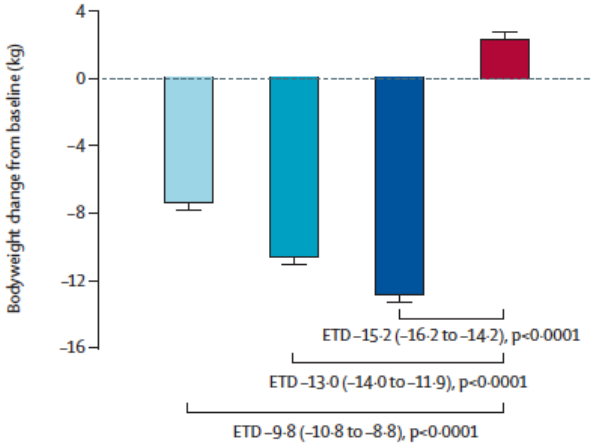
Ludvik B et al. The Lancet 2021;398:583-598

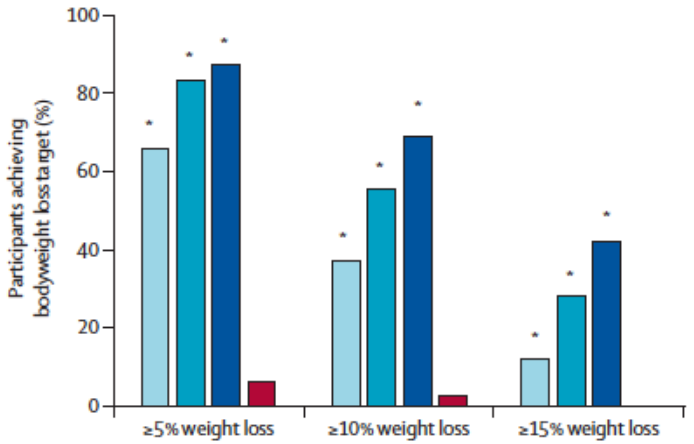
Tirzepatide vs. insulin degludec SURPASS 3

CENTRE DE RECHERCHE | CHUS

Randomized, open-label, parallel-group, multicenter phase 3 trial T2D N = 1444







Ludvik B et al. The Lancet 2021;398:583-598

Tirzepatide vs. insulin degludec SURPASS 3

CENTRE DE RECHERCHE | CHUS

	Tirzepatide 5 mg (n=358)	Tirzepatide 10 mg (n=360)	Tirzepatide 15 mg (n=359)	Insulin degludec (n=360)
Any serious adverse event	29 (8%)	20 (6%)*	26 (7%)	22 (6%)
Deaths†	1 (<1%)	2 (1%)	1 (<1%)	1 (<1%)
Adverse events leading to treatment discontinuation‡	25 (7%)	37 (10%)	39 (11%)	5 (1%)
Nausea	3 (1%)	7 (2%)	9 (3%)	1 (<1%)
Vomiting	3 (1%)	6 (2%)	3 (1%)	0
Diarrhoea	4 (1%)	1 (<1%)	3 (1%)	0
Decreased appetite	1 (<1%)	4 (1%)	1 (<1%)	0
Decreased weight	1 (<1%)	1 (<1%)	4 (1%)	0
Participants with at least one TEAE	219 (61%)	248 (69%)	263 (73%)	193 (54%)
TEAEs occurring in ≥5% of participants in any treatment group, by preferred term				
Nausea	41 (12%)	81 (23%)	85 (24%)	6 (2%)
Diarrhoea	55 (15%)	60 (17%)	56 (16%)	14 (4%)
Decreased appetite	22 (6%)	37 (10%)	43 (12%)	2 (1%)
Vomiting	21 (6%)	34 (9%)	36 (10%)	4 (1%)
Dyspepsia	15 (4%)	32 (9%)	18 (5%)	0
Increased lipase	21 (6%)	16 (4%)	20 (6%)	7 (2%)
Nasopharyngitis	11 (3%)	14 (4%)	15 (4%)	22 (6%)
Abdominal pain	7 (2%)	17 (5%)	23 (6%)	4 (1%)
Hypertension	11 (3%)	7 (2%)	11 (3%)	21 (6%)

Ludvik B et al. The Lancet 2021;398:583-598

Tirzepatide vs. insulin degludec SURPASS 3

CENTRE DE RECHERCHE | CHUS

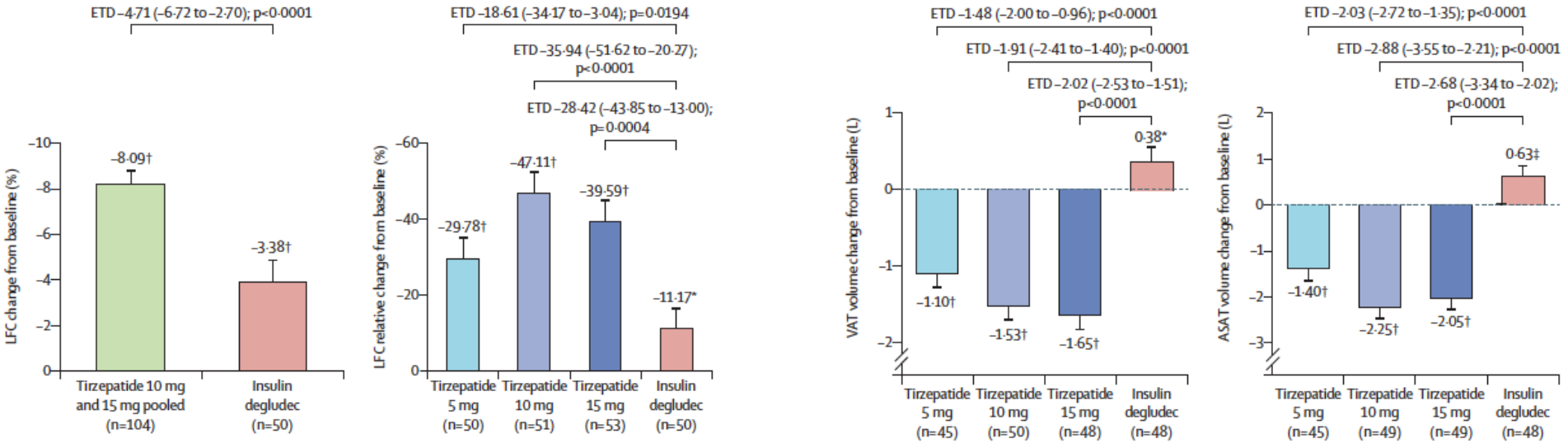
	Tirzepatide 5 mg (n=358)	Tirzepatide 10 mg (n=360)	Tirzepatide 15 mg (n=359)	Insulin degludec (n=360)
Other adverse events				
Hypoglycaemia (BG ≤70 mg/dL)	30 (8%)	49 (14%)	51 (14%)	170 (48%)
Hypoglycaemia (BG <54 mg/dL)	5 (1%)	4 (1%)	7 (2%)	26 (7%)
Severe hypoglycaemia	0	0	1 (<1%)	0
Injection site reaction	1 (<1%)	6 (2%)	8 (2%)	6 (2%)
Hypersensitivity	10 (3%)	12 (3%)	9 (3%)	5 (1%)
Cholelithiasis	2 (1%)	1 (<1%)	1 (<1%)	0
Cholecystitis	0	0	1 (<1%)	0
Diabetic retinopathy	2 (1%)	0	1 (<1%)	0
Adjudicated pancreatitis	0	0	0	0
Adjudicated MACE-4§	3 (1%)	3 (1%)	1 (<1%)	3 (1%)
Malignant neoplasms	3 (1%)	5 (1%)	3 (1%)	1 (<1%)

Ludvik B et al. The Lancet 2021;398:583-598

Tirzepatide vs. insulin degludec SURPASS 3

CENTRE DE RECHERCHE | CHUS

MRI sub-study, liver and visceral fat, T2D, N = 296



Gastaldelli A et al. The Lancet 2022;10:393-406

Tirzepatide vs. insulin glargine SURPASS 4

CENTRE DE RECHERCHE | CHUS

Randomized, open-label, parallel-group, multicenter phase 3 trial T2D at high CV risk N = 2002

	Tirzepatide 5 mg (n=326)	Tirzepatide 10 mg (n=321)	Tirzepatide 15 mg (n=334)	Insulin glargine (n=978)
HbA_{1c}, %				
Baseline	8·52 (0·049)	8·60 (0·049)	8·52 (0·048)	8·51 (0·028)
At week 52	6·29 (0·054)	6·09 (0·054)	5·95 (0·054)	7·09 (0·031)
Change from baseline at week 52*†	−2·24 (0·053)	−2·43 (0·053)	−2·58 (0·053)	−1·44 (0·030)
ETD *vs* insulin glargine	−0·80 (−0·92 to −0·68), p<0·0001‡	−0·99 (−1·11 to −0·87), p<0·0001‡	−1·14 (−1·26 to −1·02), p<0·0001‡	..
Bodyweight, kg				
Baseline	90·3 (1·03)	90·7 (1·04)	90·0 (1·02)	90·3 (0·60)
At week 52	83·4 (0·29)	81·1 (0·29)	78·9 (0·29)	92·4 (0·17)
Change from baseline at week 52†	−7·1 (0·34)	−9·5 (0·34)	−11·7 (0·33)	1·9 (0·19)
ETD *vs* insulin glargine	−9·0 (−9·8 to −8·3), p<0·0001	−11·4 (−12·1 to −10·6), p<0·0001	−13·5 (−14·3 to −12·8), p<0·0001	..

Del Prato S et al. The Lancet 2021;398:1811-1824

Tirzepatide vs. insulin glargine SURPASS 4

CENTRE DE RECHERCHE | CHUS

Randomized, open-label, parallel-group, multicenter phase 3 trial T2D at high CV risk N = 2002

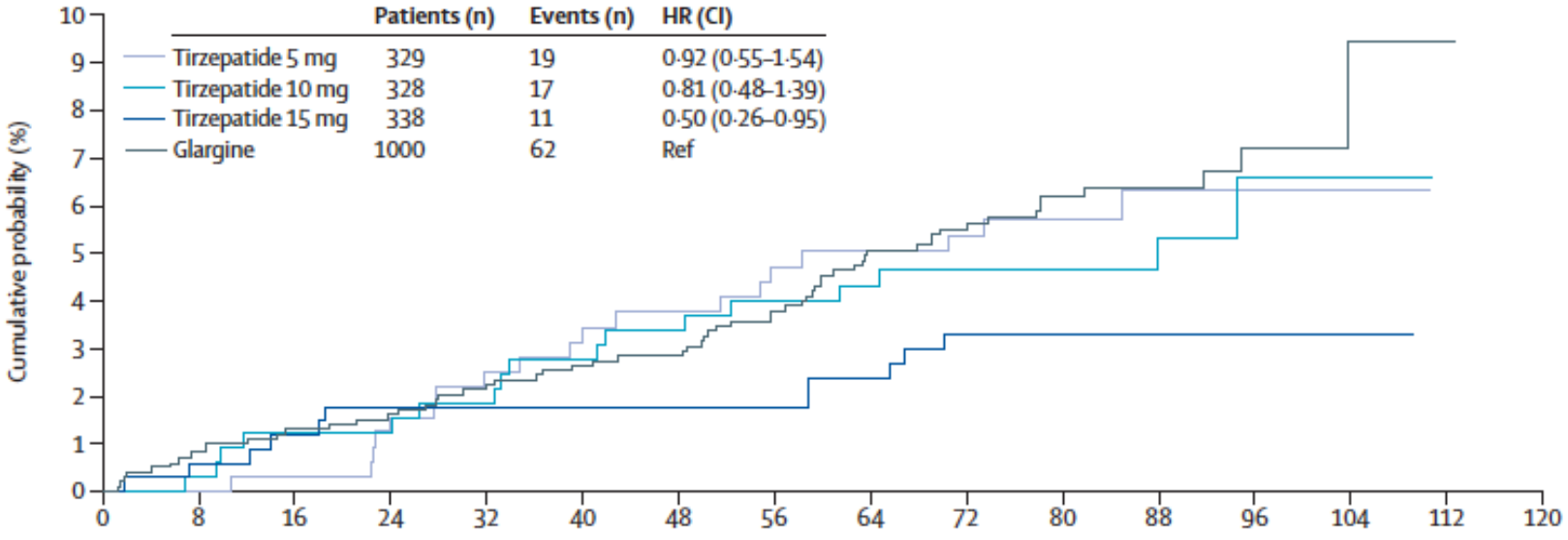
Participants achieving HbA_{1c} targets at week 52				
<7·0% (<53 mmol/mol)†	264 (81%)	283 (88%)	303 (91%)	496 (51%)
OR *vs* insulin glargine	4·78 (3·47 to 6·58), p<0·0001	9·23 (6·31 to 13·49), p<0·0001	11·87 (7·88 to 17·89), p<0·0001	..
≤6·5% (≤48 mmol/mol)	215 (66%)	244 (76%)	271 (81%)	310 (32%)
OR *vs* insulin glargine	4·86 (3·66 to 6·45), p<0·0001	8·93 (6·53 to 12·21), p<0·0001	11·84 (8·52 to 16·45), p<0·0001	..
<5·7% (<39 mmol/mol)	75 (23%)	105 (33%)	144 (43%)	33 (3%)
OR *vs* insulin glargine	9·57 (6·16 to 14·86), p<0·0001	17·11 (11·12 to 26·35), p<0·0001	26·53 (17·35 to 40·56), p<0·0001	..
Participants achieving bodyweight loss targets at week 52				
≥5% loss	205 (63%)	249 (78%)	285 (85%)	78 (8%)
OR *vs* insulin glargine	21·42 (15·35 to 29·89), p<0·0001	46·14 (32·05 to 66·42), p<0·0001	76·93 (51·76 to 114·35), p<0·0001	..
≥10% loss	117 (36%)	170 (53%)	219 (66%)	15 (2%)
OR *vs* insulin glargine	35·61 (20·61 to 61·55), p<0·0001	76·79 (44·42 to 132·75), p<0·0001	127·51 (73·52 to 221·14), p<0·0001	..
≥15% loss	45 (14%)	77 (24%)	122 (37%)	5 (<1%)
OR *vs* insulin glargine	28·58 (11·88 to 68·75), p<0·0001	59·14 (25·01 to 139·86), p<0·0001	105·74 (45·11 to 247·87), p<0·0001	..

Del Prato S et al. The Lancet 2021;398:1811-1824

Tirzepatide vs. insulin glargine SURPASS 4

CENTRE DE RECHERCHE | CHUS

Randomized, open-label, parallel-group, multicenter phase 3 trial T2D at high CV risk N = 2002



Number at risk																
Tirzepatide 5 mg	329	328	322	315	310	307	304	299	297	264	203	128	60	15	0	0
Tirzepatide 10 mg	328	325	321	319	317	314	312	307	305	280	211	137	62	12	0	0
Tirzepatide 15 mg	338	335	332	329	329	328	327	326	321	288	217	144	66	18	0	0
Glargine	1000	982	971	961	947	937	932	916	892	794	584	392	172	37	1	0

Del Prato S et al. The Lancet 2021;398:1811-1824

Tirzepatide vs. insulin glargine SURPASS 4

CENTRE DE RECHERCHE | CHUS

	Tirzepatide 5 mg (n=329)	Tirzepatide 10 mg (n=328)	Tirzepatide 15 mg (n=338)	Insulin glargine (n=1000)
Participants with at least one treatment emergent adverse event	232 (71%)	241 (74%)	259 (77%)	679 (68%)
Serious adverse events	48 (15%)	54 (17%)	41 (12%)	193 (19%)
Deaths*	15 (5%)	2 (<1%)	8 (2%)	35 (4%)
Adverse events leading to study treatment discontinuation	37 (11%)	28 (9%)	36 (11%)	54 (5%)
Adverse events occurring in at least four participants across all treatment groups leading to study treatment discontinuation				
Diarrhoea	2 (<1%)	1 (<1%)	8 (2%)	0
Vomiting	1 (<1%)	4 (1%)	4 (1%)	0
COVID-19	2 (<1%)	1 (<1%)	0	6 (<1%)
Nausea	5 (2%)	2 (<1%)	1 (<1%)	0
Acute myocardial infarction	2 (<1%)	2 (<1%)	1 (<1%)	3 (<1%)
COVID-19 pneumonia	1 (<1%)	0	2 (<1%)	4 (<1%)
Decreased appetite	2 (<1%)	1 (<1%)	2 (<1%)	0
Cardiac failure	1 (<1%)	0	1 (<1%)	2 (<1%)
Dyspepsia	1 (<1%)	2 (<1%)	1 (<1%)	0
Respiratory failure	0	0	0	4 (<1%)

Del Prato S et al. The Lancet 2021;398:1811-1824

Tirzepatide vs. insulin glargine SURPASS 4

CENTRE DE RECHERCHE | CHUS

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Serious adverse events	48 (15%)	54 (17%)	41 (12%)	193 (19%)
Deaths*	15 (5%)	2 (<1%)	8 (2%)	35 (4%)
Adverse events leading to study treatment discontinuation	37 (11%)	28 (9%)	36 (11%)	54 (5%)
Treatment emergent adverse events with at least 5% frequency in any treatment group				
Diarrhoea	41 (13%)	65 (20%)	74 (22%)	44 (4%)
Nausea	39 (12%)	53 (16%)	76 (23%)	23 (2%)
COVID-19	15 (5%)	14 (4%)	19 (6%)	59 (6%)
Nasopharyngitis	10 (3%)	16 (5%)	16 (5%)	65 (7%)
Decreased appetite	29 (9%)	36 (11%)	35 (10%)	5 (<1%)
Vomiting	16 (5%)	27 (8%)	29 (9%)	16 (2%)
Dyspepsia	18 (6%)	27 (8%)	26 (8%)	13 (1%)
Lipase increased	10 (3%)	13 (4%)	21 (6%)	18 (2%)
Constipation	17 (5%)	14 (4%)	14 (4%)	5 (<1%)

Del Prato S et al. The Lancet 2021;398:1811-1824

Tirzepatide vs. insulin glargine SURPASS 4

CENTRE DE RECHERCHE | CHUS

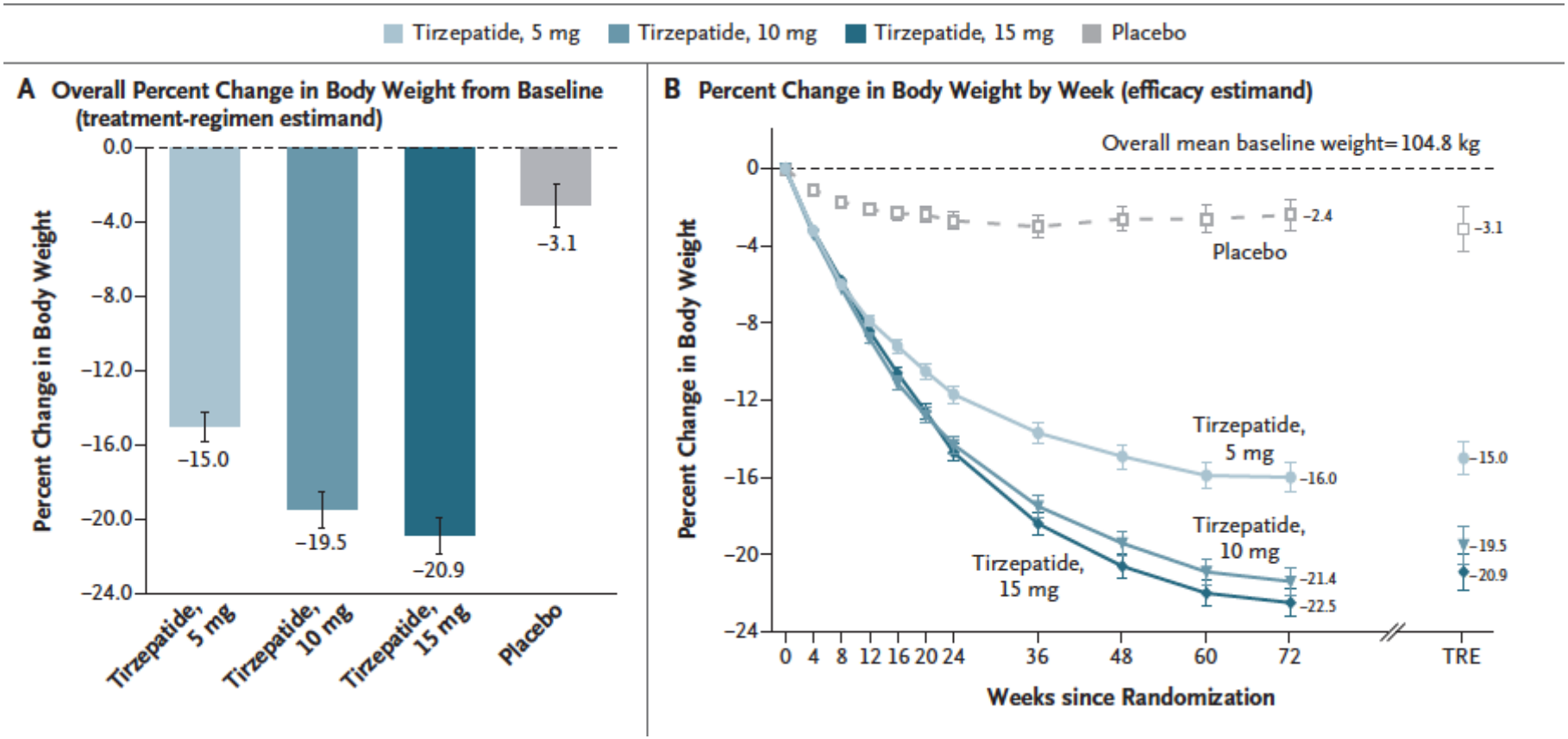
	Tirzepatide 5 mg (n=329)	Tirzepatide 10 mg (n=328)	Tirzepatide 15 mg (n=338)	Insulin glargine (n=1000)
Participants with at least one treatment emergent adverse event	232 (71%)	241 (74%)	259 (77%)	679 (68%)
Serious adverse events	48 (15%)	54 (17%)	41 (12%)	193 (19%)
Deaths*	15 (5%)	2 (<1%)	8 (2%)	35 (4%)
Adverse events leading to study treatment discontinuation	37 (11%)	28 (9%)	36 (11%)	54 (5%)
Other treatment emergent adverse events of interest				
Injection site reaction	1 (<1%)	2 (<1%)	1 (<1%)	4 (<1%)
Cholelithiasis	3 (<1%)	1 (<1%)	1 (<1%)	4 (<1%)
Cholecystitis	0	2 (<1%)	0	6 (<1%)
Pancreatitis†	3 (<1%)	2 (<1%)	1 (<1%)	1 (<1%)
Diabetic retinopathy complications	5 (2%)	5 (2%)	4 (1%)	15 (2%)
Vital signs				
Systolic blood pressure, mm Hg	−2·8 (0·77)	−3·7 (0·76)	−4·8 (0·74)	1·3 (0·44)
Diastolic blood pressure, mm Hg	−1·0 (0·45)	−0·8 (0·45)	−1·0 (0·44)	0·7 (0·26)
Pulse rate, beats per min	2·9 (0·50)	3·2 (0·50)	4·1 (0·48)	1·2 (0·29)

Del Prato S et al. The Lancet 2021;398:1811-1824

Tirzepatide vs. placebo SURMOUNT 1

CENTRE DE RECHERCHE | CHUS

Randomized, open-label, parallel-group, multicenter phase 3 trial Obesity N = 2539



Jastreboff AM et al. N Engl J Med 2022;387:205-216

Tirzepatide vs. placebo SURMOUNT 1

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Table 3. Key Secondary and Additional Secondary End Points for Pooled Tirzepatide Dose Groups (Treatment-Regimen Estimand).*

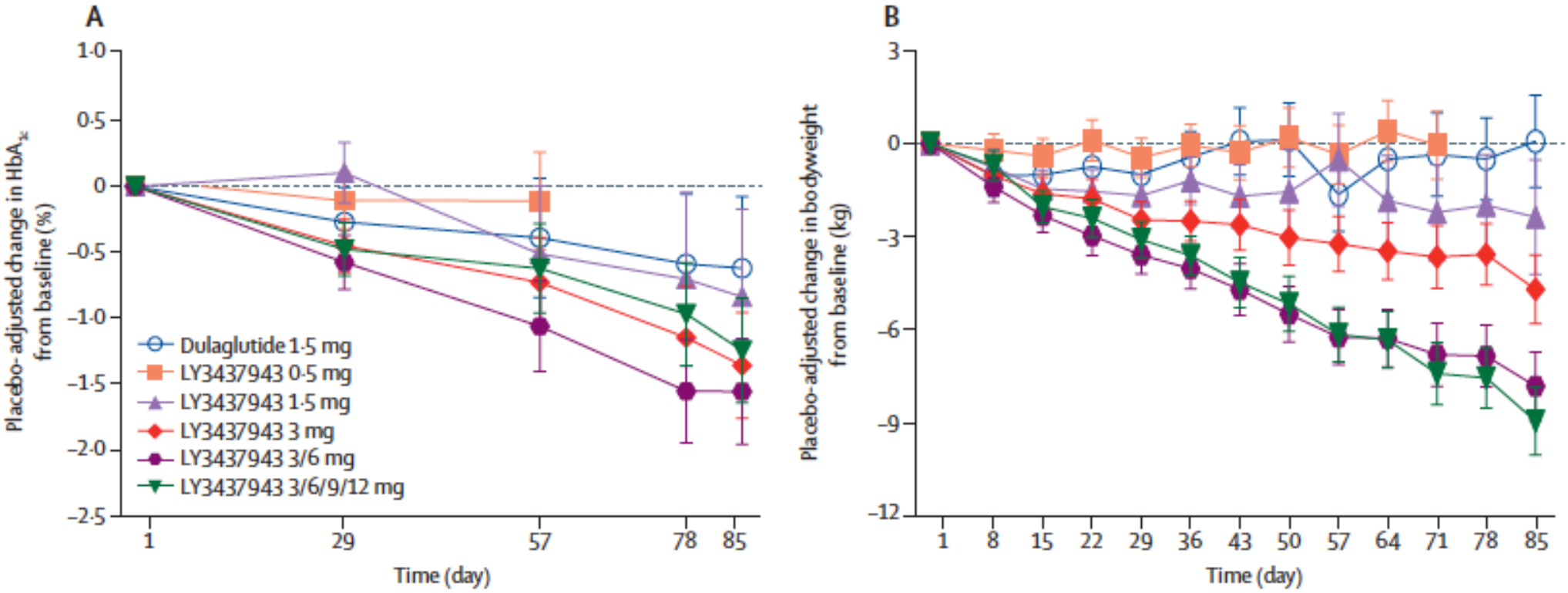
End Points	Pooled Tirzepatide Groups†	Placebo (N=643)	Estimated Treatment Difference from Placebo (95% CI)
	least-squares mean (95% CI)		
Key secondary end points‡			
Change from baseline to week 20 in body weight — kg§	−12.8 (−13.1 to −12.5)	−2.7 (−3.2 to −2.2)	−10.1 (−10.7 to −9.6)
Change in measure			
SF-36 physical function score§¶	3.6 (3.2 to 4.0)	1.7 (0.8 to 2.6)	1.9 (1.0 to 2. 9)
Systolic blood pressure — mm Hg	−7.2 (−7.8 to −6.7)	−1.0 (−2.3 to −0.3)	−6.2 (−7.7 to −4.8)
Percentage change in level‖			
Triglycerides — mg/dl	−24.8 (−26.3 to −23.1)	−5.6 (−10.0 to −1.2)	−20.3 (−24.3 to −16.1)
Non-HDL cholesterol — mg/dl	−9.7 (−10.7 to −8.6)	−2.3 (−4.9 to −0.2)	−7.5 (−10.1 to −4.9)
HDL cholesterol — mg/dl	8.0 (6.9 to 9.1)	−0.7 (−2.9 to 1.5)	8.8 (6.1 to 11.5)
Fasting insulin — mIU/liter**	−42.9 (−44.9 to −40.9)	−6.6 (−15.3 to 2.2)	−38.9 (−44.8 to −32.4)
Additional secondary end points††			
Change in diastolic blood pressure — mm Hg	−4.8 (−5.2 to −4.4)	−0.8 (−1.6 to 0.0)	−4.0 (−4.9 to −3.1)
Percentage change in level‖			
Total cholesterol — mg/dl	−4.8 (−5.6 to −4.0)	−1.8 (−3.7 to 0.1)	−3.1 (−5.2 to −1.0)
LDL cholesterol — mg/dl	−5.8 (−6.9 to −4.6)	−1.7 (−4.6 to 1.3)	−4.2 (−7.2 to −1.0)
VLDL cholesterol — mg/dl	−24.4 (−25.9 to −22.9)	−4.8 (−9.2 to −0.4)	−20.6 (−24.6 to −16.4)
Free fatty acids — mmol/liter	−7.5 (−10.7 to −4.3)	9.5 (3.8 to 15.3)	−15.6 (−20.8 to −9.9)

Jastreboff AM et al. N Engl J Med 2022;387:205-216

GLP1/GIP/glucagon agonist vs. placebo

CENTRE DE RECHERCHE | CHUS

Randomized, multicenter multiple ascending dose phase 1b trial T2D N = 72



Urva S et al. The Lancet 2022 https://doi.org/10.1016/S0140-6736(22)02033-5

Drug pipeline for type 2 diabetes

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Table 1. Overview of antidiabetic drugs in clinical development. Drug name (name of developing company).

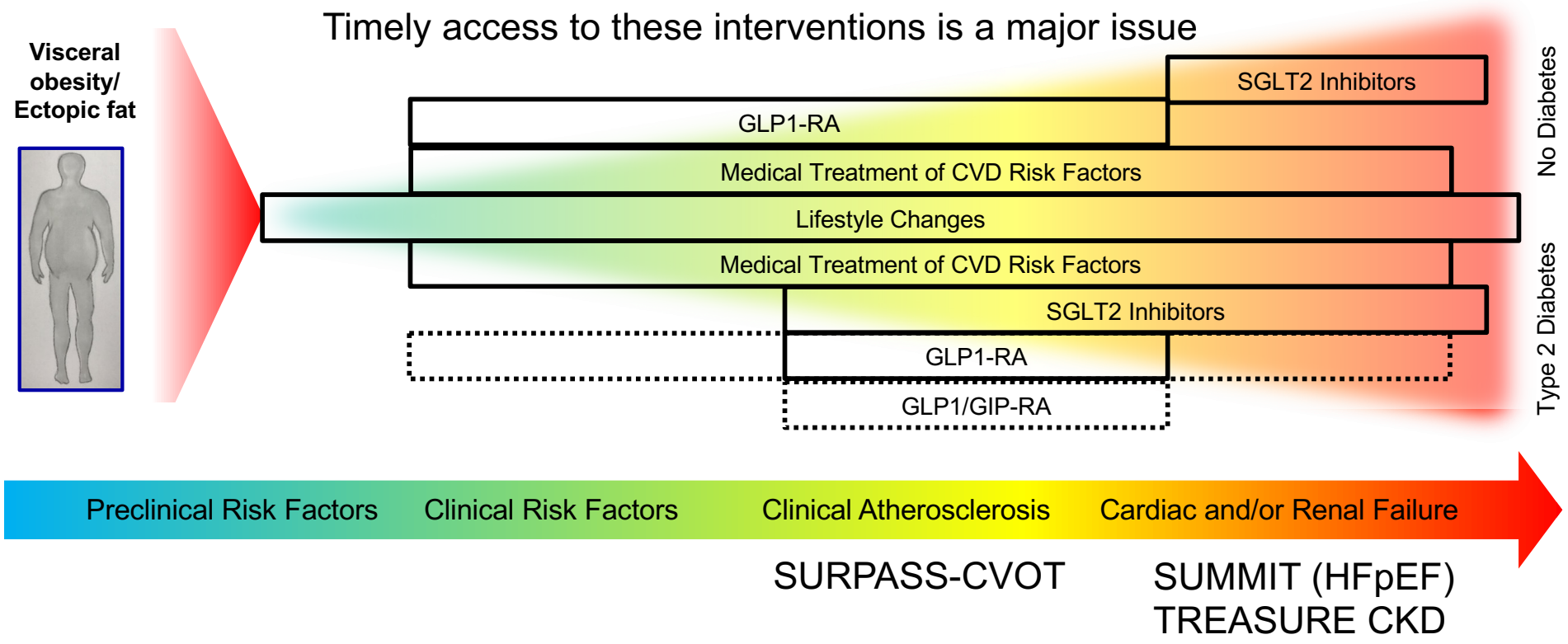
Drug class	Phase I	Phase II	Phase III
Activin type II receptor modulators		Bimagrumab (Novartis Pharmaceuticals)	
Amylin or dual amylin-calcitonin receptor agonists	KBP-089 (KeyBioscience)	KBP-042 (KeyBioscience)	
Direct AMPK activators		PXL770 (Poxel) O304 (Betagenon)	
FGF21 analogues		Pegbelfermin (Bristol-Myers Squibb)	
Fructose-1,6-biphosphatase inhibitors		VK0612 (Viking Therapeutics)	
GDF15 receptor agonists	LA-GDF15 (Novo Nordisk)		
Glucokinase activators	TMG-123 (Teijin Pharma Limited)	TTP399 (VTV Therapeutics) PF-04937319 (Pfizer)	Dorzagliatin (Hua Medicine)
Glimins			Imeglimin (Poxel)
GLP-1 receptor agonists	ORMD-0901 (Oramed Pharmaceuticals) PF-06882961 (Pfizer)	TTP-273 (VTV Therapeutics) Glutazumab (Gmax Biopharm) PB-119 (PegBio) PEX168 (Jiangsu Hengrui Medicine)	Efpeglenatide (Sanofi) ITCA-650 (Intarcia)
GLP-1 + GIP receptor agonists	CT-868 (Carmot Therapeutics)		Tirzepatide (Eli Lilly)
GLP-1 + glucagon receptor agonists		Cotadutide (MEDI-0382) (AstraZeneca) OPK88003 (OPKO Health) HM12525A (Hanmi Pharmaceutical) BI-456,906 (Boehringer Ingelheim)	
GLP-1 + glucagon + GIP receptor agonists	NN9423 (Novo Nordisk) HM15211 (Hanmi Pharmaceutical)		
Glucagon receptor antagonists		RVT-1502 (Metavant Sciences) IONIS-GCGR-Rx (Ionis Pharmaceuticals) REMD-477 (REMD Biotherapeutics) PF-06293620 (Pfizer)	
GPR119 agonists	DA-1241 (Dong-A ST)	MBX-2982 (CymaBay Therapeutics)	
Lyn kinase activators		Tolimidone (Melior Pharmaceuticals)	
PTB-1B inhibitors	KQ-791 (Kaneq Bioscience Limited)		
SGLT inhibitors	LX2761 (Lexicon Pharmaceuticals)	Henagliflozin (Jiangsu Hengrui Medicine) Licogliflozin (Novartis Pharmaceuticals)	Bexagliflozin (Theracos) Sotagliflozin (Lexicon Pharmaceuticals)

Johansson KS et al. Expert Opin Drug Discov 2020;15:1253-1265

Broader indications of anti-diabetic agents

Up to 12 % of patients with 15 mg tirzepatide did not achieve glucose control or lost weight

Timely access to these interventions is a major issue



Adapted from Després JP, Carpentier AC, Poirier P, Tchernof A, Neeland I. JACC 2021

Conclusions

CENTRE DE RECHERCHE | CHUS

Tirzepatide est le premier double agoniste GLP1/GIP testé dans plusieurs études cliniques

Le tirzepatide offre un meilleur contrôle glycémique et pondéral avec un profil de sécurité similaire aux médications actuelles

Des études sont en cours pour en vérifier l'inocuité cardiovasculaire chez des sujets vivant avec le DM2 à haut risque cardiovasculaire

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CENTRE DE RECHERCHE | CHUS

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