Sistema Socio Sanitario
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UNIVERSITÀ DEGLI STUDI DI MILANO
LA STATALE
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PEDIATRIC CLINICAL RESEARCH CENTER

New medical approaches for weight loss in type 2 diabetes

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New medical approaches for weight loss in T2D

1. Introduction
2. Metformin and acarbose
3. SGLT2 inhibitors
4. GLP1R agonists
5. Oral Semaglutide and Cagrilintide
6. Double and Triple Agonists
7. Conclusion

Introduction

Despite new advances in therapy for diabetes, many patients still don't reach the targets.

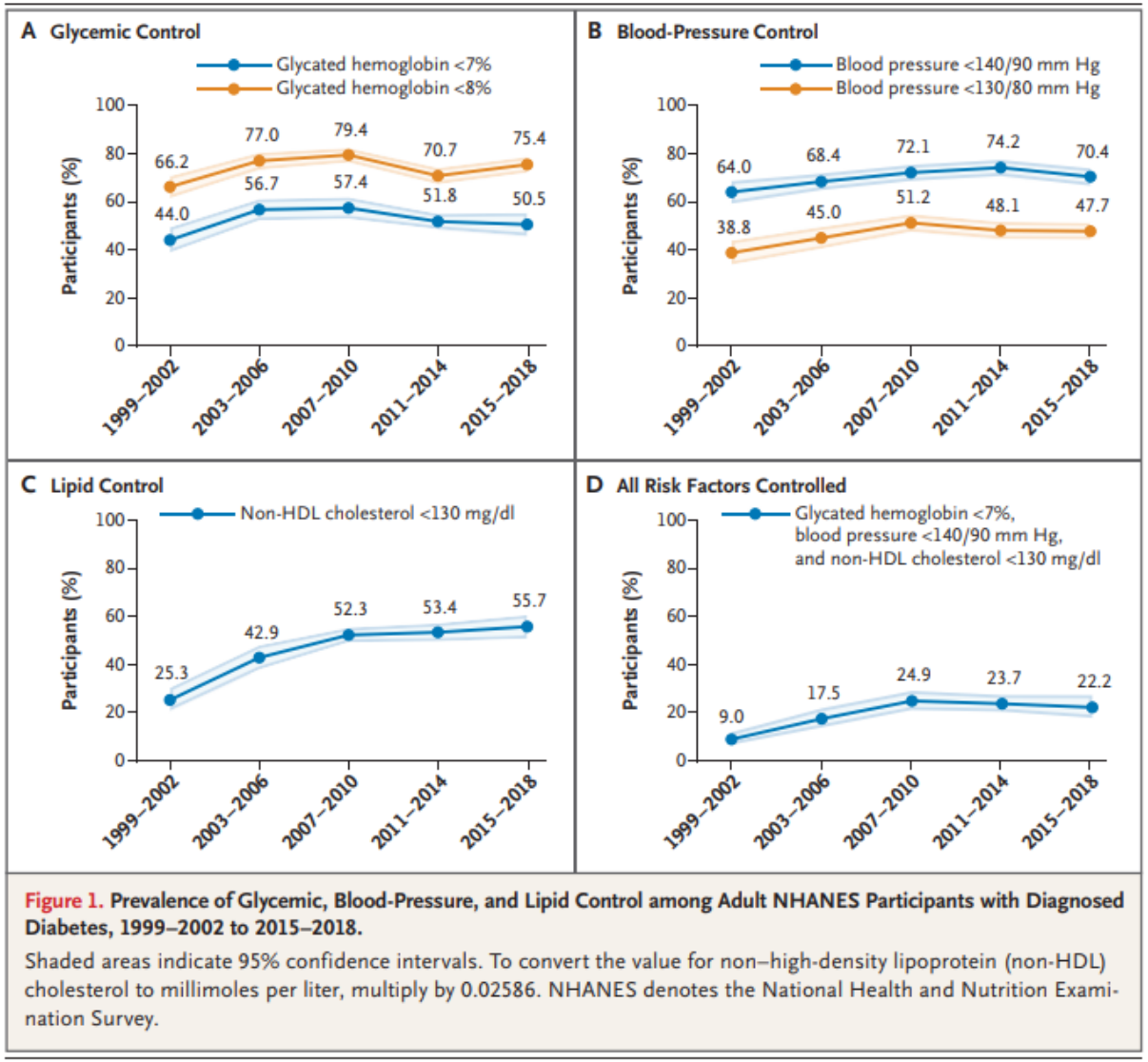
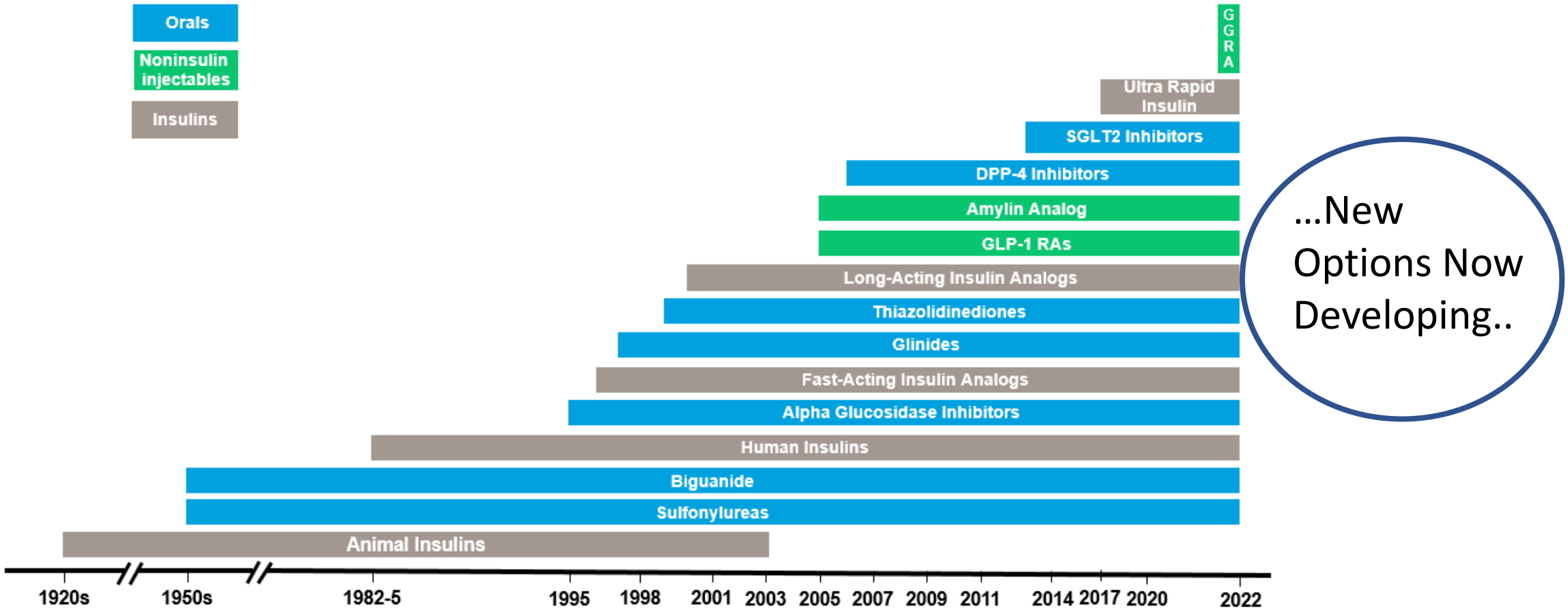


Figure 1. Prevalence of Glycemic, Blood-Pressure, and Lipid Control among Adult NHANES Participants with Diagnosed Diabetes, 1999–2002 to 2015–2018.

Shaded areas indicate 95% confidence intervals. To convert the value for non–high-density lipoprotein (non-HDL) cholesterol to millimoles per liter, multiply by 0.02586. NHANES denotes the National Health and Nutrition Examination Survey.

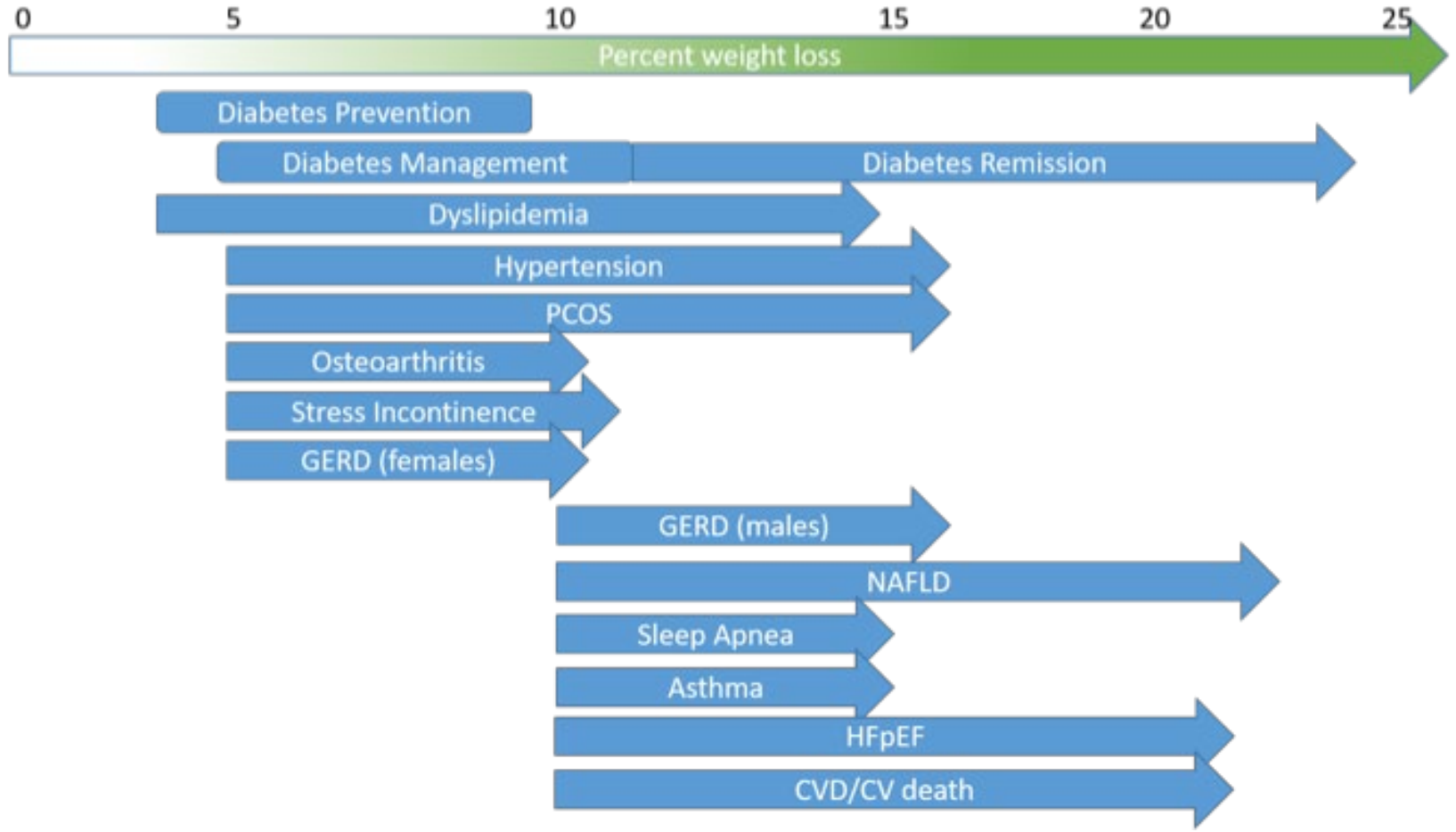
Fang M et al, NEJM 2021

Introduction



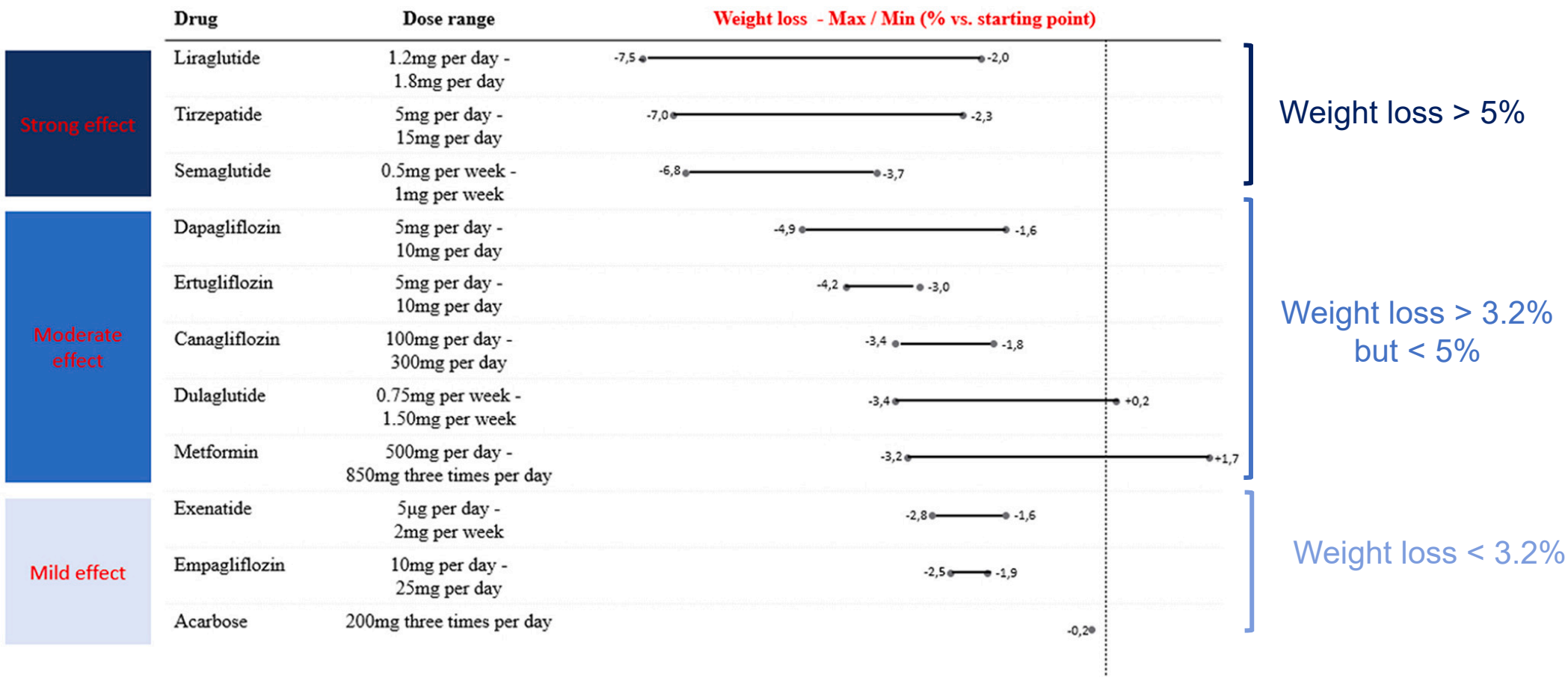
…New Options Now Developing..

The progressive therapeutic benefits of weight loss



Lingvay I et al. Lancet 2022

Anti-diabetic drugs and weight loss in T2D: our analysis



* Analysis conducted in overweight/obese T2D patients

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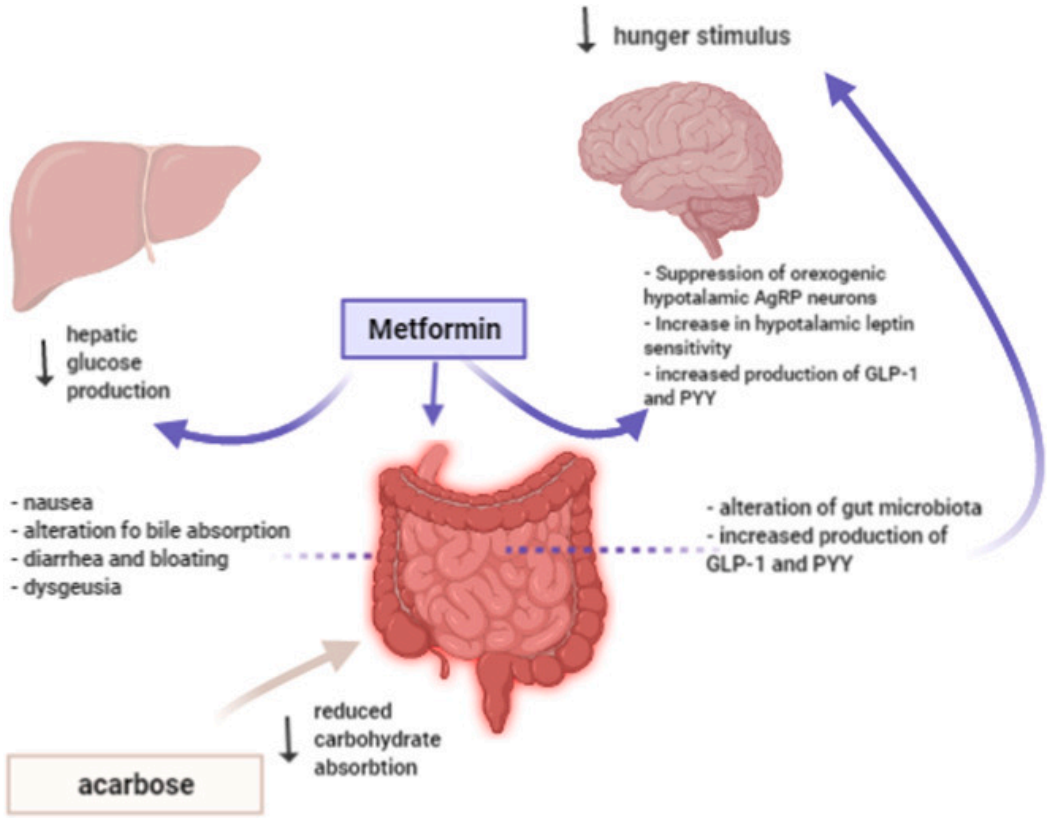
Metformin and acarbose effect on weight loss

reduction of appetite + reduced caloric intake



reduced carbohydrate absorption + reduced caloric intake

Metformin acts on weight-loss through

- its gastrointestinal side effects
- a central appetite suppressing effect
- its insulin-sensitizing effect.

Acarbose causes a reduction in the intestinal absorption of glucose, thus inducing a reduction in the daily caloric intake.

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Metformin and acarbose effect on weight loss

- Studies on metformin do not fully agree on the effect on body weight
- Moderate reduction in body weight (< 3.2% of initial weight in all studies) with metformin
- Acarbose effect on body weight is mild

Drug	Study	Dose (mg)	Average weight loss (Kg)	% of weight loss vs. baseline	Observational interval (weeks)
Metformin	Stumvoll et al.	2250 per day	-2.7 ± 1.3	-2.8%	16
	Kahn et al.	500 per day	-2.9 (CI -3.4; -2.3)	-3.2%	260
	Defronzo et al.	2250 per day	0.6 ±0.3	-0.6%	29
	Holman et al.	2250 per day	+1.5 (no CI provided)	+1.7%	312
Acarbose	Wolever et al.	200 3 times/day	-0.4± 0.3	-0.4%	52

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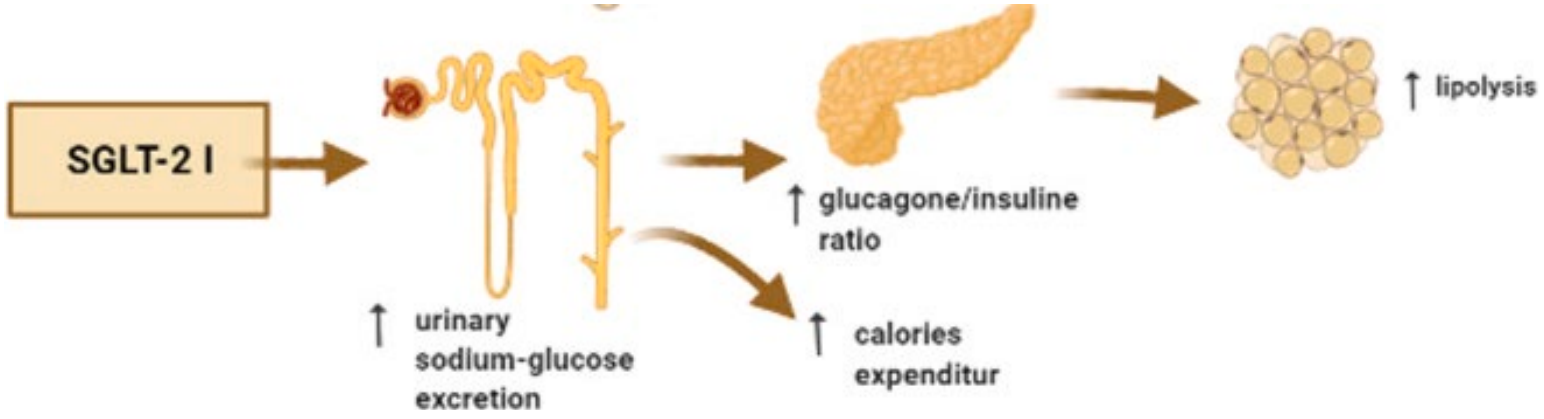
SGLT2 inhibitors effect on weight loss

- Increased urinary glucose excretion in a dose-dependent manner
- Weight-loss is mainly due to loss of fat vs. lean mass
- Slightly greater loss of visceral versus subcutaneous fat



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SGLT2 inhibitors effect on weight loss

Drug	Study	Dose (mg)	Average weight loss (Kg)	% of weight loss vs. baseline	Observational interval (weeks)
Canagliflozin	Stenlof et al.	100 per day	-1.9 ± 0.3	-2.2%	26
		300 per day	-2.9 ± 0.7	-3.3%	26
	CANVAS study	100 per day	-1.6 ± 0.1	-1.8%	188
	Rosenstock et al.	100 per day	-2.3	-2.6%	12
		300 per day	- 3.0	-3.4%	12
Dapagliflozin	Ferrarini et al.	5 per day	-2.7 ± 1.3	-3.2%	24
		10 per day	-3.2± 0.5	-3.4%	24
	Nauck et al.	10 per day	-3.2± 0.4	NA	52
	DECLARE study	10 per day	-1.8 ±0.2	NA	218
	Bailey et al.	5 per day	-2.9 ± 0.5	-3.4%	24
			-1.5 ± 0.2	-1.8%	102
		10 per day	-2.7 ± 0.5	-3.1%	24
			-1.4 ± 0.2	-1.6%	102
	Bolinder et al.	10 per day	-4.5± 0.9	-4.9%	52
Empagliflozin	EMPAREG study	25 per day	-2.0 ± 0.5	-2.5%	24
		10 per day	-1.6 ± 0.4	-1.9%	24
	EMPAREG PIO trial	25 per day	-1.5 ± 0.2	NA	24
Ertugliflozin	VERTIS SITA2 study	5 per day	-3.4 ± 0.4	NA	26
		15 per day	-3.0 ± 0.4	NA	26
	VERTIS FACTORIAL	5 per day	-2.7 ± 0.4	-3.0%	26
		15 per day	-3.7 ± 0.4	-4.2	26

- Effect on weight loss is moderate
- Empagliflozin had mild effect

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SGLT2 inhibitors effect on weight loss: inflammation?

SGLT2 inhibitors							
Matsumura *et al.* (*128*)	T2DM on insulin	Observational study of add-on SGLT2i canagliflozin for 3 days	15	ND	↔TNF-α	↑Adiponectin	↓Markers of oxidative stress
Garvey *et al.* (*127*)	T2DM inadequately controlled on metformin	RCT of SGLT2i canagliflozin versus sulfonylurea for 52 weeks	100 canagliflozin 100 sulfonylurea	↔	↓IL-6 ↑TNF-α	↓Leptin ↑Adiponectin	
Hattori (*129*)	T2DM	RCT SGLT2i empagliflozin versus placebo for 1 year	51 empagliflozin 51 placebo	↓	ND	ND	
Sato *et al.* (*145*)	T2DM with coronary artery disease	RCT SGLT2i dapagliflozin versus conventional treatment for 6 months	20 dapagliflozin 20 conventional treatment	ND	↓TNF-α	ND	
Heerspink *et al.* (*146*)	T2DM and albuminuria	RCT of SGLT2i canagliflozin versus sulfonylurea for up to 2 years	207 canagliflozin 89 sulfonylurea	ND	↓TNFR1 and IL-6 ↔CCL2, CCL5	ND	↓MMP-7 and fibronectin 1
Iannantuoni *et al.* (*147*)	T2DM	Observational study of SGLT2i empagliflozin for 24 weeks	15	↓	↑IL-10	ND	Reduction in leukocyte superoxide production
Latva-Rasku *et al.* (*148*)	T2DM	RCT SGLT2i dapagliflozin versus placebo for 8 weeks	15 dapagliflozin 16 placebo	ND	↓IL-6 ↔TNF-α and MCP-1	ND	Decreased visceral adipose tissue
Sezai *et al.* (*149*)	T2DM and heart failure	SGLT2i canagliflozin for 12 months	35	↓	ND	ND	
Bray *et al.* (*119*)	T2DM ± secondary characteristics	Systematic review of effects of SGLT2 inhibition on biomarkers of inflammation	23 studies	↓	↓IL-6 and TNF-α	↑Adiponectin	↓markers of oxidative stress
Kim *et al.* (*125*)	T2DM and high cardiovascular risk	RCT of SGLT2i empagliflozin versus sulfonylurea effects on blood-derived macrophages *ex vivo*	29 empagliflozin 32 sulfonylurea	ND	↓IL-1β and TNF-α from macrophages ex vivo	ND	
Nishimiya *et al.* (*150*)	T2DM and nonalcoholic fatty liver disease	SGLT2i canagliflozin for 6 months	9	↓	↔TNF-α	↔Adiponectin and leptin	
Sposito *et al.* (*151*)	T2DM and increased carotid intima-media thickness	RCT of SGLT2i dapagliflozin versus sulfonylurea for 12 weeks	48 dapagliflozin 49 sulfonylurea	↔	↔IL-2, IL-6, and TNF-α	ND	

Mainly reduction in TNFa and IL-6

Schleh MW et al. Sci Transl Med 2023

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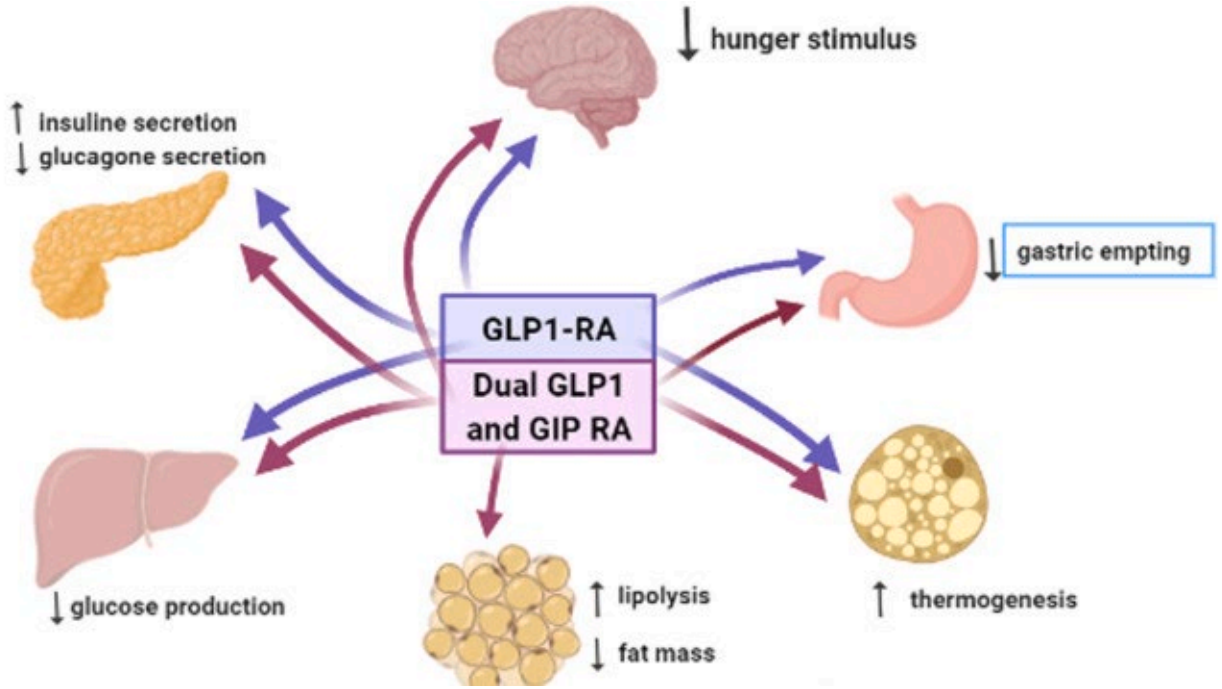
GLP-1R agonists effect on weight loss



GLP–1R effect on weight loss:

- increase the sense of satiety
- slowing the gastric emptying
- reduce food intake and body weight
- improve insulin sensitivity
- reduce hepatic glucose production
- reduce ectopic lipid accumulation
- increase insulin secretion
- reduce glucagon release

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GLP-1R agonists effect on weight loss

Drug	Study	Dose (mg)	Average weight loss (Kg)	% of weight loss vs. baseline	Observational interval (weeks)
Semaglutide	SUSTAIN 1	0.5 per week	-3.7 ± 0.8	-4.1%	30
		1.0 per week	-4.5± 0.8	-4.9%	30
	SUSTAIN 2	0.5 per week	-4.3 (no CI)	-4.8%	56
		1.0 per week	-6.1 ± 1.0	-6.8%	56
	SUSTAIN 3	1.0 per week	-5.6 (no CI)	-5.8%	56
	SUSTAIN 4	0.5 per week	-3.5 ± 0.4	-3.7%	30
		1.0 per week	-5.2 ± 0.5	-5.6%	30
	SUSTAIN 6	0.5 per week	-3.6 (no CI)	-3.9%	104
		1.0 per week	-4.9 (no CI)	-5.3%	104
	PIONEER	14.0 per day	-4.2 (no CI)	-4.8%	190
Exenatide	Vilsboll et al.	10 ug per day	-2.8 ± 1.3	NA	20
	Buse et al.	10 ug per day	-1.6 ± 0.3	-1.7%	26
	De Fronzo et al.	10 ug per day	-2.8 ± 0.5	-2.8%	30
		5 ug per day	-1.6 ± 0.4	-1.6%	26
Dulaglutide	Wysham et al.	1.5 per day	-1.3 ± 0.3	-1.4	26
		0.75 per day	+0.2± 0.3	+0.2%	26
	Nauck et al.	1.5 per day	-3.0 ± 0.2	-3.4%	52
		0.75 per day	-2.6 ± 0.2	-3.0%	52
Liraglutide	Vilsboll et al.	1.2 per day	-2.2 ± 1.3	NA	20
	Wadden et al.	3.0 per day	-8.4 ± 7.3	-7.5%	56
	Davies et al.	3.0 per day	-6.4 (no CI)	-6.0%	56
		1.8 per day	-5.0 (no CI)	-4.7%	56

Greatest benefit in weight loss.

Effect on weight was:

- *mild for exenatide*
- *modest for dulaglutide*
- *strong for liraglutide, semaglutide*

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GLP-1R agonists effect on weight loss: inflammation?

Mainly reduction in TNFa and IL-6

Lesson learnt from clinical trials.

GLP-1RAs	Dose	Median Follow up	N of patients	Population	Comparison	Effects	Reference
Exenatide	10 μg twice daily	12 weeks	24	T2D with BMI ≥ 30 kg/m^2	Placebo	↓TNF-α, ↓TLR-2, ↓TLR-4, ↓IL-1β, ↓MCP-1, ↓IL-6	[74]
Dulaglutide	1.5 mg/week	24 weeks	44	T2D with BMI ≥ 25 kg/m^2	Add-on treatment	↓IL-6	[71]
Liraglutide	0.6 mg/day for the first 2 weeks, 1.2 mg/day for the next 4 weeks and then 1.8 mg/day	24 weeks	41	T2D with BMI ≥ 25 kg/m^2	Add-on treatment	↓IL-6	[71]
	1.8 mg	12 weeks	27	T2D with UACR > 30 mg/g	Placebo	↓TNF-α	[75]
	0.6 mg /day for 2 weeks followed by 1.2 mg/ day	8 weeks	10	T2D with BMI ≥ 30 kg/m^2	/	↓sCD163, ↓TNF-α, ↓IL-1β, ↓IL-6	[65]
Semaglutide	Subcutaneous 0.05, 0.1, 0.2, 0.3 or 0.4 mg/day	52 weeks	957	Patients with BMI ≥ 30 kg/m^2	Placebo	↓hsCRP	[72]
	Oral 3 mg /day for the first 4 weeks, 7 mg for the next 4 weeks and then 14 mg/day	52 weeks	3183	T2D	Empaglifozin	↓hsCRP	[73]

Abbreviations: T2D, type 2 diabetes; BMI, body mass index; TNF, tumor necrosis factor; TLR, toll like receptor; IL, interleukin; MCP, monocyte chemoattractant protein, UACR, urine albumin creatinine ratio; CD, cluster of differentiation; hsCRP, high sensitive C-reactive protein.

Bendotti G/D'Addio F/Fiorina P Pharmacol Res 2022

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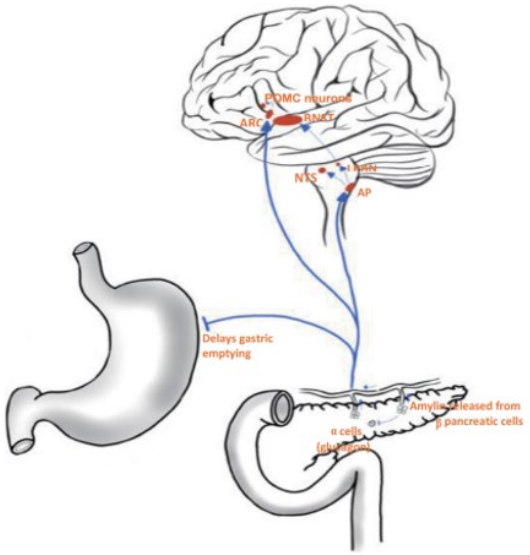
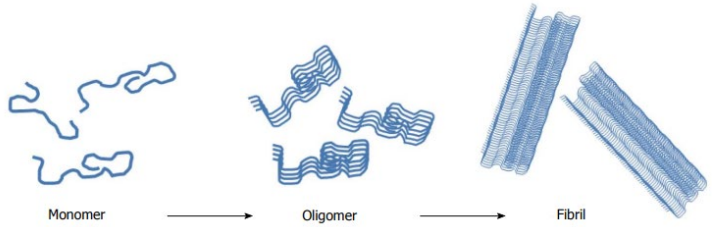


Amylin

- Amylin functions as a satiety hormone.
- Anyway amylin amyloid deposits can be found in several different organs and is thought to have disruptive functions (CNS pathology, peripheral axon pathology, heart failure, impaired renal function, and β-cell function)



Lutz TA and Meyer U. Front Neurosci 2015
Albariqi MM et al. J Clin Invest 2023
Despa S et al. Circ Res 2012
Srodulski S et al. Circulation 2014

Cagrilintide

Cagrilintide is a stable, non-fibrillating peptide and does not result in amylin deposits

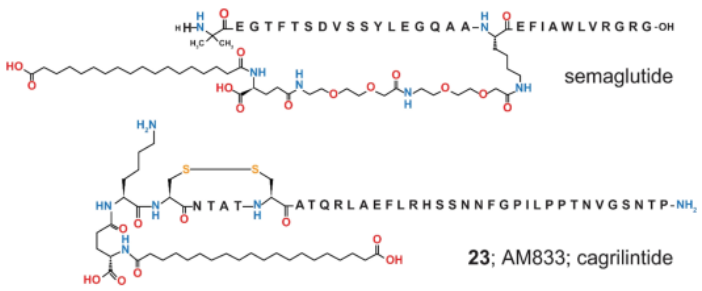


Figure 2. Chemical structures.

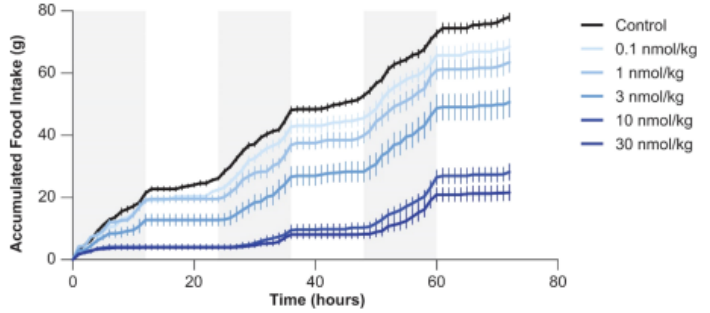


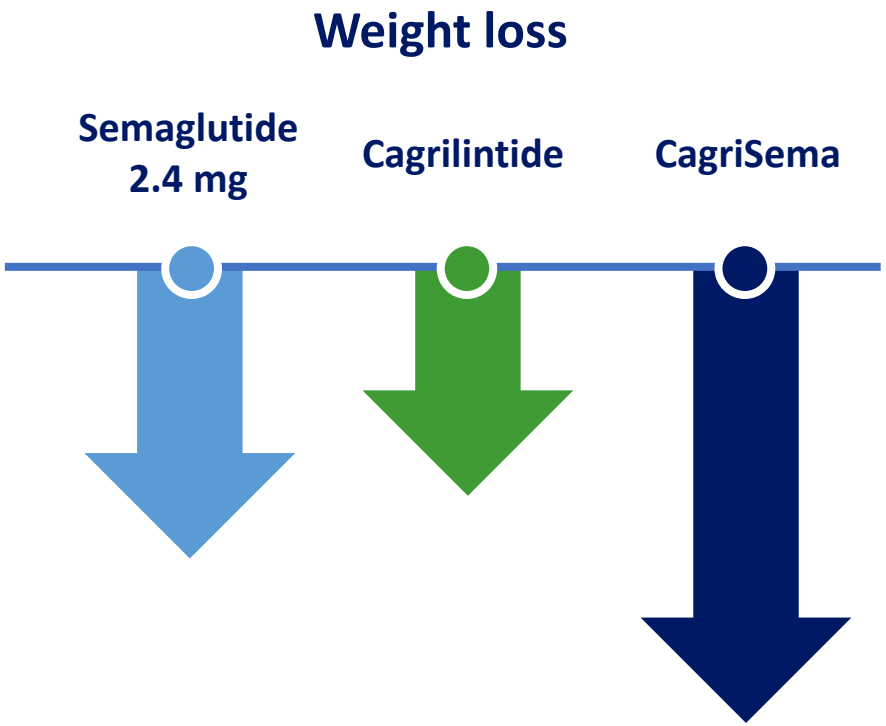
Figure 3. Food intake in rats after subcutaneous administration of **23**. Mean ± standard error of the mean; $n = 5–6$.

Kruse T, et al. J Med Chem. 2021

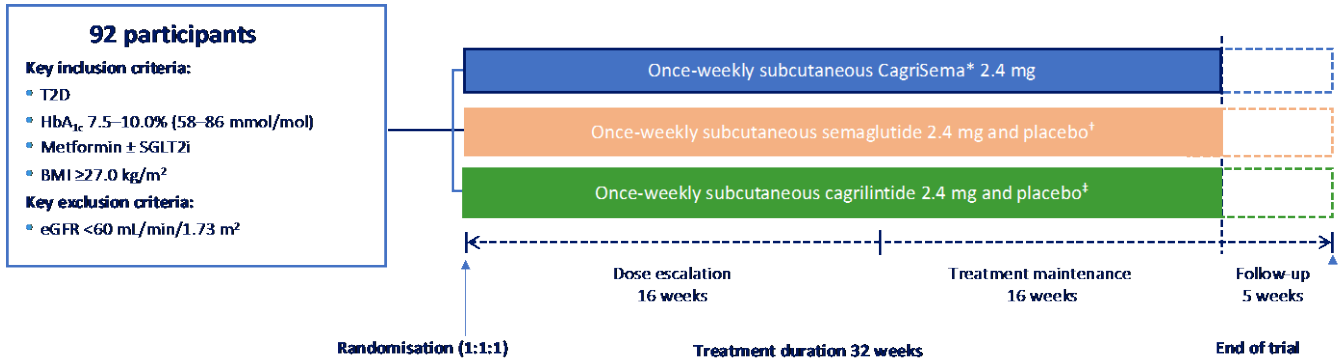
CagriSema

- Weekly oral formulation of semaglutide:
- No DPP-4 degradation
- Strong binding to albumin.
- 94% homology to human GLP-1 and t½ of 155-185 hours.

- Oral weekly formulation of cagrilintide
- Strong, but reversible, binding to albumin
- No fibrillating properties of human amylin.
- 84% homology to native human amylin and t½ of 180 hours



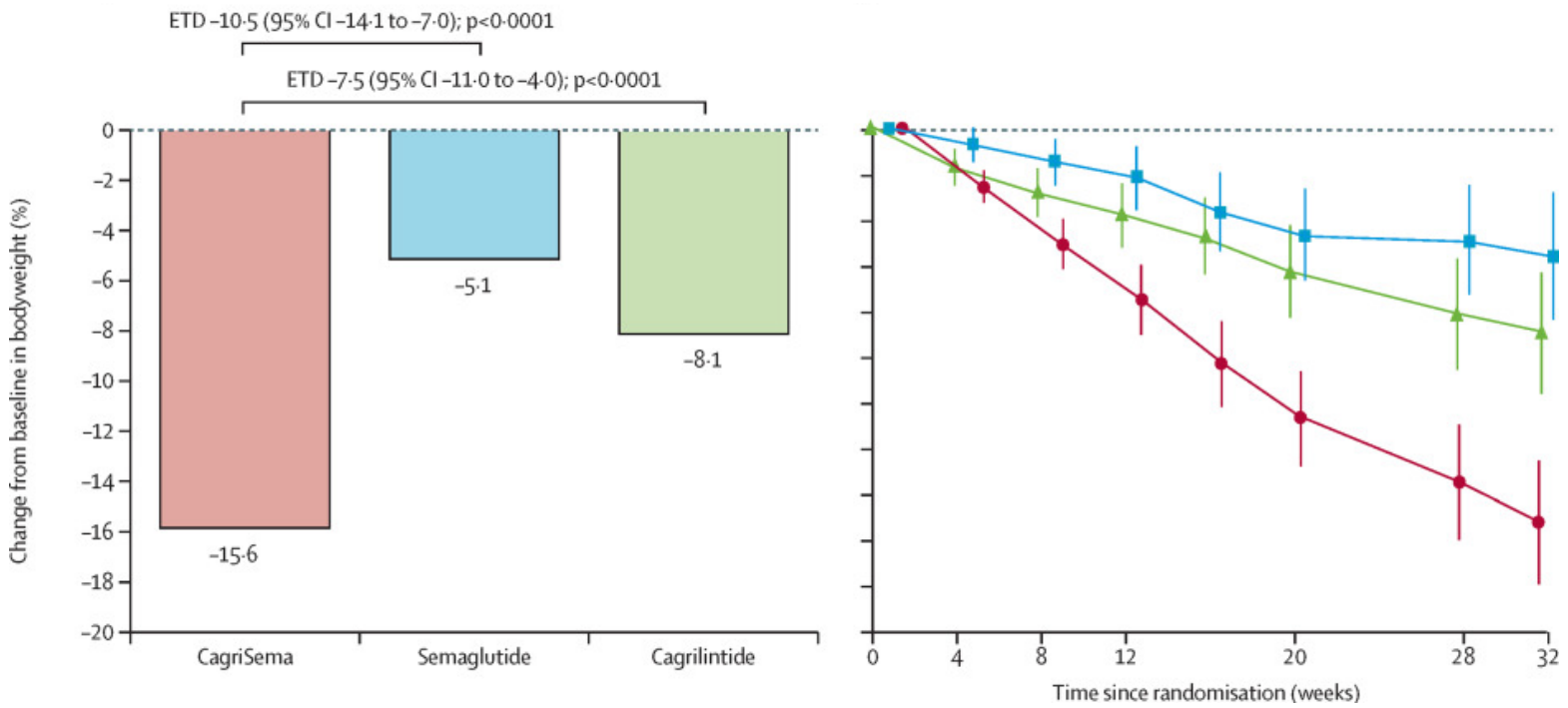
CagriSema appears to have a safe and well-tolerated profile in people with overweight/obesity and T2D



*Illustration, not to scale. *This slide includes multiple weight management products which may or may not be approved/marketed for use in your specific jurisdiction.*
AOM, anti-obesity medicines; T2D, type 2 diabetes.

CagriSema

- Improvement in glycemic control (including CGM parameters) in T2D patients.
- The mean change in HbA_{1c} was greater vs cagrilintide, but not versus semaglutide.
- Greater weight loss vs semaglutide and cagrilintide and well tolerated.



Key endpoints

- **Primary:** change from baseline to week 32 in HbA_{1c}
- **Supportive secondary**: change from baseline to week 32 in body weight, FPG, CGM
- **Safety**
- **Biomarkers:** hsCRP, leptin, soluble leptin receptor

Further investigation of CagriSema in this population in longer and larger phase 3 studies.

Frias JP Lancet 2023

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Tirzepatide effect on weight loss

- Tirzepatide is a multi-functional peptide engineered from the native GIP peptide sequence, modified to bind to GIP and GLP-1 receptors.
- It is a single molecule with two pharmacological target
- Mean half-life of ~5 days enabling once-weekly dosing

Drug	Study	Dose (mg)	Average weight loss (Kg)	% of weight loss vs. baseline	Observational interval (weeks)
Tirzepatide	Frias et al.	5 per day	-2.1 (no CI provided)	-2.3%	26
		10 per day	-4.4 (no CI provided)	-4.7%	26
		15 per day	-6.2 (no CI provided)	-7.0%	26

- Strong effect in weight loss
- Higher efficacy in weight loss than GLP1-RA
- Reduction in waist circumference

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Triple Agonist

ADA Meeting News

American Diabetes Association.

83RD SCIENTIFIC SESSIONS

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News Updates from the 83rd Scientific Sessions

Investigators to share new data on retatrutide triple therapy

Print Email

A novel triple therapy, retatrutide, could continue the string of game-changing metabolic agents that began with semaglutide, a glucagon-like peptide 1 (GLP-1) receptor agonist for type 2 diabetes and obesity, and continued with tirzepatide, a dual GLP-1/glucose-dependent insulinotropic polypeptide (GIP) receptor agonist. Retatrutide adds glucagon receptors to the GLP-1/GIP target list and could be the first type 2 diabetes agent to directly improve liver disease.

Arun J. Sanyal, MD

"Traditionally, we have employed glycemic-focused approaches to diabetes," said Arun J. Sanyal, MD, Professor of Medicine, Physiology, and Molecular Pathology and Interim-Chair of Gastroenterology, Hepatology, and Nutrition, Virginia Commonwealth University. "With GLP-1, GIP, and now glucagon receptor agonists, we may finally be able to holistically manage the multiple morbidities we see in type 2 diabetes."

Dr. Sanyal will discuss retatrutide and nonalcoholic steatohepatitis (NASH) during **Retatrutide (LY3437943), a Novel GIP/GLP-1/Glucagon Receptor Triagonist—Obesity, NAFLD, and T2D Phase 2 Trial Results** on Monday, June 26, at 1:30 p.m. PT in Ballroom 20A-C of the San Diego Convention Center. This symposium also will be available via livestream for registered meeting participants.

Initial results of a phase 2 trial for retatrutide make the drug a potential new blockbuster for type 2 diabetes, weight loss, and NASH.

Jastreboff, AM et al. NEJM 2023

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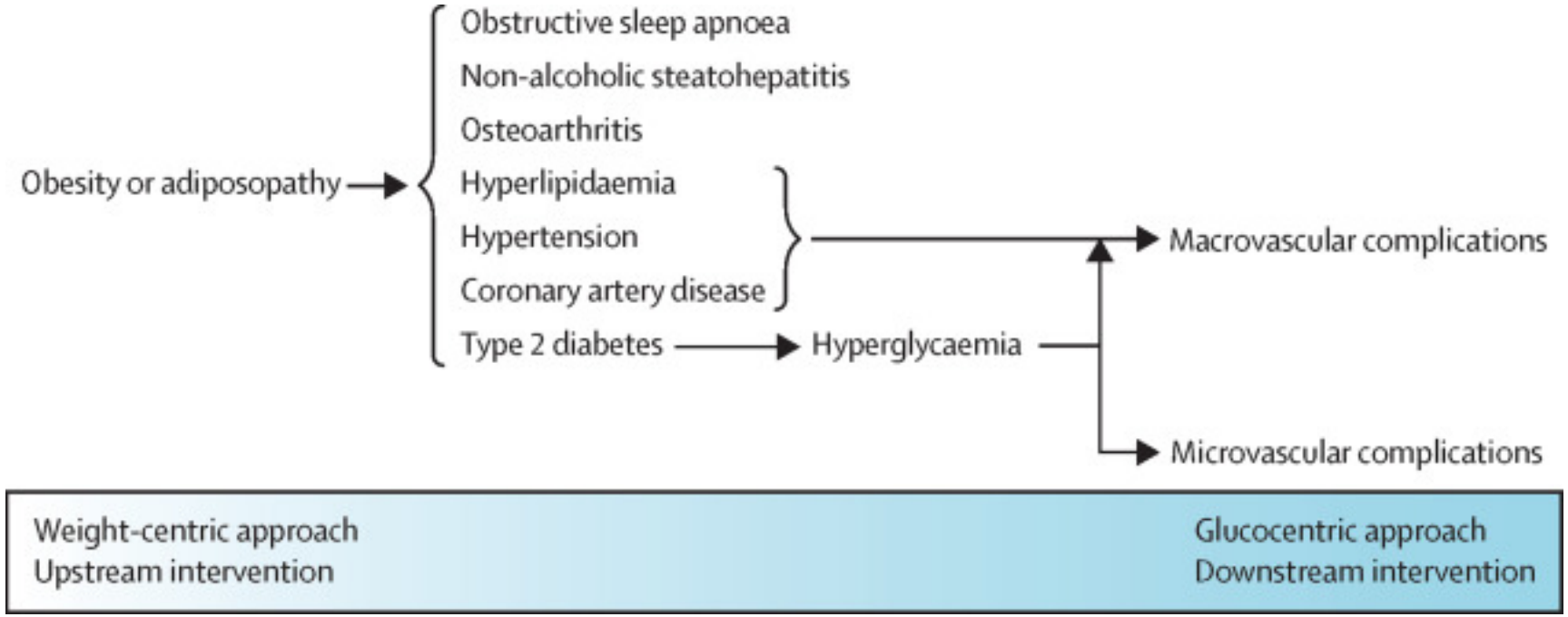
Conclusion

- Weight-loss has an important role in patients with T2D to improve glycemic control and to prevent complications
- The weight-loss strategies currently available have some limitations (lifestyle changes, after an early phase of weight loss, show a progressive recurrence of weight gain)
- Among all anti-diabetics the GLP-1 RA class is the most effective on weight loss in T2D.
- New incretin mimetic analogues combining 2 molecules or more targets (dual and triple agonists) showed promising results in phase 2/3 trials, paving the way for a paradigm change in diabetes therapy
- Combined pharmacological intervention for type 2 diabetes and obesity is underway now!

Upstream weight-centric approach vs. glucocentric management approach: potential benefits



To harness weight loss as a disease-modifying intervention for T2D patients having an adiposity-based chronic disease that is complicated by hyperglycaemia.

Lingvay I et al. Lancet 2022

Acknowledgements

It is an exciting time for the bdiabetes community!