PODEN ARRIBAR A LA REMISSIÓ DE LA DM2 I FINS QUAN ?: FÀRMACS

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XIV JORNADA DE L'ASSOCIACIÓ CATALANA DE DIABETIS
MITES I REALITATS DE LA DIABETIS

Reus, 17 de juny de 2022

Conflicts of interets

AstraZeneca, Boehringer Ingelheim, Eli Lilly, Menarini, Jansen, Merck Sharp & Dohme, Novo-Nordisk, Sanofi

Medications for T2D Remission: Five Questions to be Answered

1 Definition

2 Therapies

3 Pathophysiology

4 Medications

5 Implications

Medications for T2D Remission: Five Questions to be Answered

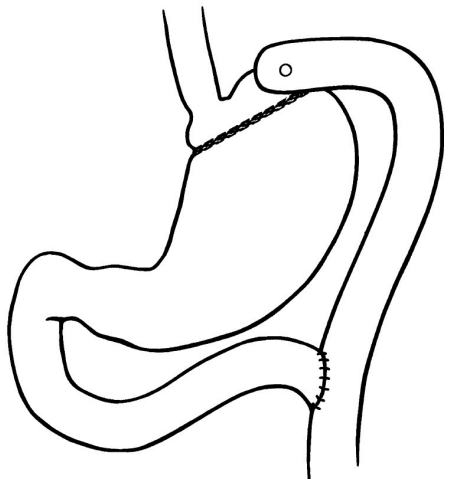
1

Definition

Who Would Have Thought It?

An Operation Proves to Be the Most Effective Therapy for Adult-Onset Diabetes Mellitus

1995



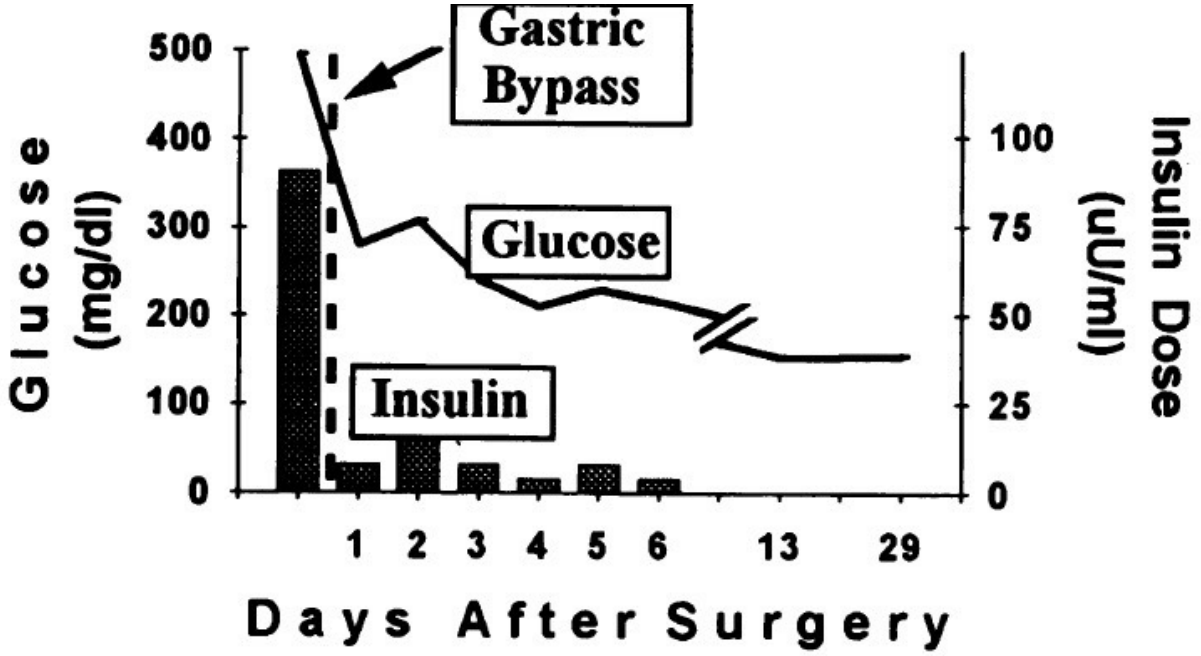


Figure 4. The correction of the hyperglycemia occurs rapidly. Patient 1 had an fasting blood glucose level of 495 mg/dL on the day before surgery despite the administration of 90 U of insulin. By the end of the 1st postoperative day, her fasting blood glucose level fell to 281 mg/dL and her insulin requirement dropped to 8 U. By the 6th postoperative day, she no longer required insulin.

Pories WJ et al. Ann Surg 1995; 222:: 339-352.

2009

CONSENSUS STATEMENT

How Do We Define Cure of Diabetes?

John B. Buse, MD, PhD[1]
Sonia Caprio, MD[2]
William T. Cefalu, MD[3]
Antonio Ceriello, MD[4]
Stefano Del Prato, MD[5]
Silvio E. Inzucchi, MD[6]
Sue McLaughlin, BS, RD, CDE, CPT[7]
Gordon L. Phillips II, MD[8]
R. Paul Robertson, MD[9]
Francesco Rubino, MD[10]
Richard Kahn, PhD[11]
M. Sue Kirkman, MD[11]

diseases. Infectious diseases could be seen as a model: acute bacterial pneumonia can be cured with antibiotics, but HIV infection, currently, can at best be stated to be in remission or converted to a chronic disease. The consensus group considered the history of childhood acute lymphoblas-

Definition of Remission used in Studies

Study	Year	A1C level	Fasting Glucose	Duration	Medications
Gregg E et al (Look Ahead) [1]	2012	5.7 - 6.5% (Partial) < 5.7%(Complete)	100-126 mg/dl < 100 mg/dl	Annually	Off All meds
Sjostrom et al (SOS) [2]	2014	nd	< 110 mg/dl (IFG or normal)	nd	Off all meds
Yska et al (UK Cohort) [3]	2015	< 6.0%		6 months	Off all meds
Purnell et al (LABS-2) [4]	2016	< 6.5%	< 125 mg/dl (if A1c unavailable)	Annually	Off all meds
Schaur et al (STAMPEDE) [5]	2018	< 6.0% < 6.5%, <7.0 %		1 year	Off all meds Off all meds, On meds
Lean MEJ et al. (DiRECT) [6]	2018	<6.5%		Assessed at 1 year	Off all meds
Madsen et al (Danish Cohort) [7]	2019	< 6.5% < 6.0%		1 year	Off all meds On metformin
Inge TH et al (Teen-LABS) [8]	2019	< 6.5%	< 126 mg/dl (if A1c unavailable)		Off all Meds

1 JAMA 2012; 308(23): 2489-2496
2 JAMA 2014; 311(22): 2297-2304
3 JAMA Surg. 2015; 150(12):1126-1133
4 Diabetes Care. 2016; 39(7):1101-7
5 N Engl J Med. 2017; 376(7):641-651
6 Lancet Diabetes Endocrinol 2019; 7(5):344-355
7 Diabetolgia 2019; 62(4):611-620
8 N Engl J Med. 2019 ; 380;2136-21453

Consensus Report: Definition and Interpretation of Remission in Type 2 Diabetes

2021

American Diabetes Association, European Association for the Study of Diabetes, Diabetes UK, the Endocrine Society, and the Diabetes Surgery Summit + 1 oncologist
(February 2019 and September 2020)

This group proposed "remission" as the most appropriate descriptive term, and HbA1c <6.5% (48 mmol/mol)* measured at least 3 months after cessation of glucose-lowering pharmacotherapy as the usual diagnostic criterion.

Not recommended. FPG (high variability)

Not recommended: 2-h plasma glucose (OGTT) (high variability, complexity)

*In some circumstances, an eA1C or GMI <6.5% can be considered an equivalent criterion.

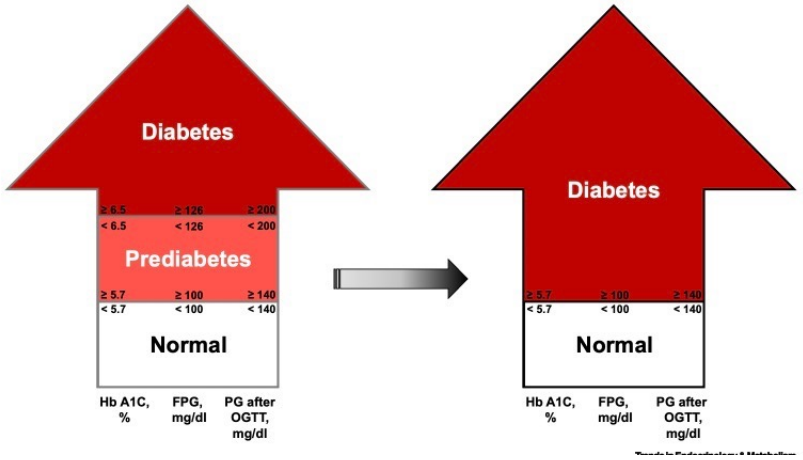
Riddle MC et al. Diabetes Care 2021;44:2438–2444

Consensus Report: Definition and Interpretation of Remission in Type 2 Diabetes

2021

Remission: HbA1c <6.5% measured at least 3 months after cessation of glucose-lowering pharmacotherapy

The time is now for new, lower diabetes diagnostic thresholds



Schwartz SS et al. Trends Endocrinol Metab 2022; 33:4-7.

Riddle MC et al. Diabetes Care 2021;44:2438–2444

Medications for T2D Remission: Five Questions to be Answered

1

Definition

2

Therapies

Therapeutic Strategies for T2D remission

Genetic and Environmental Factors

Insulin resistance

Insulin Secretion

T2D diagnosis

Treatment Guidelines

Interventions for T2D Remission

Diet

Drugs

Surgery

Medications for T2D Remission: Five Questions to be Answered

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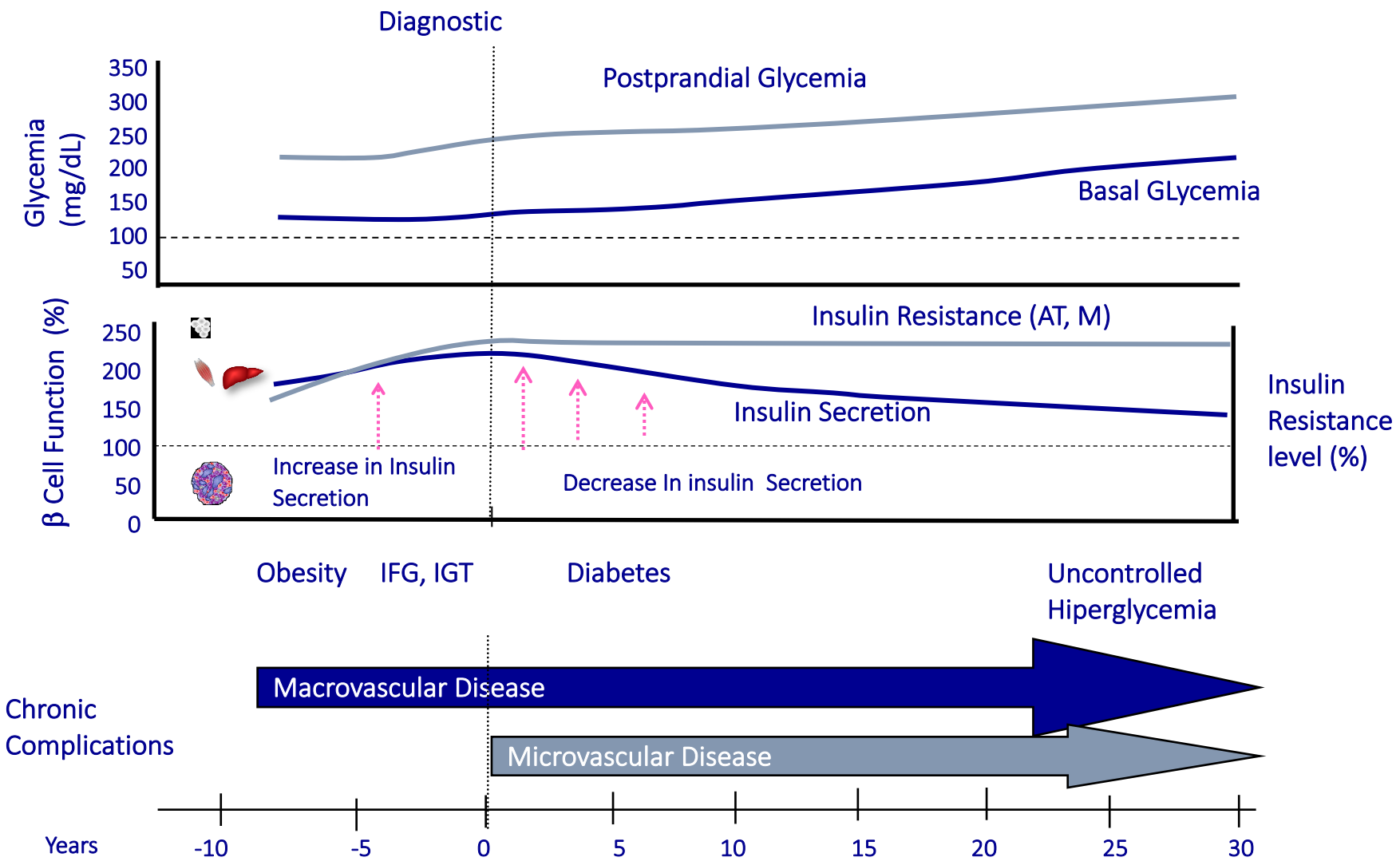
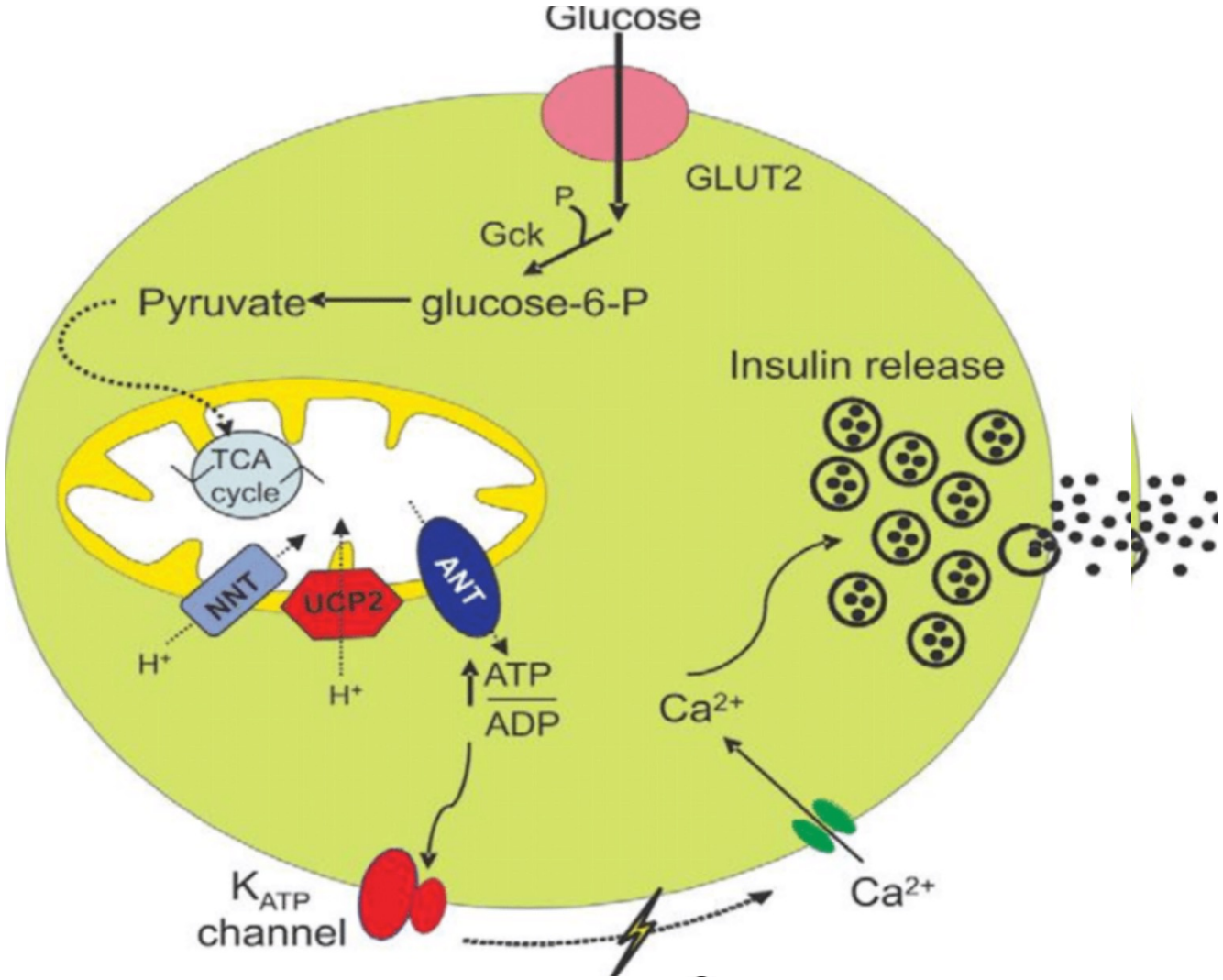
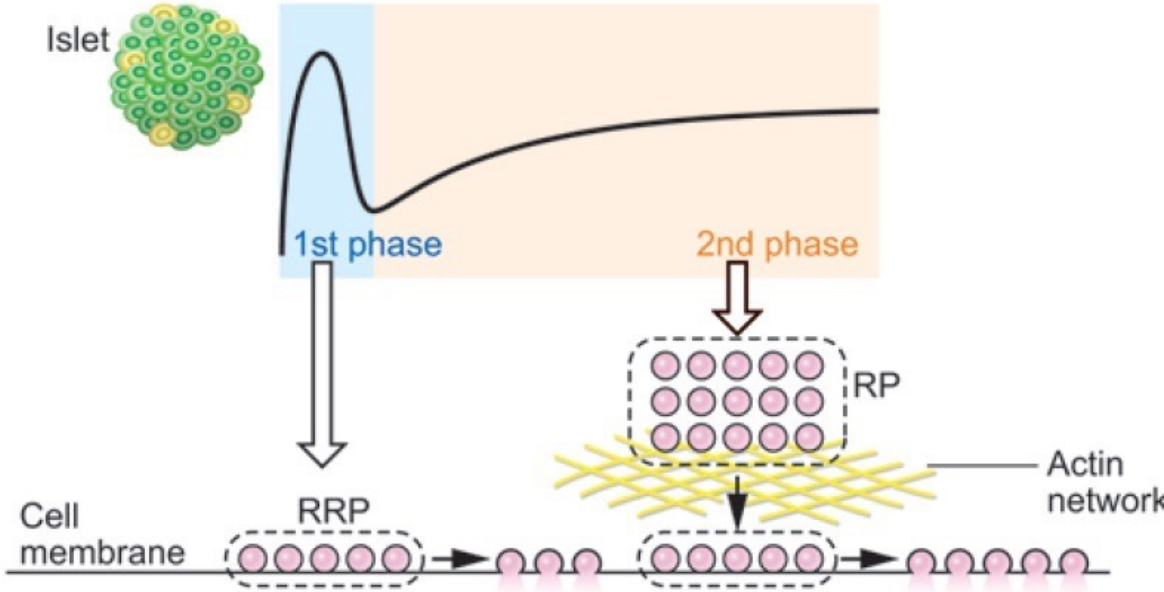
T2D: Natural History



Adaptado de Type 2 Diabetes BASICS. Minneapolis, MN: International Diabetes Center; 2000.

Healthy ß Cell: signals from glucose metabolism mediate insulin secretion

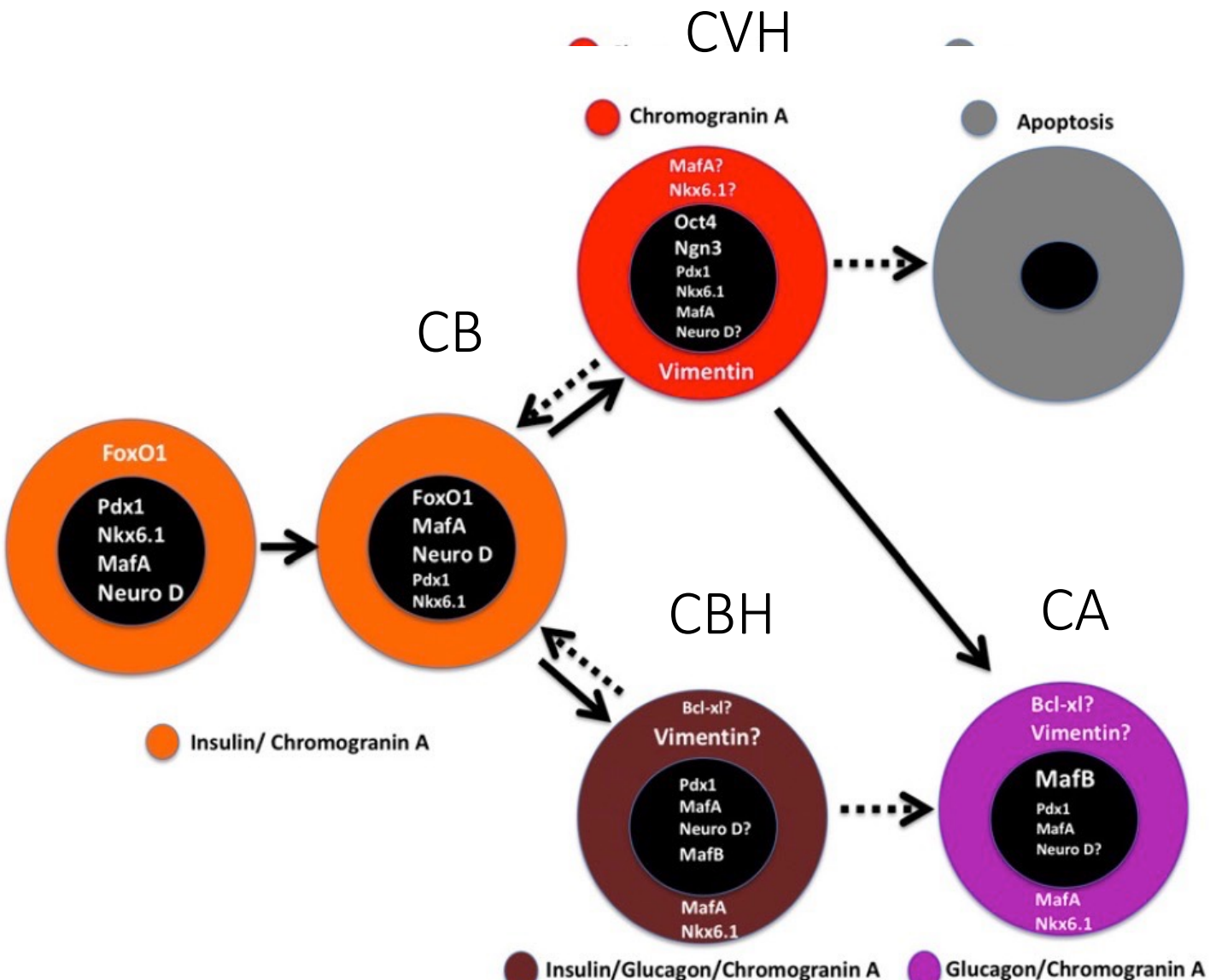




Selno S et al. J Clin Ingest 2011; 121: 2118-2125.

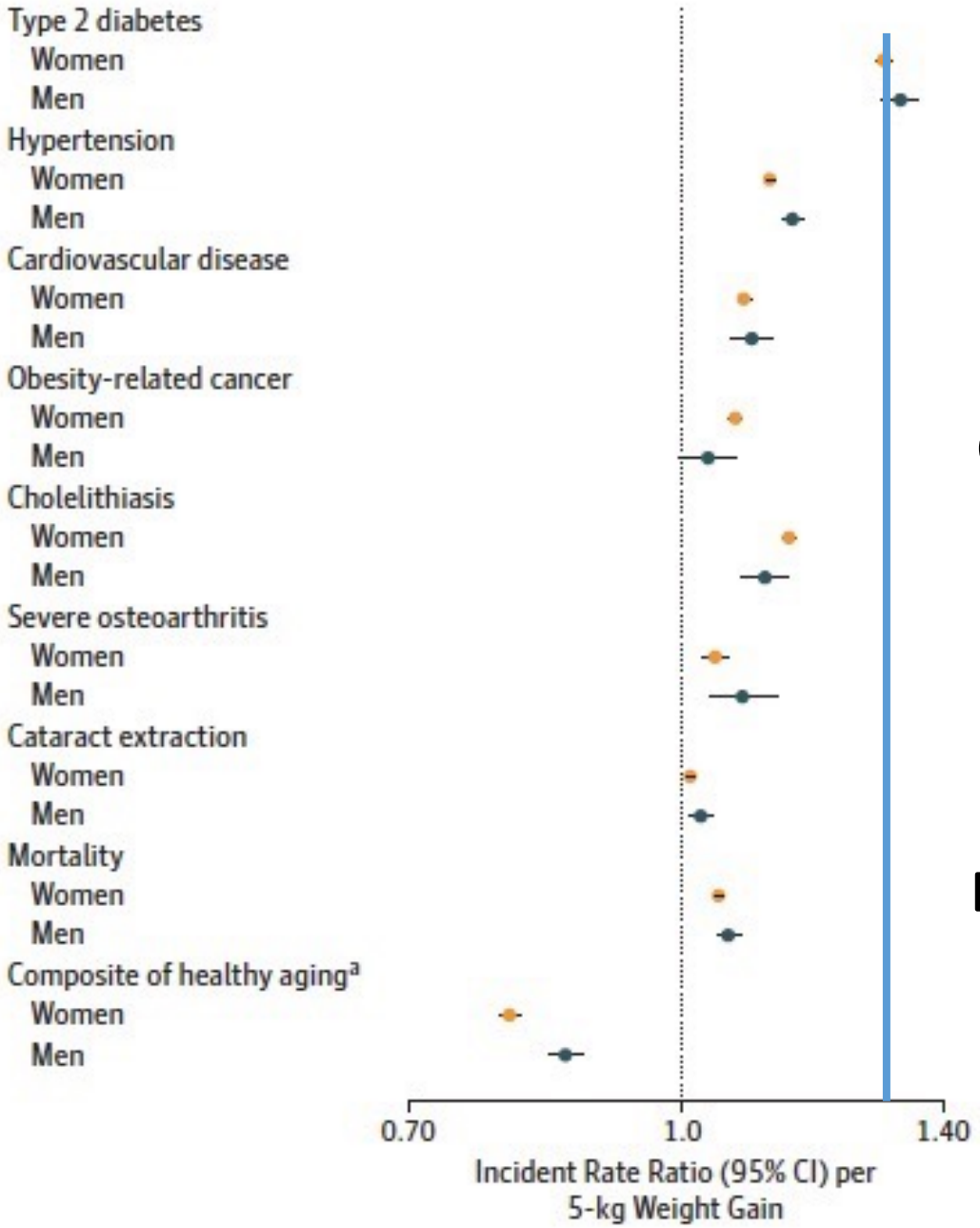
ß cell dediferentiation and T2D

FoxO1 (factor de transcripción) pasa al núcleo para proteger a la célula ß del estrés metabólico (glucolipotoxicidad). Así, oxida la glucosa y no los ácidos grasos; se produce insulina. Si persiste el estrés, FoxO1 se degrada, se oxida peor la glucosa y mejor los ácidos grasos (inflexibilidad metabólica); se genera más estrés oxidativo lo que deteriora la secreción de insulina: la célula ß se trasforma en una CVH (arriba) y sufre apoptosis, o se trasdiferencia a CBH y a CA (abajo),
CB: célula ß
CVH: célula "vacía" de hormonas
CBH: célula bihormonal
CA: célula alfa



White M et al. Diabetes Care 2016; 39: 2080-2088.

Weight gain in middle ages is a major driver for developing T2D



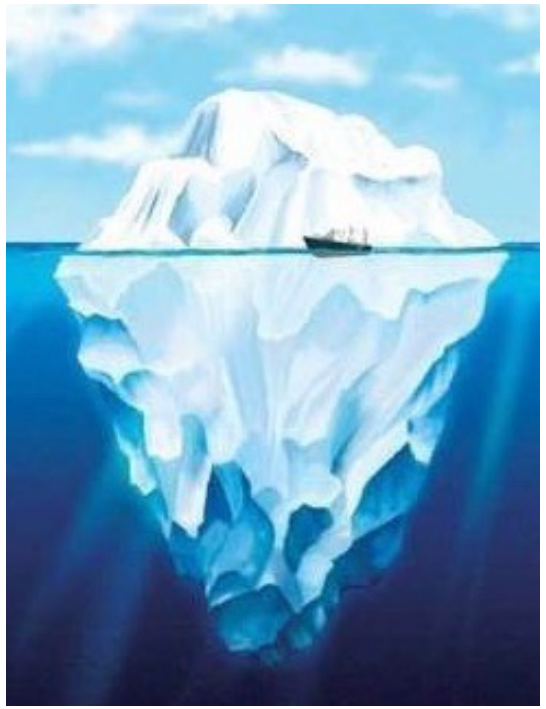
T2D

HTN

CVD

CANCER

DEATH



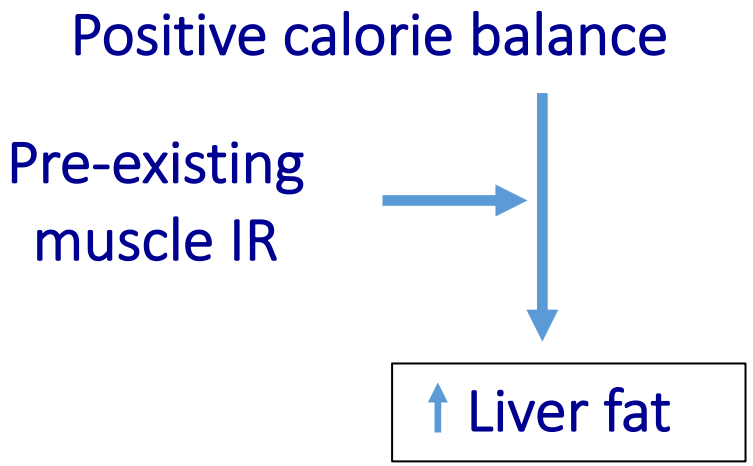
Accelerated aging (sirtuins, mTOR AMPK)

Nurses' Health Study (92837 women, weight gain: 18-55 yrs.). Health Professionals Follow-up Study (25303 men, weight gain. 23-55 yrs),

Healthy aging: no chronic diseases, no major cognitive or physical impairment

Zheng Y et al . JAMA 2017; 318: 255-69..

Twin cycle hypothesis: Calorie excess and T2D development



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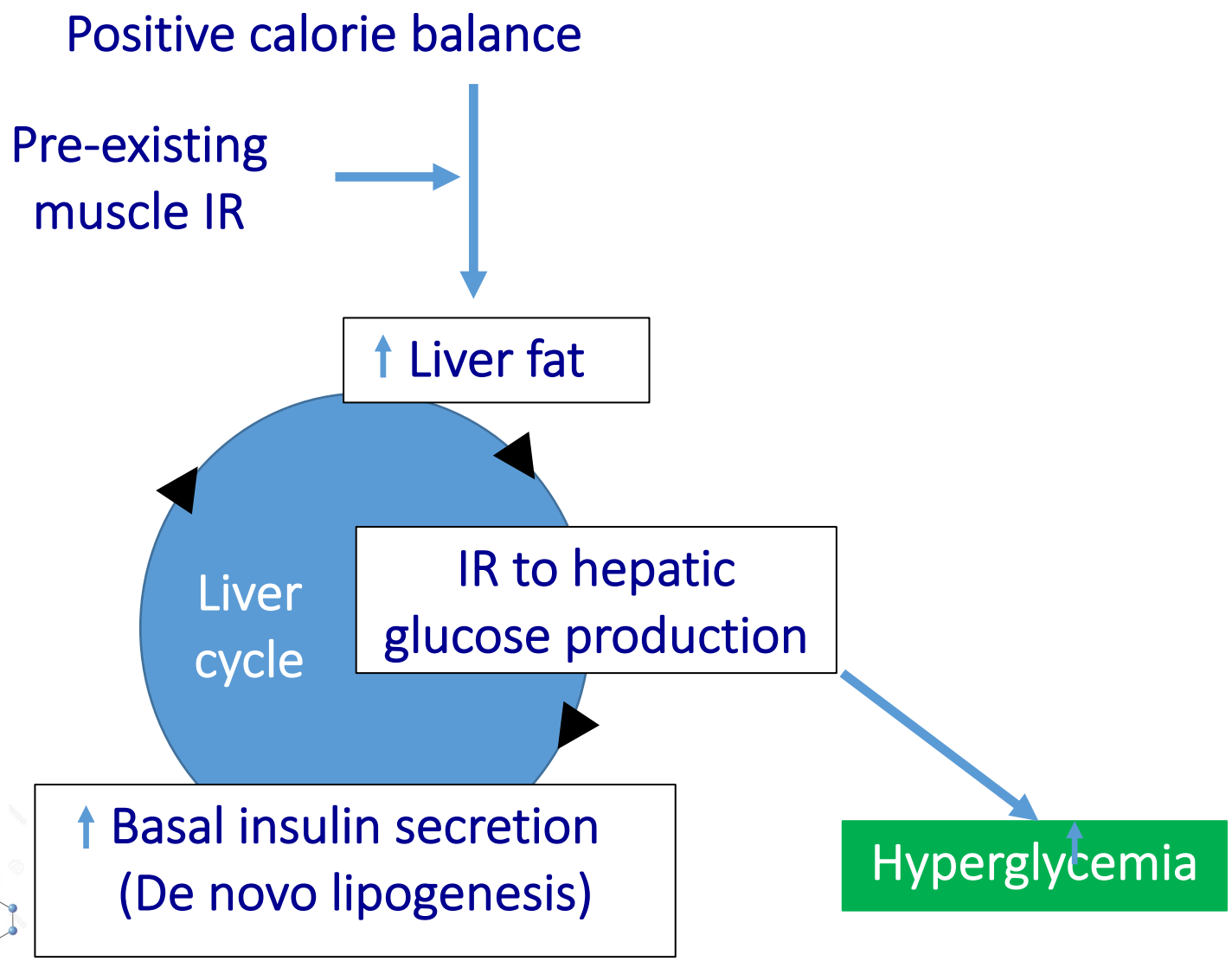

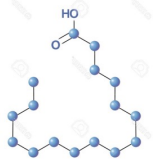

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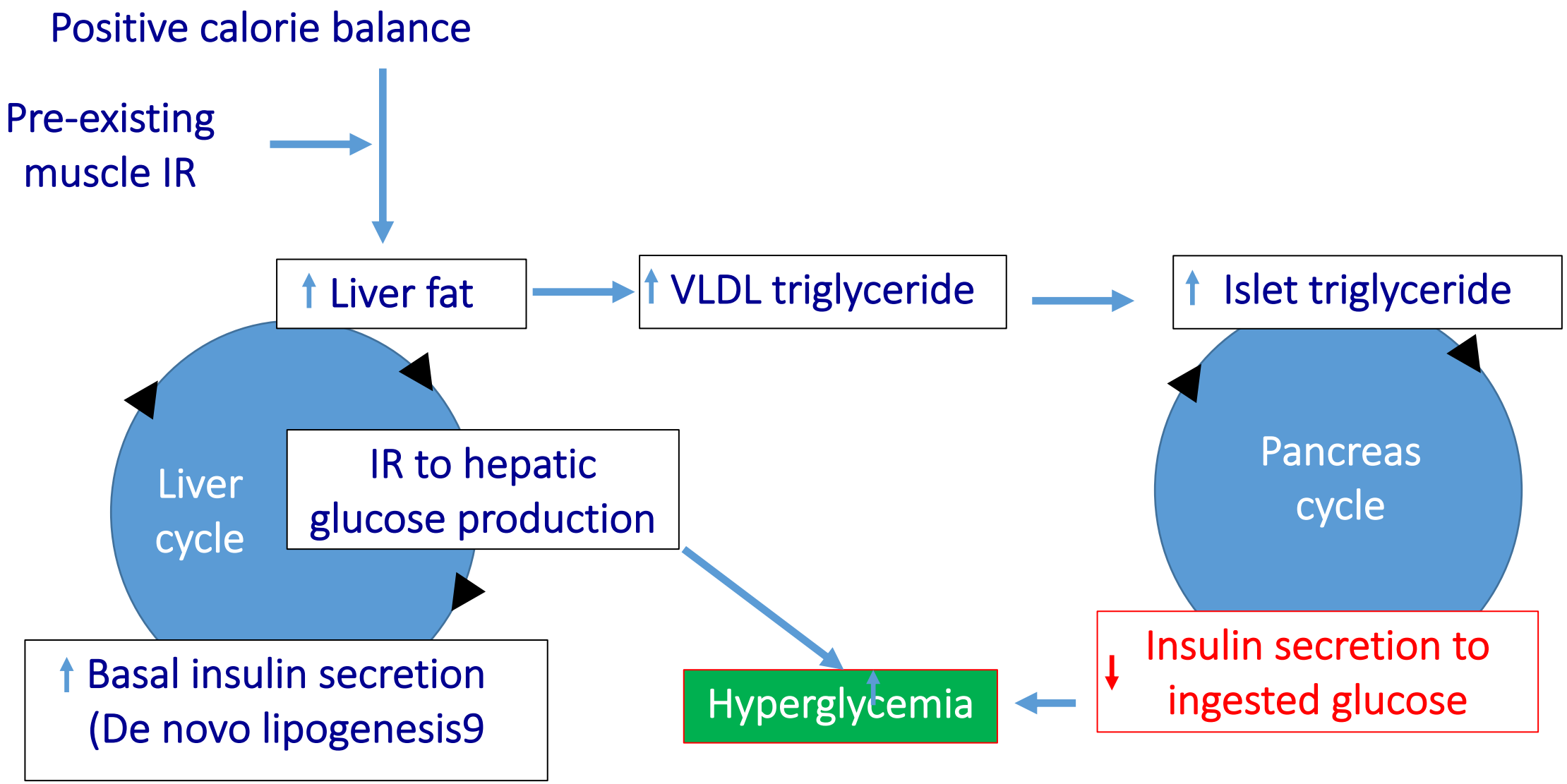

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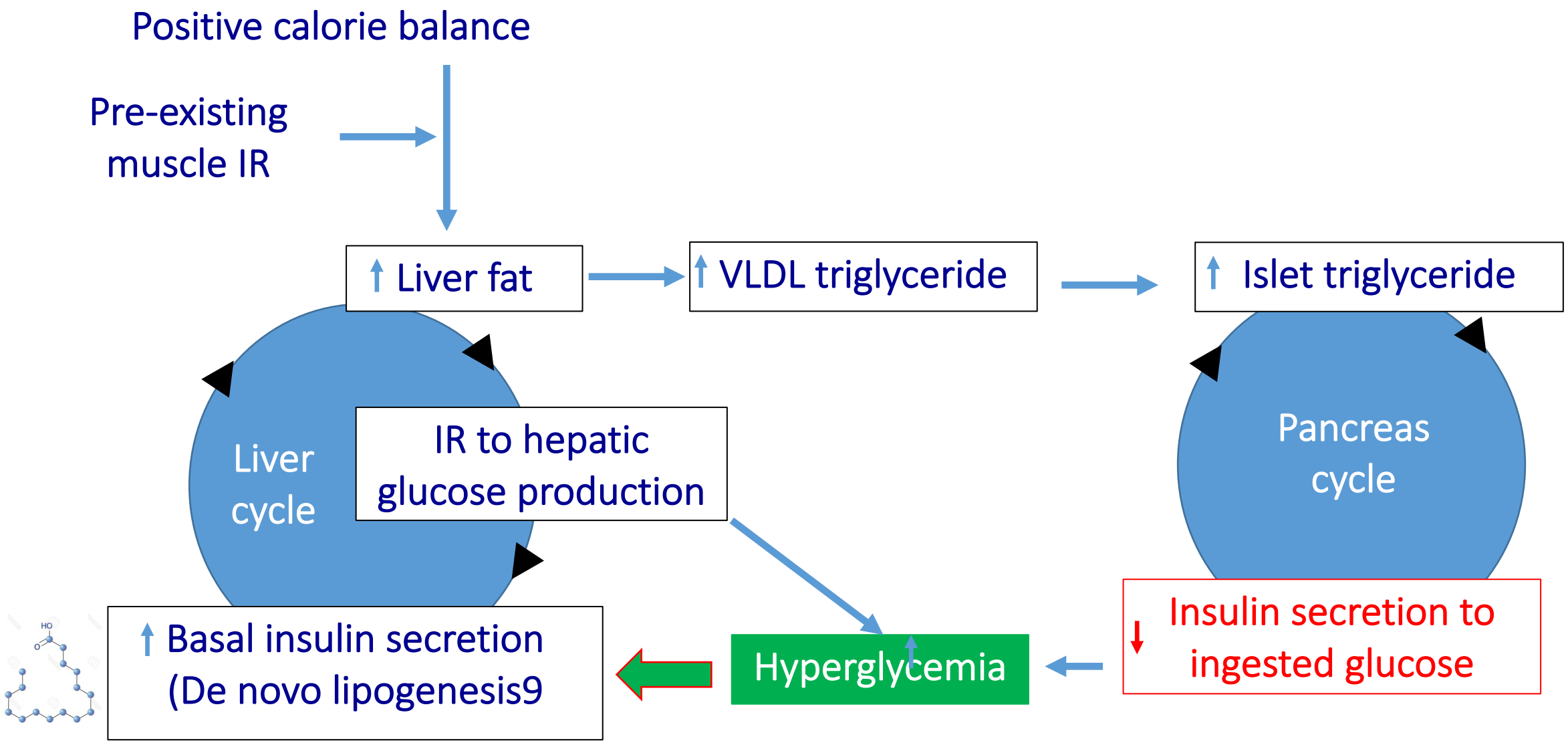

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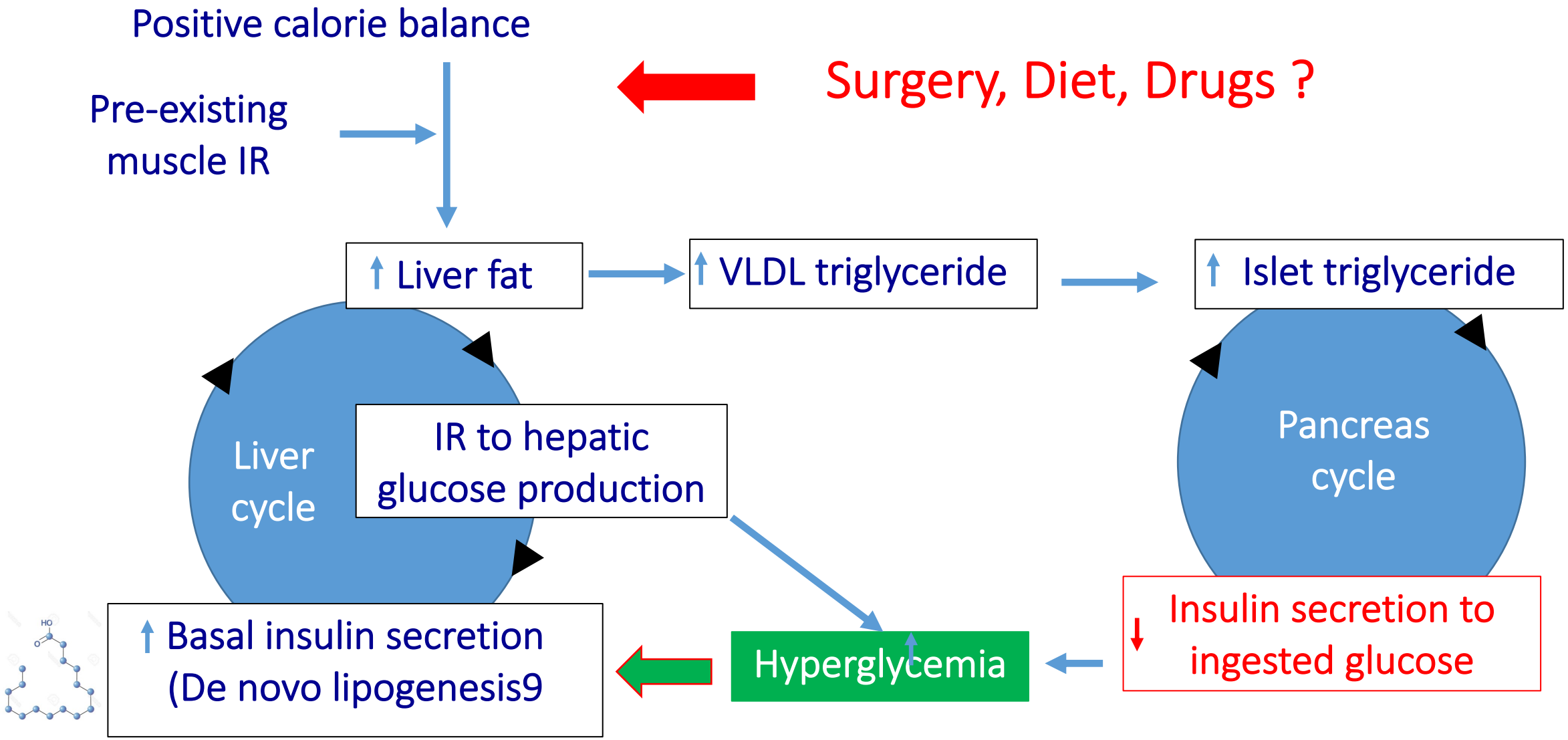

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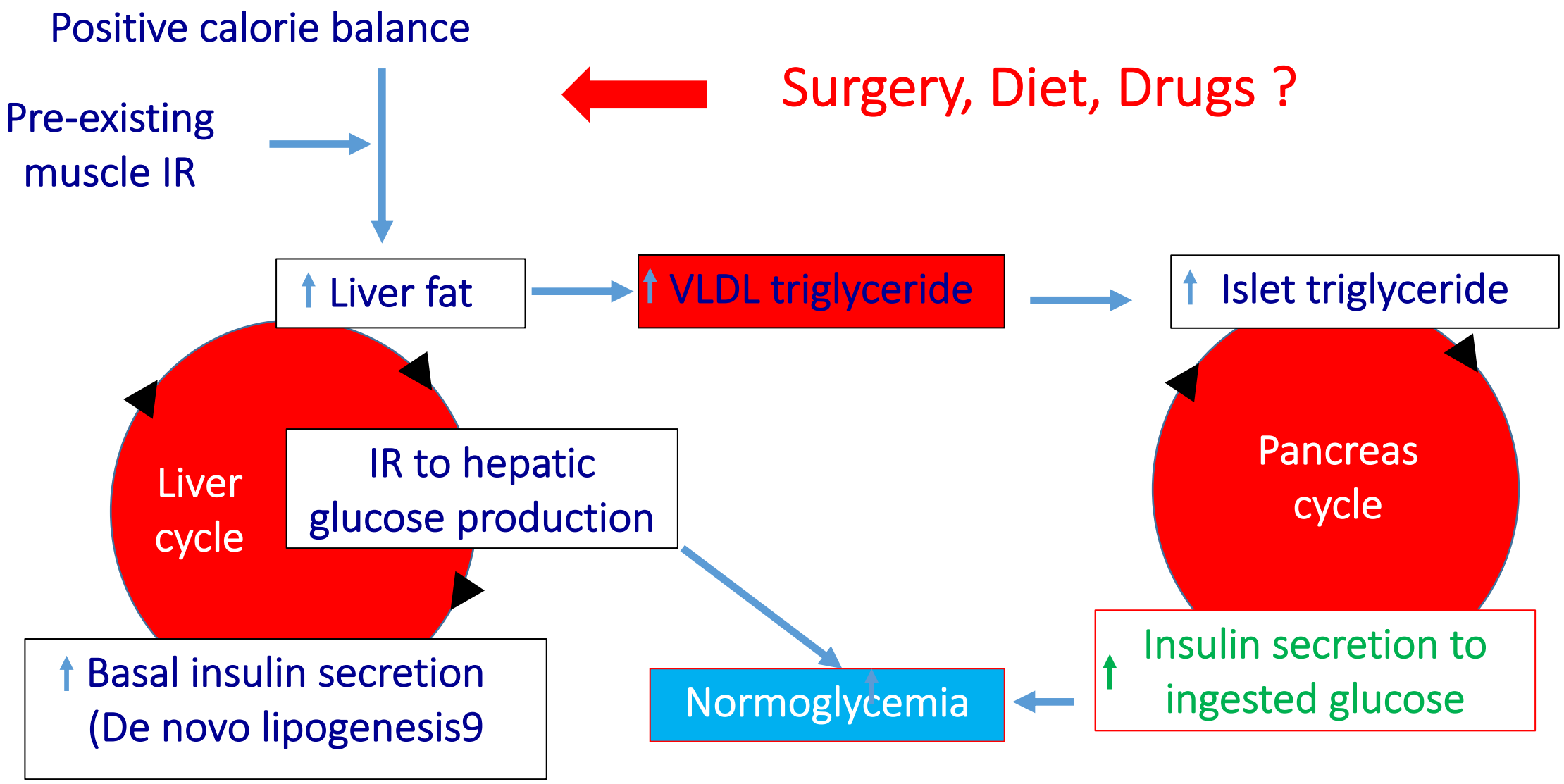

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Weighing in on Type 2 Diabetes Remission

Escalation Therapy: Metformin to insulin

Adapted from Meerasa A et al . Diabetes Care 2022; 45: 28-30 .

Weighing in on Type 2 Diabetes Remission

Escalation Therapy: Metformin to insulin

T2D

Remission

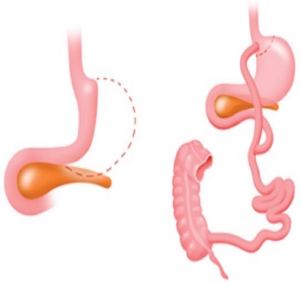
Early (< 6 yrs.)

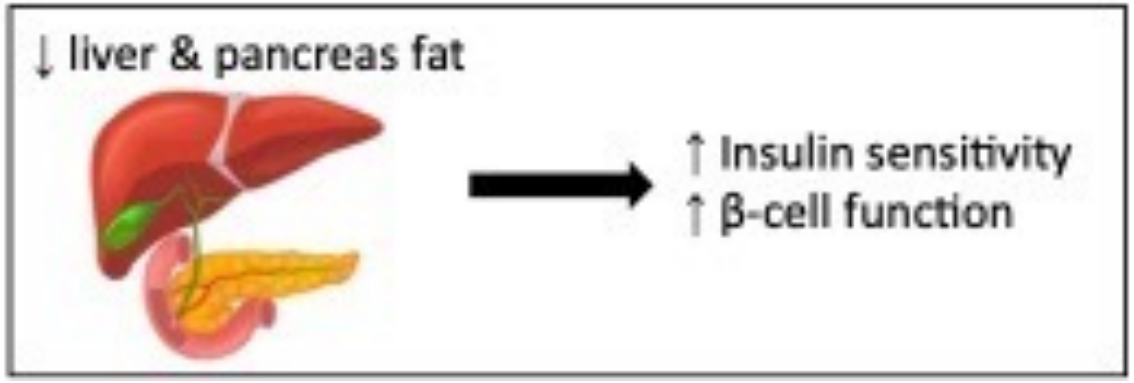
10-15 % Weight Loss

Advanced

20-25 % Weight Loss

?





Adapted from Meerasa A et al . Diabetes Care 2022; 45: 28-30 .

Weighing in on Type 2 Diabetes Remission

Escalation Therapy: Metformin to insulin

T2D

Remission

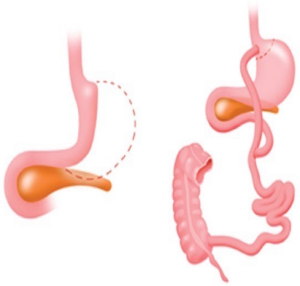
Early (< 6 yrs.)

Advanced

10-15 % Weight Loss

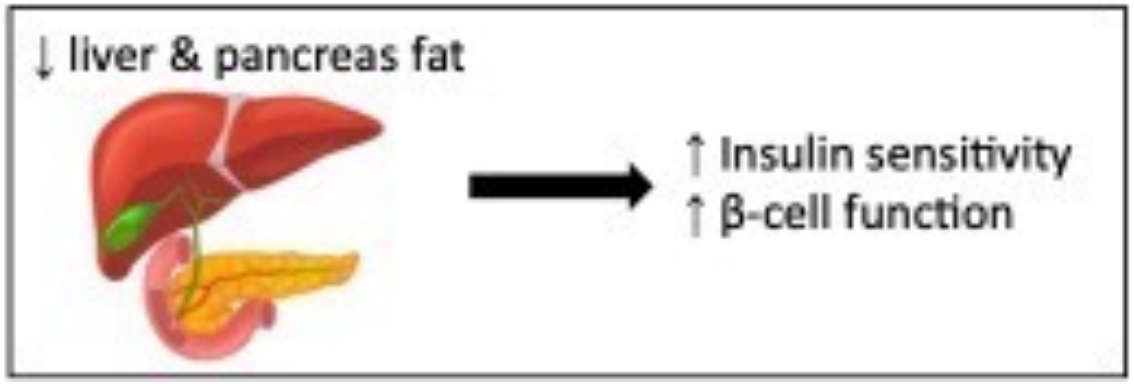
20-25 % Weight Loss

?



Predictors:

1. Age
2. Baseline HbA1c
3. N. of medications for T2D
4. Insulin use
5. T2D duration



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Medications for T2D Remission: Five Questions to be Answered

1 Definition

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4 Medications

The Impact of Traditional Drugs for T2D and Some New Ones is Limited

Effect of intensive insulin therapy on β-cell function and glycaemic control in patients with newly diagnosed type 2 diabetes: a multicentre randomised parallel-group trial

- Multicentric, China, open-label
- Randomized: CSII/MDI/OHA. Human insulins (regular and NPH). Gliclazide (up to 160 mg) Metformin (up to 2000 mg). Two phases: Intensification/follow-up. Analysis: Per protocol

Pts.:
- FPG: 126-300 mg/dL
- Naïve for glucose-lowering agents
- 25-70 yrs. GAD Abs -

CSII (137)	No euglycemia: 4 (133)	Lost: 9. (124)
MDI (124)	No euglycemia: 6 (118)	Lost: 5. (113)
OHA (121)	No euglycemia: 13, Met Intolerance: 7 (101)	Lost: 7. (94)

Weng J et al. Lancet 2008; 371:: 1753-1760..

Effect of intensive insulin therapy on β-cell function and glycaemic control in patients with newly diagnosed type 2 diabetes: a multicentre randomised parallel-group trial

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OHA (121)	No euglycemia: 13, Met Intolerance: 7 (101)	Lost: 7. (94)

Intensification (up to 2 wks.): capillary euglycemia: fasting < 110 mg/dL + 2h post-meal (3 meals): < 144 mg/dL

Follow-up: diet and exercise (1 yr.)

Primary endpoint: Time in euglycemia and T2D remission for at least 1 yr. w/o glucose-lowering drugs).

Weng J et al. Lancet 2008; 371:: 1753-1760..

Effect of intensive insulin therapy on β-cell function and glycaemic control in patients with newly diagnosed type 2 diabetes: a multicentre randomised parallel-group trial

Group	Sujetos*	Euglycemia Time to euglycemia*	Remisión DM2 (1 a)**	Hipoglucemia
CSII	97 %	4.0 (2.5) days	**51 %**	34 %
MDI	95 %	5.6 (3.8) days	**45 %**	28 %
OHA	84 %	9.3 (5,3) days	**27 %**	19 %

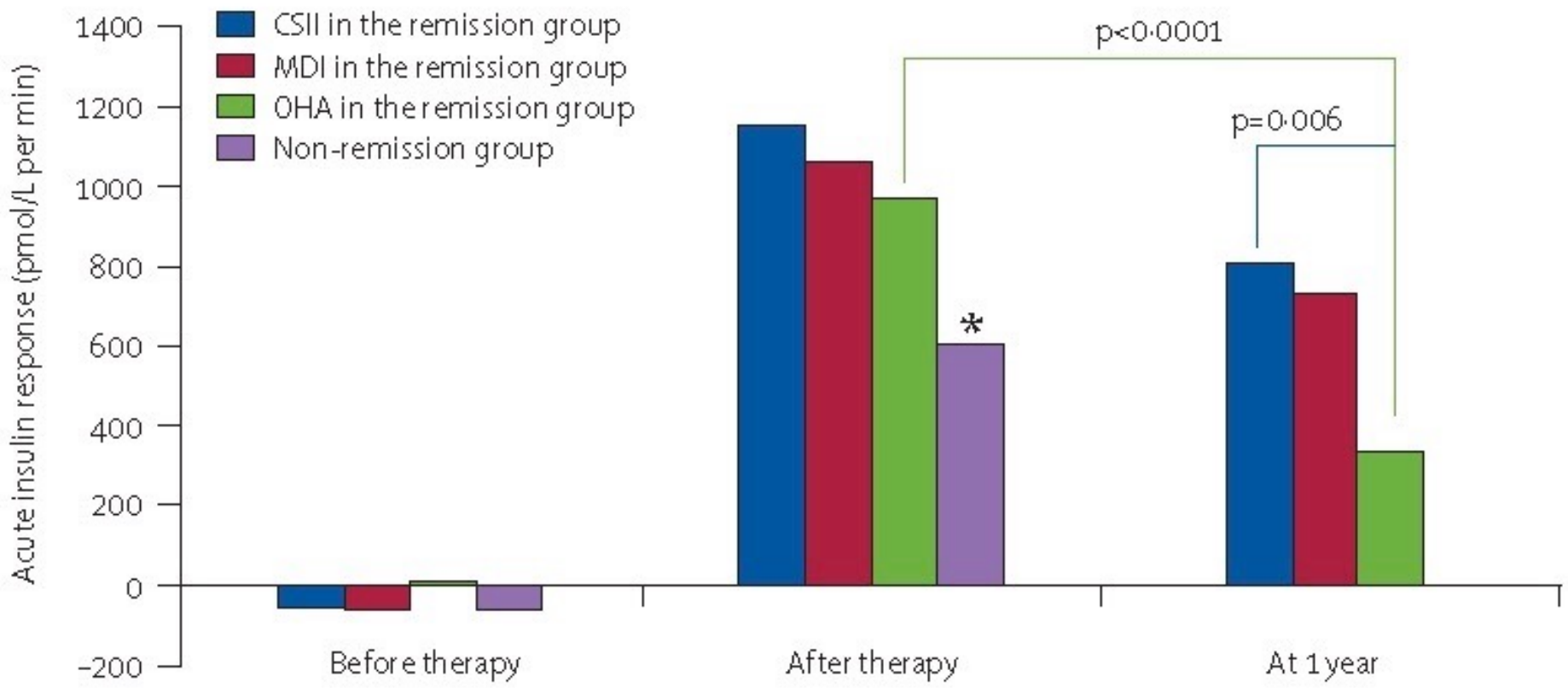
* Both were better for insulin interventions as com pared with OHA administration

** No differences in severe hypoglycemia. Hypoglycemia episode: simptoms + glycemia < 55 mg/dl. More hypos with insulins than with OHA.

Weng J et al. Lancet 2008; 371:: 1753-1760..

Effect of intensive insulin therapy on β-cell function and glycaemic control in patients with newly diagnosed type 2 diabetes: a multicentre randomised parallel-group trial

1st Pphaselinsulin Secretion



Insulin therapy improved beta cell function longer than OHAs, extending the remission period.

Weng J et al. Lancet 2008; 371:: 1753-1760. * p < 0,05 entre los que entraron y no entraron en remnisión tras la intervención.

Remission of Type 2 Diabetes Following a Short-term Intervention With Insulin Glargine, Metformin, and Dapagliflozin

N = 154, T2D duration < 8 yrs. 0-2 glucose-lowering drugs
- Open-label, randomized.
- Age: 57 yrs.; T2D duration 37 mp. HbA1c 6.7%. BMI 33. eGDR 96. Drug-naive: 55 %, Insulin: 0 %
- Primary outcome: Remission:. HbA1c < 6.5 % at 24-wk follow-up (secondary: 36, 48, 64 wks.)

	LS+ glargine + metformin + dapagliflozin (n =77)	Standard of care (n =77)
	Intervention is discontinued when HbA1c < 7.3 %	
12 wks.	HbA1c: 5.9 %. HbA1c < 7.3 %: 77 BW: - 2.9 %	HbA1c: 6.6 %HbA1c < 7.3 %: 53 BW: - 1.0 Kg
24 wks.	Remission: 24.7 %	Remission: 16.9 %

RR 1.50
(IC9%: 0.8-2.7)

McInnes N et al. J Clin Endocrinol Metab 2020; 108:: 1-9.

Remission of Type 2 Diabetes Following a Short-term Intensive Intervention With Insulin Glargine, Sitagliptin, and Metformin: Results of an Open-label Randomized Parallel-Design Trial

N = 102, T2D duration < 5 yrs. No insulin

- Open-label, randomized.
- Age: 56 yrs.; T2D duration 24 mp.. HbA1c 6.6%. BMI 32. Drug-naive: 15 %.
- Primary outcome: RR of remission:. HbA1c < 6.5 % at 24-wk follow-up, modified to HR of relapse throughout the whole study period. Relapse (primary definition): a capillary glucose level >180 mg/d on ≥ 50% of measurement over 1 wk. and no acute illness, HbA1c ≥ 6.5%, use of any glucose-lowering drug, FPG ≥ 126 mg/dL or a 2-h postprandial (OGTT) ≥ 200 mg/dL

12 wks.

LS+ glargine + metformin + sitagliptin (n =50)

Standard of care (n =52)

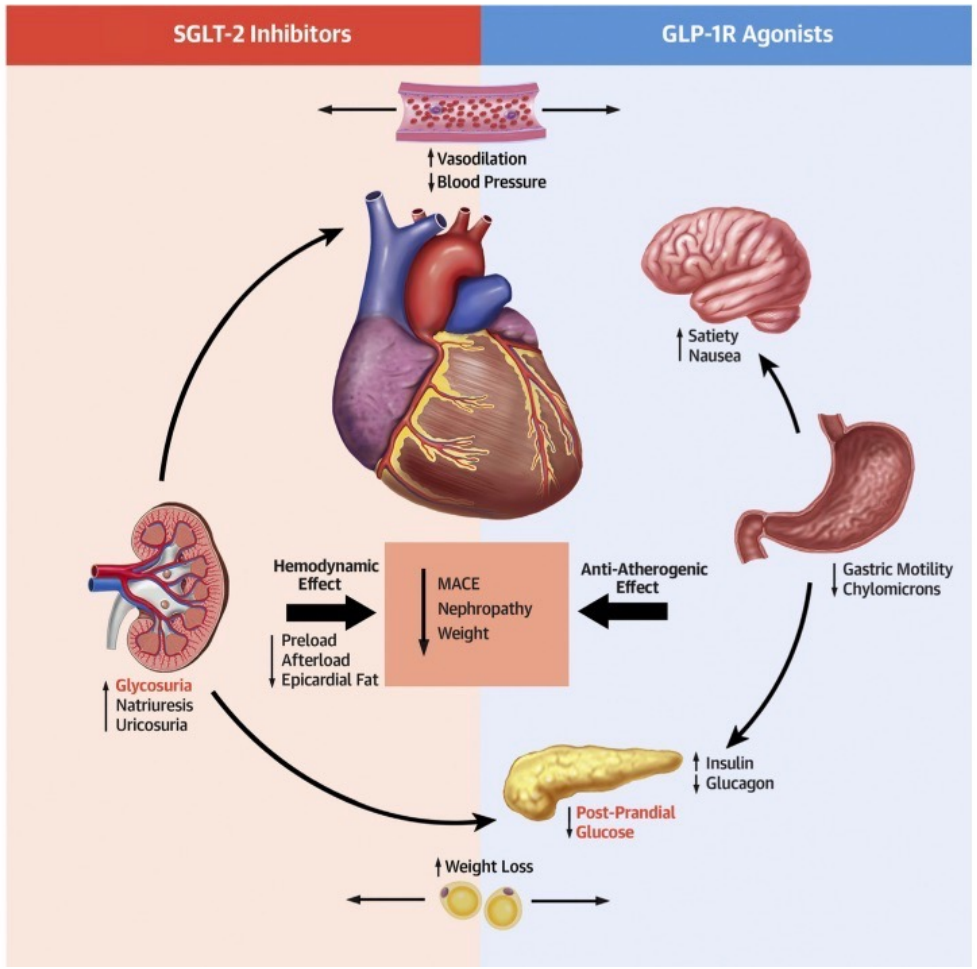
Intervention is discontinued when HbA1c < 7.3 % (100 % vs 71 %

Up to 64 wks.

With the FPG/OGTT relapse criteria included, the HR of relapse was 0.72 (95% CI 0.47–1.10) in the intervention group compared with the controlgroup (primary analysis), and the number of participants remaining inremission was not significantly different between treatment groups at 24,

McInnes N et al. Diabetes Care 2022; 45:178–185|

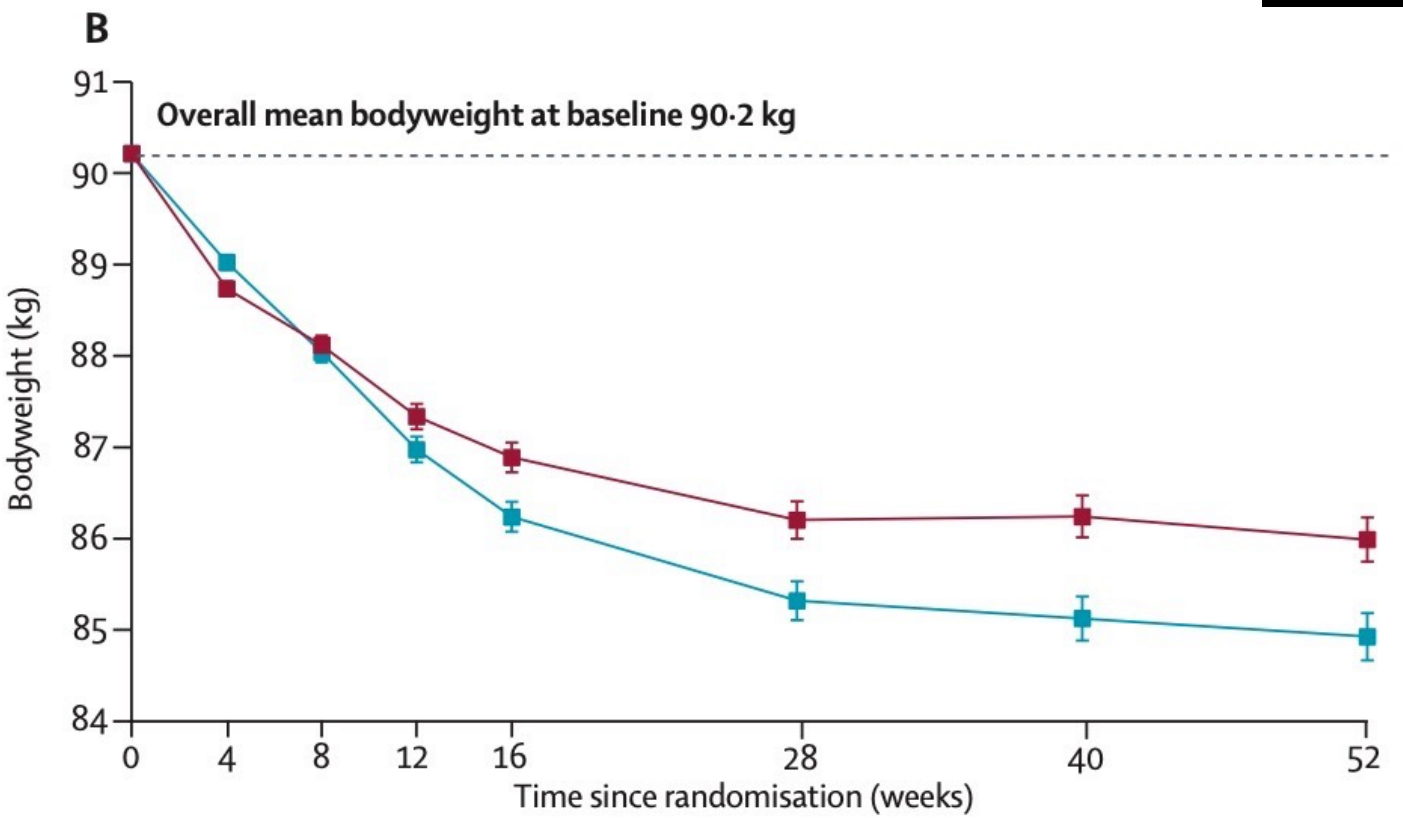
New Weight-Lowering Drugs for T2D show promise in the T2D Remission

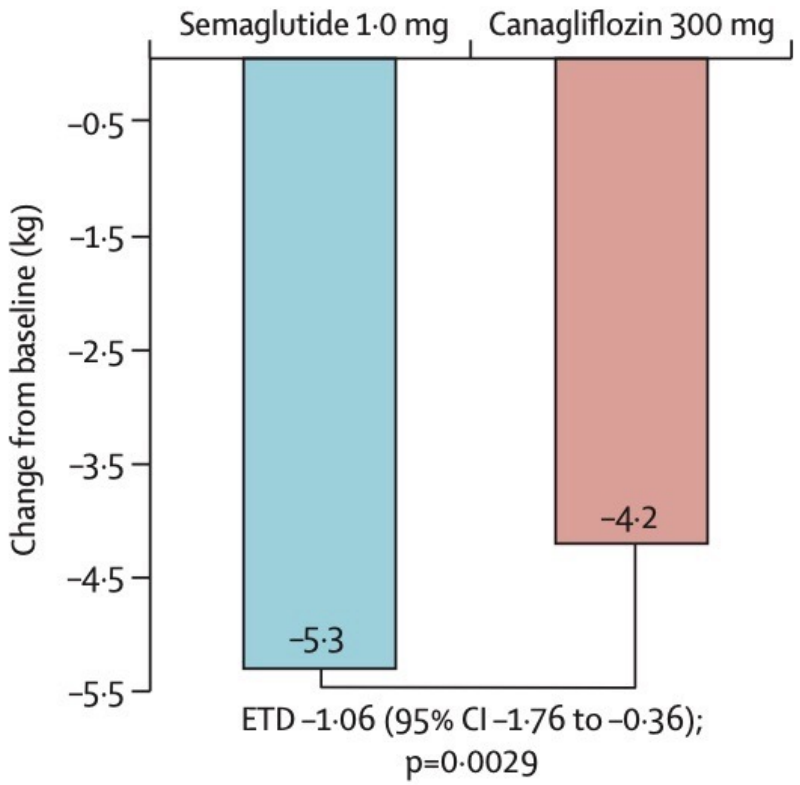


Wilcox T et al. J Am Coll Cardiol 2020; 75:1956-1974

SUSTAIN 8: Available SGLT2i for Losing Weight in T2D

BW Loss (Kg), 52 wks.





-5.9 Kg

-4.7 Kg

Lingway I et al. Lancet Diabetes Endocrinol 2019; 7: 834-844

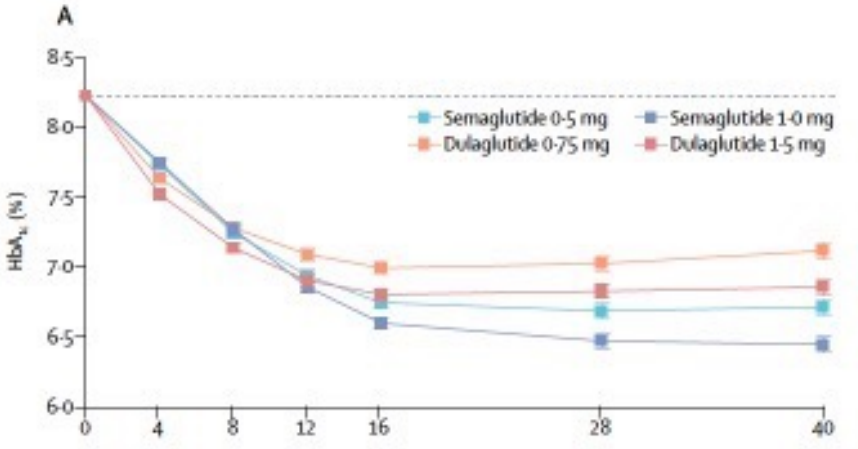
Semaglutide versus dulaglutide once weekly in patients with type 2 diabetes (SUSTAIN 7): a randomised, open-label, phase 3b trial

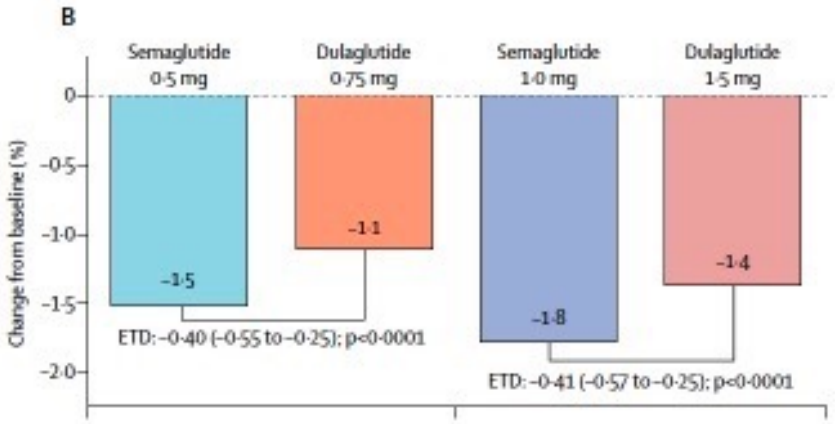
N = 1201; 40 wks
56 yrs. Females: 45 %.

TD duration: 7.4. HbA1c 8.2.
All on metformin

BW: 95. BMI: 34. WC: 111

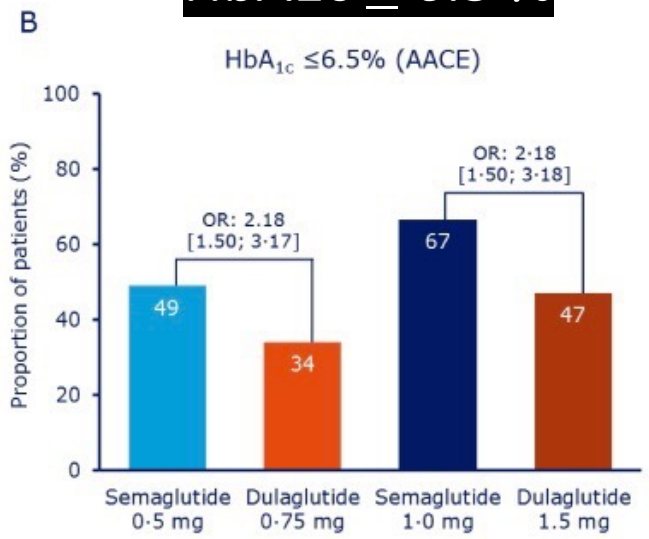
HbA1c Reduction





-1.8 | -1.4

HbA1c ≤ 6.5 %



67 % | 47 %

RCT, OL (1-1-1-1): S 0.5- D 0.75-S 1.0-D 1.5. Primary outcome: % change in HbA1c

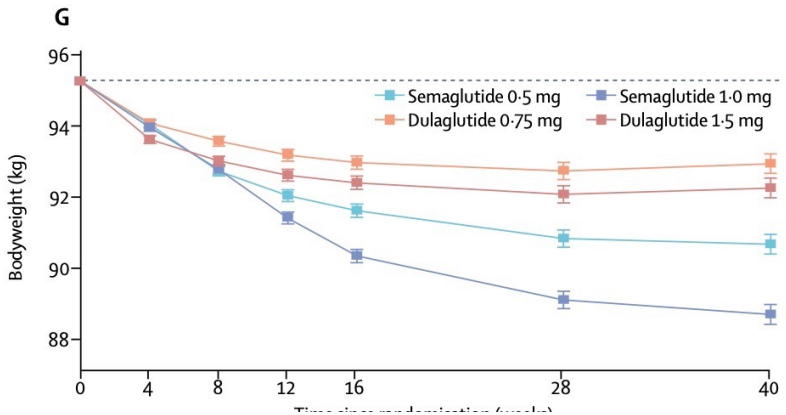
Pratley RF et al. Lancet Diabetes Endocrinol 2018; 6:275-286.

Semaglutide versus dulaglutide once weekly in patients with type 2 diabetes (SUSTAIN 7): a randomised, open-label, phase 3b trial

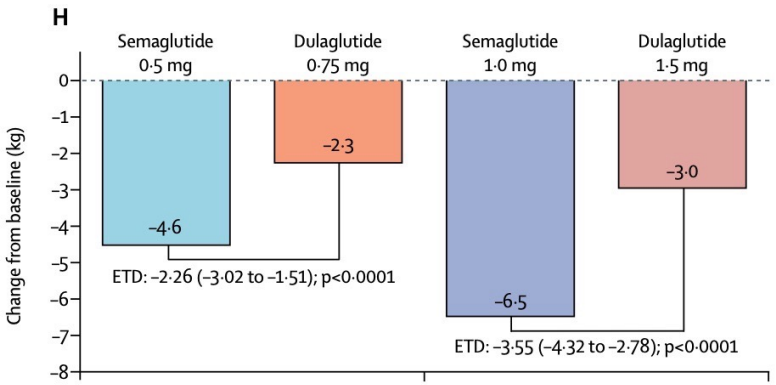
N = 1201; 40 wks
56 yrs. Females: 45 %.

TD duration: 7.4. HbA1c 8.2.
All on metformin

BW: 95. BMI: 34. WC: 111

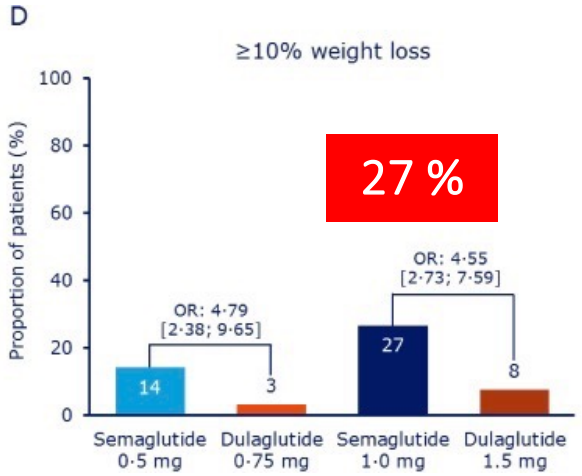


BW Loss (Kg)



-6.5 | -3.0

BW Loss ≥ 10 %.



8 %

Pratley RF et al. Lancet Diabetes Endocrinol 2018; 6:275-286.

Efficacy and safety of a novel dual GIP and GLP-1 receptor agonist tirzepatide in patients with type 2 diabetes (SURPASS-1): a double-blind, randomised, phase 3 trial

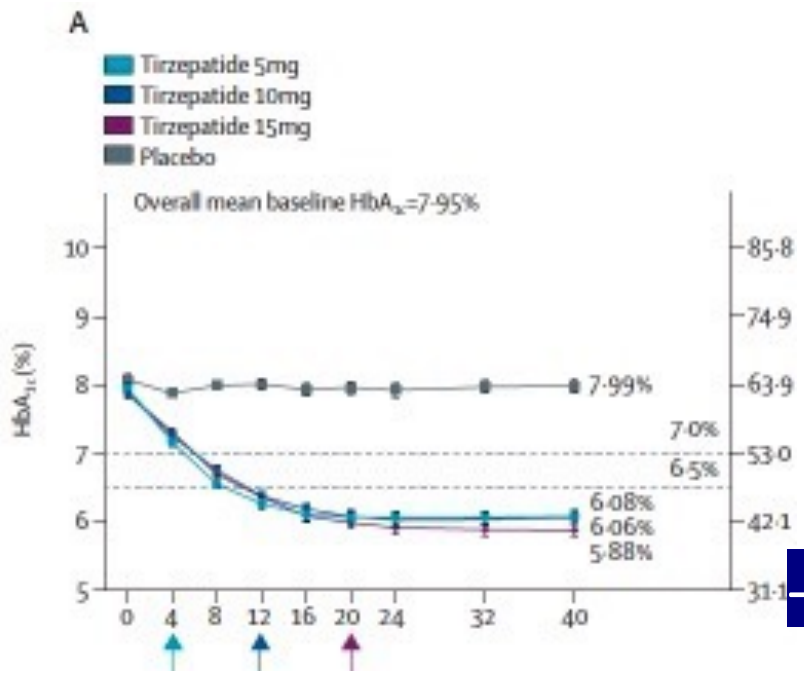
N = 478, 40 wks

54 yrs. Females: 48 %.

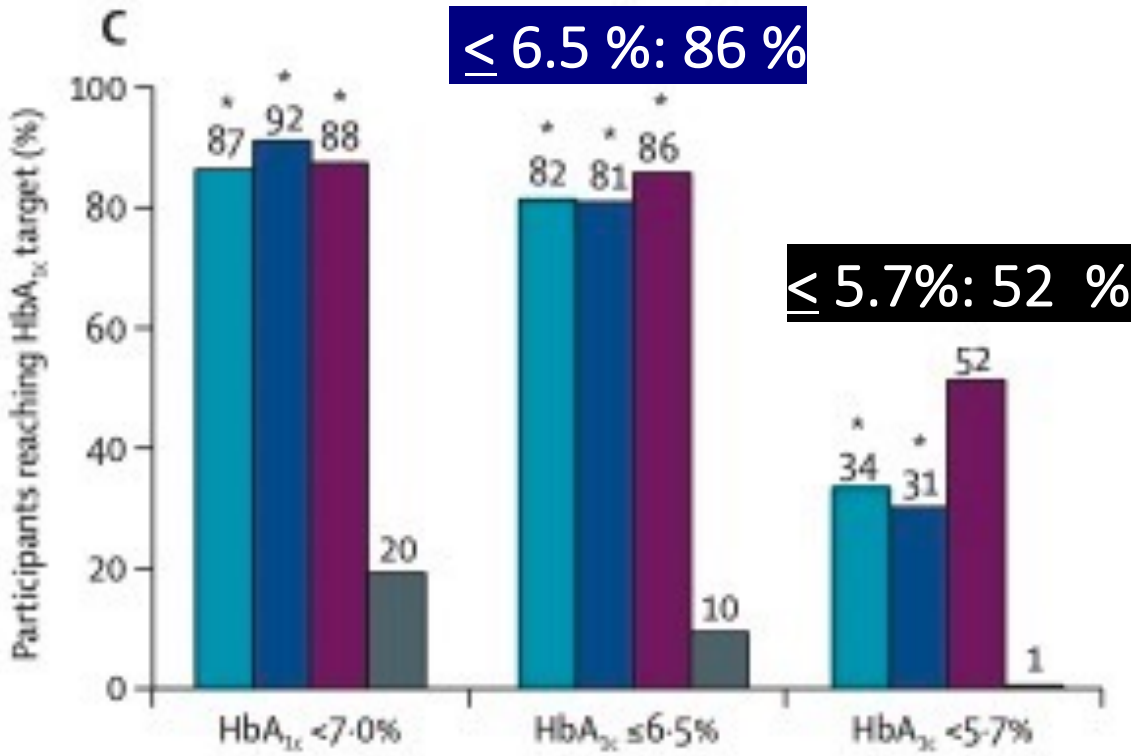
T2D duration: 4.7. HbA1c 7.9. No Insulin

BW: 86. BMI: 32. WC: ?

HbA1 Reducti



- 2.07



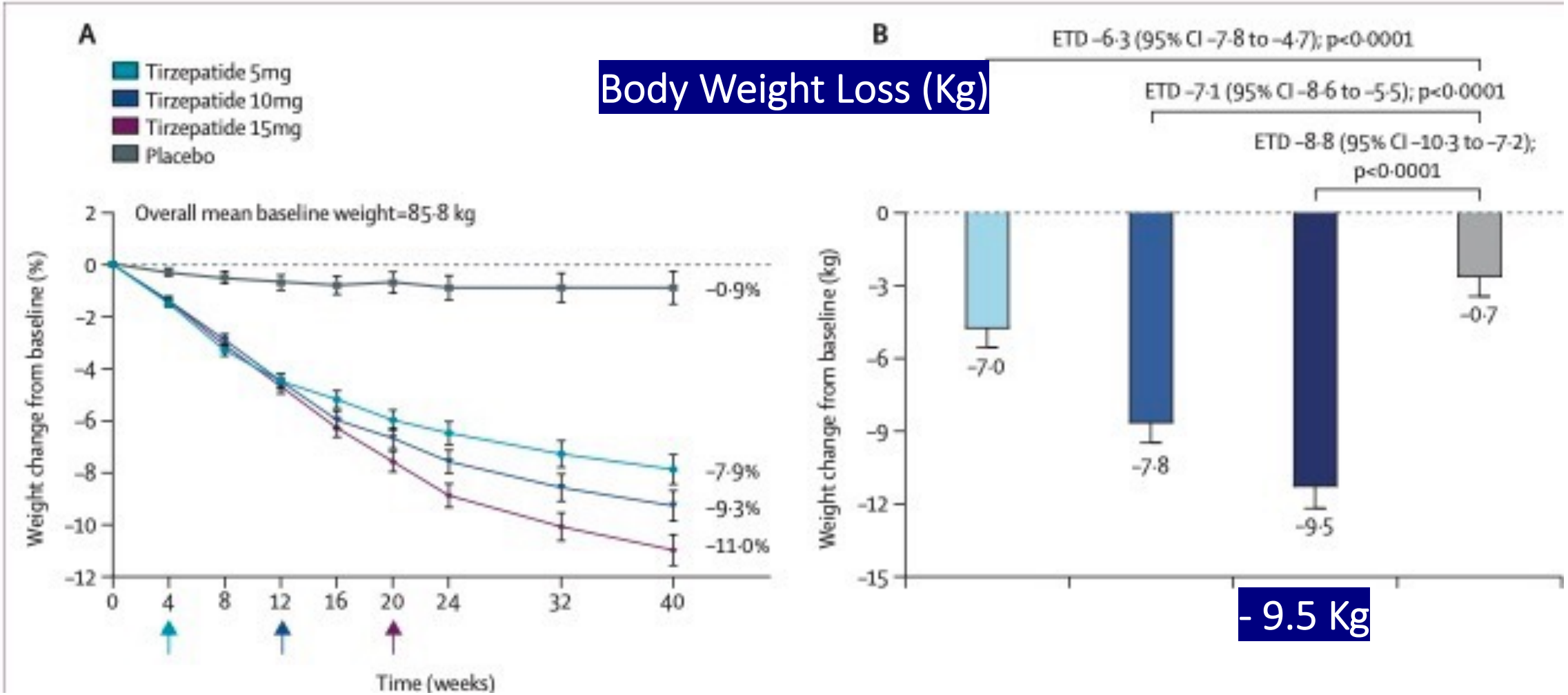
≤ 6.5 %: 86 %

≤ 5.7%: 52 %

RCT, DB (1-1-1-1): T 5- T 10- T 15-P. All: insufficiently controlled with diet and exercise and naïve for diabetes injectable drugs. Primary endpoint: % o change of HbA1c

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

Efficacy and safety of a novel dual GIP and GLP-1 receptor agonist tirzepatide in patients with type 2 diabetes (SURPASS-1): a double-blind, randomised, phase 3 trial



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

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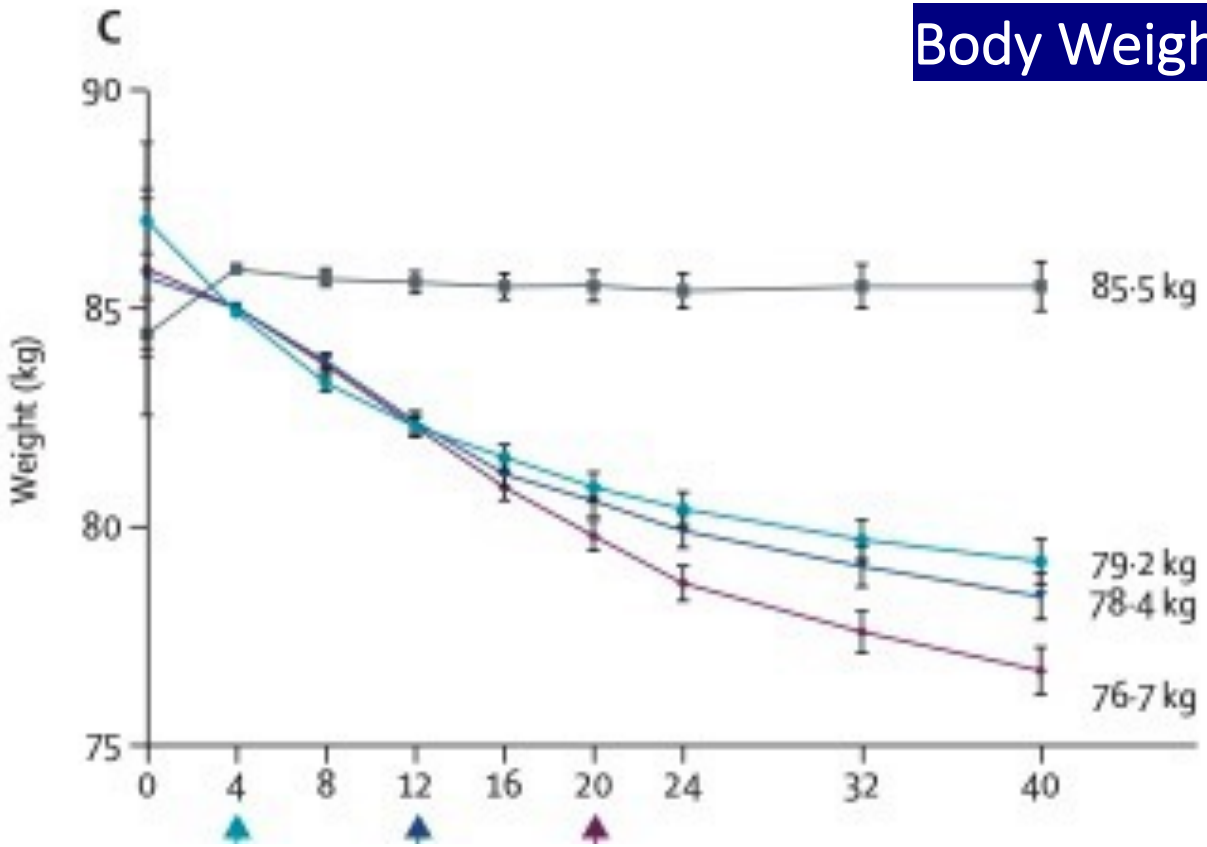
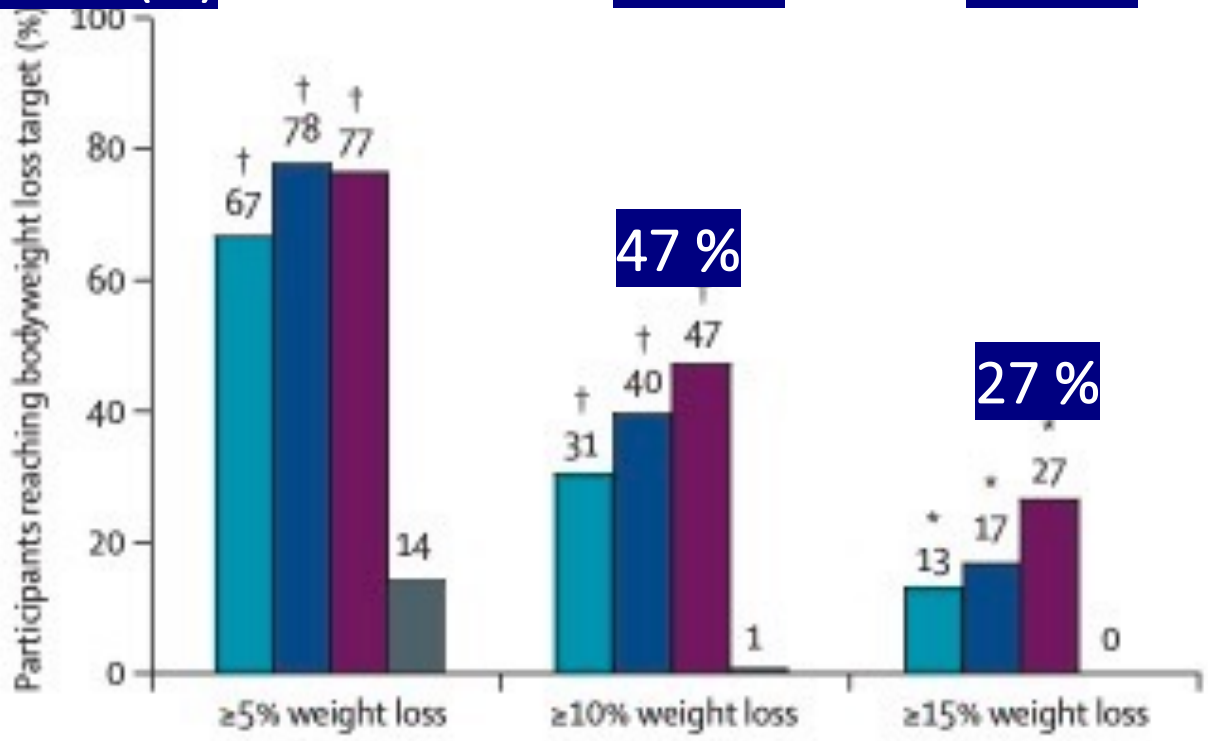


Body Weight Loss (%)

≥ 10 %

≥ 15 %



47 %

27 %

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

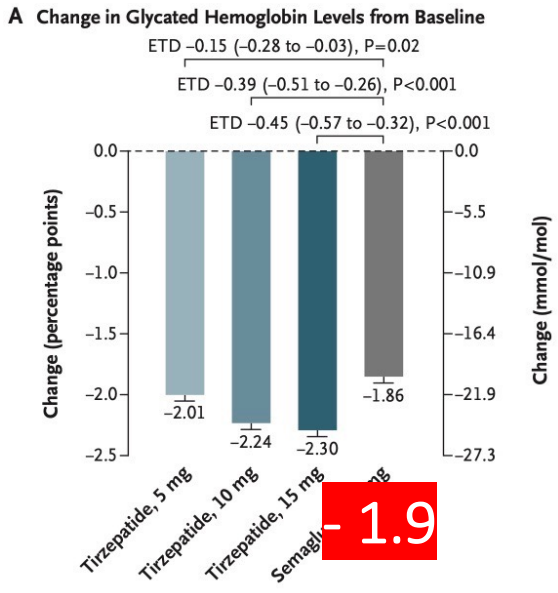
Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes

N = 1878, 40 wks
57 yrs. Females: 53 %.

T2D duration: 8. HbA1c 8.3
Not controlled with metformin

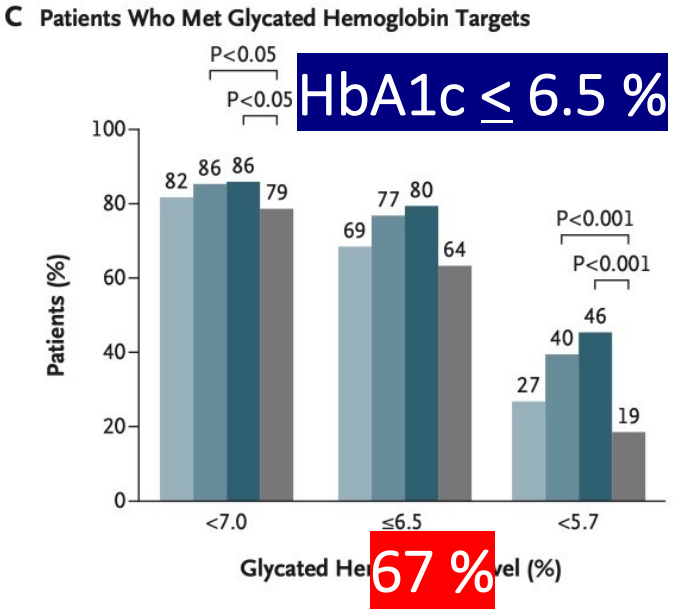
BW: 94. BMI: 34. WC: 109

HbA1c Reduction



- 1.9

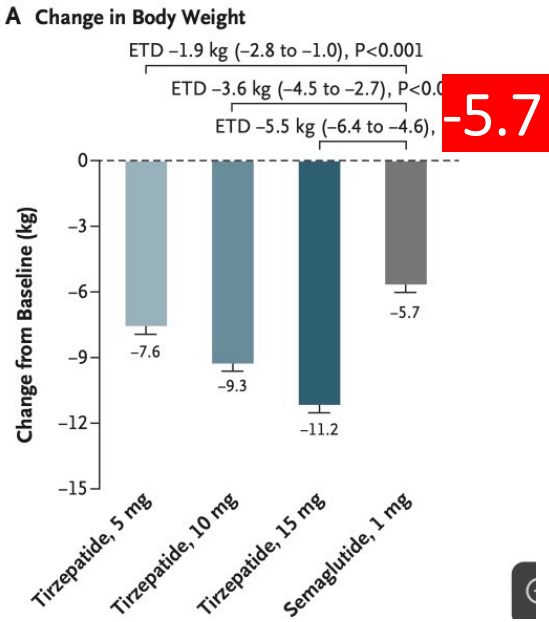
- 2.3



80 %

BW loss (Kg).

-11.2 Kg



-5.7 Kg

RCT, OL (1-1-1-1): T 5-T 10-T 15-S 1.0. Primary outcome: change in HbA1c

AE leading to discontinuation:
6.0%-8 pep.5%-8.5%-4.1%

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

2021

Efficacy and safety of once-weekly semaglutide 2·0 mg versus 1·0 mg in patients with type 2 diabetes (SUSTAIN FORTE): a double-blind, randomised, phase 3B trial

Frias JP et al. Lancet Diabetes Endocrinol 2021;9:563-574

Semaglutide 2·4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial

Davies M et al. Lancet 2021; 397:971-984.

Safety, tolerability, pharmacokinetics, and pharmacodynamics of concomitant administration of multiple doses of cagrilintide with semaglutide 2·4 mg for weight management: a randomised, controlled, phase 1b trial

Enebo LB et al. Lancet. 2021;;397:1736-1748

Efficacy and Safety of Dulaglutide 3.0 mg and 4.5 mg Versus Dulaglutide 1.5 mg in Metformin-Treated Patients With Type 2 Diabetes in a Randomized Controlled Trial (AWARD-11)

Juan P. Frias,[1] Enzo Bonora,[2] Luis Nevarez Ruiz,[3] Ying G. Li,[4] Zhuoxin Yu, Zvonko Milicevic,[4] Raleigh Malik,[4] M. Angelyn Bethel,[4] and David A. Cox[4]

Frias JP et al. Diabetes Care. 2021; 44:765–773

Medications for T2D Remission: Five Questions to be Answered

1 Definition

2 Therapies

3 Pathophysiology

4 Medications

5 Implications

Looking beyond T2D Remission

Rethinking Diabetes Care

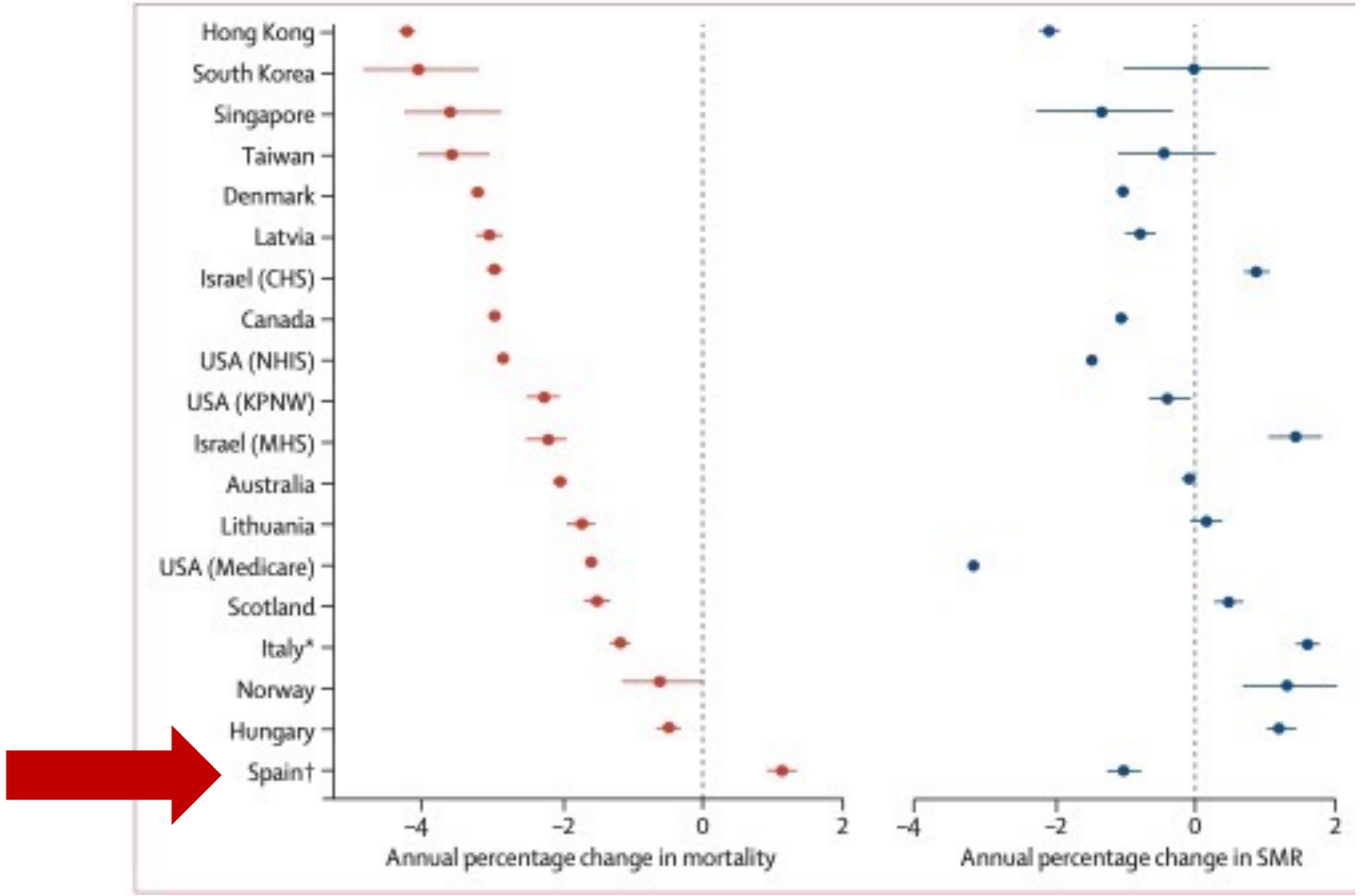
Improving Other Adiposopathies

Promoting Healthy Aging

Looking beyond T2D Remission

Rethinking
Diabetes Care

Trends in all-cause mortality among people with diagnosed diabetes in high-income settings: a multicountry analysis of aggregate data



”For instance, in Catalonia, Spain, mortality in people with diabetes increased from approximat 2012 to 2016; however, mortality increased more rapidly in populations without diabetes (in both Catalonia and Spain).”

Source: Information System for the Development of Research in Primary Care [SIDIAP]

T2D diagnosis: ICD-10.

Risk of bias (from 0 to 9): 6 (high-medium).

*The standardized mortality rate (SMR) is the ratio of the number of deaths observed in a population over a given period to the number that would be expected over the same period if the study population had the same age-specific rates as the standard population (SMR=(Observed Deaths / Expected Deaths).

Magliano DJ et al. Lancet Diabetes Endocrinol 2022;10:112-119

T2D: Current Management

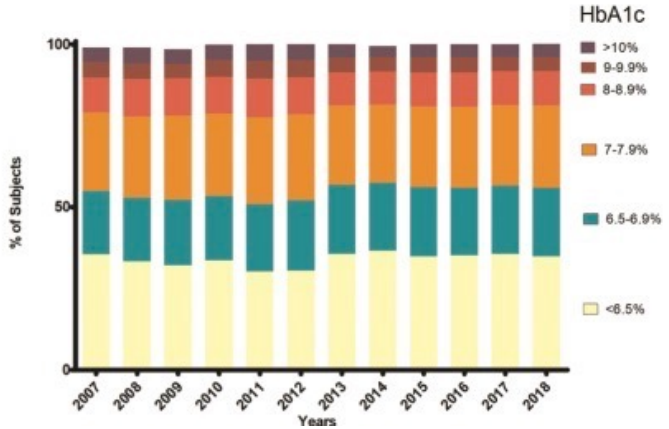
Prevention Failure

Diagnosis: Trivialized and late

Escalation Therapy,,Weight gain, chronic complications, increasing costs

T2D

Stakeholders' Inertia (Primary and Specialized Care, Patients, Caregivers)

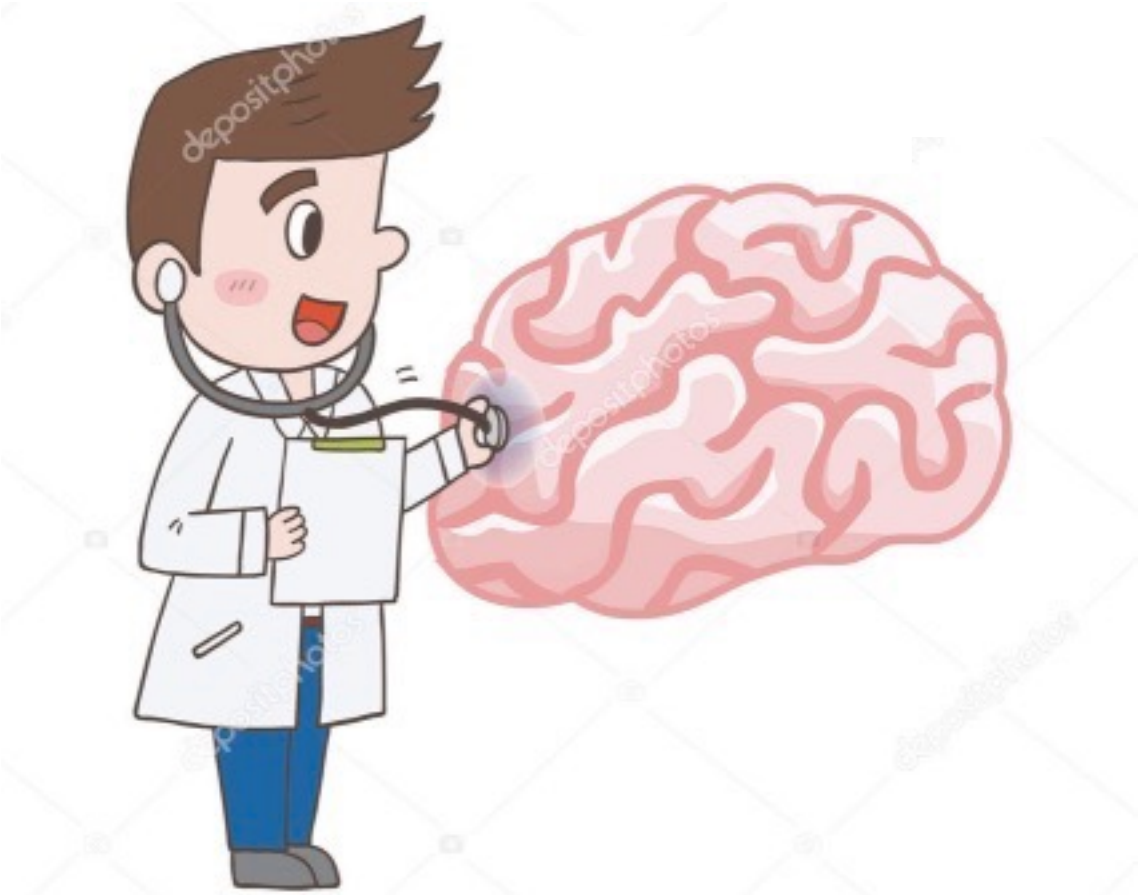


No improvement in HbA1c (2007-2018)*
Weight loss is not an objective

Mata-Cases M er al. Front Endocinol 202210;12:8

The doctor’s brain legacy effect

“Insanity is doing the same thing over and over and expecting different results”.
A. Einstein



T2D: Current Management

Prevention Failure

Diagnosis: Trivialized and late

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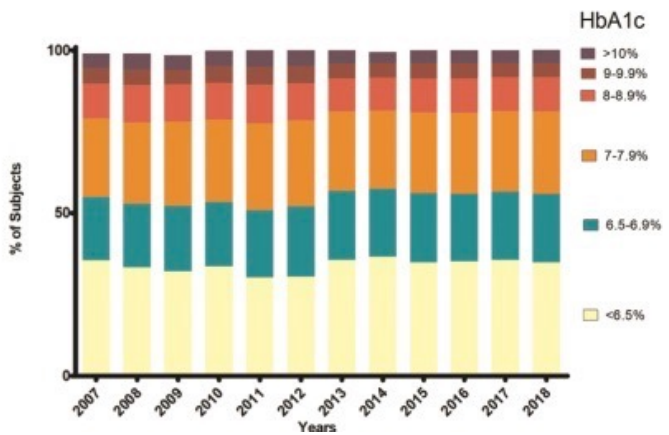
T2D

Stakeholders' Inertia (Primary and Specialized Care, Patients, Caregivers)

Remission



No improvement in HbA1c (2007-2018)*

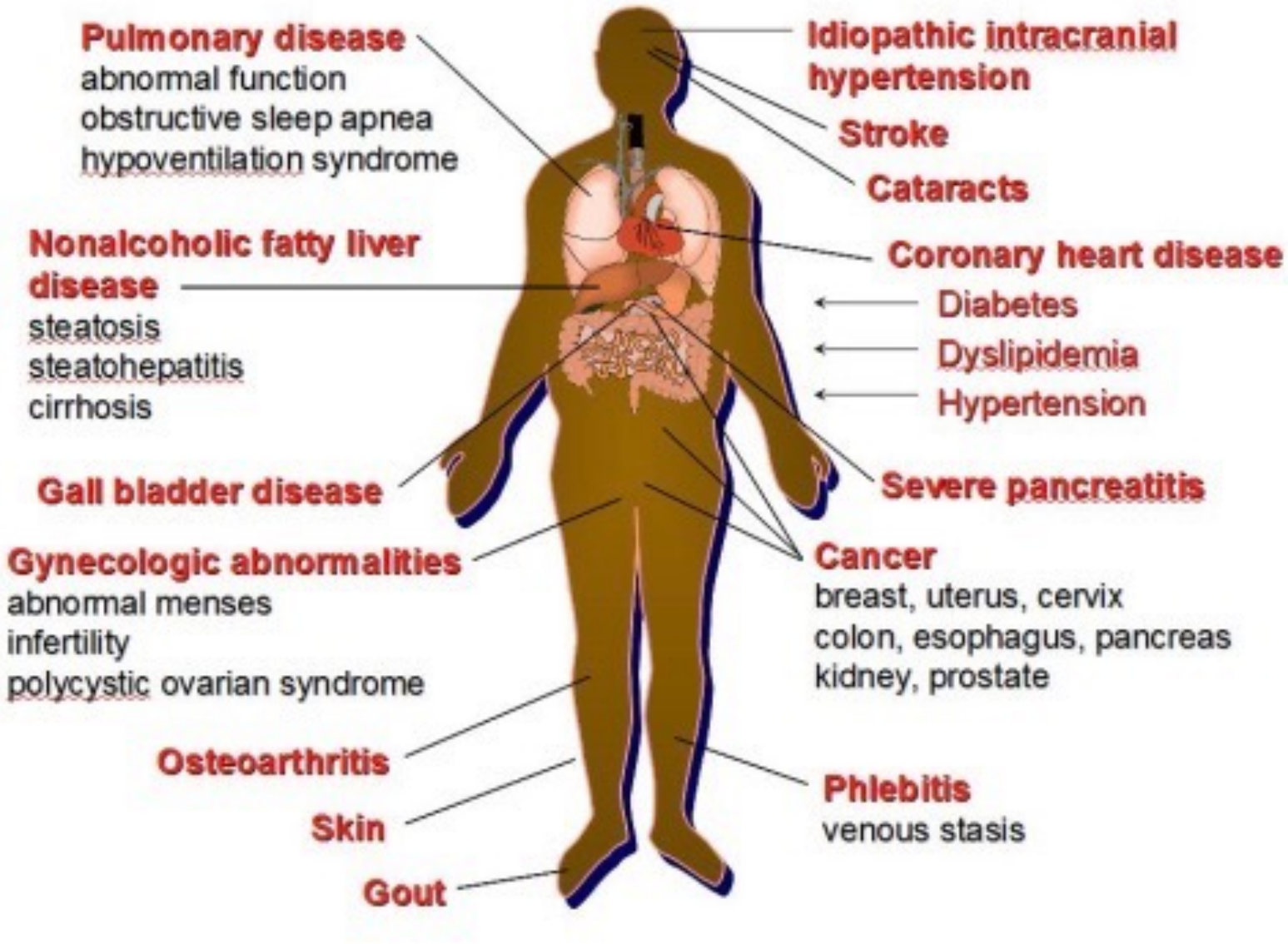
Weight loss is not an objective

Mata-Cases M er al. Front Endocinol 202210;12:8

Looking beyond T2D Remission

Improving Other
Adiposopathies

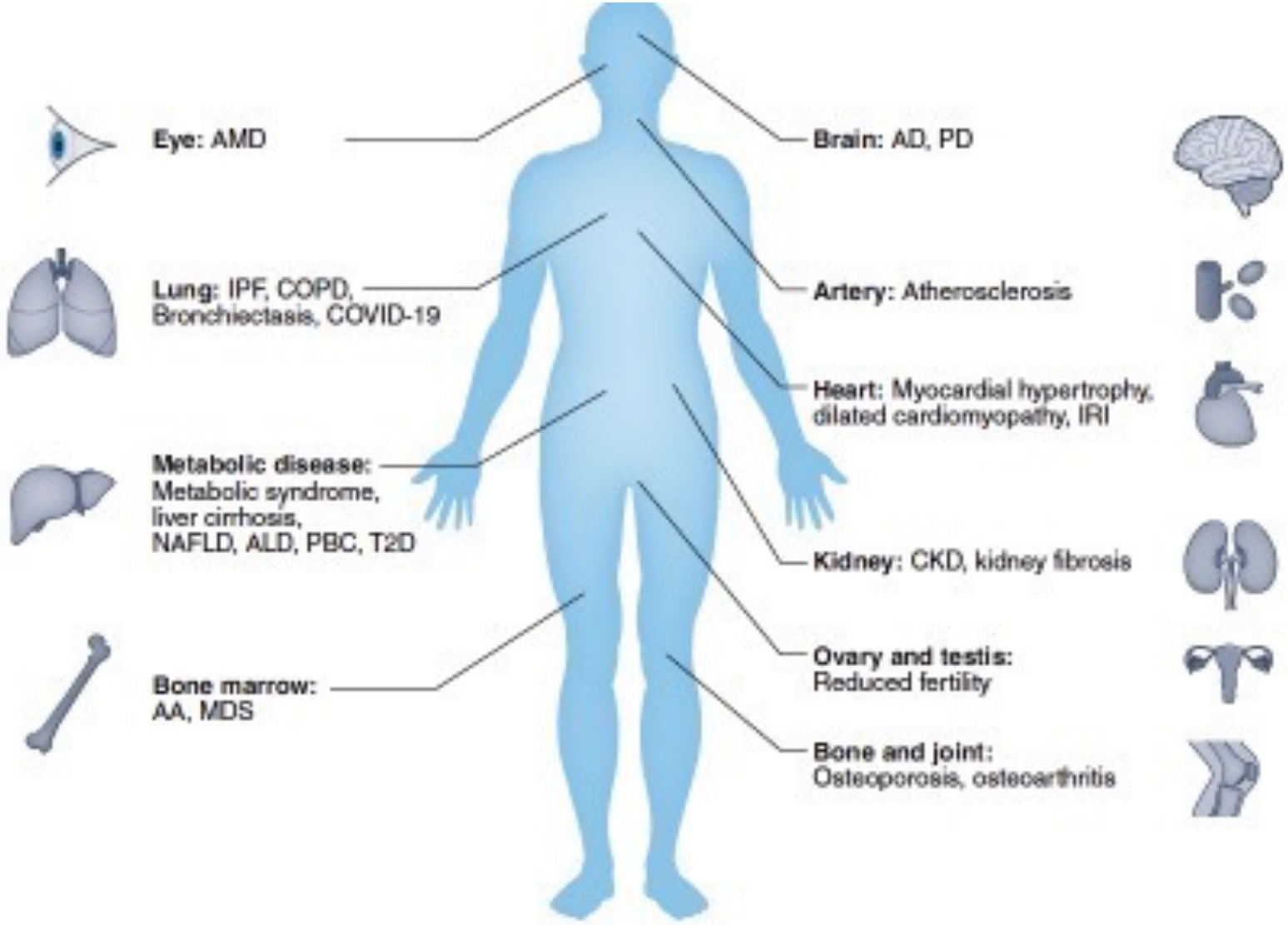
Adiposopathies



Looking beyond T2D Remission

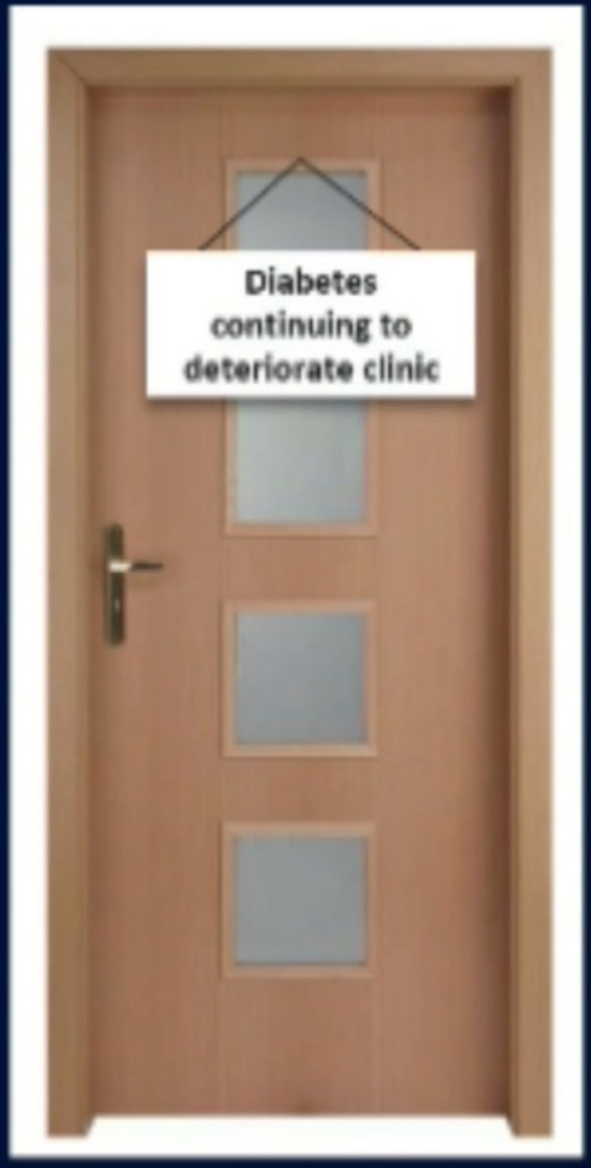
Promoting
Healthy Aging

Age-Related Conditions



Some Answers, but Many Remaining Questions

1. T2D Remission: Criteria: HbA1c < 6.5 % -– 3 mo..
2. The Most Long-Term Effective Intervention for T2D Remission is Bariatric Surgery
3. Significant Weight Loss is Critical for T2D Remission
4. New Weight-Lowering Drugs for T2D show promise for achieving T2D Remission (Less Weight Required ?)
5. T2D Remission as a Therapeutic Target might Impact on Diabetes Care Other Adiposopathies and Healthy Aging



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