REVIEWS AND NOVEL CLINICAL PERSPECTIVES OF A GLP-1RA WITH UNPRECEDENTED GLUCOSE & WEIGHT CONTROL FOR T2DM

Once-weekly semaglutide (Ozempic)

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處方藥物請參考衛生福利部核准之仿單

Clinical Application of Incretin-Based Therapy: Therapeutic Potential, Patient Selection and Clinical Use

缺乏 GLP-1 (腸促胰素 Incretin的一種)是造成糖尿病前期,及第二型糖尿病病患的胰島素阻抗性增加, 食慾增加, 體重增加, 血糖升高,及動脈硬化 的主要因素之一！

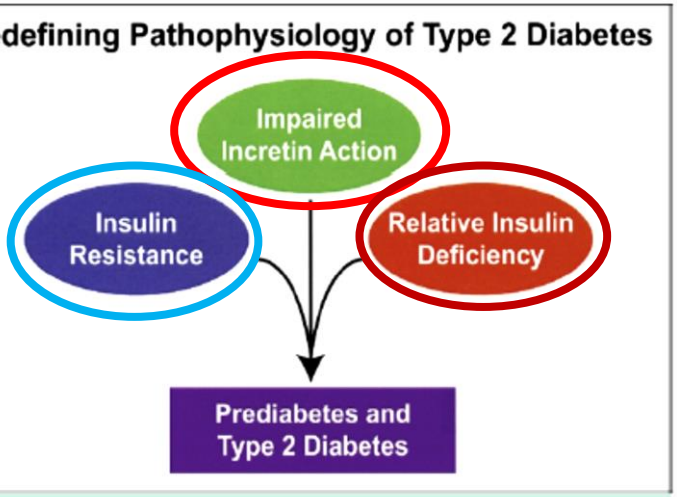


Figure 1 Postulated role of insulin resistance, β-cell dysfunction, and an impaired incretin effect in the pathogenesis of type 2 diabetes mellitus. (Adapted from *J Clin Endocrinol Metab*,[23] *Diabetes*,[24,27] *Eur J Clin Endocrinol*,[25] and *J Clin Invest*.[26])

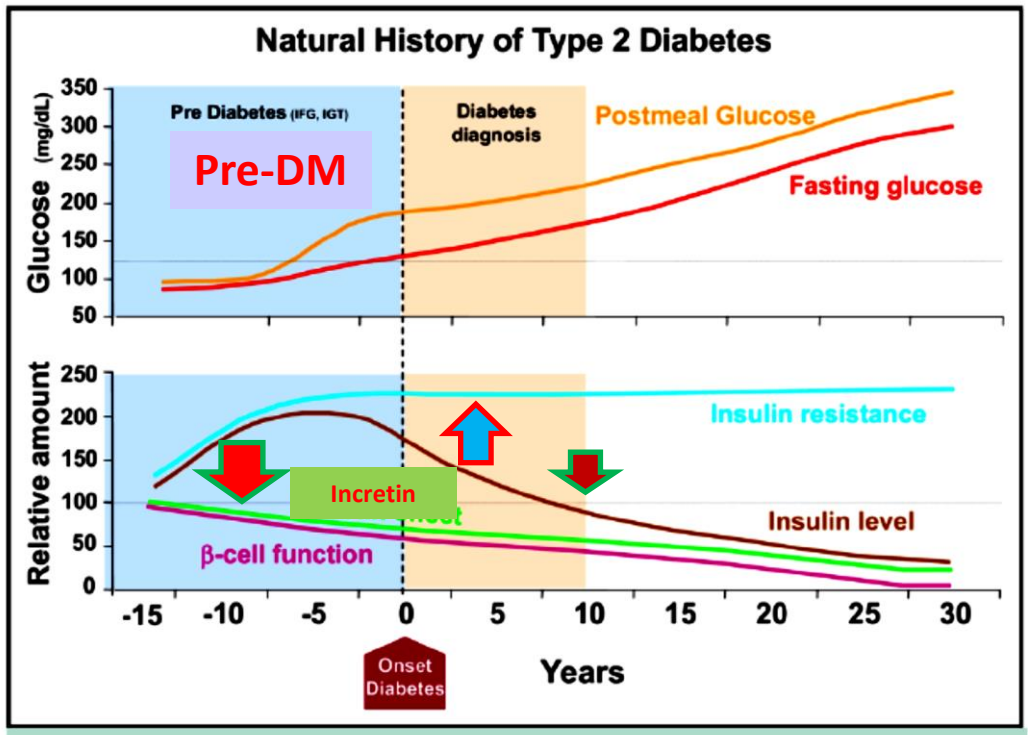


Figure 2 Representative depiction of the natural history of type 2 diabetes mellitus highlighting the role of insulin resistance, insulin deficiency, and impaired incretin effect. Both the time course and relative function are descriptive. These 3 core pathophysiologic defects likely combine to contribute to the progressive nature of the disease, and may account for much of the deterioration in glucose control observed clinical in patients with type 2 diabetes. IFG = impaired fasting glucose; IGT = impaired glucose tolerance. For glucose, 1 mg/dL = 0.5551 mmol/L. (Courtesy of the International Diabetes Center © 2008.)

David M. Kendall et al. The American Journal of Medicine 2009 (122): S37–S50.

Clinical Application of Incretin-Based Therapy: Therapeutic Potential, Patient Selection and Clinical Use

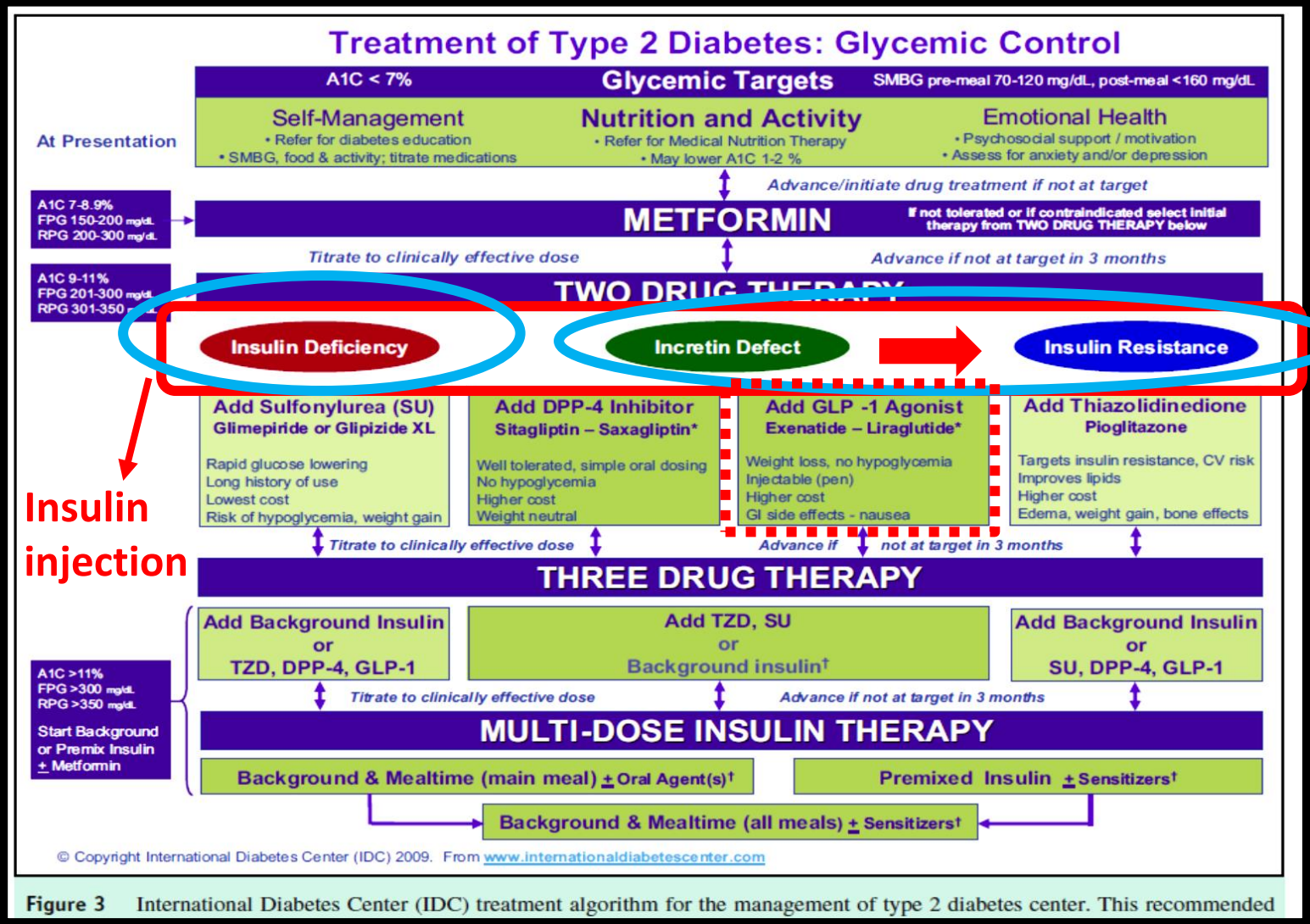


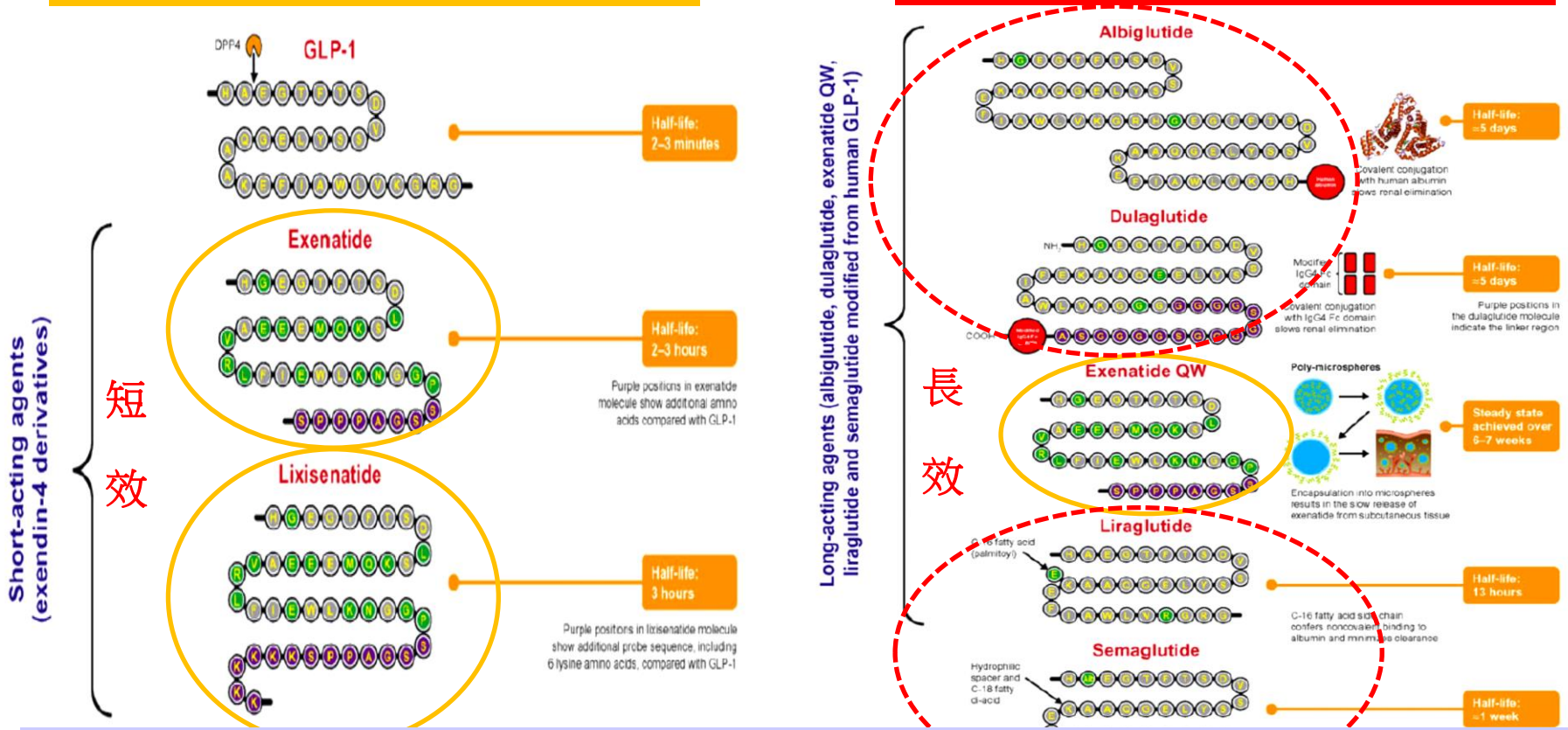
Figure 3 International Diabetes Center (IDC) treatment algorithm for the management of type 2 diabetes center. This recommended

David M. Kendall et al. The American Journal of Medicine 2009 (122): S37–S50.

Glucagon-like peptide-1 receptor agonists in type 2 diabetes treatment: are they all the same?

xenatide (exendin-4 derivatives)

glutide (modified human GLP-1)

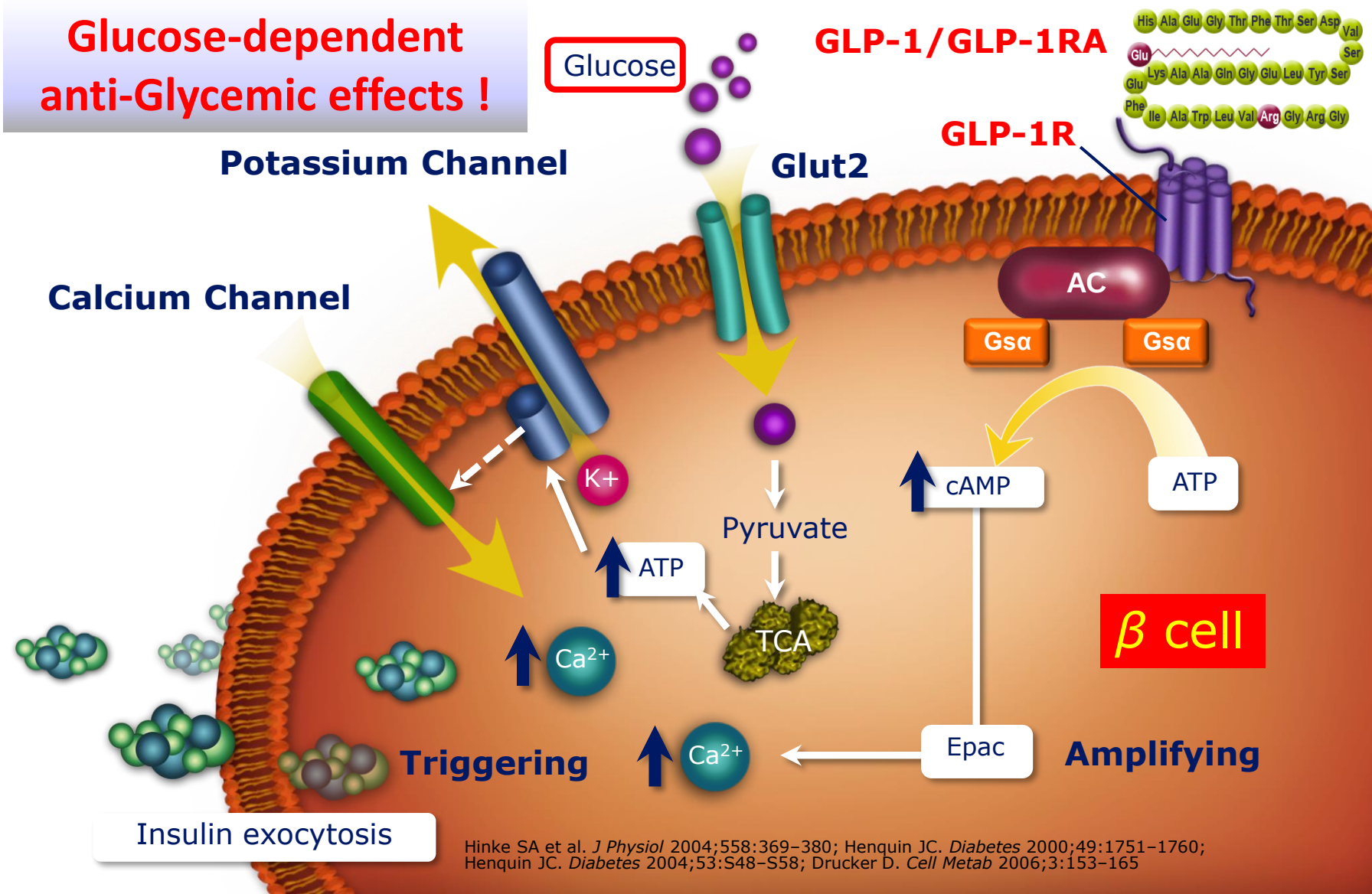


The European Medicines Agency (EMA) has approved the use of all commercially available human GLP-1 analogs up to eGFR of 15 mL/min/1.73 m2, while all exendin-4 analogs are contraindicated below 30 mL/min/1.73 m2, given the risk of accumulation and toxicity.

Raffaella Gentilella et al. Diabetes Metab Res Rev. 2019;35:e3070.

Anti-Glycemic Effects of GLP-1 RA in Type 2 DM

GLP-1/GLP-1 RA action in the β cell via GLP-1R

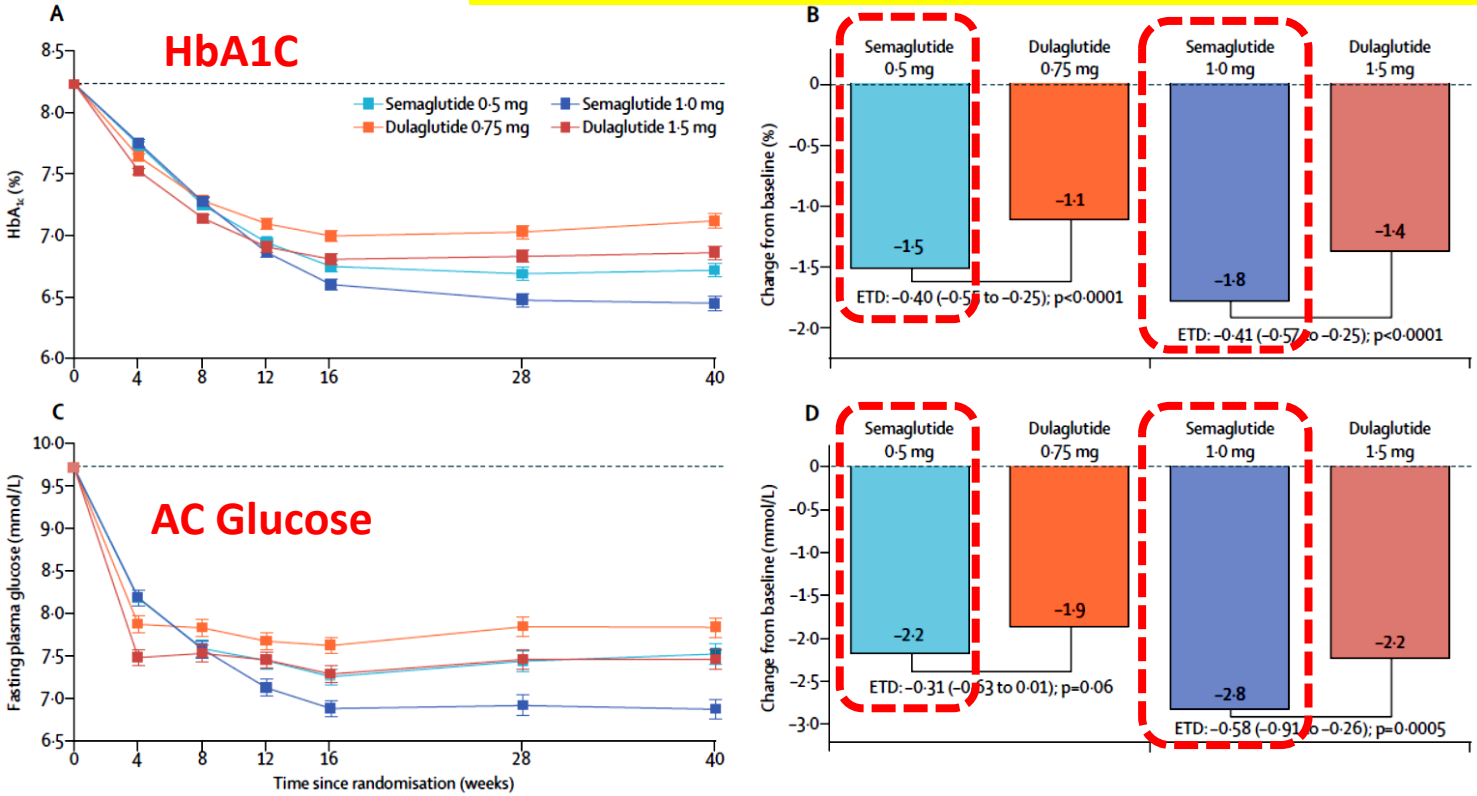


Hinke SA et al. *J Physiol* 2004;558:369–380; Henquin JC. *Diabetes* 2000;49:1751–1760; Henquin JC. *Diabetes* 2004;53:S48–S58; Drucker D. *Cell Metab* 2006;3:153–165

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

Between Jan 6, 2016, and June 22, 2016, 1201 patients were randomly assigned to treatment; of these, 301 were exposed to semaglutide 0·5 mg, 299 to dulaglutide 0·75 mg, 300 to semaglutide 1·0 mg, and 299 to dulaglutide 1·5 mg. The primary endpoint was change from baseline in percentage HbA1c; the confirmatory secondary endpoint was change in bodyweight, both at week 40.

Anti-hyperglycemic effects: semaglutide > dulaglutide



Pratley RE et al. Lancet Diabetes Endocrinol 2018 Apr;6(4):275-286.

Non-Glycemic Effects of

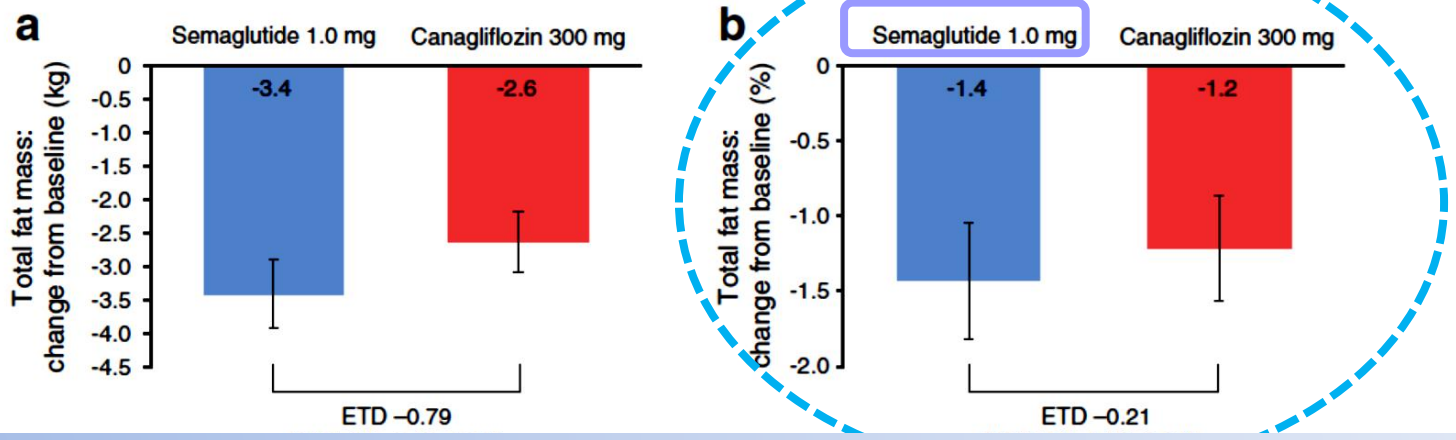
GLP-1 RA

Non-Glycemic Effects of GLP-1 RA

- 抑制食慾, 管控熱量攝取
- 燃(減)脂, 減重
- 抗發炎, 抗過氧化傷害
- 降低胰島素阻抗性, 提升貝它細胞功能與存活
- 排尿鈉, 舒張血管, 降血壓
- 阻止動脈粥狀硬化, 降蛋白尿, 保護心腎功能
- 對抗老年失智及巴金森氏症 (發展中)
- 治療脂肪肝(發展中)

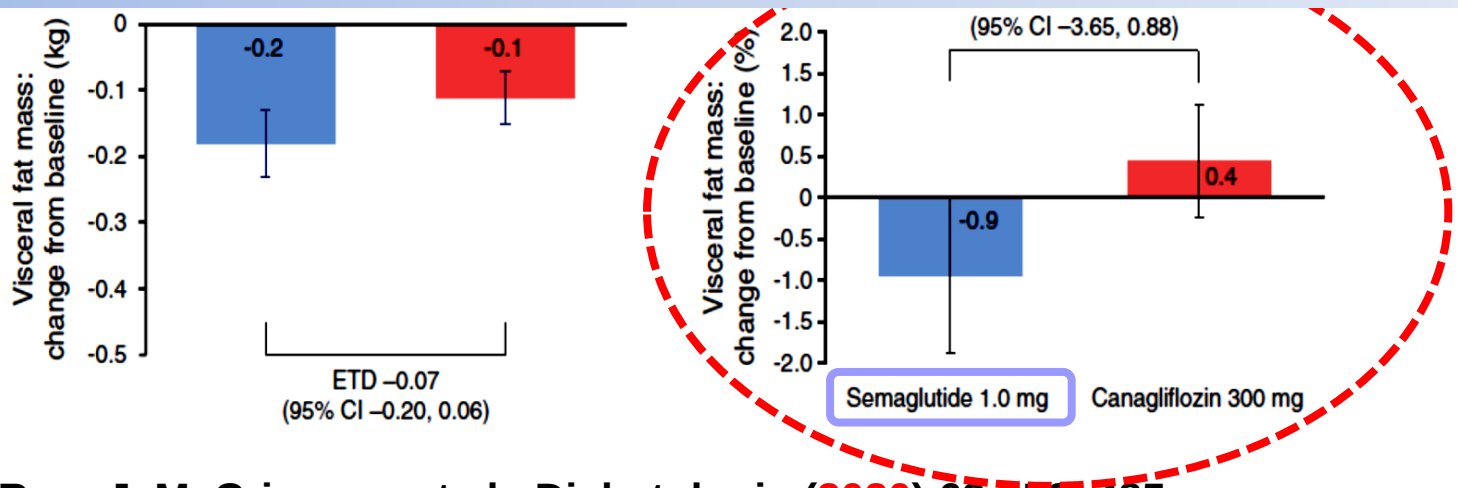
Effects of once-weekly semaglutide vs once-daily canagliflozin on body composition in type 2 diabetes: a substudy of the SUSTAIN 8 randomised controlled clinical trial

Total fat mass



Semaglutide can reduce both total and visceral fat mass !

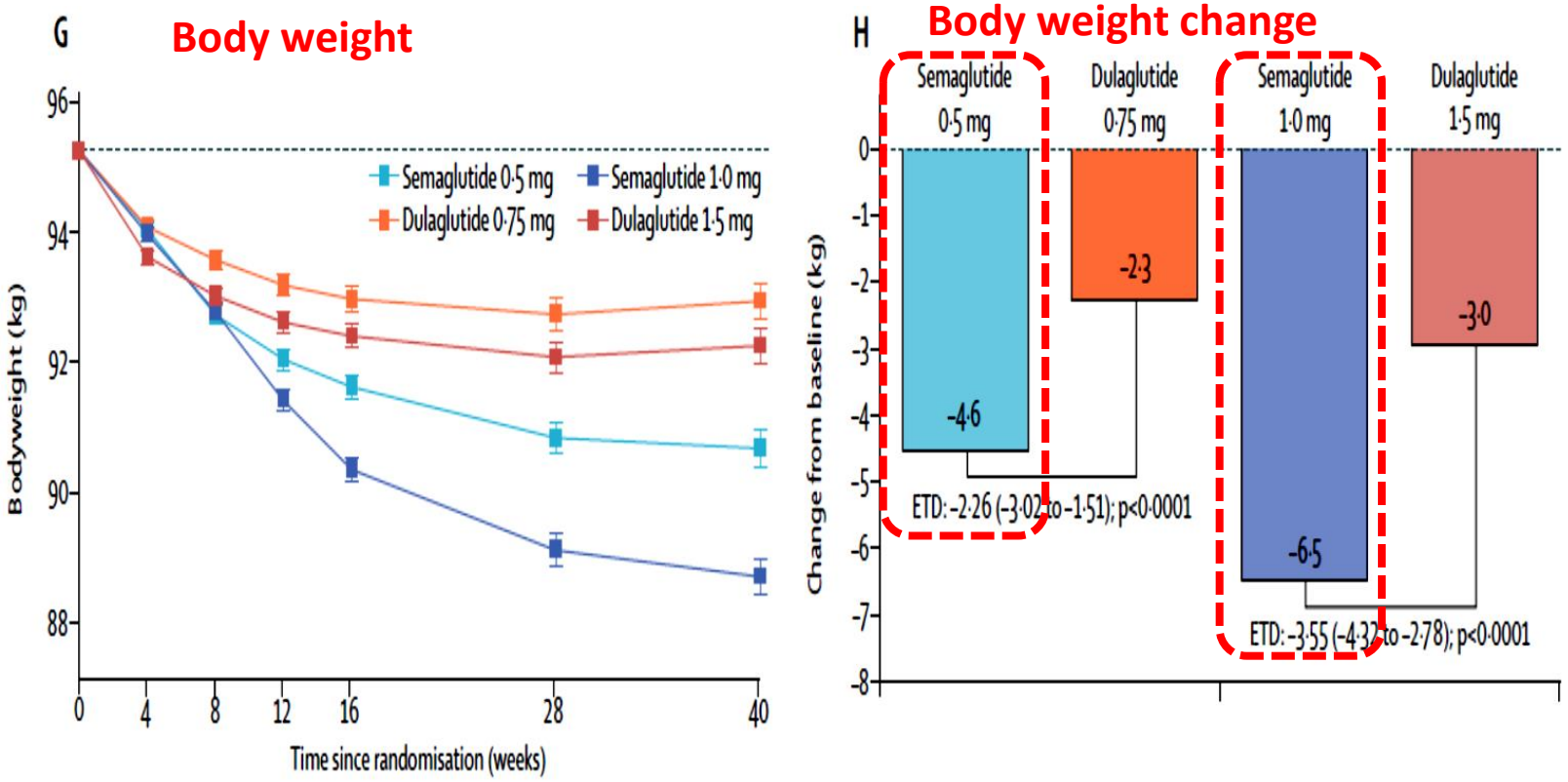
Visceral fat mass



Rory J. McCrimmon et al. Diabetologia (2020) 63:473–485.

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

At low and high doses, semaglutide was superior to dulaglutide in improving glycaemic control and reducing bodyweight, enabling a significantly greater number of patients with type 2 diabetes to achieve clinically meaningful glycaemic targets and weight loss, with a similar safety profile.



Pratley RE et al. Lancet Diabetes Endocrinol. 2018 Apr;6(4):275-286.

Treatment with GLP1 receptor agonists reduce serum CRP concentrations in patients with type 2 diabetes mellitus: A systematic review and meta-analysis of randomized controlled trials

Serum CRP

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
A. Faurschou	-0.006	0.449	0.202	-0.887	0.875	-0.013	0.99
Aaron S Kelly	0.000	0.283	0.080	-0.554	0.554	0.000	1.000
G. Derosa	-3.333	0.287	0.082	-3.896	-2.771	-11.613	0.000
Hui Fan	-0.499	0.190	0.036	-0.872	-0.126	-2.622	0.009
Jin-dan Wu	-2.837	0.591	0.349	-3.995	-1.678	-4.800	0.000
MATHIJS C. BUNCK	-2.000	0.319	0.102	-2.625	-1.375	-6.27	0.000
Ziwen Liang	-6.743	0.618	0.382	-7.954	-5.531	-10.910	0.000
	-2.148	0.696	0.484	-3.512	-0.784	-3.086	0.002

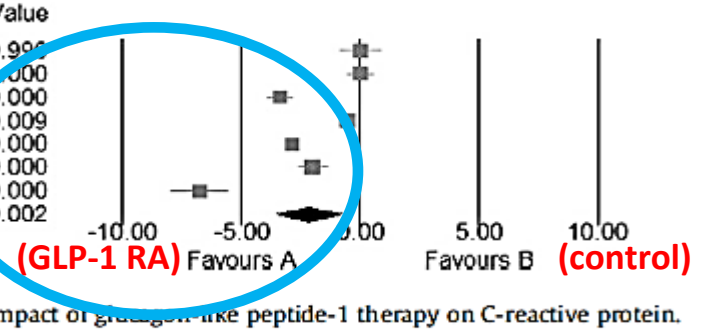


Fig. 1. Plot to display weighted mean difference and 95% confidence intervals for the impact of glucagon-like peptide-1 therapy on C-reactive protein.

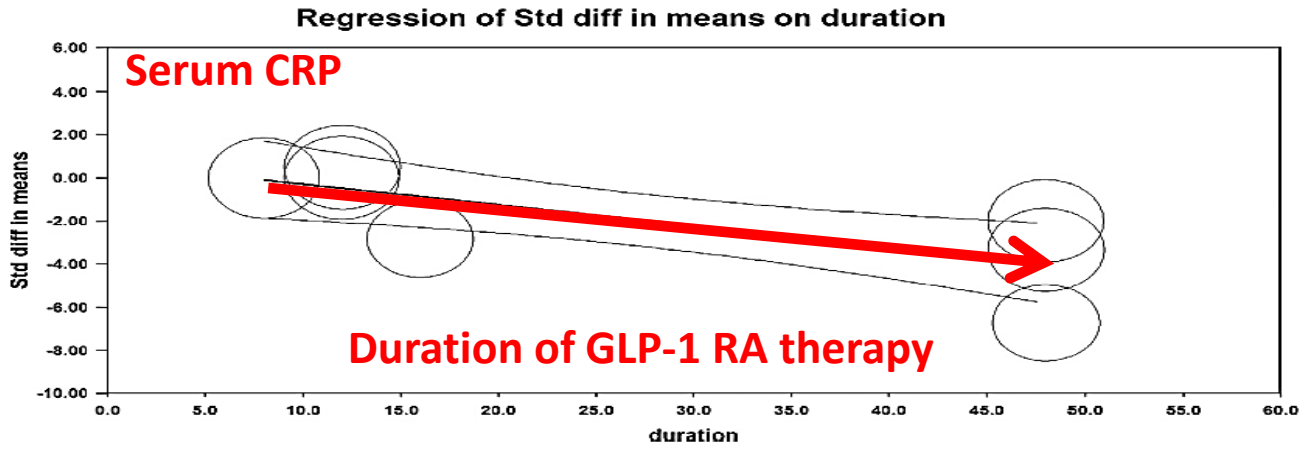
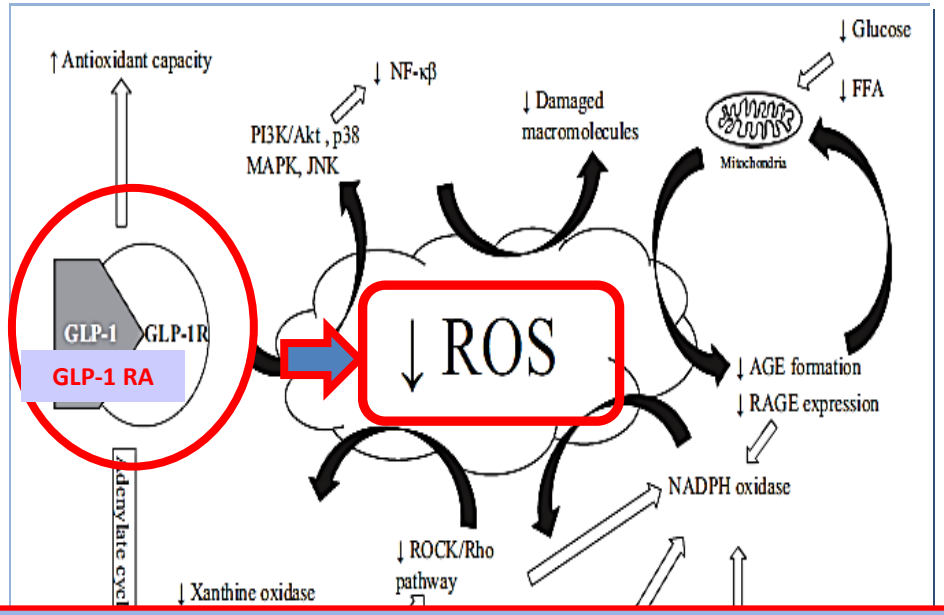


Fig. 2. Meta regression for the association between duration of glucagon-like peptide-1 therapy and standards difference of C-reactive protein.

Mohsen Mazidi et al. . Journal of Diabetes And Its Complications 2017;31(7):1237-1242.

Does Glucagon-like Peptide-1 Ameliorate Oxidative Stress in Diabetes? Evidence Based on Experimental and Clinical Studies



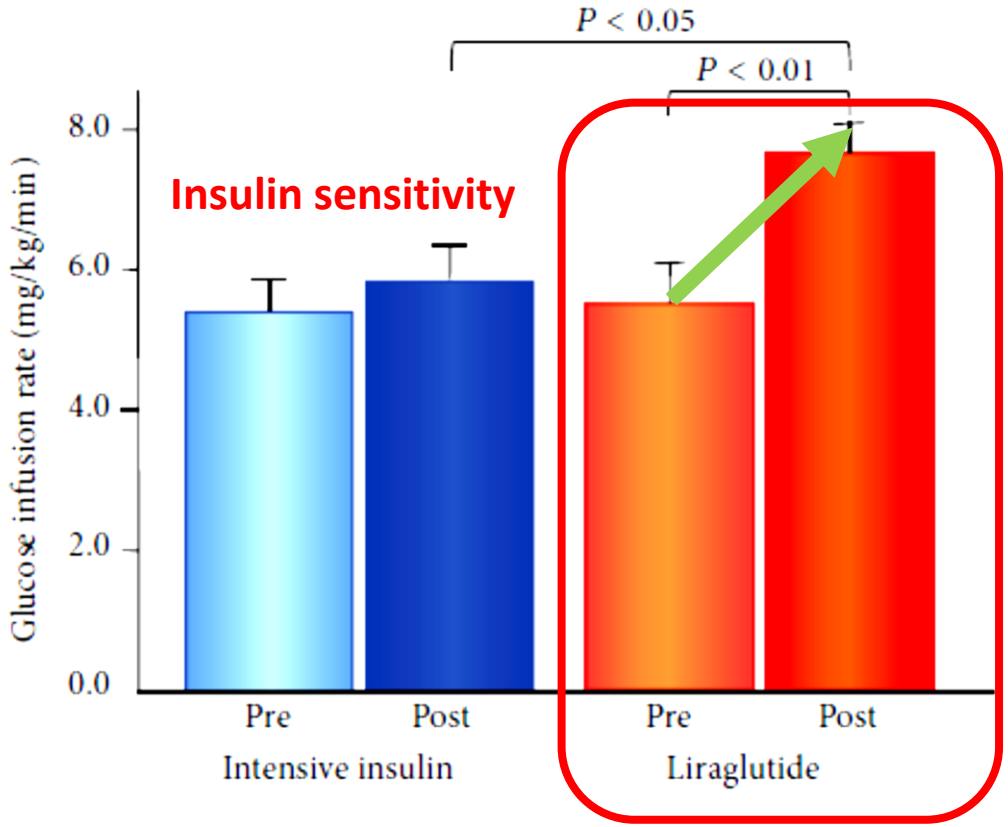
Duration of treatment	Study Design: Subjects (S), Intervention (I) and Treatment Duration (TD)	End point: Effect of GLP-1 Intervention on Oxidative Stress Markers (Compared to control Unless Otherwise Stated)	Comments
	S: T2D (n=23) on metformin and/or sulfonylurea. I: Exenatide (5 μg for 4 weeks then 10 μg twice daily). TD: 5 months.	GLP-1 interventions on Oxidative Stress markers Plasma: ↓ 8-iso-$PGF_{2\alpha}$ ($p<0.05$).	Covariance analysis indicated glucose independent effect on 8-iso-$PGF_{2\alpha}$ levels that was independent of HbA1c, mean SD, body weight, and BMI. [75]
	S: T2D (n=65) (58.7±10.2 years) no more than 15 years of disease duration. n=32 on sulfonylurea. I: Liraglutide (started at 0.3 mg/day then 0.6-0.9 mg/day (mean dose 0.74 mg/day). TD: 8 months.	Blood: ↓ d-ROMs ($p<0.05$) (compared to baseline). No change in MDA.	Decreased HbA1c and blood glucose when compared to baseline ($p<0.01$). No effect on body weight [176].
> 6 months		Plasma:	Decrease in blood glucose ($p<0.001$) and triglycerides ($p<0.05$) both compared to baseline and

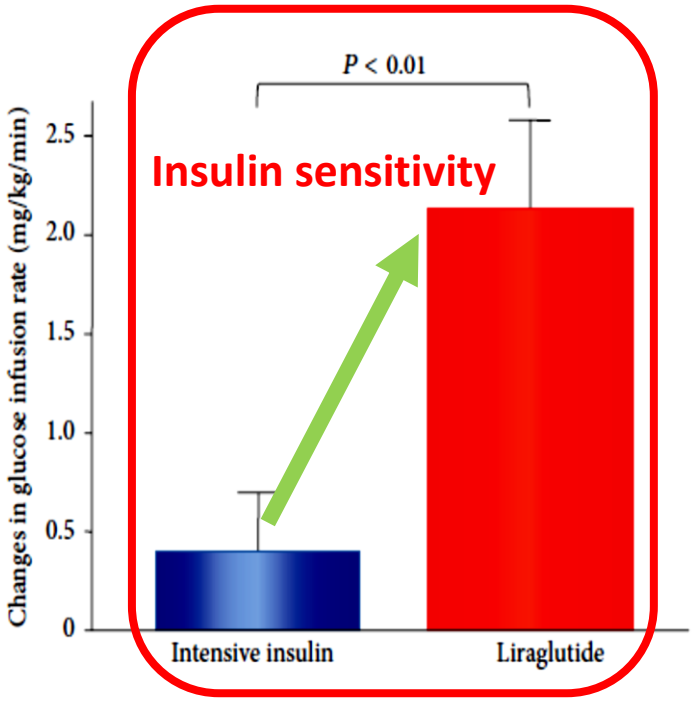
- **Collectively, the available data demonstrates that GLP-1 can decrease OS but also that this effect is dependent on dose, diabetic status, obesity etc.**
- **This effect of GLP-1 may have therapeutic potential if OS is in fact causally related to the development of late-onset diabetic complications.**

Karen Ekkelund Petersen et al. Current Diabetes Reviews, 2016, 12, 331-358

Liraglutide, a Glucagon-Like Peptide-1 Analog, Increased Insulin Sensitivity Assessed by Hyperinsulinemic-Euglycemic Clamp Examination in Patients with Uncontrolled Type 2 Diabetes Mellitus

GLP-1 RA 的主要治療機轉之一, 是經由減重及抗發炎作用來改善胰島素的阻抗性 (比密集注射胰島素還強), 讓胰島素不需那麼大量就能有效用！





4 weeks post treatment

Hideaki Jinnouchi et al. Journal of Diabetes Research Volume 2015, Article ID 706416, 8 pages

Effects of semaglutide on beta cell function and glycaemic control in participants with type 2 diabetes: a randomised, double-blind, placebo-controlled trial

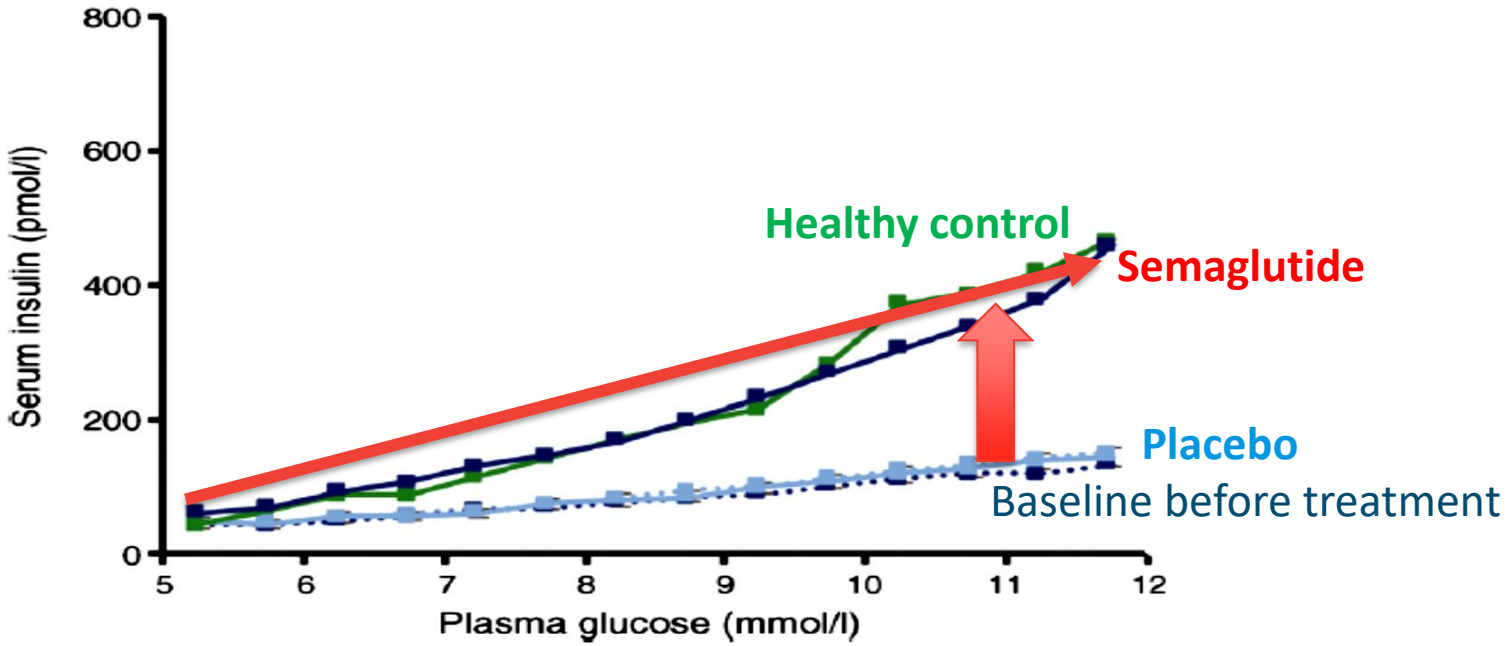
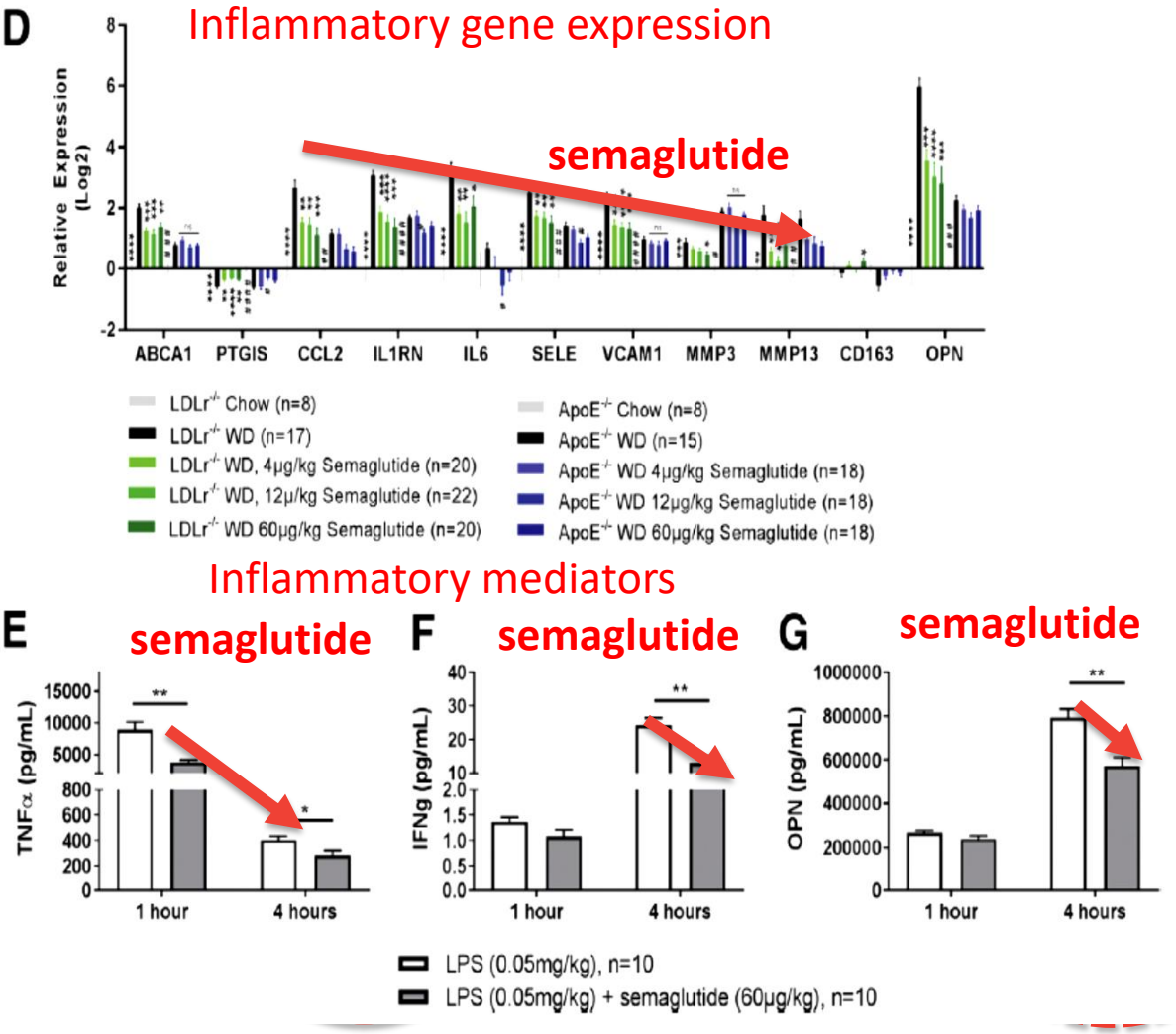


Fig. 6 Insulin response to a graded glucose infusion in participants with type 2 diabetes before and after receiving 12 weeks of treatment with

Conclusions/interpretation: Twelve weeks of once-weekly treatment with semaglutide significantly improved beta cell function and glycaemic control in participants with type 2 diabetes.

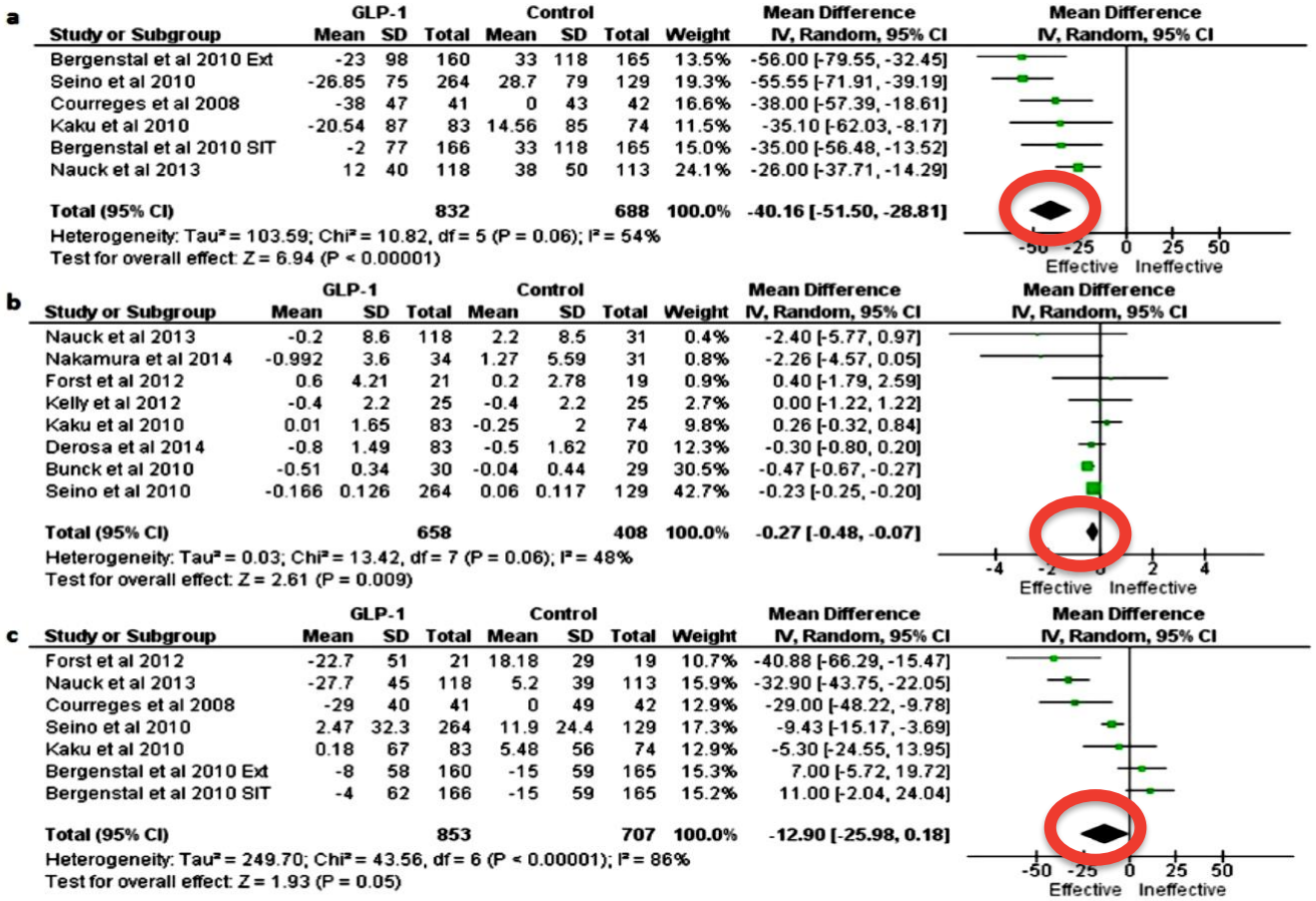
Christoph Kapitza et al. Diabetologia (2017) 60:1390–1399.

The GLP-1 Analogs Liraglutide and Semaglutide Reduce Atherosclerosis in ApoE $^{-/-}$ and LDLr $^{-/-}$ Mice by a Mechanism That Includes Inflammatory Pathways



Günaj Rakipovski et al. J Am Coll Cardiol Basic Trans Science. 2018;3(6):844–57.

Anti-atherosclerotic effects of the glucagon-like peptide-1 (GLP-1) based therapies in patients with type 2 Diabetes Mellitus: A meta-analysis



- BNP %
- hs CRP %
- PAI-1 %

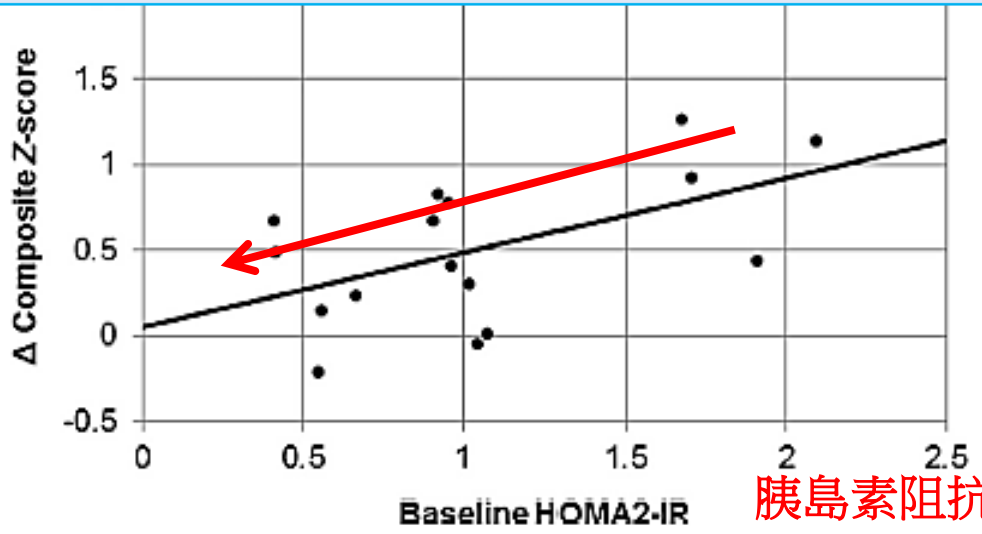
Figure 3. Forest plots showing the effects of GLP-1 based therapies on the percent changes from baseline of: a) Brain natriuretic peptide, b) high sensitivity c-reactive protein, and c) plasminogen activator inhibitor-1 levels. (In Bergenstal *et al.*, 2010: Ext, exenatide; SIT, sitagliptin).

Xiaoyan Song et al. Scientific Reports 2015; 5:10202 | DOI: 10.1038/srep10202

Liraglutide promotes improvements in objective measures of cognitive dysfunction in individuals with mood disorders: A pilot, open-label study

Liraglutide (GLP-1 RA) 改善腦部的胰島素阻抗性，因而改善認知能力及記憶！

認知障礙的嚴重度



胰島素阻抗性嚴重度

Fig. 2. Correlation between percentage change in the composite Z-score and baseline HOMA2-IR. HOMA2-IR: homeostasis model assessment - insulin resistance.

After adjustment for age and gender, there were positive associations between percent- change between baseline and endpoint in the composite z-score and baseline HOMA2-IR (β=0.409, 95% CI 0.090; 0.727, p=0.012) (Fig. 2)

Rodrigo B. Mansur et al. Journal of Affective Disorders 207 (2017) 114-120.

Evaluating oral semaglutide as a treatment for Alzheimer's disease

This clinical trial will evaluate type 2 diabetes medication in a Phase 2a clinical trial as potential treatment for Alzheimer's disease

Dr. Paul Edison and colleagues propose to test the impact of a daily tablet called "oral semaglutide" on individuals with mild Alzheimer's disease. Semaglutide is already on the market as a treatment for type 2 diabetes.

Background

Insulin is a hormone that helps the body maintain appropriate levels of sugar. Insulin can also be transported to the brain, where it helps maintain nerve cell energy levels and connections between nerve cells. Since insulin plays an important role in the brain, researchers believe insulin might also play a role in Alzheimer's progression. Past studies have shown that problems with how insulin sends signals in the brain also known as "insulin resistance" could lead to change in nerve cell networks and cause cognitive symptoms of Alzheimer's. As a result, studies have identified type 2 diabetes as a risk factor for Alzheimer's.

Research Plan

Dr. Edison and colleagues will recruit 60 individuals with Alzheimer's to the study, from the memory clinics at the Imperial College London and Imperial College Healthcare NHS trust as well as other sites across the UK. All the participants will undergo detailed cognitive tests and physical examination. The participants will also undergo different types of brain scans to measure brain volume, brain glucose metabolism (ability of brain cells to convert glucose into energy) and nerve cell function. In addition, the participants will have blood samples taken to assess their glucose levels and to measure any radioactivity in the blood.

Impact

If successful, the study will help the researchers **plan a larger study to evaluate the efficacy of the drug**. The study results may also **provide an understanding of the biological mechanisms by which insulin resistance may disrupt nerve cell function and communication in Alzheimer's disease**.

2020 Part the Cloud: Translational Research Funding for Alzheimer's Disease (PTC)

Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study

	Liraglutide	Placebo	Relative risks or mean changes (95% CI) from baseline to 48 weeks (liraglutide vs placebo)	p value*
Primary outcome				
Number of patients with paired liver biopsies	23	22	..	..
Patients with resolution of non-alcoholic steatohepatitis	9 (39%)	2 (9%)	4·3 (1·0 to 17·7)	0·019

Matthew James Armstrong et al. Lancet 2016; 387: 679–90.

A Research Study on How Semaglutide Works in People With Fatty Liver Disease and Liver Damage

Study Design

Study Type :	Interventional (Clinical Trial)
Actual Enrollment :	65 participants
Allocation:	Randomized

Condition or disease	Intervention/treatment	Phase
Non-alcoholic Steatohepatitis	Drug: Semaglutide Drug: Placebo	Phase 2

In a first-quarter earnings report (May 12, 2020), Novo Nordisk announced promising initial data from a phase 2 trial testing the efficacy of glucagon-like peptide-1 (GLP-1) agonist semaglutide (Ozempic) in individuals with nonalcoholic steatohepatitis (NASH).

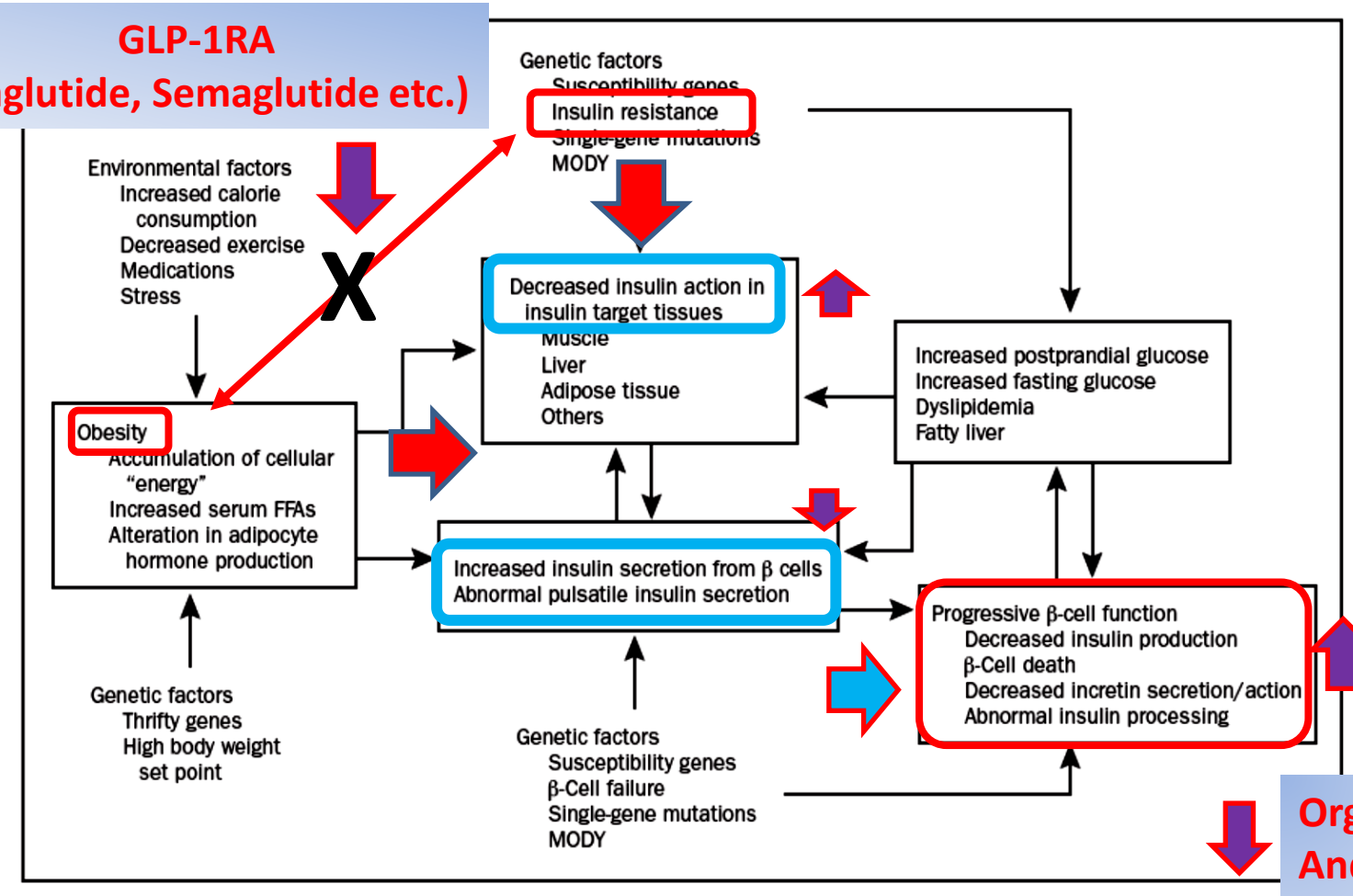
Liver biopsies performed at baseline and at the end of the trial revealed that of "patients receiving subcutaneous semaglutide 0.4 mg, 33 of 56 patients had NASH resolution compared to 10 of 58 patients on placebo (59% vs 17%)."

Actual Study Start Date :	June 18, 2019
Estimated Primary Completion Date :	January 6, 2021
Estimated Study Completion Date :	June 17, 2021

Clinical Trials.gov Identifier: NCT03987451

A Physiologic and Pharmacological Basis for Implementation of Incretin Hormones in the Treatment of Type 2 Diabetes Mellitus

GLP-1RA
(Liraglutide, Semaglutide etc.)



Beta cell Survival and Function

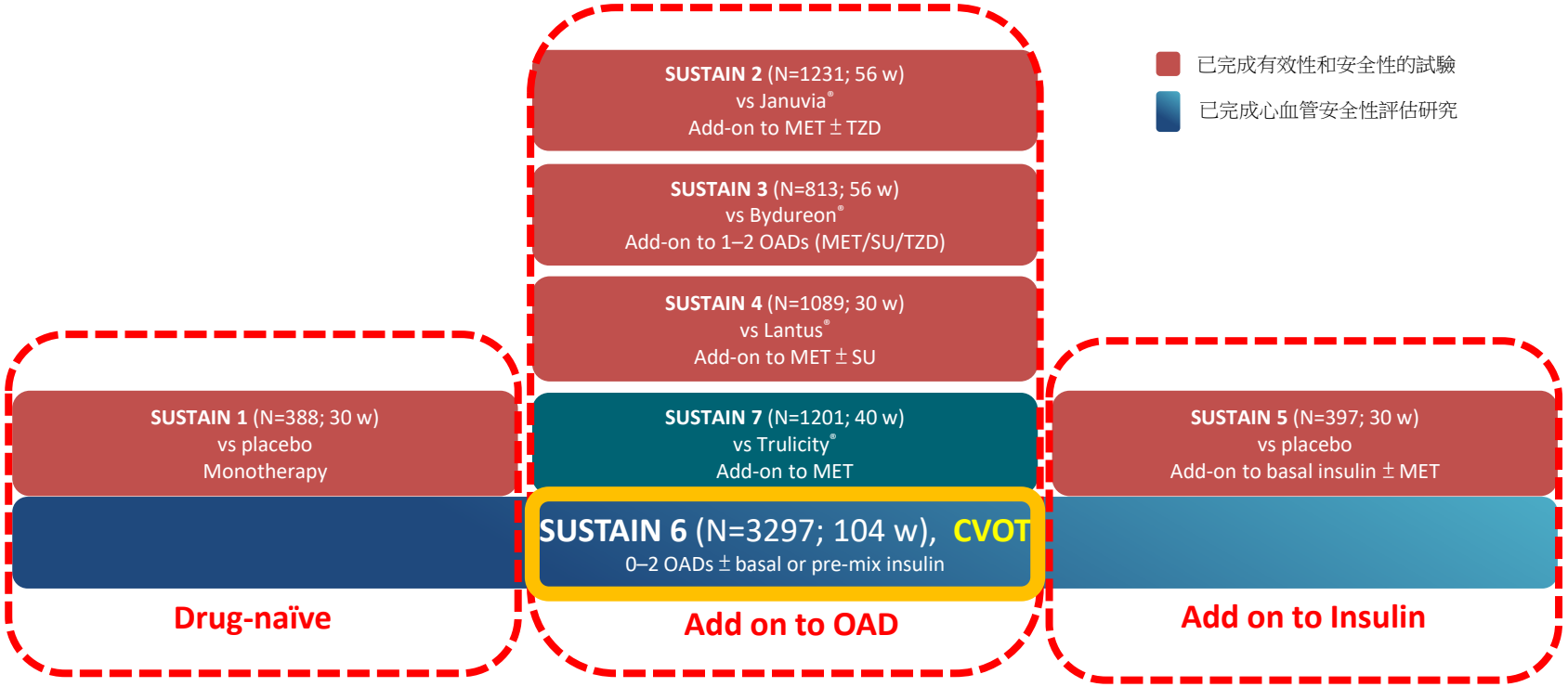
Organ failure And mortality

FIGURE 2. Pathogenesis of type 2 diabetes mellitus. The role of environmental and genetic factors on insulin secretion and insulin resistance.

Jeffrey S. Freeman, DO. Mayo Clin Proc. December 2010;85(12)(suppl):S5-S14.

Efficacy, safety and Cardiorenal outcomes Studies of Semaglutide in Type 2 DM

Semaglutide 之SUSTAIN 1-7 臨床試驗計劃



原本使用之藥物

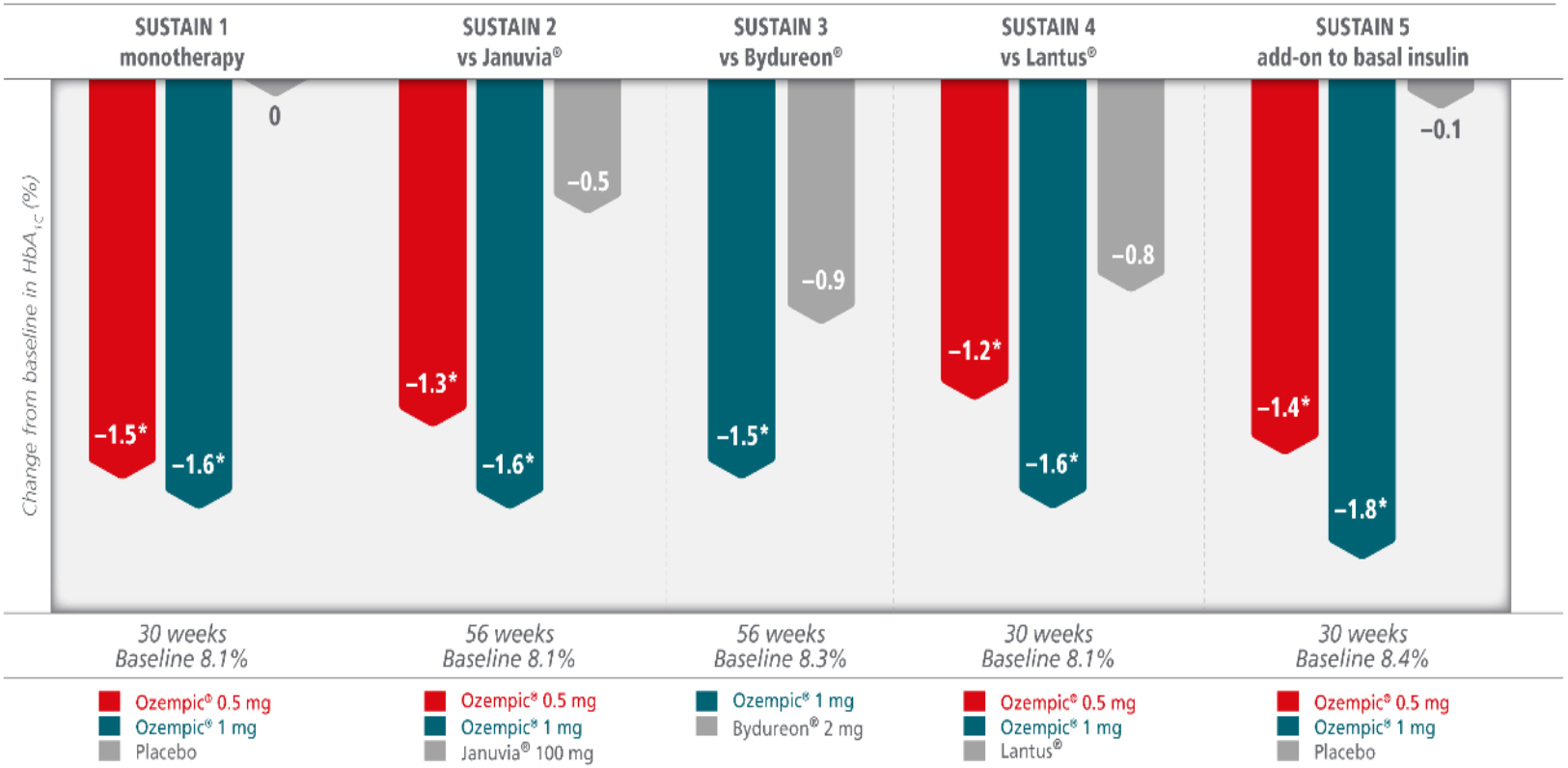
T2D=type 2 diabetes; MET=metformin; TZD=thiazolidinedione; OAD=oral antidiabetic drug; SU=sulphonylurea; w=week.

References:

1. 胰妥讚®注射劑衛生福利部核准仿單.
2. Steven PM et al. N Engl J Med 2016;375:1834-44. (SUSTAIN 6)
3. Pratley RE et al. Lancet Diabetes Endocrinol. 2018;6(4):275-286.

Anti-Glycemic Results of SUSTAIN 1-5

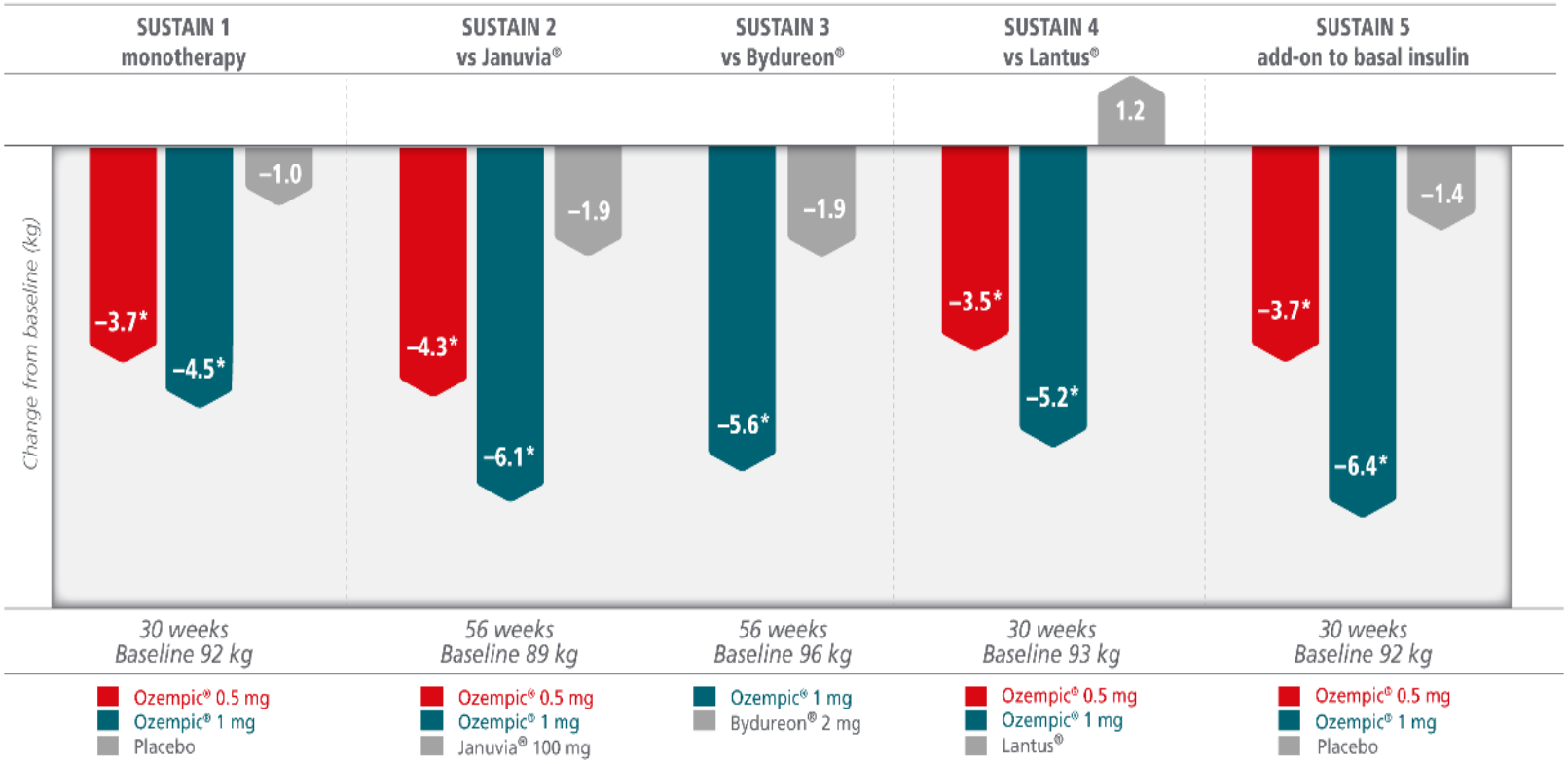
- **Semaglutide 0.5 mg QW -1.2~1.5% A1C**
- **Semaglutide 1.0 mg QW -1.6~1.8 % A1C**



***P*<0.0001 vs comparator.**

Weight Reduction Results of SUSTAIN 1-5

- **Semaglutide 0.5 mg QW -3.5~4.3 Kg**
- **Semaglutide 1.0 mg QW -4.5~6.4 Kg**



******P*<0.0001 vs comparator.**

Effects of GLP-1 receptor agonists on primary and secondary cardiovascular (CV) outcomes in the LEADER trial and SUSTAIN-6

	LEADER	SUSTAIN-6
Study duration (years)	3.5	2.0
GLP-1 receptor agonist: molecule	Liraglutide	Semaglutide
GLP-1 receptor agonist: dose	1.8 mg/day	0.5 or 1.0 mg/week
Patients (n)	9340	3297
Major CV events[a]	↓ 13% (p = 0.01)	↓ 26% (p = 0.02)
Myocardial infarction	↓ 14% (p = 0.046)	↓ 15% (NS; p = 0.38)
Non-fatal stroke	↓ 11% (p = 0.30; NS)	↓ 39% (p = 0.04)
Coronary revascularization	↓ 9% (p = 0.18; NS)	Not available
Coronary + peripheral revascularization	Not available	↓ 35% (p = 0.003)
Hospitalization for heart failure	↓ 13% (p = 0.14; NS)	→ (p = 0.57; NS)
CV death	↓ 22% (p = 0.007)	→ (p = 0.92; NS)
Total mortality	↓ 15% (p = 0.02)	→ (p = 0.79; NS)

[a]CV death, non-fatal myocardial infarction, non-fatal stroke. **2016 NEJM** **2016 NEJM**

LEADER: Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; SUSTAIN-6: Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes.

↓: decrease; →: no effect; NS: not significant

B. Vergès and B. Charbonnel. Diabetes & Metabolism 2017;43:S3-S12.

Semaglutide reduce new or worsening nephropathy in Patients with Type 2 Diabetes (SUSTAIN-6)

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

36% risk; P=0.005

Steven P. Marso et al. N Engl J Med 2016;375:1834-44.

Semaglutide Treatment and Renal Function in SUSTAIN 6 Trial

Table. UACR (change from baseline to week 104) and renal-related safety endpoints (week 104) stratified by baseline renal function in the SUSTAIN 6 trial

	Semaglutide 0.5 mg		Placebo 0.5 mg		Semaglutide 1.0 mg		Placebo 1.0 mg	
	Value	N	Value	N	Value	N	Value	N
UACR, mg/mmol [SD]								
Normal	−5.8 [61.6]	191	4.7 [59.1]	196	−0.8 [15.9]	206	5.1 [52.2]	200
Mild	−3.2 [40.5]	267	−1.0 [43.2]	261	−4.7 [36.8]	287	3.2 [36.4]	272
Moderate	−9.2 [73.4]	195	12.3 [114.1]	171	−4.9 [64.2]	168	5.4 [73.5]	173
Severe	−50.5 [132.8]	20	−43.3 [157.0]	28	−56.0 [239.2]	25	−16.0 [192.3]	31
AEs related to acute renal failure, n (%) [R]								
Normal	2 (0.8) [0.4]	247	10 (4.1) [2.6]	242	5 (2.0) [1.1]	245	7 (2.8) [1.4]	253
Mild	26 (8.0) [4.9]	327	23 (6.9) [4.5]	335	16 (4.5) [3.4]	357	25 (7.2) [4.6]	347
Moderate	37 (16.2) [11.5]	228	25 (11.7) [7.6]	214	16 (8.3) [5.8]	192	24 (12.5) [7.7]	192
Severe	1 (4.8) [3.1]	21	6 (21.4) [13.1]	28	3 (12.0) [7.2]	25	7 (21.2) [14.0]	33
New or worsening nephropathy, n (%)	36 (4.4)	826	54 (6.6)	824	23 (2.8)	822	45 (5.5)	825
Persistent macroalbuminuria, n (%)	22 (2.7)		42 (5.1)		19 (2.3)		38 (4.6)	

Renal function categories based on MDRD eGFR: Normal, ≥90 mL/min/1.73 m²; Mild, <90 mL/min/1.73 m²; Moderate, <60 mL/min/1.73 m²; Severe,

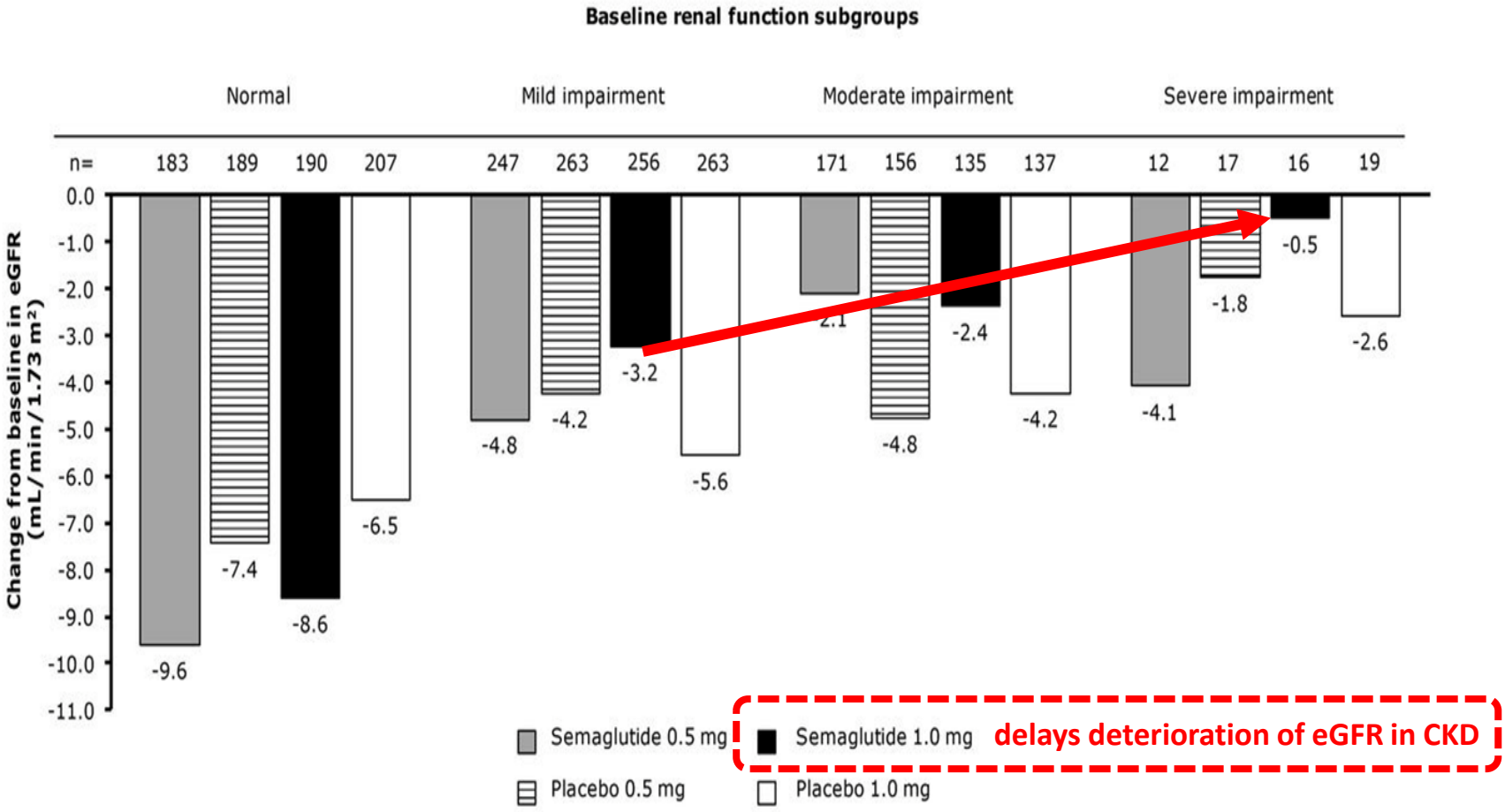
Albuminuria

AKI

- **Urine albumin-to-creatinine ratio decreased with increasing renal impairment for semaglutide 1.0 mg.**
- **AEs related to acute renal failure were generally higher with increasing baseline renal impairment, except with semaglutide 1.0 mg vs. placebo.**
- **New or worsening nephropathy was lower with both doses of semaglutide vs. placebo.**
- **No renal-related safety issues were observed with semaglutide regardless of baseline renal function in SUSTAIN 6.**

TINA VILSBØLL et al. Diabetes 2018;67:1084-P

Semaglutide Treatment and Renal Function in SUSTAIN 6 Trial



TINA VILSBØLL et al. Diabetes 2018;67:1084-P

SUSTAIN 1-7 證實 Semaglutide 的安全性

特殊族群[1]

ns[1]

下列特殊族群不需調整劑量

- 輕度、中度或重度腎功能不全的患者
- 肝功能不全的患者
- 老年人

腸胃道事件[2,9]

- 腸胃道事件的耐受性與其他 GLP-1 受體促效劑相似

低血糖[1,2,9-13]

- 在 7 項臨床試驗中，嚴重低血糖*的發生率 < 2%

胰臟炎[2-8]

- 胰臟炎相關的不良事件與對照組並無差異

心血管安全性[1]

- 為期 2 年的 CVOT 顯示於標準治療† 加上 Ozempic® 可降低 26% 心血管風險

腎病變[8]

- 為期 2 年的 CVOT 發現可降低新發生或惡化的腎病變風險 (Ozempic®：3.8%；安慰劑：6.1%)

糖尿病視網膜病變併發症[1] SUSTAIN 6

- 在為期 2 年的 CVOT 中，使用 Ozempic® 的患者判定為糖尿病視網膜病變併發症的比例 (3.0%) 高於安慰劑組 (1.8%)。
  - 此數據來自接受胰島素治療並已知罹患糖尿病視網膜病變之患者
- 糖尿病視網膜病變併發症的系統性評估僅於 SUSTAIN 6 試驗中進行
- 在為期 1 年、包含 4,807 位第 2 型糖尿病患者的臨床試驗中，Ozempic® 組與對照組曾通報的糖尿病視網膜病變相關不良事件比率相當 (Ozempic®：1.7%；對照組：2.0%)

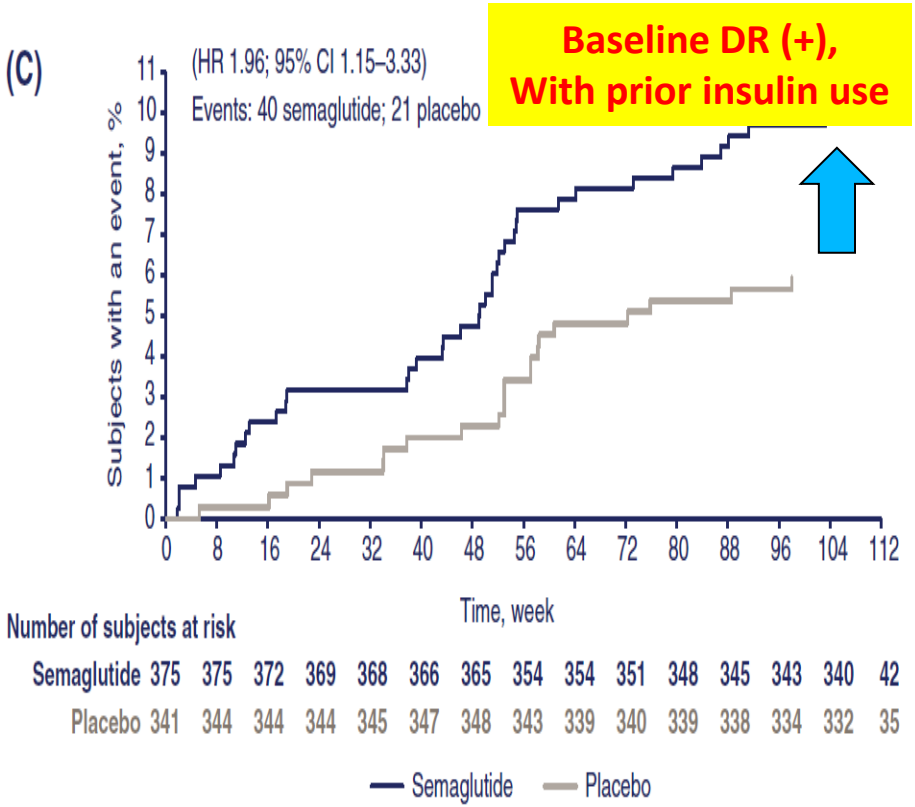
CVOT=cardiovascular outcomes trial; GI=gastrointestinal; GLP-1=glucagon-like peptide-1; CV=cardiovascular.

*Hypoglycaemia defined as severe (requiring the assistance of another person) or symptomatic in combination with a blood glucose <3.1 mmol/L.[1]

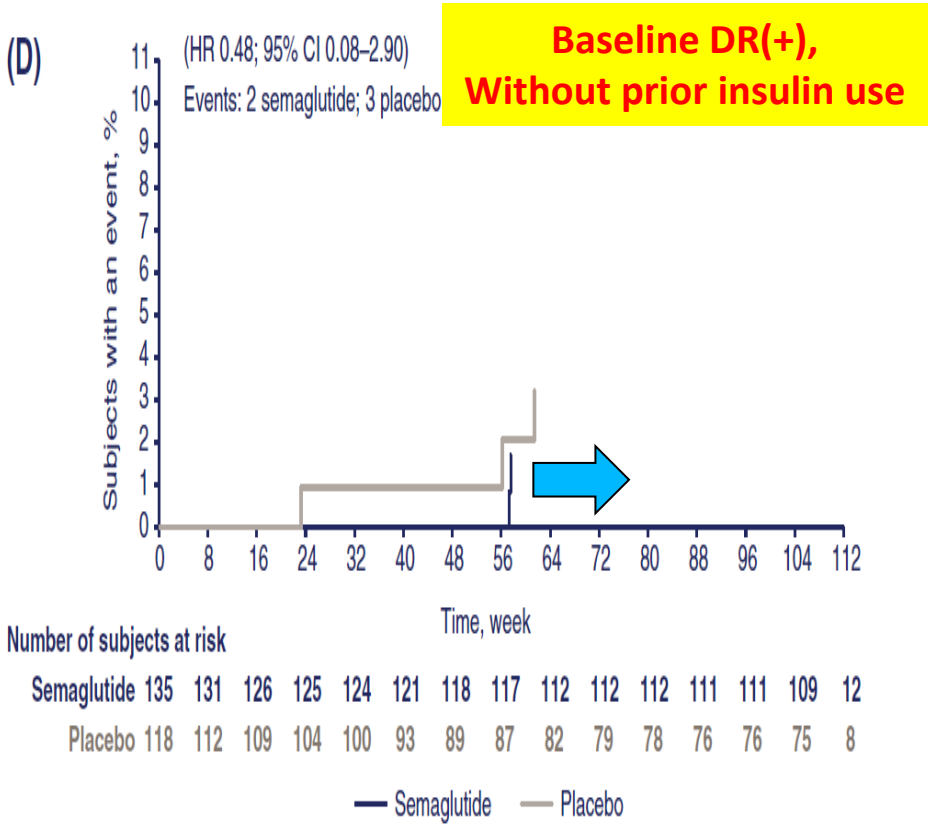
†Standard of care included oral antidiabetic treatments, insulin, antihypertensives, diuretics and lipid-lowering therapies.[9]

References: 1. 胰妥讚®注射劑衛生福利部核准仿單. **2.** Pratley RE et al. *Lancet Diabetes Endocrinol*. 2018;6(4):275-286. **3.** Ahmann AJ et al. *Diabetes Care*. 2018;41(2):258-266. **4.** Sorli C et al. *Lancet Diabetes Endocrinol*. 2017;5(4):251–260. **5.** Ahrén B et al. *Lancet Diabetes Endocrinol*. 2017;5(5):341–354. **6.** Aroda VR et al. *Lancet Diabetes Endocrinol*. 2017;5(5):355–366. **7.** Rodbard HW et al. *Clin Endocrinol Metab*. 2018;103(6)(suppl 1):1-28. **8.** Marso SP et al. *N Engl J Med*. 2016;375(19):1834-1844. **9.** Marso SP et al. *N Engl J Med*. 2016;375(suppl1):S1-S108.

Semaglutide, reduction in glycated haemoglobin and the risk of diabetic retinopathy



Patients with DR at baseline and with Insulin use prior to event



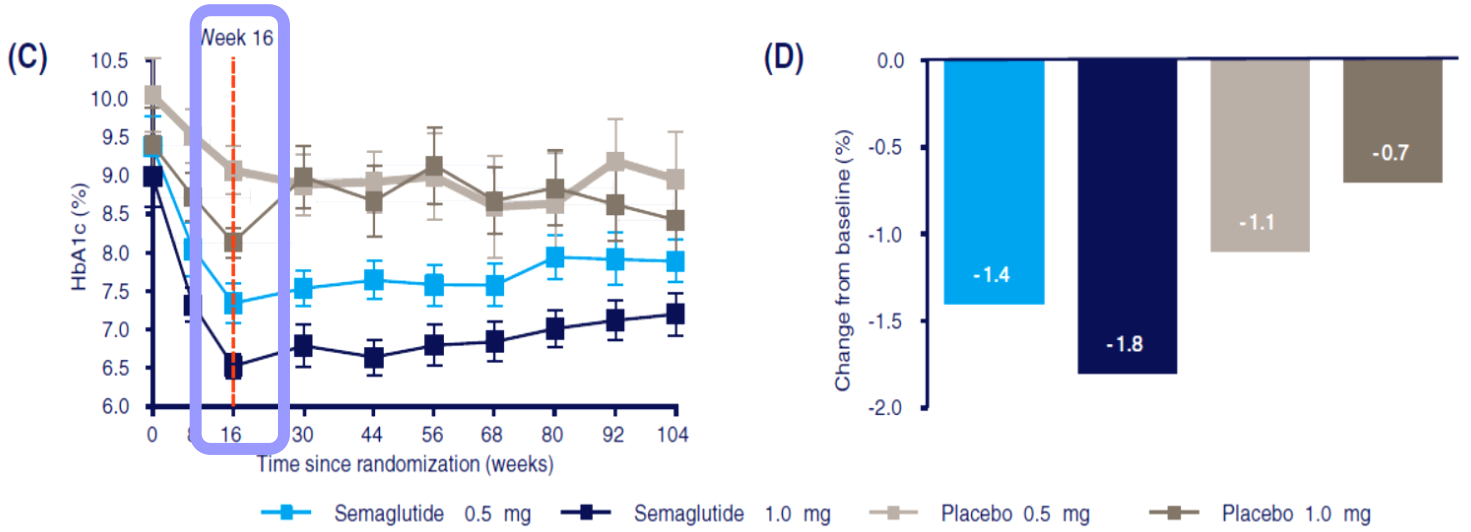
Patients with DR at baseline and without Insulin use prior to event

TINA VILSBØLL et al. Diabetes Obes Metab. 2018;20:889–897.

Semaglutide, reduction in glycated haemoglobin and the risk of diabetic retinopathy

Rapid Reduction of A1C 2~2.5% at week 16 by (OADs± insulin± GLP-1RA) will bring higher risk of diabetic retinopathy complication in baseline DR (+) patients.

Patients with DRC



(E)

	HR (95% CI) Semaglutide vs placebo	*P* values Semaglutide vs placebo	Semaglutide (N=1648) N (%)	Placebo (N=1649) N (%)
Prespecified analysis				
Total effect of treatment	1.76 (1.11; 2.78)	0.02	50 (3.0)	29 (1.8)
Post hoc mediation analysis				
Controlled direct effect of treatment	1.22 (0.71; 2.09)	0.48	50 (3.0)	29 (1.8)
Effect of change in HbA1c (%) at Week 16	1.26 (1.03; 1.57)	0.03		
Proportion eliminated	0.72			

DRC: Diabetic Retinopathy Complication

TINA VILSBØLL et al. Diabetes Obes Metab. 2018;20:889–897.

長期良好血糖控制
可降低糖尿病性視網膜病變的風險

SUSTAIN 6 – CVOT數據

- 這項為期2年的研究調查了3297名第2型糖尿病患者，這些患者具有較高的CV風險，糖尿病持續時間長且血糖控制不佳。
  - 觀察到的糖尿病視網膜病變併發症，使用Ozempic®組（3%）和安慰劑組(1.8%)
  - >80%有發生事件的病患，在基期時即具視網膜病變之病史
  - 沒視網膜病史的病患，Ozempic®組與安慰劑組事件發生比例相似

考量

- 血糖控制的過於快速改善與糖尿病性視網膜病變的暫時惡化有關。
- 長期血糖控制可降低糖尿病性視網膜病變的風險
- 在使用胰島素治療的糖尿病視網膜病變患者中，使用本產品時應格外小心。
  - 這些患者應根據臨床指引進行監測和治療

- 視網膜病變並未與藥品治療呈現相關性

Proportion of GI Upsets with GLP-1 RA [1,2]

	SUSTAIN 7 vs Trulicity®				SUSTAIN 3 vs Bydureon®	
%	Trulicity® 0.75 mg (n=299)	Ozempic® 0.5 mg (n=301)	Trulicity® 1.5 mg (n=299)	Ozempic® 1 mg (n=300)	Bydureon® 2 mg (n=405)	Ozempic® 1 mg (n=404)
Nausea	13	23	20	21	12	22
Diarrhoea	8	14	18	14	8	11
Vomiting	4	10	10	10	6	7
Discontinuation rates due to GI AEs	2	5	5	6	3	6

無差異

GI=gastrointestinal.

References:

1. Pratley RE et al. *Lancet Diabetes Endocrinol*. 2018;6(4):275-286.

2. Ahmann AJ et al. *Diabetes Care*. 2018;41(2):258-266.

每週一次的 Semaglutide (Ozempic®)

*The starting dose of 0.25 mg is not a maintenance dose and is intended to help patients adjust to treatment.

Reference: 1. 胰妥讚®注射劑衛生福利部核准仿單

Ozempic®一起始由幾個簡單的步驟開始

選擇劑量 轉動至預定的劑量

投與劑量 Ozempic®可以打在腹部、大腿或上手臂

結束給藥

目前最細的針頭
以每週給藥GLP-1RA[2]

GLP-1 RA=glucagon-like peptide-1 receptor agonist.

References: **1**. 胰妥讚®注射劑衛生福利部核准仿單 **2**. Diabetes in control web site. GLP-1 agonist medications chart. http://www.diabetesincontrol.com/wp-content/uploads/PDF/dic_glp-1_chart_2014-11-06.pdf. Accessed October 26, 2017. **3**. Ley B. Diameter of a human hair. In: Elert G, ed. *The Physics Factbook*™. http://hypertextbook.com/facts/1999/BrianLey.shtml. Published 1999. Accessed May 17, 2017.

GLP-1 RA: Clinical evidence update in treatment guidelines of type 2 DM

GLP-1 RA:
from physiology to pharmacology and outcomes in diabetes

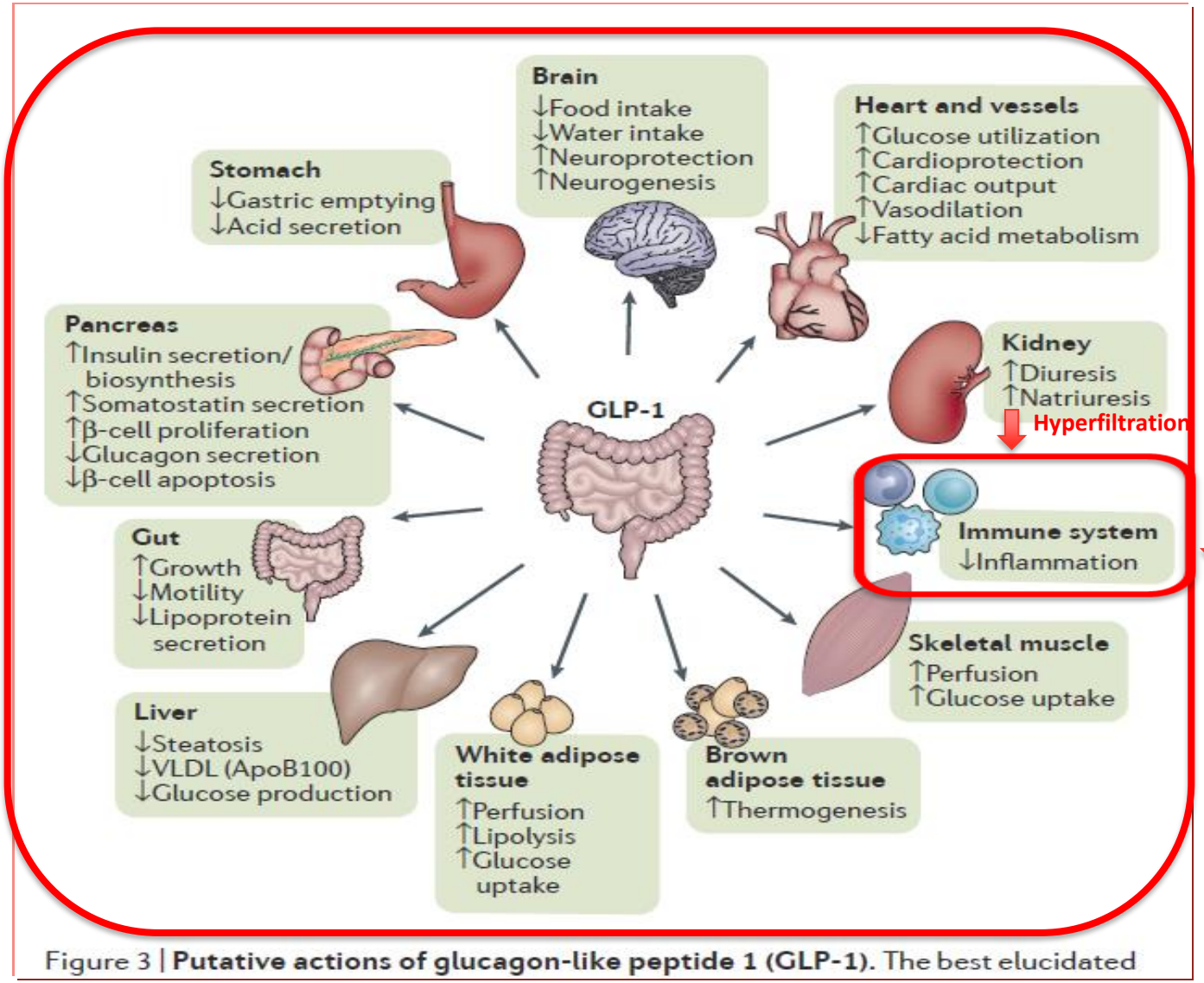
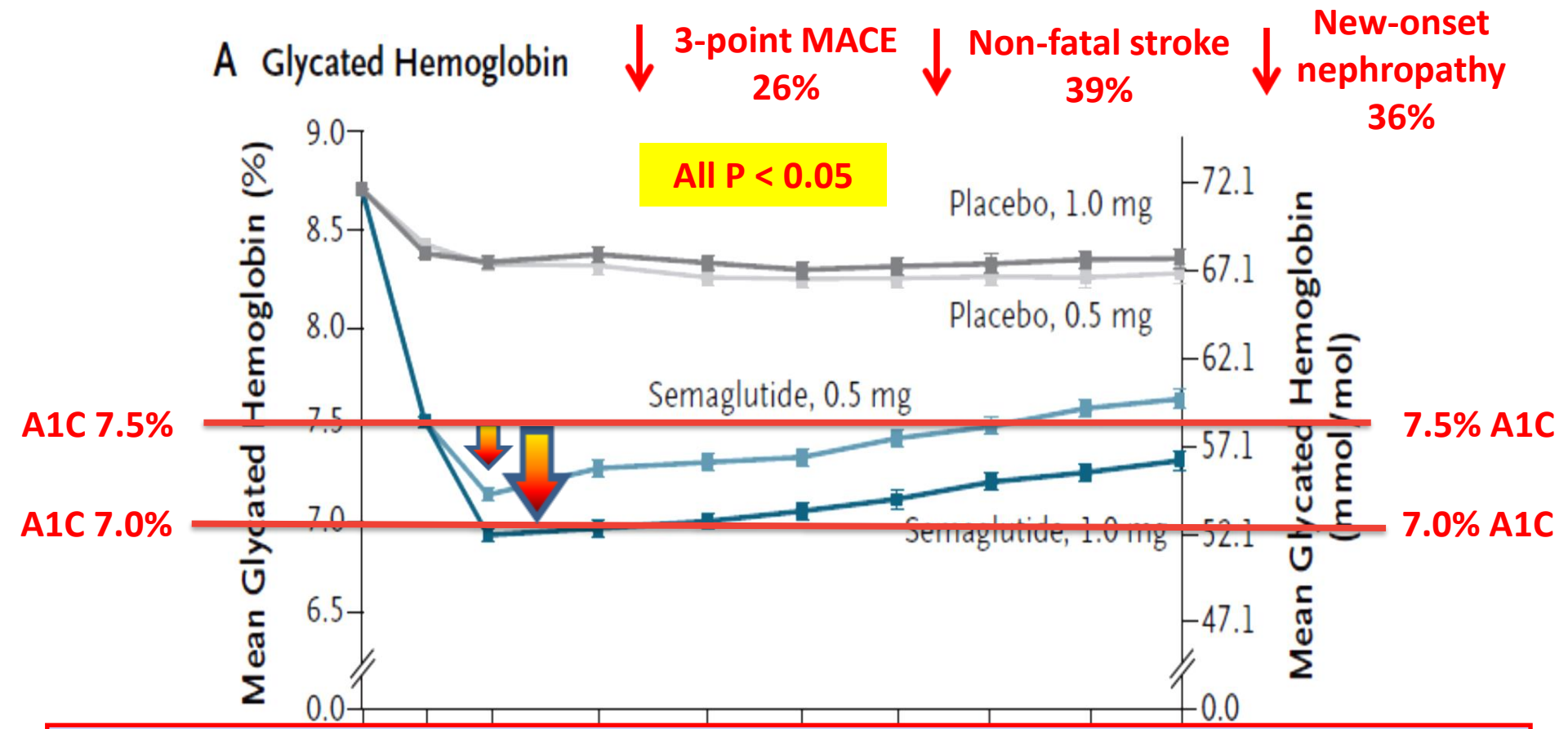


Figure 3 | **Putative actions of glucagon-like peptide 1 (GLP-1).** The best elucidated

Marcel H. A. Muskiet et al . Nature Reviews Nephrology **2017;** 13, 605–628.

Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes (SUSTAIN-6)



GLP-1 RA (e.g. Semaglutide) can correct both beta-cell dysfunction and insulin resistance at the initiation of Type 2 DM !

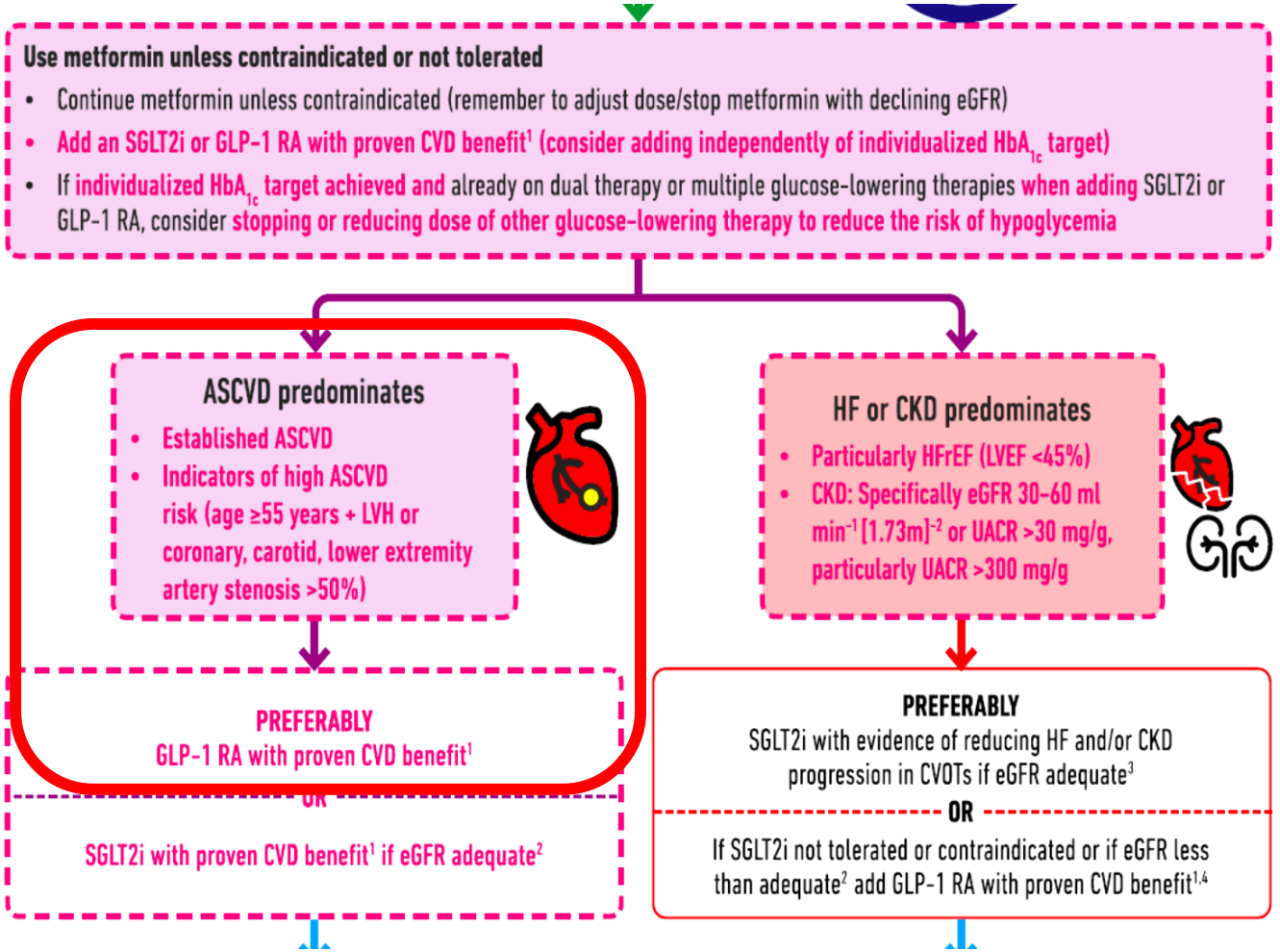
Steven P. Marso et al. N Engl J Med 2016;375:1834-44.

2019 Update to: Management of Hyperglycemia in Type 2 Diabetes, 2018.

A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

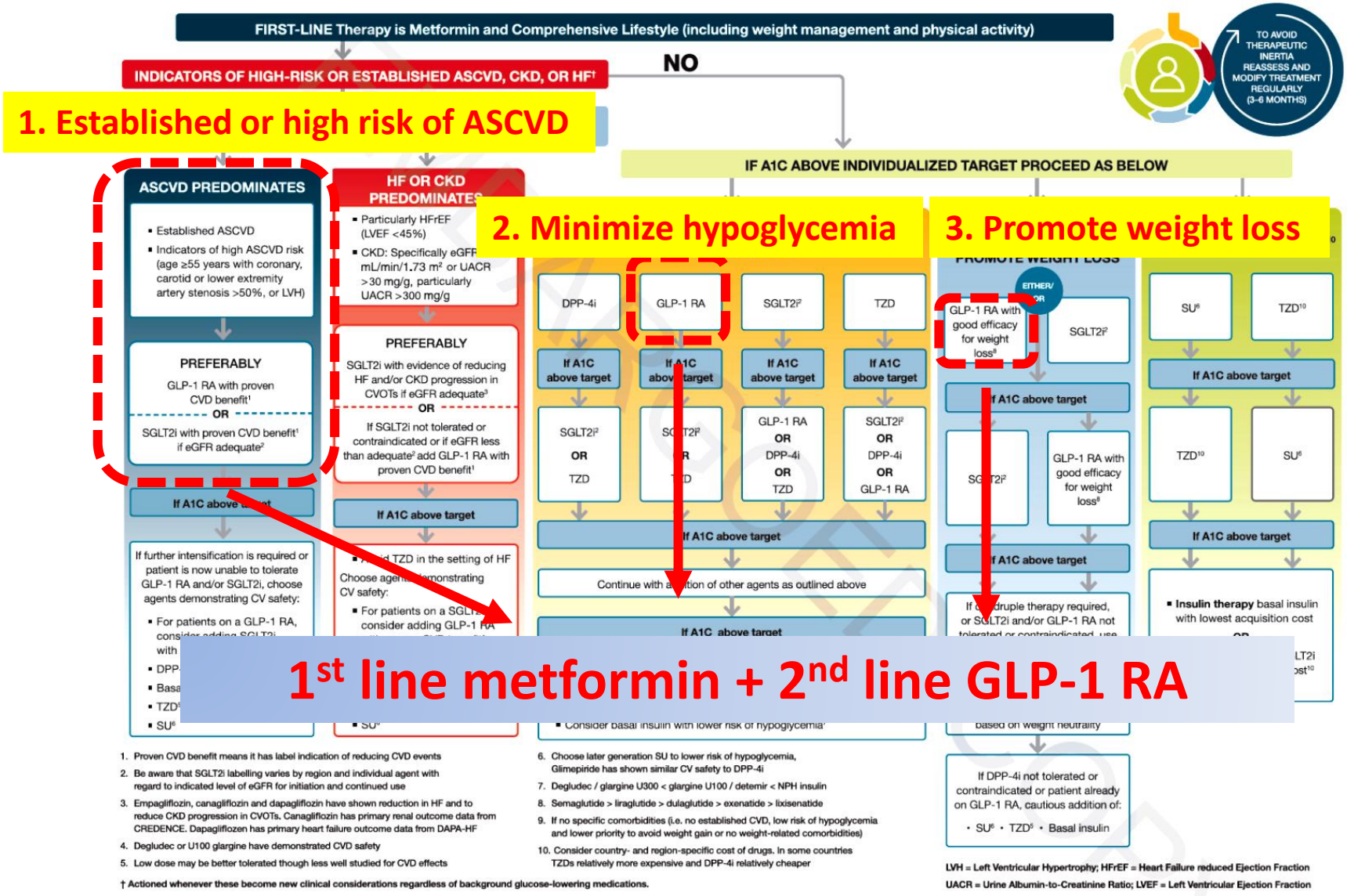
1. Metformin

2. Add-on GLP-1 RA



Diabetes Care 2020;43:487–493.

2020 ADA Standards of Care in Diabetes



Diabetes Care. January 2020; Volume 43, Supplement 1

第 2 型糖尿病人高血糖的處理流程圖
(2020年修訂版) 中華民國糖尿病學會出版

健康生活型態的飲食和運動及醫病共享決策

糖化血色素<7.5%

建議使用一種抗糖尿病藥

初診斷建議首選：Metformin

- 效果：佳
- 低血糖：低
- 體重：稍下降
- 副作用：腸胃道/乳酸血症

合併高血糖症狀

建議先以 Insulin 治療

糖化血色素 ≥ 7.5%或高於個別化目標值1.5%以上

建議使用兩種抗糖尿病藥

建議 Metformin + 以下不同機轉的抗糖尿病

合併高血糖症狀

建議先以 Insulin 治療

若單一治療未達控制目標時，宜評估心腎風險及共病，加上以下不同機轉的抗糖尿病藥

SGLT2i	GLP1-RA	TZD	DPP4i	AGI	SU/Glinide	Insulin
心血管實證：有(建議使用) 心衰竭實證：強(建議使用) 腎病變實證：強(建議使用) 控制血糖效果：中等 體重：下降 低血糖：低 副作用：糖尿病酮酸中毒 生殖泌尿道感染、骨折、截肢、脫水	心血管實證：部分有(建議使用) 心衰竭實證：中立 腎病變實證：有(蛋白尿) 控制血糖效果：佳 體重：下降 低血糖：低 副作用：腸胃道	心血管實證：有	心血管實證：中立	心血管實證：中立	心血管實證：缺	心血管實證：中立

T2DM with CV or renal risk:
1st line metformin + 2nd line GLP-1 RA

未達控制目標

再加上另一種不同機轉的抗糖尿病藥 (SU 和 Glinide 不建議合併，DPP4i 和 GLP1-RA 不建議合併)

未達控制目標

建議照會專科或強化注射型藥物治療

健保藥品給付規定 (109/5/1)

Semaglutide (如Ozempic)

5.1.3.2.Liraglutide (如Victoza)、dulaglutide(如Trulicity)、lixisenatide (如Lyxumia)(101/10/1、105/5/1、105/8/1、107/4/1、107/7/1、109/5/1)

1.限用於已接受過最大耐受劑量的metformin及/或sulfonylurea類藥物，且併用下列藥品之一持續6個月之後，HbA1c仍高於8.5%以上之第二型糖尿病患者：(109/5/1)

(1)SGLT-2抑制劑

(2)DPP-4抑制劑

(3)SGLT-2抑制劑合併DPP-4抑制劑複方藥品

(4)Insulin (只有**Basal insulin**可併用)

109/5/1起, 健保給付新規定將GLP-1RA定位於第三線降血糖藥物, 而且必須前兩種藥物合併使用達6個月以上, A1C仍大於8.5%以上才能置換或加入GLP-1RA.

2.當患者已接受口服降血糖藥物，及/或基礎胰島素治療仍未達理想血糖控制時，與口服降血糖藥物及/或基礎胰島素併用。

3.發生重大心血管事件，如心肌梗塞、接受冠狀動脈或其他動脈血管再通術(revascularization)、動脈硬化相關之缺血性腦中風等之病人，於接受過最大耐受劑量的metformin後，仍無法理想控制血糖之第二型糖尿病患者，可考慮不須使用其他口服降血糖藥品而考慮使用liraglutide或dulaglutide。

1st metformin + 2nd GLP-1RA

4.本藥品**不得與DPP-4抑制劑、SGLT-2抑制劑併用**。

Take home messages

根據Semaglutide 已完成臨床試驗計劃包括六個 3a 期試驗 SUSTAIN 1-6, 和一個 3b期試驗SUSTAIN 7 之結果, 結論如下：

Semaglutide 治療持續降低 HbA1c，FPG和PPG，與對照藥物相比，有更高比例的受試者達到血糖目標 <7.0%和 ≤6.5%.

與對照組相比，semaglutide持續降低體重和BMI，並且受試者達到 ≥5%和 ≥10%的體重減輕的比例顯著較高.

SUSTAIN 6中，Semaglutide治療的患者在主要 CVOT 綜合指標(3-pont MACE)的風險顯著降低了26%, 也減少36%的新生腎臟病之風險！


謝謝聆聽 ！