周劍文診所
Chou Chien Wen Clinic

糖尿病新藥物的介紹及應用

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109年11月1日
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Chou Chien Wen Clinic

Outline

- SGLT2 Inhibitor (Canna, Ertug)
- DDPV inhibitor/SGLT2 Inhibitor (Glyxambi, Q-Tern, Steglujan)
- Long acting Insulin (Tresiba)
- Long acting GLP1-RA (Ozempic)
- Basal Insulin and GLP-1 RA fix-ratio combination (Soliqua)
- Premix (Ryzodec)

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SGLT2 Inhibitor (Canna, Ertug)

第2 型糖尿病人高血糖的處理流程圖 (2020年修訂版)

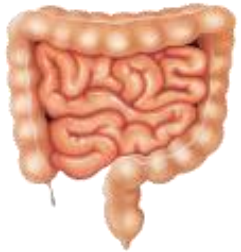
Summary - 1

- 最新糖尿病治療觀念需同時考量血糖控制和心血管風險的降低

- 針對患有ASCVD或是CHF/CKD的二型糖尿病人，在Metformin治療之後，應優先考慮加上SGLT2i或是GLP-1這兩種藥物治療，針對血糖已經達標病人若未使用以上兩類藥品，應考量置換藥品來降低病人心血管或是腎臟風險

Effect of SGLT1 / SGLT2

Intestine
SGLT1



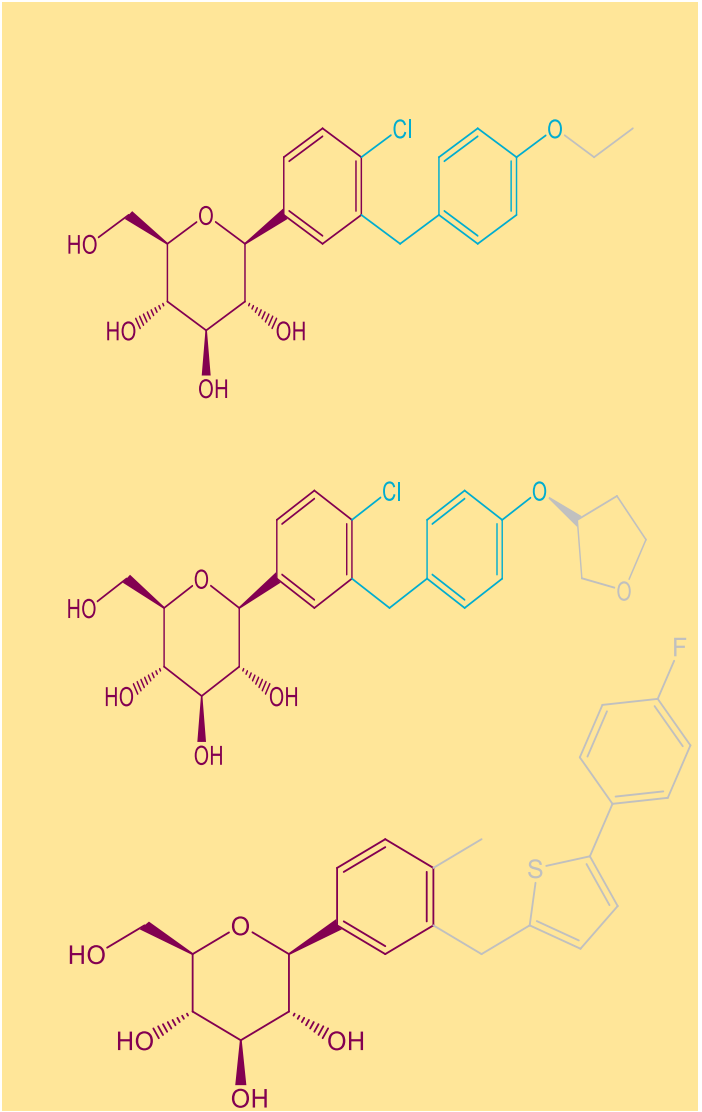
- Main uptake mechanism for glucose and galactose in the intestine
- S2 and S3 segments of the proximal renal tubule are responsible for ~10% of the renal glucose re-absorption
- **High-affinity** (K_m = ~0.5 mM), low-capacity transporter which transfers glucose and sodium with a Na^+:glucose coupling ratio of 2

Kidney
SGLT2

- Almost completely expressed in the brush-border membrane of proximal renal tubular cells in the S1 + S2 segment
- Responsible for ~90% of the total renal glucose re-absorption
- **Low-affinity** (K_m = ~2 mM), high-capacity transporter which transfers glucose and sodium with a Na^+:glucose coupling ratio of 1

1. Chao EC and Henry RR. *Nat Rev Drug Discov*. 2010;9:551–559;
2. Mather A and Pollock C. *Kidney Int Suppl*. 2011;(120):S1–6;
3. Wright EM, et al. *J Intern Med*. 2007;261:32–43.

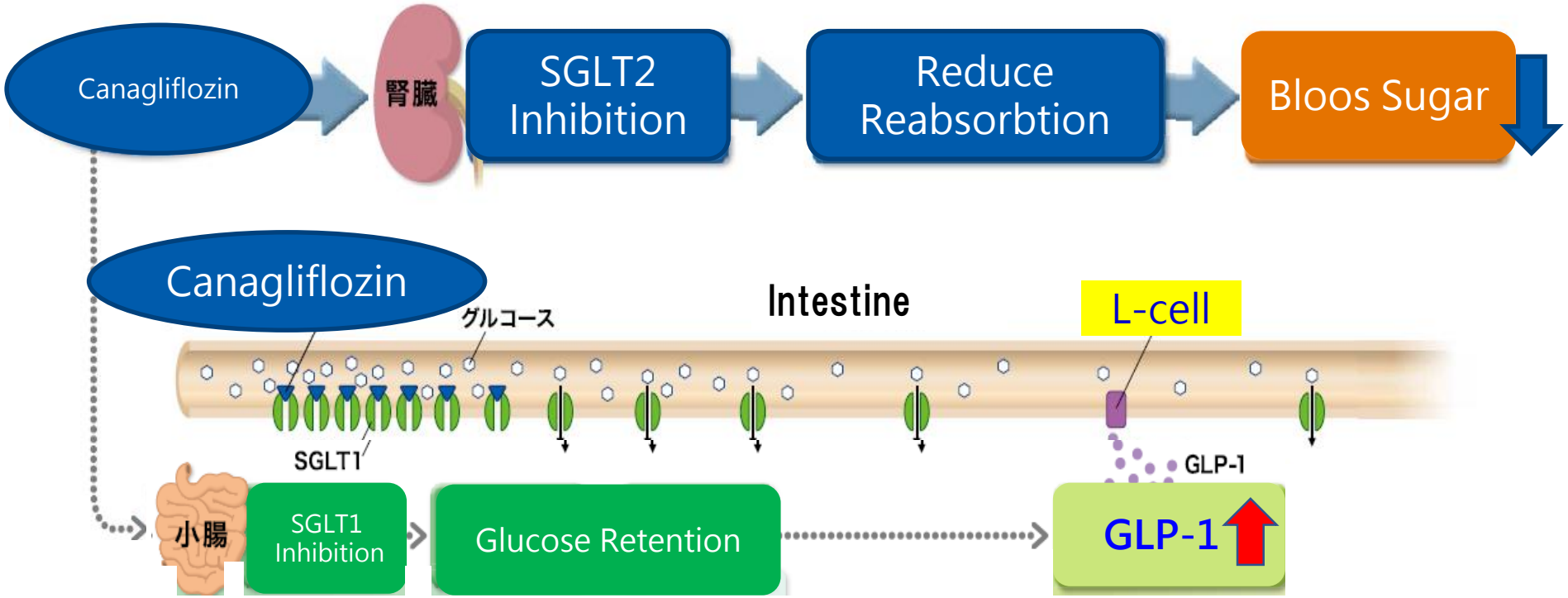
Structure and selectivity profiles for SGLT2 over SGLT1



	Selectivity SGLT-1 : SGLT-2
Dapagliflozin	1:1,400
Empagliflozin	1:5,000
Canagliflozin	1:160

Diabetes, Obesity and Metabolism 17: 188–197, 2015.

Canagliflozin increase aGLP-1 through SGLT1 inhibition



J Clin Med Res. 2017;9(9):745-753

SGLT2 inhibitors的藥理性質比較

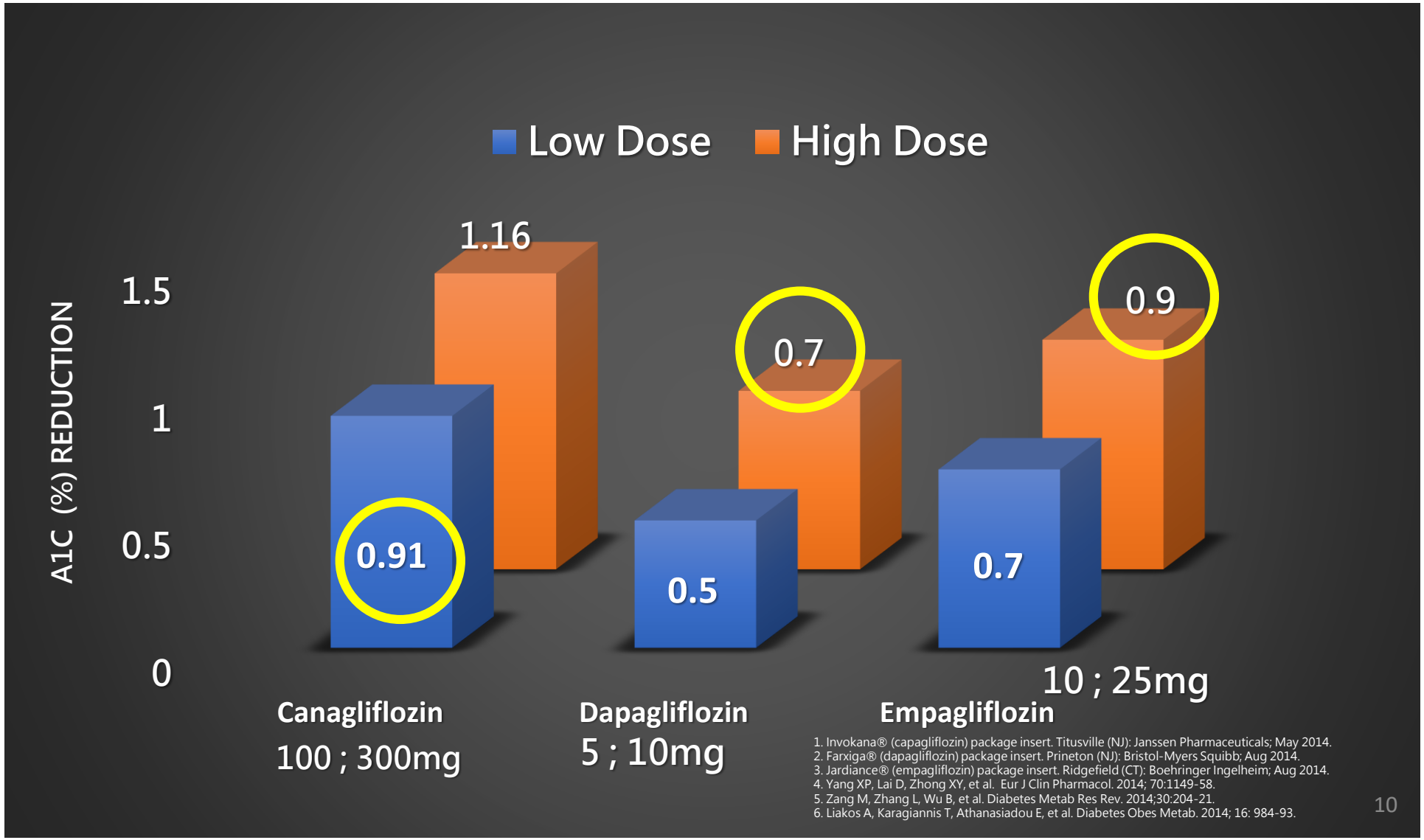
	Empagliflozin	Dapagliflozin	Canagliflozin	Ertugliflozin
Therapeutic dose (mg/day) **Starting dose**	10-25 10	5-10 5	100-300 100	5-15 5
Administration	QD With or without food	QD With or without food	QD Before the first meal of the day	QD With or without food
Peak plasma concentration (hours post-dose)	1.5	Within 2	1–2	1
Absorption (mean oral bioavailability)	≥ 60%	~ 78%	~ 65%	100%
Metabolism	Primarily glucuronidation, No active metabolite			
Elimination (half-life, hours)	Hepatic:renal 44:56 [12.4]	Hepatic:renal 22:78 [12.9]	Hepatic:renal 67:33 [13.1]*	Hepatic : renal 49.8:50.2 [16.6]
Selectivity over SGLT1	1:5000	> 1:1400	> 1:160[1]	1:2200[2,3]
Glucose excretion with higher dose (g/day)	78 (25 mg dose)	~ 70 (5 or 10mg dose)	87 (100mg dose)	75.12 (15 mgdose)[4]

SGLT, sodium glucose cotransporter; **QD,** once daily.;*For the 300 mg dose.

http://www.ema.europa.eu/.

1. Sha S, et al. Diab Obes Metab. 2015; 17:188–197; 2. Mudaliar S et al. Diabetes Care. 2015;38:2344–2353; 3. Mascitti V et al. J Med Chem. 2011;54:2952–2960; 4. Sahasrabudhe V, et al. J Clin Pharmacol. 2017;57(11):1432–1443.

Monotherapy : A1c Reductions



1. Invokana® (capagliflozin) package insert. Titusville (NJ): Janssen Pharmaceuticals; May 2014.
2. Farxiga® (dapagliflozin) package insert. Prineton (NJ): Bristol-Myers Squibb; Aug 2014.
3. Jardiance® (empagliflozin) package insert. Ridgefield (CT): Boehringer Ingelheim; Aug 2014.
4. Yang XP, Lai D, Zhong XY, et al. Eur J Clin Pharmacol. 2014; 70:1149-58.
5. Zang M, Zhang L, Wu B, et al. Diabetes Metab Res Rev. 2014;30:204-21.
6. Liakos A, Karagiannis T, Athanasiadou E, et al. Diabetes Obes Metab. 2014; 16: 984-93.

Summary – 2

- Canagliflozin具有SGLT1及SGLT2受體的雙重抑制效果，可刺激GLP-1分泌，提供持續有效的血糖和體重控制效果

- Canagliflozin 100mg每日可排出87克葡萄糖，排糖效果為SGLT2i中效果最強，降低A1C效果與Empagliflozin 25mg相當，優於Dapagliflozin 10mg

SGLT2i有關MACE的整合分析* (ASCVD vs MRF)

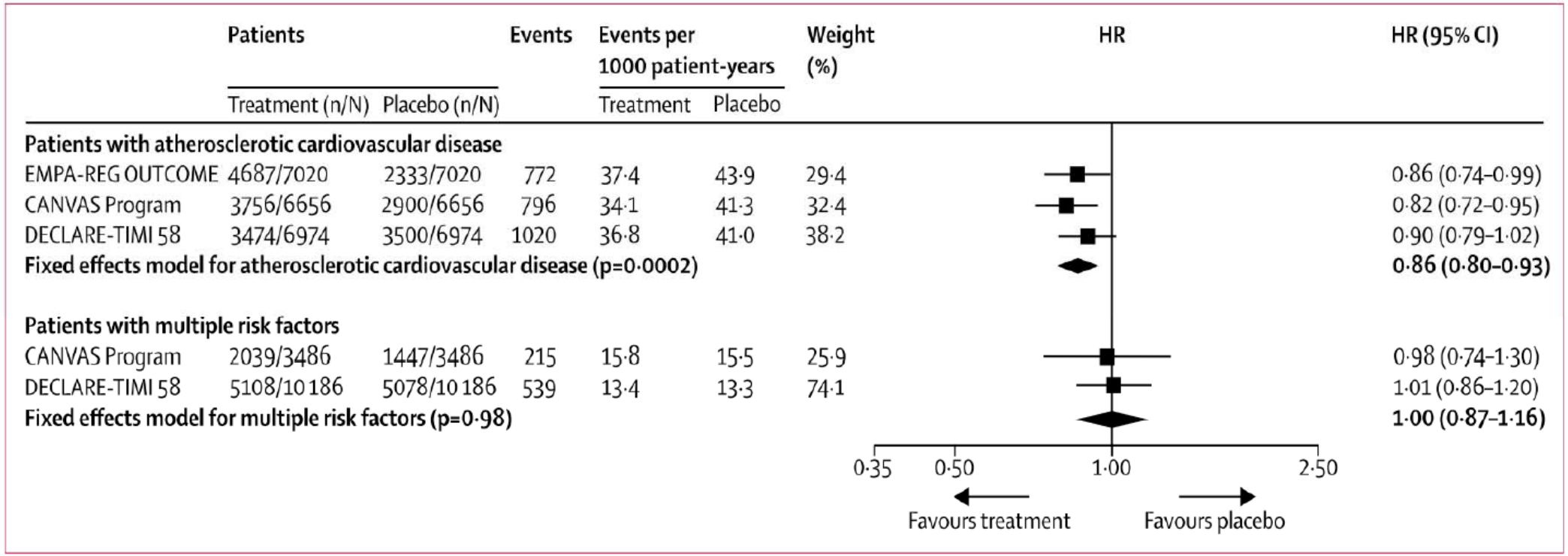


Figure 1: Meta-analysis of SGLT2i trials on the composite of myocardial infarction, stroke, and cardiovascular death (major adverse cardiovascular events) stratified by the presence of established atherosclerotic cardiovascular disease

*SGLT2i在有臨床動脈硬化心血管疾病者可以減少主要心血管事件(MACE)

Zelniker TA et al. Lancet. 2018 Nov 9. pii: S0140-6736(18)32590-X.
doi: 10.1016/S0140-6736(18)32590-X.

Cardio-Renal Syndrome Does Matter

	EMPA-REG	CANVAS	DECLARE	CREDENCE
CVD	99.2%	65.6%	40.6%	50.4%
non-CVD	0.8%	34.4%	59.4%	49.6%
Mean eGFR	74	76	85	56
Mean UACR	18	12	13	927

	EMPA-REG		CANVAS		DECLARE		CREDENCE	
	Active	Placebo	Active	Placebo	Active	Placebo	Active	Placebo
3P-MACE	37.4	**43.9**	26.9	**31.5**	22.6	**24.2**	38.7	**48.7**
HHF	9.4	**14.5**	5.5	**8.7**	6.2	**8.5**	15.7	**25.3**
CV death	12.4	**20.2**	11.6	**12.8**	7.0	**7.1**	19	**24.4**

no. of participants per 1000 patient-yr

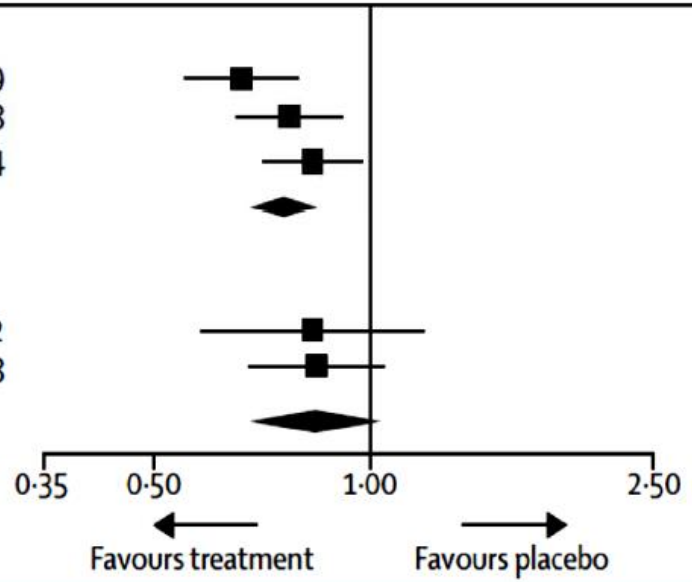
18. N Engl J Med 2015; 373:2117-2128
19. N Engl J Med 2017; 377:644-657
20. N Engl J Med 2019; 380:1880-1882
21. N Engl J Med 2019; 380:2295-2306

SGLT2i的CVOT摘要

	EMPA-REG	CANVAS Program	DECLARE	CREDENCE
Medication	empagliflozin	canagliflozin	dapagliflozin	canagliflozin
Study type	RCT	RCT	RCT	RCT
Patients	7020	10142	17160	4401
History of CVD, %	100	66	40.6	50
Follow-up, year (median)	3.1	2.4	4.2	2.62
Primary MACE Outcome, %	-14*	-14*	-7	-20*
CV Death, %	-38*	-13	-2	-22
Nonfatal MI, %	-13	-15	-11	-
Nonfatal Stroke, %	+24	-10	+1	-
Primary HHF or CV death Outcome, %	-	-	-17*	-31*
All-Cause Mortality, %	-32*	-13	-7	-17

SGLT2i有關HHF的整合分析* *(ASCVD vs MRF)*

	Patients		Events	Events per 1000 patient-years		Weight (%)	HR	HR (95% CI)
	Treatment (n/N)	Placebo (n/N)		Treatment	Placebo			
Patients with atherosclerotic cardiovascular disease								
EMPA-REG OUTCOME	4687/7020	2333/7020	463	19·7	30·1	30·9		0·66 (0·55–0·79)
CANVAS Program	3756/6656	2900/6656	524	21·0	27·4	32·8		0·77 (0·65–0·92)
DECLARE-TIMI 58	3474/6974	3500/6974	597	19·9	23·9	36·4		0·83 (0·71–0·98
Fixed effects model for atherosclerotic cardiovascular disease (p<0·0001)								**0·76 (0·69–0·84)**
Patients with multiple risk factors								
CANVAS Program	2039/3486	1447/3486	128	8·9	9·8	30·2		0·83 (0·58–1·19)
DECLARE-TIMI 58	5108/10 186	5078/10 186	316	7·0	8·4	69·8		0·84 (0·67–1·04)
Fixed effects model for multiple risk factors (p=0·0634)								**0·84 (0·69–1·01)**



*SGLT2i在有動脈心血管疾病者及多項風險因子者皆可減少心衰竭住院的發生

Zelniker TA et al. Lancet. 2018 Nov 9. pii: S0140-6736(18)32590-X. doi: 10.1016/S0140-6736(18)32590-X.

SGLT2i的CVOT摘要

	EMPA-REG	CANVAS Program	DECLARE	CREDENCE
Medication	empagliflozin	canagliflozin	dapagliflozin	canagliflozin
Study type	RCT	RCT	RCT	RCT
Patients	7020	10142	17160	4401
History of CVD, %	100	66	40.6	50
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Nonfatal Stroke, %	+24	-10	+1	-
Primary HHF or CV death Outcome, %	-	-	-17*	-31*
All-Cause Mortality, %	-32*	-13	-7	-17

TIMI Risk Score for Heart Failure in Diabetes (TRS-HFDM) in the Derivation Cohort

Risk Indicator	Adjusted HR (95% CI)	*P* Value	Points
Prior heart failure	4.22 (3.18–5.59)	<0.001	2
Atrial fibrillation	2.26 (1.62–3.14)	<0.001	1
Coronary artery disease	2.06 (1.45–2.93)	<0.001	1
eGFR <60 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$	1.85 (1.40–2.46)	<0.001	1
Urine albumin-to-creatinine ratio			
>300 mg/g	4.50 (3.18–6.36)	<0.001	2
30–300 mg/g	2.08 (1.50–2.87)	<0.001	1

- 0 points (low risk)
- 1 point (intermediate risk)
- 2 points (high risk)
- ≥3 points (very high risk)

Circulation. 2019;140:1569–1577.

Summary – 3.1

- 大型臨床試驗顯示Canagliflozin能有效降低T2DM合併心血管疾病病人的主要心血管不良事件(MACE)達14%，針對DKD更可以降低20%MACE發生率，也是唯一獲得美國FDA核准可用來降低MACE的OAD

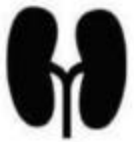
- 大型臨床試驗顯示Canagliflozin能有效降低T2DM合併CHF病人33%的住院風險，針對DKD更可以降低39%的住院風險。特別針對UACR>300mg的DKD病人，其發生CHF風險等同於已發生過CHF的病人，應積極處方SGLT2i來降低未來CHF風險

CREDENCE Result

Study design and participants

4401 patients with T2DM & UACR >300 mg/g

62 years

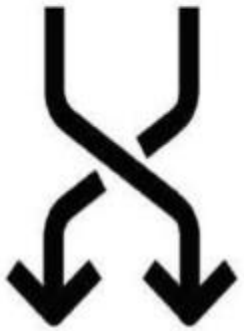


eGFR 57

UACR 927 mg/g

Intervention

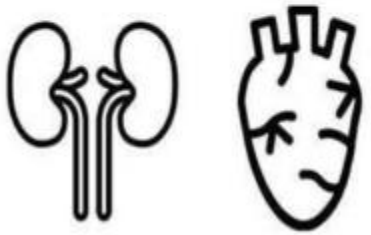
Stable on maximum dose tolerated ACEi or ARB for 4 weeks



Canagliflozin Placebo

Outcomes

Primary outcome
(Doubling of serum creatinine, ESKD, death due to cardiovascular or kidney disease)



HR 0.70
(95% CI 0.59-0.82)

NNT 21

End-stage kidney disease

HR 0.68
(95% CI 0.54-0.86)

NNT 42

No increased risk of:

Amputations

HR 1.10
(95% CI 0.79-1.56)

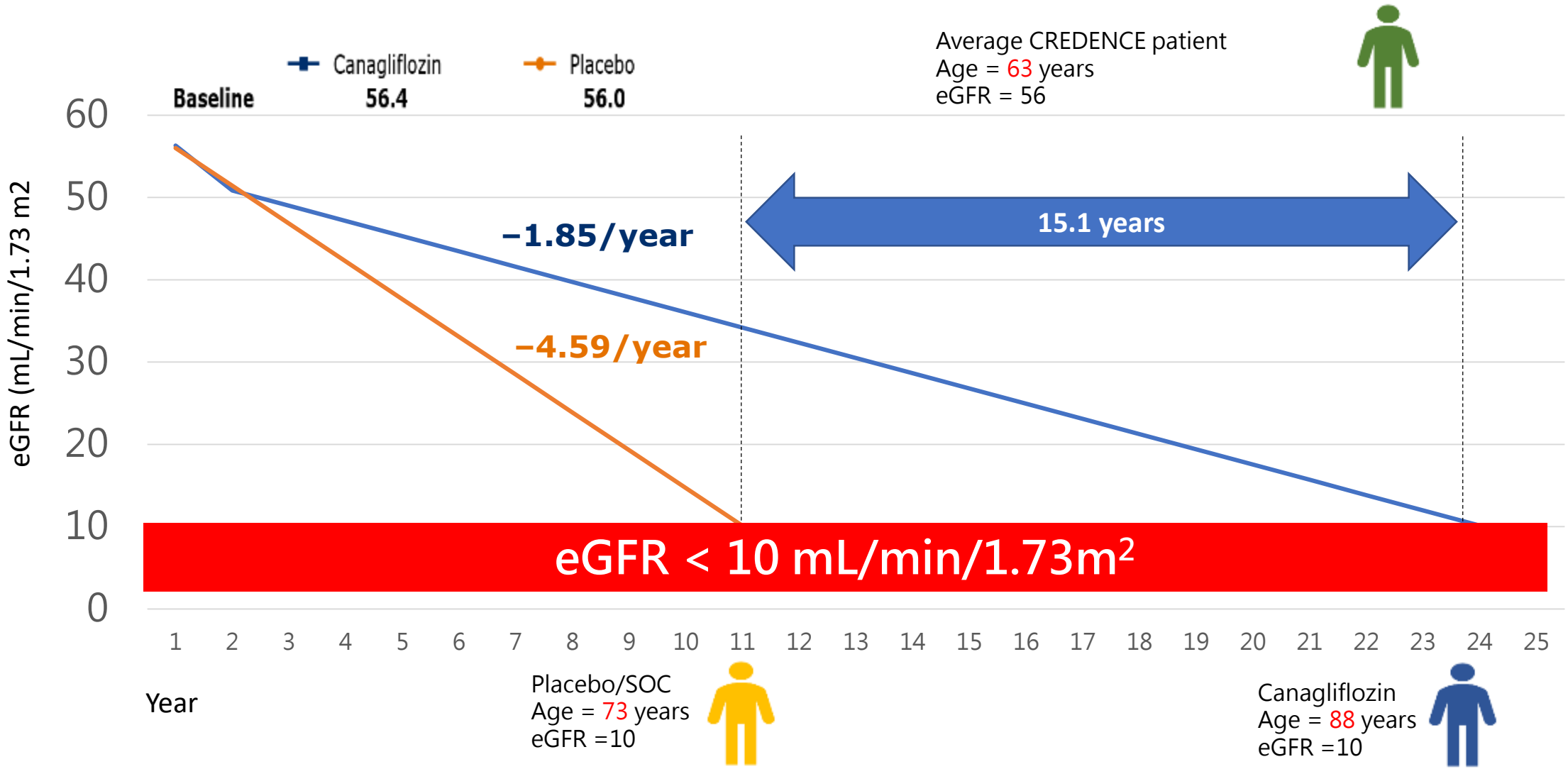
Fractures

HR 0.98
(95% CI 0.70-1.37)

Conclusion

In patients with type 2 diabetes and kidney disease, canagliflozin reduces the risk of kidney failure and cardiovascular events

根據CREDENCE Trial結論：用藥組可以延緩洗腎達15.1年

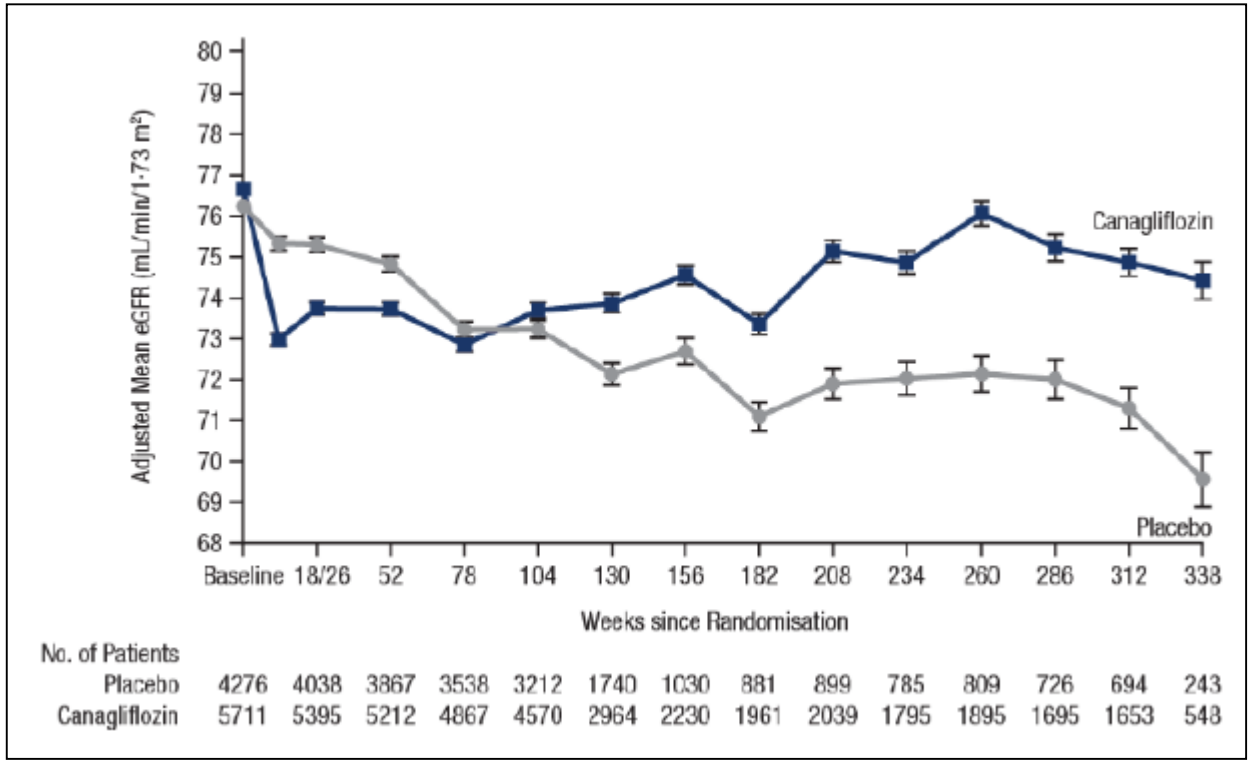


台灣地區平均壽命80.7歲

Meg J. Jardine presentation on IDF, 2019

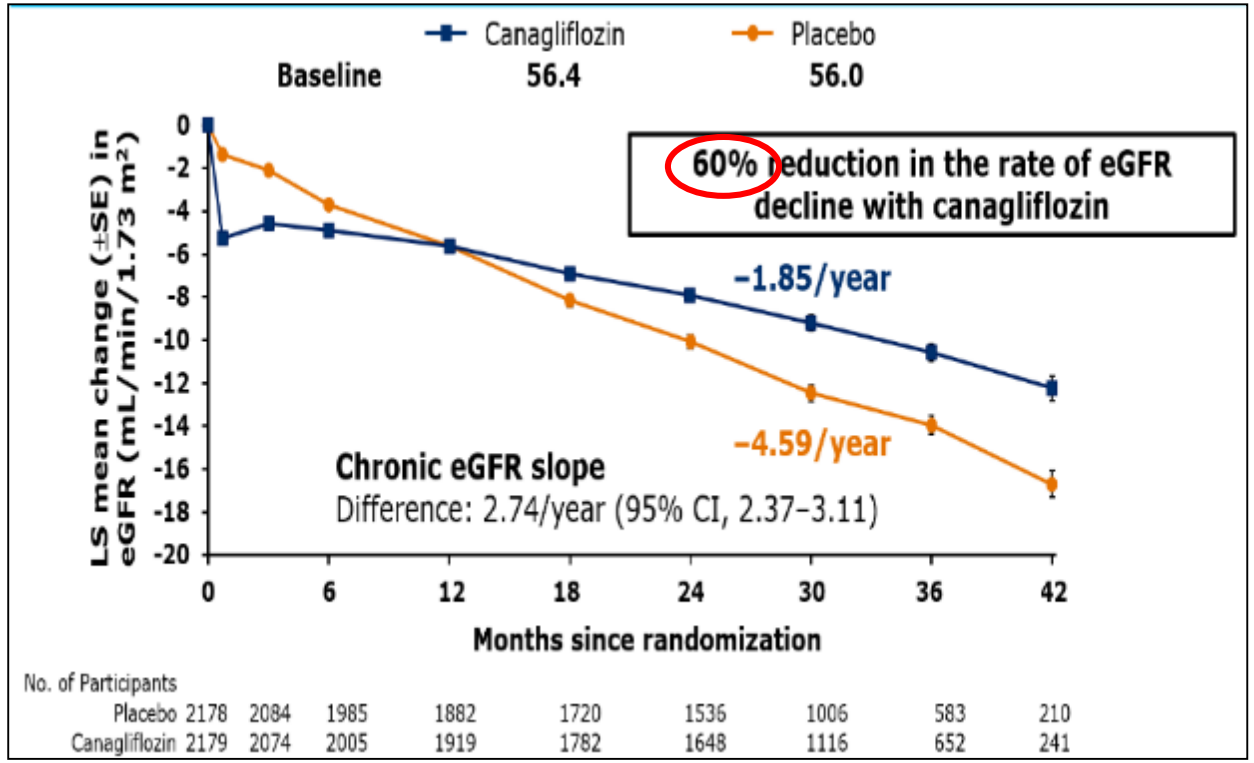
Effect on eGFR (CANVAS vs CREDENCE)

Secondary renal outcomes of the CANVAS/CANVAS R study



Mean eGFR 76 ml/min
Mean ACR 12mg/gCr

CREDENCE study

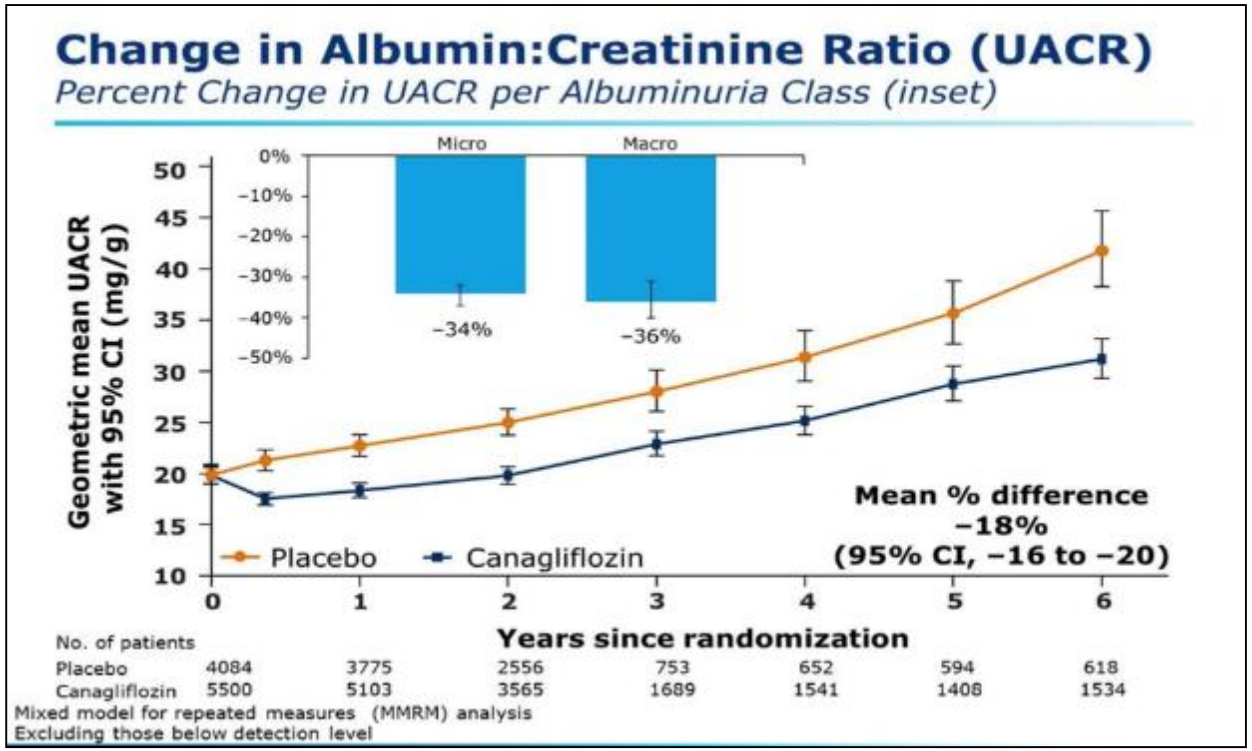


Mean eGFR 56 ml/min
Mean ACR 923 mg/gCr

N Engl J Med 2017; 377:644-657; 21. N Engl J Med 2019; 380:2295-2306; CAN-20200324.No2

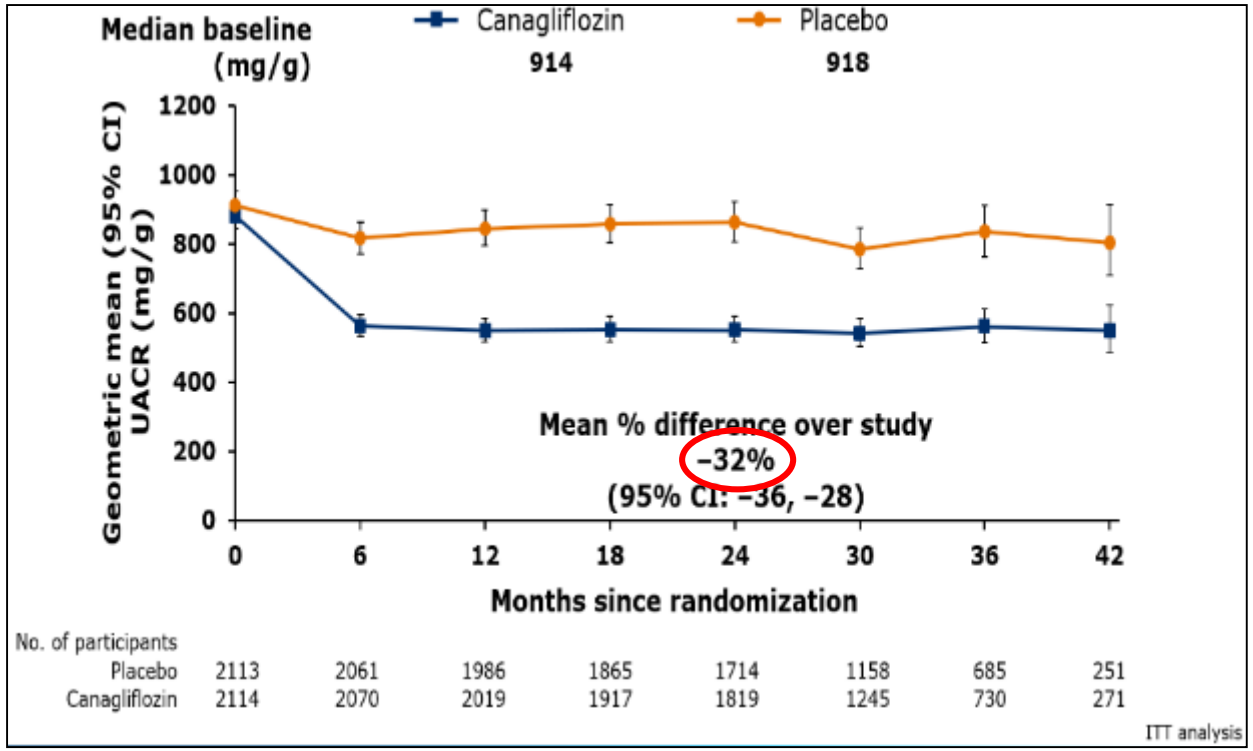
Effect on UACR (CANVAS vs CREDENCE)

Secondary renal outcomes of the CANVAS/CANVAS R study



Mean eGFR 76 ml/min
Mean ACR 12mg/gCr

CREDENCE study



Mean eGFR 56 ml/min
Mean ACR 927 mg/gCr

N Engl J Med 2017; 377:644-657; 21. N Engl J Med 2019; 380:2295-2306; CAN-20200324.No2

Summary – 3.2

- CREDENCE試驗證實，canagliflozin 100mg能有效降低DKD病人ESKD、血清肌酸酐倍增以及心腎死亡風險達30%，比起安慰劑更可以降低60%的eGFR惡化情形

- 對於沒有腎病變或是腎病變初期 (UACR 30-300mg/g)的病人，使用SGLT2i可以有效改善eGFR，建議盡早使用SGLT2i來保護腎臟

Canaglu 100mg 基本資訊

- 適應症：第二型糖尿病

- 用法用量：成人每日一次，於早餐前或早餐後口服 Canagliflozin 100 mg；eGFR低於45 mL/min/1.73 m^2時，應考慮中止投藥

- 健保代碼: BC26950100; 健保價: 28.8元/tab.

避免使用的病人類型

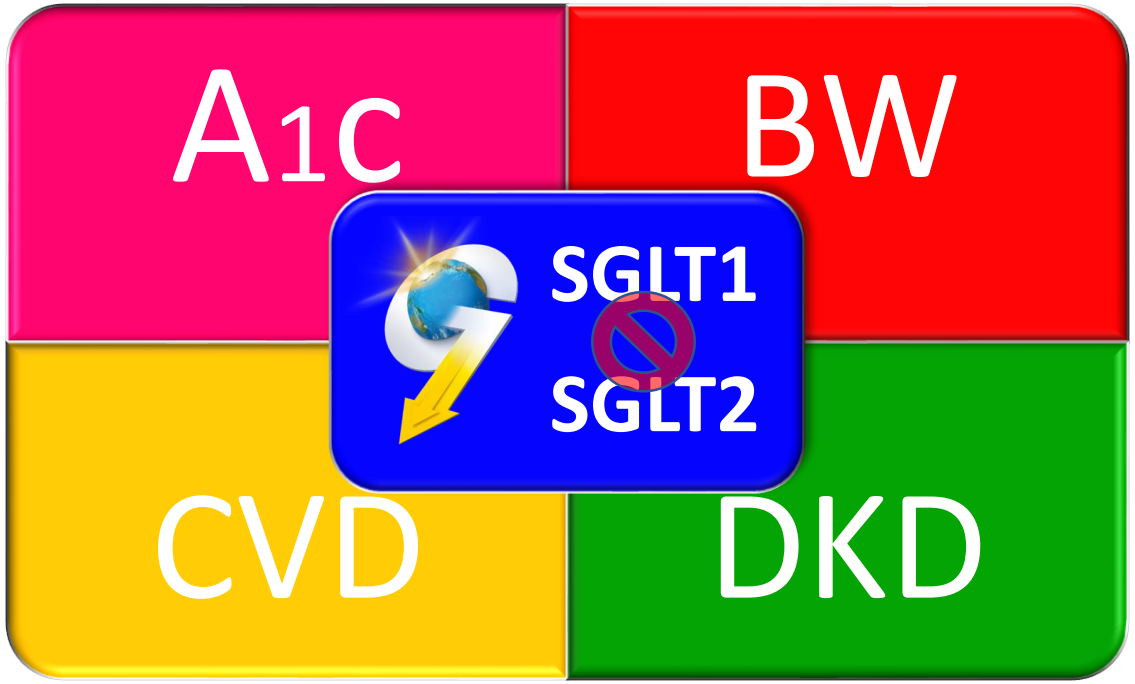
✓截肢(Amputation)

- 曾經截肢過的病人
- 患有周邊動脈阻塞疾病(PAOD)的病人(ABI<0.9)
- 患有糖尿病足潰瘍(DM foot ulcers)的病人

✓泌尿道感染(UTI)

- 無法時常喝水或常憋尿的病人(例如:作業員,工人...等)
- 年紀較大(>70歲)的病人
- 行動不便，插有導尿管或是生活無法自理的病人
- 免疫功能低下的病人

抑制1+2、降低ABCD



1	**SGLT1及SGLT2受體的雙重抑制效果** Canaglu 100mg具有SGLT1抑制效果，可延遲小腸吸收葡萄糖，並刺激GLP-1分泌，提供持續有效的血糖和體重控制效果
2	**排糖效果顯著 有效降低HbA1c** Canaglu 100mg每日可排出87克葡萄糖，降低0.8%~1.27% HbA1c，並可減輕體重達3kg (約4%)
3	**可提供T2DM病人心血管與腎臟雙重治療效益** ADA/AACE guideline建議優先處方SGLT2i包含Canagliflozin給合併ASCVD或是CHF/CKD的T2DM病人，臨床試驗證實Canagliflozin具有Primary / Secondary Prevention效果，CREDENCE是近20年唯一證實能降低T2DM末期腎病變的大型試驗，而且canagliflozin是唯一FDA核准降低MACE及DKD適應症的口服降血糖藥


POWER
FOKWARD
現在開始，適合穩糖
STEGLATRO®(Ertugliflozin)穩適妥
Steglatro®
(Ertugliflozin)

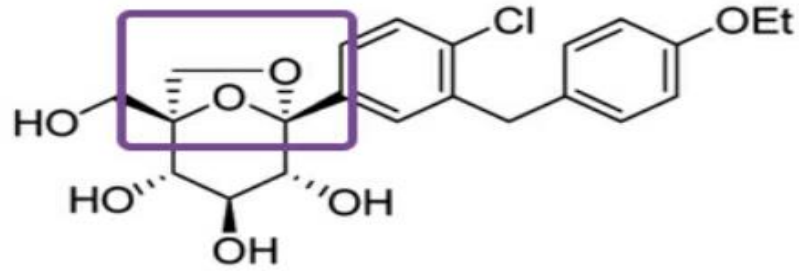
STEGLATRO 是一個高選擇性且半衰期長的SGLT-2 抑制劑

STEGLATRO SGLT2 /SGLT1選擇性超過2000倍

腎功能正常之第二型糖尿病患者中的平均排除半衰期為 16.6 小時[6]。

Compound	SGLT2 IC_{50}, nmol/L	SGLT1 IC_{50}, nmol/L	SGLT2/ SGLT1 Selectivity
Empagliflozin[2,3]	3.1	8,300	2,700
Ertugliflozin[2,4]	**0.9**	**1,960**	**2,200**
Dapagliflozin[2,3]	1.2	1,400	1,200
Canagliflozin[2,5]	4.2	663	160

STEGLATRO特殊的環狀結構
影響SGLT2選擇性與體內代謝速率[4]



Bridged Ketal System
剛性橋環結構

SGLT = sodium-glucose cotransporter; IC50 = half maximal inhibitory concentration;

1. Mascitti V et al. *J Med Chem*. 2011;54:2952–2960.
2. Mudaliar S et al. *Diabetes Care*. 2015;38:2344–2353.
3. Grempler R et al. *Diabetes Obes Metab*. 2012;14:83–90.
4. Mascitti V et al. *J Med Chem*. 2011;54:2952–2960.
5. Kuriyama C et al. *J Pharmacol Exp Ther*. 2014;351:423–431.
6. Steglatro Package Insert

VERTIS ASIA

VERTIS ASIA 收納包含台灣、中國、香港等亞洲等多國數據

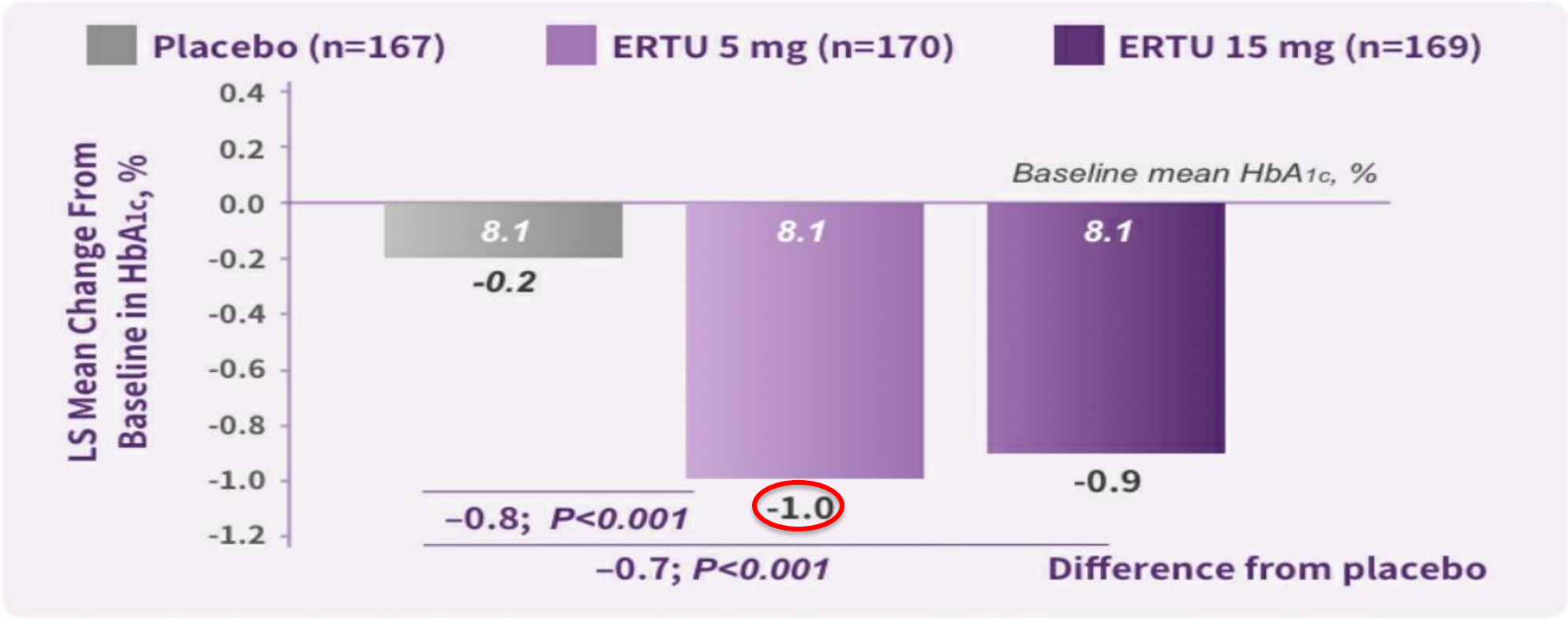
	Placebo (n=167)	ERTU 5 mg (n=170)	ERTU 15 mg (n=169)
Territory, n (%)			
China excluding HK & Taiwan	135 (80.8)	136 (80.0)	135 (79.9)
Other	32 (19.2)	34 (20.0)	34 (20.1)
Hong Kong	7 (4.2)	10 (5.9)	10 (5.9)
Korea, Republic of	9 (5.4)	13 (7.6)	10 (5.9)
Philippines	8 (4.8)	7 (4.1)	8 (4.7)
Taiwan	8 (4.8)	4 (2.4)	6 (3.6)

摘錄自Ji L et al[1]
[a]Data presented are mean (SD), unless otherwise stated.
VERTIS = eValuation of ERTugliflozin efficacy and Safety
1. *Diabetes Obes Metab*. 2019;21:1474–1482.

針對已使用Metformin 的亞洲第二型糖尿病患者

VERTIS-ASIA 研究指出STEGLATRO 可協助亞洲患者額外再提供HbA1c降幅(*p<0.001*)

Primary End Point, Full Analysis Set Population[a,b]



VERTIS-ASIA 是一個26周隨機雙盲試驗，收錄506位亞洲第二型糖尿病患(80.2%來自中國大陸)A病患依照1:1:1 比例(placebo, ertugliflozin 5 or 15 mg)隨機分派。主要療效指標為26周HbA1c基線變化。次要療效指標為26周空腹血糖基線變化、體重變化、收缩/舒張壓變化與病患HbA1c<7.0%的比例。

摘錄自 Ji L[1]

[a] The population includes all randomized patients who received at least 1 dose of study medication and had at least 1 measurement of the analysis variable (baseline or postbaseline). The mean and SD for the change from baseline are based on nonmissing values.

[b] Based on a cLDA model with fixed effects for treatment, time, prior antihyperglycemic medication (metformin monotherapy or metformin + another AHA), country (China, other), baseline eGFR (continuous), and the interaction of time by treatment. Time was treated as a categorical variable.

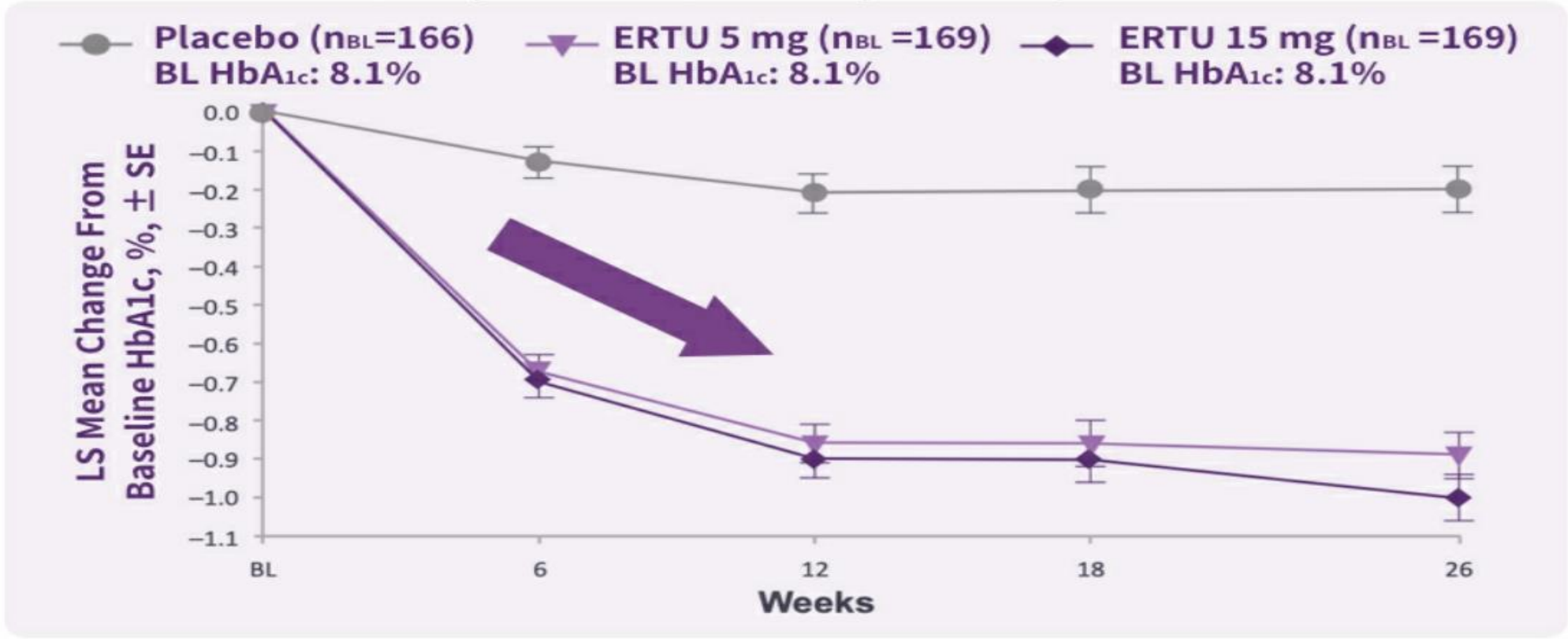
VERTIS = eValuation of ERTugliflozin efficacy and Safety; LS = least squares; ERTU = ertugliflozin; SD = standard deviation; cLDA = constrained longitudinal data analysis; AHA = antihyperglycemic agents; eGFR = estimated glomerular filtration rate. HbA1c=hemoglobin A1c

1. Diabetes Obes Metab. 2019;21:1474–1482.

針對已使用Metformin 的亞洲第二型糖尿病患者

STEGLATRO 可幫助亞洲第二型糖尿病患持續控制血糖

Primary End Point, Full Analysis Set Population[a]



VERTIS-ASIA 是一個26周隨機雙盲試驗，收錄506位亞洲第二型糖尿病患(80.2%來自中國大陸)A病患依照1:1:1 比例(placebo, ertugliflozin 5 or 15 mg)隨機分派。主要療效指標為26周HbA1c基線變化。次要療效指標為26周空腹血糖基線變化、體重變化、收縮/舒張壓變化與病患HbA1c<7.0%的比例。

摘錄自 Ji L[1]

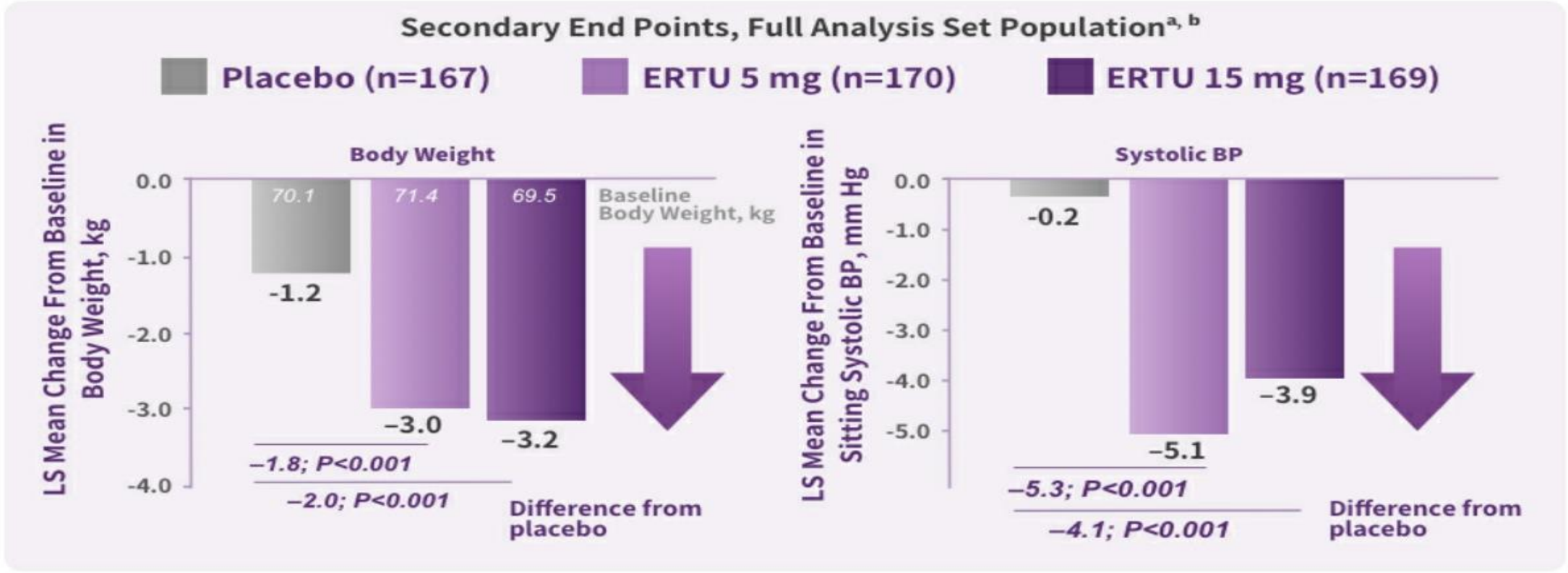
[a] aBased on cLDA model with fixed effects for treatment, time, antihyperglycemic medication status at screening, baseline eGFR (continuous), and the interaction of time by treatment. Time was treated as a categorical variable.

VERTIS = eValuation of ERTugliflozin efficacy and Safety; LS = least squares; SE = standard error; BL = baseline; ERTU = ertugliflozin; cLDA = constrained longitudinal data analysis; eGFR = estimated glomerular filtration rate; HbA1c=hemoglobin A1c

1. *Diabetes Obes Metab.* 2019;21:1474–1482.

針對已使用Metformin 的亞洲第二型糖尿病患者

STEGLATRO可額外提供顯著體重與血壓下降效果(*p<0.001*)



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主要療效指標為26周HbA1c基線變化。次要療效指標為26周空腹血糖基線變化、體重變化、收縮/舒張壓變化與病患HbA1c<7.0%的比例。

摘錄自Ji L[1]

ERTU is not indicated for weight loss or the treatment of hypertension.

[a] The population includes all randomized patients who received at least 1 dose of study medication and had at least 1 measurement of the analysis variable (baseline or postbaseline). The mean and SD for the change from baseline are based on nonmissing values.

[b] Based on a cLDA model with fixed effects for treatment, time, prior antihyperglycemic medication (metformin monotherapy or metformin + another AHA), country (China, other), baseline eGFR (continuous), and the interaction of time by treatment. Time was treated as a categorical variable.

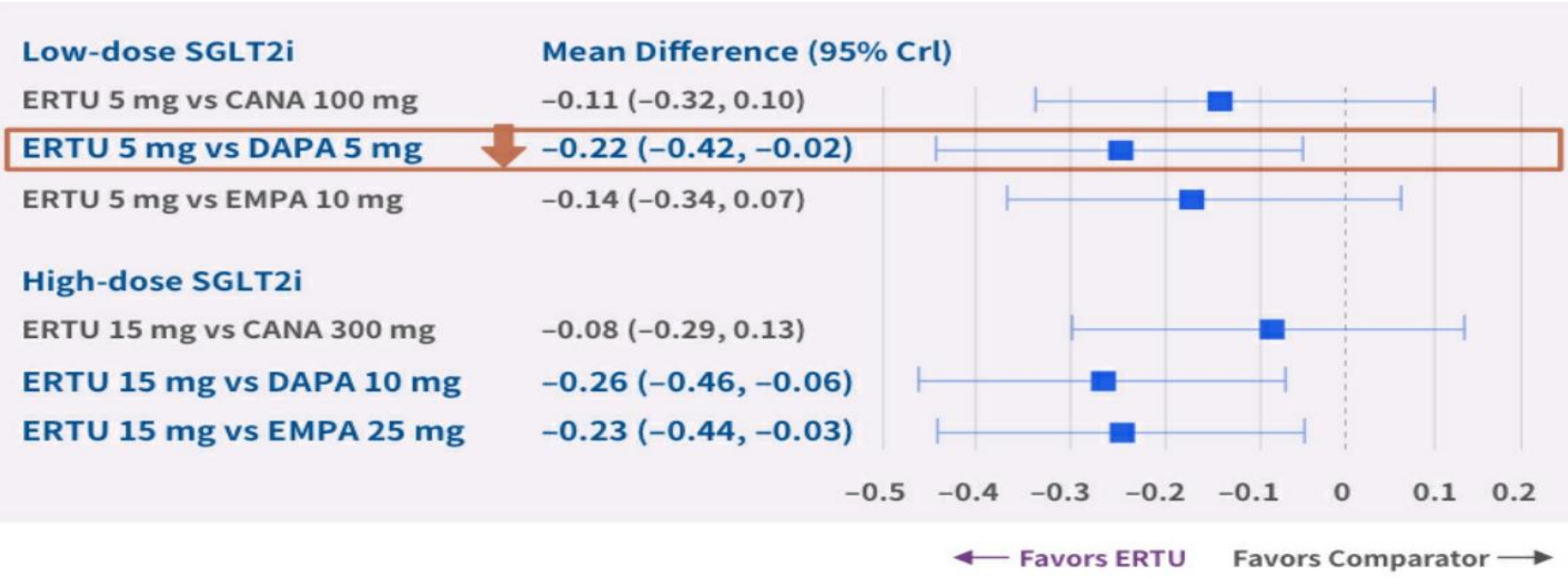
VERTIS = eValuation of ERTugliflozin efficacy and Safety; BP = blood pressure; LS = least squares; ERTU = ertugliflozin.

1. *Diabetes Obes Metab*. 2019;21:1474–1482.

網絡統合分析顯示STEGLATRO是一 強效降血糖SGLT-2抑制劑 [1]

Forest Plot for Change in HbA1c

HbA1c 變化, %



NMA methods have a number of inherent limitations.
- NMA is not considering as a head-to-head direct comparison study
- the analysis is observational in nature since patients can be randomized 'within' but not 'between' trials.
- despite searching secondary sources, such as labels, not all outcomes were available across all trials, which resulted in exclusion of some comparators for affected outcomes.
- between-study heterogeneity may have been present.

Adapted with permission from McNeill AM et al.[1]
SGLT2i = sodium-glucose cotransporter 2 inhibitor; CrI = credible interval; ERTU = ertugliflozin; CANA = canagliflozin; DAPA = dapagliflozin; EMPA = empagliflozin.
1. McNeill AM et al. *Diabetes Ther.* 2019;10:473–491.

周劍文診所
Chou Chien Wen Clinic

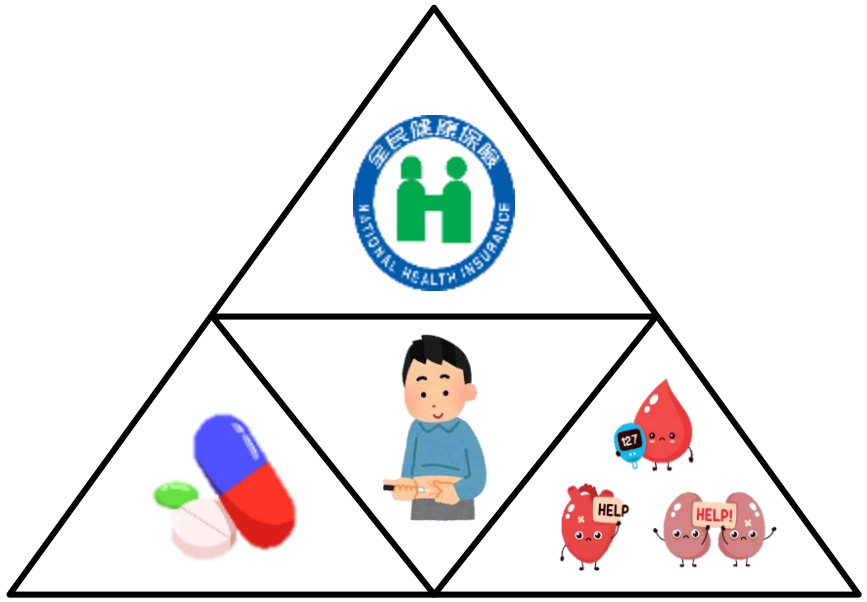
DDPV inhibitor/SGLT2 Inhibitor (Glyxambi, Q-Tern, Steglujan)

Gly x ambi

Glycemia

拉丁字根: Both

從健保給付規範、糖尿病共病與藥品特性來思考糖尿病合併用藥策略



Glyxambi® (empagliflozin/ linagliptin)

SGLT2i

每日藥費: 29~30.7

✓ 健保部份條件給付
✓ 作用機轉適合併用

X 健保不給付
✓ 作用機轉適合併用

DPP4i

每日藥費: 18.2~25

X 健保不給付
X 作用機轉不適併用

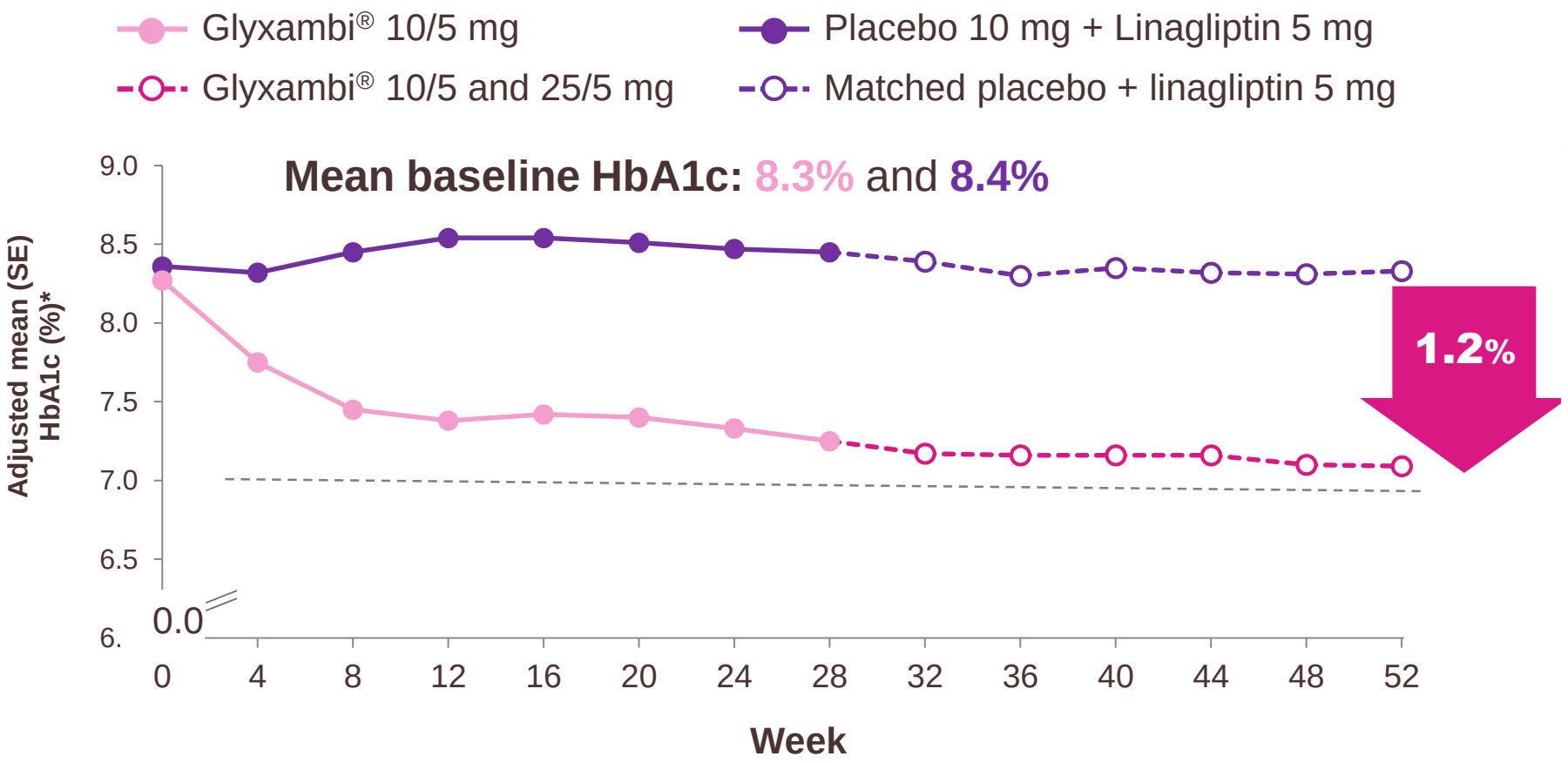
GLP1

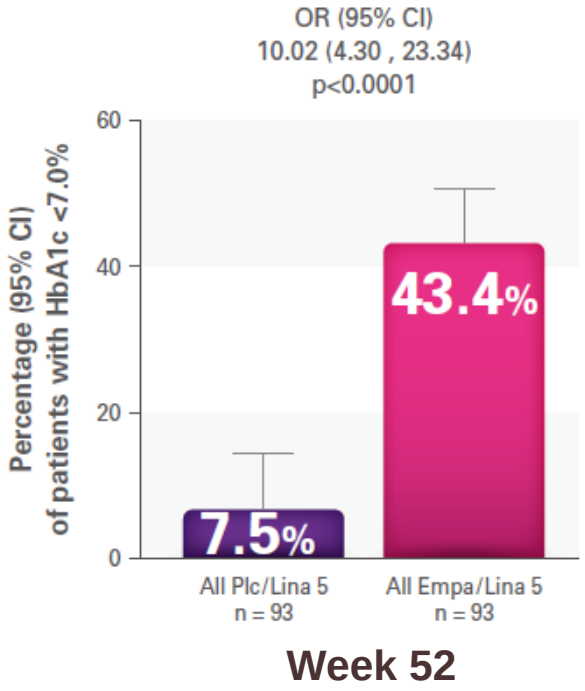
每日藥費: 110~133

Glyxambi® (empagliflozin/ linagliptin)

衛生福利部中央健康保險署

日本族群顯示，使用 **Linagliptin** 未達標患者轉換至**Glyxambi**，可顯著降低 **HbA1c** 達 **1.2%**，達標率提升將近六倍



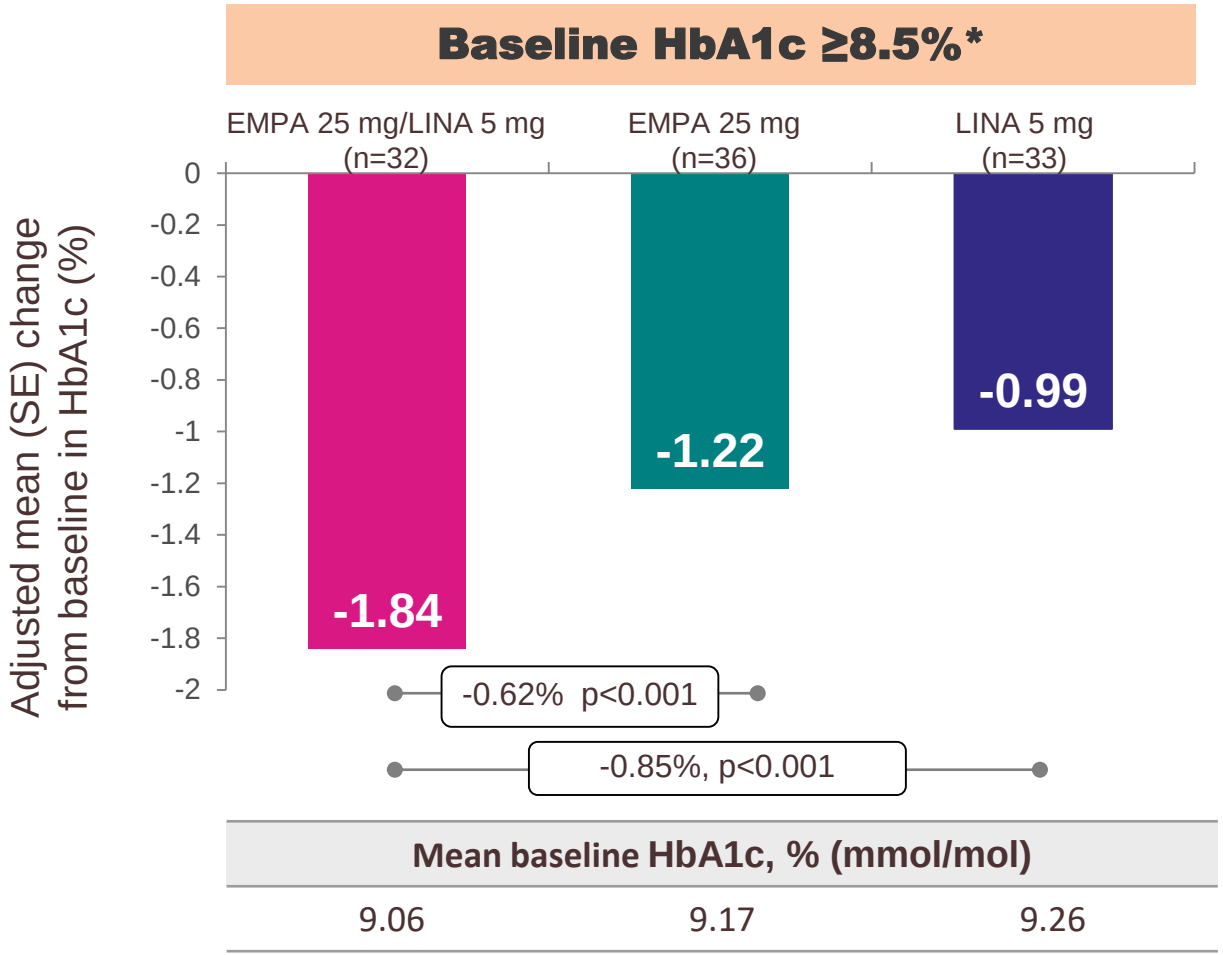


FDC, fixed-dose combination

Kawamori R *et al. Diabetes Obes Metab* 2018;20:2200

Glyxambi® (empagliflozin/linagliptin)

Glyxambi 提供強效降糖效果



*69 mmol/mol. Analysis of covariance in full analysis set (LOCF) , EMPA, empagliflozin; HbA1c, glycosylated haemoglobin; LINA, linagliptin; LOCF, last observation carried forward; SE, standard error

DeFronzo RA *et al. Diabetes Care* 2015;38:384

Glyxambi® (empagliflozin/linagliptin)

Glyxambi 安全性佳，低血糖風險低

	Glyxambi® 10/5 mg (n=135)	Glyxambi® 25/5mg (n=134)	Empagliflozin 10 mg (n=137)	Empagliflozin 25 mg (n=140)	Linagliptin 5 mg (n=128)
Overall hypoglycaemia (%)	2.2	3.6	1.4	3.5	2.3
Severe hypoglycaemia (%)	0	0	0	0	0

DeFronzo RA *et al. Diabetes Care* 2015;38:384

Glyxambi® (empagliflozin/linagliptin)

Glyxambi 藥錠小，提升服藥順服性

…**regardless of food**

…by patients with **eGFR ≥45 ml/min/1.73 m²** with **no dose adjustment** required

Glyxambi® is **not recommended** for use in patients with **persistent eGFR <45 ml/min/1.73 m²**

Glyxambi® (empagliflozin/ linagliptin)

Boehringer Ingelheim and Eli Lilly. Glyxambi® (empagliflozin and linagliptin) Prescribing Information.

Glyxambi 適合的病患族群以及處方時機 – 先前使用 Lina

原給付規範

Metformin 作為第一線用藥
合併使用過 linagliptin
A1C 仍未達標

SU	TZD	Insulin	自費 SGLT2i
- 低血糖 - 體重增加 - 服藥顆數+1	- 水腫 - 體重增加 - 心衰竭 - 服藥顆數+1	- 低血糖 - 體重增加 - 需克服打針	- 自費用藥 增加經濟負擔

病患加藥後可能須注意之事項

新給付規範

Metformin 作為第一線用藥
合併使用過 linagliptin 治療六個月
A1C 仍高於 7.5%

Glyxambi

病患用藥改變後之好處

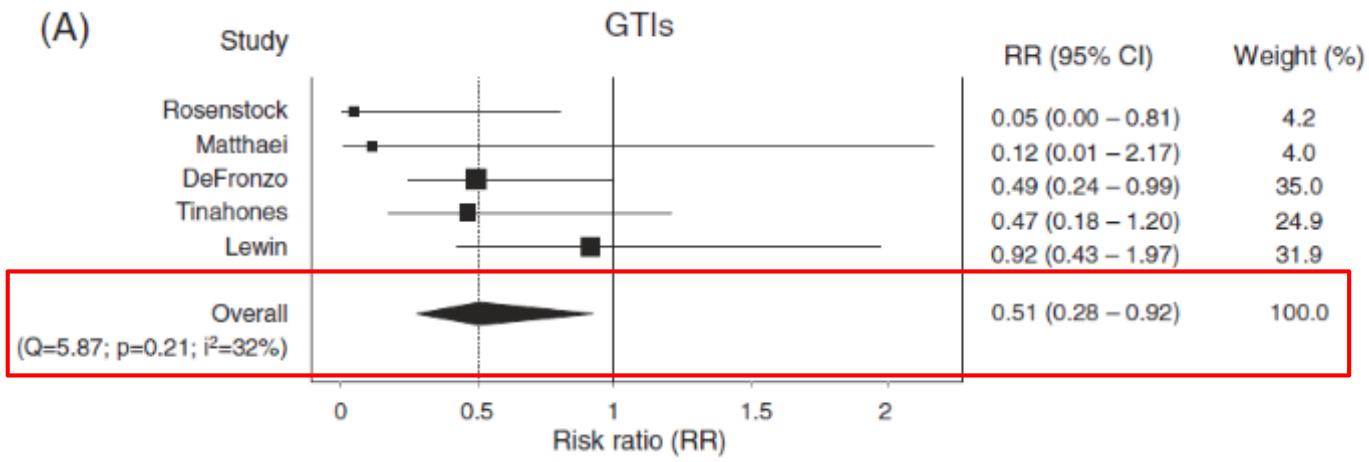
+ 服藥顆數不變
+ 降低體重與血壓
+ 增加心血管保護
+ 不增加病患經濟負擔

全民健康保險藥物給付項目及支付標準第五節激素及影響內分泌機轉藥物

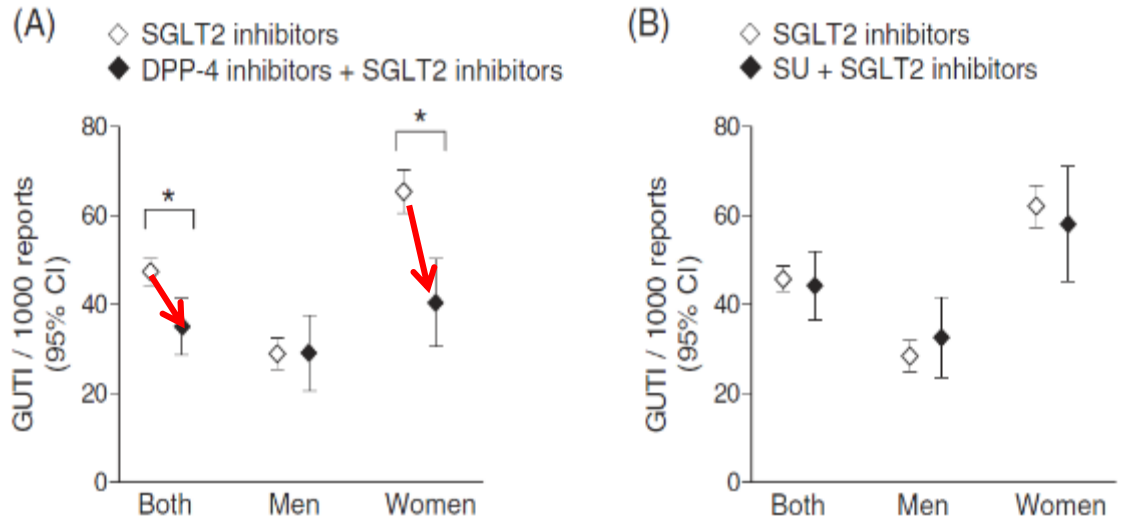
Glyxambi® (empagliflozin/linagliptin)

綜合分析顯示，相較於單獨使用SGLT2i，DPP4i/SGLT2i 治療組合可降低GTI風險達49%

Meta-analysis of 5 RCTs compared DPP4i+SGLT2i vs. SGLT2i



FDA Adverse Event Report System (2014-2016)



GTI risk 49%↓
(DPP4i/SGLT2i combination v.s.SGLT2i alone)

The risk of GUTIs was not moderated by the SU/SGLT2i combination vs SGLT2i alone

(empagliflozin/
linagliptin)

Diabetes Obes Metab. 2018 Mar;20(3):740-744.

Expert Opinion on Drug Safety

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ieds20

Safety and tolerability of empagliflozin and linagliptin combination therapy in patients with type 2 diabetes mellitus: a pooled analysis of data from five randomized, controlled clinical trials

Table 4. Adverse events of special interest.

	EMPA/LINA[a] (n = 1410)		EMPA 10 or 25 mg (n = 1015)		LINA 5 mg (n = 470)	
	n (%)	Rate/100 patient-years	n (%)	Rate/100 patient-years	n (%)	Rate/100 patient-years
Hypoglycemia[b]	11 (0.8)	1.02	16 (1.6)	2.04	6 (1.3)	1.55
Severe hypoglycemia[c]	1 (0.1)	0.09	1 (0.1)	0.13	0	0
Urinary tract infection[d]	131 (9.3)	12.85	96 (9.5)	12.91	51 (10.9)	14.17
Male	24/879 (2.7)[e]	3.56	20/591 (3.4)[e]	4.57	10/275 (3.6)[e]	4.40
Female	107/531 (20.2)[e]	30.91	76/424 (17.9)[e]	24.85	41/195 (21.0)[e]	30.90
Genital infection[f]	43 (3.0)	4.07	52 (5.1)	6.80	9 (1.9)	2.33
Male	18/879 (2.0)[e]	2.67	20/591 (3.4)[e]	4.56	3/275 (1.1)[e]	1.29
Female	25/531 (4.7)[e]	6.52	32/424 (7.5)[e]	9.81	6/195 (3.1)[e]	3.89

Publisher: Taylor & Francis & Informa UK Limited, trading as Taylor & Francis Group
Journal: Expert Opinion on Drug Safety
DOI: 10.1080/14740338.2020.1782884

2020 台灣糖尿病學會指引: SGLT2i 具有心腎臨床實證
當病患有心腎風險及共病時建議使用 SGLT2i

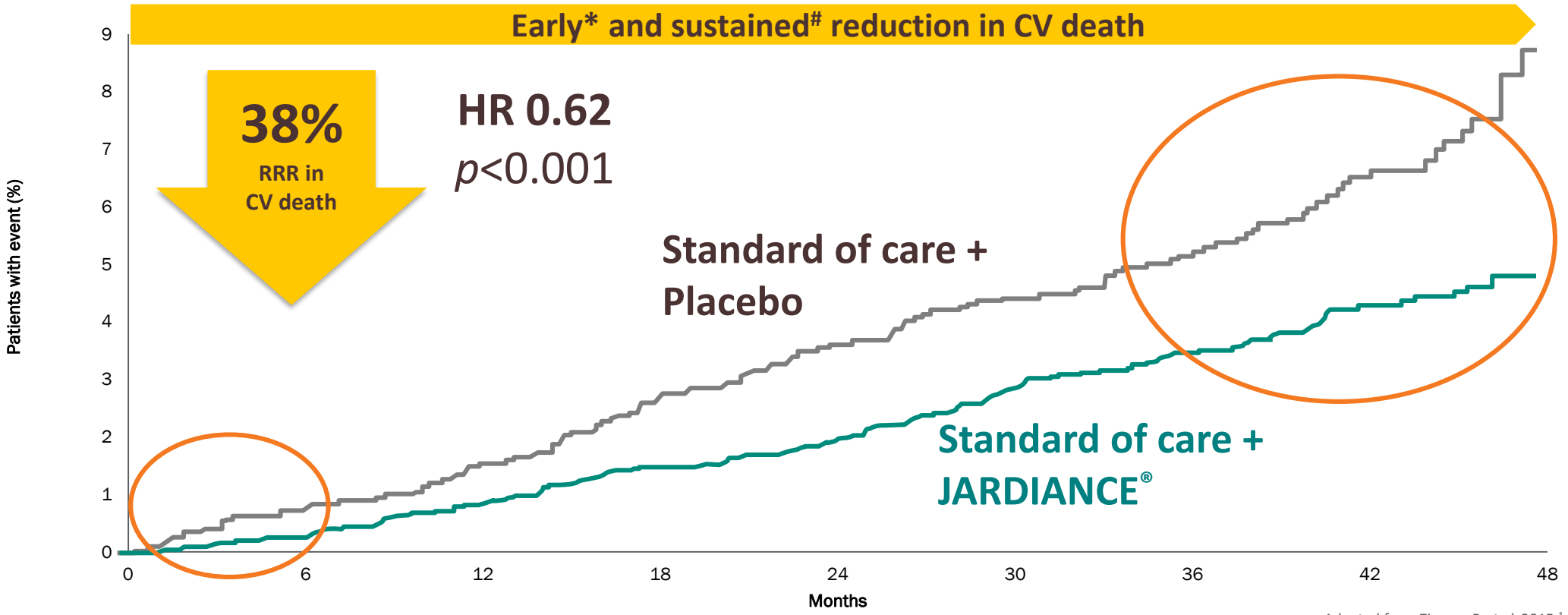
SGLT2i	GLP1-RA	TZD
心血管實證：有(建議使用) 心衰竭實證：強(建議使用) 腎病變實證：強(建議使用) 控制血糖效果：中等 體重：下降 低血糖：低 副作用：糖尿病酮酸中毒、生殖泌尿道感染、骨折、截肢、脫水	心血管實證：部分有(建議使用) 心衰竭實證：中立 腎病變實證：有(蛋白尿) 控制血糖效果：佳 體重：下降 低血糖：低 副作用：腸胃道	心血管實證：有 心衰竭實證：不建議使用 腎病變實證：缺 控制血糖效果：佳 體重：增加 低血糖：低 副作用：水腫、心衰竭、骨折

DPP4i	AGI	SU/Glinide
心血管實證：中立 心衰竭實證：部分中立 腎病變實證：有(蛋白尿) 控制血糖效果：中等 體重：無影響 低血糖：低 副作用：少見	心血管實證：中立 心衰竭實證：缺 腎病變實證：缺 控制血糖效果：中等 體重：稍下降 低血糖：低 副作用：腸胃道	心血管實證：缺 心衰竭實證：缺 腎病變實證：缺 控制血糖效果：佳 體重：增加 低血糖：中 副作用：低血糖

Glyxambi® (empagliflozin/linagliptin)

DAROC Clinical Practice Guidelines for Diabetes Care 2018 (2020修訂版)

Empagliflozin 顯著減少 38% 心血管死亡風險



Adapted from Zinman B *et al.* 2015.[1]

Results achieved on top of standard of care

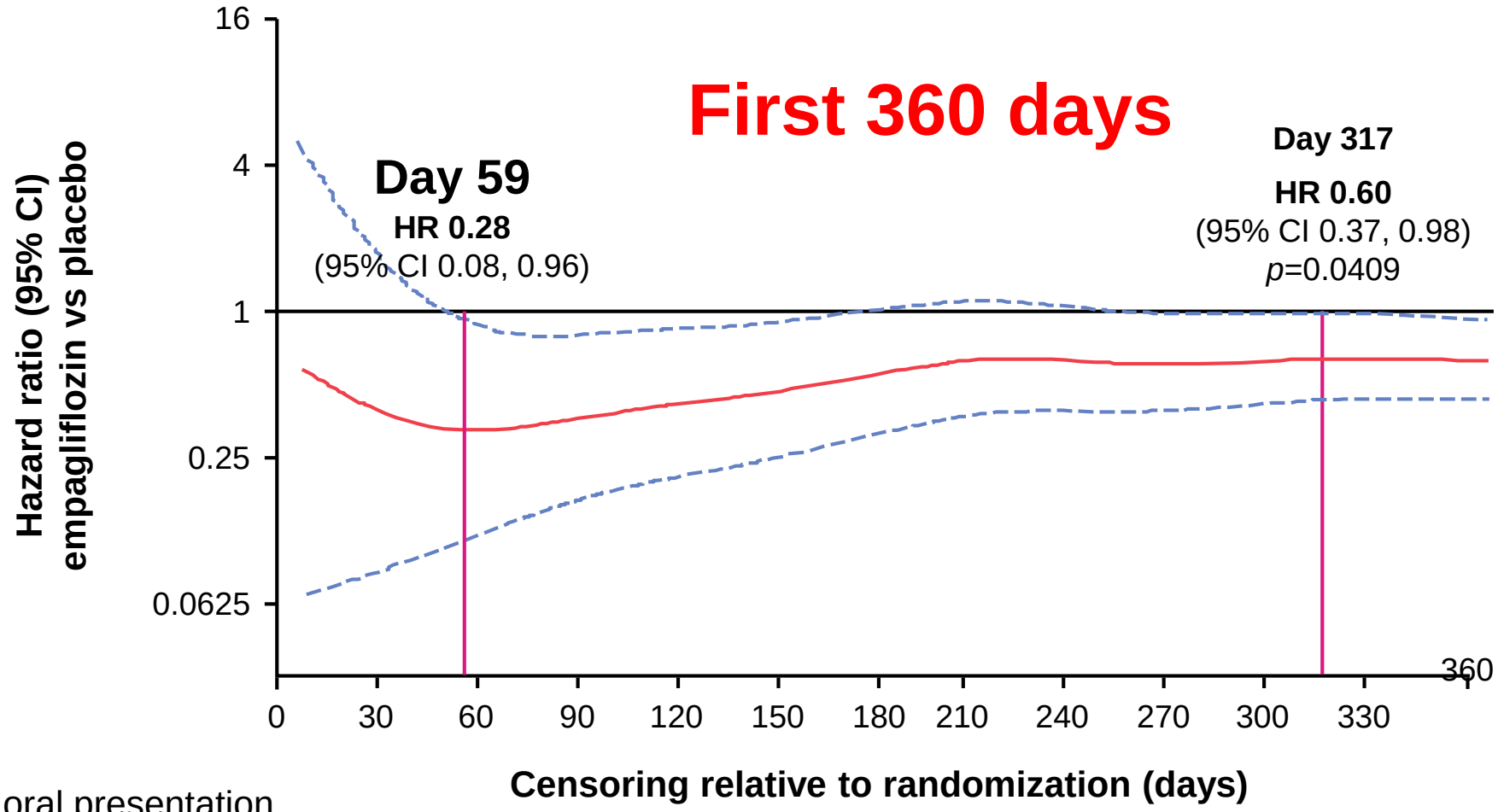
- Antihypertensive / Lipid lowering agents / Anticoagulants / Glucose lowering agents

*Within 6 months from start. #Up to 48 months from start.
CV death was a pre-specified secondary endpoint. Cumulative incidence function. HR, hazard ratio
The absolute risk for CV death was 5.9% in patients receiving standard of care plus placebo and was reduced to 3.7% in patients receiving standard of care plus JARDIANCE® (p<0.001).[1] Zinman B *et al. N Engl J Med* 2015;373:2117-28.

EMPA-REG OUTCOME®

Glyxambi® (empagliflozin/linagliptin)

根據 EMPA-REG OUTCOME 數據分析
使用 Jardiance 第 59 天就觀察到降低 CV death



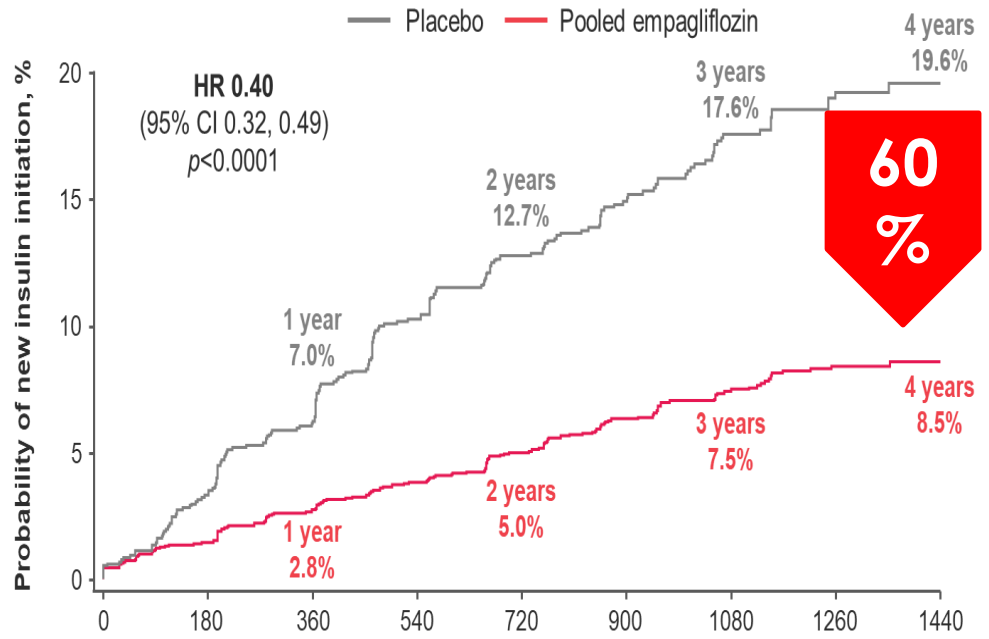
2020 ADA oral presentation

Cox regression for time to CV death, pooled empagliflozin versus placebo. Hazard ratios and 95% confidence intervals (CI) are shown in relation to time point of censoring – treated set.
CV, cardiovascular.

Glyxambi® (empagliflozin/linagliptin)

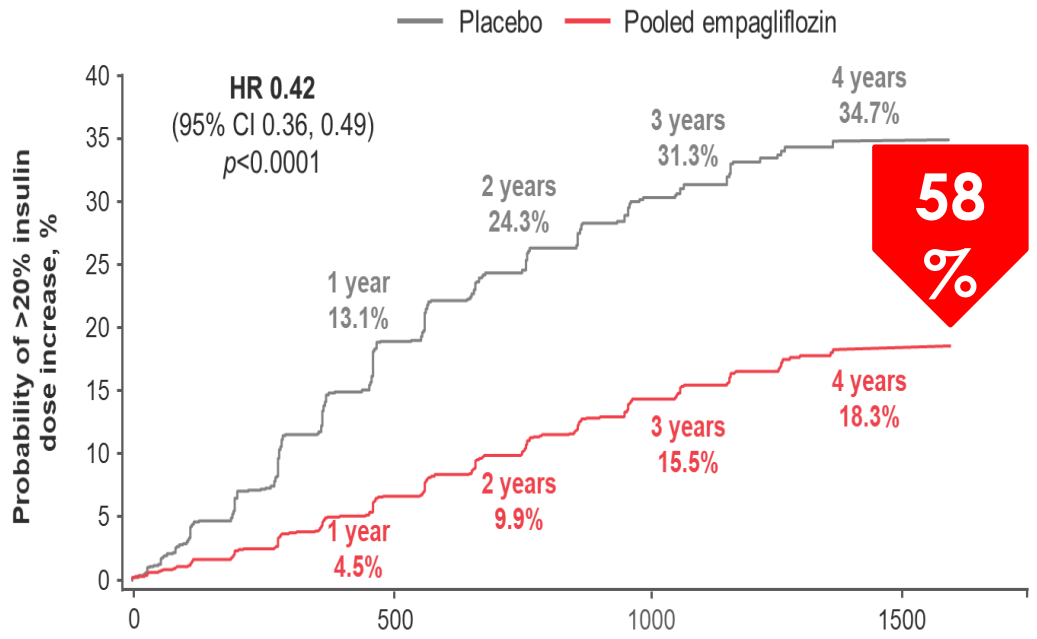
根據 EMPA-REG OUTCOME 數據分析使用 Jardiance 組別，需要額外加上胰島素或是增加劑量 >20%之比例皆較低

先前未使用胰島素 加入試驗後需要使用胰島素



No. of participants									
Placebo	1198	1132	1084	1010	888	659	550	364	86
Empagliflozin	2435	2370	2306	2234	2002	1458	1251	872	220

先前有使用胰島素 試驗後需要增加劑量 >20%

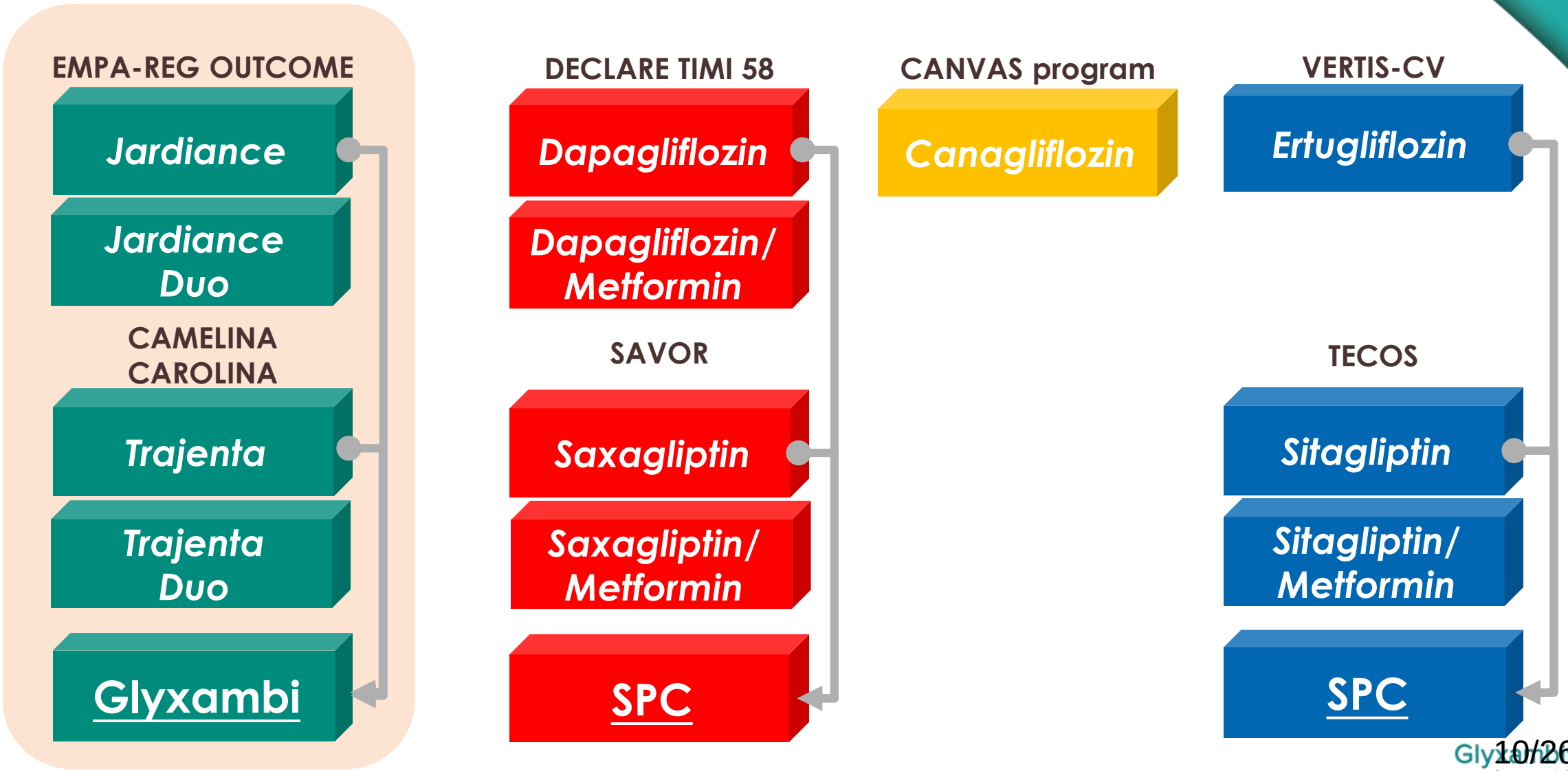


No. of participants				
Placebo	1135	877	412	4
Empagliflozin	2252	2016	1061	23

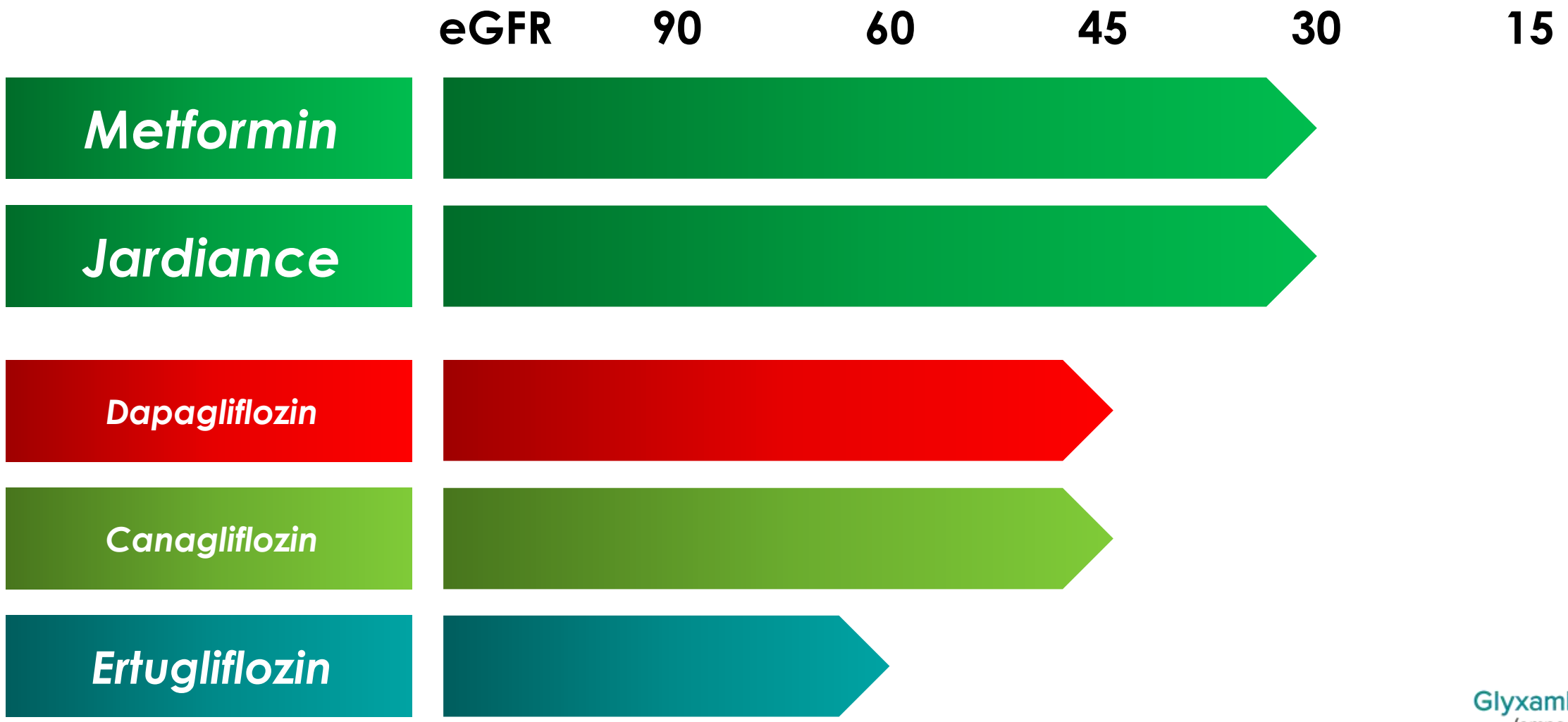
Glyxambi® (empagliflozin/linagliptin)

2020 ADA oral presentation

在健保給付規範之下，先選擇 empa 後續可選擇更好的產品組合



台灣仿單腎功能適用範圍目前 Jardiance 與 metformin 一樣，eGFR 30 ml/min/1.73 m² 以上皆可使用



Glyxambi® (empagliflozin/linagliptin)

2020 Consensus of Taiwan Society of Cardiology on the pharmacological management of patients with type 2 diabetes and cardiovascular diseases

Glyxambi®
(empagliflozin/ linagliptin)

提供血糖難以達標患者的控糖新選擇

衛福部適應症

適用於配合飲食控制及運動，以改善下列第二型糖尿病患者的血糖控制：使用metformin合併empagliflozin或linagliptin未能達到適當血糖控制者；或已在使用empagliflozin及linagliptin合併治療者。

Empagliflozin用於具第二型糖尿病且已有心血管疾病的成人病人時，可降低心血管原因死亡的風險。然而，本品糖順平用於具第二型糖尿病且已有心血管疾病的成人病人時，其降低心血管原因死亡的風險的有效性尚未被建立。

健保給付條件

1. 每日限處方1粒。
2. 限用於已接受過最大耐受劑量的metformin，且併用empagliflozin或linagliptin治療至少6個月，糖化血色素值(HbA1c)仍高於7.5%者。

健保價: 35.1元/顆

(empagliflozin/
linagliptin)

EXTEND THE LIGHT DOUBLE TO GOAL

順適控糖 加倍達標

QTERN®

(saxagliptin/dapagliflozin)

5mg/10mg tablets

控糖穩 膜衣錠

DPP4i & SGLT2i：治療指引建議不易低血糖的藥物選擇[1]

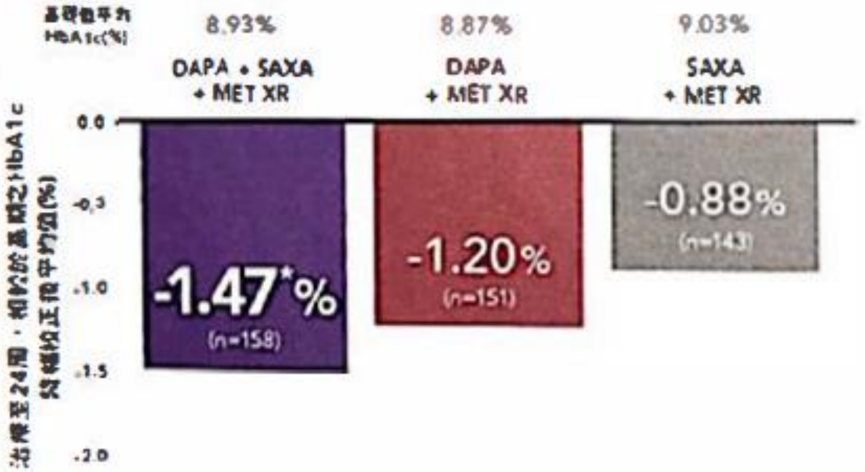
QTERN[®]：結合 SGLT2i 與 DPP4i 雙重機轉，協同增效

1
2
3
4

相較各單一成分併用於 Metformin XR 之治療

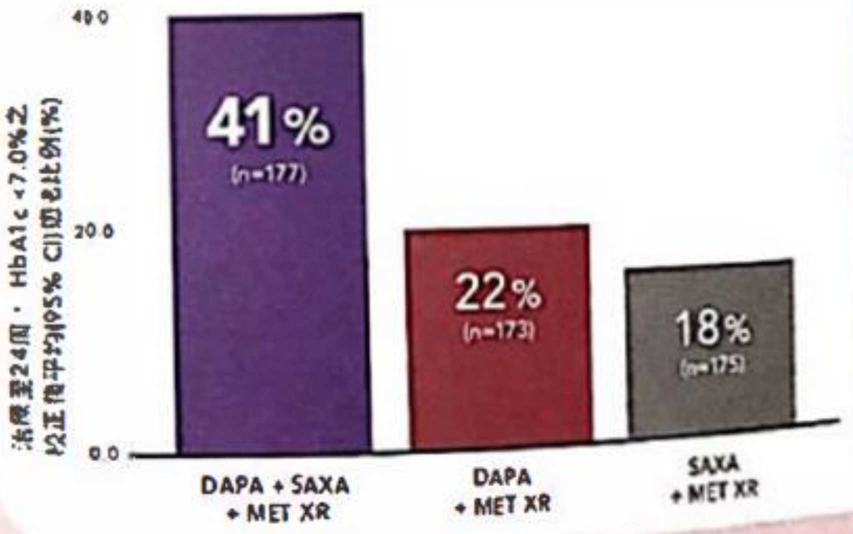
DAPA+SAXA 提供優越 HbA1c 降幅，有效提升達標率#

治療 24 周時，平均 HbA1c 降幅達 1.47%



此研究之試驗組是使用 dapagliflozin 和 saxagliptin 的自由組合 (free combination)

治療 24 周時，達標率提升近 2 倍



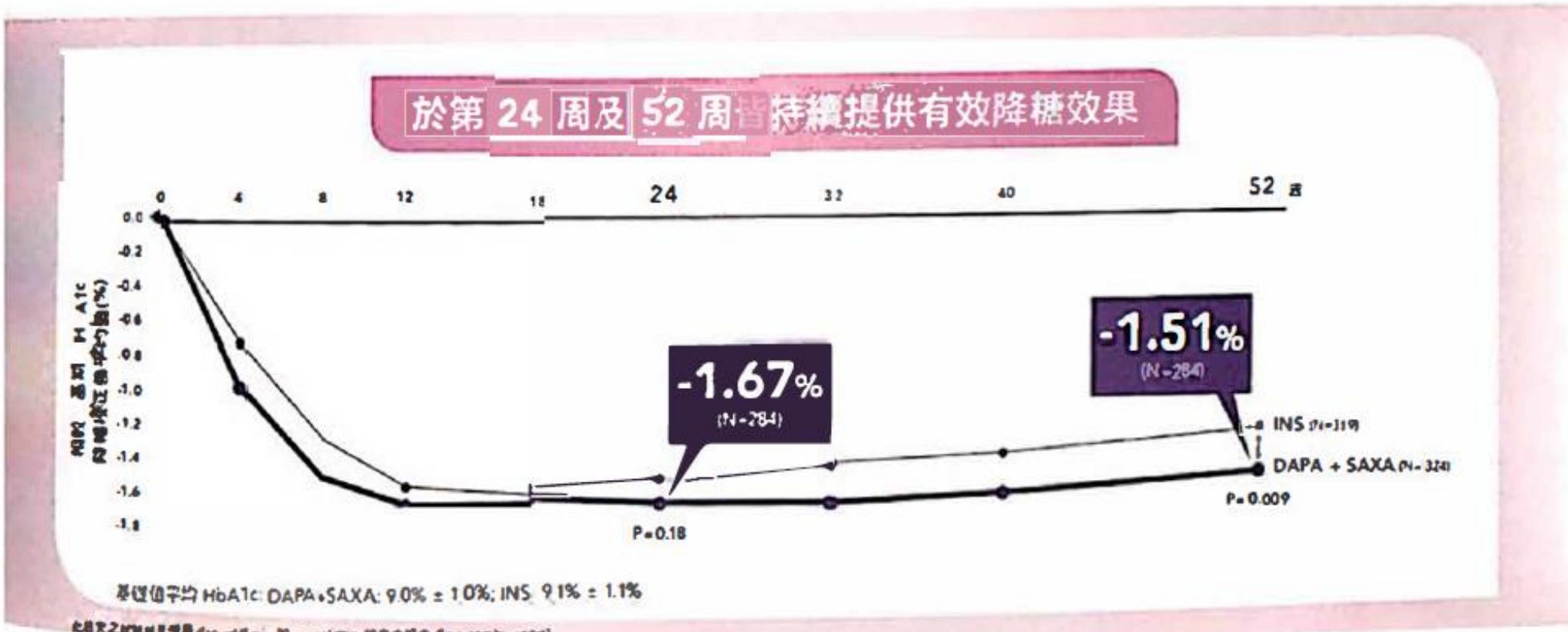
DAPA, dapagliflozin; SAXA, saxagliptin; MET, metformin # HbA1c <7 % * P<0.0001 saxagliptin vs DAPA+SAXA; P=0.0166 dapagliflozin vs DAPA+SAXA

Study design: Efficacy and safety of DAPA+SAXA were compared in a multicentre, double blind, active-controlled, phase 3 study in patients poorly controlled on metformin [illegible]

Reference: Rosenstock J, et al. Diabetes Care 2015;38(3):376–383

針對已使用 Metformin IR / XR（無論有無使用 SU）仍未達標之患者

DAPA+SAXA 可提供相當於基礎胰島素之 HbA1c 持久降幅



此研究之試驗組是使用 dapagliflozin 和 saxagliptin 的自由組合 (free combination)

DAPA+SAXA 組於 52 周時 HbA1c<7% 且無低血糖者，顯著多於 INS 組 (*DAPA+SAXA 17.6%; INS 9.1%, p<0.001*)

DAPA + SAXA: DAPA (10 mg/day) + SAXA (5 mg/day) + metformin ± SU; INS, titrated insulin glargine (100 units/ml/day) + metformin ± SU. DAPA, dapagliflozin; SAXA, saxagliptin; SU, sulfonylurea.

Study design: A international, multicenter, randomized, open label, two-arm, parallel group, phase 3b, 24 week (short term) study with a 28 week extension (long term) period open label trial to evaluate the efficacy, safety and tolerability of saxagliptin 5 mg co-administered with dapagliflozin 10 mg compared to insulin glargine with regards to HbA1c, body weight and glycaemic control in ≥18y T2D patients inadequately controlled on metformin ± SU were compared (metformin ≥1500 mg/day ± SU ≥50% of maximal dose for at least eight weeks). Mean total daily insulin dose at 52 weeks was 37.9 units.

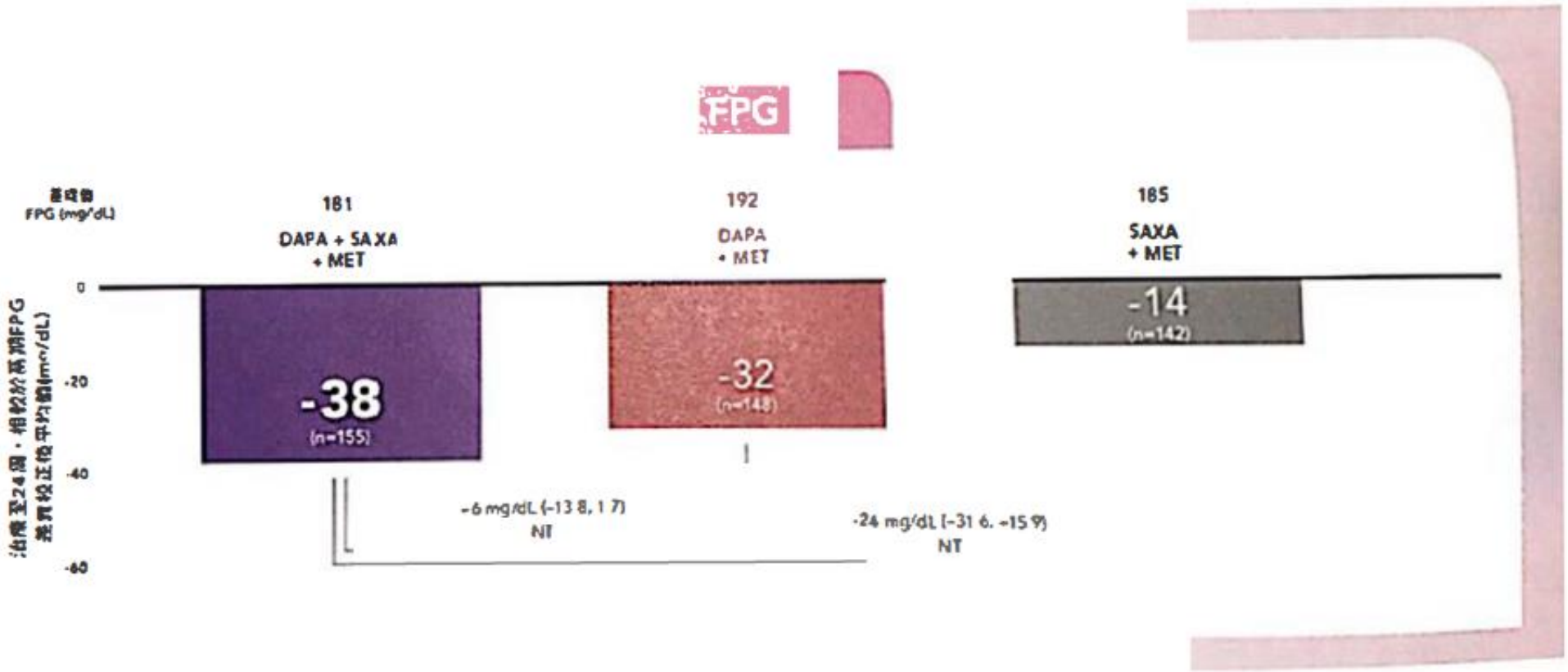
QTERN® is approved only when metformin and one of the components of QTERN® do not provide adequate glycemic control, or already being treated with the free combination of dapagliflozin and saxagliptin. AstraZeneca does not recommend the use of QTERN® other than the approved indications.

Reference: Vilsboll T et al. Tina Vilsboll et al. Diabetes Care 2019 Jun [Epub ahead of print]; European Association for the Study of Diabetes 54th Virtual Meeting (EASD); Oct 1-5, 2018; Berlin, Germany. eposter 429.

QTERN®
(saxagliptin/dapagliflozin)
控糖穩膜衣錠

針對已使用 Metformin XR 仍未達標之患者

DAPA + SAXA 可兼顧 FPG 及 PPG 控制

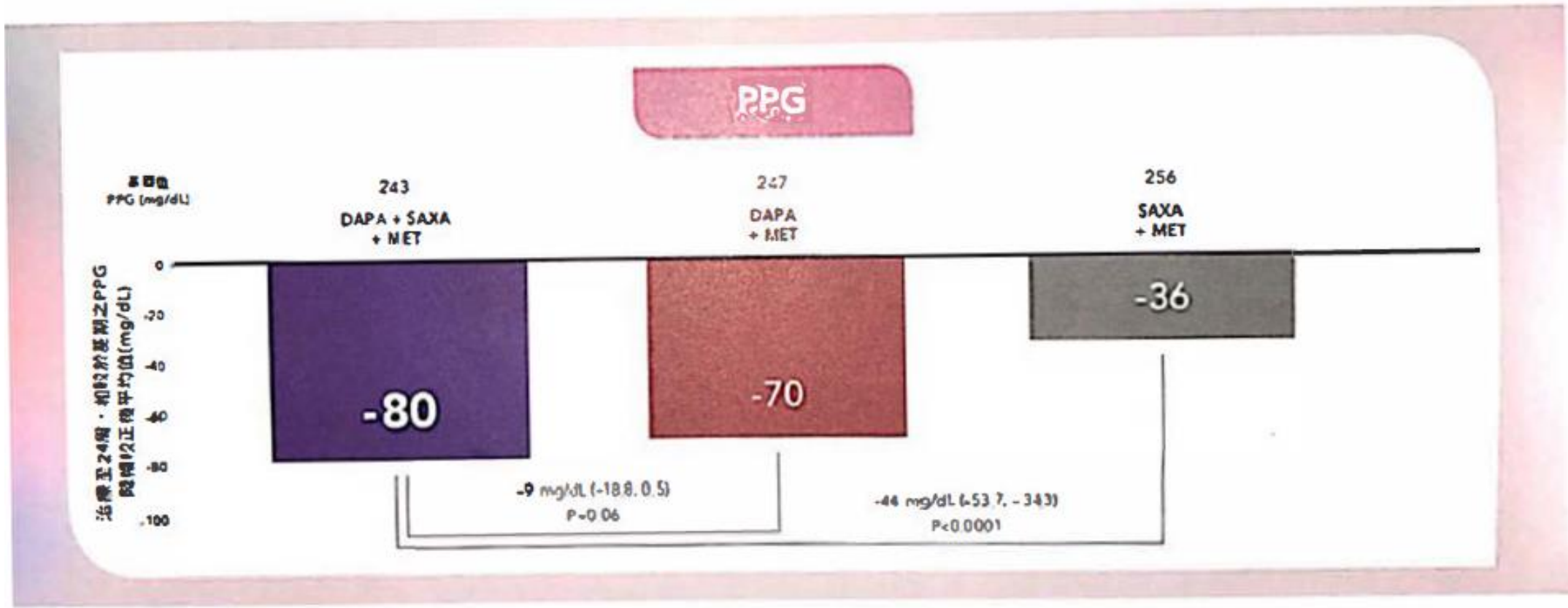


Number of randomized patients with non-missing baseline values and week 24 values (LOCF)
DAPA, dapagliflozin, FPG, fasting plasma glucose, LOCF, last observation carried forward, MET, metformin; NT, not tested under sequential testing procedure as previous tested end point was not statistically significant

Study design: Efficacy and safety of DAPA+SAXA were compared in a multicenter, double-blind, active-controlled, phase 3 study in patients poorly controlled on metformin 1500 mg per day, with HbA1c between 8.0% and 12.0%. Patients were randomized to receive saxagliptin 5 mg + dapagliflozin 10 mg free-form combination vs saxagliptin 5 mg + placebo or dapagliflozin 10 mg + placebo in addition to metformin XR. Baseline HbA1c levels for saxagliptin–dapagliflozin, saxagliptin, and dapagliflozin groups were 8.9%, 9.0%, and 8.9%, respectively.

QTERN® is approved only as an metformin and one of the components of QTERN,* do not provide adequate glycemic control or already being treated with the free combination of dapagliflozin and saxagliptin. AstraZeneca does not recommend the use of QTERN® other than the approved indications.

Reference: Rosenstock J, et al. Diabetes Care 2015;38(3):376-383.



QTERN
(saxagliptin/dapagliflozin)
控糖穩膜衣錠

相較於單一 DPP4i, SU 或胰島素，添加於 Metformin IR / XR 治療

DAPA + SAXA 皆可觀察到額外體重減少

*Treatment arms with or without sulfonylurea ^P<0.001

All treatment arms included background metformin therapy 研究之試驗組皆是使用 dapagliflozin 和 saxagliptin 的自由組合 (free combination)

DAPA=dapagliflozin, 10 mg; SAXA=saxagliptin, 5 mg; INS=insulin (Mean total daily insulin dose at 52 weeks was 37.9 units); GLIM=glimepiride (mean dose at Week 52, 4.6 mg); SITA=sitagliptin 100 mg.

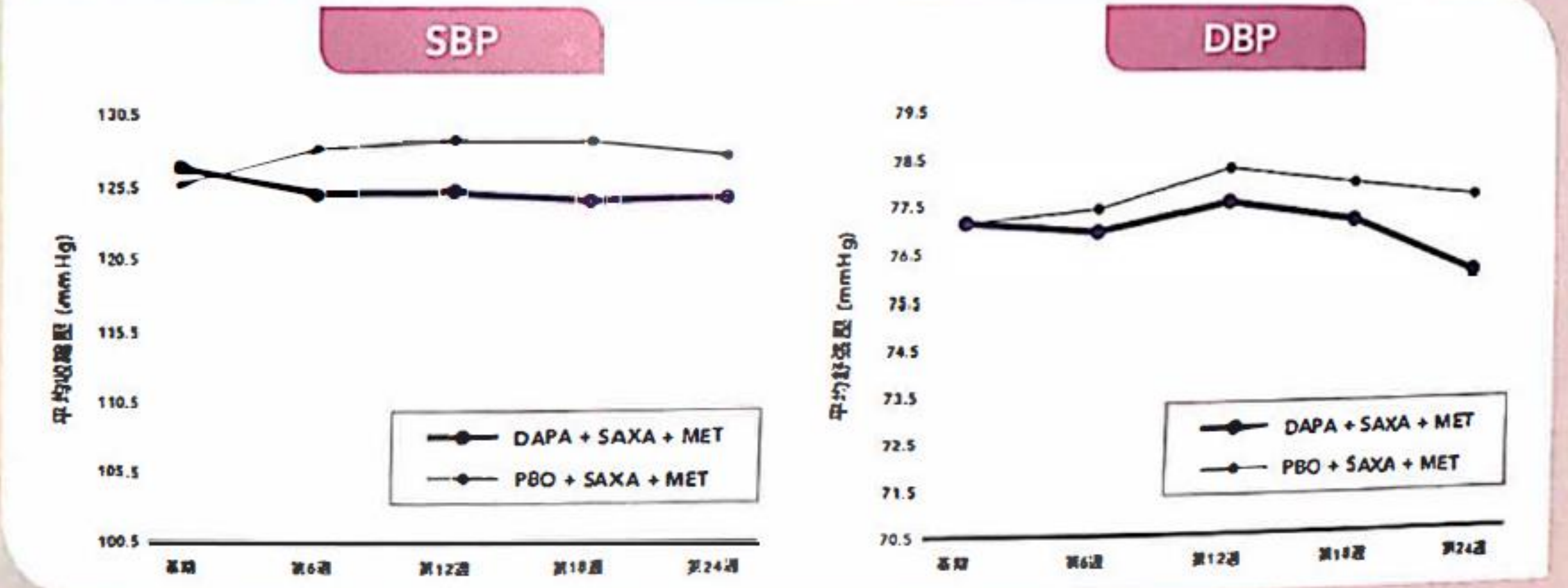
QTERN® is approved only when metformin and one of the components of QTERN® do not provide adequate glycemic control, or already being treated with the free combination of dapagliflozin and saxagliptin. AstraZeneca does not recommend the use of QTERN® other than the approved indications

QTERN® [illegible]

References: 1. Rosenstock J et al. Diabetes Care. 2015;38:376-383. 2. Tina Vilsbøll et al. European Association for the Study of Diabetes 54th Virtual Meeting (EASD), Oct 1-5, 2018, Berlin, Germany. Poster #775 3. Müller-Wieland D et al. Diabetes Obes Metab. 2018 Nov;20(11):2598-2607. 4. Handelsman Y et al. 53rd European Association for the Study of Diabetes Annual Meeting, 11-15 September 2017, Lisbon, Portugal. Study#363 (NCT02284893)

添加於 Metformin IR 治療

DAPA + SAXA 可額外觀察到穩定的血壓降幅



此研究之試驗藥物是 dapagliflozin 和 saxagliptin 的自由組合 (free combination)

DAPA, dapagliflozin; MET, metformin; PBO, placebo; SAXA, saxagliptin.

Study design: This was a multicenter, randomized, double blind, placebo-controlled, parallel group, phase 3 study. The study design consisted of a screening and open-label treatment period followed by a randomized, 24-week, short term, double blind treatment period. 320 Patients with inadequate glycemic control (HbA1c 7-10.5% [53-91 mmol/mol]) were randomized to receive placebo or dapagliflozin 10 mg/day plus saxagliptin and metformin. Baseline HbA1c levels for saxagliptin + dapagliflozin, saxagliptin, were 8.24%, 8.17%, respectively.

*Number of patients with baseline and time point values. Data are from the treated patients population (all patients who received ≥1 dose of double blind medication during the short-term double-blind treatment).

Reference: 1. Mathieu C, et al. Diabetes Care. 2015;38:2009-2017. 2. MB102129 Final Short term and Long term Clinical Study Report, July 2015. (Data on file)

QTERN® is approved only when metformin and one of the components of QTERN® do not provide adequate glycemic control, or already being treated with the free combination of dapagliflozin and saxagliptin. AstraZeneca does not recommend the use of QTERN® other than the approved indications.

QTERN® [illegible]

併用於 Metformin XR 之治療一年安全性試驗顯示

DAPA + SAXA 安全性資訊：低血糖發生率低[1]

Randomized patients, n (%)	SAXA + DAPA + MET (N = 179)	SAXA + MET (N = 176)	DAPA + MET (N = 179)
At least 1 AE	87 (49)	93 (53)	87 (49)
At least 1 SAE	2 (1)	6 (3)	2 (1)
AE leading to discontinuation	1 (0.6)	0	1 (0.6)
SAE leading to discontinuation	0	0	0
AEs of special interest			
Urinary tract infections	1 (0.6)	9 (5)	7 (5)
Genital infections	0	1 (0.6)	10 (6)
Glomerular filtration rate decrease	3 (2)	1 (0.6)	0
Fractures	0	2 (1)	1 (0.6)
Pancreatitis	1 (0.6)	0	0
Cutaneous	0	1 (0.6)	0
Hypoglycemia	2 (1)	2 (1)†	2 (1)
Major	0	0	0
Minor	1 (0.6)	1 (0.6)	1 (0.6)
Other	1 (0.6)	2 (1)	1 (0.6)

此研究之試驗藥使用 dapagliflozin 和 saxagliptin 的自由組合 (free combination)

DAPA 及 SAXA 皆經大型臨床試驗證實長期心血管安全性[2,3]

AE, adverse event; DAPA, dapagliflozin; MET, metformin; SAE, serious adverse event; SAXA, saxagliptin.

Data are n (%). †Hypoglycemia includes minor (symptomatic and asymptomatic with plasma glucose concentration <63 mg/dL, regardless of need for external assistance), major (symptomatic requiring third-party assistance due to severe impairment in consciousness or behavior with plasma glucose concentration <54 mg/dL, and prompt recovery after glucose or glucagon administration), and other (suggestive episode not meeting the criteria for major or minor episodes).

‡Patients with more than one type of hypoglycemic episode were counted within each category but only once for patients experiencing hypoglycemia.

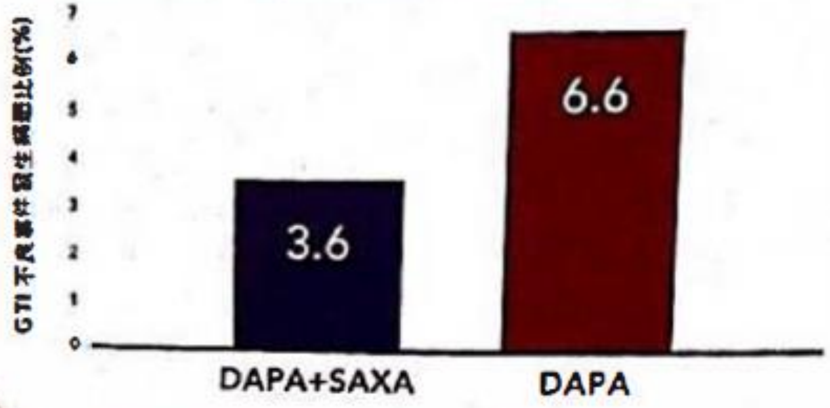
No events of worsening renal function were reported during the study that matched the specific preferred terms indicating worsening renal function.

References: 1. Rosenstock J et al. Diabetes Care 2015;38:376-383. 2. N Engl J Med. 2013 Oct 3; 369(14):1317-26 (SAVOR) 3. Raz I, Mosenzon O, Bonaca MP, et al. DECLARE-TIMI 58: participants' baseline characteristics. Diabetes Obes Metab. 2018;20(5):1102-1110.

相較於 DAPA 單方

DAPA + SAXA 可減少 GTI 發生風險[1,2]

七項試驗安全彙總分析顯示 DAPA+SAXA的GTI風險較低 且持續一年



-49%

相較於 SGLT2i 單方，合併 SGLT-2i 及 DPP-4i 之 GTI 發生事件較少[2]

(風險比 0.51, 95% CI 0.28-0.92)

DAPA, dapagliflozin 10 mg ; MET, metformin; SAXA, saxagliptin 5 mg ; UTI, urinary tract infection; GTI, Genital infections

Study Design: A Pooled Safety Analysis from seven randomized phase 3 trials [illegible] with type 2 diabetes [illegible] receiving DAPA 5/10 mg, SAXA 5 mg or DAPA 5/10 mg + SAXA 5 mg as add on to MET for 24/52 weeks were included. [illegible] long-term (LT) study pool, N= 1719) [illegible] 2016 [illegible] reporting ratios (PRRs) as previously described with [illegible]

Reference: 1. American Diabetes Association 78th Scientific Sessions (ADA), June 22-26, 2018, Orlando, Florida. [illegible] Diabetes Obes Metab 2018 Mar;20(3):740-748.

QTERN (saxagliptin/dapagliflozin) 控糖穩

DPP4i + SGLT2i 單錠複方

QTERN® 控糖穩膜衣錠

(saxagliptin/dapagliflozin)

5mg/10mg tablets

- 增效降糖相當胰島素，達標翻倍
- 額外觀察到體重減少及血壓降低
- 口服且不易低血糖的單錠選擇
- 實證心血管安全性且較少 GTI 事件發生*

*與 dapagliflozin 單方

AstraZeneca


POWER
FORWARD
STEGLUJAN®(Ertugliflozin/Sitagliptin)
釋糖健
雙效合一，釋放控糖
Steglujan®
(ertugliflozin and sitagliptin)

SGLT2 Inhibitors與DPP-4 Inhibitors為機轉互補的降血糖藥物

Mechanisms of Action	SGLT2 Inhibitor	DPP-4 Inhibitor
Insulin secretion	↔	↑
Glucagon secretion	↑	↓
Glucosuria	↑	↔
ß-cell sensitivitv function	↑	↑
Active incretin levels (GLP-1, GIP)	↔	↑

Phvsiologic Effects	SGLT2 Inhibitor	DPP-4 Inhibitor
HbA_{1c}	↓	↓
Weight	↓	↔
Blood pressure	↓	↔

摘錄自Dey J et al.[1] Ferrannini E et al[2] Roden M et al[3] Muscelli E et al[4]
SGLT2 = sodium-glucose cotransporter 2; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; GIP = gastric inhibitory polypeptide.
1. *Postgrad Med*. 2017;129:409–420. 2. *J Clin Invest*. 2014;124:499–508. 3. *Lancet Diabetes Endocrinol*. 2013;1:208–219.
4.. *J Clin Endocrinol Metab*. 2012;97:2818-26.

JANUVIA®在台灣、香港、南韓族群中之第二型糖尿病患者提供超過1% HbA1c降幅

日本

*ΔHbA1c
-0.69%†
(N=146)
(95% CI:-0.80, -0.59)
Placebo +0.36%(95% CI: 0.25-0.46)

香港 / 台灣 / 韓國

*ΔHbA1c
-1.03%†
(N=256)
(95% CI:-1.16, -0.91)
Placebo -0.04%(95% CI: -0.19,+0.12)

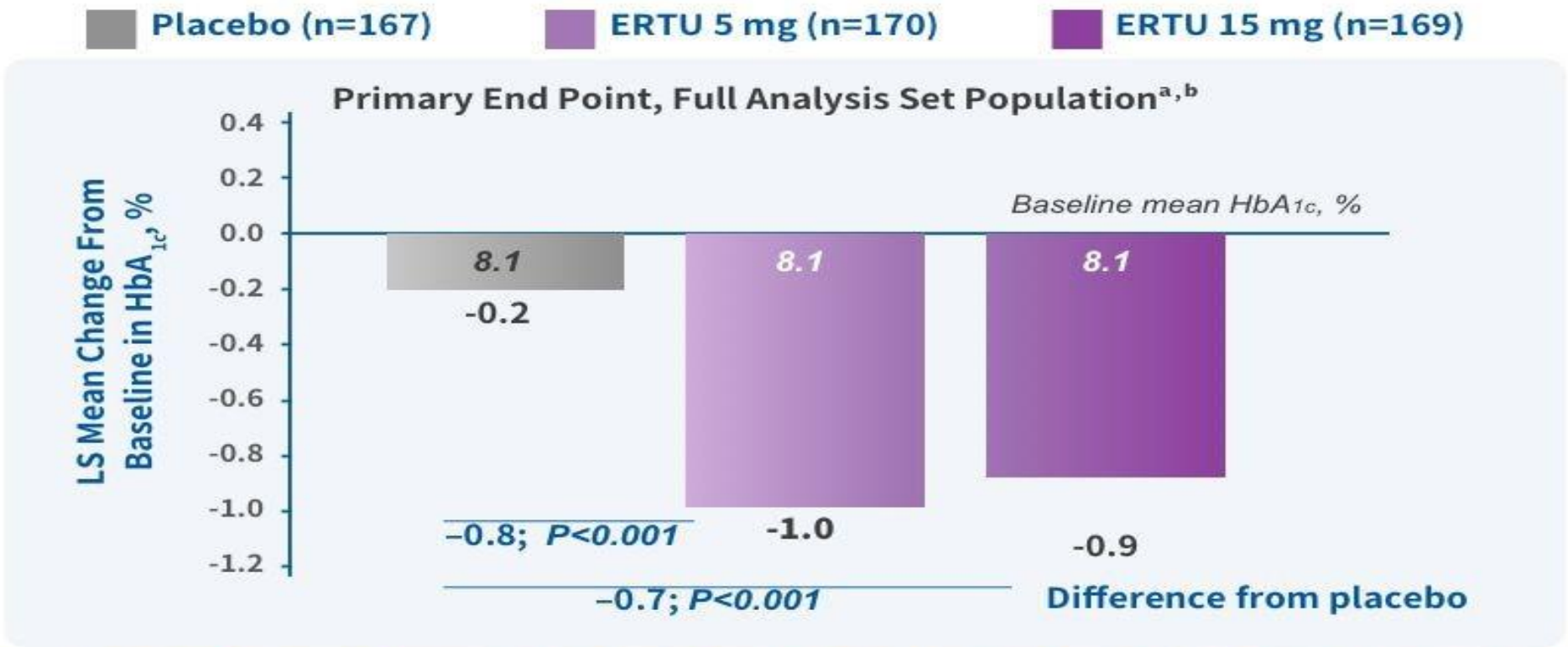
中國大陸

*ΔHbA1c
-0.90%†
(N=1089)
(95% CI:-0.95, -0.84)
Placebo -0.28%(95% CI: -0.34,-0.22)

*本整合分析(pool analysis)整合了20個隨機雙盲試驗，超過2800位來自東亞地區(中國大陸、香港、南韓、台灣)的第二型糖尿病患者，收納的患者中包含單獨使用sitagliptin 100 mg或是併用其他降血糖藥物。試驗終點為12周後的HbA1c基線變化、 12周後的飯後血糖(FPG)基線變化、12周和24/26周後HbA1c達標比率(目標分別為6.5%和7.0%)患者來自台灣、香港、南韓、中國大陸與日本。平均HbA1c基線為8.5%，平均罹患糖尿病7.4年，平均BMI為25.3 kg/m²

*Least Square Mean HbA1c Change from baseline at week 12
† %Based on ANCOVA model with terms for treatment studied and r baseline HbA1c (%) as a covariate
HbA1c = Hemoglobin A1c; FPG = Fasting plasma glucose; BMI = Body mass index ; CI = Confidence interval.
1.*American Diabetes Association 79th scientific sessions*, 2019 Poster 1188-P

VERTIS ASIA研究指出，亞洲第二型糖尿病患者使用 STEGLATRO®(ertuglifozin) 可減少HbA1c達1%



VERTIS-ASIA 是一個26周隨機雙盲試驗，收錄506位亞洲第二型糖尿病患(80.2%來自中國大陸)，病患依照1:1:1 比例(placebo, ertugliflozin 5 or 15 mg)隨機分派。主要療效指標為26周HbA1c基線變化。次要療效指標為26周空腹血糖基線變化、體重變化、收縮/舒張壓變化與病患HbA1c<7.0%的比例。

摘錄自 Ji L et al [1]

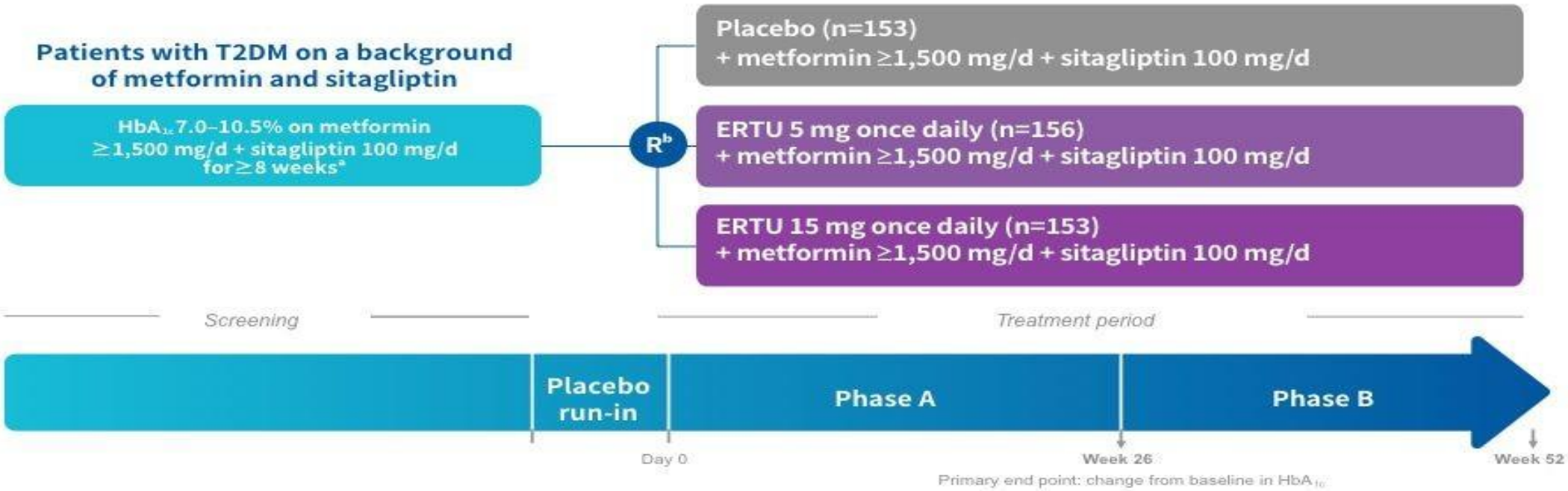
[a]The population includes all randomized patients who received at least 1 dose of study medication and had at least 1 measurement of the analysis variable (baseline or postbaseline). The mean and SD for the change from baseline are based on nonmissing values.

[b]Based on a cLDA model with fixed effects for treatment, time, prior antihyperglycemic medication (metformin monotherapy or metformin + another AHA), country (China, other), baseline eGFR (continuous), and the interaction of time by treatment. Time was treated as a categorical variable.

VERTIS = eValuation of ERTugliflozin efficacy and Safety; LS = least squares; ERTU = ertugliflozin; SD = standard deviation; cLDA = constrained longitudinal data analysis; AHA = antihyperglycemic agents; eGFR = estimated glomerular filtration rate.

1. *Diabetes Obes Metab*. 2019;21:1474–1482.

VERTIS-SITA$_2$
試驗設計[1]



此雙盲、安慰劑控制試驗收入464位已使用Metformin(≧1500 mg/day)與sitagliptin(100 mg/day)的第二型糖尿病患者，病患HbA1c介於7.0%-10.5%，估算的腎絲球過濾率(eGFR) ≧60 mL/min/1.73m²。試驗隨機平均分派患者至Ertugliflozin 5 mg/day與Ertugliflozin 15 mg/day組與安慰劑組。主要療效指標為26週HbA1c基線變化，試驗持續至52週。

摘錄自Dagogo-Jack S et al.[1]

[a]Patients on the protocol regimen for <8 weeks, on metformin ≥1500 mg/day and a sulfonylurea, or on lower doses of metformin and/or another DPP-4 inhibitor at screening were eligible to enroll if they met entry criteria after the appropriate dose/medication adjustment, stabilization, or washout period.

[b]A total of 464 patients were randomized and 2 patients in the ertugliflozin 15-mg group did not receive study medication, resulting in 462 treated patients.

T2DM = type 2 diabetes mellitus; R = randomization; ERTU = ertugliflozin; DPP-4 = dipeptidyl peptidase-4.

1. *Diabetes Obes Metab.* 2018;20:530–540.

VERTIS-SITA$_2$

病患基線[1]

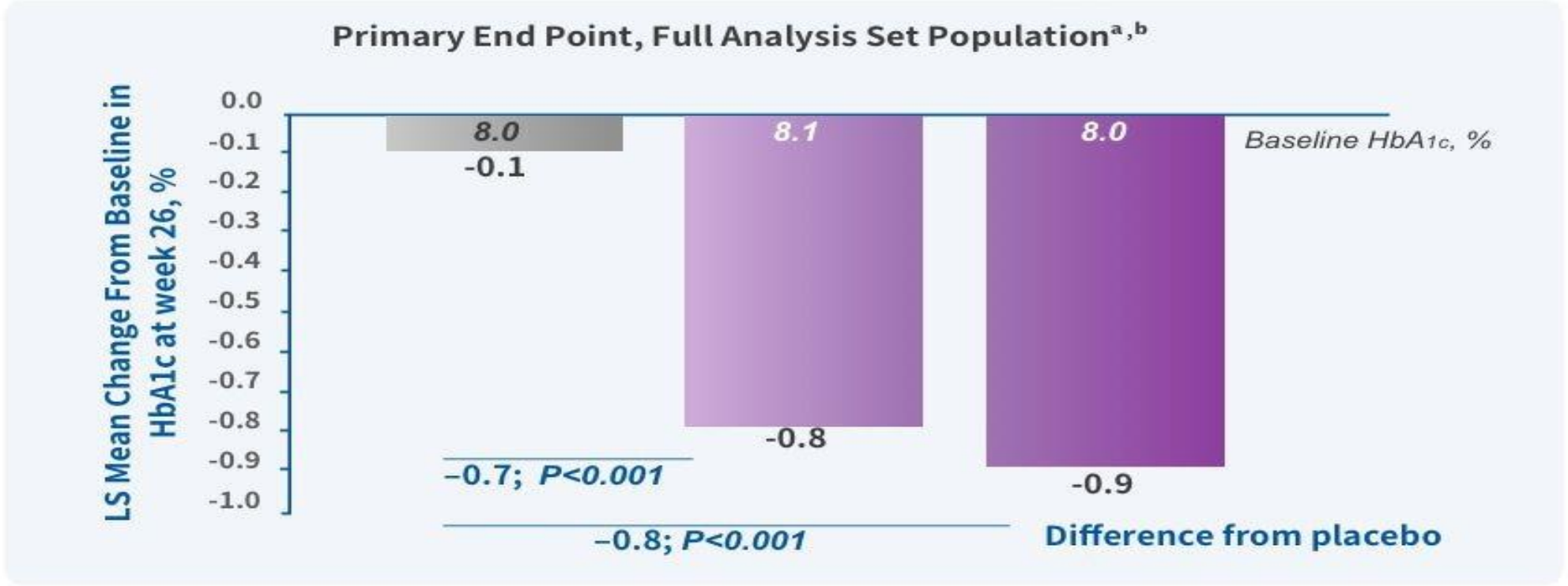
	Placebo (n=153)	ERTU 5 mg (n=156)	ERTU 15 mg (n=153)
Male, n (%)	100 (65.4)	81 (51.9)	82 (53.6)
Age, y	58.3 ± 9.2	59.2 ± 9.3	59.7 ± 8.6
Duration of T2DM, y	9.4 ± 5.6	9.9 ± 6.1	9.2 ± 5.3
Baseline HbA_{1c}, %	8.0 ± 0.9	8.1 ± 0.9	8.0 ± 0.8
FPG, mg/dL	169.6 ± 37.8	167.7 ± 37.7	171.7 ± 39.1
Body weight, kg	86.4 ± 20.8	87.6 ± 18.6	86.6 ± 19.5
BMI, kg/m^2	30.3 ± 6.4	31.2 ± 5.5	30.9 ± 6.1
SBP, mmHg	130.2 ± 13.3	132.1 ± 12.5	131.6 ± 13.2
eGFR, mL/min/1.73 m^2	89.9 ± 17.5	87.0 ± 17.5	86.9 ± 15.6

摘錄自Dagogo-Jack S et al.[1]
Values are mean ± standard deviation, unless otherwise indicated.
ERTU = ertugliflozin; T2DM = type 2 diabetes mellitus; FPG = fasting plasma glucose; BMI = body mass index; SBP = systolic blood pressure; eGFR = estimated glomerular filtration rate.
1. *Diabetes Obes Metab.* 2018;20:530–540.

VERTIS-SITA$_2$

STEGLATRO®針對已使用Metformin與JANUVIA®的第二型糖尿病患者可再額外提供HbA1c降幅

Placebo (n=153)　ERTU 5 mg (n=156)　ERTU 15 mg (n=153)



摘錄自Dagogo-Jack S[1]

[a]The population includes all randomized patients who received at least one dose of study medication and had at least 1 measurement of the analysis variable (baseline or post-baseline).Missing data were not imputed.

[b]LS means adjusted for treatment, time, prior antihyperglycemic medication, baseline eGFR, and the interaction of time by treatment.

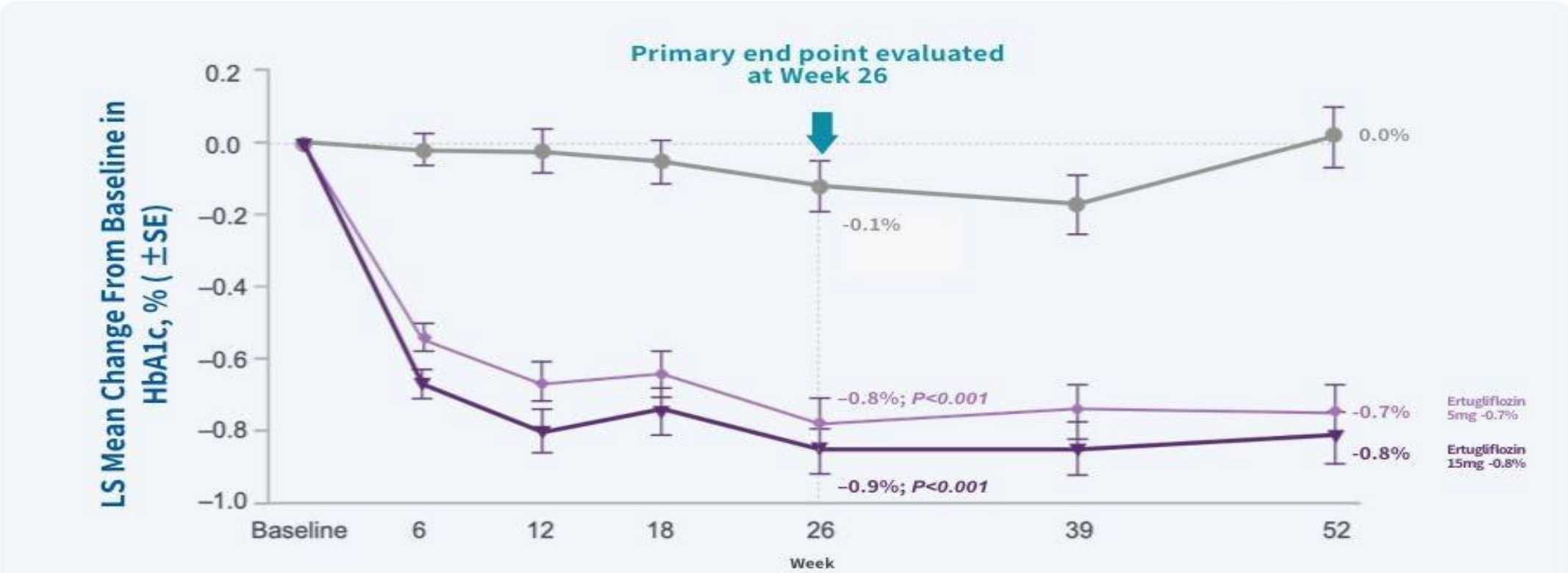
LS = least squares; ERTU = ertugliflozin; STEGLATRO® = STEGLATRO®(Ertugliflozin) ; JANUVIA® = JANUVIA®(Sitagliptin)

1. *Diabetes Obes Metab*. 2018;20:530–540.

VERTIS-SITA$_2$

52週臨床試驗顯示，額外使用STEGLATRO® 持續為第二型糖尿病患者控制血糖[a,b]

Placebo　　ERTU 5 mg　　ERTU 15 mg



摘錄自Dagogo-Jack S[1]

[a]The population includes all randomized, treated patients who had at least 1 measurement of the outcome variable.

[b]LS means adjusted for treatment, time, prior antihyperglycemic medication, baseline eGFR, and the interaction of time by treatment.

LS = least-squares; ERTU = ertugliflozin; SE = standard error; CI = confidence interval; STEGLATRO® = STEGLATRO®(Ertugliflozin)

1. *Diabetes Obes Metab*. 2018;20:530–540.

周劍文診所
Chou Chien Wen Clinic

Long acting Insulin (Tresiba)

胰島素作用及保存

胰島素類似物

胰島素製劑（筆 3 ml, 100 U/ml）	起始作用時間（小時）	最大作用時間（小時）	作用持續時間（小時）	胰島素保存		
				未開封（℃）	使用中	
					（℃）	（天）
速效型 NovoRapid® FlexPen	10～20分鐘	1～3	3～5	冷藏 2～8	室溫 ＜30	28
預混型 NovoMix® 30 FlexPen （30% 速效 ＋70% 中長效）	10～20分鐘	1～4	14～24	冷藏 2～8	室溫 ＜30	28
預混型 NovoMix®50 FlexPen （50% 速效 ＋50% 中長效）	10～20分鐘	1～4	14～24	冷藏 2～8	室溫 ＜30	28
長效型 Levemir® FlexPen® Insulin detemir	～1	6～8	～24	冷藏 2～8	室溫 ＜30 或冷藏 2～8	42
長效型 Tresiba® FlexTouch® Insulin degludec	1	9～12	42	冷藏 2～8	室溫 ＜30 或冷藏 2～8	56

較符合人體胰島素分泌模式

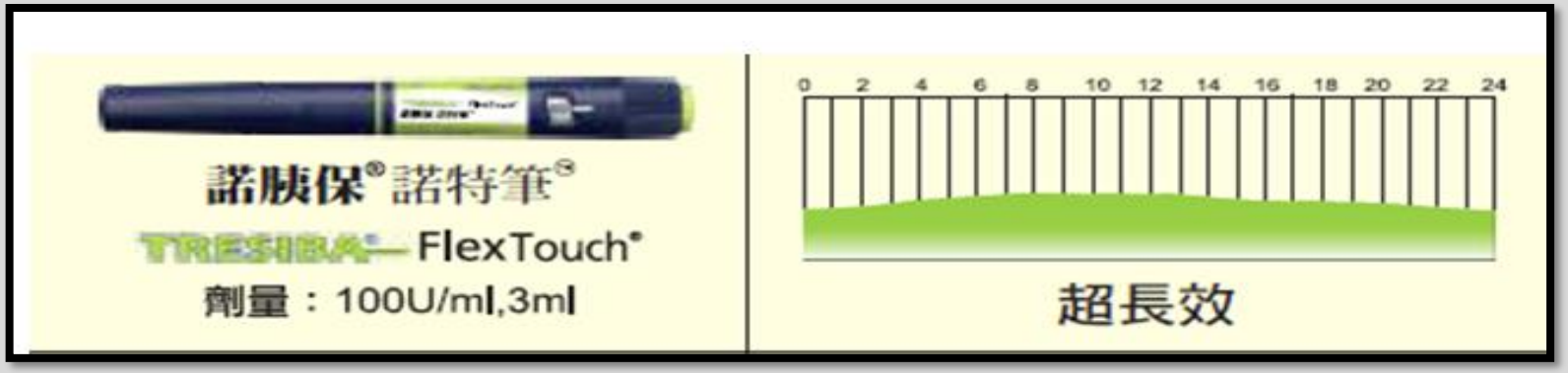
參考資料來源:中華民國糖尿病衛教學會 2018 台灣胰島素注射指引

新型超長效

- **注射時間:**固定時間注射 (成人患者，每天1次，在一天中的任意時間)
- **途徑:**皮下注射 (絕不可以靜脈注射)
- **外觀:**透明澄清
- **優勢:**超長效作用時間

  需要時可彈性調整注射時間，生活不被影響

  變異性更低，平穩降血糖，低血糖風險更低
- **適用:**一歲以上所有糖尿病患、低血糖頻繁者、生活作息無法固定者



起始作用時間
1小時
最大作用時間
9~12小時
作用持續時間
42小時

周劍文診所
Chou Chien Wen Clinic

Long acting GLP1-RA (Ozempic)

胰妥讚®注射劑

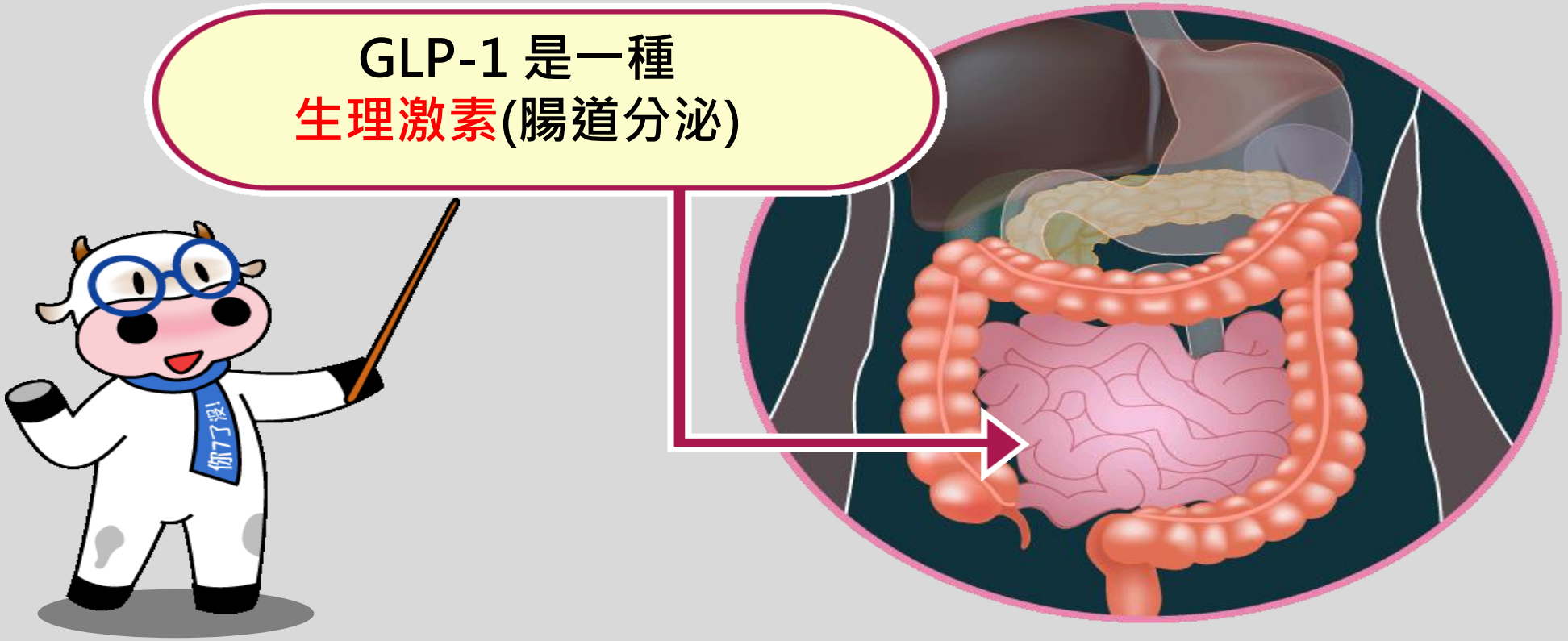
Reference: 胰妥讚® 注射劑衛生福利部核准仿單

胰妥讚®注射劑特色

- **注射時間:每週注射一次，可在一天中的任何時間注射**(不論是否進食)
- **途徑:**皮下注射 (不可以靜脈注射或肌肉注射)
- **外觀:**澄清且無色或接近無色；pH = 7.4
- **優勢:**適應症胰妥讚®單一療法或與其他糖尿病治療藥物併用，治療控制不佳的第二型糖尿病成人病人，作為飲食及運動之外的輔助治療。

胰妥讚®作用機轉

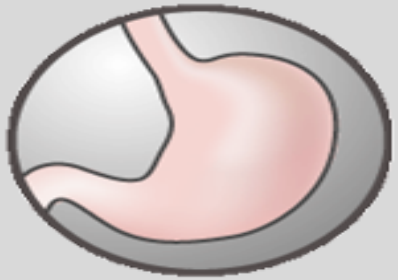
Semaglutide 是一種 GLP-1 類似物，與人類 GLP-1 有94% 序列相似度。



腸泌素(GLP-1) _促進胰島素分泌

進食

腸胃道引發
GLP-1效應



胰臟：
GLP-1作用在
α 和 β 細胞

α細胞：
GLP-1依照葡萄糖濃度
減少升糖素分泌

降血糖

β細胞：
GLP-1依照葡萄糖濃度
刺激胰島素分泌

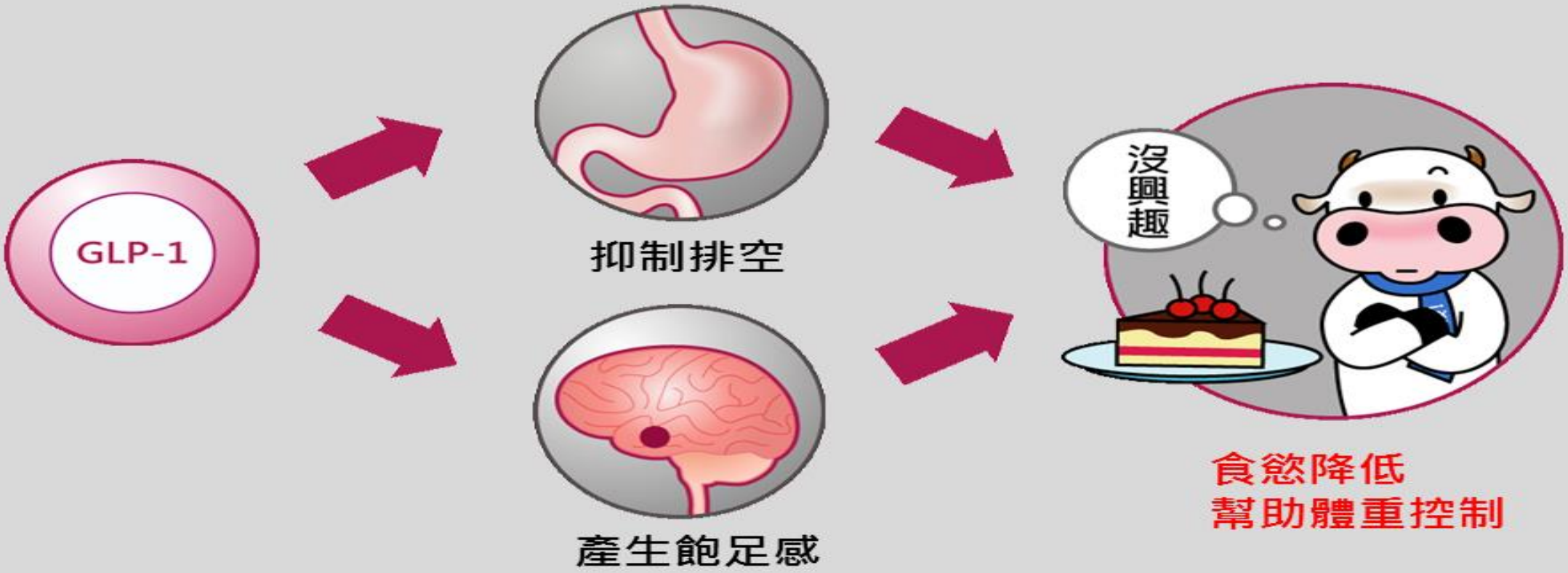
血糖高 ----- 降血糖

血糖低 ----- 作用減弱

腸泌素(GLP-1)_獨特的優點:產生飽足感

GLP-1抑制胃部排空，
並促使下視丘產生飽足感，

使食慾降低



食慾降低
幫助體重控制

人類GLP-1類似物的好處

會依照血液中葡萄糖濃度高低來調控胰島素以及升糖素的分泌[1]
當血糖濃度下降且接近正常血糖值時，胰島素分泌會減弱

不容易發生
低血糖

References:中華民國糖尿病衛教學會 2020 糖尿病衛教核心教材P92

使用人類GLP-1類似物注意事項

最常見的副作用為:噁心、食慾不佳及腹脹，甚至嘔吐。

一般在初期使用較明顯，隨使用時間增加，此副作用會減少。

資料來源:財團法人糖尿病關懷基金會 2014「糖尿病家族」http://www.dmcare.org.tw/up3/2014-2-%E8%AC%9D%E6%98%8E%E5%AE%B6.pdf

周劍文診所
Chou Chien Wen Clinic

Basal Insulin and GLP-1 RA fix-ratio combination (Soliqua)

Less is More:
The Art of Fixed Ratio Combination

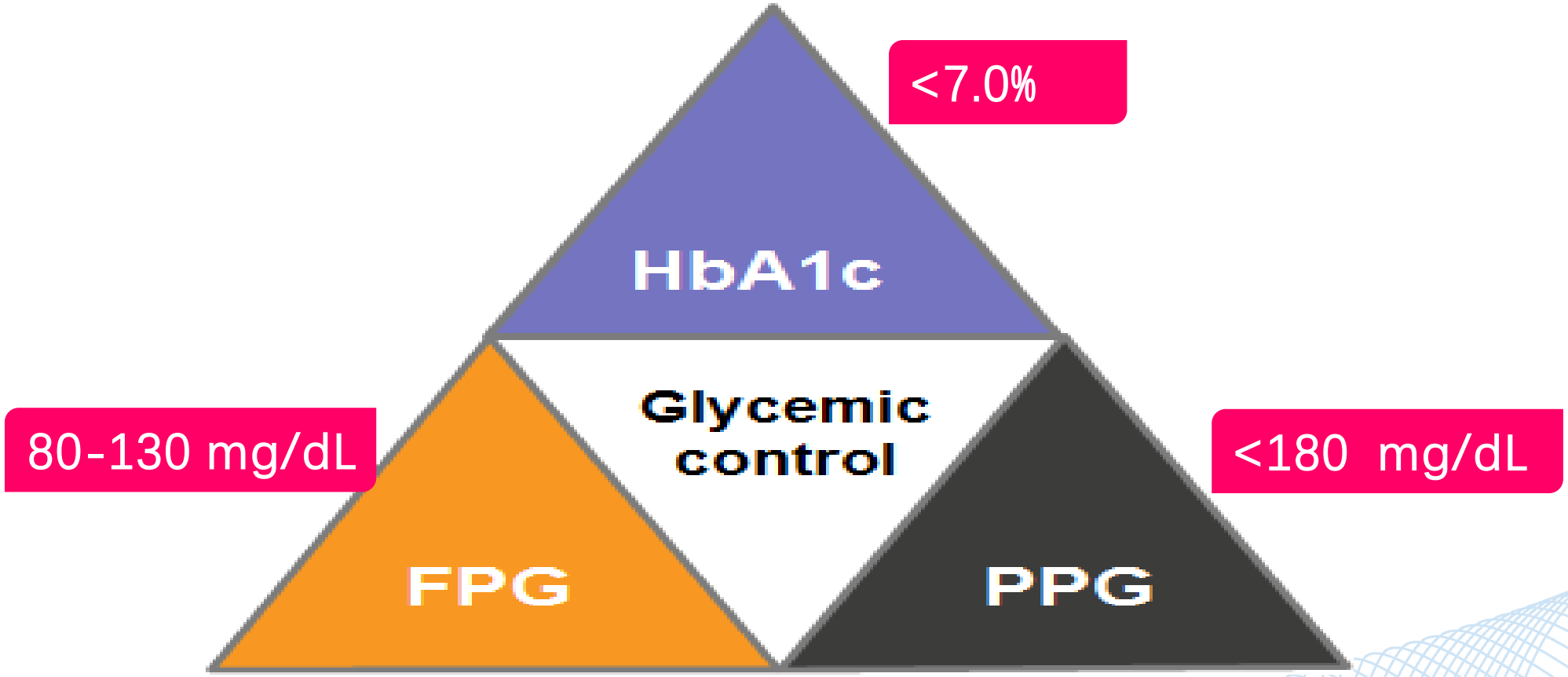
報告者：

SOLIQUA®
insulin glargine (100 U/mL) & lixisenatide

SANOFI

SATW.LALI.18.12.0446(01/19)

Achievement of glycaemic control is the primary goal of treatment for T2DM



The Role Of Insulin in in Glycaemic Control- Guideline

Basal insulin

心血管實證：中立
心衰竭實證：中立
腎病變實證：中立
控制血糖效果：最佳
體重：增加
低血糖：高
副作用：低血糖

2019中華民國
糖尿病學會治療指引

The Role Of Insulin in in Glycaemic Control

第二型糖尿病患者若在罹病第一年即搭配

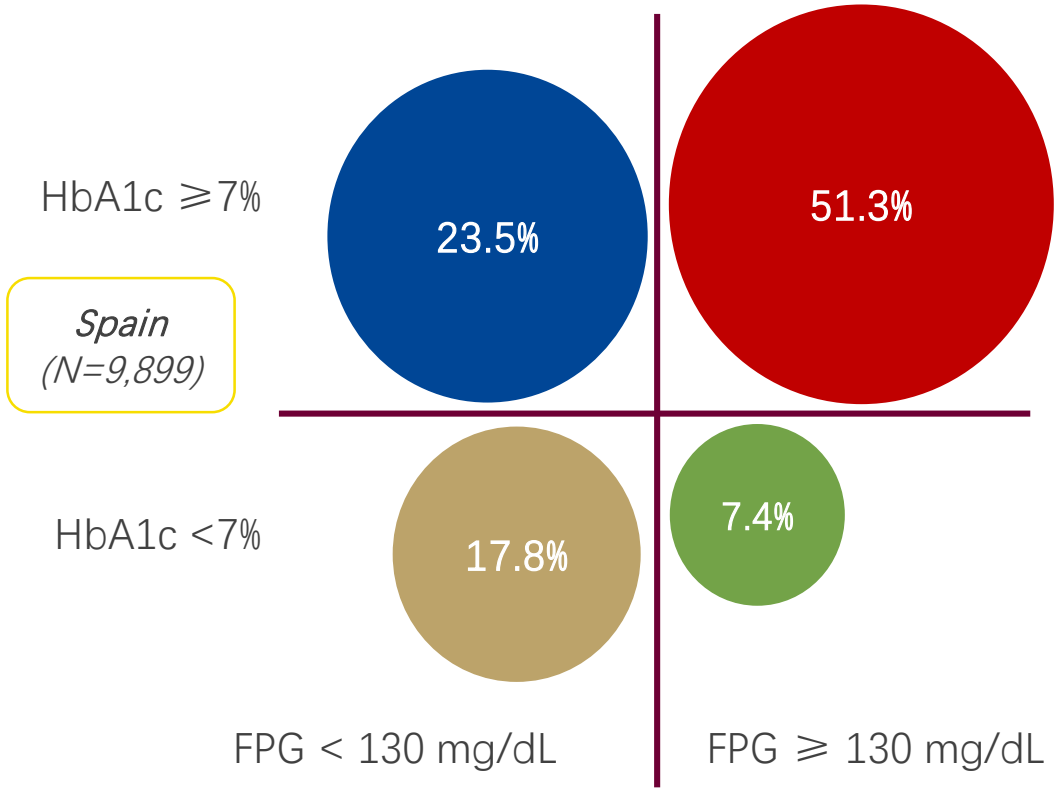
胰島素治療，和單用口服藥相較之下:

1. 可讓胰島細胞功能增加一倍，
2. 糖化血色素下降的幅度更多，
3. 更能有效控制糖尿病併發症風險。

2019糖尿病
品質調查報告

~75% T2DM patients on basal insulin have uncontrolled FPG and HbA1 or residual hyperglycemia

Distribution of the overall population according to HbA1c and FPG levels. Of a population of 126,811 T2DM subjects, **9,899 were treated with basal insulin (NPH, detemir, or glargine)**



Controlled *defined as HbA1c at target (HbA1c <7%);*

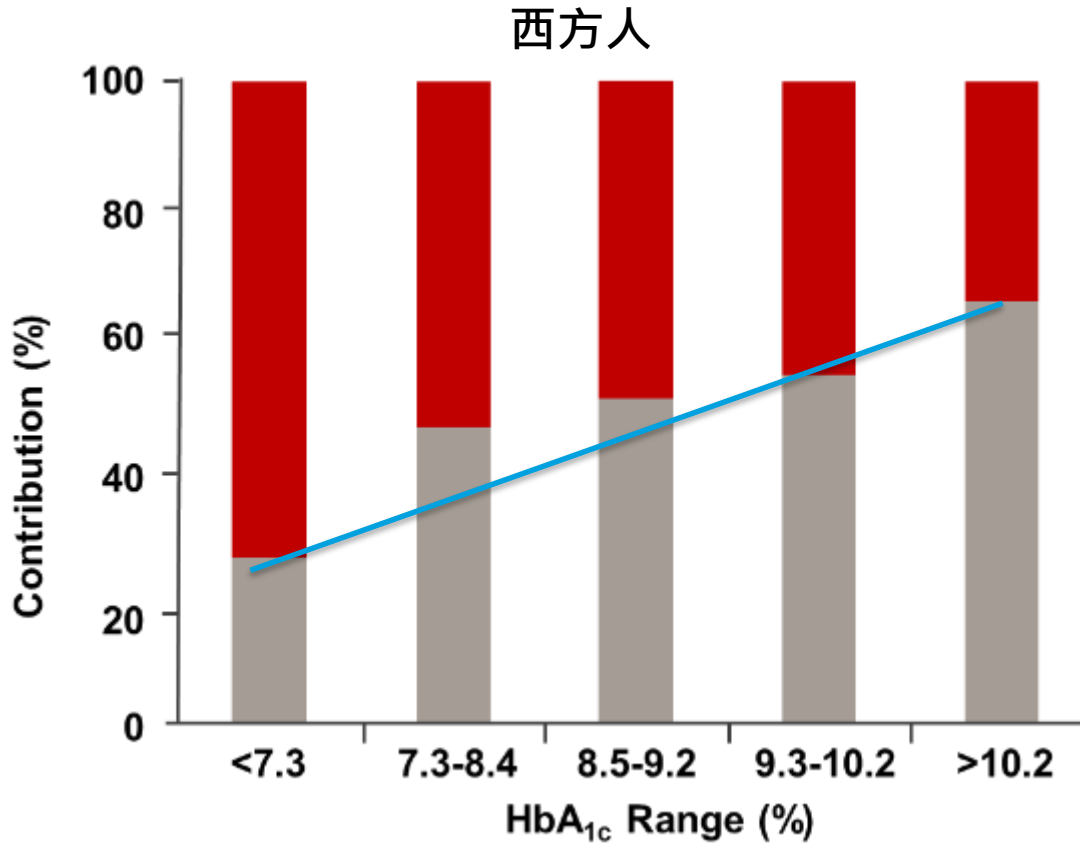
Residual hyperglycemia *defined as HbA1c above target despite FPG at target (FPG <7.2/7.8 mmol/L [<130/140 mg/dL];*

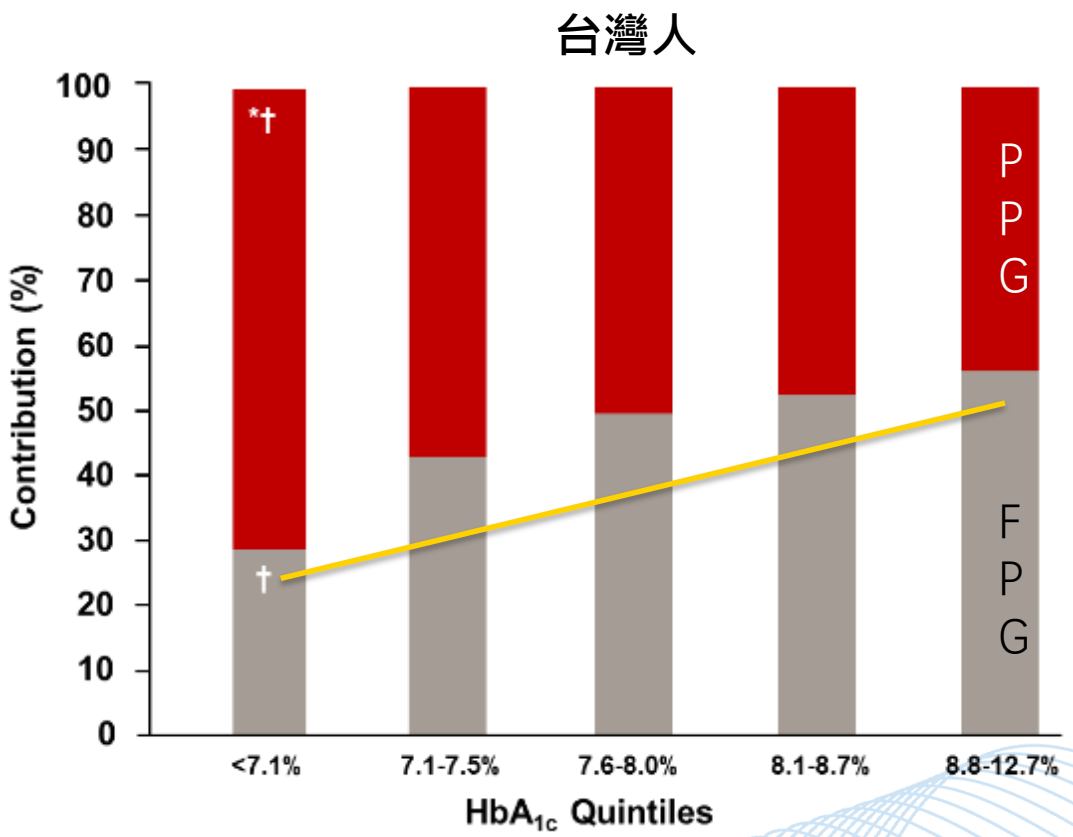
Uncontrolled *defined as neither HbA1c nor FPG at target*

A cross-sectional study on T2DM patients aged 31–90 years treated with basal insulin registered in the SIDIAPQ primary healthcare electronic database during 2010. Of a population of 126,811 T2DM subjects, 9,899 were treated with basal insulin (NPH, detemir, or glargine). Of these, 23.5% (n = 2322) achieved optimal FPG (<130 mg/dL) but an inadequate HbA1c target (>7%). Mean HbA1c values in the uncontrolled and controlled groups were 8.15% and 6.31%, respectively

Mata-Cases.M. et al, Journal of diabetes. 2016

Different between Caucasians and Asian Type 2 Diabetes

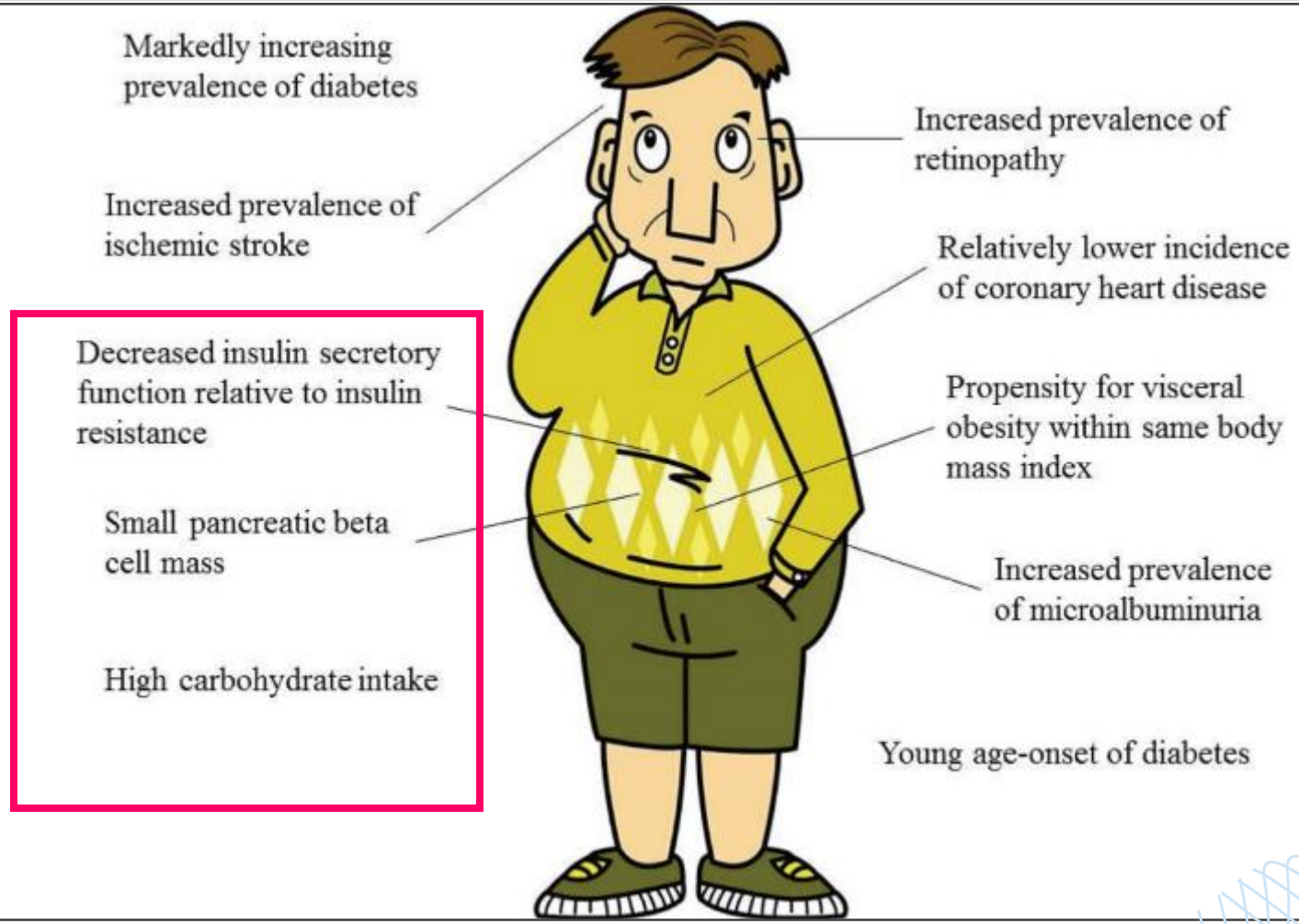




*Significant difference between FBG and PPG; †Significant difference from all other quintiles.

1. Monnier L, et al. Diabetes Care. 2003;26(3):881-885. 2.Wang JS, et al. Diabetes Metab Res Rev. 2011;27(1):79-84.

Characteristics of Asian patients with diabetes



Endocrinol Metab. 2015 Sep;30(3):263-269.
http://dx.doi.org/10.3803/EnM.2015.30.3.263

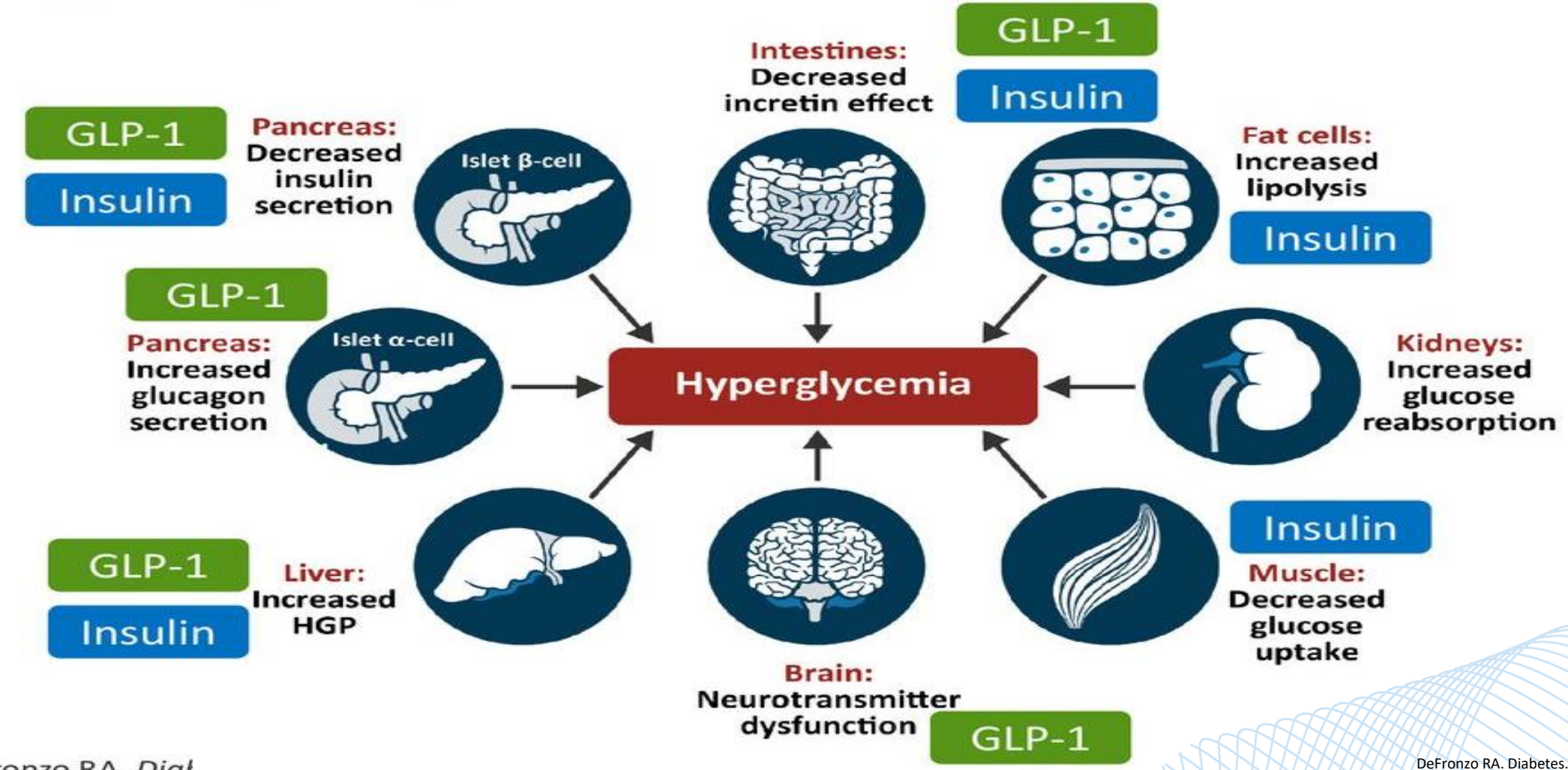
Basal Glucose Can Be Controlled, but the Prandial Problem Persisted. It's the Next Target!

Matthew C. Riddle

Diabetes Care 2017;40:291–300 | DOI: 10.2337/dc16-2380

Benefits of combination therapy of Basal Insulin and GLP-1 RA

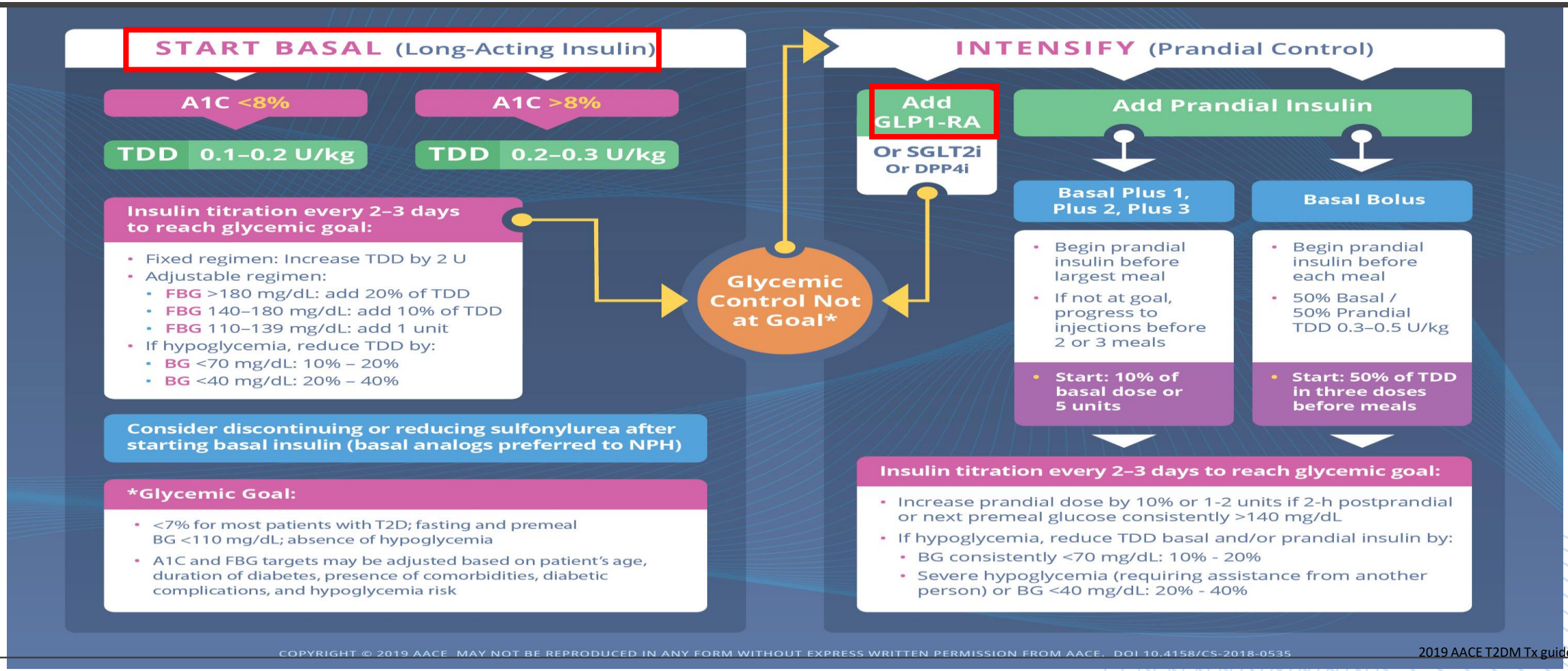
Pathophysiologic Defects in T2DM: The Ominous Octet



DeFronzo RA. *Dial*

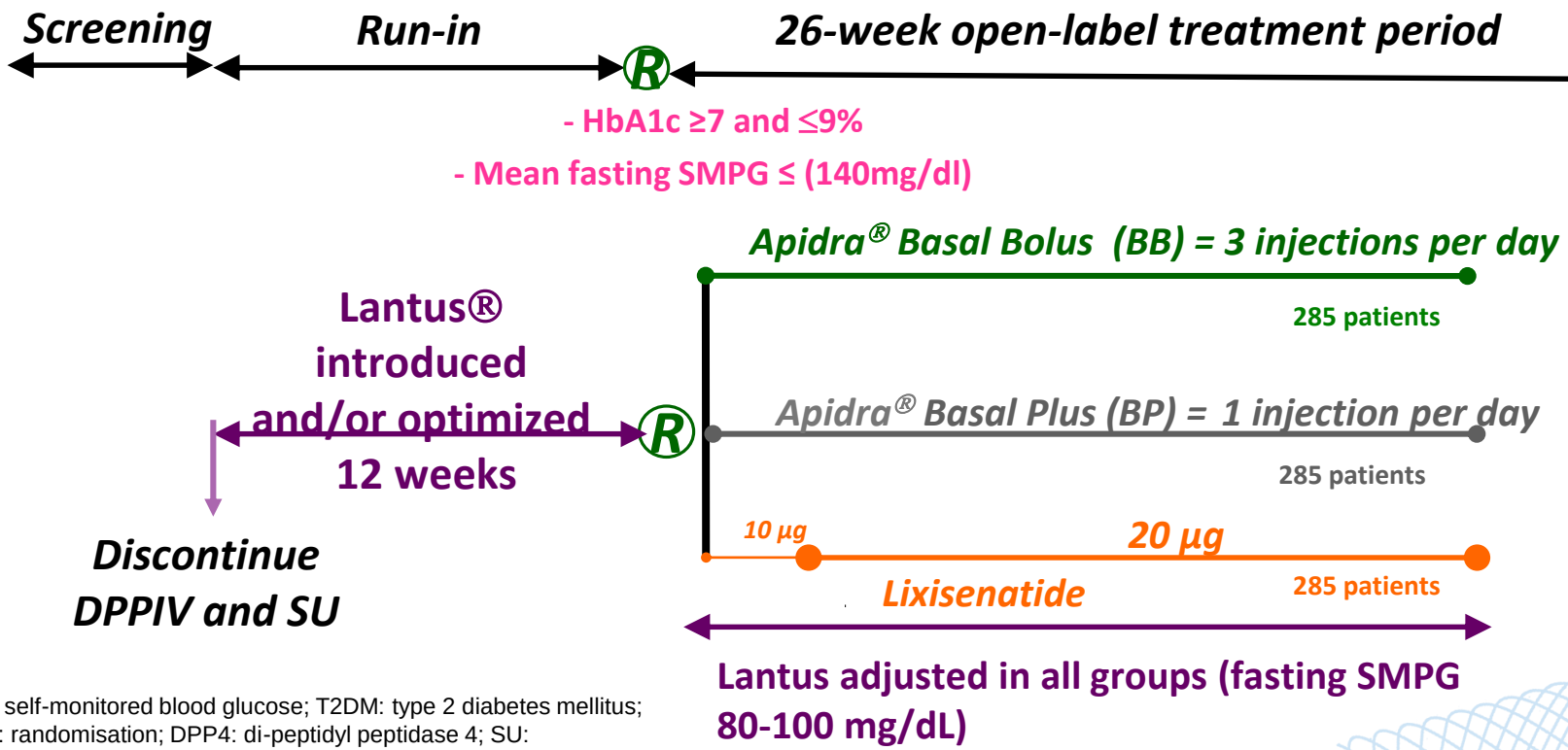
DeFronzo RA. Diabetes. 2009;58:773-795

Algorithm for Insulin Intensification - AACE



2019 AACE T2DM Tx guideline

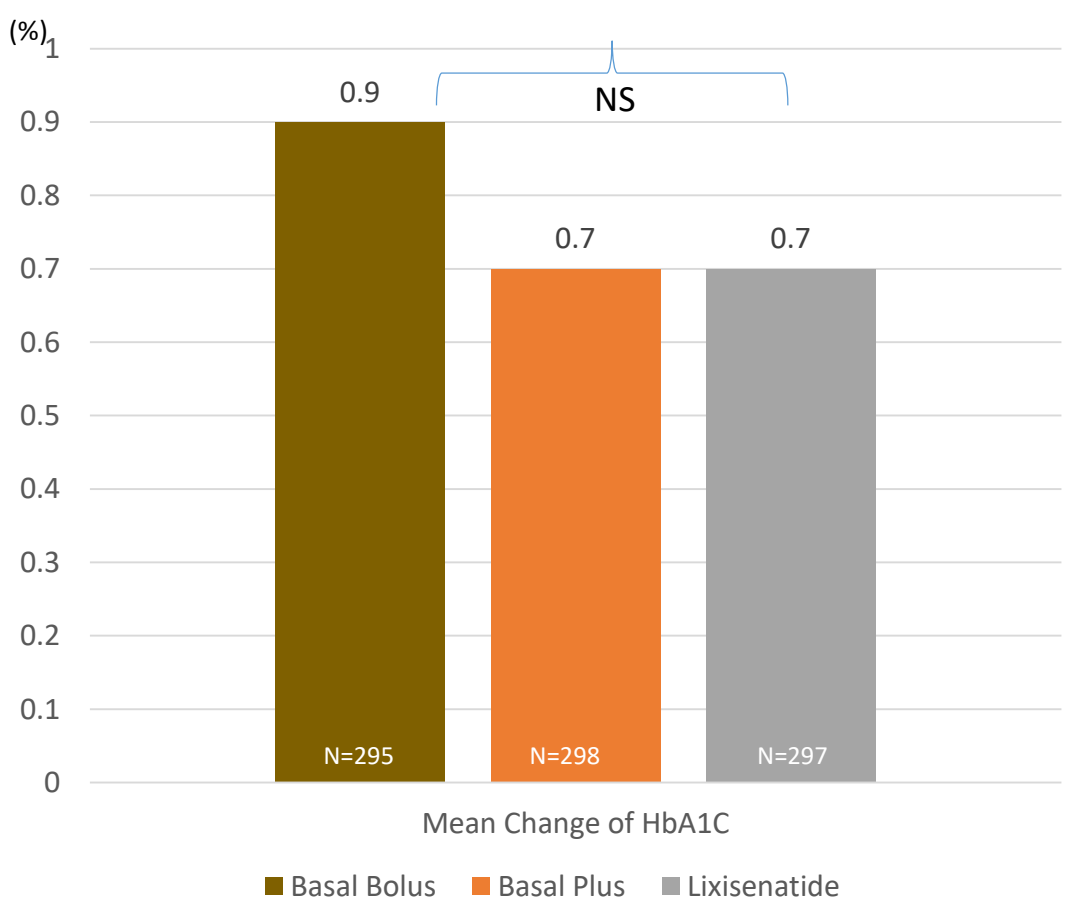
GetGoal-Duo 2: Free combination V.S BB/BP

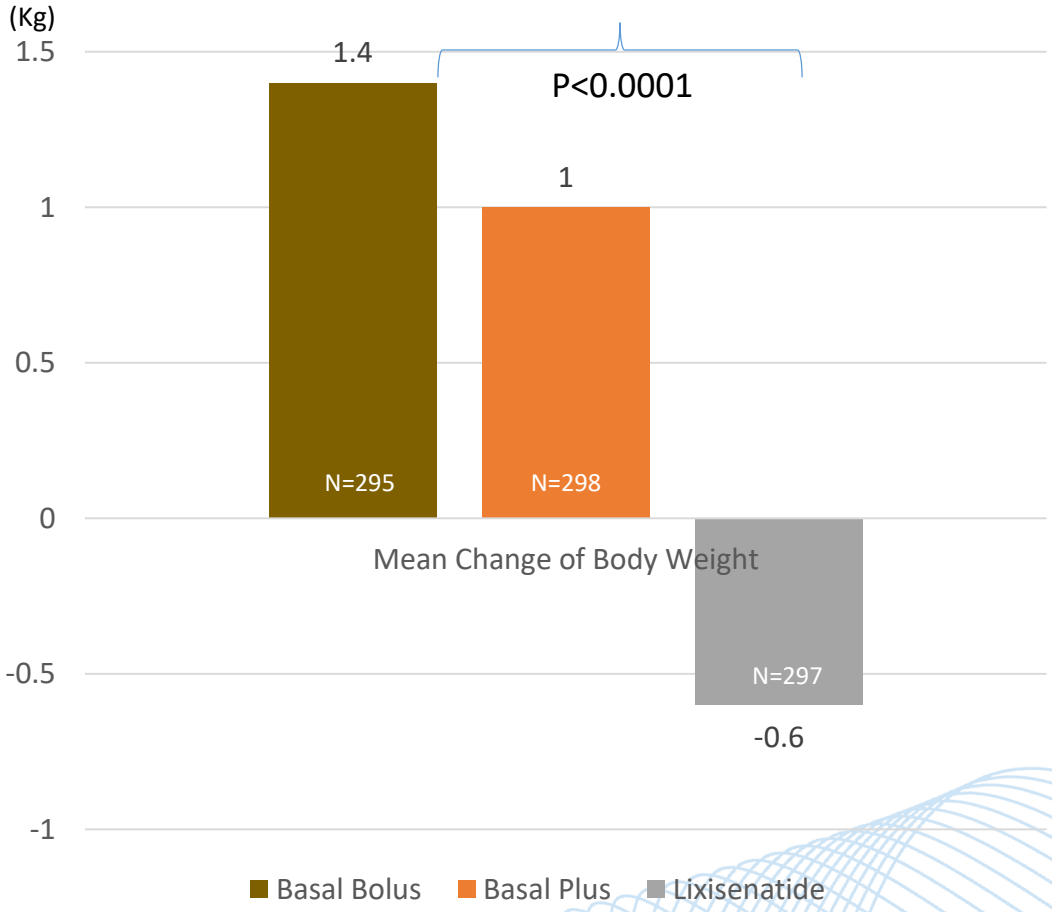


RAI: rapid acting insulin; SMBG: self-monitored blood glucose; T2DM: type 2 diabetes mellitus; OADs: oral antidiabetic drugs; R: randomisation; DPP4: di-peptidyl peptidase 4; SU: sulphonylurea.

Diabetes Care Publish Ahead of Print, published online May 23, 2016

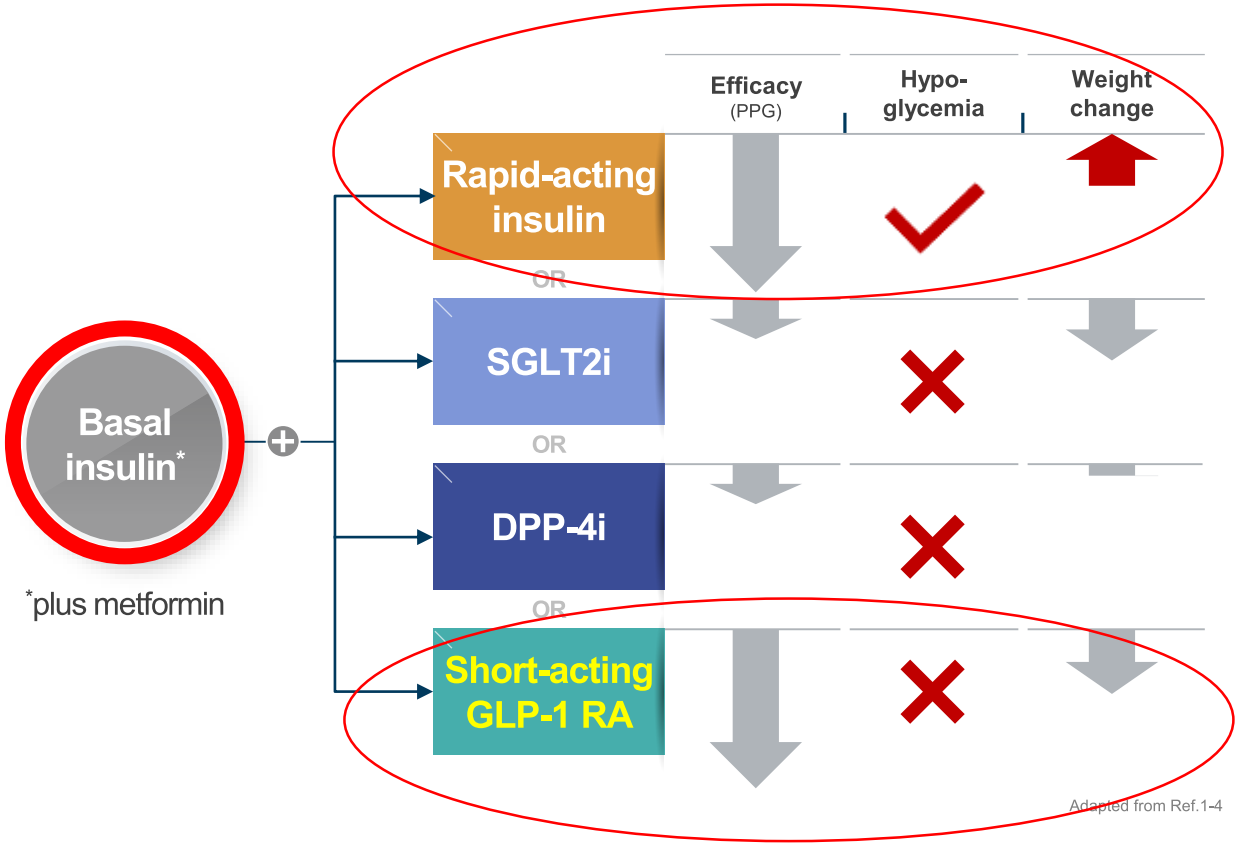
Combination of Basal Insulin/Lixisenatide provide similar HbA1C control with less weight gain





Diabetes Care Publish Ahead of Print, published online May 23, 2016

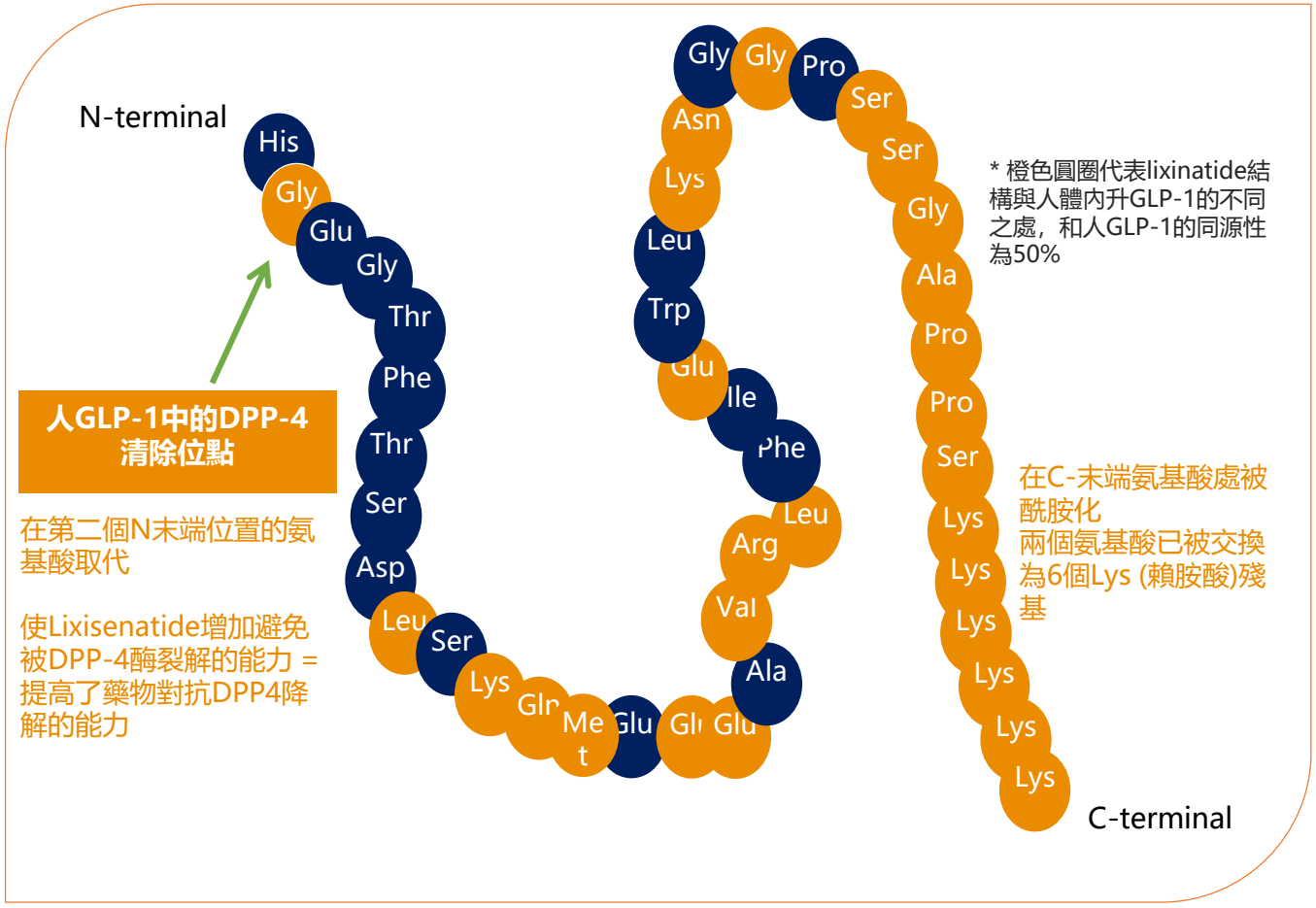
Comparison of available intensification options in patients sub-optimally controlled with basal insulin



- Traditional approach of adding **a prandial insulin increases the risk for hypoglycemia**[1,2]
- **GLP-1 RA more effective** than DPP-4i or SGLT-2i at HbA1c lowering in patients with long-standing T2DM not achieving glycemic targets[1]

1. Standard of Medical Care in Diabetes. 2018. Diabetes Care. 2018; 41(Suppl1):S1-S159
2. J Diabetes. 2016 Dec 15. [Epub ahead of print]
3. Clin Diabetes. 2015 Oct;33(4):175-80
4. J Korean Diabetes 2015;16:252-259

Lixisenatide, a selective short-acting GLP-1 RA



- Lixisenatide可抵抗DPP-4快速降解以長久維持體內活性
- 血漿半衰期約1.5-4.5h
- 親和力相對於人體GLP-1的倍數：

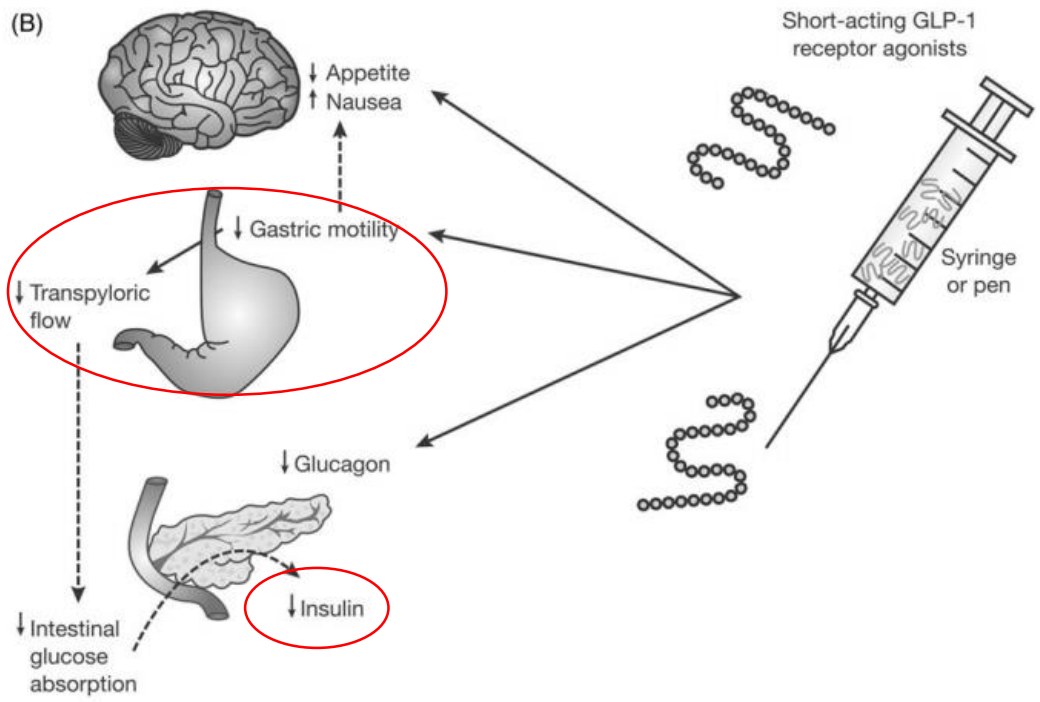
親和力相對於人體GLP-1的倍數	
Lixisenatide	**4x**
Exenatide	0.64x
Liraglutide	3x

相較於內生性GLP-1，Lixisenatide對於GLP-1 receptor具有4倍的高親和性，進而減緩半衰期，因此只需要一天一次給藥

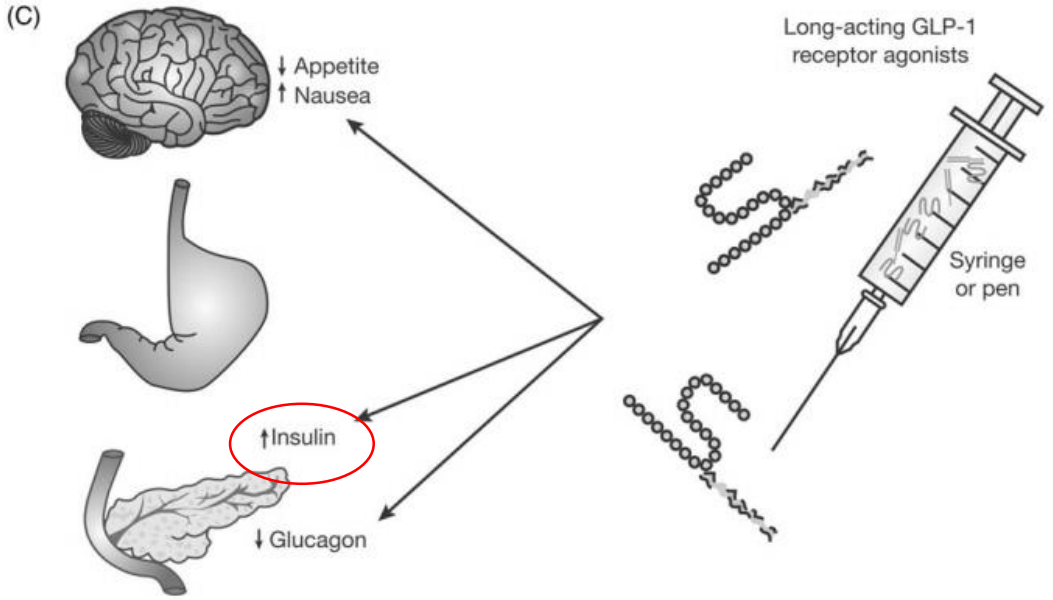
Werner U, et al. Regul Pept 2010;164:58–64
Thorkildsen C, et al. J Pharmacol Exp Ther 2003;307:490–6

Difference Mechanisms of GLP-1 RA

Short-acting GLP-1RA



Long-acting GLP-1RA



Curr Med Res Opin. 2019 May;35(5):793-804.

Difference Mechanisms of GLP-1 RA

類升糖素肽-1 受體促效劑的比較

	Pharmacokinetics		Structure		Size	
	Short-acting	Long-acting	Exendin-4-based	GLP-1-based	Small	Large
GLP-1 RA	• Exenatide BID • Lixisenatide	• Exenatide QW • Liraglutide • Albiglutide • Semaglutide • Dulaglutide	• Exenatide BID • Exenatide QW • Lixisenatide	• Liraglutide • Albiglutide • Semaglutide • Dulaglutide	• Exenatide BID • Exenatide QW • Liraglutide • Lixisenatide • Semaglutide	• Albiglutide • Dulaglutide
Effect	Gastric emptying PPG	FPG	May produce antibodies		Better penetration in the brain Better effect on appetite suppression	Smaller effect on body weight

2019中華民國
糖尿病學會治療指引

Overview of short and long acting GLP-1 RA

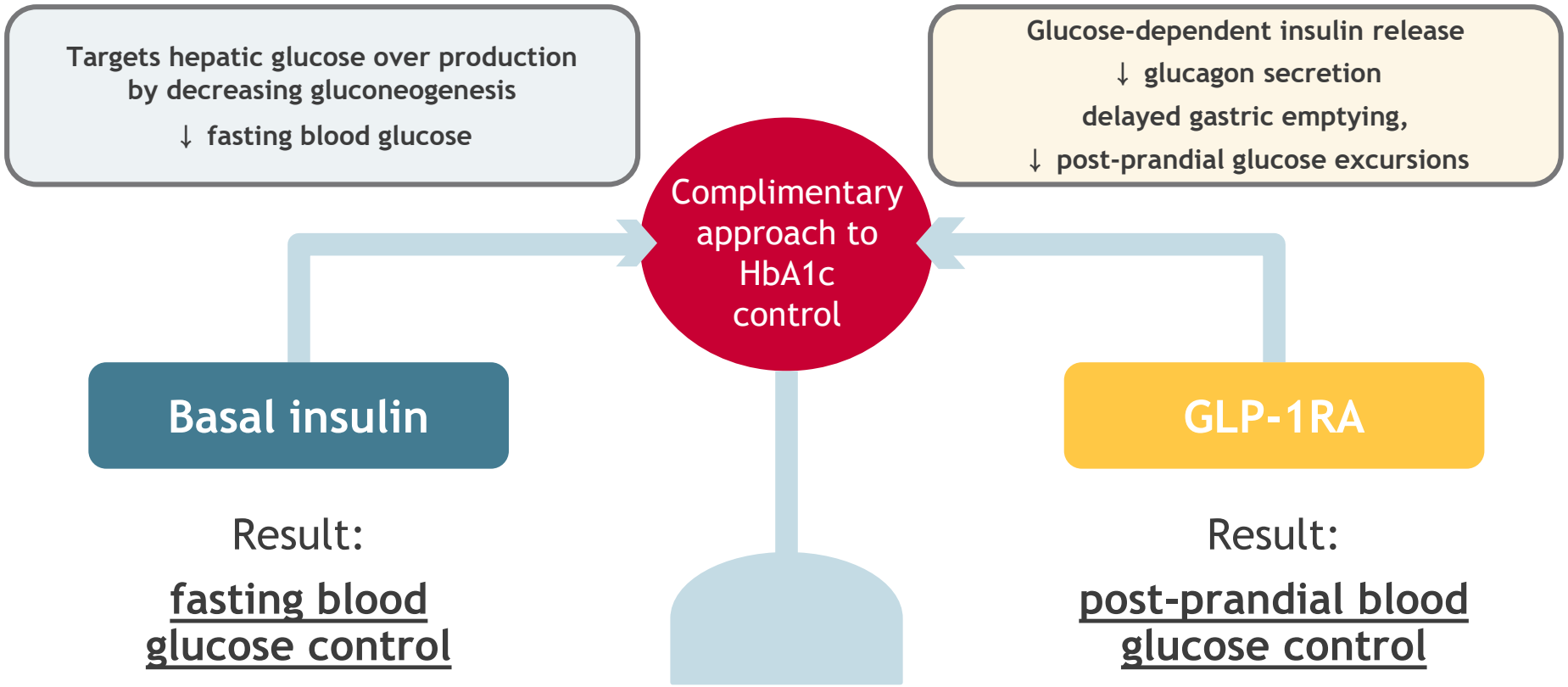
Parameters	Short-acting GLP-1 RAs	Long-acting GLP-1 RAs
Compounds	Exenatide, Lixisenatide	Albiglutide, Dulaglutide, Exenatide-LAR, Liraglutide
Half-life	2-5 h	12 h - several days
FPG levels	Modest reduction	Strong reduction
PPG levels	Strong reduction	Modest reduction
Glucagon secretion	Reduction	Reduction
Blood pressure	Reduction	Reduction
Heart rate	No effect or small increase (0-2 bpm)	Moderate increase (2-5 bpm)
Body weight reduction	1-5 Kg	2-5 Kg
Induction of nausea	20-50%, attenuates slowly (weeks to many months)	20-40%, attenuates quickly (~4-8 weeks)

Meier, JJ. *Nat Rev Endocrinol.* 2012;8(12):728-42.

爽胰達 Soliqua®

Composition	**Soliqua SoloStar® 300 units of insulin glargine and 150 µg lixisenatide in 3 mL solution (100 units/mL + 50 µg/mL)**
Lixisenatide concentration	50 µg/mL
Ratio Glargine: lixisenatide	2 IU : 1 µg
Dose range	10 IU to 40 IU insulin glargine **10-40 units** 合併 lixisenatide **5-20 µg**
Color	**Peach 黃桃色**

The complementary modes of action of basal insulins and GLP-1 RAs provide control of both FPG and PPG



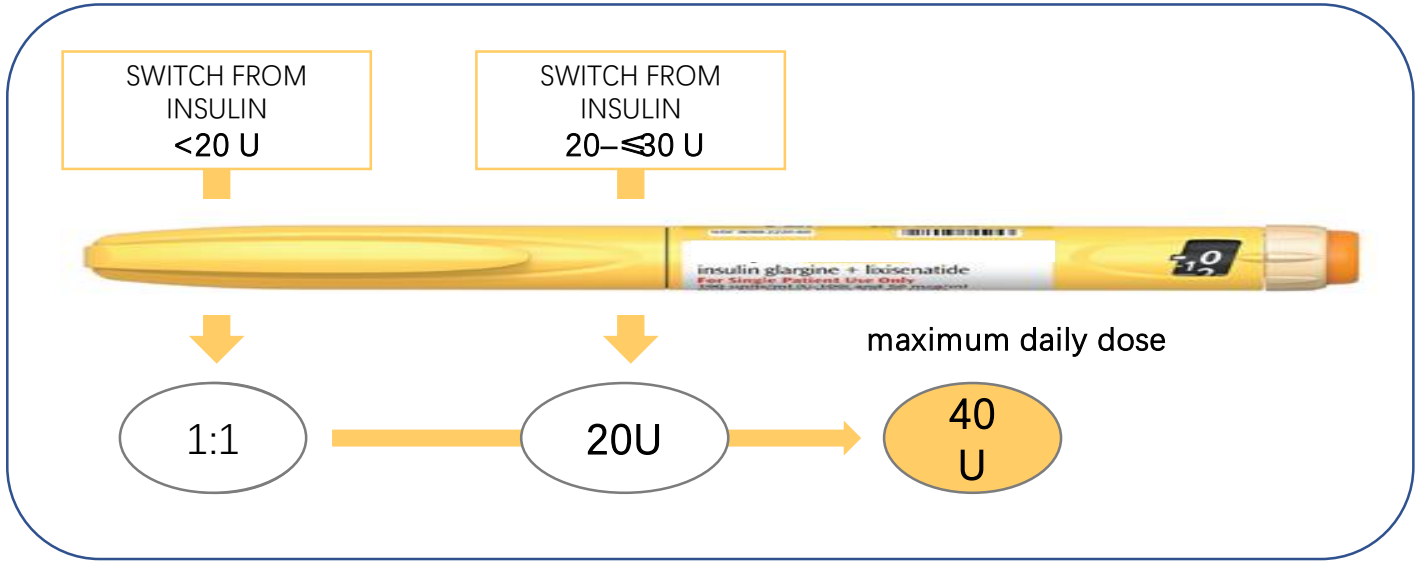
1. Balena R, et al. Diab Obes Metab 2013;15:485–502
2 Baggio LL and Drucker DJ. Gastroenterol 2007;132: 2131–57
3. Wang Z, et al. Diab Care 2010;33:1555–60;
4. Holst JJ, et al. Physiol Rev 2007;87:1409–39

劑量及用法

起始劑量

Soliqua開始給藥前應先停用基礎胰島素或lixisenatide。

Soliqua的起始劑量乃依先前的抗糖尿病治療而定，且 **lixisenatide的起始建議劑量不得超過10μg**：



****若使用不同的基礎胰島素：**

•若基礎胰島素為**每日給藥2次**或**使用insulin glargine (300 units/mL)**，則先前給藥的**每日總劑量應下調20%**以作為Soliqua起始劑量的選擇依據。

Example for patients switching from insulin glargine 300 U/mL less than 20 units

Switching from previous dose of 20 U/day **insulin glargine U300**

Reduce the dose by 20% to get starting dose of iGlarLixi

Starting dose **16**

Insulin glargine	Lixisenatide
10 U	5 ug
11	5.5
12	6
13	6.5
14	7
15	7.5
16	8
17	8.5
18	9
19	9.5
20	10
21	10.5
22	11
23	11.5
24	12
25	12.5
26	13
27	13.5
28	14
29	14.5
30	15
31	15.5
32	16
33	16.5
34	17
35	17.5
36	18
37	18.5
38	19
39	19.5
40	20

10–40 Pen

(2 U:1 µg ratio)

Soliqua 仿單

Example for patients switching from insulin glargine 300 U/mL more than 20 units

Switching from previous dose of 30 U/day **insulin glargine U300**

Reduce the total dose by 20% to get starting dose of iGlarLixi (=24 Units)

Check label to determine starting Soliqua dose based on this reduced total daily dose (e.g. ≥20–<30 U/day starts at 20 U/day of iGlarLixi)

Starting dose **20**

lixisenatide的起始建議劑量不得超過10μg

Insulin glargine	Lixisenatide
10 U	5 ug
11	5.5
12	6
13	6.5
14	7
15	7.5
16	8
17	8.5
18	9
19	9.5
20	10
21	10.5
22	11
23	11.5
24	12
25	12.5
26	13
27	13.5
28	14
29	14.5
30	15
31	15.5
32	16
33	16.5
34	17
35	17.5
36	18
37	18.5
38	19
39	19.5
40	20

10–40 Pen

(2 U:1 μg ratio)

Soliqua 仿單

儲存條件

架儲期

- 24 個月
- 首次使用後的注射筆:

	儲存溫度	儲存天數
第一次使用後的注射筆，請選擇一項儲存溫度，並依照相對應之天數儲存：	放在低於25℃之室溫，不可冷藏，不可冷凍。	至多保存28天，如未使用完應丟棄。
	放在低於30℃之室溫，不可冷藏，不可冷凍。	至多保存14天，如未使用完應丟棄。

- 儲存時應拔下針頭。
- 注射筆之儲存應遠離直射熱源或光源。每次注射完畢應套回筆蓋以避免光照。

儲存之特別注意事項

- 未使用過的注射筆
- 應儲存於冰箱(2℃ - 8℃)。
- 不可冷凍或放在冷凍室旁或冰袋旁。
- 預填注射筆應存放在原有的外盒內以避免光照。

Soliqua 仿單

Soliqua 健保給付 2019/07/01生效

適應症

- Soliqua適用於基礎胰島素(每日劑量少於60單位)或lixisenatide治療時血糖控制不佳的第二型糖尿病成人病人，在飲食與運動外，做為改善血糖之輔助治療

健保核價

- 本案藥品為健保已收載長效型胰島素insulin glargine成分，合併GLP-1促效劑lixisenatide成分之複方製劑，可增加臨床醫師及病患用藥選擇，**同意納入健保給付**，屬第2B類新藥，**支付價均核為每支1,215元***

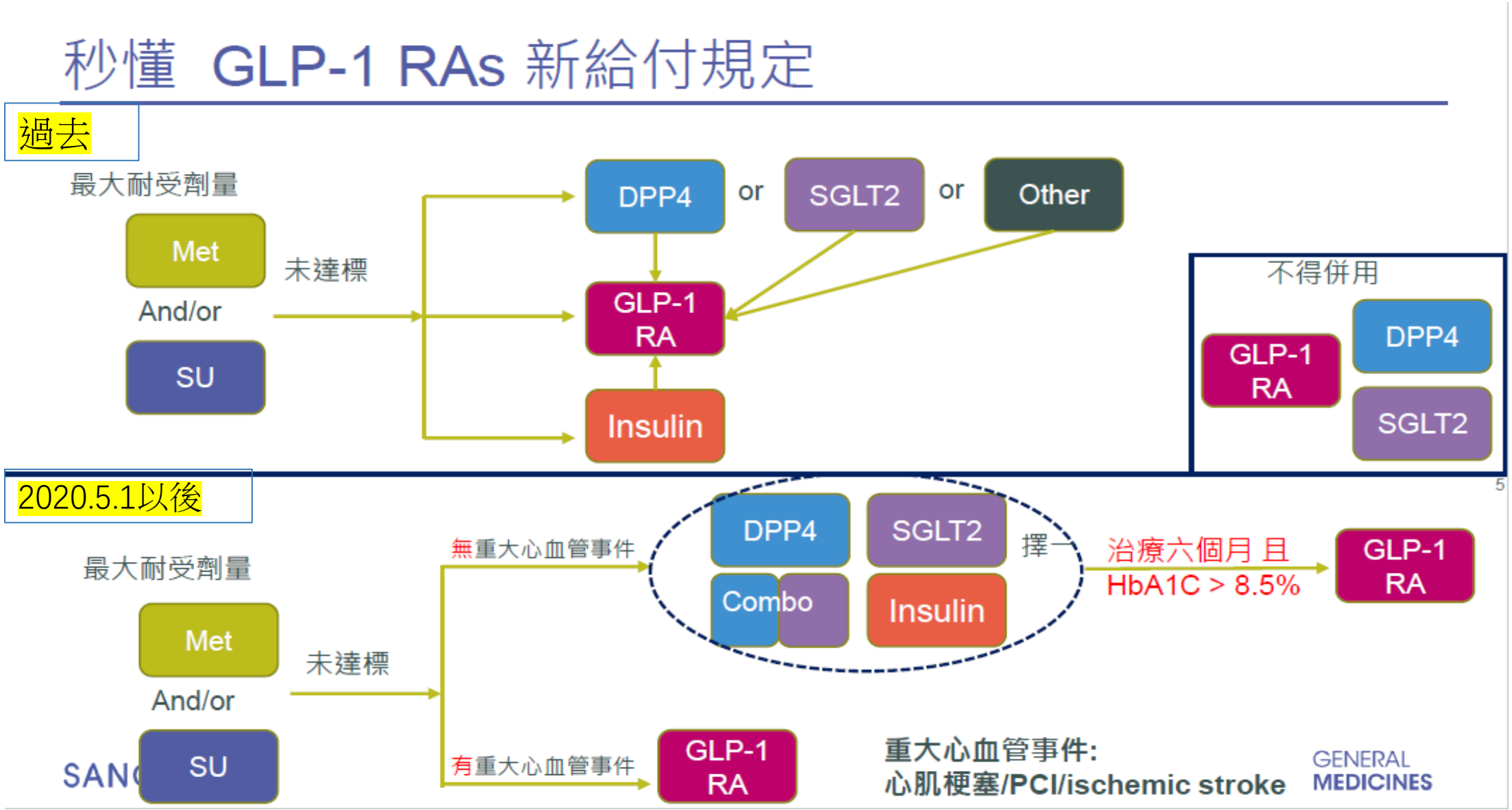
給付條件

- 含 lixisenatide 及 insulin glargine 之複方製劑(如 Soliqua)

1. 限用於第二型糖尿病成人病人，當患者已接受 lixisenatide 或**基礎胰島素治療仍未達理想血糖控制時，與口服降血糖藥物併用**
2. 本藥品**不得與DPP-4 抑制劑 、SGLT-2 抑制劑併用**

**全民健康保險藥物共同擬訂會議藥品部分第37次(108年4月)會議紀錄*

GLP1健保修改給付 2020/05/01生效



周劍文診所
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Premix (Ryzodec)

New option

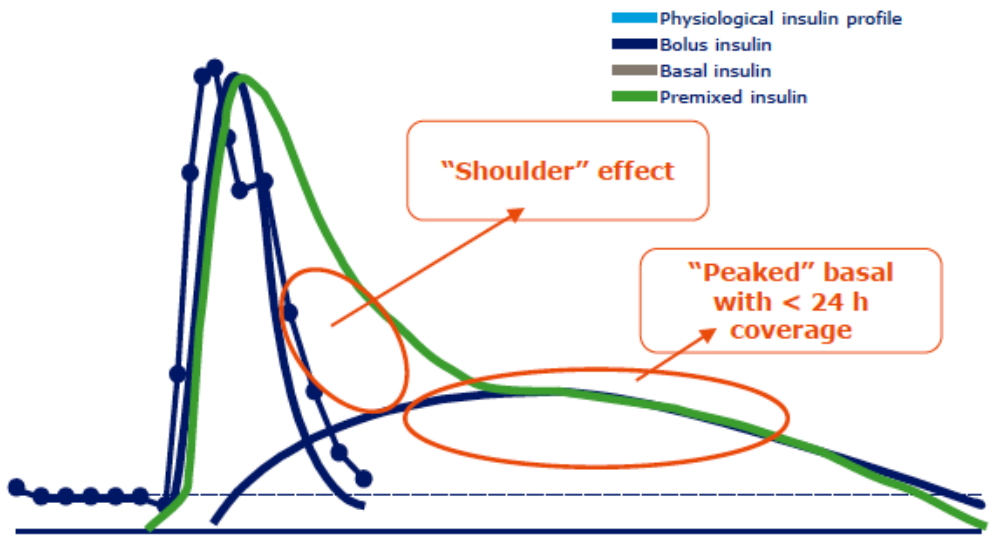
The first insulin co-formulation:
IDegAsp (Ryzodeg)

Insulin Treatment Options in Taiwan

Insulin types			Onset	Peak	Duration
Human insulin	Short acting	Regular insulin	30-60 mins	2-3 hrs	5-8 hrs
	Intermediate acting	NPH insulin	2-4 hrs	4-10 hrs	10-16 hrs
	Premixed insulin	70/30 human insulin	30-60 mins	2-8 hrs	10-16 hrs
Insulin analogues	Rapid acting insulin	Insulin lispro Insulin aspart Insulin glulisine	5-15 mins	30-90 mins	3-5 hrs
	Basal insulin	Insulin glargine (U-100) Insulin detemir (U-100) Insulin glargine (U-300) Insulin degludec (U-100)	2-4 hrs 1-3 hrs 6 hrs 1 hr	No obvious peak	20-24 hrs 20-24 hrs 24 hrs 25 hrs
	Premixed insulin	**70/30 aspart insulin** **50/50 aspart insulin** 75/25 lispro insulin 50/50 lispro insulin	5-15 mins	1-4 hrs	10-16 hrs
	Soluble co-formulation	**Insulin degludec/aspart 70/30**	14 mins	72 mins	25 hrs(degludec)

1. *DAROC Clinical Practice Guidelines for Diabetes Care- 2018*, Taiwan, Diabetes Association of the R.O.C., 2018.
2. Ryzodeg 仿單

Limitations of premixed insulin and basal-bolus insulin regimens



Limitations of premixed insulins based on protamination:

- Variability in glycaemic control
- Hypoglycaemia risk
- Shoulder effect
- NPH-like peaked basal profile
- Incomplete 24-hour basal coverage
- Need for re-suspension

Limitations of a basal-bolus insulin regimen:

- Burden of multiple injections
- Complex titration schedule

Atkin. *Ther Adv Chronic Dis*. 2015;6:375–88; Kruszynska *et al. Diabetologia*. 1987;30:16–21.

Pharmacological differences between IDegAsp co-formulation and premixes

Co-formulation

Involves mixing two biologically active solutions together in a fixed-ratio combination[1]

- Insulin degludec and IAsp
- Mimics physiological insulin secretion closely
- Avoid the "shoulder effect" and variability of protaminated premixed insulins, thereby reducing the risk of hypoglycaemia
- Insulin degludec component provides full 24-hour, flat and steady basal insulin coverage (low variability)
- Simplify the insulin regimen without requiring resuspension and lower the injection burden

VS

Premixes

Involves a suspension of one biologically active solution with an insoluble biologically inactive precipitate in a fixed-ratio combination[2]

e.g.: Biphasic human insulin and protaminated IAsp

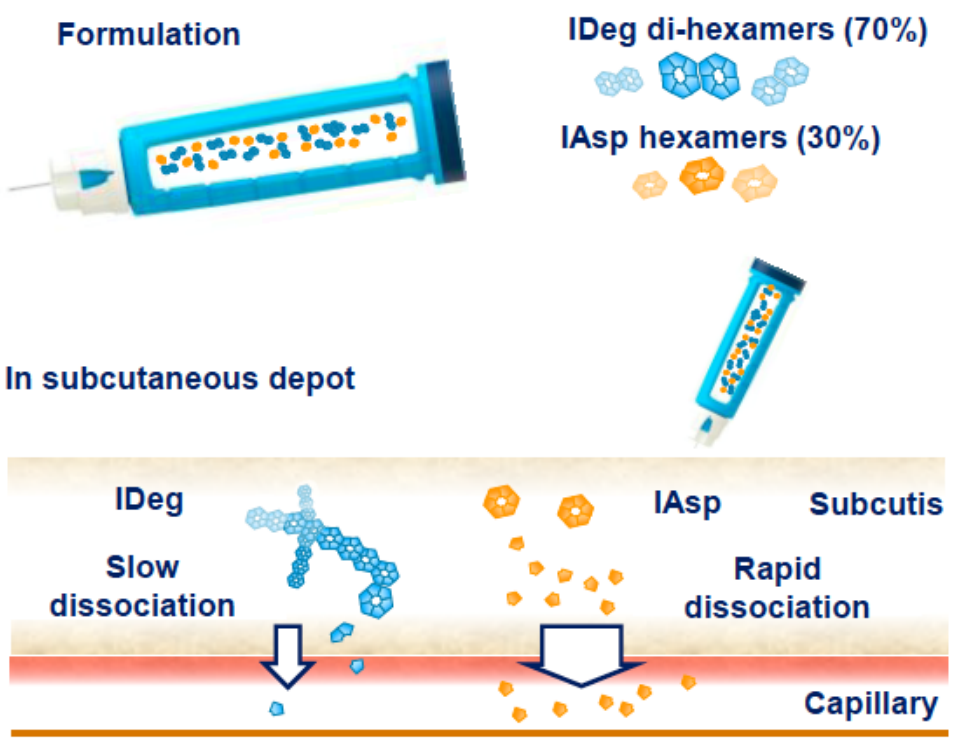
Limitations of premixed insulins due to protamination[2]:

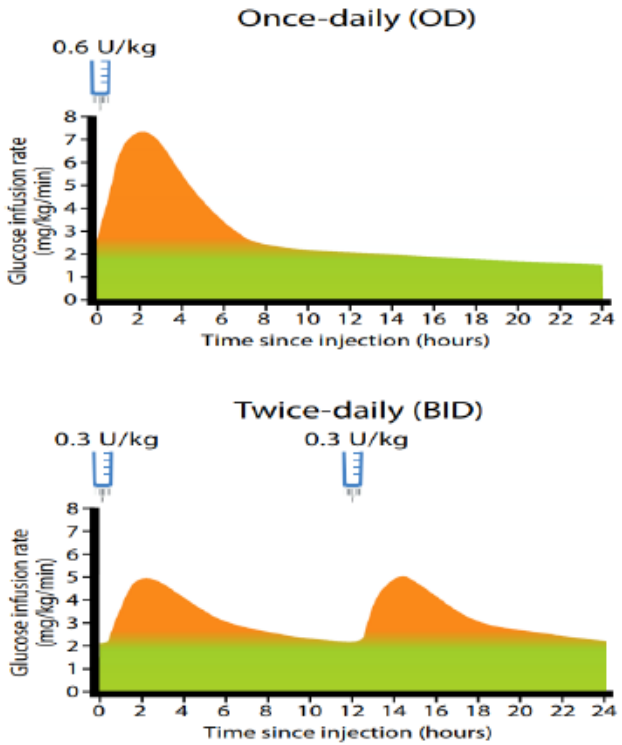
- Variability in glycaemic control
- Incomplete 24-hour basal coverage
- Need for re-suspension

IAsp, insulin aspart

1. Atkin *Ther Adv Chronic Dis* 2015;6:375–88; 2. Kruszynska *et al. Diabetologia* 1987;30:16–21

IDegAsp - A soluble co-formulation of insulin degludec and insulin aspart with distinct characteristics





IDegAsp: Insulin degludec/insulin aspart;
Havelund S. Pharm Res. 2015 Jul;32(7):2250-8.; Haahr H et al. Clin Pharmacokinet (2017) 56:339–354

Overall Summary

IDegAsp provides:

Similar glycaemic control among all the trials:

- Lower insulin dose
- Reduction in nocturnal, overall & severe hypoglycaemia vs. comparators

FPG and PPG control achieved with flexible dosing at the main meals

Simple intensification option and flexible dosing vs. basal bolus

Comparators: BIAsp 30 (start twice daily, Intensify Premix I and ALL, China, Ramadan); Insulin degludec OD + IAsp (twice daily vs. basal bolus); IDet (BOOST T1); IGlar U100 + IAsp (step-by-step intensification trial)
BIAsp, biphasic insulin aspart; BID, twice daily; IDegAsp, insulin degludec/insulin aspart; IDet, insulin detemir; IGlar U100, insulin glargine U100; FPG, fasting plasma glucose; PPG, post prandial glucose; T2D, type 2 diabetes; OD, once daily

Thank You For Attention