## **Injectable Anti-diabetic Medications** in Hong Kong 2023



Vice president, Diabetes HongKong

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# Agenda

- Available injectable antidiabetic treatment in HK
- T2DM treatment algorithm
- Short acting Vs long acting GLP-1 RA
- Benefit of GLP-1 RA CVOT outcome
- Clinical Recommendations to manage GI adverse events with GLP-1RAs
- Case sharing

# **Injectable Anti-diabetic Treatment in HK**

### **GLP-1RA**

- Victoza (Liraglutide)
- Bydureon bcise (Exenatide extended release)
- Trulicity (Dulaglutide)
- Ozempic (Semaglutide)

### **GLP-1RA+ insulin**

- Soliqua (Glargine / Lixisenatide )
- Xultophy ( Degludec /Liruglutide)

### GIP/GLP-1RA (not available in HK yet)

• Tirzepatide

### Insulin

- Short acting
- Intermediate acting
- Rapid acting
- Long acting
- Premixed insulin



### **USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES**

#### HEALTHY LIFESTYLE BEHAVIORS; DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT (DSMES); SOCIAL DETERMINANTS OF HEALTH (SDOH)

Goal: Cardiorenal Risk Reduction in High-Risk Patients with Type 2 Diabetes (in addition to comprehensive CV risk management)\*

# For GLP-1 RA, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke, and renal endpoints in individuals with T2D with established/high risk of CVD.

**Goal: Achievement and Maintenance of Glycemic and Weight Management Goals** 

TO AVER THERAPEUTIC INTETLA REASSESS AND MODIFY TREATMEN BEDULARLY

D-4 MONTHS



Pharmacologic Approaches to Glycemic Treatment Diabetes Care Volume 46, Supplement 1, January 2023

#### Goal: Cardiorenal Risk Reduction in High-Risk Patients with Type 2 Diabetes (in addition to comprehensive CV risk management)\*









Pharmacologic Approaches to Glycemic Treatment Diabetes Care Volume 46, Supplement 1, January 2023

#### **Goal: Achievement and Maintenance of Glycemic and Weight Management Goals**

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## When to use GLP-1RA ?

- 1<sup>st</sup> injectable treatment in Type 2 DM when OAD failure
- Diabesity
- ASCVD ( atherosclerotic cardiovascular disease )
- CKD (if SGLT-2 inhibitor intolerated or contraindicated)

# What is GLP-1/GIP? Pathophysiology

The incretins glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP)

- gut-derived hormones that potentiate insulin secretion
- contribute to glucose metabolism through a wide range of physiological actions





Nature Reviews Nephrology volume 13, pages605–628 (2017) Progress in biophysics and molecular biology vol107, issue2, Nov2011 ,pages248-256

Half-life Drug Approval date (US, Phase III Base Homology Dose and Route Tmax EMA) clinical trial to native frequency GLP-1 (%) program SC 2.1 h 2.4h Exenatide 28 April 2005, AMIGO 53 Short-Exendin-4 5-10 mcg (Byetta®) 20 November 2006 acting twice daily Lixisenatide 28 July 2016. 10-20 mcg SC 1-3.5h 3h GetGoal Exendin-4 50 (Adlyxin<sup>®</sup>, 1 February 2013 once daily Lyxumia<sup>®</sup>) Liraglutide LEAD 97 0.6-1.8 mg SC 8-12h 13h Long-25 January 2010, Human (Victoza®) 30 June 2009 GLP-1 once daily acting NR Exenatide DURATION 2.1 -26 January 2012, Exendin-4 53 2 mg once SC (Bydureon®) 5.1 h 17 June 2011 weekly Dulaglutide AWARD 90 24-72h 18 September 2014, Human 0.75-1.5 mg SC 5days (Trulicity<sup>®</sup>) 21 November 2014 GLP-1 once weekly SUSTAIN 94 SC 1-Semaglutide 5 December 2017. Human 0.25-1 mg 1week (Ozempic<sup>®</sup>) 8 February 2018 GLP-1 3 days once weekly PO Oral 20 September 2019, PIONEER Human 94 3-14 mg 1h 1week Semaglutide 3 April 2020 GLP-1 once daily (Rybelsus®)

Table 1. Currently available GLP-1 RAs.

EMA, European Medicines Agency; FDA, Food and Drug Administration; GLP-1 RA, glucagon-like peptide-1 receptor agonists; NR, not reported; PO, by mouth; SC, subcutaneous; US, United States.

	Daily SC	injection			Weekly SC injection				Fixed-dose combinations (GLP-1 RA/basal insulin)		
Pen devices for injection	Jacks Dy			Here are a		fructy (and	and a grant of				
Drug: Generic/ commercial	Exenatide b.i.d. Byetta®	Lixisenatide Lyxumia®	Liraglutide Victoza®	Exenatide Bydureon <sup>e</sup>	once weekly, Bydureon® BCise	Dulalgutide Trulicity®	Albiglutide Eperzan®/ Tanzeum®	Semaglutide Ozempic®	iDegLira Xultophy®	iGlarLixi Soliqua®/ Suliqua®	
Single (1) or multiple (x) use?	x	×	x	1	1	1	1	x	x	×	
Predefined(p) or variable(v) dosing	P	P	v	P	p	P	P	P	v (for titration)	v (for titration)	
Pens available (maximum dose)	а. 5 µg b. 10 µg	а. 10 µg b. 20 µg	a. 0.6 mg b. 1.2 mg c. 1.8 mg	2 mg	2 mg	a. 0.75 mg b. 1.5 mg	a. 30 mg b. 50 mg	a. 0.25 mg b. 0.5 mg c. 1.0 mg	1.8 mg/ a iDeg 50 IU perdose b	20 µg/iGlar 40 IU per dose or 20 µg/iGlar 60 IU per dose	
Resuspension necessary?	no	no	no	yes	no*	no	yes	no	no	no	
Ease of use	+	+	+		(-)	***	(-)	+	+	+	

# Short Vs long acting GLP-1RA



### Short-acting GLP-1 receptor agonists

inhibit gastric motility, reducing transpyloric flow (solid lines).

- lead to delayed intestinal glucose absorption and, indirectly, to a reduction in postprandial insulin secretion
- appetite suppression and induction of nausea (dashed lines).
- have direct effects on the CNS and on glucagon

### secretion

Fasting blood glucose levels	Modest reduction	Strong reduction	
Postprandial hyperglycaemia	Strong reduction	Modest reduction	
Fasting insulin secretion	Modest stimulation	Strong stimulation	
Postprandial insulin secretion	Reduction	Modest stimulation	
Glucagon secretion	Reduction	Reduction	
Gastric emptying rate	Deceleration	No effect	
Blood pressure	Reduction	Reduction	
Blood pressure Heart rate	Reduction No effect or small increase (0–2 bpm)	Reduction Moderate increase (2–5 bpm)	
Blood pressure Heart rate Body weight reduction	Reduction No effect or small increase (0–2 bpm) 1–5 kg	Reduction Moderate increase (2–5 bpm) 2–5 kg	

Abbreviations: GLP-1, glucagon-like peptide 1; LAR, long-acting release.

# Long acting GLP-1 RAs better in

- Lowering Hba1c
- Achieving target Hba1
- Lowering fasting plasma glucose
- Lowering in body weight



Nat. Rev. Endocrinol. 8, 728–742 (2012) Molecular Metabolism 46 (2021) 101102

# Changes in A1C values with GLP-1 RAs in head-to-head clinical studies.



\* p<0.05, + p<0.05 for a pre-defined non-inferiority margin

## Changes in weight with GLP-1 RAs in head-tohead clinical studies



## Changes in fasting plasma glucose with GLP-1 RAs



## Short acting GLP-1 RA like Lixisenatide showed significant reduction in **PPG excursions** lasting for at least 1-2 main meals of the day meals of the day

SE 7-point mmol/L

Mean ± S SMPG,

SП





Significant reduction in PPG excursions for the main meal of the day (Patients may inject **iGlarLixi** with whichever their largest meal\*)

### \*REALI study

Efficacy and safety of once-weekly semaglutide versus once-daily insulin glargine as add-on to metformin (with or without sulfonylureas) in insulin-naive patients with type 2 diabetes (SUSTAIN 4); Published:March 23, 2017DOI:https://doi.org/10.1016/S2213-8587(17)30085-2

## **Unique Characteristics of T2DM in Asian Populations**



BMI = body mass index; PPG = postprandial glucose.

1. Tsai S, et al. J Diabetes. 2011;3(3):208-216. 2. Kim S, et al. Acta Diabetol. 2014;51(4):655-661. 3. Monami M, et al. J Endocrinol Invest. 2006;29(7):619-624. 4. Freemantle N, et al. Diabetes Obes Metab. 2012;14(10):901-909. 5. Møller JB, et al. J Clin Endocrinol Metab, 2014;99(11):4273-4280. 6. Chan JC, et al. JAMA. 2009;301(20):2129-2140. 7. Ma R and Chan JC. Ann NY Acad Sci. 2013;1281(2013):64-91. 8. Venn BJ, et al. Diabet Med. 2010;27(10):1205-1208. 9. ChartsBin statistics collector team 2011, chartsbin.com/view/1154. Accessed 7 July 2015.

### Unlike basal insulin alone,

### fixed-ratio combination (FRCs)can help address both PPG and FPG challenges

FRCs: Titratable, co-administration of BI/GLP-1RA in a single once-daily injection with greater reduction in HbA1c, improving convenience and mitigating GI symptoms due to gradual dose increment (compared with each component alone)<sup>1</sup>

Basal insulin is the most effective agent to lower FPG but it is associated with hypoglycemia and weight gain<sup>2,3</sup> GLP-1 RAs can lower both **FPG and PPG** without an intrinsic effect to cause hypoglycemia, while promoting weight loss<sup>4–6</sup>

Perreault L, et al. Adv Ther 2019;36:265–77
Buse JB, et al. Diabetes Obes Metab 2015;17:145–151
Balena R, et al. Diabetes Obes Metab 2013;15:485–502
Diamant M, et al. Diabetes Care 2014;37:2763–73
Rosenstock J, et al. Diabetes Care 2014;37:2317–25
Porcellati F, et al. Diabetes Metab 2015;41:6516–20



## Benefit of GLP-1 RA - CVOT outcome

## Results of cardiovascular outcome studies comparing GLP-1 RAs with placebo on a background of standard of care



3-component MACE: cardiovascular death, myocardial infarction and stroke

GLP-1 RA drug class as a whole appears to be associated with a 14% reduction in 3-component MACE( cardiovascular death, myocardial infarction and stroke) (HR=0.86; 95% CI=0.8-0.93

# Kidney outcomes with GLP-1 receptor agonists.



GLP-1 RA drug class as a whole appears to be associated with a 21% reduction in incident kidney risk (HR=0.79; 95% CI=0.73–0.87) as evaluated using a composite kidney outcome that included macroalbuminuria



# Clinical Recommendations to manage GI adverse events with GLP-1RAs





### Key messages

- Clear instruction
- Good hydration
- Start from low dose
- Frequent small meal
- STOP and seek medical advice
- if any severe abdominal symptoms

Clinical Recommendations to Manage Gastrointestinal Adverse Events in Patients Treated with Glp-1 Receptor Agonists: A Multidisciplinary Expert Consensus, J. Clin. Med. 2023, 12(1), 145;



Clinical Recommendations to Manage Gastrointestinal Adverse Events in Patients Treated with Glp-1 Receptor Agonists: A Multidisciplinary Expert Consensus, J. Clin. Med. 2023, 12(1), 145;



Clinical Recommendations to Manage Gastrointestinal Adverse Events in Patients Treated with Glp-1 Receptor Agonists: A Multidisciplinary Expert Consensus, J. Clin. Med. 2023, 12(1), 145;

# Case sharing



# Mr Chan 72/M

Body Weight: 90.6 kg Height: 1.65 m BMI: 33.28 BP: 125/61 mmHg Pulse: 97/min

- T2 DM since 1997, complicated by Non sight threatening retinopathy and Microalbuminuria, CKD stage 3B (eGFR 41)
- HT, Hyperlipidaemia, OSA

A SPIRIN TABLET 80MG (ORAL) TAKE WITH / AFTER MEAL <1> TABLET(S) DAILY
BUDE SONIDE 80MCG + FORMOTEROL INHALE <1> PUFF(S) TWICE DAILY WHEN NECESSARY 4.5MCG INHALER 120DOSE(S) (INHALATION)
CALCITRIOL CAPSULE 0.25MCG (ORAL) TAKE <1> CAPSULE(S) AT NIGHT (ON EVERY MON,
EMPAGLIFLOZIN TABLET 10MG (ORAL) TAKE WITH MEAL <1> TABLET(S) DAILY
FAMOTIDINE TABLET 20MG (ORAL) TAKE <1> TABLET(\$) TWICE DAILY
FELODIPINE EXTENDED RELEASE TAB TAKE <1> TABLET(\$) DAILY 10MG (ORAL)
GLICLAZIDE TABLET 80MG (ORAL) TAKE WITH MEAL <2> TABLET(S) IN THE MORNING
LORATADINE TABLET 10MG (ORAL) TAKE <1> TABLET(\$) DAILY
METFORMIN HCL TABLET 500MG (ORAL) TAKE WITH MEAL <1> TABLET(S) TWICE DAILY
SIMVA STATIN TABLET 20MG (ORAL) TAKE <15 TABLET(S) AT NIGHT
SIMUASIATIN TABLET 2010 (OTAL) TARE STE TABLET (3) AT MOTT

\*\*\*\*\* Lab Results \*\*\*\*\* (09/08/22) HbA1c: 8.4 % (H) (09/08/22) Fasting Glucose: 7.3 mmol/L (H) (09/08/22) TC: 3.70 mmol/L (09/08/22) LDL-C: 2.11 mmol/L (09/08/22) HDL-C: 0.86 mmol/L (09/08/22) TG: 1.60 mmol/L (09/08/22) Serum K: 4.5 mmol/L (09/08/22) Serum Na: 140.0 mmol/L (09/08/22) Serum Cr: 147 umol/L (H) (09/08/22) Estimated GFR: 41 ml/min/1.73 sq. m. (by CKD-EPI formula) (09/08/22) Bilirubin, Total: 9.0 umol/L (09/08/22) ALP: 68 U/L (09/08/22) ALT: 34 U/L (09/08/22) Haemoglobin: 13.2 g/dL (L) (09/08/22) Urine protein/Cr ratio: 0.3 mg/mg Cr (H)

# DM nurse clinic 10/2022

- Social history : Retired (previously worked as chief) , Live with wife, Children live apart
- Meal patterns:
  - 6-7am: sandwiches + 4-5 scoops of milk powder
  - noon: 1 bowl of rice / noodle + pork / fish +/- veg
  - 3-4pm: snack with a fruit /milk / a pack of biscuit
  - 7-8pm: same as lunch + starchy soup
  - 11pm: sleep
- Exercise :
  - Walking or limbs exercise 15mins / day
- Medication adherence:
  - claimed may forget om dose medication 1x/week
  - Misunderstood and not taking empagliflozin and resume recently



# Diabetic intensification Clinic 1/2023

- Problem identification
  - Lifestyle modification for 3/12 (poor compliance)
  - Fair drug compliance as well as forgetfulness



BMI 33.2 >31.8 Hba1c 8.4 >8.1 eGFR 41 Urine protein/Cr ratio: 0.3 mg/mg Cr

Metformin 500mg BD Empagliflozin 10 mg daily Diamciron 160 mg OM

# What will you do ?

# What will you do?

A. Lifestyle modification

- B. Add basal insulin SC
- C. Add GLP-1RA SC
- D. A+B
- E. A+C
- F. A+B+C



BMI 33.2 >31.8 Hba1c 8.4 >8.1 eGFR 41 Urine protein/Cr ratio: 0.3 mg/mg Cr

Metformin 500mg BD Empagliflozin 10 mg daily Diamciron 160 mg OM



## What we did ...



BMI 33.2 >31.8 Hba1c 8.4 >8.1 eGFR 41 Urine protein/Cr ratio: 0.3 mg/mg Cr

Metformin 500mg BD Empagliflozin 10 mg daily Diamciron 160 mg OM

- Lifestyle modification
- Drug simplification (metformin +empagliflozin > Xigduo (Dapagliflozin +metformin)
- Omit DM medication which may have weight gain effect (Diamicron)
- Add GLP-1RA (Victoza)

TAKE WITH / AFTER MEAL <1> TABLET(S) DAILY
GTAKE <1> TABLET(\$) DAILY
INHALE <1> PUFF(S) TWICE DAILY WHEN NECESSARY
TAKE <1> CAPSULE(S) AT NIGHT (ON EVERY MON, THU)
TAKE <1> TABLET(S) TWICE DAILY
TAKE <1> TABLET(\$) DAILY
NINJECT SUBCUTANEOUSLY <1.2> MG DAILY FOR 28 DAY(S) THEN <1.8> MG DAILY FOR 56 DAY(S).
TAKE <1> TABLET(S) AT BEDTIME
TAKE <1> TABLET(\$) WITH DINNER

Victoza

- DM control
- Weight control
- Renal benefit

## **Patient's journey**





#### Selected Dates: 1 Apr - 14 Apr 2023 (14 Days)



## **CGM** report

### CGM end July 2023 – Aug 2023

Time Sensor Active:

Selected Dates: 25 Jul - 7 Aug 2023 (14 Days)

0%

7%

1%

0%

6.7

6.3

7.2

6.8

6.8

Very High >13.9 mmol/L

High 10.1 - 13.9

Target 3.9-10.0

Low 3.0 - 3.8

Glucose

Tue 25 Jul

Jul

8 Jul

9 Jul

30 Jul

Mon 31 Jul

Very Low <3.0

**Time in Ranges** 





### CGM april 2023



8.4

7.8

7.8

9.5

8.6

8.6

Advise him to cut intake of fruits and sugary milk drink

+LSM + drug treatment

# Take home message



- GLP-1RA is used as first line treatment for <u>T2DM with cardiovascular</u>/ renal comorbidities
- GLP-1RA can be used
  - as first line injectable treatment upon OAD failure
  - in diabesity with both glycaemic and weight control effect
- The most common side effect of GLP-1RAs are GI-related
- Fixed dose combination of insulin and GLP-1 RA can have effective glycaemic control in Asian T2DM

## Patient empowerment work in TMH







Serve >1 M population cover NTW cluster

Patient Resource Center



Council members of "Sweetie Buddies "

" Sweetie buddies " NGOs



香港復康會 The Hong Kong Society for Rehabilitation



## 糖糖正正

病友組織「糖糖正正」由屯門醫院糖尿及內分泌 專科及病人資源中心成立,為糖尿患者提供病 人賦能活動、義工服務及「同路人」分享等,提升 患者的生活質素。



## Patient empowerment work in TMH



## Webinar talk during covid-19

## Hybrid educational talk



# WDD 2022

加洁相





Hiking



### Exercise class in district health center



### Cooking class





## Healthy recipe verify by dietician





