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Management of people with diabetes and cardiovascular disease- what's new?

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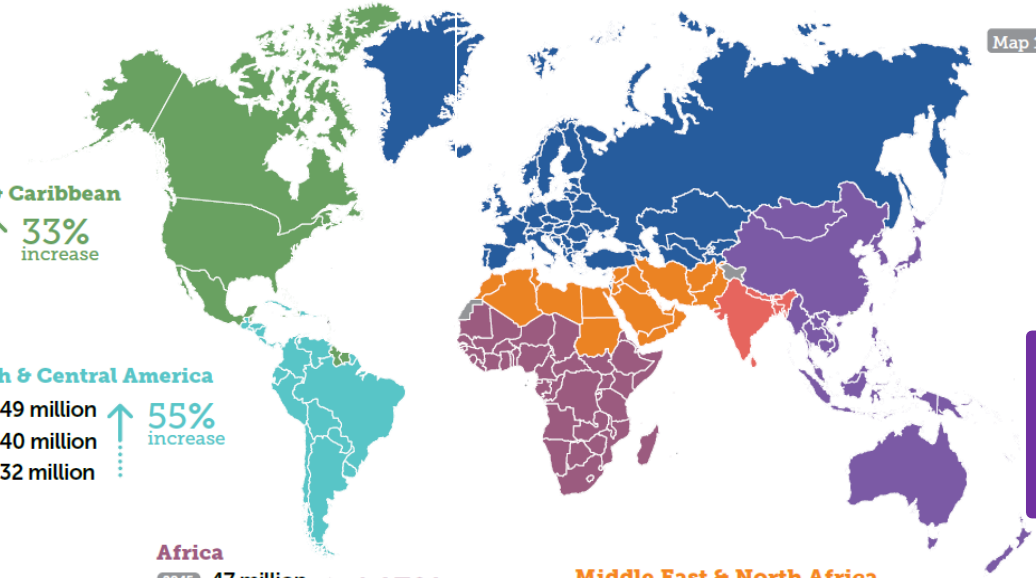
Disclosure

- Alice Kong had received research grants and/or honorarium for consultancy or giving lectures from Abbott, Astra Zeneca, Bayer, Eli-Lilly, Merck Serono, Nestle, Novo-Nordisk, Pfizer and Sanofi.

Nearly half a billion people are living with diabetes worldwide



Map 1 Number of people with diabetes worldwide and per IDF Region in 2019, 2030 and 2045 (20–79 years)

North America & Caribbean
2045 63 million
2030 56 million
2019 48 million
33% increase

Europe
2045 68 million
2030 66 million
2019 59 million
15% increase

South & Central America
2045 49 million
2030 40 million
2019 32 million
55% increase

South-East Asia
2045 153 million
2030 115 million
2019 88 million
74% increase

WORLD
2045 700 million
2030 578 million
2019 463 million
51% increase

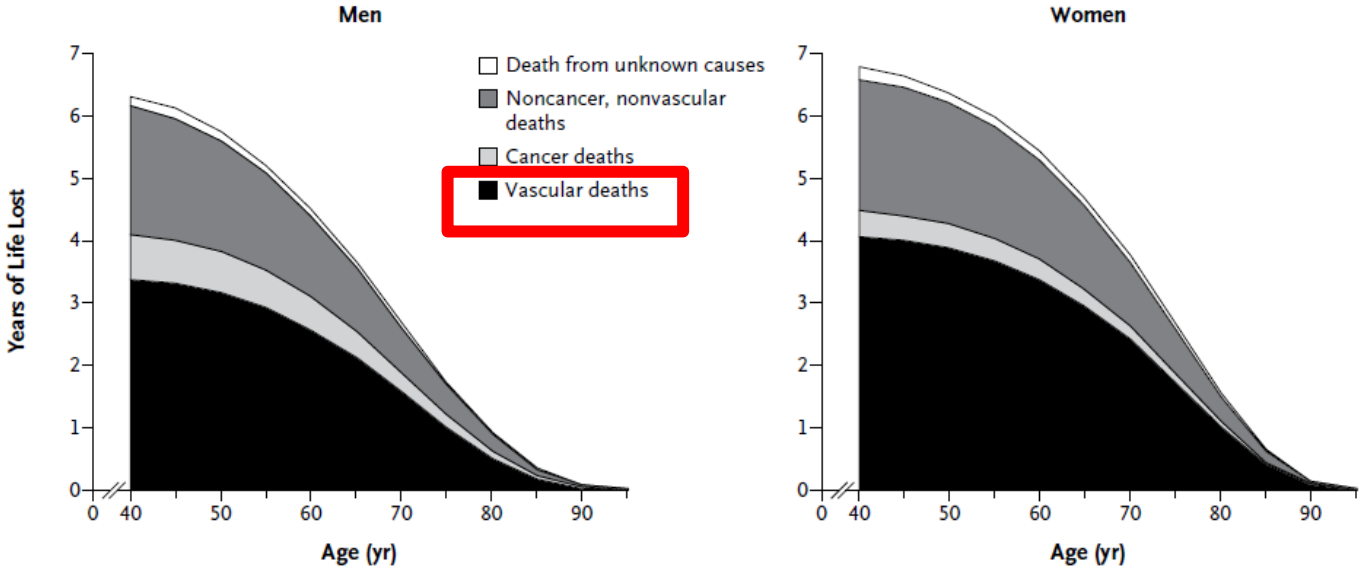
Africa
2045 47 million
2030 29 million
2019 19 million
143% increase

Middle East & North Africa
2045 108 million
2030 76 million
2019 55 million
96% increase

Western Pacific
2045 212 million
2030 197 million
2019 163 million
31% increase

https://www.diabetesatlas.org/upload/resources/2019/IDF_Atlas_9th_Edition_2019.pdf

Emerging Risk Factor Collaboration
Average loss of 6 years of life in diabetes



Seshasai, SR et al NEJM 2011

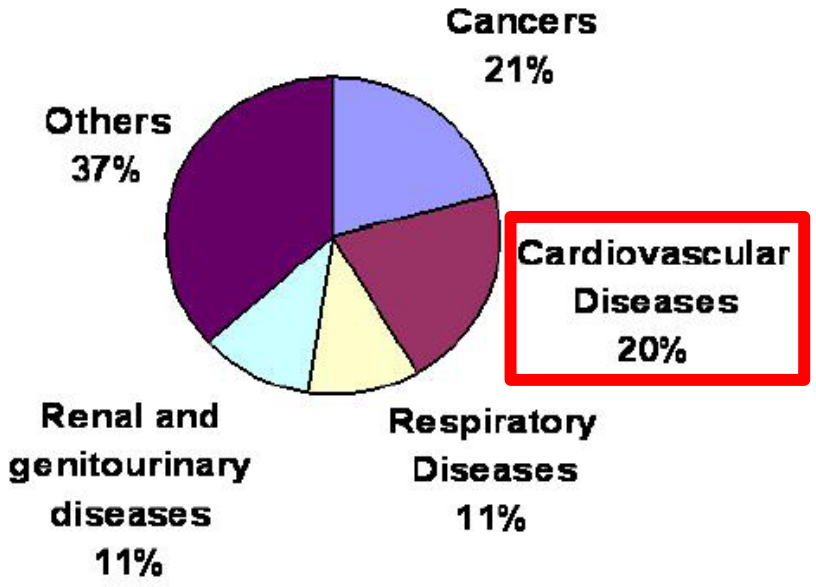
Mortality in Patients with Type 2 Diabetes: (Data from Hong Kong Diabetes Registry)

Hong Kong Diabetes Registry

Causes of death

In 7000 T2D

FU 6 years



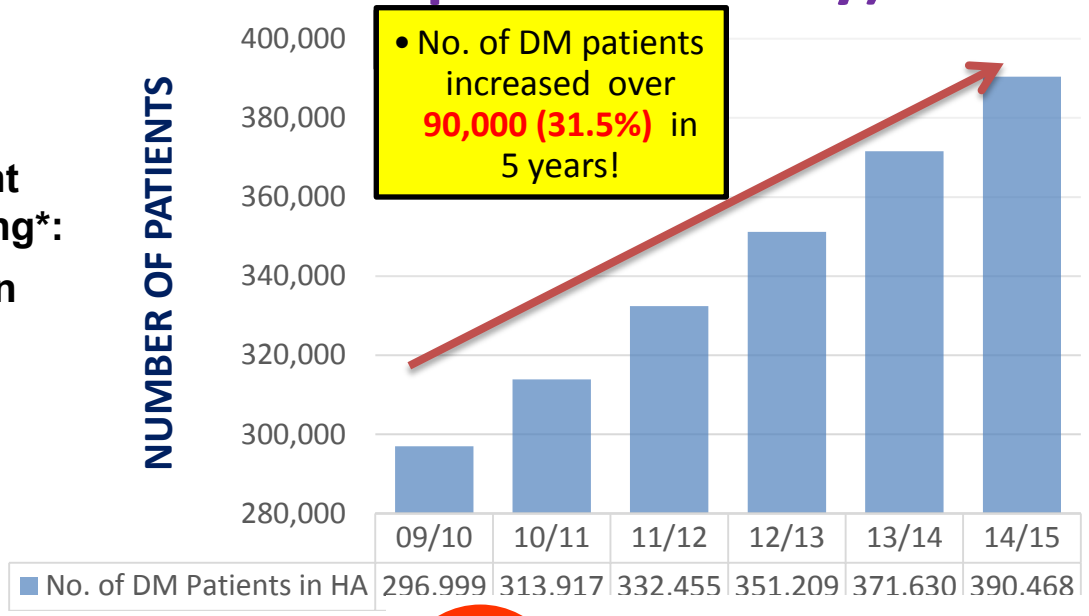
So WY, et al. Diabetes Metab Res Rev. 2008 Mar-Apr;24(3):238-46

Burden on Public Health Care System in HK (Data from Hospital Authority)

2016-17 Recurrent Government Funding*:

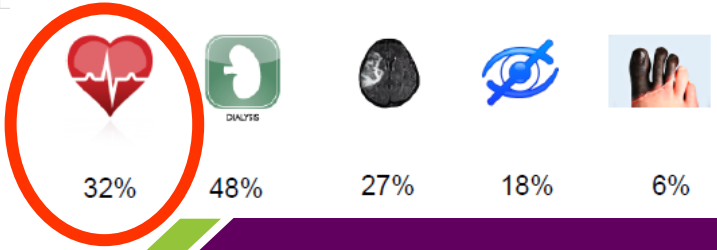
~ HK$50.76 billion

(US$6.54 billion)



~200,000 admissions (18% of all admissions)

~1 million specialist out-patient visits (14% of all attendance)



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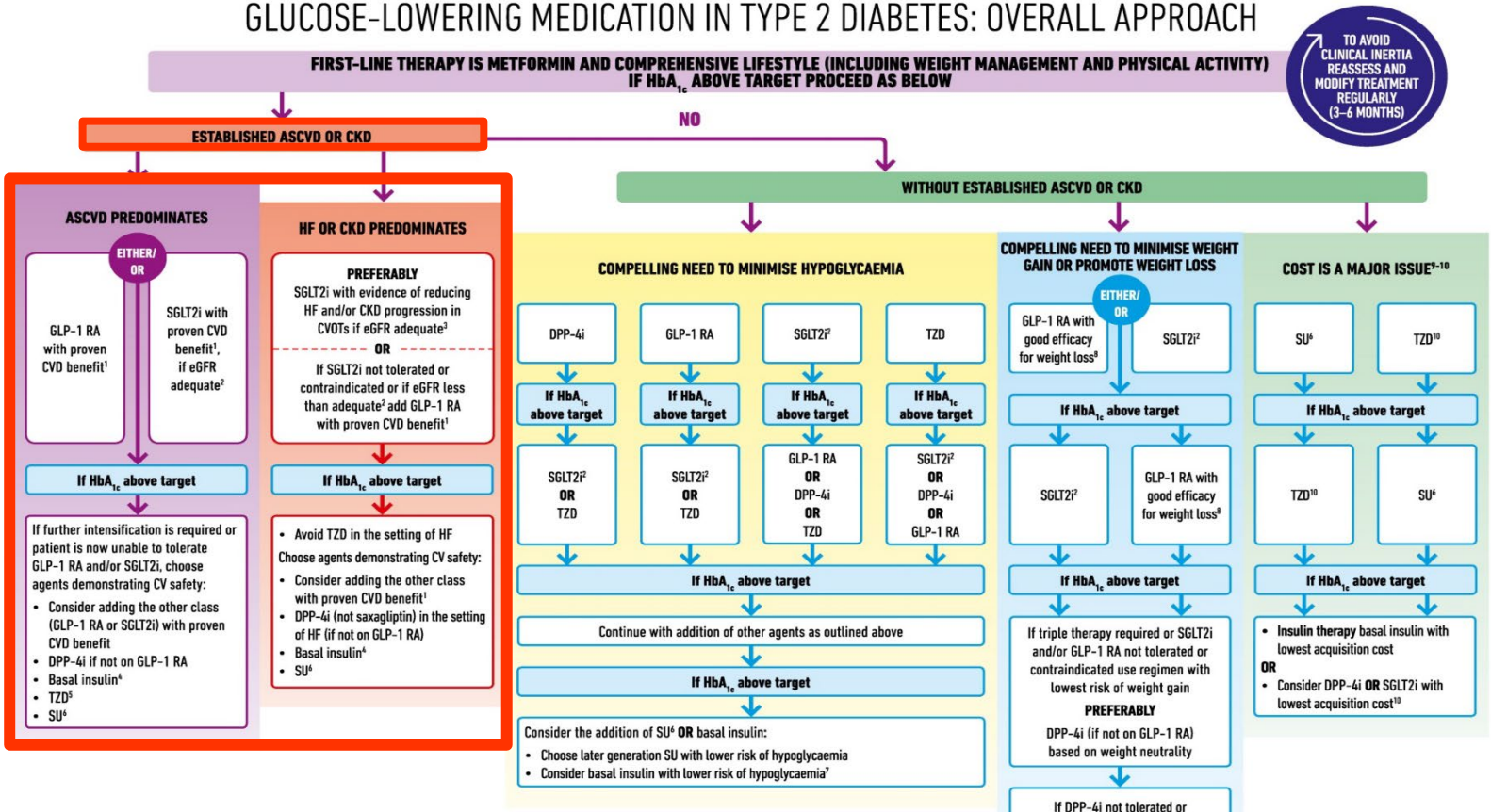
Diabetologia (2018) 61:2461–2498
https://doi.org/10.1007/s00125-018-4729-5

CONSENSUS REPORT

Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

Melanie J. Davies[1,2] · David A. D'Alessio[3] · Judith Fradkin[4] · Walter N. Kernan[5] · Chantal Mathieu[6] · Geltrude Mingrone[7,8] · Peter Rossing[9,10] · Apostolos Tsapas[11] · Deborah J. Wexler[12,13] · John B. Buse[14]

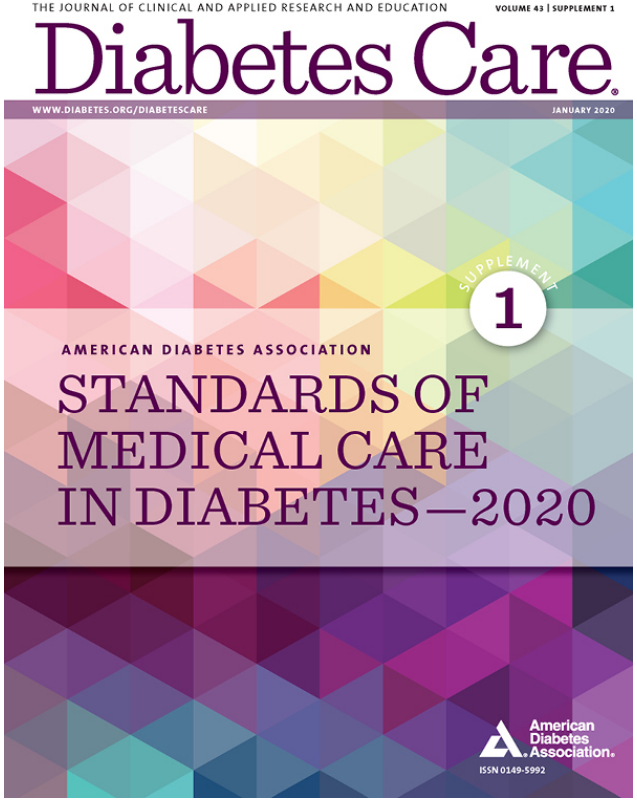
Published online: 5 October 2018



1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.
2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVOTs
4. Degludec or U100 glargine have demonstrated CVD safety
5. Low dose may be better tolerated though less well studied for CVD effects
6. Choose later generation SU with lower risk of hypoglycaemia
7. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin
8. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
9. If no specific comorbidities (i.e. no established CVD, low risk of hypoglycaemia and lower priority to avoid weight gain or no weight-related comorbidities)
10. Consider country- and region-specific cost of drugs. In some countries TZDs relatively more expensive and DPP-4i relatively cheaper

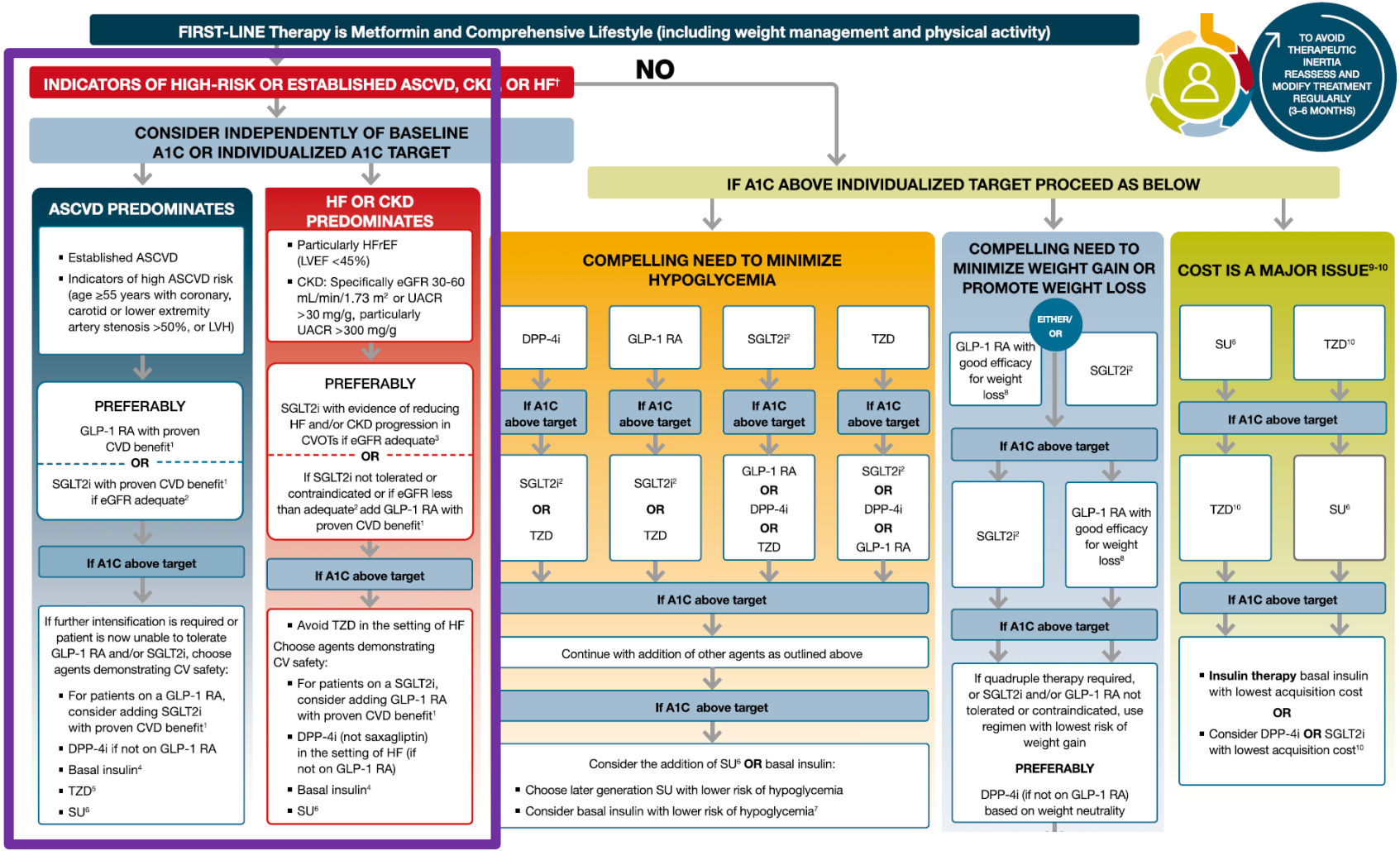
Fig. 2 Glucose-lowering medication in type 2 diabetes: overall approach

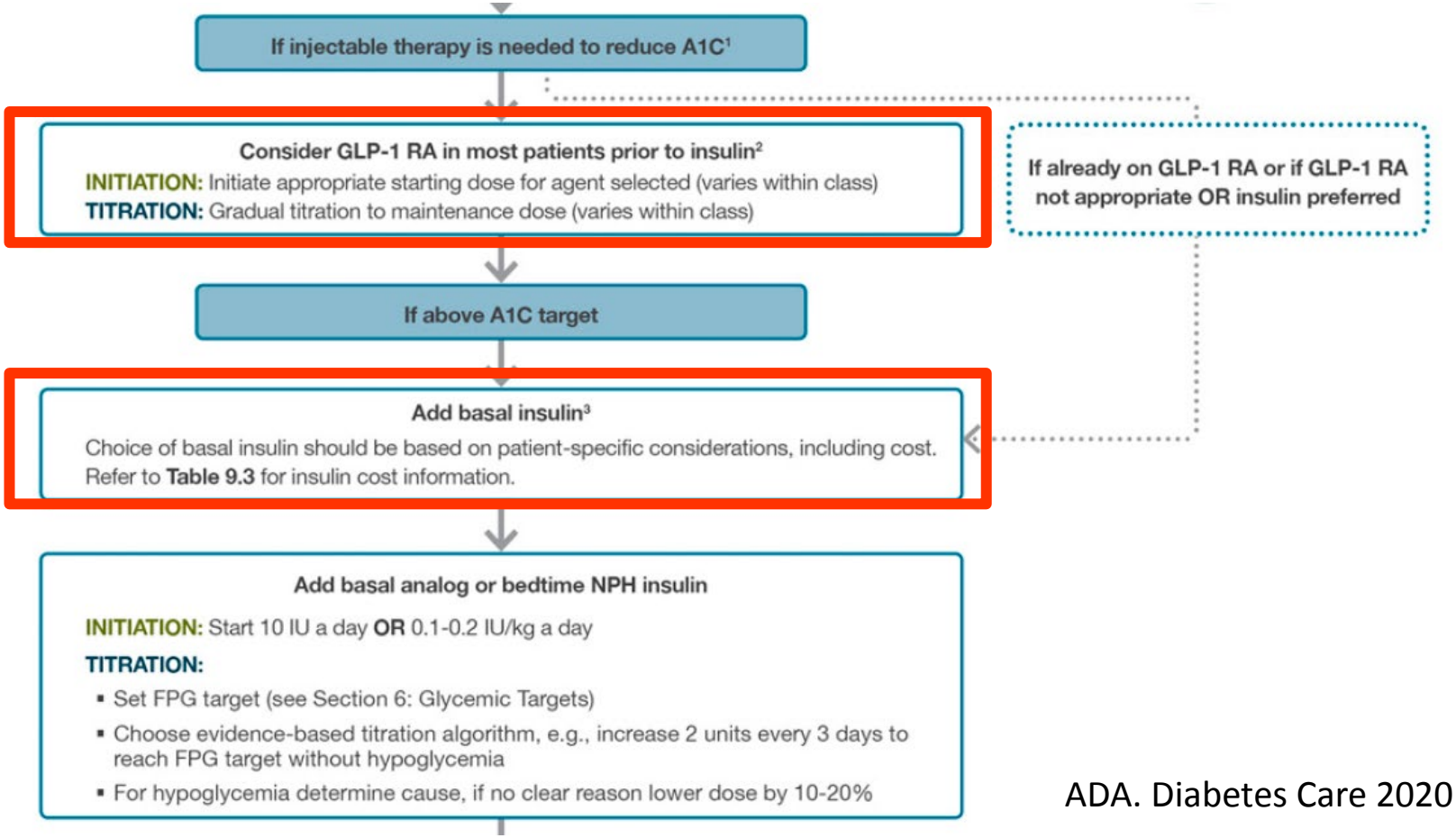
ADA: Standards of Medical Care in Diabetes 2020



9. Pharmacologic Approaches to Glycemic Treatment: *Standards of Medical Care in Diabetes—2020*

Diabetes Care 2020;43(Suppl. 1):S98–S110 | https://doi.org/10.2337/dc20-S009


FIRST-LINE Therapy is Metformin and Comprehensive Lifestyle (including weight management and physical activity)
INDICATORS OF HIGH-RISK OR ESTABLISHED ASCVD, CKD OR HF†
CONSIDER INDEPENDENTLY OF BASELINE A1C OR INDIVIDUALIZED A1C TARGET
ASCVD PREDOMINATES
Established ASCVD
Indicators of high ASCVD risk (age ≥55 years with coronary, carotid or lower extremity artery stenosis >50%, or LVH)
PREFERABLY
GLP-1 RA with proven CVD benefit[1]
OR
SGLT2i with proven CVD benefit[1] if eGFR adequate[2]
If A1C above target
If further intensification is required or patient is now unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV safety:
For patients on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit[1]
DPP-4i if not on GLP-1 RA
Basal insulin[4]
TZD[5]
SU[6]
HF OR CKD PREDOMINATES
Particularly HFrEF (LVEF <45%)
CKD: Specifically eGFR 30-60 mL/min/1.73 m² or UACR >30 mg/g, particularly UACR >300 mg/g
PREFERABLY
SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate[3]
OR
If SGLT2i not tolerated or contraindicated or if eGFR less than adequate[2] add GLP-1 RA with proven CVD benefit[1]
If A1C above target
Avoid TZD in the setting of HF
Choose agents demonstrating CV safety:
For patients on a SGLT2i, consider adding GLP-1 RA with proven CVD benefit[1]
DPP-4i (not saxagliptin) in the setting of HF (if not on GLP-1 RA)
Basal insulin[4]
SU[6]
NO
IF A1C ABOVE INDIVIDUALIZED TARGET PROCEED AS BELOW
TO AVOID THERAPEUTIC INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)
COMPELLING NEED TO MINIMIZE HYPOGLYCEMIA
DPP-4i
GLP-1 RA
SGLT2i[2]
TZD
If A1C above target
SGLT2i[2] OR TZD
SGLT2i[2] OR TZD
GLP-1 RA OR DPP-4i OR TZD
SGLT2i[2] OR DPP-4i OR GLP-1 RA
If A1C above target
Continue with addition of other agents as outlined above
If A1C above target
Consider the addition of SU[6] OR basal insulin:
Choose later generation SU with lower risk of hypoglycemia
Consider basal insulin with lower risk of hypoglycemia[7]
COMPELLING NEED TO MINIMIZE WEIGHT GAIN OR PROMOTE WEIGHT LOSS
EITHER/ OR
GLP-1 RA with good efficacy for weight loss[8]
SGLT2i[2]
If A1C above target
SGLT2i[2]
GLP-1 RA with good efficacy for weight loss[8]
If A1C above target
If quadruple therapy required, or SGLT2i and/or GLP-1 RA not tolerated or contraindicated, use regimen with lowest risk of weight gain
PREFERABLY
DPP-4i (if not on GLP-1 RA) based on weight neutrality
COST IS A MAJOR ISSUE[9-10]
SU[6]
TZD[10]
If A1C above target
TZD[10]
SU[6]
If A1C above target
Insulin therapy basal insulin with lowest acquisition cost
OR
Consider DPP-4i OR SGLT2i with lowest acquisition cost[10]



ADA. Diabetes Care 2020

Development of Exenatide: An Incretin Mimetic

Exenatide (Exendin-4)

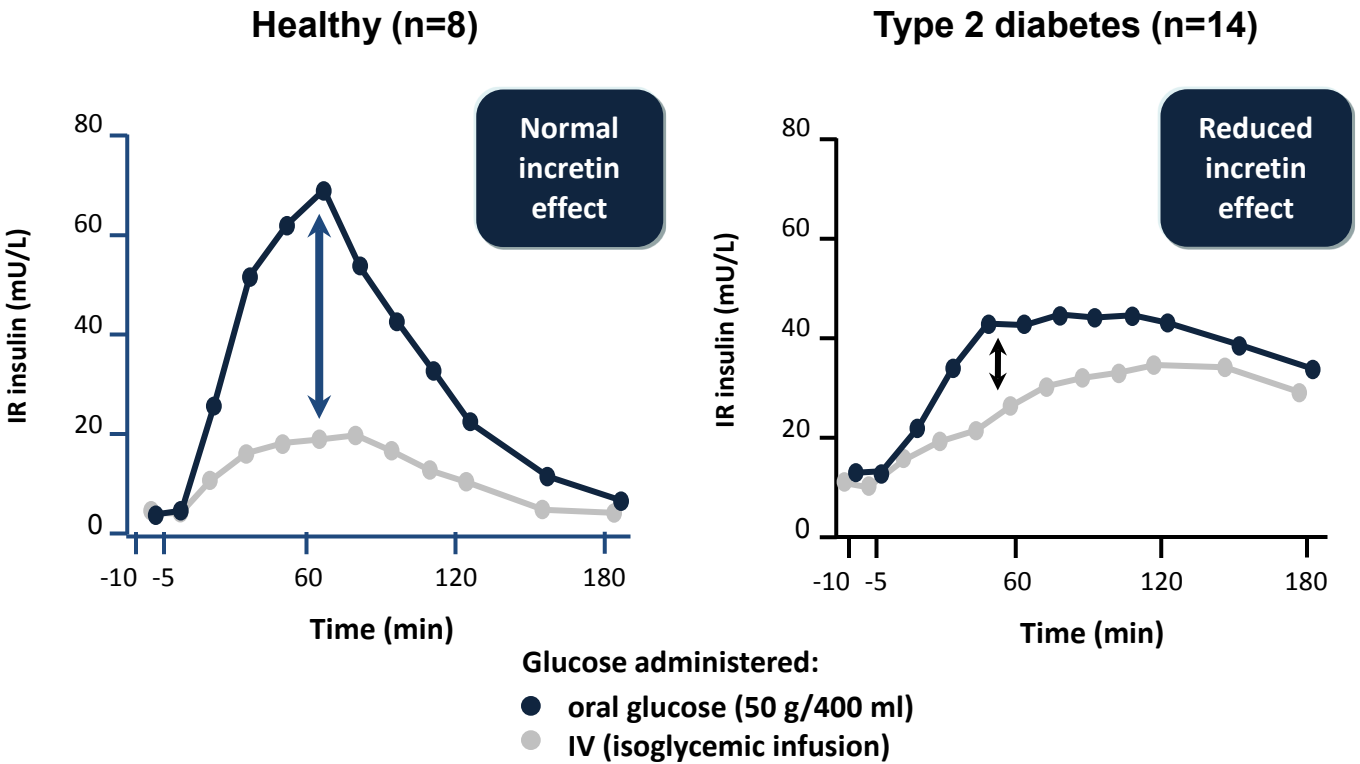
- Synthetic version of salivary protein found in the Gila monster
- Approximately 50% identity with human GLP-1
  - Binds to known human GLP-1 receptors on β cells *in vitro*
  - Resistant to DPP-4 inactivation

Exenatide	H G E G T F T S D L S K Q M E E E A V R L F I E W L K N G G P S S G A P P P S – NH_2
GLP-1 Human	H A E G T F T S D V S S Y L E G Q A A K E F I A W L V K G R – NH_2

Site of DPP-4 Inactivation

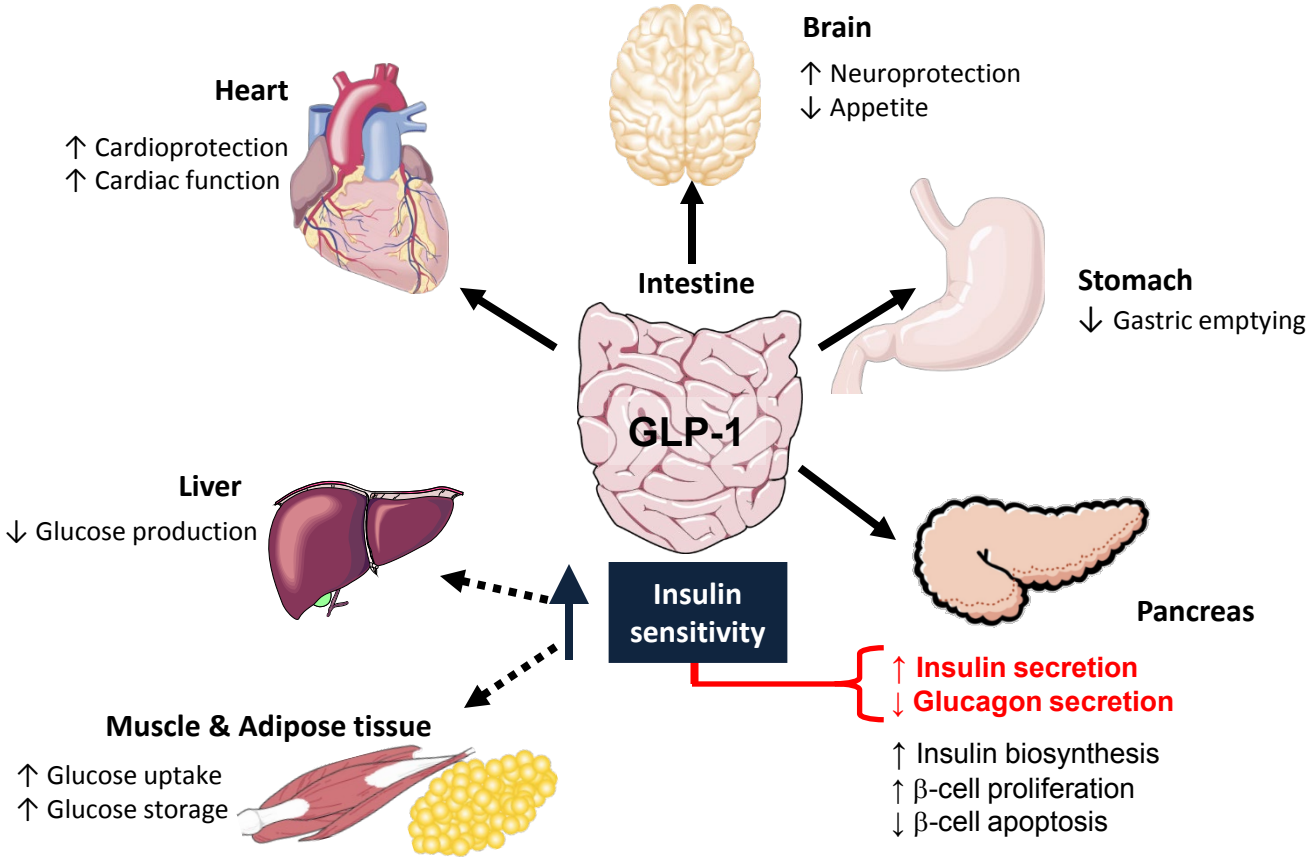
Adapted from Nielsen LL, et al. *Regulatory Peptides*. 2004;117:77-88. Reprinted from *Regulatory Peptides*, 117, Nielsen LL, et al, Pharmacology of exenatide (synthetic exendin-4): a potential therapeutic for improved glycaemic control of type 2 diabetes, 77-88, 2004, with permission from Elsevier for English use only.

The incretin effect is reduced in type 2 diabetes



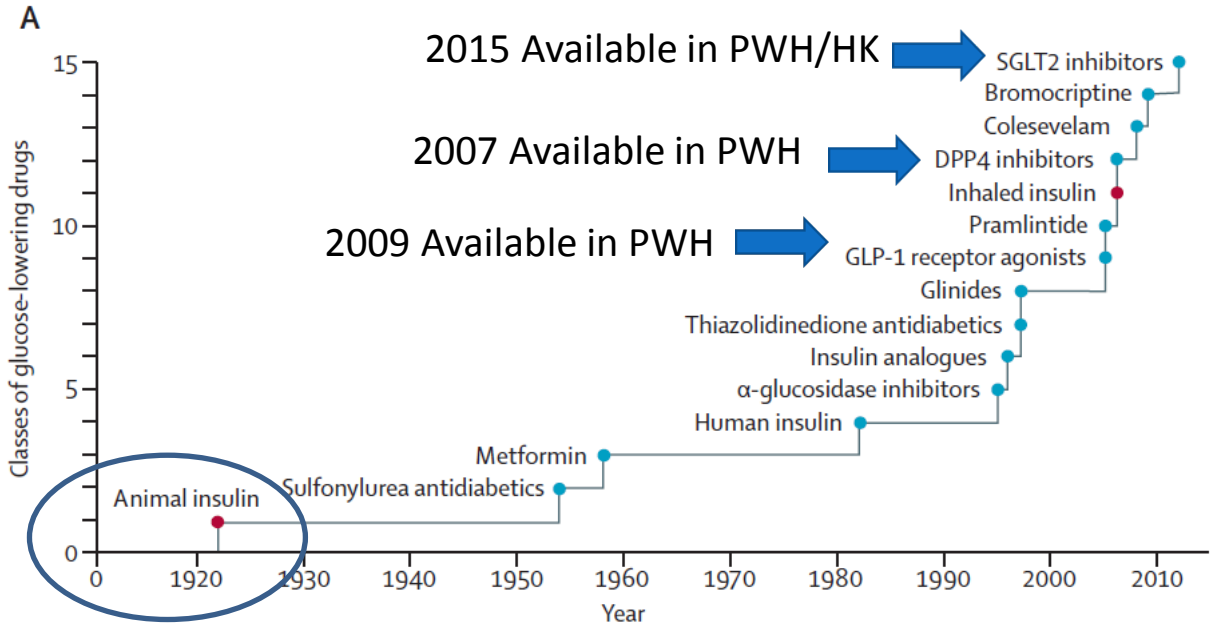
Nauck M, et al. *Diabetologia*. 1986;29:46–52.

GLP-1 has wide-ranging biological activity



Baggio & Drucker. *Gastroenterol.* 2007;132:2131–57.

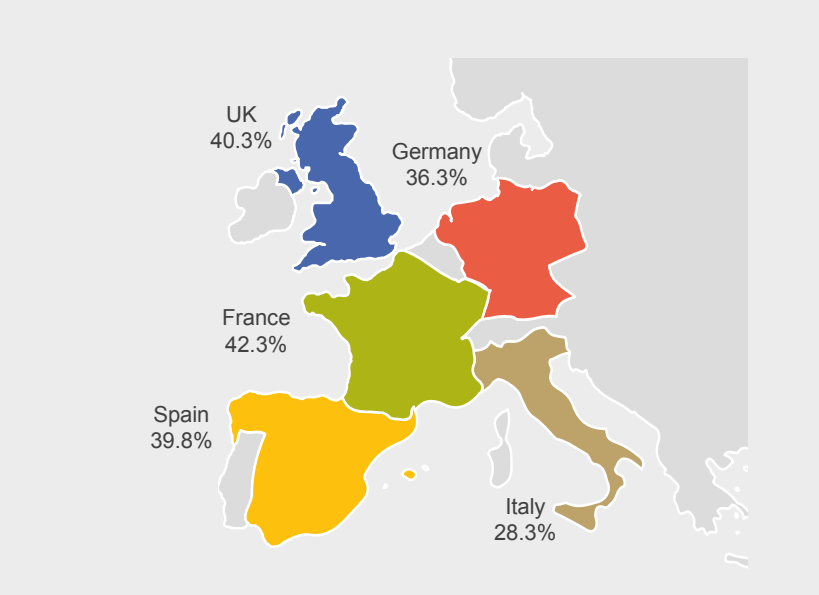
Development of anti-diabetic medications



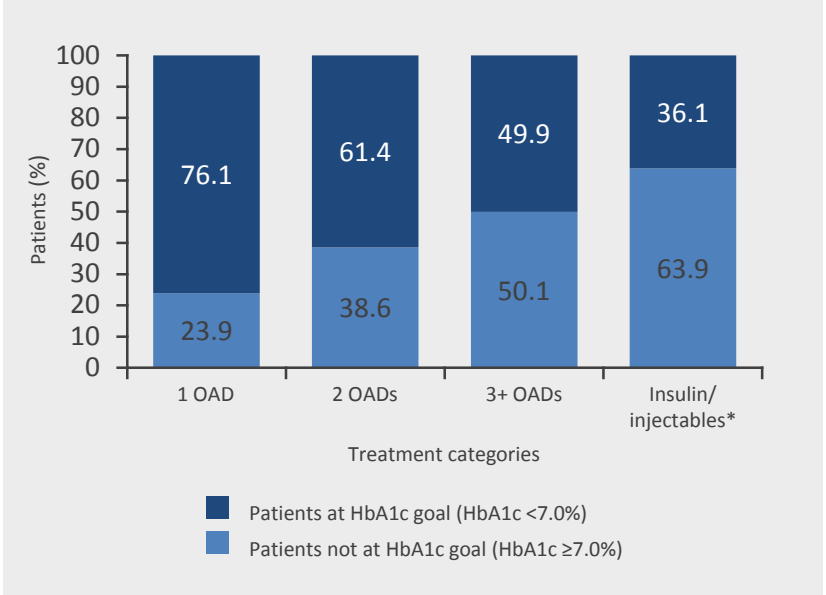
Lancet 2014 Mar 22 (383):1068-1083

Many T2D patients do not achieve glycemic target despite receiving multiple OADs and/or insulin/injectables[1]*

Patients (%) not at target HbA1c <7.0%[1]



Patients (%) not at target HbA1c <7.0%[1]



Insulin or GLP-1 analogs.

PANORAMA study: 5817 T2DM patients aged ≥40 years (May 2009–April 2010).

OAD, oral antidiabetic drug.

1. de Pablos-Velasco P, et al. Clin Endocrinol (Oxf) 2014;80:47–56.

ORIGINAL ARTICLE

Effects of Treatment Targets on Subsequent Cardiovascular Events in Chinese Patients With Type 2 Diabetes

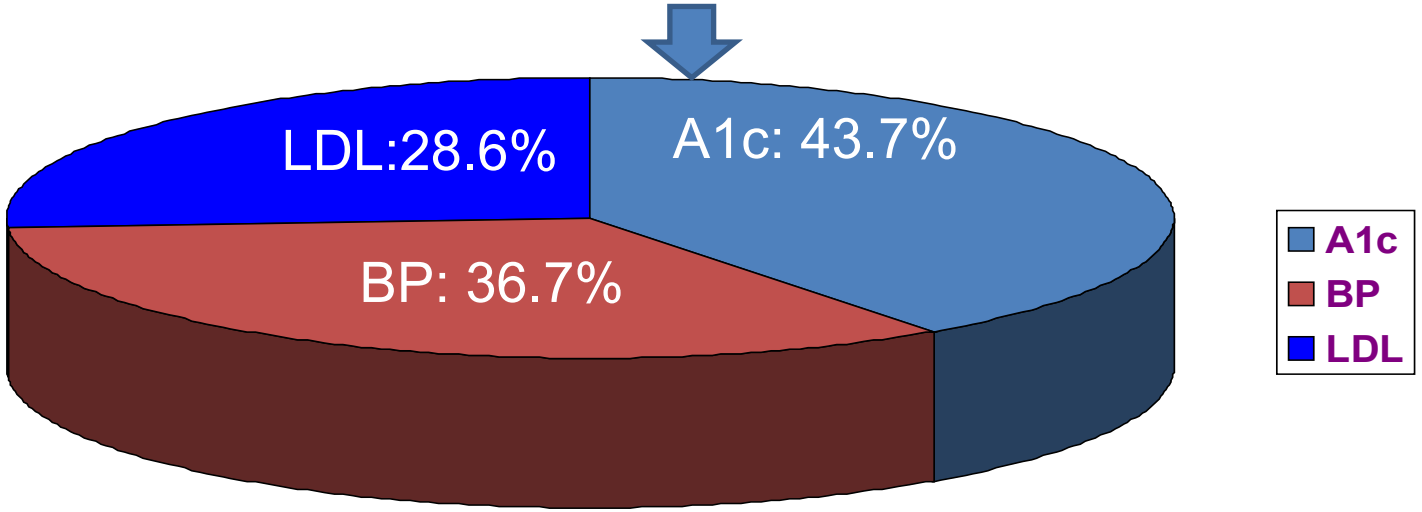
ALICE P.S. KONG, FRCP[1,2]
XILIN YANG, PHD[1]
GABY T.C. KO, MD[3]
WING-TAK SO, FRCP[3]
WING-BUN CHAN, FRCP[3,4]
RONALD C.W. MA, MRCP[3]
VANESSA W.S. NG, MRCP[3]
CHUN-CHUNG CHOW, FRCP[3]
CLIVE S. COCKRAM, MD[3]
PETER C.Y. TONG, PHD[3]
VIVIAN WONG, MD[3]
JULIANA C.N. CHAN, MD[3]

- Between 1995 and 2005, 6,386 Chinese type 2 diabetic patients without history of CHD or stroke were recruited.
- Classified according to the number of treatment targets attained at baseline, and their cardiovascular outcomes were compared.

Kong AP, et al. Diabetes Care 2007

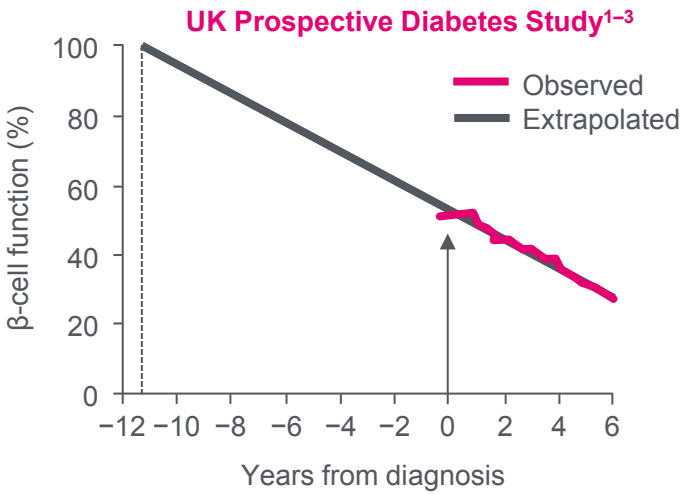
ABC targets in Hong Kong T2D

Less than half of T2D in HK achieve A1c goal <7%



Kong AP, et al. Diabetes Care 2007

T2DM is a progressive disease

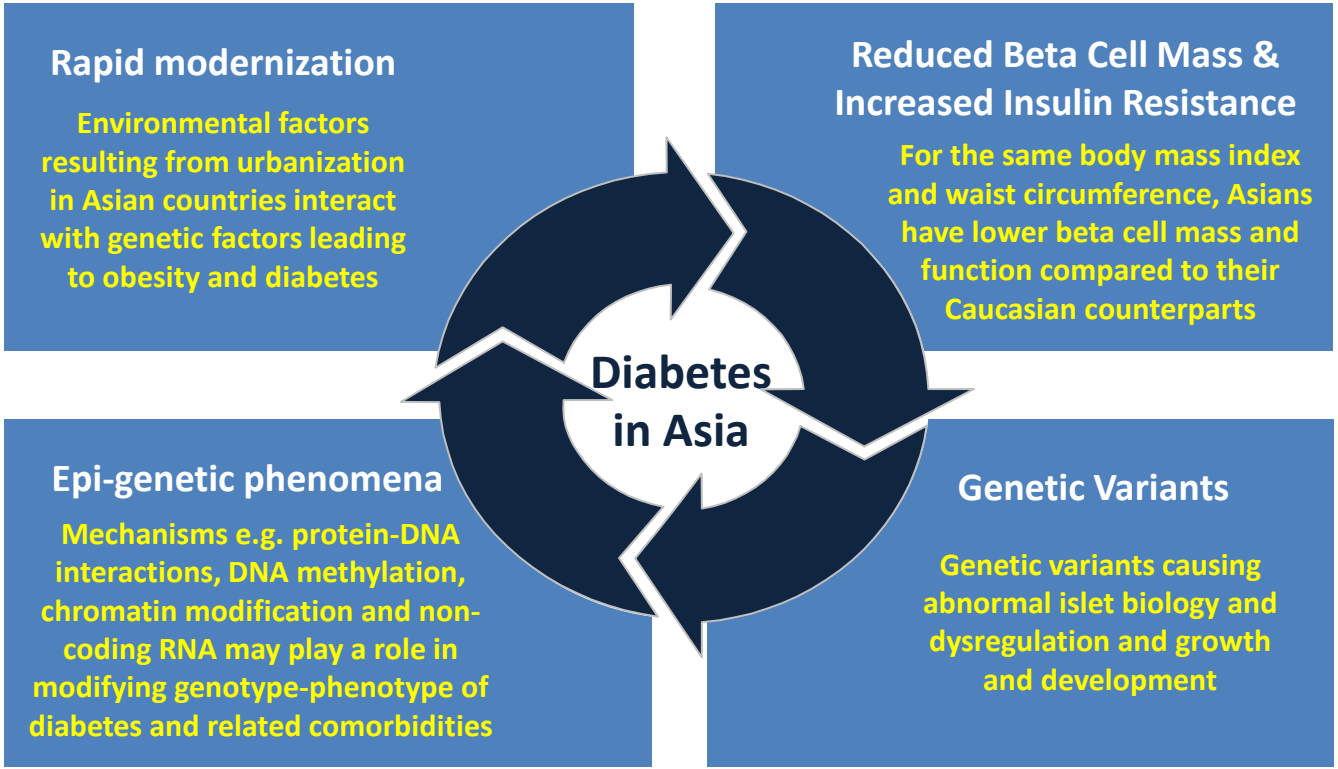


- At diagnosis, β-cell function is already reduced by ~50%[2,3] and continues to decrease regardless of therapy with diet, sulfonylurea, or metformin[2]
- Because of the progressive nature of T2DM, many patients will ultimately need insulin treatment alone or in combination with other agents for glucose control[4,5]

- **In the US in 2007, ~22% of adults with T2DM were taking insulin[6]**

1. UK Prospective Diabetes Study Group. *Diabetes* 1995;44:1249–58;
2. Holman. *Diabetes Res Clin Pract* 1998;40(Suppl):S21–5;
3. Lebovitz. *Diabetes Rev* 1999;7:139–53; 4. ADA. *Diabetes Care* 2016;39(Suppl 1):S1–112;
5. Inzucchi et al. *Diabetes Care* 2012;35:1364–79; 6. Li et al. *J Diabetes Complications* 2012;26:17–22

Type 2 Diabetes in Asia



Kong AP, et al. Nature Reviews Endocrinology 2013

Received: 31 October 2019 | Revised: 18 December 2019 | Accepted: 26 December 2019

DOI: 10.1111/dom.13950

ORIGINAL ARTICLE

WILEY

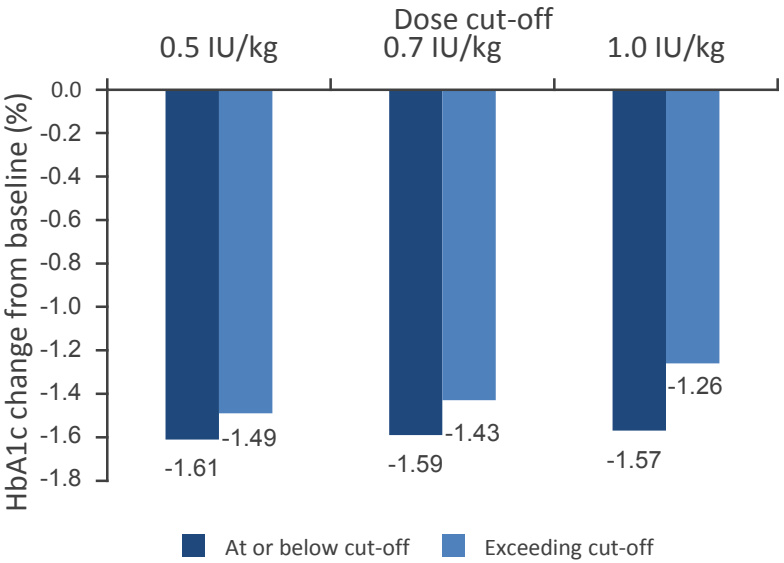
Real-world data reveal unmet clinical needs in insulin treatment in Asian people with type 2 diabetes: the Joint Asia Diabetes Evaluation (JADE) Register

- Among 108,637 patients from 11 Asian countries/regions (2007-2017), 90% had T2D.
- Among T2D, 20,031 were insulin-users (20.5%).
- Premixed (44%) and basal-only (42%) were the most common regimens.

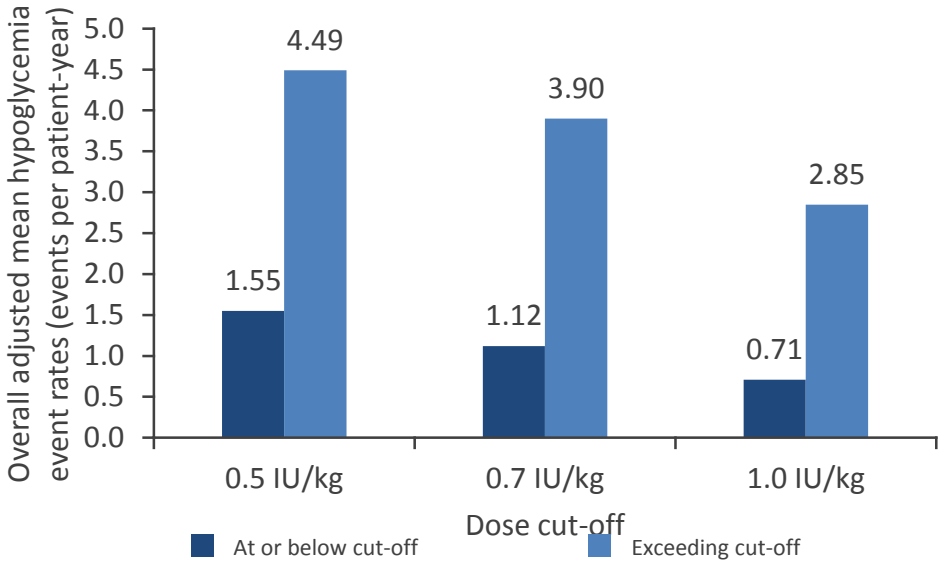
Kong AP, et al. Diabetes Obes Metab 2020;1-11

Up-titrating basal insulin may not improve glycemic control and could increase hypoglycemia risk[1]

HbA1c change from baseline by insulin dose[1]



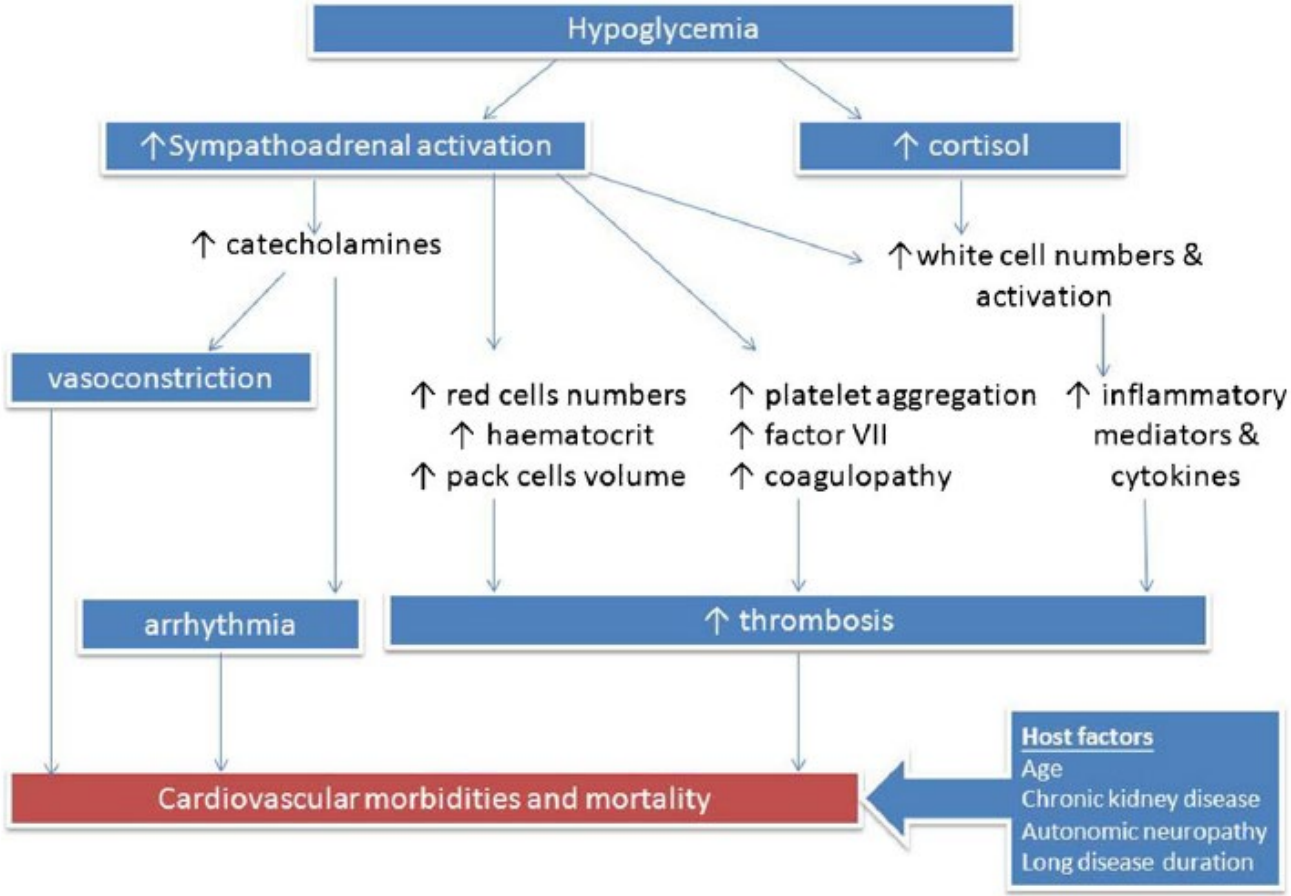
Hypoglycemia event rate by insulin dose[1]



Hypoglycemia defined as plasma glucose <3.9 mmol/L or 70 mg/dL.

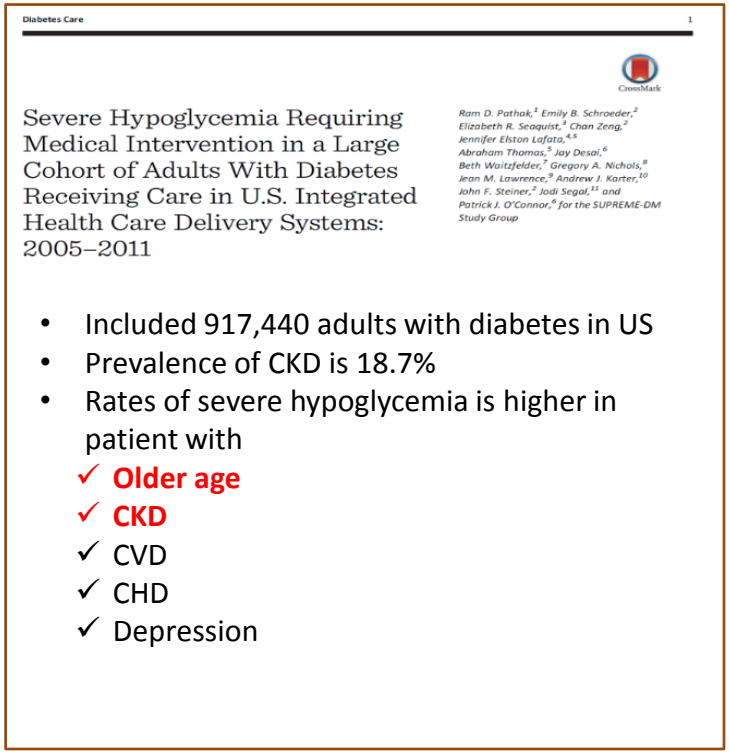
Patient-level data were pooled from 15 treat-to-target trials in which 2837 insulin-naïve T2DM patients with insulin glargine ± OADs for≥ 24 weeks. Data were stratified according to whether patients exceeded three insulin dose cut-off levels.

1.Reid T, et al. Int J Clin Pract 2016;70:56–65.



Kong AP and Chan JC. Current Dia Rep 2015

Risk Factors of Severe Hypoglycemia in Type 2 Diabetes

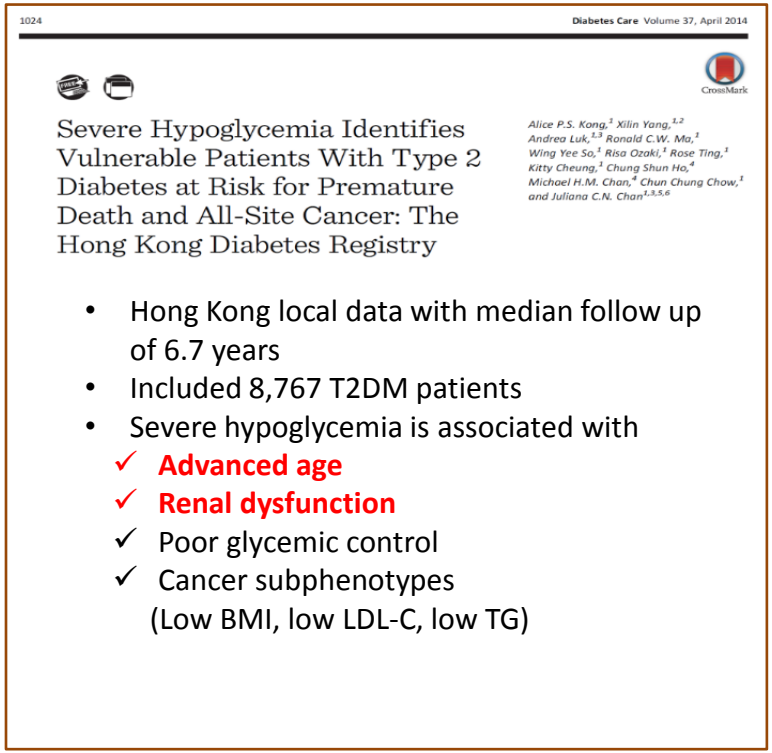


Diabetes Care 1

Severe Hypoglycemia Requiring Medical Intervention in a Large Cohort of Adults With Diabetes Receiving Care in U.S. Integrated Health Care Delivery Systems: 2005–2011

Ram D. Pathak,[1] Emily B. Schroeder,[2] Elizabeth R. Seaquist,[3] Chan Zeng,[2] Jennifer Elston Lafata,[4,5] Abraham Thomas,[5] Jay Desai,[6] Beth Waitzfelder,[7] Gregory A. Nichols,[8] Jean M. Lawrence,[9] Andrew J. Karter,[10] John F. Steiner,[2] Jodi Segal,[11] and Patrick J. O'Connor,[6] for the SUPREME-DM Study Group

- Included 917,440 adults with diabetes in US
- Prevalence of CKD is 18.7%
- Rates of severe hypoglycemia is higher in patient with
  - ✓ **Older age**
  - ✓ **CKD**
  - ✓ CVD
  - ✓ CHD
  - ✓ Depression



1024 Diabetes Care Volume 37, April 2014

Severe Hypoglycemia Identifies Vulnerable Patients With Type 2 Diabetes at Risk for Premature Death and All-Site Cancer: The Hong Kong Diabetes Registry

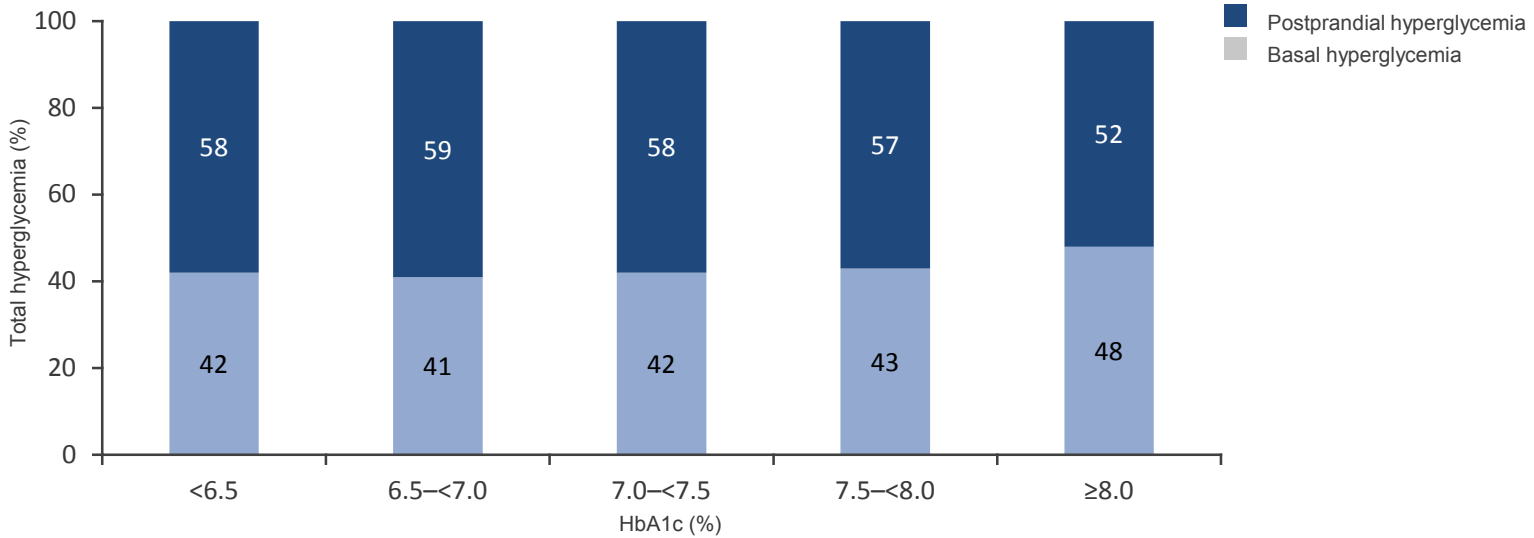
Alice P.S. Kong,[1] Xilin Yang,[1,2] Andrea Luk,[1,3] Ronald C.W. Ma,[1] Wing Yee So,[1] Risa Ozaki,[1] Rose Ting,[1] Kitty Cheung,[1] Chung Shun Ho,[4] Michael H.M. Chan,[4] Chun Chung Chow,[1] and Juliana C.N. Chan[1,3,5,6]

- Hong Kong local data with median follow up of 6.7 years
- Included 8,767 T2DM patients
- Severe hypoglycemia is associated with
  - ✓ **Advanced age**
  - ✓ **Renal dysfunction**
  - ✓ Poor glycemic control
  - ✓ Cancer subphenotypes (Low BMI, low LDL-C, low TG)

Pathak RD et al. Diabetes Care 2016; 39:363-370
Kong AP et al. Diabetes Care 2014; 37:1024-1031

Postprandial hyperglycemia is a major obstacle to achieving better glycemic control[1]

Relative contributions of basal and postprandial hyperglycemia to overall hyperglycemia at Weeks 24–28 of insulin treatment[1]

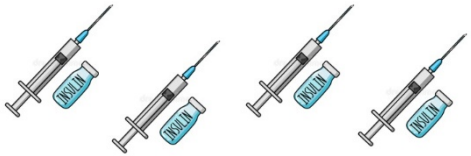


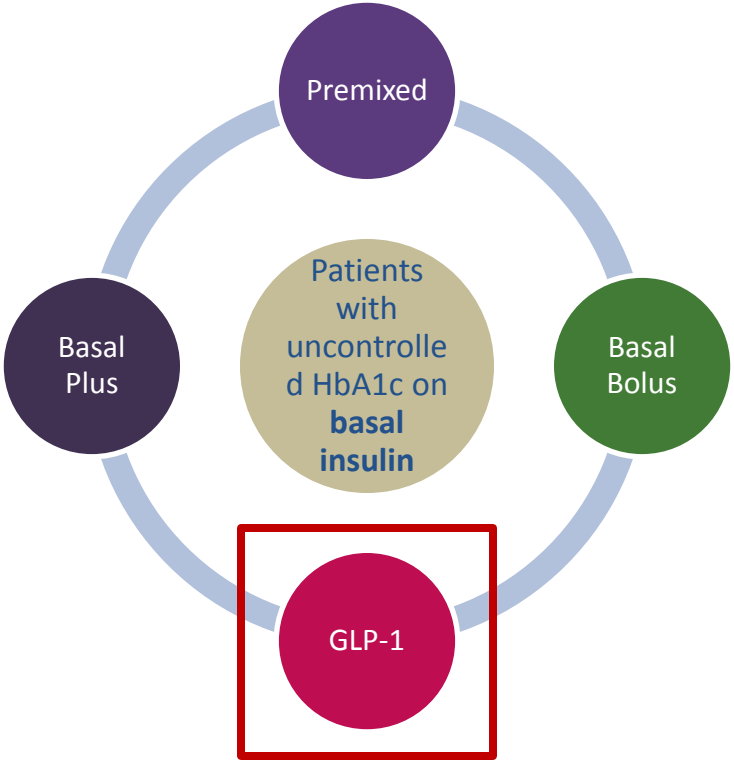
Pooled analysis of 6 similarly designed trials in which 1699 patients with poorly controlled T2DM were treated with basal insulin.

1. Riddle M, et al. Diabetes Care 2011;34:2508–14.

Unmet Need from Current Treatment… Any Alternative?

- Hypoglycemia Risk
- Weight Gain
- Poor Compliance





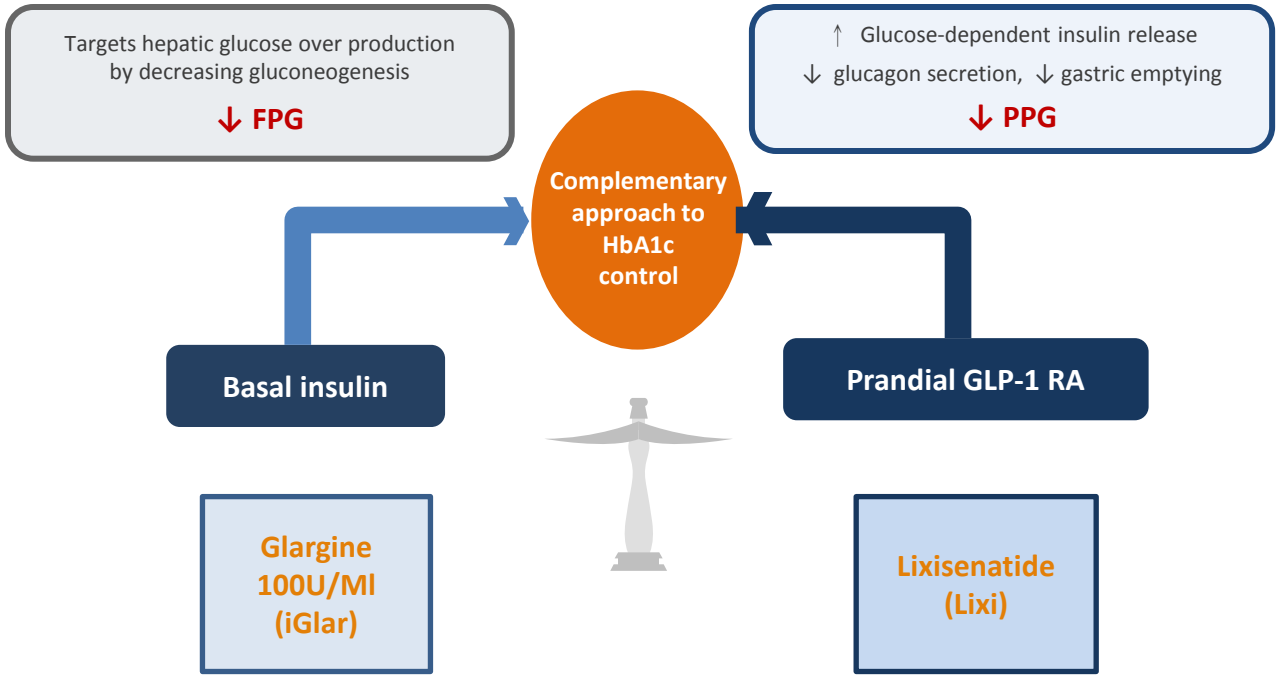
Prandial GLP-1 RAs are more effective in lowering PPG and delay gastric Emptying

Parameters	Short-acting GLP-1 receptor agonists	Long-acting GLP-1 receptor agonists
Compounds	Exenatide Lixisenatide	Albiglutide Dulaglutide Exenatide LAR Liraglutide
Half life	2–5 h	12 h–several days
Effects		
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
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)

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

Ther Adv Endocrinol Meta 2014, Vol. 5(5) 95-123

iGlarLixi -
Complementary modes of action of basal insulins & GLP-1 RA



- 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

iGlarLixi fixed-ratio combination is administered once daily in an easy-to-use pen[1,2]

- Similar physicochemical features of insulin glargine and lixisenatide allow co-formulation in a defined fixed ratio for delivery as a single daily injection[1]
- iGlarLixi is available in two pre-filled pens, providing different dosing options[2]

SoloStar® pen

Familiar to patients, nurses and PCPs due to usage with Lantus® (insulin glargine 100 U/mL)[3]

iGlarLixi 10–40 U pen[1,2]

Insulin glargine 100 U/mL: 10–40 U/day
Lixisenatide 50 µg/mL: 5–20 µg/day
(2:1 dose ratio iGlar:Lixi)

iGlarLixi 30–60 U pen[1,2]

Insulin glargine 100 U/mL: 30–60 U/day
Lixisenatide 33 µg/mL: 10–20 µg/day
3:1 dose ratio iGlar:Lixi

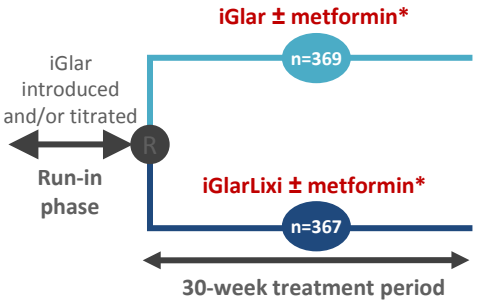
PCP, primary care provider.

1. Rosenstock J, et al. Diabetes Care 2016;39:2026–35.
2. Suliqua® (insulin glargine 100 U/mL and lixisenatide 50 µg/mL) Summary of Product Characteristics, 2017.
3. Toscano D, et al. J Diabetes Sci Technol 2012;6:686–94.

iGlarLixi: Phase 3 study designs

LixiLan-L

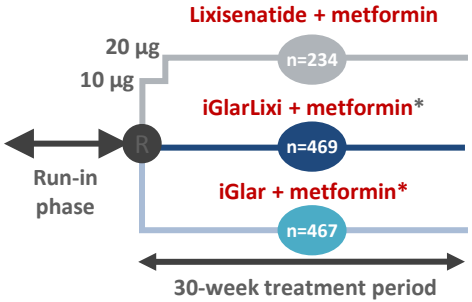
T2DM patients receiving basal insulin for >6 months ± OADs
Stable basal insulin dose (15–40 U/day) for >2 months
HbA1c ≥7.5% and ≤10%
FPG ≤140 mg/dL at the end of run-in



Primary objective: Superiority of iGlarLixi over iGlar in HbA1c change at Week 30

LixiLan-O

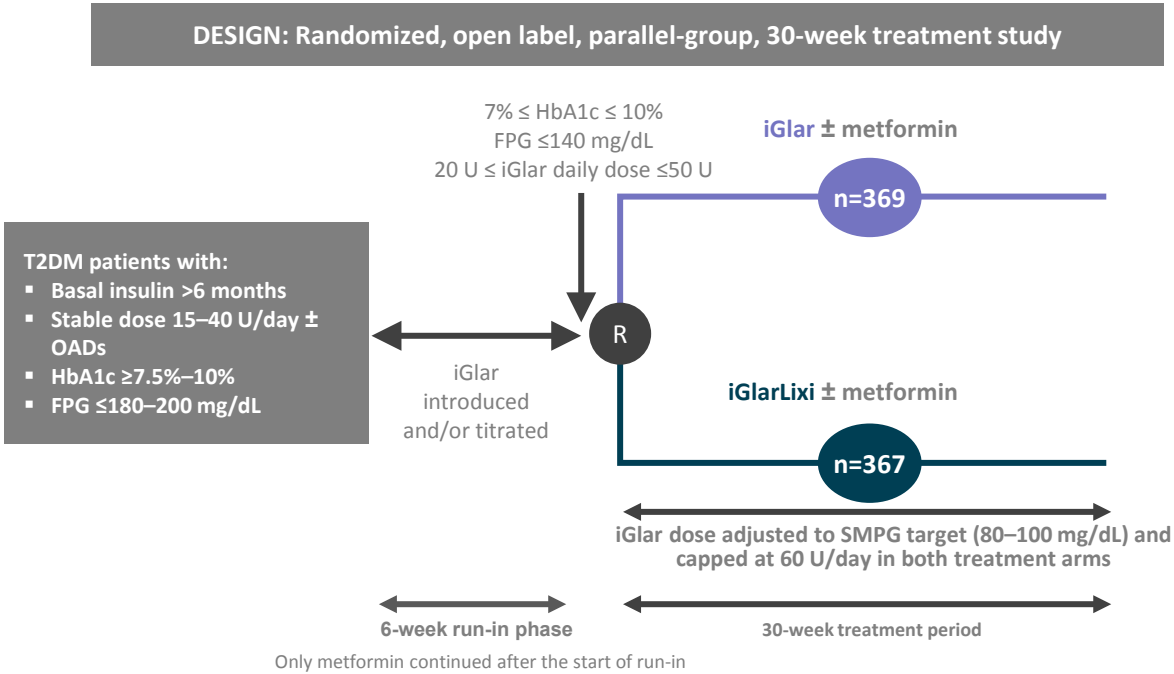
T2DM patients receiving metformin ± an additional OAD
HbA1c 7–9% if receiving two OADs
HbA1c 7.5–10% if receiving metformin alone



Primary objective: superiority of iGlarLixi over lixisenatide and non-inferiority of iGlarLixi over iGlar (if non-inferiority shown, superiority tested) in HbA1c change at Week 30

*iGlar dose was adjusted to FPG target and capped at 60 U/day
Two fixed ratio pens (10–40 Pen and 30–60 Pen) allow titration of iGlar from 10–60 U/day, with lixisenatide daily dose capped at 20 µg QD. Sanofi data on file – LixiLan-O CSR pages 22-23; Sanofi data on file – LixiLan-L CSR pages 21-22

LixiLan-L: Patients with T2DM not controlled on basal insulin

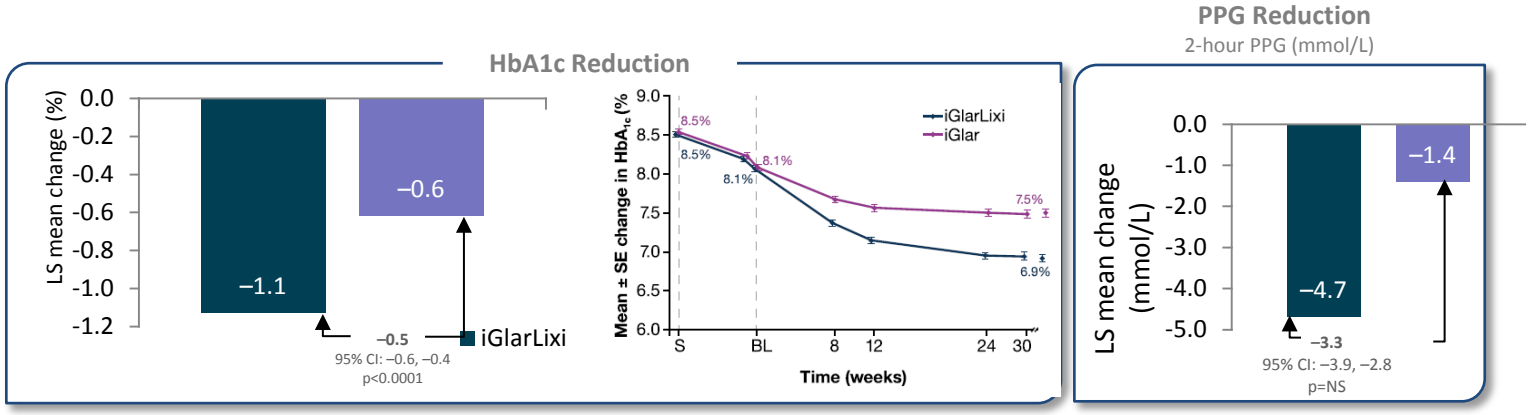


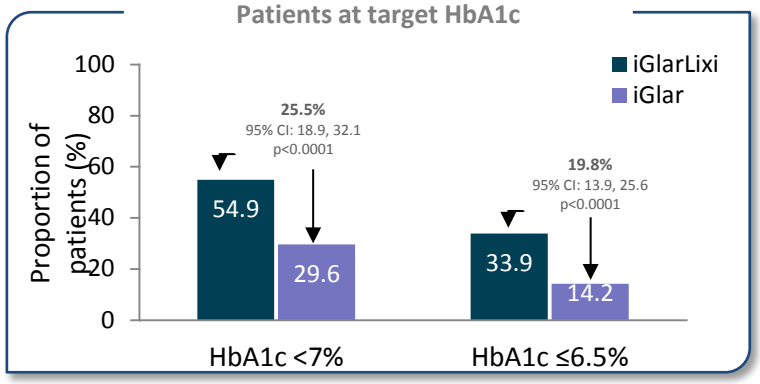
Primary objective: superiority of iGlarLixi over iGlar in HbA1c change at Week 30

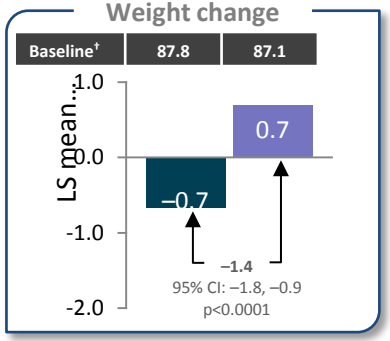
Two fixed ratio pens (10–40 Pen and 30–60 Pen) allow titration of iGlar from 10–60 U/day, with lixisenatide daily dose capped at 20 µg once daily

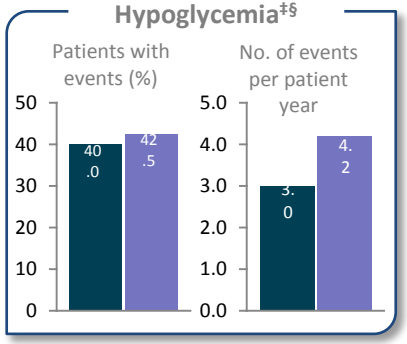
Aroda V, et al. Diabetes Care 2016;epub ahead of print: dc161495

LixiLan-L: Key results







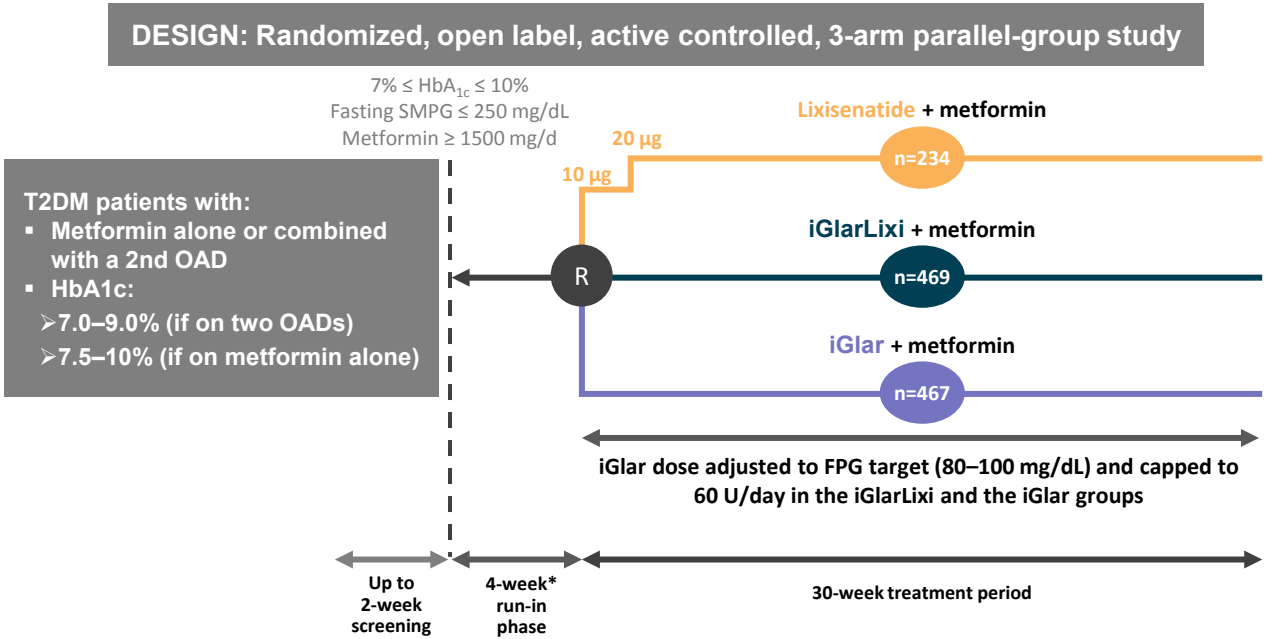


Aroda V, et al. Diabetes Care 2016;epub ahead of print: dc161495

†Mean body weight (kg) at baseline; ‡Documented symptomatic hypoglycemia, defined as plasma glucose ≤70 mg/dL

§Severe hypoglycemia was reported in 4 (1.1%) patients in the iGlarLixi group and 1 (0.3%) patient in the iGlar group

LixiLan-O: Patients with T2DM not controlled on OADs



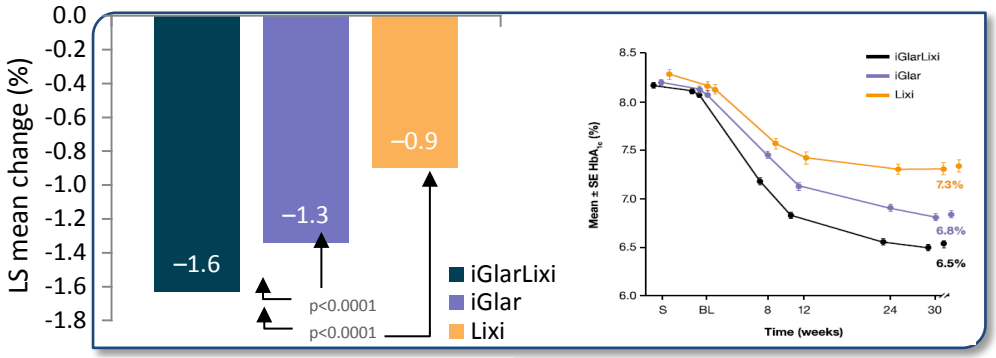
Primary objective: superiority of iGlarLixi over lixisenatide and non-inferiority of iGlarLixi over iGlar (pre-specified sequential non-inferiority then superiority tested) in HbA1c change at Week 30

*Stop 2nd OAD, and titrate metformin up to ≥2,000 mg/day or maximal tolerated dose (≥1,500 mg/day to allow randomization)
Two fixed ratio pens (10–40 Pen and 30–60 Pen) allow titration of iGlar from 10–60 U/day, with lixisenatide daily dose capped at 20 µg once daily

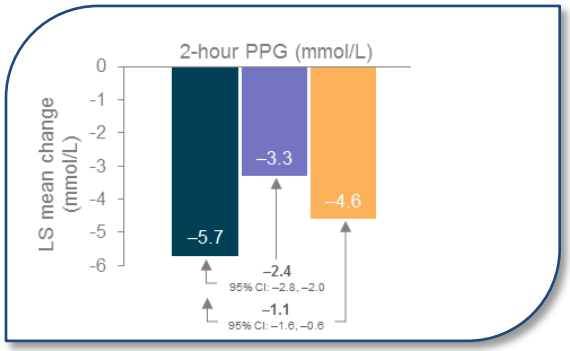
Rosenstock J, et al. Diabetes Care 2016;epub ahead of print: dc160917

LixiLan-O: Key results

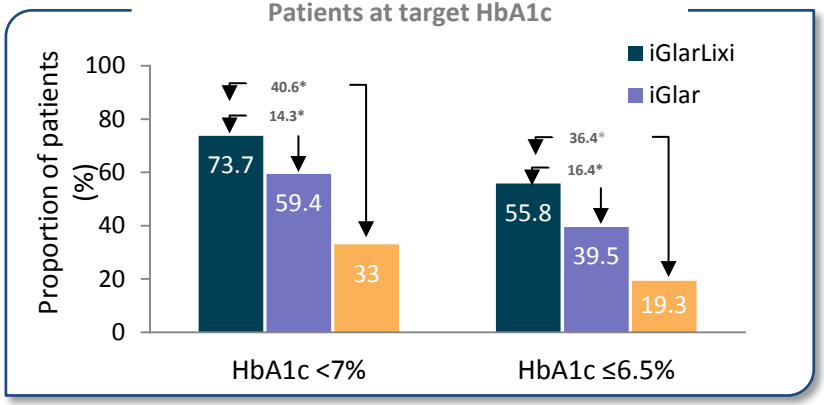
HbA1c Reduction



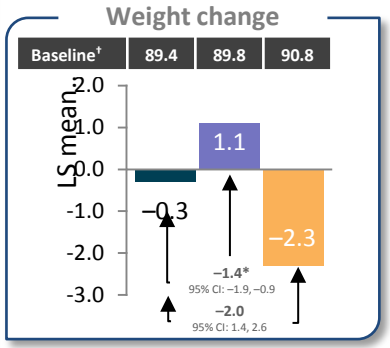
PPG Reduction



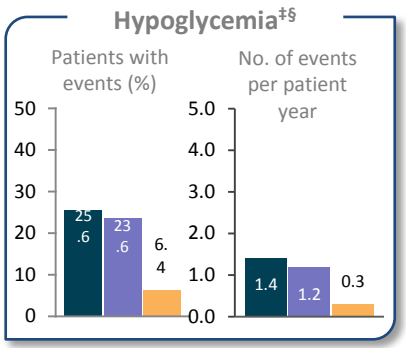
Patients at target HbA1c



Weight change



Hypoglycemia‡§



*p<0.0001; †Mean body weight (kg) at baseline; ‡Documented symptomatic hypoglycemia, defined as plasma glucose ≤70 mg/dL §One event of severe hypoglycemia was reported during the study and occurred in the iGlar group

Rosenstock J, et al. Diabetes Care 2016

GI Side Effect is Much Reduced by iGlarLixi than Lixi alone

LixiLan-O Study

Rosenstock J, et al. Diabetes Care 2016; epub ahead of print: pii, dc160917

Patients, n (%), with at least one…	iGlarLixi (n=469)	iGlar (n=467)	Lixisenatide (n=233)
AE			
Any	267 (56.9%)	227 (48.6%)	157 (67.4%)
Serious	18 (3.8%)	19 (4.1%)	9 (3.9%)
Leading to Death	2 (0.4%)	3 (0.6%)	1 (0.4%)
Leading to Discontinuation	12 (2.6%)	9 (1.9%)	21 (9%)
GI AEs (%)			
Nausea	**9.6%**	**3.6%**	**24.0%**
↳ ***discontinuation***	*0.4%*	*0*	*2.6%*
Vomiting	**3.2%**	**1.5%**	**6.4%**
↳ *discontinuation*	*0.4%*	*0*	*1.7%*
Diarrhea	**9.0%**	**4.3%**	**9.0%**
↳ *discontinuation*	*0.2%*	*0*	*0.9%*

Switching to iGlarLixi Versus Continuing Daily or Weekly GLP-1 RA in Type 2 Diabetes Inadequately Controlled by GLP-1 RA and Oral Antihyperglycemic Therapy: The LixiLan-G Randomized Clinical Trial

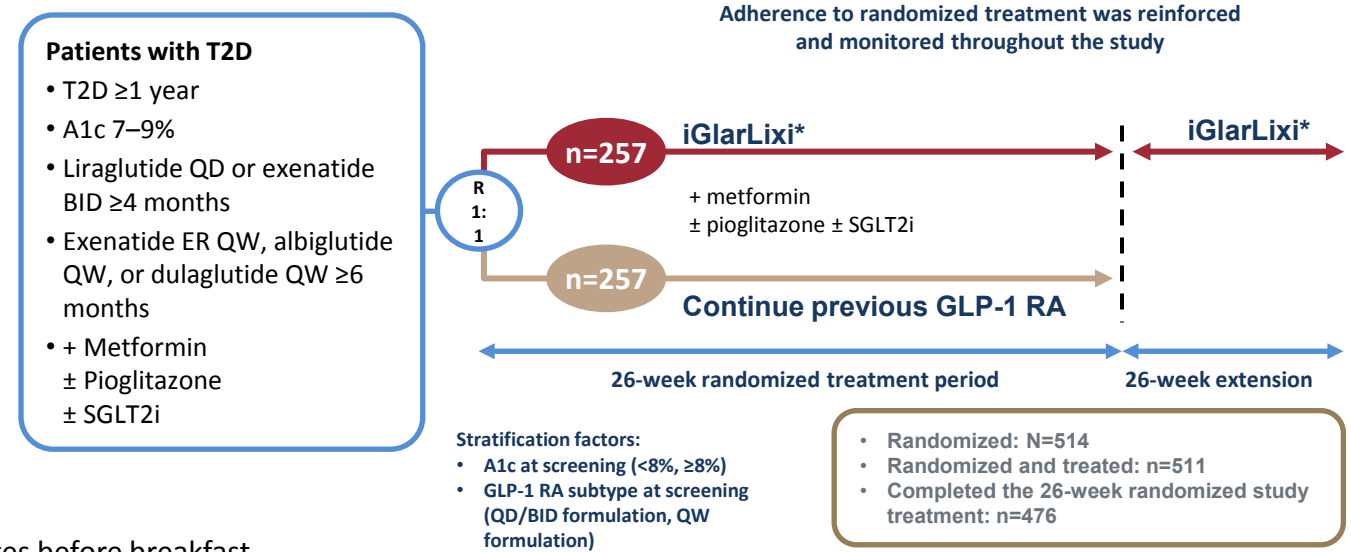
Lawrence Blonde,[1] Julio Rosenstock,[2] Stefano Del Prato,[3] Robert Henry,[4] Naim Shehadeh,[5] Juan Frias,[6] Elisabeth Niemoeller,[7] Elisabeth Souhami,[8] Chen Ji,[9] and Vanita R. Aroda[10,11]

Diabetes Care 2019;42:2108–2116 | https://doi.org/10.2337/dc19-1357

Blonde L, et al. Diabetes Care 2019;42:2108-2116.

Study Design

- Randomized, open-label, parallel-group, 26-week trial



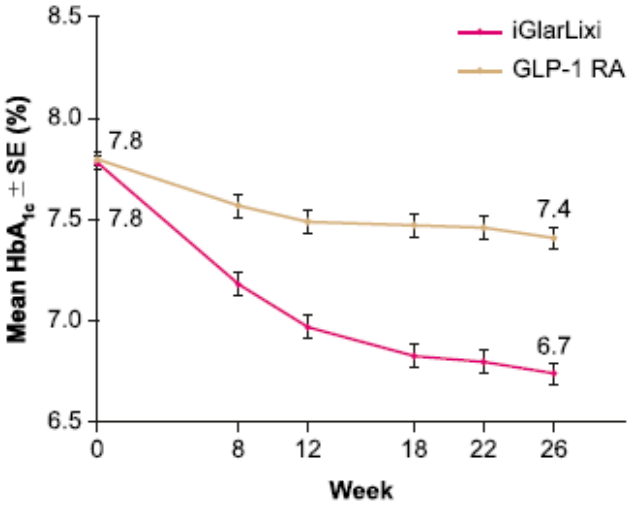
*0–60 minutes before breakfast.

BID: twice daily; ER: extended release; GLP-1 RA: glucagon-like peptide-1 receptor agonist; iGlarLixi: insulin glargine:lixisenatide; QD: once daily; QW: once weekly; R: randomization; SGLT2i: sodium-glucose cotransporter-2 inhibitor; T2D: type 2 diabetes.

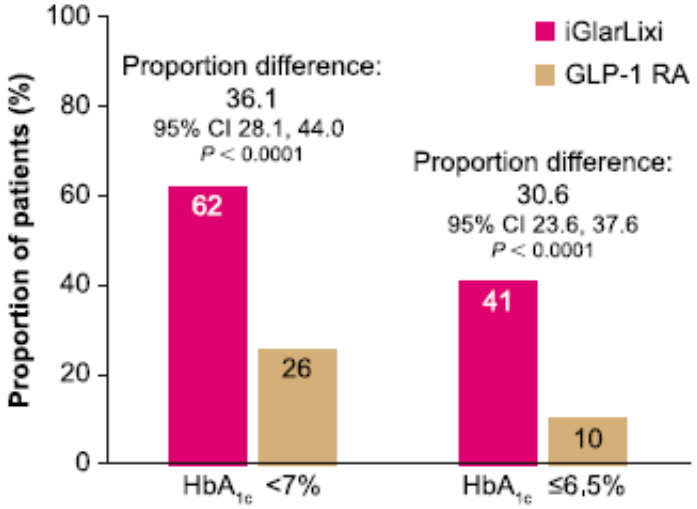
Blonde L, et al. Diabetes Care 2019;42:2108-2116.

Results

Change in HbA_{1c}



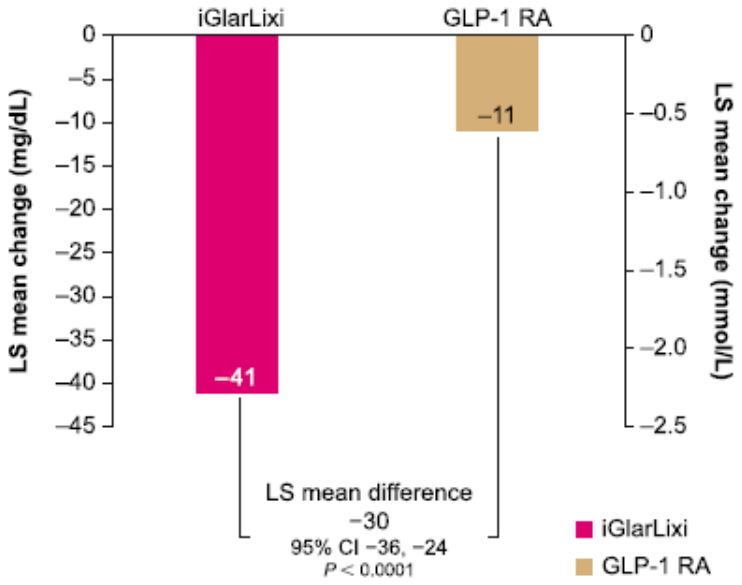
Participants at target HbA_{1c}



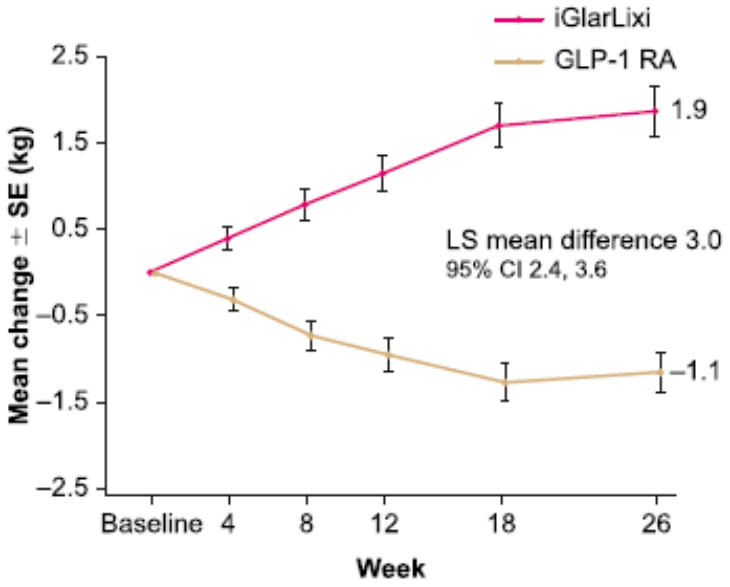
Blonde L, et al. Diabetes Care 2019;42:2108-2116.

Results

Change in FPG



Change in mean weight from baseline at week 26



Blonde L, et al. Diabetes Care 2019;42:2108-2116.

Precautions for Use of Soliqua

SOLIQUA SmPC

Hypoglycemia

- Hypoglycaemia was the most frequently reported observed adverse reaction during treatment with Soliqua (see section 4.8). Hypoglycaemia may occur if the dose of Soliqua is higher than required. Factors increasing the susceptibility to hypoglycaemia require particularly close monitoring and may necessitate dose adjustment.

Acute pancreatitis

- Use of GLP-1 receptor agonists has been associated with a risk of developing acute pancreatitis. There have been few reported events of acute pancreatitis with lixisenatide although a causal relationship has not been established. Patients should be informed of the characteristic symptoms of acute pancreatitis: persistent, severe abdominal pain. If pancreatitis is suspected, Soliqua should be discontinued

Severe gastrointestinal disease

- Use of GLP-1 receptor agonists may be associated with gastrointestinal adverse reactions. Soliqua has not been studied in patients with severe gastrointestinal disease, including severe gastroparesis and therefore, the use of Soliqua is not recommended in these patients.

Severe renal impairment

- There is no therapeutic experience in patients with severe renal impairment ***(creatinine clearance less than 30 mL/min)*** or end-stage renal disease. Use is not recommended in patients with severe renal impairment or end-stage renal disease

Dehydration

- Patients treated with Soliqua should be advised of the potential risk of dehydration in relation to gastrointestinal adverse reactions and take precautions to avoid fluid depletion.

Case sharing

- 70 year-old man, retired government servant, labourer, ex-smoker, ex-drinker
- Father of 1 son, lives with family
- Type 2 diabetes since 2000
  - Complicated with bilateral non-proliferative retinopathy, albuminuria, CKD, IHD (PCI to LAD done 2008)
- Other co-morbidities: Hypertension, Dyslipidemia, Fatty liver, Asbestos-related pleural disease

Case sharing (Continued)

- added supplementary insulin->twice daily->basal-bolus regimen (Actrapid thrice daily and Lantus nocte)
- Oral drugs:
  - Galvumet 50mg/1000mg per tab, tab one twice daily
  - Empagliflozin 10mg daily
  - Losartan 75mg daily
  - Aspirin 100mg daily
  - Zocor 20mg nocte

Case sharing (Continued)

- But worsening of HbA_{1c} as he was unable to comply to complex regimen and missed injections
- Clinic consultation on 12 April 2019
  - BMI 23.1 kg/m^2, BP 100/68 mmHg
  - HbA_{1c} 12.8%, FPG 11.6mmol/L, LDL-C 2.21 mmol/L
  - eGFR 52 ml/min/1.73 sq.m (by modified MDRD formula)
  - Urine ACR 5.4 mg/mmol

Chemical Pathology Laboratory

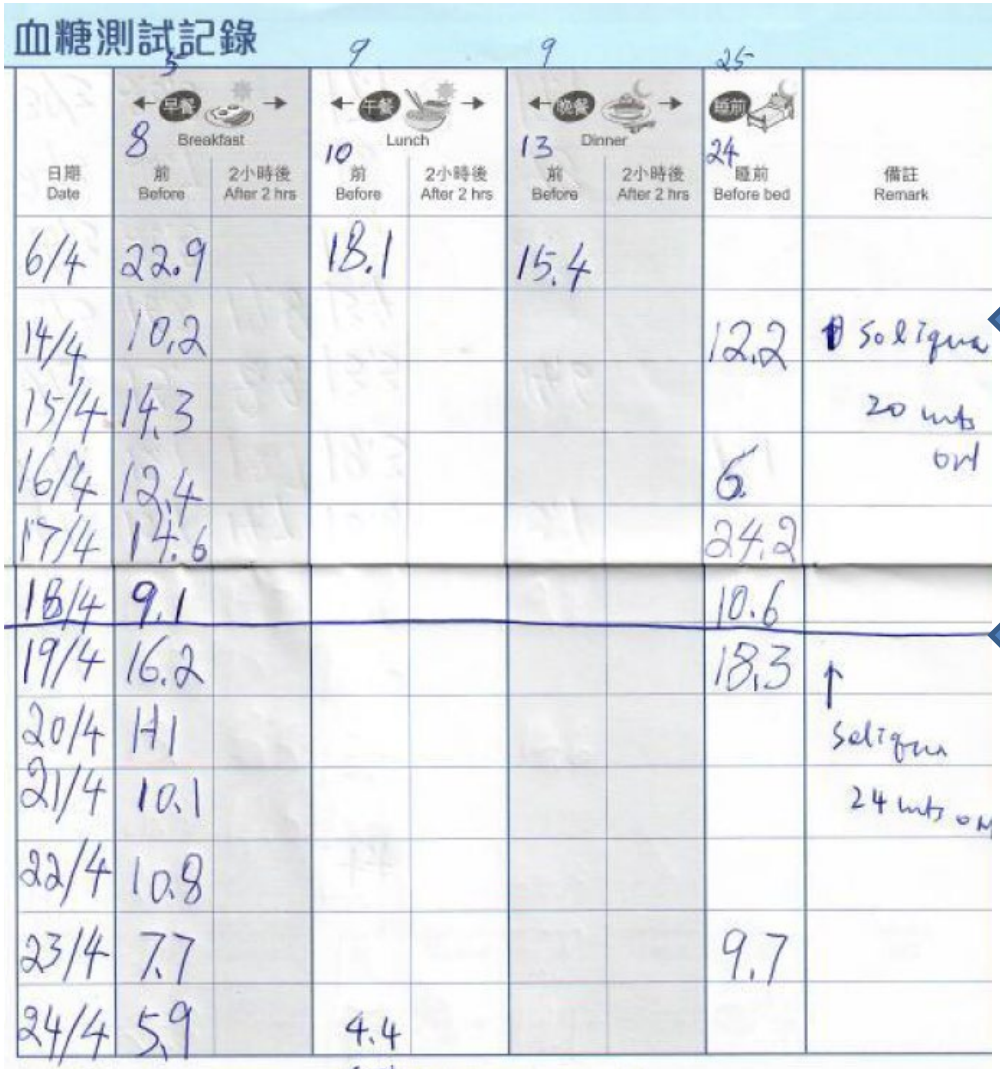
Sex/Age: M/70Y DOB: 26/10/
Req. Loc.: PWH/MED/DM
Doctor: KONG, Pik Shan Alice

Date Collected : 04/04/2019 09:12
Date Received : 04/04/2019 09:54

Haemoglobin A1c

		Conv. unit 4.8 - 6.0 %	IFCC unit 29 - 42 mmol/mol
Apr 07 2016	16D5261547	9.7 *	83 *
Jun 27 2016	16D5517688	6.6 *	49 *
Nov 18 2016	16D5985742	7.7 *	60 *
Mar 24 2017	17D5276738	9.1 *	76 *
Jul 28 2017	17D5722370	9.3 *	78 *
Dec 15 2017	17D6201687	8.8 *	73 *
May 18 2018	18D5485369	10.4 *	90 *
Sep 18 2018	18D5949762	11.7 *	105 *
Oct 19 2018	18D6063898	SEE BELOW	CANCEL
Apr 04 2019	19D5363308	12.8 *	117 *

Switched from bd pre-mixed insulin to basal-bolus regimen since 4 Jan 2019



血糖測試記錄

日期 Date	早餐 Breakfast 前 Before	早餐 Breakfast 2小時後 After 2 hrs	Lunch 前 Before	Lunch 2小時後 After 2 hrs	Dinner 前 Before	Dinner 2小時後 After 2 hrs	睡前 Before bed	備註 Remark
6/4	22.9		18.1		15.4			
14/4	10.2						12.2	Soliqua
15/4	14.3							20 units
16/4	12.4						6	om
17/4	14.6						24.2	
18/4	9.1						10.6	
19/4	16.2						18.3	↑
20/4	H1							Soliqua
21/4	10.1							24 units om
22/4	10.8							
23/4	7.7						9.7	
24/4	5.9		4.4					

Switch from basal bolus insulin to Soliqua (Glargine + Lixisenatide) 20 units om since 14 April 2019

Increase Soliqua to 24 units om since 18 April 2019

Sex/Age:	M/70Y DOB: 26/10/
Req. Loc.:	PWH/MED/DM
Doctor:	KONG, Pik Shan Alice

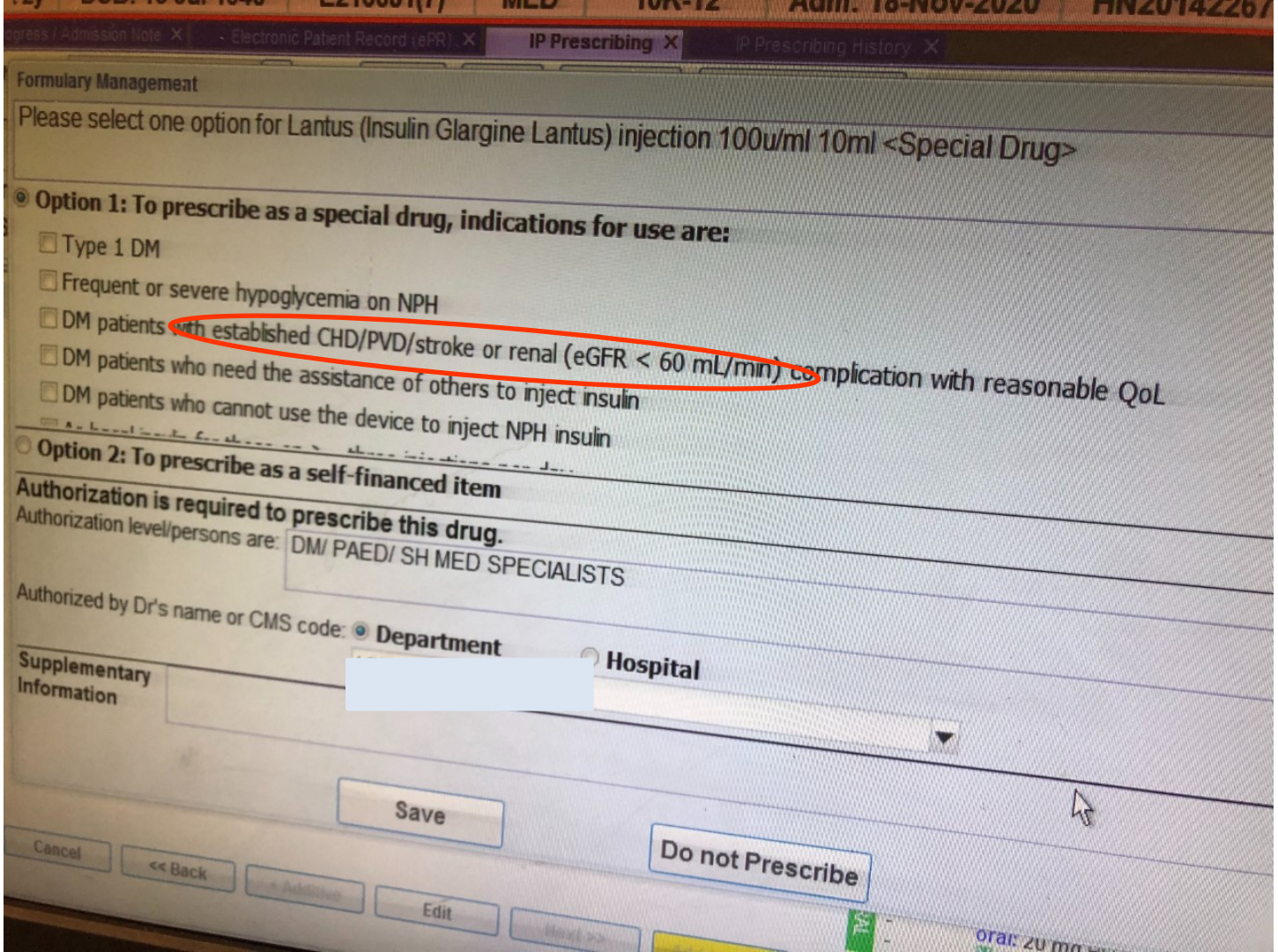
Chemical Pathology Laboratory

Date Collected : 12/07/2019 08:14
Date Received : 12/07/2019 09:41

Haemoglobin A1c

		Conv. unit 4.8 - 6.0 %	IFCC unit 29 - 42 mmol/mol
Jun 27 2016	16D5517688	6.6 *	49 *
Nov 18 2016	16D5985742	7.7 *	60 *
Mar 24 2017	17D5276738	9.1 *	76 *
Jul 28 2017	17D5722370	9.3 *	78 *
Dec 15 2017	17D6201687	8.8 *	73 *
May 18 2018	18D5485369	10.4 *	90 *
Sep 18 2018	18D5949762	11.7 *	105 *
Oct 19 2018	18D6063898	SEE BELOW	CANCEL
Apr 04 2019	19D5363308	12.8 *	117 *
Jul 12 2019	19D5756698	8.5 *	70 *

Switched from basal bolus insulin to Soliqua daily since 14 Apr 2019


Progress / Admission Note
Electronic Patient Record (ePR)
IP Prescribing
IP Prescribing History
Formulary Management
Please select one option for Lantus (Insulin Glargine Lantus) injection 100u/ml 10ml <Special Drug>
Option 1: To prescribe as a special drug, indications for use are:
Type 1 DM
Frequent or severe hypoglycemia on NPH
DM patients with established CHD/PVD/stroke or renal (eGFR < 60 mL/min) complication with reasonable QoL
DM patients who need the assistance of others to inject insulin
DM patients who cannot use the device to inject NPH insulin
Option 2: To prescribe as a self-financed item
Authorization is required to prescribe this drug.
Authorization level/persons are: DM/ PAED/ SH MED SPECIALISTS
Authorized by Dr's name or CMS code: Department Hospital
Supplementary Information
Save
Do not Prescribe
Cancel
<< Back
Edit

Conclusions

- CVD remains a major morbidity and mortality in T2D.
- For T2D with ASCVD or those with high-risk, GLP-1RA or SGLT2 inhibitor with demonstrated CV benefit is recommended.
- There is compelling need to minimize hypoglycemia in choosing glucose lowering medications in T2D, especially for those with CVD.
- Fixed-ratio combinations of basal insulin and a GLP-1RA are recent addition to the treatment intensification options for T2D.

Thank You for Listening!

Email: alicekong@cuhk.edu.hk

https://www.mect.cuhk.edu.hk/people/alicekong.html