Use of GLP-1 Agonist

Dr. Ng Man Yuk, Tellus
Endocrinologist
Associate Consultant , Department of Medicine and Geriatrics, Tuen Mun Hospital

Case 1

- 30 years office lady
- Strong FH of T2DM
- T2DM since 1 year ago, presented with polyuria and polydipsia, no DKA
- Hba1c was 9.5 % , LDL 3.0 upon diagnosis, given with metformin 1g BD, diamicron 160mg BD, Actos 30 mg daily
- BW 80 kg, 1.6 m, BMI =31.26
- Good motivation on diet control and exercise
- Good compliance to medications

- Latest Hba1c = 8.5 % , LDL 2.65 , weight gain for 5kg after treatment , BW 83 kg BMI=32.4
- How will you help this patient?
- A. start basal insulin
- B. start GLP-1 agonist
- C. start SGLT-2 inhibitor
- D. Stop diamicron

Case 2

- 45 years old, private tutor, busy working schedule
- FH of T2DM
- T2DM since 42 years old, hypertension, hyperlipidaemia
- On metformin 1g BD, Actos 30 mg daily, diamicron 160 m BD, Dapagliflozin 10 mg daily
- Latest Hba1c 9% BW 80 kg BH 1.6 m BMI 31.2
- Infrequent SMBG:
- 1) 8-9
- 2) 10-12/14-18
- 3)12/14
- 4)---
- Refused insulin as worrying of weight gain

- How will you help this lady ?
- A. lifestyle modification
- B. stop diamicron/Actos, start GLP-1 agoinist
- C stop diamicron , start GLP-1 agonist
- D. start GLP-1 agonist

- Patient opted to start GLP-1 agonist , which agent will you suggest to her?
- A. Victoza daily SC
- B. Bydureon once per week SC
- C. lyxumia daily SC
- D. Trulicity once per week SC.

Case 3

- 60 years old gentlemen, businessman, ex-smoker , ex-drinker
- T2DM since 50 years old, IHD with PCI done one month ago, hyperlipidaemia, hx of TIA
- Latest Hba1c 8.0, LDL 1.85, BP/P 120/80 , BMI 32 eGFR 50
- On aspirin 80 mg daily, plavix 75 mg daily, lipitor 20 mg daily, losartan 75 mg daily, metformin 500mg BD(only can tolerate this dose), diamicron 160 mg BD, actos 15 g daily(only can tolerate this dose as ankle edema), linagliptin 5 mg daily
- SMBG:
- 1)4-7/10
- 2)8-9/12
- 3)9-10/14
- 4)5-6/12-14

- What will you suggest to him ?
- A. add empagliflozin
- B. start Victoza daily SC
- C. start weekly bydureon SC
- D. start weekly trulicity SC

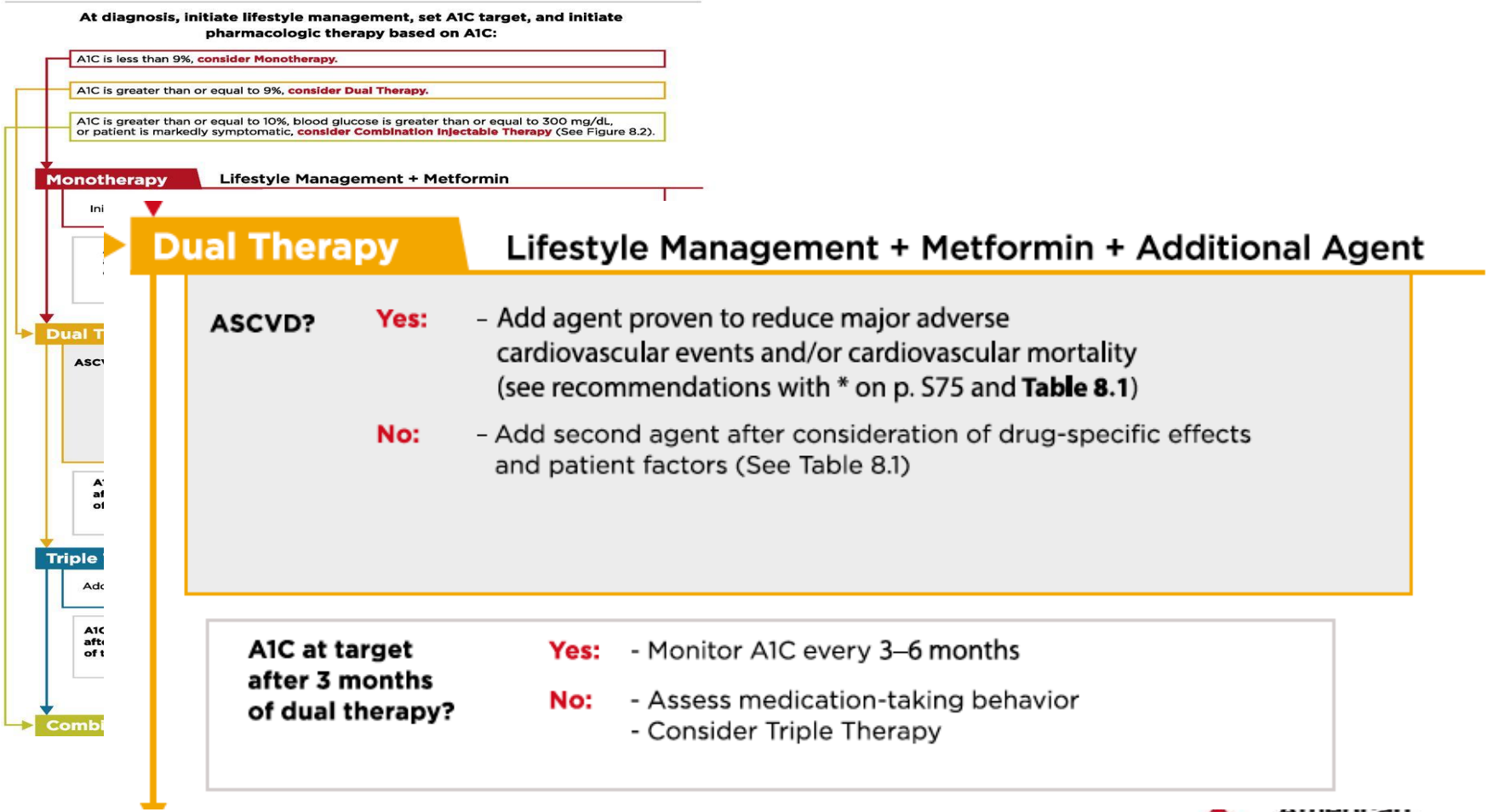
Case 4

- 50 years old, housewife
- T2DM since 20 years old, HT, hyperlipidaemia
- Hx of acute pancreatitis
- Hba1c 12%, LDL 2.6, eGFR 60 , BP 130/80, BMI 22
- Currently on metformin 1g BD, diamicron 160 mg BD, Dapagliflozin 10 mg daily, actos 30 mg daily. Refused insulin all along.
- SMBG:
- 1)4-12
- 2)3.5-14
- 3)4-20/Hi
- 4) 3.5-20

- What will you give to this lady ?
- A. start GLP-1 agonist
- B start insulin
- C. stop diamicron
- D. lifestyle modification

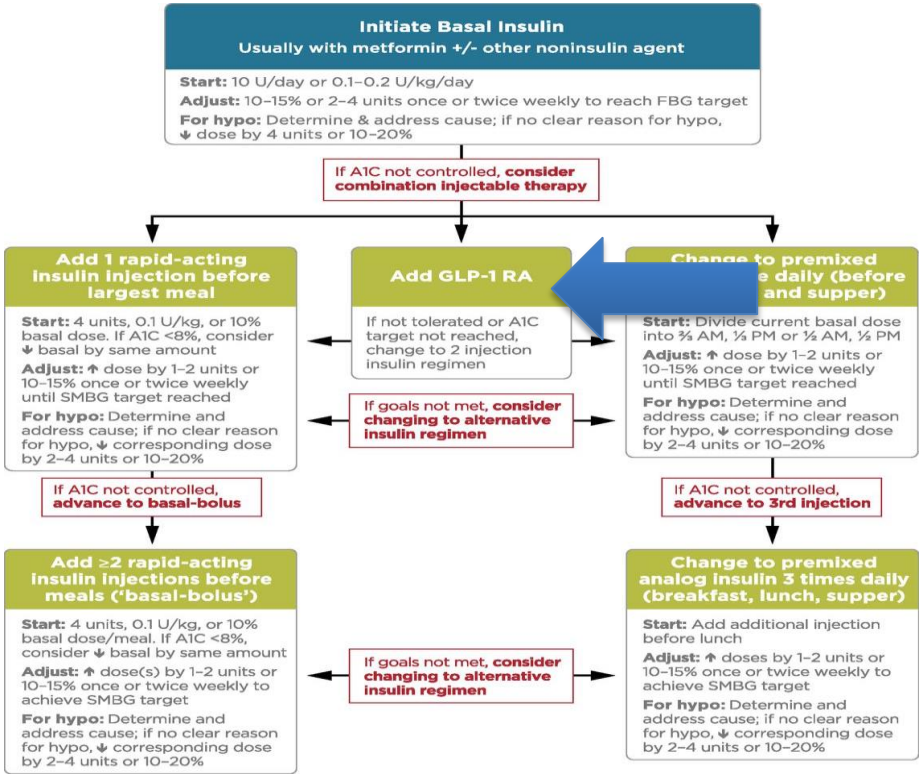
Guidelines

Antihyperglycemic Therapy in Adults with Type 2 Diabetes



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Combination injectable therapy for type 2 diabetes.



American Diabetes Association Dia Care 2018;41:S73-S85

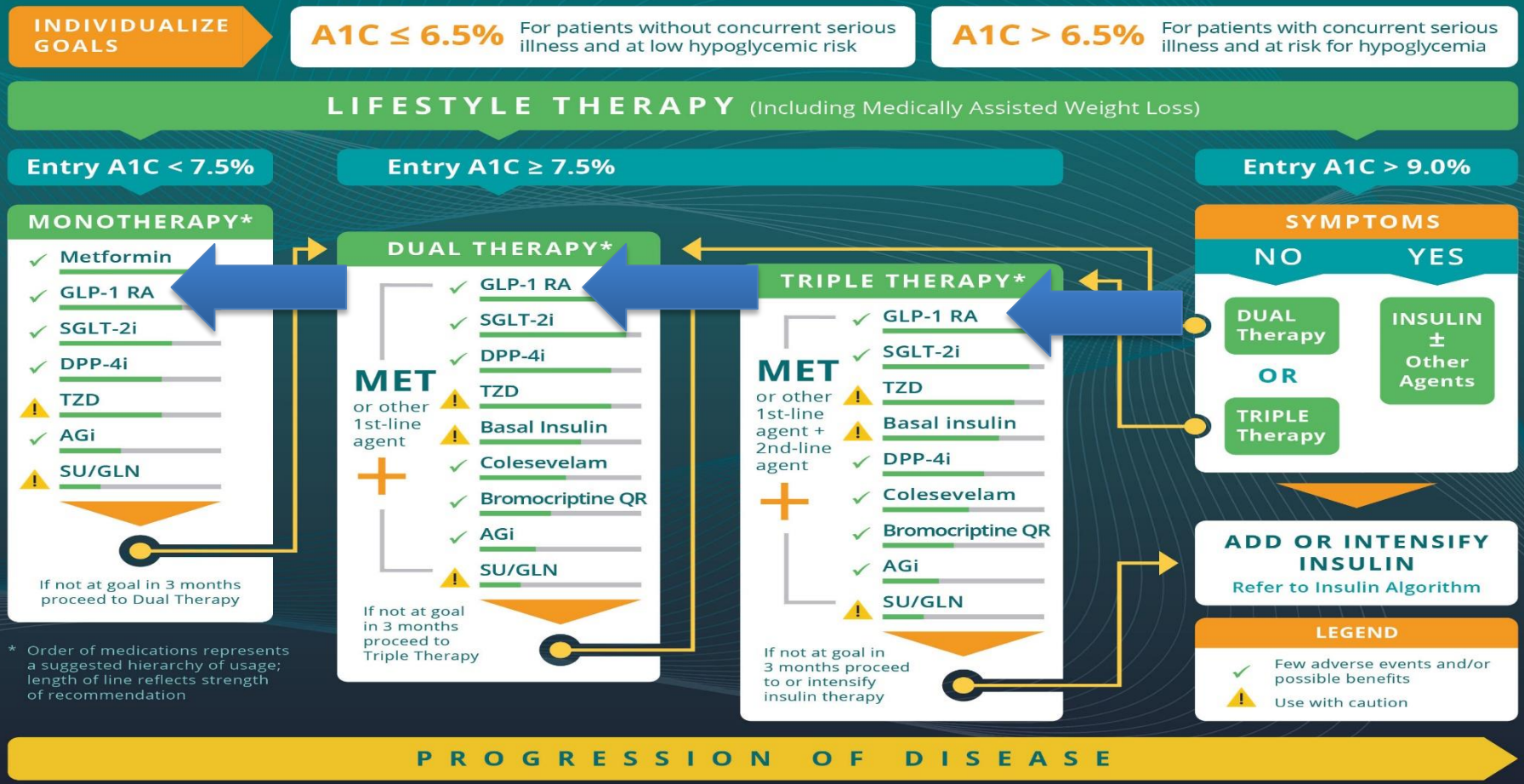
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Table 8.1—Drug-specific and patient factors to consider when selecting antihyperglycemic treatment in adults with type 2 diabetes

	Efficacy*	Hypoglycemia	Weight Change	CV Effects		Cost	Oral/SQ	Renal Effects		Additional Considerations
				ASCVD	CHF			Progression of DKD	Dosing/Use considerations	
Metformin	High	No	Neutral (Potential for Modest Loss)	Potential Benefit	Neutral	Low	Oral	Neutral	▪ Contraindicated with eGFR <30	▪ Gastrointestinal side effects common (diarrhea, nausea) ▪ Potential for B12 deficiency
SGLT-2 Inhibitors	Intermediate	No	Loss	Benefit: canagliflozin, empagliflozin†	Benefit: canagliflozin, empagliflozin	High	Oral	Benefit: canagliflozin, empagliflozin	▪ Canagliflozin: not recommended with eGFR <45 ▪ Dapagliflozin: not recommended with eGFR <60; contraindicated with eGFR <30 ▪ Empagliflozin: contraindicated with eGFR <30	▪ **FDA Black Box:** Risk of amputation (**canagliflozin**) ▪ Risk of bone fractures (canagliflozin) ▪ DKA risk (all agents, rare in T2DM) ▪ Genitourinary infections ▪ Risk of volume depletion, hypotension ▪ ↑LDL cholesterol
GLP-1 RAs	High	No	Loss	Neutral: lixisenatide, exenatide extended release Benefit: liraglutide†	Neutral	High	SQ	Benefit: liraglutide	▪ Exenatide: not indicated with eGFR <30 ▪ Lixisenatide: caution with eGFR <30 ▪ Increased risk of side effects in patients with renal impairment	▪ **FDA Black Box:** Risk of thyroid C-cell tumors (**liraglutide, albiglutide, dulaglutide, exenatide extended release**) ▪ Gastrointestinal side effects common (nausea, vomiting, diarrhea) ▪ Injection site reactions ▪ ?Acute pancreatitis risk
DPP-4 Inhibitors	Intermediate	No	Neutral	Neutral	Potential Risk: saxagliptin, alogliptin	High	Oral	Neutral	▪ Renal dose adjustment required; can be used in renal impairment	▪ Potential risk of acute pancreatitis ▪ Joint pain
Thiazolidinediones	High	No	Gain	Potential Benefit: pioglitazone	Increased Risk	Low	Oral	Neutral	▪ No dose adjustment required ▪ Generally not recommended in renal impairment due to potential for fluid retention	▪ **FDA Black Box:** Congestive heart failure [**pioglitazone, rosiglitazone**] ▪ Fluid retention (edema; heart failure) ▪ Benefit in NASH ▪ Risk of bone fractures ▪ Bladder cancer (pioglitazone) ▪ ↑LDL cholesterol (rosiglitazone)
Sulfonylureas (2nd Generation)	High	Yes	Gain	Neutral	Neutral	Low	Oral	Neutral	▪ Glyburide: not recommended ▪ Glipizide & glimepiride: initiate conservatively to avoid hypoglycemia	▪ FDA Special Warning on increased risk of cardiovascular mortality based on studies of an older sulfonylurea (tolbutamide)
Insulin — **Human Insulin**	Highest	Yes	Gain	Neutral	Neutral	Low	SQ	Neutral	▪ Lower insulin doses required with a decrease in eGFR; titrate per clinical response	▪ Injection site reactions ▪ Higher risk of hypoglycemia with human insulin (NPH or premixed formulations) vs. analogs
Insulin — **Analogs**						High	SQ			

Glycemic Control Algorithm



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Algorithm for Adding/Intensifying Insulin

START BASAL (Long-Acting Insulin)

A1C < 8% — **TDD** 0.1–0.2 U/kg

A1C > 8% — **TDD** 0.2–0.3 U/kg

Insulin titration every 2–3 days to reach glycemic goal:

- Fixed regimen: Increase TDD by 2 U
- Adjustable regimen:
  - FBG > 180 mg/dL: add 20% of TDD
  - FBG 140–180 mg/dL: add 10% of TDD
  - FBG 110–139 mg/dL: add 1 unit
- If hypoglycemia, reduce TDD by:
  - BG < 70 mg/dL: 10% – 20%
  - BG < 40 mg/dL: 20% – 40%

Consider discontinuing or reducing sulfonylurea after starting basal insulin (basal analogs preferred to NPH)

***Glycemic Goal:**

- <7% for most patients with T2D; fasting and premeal BG < 110 mg/dL; absence of hypoglycemia
- A1C and FBG targets may be adjusted based on patient's age, duration of diabetes, presence of comorbidities, diabetic complications, and hypoglycemia risk

Glycemic Control Not at Goal*

INTENSIFY (Prandial Control)

Add GLP-1 RA

Or SGLT-2i
Or DPP-4i

Add Prandial Insulin

Basal Plus 1, Plus 2, Plus 3

- Begin prandial insulin before largest meal
- If not at goal, progress to injections before 2 or 3 meals
- **Start: 10% of basal dose or 5 units**

Basal Bolus

- Begin prandial insulin before each meal
- 50% Basal / 50% Prandial TDD 0.3–0.5 U/kg
- **Start: 50% of TDD in three doses before meals**

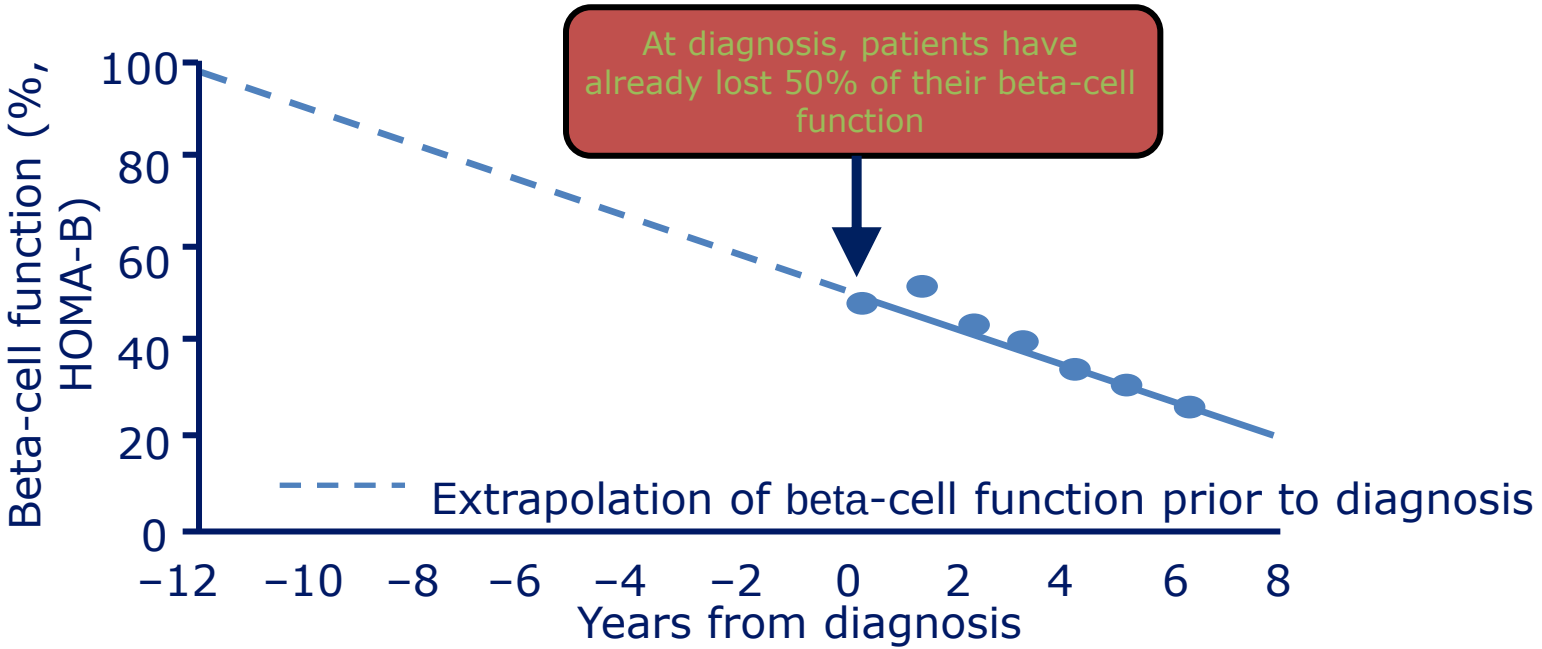
Insulin titration every 2–3 days to reach glycemic goal:

- Increase prandial dose by 10% or 1-2 units if 2-h postprandial or next premeal glucose consistently > 140 mg/dL
- If hypoglycemia, reduce TDD basal and/or prandial insulin by:
  - BG consistently < 70 mg/dL: 10% - 20%
  - Severe hypoglycemia (requiring assistance from another person) or BG < 40 mg/dL: 20% - 40%

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Background knowledge about T2DM

Decline of beta-cell function is the key driver of type 2 diabetes disease progression



Lebovitz, *Diabetes Reviews* 1999;7:139–53 (data are from the UKPDS population: UKPDS 16. *Diabetes* 1995;44:1249–58); DeFronzo. Presented at the Banting lecture, ADA 2008

Disease progression and the unmet need in type 2 diabetes

Decline in beta-cell function

Deterioration in HbA_{1c}, FPG and PPG over time

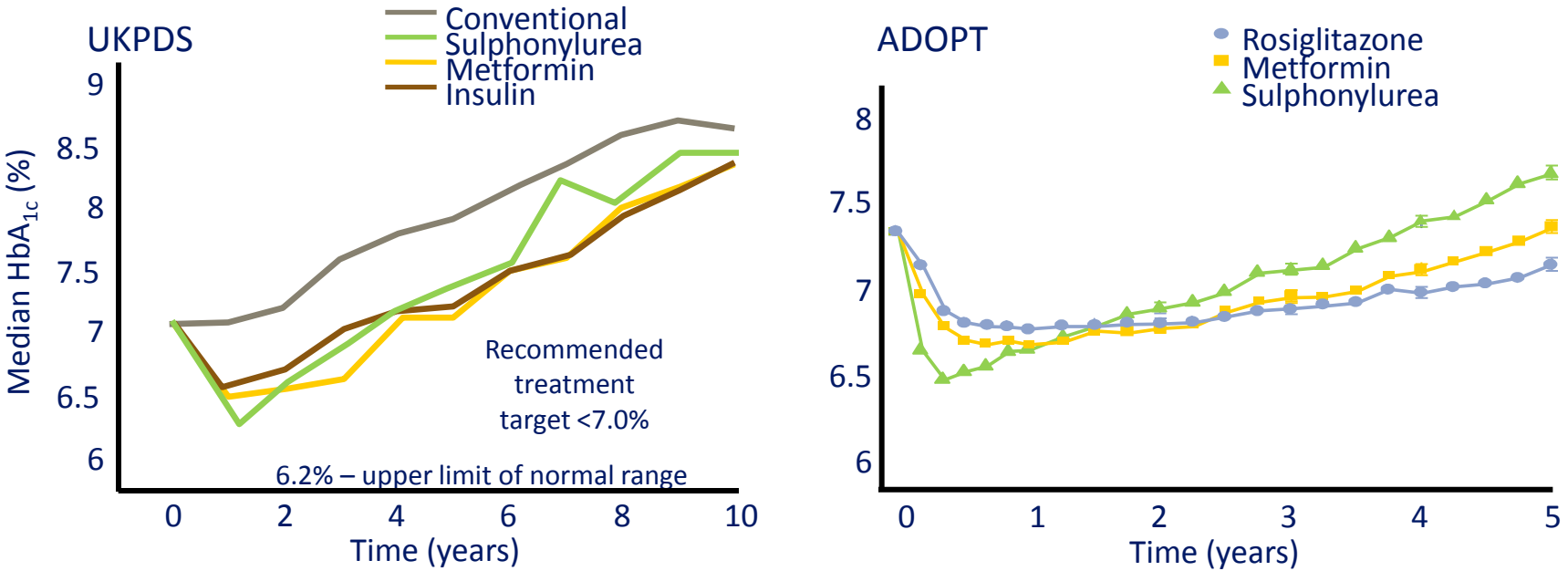
Increased systolic blood pressure

'Conventional' therapies associated with weight gain and/or hypoglycaemia

- 43% of patients do not achieve HbA_{1c} target (<7.0%)[1]
- Early intervention is essential to maintain glycaemic control

1. Ford *et al.* (NHANES). *Diabetes Care* 2008;31:102–4

Glycaemic control deteriorates over time with ‘conventional’ therapies



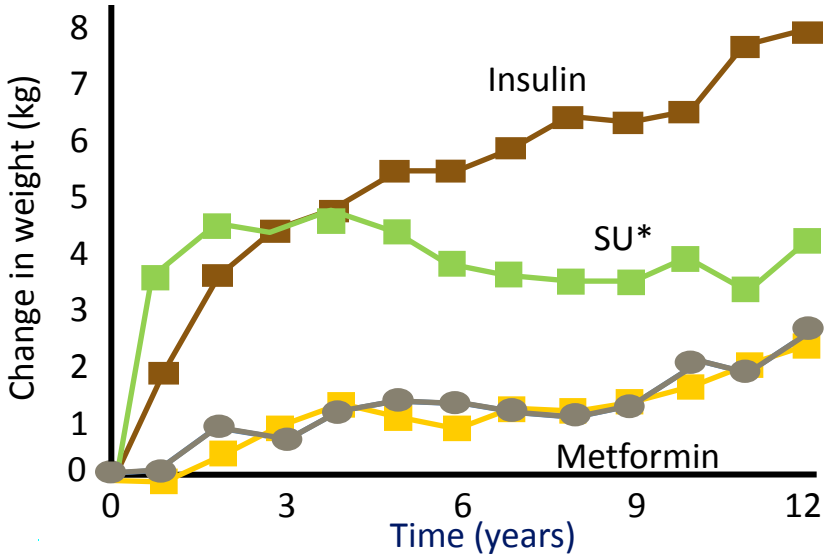
Conventional treatment: diet initially then SUs, insulin and/or metformin if FPG >15 mmol/L

*Sulphonylurea (SU) = glibenclamide/glyburide

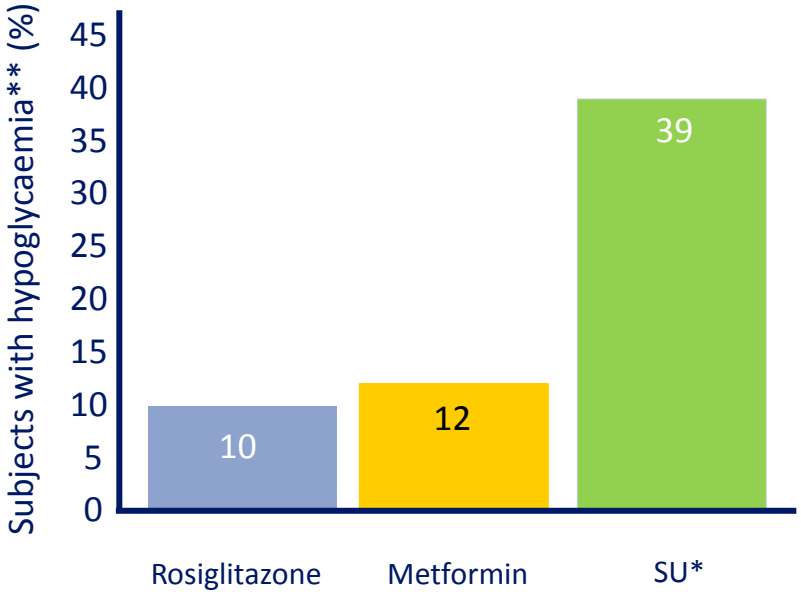
UKPDS 34. *Lancet* 1998:352:854–65; Kahn *et al.* (ADOPT). *N Engl J Med* 2006;355:2427–43

‘Conventional’ therapies increase the risk of weight gain and hypoglycaemia

Weight gain during UKPDS (up to 8 kg in 12 years)[1]



Hypoglycaemia during ADOPT[2,3]



Conventional treatment: diet initially then SUs, insulin and/or metformin if FPG >15 mmol/L

*SU = glibenclamide/glyburide; **patients self-reporting (unconfirmed) hypoglycaemia

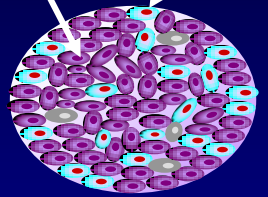
1. UKPDS 34. *Lancet* 1998:352:854–65; 2. Riddle *et al. Diabetes Care* 2003;26:3080; 3. Kahn *et al. N Engl J Med* 2006;355:2427–43

What is incretin hormones?

Glucagon-like peptide-1 and incretin effect



Intestinal L cell



Pancreatic islet

Food intake → **GLP-1** → **Incretin effect**

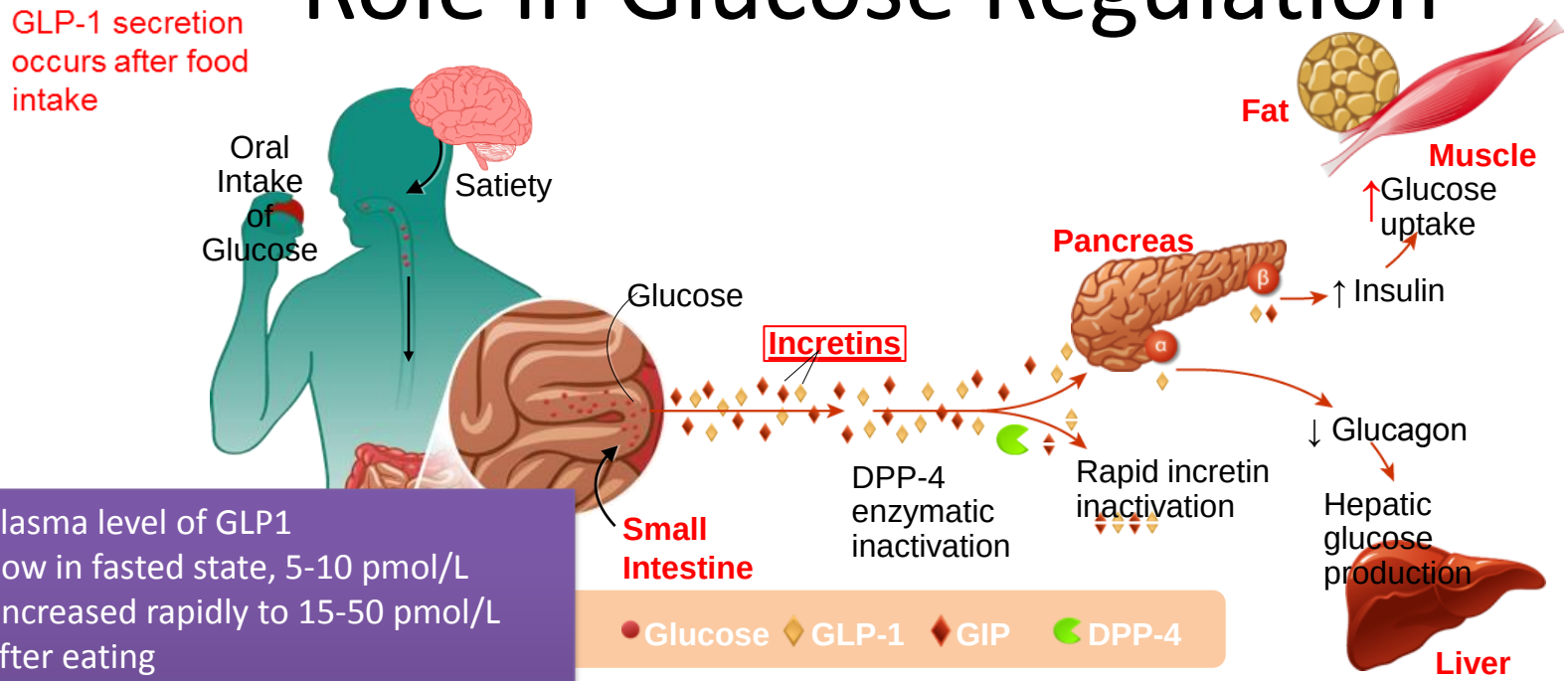
β-cell **α-cell**

Normal Accounts for up to 70% of insulin secretion in glucose-dependent manner

T2DM Incretin effect is impaired

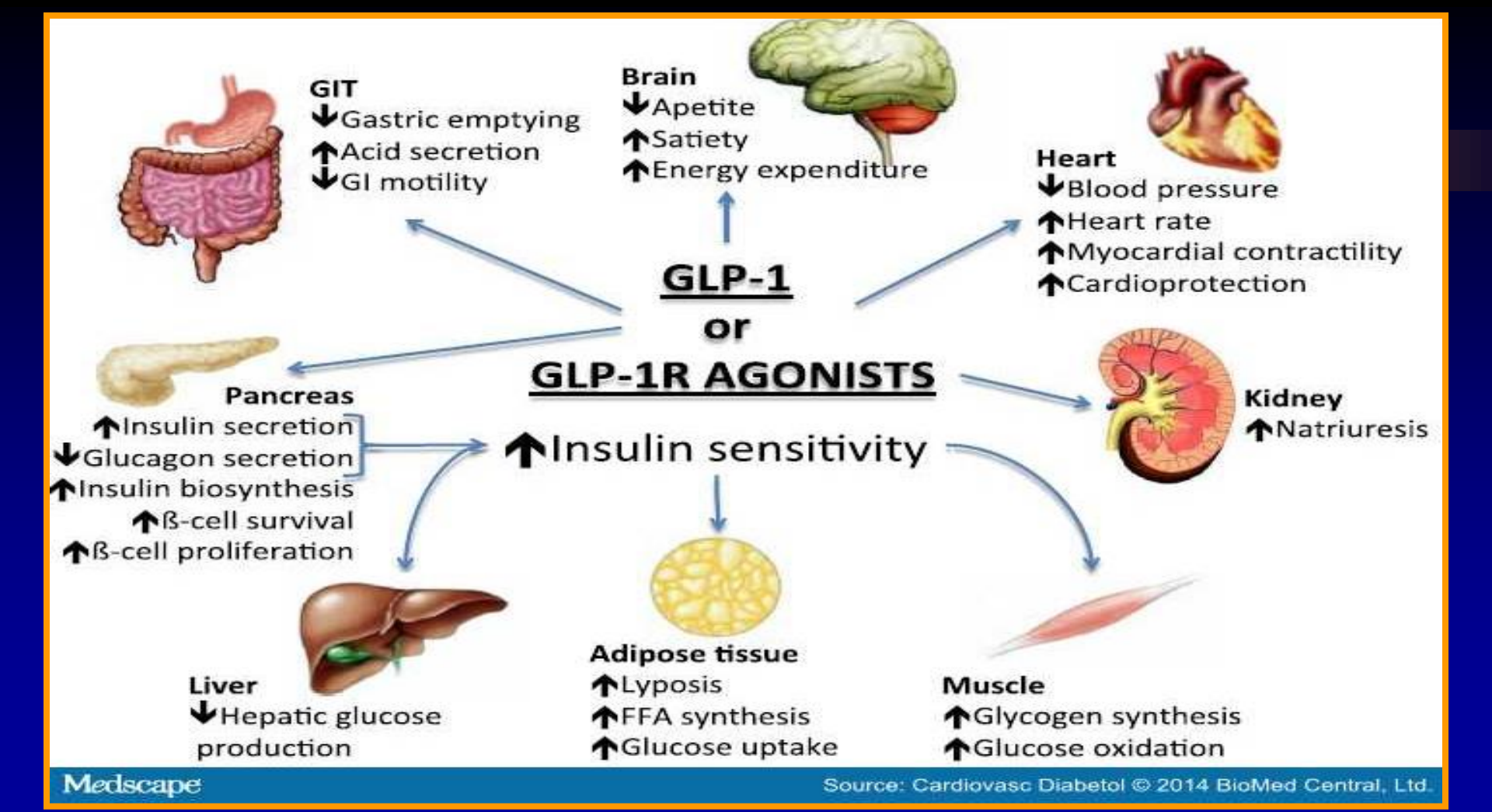
Adapted from Drucker D. *Diabetes Care.* 2003;26:2929-2940; and Wang Q, et al. *Diabetologia.* 2004;47(3):478-487.

Incretin Hormones Play a importatnt Role in Glucose Regulation



Plasma level of GLP1
-low in fasted state, 5-10 pmol/L
-increased rapidly to 15-50 pmol/L after eating
-decreases rapidly because of enzymatic inactivation (mainly DPP4) and renal clearance
-Short half-life of ~2 minutes only

Drucker 2006; Nauck 2009; Kendall 2009



http://www.medscape.com/viewarticle/835947

The current approaches to enhance incretin action in patients with type 2 diabetes

1) GLP-1 receptor agonists *:
as Exendin -4 or
Exenatide
(Half-life of 2-4 h)
(synthetic exendin-4)
(Byetta ®)

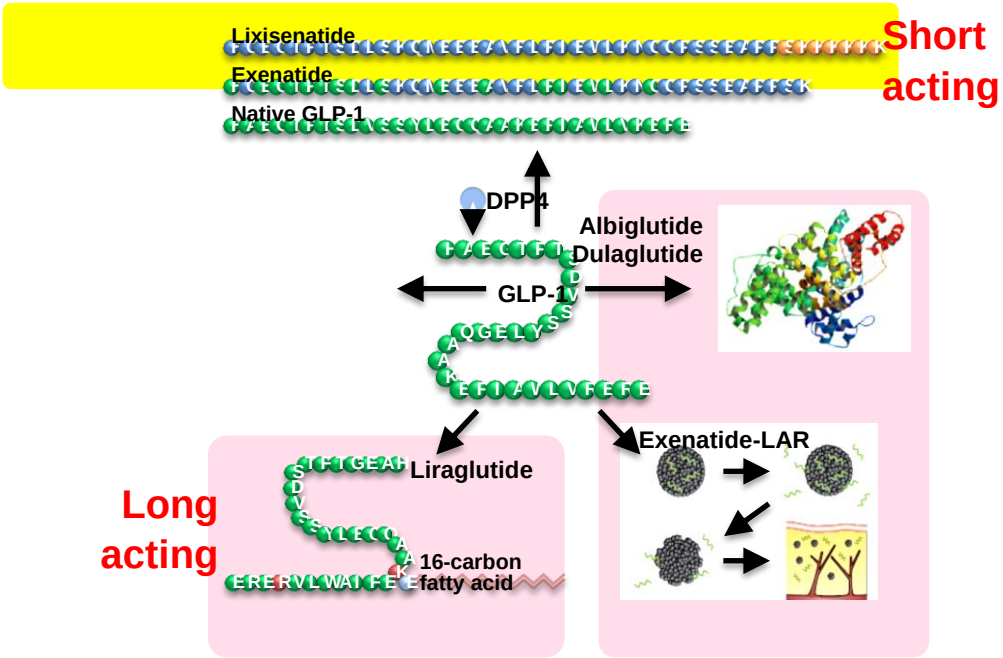
2) GLP-1 analogues *:
as liraglutide
(Half-life of 12-14 h)
by conjugation of GLP-1
to circulating albumin
(Victoza ®)

DDP-4
degradation-resistant and
can produce GLP-1
levels that are more than
5 times a patient's
physiologic levels.

Incretin mimetics
(used by SC
injection)

- * Amori RE, et al.JAMA.2007;298:194-206
- Liraglutide: Blonde L., et al. Can J Diabetes. 2008;32 (Supp):A107

GLP-1 Analogues: Structures and pharmacokinetics



Meier JJ. 2012 Nature Reviews Endocrinology; 8: 728-742

GLP-1 RAs: Dosing

Drug	Initial	Titrate	Max	Dose Adjustments
Exenatide IR (Byetta®) FDA 2005	5 mcg BD within 60 mins of a meal (≥ 6H between doses)	↑ to 10 mcg bd after 1 month	10 mcg bd	Renal impairment: CrCl 30-50 mL/min: use caution; CrCl < 30 mL/min not recommended Hepatic impairment: not studied
Exenatide ER (Bydureon®) FDA 2012	2 mg once weekly	N/A	2 mg once weekly	
Liraglutide (Victoza®) FDA 2009	0.6 mg qd x 1/52	1.2 mg qd	1.8 mg qd	Renal & hepatic impairment: use caution – limited experience
Lixisenatide (Lyxumia®) FDA 2016	10 mcg qd x 2/52	20 mcg qd	20 mcg qd	Renal impairment: use caution
Albiglutide (Tanzeum®)	30 mg once weekly	50 mg once weekly	50 mg once weekly	Renal impairment: use caution when initiating or escalating doses Hepatic impairment: not studied, unlikely required
Dulaglutide (Trulicity®) FDA 2014	0.75 mg once weekly	1.5 mg once weekly	1.5 mg once weekly	Renal impairment: use caution when initiating or escalating doses Hepatic impairment: use with caution

Exenatide (byetta)	Not recommended with eGFR< 30
Exenatide extended release (bydureon)	Not recommended with eGFR<30
Liraglutide (victoza)	No specific dose adjustment recommended by the manufacturer; limited experience in patients with severe renal impairment
Lixisenatide (Lyxumia)	No dose adjustment for eGFR 60-89 No dose adjustment for eGFR 30-59; but patient should be monitored for adverse effects and changes in kidney function
Dulaglutide (Trulicity)	No specific dose adjustment recommended by the manufacturer; limited experience in patients with severe renal impairment.

Effects of the short- and continuous-acting GLP-1R agonists.

	Short-acting	Continuous-acting
	Exenatide Lixisenatide	Liraglutide Exenatide* Albiglutide Dulaglutide Semaglutide
Clinical effects		
GLP-1R activation	Intermittent	Continuous
HbA_{1c} reduction	+	++
FPG reduction	+	++
PPG reduction	++	+
Gastric emptying deceleration	++	Neutral
Body weight reduction	++	++
Blood pressure reduction	+	+
Heart rate increase	Neutral	+

Abbreviations: GLP-1R, glucagon-like peptide-1 receptor; HbA_{1c}, glycated haemoglobin; FPG, fasting plasma glucose; PPG, postprandial glucose.

* Exenatide once-weekly.

GLP-1 RA

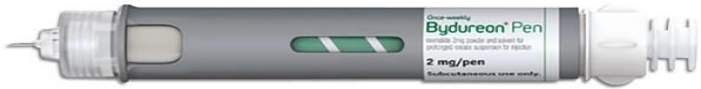
Contraindications	Family hx of medulary thyroid carcinoma, multiple endocrine neoplasia syndrome type 2*
Black Box Warning	Risk of thyroid tumors (shown in animal models)*
Adverse Effects	Nausea, vomiting, diarrhea, weight loss, ?pancreatitis, injection site reaction (skin nodules)
Monitoring	FBG, HbA1C, RFT
Interactions	- Agents that induce hypoglycemia - GLP-1 agonists may reduce rate of absorption of orally administered drugs
Clinical pearls	- Low hypoglycemia risk - 1-1.5 % ↓ in A1C - Injectable sc pens - Avoid in patients with gastroparesis - Contraindicated in stages 4 and 5 CKD. - May need to reduce dose of insulin and/or secretagogues - Pregnancy category C - Cost (~2000/month)

Bydureon

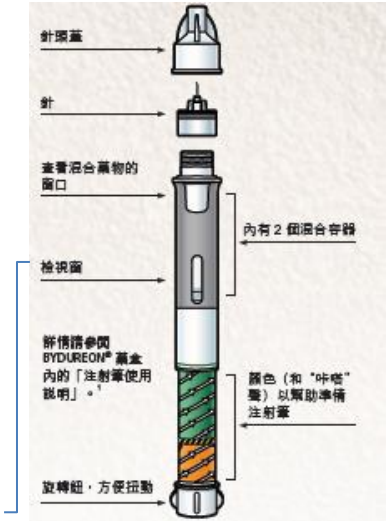
Microsphere technology to deliver continuous therapeutic levels of GLP-1 RA

- Biodegradable microspheres allow continuous systemic exposure to exenatide without modification of the active protein
  - Steady-state levels of exenatide with just 1 injection per week[1]
  - Minimal peak-to-trough fluctuations[1,2]
  - Improved tolerability due to the gradual accumulation of exenatide plasma concentrations[3,4]





0.65ml per injection



Abbreviation: RA, receptor agonist.

1. Kim et al. *Diabetes Care*. 2007;30(6):1487-1493. 2. DeYoung et al. *Diabetes Technol Ther*. 2011;13(11):1145-1154. 3. Ridge et al. *Diabetes Obes Metab.* 2012;14(12):1097-1103. 4. Fineman et al. *Diabetes Metab Res Rev.* 2004;20(5):411-417.

Once-weekly

BYDUREON® BCise™

exenatide extended-release injectable suspension 2 mg



BYDUREON BCise

Learn more about once-weekly BYDUREON BCise for adults with type 2 diabetes in an easy-to-use device.*

*In a study, 85% of people rated the overall injection process with BYDUREON BCise as "easy" or "very easy."

Click Here for BYDUREON BCise >

BYDUREON Pen

Learn more about once-weekly BYDUREON Pen for adults with type 2 diabetes.

Click Here for BYDUREON Pen >

Once-weekly

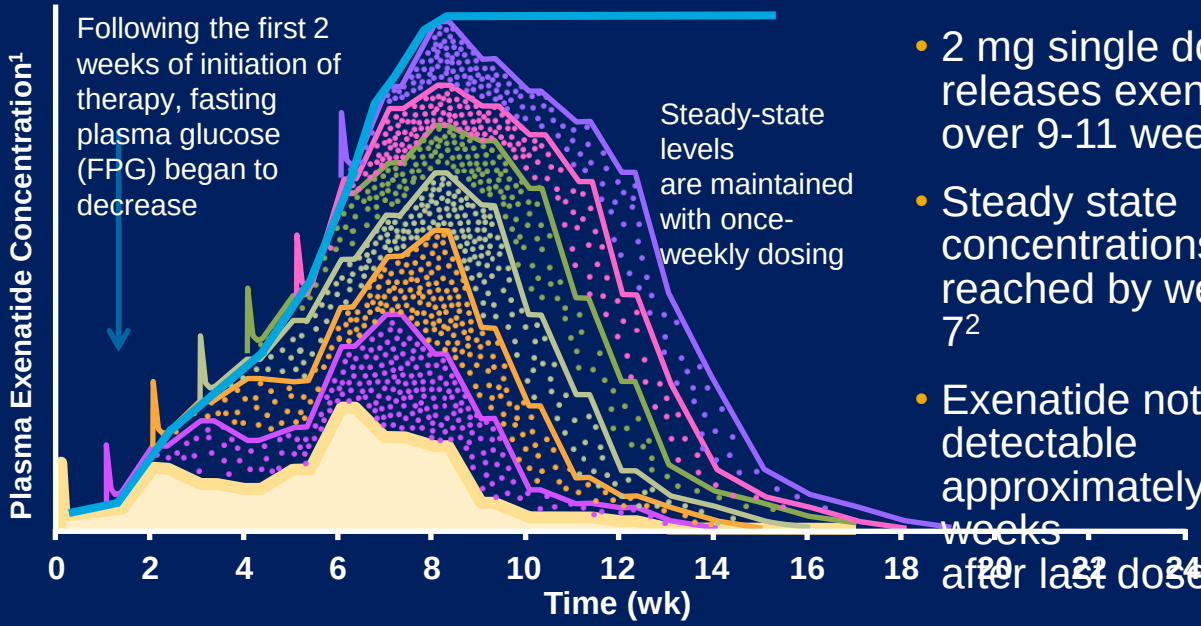
BYDUREON® Pen

exenatide 2mg powder and solvent for prolonged release suspension for injection



Pharmacokinetic Profile of Exenatide QW

Steady State Maintained With Subsequent Doses



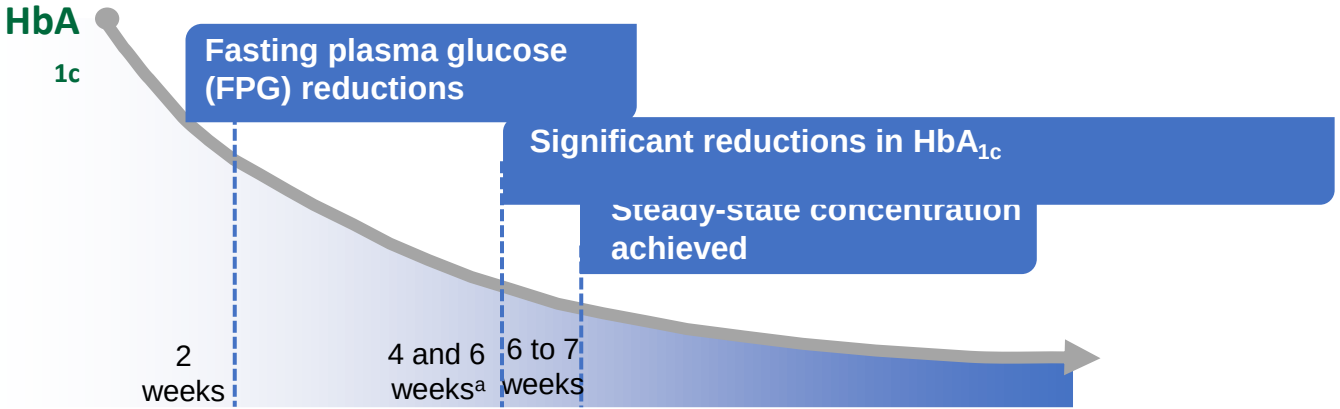
- 2 mg single dose releases exenatide over 9-11 weeks[1]
- Steady state concentrations are reached by week 6-7[2]
- Exenatide not detectable approximately 10 weeks after last dose[1,2]

Fineman 2011; Bydureon Prescribing Information

Therapeutic benefits of BYDUREON® observed as steady-state levels of exenatide are achieved

Reductions in FPG as early as 2 weeks and significant reductions in HbA_{1c} vs pioglitazone and sitagliptin at 4 and 6 weeks, respectively[1,2]

Therapeutic effects of BYDUREON[1-3]



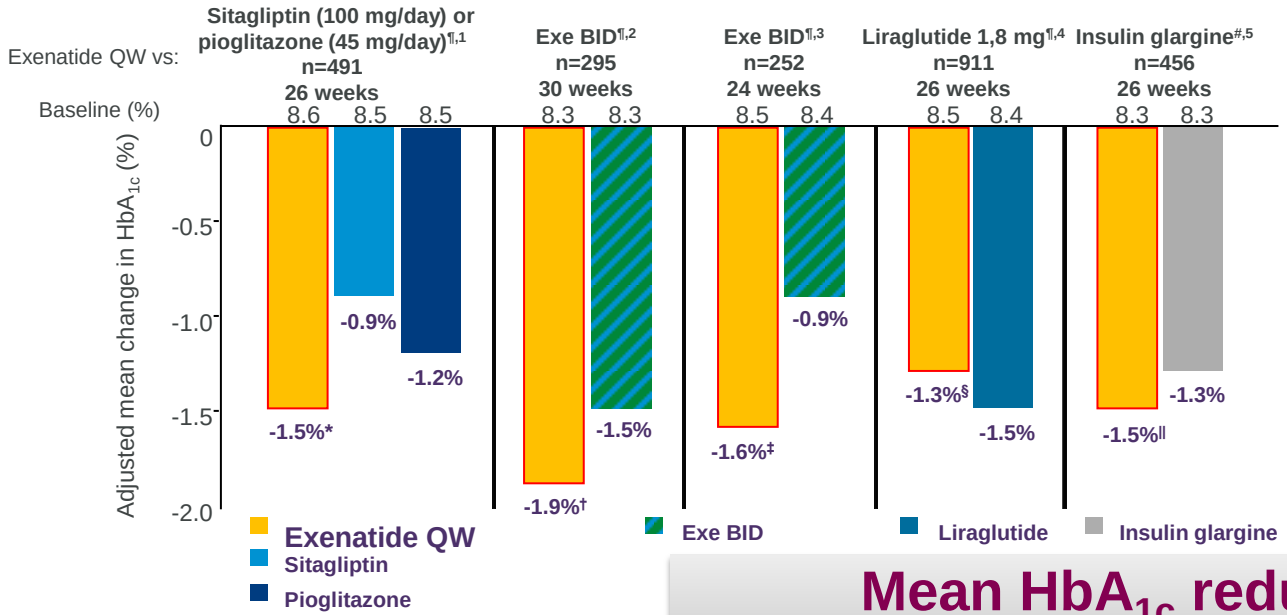
[a]Patients treated with BYDUREON demonstrated significant reductions in HbA_{1c} by week 4 compared to pioglitazone and by week 6 compared to sitagliptin.[3]

1. Kim et al. *Diabetes Care*. 2007;30(6):1487-1493. 2. Bergenstal et al. *Lancet*. 2010;376(9739):431-439.
3. BYDUREON Summary of Product Characteristics (May 2013).

Table 2 Phase 3 DURATION Trials with Exenatide ER[16-22]

Trial	Study drug	Exenatide ER outcomes vs comparator drugs
DURATION-1	Exenatide ER 2 mg vs exenatide 10 mcg twice daily	Greater HbA_{1c} reduction: –1.9% vs –1.5% Greater reduction in lipid profile, total cholesterol, triglycerides Better glucose control, body weight reduction, systolic blood pressure reduction Reduced nausea
DURATION-2	Exenatide ER vs pioglitazone vs sitagliptin; all agents taken with metformin	Greater HbA_{1c} reduction w/ exenatide ER: –1.5% vs –0.9% vs –1.2% Greater weight loss: –2.3 kg vs –0.8 kg vs +2.8 kg Less nausea (5% vs 10.8% vs 9.6%) No hypoglycemia w/ exenatide ER
DURATION-3	Exenatide ER vs insulin glargine, titrated to goal <100 mg/dL	Greater HbA_{1c} reduction w/ exenatide ER: –1.5% vs –1.3% 3 × lower hypoglycemia rate w/ exenatide ER
DURATION-4	Exenatide ER vs metformin vs pioglitazone vs sitagliptin; all in treatment-naïve patients	HbA_{1c} reduction: –1.53% vs 1.48% vs 1.63% vs 1.15% Weight loss: –2.0 kg vs –2.0 kg vs +1.5 kg vs –0.8 kg Nausea & diarrhea: 11.3% and 10.9% w/ exenatide ER No major hypoglycemia occurred
DURATION-5	Exenatide ER vs exenatide; this is similar to DURATION-1	At 24 weeks, greater HbA_{1c} reduction: –1.6% vs –0.9% Greater fasting glucose reduction: –35 mg/dL vs –12 mg/dL Similar weight reduction, adverse effects
DURATION-6	Exenatide ER vs liraglutide	Greater HbA_{1c} reduction w/ liraglutide: –1.48% vs –1.28% More patients reached goal w/ liraglutide: 60% vs 53% Greater weight loss w/ liraglutide

HbA_{1c} improvement can be reached with Exenatide QW

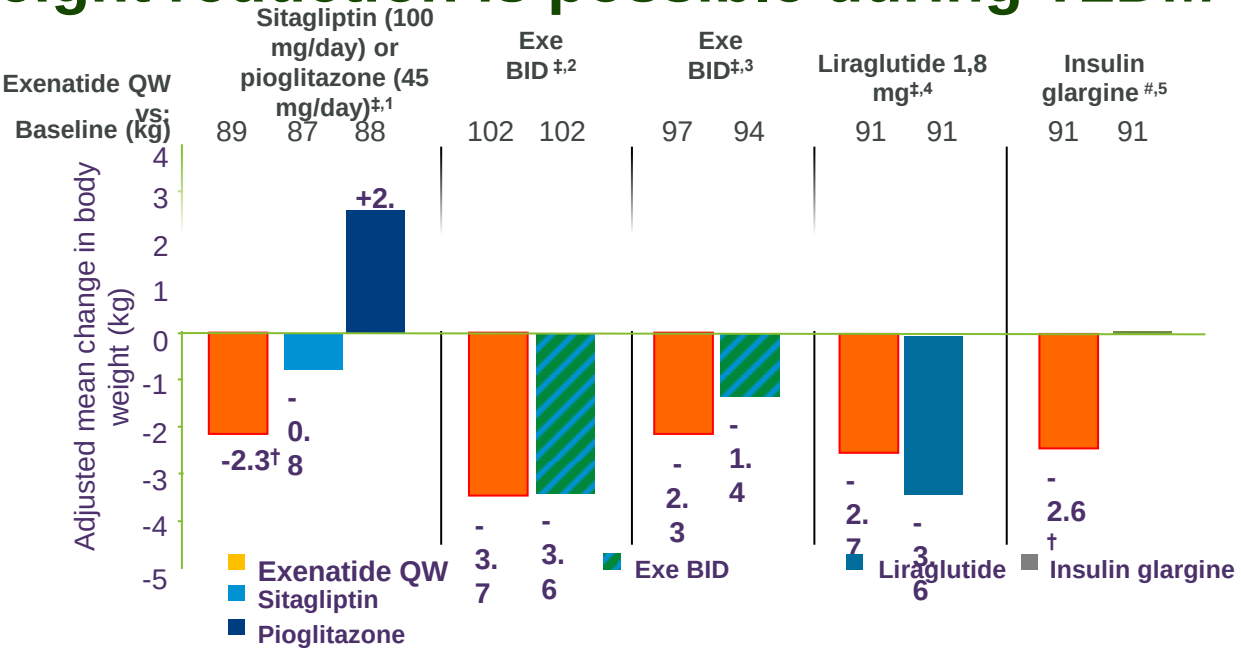


Mean HbA_{1c} reduction from 1.3 % to 1.9 %[1-5]

Data after 24-30 weeks; **P*<0.0001 vs. sitagliptin and *P*=0.0165 vs. pioglitazone, respectively; †*P*=0.0023; ‡*P*<0.0001; §*P*=0.02; ‖*P*=0.017; ¶ITT population; #modified ITT population; Exe=exenatide.

Modified from **1.** Bergenstal RM, et al. *Lancet* 2010; 376:431-9; **2.** Drucker DJ, et al. *Lancet* 2008; 372:1240-50; **3.** Blevins T, et al. *J Clin Endocrinol Metab* 2011; 96:1301-10; **4.** Buse JB, et al. *Lancet* 2013; 381:117-24; **5.** Diamant M, et al. *Lancet* 2010; 375:2234-43.

Exenatide QW has shown throughout all DURATION trials, that weight reduction is possible during T2DM treatment



*Exenatide is not indicated for the management of obesity, and weight change was a secondary endpoint in clinical trials.

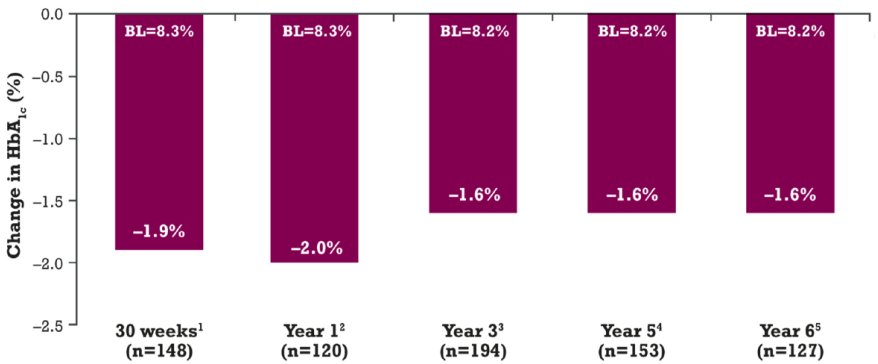
Data after 24-30 weeks; †p=0.0002 vs. sitagliptin and p<0.0001 vs pioglitazone; ‡p<0.0001; ‡ITT population; #modified ITT population; Exe=exenatide.

Modified from **1.** Bergenstal RM, et al. Lancet 2010; 376:431-9; **2.** Dru... Blevins T, et al. J Clin Endocrinol Metab 2011; 96:1301-10; **4.** Buse JB... M, et al. Lancet 2010; 375:2234-43.

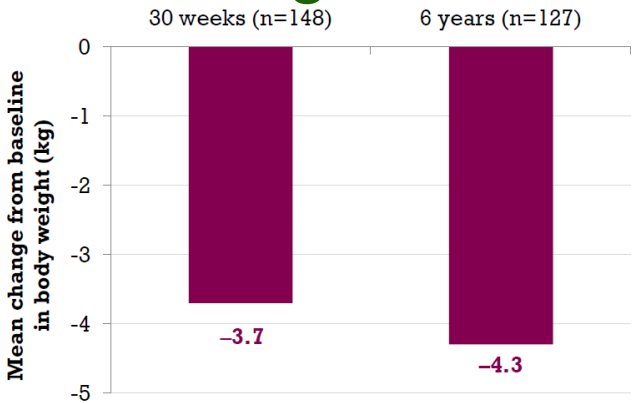
Mean body weight reduction* from 2.3 kg to 3.7 kg[1-5]

Exenatide QW also the only weekly GLP1 provides 6 years long-term data concerning efficacy

HbA_{1c} change



Body weight change

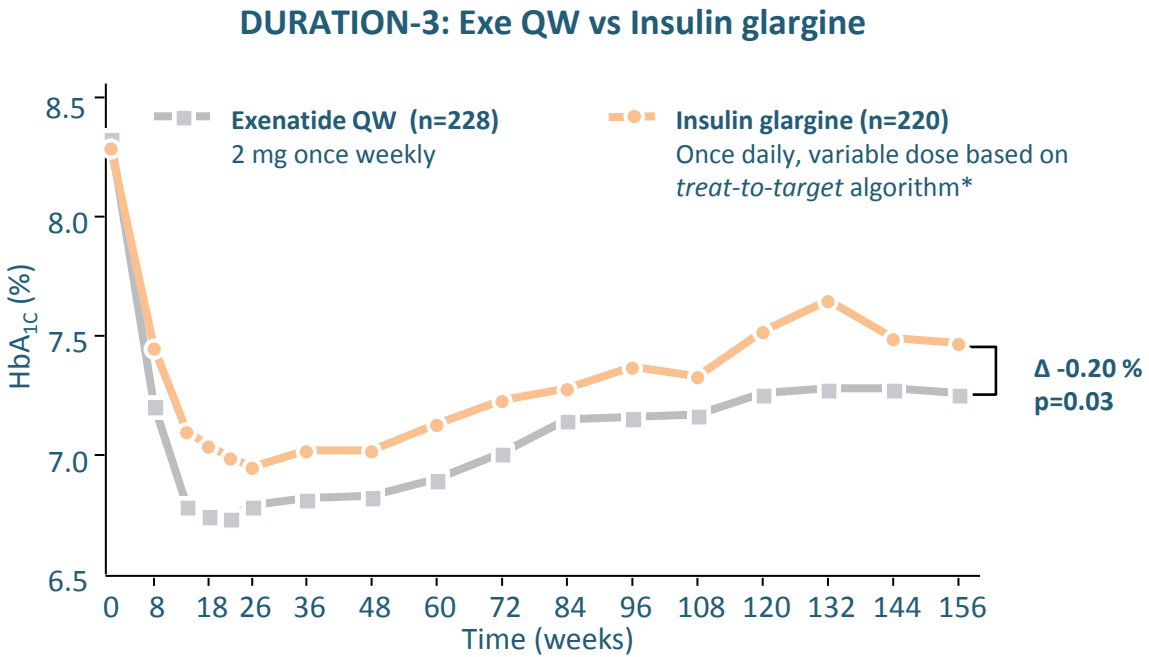


Exenatide QW was associated with significant, sustained improvements in glycaemic control and weight over 6 years

*Exenatide is not indicated for treatment of obesity. Weight reduction is an additional effect and was a secondary endpoint in clinical studies;

1. Drucker DJ, et al.Lancet 2008;372:1240–50; 2. Buse JB, et al.Diabetes Care 2010;33:1255–61; 3. MacConell L, et al.Diabetes Metab Syndr Obes2013;6:31–41; 4. Wysham CH, et al. Mayo Clin Proc2015;90:356–65; 5. Henry RR, et al. Poster 38-P presented at the 50th Annual Meeting of the DeutschenDiabetes Gesellschaft(DDG), 13–16 May 2015, Berlin, Germany.

The HbA_{1c} improvement with Exenatide QW is significantly greater compared to titrated insulin glargine

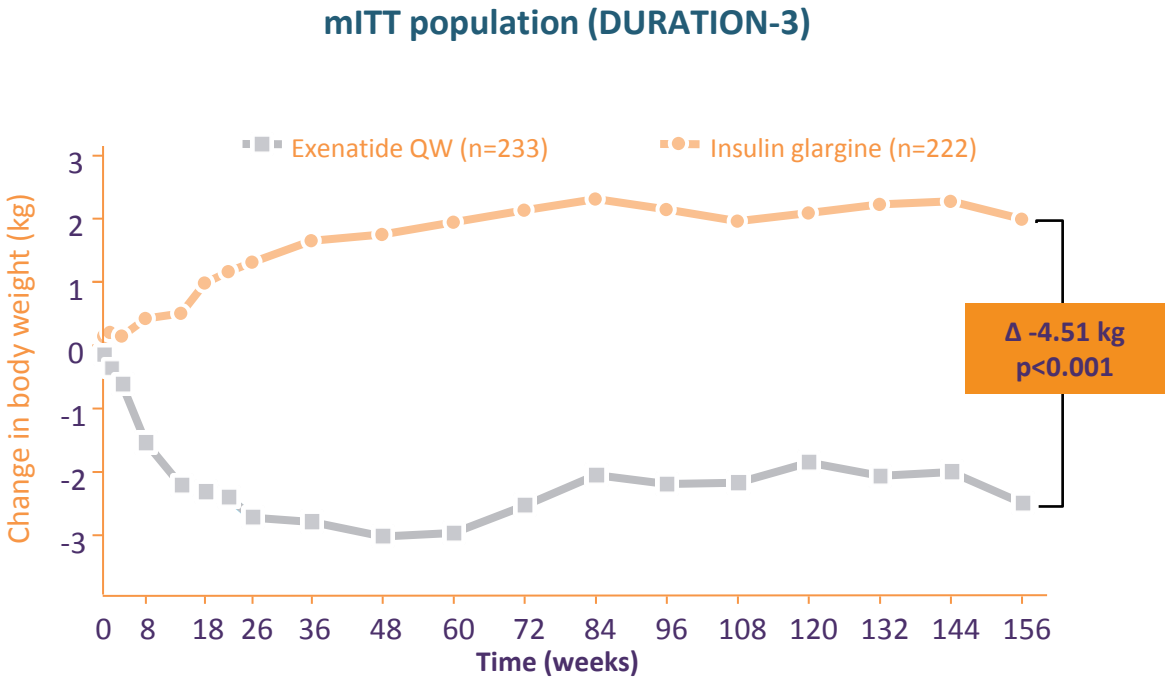


*The daily dose of insulin glargine was based on the INITIATE algorithm (Initiate Insulin by Aggressive Titration and Education) and was individually adjusted to achieve fasting glucose values of 4.0–5.5 mmol/l.

In the Insulin glargine arm, from a starting daily insulin dose of 10IU/day, mean dose increased to 31 IU/day at 26 weeks and 39 IU/day at 3 years.

Modified from Diamant M, et al. *Lancet Diabetes Endocrinol* 2014; 2:464-73.

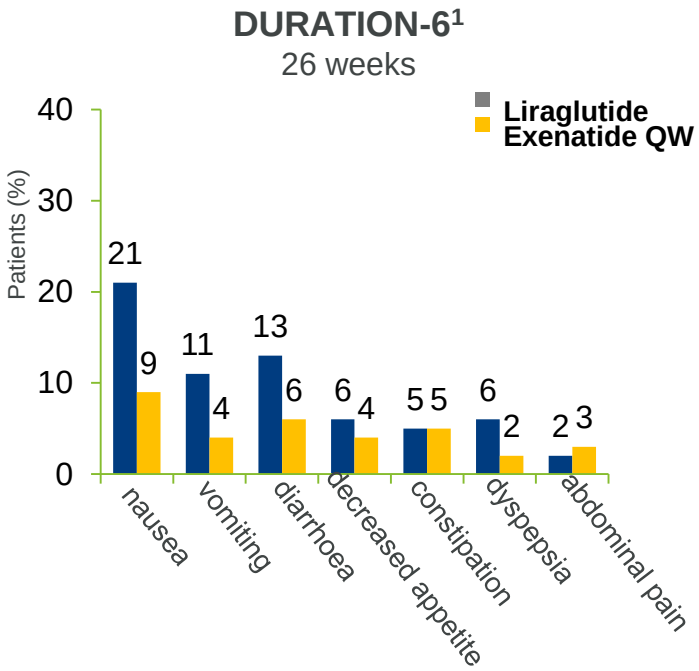
Whereas there is a mean gain of weight during insulin treatment*

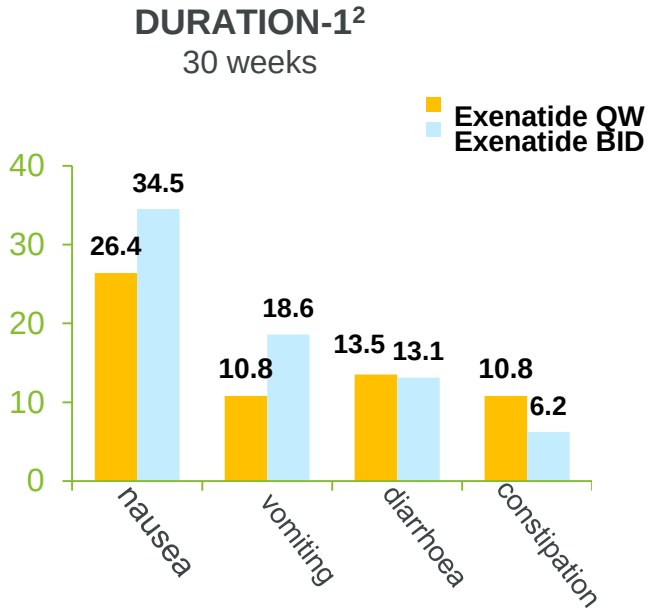


*Exenatide is not indicated for the management of obesity, and weight change was a secondary endpoint in clinical trials.

Modified from Diamant M, et al. Lancet Diabetes Endocrinol 2014; 2:464-73.

Better GI tolerability vs daily GLP-1s has been shown with Exenatide QW, which often has an impact on adherence





Modified from: 1. Buse JB, et al. *Lancet* 2013; 381:117-24; 2. Drucker DJ, et al. *Lancet* 2008; 372:1240-50.

Liraglutide



Dosing of liraglutide

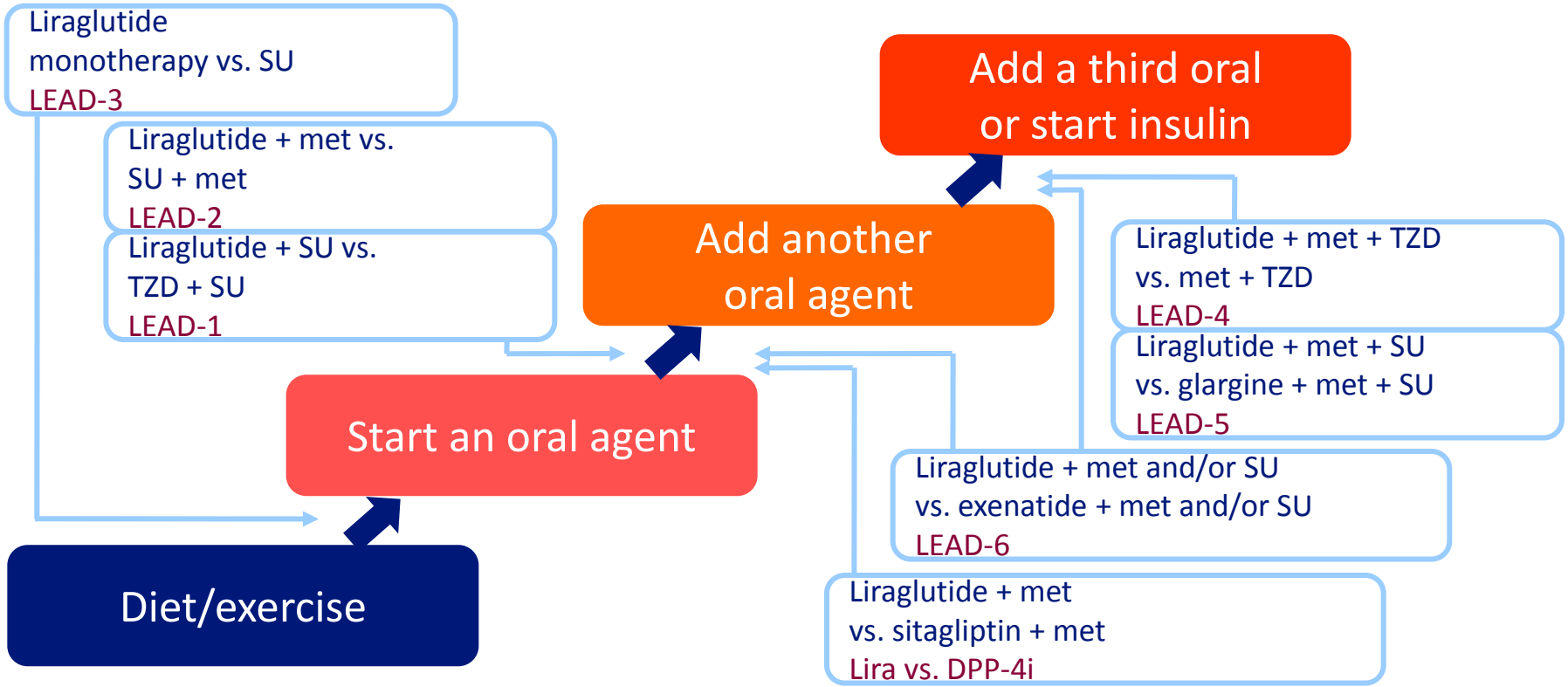
- Once-daily injection from a prefilled pen device
- Injection irrespective of meals, any time of day
- To improve gastrointestinal tolerability, the starting posology is 0.6 mg, increasing to a 1.2 mg maintenance dose, then intensified to 1.8 mg, if required



*Some patients are expected to benefit from an increase in dose from 1.2 to 1.8 mg and, based on clinical response, after at least 1 week, the dose can be increased to 1.8 mg to further improve glycaemic control. Daily doses higher than 1.8 mg are not recommended

1. Novo Nordisk. Victoza® SmPC; July 2011

The liraglutide phase 3 clinical trial programme (LEAD) covers the continuum of type 2 diabetes care



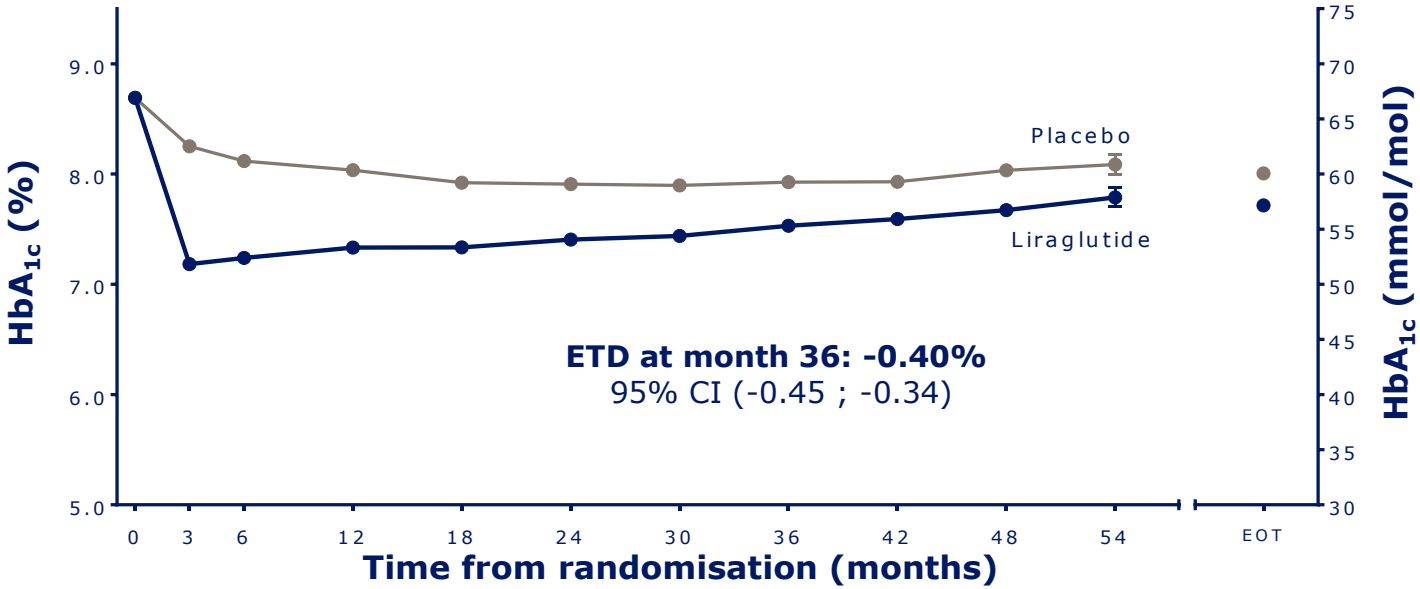
LEAD, Liraglutide Effect and Action in Diabetes; TZD, thiazolidinedione

Marre *et al. Diabetic Medicine* 2009;26;268–78 (LEAD-1); Nauck *et al. Diabetes Care* 2009;32;84–90 (LEAD-2); Garber *et al. Lancet* 2009;373:473–81 (LEAD-3); Zinman *et al. Diabetes Care* 2009;32:1224–30 (LEAD-4); Russell-Jones *et al. Diabetologia* 2009;52:2046–55 (LEAD-5); Buse *et al. Lancet* 2009; 374:39–47 (LEAD-6); Pratley *et al. Lancet* 2010:375;1447–56 (Lira vs. DPP-4i).

Table 3 Phase 3 LEAD Trials with Liraglutide[28-33]

Trial	Study drug	Liraglutide outcomes vs comparator drugs
LEAD-1	Liraglutide 1.2 mg & 1.8 mg once daily vs rosiglitazone 4 mg once daily; all concurrently taking sulfonylurea	Significant HbA_{1c} reduction w/ liraglutide 1.2 mg & 1.8 mg: 1.1% vs –0.4% w/ rosiglitazone 4 mg Significant decrease in FPG & PPG w/ liraglutide vs rosiglitazone Minor hypoglycemia, <10%; nausea, <11%; vomiting, <5%; diarrhea, <8%
LEAD-2	Liraglutide 1.2 mg & 1.8 mg vs glimepiride 4 mg; all concurrently taking metformin	Noninferior HbA_{1c} reduction in liraglutide groups: mean decrease, –1% Body weight –2.8 kg w/ 1.8-mg liraglutide vs +1.0 kg w/ glimepiride Less hypoglycemic events in liraglutide groups: 3% vs 17% w/ glimepiride Increased nausea in liraglutide groups
LEAD-3	Liraglutide 1.2 mg & 1.8 mg once daily vs glimepiride 8 mg once daily	HbA_{1c} reductions: –0.84% & –1.23% w/ liraglutide 1.2 mg & 1.8 mg vs 0.51% w/ glimepiride 8 mg No major hypoglycemic events Significantly less minor hypoglycemia: 8% & 12% vs 24%
LEAD-4	Liraglutide 1.2 mg & 1.8 mg vs placebo; all concurrently taking metformin and rosiglitazone	HbA_{1c} reduction: –1.5% vs –0.5% Significant FPG and PPG reductions w/ 1.2-mg & 1.8-mg liraglutide Body weight reductions: –1.0 kg & –2.0 kg w/ liraglutide 1.2 mg & 1.8 mg vs +0.6-kg weight gain w/ placebo Systolic BP reductions: –6.7 mm Hg & –5.6 mm Hg w/ liraglutide 1.2 mg & 1.8 mg vs –1.1 mm Hg w/ placebo Minor hypoglycemia: 7.9% & 9% vs 5.1% No major hypoglycemic events
LEAD-5	Liraglutide 1.8 mg vs insulin glargine; all concurrently taking metformin and glimepiride	Significantly greater HbA_{1c} reduction: –1.33% vs –1.09% Significantly greater weight loss w/ liraglutide: –1.39 kg vs +3.43 kg Systolic BP reduction: –4 mm Hg vs +0.5 mm Hg Major & minor hypoglycemia rates: 0.06 & 1.2 vs 0 & 1.3 events/patient annually
LEAD-6	Liraglutide 1.8 mg vs exenatide 10 µg twice daily, all concurrently taking metformin and sulfonylurea	Significant HbA_{1c} reduction: –1.12% vs –0.79% Greater FPG reduction vs exenatide Weight loss: 3.24 kg vs 2.87 kg (difference not significant) Significantly less minor hypoglycemia w/ liraglutide: 25.5% vs 33.6% 2 patients taking exenatide & sulfonylurea had major hypoglycemia Less nausea w/ liraglutide

HbA_{1c}

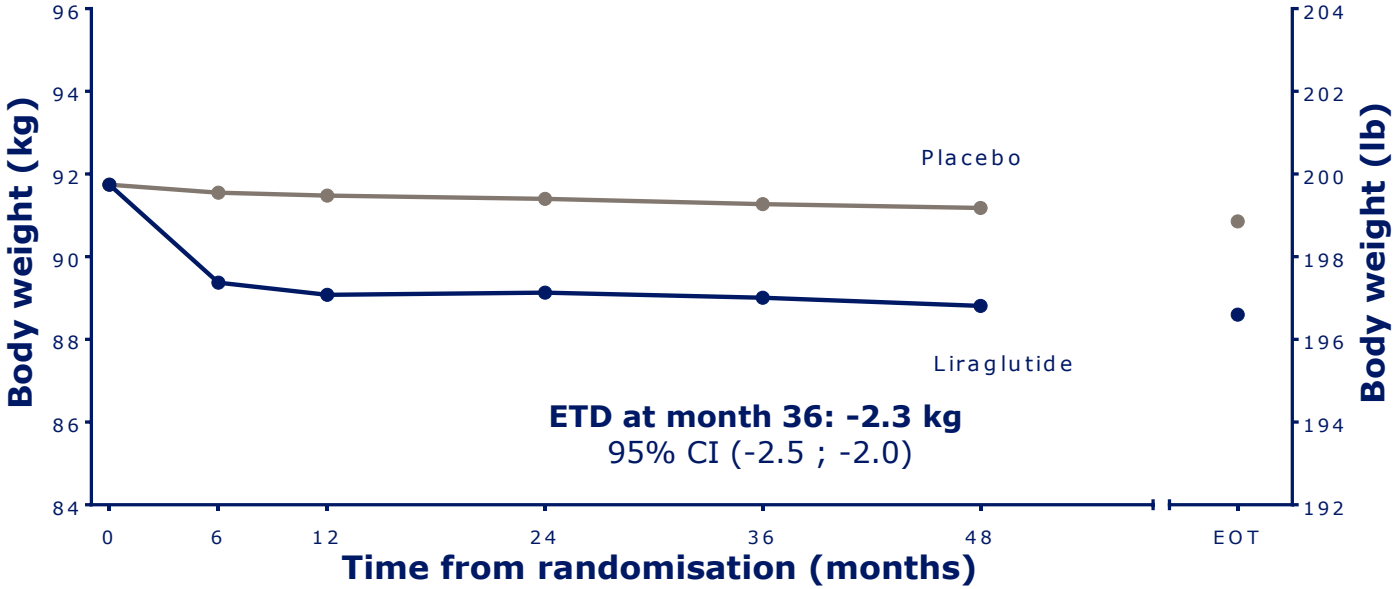


Number of patients at each visit

Liraglutide	4668	4402	4355	4295	4135	4034	3877	3810	2349	809	101	3705
Placebo	4672	4413	4355	4235	4030	3905	3742	3640	2303	756	87	3561

Data are estimated mean values from randomisation to EOT.
CI, confidence interval; EOT, end of trial; ETD, estimated treatment difference; HbA_{1c}, glycosylated haemoglobin.
Marso SP et al. *N Engl J Med* 2016. DOI: 10.1056/NEJMoa1603827.

Body weight

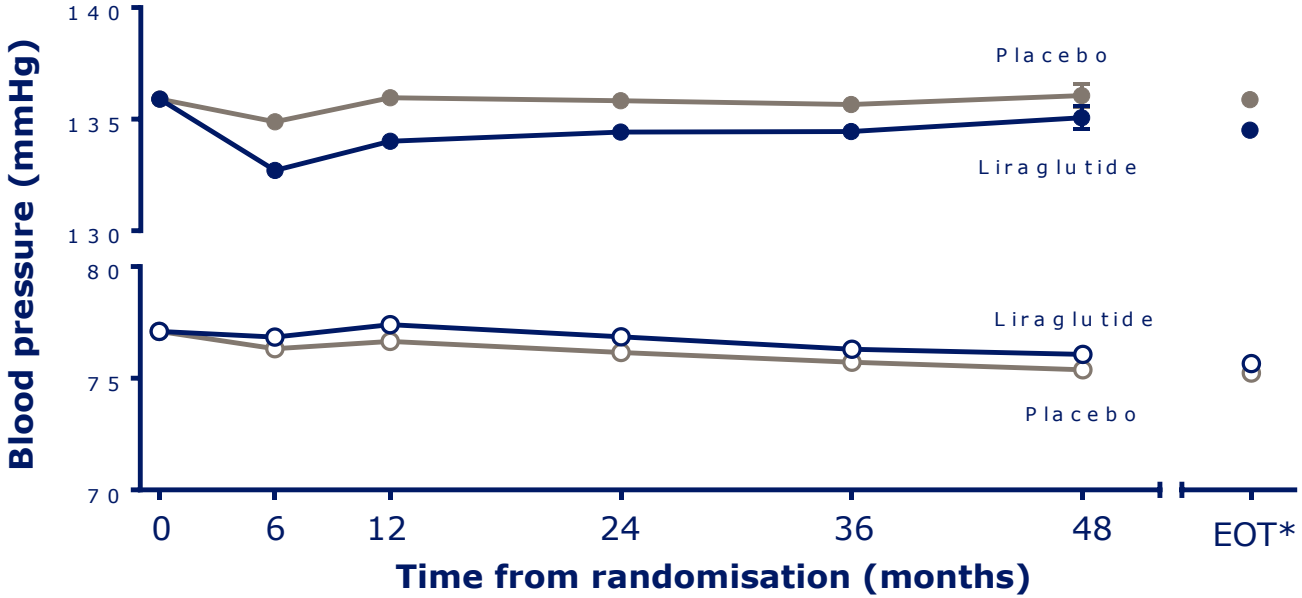


Number of patients at each visit

Liraglutide	4667	4434	4324	4088	3835	824	3708
Placebo	4671	4423	4285	3970	3680	766	3555

Data are estimated mean values from randomisation to EOT.
CI, confidence interval; EOT, end of trial; ETD, estimated treatment difference.
Marso SP et al. *N Engl J Med* 2016. DOI: 10.1056/NEJMoa1603827.

Blood pressure



SBP
ETD at month 36: -1.2 mmHg
95% CI (-1.9 ; -0.5)

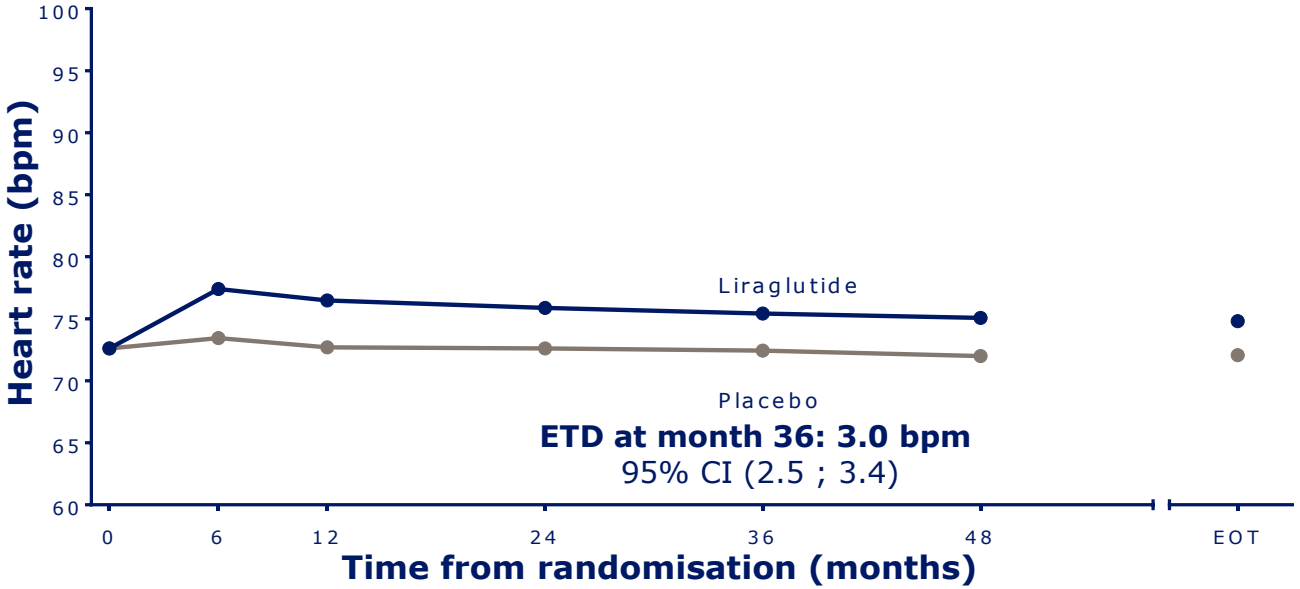
DBP
ETD at month 36: 0.6 mmHg
95% CI (0.2 ; 1.0)

Number of patients at each visit

Liraglutide	4668	4445	4332	4107	3859	823	3722
Placebo	4672	4435	4295	3975	3699	767	3570

Data are estimated mean values from randomisation to EOT; *EOT may be any time from month 42 onwards.
CI, confidence interval; DBP, diastolic blood pressure; EOT, end of trial; ETD, estimated treatment difference; SBP, systolic blood pressure.
Marso SP et al. *N Engl J Med* 2016. In press.

Heart rate

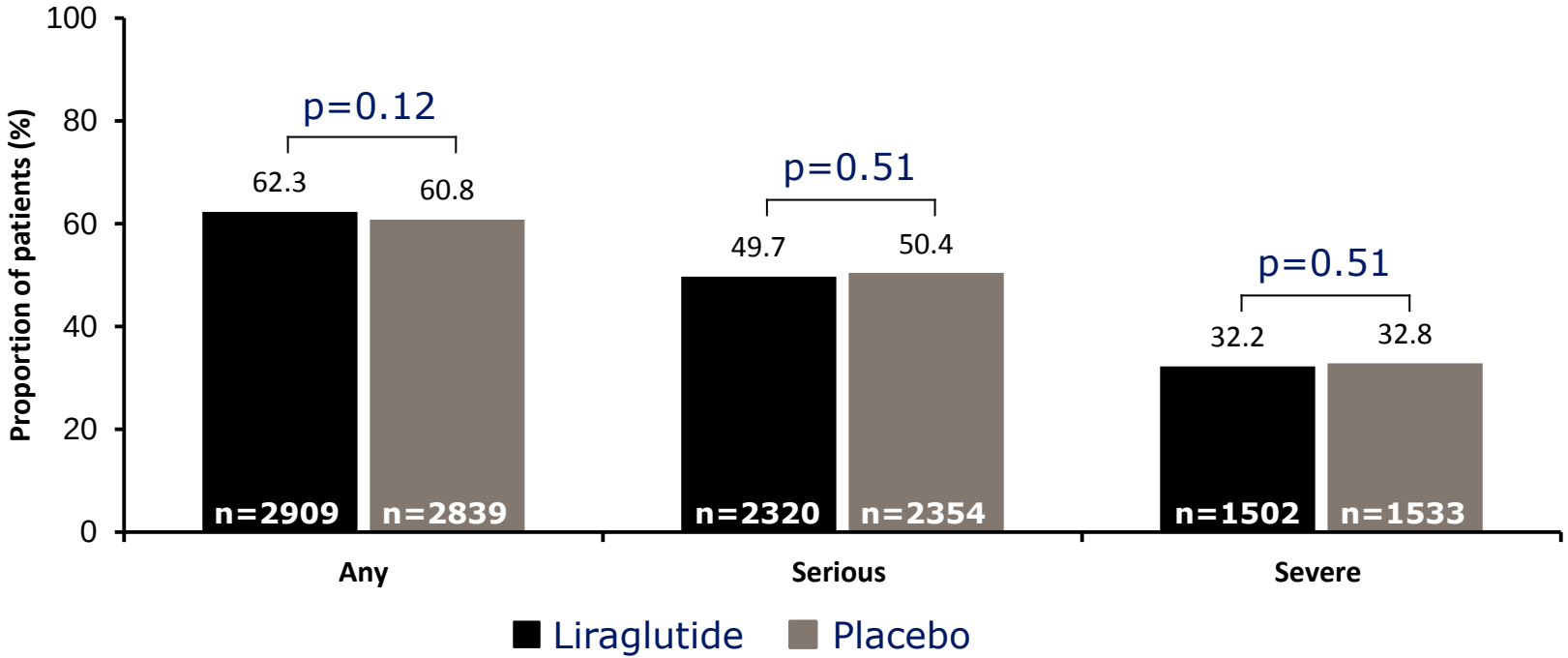


Number of patients at each visit

Liraglutide	4668	4442	4330	4099	3853	824	3722
Placebo	4672	4434	4294	3971	3695	767	3569

Data are estimated mean values from randomisation to EOT.
Bpm, beats per minute; CI, confidence interval; EOT, end of trial; ETD, estimated treatment difference.
Marso SP et al. *N Engl J Med* 2016. DOI: 10.1056/NEJMoa1603827.

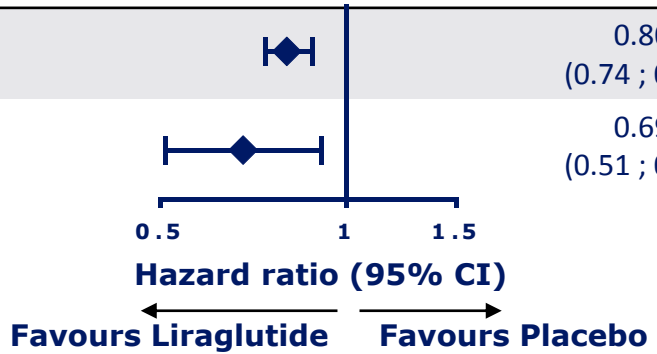
Adverse events



Full analysis set.
A serious adverse event was defined as an experience that at any dose resulted in any of the following: death, a life-threatening experience, in-patient hospitalisation or prolongation of hospitalisation, persistent or significant disability/incapacity, congenital anomaly/birth defect, important medical events that may jeopardise the patient based upon appropriate medical judgement. A severe adverse event was defined as a non-serious adverse event that resulted in considerable interference with the patient's daily activities. N, number of patients.
Marso SP et al. *N Engl J Med* 2016. DOI: 10.1056/NEJMoa1603827.

Hypoglycemia

	Rate ratio (95% CI)	p-value	Liraglutide N	Liraglutide %	Placebo N	Placebo %
Confirmed hypoglycemia	0.80 (0.74 ; 0.88)	<0.001	2039	43.7	2130	45.6
Severe hypoglycemia	0.69 (0.51 ; 0.93)	0.016	114	2.4	153	3.3



Confirmed hypoglycaemia was defined as plasma glucose level of less than 56 mg per decilitre (3.1 mmol per litre) or a severe event. Severe hypoglycaemia was defined as hypoglycaemia for which the patient required assistance from a third party. Analysed using a negative binomial regression model.
CI, confidence interval.
Marso SP et al. *N Engl J Med* 2016. DOI: 10.1056/NEJMoa1603827.

Pancreatitis (confirmed by adjudication)

	Liraglutide		Placebo		p-value
	N	%	N	%	
Acute pancreatitis	18	0.4	23	0.5	0.44
Chronic pancreatitis	0	0.0	2	0.0	0.16

Full analysis set. The occurrence of pancreatitis was adjudicated by the event adjudication committee. P-values were calculated by means of Pearson's chi-square test
%, proportion of patients; N, number of patients.
Marso SP et al. *N Engl J Med* 2016. DOI: 10.1056/NEJMoa1603827.

Lyxumia



Lixisenatide is an once daily prandial GLP1

Lixisenatide is indicated for the treatment of adults with T2DM to achieve glycemic control in combination with oral glucose-lowering medicinal products and/or basal insulin when these, together with diet and exercise, do not provide adequate glycaemic control





Starting dose: 10 µg QD for 14 days

Fixed maintenance dose: 20 µg QD is started on day 15

SmPC July 2014.

Short-acting GLP-1 RAs are more effective in lowering PPG, insulin secretion and Gastric Emptying Rate

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)

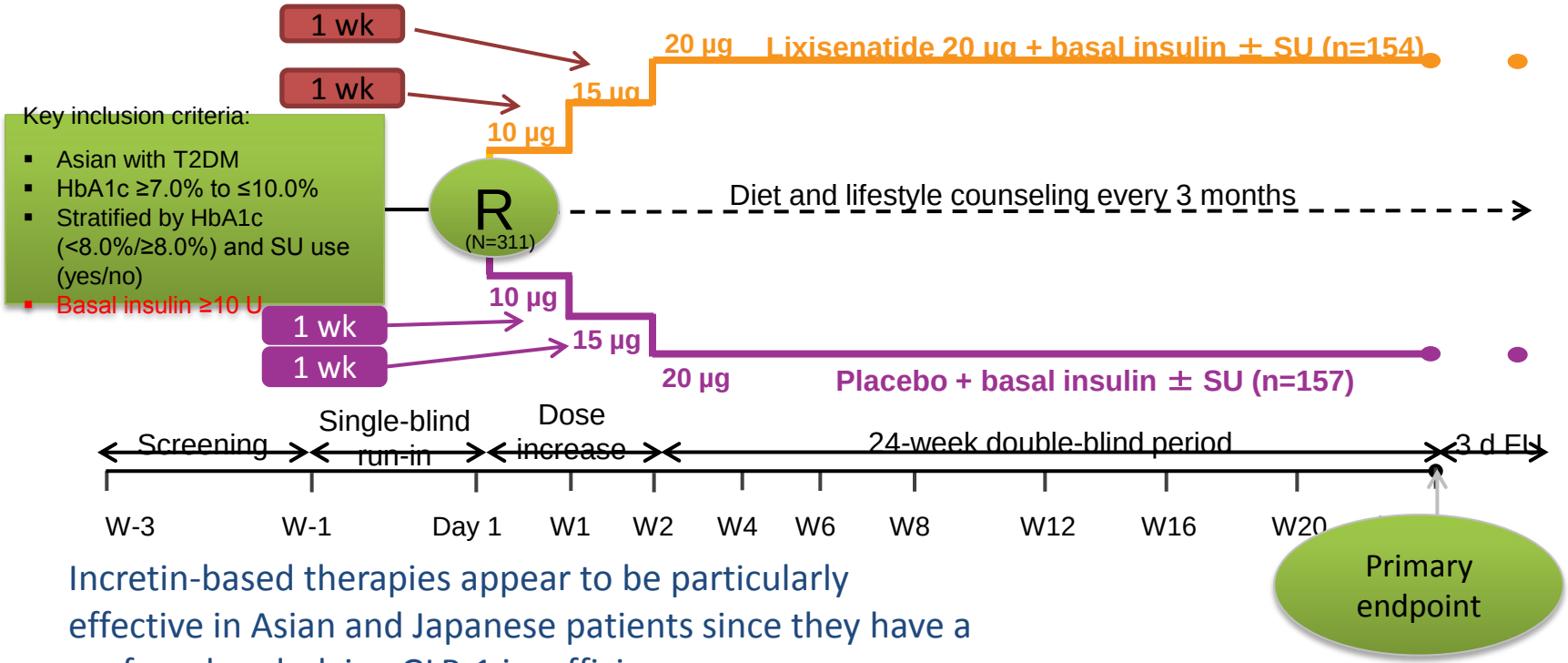
GLP-1, glucagon-like peptide 1; LAR, long-acting release.

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

Table 6 Phase 3 GETGOAL Trials with Lixisenatide[56-64]

Trial	Study drug	Lixisenatide outcomes vs comparator drugs
GETGOAL-Mono	Lixisenatide 1-step AM vs 2-step AM vs placebo; 12-week study	HbA_{1c}: –0.66% 1-step vs –0.54% 2-step Achieved HbA_{1c} goal (<7%): 46.5% 1-step vs 52.2% 2-step Decrease in body weight: ~2 kg in both groups Symptomatic hypoglycemia: 1.7% in lixisenatide groups vs 1.6% in placebo groups Significant improvements in HbA_{1c}: 2-hr PPG, FPG vs placebo
GETGOAL-F1	Lixisenatide 1-step AM vs 2-step AM; all concurrently taking metformin; 24-week study	HbA_{1c}: –0.9% vs –0.8% vs –0.4% Improved FPG: –0.5 vs –0.6 vs +0.1 mmol/L Body weight: –2.6 kg vs –2.7 kg vs –1.6 kg Symptomatic hypoglycemia: 1.9% vs 2.5% vs 0.6%
GETGOAL-S	Lixisenatide 2-step AM vs placebo; all concurrently taking sulfonylurea; 24-week study	HbA_{1c}: –1.1% mean significant difference vs placebo Significant 2-hr postprandial glucose & FPG vs placebo Body weight: –1.12 kg vs –1.02 kg GI adverse effects: 52.6% vs 29.4% Symptomatic hypoglycemia: 17.1% vs 9.8% No cases of severe symptomatic hypoglycemia in either group
GETGOAL-M-ASIA	Lixisenatide 2-step AM vs placebo; all concurrently taking metformin + sulfonylurea; 24-week study	HbA_{1c} reduction: –0.57% (significant difference) Superior to placebo in lowering 2-hr postprandial glucose Body weight in lixisenatide group trended to decrease
		Significantly less nausea events: 24.5% vs 35.1%
GETGOAL-M	Lixisenatide 2-step AM or PM vs placebo; all concurrently taking metformin; 24-week study (similar to GETGOAL-F1)	Significant HbA_{1c} reduction: –0.36% difference vs placebo Significant reduction in 2-hr PPG vs placebo No difference in weight loss Nausea: 16.3% vs 2.6% Symptomatic hypoglycemia: 5.6% vs 2.6% No severe symptomatic hypoglycemia
GETGOAL-Mono JAPAN LTS	Lixisenatide 1-step AM vs 2-step AM; 52-week study with primary end point on safety measures	Nausea: 59% vs 36.4% Symptomatic hypoglycemia: 0% vs 6.1% HbA_{1c}, FPG, body weight reduced from baseline
GETGOAL-L-ASIA	Lixisenatide 2-step AM vs placebo; all concurrently taking basal insulin; 24-week study (similar to GETGOAL-S)	HbA_{1c} reduction: –0.88% vs placebo Significant improvement in 2-hr postprandial glucose Nausea and vomiting: 18.2% vs 1.9% Symptomatic hypoglycemia: 42.9% vs 23.6% No severe hypoglycemia
GETGOAL-M-ASIA	Lixisenatide 2-step AM vs placebo; all concurrently taking metformin + sulfonylurea; 24-week study	HbA_{1c} reduction: –0.57% (significant difference) Superior to placebo in lowering 2-hr postprandial glucose Body weight in lixisenatide group trended to decrease

GetGoal-L-Asia: Adding lixisenatide to basal insulin in the Asia population



Incretin-based therapies appear to be particularly effective in Asian and Japanese patients since they have a profound underlying GLP-1 insufficiency

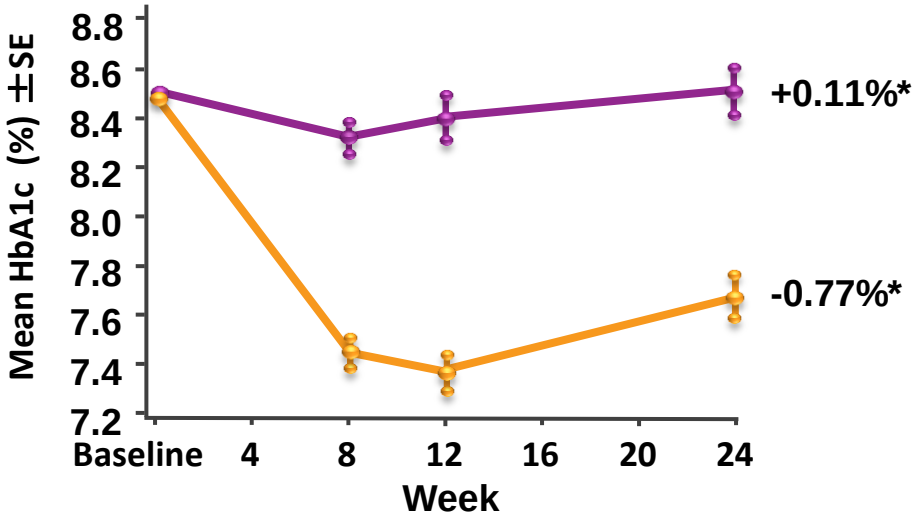
FU: follow-up; R: randomisation; HbA1c: glycated haemoglobin; T2DM: type 2 diabetes mellitus; SU: sulphonylurea.

Seino Y, et al. Diabetes Obes Metab. 2012;14:910–917.

GetGoal-L-Asia:

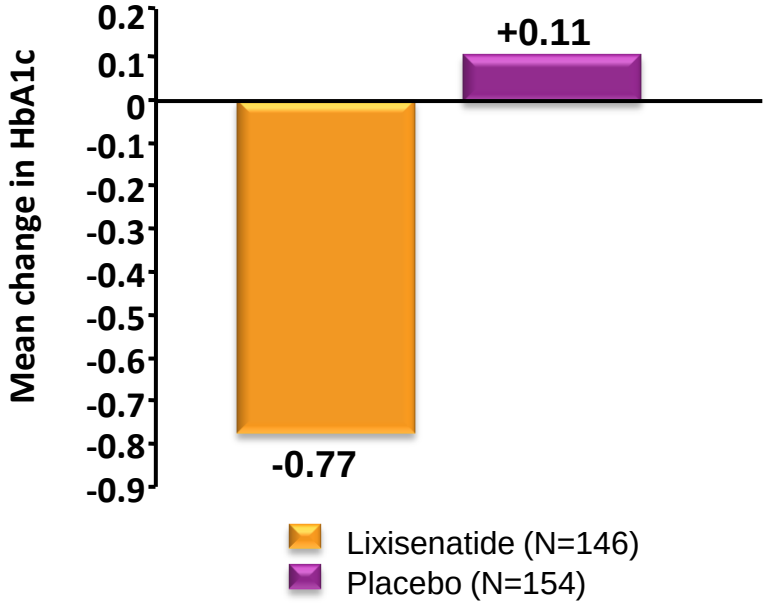
Lixisenatide lowered HbA1c by ~0.9%

Mean change (± SE) in HbA1c over 24 weeks



LS mean change in HbA1c vs placebo after 24 weeks:

-0.88% [95% CI=-1.116, -0.650]; *P*<0.0001

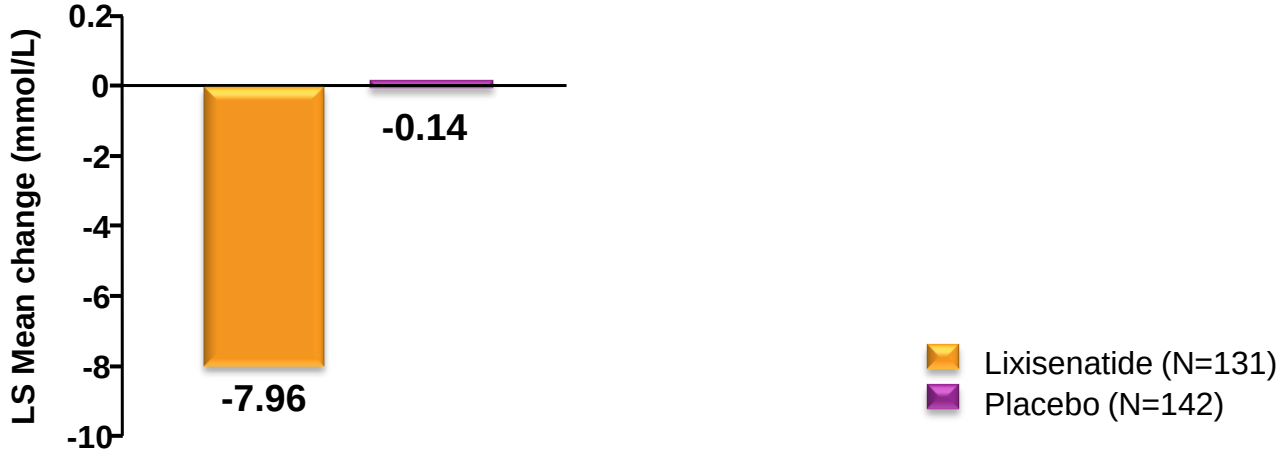


LS: least squares; CI: confidence interval; SE: standard error.

Seino Y, et al. Diabetes Obes Metab. 2012;14:910–917.

GetGoal-L-Asia:
Lixisenatide lowered 2h PPG by ~8mmol/L

LS mean change in 2-hour PPG after 24 weeks:
LS mean difference vs placebo: –7.83 mmol/L
[95% CI: –8.89, –6.77]; p<0.0001



- Significant differences vs placebo were also achieved for LS mean changes in:
  - **Average 7-point SMPG**: –1.91 ± 0.27 mmol/l for lixisenatide vs –0.56 ± 0.27 mmol/l for placebo (p<0.0001)
  - **FPG**: –0.42 ± 0.31mmol/l for lixisenatide vs +0.25 ± 0.30 mmol/l for placebo (p=0.0187)
  - **Daily basal insulin dose**: –1.39 ± 0.46 U for lixisenatide vs –0.11 ± 0.44 U for placebo (p=0.0019)

Seino Y, et al. Diabetes Obes Metab. 2012;14:910–917.

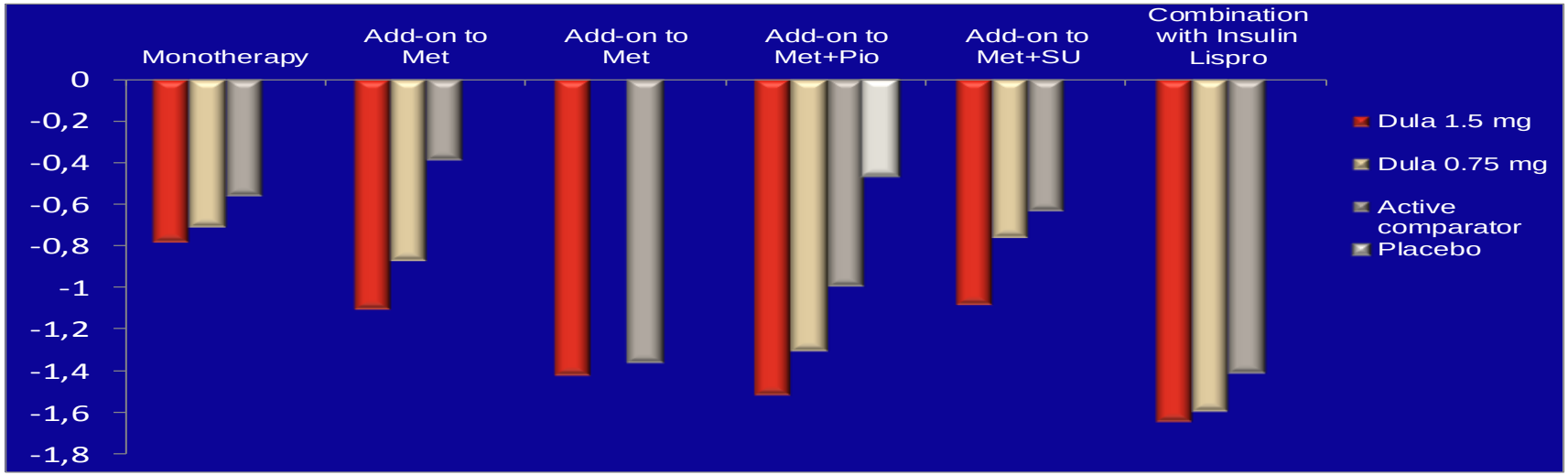
Trulicity


trulicity.
(dulaglutide)
injection
1.5 mg/0.5 mL
trulicity.
(dulaglutide)
injection
0.75 mg/0.5 mL

Dulaglutide AWARD Programme

HbA_{1c} Reduction Across Trials

Baseline HbA_{1c} (%)	**7.6**	**8.1**	**8.1**	**8.1**	**8.1**	**8.5**
	AWARD-3[1]	AWARD-5[2]	AWARD-6[3]	AWARD-1[4]	AWARD-2[5]	AWARD-4[6]
	Monotherapy	Add-on to Met	Add-on to Met	Add-on to Met+Pio	Add-on to Met+SU	Combination with Insulin Lispro
	vs	vs	vs	vs	vs	vs
	Metformin	Sitagliptin	Liraglutide	Exenatide	Glargine	Glargine & lispro



1. Umpierrez G et al. *Diabetes Care* 2014;37(8):2168–76; 2. Nauck MA et al. *Diabetes Care* 2014;37(8):2149–58;
3.Dungan KM et al Lancet. 2014 Oct 11;384(9951):1349-57.doi: 10.1016/S0140-6736(14)60976-4.Epub 2014 Jul 10
4. Wysham C et al. *Diabetes Care* 2014;37(8):2159–67; 5. Giorgino F et al. *Session: OP 07 GLP-1 analogues: clinical efficacy;* 50th EASD Annual Meeting, Vienna, Austria, 15–19 September 2014; 6. Jendle J et al *Session: OP 07 GLP-1 analogues: clinical efficacy*, 50th EASD Annual Meeting, Vienna, Austria, 15–19 September 2014.

Table 5 Phase 3 AWARD Trials with Dulaglutide[48-54]

Trial	Study drug	Dulaglutide outcomes vs comparator drugs
AWARD-1	Dulaglutide 1.5 mg once weekly vs dulaglutide 0.75 mg vs exenatide 10 µg twice daily; all concurrently taking metformin and pioglitazone (26-week study)	HbA_{1c}: –1.51% vs –1.3% vs –0.99% Body weight: –1.3 kg vs +0.2 kg vs –1.07 kg No severe hypoglycemia w/ dulaglutide Very similar rates of nausea, vomiting, & diarrhea with dulaglutide 1.5 mg & exenatide Less adverse effects w/ dulaglutide 0.75 mg
AWARD-2	Dulaglutide 1.5 mg vs dulaglutide 0.75 mg vs insulin glargine; all concurrently taking metformin and glimepiride (52-week study)	HbA_{1c}: –1.08% vs -0.76% vs –0.63% Superiority met w/ dulaglutide 1.5 & noninferiority w/ 0.75-mg dose Hypoglycemia rates lower w/ dulaglutide More nausea and diarrhea w/ dulaglutide than glargine
AWARD-5	Dulaglutide 1.5 mg vs dulaglutide 0.75 mg vs sitagliptin 100 mg; all concurrently taking metformin (52-week study)	HbA_{1c}: –1.10% vs –0.87% vs –0.39% Both doses met superiority to sitagliptin More nausea, diarrhea, & vomiting w/ dulaglutide
AWARD-6	Dulaglutide 1.5 mg vs liraglutide 1.8 mg; all concurrently taking metformin (26-week study)	HbA_{1c}: –1.42% vs –1.36%; met noninferiority criteria Greater weight loss w/ liraglutide (–2.9 kg vs –3.61 kg) Nausea: 20% vs 18% Diarrhea: 12% vs 12% Dyspepsia: 8% vs 6% Vomiting: 7% vs 8%
AWARD-8	Dulaglutide 1.5 mg vs placebo; all concurrently taking glimepiride	HbA_{1c} difference: –1.3%; superior to placebo Fasting plasma glucose difference: –33.54 mg/dL; superior to placebo Weight loss was significant from baseline w/ dulaglutide, but between-groups difference not significant Hypoglycemia higher w/ dulaglutide (2.37 vs 0.07 events/participant annually) No severe hypoglycemic events

AWARD-6 Dulaglutide 1.5 mg vs liraglutide 1.8 mg; all concurrently taking metformin (26-week study)

HbA_{1c}: –1.42% vs –1.36%; met noninferiority criteria
Greater weight loss w/ liraglutide (–2.9 kg vs –3.61 kg)
Nausea: 20% vs 18%
Diarrhea: 12% vs 12%
Dyspepsia: 8% vs 6%
Vomiting: 7% vs 8%

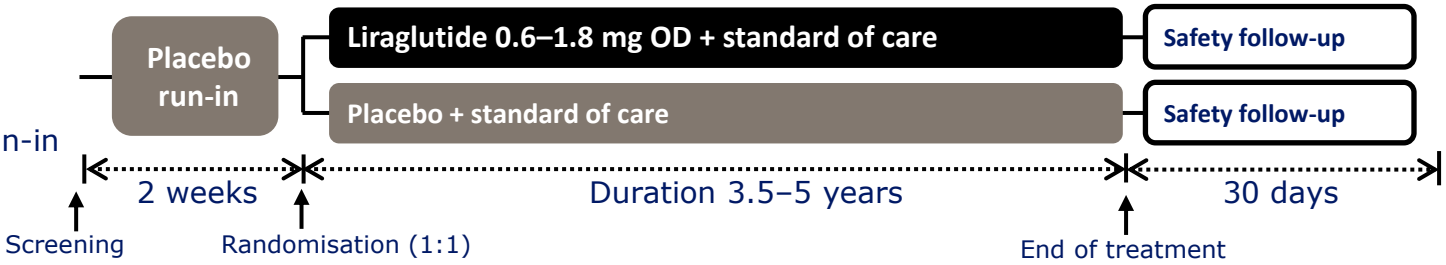
CVOT trial of GLP-1 agonist

CV outcome study	GLP1 RA	Patient size	Patient Type	Major Result	Status
ELIXA	Lixisenatide	6,068	T2DM, ACS within 180 days	Show non-inferior to 4 points MACE to placebo arm for primary composite end point of cardiovascular death, myocardial infarction, stroke, or hospitalization for unstable angina	Completed & Published in 2015
LEADER	Liraglutide	9,340	T2DM with established CVD or CHF	Show superiority to placebo in reducing first occurrence of primary composite endpoint :death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.	Completed & Published in 2016
SUSTAIN-6** (Semaglutide not available in market)	Semaglutide	3,297	T2DM with established CVD or CHF or CKD	Show superiority to placebo in reducing first occurrence of primary composite endpoint :death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.	Completed & Published in 2016
EXSCEL	Exenatide QW	14,752	T2DM, with or without additional cardiovascular risk factors or prior cardiovascular events	Non-inferior to placebo with respect to safety (P<0.001 for noninferiority) but with fewer CV events. Significant reduce all-cause mortality	Completed & Published in Sept 2017

LEADER: Study design

9340 patients

- Double blinded
- 2-week placebo run-in



Key inclusion criteria

- T2DM, HbA_{1c} ≥7.0%
- Antidiabetic drug naïve; OADs and/or basal/premix insulin
- Age ≥50 years and established CV disease or chronic renal failure
  or
- Age ≥60 years and risk factors for CV disease

Key exclusion criteria

- T1DM
- Use of GLP-1RAs, DPP-4i, pramlintide, or rapid-acting insulin
- Familial or personal history of MEN-2 or MTC

CV, cardiovascular; HbA_{1c}, glycosylated haemoglobin; OAD, oral antidiabetic drug; OD, once daily; T2DM, type 2 diabetes mellitus.
Marso SP et al. *N Engl J Med* 2016. DOI: 10.1056/NEJMoa1603827.

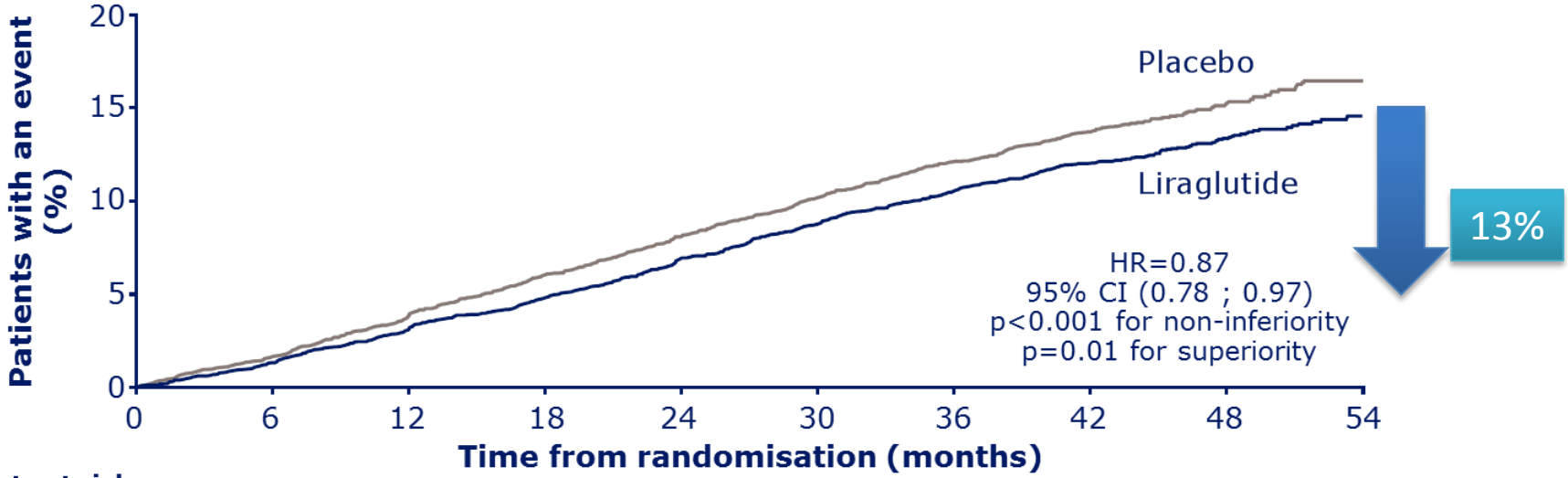
Primary and key secondary outcomes

Primary outcome	**Time to first MACE composed of** • CV death • Non-fatal MI • Non-fatal stroke
Key secondary outcomes	**Time to first occurrence of** • Expanded composite CV outcome (CV death, non-fatal MI, non-fatal stroke, coronary revascularisation, unstable angina pectoris requiring hospitalisation, or hospitalisation for heart failure) • All-cause death • Each individual component of expanded composite CV outcome

CV, cardiovascular; MACE, major adverse cardiovascular event; MI, myocardial infarction.
Marso SP et al. *N Engl J Med* 2016. DOI: 10.1056/NEJMoa1603827.

Primary outcome

CV death, non-fatal myocardial infarction, or non-fatal stroke



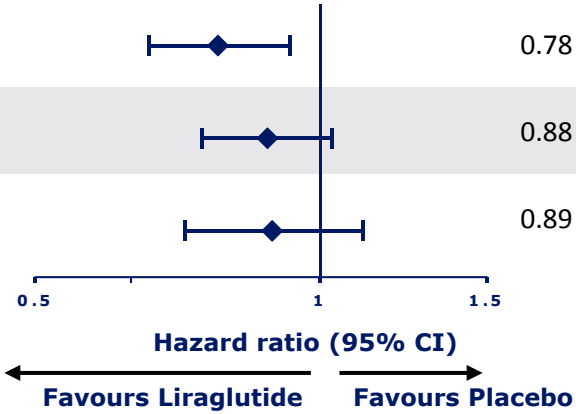
Patients at risk

Liraglutide	4668	4593	4496	4400	4280	4172	4072	3982	1562	424
Placebo	4672	4588	4473	4352	4237	4123	4010	3914	1543	407

The primary composite outcome in the time-to-event analysis was the first occurrence of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke. The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months, because less than 10% of the patients had an observation time beyond 54 months.
CI: confidence interval; CV: cardiovascular; HR: hazard ratio.
Marso SP et al. *N Engl J Med* 2016. DOI: 10.1056/NEJMoa1603827.

Individual components of the primary endpoint

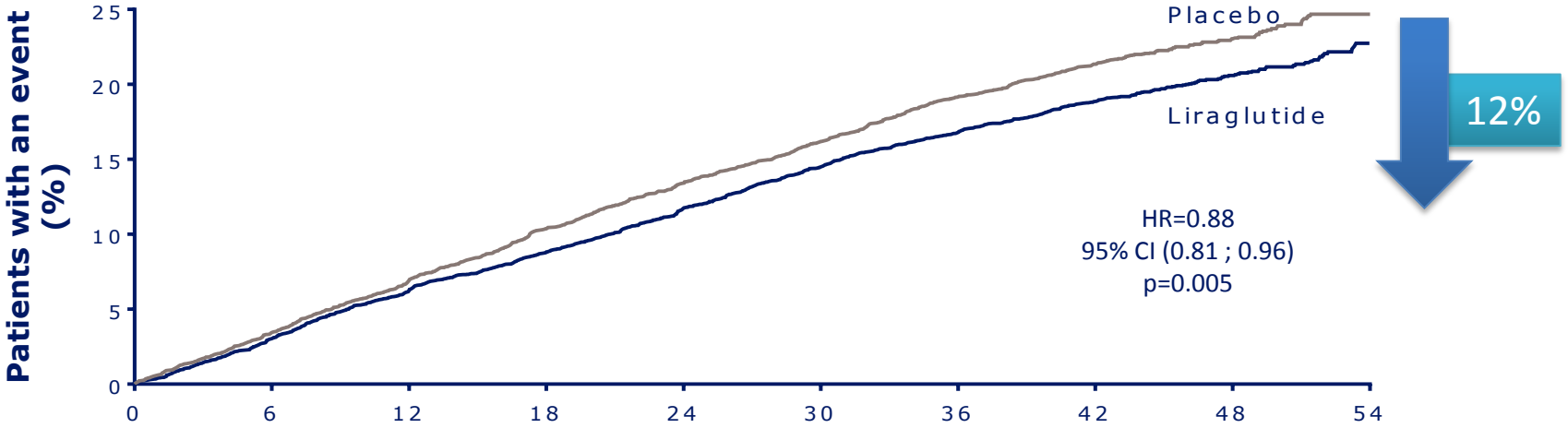
	Hazard ratio (95% CI)	p-value	Liraglutide N	Liraglutide %	Liraglutide R	Placebo N	Placebo %	Placebo R
Number of patients			**4668**	**100.0**		**4672**	**100.0**	
CV death	0.78 (0.66 ; 0.93)	0.007			1.2	278	6.0	1.6
Non-fatal MI	0.88 (0.75 ; 1.03)	0.11	281	6.0	1.6	317	6.8	1.8
Non-fatal stroke	0.89 (0.72 ; 1.11)	0.30	159	3.4	0.9	177	3.8	1.0



Hazard ratios and p-values were estimated with the use of a Cox proportional-hazards model with treatment as a covariate.
%, percentage of group; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; N, number of patients; R, incidence rate per 100 patient-years of observation.
Marso SP et al. *N Engl J Med* 2016. DOI: 10.1056/NEJMoa1603827.

Expanded MACE

CV death, non-fatal MI, non-fatal stroke, coronary revascularisation, or hospitalisation for unstable angina pectoris or heart failure

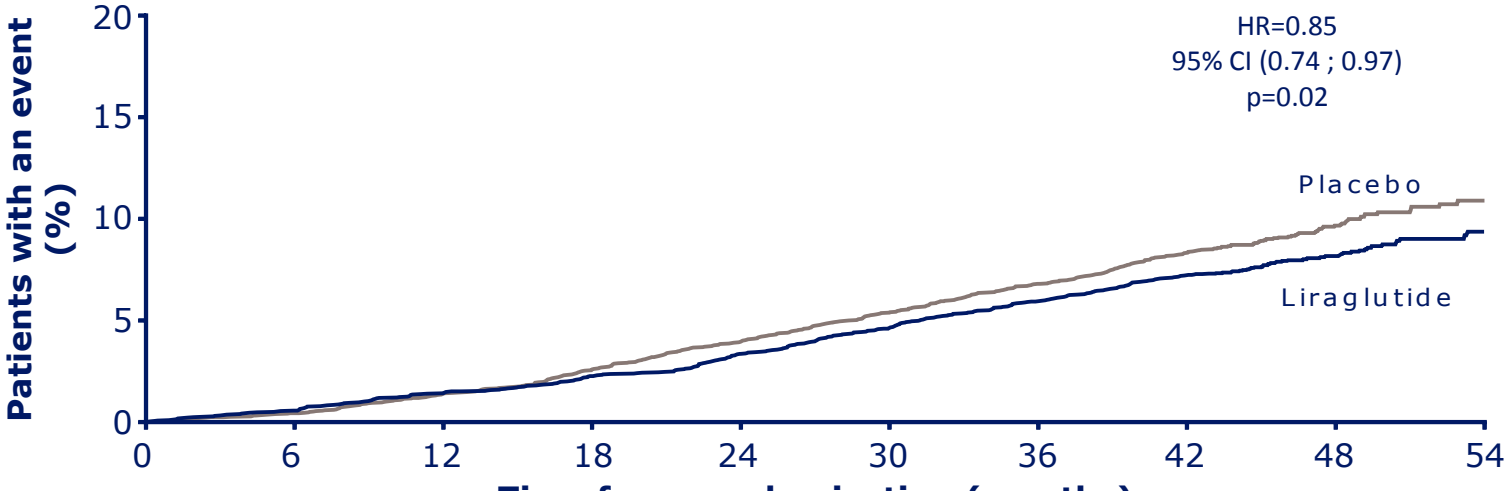


Patients at risk

Liraglutide	4668	4515	4356	4221	4063	3914	3793	3682	1452	395
Placebo	4672	4506	4336	4157	4002	3857	3697	3581	1410	366

The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months, because less than 10% of the patients had an observation time beyond 54 months.
CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular event.
Marso SP et al. *N Engl J Med* 2016. DOI: 10.1056/NEJMoa1603827.

All-cause death



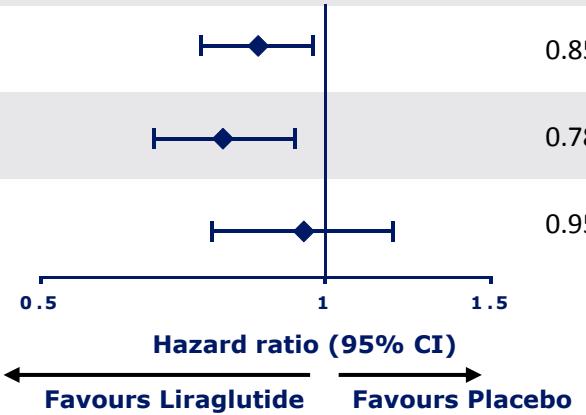
Patients at risk

Liraglutide	4668	4641	4599	4558	4505	4445	4382	4322	1723	484
Placebo	4672	4648	4601	4546	4479	4407	4338	4268	1709	465

The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months, because less than 10% of the patients had an observation time beyond 54 months.
CI, confidence interval; HR, hazard ratio.
Marso SP et al. *N Engl J Med* 2016. DOI: 10.1056/NEJMoa1603827.

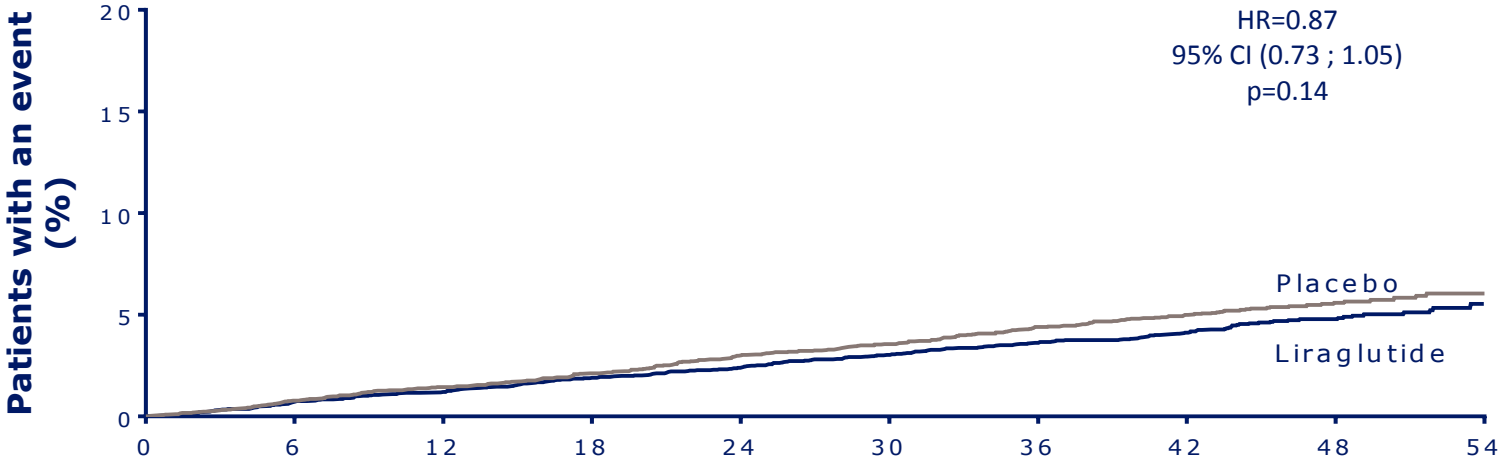
Time to all-cause, CV and non-CV death

	Hazard ratio (95% CI)	p-value	Liraglutide N	Liraglutide %	Liraglutide R	Placebo N	Placebo %	Placebo R
Number of patients			**4668**	**100.0**		**4672**	**100.0**	
All-cause death	0.85 (0.74 ; 0.97)	0.02			2.1	447	9.6	2.5
CV death	0.78 (0.66 ; 0.93)	0.007			1.2	278	6.0	1.6
Non-CV death	0.95 (0.76 ; 1.18)	0.66	162	3.5	0.9	169	3.6	1.0



Hazard ratios and p-values were estimated with the use of a Cox proportional-hazards model with treatment as a covariate.
%, percentage of group; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; N, number of patients; R, incidence rate per 100 patient-years of exposure.
Marso SP et al. *N Engl J Med* 2016. DOI: 10.1056/NEJMoa1603827.

Hospitalisation for heart failure



Patients at risk

Liraglutide	4668	4612	4550	4483	4414	4337	4258	4185	1662	467
Placebo	4672	4612	4540	4464	4372	4288	4187	4107	1647	442

The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months, because less than 10% of the patients had an observation time beyond 54 months.
CI, confidence interval; HR, hazard ratio.
Marso SP et al. *N Engl J Med* 2016. DOI: 10.1056/NEJMoa1603827.

Secondary outcomes

Myocardial infarction, stroke, transient ischaemic attack and coronary revascularisation

	Liraglutide (N=4668)			Placebo (N=4672)			HR	95% CI	p-value
	N	%	R	N	%	R			
Myocardial infarction*	292	6.3	1.6	339	7.3	1.9	0.86	0.73 ; 1.00	0.046
Fatal*	17	0.4	0.1	28	0.6	0.2	0.60	0.33 ; 1.10	0.10
Non-fatal	281	6.0	1.6	317	6.8	1.8	0.88	0.75 ; 1.03	0.11
Silent*	62	1.3	0.3	76	1.6	0.4	0.86	0.61 ; 1.20	0.37
Stroke*	173	3.7	1.0	199	4.3	1.1	0.86	0.71 ; 1.06	0.16
Fatal*	16	0.3	0.1	25	0.5	0.1	0.64	0.34 ; 1.19	0.16
Non-fatal	159	3.4	0.9	177	3.8	1.0	0.89	0.72 ; 1.11	0.30
Transient ischaemic attack*	48	1.0	0.3	60	1.3	0.3	0.79	0.54 ; 1.16	0.23
Coronary revascularisation	405	8.7	2.3	441	9.4	2.5	0.91	0.80 ; 1.04	0.18

*This analysis was not pre-specified. Hazard ratios and p-values estimated using a Cox proportional-hazards model with treatment as a covariate.

%, percentage of group; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; N, number of patients; R, incidence rate per 100 patient-years of observation.

Marso SP et al. *N Engl J Med* 2016. DOI: 10.1056/NEJMoa1603827.

Secondary outcomes

Hospitalisation for UAP, hospitalisation for heart failure, and microvascular events

	Liraglutide (N=4668)			Placebo (N=4672)			HR	95% CI	p-value
	N	%	R	N	%	R			
Hospitalisation for UAP	122	2.6	0.7	124	2.7	0.7	0.98	0.76 ; 1.26	0.87
Hospitalisation for heart failure	218	4.7	1.2	248	5.3	1.4	0.87	0.73 ; 1.05	0.14
Microvascular event	355	7.6	2.0	416	8.9	2.3	0.84	0.73 ; 0.97	0.02
Retinopathy	106	2.3	0.6	92	2.0	0.5	1.15	0.87 ; 1.52	0.33
Nephropathy	268	5.7	1.5	337	7.2	1.9	0.78	0.67 ; 0.92	0.003

Hazard ratios and p-values estimated using a Cox proportional-hazards model with treatment as a covariate.
%, percentage of group; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; N, number of patients; R, incidence rate per 100 patient-years of observation; UAP, unstable angina pectoris.
Marso SP et al. *N Engl J Med* 2016. DOI: 10.1056/NEJMoa1603827.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

EXSCEL

Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes

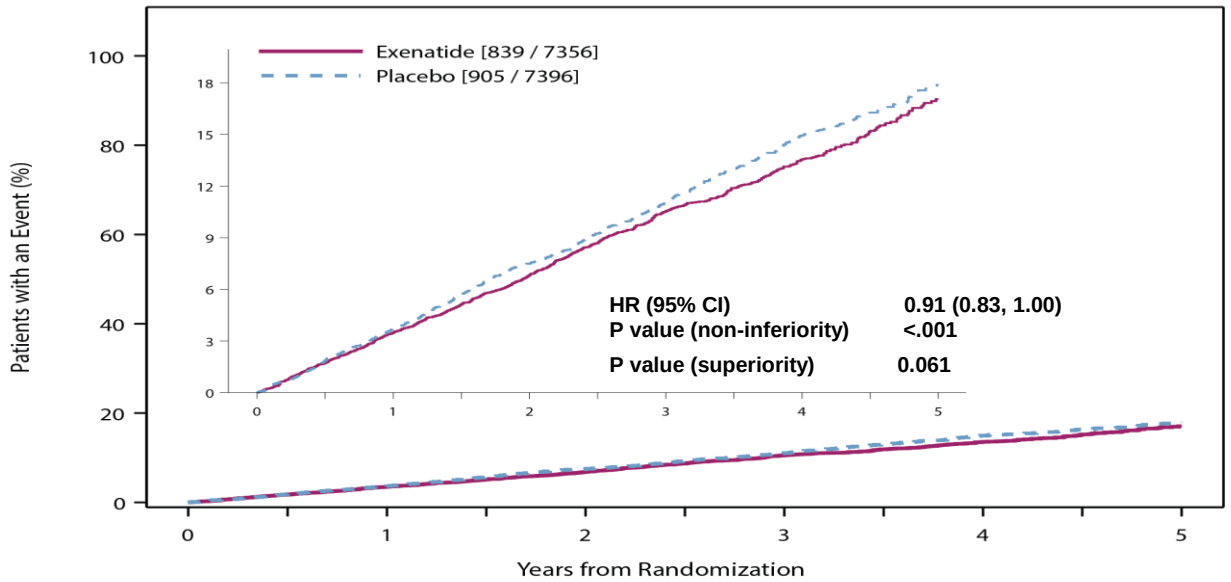
- Study Drug: Exenatide QW
- 14,752 T2DM
  - T2DM +/-previous CVD
  - Median FU 3.2 yrs, once weekly Exenatide QW

- Non-inferior to placebo with respect to safety ($P<0.001$ for noninferiority) but was not superior to placebo with respect to efficacy ($P = 0.06$ for superiority) of MACE (first occurrence of cardiac death, nonfatal MI or nonfatal stroke)
  - Fewer CV events (RRR 9%) but not achieve the superiority.

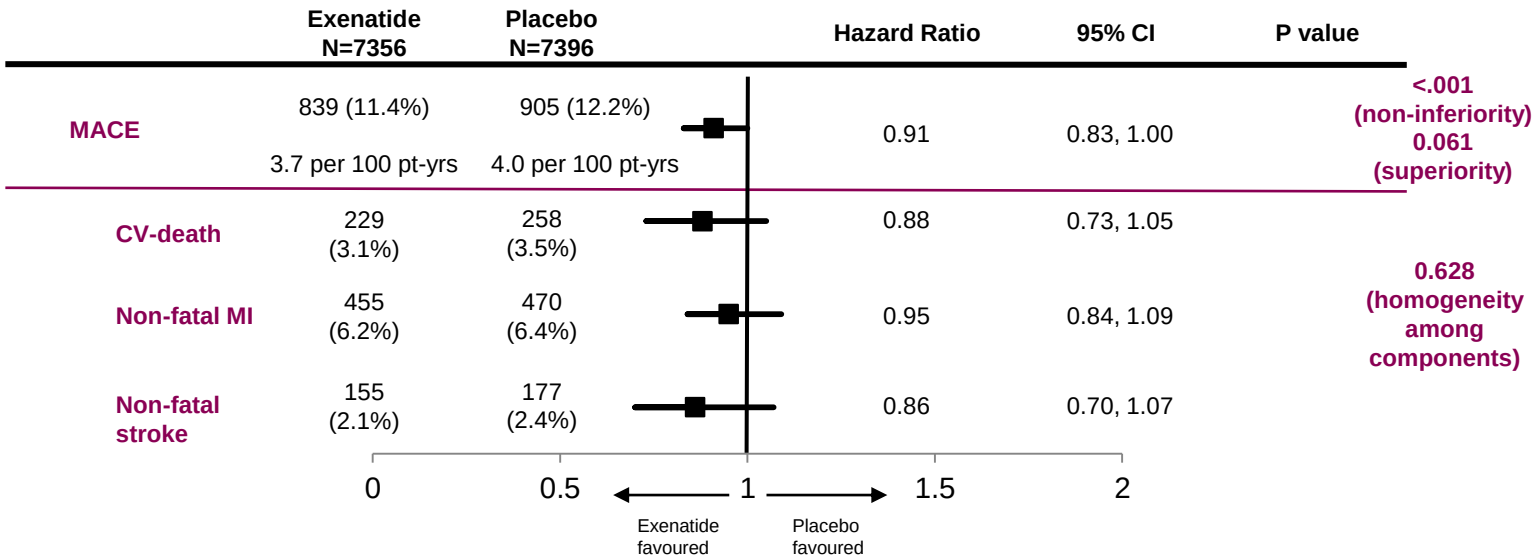
- In a prespecified secondary endpoint, patients on Bydureon had a 14% lower incidence of all-cause mortality

Primary Composite Cardiovascular Outcome

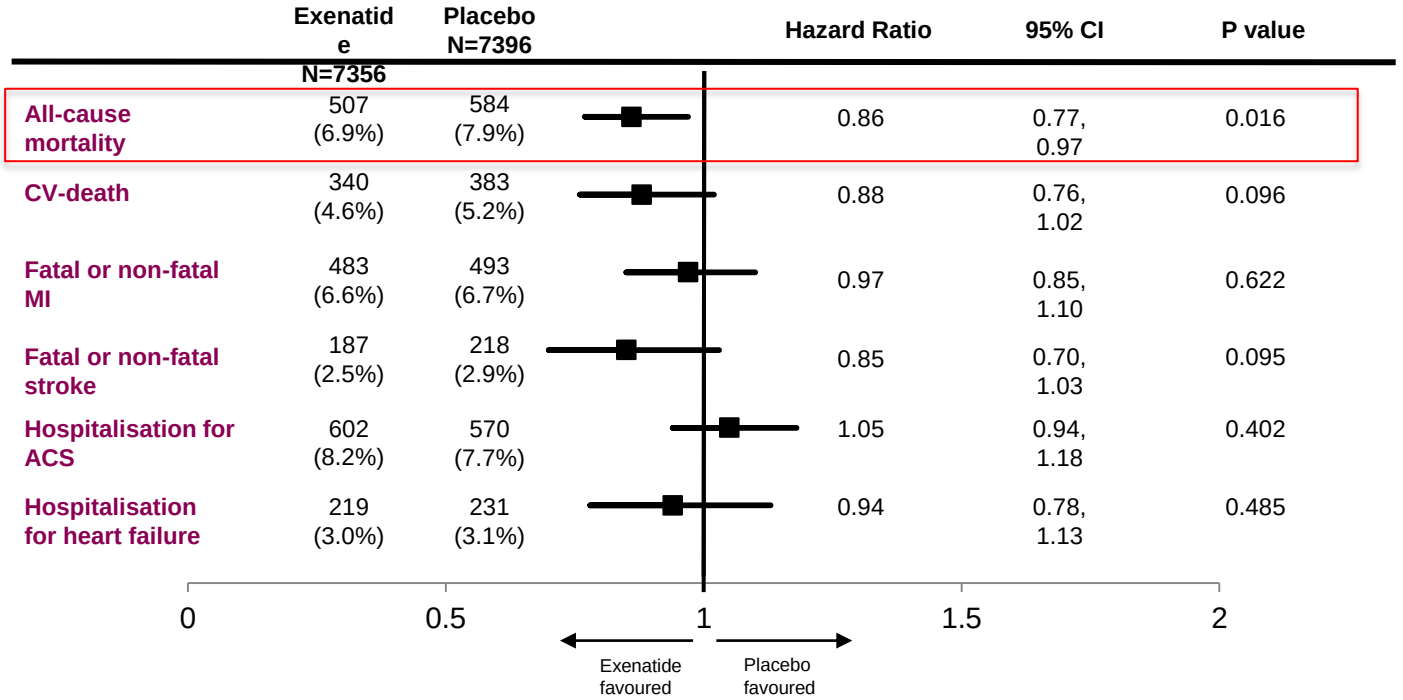
Intention-to-Treat Analysis for Non-inferiority & Superiority



Primary Composite Cardiovascular Outcome
Intention-to-Treat Analysis



Forest Plot of Secondary Endpoints (Intention-to-Treat Analysis)

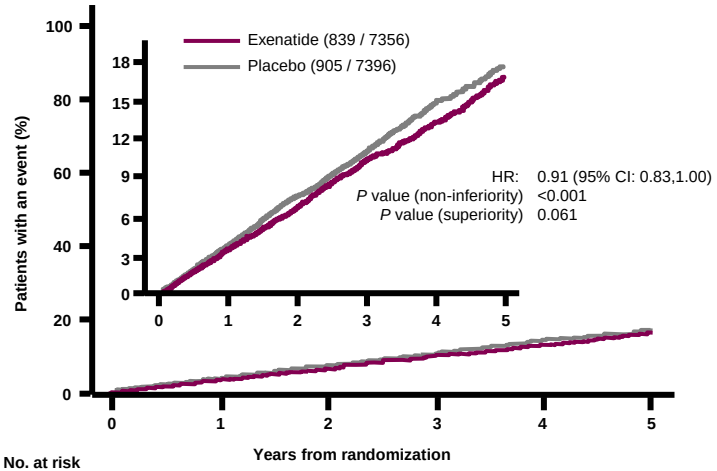


ESXCEL Primary Endpoint: CV Death, Non-fatal MI and Non-fatal stroke (MACE)

- **Showed non-inferior to placebo with respect to safety**
- **direction and magnitude of the cardiovascular outcomes observed were not inconsistent with those seen in LEADER**

EXSCEL

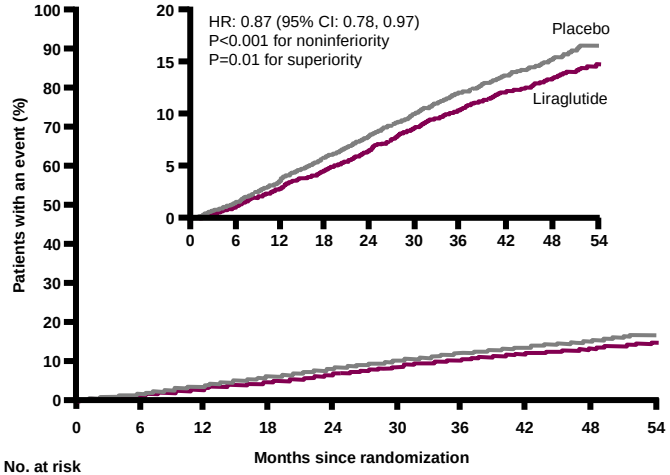
Primary cardiovascular outcome



No. at risk											
Exenatide	7356	7101	6893	6580	5912	4475	3595	3053	2281	1417	727
Placebo	7396	7120	6897	6565	5908	4468	3565	2961	2209	1366	687

LEADER

Primary outcome

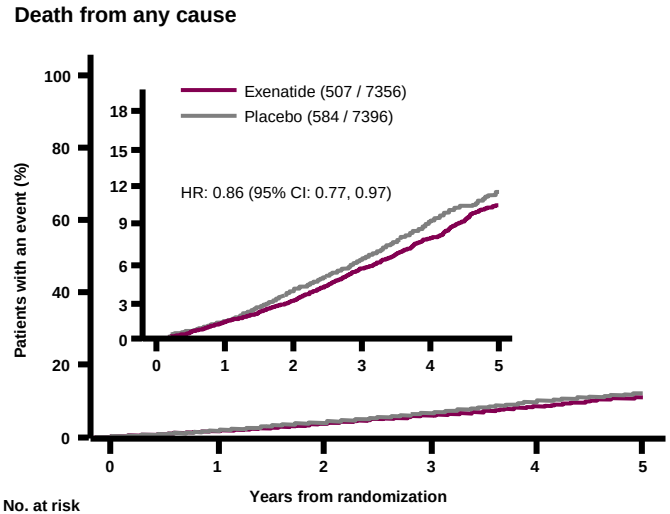


No. at risk											
Liraglutide	4668	4593	4496	4400	4280	4172	4072	3982	1562	424	
Placebo	4672	4588	4473	4352	4237	4123	4010	3914	1543	407	

CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular event; MI, myocardial infarction

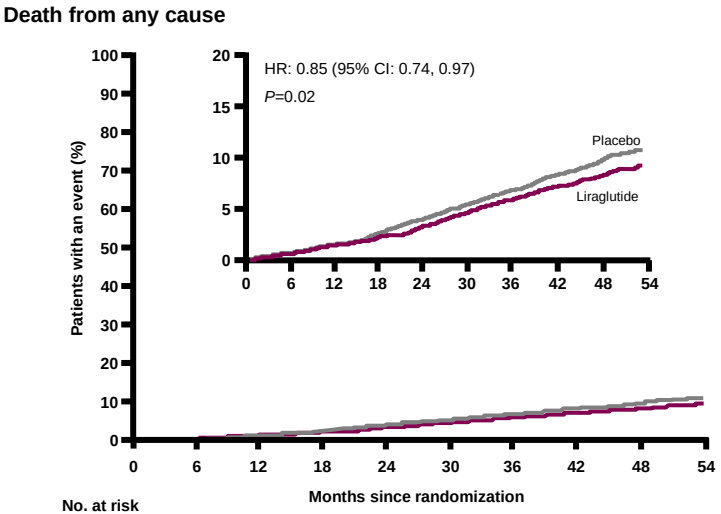
“Death from any cause” in EXSCEL was achieved 14% risk reduction which consistent is similar to the trend of LEADER

EXSCEL



No. at risk											
Exenatide	7356	7304	7234	7028	6433	4991	4095	3518	2698	1726	907
Placebo	7396	7344	7274	7058	6470	5019	4091	3478	2666	1695	892

LEADER

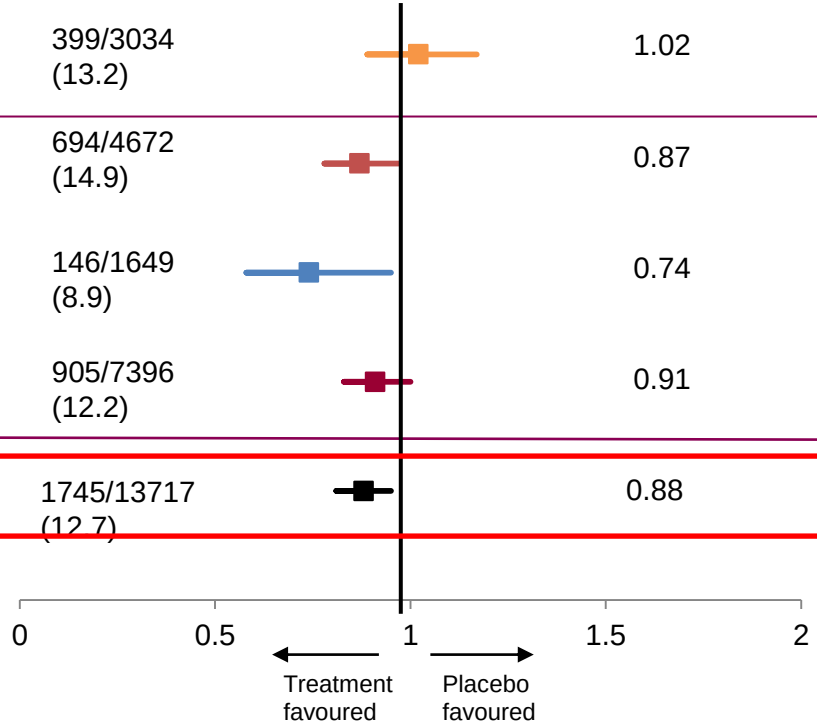


No. at risk											
Liraglutide	4668	4641	4599	4558	4505	4445	4382	4322	1723	484	
Placebo	4672	4648	4601	4546	4479	4407	4338	4268	1709	465	

CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular event; MI, myocardial infarction

3-Point MACE Meta-analysis

	Study drug n/N (%)	Placebo n/N (%)	Hazard Ratio	95% CI	P value
ELIXA (1) ¶ lixisenatide vs. placebo	406/3034 (13.4)	399/3034 (13.2)	1.02	0.89, 1.17	<0.01 (NI) 0.81 (S)
LEADER® (2) liraglutide vs. placebo	608/4668 (13.0)	694/4672 (14.9)	0.87	0.78, 0.97	<0.001 (NI) 0.01 (S)
SUSTAIN-6 (3) semaglutide vs. placebo	108/1648 (6.6)	146/1649 (8.9)	0.74	0.58, 0.95	<0.001 (NI) 0.02 (S)
EXSCEL exenatide vs. placebo	839/7356 (11.4)	905/7396 (12.2)	0.91	0.83, 1.00	<0.001 (NI) 0.061 (S)
Overall *	1555/13672 (11.3)	1745/13717 (12.7)	0.88	0.81, 0.95	0.002



Test for heterogeneity
I^2 = 22%
Q test p-value = 0.28

NI = non-inferiority
S = superiority

[1] Pfeffer MA et al. N Engl J Med 2015; 373: 2247–2257
[2] Marso SP et al. N Engl J Med 2016; 375: 311–322
[3] Marso SP et al. N Engl J Med 2016; 375: 1834–1844

¶ Use of MACE-4 primary composite endpoint

* Excludes data from ELIXA

Key Message

- LEADER and SUSTAIN-6 trials showed GLP-1 receptor agonist is superior to placebo in reducing first occurrence of primary composite endpoint point of death from CV causes, non-fatal MI and non-fatal stroke.
- ELIXA trial showed GLP-1 receptor agonist is non-inferiority to placebo for primary composite end point of CV death, MI, stroke, or hospitalization for unstable angina
- EXSCEL trial for Exenatide QW showed non-inferiority to placebo for primary composite endpoint of CV death, nonfatal MI, or non-fatal stroke. Superiority was shown in the secondary endpoint of all cause mortality reduction.
- GLP-1 receptor agonist showed positive results in CV protection

Case 1

- 30 years office lady
- Strong FH of T2DM
- T2DM since 1 year ago, presented with polyuria and polydipsia, no DKA
- Hba1c was 9.5 % , LDL 3.0 upon diagnosis, given with metformin 1g BD, diamicron 160mg BD, Actos 30 mg daily
- BW 80 kg, 1.6 m, BMI =31.26
- Good motivation on diet control and exercise
- Good compliance to medications

Case of Diabesity with suboptimal control

- Latest Hba1c = 8.5 % , L
  5kg after treatment , B
- How will you help this p
- A. start basal insulin
- B. start GLP-1 agonist SC
- C. start SGLT-2 inhibitor oral
- D. Stop diamicron

Answer:

B or/and C: Hba1c and weight reduction effect

D prevent further weight gain by diamicron

Case 2

- 45 years old, private tutor, busy working schedule
- FH of T2DM
- T2DM since 42 years old, hypertension, hyperlipidaemia
- On metformin 1g BD, Actos 30 mg daily, diamicron 160 m BD, Dapagliflozin 10 mg daily
- Latest Hba1c 9% BW 80 kg BH 1.6 m BMI 31.2
- Infrequent SMBG:
- 1) 8-9
- 2) 10-12/14-18
- 3)12/14
- 4)---
- Refused insulin as worrying of weight gai

Case of Diabesity with suboptimal control
High FFG/PPG
Busy working schedule
Doubtful of compliance
Refusal of insulin
Worrisome of weight gain

Case of Diabesity with suboptimal control
High FFG/PPG
Busy working schedule
Doubtful of compliance
Refusal of insulin
Worrisome of weight gain

- How will you help this lady
- A. lifestyle modification
- B. stop diamicron/Actos, start GLP-1 agoinist
- C stop diamicron , start GLP-1 agonist
- D. start GLP-1 agonist

Answer:
A always: lifestyle modification is a must
C >D> B :avoid drugs with weight gain effect

Case of Diabesity with suboptimal control
High FFP/PPG
Busy working schedule
Doubtful of compliance
Refusal of insulin
Worrisome of weight gain

- Patient opted to start GLP-1 agonist , which agent will you suggest to her?
- A. Victoza daily SC
- B. Bydureon once per we
- C. lyxumia daily SC
- D. Trulicity once per wee

Answer :

B or D > A

Use of once week dose long acting GLP-1agonist increase drug compliance And correct FPG and PPG

Depends on availability and costs

Case 3

- 60 years old gentlemen, businessman, ex-smoker , ex-drinker
- T2DM since 50 years old, IHD with PCI done one month ago, hyperlipidaemia, hx of TIA
- Latest Hba1c 8.0, LDL 1.85, BP/P 120/80 , BMI 32 eGFR 50
- On aspirin 80 mg daily, plavix 75 mg daily, lipitor 20 mg daily, losartan 75 mg daily, metformin 500mg BD(only can tolerate this dose), diamicron 160 mg BD, actos 15 g daily(only can tolerate this dose as ankle edema), linagliptin 5 mg daily
- SMBG:
- 1)4-7/10
- 2)8-9/12
- 3)9-10/14
- 4)5-6/12-14

Case of DM with CV complication (IHD/TIA/nephropathy)
Suboptimal control on max OAD

- What will you suggest to h
- A. add empagliflozin
- B. start Victoza daily SC
- C. start weekly bydure
- D. start weekly trulicity

Case of DM with CV complication
(IHD/TIA/nephropathy)
Suboptimal control on max OAD

Answer:

B > A > C/D
Superiority of CVOT results for Victoza
And empagliflozin

Case 4

- 50 years old, housewife
- T2DM since 20 years old, HT, hyperlipidaemia
- Hx of acute pancreatitis
- Hba1c 12%, LDL 2.6, eGFR 60 , BP 130/80, BMI 22
- Currently on metformin 1g BD, diamicron 160 mg BD, Dapagliflozin 10 mg daily, actos 30 mg daily. Refused insulin all along.
- SMBG:
- 1)4-12
- 2)3.5-14
- 3)4-20/Hi
- 4) 3.5-20

Case of Long standing T2DM with poor control
Hx of pancreatitis
Brittle SMBG profile

- What will you give to this lady ?
- A. start GLP-1 agonist
- B start insulin
- C. stop diamicron
- D. lifestyle modific

Case of Long standing T2DM with poor control
Hx of pancreatitis
Brittle SMBG profile

Answer

D+B+/- C

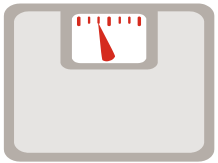
Beta-cell failure, needs of insulin therapy
Hx of pancreatitis is C/I for starting GLP-1 agonist

GLP-1 Agonists: Key Efficacy and Safety



HbA_{1c}

Effective in lowering HbA_{1c}[1,2,3]



Weight

Potential for weight loss[1,2,3]



Hypoglycaemia

Low potential for incidents[1,2]



GI adverse events

Nausea, diarrhoea, and vomiting that are mild to moderate in severity and transient in nature[2,4]

1. Karagiannis T, et al. *Diabetes Obes Metab*. 2015;17(11):1065-1074.
2. Liu FP, et al. *J Diabetes*. 2015;7(3):322-328.
3. Singh S, et al. Diabetes Obes Metab. 2017;19(2):228-238.
4. Prasad-Reddy L, et al. *Drugs Context*. 2015;9(4). DOI: 10.7573/dic.212283.

Which GLP-1 Agonist to be chosen for your patients ?

- Individualised
- Personalised target : age, co-mordities
- Risk of Rx : hypoglycaemia , weight gain

  - Efficacy Vs Adverse effect Vs CV benefits
  - Patient's preference / Compliance
  - Availability
  - Cost

THANK YOU