CHANGING THE WAY WE MANAGE DIABETES - NEW DEVELOPMENTS IN INJECTABLE AGENTS FOR TYPE 2 DIABETES

Presenter Disclosure

- **Speaker: Dr Luciana Parlea**

- **Relationships with commercial interests:**
  Grants/Research Support: n/a

  Speakers Bureau/Honoraria: Boehringer-Ingelheim, Dexcom, Janssen, Lilly, Novo Nordisk, Sanofi

  Consulting Fees: Abbott, Janssen, Lilly, Novo Nordisk, Valeant,

  Other: n/a

Disclosure of Financial Support

- **<u>Potential for conflict(s) of interest</u>:**

  This program has received:

  - Financial support from Abbott Diabetes Care, NovoNordisk and Boehringer Ingelheim in the form of an educational grant,
  - I am receiving an honorarium from Langs

- **Potential for conflict of interest:**

  Pharmaceutical products will be discussed during the presentation, but will be evidence-based.

Mitigating Potential Bias

- **Bias in this program has been mitigated using independent content validation as follows:**
- Includes evidence based information related to diabetes management but is not influenced by the sponsoring organizations.
- All support used in justification of patient care recommendations conforms to generally accepted standards, Diabetes Canada 2018 Clinical Practice Guidelines, as well as the most recently available clinical data.

Program objectives

- Review the latest GLP-1 receptor agonist therapies
- Identify the role of GLP-1 receptor agonists in the diabetes treatment algorithm
- Evaluate the latest advancements in basal insulin therapy (insulin degludec, insulin glargine u300)
- Review fixed ratio insulin –GLP 1 RA combination therapy

Question 1

Larry is a 67 year old retired engineer. His latest is Hba1c = 8%.

- PMHx:
  - DM2 x 10 years
  - CKD (GFR = 29)

- Current diabetic regimen:
  - Gliclazide MR 60 mg (prior hypoglycemia on higher dose)
  - Linagliptin 5 mg

In order to intensify his glycemic control, you would:

- A. Add basal insulin
- B. Stop the gliclazide and change to a basal – bolus regimen
- C. Stop the linagliptin and start a once weekly GLP-1 receptor agonist
- D. Start a fixed ratio insulin-GLP-1 RA combination

Question 2

- Mary is a 69 year old retired teacher. Her latest HbA1c is 7.8%

- PMHx
  - diabetes x 12 years
  - stroke 2 years ago

- Current diabetic regimen
  - sitagliptin/metformin 50/1000 bid
  - empagliflozin 25 mg
  - gliclazide mr 120mg daily
  - insulin degludec u200 80u at bedtime.

In order to intensify his glycemic control, you would:

- A. Stop the gliclazide MR and introduce bolus insulin with all meals.
- B. Add bolus insulin with her largest meal only.
- C. Stop the sitagliptin and add a once weekly GLP-1 receptor agonist
- D. Stop the sitagliptin and insulin degludec and transition to a fixed ratio insulin-GLP-1 RA combination.

Growing number of GLP-1 RAs:
Comparing available options

Molecule name	Brand name	Homology to human GLP-1	Elimination route	Half-life	Admin	Titratable dosing?	Device details
Long-acting GLP-1 RAs							
Liraglutide (Approved in 2010)	Victoza®	97% (Modified human GLP-1)	Endogenously metabolized	8–13 hours	QD/SC	0.6 mg 1 week; increase to 1.2 mg; max dose 1.8 mg*	Adjustable pen; visible needle
Dulaglutide (Approved in 2015)	Trulicity®	90% (Modified human GLP-1)	Endogenously metabolized	~5 days	QW/SC	0.75 mg 1 week; max dose 1.50 mg*	Not adjustable; no visible needle
Exenatide ER (Approved in 2015)	Bydureon®	53% (Exendin-4)	Glomerular filtration	7–14 days	QW/SC	No	Not adjustable; visible needle
Lixisenatide (Not widely available or marketed in Canada)	Adlyxine™	50% (Modified exendin-4)	Glomerular filtration	2–5 hours	QD/SC	10 µg for 14 days; 20 µg day 15 & onwards	Not adjustable; visible needle
Semaglutide (Approved in 2018)	Ozempic®	94% (Modified human GLP-1)	Endogenously metabolized	~7 days	QW/SC	0.25 mg for 4 weeks; increase to 0.5 mg; max dose 1.0 mg	Adjustable, FlexTouch® pen; visible needle

N.B.: although Byetta® (Exenatide BID) is available in Canada, it is no longer being promoted by AstraZeneca Canada Inc.
*Based on clinical response and after at least one week the dose can be increased to maximum dose to achieve maximum efficacy for glycemic control
ER, extended release; QW, once weekly; SC, subcutaneous
Dulaglutide Product Monograph, Eli Lilly Canada Inc., 2017; Exenatide ER Product Monograph, AstraZeneca Canada Inc., 2017; Liraglutide Product Monograph, Novo Nordisk Canada Inc., 2017; Lixisenatide Product Monograph, Sanofi-Aventis Canada Inc., 2017; Lovshin JA. *Can J Diabetes*. 2017;41(5):524-535; Semaglutide Product Monograph, Novo Nordisk Canada Inc., 2018

Indications for GLP-1 RA therapies

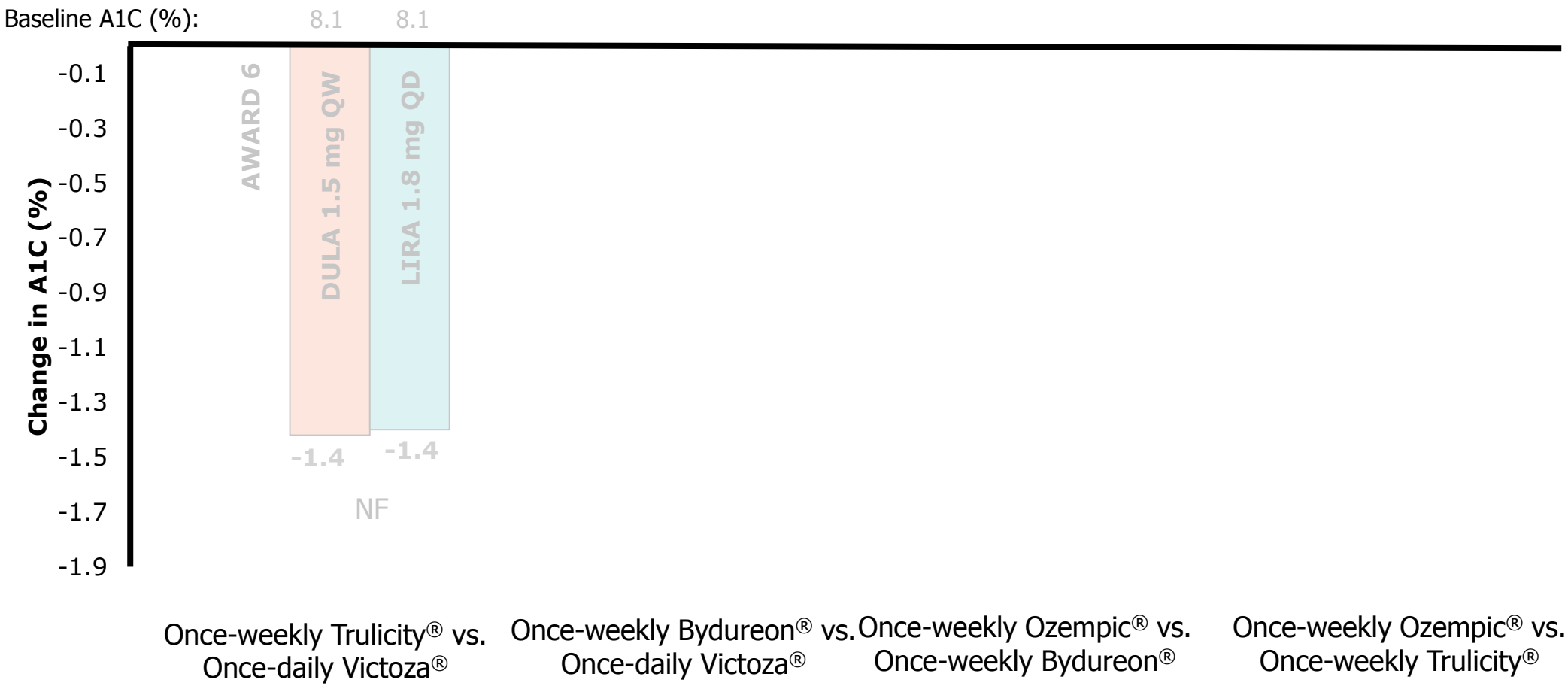
	In combination with diet and exercise*	Add-on to MET	Add-on to SU	Add-on to MET + SU	Combination with insulin	For patients with CVD
GLP-1 RAs						
Dulaglutide	✓	✓		✓	Basal + MET Prandial + MET	
Exenatide ER	✓	✓	✓	✓	Not indicated	
Liraglutide	✓	✓		✓	Basal + MET	✓
Lixisenatide		✓	✓	✓	Basal ± MET	
Semaglutide	✓	✓		✓	Basal + MET	

*In patients for whom metformin is inappropriate
CVD, cardiovascular disease; MET, metformin; SU, sulfonylurea
Dulaglutide Product Monograph, Eli Lilly Canada Inc., 2017; Exenatide ER Product Monograph, AstraZeneca Canada Inc., 2017; Liraglutide Product Monograph, Novo Nordisk Canada Inc., 2017; Lixisenatide Product Monograph, Sanofi-Aventis Canada Inc., 2017; Lovshin JA. *Can J Diabetes*. 2017;41(5):524-535; Semaglutide Product Monograph, Novo Nordisk Canada Inc., 2018

ODB Coverage

- Semaglutide has been added to the ODB formulary as of September 30
- No LU code
- Therapeutic note:
  - In addition to maximum tolerated metformin and sulfonylurea for patients not at target

GLP-1 RA head-to-head comparisons:
Change in A1C

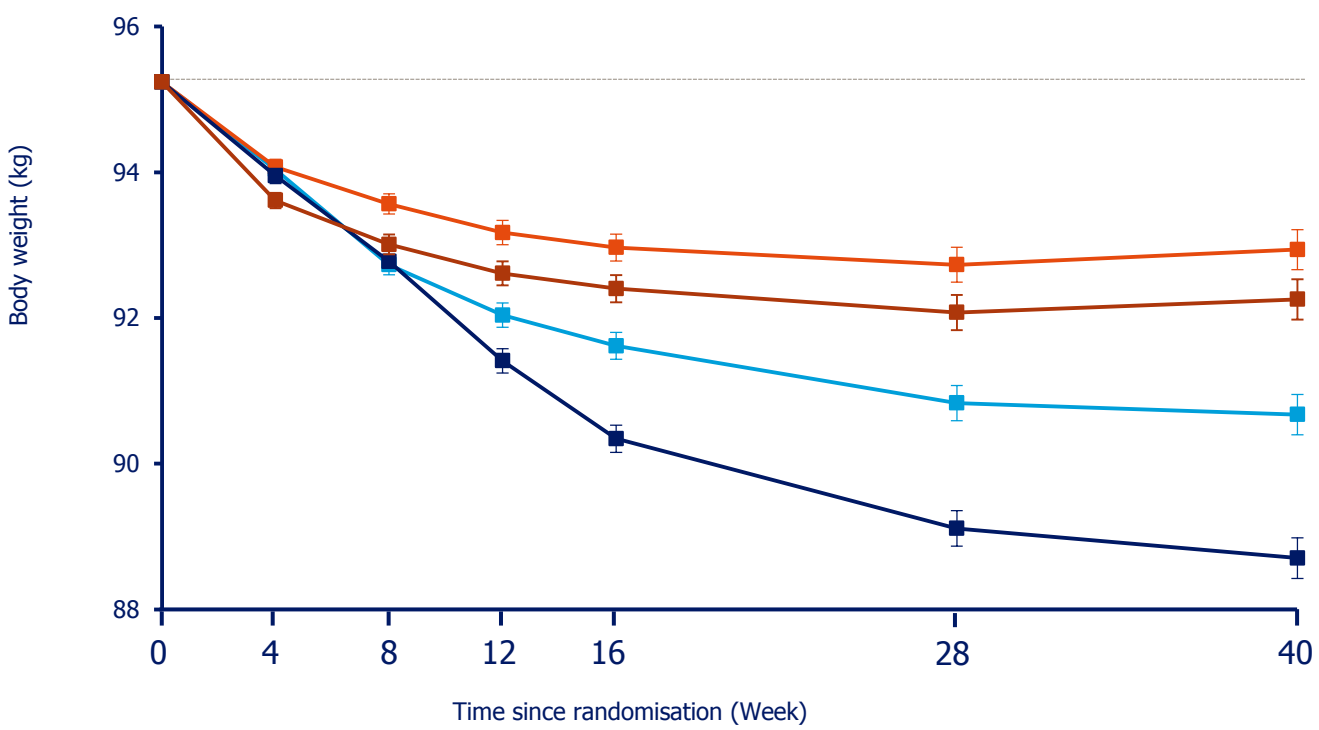


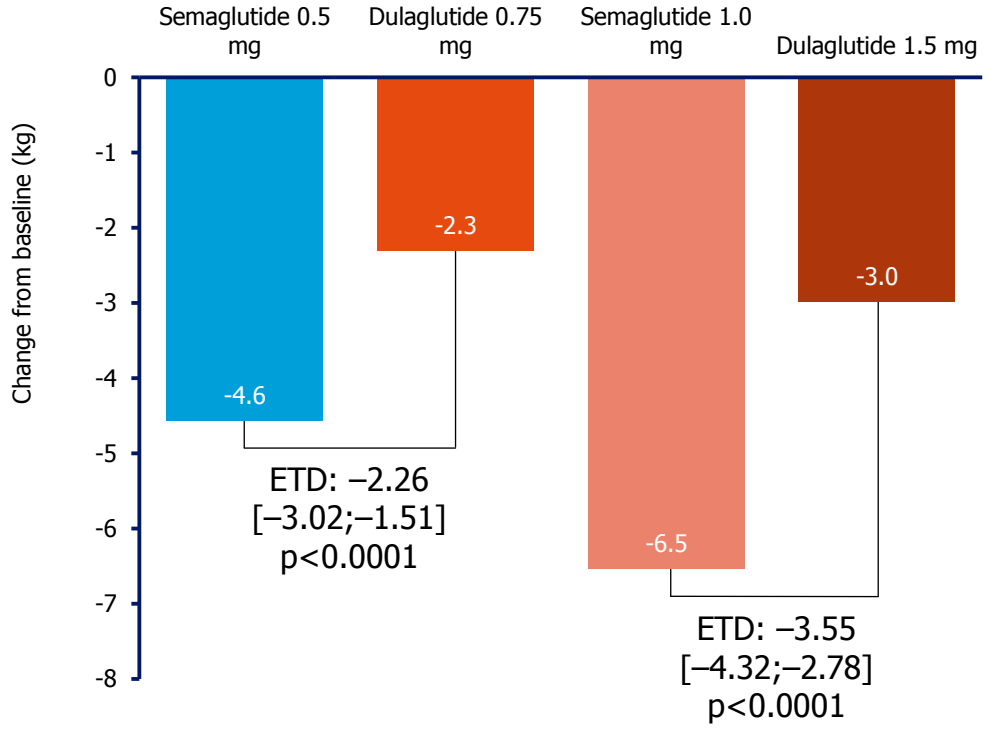
p-values are for statistical superiority unless otherwise noted as non-inferiority (NF) **p*=0.0005; †*p*<0.0001
DULA, dulaglutide; Comp, comparator; EXEN, exenatide; LIRA, liraglutide; QD, once daily; QW, once weekly; SEMA, semaglutide; Ahmann A, et al. *Diabetes*. 2016;65(Suppl 1):A49; Pratley RE, et al. *Lancet Diabetes Endocrinol*. 2018. Trujillo JM, et al. *Ther Adv Endocrinol Metab*. 2015;6(1):19-28; Wysham C, et al. *Diabetes Care*. 2014;37:2159-2167

Body weight

ESTIMATED MEAN BY WEEK AND CHANGE FROM BASELINE AT WEEK 40

Overall mean at baseline: 95.2 kg

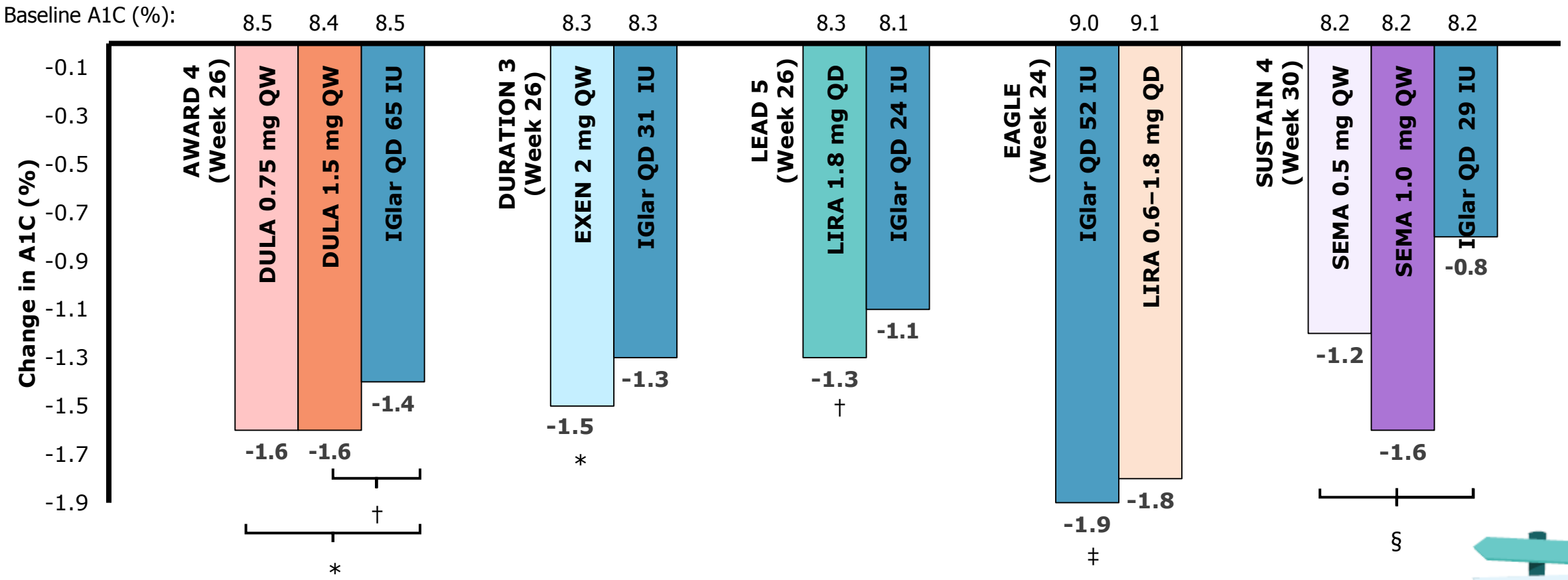




Semaglutide 0.5 mg — Dulaglutide 0.75 mg — Semaglutide 1.0 mg — Dulaglutide 1.5 mg

Adapted from Figure 2.
Values are estimated means with associated ETDs and 95% confidence intervals from a mixed model for repeated measurements analysis using data from all randomised patients exposed to at least one dose of trial product (full analysis set) using data obtained while on treatment and prior to onset of rescue medication. Dashed line indicates the overall mean value at baseline. ETD, estimated treatment difference.

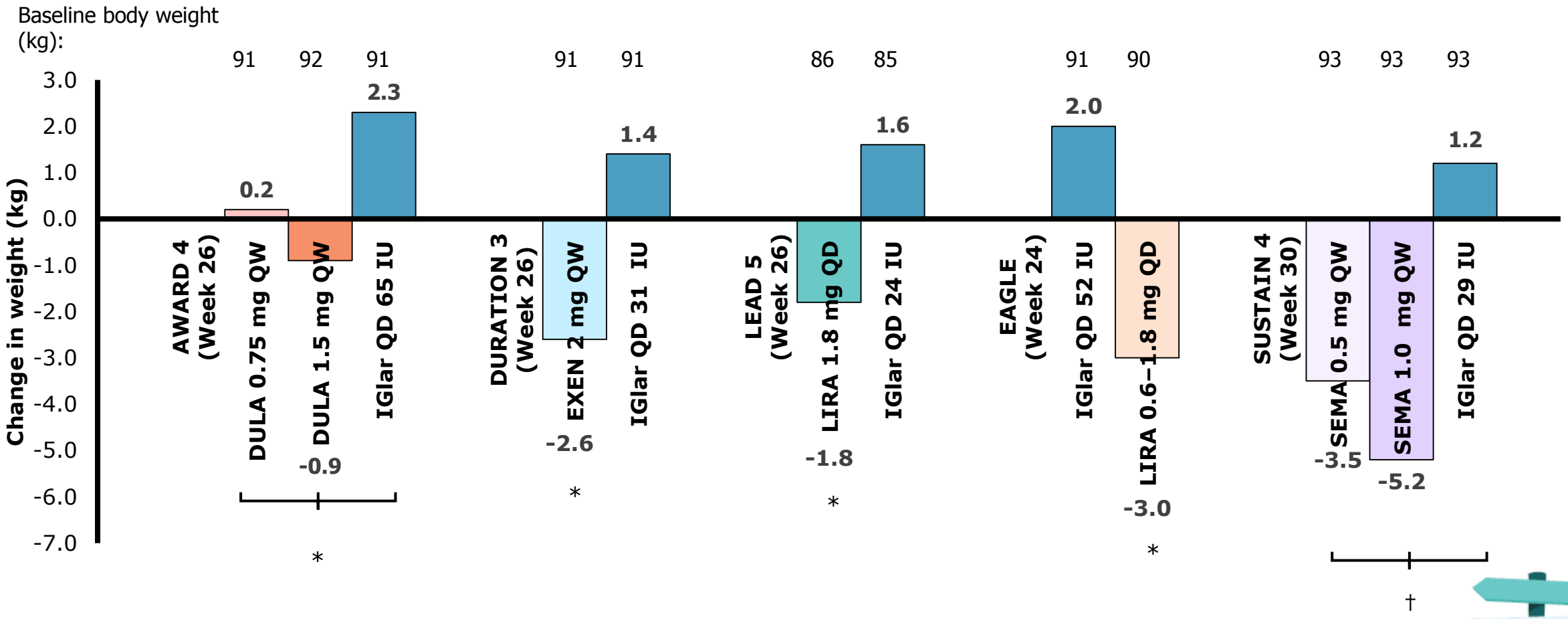
Comparison of GLP-1 RAs vs. insulin:
Change in A1C



*p<0.05 †p<0.01 ‡p<0.05 (2° endpoint) Similar numbers of subjects in both groups attained an A1C level of <7% (48.4 vs. 45.9%); therefore, superiority of glargine over liraglutide was not observed (p=0.44) §p<0.0001

IGlar, insulin glargine; Levin PA, et al. Diabetes *Metab Syndr Obes.* 2017;10:123-139; Lovshin JA. *Can J Diabetes.* 2017;41(5):524-535. AWARD 4: Blonde L, et al. *Lancet*. 2015;385(9982):2057-2066; DURATION 3: Diamant M, et al. *Lancet Diabetes Endocrinol*. 2014;2(6):464-473; LEAD 5: Russell-Jones D, et al. *Diabetologia*. 2009;52(10):2046-2055; EAGLE: D'Alessio D, et al. *Diabetes Obes Metab*. 2015;17(2):170-178. SUSTAIN 4: Aroda VR, et al. *Lancet Diabetes Endocrinol*. 2017;5(5):355-366

Comparison of GLP-1 RAs vs. insulin:
Change in body weight



*p<0.001 †p<0.0001

Levin PA, et al. Diabetes *Metab Syndr Obes.* 2017;10:123-139; Lovshin JA. *Can J Diabetes.* 2017;41(5):524-535. AWARD 4: Blonde L, et al. *Lancet.* 2015;385(9982):2057-2066; DURATION 3: Diamant M, et al. *Lancet Diabetes Endocrinol.* 2014;2(6):464-473; LEAD 5: Russell-Jones D, et al. *Diabetologia.* 2009;52(10):2046-2055; EAGLE: D'Alessio D, et al. *Diabetes Obes Metab.* 2015;17(2):170-178. SUSTAIN 4: Aroda VR, et al. *Lancet Diabetes Endocrinol.* 2017;5(5):355-366

GLP-1 RAs: Most frequently reported side effects

- The most common side effects are nausea, vomiting, and diarrhea
- Weight loss associated with GLP-1 RAs is independent of GI side effects
- The incidence and severity of nausea can often be reduced using a dose-escalation strategy

Quick tips:
Remind patients that most GI side effects are **transient** and **of short duration**, as well as **encourage** them to continue treatment

Tella SH, Rendell MS. *Ther Adv Endocrinol Metab* 2015;6(3):109-34; Meier JJ. *Nat Rev Endocrinol.* 2012;12:728-42

Thyroid C-cell tumours and the risk for medullary thyroid cancer

- In animal studies, some GLP-1 RAs have been associated with dose-dependent and treatment-duration-dependent C-cell hyperplasia and adenoma (after long-term exposure) at clinically relevant doses
- It is unknown whether GLP-1 RAs lead to thyroid C-cell tumorigenesis in humans
- However, GLP-1 RA use is contraindicated in patients with personal or family histories of medullary thyroid carcinoma or multiple endocrine neoplasia (type 2) syndrome

Lovshin JA. Can J Diabetes. 2017;41(5):524-535

Gallbladder-related events/disease

- Very low, yet statistically significant, rates of acute gallstone disease were reported in the LEADER trial
  - However, there were no increases in gallbladder-related events reported in the ELIXA and SUSTAIN 6 trials
- These effects on gallstone disease may be related to rapid weight loss or an effect of GLP-1 RAs in slowing gallbladder motility

Lovshin JA. Can J Diabetes. 2017;41(5):524-535

Semaglutide diabetic retinopathy considerations

Semaglutide product monograph:
Diabetic retinopathy

- In a 2-year trial involving patients with T2D and high CV risk, more events of diabetic retinopathy complications with semaglutide (3.0%) compared to placebo (1.8%)
- The absolute risk increase for diabetic retinopathy complications was larger among patients with a history of diabetic retinopathy
- Long-term glycemic control may decrease the risk of diabetic retinopathy
- Patients with a history of diabetic retinopathy should be monitored for progression of diabetic retinopathy

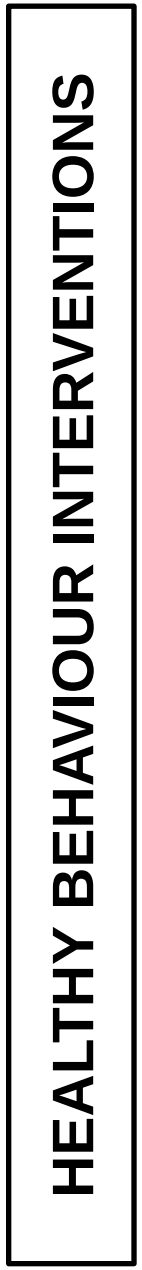
FDA briefing book: Ophthalmologist conclusion

"It is better to reduce HbA1c as soon as possible, regardless of whether or not it results in an initial increase in the progression of retinopathy."

"There is no reason to restrict semaglutide with respect to population or dosing schedule. There is also no reason to require any more or less ophthalmic follow-up."

Semaglutide Product Monograph. Novo Nordisk Canada Inc. January 4, 2018; Semaglutide FDA Briefing Document. Endocrinologic and Metabolic Drugs Advisory Committee Meeting October 18, 2017. Retrieved from: https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM580460.pdf

2018



AT DIAGNOSIS OF TYPE 2 DIABETES

Start healthy behaviour interventions
(nutritional therapy, weight management, physical activity) +/- metformin

A1C <1.5% above target	A1C ≥1.5% above target	Symptomatic hyperglycemia and/or metabolic decompensation
If not at glycemic target within 3 months, start/increase metformin	Start metformin immediately Consider a second concurrent antihyperglycemic agent	Initiate insulin +/- metformin
If not at glycemic target		If not at glycemic target

Clinical CVD?

- YES → Start antihyperglycemic agent with demonstrated CV benefit
  - empagliflozin (Grade A, Level 1A)
  - liraglutide (Grade A, Level 1A)
  - canagliflozin* (Grade C, Level 2)
  - If not at glycemic target → See next page
- NO → See next page

* Avoid in people with prior lower extremity amputation

DIABETES CANADA

Cardiovascular safety trials with GLP-1 Receptor Agonists

	ELIXA	LEADER	SUSTAIN 6	EXSCEL	HARMONY	REWIND
N	6068	9340	3297	14752	9463	9901
Drug Tested	Lixi/d	Lira/d	Sema/wk	Exena/d	Albig/wk	Dula/wk
Prior CVD	100%	81%	83%	73%	100%	31%
Mean Age	60 y	64 y	54 y	62 y	64 y	66 y
Women	30%	36%	39%	38%	31%	46%
Median F/U	2.1 y	3.8 y	2.1 y	3.2 y	1.6 y	5.4 y
DM Duration	9.2 y	12.8 y	13.9 y	13.1 y	14.2 y	10.5 y
Baseline A1c	7.7%	8.7%	8.7%	8.1%	8.8%	7.3%
Baseline eGFR	76	~75	~75	76	79	77
Insulin Use	39%	45%	58%	46%	59%	24%

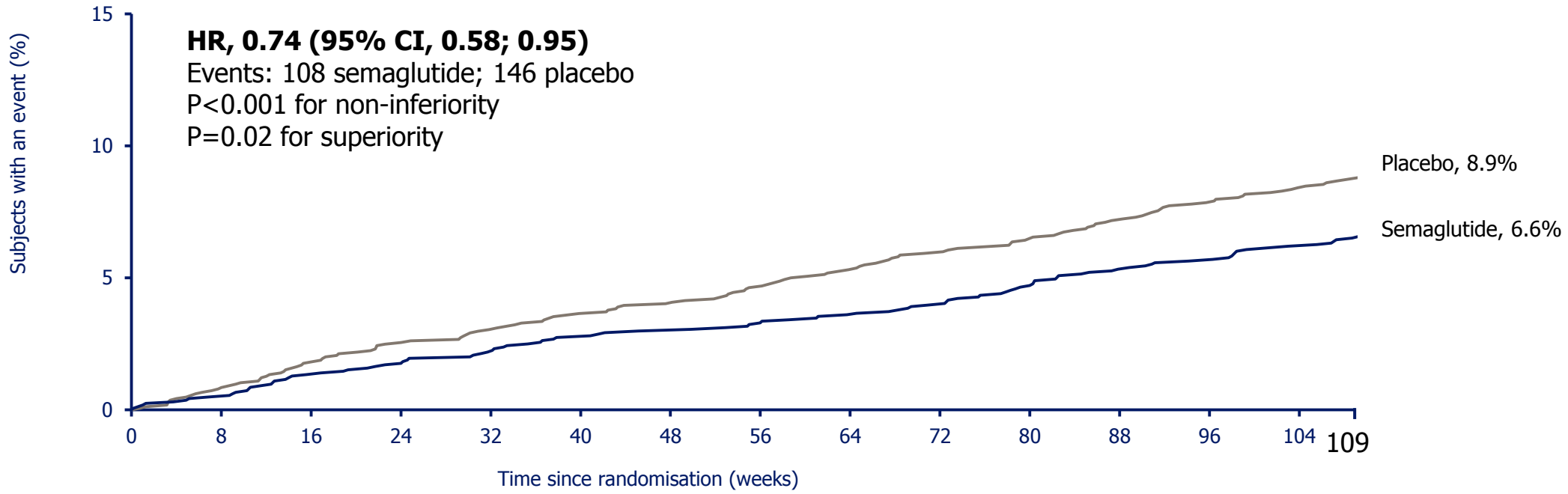
***GLP-1 RA CVOT trials cannot be directly compared due to differences in study design, population and key inclusion/exclusion criteria**

Gerstein, H. Once weekly dulaglutide and major cardiovascular events—Results of the REWIND Trial--Oral presentation at: American Diabetes Association 79th Scientific Sessions; June, 2019; San Francisco, CA.

REWIND
Dulaglutide CV Outcomes Trial

SUSTAIN 6

Primary outcome: time to 1st occurrence of CV death, non fatal MI, non fatal stroke



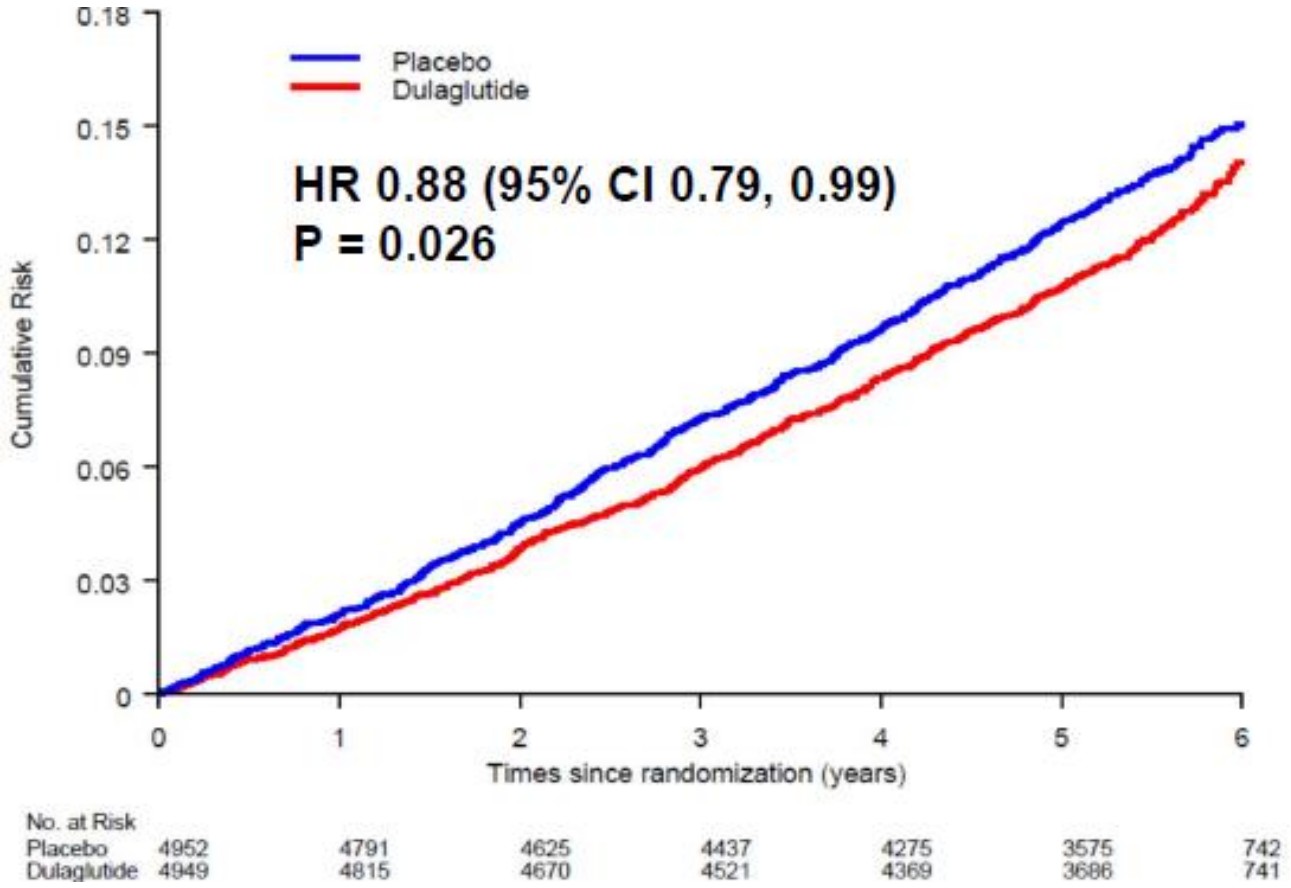
Number of subjects at risk

Semaglutide	**1648**	**1619**	**1601**	**1584**	**1568**	**1543**	**1524**	**1513**
Placebo	**1649**	**1616**	**1586**	**1567**	**1534**	**1508**	**1479**	**1466**

Figure 1A. Kaplan Meier plot for first event adjudication committee-confirmed CV death, non-fatal MI and non-fatal stroke using 'in-trial' data from subjects in the full analysis set.
*Not prespecified. CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction.
Marso et al. *NEJM* [in press]

REWIND

Primary Outcome: Time to 1st Occurrence of CV death, Nonfatal MI, Nonfatal stroke

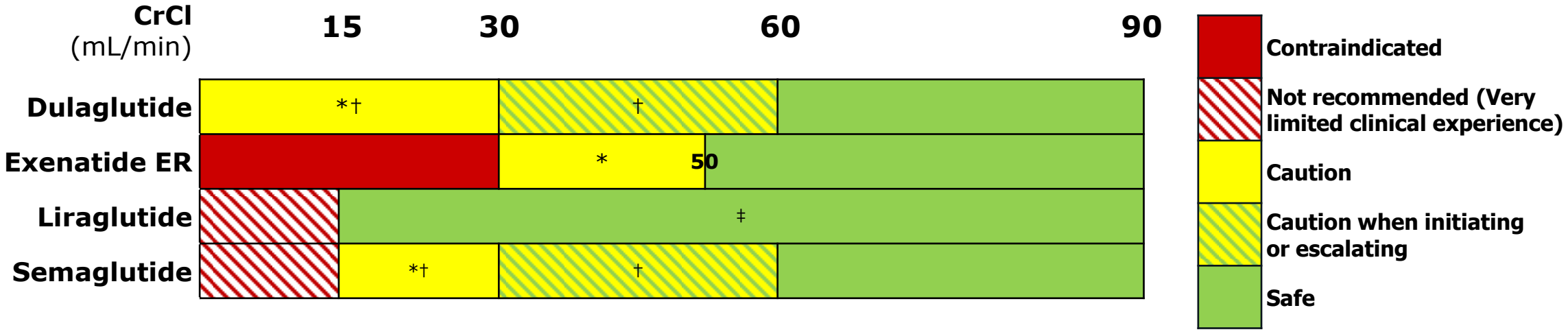


HR = hazard ratio; CI = confidence interval; MACE = major adverse cardiovascular event

Gerstein, H. Once weekly dulaglutide and major cardiovascular events—Results of the REWIND Trial--Oral presentation at: American Diabetes Association 79th Scientific Sessions; June, 2019; San Francisco, CA.

REWIND
Dulaglutide CV Outcomes Trial

Considerations for GLP-1 RA use:
Renal impairment



No dose adjustments for GLP-1 RAs are required in patients with CKD when indicated for use

*Limited clinical experience †Monitor renal function in patients with renal insufficiency reporting severe adverse gastrointestinal reactions ‡Use caution in patients who experience dehydration
CKD, chronic kidney disease; CrCl, creatinine clearance
Dulaglutide Product Monograph, 2017; Exenatide ER Product Monograph, 2017; Liraglutide Product Monograph, 2017; Semaglutide Product Monograph, 2018

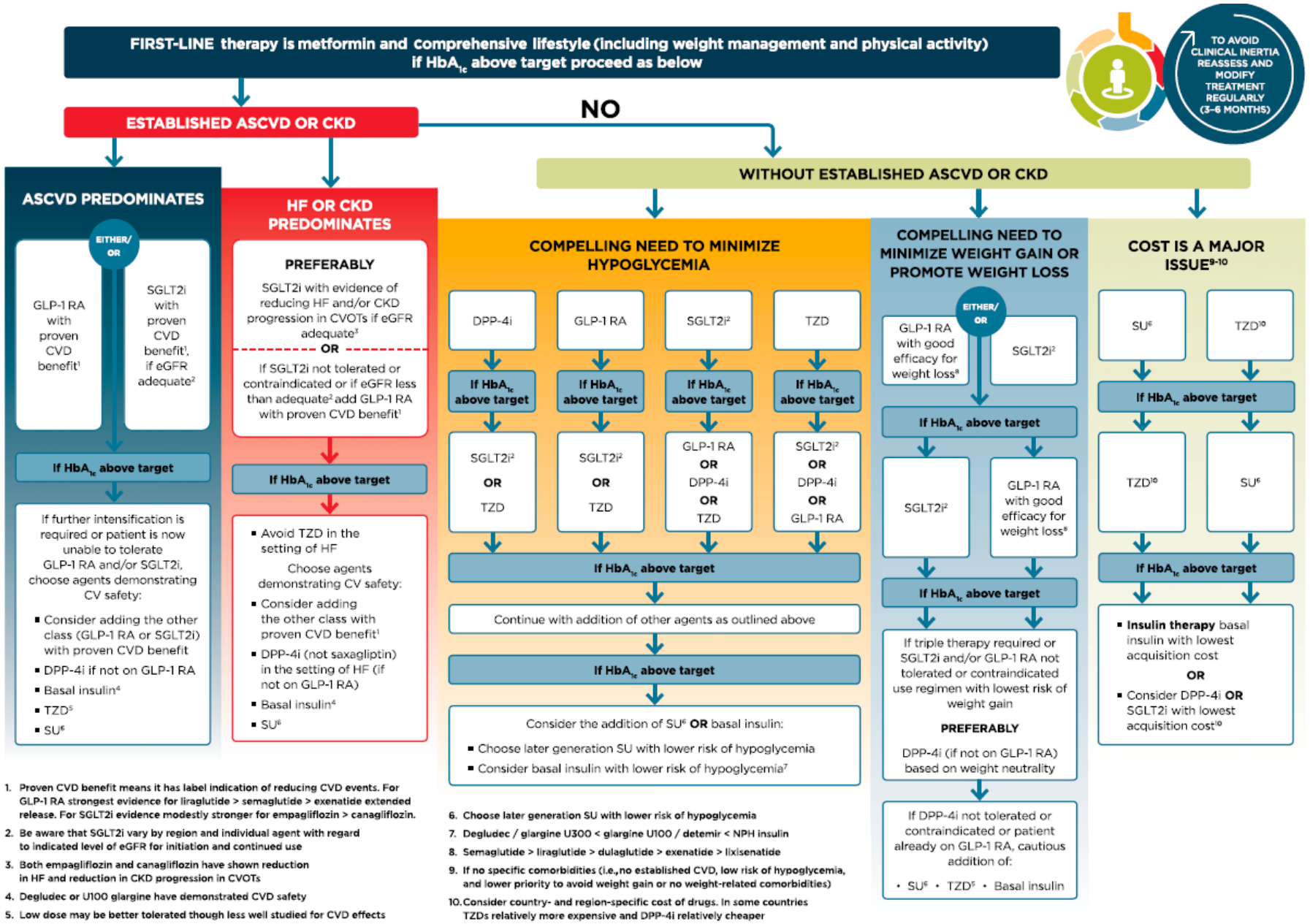
Additional considerations for GLP-1 RAs:
Use in special populations

	Pregnancy	Geriatrics (>65 years)	Hepatic Impairment
Exenatide ER		*†	
Liraglutide		*‡	§
Dulaglutide		¶	§
Semaglutide		*†	§

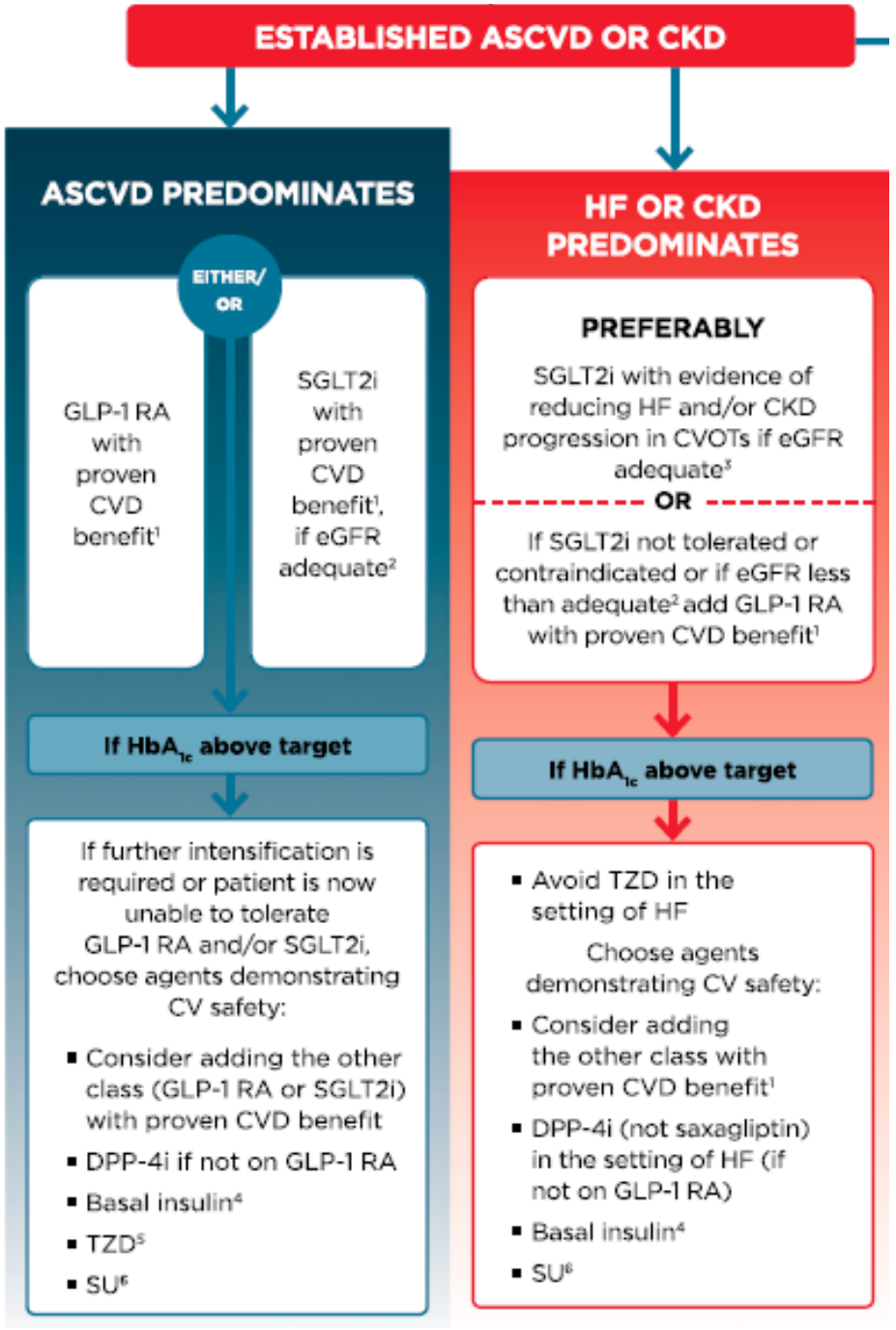
Contraindicated
Caution
No dose adjustment

* Greater sensitivity of older individuals cannot be ruled out † Clinical experience in patients 75 years of age and older is very limited ‡ The rate of gastrointestinal disorders in liraglutide treated subjects increased with age, especially at the 1.8 mg dose of liraglutide § There is limited clinical experience in patients with hepatic insufficiency ¶ Dulaglutide was studied in a limited number of patients 65 years of age or older and in few patients 75 years of age or older

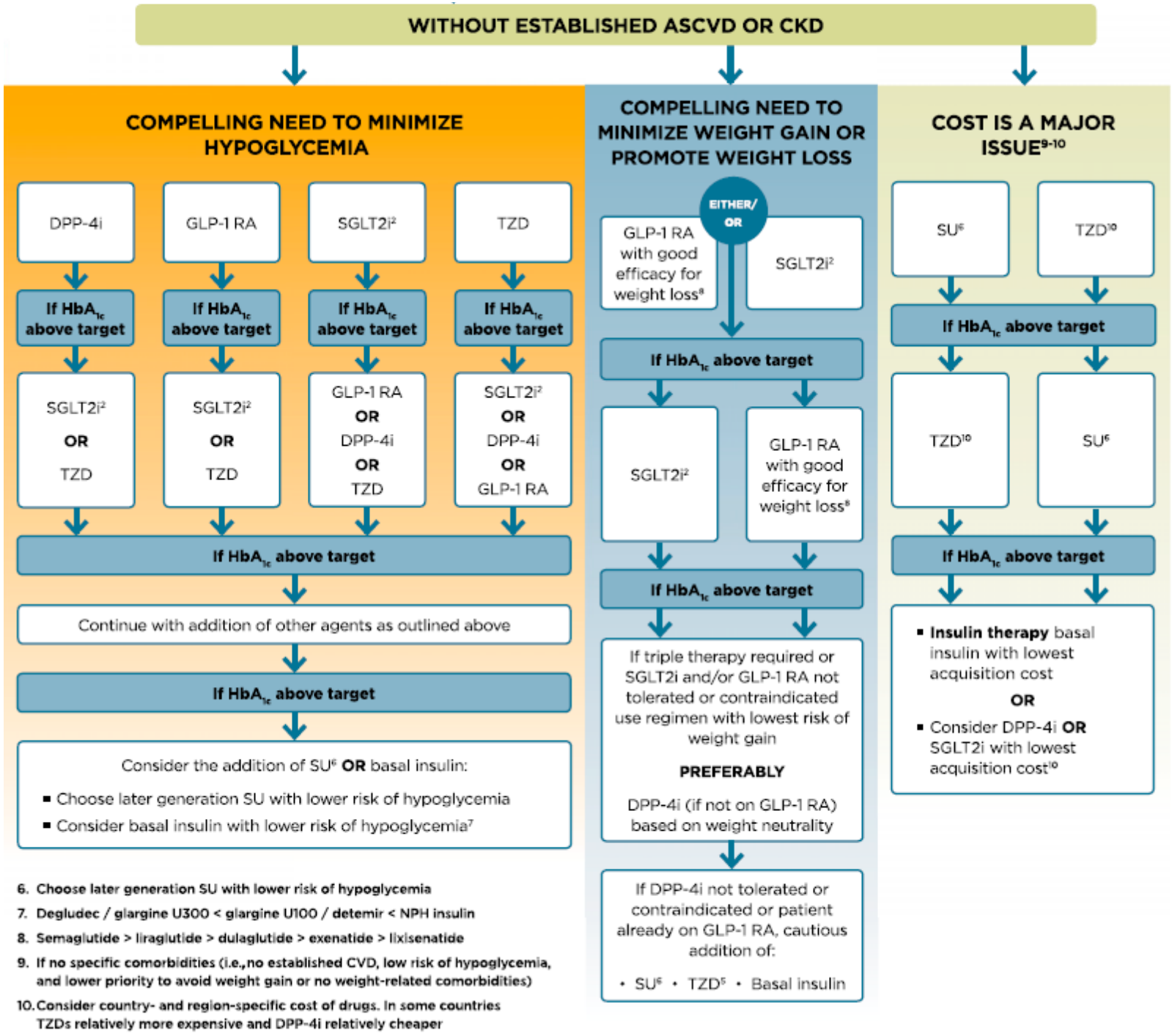
Dulaglutide Product Monograph, 2017; Exenatide ER Product Monograph, 2017; Liraglutide Product Monograph, 2017; Semaglutide Product Monograph, 2018



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 hypoglycemia
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 hypoglycemia, 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



- If A1C is above target despite recommended first-line treatment and the patient has ASCVD or CKD:
  - **ASCVD Predominates:**
    - Add GLP-1 RA with proven CVD benefit, OR
    - Add SGLT-2 inhibitor with proven CVD benefit (if eGFR adequate)
  - **If HF or CKD Predominates:**
    - Add SGLT-2 inhibitor with evidence of benefit
    - If can't take an SGLT-2 inhibitor, use a GLP-1 RA with proven CVD benefit



6. **Choose later generation SU with lower risk of hypoglycemia**
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 hypoglycemia, 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**

GLP-1 RAs Summary

GLP-1 RAs demonstrated:

- A1C reductions >1% from baseline
  - Comparable or better A1C reduction to basal insulin without the associated weight gain or risk of hypoglycemia
- Significant weight loss from baseline
- CV safety in patients with T2D and CVD
  - Benefit with liraglutide, semaglutide, dulaglutide

- Should be considered early in the treatment algorithm for type 2 diabetes, if cost allows

- The most common adverse events are GI in nature, and usually transient

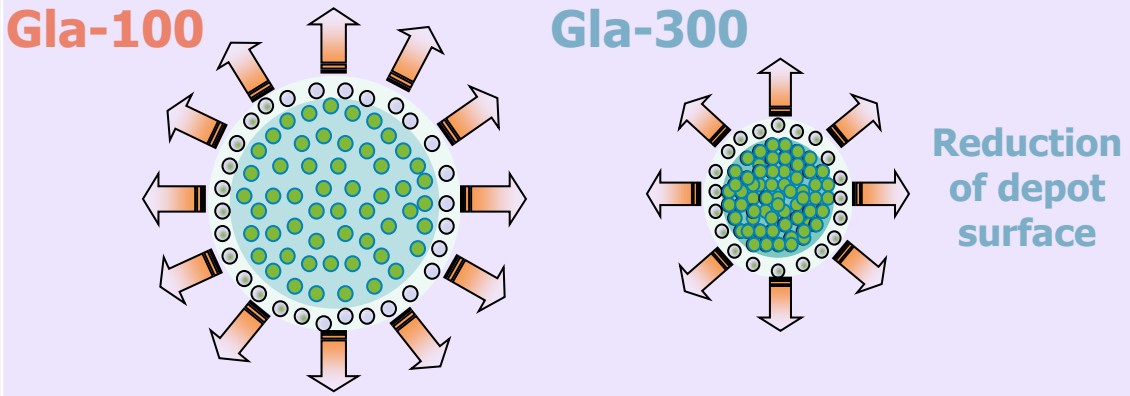
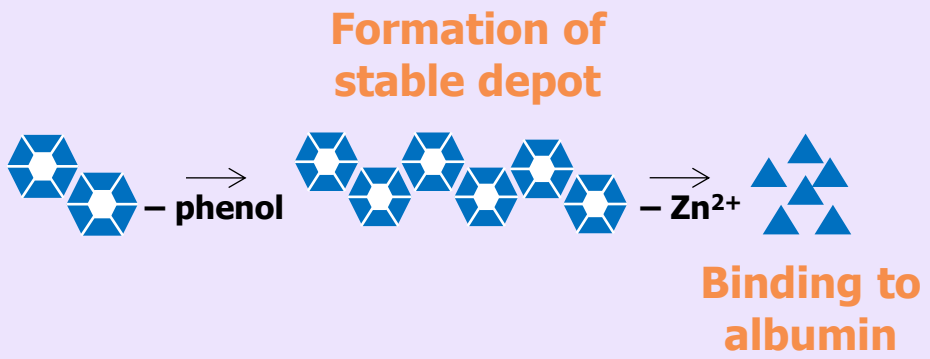
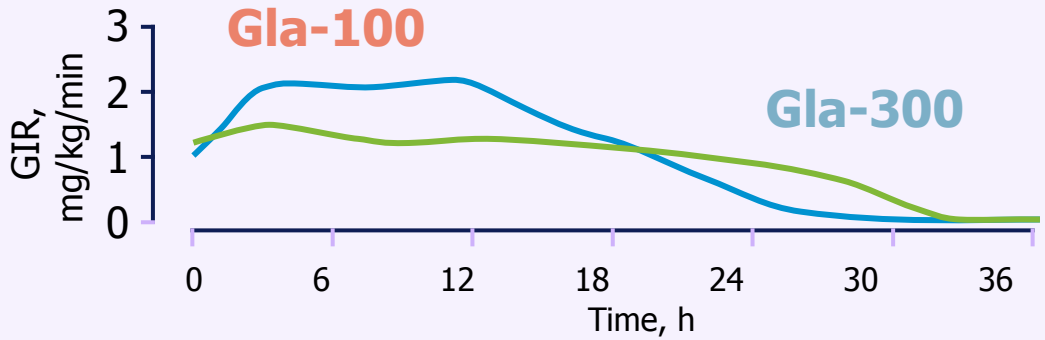
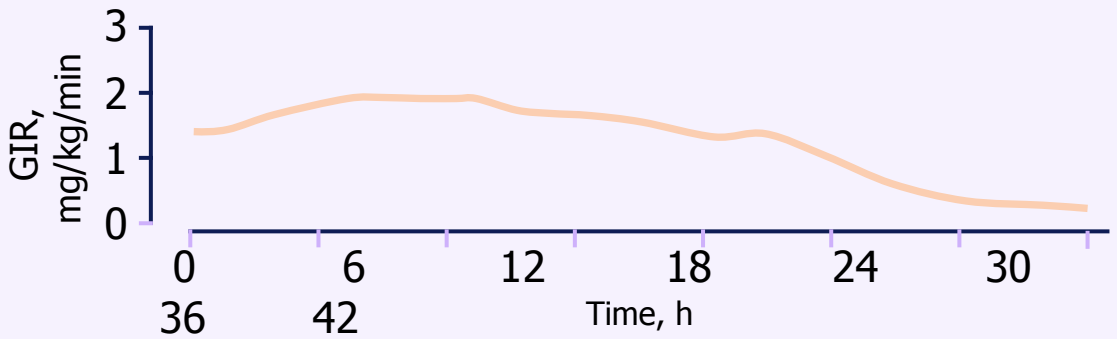
Basal insulin prefilled product options and features

	Brand name	Total units per pen (units)	Maximum dose for injection (units)	Time allowed outside of fridge (days)	Prefilled pens
NPH	Humulin® N 100 units/mL	300	60	28	KwikPen® 
Insulin detemir	Levemir® 100 units/mL	300	80	42	FlexTouch® 
Insulin glargine	Lantus® 100 units/mL	300	80	28	SoloSTAR® 
	Basaglar™ 100 units/mL	300	60	28	KwikPen® 
	Toujeo™ 300 units/mL	450	80	42	SoloSTAR® 
Insulin degludec	Tresiba® 100 units/mL	300	80	56	FlexTouch® 
	Tresiba® 200 units/mL	600	160	56	FlexTouch® 

Novolin®ge NPH is not available in a prefilled pen

1. Eli Lilly Canada Inc. Humulin® N Product Monograph. 2016; 2. Novo Nordisk Canada Inc. Levemir® Product Monograph. 2017; 3. Sanofi-aventis Canada Inc. Lantus® Product Monograph. 2017; 4. Eli Lilly Canada Inc. BASAGLAR™ Product Monograph. 2017; 5. Sanofi-aventis Canada Inc. Toujeo™ Product Monograph. 2015; 6. Novo Nordisk Canada Inc. Tresiba® Product Monograph. 2017.

Newer Generation Long-Acting Basal Insulins at a Glance

	Insulin glargine 300 U/mL	Insulin degludec
Action		
PK/PD	Half life: 21–24 h Steady state: 4 d Duration of action: ~36h 	Half-life: ~ 25 h Steady state: 3-4 d Duration of action: ~42h 

Eliaschewitz FG and Barreto T, *Diabetol Metab Syndr* (2016) 8:2; Jonassen I, et al, *Pharm Res* (2012) 29:2104–2114; Toujeo™ SoloSTAR® Product Monograph July 4, 2018, accessed Sept 6, 2018; Tresiba® Product Monograph August 25, 2017, accessed Feb 5, 2018.

Advantages of new basal insulins

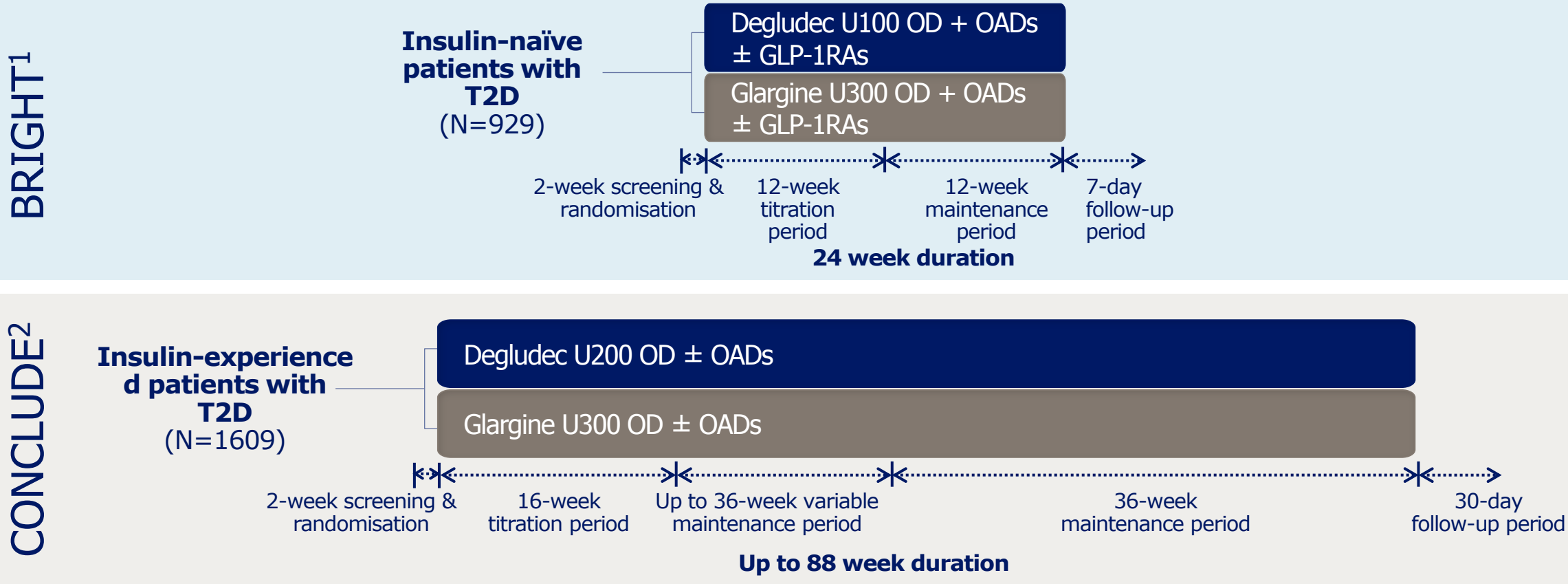
- Insulin degludec[1]
  - Non inferior Hba1c reduction to glargine U100
  - Less overall hypoglycemia
  - Less nocturnal hypoglycemia
  - Less severe hypoglycemia
- Insulin glargine U300[2]
  - Non inferior Hba1c reduction to glargine U100
  - Less confirmed hypoglycemia and severe hypoglycemia
  - Less nocturnal confirmed and severe hypoglycemia

1. Wysham et al. *JAMA* 2017;318(1):45-56

2. Yki-Järvinen H, et al. *Diabetes Care.* 2014;37:3235–3243

BRIGHT versus CONCLUDE

Trial design

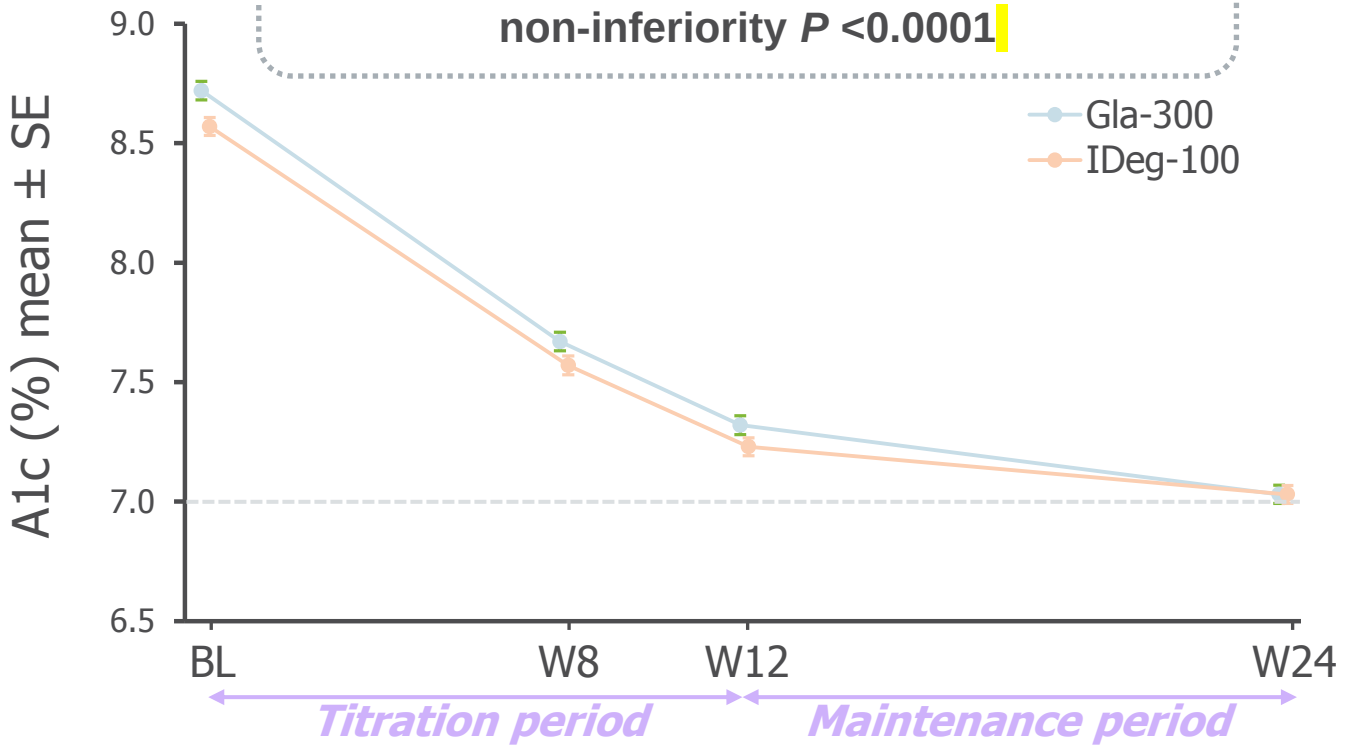


Glargine U300, insulin glargine 300 units/mL; GLP-1RA, glucagon-like peptide-1 receptor agonist; OAD, oral antidiabetic drug; OD, once daily; T2D, type 2 diabetes

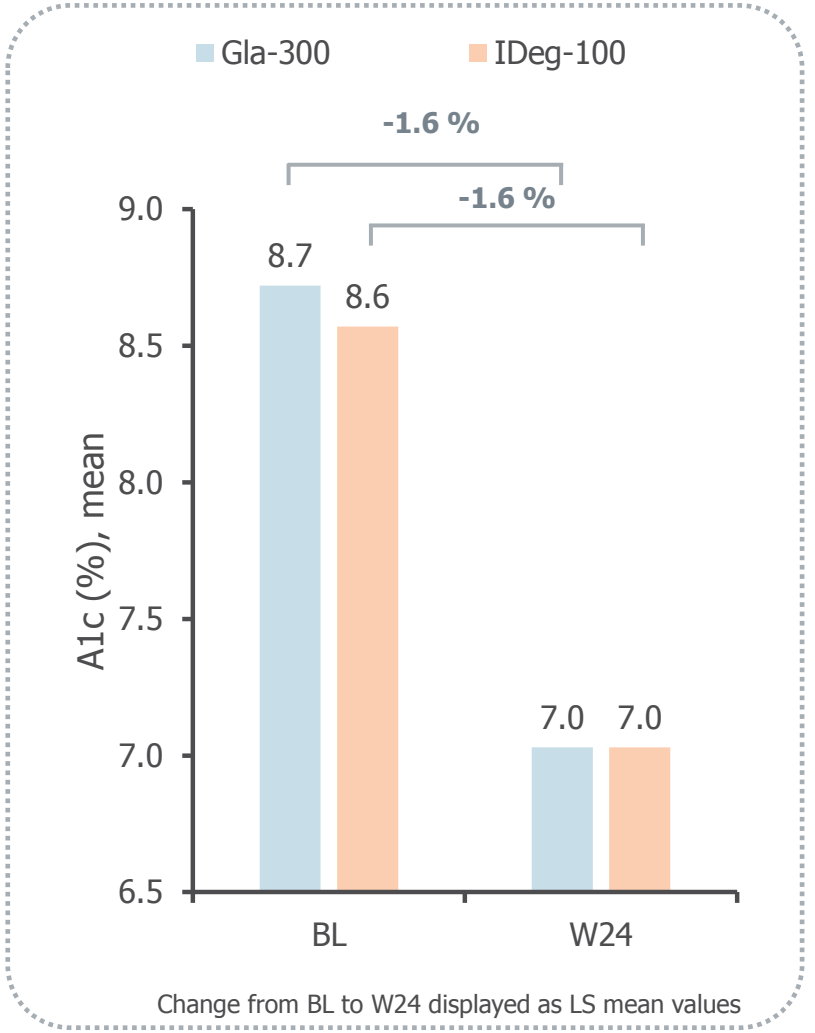
1. Rosenstock *et al. Diabetes Care* 2018;41:2147–54; 2. Philis-Tsimikas *et al. J Diabetes Sci Technol* 2019;13:498–506

BRIGHT: Study Results

LS mean difference for Gla-300 vs IDeg-100: -0.05% (95% CI: -0.15 to 0.05), non-inferiority *P* <0.0001



No. of participants:	BL	W8	W12	W24
Gla-300	462	448	448	430
IDeg-100	462	447	445	425



Non-inferiority of Gla-300 vs IDeg-100 in A1c reduction at study end

ITT population.
BL, baseline; CI, confidence interval; ITT, intention-to-treat; LS, least square; SE, standard error; W, week.
Rosenstock J, et al, *Diabetes Care*. 2018 Aug; dc180559; DOI: 10.2337/dc18-0559.

BRIGHT: Anytime (24 h) Hypoglycemia

Click icon for more on hypoglycemia data: incidence vs rates

Incidence

	Incidence, %				Favors Gla-300 ←	→ Favors IDeg-100
	Gla-300	IDeg-100	OR (95% CI)	p-value		
Full study period (0–24 weeks)						
Confirmed (≤3.9 mmol/L)	66.5	69.0	0.88 (0.66 to 1.17)	0.371		
Confirmed (<3.0 mmol/L)	14.7	18.4	0.76 (0.53 to 1.08)	0.123		
Titration period (0–12 weeks)						
Confirmed (≤3.9 mmol/L)	47.4	54.3	0.74 (0.57 to 0.97)	0.030		
Confirmed (<3.0 mmol/L)	7.8	11.7	0.63 (0.40 to 0.99)	0.044		
Maintenance period (13–24 weeks)						
Confirmed (≤3.9 mmol/L)	54.1	55.8	0.93 (0.72 to 1.22)	0.618		
Confirmed (<3.0 mmol/L)	9.8	11.2	0.86 (0.56 to 1.33)	0.505		

OR (95% CI) 0.3 1.0 3.0

Event rates

	Events per patient-year				Favors Gla-300 ←	→ Favors IDeg-100
	Gla-300	IDeg-100	RR (95% CI)	p-value		
Full study period (0–24 weeks)						
Confirmed (≤3.9 mmol/L)	9.34	10.83	0.86 (0.71 to 1.04)	0.130		
Confirmed (<3.0 mmol/L)	0.61	0.88	0.69 (0.45 to 1.08)	0.104		
Titration period (0–12 weeks)						
Confirmed (≤3.9 mmol/L)	8.08	10.47	0.77 (0.62 to 0.96)	0.023		
Confirmed (<3.0 mmol/L)	0.49	0.86	0.57 (0.34 to 0.97)	0.038		
Maintenance period (13–24 weeks)						
Confirmed (≤3.9 mmol/L)	10.64	11.21	0.95 (0.76 to 1.19)	0.650		
Confirmed (<3.0 mmol/L)	0.73	0.91	0.81 (0.48 to 1.39)	0.448		

RR (95% CI) 0.3 1.0 3.0

Incidence and rates of anytime hypoglycemia were lower with Gla-300 in the titration period

Confirmed hypoglycemia included documented symptomatic or asymptomatic hypoglycemia (≤3.9 mmol/L or <3.0 mmol/L), and severe events if any; only 1 participant experienced severe hypoglycemia (1 event), in the Gla-300 group, due to a skipped evening meal and not reducing her insulin dose after a non-severe event 2 days earlier.
All p-values presented are nominal. Safety population (Gla-300, n=463; IDeg-100, n=462). CI, confidence interval; OR, odds ratio; RR, rate ratio.
Rosenstock J, et al, *Diabetes Care*. 2018 Aug; dc180559; DOI: 10.2337/dc18-0559.

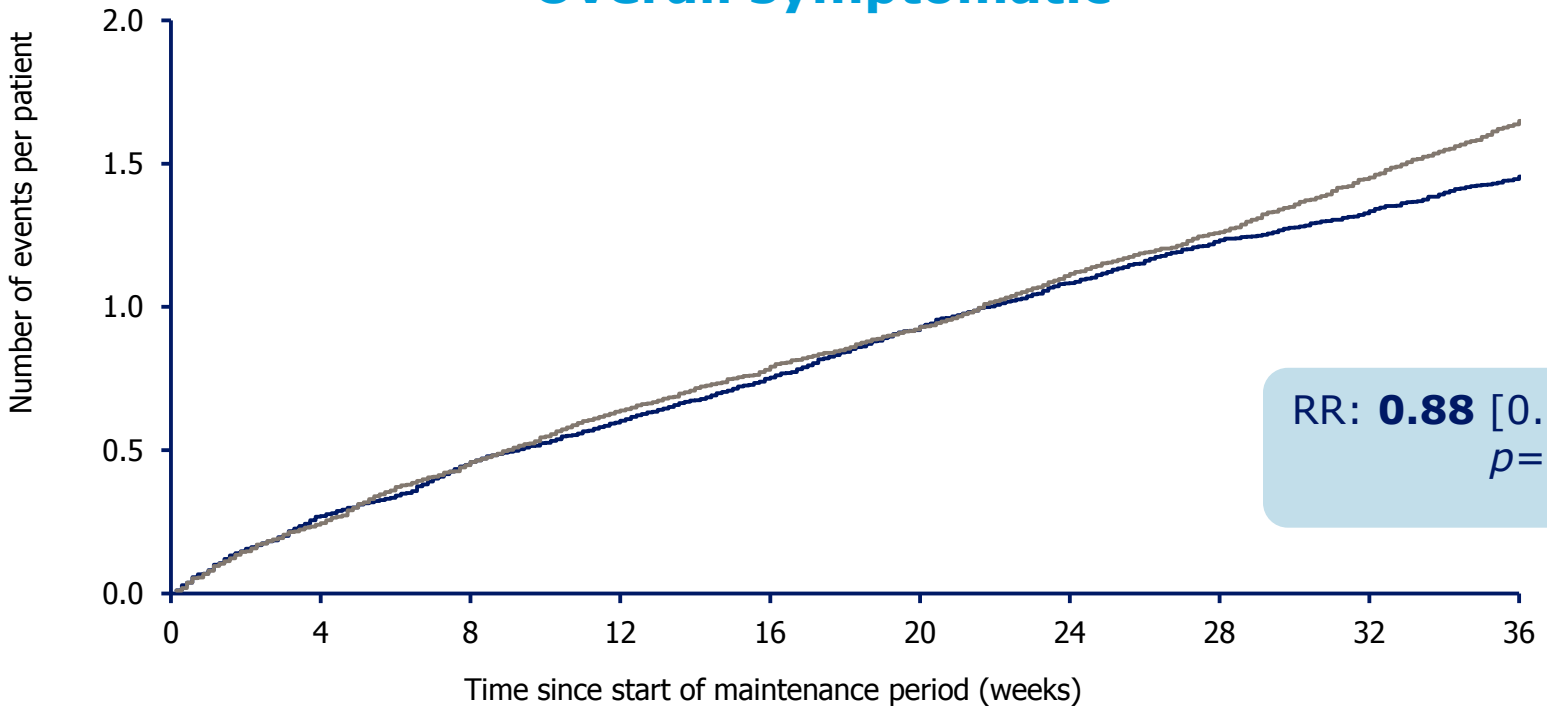
CONCLUDE - Hypoglycaemia endpoints

MAINTENANCE period – primary endpoint

Pre-specified analysis

Degludec Glargine U300

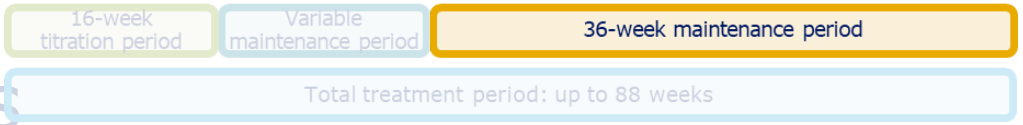
Overall symptomatic*



RR: **0.88** [0.73; 1.06]$_{95\%\ CI}$
p=0.17

Not significant

*Event defined as severe (requiring third-party assistance) or blood glucose <3.1 mmol/L confirmed with symptoms
CI, confidence interval; glargine U300, insulin glargine 300 units/mL; RR, rate ratio
Philis-Tsimikas. Presented at EASD, 2019, Barcelona: OP#90; Philis-Tsimikas. Presented at EASD, 2019, Barcelona: S#38.2



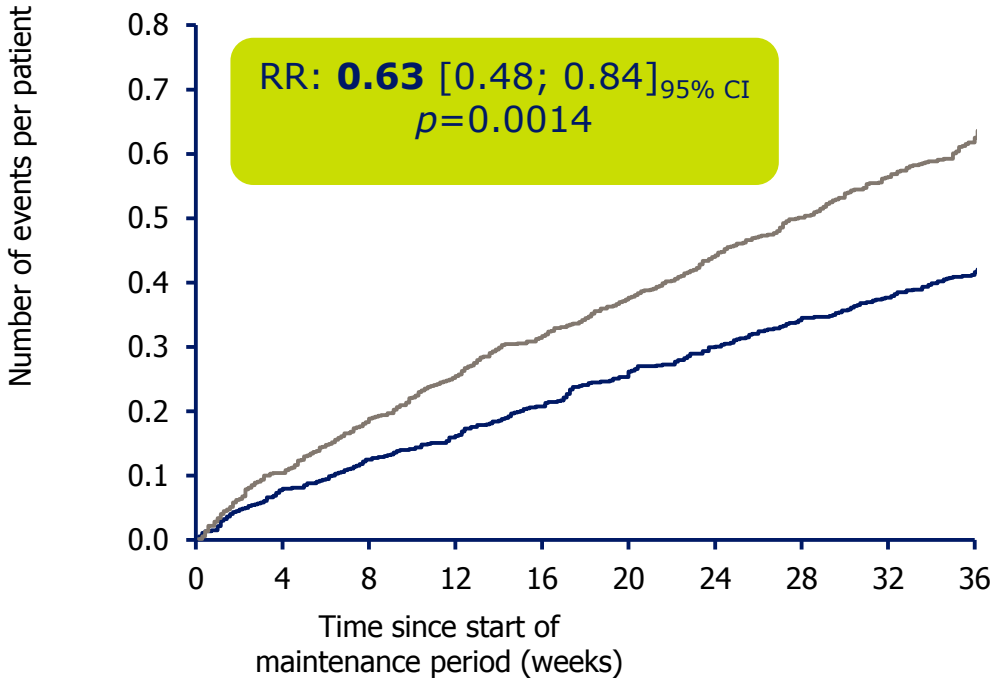
CONCLUDE Hypoglycaemia endpoints

MAINTENANCE period

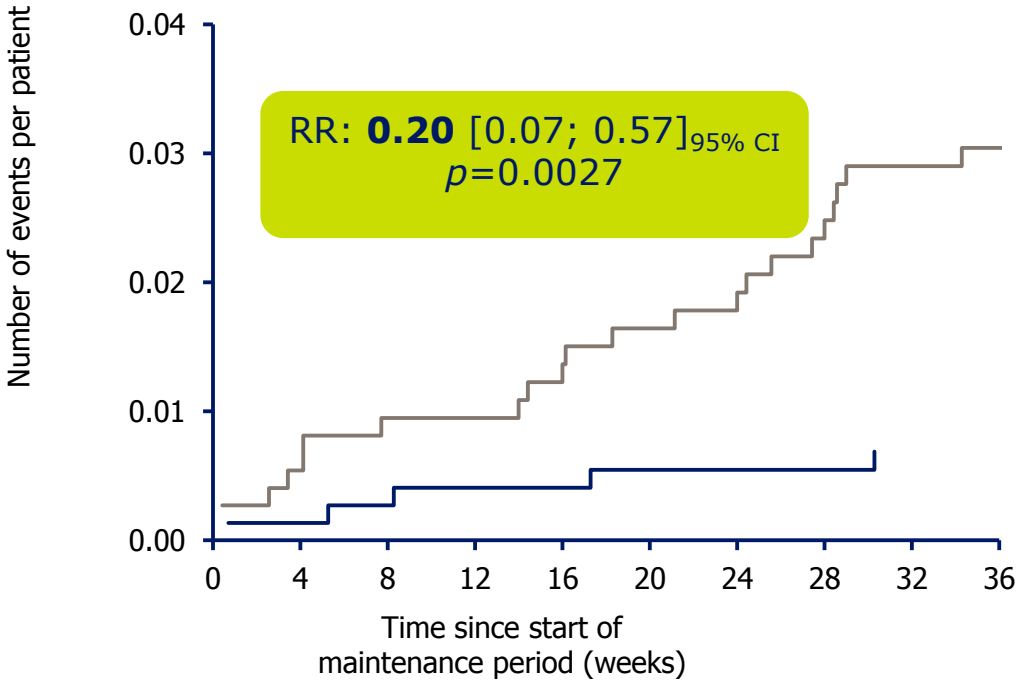
Pre-specified analyses

Degludec Glargine U300

Nocturnal symptomatic*



Severe*



Significant

*Event defined as severe (requiring third-party assistance) or blood glucose <3.1 mmol/L confirmed with symptoms. All nocturnal hypoglycaemia reported between 00:01 and 05:59. Severe hypoglycaemia an event requiring third party assistance

CI, confidence interval; glargine U300, insulin glargine 300 units/mL; RR, rate ratio

Philis-Tsimikas. Presented at EASD, 2019, Barcelona: OP#90; Philis-Tsimikas. Presented at EASD, 2019, Barcelona: S#38.2

Practical usage tips

Start

For all basal insulins

10 units

Switch

From once-daily basal insulin

1:1

From glargine U300

↓20%

From BID basal

↓20%

1. Novo Nordisk Canada Inc. Levemir® Product Monograph. 2017; 2. Sanofi-aventis Canada Inc. Lantus® Product Monograph. 2017; 3. Eli Lilly Canada Inc. BASAGLAR™ Product Monograph. 2017; 4. Sanofi-aventis Canada Inc. Toujeo™ Product Monograph. 2015; 5. Novo Nordisk Canada Inc. Tresiba® Product Monograph. 2017; 6. Novo Nordisk A/S. Tresiba® Summary of Product Characteristics (SmPC). Bagsværd, Denmark. 2015; 7. Canadian Diabetes Association. Appendix 3: Examples of Insulin Initiation and Titration Regimens in People with Type 2 Diabetes. Available at: http://guidelines.diabetes.ca/browse/appendices/appendix3; 8. Philis-Tsimikas A, et al. Insulin degludec once-daily in type 2 diabetes: simple or step-wise titration (BEGIN: once simple use). *Adv Ther.* 2013;30(6):607–622.

Practical usage tips

Titrate
(Examples)

For ultra-long-acting basal insulins (e.g., insulin degludec) **Adjust dose weekly:**

For long-acting basal insulins (e.g., insulin glargine U100, U300) **Adjust dose daily:**

Starting insulin is not enough—titration is needed

1. Novo Nordisk Canada Inc. Levemir® Product Monograph. 2017; 2. Sanofi-aventis Canada Inc. Lantus® Product Monograph. 2017; 3. Eli Lilly Canada Inc. BASAGLAR™ Product Monograph. 2017; 4. Sanofi-aventis Canada Inc. Toujeo™ Product Monograph. 2015; 5. Novo Nordisk Canada Inc. Tresiba® Product Monograph. 2017; 6. Novo Nordisk A/S. Tresiba® Summary of Product Characteristics (SmPC). Bagsværd, Denmark. 2015; 7. Canadian Diabetes Association. Appendix 3: Examples of Insulin Initiation and Titration Regimens in People with Type 2 Diabetes. Available at: http://guidelines.diabetes.ca/browse/appendices/appendix3; 8. Philis-Tsimikas A, et al. Insulin degludec once-daily in type 2 diabetes: simple or step-wise titration (BEGIN: once simple use). *Adv Ther.* 2013;30(6):607–622.

Recommendations for missed or delayed insulin doses

Insulin glargine (Lantus®, Toujeo™, Basaglar™)	Insulin degludec (Tresiba®)
Taken at the same time each day	Taken at the same time each day, with flexibility in dosing time when needed
When missed or delayed: Check blood sugar frequently Do not take a double dose to make up for a forgotten dose	When missed or delayed: Take the dose upon discovery Continue with regular schedule; ensure >8 hours between doses

Changing dosing times* with insulin degludec did not compromise A1C efficacy or increase the risk of hypoglycemia

*Extreme intervals of 8–40 hours

1. Sanofi-aventis Canada Inc. Lantus® Product Monograph. 2017; 2. Eli Lilly Canada Inc. BASAGLAR™ Product Monograph. 2017; 3. Sanofi-aventis Canada Inc. Toujeo™ Product Monograph. 2015; 4. Novo Nordisk Canada Inc. Tresiba® Product Monograph. 2017; 5. Meneghini L et al. The efficacy and safety of insulin degludec given in variable once-daily dosing intervals compared with insulin glargine and insulin degludec dosed at the same time daily: a 26-week, randomized, open-label, parallel-group, treat-to-target trial in individuals with type 2 diabetes. *Diabetes Care*. 2013;36(4):858–864.

Basal insulin summary

- Insulin degludec and insulin glargine u300 have longer duration of action and less variability than glargine u100, non inferior glycemic control, less hypoglycemia.

- In insulin naïve patients, insulin glargine u300 has similar hba1c reduction to insulin degludec; less hypoglycemia during titration but overall no difference in hypoglycemia (secondary safety end points).

- In patients on basal insulin at high risk of hypoglycemia, insulin degludec was not superior to insulin glargine u300 in decreasing hypoglycemia during maintenance period; less nocturnal and severe hypoglycemia (pre-specified secondary end points when primary end point not met).

- Both degludec and glargine u300 are ODB covered and should be considered as first option in basal insulin.

FIXED RATIO INSULIN – GLP1RA COMBINATIONS

Newly approved fixed ratio insulin-GLP-1 RA combinations

- IdegLira – Xultophy
  - Approved for patients who are not at target on metformin+/- SU and either basal insulin or liraglutide
  - Insulin degludec 100 u/ml and liraglutide 3.6 u/ML
  - Dose given qhs
  - Start with 16 dose steps(16u degludec + 0.58 ml liraglutide) at bedtime
  - To titrate - increase by 2u every 3-4 days until fasting sugars < 7; up to maximum dose of 50 steps (50u insulin degludec + 1.8ml of liraglutide)
  - Not recommended if basal insulin requirement < 16 or > 50

- IglarLixi – Soliqua
  - Approved for patients who are not at target on insulin glargine +/- metformin
  - Insulin glargine 100u/ml and lixisenatide 33 mcg/ml
  - Dose ac largest meal
  - Start with 15 dose steps (15u glargine + 5 mcg lixisenatide) if uncontrolled on < 30u basal insulin;
  - Start with 30 dose steps (30u glargine + 10 mcg lixisenatide) if uncontrolled on > 30u basal
  - Titrate by 2 u weekly until fasting sugar in range or maximum dose reached – 60 dose steps (60u glargine + 20 mcg lixisenatide).

Benefits of fixed ratio combinations

- Simplicity
  - One single injection
  - Need to monitor once daily
- Tolerability
  - Less GI side effects due to very slow titration
- Effectiveness
  - Better hba1c reduction than either basal insulin or GLP-1 RA
  - Equivalent Hba1c reduction to basal-bolus regimen with no weight gain and less hypoglycemia

Question 1

Larry is a 67 year old retired engineer. His latest is Hba1c = 8%.

- PMHx:
  - DM2 x 10 years
  - CKD (GFR = 29)
- Current diabetic regimen:
  - Gliclazide MR 60 mg (prior hypoglycemia on higher dose)
  - Linagliptin 5 mg

In order to intensify his glycemic control, you would:

- A. Add basal insulin
- B. Stop the gliclazide and change to a basal – bolus regimen
- C. Stop the linagliptin and start a once weekly GLP-1 receptor agonist
- D. Start a fixed ration insulin - GLP-1 RA combination

Question 2

- Mary is a 69 year old retired teacher. Her latest HbA1c is 7.8%

- PMHx
  - diabetes x 12 years
  - stroke 2 years ago

- Current diabetic regimen
  - sitagliptin/metformin 50/1000 bid
  - empagliflozin 25 mg
  - gliclazide mr 120mg daily
  - insulin degludec u200 80u at bedtime.

In order to intensify his glycemic control, you would:

- A. Stop the gliclazide MR and introduce bolus insulin with all meals.
- B. Add bolus insulin with her largest meal only.
- C. Stop the sitagliptin and add a once weekly GLP-1 receptor agonist
- D. Stop the sitagliptin and insulin degludec and transition to a fixed ratio insulin-GLP-1 RA combination.

Summary

- GLP1 RA should be considered early in the treatment of type 2 diabetes
- Insulin Degludec and Insulin Glargine U300 should be the preferred basal insulins
- Fixed ratio combination insulin-GLP 1RA receptor agonists present a simple and effective option for DM2 management