Renal function and glucose control with basal insulins

Alice Cheng

University of Toronto, Toronto, ON, Canada

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Disclosures

- Advisory board member or equivalent with a commercial organization:
  - Abbott, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Novo Nordisk, Sanofi, HLS Therapeutics, Medtronic
- Speakers' bureau member:
  - Abbott, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Novo Nordisk, Sanofi
- I am currently participating, or have participated within the past two years, a clinical trial:
  - Eli Lilly, Sanofi, Boehringer Ingelheim

Objectives

1. Describe the key findings from the BRIGHT study
2. Present results of the sub-analysis in patients with renal impairment and consider the clinical implications of these results

Introduction

- 2nd generation basal insulin analogs, Gla-300 and IDeg-100, have smoother PK/PD profiles than Gla-100[1,2]
- Gla-300 and IDeg-100 both provide similar HbA1c reductions to Gla-100 but with less hypoglycemia in people with T2D[3,4]

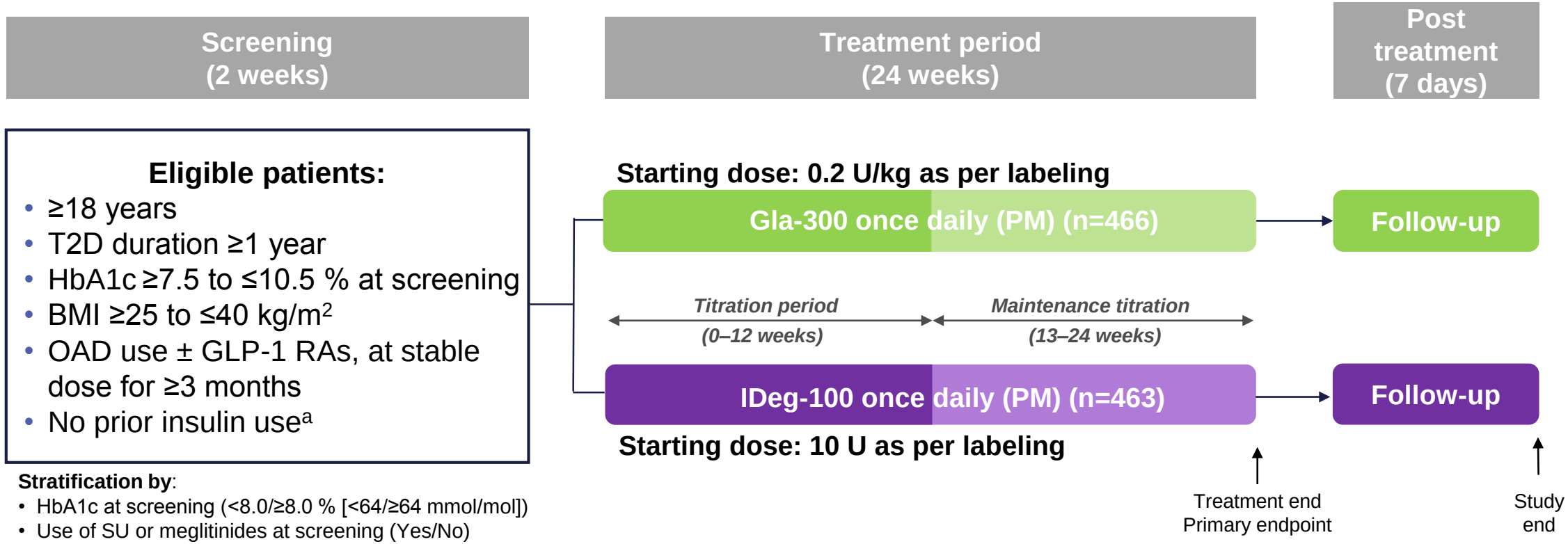
The BRIGHT study was the first head-to-head RCT designed to compare the efficacy and safety of Gla-300 with IDeg-100 in participants with T2D

Gla-300, insulin glargine 300 U/mL; IDeg-100, insulin degludec 100 U/mL; PK/PD, pharmacokinetic/pharmacodynamic; RCT, randomized clinical trial; T1D, type 1 diabetes; T2D, type 2 diabetes

1. Becker RH, et al. Diabetes Care 2015;38:637–643; 2. Heise T, et al. Diabetes Obes Metab 2012;14:859–864 3. Ratner RE, et al. Diabetes Obes Metab 2013;15:175–184; 4. Ritzel R, et al. Diabetes Obes Metab 2015;17:859–867

The BRIGHT study design

Multicenter, open-label, 1:1 randomized, active-controlled, 2-arm parallel-group, non-inferiority study in adult participants with uncontrolled T2D



[a]With the exception of a maximum of 8 consecutive days or 15 days total prior insulin use
BMI, body mass index; GLP-1 RA, glucagon-like peptide-1 receptor agonist;
OAD, oral antihyperglycemic drug; SMPG, self-monitored plasma glucose; SU, sulfonylureas

Rosenstock J, et al. Diabetes Care 2018;41:2147–54

The BRIGHT study aims

The study was designed to evaluate the efficacy and safety of Gla-300 versus IDeg-100 in insulin-naïve patients with T2D inadequately controlled on OADs ± GLP-1 RAs, during the active titration and maintenance periods

Primary efficacy endpoint:

- **Change in HbA1c from baseline to week 24**
  - Analyzed using a MMRM approach, adjusted for covariates including baseline HbA1c
  - Non-inferiority margin was 0.3 % (HbA1c units)

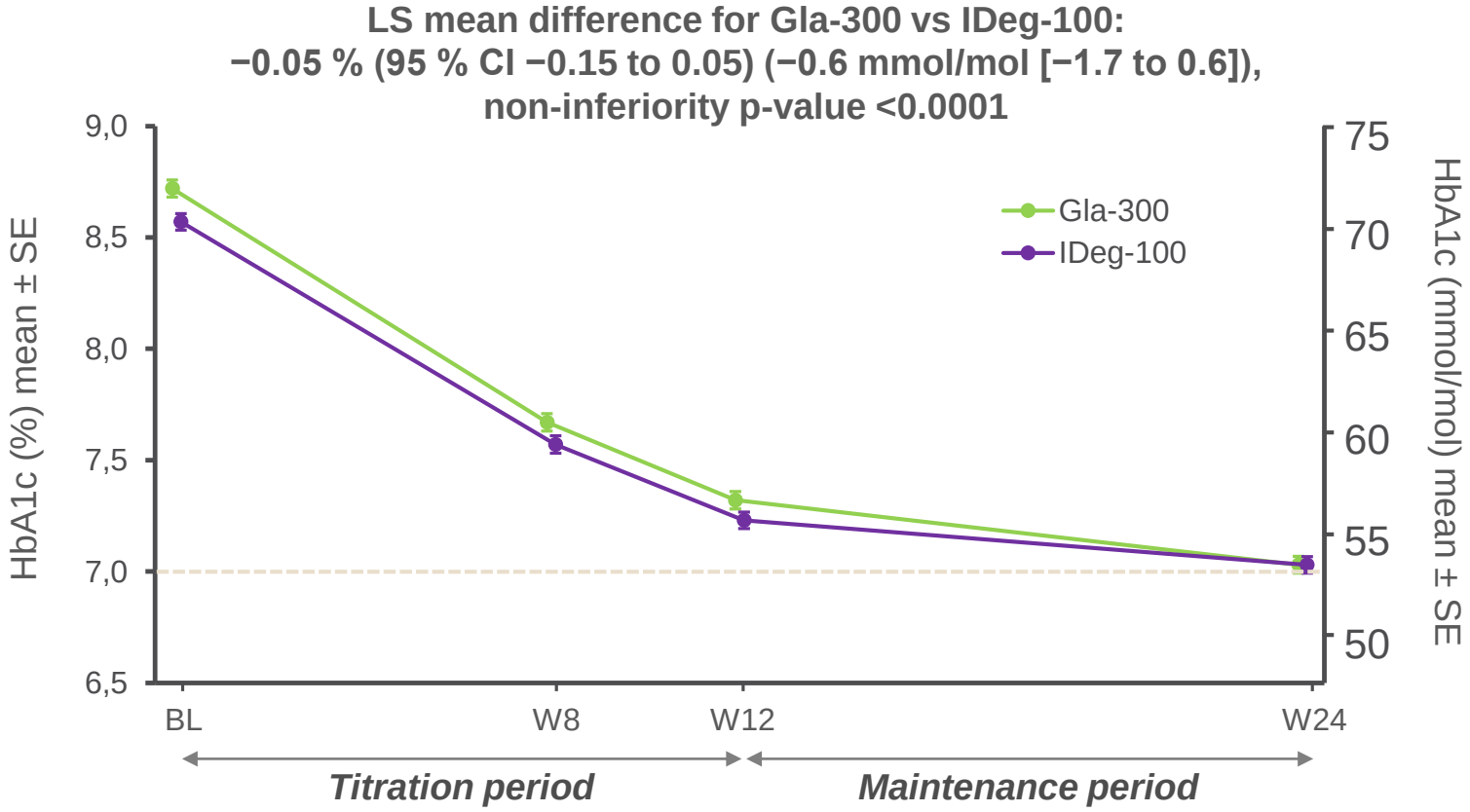
Secondary efficacy and safety endpoints included:

- **Change in HbA1c and fasting SMPG from baseline to week 12**
- **Change in FPG, fasting SMPG and 8-point SMPG profiles from baseline to week 24**
- **Variability of 8-point SMPG profiles**
- **Hypoglycemia (Levels 1, 2 and 3) during the titration, maintenance and whole study periods**

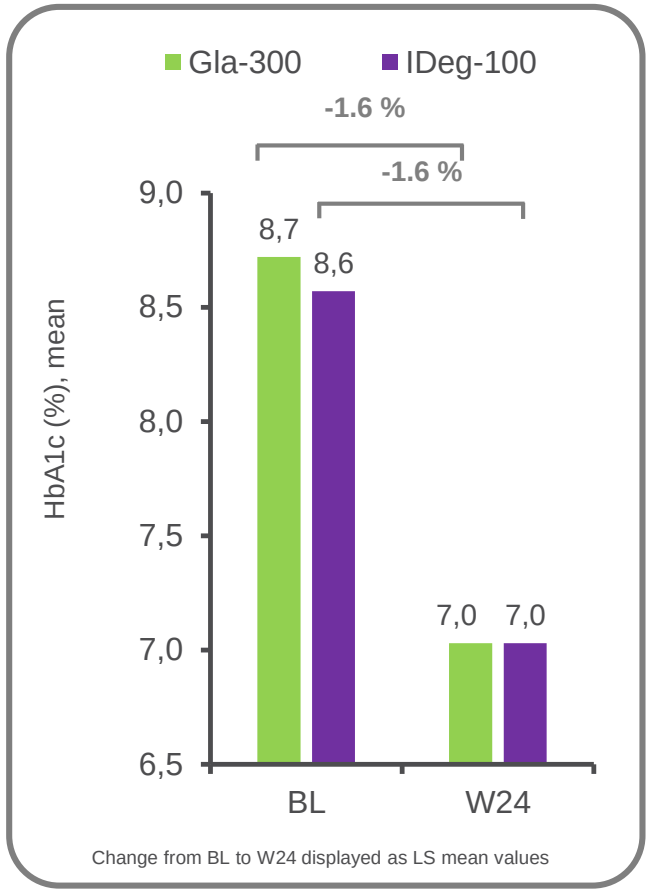
eGFR, estimated glomerular filtration rate; FPG, Fasting plasma glucose;
MMRM, Mixed effect Model for Repeat Measurement

Rosenstock J, et al. Diabetes Care 2018; 41(10): 2147–54.

Non-inferiority of Gla-300 vs IDeg-100 in HbA1c reduction at study end



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

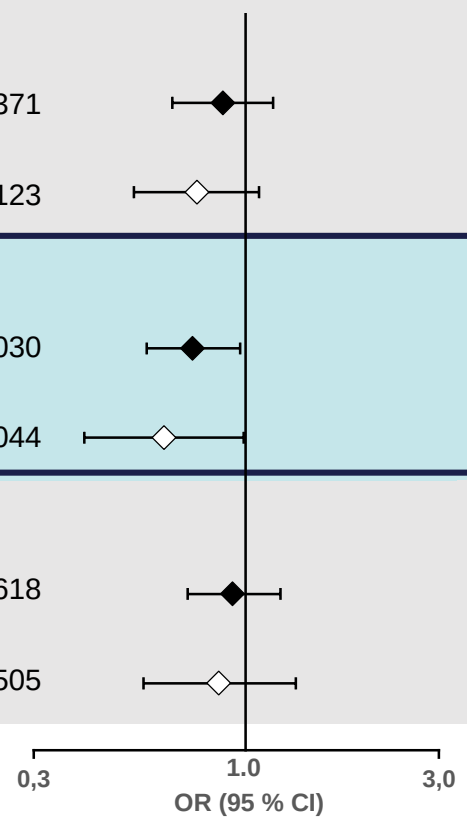


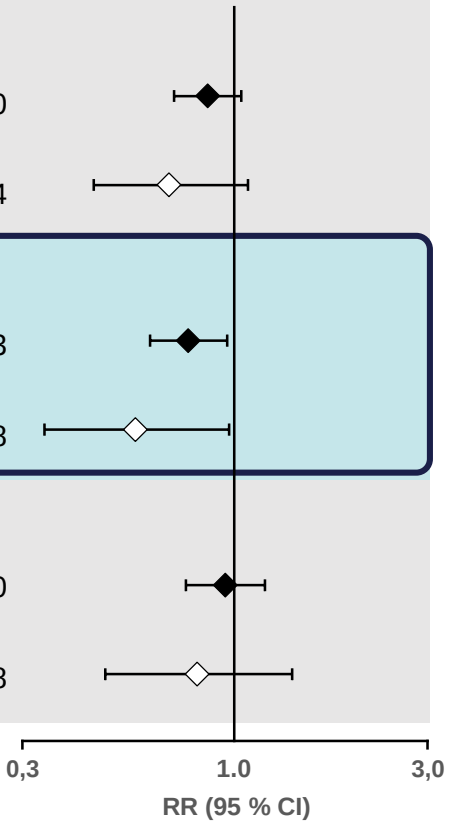
ITT population. BL, baseline; ITT, intention-to-treat; LS, Least square; SE, standard error; W, week

Rosenstock J, et al. Diabetes Care 2018;41:2147–54

Anytime (24 h) hypoglycemia

	Incidence, %				Events per patient-year			
	Gla-300	IDeg-100	OR (95 % CI)	p-value	Gla-300	IDeg-100	RR (95 % CI)	p-value
Full study period (0–24 weeks)								
Confirmed (≤3.9 mmol/l [≤70 mg/dl])	66.5	69.0	0.88 (0.66 to 1.17)	0.371	9.34	10.83	0.86 (0.71 to 1.04)	0.130
Confirmed (<3.0 mmol/l [<54 mg/dl])	14.7	18.4	0.76 (0.53 to 1.08)	0.123	0.61	0.88	0.69 (0.45 to 1.08)	0.104
Titration period (0–12 weeks)								
Confirmed (≤3.9 mmol/l [≤70 mg/dl])	47.4	54.3	0.74 (0.57 to 0.97)	0.030	8.08	10.47	0.77 (0.62 to 0.96)	0.023
Confirmed (<3.0 mmol/l [<54 mg/dl])	7.8	11.7	0.63 (0.40 to 0.99)	0.044	0.49	0.86	0.57 (0.34 to 0.97)	0.038
Maintenance period (13–24 weeks)								
Confirmed (≤3.9 mmol/l [≤70 mg/dl])	54.1	55.8	0.93 (0.72 to 1.22)	0.618	10.64	11.21	0.95 (0.76 to 1.19)	0.650
Confirmed (<3.0 mmol/l [<54 mg/dl])	9.8	11.2	0.86 (0.56 to 1.33)	0.505	0.73	0.91	0.81 (0.48 to 1.39)	0.448



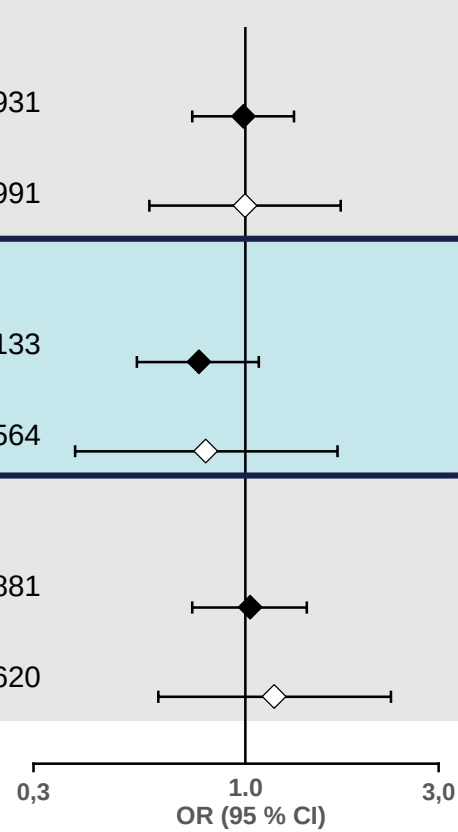


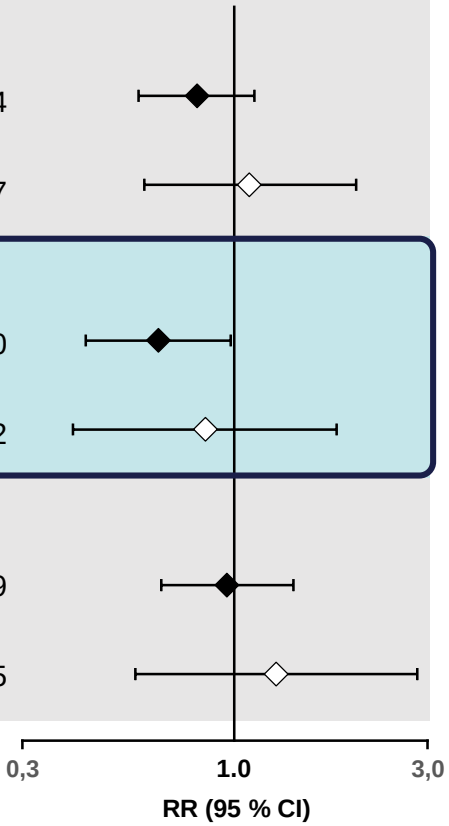
Confirmed hypoglycemia included documented symptomatic or asymptomatic hypoglycemia (≤70 mg/dL or <54 mg/dL), and severe events if any; only 1 participant experienced severe hypoglycemia (1 event), in the Gla-300 group, due to a skipped evening meal and not reducing her insulin dose after a non-severe event 2 days earlier. All p-values presented are nominal. Safety population (Gla-300, n=463; IDeg-100, n=462). OR, odds ratio; RR, rate ratio

Rosenstock J, et al. Diabetes Care 2018;41:2147–54

Nocturnal (00:00–06:00 h) hypoglycemia

	Incidence				Event rates			
	Incidence, %				Events per patient-year			
	Gla-300	IDeg-100	OR (95 % CI)	p-value	Gla-300	IDeg-100	RR (95 % CI)	p-value
Full study period (0–24 weeks)								
Confirmed (≤3.9 mmol/l [≤70 mg/dl])	28.6	28.8	0.99 (0.74 to 1.32)	0.931	1.83	2.26	0.81 (0.58 to 1.12)	0.204
Confirmed (<3.0 mmol/l [<54 mg/dl])	6.1	6.1	1.00 (0.58 to 1.72)	0.991	0.24	0.22	1.09 (0.60 to 2.00)	0.777
Titration period (0–12 weeks)								
Confirmed (≤3.9 mmol/l [≤70 mg/dl])	15.2	18.8	0.77 (0.54 to 1.08)	0.133	1.42	2.20	0.65 (0.43 to 0.98)	0.040
Confirmed (<3.0 mmol/l [<54 mg/dl])	2.8	3.5	0.80 (0.38 to 1.69)	0.564	0.16	0.19	0.85 (0.40 to 1.79)	0.662
Maintenance period (13–24 weeks)								
Confirmed (≤3.9 mmol/l [≤70 mg/dl])	21.4	21.0	1.03 (0.74 to 1.42)	0.881	2.24	2.33	0.96 (0.66 to 1.40)	0.839
Confirmed (<3.0 mmol/l [<54 mg/dl])	4.5	3.8	1.18 (0.61 to 2.29)	0.620	0.33	0.26	1.27 (0.57 to 2.83)	0.555





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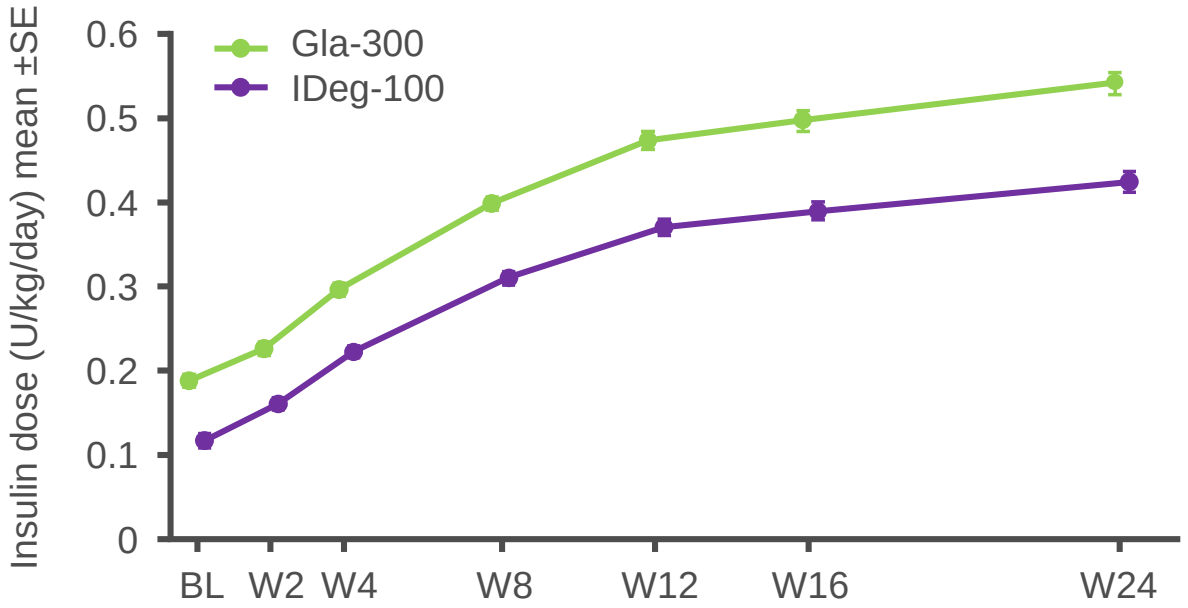
Rosenstock J, et al. Diabetes Care 2018;41:2147–54

Basal insulin dose and body weight over 24 weeks

Mean daily insulin dose



Mean body weight

	Gla-300 (n=462)	IDeg-100 (n=462)
	kg	kg
Baseline	90.6 ± 16.1	88.7 ± 15.9
Week 24	92.5 ± 16.6	91.4 ± 16.7
Change from baseline to week 24	2.0 ± 3.8	2.3 ± 3.6

Data are mean ± SD

Safety population. SD, standard deviation

Rosenstock J, et al. Diabetes Care 2018;41:2147–54

BRIGHT summary

1. BRIGHT was the first direct comparison of Gla-300 vs IDeg-100 in an RCT setting: Similar glycemic control for HbA1c and fasting SMPG
2. During the full study and maintenance periods, anytime and nocturnal confirmed hypoglycemia were comparable
3. During the titration period (0–12 weeks), the rate of anytime and nocturnal confirmed hypoglycemia was lower with Gla-300 vs IDeg-100

Why is renal impairment of interest?

It is common

- CKD prevalence in people with T2D is estimated at ~**38%**[1]
- ~**20%** of people with T2D have moderately to severely reduced kidney function (Stage 3a to 4)[1]

Hypo risk is increased

- CKD is an independent **risk factor** for hypoglycemia and adds to the risk of hypoglycemia in people with T2D[2]

CV risk is increased

- CKD increases morbidity and mortality associated with CV disease[2]

Owing to the increased risk of hypoglycemia and reduced renal clearance in people with T2D and CKD, some anti-hyperglycemic therapies, including insulin, must be used with caution.[2] As such, establishing safety and efficacy of insulin therapy in this population is important

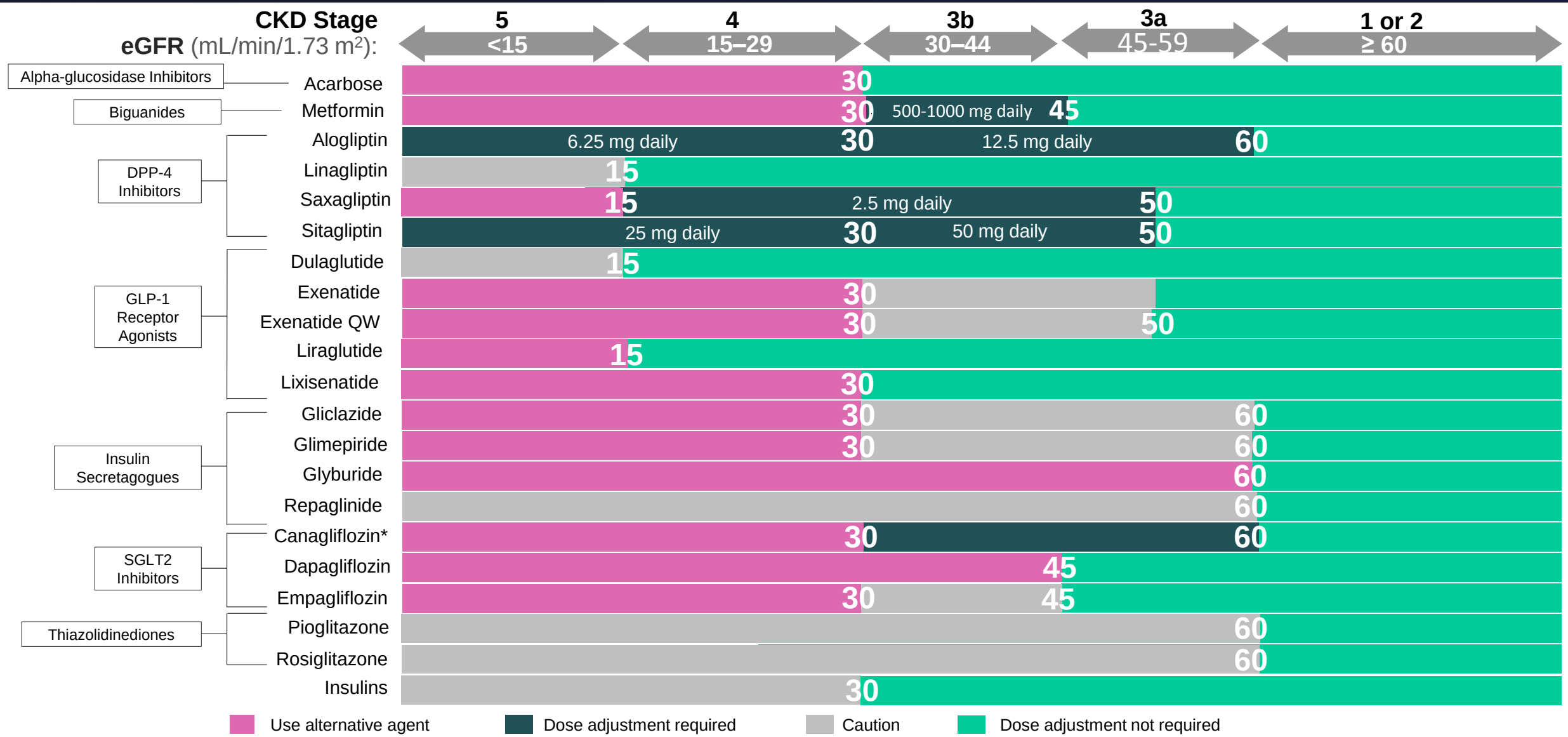
CV, cardiovascular

1. Wu B, et al. BMJ Open Diabetes Res Care 2016; 4: e000154
2. Alsahli M and Gerich JE. Mayo Clin Proc 2014; 89: 1564–71

Question: How do you manage patients with T2D and renal impairment (eGFR <60 mL/min/1.73m^2) who are taking insulin?

- Reduce insulin dose
- Change to an insulin with proven efficacy and safety in patients with renal impairment
- Reduce doses or stop other diabetes medications
- No change

Antihyperglycemic Agents and Renal Function



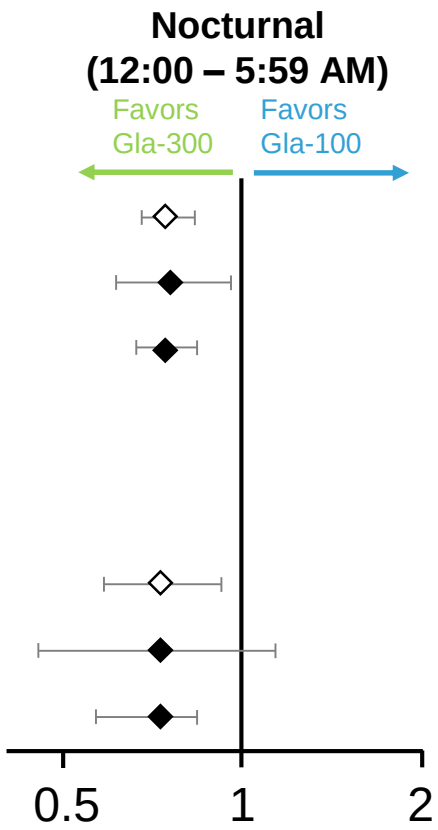
* May be used for cardiorenal benefits in those with clinical CVD, A1C above target and eGFR >30 mL/min/1.73m²

2018 Diabetes Canada CPG – Chapter 13. Pharmacologic Glycemic Management of Type 2 Diabetes

EDITION 1, 2, and 3: Lower risk of nocturnal hypoglycemia with Gla-300 vs Gla-100 in T2D regardless of renal function*

Relative risk of experiencing ≥1 hypoglycemic event with Gla-300 vs Gla-100 by renal function subgroup (safety population)

Renal function subgroup, baseline eGFR (mL/min/1.73m²)	Relative risk (95% CI) Gla-300 vs Gla-100
Confirmed (≤3.9 mmol/L [≤70 mg/dL]) or severe	
Overall	0.75 (0.68 to 0.83)
<60	0.76 (0.62 to 0.94)
≥60	0.75 (0.67 to 0.85)
Confirmed (<3.0 mmol/L [<54 mg/dL]) or severe	
Overall	0.73 (0.59 to 0.91)
<60	0.73 (0.46 to 1.14)
≥60	0.73 (0.57 to 0.94)



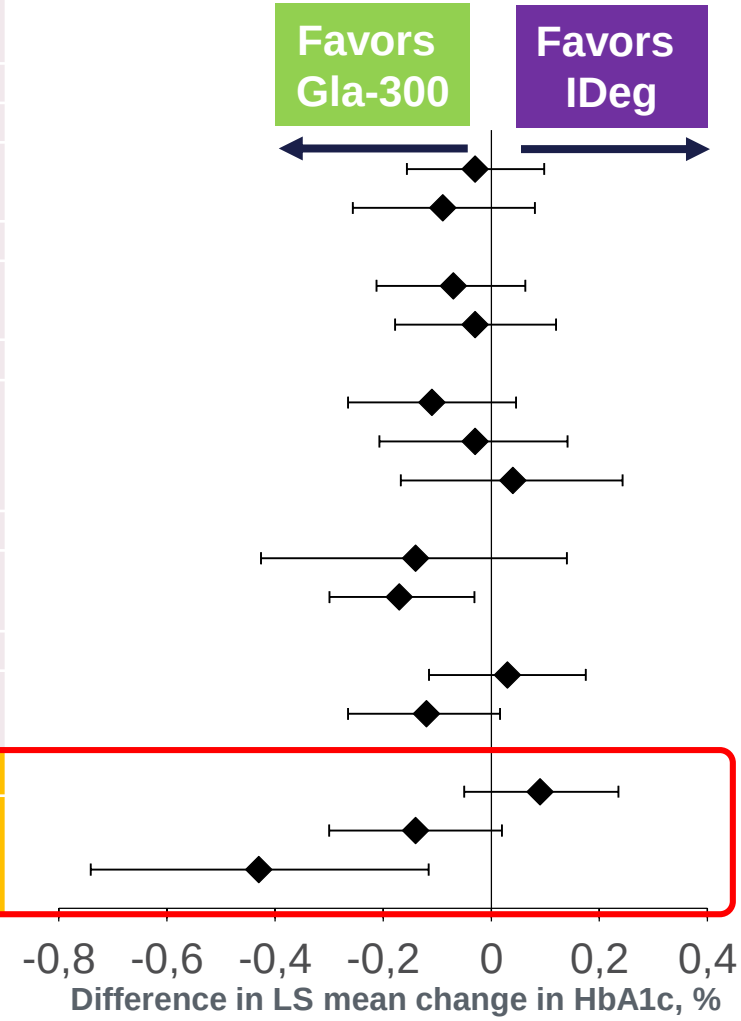
Heterogeneity of treatment effect across subgroup: p=0.662† (nocturnal); p=0.794† (anytime)

*Post-hoc patient-level meta-analysis of people with T2DM treated with Gla-300 or Gla-100 for 6 months in the EDITION 1, 2 and 3 studies by eGFR (N=2496)
†Logistic method; p<0.05 corresponds to significant heterogeneity of treatment effect. CI, confidence interval;.
The decrease in glycated haemoglobin (HbA1c) after 6 months and the proportion of individuals with T2D achieving HbA1c targets were similar in the Gla-300 and Gla-100 groups, for both renal function subgroups
Treatment-emergent adverse events (TEAEs) were observed more commonly in participants in the eGFR <60 mL/min/1.73 m2 vs the ≥60 mL/min/1.73 m2 subgroup

Escalada J et al. Diabetes Obes Metab. 2018 Dec;20(12):2860–8.

Predefined subgroup analysis from BRIGHT: Greater HbA1c reduction with Gla-300 vs IDeg in patients with renal impairment

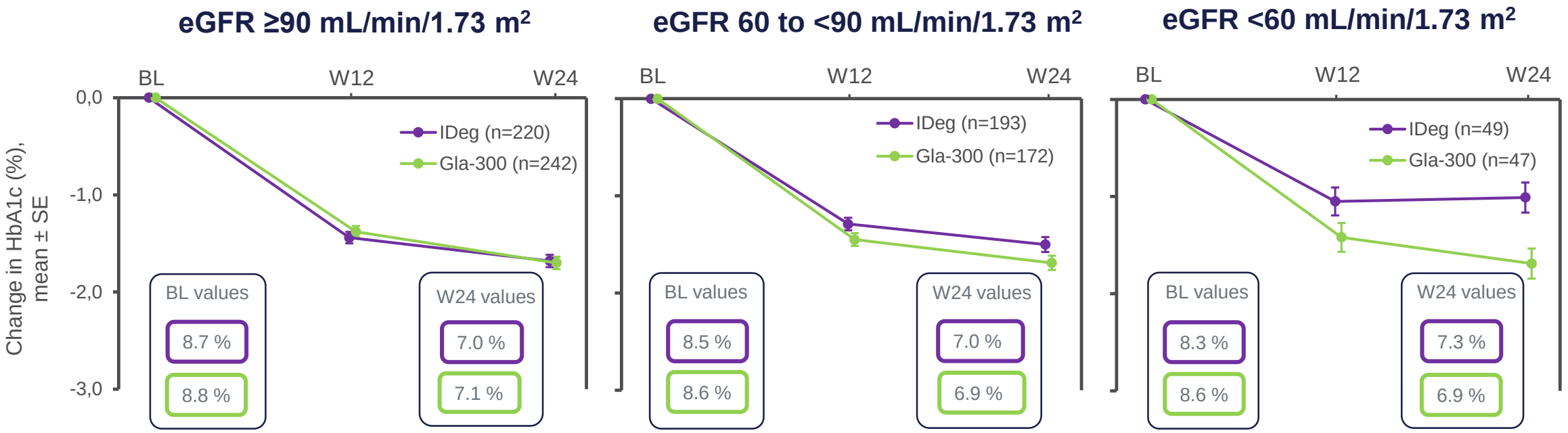
	Difference in LS mean HbA1c change, baseline to week 24, %		p value*
	Difference Gla-300 vs IDeg	95% CI	
Age group, years			
<65	−0.03	−0.156 to 0.098	0.60
≥65	−0.09	−0.256 to 0.081	
Sex			
Male	−0.07	−0.212 to 0.063	0.40
Female	−0.03	−0.178 to 0.120	
Baseline BMI, kg/m^2			
<30	−0.11	−0.265 to 0.046	0.56
30 to <35	−0.03	−0.207 to 0.141	
≥35	0.04	−0.167 to 0.243	
Screening HbA_{1c}, %			
<8	−0.14	−0.426 to 0.140	0.50
≥8	−0.17	−0.299 to −0.031	
Diabetes duration, years			
<10	0.03	−0.115 to 0.175	0.27
≥10	−0.12	−0.265 to 0.016	
Baseline eGFR, mL/min/1.73 m^2			
≥90	0.09	−0.050 to 0.235	**0.02**
60 to <90	−0.14	−0.300 to 0.020	
<60	**−0.43**	**−0.741 to −0.116**	



*treatment by subgroup interaction assessing heterogeneity of treatment effect across subgroups. p-values are not adjusted for multiplicity and are provided for descriptive purpose. LS mean data and 95% CI derived from a Mixed effect Model for Repeat Measurements (MMRM)

Haluzik M, et al. ADA 2019. Abstract 146-OR

Change in HbA1c by renal function subgroup



LS mean difference [95% CI] in change from BL to W24, Gla-300 vs IDeg

0.09 [−0.05 to 0.24]

LS mean difference [95% CI] in change from BL to W24, Gla-300 vs IDeg

−0.14 [−0.30 to 0.02]

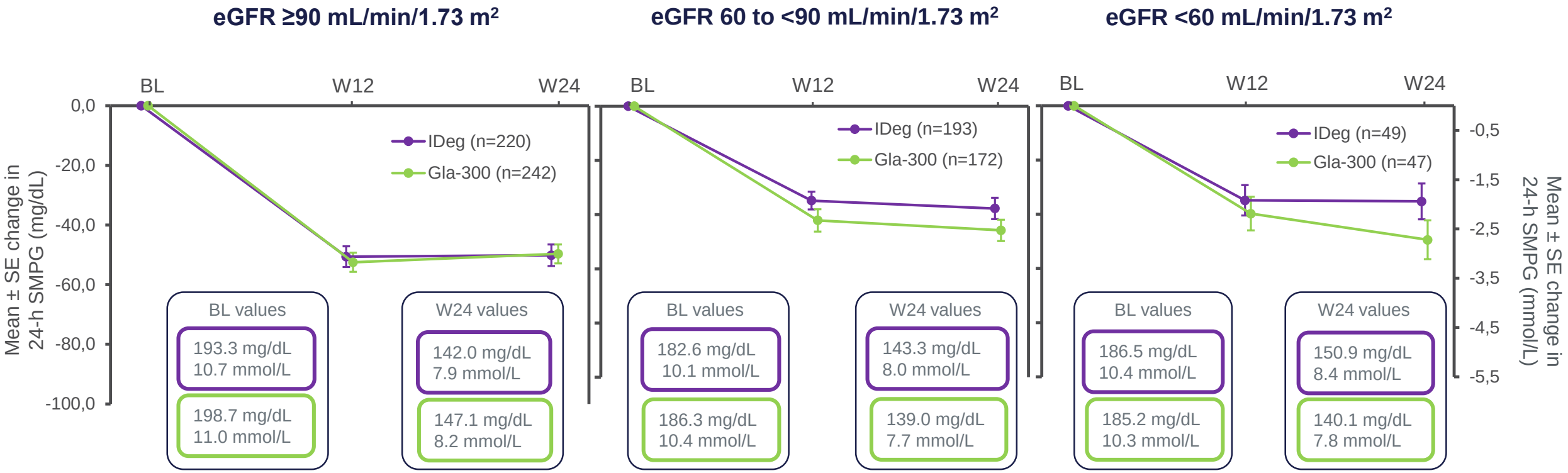
LS mean difference [95% CI] in change from BL to W24, Gla-300 vs IDeg

−0.43 [−0.74 to −0.12]

BL, baseline; CI, confidence interval; eGFR, estimated glomerular filtration rate; Gla-300, insulin glargine 300 U/mL; IDeg, insulin degludec 100 U/mL; LS, least squares; SE, standard error

Haluzik M, et al. ADA 2019. Abstract 146-OR

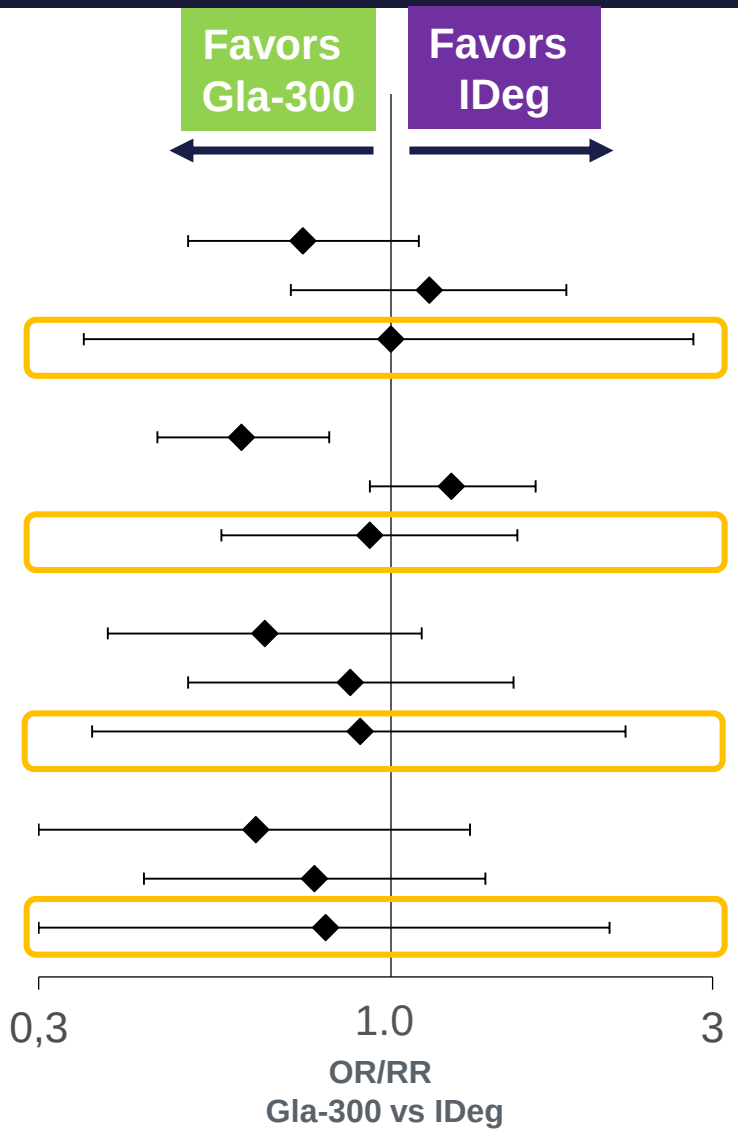
Reductions in mean daily SMPG (from 8-point test) by renal function subgroup showed a similar pattern to that seen for HbA1c



Haluzik M, et al. ADA 2019. Abstract 146-OR

Hypoglycemia with Gla-300 versus IDeg over 24 weeks according to renal function

Baseline eGFR, mL/min/1.73 m²	OR/RR	95% CI
	Incidence of confirmed (≤70 mg/dL [≤3.9 mmol/L]) hypoglycemia	
≥90	0.74	0.50 to 1.10
60 to <90	1.14	0.71 to 1.82
<60	1.00	0.35 to 2.81
	Rate of confirmed (≤70 mg/dL [≤3.9 mmol/L]) hypoglycemia	
≥90	0.60	0.45 to 0.81
60 to <90	1.23	0.93 to 1.64
<60	0.93	0.56 to 1.54
	Incidence of confirmed (<54 mg/dL [<3.0 mmol/L]) hypoglycemia	
≥90	0.65	0.38 to 1.11
60 to <90	0.87	0.50 to 1.52
<60	0.90	0.36 to 2.23
	Rate of confirmed (<54 mg/dL [<3.0 mmol/L]) hypoglycemia	
≥90	0.63	0.30 to 1.31
60 to <90	0.77	0.43 to 1.38
<60	0.80	0.30 to 2.11



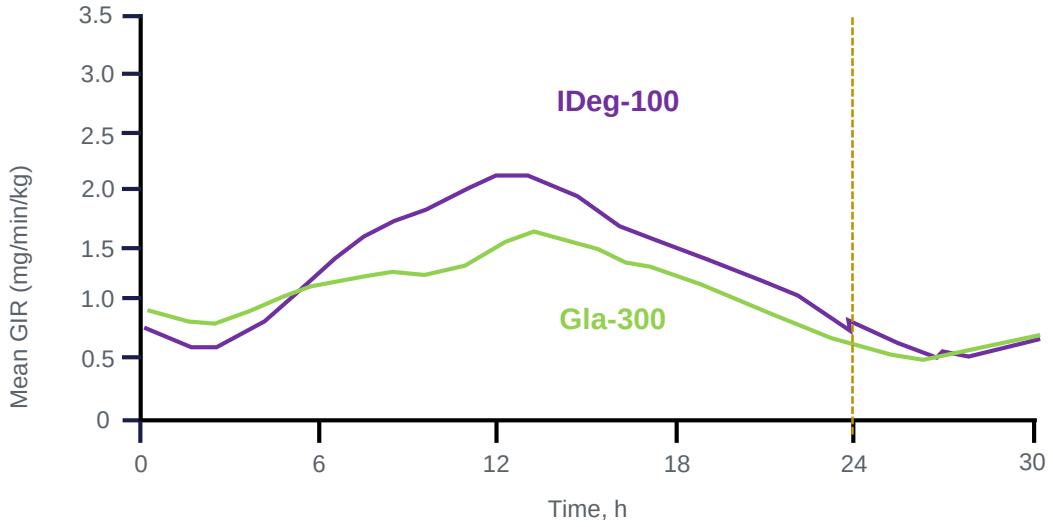
Rate ratios and CIs are based on an overdispersed Poisson regression model. Odds ratios and CIs are based on a logistic regression analysis

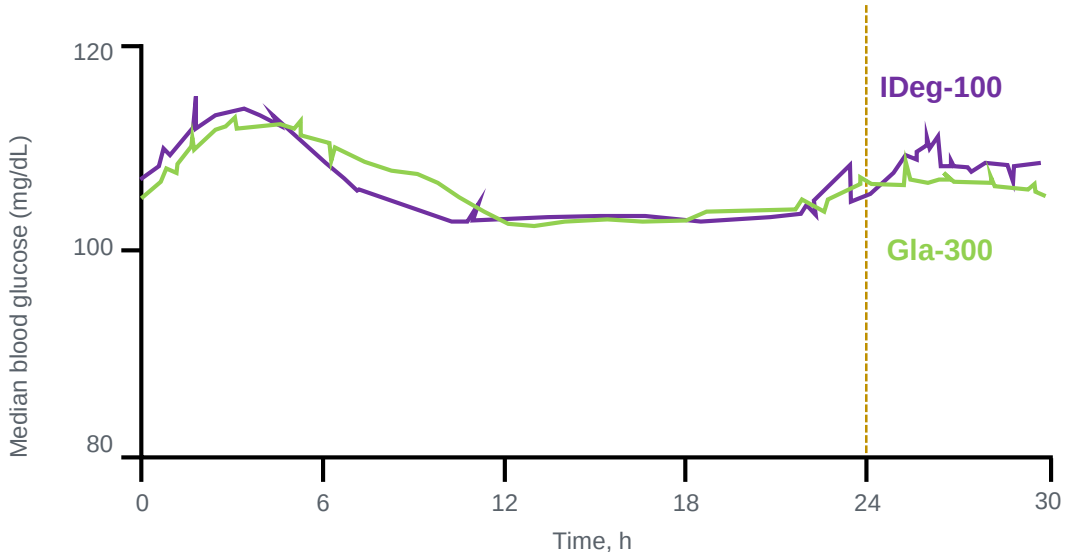
Haluzik M, et al. ADA 2019. Abstract 146-OR

Potential explanations and further investigations

Hypothesis: Results could be explained by some differences in insulin characteristics

- **Differences in PK/PD** profile (differences in PK related to renal function?)



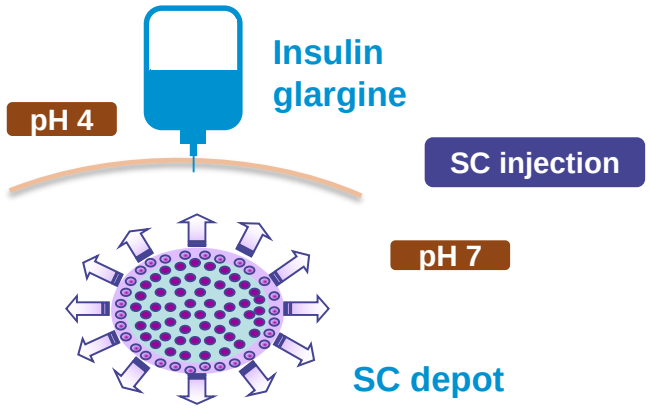


Adapted from Bailey TS et al. Diabetes Metab. 2018 Feb;44(1):15-21

Hypothesis: Results could be explained by some differences in insulin characteristics

- Different **modes of action** (i.e. albumin binding)

Gla-300

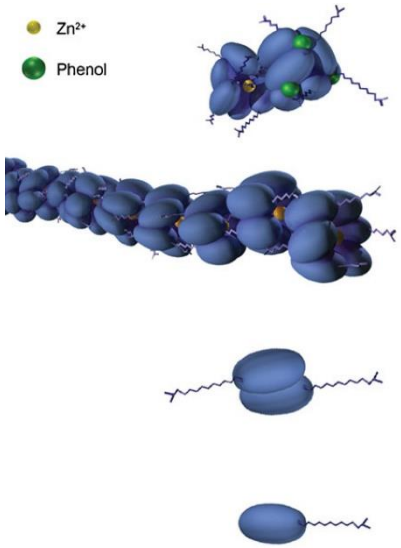


For illustrative purposes only

Following SC injection, insulin glargine precipitates amorphously creating a SC depot at physiological pH

Active metabolite, 21A-Gly-human insulin, forms and is released slowly from the depot to the circulation

IDeg



Degludec binds strongly but reversibly to albumin via its fatty di-acid side chain resulting in plasma protein binding of more than 99%

Vora et al. Diabetes Res Clin Pract. 2015 Jul;109(1):19-31. Jonassen I, et al. , Pharm Res 2012; 29:2104–2114. Monnier L, et al. Diabetes & Metabolism 2013; 39: 468-476; Hedrington MS et al. Diabetes Technol Ther. 2011;13 Suppl 1:S33-42; Becker RH et al. Diabetes Care. 2015;38:637–43

Hypothesis: Results could be explained by some differences in insulin characteristics

- **Differences in titration**

Titration algorithms should be **SAFER** and **EASIER**

SAFER

Gla-300 shows a lower risk of hypoglycemia during the titration period compared to Gla-100 and IDeg[1–5]

Similar glycemic control was demonstrated between Gla-100 and Gla-300 during the titration period in people with T2D[4,6]

EASIER

Titration proven with different algorithms (daily, every 3 days, weekly)[7,8]

Gla-300 titration can also be supported with dosing decision tools[9]

1. Riddle MC et al. Diabetes Care. 2014;37:2755–62; 2. Yki-Järvinen H et al. Diabetes Care. 2014;37:3235–43; 3. Bolli GB et al. Diabetes Obes Metab. 2015;17:386–94; 4. Home PD et al. Diabetes Care. 2015;38:2217–25; 5. Rosenstock J, et al. Diabetes Care 2018; DOI: 10.2337/dc18-0559; 6. Mauricio D, et al. European Endocrinology. 2018;14(Suppl 1):2–9; 7. Ritzel R et al. Diabetes Obes Metab. 2015;17:859–67; 8. Yale J, et al. Can J Diabetes. 2017;41:478–84; 9. Davies M, et al. J Diabetes Sci Technol 2019;13:881-9

Take home messages

1. BRIGHT was the first direct comparison of Gla-300 vs IDeg-100 in an RCT setting: Similar glycemic control for HbA1c and fasting SMPG
2. During the full study and maintenance periods, anytime and nocturnal confirmed hypoglycemia were comparable
3. During the titration period (0–12 weeks), the rate of anytime and nocturnal confirmed hypoglycemia was lower with Gla-300 vs IDeg-100
4. In a pre-specified sub-group analysis, greater HbA1c reduction was seen with Gla-300 vs IDeg-100 in patients with impaired renal function, and similar hypoglycemia incidence or rates over the full study period
5. Further investigation is required to determine if Gla-300 may allow for more effective and safer glycemic management in this vulnerable population

55th EASD Annual Meeting

Diabetes journey: Innovative solutions for individual needs

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