Treatment Effects of Once-Weekly Dulaglutide Versus Insulin Glargine in Patients With Different Baseline Glycemic Patterns (Based on High/Low Fasting or High/Low Postprandial Glucose): A Post Hoc Analysis of the AWARD-2 Clinical Trial

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OBJECTIVE

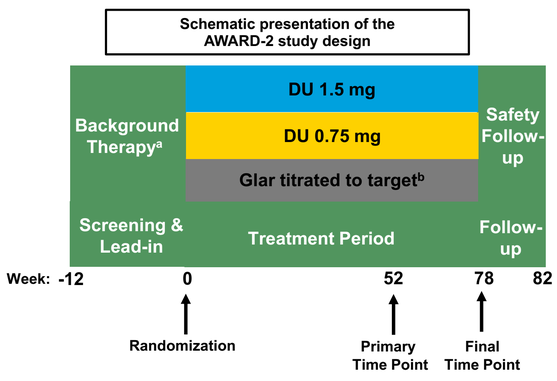
Question: What is the effect of dulaglutide (DU) 1.5 mg versus insulin glargine (Glar) in patients with type 2 diabetes (T2D) that have different glycemic patterns?

- **The effects of DU 1.5 mg and Glar were compared in patients with T2D at 52 weeks from the AWARD-2 study with prevalent elevations in fasting glucose (FG), postprandial glucose (PPG), or both FG and PPG at baseline**
- **Changes in glycated hemoglobin (A1c), FG, PPG, body weight, and hypoglycemia were investigated**

STUDY DESIGN

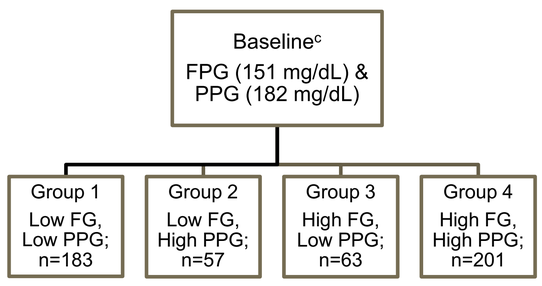
This is a post hoc analysis from the AWARD-2 study.[1]

Schematic presentation of the AWARD-2 study design



Schematic presentation depicting how patients were categorized into 4 groups based on combinations of low and high FG and PPG, with median baseline values of FG (151 mg/dL) and PPG (182 mg/dL) being used as threshold for low and high, respectively.

Cutoffs: Low FG (≤151); High FG (>151); Low PPG (≤182); High PPG (>182)

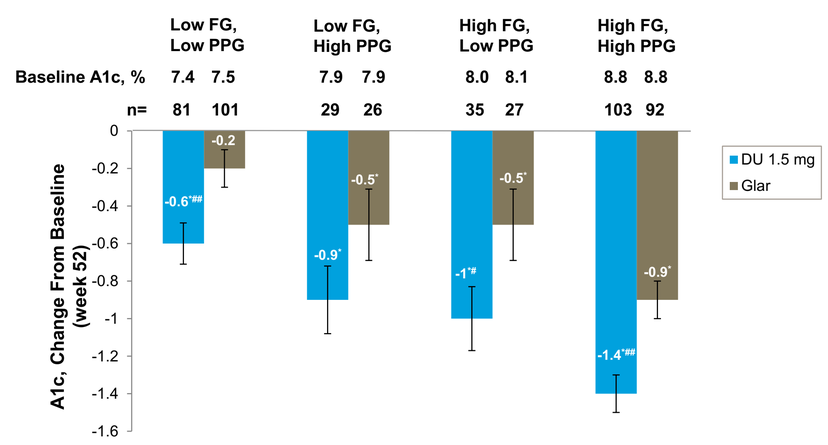


[a] During the lead-in period, metformin (≥1500 mg) and glimepiride (≥4 mg) were titrated up to maximum tolerated dose, then doses were stable for 6 to 8 weeks. Oral anti-hyperglycemic medications continued for the duration of the trial. [b] FG target: <100 mg/dL.[43]
[c] Median baseline values of FPG and PPG being used as threshold to define low and high values, respectively.
Abbreviations: DU, dulaglutide; FG, fasting glucose; FPG, fasting blood glucose; Glar, insulin glargine; PPG, postprandial glucose.

KEY RESULT

DU 1.5 mg resulted in a greater reduction of A1c when compared with Glar among patients with different glycemic patterns at 52 weeks

Glycemic patterns of glucose: A1c change from baseline at week 52



Least square mean for change in baseline at week 52.
*p<.001 change from baseline; #p<.05 for comparison with Glar; ##p<.01 for comparison with Glar.
Abbreviations: A1c, glycated hemoglobin; DU, dulaglutide; FG, fasting glucose; Glar, insulin glargine; PPG, postprandial glucose.

CONCLUSION

- DU 1.5 mg resulted in a greater reduction in A1c compared with Glar at 52 weeks among patients with different glycemic patterns defined by FG and PPG levels at baseline
  - Despite the limited sample size, statistically significant differences between treatments were found among the subgroups except for the low FG/high PPG subgroup
- DU 1.5 mg resulted in a greater reduction in weight compared with Glar, whereas Glar increased weight among patients with different glycemic patterns
- Results for documented symptomatic hypoglycemia were consistently lower for DU 1.5 mg versus Glar in all subgroups

Limitations

- This post hoc analysis had small sample sizes, especially for low FG/high PPG and high FG/low PPG subgroups
- The median was chosen as the cutoff (i.e., not the clinical cut) due to sample size
  - This may have influenced the results because the phenotype is less strictly defined

Background

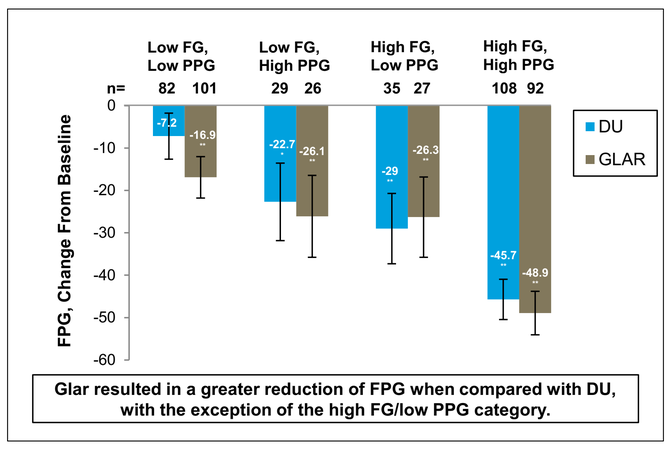
- Glar exerts its action primarily through a decrease in hepatic glucose production and consequent lowering of FG with smaller effects on PPG and glucose excursions after meals
- DU, a once-weekly GLP-1 receptor agonist (GLP-1RA), stimulates insulin secretion and suppresses glucagon levels both in the fasting and postprandial states, resulting in reductions of both FG and PPG
- DU demonstrated greater reductions in A1c than Glar in AWARD-2 with better weight control and less hypoglycemia[1]
- Patients with T2D are characterized by distinct glycemic patterns, with some of the patterns showing prevalent elevations in FG and/or PPG[2]

Demographics and Baseline Characteristics

Variables	Low FG, Low PPG n=292	Low FG, High PPG n=90	High FG, Low PPG n=92	High FG, High PPG n=292	Overall n=766
Age (years), mean (SD)	56.4 (10.01)	56.3 (8.76)	56.3 (9.50)	56.8 (9.29)	56.51 (9.52)
Male, n (%)	141 (48.3)	53 (58.9)	51 (55.4)	150 (51.4)	395 (51.6)
Duration of diabetes (years), mean (SD)	8.8 (6.29)	8.2 (5.23)	8.9 (6.69)	9.6 (5.83)	9.04 (6.06)
A1c at baseline (%), mean (SD)	7.58 (0.71)	7.93 (0.78)	7.98 (0.75)	8.78 (0.97)	8.13 (0.99)
Weight, kg	84.87 (18.99)	83.16 (19.19)	86.04 (18.99)	88.70 (17.60)	86.27 (18.57)
Baseline FPG, mg/dL	126.30 (15.76)	134.09 (11.81)	167.27 (12.26)	195.11 (35.43)	158.37 (39.91)
Baseline PPG, mg/dL	150.54 (20.47)	206.90 (20.70)	163.48 (14.03)	233.01 (39.84)	190.15 (47.49)

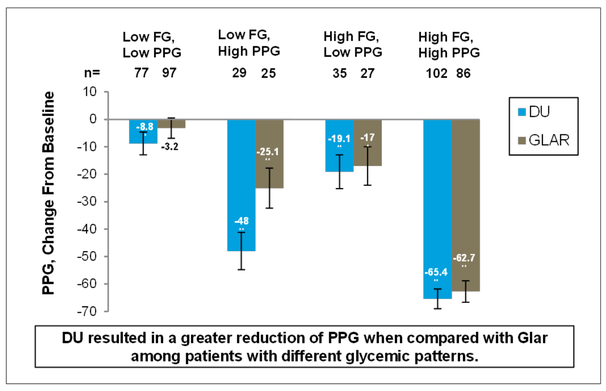
Abbreviations: A1c, glycated hemoglobin; FG, fasting glucose; FPG, fasting plasma glucose; PPG, postprandial glucose; SD, standard deviation.

Changes from Baseline for Fasting Plasma Glucose, Postprandial Glucose, and Body Weight at 52 Weeks

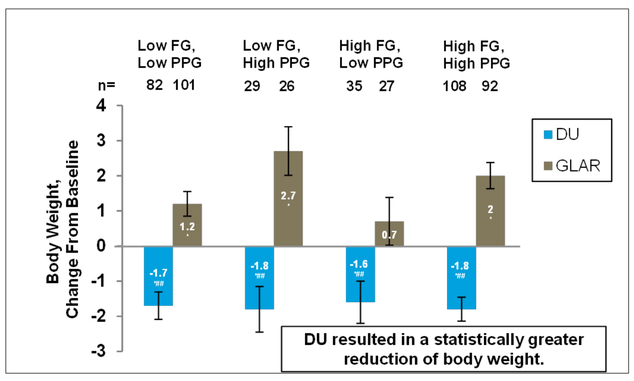


Glar resulted in a greater reduction of FPG when compared with DU, with the exception of the high FG/low PPG category.

Glucose values for FG and PPG are from self-monitored plasma glucose and central laboratory, respectively.
Least square mean for change from baseline at week 52. *p<.05 and **p<.001 change from baseline; ##p<.01 for comparison with Glar.
Abbreviations: DU, dulaglutide; FG, fasting glucose; FPG, fasting plasma glucose; Glar, insulin glargine; PPG, postprandial glucose.



DU resulted in a greater reduction of PPG when compared with Glar among patients with different glycemic patterns.



DU resulted in a statistically greater reduction of body weight.

Documented Symptomatic Hypoglycemia for DU and GLAR and GLAR Dose in Subgroups

Variables	Low FG, Low PPG		Low FG, High PPG		High FG, Low PPG		High FG, High PPG	
	DU 1.5 n=82	GLAR n=101	DU 1.5 n=30	GLAR n=27	DU 1.5 n=35	GLAR n=28	DU 1.5 n=108	GLAR n=93
Documented symptomatic hypoglycemia at 52 weeks								
n (%)	32 (39.0)	44 (43.6)	12 (40.0)	14 (51.9)	14 (40.0)	12 (42.9)	38 (35.2)	47 (50.5)
GLAR dose at 52 weeks, units								
Mean (SD)	--	24.22 (20.35)	--	30.15 (39.15)	--	24.57 (11.96)	--	33.05 (19.90)

Abbreviations: DU, dulaglutide; FG, fasting glucose; GLAR, insulin glargine; PPG, postprandial glucose; SD, standard deviation.

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References:
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2. Bonora E, et al. *Diabetologia*. 2006;49:846-54.
3. Kennedy L, et al. *Diabetes Care*. 2006;29(1):1-8.

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