The basal plus strategy

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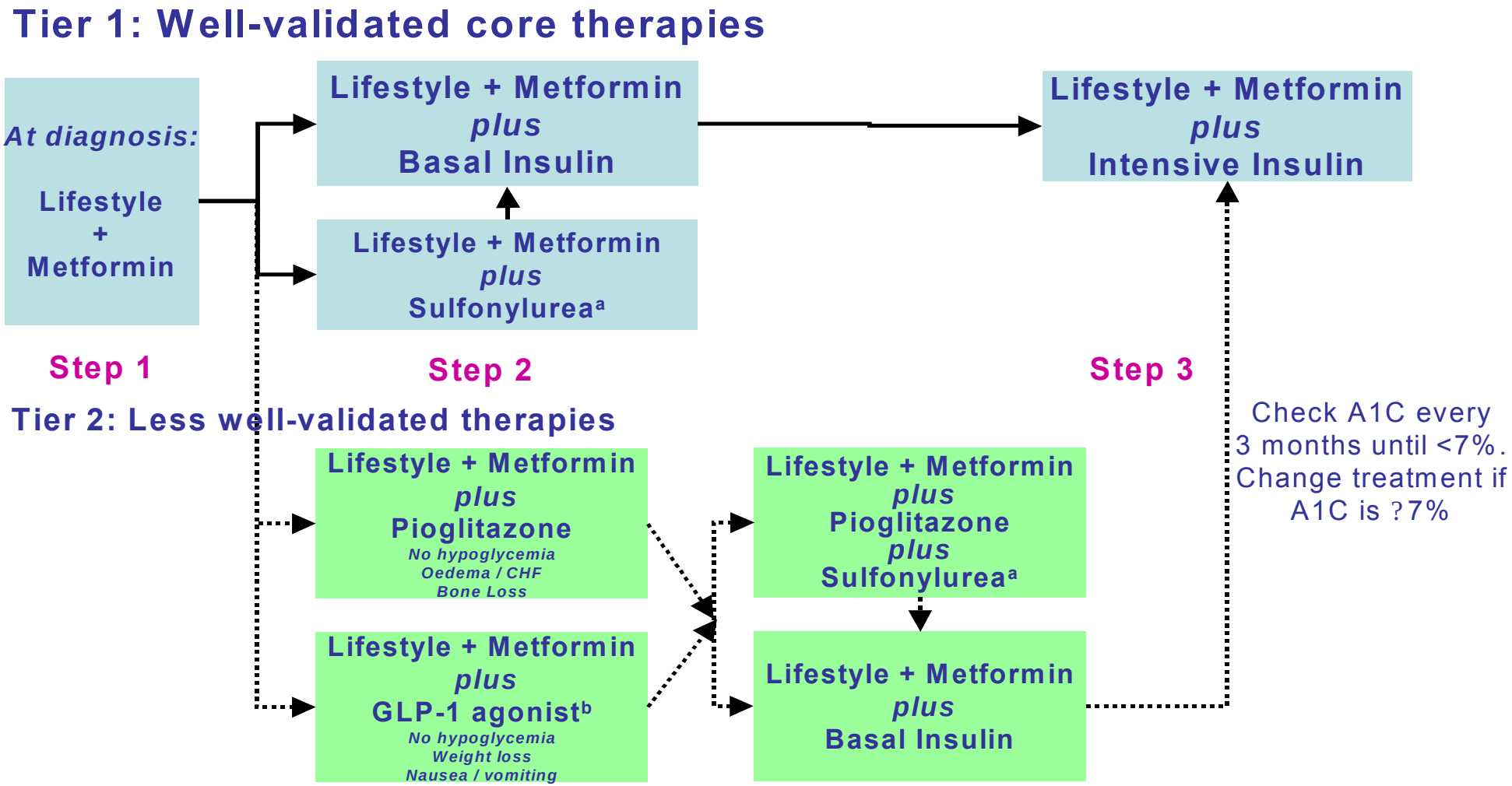
ADA/EASD guidelines recommend use of basal insulin as early as the second step in type 2 diabetes management



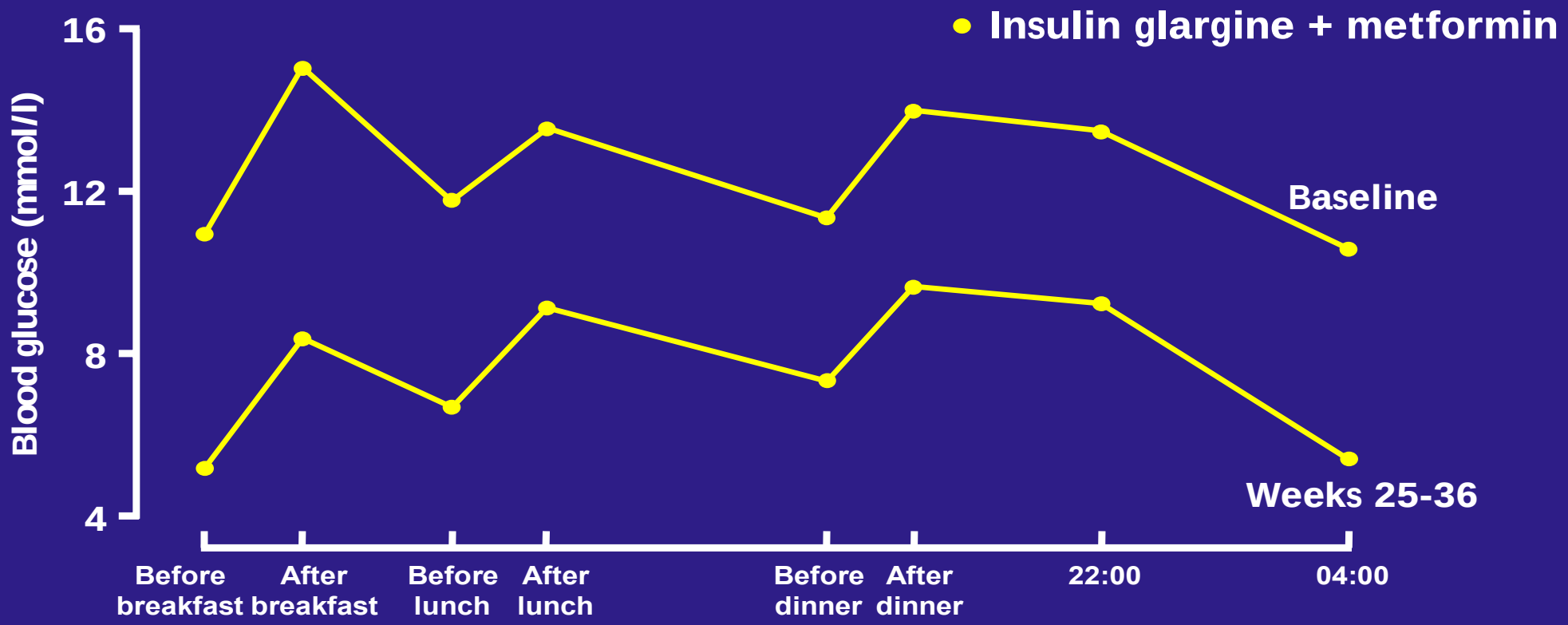
ADA/EASD Guidelines. Diabetes Care 2008;31(12):1–11

a Sulfonylureas other than glybenclamide or chlorpropamide.
b Insufficient clinical safety data; CHF, congestive heart failure

The concept of basal insulin therapy

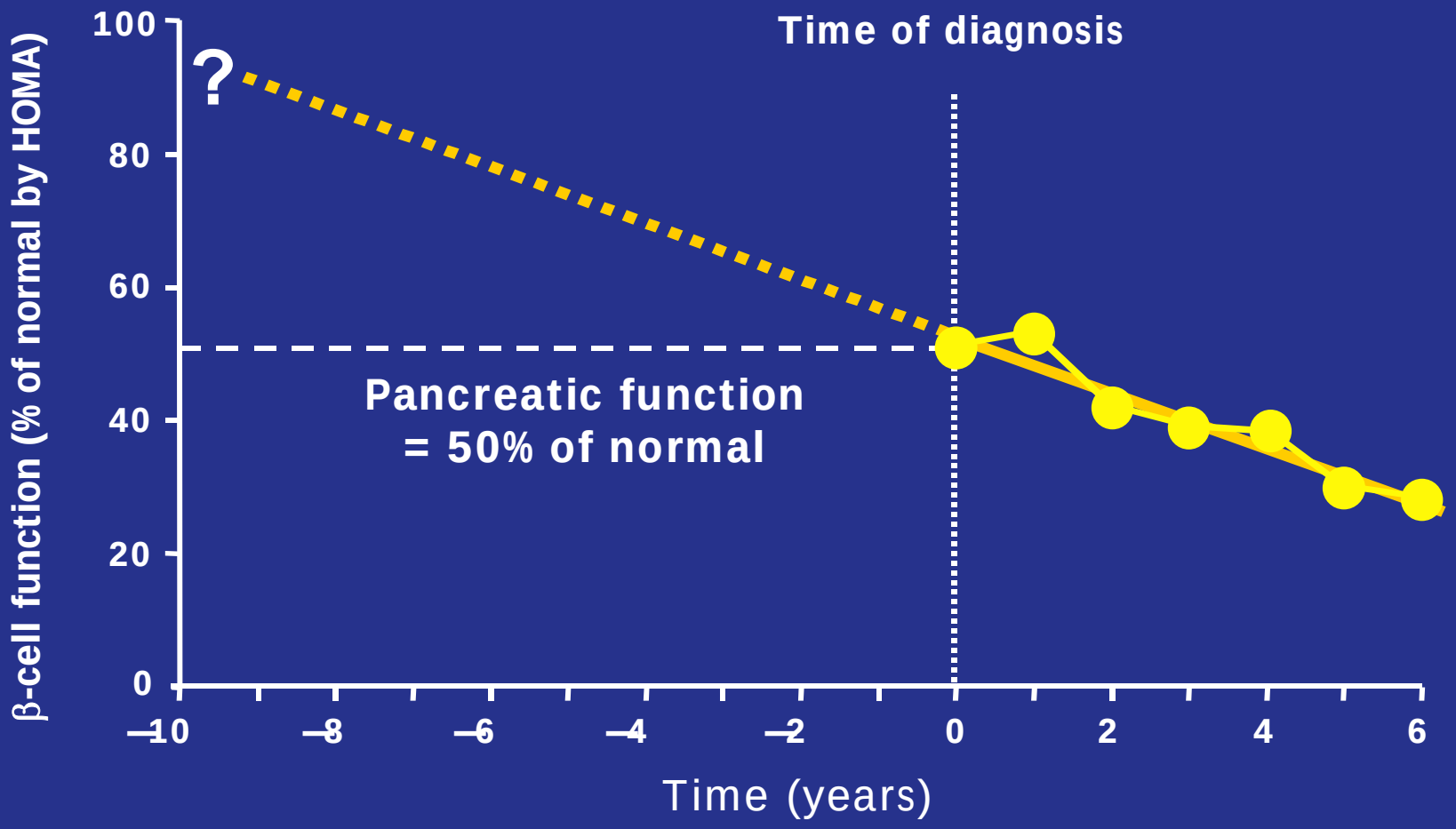
Postprandial hyperglycemia persists despite treatment of FBG using basal insulin

- Basal insulin therapy reduces the entire 24-hour blood glucose profile, but postprandial hyperglycaemia persists — LANMET study data



Yki-Järvinen H, et al. Diabetologia 2006;49:442-51.

Decline of β-cell function determines the progressive nature of T2DM



HOMA=homeostasis model assessment.
UKPDS Group. Diabetes 1995;44:1249–58.
Adapted from Holman RR. Diabetes Res Clin Pract 1998;40(suppl 1):S21–5.

Insufficiency of basal insulin + OAD

Definition

- FBG < 100mg/dl,
- with HbA1c > 7% and/or PPG > 140-160 mg/dl,
- Suggesting that OAD (insulin secretagogues) loose their capability to control PPG, and that prandial insulin supplementation must be considered.

Insufficiency of basal insulin + OAD different situations

- 30 to 50% of patients treated by basal insulin do not reach the HbA1c target, at initiation, and despite optimisation of the dose (basal insulin is not enough)

Riddle M et al. Treat To Target. Diabetes Care 2005

- Natural history of the pancreatic disease in type 2 diabetes (basal insulin is no longer enough with time)

- Hypoglycemic risk during the titration of basal insulin making difficult to reach the FBG target

- Very high dose of basal insulin without significant effect on FBG, and weight gain (severe insulin resistance)

Monnier et coll. Diab Metab 2006

What options are available when basal insulin therapy is no longer sufficient for glycemic control ?

Insulin intensification

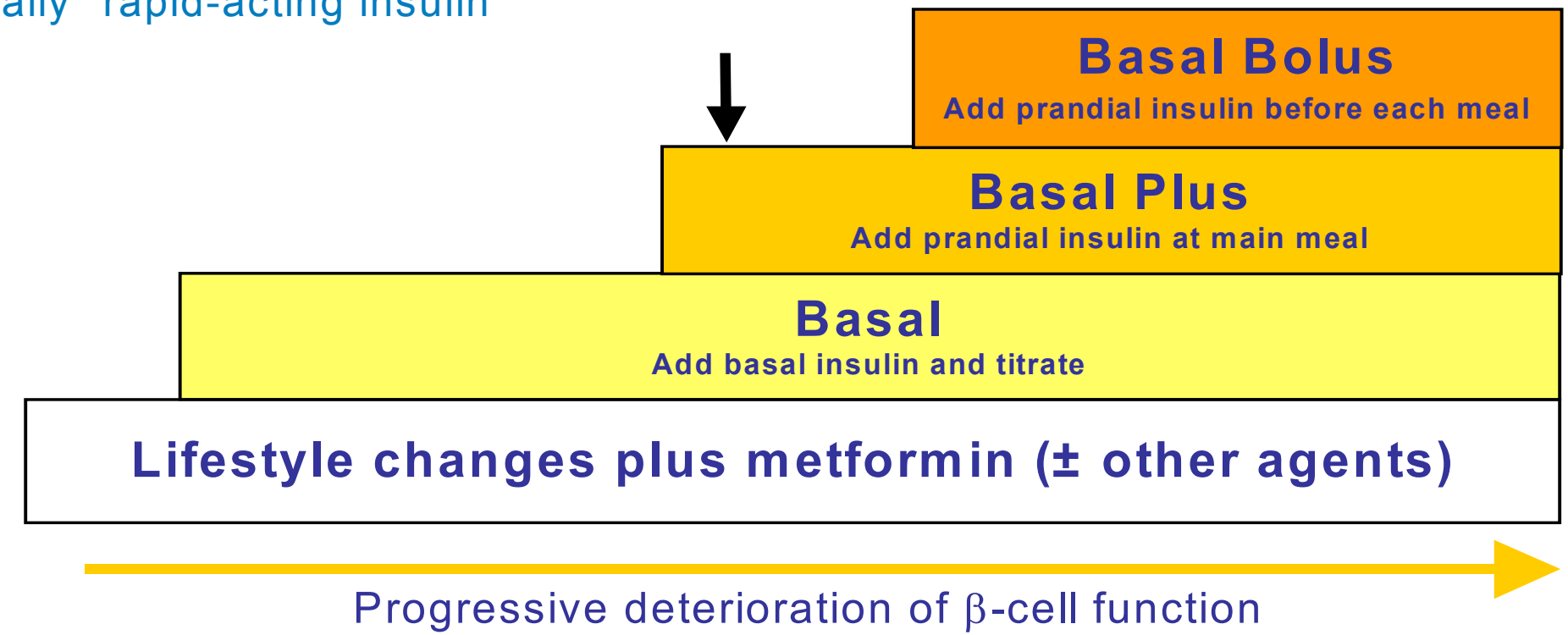
1- Premix insulin

2- Basal Bolus regimen

3- The Basal Plus strategy

Type 2 diabetes: matching treatment to disease progression using a stepwise approach

Basal Plus: once-daily basal insulin plus once daily* rapid-acting insulin



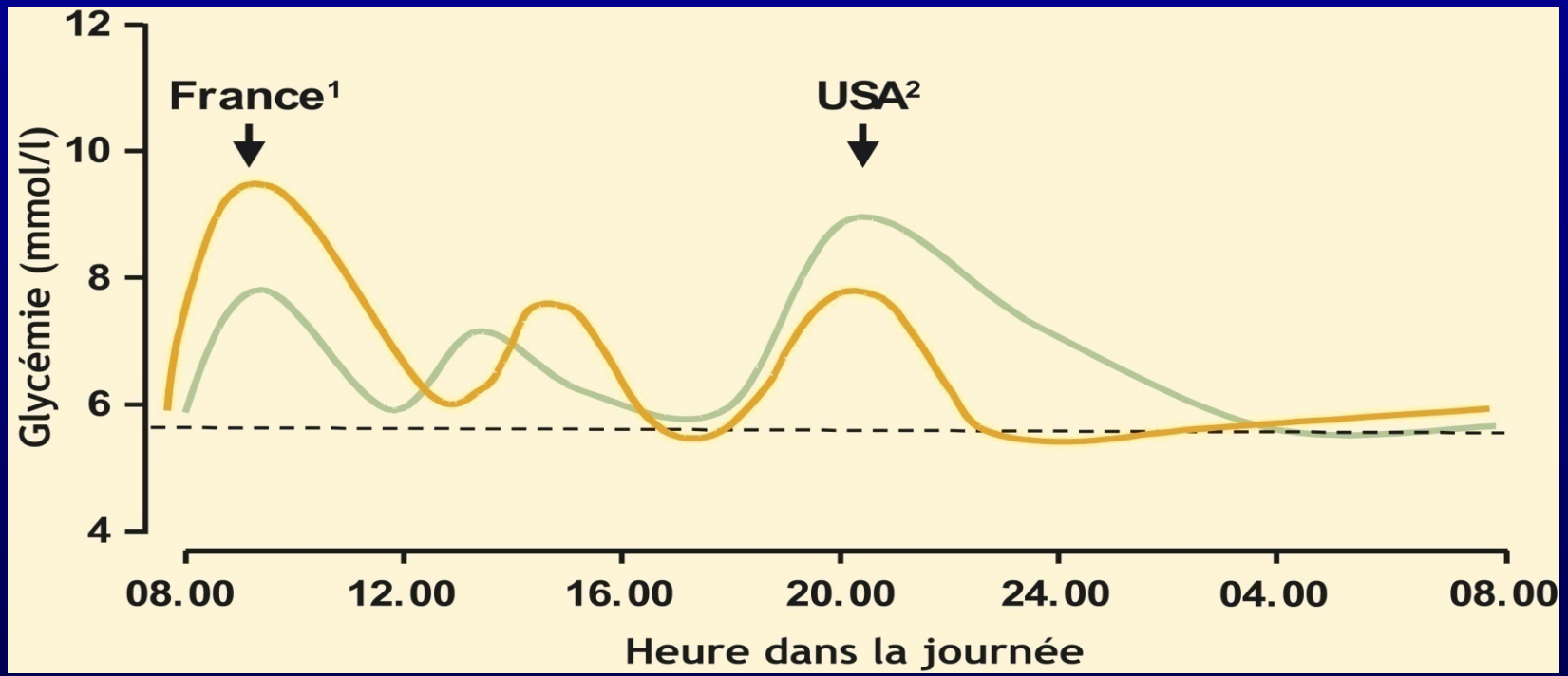
*As the disease progresses, a second daily injection of prandial insulin may be added

Adapted from Raccah D, et al. Diabetes Metab Res Rev 2007; 23(4):257?64

Rationale for the « basal plus » strategy

- PPG is correlated to HbA1c
- The PPG is not the same according to the meals of the day, and vary from one patient to another, and from one country to another (the highest being after breakfast in France, and after dinner in USA)
- The control of the highest PPG could influence the rest of the day.

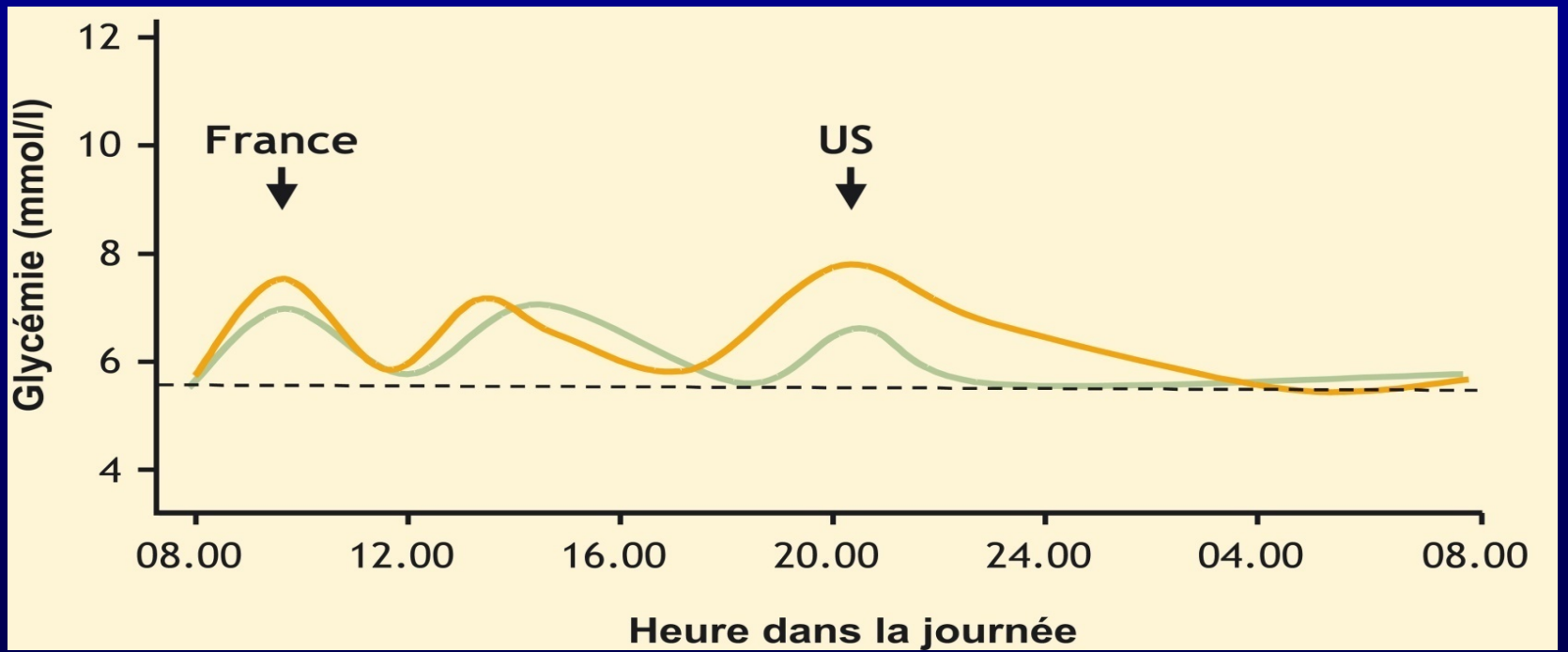
Glycemic profile according to the country



1] Monnier J et coll. Diabetes Care 2002;25:737-41
[2]Rosenstock J et coll. Chapter 9. In:CADRE Handbook of diabetes management.New York:Medical information press;2004:pp145-68

« Basal Plus »

Basal insulin + prandial insulin at the main meal



Raccah D et al. Diabetes Metab Res Rev 2007

Basal Plus: general considerations for treatment with once-daily basal insulin plus once daily rapid prandial insulin

- **Fix fasting first**
  - Titrate basal insulin to control fasting BG
- **For some patient candidates, basal will not be enough**
  - Intensify treatment
- **Add prandial insulin to control postprandial BG for efficacy and safety in patient candidates with:**
  - HbA1c >7% to <9% despite optimal titration of basal insulin[1]
  - And FBG control close to or at target[2]

Raccah D, et al. Diabetes Metab Res Rev 2007;23:257–64

POC: comparing Basal Plus therapy with insulin glargine alone

Patients:

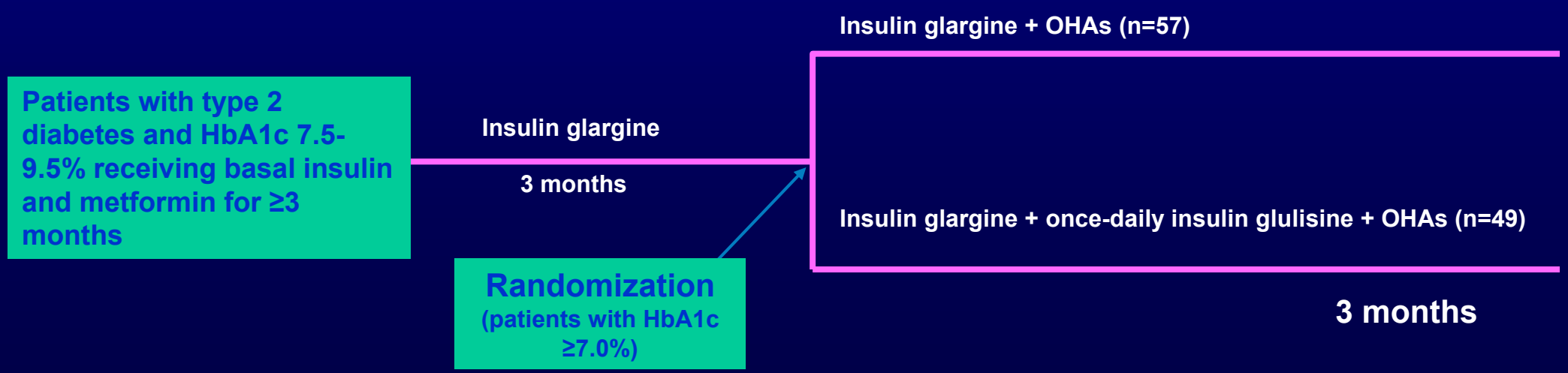
- Previously received basal insulin for ≥3 months
- Previously received metformin, and continued to receive OHAs during the study

Design:

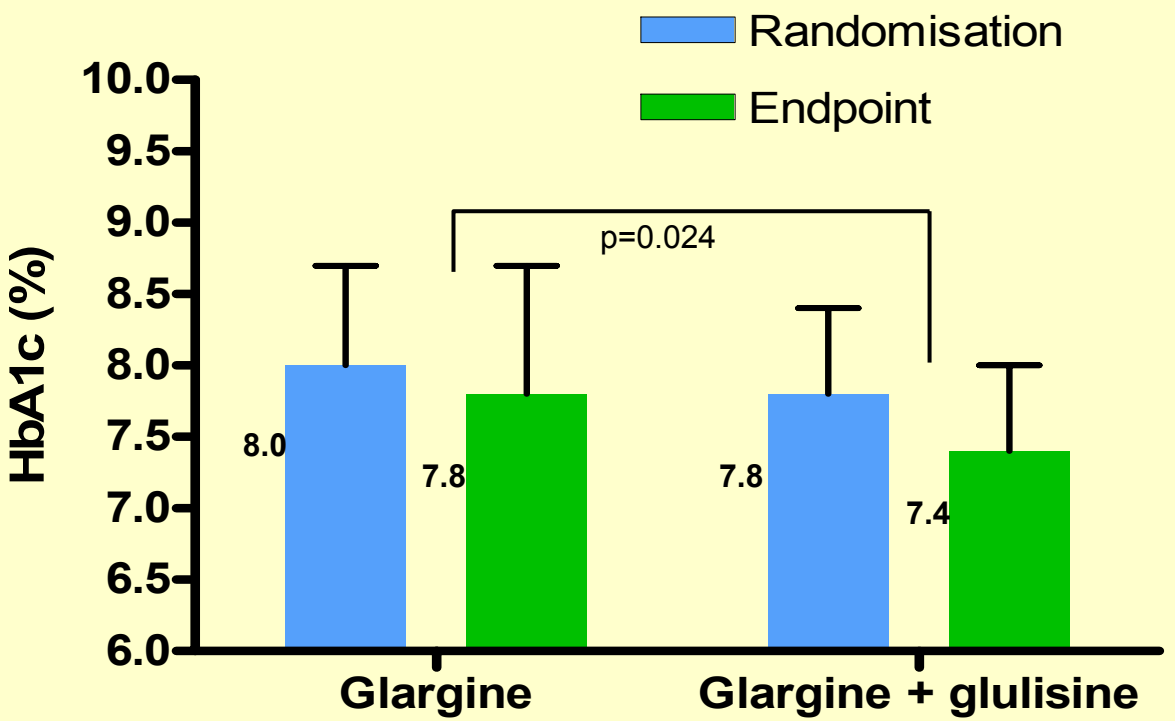
Mean baseline values:

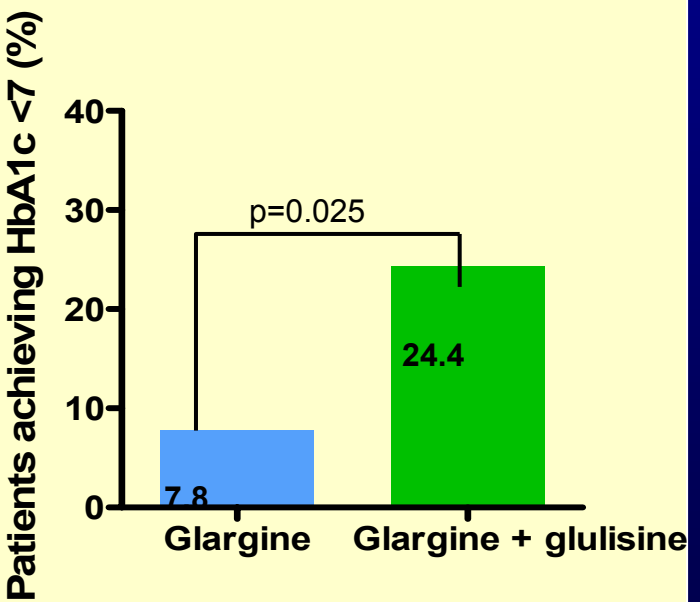
- HbA1c (%): 8.5
- BMI (kg/m^2): 33.1
- Duration of diabetes (years): 11.5

Open-label, multinational trial



POC: adding glulisine to glargine increases efficacy and improves glycemic control





POC: the Basal Plus approach is safe and associated with only minor weight gain and hypoglycemic risk

	Insulin glargine (n=57)	Insulin glargine + insulin glulisine (n=49)
BW change from baseline (kg)	**+0.2 ± 1.8**	**+0.5 ± 2.5**
Symptomatic hypoglycemia (event/pt.yr)	**7.68 ± 14.00**	**8.19 ± 14.60**
Severe symptomatic hypoglycemia (event/pt.yr)	**0.20 ± 0.10**	**0**

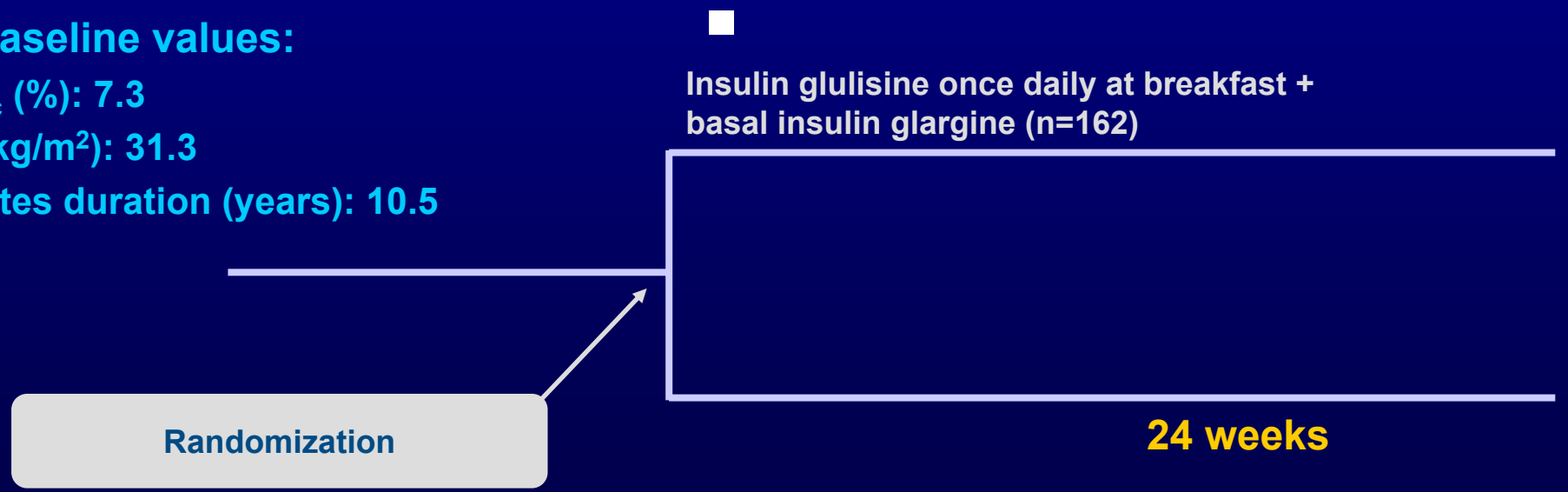
OPAL study: assessment of Basal Plus efficacy comparing glulisine added at breakfast or main meal

Subjects:

- 316 insulin treated with poorly controlled type 2 diabetes (HbA_{1c} >6.5–9.0%)
- Previously received basal insulin glargine for ≥3 months (OHAs continued during the study)

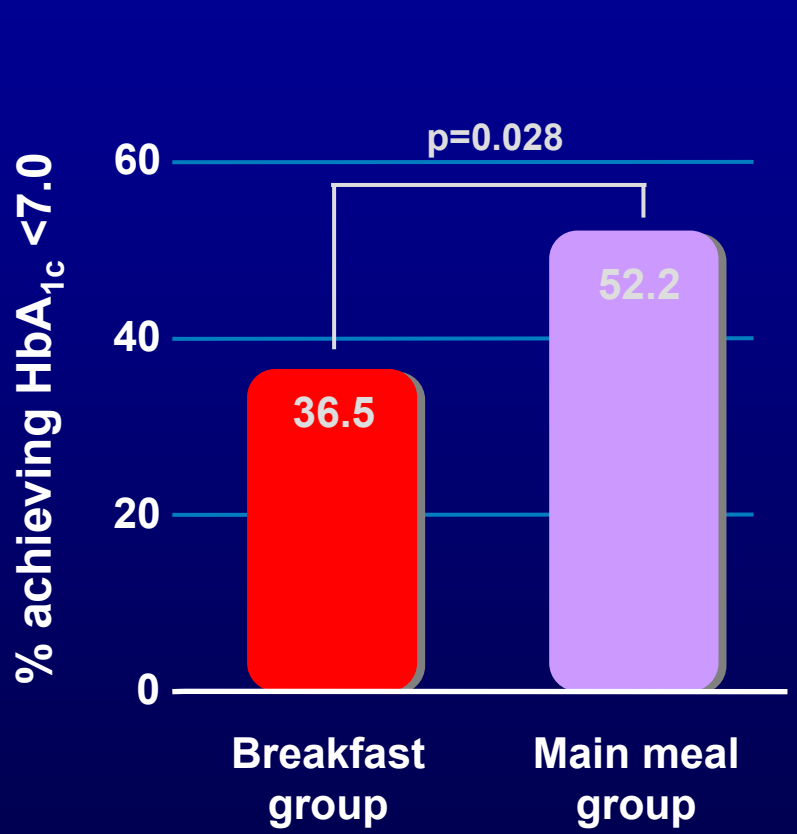
Mean baseline values:

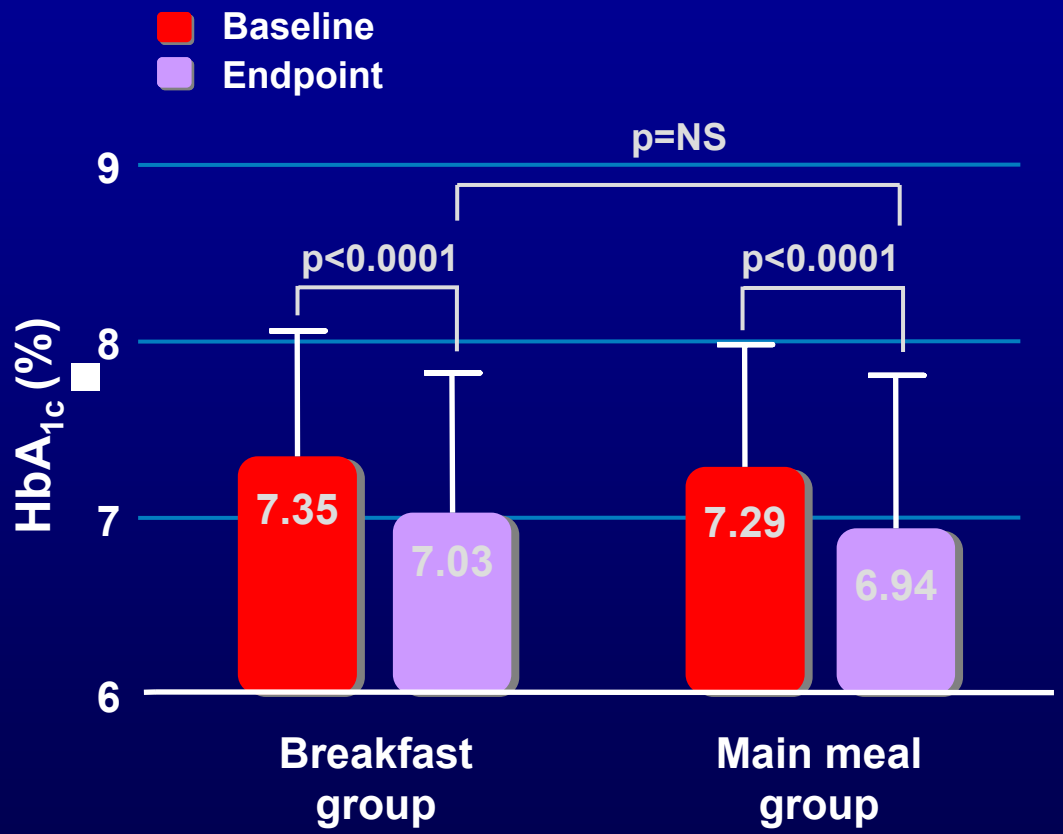
- HbA_{1c} (%): 7.3
- BMI (kg/m^2): 31.3
- Diabetes duration (years): 10.5



Lankisch M, et al. Diabetes Obes Metab 2008;10:1178–85

OPAL study: glargine + glulisine improves glycemic control irrespective of whether glulisine is given with breakfast or the main meal

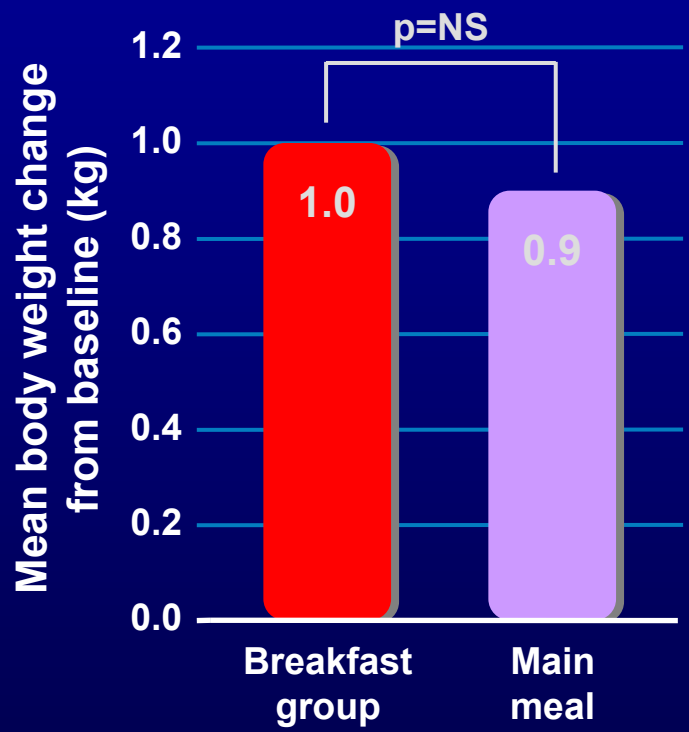


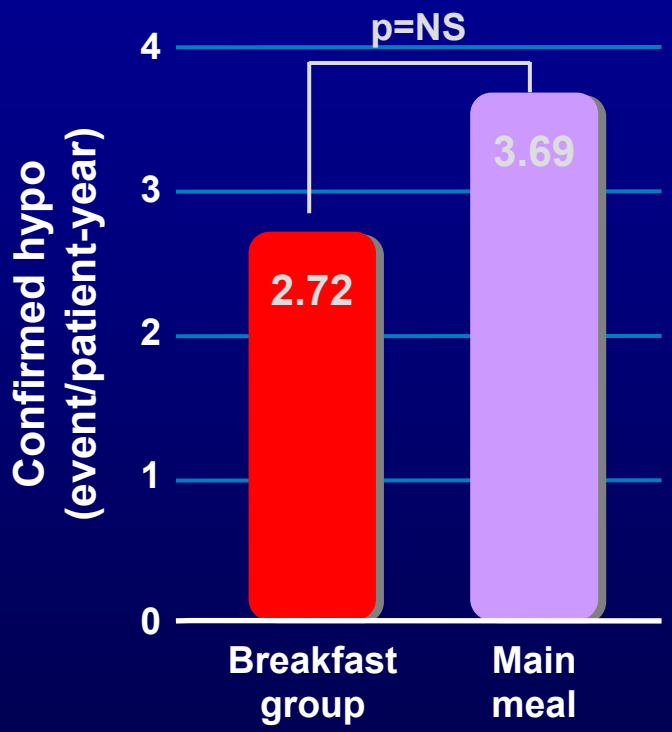


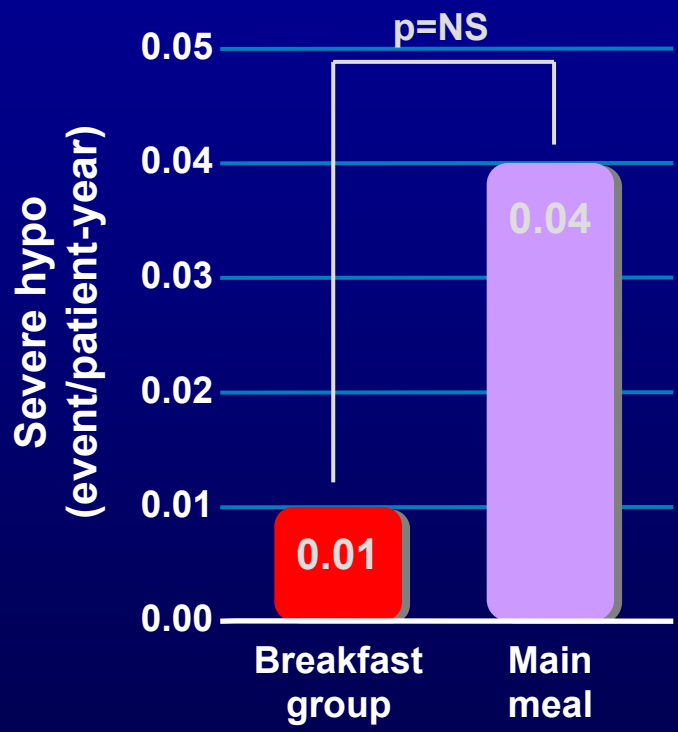
The main meal group also included subjects whose main meal was breakfast

Lankisch M, et al. Diabetes Obes Metab 2008;10:1178–85

OPAL study: the timing of glulisine addition to glargine does not affect safety or weight gain

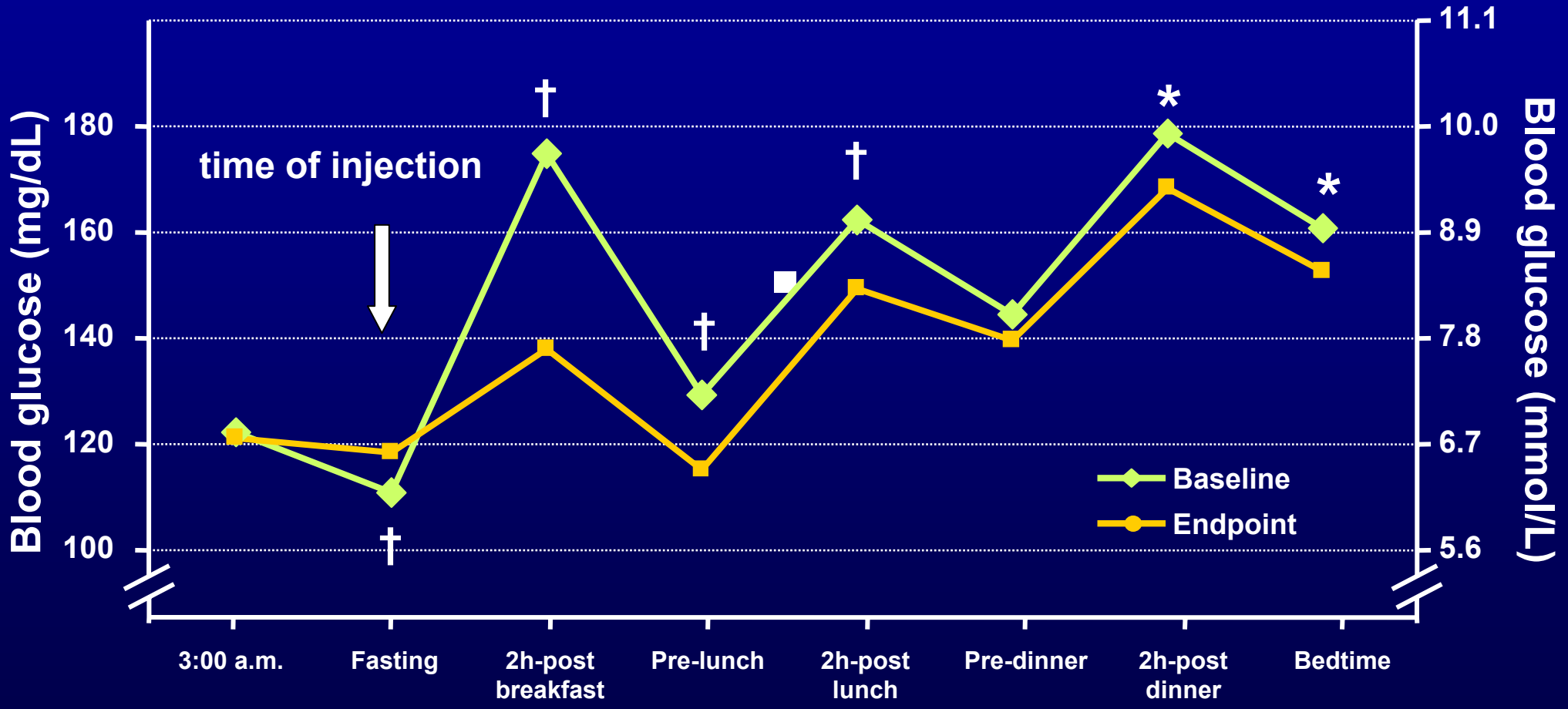






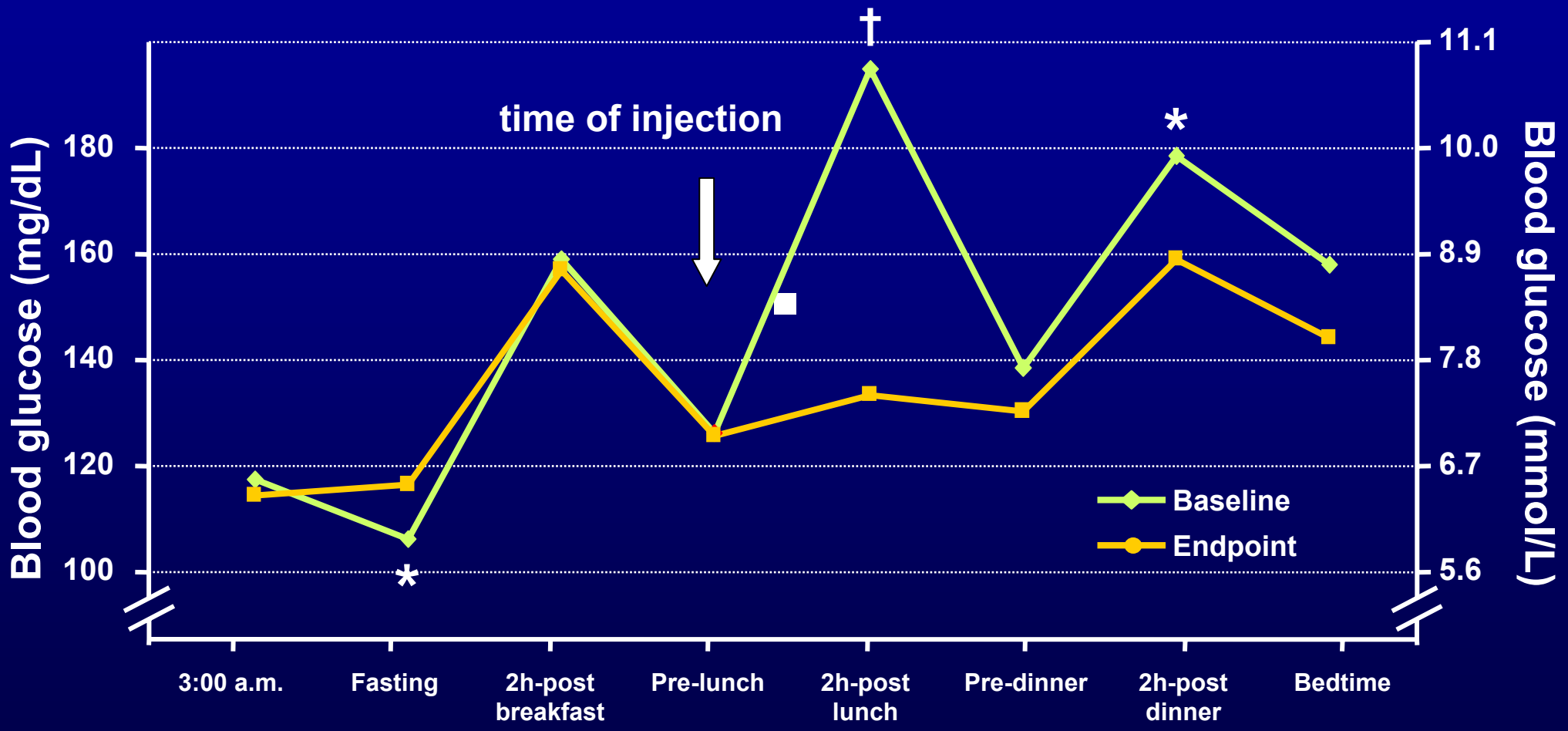
Lankisch M, et al. Diabetes Obes Metab 2008;10:1178–85

Results: 8-point blood glucose profile injection at breakfast



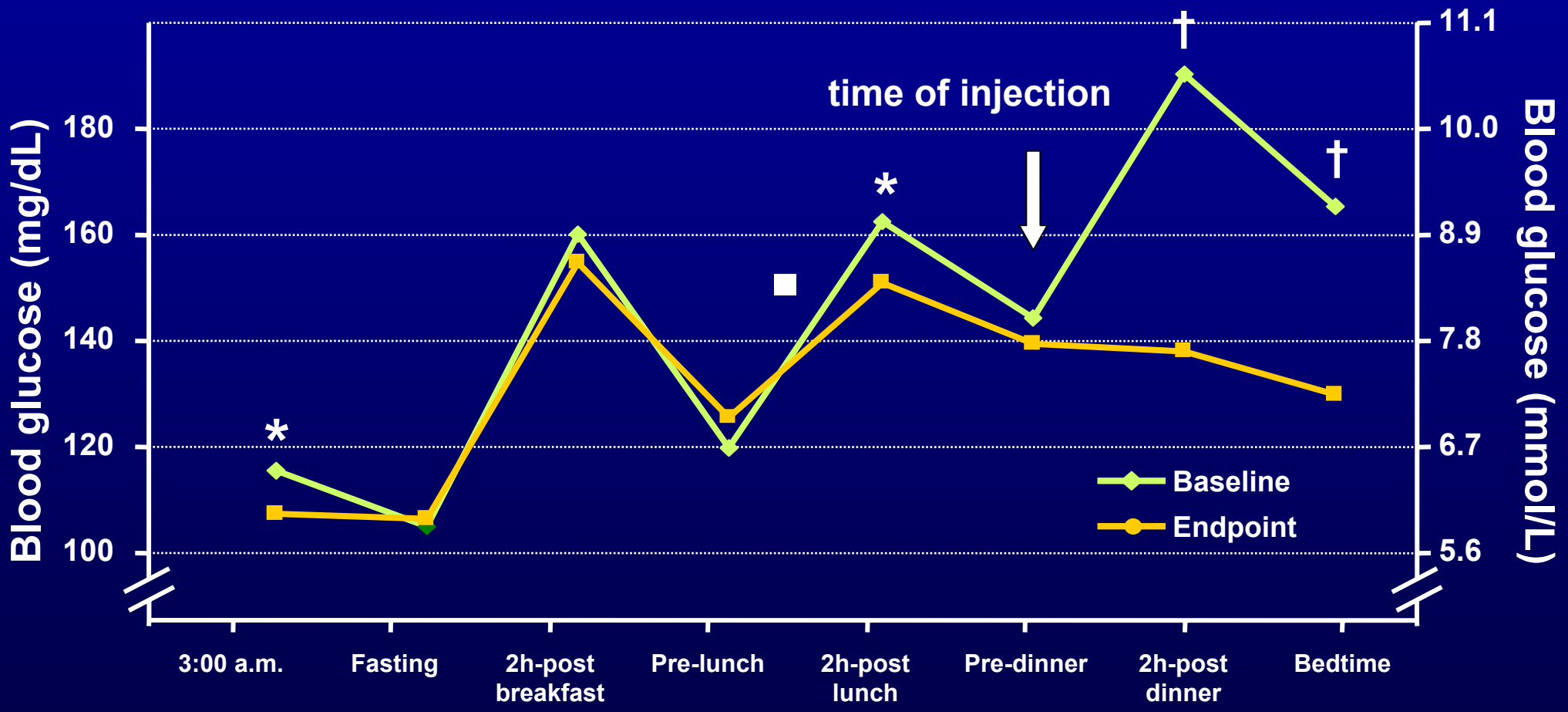
Calculated for the per-protocol analysis set (N=316); data are mean; *p<0.05; †p<0.0001

Results: 8-point blood glucose profile injection at lunch



Calculated for the per-protocol analysis set (N=316); data are mean; *$p<0.05$; †$p<0.0001$

Results: 8-point blood glucose profile injection at dinner



Calculated for the per-protocol analysis set (N=316); data are mean; *p<0.05; †p<0.0001

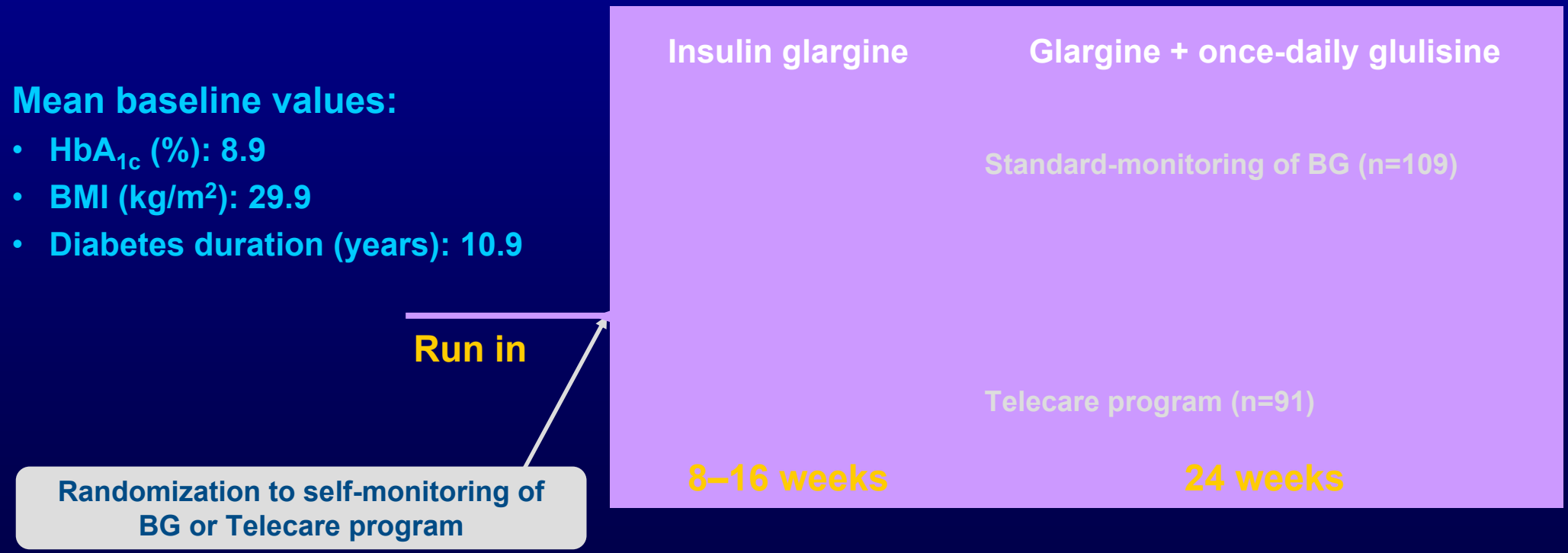
ELEONOR: evaluating glycemic control with Basal Plus using two dose adjustment methods

Subjects:

- 200 insulin naïve with poorly controlled type 2 diabetes
- Receiving ≥1 OHA (metformin continued, other OHAs stopped)

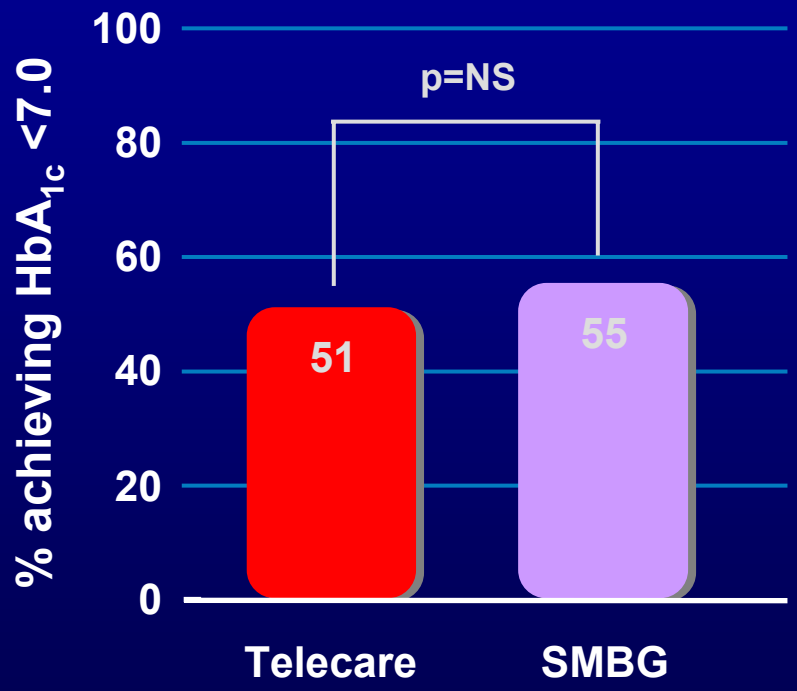
Mean baseline values:

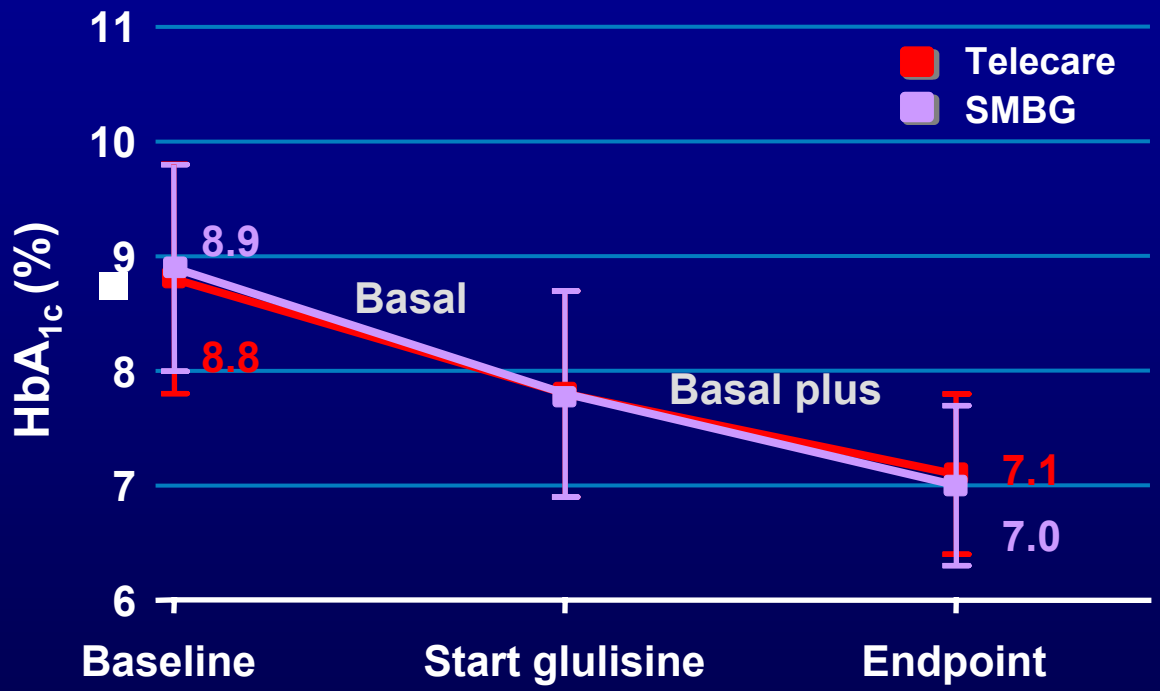
- HbA_{1c} (%): 8.9
- BMI (kg/m^2): 29.9
- Diabetes duration (years): 10.9



Del Prato S, et al. Diabetologia 2008;51 Suppl. 1:S452

ELEONOR: efficacy of Basal Plus approach is unaffected by the method of dose adjustment used

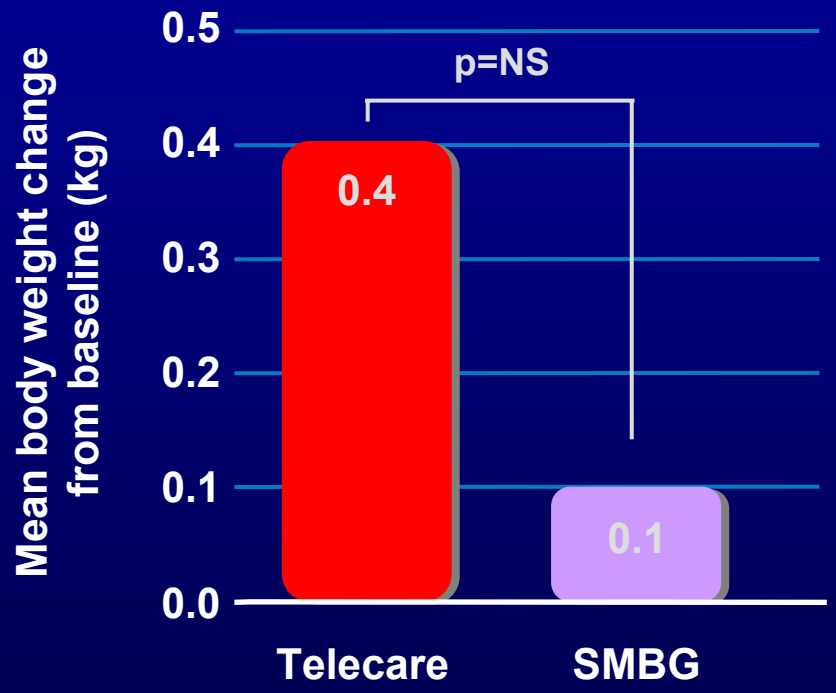


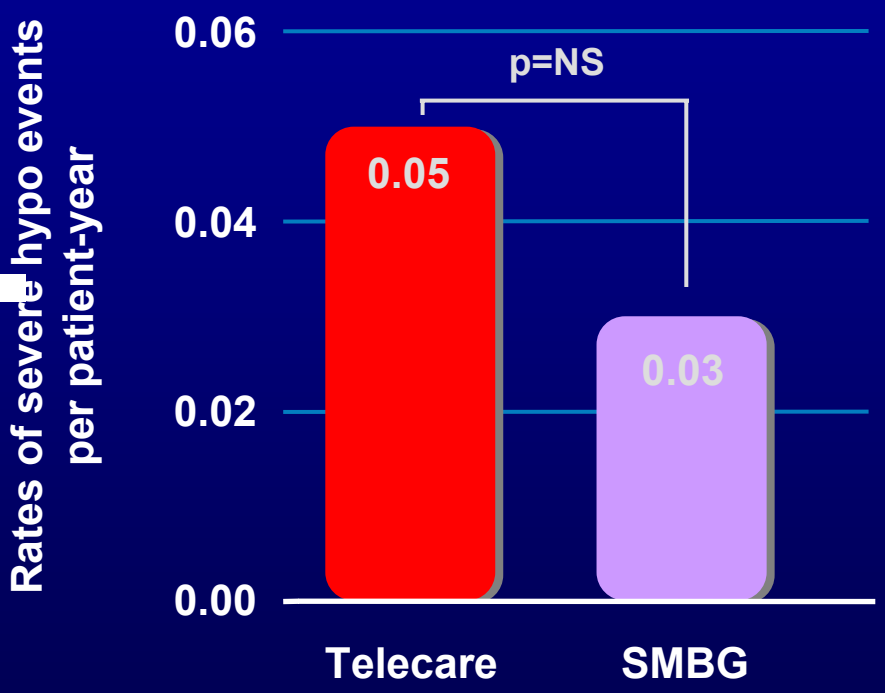


SMBG = self monitoring of blood glucose

Del Prato S, et al. Diabetologia 2008;51 Suppl. 1:S452

ELEONOR: the Basal Plus approach is associated with only minor weight gain and few hypoglycemic events





SMBG = self monitoring of blood glucose

Del Prato S, et al. Diabetologia 2008;51 Suppl. 1:S452

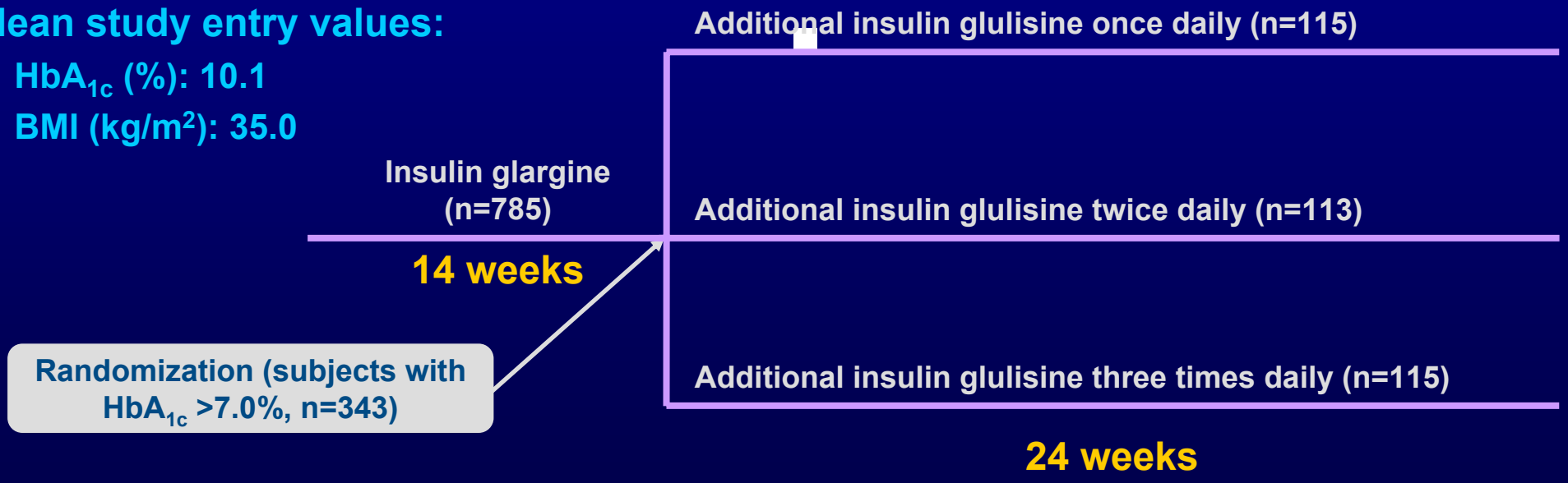
1.2.3 study: insulin glargine with addition of one, two or three daily doses of glulisine

Subjects:

- Insulin naïve (785 entered study, 343 randomized) with type 2 diabetes (HbA_{1c} ≥8.0%)
- Receiving 2 or 3 OHAs for ≥3 months (OHAs continued except sulfonylurea)

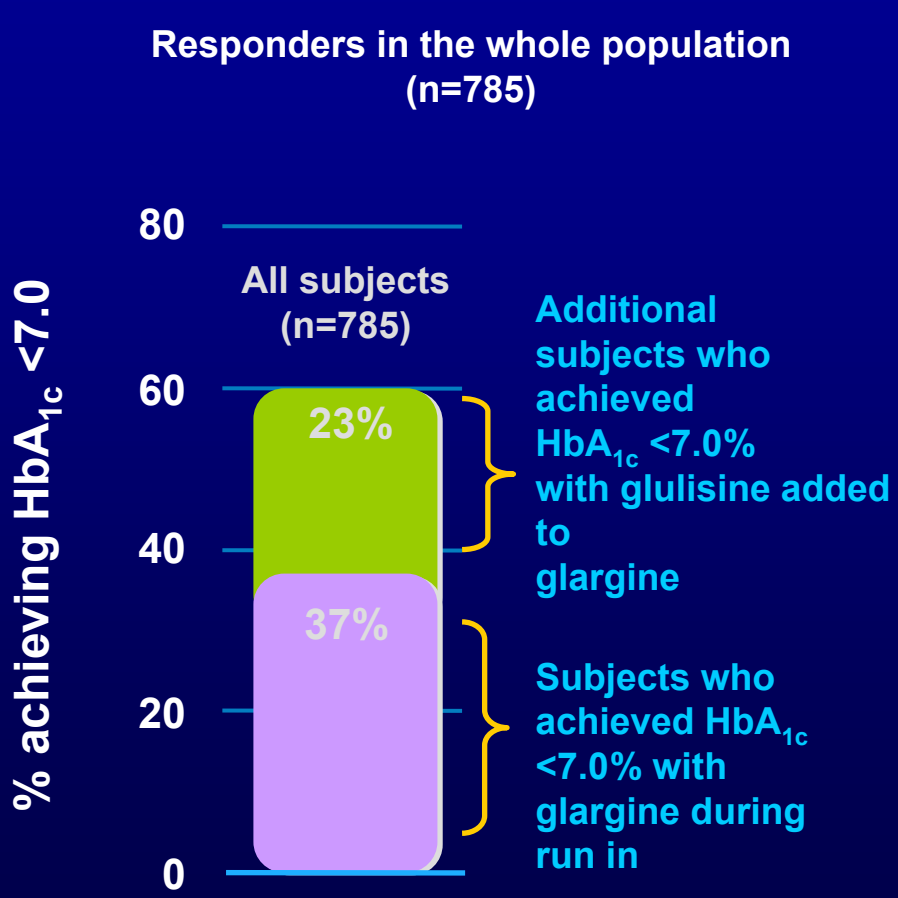
Mean study entry values:

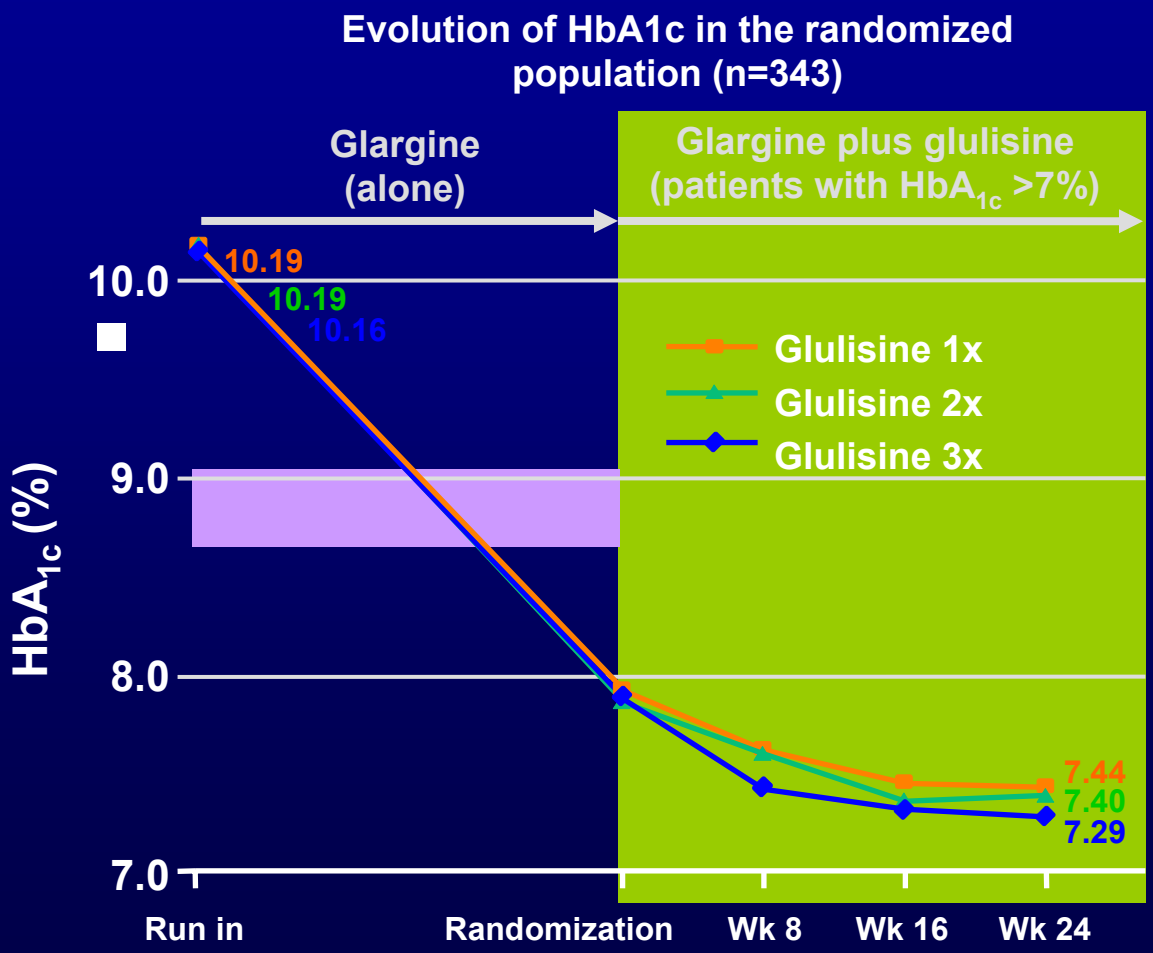
- HbA_{1c} (%): 10.1
- BMI (kg/m^2): 35.0



Sanofi-aventis data on file (1.2.3 study)

1.2.3 study: intensification of Basal insulin with mealtime glulisine injections improves glycemic control

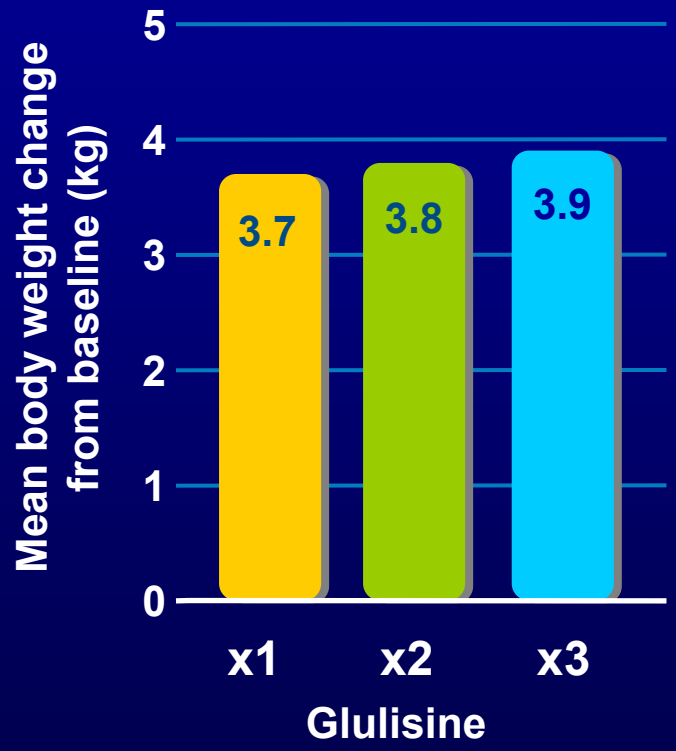


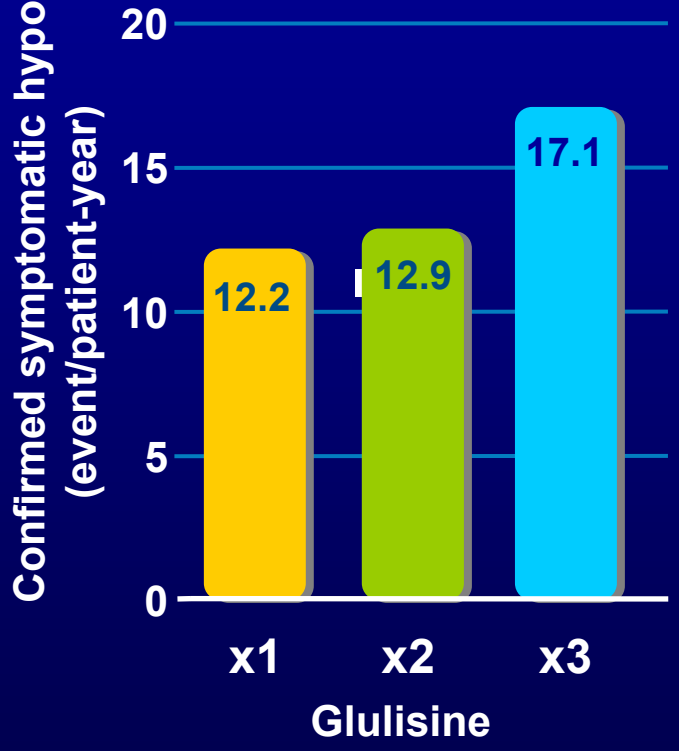


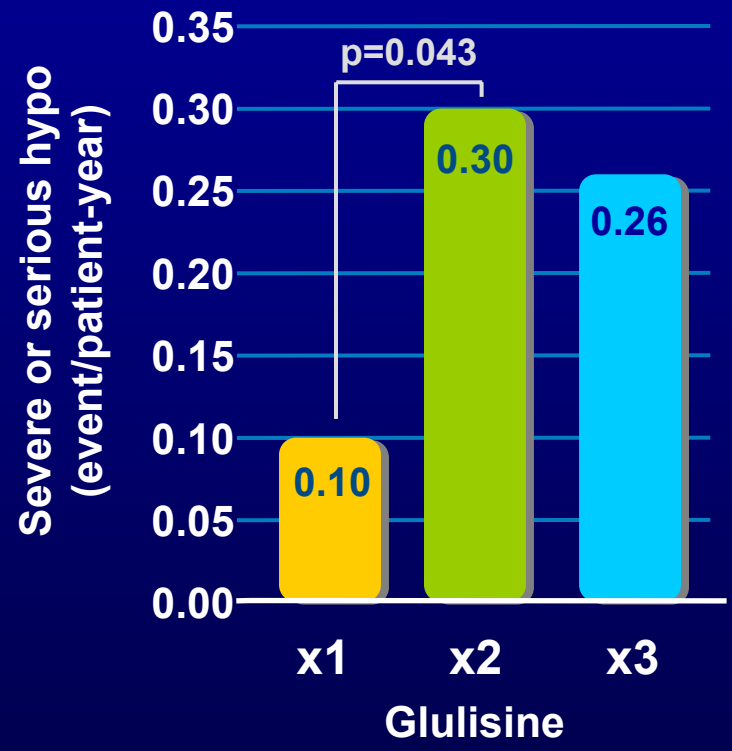
Sanofi-aventis data on file (1.2.3 study)

1.2.3 study: The Basal Plus strategy is associated with a reduced level of hypoglycaemia

p=NS for all other pairwise comparisons







Sanofi-aventis data on file (1.2.3 study)

« Basal Plus » in clinical practice

Initiation

- 6 point glycemic profile during 3 consecutive days
- Identification of the main meal (highest PPG, greatest glycemic delta)
- Add one injection of rapid-acting insulin analog at this main meal: initial dose:0,05 U / Kg

Titration

Mean value of PPG at this meal for the two previous days	**Mean PPG> 140 mg/dl**	**Increase 2 U**
	Mean PPG between 100 and 140 mg/dl	**No change**
	Mean PPG < 100 mg/dl	**Decrease 2 U**

What's about the OAD?

- Some patients may stop or decrease the insulin-secretagogues (based on glycemic profile)
- Continuation of metformin

What's about the basal insulin dose?

- No change

[1]Del Prato S et coll. Diabetologia 2008 ; 51 Suppl. 1 : S452, et Sanofi-aventis, données internes ; [2]Nathan DM et coll. Diabetes Care 2008 ; 31 : 1–11 ; [3]Raccah D et coll. Diabetes Metab Res Rev 2007 ; 23 : 257–64 ; [4]Halbron M et coll. Diabetes Metab 2007 ; 33 : 316–20

Basal Plus – Conclusion 1

- Basal Plus is once-daily basal insulin plus once-daily rapid-acting insulin (before the main meal)
- Adding once-daily rapid insulin to basal insulin gives a significant improvement in HbA1c
  - Further reductions in HbA1c concentrations
  - Additional patients able to achieve HbA1c <7.0% goal (between 30 and 50 % according to the studies)
- When added to once-daily basal insulin, giving prandial insulin before breakfast is as effective as giving it before the main meal
- Basal Plus is the first intensification step to consider after optimization of the basal insulin dose
- Basal plus strategy is safe in terms of hypoglycemic risk

Basal Plus – Conclusion 2

When basal insulin is no longer enough

- Basal Plus will be compared to premix insulin
  (ALL TO TARGET study)

■

- Stepwise addition of rapid acting insulin will be compared
  to full basal-bolus regimen
  (OSIRIS study)

The basal plus strategy

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