Insulin Initiation: Basal Insulin

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Agenda

- Ideal basal insulin
- NPH vs Glargine and detemir
- Glargine vs Detemir
- Glargin 100U/ml vs Glargine 300U/ml
- Conclusion

- **Natural course of DM type 2**

Progressive beta cell damage

- Type 2 diabetes is a progressive disease

- At the time of diagnosis, patients with type 2 diabetes have an estimated loss of about 50% of their insulin-producing

Beta-cell loss starts long before diagnosis

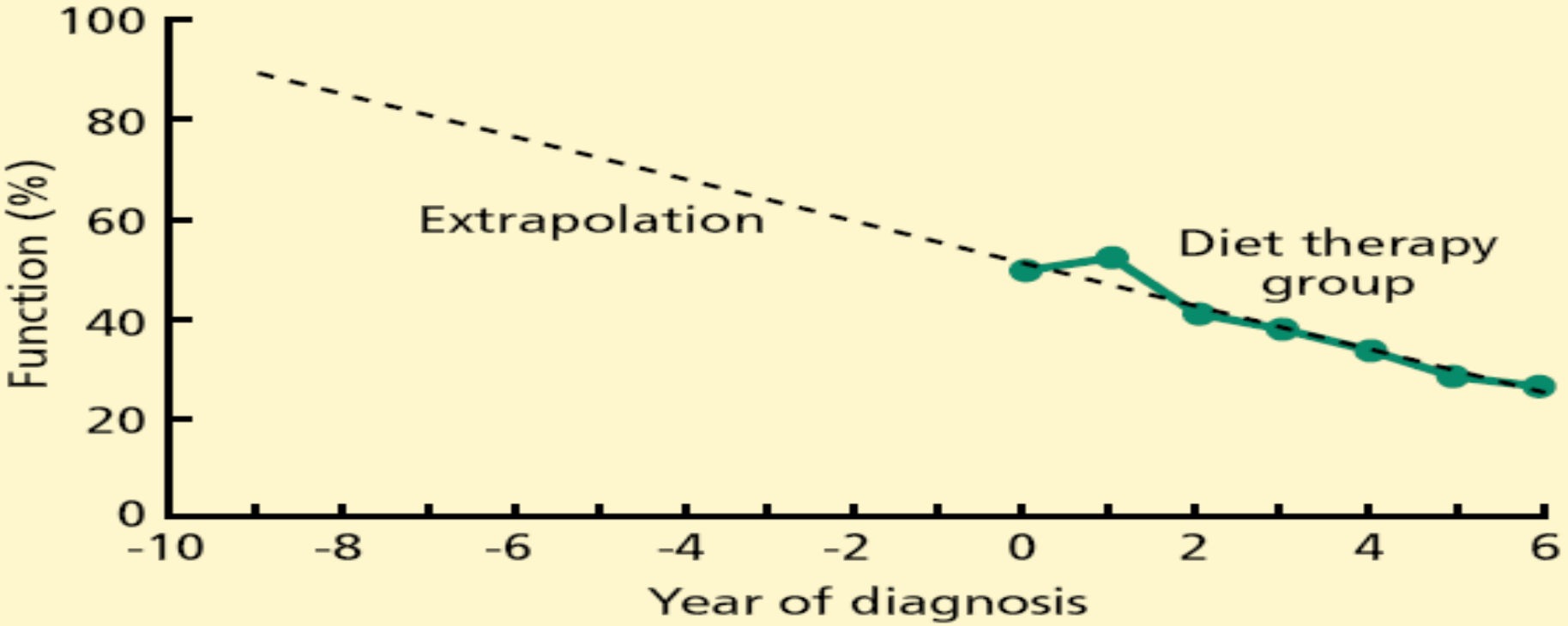


FIGURE 3. Progressive decline of beta-cell function in patients on conventional therapy (primarily diet) in the UKPDS, beginning with the year of diagnosis (green line). Extrapolating back from the data (dotted line) shows beta-cell loss begins almost a decade before diagnosis.

UK PROSPECTIVE DIABETES STUDY GROUP. UK PROSPECTIVE DIABETES STUDY 16. OVERVIEW OF 6 YEARS' THERAPY OF TYPE II DIABETES: A PROGRESSIVE DISEASE. DIABETES 1995; 44:1249–1258.

Type 2 diabetes: A progressive disease

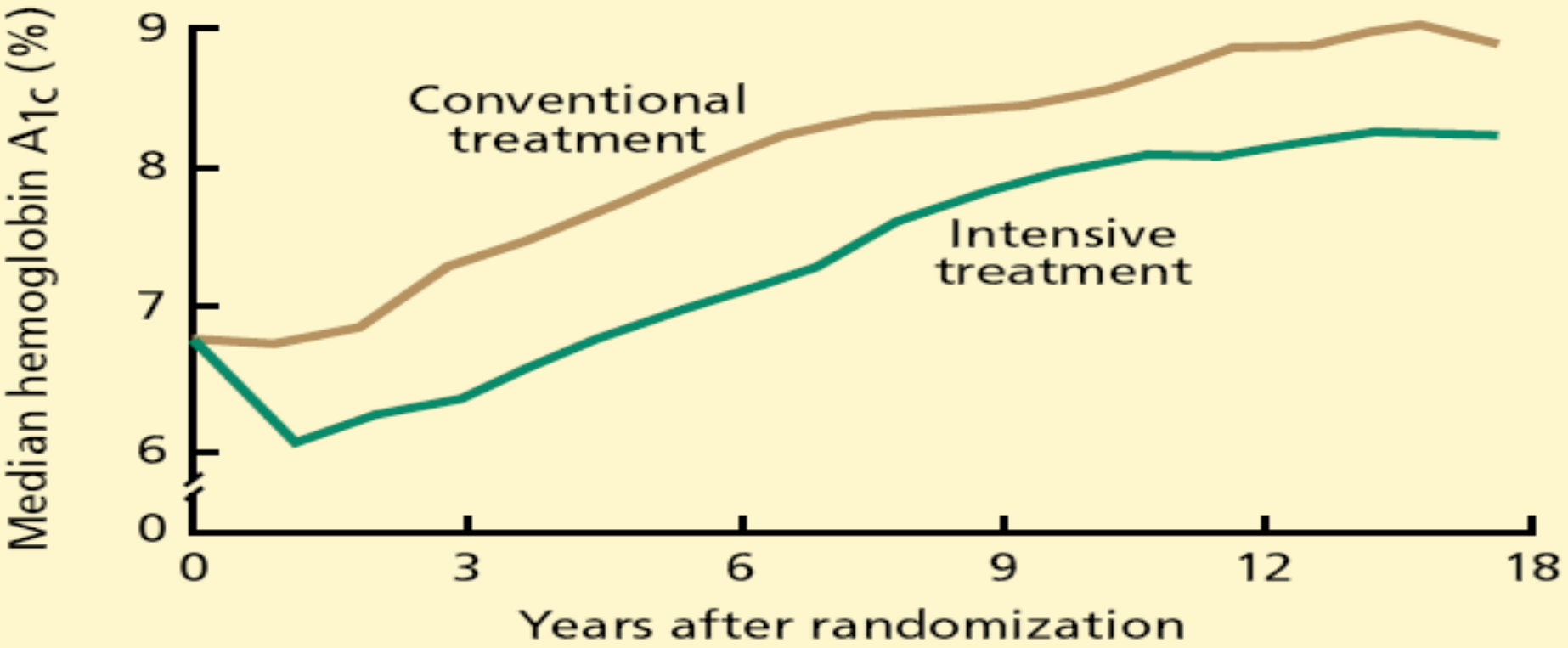


FIGURE 1. Progressive increase in hemoglobin A_{1c} in patients with type 2 diabetes, regardless of treatment, in the United Kingdom Prospective Diabetes Study (UKPDS).

ADAPTED FROM UK PROSPECTIVE DIABETES STUDY (UKPDS) GROUP. INTENSIVE BLOOD-GLUCOSE CONTROL WITH SULPHONYLUREAS OR INSULIN COMPARED WITH CONVENTIONAL TREATMENT AND RISK OF COMPLICATIONS IN PATIENTS WITH TYPE 2 DIABETES (UKPDS 33). LANCET 1998; 352:837–853. WITH PERMISSION FROM ELSEVIER.

Need for Insulin

- Insulin therapy is thus frequently required during the course of the disease to maintain glycemic control and prevent diabetes complications.

- In the UK Prospective Diabetes Study, 9 years after diagnosis almost 80%of patients on oral agents required insulin supplementation

Insulin remains the most potent antihyperglycemic agent available for uncontrolled T2DM patients

Intervention	Expected ↓ in HbA_{1c}
Insulin	No upper limit
Metformin	1.5%
Sulfonylureas	1.5%
Glinides	1 to 1.5%[a]
TZDs	0.5 to 1.4%
α-Glucosidase inhibitors	0.5 to 0.8%
GLP-1 agonist	0.5 to 1.0%
Pramlintide	0.5 to 1.0%
DPP-IV inhibitors	~0.8%

[a] Repaglinide is more effective than nateglinide

Adapted from Nathan DM *et al*. *Diabetes Care* 2006;29(8):1963-72.

Goal achievement?

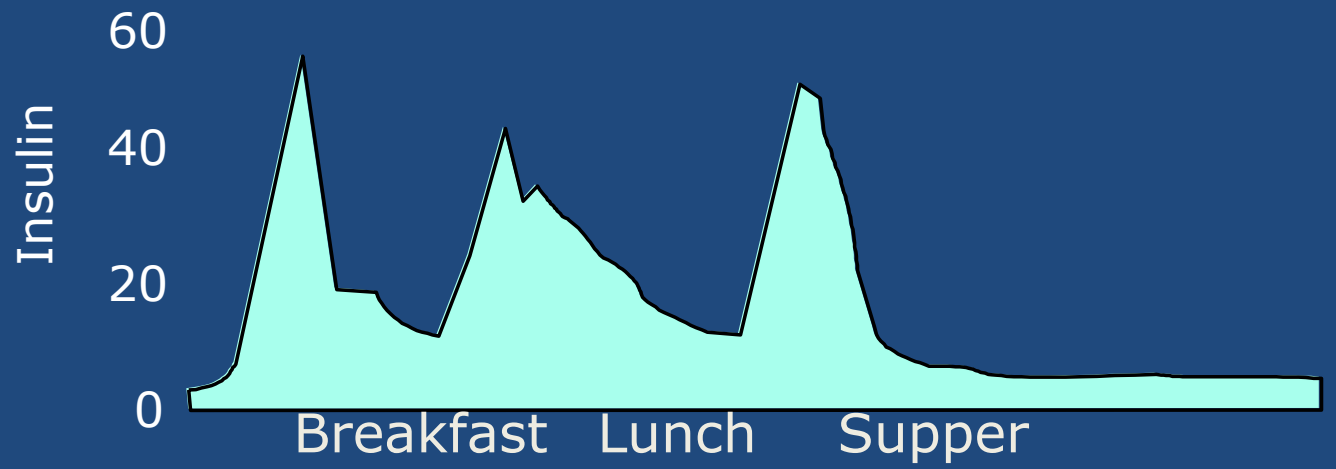
- Attainment of glycemic targets using insulin remains difficult

- In a recent review of 48 randomized clinical trials using insulin in T2DM patients with a mean baseline HbA1c of 8.7%, only 40–54% achieved an HbA1c of less than7%

Diabetes Res Clin Pract2011, 92:1–10

Insulin

- A hormone secreted by the beta cells
- Secreted in response to glucose or other stimuli, such as amino acids
- Normal response characterized by low basal levels of insulin, with surges of insulin triggered by a rise in blood glucose



MIMICKING NATURE WITH INSULIN THERAPY

The Basal/Bolus Insulin Concept

- Basal Insulin
  - **Suppresses glucose production between meals and overnight**
  - **Nearly constant levels**
  - **50% of daily needs**
- Bolus Insulin (Mealtime or Prandial)
  - **Limits hyperglycemia after meals**
  - **Immediate rise and sharp peak at 1 hour**
  - **10% to 20% of total daily insulin requirement at each meal**

Ideal Basal Insulin

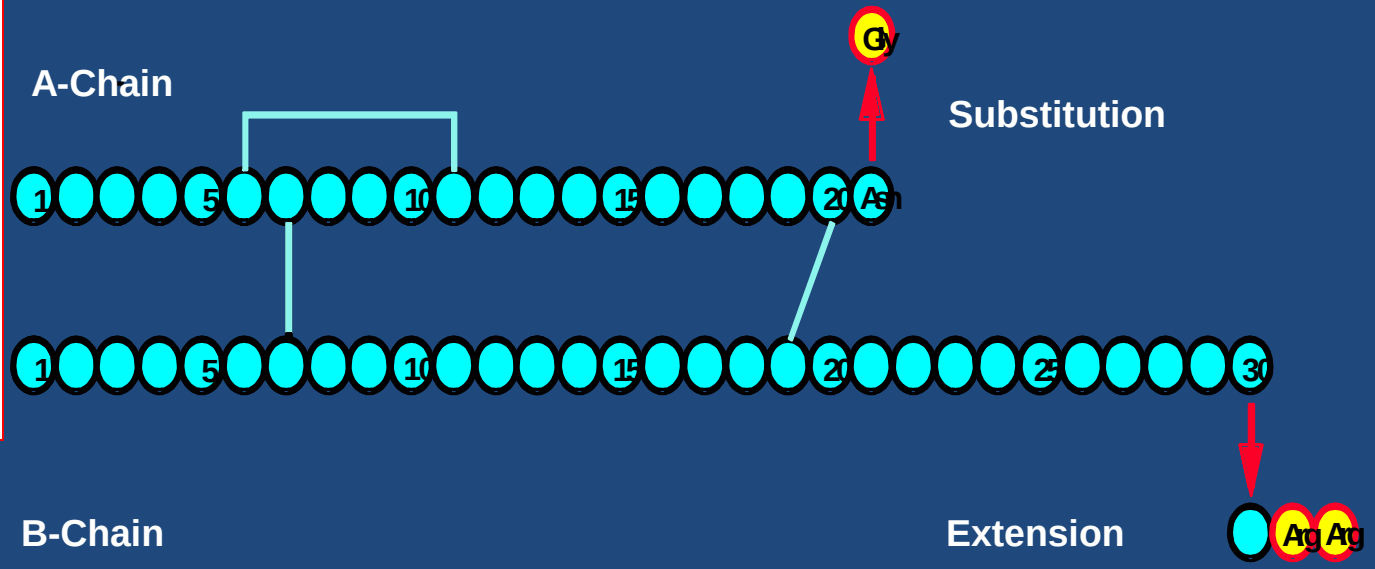
- Closely mimic normal pancreatic basal insulin secretion
- No distinct peak effect
- Continued effect over 24 hours
- Once-daily administration for patient compliance
- Good glycemic control
- Low incidence of hypoglycemia
- Less weight gain
- Predictable
- Safe

Insulin Preparations

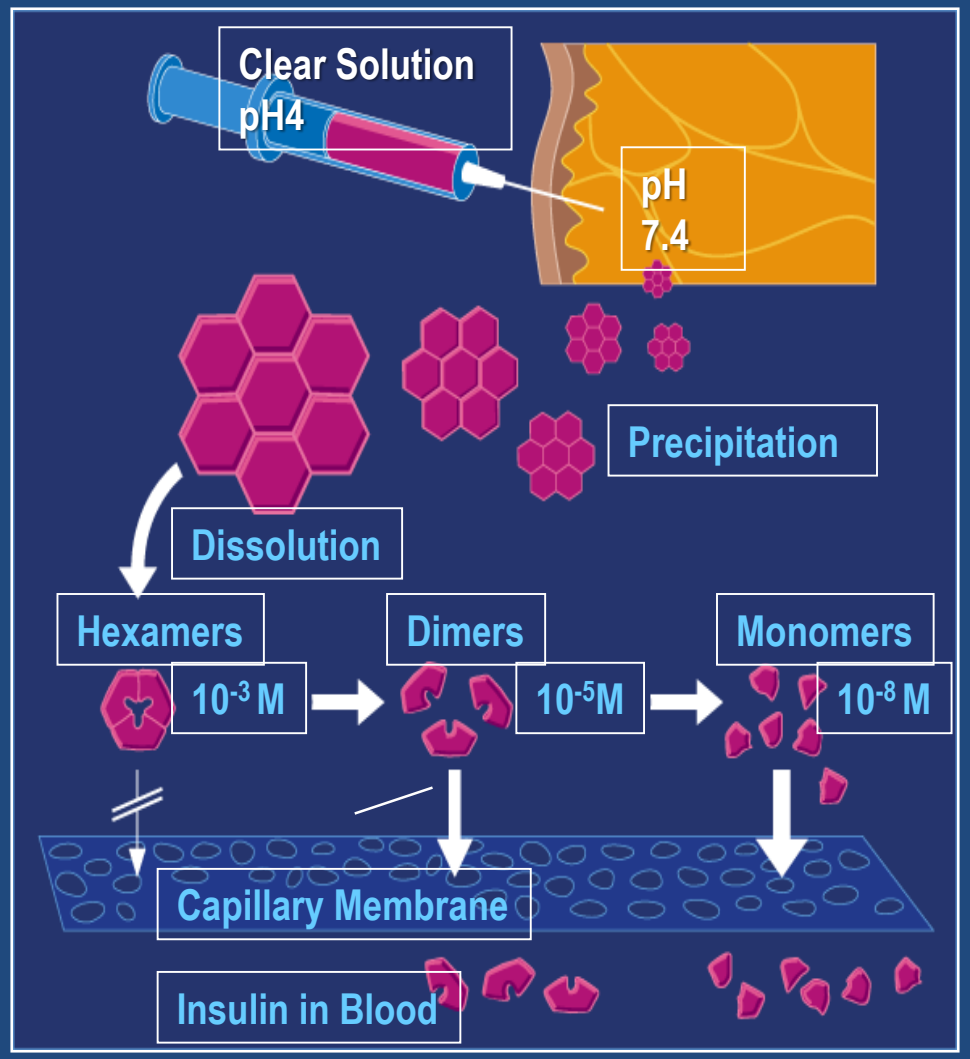
Insulin	Onset (hr)	Peak (hr)	Duration (hr)
Lispro, Aspart, Glulisine	<0.25	1-2	3-4
Regular	0.5-1	2-3	3-6
NPH	2-4	4-10	10-16
Glargine	1-2	Flat	24
Detemir	1-2	Flat	12-24

INSULIN GLARGINE

- A-chain has an Asparagine to Glycine substituiation at position A21
- Two positively charged Arginine are added at the C terminus of the B chain

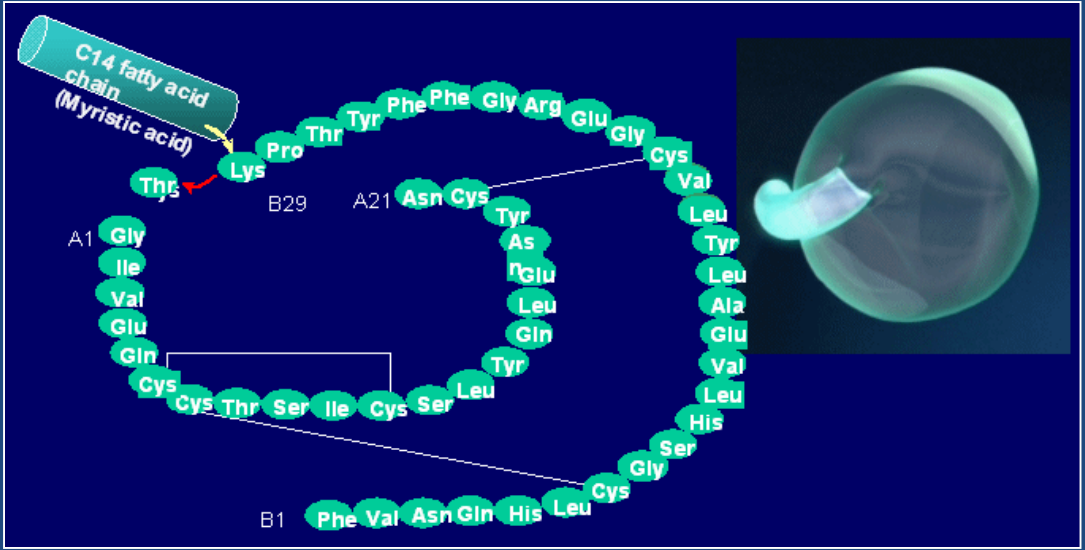


GLARGINE: Mechanism of Action



- Injection of an acidic solution (pH 4.0)
- Precipitation of insulin glargine in subcutaneous tissue (pH 7.4)
- Slow dissolution of free insulin glargine hexamers from micro precipitates (stabilized aggregates)
- Protracted action

INSULIN DETEMIR



- ✓ A soluble derivative of human insulin
- ✓ Threonine has been removed at position B30
- ✓ A 14-carbon fatty acid side-chain has been attached to position B29

The Treat-to-Target Trial

Randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients

OBJECTIVE — To compare the abilities and associated hypoglycemia risks of insulin glargine and human NPH insulin added to oral therapy of type 2 diabetes to achieve 7% HbA_{1c}.

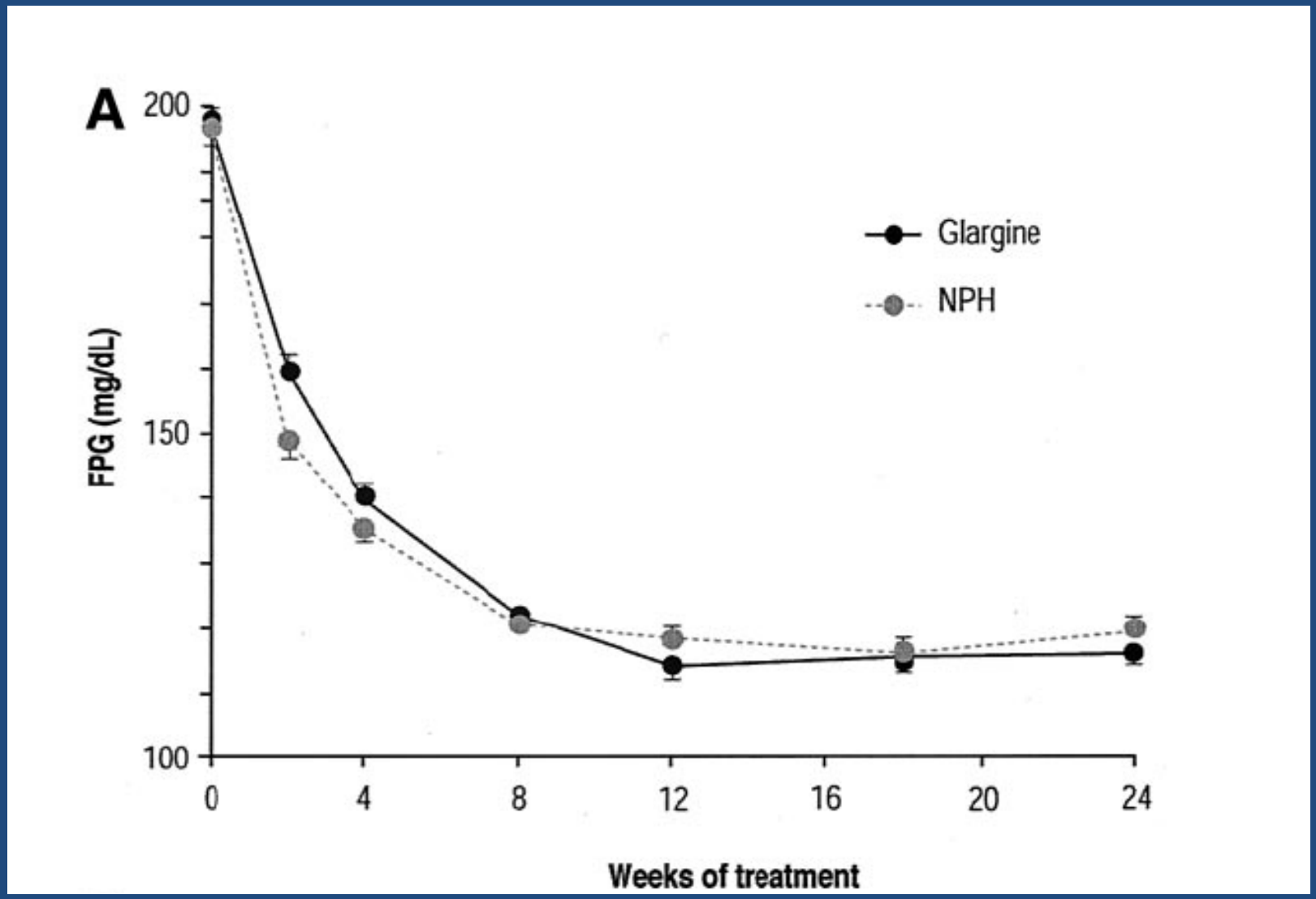
Diabetes Care 26:3080–3086, 2003

Table 2—*Baseline characteristics of subjects in the study*

	Glargine	NPH
n	367	389
Sex (F/M) (%)	45/55	44/56
Age (years)	55 ± 9.5	56 ± 8.9
Duration of diabetes (years)	8.4 ± 5.55	9.0 ± 5.57
BMI (kg/m^2)	32.5 ± 4.64	32.2 ± 4.80
FPG (mg/dl [mmol/l])	198 (11.0) ± 49 (2.71)	194 (10.8) ± 47 (2.61)
HbA_{1c} (%)	8.61 ± 0.9	8.56 ± 0.9
Ethnicity (%)		
White	84	83
Black	11	13
Asian	3	3
Multiracial	1	1
Hispanic heritage (%)	10	6
Prior therapy (%)		
SU + metformin	71	74
SU only	11	10
Metformin only	8	7
SU + TZD	6	5
Metformin + TZD	3	3
TZD only	<1	<1

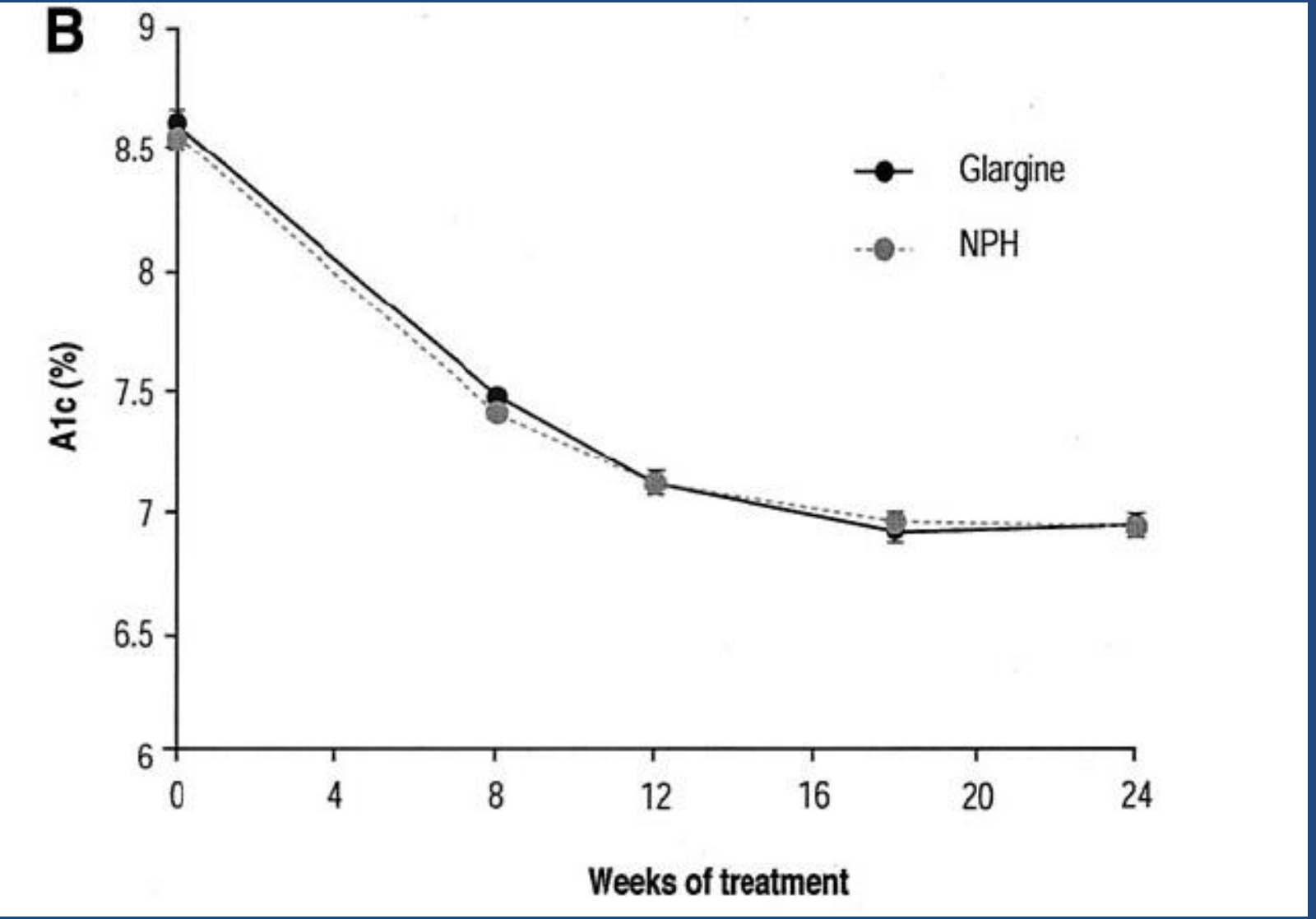
Data are means ± SD, unless otherwise noted. SU, sulfonylurea; TZD, thiazolidinedione.

Length of F/U = 24 weeks



Mean FPG at end point was similar with glargine and NPH (117 vs. 120 mg/dl)

Both insulins reduced mean HbA1c from 8.6% at baseline to 7% at end point, with nearly 60% of patients reaching 7% or less.



Mean HbA1c at end point was similar with glargine and NPH ((6.96 vs.6.97%).

Dosage of Insulin

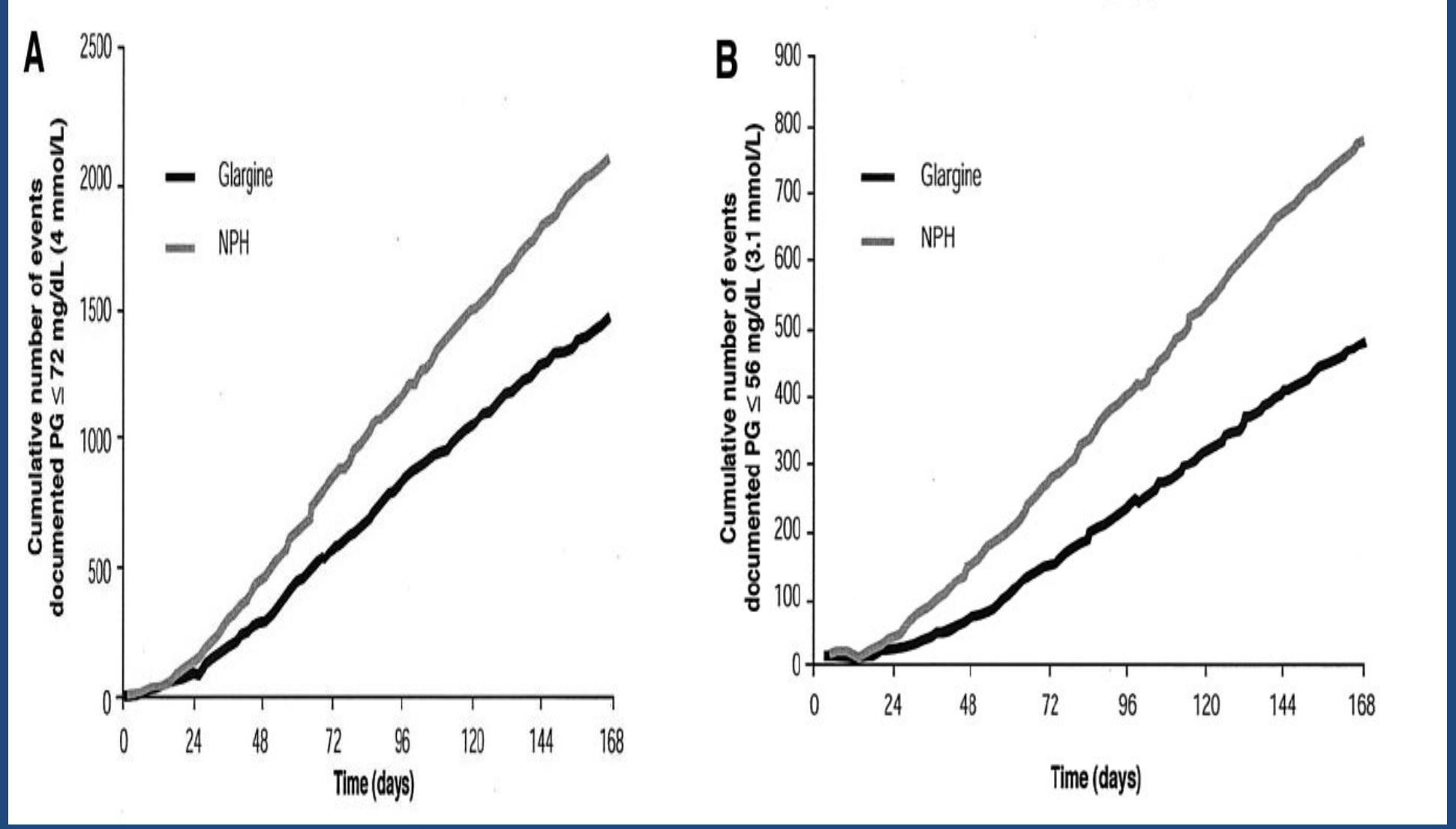
- At wk 24, mean insulin glargine dose was **higher** than mean NPH insulin dose:

Insulin glargine	NPH insulin
48.8 IU/day	**42.4 IU/day , *P*<0.001**

Rosenstock J, Riddle M, HOE901/4002 Study Group. *Diabetes* 2002;51(suppl 2):A482. Abstract 1982-PO

Hypoglycemia

- Nocturnal Hypoglycemia reduced by 40% in the Glargine group (532 events) vs NPH group (886 events)



Fewer events occurred with glargine than NPH, especially those confirmed by glucose tests , with no tendency for the between treatment difference to decline over time

Reduced Hypoglycemia Risk With Insulin Glargine

A meta-analysis comparing insulin glargine with human NPH insulin in type 2 diabetes

- Objective: To determine risk for hypoglycemia in a meta-analysis of controlled trials of a similar design for insulin glargine versus once- or twice-daily NPH insulin in adults with type 2 diabetes

Diabetes Care 28:950–955, 2005

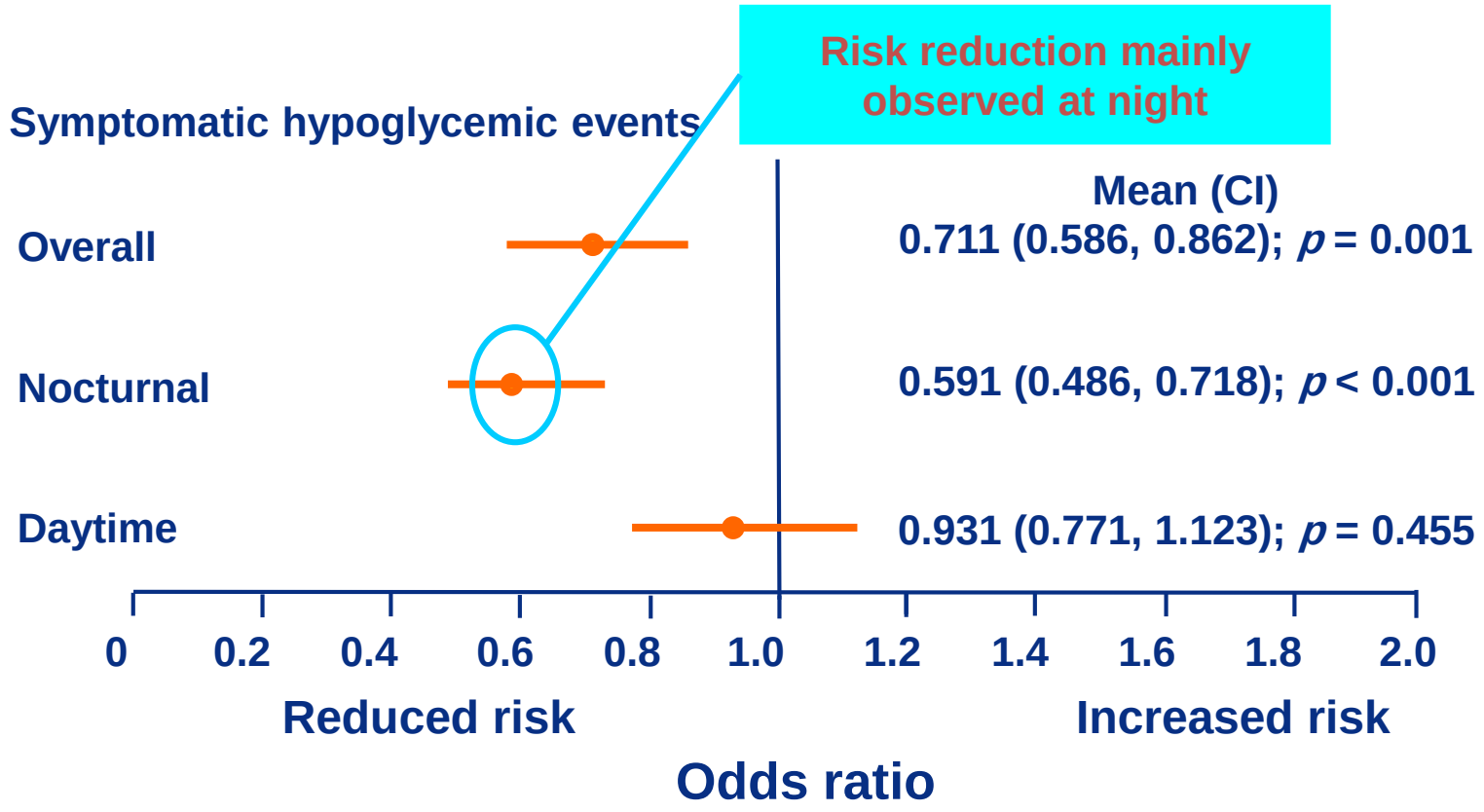
Table 1—*Studies included in the integrated analysis*

Study (ref. no.)	Number of randomized and treated patients	Study duration	Prestudy treatment	Study treatment	Additional antidiabetic treatment
3002 (8,14)	570	52 weeks*	OAD and once-daily insulin or OAD alone	Once daily at bedtime: insulin glargine or NPH insulin	OAD(s)
3006 (12,15)	518	28 weeks	Insulin for >3 months (no OAD)	Insulin glargine once daily at bedtime or NPH once or twice daily	Regular human insulin
4001 (16)†	460	28 weeks	OAD for >6 months	Once daily at bedtime: insulin glargine or NPH insulin	OAD (glimepiride)
4002 (13)	756	24 weeks	OAD alone	Once daily at bedtime: insulin glargine or NPH insulin	OAD(s)

A total of 2,304 patients with type 2 diabetes were included in these studies: 1,142 in the insulin glargine and 1,162 in the NPH insulin treatment groups

Insulin glargine reduces hypoglycemic risk versus NPH in T2DM: Meta analysis

Risk of severe hypoglycemia and severe nocturnal hypoglycemia reduced by 46% (p = 0.04) and 59% (p = 0.02), respectively, with insulin glargine



Rosenstock J, *et al. Diabetes Care* 2005;28:950–5.

Key message

- This meta-analysis in type 2 diabetes shows that with regard to attempting to improve glycemic control while avoiding severe and nocturnal hypoglycemia, insulin glargine provides a safer basal insulin supply than NPH insulin.

Insulin detemir versus insulin glargine for type 2 diabetes mellitus (Review)

Swinnen SG, Simon ACR, Holleman F, Hoekstra JB, DeVries JH

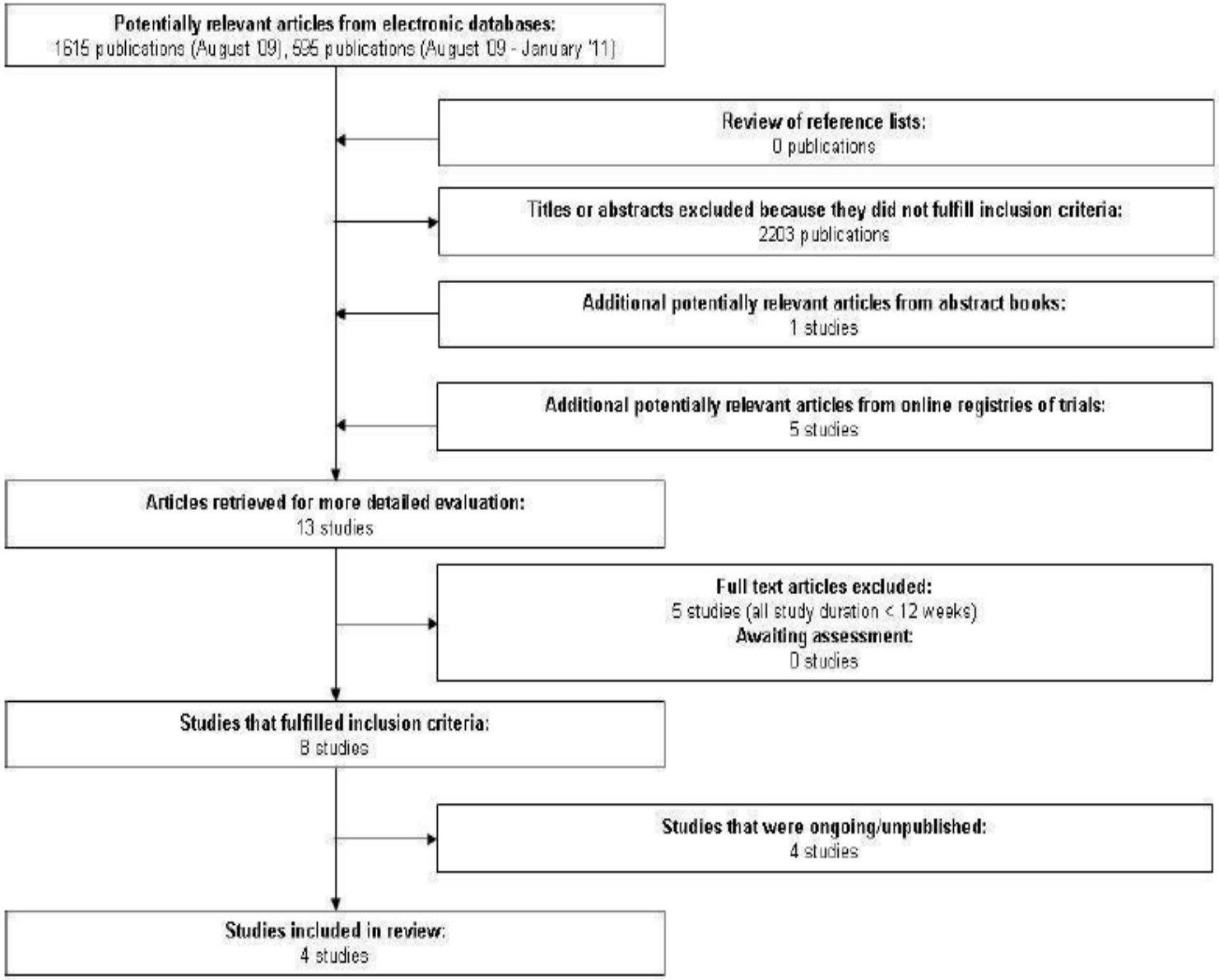
THE COCHRANE COLLABORATION®

Swinnen SG, Simon ACR, Holleman F, Hoekstra JB, DeVries JH. Insulin detemir versus insulin glargine for type 2 diabetes mellitus. *Cochrane Database of Systematic Reviews* 2011, Issue 7

Methods

- Objective: To assess the effects of insulin detemir and insulin glargine compared with each other in the treatment of type 2 diabetes mellitus

- Selection criteria: All randomized controlled trials comparing insulin detemir with insulin glargine with a duration of 12 weeks or longer were included


Potentially relevant articles from electronic databases:
1615 publications (August '09), 595 publications (August '09 - January '11)
Review of reference lists:
0 publications
Titles or abstracts excluded because they did not fulfill inclusion criteria:
2203 publications
Additional potentially relevant articles from abstract books:
1 studies
Additional potentially relevant articles from online registries of trials:
5 studies
Articles retrieved for more detailed evaluation:
13 studies
Full text articles excluded:
5 studies (all study duration < 12 weeks)
Awaiting assessment:
0 studies
Studies that fulfilled inclusion criteria:
8 studies
Studies that were ongoing/unpublished:
4 studies
Studies included in review:
4 studies

Detemir vs. Glargine: Head-to-Head Comparisons

- Hollander P, et al. Clin Ther.. 2008; 30:1976–1987
  - A 52-week, multinational, open-label, parallel-group, non-inferiority, treat-to-target trial comparing insulin detemir with insulin glargine in a basal-bolus regimen with mealtime insulin aspart in patients with type 2 diabetes.

- Rosenstock J, et al. Diabetologia. 2008; 51:408–416.
  - A randomised, 52-week, treat-to-target trial comparing insulin detemir with insulin glargine when administered as add-on to glucose-lowering drugs in insulin-naive people with type 2 diabetes.

Detemir vs. Glargine: Head-to-Head Comparisons

- Raskin P, et al. Diabetes Metab Res Rev. 2009; 25:542–548.
  - Comparison of insulin detemir and insulin glargine using a basal-bolus regimen in a randomized, controlled clinical study in patients with type 2 diabetes.

- Swinnen SG, et al. Diabetes Care. 2010; 33:1176-8.
  - A24-week, randomized, treat-to-target trial comparing initiation of insulin glargine once-daily with insulin detemir twice-daily in patients with type 2 diabetes inadequately controlled on oral glucose-lowering drugs

Analysis 1.1. Comparison 1 Detemir versus Glargine, Outcome 1 HbA1c at study endpoint.

Review: Insulin detemir versus insulin glargine for type 2 diabetes mellitus

Comparison: 1 Detemir versus Glargine

Outcome: 1 HbA1c at study endpoint

Study or subgroup	Detemir N	Mean(SD)	Glargine N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Hollander 2008	214	7.19 (1)	105	7.03 (1)		22.8 %	0.16 [-0.07, 0.39]
Raskin 2009	254	7.33 (1.21)	131	7.02 (1.1)		22.4 %	0.31 [0.07, 0.55]
Rosenstock 2008	291	7.16 (1.36)	291	7.12 (1.36)		23.7 %	0.04 [-0.18, 0.26]
Swinnen 2010a	486	7.1 (0.9)	478	7.2 (0.9)		31.1 %	-0.10 [-0.21, 0.01]
Total (95% CI)	**1245**		**1005**			**100.0 %**	**0.08 [-0.10, 0.27]**

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 11.26$, df = 3 (P = 0.01); $I^2 = 73\%$

Test for overall effect: Z = 0.87 (P = 0.38)

Test for subgroup differences: Not applicable

Analysis 1.3. Comparison 1 Detemir versus Glargine, Outcome 3 Percentage of participants achieving HbA1c ≤7%.

Review: Insulin detemir versus insulin glargine for type 2 diabetes mellitus

Comparison: 1 Detemir versus Glargine

Outcome: 3 Percentage of participants achieving HbA1c ≤7%

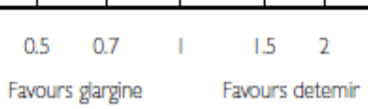
Study or subgroup	Detemir n/N	Glargine n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
Hollander 2008	72/199	36/98		16.1 %	0.98 [0.72, 1.35]
Raskin 2009	93/216	66/115		23.4 %	0.75 [0.60, 0.93]
Rosenstock 2008	129/248	135/259		28.3 %	1.00 [0.84, 1.18]
Swinnen 2010a	250/471	227/472		32.2 %	1.10 [0.97, 1.25]
Total (95% CI)	**1134**	**944**		**100.0 %**	**0.96 [0.81, 1.14]**

Total events: 544 (Detemir), 464 (Glargine)

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 8.91$, df = 3 (P = 0.03); $I^2 = 66\%$

Test for overall effect: Z = 0.45 (P = 0.65)

Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1 Detemir versus Glargine, Outcome 4 Percentage of participants achieving HbA1c ≤ 7% without hypoglycaemia.

Review: Insulin detemir versus insulin glargine for type 2 diabetes mellitus

Comparison: 1 Detemir versus Glargine

Outcome: 4 Percentage of participants achieving HbA1c ≤ 7% without hypoglycaemia

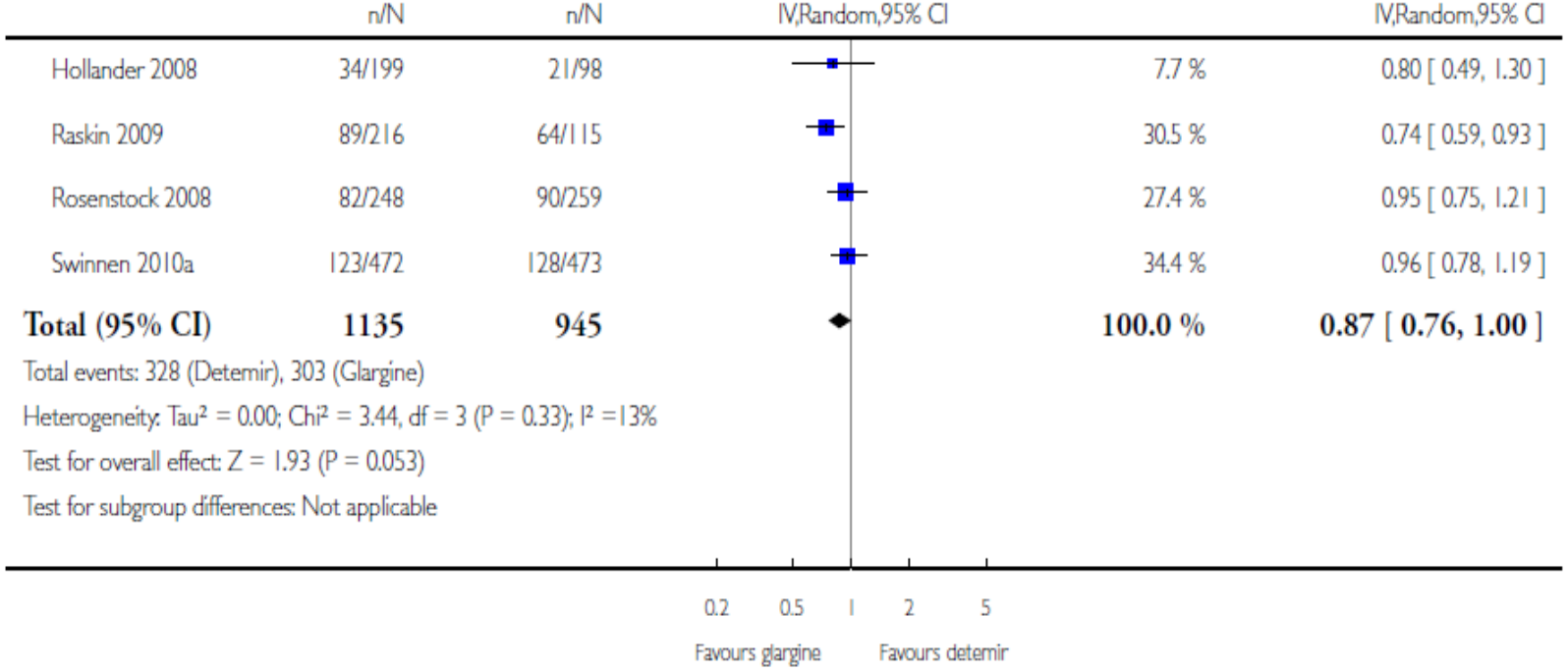
Study or subgroup	Detemir n/N	Glargine n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
Hollander 2008	34/199	21/98		7.7 %	0.80 [0.49, 1.30]
Raskin 2009	89/216	64/115		30.5 %	0.74 [0.59, 0.93]
Rosenstock 2008	82/248	90/259		27.4 %	0.95 [0.75, 1.21]
Swinnen 2010a	123/472	128/473		34.4 %	0.96 [0.78, 1.19]
Total (95% CI)	**1135**	**945**		**100.0 %**	**0.87 [0.76, 1.00]**

Total events: 328 (Detemir), 303 (Glargine)

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.44$, df = 3 (P = 0.33); $I^2 = 13\%$

Test for overall effect: Z = 1.93 (P = 0.053)

Test for subgroup differences: Not applicable



Analysis 1.5. Comparison 1 Detemir versus Glargine, Outcome 5 Fasting plasma glucose at study endpoint.

Review: Insulin detemir versus insulin glargine for type 2 diabetes mellitus

Comparison: 1 Detemir versus Glargine

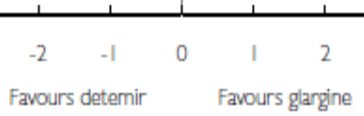
Outcome: 5 Fasting plasma glucose at study endpoint

Study or subgroup	Detemir N	Mean(SD)	Glargine N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Hollander 2008	214	7.05 (2.67)	105	6.68 (2.67)		18.1 %	0.37 [-0.25, 0.99]
Raskin 2009	254	7.52 (2.79)	131	7.59 (2.79)		19.4 %	-0.07 [-0.66, 0.52]
Rosenstock 2008	291	7.14 (3.58)	291	6.98 (3.58)		19.7 %	0.16 [-0.42, 0.74]
Swinnen 2010a	486	6.6 (1.8)	478	6 (1.3)		42.8 %	0.60 [0.40, 0.80]
Total (95% CI)	**1245**		**1005**			**100.0 %**	**0.34 [0.01, 0.67]**

Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 6.05$, df = 3 (P = 0.11); $I^2 = 50\%$

Test for overall effect: Z = 2.02 (P = 0.043)

Test for subgroup differences: Not applicable

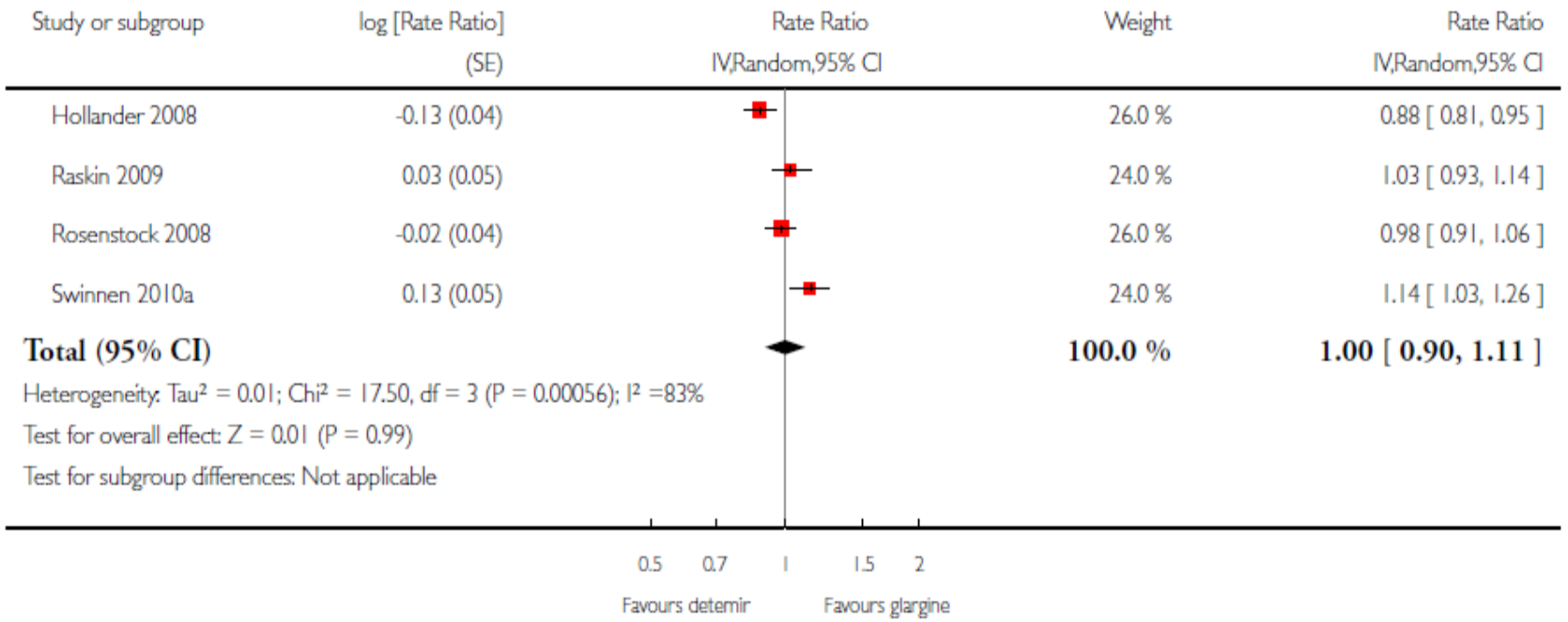


Analysis 1.8. Comparison 1 Detemir versus Glargine, Outcome 8 Event rate for overall hypoglycaemia per patient-year.

Review: Insulin detemir versus insulin glargine for type 2 diabetes mellitus

Comparison: 1 Detemir versus Glargine

Outcome: 8 Event rate for overall hypoglycaemia per patient-year



Analysis 1.9. Comparison 1 Detemir versus Glargine, Outcome 9 Percentage of participants having at least one nocturnal hypoglycaemic event.

Review: Insulin detemir versus insulin glargine for type 2 diabetes mellitus

Comparison: 1 Detemir versus Glargine

Outcome: 9 Percentage of participants having at least one nocturnal hypoglycaemic event

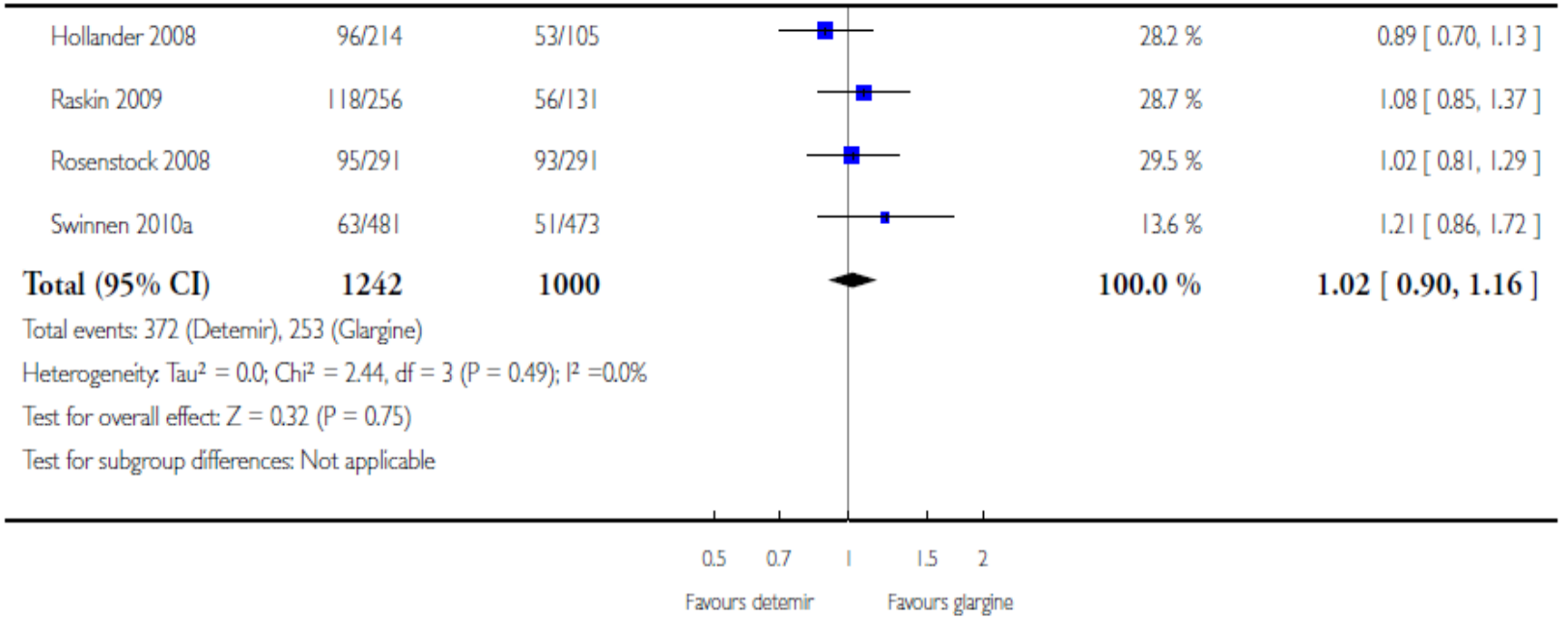
Study or subgroup	Detemir n/N	Glargine n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
Hollander 2008	96/214	53/105		28.2 %	0.89 [0.70, 1.13]
Raskin 2009	118/256	56/131		28.7 %	1.08 [0.85, 1.37]
Rosenstock 2008	95/291	93/291		29.5 %	1.02 [0.81, 1.29]
Swinnen 2010a	63/481	51/473		13.6 %	1.21 [0.86, 1.72]
Total (95% CI)	**1242**	**1000**		**100.0 %**	**1.02 [0.90, 1.16]**

Total events: 372 (Detemir), 253 (Glargine)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2.44$, df = 3 (P = 0.49); $I^2 = 0.0\%$

Test for overall effect: Z = 0.32 (P = 0.75)

Test for subgroup differences: Not applicable



Analysis 1.13. Comparison 1 Detemir versus Glargine, Outcome 13 Weight gain.

Review: Insulin detemir versus insulin glargine for type 2 diabetes mellitus

Comparison: 1 Detemir versus Glargine

Outcome: 13 Weight gain

Study or subgroup	Detemir N	Mean(SD)	Glargine N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Hollander 2008	214	2.8 (4.42)	105	3.8 (4.42)		8.5 %	-1.00 [-2.03, 0.03]
Raskin 2009	254	1.2 (3.96)	131	2.7 (3.94)		13.1 %	-1.50 [-2.33, -0.67]
Rosenstock 2008	291	2.7 (4.45)	291	3.5 (4.45)		17.4 %	-0.80 [-1.52, -0.08]
Swinnen 2010a	486	0.6 (2.9)	478	1.4 (3.2)		61.0 %	-0.80 [-1.19, -0.41]
Total (95% CI)	**1245**		**1005**			**100.0 %**	**-0.91 [-1.21, -0.61]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2.36$, df = 3 (P = 0.50); $I^2 = 0.0\%$

Test for overall effect: Z = 5.91 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 1.14. Comparison 1 Detemir versus Glargine, Outcome 14 Percentage of participants having at least one injection site reaction.

Review: Insulin detemir versus insulin glargine for type 2 diabetes mellitus

Comparison: 1 Detemir versus Glargine

Outcome: 14 Percentage of participants having at least one injection site reaction

Study or subgroup	Detemir n/N	Glargine n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Hollander 2008	4/214	0/105		13.2 %	4.44 [0.24, 81.65]
Raskin 2009	4/256	2/131		36.9 %	1.02 [0.19, 5.51]
Rosenstock 2008	9/291	1/291		25.5 %	9.00 [1.15, 70.58]
Swinnen 2010a	6/486	1/478		24.3 %	5.90 [0.71, 48.83]
Total (95% CI)	**1247**	**1005**		**100.0 %**	**3.31 [1.13, 9.73]**

Total events: 23 (Detemir), 4 (Glargine)

Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 3.20$, df = 3 (P = 0.36); $I^2 = 6\%$

Test for overall effect: Z = 2.18 (P = 0.029)

Test for subgroup differences: Not applicable

Analysis 1.15. Comparison 1 Detemir versus Glargine, Outcome 15 Daily basal insulin dose in units per kg.

Review: Insulin detemir versus insulin glargine for type 2 diabetes mellitus

Comparison: 1 Detemir versus Glargine

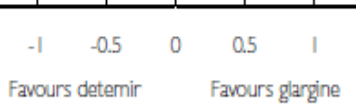
Outcome: 15 Daily basal insulin dose in units per kg

Study or subgroup	Detemir N	Mean(SD)	Glargine N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Hollander 2008	214	0.82 (0.5)	105	0.59 (0.3)		24.3 %	0.23 [0.14, 0.32]
Raskin 2009	254	0.81 (0.5)	131	0.75 (0.3)		24.7 %	0.06 [-0.02, 0.14]
Rosenstock 2008	291	0.78 (0.5)	291	0.44 (0.3)		25.2 %	0.34 [0.27, 0.41]
Swinnen 2010a	486	0.9 (0.5)	478	0.5 (0.3)		25.8 %	0.40 [0.35, 0.45]
Total (95% CI)	**1245**		**1005**			**100.0 %**	**0.26 [0.11, 0.41]**

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 52.48$, df = 3 ($P<0.00001$); $I^2 = 94\%$

Test for overall effect: Z = 3.48 (P = 0.00049)

Test for subgroup differences: Not applicable



Analysis 1.16. Comparison 1 Detemir versus Glargine, Outcome 16 Variability of fasting plasma glucose at study endpoint.

Review: Insulin detemir versus insulin glargine for type 2 diabetes mellitus

Comparison: 1 Detemir versus Glargine

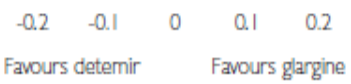
Outcome: 16 Variability of fasting plasma glucose at study endpoint

Study or subgroup	Detemir N	Mean(SD)	Glargine N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Hollander 2008	214	0.21 (0.15)	105	0.23 (0.17)		18.5 %	-0.02 [-0.06, 0.02]
Raskin 2009	254	0.27 (0.21)	131	0.24 (0.18)		17.5 %	0.03 [-0.01, 0.07]
Rosenstock 2008	291	0.18 (0.13)	291	0.17 (0.13)		29.0 %	0.01 [-0.01, 0.03]
Swinnen 2010a	486	0.14 (0.09)	478	0.16 (0.1)		34.9 %	-0.02 [-0.03, -0.01]
Total (95% CI)	**1245**		**1005**			**100.0 %**	**0.00 [-0.03, 0.02]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 10.15$, df = 3 (P = 0.02); $I^2 = 70\%$

Test for overall effect: Z = 0.22 (P = 0.83)

Test for subgroup differences: Not applicable

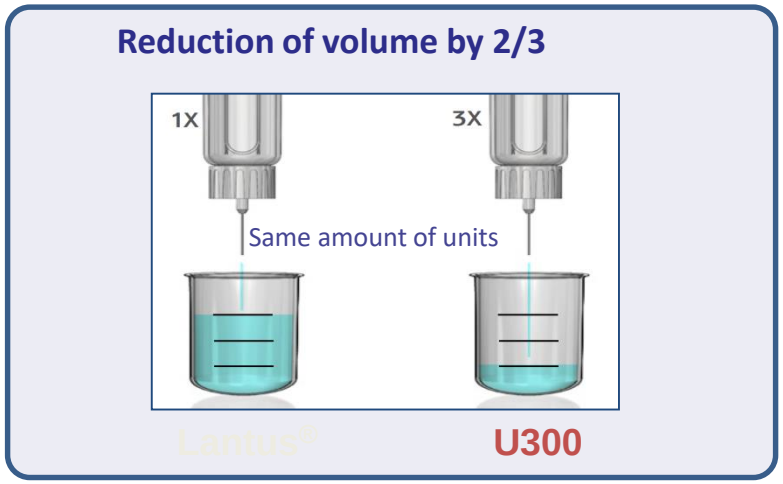


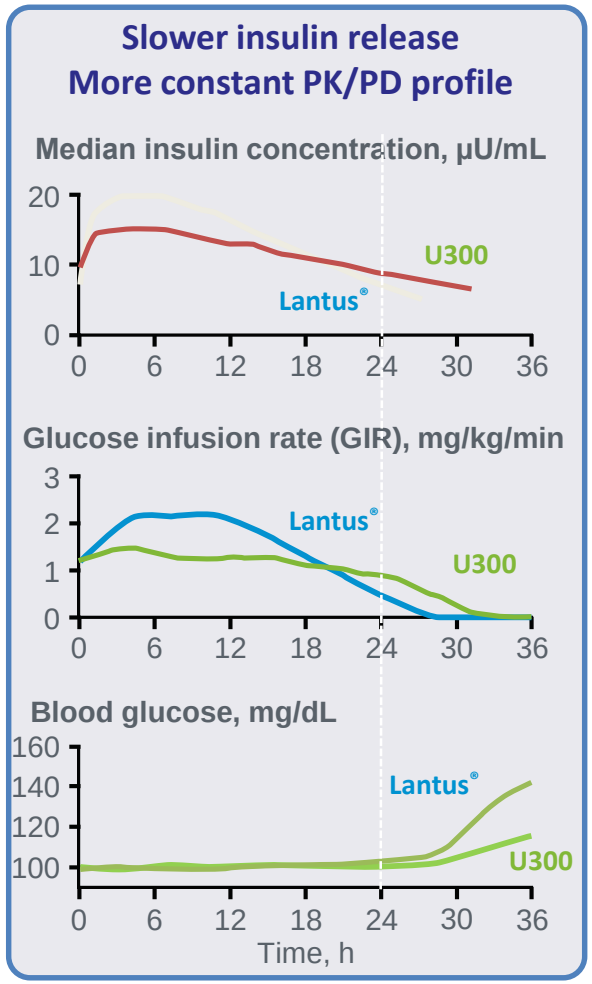
Conclusion

- There is no clinically relevant difference in efficacy or safety between insulin detemir and insulin glargine for targeting hyperglycaemia.

- However, to achieve the same glycemic control insulin detemir was often injected twice-daily in a higher dose but with less weight gain, while insulin glargine was injected once-daily, with somewhat fewer injection site reactions.

U300 is a new long-acting basal insulin with a more constant and prolonged PK/PD profile vs Lantus®

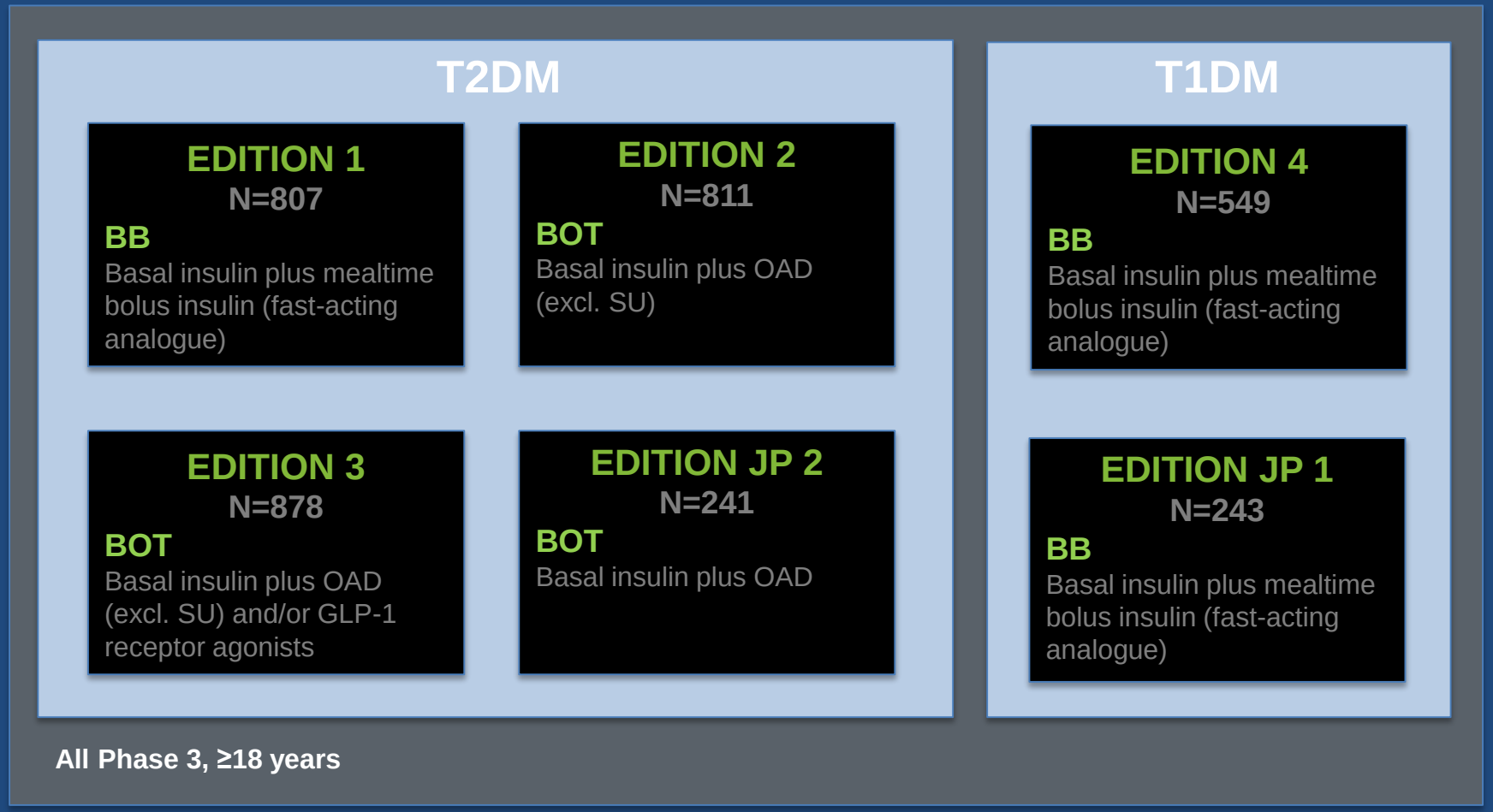




Jax T et al. Poster presented at EASD 2013; Abstract 1029. Available at http://www.easdvirtualmeeting.org/resources/6226 Accessed May 2014
Steinstraesser A et al. Diabetes Obes Metab. 2014 Feb 26. doi: 10.1111/dom.12283. [Epub ahead of print]

EDITION program

Testing U300 vs Lantus® in several populations



BB, basal-bolus therapy; BOT, basal only therapy; GLP-1, glucagon-like peptide; OAD, oral antidiabetic drugs; SU, sulfonylureas

•. 2014 Oct;37(10):2755-62

New Insulin Glargine 300 Units/mL Versus Glargine 100 Units/mL in People With Type 2 Diabetes Using Basal and Mealtime Insulin: Glucose Control and Hypoglycemia in a 6-Month Randomized Controlled Trial (EDITION 1)

Matthew C. Riddle,[1] Geremia B. Bolli,[2] Monika Ziemen,[3] Isabel Muehlen-Bartmer,[3] Florence Bizet,[4] and Philip D. Home,[5] on behalf of the EDITION 1 Study Investigators

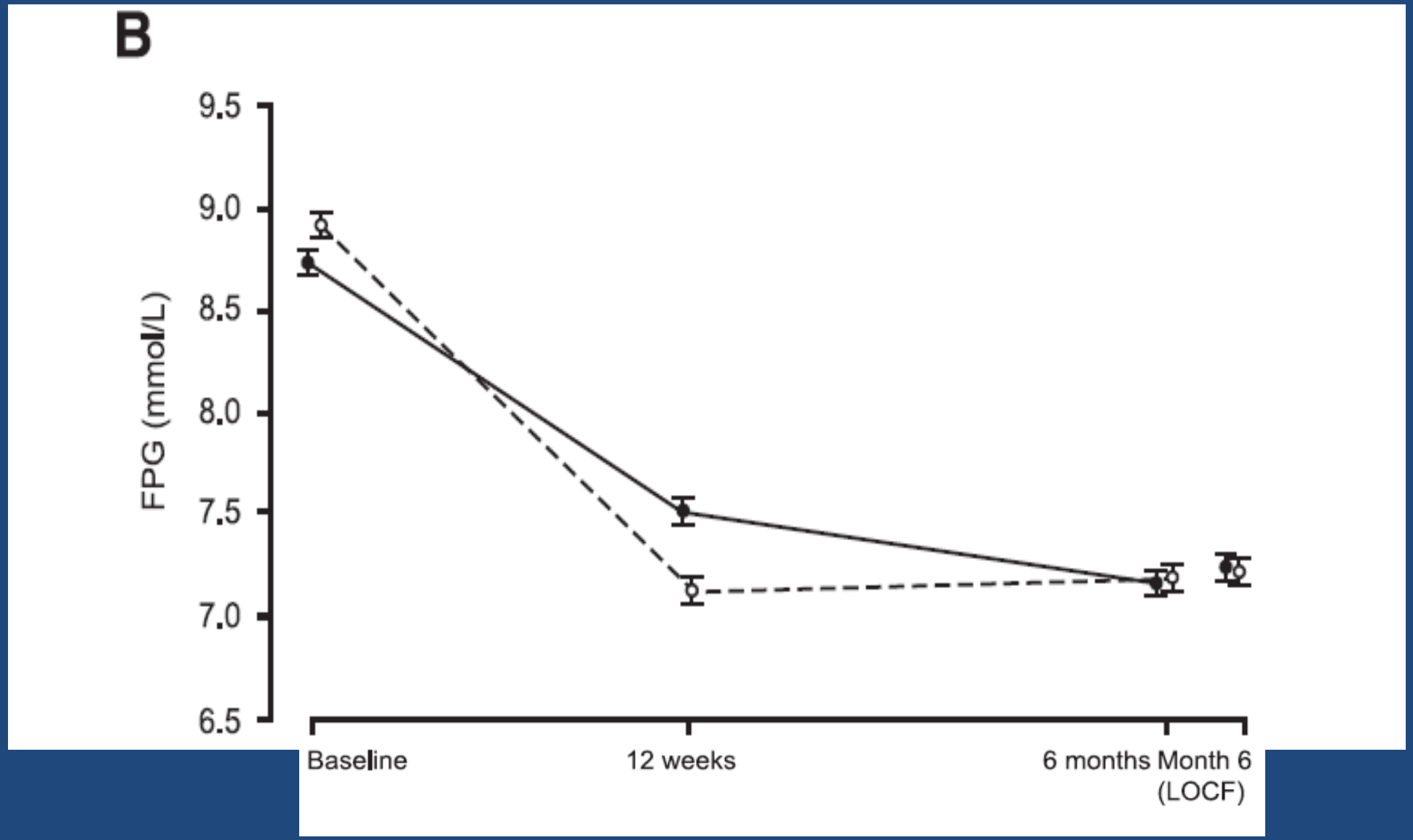
Objective: To compare the efficacy and safety of new insulin glargine 300 units/mL (Gla-300) with glargine 100 units/mL (Gla-100) in people with type 2 diabetes on basal insulin (≥42 units/day) plus mealtime insulin

Diabetes Care. 2014 Oct;37(10):2755-62

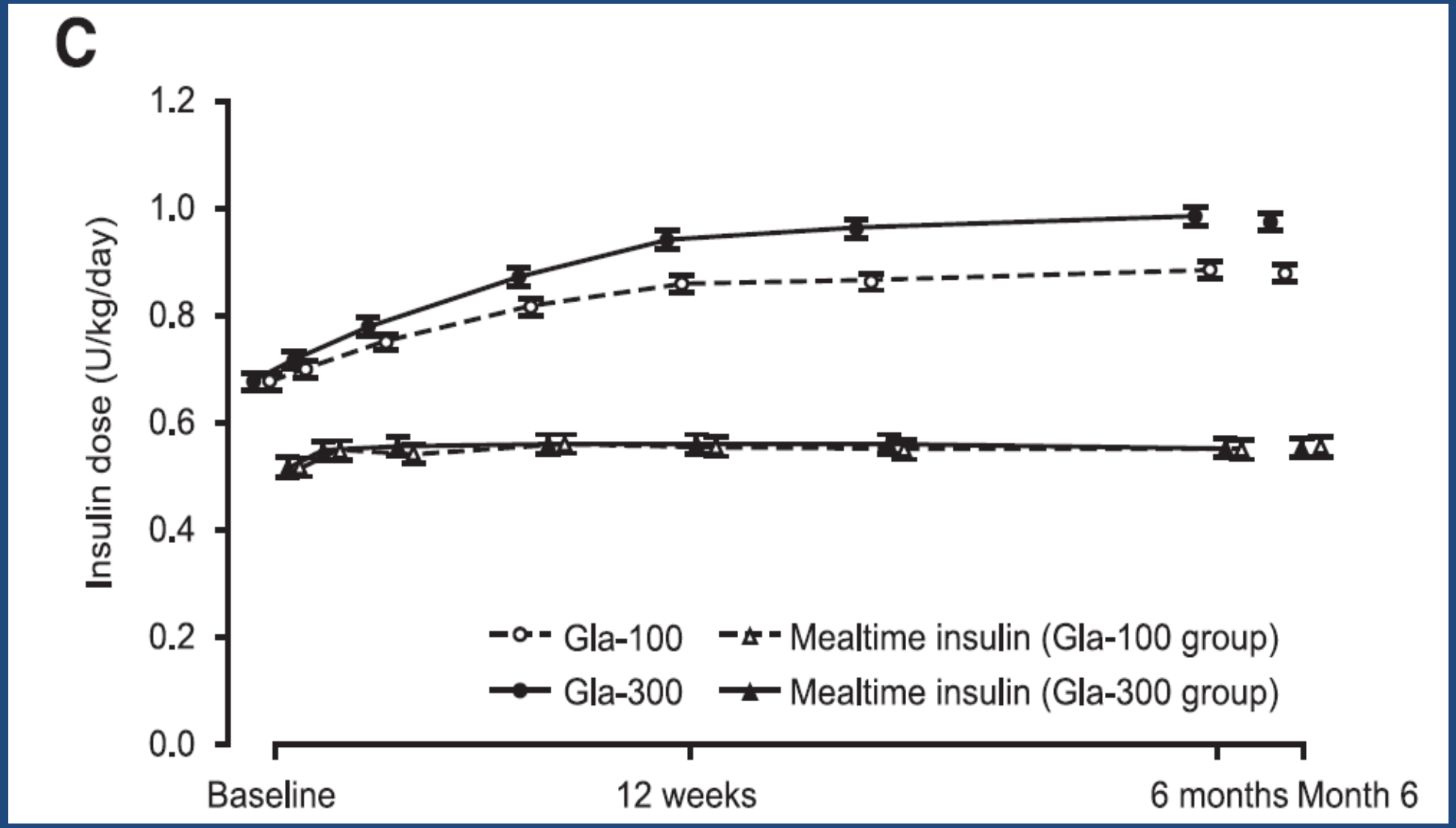
Baseline characteristics

Age (years)	60.1 (8.5)	59.8 (8.7)
Sex (male), *n* (%)	217 (53.7)	210 (52.1)
Ethnic group, *n* (%)		
Caucasian	371 (91.8)	374 (92.8)
Black	26 (6.4)	21 (5.2)
Asian/Oriental	6 (1.5)	5 (1.2)
Other	1 (0.2)	3 (0.7)
Body weight (kg)	106.2 (21.5)	106.4 (20.0)
BMI (kg/m^2)	36.6 (6.8)	36.6 (6.1)
Duration of diabetes (years)	15.6 (7.2)	16.1 (7.8)
Duration of basal insulin treatment (years)	6.7 (4.7)	6.5 (4.8)
Basal insulin dose		
(units/kg/day)	0.67 (0.26)	0.67 (0.24)
(units/day)	70.0 (30.4)	70.3 (28.5)
Mealtime insulin dose		
(units/kg/day)	0.54 (0.34)	0.54 (0.32)
(units/day)	57.1 (36.5)	58.4 (37.9)
Total insulin dose		
(units/kg/day)	1.19 (0.48)	1.20 (0.45)
(units/day)	126.3 (56.7)	128.0 (56.1)
Prior use of insulin glargine, *n* (%)	373 (92.3)	369 (91.6)
Prior use of metformin, *n* (%)	227 (56.2)	236 (58.6)
FPG		
(mmol/L)	8.8 (2.9)	8.9 (2.9)
(mg/dL)	158.3 (51.8)	160.7 (52.8)
HbA_{1c}		
(%)	8.15 (0.78)	8.16 (0.77)
(mmol/mol)	65.6 (8.5)	65.7 (8.4)

At the end of treatment, HbA1c was 7.25% (0.85) with Gla-300, and 7.28% (0.92)with Gla-100



Final total daily dosage was 1.53 units/kg/day (0.61) with Gla-300 and 1.43 units/kg/day (0.60) with Gla-100



Fewer participants reported one or more confirmed (<70 mg/dl) or severe nocturnal hypoglycemic events with Gla-300 (36 vs. 46% with Gla-100; relative risk 0.79 (95% CI 0.67–0.93)

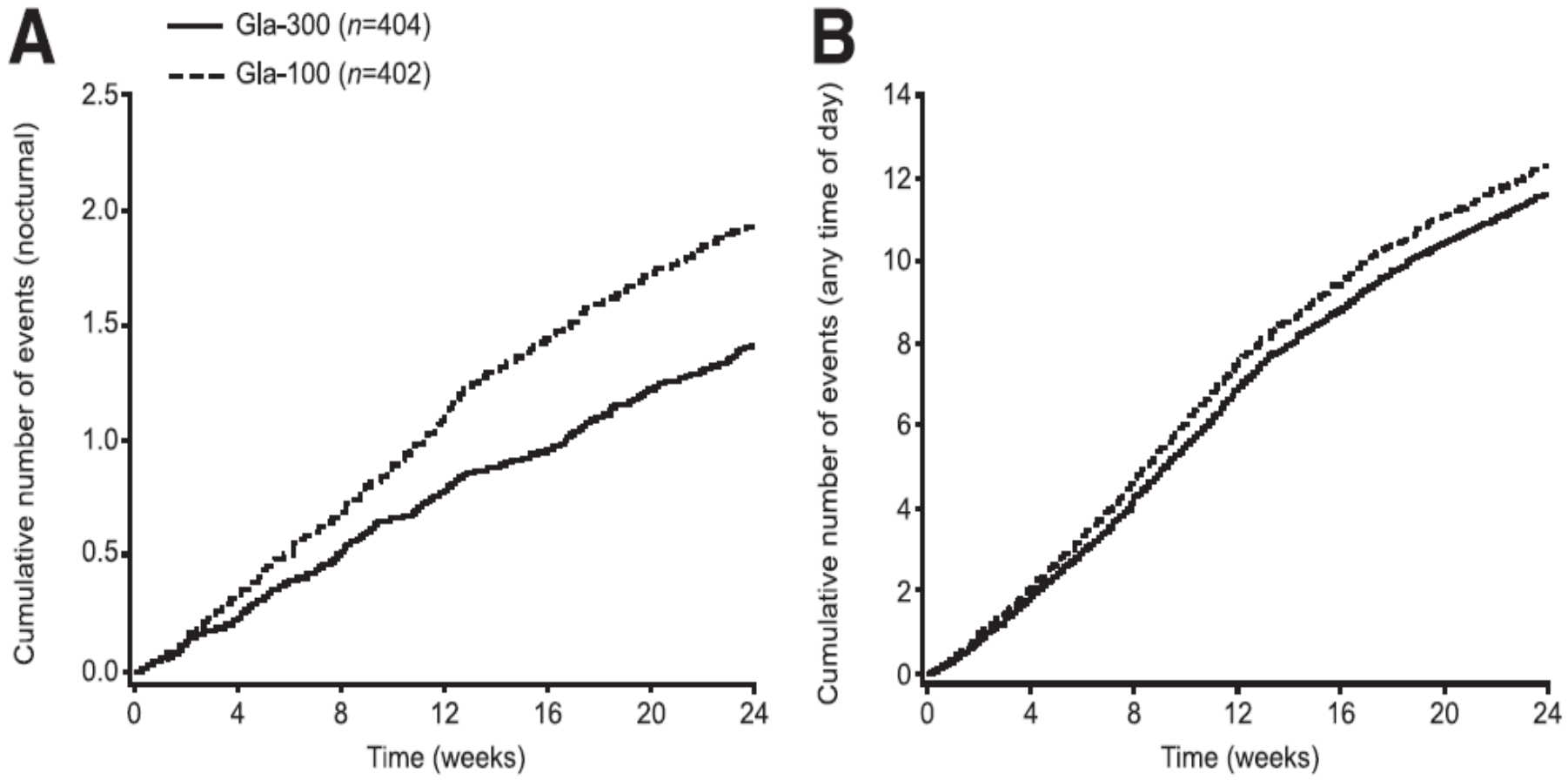


Figure 2—Cumulative mean numbers of confirmed (plasma glucose ≤3.9 mmol/L [70 mg/dL]) or severe hypoglycemic events per participant during the main 6-month treatment period in the safety population. *A*: Nocturnal events. *B*: Events at any time of day or night (24 h).

Key message

- Gla-300 controls HbA1c as well as Gla-100 for people with type 2 diabetes treated with basal and mealtime insulin, but with consistently less risk of nocturnal hypoglycemia

Titrate basal insulin as long as FPG > target

INITIATE

- Bedtime or morning long-acting insulin
  Daily dose: 10 units or 0.2 units/kg

Check FPG daily

TITRATE

- Increase dose by 2 units every 3 days until FPG is (70–130 mg/dL)
- If FPG is >180 mg/dL), increase dose by 4 units every 3 days

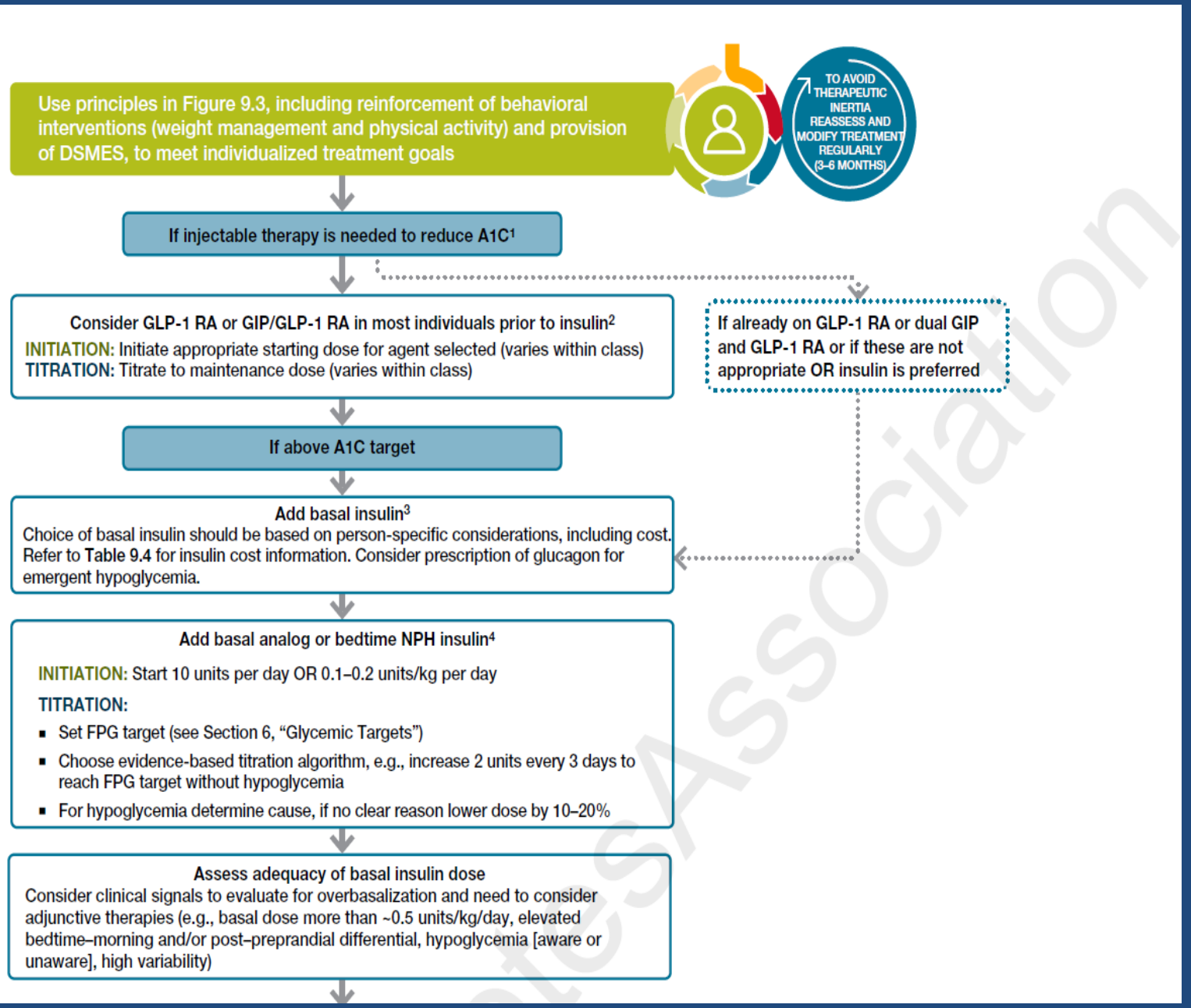
In the event of hypoglycemia or FPG level < 70 mg/dL

- Reduce bedtime insulin dose by ≥4 units, or by 10% if >60 units

MONITOR

Continue regimen and check HbA_{1c} every 3 months

ADA 2024


Use principles in Figure 9.3, including reinforcement of behavioral interventions (weight management and physical activity) and provision of DSMES, to meet individualized treatment goals
TO AVOID THERAPEUTIC INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)
If injectable therapy is needed to reduce A1C[1]
Consider GLP-1 RA or GIP/GLP-1 RA in most individuals prior to insulin[2]
INITIATION: Initiate appropriate starting dose for agent selected (varies within class)
TITRATION: Titrate to maintenance dose (varies within class)
If already on GLP-1 RA or dual GIP and GLP-1 RA or if these are not appropriate OR insulin is preferred
If above A1C target
Add basal insulin[3]
Choice of basal insulin should be based on person-specific considerations, including cost. Refer to Table 9.4 for insulin cost information. Consider prescription of glucagon for emergent hypoglycemia.
Add basal analog or bedtime NPH insulin[4]
INITIATION: Start 10 units per day OR 0.1–0.2 units/kg per day
TITRATION:
Set FPG target (see Section 6, "Glycemic Targets")
Choose evidence-based titration algorithm, e.g., increase 2 units every 3 days to reach FPG target without hypoglycemia
For hypoglycemia determine cause, if no clear reason lower dose by 10–20%
Assess adequacy of basal insulin dose
Consider clinical signals to evaluate for overbasalization and need to consider adjunctive therapies (e.g., basal dose more than ~0.5 units/kg/day, elevated bedtime–morning and/or post–preprandial differential, hypoglycemia [aware or unaware], high variability)

How to Switch Between Insulin Products

Clinical Scenario	Recommendation/Comments
NPH to Long-acting	
NPH to insulin detemir (*Levemir*)	• Convert unit-per-unit.[1] • Some patients on basal-bolus insulin may require more *Levemir* than NPH.[1] • Give *Levemir* once daily, or divided twice daily if necessary for control.[1] • Do not mix *Levemir* with other insulins.[1]
NPH to insulin glargine (*Lantus*)	• NPH once daily: convert unit-per-unit and give once daily.[2] • NPH twice daily: reduce daily dose by 20% and give once daily.[2] • Do not mix *Lantus* with other insulins.[2]
Long-acting to NPH	
Insulin detemir (*Levemir*) to NPH	• Convert unit-per-unit.[3] • Give NPH at bedtime or split twice daily (e.g., 50:50 or 2/3 in AM and 1/3 before dinner or at bedtime).[3,4,5]
Insulin glargine (*Lantus*) to NPH	• Convert unit-per-unit.[3] • Give NPH at bedtime or split twice daily (e.g., 50:50 or 2/3 in AM and 1/3 before dinner or at bedtime).[3,4,5]

Key elements

- Duration of action
- Flatness
- Number of injections
- Injection site reactions
- Rate of hypoglycemia
- Goal achievement of glycemia
- Dose requirement
- Variability
- Weight gain
- Quality of life
- Cardiovascular effect
- Cost


Thank You

Overbasalization

- Titration of basal insulin beyond an appropriate dose in an attempt to achieve glycemic targets.

- It can be identified by a basal insulin dose.0.5 units/kg/day, postmeal blood glucose levels>180 mg/dL, A1C not at goal despite attainment of the fasting blood glucose target, or a Bedtime-AM differential ≥50 mg/dL

Clin Diabetes 2020;38:304–310

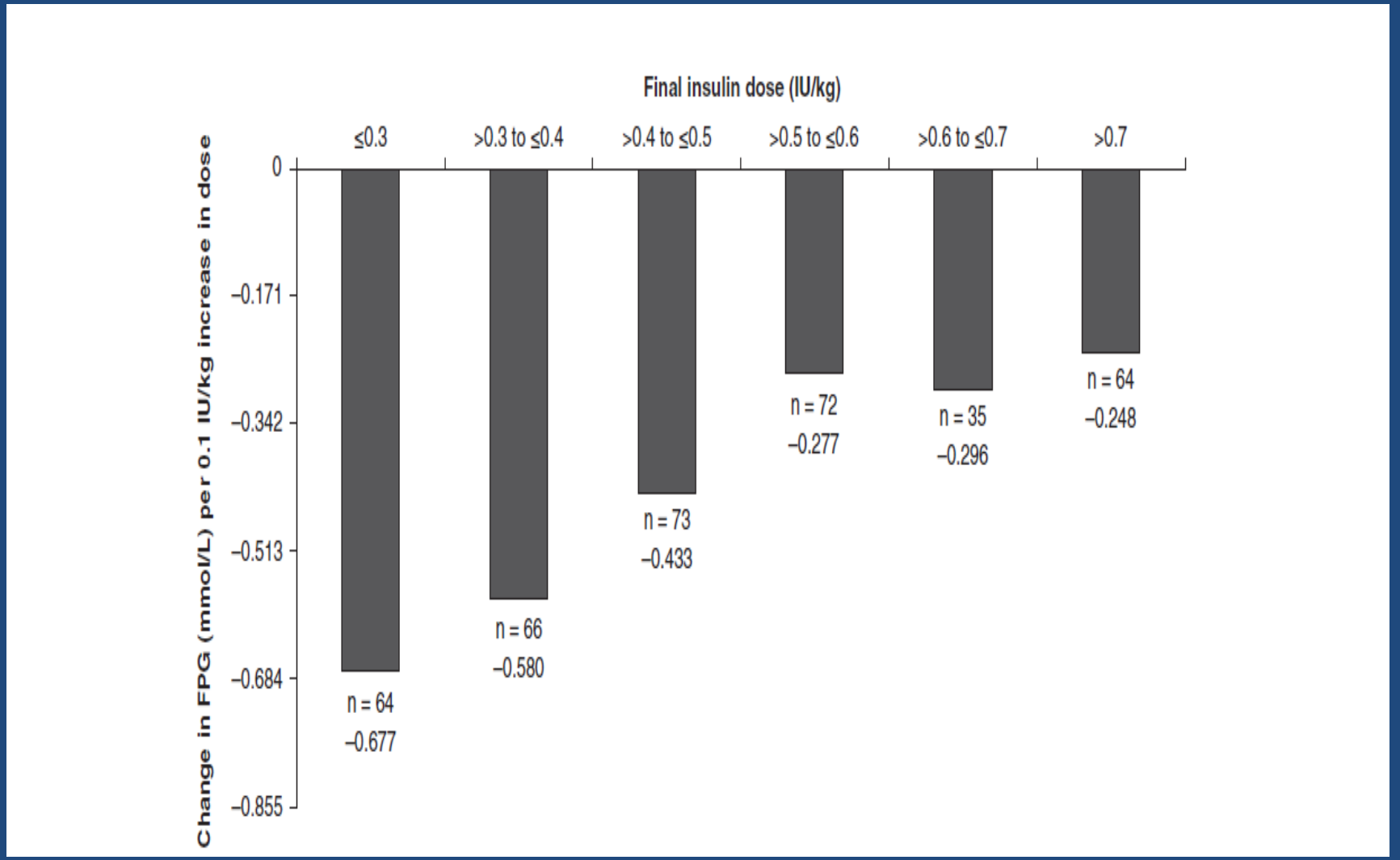
ORIGINAL ARTICLE

When basal insulin is not enough: A dose–response relationship between insulin glargine 100 units/mL and glycaemic control

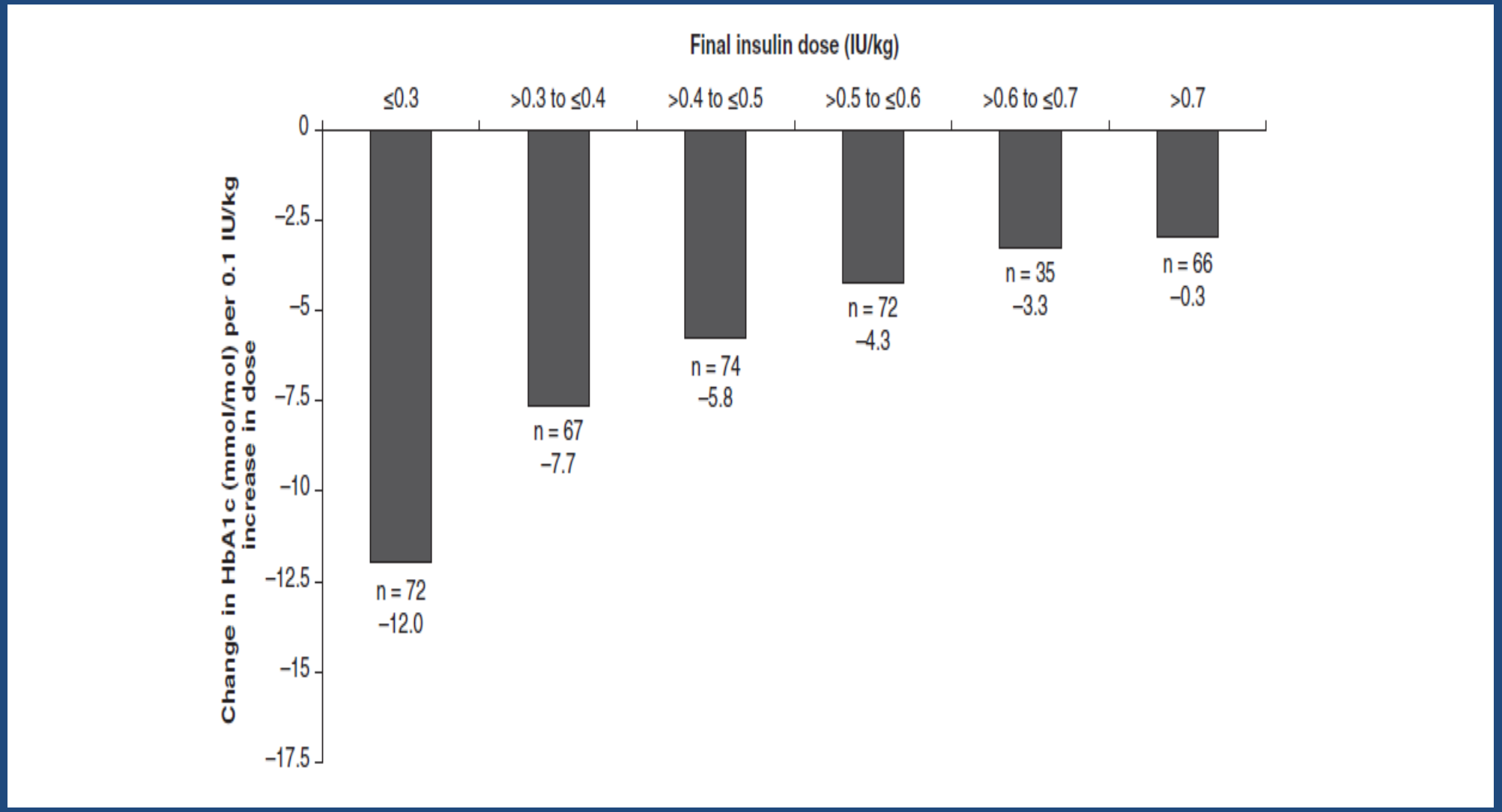
- Aim: A post-hoc analysis to assess the impact in people with type 2 diabetes, of increasing doses of basal insulin on glycemic measures, body weight and hypoglycemia
- Data from prospective, randomized controlled treat-to-target trials of ≥24 weeks' duration in people with type 2 diabetes, uncontrolled on metformin and sulphonylureas, and treated with insulin glargine 100 units/mL (U100), who had at least six fasting plasma glucose measurements were included
- The impact of insulin dose on HbA1c values, FPG, hypoglycemia incidence 70 mg/dl, and body weight was analyzed.
- A total of 458 participants from three eligible trials were included

Diabetes Obes Metab.2019 Jun;21(6):1305-1310

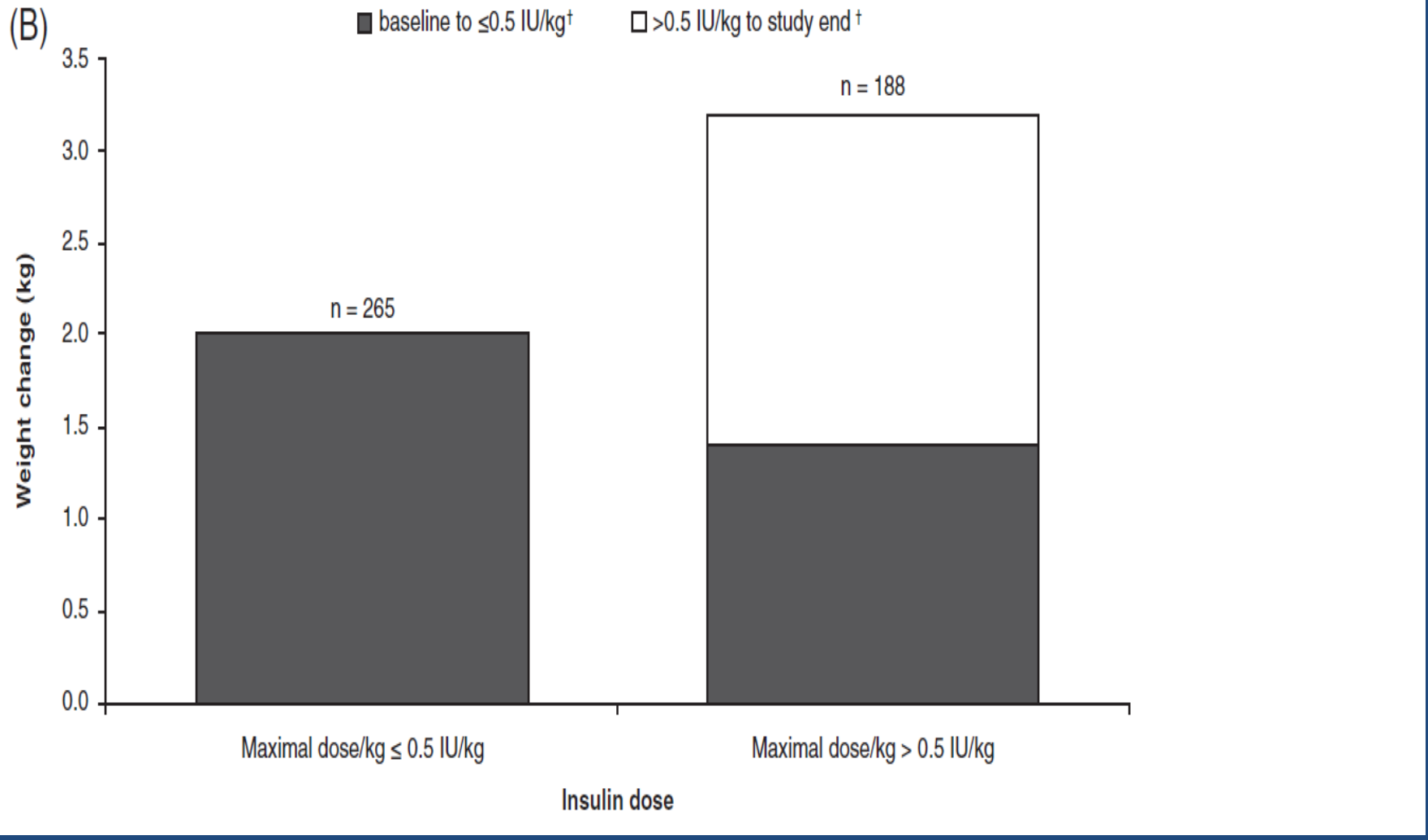
Effect of 0.1-IU/kg/d increases in daily insulin dose on the change in fasting plasma glucose



Effect of 0.1-IU/kg/d increases in insulin dose on the change in glycated HbA1c



Weight change from baseline to study end by daily basal insulin dose (maximal dose/kg/day)



Key messages

- This study indicates a non-linear clinical response curve for basal insulin, with diminishing glycemic efficacy for doses of insulin >0.3 to 0.5 IU/kg/d and a plateauing glycemic effect with doses >0.5 IU/kg/d

- This is associated with the disadvantage of additional weight gain. Clinicians should consider anti-hyperglycemic treatment intensification at doses approaching 0.5 IU/kg/d