Dibattito
Basal bolus o Insulina long acting + GLP-1RA?
Insulina long acting + GLP-1RA

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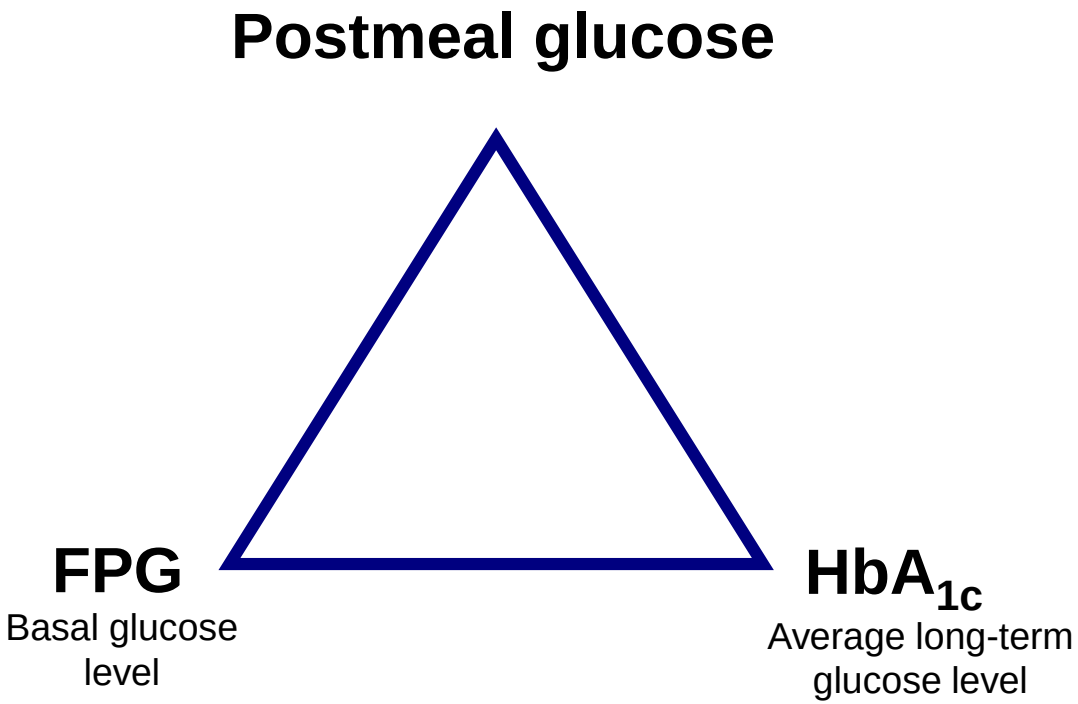
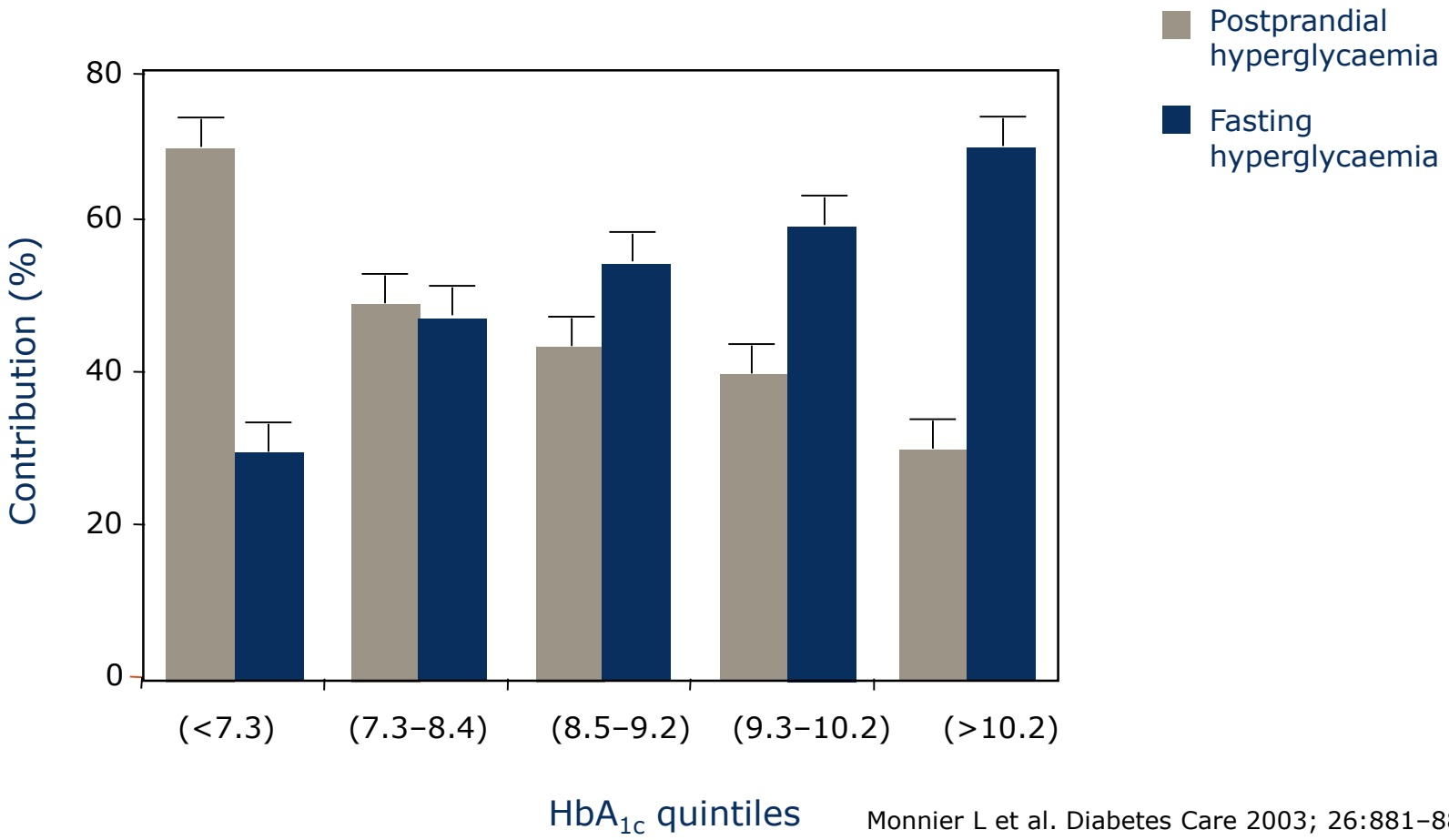
‘Glucose triad’ of diabetes management



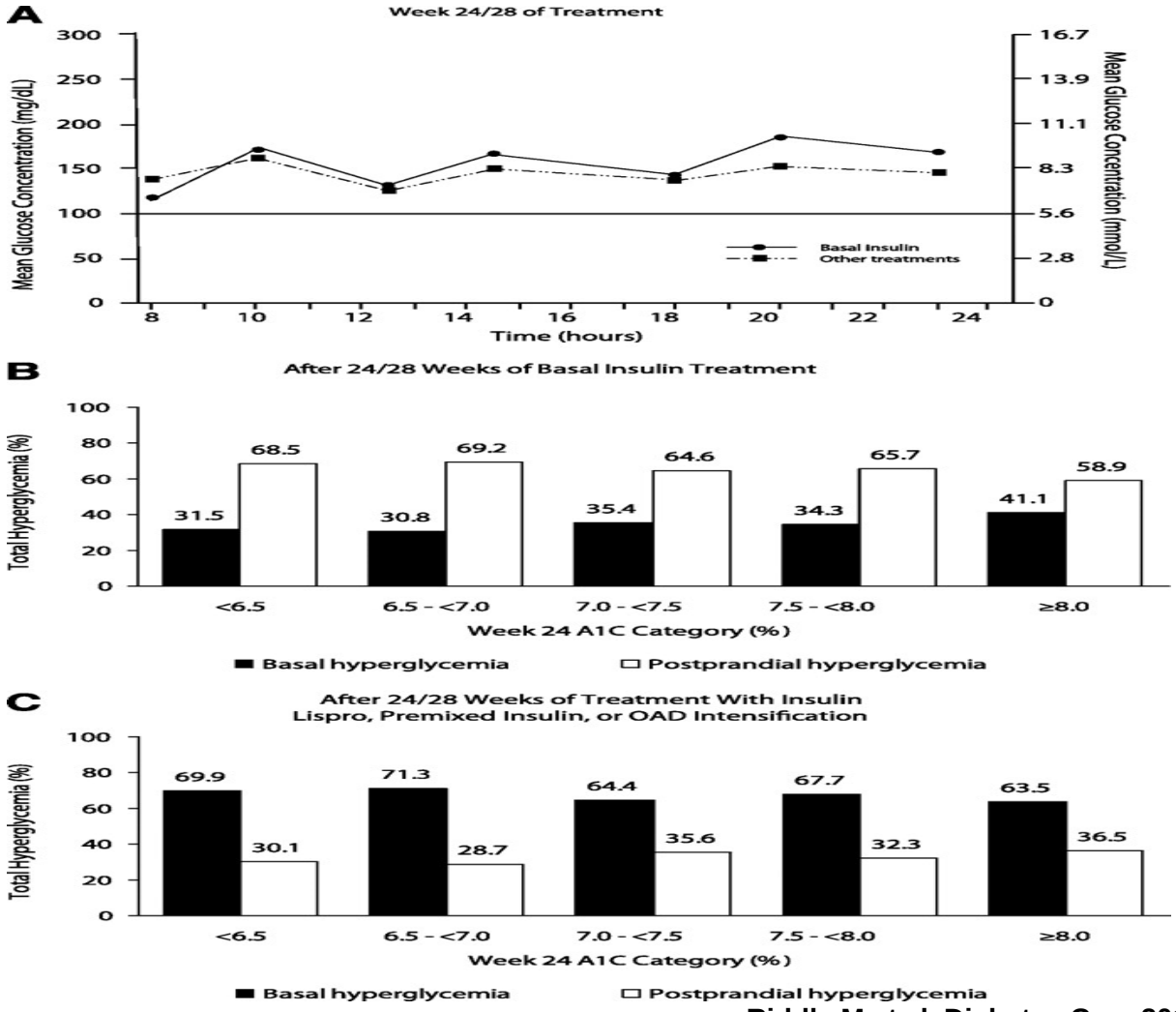
HbA_{1c} = glycated haemoglobin
FPG = fasting plasma glucose

Postprandial glucose makes a major contribution to overall glycaemia across a range of HbA_{1c} values



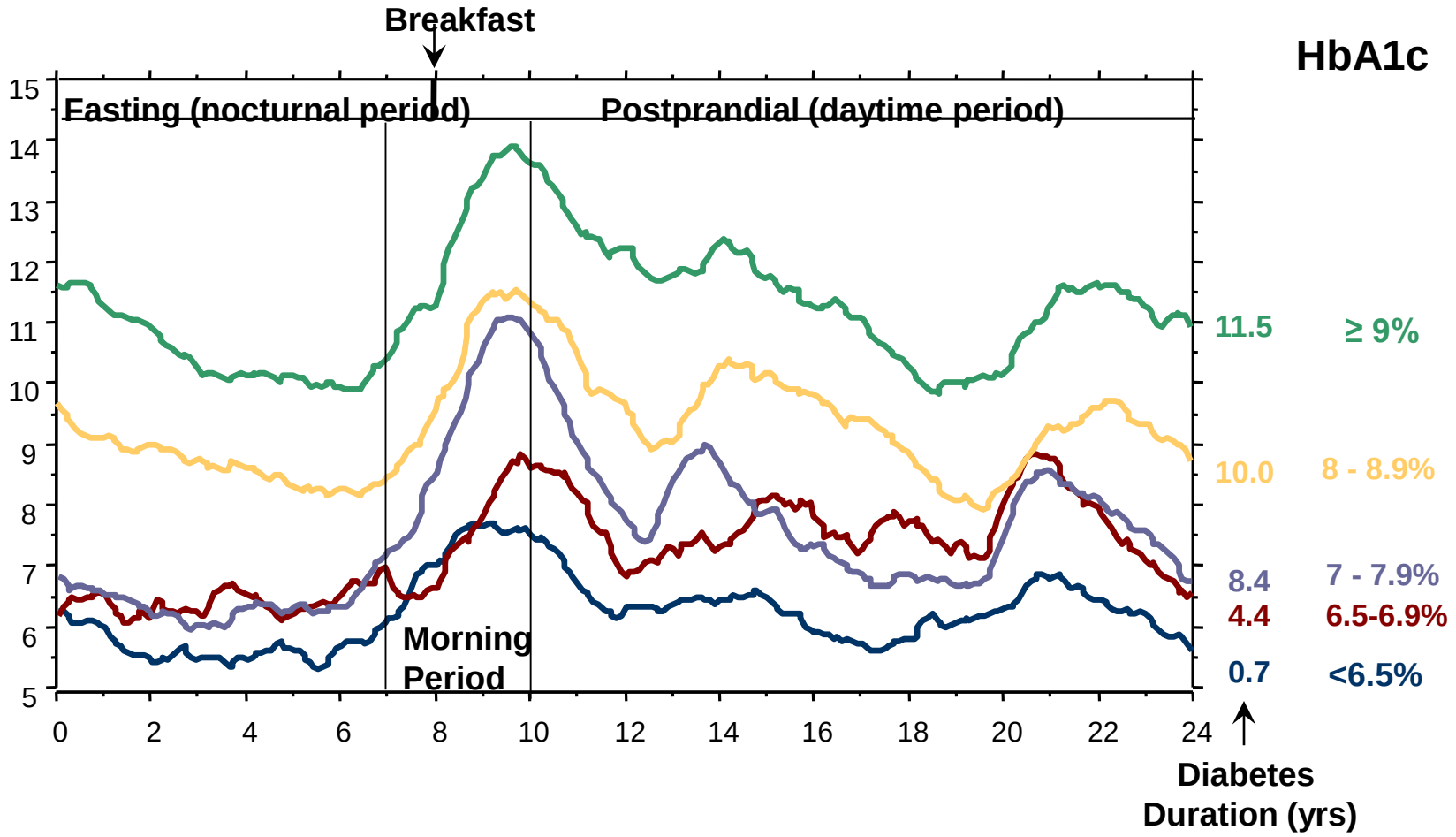
Monnier L et al. Diabetes Care 2003; 26:881–885

A: The seven-point glucose profiles for patients on basal insulin versus other treatments at week 24 or 28.



Riddle M et al. Diabetes Care 2011;34:2508-2514

Daily glycemic variation (mmol/L) with worsening glycaemic control in type 2 diabetes



L Monnier ,C Colette, G Dunseath and D Owens, Diabetes Care 2007

Efficacy of Insulin Analogs in Achieving the Hemoglobin A_{1c} Target of <7% in Type 2 Diabetes

Meta-analysis of randomized controlled trials

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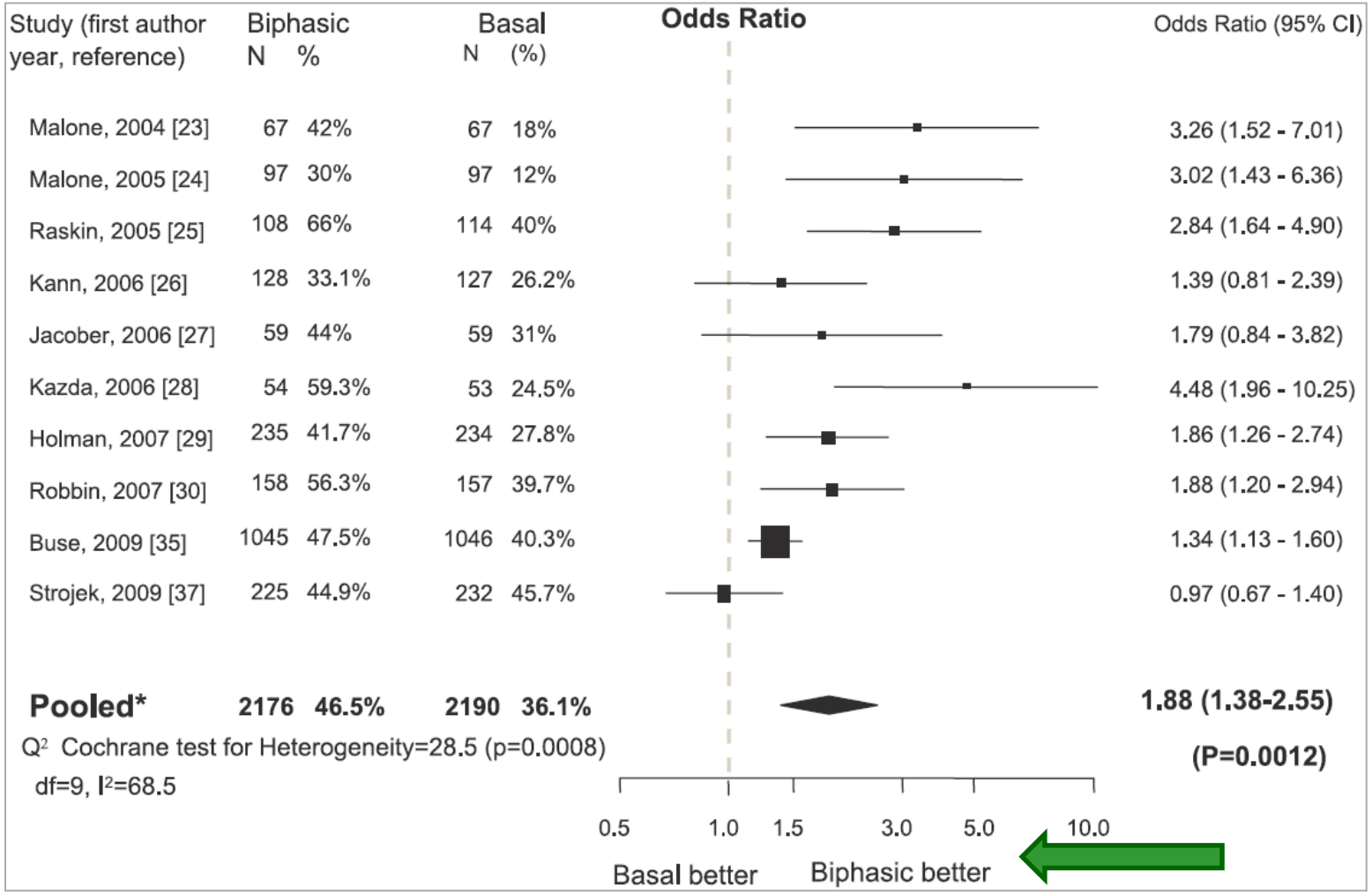
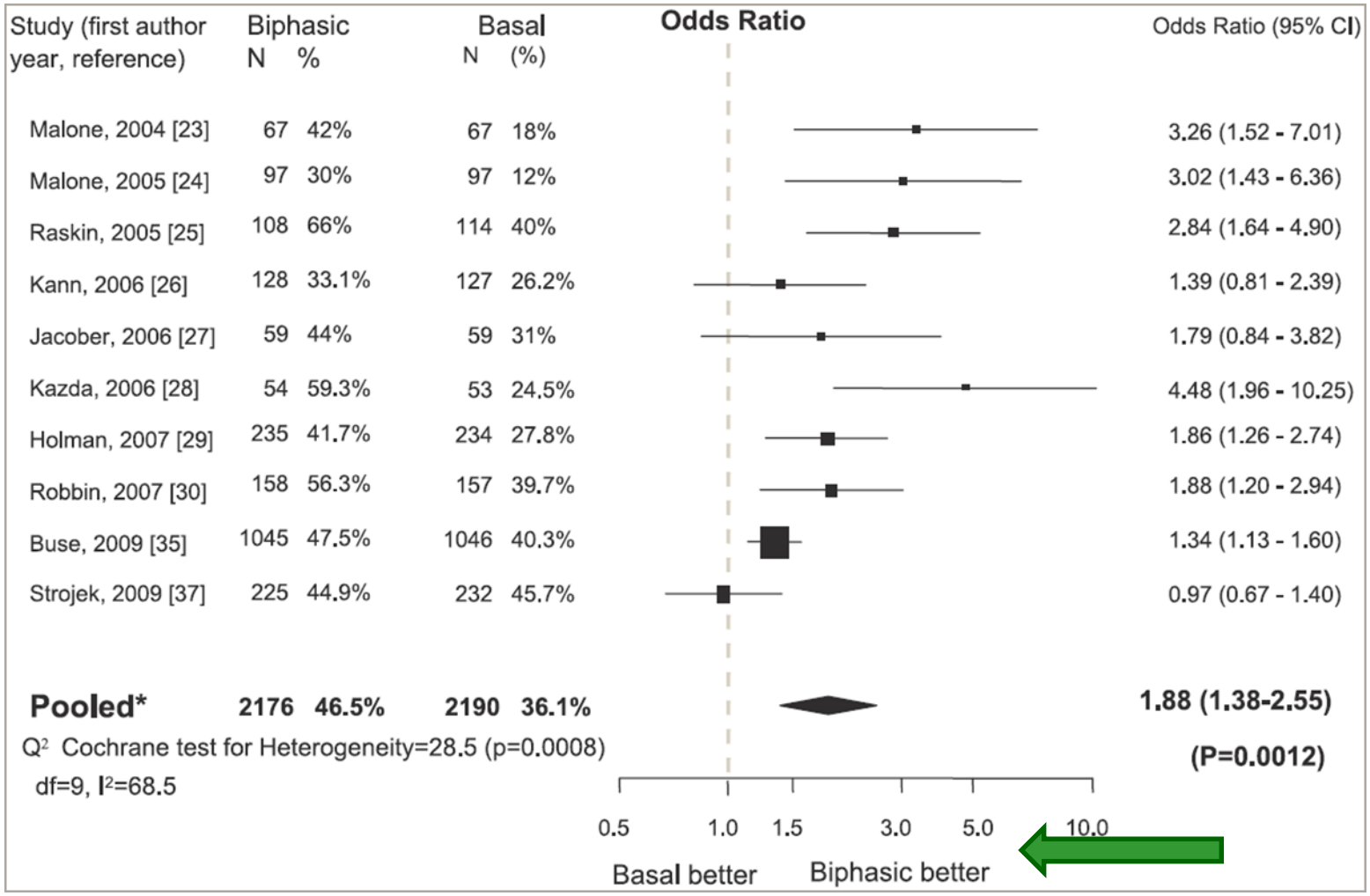
Diabetes Care 34:510–517, 2011

Percent of patients with Hb A1c <7%:



Giugliano D Diabetes Care 2011; 34:510–5

Risk of Hypoglycemia:



Giugliano D Diabetes Care 2011; 34:510–517

Hypoglycemia as Pro-atherosclerotic factor

EDITORIAL (SEE P. 1529 AND P. 1591)

Proinflammatory and Prothrombotic Effects of Hypoglycemia

Hypoglycemia is known to be intrinsic to the treatment of diabetes because insulin is a powerful glucose-lowering agent and sulfonylureas exert their effect through insulin release by the pancreatic β-cells. Hypoglycemia occurs in association with these two common modes of therapy and was previously accepted as a part of the treatment of this condition. With the arrival of other modes of diabetes treatment, such as metformin, thiazolidenediones, α2-glucosidase inhibitors, and incretins, which do not induce hypoglycemia except when administered in combination with insulin and sulfonylureas, the issue of hypoglycemia has to be assessed in the context of both the immediate risk related to neuroglycopenia and the possible long-term risk of diabetic vascular complications.

Vascular complications of hypoglycemia have to be tackled with greater urgency now because two recent trials of intensified diabetes treatment with insulin, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial and Veteran's Affairs Diabetes Trial (VADT), did not demonstrate a reduction in cardiovascular events (1,2). In fact, the intensified insulin treatment arm of the ACCORD trial had to be halted because of an increase in overall mortality, despite a reduction in acute myocardial infarction. The rate of hypoglycemia in both trials was significantly increased with intensified insulin treatment. Although the analysis of the ACCORD data did not support the hypothesis that the increased mortality in the study was a result of hypoglycemia, the fact that hypoglycemia may often be asymptomatic leaves us with the possibility that it may be responsible.

The fact that hypoglycemia results in platelet hyperaggregability (3) and an increase in several factors involved in the coagulation cascade has been known for over 2 decades. Activated partial thromboplastin time is shortened, fibrinogen and factor VIII increase, and platelet counts fall in association with hypoglycemia (4). More recently, two studies have shown that hypoglycemia induces proinflammatory changes including an increase in the plasma concentration of interleukin (IL)-6 (5) and increases in other proinflammatory mediators, including leucocytosis, reactive oxygen species (ROS) generation, lipid peroxidation, and levels of tumor necrosis factor-α (TNFα), IL-1β, and IL-8 (5). Two studies published in this issue of *Diabetes Care* confirm that hypoglycemia does, indeed, induce an increase in proinflammatory mediators and platelet activation, and has an inhibitory effect on fibrinolytic mechanisms. Wright et al. (6) and Gogitidze Joy et al. (7) both used an insulin infusion to gradually induce hypoglycemia and then clamped glucose at hypoglycemic levels of 2.5 and 2.9 mmol/l, respectively. The former maintained hypoglycemia for 60 min while the latter maintained it for 120 min. As is evident from the data, the effects of the longer duration of hypoglycemia in the study by Gogitidze Joy et al. are more impressive as reflected in the increase in proinflammatory mediators, in spite of the fact that glucose concentrations were not as low as those in the study by Wright et al. The increases in the indexes of inflammation and oxidative stress in the study by Razavi Nematollahi et al. (5) were even more impressive, probably because the mode of induction of hypoglycemia was by a bolus intravenous injection, which led to a rapid fall in blood glucose concentrations leading to a rapid release of catecholamines and the stimulation of the inflammatory response. In the study by Wright et al., hypoglycemia induced an increase in CD40 expression on mononuclear cells and plasma concentration of CD40L, as well as an increase in platelet-monocyte aggregates and P-selectin concentrations with a trend toward an increase in von Willebrand factor concentrations. In the study by Gogitidze Joy et al., hypoglycemia led to an increase in intercellular adhesion molecule (ICAM), vascular cell adhesion molecule (VCAM), P-selectin, and E-selectin, as well as plasminogen activator inhibitor-1 (PAI-1), TNFα, IL-6, and vascular endothelial growth factor (VEGF).

Both of these studies included control arms in which the effect of insulin infusions administered at the same rates as above were investigated while maintaining glucose concentrations in the normal range through the appropriate titration of glucose infusion rates. Both studies confirmed the presence of an anti-inflammatory effect of insulin during infusions when euglycemia was maintained (8). Again, the anti-inflammatory effects of insulin were more impressive in the study by Gogitidze Joy et al. because they maintained the infusion of insulin for 120 min, whereas the study by Wright et al. infused insulin for only 60 min. Previous work has consistently shown impressive anti-inflammatory effects of insulin infused for 120 min or more (8). Thus, in situations where insulin infusions are used for the anti-inflammatory and cardioprotective actions of insulin, extreme care has to be exercised because hypoglycemia reverses the effects of euglycemic hyperinsulinemia. It is of interest that hypoglycemia exerts proinflammatory effects similar to those of hyperglycemia and glucose intake (9,10).

Clearly, hypoglycemia results in the induction of rapid inflammatory, platelet proaggregatory, antifibrinolytic, and prothrombotic responses. This effect of hypoglycemia overrides the anti-inflammatory, antiplatelet, and profibrinolytic effects of insulin observed under euglycemic conditions. In addition, there is also an increase in ROS generation and lipid peroxidation, reflecting oxidative stress. Although the hypoglycemic episodes are transient, repeated occurrences of such episodes may have cumulative effects that are detrimental to inflammation-based processes such as atherogenesis and its thrombotic complications. These detrimental effects would add to the previously demonstrated relationship between both silent and symptomatic hypoglycemia on cardiac angina. In one study involving diabetic patients with coronary heart disease who were continuously monitored for blood glucose concentrations and electrocardiographic changes, it was demonstrated that there was chest pain associated with hypoglycemia in 20% of the patients, of whom 40% had concomitant electrocardiogram (ECG) changes consistent with ischemia (11).

DIABETES/METABOLISM RESEARCH AND REVIEWS
Diabetes Metab Res Rev 2008; 24: 353–363.
Published online 7 May 2008 in Wiley InterScience (www.interscience.wiley.com) DOI: 10.1002/dmrr.865

REVIEW ARTICLE

Vascular disease and diabetes: is hypoglycaemia an aggravating factor?

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Summary

Acute hypoglycaemia provokes profound physiological changes affecting the cardiovascular system and several haematological parameters, principally as a consequence of sympatho-adrenal activation and counter-regulatory hormonal secretion. Many of these responses have an important role in protecting the brain from neuroglycopenia, through altering regional blood flow and promoting metabolic changes that will restore blood glucose to normal. In healthy young adults the cardiovascular effects are transient and have no obvious detrimental consequences. However, some of the effected changes are potentially pathophysiological and in people with diabetes who have developed endothelial dysfunction, they may have an adverse impact on a vasculature that is already damaged. The acute haemodynamic and haematological changes may increase the risk of localized tissue ischaemia, and major vascular events can certainly be precipitated by acute hypoglycaemia. These include myocardial and cerebral ischaemia and occasionally infarction. Established diabetic retinopathy often deteriorates after strict glycaemic control is instituted, the latter being associated with a threefold increase in frequency of severe hypoglycaemia, and enhanced exposure to mild hypoglycaemia. The possible mechanisms underlying these hypoglycaemia-induced effects include haemorrheological changes, white cell activation, vasoconstriction, and the release of inflammatory mediators and cytokines. The concept that acute hypoglycaemia could aggravate vascular complications associated with diabetes is discussed in relation to evolving comprehension of the pathogenesis of atherosclerosis and blood vessel disease. Copyright © 2008 John Wiley & Sons, Ltd.

Keywords diabetes; hypoglycaemia; coagulation; inflammation; vascular complications

Hypoglycaemia is a common and much feared side effect of insulin treatment for diabetes, and is the major barrier to achieving and maintaining optimal glycaemic control. Strict glycaemic control using intensive insulin therapy increases the risk of severe hypoglycaemia threefold [1]. Despite the frequency of this metabolic problem, the short-term consequences of exposure to hypoglycaemia are not fully elucidated. Although the immediate effects on the brain affecting cognition, mood, and conscious level are widely recognized, it is often overlooked that hypoglycaemia also exerts profound effects on various constituents of the blood and on the vasculature. Although the effects are transient and unlikely to exert any long-term consequences on a healthy circulation, the potentially deleterious effects on a damaged vasculature should be considered. People with diabetes have an increased risk of developing vascular disease, and many have established micro- and macrovascular complications of varying severity. Figure 1 depicts the

"Pharmacotherapy: GLP-1 analogues and insulin: sound the wedding bells?"

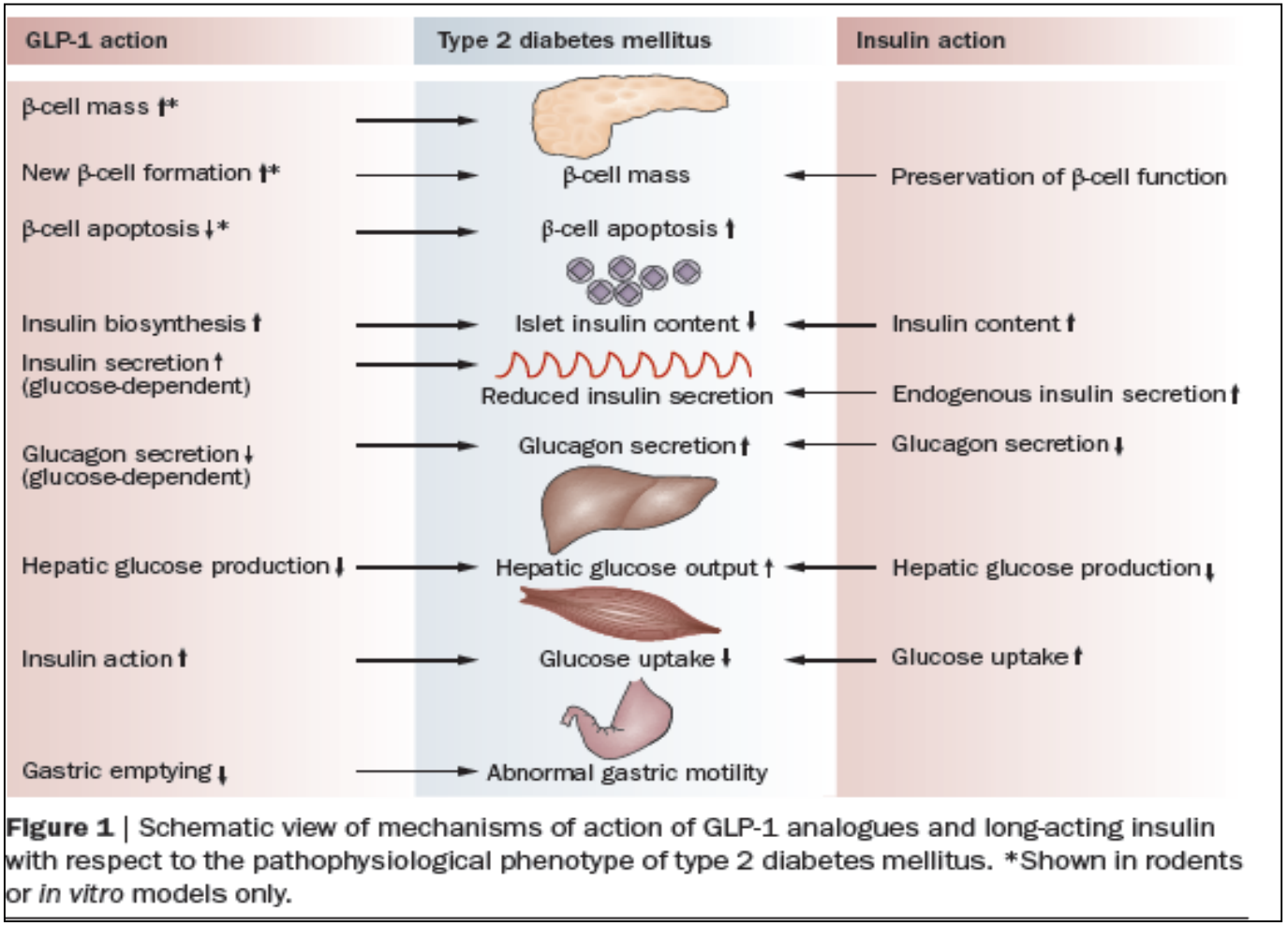
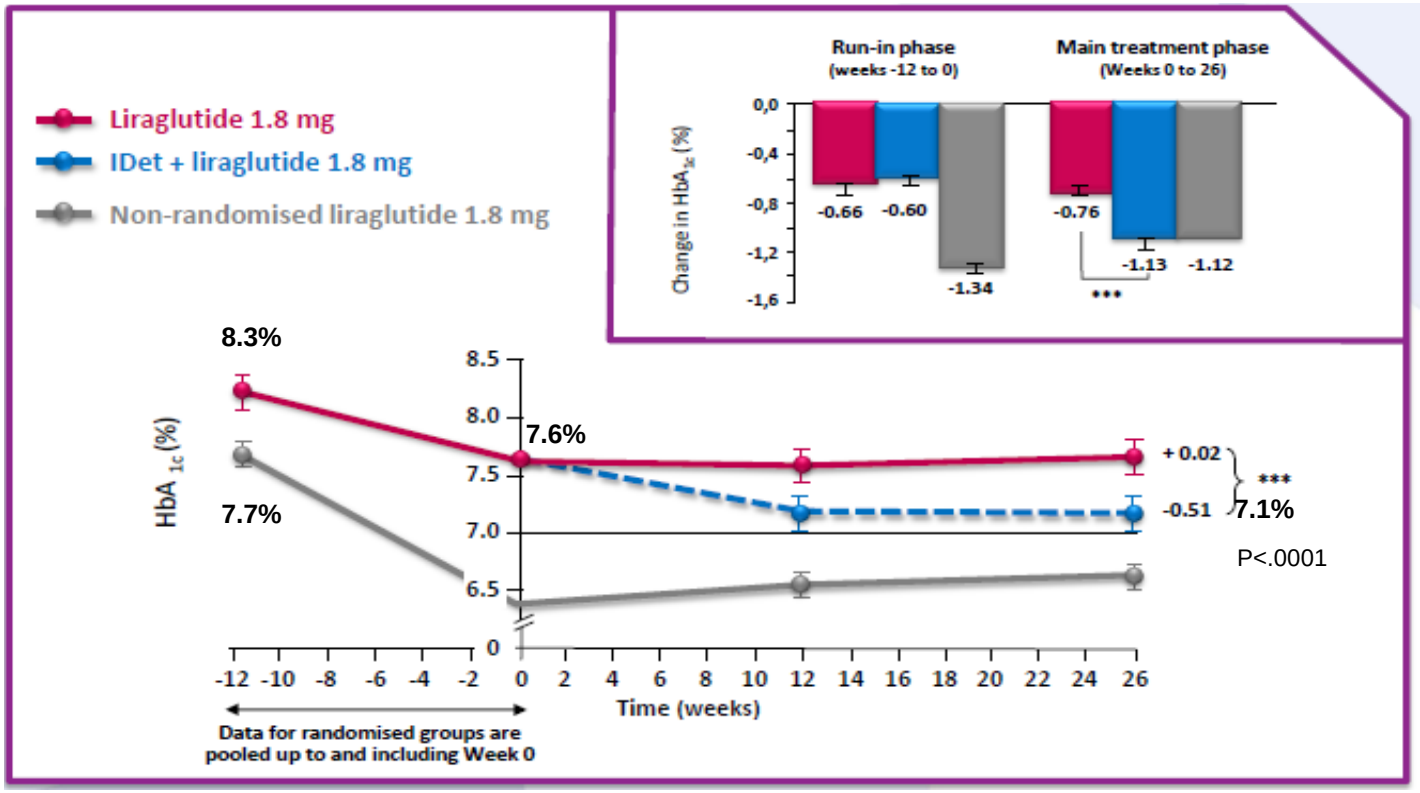


Figure 1 | Schematic view of mechanisms of action of GLP-1 analogues and long-acting insulin with respect to the pathophysiological phenotype of type 2 diabetes mellitus. *Shown in rodents or *in vitro* models only.

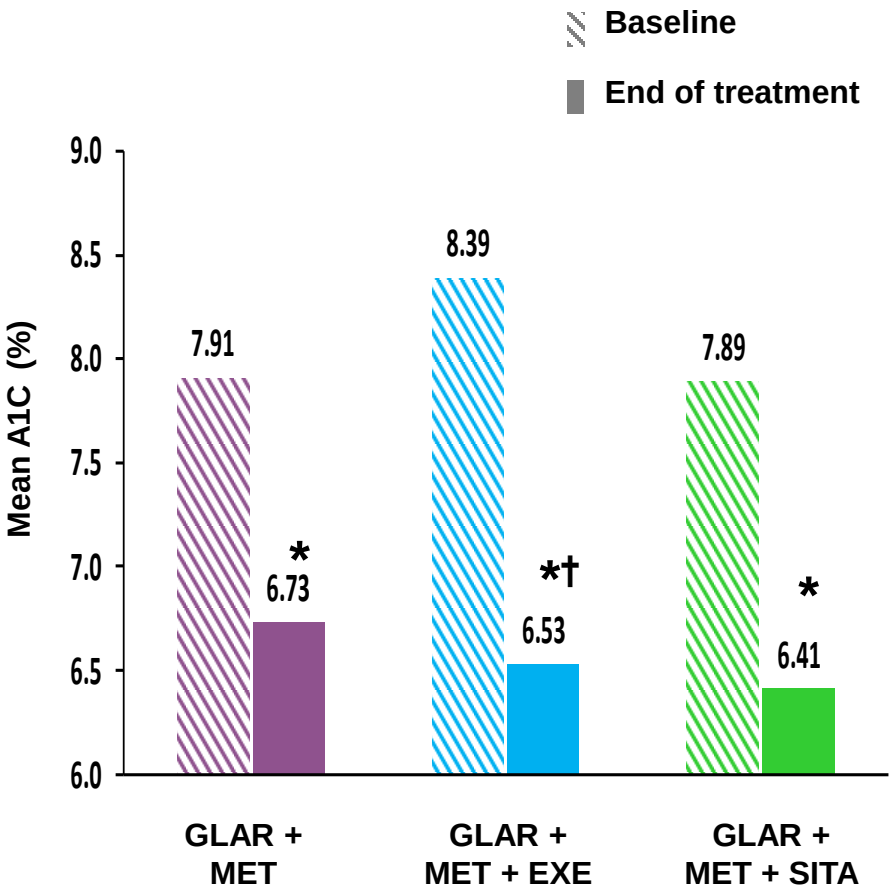
Nauck MA & Meier J.J » Nat. Rev. Endocrinol. 2011 Apr;7(4):193-5

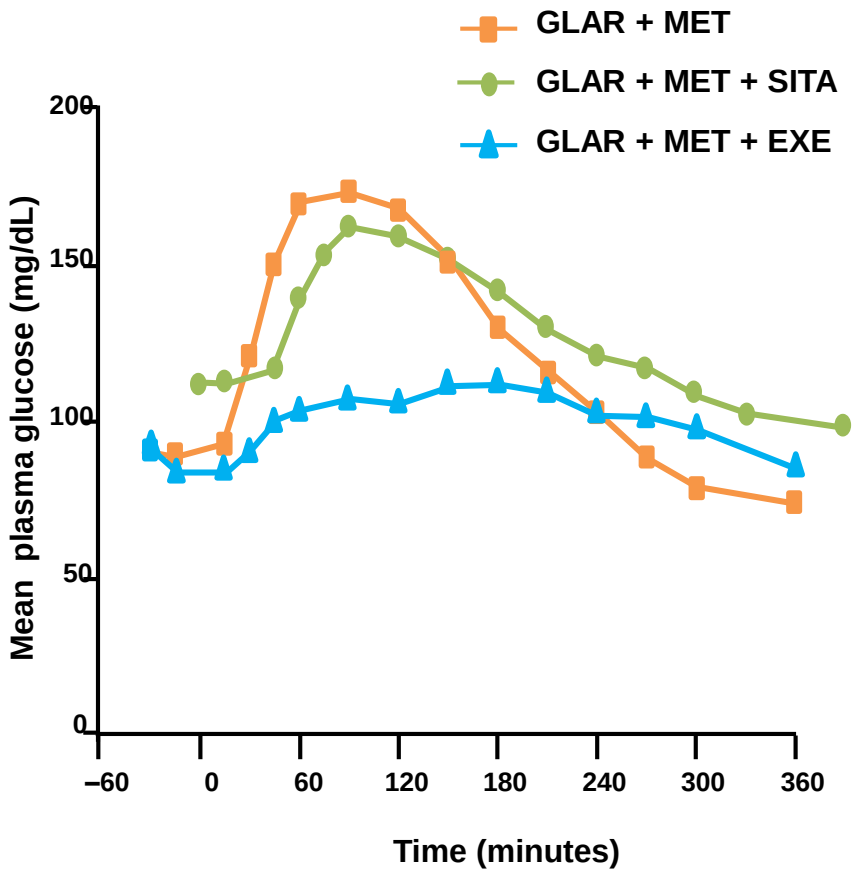
Liraglutide added to detemir (IDet) : HbA1c values after 26 weeks



DeVries JH et al. Diabetes Care 35:1446–1454, 2012

Sitagliptin or Exenatide added to Insulin Glargine: Effects on HbA1c and on Postprandial Hyperglycemia





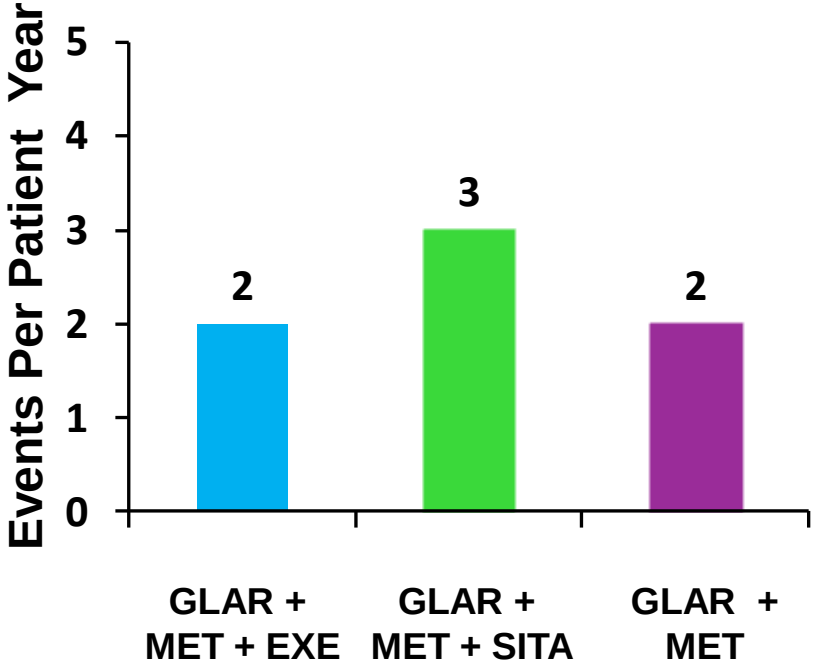
*$p < 0.05$ vs. screening; †$p < 0.05$ vs. GLAR + MET

Source: Arnolds S, et al. Diabetes Care 2010;33:1509–15.

Sitagliptin or Exenatide added to Insulin Glargine: Effects on Hypoglycemia and Body Weight

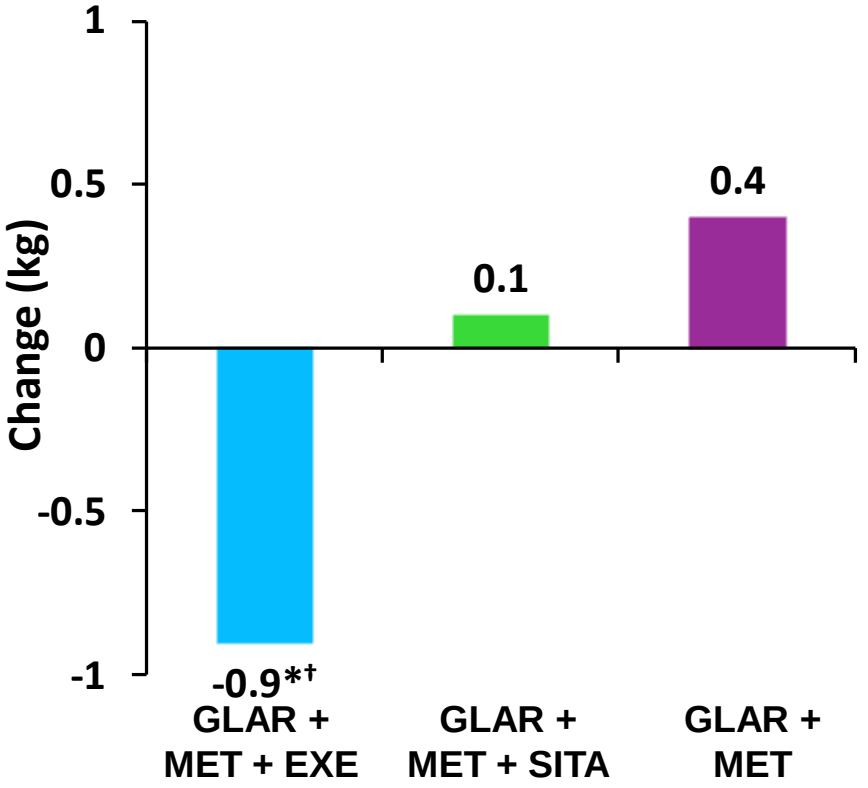
Hypoglycemia

(BG <2.8 mmol/L [50 mg/dL])



p = NS between groups

Body Weight

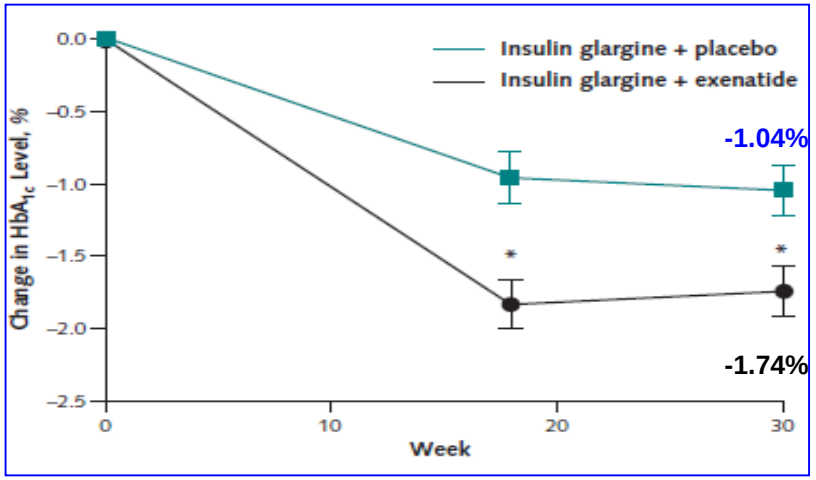


**p* = 0.05 vs. Baseline, †*p* < 0.05 vs. GLAR + MET

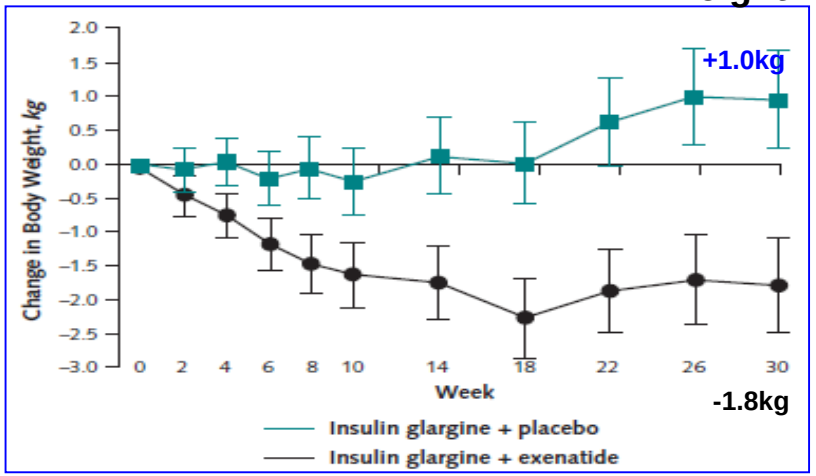
Source: Arnolds S, et al. Diabetes Care 2010;33:1509–15.

Exenatide "twice-a-day" plus Insulin Glargine – effects on HbA1c and Body Weight

HbA1c

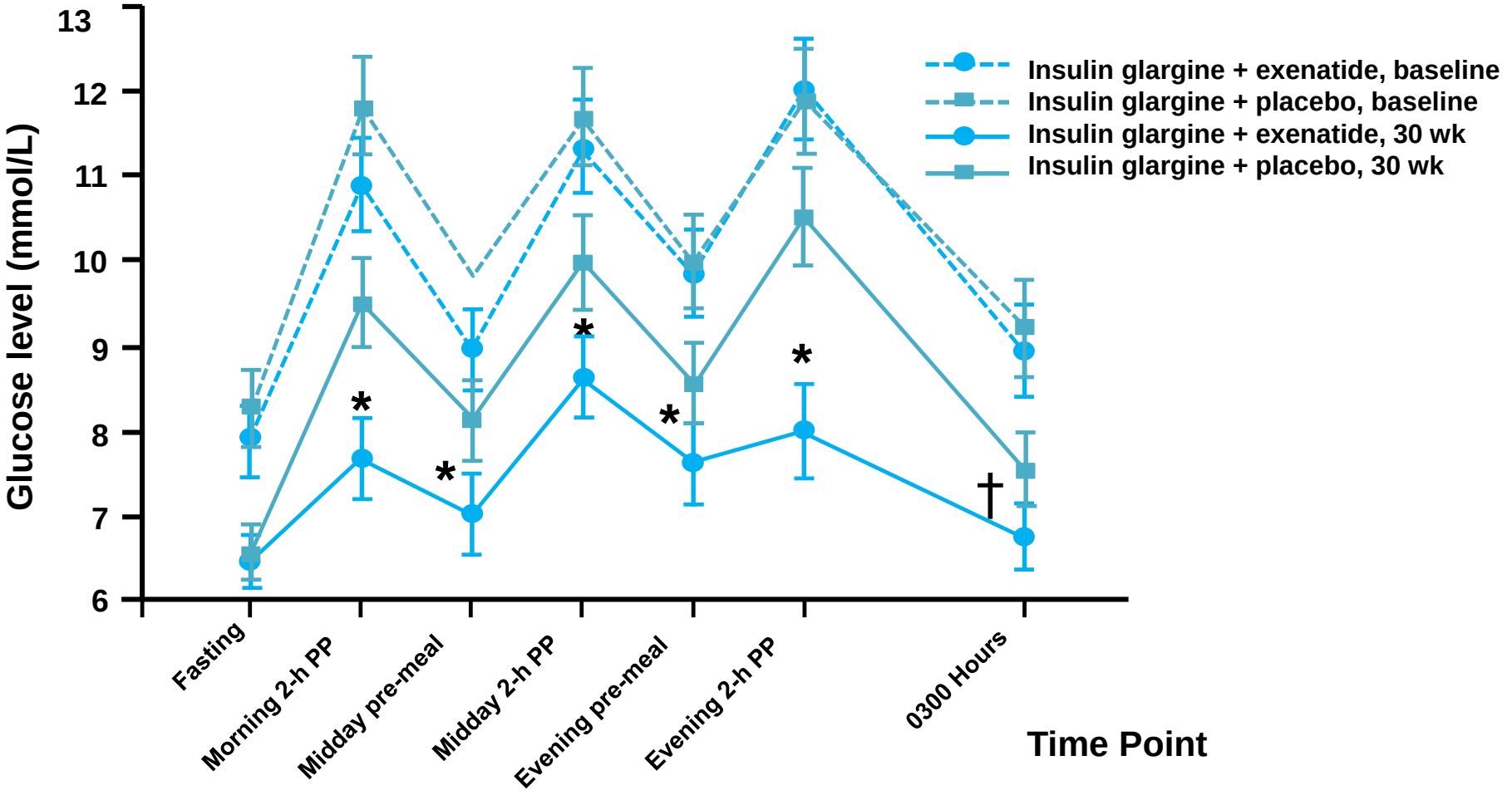


Weight



Source: Buse JB, et al. Ann Intern Med 2011;154:103–12.

Exenatide "twice-a-day" plus Insulin Glargine – effects on Glucose Profiles



Data are LS mean ± CI; $^{*}p < 0.001$; $^{\dagger}p < 0.01$ for between-group comparison

Buse JB, et al. Ann Intern Med 2011;154:103–12.

The GetGoal Program: Lixisenatide plus Insulin Glargine

Basal Insulin

- Simple to initiate
- Control FPG while limiting nocturnal hypoglycemia
- Decrease hepatic glucose production and improve β-cell function
- Less hypoglycemia risk vs. NPH
- Weight gain ~1–3 kg

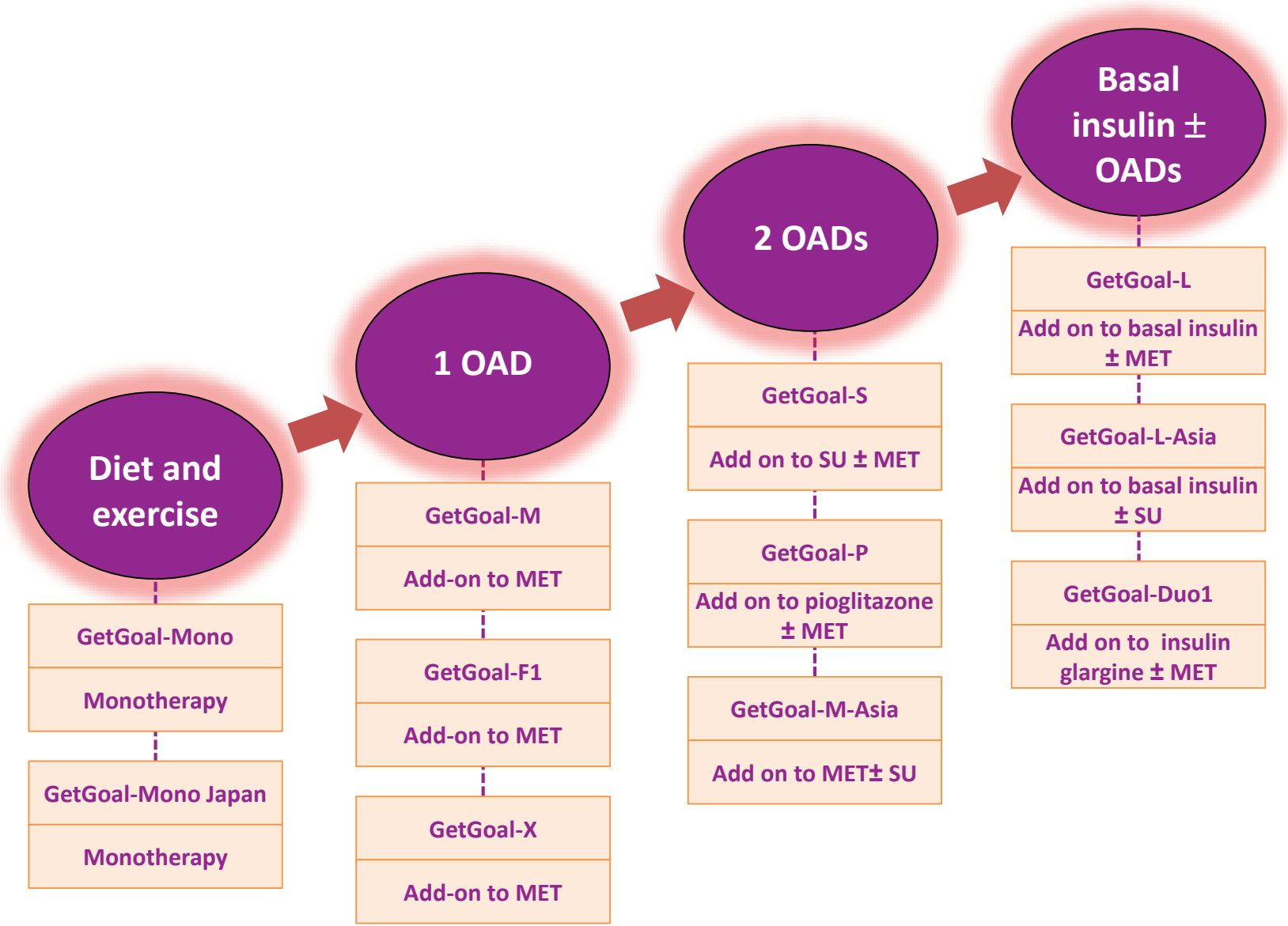
GLP-1 RA

- Simple to use
- Control PPG and some FPG
- Decrease gastric emptying, improves β-cell function
- Control glucagon overexpression
- No or reduced increase in hypoglycemia
- Weight loss ~1–3 kg

Synergic Effects

Optimal HbA1C control

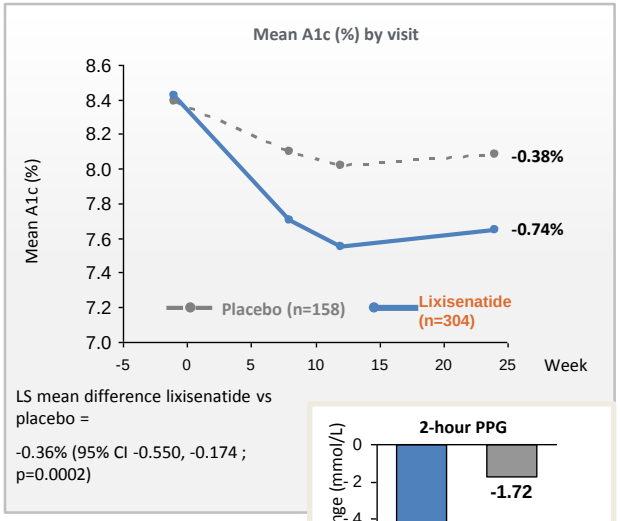
Lixisenatide in the treatment of Type 2 diabetes



www.clinicaltrials.gov; Horowitz M. et al. Adv Ther (2013), DOI 10.1007/s12325-013-0009-4; Raccah D. et al. Expert Rev. Endorcinol. Metab. 8(2) doi 10.1586 EEM.12.82 (2013); RCP lixisenatide

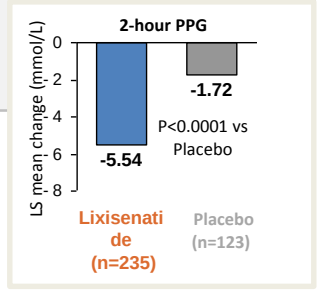
Changes in HbA1c with Lixisenatide on top of basal insulin +/- OHG

GetGoal-L[(1)]

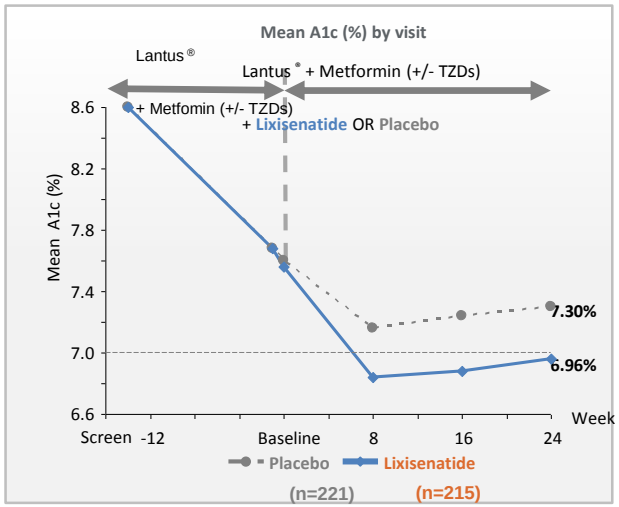


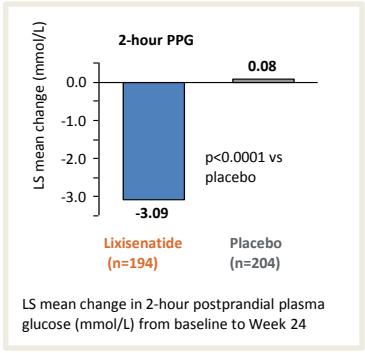
LS mean difference lixisenatide vs placebo =

-0.36% (95% CI -0.550, -0.174 ; p=0.0002)



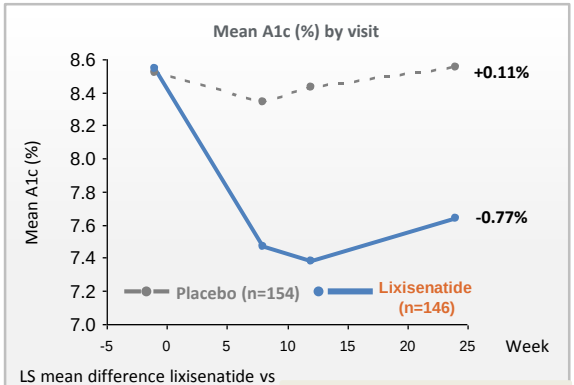
GetGoal-DUO-1[(3)]





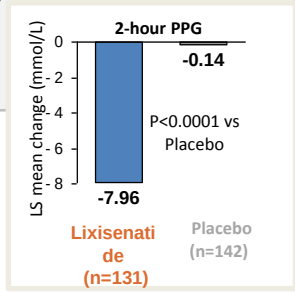
LS mean change in 2-hour postprandial plasma glucose (mmol/L) from baseline to Week 24

GetGoal-L Asia[(2)]



LS mean difference lixisenatide vs placebo =

-0.88% (95% CI -1.116, -0,650 ; p<0.0001)



(1) Lixisenatide on top of basal insulin (Lantus® 50.1% of pts) +/- metformin
Duration of T2DM at screening Lixisenatide (L) 12.5 years / Placebo (P) 12.4 years
BMI (kg/m²) at baseline L 31.9/ P 32.6 – Lantus® dose at baseline L 54.0U / P 57.6U
MC Riddle, ADA 2012 (abstract 983-P)

(3) Duration of T2D at screening: Lixisenatide (L) 9,6 years / Placebo (P) 8,7 years – BMI (kg/m²) at baseline: L 32.0 / P 31.7 – Lantus® dose at baseline L 43.4U / P 44.2U
LS mean difference L vs P in body weight (kg) change from baseline to endpoint: -0,89 (95%CI: -1.42 to -0.35 ; p=0.0012) LS mean difference L vs P in Lantus® dose from baseline to endpoint: -2.24U (95%CI: -4.26 to -0.22 ; p=0.03); J. Rosenstock, ADA 2012 (abstract 62-OR)

(2) Lixisenatide on top of basal insulin (Lantus® 60% of pts) +/- sulfonylurea
Duration of T2DM at screening L 13.7 years / P 14.1 years
BMI (kg/m²) at baseline L 25.4 / P 25.2 – Lantus® dose at baseline L 24.9U / P 24.1U; Y Seino, et al. Diabetes, Obesity and Metabolism online, May 30, 2012

Raccah D. et al. Expert Rev. Endorcinol. Metab. 8(2) doi 10.1586 EEM.12.82 (2013); RCP lixisenatide

Pharmacodynamic characteristics of lixisenatide once daily versus liraglutide once daily in patients with type 2 diabetes insufficiently controlled on metformin

Kapitza C, Forst T, Coester HV, Poitiers F, Ruus P, Hincelin-Méry A

Diabetes Obes Metab. 2013

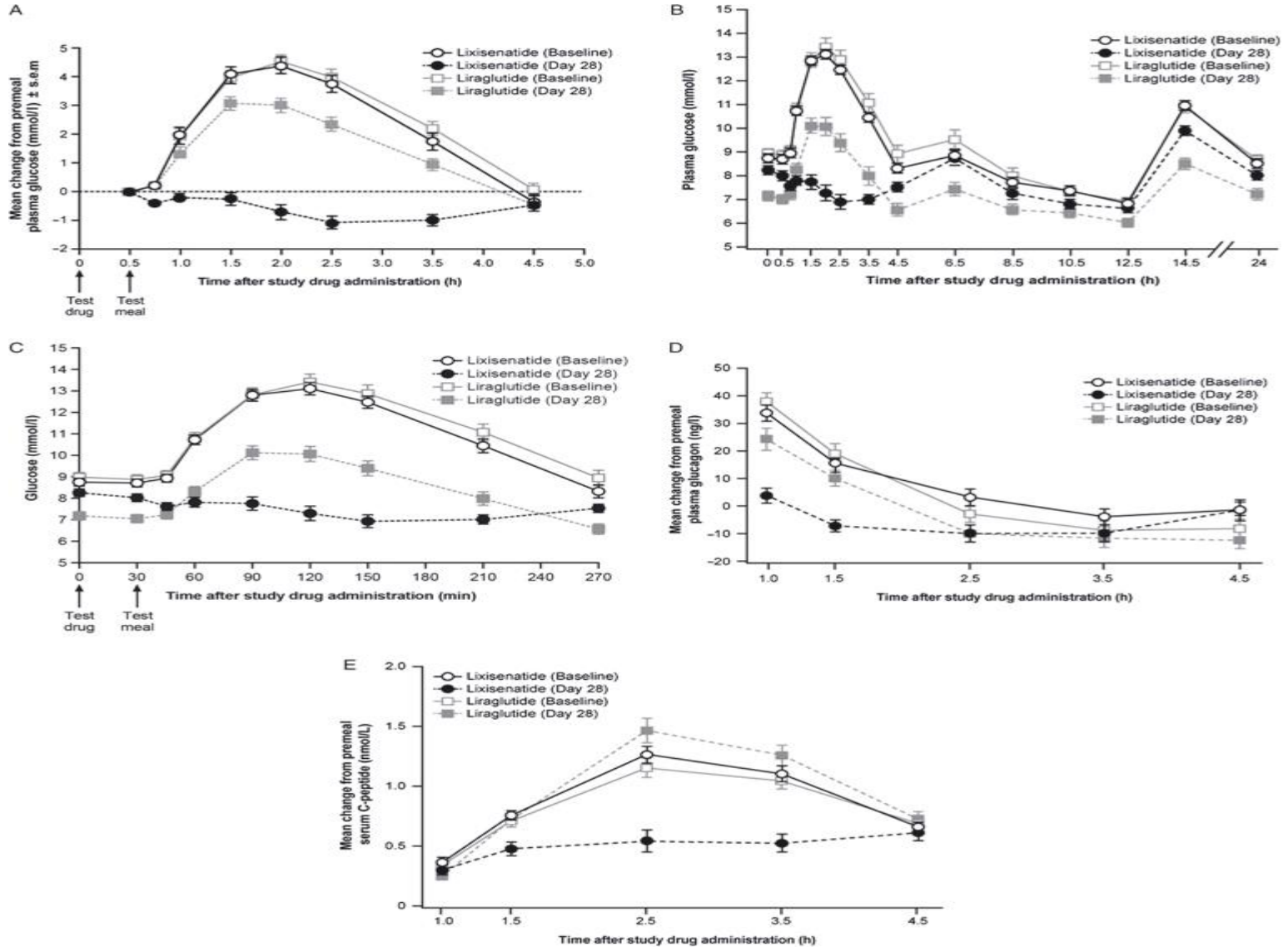


Figure 1. Postprandial plasma glucose pharmacodynamics. (A) Mean ± s.e.m. postprandial plasma glucose change from premeal values at baseline and day 28; (B)Mean ± s.e.m. of raw data for 24-h postprandial plasma glucose profiles at baseline and day 28; (C)Mean ± s.e.m. of raw data for postprandial plasma glucose profiles at baseline and day 28, for the first 270 min after study drug administration; (D) Mean ± s.e.m. plasma postprandial glucagon change from premeal concentration at baseline and day 28; (E) Mean ± s.e.m. postprandial serum C-peptide change from premeal concentration atbaseline and day 28; PPG, postprandial plasma glucose; s.e.m., standard error of the mean.

Kapitza et al. *Diabetes Obes Metab.* 2013

A comparison of adding liraglutide versus a single daily dose of insulin aspart to insulin degludec in subjects with type 2 diabetes (BEGIN: VICTOZA ADD-ON).

Mathieu C, Rodbard HW, Cariou B, Handelsman Y, Philis-Tsimikas A, Ocampo Francisco AM, Rana A, Zinman B; BEGIN: VICTOZA ADD-ON (NN1250-3948) study group.

Deg+Lira improved long-term glycaemic control, with weight loss and less hypoglycaemia versus adding a single daily dose of IAsp in patients with T2DM inadequately controlled with IDeg + metformin.

Diabetes Obes Metab 2014;16:636-644

A comparison of adding liraglutide versus a single daily dose of insulin aspart to insulin degludec in subjects with type 2 diabetes (BEGIN: VICTOZA ADD-ON)

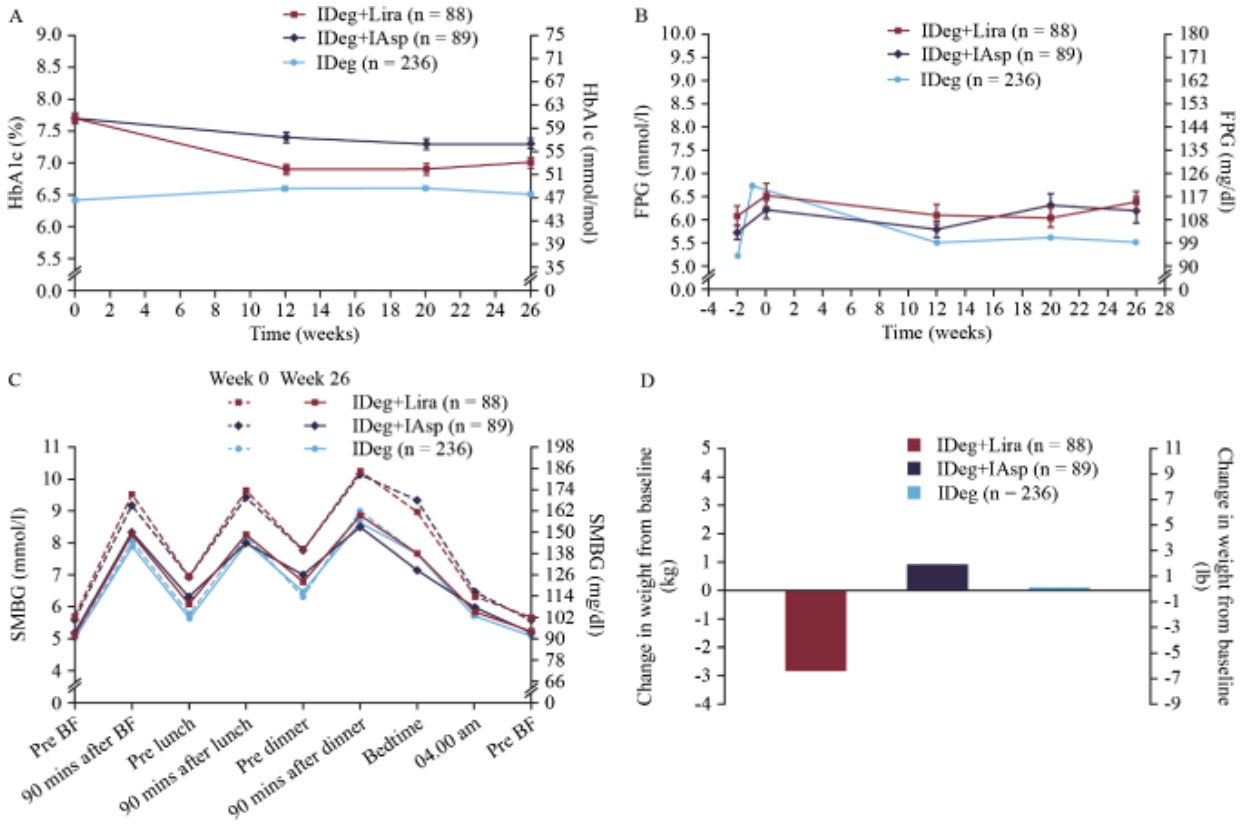


Figure 1.
Efficacy measures: (A) mean HbA1c ± s.e.m. over time (FAS, NAS); (B) mean FPG ± s.e.m. over time (FAS, NAS); (C) 9-point profile of SMBG at baseline and week 26 (FAS, NAS); (D) mean change in body weight from baseline (FAS, NAS). No statistical comparisons were made between the FAS (randomized subjects) and NAS (non-randomized subjects). The values presented at week −2 are from end-of-treatment in Trial 3643. BF, breakfast; FAS, full analysis set; IDeg, insulin degludec; IAsp, insulin aspart; Lira, liraglutide; NAS, non-randomized analysis set; s.e.m., standard error of the mean.

Diabetes Obes Metab 2014;16:636-644.

A comparison of adding liraglutide versus a single daily dose of insulin aspart to insulin degludec in subjects with type 2 diabetes (BEGIN: VICTOZA ADD-ON)

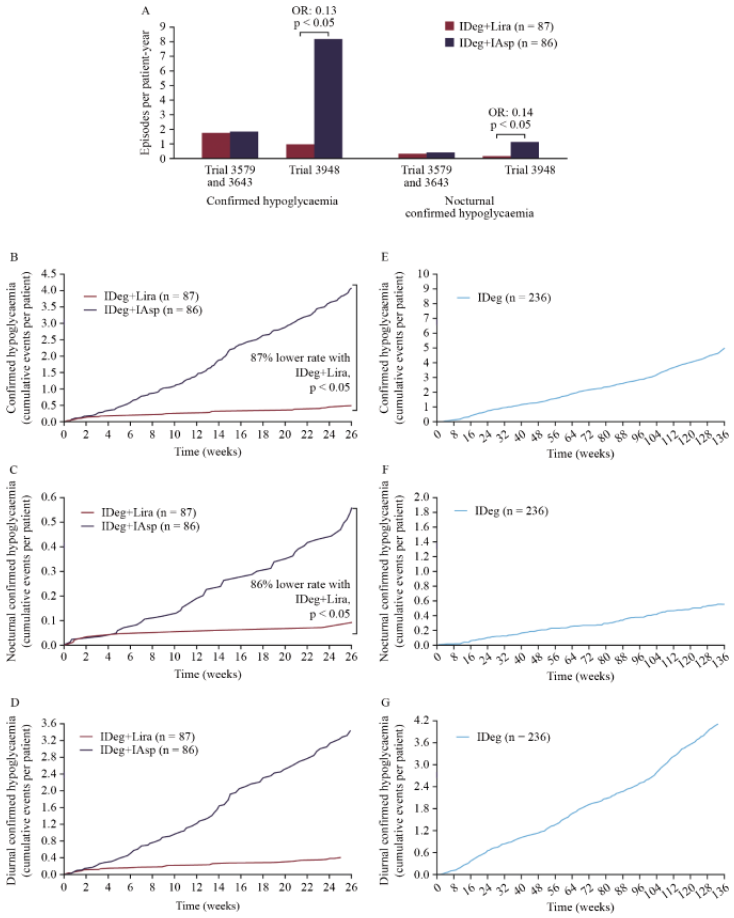


Figure 2.
Hypoglycaemia: (A) overall confirmed and nocturnal confirmed hypoglycaemia rates during Trials 3579 and 3643 and during Trial 3948 (SAS). Mean cumulative function of confirmed [B (SAS); E (NAS)], nocturnal confirmed [C (SAS); F (NAS)] and diurnal confirmed [D (SAS); G (NAS)] hypoglycaemic episodes. Plots B, C and D include data from Trial 3948. Plots E, F and G include data from Trials 3579, 3643 and 3948. Treatment during Trials 3579 and 3643 was with IDeg + metformin. Statistical comparisons are based on FAS. No statistical comparisons were made between the FAS (randomized subjects) and NAS (non-randomized subjects). Diurnal period: the period between 06:00 and 00:00 hours (both included). FAS, full analysis set; IDeg, insulin degludec; IAsp, insulin aspart; Lira, liraglutide; NAS, non-randomized analysis set; OR, odds ratio; SAS, safety analysis set.

Diabetes Obes Metab 2014;16:636-644

Efficacy and safety of a fixed-ratio combination of insulin degludec and liraglutide (IDegLira) compared with its components given alone: results of a phase 3, open-label, randomised, 26-week, treat-to-target trial in insulin-naive patients with type 2 diabetes

Gough SCL, Bode B, Woo V, et al.

IDegLira combines the clinical advantages of basal insulin and GLP-1 receptor agonist treatment, resulting in improved glycaemic control compared with its components given alone.

Lancet Diabetes Endocrinol. 2014; 2:885-893.

Better Glycemic Control and Less Weight Gain with Once Weekly Dulaglutide versus Once Daily Insulin Glargine, Both Combined with Pre-Meal Insulin Lispro, in Type 2 Diabetes Patients (AWARD-4)

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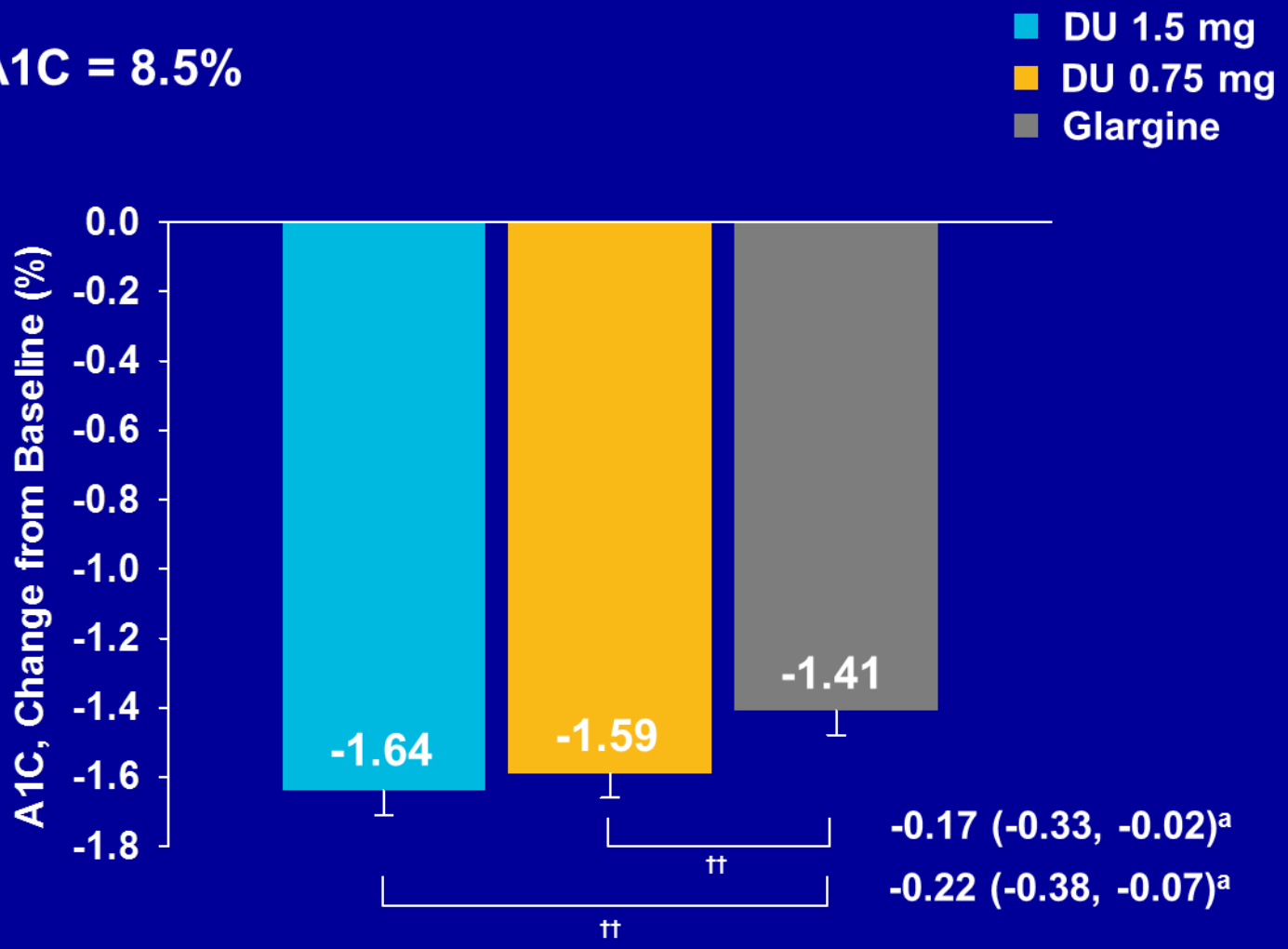
Poster presented at: American Diabetes Association 74th Annual Scientific Sessions, June 13-17, 2014 San Francisco, CA. Poster 962-P

Study Rationale

The AWARD-4 trial is the first study exploring use of a GLP-1 receptor agonist with mealtime insulin and was designed to compare dulaglutide to basal insulin glargine, both in combination with prandial insulin lispro, in patients poorly controlled on conventional insulin therapy

A1C Change from Baseline at 26 Weeks

Baseline A1C = 8.5%



††p <0.025 superiority vs glargine
Data presented are LS means ± SE
[a]Treatment difference (nominal 95% CI), ITT, ANCOVA LOCF analysis

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Composite Endpoints

Patients Achieving A1C <7.0%	DU 1.5 mg N = 295 n (%)	DU 0.75 mg N = 293 n (%)	Glargine N = 296 n (%)
Without Documented Symptomatic Hypoglycemia			
Week 26	57 (20.7)[#]	58 (20.9)[#]	36 (12.9)
Week 52	54 (19.6)[#]	52 (18.8)	35 (12.5)
Without Nocturnal or Severe Hypoglycemia			
Week 26	148 (53.8)[##]	151 (54.5)[##]	79 (28.2)
Week 52	121 (44.0)[##]	122 (44.0)[##]	75 (26.8)
Without Weight Gain and Nocturnal or Severe Hypoglycemia			
Week 26	90 (32.7)[##]	68 (24.5)[##]	17 (6.1)
Week 52	54 (19.6)[##]	52 (18.8)[##]	14 (5.0)

[#]p <0.05 vs glargine, [##]p <0.001 vs glargine
Note: Weeks 26 and 52 values were based on the last visit information (ITT, LOCF)

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Conclusions

Dulaglutide (± metformin), in combination with insulin lispro, is an effective and safe option for treatment intensification in patients with type 2 diabetes and inadequate control on 1 to 2 doses of insulin

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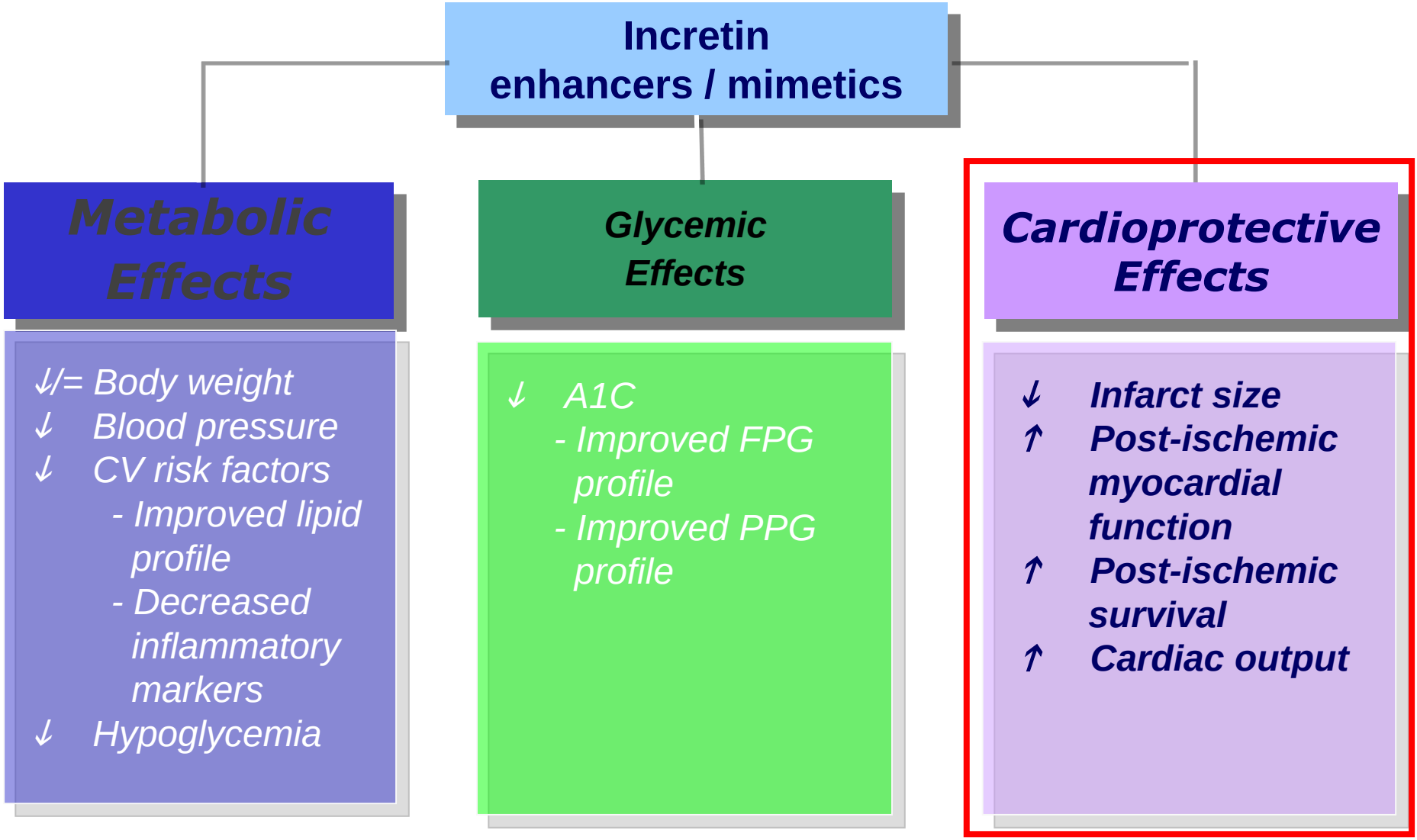
Incretin-based Therapies : Benefits beyond Glycemic Control



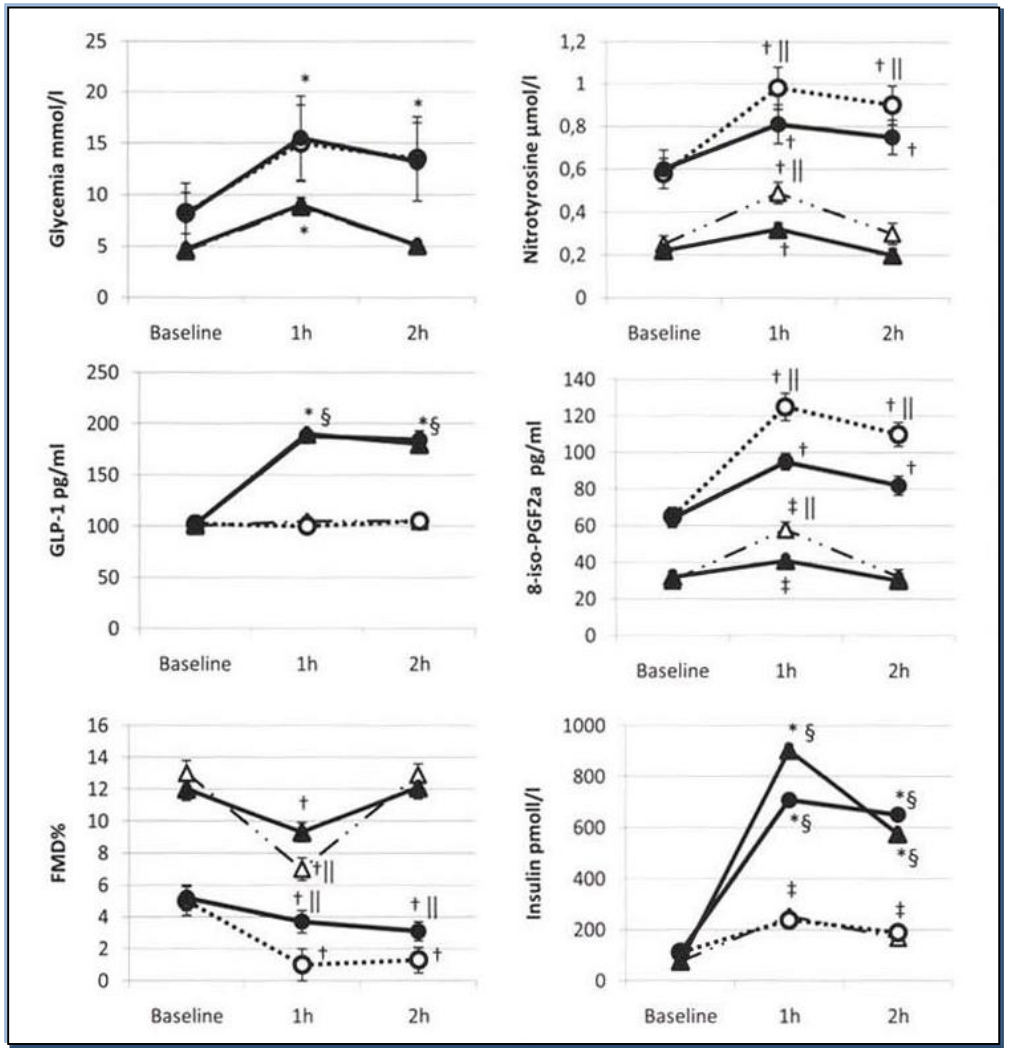
Greeve et al. *Br J Pharmacol 2009; 157: 1340-51*. **Mudaliar & Henry.** *Am J Med 2009; 122: S25-36*

GLP-1 reduces endothelial dysfunction, inflammation and oxidative stress induced by both hyperglycemia and hypoglycemia in type 1 diabetes

Ceriello A, Novials A, Ortega E, Canivell S, La Sala L, Pujadas G, Esposito K, Giugliano D, Genovese S

Diabetes Care 2011; 34:1–6

Protective effect of GLP-1 during both hypoglycemia and hyperglycemia in T1DM



Both hyperglycemia and hypoglycemia acutely induced oxidative stress, inflammation and endothelial dysfunction.

GLP-1 significantly counterbalanced these effects.

Ceriello A, et al. *Diabetes Care* 2011; 34:1–6.

Simultaneous GLP-1 and Insulin Administration Acutely Enhances Their Vasodilatory, Antiinflammatory, and Antioxidant Action in Type 2 Diabetes

Ceriello A, Novials A, Canivell S, La Sala L, Pujadas G, Esposito K, Testa R, Bucciarelli L, Rondinelli M, Genovese S.

Diabetes Care 2014;37: 1938-1943

Changes in glycemia, FMD, IL-6, sICAM-1, nitrotyrosine, and 8-iso-PGF2α during normoglycemic-normoinsulinemic and normoglycemic-hyperinsulinemic clamps in type 2 diabetes (n = 12).

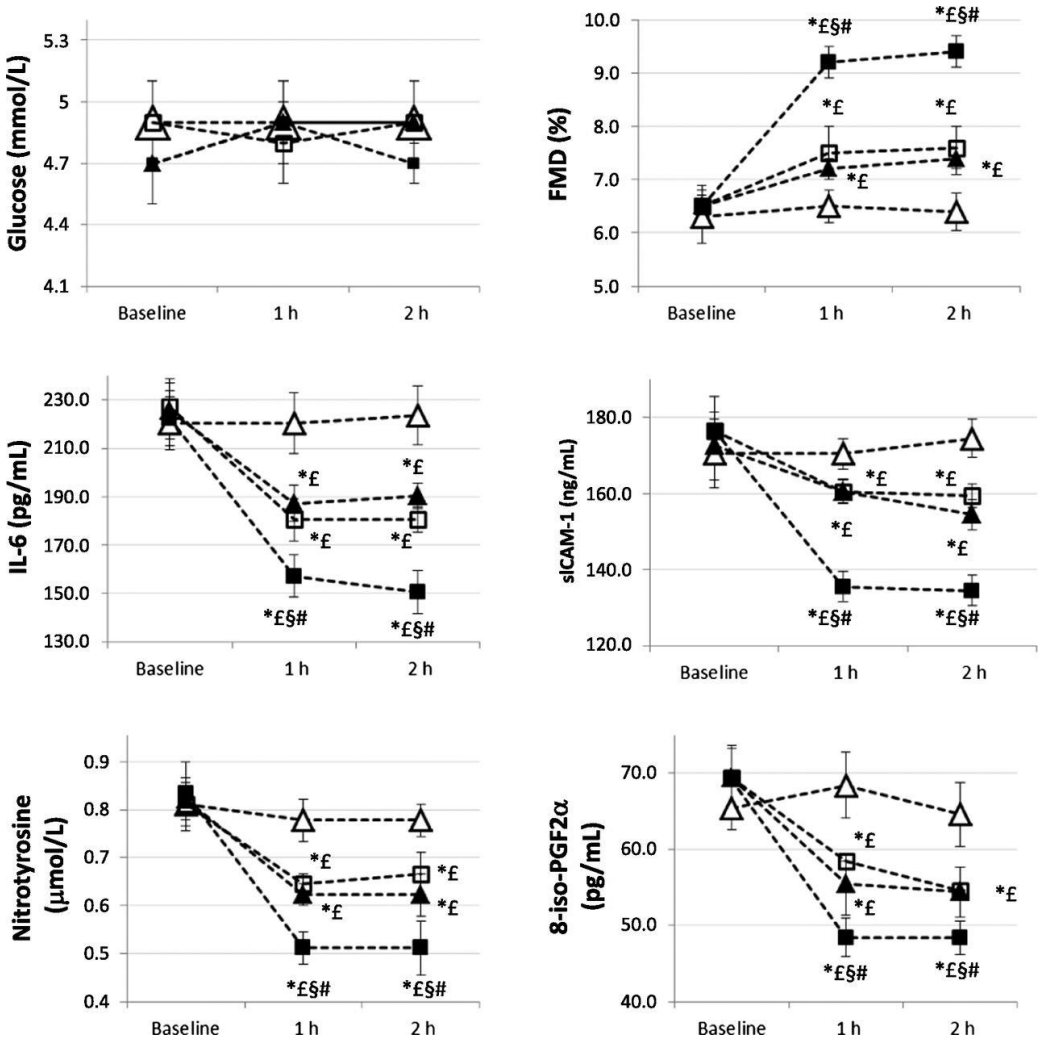


Figure 1 Changes in glycemia, FMD, IL-6, sICAM-1, nitrotyrosine, and 8-iso-PGF2α during normoglycemic-normoinsulinemic and normoglycemic-hyperinsulinemic clamps in type 2 diabetes (*n* = 12). Glycemia, FMD, IL-6, sICAM-1, nitrotyrosine, and 8-iso-PGF2α changes during normoglycemic-normoinsulinemic clamp (△), normoglycemic-normoinsulinemic clamp plus GLP-1 (▲), normoglycemic-hyperinsulinemic clamp (□), and normoglycemic-hyperinsulinemic clamp plus GLP-1 (■). Data are means ± SEM. **P* < 0.01 vs. basal. £*P* < 0.05 vs. normoglycemic-normoinsulinemic clamp. §*P* < 0.05 vs. normoglycemic-normoinsulinemic clamp plus GLP-1. #*P* < 0.05 vs. normoglycemic-hyperinsulinemic clamp.

Ceriello A. et al. Dia Care 2014;37:1938-1943

Changes in glycemia, FMD, IL-6, sICAM-1, nitrotyrosine, and 8-iso-PGF2α during hyperglycemic-normoinsulinemic and hyperglycemic-hyperinsulinemic clamps in type 2 diabetes (n = 12).

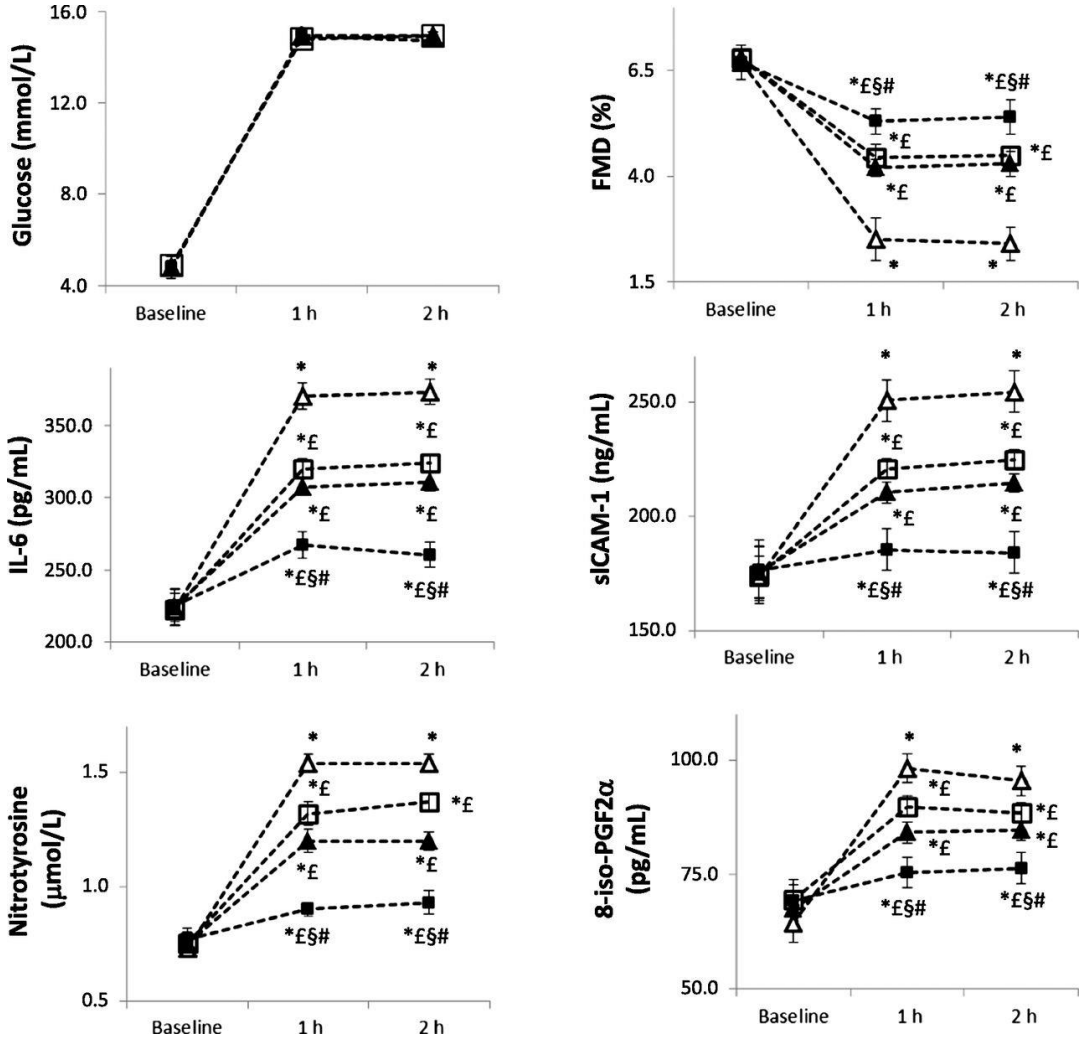


Figure 2 Changes in glycemia, FMD, IL-6, sICAM-1, nitrotyrosine, and 8-iso-PGF2α during hyperglycemic-normoinsulinemic and hyperglycemic-hyperinsulinemic clamps in type 2 diabetes (*n* = 12). Glycemia, FMD, IL-6, sICAM-1, nitrotyrosine, and 8-iso-PGF2α changes during hyperglycemic-normoinsulinemic clamp (△), hyperglycemic-normoinsulinemic clamp plus GLP-1 (▲), hyperglycemic-hyperinsulinemic clamp (□), and hyperglycemic-hyperinsulinemic clamp plus GLP-1 (■). Data are mean ± SEM. **P* < 0.01 vs. basal. £*P* < 0.05 vs. hyperglycemic-normoinsulinemic clamp. §*P* < 0.05 vs. hyperglycemic-normoinsulinemic clamp plus GLP-1. #*P* < 0.05 vs. hyperglycemic-hyperinsulinemic clamp.

o Ceriello A. et al. Dia Care 2014;37:1938-1943

CONCLUSIONS

- **Post-prandial hyperglycemia is a key component of the glycemic control;**
- **The association of basal insulin and GLP-1 RA agonist targets both fasting and post-prandial hyperglycemia, with less hypoglycemia and increase in body weight;**
- **GLP-1 RA agonist may offer a cardiovascular protection independent from their hypoglycemic activity.**

GRACIAS

THANK YOU

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