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

*Insulina long acting + GLP-1RA*

Antonio Ceriello

Institut d'Investigacions Biomèdiques
August Pi i Sunyer (IDIBAPS)
Barcelona
Spain
‘Glucose triad’ of diabetes management

Postmeal glucose

FPG
Basal glucose level

HbA$_{1c}$
Average long-term glucose level

HbA$_{1c}$ = glycated haemoglobin
FPG = fasting plasma glucose
Postprandial glucose makes a major contribution to overall glycaemia across a range of HbA$_{1c}$ values.

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\textsubscript{1c} Target of <7% in Type 2 Diabetes

Meta-analysis of randomized controlled trials

DARIO GIUGLIANO, MD, PHD\textsuperscript{1}
MARIA IDA MAIORINO, MD\textsuperscript{1}
GIUSEPPE BELLASTELLA, MD\textsuperscript{1}
PAOLO CHIODINI, MD\textsuperscript{2}
ANTONIO CERIELLO, MD\textsuperscript{3}
KATHERINE ESPOSITO, MD, PHD\textsuperscript{1}

Diabetes Care 34:510–517, 2011
Percent of patients with Hb A1c <7%:

<table>
<thead>
<tr>
<th>Study (first author year, reference)</th>
<th>Biphasic N</th>
<th>Basal N (%)</th>
<th>Odds Ratio</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malone, 2004 [23]</td>
<td>67 42%</td>
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<td></td>
<td>3.26 (1.52 - 7.01)</td>
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<td>Malone, 2005 [24]</td>
<td>97 30%</td>
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<td>Raskin, 2005 [25]</td>
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<td></td>
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</tr>
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</tr>
<tr>
<td>Holman, 2007 [29]</td>
<td>235 41.7%</td>
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</tr>
<tr>
<td>Robbin, 2007 [30]</td>
<td>158 56.3%</td>
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</tr>
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</table>

**Pooled***

- Biphasic 2176 46.5%
- Basal      2190 36.1%

Q² Cochrane test for Heterogeneity=28.5 (p=0.0008)

df=9, I²=68.5

Odds Ratio = 1.88 (1.38-2.55)
(P=0.0012)

Giugliano D Diabetes Care 2011; 34:510-5.
Risk of Hypoglycemia:

<table>
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<tr>
<th>Study (first author year, reference)</th>
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<th>Basal N (%)</th>
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Average: 2176 46.5% 2190 36.1%

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df=9, I²=68.5

Odds Ratio (95% CI): 1.88 (1.38-2.55)  
(P=0.0012)
Hypoglycemia as an atherogenic factor

Proinflammatory and Prothrombotic Effects of Hypoglycemia

Hypoglycemia is known to be a risk factor for the development of cardiovascular disease. However, the role of hypoglycemia in the pathogenesis of atherosclerosis is less clear.

Recent studies have shown that hypoglycemia can trigger proinflammatory and prothrombotic responses in the body. These responses can lead to the accumulation of inflammatory cells and platelets, which can contribute to the development of atherosclerotic plaques.

The inflammatory and prothrombotic effects of hypoglycemia are mediated through a variety of mechanisms. For example, hypoglycemia can activate the renin-angiotensin system, which can stimulate the release of proinflammatory cytokines. Hypoglycemia can also activate the sympathetic nervous system, which can release norepinephrine and increase the production of reactive oxygen species.

These proinflammatory and prothrombotic effects of hypoglycemia can contribute to the development of atherosclerotic plaques and the risk of cardiovascular disease. Therefore, managing hypoglycemia in patients with diabetes is important to prevent the development of cardiovascular disease.

Vascular disease and diabetes: is hypoglycaemia an aggravating factor?

Summary

Vascular disease and diabetes are closely linked conditions. The presence of one can worsen the severity and progression of the other. Hypoglycemia can play a role in this relationship.

Hypoglycemia is a common and severe complication of diabetes that can lead to cardiovascular disease. It occurs when blood glucose levels fall below 70 mg/dL. Although hypoglycemia is usually associated with insulin or oral hypoglycemic agents, it can also occur spontaneously, for example due to excessively rigorous dietary restrictions.

Studies have shown that hypoglycemia can trigger proinflammatory and prothrombotic responses in the body. These responses can contribute to the development of atherosclerotic plaques and the risk of cardiovascular disease. Therefore, managing hypoglycemia in patients with diabetes is important to prevent the development of cardiovascular disease.
“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.
Liraglutide added to detemir (IDet) : HbA1c values after 26 weeks

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

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Event Rate (Per Patient Year)</th>
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</thead>
<tbody>
<tr>
<td>GLAR + MET + EXE</td>
<td>2</td>
</tr>
<tr>
<td>GLAR + MET + SITA</td>
<td>3</td>
</tr>
<tr>
<td>GLAR + MET</td>
<td>2</td>
</tr>
</tbody>
</table>

Change (kg)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Change (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLAR + MET + EXE</td>
<td>-0.9*†</td>
</tr>
<tr>
<td>GLAR + MET + SITA</td>
<td>0.1</td>
</tr>
<tr>
<td>GLAR + MET</td>
<td>0.4</td>
</tr>
</tbody>
</table>

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

p = NS between groups

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

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

Data are LS mean ± CI; *p < 0.001; †p < 0.01 for between-group comparison

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

Diet and exercise

1 OAD
- GetGoal-Mono
  - Add-on to MET
- Monotherapy
- GetGoal-Mono Japan
  - Monotherapy
- GetGoal-F1
  - Add-on to MET
- GetGoal-X
  - Add-on to MET

2 OADs
- GetGoal-S
  - Add on to SU ± MET
- GetGoal-P
  - Add on to pioglitazone ± MET
- GetGoal-M-Asia
  - Add on to MET ± SU

Basal insulin ± OADs
- GetGoal-L
  - Add on to basal insulin ± MET
- GetGoal-L-Asia
  - Add on to basal insulin ± SU
- GetGoal-Duo1
  - Add on to insulin glargine ± MET

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

GetGoal-L(1)

Mean A1c (%) by visit

LS mean difference lixisenatide vs placebo = -0.36% (95% CI: -0.550, -0.174; p=0.0002)

GetGoal-DUO-1(3)

Mean A1c (%) by visit

LS mean difference lixisenatide vs placebo = -0.88% (95% CI: -1.116, -0.650; p<0.0001)

GetGoal-L Asia(2)

Mean A1c (%) by visit

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

Lixisenatide (n=194) Placebo (n=204)

-3.09 p<0.0001 vs placebo

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

(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)

(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

(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)
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 at baseline and day 28; PPG, postprandial plasma glucose; s.e.m., standard error of the mean.
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).


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.

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.
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.*

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)

Johan Jendle,¹ Julio Rosenstock,² Lawrence Blonde,³ Vincent Woo,⁴ Jorge Gross,⁵ Honghua Jiang,⁶ Zvonko Milicevic,⁷

¹Endocrine and Diabetes Center, Karlstad and Faculty of Health Sciences and Medicine, Örebro University, Sweden; ²Dallas Diabetes and Endocrine Center, Dallas, TX, USA; ³Ochsner Medical Center, New Orleans, LA, USA; ⁴University of Manitoba, Winnipeg, Manitoba, Canada; ⁵Federal University of Rio Grande do Sul, Porto Alegre, Brazil; ⁶Eli Lilly and Company, Indianapolis, IN, USA; ⁷Eli Lilly and Company, Vienna, Austria

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
^Treatment difference (nominal 95% CI), ITT, ANCOVA LOCF analysis

American Diabetes Association 74th Annual Scientific Sessions, June 13-17, 2014 San Francisco, CA. Poster 962-P
## Composite Endpoints

<table>
<thead>
<tr>
<th>Patients Achieving</th>
<th>DU 1.5 mg N = 295</th>
<th>DU 0.75 mg N = 293</th>
<th>Glargine N = 296</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C &lt;7.0%</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Without Documented Symptomatic Hypoglycemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 26</td>
<td>57 (20.7)#</td>
<td>58 (20.9)#</td>
<td>36 (12.9)</td>
</tr>
<tr>
<td>Week 52</td>
<td>54 (19.6)#</td>
<td>52 (18.8)</td>
<td>35 (12.5)</td>
</tr>
<tr>
<td>Without Nocturnal or Severe Hypoglycemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 26</td>
<td>148 (53.8)##</td>
<td>151 (54.5)##</td>
<td>79 (28.2)</td>
</tr>
<tr>
<td>Week 52</td>
<td>121 (44.0)##</td>
<td>122 (44.0)##</td>
<td>75 (26.8)</td>
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<td>Without Weight Gain and Nocturnal or Severe Hypoglycemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 26</td>
<td>90 (32.7)##</td>
<td>68 (24.5)##</td>
<td>17 (6.1)</td>
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<td>Week 52</td>
<td>54 (19.6)##</td>
<td>52 (18.8)##</td>
<td>14 (5.0)</td>
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*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)
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.
Incretin-based Therapies: Benefits beyond Glycemic Control

**Incretin enhancers / mimetics**

**Metabolic Effects**
- ↓/= Body weight
- ↓ Blood pressure
- ↓ CV risk factors
  - Improved lipid profile
  - Decreased inflammatory markers
- ↓ Hypoglycemia

**Glycemic Effects**
- ↓ A1C
  - Improved FPG profile
  - Improved PPG profile

**Cardioprotective Effects**
- ↓ Infarct size
- ↑ Post-ischemic myocardial function
- ↑ Post-ischemic survival
- ↑ Cardiac output

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.

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


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.
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
GRAZIE