

Diabetes Update 2011

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QE II HSC

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Overview

- Use of A1c to diagnose diabetes
- Escalation of therapy
- GI effects of incretin agents

Diagnosis of DM: US vs Canada



FPG	≥ 7	≥ 7
PG post 75g OGTT	≥ 11.1	≥ 11
Casual PG + symptoms	≥ 11.1	≥ 11.1
A1c		not yet

What qualifies as diabetes in the 2010 US guidelines?

■ $A1c \leq 6.5\%$

■ $A1c \leq 7\%$

■ $A1c \leq 8\%$

Diagnosis of DM: US vs Canada



FPG	≥ 7	≥ 7
PG post 75g OGTT	≥ 11.1	≥ 11
Casual PG + symptoms	≥ 11.1	≥ 11.1
A1c	$\leq 6.5\%$	not
yet		

In the US, if $A1c \leq 6.5\%$ qualifies as DM, then what is the target A1c?

■ $A1c \leq 6\%$

■ $A1c \leq 6.5\%$

■ $A1c \leq 7\%$

A 56 yo has an A1c of 5.9%

- She is relieved to know that this is “normal”, so she will not have to change her lifestyle.
- What do you tell her?

Categories for increased risk for DM: US guidelines

- FPG 5.6 to 6.9 mmol/L
- 2h PG in the 75g OGTT 7.8 to 11 mmol/L
- A1c 5.7 – 6.4%

For all 3 tests, risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at higher ends of the range.

A1c vs retinopathy

Role of the A1c assay in the diagnosis of diabetes

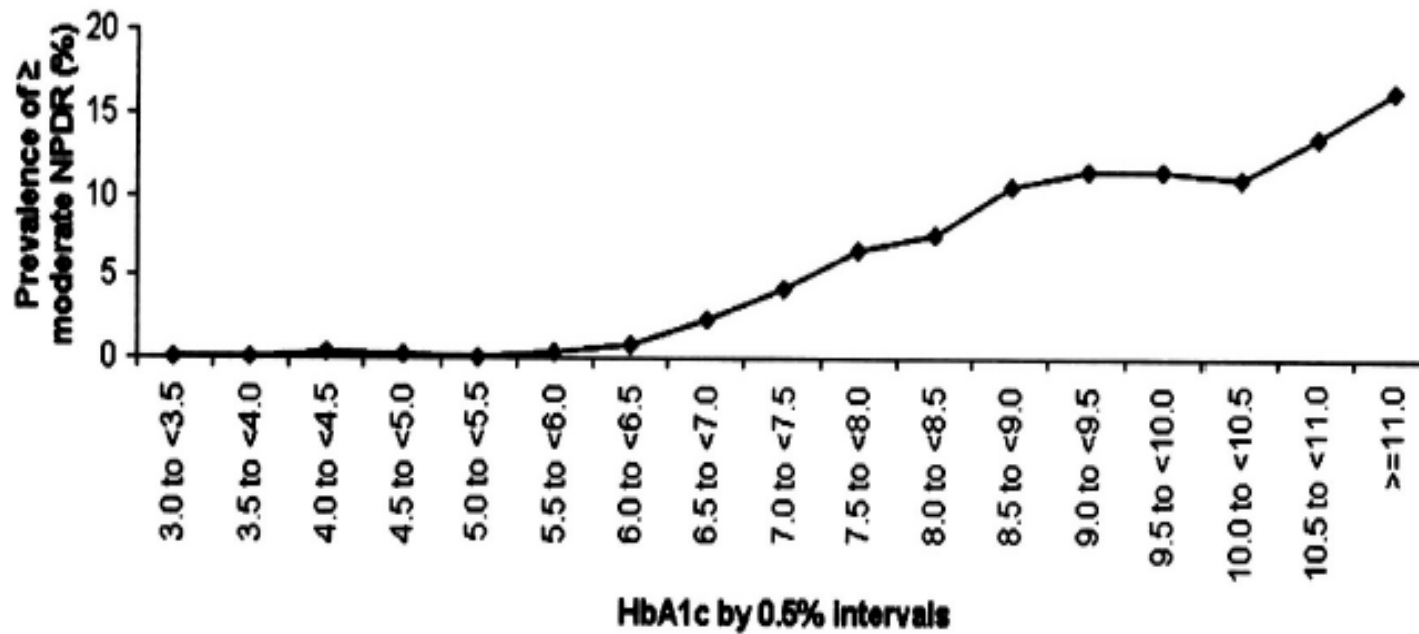


Figure 2—Prevalence of retinopathy by 0.5% intervals and severity of retinopathy in participants aged 20–79 years. NPDR, nonproliferative diabetic retinopathy. Adapted with permission from (S. Colagiuri, personal communication).

Diagnosis of DM: Canada



FPG	≥ 7
PG post 75g OGTT	≥ 11
Casual PG + symptoms	≥ 11.1
A1c	not yet

FPG and OGTT

- Both tests have limited overlap
- Lack of reproducibility
- Neither used to manage DM once it is diagnosed

Diabet Med. 2002;19:708-723; Diabetes Care. 2007;30:753-759;
Diabetes Care. 2009;32:S13-S61.

Disadvantages of FPG

- Sample not stable
- Needs to be performed in the morning
- Requires fast ≥ 8 hours
- Subject to interference (stress, acute illness)
- Less tightly linked to DM complications (vs A1c)
- Reflects glucose homeostasis at a single point in time

Disadvantages of 75g OGTT

- Sample not stable
- Needs to be performed in the morning
- Time consuming and inconvenient
- Unpalatable

Advantages of HgA1c

- No need for fasting
- No need for morning test
- Not altered by acute factors
- Reflects long term glucose concentration
- Assay is now standardized
- Used to guide treatment
- Predicts the development of DM related complications

Disadvantages of HgA1c

- Pregnancy and children
- Rapidly progressing T1DM
- Cost

Screening for type 2 diabetes using a fasting plasma glucose (FPG) should be performed every 3 years in individuals ≥ 40 years of age.

Escalation of therapy

- Case: 57 YO female T2DM x 6 years
- Current meds
 - Metformin 750mg BID
 - Gliclazide 90mg MR daily
- A1c = 8.4%
- What would you recommend?

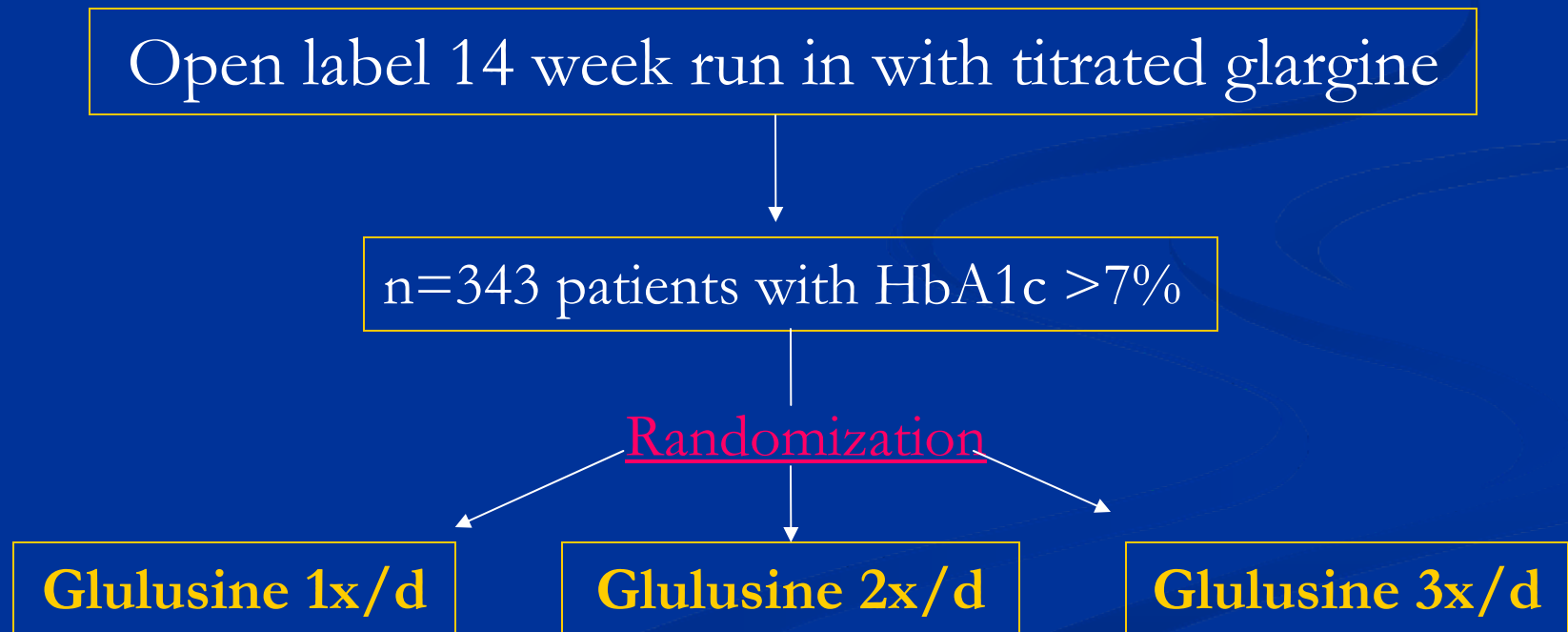
Same case 2 years later

- Case: 57 YO female T2DM x 6 years
- Current meds
 - Metformin 1000mg BID
 - Gliclazide 120mg MR daily
 - Glargine 32 units HS
- A1c = 8.4%
- FBG = 7-9 mmol/L

- What would you recommend?

1 vs 2 vs 3 injections of prandial insulin

- OL study, original n = 785
- T2DM pts on oral agents with HbA1c $\geq 8\%$



1 vs 2 vs 3 injections of prandial insulin

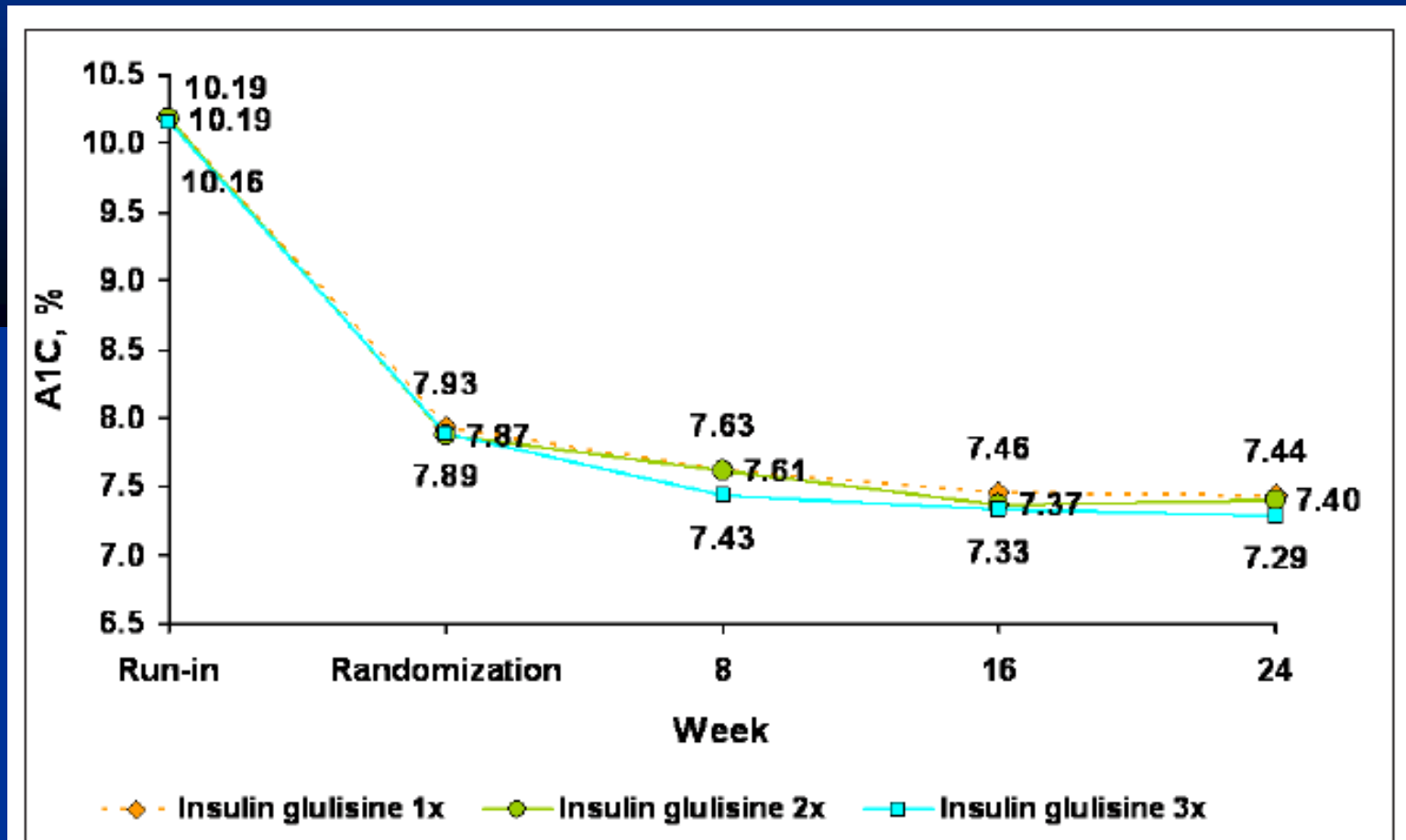


Fig. 3. Glycated hemoglobin A_{1c} (A1C) levels. Insulin glulisine 1x = insulin glulisine administered before the meal of greatest glycemic impact; insulin glulisine 2x = insulin glulisine administered before the 2 meals of greater glycemic impact; insulin glulisine 3x = insulin glulisine administered before all 3 meals.

In T2DM patients poorly controlled on basal insulin, what is the role of addition of a GLP1 agonist?

Addition of exenatide to basal insulin

- T2DM, poorly controlled (average A1c = 8.4%)
- on glargine (average dose 48 units/d)

Randomized to:

Exenatide 5mcg BID AC +
Glargine (titrated to FBG <5.6)

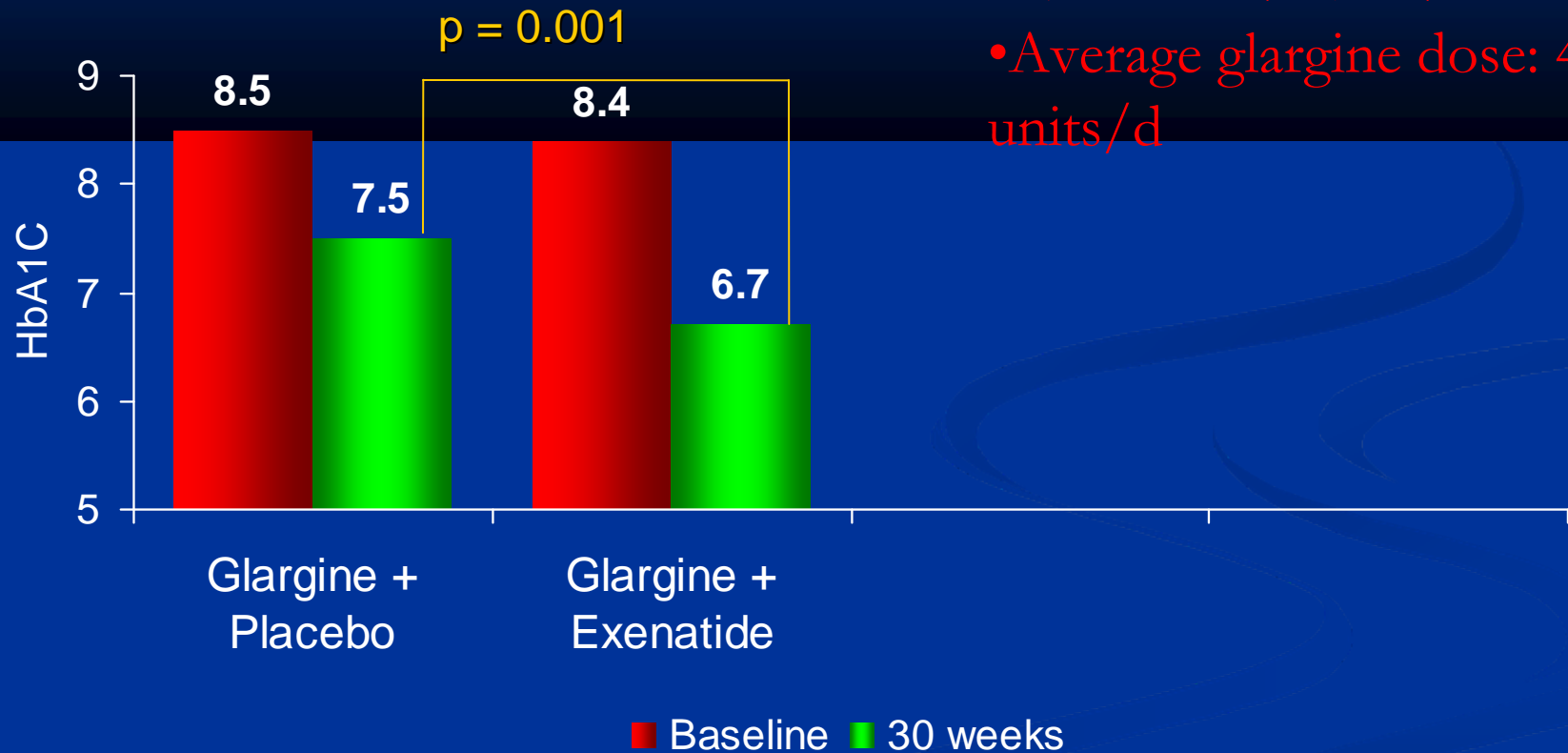
OR

Exenatide 5mcg BID AC +
Glargine (titrated to FBG <5.6)

Exenatide 10mcg BID AC +
Glargine (titrated to FBG <5.6)

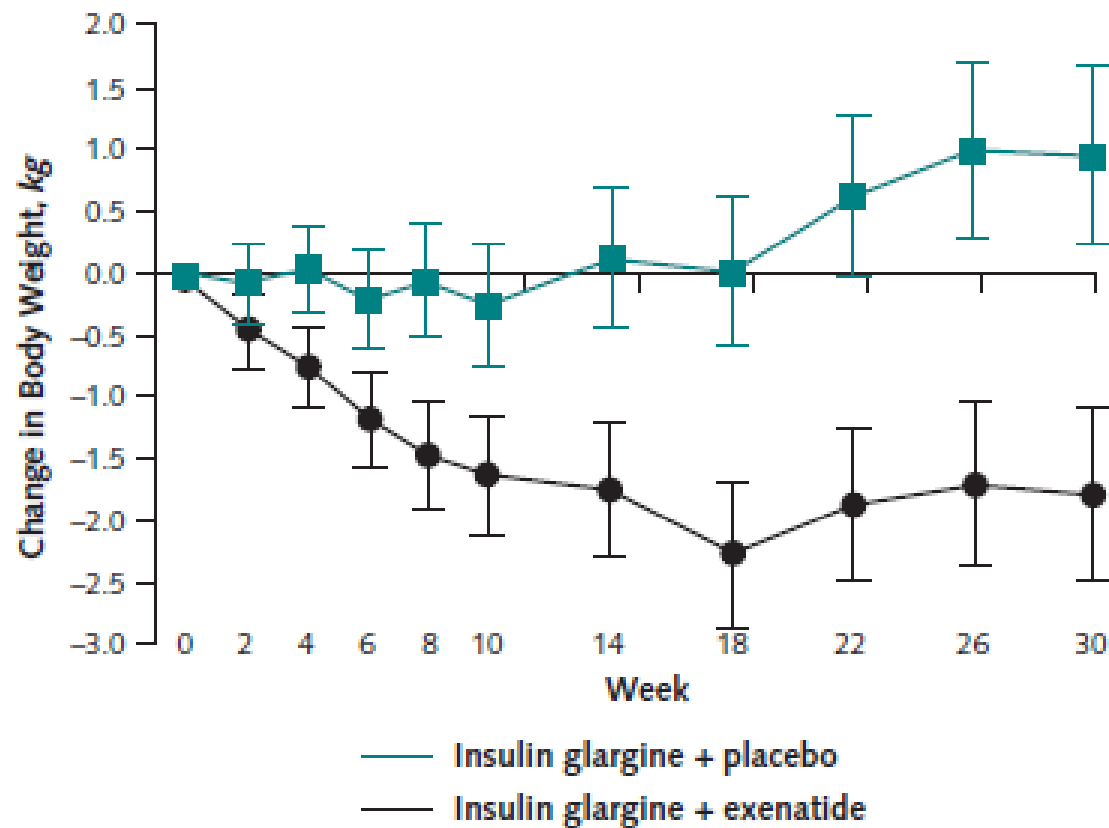
Exenatide vs placebo

- Hypoglycemia was similar
- Nausea 41% vs 8%
- Average glargine dose: 48 units/d



Exenatide vs placebo: weight

Figure 3. Changes in body weight and glucose levels over 30 weeks.



In a patient failing to achieve target A1c on basal insulin, what is the next step?

- Victoza (liraglutide): \$160 to \$200/ month
- Byetta (exenatide): \$150/ month

Weight loss/ GI side effects of GLP1 agonists

Multiple Sites of Action of GLP-1



CNS:

Promotes satiety and reduction of appetite

Liver:

Reduces hepatic glucose output by inhibiting glucagon release

Alpha cell:

Inhibits glucagon secretion in a glucose dependent fashion

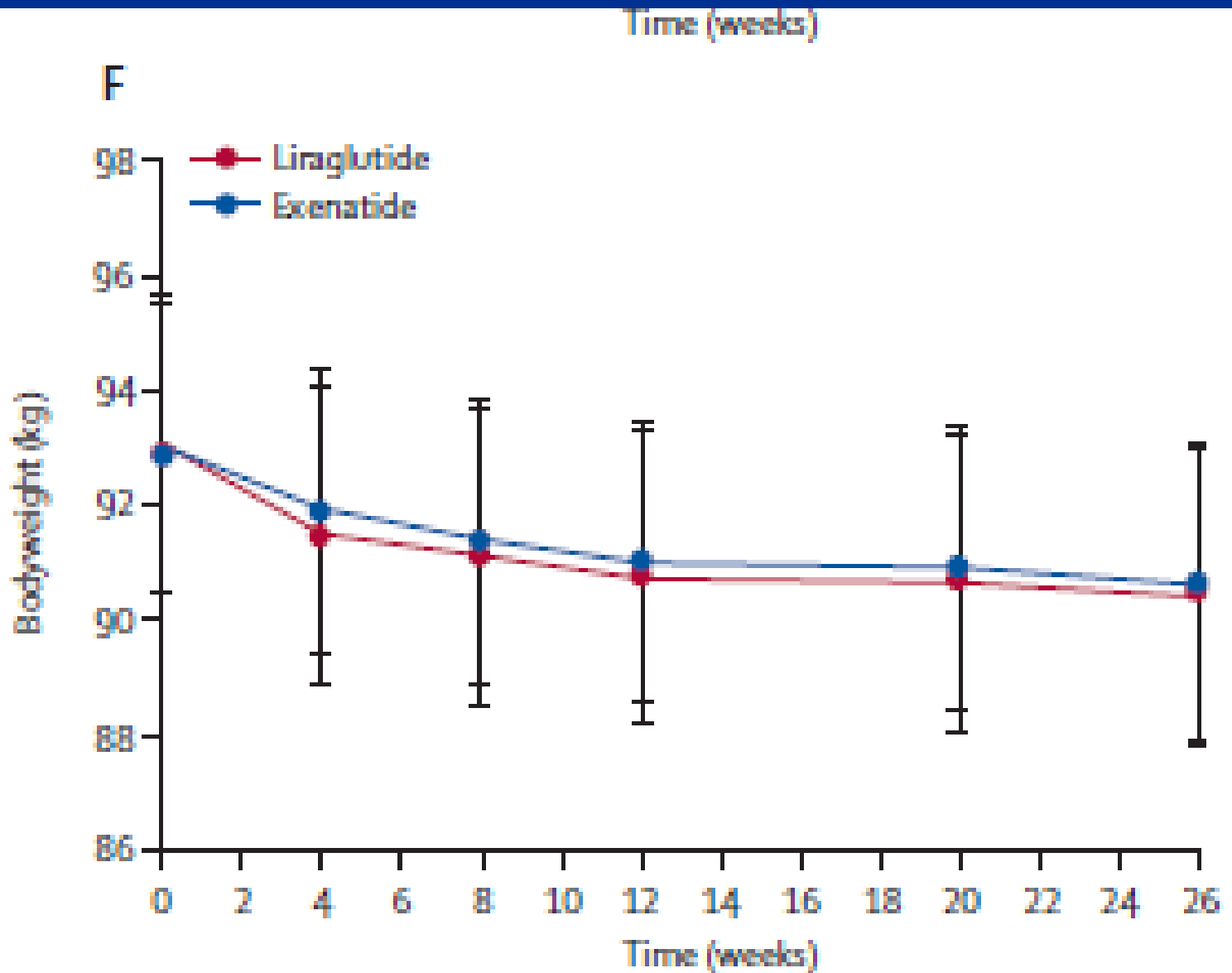
Beta cell:

Stimulates glucose-dependent insulin secretion
Increases beta cell mass

Stomach:

Slows gastric emptying

LEAD- 6: Change in body weight



LEAD 6: Proportion of patients with an episode of nausea between baseline and week 26

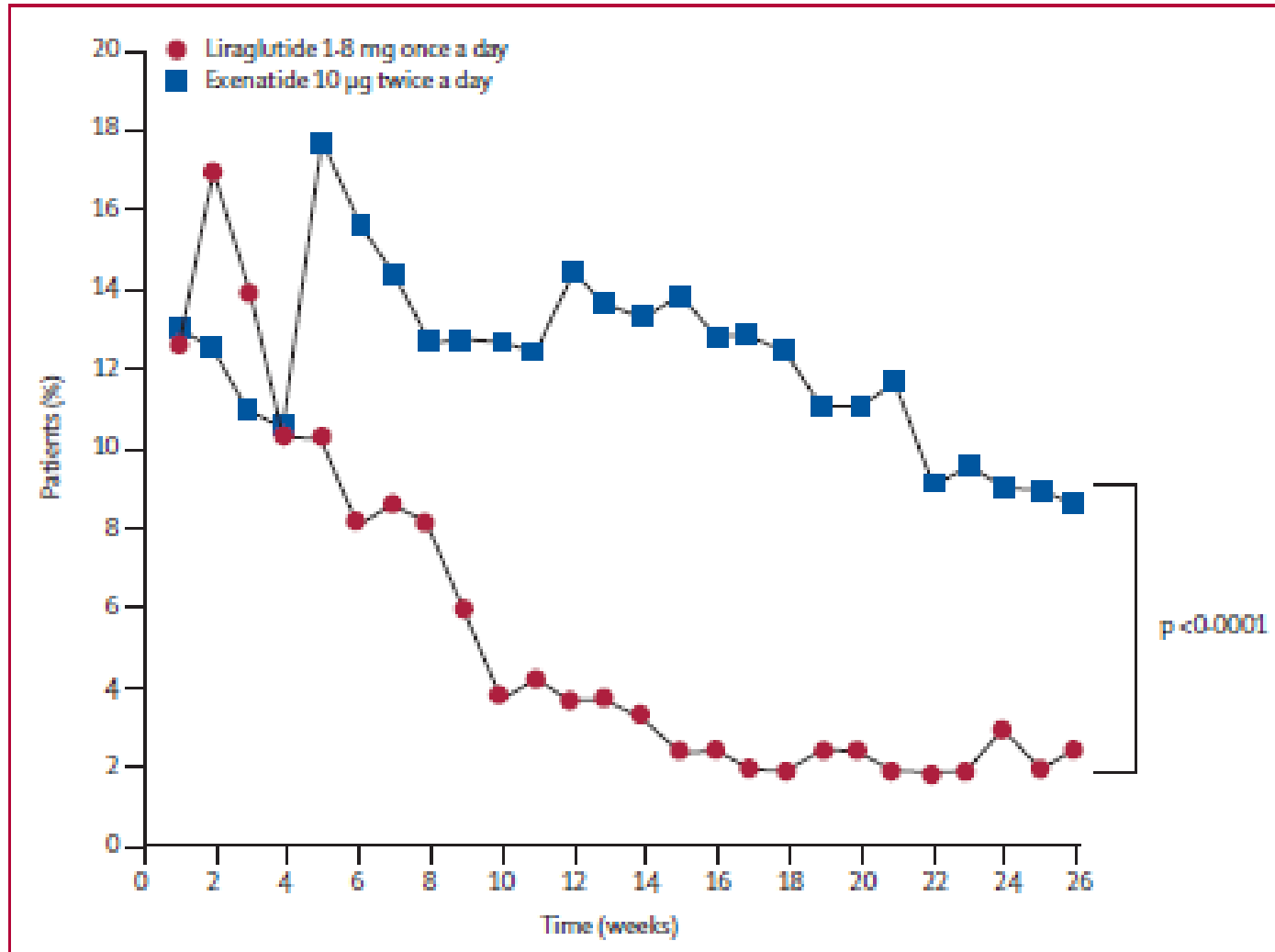


Figure 3: Proportion of patients with an episode of nausea between baseline and week 26

Lancet 2009;
374:39-47

Patient education issues with GLP1 analogs

- Nausea generally subsides with time
 - Most patients can continue
- Nausea does not correlate with weight loss
- These are not weight loss drugs
 - Weight loss does not correlate with ↓ in A1c
 - Not all patients lose weight
- Report abdominal pain/ severe nausea

Patient education issues with GLP1 analogs

- Timing issues:
 - Liraglutide: none
 - Exenatide
 - Can inject right before meal (2h peak)
 - As tolerated, move ≥ 30 minutes per meal

Patient education issues with GLP1 analogs

- Avoid forced titration
- Change in eating habits may be necessary
 - Eat slow
 - Stop when feel full

Is weight loss an appropriate endpoint?

Health Canada Endorsed Important Safety Information on
MERIDIA® (Sibutramine Hydrochloride Monohydrate)



Subject: Voluntary withdrawal of Meridia® (sibutramine) capsules from the Canadian market.

October 14th, 2010

Dear Healthcare Professional,

Look AHEAD: 1 year data

