

INSULIN THERAPY IN TYPE 2 DIABETES

**SHOULD WE FOCUS ON FASTING
OR POSTPRANDIAL FIRST ?**

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CONFLICT OF INTEREST

None for the present conference

Like any therapeutic agent involved in the management of type 2 diabetes **insulin** should attempt to achieve the better and earlier

EFFICIENCY

**But what is exactly
efficiency ?**

At first glance **EFFICIENCY** can be considered as a cluster of several parameters that include :

- Efficacy
- Safety
- Quality of life
- Patient's satisfaction
- Economic considerations : cost / benefit ratio

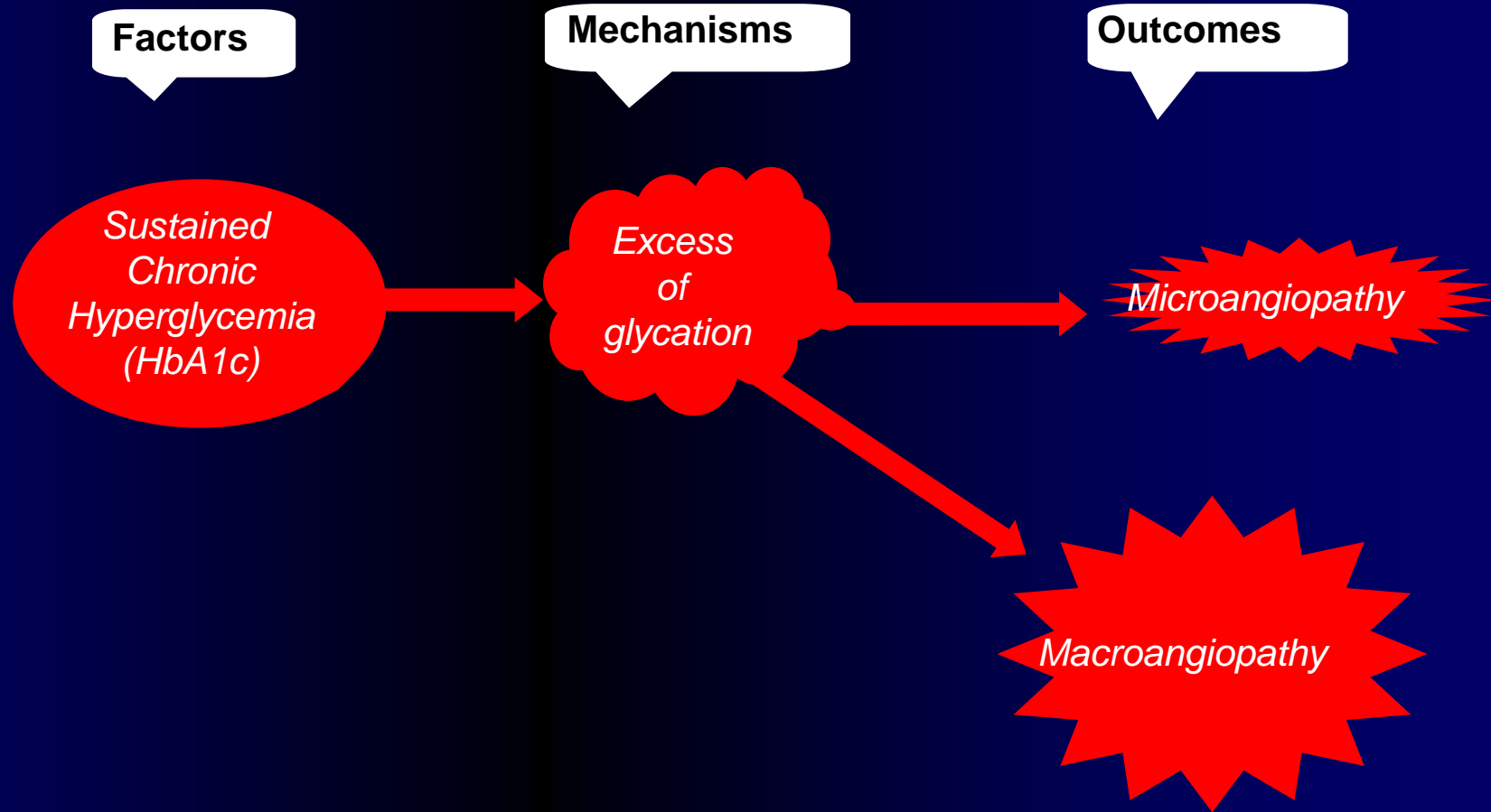
**Consider only the two first components of efficiency :
EFFICACY and SAFETY**

- (a) How we can define the glycemetic disorders : the glucose triad and tetrad ?**
- (b) How to manage the different components of the glucose triad and tetrad with insulin ?**
- (c) Is the lower , the better?**
- (d) However is the lower , the safer ?**

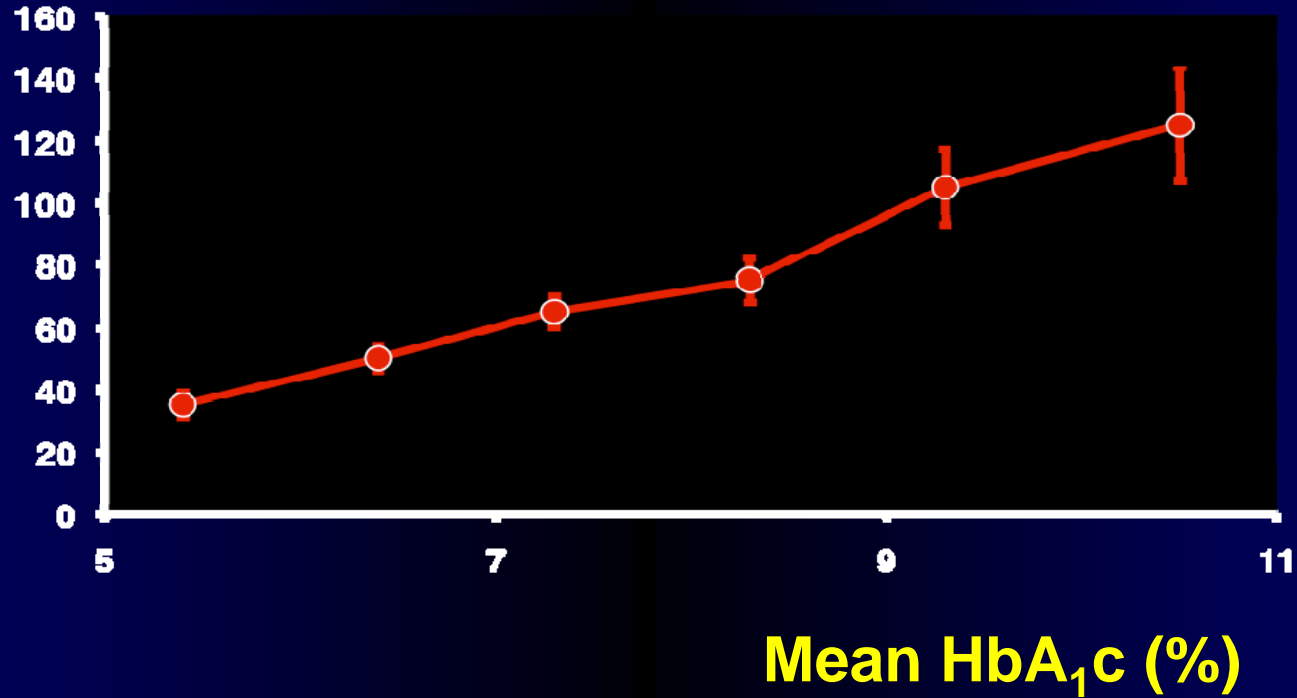
THE COMPONENTS OF EFFICACY: How we can define the glycemie disorders in type 2 diabetes?

- **THE GLUCOSE TRIAD** : Fasting and postprandial glucose
- **THE GLUCOSE TETRAD** : an additional parameter :
the glucose variability

A catenary model

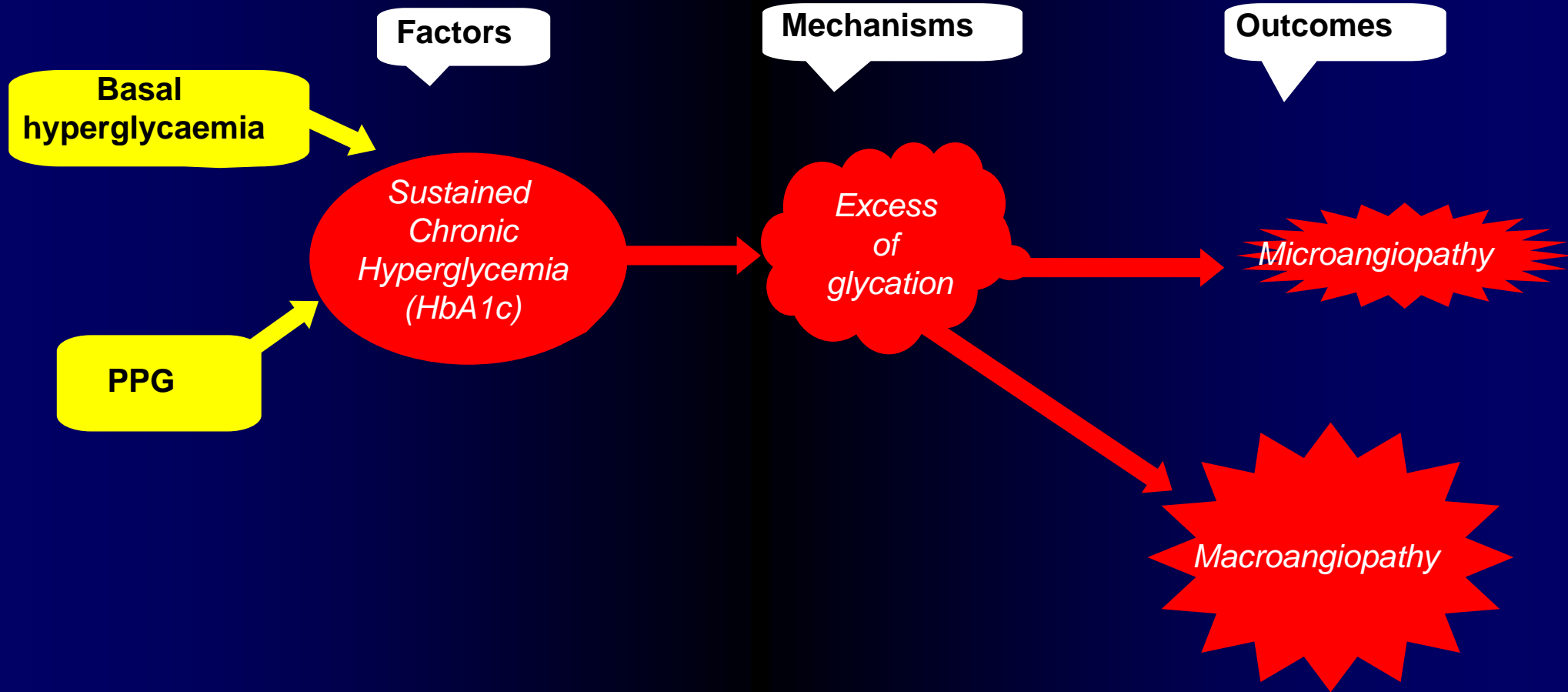


Incidence per 1000 person-years (%)



UKPDS BMJ 2000; 321: 405- 412

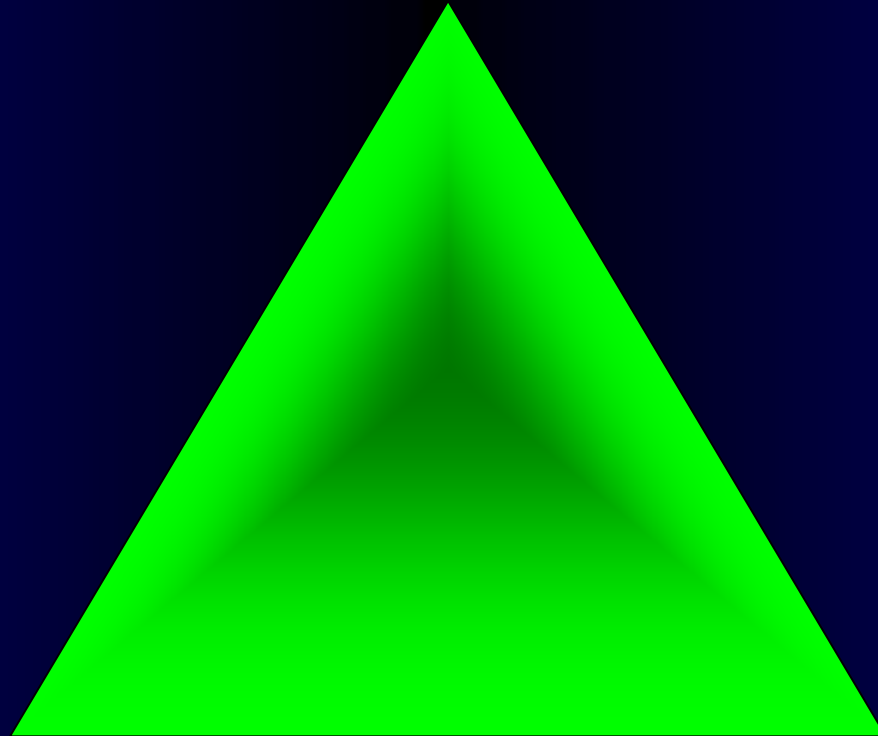
A catenary model with the contribution of basal and postprandial hyperglycemia



**The glucose triad:
for optimal management we should target...**

HbA_{1c}

The long-term average glucose level



FPG

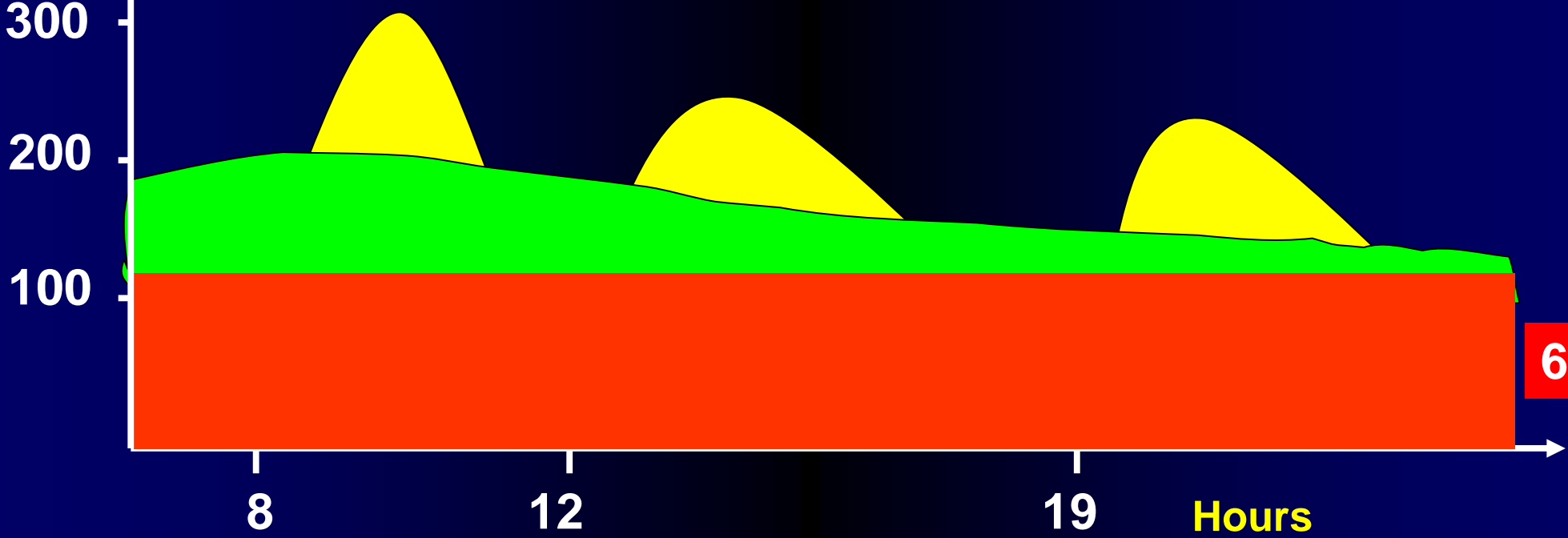
**The basal
glucose level**

PPG

**The peak
glucose level**

**Type 2 diabetic patient with
HbA_{1c} = 8%**

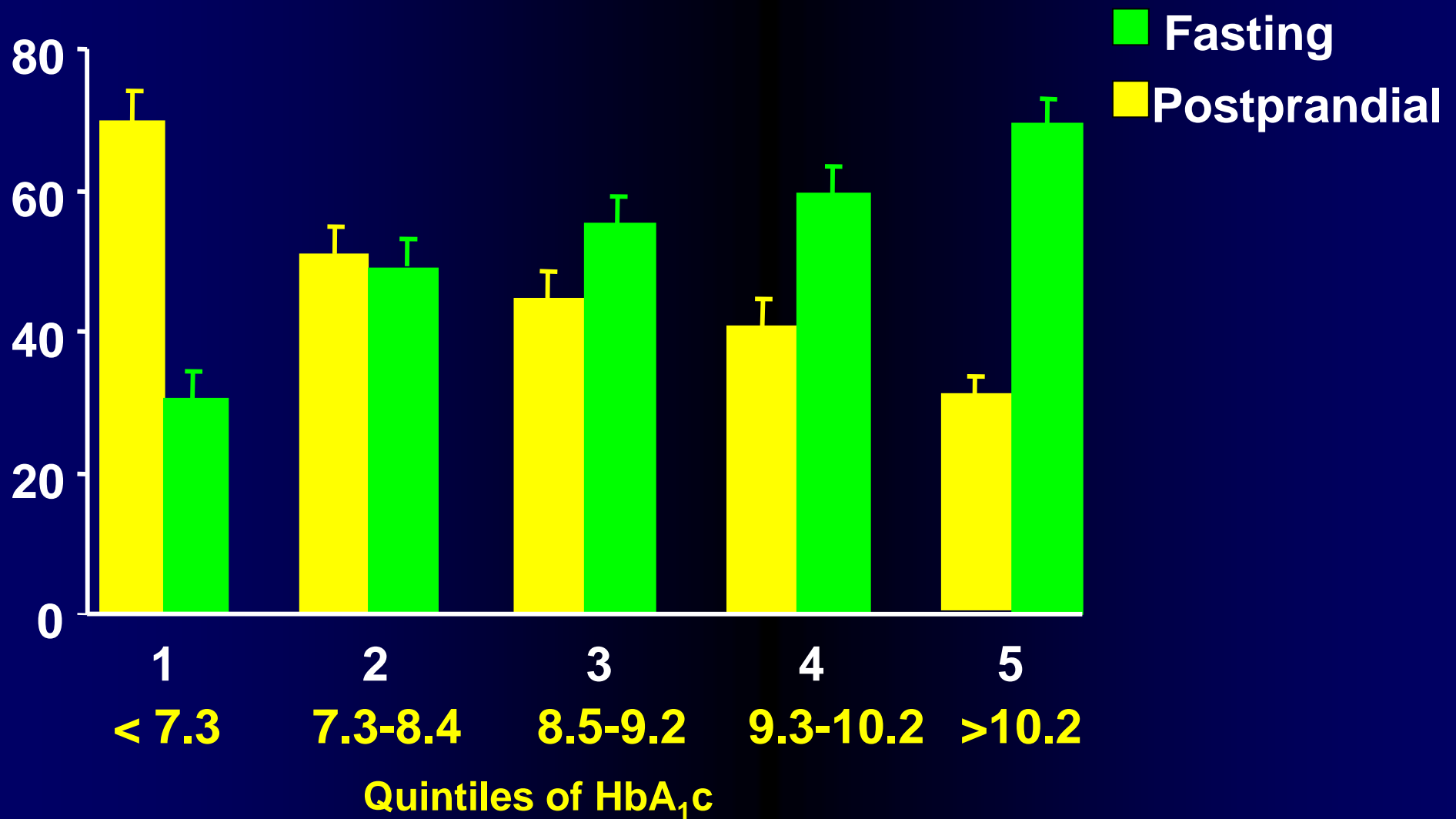
Glycemia (mg/dl)



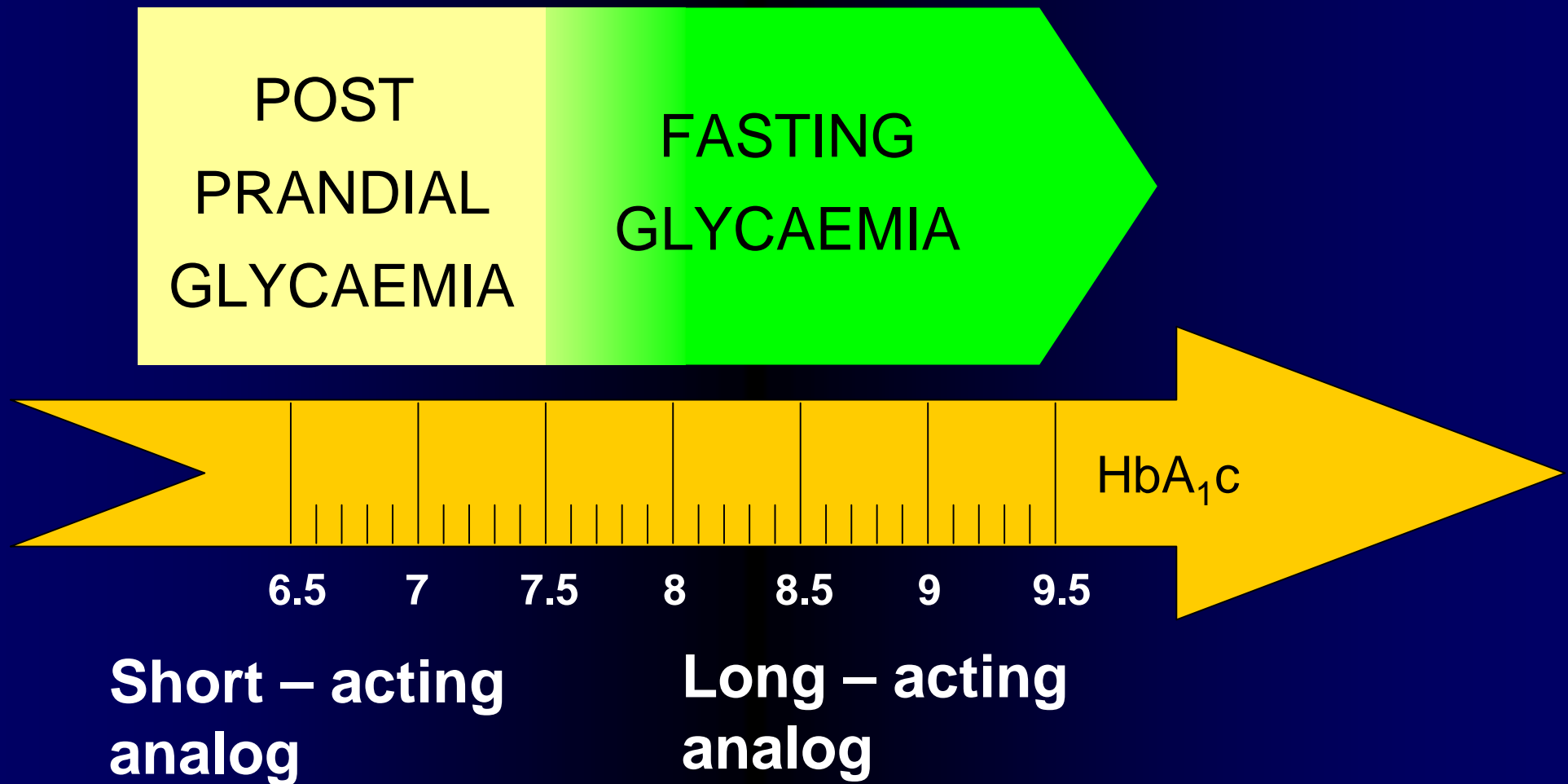
Basal + Postprandial Hyperglycemia = 2% of HbA_{1c}

6%

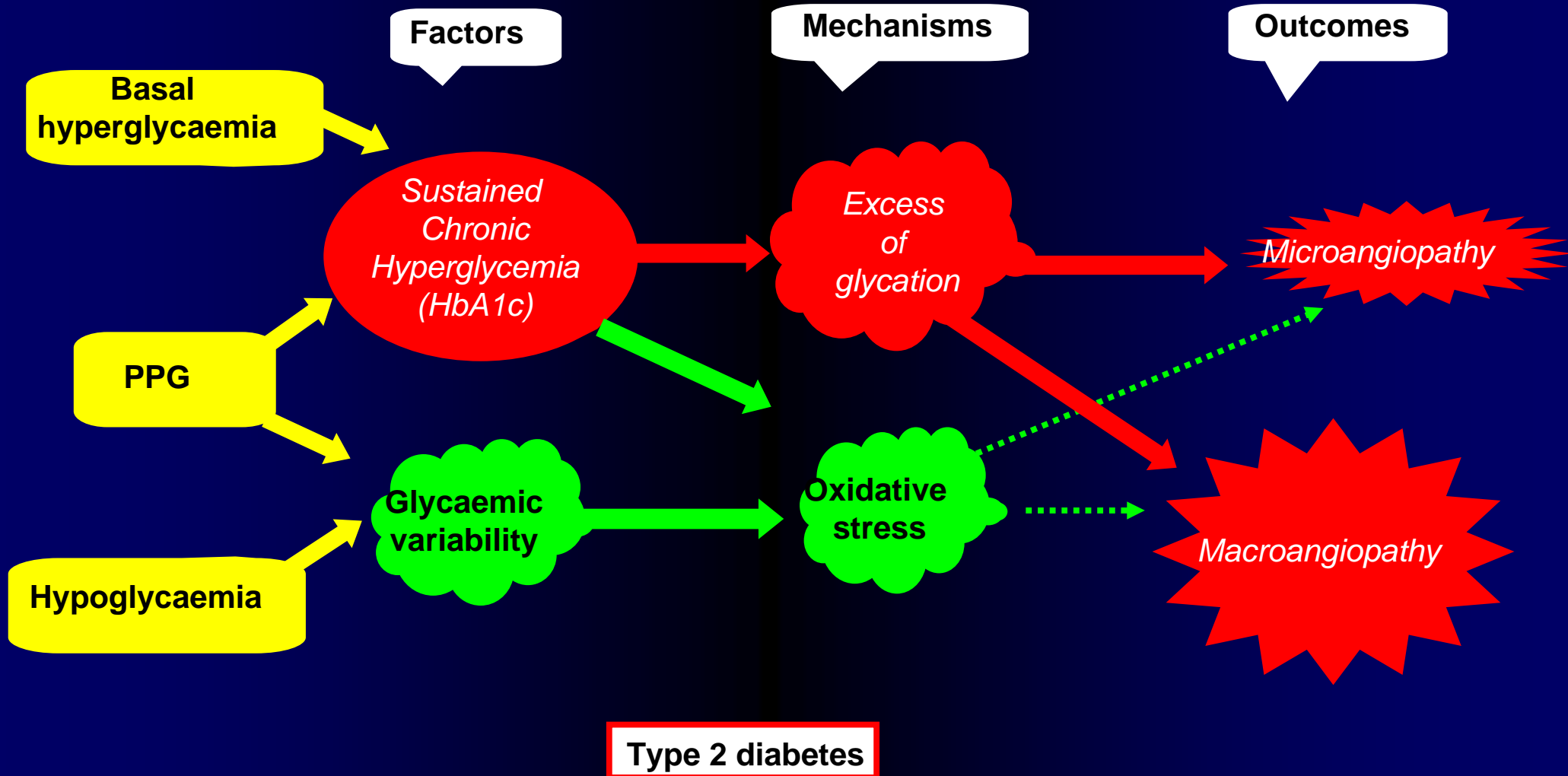
Relative contribution (%)



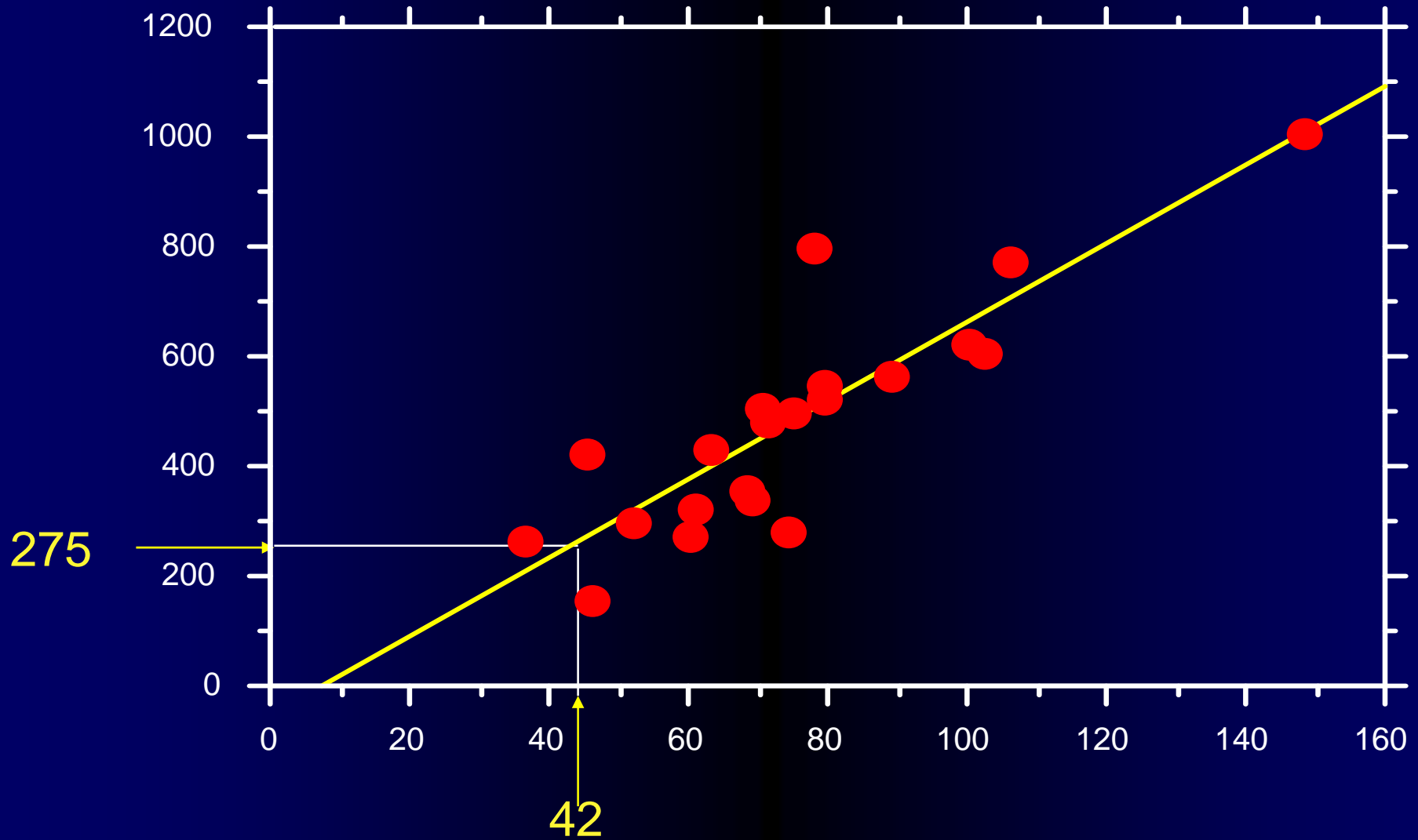
In a patient treated with OHAs at maximal tolerated doses and who requires an insulin treatment use an insulin preparation acting on:



A catenary parallel model introducing glycemic variability



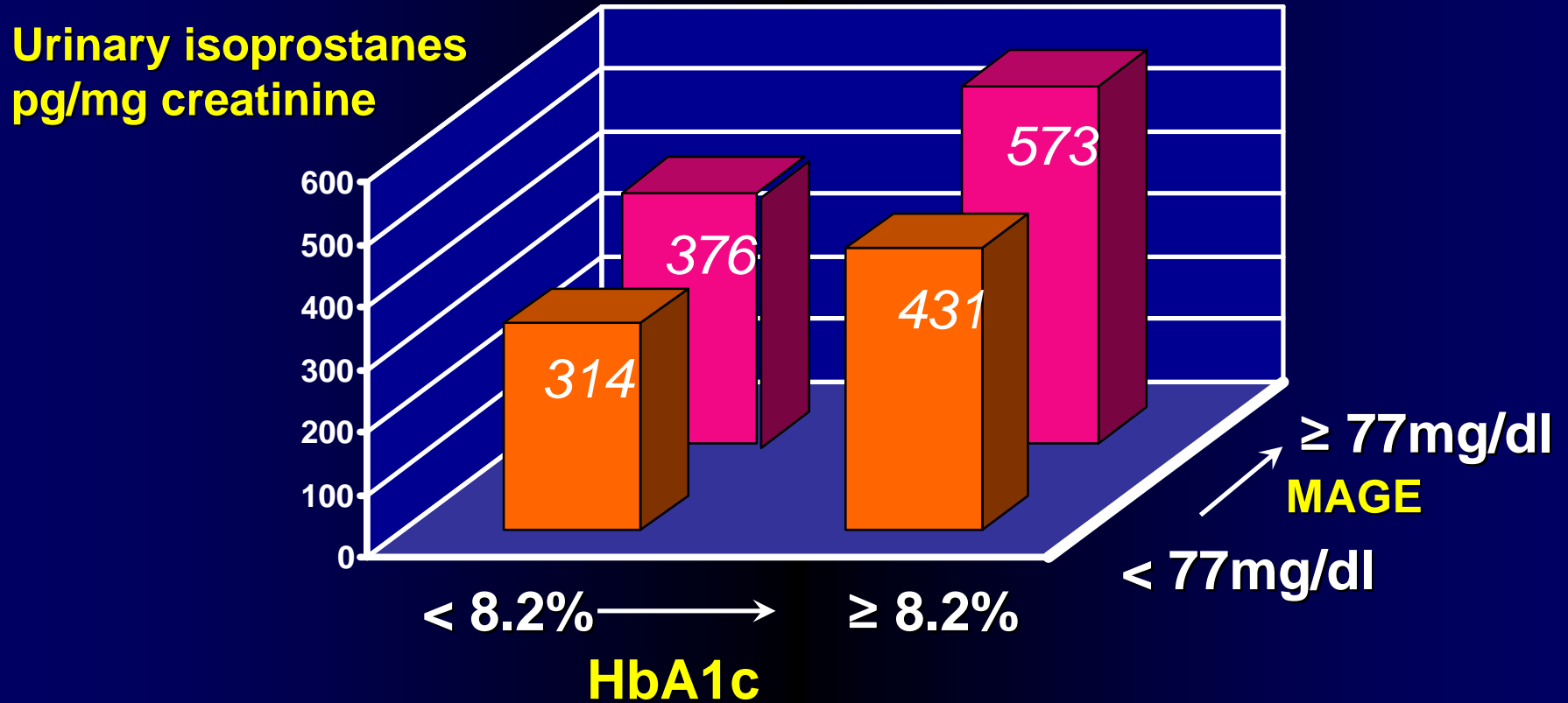
Urinary 8-Iso PGF2a Excretion Rate, pg/mg of Creatinine

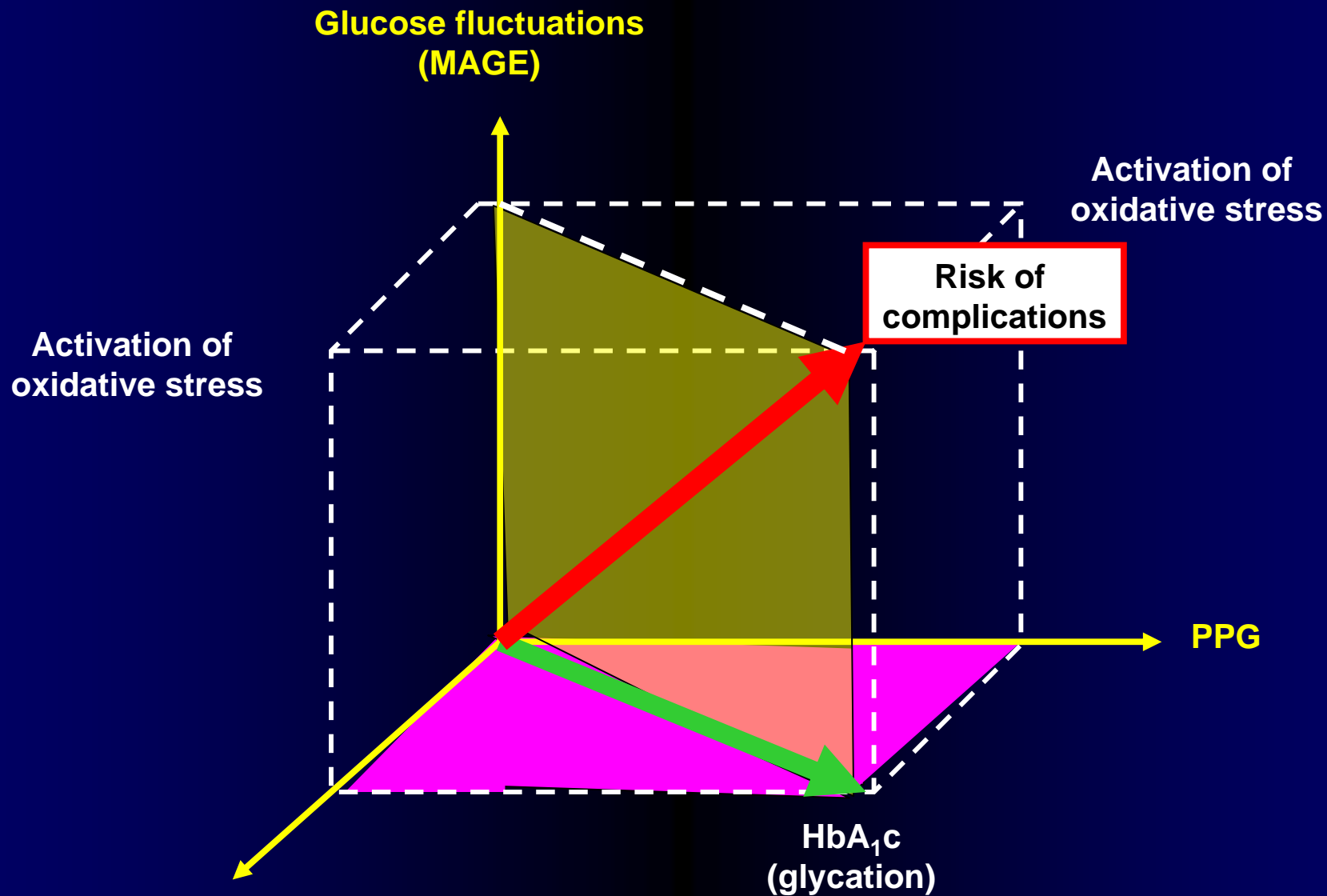


Mean Amplitude of Glycemic Excursions (MAGE, mg/dl)

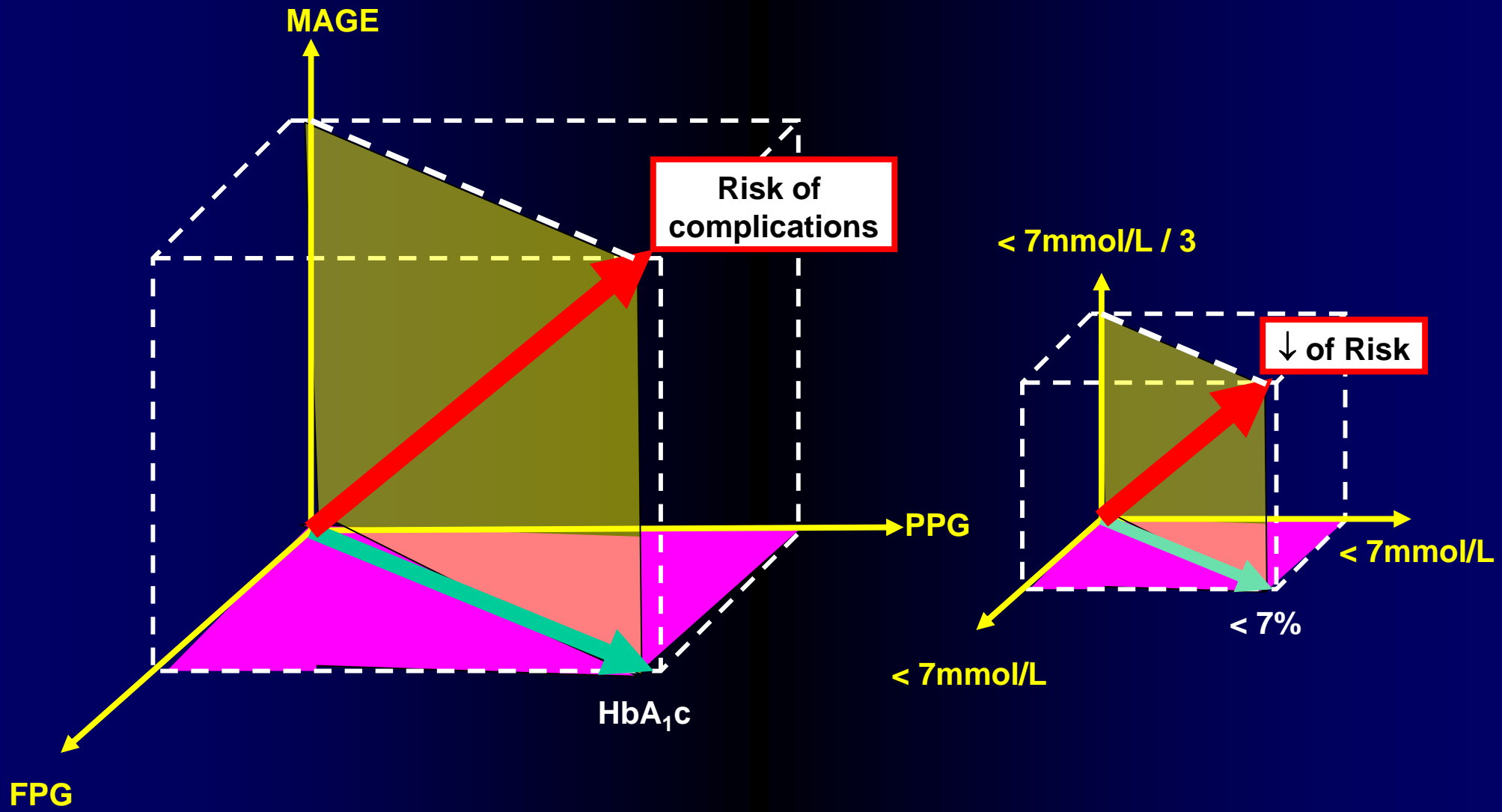
Monnier et al. JAMA. 2006;295:1681-1687

Type 2 patients treated with OHAs (n = 60)



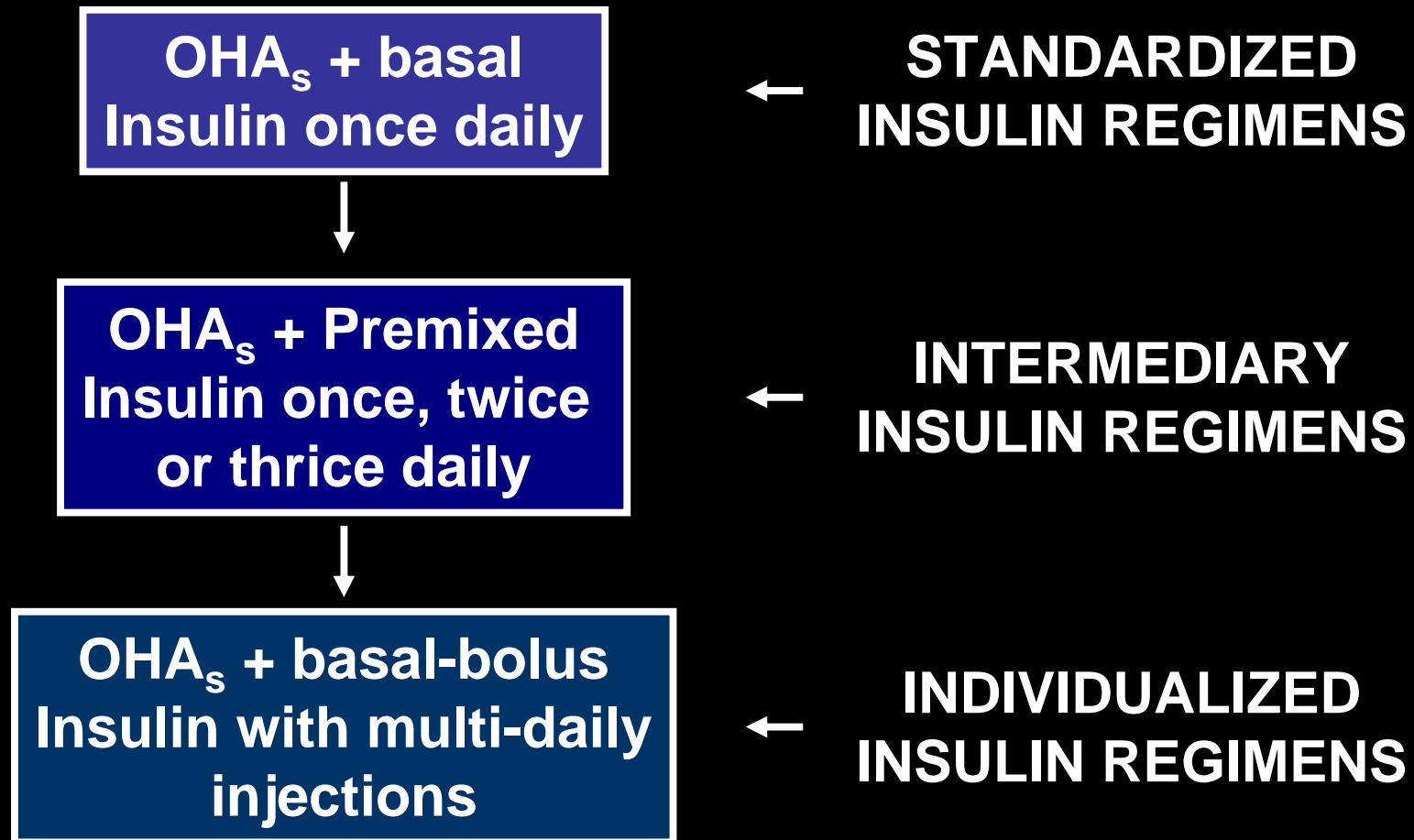


The pathophysiology of diabetic complications
 Three glycemic factors and 2 main mechanisms.



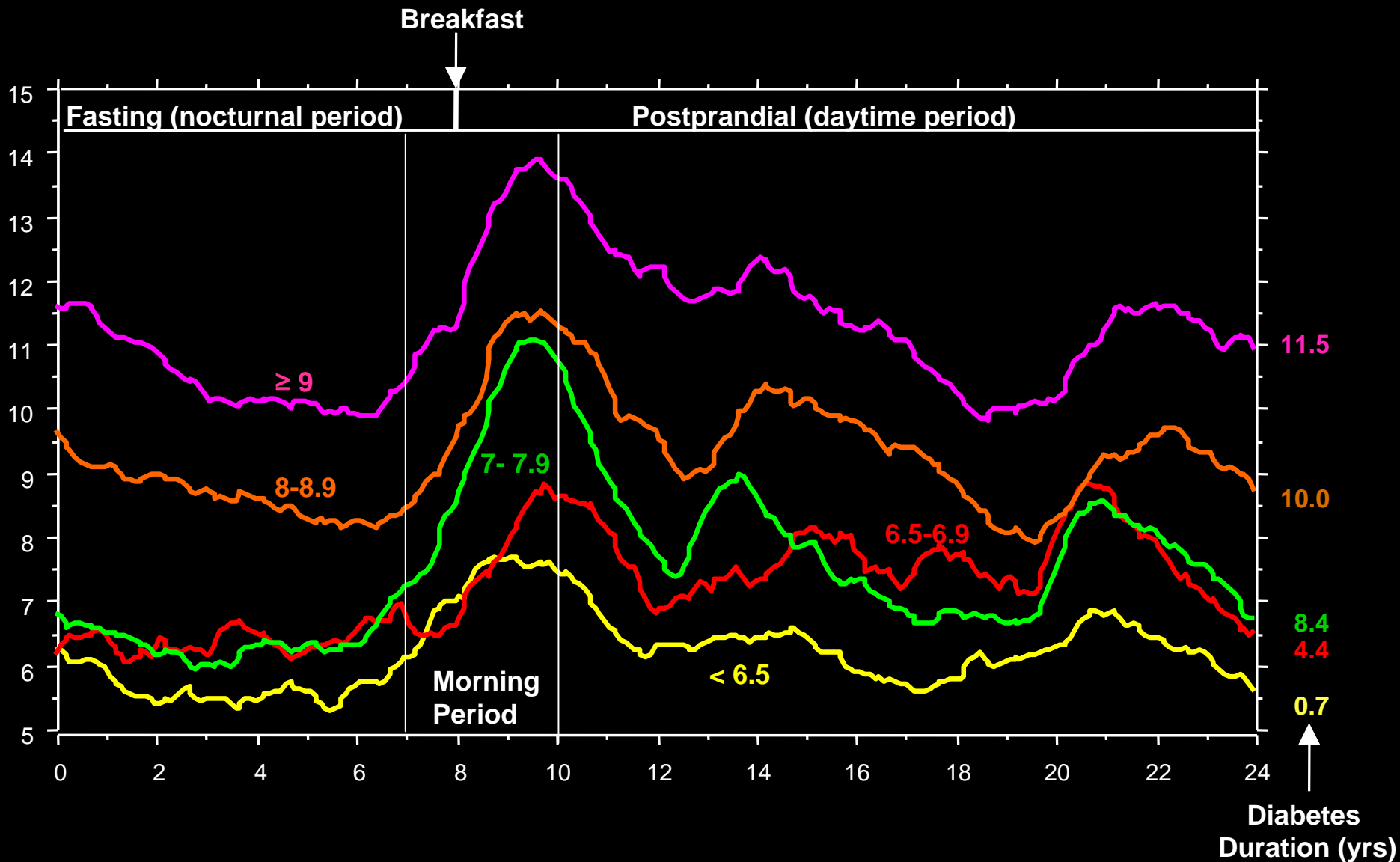
**How to manage the different components
of efficacy with insulin ?**

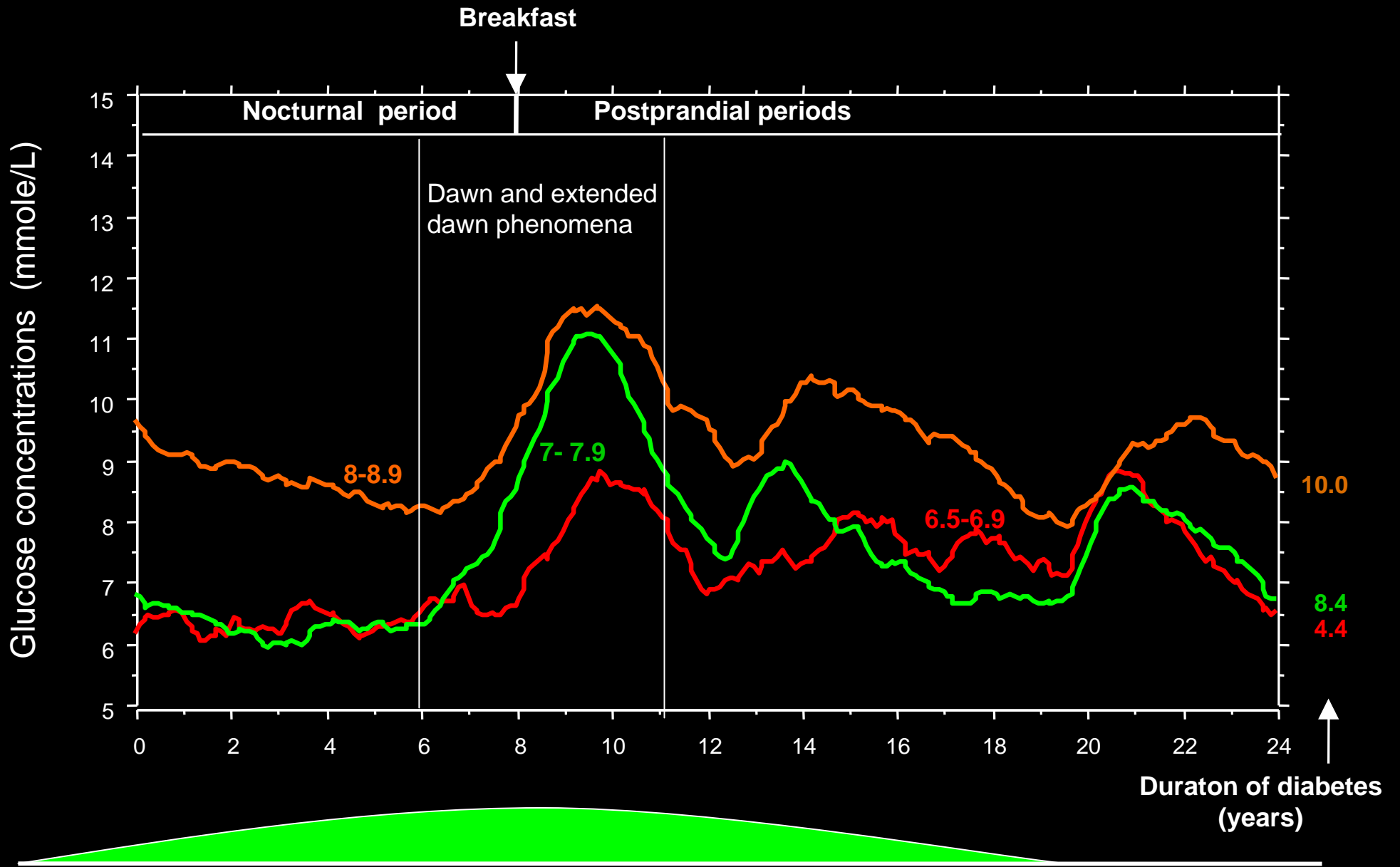
Different types of insulin regimens have been proposed in type 2 diabetes



**The rationale for basal
insulin once daily**

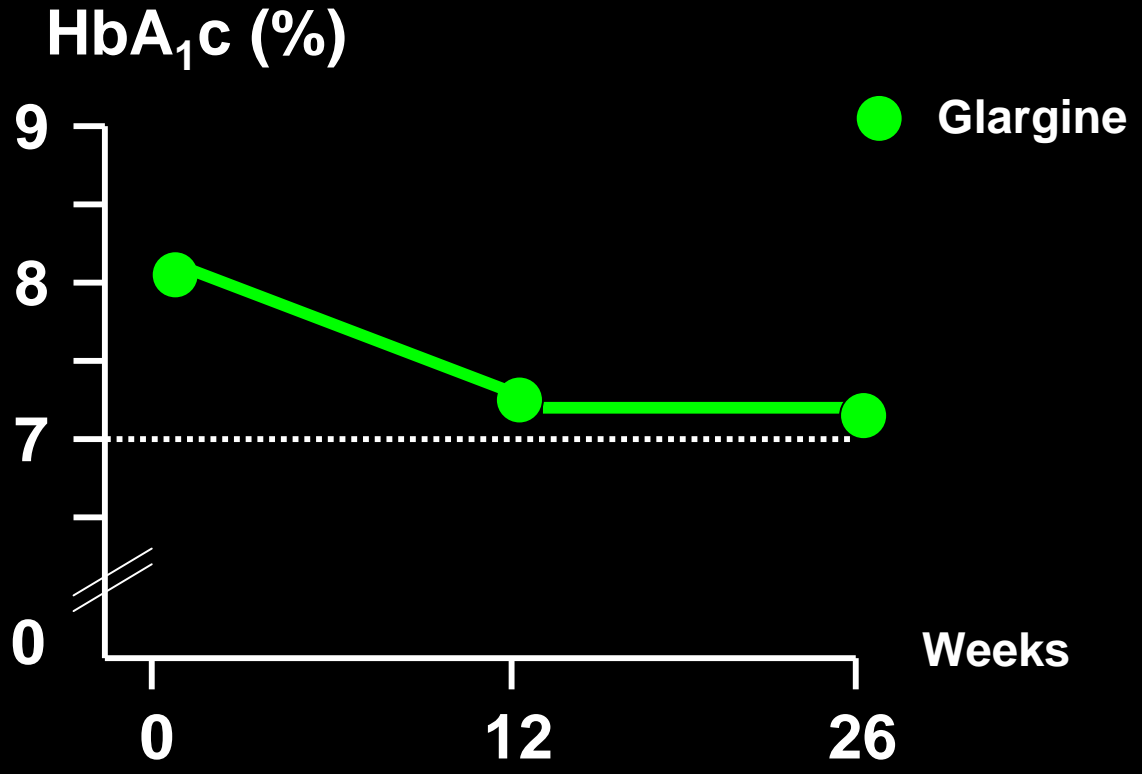
Daily glycemc variation (mmol/L) with worsening type 2 diabetes





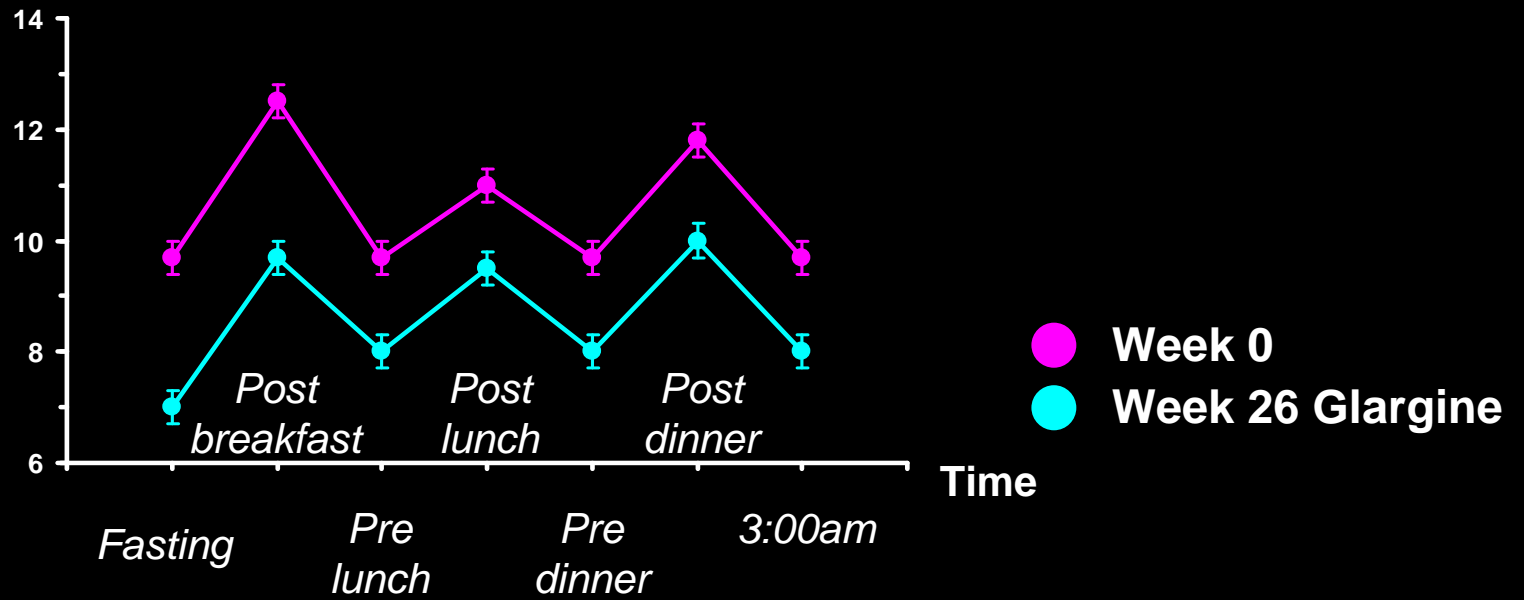
22 hours

Long – acting insulin analog



RJ HEINE Ann Int Med 2005;143:559-569

Blood glucose level mmol/l

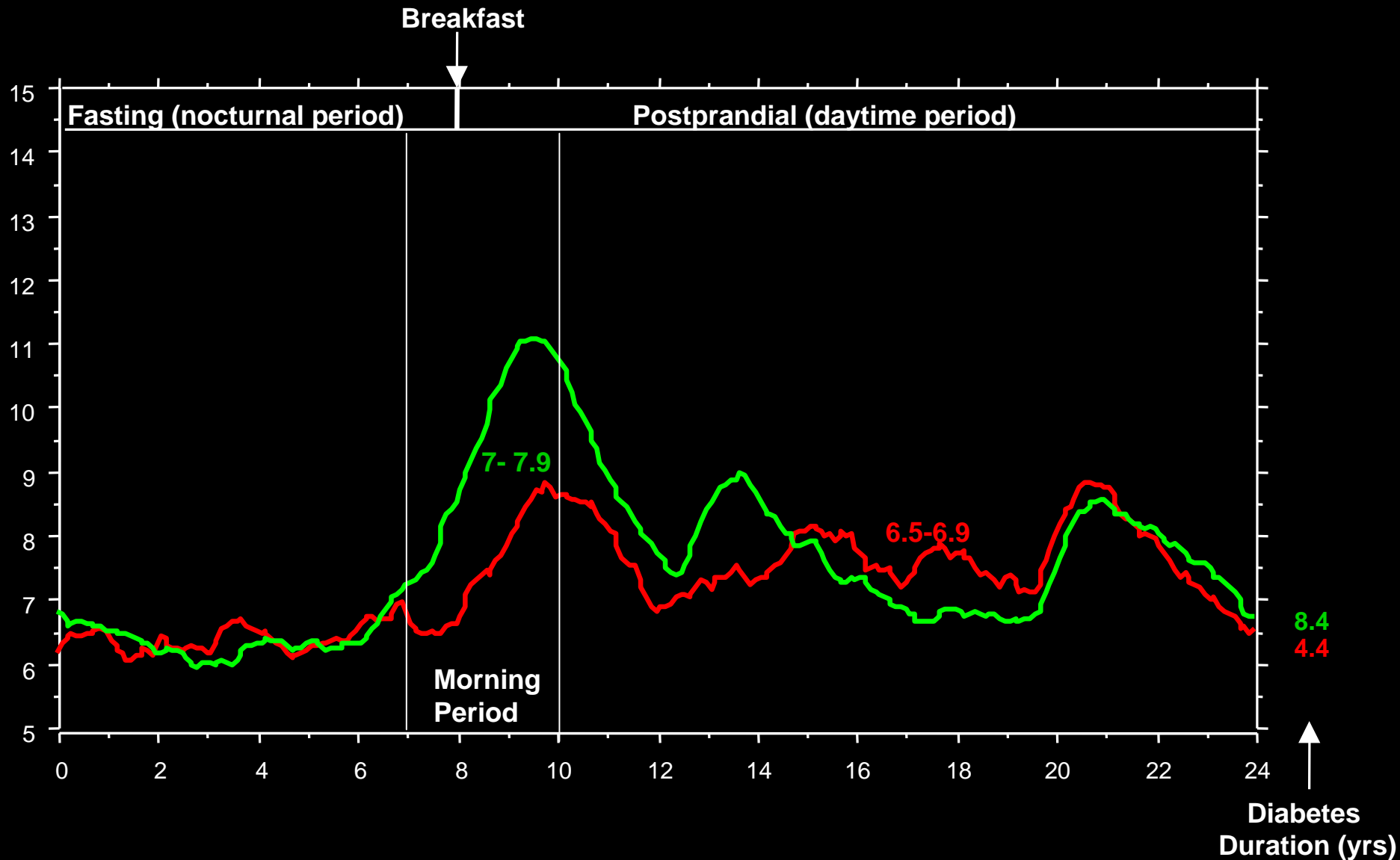


Glargine in type 2 diabetes

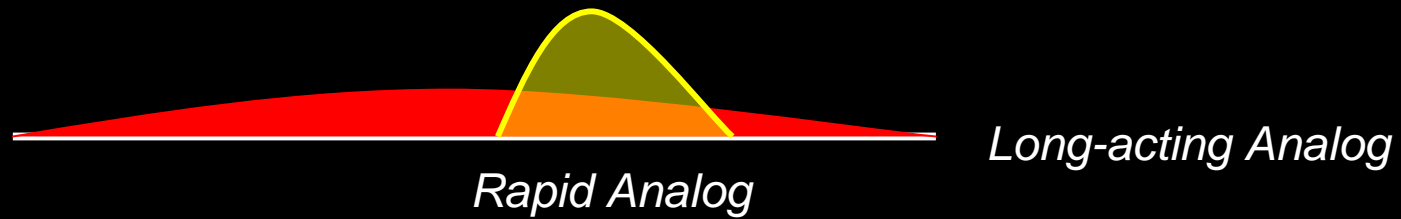
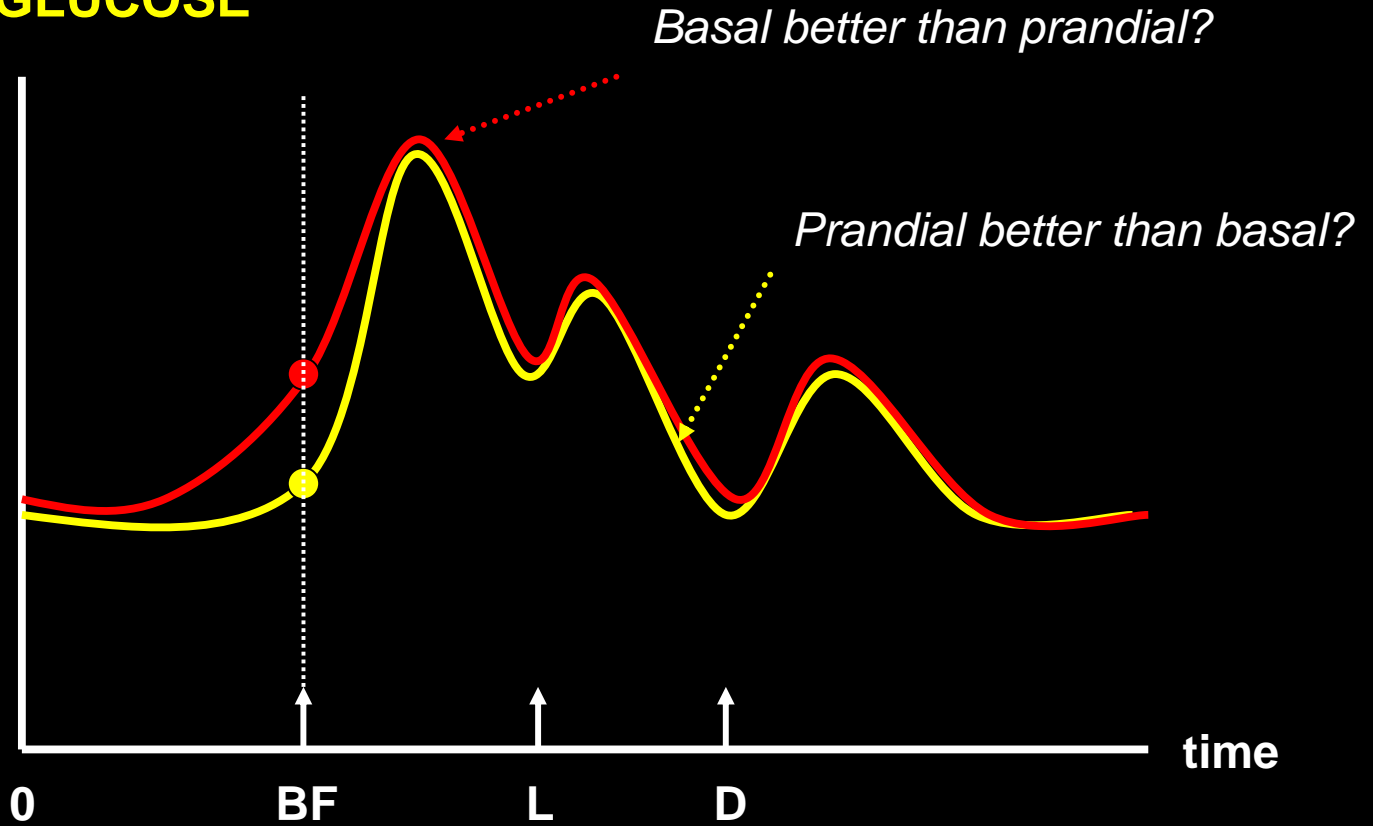
RJ Heine Ann Int Med 2005;143:559-569

**The rationale for prandial
insulin regimens**

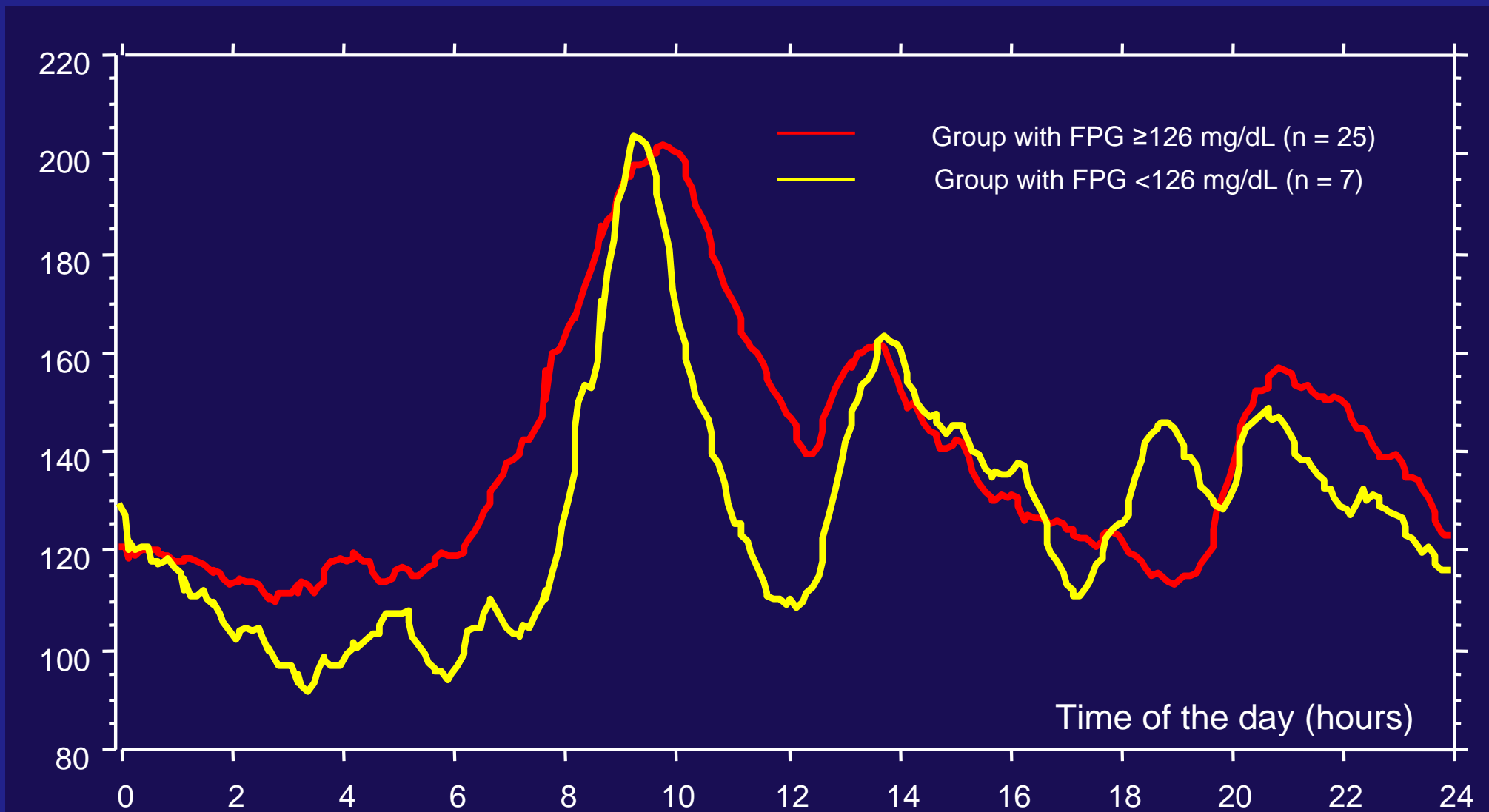
Daily glycemc variation (mmol/L) with worsening type 2 diabetes



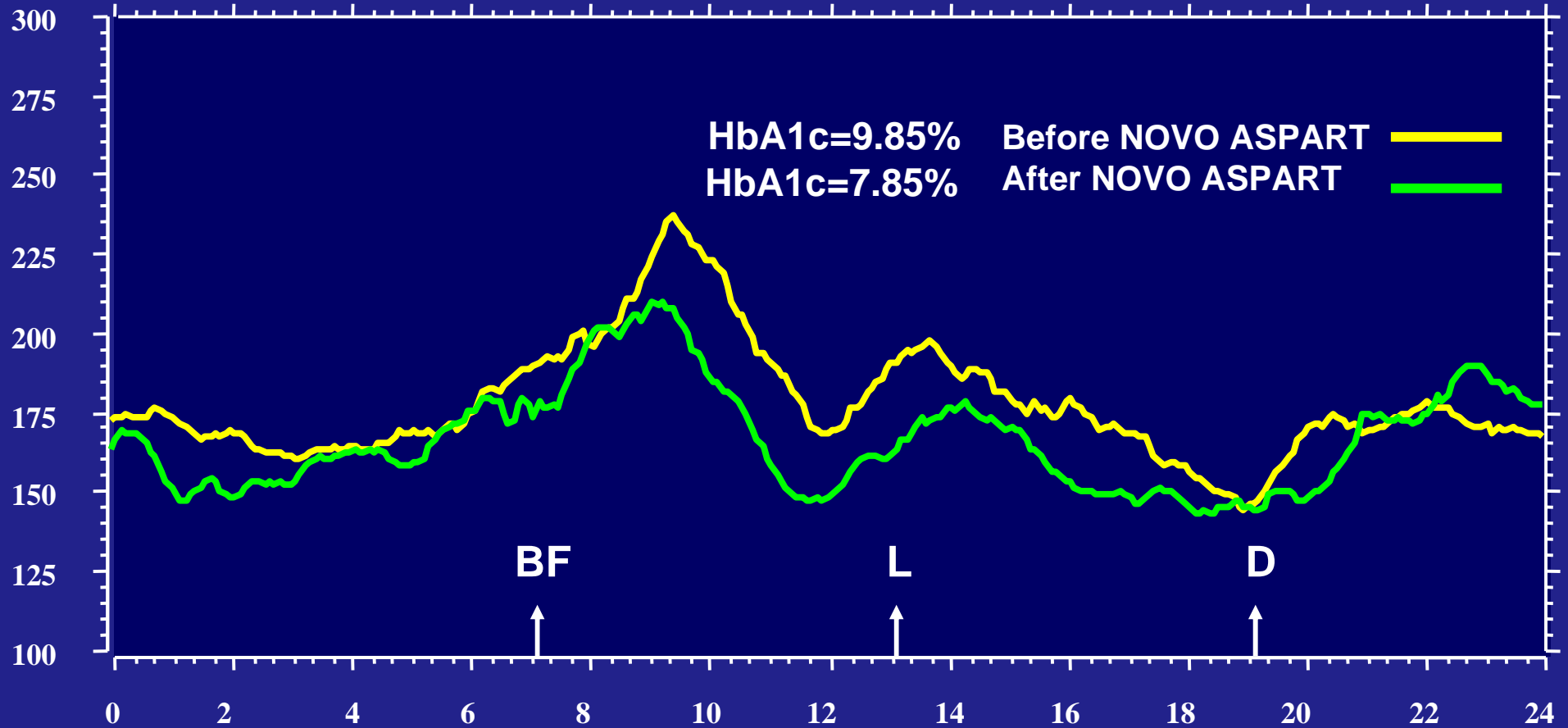
BLOOD GLUCOSE



24h- glucose profiles in patients with type 2 diabetes HbA1c between 7% and 7.9%



GLUCOSE CONCENTRATION (mg/dl)

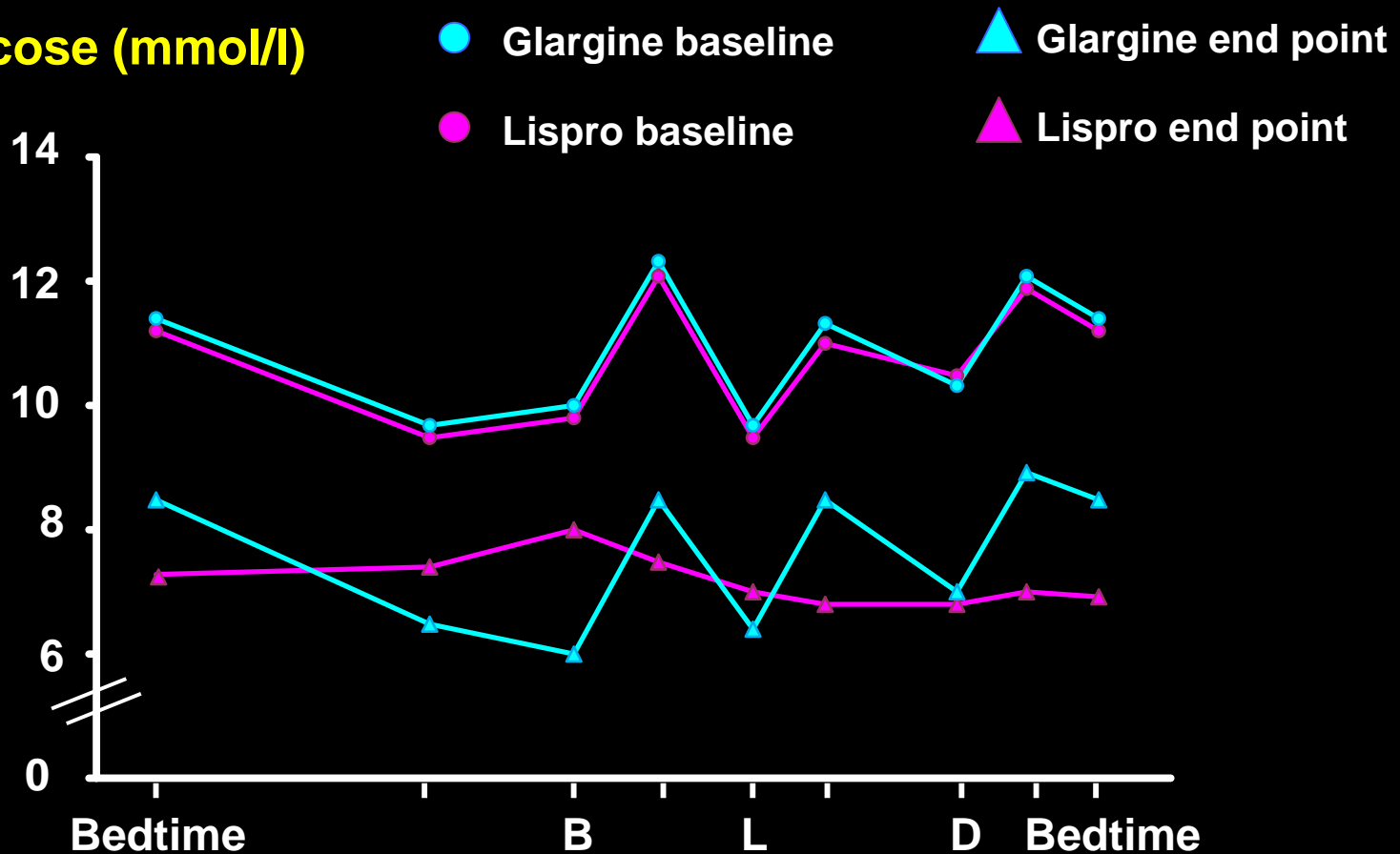


Continuous glucose monitoring before and after treatment with one single injection of **NOVO ASPART** at breakfast time

Comparisons of insulin regimens:

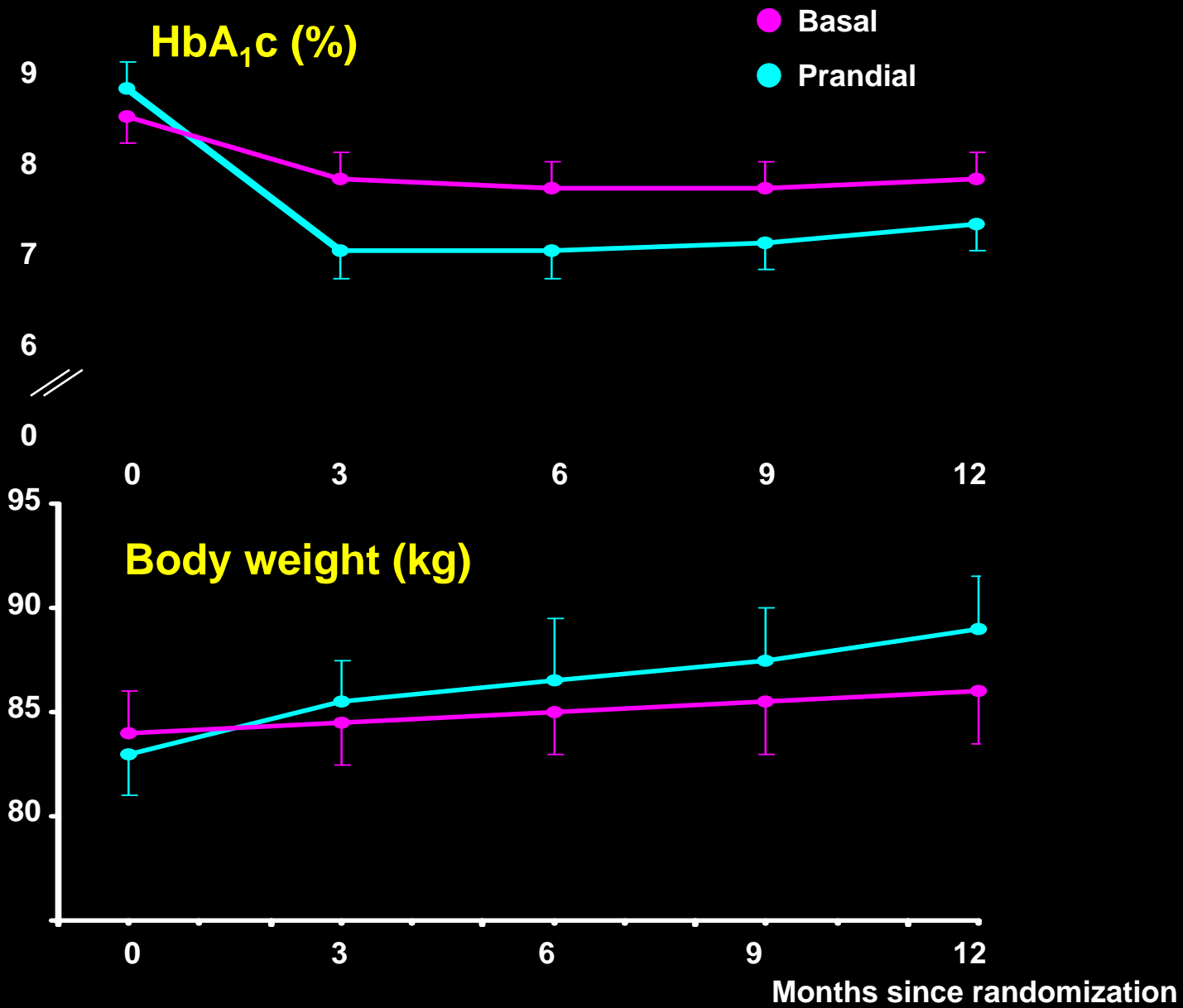
- **Basal once daily**
- **Intermediary with biphasic insulin twice daily**
- **Prandial thrice daily**

Blood glucose (mmol/l)



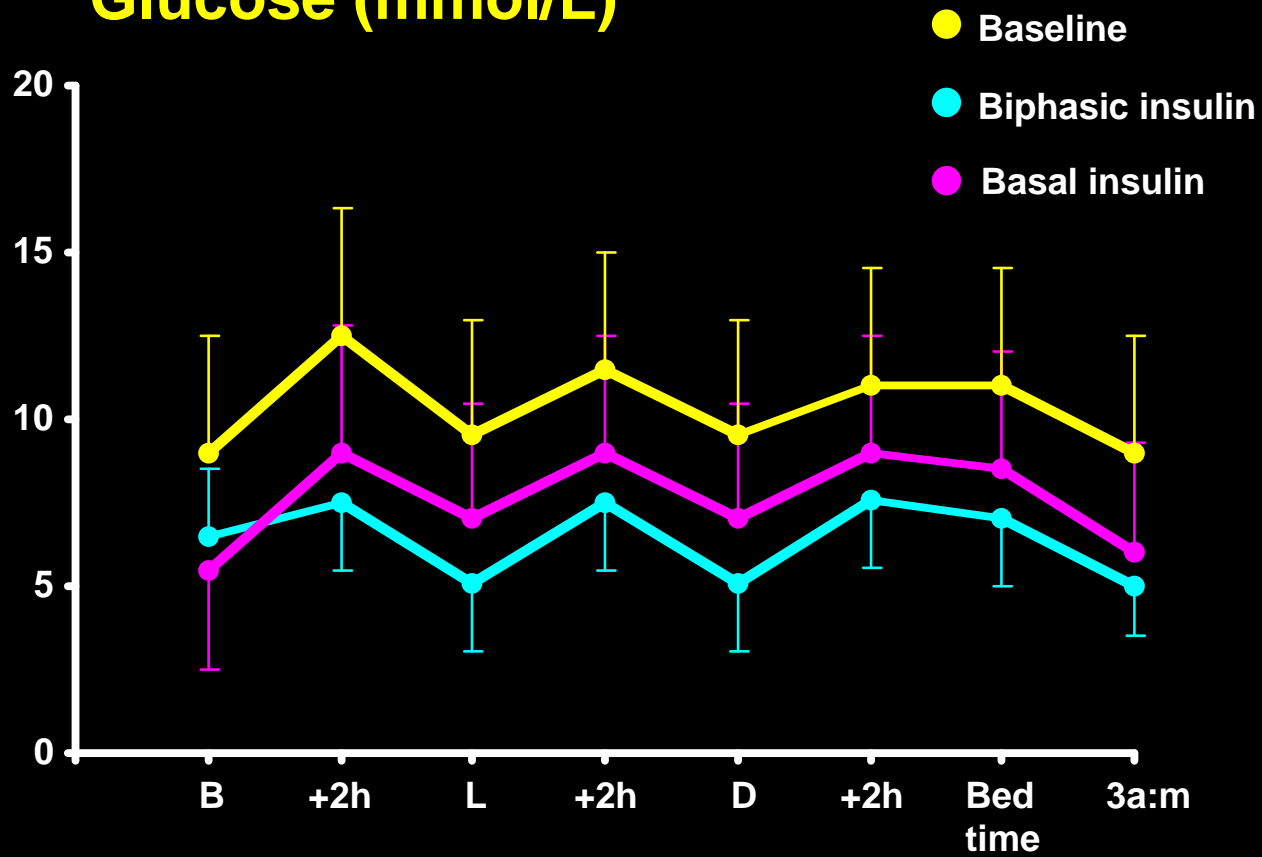
24h SMBG patterns at baseline and endpoint in insuline glargine and insulin lispro treatment groups (APOLLO)

Lancet 2008;371:1073-84

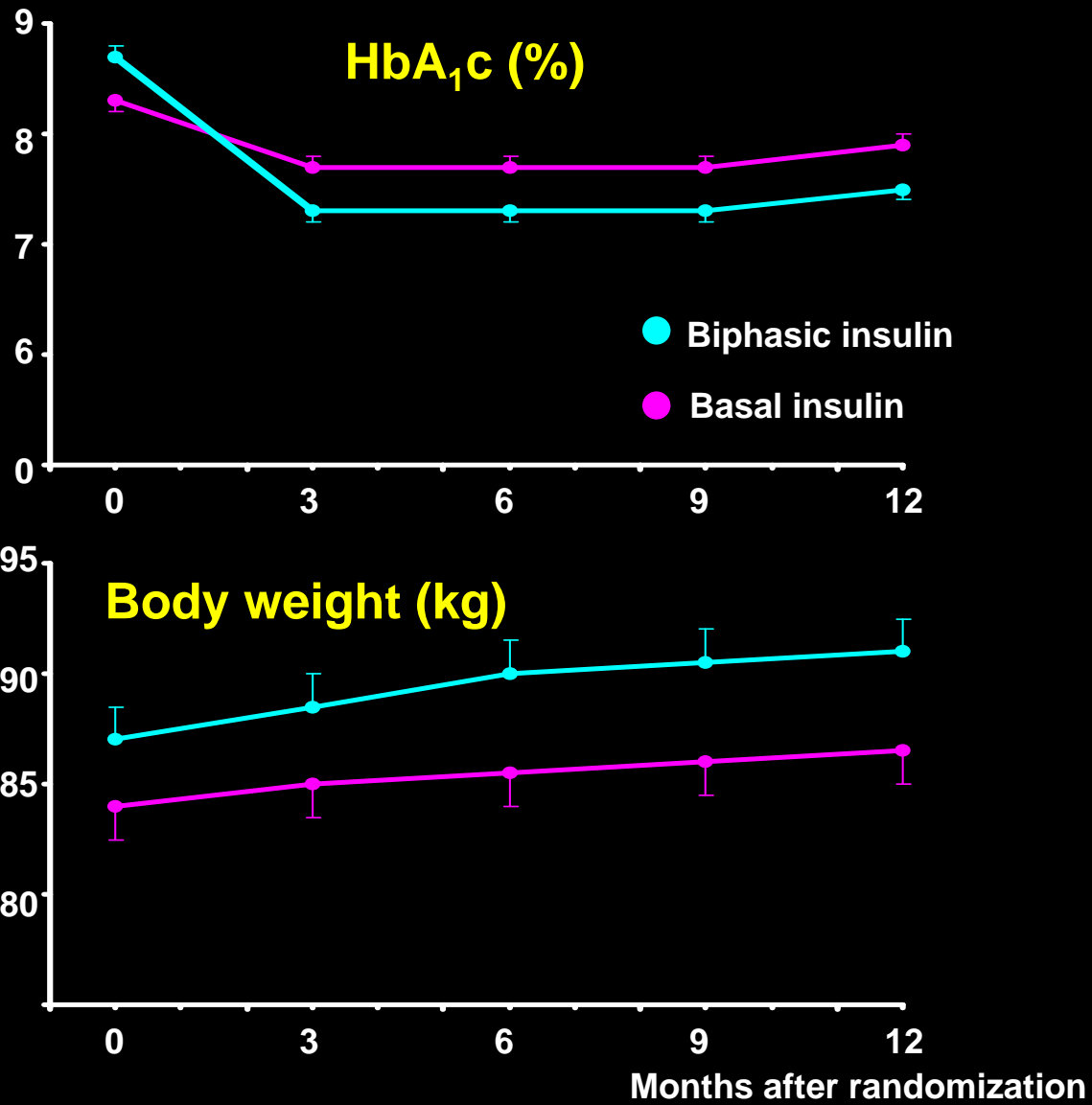


R.Holman et al N.Engl.J.Med. 2007;357:1716-1730







Glucose (mmol/L)



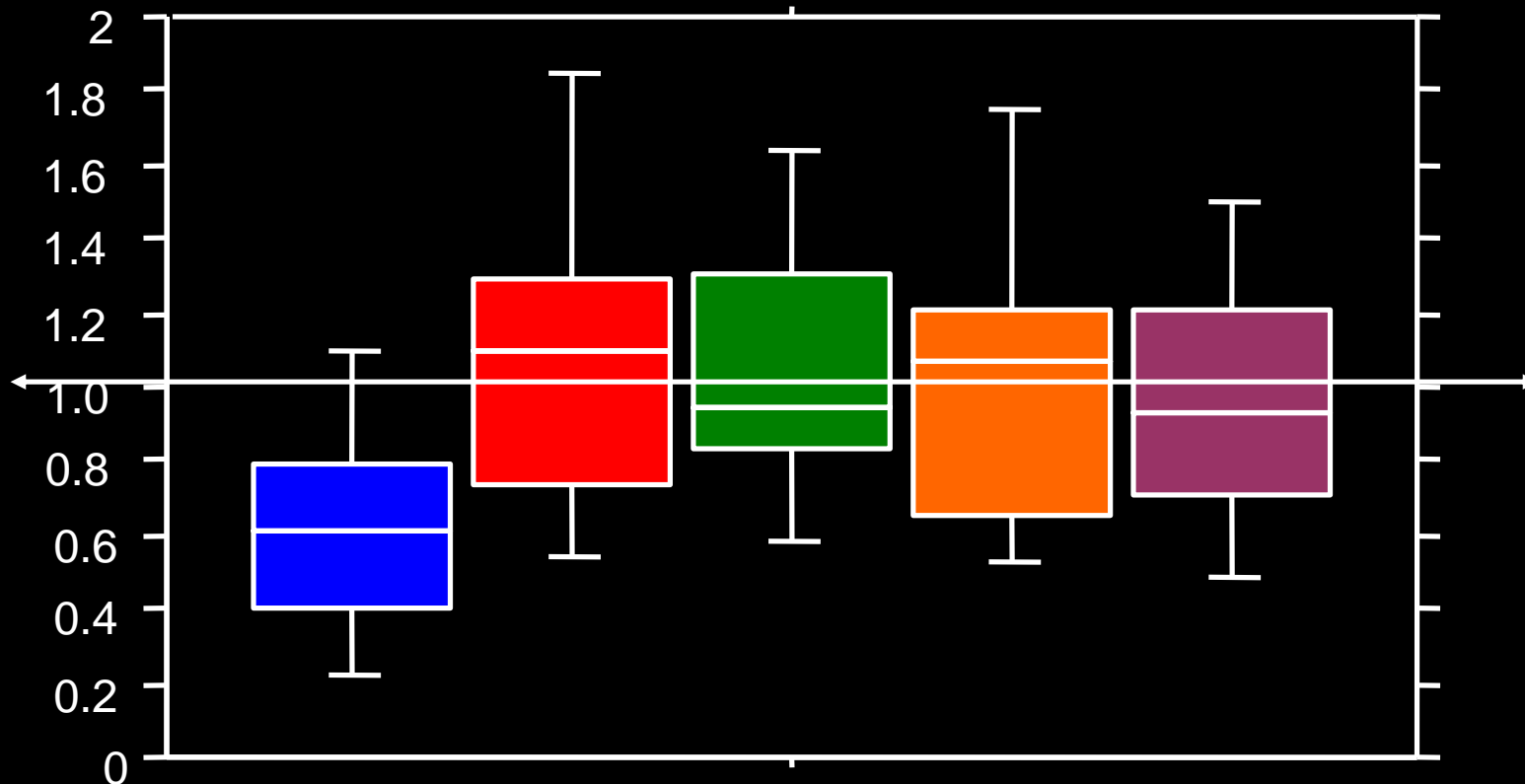
R.Holman et al N.Engl.J.Med. 2007;357:1716-1730



R.Holman et al N.Engl.J.Med. 2007;357:1716-1730

Parameters	HbA _{1c}	Glycemic variability	Hypos
APOLLO (GLARGINE) <ul style="list-style-type: none">• BASAL• PRANDIAL			
4-T (LEVEMIR) <ul style="list-style-type: none">• BASAL• PRANDIAL			

Absolute impact of PPG on HbA1c (%)



Groups

1

2

3

4

5

Mean HbA1c (%)

5.9

6.8

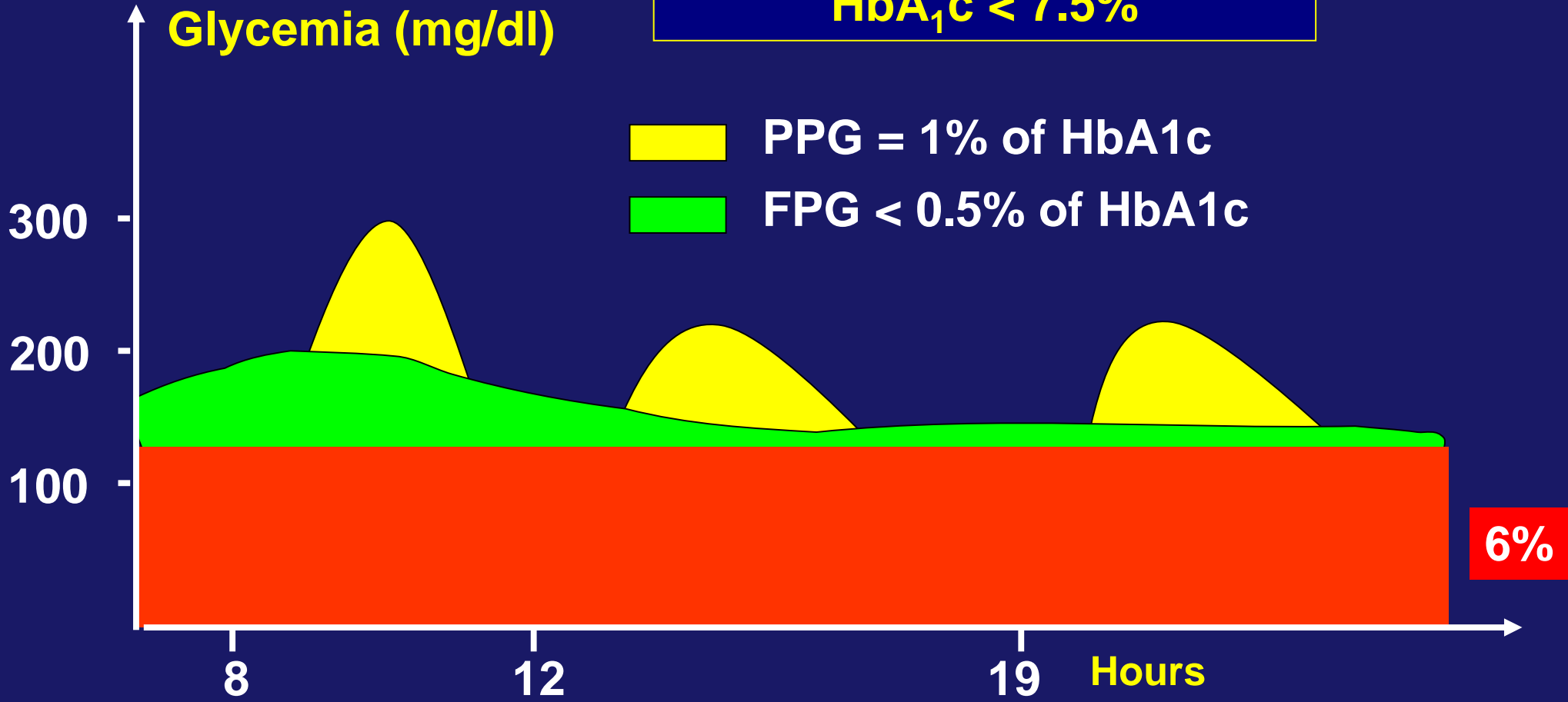
7.4

8.3

10.2

**Type 2 diabetic patient with
HbA_{1c} < 7.5%**

Glycemia (mg/dl)



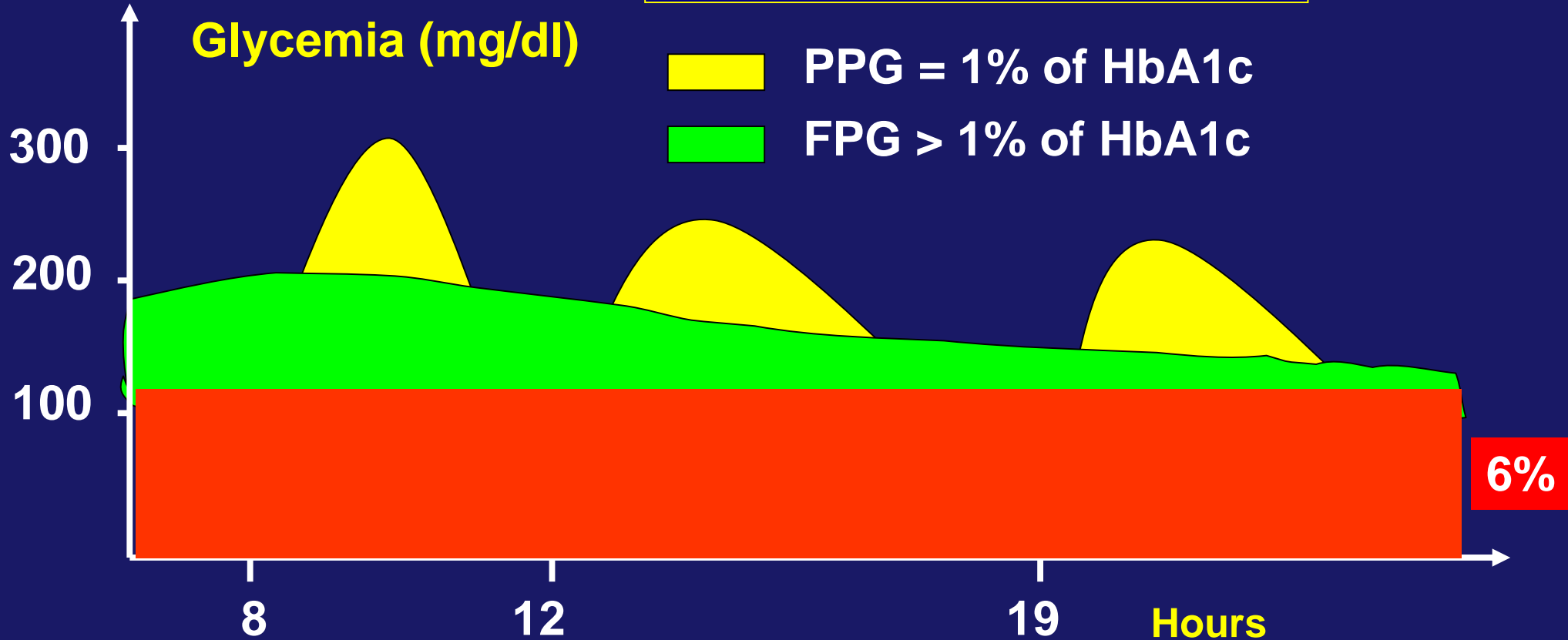
Postprandial > Basal hyperglycemia

Prandial insulin is more appropriate than basal insulin

**Type 2 diabetic patient with
HbA_{1c} > 8%**

Glycemia (mg/dl)

PPG = 1% of HbA_{1c}
FPG > 1% of HbA_{1c}



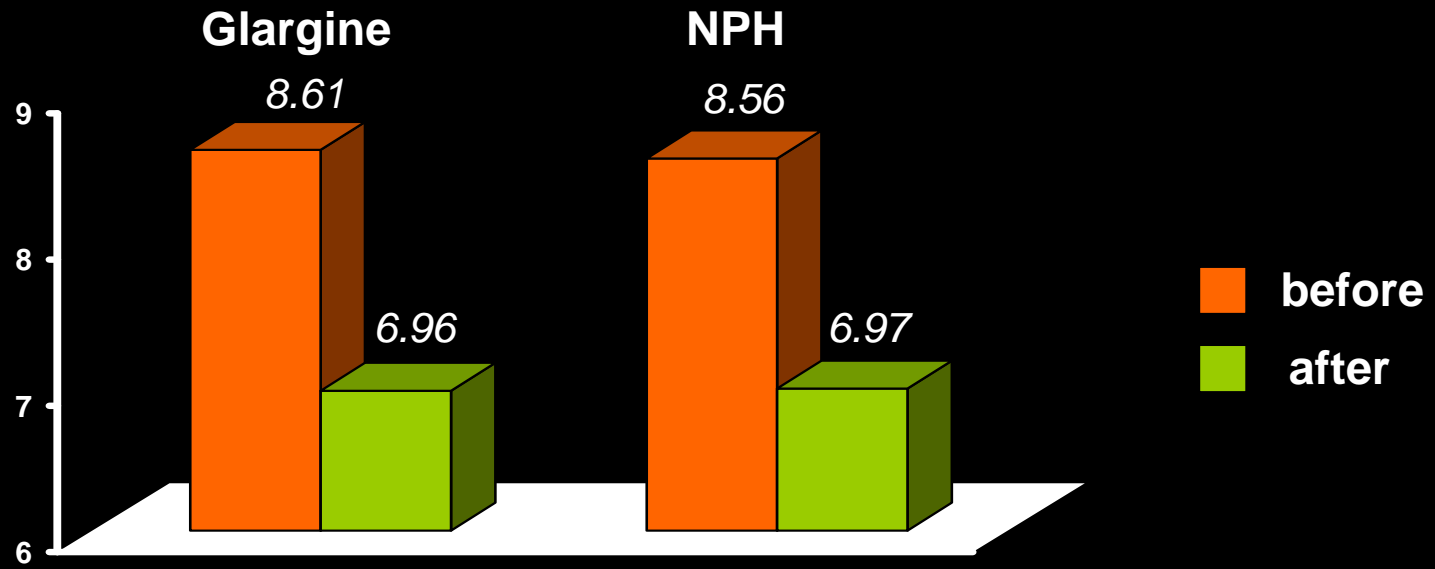
Basal > Postprandial Hyperglycemia

**Basal insulin is more appropriate than prandial insulin.
However prandial insulin should be added to basal insulin
as soon as HbA_{1c} becomes lower than 7.5% on basal insulin**

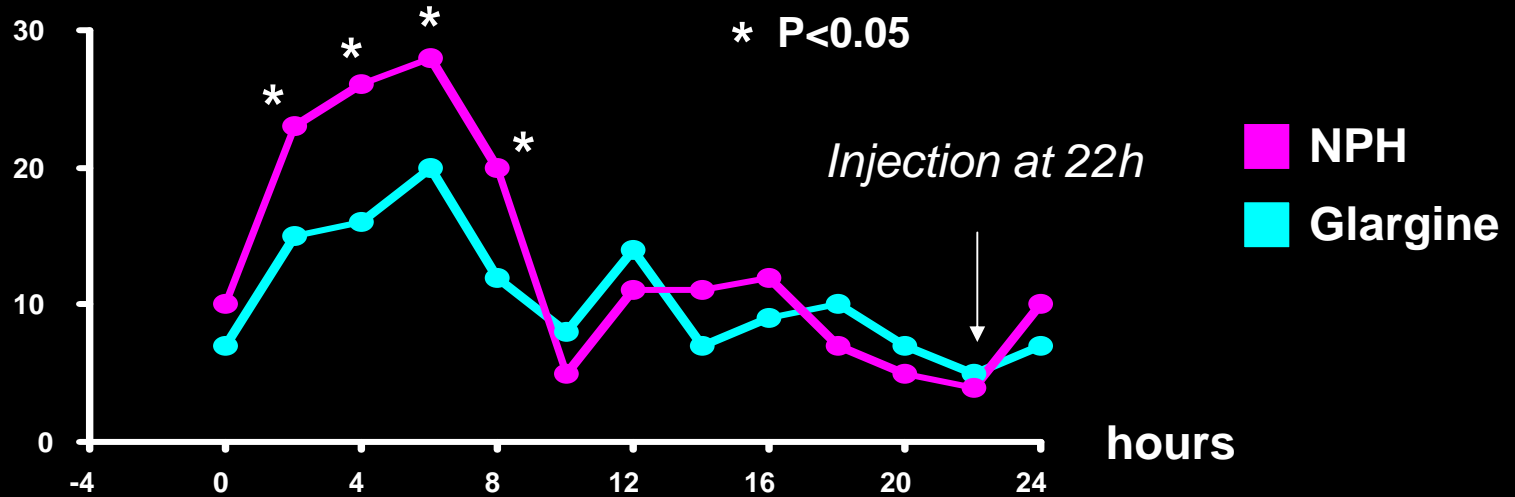
THE COMPONENTS OF SAFETY

- **THE RISK FOR HYPOGLYCEMIC EPISODES**
- **THE RISK FOR BODY WEIGHT GAIN**

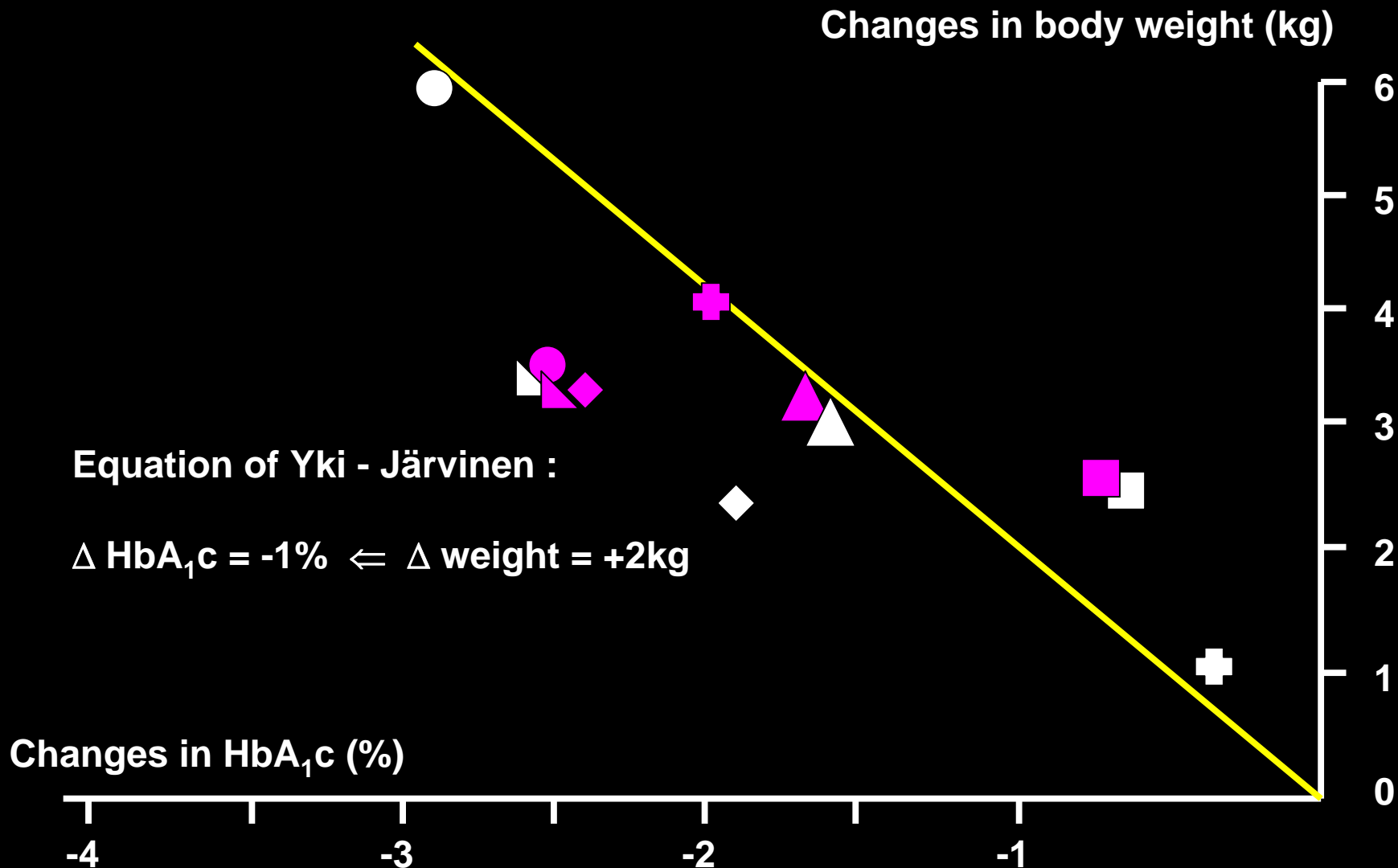
HbA_{1c} (%)



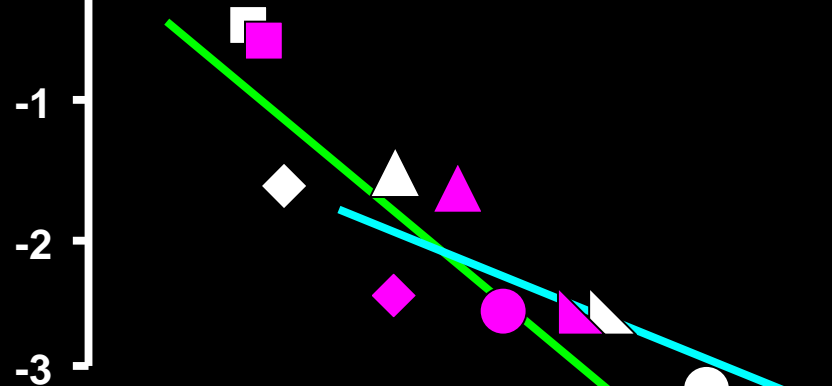
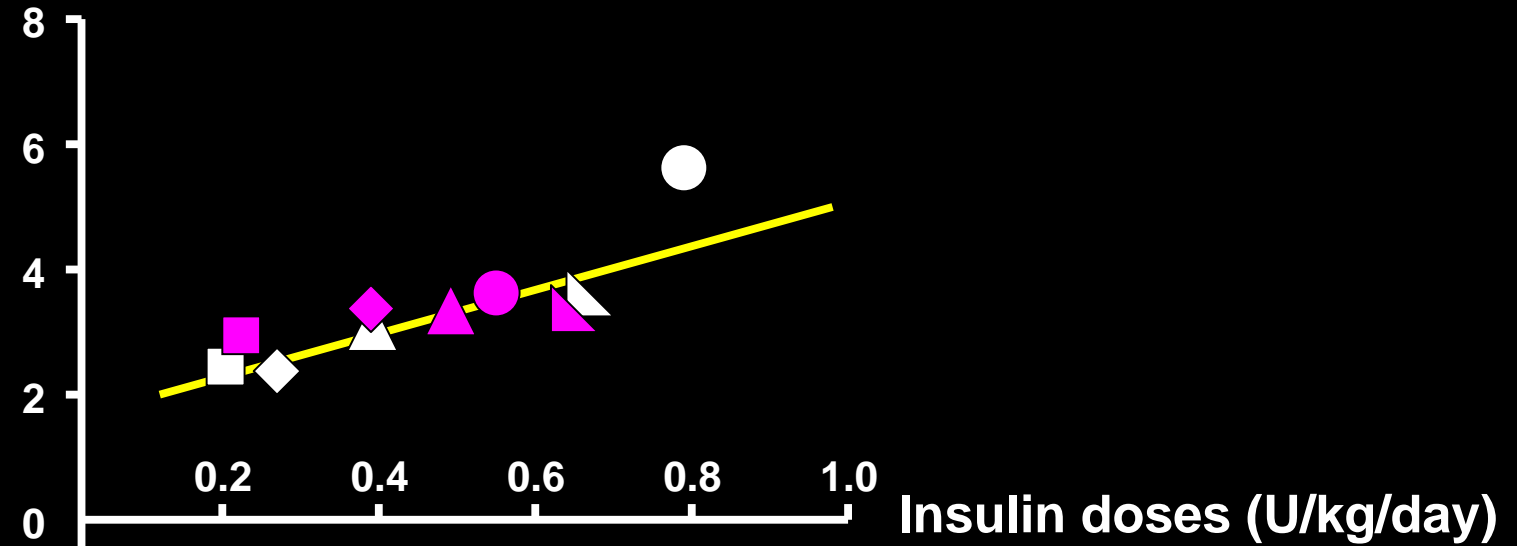
Percentage of patients with plasma glucose < 72mg/dl



Relationship between decrements in HbA_{1c} and weight gain



Changes in body weight (kg)



Changes in HbA_{1c} (%)

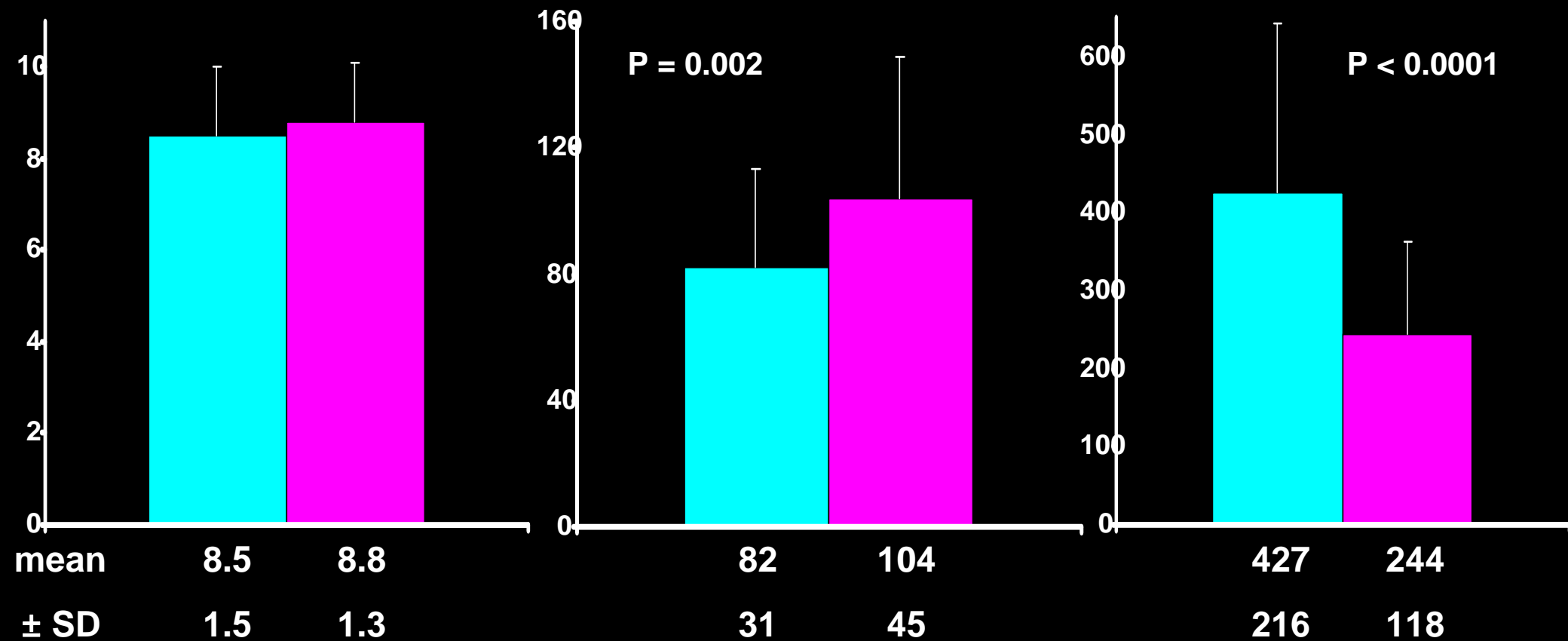
Insulin doses vs weight gain (upper panel) and vs decrements in HbA_{1c} (lower panel).

Monnier L ,Colette C. Diabetes Metab. 2006;32:7-13

HbA_{1c} (%)

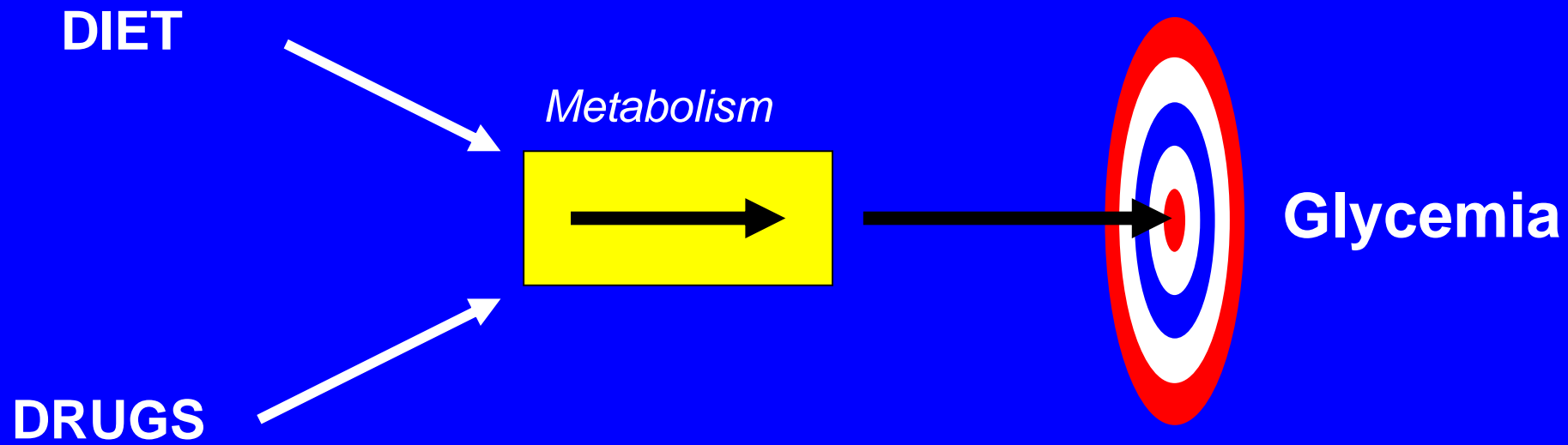
MAGE (mg/dl)

8-isoPGF₂∞

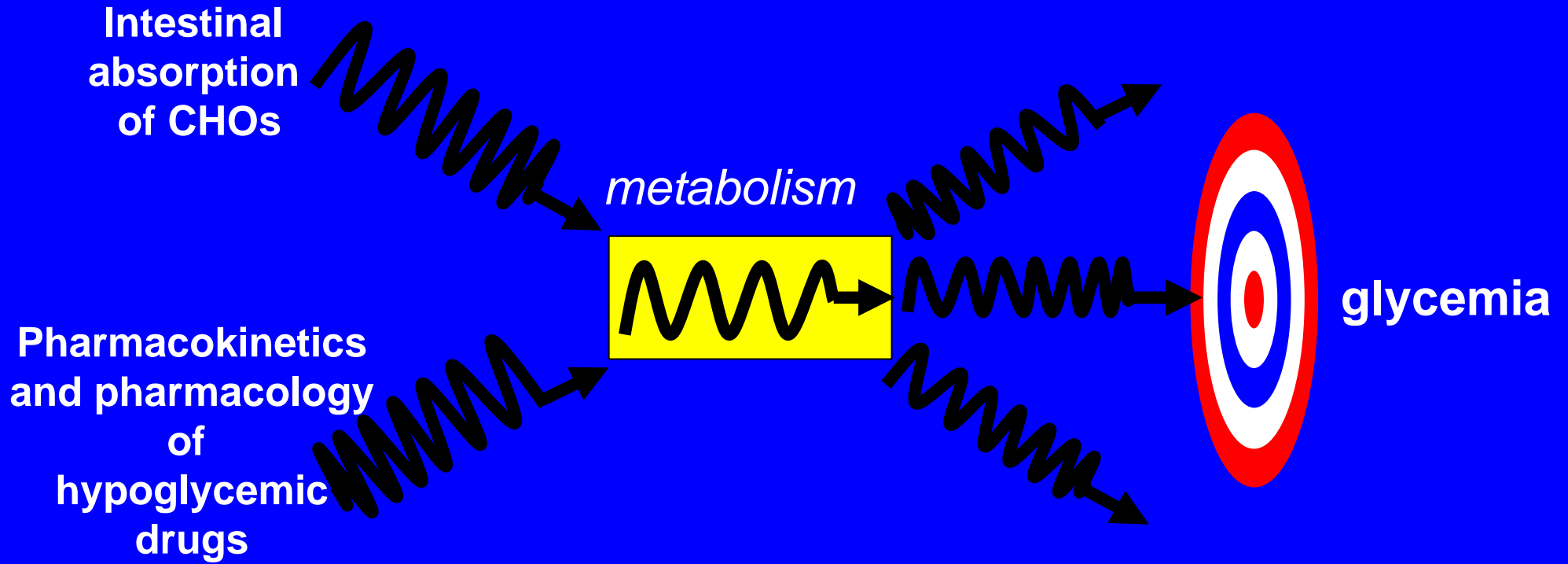


Comparisons of HbA_{1c}, MAGE and urinary excretion rates of 8-isoPGF₂∞ in Type 2 diabetes treated with OHAs alone (n=60) and Type 2 diabetes treated with OHAs + insulin (n=32)

The limitations of insulin therapy are mainly due to the fact that we are always in the search of deterministic solutions for stochastic phenomena (metabolic events and pharmacological treatments) that are governed by probability.



DETERMINISTIC MODEL



STOCHASTIC MODEL



Old medical school of Montpellier founded in the XIIIth century