“Nuove evidenze sul controllo della variabilità glicemica nel DMT2”

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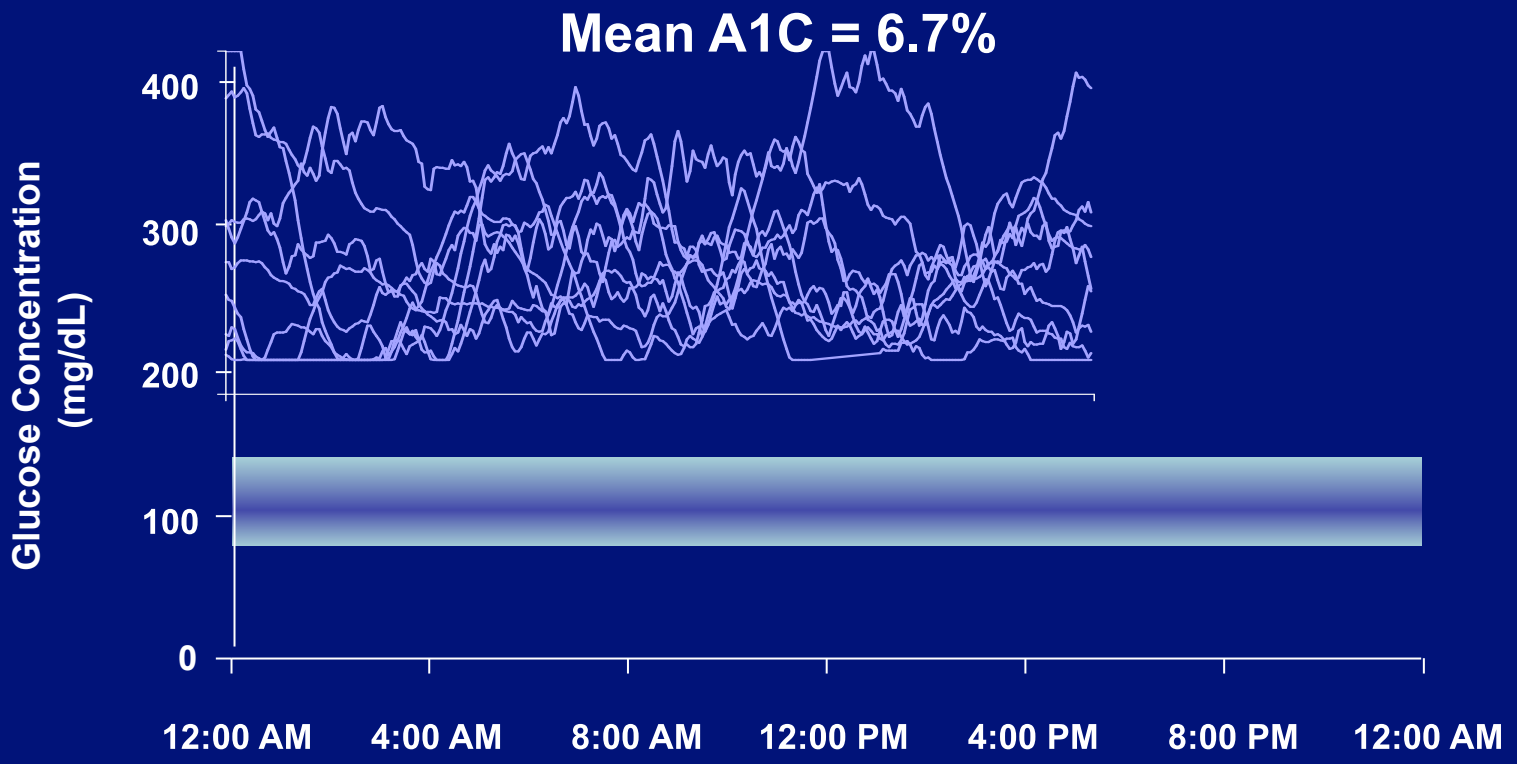
August Pi i Sunyer

Excessive Glucose Fluctuations With Same A_{1C} Values



24-h CGMS glucose sensor data in 9 subjects with type 1 diabetes

Type 1 diabetes (N = 9)

Common measures of glucose variability

- Consecutive fasting blood glucose (FBG) values
  - SD or CV of FBG values
- Self-monitoring blood glucose (SMBG) profiles
  - SD or CV of blood glucose values
  - Average daily risk range
    - Computed average daily blood glucose range over 30 days
- Continuous glucose monitoring system (CGMS)
  - Mean blood glucose levels
  - SD of blood glucose levels
  - Mean amplitude of glucose excursions (MAGEs)
    - Measured as the mean of the differences between consecutive peaks and dips provided that the differences are greater than 1 SD of the mean glucose value

SD, standard deviation; CV, coefficient of variation

EVIDENCE IN TYPE 1 DIABETES

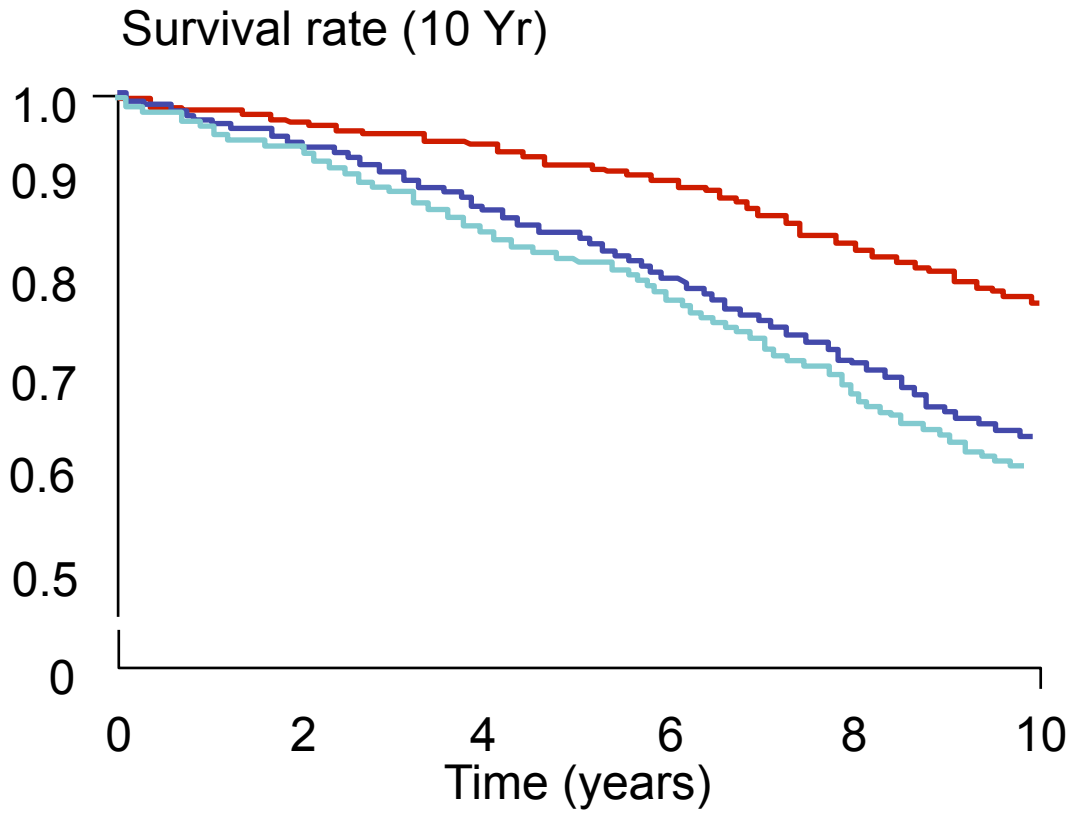
Kilpatrick reported:

- **that glycemic instability is not a predictor of microvascular complications in patients from the DCCT (Diabetes Care 2006; 29:1486-90).**

- **that mean daily glucose as well as pre and postprandial hyperglycaemia are predictors for cardiovascular disease in the same cohort (Diabetologia 2008; 51:365-71).**

- **more recently, that HbA1c instability is a predictor of microvascular complications in the same patient cohort (Diabetes Care 2008; 31:2198-202).**

Variability of blood glucose and CV mortality in Type 2 diabetes



Variability of fasting glucose

Group 1 (8.5%)

Group 2 (14.8%)

Group 3 (27.7%)

Verona Diabetes Study

Muggeo M et al. Diabetes Care. 2000;23:45-50

Time-dependent variation of fasting plasma glucose is a strong predictor of all-cause and cause-specific mortality in patients with Type 2 diabetes mellitus: The Taichung Diabetes Study

METHODS:
A computerized database of all patients with type 2 diabetes aged 30 years and over (n = 5008) enrolled in the Diabetes Care Management Program of China Medical University Hospital before 2007 was used in a time-dependent Cox proportional hazard regression model.

Lin CC et al. Am J Med, 2012

Time-dependent variation of fasting plasma glucose is a strong predictor of all-cause and cause-specific mortality in patients with Type 2 diabetes mellitus: The Taichung Diabetes Study

CONCLUSIONS:
Time-dependent variation of FPG was a strong predictor of all-cause, expanded, and nonexpanded cardiovascular disease-related mortality in patients with type 2 diabetes, suggesting that glucose variation may become a measure in clinical practice for the goal in the management of these patients.

Lin CC et al. Am J Med, 2012

Annual fasting plasma glucose variation increases risk of cancer incidence and mortality in patients with type 2 diabetes: the Taichung diabetes study.

A computerized database of patients with type 2 diabetes 30 years old and older (n = 4,805) enrolled in the Diabetes Care Management Program of a medical center before 2006 was analyzed using a time-dependent Cox's proportional hazards regression model.

Lin CC et al. Endocr Relat Cancer, 2012

Impact of glycemic and blood pressure variability on surrogate measures of cardiovascular outcomes in type 2 diabetic patients.

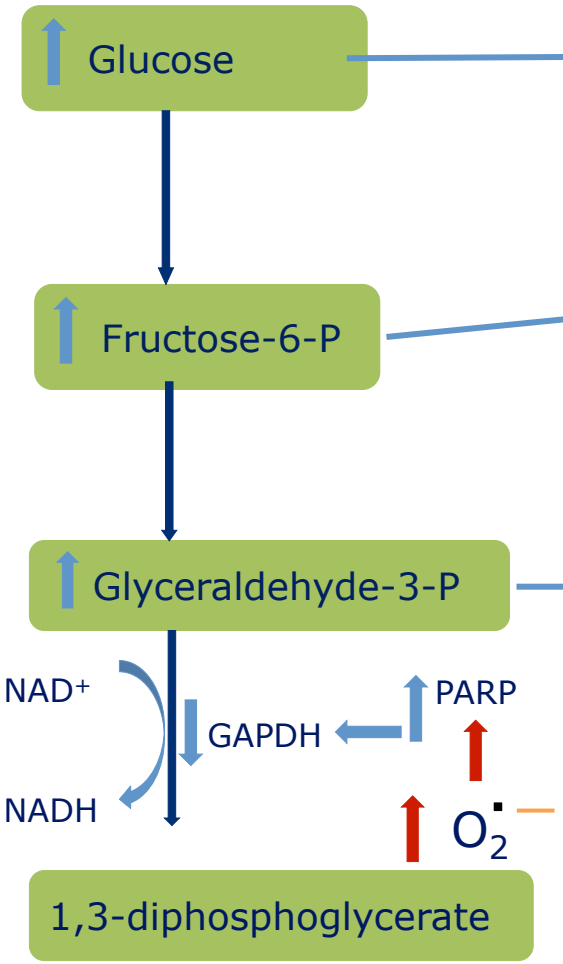
- ***CONCLUSIONS:***
- An impaired GV and BP variability is associated with endothelial and cardiovascular damage in short-term diabetic patients with optimal metabolic control. Oxidative stress is the only independent predictor of increased LV mass and correlates with glucose and BP variability.

D. Flaviani et al. Diabetes Care 2011: 34: 1605-1609

Glucose Variability and Diabetic Complications

Which Mechanisms ?

Four pathways of hyperglycaemic damage



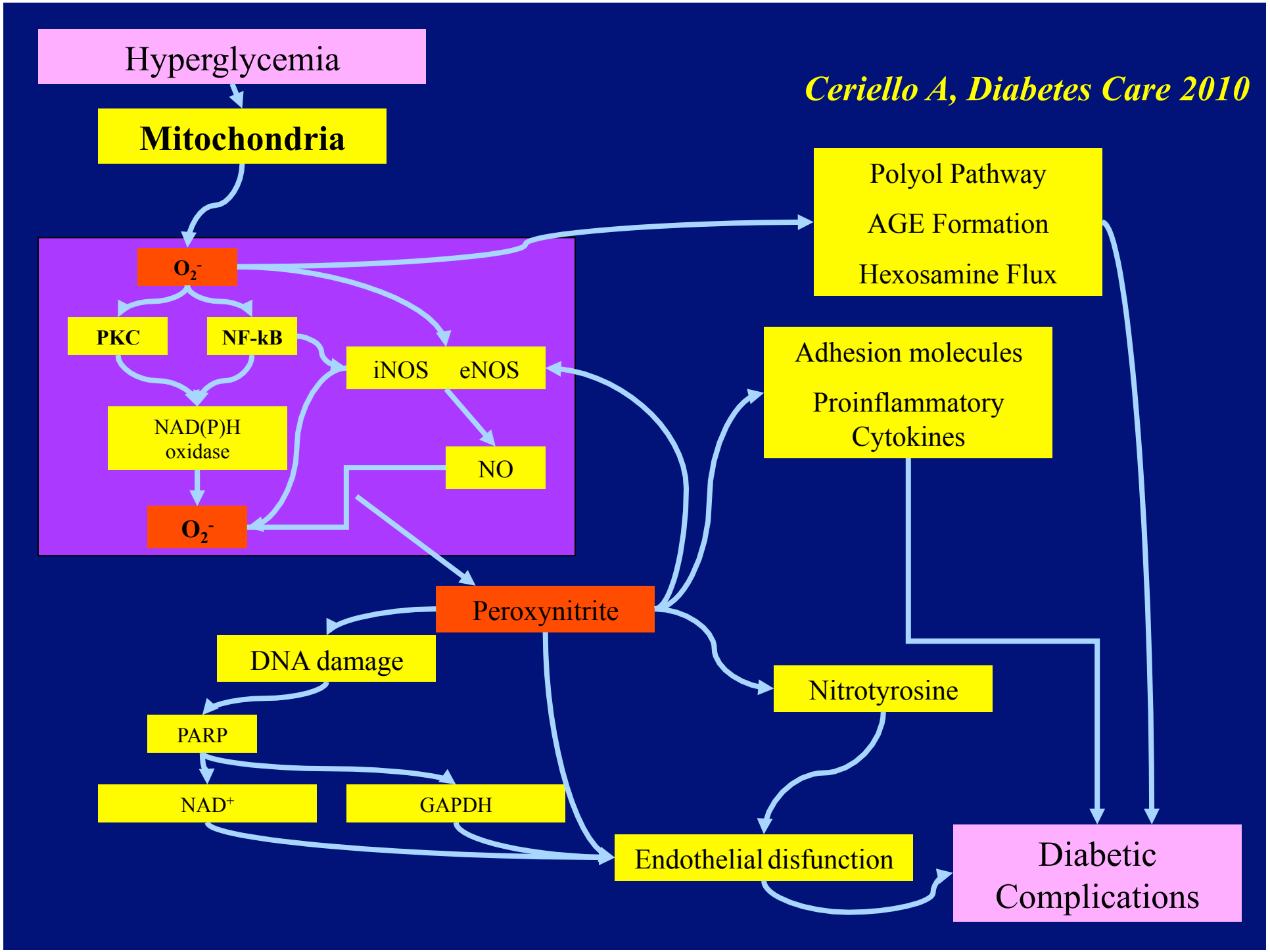
Polyol pathway: depletes NADPH, resulting in decreased nitric oxide and glutathione and increased ROS concentrations

Hexosamine pathway: increased production of N-acetyl glucosamine alters signalling pathways, leading to induction of transcription factors

PKC pathway: results in bloodflow abnormalities, capillary occlusion and proinflammatory gene expression

AGE pathway: end products alter intracellular signalling, activate inflammatory pathways and promote extracellular fibrosis

Brownlee. *Nature* 2001;414:813–20; Giardino *et al*. *J Clin Invest* 1994;94:110–7;
Abordo *et al*. *Immunol Lett* 1997;58:139–47; Charonis *et al*. *Diabetes* 1990;39:807–14


Hyperglycemia
Mitochondria
Ceriello A, Diabetes Care 2010
Polyol Pathway
AGE Formation
Hexosamine Flux
O2-
PKC
NF-kB
iNOS
eNOS
NAD(P)H oxidase
NO
O2-
Adhesion molecules
Proinflammatory Cytokines
Peroxynitrite
DNA damage
Nitrotyrosine
PARP
NAD+
GAPDH
Endothelial disfunction
Diabetic Complications

Intermittent high glucose enhances apoptosis in human umbilical vein endothelial cells in culture.

Risso A, Mercuri F, Quagliaro L, Damante G, Ceriello A.

Am J Physiol, 2001

STUDY DESIGN:

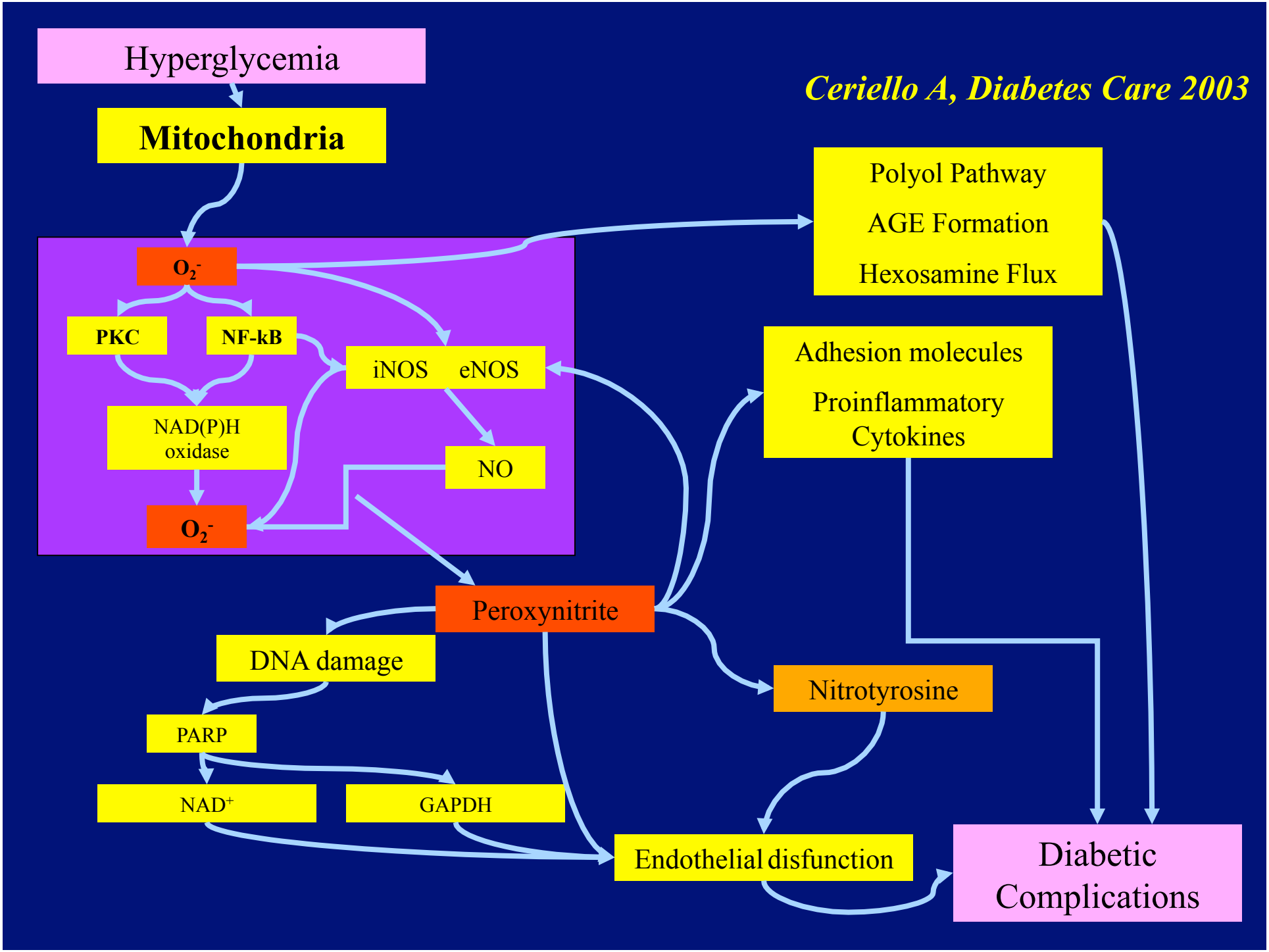
Normal glucose (5mM)

High glucose (20mM)

Alternating glucose (5/20mM)

14 days

Cell death of HUVECs cultured with different concentrations of glucose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Ceriello A, Diabetes Care 2003
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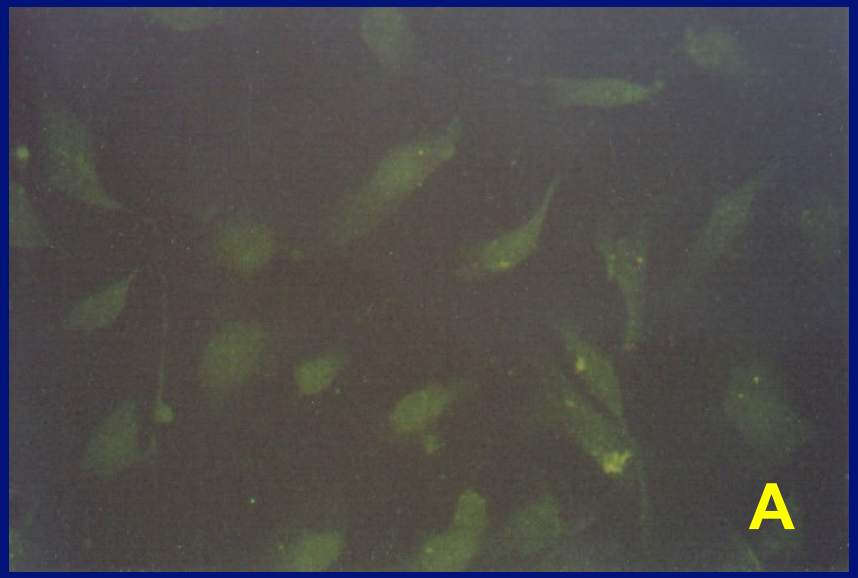
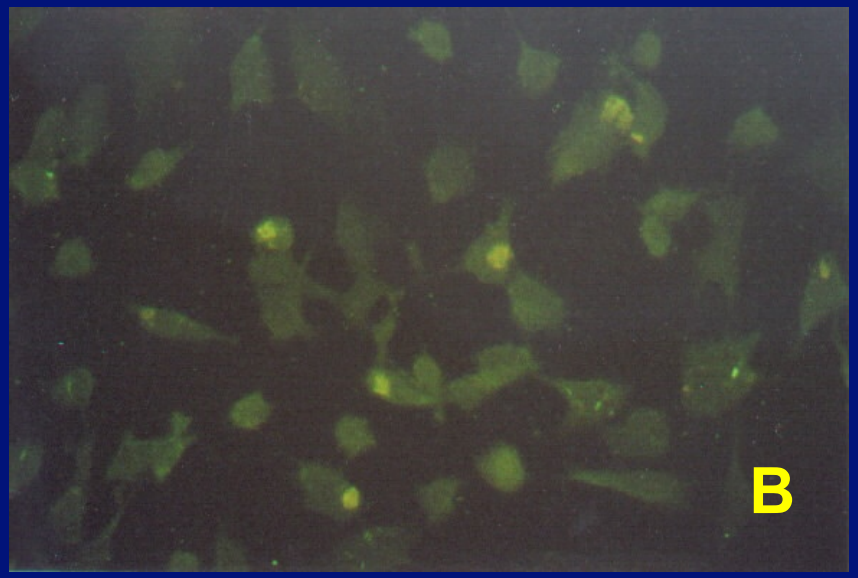
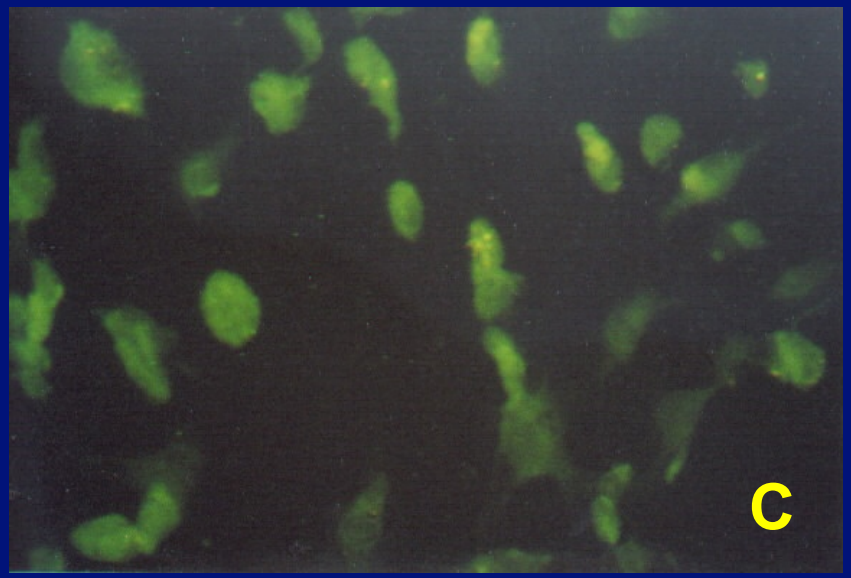
Endothelial disfunction
Diabetic Complications

Immunocitochemestry for NT



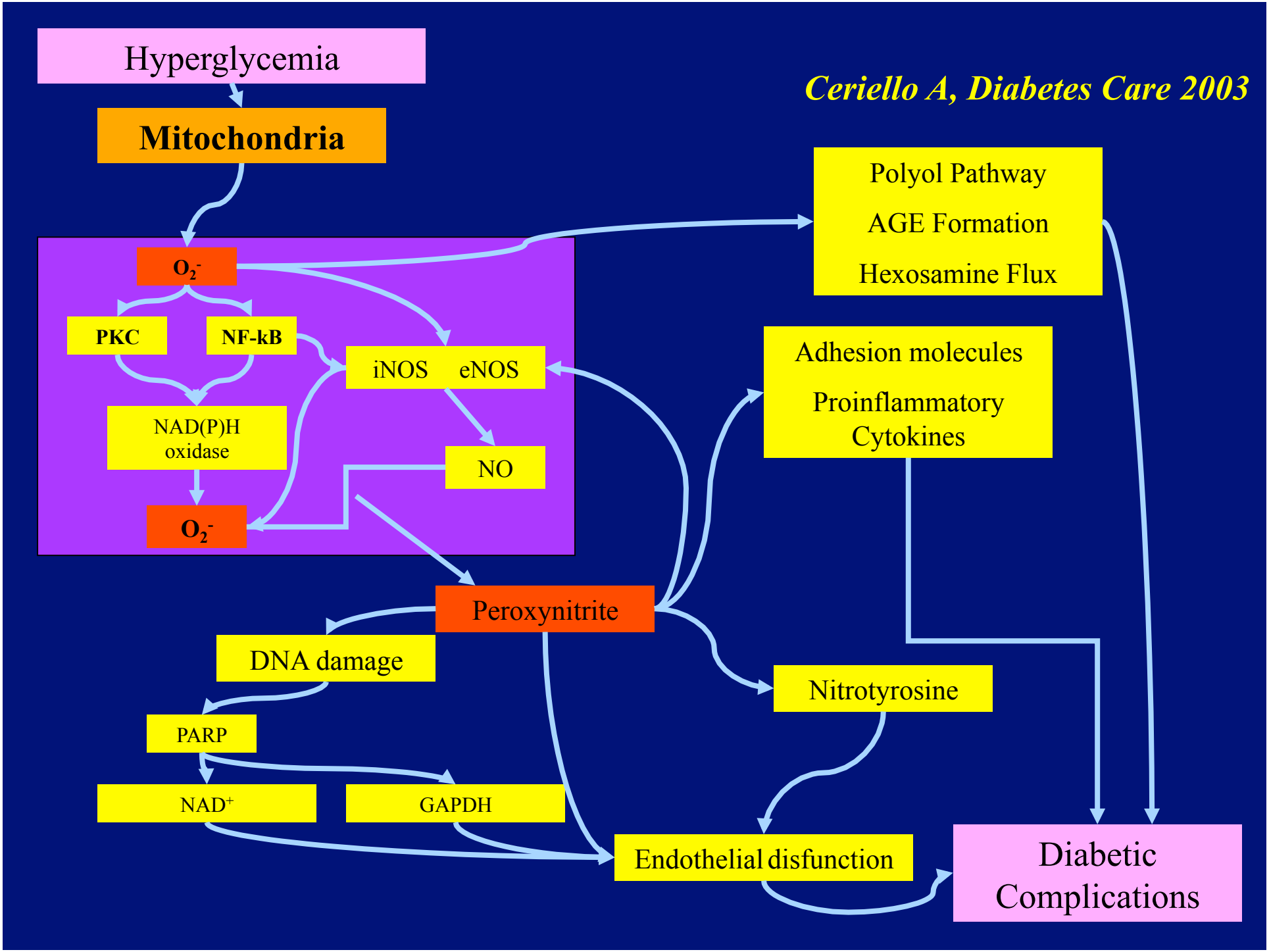




A= normal glucose **(5mM)**

B= high glucose **(20mM)**

C= intermittent glucose **(5-20mM)**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Adhesion molecules
Proinflammatory Cytokines
Peroxynitrite
DNA damage
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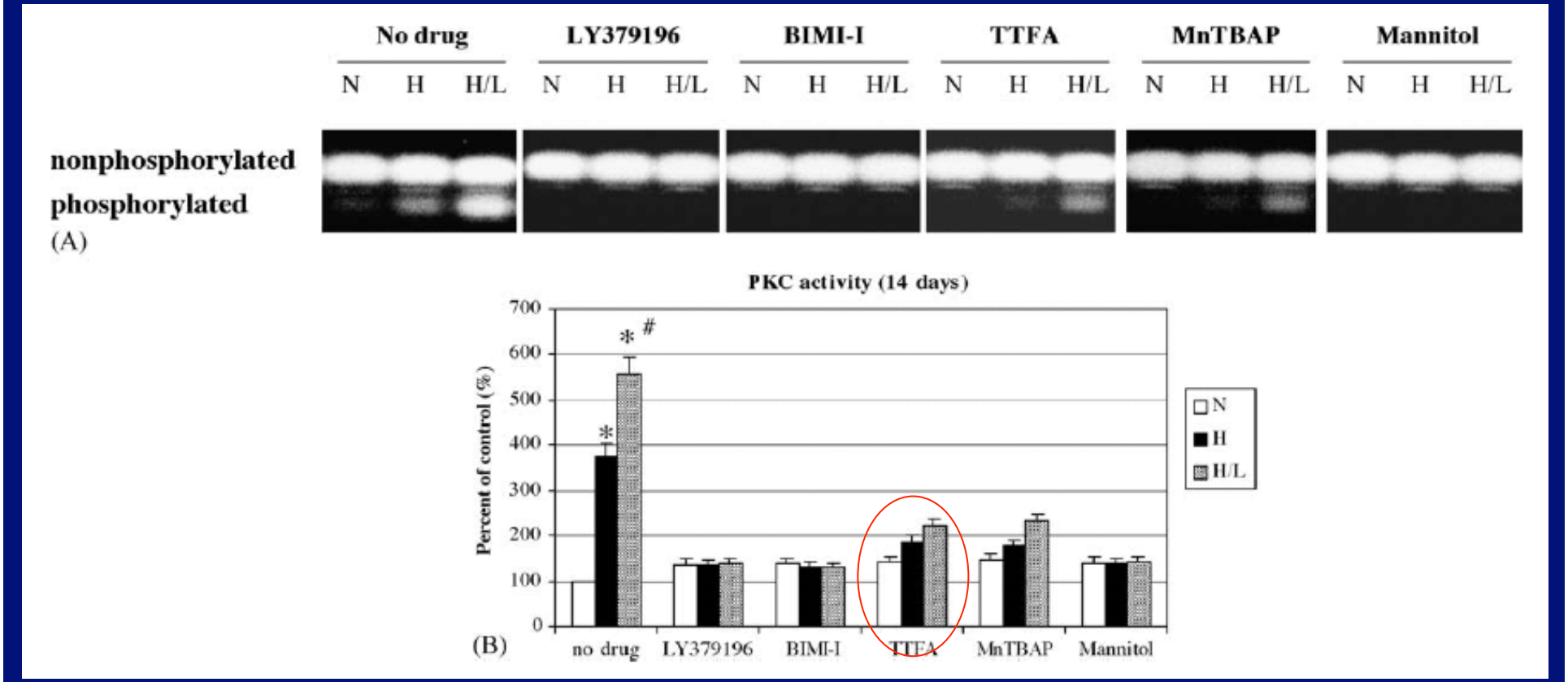
GAPDH
Endothelial disfunction
Diabetic Complications

Protein kinase C activity after 14 days of experiment.



(A) Representative gel for protein kinase C activity detection after 14 days of experiment. (B) Quantitation of Protein kinase C activity by densitometry after 14 days of experiment.

L. Quagliaro et al. Atherosclerosis 183 (2005) 259–267

Animal Studies

Azuma K, Kawamori R, Toyofuku Y, Kitahara Y, Sato F, Shimizu T, Miura K, Mine T, Tanaka Y, Mitsumata M, Watada H. Repetitive fluctuations in blood glucose enhance monocyte adhesion to the endothelium of rat thoracic aorta.

Arterioscler Thromb Vasc Biol 2006; 26: 2275-2280

Mita T, Otsuka A, Azuma K, Uchida T, Ogihara T, Fujitani Y, Hirose T, Mitsumata M, Kawamori R, Watada H.

Swings in blood glucose levels accelerate atherogenesis in apolipoprotein E-deficient mice.

Biochem Biophys Res Commun 2007; 358: 679-685

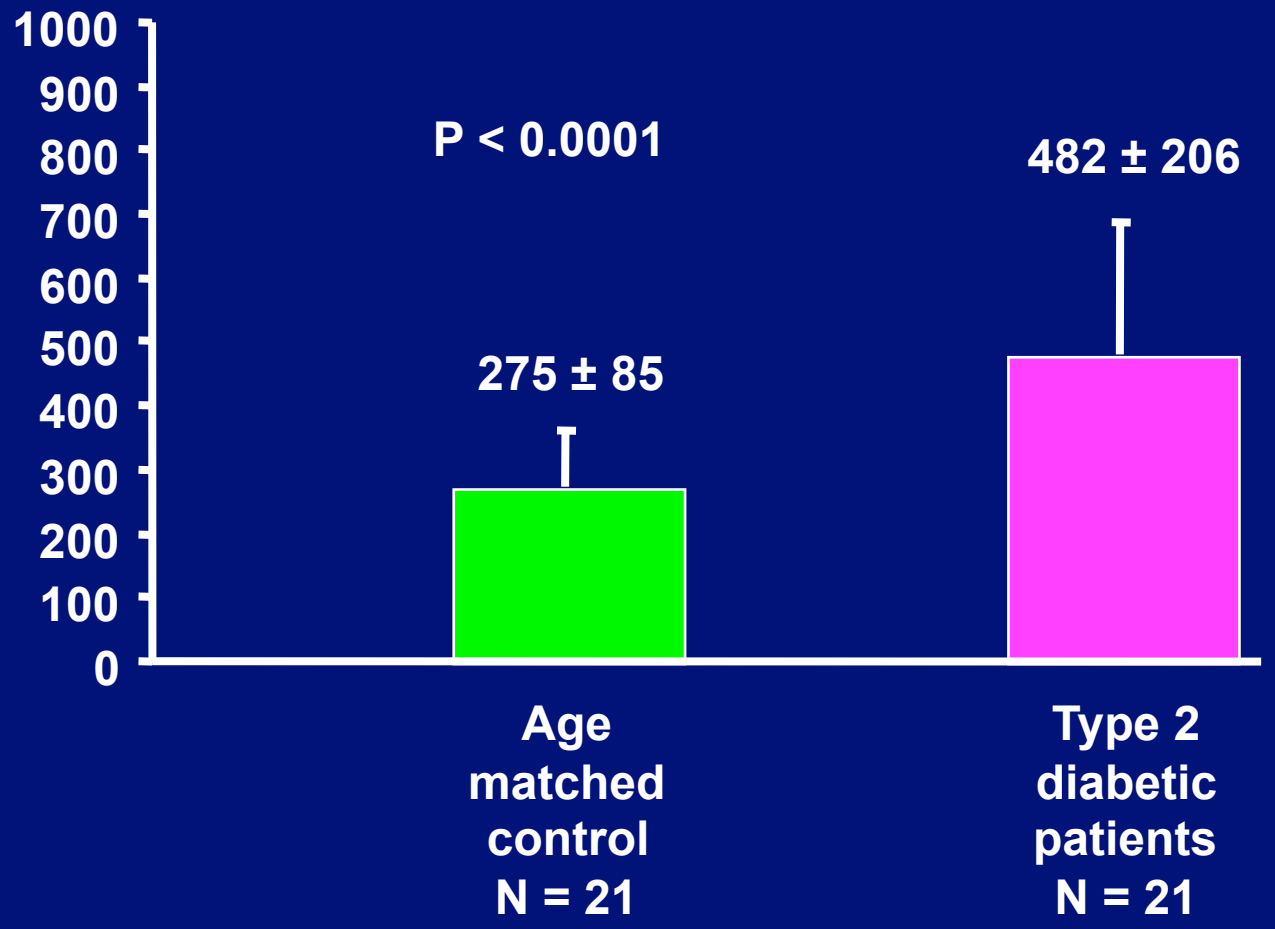
Horváth EM, Benkő R, Kiss L, Murányi M, Pék T, Fekete K, Bárány T, Somlai A, Csordás A, Szabo C.

Rapid “glycaemic swings” induce nitrosative stress, activate poly(ADP-ribose) polymerase and impair endothelial function in a rat model of diabetes mellitus.

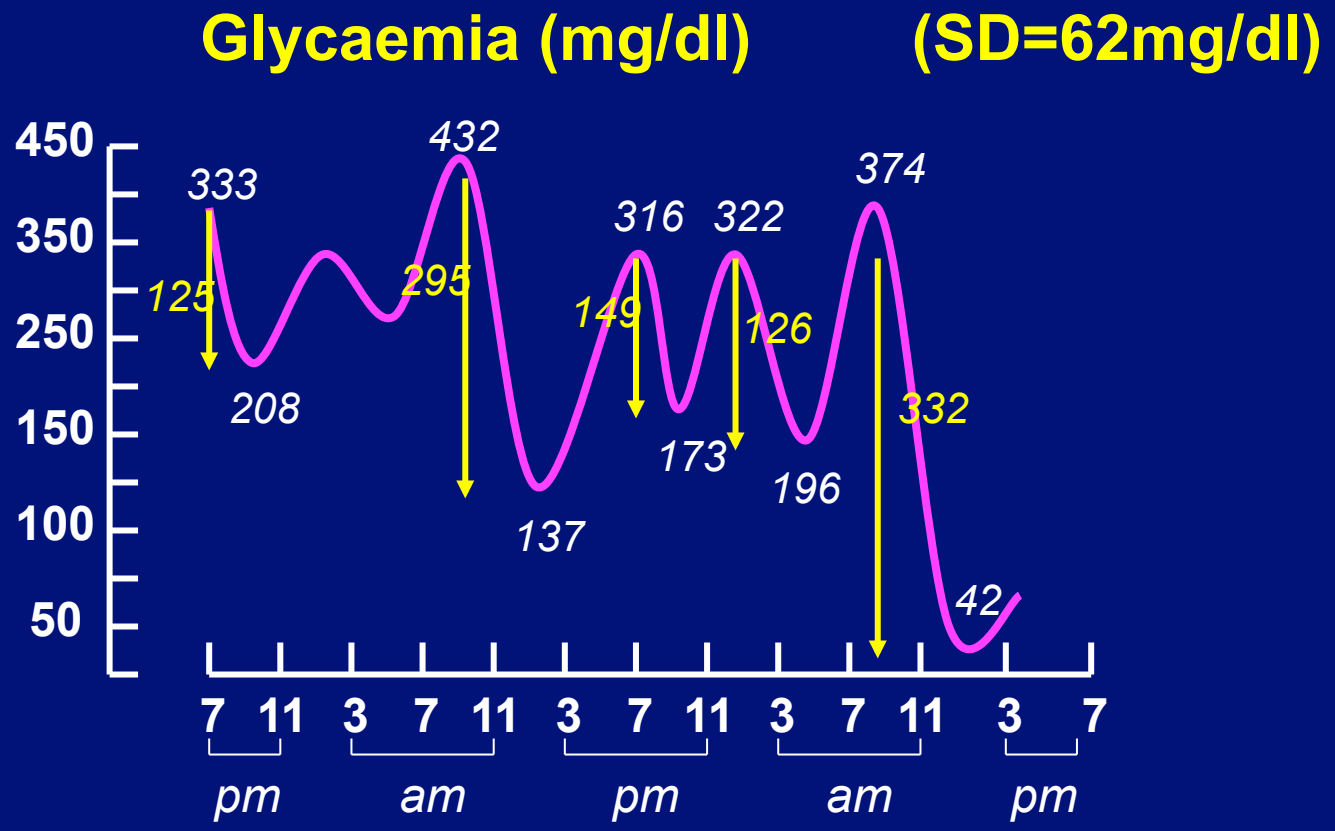
Diabetologia. 2009 Mar 5. [Epub ahead of print]

“The Role of Oxidative Stress : The Clinical Evidences”

Urinary excretion rates of isoprostanes (pg/mg creatinine)



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



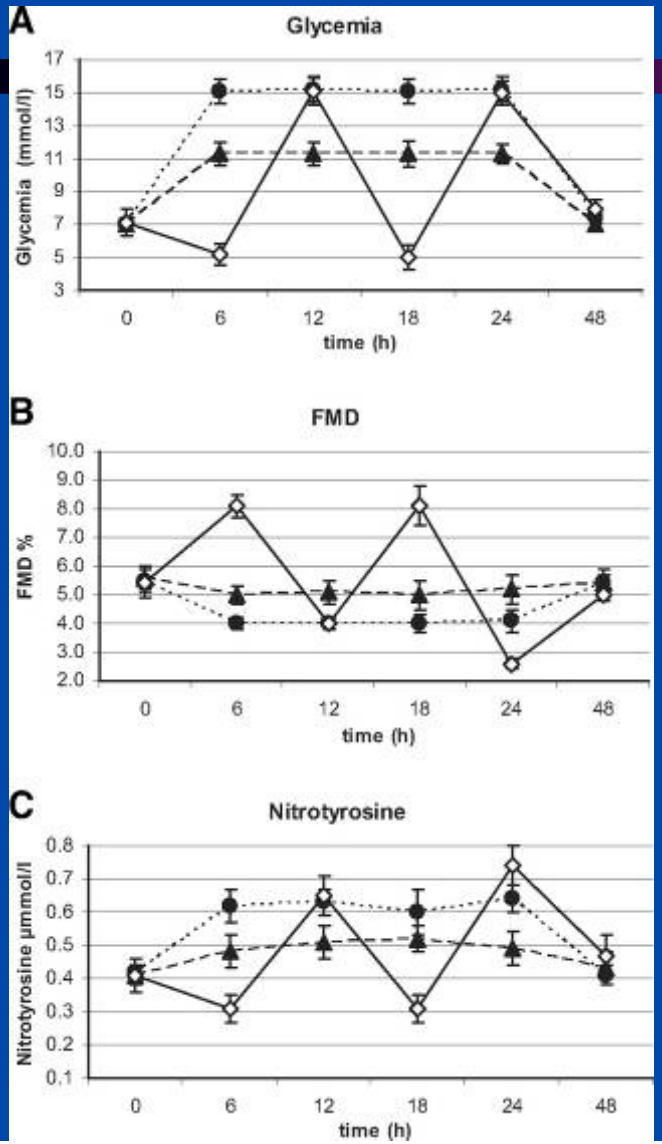
Principle of MAGE assessment
(from Molnar et Service)

Postprandial spikes and glucose ‘swings’ linked to oxidative stress generation

Factor	Multiple regression analysis (*P* value)
FPG (fasting glucose plasma)	NS
Mean glucose level	NS
HbA_{1C}	NS
Fasting plasma insulin level	NS
MAGE (mean amplitude of glycaemic excursions)	**<0.001**
AUCpp (area under curve attributable to PPG)	**= 0.009**
Total Cholesterol	NS
HDL-C	NS
LDL-C	NS
Triglycerides	NS
Free fatty acids	NS

Monnier et al. *JAMA* 2006; 295:1681–1687.

Effect of GV on FMD and oxidative stress



27 patients with type 2 diabetes

…… 15mmol/L

---------10mmol/L

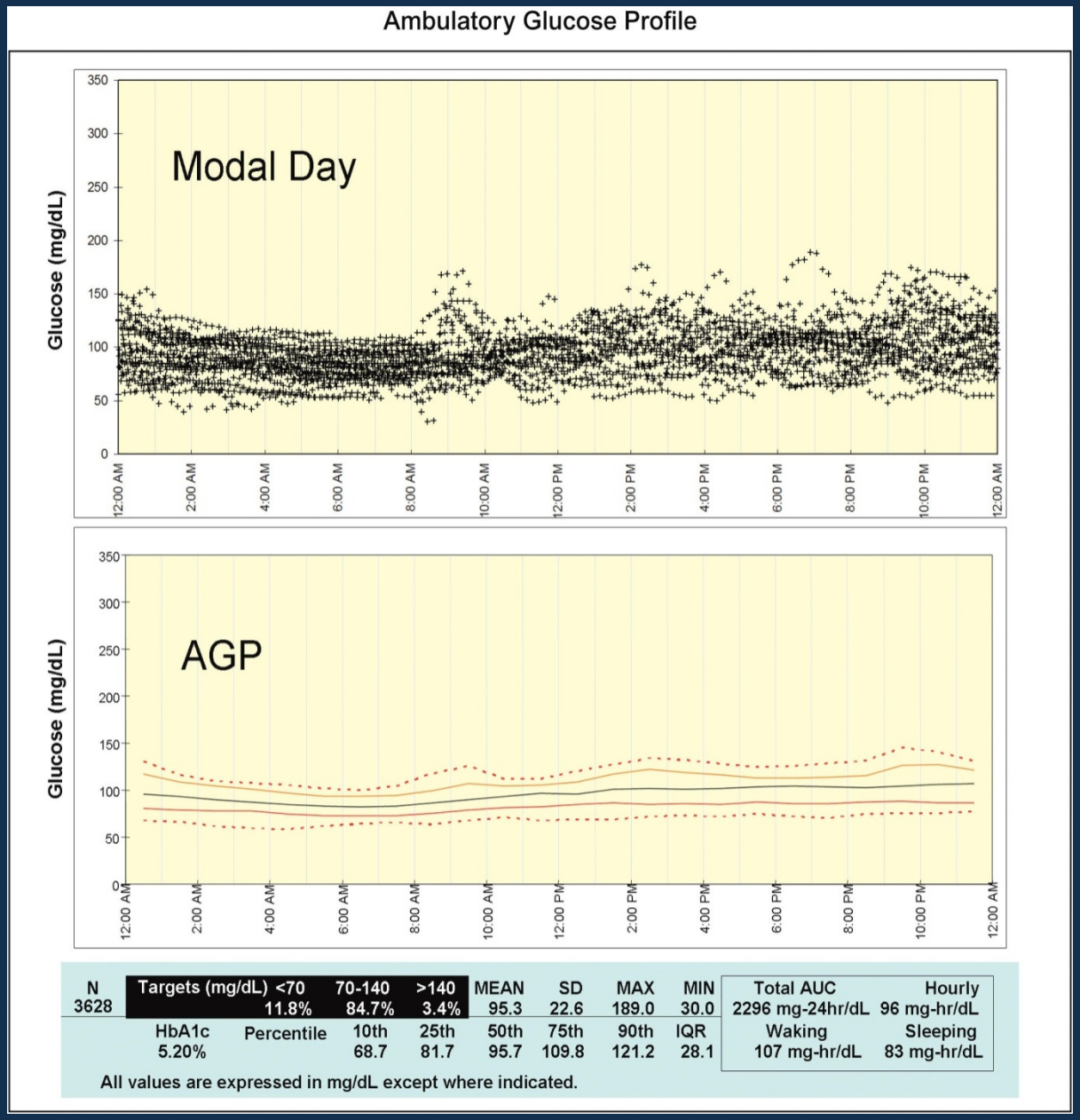
_____ 5-15mmol/L

Ceriello et al Diabetes 57:1349-1354, 2008

Characterizing Glucose Exposure for Individuals with Normal Glucose Tolerance Using Continuous Glucose Monitoring and Ambulatory Glucose Profile Analysis

R.S. MAZZE, E. STROCK, D. WESLEY, S. BORGMAN, B. MORGAN, R. BERGENSTAL and R. CUDDIHY

DIABETES TECHNOLOGY & THERAPEUTICS
Volume 10, Number 3, 2008

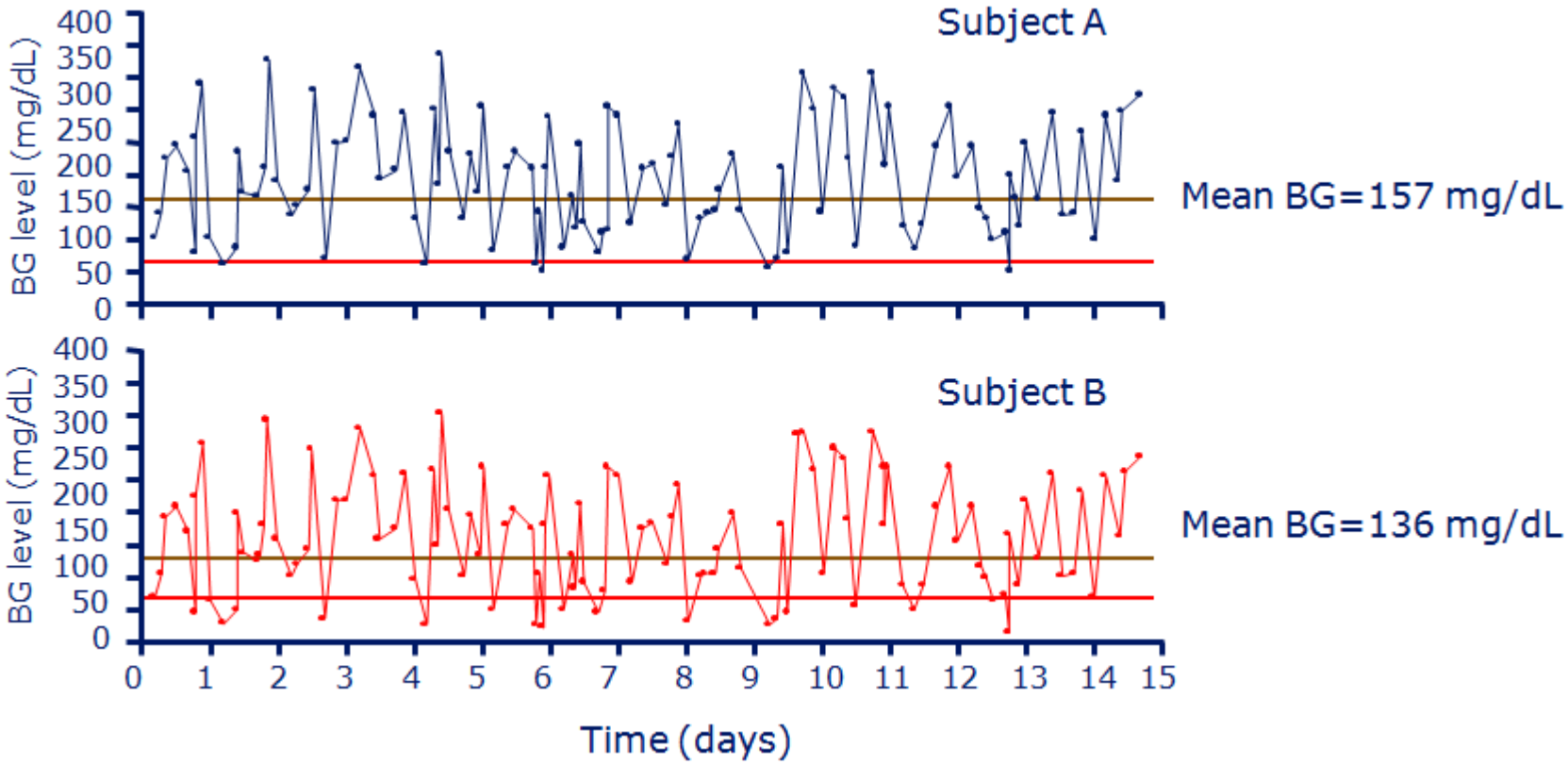


The modal day and the AGP depict 3,628 continuous glucose readings measured for 30 days. The modal day shows each data point graphed without regard to date. The AGP replaces the individual data points with five smoothed frequency curves, which represent the underlying glycemic pattern. (accounting for outlier values). The statistical summary (shown separately, but contained in the AGP report) is customizable.

Center solid line is the median, next two outer solid lines (25th and 75th percentiles) represent the IQR, the dotted lines depict the 10th and 90th percentiles

THERAPEUTIC PERSPECTIVES

Reducing average glycaemia without reducing variability may be dangerous



- Reduction in average glycaemia without reducing glucose variability is indicated by downward shift of the glucose profile from the upper panel to the lower panel
- This results in increased occurrence and severity of hypoglycaemic episodes

Kovatchev *et al. J Diabetes Sci Technol* 2009;3:1058–65

Journal of Diabetes and its Complications
ELSEVIER

Effects of vildagliptin twice daily vs. sitagliptin once daily on 24-hour acute glucose fluctuations

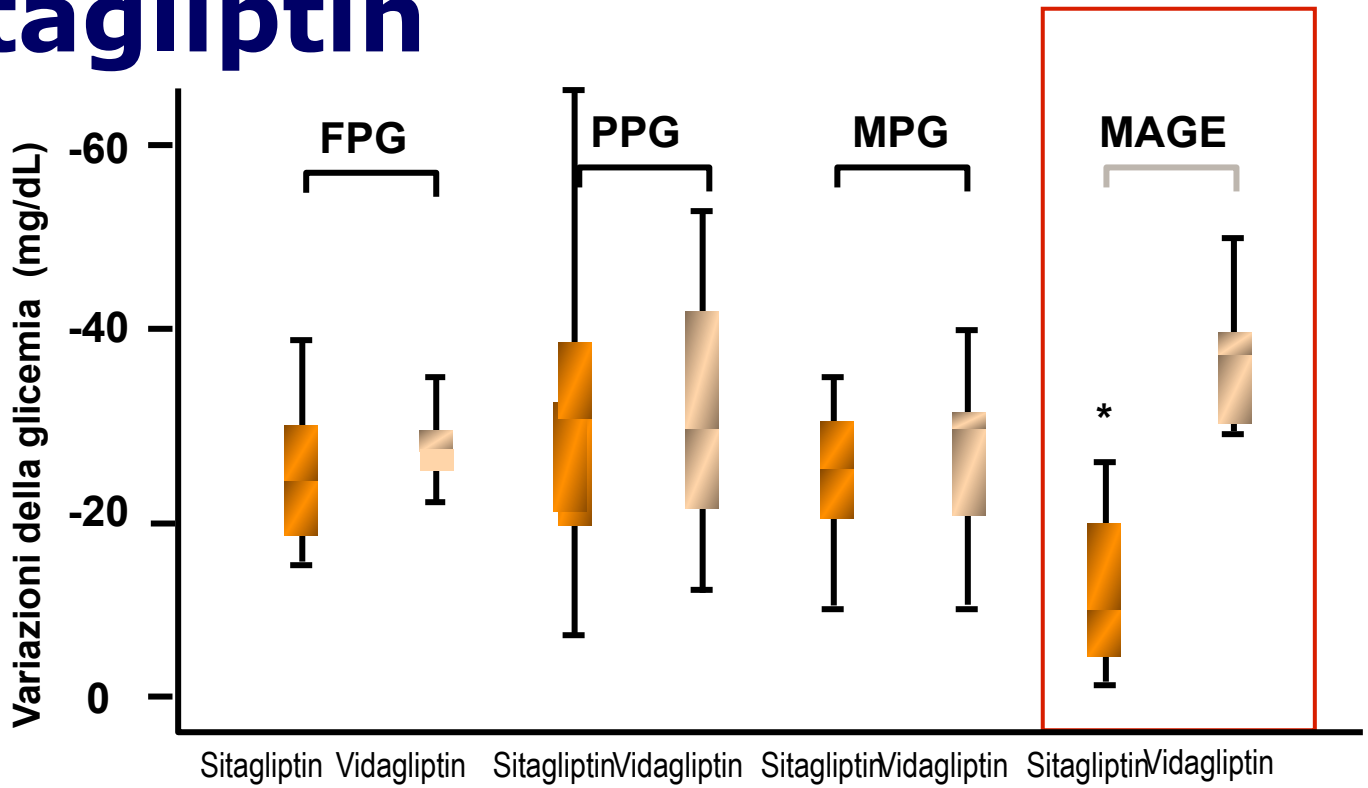
Raffaele Marfella[a,*], Michelangela Barbieri[a], Rodolfo Grella[a], Maria Rosaria Rizzo[a], Giovanni Francesco Nicoletti[b], Giuseppe Paolisso[a]

Clinical characteristics and metabolic profile before and 3 months after vildagliptin 50 mg twice daily or sitagliptin 100 mg once daily

	Sitagliptin 100 mg once daily			Vildagliptin 50 mg twice daily		
Variables	Baseline	After 3 months	*P*	Baseline	After 3 months	*P*
Age (years)	61±7	–	–	60±6	–	–
Male/female gender (*n*)	11/9	11/9	–	9/9	9/9	–
Body mass index (kg/m^2)	29.7±5	29.4±3	NS	29.6±4	29.2±2	NS
Systolic blood pressure (mmHg)	124±16	123±12	NS	125±13	126±10	NS
Diastolic blood pressure (mmHg)	82±4	83±3	NS	81±4	80±5	NS
Diabetes duration (years)	7.7±4	–	–	7.8±6	–	–
Risk factors						
Hypertension [*n* (%)]	5 (25)	/	–	4 (22)	–	–
Hypercholesterolemia [*n* (%)]	3 (15)	–	–	2 (12)	–	–
Obesity [*n* (%)]	3 (15)	–	–	3 (16)	–	–
Laboratory						
Fasting glycemia (mg/dl)	169±24	145±13	.01	171±31	146±14	.01
2-h postprandial glycemia (mg/dl)	196±22	166±17	.01	197±19	165±15	.01
MAGE (mg/dl of glucose)	69±18	59±16 *	NS	70±22	34±7	.01
HbA_{1c} (%)	8.3±0.6	7.5±0.4	.01	8.4±0.5	7.4±0.5	.01
24-h mean glycemia (mg/dl)	159±31	131±27	.01	157±39	128±36	.01
Insulin (pmol/l)	–	207±84	–	–	221±98	–
2-h postmeal insulin (pmol/l)	–	413±124	–	–	428±148	–
Triglycerides (mg/dl)	189±47	188±41	NS	191±39	187±42	NS
Total cholesterol (mg/dl)	209±38	206±44	NS	210±45	205±40	NS
ACE inhibitors [*n* (%)]	5 (25)	–	–	4 (22)	–	–
AT_2 antagonists [*n* (%)]	4 (20)	–	–	4 (22)	–	–
Diuretics [*n* (%)]	2 (10)	–	–	2 (12)	–	–
β-Blockers [*n* (%)]	3 (15)	–	–	3 (16)	–	–
Aspirin [*n* (%)]	10 (50)	–	–	10 (55)	–	–
Statins [*n* (%)]	8 (40)	–	–	7 (39)	–	–
Duration of metformin treatment (months)	28.5±6	–	–	29.1±7	–	–
Duration of sitagliptin treatment (months)	4.4±1.4	–	–	–	–	–
Duration of vildagliptin treatment (months)	4.5±1.4					

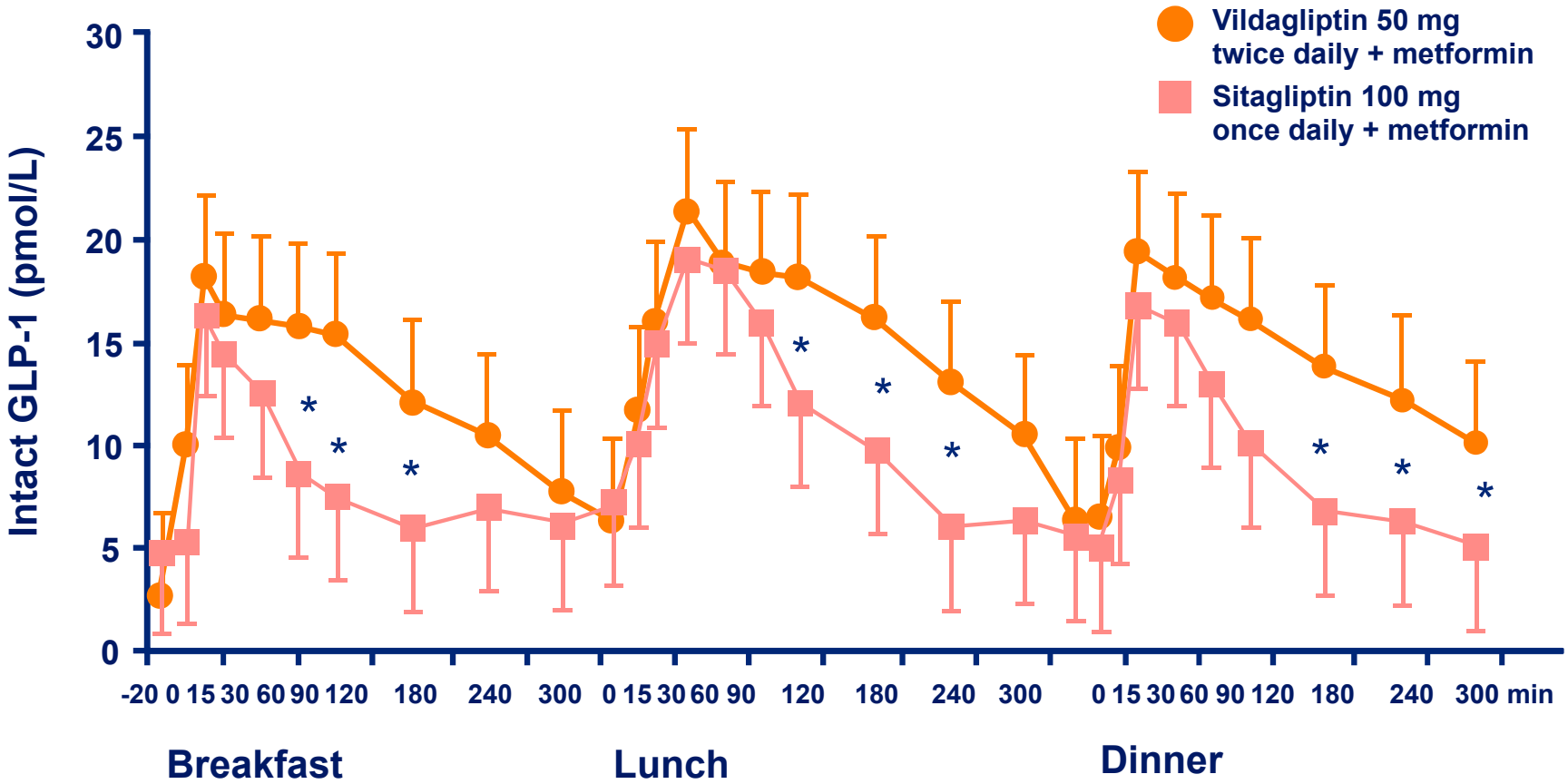
Marfella R et Al *J Diabetes and Its Complications 2010*

Reduction of variabil (MAGE) Vildagliptin vs Sitagliptin



Marfella R et Al J *Diabetes and Its Complications 2010*

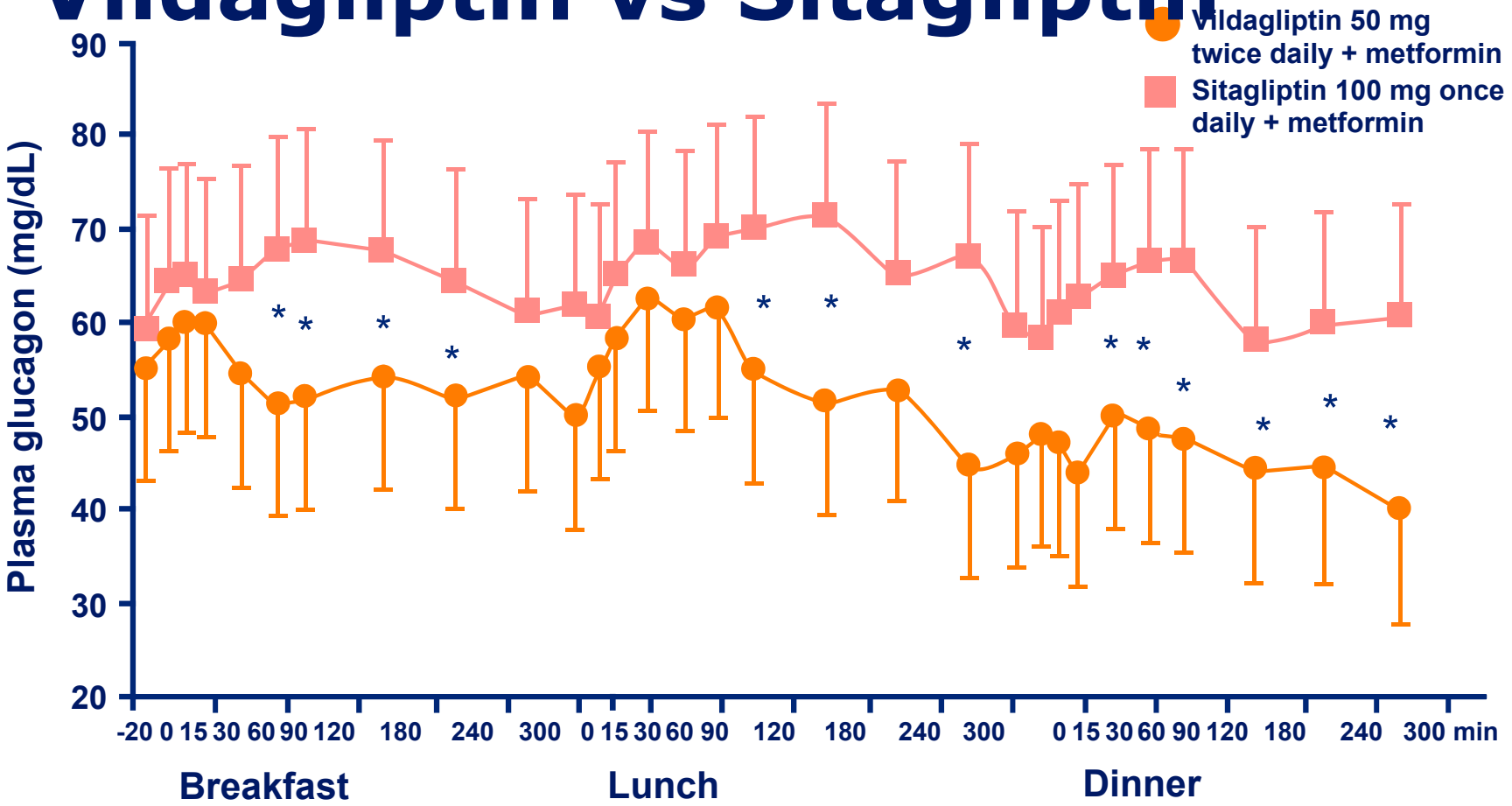
Interprandial level GLP-1
Vildagliptin vs Sitagliptin



GLP-1=glucagon-like peptide-1. **P* <0.05 vs vildagliptin group.
Plasma levels during 24-h sampling comprising three standardised meals after 3 months of treatment in type 2 diabetic patients.

Marfella R, et al. *J Diabetes Complications* 2010;24:79–83

Interprandial supression of Glucagon Vildagliptin vs Sitagliptin



*P <0.05 vs vildagliptin group. Plasma levels during 24-h sampling comprising three standardised meals after 3 months of treatment in type 2 diabetic patients

Marfella R, et al. *J Diabetes Complications* 2010;24:79–83

DPP4 binding difference : Substrate-enzyme blocker (vildagliptin) verses a competitive enzyme inhibitor (sitagliptin)

Vilda
and

HO

Sitag

F

Off-rate kinetics comparison

Compound	K_{off} (s^{-1})	Half-life of enzyme-inhibitor (EI) complex
Vildagliptin	2.5×10^{-4}	55 min§
Sitagliptin	$>1 \times 10^{-3}$	negligible€

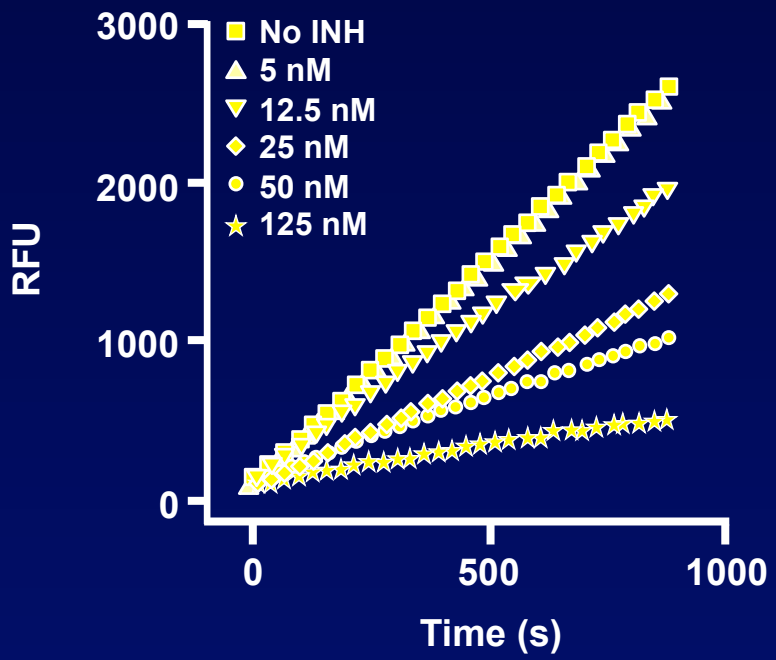
§Expected from a covalently bound inhibitor
€Expected from a non-covalent competitive inhibitor

Potashman, Duggan. J Med Chem 2009;52:1231–46;
Davis et al. Indian J Pharmacol 2010;42:229–33
Ahren et al. Diabetes Obes Metab 2011; 13:775-783

Gao, et al. Bioorganic & Medicinal Chemistry Letters 17 (2007) 3877-3879

Binding to DPP-4: sitagliptin vs vildagiptin

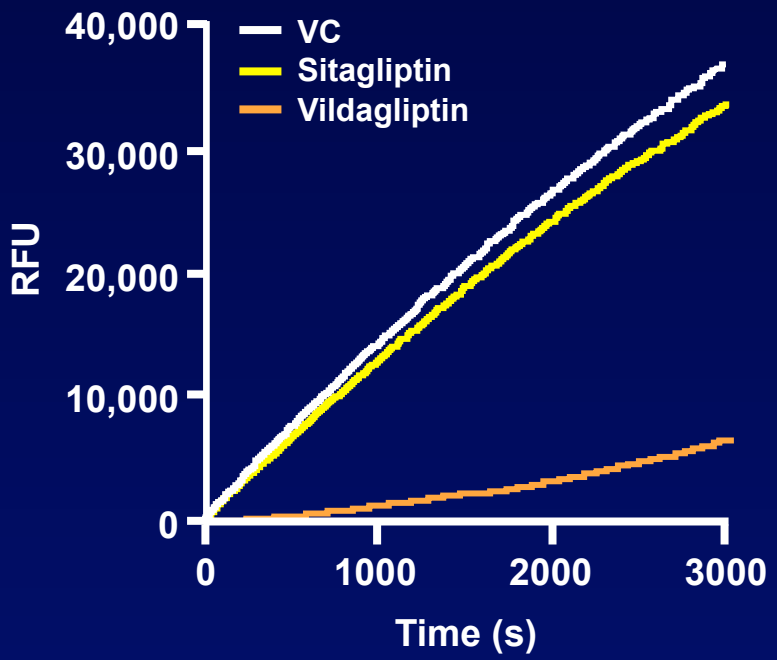
A



Fast binding nature of sitagliptin

Inhibition studies performed by the addition of enzyme to pre-incubated mixture of substrate and various concentrations of sitagliptin (0, 5, 12.5, 25, 50 and 125 nM final)

B



Sitagliptin inhibition is reversible

The human recombinant DPP-4 (10 ng) pre-incubated without (VC) or with sitagliptin (500 nM) or vildagliptin (50 nM) diluted more than 100-fold into 0.5 mM H-Gly-Pro-AMC and the DPP-4 activity measured. Both A and B represent one experiment (n=3)

DDP-4=dipeptidyl peptidase-4.

Davis JA, et al. *Indian J Pharmacol.* 2010;42:229–233.

DiabetesCare 2012

Pathophysiology/Complications
ORIGINAL ARTICLE

Reduction of Oxidative Stress and Inflammation by Blunting Daily Acute Glucose Fluctuations in Patients With Type 2 Diabetes

Role of dipeptidyl peptidase-IV inhibition

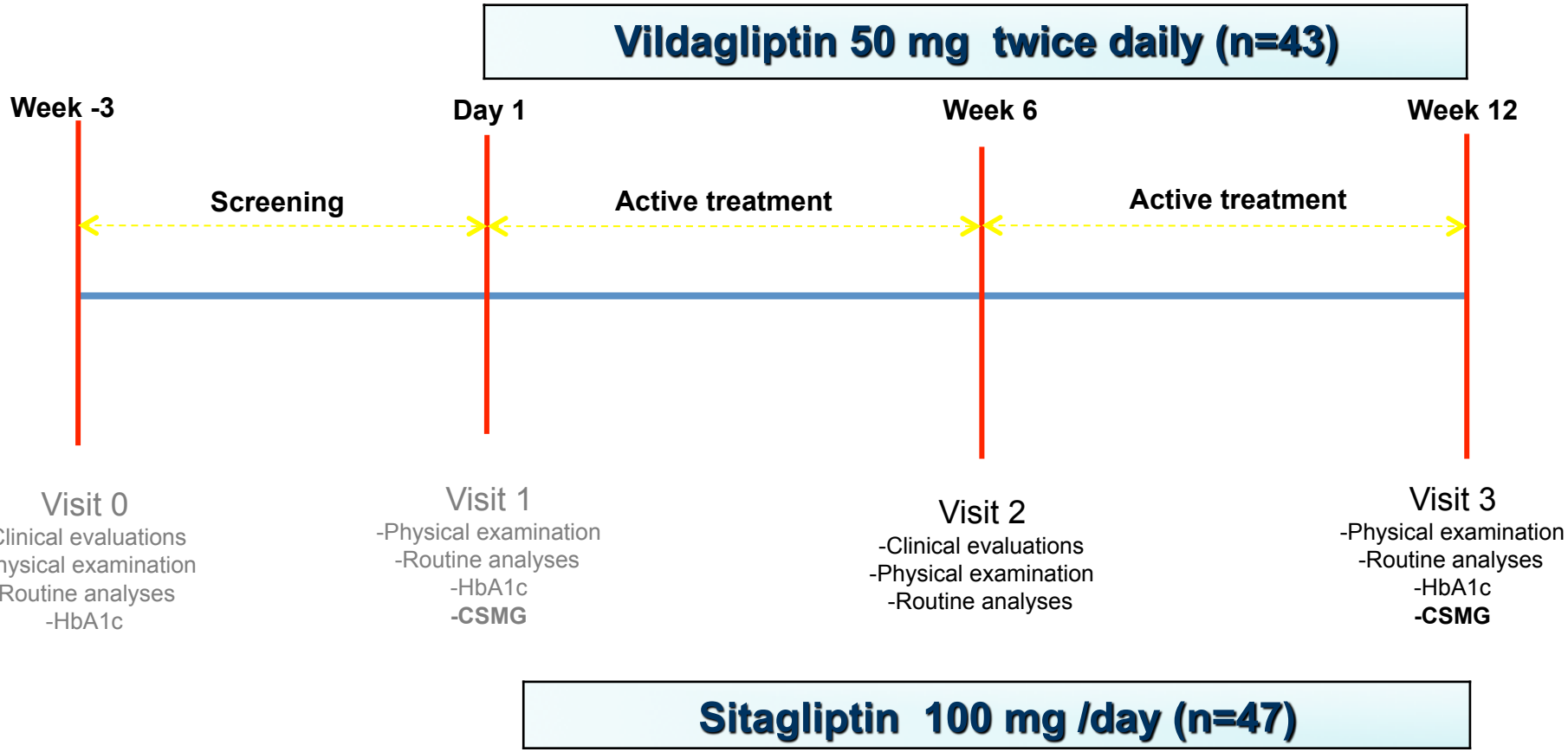
MARIA ROSARIA RIZZO, MD, PHD
MICHELANGELA BARBIERI, MD, PHD
RAFFAELE MARFELLA, MD, PHD
GIUSEPPE PAOLISSO, MD, PHD

Il più grande studio di confronto testa a testa Vildagliptin vs Sitagliptin pubblicato fino ad oggi (n=90)

REDUCTION OF OXIDATIVE STRESS AND INFLAMMATION BY BLUNTING DAILY ACUTE GLUCOSE FLUCTUATIONS IN PATIENTS WITH TYPE 2 DIABETES: ROLE OF DIPEPTIDYL PEPTIDASE-4 INHIBITION

Study design

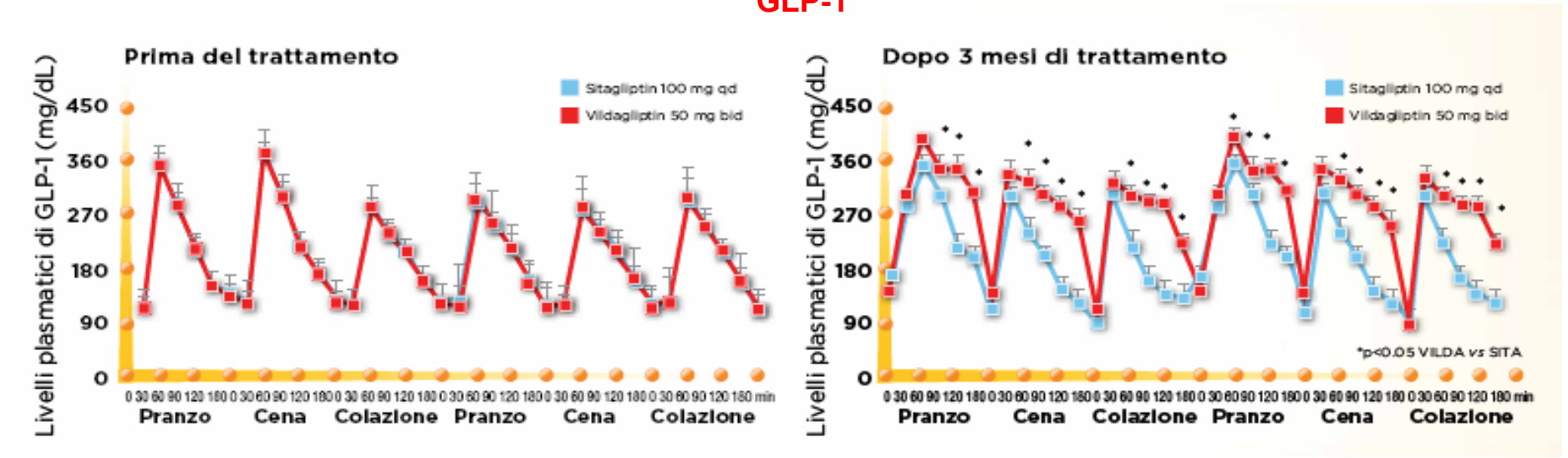
PROBE design: Prospective, randomized, open-label parallel group with a blinded-endpoint from May 2010 to June 2011



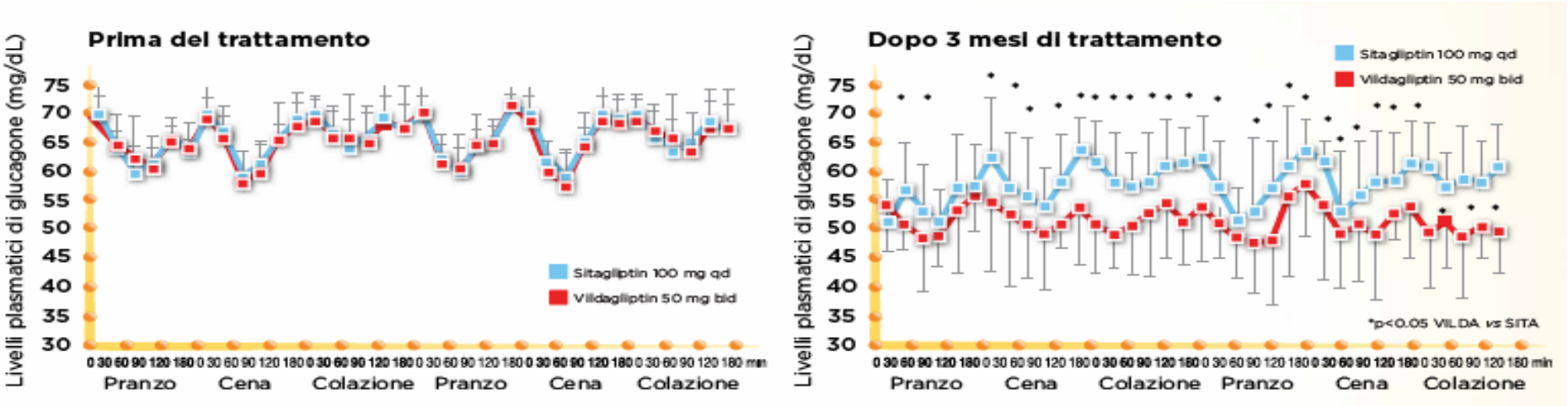
Diabetes Care 2012

PLASMA GLUCAGON AND GLP1 LEVELS DURING 48 H SAMPLING AFTER 12 WEEKS OF TREATMENT WITH VILDAGLIPTIN OR SITAGLIPTIN

GLP-1



GLUCAGONE



Diabetes Care 2012

Comparison of vildagliptin twice daily vs. sitagliptin once daily using continuous glucose monitoring (CGM): Crossover pilot study (J-VICTORIA study)

Cardiovascular Diabetology 2012, **11**:92 doi:10.1186/1475-2840-11-92

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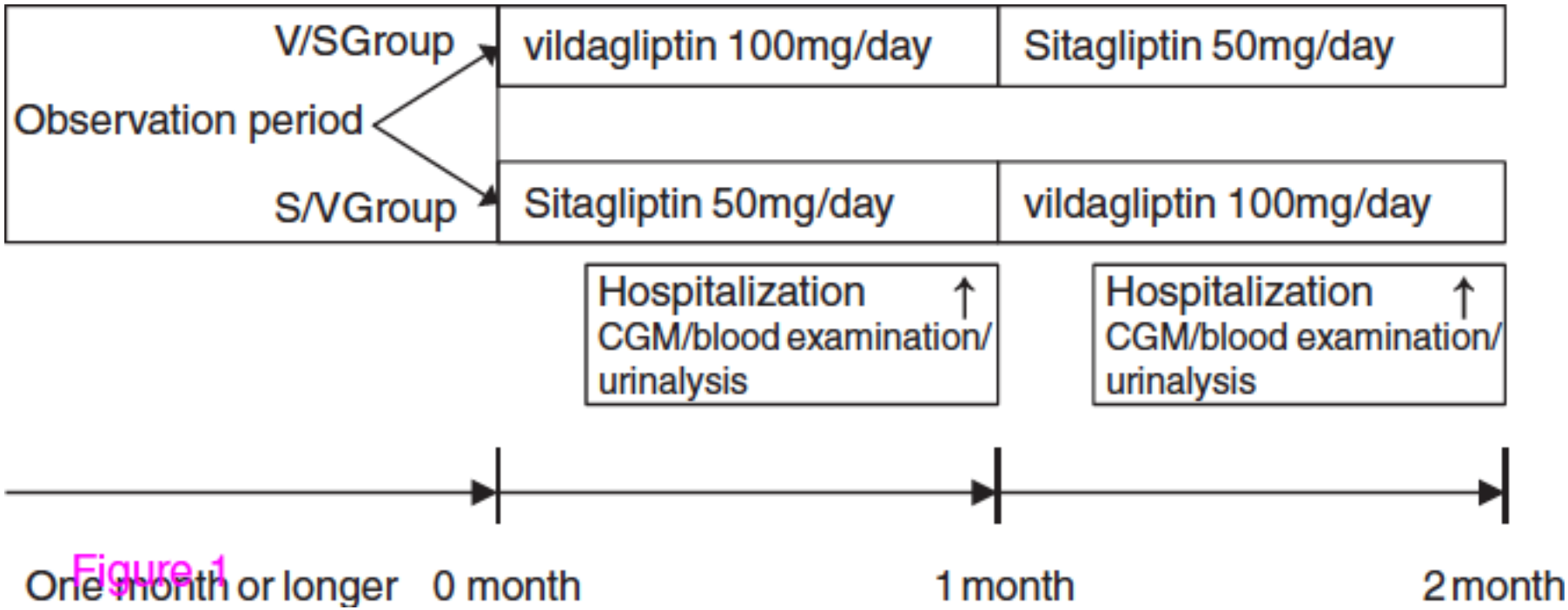
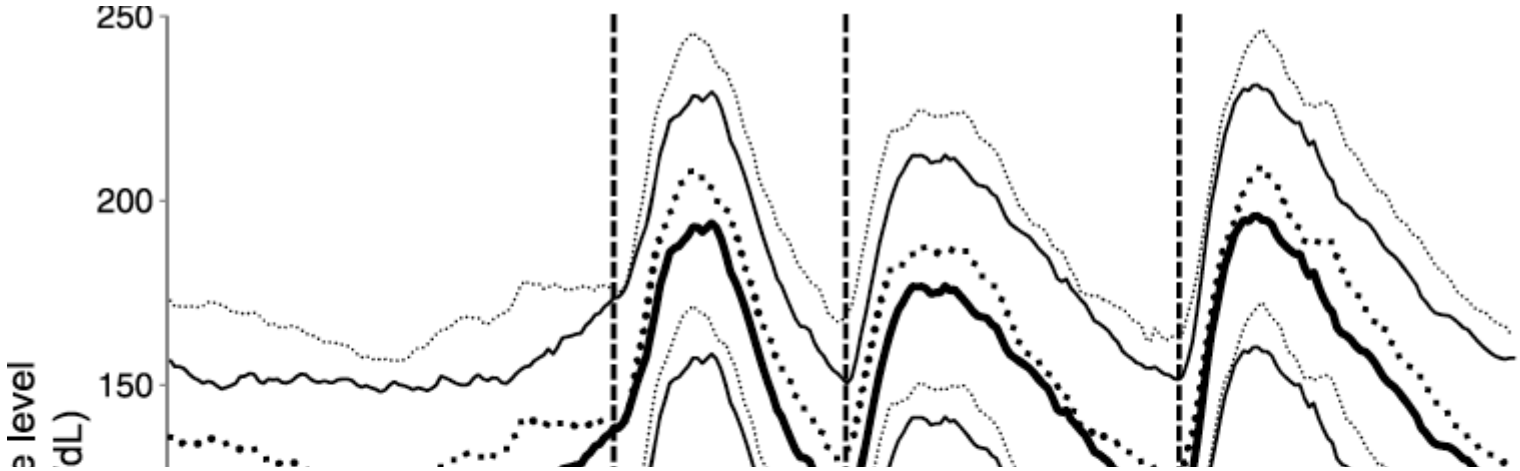


Figure 1



Conclusions

CGM showed that mean 24-h blood glucose, MAGE, highest blood glucose level after supper, and hyperglycemia after breakfast were significantly lower in patients with type 2 diabetes mellitus taking vildagliptin than those taking sitagliptin. There were no significant differences in BNP and PAI-1 levels between patients taking vildagliptin and sitagliptin.

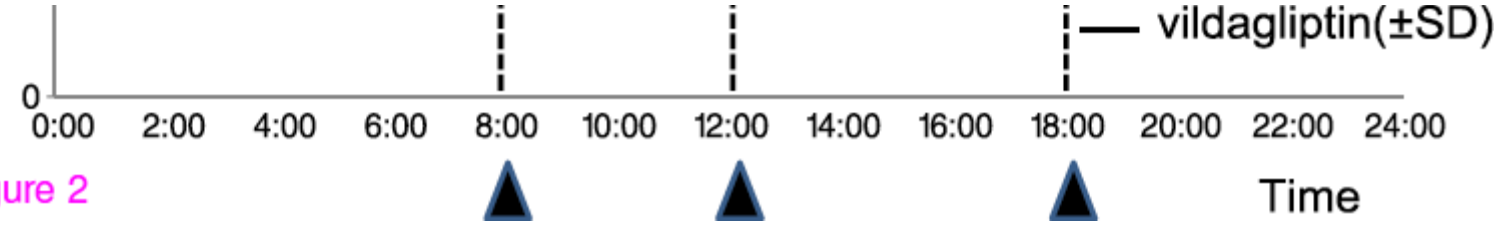


Figure 2

Vildagliptin and Oxidative Stress

Vildagliptin preserves the mass and function of pancreatic β cells via the developmental regulation and suppression of oxidative and endoplasmic reticulum stress in a mouse model of diabetes.
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DOI: 10.1111/j.1464-5491.2010.02967.x

Review Article

'Glycaemic variability': a new therapeutic challenge in diabetes and the critical care setting

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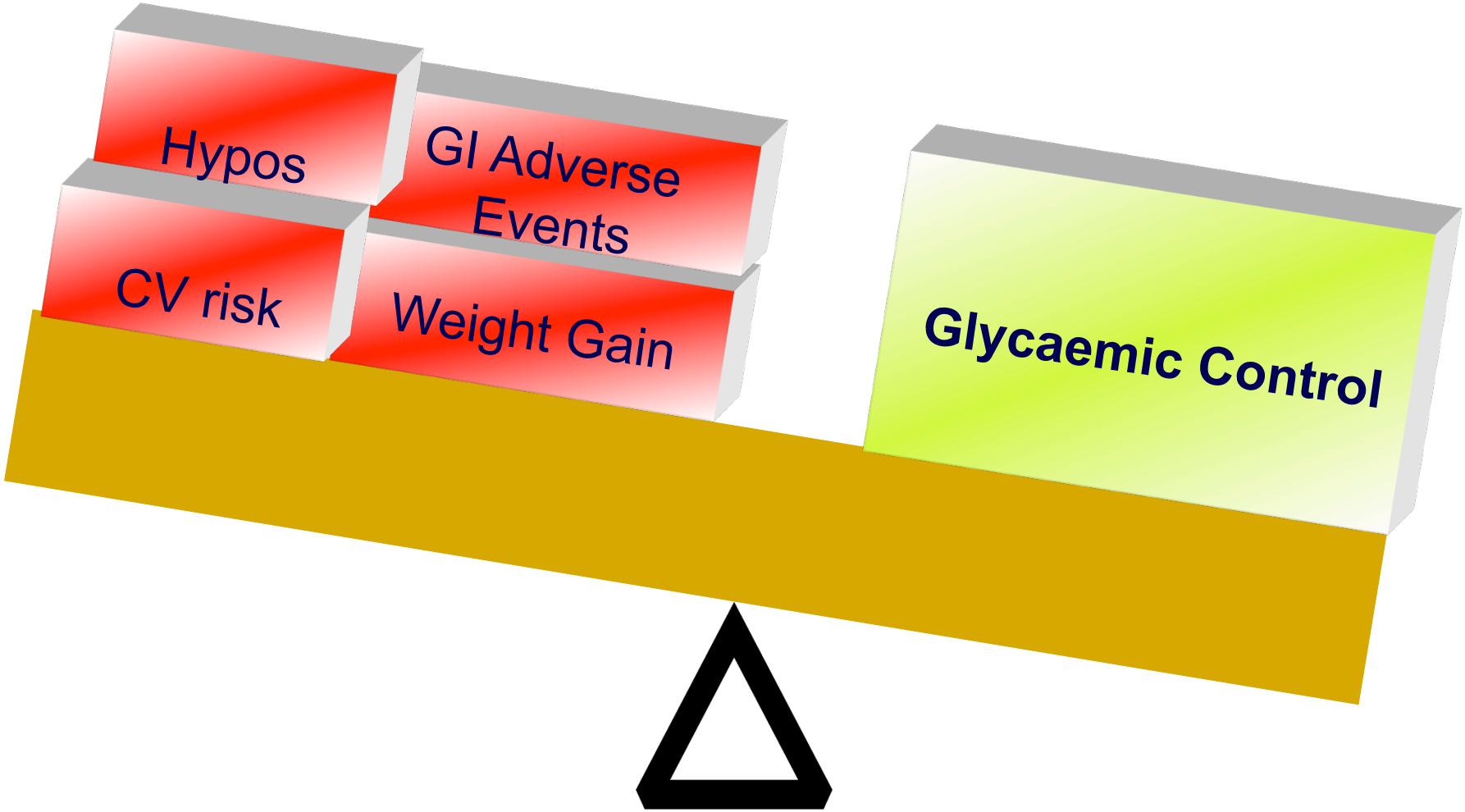
The Benefits *vs.* Risks of Diabetes Therapy Must be Assessed for Each Patient




REWARD!
LOST
PUPPY

GRACIAS

THANK YOU

GRAZIE