# Lezione dal “paziente Ramadan”:la variabilità glicemica come fattore di rischio indipendente

# LA VARIABILITÀ NEI FENOMENI BIOLOGICI È IN GENERE DANNOSA

## OHASAMA STUDY: 20 ANNI DI OSSERVAZIONE

La variabilità giornaliera della PA è predittiva di eventi cardio e cerebrovascolari più della esposizione media giornaliera



## REBOUND LIPIDICO

La sospensione della terapia con statine e la fluttuazione del colesterolo aumenta la mortalità per ictus



Colivicchi et al Stroke. 2007 Oct;38(10):2652-7

## WEIGHT CYCLING E MORTALITA'

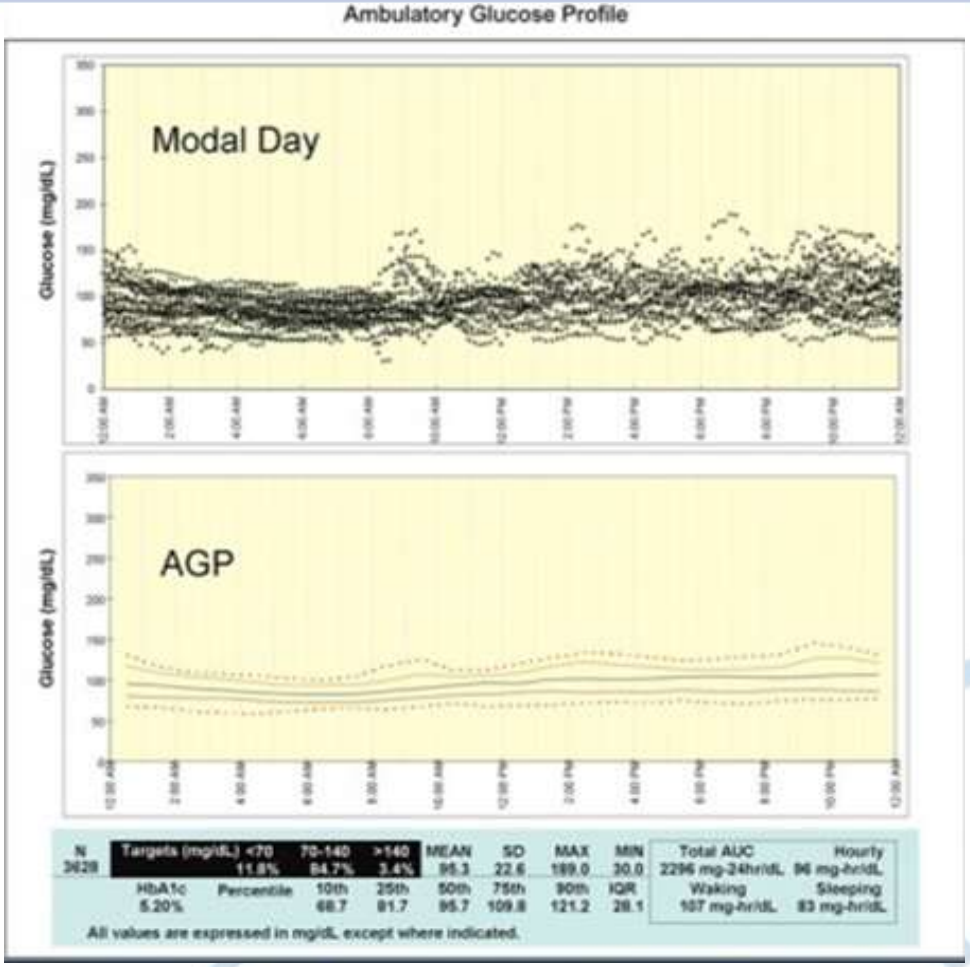
La variazione del peso corporeo è un forte predittore di mortalità totale e coronarica

(Presa di posizione dell'NIH contro le yo-yo diets)



# Continuous glucose monitoring in non diabetic individuals

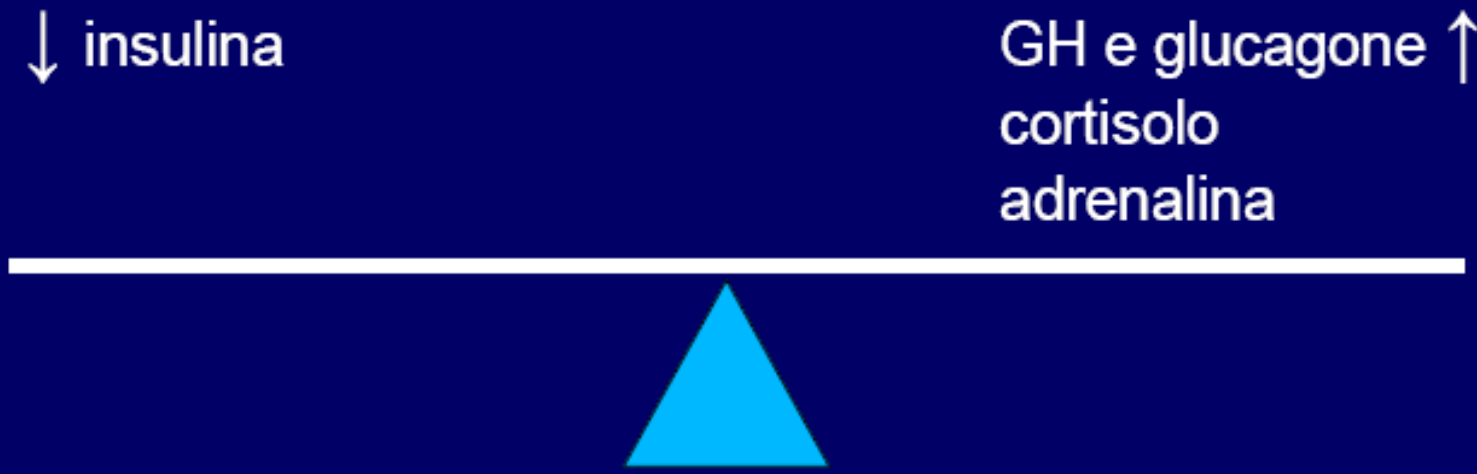




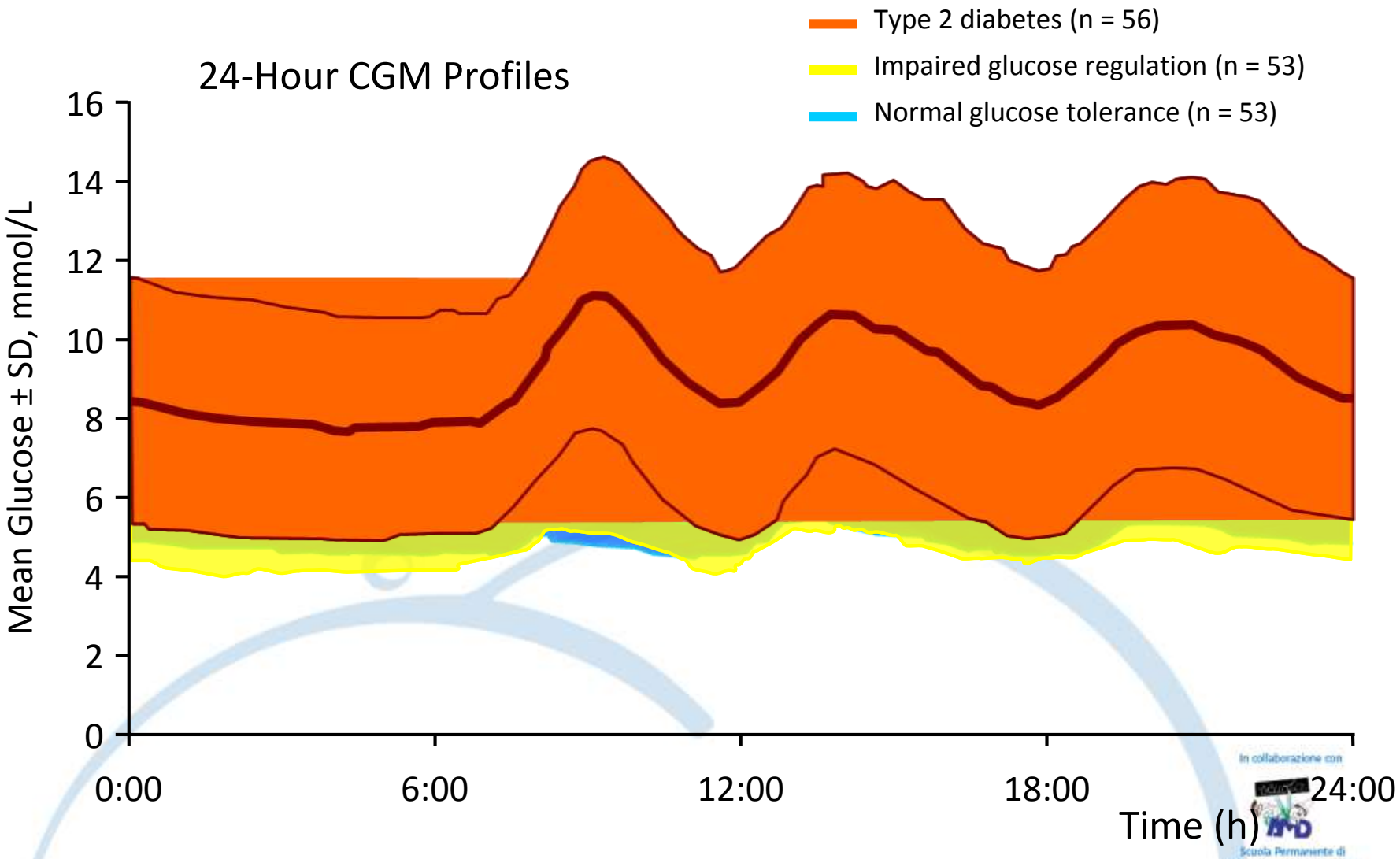

Nel soggetto non diabetico variabilità glicemica pari a 21 mg/dl e con variazioni mediane di 3 +/- mg/dl/ora

Mazze RS,Diab Thecn Therap 2008

# L'OMEOSTASI GLICEMICA

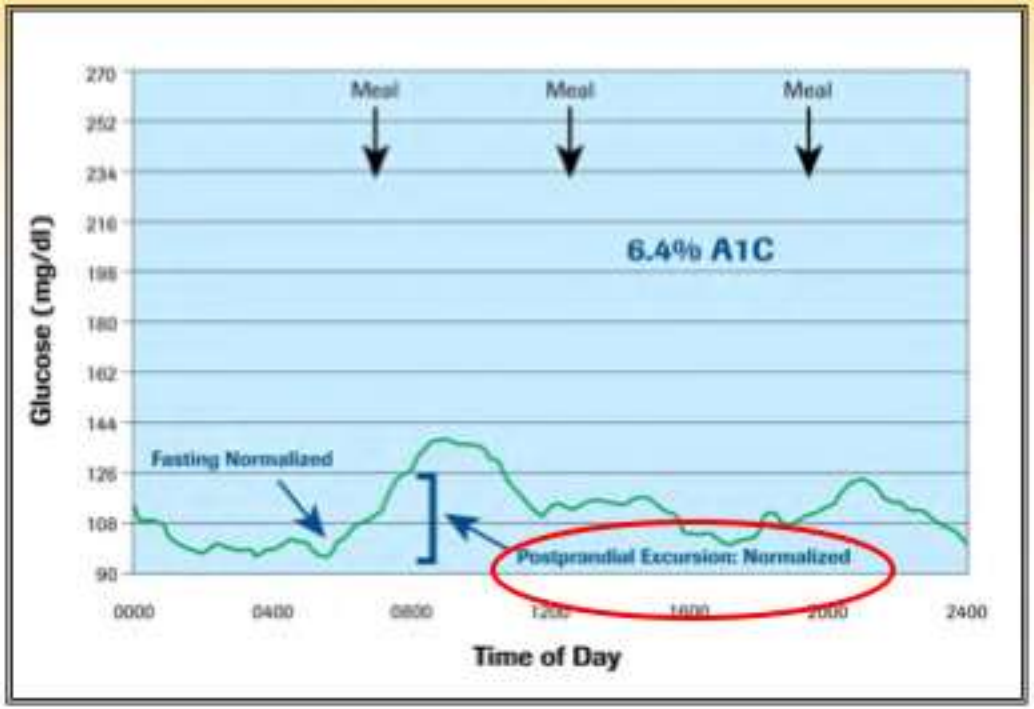


# Glycemic Variability Increases in Patients With Type 2 Diabetes




*(Wang, C et al Clinical Endocrinology 2011)*

# LA VARIABILITÀ GLICEMICA COME INDICATORE DEL CONTROLLO GLICEMICO (2)




**Conclusioni**:Il deterioramento dell'omeostasi del glucosio nei soggetti con diabete di tipo 2 progredisce da una iperglicemia postprandiale ad una iperglicemia a digiuno dopo **un processo in tre fasi**.La prima fase è una iperglicemia postprandiale a cui segue una iperglicemia al mattino ed infine una iperglicemia notturna .

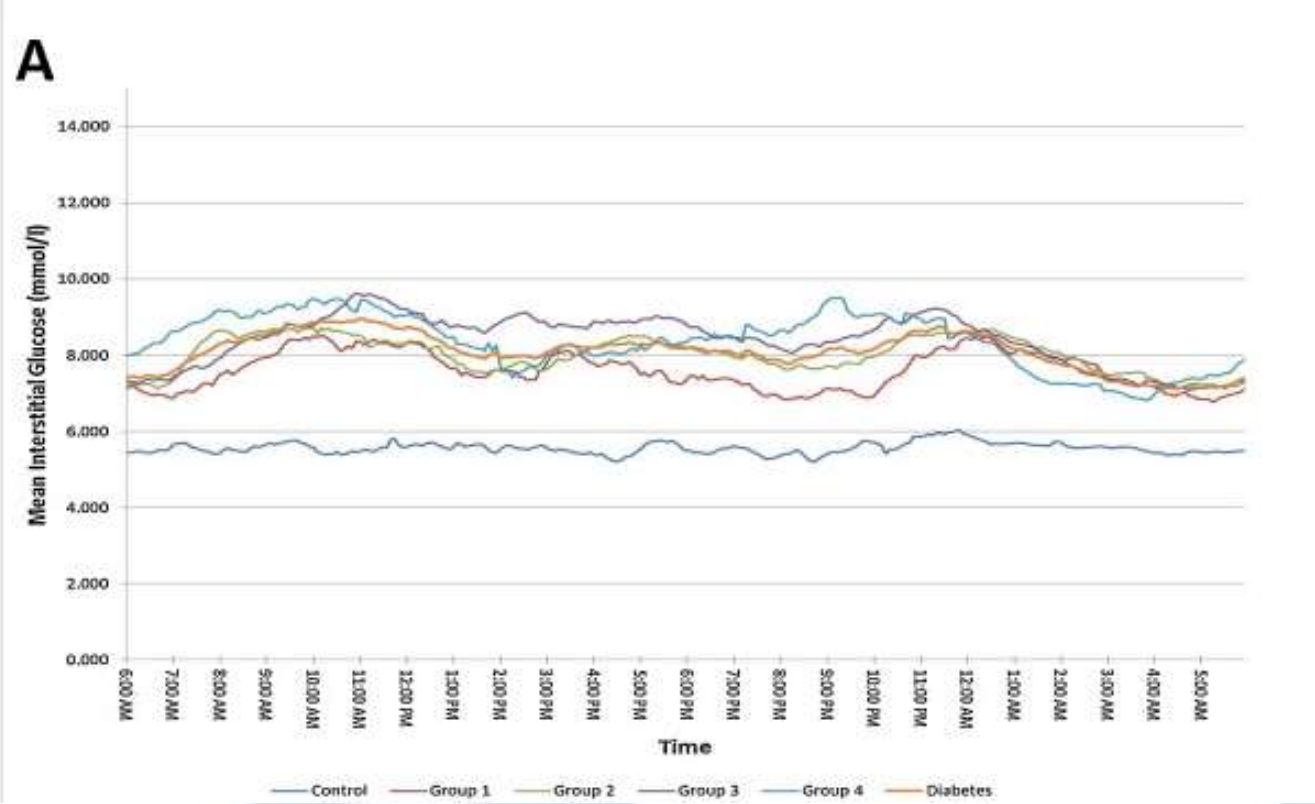
Valori normali della glicemia a digiuno e dell'escursione post-prandiale in pazienti con controllo glicemico ottimale (HbA1c 6.4%)

**→ Il SMBG costituisce il metodo più pratico per raggiungere il controllo glicemico ottimale**

Diabetes Care

*Monnier et al. Diabetes Care, 2007, Vol 30, 263-269*

# Glucose excursions and glycaemic control during Ramadan fasting in diabetic patients: Insights from continuous glucose monitoring (CGM)




Diabetes & Metabolism, Volume 41, Issue 1, 2015, 28 - 36

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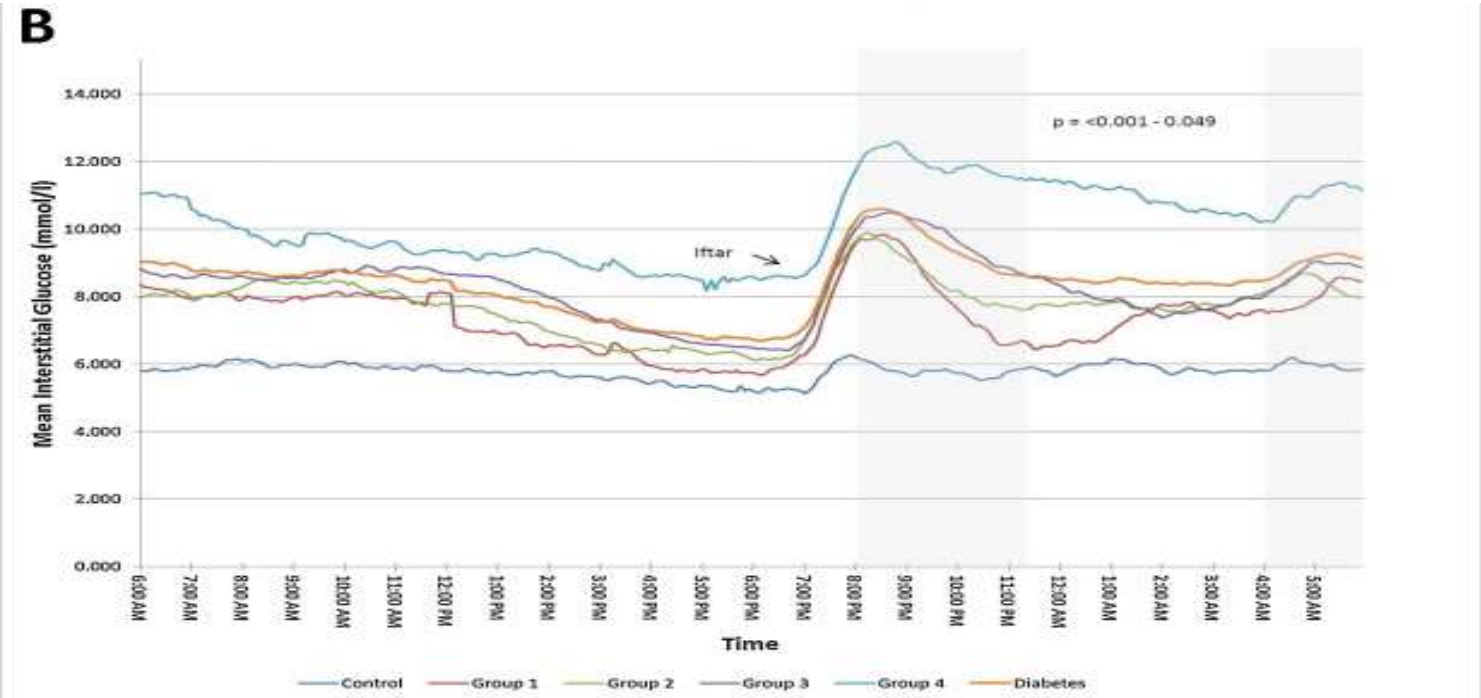



Fig. 1.

Mean continuous glucose monitoring (CGM) recordings for diabetes patients and control subjects during non-fasting (A) and fasting (B) by type of treatment: group 1: diet with/without metformin; group 2: gliptin with/without metformin; group 3: sulphonylurea with/without other oral agent(s); group 4: insulin with/without other oral antidiabetic agents (OADs). The difference between patient groups and controls was highly significant ($P < 0.05$, Wilcoxon's signed-ranked test) for mean interstitial glucose during *iftar* and the predawn meal *suhoor* (shaded areas, B).

Diabetes & Metabolism, Volume 41, Issue 1, 2015, 28 - 36

# Abstract

## Aim

Ramadan fasting represents a major shift in meal timing and content for practicing Muslims. This study used continuous glucose monitoring (CGM) to assess changes in markers of glycaemic excursions during Ramadan fasting to investigate the short-term safety of this practice in different groups of patients with diabetes.

## Methods

A total of 63 subjects (56 with diabetes, seven healthy volunteers; 39 male, 24 female) had CGM performed during, before and after Ramadan fasting. Mean CGM curves were constructed for each group for these periods that were then used to calculate indicators of glucose control and excursions. Post hoc data analyses included comparisons of different medication categories (metformin/no medication, gliptin, sulphonylurea and insulin). Medication changes during Ramadan followed American Diabetes Association guidelines.

## Result

Among patients with diabetes, there was a significant difference in mean CGM curve during Ramadan, with a slow fall during fasting hours followed by a rapid rise in glucose level after the sunset meal (iftar). The magnitude of this excursion was greatest in the insulin-treated group, followed by the sulphonylurea-treated group. Markers of control deteriorated in a small number (n=3) of patients. Overall, whether fasting or non-fasting, subjects showed no statistically significant changes in mean interstitial glucose (IG), mean amplitude of glycaemic excursion (MAGE), high and low blood glucose indices (HBGI/LBGI), and number of glucose excursions and rate of hypoglycaemia.

## Conclusion

The main change in glycaemic control with Ramadan fasting in patients with diabetes is in the pattern of excursions. Ramadan fasting caused neither overall deterioration nor improvement in the majority of patients with good baseline glucose control.

# One cannot control average glucose level unless one first reduces GV !!

- **Mean glucose level = 100 mg %**
- **DS = ± 40 mg %**

David Rodbard,Diab Tech 2011;13:1077

World Journal of Diabetes

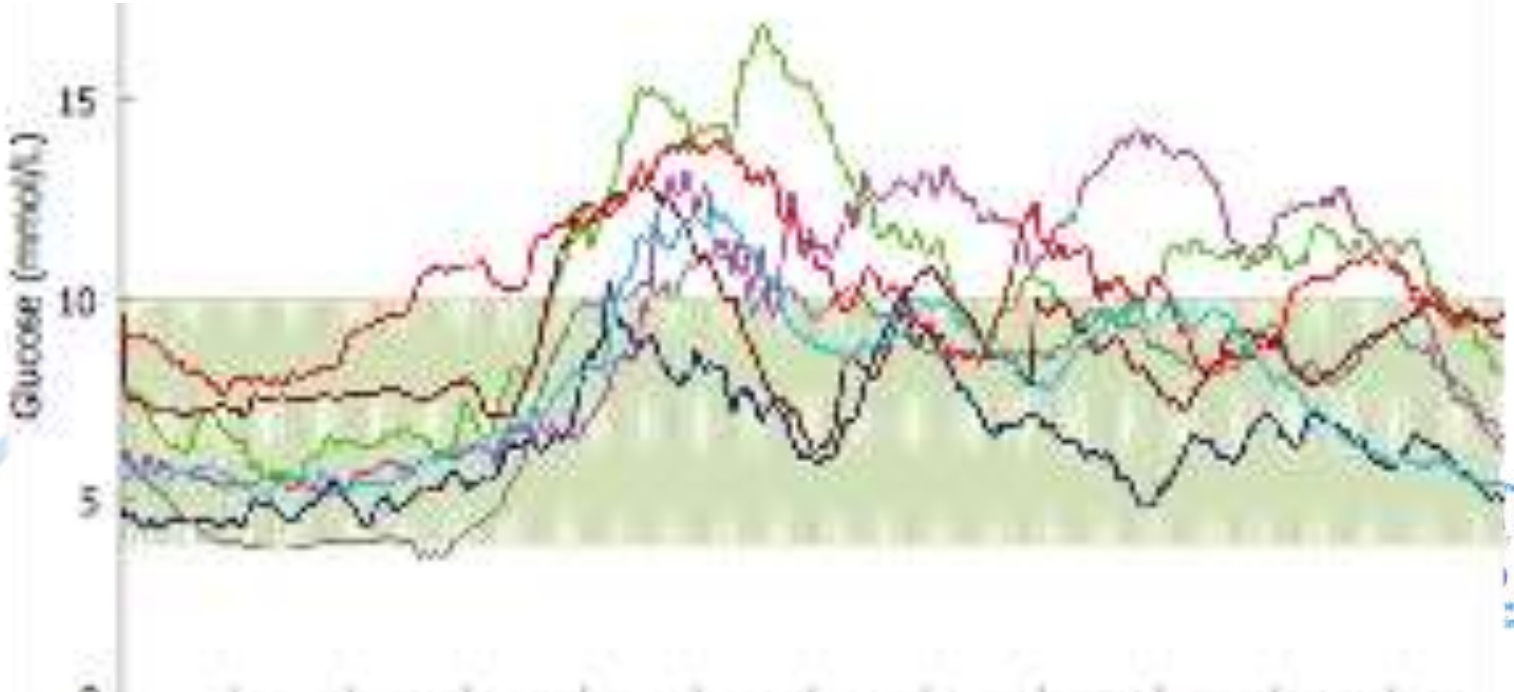
Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4239/wjd.v6.i1.17

*World J Diabetes* 2015 February 15; 6(1): 17-29
ISSN 1948-9358 (online)
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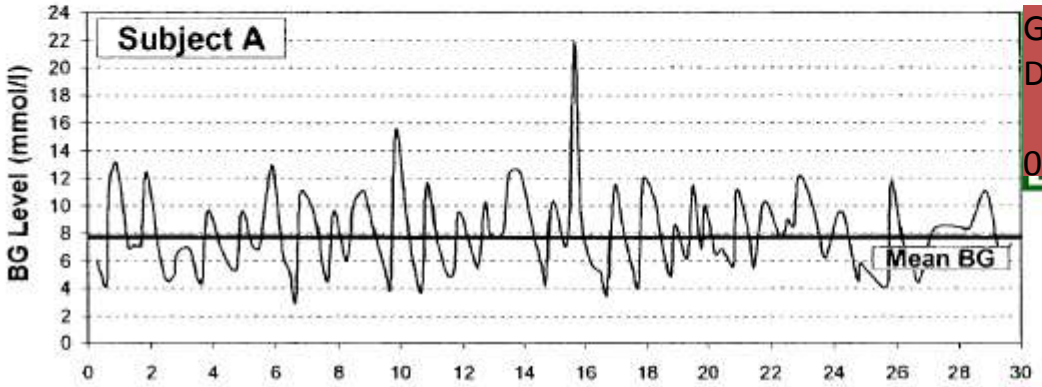
TOPIC HIGHLIGHT

WJD 5th Anniversary Special Issues (4): Diabetes-related complications

# Utility of different glycemic control metrics for optimizing management of diabetes

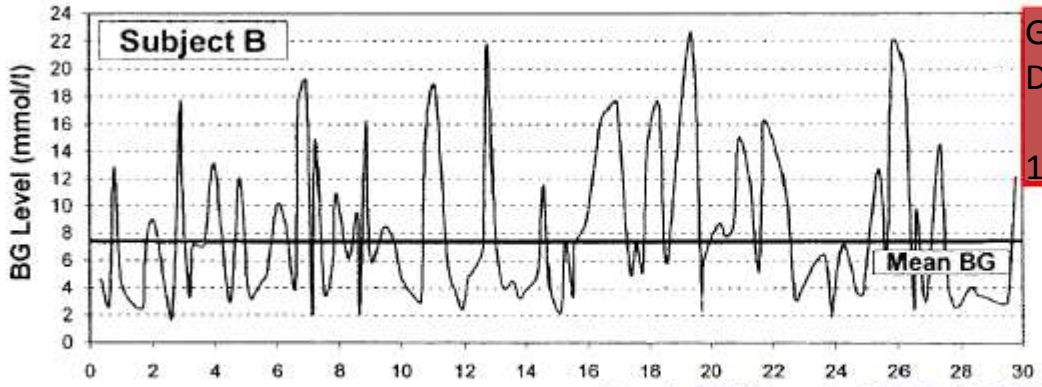


# Glicemia media variabilità glicemica e predizione dell'ipoglicemia




Glicemia media 157 mg/dl
D.S. 54 mg%

0 ipoglicemie gravi



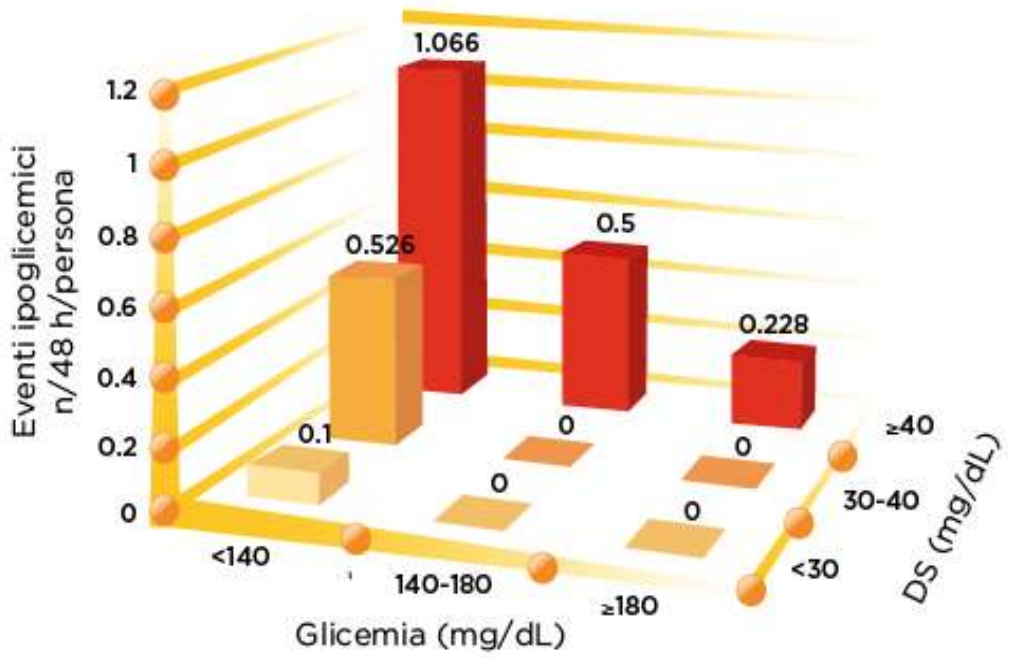

Glicemia media 136 mg/dl
D.S. 97 mg%

10 ipoglicemie gravi

*Kovatchev BP Diabetes Care 2006; 29: 2433– 2438*

# Variabilità glicemica e rischio di ipoglicemie asintomatiche

Frequenze di ipoglicemie asintomatiche in funzione dei livelli di glicemia e variabilità glicemica (Deviazione Standard - DS) [5]



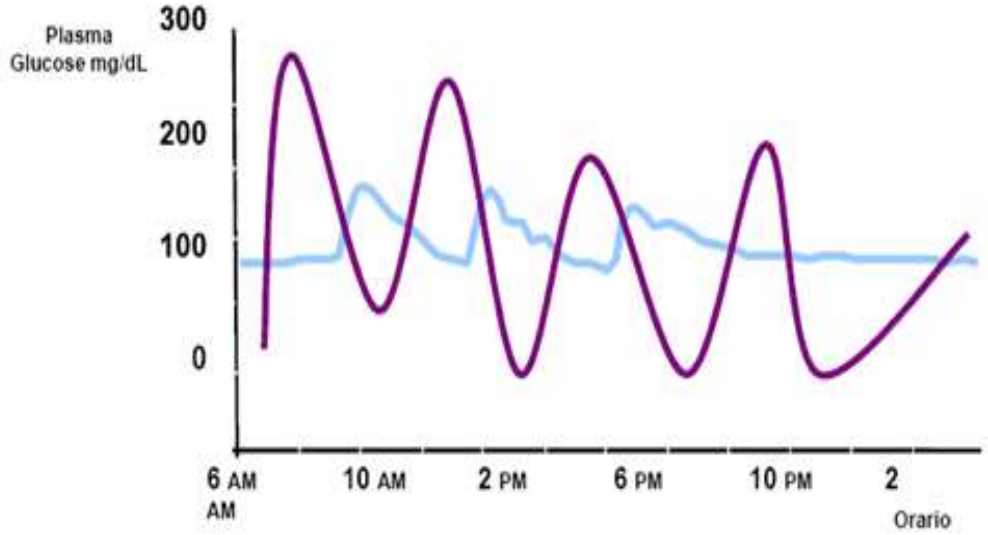

Monnier et al Diabetes Technology & Therapeutics 2011

# Variabilità glicemica e complicanze

- La variabilità glicemica correla con le complicanze acute (ipoglicemie) e la qualità della vita

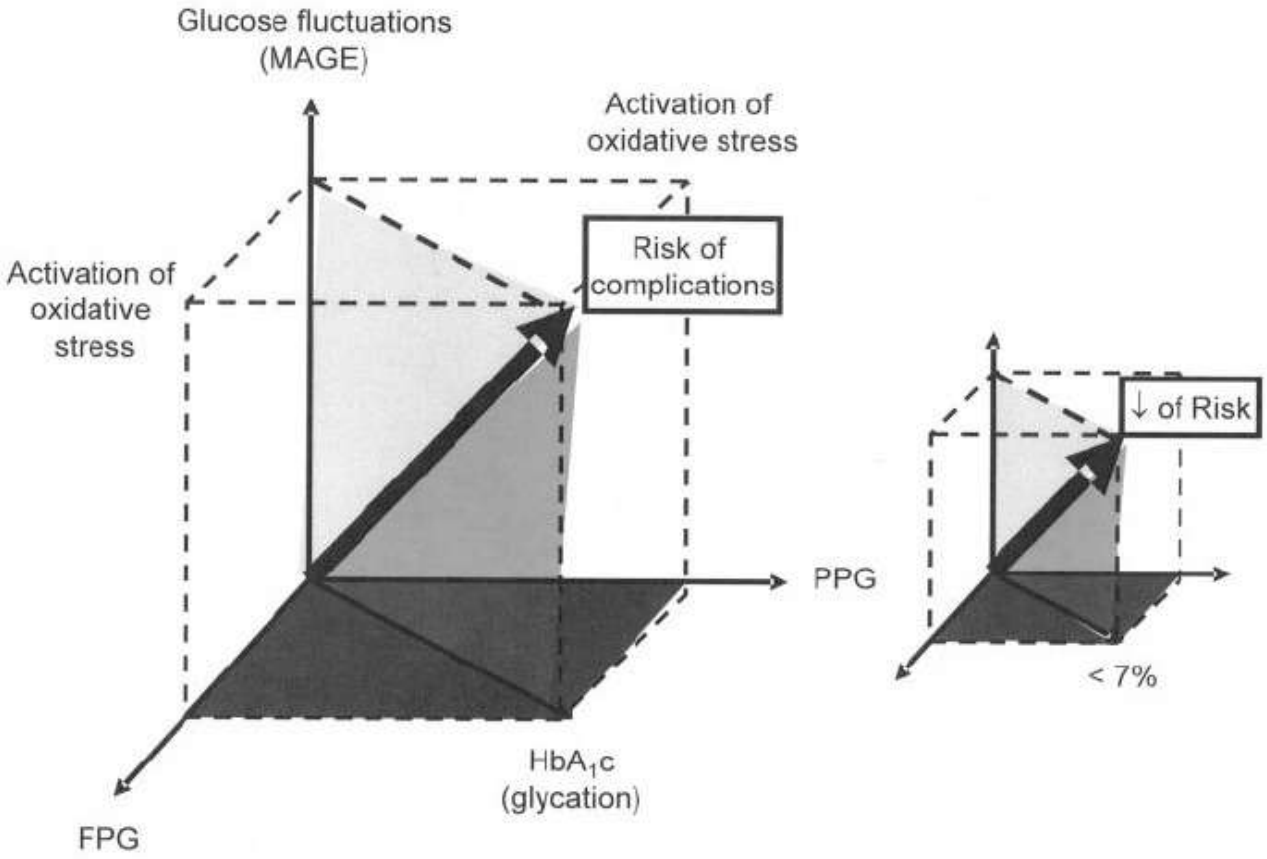
Le Monier,Jama 2006

# VARIABILTA’ GLICEMICA




**Oscillazione dei valori glicemici intorno al valore glicemico medio**

# Una ipotesi unificante del ruolo dei diversi parametri di controllo glicemici ed il rischio di complicanze



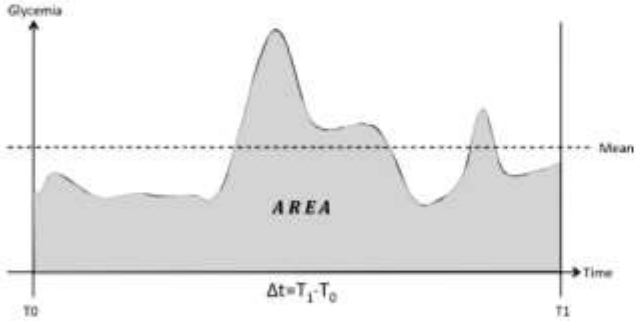

*Monnier L., Colette C., Glycemic Variability Diabetes care 2008, 31 (suppl. 2):S150-S154*

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# Definizioni

## Esposizione glicemica

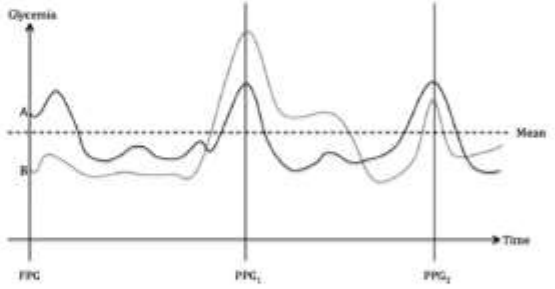
**Media** delle glicemie del periodo precedente espressa dalla HbA1c




**MGV = AUC/$\Delta t$.**

## Variabilità glicemica

**La frequenza e l'ampiezza dell'oscillazione attorno alla media** dei valori glicemici del paziente, esprimibile mediante la deviazione standard **(DS)** o per mezzo di altri indici



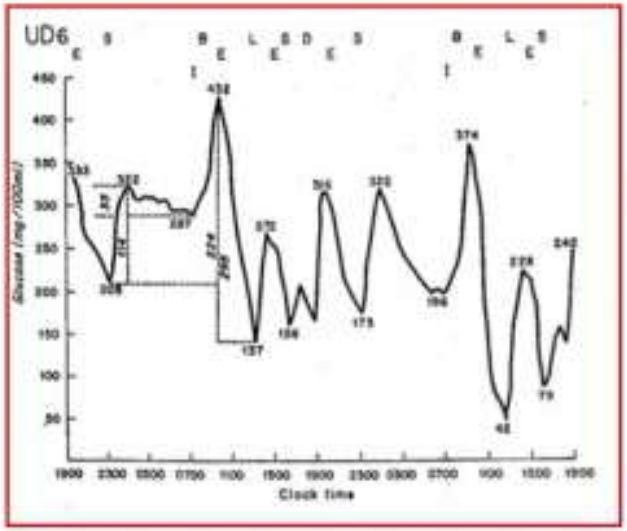

**MGV = f (FPG,PPG,GS).**

MGV: mean glucose level; FPG: fasting plasma glucose;
PPG: postprandial plasma glucose; GS: glycemic swings
AUC: area under the curve

*Zaccardi F Diabetes Metab Res Rev. 2009; 25: 199- 207*

# Mean Amplitude of Glycemic Excursion

Service et al. Diabetes 1970,19(9):644-655




- E' la media delle escursioni glicemiche giornaliere che eccedono la SD misurata nelle 24 ore.
- Si fonda sull'utilizzo di un monitoraggio glicemico continuo delle 24 ore o, anche se con alcune riserve, su profili glicemici completi a 7 punti per calcolare la media e la SD.
- L'obiettivo di questo indicatore è quello di considerare le escursioni glicemiche maggiori e ignorare quelle meno importanti

# Quali sono le componenti della VG ?

**Diabete tipo 1 :**

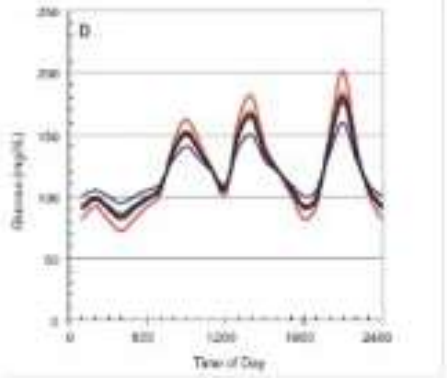
- Variabilità assorbimento insulina
- Mancata copertura postprandiale dell'insulina
- Carboidrati
- Attività fisica

**Diabete tipo 2 :**

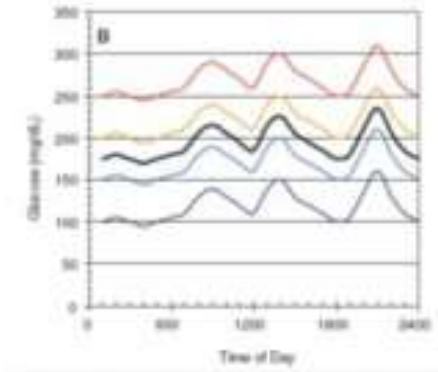
- La glicemia postprandiale
- La terapia (SU)
- Attività fisica

# Quale Variabilità Glicemica

- Intra-giornaliera
  - Pasti
  - Esercizio fisico



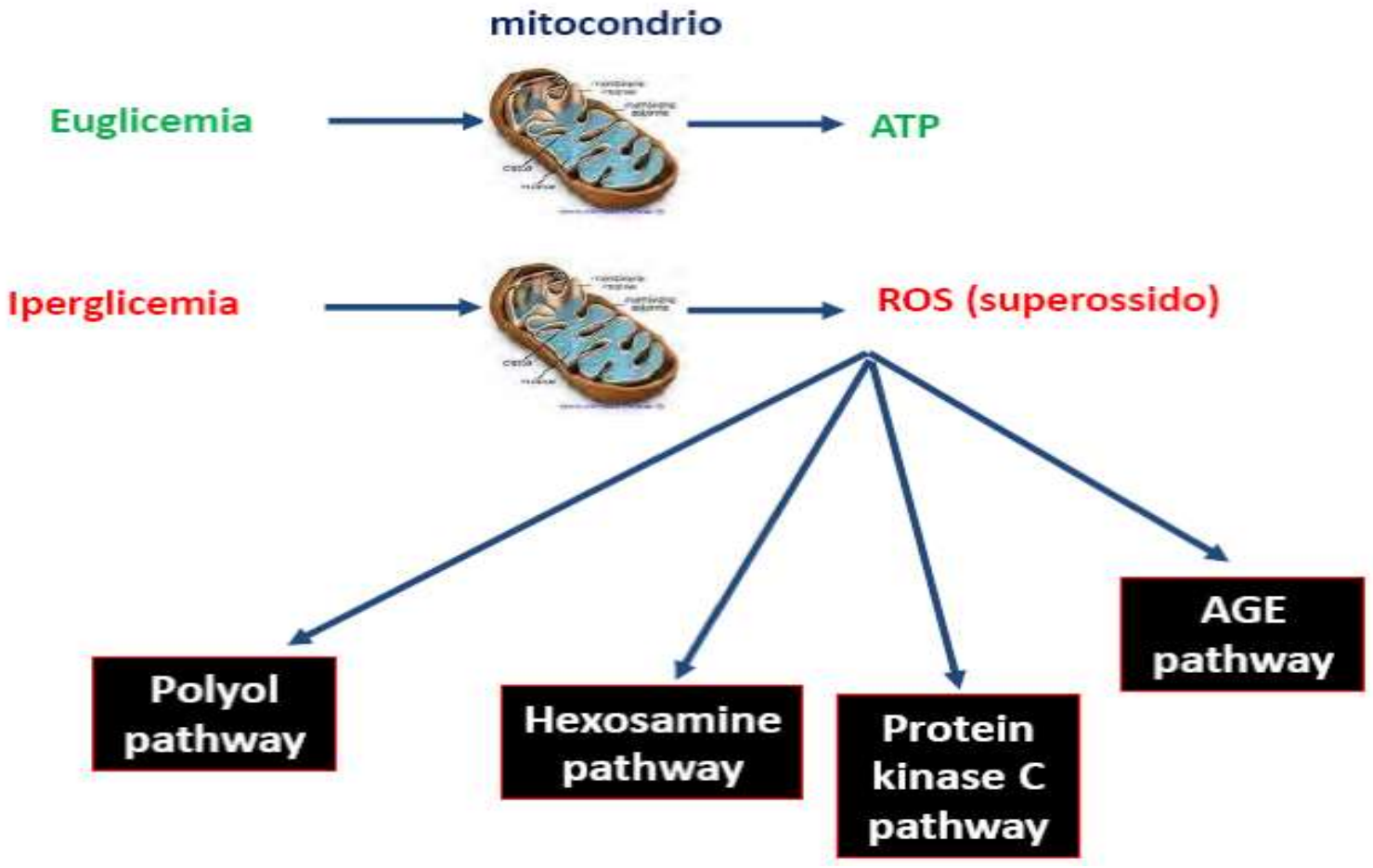

- Infra-giornaliera
  - Basalizzazione
  - Errata scelta ipoglicemizzante



# GLUCOSE VARIABILITY and DIABETIC COMPLICATIONS

## Which Mechanisms ?

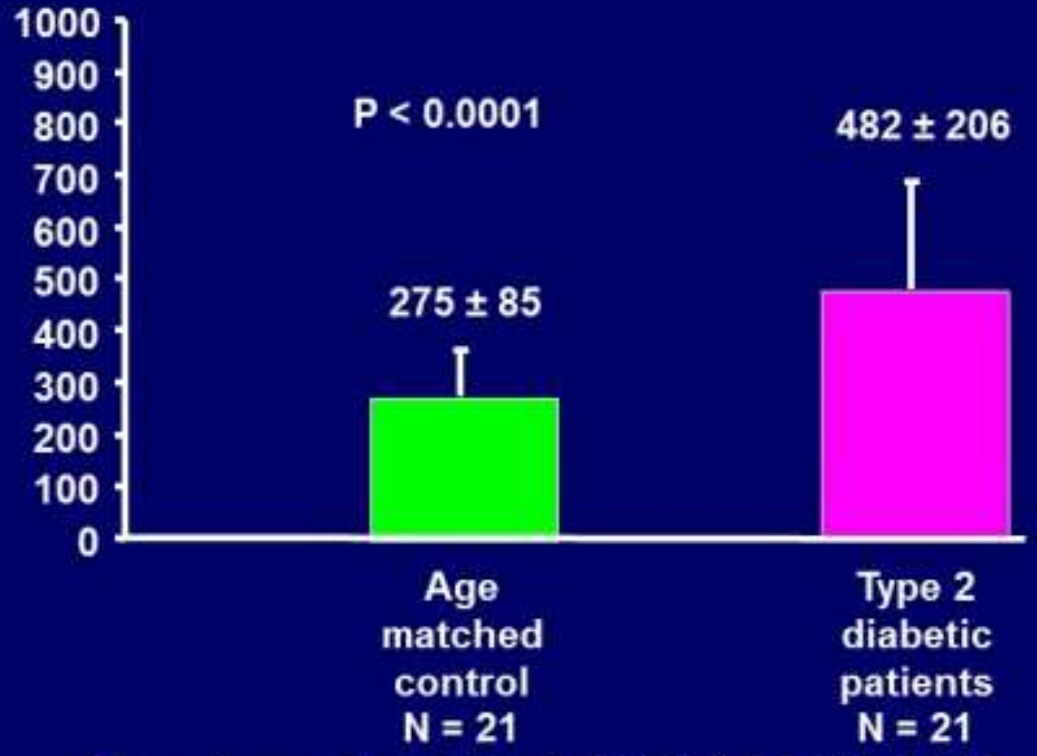
# TEORIA UNIFICANTE DI BROWNLEE



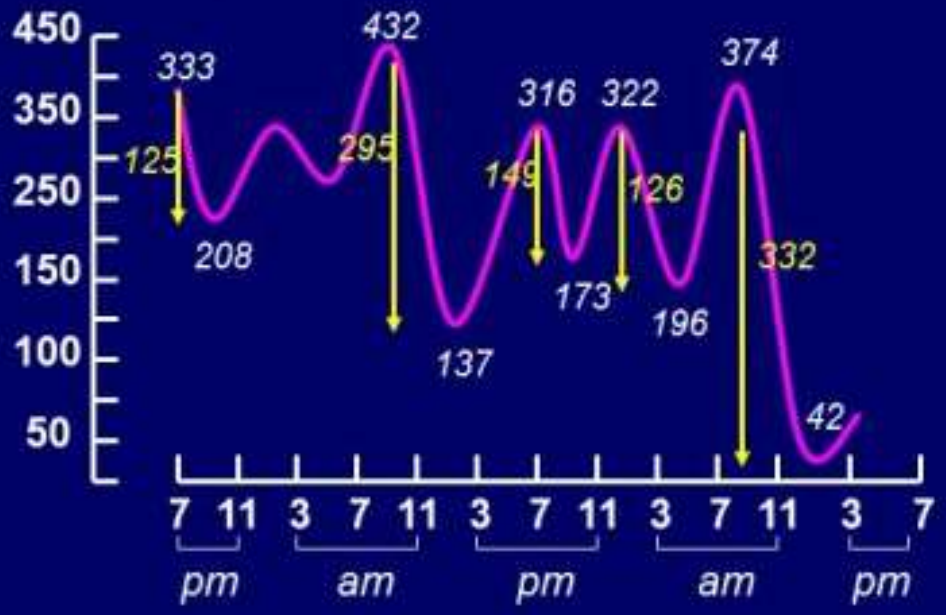

Brownlee M. Biochemistry and molecular cell biology of diabetic complications.Nature,2001

# " 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.

Abstract

CONTEXT:

Glycemic disorders, one of the main risk factors for cardiovascular disease, are associated with activation of oxidative stress.

OBJECTIVE:

To assess the respective contributions of sustained chronic hyperglycemia and of acute glucose fluctuations to oxidative stress in type 2 diabetes.

DESIGN, SETTING, AND PARTICIPANTS:

Case-control study of 21 patients with type 2 diabetes (studied 2003-2005) compared with 21 age- and sex-matched controls (studied in 2001) in Montpellier, France.

MAIN OUTCOME MEASURES:

Oxidative stress, estimated from 24-hour urinary excretion rates of free 8-iso prostaglandin F2alpha (8-iso PGF2alpha). Assessment of glucose fluctuations was obtained from continuous glucose monitoring system data by calculating the mean amplitude of glycemic excursions (MAGE). Postprandial contribution to glycemic instability was assessed by determining the postprandial increment of glucose level above preprandial values (mean postprandial incremental area under the curve [AUCpp]). Long-term exposure to glucose was estimated from hemoglobin A1c, from fasting glucose levels, and from mean glucose concentrations over a 24-hour period.

RESULTS:

Mean (SD) urinary 8-iso PGF2alpha excretion rates were higher in the 21 patients with diabetes (482 [206] pg/mg of creatinine) compared with controls (275 [85] pg/mg of creatinine). In univariate analysis, only MAGE ($r = 0.86$; $P<.001$) and AUCpp ($r = 0.55$; $P = .009$) showed significant correlations with urinary 8-iso PGF2alpha excretion rates. Relationships between 8-iso PGF2alpha excretion rates and either MAGE or AUCpp remained significant after adjustment for the other markers of diabetic control in multiple linear regression analysis (multiple $R2 = 0.72$ for the model including MAGE and multiple $R2 = 0.41$ for the model including AUCpp). Standardized regression coefficients were 0.830 ($P<.001$) for MAGE and 0.700 ($P = .003$) for AUCpp.

CONCLUSIONS:

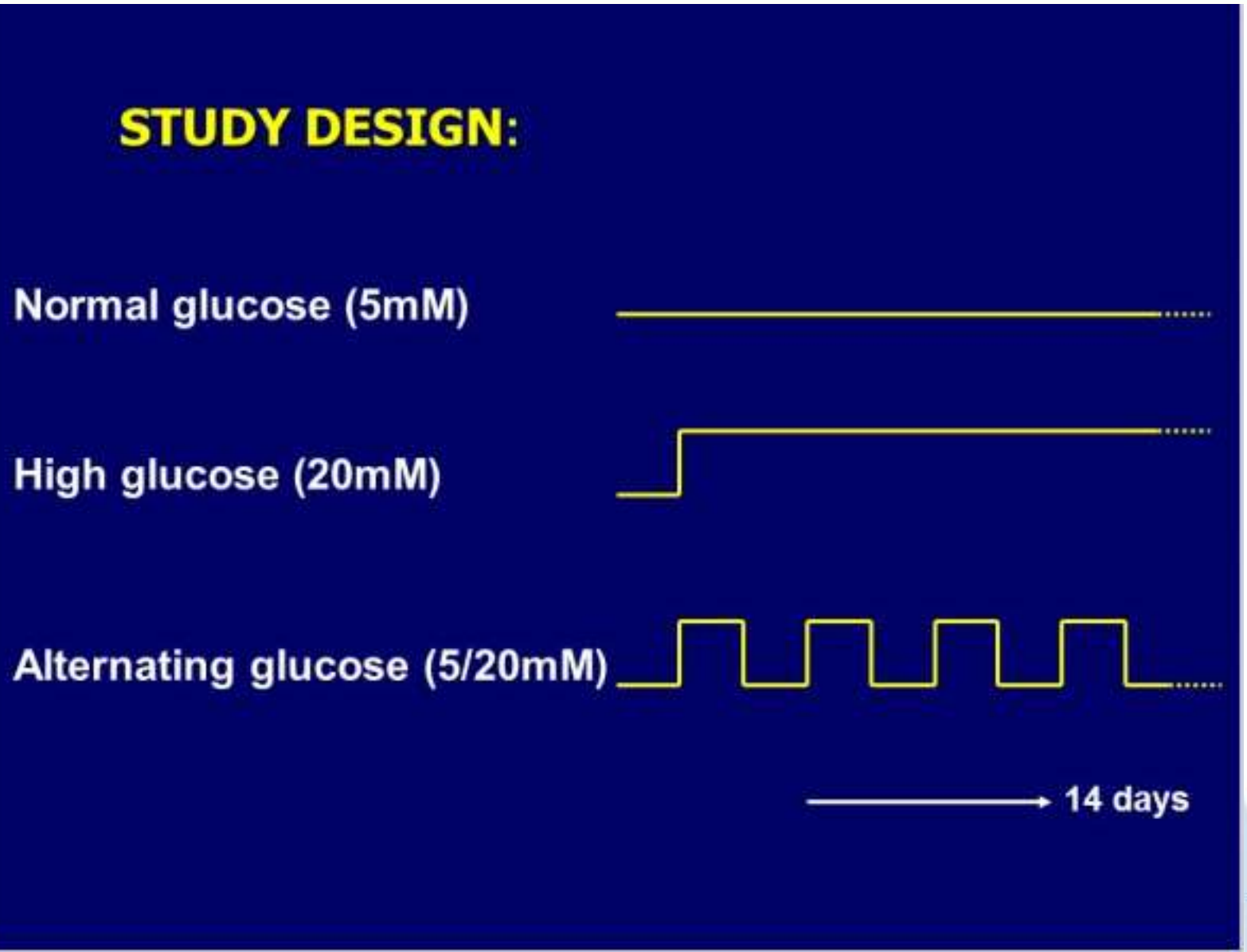
Glucose fluctuations during postprandial periods and, more generally, during glucose swings exhibited a more specific triggering effect on oxidative stress than chronic sustained hyperglycemia. The present data suggest that interventional trials in type 2 diabetes should target not only hemoglobin A1c and mean glucose concentrations but also acute glucose swings.

# Intermittens high glucose enhances apoptosis in human umbilical vein endothelial cells in culture

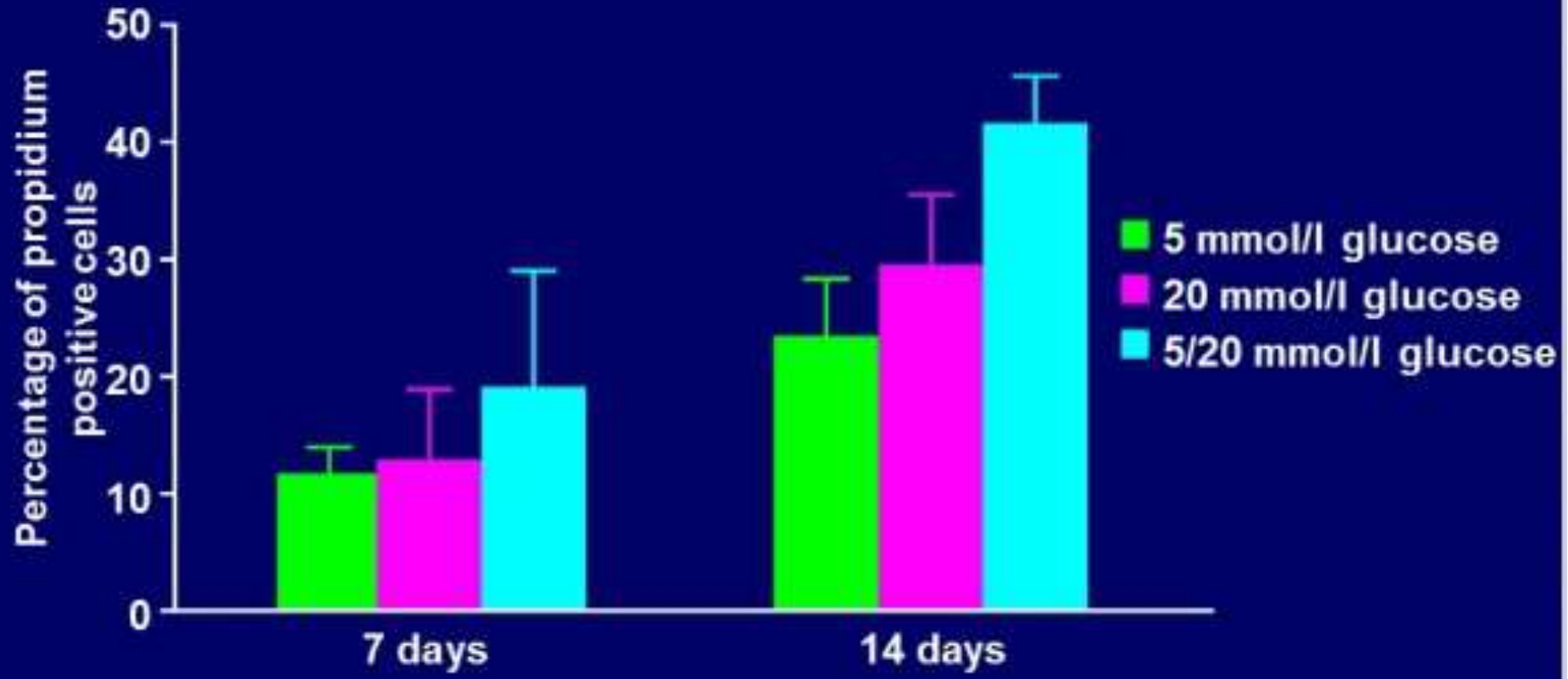
Risso A,Mercuri F,Quagliaro L,Damante G,Ceriello A.

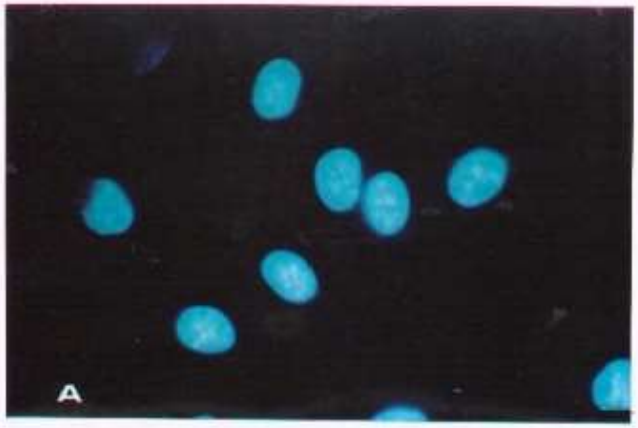
AM J Physiol,2001

# STUDY DESIGN:



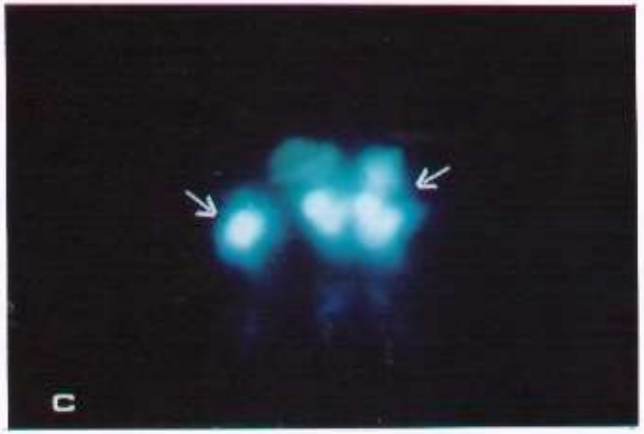
# Cell death of HUVECs cultured with different concentrations of glucose












A = Concentrazioni normali di glucosio (5mM)

B = Concentrazioni elevate di glucosio (20mM)

C = Concentrazioni alternate di glucosio (5/20mM)

# Evidenze cliniche

# DATI EPIDEMIOLOGICI

## Evidence in type 1 diabetes

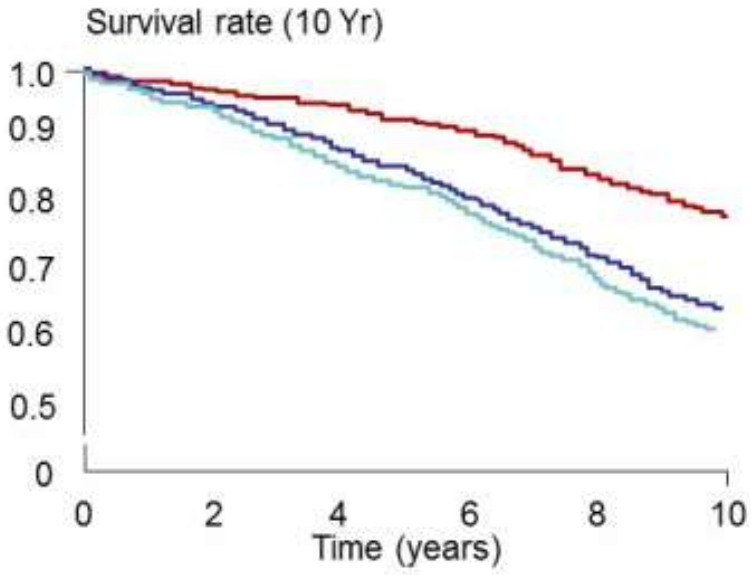
**Kilpatrick reported:**

- **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 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

# San Luigi Gonzaga Diabetes Study

- 529 (284 men and 245 women) consecutive type 2 diabetic patients;[1]
- 77 events over 5 years;[1]
- Multivariate analysis including HbA1c, pre- and postprandial glucose showed only post-lunch glucose to be predictive;[1]
- Long-term follow-up (10 years) confirms this evidence.[2]

[1] JCEM 2005;91,813-819
[2] Diabetes Care 2011; 34:2237-2243

# Trials d'intervento

## Studies have investigated postprandial glycaemic excursions and CV risk

- Intervention trials:
  - Positive in primary prevention (STOP-NIDDM)[1]
  - Negative in secondary prevention (HEART2D-NAVIGATOR)[2,3]

    (In both HEART2D[2] and NAVIGATOR[3] the goal of reducing PPG was not achieved)
  - Positive, in a post-hoc analysis of the HEART2D Study, in the older patients and in patients with longer duration of the disease[4]

International Diabetes Federation

1. Chiasson JL, et al. JAMA 2003;290:486-94.
2. Raz I, et al. Diabetes Care 2009;32:381-386.
3. NAVIGATOR study Group. N Engl J Med 2010;362:1463-1476
4. Raz et al Diabetes care, 2011;34:1511-1513

# Impact of Visit-to-Visit Glycemic Variability on the Risks of Macrovascular and Microvascular Events and All-Cause Mortality in Type 2 Diabetes: The ADVANCE Trial

## RESULTS

- **Among 4,399 patients in the intensive group, an increase in visit-to-visit variability (VVV) of HbA1c was associated with an increased risk of vascular events** (P = 0.01) and with mortality (P < 0.001): highest versus lowest tenth hazard ratio (95% CI) 1.64 (1.05–2.55) and 3.31 (1.57–6.98), respectively, after multivariable adjustment.

- **A clear association was also observed between VVV of fasting glucose and increased risk of vascular events** (P < 0.001; 2.70 [1.65–4.42]).

- **HbA1c variability was positively associated with the risk of macrovascular events (P = 0.02 for trend), whereas glucose variability was associated with both macro- and microvascular events** (P = 0.005 and P < 0.001 for trend, respectively).

*Hirakawa et al, Diabetes Care May 8, 2014*

original article

*Diabetes, Obesity and Metabolism* 12: 288–298, 2010.
© 2010 Blackwell Publishing Ltd

ORIGINAL ARTICLE

# Glycaemic variability and complications in patients with diabetes mellitus: evidence from a systematic review of the literature

L. Nalysnyk[1], M. Hernandez-Medina[1] & G. Krishnarajah[2]

- In base alle prove disponibili , la variabilità di glucosio, caratterizzata da escursioni estreme di glucosio, potrebbe essere un predittore di complicanze diabetiche, indipendente dai livelli di HbA1c , in pazienti con DM tipo 2 .

- E' importante migliorare le escursioni giornaliere del glucosio , soprattutto nel periodo postprandiale, per ridurre il rischio di complicanze diabetiche.

•**Diabetes, Obesity and Metabolism**
•Volume 12, Issue 4, pages 288–298, April 2010

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AIM:

The objective of this review was to assess the published evidence for an association between glycaemic variability and the development of chronic micro- and macrovascular complications in patients with diabetes mellitus (DM).

METHODS:

A systematic review of English-language literature published from January 1990 through November 2008 was performed. Interventional and observational studies in patients with type 1 or type 2 DM reporting a measure of glycaemic variability and its impact on the development or progression of micro- and macrovascular diabetic complications were assessed.

RESULTS:

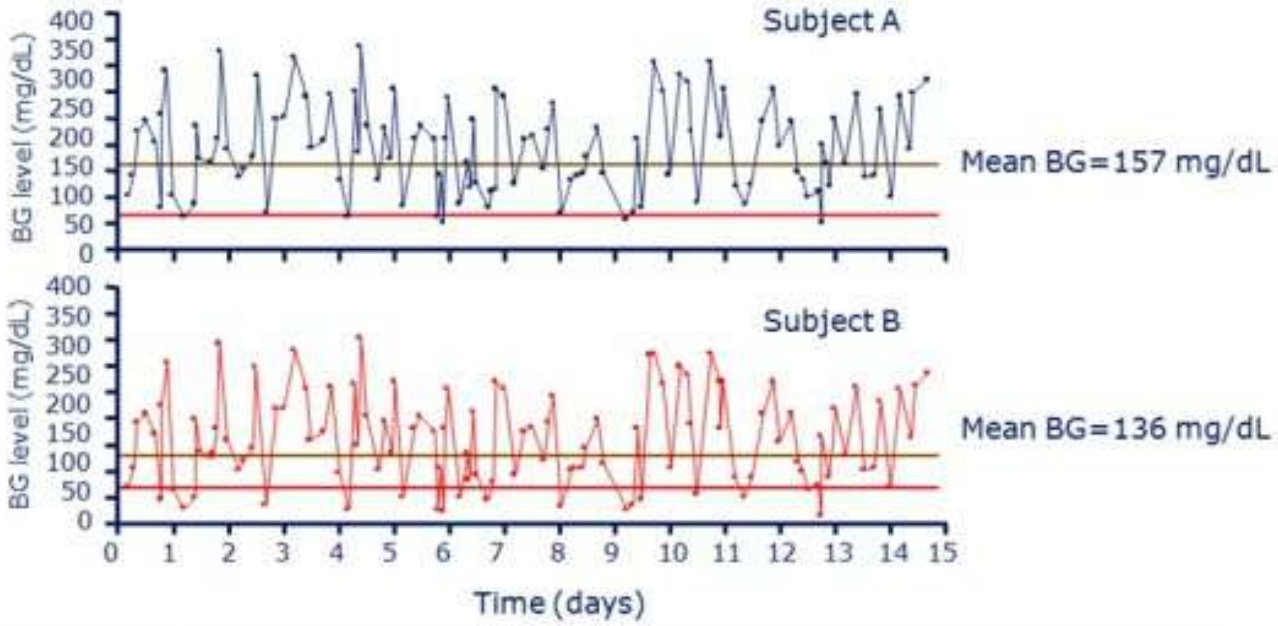
A total of 18 studies -8 on type 1 DM and 10 on type 2 DM patients-meeting the inclusion criteria were identified. Studies in patients with type 1 DM revealed that glucose variability has little impact on the development of diabetic complications. Only in two of the eight type 1 DM studies did glucose variability have a significant association with microvascular complications, but not with macrovascular complications. Among type 2 DM studies, a significant positive association between glucose variability and the development or progression of diabetic retinopathy, cardiovascular events and mortality was reported in 9 of 10 studies. Only one type 2 DM study reported no association between glucose variability and progression of retinopathy.

CONCLUSIONS:

Based on this overview of the available evidence, there appears to be a signal suggesting that glucose variability, characterized by extreme glucose excursions, could be a predictor of diabetic complications, independent of HbA1c levels, in patients with type 2 DM. Better daily control of blood glucose excursions, especially in the postprandial period, may reduce the risk of these complications. Future prospective trials evaluating and comparing the effect of the control of glycaemic variability on the development of diabetic micro- and macrovascular complications are needed to further strengthen the evidence base.

# THERAPEUTIC PERSPECTIVES

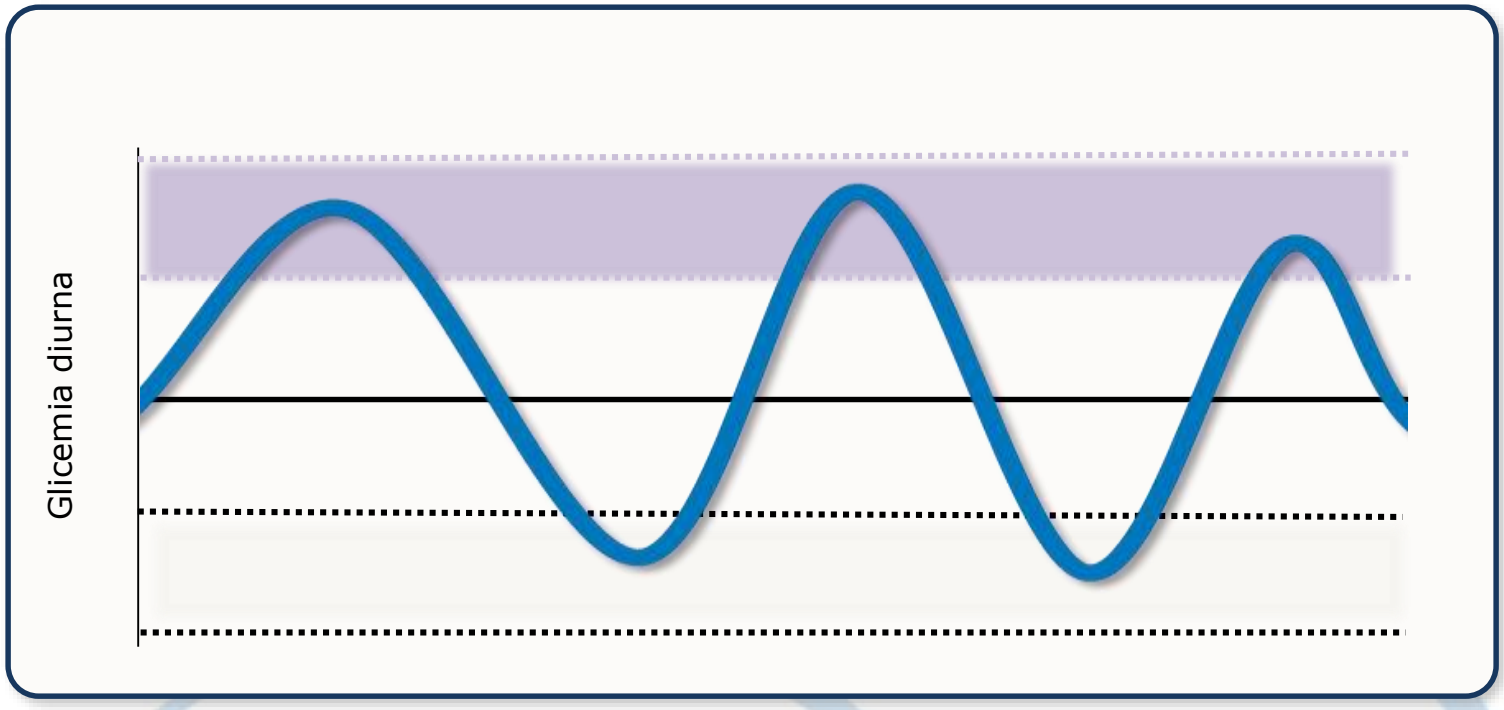
# Reducing average glycaemia without reducing variability may be dangerous




- 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

# Efficacia dei DPP IV inibitori sulla Variabilità Glicemica: quali evidenze abbiamo?




Kleefstra N, et al. Neth J Med. 2005;63:215-21. Monnier L, et al. JAMA. 2006;295:1681-7. Cerriello A, et al. Nutr Metab Cardiovasc Dis. 2006;16:453-6. Mitri J, Hamdy O. Expert Opin Drug Saf. 2009;8:573-84. Marrett E, et al. Diabetes Obes Metab. 2009;11:1138-44.

DIAlogue
Diabete e relazioni transculturali
GISED
Gruppo di studio ADI-AMD-SID "Nutrizione e diabete"

Sakamoto *et al. Cardiovascular Diabetology* 2012, **11**:92
http://www.cardiab.com/content/11/1/92

CARDIO VASCULAR DIABETOLOGY

**ORIGINAL INVESTIGATION** **Open Access**

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

Masaya Sakamoto[1*], Rimei Nishimura[1,2], Taiga Irako[1], Daisuke Tsujino[1], Kiyotaka Ando[1] and Kazunori Utsunomiya[1]

In collaborazione con
AMD
Scuola Permanente di Formazione Continua AMD

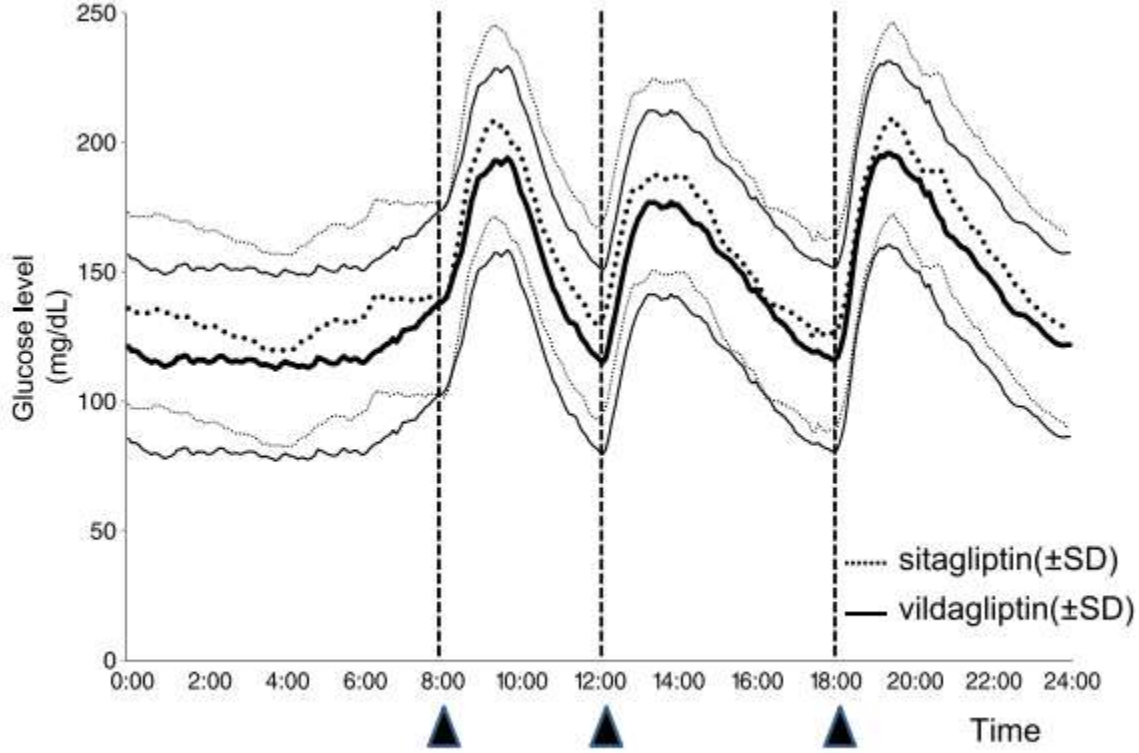



**Figure 2 Glucose levels over 24 h during treatment with vildagliptin or sitagliptin in 20 patients.** Data are mean ± standard deviation.

Vildagliptin vs sitagliptin p-value HbA1c (%) 7.54 ± 0.93 7.64 ± 0.93 0.211

MAGE was significantly lower in patients taking vildagliptin than patients taking sitagliptin (p = 0.040)

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

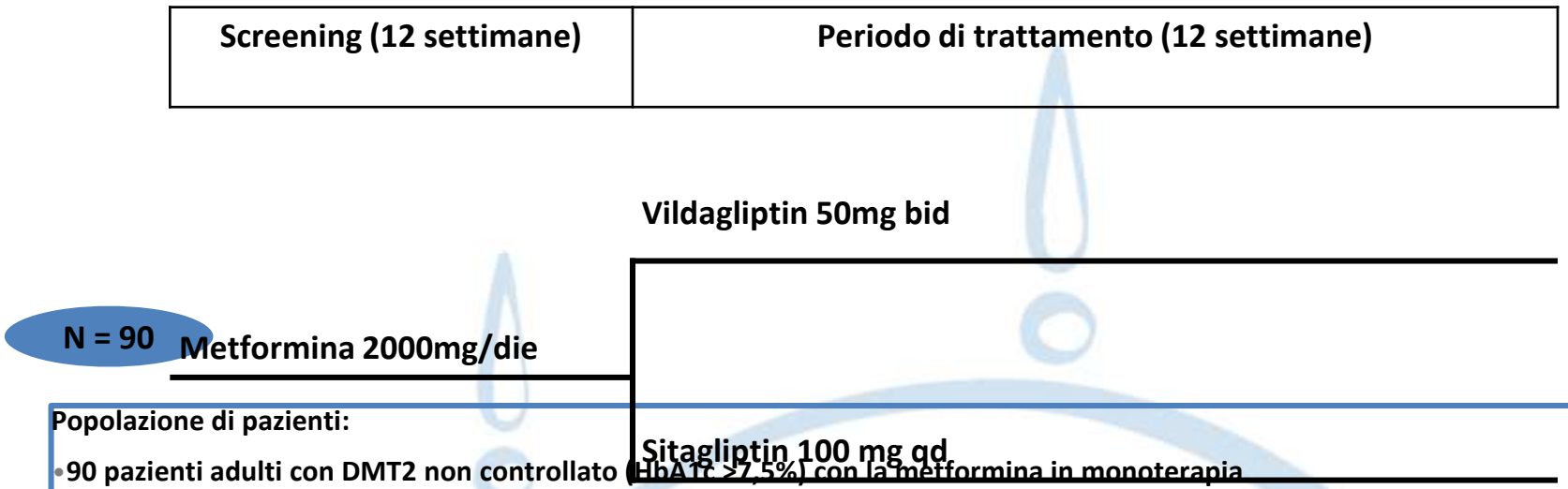
## Role of dipeptidyl peptidase-IV inhibition

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

Rizzo et al. Diabetes Care 2012

# Vildagliptin 50 mg bid vs. sitagliptin 100 mg qd, in add-on a metformina, su variabilità glicemica, stress ossidativo e infiammazione

**Disegno dello studio: studio prospettico, randomizzato, open-label con blinded endpoint (PROBE design), di 12 settimane di trattamento**




**Popolazione di pazienti:**

- **90 pazienti adulti con DMT2 non controllato (HbA1c >7,5%) con la metformina in monoterapia**

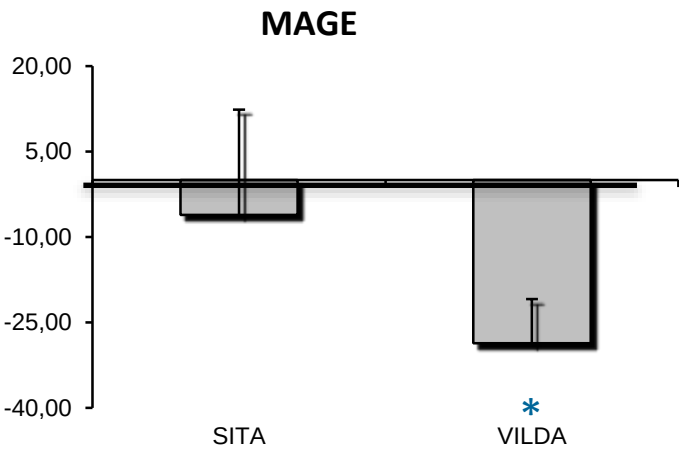
**Obiettivi:**

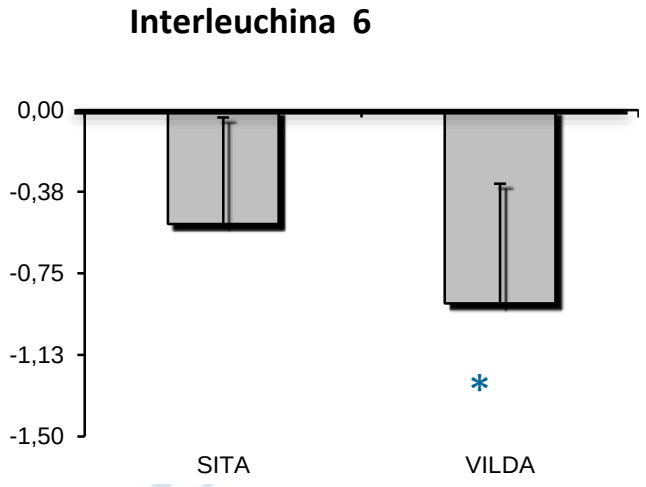
- Confrontare l'effetto di vildagliptin 50 mg bid vs. sitagliptin 100 mg qd (entrambi in add-on a merformina) sulle **fluttuazioni glicemiche acute giornaliere**, valutate **in cieco** attraverso il MAGE (mean amplitude of glycemic excursions), dopo un periodo di 12 settimane di trattamento randomizzato
- Confrontare gli effetti di vildagliptin e quelli di sitagliptin sullo **stress ossidativo**, valutato attraverso i livelli di nitrotirosina plasmatica
- Confrontare vildagliptin e sitagliptin relativamente all'**infiammazione**, valutata attraverso le citochine infiammatorie IL-6, IL-18 & TNF-α

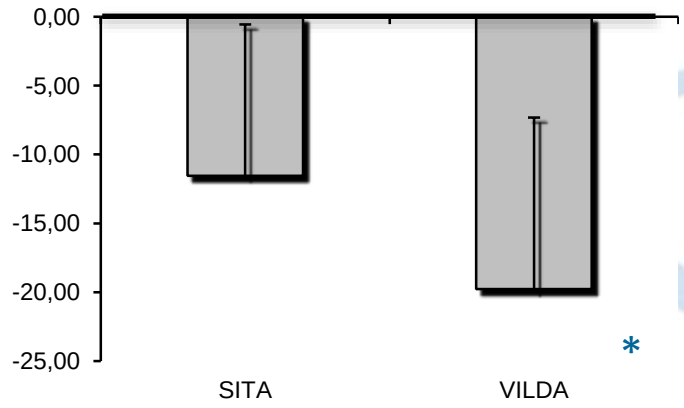
Scuola Permanente di Formazione Continua AMD

Rizzo et al. Diabetes Care 2012

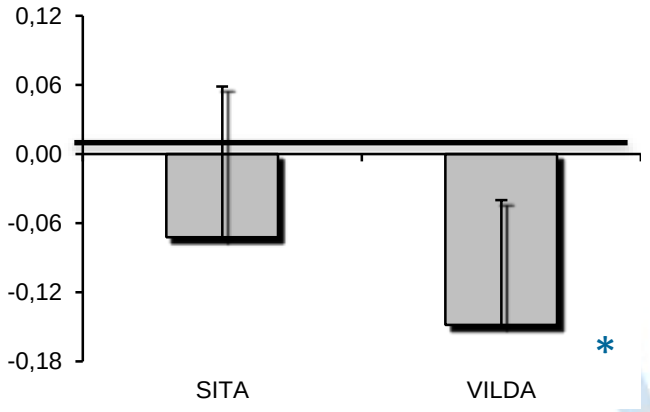
# Variazioni dopo 3 mesi di terapia a base di Vildagliptin o Sitagliptin in aggiunta a Metformina




Interleuchina 18



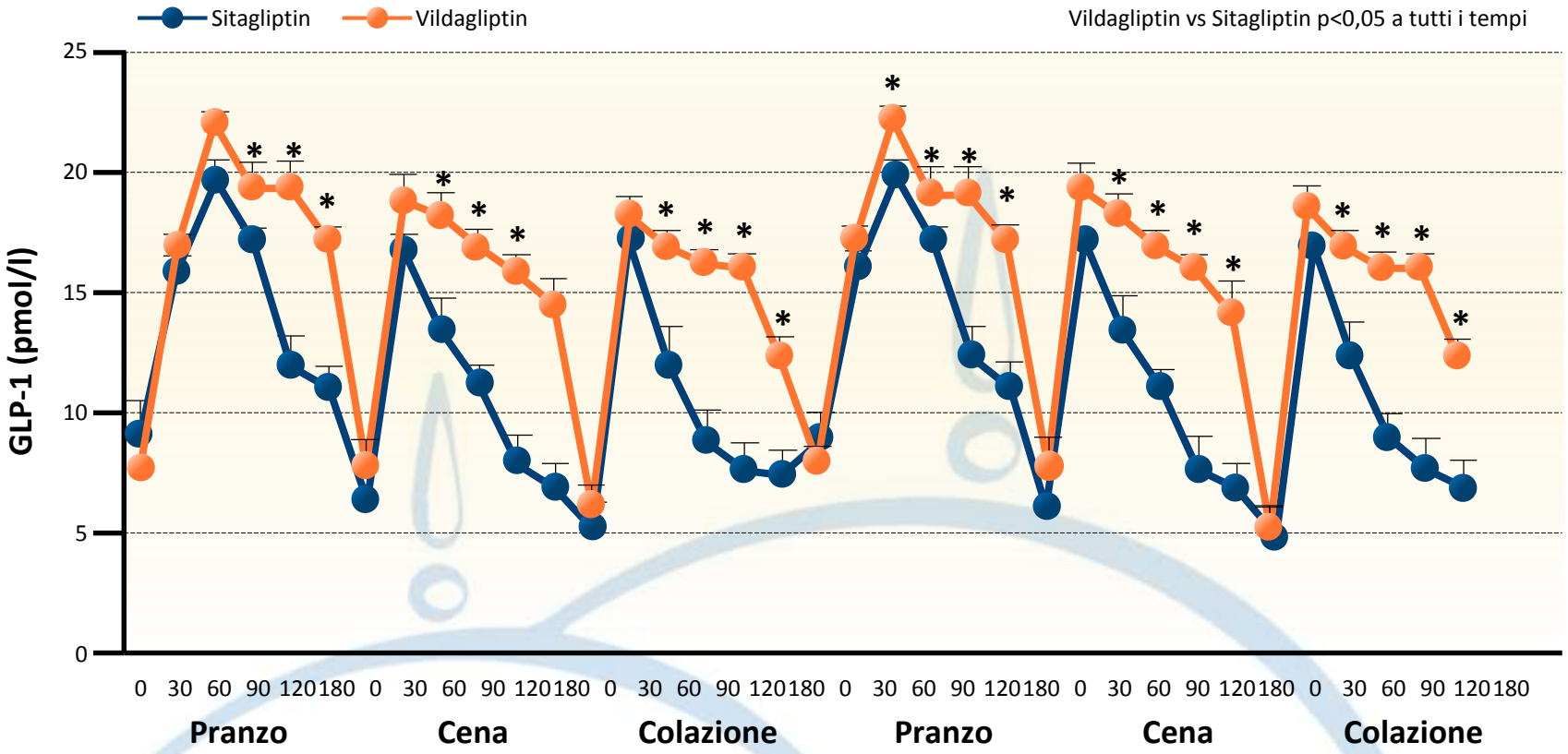

Nitrotirosina

*P<0.05

Rizzo et al. Diabetes Care 2012

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# Livelli post prandiali ed interprandiali di GLP-1 in pazienti trattati con Vildagliptin o Sitagliptin




Livelli di GLP1 dopo 12 settimane di trattamento con vildagliptin (50 mg due volte al giorno) o sitagliptin (100 mg una volta al giorno)

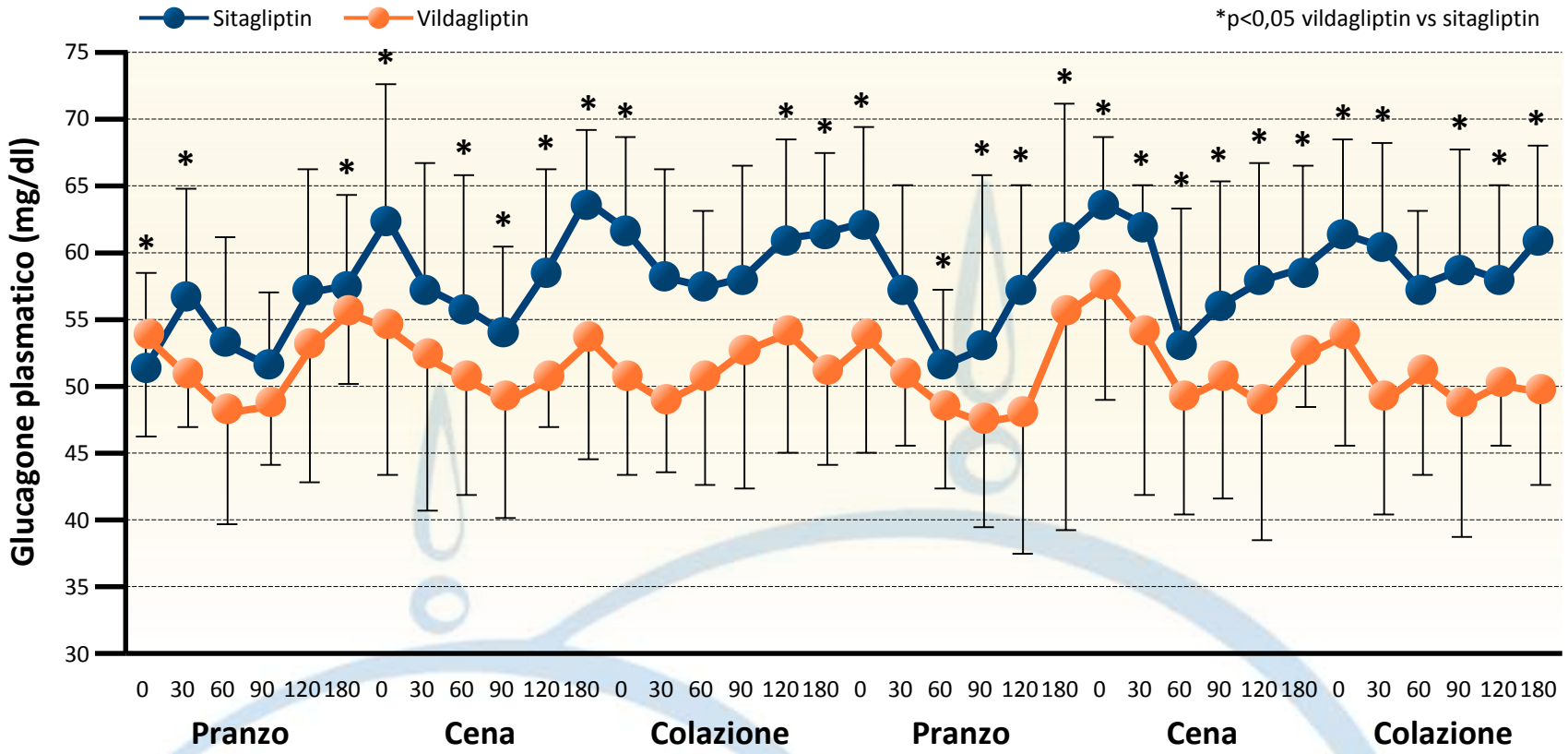
In collaborazione con

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Rizzo et al. Diabetes Care 2012

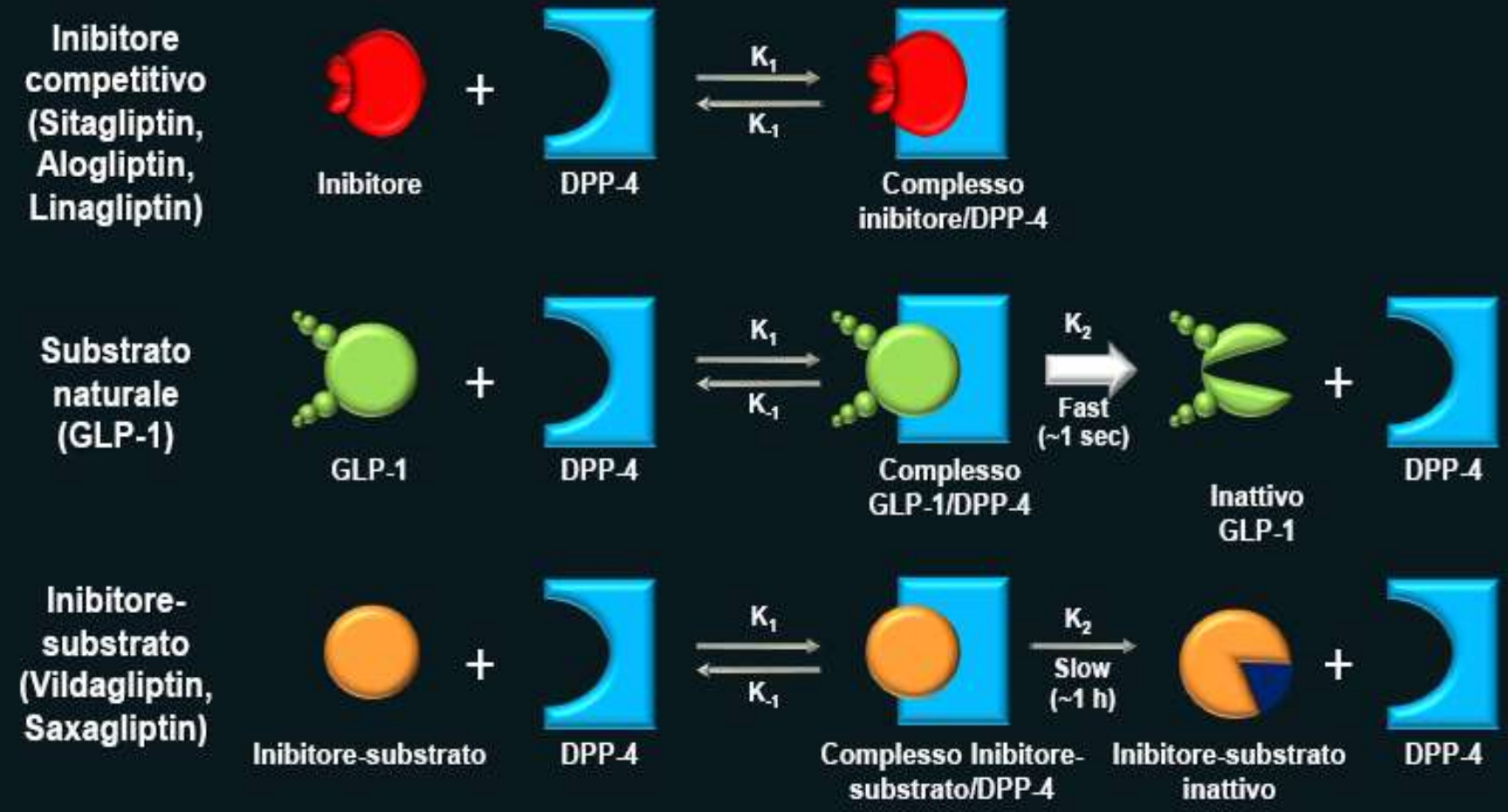
# Livelli post prandiali ed interprandiali di glucagone in pazienti trattati con Vildagliptin o Sitagliptin




Glucagone plasmatico dopo 12 settimane di trattamento con vildagliptin (50 mg due volte al giorno) o sitagliptin (100 mg una volta al giorno)

Rizzo et al. Diabetes Care 2012

# Cinetica di Legame con la DPP-4 e Meccanismo di Inibizione




DPP-4=dipeptidyl peptidase-4; GLP-1=glucagon-like peptide-1.

Burkey BF, et al. Poster 0788 presented at EASD 2006; Deacon CF, Holst JJ. *Adv Ther*. 2009; 26: 488–499; Miller SA, St Onge EL. *Ann Pharmacother*. 2006; 40: 1336–1343; Neumiller JJ. *J Am Pharm Assoc*. 2009; 49: S16–S29; White JR. *Clin Diabetes*. 2008; 26: 53–57.

# Comparison of the dipeptidyl peptidase-4 inhibitor vildagliptin and the sulphonylurea gliclazide in combination with metformin, in Muslim patients with type 2 diabetes mellitus fasting during Ramadan: results of the VECTOR study

**Objective:**
To compare the incidence of hypoglycaemic events (HEs) in a real-world setting in Muslim patients with type2 diabetes mellitus fasting during Ramadan.
**Research design and methods:**
We performed a 16-week prospective, non-interventional, two-cohort study. Data were collected 1–6 weeks before and 6 weeks after fasting. Patients were enrolled who had been receiving vildagliptin (50 mg twice daily) or sulphonylurea (SU) as add-on to metformin at least 4 weeks prior to fasting.
**Main outcome measures:**
The primary efficacy endpoint was incidence of HEs during the Ramadan fast. Changes in glycated haemoglobin (HbA1c) and body weight, as well as adherence to treatment, were also assessed.

**Current Medical Research & Opinion Vol. 27, No. 7, 2011, 1367–1374**

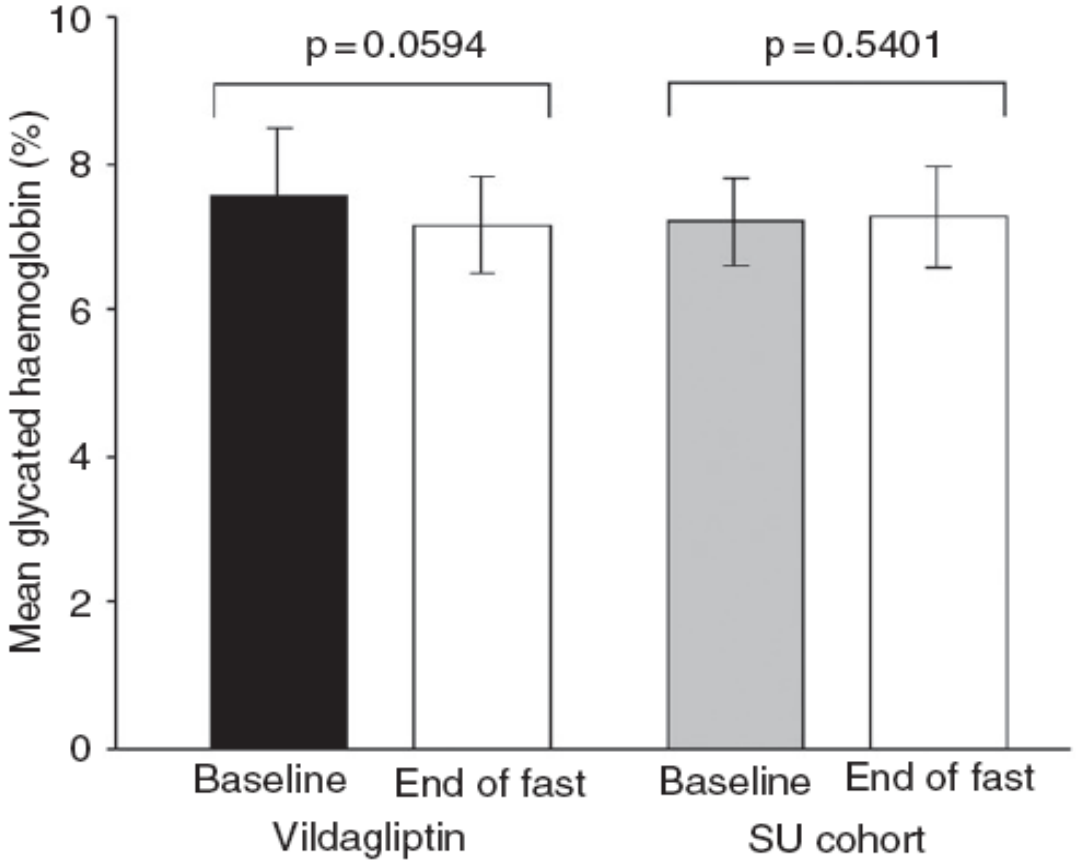



Figure 1. Mean (SD) glycated haemoglobin ($HbA_{1c}$) at baseline and following Ramadan fasting in patients who had both $HbA_{1c}$ assessments (vildagliptin, $n = 20$; SU, $n = 32$). Mean between-group difference (vildagliptin cohort minus SU cohort) in $HbA_{1c}$ change from baseline: −0.5% (95% CI −0.9%, −0.1%) ($p = 0.0262$). SU, sulphonylurea.

**Current Medical Research & Opinion Vol. 27, No. 7, 2011, 1367–1374**

Table 2. Number of HEs and severe HEs reported during Ramadan fasting in the per protocol population ($n = 59$).

| | Vildagliptin cohort $n = 23$ | SU cohort $n = 36$ |
|---|---|---|
| HEs* | | |
| Experienced ≥1 event | 0 | 15 |
| Mean (SD) | 0.0 (0.0) | 0.9 (1.3) |
| Range | 0 | 0–4 |
| 95% CI | (0, 0) | (0.5, 1.4) |
| Total | 0 | 34 |
| Severe (grade 2) HEs† | | |
| Experienced ≥1 event | 0 | 1 |
| Mean (SD) | 0.0 (0.0) | 0.0 (0.2) |
| Range | 0 | 0–1 |
| 95% CI | (0, 0) | (0.0, 0.1) |
| Total | 0 | 1 |

The mean between-group difference for the proportion of patients who experienced at least one HE (SU minus vildagliptin cohort) was 41.7% (95% CI 25.6%, 57.8%) ($p = 0.0002$).

*Mean between-group difference (vildagliptin cohort minus SU cohort) in the number of HEs: −0.9 (95% CI −1.5, −0.4) ($p = 0.0013$).

Current Medical Research & Opinion Vol. 27, No. 7, 2011, 1367–1374

# The effect of vildagliptin relative to sulphonylureas in Muslim patients with type 2 diabetes fasting during Ramadan: the VIRTUE study

M. Al-Arouj,[1] A. A. K. Hassoun,[2] R. Medlej,[3] M. F. Pathan,[4] I. Shaltout,[5] M. S. Chawla,[6] S. Hristoskova,[7] S. DiTommaso,[7] M. Y. Kadwa[7]

**Aims**: To assess, in a real-world setting, the effect of vildagliptin compared with sulphonylurea (SU) treatment on hypoglycaemia in Muslim patients with type 2 diabetes mellitus (T2DM) fasting during Ramadan.

**Methods**: This multinational, non-interventional study, conducted in Asia and the Middle East, included Muslim adult patients with T2DM who received treatment with vildagliptin or SU as addon to metformin or monotherapy. During a ~16-week observation period, data were collected up to 6 weeks before and 6 weeks after Ramadan fasting. The primary study objective was to compare the proportion of patients with ≥ 1 hypoglycaemic
event (HE) during fasting.

**Int J Clin Pract doi: 10.1111/ijcp.12243**

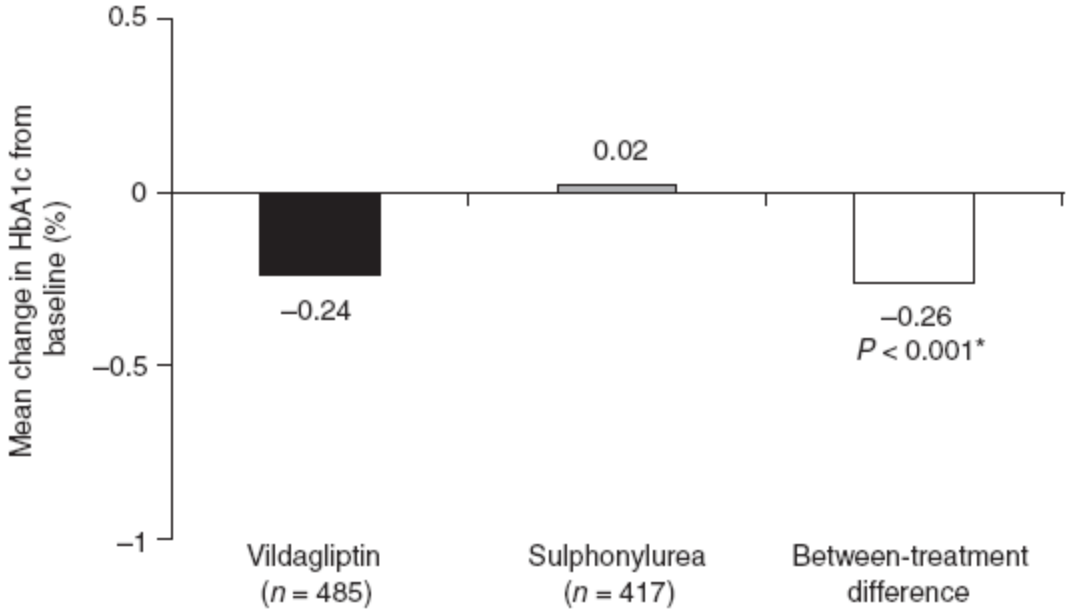



**Figure 2** Mean change in HbA1c pre- to post-Ramadan in vildagliptin and SU cohorts. Primary analysis set of patients with both pre- and post-Ramadan HbA1c measurements. *Two sample *t*-test. Last observation carried forward

**Int J Clin Pract doi: 10.1111/ijcp.12243**

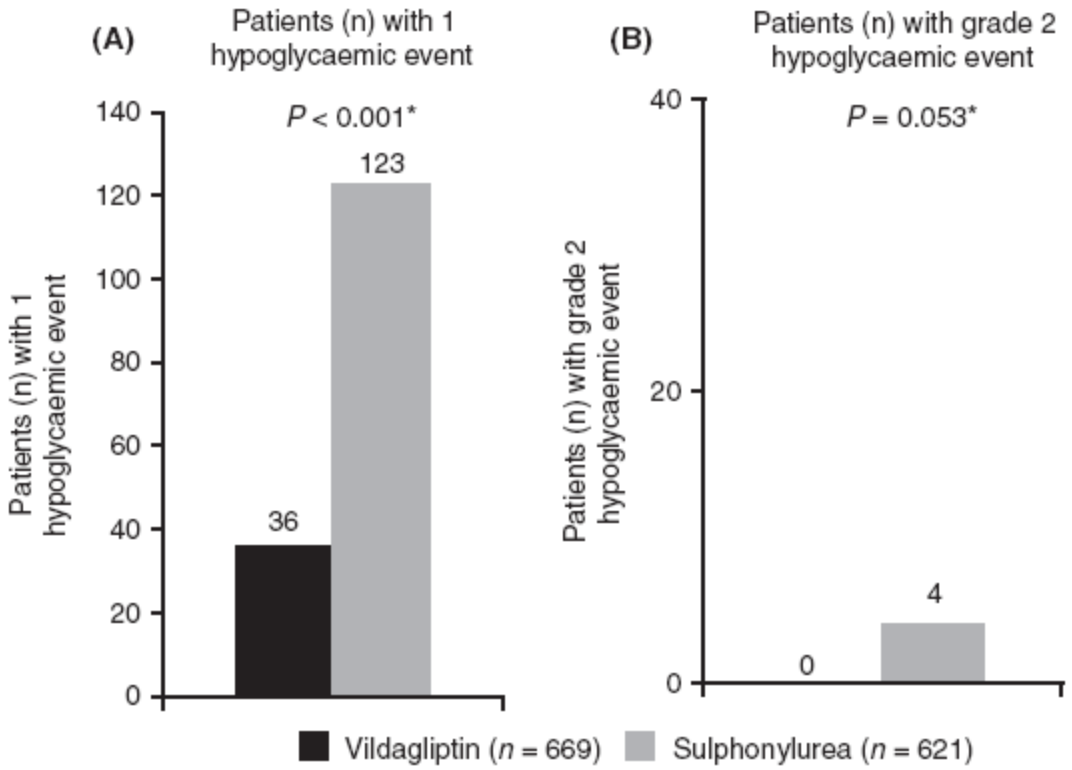
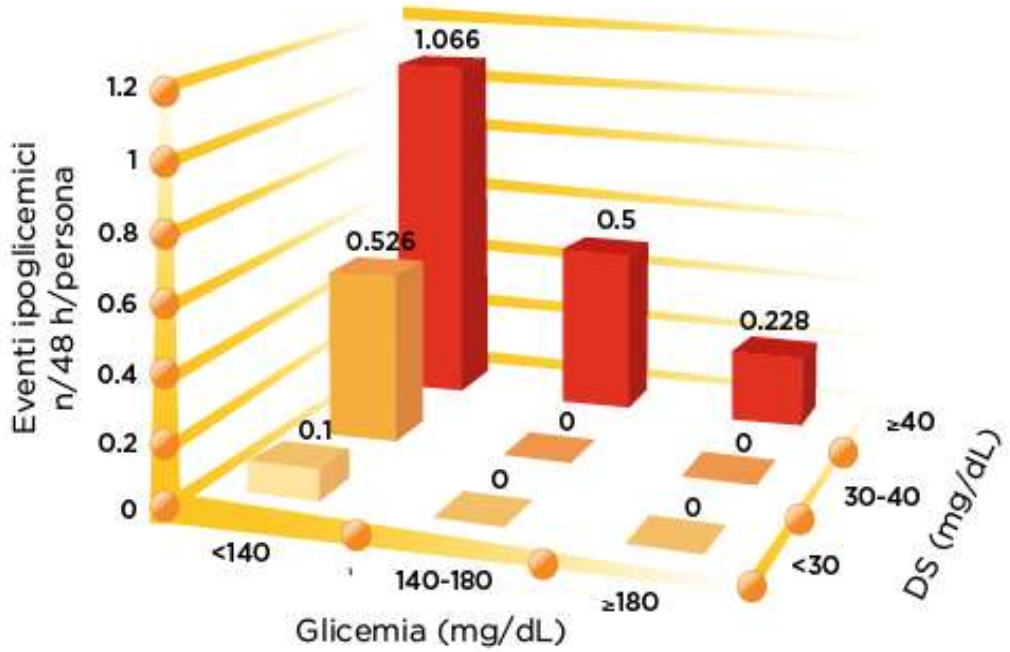



**Figure 1** Number of patients with hypoglycaemic events (HEs) during Ramadan fasting. Includes patients with a postbaseline assessment of HEs. *Fishers exact test

**Int J Clin Pract doi: 10.1111/ijcp.12243**

# Variabilità glicemica e rischio di ipoglicemie asintomatiche

Frequenze di ipoglicemie asintomatiche in funzione dei livelli di glicemia e variabilità glicemica (Deviazione Standard - DS) [5]



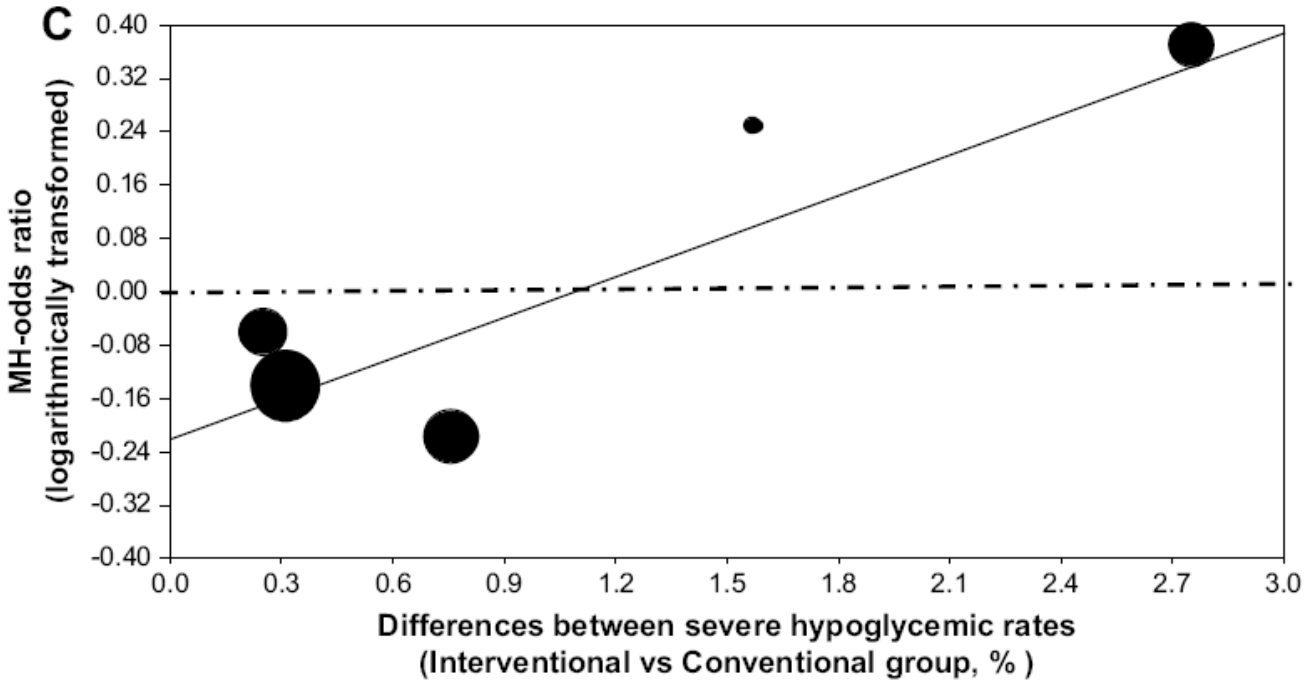

Monnier et al Diabetes Technology & Therapeutics 2011

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## Prevention of cardiovascular disease through glycemic control in type 2 diabetes: A meta-analysis of randomized clinical trials

E. Mannucci*, M. Monami, C. Lamanna, F. Gori, N. Marchionni

Cardiovascular mortality



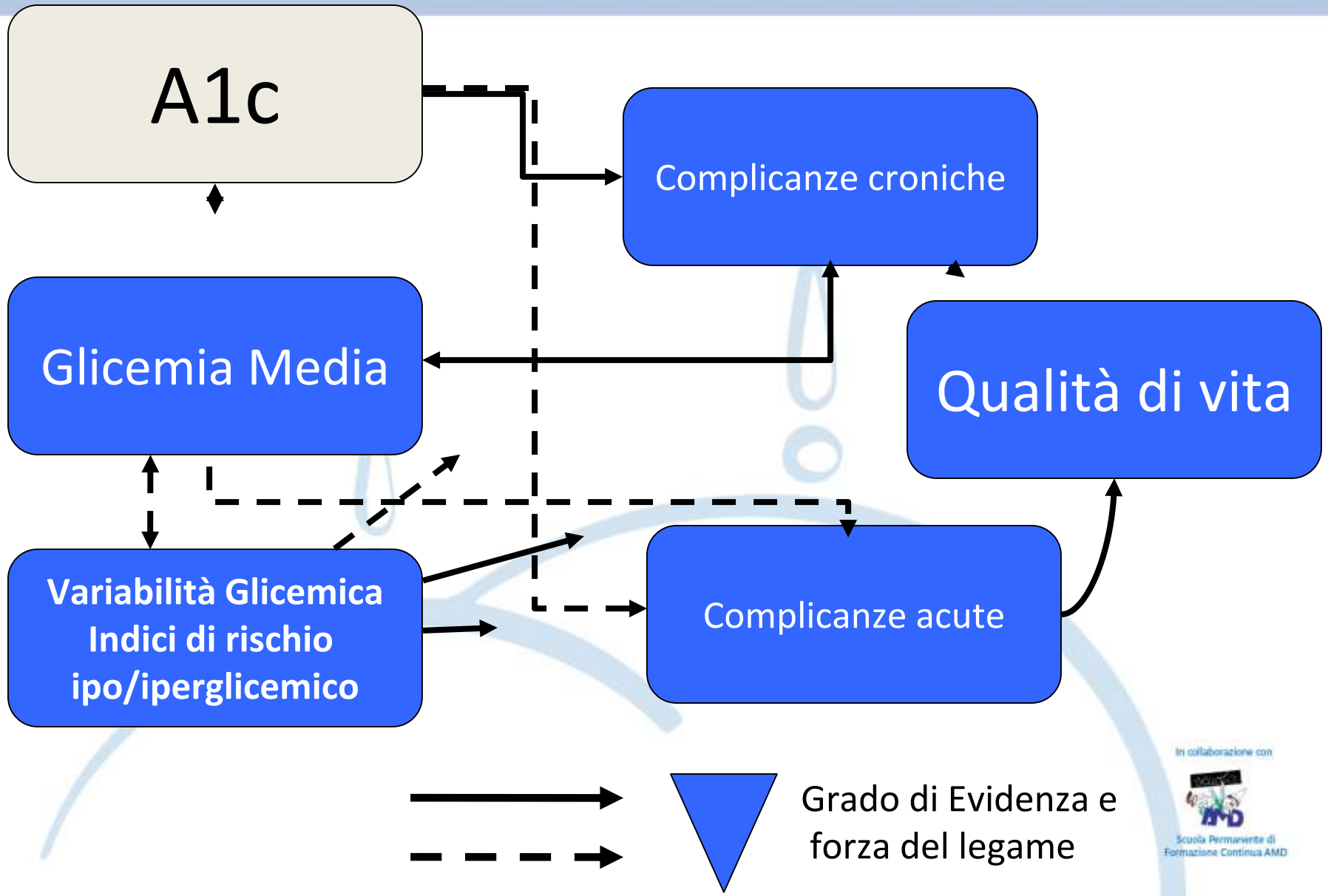

*In trials in which the reduction of HbA1c was obtained with a higher incidence of hypoglycaemia, CV MORTALITY is increased*

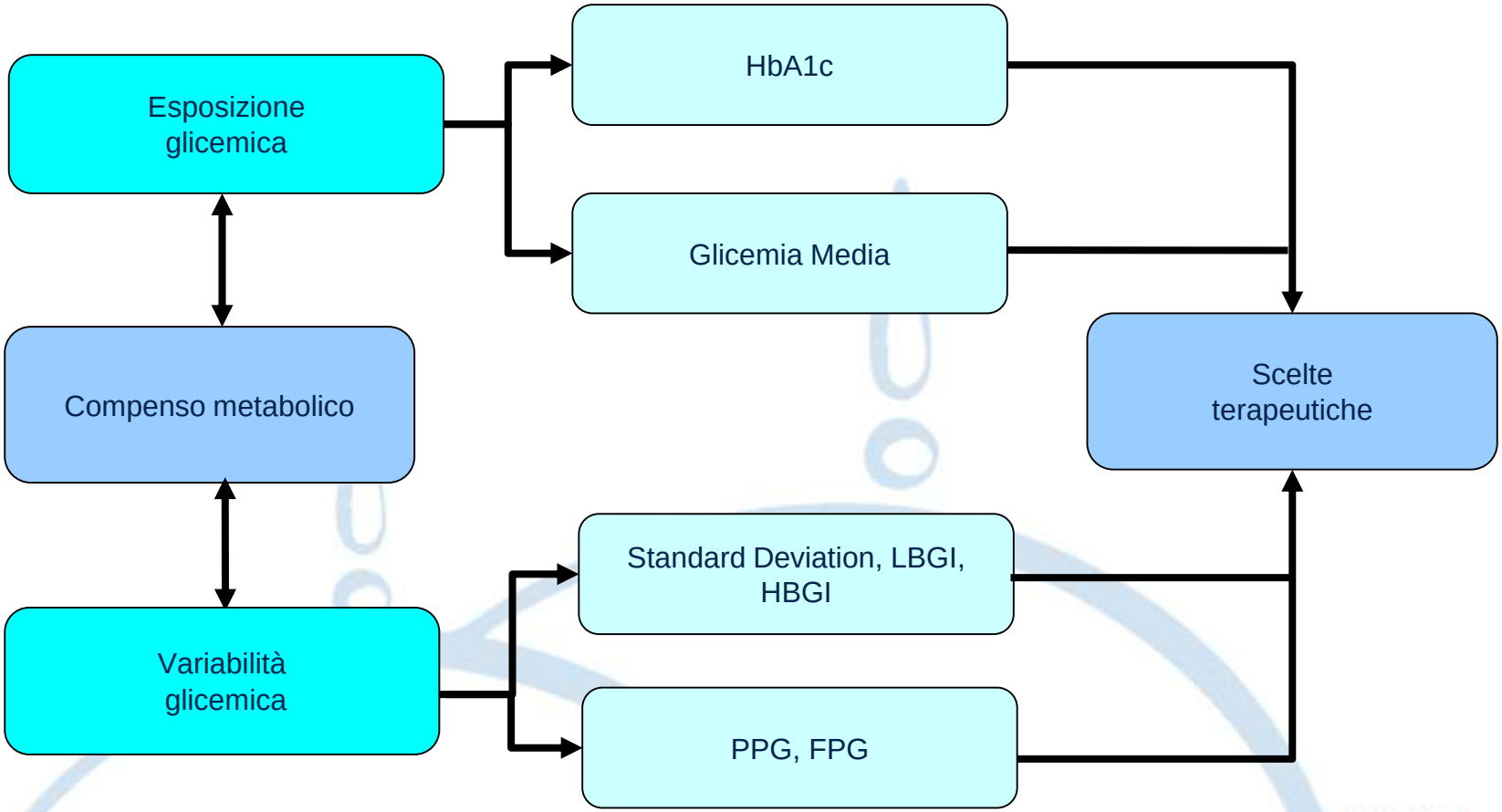
Nutrition, Metabolism & Cardiovascular Diseases (2009)

## Nessun evento ipoglicemico (compresi quelli di grado severo) nei pazienti di età ≥75 anni trattati con Vildagliptin

| | Monoterapia | | Terapia di Add-on | |
|---|---|---|---|---|
| **Età (anni)** | <75 | **≥75** | <75 | **≥75** |
| **Ipoglicemie totali** | 8 (0,3%) | **0 (0,0%)** | 23 (0,8%) | **0 (0,0%)** |
| **Ipoglicemie severe** | 0 (0,0%) | **0 (0,0%)** | 0 (0,0%) | **0 (0,0%)** |

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A1c
Complicanze croniche
Glicemia Media
Qualità di vita
Variabilità Glicemica
Indici di rischio
ipo/iperglicemico
Complicanze acute
Grado di Evidenza e
forza del legame


Esposizione glicemica
HbA1c
Glicemia Media
Compenso metabolico
Scelte terapeutiche
Standard Deviation, LBGI, HBGI
Variabilità glicemica
PPG, FPG

# IN CONCLUSIONE

L'analisi della variabilità glicemica rappresenta un elemento aggiuntivo nella valutazione globale del controllo glicemico e può rappresentare una guida per il clinico nella gestione della terapia e per il paziente nella prevenzione delle complicanze acute, in particolare ipoglicemiche, contribuendo a migliorarne la vita.