La glicemia come modello di biomarker per la diagnosi, il controllo e la ricerca nel diabete

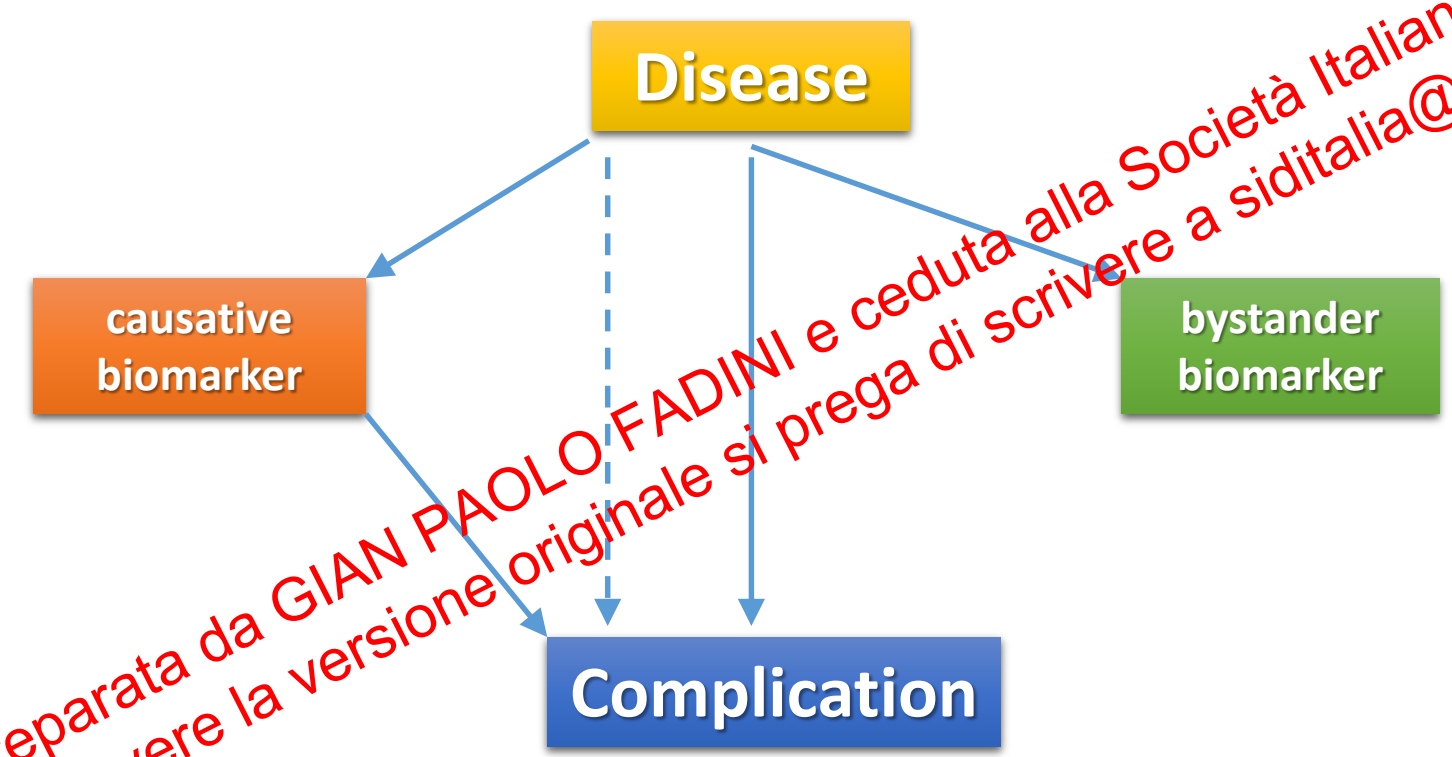
Gian Paolo Fadini

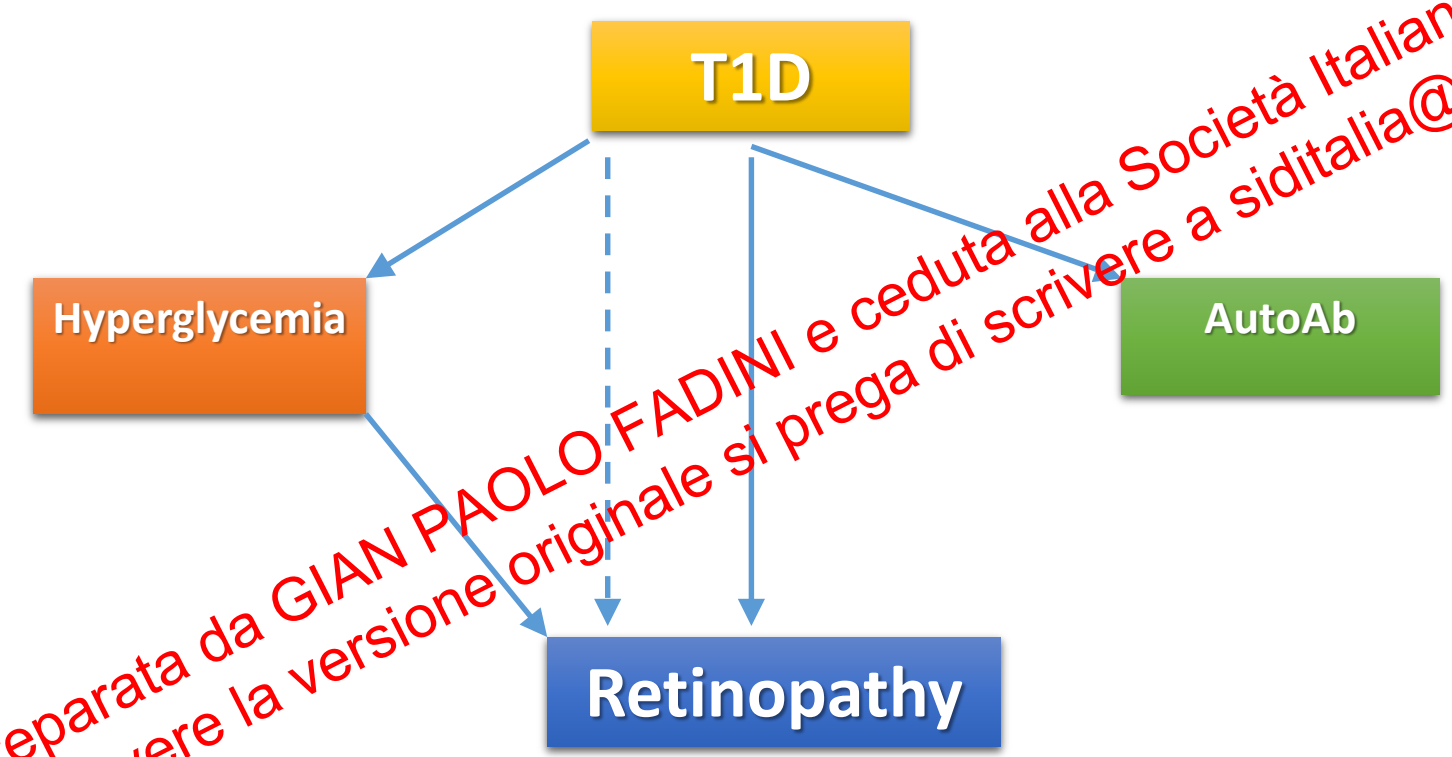
Università di Padova

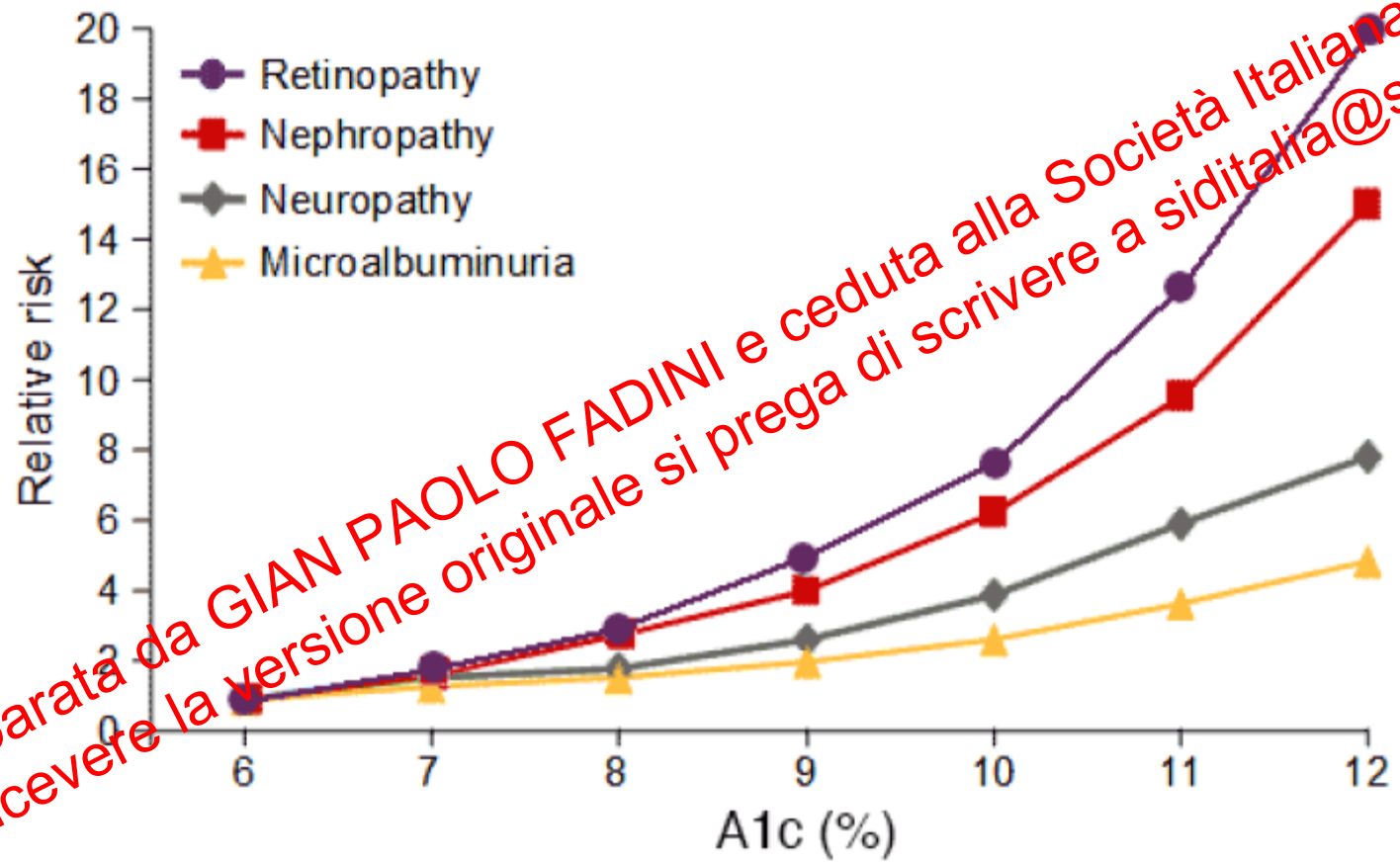
Il Prof. Gian Paolo Fadini dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

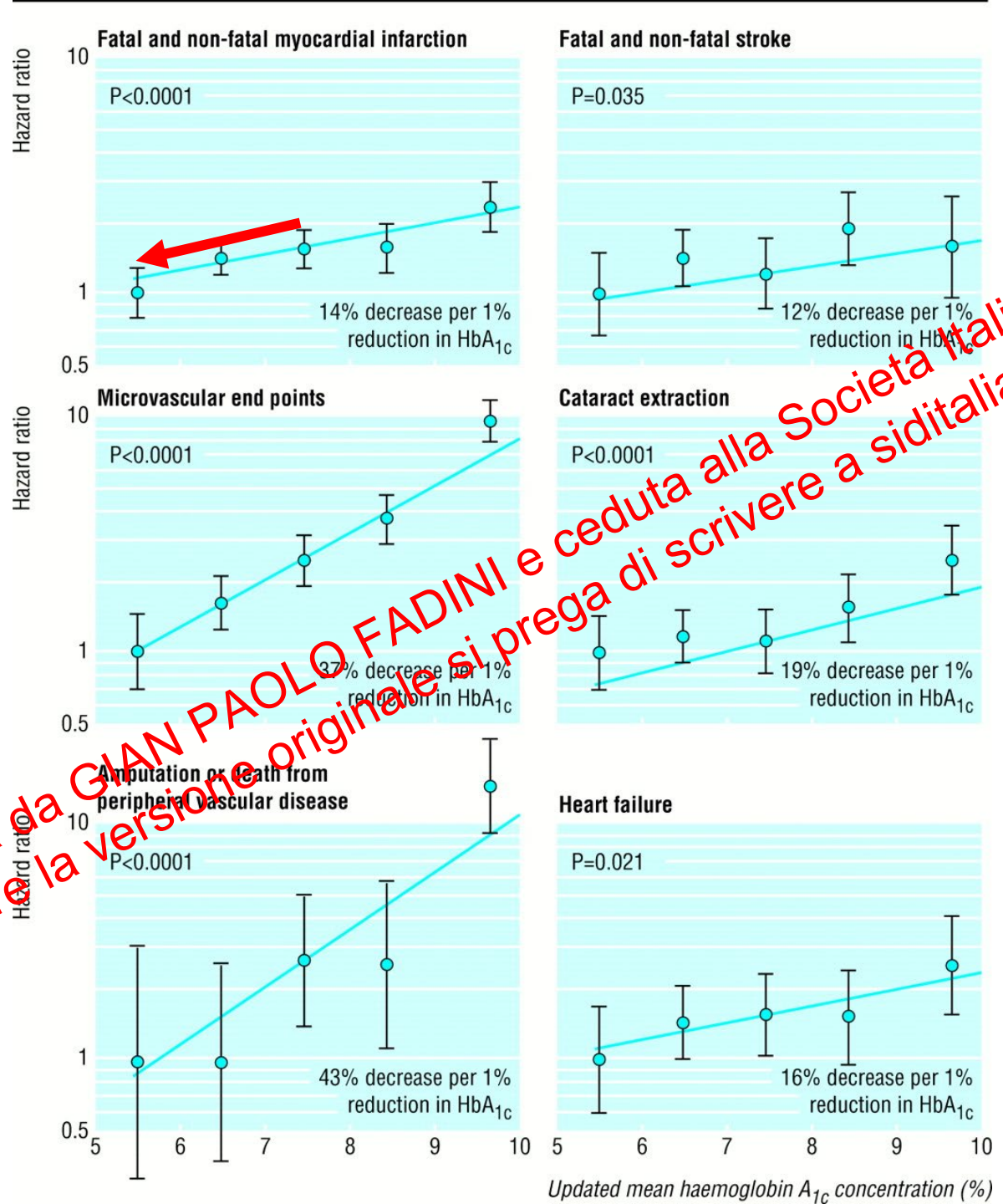
- Abbott
- AstraZeneca
- Boehringer
- Lilly
- MSD
- novartis
- NovoNordisk
- Sanofi

Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.)









Il paziente diabetico ed il rischio di malattia CV

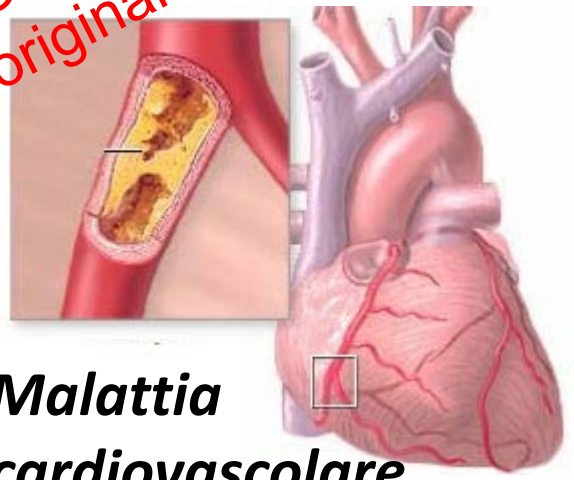
DIABETE =

Ipertensione

Iperglicemia

Obesità

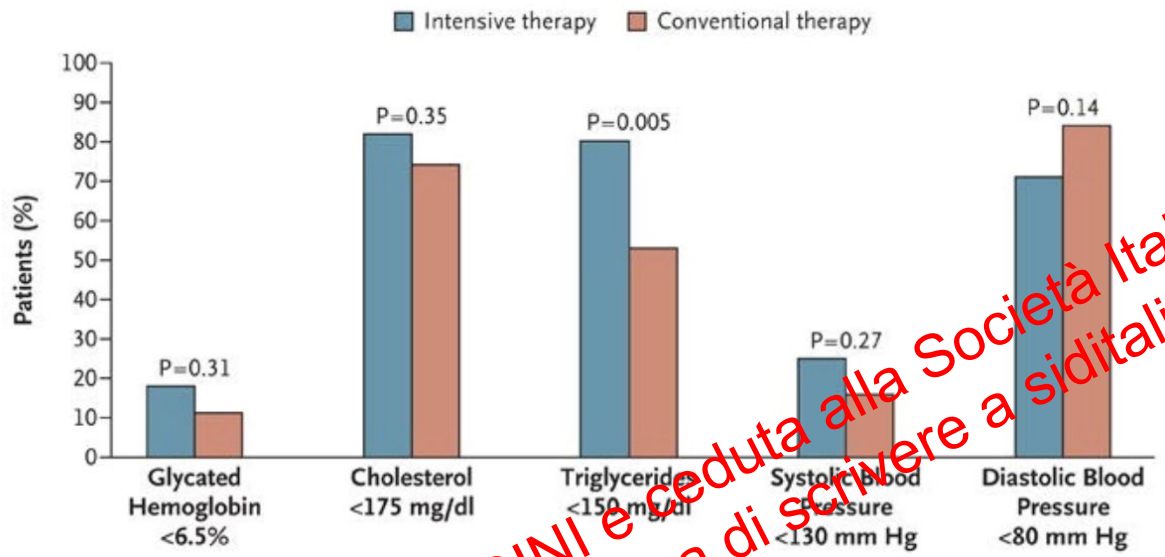
Dislipidemia

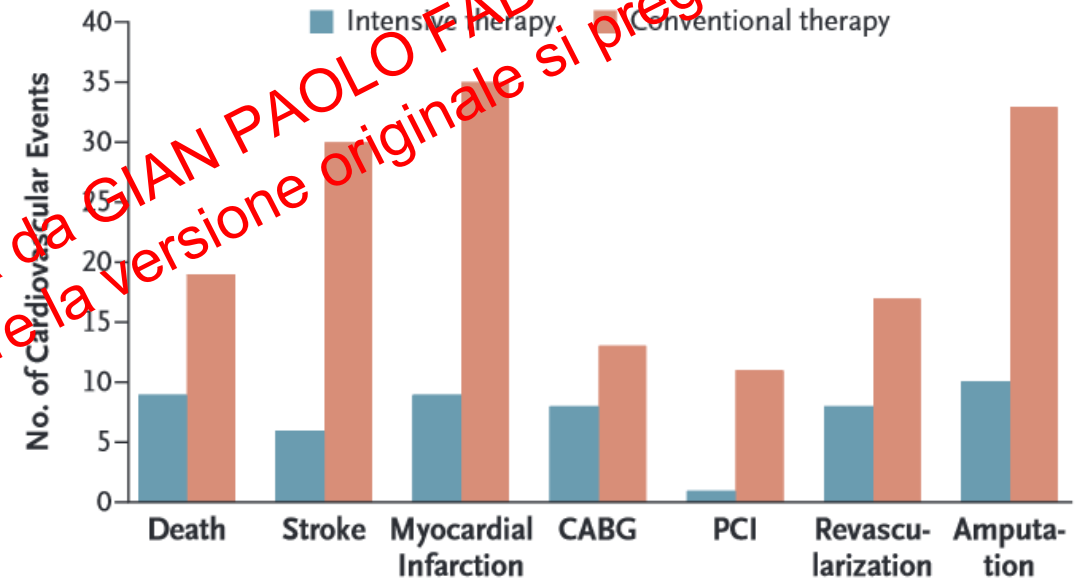


Malattia cardiovascolare

Durata del DM
Memoria iperglicemica
Ipoglicemie
Genetica
… … … …

Effect of a multifactorial intervention on mortality in T2D

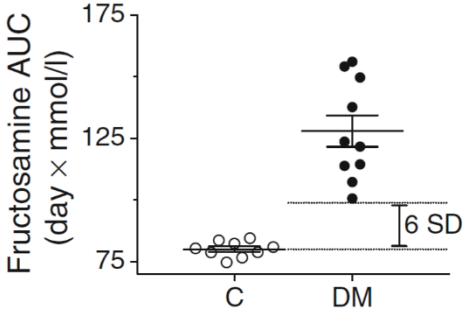


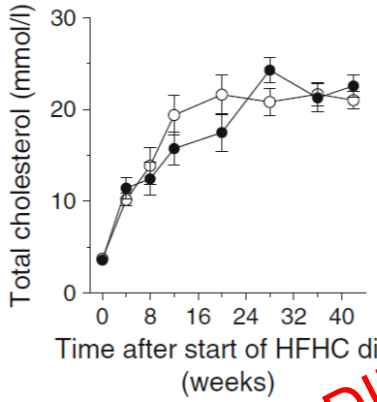


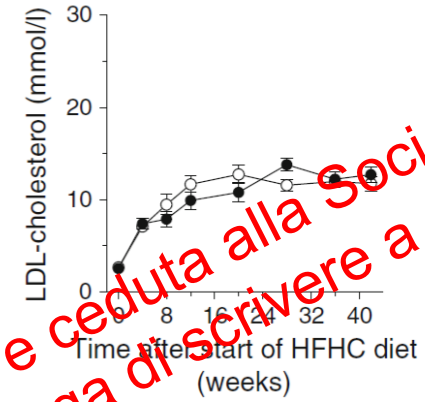
Gaede et al. NEJM 2008

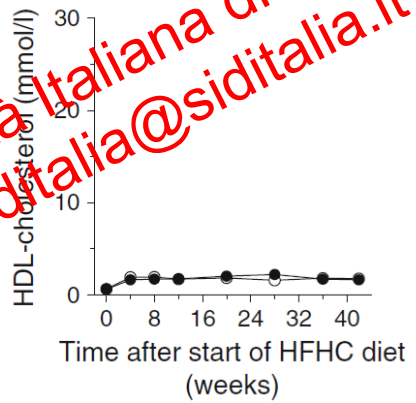
Il ruolo dell'iperglicemia «*per se*»

Diabetes with poor glycaemic control does not promote atherosclerosis in genetically modified hypercholesterolaemic minipigs

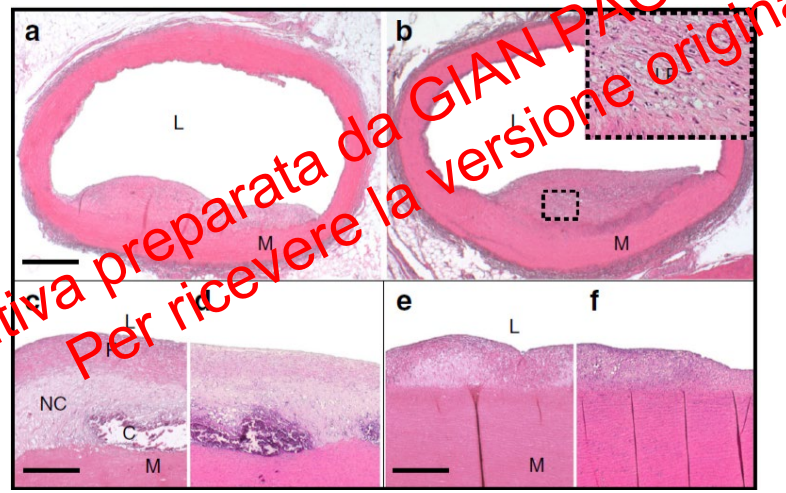




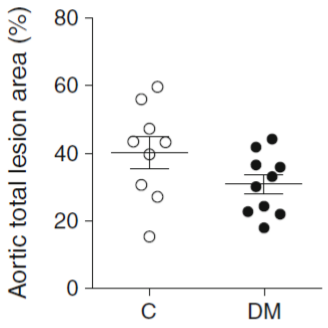


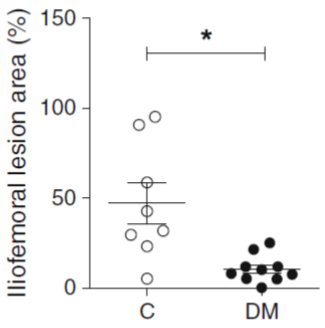


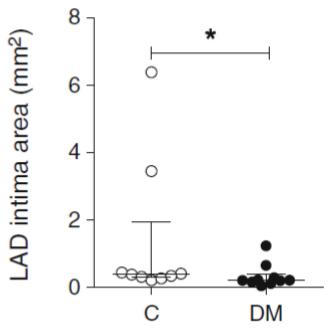
Non-diabetic Diabetic



Aorta Arti inferiori Coronarie







Al-Mashhadi et al. Diabetologia 2015

L'iperglicemia come «*moltiplicatore*»

Ipertensione

Disf.endoteliale, aumento della stiffness

Dislipidemia

Glicazione e ossidazione delle LDL

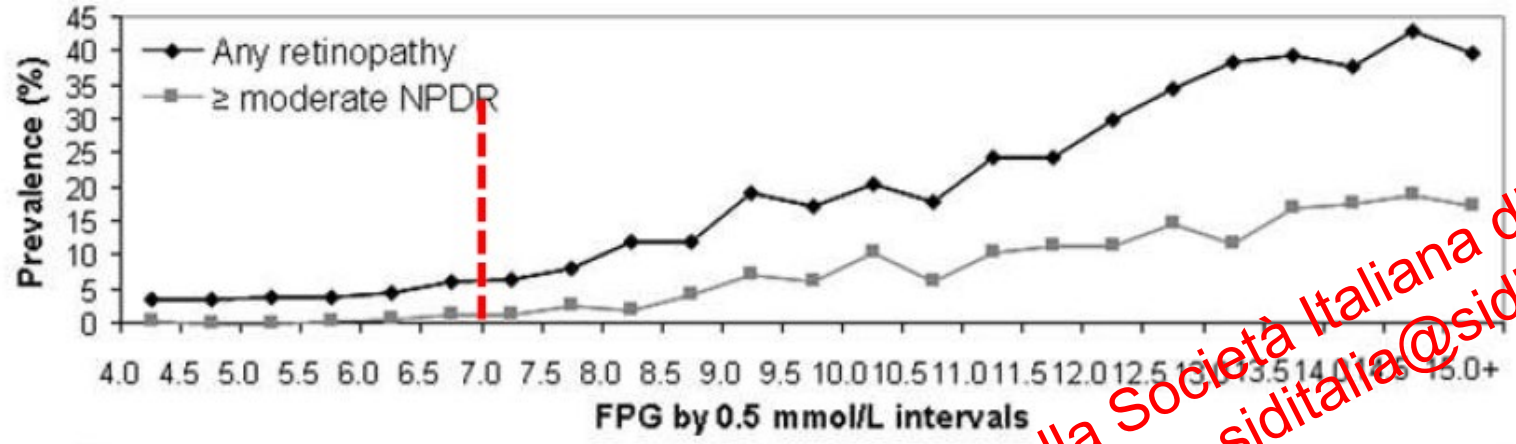
Iperglicemia

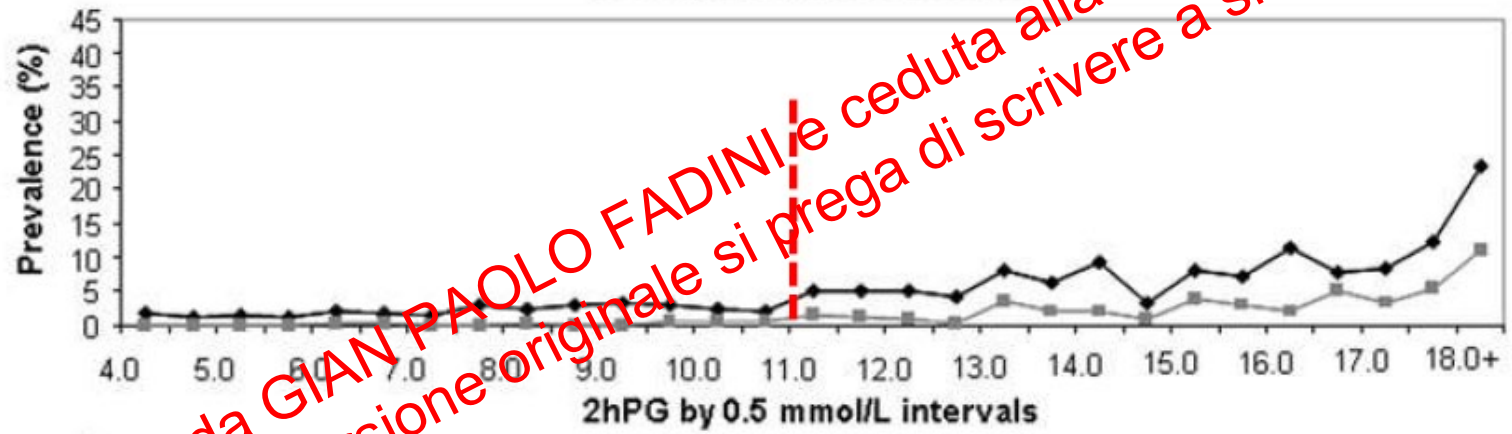
Fumo

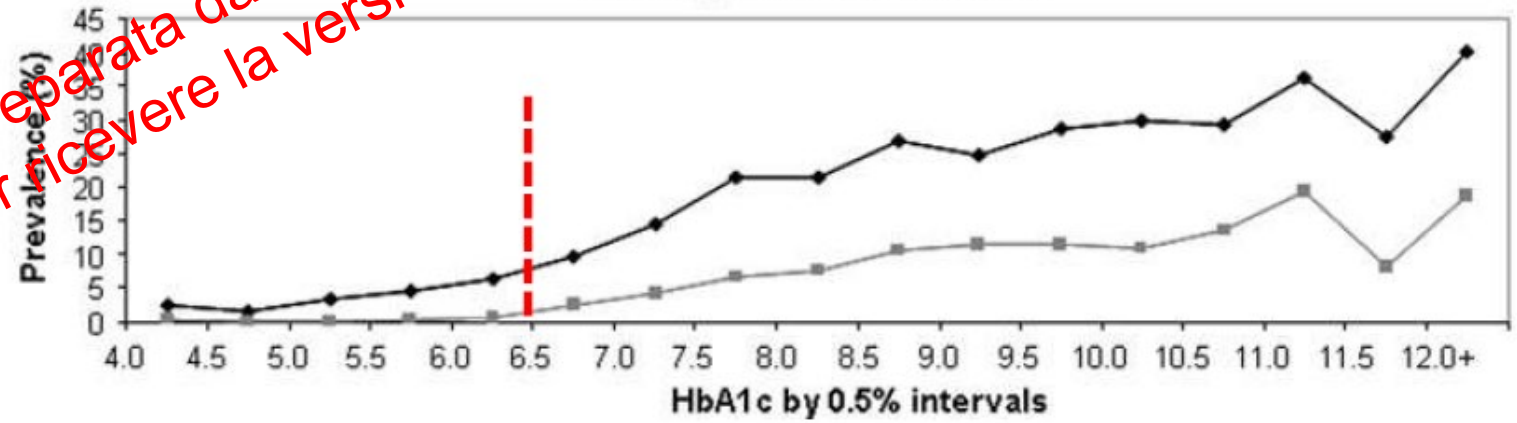
Riduzione potere anti-ossidante

Obesità

Infiammazione sarcopenia, …







History of Diabetes Diagnosis

1674

Physician **Thomas Willis**
"**Sweet flavor of urine** in patients with diabetes."
: presence of sugar in the "**urine**"

History of Diabetes Diagnosis

Early 1900s

1917: Jacobsen **Oral glucose tolerance test**
1923: Jorgensen **IV glucose tolerance test**
"carbohydrate ingestion results in blood glucose fluctuations"


Oral glucose tolerance test

Diabetes was defined using statistical criteria as glucose levels greater than the mean values plus 2 standard deviations 60, 90, and 120 min after the oral glucose load.

" but at least six different criteria used until 1979"

History of Diabetes Diagnosis

1979

Classification and criteria for Diabetes
from **NDDG** (National Diabetes Data Group)
* 1980 endorsed by WHO.

Diabetes:
- FPG ≥140 mg/dL or
- OGTT 2-hr glucose ≥200 mg/dL or
- Classic symptoms present

Impaired glucose tolerance:
- FPG ≤ 140 mg/dL and
- OGTT 2-hr glucose 140-200 mg/dL

Classification of Diabetes:
- Insulin-dependent diabetes mellitus (**IDDM**)
- Non-insulin dependent diabetes mellitus (**NIDDM**)
- Gestational diabetes mellitus (**GDM**)
- Malnutrition-related diabetes mellitus
- "Other" diabetes mellitus

History of Diabetes Diagnosis

1997

1997 ADA Expert committee

To make FPG concentration and 2-hour OGTT glucose equivalent
Relationship between glucose levels and presence of long-term complications.

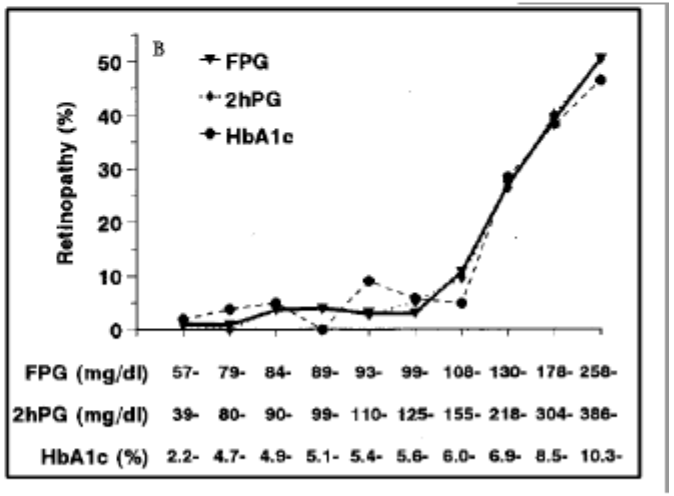
FPG criteria: lowered to ≥126 mg/dL
IDDM/NIDDM ⇒ Type 1 and Type 2 DM
Impaired fasting glucose
Criteria based on Retinopathy

Classification of Diabetes:
- T1DM
- T2DM
- Other specific types
- GDM

Diabetes:
- **FPG** ≥126 mg/dl (8hr fast) or
- **75g OGTT 2hr glucose** ≥200 mg/dl or
- Symptoms with **Casual glucose** ≥200 mg/dL

Prediabetes:
- IFG: FPG 110~126 mg/dL
- IGT: 2-hour OGTT glucose 140-200 mg/dL

* **FPG is preferred over 2HPG**
More convenient
Less costly and time-consuming
Better repeat-test reproducibility
* Consider A1C for diagnosis
Lack of standardization



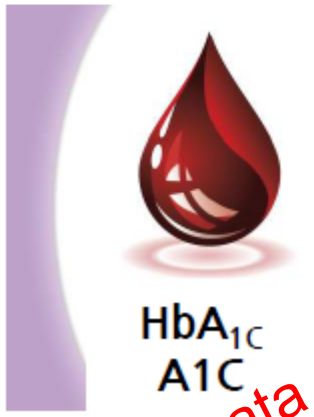
History of Diabetes Diagnosis

2003

1997 ADA Expert committee

Prediabetes:
- **IFG:** FPG 100~126 mg/dL
- **Equivalent with IGT**

* Consider A1C for diagnosis
Still lack of standardization

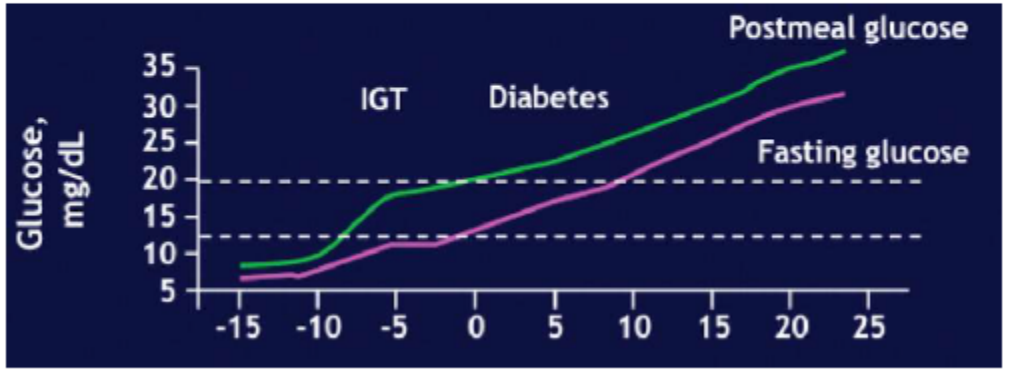


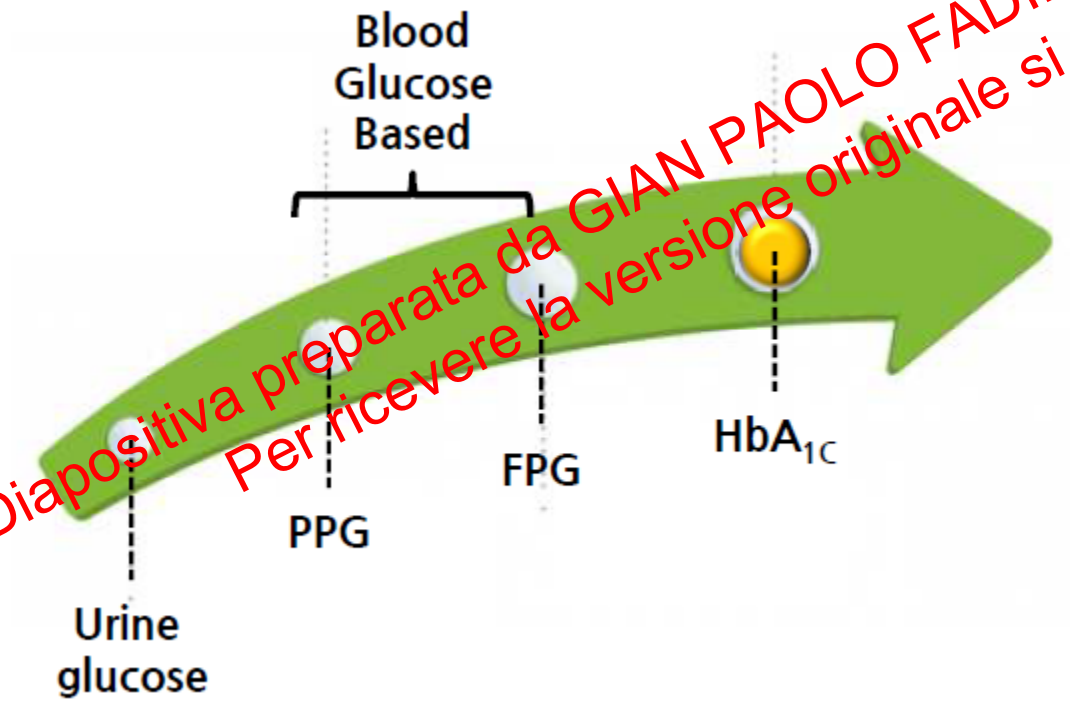
HbA_{1C}
A1C

"Can the **A1C** test be used to diagnose diabetes?"

- To be of clinical use: **accurate**
  specific
  standardised
  convenient
  inexpensive

History of Diabetes Diagnosis





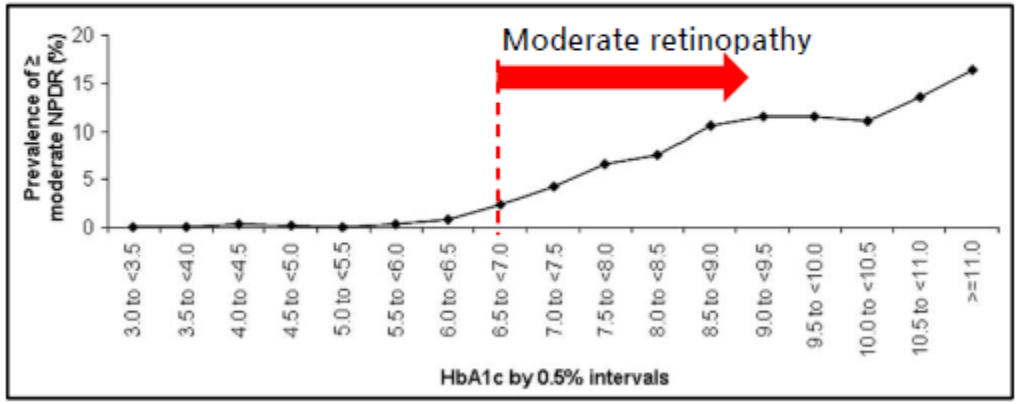
2009

1997 ADA Expert committee

A1C used for diagnosis.
Long-term glycemic exposure: better marker

Diabetes:
- A1C ≥ 6.5%
- FPG ≥ 126 mg/dl (8hr fast) or
- 75g OGTT 2-hr glucose ≥200 mg/dl or
- Symptoms with Casual glucose ≥200 mg/dL

High risk for diabetes:
- IFG: FPG 110~126 mg/dL
- IGT: 2-hour OGTT glucose 140-200 mg/dL
- A1C: 6%~6.5%



History of Diabetes Diagnosis

2011

A1C for prediabetes.

	Healthy	Prediabetes	Diabetes
Morning Blood Glucose	70-99 mg/dl (3.89-5.55 mmol/l)	100-125 mg/dl (5.56-6.94 mmol/l)	>126 mg/dl (7 mmol/l)
Hemoglobin A1c	<5.7%	5.7-6.4%	>6.5%
Post-Meal (two hours after the start)	<140 mg/dl (7.78 mmol/l)	140-199 mg/dl (7.78-11.06 mmol/l)	> 200 mg/dl (11.11 mmol/l)

- 2009 high risk: 6.0 ~ 6.5%
- IFG 110 = A1C 5.6%
- IFG 100 = A1C 5.4%
- DPP: high risk 5.7%

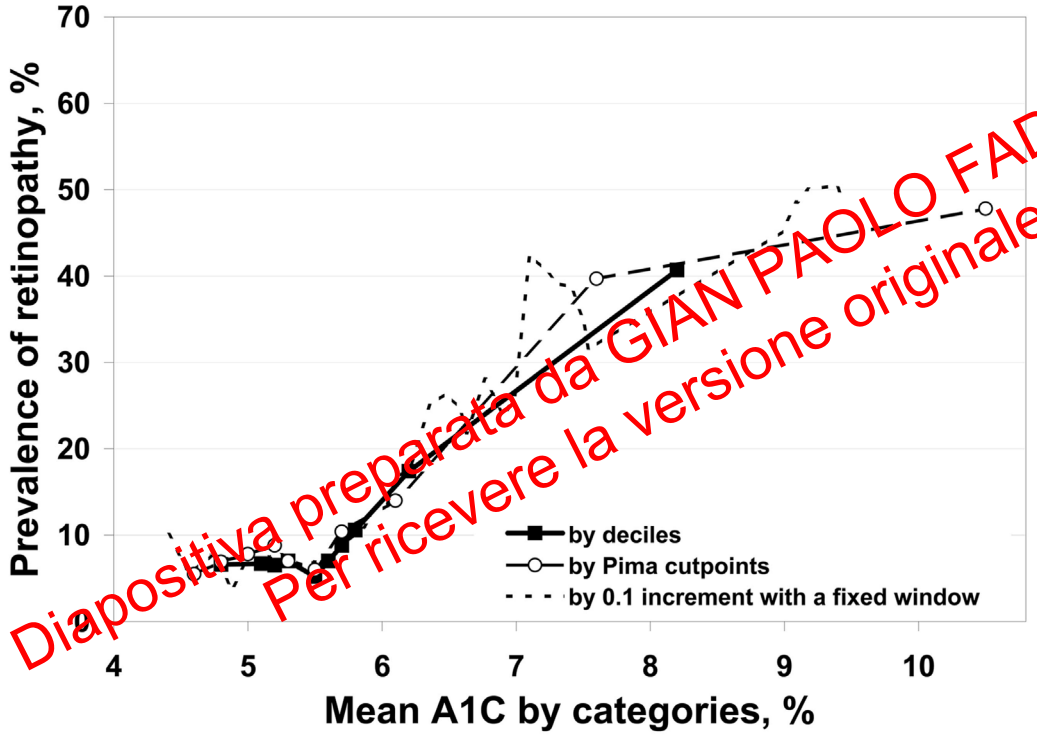
* NHANES (1999-2006)
ROC for IFG cut point: 5.7%
  - sensitivity (39%)
  - specificity (91%)
Identify IFG or IGT

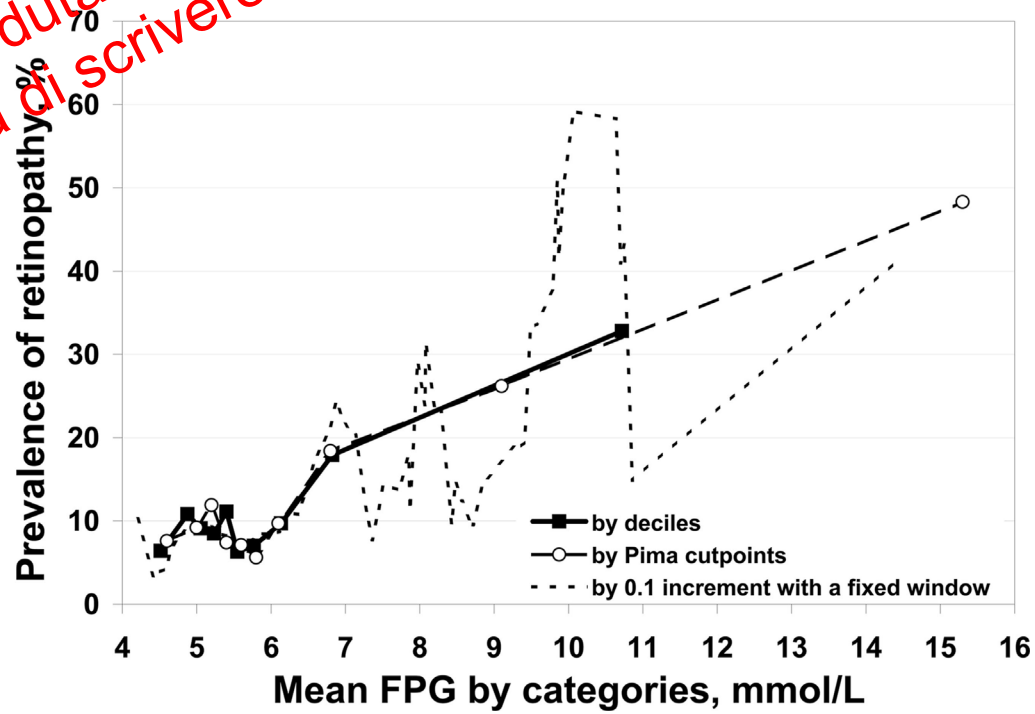
Association of A1C and Fasting Plasma Glucose Levels With Diabetic Retinopathy Prevalence in the U.S. Population

Implications for diabetes diagnostic thresholds

YILING J. CHENG, MD, PHD[1]
EDWARD W. GREGG, PHD[1]
LINDA S. GEISS, MA[1]
GIUSEPPINA IMPERATORE, MD, PHD[1]
DESMOND E. WILLIAMS, MD, PHD[1]
XINZHI ZHANG, MD, PHD[1]
ANN L. ALBRIGHT, PHD, RD[1]
CATHERINE C. COWIE, PHD[2]
RONALD KLEIN, MD, MPH[3]
JINAN B. SAADDINE, MD[1]

" the change points for the greatest increase in retinopathy prevalence were A1C 5.5% and FPG 7.0 mmol/L"





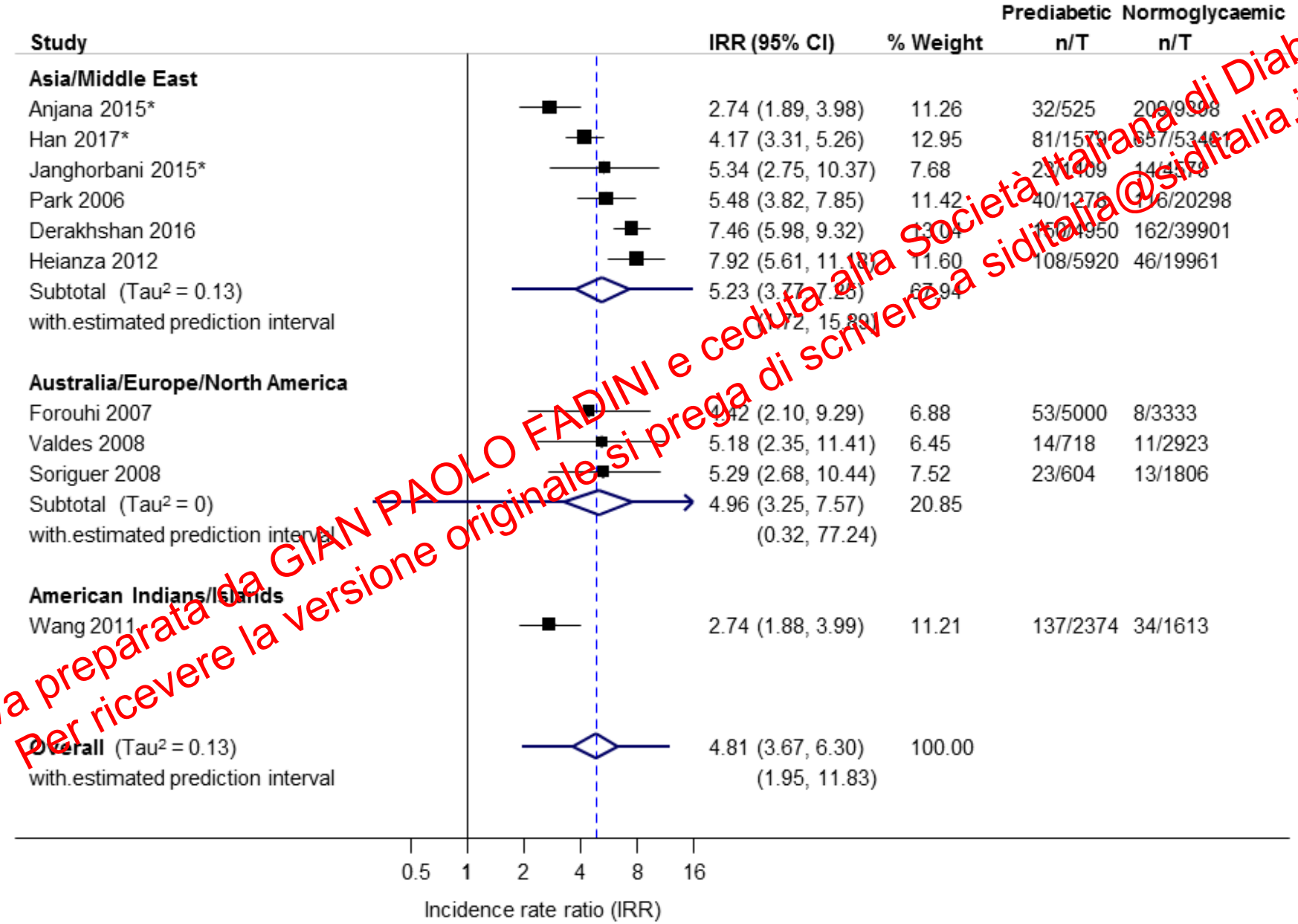
Cochrane Library

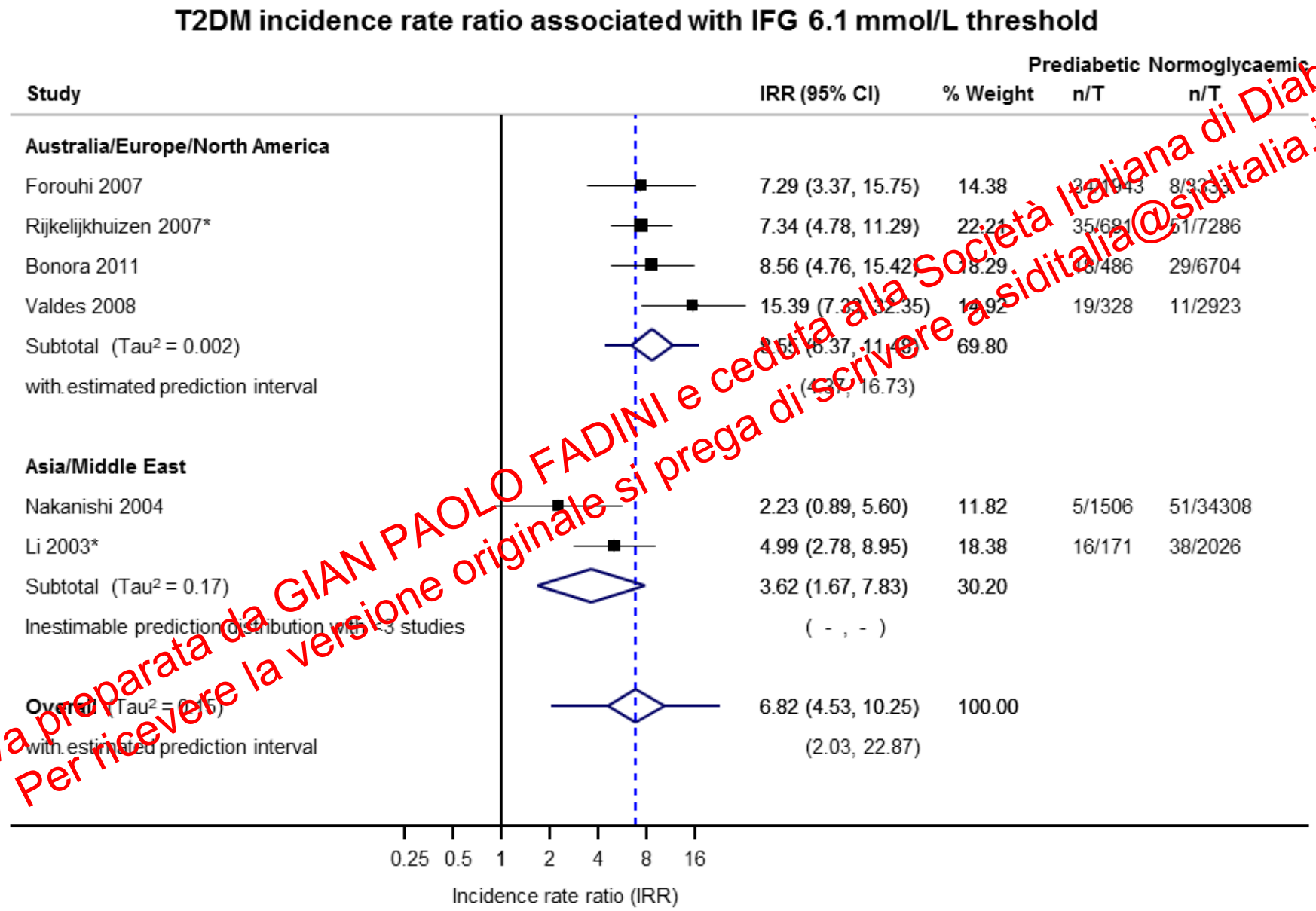
Cochrane Database of Systematic Reviews

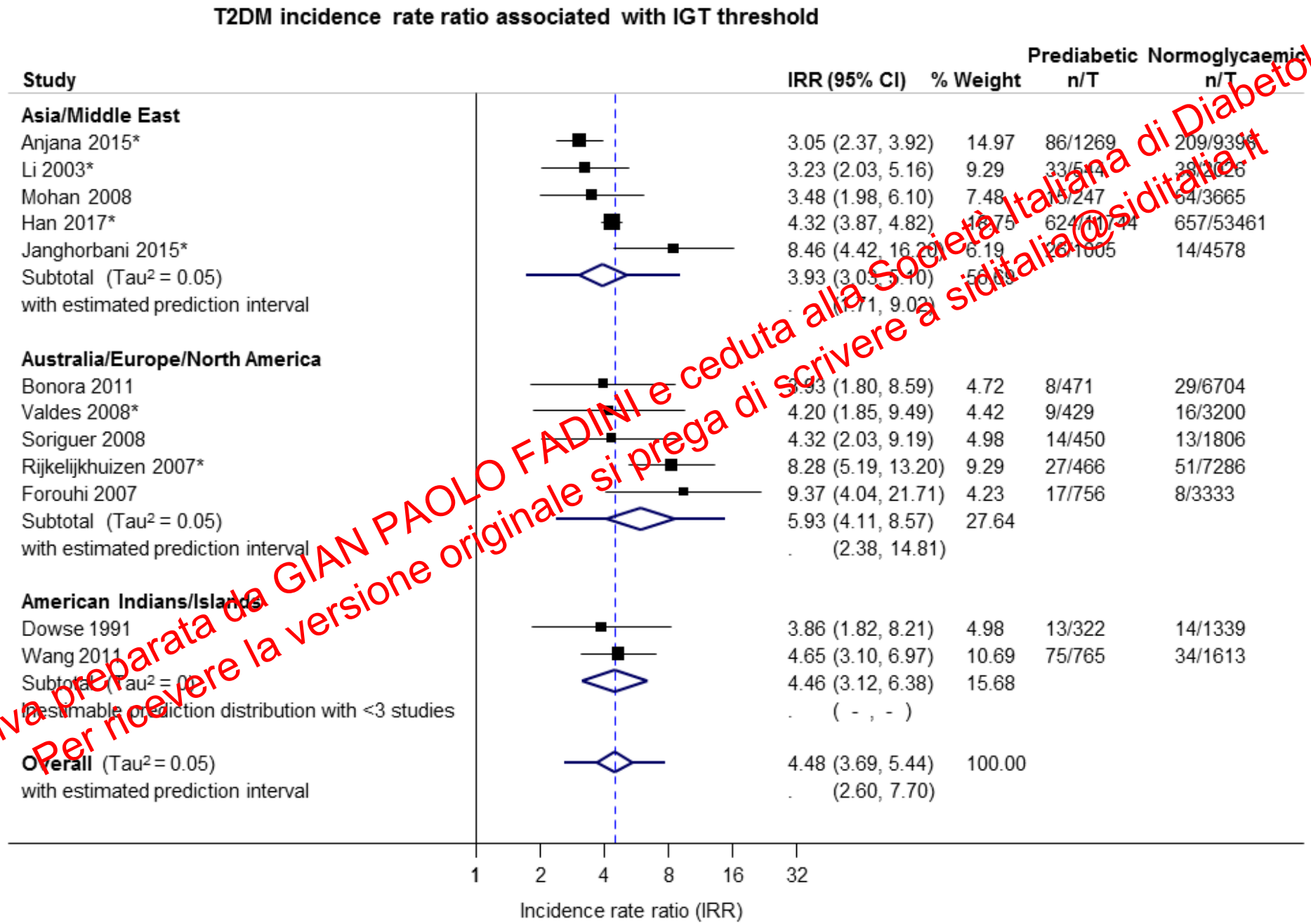
Development of type 2 diabetes mellitus in people with intermediate hyperglycaemia (Review)

Richter B, Hemmingsen B, Metzendorf MI, Takwoingi Y

T2DM incidence rate ratio associated with IFG 5.6 mmol/L threshold



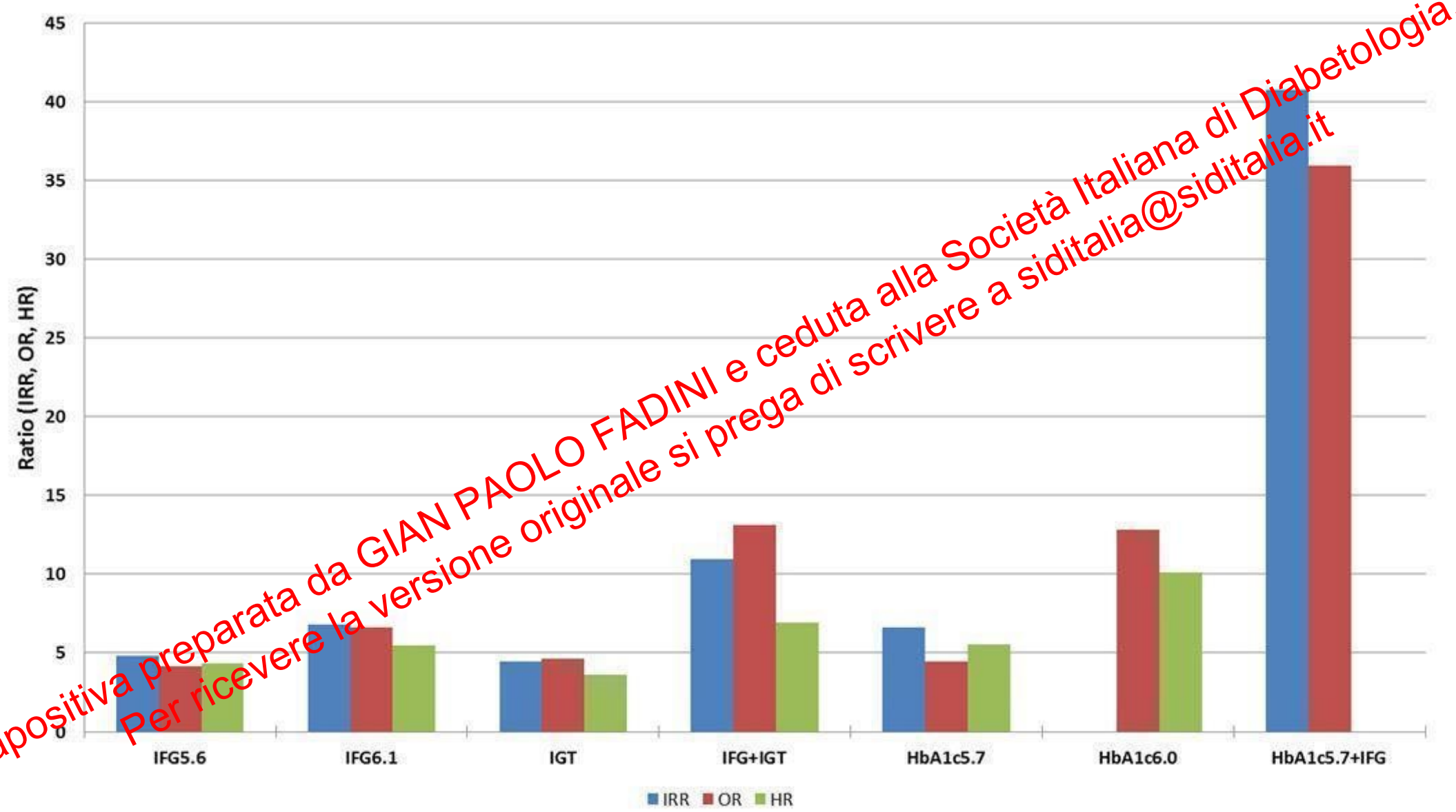




qnow 1

Quale delle seguenti categorie ha un rischio di T2DM maggiore?

A. IGT
B. IFG + IGT
C. HbA1c >6%
D. IFG + HbA1c >6%



Implications for practice

Several uncertainties

- Glycaemic status can be measured in various ways
- Many of the prospective cohort studies did not adequately investigate other factors or covariates
- Results varied widely, making it difficult to specify the best definition for IH
- With increasing years of follow-up, T2DM incidence increased, but regression from IH to normoglycaemia was also high

Due to the fluctuating stages of normoglycaemia, IH and T2DM, practitioners should be careful about the potential implications of any active intervention for people 'diagnosed' with IH.

Implications for research

Future investigations

- Minimise secondary analyses of cohort studies where investigators synthetically form a subgroup of people with prediabetes, as such analyses are suboptimal
- Urgent need for data from Eastern Europe and Africa
- Urgent need for prospective cohort studies to examine the relationship between IH and normoglycaemia, T2DM incidence and the development of diabetic complications
- Studies should be adequately powered and analysed using suitable statistical techniques such as time-dependent regression methods

HbA1c

- Range dinamico limitato (n=150k: range 3-22)
- Latenza temporale
- Regressione verso la media
- Self-limiting

Glucose Management Indicator (GMI): A New Term for Estimating A1C From Continuous Glucose Monitoring

Richard M. Bergenstal,[1] Roy W. Beck,[2] Kelly L. Close,[3] George Grunberger,[4] David B. Sacks,[5] Aaron Kowalski,[6] Adam S. Brown,[7] Lutz Heinemann,[8] Grazia Aleppo,[9] Donna B. Ryan,[10] Tonya D. Riddlesworth,[2] and William T. Cefalu[11]

Diabetes Care 2018;41:2275–2280 | https://doi.org/10.2337/dc18-1581

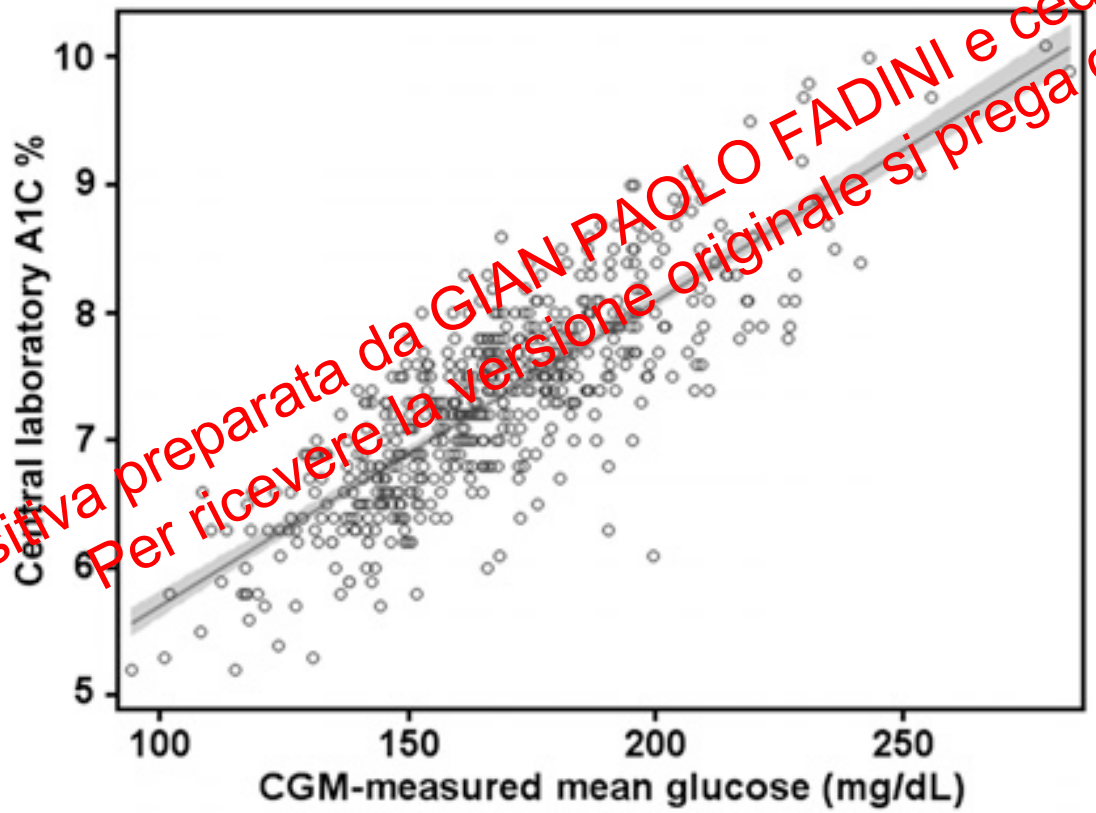


Table 1—GMI calculated for various CGM-derived mean glucose concentrations

CGM-derived mean glucose (mg/dL)	GMI (%)*
100	5.7
125	6.3
150	6.9
175	7.5
200	8.1
225	8.7
250	9.3
275	9.9
300	10.5
350	11.7

Factors that influence HbA1c and its measurement

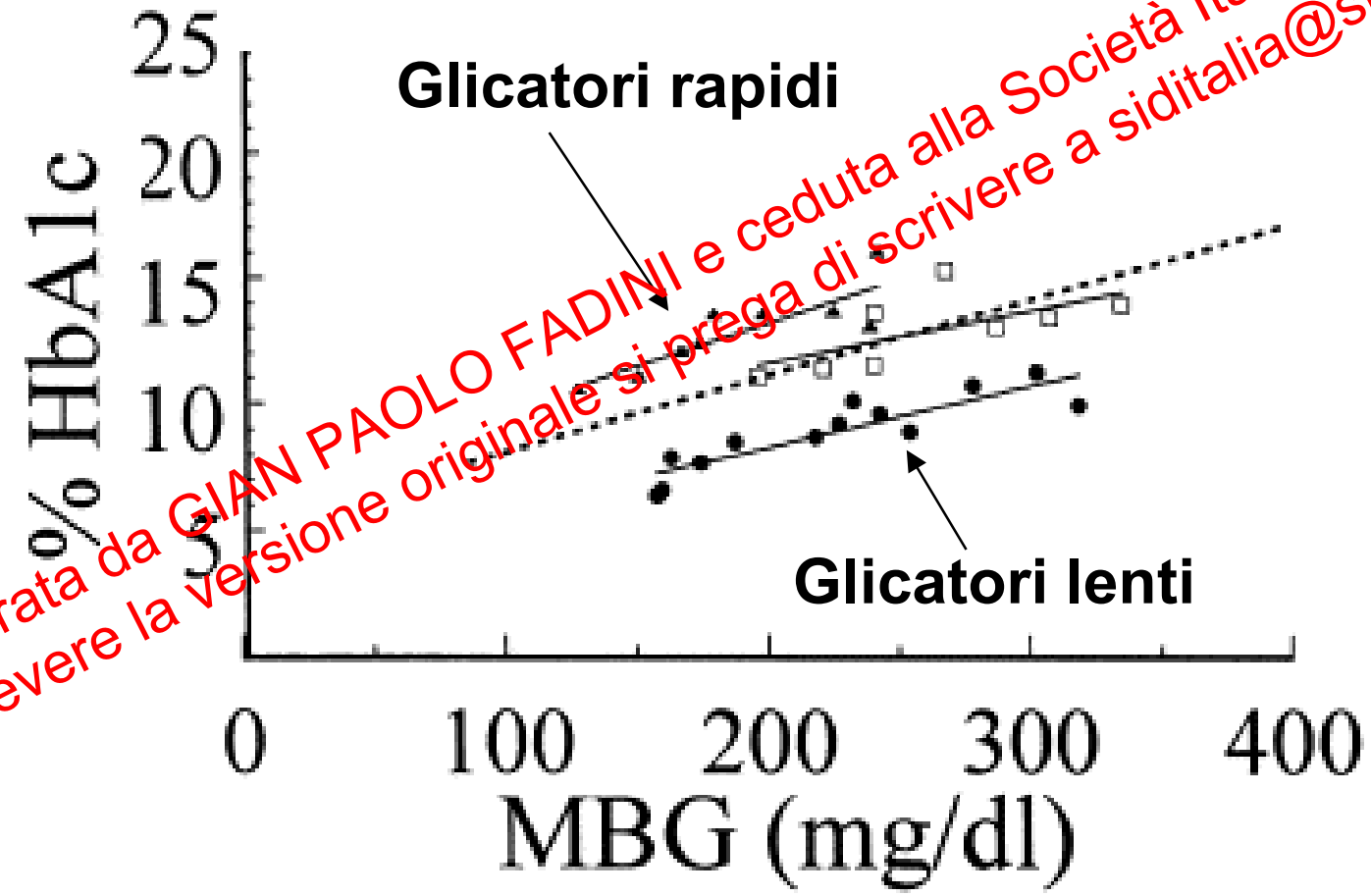
Availability of glucose	Blood glucose concentration
	Erythrocyte membrane permeability [28]
Glycation rate	Genetics [26, 70]
	Regular aspirin ingestion [11][a]
	High doses of vitamins C and E [71, 72][a]
	Oxidative stress [73]
Erythrocyte lifespan	Reduced erythropoiesis
	Iron and vitamin B12 deficiency [74–76]
	Renal failure [77]
	Bone marrow suppression (e.g. pregnancy, alcoholism) [78]
	Increased erythropoiesis
	Iron or erythropoietin therapy [79]
	Reduced haemolysis
	Splenectomy [80]
	Increased haemolysis
	Haemolytic anaemia [81]
	Thalassaemia [82]
	Haemoglobinopathies [83]
	Splenomegaly [11]
	Chronic liver disease [84, 85]
	Drugs (e.g. ribavirin, dapsone) [86–88][b]
	Interindividual heterogeneity [28]

Race and ethnicity
High in African Americans, Hispanics, Asians

Factors reported to interfere with some HbA1c assays

Haemoglobinopathies
Structural variants
HbS [92]
HbC [92]
HbE [93]
HbD [93]
Hereditary persistence of HbF [94]
Chemical derivatives of haemoglobin
Carbamylated haemoglobin (e.g. as a result of uraemia) [95]
Acetylated haemoglobin (e.g. as seen with large aspirin doses) [95]
Others
Hypertriglyceridaemia [96]
Hyperbilirubinaemia [11]
Alcoholism [11]
Chronic opiate use [97]

Glicatori rapidi / lenti



Diabetes Volume 67, January 2018

Evidence That Differences in Fructosamine-3-Kinase Activity May Be Associated With the Glycation Gap in Human Diabetes

Simon J. Dunmore,[1] Amr S. Al-Dewik,[1] Ananth U. Nayak,[2] Aruna Narshi,[1] Alan M. Nevill,[3] Anne Hellwig,[4] Andrew Majebi,[1] Paul Kirkham,[5] James E. Brown,[6] and Baldev M. Singh[1,7]

Diabetes 2018;67:131–136 | https://doi.org/10.2337/db17-0441

QuestionNow! (qnow.it)

qnow 2

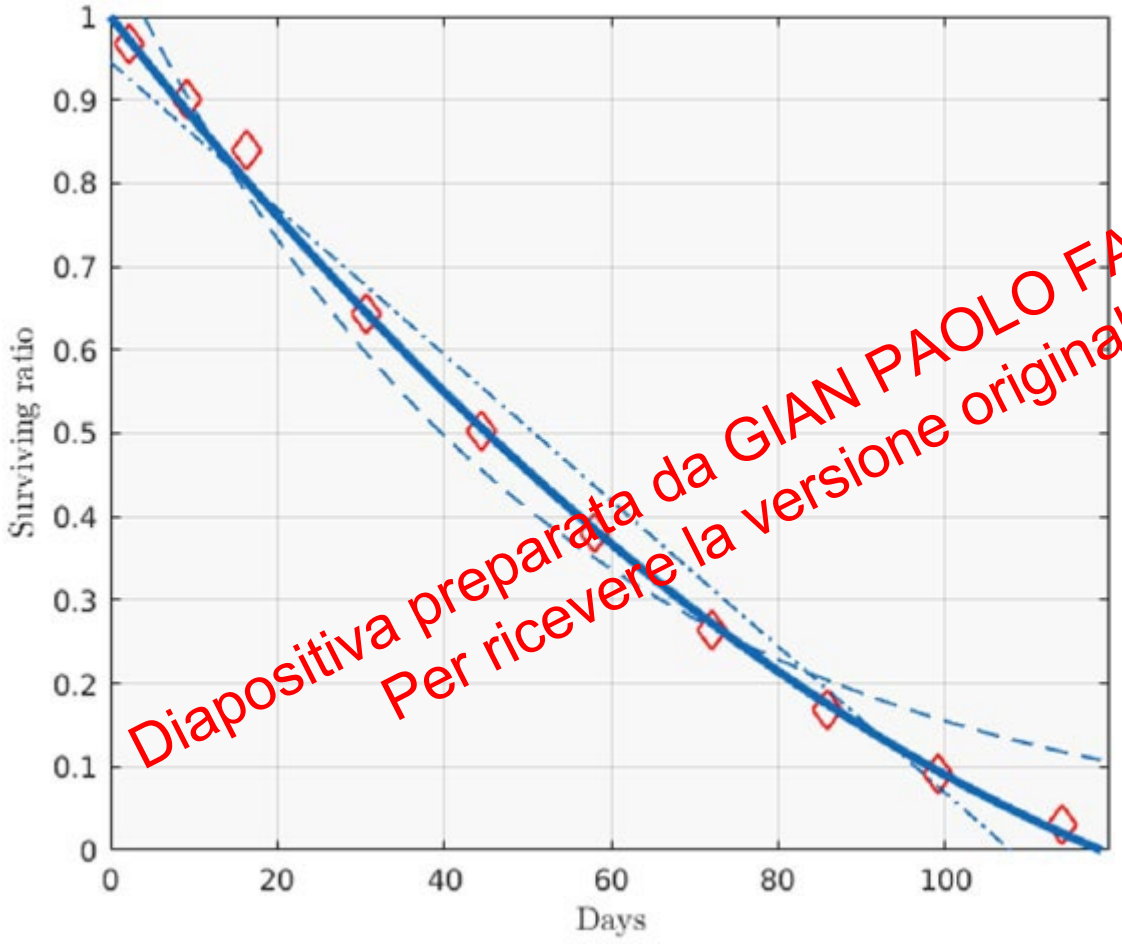
Qual è l'impatto relativo dell'andamento glicemico nell'ultimo mese nella determinazione della HbA1c?

A. 20%
B. 33%
C. 50%
D. 75%

Glycated Hemoglobin, Plasma Glucose, and Erythrocyte Aging

Deltran Del Rio et al. JDST 2016

RBC survival curve



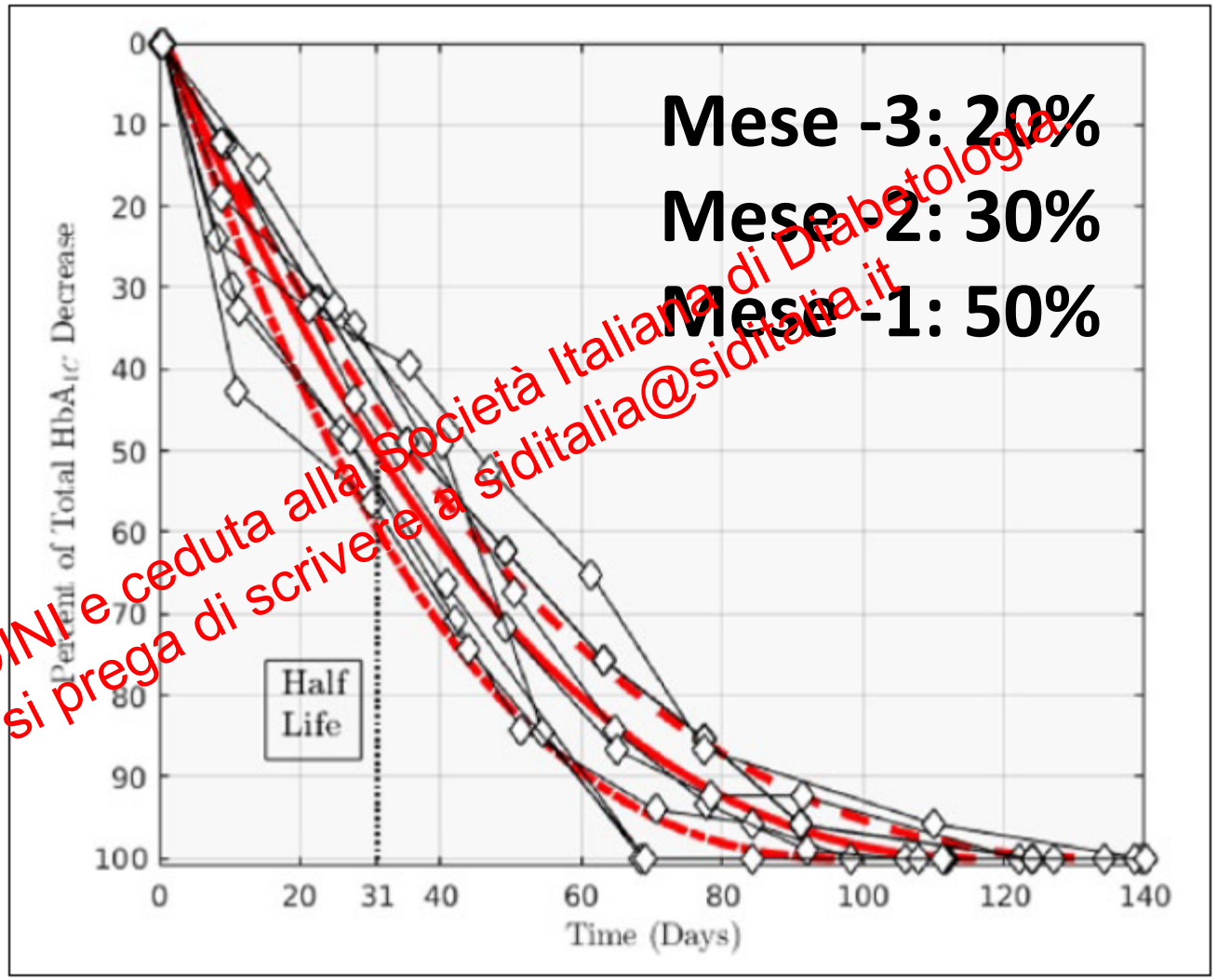


Figure 3. Rate for change of HbA1c % after a stepwise change in MBG. The 3 estimates correspond to calculations based on different erythrocyte life spans: MEL = 117d, solid line; MEL = 140d, dashed line; MEL = 97d, dot-dashed line. Data in diamonds are measurements from Tahara and Shima.[3]

Regression towards the mean

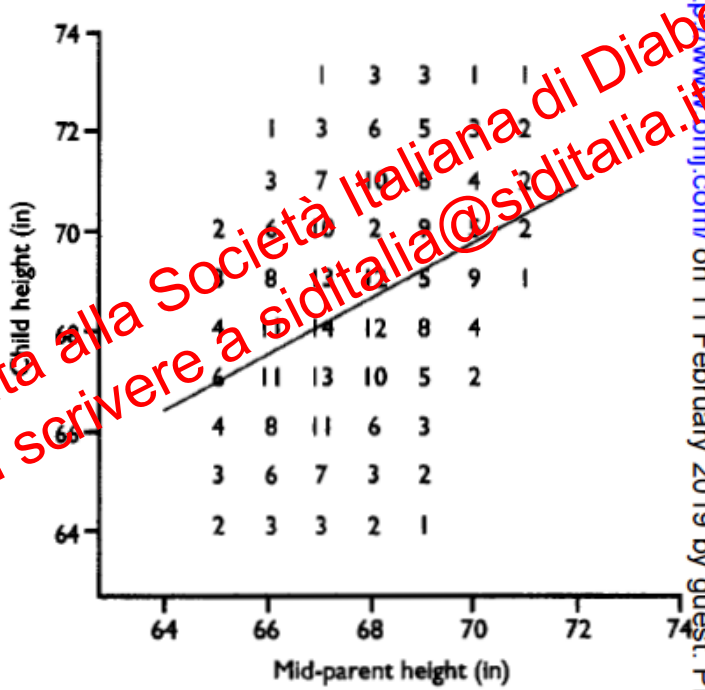
J Martin Bland, Douglas G Altman

This is the second in a series of occasional notes on medical statistics.

The statistical term "regression," from a Latin root meaning "going back," was first used by Francis Galton in his paper "Regression towards Mediocrity in Hereditary Stature."[1] Galton related the heights of children to the average height of their parents, which he called the mid-parent height (figure). Children and parents had the same mean height of 68·2 inches. The ranges differed, however, because the mid-parent height was an average of two observations and thus had its range reduced. Now, consider those parents with a mid-height between 70 and 71 inches. The mean height of their children was 69·5 inches, which was closer to the mean height of all children than the mean height of their parents was to the mean height of all parents. Galton called this phenomenon "regression towards mediocrity"; we now call it "regression towards the mean." The same thing happens if we start with the children. For the children with height between 70 and 71 inches, the mean height of their parents was 69·0 inches. This is a statistical, not a genetic phenomenon.

If we take each group of mid-parents by height and calculate the mean height of their children, these means will lie close to a straight line. This line came to be called the regression line, and hence the process of fitting such lines became known as "regression."

In mathematical terms, if variables X and Y have standard deviations s_X and s_Y, and correlation r, the slope of the familiar least squares regression line can be written rs_Y/s_X. Thus a change of one standard deviation in X is associated with a change of r standard deviations in Y. Unless X and Y are exactly linearly related, so that all the points lie along a straight line, r is less than 1. For a given value of X the predicted value of Y is always fewer standard deviations from its mean than is X from its mean. Regression towards the mean occurs unless $r=1$, perfect correlation, so it always occurs in practice. We give some examples in a subsequent note.



Galton's original data showing the relation between the heights of children and their parents, with regression line[1]

Department of Public Health Sciences, St George's Hospital Medical School, London SW17 0RE
J Martin Bland, *reader in medical statistics*

Medical Statistics Laboratory, Imperial Cancer Research Fund, London WC2A 3PX
Douglas G Altman, *head*

BMJ 1994;308:1499

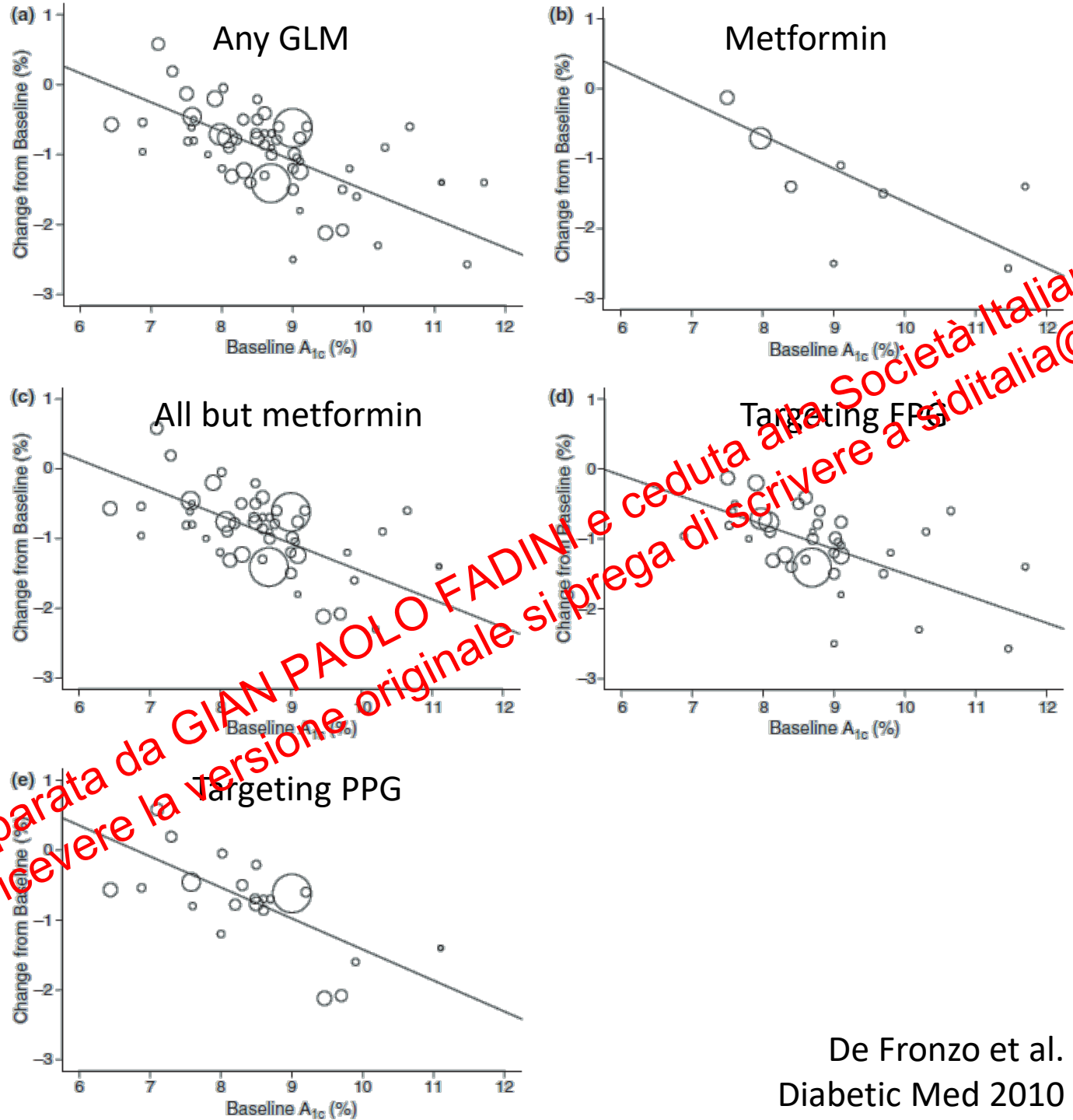
1 Galton F. Regression towards mediocrity in hereditary stature. *Journal of the Anthropological Institute* 1886;15:246-63.

This is the seventh in a series of occasional notes on medical statistics.

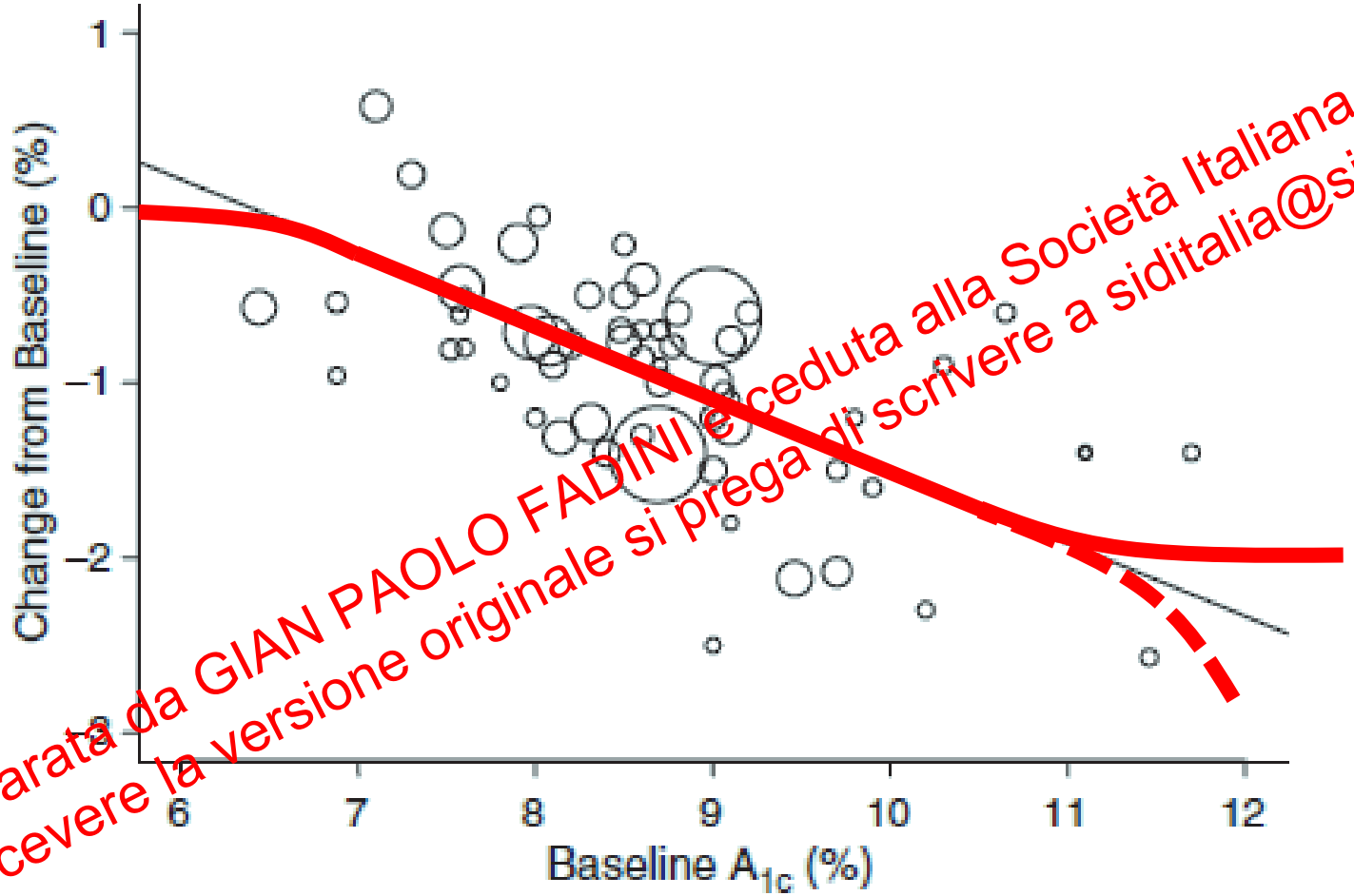
Statistics Notes

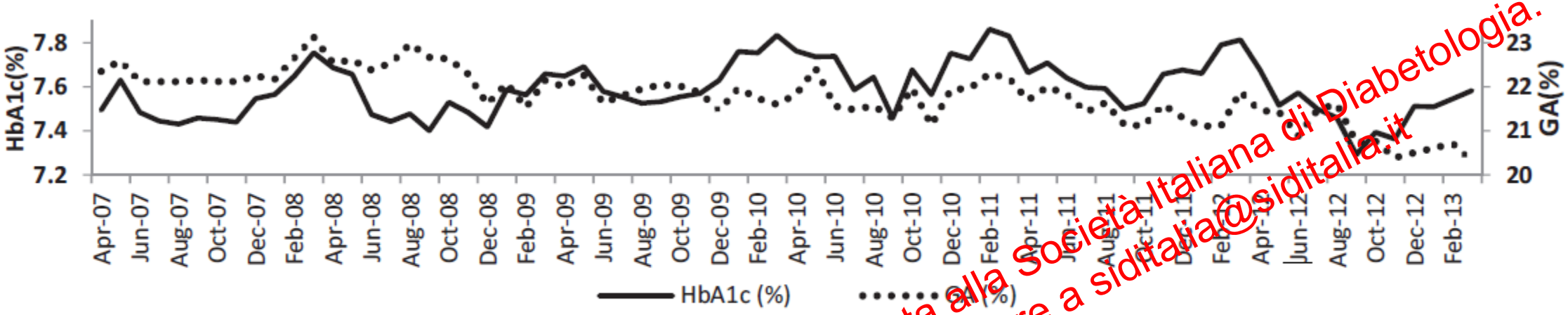
Some examples of regression towards the mean

J Martin Bland, Douglas G Altman

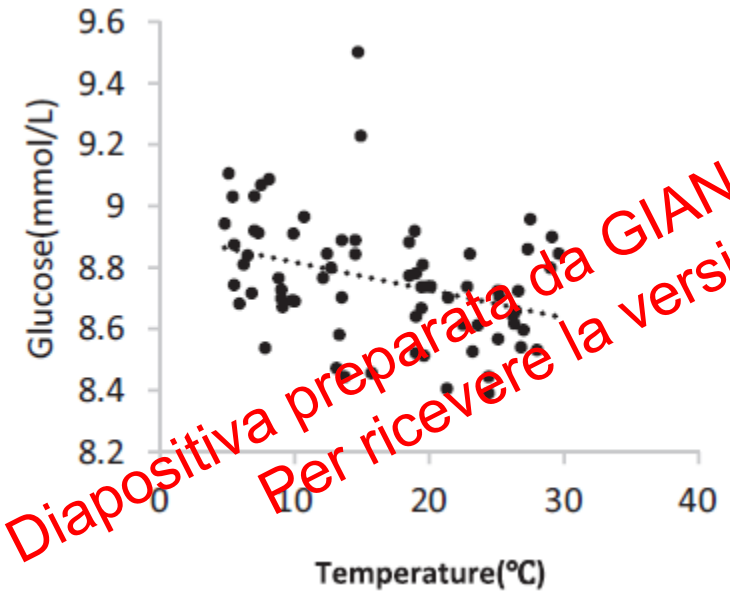


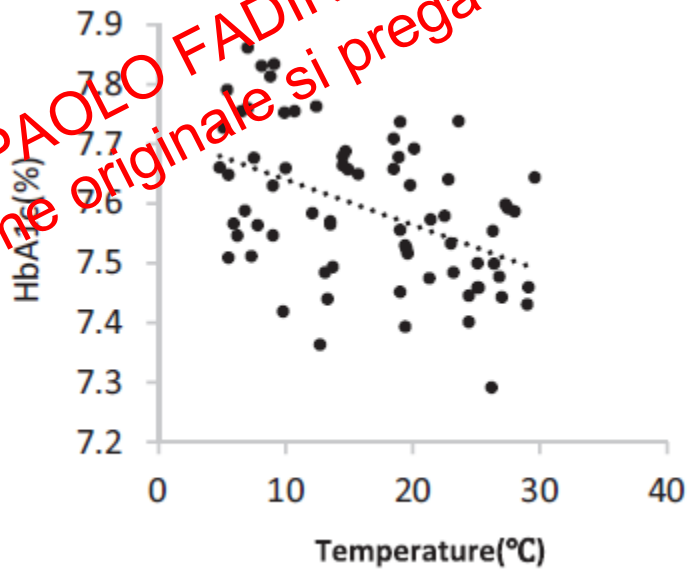
De Fronzo et al.
Diabetic Med 2010



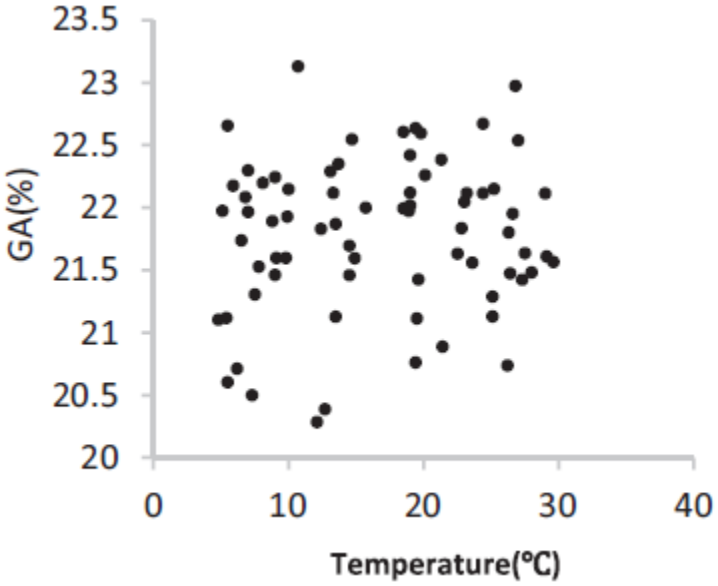


(e)

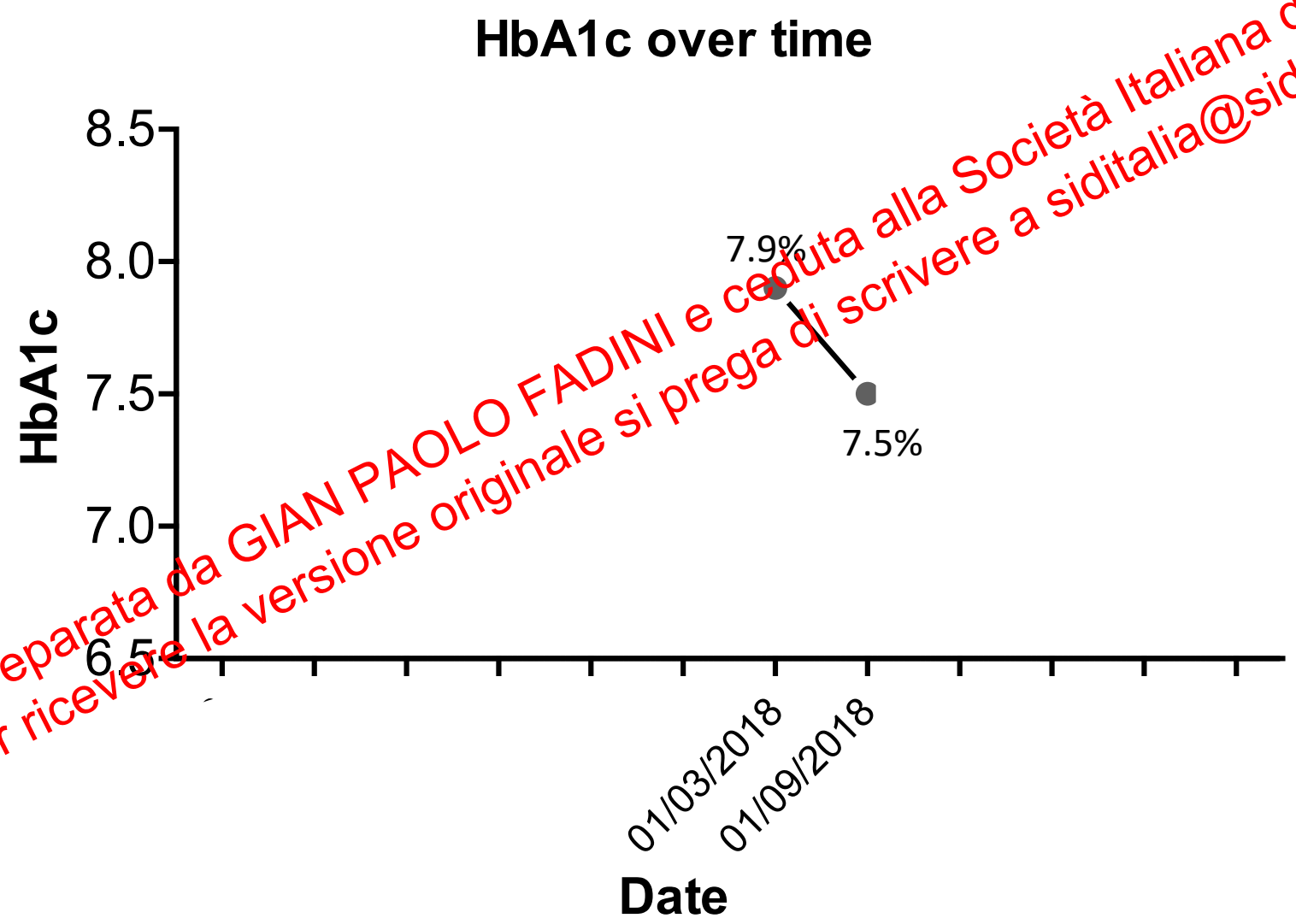




(f)



Young T1D uncontrolled, started SGLT2i off-label on March 2018
A1c down from 7.9% to 7.5%



Regressione verso la media

Implicazioni pratiche

- Un valore di HbA1c sopra la media per quel paziente sarà seguito, con maggiore probabilità, da un valore più basso
- Più è alta HbA1c maggiore è la riduzione da attendersi

Implicazioni in ricerca

- Riduzione HbA1c sempre proporzionale a Hb1Ac basale con qualsiasi trattamento
- Riduzioni di HbA1c maggiori per valori medi di HbA1c elevati nella popolazione
- Riduzione HbA1c anche nel gruppo placebo

Magnitude and Pattern of Placebo Response in Clinical Trials of Oral Antihyperglycemic Agents: Data From the U.S. Food and Drug Administration, 1999–2015

Arif Khan,[1,2] Kaysee Fahl Mar,[1] Joshua Schilling,[3] and Walter A. Brown[4]

Diabetes Care 2018;41:994–1000 | https://doi.org/10.2337/dc17-1316

Regressione verso la media

RCT

- A1c media basale della popolazione
- Effetto «placebo»
- Correlazione $A1c_{basale}$ $A1c_{delta}$

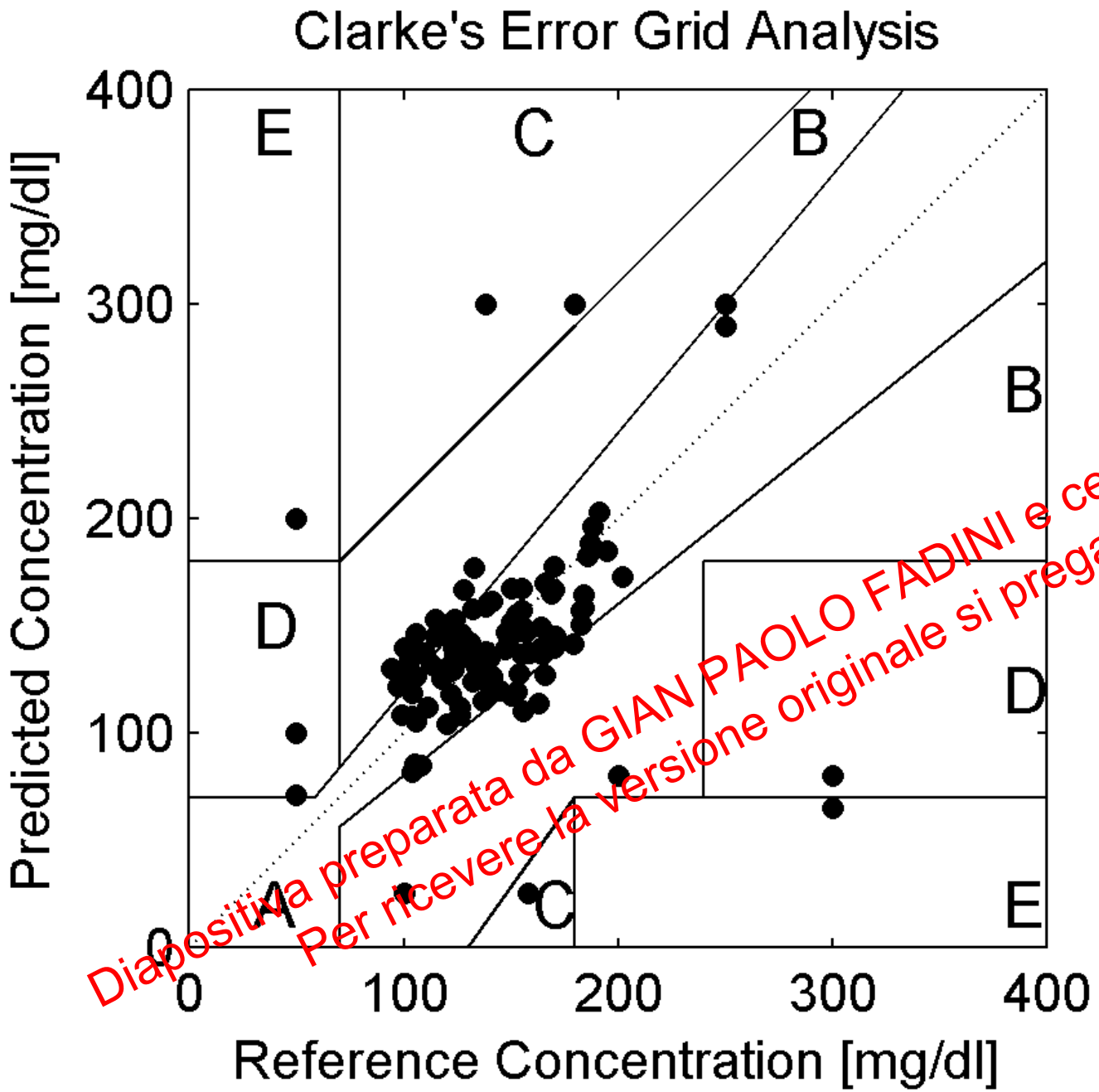
RWE

- A1c media basale della popolazione
- Correlazione $A1c_{basale}$ $A1c_{delta}$
- Importanza di un gruppo di controllo
- Valutazione della variabilità pre-trattamento per stimare la regressione verso la media

Glucosio

- Plasma
- Siero
- Sangue intero
- Urine
- Liquido interstiziale
- … …
- … …

Google Smart Content Lenses



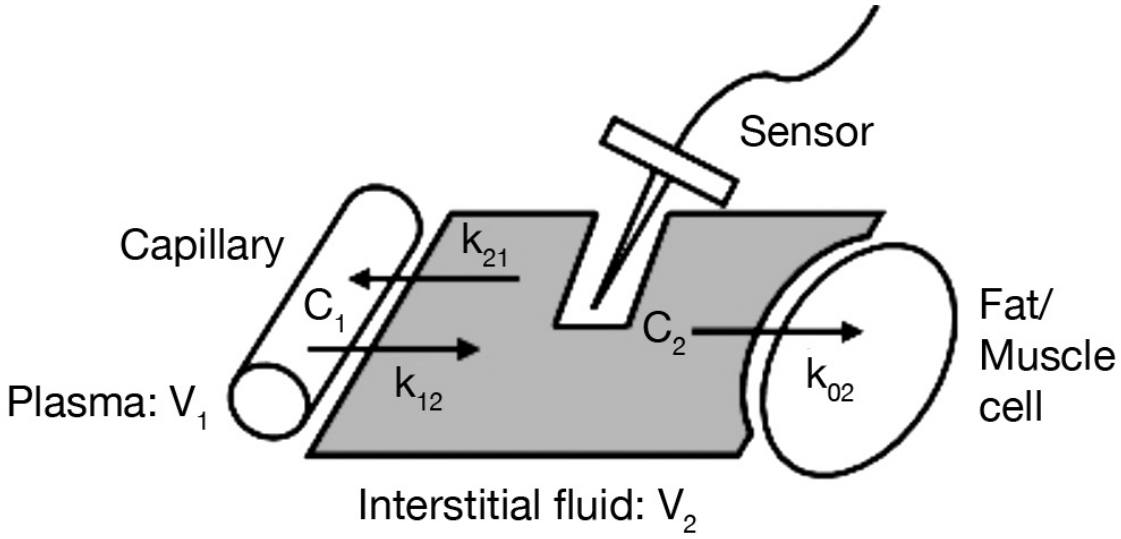
A are those values within 20% of the reference sensor,

B contains points that are outside of 20% but would not lead to inappropriate treatment,

C are those points leading to unnecessary treatment,

D are those points indicating a potentially dangerous failure to detect hypoglycemia or hyperglycemia ,

E are those points that would confuse treatment of hypoglycemia for hyperglycemia and vice versa.



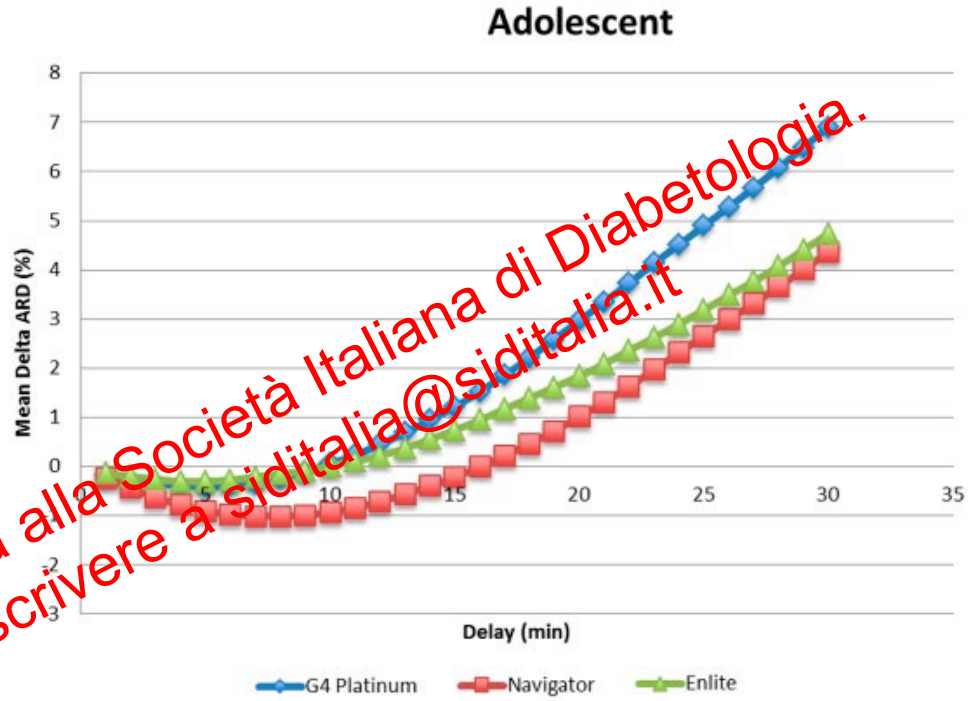


Table 1. Estimated delay by sensor for adolescents and adults.

	G4 Platinum	G4 Platinum vs Navigator	Navigator	Navigator vs Enlite	Enlite	Enlite vs G4 Platinum
	Mean ± SD (min)	*P* value	Mean ± SD (min)	*P* value	Mean ± SD (min)	*P* value
Adolescent	5.6 ± 0.9	.0396	7.8 ± 2.0	.0028	4.3 ± 1.0	.5176
Adolescent vs adult *P* value	.02		.02		.02	
Adult	8.1 ± 0.7	.0107	10.8 ± 1.0	.1113	8.3 ± 0.9	.3584

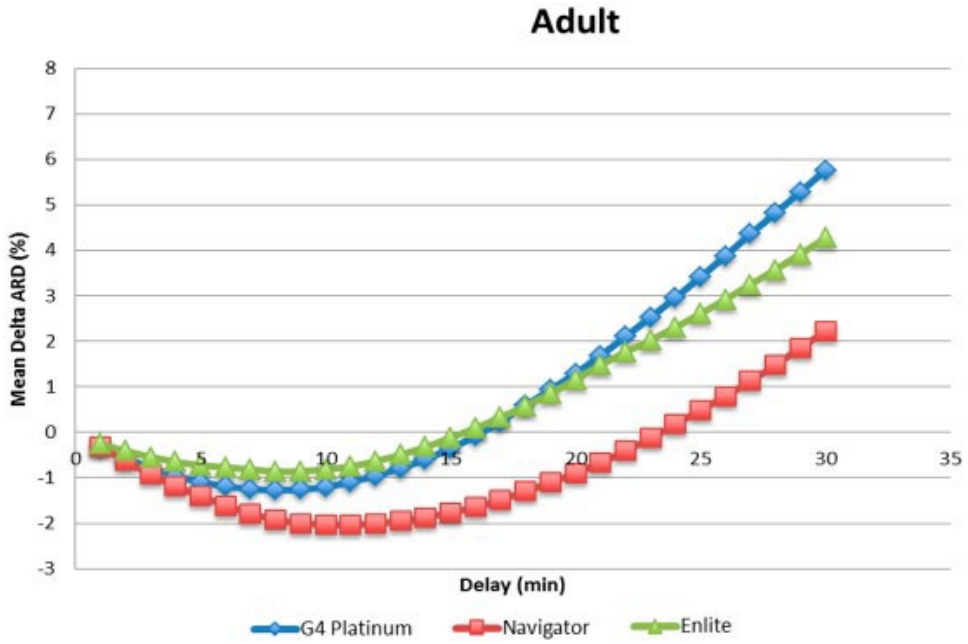


Table 1.
Manufacturer-Reported Delays in CGM Devices

Product	Manufacturer	Technology	Reported delay (min)
CGMS Gold	Medtronic MiniMed	Transcutaneous	3+ ISF
Guardian RT	Medtronic MiniMed	Transcutaneous	8.25+ ISF
SEVEN	Dexcom, Inc.	Transcutaneous	5[a]
Freestyle Navigator	Abbott Diabetes	Transcutaneous	12.6[23,24]
Glucoday	Menarini Diagnostics	Microdialysis	1.7–6.2[10,19]
GlucoWatch	J&J, Animas	Reverse iontophoresis	10+ ISF[14]

[a]DexCom marketing literature.

qnow 3

Quale caratteristica del CGM è più importante nella pratica clinica?

A. Accuratezza
B. Delay
C. Praticità
D. Durata

Implicazioni cliniche

- CGM RT o FGM: delay e accuratezza equamente importanti

Implicazioni in ricerca

- CGM blind: accuratezza più importante del delay

Glucose Management Indicator (GMI): A New Term for Estimating A1C From Continuous Glucose Monitoring

Richard M. Bergenstal,[1] Roy W. Beck,[2] Kelly L. Close,[3] George Grunberger,[4] David B. Sacks,[5] Aaron Kowalski,[6] Adam S. Brown,[7] Lutz Heinemann,[8] Grazia Aleppo,[9] Donna B. Ryan,[10] Tonya D. Riddlesworth,[2] and William T. Cefalu[11]

Diabetes Care 2018;41:2275–2280 | https://doi.org/10.2337/dc18-1581

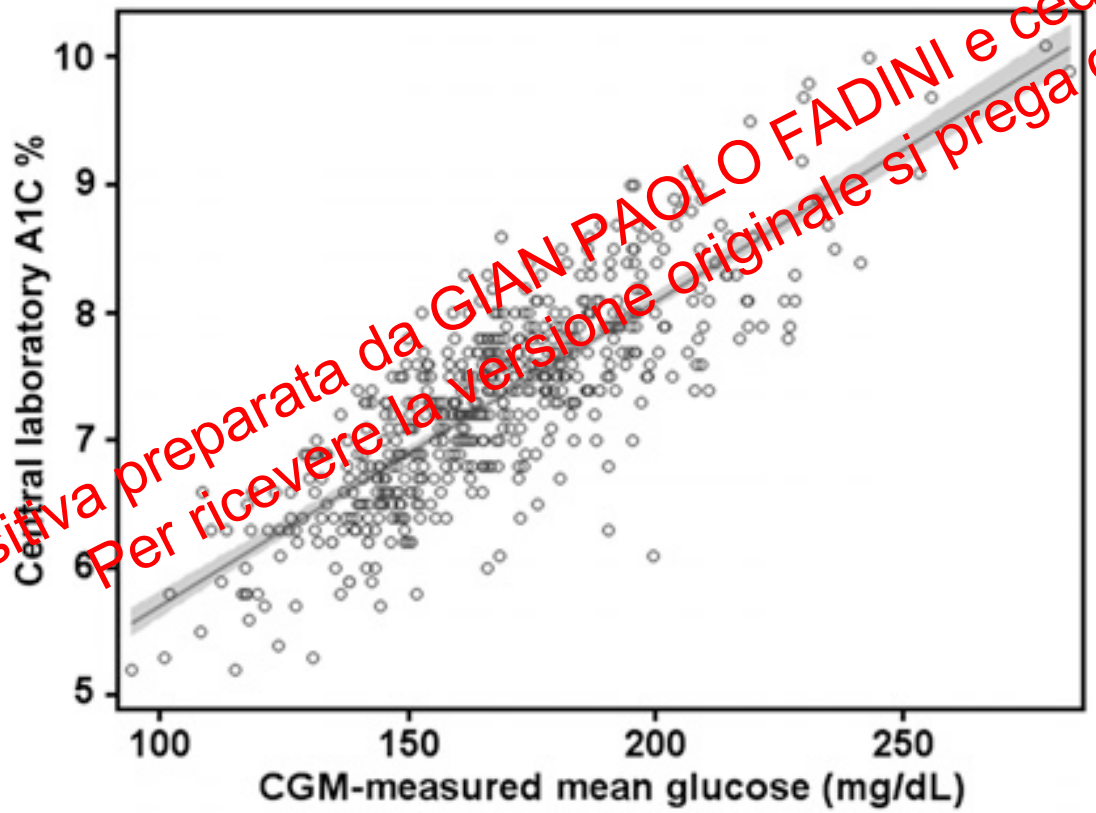


Table 1—GMI calculated for various CGM-derived mean glucose concentrations

CGM-derived mean glucose (mg/dL)	GMI (%)*
100	5.7
125	6.3
150	6.9
175	7.5
200	8.1
225	8.7
250	9.3
275	9.9
300	10.5
350	11.7

TABLE 1. METRICS TO CHARACTERIZE GLYCEMIC VARIABILITY

Methods to characterize glycemic variability

1. SD (for various subsets of data, within-days, between-days)
2. %CV (SD expressed as a percentage of the mean)
3. Simplified frequency distribution (% of glucose values within target ranges, % in hypoglycemic ranges, % in hyperglycemic ranges, and other ranges as desired)
4. Glucose frequency distribution and cumulative frequency distribution
5. AGP (smoothed glucose percentiles by time of day)
6. MAGE, MODD, ADRR, $CONGA_n$, $CONGA_{24}$, IQR, MAD
7. GVP, MAG, DT
8. Time series analysis (Fourier analysis, periodogram, spectral frequency density, Multiscale Entropy (MSE), Complexity analysis)

ADRR, Average Daily Risk Range; AGP, Ambulatory Glucose Profile; %CV, %Coefficient of Variation; DT, Distance Traveled; IQR, Inter-Quartile Range; MAD, Mean Absolute Deviation; MAG, Mean Absolute Glucose change per unit time; MAGE, Mean Amplitude of Glycemic Excursion; MODD, Mean Of Daily Differences; SD, Standard Deviation.

Association of Glycemic Variability in Type 1 Diabetes With Progression of Microvascular Outcomes in the Diabetes Control and Complications Trial

*Jaime M. Lachin,[1] Ionut Bebu,[1] Richard M. Bergenstal,[2] Rodica Pop-Busui,[3] F. John Service,[4] Bernard Zinman,[5] and David M. Nathan,[6] for the DCCT/EDIC Research Group**

Diabetes Care 2017;40:777–783 | https://doi.org/10.2337/dc16-2426

Overall within-day glycemic variability, as determined from quarterly glucose profiles, does not play an apparent role in the development of microvascular complications beyond the influence of the mean glucose.

Association of Time in Range, as Assessed by Continuous Glucose Monitoring, With Diabetic Retinopathy in Type 2 Diabetes

Yingyi Lu,[1] Xiaojing Ma,[1] Jian Zhou,[1] Lei Zhang,[1] Yifei Mo,[1] Lingwen Ying,[1] Wei Lu,[1] Wei Zhu,[1] Yuqian Bao,[1] Robert A. Vigersky,[2,3] and Weiping Jia[1]

Diabetes Care 2018;41:2370–2376 | https://doi.org/10.2337/dc18-1131

Retinopathy associated with Time In Range independently from GV

Artificial pancreas *at a glance*

Prospettive future

- Impatto clinico di eA1c (o GMI) vs HbA1c
- Definizione, identificazione e gestione dei fenotipi glicatori
- Nuovi sistemi di misurazione non invasiva della glicemia
- Ruolo predittivo della variabilità glicemica da CGM
- Sistemi di predizione dell'andamento glicemico in AP