

GIORNATE
DIABETOLOGICHE
DI PALAZZO DUCALE

Genova, Palazzo Ducale
18/19 Novembre 2011

SAVE THE DATE


Società
Italiana
Diabetologia

Le terapie
delle complicanze
del diabete mellito:
il futuro presente,
il futuro che verrà

"Non penso mai al futuro,
arriva così presto"
Albert Einstein (1879-1955)



Il diabete o l'arte del mosaico

Enzo Bonora

Endocrinologia, Diabetologia e Metabolismo
Università e Azienda Ospedaliera Universitaria
Integrata di Verona



3° CONVEGNO INTERATTIVO
DI FORMAZIONE E AGGIORNAMENTO CLINICO

VERONA Endocrinologia & Metabolismo 2012

21-24 Marzo

PALAZZO DELLA GRAN GUARDIA



Diapositiva preparata da Enzo Bonora e ceduta alla Società Italiana di Diabetologia.
Per avere una versione originale si prega di scrivere a siditalia@siditalia.it

Virgilio – Volti e Immagini del Poeta

Mantova – Palazzo Te

16 Ottobre 2011-8 Gennaio 2012



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Enzo Bonora – un mosaico di trasparenti e lecite interazioni con aziende dell'area del diabete (Disclosure of Interest)

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Diabete: un mosaico di malattie diverse

Tipo 2

Tipo 1

LADA

Gestazionale

MODY

Altri monogenici

Secondario

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Diabete: un mosaico di geni coinvolti

Geni della disfunzione beta cellulare

- KCNJ11
- TCF7L2
- IGF2BP2
- WSF1
- SLC30A8
- CDC123
- TSPAN8
- KCNQ1
- MTNR1B
- HHEX
- CDKAL1
- CDKN2A/B
- HNF1B
- JAZF1
- GCKR
- ecc.

Geni dell'insulino-resistenza

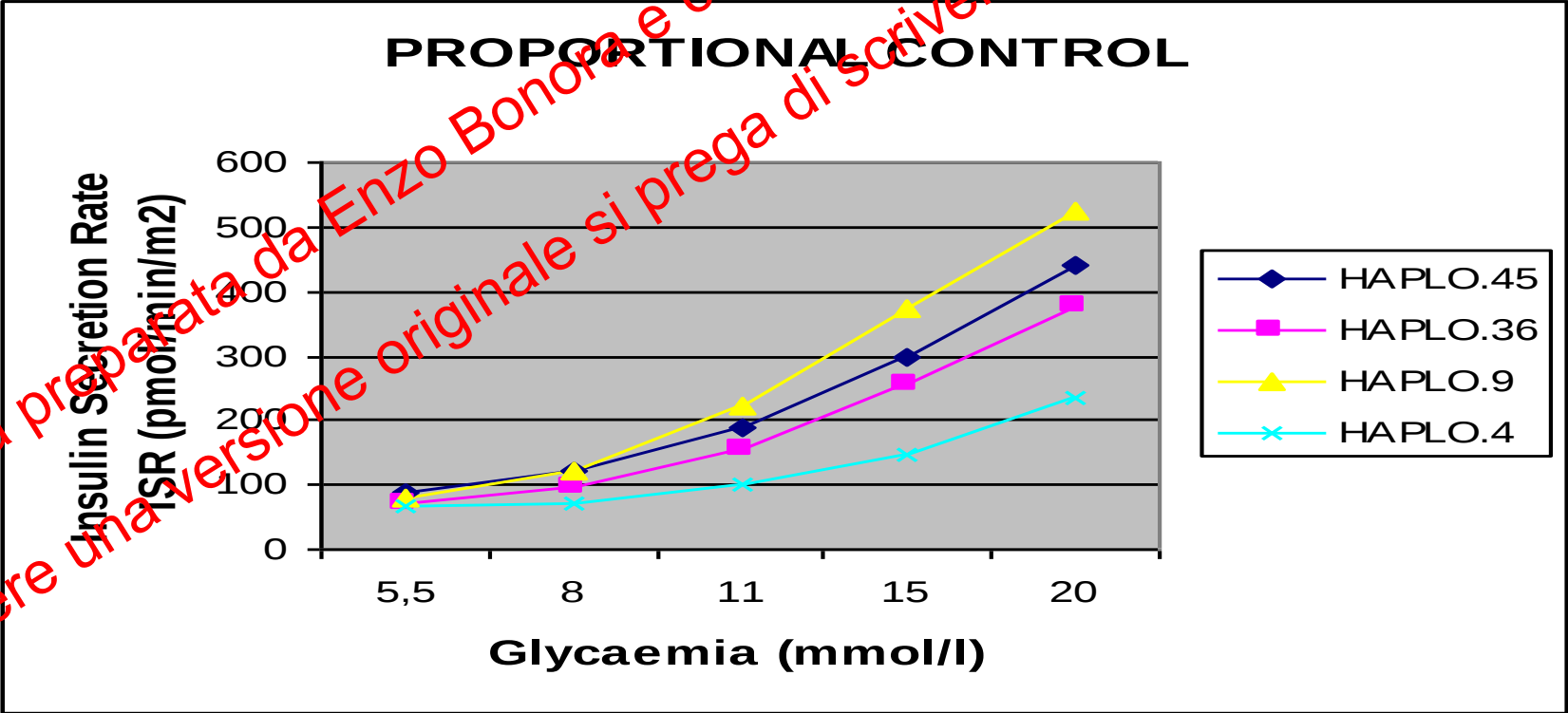
- ENPP1 (PC-1)
- PPARG
- ADAMTS9



Haplotype analysis of TCF7L2 polymorphisms and glucose stimulated insulin secretion in newly-diagnosed T2DM

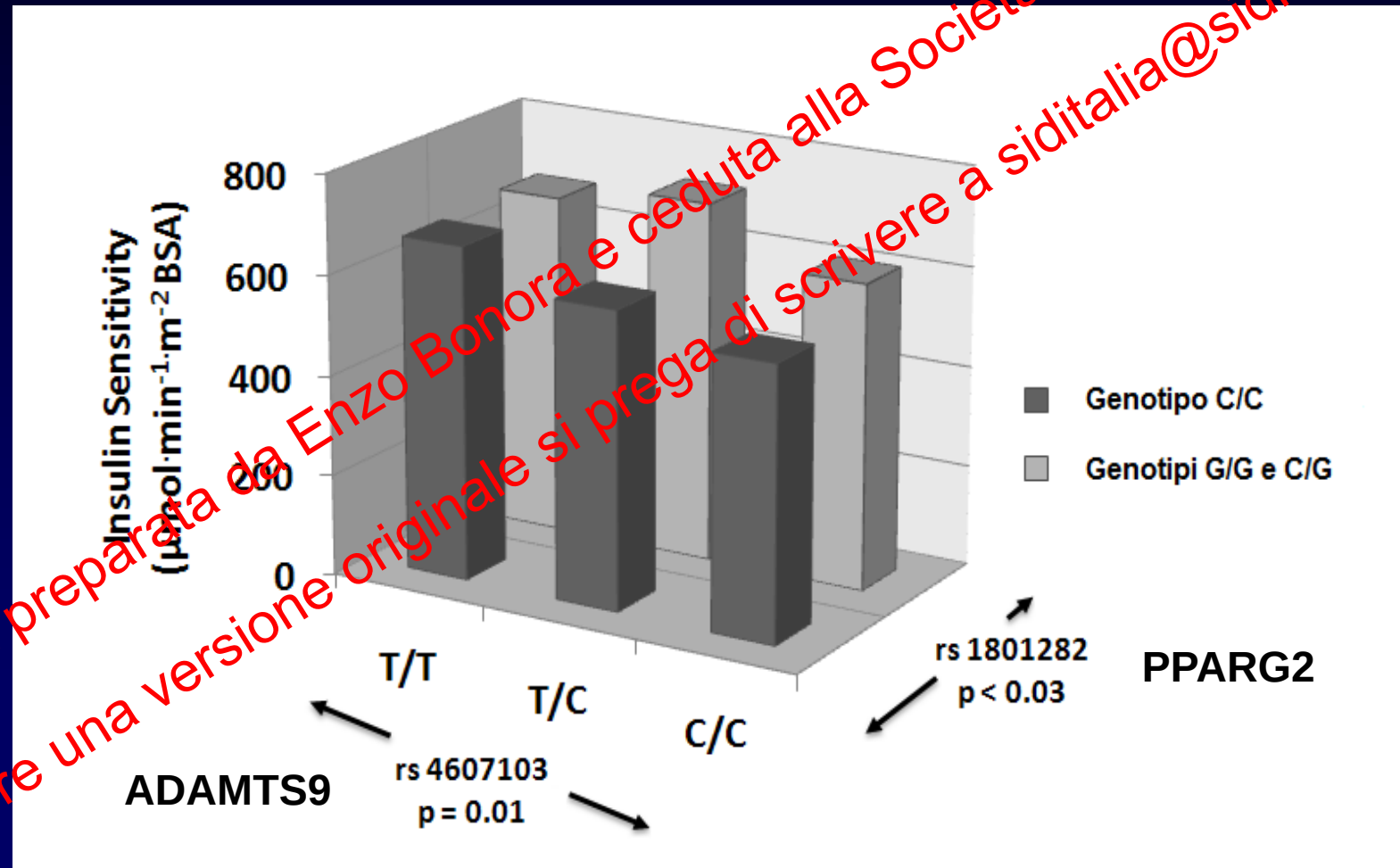
(Bonetti et al – JCE&M, 96: E389, 2011)

	rs7901695	rs7903146	rs11196205	rs12253372	Haplotype frequency
haplo.4	C	T	C	G	0,0383
haplo.36	C	T	C	T	0,3479
haplo.9	T	C	C	G	0,0864
haplo.45	T	C	G	G	0,4559



Sensibilità insulinica (M-clamp) nei soggetti diabetici del VNDS in funzione della presenza o meno dell'allele di rischio di PPARG2 e dell'allele di rischio di ADAMTS9

(Bonetti et al – submitted)



Diabete: un mosaico di organi, tessuti, cellule coinvolti nella patogenesi dell'iperglicemia



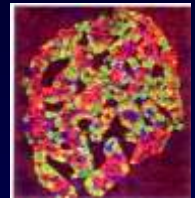
Liver
Increased endogenous glucose production



Skeletal muscle
Impaired glucose utilization
(transport, storage, oxidation)



Endocrine pancreas
Impaired insulin secretion
Exaggerated glucagon secretion



Hyperglycemia



Adipose tissue
Release of diabetogenic molecules (FFA, adipocytokines)



Gut
Impaired incretin effect



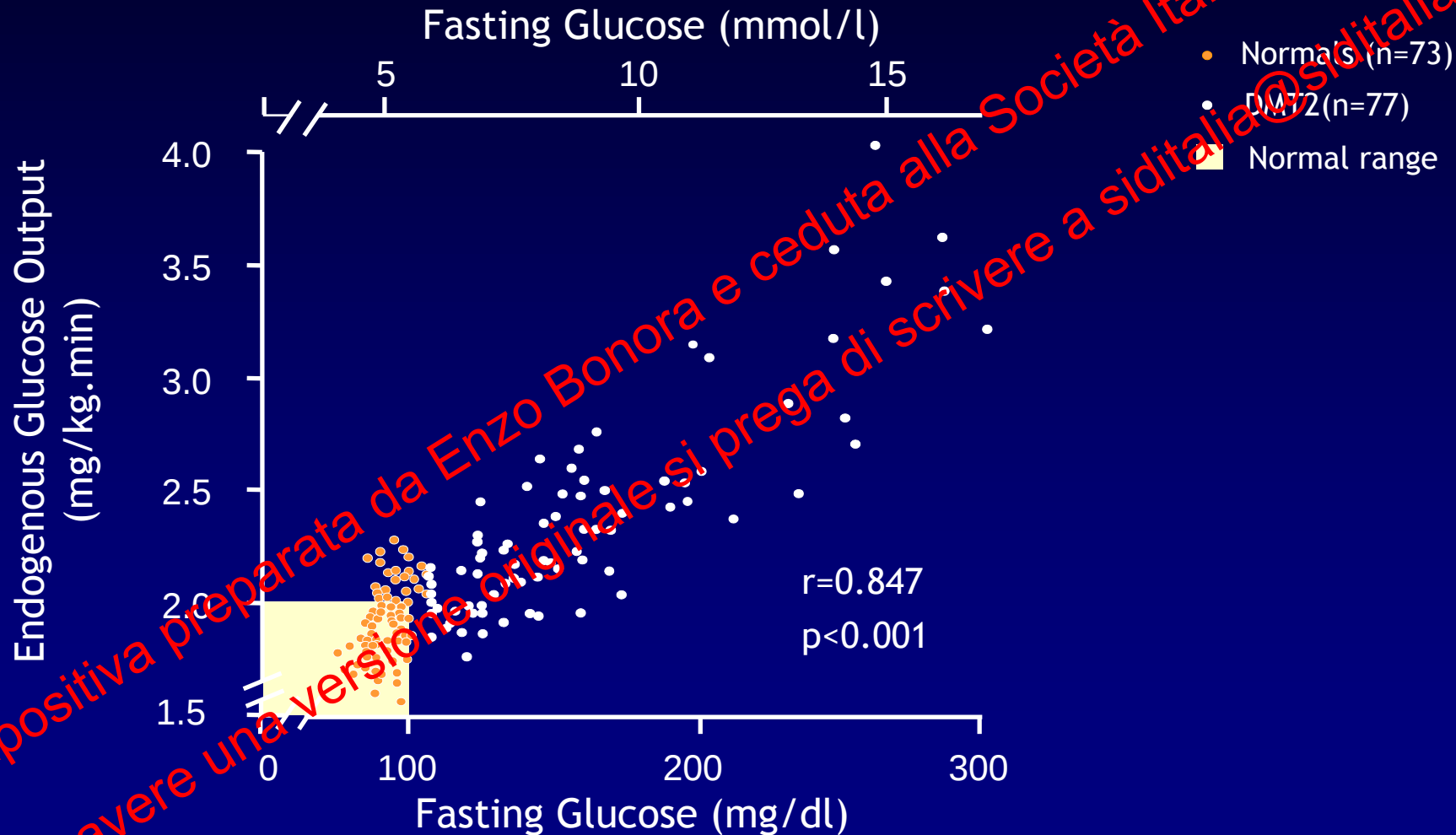
Kidney
Increased glucose reabsorption



Brain
Abnormal metabolic control

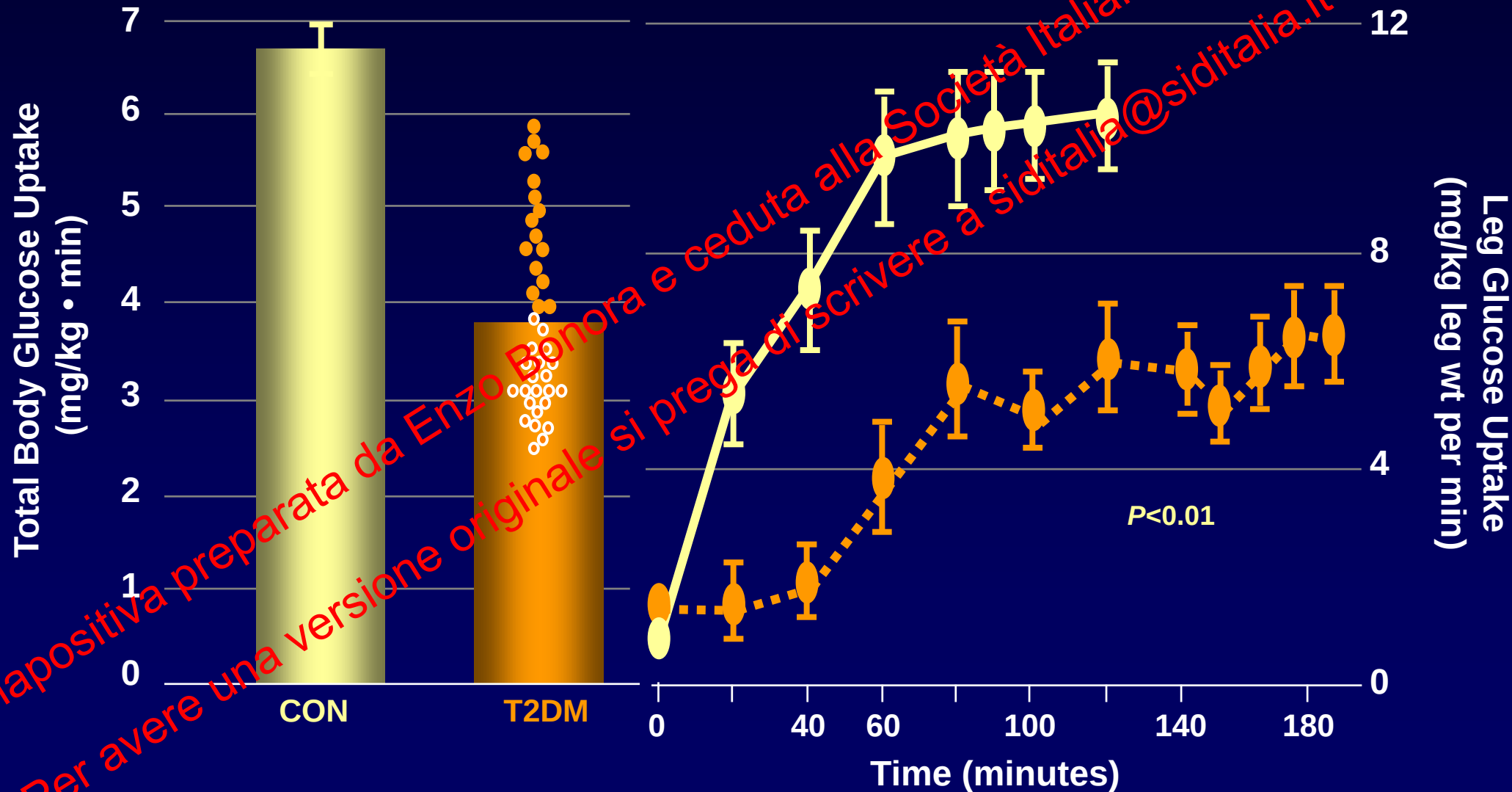
Relationship Between Fasting Glucose Levels and Endogenous Glucose Output

(DeFronzo RA - Diabetes 1988; 37:667-87)



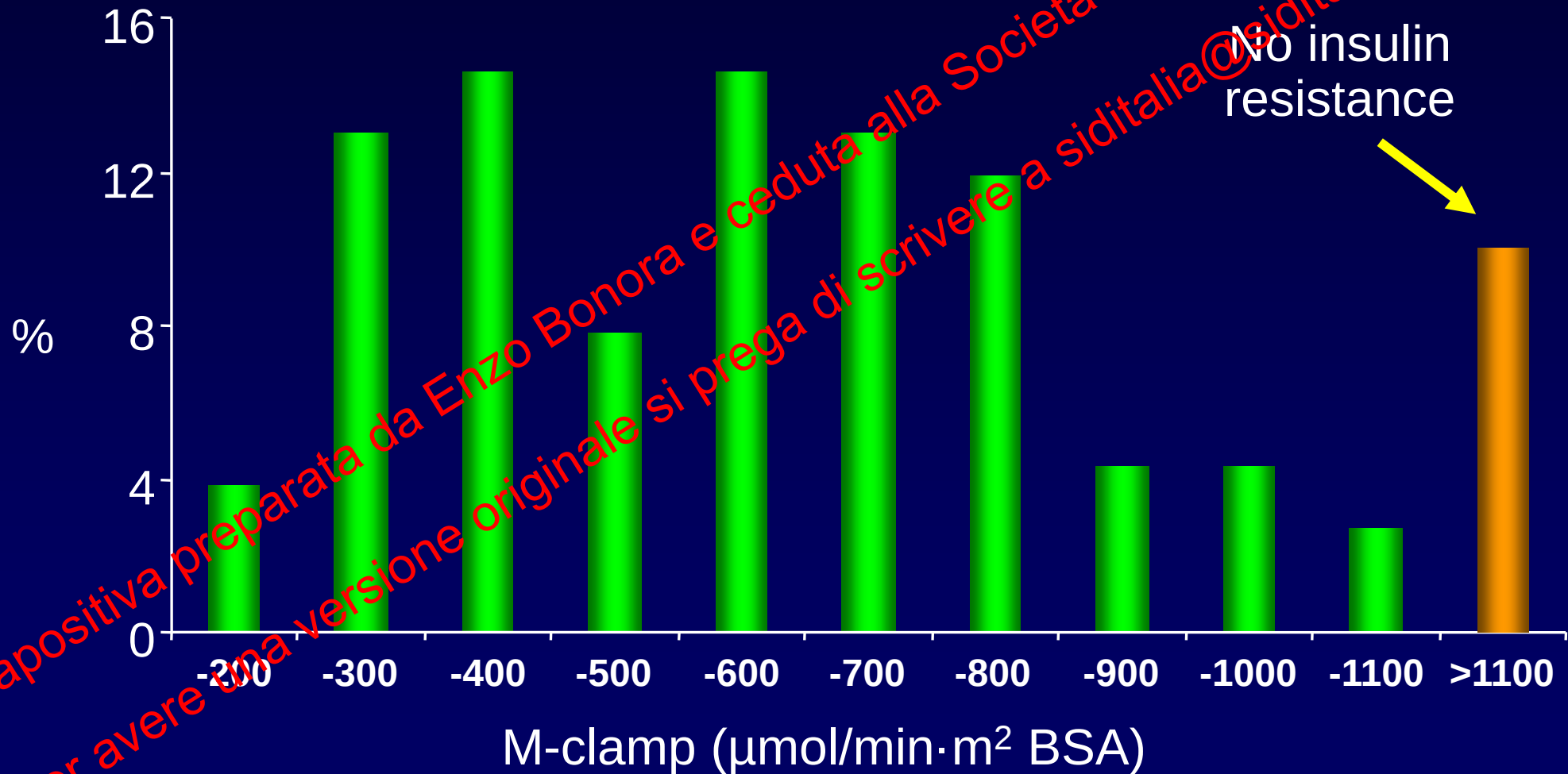
Whole Body and Muscle Insulin Resistance in T2DM

(De Fronzo et al; J Clin Invest 1979 and 1985)



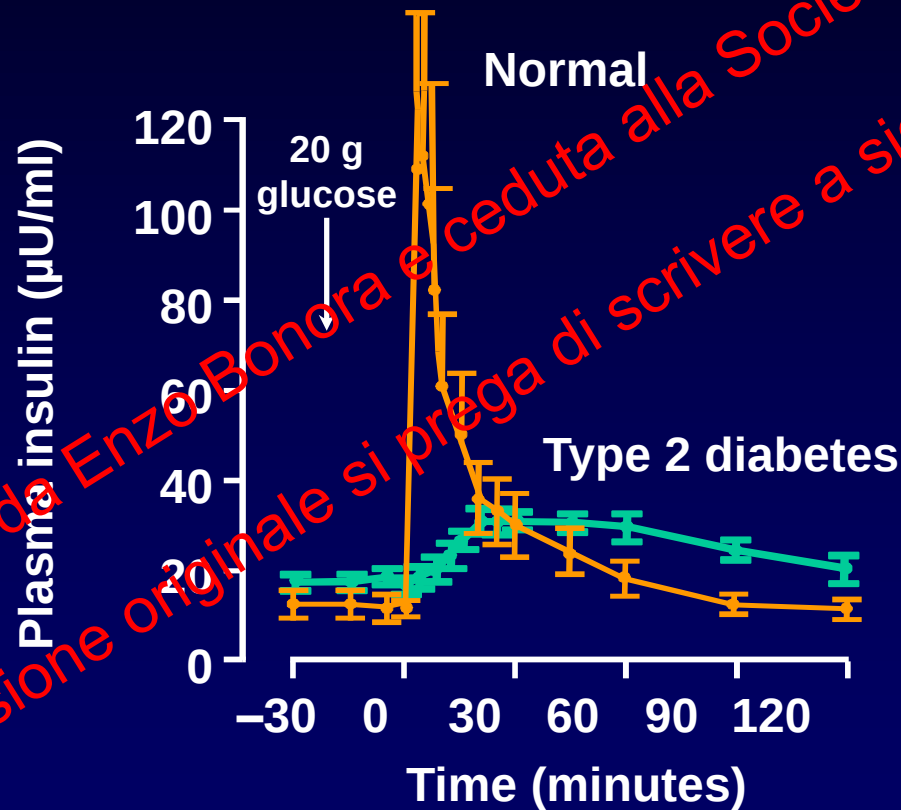
Frequency Distribution of M-clamp in Subjects with Newly-diagnosed T2DM

Threshold of insulin resistance = upper limit of bottom quintile of M-clamp in 515 non-obese healthy subjects



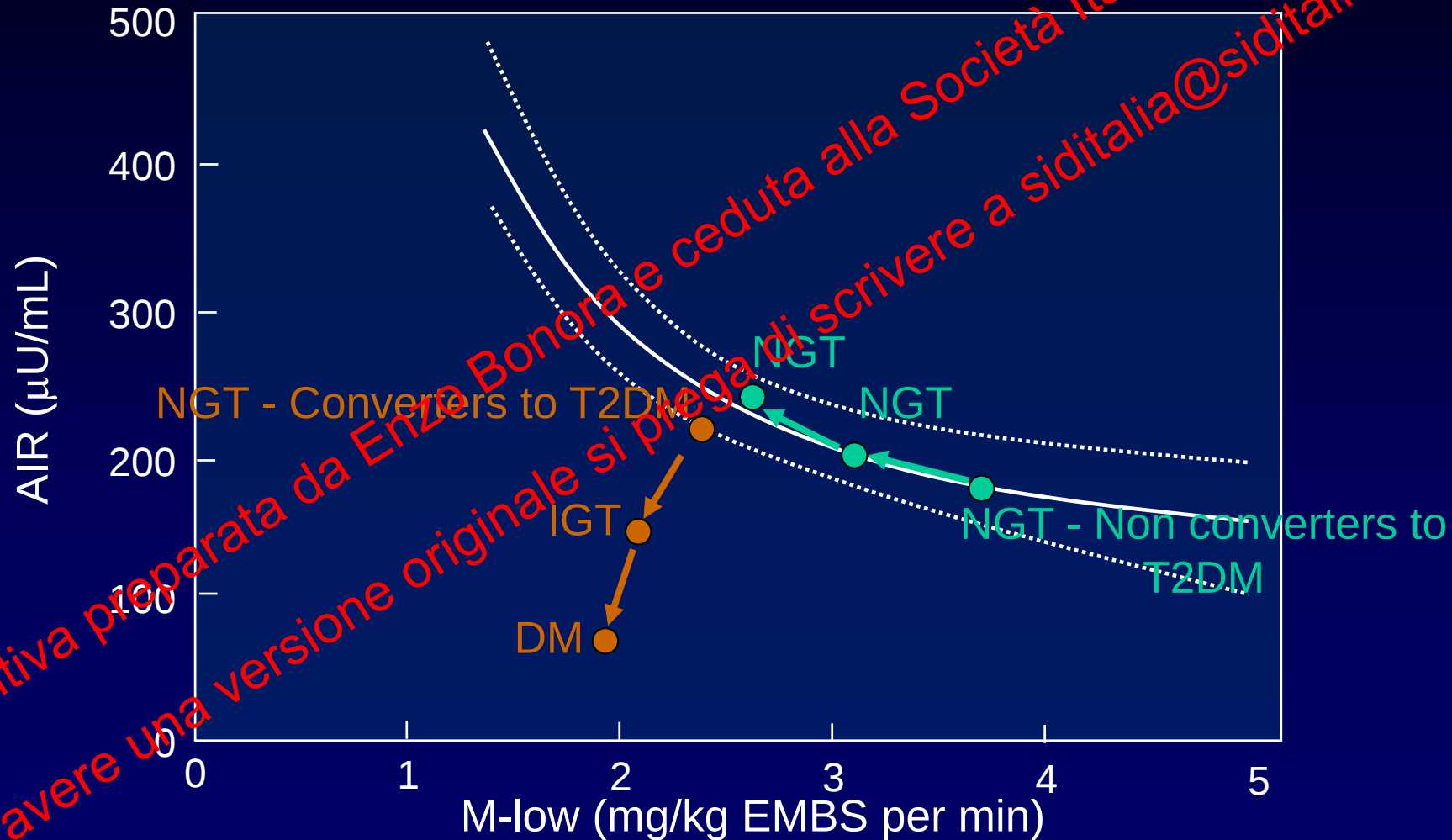
Loss of First-Phase Insulin Secretion after i.v. Glucose in T2DM

(Ward WK et al; Diabetes Care 7:491, 1984)



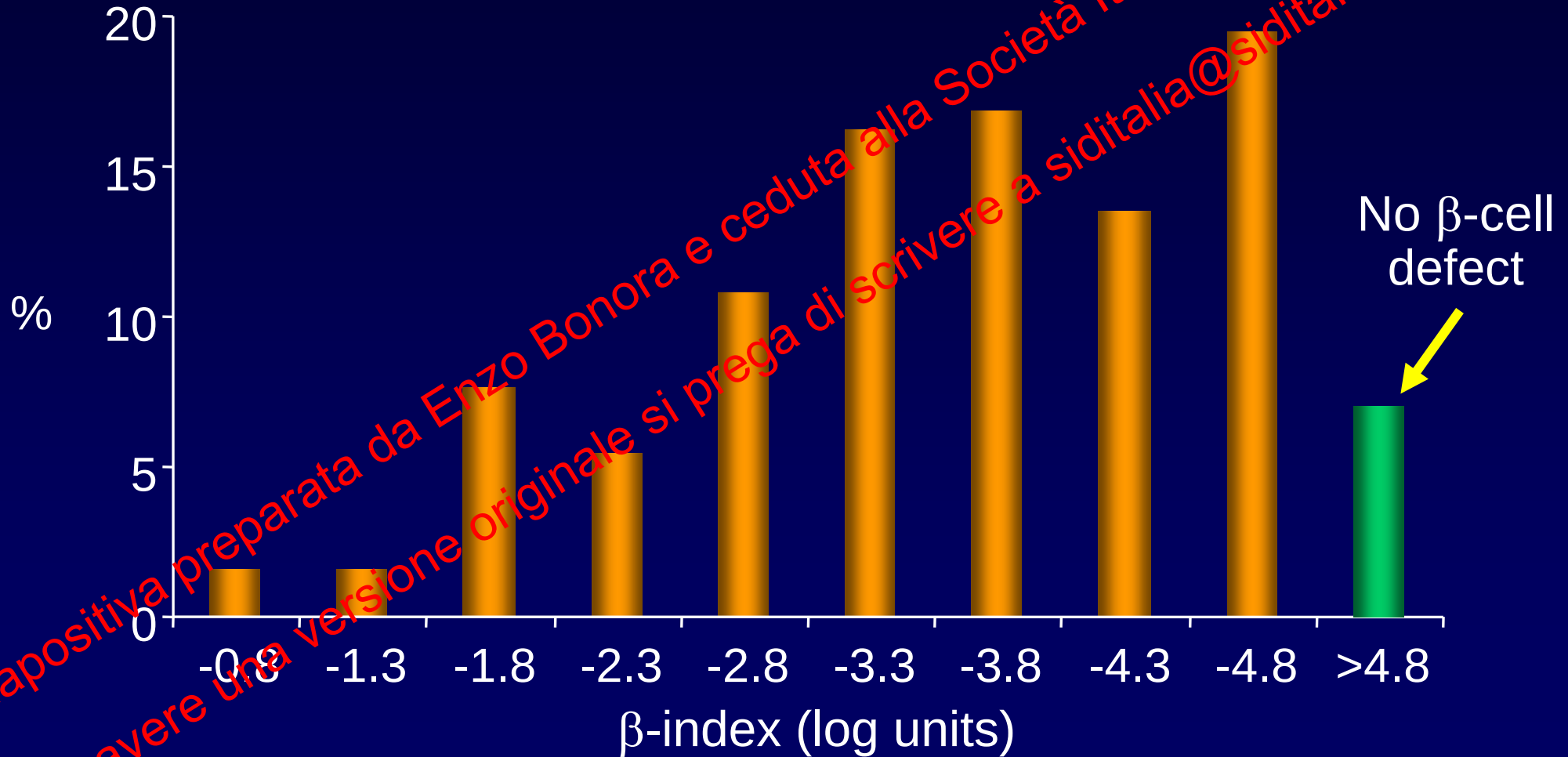
Changes in Insulin Secretion and Sensitivity are Associated to the Development of T2DM

(Weyer C et al; J Clin Invest 104:787, 1999)

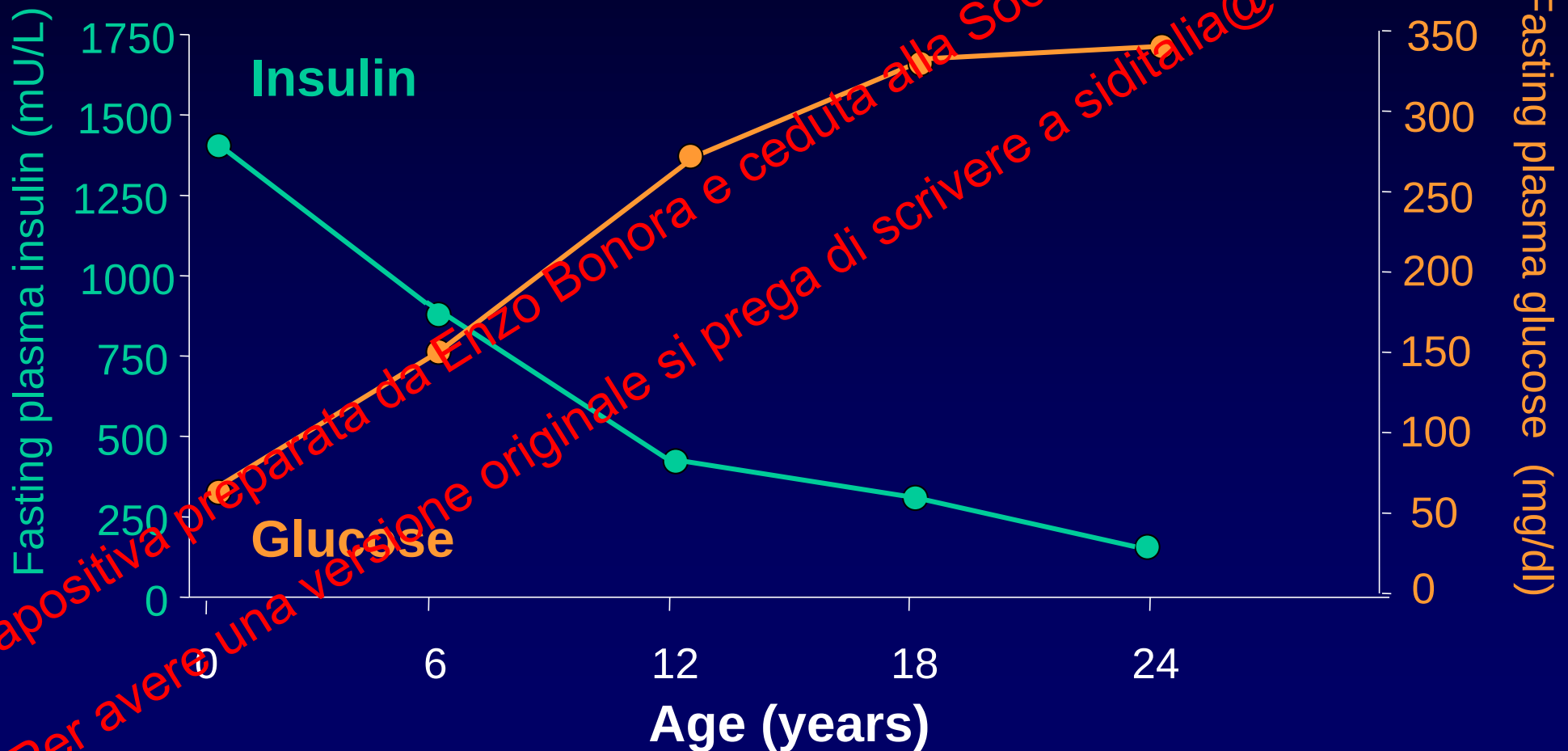


Frequency Distribution of β -Index in Subjects with Newly-Diagnosed T2DM

Threshold of β -cell defect = upper limit of bottom quintile of β -index in 125 non-obese healthy subjects



A Proof-of-Concept from Mother Nature: A Girl with Leprechaunism



Beta-Cells are Reduced and Alpha-Cells are Increased in Human Pancreatic Islets from T2DM

(Deng et al; Diabetes 53: 624, 2004)

Nondiabetic



35% α -cells
65% β -cells

T2DM



52% α -cells
48% β -cells

$P < 0.01$

Plasma glucagon levels and endogenous glucose production during an OGTT in T2DM

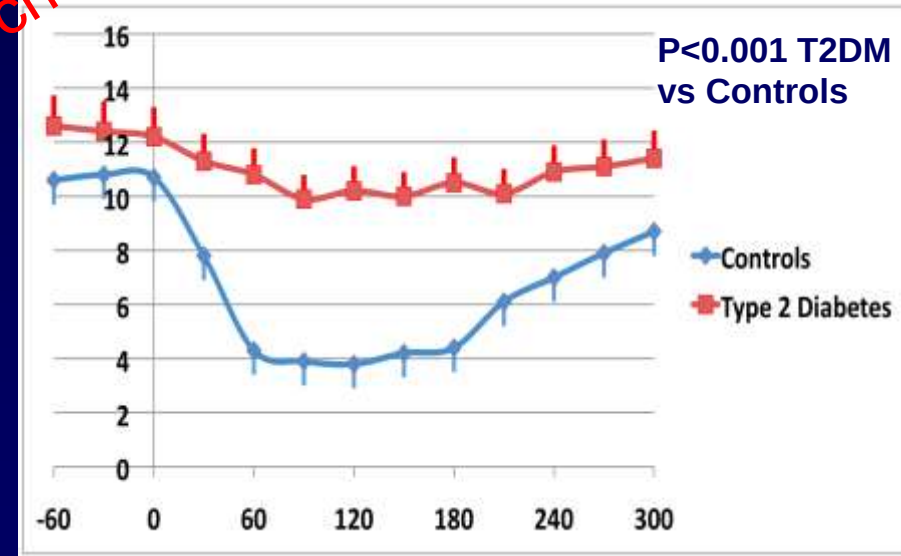
(Mitrakou A et al.; Diabetes 1990)

Plasma Glucagon
(fmol/L)



Time (min)

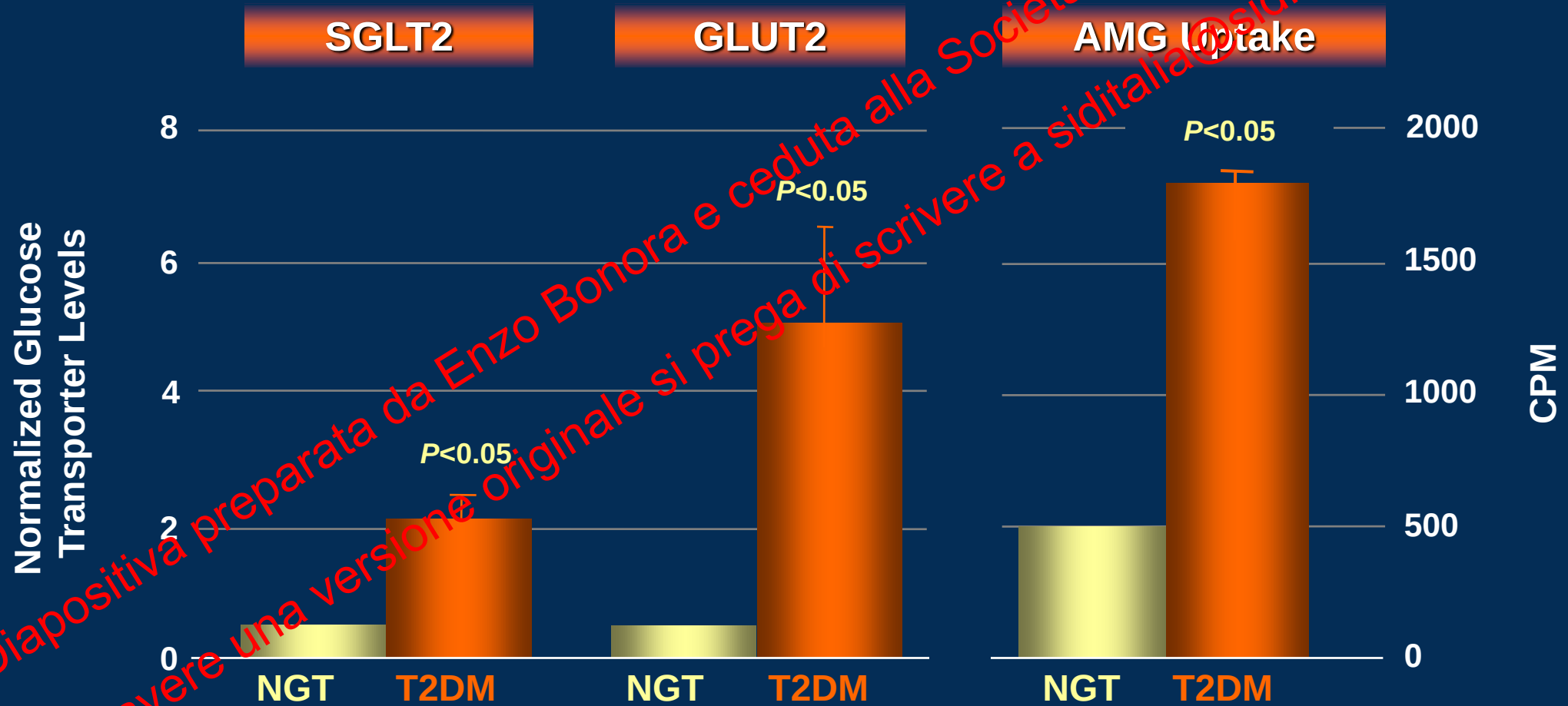
Endogenous Glucose Production
($\mu\text{mol}/\text{min}/\text{kg FFM}$)



Time (min)

Increased Glucose Transporter Proteins and Activity in Type 2 Diabetes

(Rahmoune et al, Diabetes 2005; 54:3427-3434)



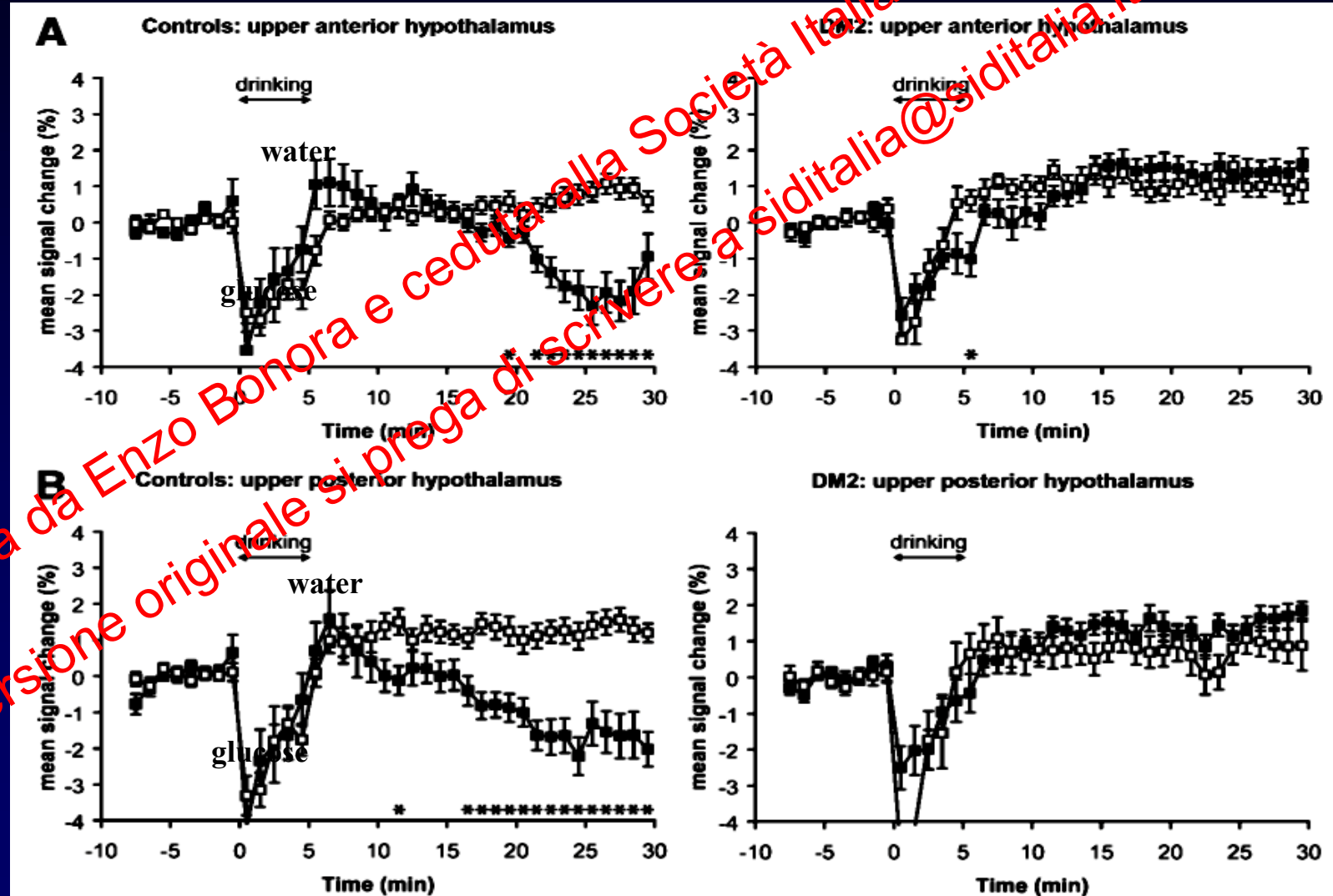
AMG=methyl- α -D-[U¹⁴C]-glucopyranoside; CPM=counts per minute.

Upper Hypothalamus Is Completely Unresponsive to an Oral Glucose Load in Type 2 Diabetes. A functional MRI Study.

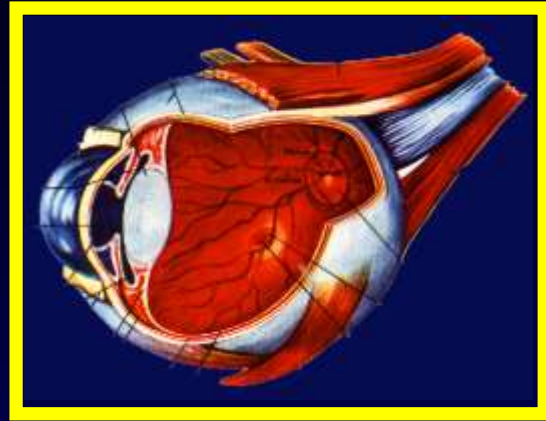
(Vidarsdottir S et al - Diabetes 56: 2547-2550, 2007)



-2.0 -4.0
+2.0 +4.0
10 mm



Diabete: un mosaico di danni d'organo



Cute

Gonadi

Apparato
osteoarticolare



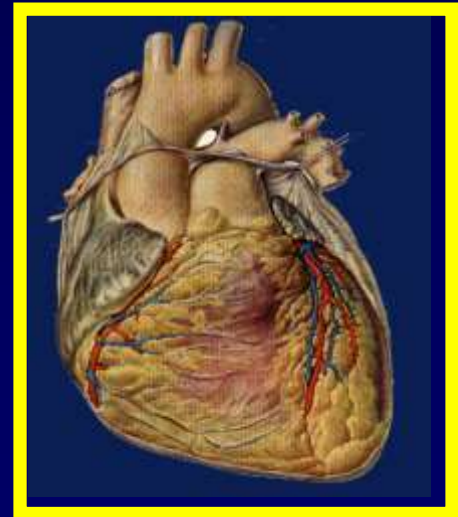
Diabete



Tubo
digerente

Cervello

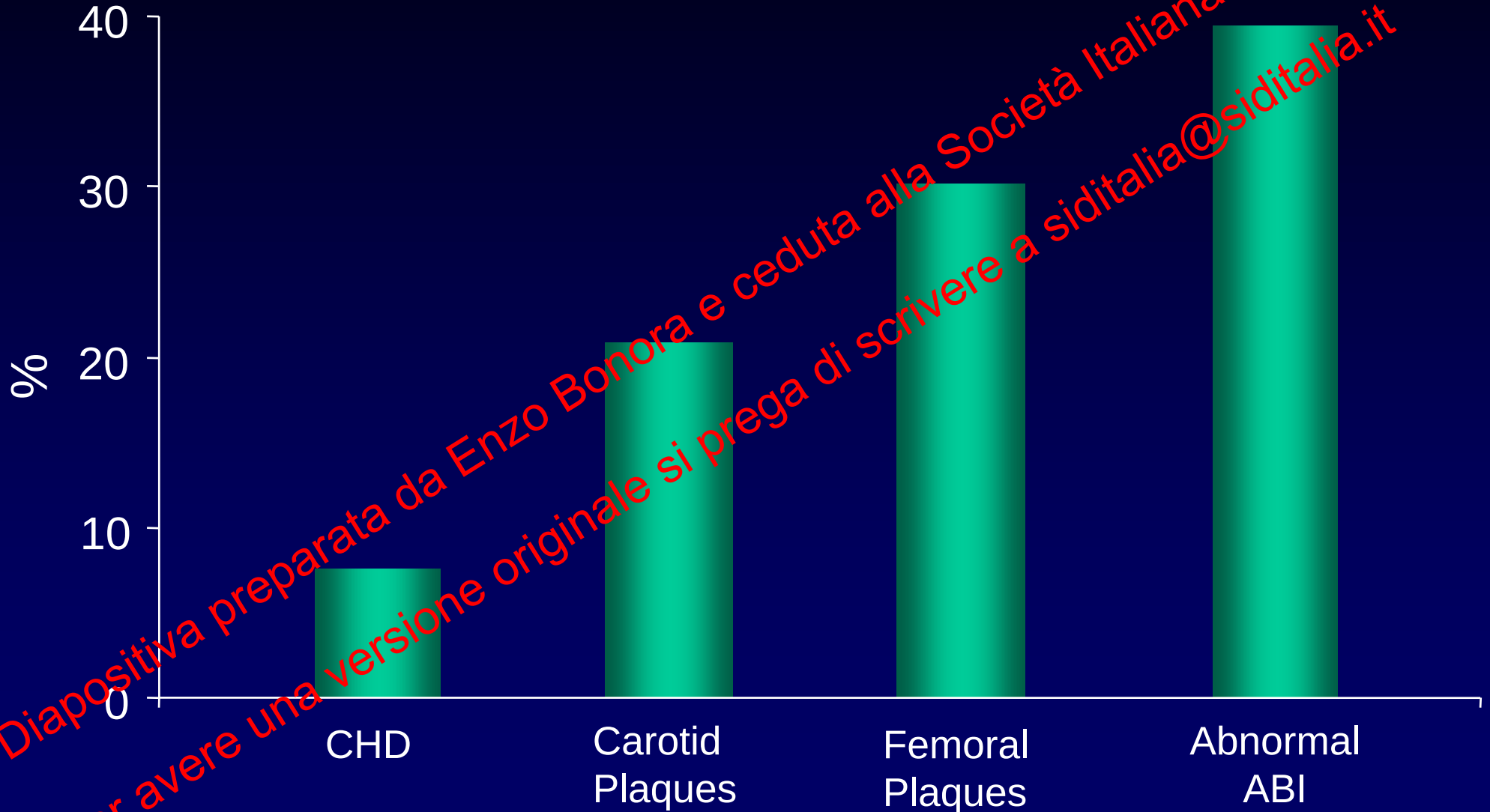
Sistema
immune



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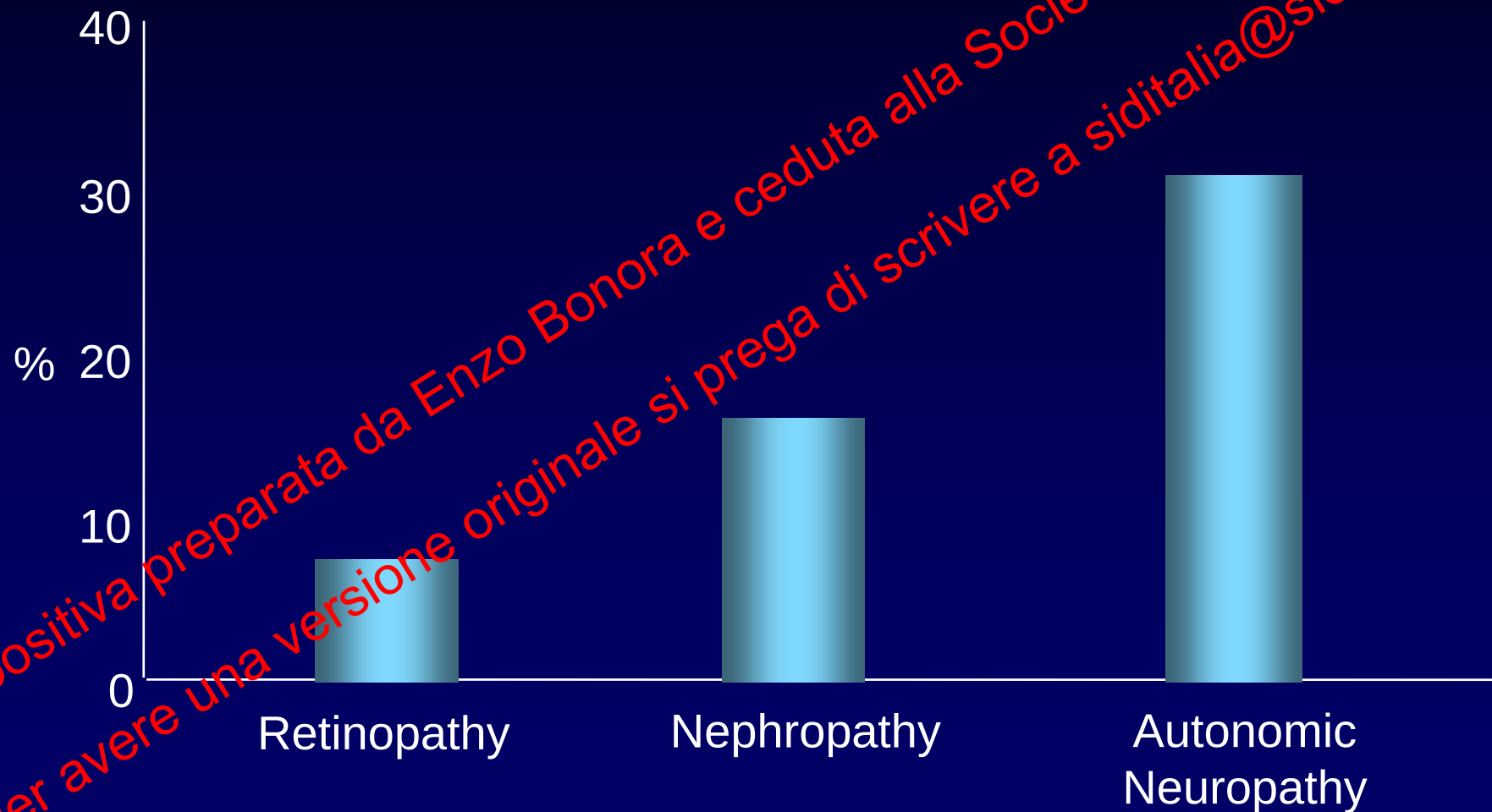
Prevalence of macrovascular complications at time of diagnosis of T2DM

(Verona Newly Diagnosed Diabetes Study; unpublished)



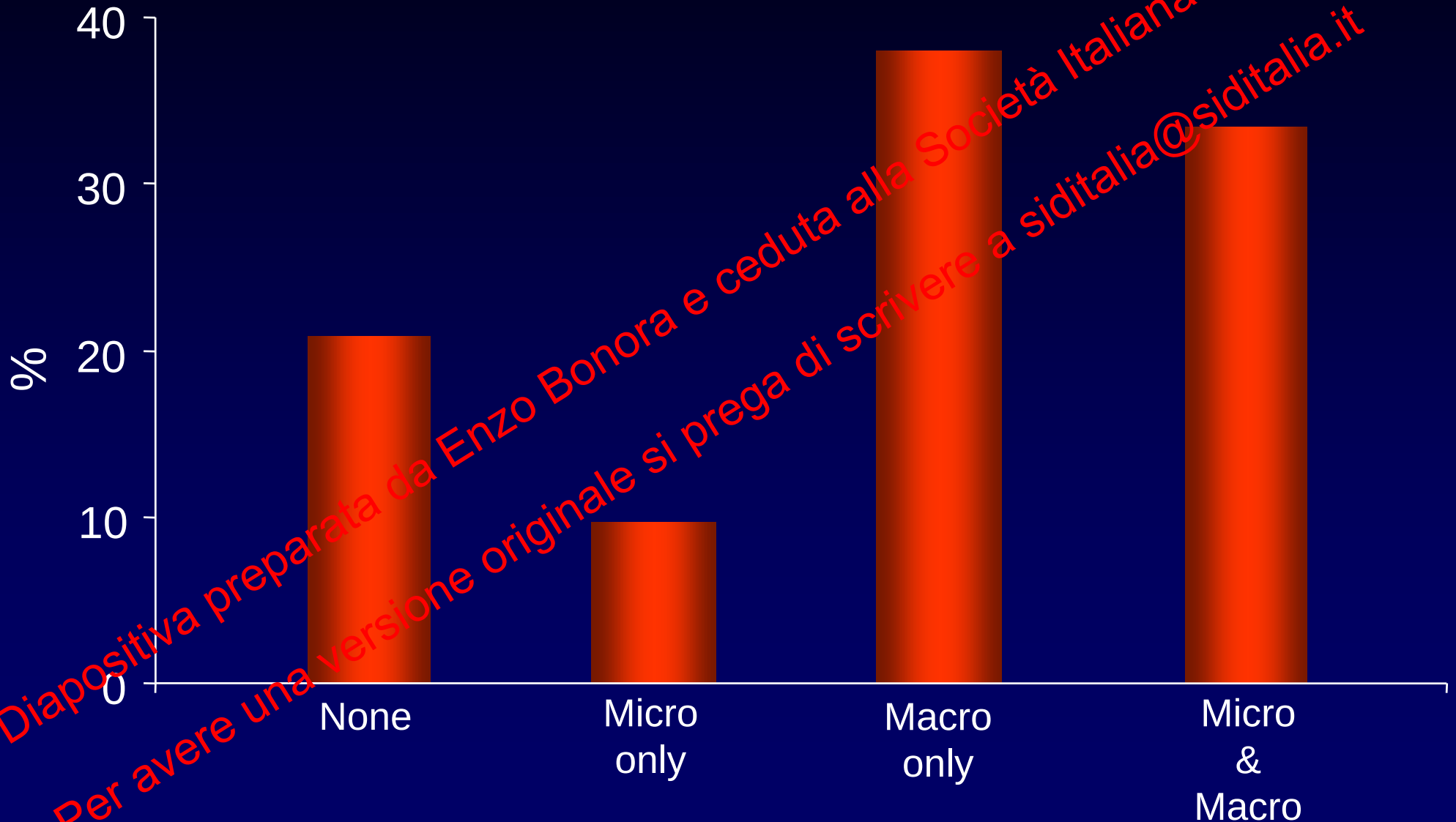
Prevalence of microvascular complications at time of diagnosis of T2DM

(Verona Newly Diagnosed Diabetes Study; unpublished)

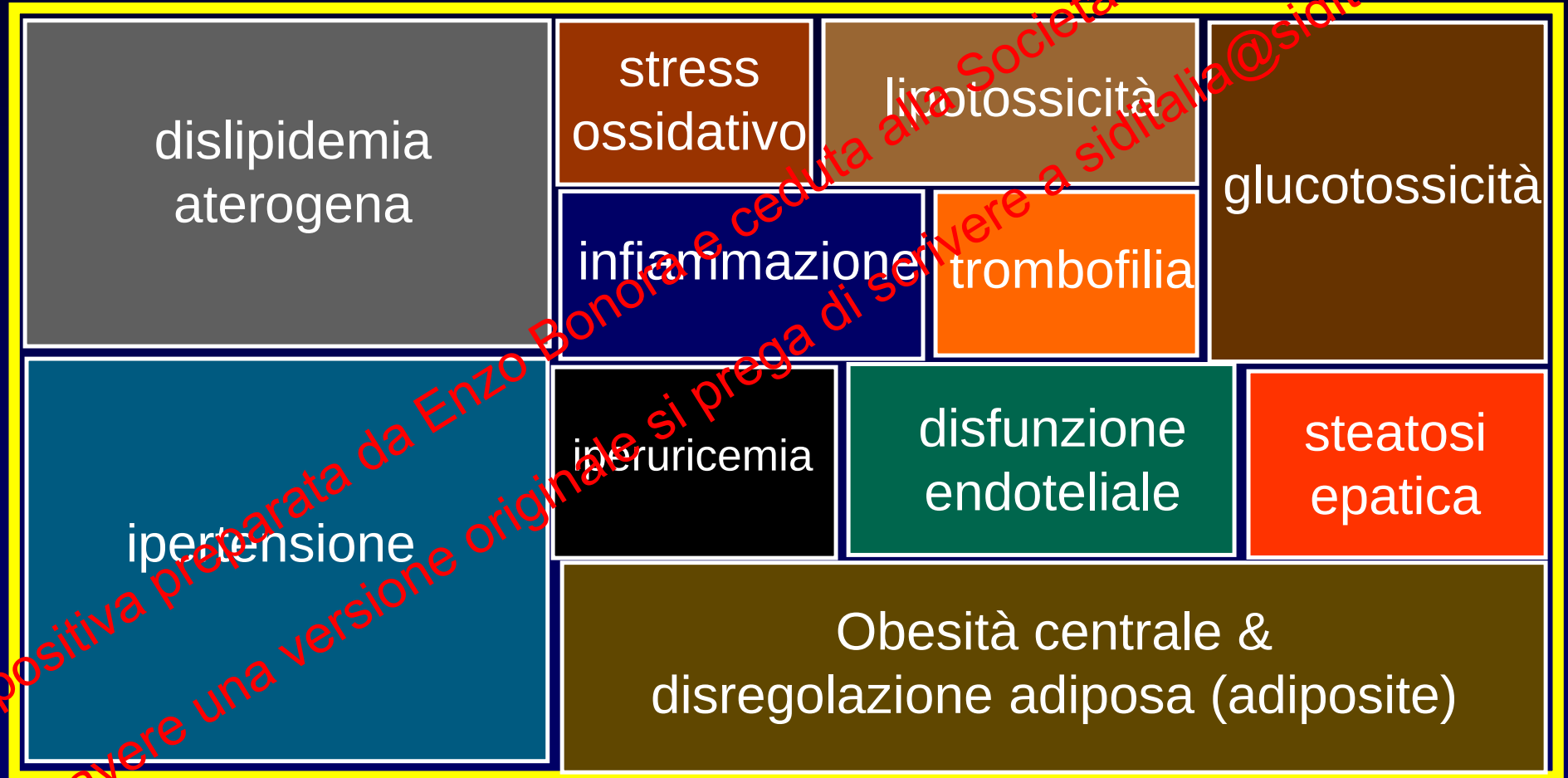


Prevalence of micro- and/or macrovascular complications at time of diagnosis of T2DM

(Verona Newly Diagnosed Diabetes Study; unpublished)

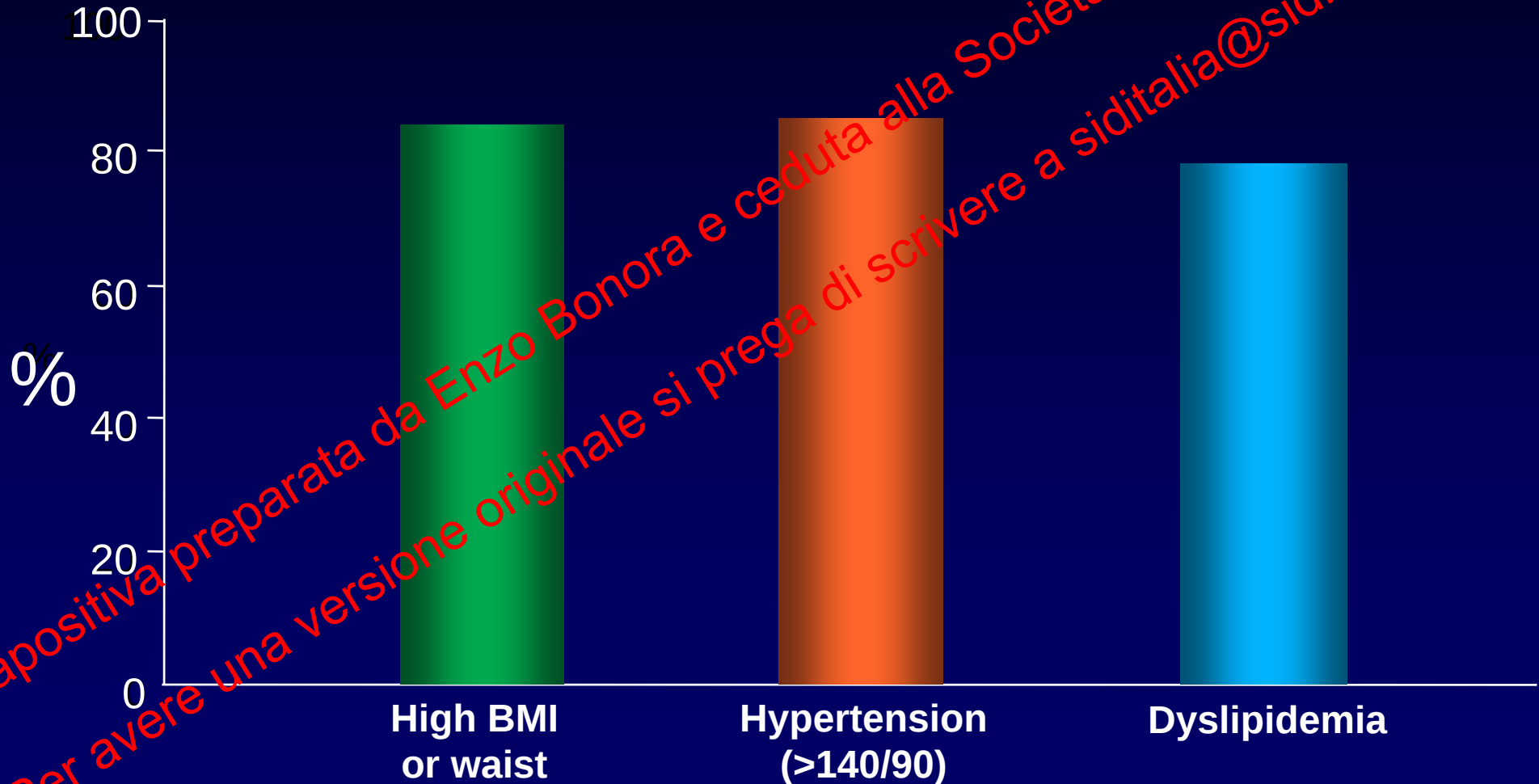


Diabete: un mosaico di alterazioni ancillari che contribuiscono alle complicanze e all'outcome



Prevalence of “Non-Glycemic” Cardiovascular Risk Factors in Subjects with T2DM

(Verona Diabetes Complications Study; Bonora et al, Diabet Med 21: 52, 2004)



Metabolic Syndrome predicts CVD in T2DM

(Verona Diabetes Complications Study; Bonora et al, Diabetic Med 21: 52, 2004)

	OR	C.I.
Age (per year)	1.05	1.03-1.07
Smoking (yes vs no)	1.63	1.01-2.64
HbA1c (per unit)	1.18	1.03-1.36
Metabolic Syndrome (yes vs no)	4.89	1.16-20.7

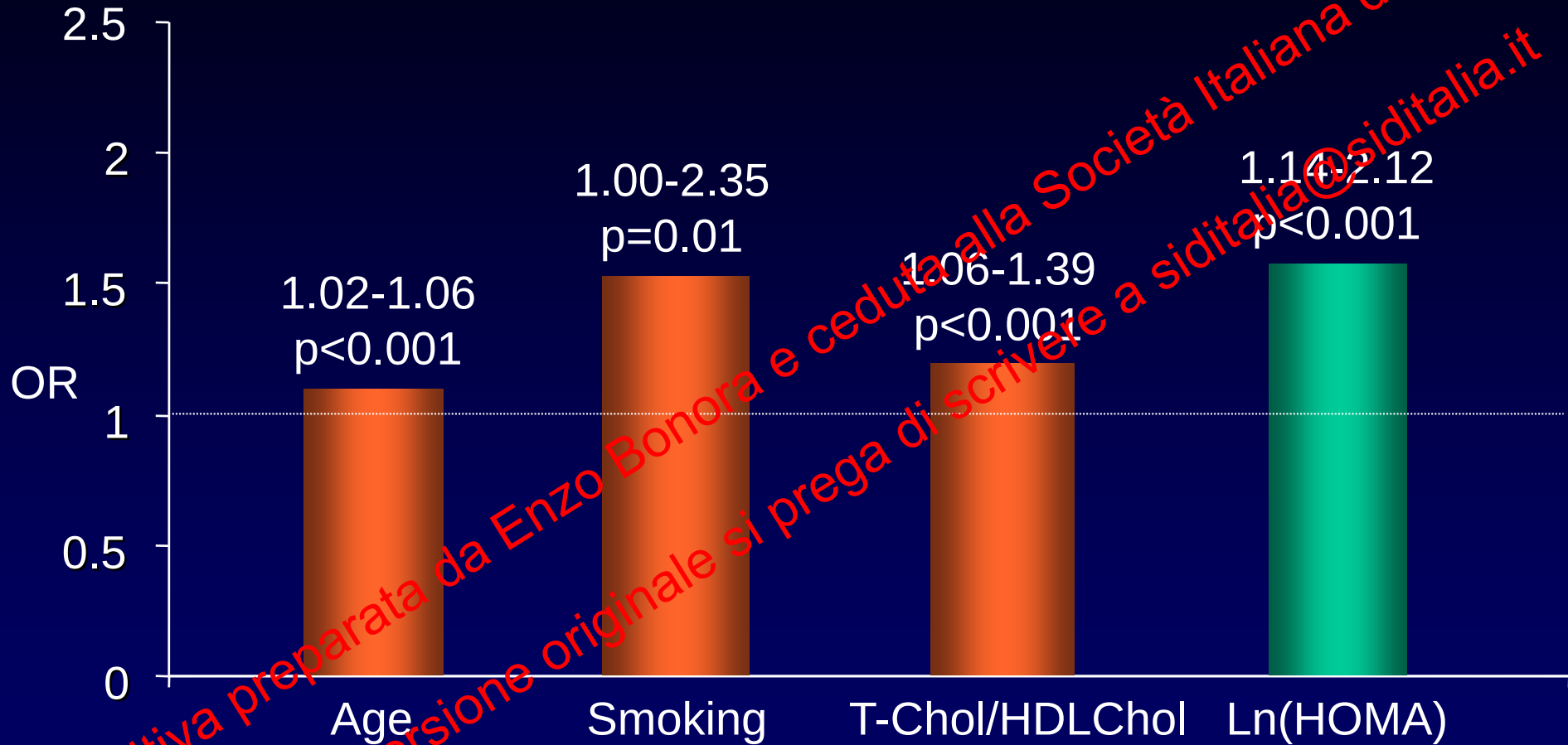
n= 559; age 65 yr; duration 9 yr; follow-up 4.5 yr

CVD= cardiovascular death, nonfatal MI or stroke, angina, TIA, asymptomatic CHD, carotid or peripheral atherosclerosis (echo-doppler)

Sex, duration, treatment and LDL concentration did not enter in the model

Insulin Resistance Predicts CVD in T2DM

(Verona Diabetes Complications Study; Bonora et al, Diabetes Care 25: 1235, 2002)

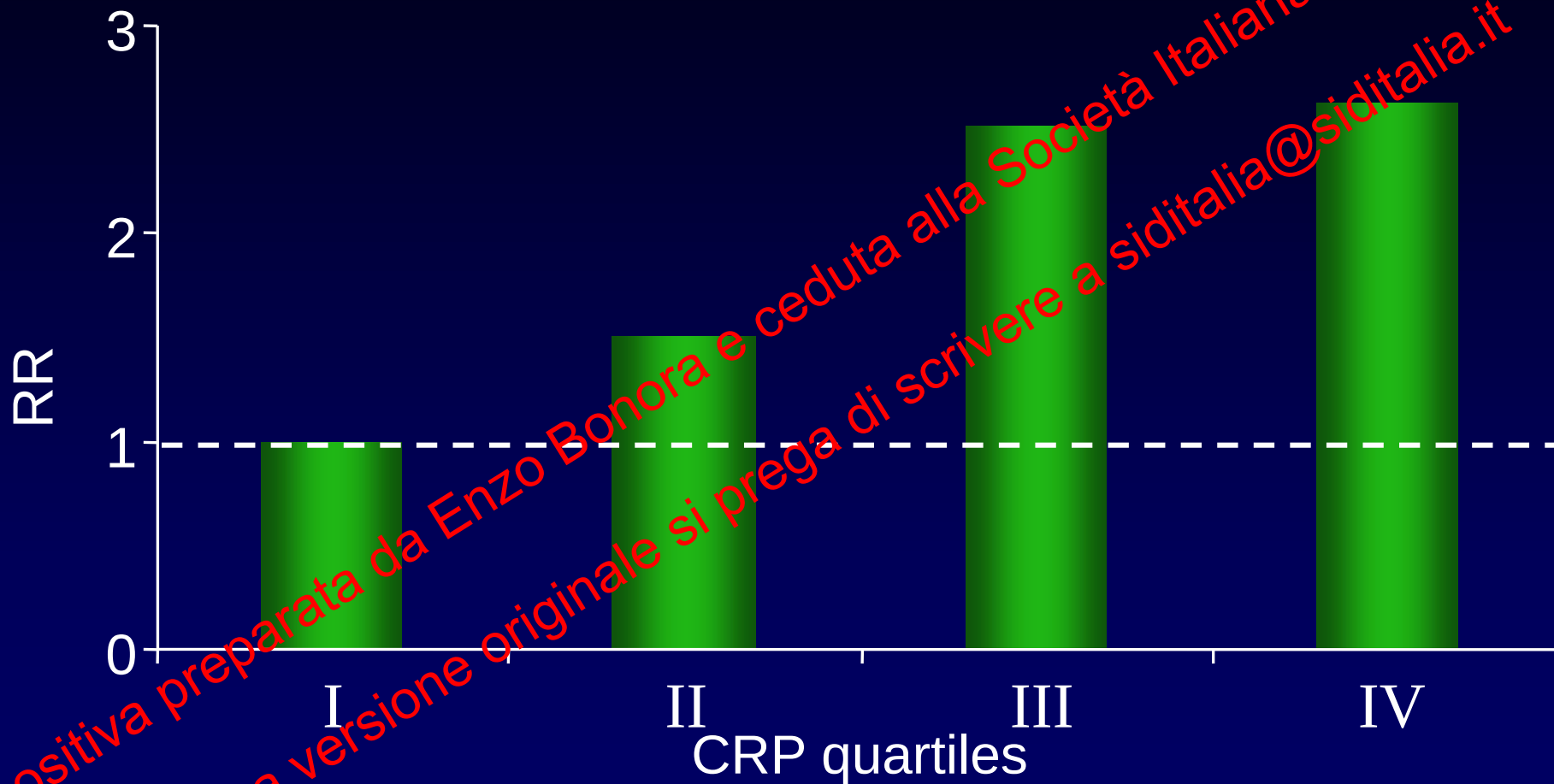


N=627, follow-up 4,5 yr. Model including also sex, duration, BMI, hypertension, HbA1c.

CVD= cardiovascular death, nonfatal MI or stroke, angina, TIA, asymptomatic CHD, carotid or peripheral atherosclerosis (echo-doppler)

CRP Predicts CVD in Men with T2DM

(Health Professional Study; Schulze et al, Diabetes Care 27: 889, 2004)

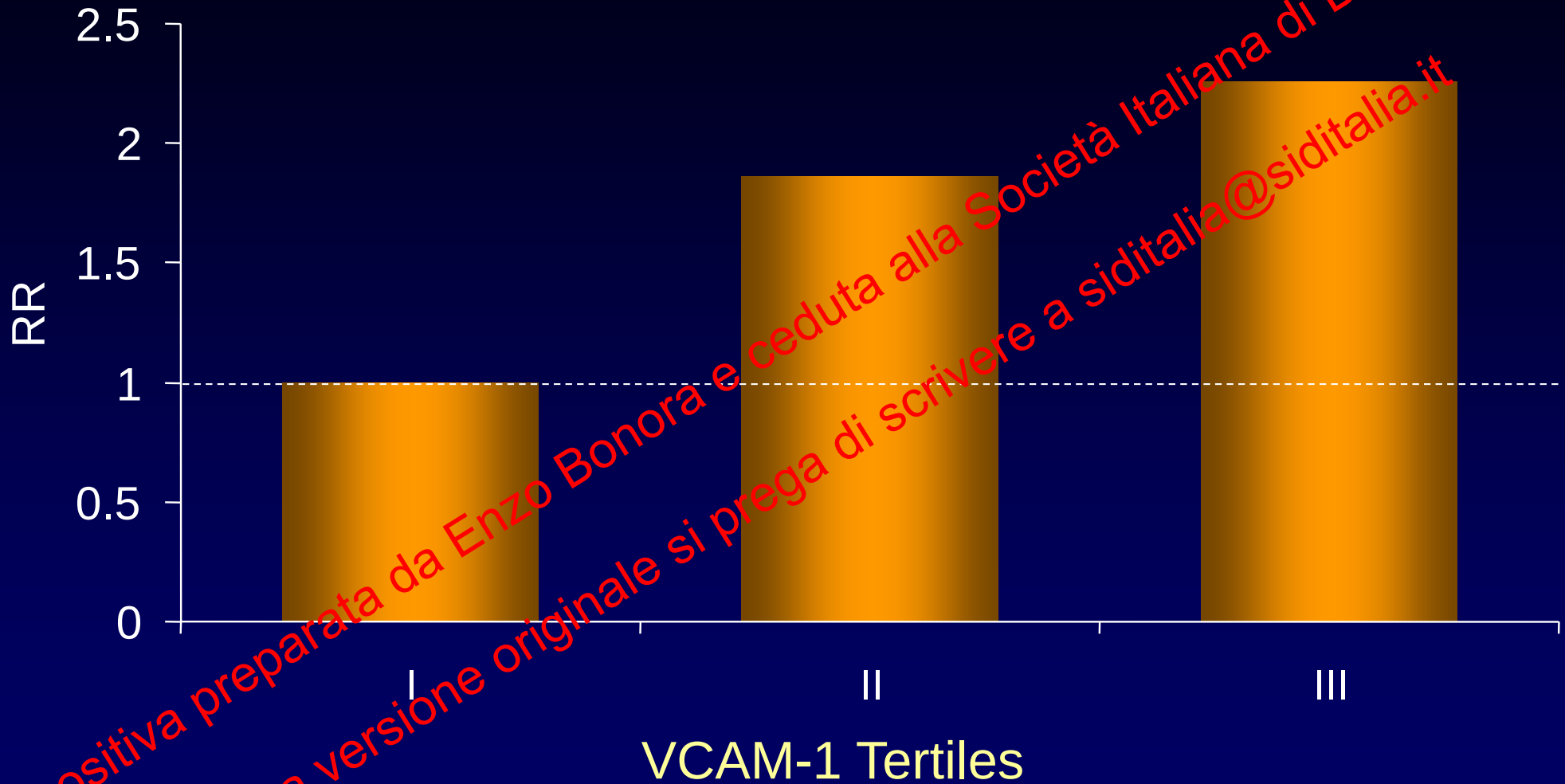


Data adjusted for age, life-style factors, hypertension, cholesterol, BMI

N=746; follow-up 5 years

VCAM-1 Predicts Mortality in T2DM

(Stehouwer et al; Diabetes 51:1157, 2002)

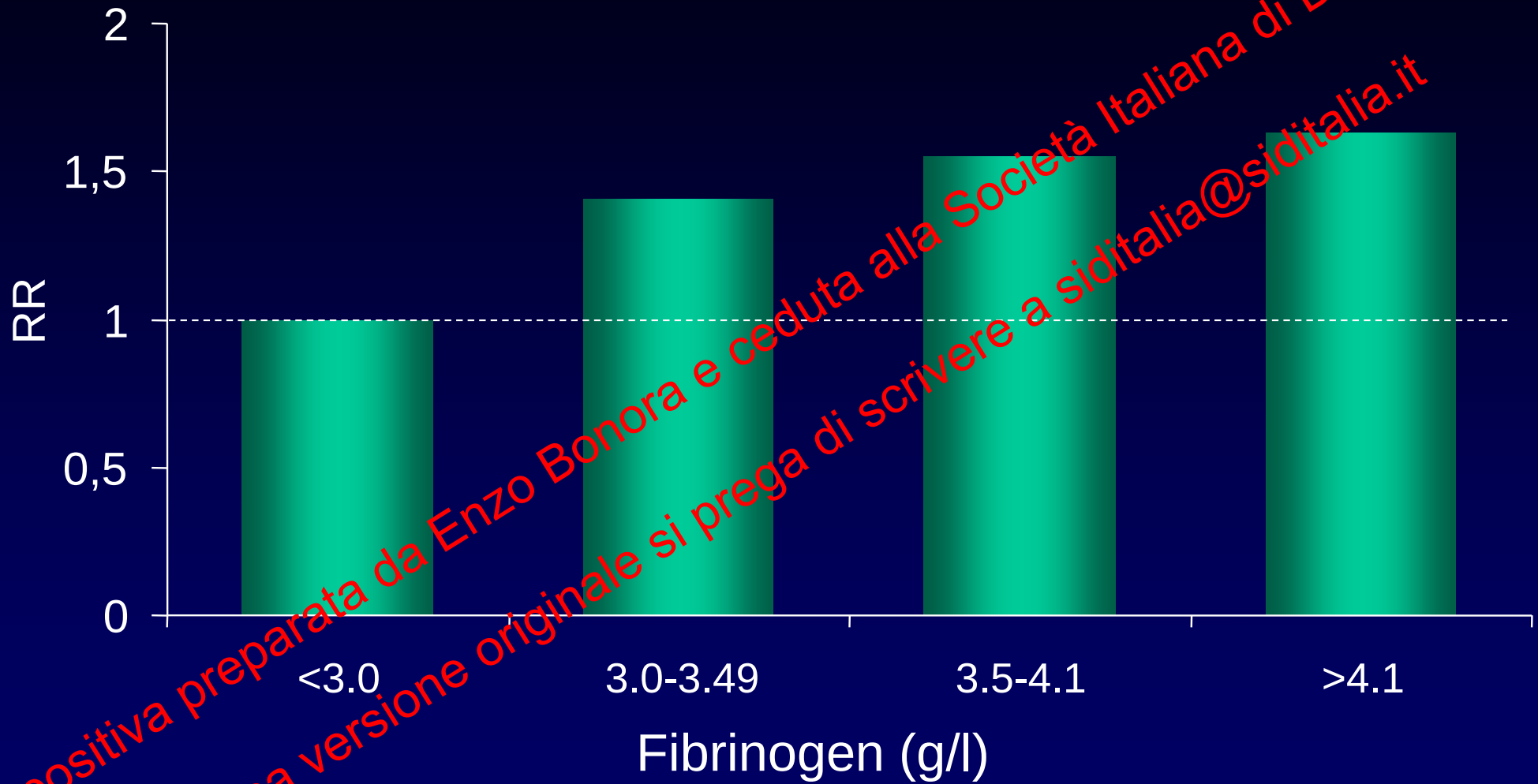


n=328; follow-up 9 years

Data adjusted for age, sex, duration, prior CVD, UAE, BMI, SBP, cholesterol, HbA1c

Fibrinogen Predicts CVD Mortality in T2DM

(Bruno et al; Diabetologia 48:427, 2005)



n=1565; follow-up 11 years

Adjusted for age, sex, HbA1c, LDL, HDL-C ratio, hypertension, smoking, baseline CHD

Serum Uric Acid Independently Predicts CVD Mortality in T2DM

(Zoppini et al; Diabetes Care 32: 1716-1720, 2009)

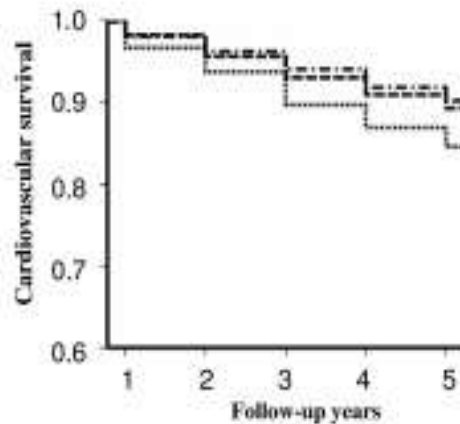


Figure 1—Kaplan-Meier curves of cardiovascular mortality in 2,726 type 2 diabetic patients stratified by sex-specific tertiles of serum uric acid levels. Statistical significance was estimated by the log-rank test ($P < 0.001$ for the third tertile vs. the other two tertiles).

Table 2—Predictors of cardiovascular mortality as assessed by multivariate Cox proportional hazards models

	Multivariate model 1	P	Multivariate model 2	P	Multivariate model 3	P
Serum uric acid ($\mu\text{mol/l}$)	1.21 (1.10–1.33)	<0.001	1.09 (1.02–1.38)	0.024	1.27 (1.01–1.61)	0.046
Age (years)	3.34 (2.95–4.38)	<0.001	2.76 (2.03–3.74)	<0.001	3.12 (2.11–4.62)	<0.001
Sex (male vs. female)	1.37 (0.91–1.87)	NS	1.38 (0.93–2.05)	NS	0.95 (0.57–1.58)	NS
Current smoking	1.30 (0.76–2.27)	NS	1.25 (0.69–2.23)	NS	1.18 (0.56–2.53)	NS
Diabetes duration	1.20 (1.01–1.44)	0.050	1.17 (0.97–1.42)	NS	1.26 (0.98–1.61)	NS
BMI (kg/m^2)	0.96 (0.77–1.20)	NS	0.96 (0.76–1.20)	NS	0.87 (0.65–1.15)	NS
A1C (%)	1.10 (0.90–1.35)	NS	1.01 (0.82–1.25)	NS	1.02 (0.78–1.35)	NS
Hypertension (mmHg)	0.99 (0.49–1.70)	NS	0.83 (0.41–1.69)	NS	0.64 (0.24–1.65)	NS
Atherogenic dyslipidemia	0.77 (0.53–1.16)	NS	0.69 (0.51–1.12)	NS	0.73 (0.45–1.19)	NS
LDL cholesterol (mmol/l)	1.17 (0.99–1.39)	NS	1.12 (0.94–1.34)	NS	1.16 (0.93–1.46)	NS
Oral hypoglycemic drugs	0.69 (0.36–1.35)	NS	0.93 (0.43–1.99)	NS	0.69 (0.26–1.81)	NS
Insulin therapy	1.28 (0.63–2.60)	NS	1.39 (0.62–3.15)	NS	1.00 (0.39–2.63)	NS
Antidiabetic agents	1.07 (0.74–1.55)	NS	1.11 (0.76–1.65)	NS	1.46 (0.89–2.39)	NS
Allopurinol therapy	1.24 (0.71–2.16)	NS	1.10 (0.62–1.95)	NS	1.12 (0.57–2.22)	NS
eGFR			0.56 (0.44–0.72)	<0.001	0.72 (0.53–0.96)	0.040
Microalbuminuria					1.55 (0.89–2.72)	NS
Macroalbuminuria					3.01 (1.55–5.81)	0.001

Data are HRs (95% CI). Cohort size, $n = 2,726$. The HRs for continuous variables were computed for 1-SD change. Atherogenic dyslipidemia was defined as triglycerides ≥ 1.7 mmol/l and/or low HDL cholesterol <1.04 mmol/l or on treatment. Hypertension was defined as blood pressure $\geq 140/90$ mmHg or receiving treatment.

$n = 2,726$; mean follow-up: 4.7 years

Ultrasonography-Diagnosed NAFLD is an Independent Predictor of CVD in T2DM

Targher G et al – *Diabetes* 2005; 12: 3541-3546

Variable	Model 1	Model 2	Model 3
Age (per 10 yr)	1.13 (1.07-1.14)	1.13 (1.07-1.14)	1.12 (1.06-1.14)
Sex (M vs F)	1.48 (1.1-2.0)	1.46 (1.2-1.9)	1.46 (1.2-1.9)
Smoking (yes vs. no)	1.42 (1.1-2.0)	1.40 (1.1-1.9)	1.40 (1.1-1.9)
NAFLD (yes vs. no)	1.91 (1.4-2.2)	1.84 (1.4-2.1)	1.53 (1.1-1.7)

N=744, follow-up 5 yrs

Model 1: age and sex

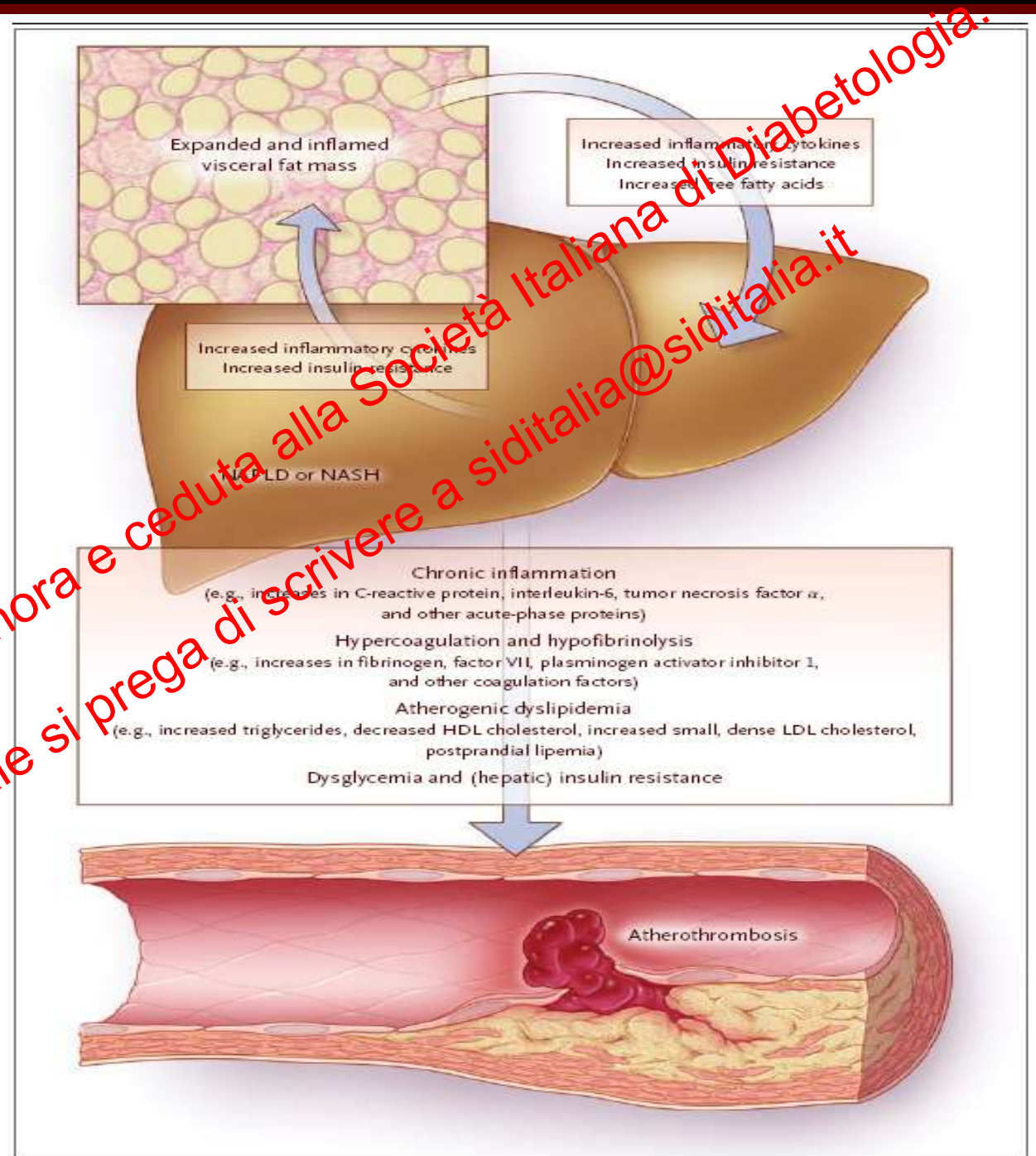
Model 2: + smoking history, diabetes duration, HbA1C, LDL cholesterol, GGT levels, and use of medications (i.e., hypoglycemic, antihypertensive, lipid-lowering, or antiplatelet drugs)

Model 3: + metabolic syndrome

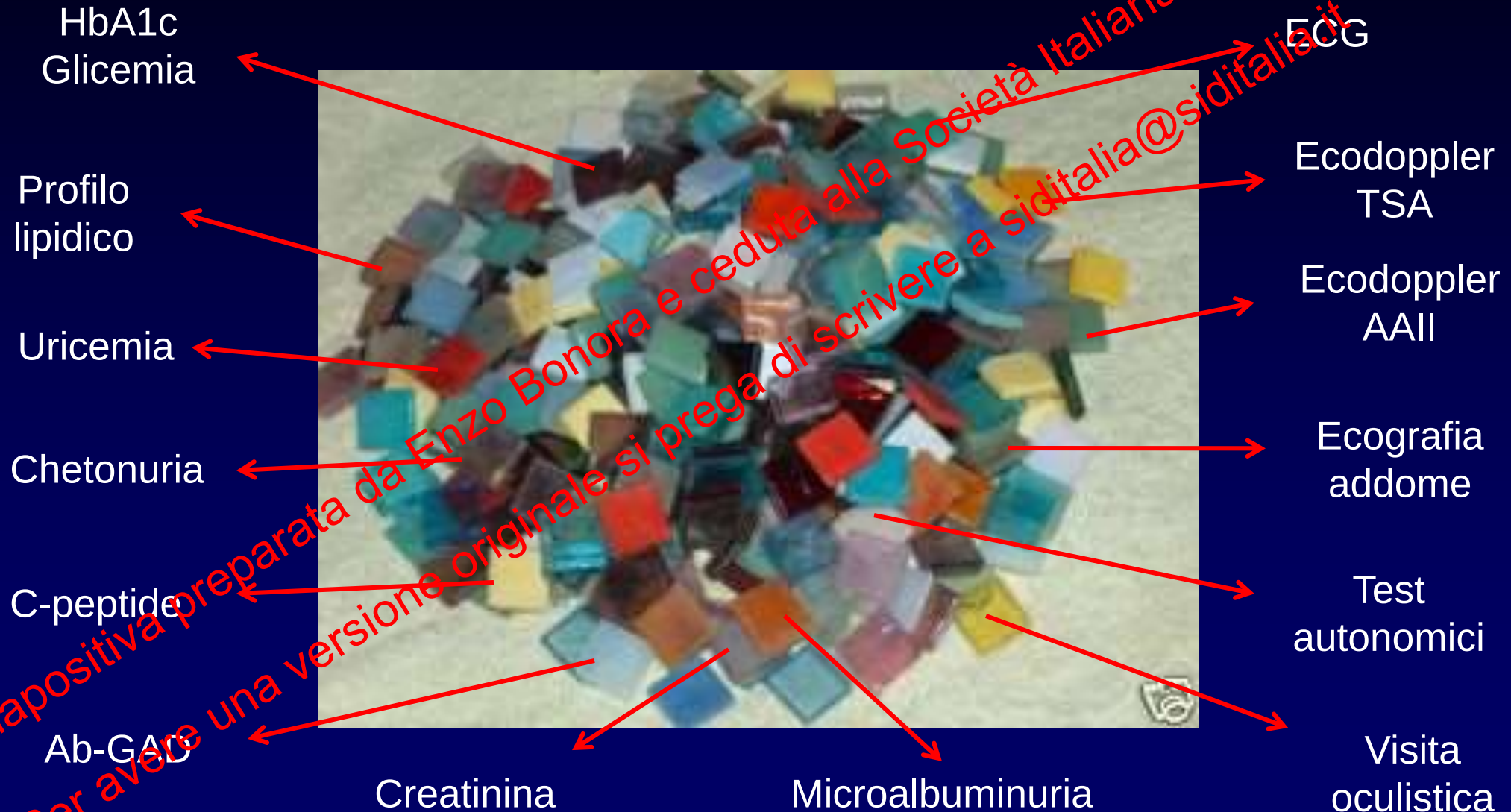
Liver steatosis is an independent risk factor of CVD

Targher G, Day C, Bonora E
New Engl J Med 2010;
363:1341-1350

Chronic inflammation
Thrombophilia
Atherogenic Dyslipidemia
Dysglycemia
Insulin Resistance



Diabete: le tessere del mosaico dei parametri di laboratorio, esami strumentali e visite di consulenza



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Diabete: un mosaico di parametri glicemici da correggere

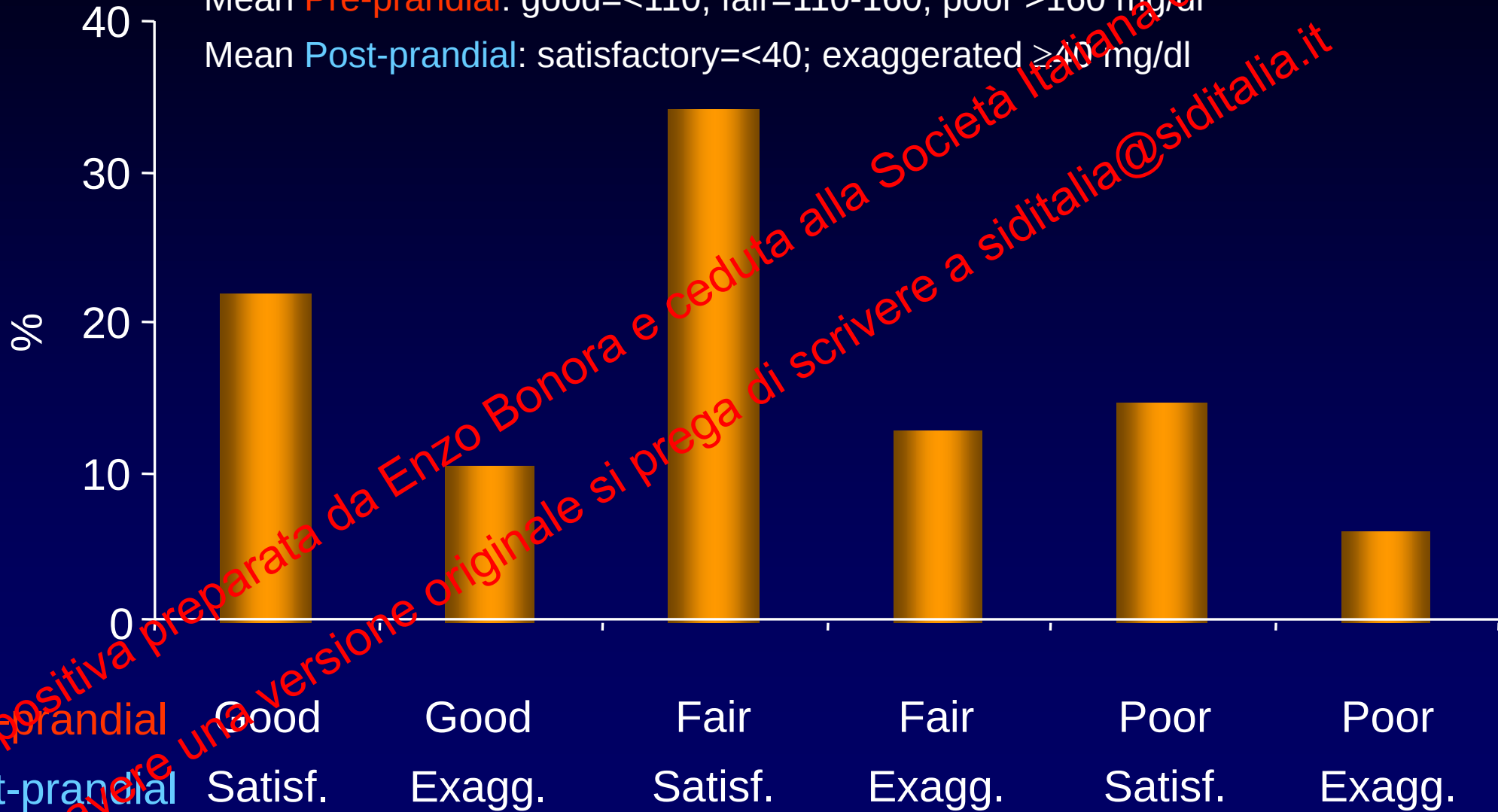


Glycemic Phenotypes in Treated T2DM

(Bonora et al, Diabetologia 49:846, 2006; n=3284)

Mean **Pre-prandial**: good= ≤ 110 ; fair=110-160; poor > 160 mg/dl

Mean **Post-prandial**: satisfactory= ≤ 40 ; exaggerated ≥ 40 mg/dl



Post-Prandial Glucose and CVD in T2DM

(Cavalot et al; JCEM 91: 813, 2006)

Independent
predictors

Fasting glucose

no

HbA1c

no

Post-prandial glucose

yes

HRs PPG T3 vs. T1-2

men 2.19

women 5.69

After adjusting for FBG
and other confounders

HRs PPG T3 vs. T1-2

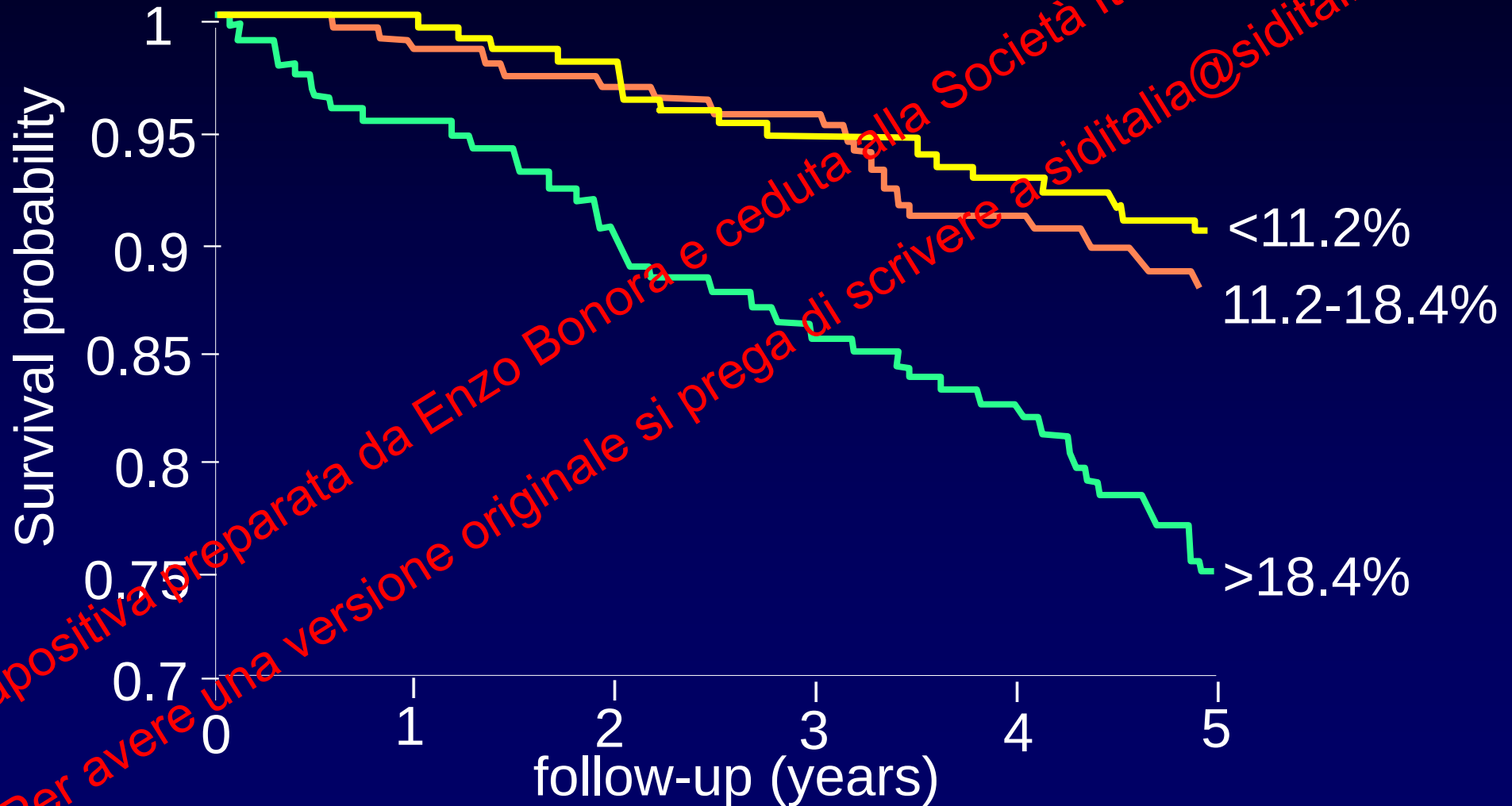
men 2.13

women 8.39

After adjusting for HbA1c
and other confounders

Cardiovascular Mortality in Elderly Patients with Type 2 Diabetes Stratified According to Variability of Fasting Plasma Glucose (CV-FPG)

(Verona Diabetes Study; Muggeo et al, Circulation 1997)



VADT - Predictors of CVD Death

(Duckworth et al – NEJM 2009; 360: 129-139)

Variable	Hazard Ratio	P Value
Prior CVD event	3.116	0.0001
Age (per 10 yr)	2.090	<.0001
HDL (per 10 mg)	0.699	0.0079
Baseline HbA1c (per 1%)	1.213	0.0150
Severe Hypoglycemia	4.042	0.0076

Diabete: un mosaico di fenotipi clinici fra cui districarsi



A New Paradigm in Diabetes Care: Customized HbA1c Targets

- **“Recruit” patient** (newly diagnosed T2DM, middle age, no prior CVD, any HbA1c)
HbA1c Target = $<6.5\%$; “no mercy”
- **“Veteran” patient** (long standing T2DM, older age, no prior CVD, previously fairly controlled diabetes)
HbA1c target = $6.5-7.5\%$; “smooth decline”
- **“Injured Veteran” patient** (long standing T2DM, prior CVD, severely uncontrolled diabetes; “hyperglycemia addicts” who need progressive adaptation to lower glucose levels?)
HbA1c target = $7.5-8.5\%$; “handle with care”



Diabete: un mosaico di farmaci

Anti-diabetici

Metformina

Anti-ipertensivi

ACE-inibitori

Più sono i farmaci fra cui scegliere,
più facile è sbagliare e
più serve competenza ed esperienza
cioè....

più serve il **Diabetologo!**

Statine

Fibrati

Ezetimibe

Acido nicotinico

Allopurinolo

Gabapentin

Pregabalin

ecc. ecc. ecc.

Anti-diabetici a confronto: benefici ancillari

	MET	SU	REP	PIO	DPP-4	Acarb	GLP-1
BMI	↓	↑	↑	↑ ↑	=	=	↓↓
TG	(↓)	=	=	↓	=	=	↓
HDL	(↑)	=	=	↑	=	=	↑
BP	(↓)	=	=	↓	=	=	↓
U-Alb	-	=	=	↓	=	=	=
CPR	↓	=	=	↓	=	=	↓
PAI-1	↓	=	=	↓	=	=	↓
ATS	=	=	=	↓	=	=	=
CVD	↓ ↓	↑	↑	↓ ↓	↓ (?)	↓	↓ (?)

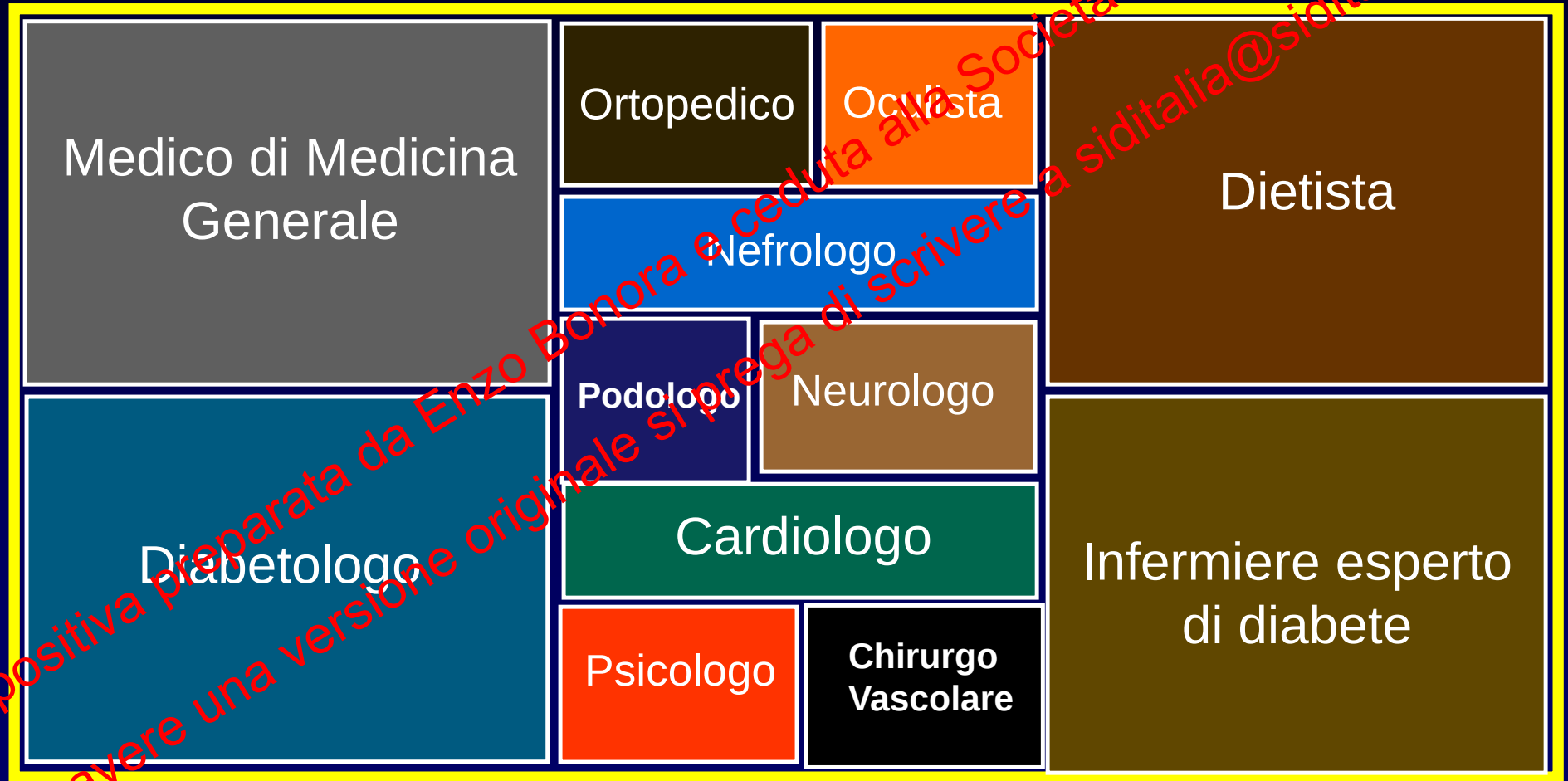
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Anti-diabetici a confronto: aspetti clinici

	MET	SU	REP	PIO	DPP-4	Acarb	GLP-1
Ipoglicemia		+	+				
Vomito							++
Diarrea	(+)					+++	+
Fratture				+			
Edema				+			
Iniezioni							+
N. sommin.	+	+	++			+++	(+)
Titolazione	++	+	+			+++	(+)
SMBG		+	+				
Interazioni		+++	+	+			

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Diabete: un mosaico di professionisti che condividono la cura



Diabete: un mosaico di centri diabetologici

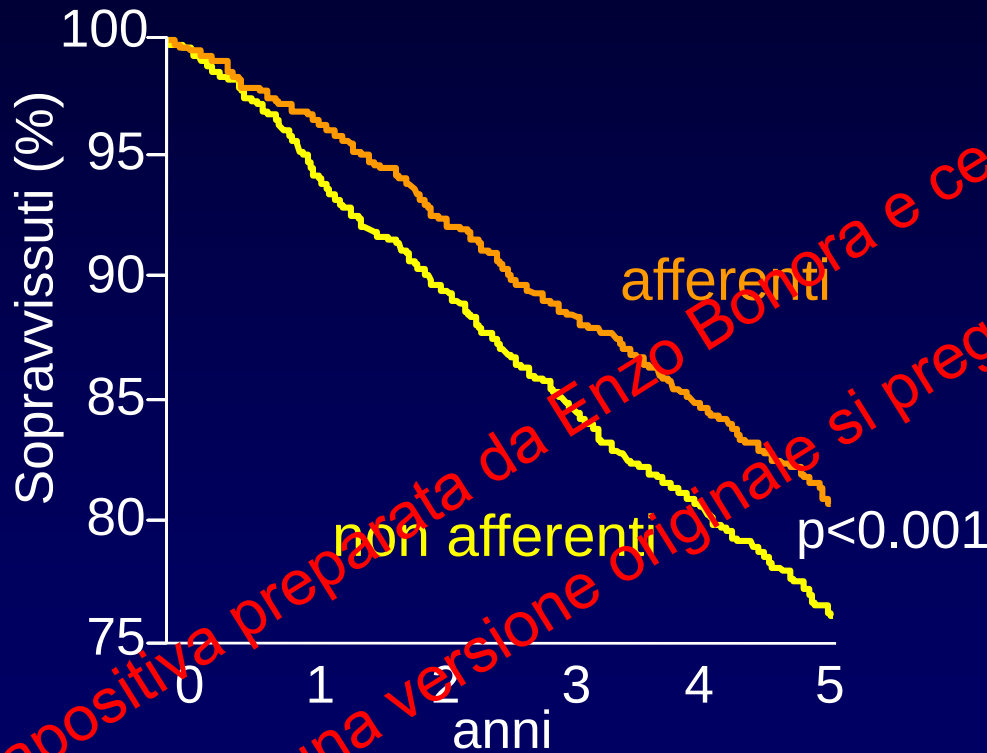


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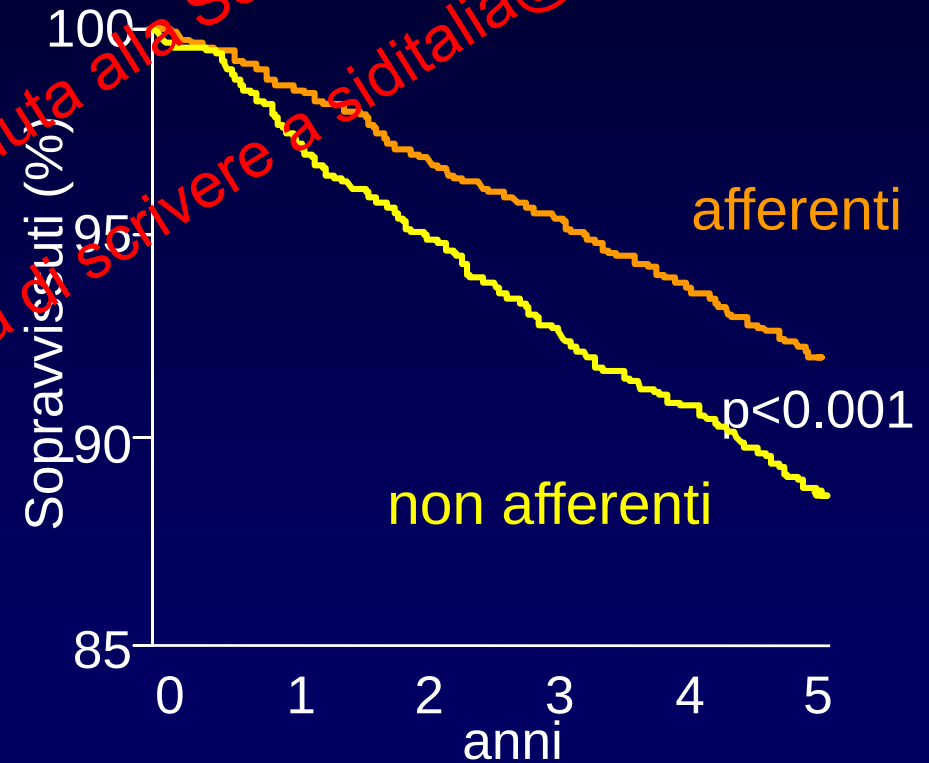
Sopravvivenza dei diabetici assistiti presso il centro di diabetologia rispetto ai non afferenti

(Verona Diabetes Study – Verlato G et al; Diabetes Care 19:211, 1996)

Mortalità per tutte le cause



Mortalità cardiovascolare



n=7,488; follow-up= 5 anni

Diabete: un mosaico di spese per la cura

Spesa media annua pro-capite circa € 2.750 (>75% complicanze)



**Ricoveri
Ospedalieri
(57%)**

**Altri farmaci
(23%)**

**Esami di laboratorio e
strumentali
e visite mediche e
specialistiche
(14%)**

**Anti-
diabetici
(6%)**

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Le tre emergenza sanitarie del mondo secondo l'Organizzazione Mondiale della Sanità

- Tubercolosi
- Malaria
- Diabete mellito



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Risoluzione dell'ONU n. 61/225 del 20 Dicembre 2006

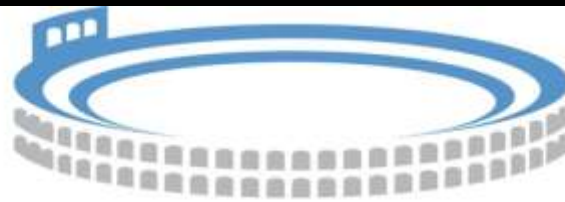
(omissis) aumentare la consapevolezza pubblica sul diabete e le relative complicanze, promuovere la sua prevenzione e terapia, anche mediante l'educazione e i mass media



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Diabete: un mosaico di collaborazioni per fronteggiare l'emergenza





PROGETTO VERONADIABETE
INFORMAZIONE • PREVENZIONE • CURA

Sito web

**Giornalino
quadrimestrale**

**Opuscoli
e altro materiale
divulgativo**

**Conferenze
ai
cittadini**

Manifesti

**Misurazioni
glicemiche in piazza**

**Interventi
TV e radio locali**

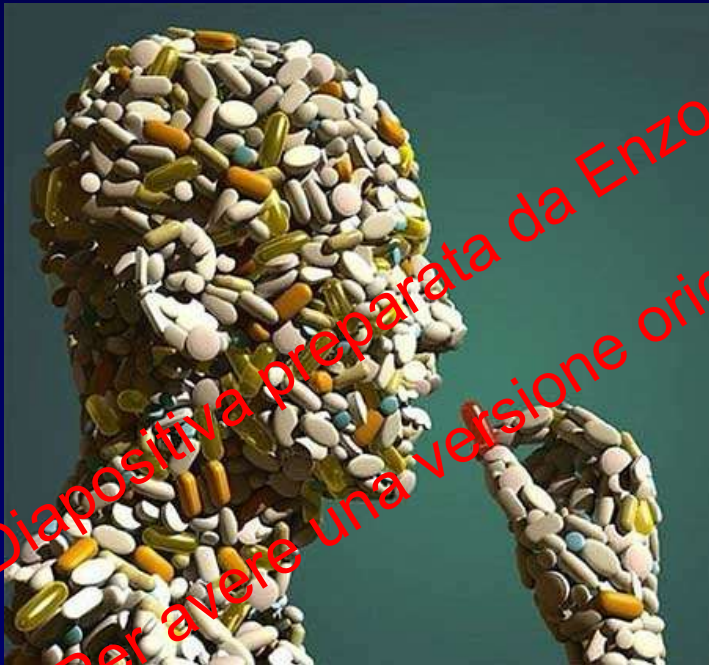
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Diabete: un mosaico di atti richiesti al paziente (partecipazione alla cura)



Lifelong Adherence Requested to Diabetic Patients

During his/her life up to 100,000 times a person with diabetes has to adhere to prescriptions, recommendations, suggestions made by a doctor, a nurse, a dietician !!!



Diapositiva preparata da Enzo Bonora e ceduta alla Societa Italiana di Diabetologia.
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Diabete: un mosaico coi pezzi al posto giusto...

.... come un puzzle in cui i vari pezzi combaciano perfettamente

...

....e non un (in)cubo di Rubik



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Fine e grazie



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