



WORLD DIABETES CONGRESS DUBAI
4-8 DECEMBER 2011

HbA1c, SMBG or both?

Enzo Bonora

Endocrinology, Diabetes and Metabolic Diseases
University and University Hospital of Verona
Verona, Italy



Key messages of the talk

- Glycemic targets are not limited to HbA1c because the latter does not describe fasting, pre-prandial, post-prandial plasma glucose and neither plasma glucose excursions with meals, i.e. the glycemic phenotype, which should be the guide for treatment decisions
- HbA1c does not unveil post-prandial peaks, hypoglycemia and glucose variability, which have been associated to a poorer outcome
- HbA1c is not always reliable due to high/low Hb susceptibility to glycation, certain clinical conditions or analytical problems
- SMBG provides information on daily glycemic profile and help to reach and maintain a better glycemic control
- SMBG seems to be associated to a better outcome

Key messages of the talk

- Glycemic targets are not limited to HbA1c because the latter does not describe fasting, pre-prandial, post-prandial plasma glucose and neither plasma glucose excursions with meals, i.e. the glycemic phenotype, which should be the guide for treatment decisions
- HbA1c does not unveil post-prandial peaks, hypoglycemia and glucose variability, which have been associated to a poorer outcome
- HbA1c is not always reliable due to high/low Hb susceptibility to glycation, certain clinical conditions or analytical problems
- SMBG provides information on daily glycemic profile and help to reach and maintain a better glycemic control
- SMBG seems to be associated to a better outcome

Question: Would you recommend SMBG or would you be satisfied with just HbA1c in the case of Mr. John?

- Man
- Age 61 yr
- Diagnosed at 59 yr
- No prior CVD or other major medical problems
- BMI 32.9
- HbA1c 7.4%
- Taking metformin 1000 mg at breakfast and dinner and Pioglitazone 30 mg at lunch

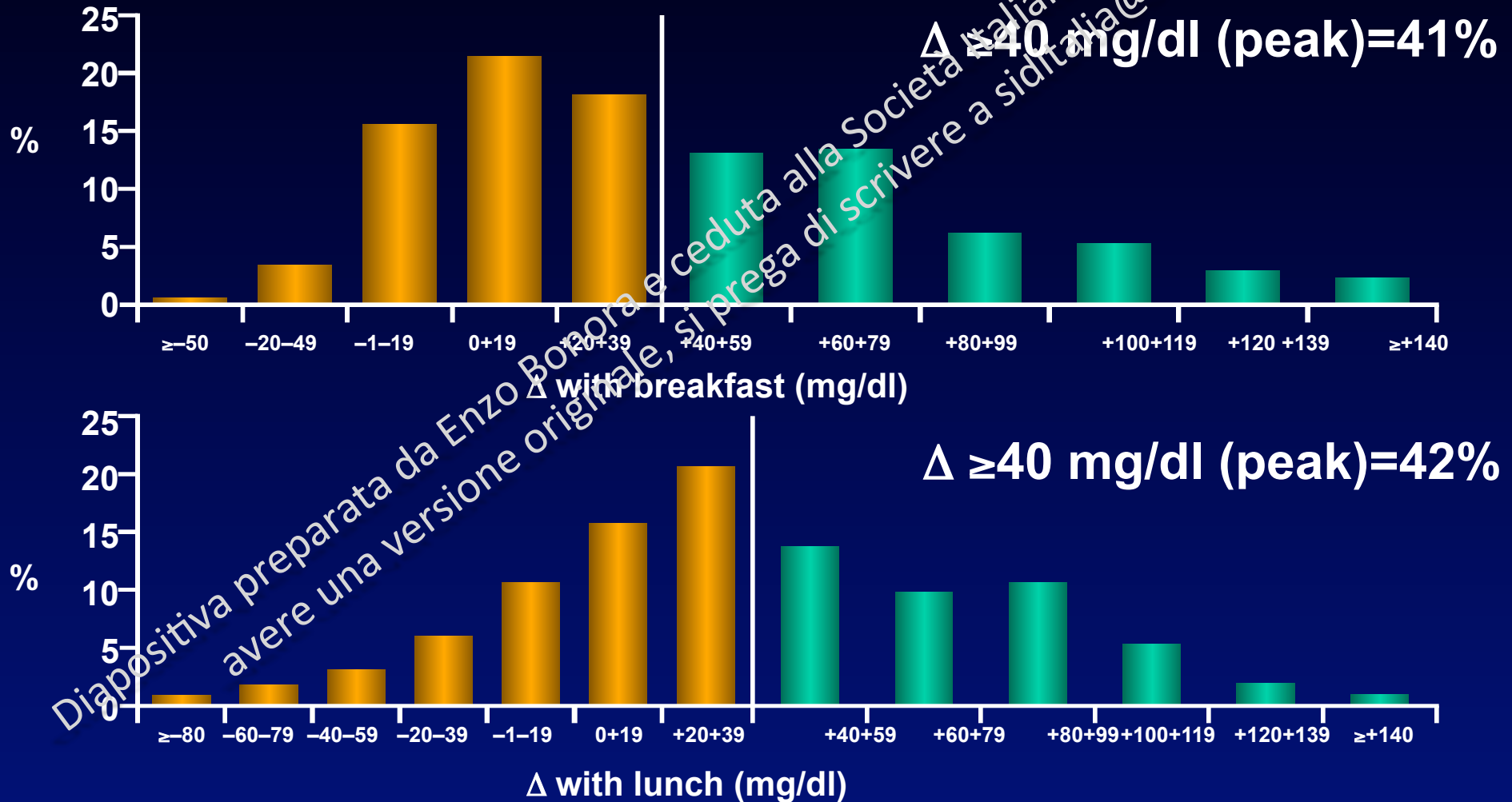
Glycemic phenotype in T2DM: fair control, very good pre-prandial, post-prandial peaks

John, man, age 61, HbA1c 7.4%

		Time of the day					
		7	9	13	15	20	22
Day of the month	1	95	210	90	192	106	194
	2	103	242	116	166	108	171
	3	93	188	99	145	91	229
	4	116	194	108	278	74	193
	5	104	189	101	169	84	164
	6	108	241	107	266	91	229

Frequency distribution of change in plasma glucose (lab assessment) following breakfast and lunch in 371 non-insulin-treated outpatients with T2DM

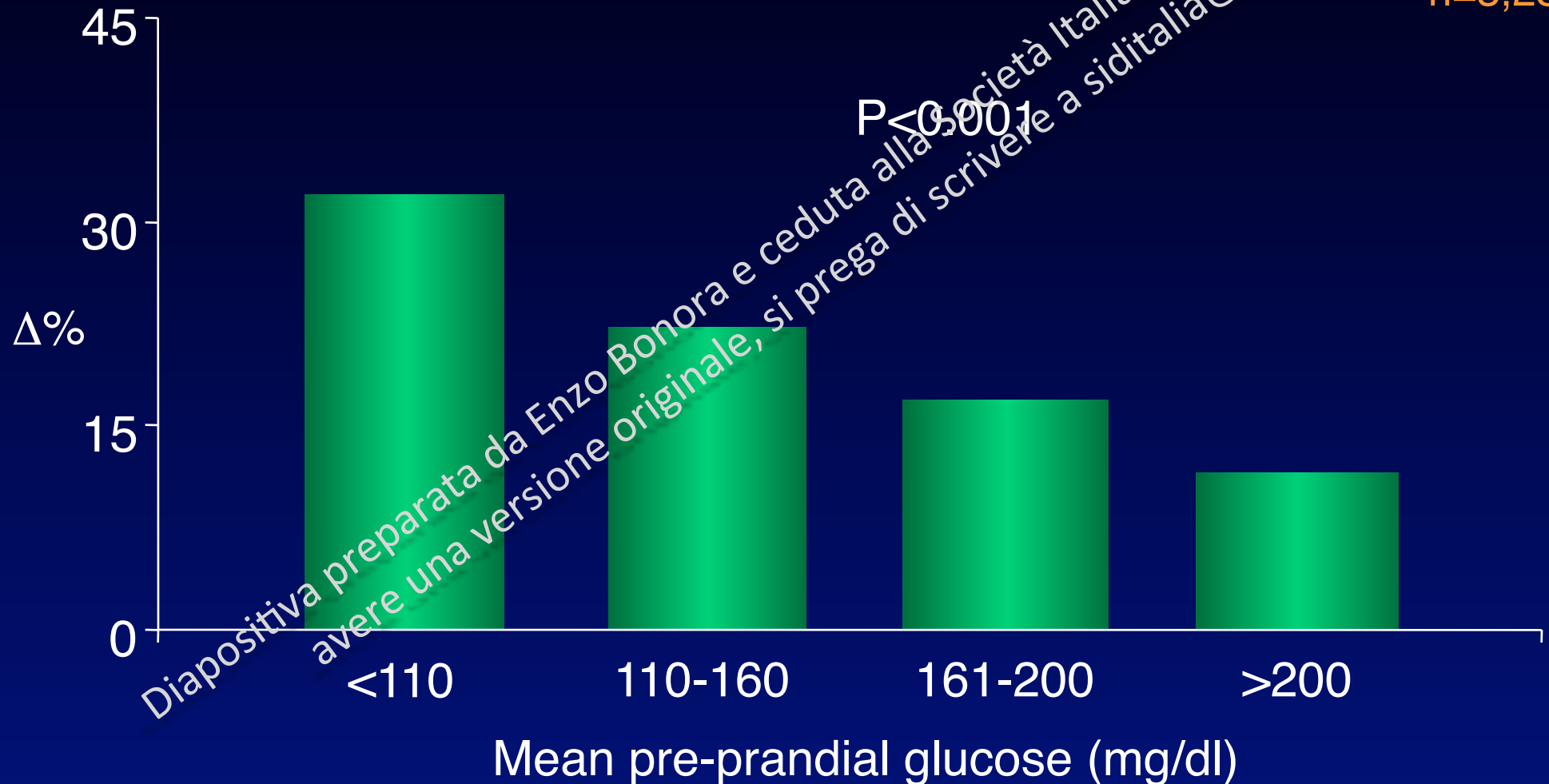
(Bonora et al - Diabetes Care 24: 2023, 2001)



Mean percentage glucose excursion after meals according to mean pre-prandial glucose levels

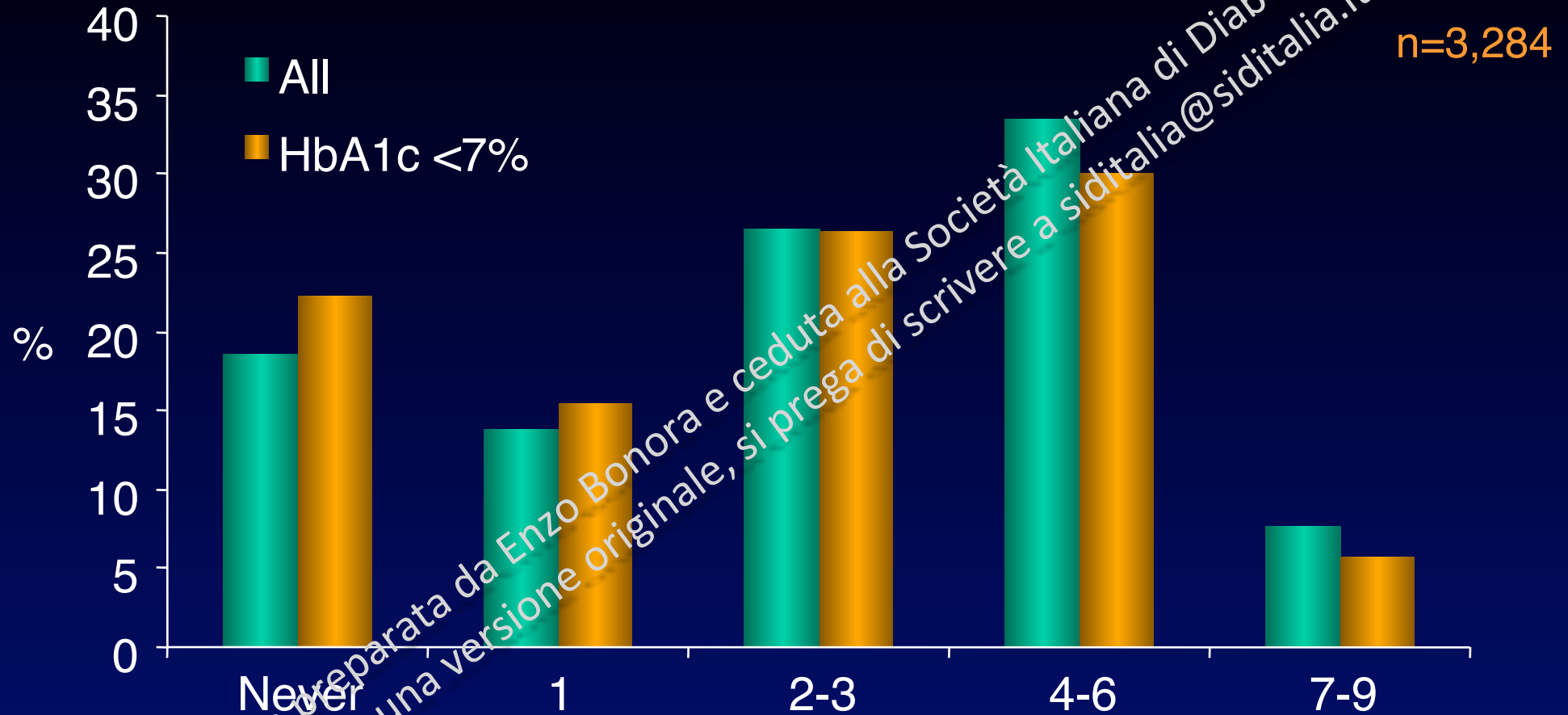
(Bonora et al - Diabetologia 49: 846, 2006)

n=3,284



Frequency of postprandial peaks in T2DM

(Bonora et al - Diabetologia 49:846, 2006)



Six home blood glucose readings per day for 3 days (before and 2 h after the three meals). Nine meals monitored. Peak=increase with meal >40 mg/dl.

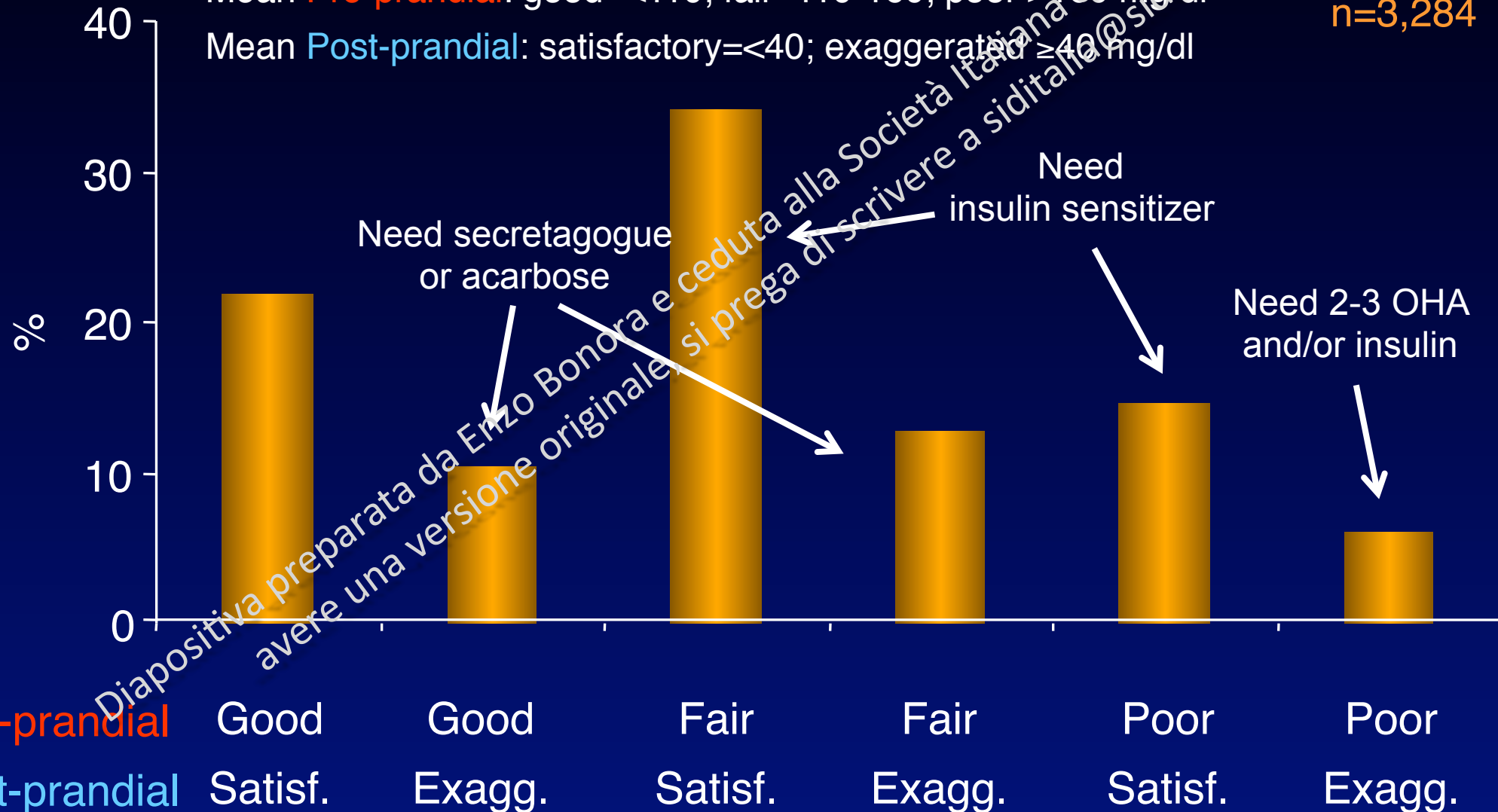
Glycemic phenotypes to guide treatment

(Bonora et al - Diabetologia 49: 846, 2006)

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

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

n=3,284



Key messages of the talk

- Glycemic targets are not limited to HbA1c because the latter does not describe fasting, pre-prandial, post-prandial plasma glucose and neither plasma glucose excursions with meals, i.e. the glycemic phenotype, which should be the guide for treatment decisions
- HbA1c does not unveil post-prandial peaks, hypoglycemia and glucose variability, which have been associated to a poorer outcome
- HbA1c is not always reliable due to high/low Hb susceptibility to glycation, certain clinical conditions or analytical problems
- SMBG provides information on daily glycemic profile and help to reach and maintain a better glycemic control
- SMBG seems to be associated to a better outcome

Post-prandial glucose and CVD in T2DM

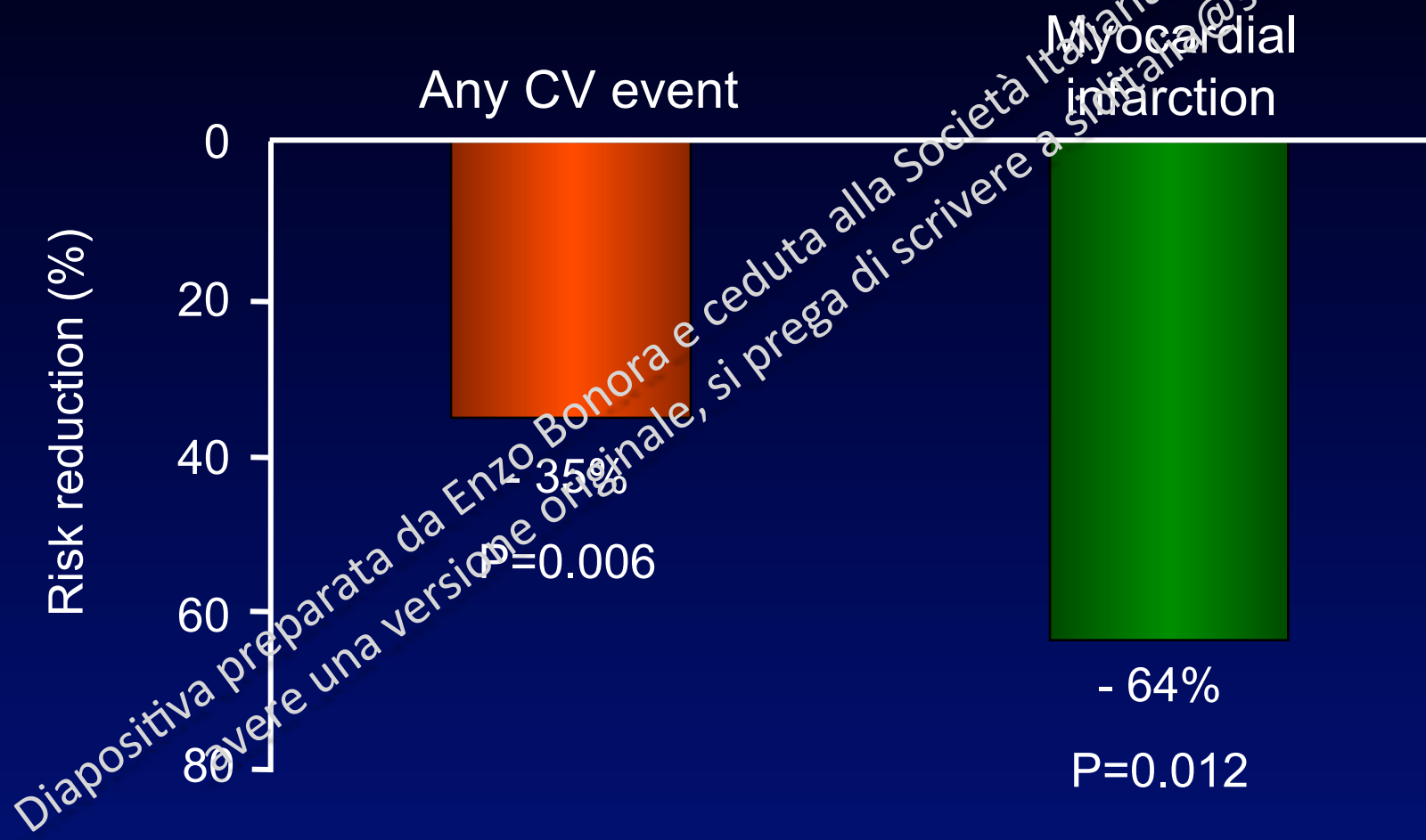
(Cavalot et al - Diabetes Care 34: 2237, 2011)

	HR	95% CI	P value
HbA1c >7%	1.732	1.187-2.526	0.004
Post-lunch glucose >180 mg/dl	1.452	1.057-1.994	0.021

N=505; age 62 yr, duration 9 yr, follow-up 14 yr; multivariate model including many potential confounding factors

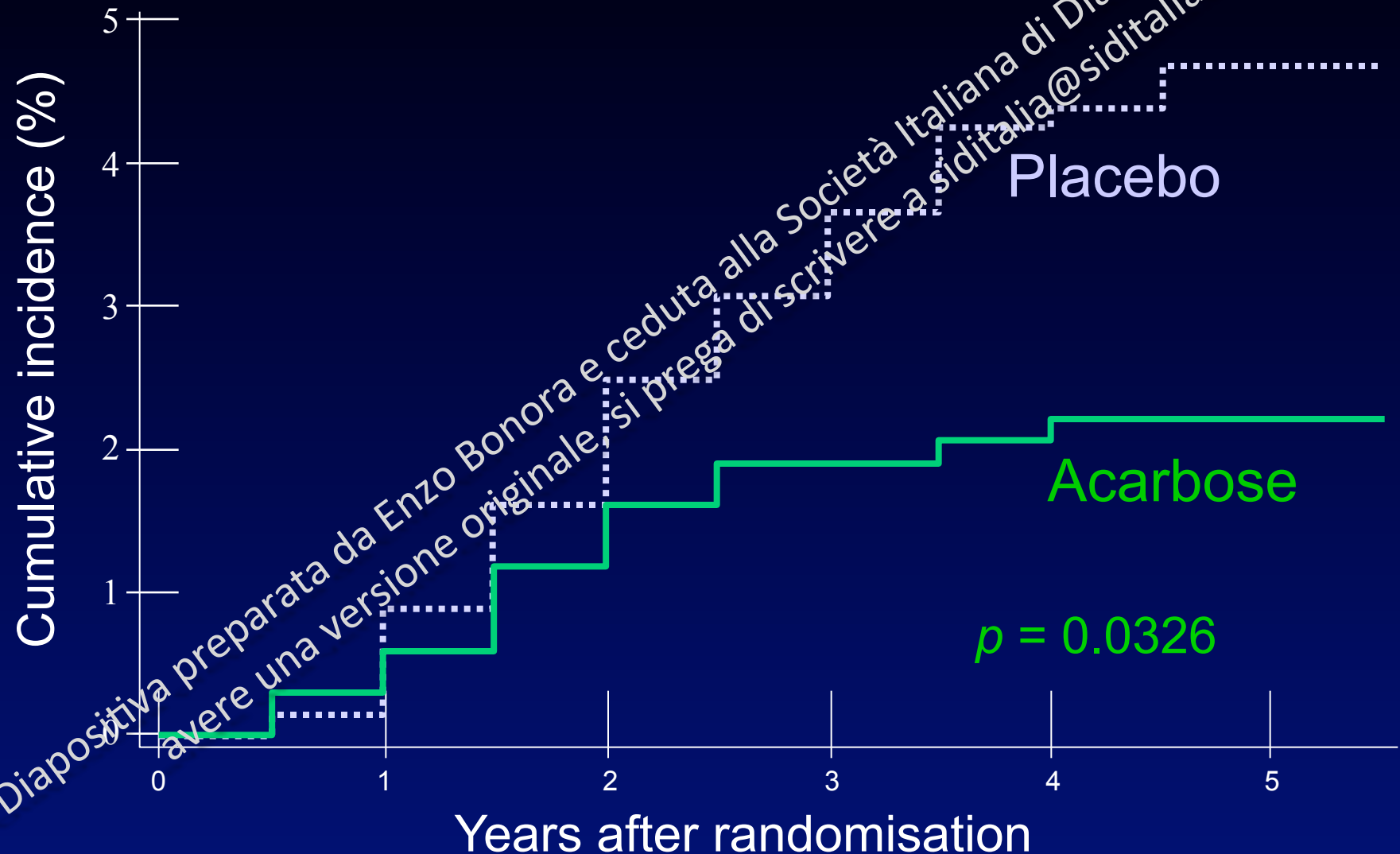
Cardiovascular risk reduction by acarbose in T2DM

(Pool of trial data; Hanefeld et al - Eur Heart J 25: 10, 2004)



Effect of acarbose on the incidence of CVD in IGT

(STOP-NIDDM; Chiasson et al - JAMA 290: 486, 2003)



Thrombosis
Oxidative stress
Mild chronic inflammation
Endothelial dysfunction

Blood glucose

Peak

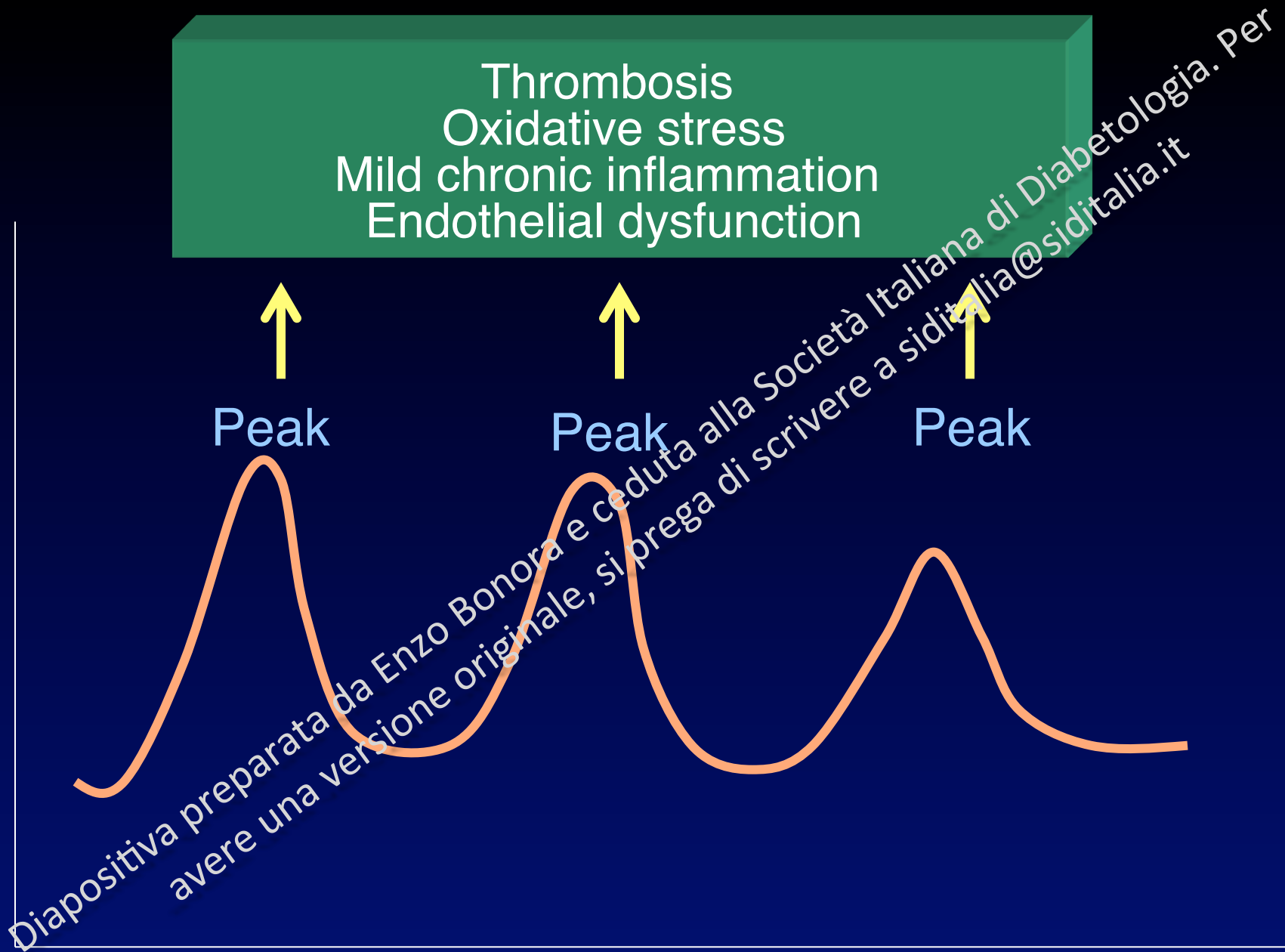
Peak

Peak

Breakfast

Lunch

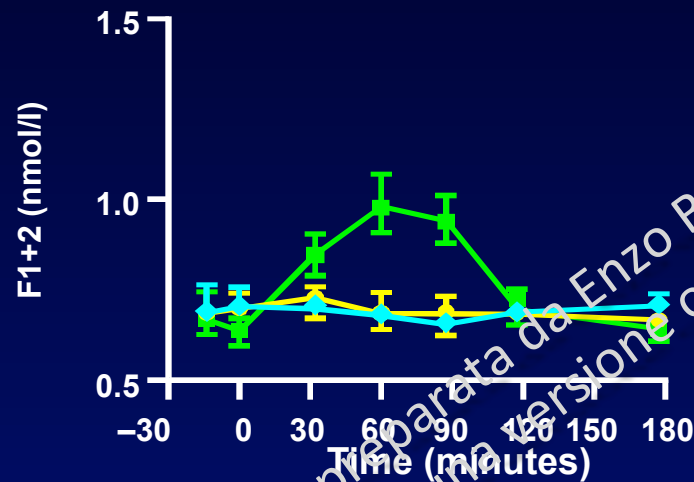
Dinner



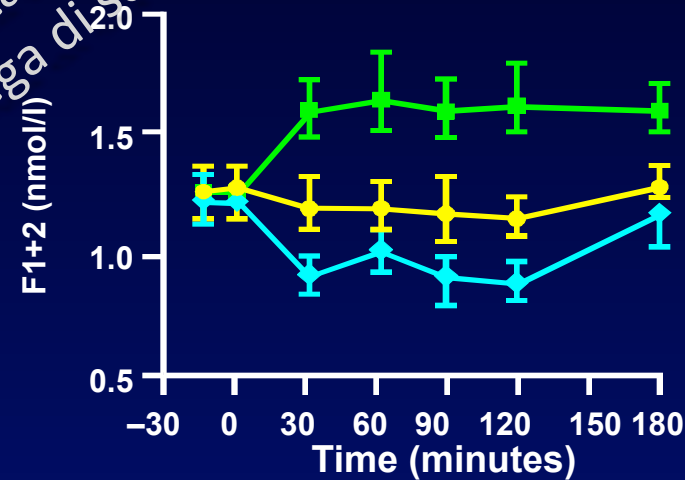
Prothrombin fragments (F1 + 2) variations during OGTT in normal and T2DM subjects

(Ceriello et al - Diabetes 44: 924, 1995)

Normal



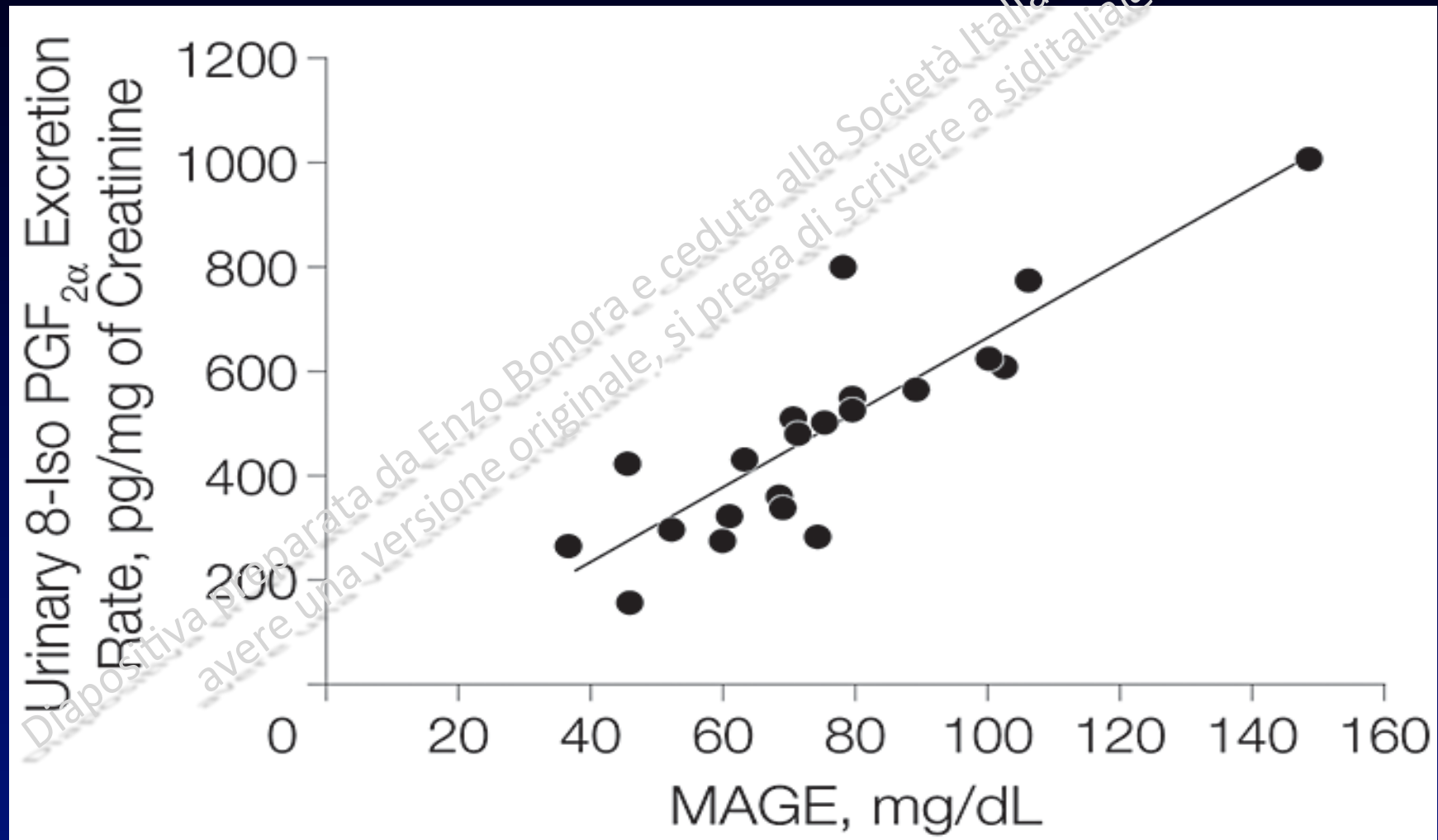
T2DM



■ OGTT ● OGTT + glutathione ◆ Glutathione

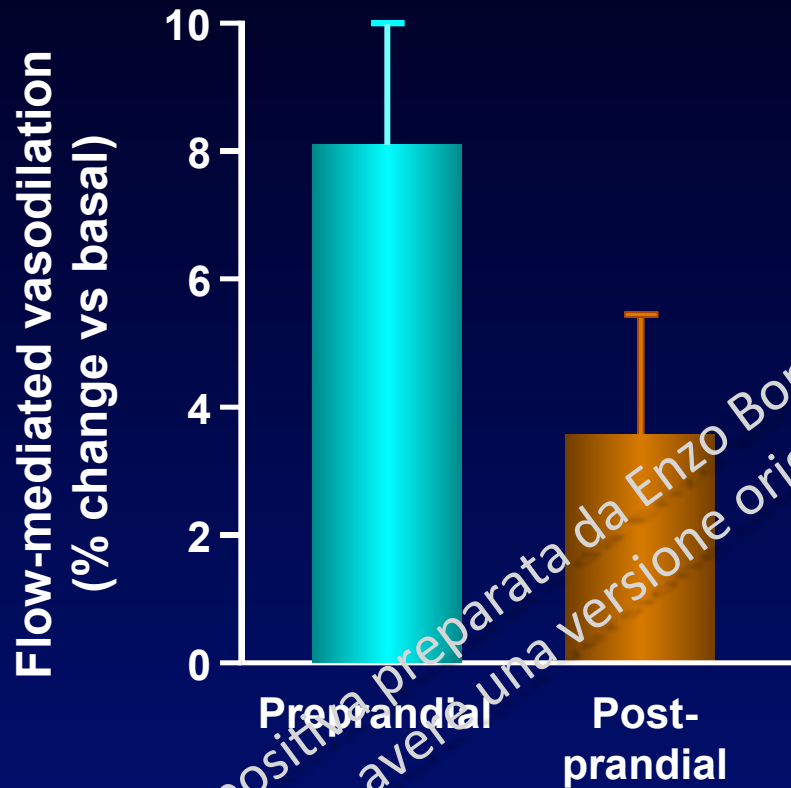
Linear correlation between mean amplitude of glycemc excursions (MAGE) and 24-hour urinary excretion rates of 8-Iso prostaglandin F₂ α (PGF₂ α) a marker of oxidant stress

(Monnier et al - JAMA 295: 1681, 2006)



Endothelium-dependent flow-mediated brachial artery vasodilation in the post-prandial state in T2DM

(Shige et al - Am J Cardiol 84:1272, 1999)



Ultrasound technique

The **greater** was the postprandial increase in plasma glucose, the **smaller** was the postprandial change in flow-mediated vasodilation ($r = -0.84, p < 0.05$)

Glycemic phenotype in T2DM: good control (?) with some peak and hypoglycemia

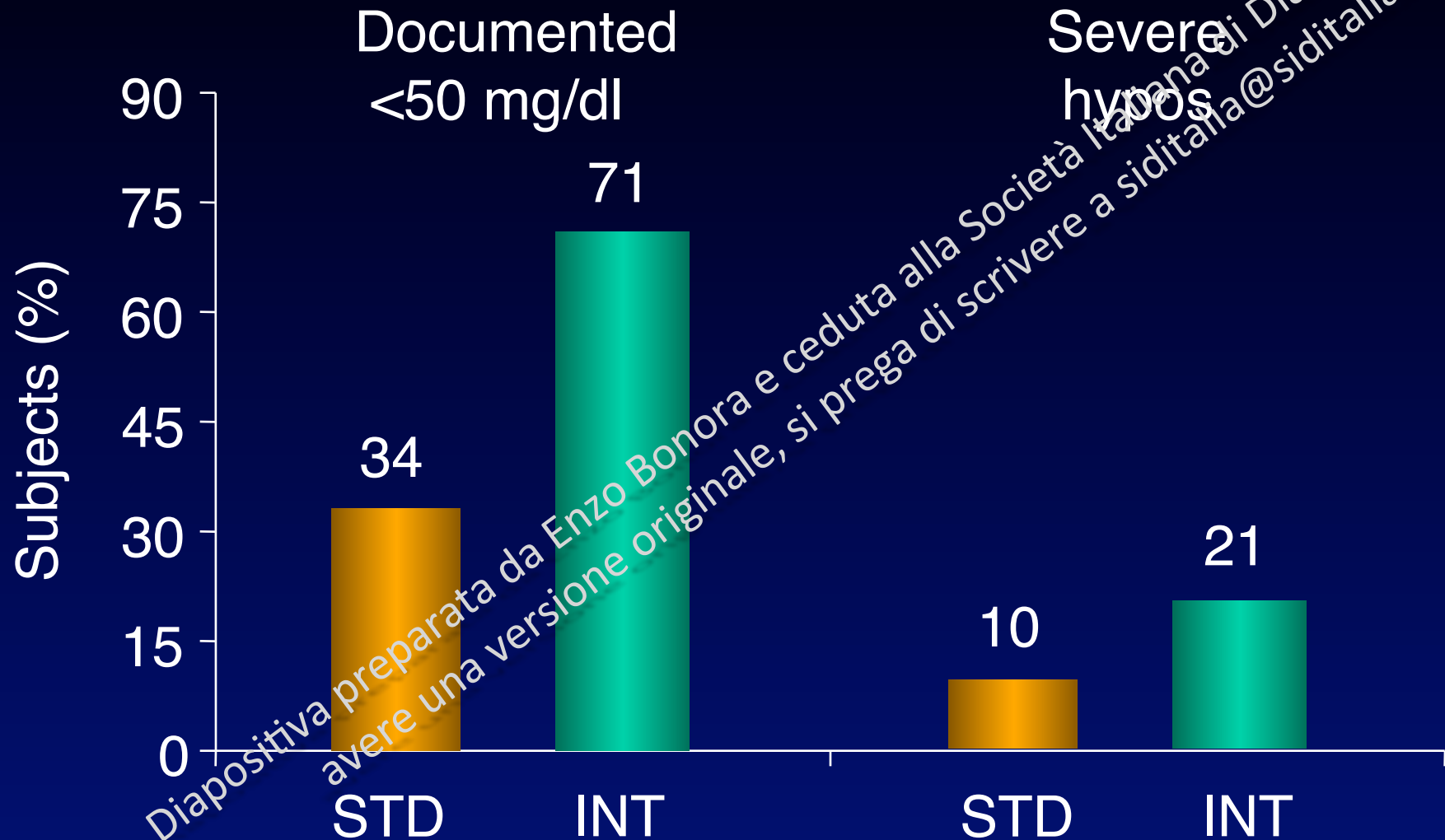
B.V., man, age 56, HbA1c 7.0%

Time of the day

Day of the month

	7	9	13	15	20	22
1	95	88	70	81	224	194
2	71	242	119	96	58	314
3	180	112	69	157	81	101
4	66	294	118	97	174	126
5	124	119	67	199	44	234
6	108	101	97	106	91	86

VADT - Hypoglycemic episodes



VADT - Predictors of CVD Death

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

Association of hypoglycemia and rapid hyperglycemia with cardiac ischemia in T2DM. A study based upon continuous glucose and ECG monitoring

(Desouza et al - Diabetes Care 26: 1485, 2003)

	Total episodes	Episodes with cardiac pain	Episodes with ECG abnormalities
Hypoglycemia	54	10	6
Asymptomatic	28	-	2
Symptomatic	26	10	4
Normoglycemia	-	0	0
Hyperglycemia	59	1	0
Glucose increase >100 mg in 1 h	50	9	2

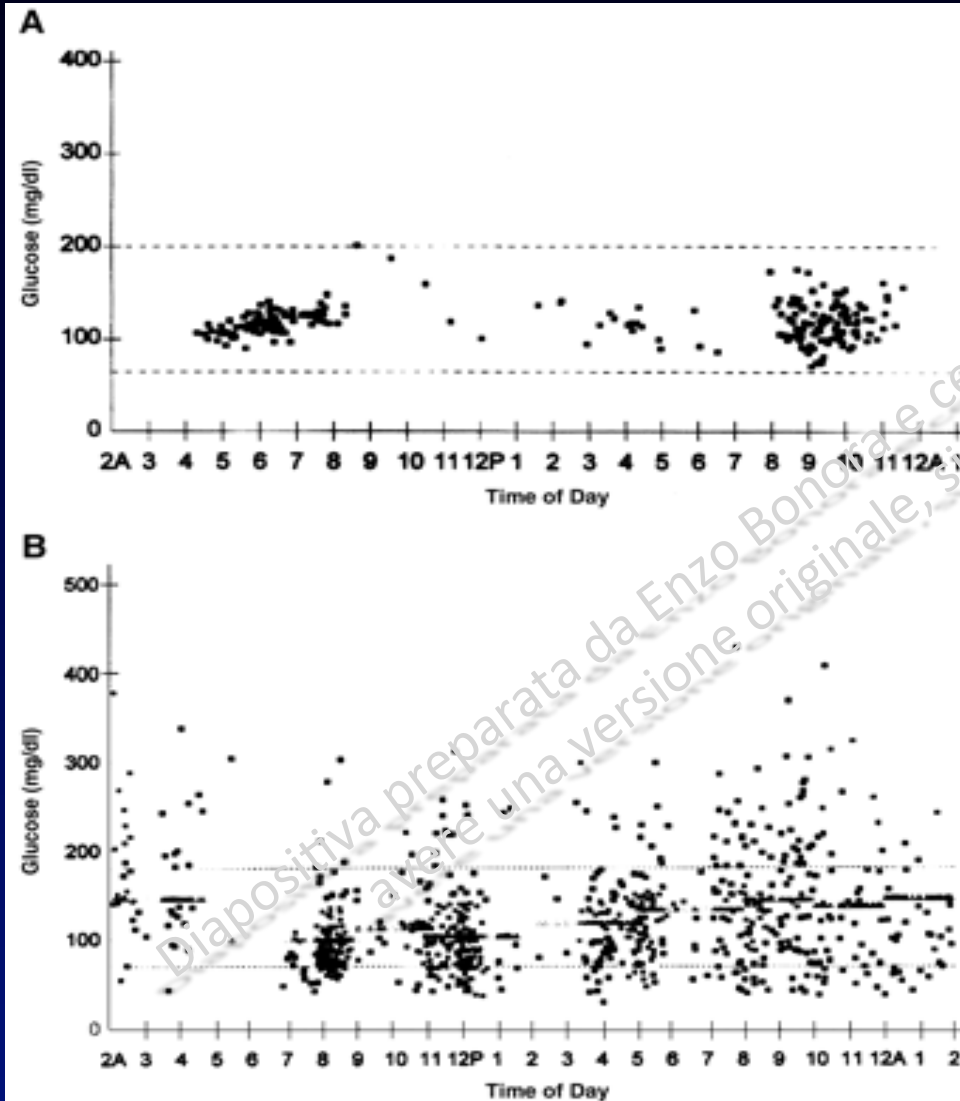
Glycemic phenotype in T2DM: poor control with glucose instability (high CV of FPG and PPG)

T.A., man, age 62, HbA1c 8.2%

		Time of the day					
		7	9	13	15	20	22
Day of the month	1	195	210	170	192	136	194
	2	173	242	119	126	118	131
	3	140	188	99	115	91	329
	4	66	264	178	238	174	193
	5	124	159	101	199	64	234
	6	118	241	207	266	201	229

Stable vs. unstable glucose levels with the same mean blood glucose value

(Derr et al – Diabetes Care 26: 2728, 2003)

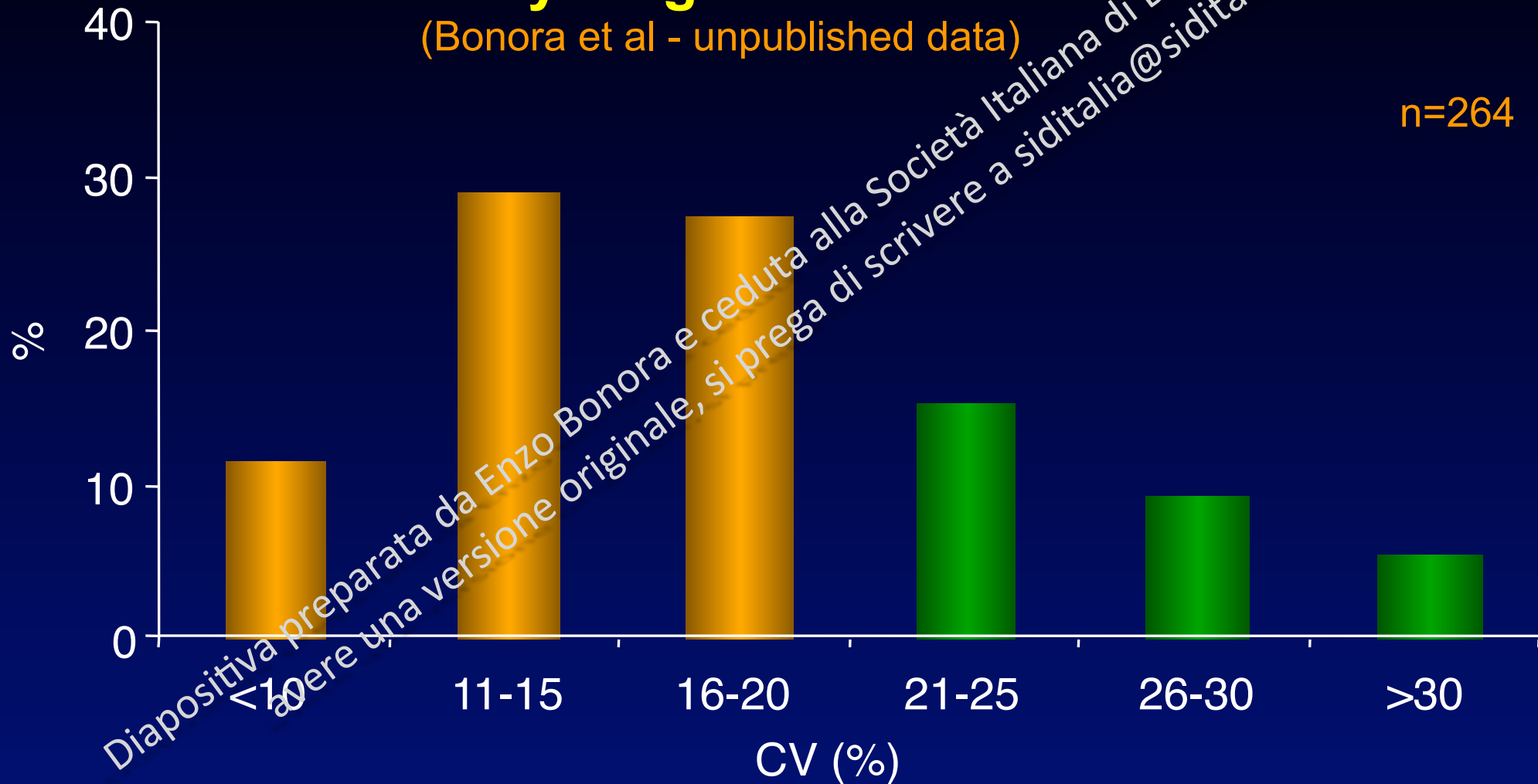


A patient with stable glucose levels
(MBG 119 mg/dl; SD 20 mg/dl)

A patient with unstable glucose levels
(MBG 121 mg/dl; SD 61 mg/dl)

Frequency distribution of coefficient of variation (CV) of pre-prandial blood glucose in untreated newly-diagnosed T2DM

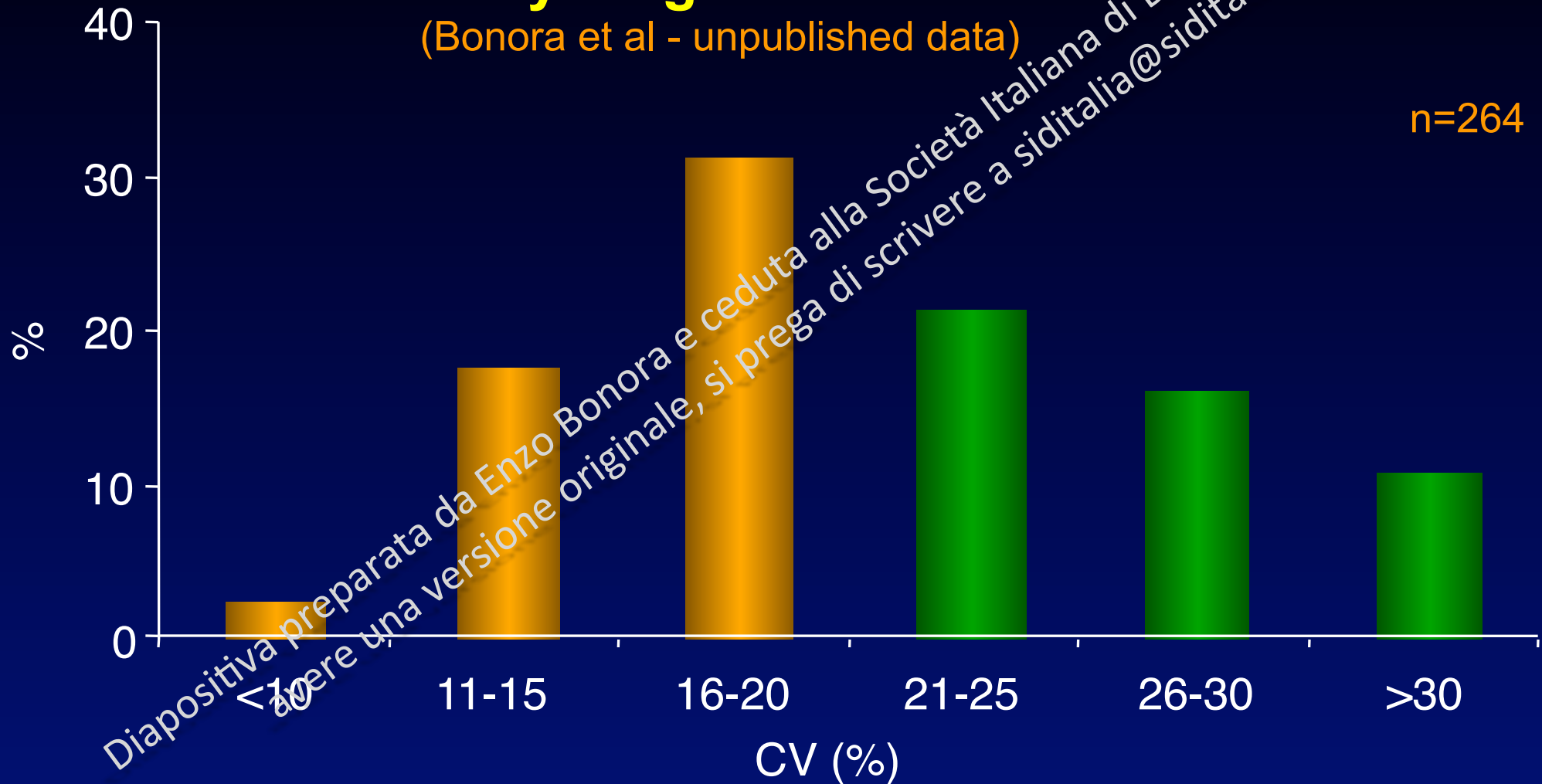
(Bonora et al - unpublished data)



Six home blood glucose readings per day for 5 days (before and 2 h after the 3 meals).

Frequency distribution of coefficient of variation (CV) of post-prandial blood glucose in untreated newly-diagnosed T2DM

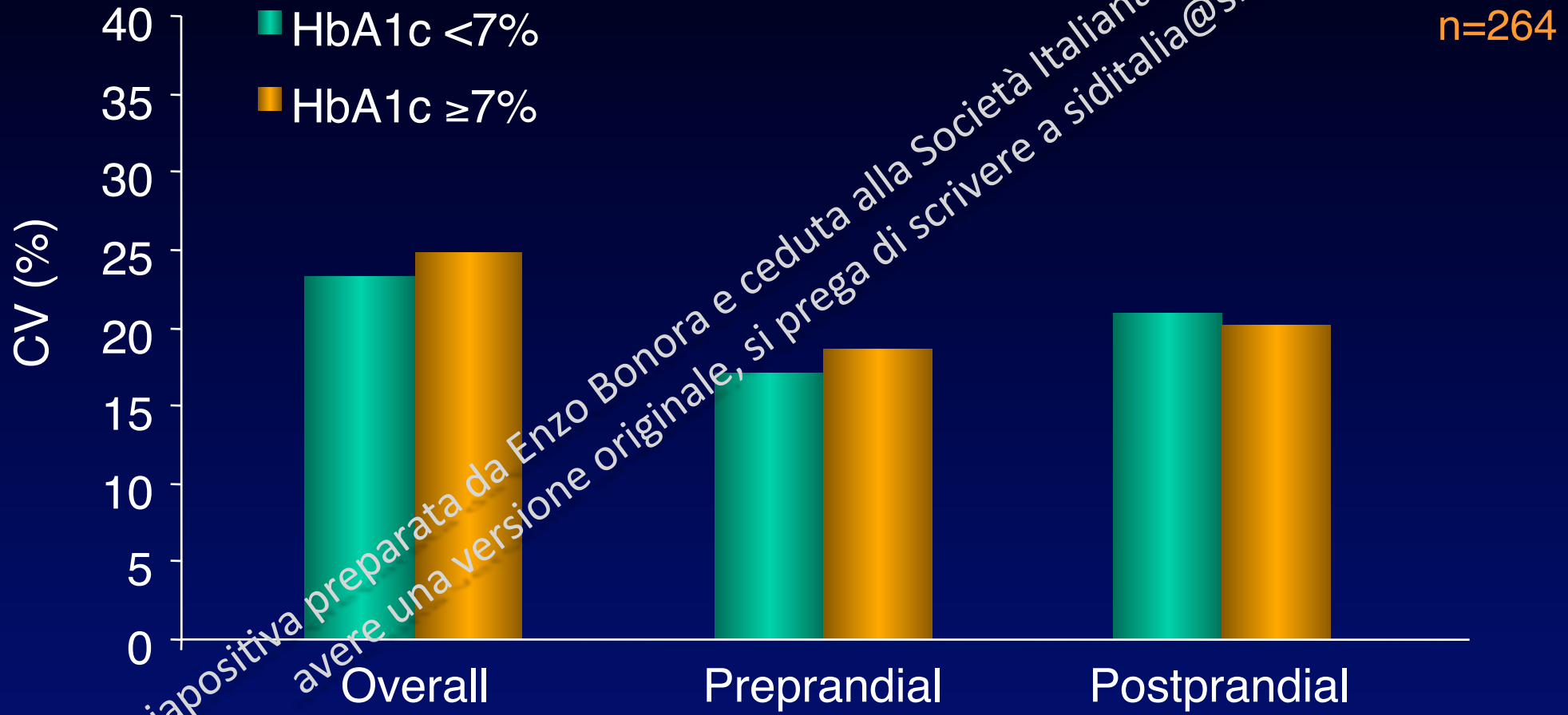
(Bonora et al - unpublished data)



Six home blood glucose readings per day for 5 days (before and 2 h after the 3 meals).

Mean CV of blood glucose according to HbA1c in untreated newly-diagnosed T2DM

(Bonora et al - unpublished data)



Six home blood glucose readings per day for 5 days (before and 2 h after the 3 meals).

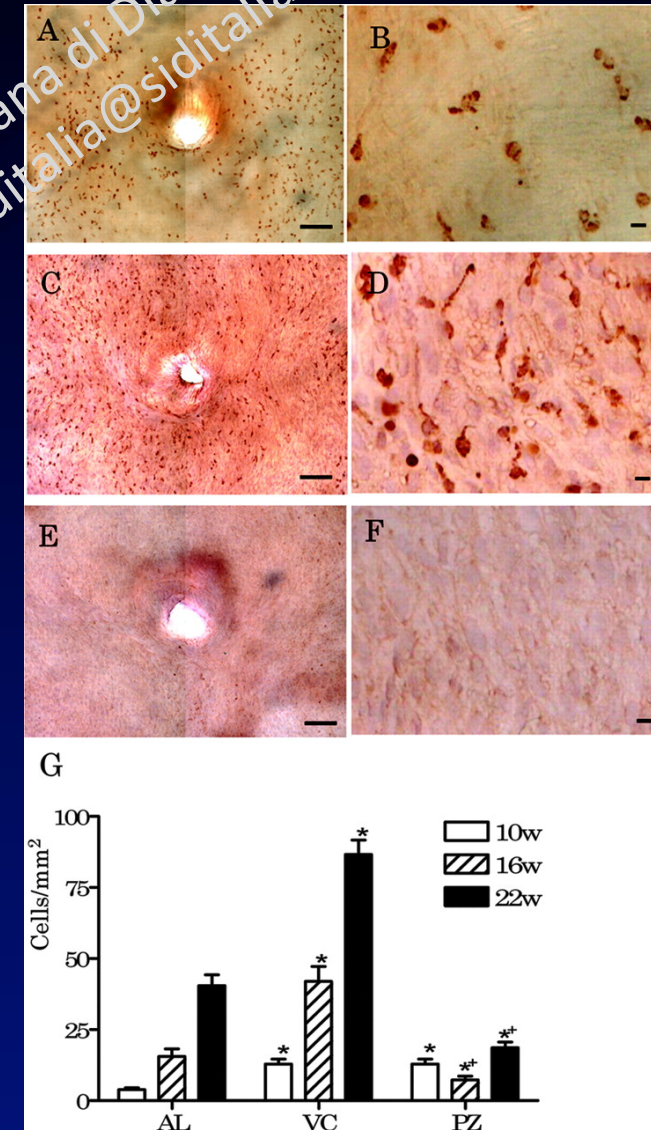
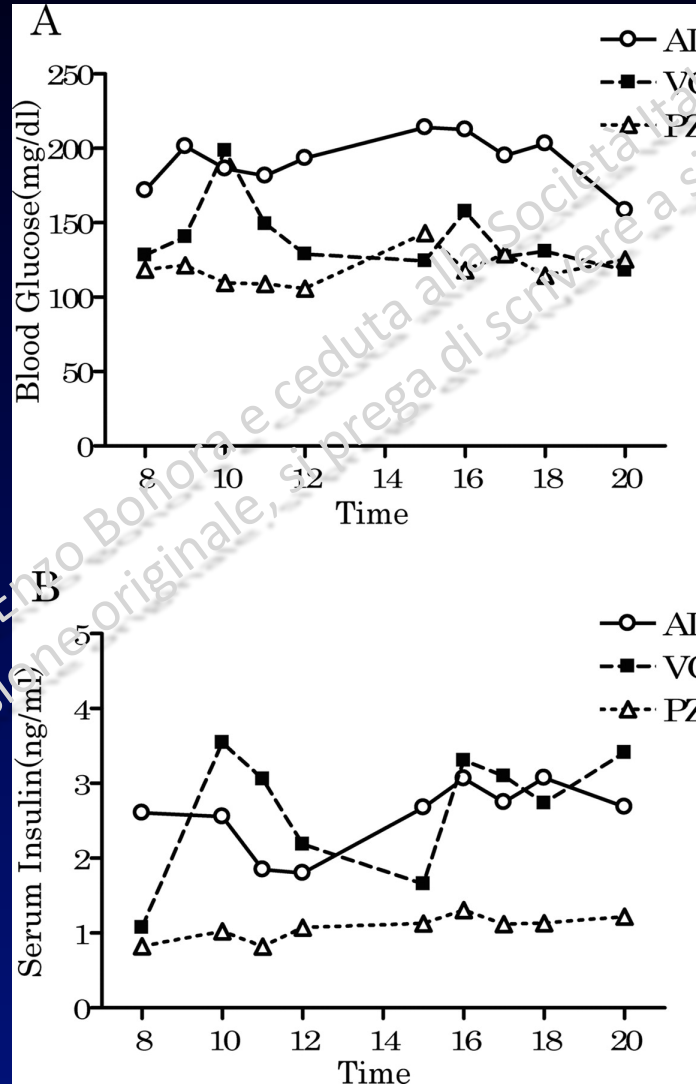
Repetitive fluctuations in blood glucose enhance monocyte adhesion to the endothelium of thoracic aorta in diabetic rats

(Azuma et al - ATVB 26: 2275, 2006)

AL= ad libitum food and stable hyperglycemia

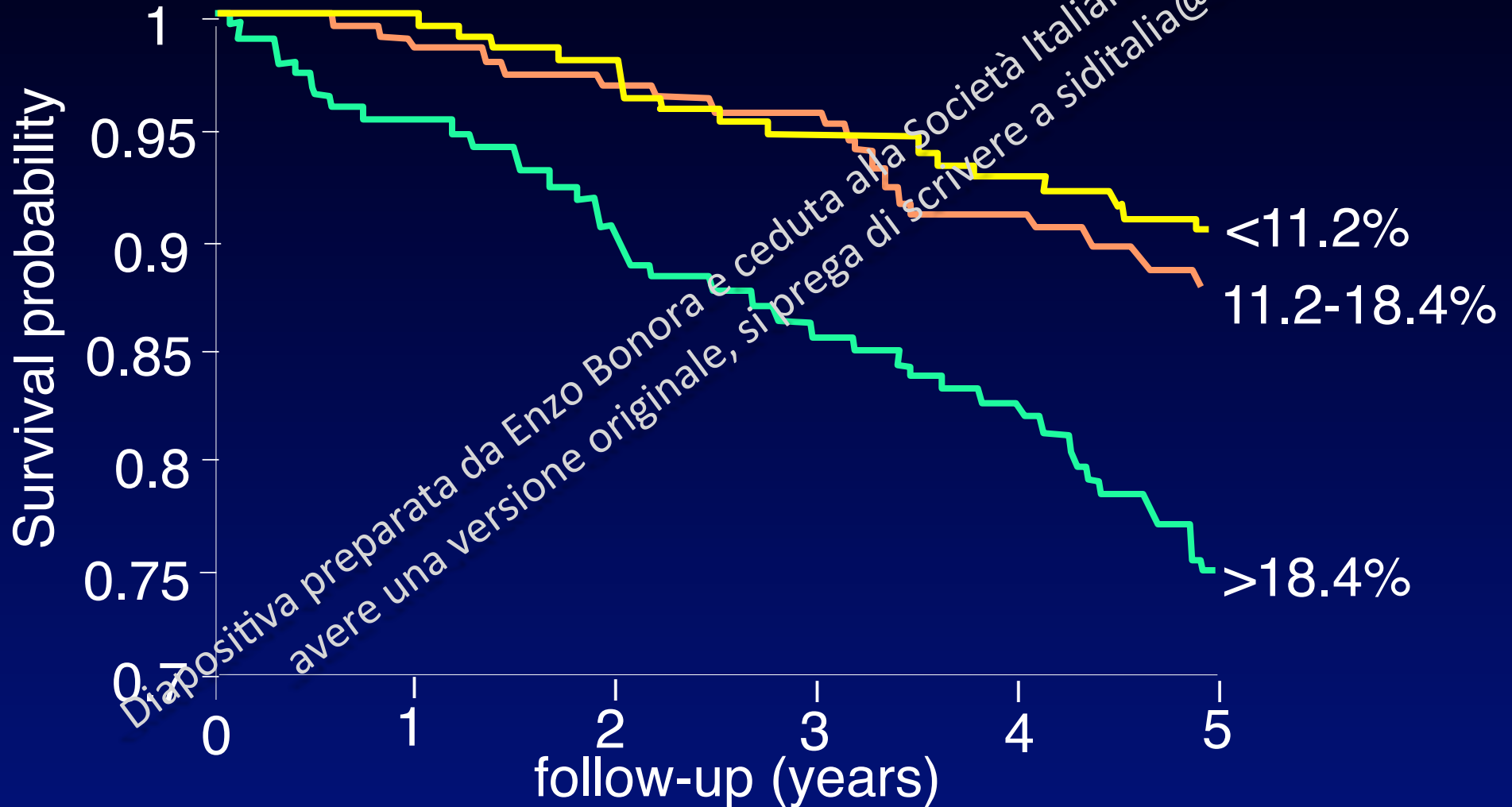
VC= periodical food and intermittent hyperglycemia

PZ= ad libitum food but normoglycemia by phlorizin



Cardiovascular mortality in elderly patients with T2DM stratified according to the variability of fasting plasma glucose (CV-FPG)

(Verona Diabetes Study; Muggeo et al - Circulation 96: 1750, 1997)



HbA1c and fasting glucose variability as predictors of CVD in T2DM

(Verona Diabetes Complications Study; Bonora et al - unpublished data)

	OR	p
Sex (M vs F)	1.22	0.047
Age (per year)	1.05	<0.001
Smoking (yes vs. no)	1.34	<0.001
Hypertension (yes vs. no)	1.24	0.003
LDL cholesterol (per 10 mg/dl)	1.05	0.011
Mean HbA1c during follow-up (per 1%)	1.23	<0.001
CV-FPG during follow-up (per 10%)	1.20	0.030

n=1,023; follow-up= 52 ± 19 months; diabetes duration= 9±7 years

CVD = CVD death, non-fatal AMI and stroke, angina pectoris, carotid or lower limb severe atherosclerosis

Key messages of the talk

- Glycemic targets are not limited to HbA1c because the latter does not describe fasting, pre-prandial, post-prandial plasma glucose and neither plasma glucose excursions with meals, i.e. the glycemic phenotype, which should be the guide for treatment decisions
- HbA1c does not unveil post-prandial peaks, hypoglycemia and glucose variability, which have been associated to a poorer outcome
- HbA1c is not always reliable due to high/low Hb susceptibility to glycation, certain clinical conditions or analytical problems
- SMBG provides information on daily glycemic profile and help to reach and maintain a better glycemic control
- SMBG seems to be associated to a better outcome

Glycemic phenotype in insulin-treated T2DM: The “high glyicator” patient

M.M., woman, age 48, HbA1c 8.9%

		Time of the day					
		7	9	13	15	20	22
Day of the month	1	124	175	123	162	119	184
	2	132	159	131	146	128	157
	3	139	170	99	135	91	131
	4	145	142	117	139	171	187
	5	137	169	113	125	93	126
	6	126	154	141	183	121	169

Glycemic phenotype in insulin-treated T2DM: The “low glyicator” patient

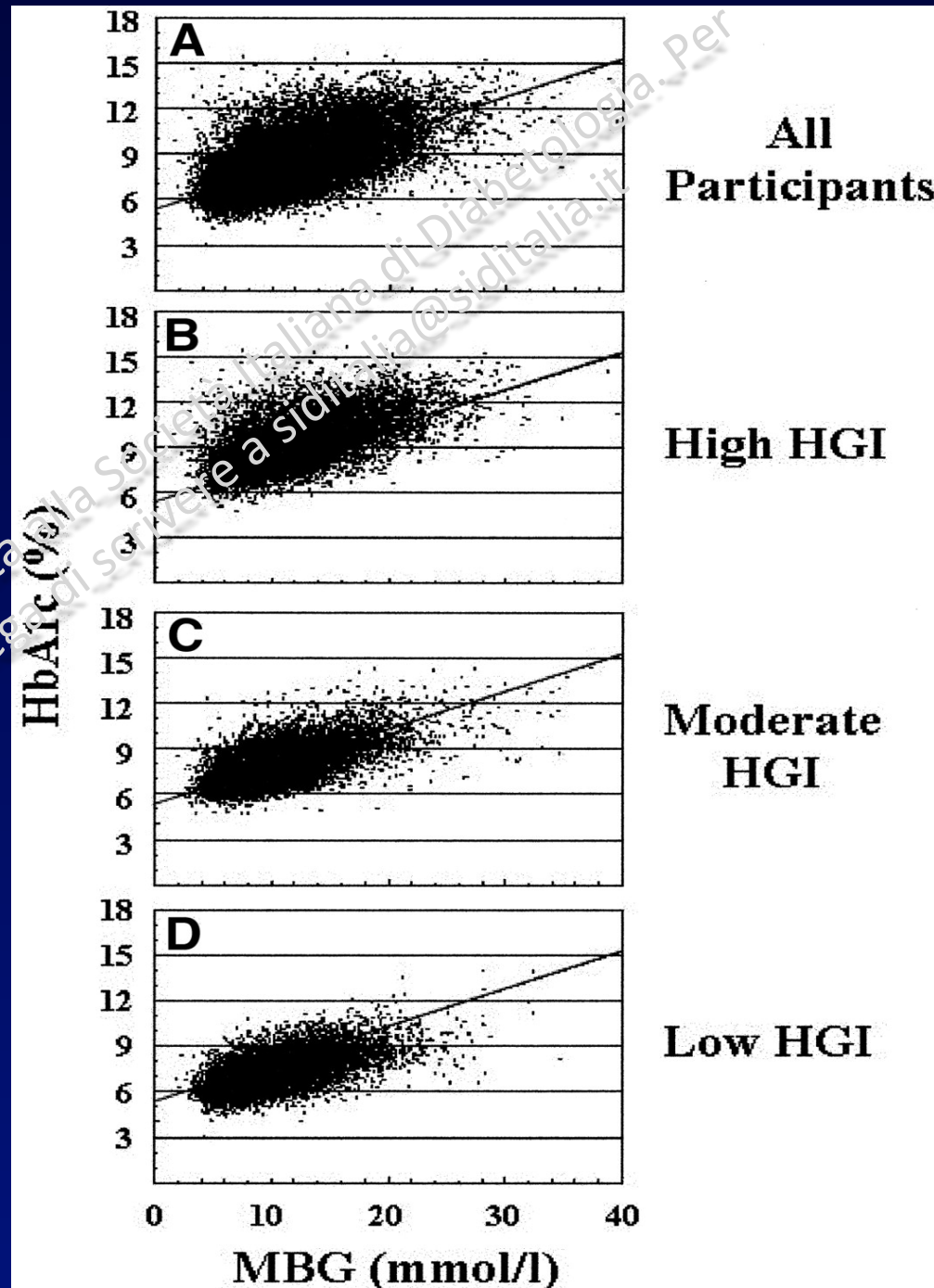
A.G., woman, age 57, HbA1c 7.6%

		Time of the day					
		7	9	13	15	20	22
Day of the month	1	223	277	229	261	227	314
	2	230	269	138	198	228	261
	3	241	271	199	235	191	329
	4	216	277	298	288	274	293
	5	234	269	211	329	284	334
	6	218	264	197	286	221	269

Relationship between HbA1c and mean blood glucose is affected by individual susceptibility to glycation of Hb

(DCCT; McCarter et al -
Diabetes Care 27: 1259, 2004)

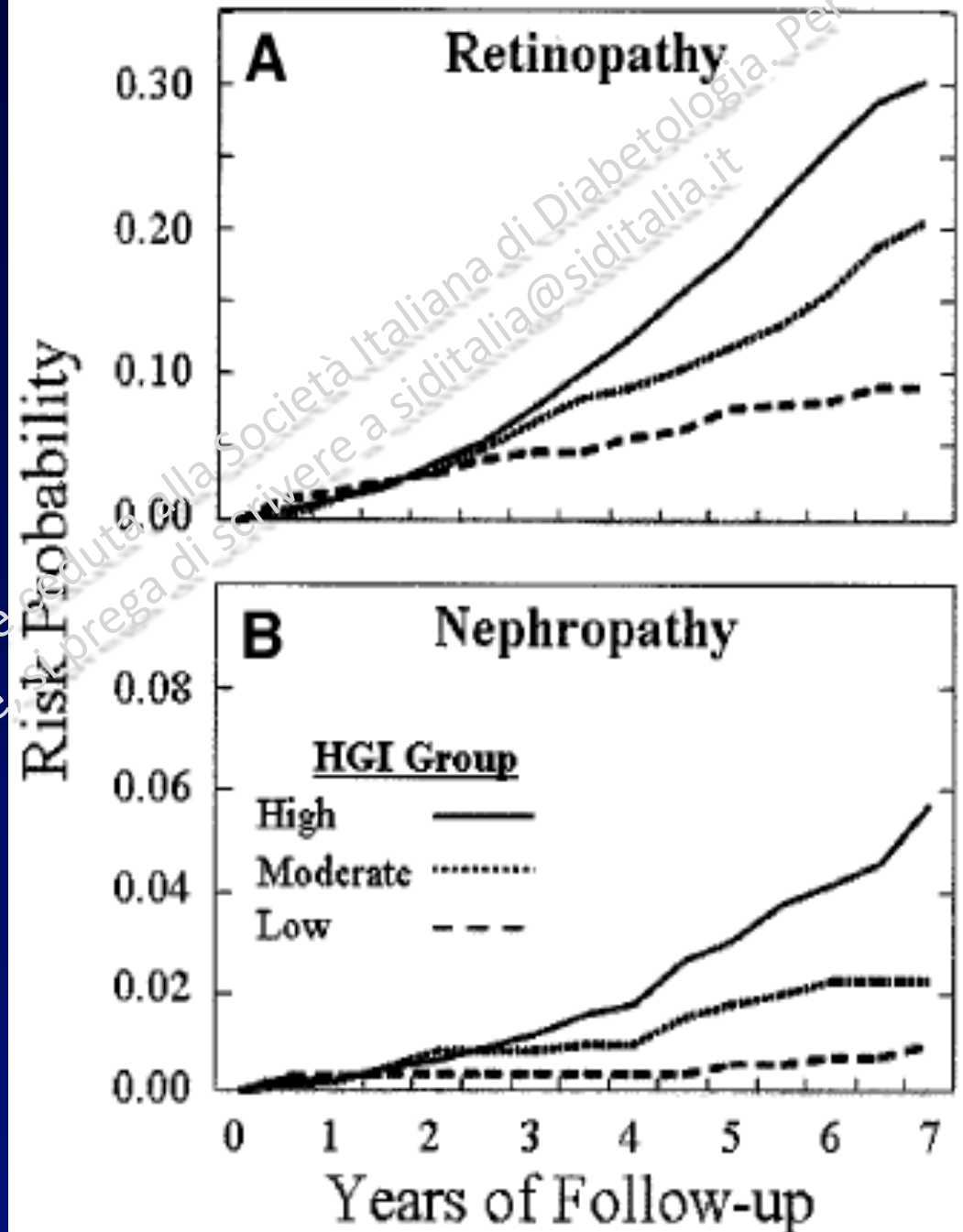
Hemoglobin Glycation Index (HGI) =
Observed - Predicted HbA1c level



Individual susceptibility to glycation of Hb predicts microangiopathy in T1DM

(DCCT; McCarter et al -
Diabetes Care 27: 1259, 2004)

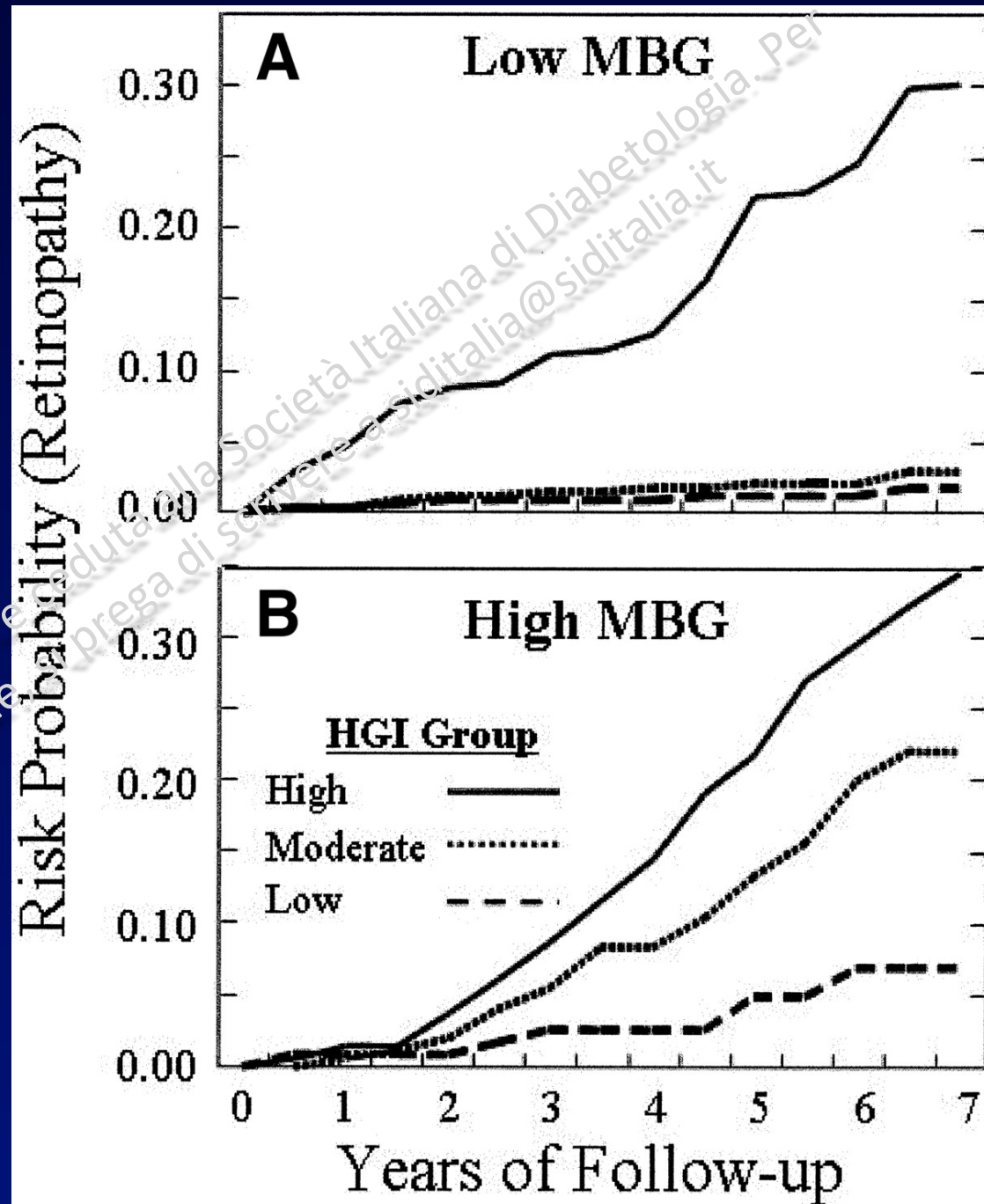
Hemoglobin Glycation Index (HGI) =
Observed - Predicted HbA1c level



**Individual
susceptibility to
glycation of Hb
predicts
microangiopathy in
T1DM irrespective of
mean blood glucose**

(DCCT; McCarter et al
Diabetes Care 27: 1259, 2004)

Hemoglobin Glycation Index (HGI) =
Observed - Predicted HbA1c level



Clinical conditions increasing HbA1c

- hemoglobinopathies (HbF; thalassemia)
- high triglycerides
- high bilirubin
- high WBC
- alcoholism
- drugs (opioids, high dose salicylates)
- kidney failure (uremia)
- splenectomy
- aging

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

Clinical conditions reducing HbA1c

- pregnancy
- malaria
- hemolysis
- chronic anemias
- major blood loss
- hemoglobinopathies (Hb C)

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

Standardization of HbA1c measurement: still a problem

Diabetologia
DOI 10.1007/s00125-007-0789-7

CONSENSUS STATEMENT

Consensus statement on the worldwide standardisation of the HbA_{1c} measurement

The American Diabetes Association, European Association for the Study of Diabetes,
International Federation of Clinical Chemistry and Laboratory Medicine,
and the International Diabetes Federation

Consensus Committee

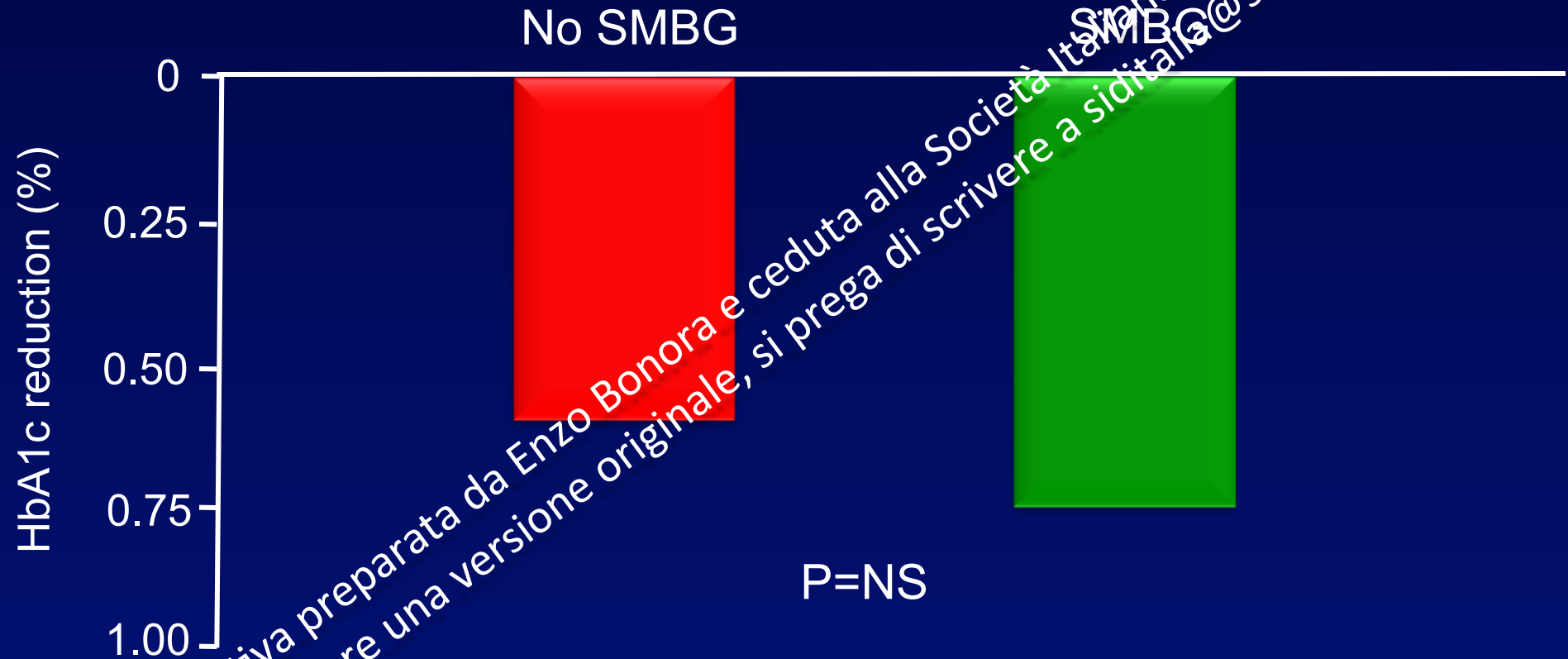
- Place: UK
- Year: 2009
- Participating laboratories: 251
- Standard sample issue to labs: HbA1c 6.5%
- Performance in various labs: HbA1c ranging 5.8 – 7.2

Key messages of the talk

- Glycemic targets are not limited to HbA1c because the latter does not describe fasting, pre-prandial, post-prandial plasma glucose and neither plasma glucose excursions with meals, i.e. the glycemic phenotype, which should be the guide for treatment decisions
- HbA1c does not unveil post-prandial peaks, hypoglycemia and glucose variability, which have been associated to a poorer outcome
- HbA1c is not always reliable due to high/low Hb susceptibility to glycation, certain clinical conditions or analytical problems
- SMBG provides information on daily glycemic profile and help to reach and maintain a better glycemic control
- SMBG seems to be associated to a better outcome

Effect of SMBG on HbA1c in T2DM - A RCT

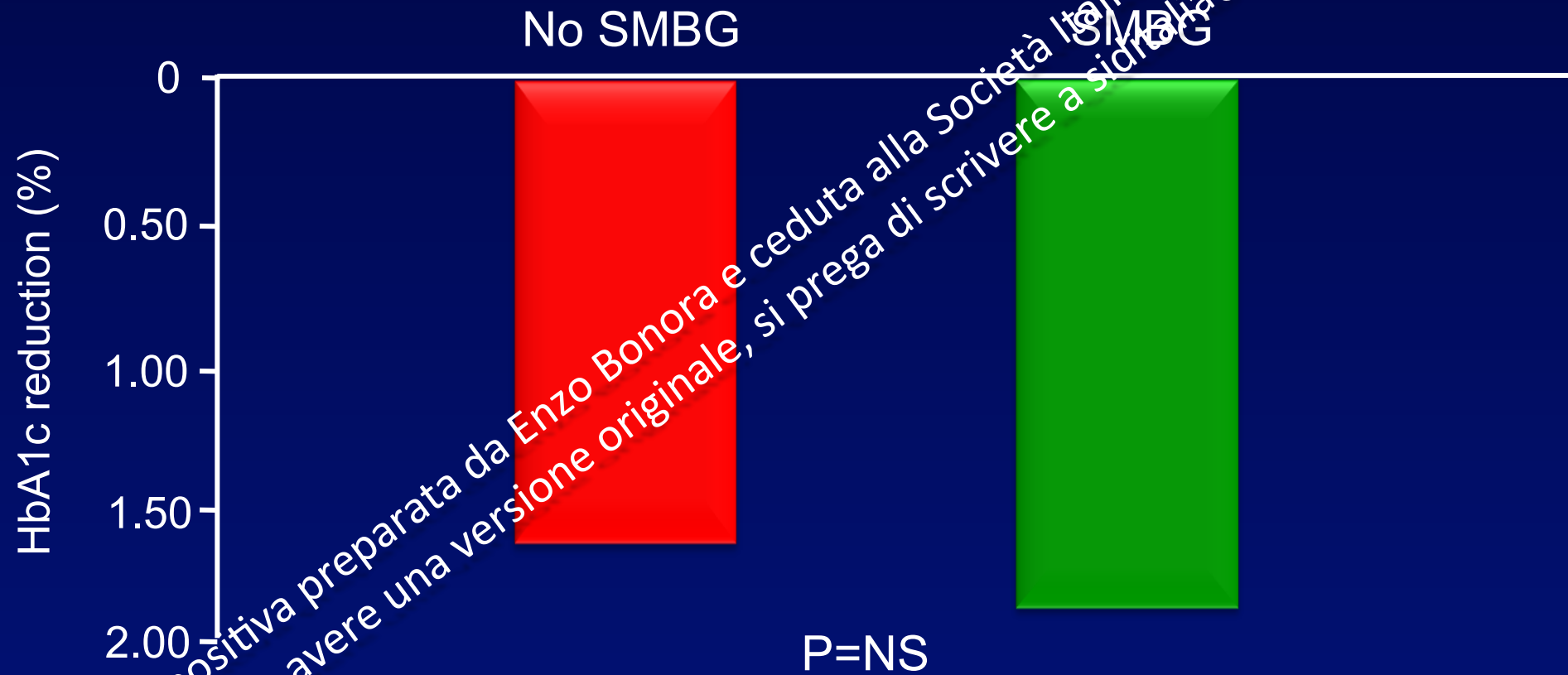
(Davidson et al – Am J Med 118: 422, 2005)



N=89, age 50 yr, duration 5.5 yr, HbA1c 8.5%, follow-up 6 months

Effect of SMBG in newly diagnosed & non-insulin-treated T2DM – A RCT

(ESMON Study; O'Kane et al - BMJ 336: 7654-7658, 2008)

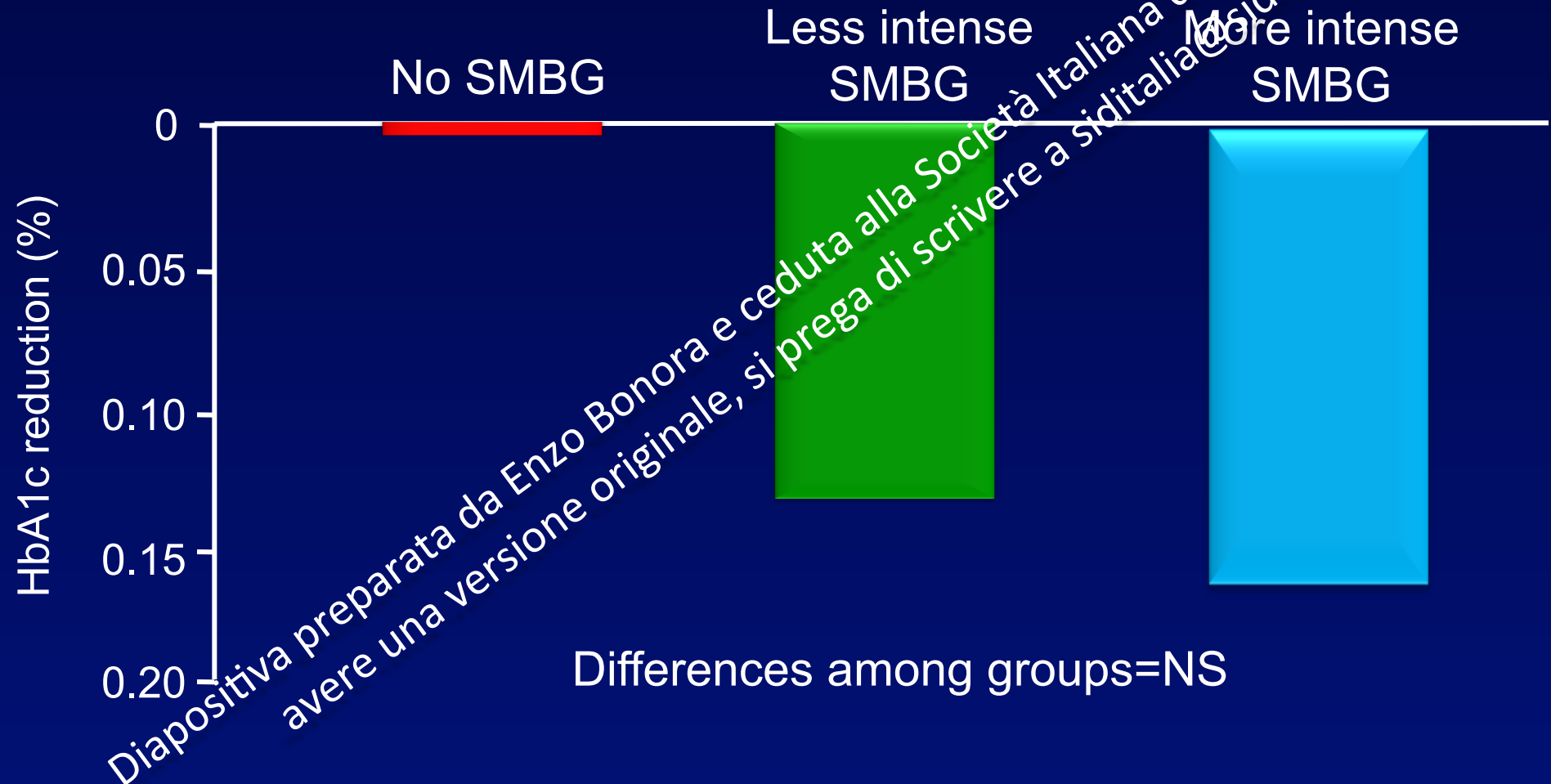


N=184, age 58 yr, HbA1c 8.7%, follow-up 12 months

Impact of SMBG in non-insulin treated T2DM

A RCT

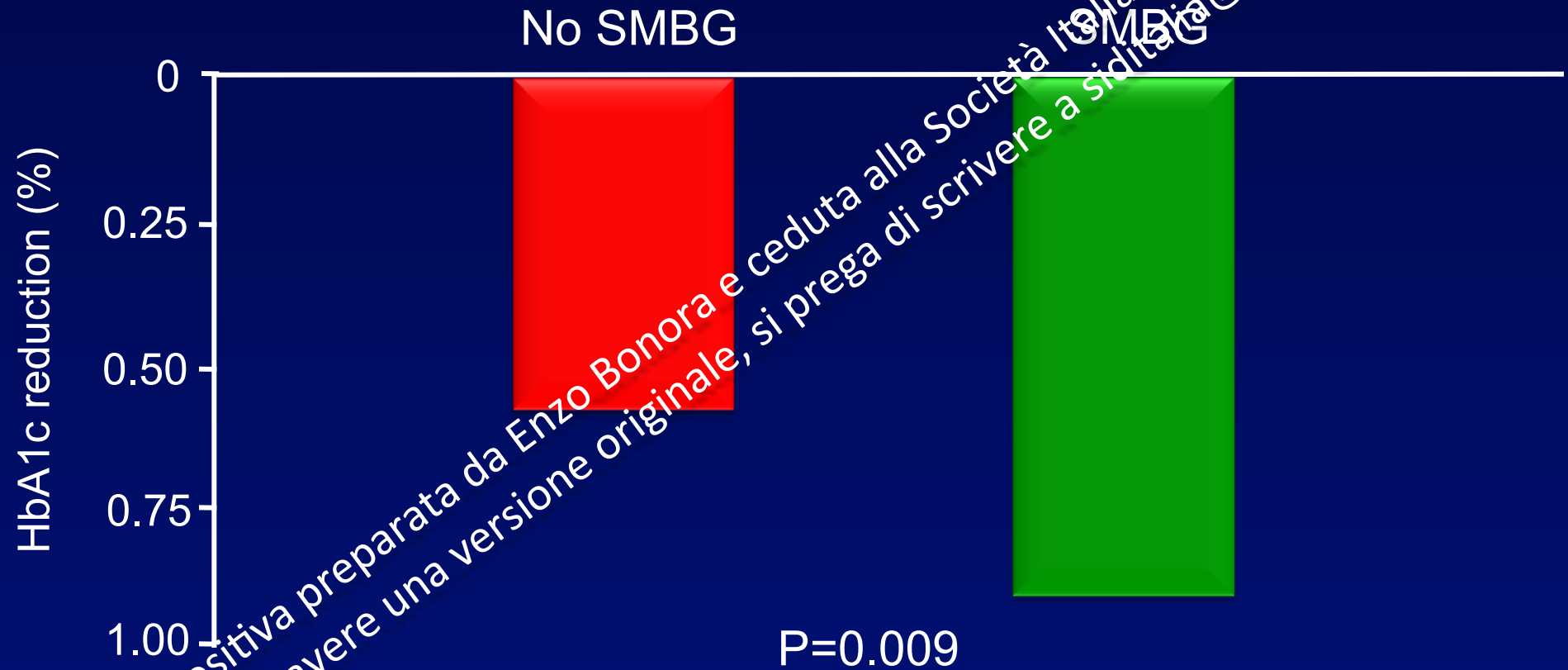
(DiGEM Study; Farmer et al – BMJ 335: 7611, 2007)



N=453, age 66 yr, HbA1c 7.5%, follow-up 12 months

Effect of SMBG on HbA1c in non-insulin-treated T2DM - A RCT

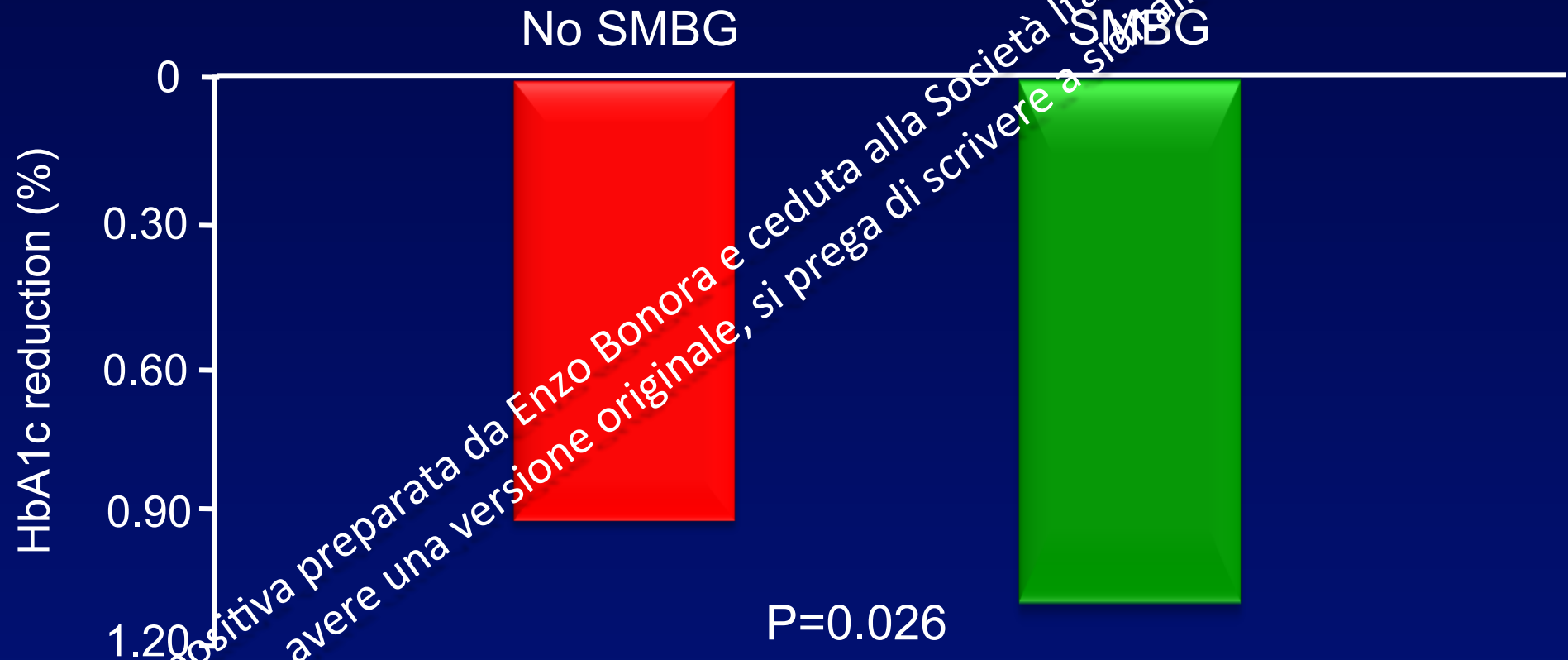
(ASIA Study; Guerçi et al – Diabet Metabol 29: 587-2003)



N=620, age 61 yr, duration 7.8 yr, HbA1c 9.0%, follow-up 6 months

Effect of SMBG in T2DM treated with a gliclazide modified release-based regimen – A RCT

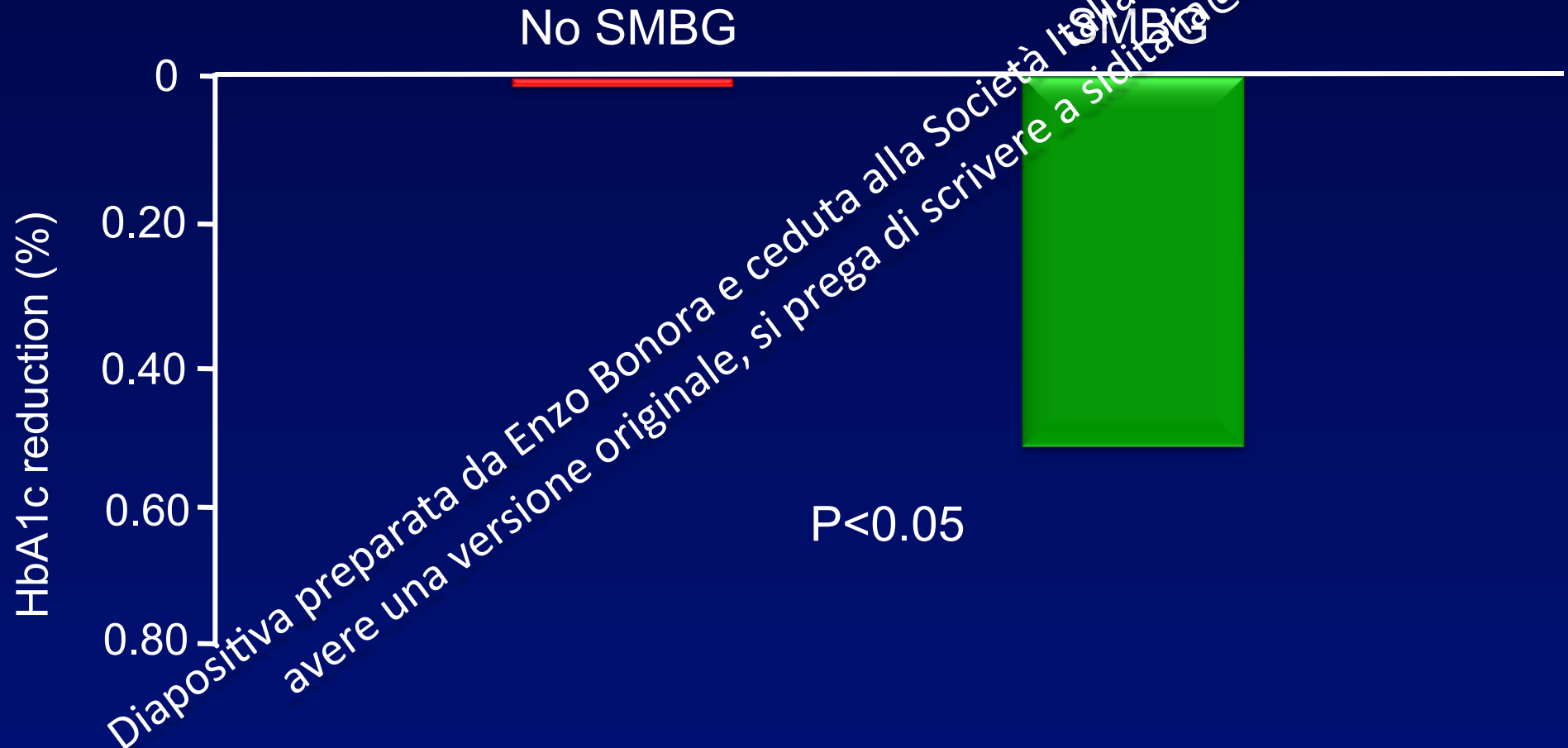
(Dinamic 1 Study; Barnett et al – Diab Obes Metab 10:1236, 2008)



N=519, age 56 yr, duration 2.8 yr, HbA1c 8.1%, follow-up 6 months

Effect of SMBG on HbA1c in newly-diagnosed T2DM - A RCT

(St Carlos Study; Duran et al – J Diabet 2: 203, 2010)



N=161, HbA1c 6.6%, follow-up 12 months

Effect of SMBG in T2DM

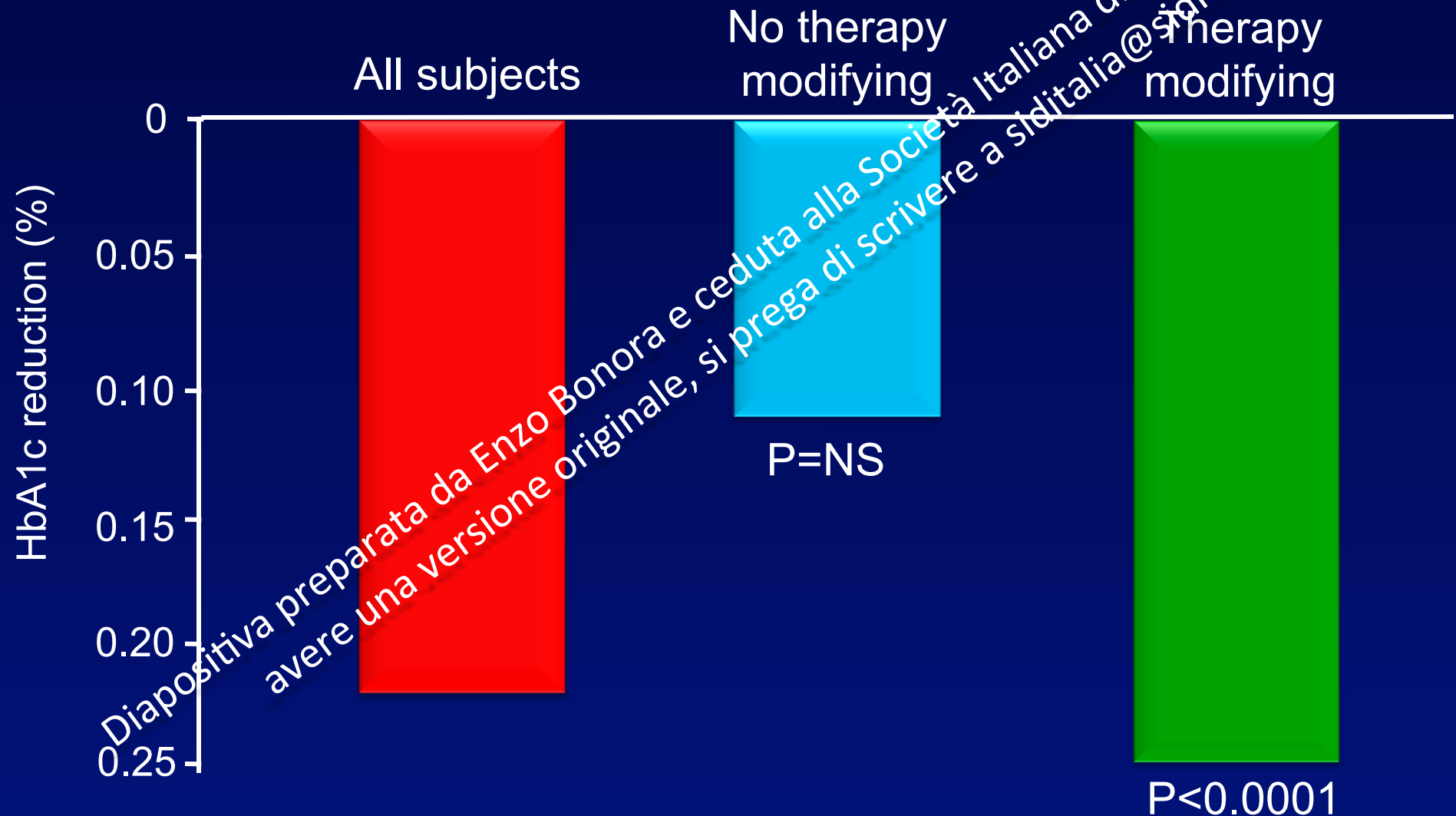
A synopsis of meta-analyses of RCTs

	No. RCTs	Absolute HbA1c reduction (%) with SMBG
Welschen – Diab Care 2005	5	-0.39 (-0.56, -0.21)
Sarol – Curr Med Res Opin 2005	8	-0.39 (-0.54, -0.23)
Jansen – Curr Med Res Opin 2006	7	-0.40 (-0.70, -0.07)
Towfigh – Am J Manag Care 2008	5	-0.21 (-0.38, -0.04)
Poolsup – Diab Techn Therap 2008	6	-0.24 (-0.34, -0.14)
Allemann – Curr Med Res Opin 2009	13	-0.31 (-0.44, -0.17)
McIntosh – Open Med 2010	7	-0.25 (-0.36, -0.15)
St John – J Diab Compl 2010	5	-0.22 (-0.34, -0.11)
Clar – Health Techn Assess 2010	10	-0.21 (-0.31, -0.10)

Effect of SMBG on HbA1c in T2DM

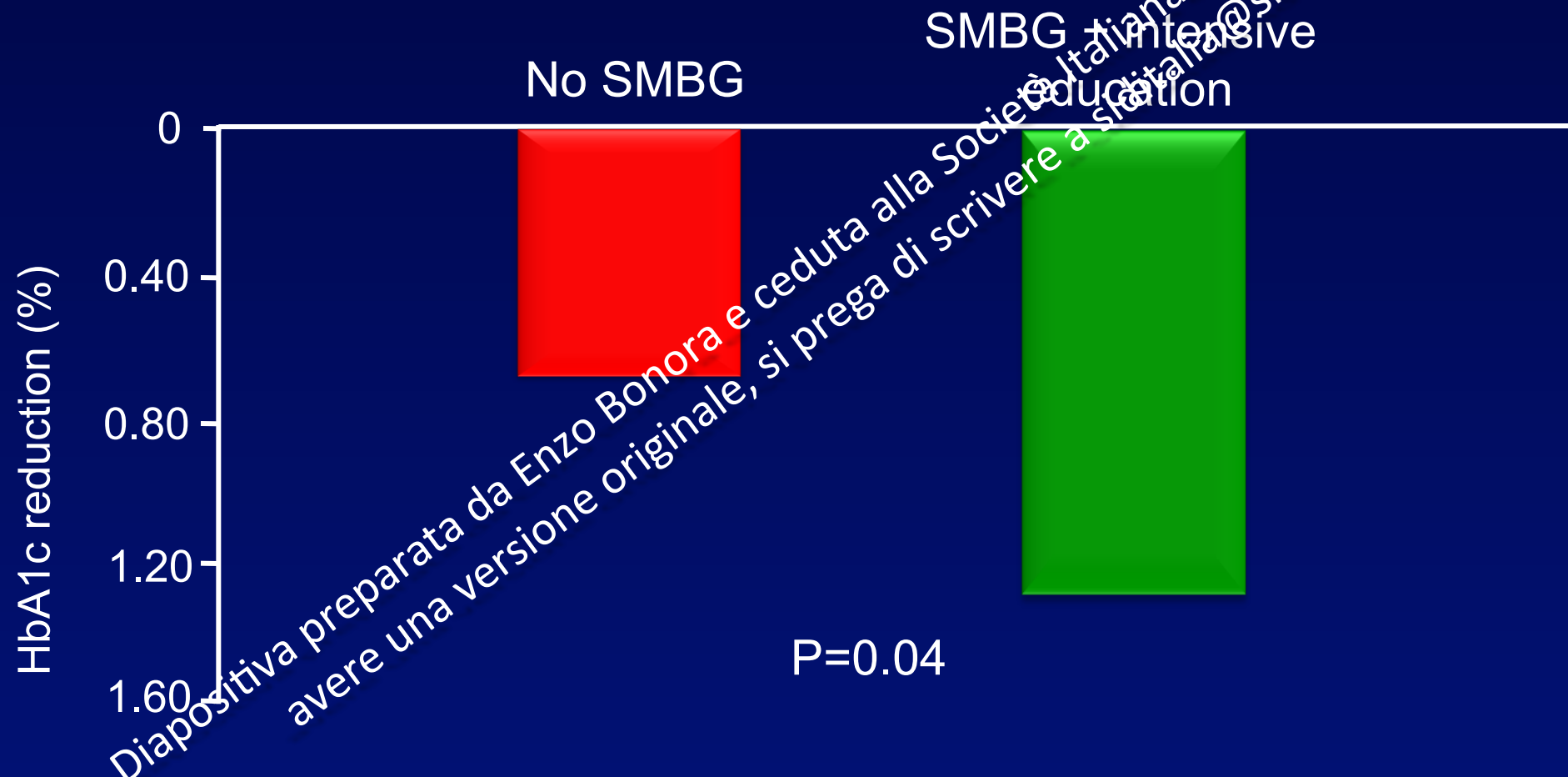
A systematic review and meta-analysis

(Poolsup et al – Diab Techn Therap 10: S51, 2008)



Effect of SMBG and intensive education in non-insulin-treated T2DM – A Pilot RCT

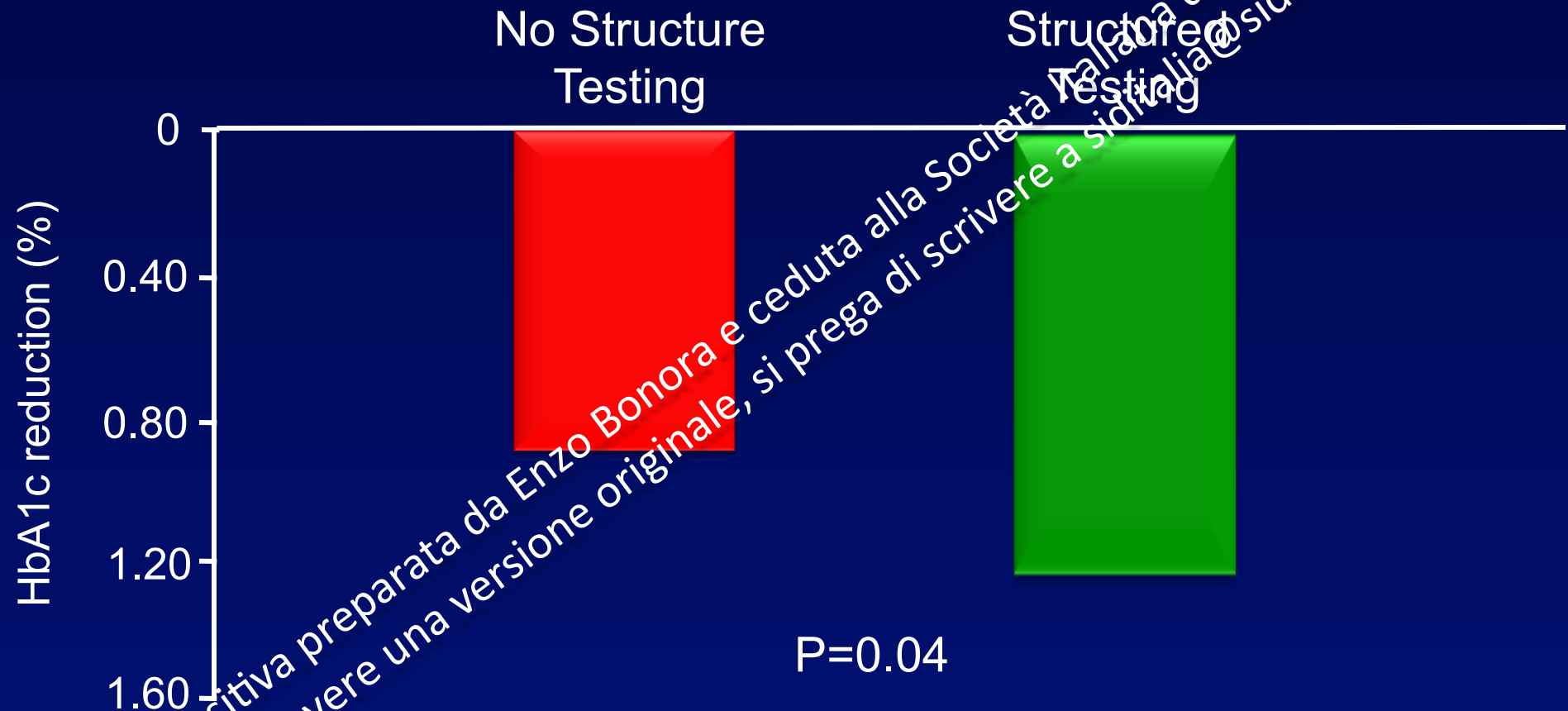
(ROSES Study; Franciosi et al – Diabet Med 28: 789-2011)



N=62, age 49 yr, duration 3.4 yr, HbA1c 7.9%, follow-up 6 months

Effect of structured SMBG in poorly controlled non-insulin treated T2DM – A RCT

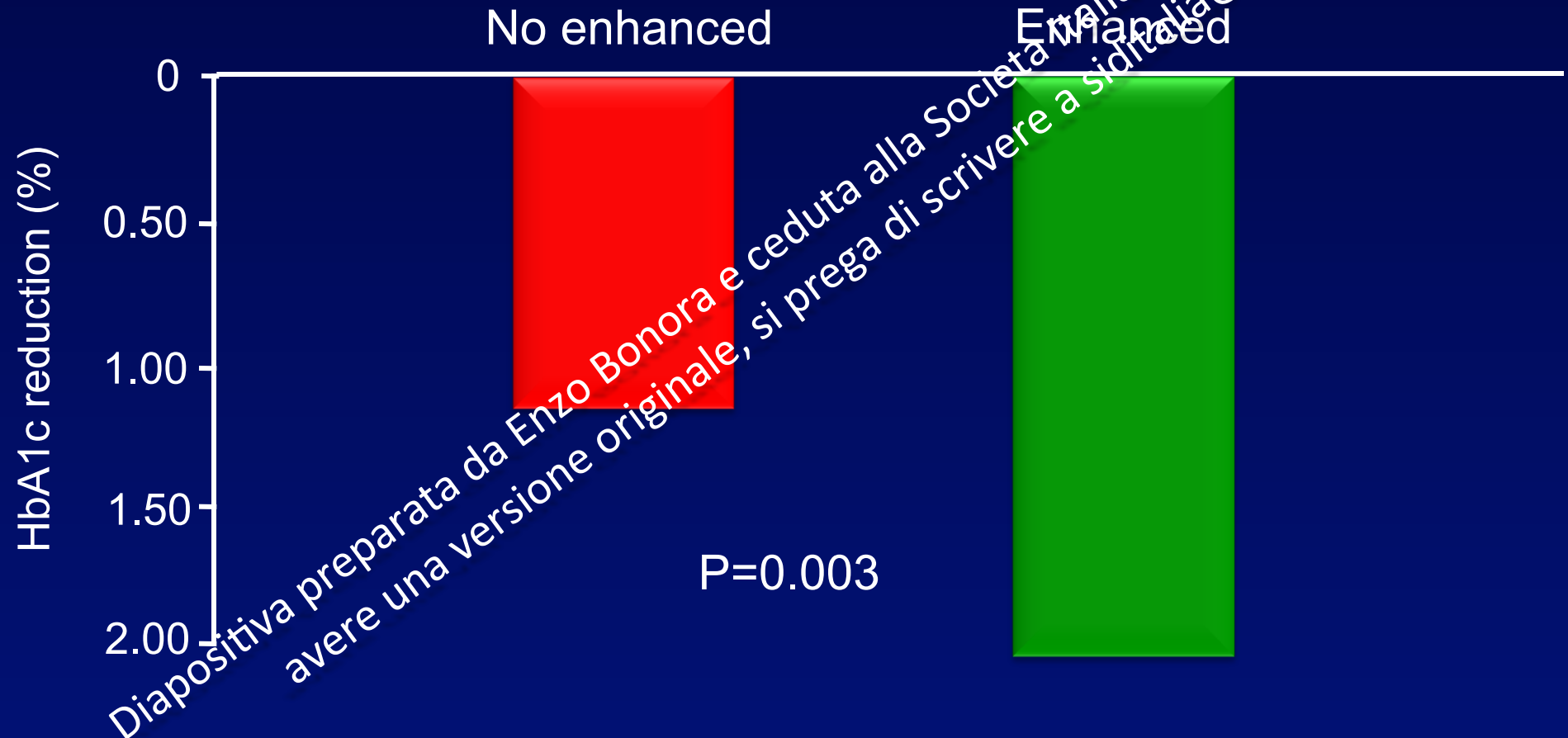
(Polonsky et al – Diabetes Care 34: 262, 2011)



N=483, age 56 yr, HbA1c 8.9%, follow-up 12 months, cluster randomized

Effect of enhanced SMBG (weekly visits at the clinic with data review) on HbA1c in T2DM - A RCT

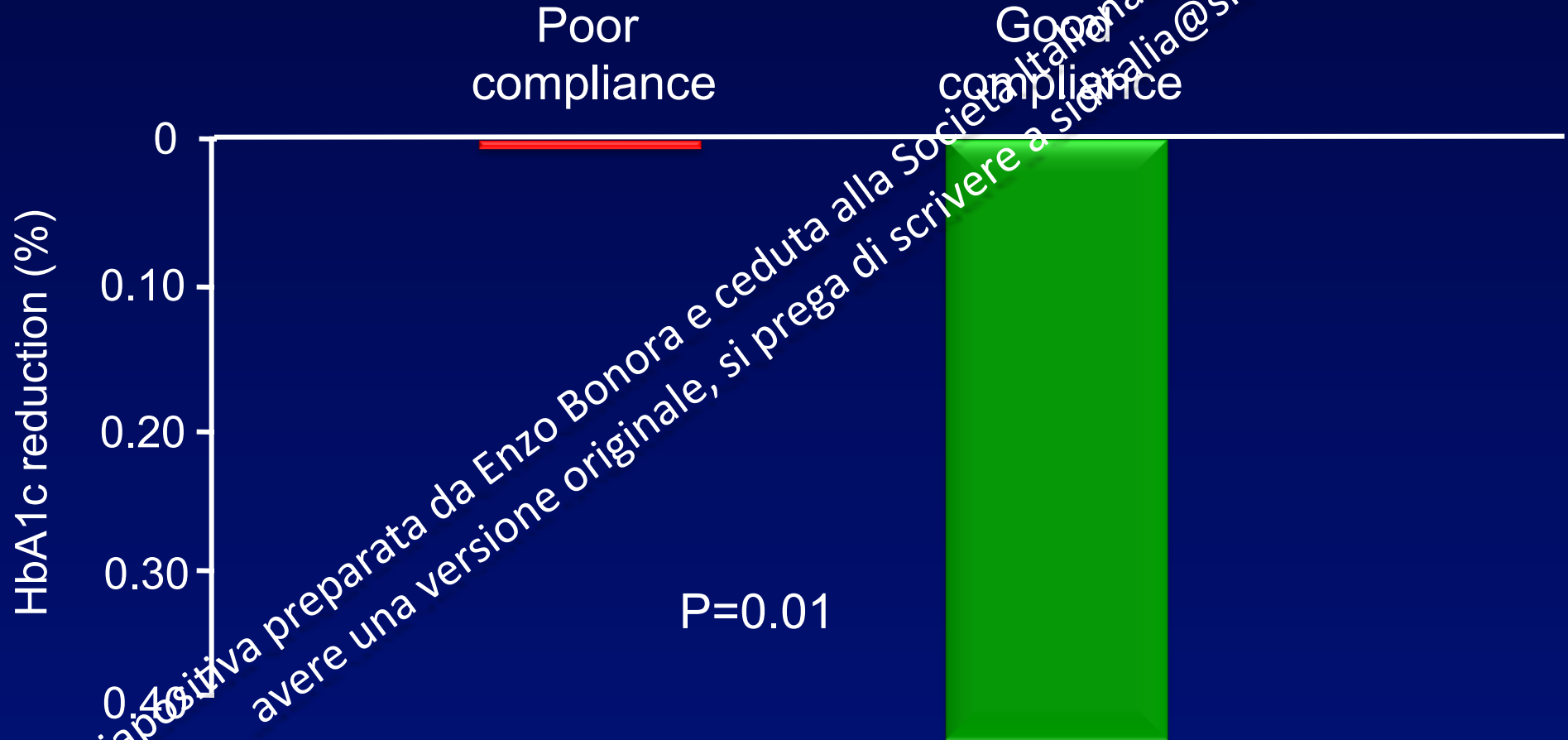
(Pimazoni-Netto et al – Diab Techn Ther 2011)



N=63, age 56 yr, duration 12 yr, HbA1c 10.3%, follow-up 3 months; OAD ± insulin

Effect of more or less intensive SMBG on HbA1c in T2DM - A RCT

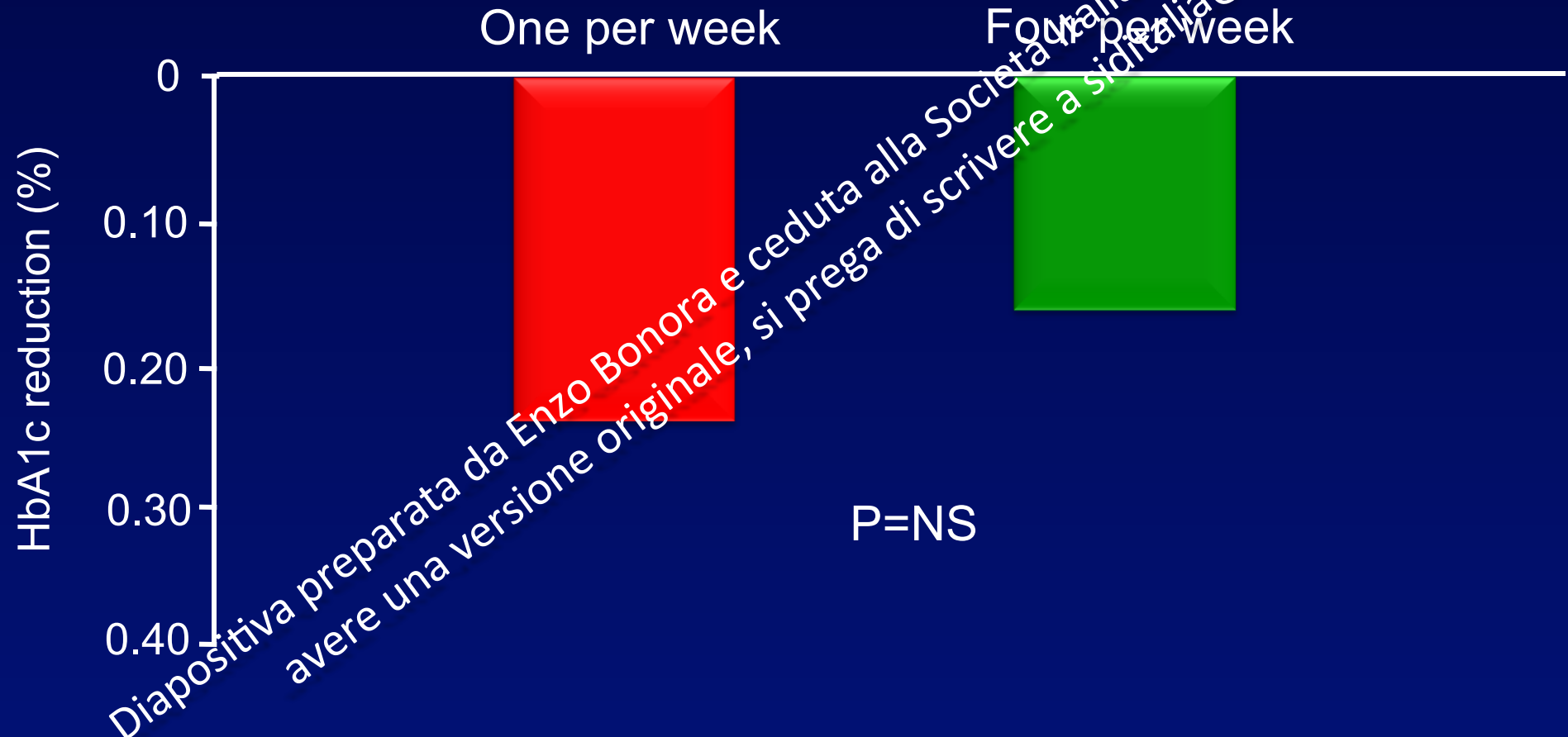
(Bonomo et al – Diab Res Clin Pract 87: 246, 2016)



N=273, age 63 yr, duration 10 yr, HbA1c 8.0%, follow-up 6 months

Effect of less or more frequent SMBG on HbA1c in non-insulin-treated T2DM - A RCT

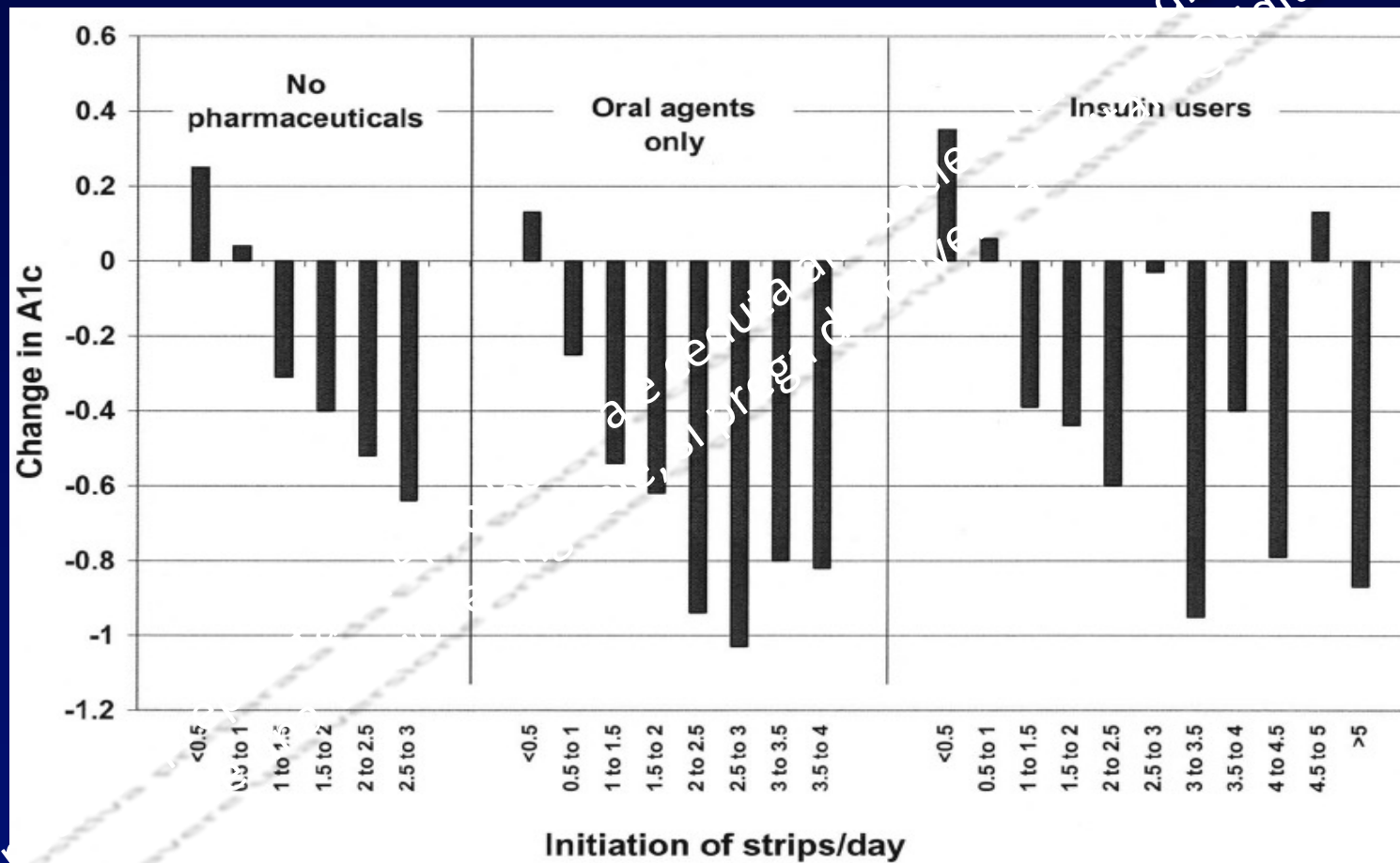
(Scherbaum et al – PLoS One 3: e3087, 2008)



N=202, age 61 yr, duration 7.8 yr, HbA1c 7.2%, follow-up 6 months; OAD ± insulin

Effect of less or more intense SMBG initiation on 4-yr HbA1c change in 16,901 T2DM patients

(Karter et al – Diabetes Care 29: 1757, 2006)



Models adjusted for age, sex, insulin injection frequency (insulin model only), comorbidity index, oral medication refill adherence (OHA model only), appointment keeping, inpatient and outpatient utilization, smoking status, type of primary care provider, socioeconomic status indicators, timing of A1C test, and baseline A1C.

Reasonable strategy of glucose monitoring in uncontrolled and/or insulin-treated T2DM - 12 Strips per Week

Time of the day

Day of the week

	7	9	13	15	20	22
1	X	X				
2			X			
3					X	X
4		X				
5			X	X		
6					X	X

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

Acceptable strategy of glucose monitoring in well controlled and SU-treated T2DM - Six Strips per Week

Time of the day

Day of the week	7	9	13	15	20	22
1	X	X				
2						
3			X	X		
4						
5					X	X
6						

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

Sustainable strategy of glucose monitoring in well controlled and no SUI-treated T2DM - 6 Strips per Month

Time of the day

Day of the month

	7	9	13	15	20	22
5	X	X				
10						
15			X	X		
20						
25					X	X
30						

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

Glucose readings in 50 consecutive Type 2 diabetic patients

	% of patients
Before breakfast	90
After breakfast	17
Before lunch	35
After lunch	69
Before dinner	58
After dinner	41

Not bad!

Glucose readings in 50 consecutive Type 2 diabetic patients

	% of readings
Before breakfast	83
After breakfast	0.9
Before lunch	2.7
After lunch	1.4
Before dinner	7.9
After dinner	4.1

Readings exactly as requested: 3% of patients!

Key messages of the talk

- Glycemic targets are not limited to HbA1c because the latter does not describe fasting, pre-prandial, post-prandial plasma glucose and neither plasma glucose excursions with meals, i.e. the glycemic phenotype, which should be the guide for treatment decisions
- HbA1c does not unveil post-prandial peaks, hypoglycemia and glucose variability, which have been associated to a poorer outcome
- HbA1c is not always reliable due to high/low Hb susceptibility to glycation, certain clinical conditions or analytical problems
- SMBG provides information on daily glycemic profile and help to reach and maintain a better glycemic control
- SMBG seems to be associated to a better outcome

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

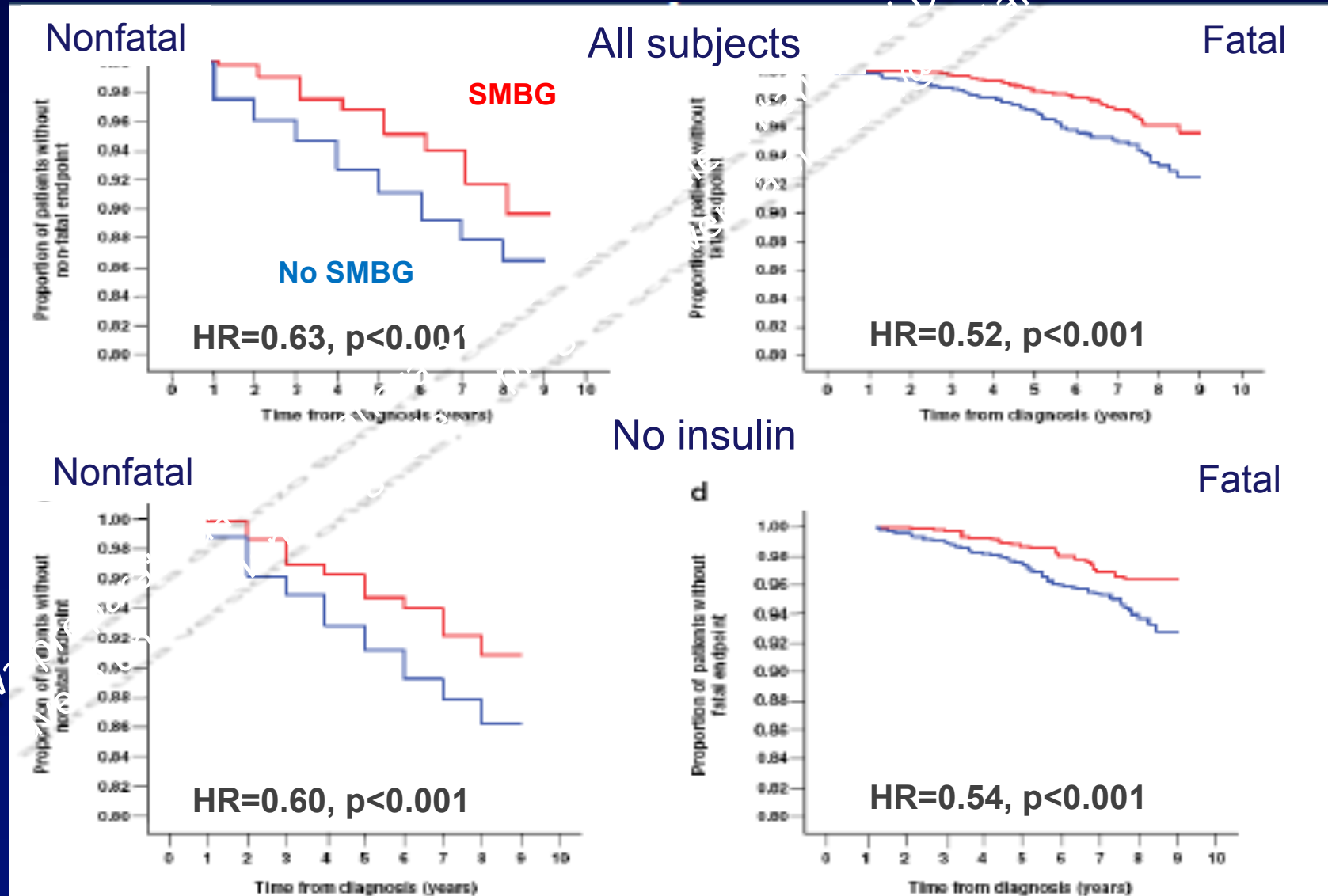
Survival without nonfatal and fatal endpoints in newly diagnosed T2DM according to SMBG

(ROSSO Study; Martin et al - Diabetologia 49: 271, 2006)

Retrospective
German
observational
study (ROSSO)
N=3,268
Age 62 yr,
HbA1c 7.8%,
follow-up 6.5 ± 1.6
yr

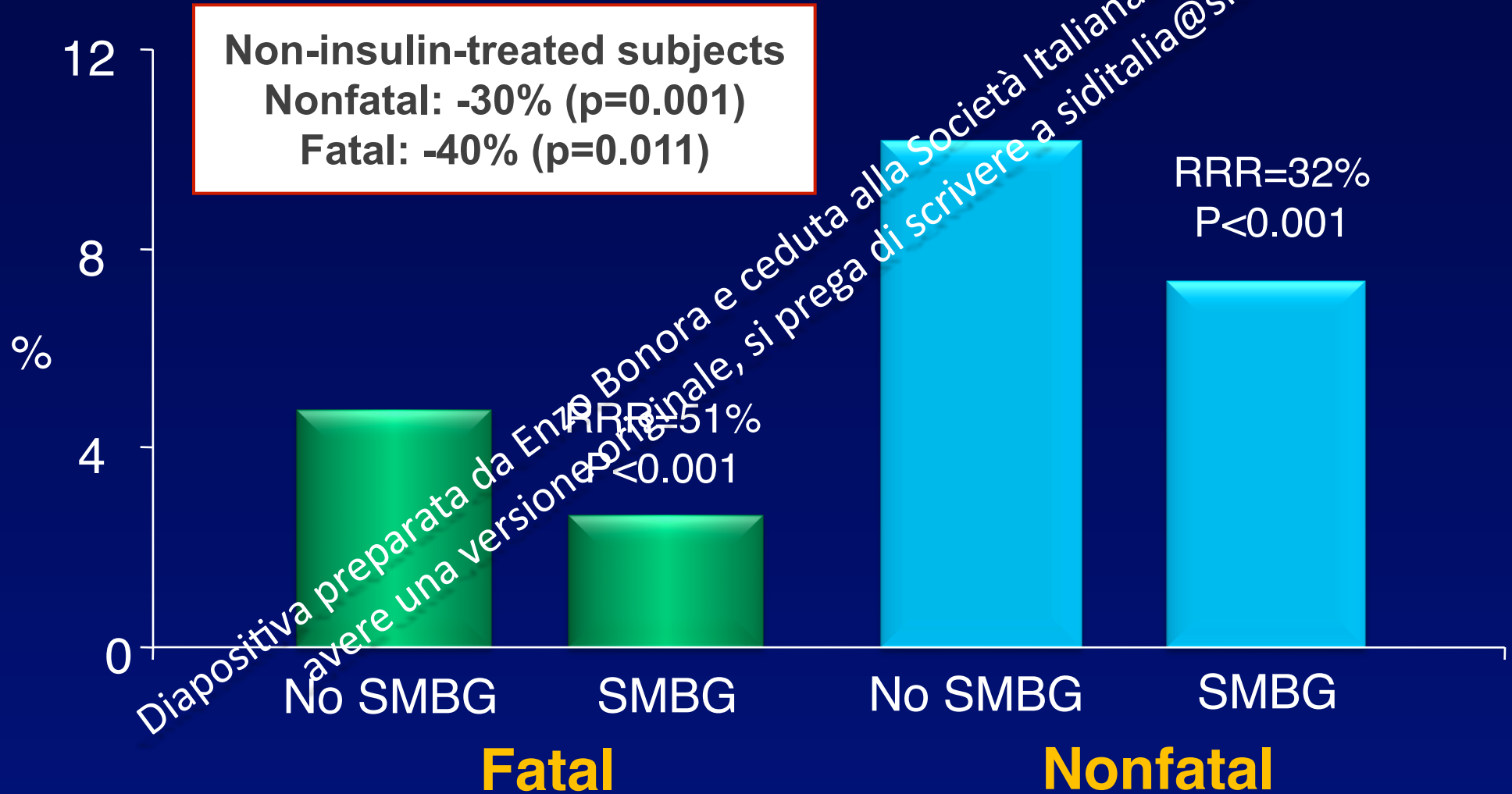
No insulin
n=2,515

Endpoints
Fatal=all-cause
mortality
Nonfatal=macro-
+microvascular
events



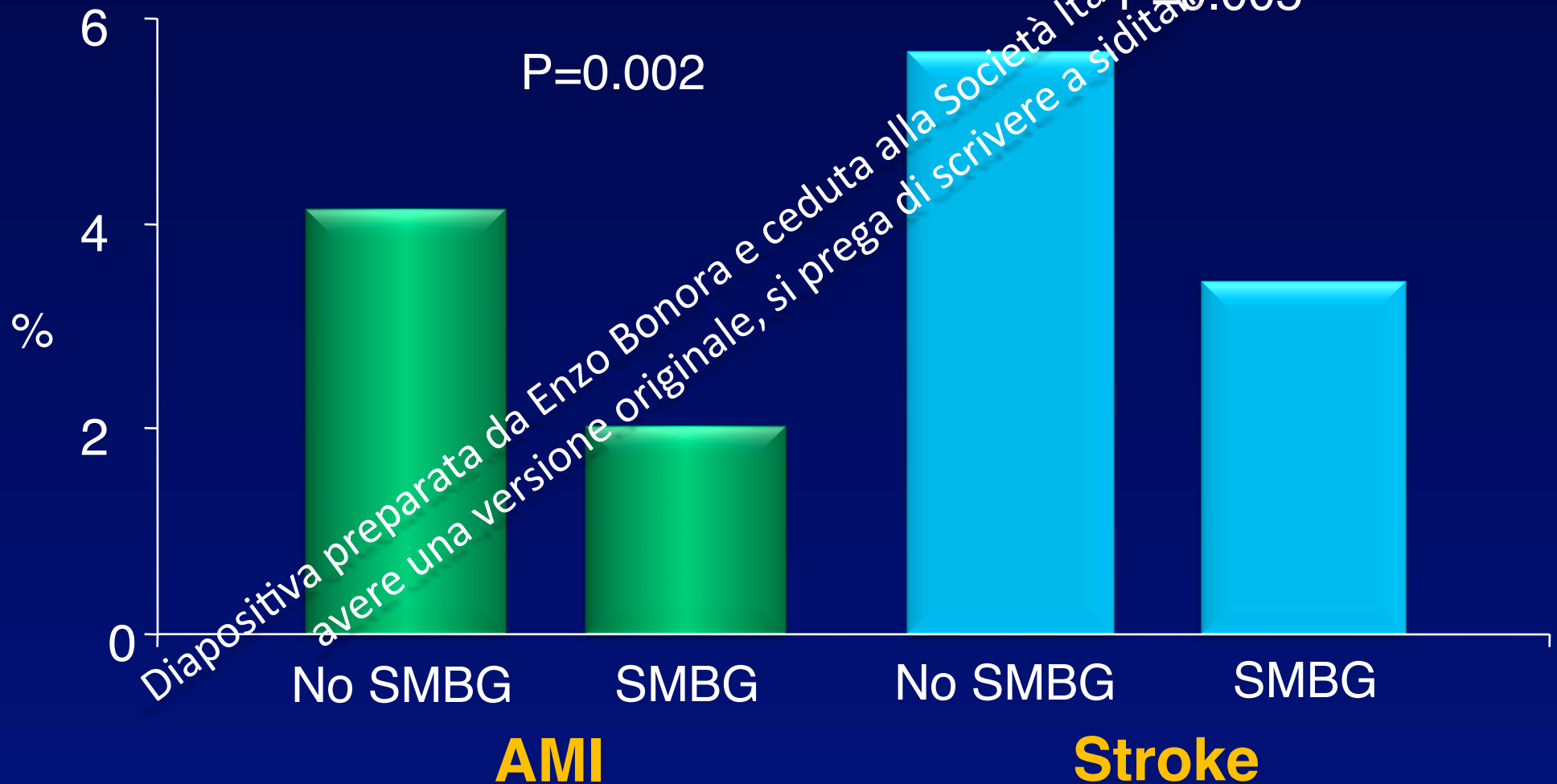
Fatal and nonfatal cumulative incidence according to SMBG in newly-diagnosed T2DM

(ROSSO Study; Martin et al - Diabetologia 49: 271, 2006)



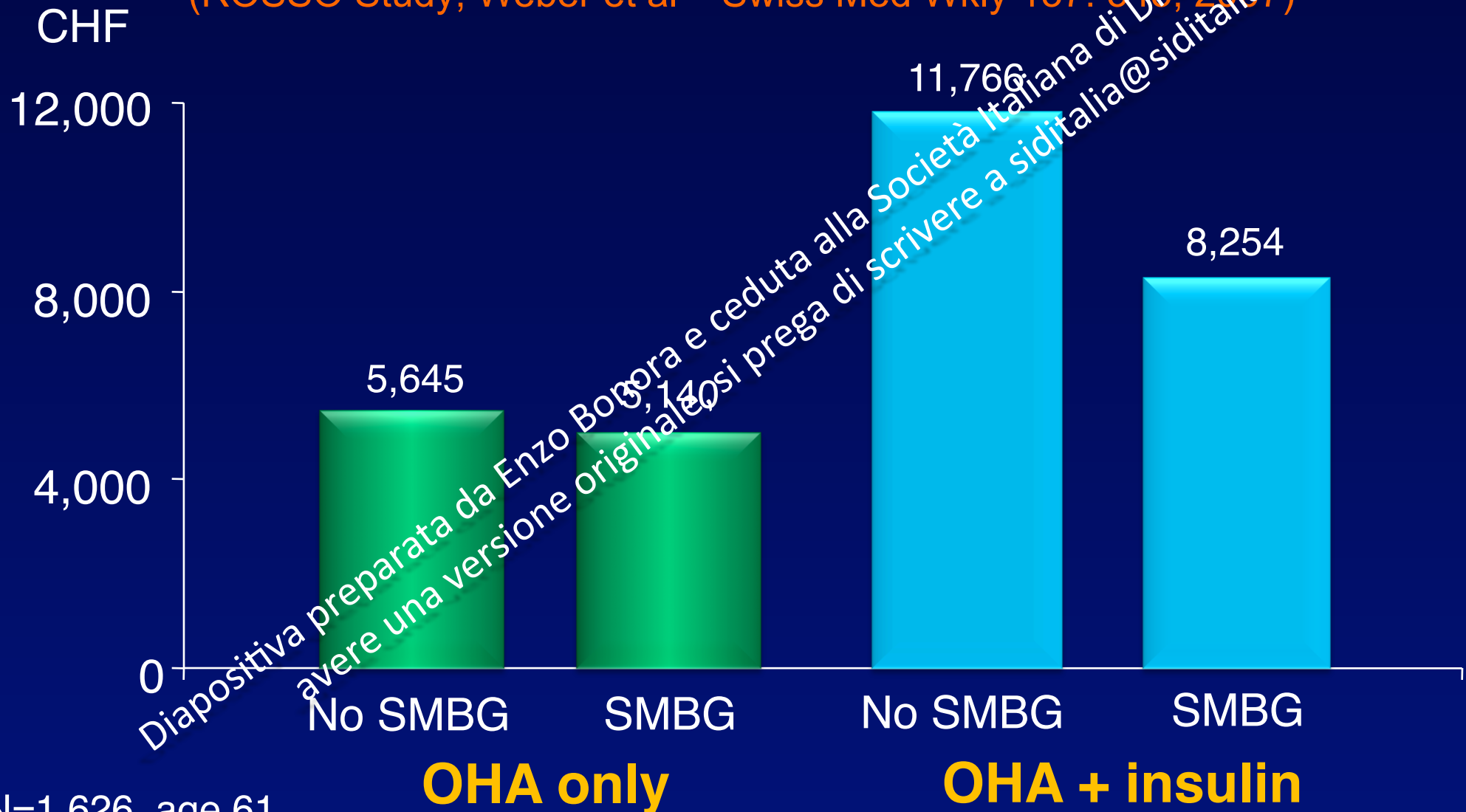
Cumulative incidence of myocardial infarction and stroke according to SMBG in newly-diagnosed T2DM

(ROSSO Study; Martin et al – Diab Techn Therap 11: 234-2009)



Cost impact of SMBG on diabetes complications in T2DM

(ROSSO Study; Weber et al – Swiss Med Wkly 137: 546, 2007)



Conclusions (1)

- Study results vary and not few of them do not support a benefit of regular SMBG on HbA1c, especially in non-insulin-treated type 2 diabetic subjects.
- A benefit was mainly observed in newly-diagnosed patients, poorly-controlled patients, compliant patients, subjects who can efficaciously modify the therapy.
- In order to have a clear benefit, SMBG should be done in an appropriate way (structured testing), after a specific training and with a frequent feed-back with health care professionals: measuring without reacting when necessary (“active control”) is meaningless and not cost-effective.

Conclusions (2)

- Although in many subjects a clear benefit in terms of HbA1c might not be expected, still SMBG is crucial to detect hypoglycemia, to identify post-prandial peaks, to appreciate glucose variability, to understand the impact of foods and exercise on glycemia, to verify the efficacy of anti-diabetic drugs, to promptly unveil decompensation during intercurrent illness or stress, to have patients more responsible and participating in diabetes care.
- SMBG is also mandatory when HbA1c assessment is unreliable (analytical problems, particular conditions) or in subjects with a dissociation between glycemia and HbA1c (high or low “glycators”).
- The control of post-prandial glucose is among glycemic goals included in standard of care recommended by IDF, ADA and many other national diabetes societies. Therefore.....

Question: HbA1c, SMBG or both?

EBM Answer: Both!!!

EBM =

Evidence Based Medicine or
Enzo Bonora Medicine

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.

The end
Thank you so much



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

Verona, Italy
The Opera at the Roman Arena