Corso "Aspetti Metabolici del Rischio Cardiovascolare: Come affrontarli in maniera efficace"

Desenzano del Garda (BS), 21-22 Ottobre 2011

Malattie cardiovascolari nel diabete mellito

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Endocrinologia e Malattie Metaboliche

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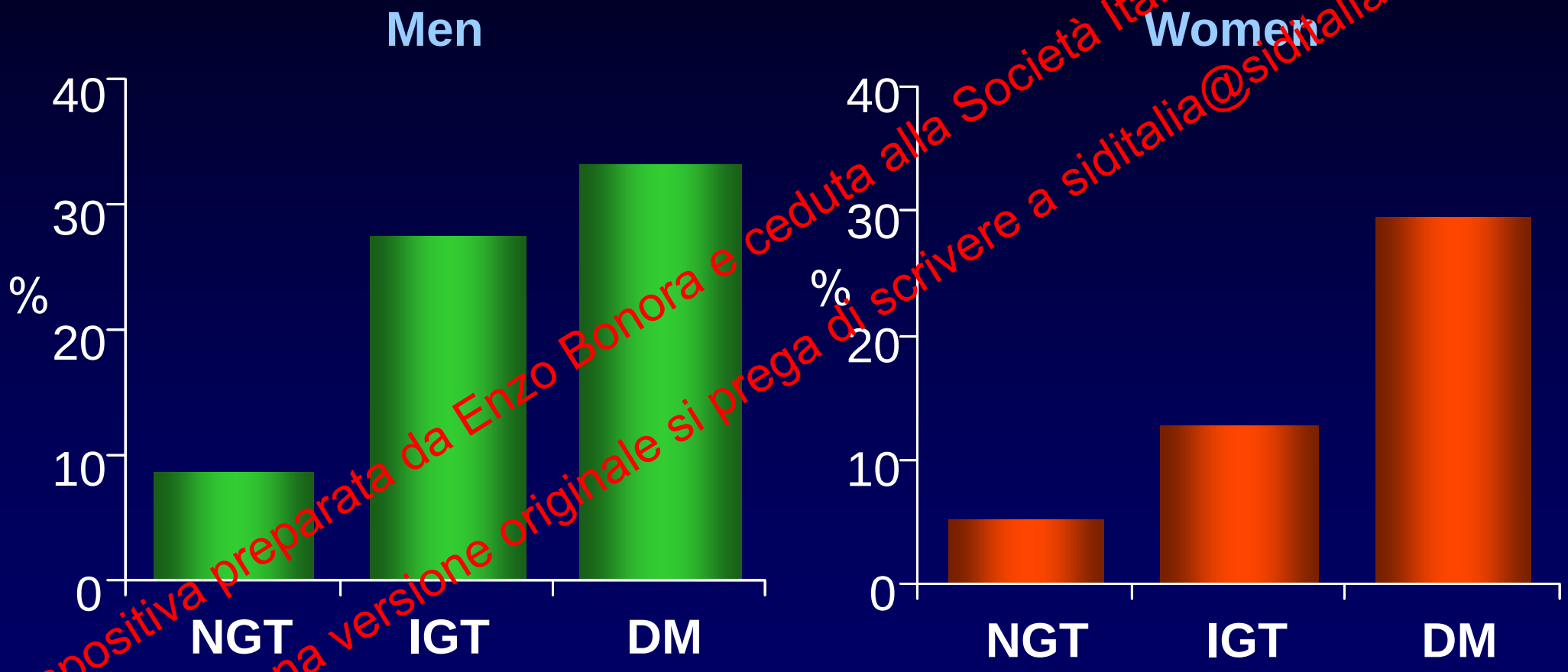
Menu of Today

- Prevalence of CVD in diabetes
- Incidence of CVD in diabetes
- Outcome after AMI and stroke in diabetes
- Risk factors of CVD in diabetes: not only glucose but….
- Don’t neglect glucose/HbA1c

CHD According to Glucose Tolerance

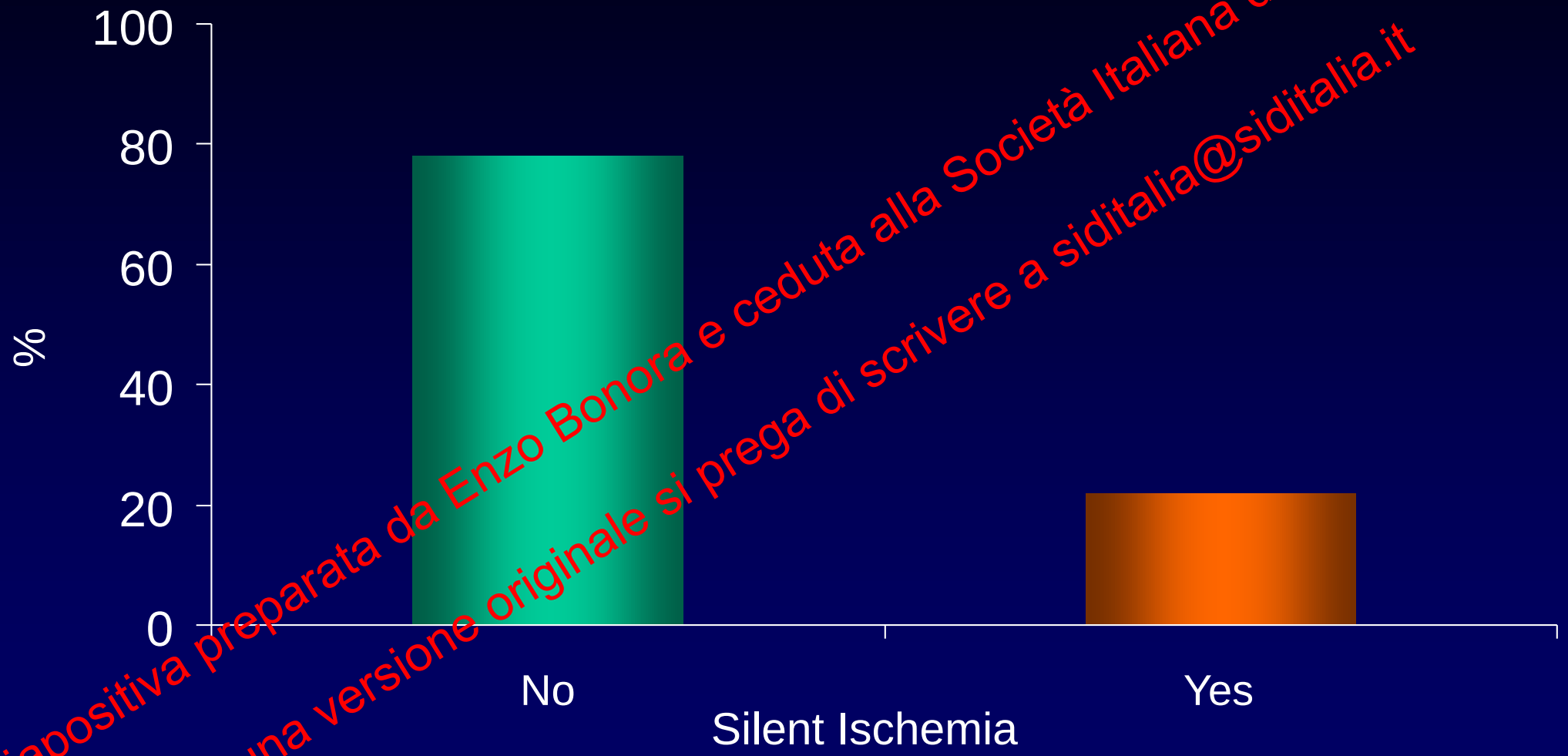
(Bruneck Study; Bonora et al, Diabetes Care 21: 221, 1998)



N=914, age 40-79 years. CHD definite+probable+possible.

Silent Myocardial Ischemia in T2DM

(DIAD Study; Wackers et al, Diabetes Care 27:1954, 2004)



N=532, age 50-75, asymptomatic+normal ECG, positive stress scintiscan

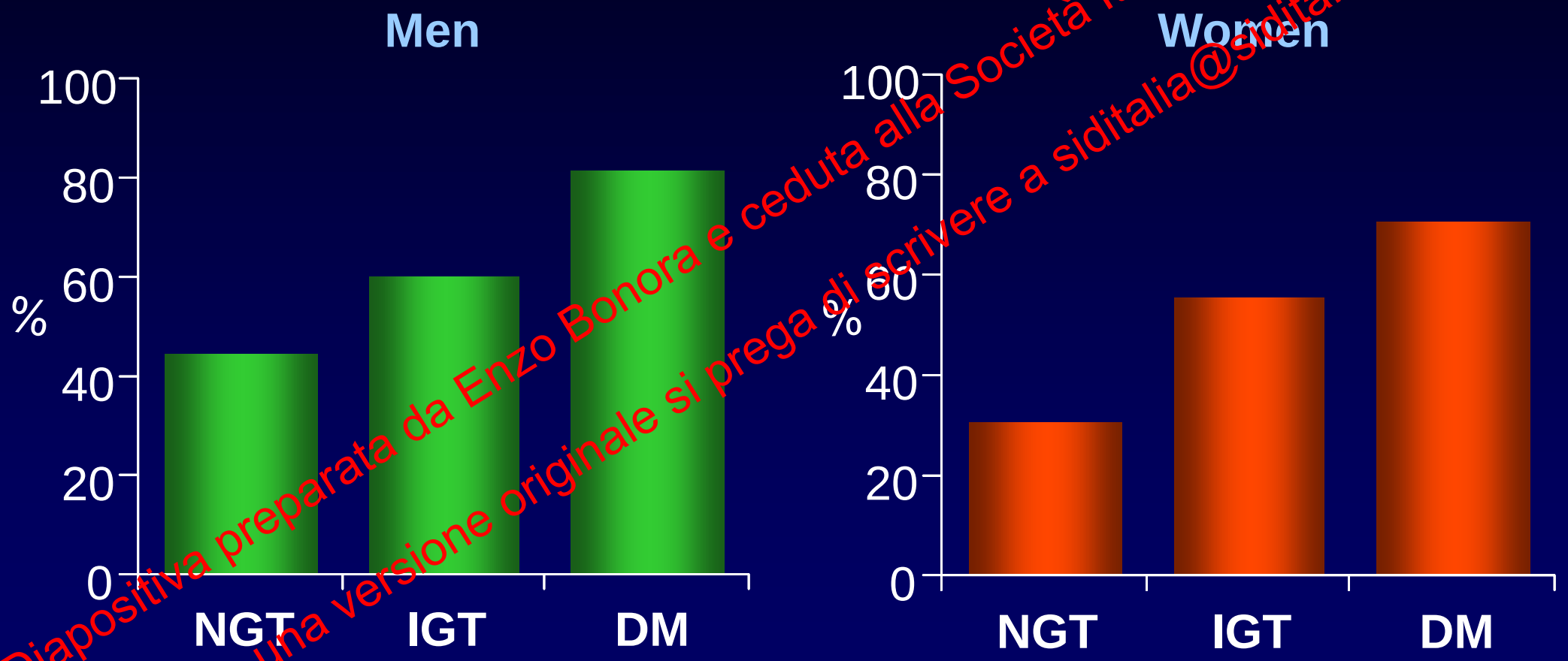
CHD in Type 2 Diabetes

As many as 50% of T2DM patients have CHD.

As many as 50% of those affected are undiagnosed (because they are asymptomatic and have normal ECG).

Carotid Atherosclerosis (Any Plaque, Any Size) According to Glucose Tolerance

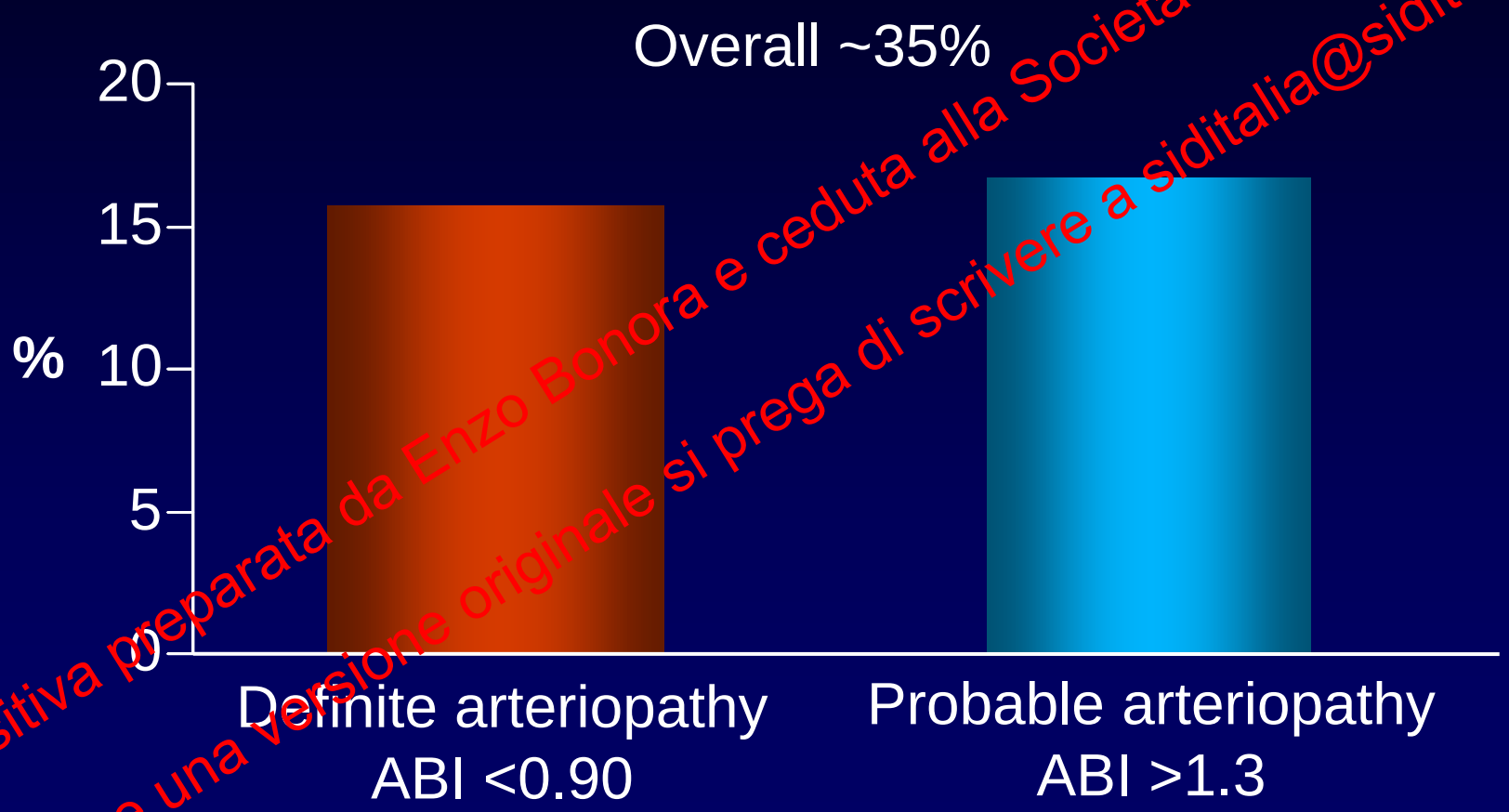
(Bruneck Study; Bonora et al, Stroke 28: 1147, 1997)



N=914; age 40-79 years. Plaques of any size in CCA/ICA.

Prevalence of lower limb arteriopathy in T2DM by ankle/brachial index (Winsor Index)

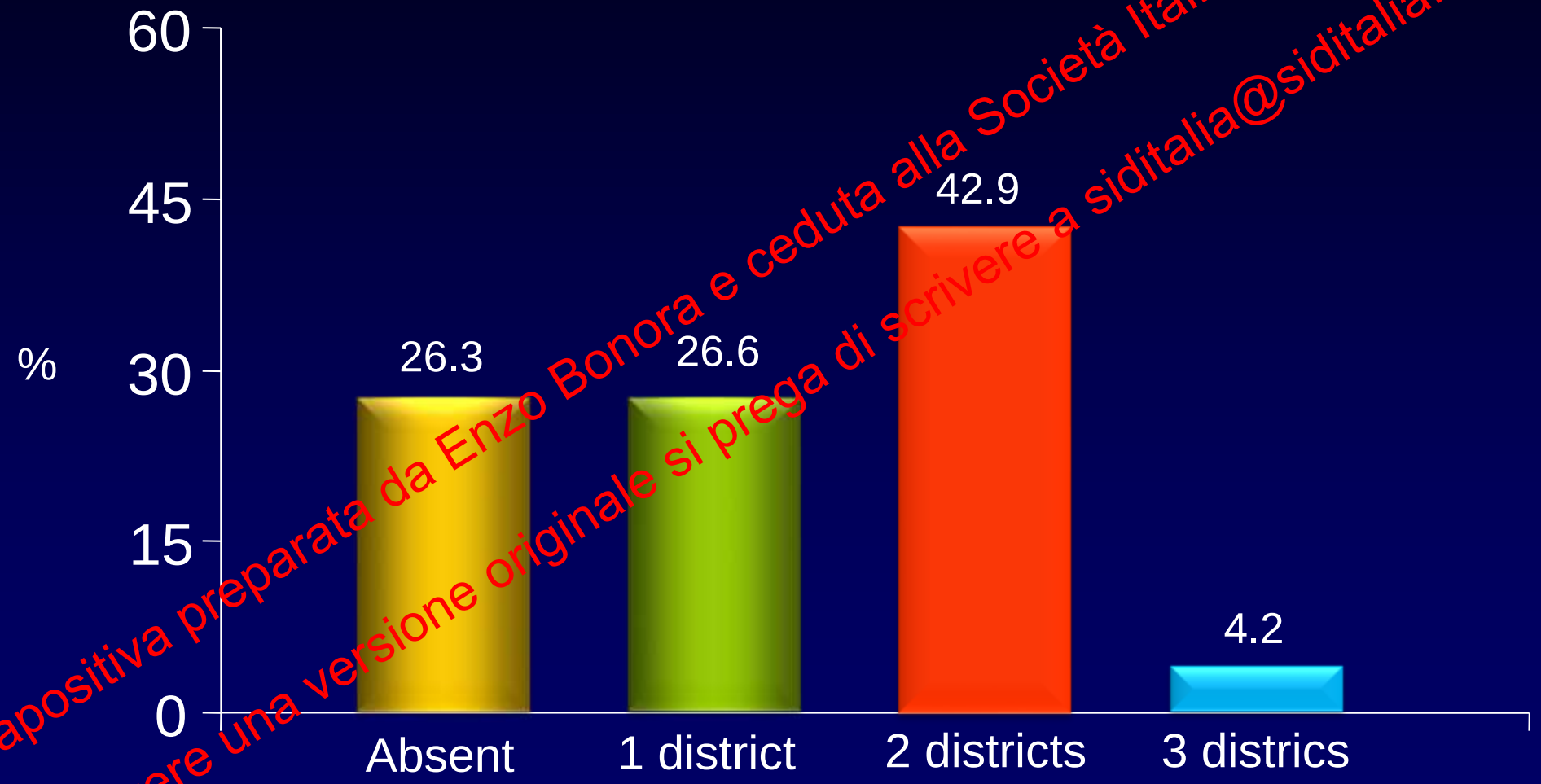
(Verona Diabetes Study; Bonora et al, unpublished)



N=1380

Prevalence of macrovascular disease in newly diagnosed type 2 diabetic subjects

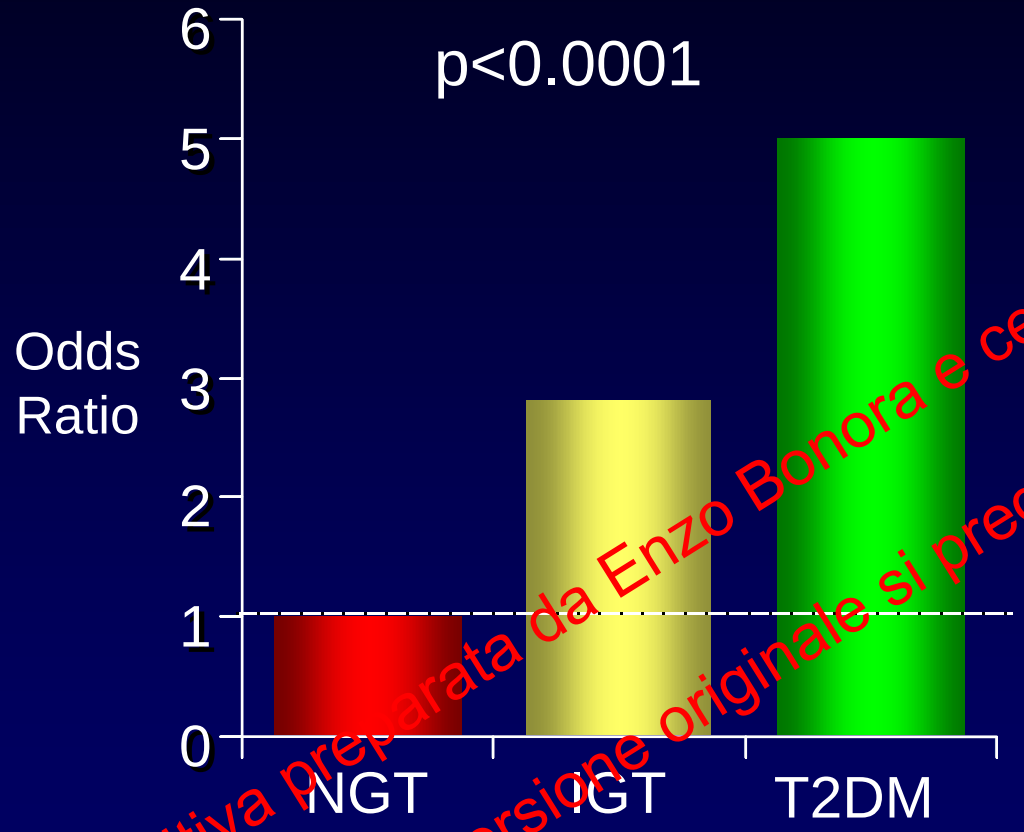
(Verona Newly Diagnosed Type 2 Diabetes Study; unpublished)



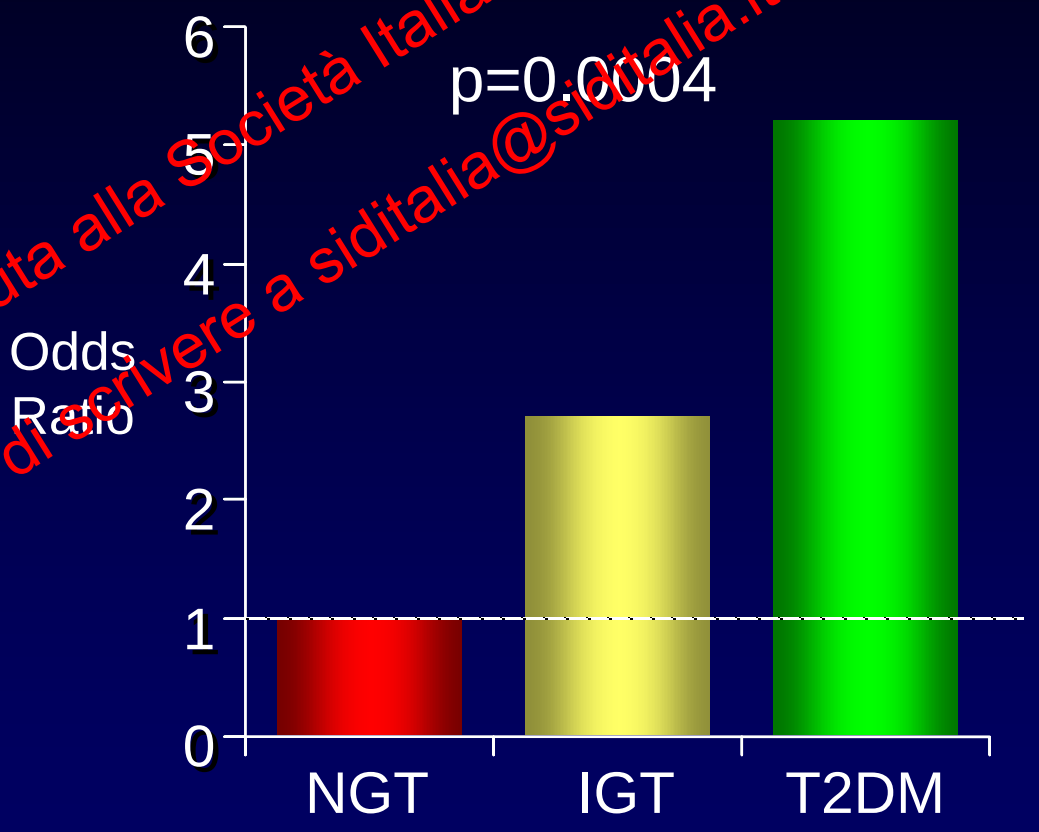
N=595; clinical history, baseline ECG, carotid and lower limb echodoppler

Incident of Stenotic Carotid Atherosclerosis According to Glucose Tolerance

(Bruneck Study; Bonora et al, Diabetologia 43: 156, 2000)



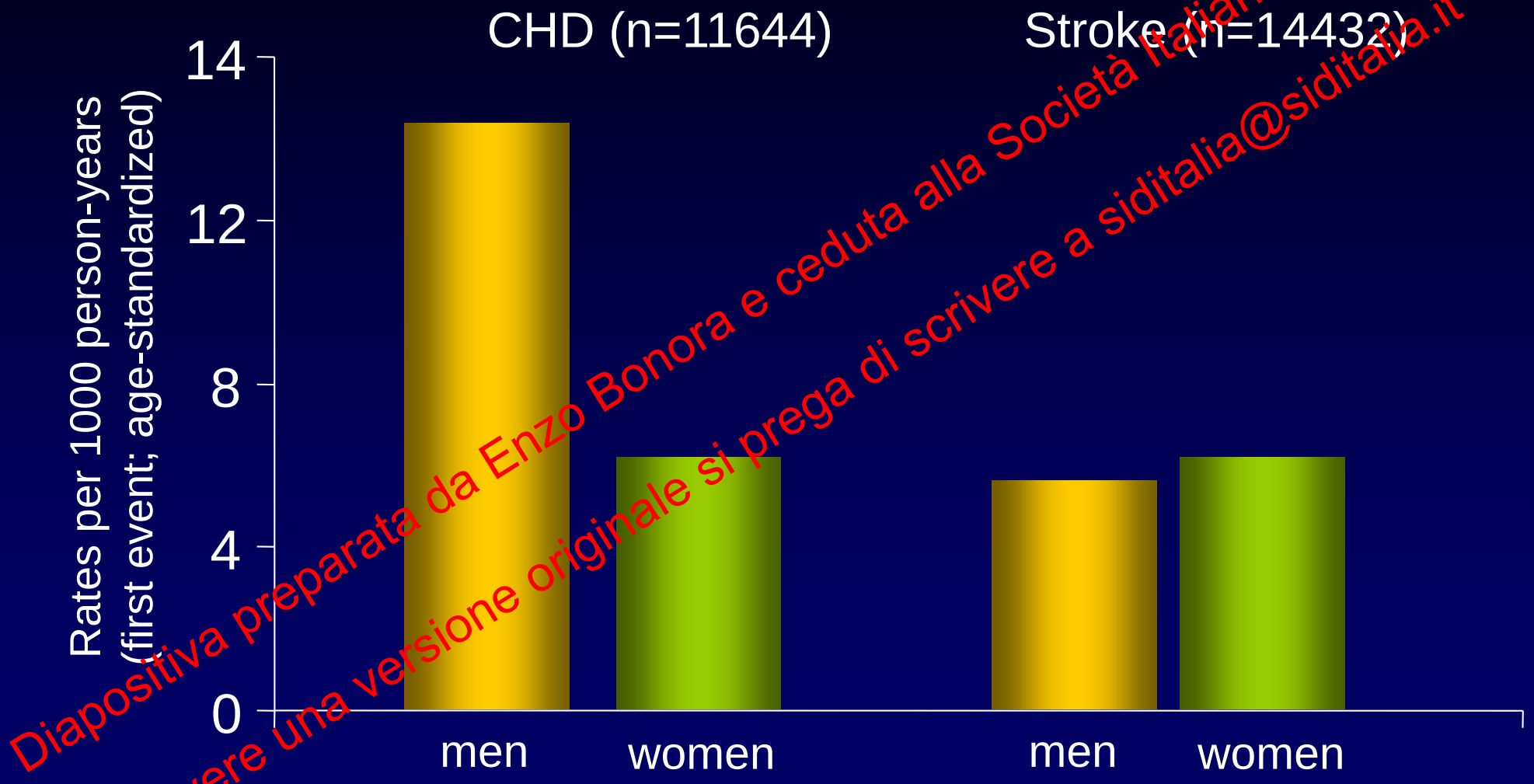
N=888. Adjusted for age, smoking, alcohol, fibrinogen, antithrombin III, factor V mutation, Lp(a) >32mg/dl



N=888. Adjusted also for BMI, WHR, hypertension, Apo A & B, TG, urate, insulin, ferritin, physical activity, leukocyte count

Incidence of CHD and Stroke in Type 2 Diabetes in Italy

(DAI Study; Avogaro et al, Diabetes Care 2007; Giorda et al, Stroke 2007)



CHD = AMI, CABG, PTCA; follow-up 4 years

Incidence of CVD in Type 2 Diabetes

Within 10 years

~1 man out of 8 and 1 woman out of 16

will suffer from myocardial infarction or will need revascularization

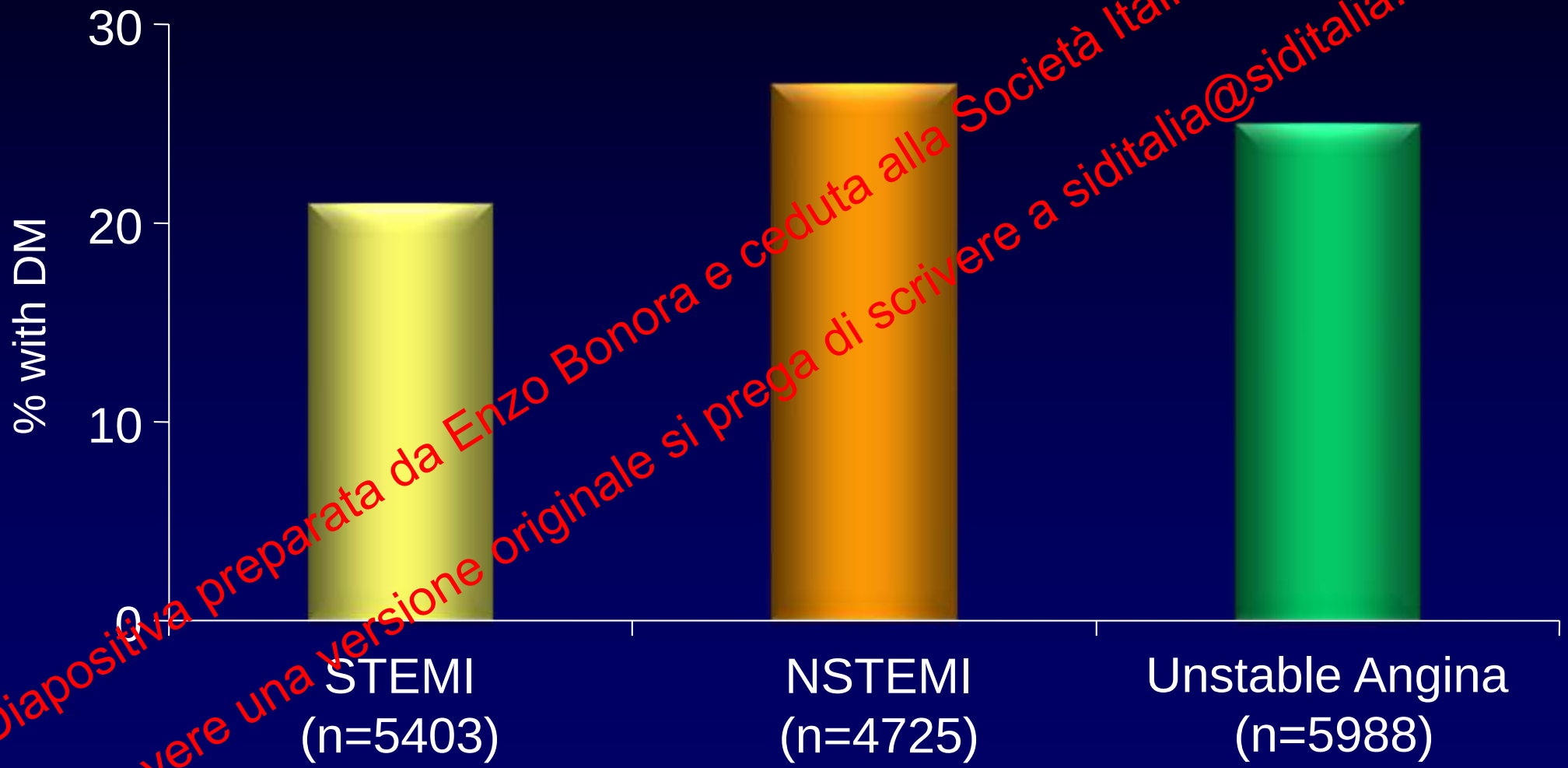
Within 10 years

~1 man out of 16 and 1 women out of 16

will suffer from stroke

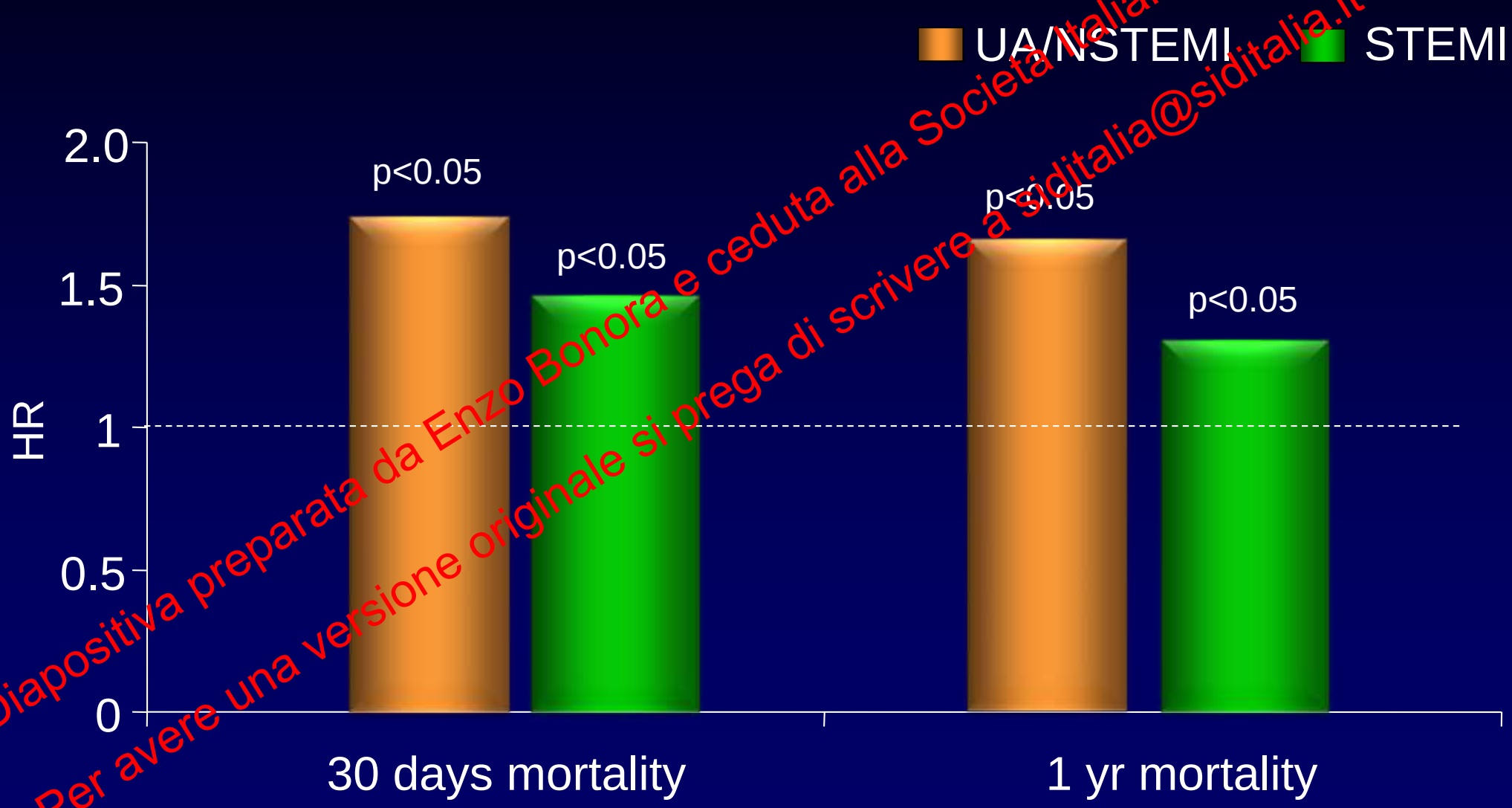
Diabetes in the Global Registry of Acute Coronary Syndromes

(GRACE Study; Franklin et al; Arch Intern Med 164:1457, 2004)



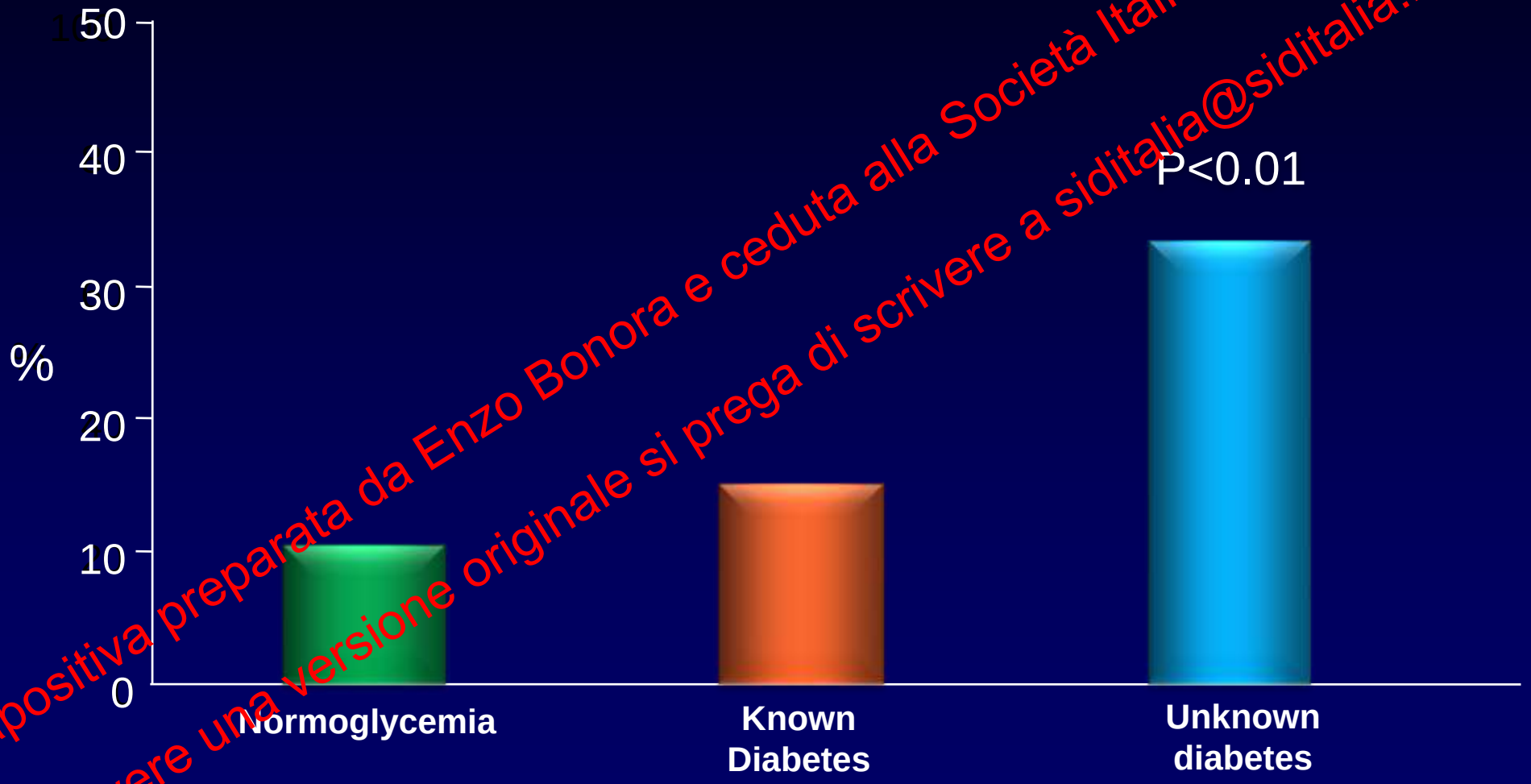
Mortality in Diabetes after Acute Coronary Syndromes

(Donahoe et al; JAMA 298: 765, 2007)



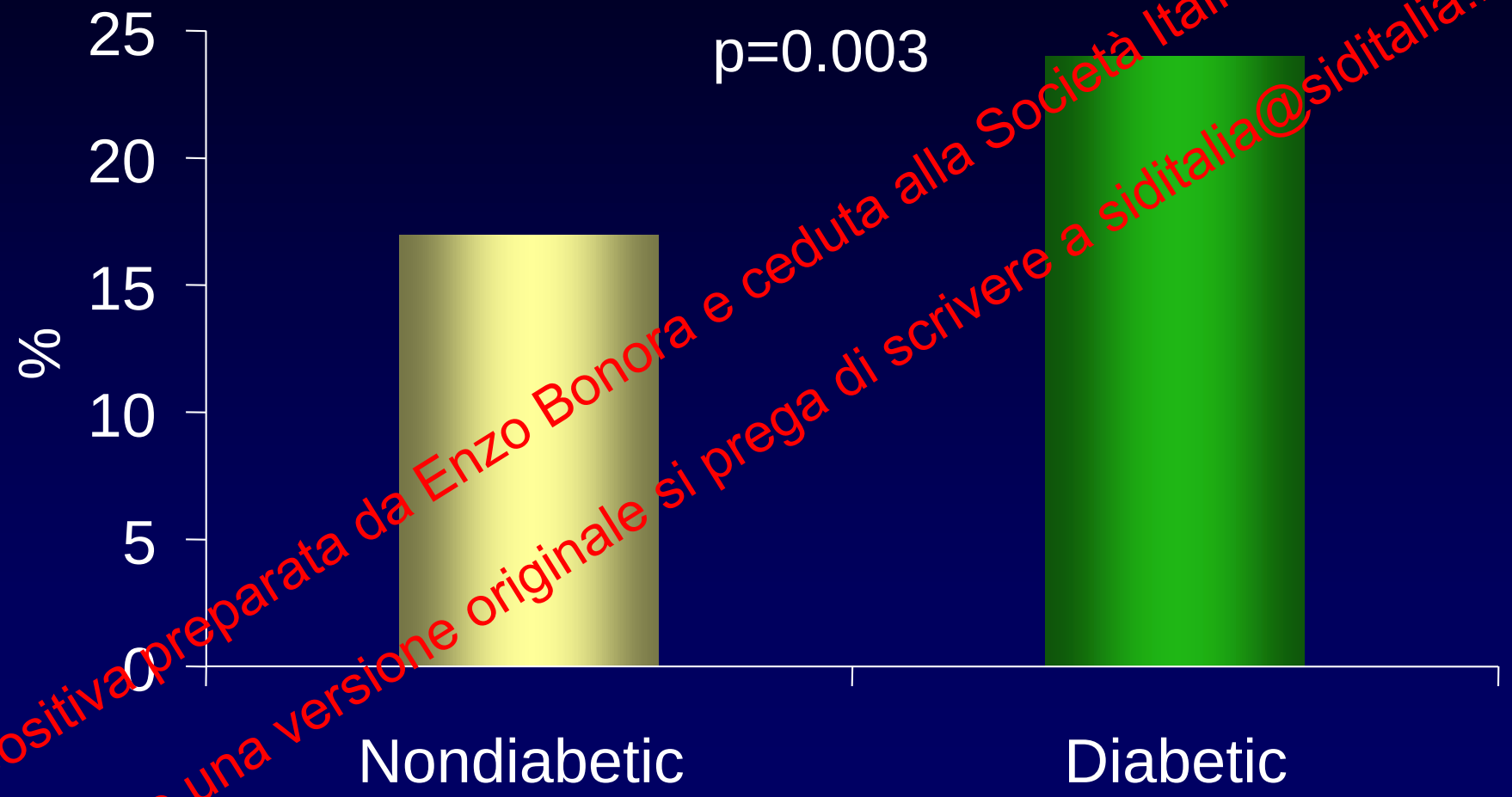
Very Early (ICU) Mortality in Patients with Unknown Diabetes is Higher than in Known Diabetes

(Umpierrez et al; JCE&M 87: 987, 2002)



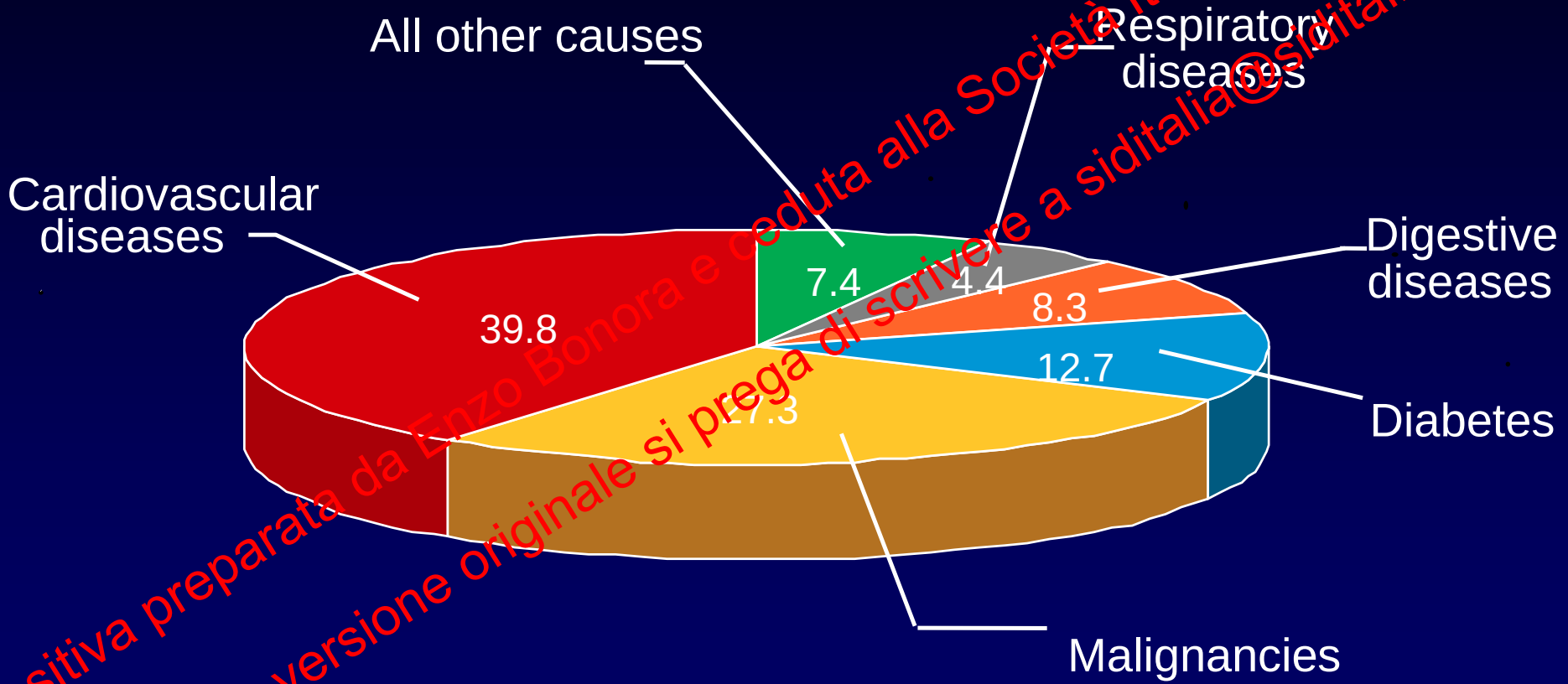
Early Mortality After First Stroke in Diabetic Patients

(Copenhagen Stroke Study; Stroke 344:156-159, 1994)



Cause-Specific Mortality in Type 2 Diabetes

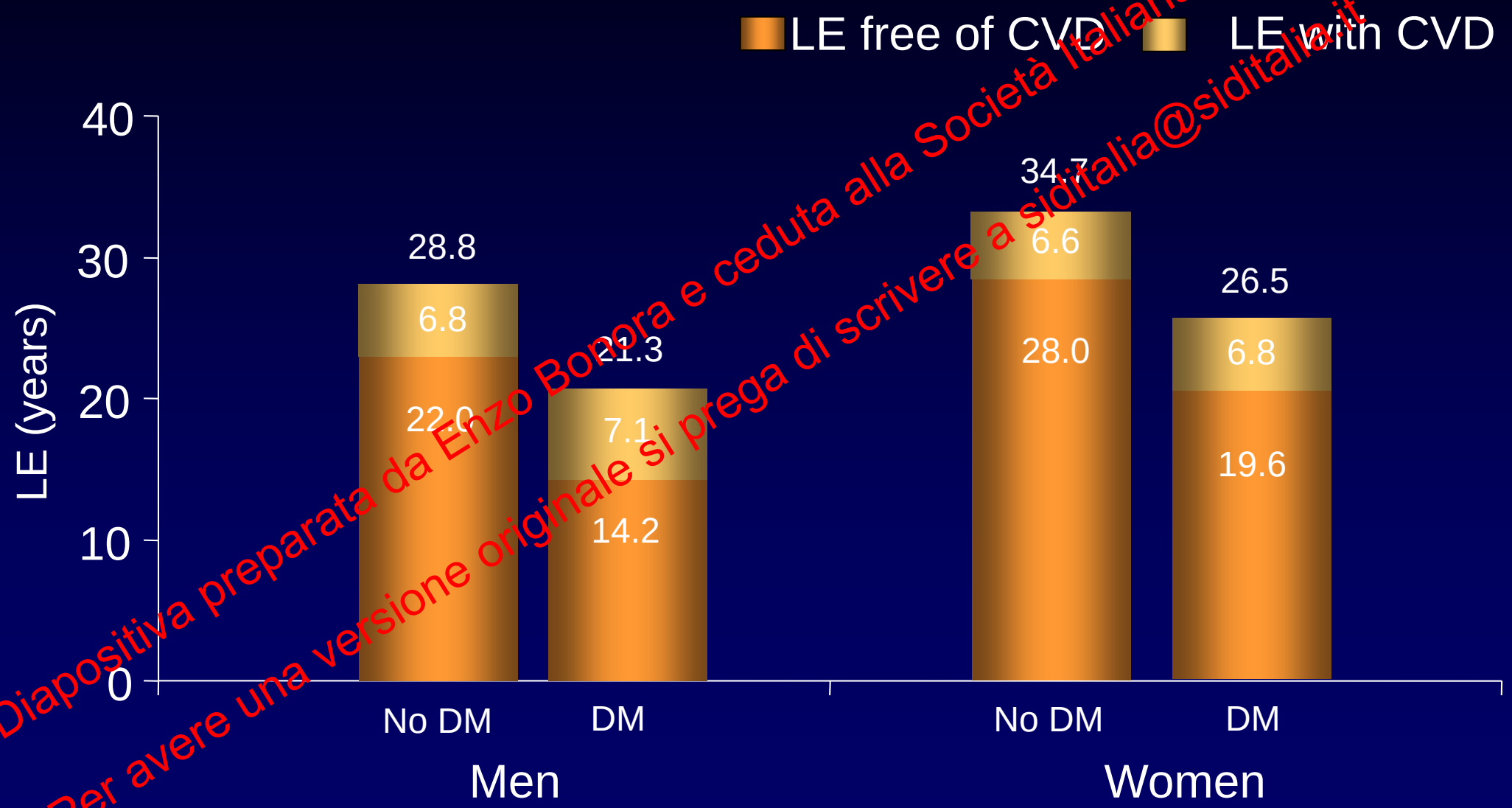
(Verona Diabetes Study; De Marco et al, Diabetes Care 22:756, 1999)



N=7148, 10-yr follow-up (1986-1995)

Life Expectancy with and without CVD at age 50 in Diabetic and Nondiabetic Subjects

(Franco et al; Archiv Int Med 167:1145, 2007)

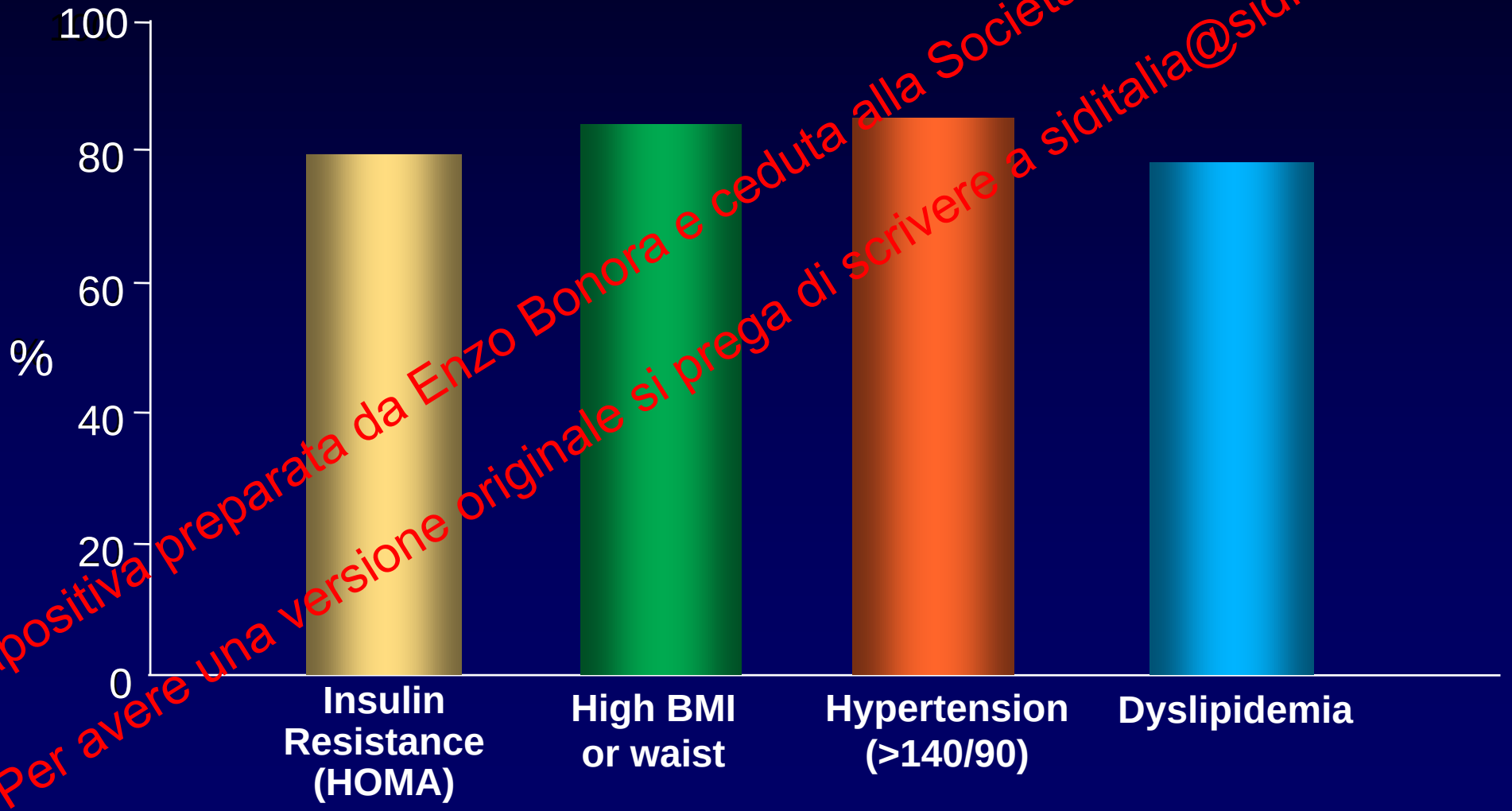


Question

Why are CHD and CVD so common in diabetes?

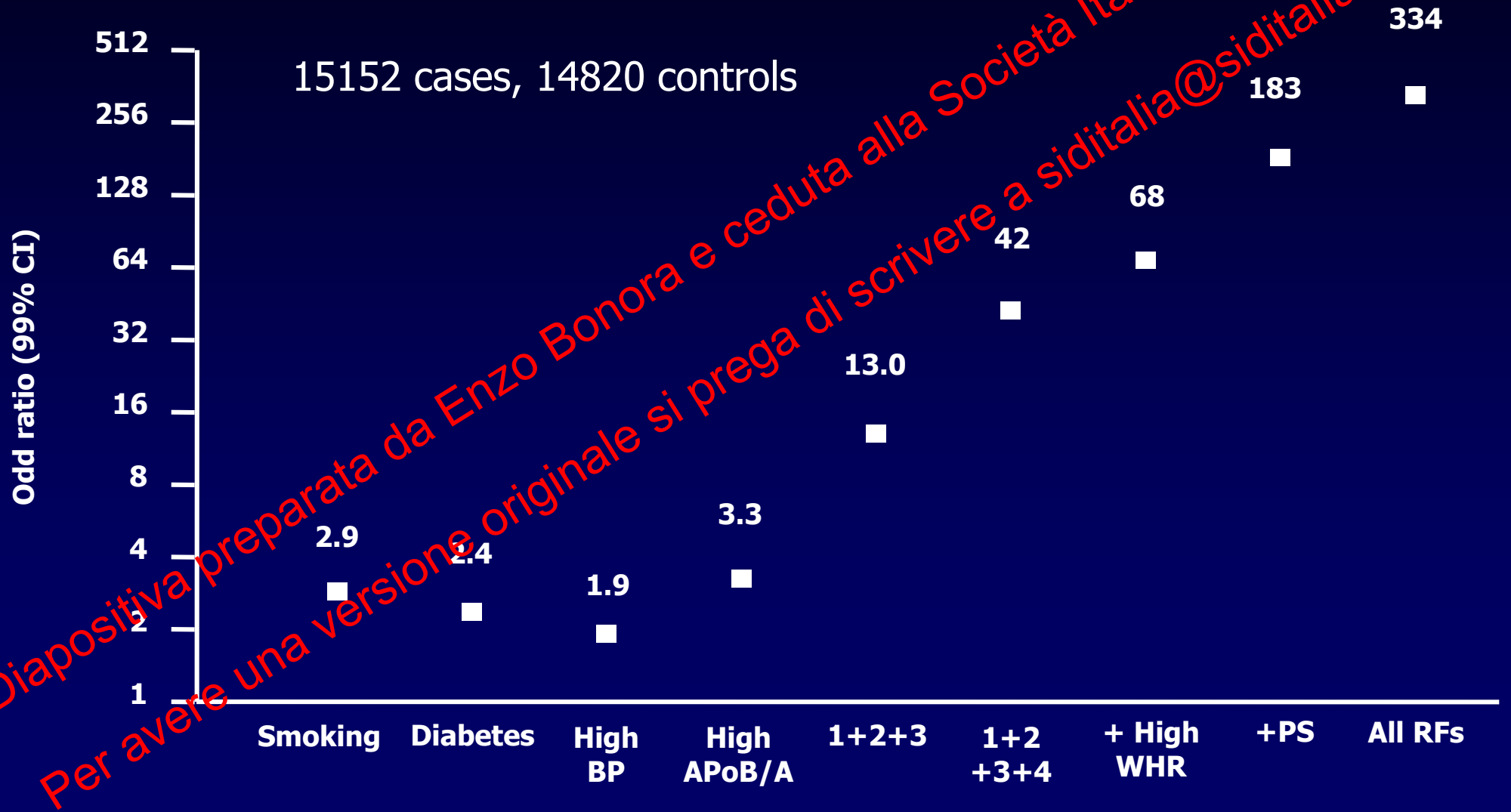
Prevalence of "Non-Glycemic" Cardiovascular Risk Factors in Subjects with T2DM

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



Risk Factors Associated with Myocardial Infarction: INTERHEART Study

(Yusuf S et al; Lancet 364: 937-952 , 2004)



The killing triad in type 2 diabetes

Hyperglycemia

Dyslipidemia

Hypertension

Predictors of CVD morbility and mortality (aggregate end-point) in patients with T2DM

(Verona Diabetes Complications Study, 1988-1998)

Variable	QR	p-value
Age (per year)	1.08	<0.001
Smoking (yes vs. no)	1.61	<0.001
Hypertension (yes vs. no)	1.27	0.003
Total/HDL cholesterol	1.25	<0.001
Mean HbA1c (per 1%)	1.21	<0.001

n= 871; age 64 yrs; duration 9 yrs; follow-up 4.5 yrs

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

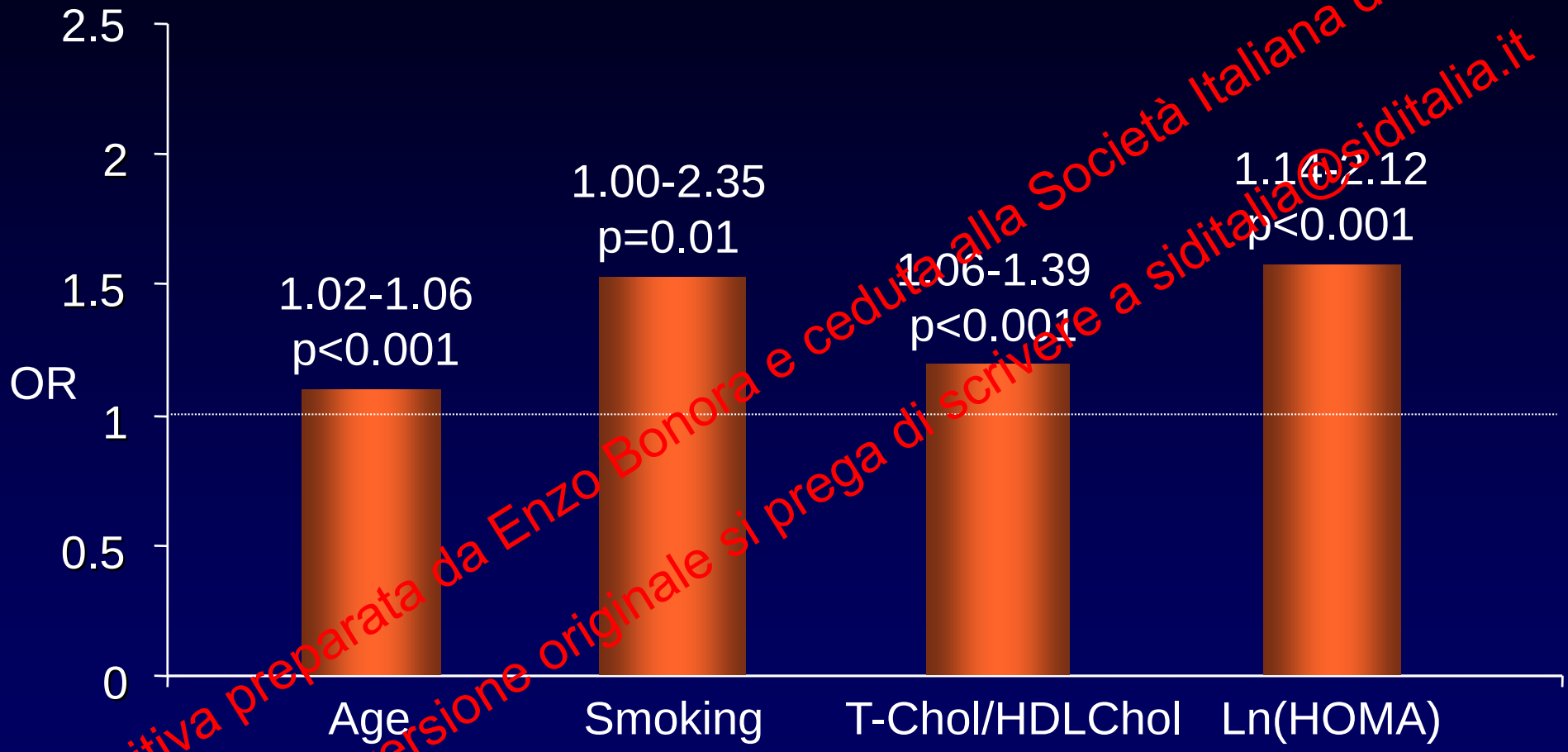
n= 559; age 65 yr; duration 9 yr; follow-up 4.5 yr

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: 1135, 2002)

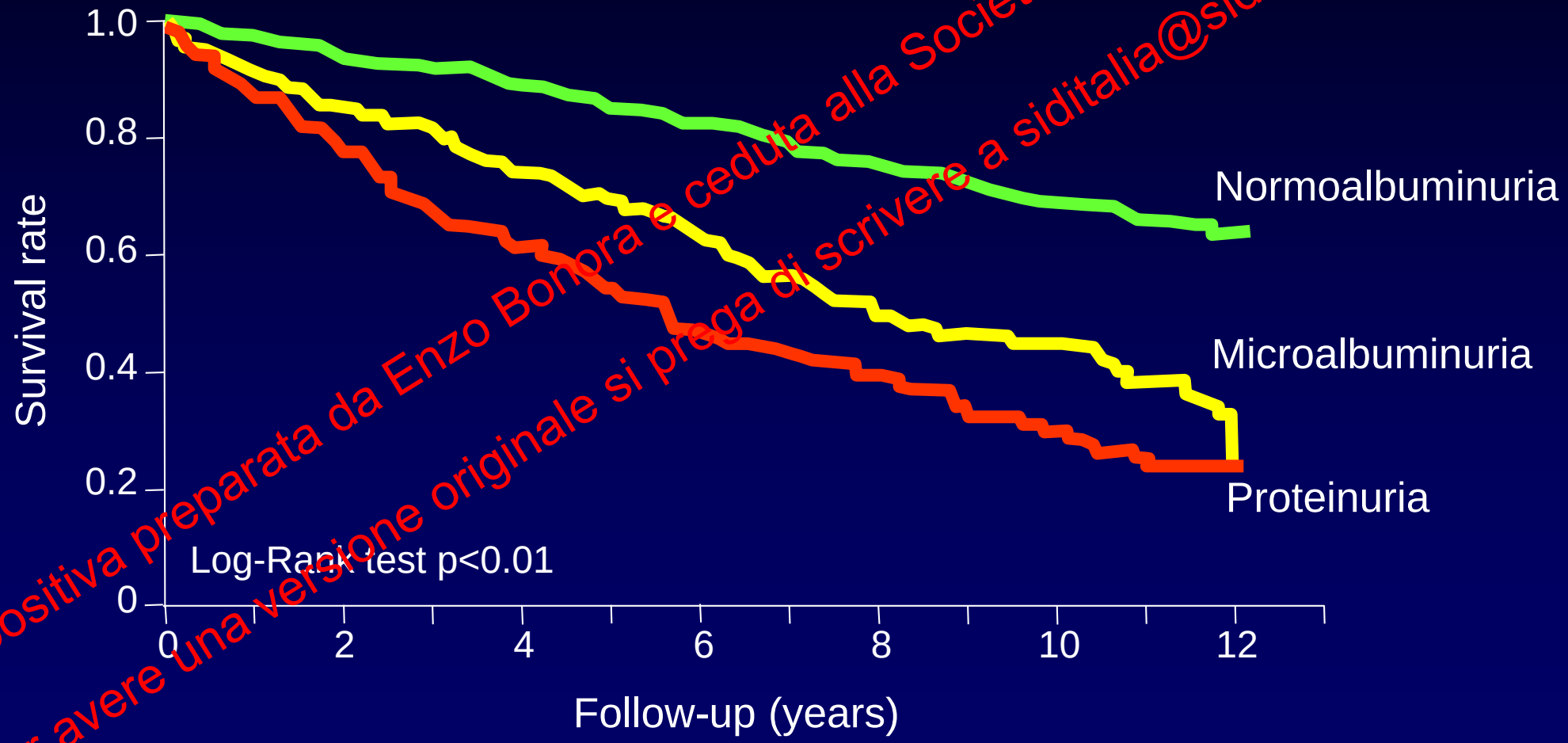


N=627, follow-up 4,5 yr. Model including also sex, duration, BMI, hypertension, HbA1c.

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

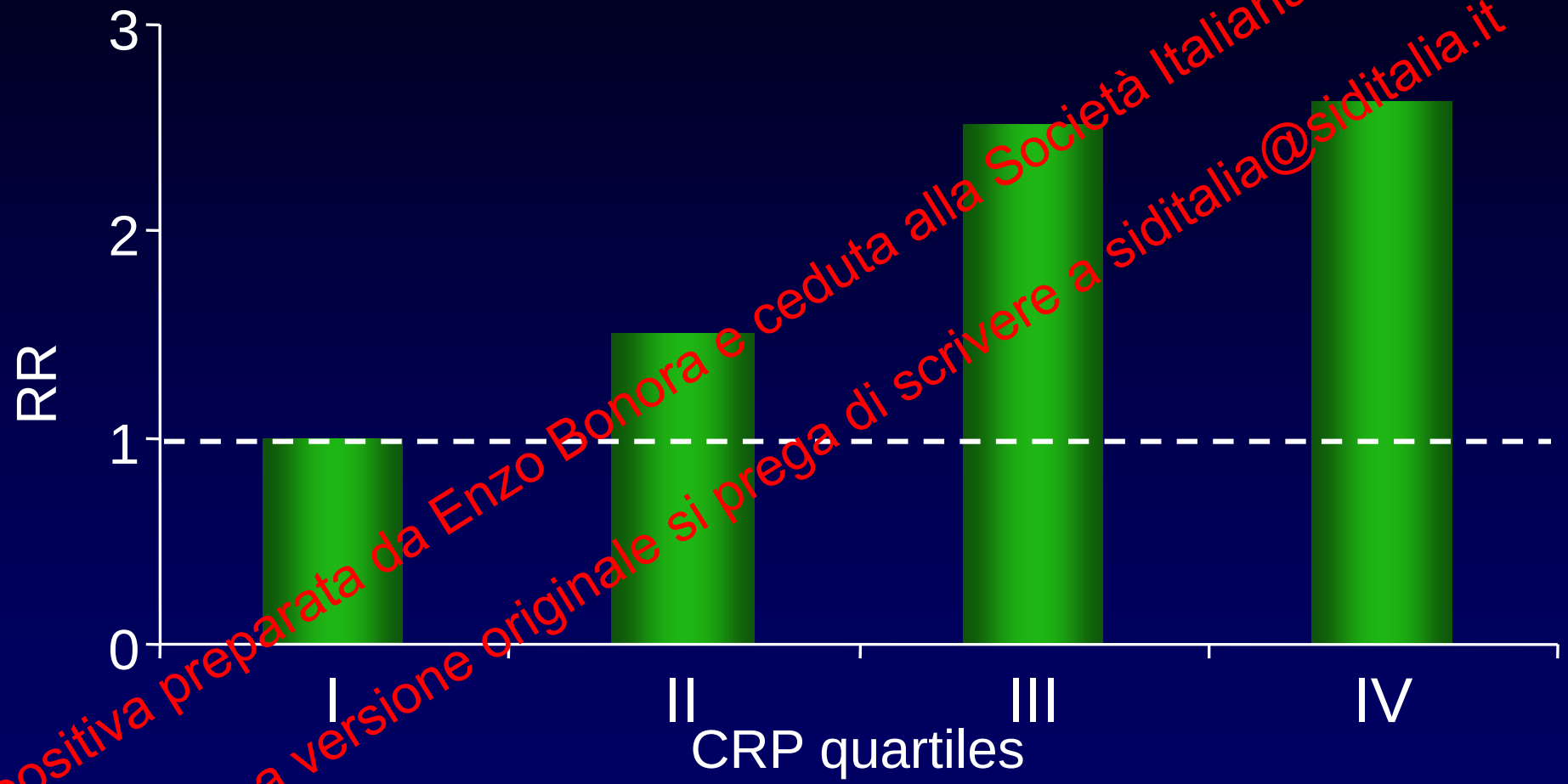
Microalbuminuria and Proteinuria Increase the Risk of Cardiovascular Mortality in T2DM

(Valmadrid CT et al; Arch Intern Med 2000)



CRP Predicts CVD in Men with T2DM

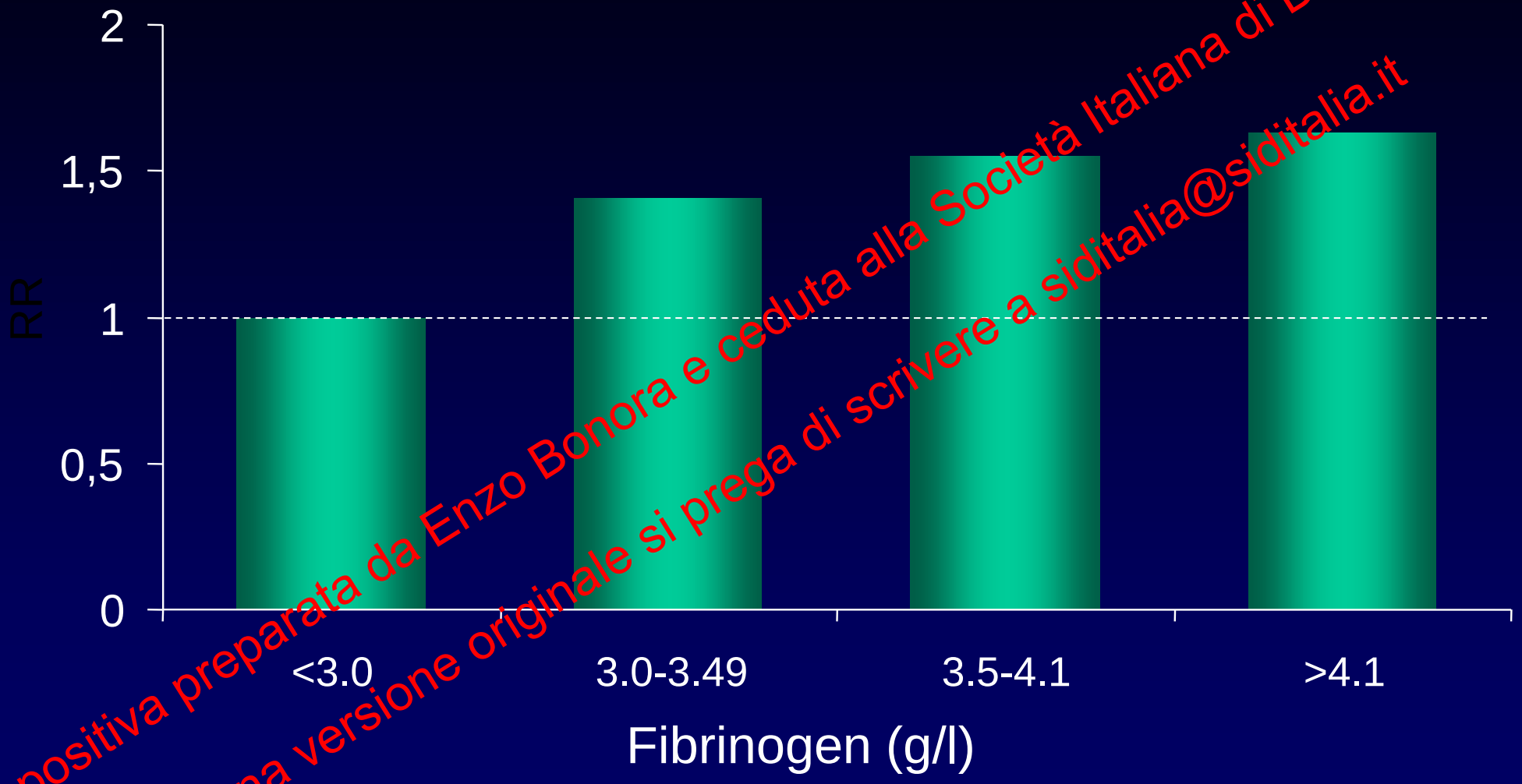
(Health Professional Study; Schulze et al, Diabetes Care 27: 889, 2004)



Data adjusted for age, life-style factors, hypertension, cholesterol, BMI
N= 746; follow-up 5 years

Fibrinogen Predicts CVD Mortality in T2DM

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

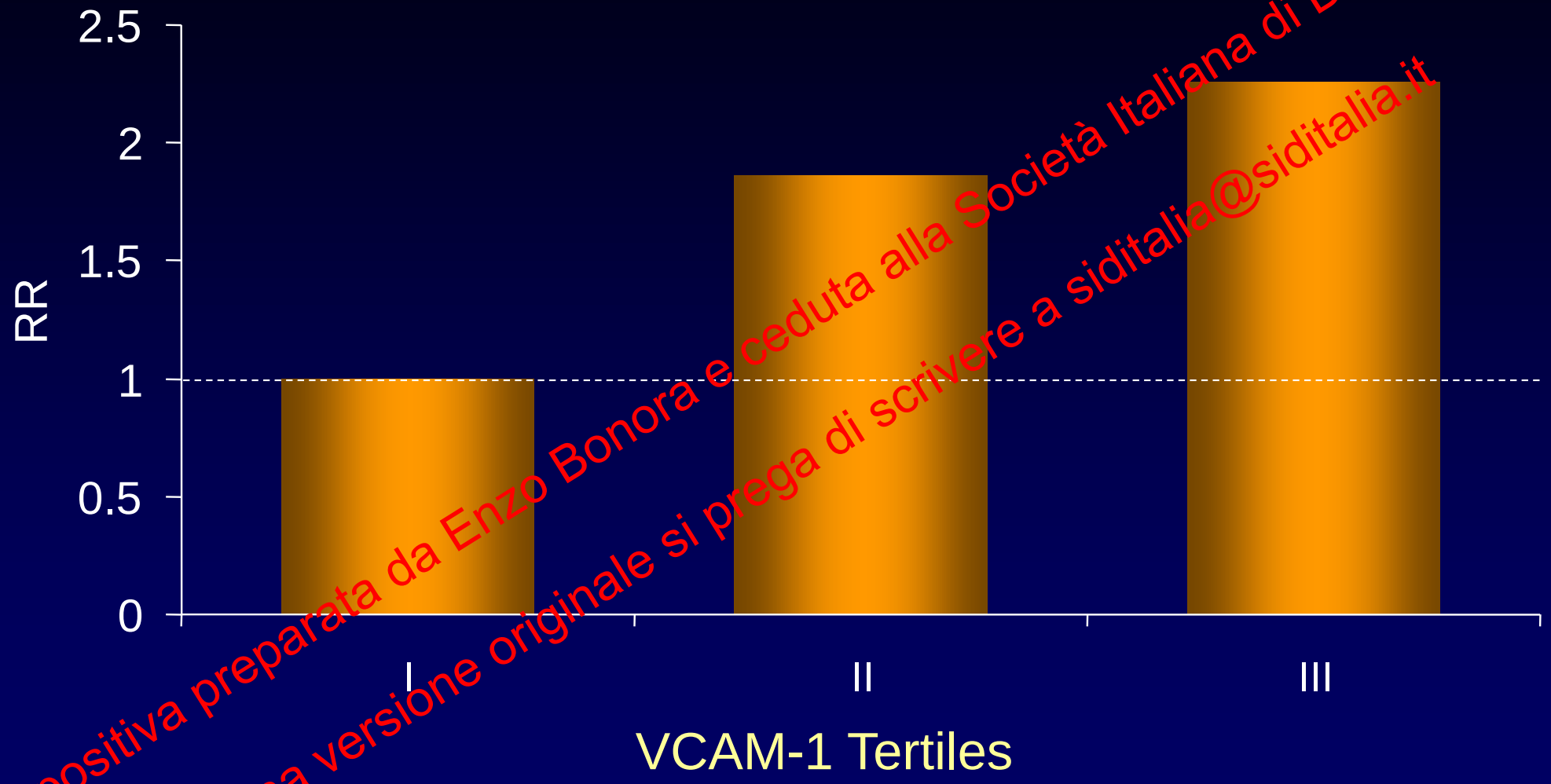


n=1565; follow-up 11 years

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

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

Elevated Serum Uric Acid Concentrations Independently Predict Cardiovascular Mortality in Type 2 Diabetic Patients

Diabetes Care 32:1716–1720, 2009

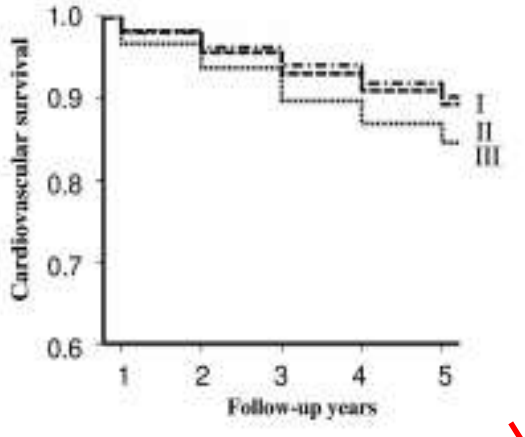


Figure 1—*Kaplan-Meier curves of cardiovascular mortality in 2,726 type 2 diabetic patients stratified by sex-specific tertiles of serum uric acid levels. Statistical significance was estimated by the log-rank test ($P < 0.001$ for the third tertile vs. the other two tertiles).*

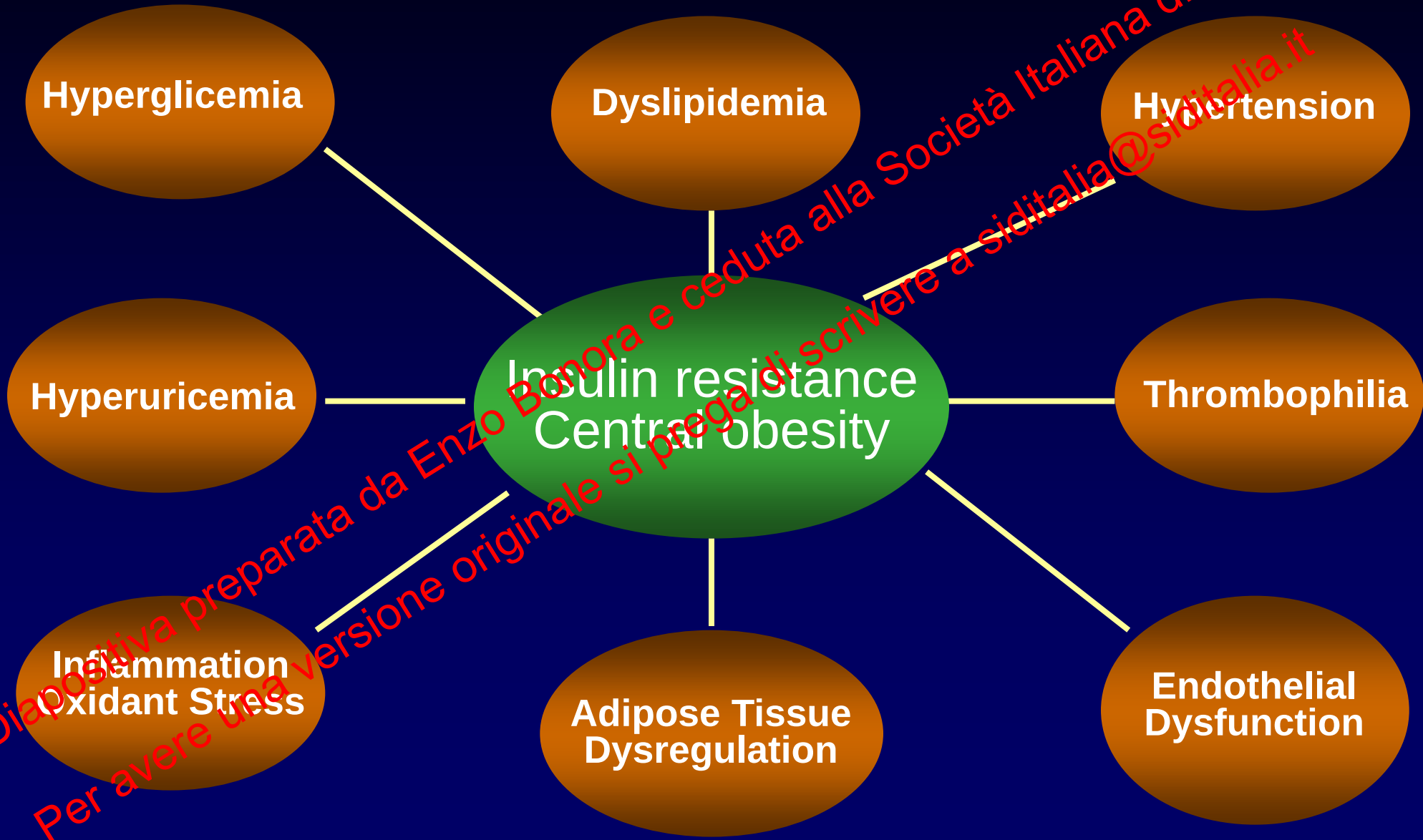
Table 2—*Predictors of cardiovascular mortality as assessed by multivariate Cox proportional hazards models*

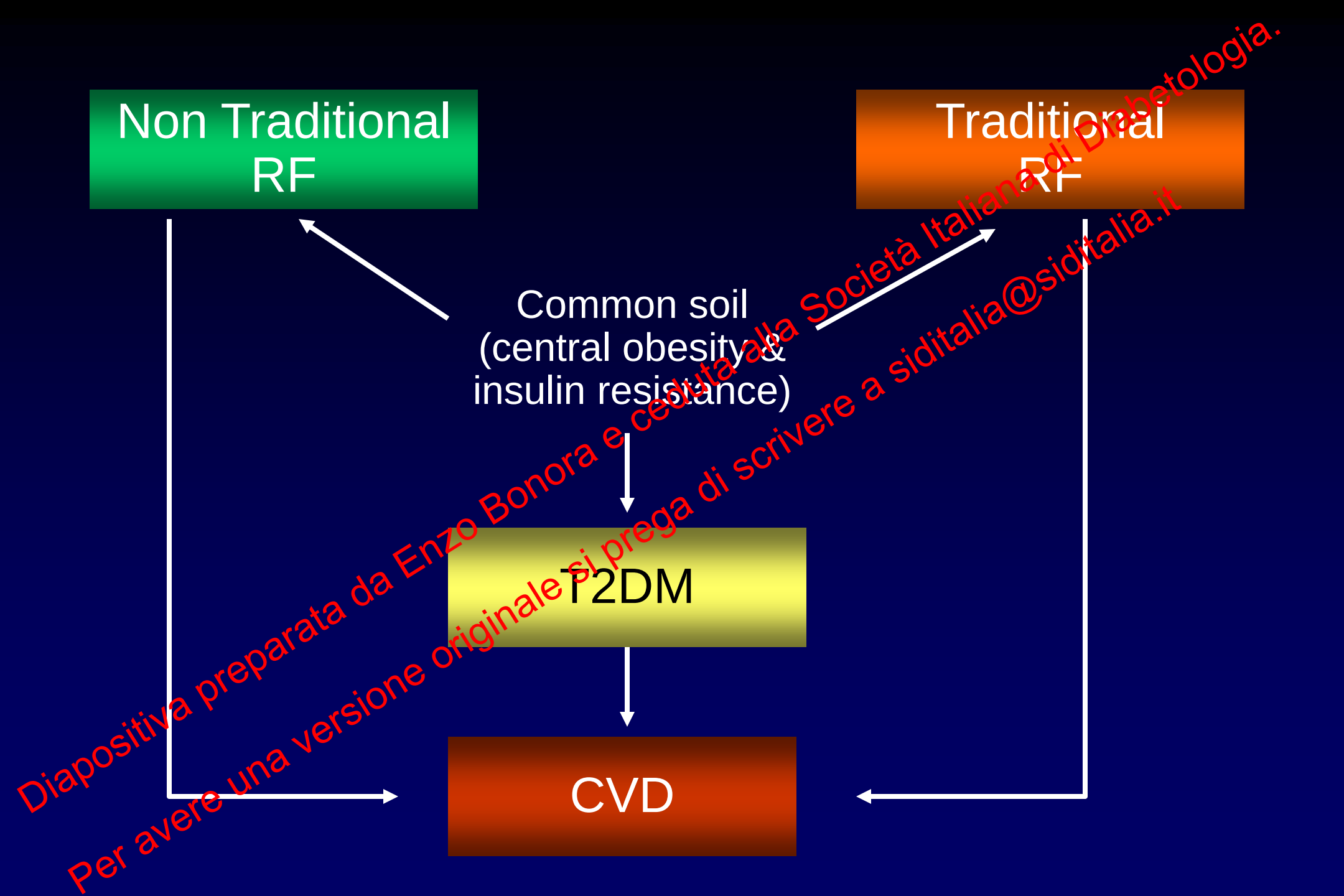
	Multivariate model 1	P	Multivariate model 2	P	Multivariate model 3	P
Serum uric acid (μmol/l)	1.21 (1.10–1.33)	<0.001	1.19 (1.02–1.38)	0.024	1.27 (1.01–1.61)	0.046
Age (years)	3.48 (2.54–4.38)	<0.001	2.76 (2.03–3.74)	<0.001	3.12 (2.11–4.62)	<0.001
Sex (male vs. female)	1.30 (0.91–1.87)	NS	1.38 (0.93–2.05)	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/m²)	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)	0.91 (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
Antiplatelet 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 ≥140/90 mmHg or receiving treatment.

n= 2726 type 2 diabetic men and women. Mean follow-up: 4.7 years

Underlying Disorders (“Common Soil”) in T2DM



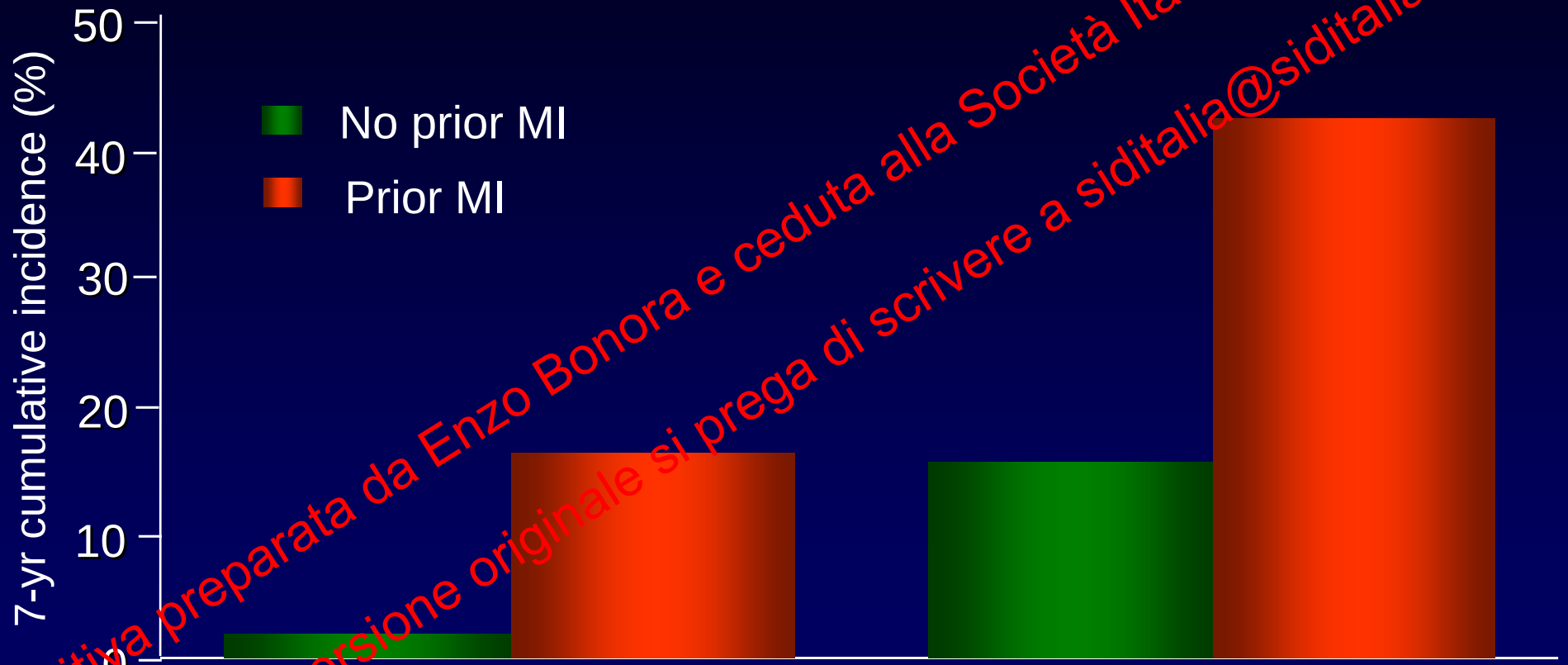


Due to the cluster of dozens of CHD risk factors

Diabetes is ranked as a cardiovascular disease equivalent

Cardiovascular Mortality in Subjects With and Without Prior Myocardial Infarction

(Haffner et al; NEJM 339: 229, 1998)



Adjusted for sex and age

The deadly glycemic quartet in type 2 diabetes

Fasting hyperglycemia

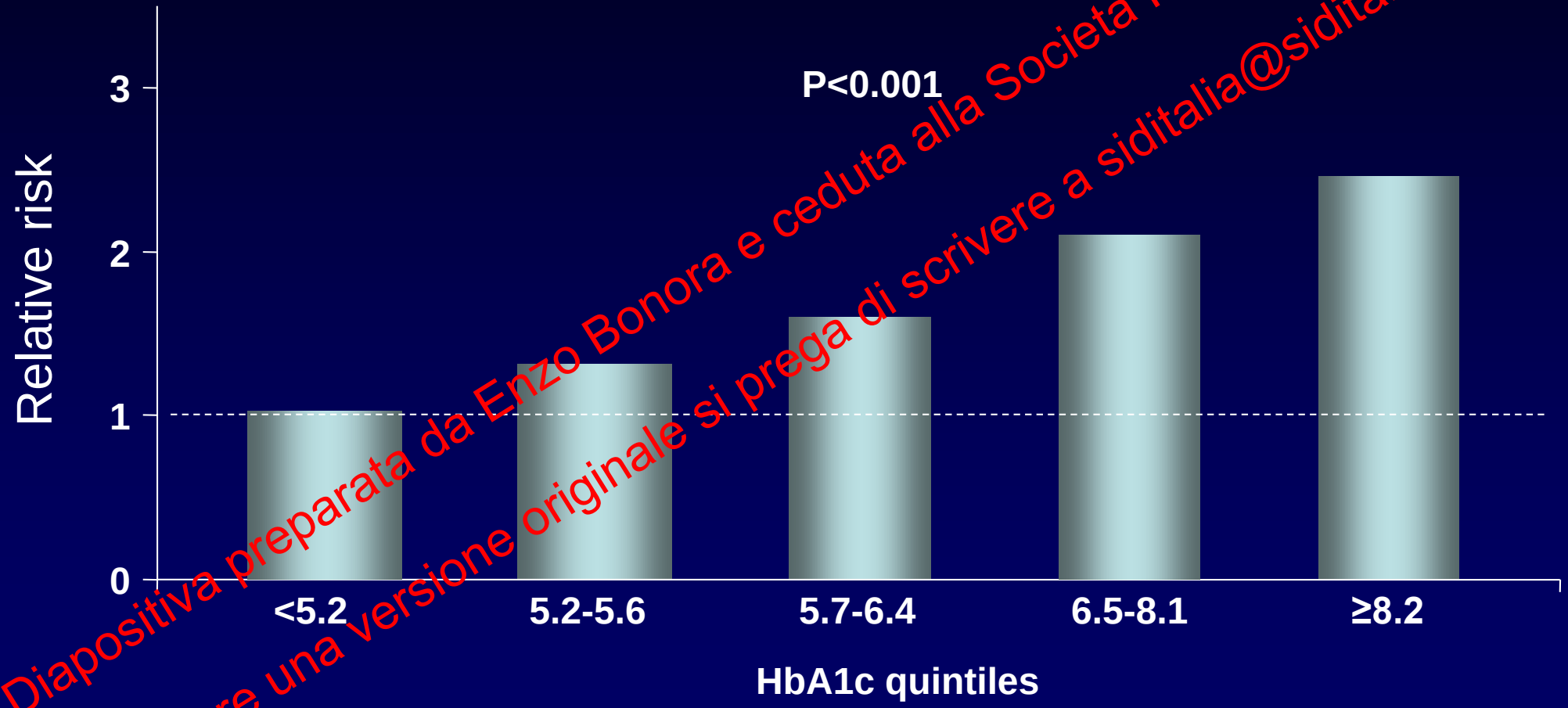
Post-prandial hyperglycemia

Blood Glucose Variability

Hypoglycemia

HbA1c and Risk of CHD in T2DM

(ARIC Study; Selvin et al – Arch Intern Med 165: 1919, 2005)



Adjusted for age, sex, race, center, LDL-C, HDL-C, sBP, medication, smoking, WHR, BMI

Post-Prandial Glucose and CVD in T2DM

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

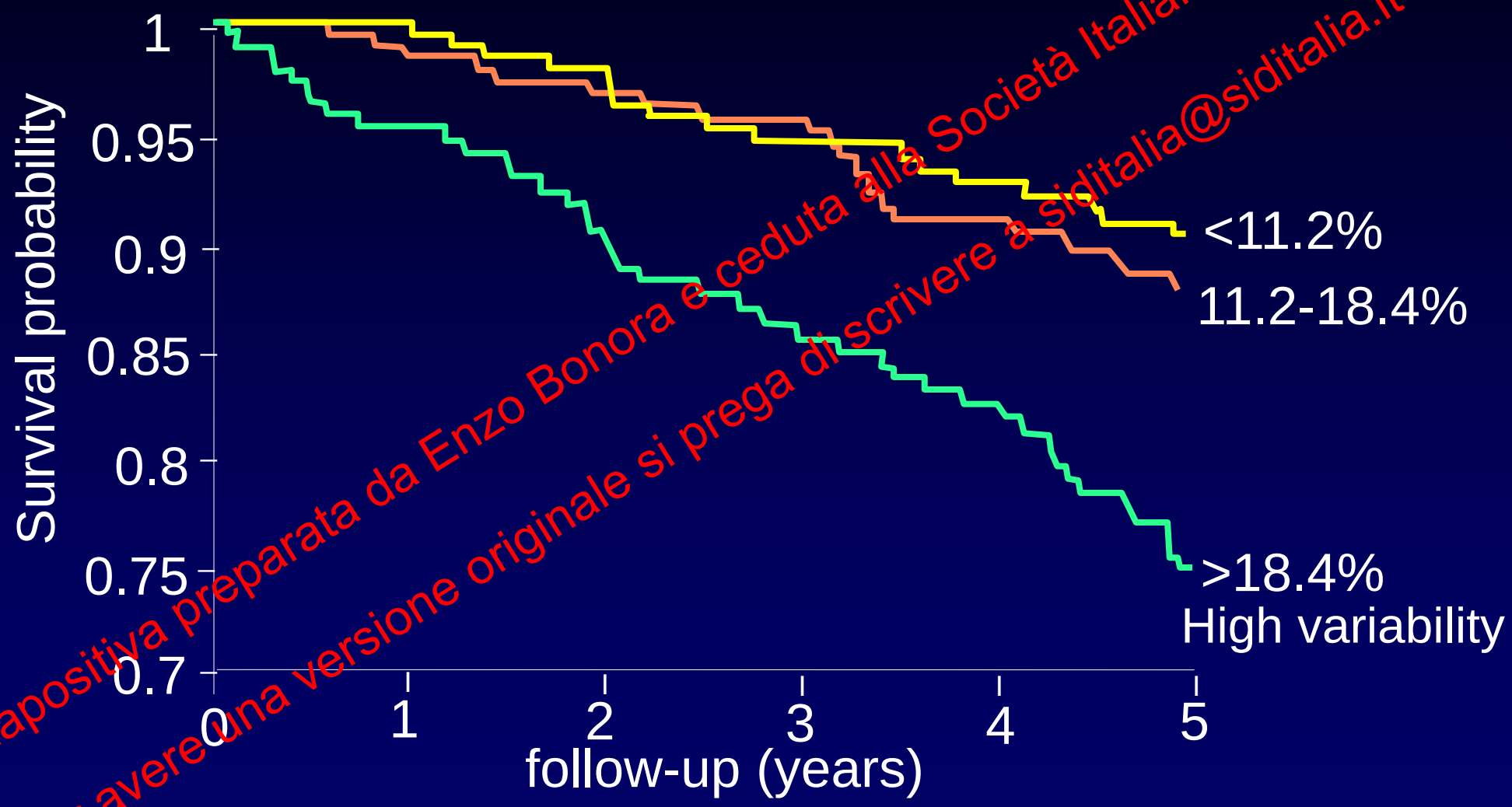
	Independent predictors
Fasting glucose	no
HbA1c	no
Post-prandial glucose	yes

HRs PPG T3 vs. T1-2
men 2.19
women 5.69
After adjusting for FBG and other confouders

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 T2DM as a Function of Variability of Fasting Plasma Glucose (CV-FPG)

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

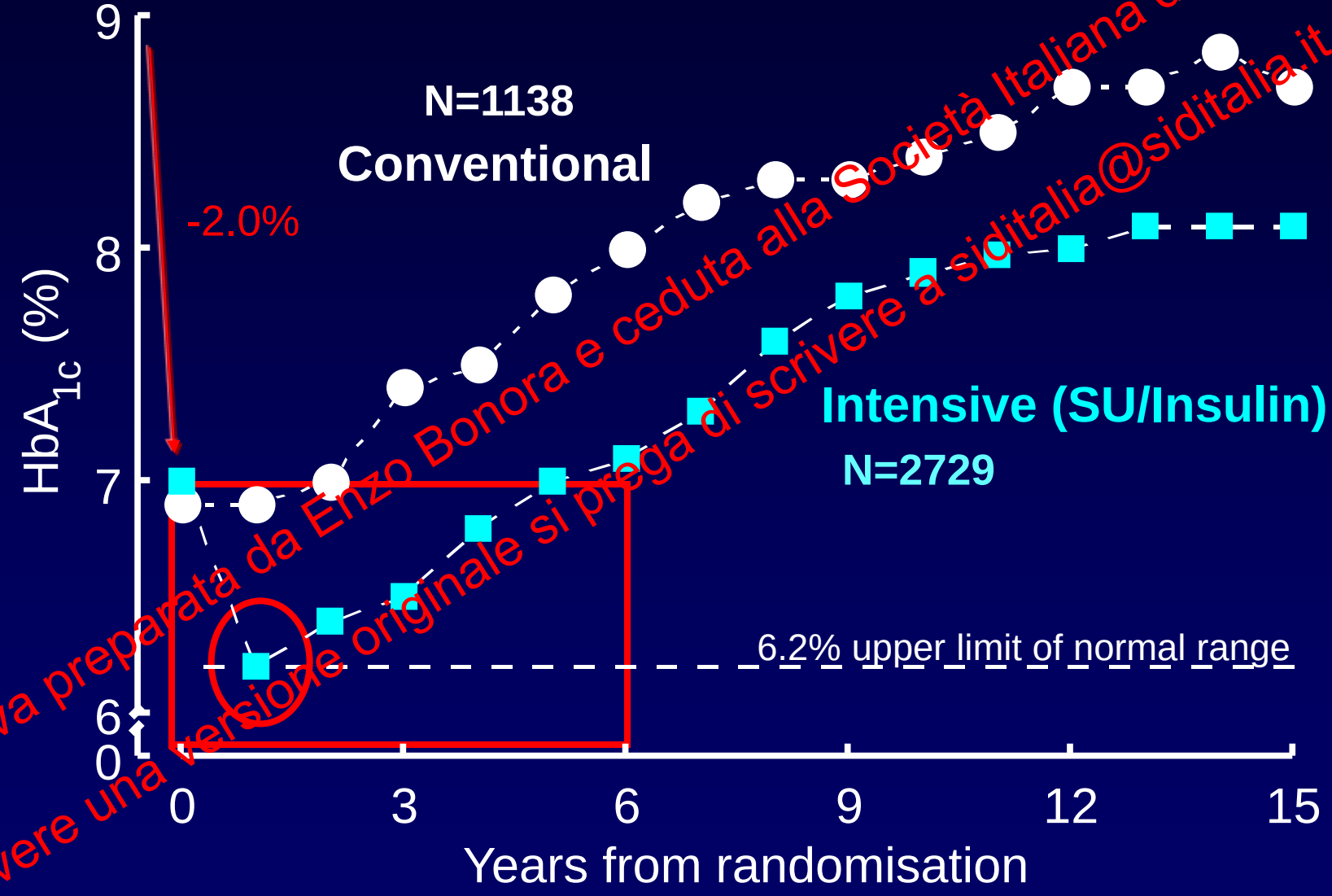


Association of Hypoglycemia and Rapid Hyperglycemia with Cardiac Ischemia in T2DM. A Study based upon Continuous Glucose and ECG Monitoring

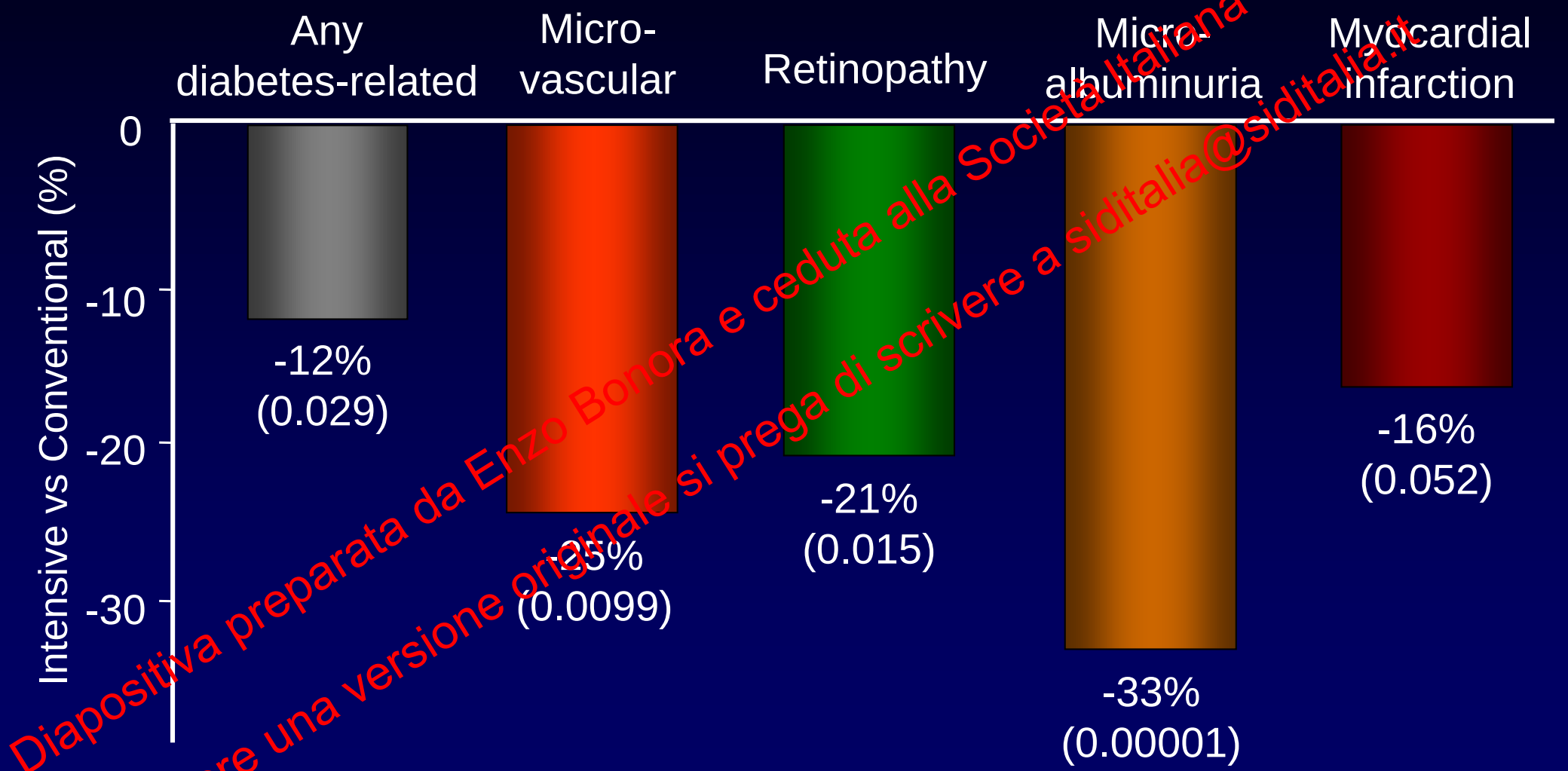
(Desouza et al; Diabetes Care 26: 1485, 2003)

	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

United Kingdom Prospective Diabetes Study (UKPDS)
Progressive Loss of Glucose Control

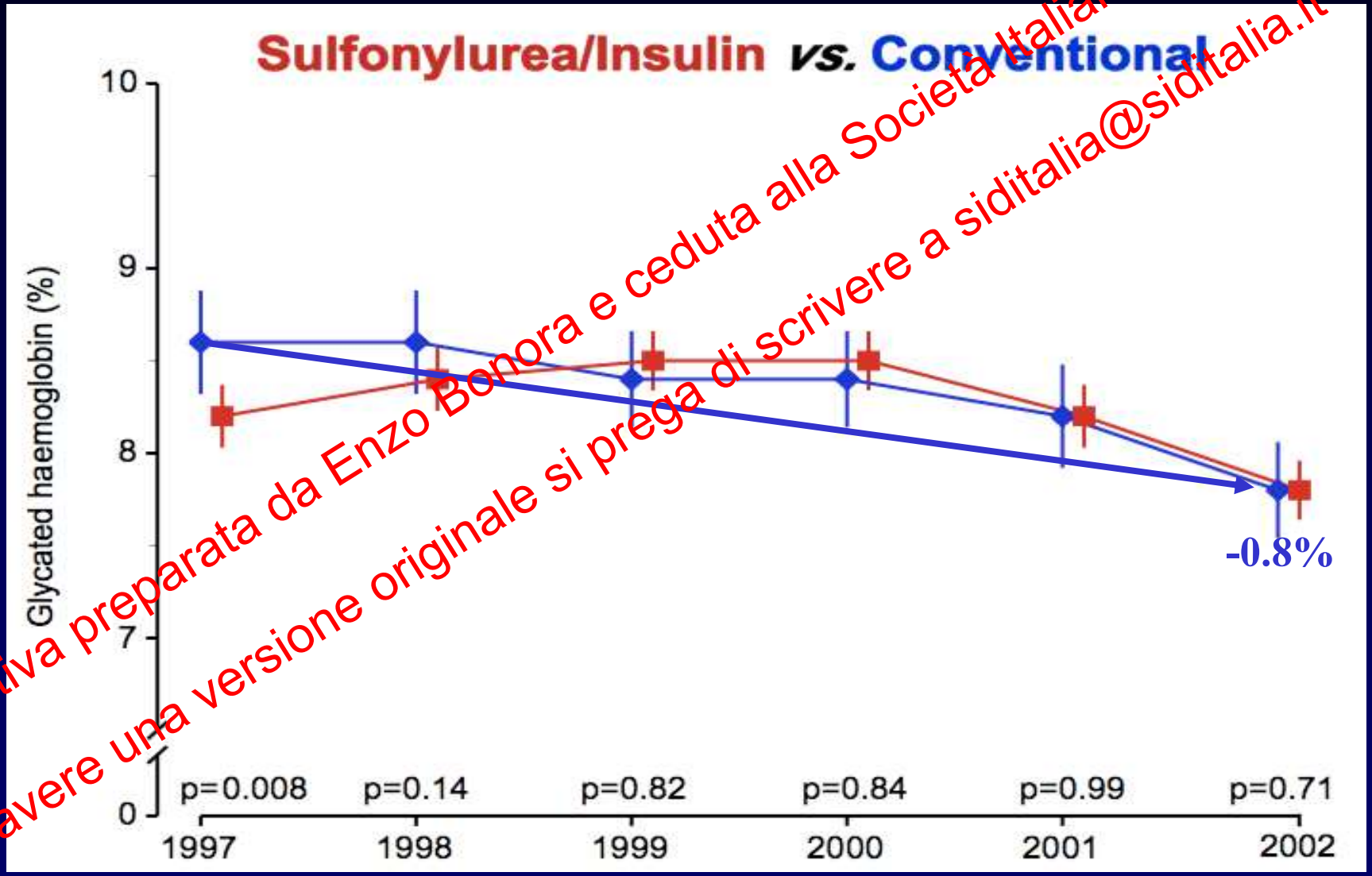


Effects of Intensive Treatment with SU/Insulin on Main Outcomes In Type 2 Diabetic Patients of the UKPDS



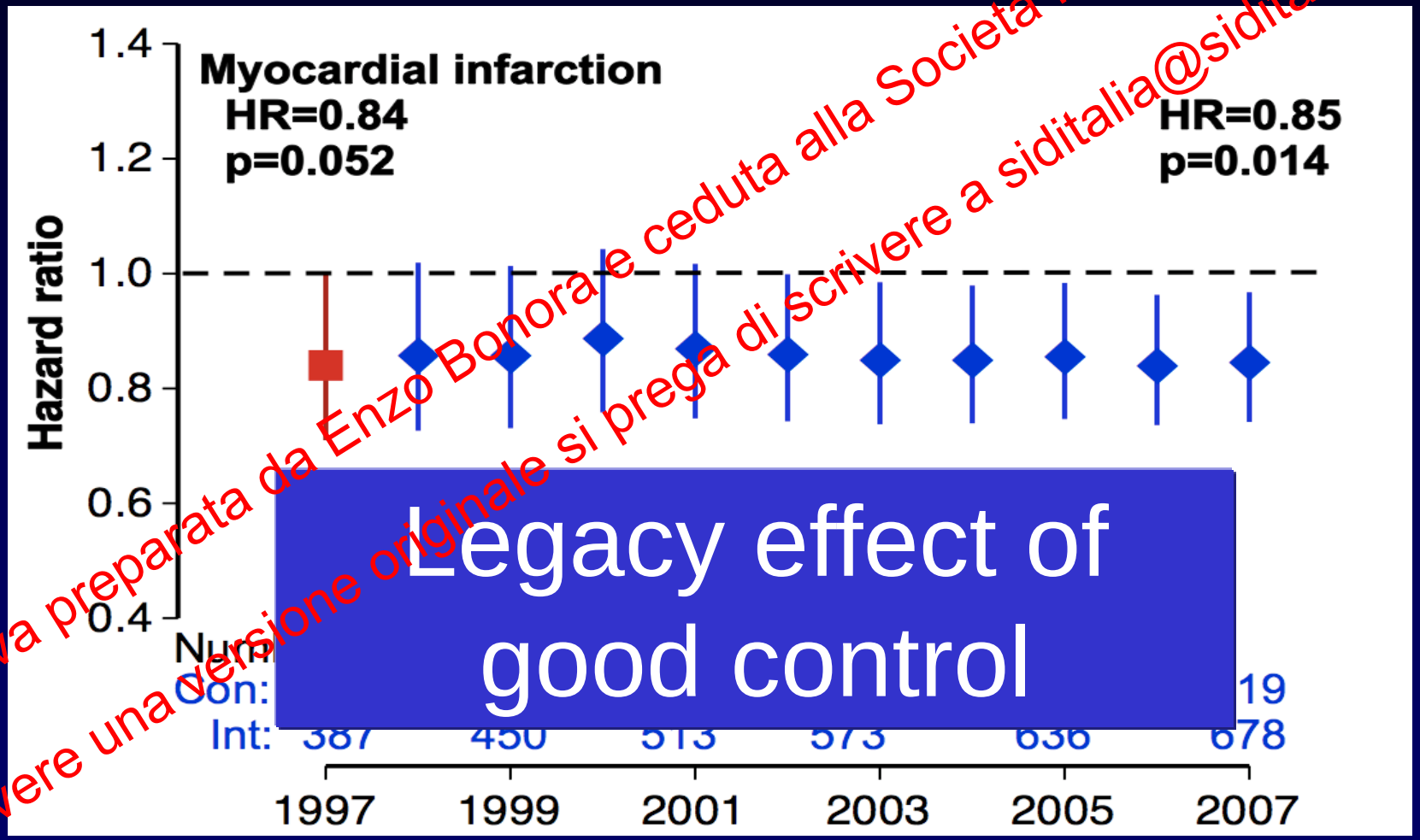
UKPDS: Post-Trial Changes in HbA_{1c}

(NEJM, 359: 1577-1589, 2008)



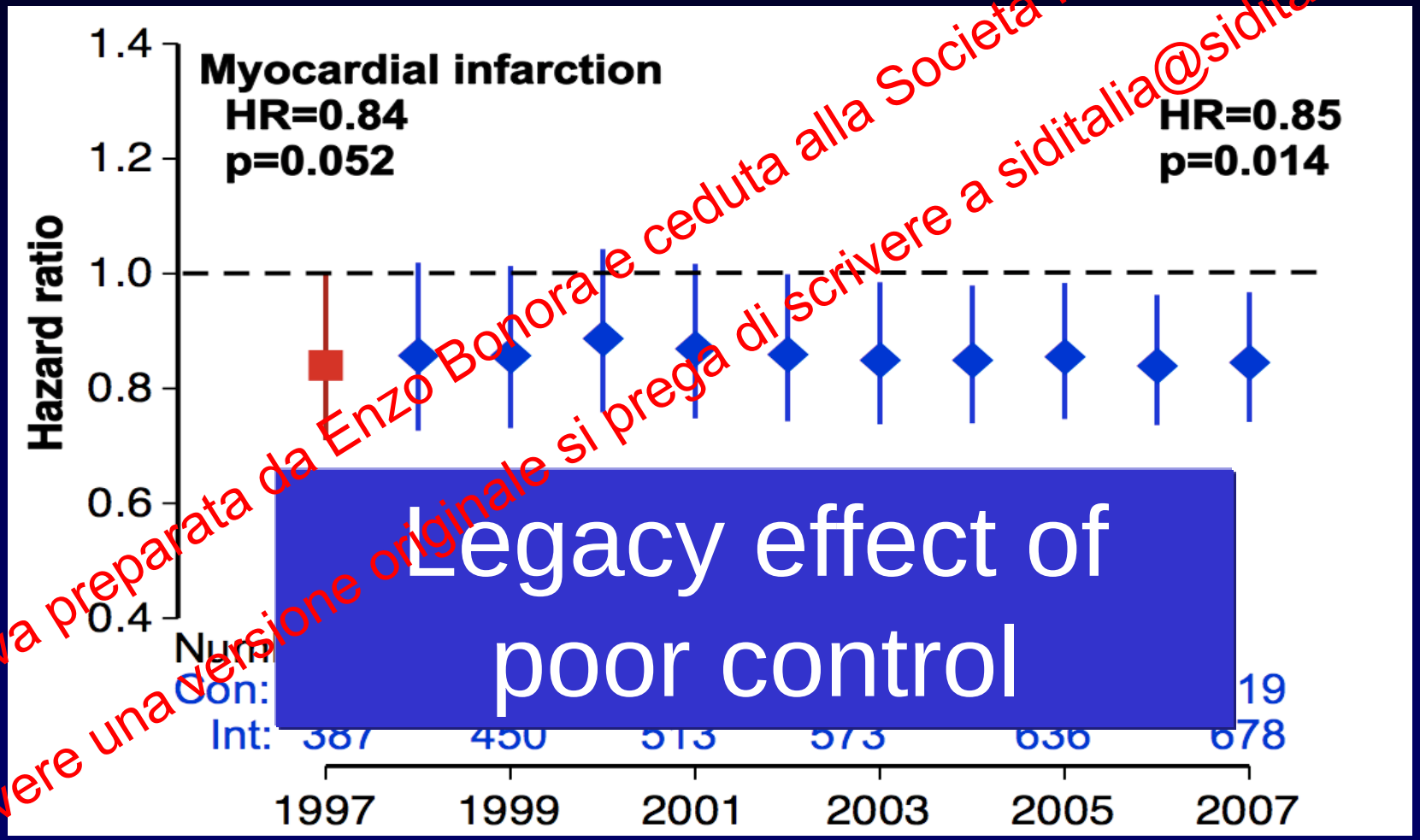
UKPDS – Risk of Myocardial Infarction in the Post Trial Monitoring (SU/Ins vs. Conventional)

(NEJM, 359: 1577-1589, 2008)

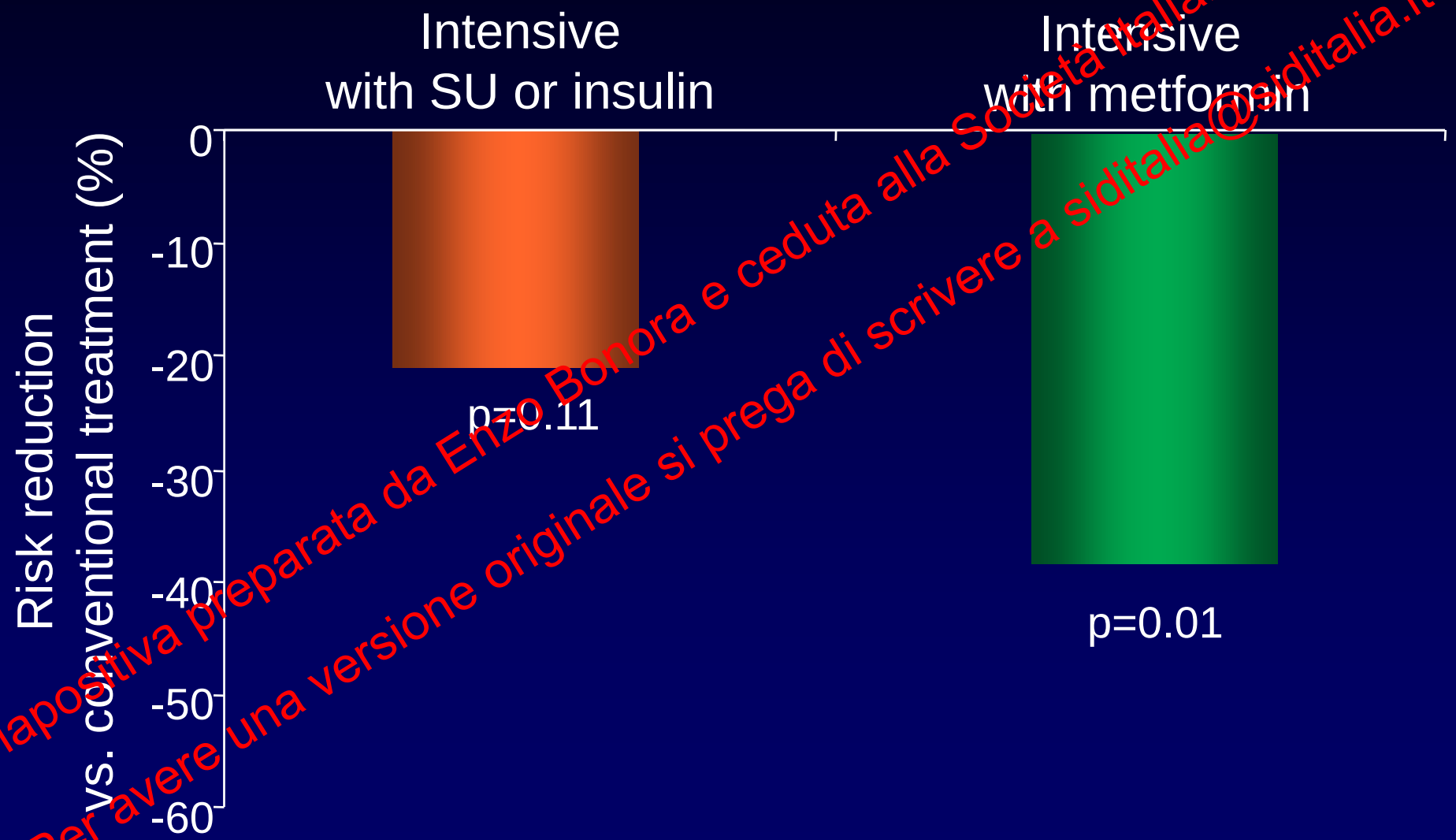


UKPDS – Risk of Myocardial Infarction in the Post Trial Monitoring (SU/Ins vs. Conventional)

(NEJM, 359: 1577-1589, 2008)

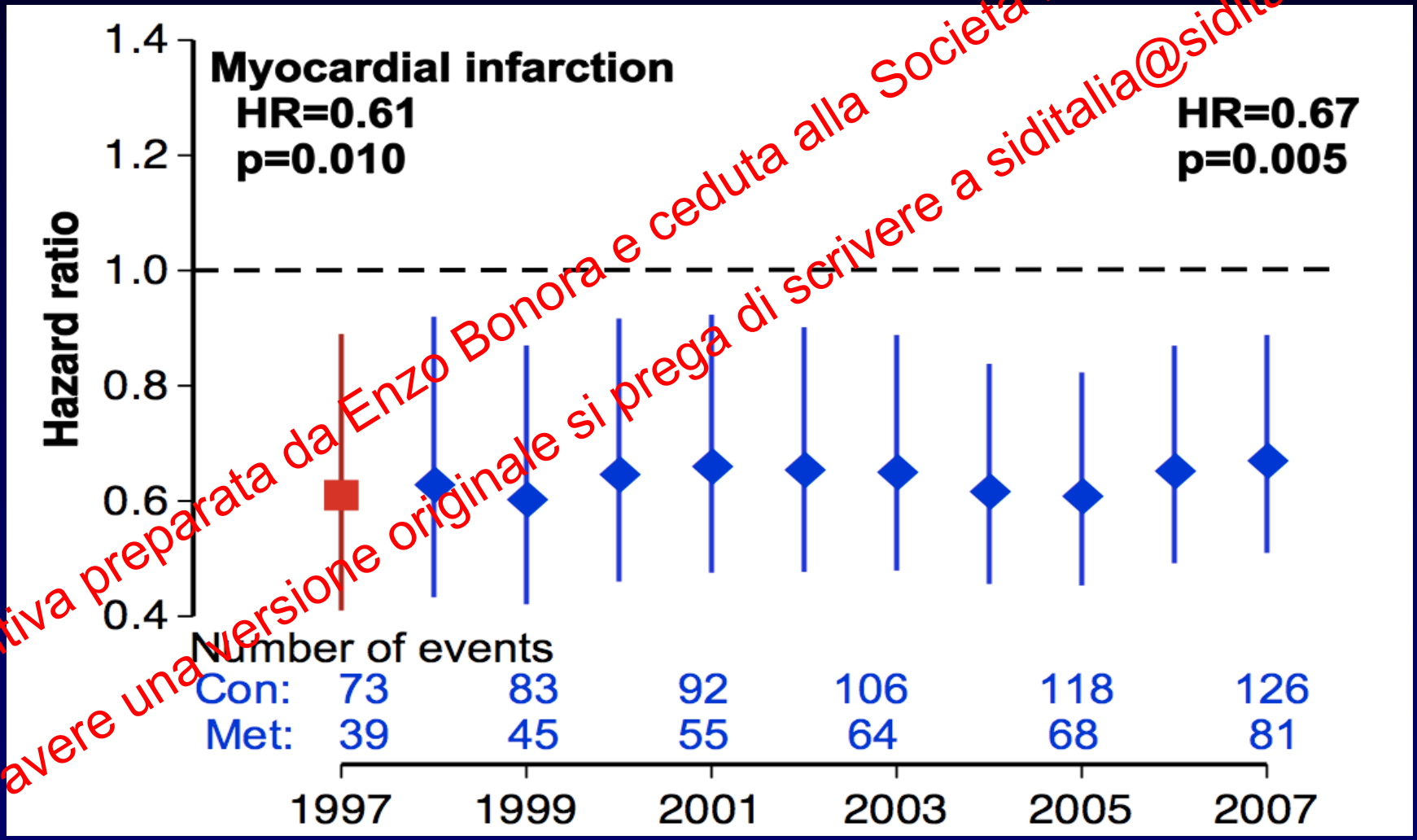


Effects of Different Intensive Treatment on the Incidence of Myocardial Infarction in Overweight (mean BMI=31) Type 2 Diabetic Patients of the UKPDS



UKPDS – Risk of Myocardial Infarction in the Post Trial Monitoring (MET vs. Conventional)

(NEJM, 359: 1577-1589, 2008)



Glycemic Targets in Diabetes Care

The lower the better?

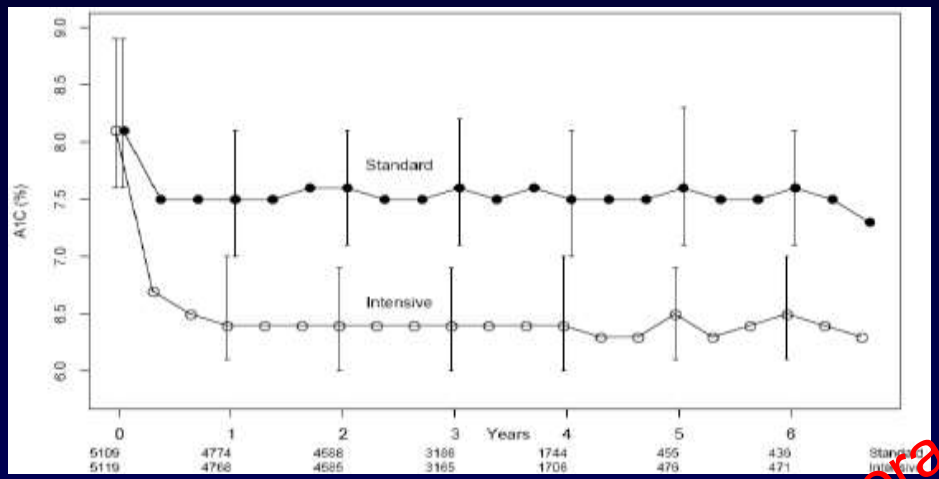
Reasonable but where is the evidence?

Effect of Intensive Glucose Control on CVD in T2DM
Baseline data from Recent RCTs and UKPDS

	No.	Mean Follow - up (yrs)	Age (yrs)	Time from diagnosis (yrs)	Prior CVD (%)	BMI	HbA1c (%)
ACCORD	10251	3.5	62	10	35	32	8.3
ADVANCE	11140	5	66	8	32	28	7.5
VADT	1791	6.3	60	11.5	40	31	9.4
UKPDS	4209	10+10	53	0	0	28	9.1

HbA1c in Recent Glucose Control Trials

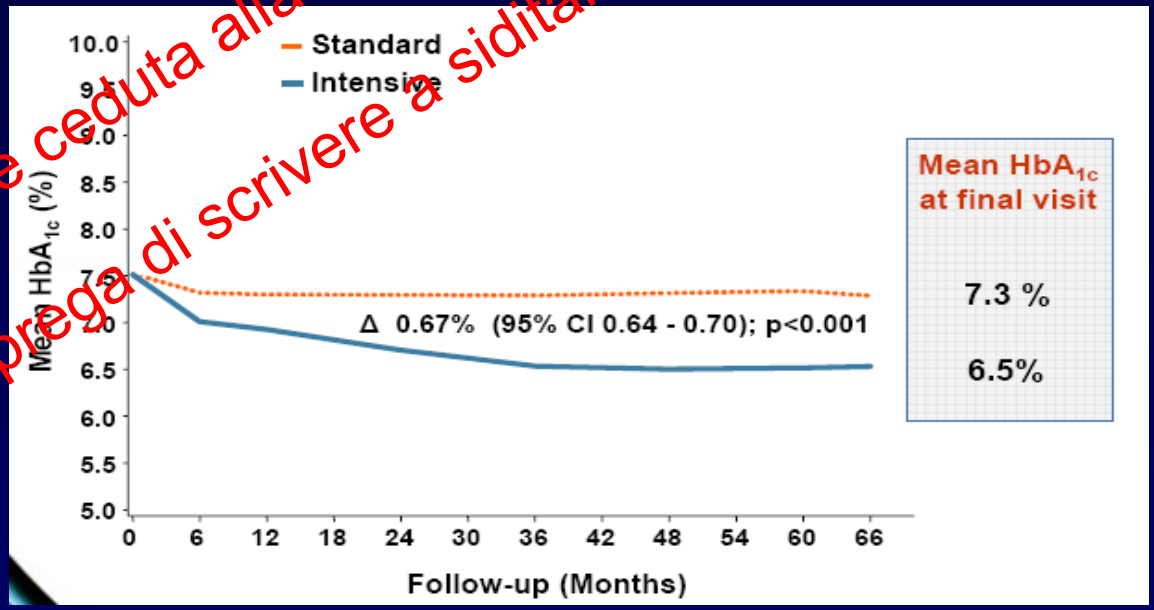
ACCORD



VADT

Figure 2. Changes in Median Glycated Hemoglobin Levels from Baseline through 78 Months.
The vertical bars represent interquartile ranges.

ADVANCE



ACCORD, ADVANCE AND VADT
HRs for composite CVD outcome and CVD death

Outcome	ACCORD	ADVANCE	VADT
Compo			0.87 73-1.04)
CVD D			1.25 77-2.05)

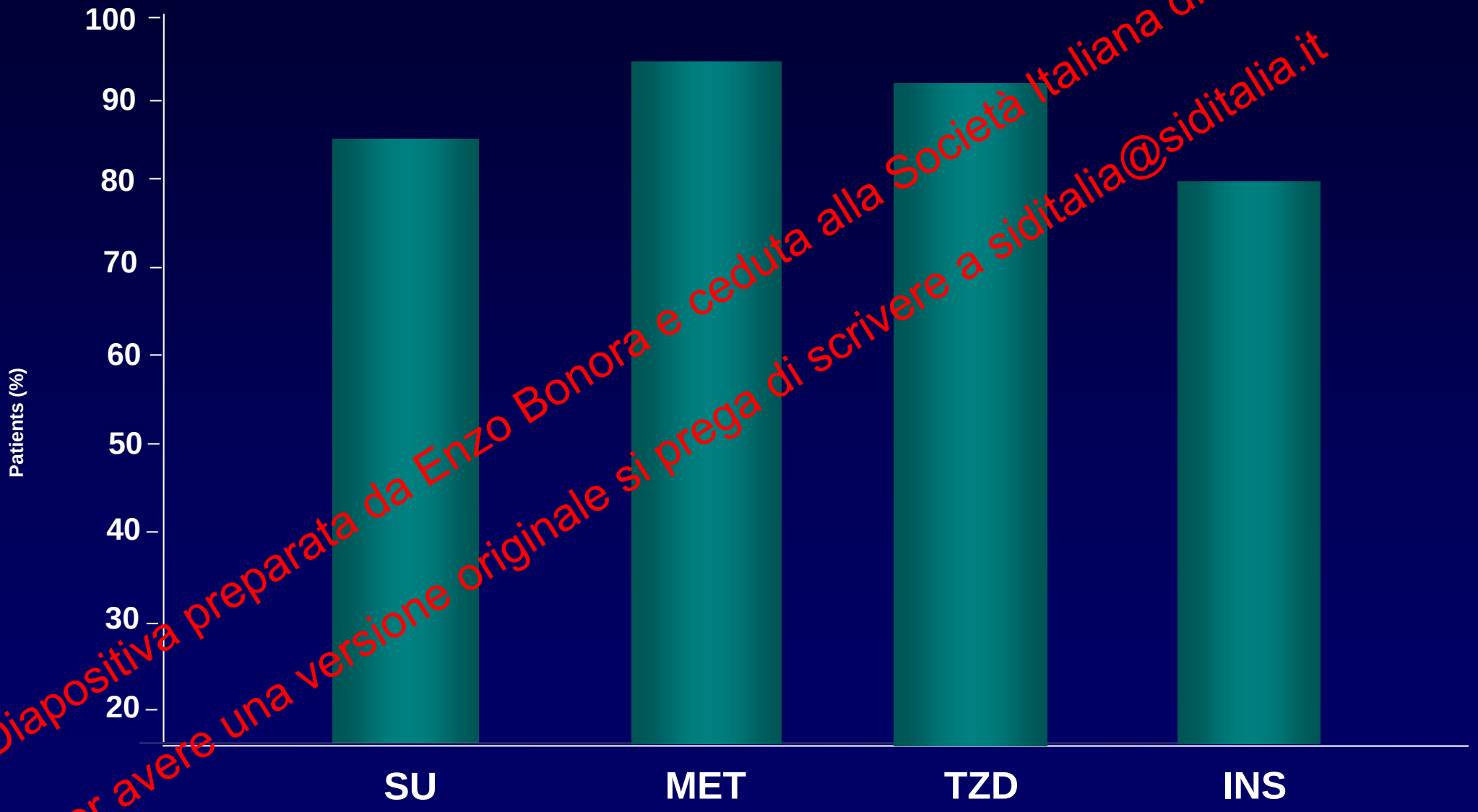
Legacy effect of poor control?

ACCORD = CVD death + nonfatal AMI and stroke
ADVANCE = CVD death + nonfatal AMI and stroke
VADT = CVD death + nonfatal AMI and stroke + CHF + severe CHD + vascular amputation + any revascularization

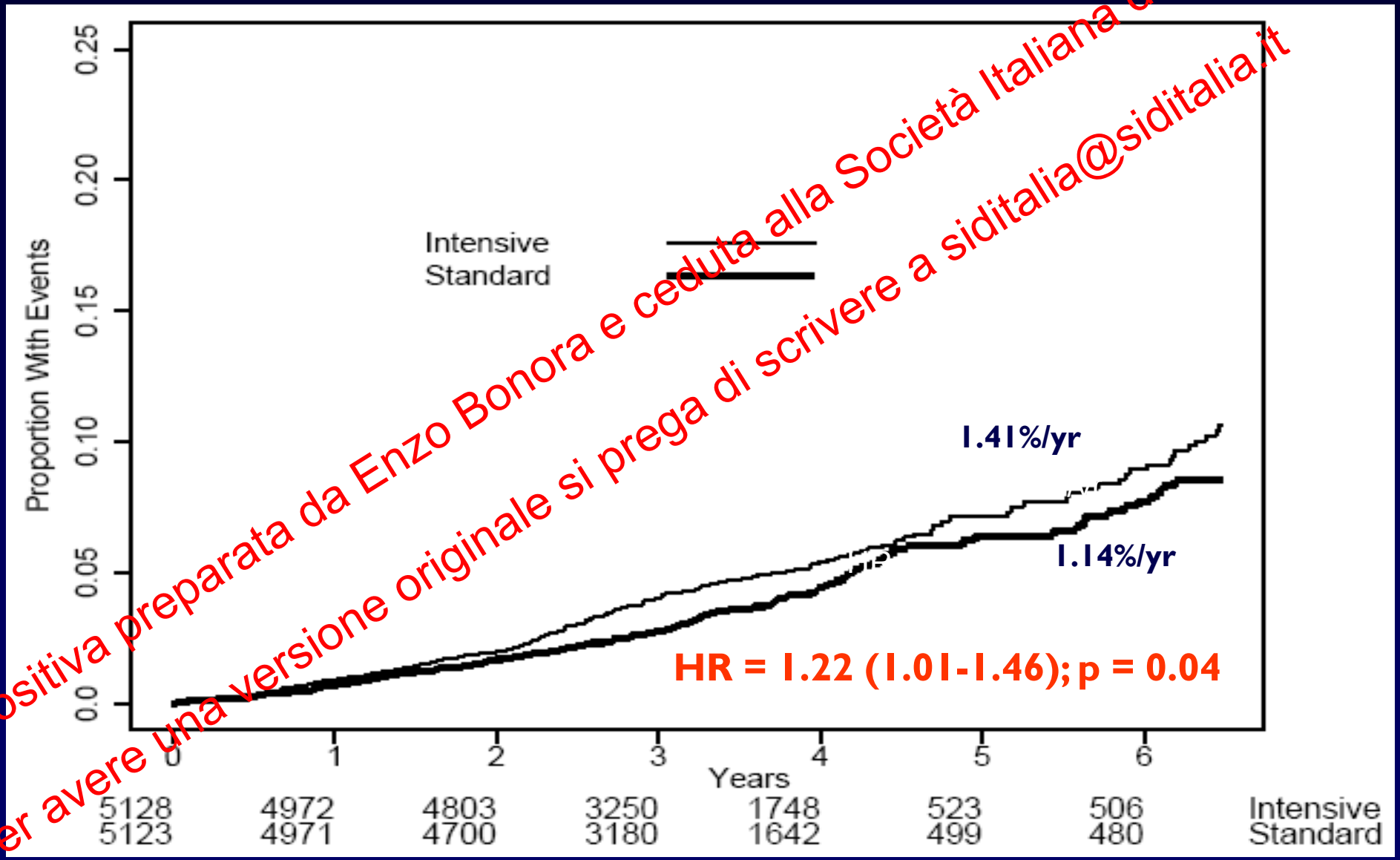
CVD not Reduced in ACCORD: Hypotheses

- Are negative data explained by inadequate statistical power (fewer than expected clinical CVD events; relatively small sample size; too short trial)?
- Is the impact of glucose on CVD truly negligible? If so, what about the bulk of experimental and observational data on glucose and CVD? And what about results of post-trial monitoring of UKPDS?
- Is the impact of glucose control on CVD virtually negligible when other risk factors are powerfully targeted?
- Are CVD benefits of lower glucose levels blunted by undesirable adverse effects, such as more frequent and more severe hypoglycemia and/or CVD adverse effects of anti-diabetic drugs?

ACCORD – Intensive Treatment Strategy



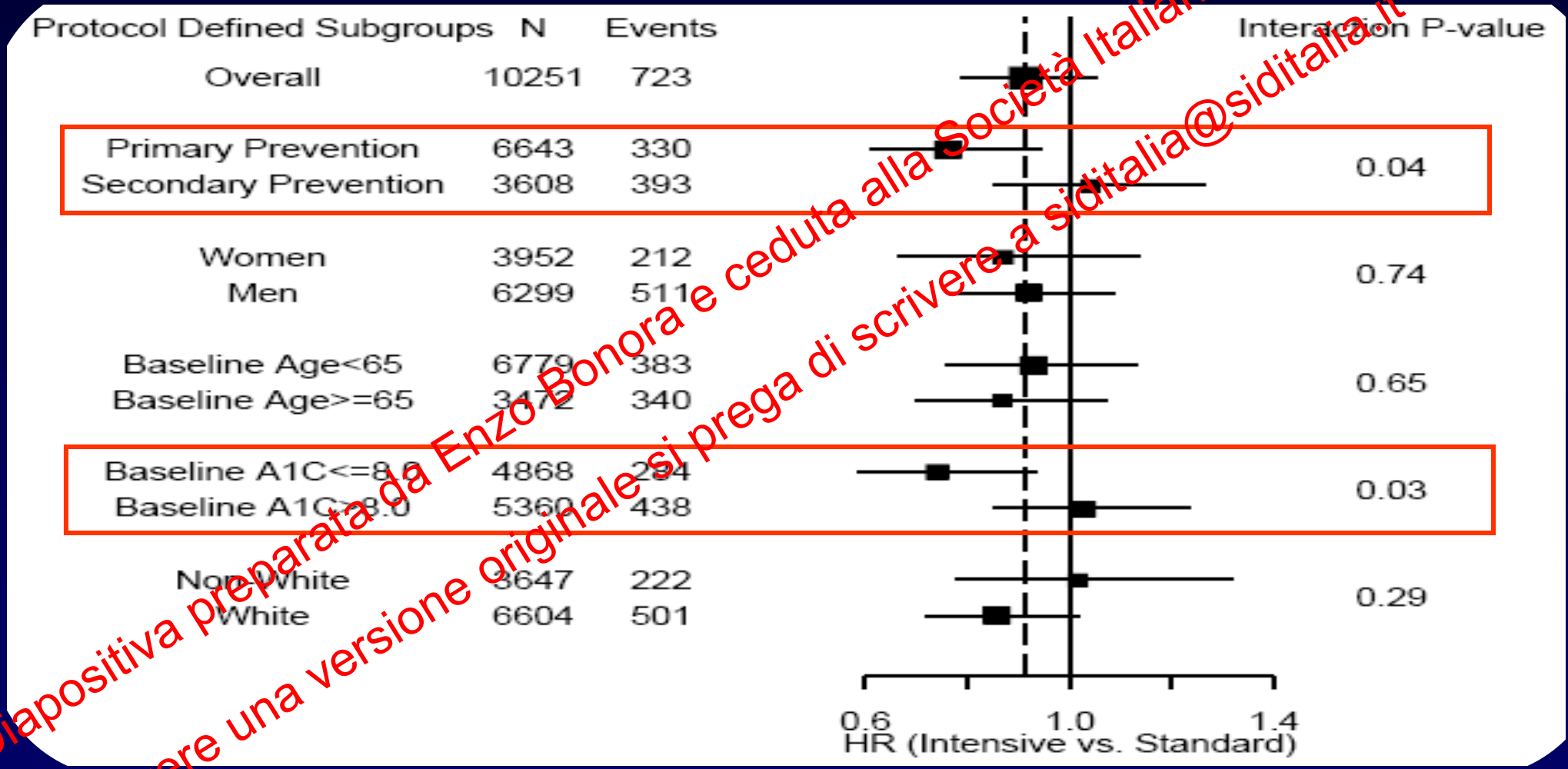
ACCORD - All-Cause Mortality



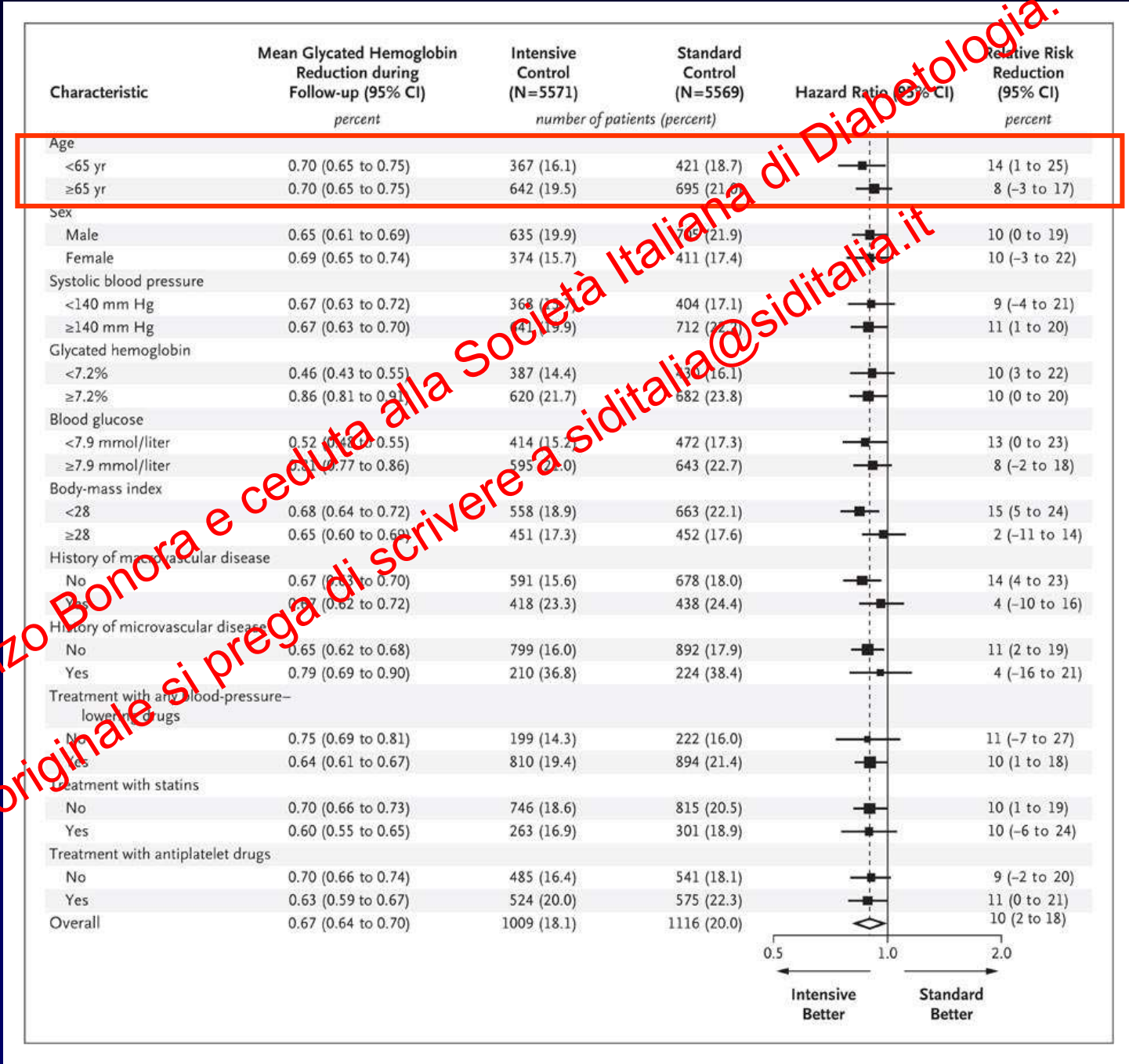
Fundamental Question after ACCORD

Is the lack of CVD benefits with more stringent glucose control (HbA1c target <6.0-6.5%) generalizible in all T2DM patients?

ACCORD: Primary Outcome by Subgroups

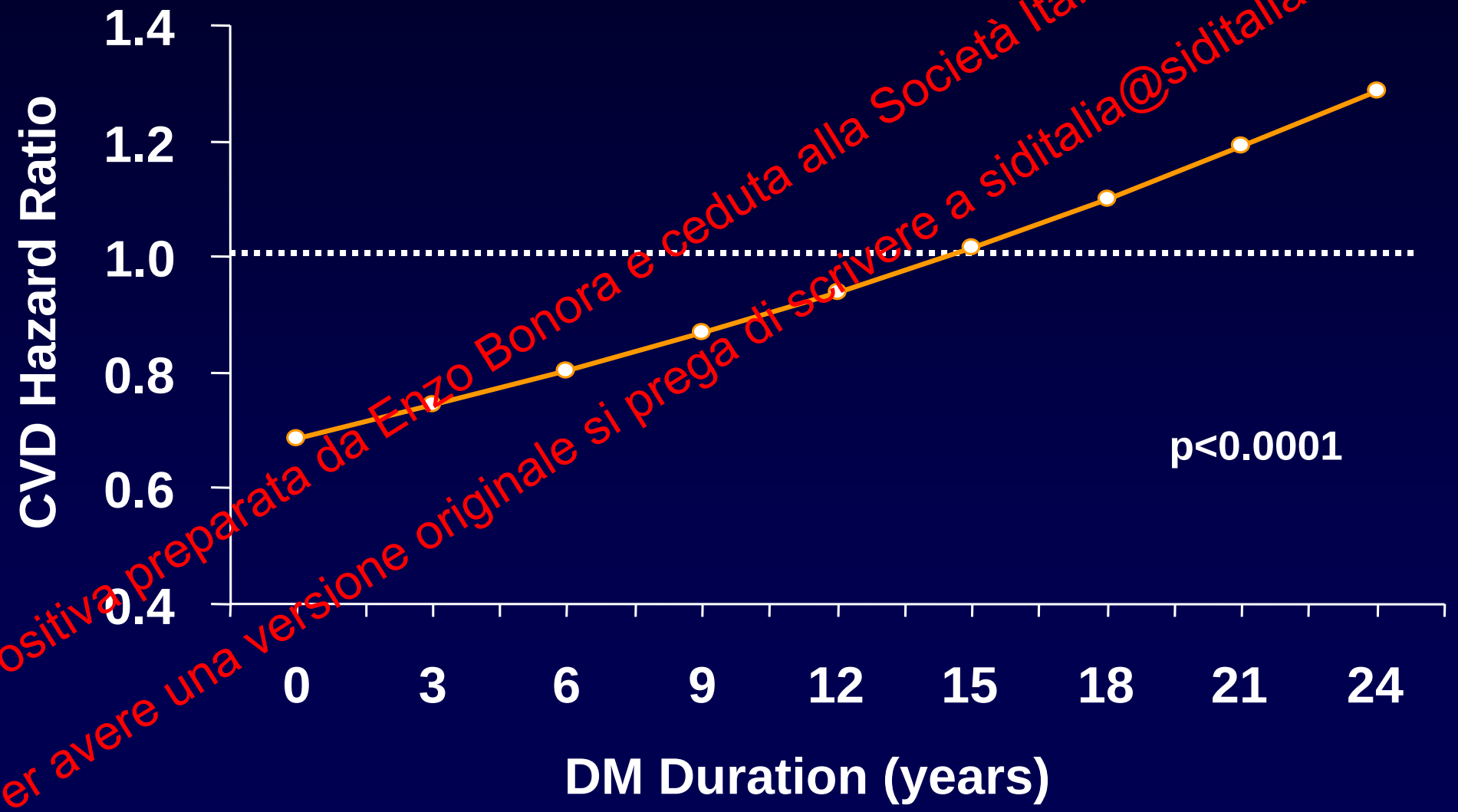


Advance main outcome in subgroups



Characteristic	Mean Glycated Hemoglobin Reduction during Follow-up (95% CI)	Intensive Control (N=5571)	Standard Control (N=5569)	Relative Risk Reduction (95% CI)
	percent	*number of patients (percent)*		*percent*
Age				
<65 yr	0.70 (0.65 to 0.75)	367 (16.1)	421 (18.7)	14 (1 to 25)
≥65 yr	0.70 (0.65 to 0.75)	642 (19.5)	695 (21.0)	8 (–3 to 17)
Sex				
Male	0.65 (0.61 to 0.69)	635 (19.9)	709 (21.9)	10 (0 to 19)
Female	0.69 (0.65 to 0.74)	374 (15.7)	411 (17.4)	10 (–3 to 22)
Systolic blood pressure				
<140 mm Hg	0.67 (0.63 to 0.72)	368 (15.7)	404 (17.1)	9 (–4 to 21)
≥140 mm Hg	0.67 (0.63 to 0.70)	641 (19.9)	712 (22.1)	11 (1 to 20)
Glycated hemoglobin				
<7.2%	0.46 (0.43 to 0.55)	387 (14.4)	430 (16.1)	10 (3 to 22)
≥7.2%	0.86 (0.81 to 0.91)	620 (21.7)	682 (23.8)	10 (0 to 20)
Blood glucose				
<7.9 mmol/liter	0.52 (0.48 to 0.55)	414 (15.2)	472 (17.3)	13 (0 to 23)
≥7.9 mmol/liter	0.81 (0.77 to 0.86)	595 (22.0)	643 (22.7)	8 (–2 to 18)
Body-mass index				
<28	0.68 (0.64 to 0.72)	558 (18.9)	663 (22.1)	15 (5 to 24)
≥28	0.65 (0.60 to 0.69)	451 (17.3)	452 (17.6)	2 (–11 to 14)
History of macrovascular disease				
No	0.67 (0.63 to 0.70)	591 (15.6)	678 (18.0)	14 (4 to 23)
Yes	0.67 (0.62 to 0.72)	418 (23.3)	438 (24.4)	4 (–10 to 16)
History of microvascular disease				
No	0.65 (0.62 to 0.68)	799 (16.0)	892 (17.9)	11 (2 to 19)
Yes	0.79 (0.69 to 0.90)	210 (36.8)	224 (38.4)	4 (–16 to 21)
Treatment with any blood-pressure–lowering drugs				
No	0.75 (0.69 to 0.81)	199 (14.3)	222 (16.0)	11 (–7 to 27)
Yes	0.64 (0.61 to 0.67)	810 (19.4)	894 (21.4)	10 (1 to 18)
Treatment with statins				
No	0.70 (0.66 to 0.73)	746 (18.6)	815 (20.5)	10 (1 to 19)
Yes	0.60 (0.55 to 0.65)	263 (16.9)	301 (18.9)	10 (–6 to 24)
Treatment with antiplatelet drugs				
No	0.70 (0.66 to 0.74)	485 (16.4)	541 (18.1)	9 (–2 to 20)
Yes	0.63 (0.59 to 0.67)	524 (20.0)	575 (22.3)	11 (0 to 21)
Overall	0.67 (0.64 to 0.70)	1009 (18.1)	1116 (20.0)	10 (2 to 18)

VADT - Relationship of DM Duration and HR for CVD Events with Intensive Therapy



Key Conceps in Setting Glycemic Goals

(ADA Clinical Recommendations, 2010)

Goals should be individualized based on:

- Duration of diabetes
- Age/life expectancy
- Comorbid conditions
- Known CVD or advanced microvascular complications
- Hypoglycemia unawareness
- Individual patient considerations

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 = <7.0%; "smooth decline"

- **"Injured Veteran" patient** (long standing T2DM, prior CVD, severely uncontrolled diabetes; "hyperglycemia addicts" who need adaptation to lower glucose levels)
  HbA1c target = 7.0-8.0%; "handle with care"

Conclusions

- CHD is very common in diabetes.
- Many subjects with diabetes will suffer from AMI and stroke.
- The outcome after AMI and stroke is poorer in diabetes, especially when the disease has not been previously diagnosed or when hyperglycemia is neglected.
- CHD and stroke are the major cause of hospitalization and death in diabetes.
- CHD and stroke are common in diabetes because the disease is featured by a cluster of traditional and non-traditional risk factors.
- Different facets of poor glucose control contribute to CVD in diabetes.
- Glucose/HbA1c targets need to be personalized in diabetes In order to achieve a true CVD advantage

The end… thank you so much!