

Beyond Glycemia **Rischio cardiovascolare nel paziente diabetico**

Milano, 10 Settembre 2014

Fattori di rischio cardiovascolare in pazienti con diabete tipo 2

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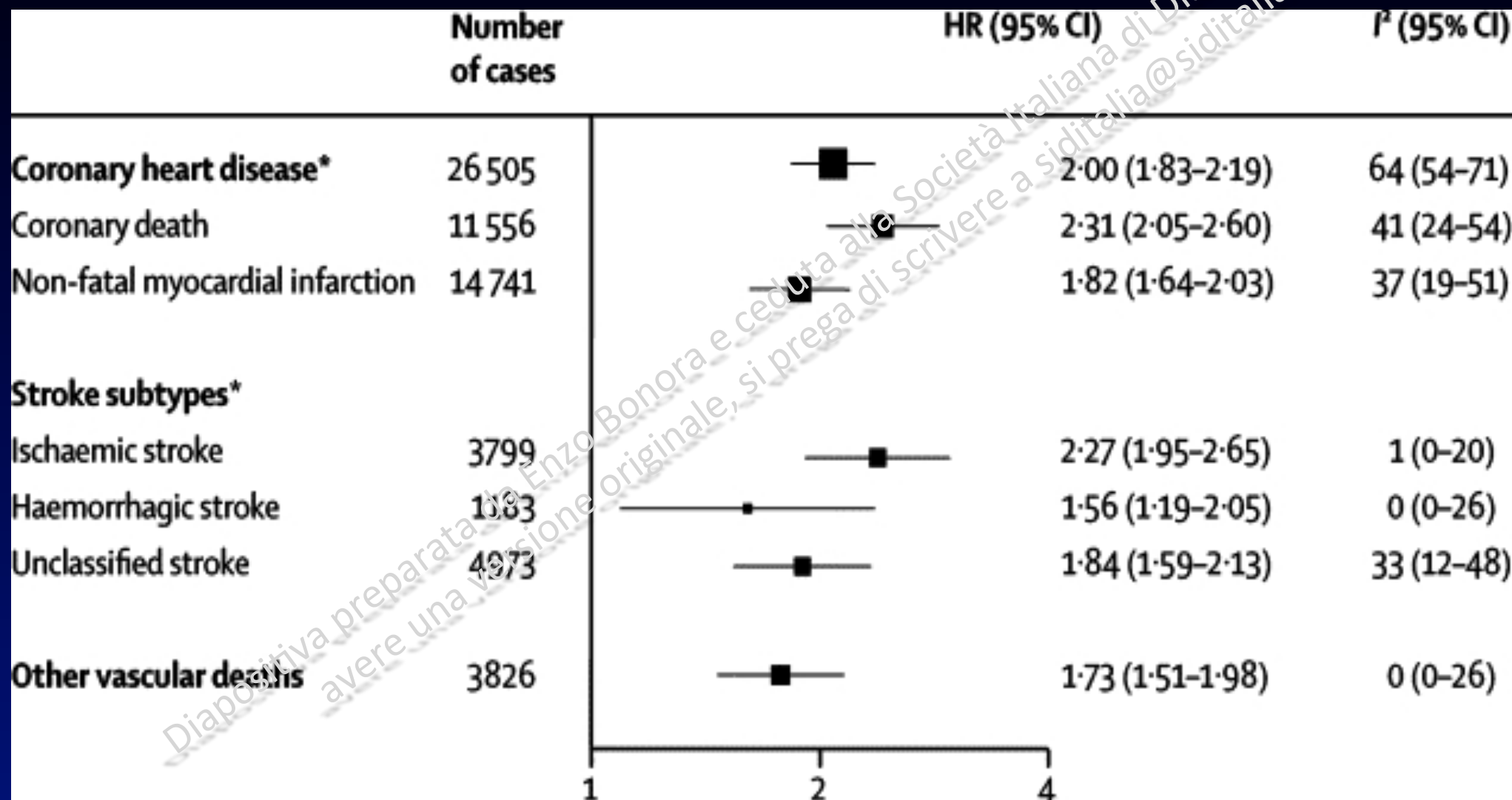


Outline

- Epidemiology of CVD in type 2 diabetes
- Traditional CVD risk factor in type 2 diabetes
- Nontraditional CVD risk factors in type 2 diabetes
- Benefit of treating risk factors

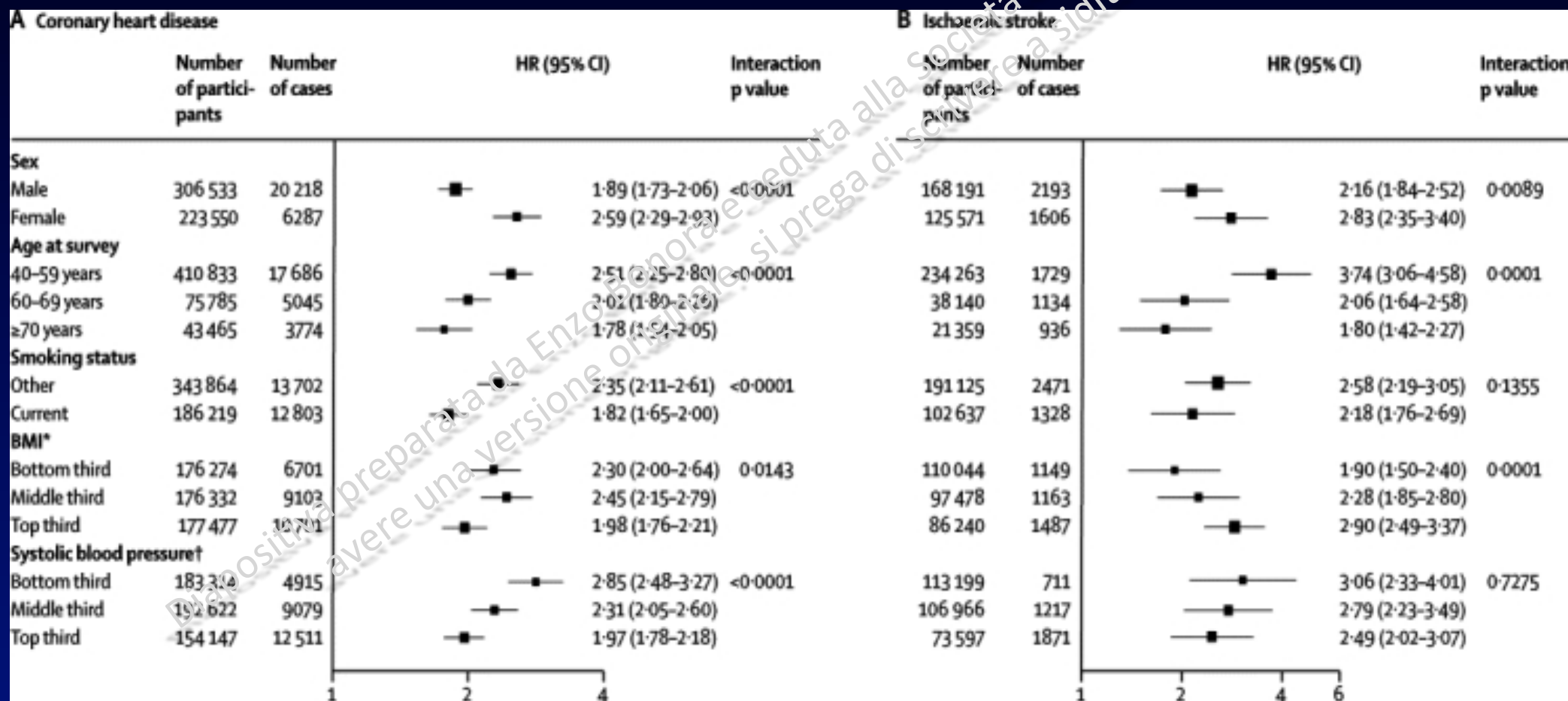
Risk of CVD in diabetes vs. no diabetes

Emerging Risk Factors Collaboration – Lancet 2010; 375: 2215-2222



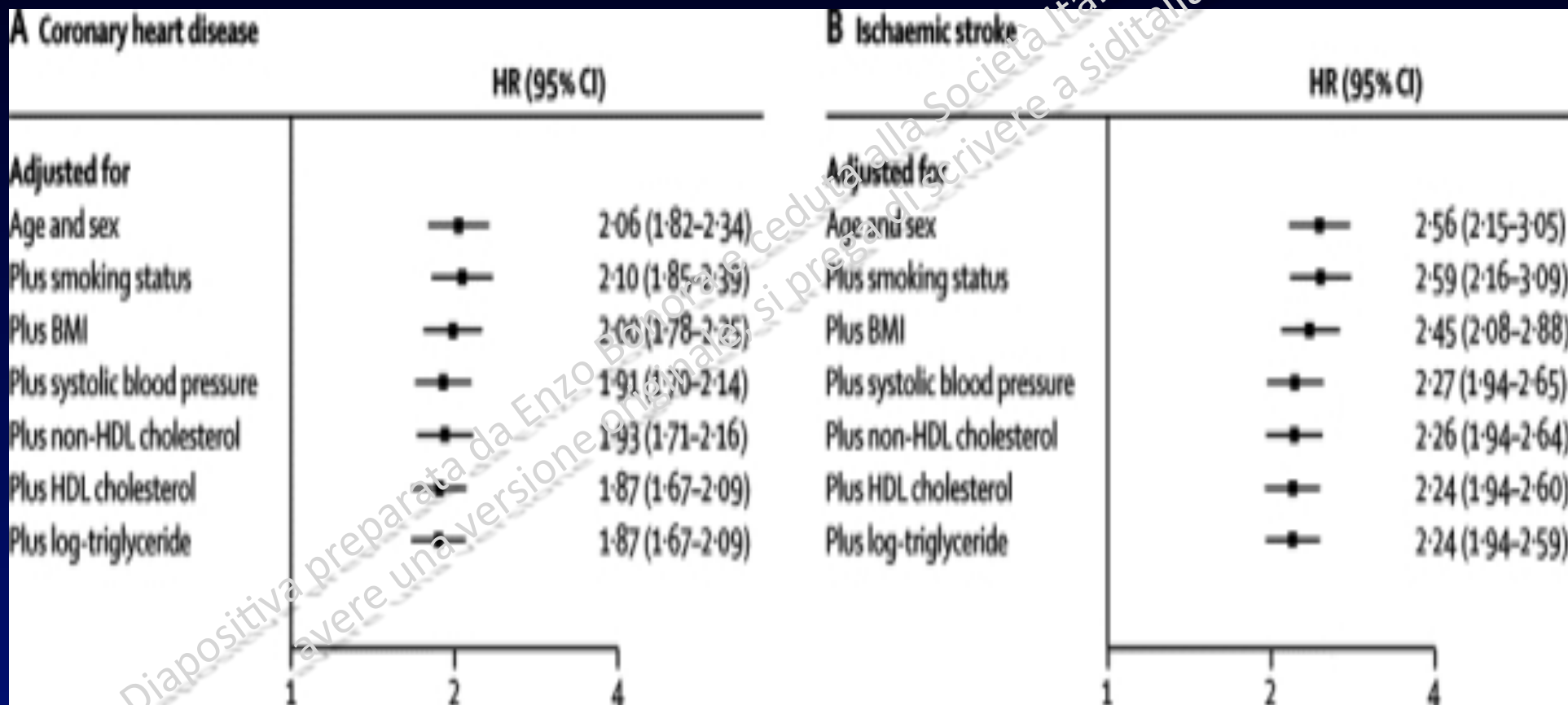
Risk of CVD in diabetes vs. no diabetes after stratification by main clinical features

Emerging Risk Factors Collaboration – Lancet 2010; 375: 215-222



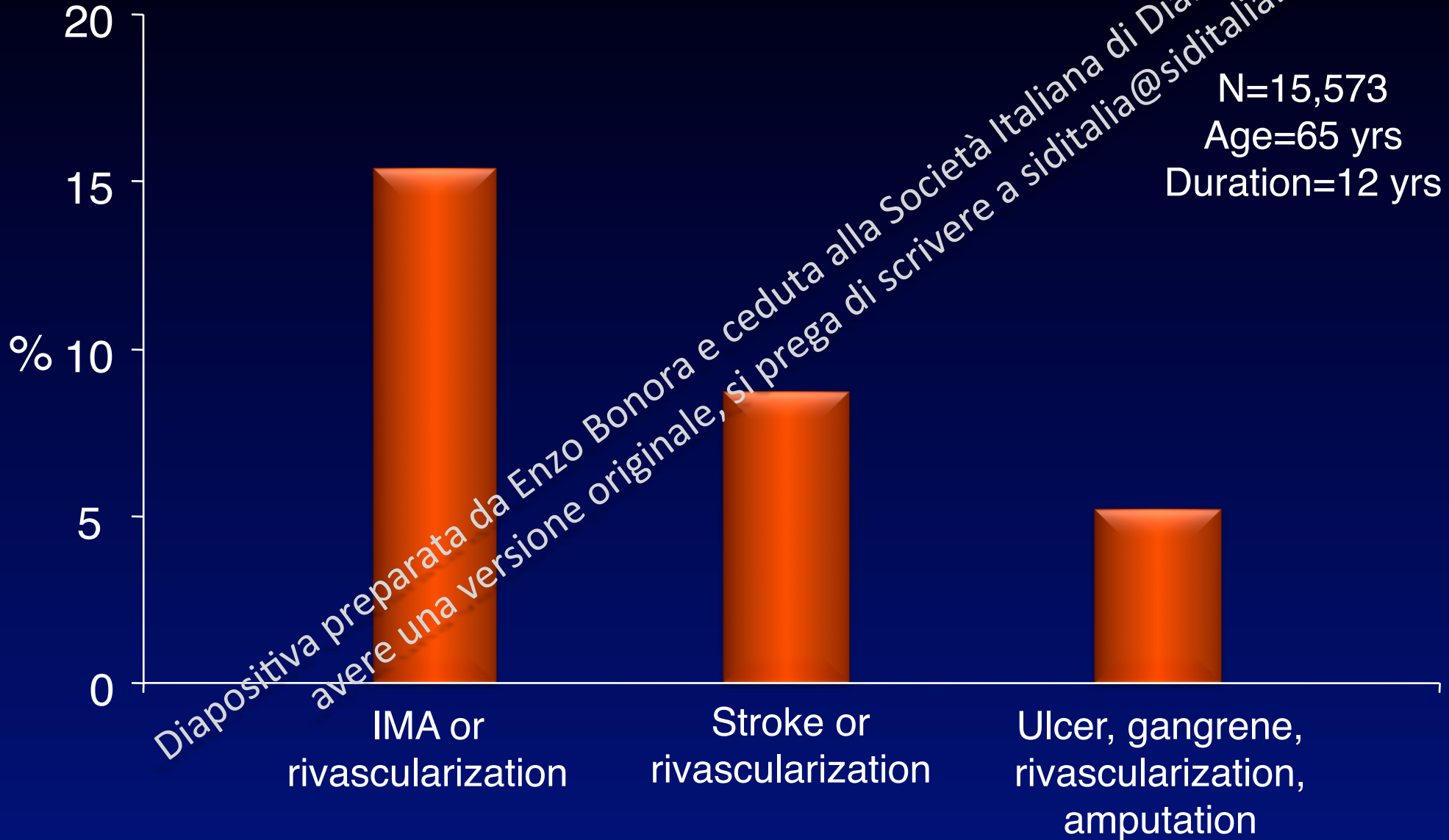
Risk of CVD in diabetes vs. no diabetes after adjusting for possible confounding factors

Emerging Risk Factors Collaboration – Lancet 2010; 375: 215-222

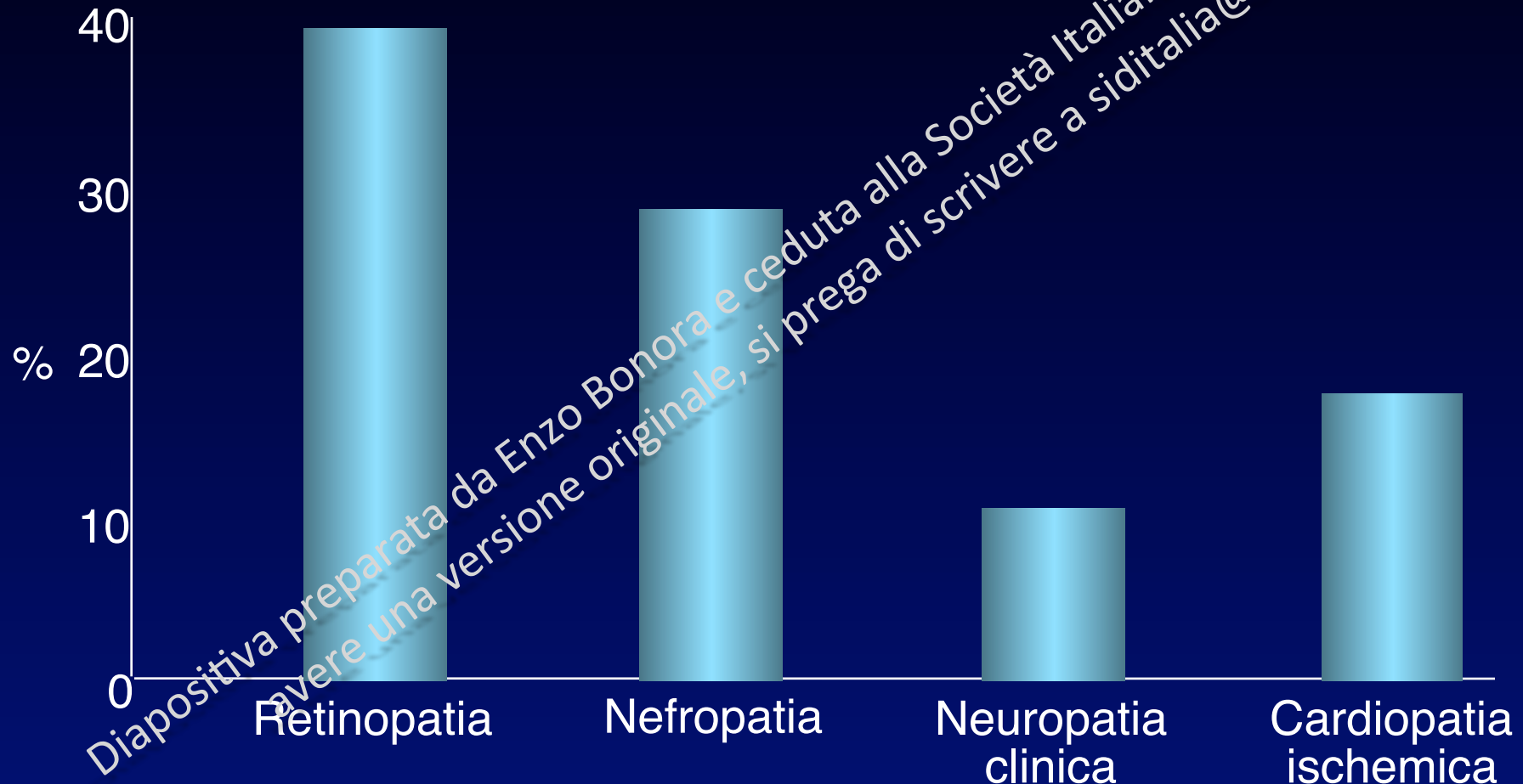


Macrovascular disease in T2DM

Riace – SID Study

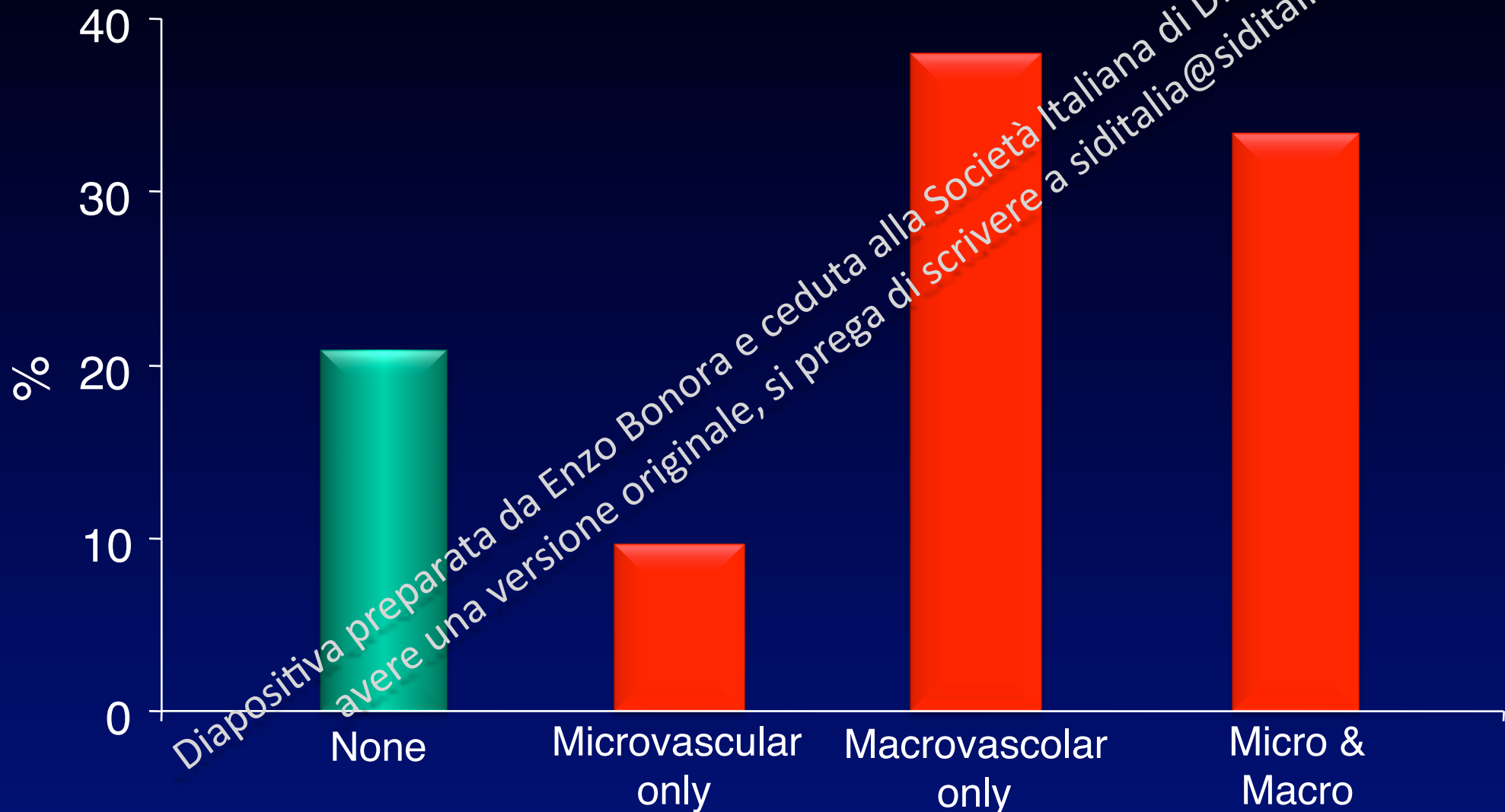


Complicanze croniche del diabete tipo 2 alla diagnosi (UKPDS - fine anni settanta)



Prevalence of Complications at Time of Diagnosis of Type 2 Diabetes in Verona

Verona Newly Diagnosed Diabetes Study; Bonora et al; unpublished data



Incidenza di infarto e ictus nel diabete tipo 2 in Italia

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

In 10 anni

1 maschio ogni 8 e 1 donna ogni 16

Avranno un infarto (più spesso fatale rispetto ad un non diabetico) o saranno sottoposti ad una rivascolarizzazione coronarica

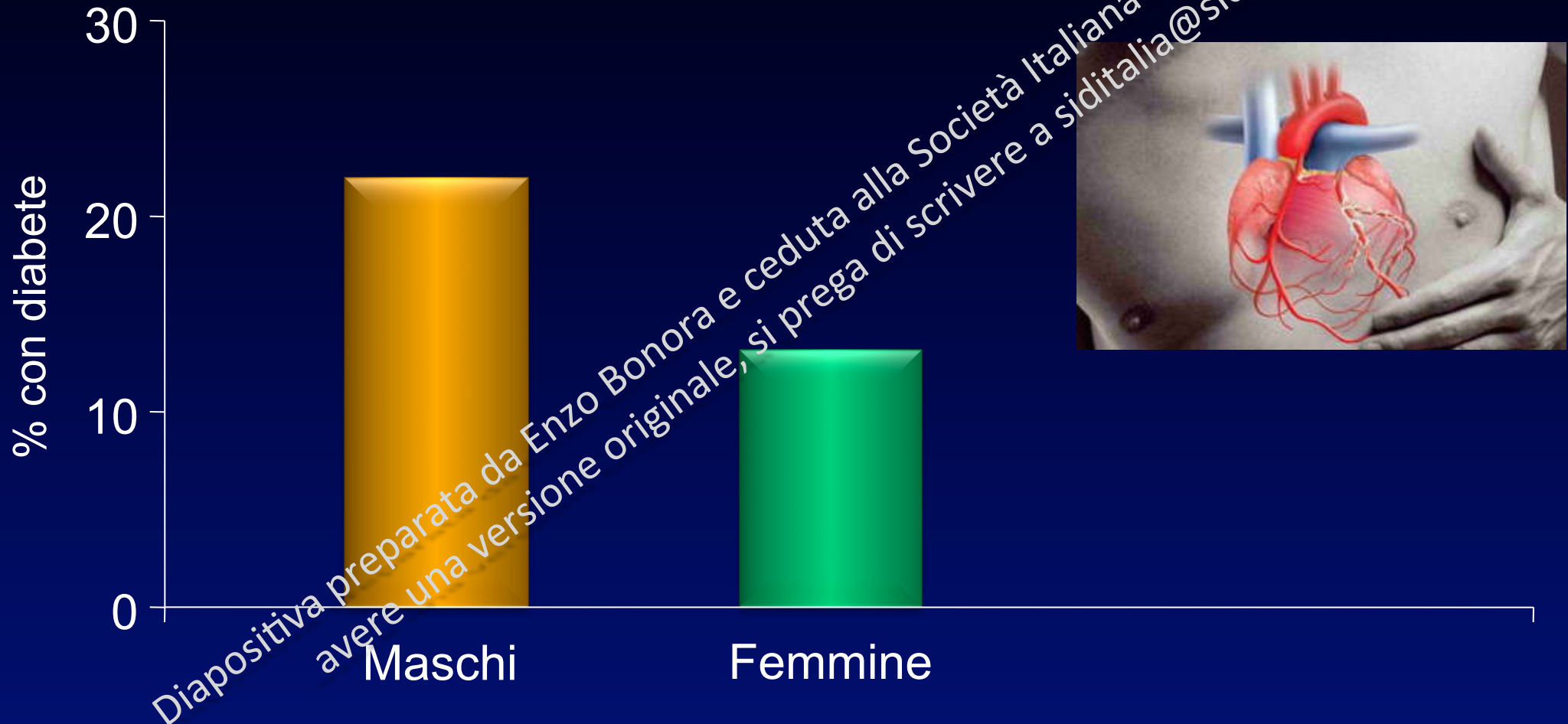
1 maschio ogni 16 ed 1 donna ogni 16

Avranno un ictus (più spesso fatale rispetto ad un non diabetico)



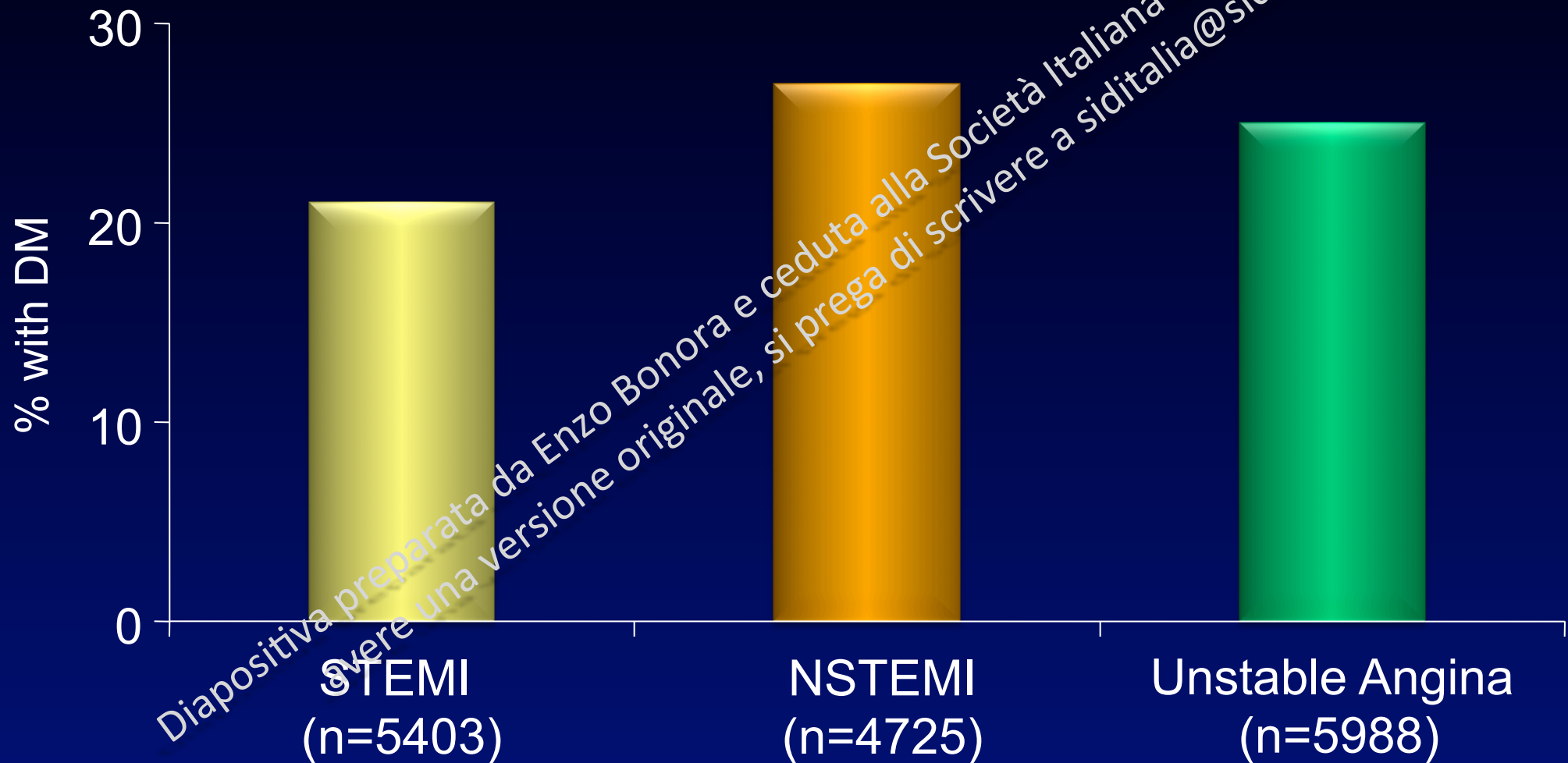
Diabete fra i soggetti accolti in Unità Coronarica a Verona (anno 2011)

Vassanelli et al; dati non pubblicati



Diabetes in the Global Registry of Acute Coronary Syndromes

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



Type 2 Diabetes Increases the Risk of Incident Congestive Heart Failure

The Kaiser Permanente Northwest study
n=8,231 patients with diabetes and 8,845 non-diabetic patients; follow up duration: 6 years

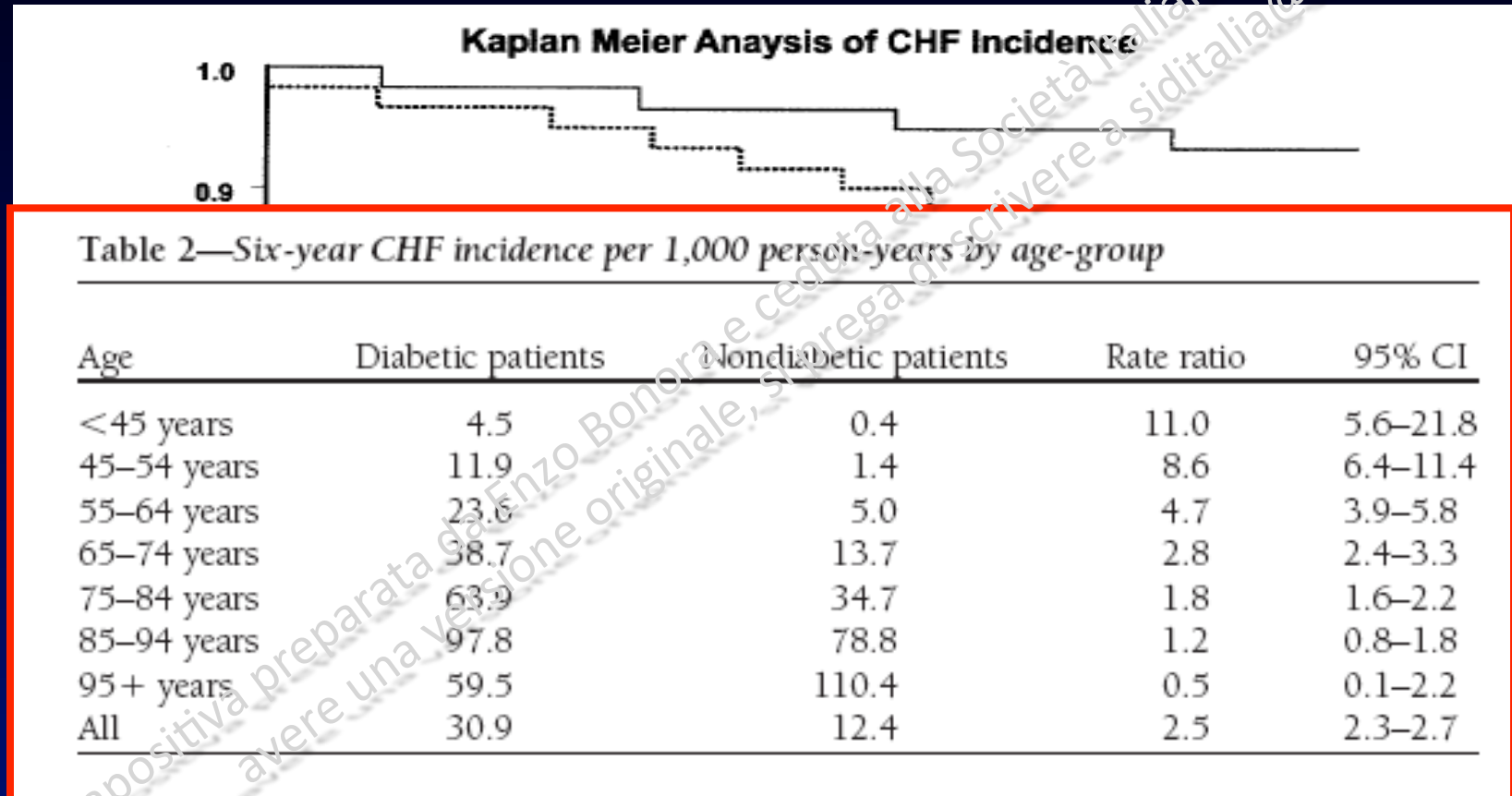


Figure 1—Kaplan-Meier analysis of CHF incidence comparing the diabetic (---) and nondiabetic (—) cohorts. The cohorts are significantly different ($P < 0.001$).

Prime 10 cause di ricovero nei diabetici

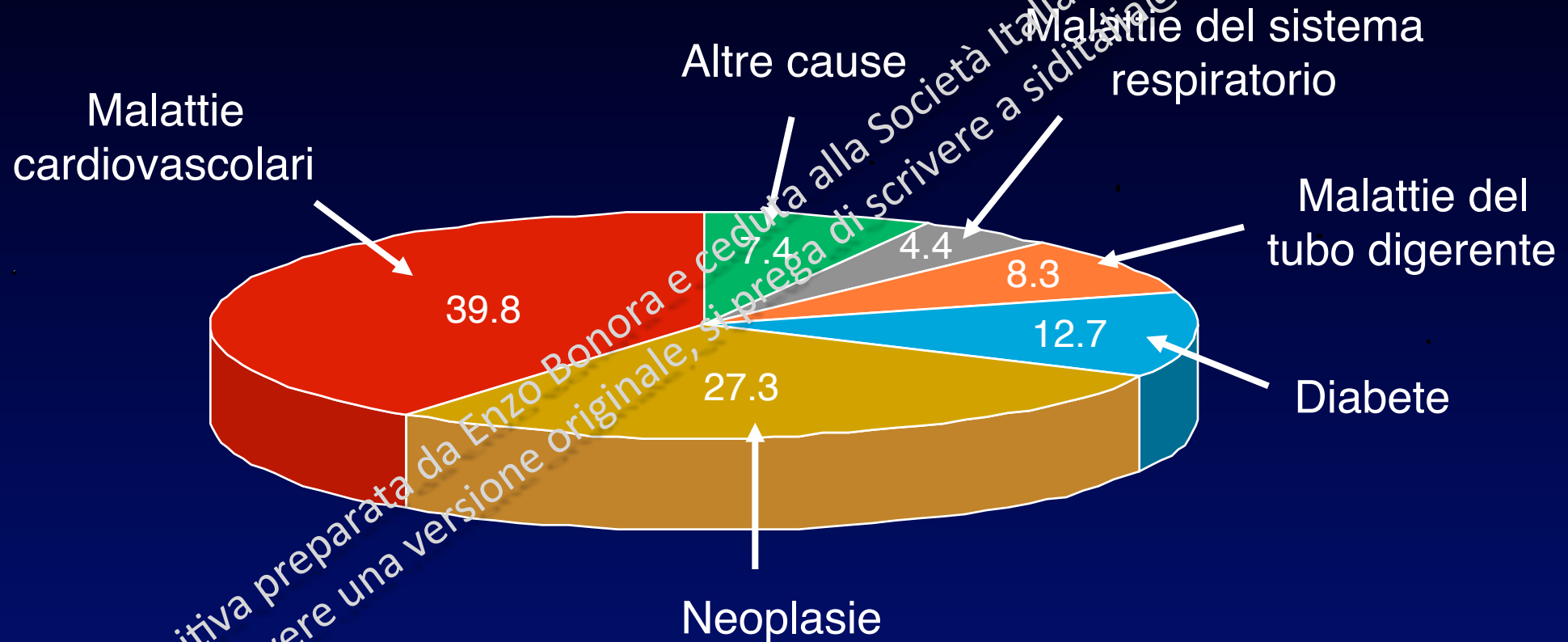
ARNO Diabete 2012

Causa principale sulla SDO	Tassi per 1000 diabetici	Tassi per 1000 non diabetici	Differenza rispetto a non diabetici (%)
Insufficienza cardiaca	15.7	4.3	+263
Altre malattie del polmone	9.3	2.6	+259
Infarto del miocardio	7.3	2.7	+172
Altre forme di cardiopatia ischemica	6.1	1.9	+213
Aritmie cardiache	5.8	3.3	+75
Fratture collo femore	5.0	3.4	+47
Artrosi	5.0	4.6	+8
Occlusione arterie cerebrali	4.7	1.8	+169
Colelitiasi	4.4	3.3	+31
Broncopneumite	4.0	1.5	+170

Circa 5 diabetici su 100 in un anno si ricoverano per CVD; circa 20 ricoveri su 100 sono per CVD

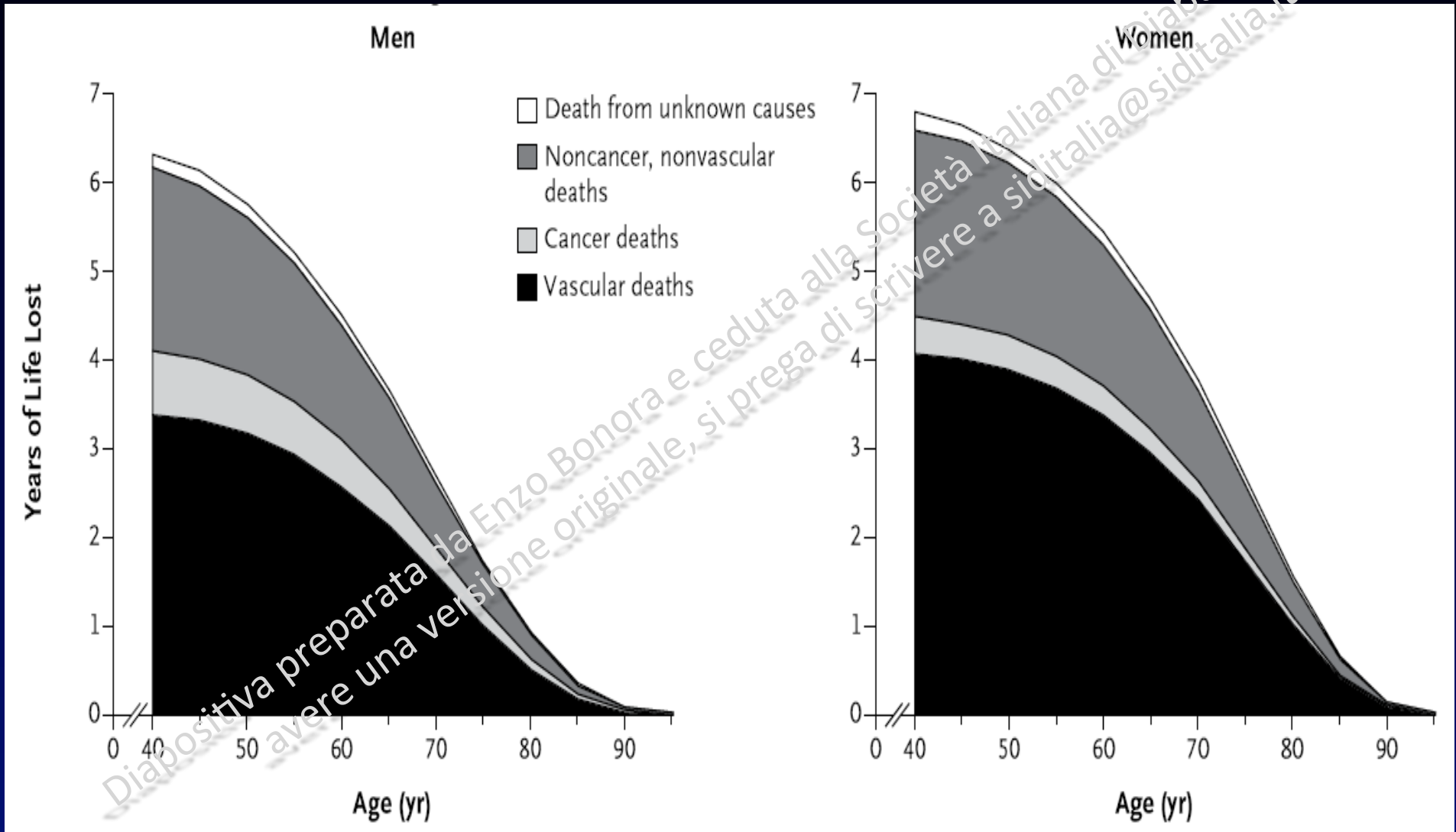
Cause di morte fra i diabetici italiani

(Verona Diabetes Study, 1986-1996)



Estimated Years of Life Lost due to DM

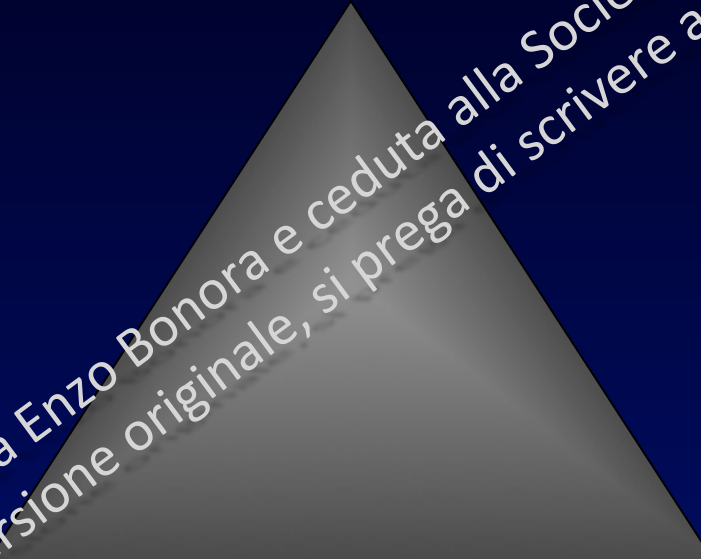
Emerging Risk Factors Collaboration – N Engl J Med 2011; 364:829-841



N= 700.000

The Killing Glycemic Triad in T2DM

Hyperglycemia (including peaks)



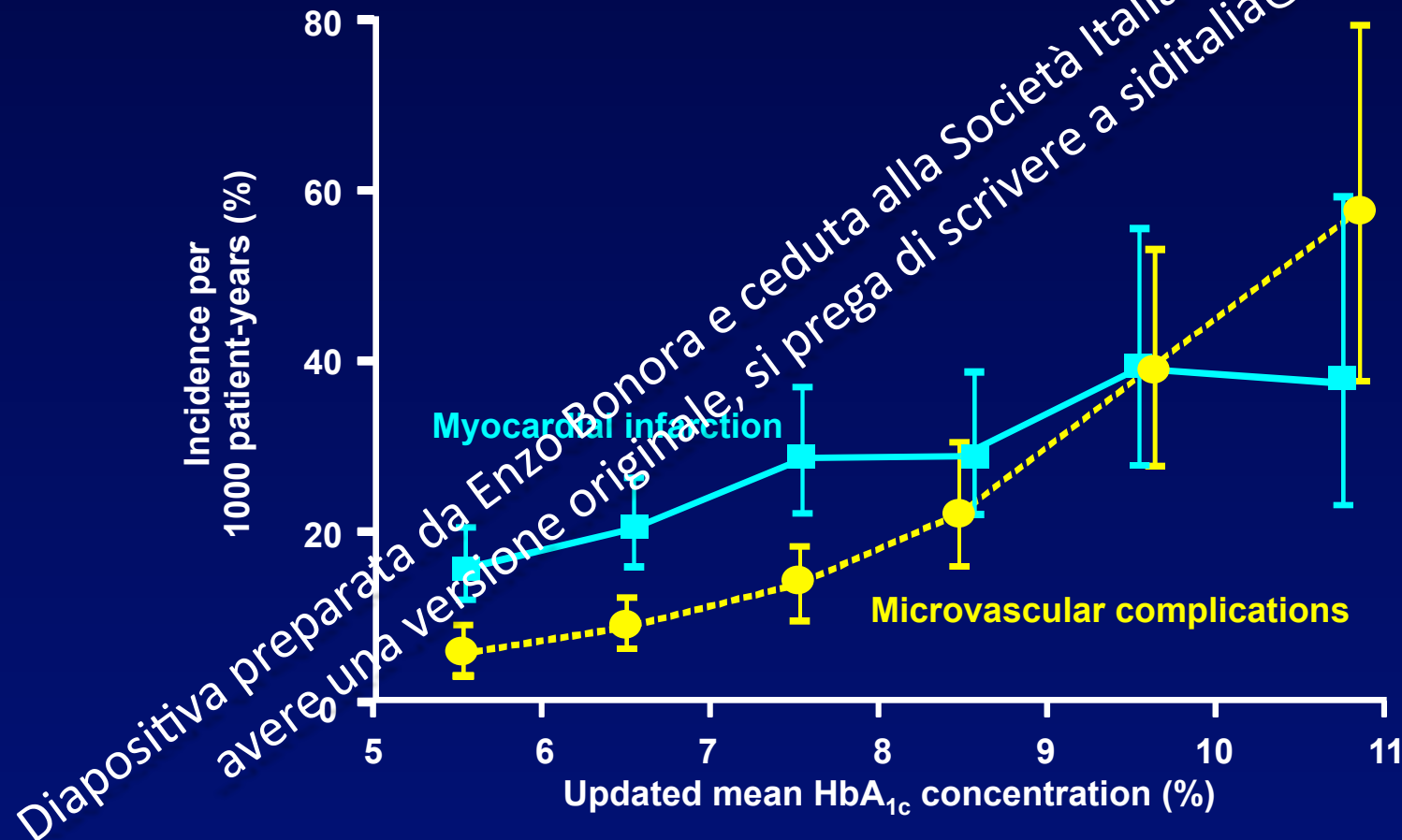
Hypoglycemia

Glucose variability

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

Incidence of Myocardial Infarction and Microvascular Complications in T2DM According to HbA1c – Observational Analysis

UKPDS 35 - BMJ 2000; 321:405–412



Adjusted for age, sex, and ethnic group

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

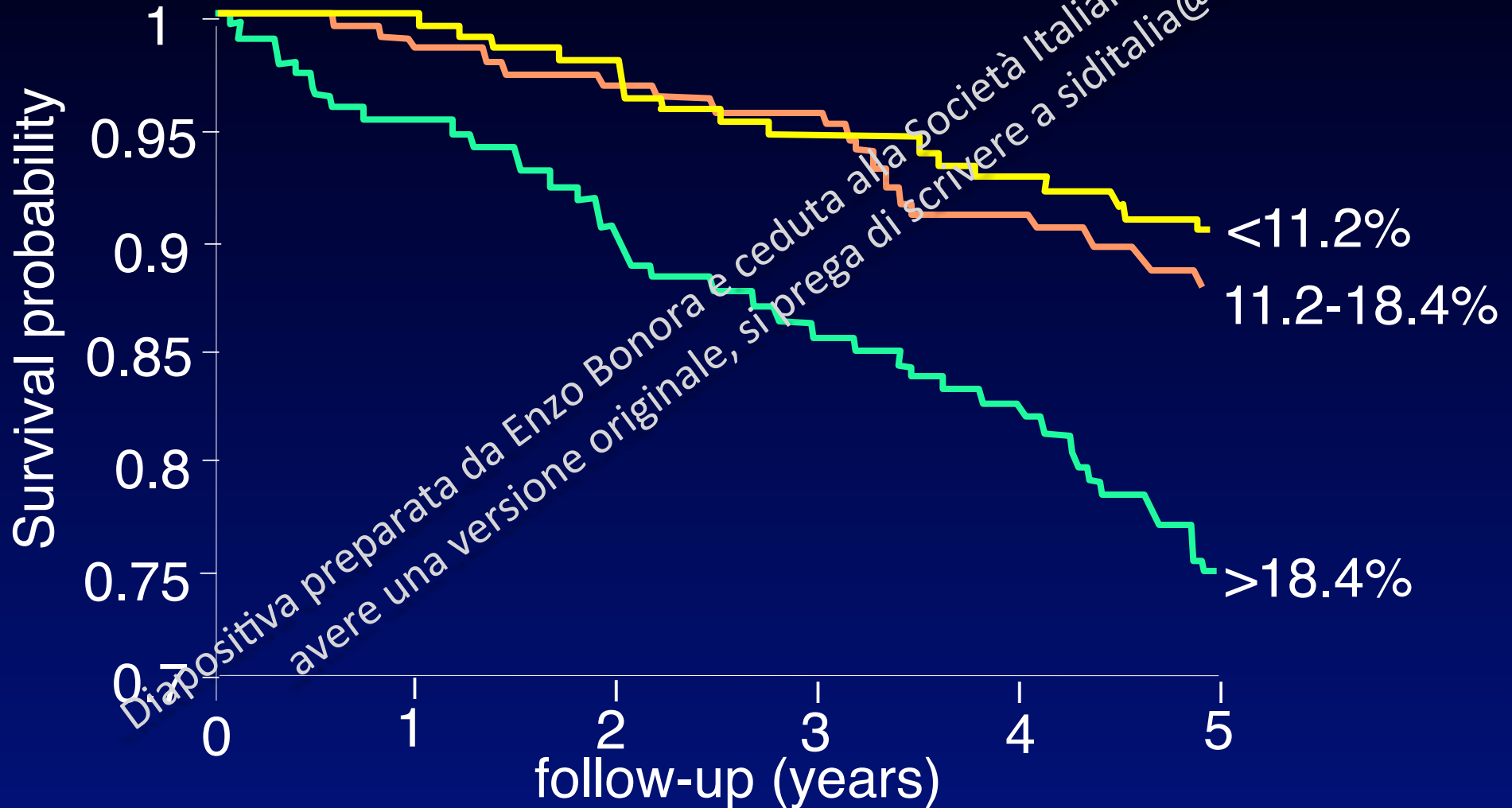
VADT - Predictors of CVD Death

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 HbA _{1c} per 1%	1.213	0.0150
Severe Hypoglycemia	4.042	0.0076

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

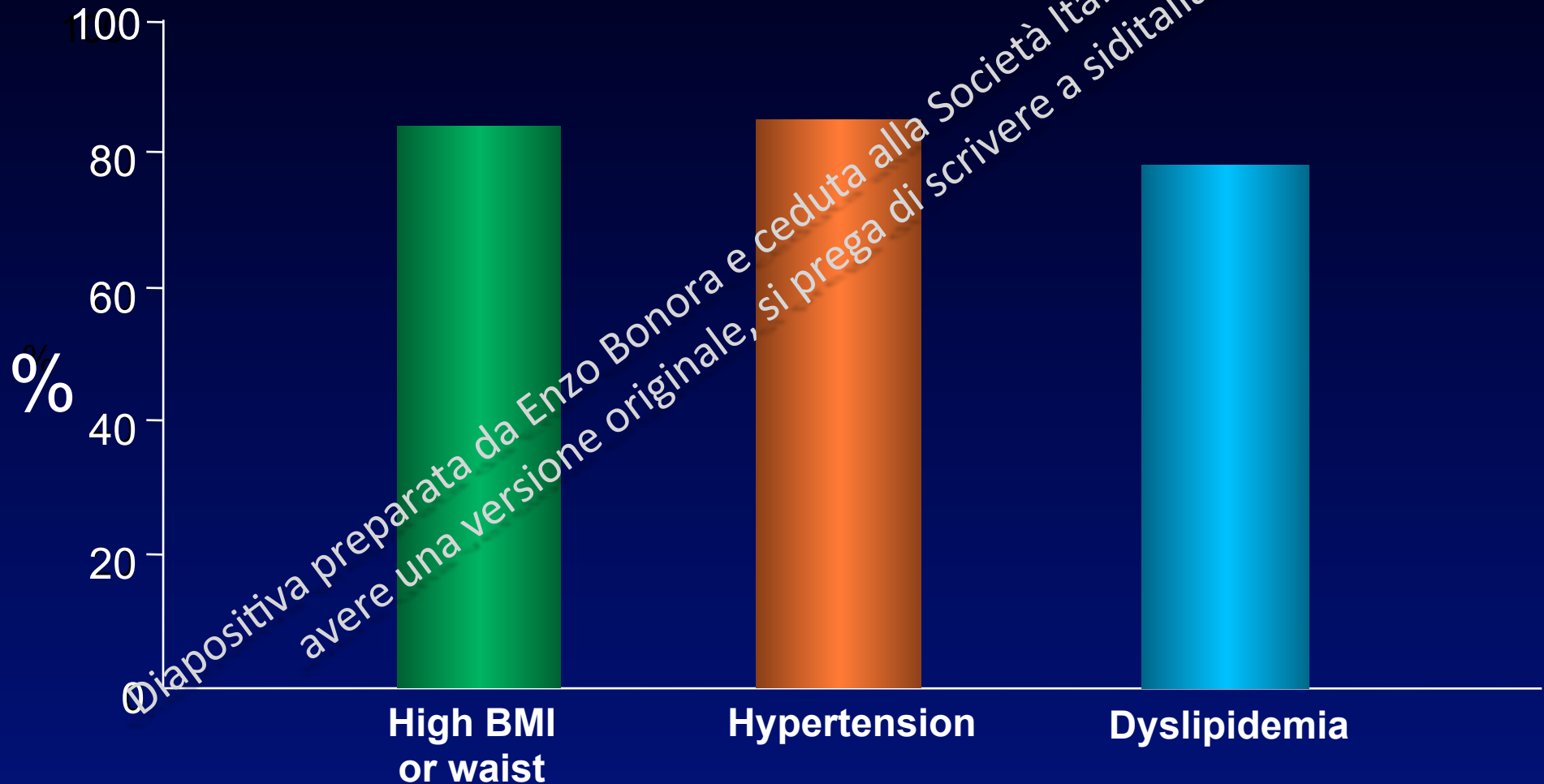
Cardiovascular mortality in elderly patients with T2DM stratified according to the variability of fasting plasma glucose (CV-FPG)

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



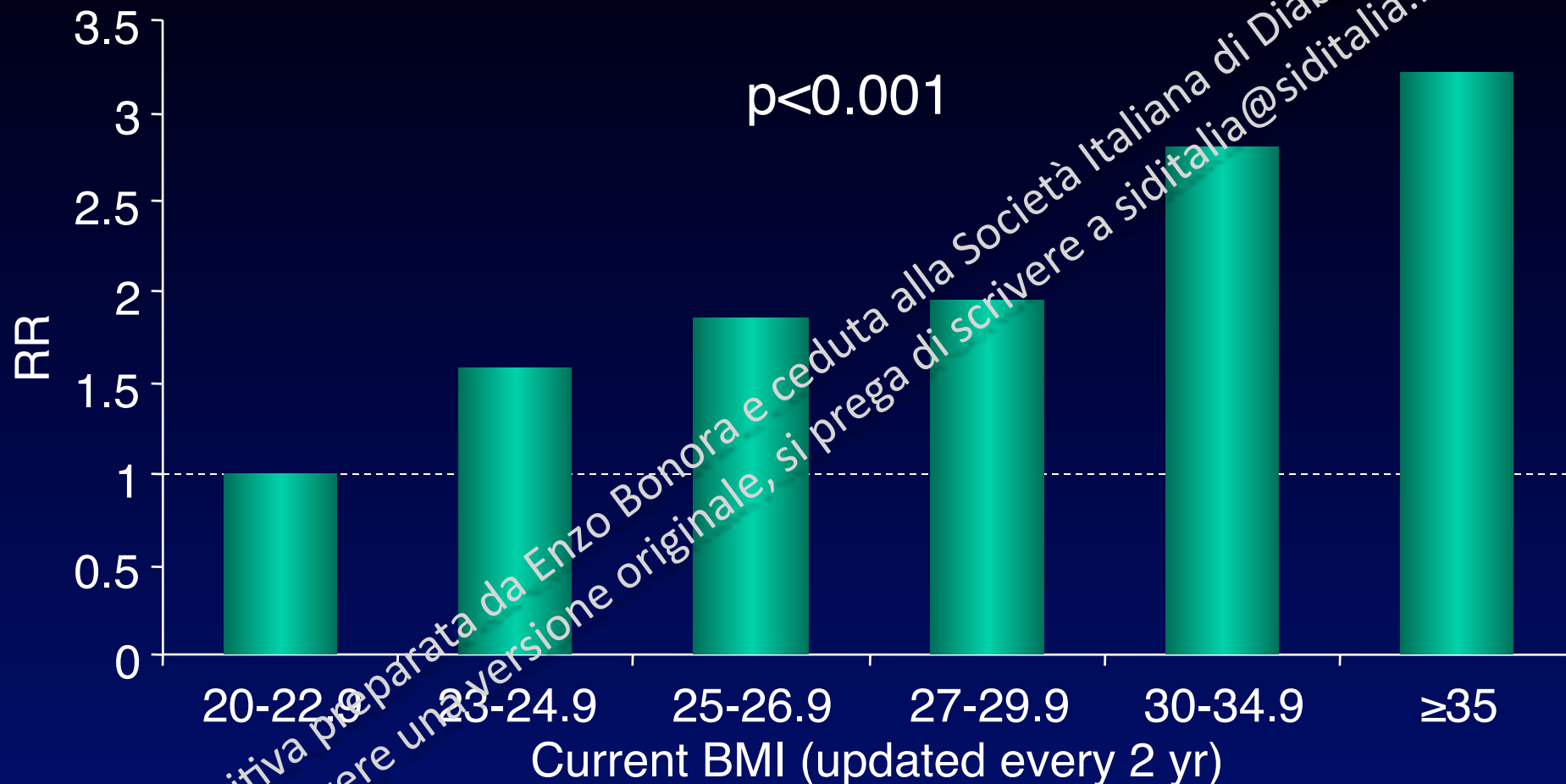
Prevalence of “Traditional non Glycemic Cardiovascular Risk Factors in Subjects with T2DM

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



BMI and risk of CHD in diabetic women from Nurses' Health Study: 20-yr follow-up

(Cho et al; Diabetes Care 25: 1142, 2002)



Adjusted for age, family history of CVD, smoking, hypertension, cholesterol, HRT, duration of diabetes, OHA/insulin

Separate and combined associations of body-mass index and abdominal adiposity with cardiovascular disease: collaborative analysis of 58 prospective studies

The Emerging Risk Factors Collaboration*

58 prospective studies: 221,934 people, 70% of these participants also had data on smoking status, systolic blood pressure, history of diabetes, and total and HDL cholesterol.

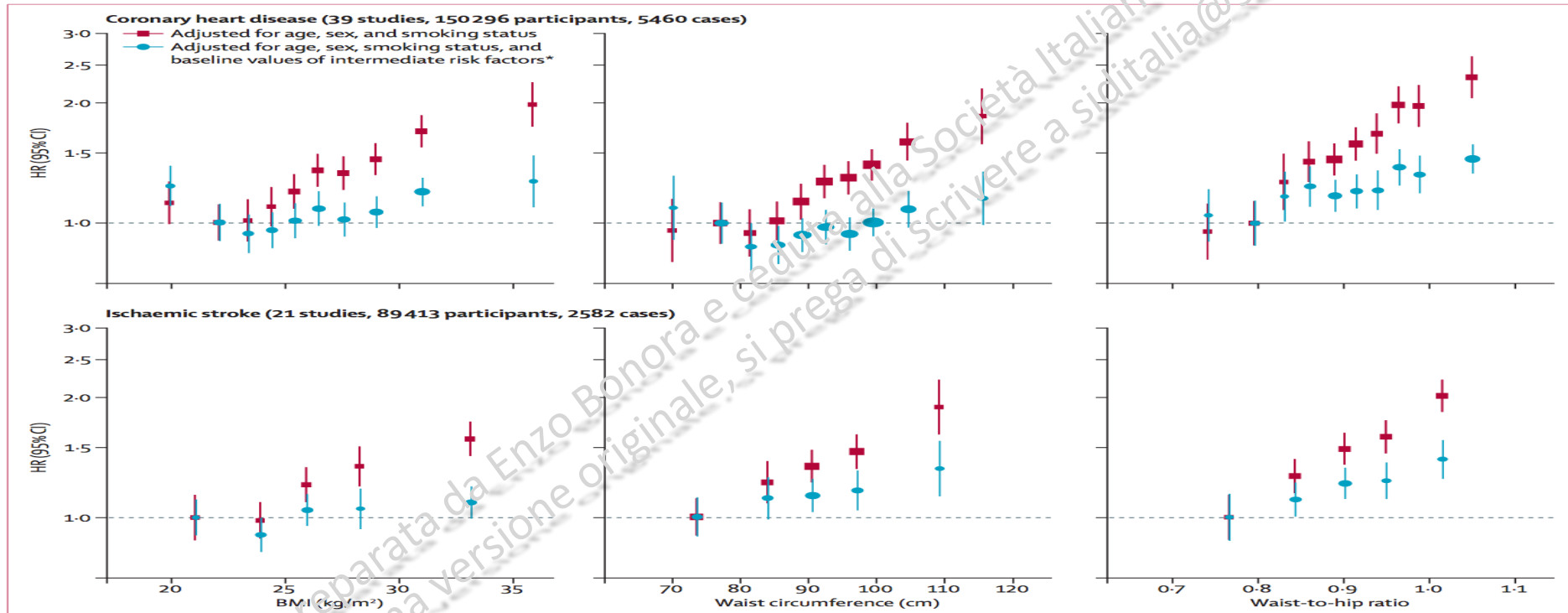
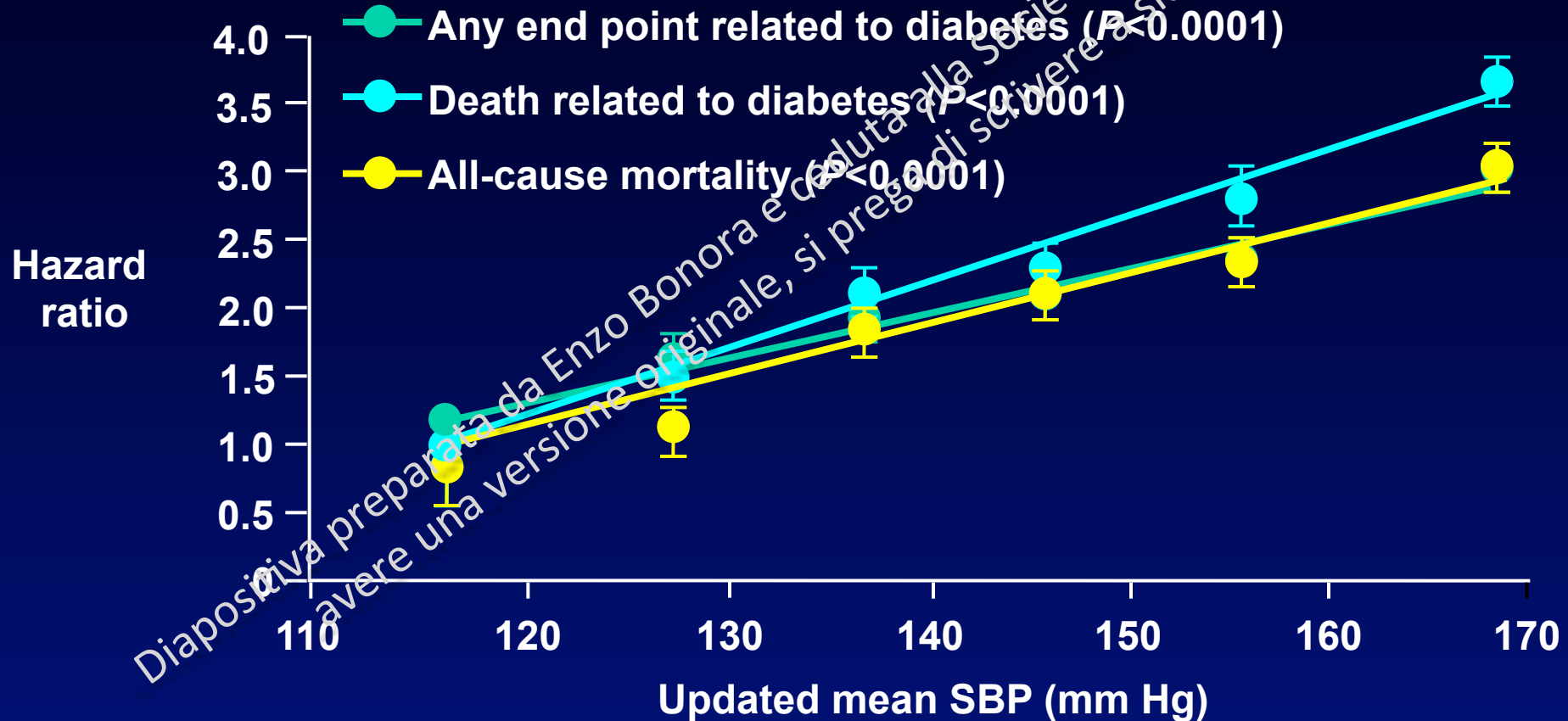


Figure 1: HRs for coronary heart disease and ischaemic stroke across quantiles of baseline BMI, waist circumference, and waist-to-hip ratio
Regression analyses were stratified, where appropriate, by sex. Adjusted study-specific log HRs were combined by multivariate random-effects meta-analysis. Y-axes are shown on a log scale. Reference groups are the second deciles in the plots for coronary heart disease and the first quintiles in the plots for ischaemic stroke. HR=hazard ratio. BMI=body-mass index. *Intermediate risk factors were systolic blood pressure, history of diabetes, and total and HDL cholesterol.

Interpretation BMI, waist circumference, and waist-to-hip ratio, whether assessed singly or in combination, do not importantly improve cardiovascular disease risk prediction in people in developed countries when additional information is available for systolic blood pressure, history of diabetes, and lipids.

End Point Hazard Ratios Associated with Increase in SBP – UKPDS Observational

(Adler A et al. - BMJ 2000; 321:412–419)



Impact of low-density lipoprotein cholesterol on cardiovascular outcomes in people with type 2 diabetes: A meta-analysis of prospective cohort studies

16 prospective studies with approximately 40,000 T2DM pts; follow-up range of 4.8-11 years.
Study outcome: CVD death.

B. CVD mortality
Study, publication years

ES (95% CI) Weight %

Niskanen et al., 1996

1.12 (0.56, 2.25) 6.93

Lehto et al., 1997

1.38 (0.93, 2.05) 21.52

Mattock et al., 1998

1.90 (1.22, 2.97) 16.89

Van Hateren et al., 2009 60-75

1.49 (1.16, 1.91) 54.66

Overall (I-squared = 0.0%, p = 0.589)

1.50 (1.25, 1.80) 100.00

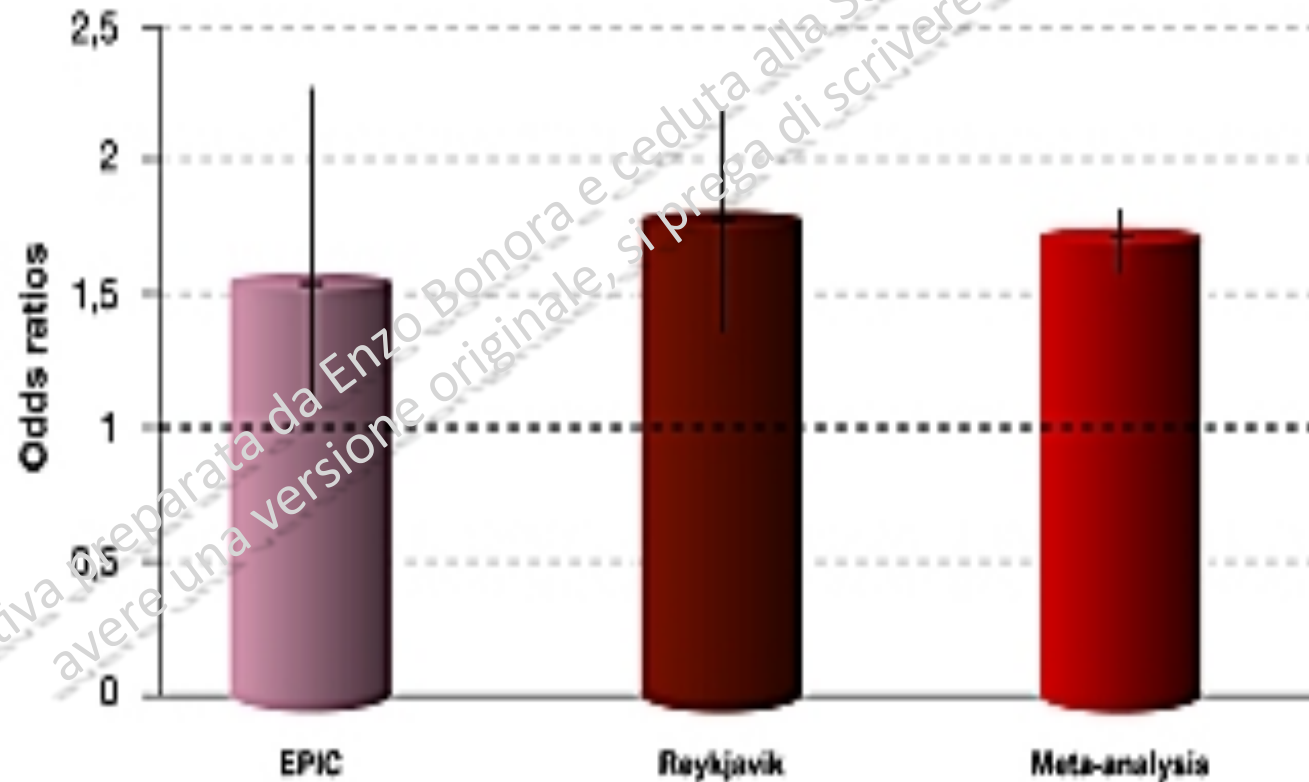
NOTE: Weights are from random effects analysis

.5 .8 1 2 3 4

Fig. 2 – Forest plot of relative risks (RRs) and 95% confidence intervals (CIs) for the association between per 1 mmol/L increase in low-density lipoprotein cholesterol and the main study outcomes risks in type 2 diabetes.

Odds ratios for incident CHD events in individuals in the upper tertile of triglycerides concentrations compared with those in the lowest tertile in the EPIC-Norfolk study, the Reykjavik study and in a meta-analysis of 29 prospective studies

(Sarwar N et al - Circulation 2007;115:450-459)



Metabolic Syndrome predicts CVD in T2DM

(Verona Diabetes Complications Study; Bonora et al, Diabetic Medicine: 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

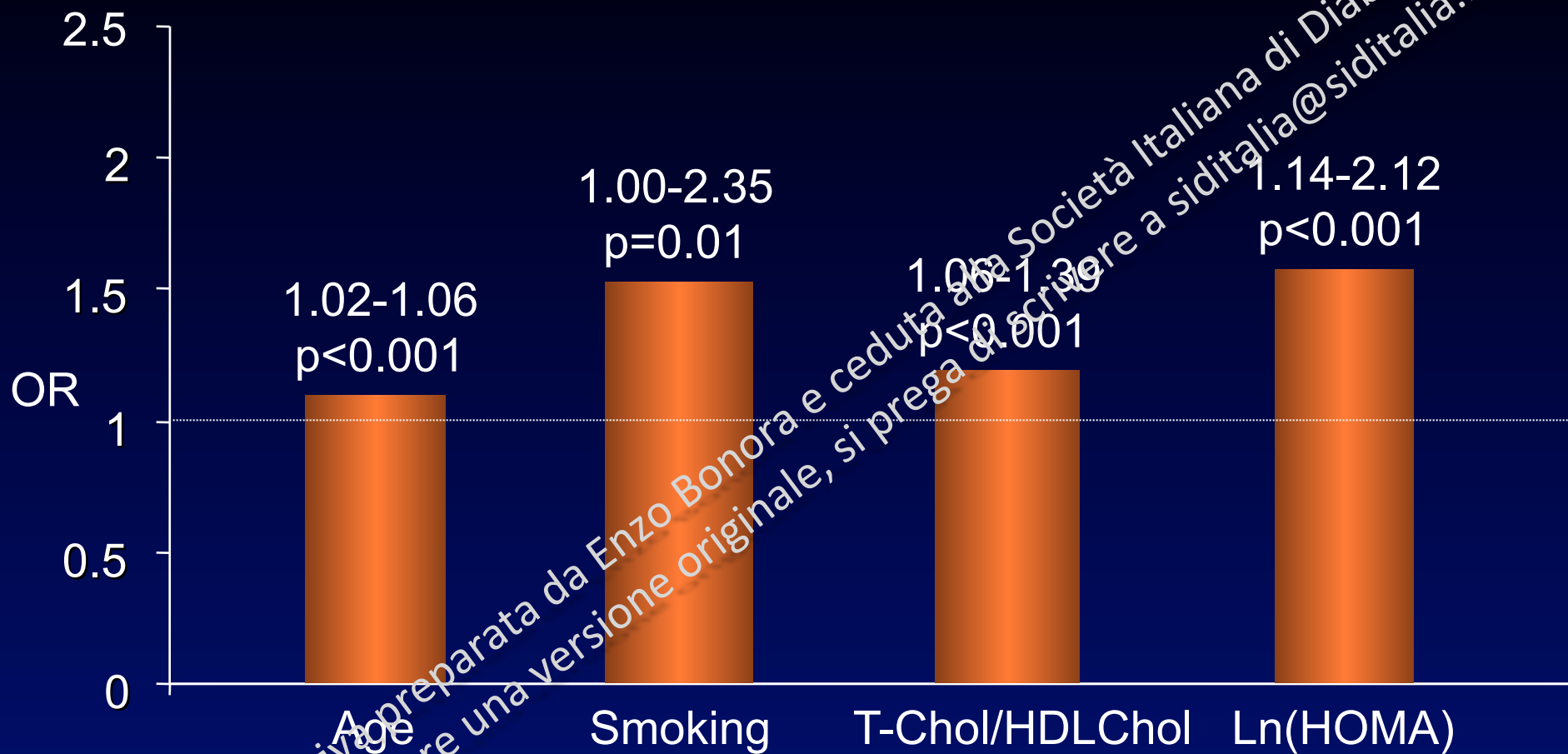
n= 559; age 65 yr; duration 9 yr; follow-up 4.5 yr

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)

Cardiovascular Risk Factors in Diabetes

Traditional

- Male sex
- Age
- FH CVD
- Glucose
- LDL cholesterol
- HDL cholesterol
- Triglycerides
- Blood pressure
- Smoking
- BMI
- Prior CVD

Non-traditional

- Lp(a)
- Homocystein
- Fibrinogen
- PAI-1
- CRP
- Microalbuminuria
- Uric acid
- GFR
- NAFLD
- VCAM-1 & Co.
- vWF
- ADMA
- Zinc
- NT-pro-BNP
-
-
-

Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis

1,024,977 participants (128,505 with diabetes) from 30 general population and high-risk cardiovascular cohorts and 13 chronic kidney disease cohorts, during a mean follow-up of 8.5 years

ACR

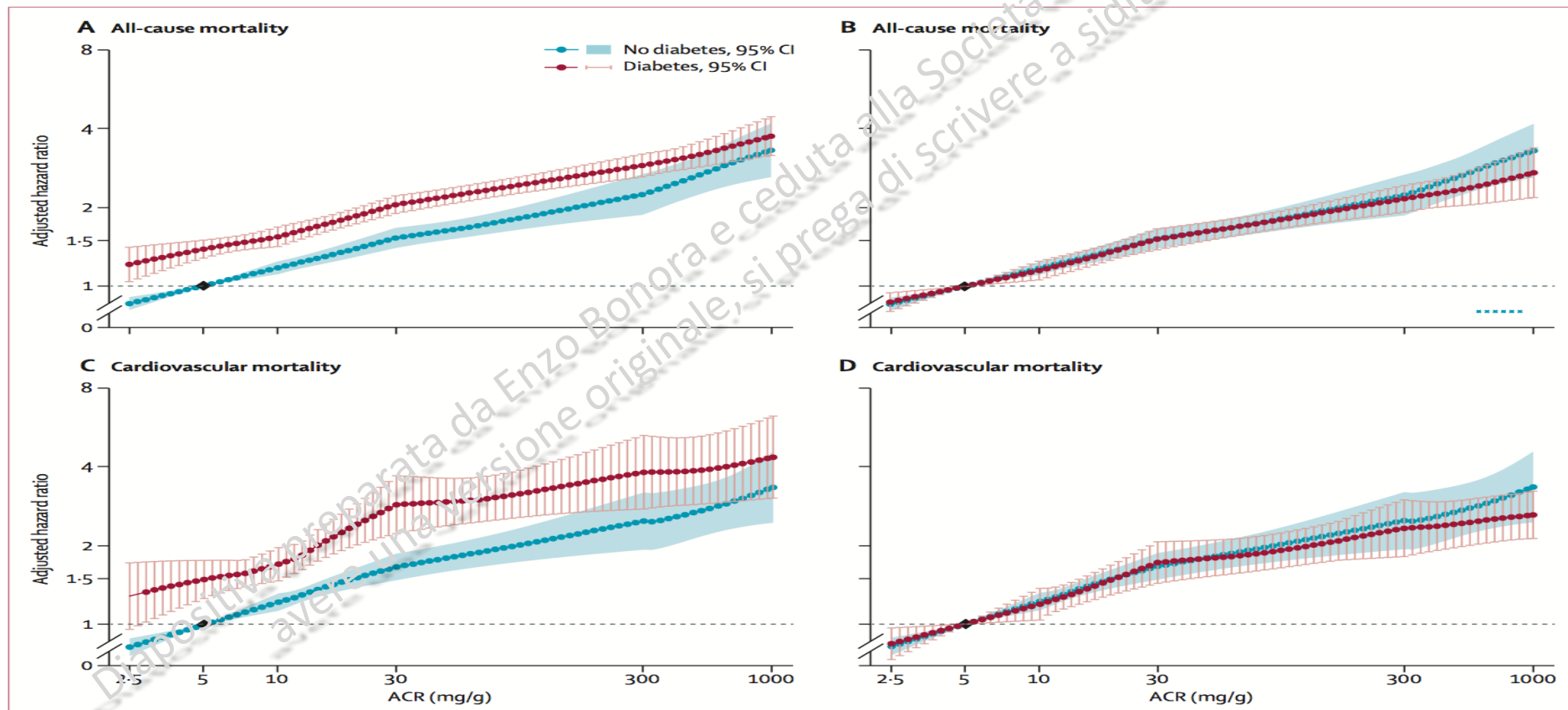


Figure 2: Hazard ratios for all-cause and cardiovascular mortality in the combined general and high-risk populations according to ACR in participants with and without diabetes

Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis

e-GFR

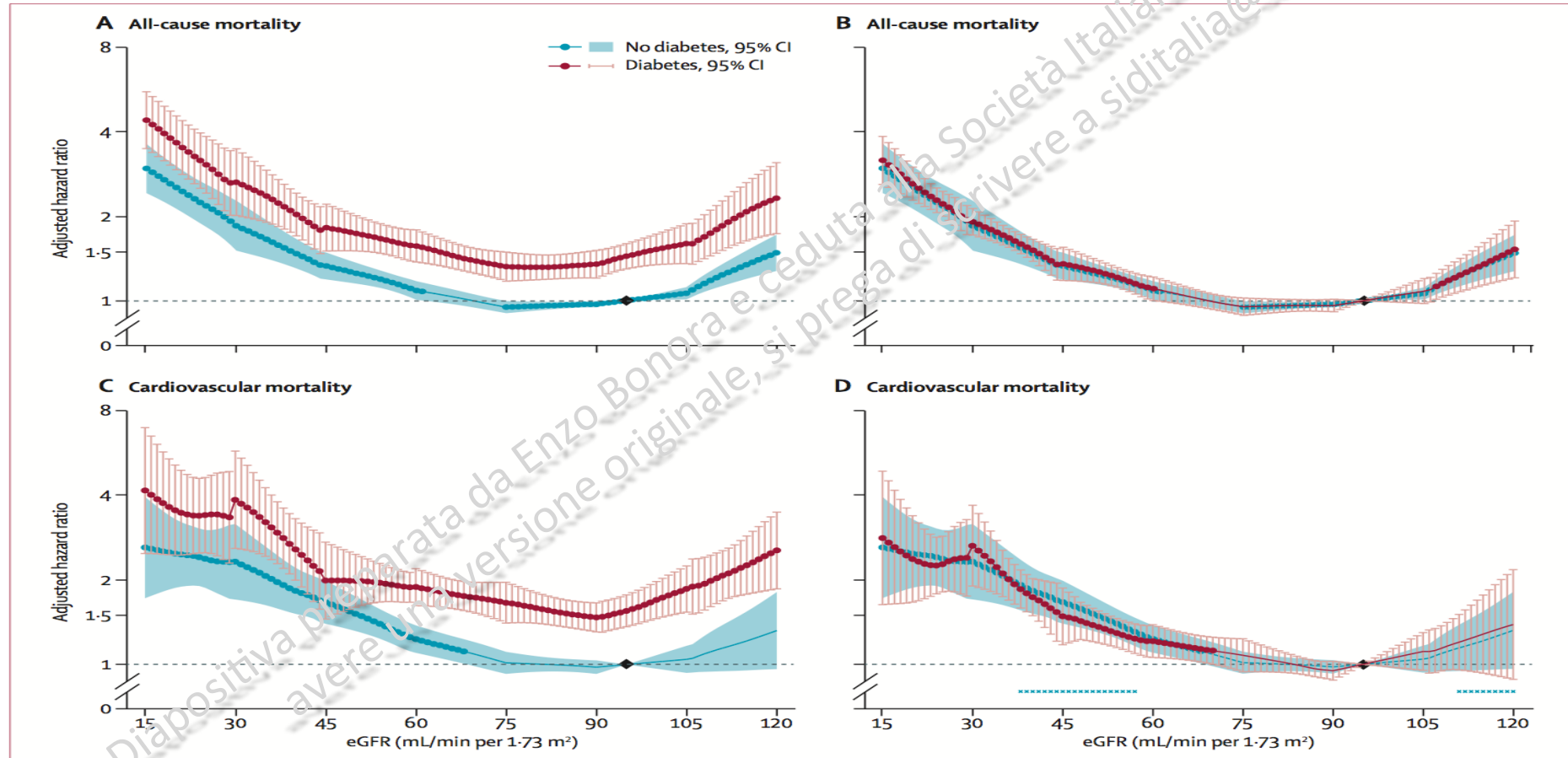
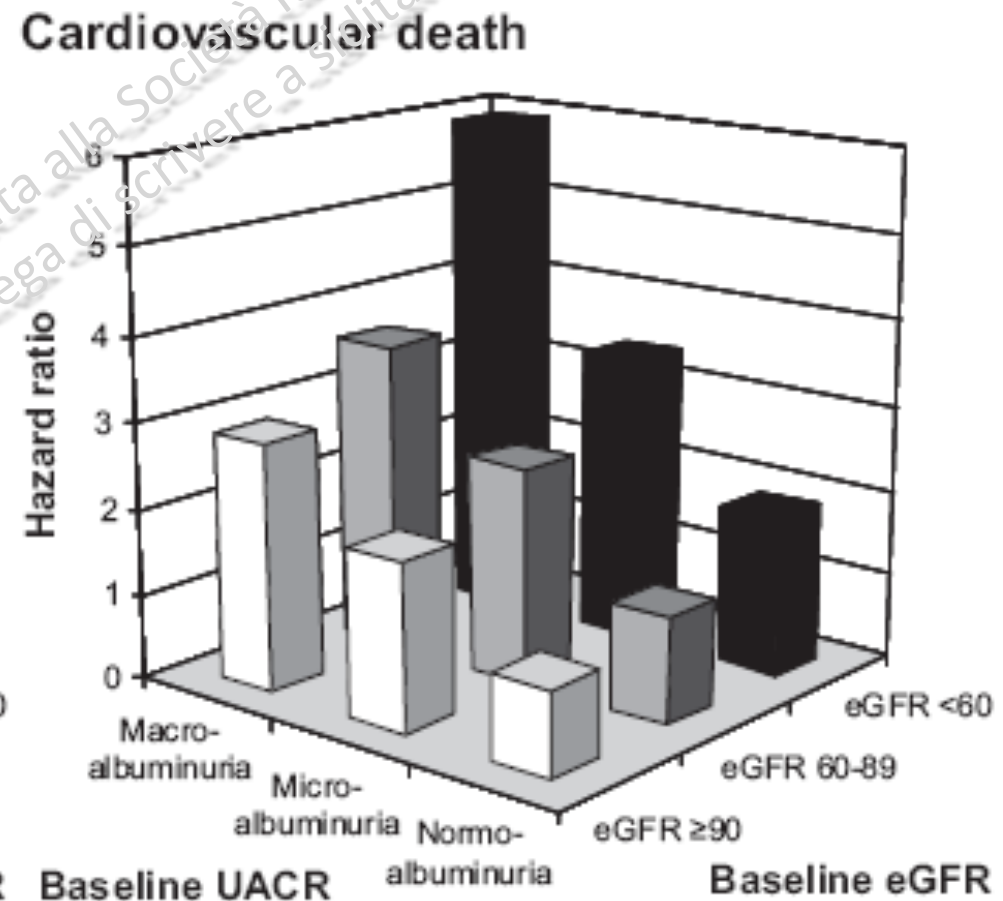
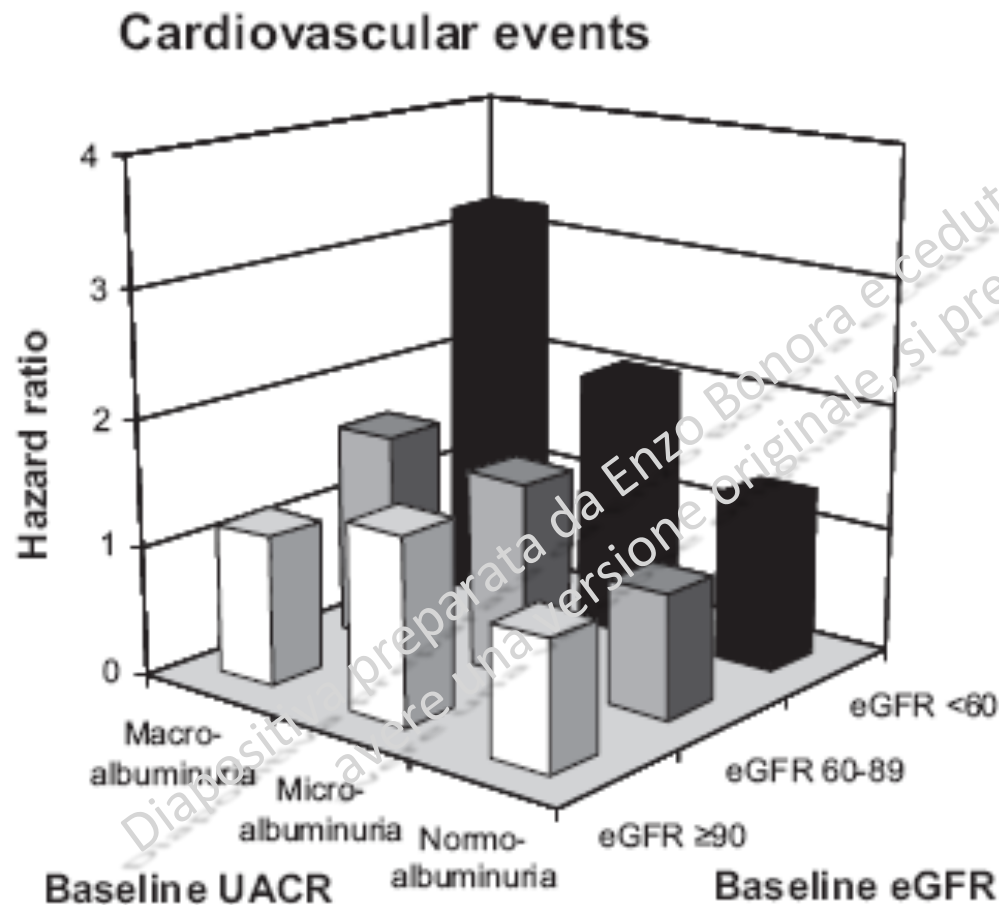


Figure 1: Hazard ratios for all-cause and cardiovascular mortality in the combined general and high-risk populations according to eGFR in individuals with and without diabetes

Risk of Cardiovascular Events and Death as a function of eGFR and albuminuria in T2DM

ADVANCE Study; Ninomiya T. et al. JASN, 2009; 20: 1811-21



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)	1.80 (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

Non-Traditional Risk Factors in T2DM

(Bruneck Study; unpublished)

	NGT	T2DM	p
Waist (cm)	86	92	0.03
Adiponectin (mg/dl)	12.7	8.9	0.001
Leptin (ng/ml)	8.9	12.6	0.001
Uric Acid (mg/dl)	5.28	5.92	0.001
ApoA1 (mg/dl)	165	154	0.002
ApoB (mg/dl)	119	135	0.001
LDL-C (mg/dl)	32	37	0.002

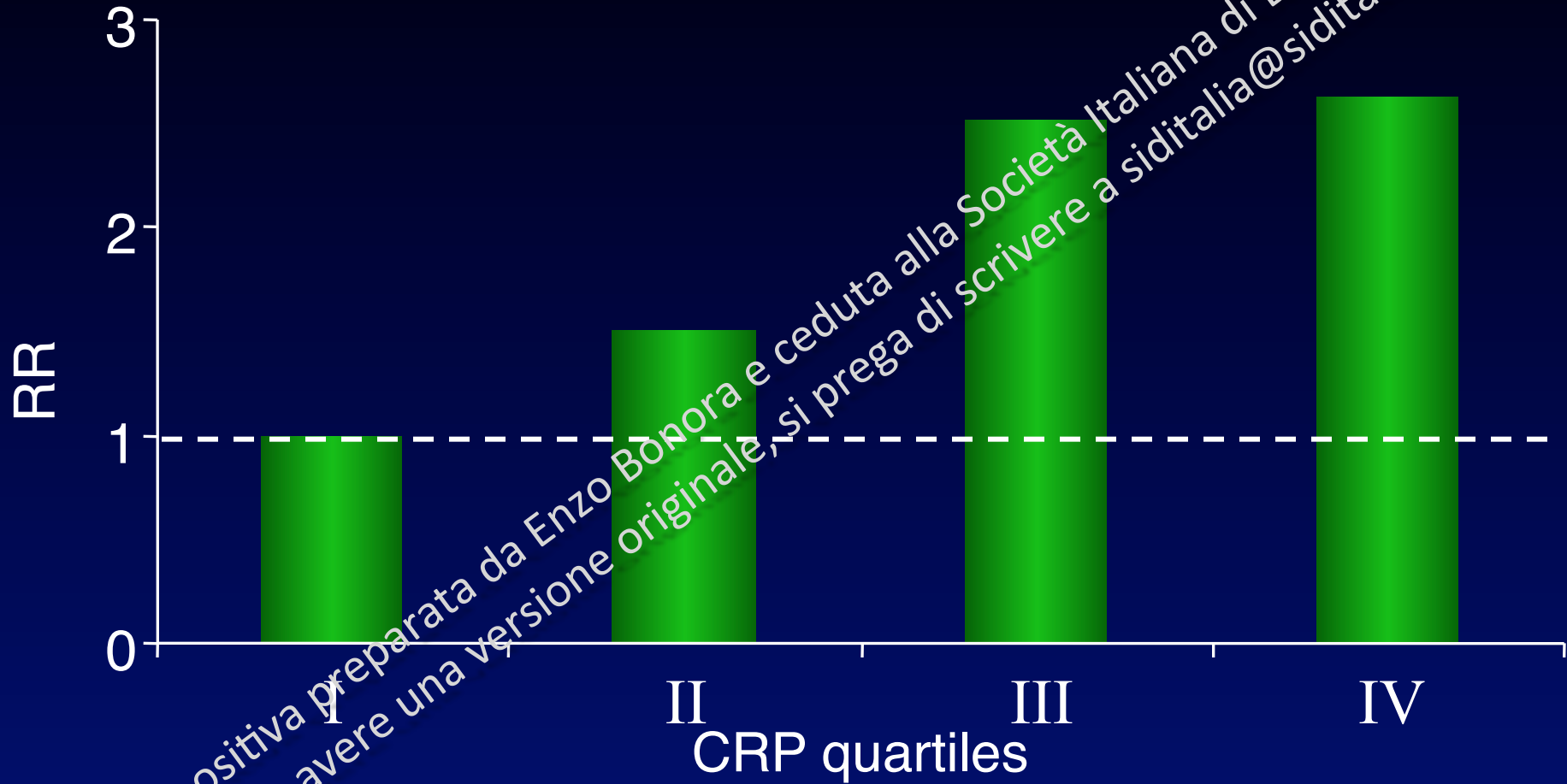
Non-Traditional Risk Factors in T2DM

(Bruneck Study; unpublished)

	NGT	T2DM	P
Ferritin (µg/l)	135	266	0.001
WBC (per mm ³)	6379	7560	0.001
hs-CRP (mg/l)	0.15	0.40	0.001
ICAM-1 (ng/ml)	327	378	0.001
VCAM (ng/ml)	688	777	0.031
E-selectin (ng/ml)	52	68	0.001
MMP-9 (ng/ml)	285	375	0.001

CRP Predicts CVD in Men with T2DM

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

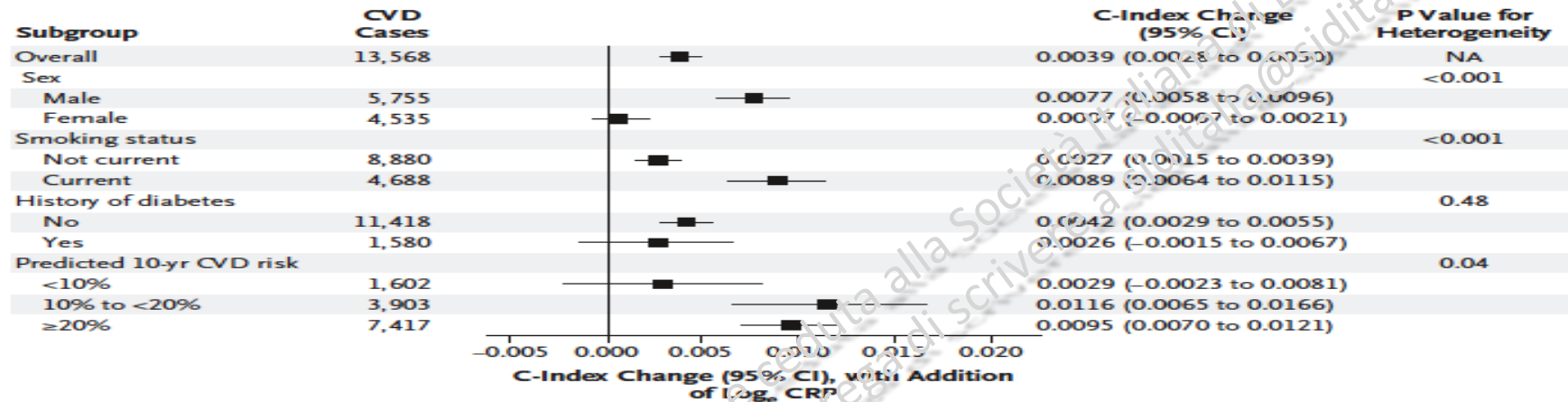


Data adjusted for age, life-style factors, hypertension, cholesterol, BMI
N= 746; follow-up 5 years

C-Reactive Protein, Fibrinogen, and Cardiovascular Disease Prediction

The Emerging Risk Factors Collaboration*

A C-Reactive Protein



B Fibrinogen

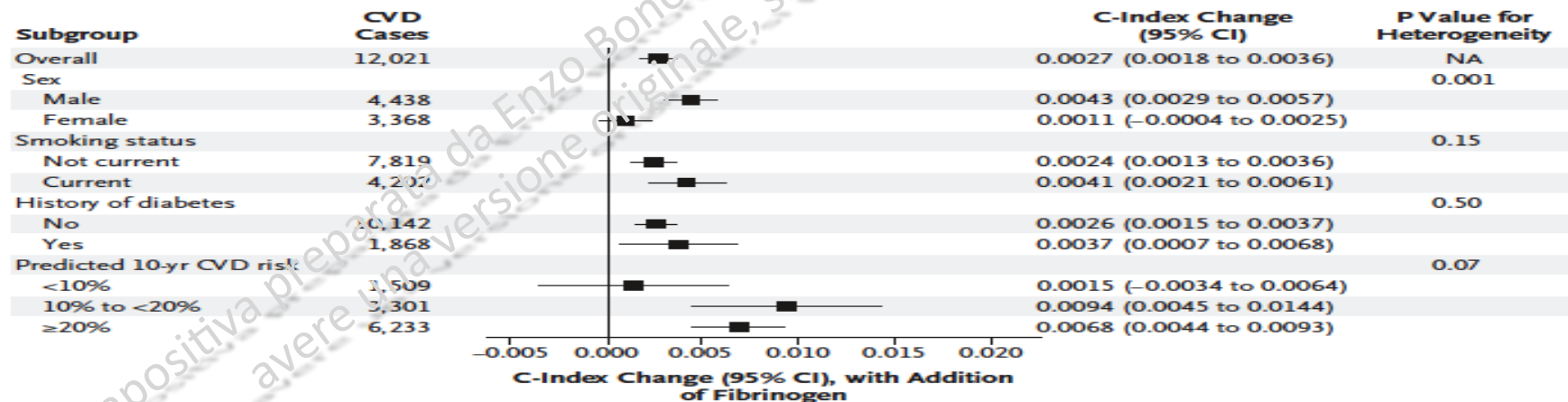
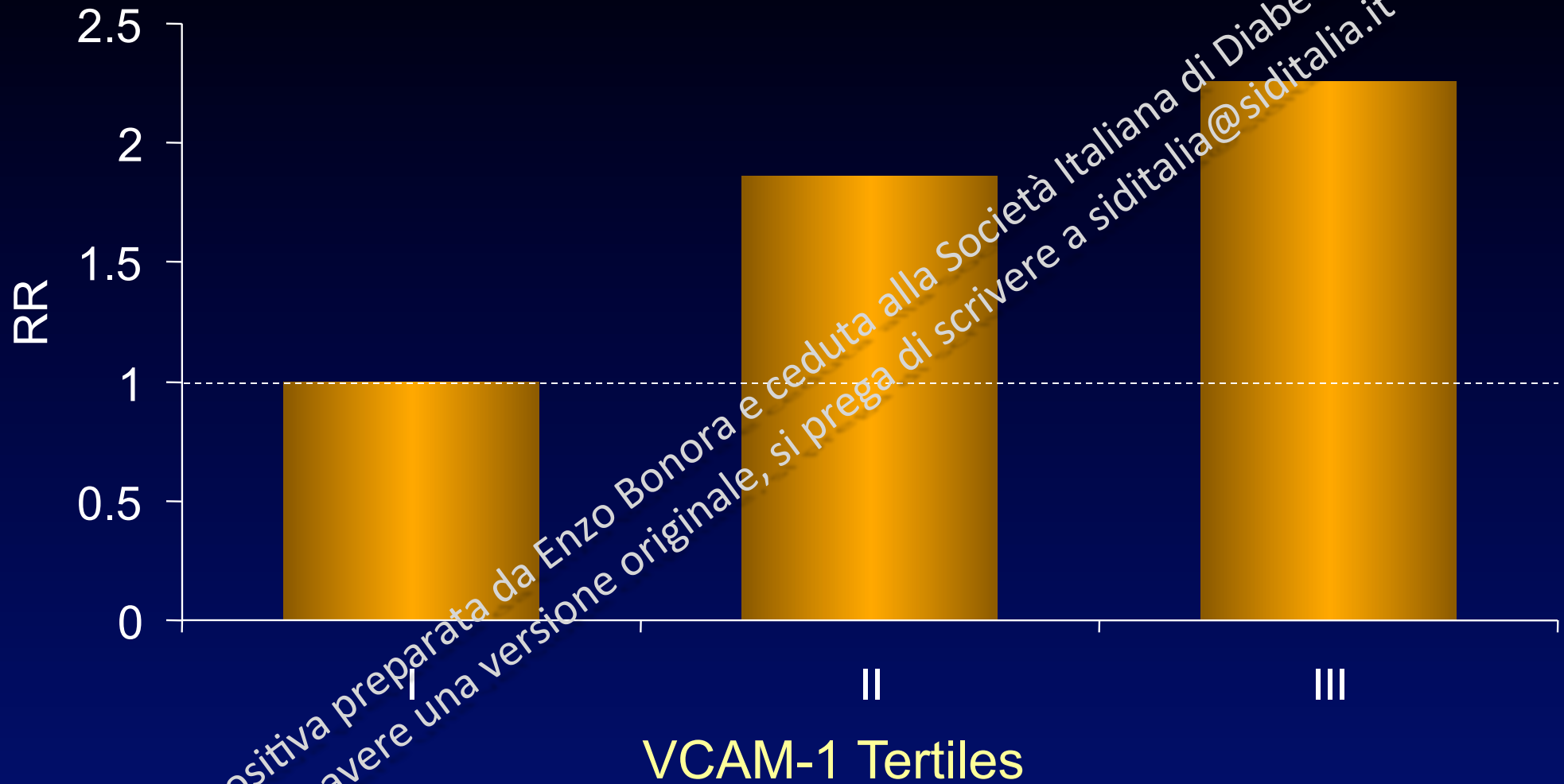


Figure 2. Changes in the C-Index with the Addition of Information on C-Reactive Protein or Fibrinogen to a Model with Conventional Risk Factors, According to Subgroup.

VCAM-1 Predicts Mortality in T2DM

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

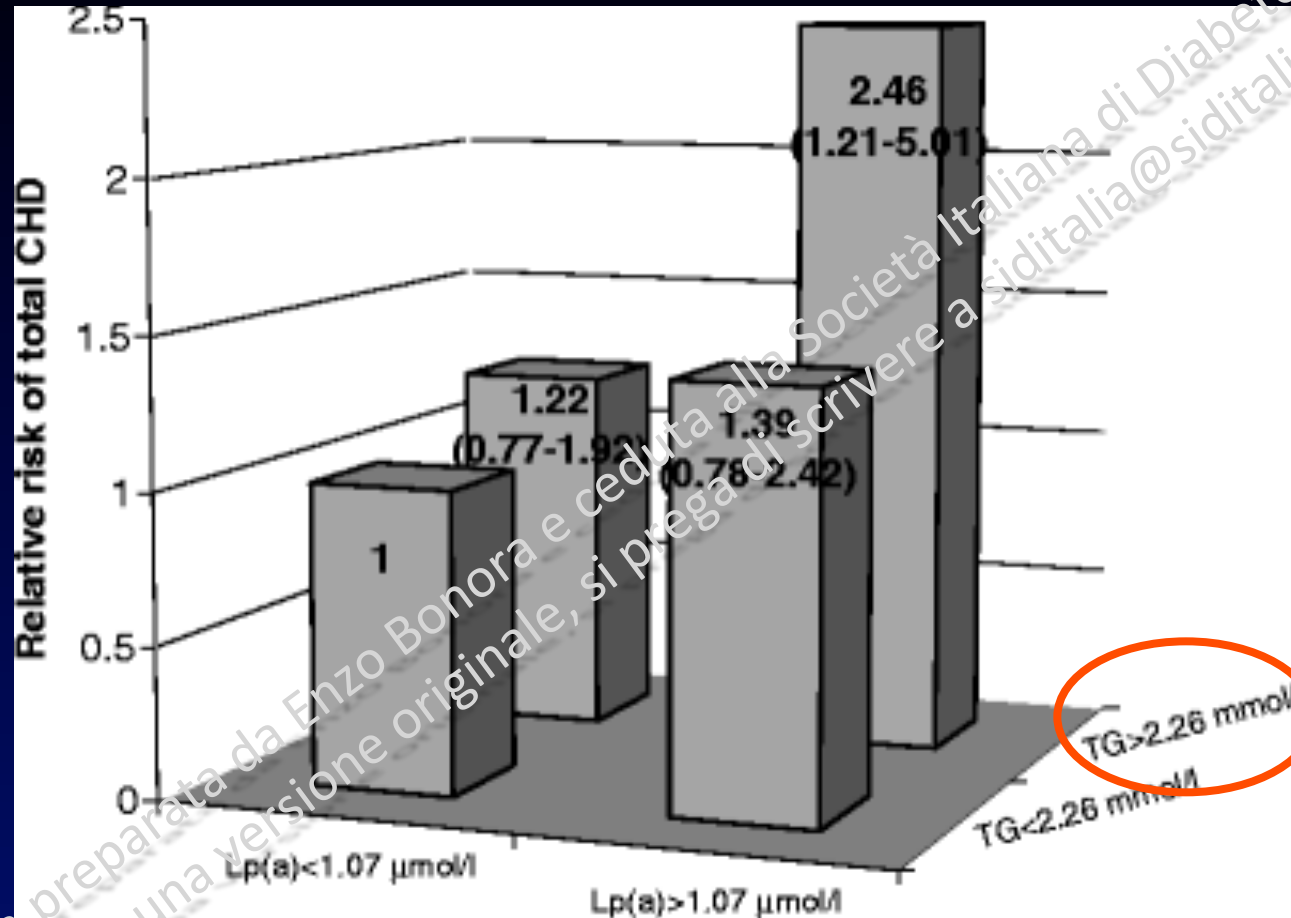


n=328; follow-up 9 years

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

Lp(a) Predicts CHD in Diabetic Women

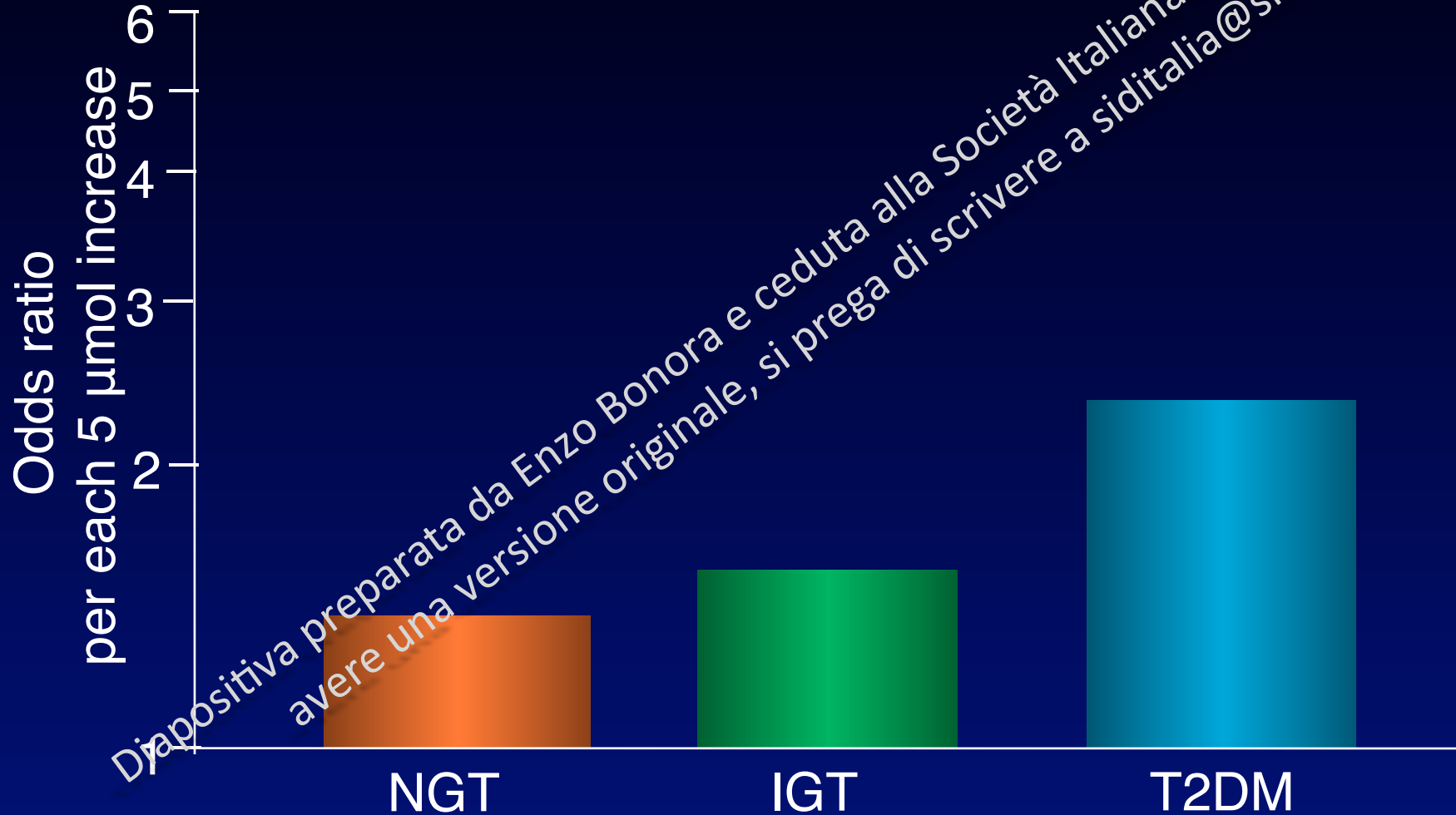
(Nurses' Health Study; Shai et al; Diabetologia 48: 1469, 2005)



N=921, follow-up 10 years. Adjusted for age, smoking, alcohol, physical activity, HRT, BMI, Aspirin, LDL-cholesterol, HDL-cholesterol, hypertension, HbA1c

Homocystein Predicts CVD in Subjects with Various Degrees of Glucose Tolerance

(Hoorn Study; Hoogeveen et al, ATVB 18: 133, 1998)

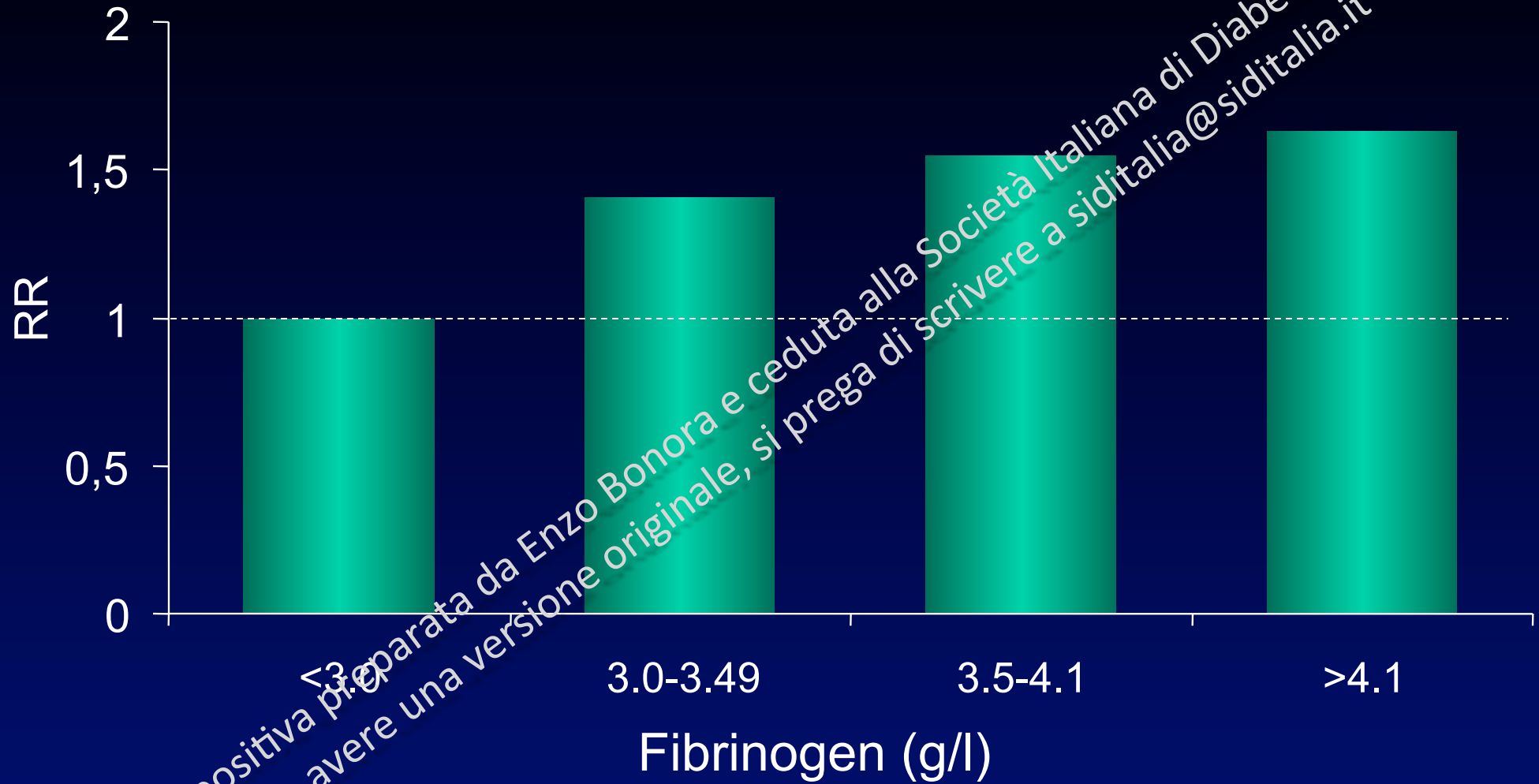


Diapositiva preparata da Enzo Bonora e ceduta alla Società Italiana di Diabetologia. per avere una versione originale, si prega di scrivere a siditalia@siditalia.it

N=631. Data adjusted for classic risk factors and creatinine

Fibrinogen Predicts CVD Mortality in T2DM

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

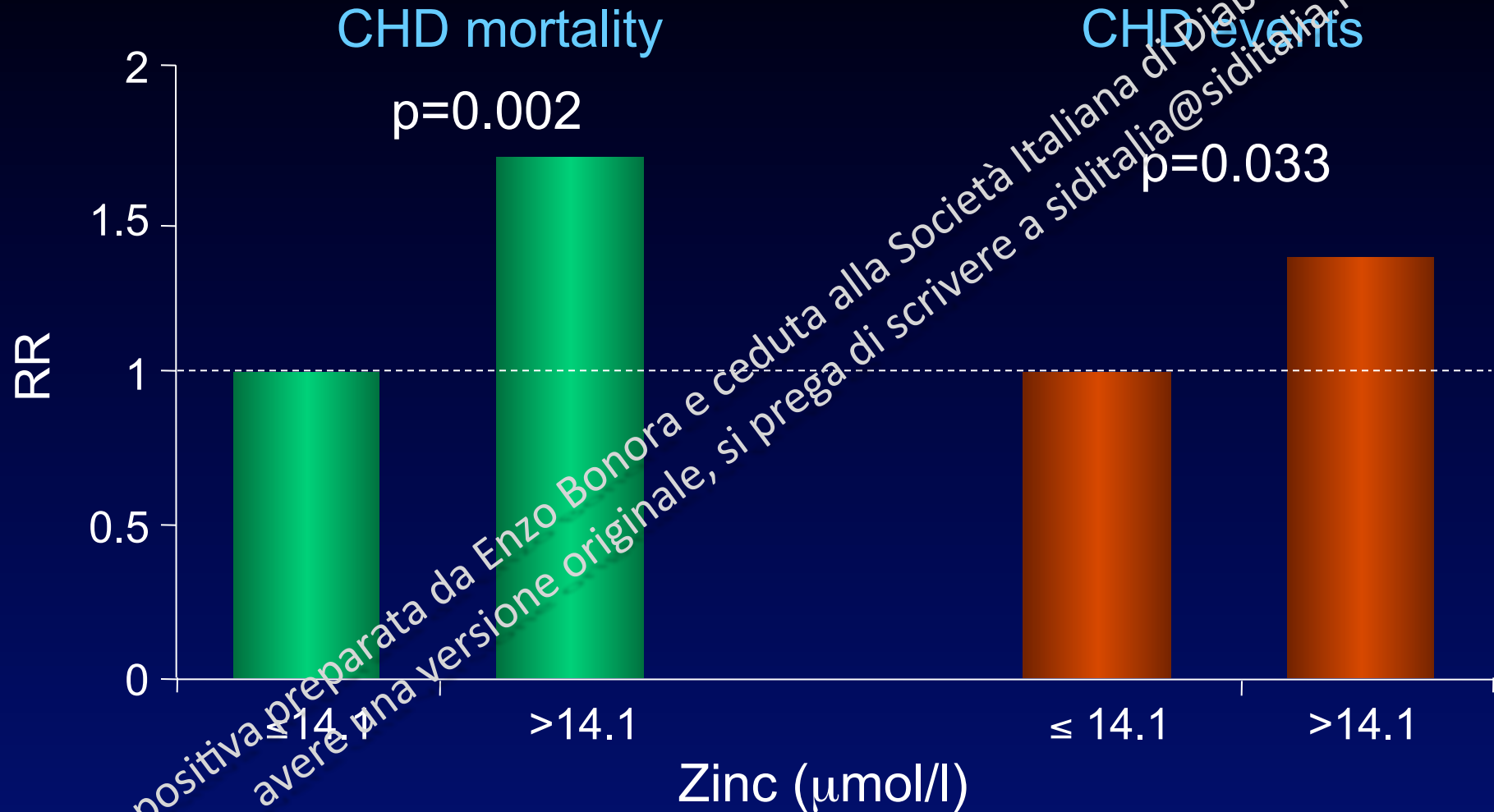


n=1565; follow-up 11 years

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

Serum Zinc predicts CHD in T2DM

(Soinio et al; Diabetes Care 30:523, 2007)

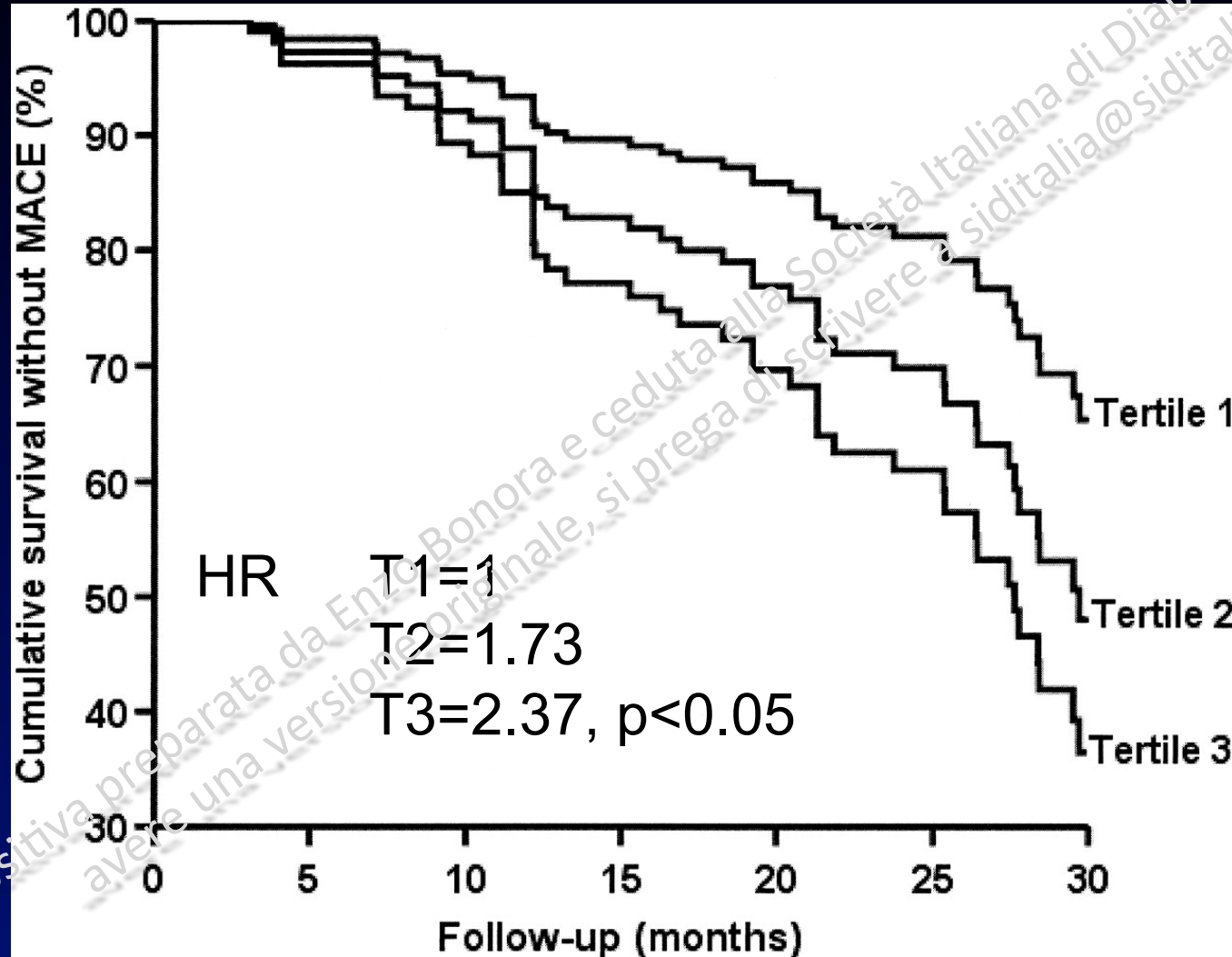


n= 1059; age 45-64 yr; follow-up 8 years

Adjusted for age, sex, duration, cholesterol, HDL-C, triglycerides, HbA1c, GFR, hypertension, smoking, BMI, treatment

ADMA predicts CVD (MACE) in T2DM

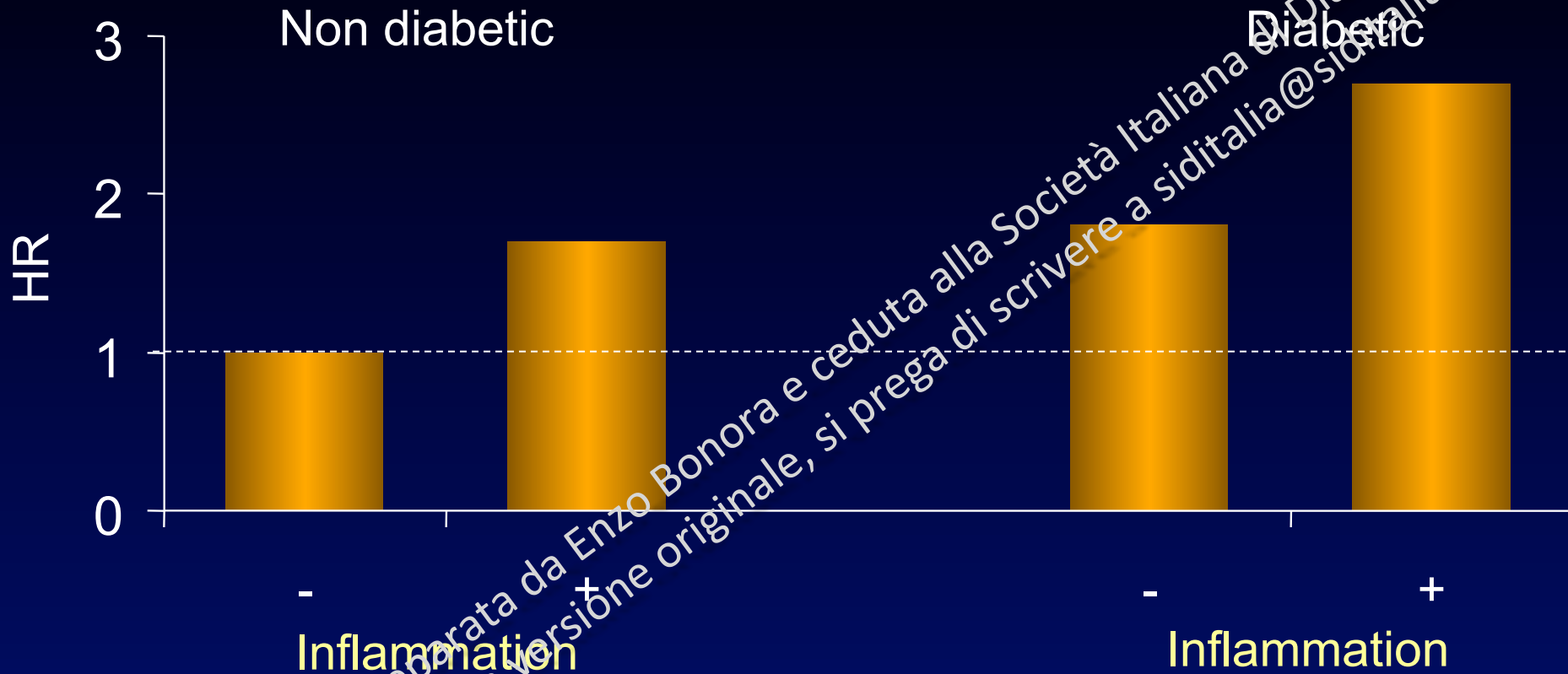
(Kryzanowska et al; Diabetes Care 30: 1834, 2007)



N=125; follow-up 21 months; adjusted for sex, age, baseline CVD and GFR

Inflammation biomarkers and CVD mortality in diabetes

(Engstrom et al; Diabetes 52:442, 2003)



n= 6050; men; followup 19 yrs

Inflammation+ = two or more biomarkers in top quartile

Biomarkers= fibrinogen, α -1-antitrypsin, haptoglobin, ceruloplasmin, orosomucoid

Adjusted for age, BMI, smoking, cholesterol, triglycerides, hypertension, physical activity

Uric acid predicts stroke in T2DM

(Lehto et al; Stroke 29: 635, 1998)

	Hazard ratio	95% C.I.	P value
Unadjusted	1.93	1.30 2.86	<0.001
Age, gender, smoking, cholesterol, hypertension	1.74	1.16 2.61	<0.01
Age, gender, smoking, cholesterol, hypertension, and other risk factors ¹	1.91	1.24 2.94	<0.005

¹Body mass index, triglycerides, HDL cholesterol, plasma glucose, previous history of stroke, use of diuretics, and duration of diabetes.

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

Diabetes Care 32:1716–1720, 2009

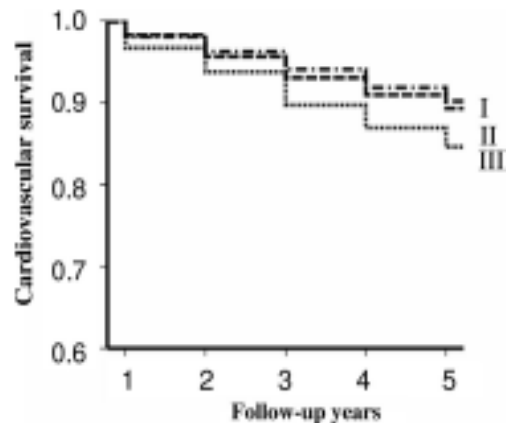


Figure 1—Kaplan-Meier curves of cardiovascular mortality in 2,726 type 2 diabetic patients stratified by sex-specific tertiles of serum uric acid levels. Statistical significance was estimated by the log-rank test ($P < 0.001$ for the third tertile vs. the other two tertiles).

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 ($\mu\text{mol/l}$)	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)	3.34 (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	1.33 (0.76–2.37)	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)	0.91 (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 $\geq 140/90$ mmHg or receiving treatment.

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

Uric acid and mortality from all-causes and cardiovascular disease among adults with and without diagnosed diabetes: Findings from the National Health and Nutrition Examination Survey III Linked Mortality Study[☆]

13,802 participants: 978 with diagnosed diabetes (550 total deaths; 249 from major CVD) and 12,824 without diagnosed diabetes (2669 total deaths; 1146 from major CVD).

Table 1 – Hazard ratios and 95% confidence intervals for serum uric acid and all-cause mortality among U.S. adults aged ≥20 years, National Health and Nutrition Examination Survey III, 1988–1994 to 2006.

	Uric acid (mg/dl)					
	Quintiles					
	≤3.9 (232 μmol/L)	4.0–4.7 (238–280 μmol/L)	4.8–5.5 (286–327 μmol/L)	5.6–6.4 (333–381 μmol/L)	≥6.5 (387 μmol/L)	Continuous (per 1 mg/dl or 59.48 μmol/L)
All-cause mortality						
Participants with diagnosed diabetes*						
No. deaths/no. at risk	83/184	96/202	97/184	95/163	179/245	550/978
Model 1	Referent	1.00 (0.61, 1.62)	0.97 (0.62, 1.51)	1.10 (0.63, 1.92)	1.56 (1.04, 2.33)	1.16 (1.07, 1.26)
Model 2	Referent	1.00 (0.70, 1.58)	0.90 (0.59, 1.35)	0.97 (0.60, 1.59)	1.45 (0.85, 2.47)	1.14 (1.01, 1.28)
Participants without diagnosed diabetes						
No. deaths/no. at risk	274/2294	423/2432	567/2782	578/2572	827/2744	2669/12,824
Model 1	Referent	1.17 (0.98, 1.39)	1.24 (1.04, 1.49)	1.32 (1.11, 1.58)	1.82 (1.58, 2.10)	1.14 (1.11, 1.17)
Model 2	Referent	1.12 (0.93, 1.34)	1.16 (0.96, 1.40)	1.10 (0.92, 1.31)	1.38 (1.14, 1.67)	1.06 (1.02, 1.11)
Major cardiovascular disease†						
Participants with diagnosed diabetes						
No. deaths/no. at risk	37/184	44/202	41/184	39/163	88/245	249/978
Model 1	Referent	1.27 (0.58, 2.78)	0.91 (0.48, 1.72)	1.31 (0.64, 2.67)	1.45 (0.78, 2.72)	1.13 (1.01, 1.27)
Model 2	Referent	1.43 (0.66, 3.11)	0.94 (0.46, 1.94)	1.33 (0.64, 2.77)	1.33 (0.64, 2.75)	1.10 (0.97, 1.24)
Participants without diagnosed diabetes						
No. deaths/no. at risk	105/2294	168/2432	238/2782	260/2572	375/2744	1146/12,824
Model 1	Referent	1.11 (0.81, 1.52)	1.24 (0.95, 1.63)	1.49 (1.14, 1.94)	2.08 (1.61, 2.70)	1.18 (1.13, 1.25)
Model 2	Referent	1.02 (0.74, 1.40)	1.11 (0.84, 1.46)	1.11 (0.83, 1.49)	1.27 (0.94, 1.72)	1.04 (0.97, 1.11)

Values are reported in milligrams per deciliter; to convert to micromoles per liter, multiply by 59.48.

^{*} Diagnosed diabetes was defined from the question "Have you ever been told by a doctor that you have diabetes or sugar diabetes?"

[†] Major cardiovascular disease: International Classification of Diseases, 10th Revision: I00-I78.

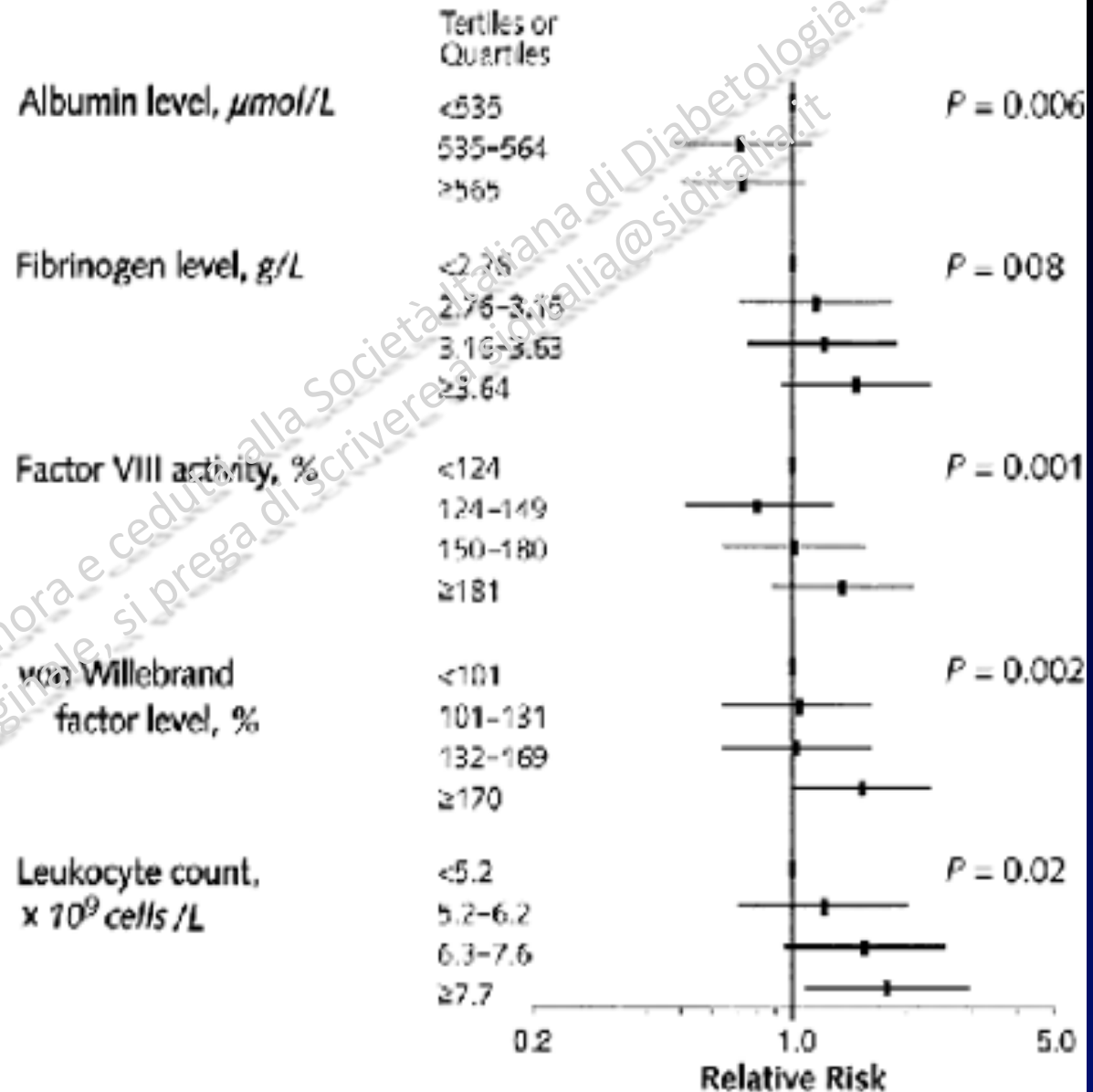
Model 1: adjusted for age.

Model 2: adjusted for age, sex, race or ethnicity, educational status, smoking status, systolic blood pressure, use of antihypertensive medications, concentrations of non-high-density lipoprotein cholesterol and high-density lipoprotein cholesterol, physical activity, alcohol intake, concentration of C-reactive protein, concentration of HbA1c, urinary albumin-creatinine ratio, estimated glomerular filtration rate, body mass index, self-rated health, duration of diabetes, and histories of myocardial infarction, stroke, congestive heart failure, cancer, arthritis, and gout.

Non traditional risk factors and CHD in T2DM

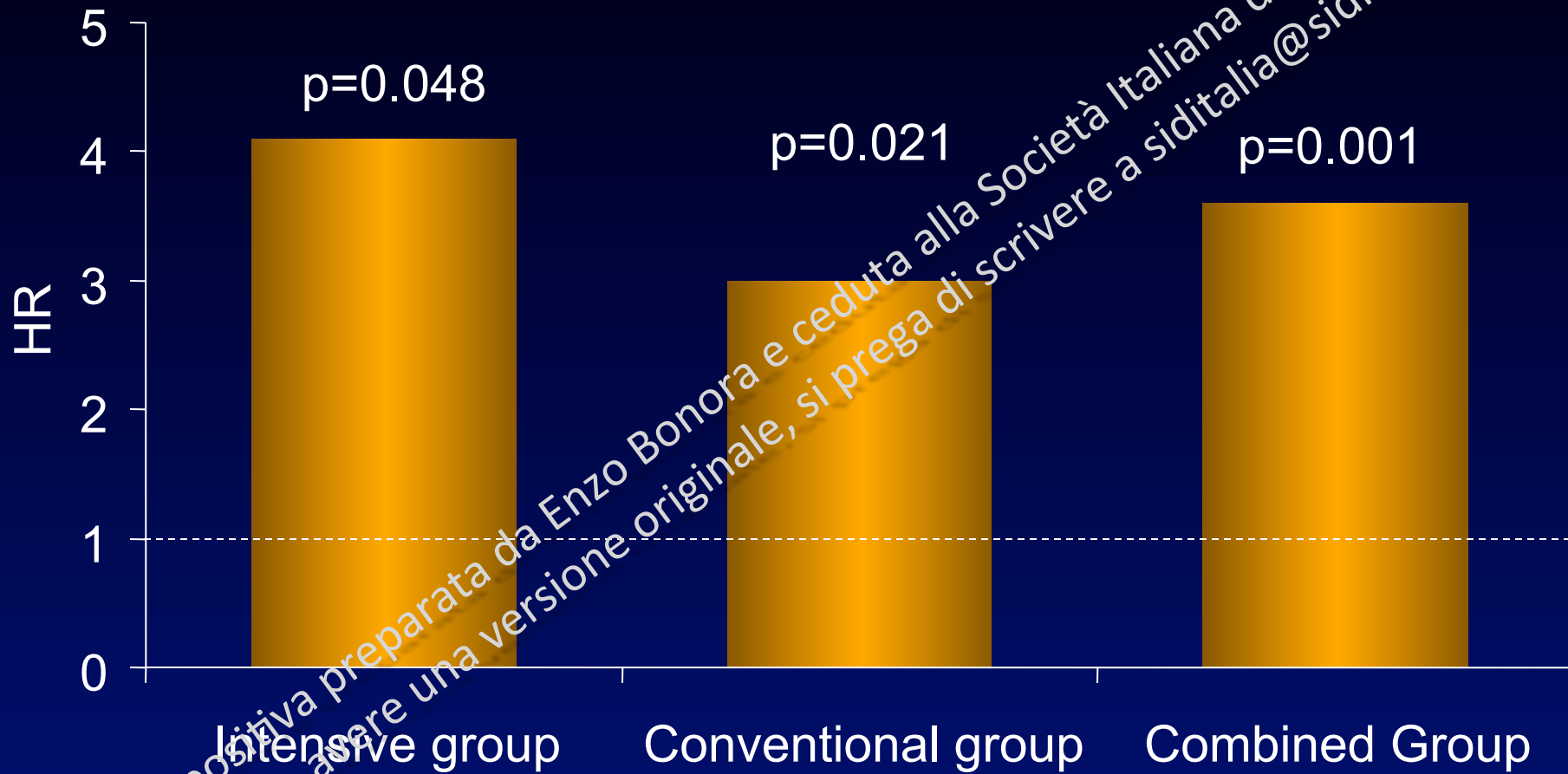
(ARIC Study – Saito et al;
Ann Int Med 133: 81, 2000)

N=1676; follow-up 8 years



Plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) predicts CVD in T2DM

(Steno Study, Gaede et al; Diabetologia 48:158, 2005)



Adjusted for baseline CVD, duration, age, sex, SBP, cholesterol, triglycerides, AER

Multiple biomarkers for the prediction of death and CVD (MACE)

(Framingham Heart Study; Wang et al, NEJM 355: 2631, 2006)

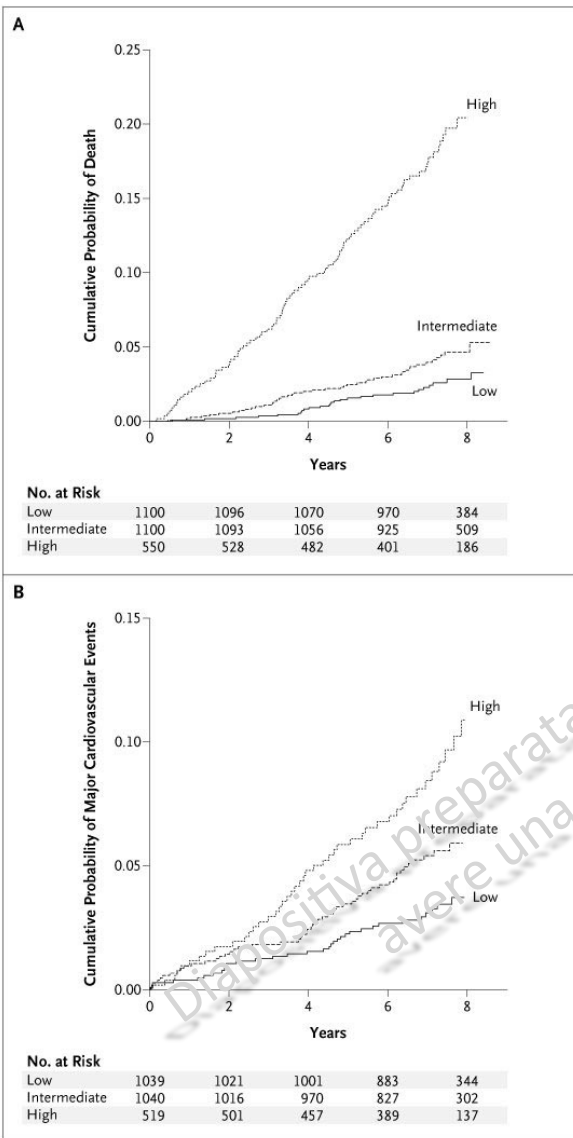


Table 3. Relation of Multimarker Risk Score to Outcomes.*

Multimarker Score	Death	Major Cardiovascular Events
	adjusted hazard ratios (95% CI)	
Low	1.0 (reference group)	1.0 (reference group)
Intermediate	1.34 (0.83–2.18)	1.54 (0.98–2.40)
High	4.08 (2.51–6.62)	1.84 (1.11–3.05)
P value for trend	<0.001	0.02

* Hazard ratios were adjusted for age; sex; body-mass index; categories of blood pressure, total cholesterol, and high-density lipoprotein cholesterol; smoking status; presence or absence of diabetes; serum creatinine level; and presence or absence of prevalent cardiovascular disease (for the model with death).

N=3209; follow-up 7.4 years

Biomarkers: B-NP, NT-proANP, CRP, aldosterone, renin, fibrinogen, PAI-1, D-dimer, homocystein, ACR

Multimarker score for death= B-NP, homocysteine, renin, CRP, ACR

Multimarker score for MACE= B-NP, ACR

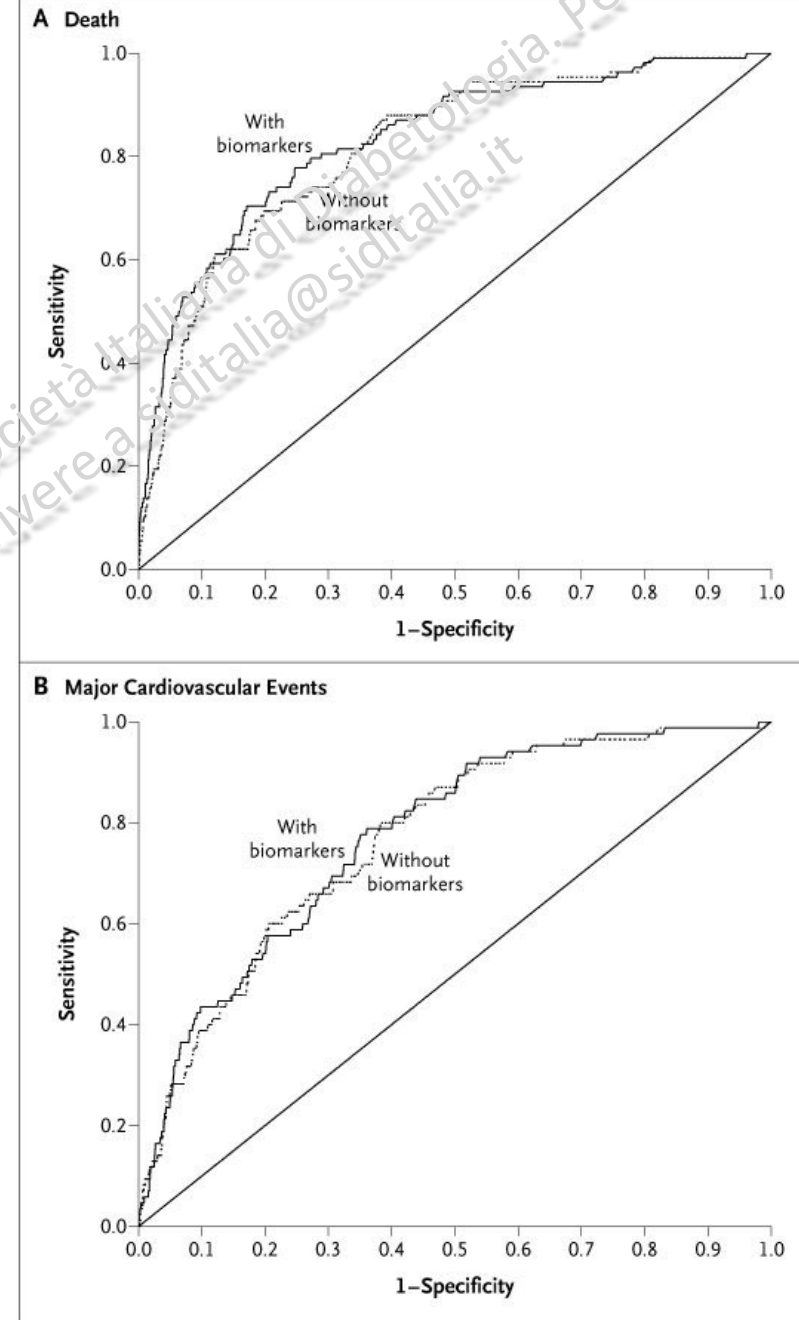
Multiple biomarkers for the prediction of death and CVD (MACE)

(Framingham Heart Study; Wang et al, NEJM 355: 2631, 2006)

N=3209; follow-up 7.4 years

Multimarker score for death= B-NP, homocysteine, renin, CRP, ACR

Multimarker score for CVD= B-NP, ACR



Prediction of CHD (ROC analysis) in T2DM

(ARIC Study; Folsom et al, Diabetes Care 26: 2777, 2003)

	Women	Men
Basic model	0.721	0.672
+ BMI	0.731	0.674
+ WHR	0.723	0.689
+ creatinine	0.732	0.672
+ LP(a)	0.720	0.672
+ Apo B	0.718	0.671
+ fibrinogen	0.723	0.673
+ vWF	0.736	0.693
+ multiple Risk Factors*	0.771	0.740

Basic model = age, race, cholesterol, HDL-C, SBP or drugs, smoking

* Also including heart rate, sport activity, diet score, residual FEV₁, ApoA1, albumin, factor VII, WBC

Cardiovascular Risk Factors

Paradigm #1

A risk factor does not necessarily improve prediction

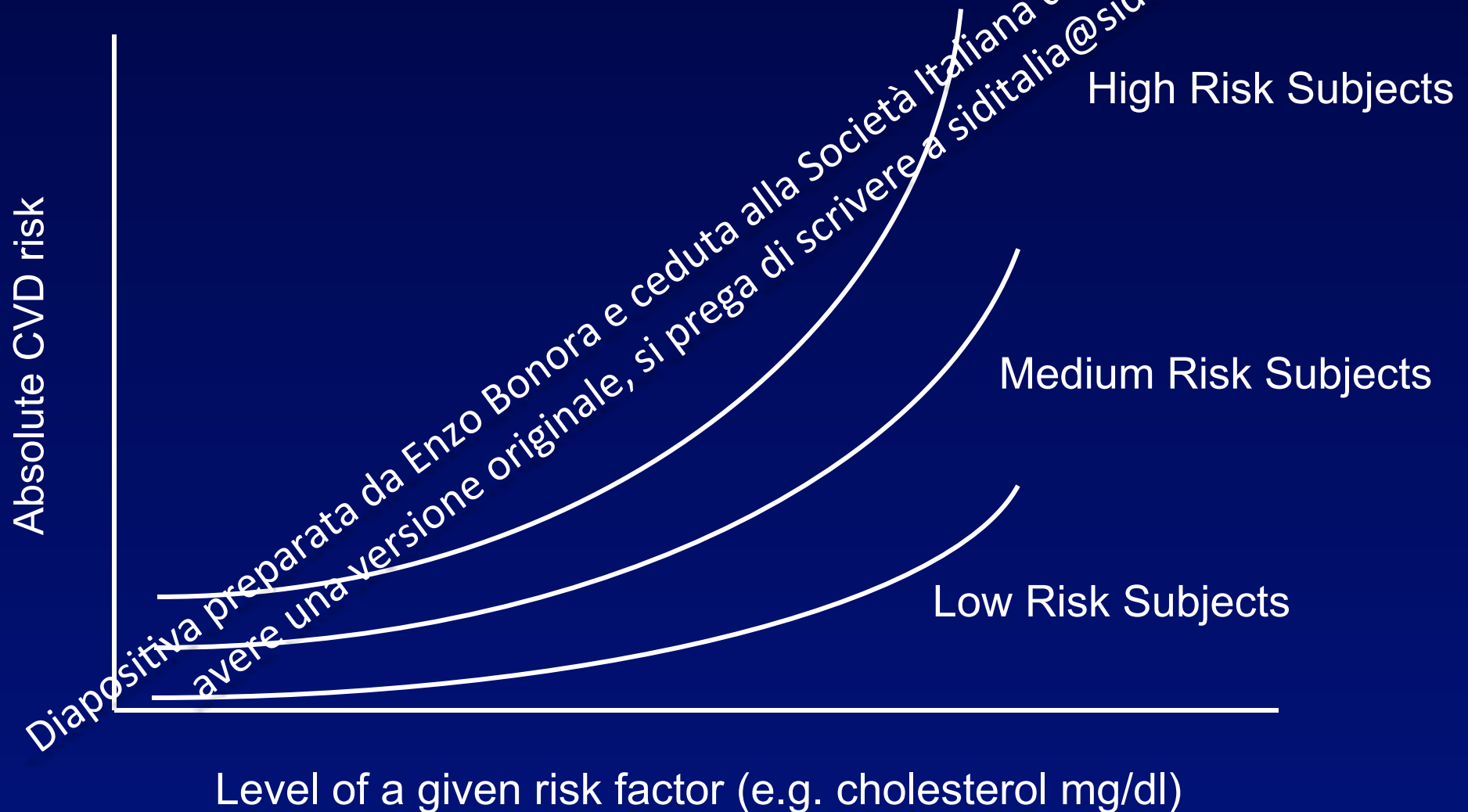
Paradigm #2

A risk factor does not necessarily imply causality in the statistical association. It might be just a marker, i.e. good for identifying subjects at risk and/or improving prediction but unsuitable for being a target of treatment

Paradigm #3

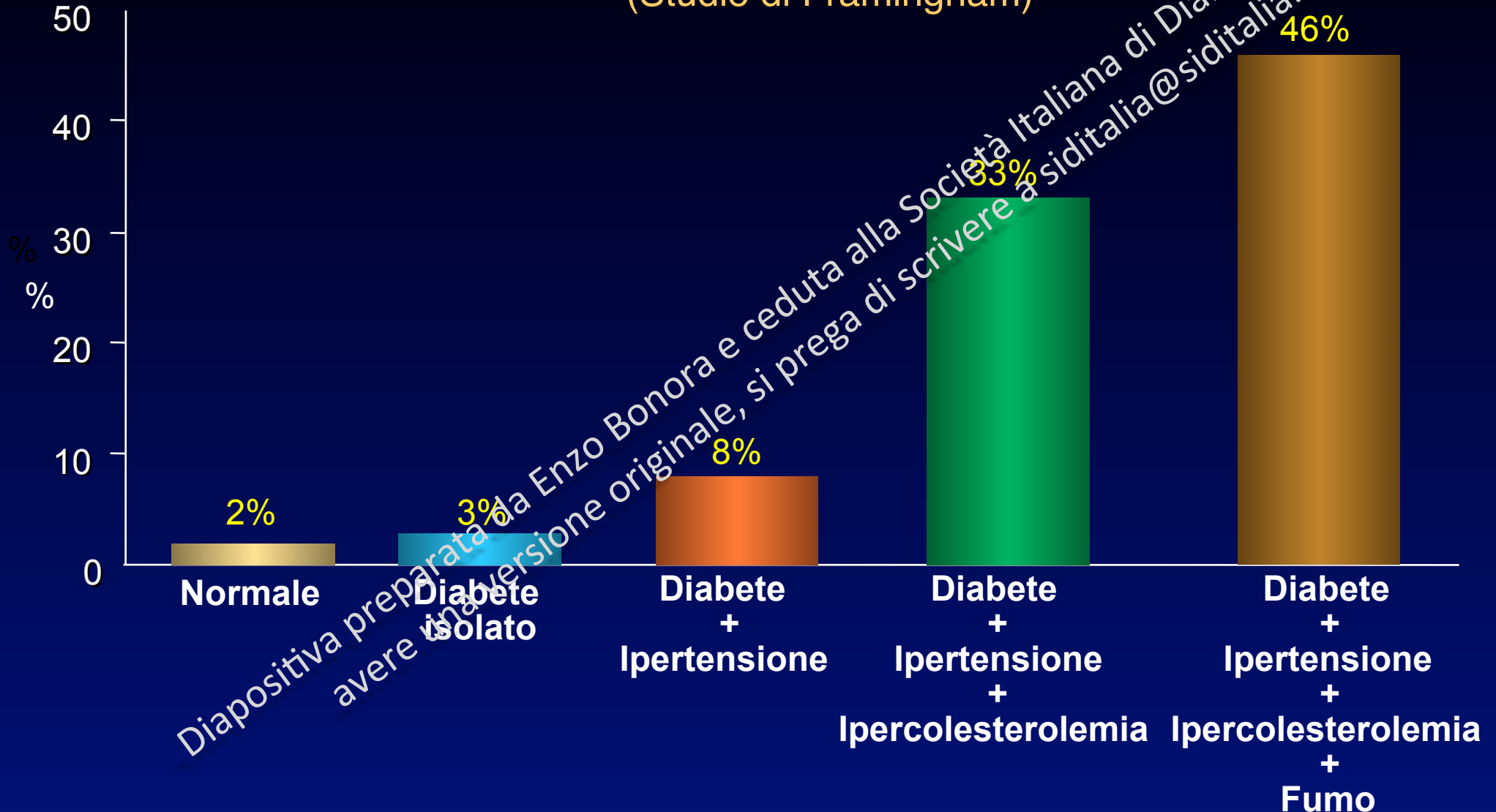
Cause-effect associations require, consistency, strength, specificity, biological plausibility (coherence), temporality

The risk associated to a given clinical/biochemical trait can change according to the presence/absence of other traits

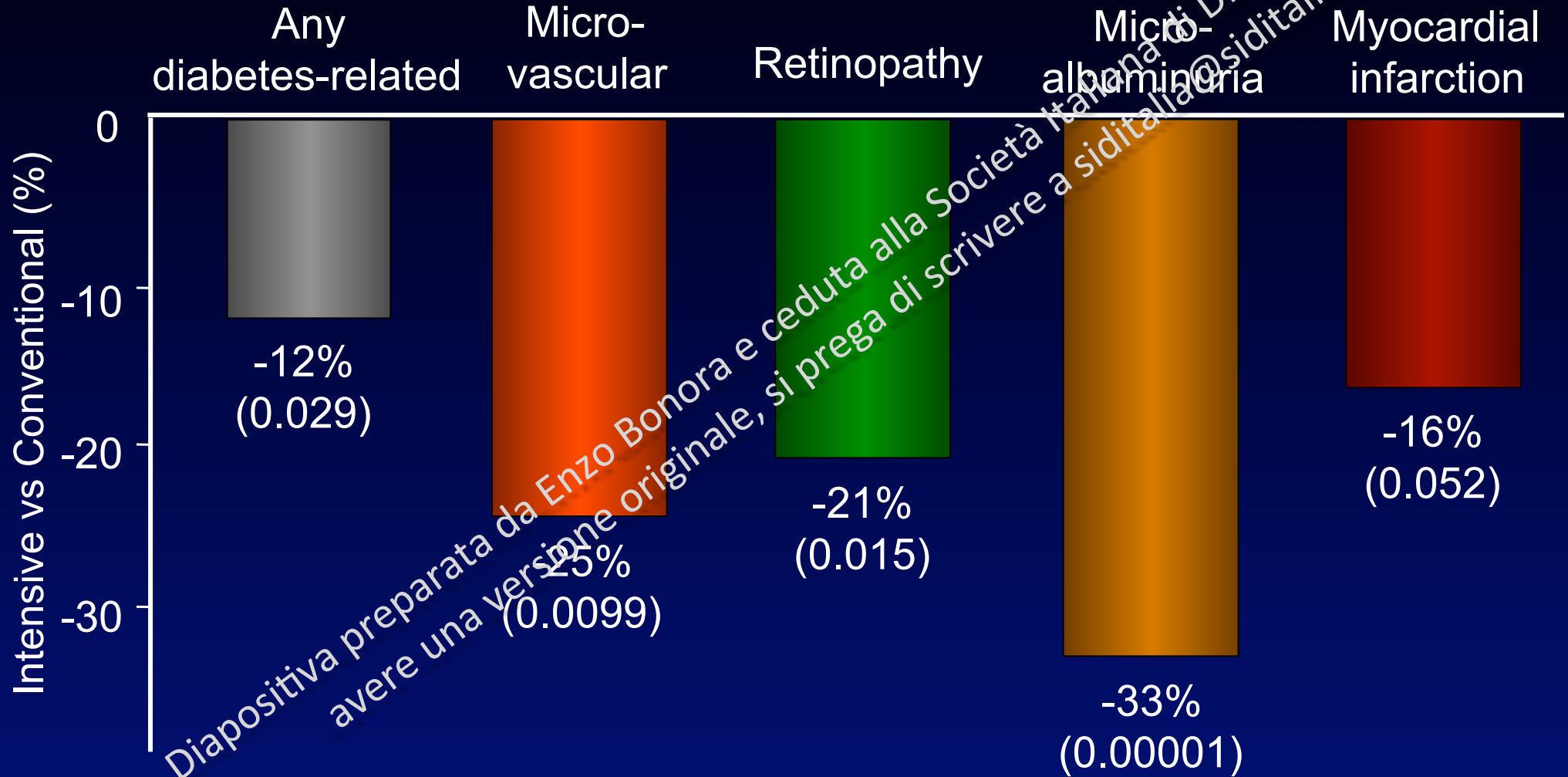


Incidenza cumulativa di CVD nell' arco di 8 anni in 50enni diabetici

(Studio di Framingham)

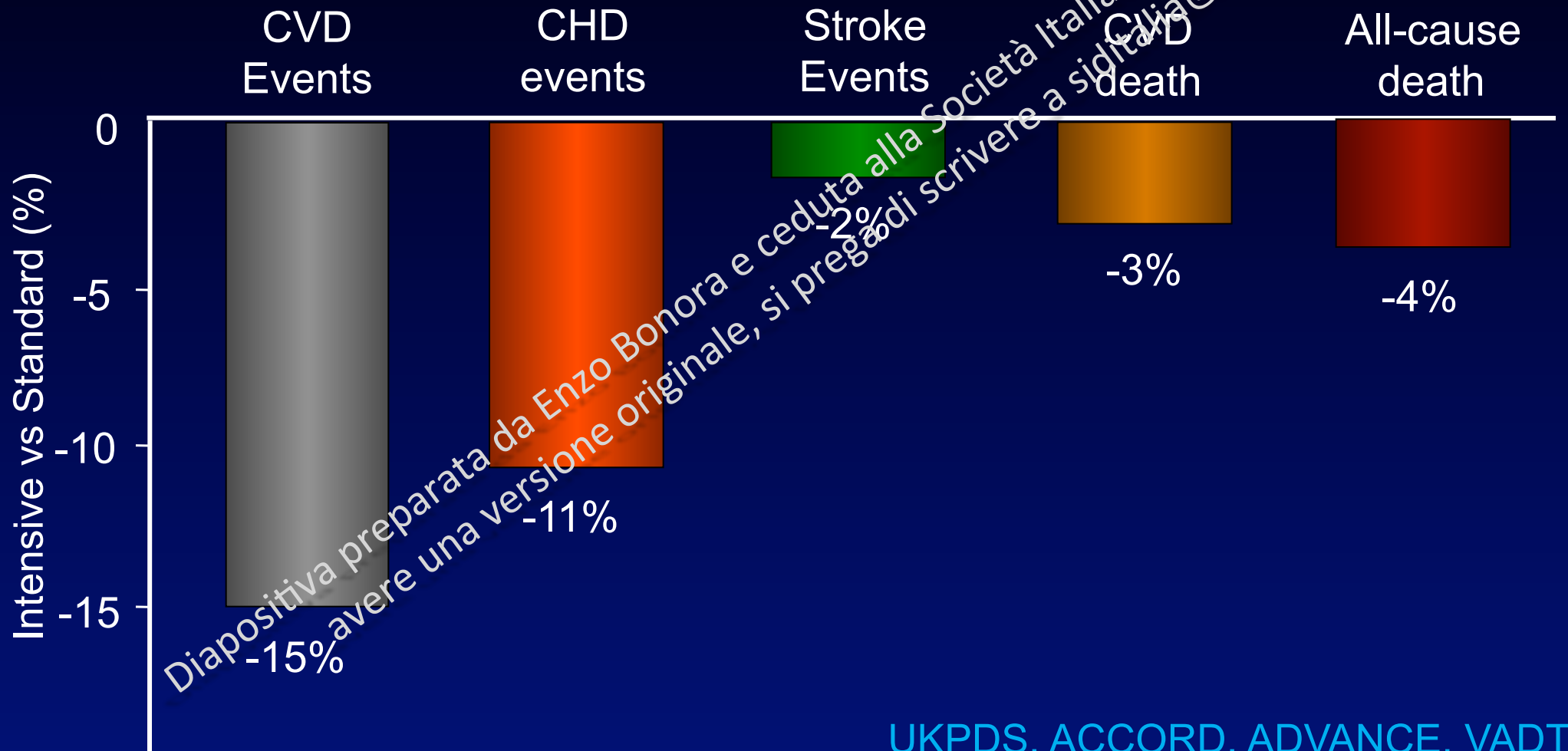


UKPDS - Main Results of the Glucose Control Study



Effects of Intensive Glycemic Control on CVD and All-Cause Death in T2DM – A Meta-Analysis

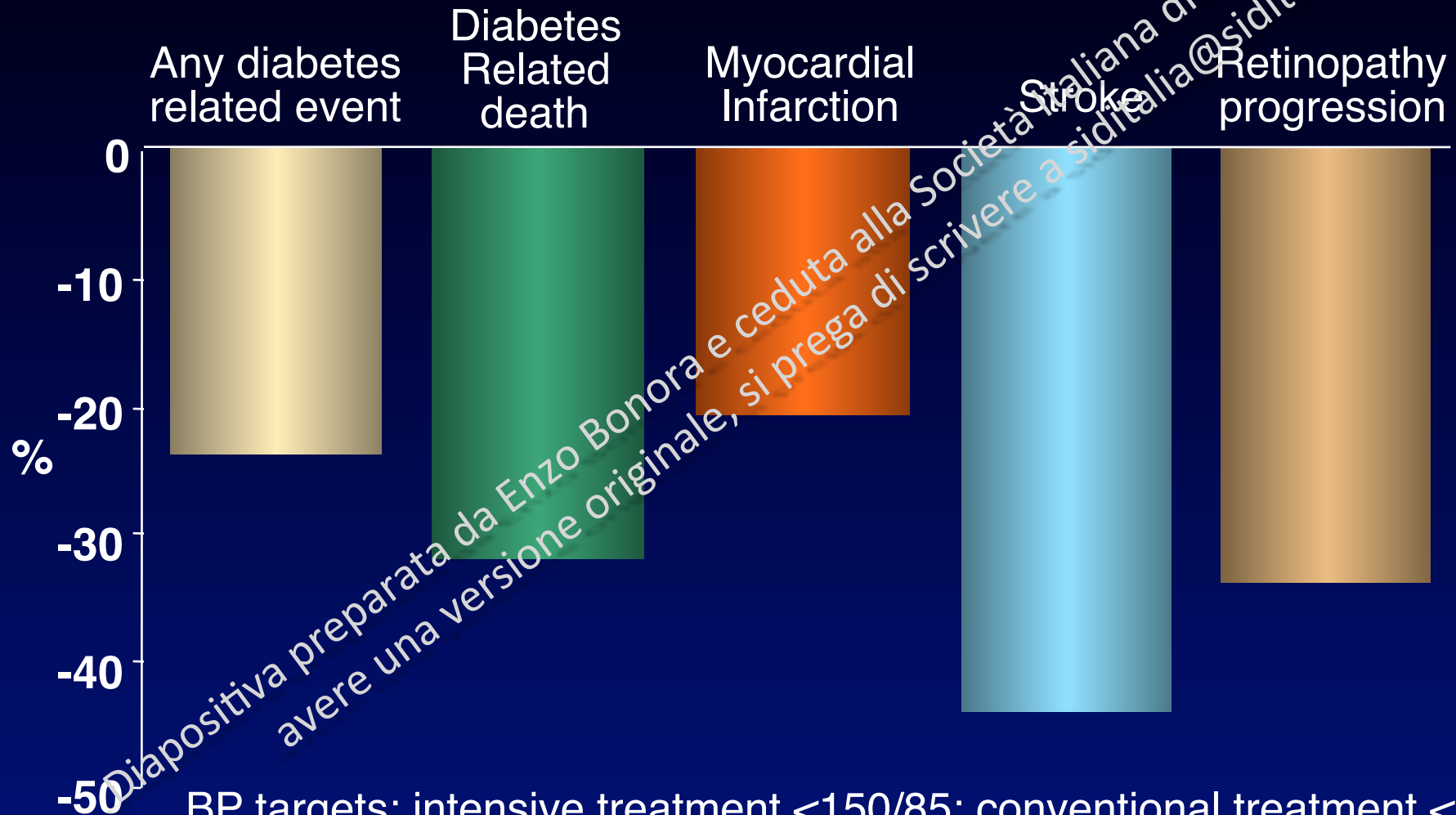
Kelly et al - Ann Intern Med 2009;151: 394-403



UKPDS, ACCORD, ADVANCE, VADT

Reduction of Events with Intensive Control of Blood Pressure in T2DM

(UKPDS, 1998)

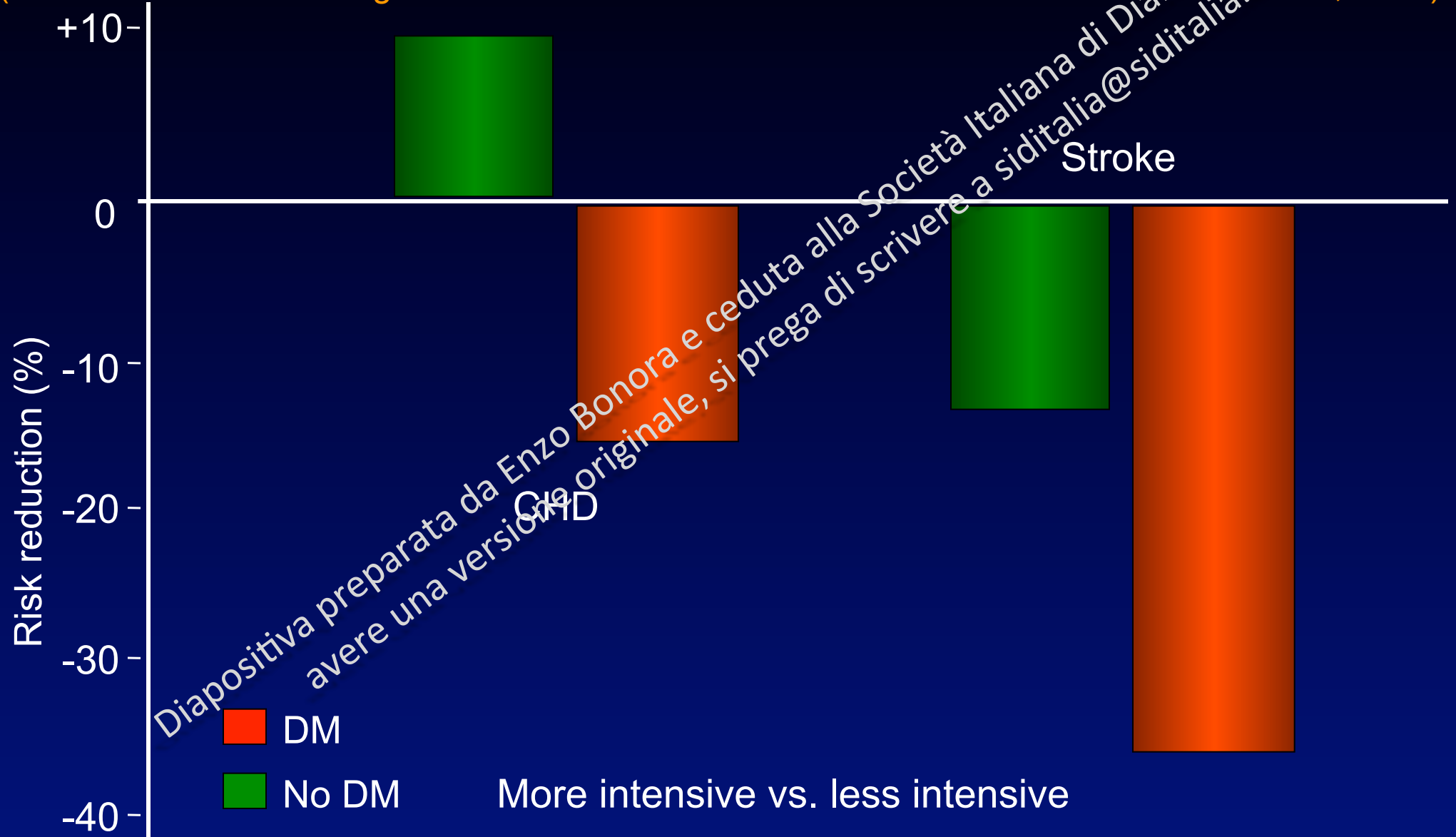


BP targets: intensive treatment $<150/85$; conventional treatment $<180/105$

Mean BP: intensive 144/82, conventional = 154/87

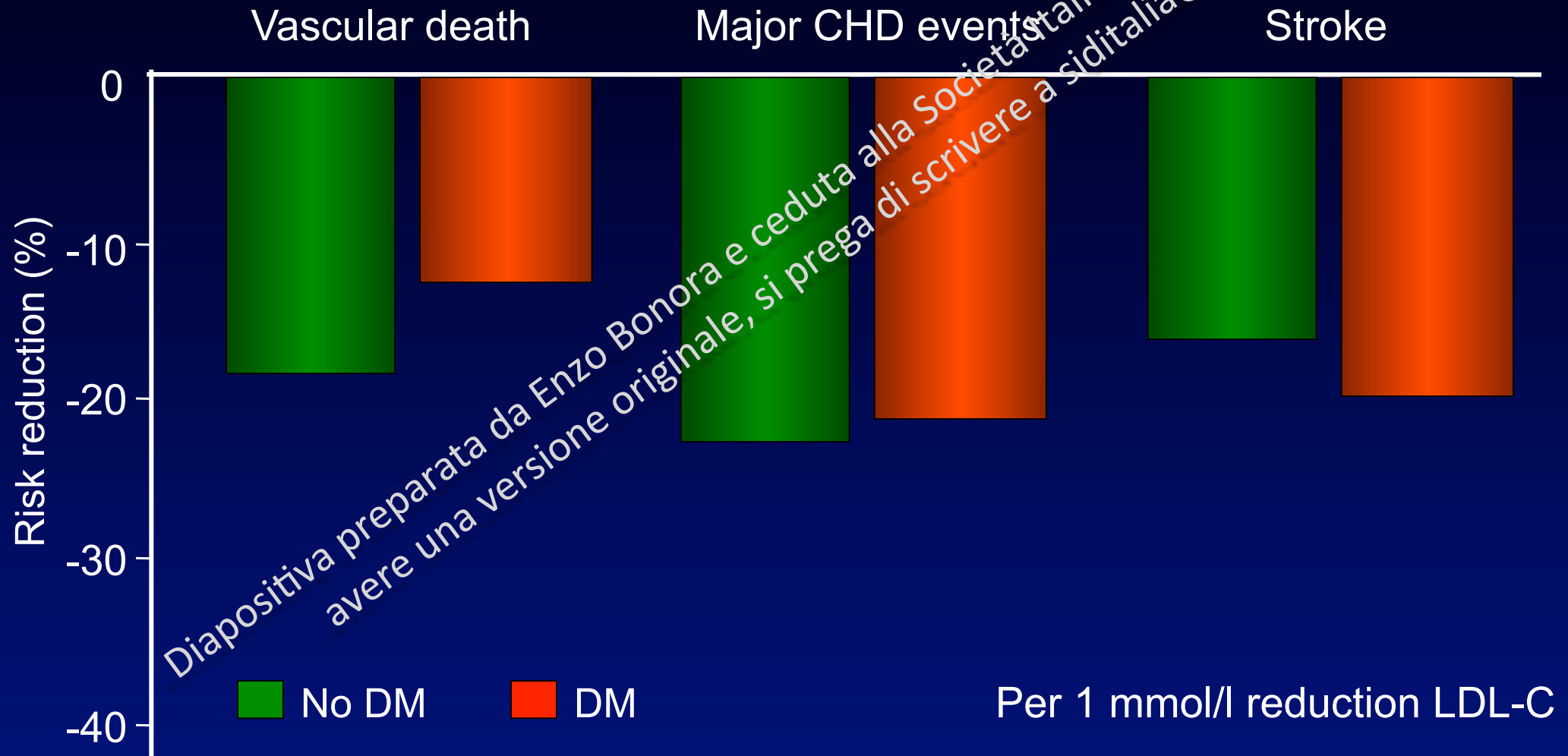
Effect of blood pressure lowering therapy on CVD in T2DM - A Meta-analysis

(Blood Pressure Lowering Treatment Trialists' Collaboration - Arch Intern Med 165:1410, 2005)



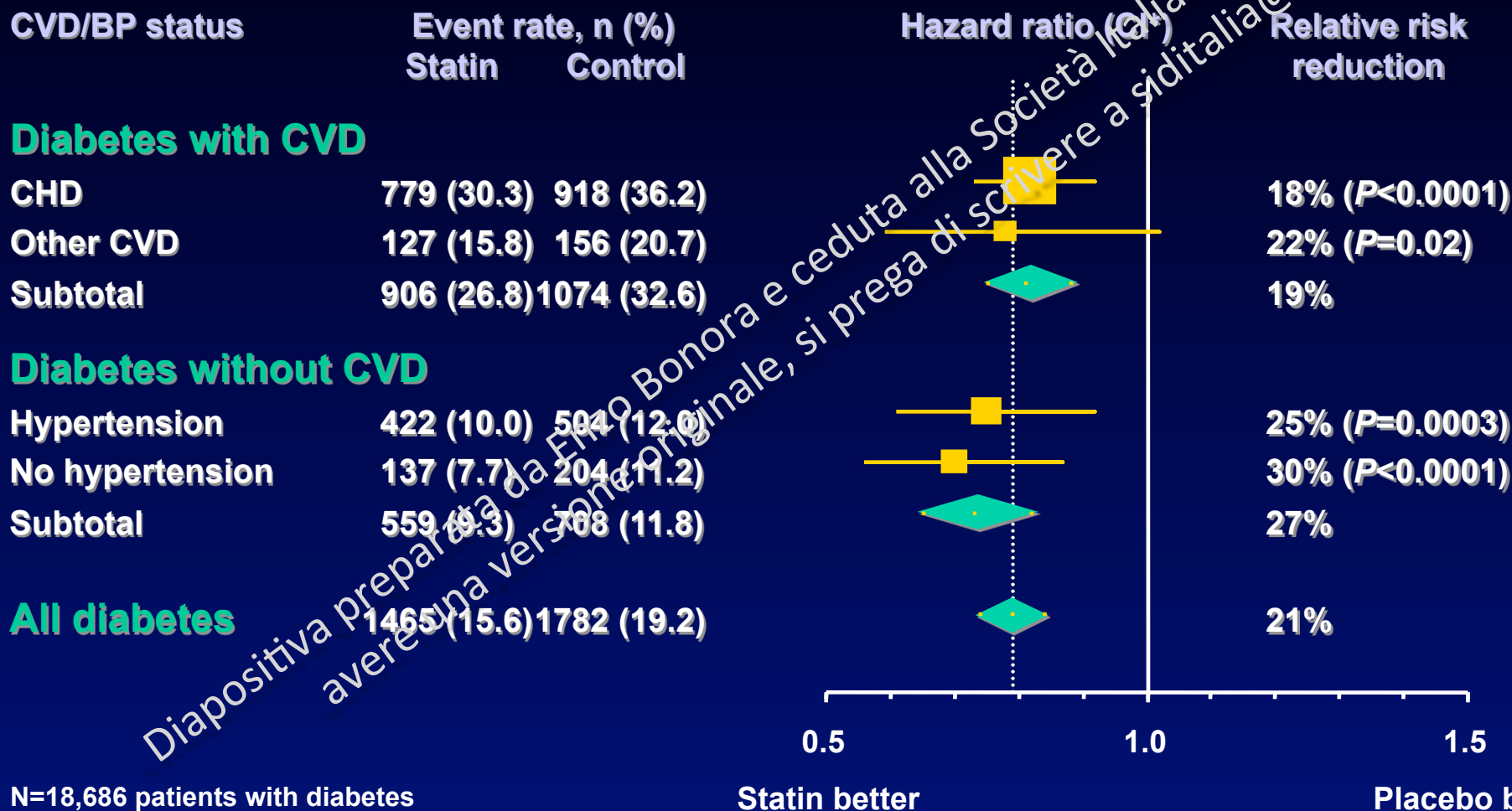
Effect of cholesterol lowering therapy on CVD in T2DM - A Meta-analysis

(Cholesterol Treatment Trialists Collaboration; Lancet 371: 117, 2008)



Cholesterol Treatment Trialists' Collaboration: Reduction of MACE in Diabetes per 1 mmol

(Cholesterol Treatment Trialists Collaboration – Lancet 2008; 371:17-25)



N=18,686 patients with diabetes

* 95% CI 99% CI

Statins for the primary prevention of cardiovascular disease

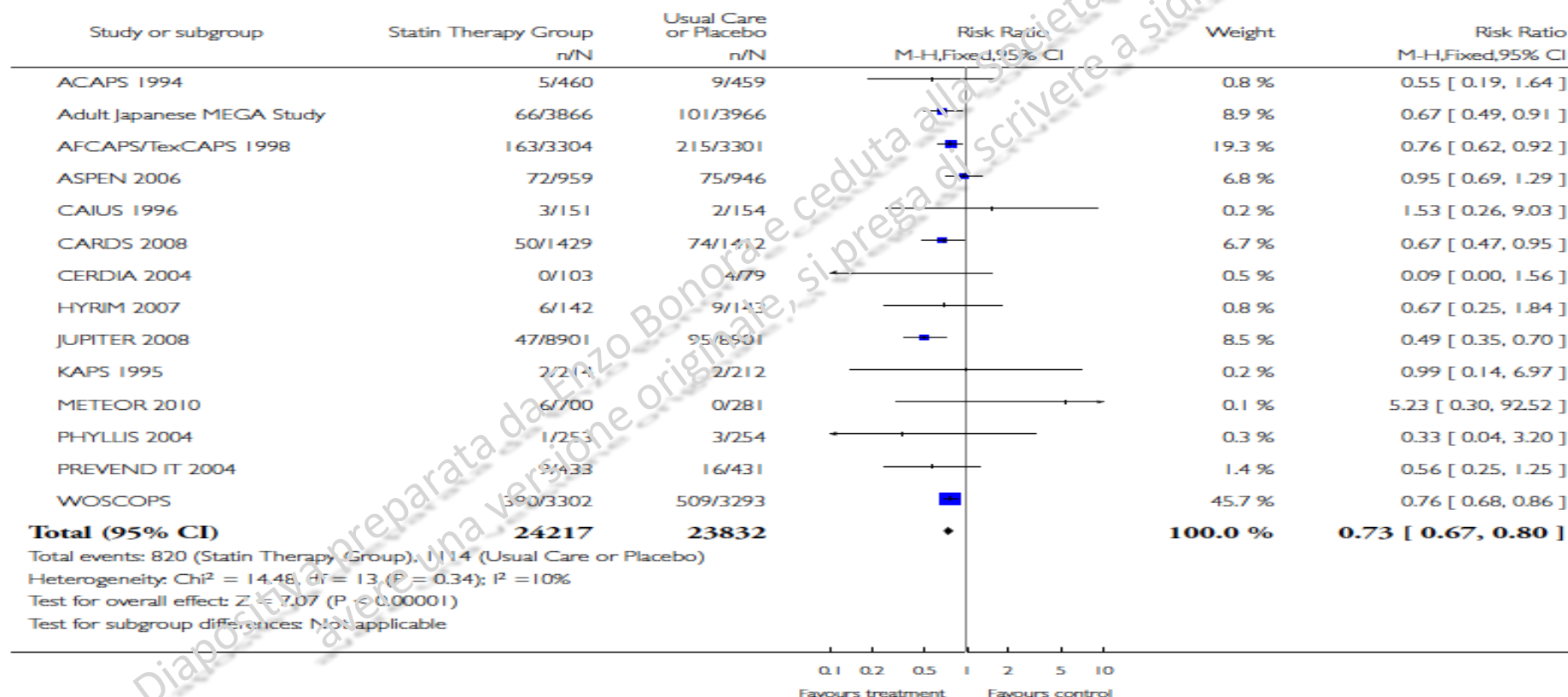
18 trials recruited 56,934 participants and observed outcomes ranging from 1 to 5.3 years

Analysis 1.2. Comparison 1 Mortality and Morbidity, Outcome 2 Total Number of CHD Events.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 1 Mortality and Morbidity

Outcome: 2 Total Number of CHD Events



Fine

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