



MILANO
9 OTTOBRE 2019

CORRETTA
GESTIONE
DEL PAZIENTE
CON **DIABETE TIPO 2**
AD ALTO RISCHIO
CARDIOVASCOLARE



Inquadramento e quantificazione del **rischio cardiovascolare** nel paziente con diabete tipo 2



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di Verona



Diapositiva preparata da ENZO BONORA e ceduta alla Società Italiana di Diabetologia.
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Ringraziamento

Esprimo massima gratitudine alla **Società Italiana di Diabetologia** per avermi formato, guidato, stimolato, sostenuto e gratificato in 40 anni di professione (1979-2019).

La SID è la mia casa e la SID è nel profondo del mio cuore.



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Disclosures (last 10 years)

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Research Grants

Astrazeneca, Genzyme, Menarini Diagnostics, Novo Nordisk, Roche Diagnostics, Takeda

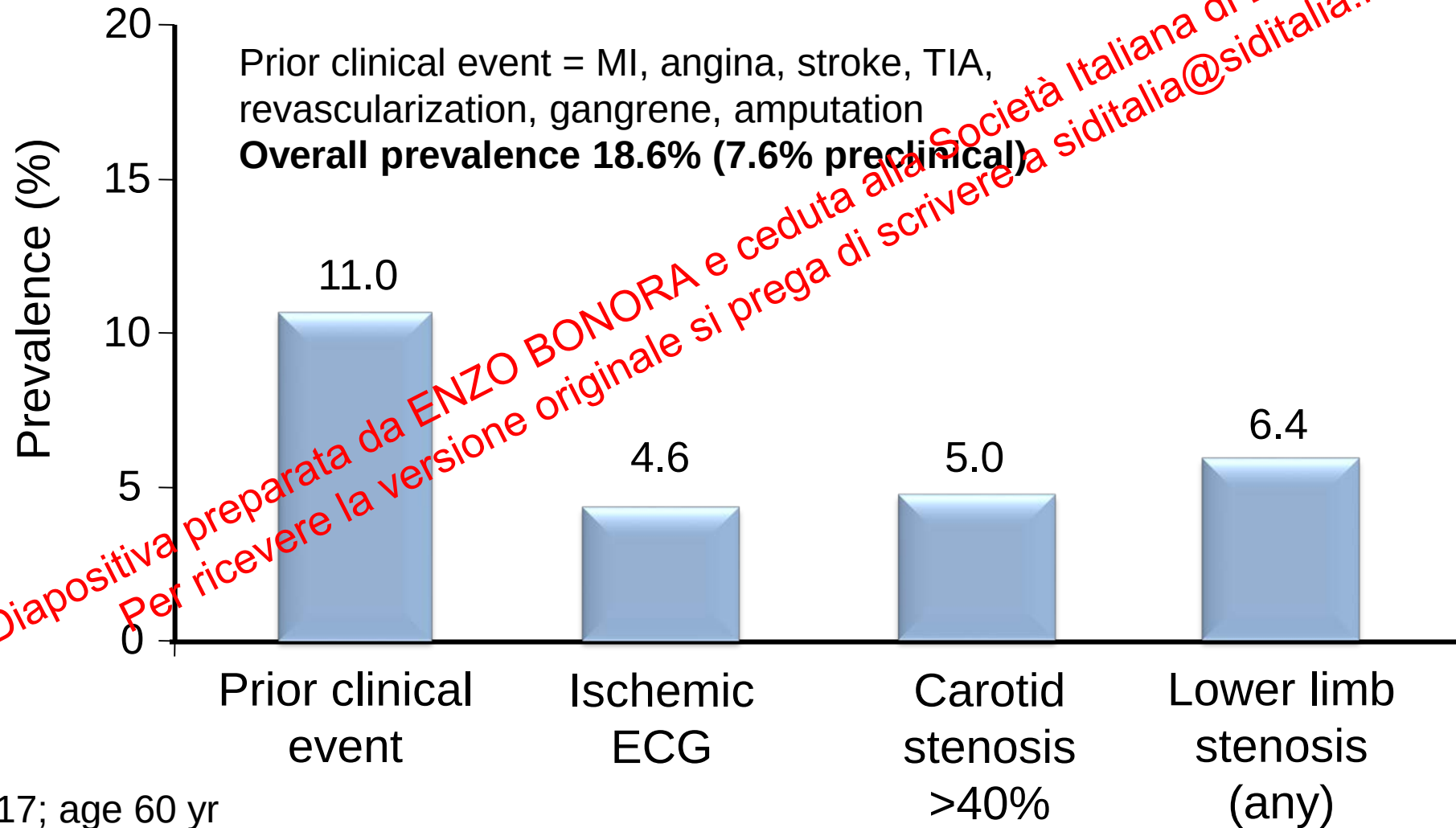
Agenda

- Epidemiologia della malattia cardiovascolare nel diabete in Italia
- Inquadramento del rischio (approccio qualitativo)
- Quantificazione del rischio (approccio quantitativo)
- Stratificazione in base al rischio (approccio semi-quantitativo)

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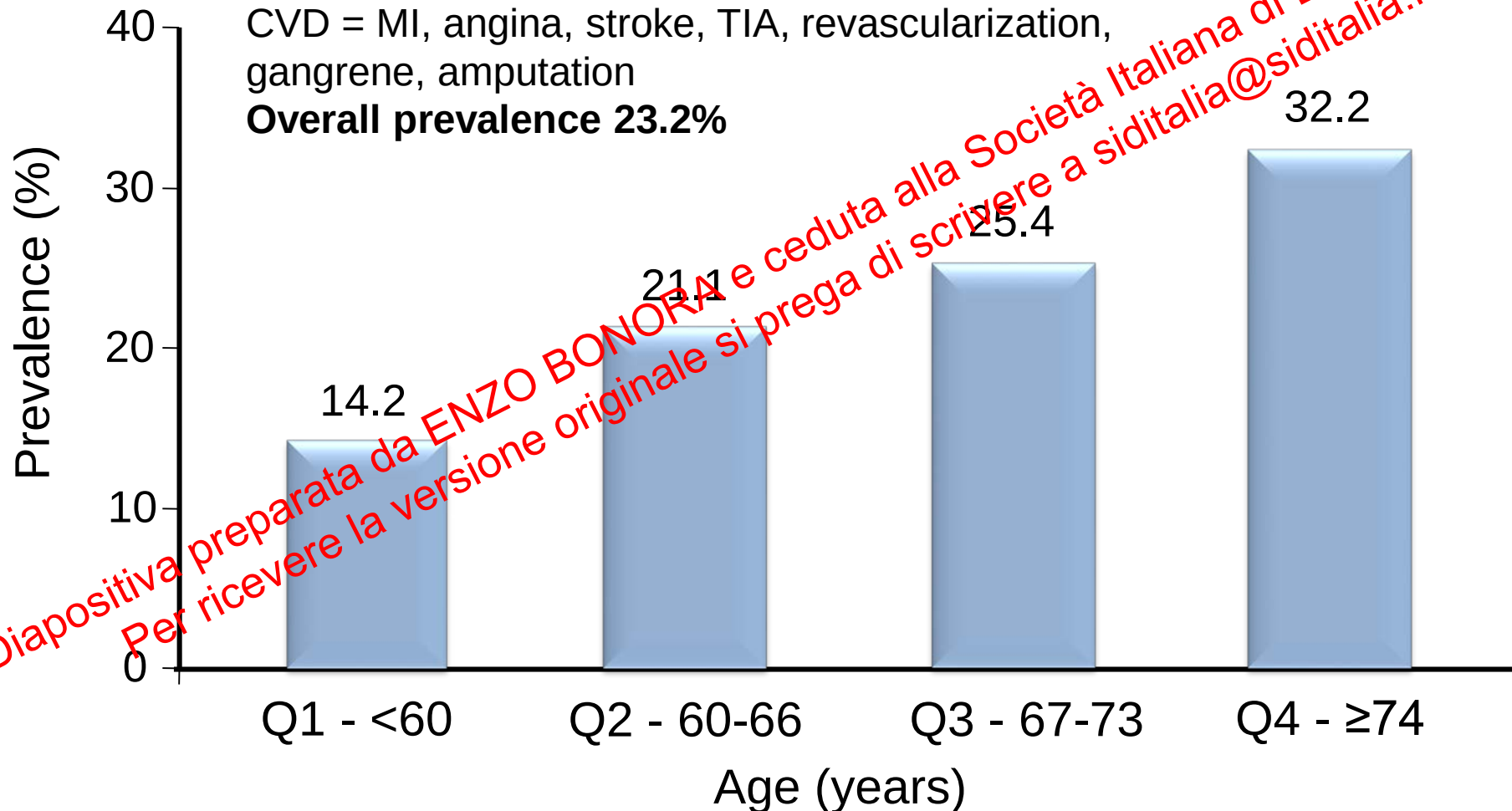
Prevalence of CVD in subjects with newly diagnosed T2DM attending the Verona Diabetes Clinic in 2003-2008

Dauriz M et al - unpublished



Prevalence of CVD in subjects with T2DM attending Diabetes Clinics in Italy in 2007-2008

RIACE Study – Solini A et al - JAGS 2013; 61:1253



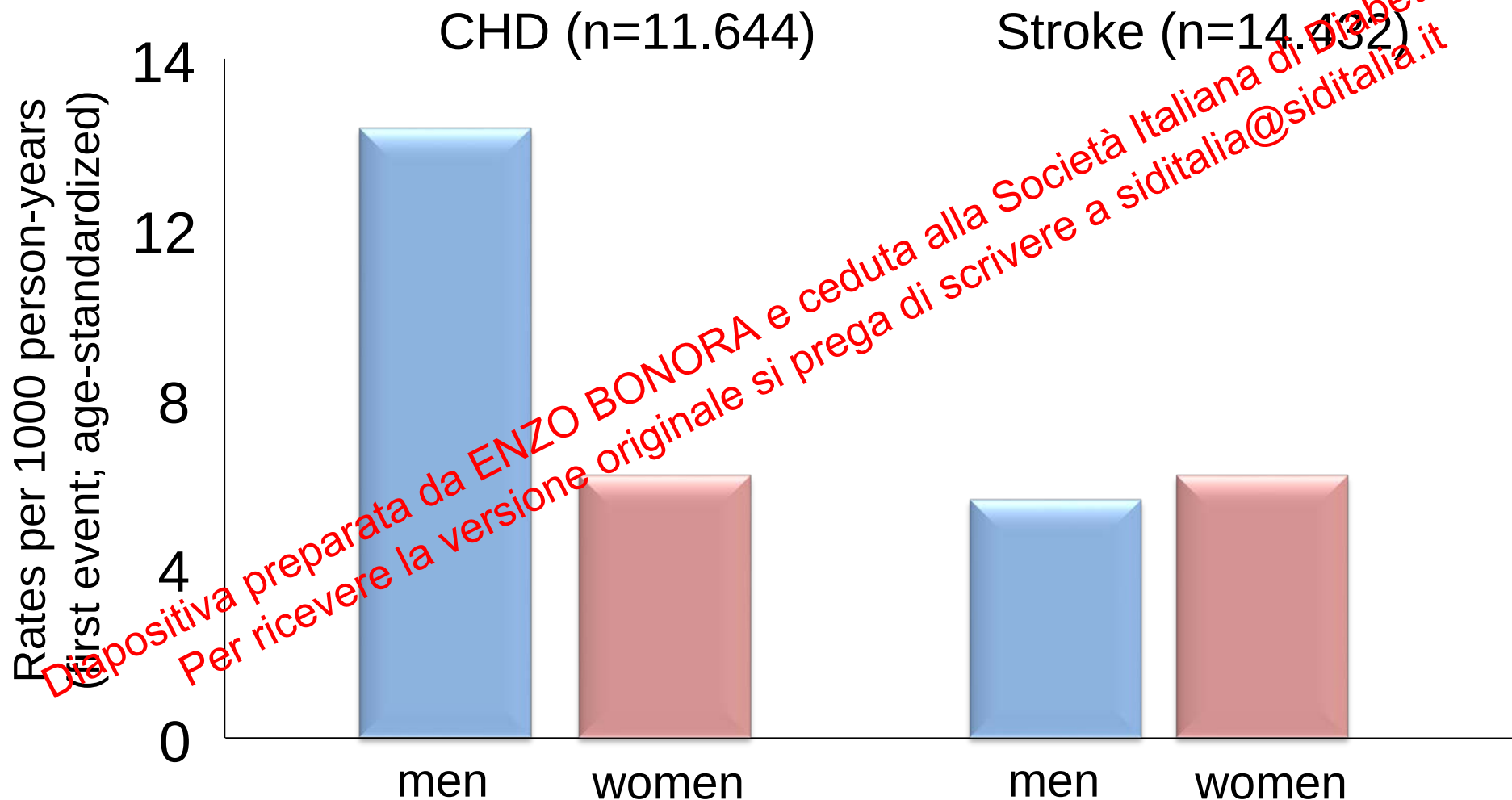
19 Diabetes Centers; n=15,773; age 67 yr; duration 11 yr

Prediction from extrapolation

- At diagnosis of diabetes 11% with a prior clinical CVD event
- After 11 years since diagnosis 23% with a prior clinical CVD event
- In 10 years since diagnosis of T2DM as many as 10% of subjects seem to experience a clinical CVD event (i.e., 10 per 1000 person-years; i.e. 1 per 100 p-y)
- Is this prediction reasonable?

Incidence of CHD and stroke in Italian T2DM subjects attending diabetes clinics in early 2000

DAI Study; Avogaro et al, Diabetes Care 2007; Giorda et al, Stroke 2009



CHD = AMI, CABG, PTCA; follow-up 4 years; age 65 yr; duration 9 yr

Incidence of CVD in Italian diabetic subjects in 2012

Baviera M et al – NMCD 2017; 27: 54

	Rate per 1000 patient-year (% of subjects with DM)	OR DM vs No DM (95% CI)
Myocardial infarction*	8.72 (0.9)	2.49 (2.35-2.65)
Stroke*	7.67 (0.7)	2.09 (1.96-2.22)
Major amputation	0.92 (0.1)	7.30 (5.72-9.31)
All-cause death	33.76 (3.3)	2.22 (2.16-2.29)

*Hospital admissions

No diabetes 1,981,037 - Diabetes n=183,286 - Age 45-84 yr (average 65)

CVD diagnosis at discharge from hospital in diabetic persons in Italy in 2016

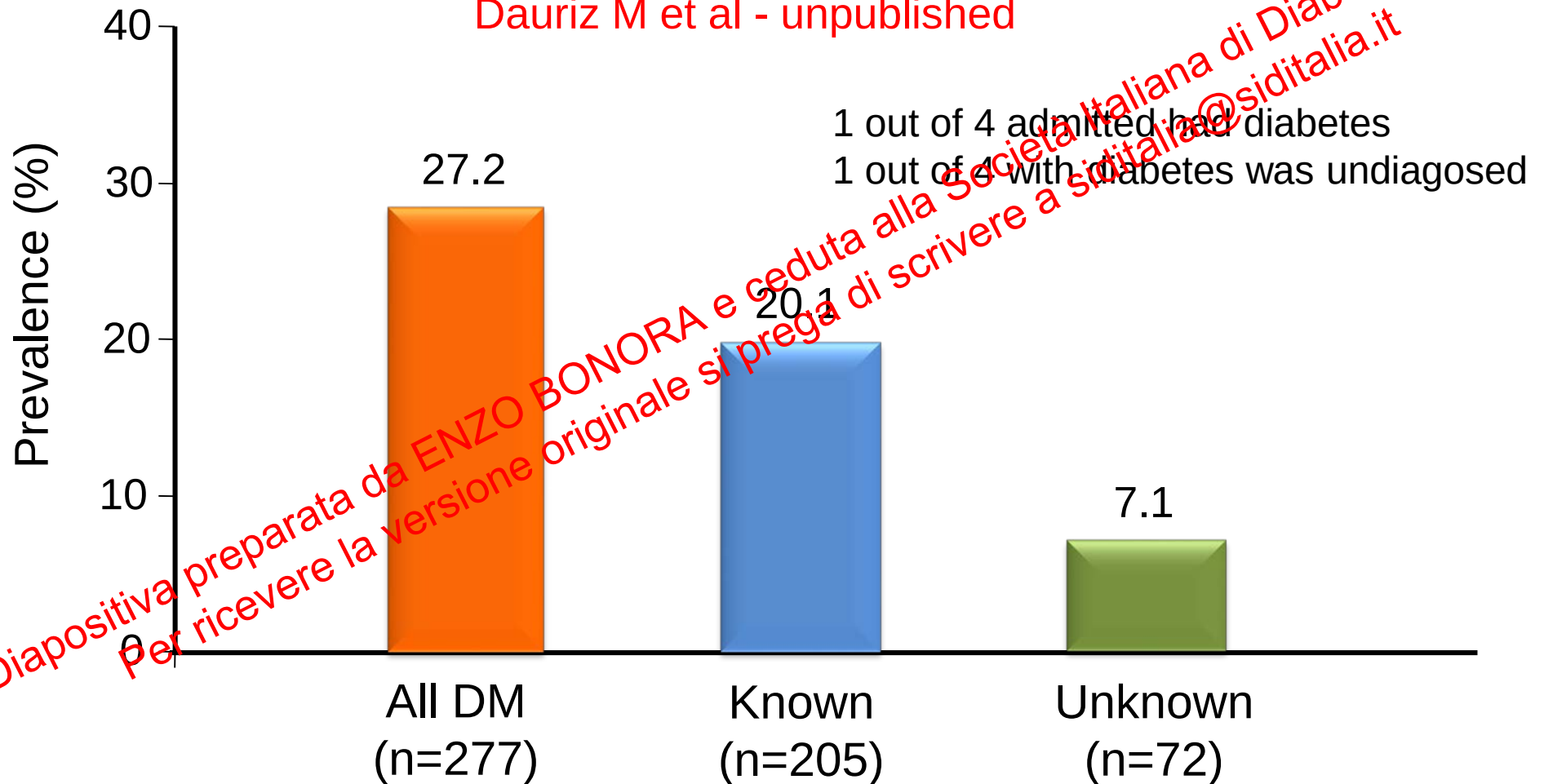
CINECA-SID - ARNO Diabetes Observatory - 2017 Report - All ages

	Rate (per 1000 person-year)
Heart Failure	11.5
Chronic CHD	8.4
Acute myocardial infarction	4.7
Cardiac arrhythmias	4.0
Stroke	3.9

No diabetes 9,501,465 - Diabetes n=640,846 - All ages (0-100 and over)

Prevalence of DM in all subjects admitted for MI in the Verona Hospital Coronary Intensive Care Unit in 2015-2016

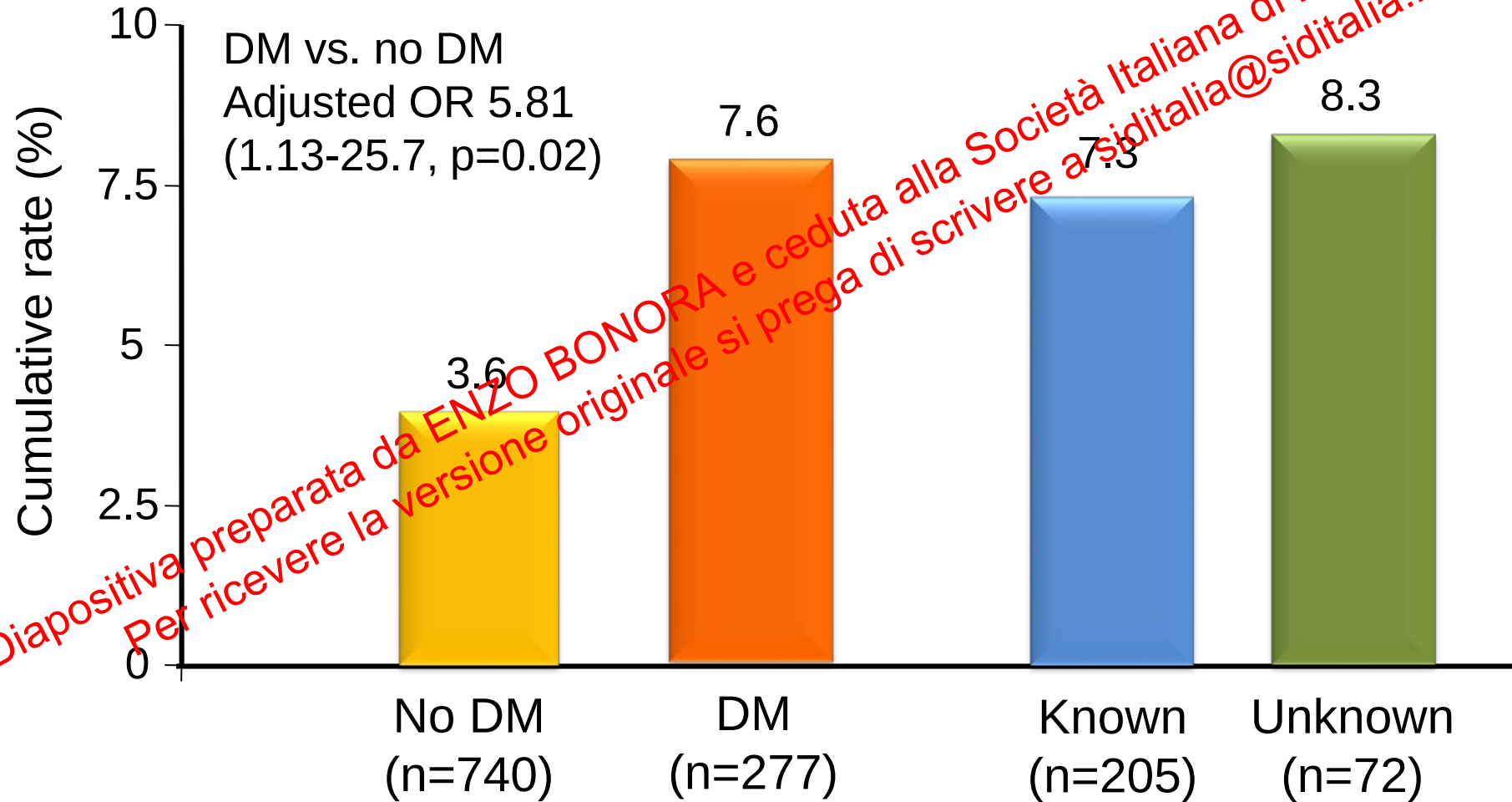
Dauriz M et al - unpublished



N=1017; age 70 yr; men 66%

Mortality in subjects admitted for MI in the Verona Hospital Coronary Intensive Care Unit in 2015-2016

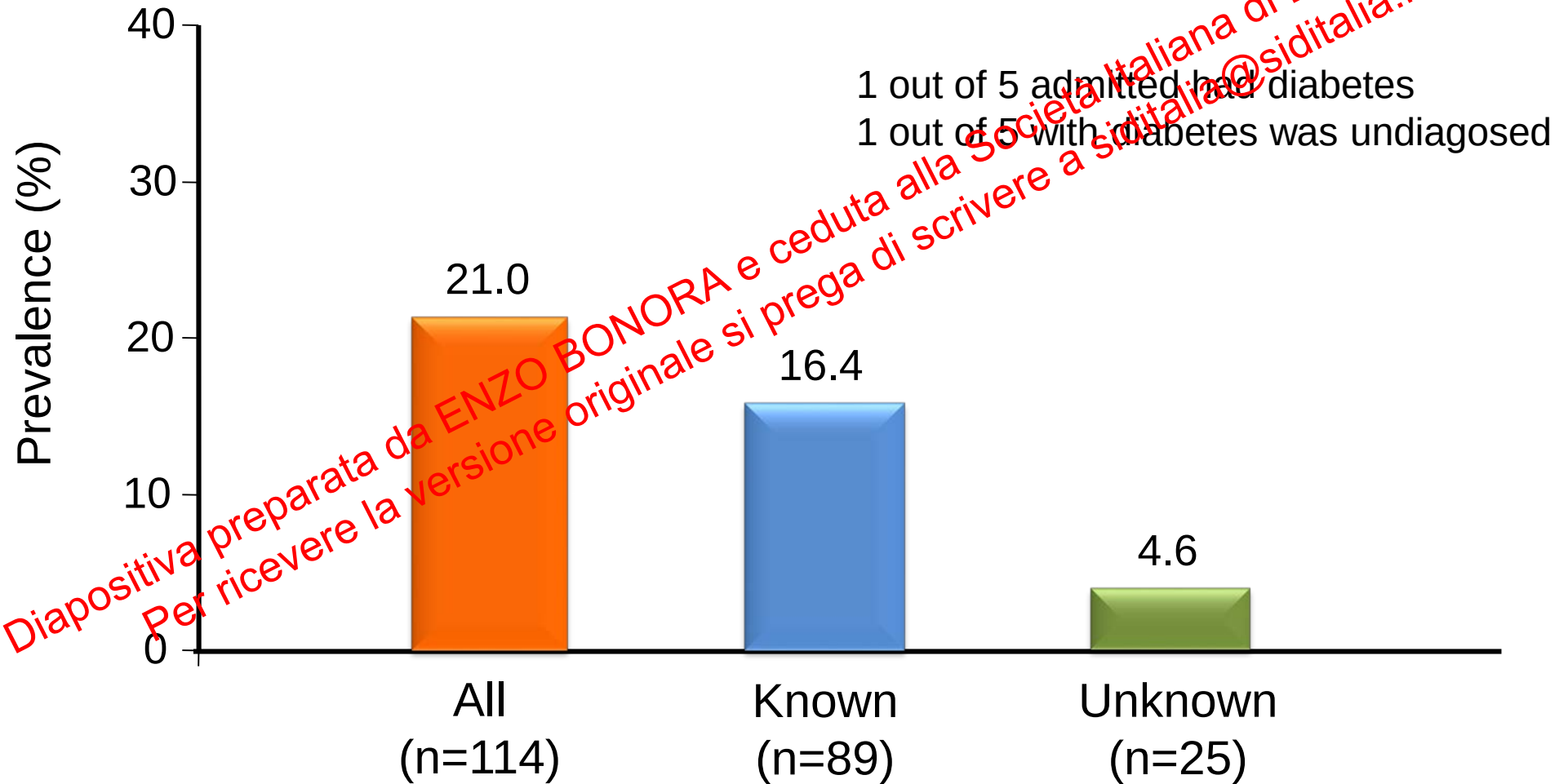
Dauriz M et al - unpublished



N=1017; age 70 yr; men 66%

Prevalence of DM in all subjects admitted for stroke in the Verona Hospital Stroke Unit in 2015-16

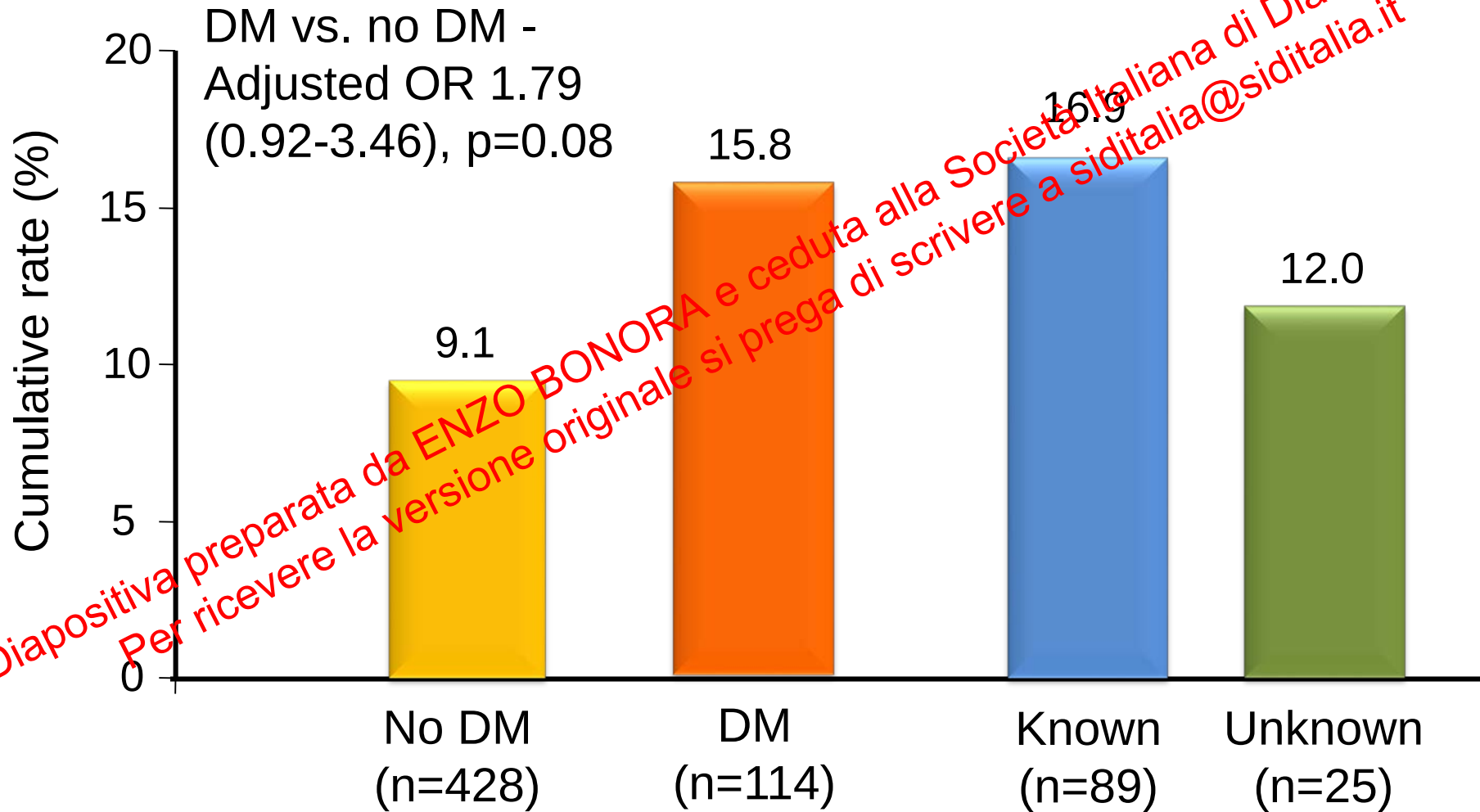
Dauriz M et al - unpublished



N=542; age 74 yr; men 52%

Mortality in subjects admitted for stroke in the Verona Hospital Stroke Unit in 2015-2016

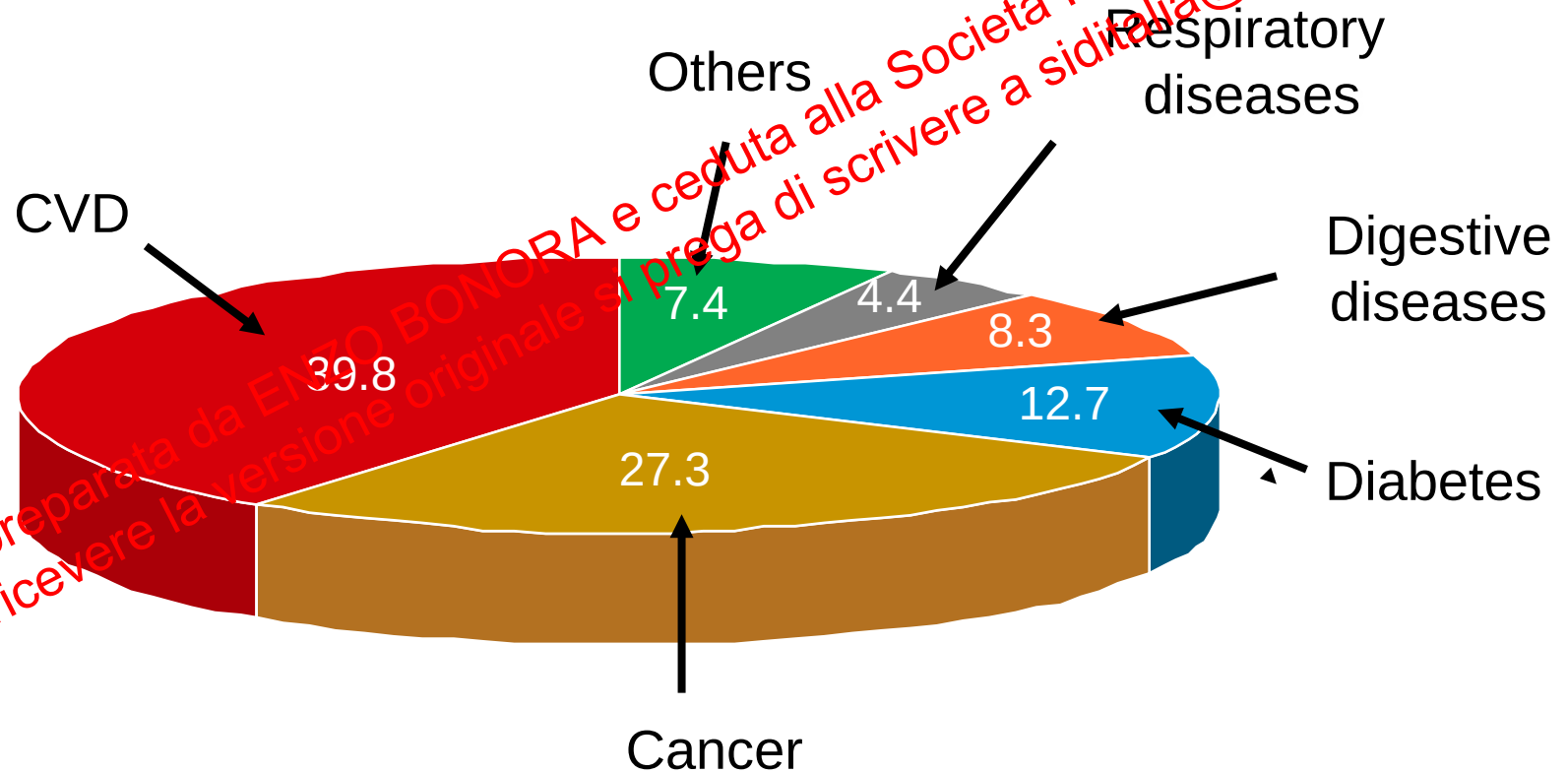
Dauriz M et al - unpublished



N=542; age 74 yr; men 52%

Causes of death in Italian type 2 diabetic persons in 1987-1991

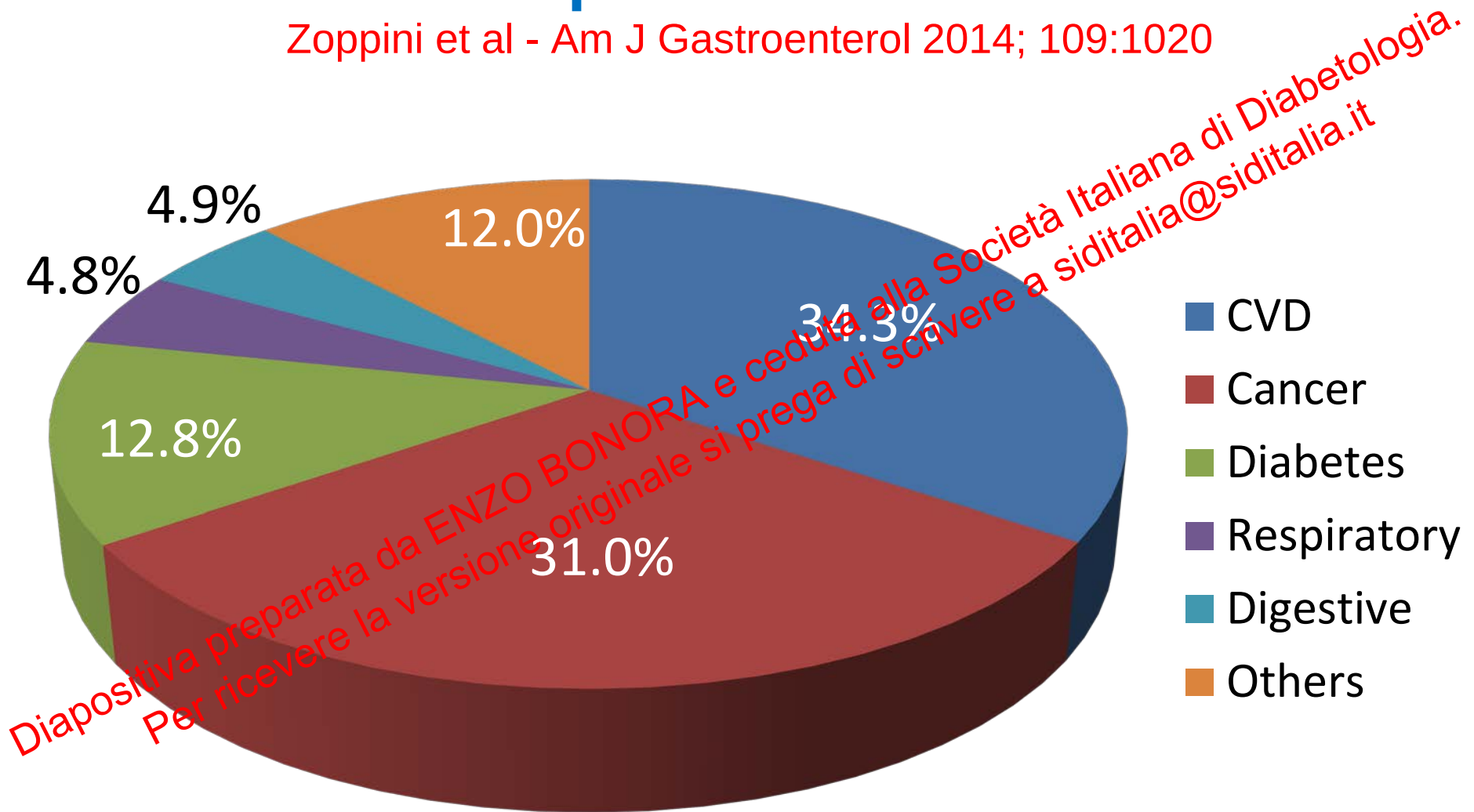
Verona Diabetes Study - De Marco et al - Diabetes Care 1999; 22:756-760



N=7,148; age 67 yr; duration 10 yr; crude death rate 4.8% per year

Causes of death in Italian diabetic persons in the period 2007-2010

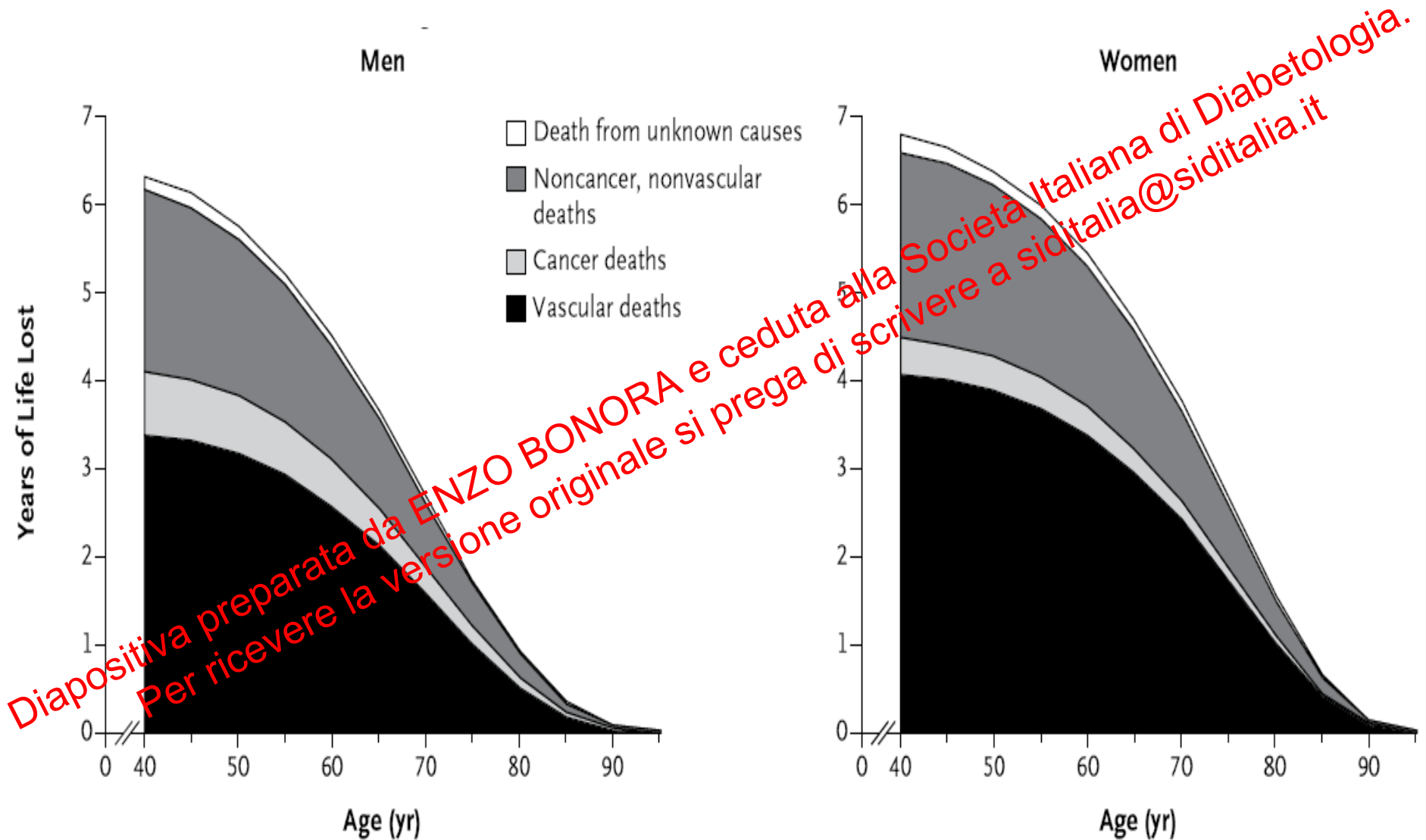
Zoppini et al - Am J Gastroenterol 2014; 109:1020



Baseline 2007; follow-up 3 years; diabetes n=167,621; deaths n=17,134 (9.78%)

Reduction of life expectancy in diabetes

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

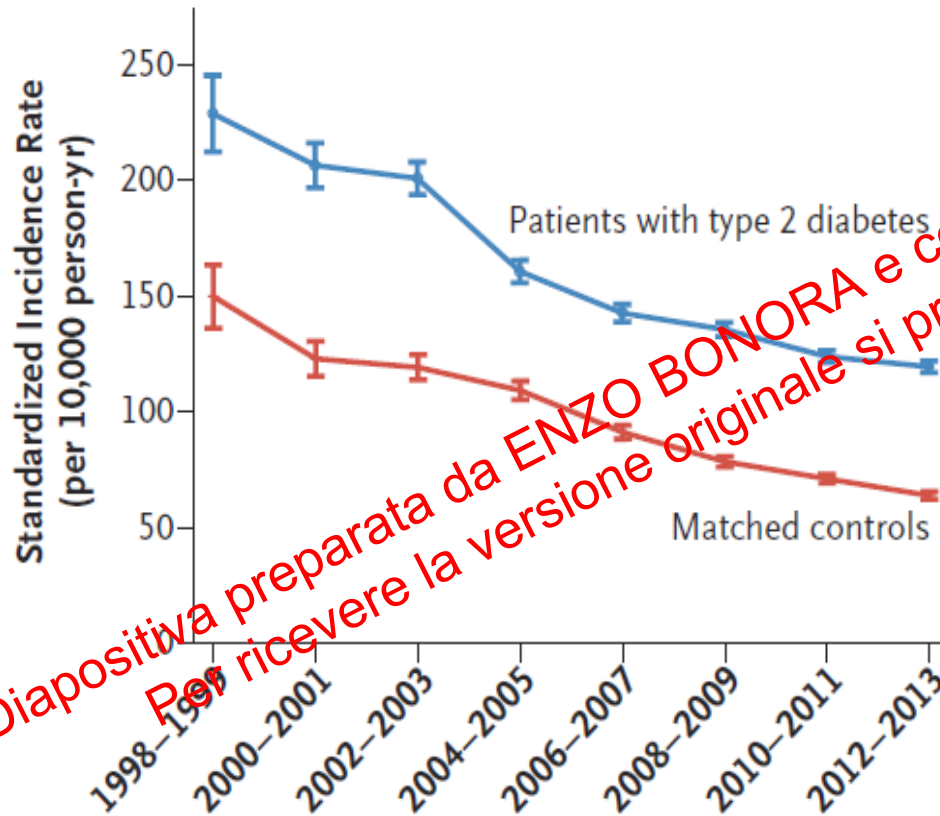


No diabetes n=674,945 - Diabetes n=40,116

Death from CVD in Sweden across years in people with and without T2DM

Rawshani et al – NEJM 2017; 376: 1407

B Death from Cardiovascular Disease



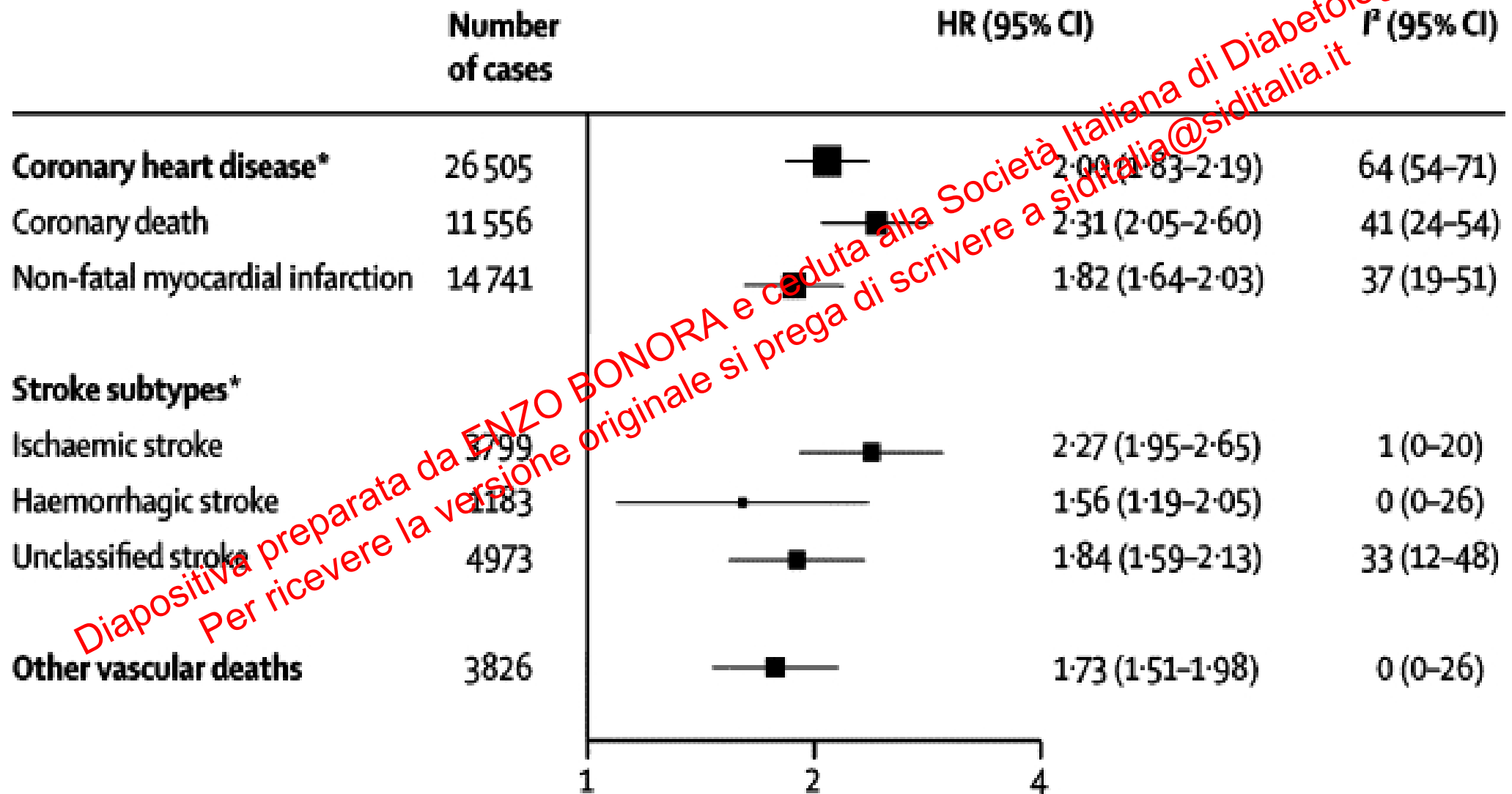
N = 457,473

Relative risk remains
about 2.0-2.5
in DM vs. no DM

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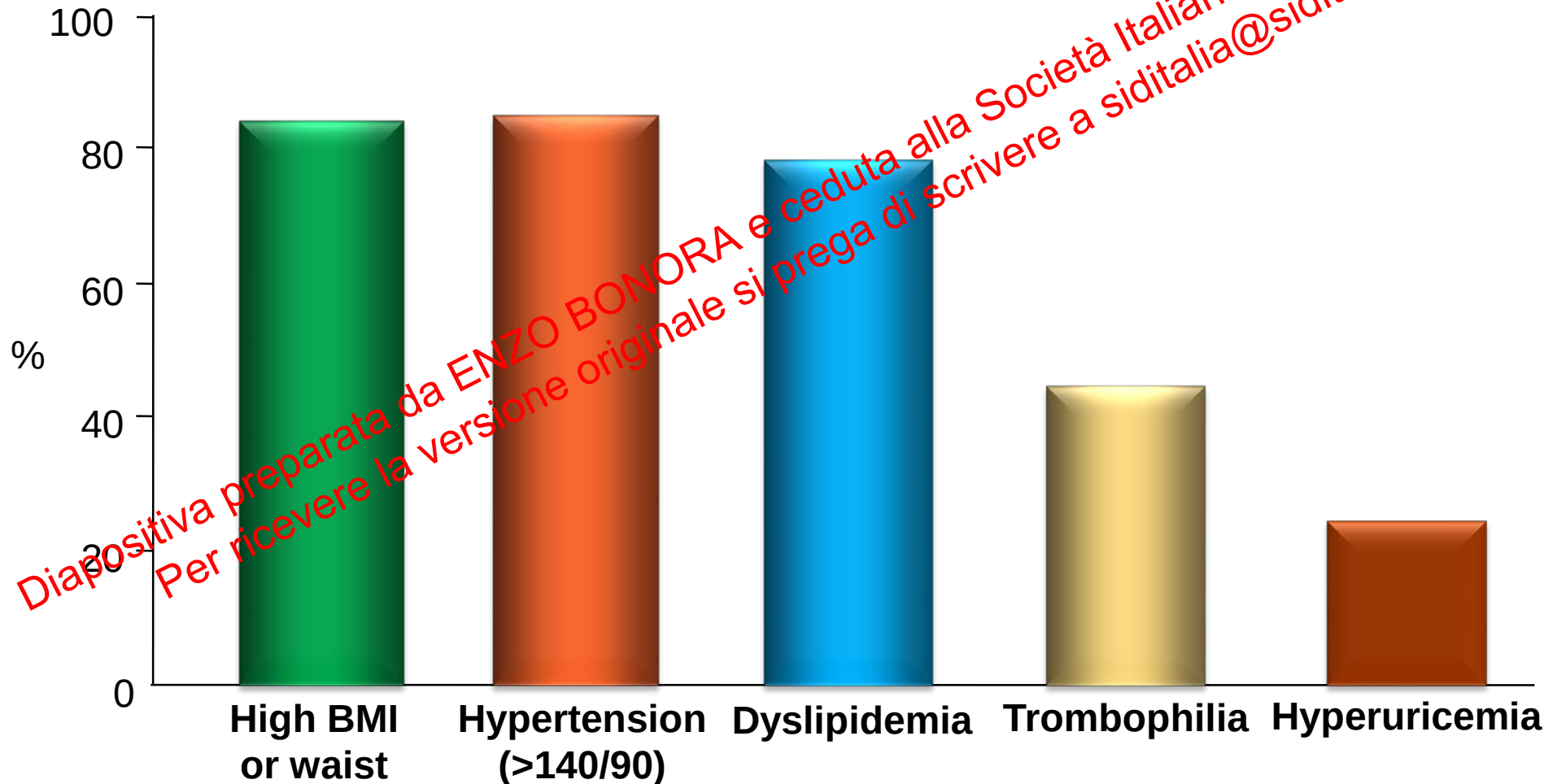
Risk of CVD in diabetes vs. no diabetes

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



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

Verona Diabetes Complications Study; Bonora et al - Diabet Med 21: 523-529, 2004



Diabetes increases risk of CHD and stroke independently of classic risk factors

Emerging Risk Factors Collaboration – Lancet 2010; 375: 2215

A Coronary heart disease

HR (95% CI)

Adjusted for		
Age and sex		2.06 (1.82-2.34)
Plus smoking status		2.10 (1.85-2.39)
Plus BMI		2.08 (1.78-2.25)
Plus systolic blood pressure		1.91 (1.70-2.14)
Plus non-HDL cholesterol		1.93 (1.71-2.16)
Plus HDL cholesterol		1.87 (1.67-2.09)
Plus log-triglyceride		1.87 (1.67-2.09)

B Ischaemic stroke

HR (95% CI)

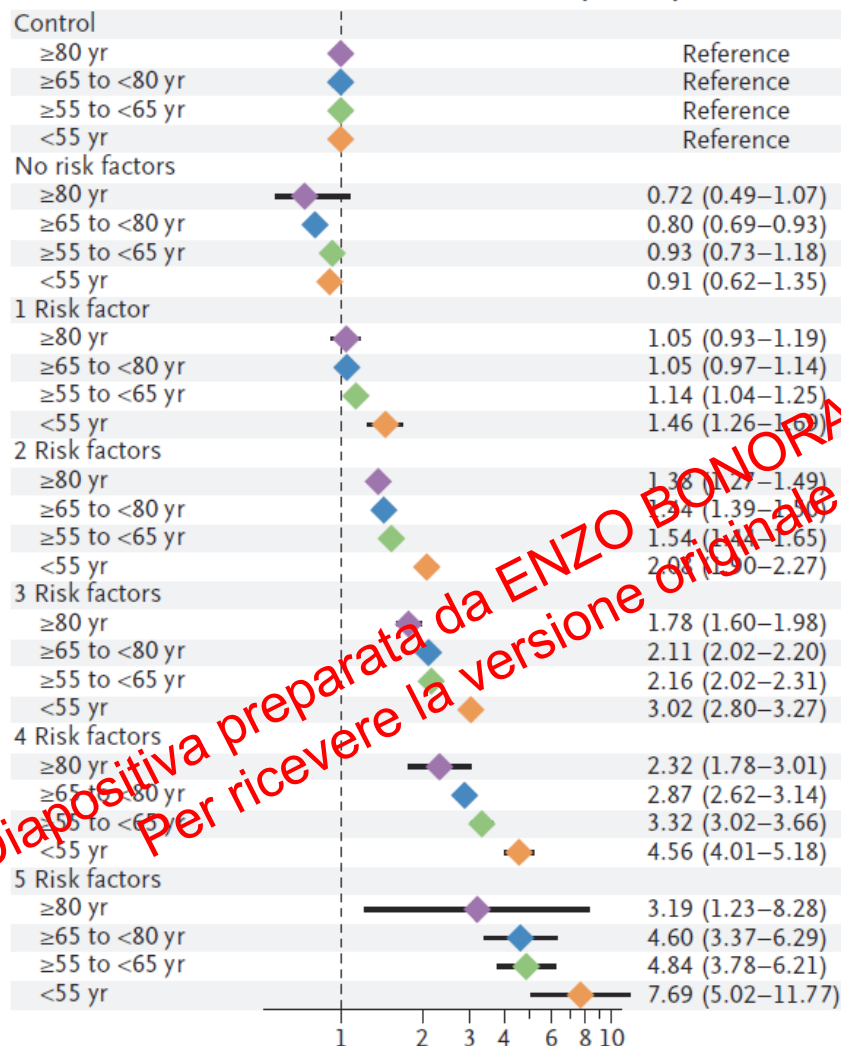
Adjusted for		
Age and sex		2.56 (2.15-3.05)
Plus smoking status		2.59 (2.16-3.09)
Plus BMI		2.45 (2.08-2.88)
Plus systolic blood pressure		2.27 (1.94-2.65)
Plus non-HDL cholesterol		2.26 (1.94-2.64)
Plus HDL cholesterol		2.24 (1.94-2.60)
Plus log-triglyceride		2.24 (1.94-2.59)

N= 264,353 - Known and newly diagnosed diabetes

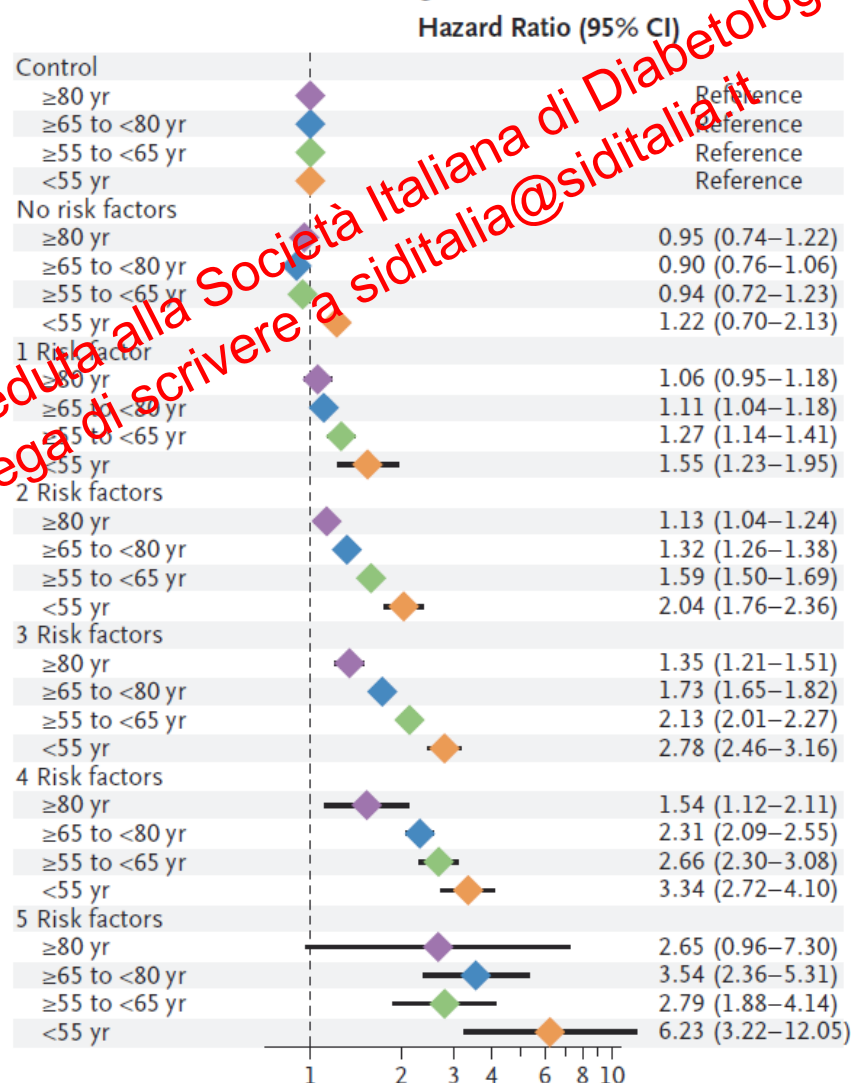
CVD according to risk factors control in T2DM

Rawshani et al – N Engl J Med 2018; 379: 633

B Excess Acute Myocardial Infarction in Relation to Range of Risk-Factor Control



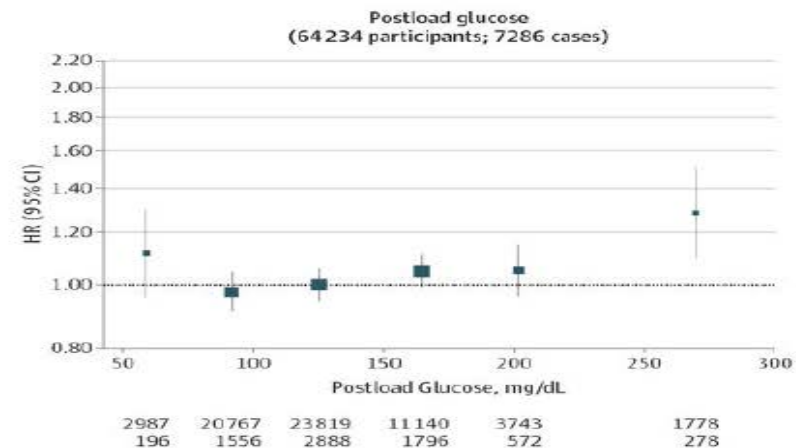
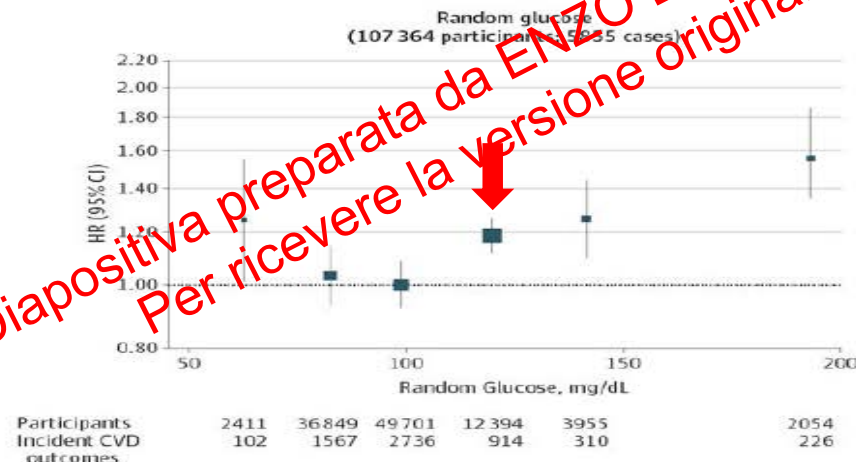
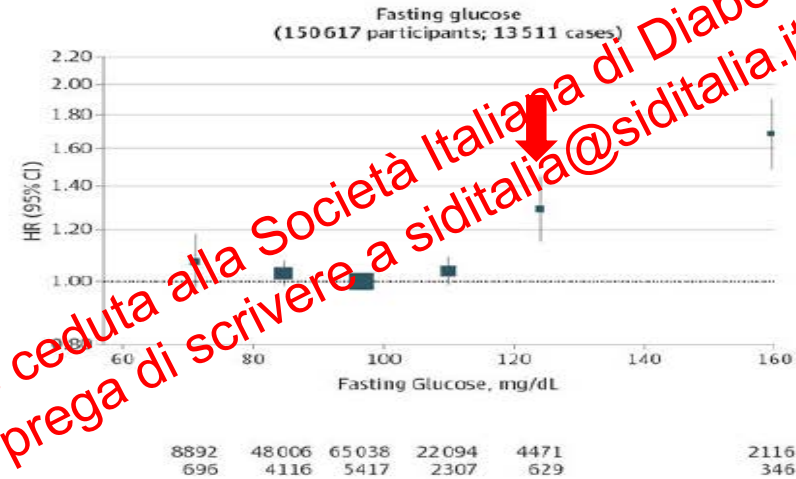
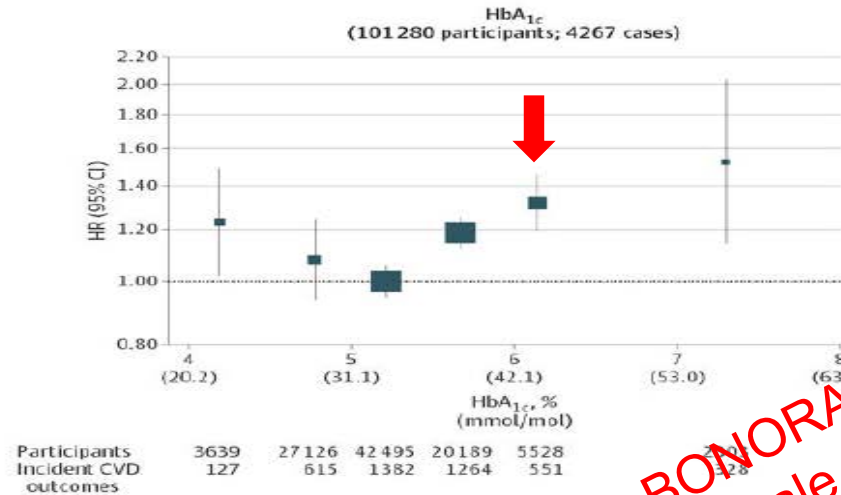
C Excess Stroke in Relation to Range of Risk-Factor Control



Controls n=1,355,870, T2DM n=271,174 - 5 risk factors: HbA1c, LDL-C, sBP, albuminuria, smoking

Mild increases in glycemc parameters predict CVD in subjects without known diabetes

Emerging Risk Factors Collaboration – JAMA 2014; 311: 1225



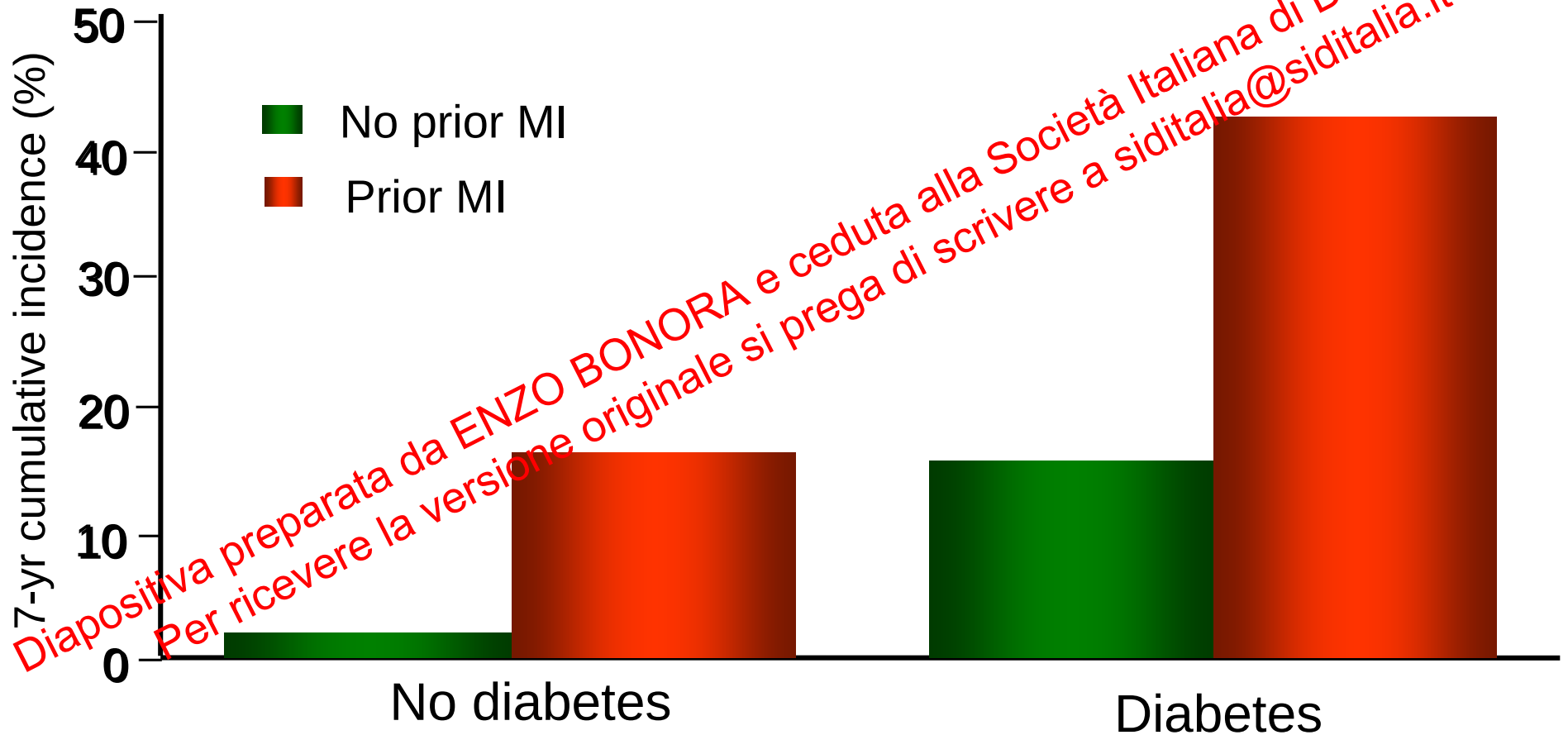
N= 294,998 - No history of DM or CVD at baseline -
Adjusted for demographics, smoking, blood pressure, lipids

Mild diabetes doesn't exist!

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Cardiovascular mortality in subjects with and without prior myocardial infarction

Haffner et al - NEJM 1998; 339: 229



Cardiovascular risk factors in Diabetes

Old fashioned

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

New but already classic

- Waist and WHR
- Albuminuria
- eGFR
- Uric acid
- CRP
- Lp(a)
- Homocystein
- Fibrinogen
- PAI-1
- Insulin resistance
- Metabolic Syndrome
- NAFLD

Novel

- VCAM-1 & Co.
- MMP-1,2,3,etc.
- TIMP-1
- IL-6, IL-15
- TNFR-1 & 2
- vWF
- ADMA
- Zinc
- NT-pro-BNP
- hsTnT
- sRAGE
- GDF-15
- Many others

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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)	1.90 (1.4-2.2)	1.84 (1.4-2.1)	1.53 (1.1-1.7)

NAFLD diagnosed by ultrasonography

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

Metabolic Syndrome and risk of 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

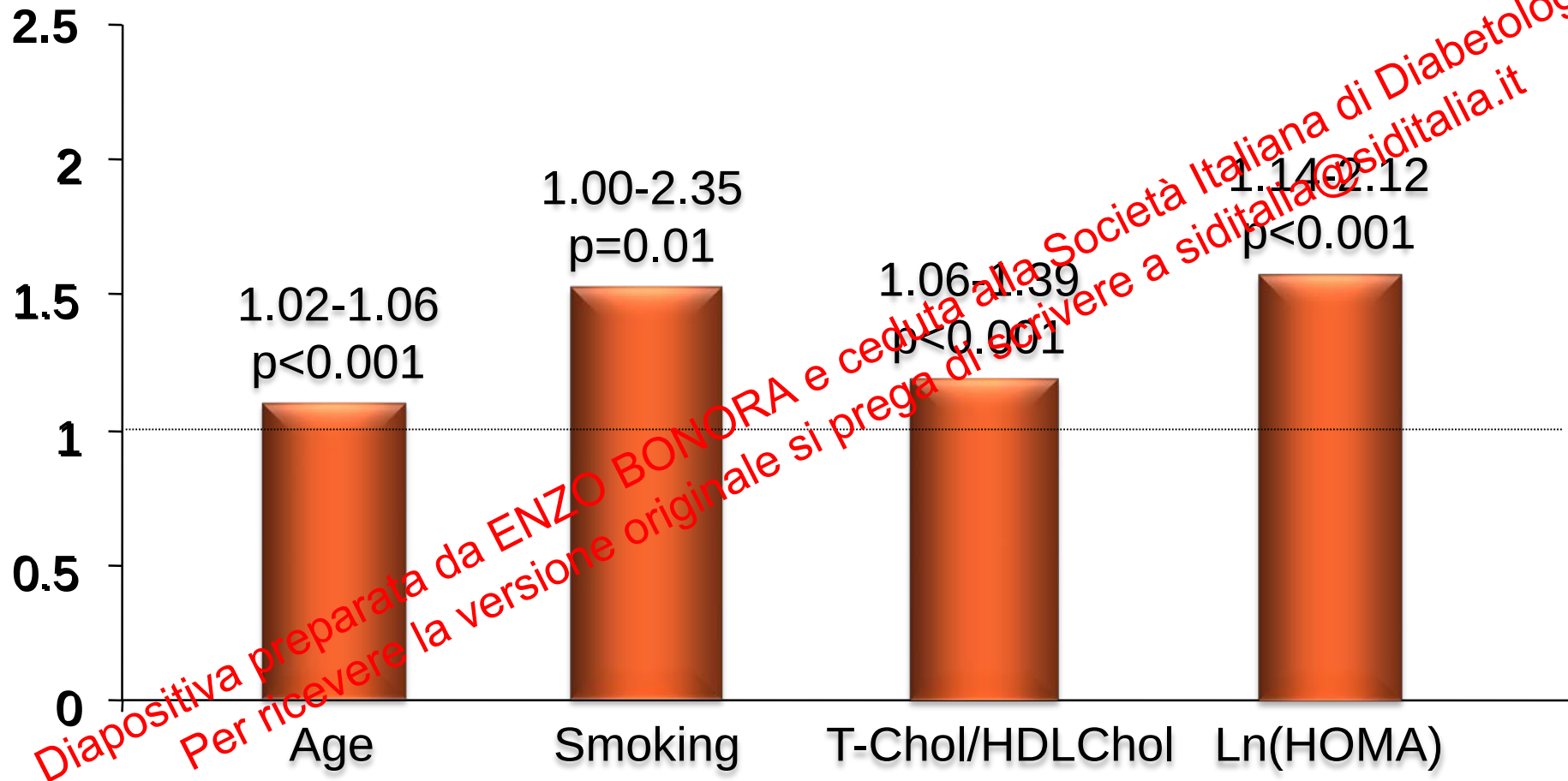
n= 559; age 65 yr; duration 9 yr; follow-up 4.5 yr

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 into the model

Insulin Resistance and risk of CVD in T2DM

Verona Diabetes Complications Study; Bonora et al, Diabetes Care 25: 1135, 2002

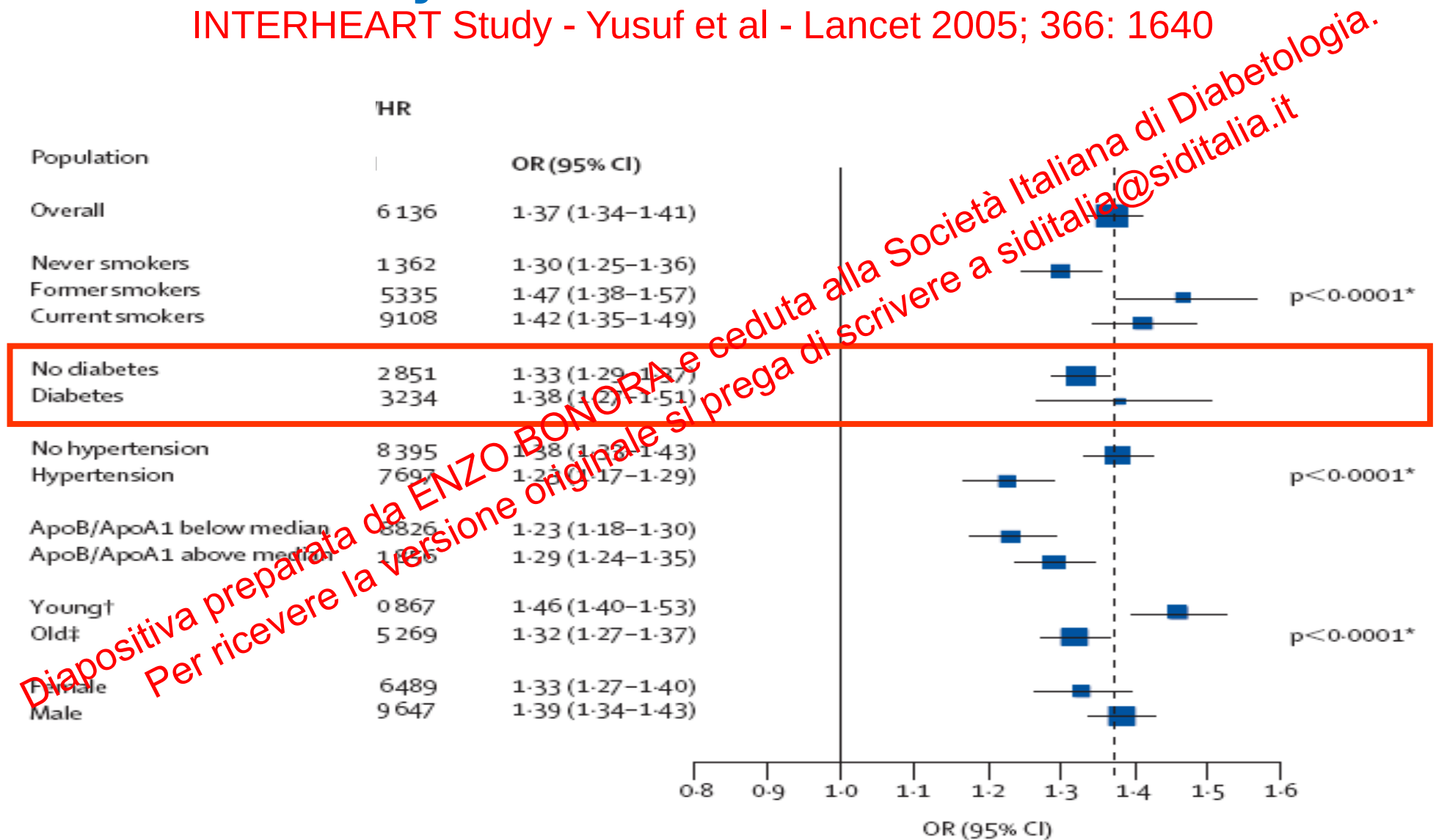


N=627, follow-up 4,5 yr. Model including also sex, duration, BMI, hypertension, HbA1c.

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

WHR and myocardial infarction in 27,000 subjects from 52 countries

INTERHEART Study - Yusuf et al - Lancet 2005; 366: 1640



Plasma uric acid and CVD risk in T2DM

Zoppini G *et al* – Diabetes Care 2009; 32: 1716-20

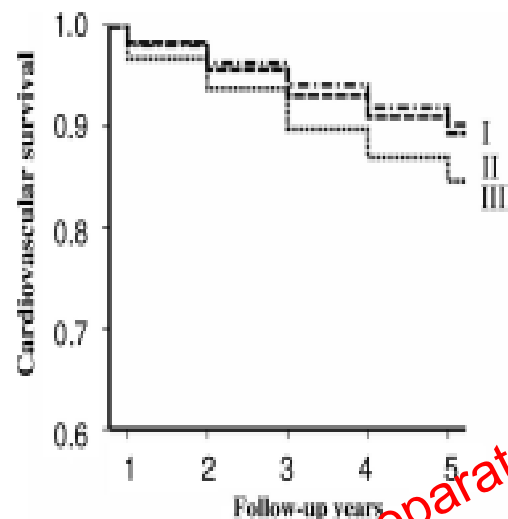


Figure 1—Kaplan-Meier curves of cardiovascular mortality in 2,726 type 2 diabetic patients stratified by sex-specific tertiles of serum uric acid levels. Statistical significance was estimated by the log-rank test ($P < 0.001$ for the third tertile vs. the other two tertiles).

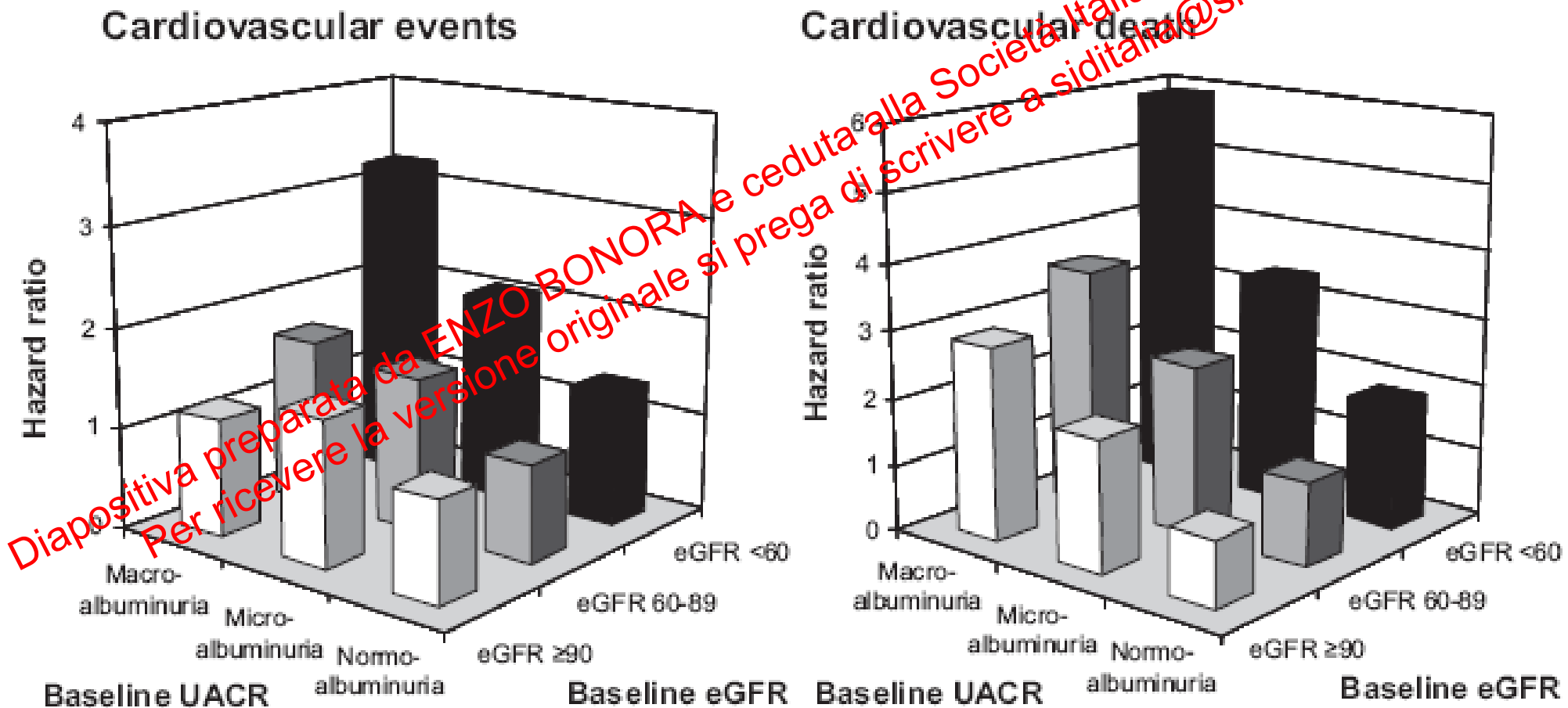
Table 2—Predictors of cardiovascular mortality as assessed by multivariate Cox proportional hazards models

	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 (0.99–1.67)	NS	1.38 (0.93–2.05)	NS	0.95 (0.57–1.58)	NS
Current smoking	1.30 (0.76–2.23)	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)	0.98 (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.

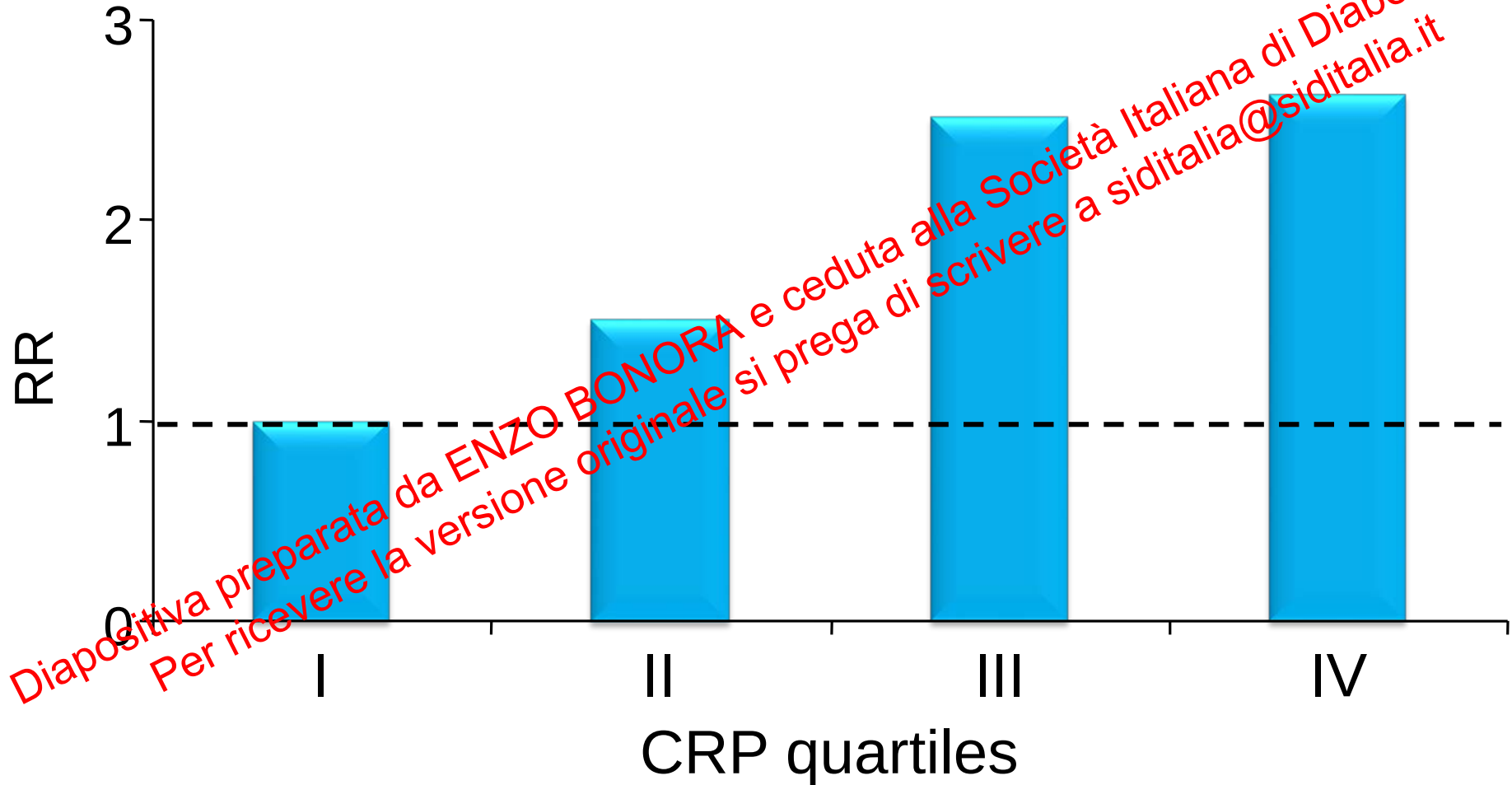
Risk of CVD events and death as a function of eGFR and albuminuria in T2DM

ADVANCE Study - Ninomiya T. et al. - JASN, 2009; 20:1813-21



Serum CRP and CVD risk in men with T2DM

Health Professional Study - Schulze et al - Diabetes Care 2004; 27:889

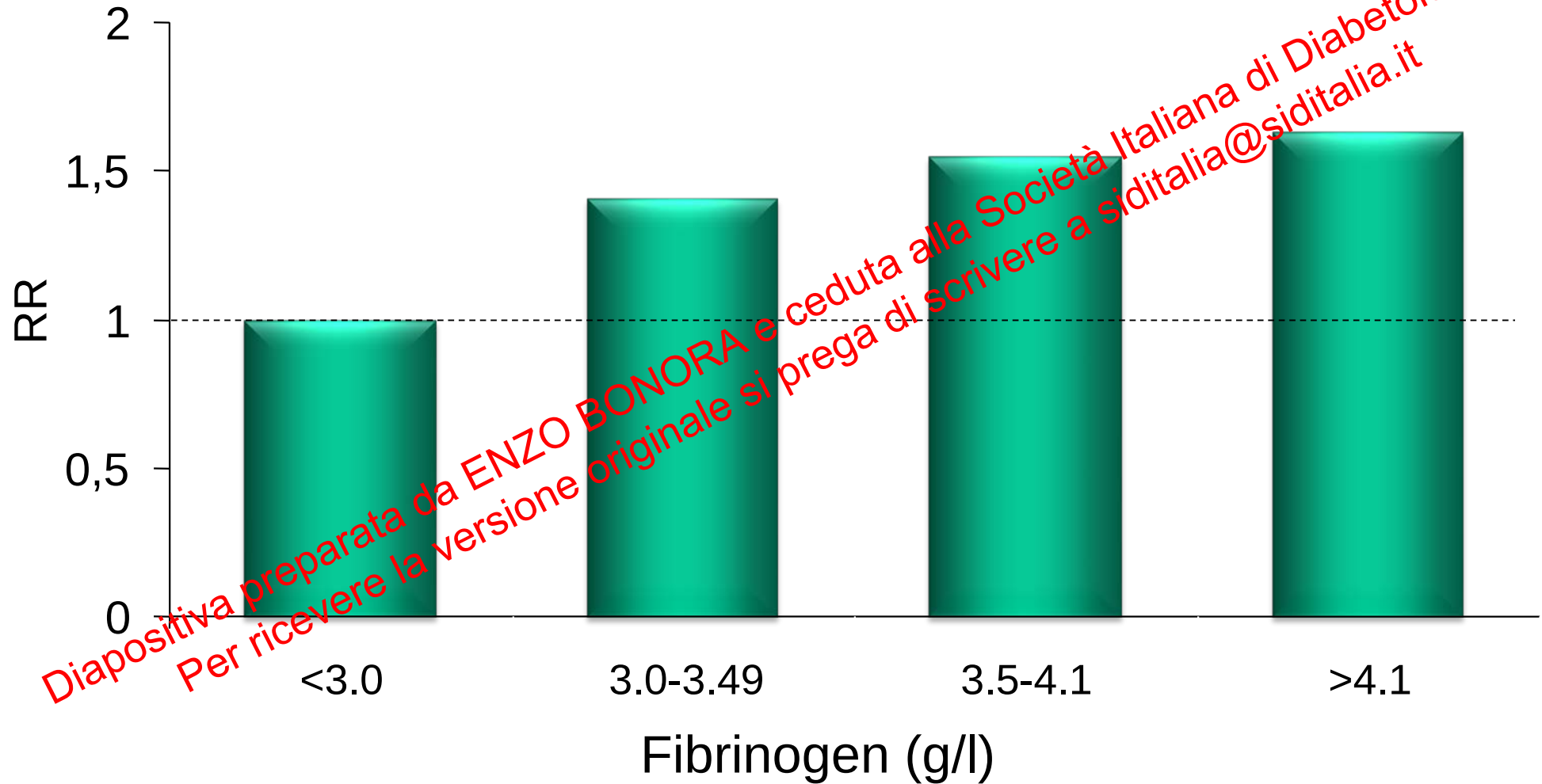


N= 746; follow-up 5 years

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

Plasma fibrinogen and risk of CVD mortality in T2DM

Bruno G et al - Diabetologia 2005; 48:427

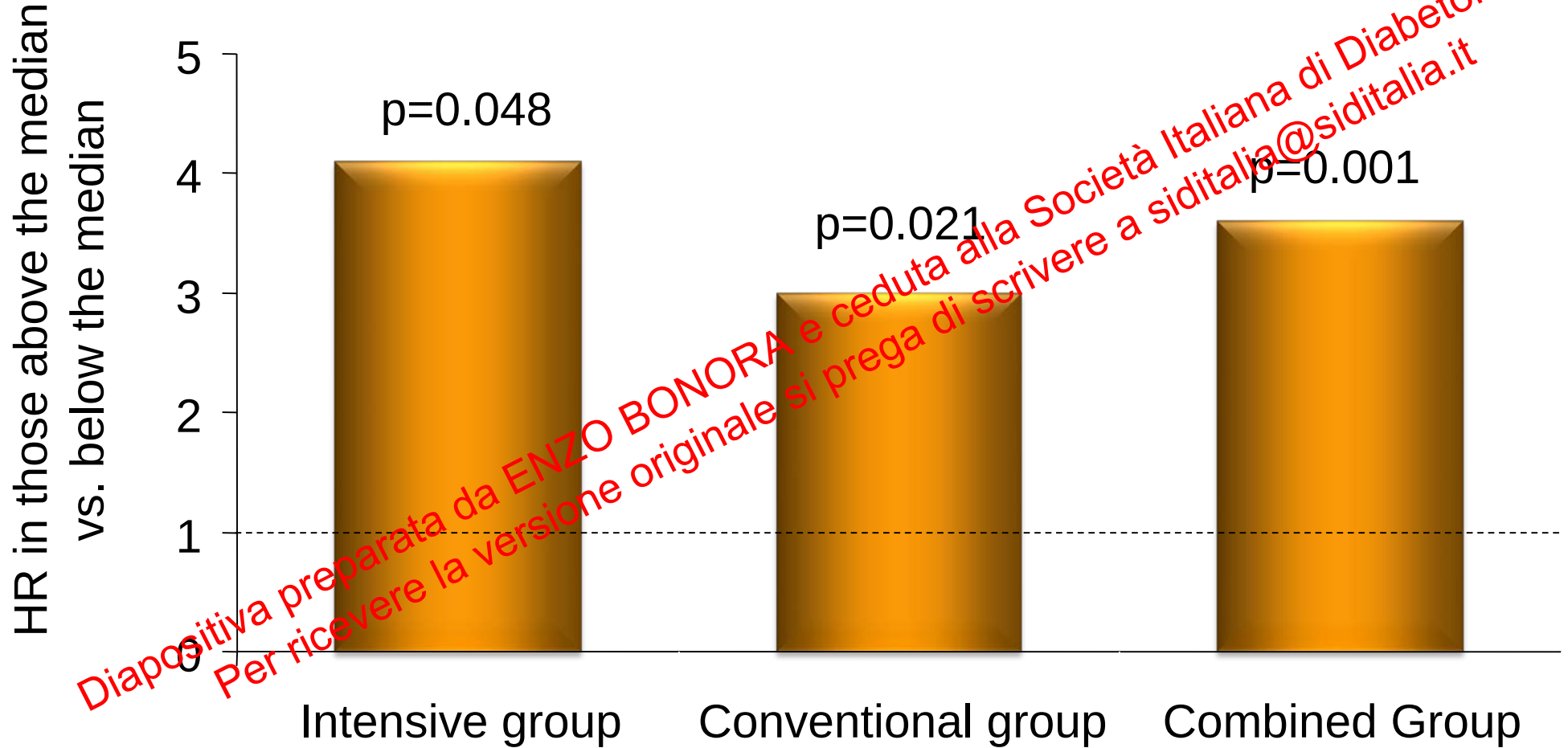


n=1565; follow-up 11 years

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

Plasma N-terminal pro-Brain Natriuretic Peptide (NT-proBNP) and CVD risk in T2DM

Steno Study - Gaede et al - Diabetologia 2005; 48:156



N=160, age 55, microalbuminuria +; follow-up 7.8 yrs

Adjusted for baseline CVD, duration of DM, age, sex, sBP, cholesterol, triglycerides, AER

Prediction of CHD (ROC analysis) in T2DM

ARIC Study Folsom et al - Diabetes Care 2003; 26: 2777

	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

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

Framingham Heart Study - Wang et al - NEJM 2006; 355: 2631

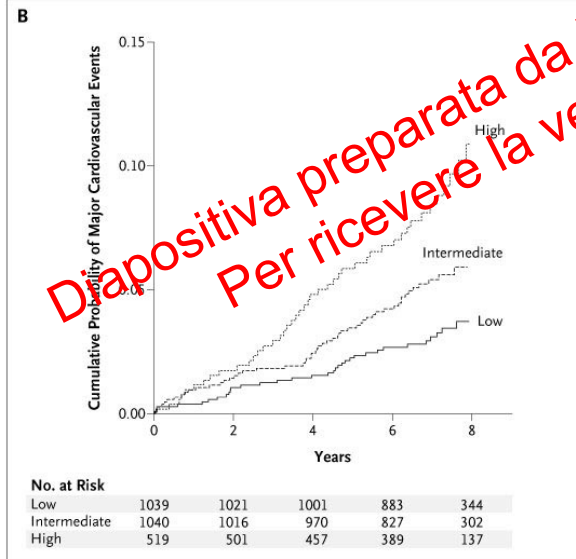
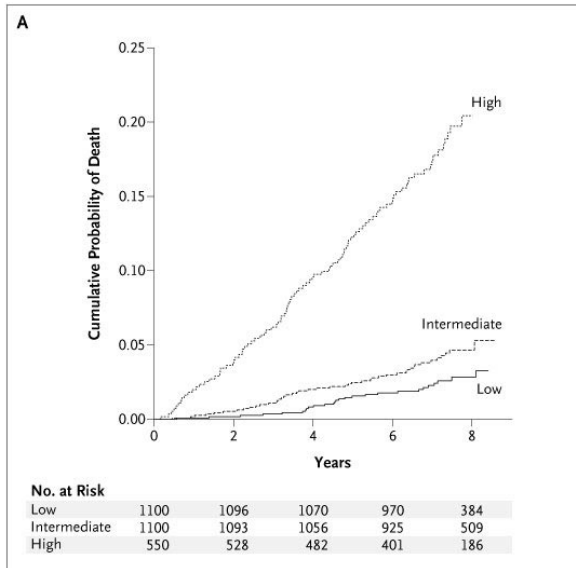


Table 3. Relation of Multimarker Risk Score to Outcomes.*

Multimarker Score	Death adjusted hazard ratio (95% CI)	Major Cardiovascular Events adjusted hazard ratio (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	3.08 (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

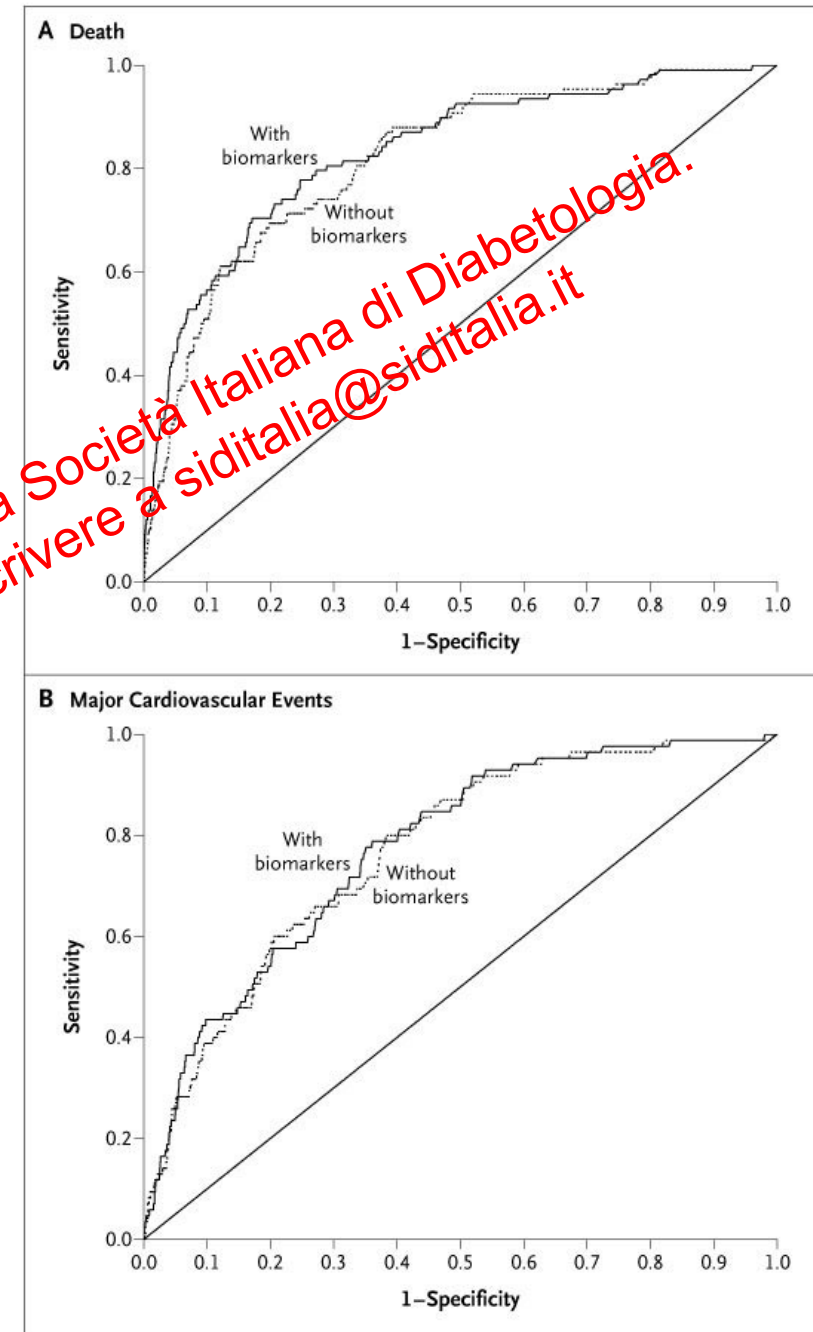
Multimarker score for death= B-NP, homocysteine, renin, CRP, ACR

Multimarker score for MACE= B-NP, ACR

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

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

N=3209; follow-up 7.4 years



Novel biomarkers for predicting CVD in T2DM

Gerstein H et al -
Circulation 2015; 132: 2297

Supplementary Table 1a: Independent Biomarkers of Outcomes in the Model Building Set

Risk Factor	CV Composite		Expanded CV Composite		Death	
	HR (95%CI) ^a	p ^b	HR (95%CI) ^a	p ^b	HR (95%CI) ^a	p ^b
Clinical Factors						
Prior CV Event	1.37 (1.18, 1.59)	4.7E-5	1.58 (1.41, 1.78)	2.0E-14	1.10 (0.95, 1.28)	2.0E-1
Albuminuria	0.98 (0.85, 1.14)	8.2E-1	1.00 (0.89, 1.11)	9.3E-1	0.90 (0.78, 1.04)	1.5E-1
Men	1.55 (1.31, 1.83)	2.5E-7	1.60 (1.41, 1.82)	3.3E-13	1.15 (0.98, 1.36)	9.2E-2
Men ≥ 55, Women ≥ 65	1.15 (0.95, 1.40)	1.5E-1	1.12 (0.97, 1.29)	1.1E-1	1.54 (1.25, 1.90)	4.8E-5
LDL/HDL	1.10 (1.03, 1.18)	3.2E-3	1.11 (1.06, 1.17)	5.2E-6	1.15 (1.08, 1.22)	7.5E-6
Current Smoking	1.46 (1.21, 1.75)	5.6E-5	1.21 (1.05, 1.40)	8.4E-3	1.68 (1.39, 2.04)	9.4E-8
Prior diabetes	1.11 (0.93, 1.33)	2.4E-1	1.01 (0.88, 1.14)	9.7E-1	1.23 (1.01, 1.49)	3.9E-2
Hypertension	1.15 (0.97, 1.37)	1.1E-1	1.29 (1.13, 1.47)	1.7E-4	1.43 (1.19, 1.73) ^c	7.8E-3
Identified Biomarkers						
NT-proBNP	1.28 (1.21, 1.36)	2.2E-16	1.18 (1.13, 1.24)	2.9E-14	1.17 (1.10, 1.24) ^c	4.0E-4
Trefoil Factor 3	1.32 (1.24, 1.42)	2.3E-15	N/A		1.22 (1.13, 1.33)	1.1E-6
Alpha-2-Macroglobulin	1.22 (1.13, 1.31)	1.3E-7	N/A		1.22 (1.14, 1.31)	3.1E-8
Glutathione S Transferase alpha	0.84 (0.78, 0.90)	2.2E-7	0.90 (0.86, 0.95)	4.4E-5	0.83 (0.77, 0.89) ^c	4.5E-2
Apolipoprotein B	1.17 (1.09, 1.26)	1.6E-5	N/A		N/A	
Peroxiredoxin-4	1.16 (1.08, 1.24)	1.8E-5	N/A		1.14 (1.07, 1.22)	1.3E-4
Angiopoietin-2	1.15 (1.07, 1.23)	8.7E-5	1.16 (1.10, 1.22)	6.2E-8	1.20 (1.12, 1.29)	5.3E-7
Osteoprotegerin	1.16 (1.07, 1.25)	1.6E-4	N/A		N/A	
Growth/Differentiation Factor 15	N/A		1.15 (1.09, 1.22)	1.4E-6	1.23 (1.13, 1.34)	2.1E-6
VEGF D	N/A		1.13 (1.07, 1.19)	2.6E-6	N/A	
Kidney Injury Mol-1	N/A		1.09 (1.05, 1.13)	2.3E-5	N/A	
Tamm Horsfall Urine Glycoprotein	N/A		0.89 (0.84, 0.94)	2.7E-5	N/A	
Macrophage Derived Chemokine	N/A		N/A		0.84 (0.79, 0.90)	9.9E-7
YKL-40	N/A		N/A		1.17 (1.10, 1.26)	4.3E-6
IGF Binding Protein 2	N/A		N/A		1.13 (1.04, 1.23)	5.6E-3

CV Composite = MACE
Expanded CV = MACE +
HHF + revascularization

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Novel biomarkers for predicting CVD in T2DM

Gerstein H et al - Circulation 2015; 132: 2297

Supplementary Table 4: Performance of Models Containing the Clinical Risk Factors and Only NT-proBNP versus all of the Identified Biomarkers

	A: Basic Clinical C (95%CI)	B: Basic + NT proBNP C (95% CI)	C: Full Model C ^b (95% CI)	B vs. A ^a NRI (95%CI)	C vs. B ^{ab} NRI (95%CI)
Cardiovascular Composite Outcome					
All Participants	0.64 (0.63, 0.65)	0.68 (0.66, 0.69)	0.71 (0.69, 0.72)	0.14 (0.11, 0.17)	0.10 (0.07, 0.13)
Expanded Cardiovascular Composite Outcome					
All Participants	0.64 (0.62, 0.65)	0.66 (0.65, 0.67)	0.68 (0.67, 0.69)	0.06 (0.05, 0.07)	0.05 (0.03, 0.06)
Death from All Causes					
All Participants	0.64 (0.63, 0.66)	0.68 (0.67, 0.70)	0.75 (0.74, 0.76)	0.12 (0.09, 0.15)	0.24 (0.21, 0.28)

NRI = net reclassification improvement values during a maximum follow-up of approximately 7.8 years are shown; ^a all P values <0.001; ^b bootstrap optimism-adjusted

CVD Composite = MACE

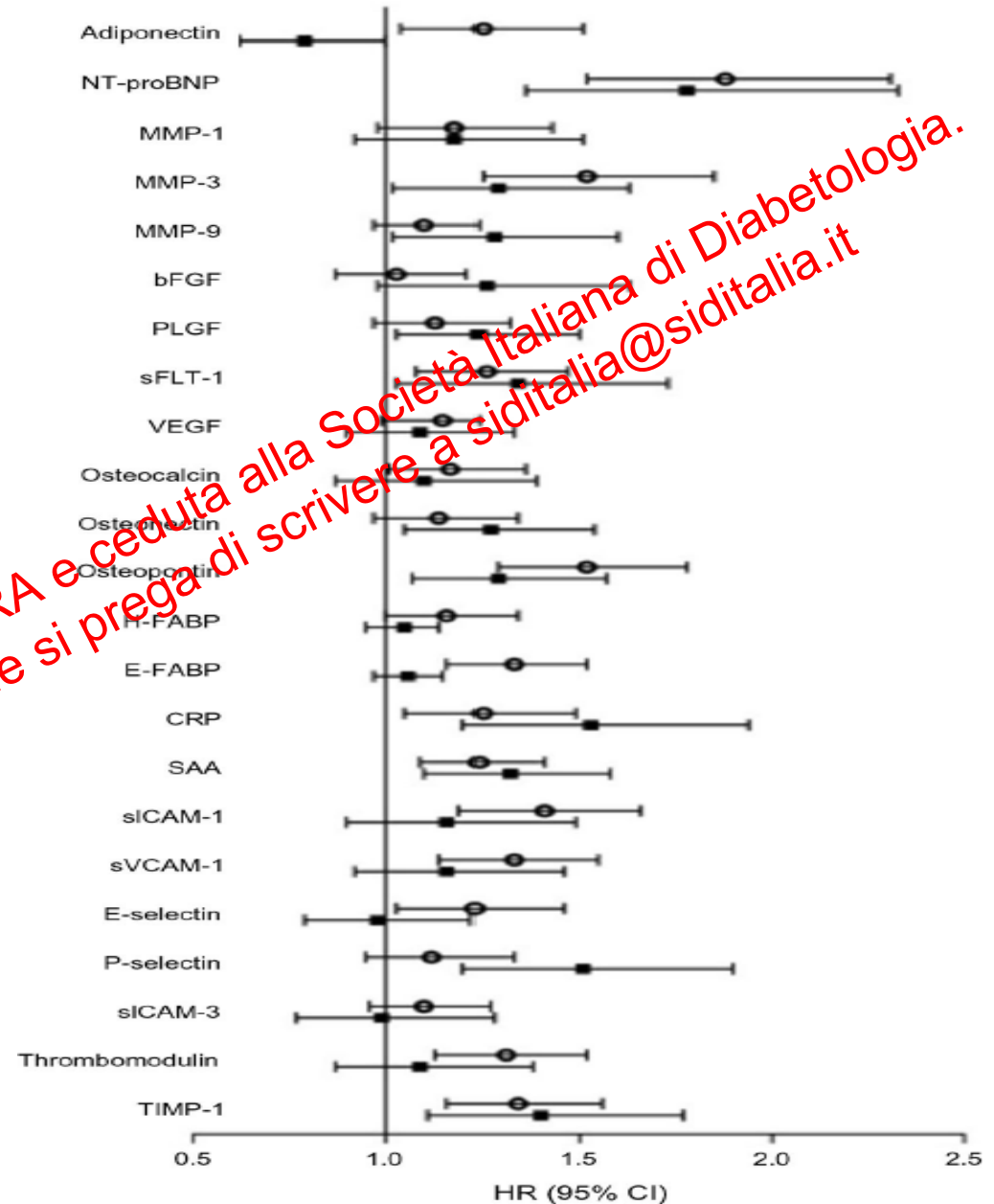
Expanded CVD Composite = MACE + HHF + revascularization

Multivariable adjusted HRs for risk of MACE for the highest vs. the lowest quartile of each candidate biomarker in two cohorts with T2DM

Van der Leeuw J et al -
J Am Heart Assoc 2016

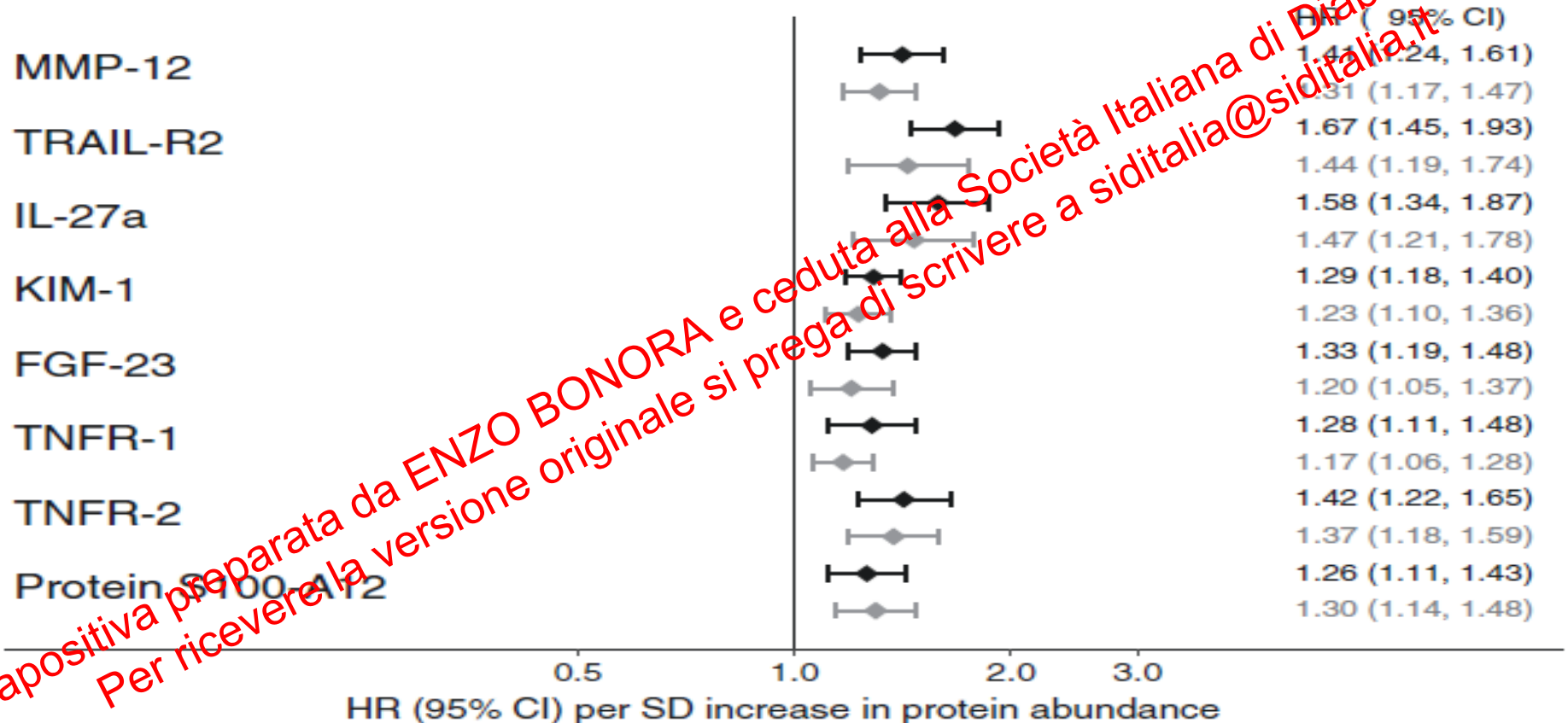
Adjusted for sex, smoking, age at diagnosis, duration of diabetes, BMI, HbA1c, sBP, total/HDL cholesterol ratio, U-ACR, previous CVD

Open circle = SMART study
Black Squares = EPIC-NL study



Multiplex proteomics for prediction of MACE in T2DM

Nowak C et al - Diabetologia 2018; 61:1748–1757

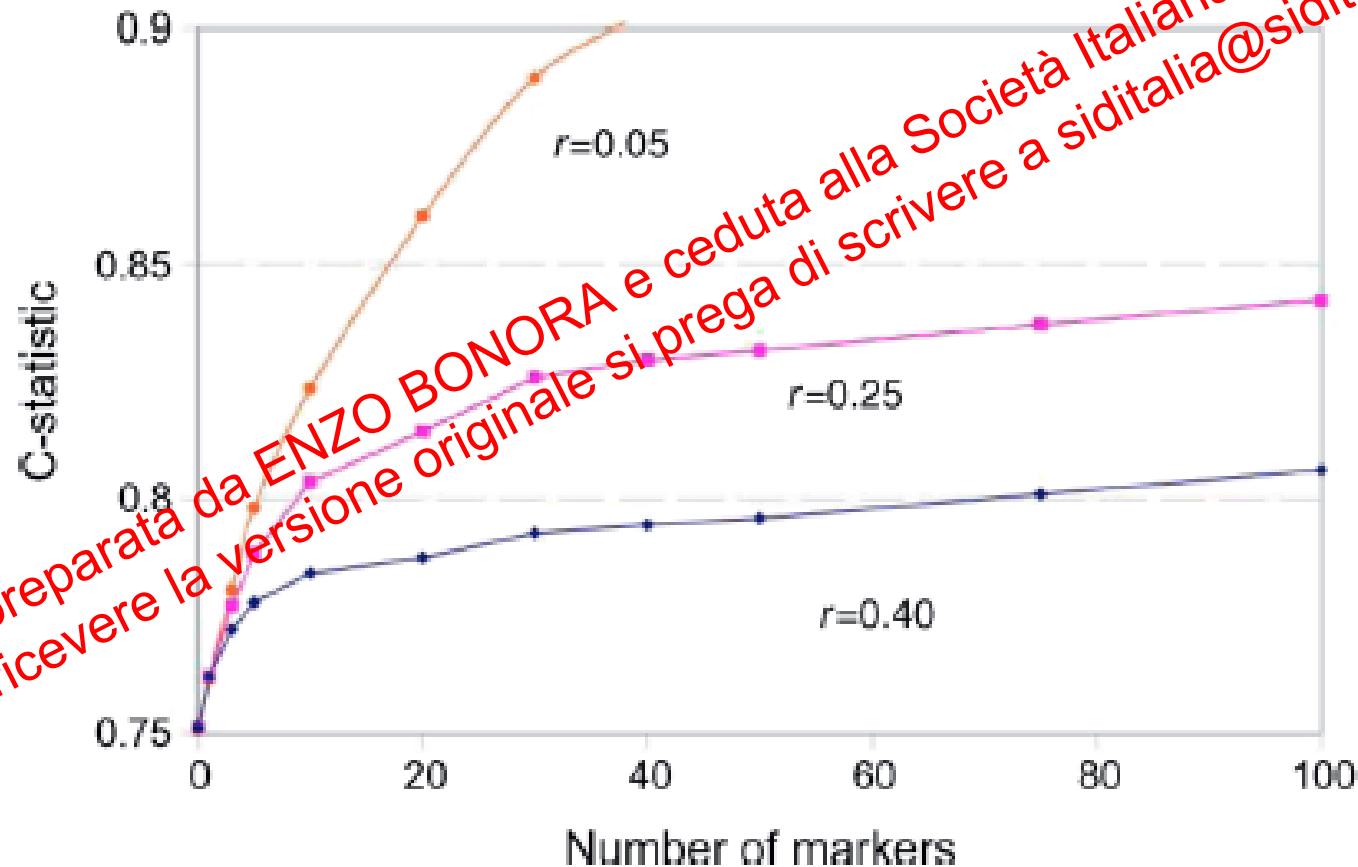


Combined data from 6 prospective epidemiological studies of 30–77-year-old individuals with T2DM in whom 80 circulating proteins were measured.

Adjusted for sex and age (black symbols) and also for duration of DM, BMI, HbA1c, smoking, AF, LDL-C, statin use, sBP, Albuminuria, eGFR, prior CVD (grey symbols)

Increase in the discrimination achieved by adding simulated biomarkers according to their degree of correlation

Bachmann KN and Wang TJ - Diabetologia 2018; 61: 917-924



r=coefficient of correlation between biomarkers

Genetic risk scores (13 or 30 SNPs) and CVD risk in T2DM

Fox A et al - Diabetes Care 2014; 37: 1157

Table 2—Association of ordinal measure (low, moderate, high) of GRS13 and GRS30 with history of CVD, all-cause mortality, CVD mortality, and CAC in EAs (n = 1,175) from the DHS

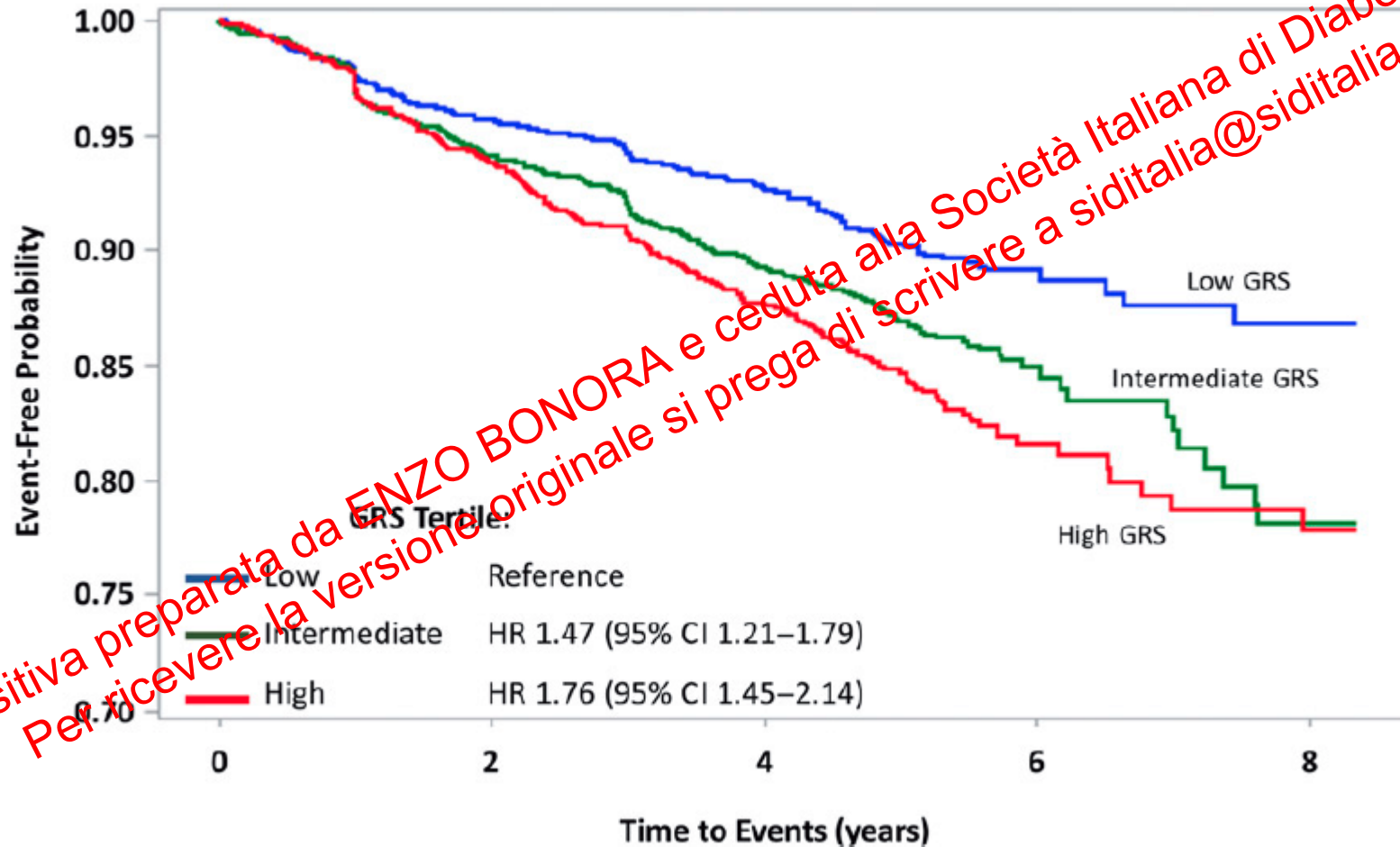
Trait	Unadjusted		Partially adjusted*		Fully adjusted†	
	Effect (95% CI)	P value	Effect (95% CI)	P value	Effect (95% CI)	P value
Unweighted GRS13	—	—	—	—	—	—
Prior CVD	OR: 1.23 (1.04–1.47)	0.02	OR: 1.30 (1.08–1.56)	0.005	OR: 1.14 (1.11–1.62)	0.002
All-cause mortality	HR: 0.96 (0.80–1.16)	0.68	HR: 1.05 (0.88–1.26)	0.58	HR: 1.06 (0.88–1.27)	0.54
CVD mortality	HR: 1.06 (0.81–1.39)	0.68	HR: 1.14 (0.87–1.49)	0.36	HR: 1.15 (0.88–1.51)	0.31
CAC	β : 0.02 (–0.23 to 0.26)	0.88	β : 0.05 (–0.15 to 0.25)	0.45	β : 0.07 (–0.12 to 0.26)	0.48
Weighted GRS13	—	—	—	—	—	—
Prior CVD	OR: 1.35 (1.11–1.64)	0.003	OR: 1.45 (1.18–1.77)	0.0004	OR: 1.51 (1.22–1.86)	0.0002
All-cause mortality	HR: 1.05 (0.67–1.28)	0.61	HR: 1.13 (0.84–1.37)	0.20	HR: 1.14 (0.94–1.38)	0.18
CVD mortality	HR: 1.26 (0.95–1.67)	0.10	HR: 1.34 (1.01–1.79)	0.04	HR: 1.35 (1.01–1.81)	0.04
CAC	β : 0.13 (–0.13 to 0.39)	0.13	β : 0.19 (–0.02 to 0.40)	0.08	β : 0.22 (0.02–0.43)	0.04
Unweighted GRS30	—	—	—	—	—	—
Prior CVD	OR: 1.38 (1.10–1.75)	0.006	OR: 1.41 (1.12–1.78)	0.004	OR: 1.45 (1.14–1.84)	0.002
All-cause mortality	HR: 1.28 (1.02–1.61)	0.04	HR: 1.32 (1.06–1.63)	0.01	HR: 1.29 (1.04–1.60)	0.02
CVD mortality	HR: 1.54 (1.09–2.17)	0.01	HR: 1.56 (1.12–2.17)	0.009	HR: 1.58 (1.13–2.21)	0.008
CAC	β : 0.47 (0.20–0.75)	0.0008	β : 0.45 (0.23–0.68)	7.34×10^{-5}	β : 0.44 (0.22–0.66)	8.19×10^{-5}
Weighted GRS30	—	—	—	—	—	—
Prior CVD	OR: 1.22 (1.00–1.49)	0.05	OR: 1.28 (1.04–1.57)	0.02	OR: 1.33 (1.08–1.65)	0.008
All-cause mortality	HR: 1.20 (0.97–1.48)	0.09	HR: 1.28 (1.05–1.56)	0.02	HR: 1.28 (1.05–1.56)	0.01
CVD mortality	HR: 1.37 (1.01–1.86)	0.04	HR: 1.43 (1.06–1.93)	0.02	HR: 1.46 (1.08–1.96)	0.01
CAC	β : 0.22 (–0.04 to 0.47)	0.10	β : 0.27 (0.05–0.48)	0.01	β : 0.29 (0.08–0.50)	0.006

*Adjusted for age, sex, and T2DM affection status. †Adjusted for age, sex, T2DM affection status, BMI, current smoking, hypertension, and dyslipidemia.

Weighted = weighted by the previously reported effect size of the single SNP on CVD risk in GWAS

Genetic risk scores and CVD risk in T2DM

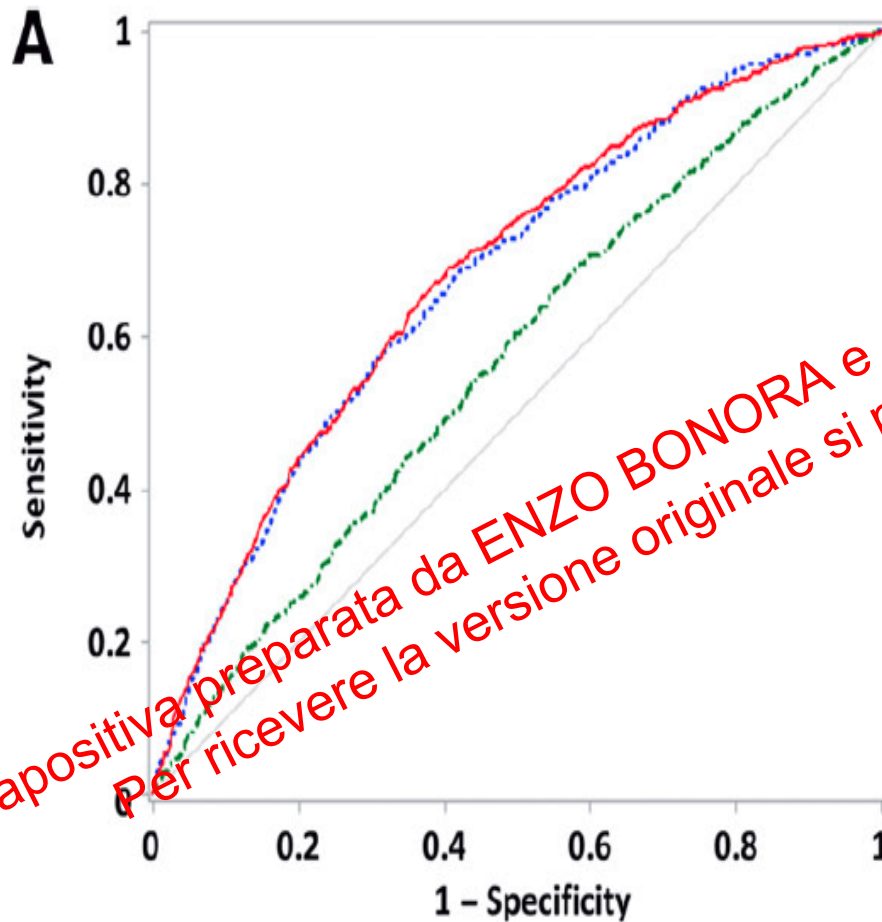
Morieri ML et al - Diabetes Care 2018



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Genetic risk scores and CVD risk in T2DM - ROC analysis

Morieri ML et al - Diabetes Care 2018



Area Under ROC:

Genetic 0.567
Clinical 0.575
Combined 0.681
AUC Difference 0.007 ($P = 0.04$)

Addition of GRS (2017) on top of Clinical model:

rIDI 8 % ; $P = 0.0007$

NRI 0.16; $P < 0.0001$

8% Event Correctly Reclassified, $P = 0.048$

9% Nonevent Correctly Reclassified, $P < 0.0001$

CVD risk assessment: calculators

- Framingham Risk Score
- Prospective Cardiovascular Munster (PROCAM) Score
- UKPDS Risk Engine (newly diagnosed type 2 diabetes)
- Systematic Coronary Risk Evaluation (SCORE) by ESC
- DECODE risk equation
- QRISK2 equation
- Progetto Cuore
- Molti altri

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UKPDS Risk Engine

UKPDS Risk Engine v2.0

Input

Age Now : 62 years

Duration of Diabetes : 11 years

Sex : ☒ Male ☐ Female

Atrial Fibrillation : ☒ No ☐ Yes

Ethnicity : White

Smoking : Non-Smoker

HbA1c : 8.3 %

Systolic BP : 145 mmHg

Total Cholesterol : 5.8 mmol/l

HDL Cholesterol : 1.1 mmol/l

Options >

Output

10 Year risk 0 15 30 100

CHD :	35.3%	
Fatal CHD :	24.4%	
Stroke :	11.6%	
Fatal Stroke :	1.8%	

Adjusted for regression dilution

Details

Copy

Print

Help

Exit

Calcolatore del rischio cardiovascolare in Italia - Progetto Cuore

Calcolo del rischio cardiovascolare

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Calcola

Sesso	☐ M ☐ F
Età	anni
Pressione sistolica	mm Hg
Fumatore	☐ No ☐ Si
Colesterolo totale	mg/dl
Diabete	☐ No ☐ Si
Colesterolo HDL	mg/dl
Iperlipidemia * * Frequenza di ipertensione arteriosa per cui il medico ha prescritto farmaci anti-ipertensivi.	☐ No ☐ Si

Risultato %

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13:16 03/10/2019

Prognostic value of the Framingham cardiovascular risk equation and the UKPDS risk engine for CHD in newly diagnosed T2DM

Gudzer RN et al - Diabetic Medicine 2005; 22:554–562

Table 4 Sensitivities and specificities for cardiovascular disease of approaches based on multifactorial risk assessment and lipid risk factor thresholds

	Sensitivity percentage (95% CI; P)	Specificity percentage (95% CI; P)
30% 10-year CHD risk and TC > 5 mmol/l		
Framingham model	29.6 (22.2–37.2; < 0.001)	88.5 (86.3–90.7; < 0.001)
UKPDS risk engine	50.0 (39.7–60.3; < 0.001)	69.1 (63.8–74.0; < 0.001)
15% 10-year CHD risk only		
Framingham model	85.7 (77.8–91.5; 0.21)	33.0 (30.7–34.7; < 0.001)
UKPDS risk engine	89.8 (82.0–95.0; 0.34)	30.3 (25.4–35.6; < 0.001)
LDLc ≥ 2.6 mmol/l or TG ≥ 4.5 mmol/l	93.9 (87.8–97.4)	12.1 (10.3–13.2)

CHD, coronary heart disease; TC, total cholesterol; LDLc, LDL-cholesterol; TG, triglycerides significance (P) vs. last row (LDLc ≥ 2.6 mmol/l or TG ≥ 4.5 mmol/l).

A community-based cohort (n=428; age 30-74 years) free of clinically evident CVD and with newly diagnosed T2DM follow-up of 4.2 years.

Prediction of CHD Risk in a General, Pre-Diabetic, and Diabetic Population During 10 Years of Follow-up

Diabetes Care - 2009; 32:2094

Table 2—Discriminatory ability of the Framingham, SCORE, and UKPDS risk functions

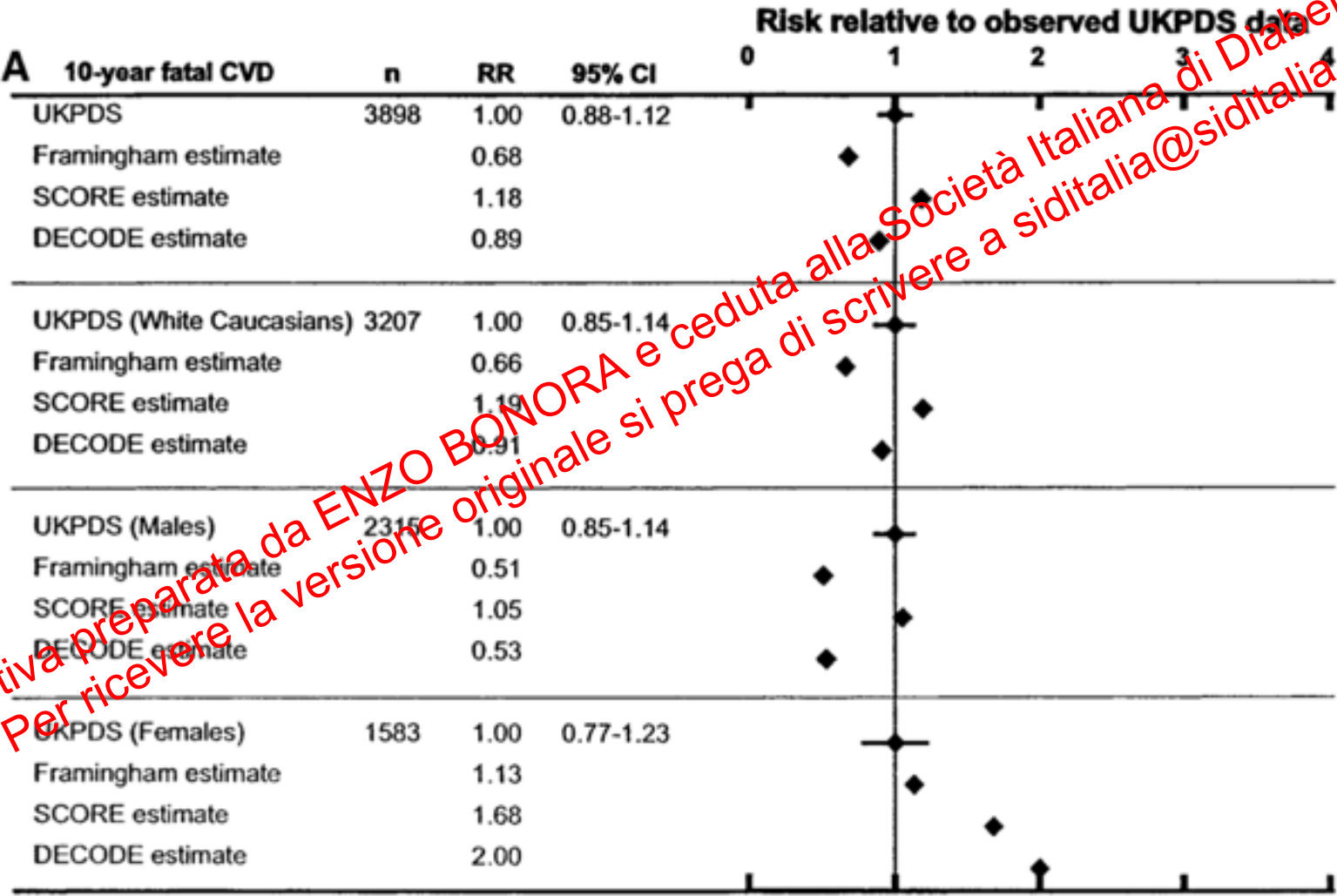
	NGT group	Intermediate hyperglycemia group	Diabetic group
First CHD			
Framingham	0.68 (0.63–0.74)	0.60 (0.47–0.74)	0.63 (0.50–0.76)
SCORE	0.71 (0.66–0.76)	0.70 (0.60–0.79)	0.66 (0.54–0.79)
UKPDS	0.71 (0.66–0.75)	0.70 (0.60–0.80)	0.66 (0.56–0.78)
Fatal CHD			
Framingham	0.71 (0.61–0.82)	0.76 (0.65–0.88)	0.61 (0.37–0.86)
SCORE	0.79 (0.70–0.87)	0.70 (0.50–0.89)	0.74 (0.56–0.93)
UKPDS	0.77 (0.68–0.86)	0.84 (0.74–0.94)	0.72 (0.55–0.89)

Data are AUROC (95% CI).

1,482 Caucasian men and women, 50-75 years of age, who participated in the Hoorn Study

Framingham, SCORE, and DECODE Risk Equations do not provide reliable CVD risk estimates in T2DM

Coleman RL et al - Diabetes Care 2007; 30:1292



3,898 UK patients with newly diagnosed type 2 diabetes followed for median period of 10.4 years

Performance of Cardiovascular Disease Risk Scores in People Diagnosed With T2DM

Read SH et al - Diabetes Care 2018; 41:2010-2018

Table 3—Age-stratified calibration and discrimination statistics for QRISK2 and five diabetes-specific risk scores

Risk score	Age-group (years)	Observed 5-year risk	Predicted 5-year risk, %, median (IQR)	Calibration in the large	Calibration slope	C statistic (discrimination)
QRISK2	Overall	9.7	24.07 (21.21)	−0.14	0.376 (0.376, 0.377)	0.674 (0.669, 0.679)
	30–45	3.4	8.73 (9.71)	−0.06	0.208 (0.208, 0.208)	0.686 (0.644, 0.689)
	46–60	6.8	18.26 (13.81)	−0.11	0.272 (0.272, 0.273)	0.632 (0.623, 0.641)
	61–75	11.5	29.51 (16.54)	−0.19	0.317 (0.317, 0.317)	0.604 (0.597, 0.612)
	>75	21.0	45.01 (17.55)	−0.24	0.374 (0.374, 0.375)	0.578 (0.568, 0.588)
ADVANCE	Overall	9.7	2.00 (2.53)	0.08	1.808 (1.805, 1.811)	0.666 (0.661, 0.671)
	30–45	3.4	0.58 (0.45)	0.02	3.283 (3.277, 3.289)	0.628 (0.605, 0.651)
	46–60	6.8	1.33 (0.96)	0.06	2.353 (2.350, 2.356)	0.595 (0.586, 0.605)
	61–75	11.5	2.93 (2.09)	0.08	1.657 (1.655, 1.660)	0.594 (0.587, 0.602)
	>75	21.0	6.27 (4.57)	0.15	0.973 (0.970, 0.976)	0.575 (0.565, 0.585)
CHS	Overall	9.7	11.71 (11.71)	−0.02	0.631 (0.631, 0.632)	0.674 (0.669, 0.679)
	30–45	3.4	4.58 (2.92)	−0.02	0.760 (0.759, 0.760)	0.638 (0.615, 0.661)
	46–60	6.8	8.68 (5.34)	−0.02	0.742 (0.742, 0.742)	0.622 (0.613, 0.632)
	61–75	11.5	16.1 (8.64)	−0.05	0.546 (0.545, 0.547)	0.603 (0.596, 0.611)
	>75	21.0	26.7 (15.56)	−0.05	0.398 (0.396, 0.400)	0.575 (0.565, 0.585)
Fremantle	Overall	9.7	5.24 (7.63)	0.05	0.738 (0.737, 0.738)	0.665 (0.660, 0.670)
	30–45	3.4	1.2 (0.88)	0.02	2.025 (2.023, 2.027)	0.626 (0.603, 0.648)
	46–60	6.8	3.23 (2.2)	0.04	1.157 (1.156, 1.159)	0.591 (0.582, 0.600)
	61–75	11.5	8.49 (5.52)	0.03	0.736 (0.735, 0.736)	0.593 (0.585, 0.600)
	>75	21.0	20.63 (12.11)	0.00	0.497 (0.496, 0.497)	0.580 (0.570, 0.590)
NZ DCS	Overall	9.7	16.17 (10.87)	−0.06	0.725 (0.725, 0.725)	0.670 (0.665, 0.674)
	30–45	3.4	7.7 (2.9)	−0.05	0.679 (0.676, 0.683)	0.645 (0.622, 0.667)
	46–60	6.8	12.67 (4.37)	−0.06	0.740 (0.739, 0.741)	0.609 (0.599, 0.618)
	61–75	11.5	20.23 (6.39)	−0.09	0.725 (0.725, 0.726)	0.599 (0.591, 0.606)
	>75	21.0	30.45 (8.42)	−0.09	0.635 (0.633, 0.638)	0.573 (0.563, 0.583)
Swedish NDR	Overall	9.7	8.26 (6.79)	0.02	0.955 (0.954, 0.955)	0.663 (0.658, 0.668)
	30–45	3.4	3.67 (2.26)	−0.01	0.871 (0.871, 0.871)	0.632 (0.609, 0.654)
	46–60	6.8	6.44 (3.56)	0.01	0.869 (0.869, 0.870)	0.602 (0.592, 0.611)
	61–75	11.5	10.54 (5.62)	0.00	0.727 (0.727, 0.727)	0.589 (0.582, 0.596)
	>75	21.0	16.79 (8.74)	0.04	0.576 (0.575, 0.576)	0.566 (0.556, 0.575)



A cohort of nearly 180,000 people with T2DM from the Scottish National Diabetes Register

Stratification of diabetes according to CVD risk in the 2019 ESC guidelines

Europ Heart J 2019 on line

Very high risk	Patients with DM and established CVD ^a or other target organ damage ^b or three or more major risk factors ^c or early onset T1DM or long duration (>20 years)
High risk	Patients with DM duration ≥10 years without target organ damage plus any other additional risk factor
Moderate risk	Young patients (T1DM aged <35 years or T2DM aged <50 years) with DM duration <10 years, without other risk factors

© ESC 2019

CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

^aModified from the 2016 European Guidelines on cardiovascular disease prevention in clinical practice.²⁷

^bProteinuria, renal impairment defined as eGFR ≥30 mL/min/1.73 m², left ventricular hypertrophy, or retinopathy.

^cAge, hypertension, dyslipidemia, smoking, obesity.

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The end

Thank you

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