Seminario all'Università degli Studi di Varese

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Obiettivi glicemici individualizzati nel diabete tipo 2: un nuovo paradigma

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Glycemic Targets in Diabetes Care

(ADA Clinical Recommendations, 2011)

HbA1c	<7%
Pre-prandial glucose	70-130 mg/dl
Post-prandial glucose (1-2 h; at peak)	<180 mg/dl

More or less stringent glycemic goals may be appropriate for individual patients

Key Concepts in Setting Glycemic Goals

(ADA Clinical Recommendations, 2011)

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

Key Concepts in Setting Glycemic Goals

(ADA Clinical Recommendations, 2011)

Goals should be individualized based on:

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

Time (years) needed to achieve clinical benefits with treatment of major risk factors in diabetes according to glucose/lipids/blood pressure trials

	Microvascular	Macrovascular
Control of:		
Cholesterol	N/A (?)	3-4
Blood pressure	5-6	3-4
Glucose	5-6	>10

Glycemic Targets in Elderly Diabetics

(European Diabetes Working Party on Older People, 2010)

For older patients with type 2 diabetes, with single system involvement (free of other major co-morbidities), a target HbA1c range of 7.0-7.5% should be aimed for (DCCT aligned). *Evidence level 1+, Grade of recommendation A. The precise target agreed will depend on existing cardiovascular risk, presence of microvascular complications, and ability of individual to self-manage.*

For frail patients (dependent; multisystem disease; care home residency including those with dementia) in whom the hypoglycemia risk is high and symptom control and avoidance of metabolic decompensation is paramount, the target HbA1c range should be 7.5-8.5%. *Evidence level 1+, Grade of recommendation A.*

Obiettivi glicemici per il diabetico anziano

(Standard di Cura AMD/SID 2009-2010)

Nei diabetici anziani gli obiettivi glicemici dovrebbero essere individualizzati. Se le condizioni generali sono relativamente buone, il valore di HbA1c potrà essere compreso fra 6.5 e 7.5%. Livello della prova VI, forza della raccomandazione B.

Negli anziani fragili (con complicanze, affetti da demenza, con pluripatologia, nei quali il rischio di ipoglicemia è alto e nei quali il rischio di un controllo glicemico intensivo supera I benefici attesi) è appropriato un obiettivo meno restrittivo, con valori di HbA1c compresi fra 7.5 e 8.5%. Livello della prova VI, forza della raccomandazione B.

Glycemic Targets in Diabetes Care

(AMD-SID Standards of Care, 2009-2010)

HbA1c	<7%
Pre-prandial glucose	70-130 mg/dl
Post-prandial glucose (1-2 h; at peak)	<180 mg/dl

HbA1c Target in Diabetes Care

HbA1c <7%

Where does it come from?
What is the evidence?

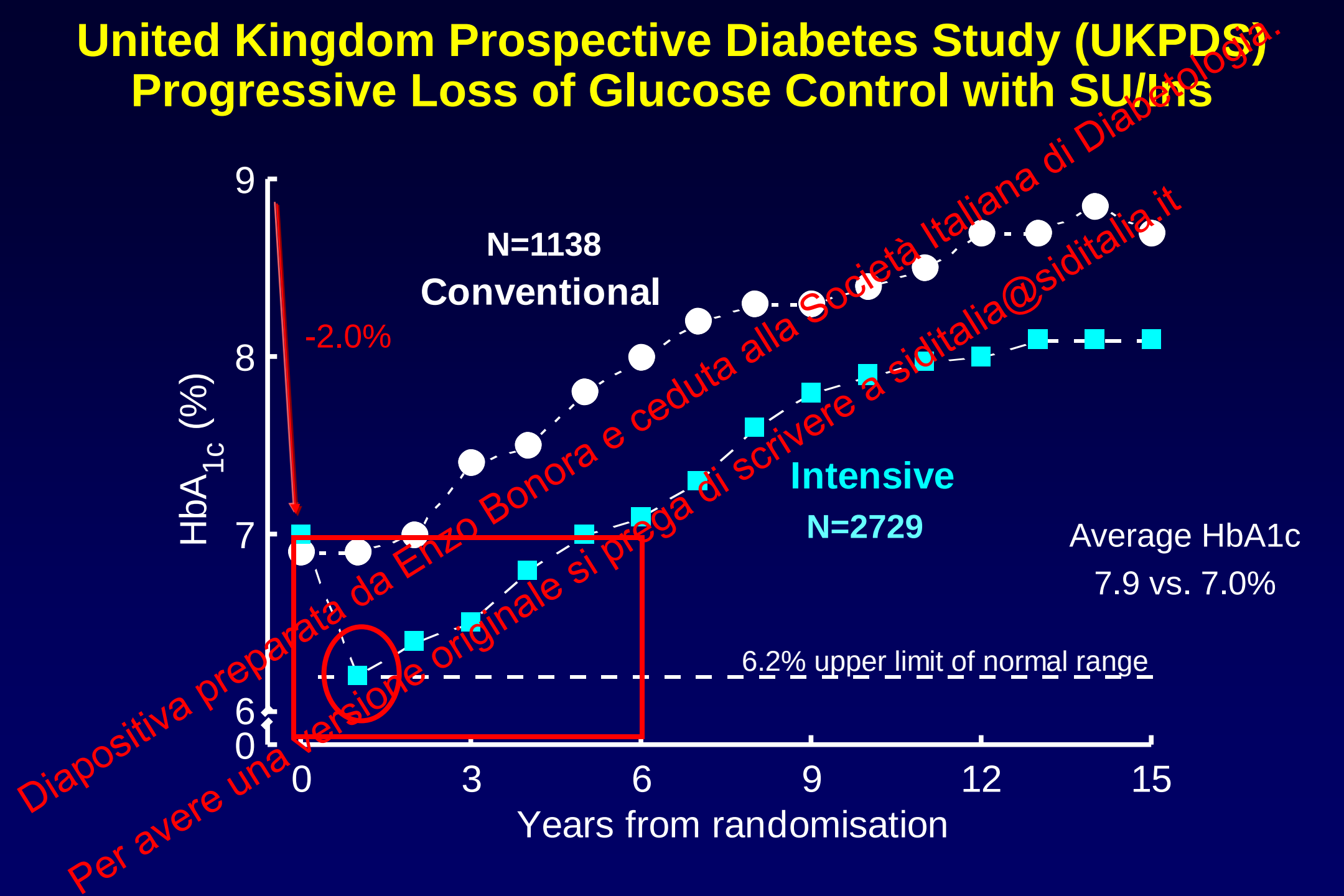
UKPDS!

UKPDS – Main question and primary outcome

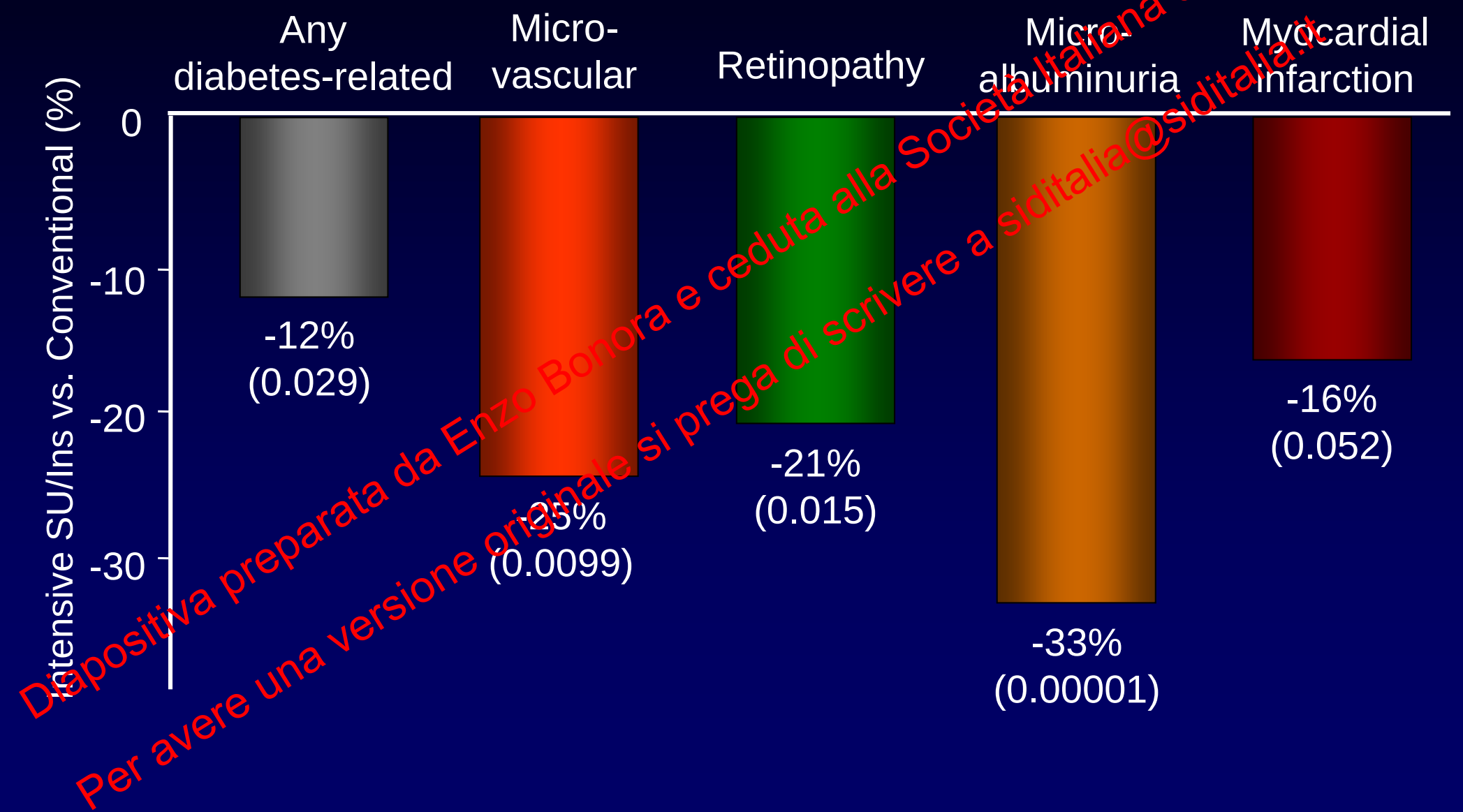
Main Question: In middle aged (mean 53 y) newly diagnosed people with type 2 DM without prior CVD, does a therapeutic strategy that targets a FPG< 6 mmol/l reduce chronic complications more than a strategy that targets a FPG < 15 mmol/l?

Outcomes: Any diabetes-related endpoint, diabetes-related death, microvascular endpoints, myocardial infarction, etc.

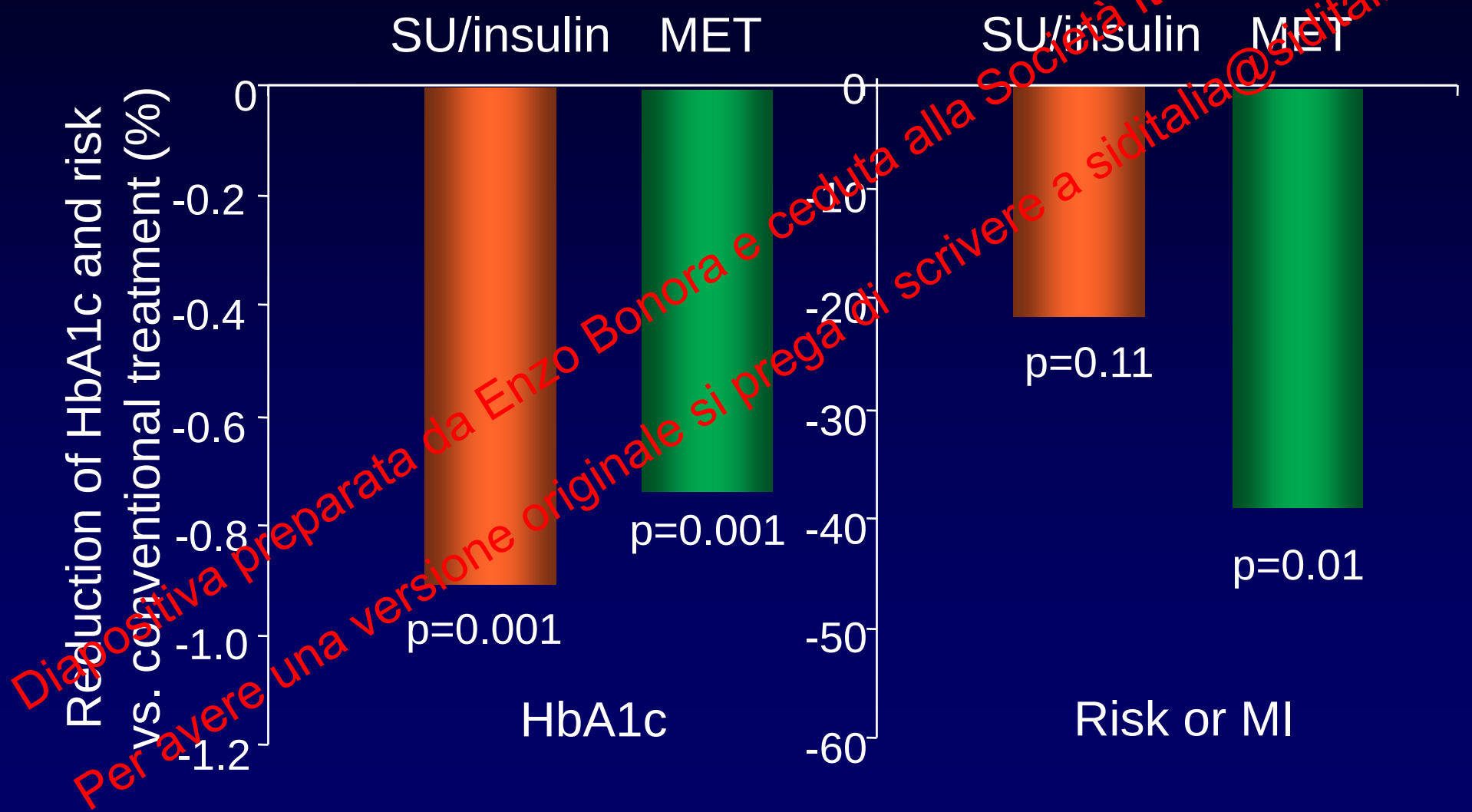
United Kingdom Prospective Diabetes Study (UKPDS)
Progressive Loss of Glucose Control with SU/Ins



UKPDS - Main Results of the Glucose Control Study

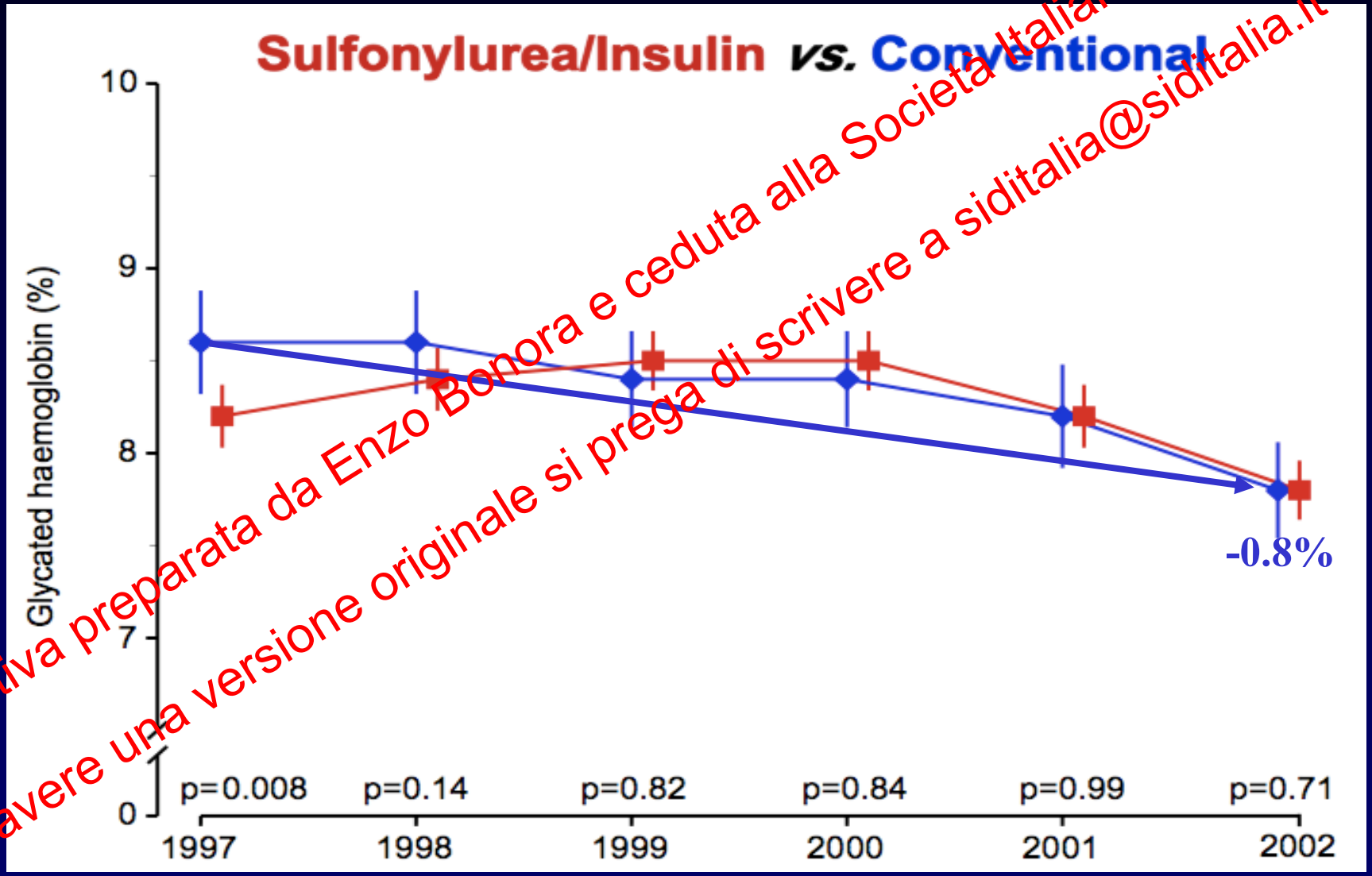


Effects of Intensive Treatment on HbA1c and the Risk of Myocardial Infarction in Overweight (mean BMI=31) Type 2 Diabetic Patients of the UKPDS



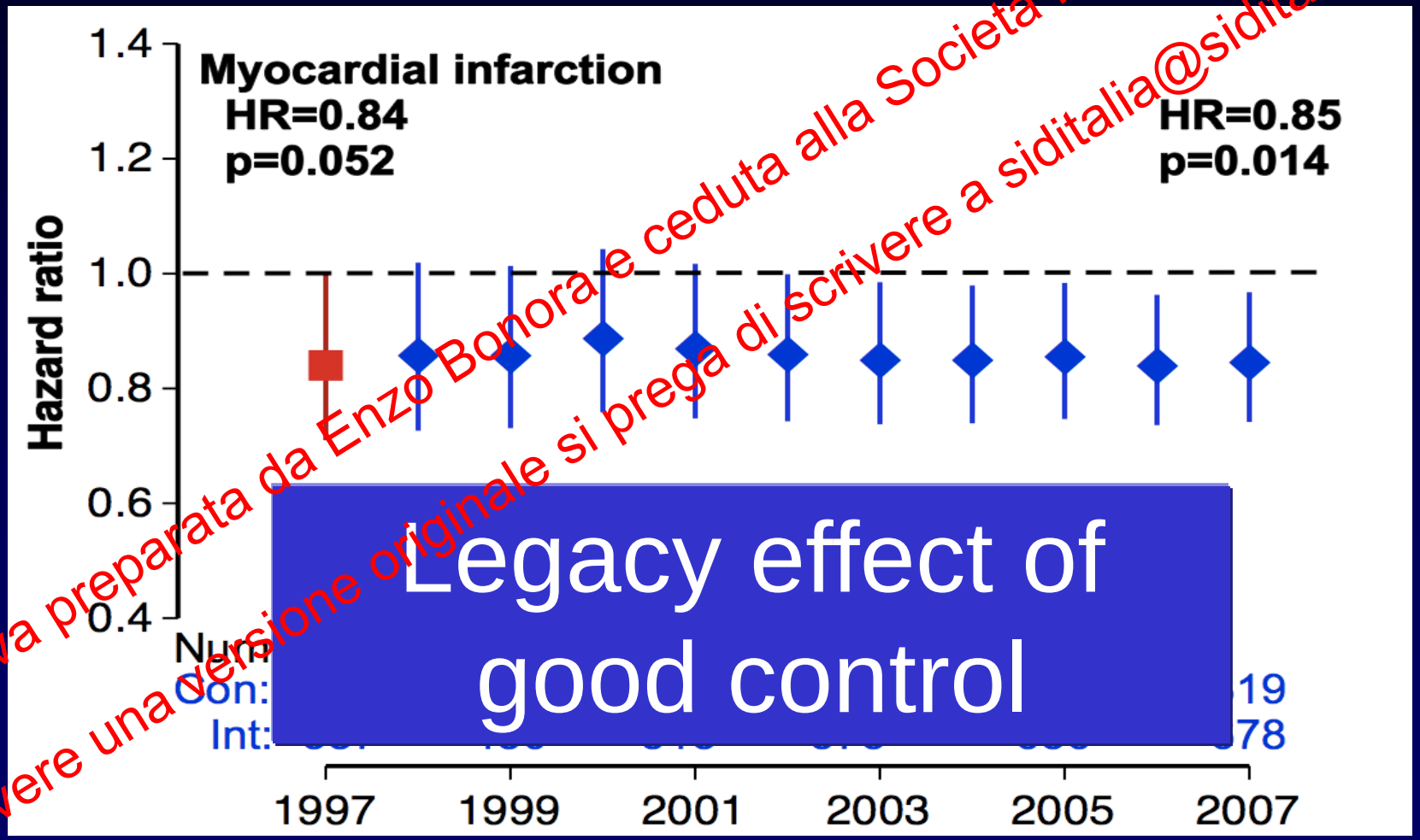
UKPDS: Post-Trial Changes in HbA_{1c}

(NEJM, 359: 1577-1589, 2008)



UKPDS – Risk of Myocardial Infarction in the Post Trial Monitoring

(NEJM, 359: 1577-1589, 2008)



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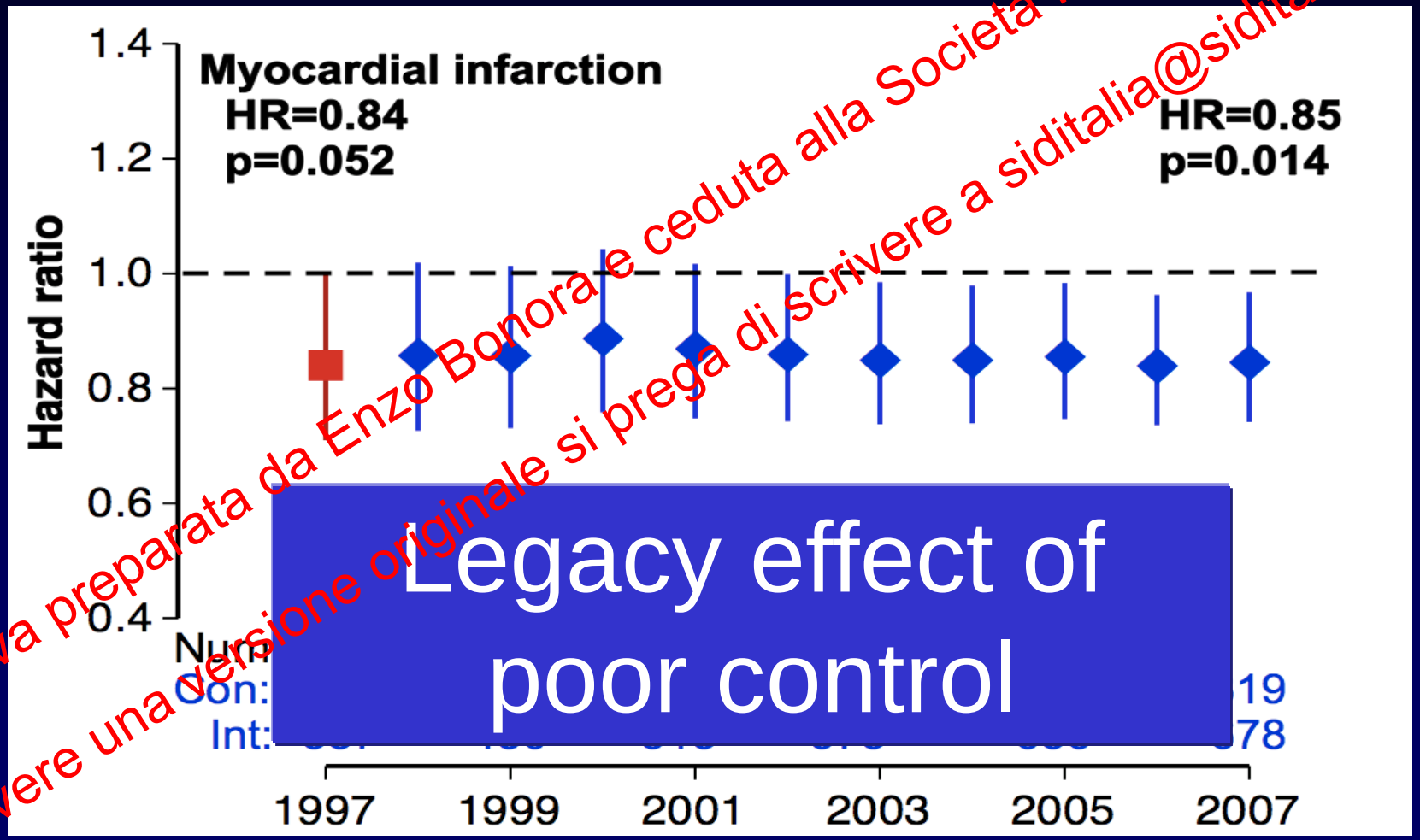
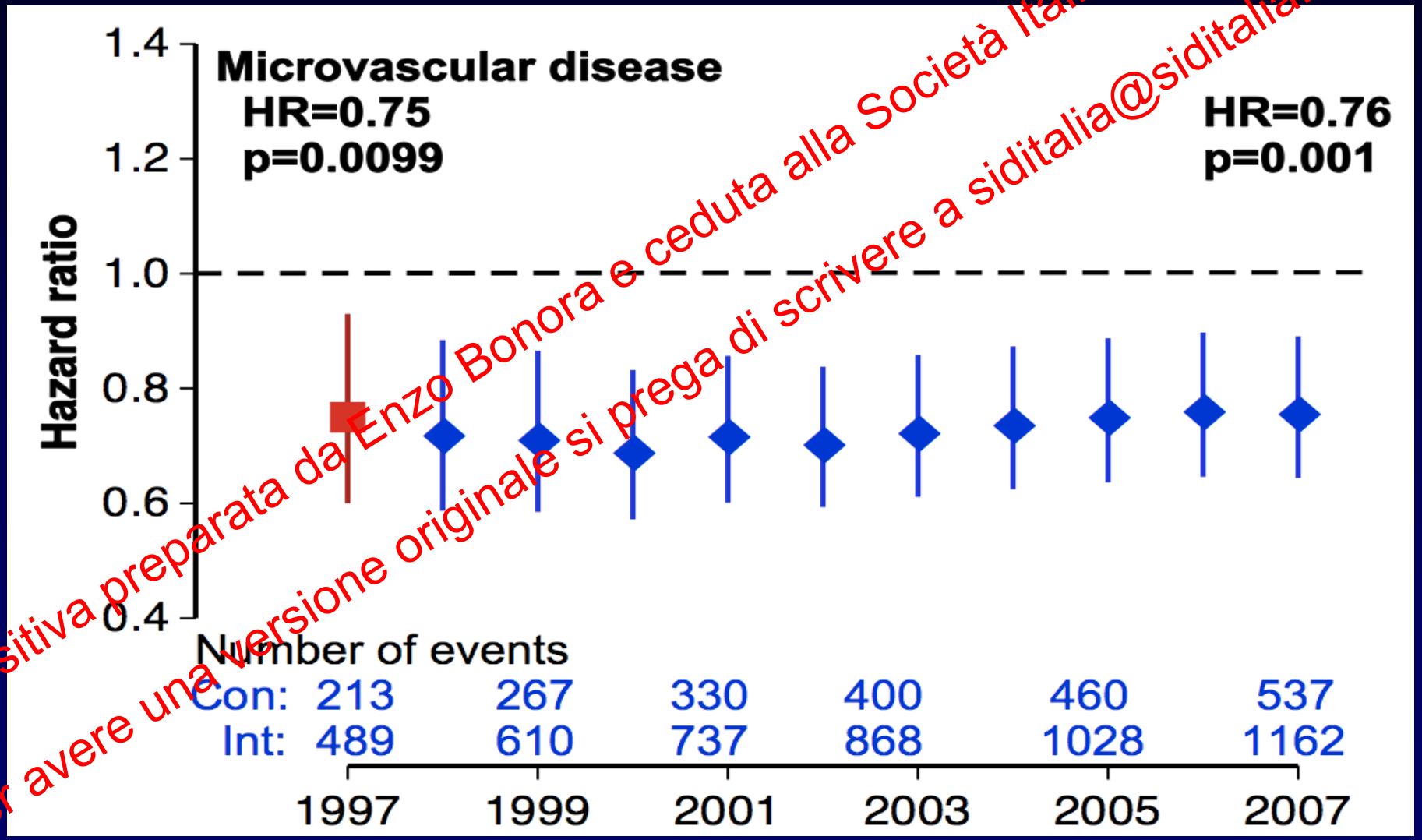


Legacy effect of poor control

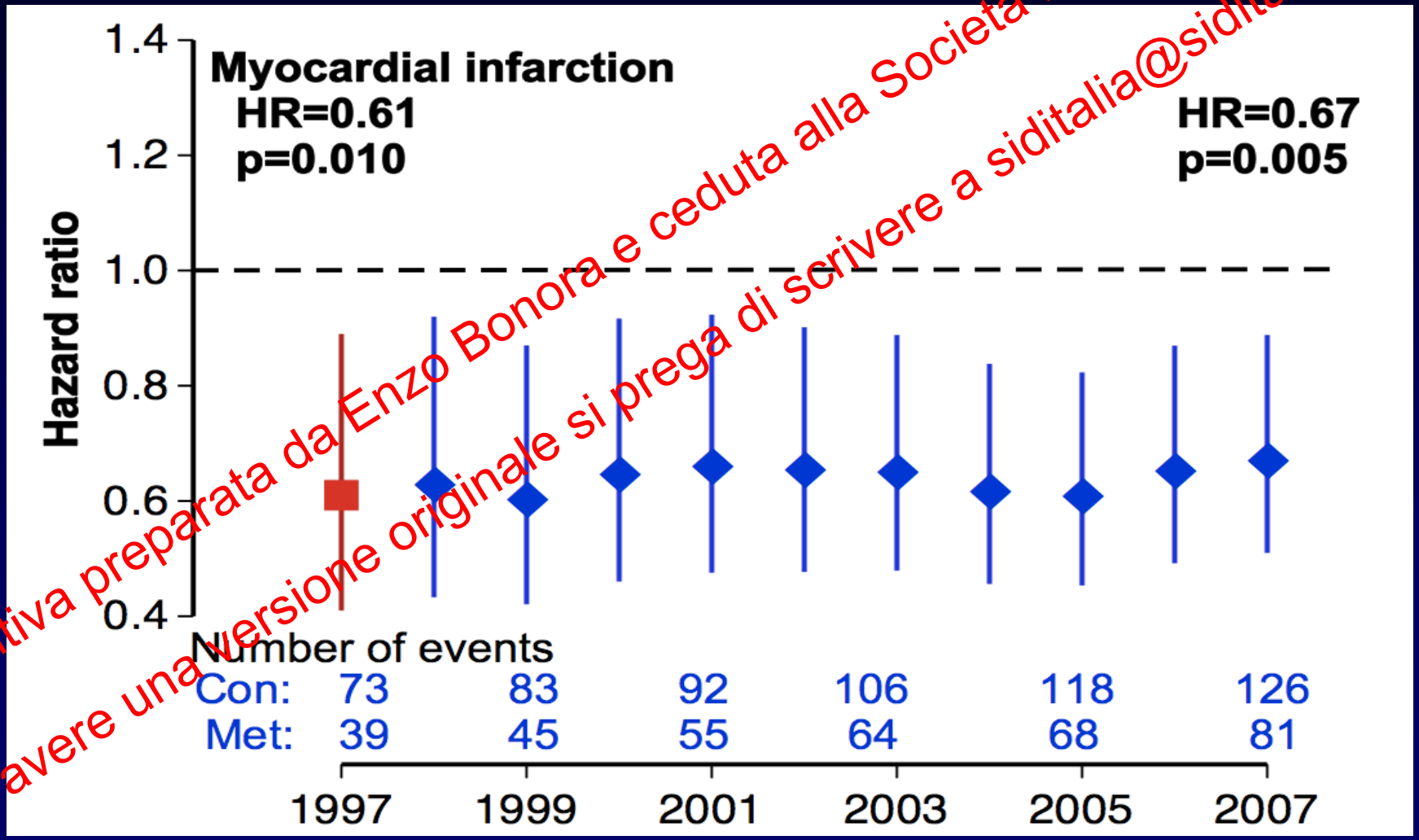
UKPDS – Risk of Microvascular Disease in the Post Trial Monitoring (SU/Ins vs. Conventional)

(NEJM, 359: 1577-1589, 2008)



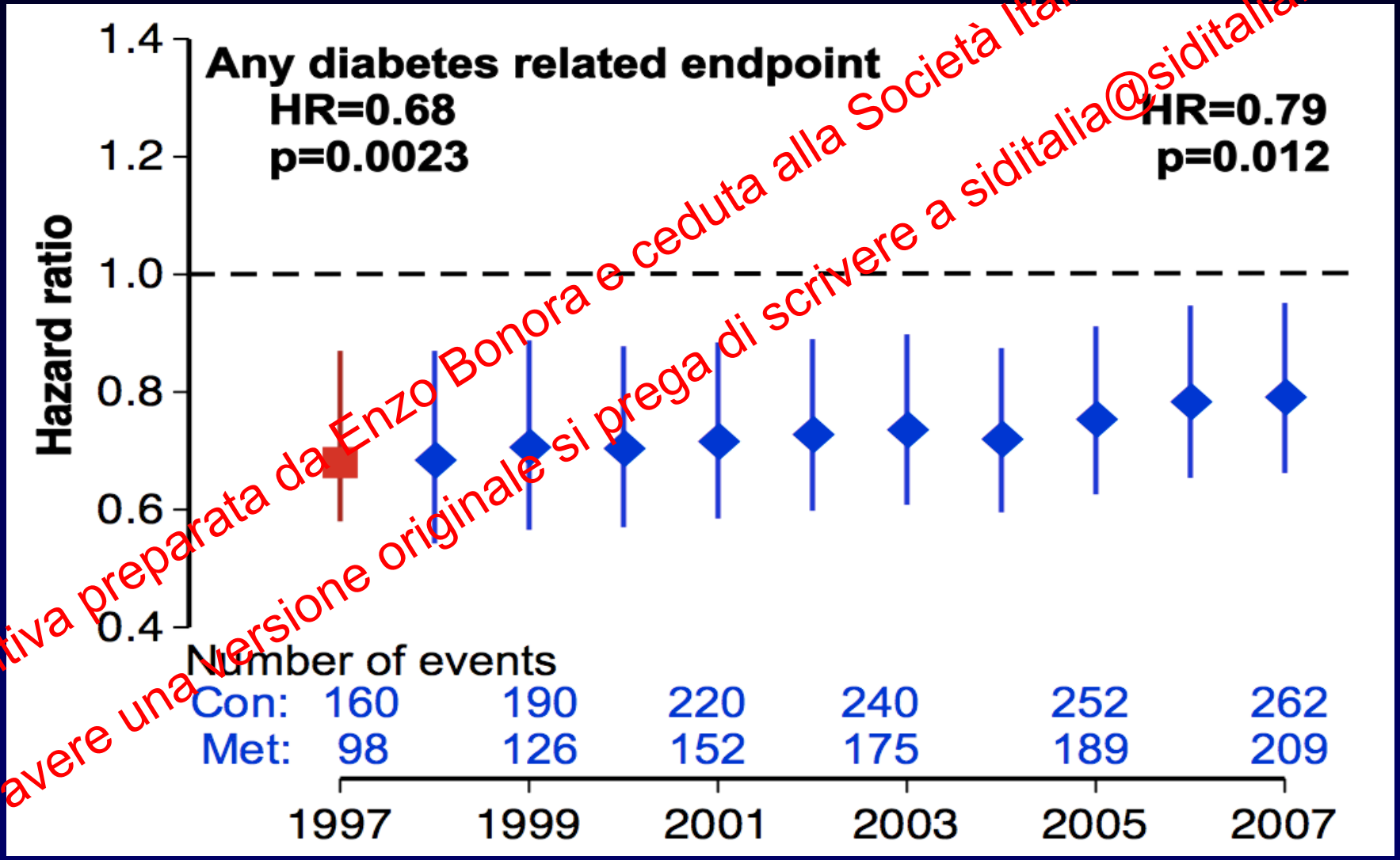
UKPDS – Risk of Myocardial Infarction in the Post Trial Monitoring (MET vs. Conventional)

(NEJM, 359: 1577-1589, 2008)



UKPDS – Risk of Any Diabetes Related Endpoint in the Post Trial Monitoring (MET vs. Conventional)

(NEJM, 359: 1577-1589, 2008)

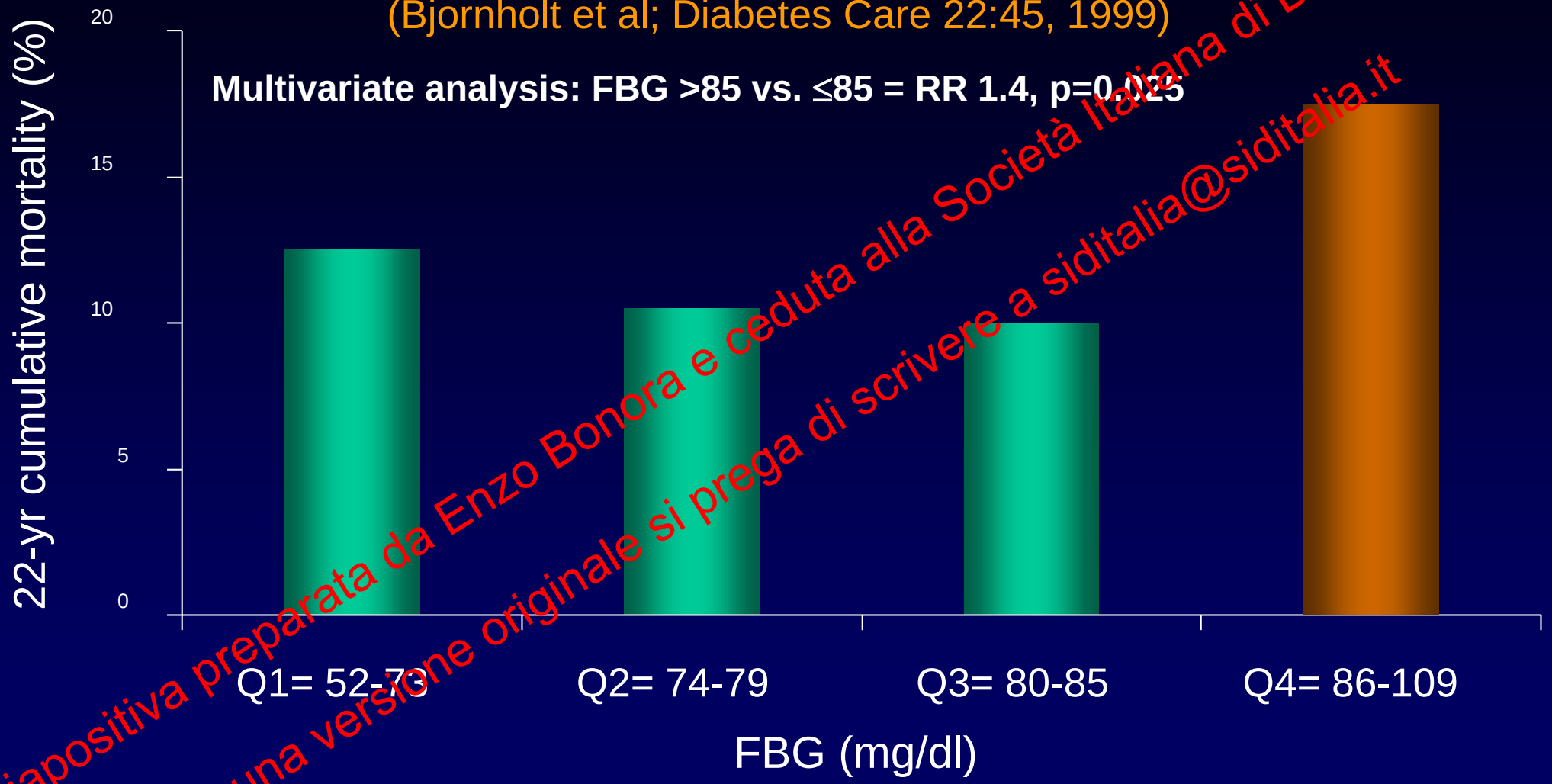


Hypothesis

HbA1c <6.5% (or even lower) in diabetes should carry an additional benefit because IFG/IGT subjects have an increased CVD risk and T2DM patients with HbA1c <7% have an incresed risk

Fasting Blood Glucose and CVD Death in Men with Normal Fasting Glucose

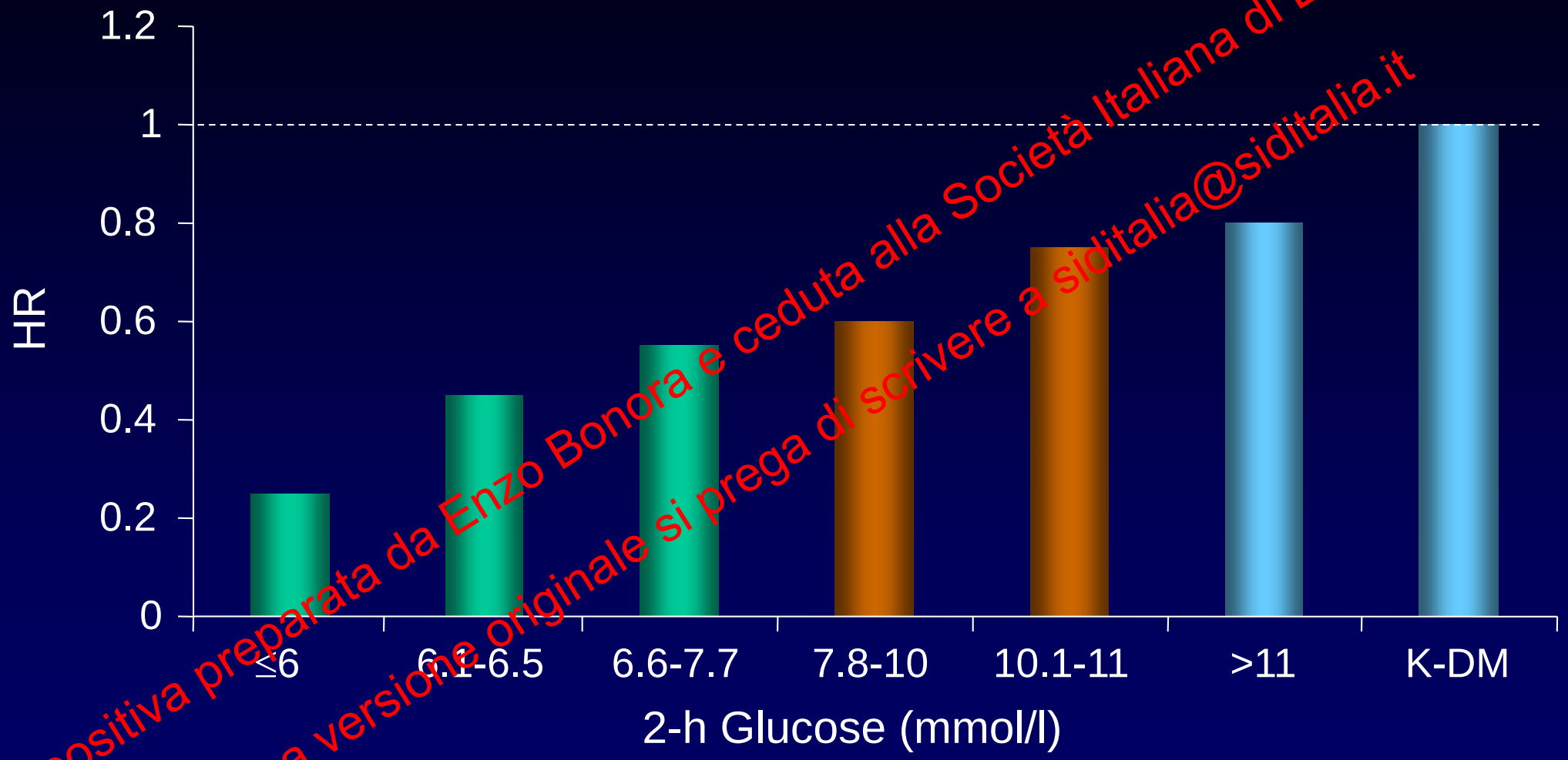
(Bjornholt et al; Diabetes Care 22:45, 1999)



N=1973, age 40-59, follow-up 22 yr, FBG <110 mg/dl

Risk of CVD death according to 2-h OGTT glucose

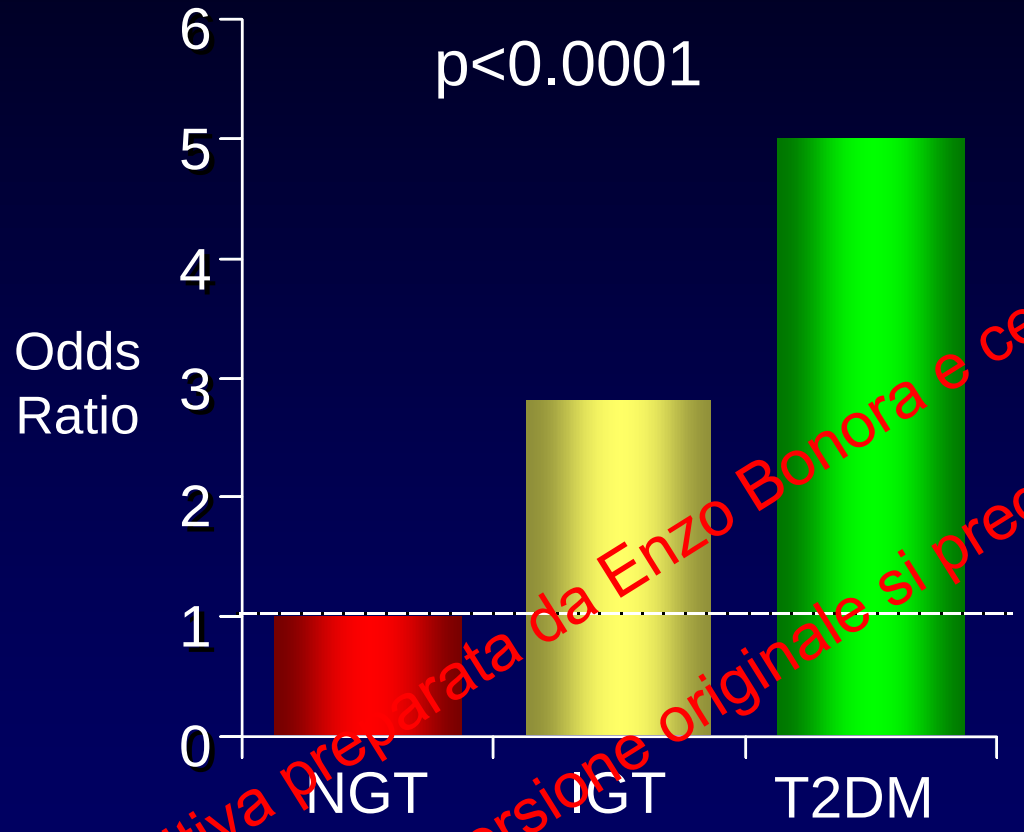
(DECODE Study; Diabetes Care 26:688, 2004)



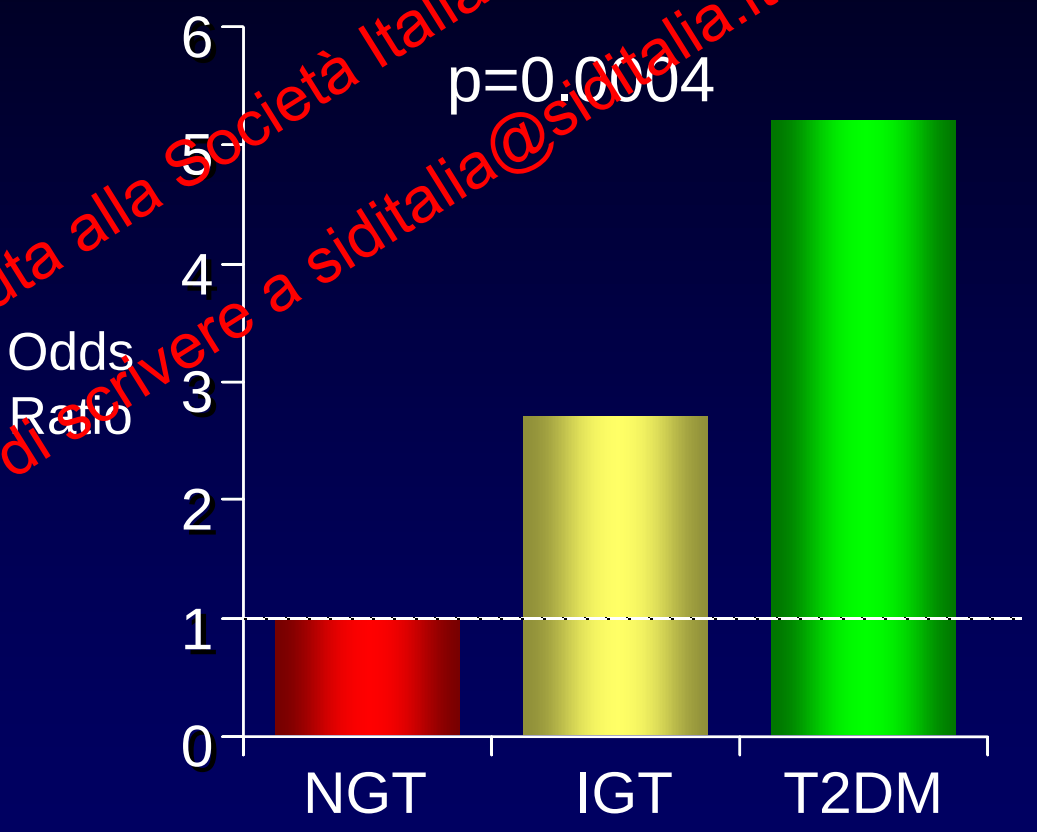
Adjusted for sex, age, BMI, blood pressure, cholesterol, smoking

Incident of Stenotic Carotid Atherosclerosis According to Glucose Tolerance

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



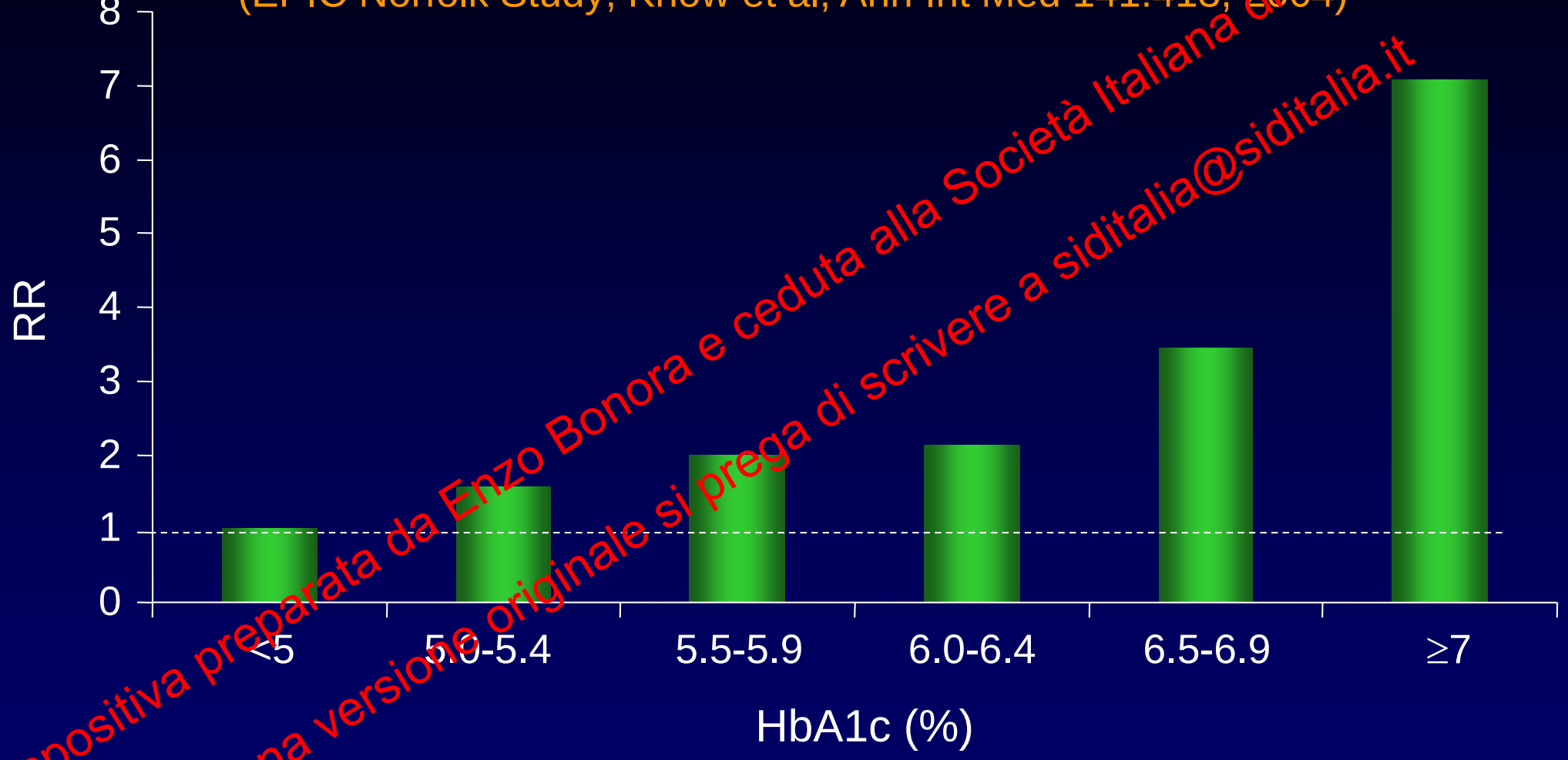
N=888. Adjusted for age, smoking, alcohol, fibrinogen, antithrombin III, factor V mutation, Lp(a) >32mg/dl



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

Risk of CHD in men without known diabetes as a function of HbA1c

(EPIC Norfolk Study; Khow et al; Ann Int Med 141:413, 2004)

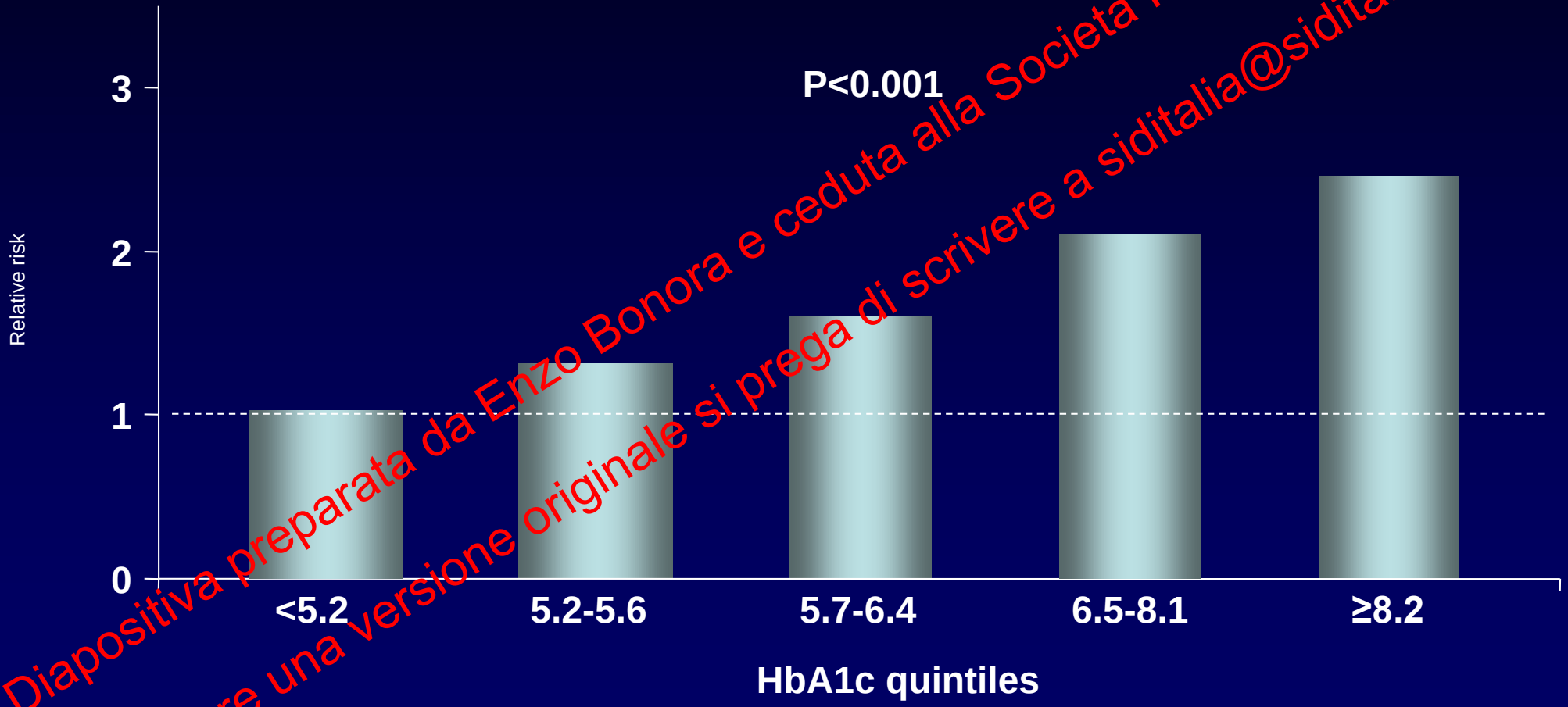


N= 4662, age 45-79 yrs, follow-up 7 yrs

Adjusted for age, BMI, WHR, blood pressure, cholesterol, smoking, prior MI

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

Glucose Targets in Diabetes Care

(IDF Guidelines, 2005)

HbA1c	<6.5%
Pre-prandial glucose	<110 mg/dl
Post-prandial glucose	<145 mg/dl

Glycemic Targets in Diabetes Care

The lower the better!

Reasonable but where is the evidence?
Please, show me the results of a specific trial

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

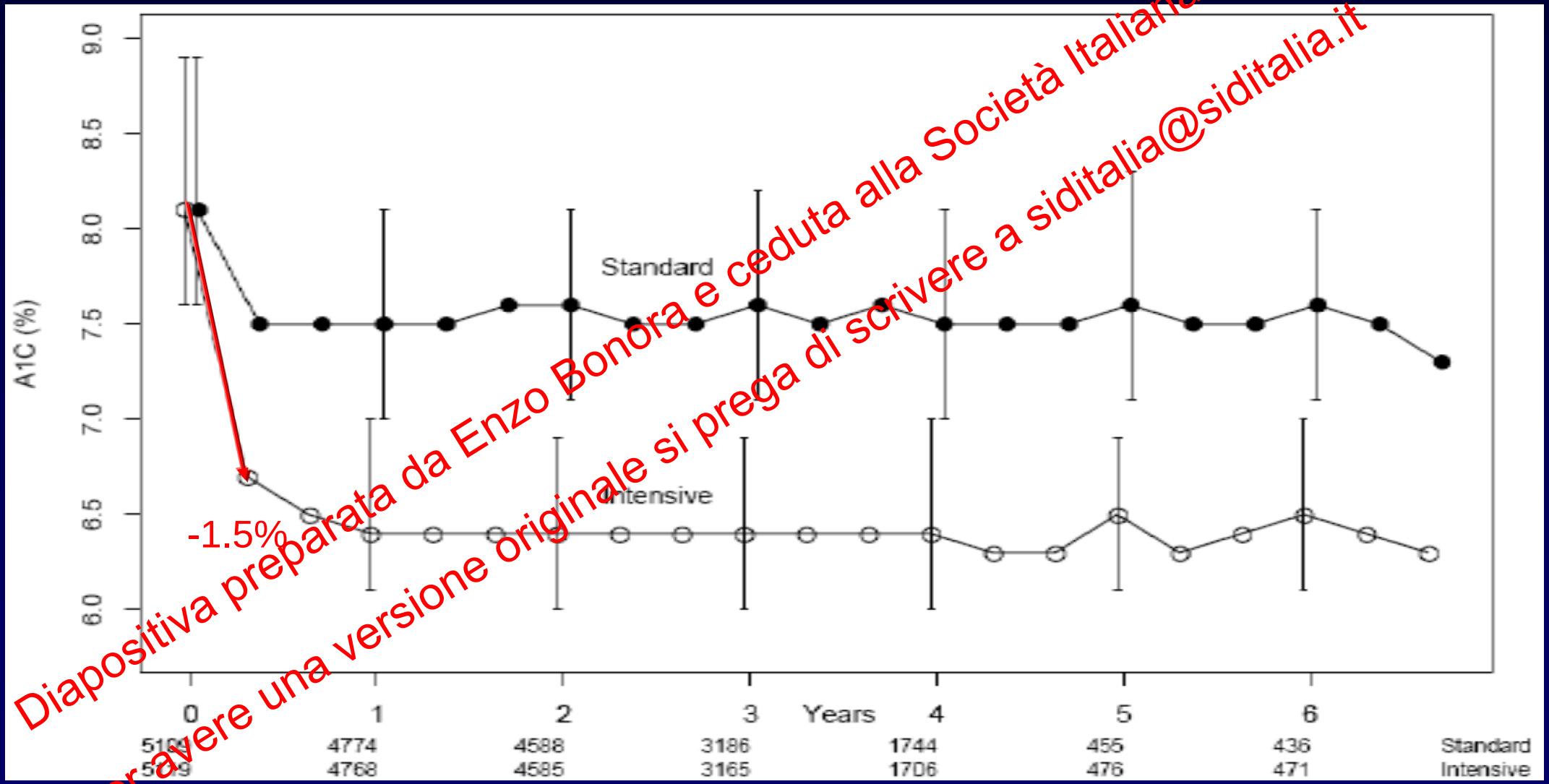
	No.	Mean Follow - up (yrs)	Age (yrs)	Time from diagnosis (yrs)	Prior CVD (%)	BMI	HbA1c (%)
ACCORD	10251	3.5	62	10	35	32	8.3
ADVANCE	11140	5	66	8	32	28	7.5
VADT	1791	6.3	60	11.5	40	31	9.4
UKPDS	4209	10+10	53	0	0	28	7.1

ACCORD – Main question and primary outcome

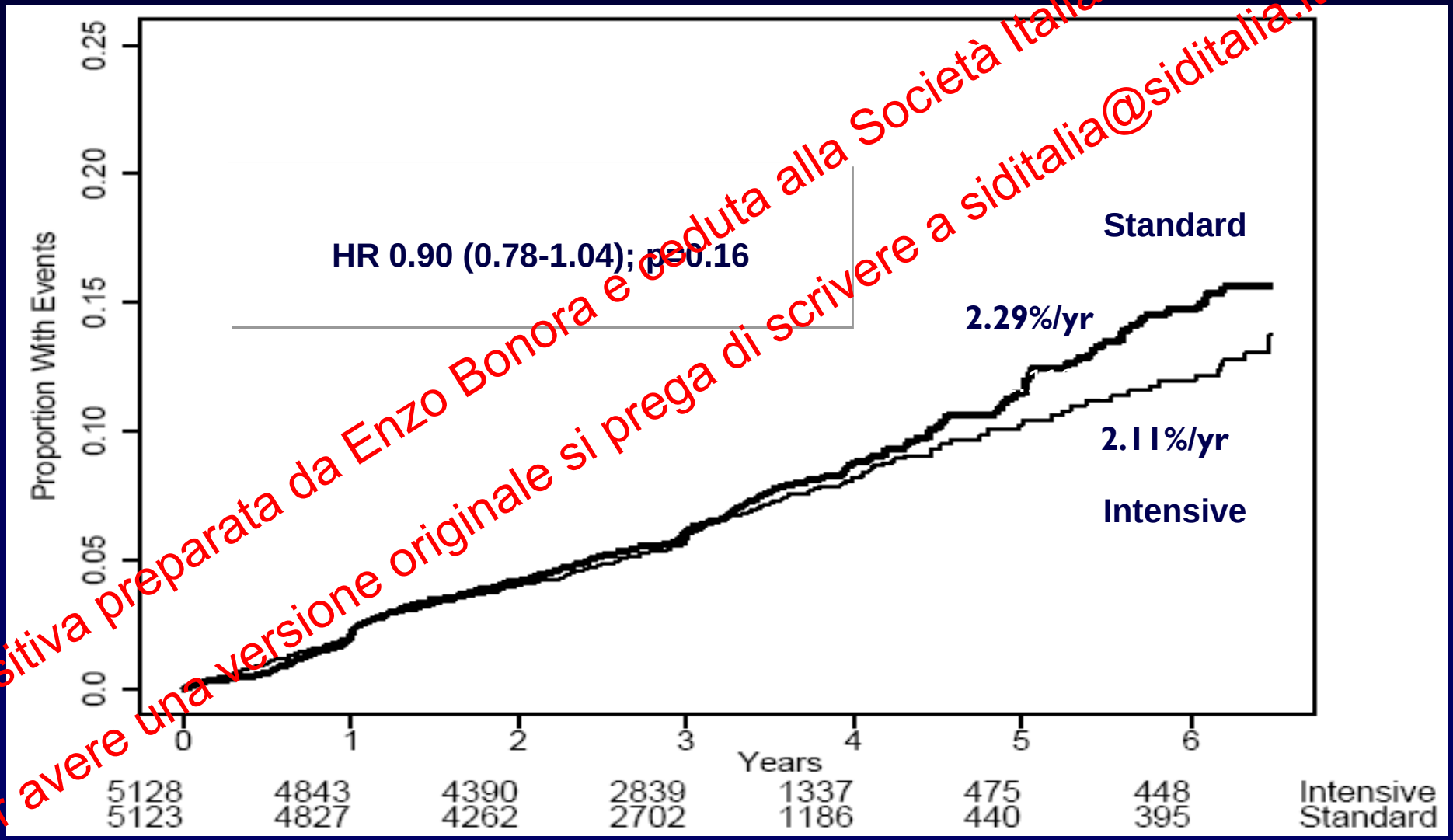
Main Question: In middle aged/older people with type 2 DM at high risk for CVD and with poor control, does a therapeutic strategy that targets an HbA1C < 6.0% reduce CVD event rates more than a strategy that targets an HbA1C between 7.0% and 7.9%?

Primary Outcome: Cardiovascular death + nonfatal AMI and stroke

ACCORD - Median HbA1c



ACCORD - Primary Outcome (Nonfatal AMI and Stroke and CVD Death)

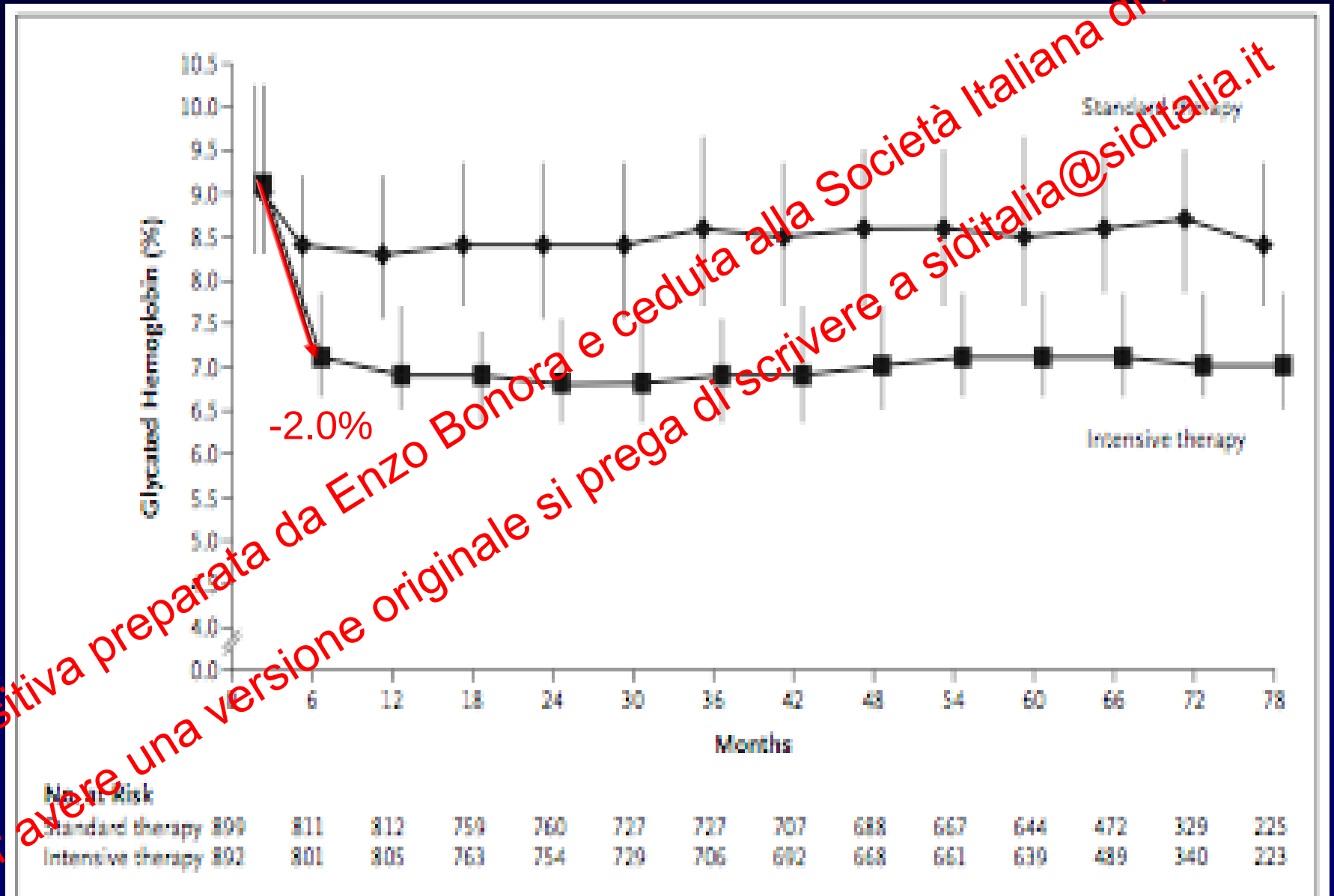


VADT – Main question and primary outcome

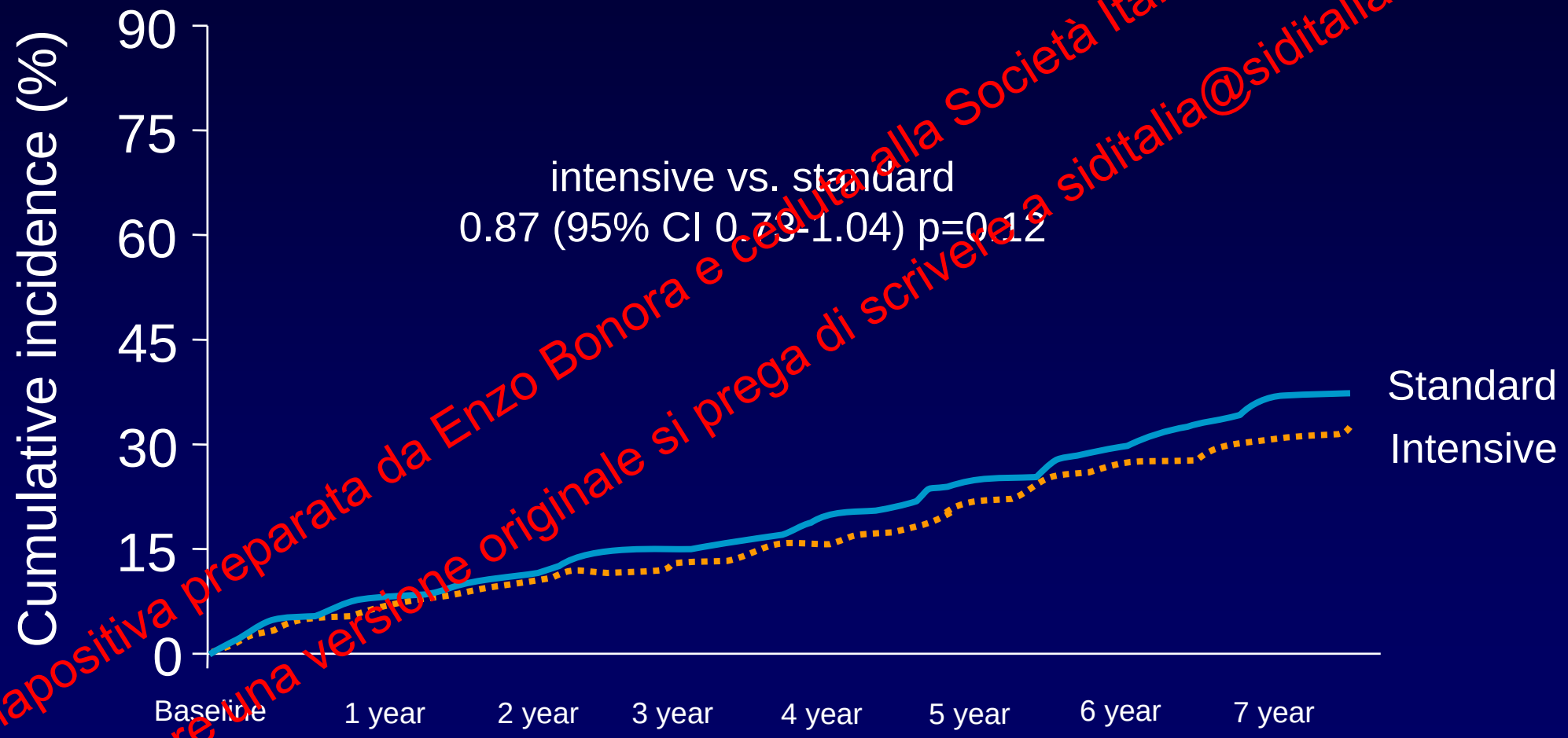
Main Question: In middle aged/older people with type 2 DM at high risk for a CVD event and a very poor control does a therapeutic strategy that targets an HbA1C reduction of at least 1.5% reduce chronic complications more than a standard strategy?

Primary Outcome: CVD death + nonfatal AMI and stroke + severe CHD + CHF + vascular amputation + any revascularization

VADT – HbA1c



VADT – Primary outcome (CVD death + nonfatal AMI and stroke + severe CHD + CHF + vascular amputation + any revascularization)



VADT Microvascular outcomes

Table 3. Microvascular Outcomes.*

Outcome	Standard Therapy (N=899)	Intensive Therapy (N=892)	P Value†
	no./total no. (%)		
Ophthalmologic disorder			
Cataract surgery			
Any	139/772 (18.0)	144/769 (18.7)	0.71
New	74/719 (10.2)	83/718 (11.6)	0.39
Photocoagulation			
Any	121/772 (15.7)	119/769 (15.5)	0.91
New	66/746 (8.8)	50/719 (7.0)	0.18
Vitrectomy			
Any	34/772 (4.4)	36/769 (4.7)	0.79
New	24/804 (3.0)	26/785 (3.3)	0.71
Retinopathy‡			
Progression to proliferative disease	16/399 (4.0)	23/406 (5.7)	0.27
Progression to clinically significant macular edema	17/361 (4.7)	12/371 (3.2)	0.31
Increase of 2 steps in severity of disease	88/399 (22.1)	69/406 (17.0)	0.07
New onset	66/135 (48.9)	54/128 (42.2)	0.27
Nephropathy			
Serum creatinine			
Doubling of level	78/884 (8.8)	78/882 (8.8)	0.99
>3 mg/dl (265 μmol/liter)	16/884 (1.8)	18/882 (2.0)	0.72
Glomerular filtration rate <15 ml/min	11/884 (1.2)	7/882 (0.8)	0.35
Change in albumin level			
From normal to microalbuminuria	61/463 (13.2)	43/442 (9.7)	0.12
From normal to macroalbuminuria	7/463 (1.5)	1/442 (0.2)	0.07
From microalbuminuria to macroalbuminuria	29/240 (12.1)	19/251 (7.6)	0.10
From normal to microalbuminuria or macroalbuminuria	68/463 (14.7)	44/442 (10.0)	0.03
From normal to microalbuminuria to macroalbuminuria	36/703 (5.1)	20/693 (2.9)	0.04
Any increase in albuminuria	97/703 (13.8)	63/693 (9.1)	0.01
New neuropathy			
Any	218/498 (43.8)	202/464 (43.5)	0.94
Mononeuropathy	20/498 (4.0)	22/464 (4.7)	0.58
Peripheral	199/498 (40.0)	178/464 (38.4)	0.61
Autonomic	26/498 (5.2)	38/464 (8.2)	0.07

* All microvascular outcomes were new events except for eye procedures. The denominators are the numbers of patients in each category who underwent evaluation at baseline.
† P values have not been adjusted for multiple comparisons.
‡ The 23-point Early Treatment Diabetic Retinopathy Study grading scale was used to define progression.

ADVANCE – Main question and primary outcome

Main Question: In middle aged/older people with type 2 DM at high risk for CVD and fair control does a therapeutic strategy based upon gliclazide that targets an HbA1C ≤ 6.5% reduce chronic diabetes complications more than a strategy that targets an HbA1C at values recommended by local guidelines?

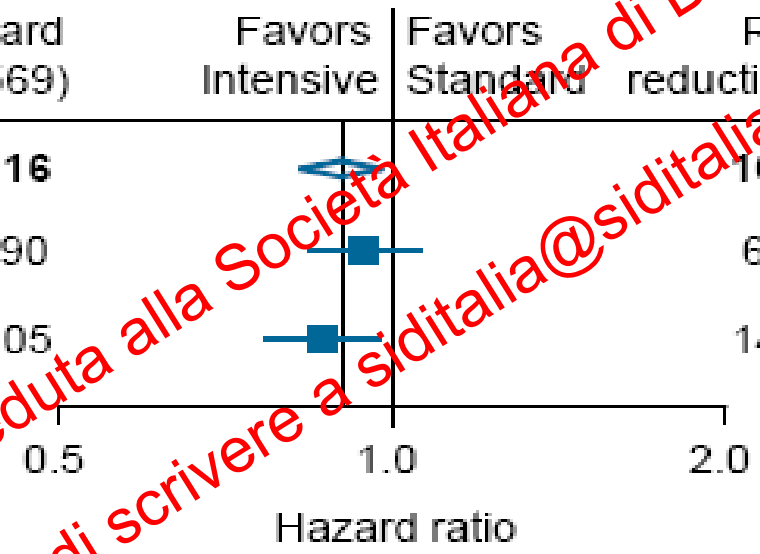
Primary Outcome: CVD death + nonfatal AMI and stroke + new or worsening nephropathy or retinopathy

ADVANCE - HbA1c

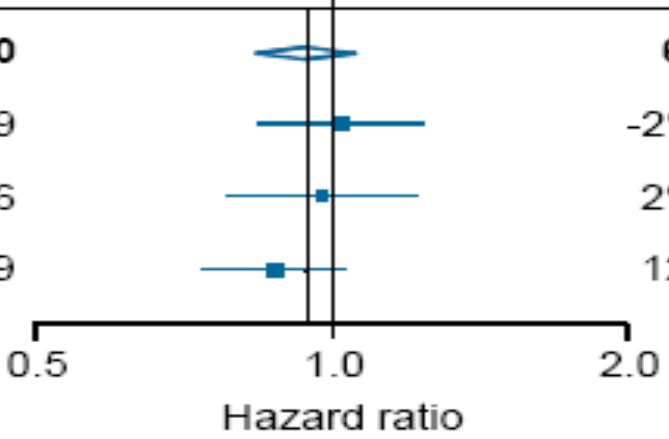
Value							
Standard	7.32	7.30	7.29	7.29	7.31	7.33	7.29
Intensive	7.01	6.93	6.70	6.53	6.50	6.52	6.53

ADVANCE: Main Outcomes

	Number of patients with event: Intensive (n=5,571)	Standard (n=5,569)	Relative risk reduction (95% CI)
Combined macro+micro	**1009**	**1116**	**10% (2 to 18)†**
Macrovascular	557	590	6% (-6 to 16)
Microvascular	526	605	14% (3 to 23)‡



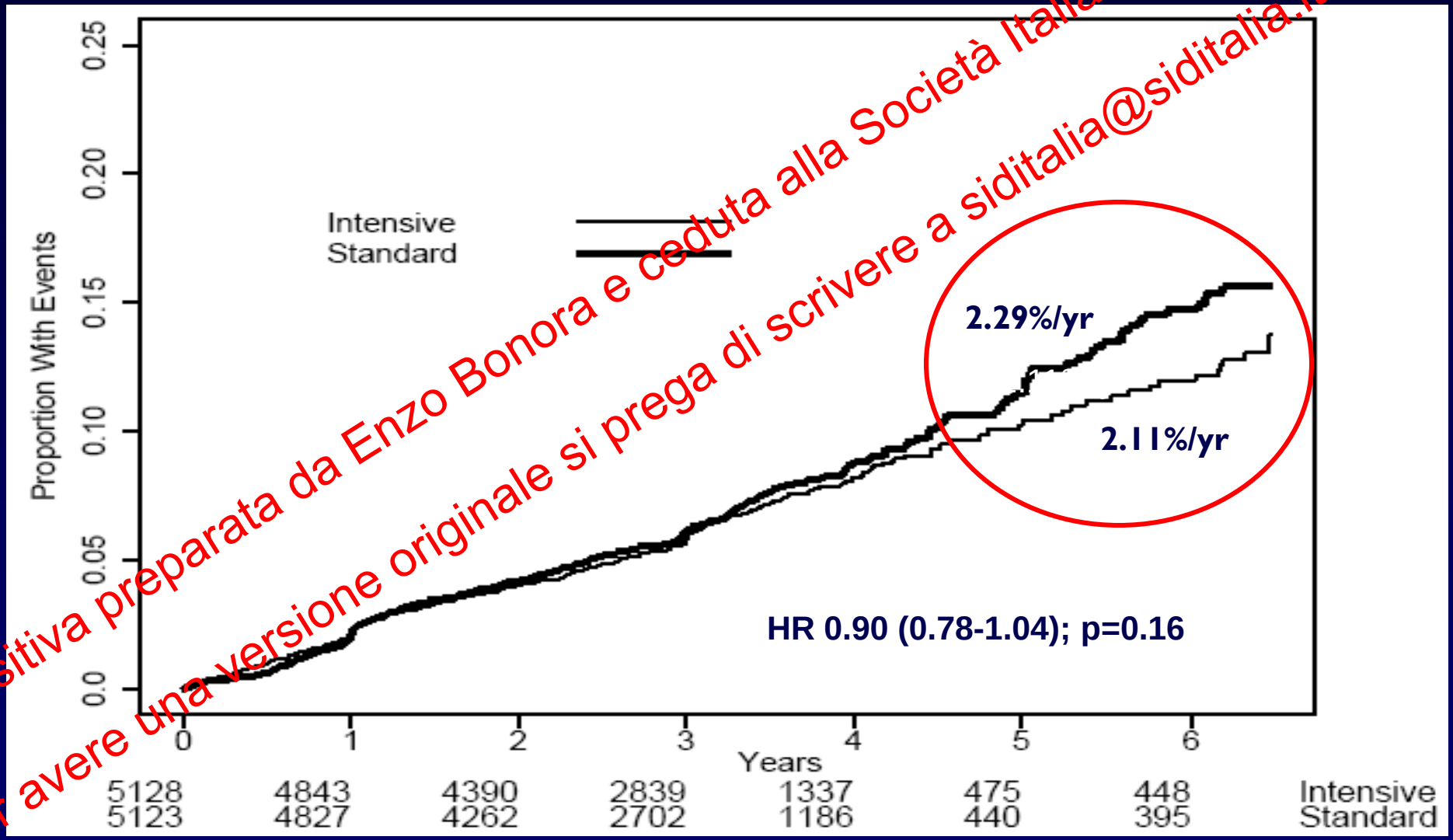
	Number of patients with event: Intensive (n=5,571)	Standard (n=5,569)	Relative risk reduction (95% CI)
Macrovascular	**557**	**590**	**6% (-6 to 16)**
Non-fatal stroke	214	209	-2% (-24 to 15)
Non-fatal MI	153	156	2% (-23 to 22)
Cardiovascular death	253	289	12% (-4 to 26)



Why CVD was not reduced in recent glucose trials?

- 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 relating glucose and CVD? And what about results of post-trial monitoring of UKPDS (and DCCT-EDIC in T1DM)?
- 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 of medications and/or more frequent and more severe hypoglycemia?

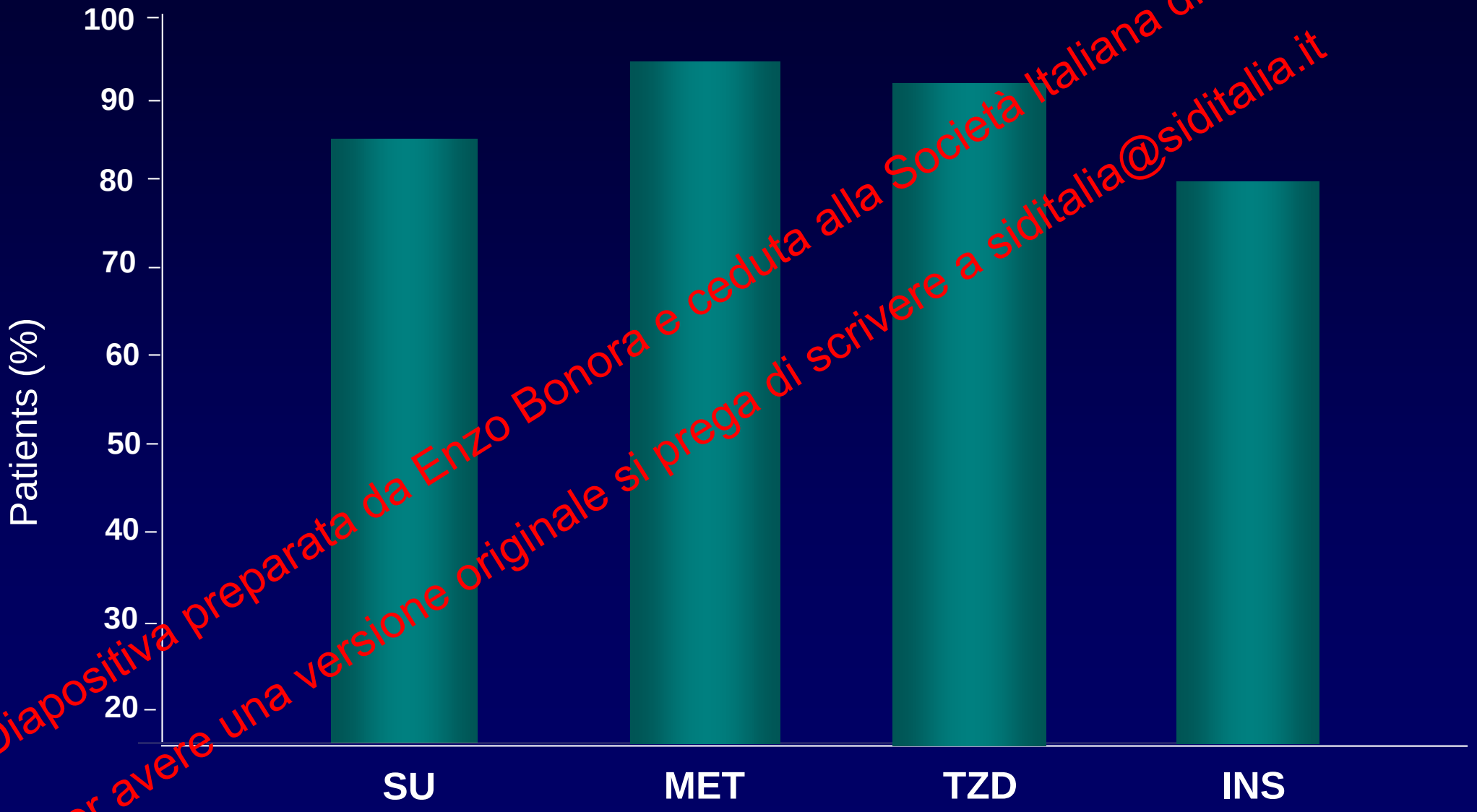
ACCORD - Primary Outcome (Nonfatal AMI and Stroke and CVD Death)



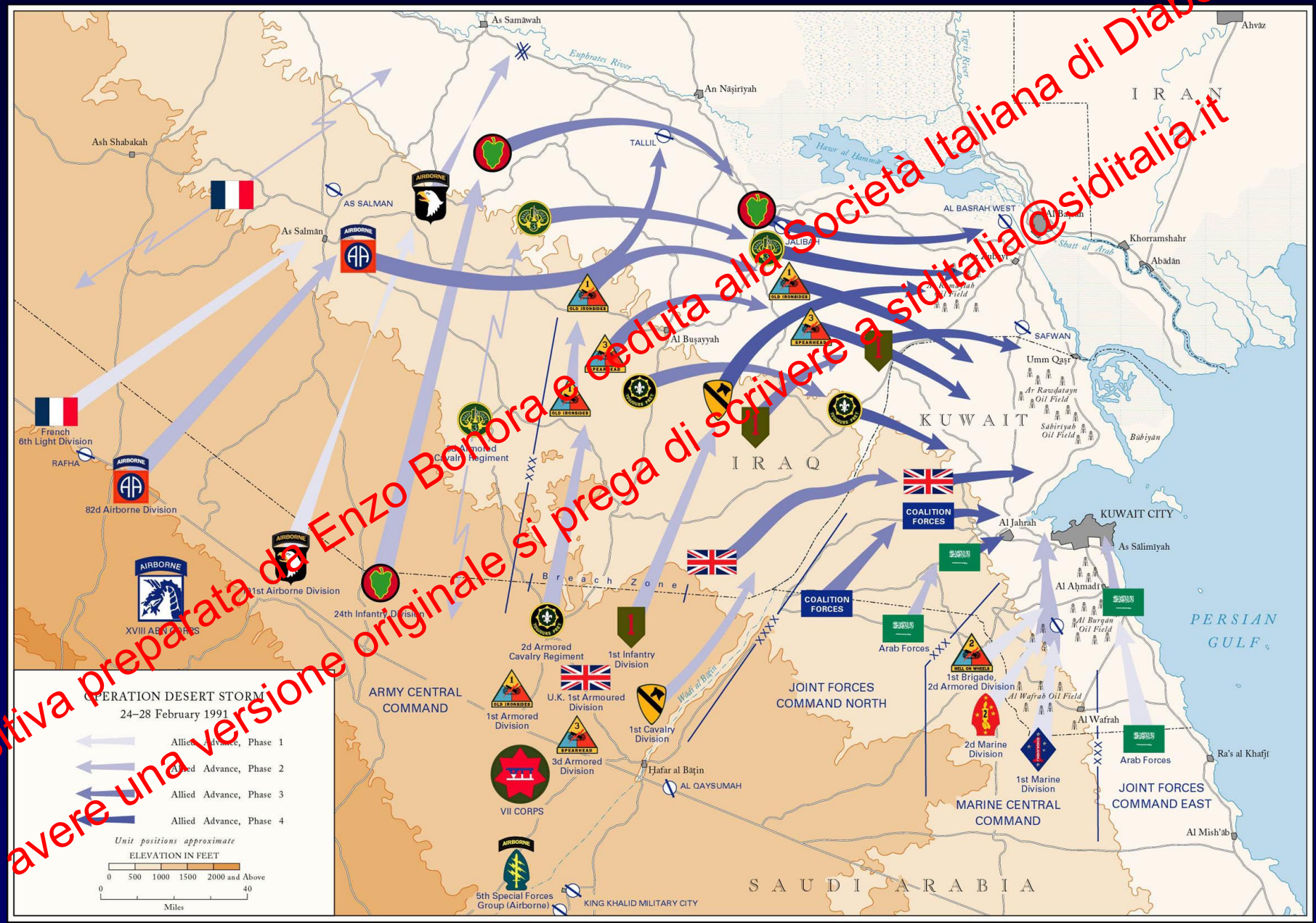
ACCORD
Medications for Other Risk Factors at Follow-Up

	On treatment
Lipid lowering	Standard 88%, Intensive 88%
BP lowering	Standard 92%, Intensive 91%
Antiplatelet	Standard 75%, Intensive 75%

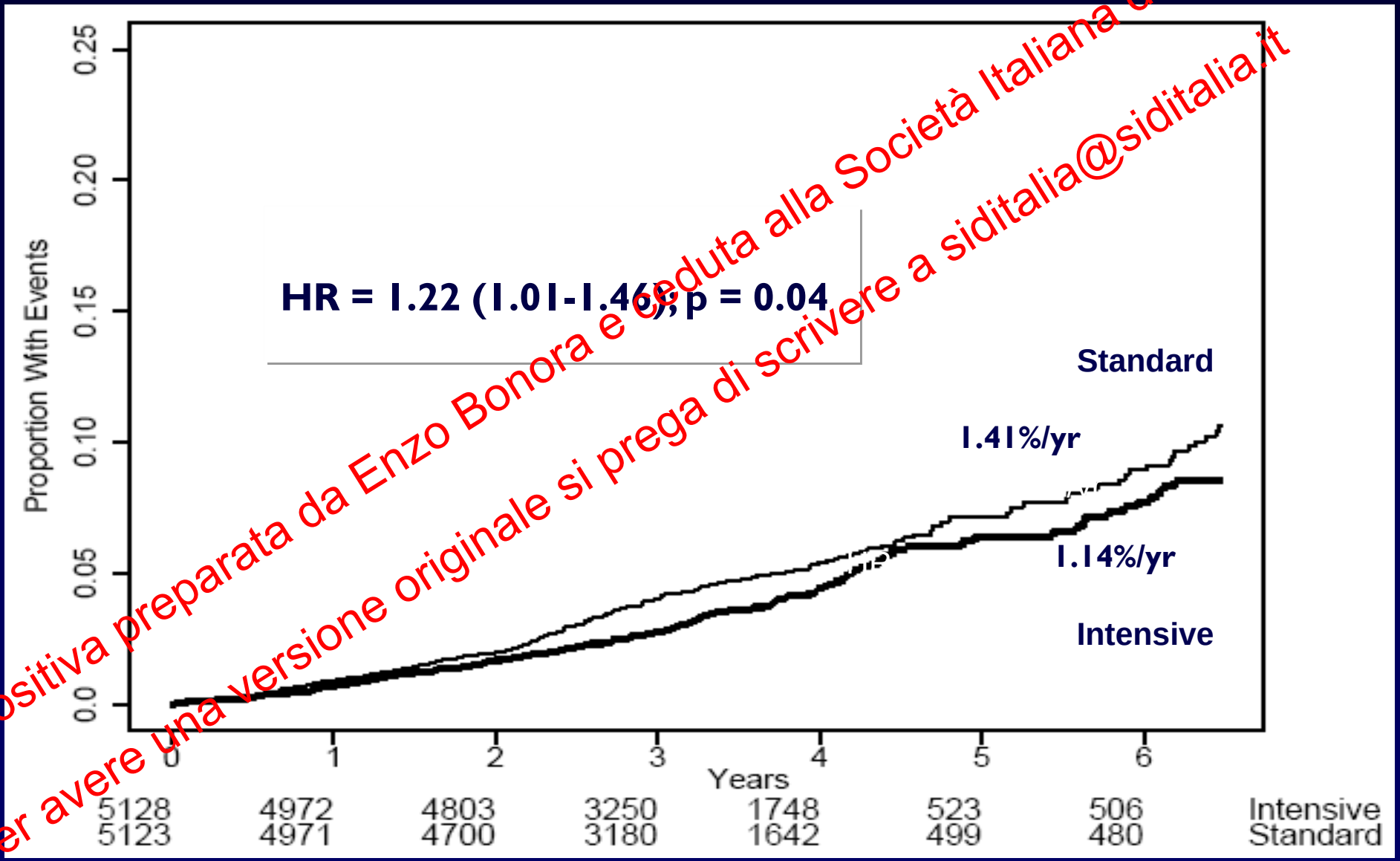
ACCORD – Intensive Treatment Strategy



ACCORD or Operation “Desert Storm”?



ACCORD - All-Cause Mortality

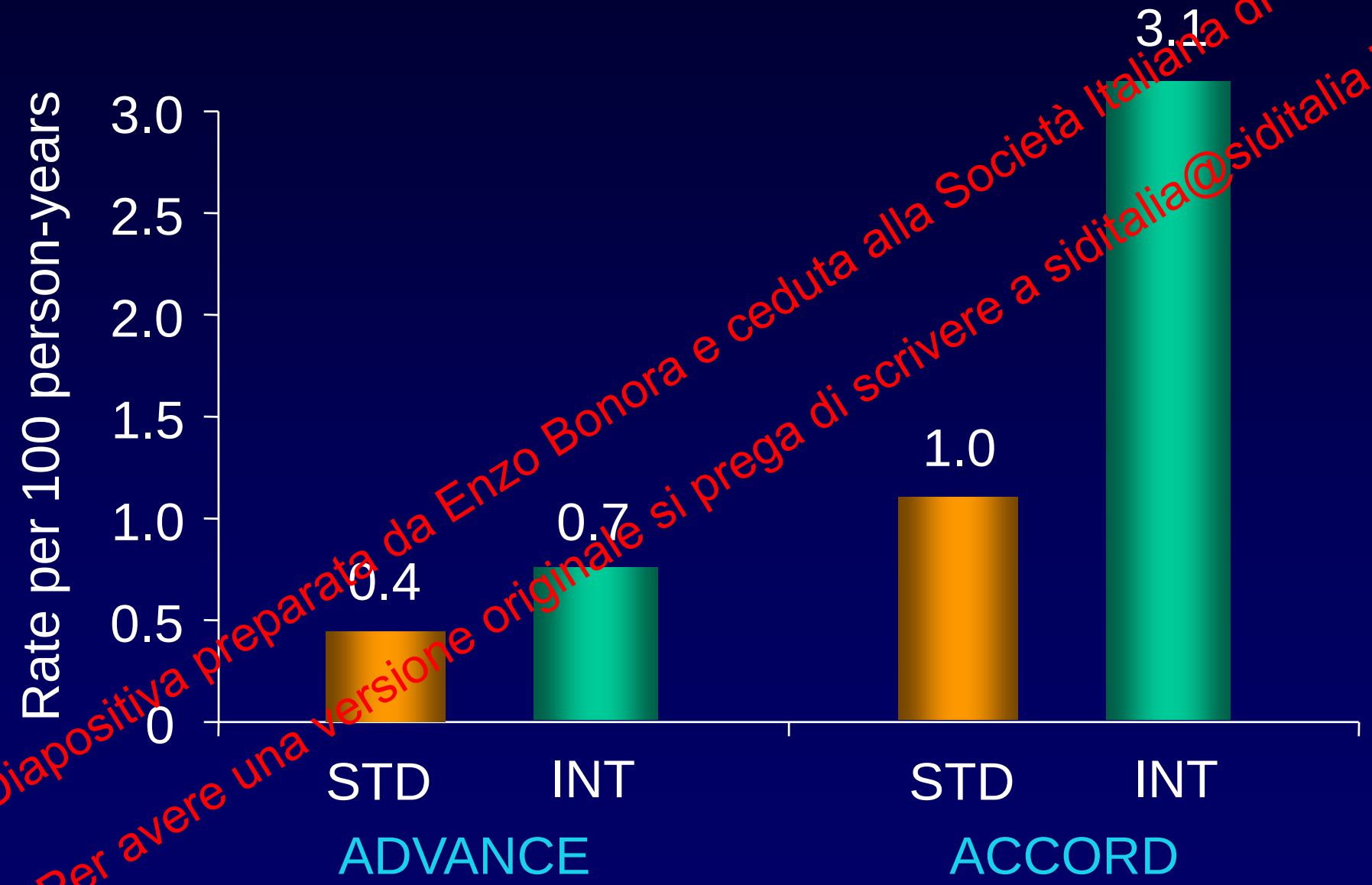


ACCORD, ADVANCE AND VADT
HRs for composite CVD outcome and CVD death

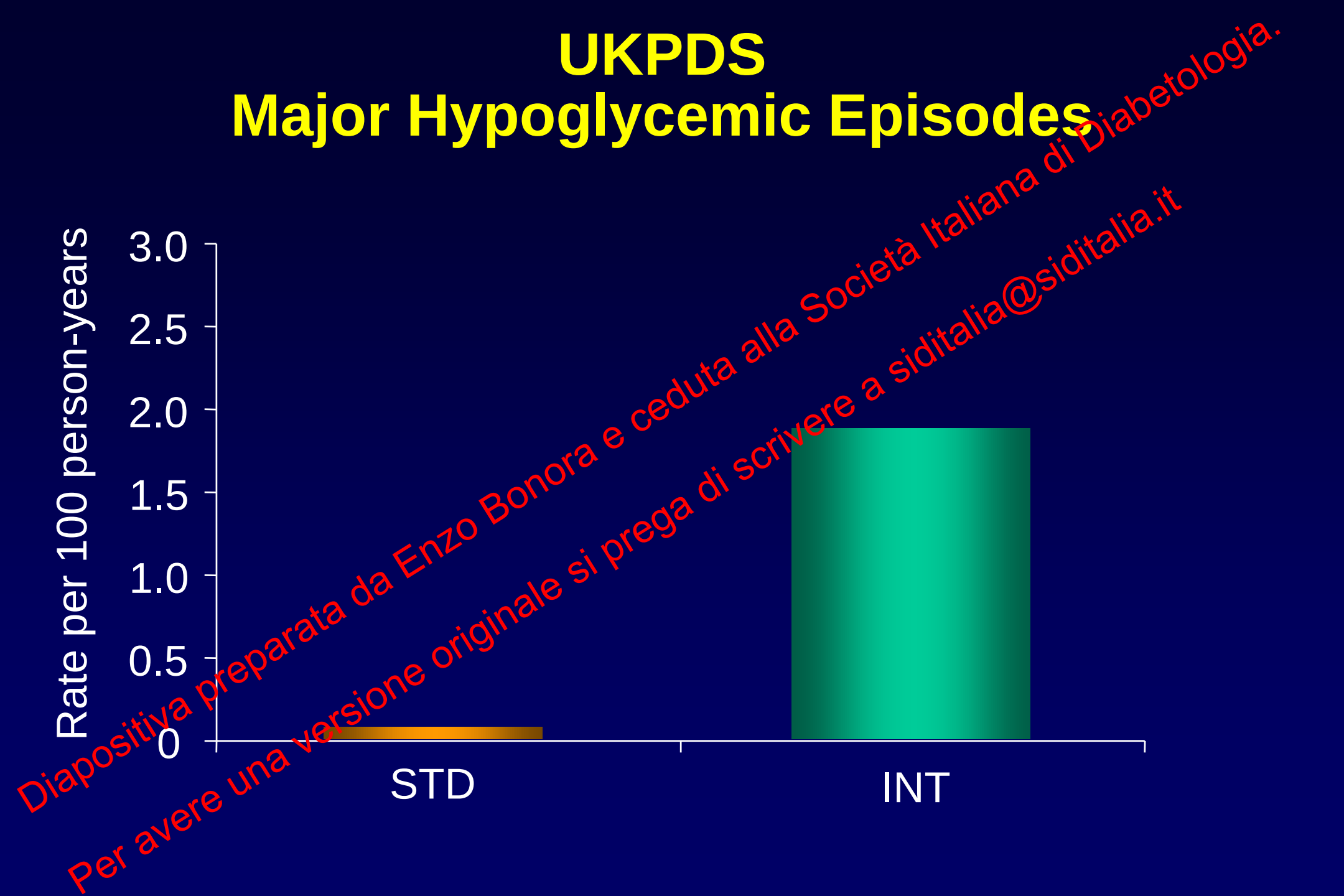
Outcome	ACCORD	ADVANCE	VADT
Composite CVD	0.90 (0.78-1.04)	0.94 (0.84-1.06)	0.87 (0.73-1.04)
CVD Death	1.35 (1.04-1.76)	0.88 (0.76-1.04)	1.25 (0.77-2.05)

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

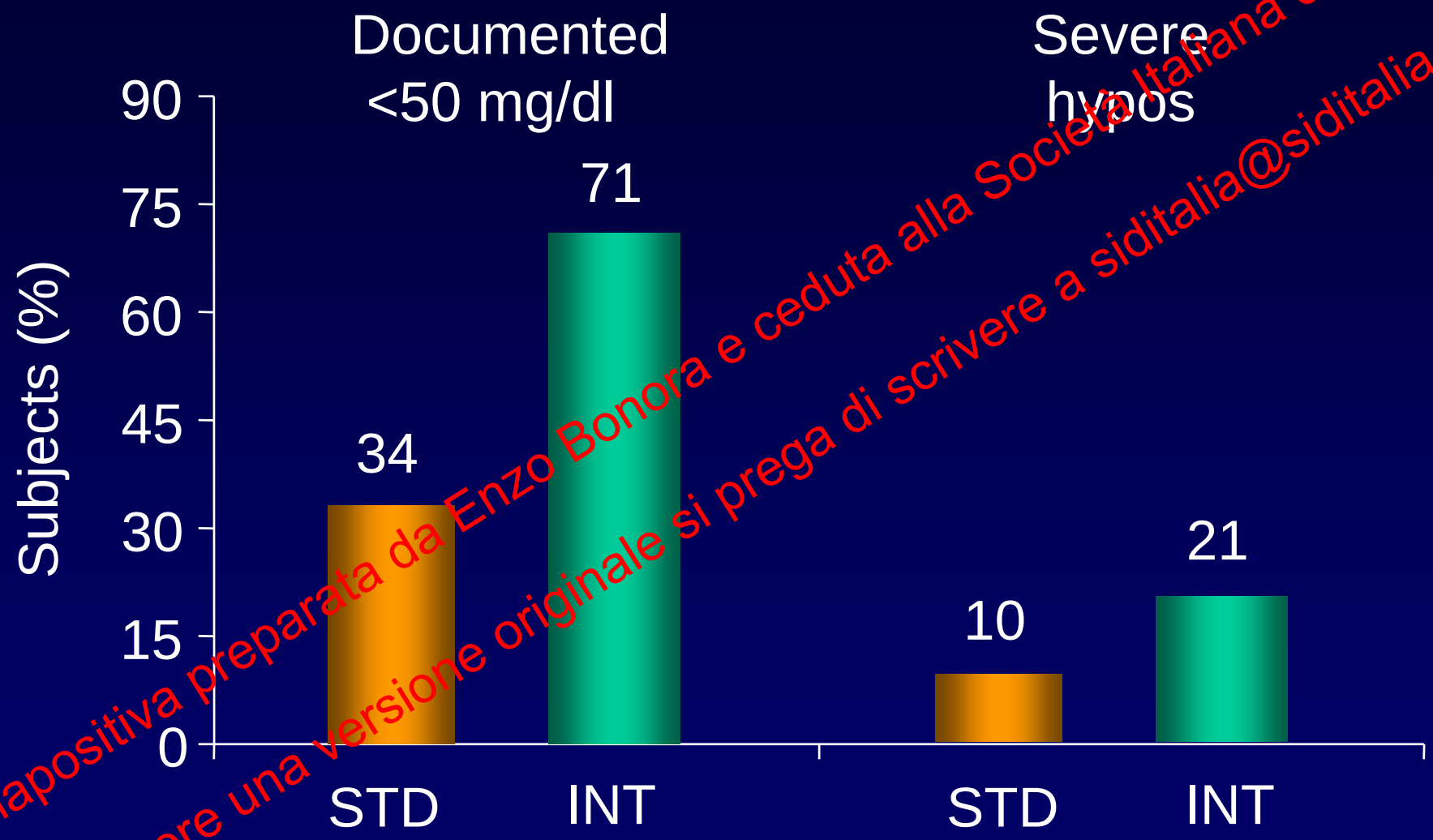
ADVANCE AND ACCORD
Severe hypoglycemic episodes



UKPDS
Major Hypoglycemic Episodes



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

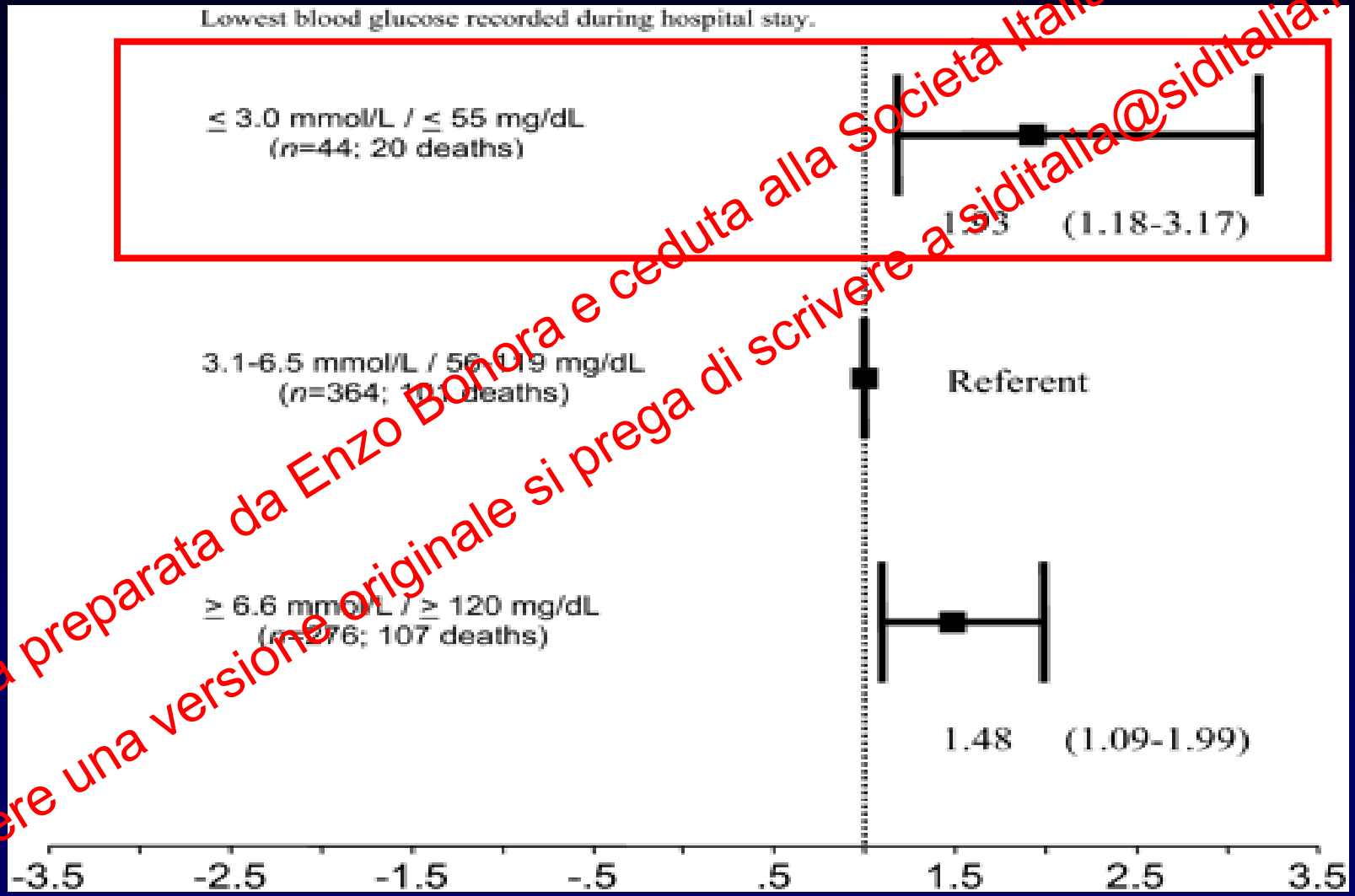
Association of Hypoglycemia and Rapid Hyperglycemia with Cardiac Ischemia in T2DM. A Study based upon Continuous Glucose and ECG Monitoring

(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

Association of Lowest Blood Glucose Recorded during Hospital Stay after AMI and 2-Year Mortality in T2DM

(Svensson et al; Europ Hearth J 26: 1255, 2005)



Factors predisposing to hypoglycemia

- Poor nutrition or irregular meals
- Cognitive impairment/dementia/depression
- Inability to face hypoglycemia/hypoglycemia unawareness
- Vision problems (difficulties with pills, glucometer, syringes)
- Organ failure (kidney, liver, etc.), comorbidities
- Polypharmacy

Interazioni farmacologiche della glibenclamide (da scheda tecnica)

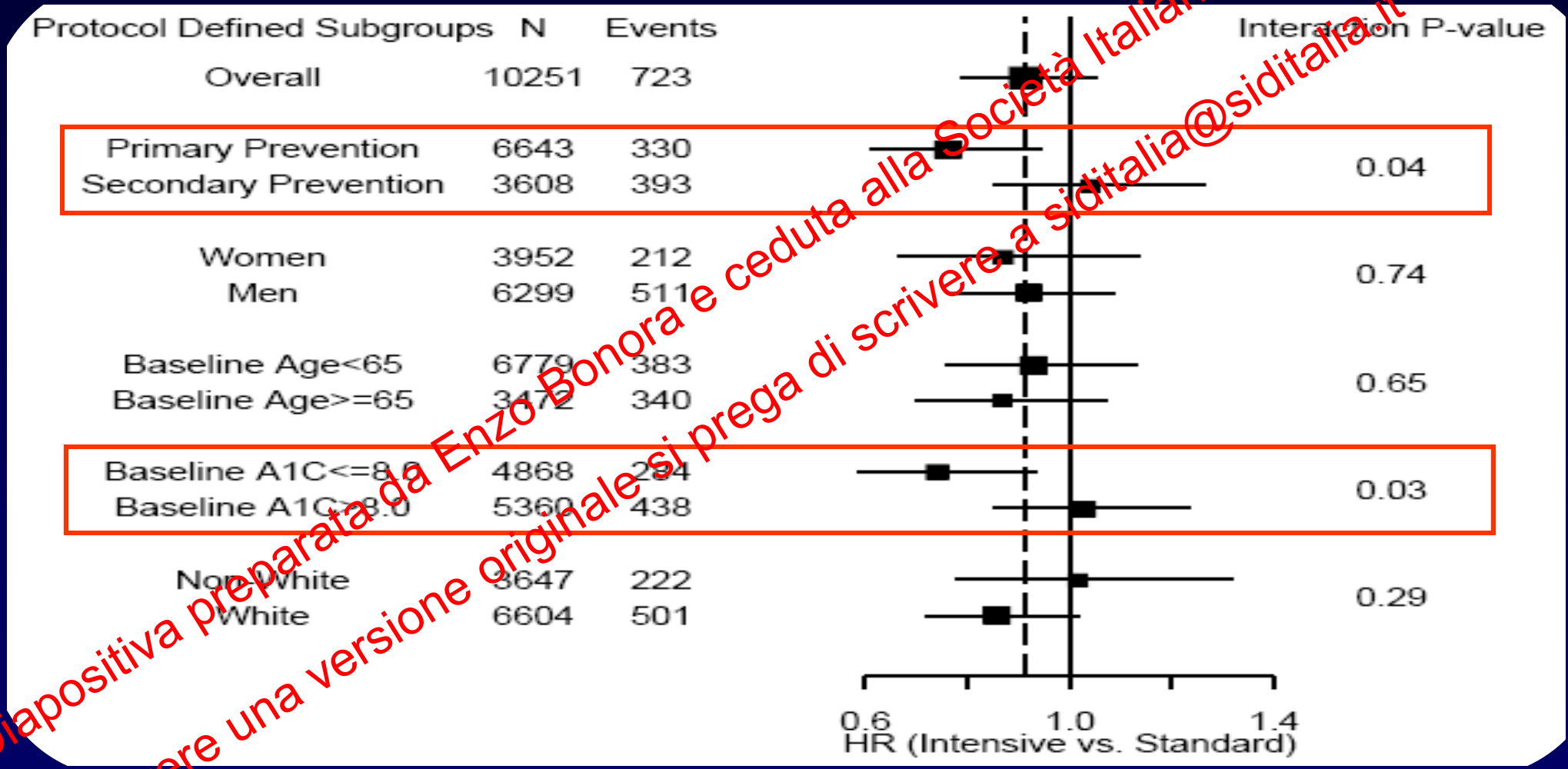
Potenziamento dell'effetto ipoglicemizzante con:

acido para-aminosalicilico, anabolizzanti, azapropazone, ciclofosfamide, chinolonici, cloramfenicolo, derivati cumarinici, disopiramide, fenfluramina, fenilbutazone, feniramidolo, fibrati, fluoxetina, H2-antagonisti, ifosfamide, inibitori delle MAO, miconazolo, pentossifillina (per via parenterale ad alte dosi), ossifenbutazone, probenecid, salicilati, simpaticolitici quali beta-bloccanti e guanetidina, sulfamidici, sulfinpirazone, tetracicline, tritoqualina, trofosfamide

Fundamental questions after ACCORD, ADVANCE and VADT results

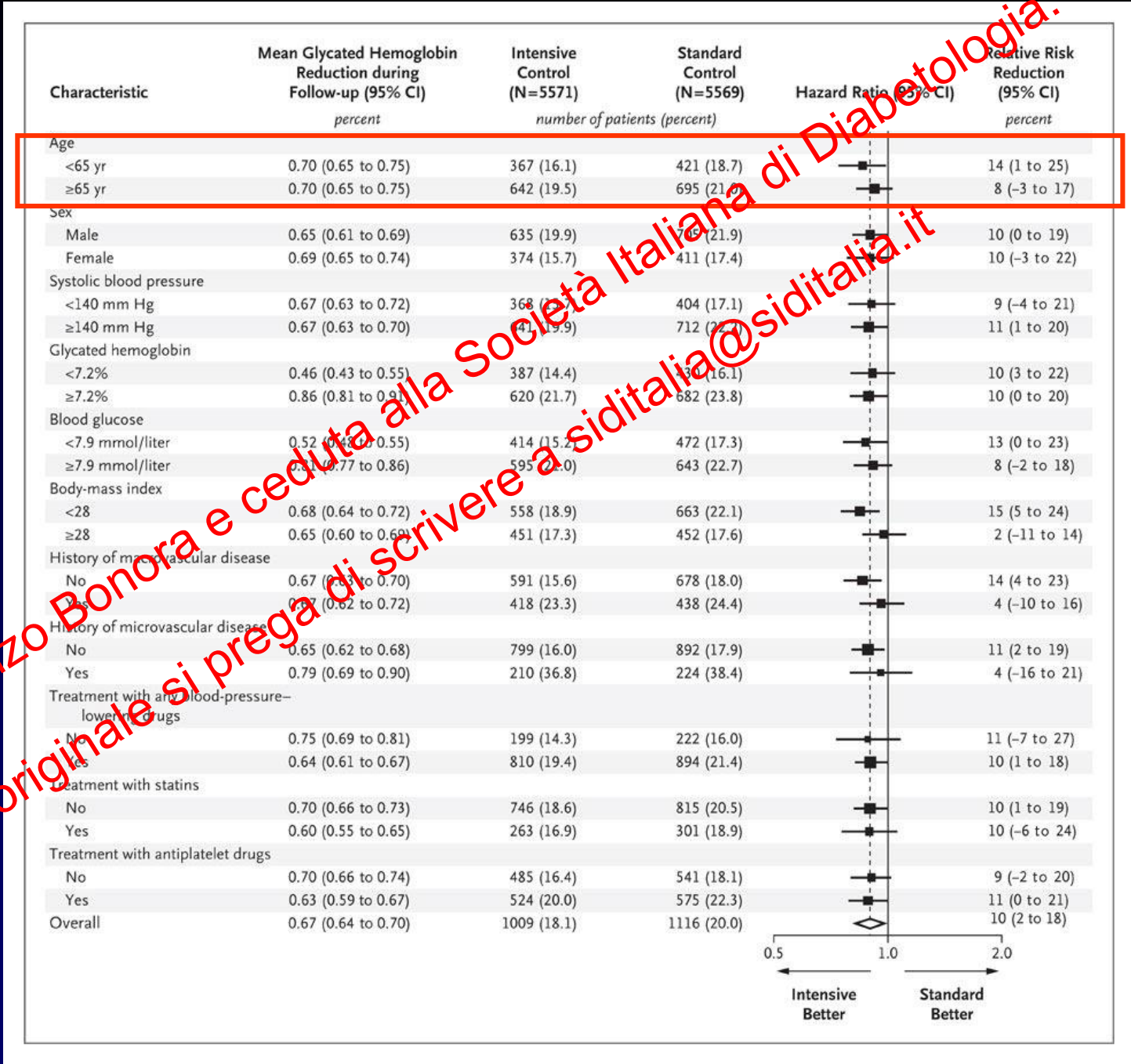
Is the lack of CVD benefits with more stringent glucose control generalizible in T2DM?

ACCORD: Primary Outcome by Subgroups



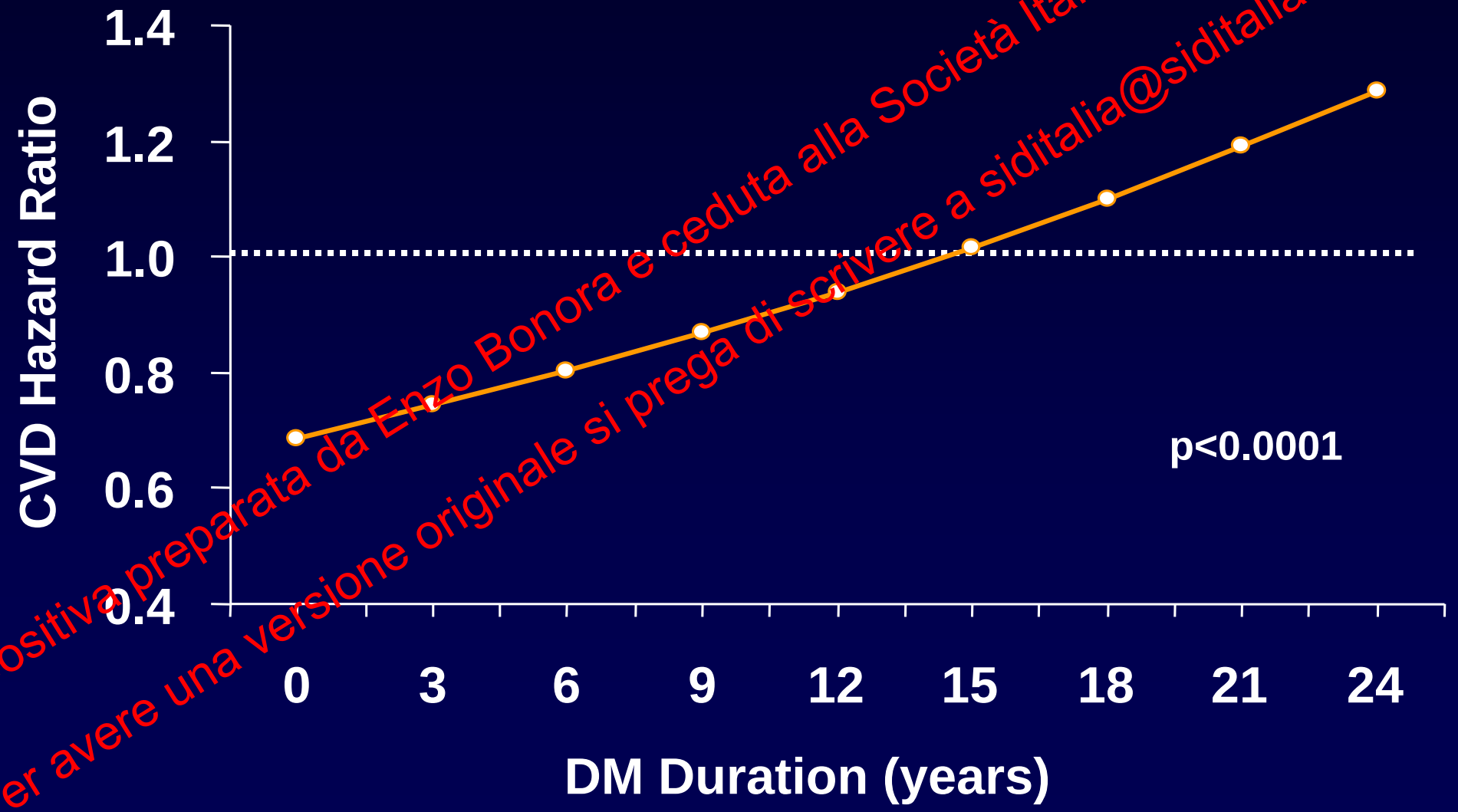
Advance

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



Main and fundamental questions after ACCORD, ADVANCE and VADT Trials

- Do we have to reconsider the HbA1c target in T2DM? **YES**
- Is it reasonable to conclude that targets should be customized according to clinical features of patients? **YES**

A New Paradigm in Diabetes Care: Customized HbA1c Targets

- **"Recruit" patient** (newly diagnosed T2DM, middle age, no prior CVD, any HbA1c)
  HbA1c Target = <6.5%; "no mercy"

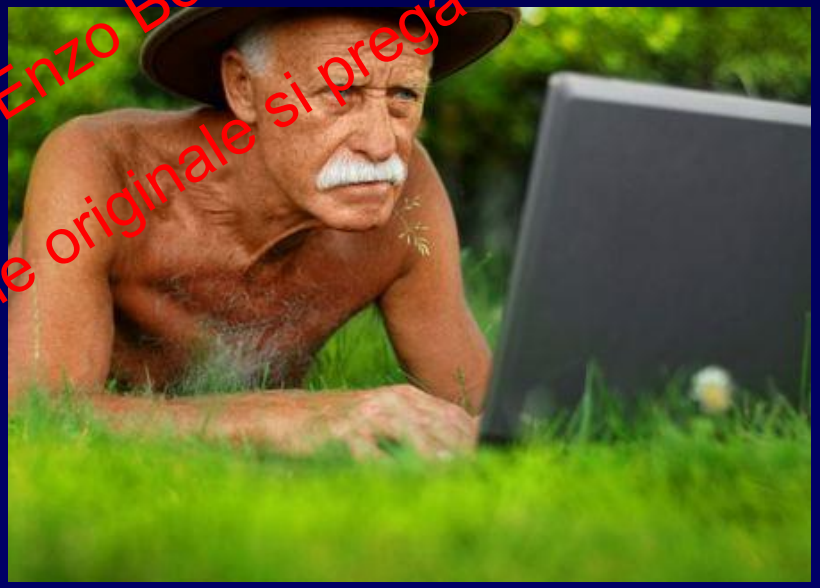
- **"Veteran" patient** (long standing T2DM, older age, no prior CVD, previously fairly controlled diabetes)
  HbA1c target = 6.5-7.5%; "smooth decline"

- **"Injured Veteran" patient** (long standing T2DM, prior CVD, severely uncontrolled diabetes; "hyperglycemia addicts" who need progressive adaptation to lower glucose levels?)
  HbA1c target = 7.5-8.5%; "handle with care"

Commitment in Diabetes Care

It is not TTT= Treat-to-Target

but rather TTB= Treat-to-Benefit



HbA1c Targets in Diabetes Care

(AMD-SID Standards of Care, 2009-2010)

Obiettivo generale	<7%
Nuova diagnosi o breve durata, discreto compenso pregresso	<6.5%
Lunga durata, CVD o comorbidità/fragilità, cattivo compenso pregresso	7-8%

Obiettivo HbA1c

	Caso #1	Caso #2	Caso #3
Età	56	64	72
Durata	1	9	17
HbA1c media	7.8	7.8	7.8
CVD	No	Sì	Sì
Aspettativa di vita	>10 anni	>5 anni	<5 anni
Obiettivo di HbA1c	<6.5	6.5-7.5	7.5-8.5

Final remarks

- Diabetes often severely injures or kills people
- Physicians can severely injure or kill diabetic patients by means of:
  late and/or too gentle intervention
  clinical inertia and/or resignation
  inappropriate aggressiveness
  neglecting the key role of clinical judgment

The end

Thank you for your attention