Terapia insulinica e rischio cardiovascolare

Enzo Bonora
Endocrinologia, Diabetologia e Metabolismo
Università e Azienda Ospedaliera Universitaria
Integrata di Verona

Quesiti

1. Il trattamento insulinico può aumentare il rischio CVD nel diabete?

2. In caso affermativo, ci sono insuline più sicure e altre meno sicure in termini di rischio CVD?

Trattamento insulinico e rischio CVD

1. Effetti pro-aterogeni dell'insulina
2. Effetti anti-aterogeni dell'insulina
3. Ipoglicemia e CVD

Exposure to hypo- and hyperglycemia in well-controlled T1DM patients as assessed by CGM

Kovalski AJ. Diabetes Technology & Therapeutics, 2009, suppl 1

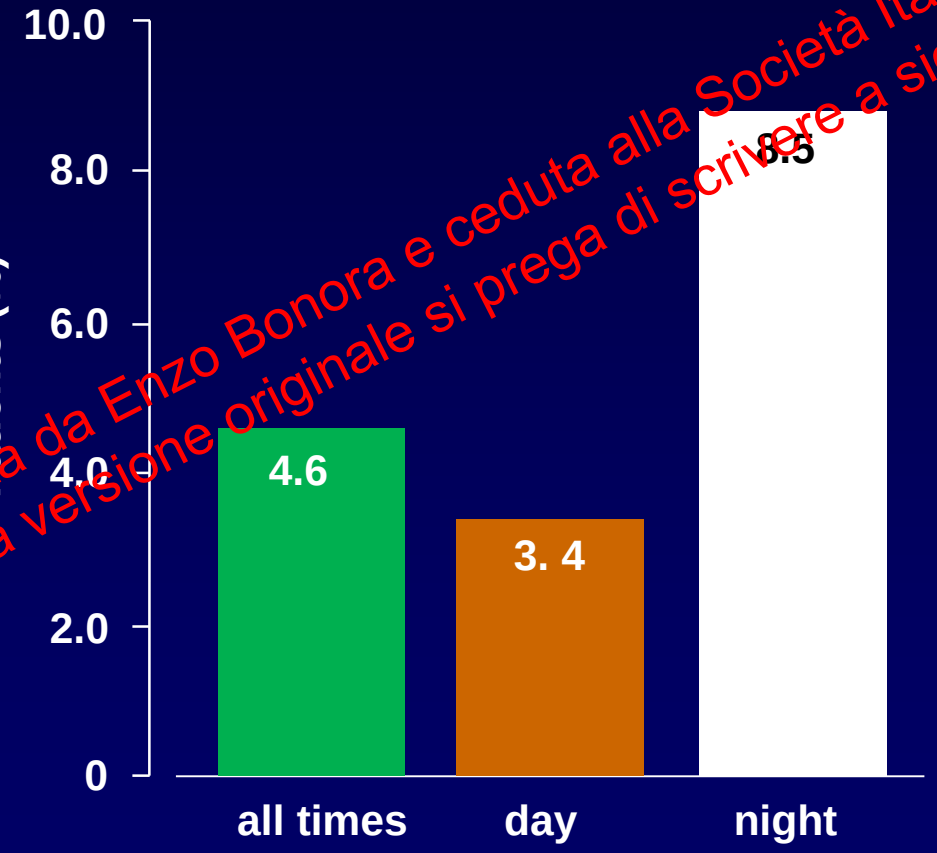
TABLE 1. GLYCEMIC EXPOSURE

	HbA1c in reference				
			JDRF CGM Study[13]		
	NR in Bode et al.[15]	*7.1% in DirecNet*[12]	*7.6%*	*8.0%*	*8.0%*
Average age (years)	45.3	11.2	42.9	18.5	11.5
Exposure					
<70 mg/dl	**2.3**	**1.1**	**1.4**	**1.7**	**0.9**
70–180 mg/dl	14.5	12.5	13.9	11.6	11.3
>180 mg/dl	**7.2**	**10.4**	**8.7**	**10.7**	**11.8**

Exposure in hours to hypo- and hyperglycemia in three studies demonstrates significant exposure in well-controlled patients. NR, not reported. Numbers in bold type highlight time spent hypo- and hyperglycemic, respectively.

Hypoglycaemia in people with Type 2 diabetes

McNally et al, Diabetes Care 30: 1044, 2007

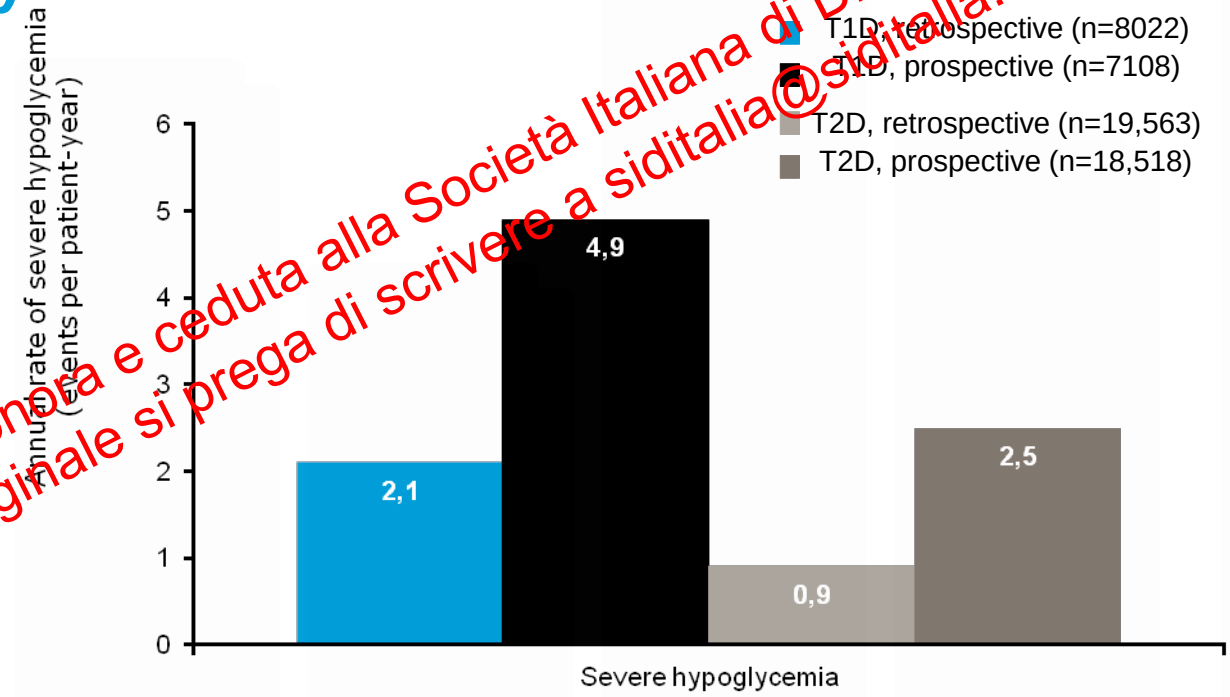


Annual rate of severe hypoglycemia is higher than previously observed

Results from the HAT study

HAT study

- Non-interventional, global, 6-month retrospective and 1-month prospective study of patient self-reported hypoglycemic events
- n=27,585 (T1D: 8022; T2D: 19,563)



Prospective data suggest higher than previously observed rates of hypoglycemia in both T1D and T2D, in particular severe events

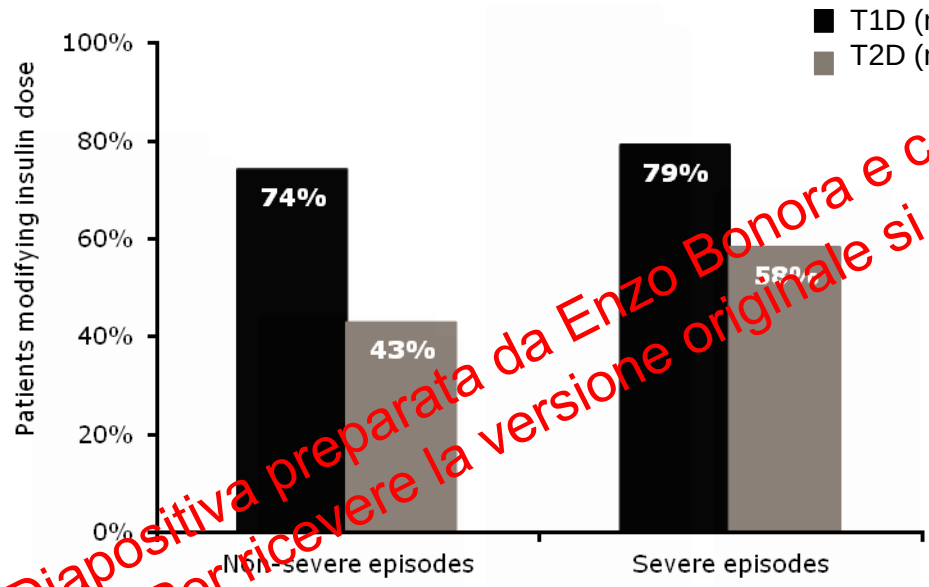
DEVOTE
DEGLUDEC CARDIOVASCULAR OUTCOMES TRIAL

HAT, Hypoglycaemia Assessment Tool; T1D, type 1 diabetes
Khunti *et al. Diabetes Obes Metab* 2016;18:907–15; Khunti *et al.* Poster presented at the 10th International Diabetes Federation-Western Pacific Region Congress, 21–24 November 2014, Singapore

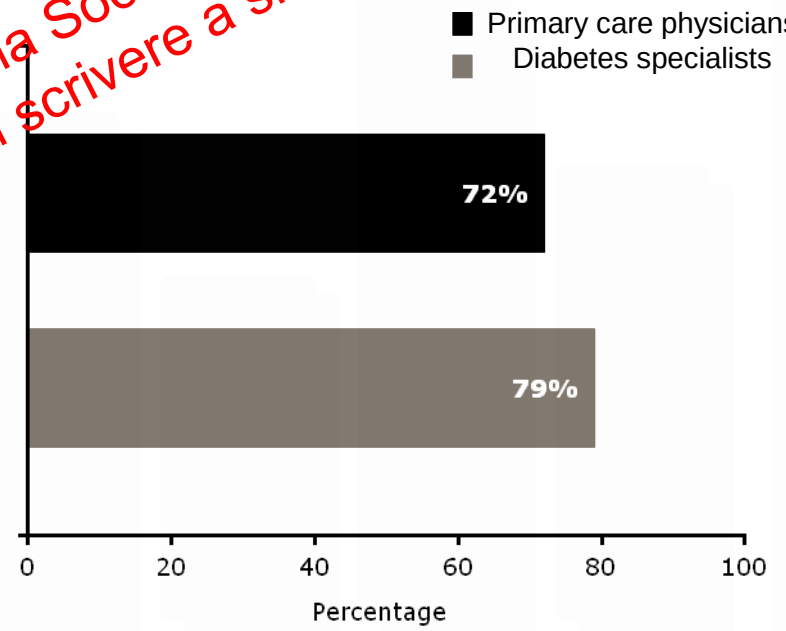
Presented at the American Diabetes Association 77th Scientific Sessions, Session 3-CT-SY22. June 12 2017, San Diego, CA, USA

Fear of hypoglycemia conflicts with treatment success for both patients and clinicians

Percentage of patients decreasing their insulin dose following a hypoglycemic event[1]



I would treat my patients more aggressively if there was no concern about hypoglycemia[2]



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1. Leiter *et al. Can J Diabetes* 2005;29:186–92; 2. Peyrot *et al. Diabet Med* 2012;29:682–9, GAPP™ (A global internet survey of patient and physician beliefs regarding insulin therapy): n=1250 physicians

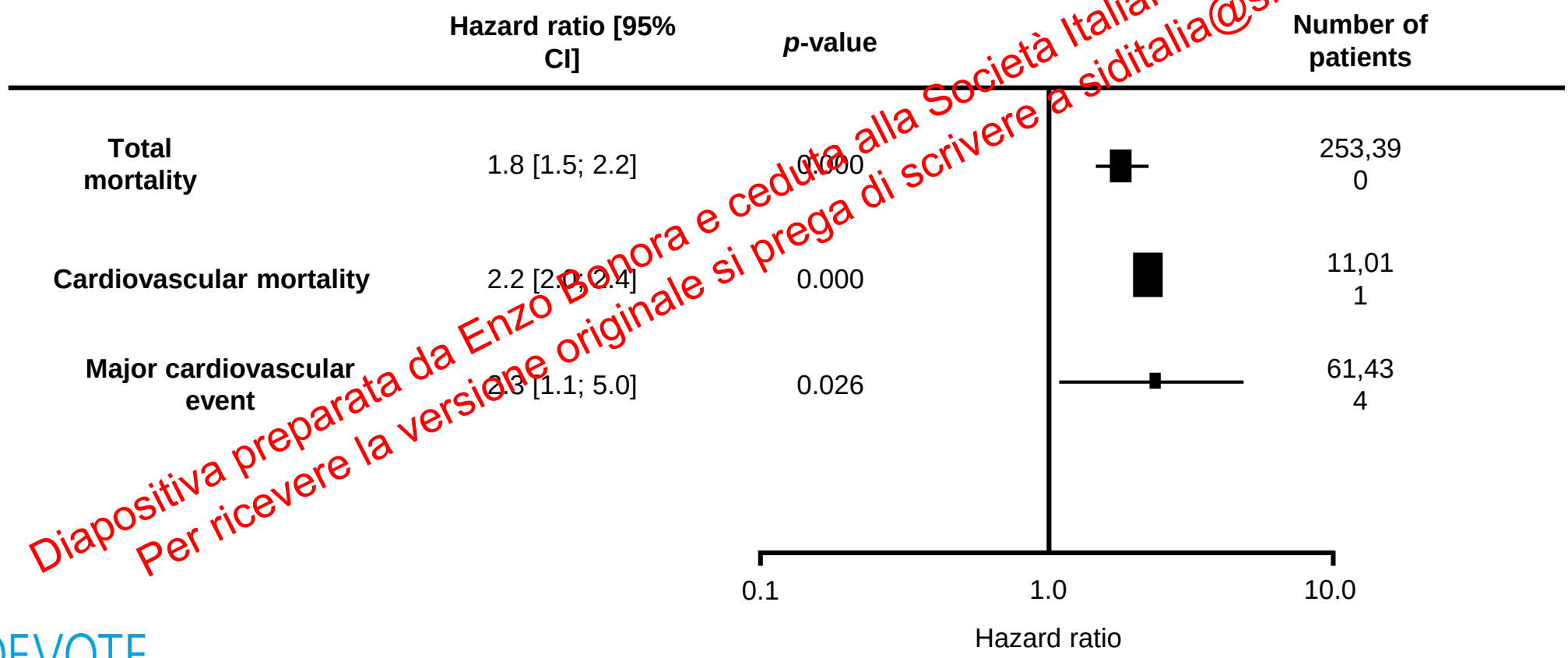
Presented at the American Diabetes Association 77th Scientific Sessions, Session 3-CT-SY22. June 12 2017, San Diego, CA, USA

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

Systematic review: association of hypoglycemia with outcomes



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DEGLUDEC CARDIOVASCULAR OUTCOMES TRIAL

Adapted from Yeh *et al. Acta Diabetol* 2016;53:377–92

Presented at the American Diabetes Association 77th Scientific Sessions, Session 3-CT-SY22. June 12 2017, San Diego, CA, USA

Trattamento insulinico e rischio CVD

1. Studi osservazionali
2. Studi di intervento

Association of various diabetes treatment with MACE and other endpoint in T2DM

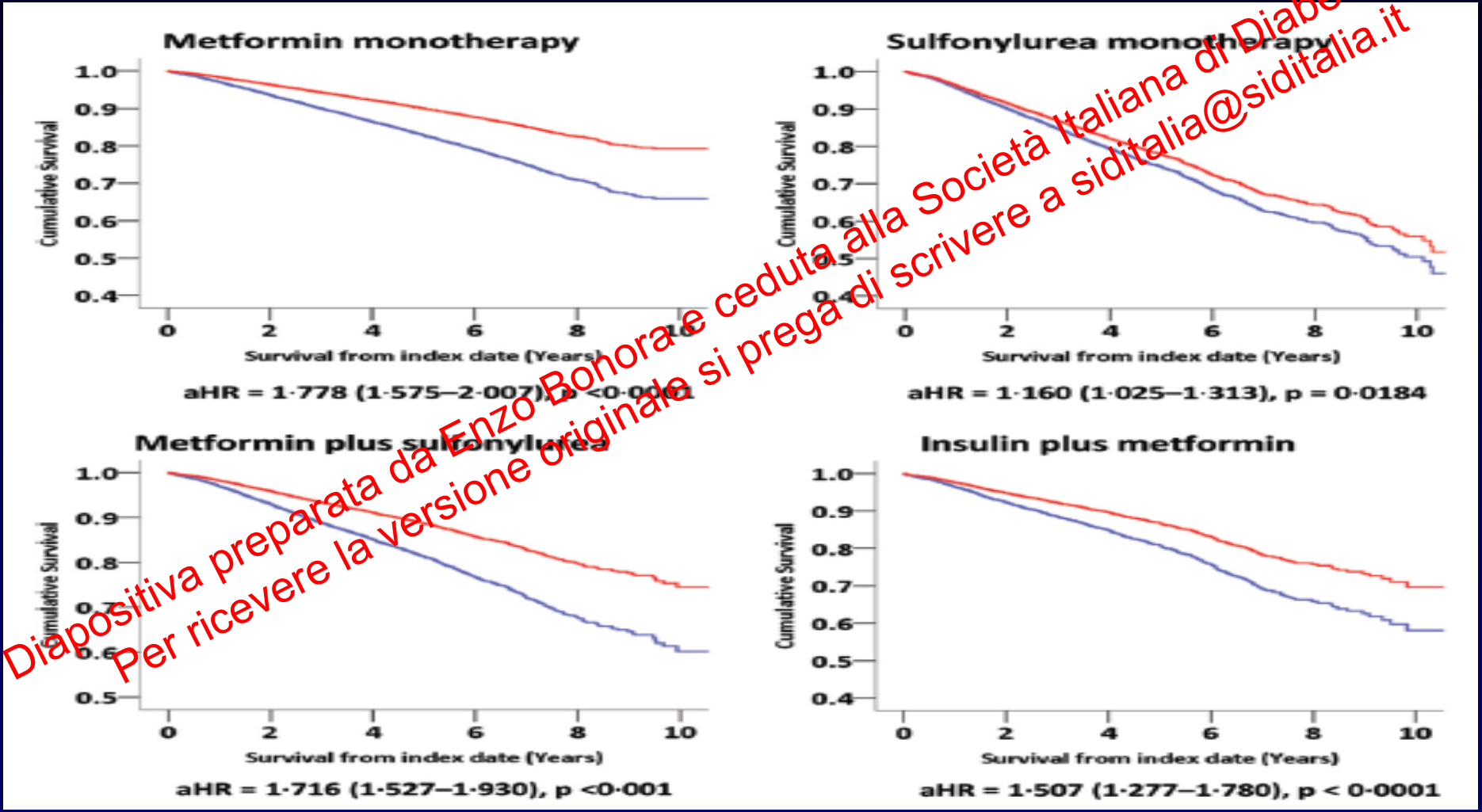
Currie et al – JCEM 2013; 98: 228

Parameter	MACE aHR	95% CI		*P* Value	Cancer aHR	95% CI		*P* Value
Metformin monotherapy (referent)	1.000				1.000			
Sulfonylurea monotherapy	1.392	1.251	1.549	<.0001	1.097	1.004	1.199	.0410
Metformin + Sulfonylurea	1.095	0.982	1.221	.1035	0.956	0.877	1.043	.3120
Insulin monotherapy	1.736	1.541	2.092	<.0001	1.437	1.234	1.674	<.0001
Insulin + metformin	1.217	0.963	1.539	.1001	1.394	1.176	1.651	.0001
	Renal Complications				**Combined Microvascular**			
Metformin monotherapy (referent)	1.000				1.000			
Sulfonylurea monotherapy	2.632	2.198	3.151	<.0001	1.097	1.033	1.165	.0024
Metformin + sulfonylurea	1.389	1.122	1.720	.0026	1.214	1.153	1.279	<.0001
Insulin monotherapy	3.504	2.718	4.518	<.0001	1.363	1.240	1.498	<.0001
Insulin + metformin	1.667	1.091	2.547	.0182	1.326	1.196	1.470	<.0001

UK General Practice Research Database 2000-2010; n= 84,622

Association of various diabetes treatment with MACE in T2DM

Currie et al – JCEM 2013; 98: 228



UK General Practice Research Database 2000-2010; n= 84,622

Studi osservazionali, trattamento insulinico e rischio CVD – Quesito chiave

E’ l’insulina oppure è la condizione clinica che ha richiesto la terapia insulinica a causare l’evento CVD che è stato osservato?

In genere è difficile se non impossibile tener conto nell’analisi di tutti i fattori confondenti.

Rassicurazioni

Nel DCCT (T1DM) il trattamento insulinico intensivo ha ridotto non solo le complicanze microvascolari ma anche, nel lungo periodo, quelle macrovascolari.

Nello UKPDS il trattamento intensivo, spesso basato solo o anche su insulina, ha ridotto non solo le complicanze microvascolari ma anche, nel lungo periodo, quelle macrovascolari.

Negli studi ACCORD, ADVANCE e VADT il trattamento intensivo, spesso basato anche su insulina, non ha aumentato gli eventi cardiovascolari ma anzi, in alcuni sottogruppi (ACCORD) e a lungo termine (VADT) li ha ridotti.

E poi ci sono i risultati di ORIGIN.

Outcome Reduction with an Initial Glargine INtervention

ORIGIN investigators – NEJM June 2012

The Big Picture - ORIGIN

- A large international RCT in people with new or recently diagnosed diabetes, IFG or IGT & additional CV risk factors lasting > 6 years
- Assessed the effect of 2 independent therapies on serious CV outcomes in > 12,500 people:
  a) titrated basal insulin using insulin glargine
  b) 1 g of omega 3 FA

ORIGIN Research Questions

*In **high risk** people with IFG, IGT or early diabetes,*

a) does insulin replacement therapy targeting fasting normoglycemia (≤ 5.3 mM or 95 mg/dl) with insulin glargine, reduce CV outcomes more than standard approaches to dysglycemia?

b) does adding omega 3 FA reduce CV death?

Participants (Key Inclusion Criteria)

- **Age ≥ 50 yrs**
- **Dysglycemia**
  - *EITHER* IFG or IGT or new type 2 DM by OGTT
    [i.e. FPG ≥ 110 (6.1); or 2 Hr PG ≥ 140 (7.8)]
  - *OR* prior type 2 DM @ stable dose ≥ 10 wks & …
    - on no OADs + HbA1c < 9.0%
    - < half-max 1 OAD + HbA1c < 8.5%
    - ≥ half-max 1 OAD + HbA1c < 8.0%
- **High CV Risk**
  - *EITHER* Prior MI, stroke, revasc, angina + doc. ischemia
  - *OR* MA, proteinuria, LVH, 50% art. stenosis, ABI < 0.9

AND

AND

Major Outcomes: Glargine Trial

Primary

- CV death OR MI OR stroke (MACE)
- CV death OR MI OR stroke OR revasc OR CHF hospitalization

Secondary

- Microvascular composite

  (i.e. doubling of serum Cr, progression of albuminuria category, dialysis/renal transplant, laser Rx/vitrectomy for retinopathy)
- New type 2 diabetes (in those without baseline diabetes)
- All cause death

Baseline Characteristics

Mean Age = 63.5 yrs; Females = 35%

Characteristic	%
Smoking	12
Hypertension	80
Any Albuminuria	15
Previous CVD	59

Drug Use	%
Statin	54
ACE-I/ARB	69
Thiazide	19
Beta Blocker	53
Other BP Drug	41
Antiplatelet	69

Baseline Glycemia (N=12,537)

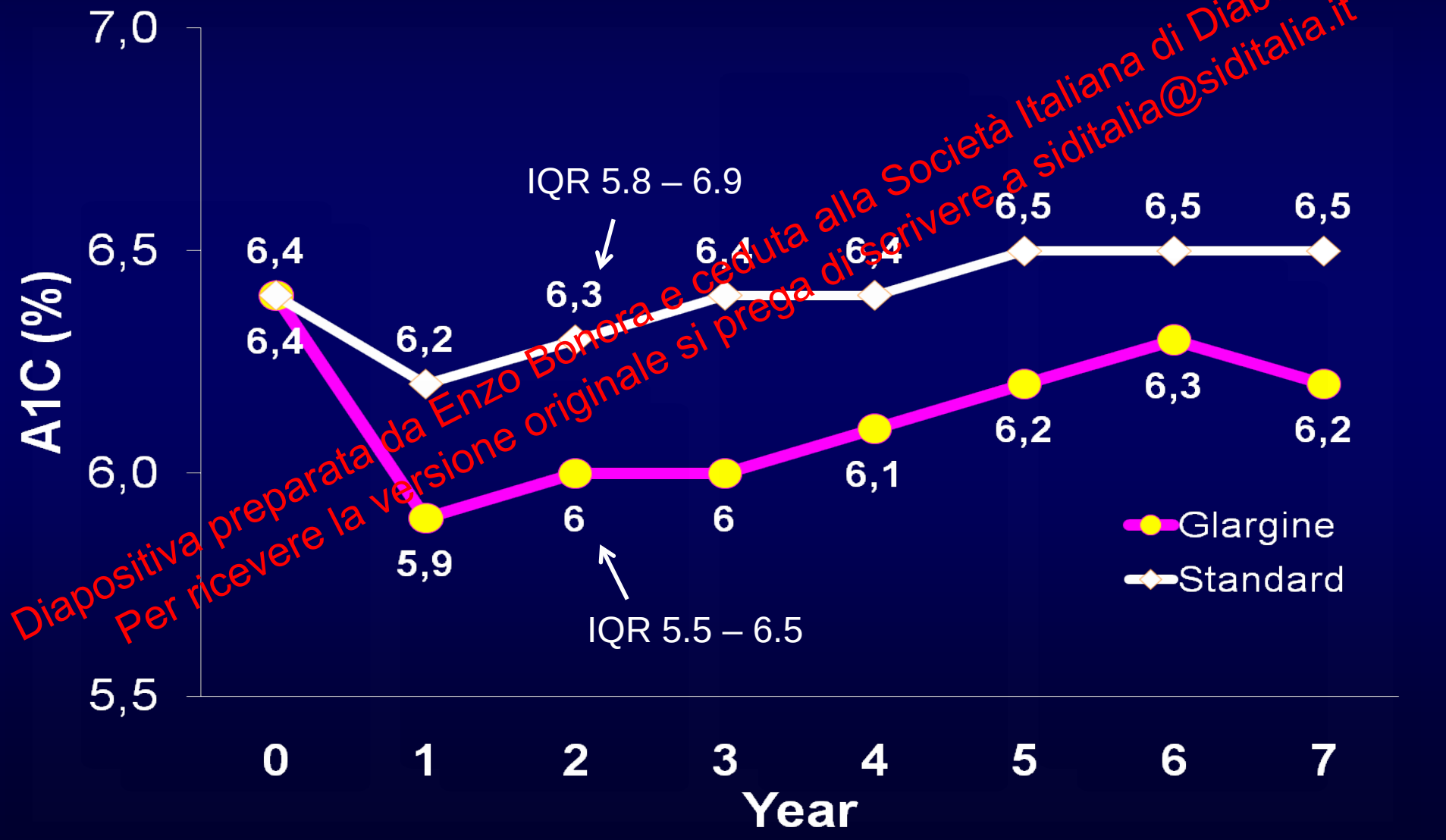
	N	%
Prior Diabetes (for ~ 5.4 y)	10321	82
New Diabetes	760	6
IFG &/or IGT	1452	12
No G Drug	5052	40
Metformin	3435	27
Sulfonylurea	3711	30
Other G Drug	351	3

Median FPG	125 mg/dl	6.9 mM
Median A1C	6.4%	

Baseline Characteristics (Mean Level)

	Conventional Units	SI Units
BMI (kg/m^2)	29.8	29.8
Blood Pressure (mm)	146/84	146/84
Cholesterol (mg/dl or mM)	190	4.9
LDL (mg/dl or mM)	112	2.90
HDL (mg/dl or mM)	46	1.19
TG (Median mg/dl or mM)	140	1.58

Median A1C Levels



Adherence to Insulin Glargine

in 6264 Allocated to Insulin

	Permanently Stopped During the Trial (%)
N stopped drug	19
Reason for Stopping	
Refusal	90
Hypoglycemia	4
Weight Gain	0.3
Hyperglycemia	0.3
Other	5

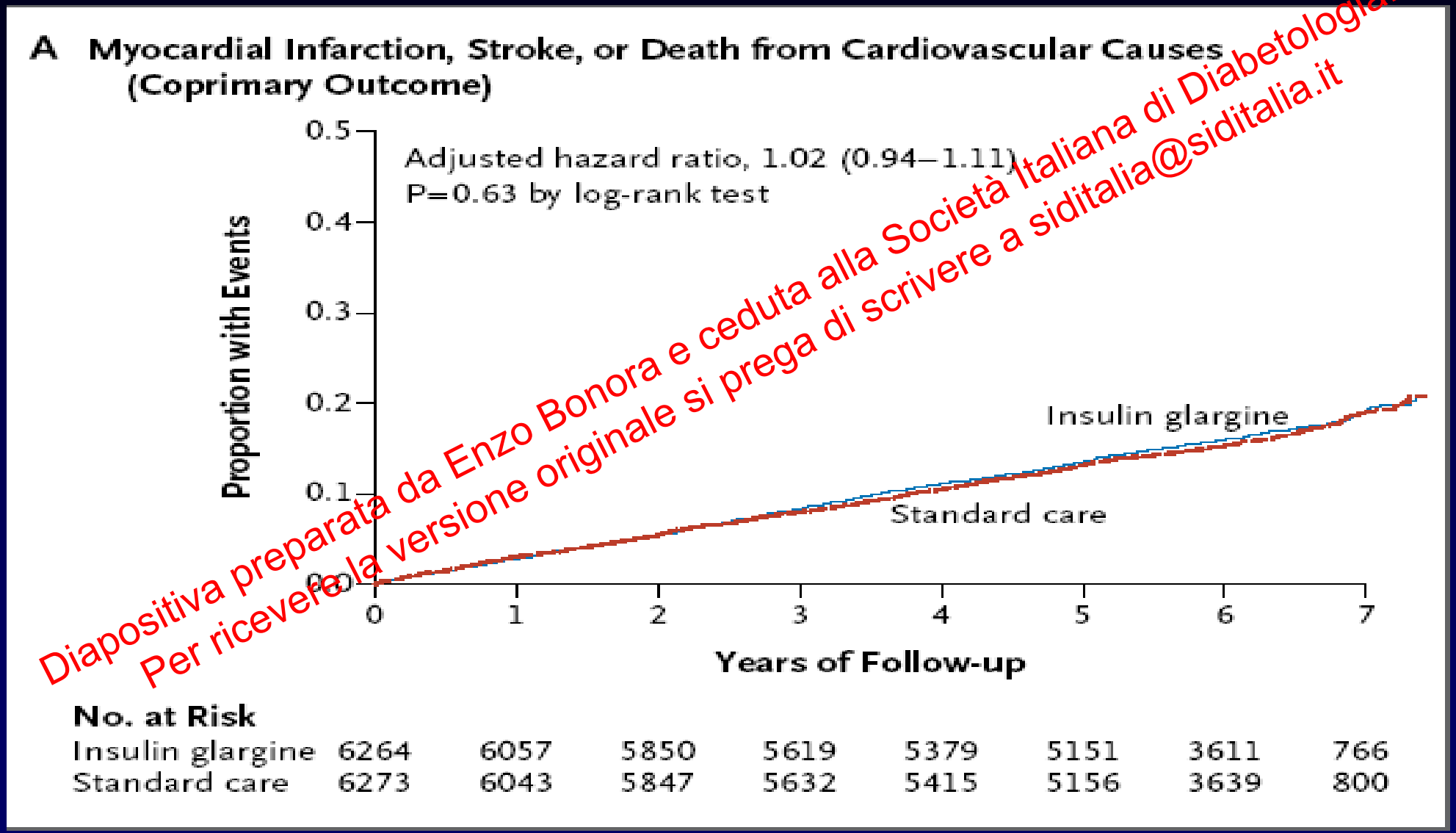
Drug Use at Study End

Before Stopping Insulin in People without Diabetes

	Insulin Glargine	Standard Care	P
No Oral Agents (%)	35	19	<0.001
1 Oral Agents (%)	51	39	<0.001
2 Oral Agents (%)	12	28	<0.001
≥ 3 Oral Agents (%)	3	14	<0.001
Rapid insulin (%)	2	5	<0.001
Any insulin (%)	80	11	<0.001
Metformin (%)	47	60	<0.001
Sulfonylurea (%)	25	47	<0.001

ORIGIN – Primary outcome

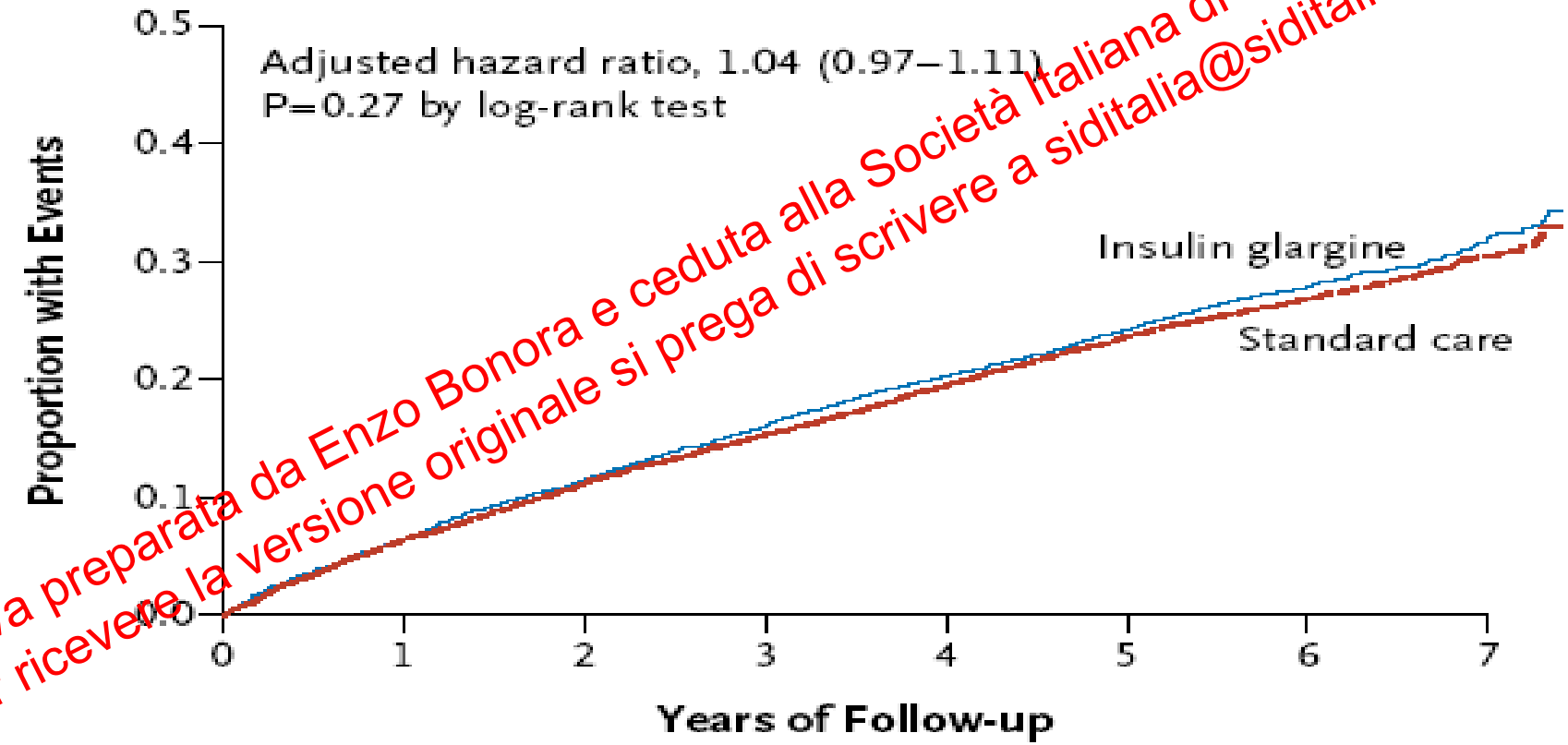
ORIGIN investigators – NEJM June 2012



ORIGIN – MACE Plus Plus

ORIGIN investigators – NEJM June 2012

B Coprimary Outcome plus Revascularization or Hospitalization for Congestive Heart Failure

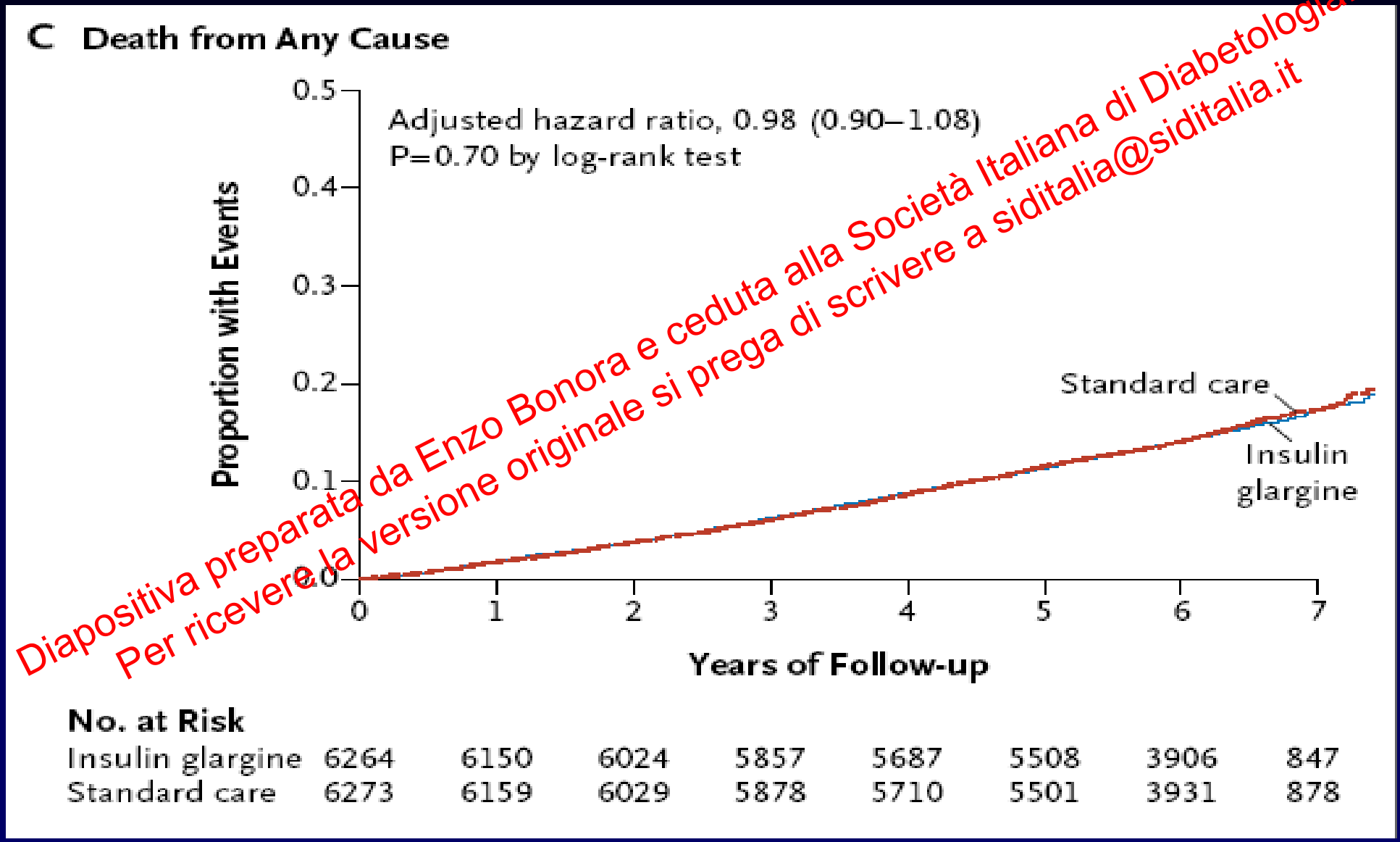


No. at Risk

Insulin glargine	6264	5827	5474	5153	4835	4523	3076	631
Standard care	6273	5833	5493	5186	4880	4555	3142	663

ORIGIN – Death from Any Cause

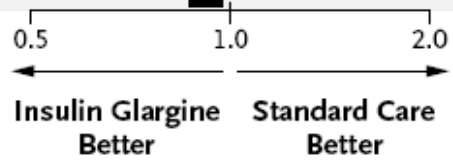
ORIGIN investigators – NEJM June 2012



ORIGIN – Primary and secondary outcomes

ORIGIN investigators – NEJM June 2012

Outcome	Insulin Glargine (N=6264) no. (%)	Insulin Glargine (N=6264) no./100 patient-yr	Standard Care (N=6273) no. (%)	Standard Care (N=6273) no./100 patient-yr	Hazard Ratio (95% CI)	P Value
First coprimary outcome	1041 (16.6)	2.94	1013 (16.1)	2.85	1.02 (0.94–1.11)	0.63
Second coprimary outcome	1792 (28.6)	5.52	1727 (27.5)	5.28	1.04 (0.97–1.11)	0.27
Microvascular outcomes	1323 (21.1)	3.87	1363 (21.7)	3.99	0.97 (0.90–1.05)	0.43
Total mortality	951 (15.2)	2.57	965 (15.4)	2.60	0.98 (0.90–1.08)	0.70
Total myocardial infarctions	336 (5.4)	0.93	326 (5.2)	0.90	1.02 (0.88–1.19)	0.75
Total strokes	331 (5.3)	0.91	319 (5.1)	0.88	1.03 (0.89–1.21)	0.69
Death from cardiovascular causes	580 (9.3)	1.57	576 (9.2)	1.55	1.00 (0.89–1.13)	0.98
Hospitalization for congestive heart failure	310 (4.9)	0.85	353 (5.5)	0.95	0.90 (0.77–1.05)	0.16
Revascularization	908 (14.5)	2.69	860 (13.7)	2.52	1.06 (0.96–1.16)	0.24
Angina	709 (11.3)	2.07	743 (11.8)	2.17	0.95 (0.85–1.05)	0.29
Unstable	238 (3.8)	0.66	261 (4.2)	0.72	0.91 (0.76–1.08)	0.28
New	100 (1.6)	0.27	138 (2.2)	0.38	0.72 (0.56–0.93)	0.01
Worsening	455 (7.3)	1.29	446 (7.1)	1.26	1.02 (0.89–1.16)	0.80
Limb or digit amputation	47 (0.8)	0.13	53 (0.8)	0.14	0.89 (0.60–1.31)	0.55
Cardiovascular hospitalization	2081 (33.2)	6.98	2071 (33.0)	6.91	1.00 (0.94–1.07)	0.90
Noncardiovascular hospitalization	2339 (37.3)	7.90	2349 (37.4)	7.93	0.99 (0.94–1.05)	0.85
Any cancer	476 (7.6)	1.32	477 (7.6)	1.32	1.00 (0.88–1.13)	0.97
Death from cancer	189 (3.0)	0.51	201 (3.2)	0.54	0.94 (0.77–1.15)	0.52



ORIGIN – Severe hypoglycemia

ORIGIN investigators – NEJM June 2012

Table 3. Incidence of a First Episode of Severe Hypoglycemia.

Variable	Insulin Glargine (N=6264)	Standard Care (N=6273)	P Value
Severe hypoglycemia*			
Participants with ≥1 episode — no. (no./100 person-yr)	359 (1.00)	113 (0.31)	<0.001
Total episodes during follow-up — no.	457	134	
Confirmed nonsevere symptomatic hypoglycemia†			
Participants with ≥1 episode — no. (no./100 person-yr)	2614 (9.83)	904 (2.68)	<0.001
Episodes/yr in participants with ≥1 episode — median (interquartile range)	0.5 (0.2–1.4)	0.3 (0.2–0.8)	<0.001
Participants with no confirmed episodes during follow-up — no. (%)	3650 (58.3)	5369 (85.6)	<0.001
Any nonsevere symptomatic hypoglycemia			
Participants with ≥1 episode — no. (no./100 person-yr)	3575 (16.72)	1580 (5.16)	<0.001
Episodes/yr in participants with ≥1 episode — median (interquartile range)	1.1 (0.4–3.1)	0.5 (0.2–1.3)	<0.001
Participants with no episodes during follow-up — no. (%)	2689 (42.9)	4693 (74.8)	<0.001

Conclusione da ORIGIN

1. Bicchiere mezzo vuoto: l'uso precoce dell'insulina nel diabete tipo 2 non determina benefici CV (nonostante determini un compenso glicemico lievemente migliore)

2. Bicchiere mezzo pieno: l'uso precoce dell'insulina nel diabete tipo 2 non determina malefici CV (nonostante un maggiore numero di ipoglicemie)

DEVOTE

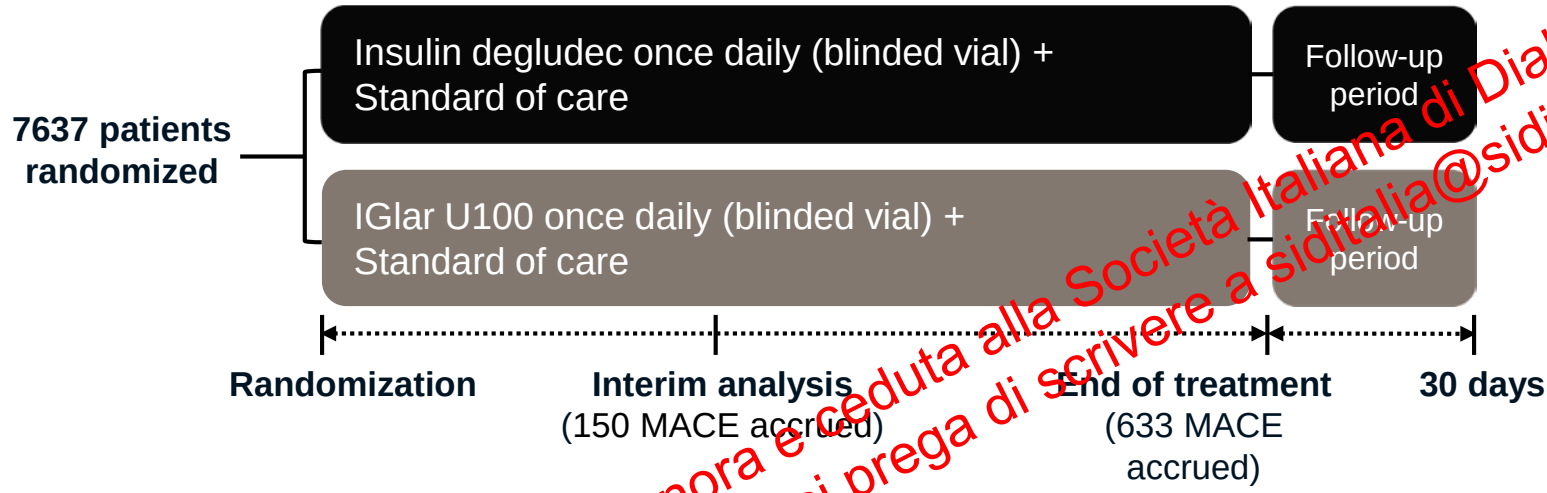
Degludec Cardiovascular Outcomes Trial

Comparing Cardiovascular Safety of Insulin Degludec versus Insulin Glargine in Patients with Type 2 Diabetes at High Risk of Cardiovascular Events

DEVOTE
DEGLUDEC CARDIOVASCULAR OUTCOMES TRIAL

Presented at the American Diabetes Association 77th Scientific Sessions, Session 3-CT-SY22. June 12 2017, San Diego, CA, USA

DEVOTE: trial design



Primary endpoint	Time from randomization to first occurrence of a 3-point MACE: cardiovascular death*†, non-fatal myocardial infarction* or non-fatal stroke*
Secondary endpoints	• Rate of severe hypoglycemic episodes*‡ • Incidence of severe hypoglycemic episodes*‡

DEVOTE
DEGLUDEC CARDIOVASCULAR OUTCOMES TRIAL

*Confirmed by the Event Adjudication Committee; †cardiovascular death includes undetermined cause of death; ‡severe defined as an episode requiring the assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions. BG concentrations may not be available during an event, but neurological recovery following the return of BG to normal is considered sufficient evidence that the event was induced by a low BG concentration
BG, blood glucose; MACE, major adverse cardiovascular event

Presented at the American Diabetes Association 77th Scientific Sessions, Session 3-CT-SY22. June 12 2017, San Diego, CA, USA

Key inclusion criteria: cardiovascular profile

Type 2 diabetes

High cardiovascular risk profile

- cardiovascular or chronic kidney disease and aged ≥50

OR

- risk factors for cardiovascular disease and aged ≥60

Current treatment with ≥1 oral or injectable antidiabetic agent(s)

HbA_{1c} ≥7.0%

OR

HbA_{1c} <7.0% and basal insulin treatment ≥20 U/day

DEVOTE
DEGLUDEC CARDIOVASCULAR OUTCOMES TRIAL

U, units

Presented at the American Diabetes Association 77th Scientific Sessions, Session 3-CT-SY22. June 12 2017, San Diego, CA, USA

Baseline characteristics

Parameter	Insulin degludec	IGlar U100
Total number of patients, n	3818	3819
Age, years*	64.9	65.0
Sex, Male, %	62.8	62.4
Duration of diabetes, years*	16.6	16.2
CV risk profile		
Established CV or CKD and age ≥50 years, %	85.5	84.9
With CV risk factors and age ≥60 years, %	14.1	14.8
BMI, kg/m^2*	33.6	33.6
HbA_{1c}, %*	8.4	8.4
FPG, mg/dL* [mmol/L]*	169.8 [9.4]	173.5 [9.6]

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DEGLUDEC CARDIOVASCULAR OUTCOMES TRIAL

*Mean value. HbA_{1c} and FPG measured at randomization. All other parameters measured at the screening visit
BMI, body mass index; CKD, chronic kidney disease; CV, cardiovascular; FPG, fasting plasma glucose; IGlar U100, insulin glargine U100

Presented at the American Diabetes Association 77th Scientific Sessions, Session 3-CT-SY22. June 12 2017, San Diego, CA, USA

Baseline medications

Parameter	Insulin degludec	IGlar U100
Total number of patients, n	3818	3819
Antihyperglycemic treatment (excluding insulins), %		
Metformin	60.1	59.4
Sulfonylurea	29.3	29.1
Dipeptidyl peptidase-4 inhibitors	11.1	12.6
Glucagon-like peptide-1 receptor agonists	7.9	8.0
Thiazolidinedione	3.8	3.2
Sodium-dependent glucose transporter-2 inhibitors	2.1	2.3
Alpha-glucosidase inhibitors	1.7	1.8
Others	1.3	1.8
Insulins, %		
Any insulin	**84.2**	**83.7**
Basal insulin only	38.1	37.7
Basal–bolus insulin (including bolus-only and pre-mix)	46.1	46.0
Cardiovascular medications, %		
Antihypertensive therapy*	93.2	93.0
Lipid-modifying medications*	82.4	81.9
Platelet aggregation inhibitors*	72.0	71.8
Anti-thrombotic medication*	8.1	7.6

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DEGLUDEC CARDIOVASCULAR OUTCOMES TRIAL

*Nine patients have missing initiation drug date; they are assumed to be on treatment at baseline

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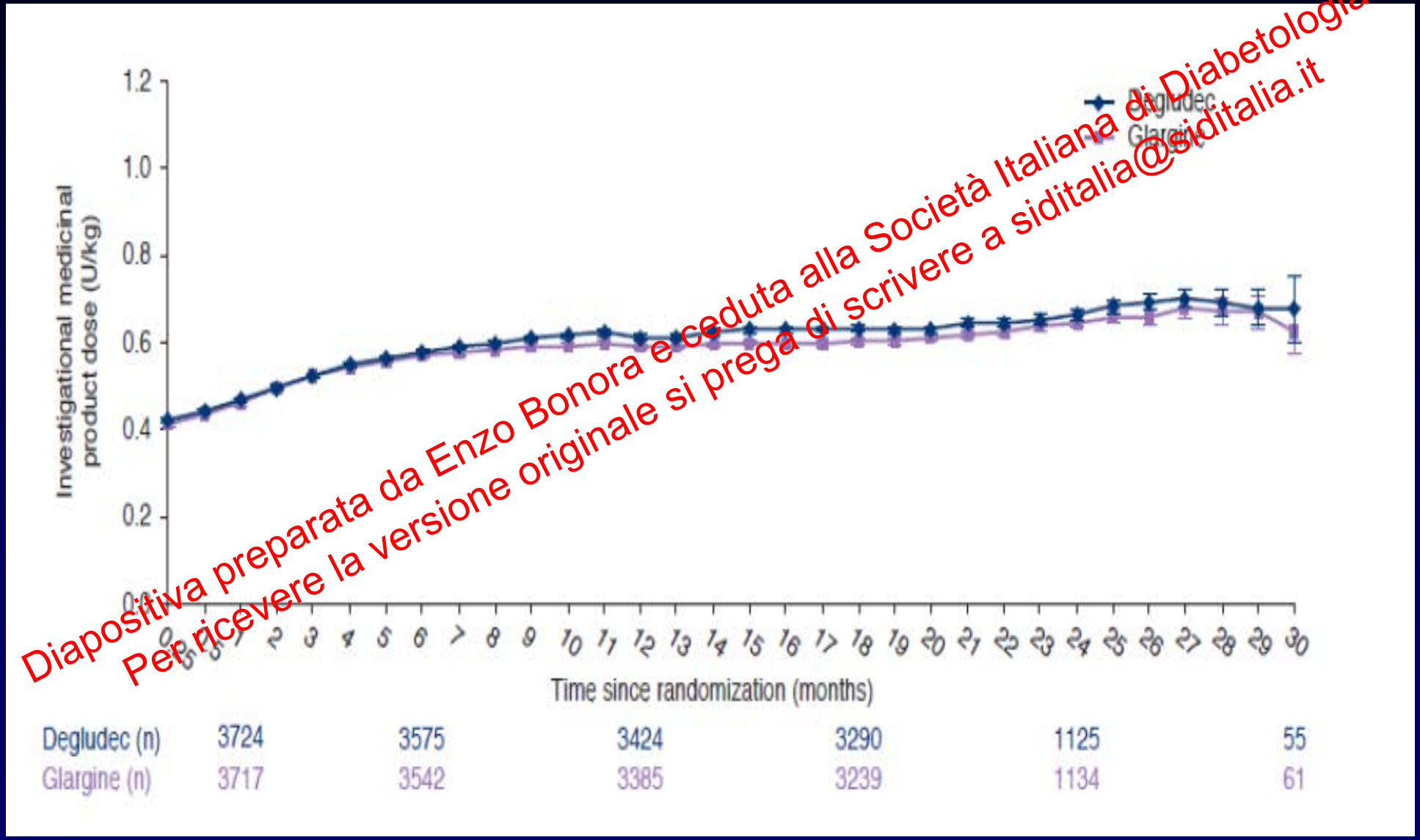
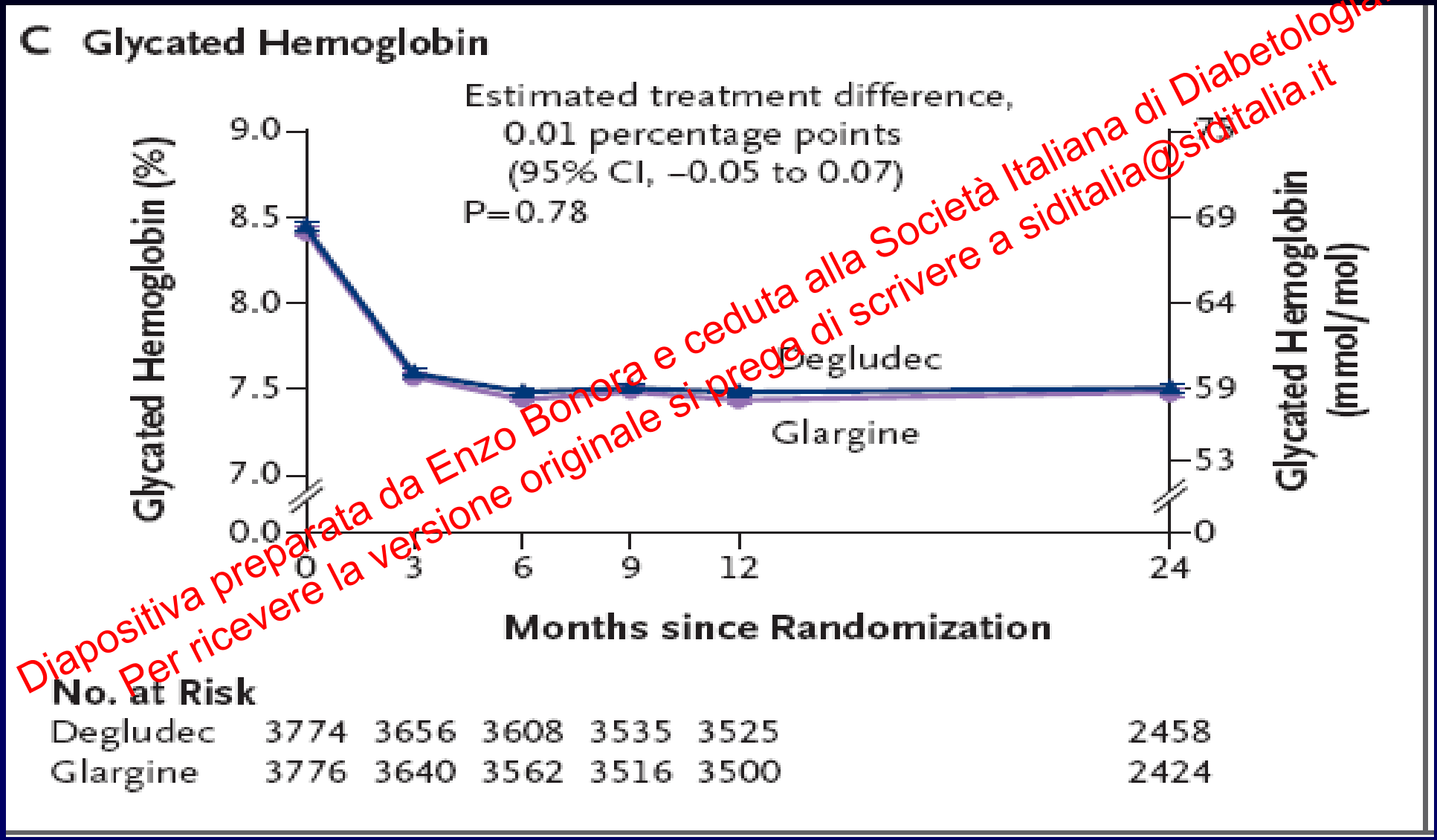
DEVOTE - Basal insulin dose

Marso et al – NEJM June 2017



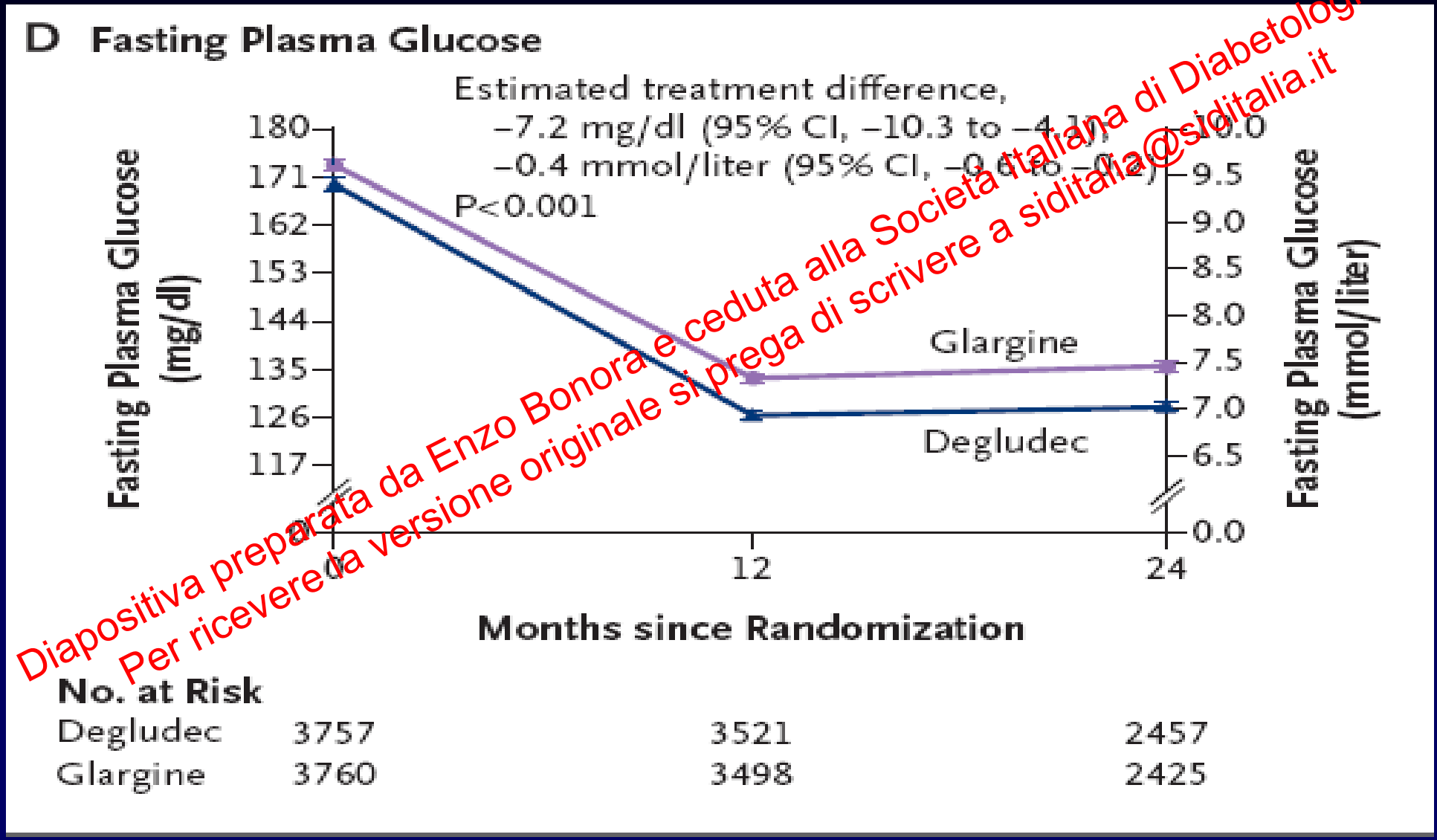
DEVOTE - Secondary Outcomes

Marso et al – NEJM June 2017



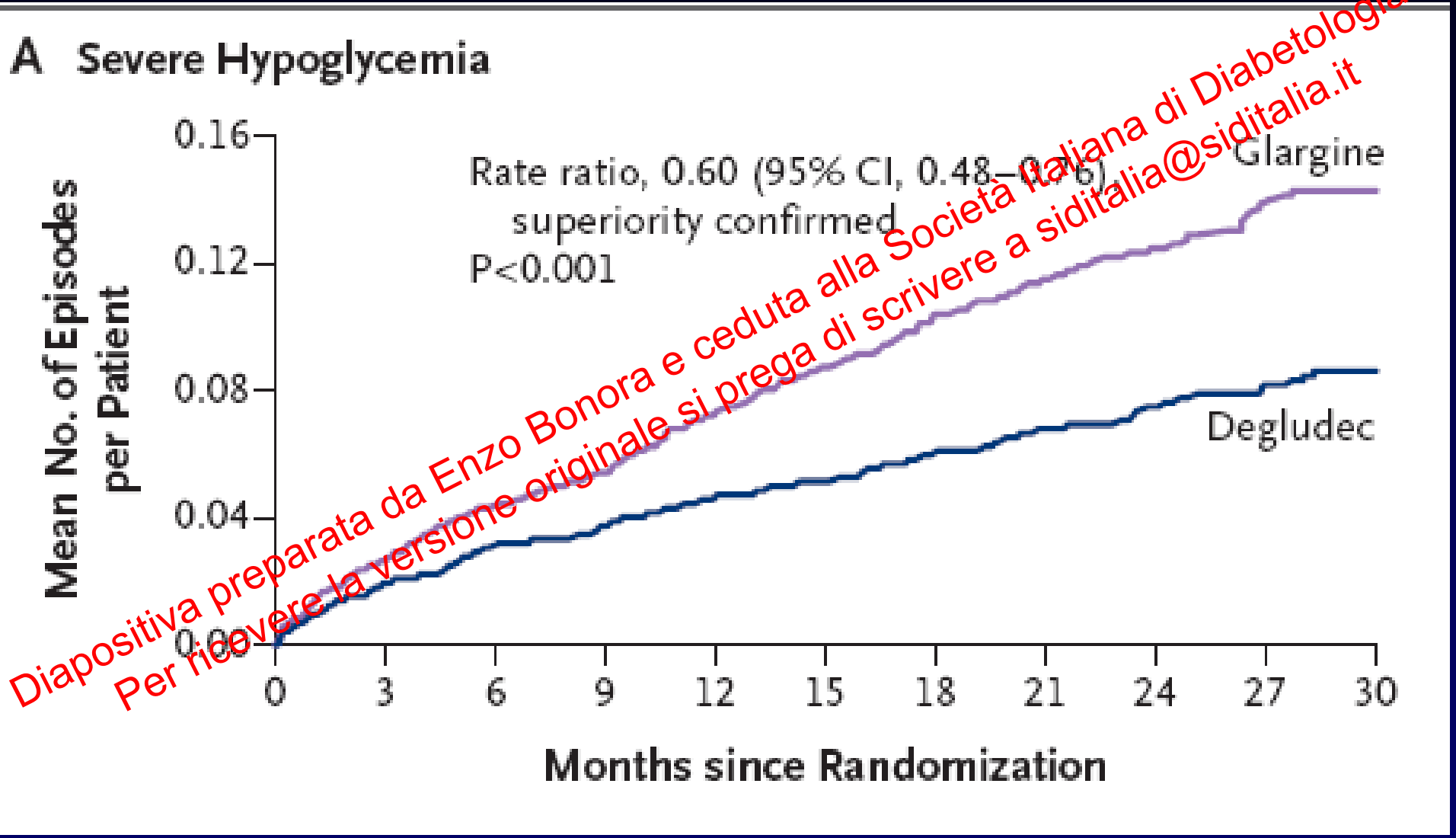
DEVOTE - Secondary Outcomes

Marso et al – NEJM June 2017



DEVOTE - Secondary Outcomes

Marso et al – NEJM June 2017



DEVOTE - Secondary Outcomes

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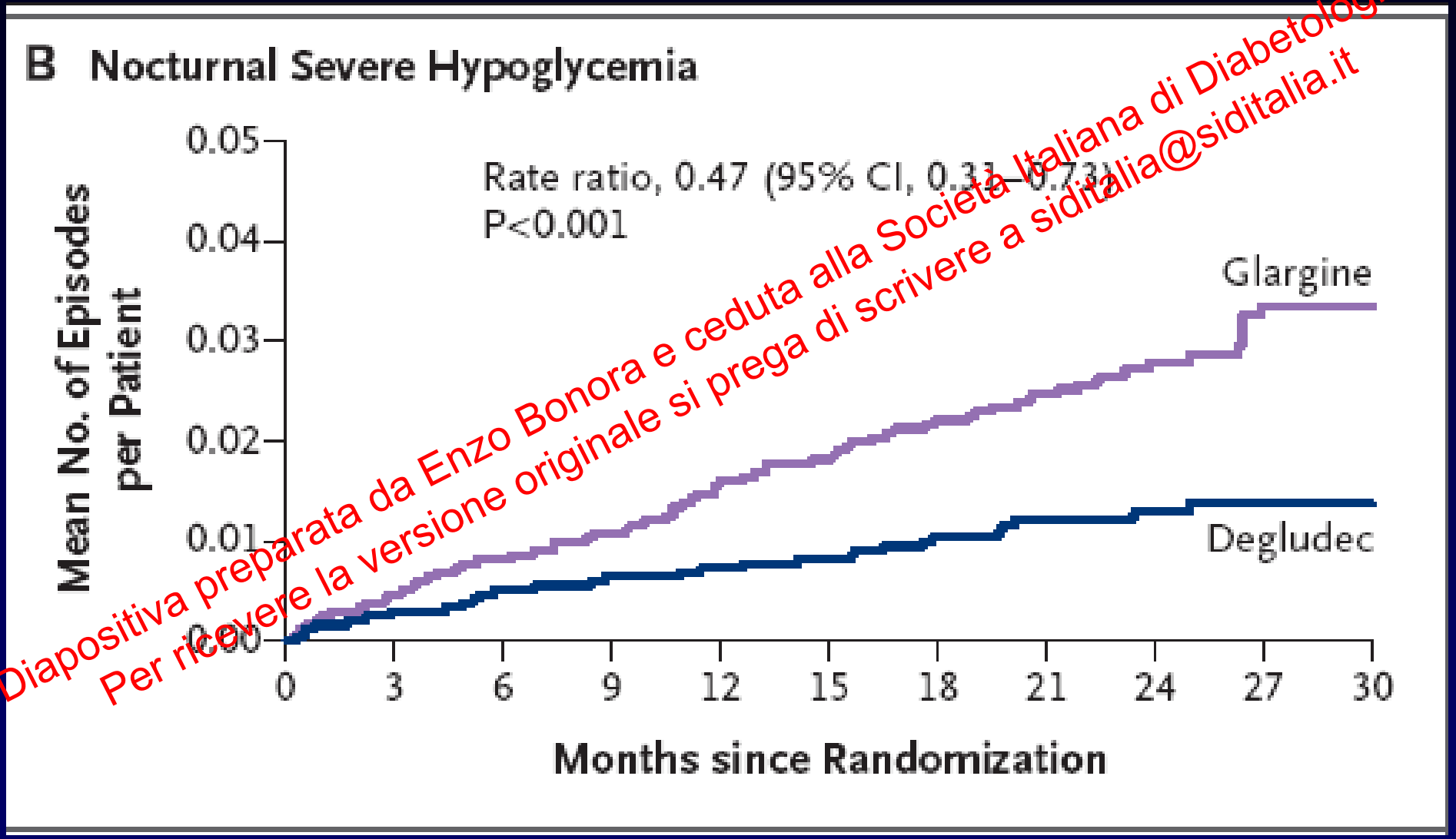

DEVOTE - Primary Composite Outcome

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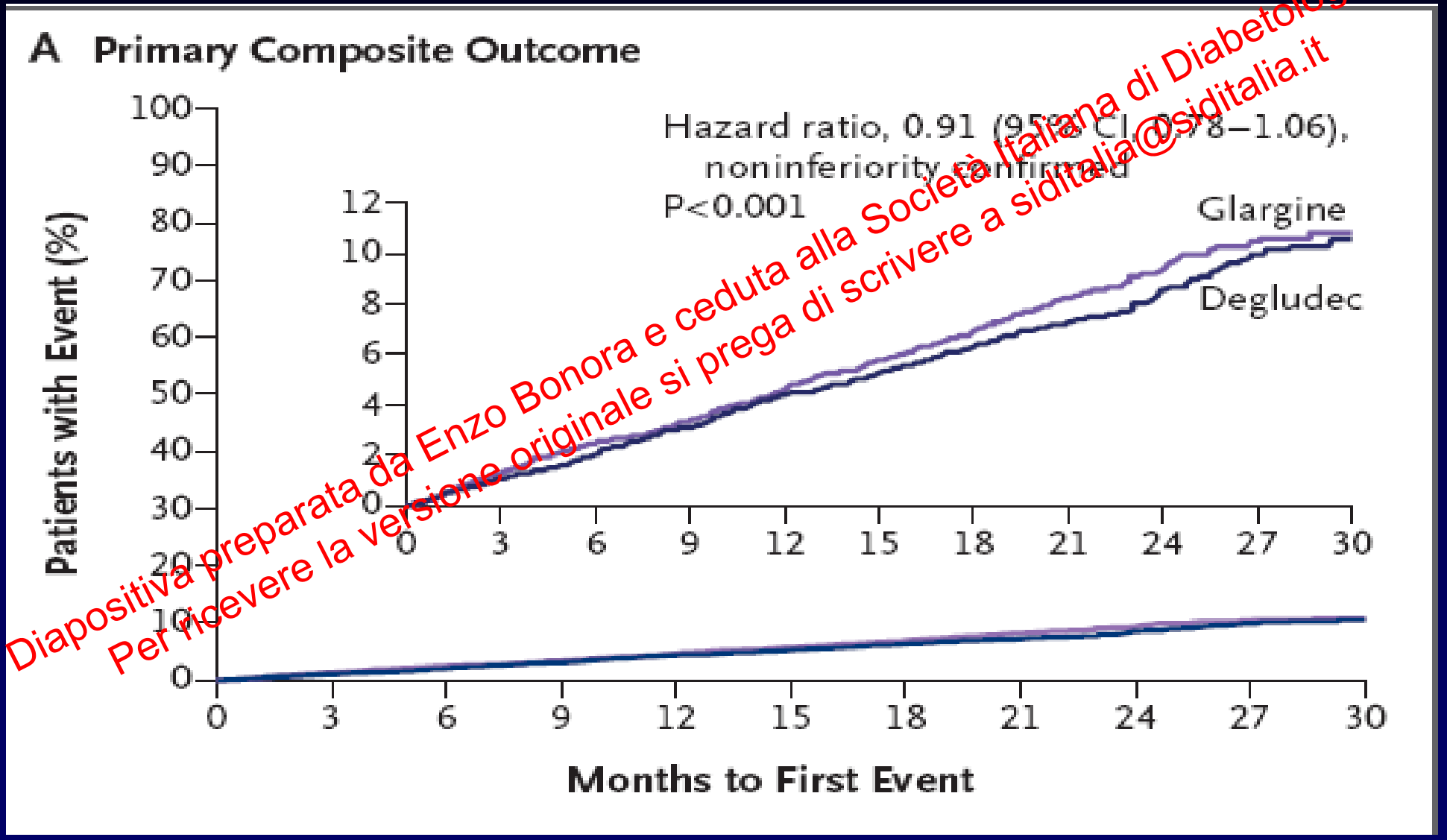

DEVOTE - Primary Outcomes

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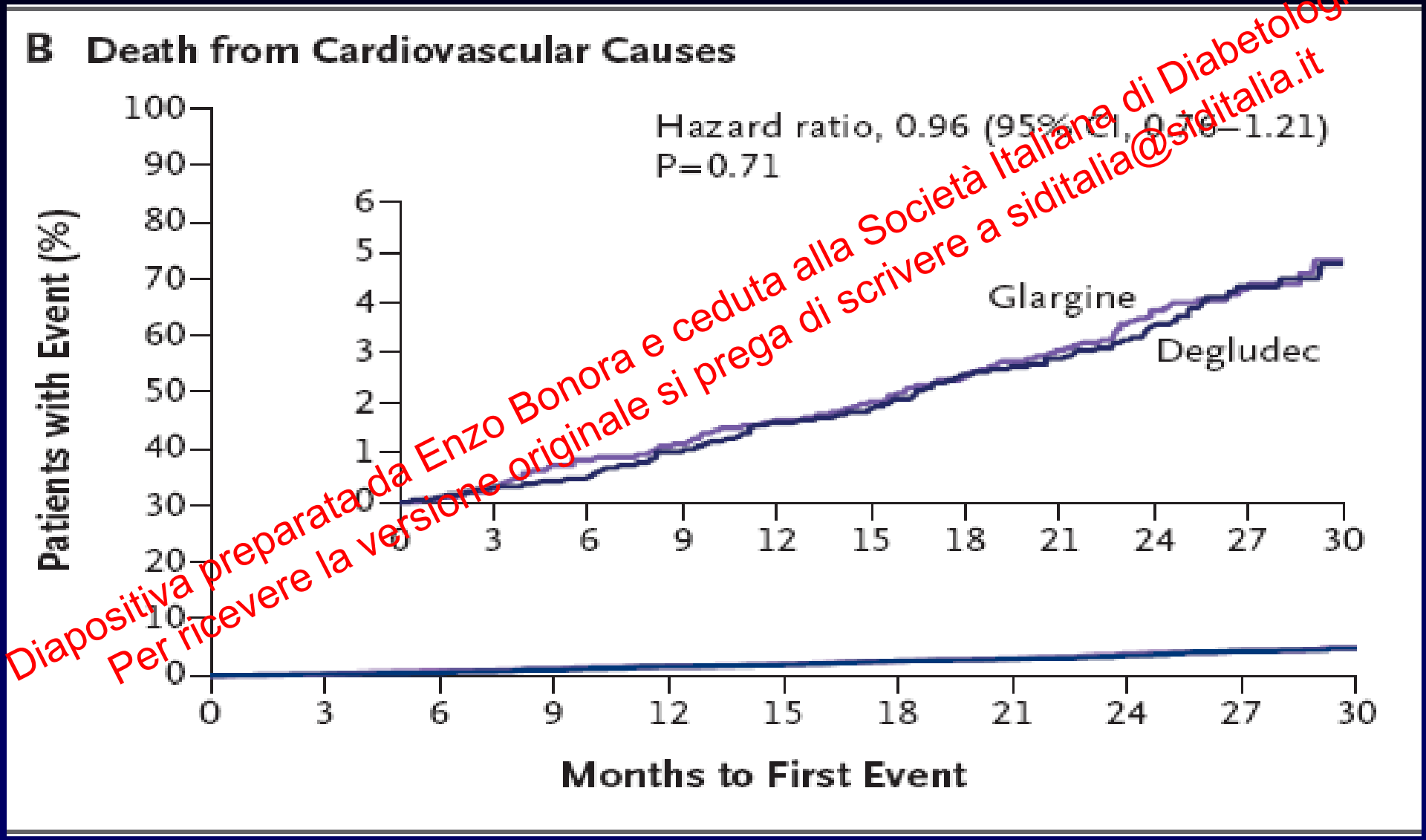

DEVOTE - Primary Outcomes

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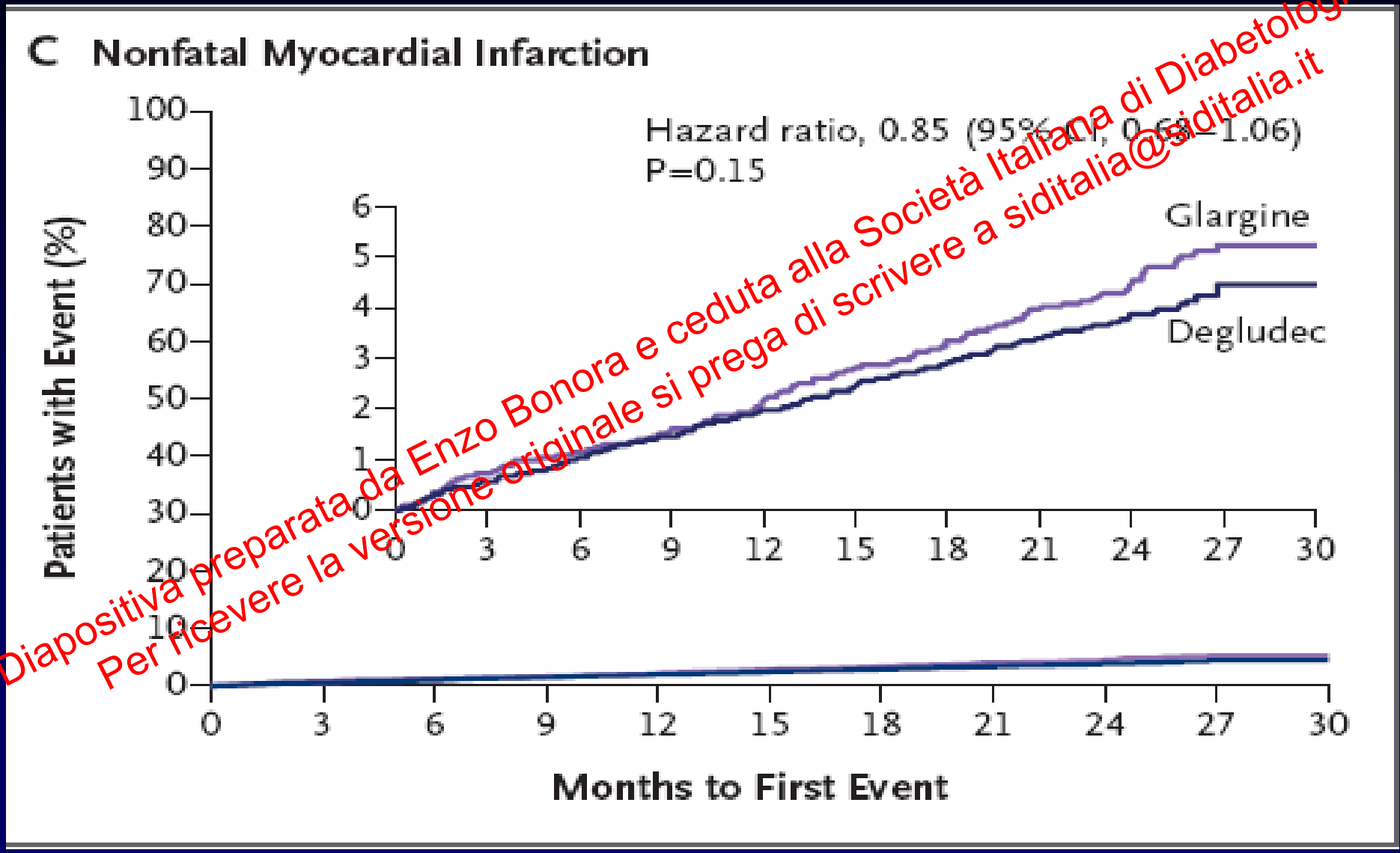

DEVOTE - Primary Outcomes

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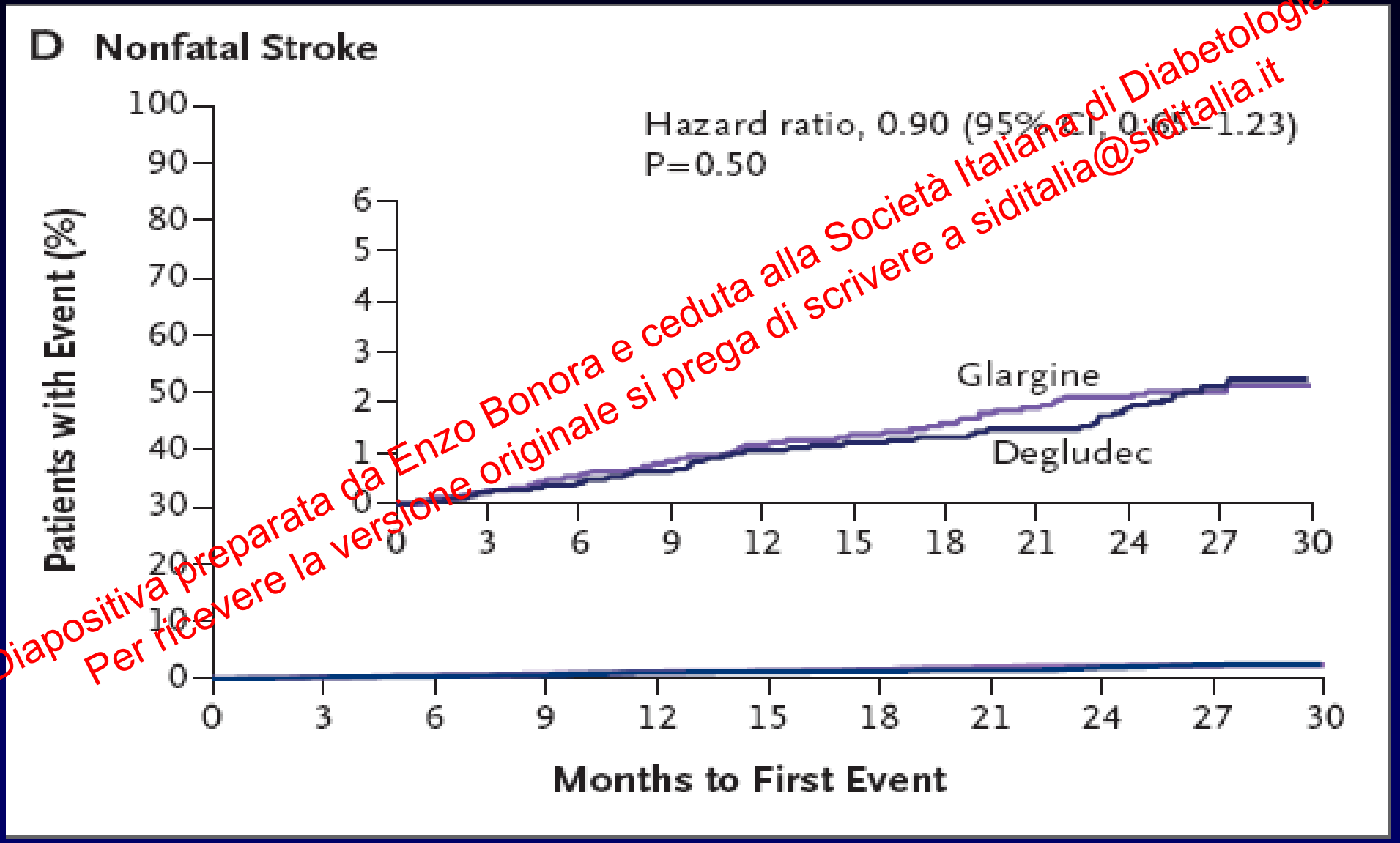

DEVOTE - Primary Outcomes

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Table 1. Primary Outcomes.*

Outcome	Degludec (N=3818)		Glargine (N=3819)		Hazard Ratio (95% CI)	P Value
	Patients	Event Rate	Patients	Event Rate		
	no. (%)	*no./100 patient-yr*	*no. (%)*	*no./100 patient-yr*		
Primary composite cardiovascular outcome	325 (8.5)	4.29	356 (9.3)	4.71	0.91 (0.78–1.06)	<0.001†
Expanded composite cardiovascular outcome‡	386 (10.1)	5.10	419 (11.0)	5.54	0.92 (0.80–1.05)	0.22
Component outcomes						
Death from any cause	202 (5.3)	2.67	221 (5.8)	2.92	0.91 (0.76–1.11)	0.35
Noncardiovascular death	66 (1.7)	0.87	79 (2.1)	1.05	0.84 (0.60–1.16)	0.28
Cardiovascular death	136 (3.6)	1.80	142 (3.7)	1.88	0.96 (0.76–1.21)	0.71
Cardiovascular death excluding undetermined cause of death	97 (2.5)	1.28	106 (2.8)	1.40	0.91 (0.69–1.20)	0.52
Nonfatal myocardial infarction	144 (3.8)	2.27	169 (4.4)	2.47	0.85 (0.68–1.06)	0.15
Nonfatal stroke	71 (1.9)	0.98	79 (2.1)	1.16	0.90 (0.65–1.23)	0.50
Unstable angina leading to hospitalization	71 (1.9)	1.04	74 (1.9)	1.10	0.95 (0.68–1.31)	0.74

DEVOTE Primary Outcomes Sensitivity analysis

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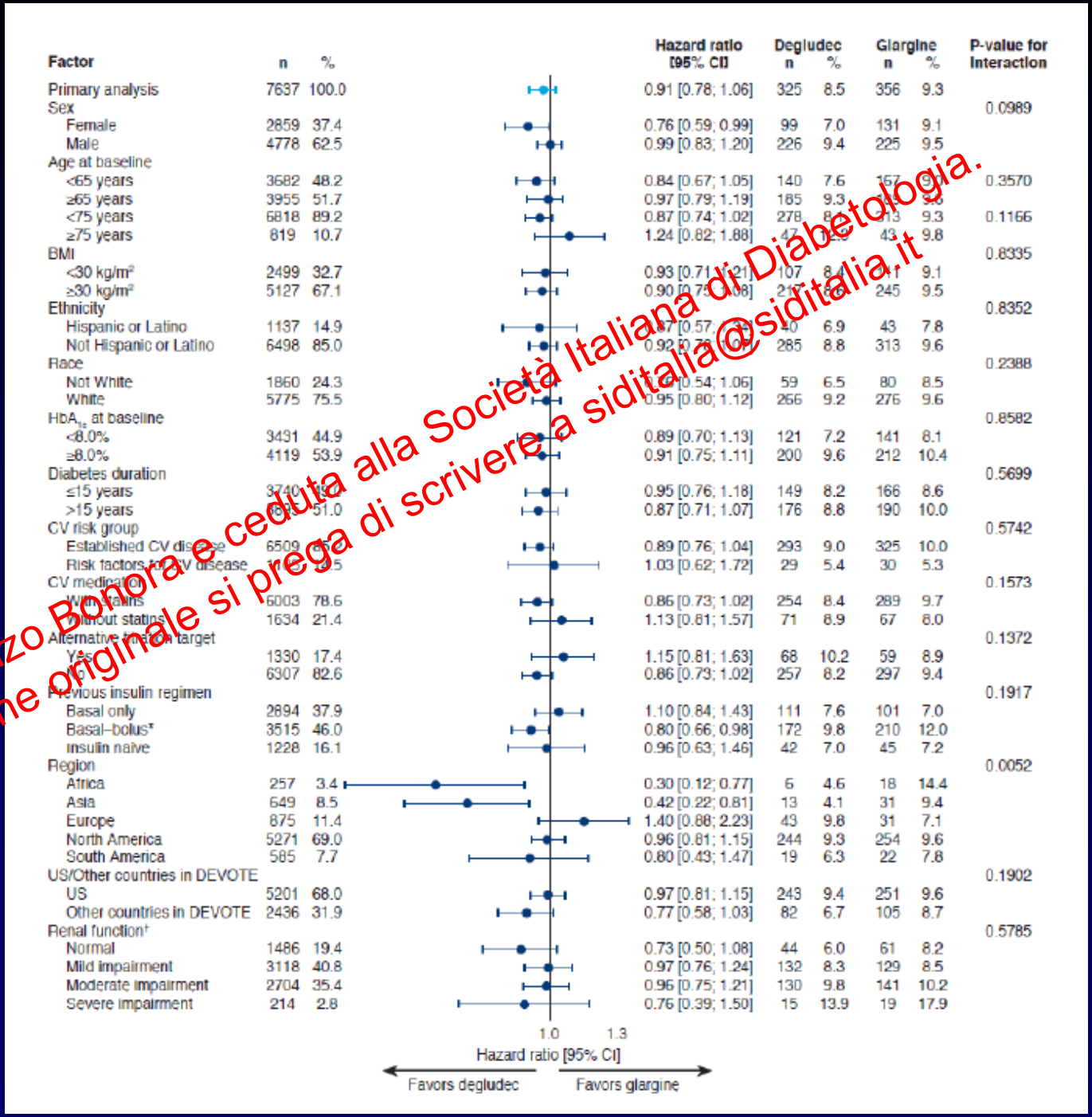

Factor	n	%	Hazard ratio [95% CI]	Degludec n	Degludec %	Glargine n	Glargine %	P-value for Interaction
Primary analysis	7637	100.0	0.91 [0.78; 1.06]	325	8.5	356	9.3	
Sex								0.0989
Female	2859	37.4	0.76 [0.59; 0.99]	99	7.0	131	9.1	
Male	4778	62.5	0.99 [0.83; 1.20]	226	9.4	225	9.5	
Age at baseline								
<65 years	3682	48.2	0.84 [0.67; 1.05]	140	7.6	167	9.0	0.3570
≥65 years	3955	51.7	0.97 [0.79; 1.19]	185	9.3	189	9.6	
<75 years	6818	89.2	0.87 [0.74; 1.02]	278	8.1	313	9.3	0.1166
≥75 years	819	10.7	1.24 [0.82; 1.88]	47	11.5	43	9.8	
BMI								0.8335
<30 kg/m²	2499	32.7	0.93 [0.71; 1.21]	107	8.4	111	9.1	
≥30 kg/m²	5127	67.1	0.90 [0.75; 1.08]	218	8.6	245	9.5	
Ethnicity								0.8352
Hispanic or Latino	1137	14.9	0.87 [0.57; 1.33]	40	6.9	43	7.8	
Not Hispanic or Latino	6498	85.0	0.92 [0.78; 1.09]	285	8.8	313	9.6	
Race								0.2388
Not White	1860	24.3	0.74 [0.54; 1.06]	59	6.5	80	8.5	
White	5775	75.5	0.95 [0.80; 1.12]	266	9.2	276	9.6	
HbA_{1c} at baseline								0.8582
<8.0%	3491	44.9	0.89 [0.70; 1.13]	121	7.2	141	8.1	
≥8.0%	4119	53.9	0.91 [0.75; 1.11]	200	9.6	212	10.4	
Diabetes duration								0.5699
≤15 years	3740	48.9	0.95 [0.76; 1.18]	149	8.2	166	8.6	
>15 years	3893	51.0	0.87 [0.71; 1.07]	176	8.8	190	10.0	
CV risk group								0.5742
Established CV disease	6509	85.2	0.89 [0.76; 1.04]	293	9.0	325	10.0	
Risk factors for CV disease	1128	14.8	1.03 [0.62; 1.72]	29	5.4	30	5.3	
CV medication								0.1573
With statins	6003	78.6	0.86 [0.73; 1.02]	254	8.4	289	9.7	
Without statins	1634	21.4	1.13 [0.81; 1.57]	71	8.9	67	8.0	
Alternative treatment target								0.1372
Yes	1330	17.4	1.15 [0.81; 1.63]	68	10.2	59	8.9	
No	6307	82.6	0.86 [0.73; 1.02]	257	8.2	297	9.4	
Previous insulin regimen								0.1917
Basal only	2894	37.9	1.10 [0.84; 1.43]	111	7.6	101	7.0	
Basal–bolus†	3515	46.0	0.80 [0.66; 0.98]	172	9.8	210	12.0	
Insulin naive	1228	16.1	0.96 [0.63; 1.46]	42	7.0	45	7.2	
Region								0.0052
Africa	257	3.4	0.30 [0.12; 0.77]	6	4.6	18	14.4	
Asia	649	8.5	0.42 [0.22; 0.81]	13	4.1	31	9.4	
Europe	875	11.4	1.40 [0.88; 2.23]	43	9.8	31	7.1	
North America	5271	69.0	0.96 [0.81; 1.15]	244	9.3	254	9.6	
South America	585	7.7	0.80 [0.43; 1.47]	19	6.3	22	7.8	
US/Other countries in DEVOTE								0.1902
US	5201	68.0	0.97 [0.81; 1.15]	243	9.4	251	9.6	
Other countries in DEVOTE	2436	31.9	0.77 [0.58; 1.03]	82	6.7	105	8.7	
Renal function†								0.5785
Normal	1486	19.4	0.73 [0.50; 1.08]	44	6.0	61	8.2	
Mild impairment	3118	40.8	0.97 [0.76; 1.24]	132	8.3	129	8.5	
Moderate impairment	2704	35.4	0.96 [0.75; 1.21]	130	9.8	141	10.2	
Severe impairment	214	2.8	0.76 [0.39; 1.50]	15	13.9	19	17.9	

Conclusione da DEVOTE

1. Rispetto a glargina (il precedente gold standard della terapia insulinica basale) degludec non mostra benefici né malefici CVD nel diabete tipo 2.

2. Rispetto a glargina il trattamento con degludec nel diabete tipo 2 riduce in maniera importante l'incidenza della ipoglicemia.

Conclusioni generali (1)

- Nel diabete tipo 1 il trattamento insulinico è necessario per evitare la morte.
- Nel LADA (prevalenza simile a quella del tipo 1) il trattamento insulinico fin dal momento della sua individuazione è un'opzione ragionevole che ad un certo punto diventa comunque indispensabile.
- In alcune forme di diabete secondario (es. pancreatopatia o CKD) o di altro tipo (es. severa insulino-resistenza) il trattamento insulinico è necessario oppure non ha valide alternative.
- Nel diabete tipo 2 il trattamento insulinico è talora necessario (in caso di deficit importante della secrezione) o inevitabile (impossibilità di ottenere un buon controllo con altri mezzi; controindicazioni all'uso di altri farmaci).

Conclusioni generali (2)

- Il trattamento insulinico non determina di per sé benefici né malefici di carattere cardiovascolare.
- Il trattamento insulinico non deve essere iniziato troppo presto e neppure troppo tardi. Il diabetologo deve saper scegliere il momento giusto.
- Long live INSULIN!!!