Terapia insulinica e rischio cardiovascolare

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Disclosures

Astrazeneca, Boheringher Ingelheim, Bristol Myers Squibb, Janssen, Eli Lilly, MSD, Novartis, Novo Nordisk, Sanofi, Takeda

Agenda

- Effetti dell'insulina su aterogenesi
- Ipoglicemia e rischio CV
- Che cosa ci dicono gli studi
  - studi osservazionali
  - studi di intervento
- Conclusioni

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  - effetti pro-aterogeni
  - effetti anti-aterogeni
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Exposure to hypo- and hyperglycemia in well-controlled T1DM patients as assessed by CGM

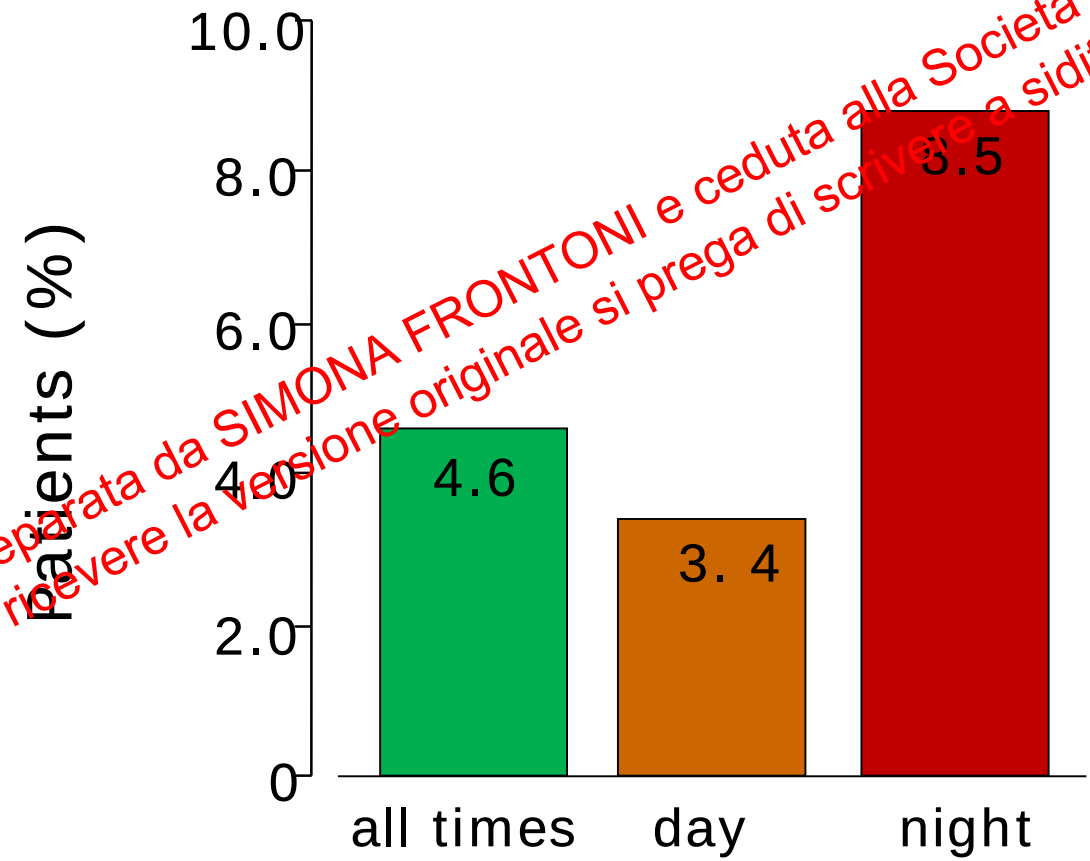
TABLE 1. GLYCEMIC EXPOSURE

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

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

Hypoglycemia in T2DM patients



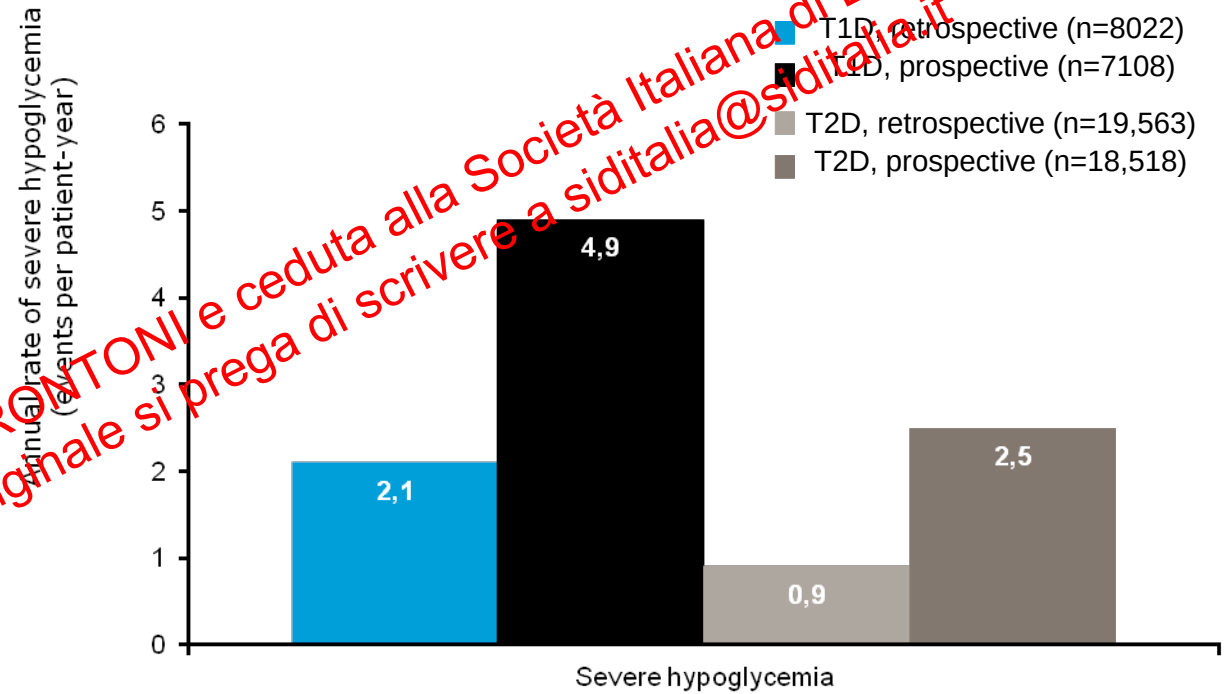
McNally et al, Diabetes Care 30: 1044, 2007

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

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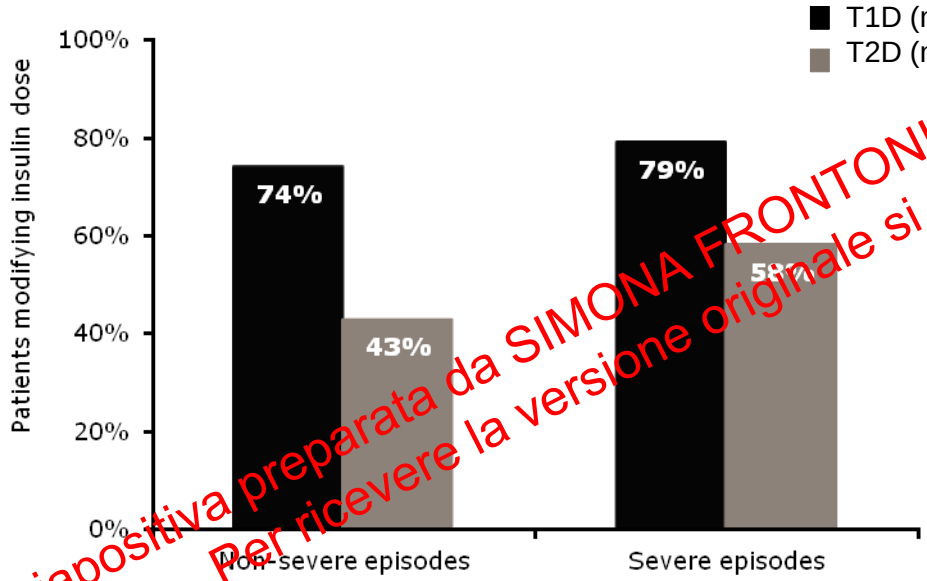
HAT, Hypoglycaemia Assessment Tool; T1D, type 1 diabetes
Khunti *et al. Diabetes Obes Metab* 2016;18:907–15; Khunti *et al.* Poster presented at the 10th International Diabetes Federation-Western Pacific Region Congress, 21–24 November 2014, Singapore

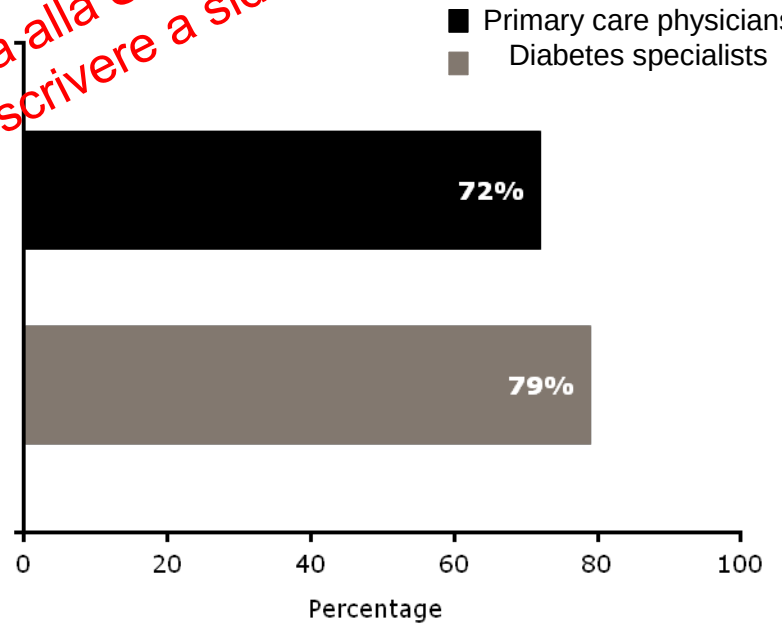
Presented at the American Diabetes Association 77th Scientific Sessions, Session 3-CT-SY22. June 12 2017, San Diego, CA, USA

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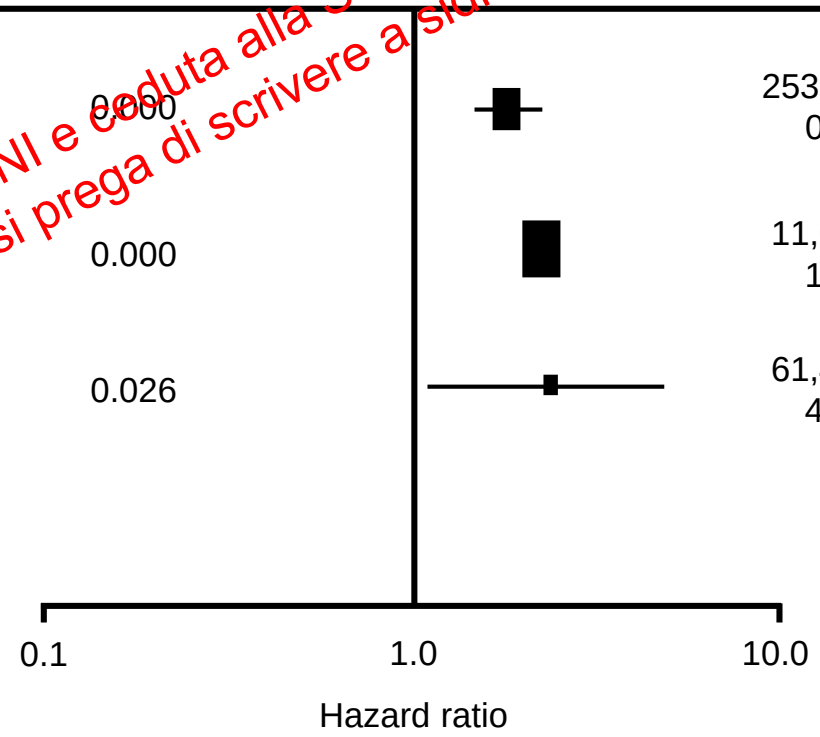
1. Leiter *et al. Can J Diabetes* 2005;29:186–92; 2. Peyrot *et al. Diabet Med* 2012;29:682–9, GAPP™ (A global internet survey of patient and physician beliefs regarding insulin therapy): n=1250 physicians

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

Systematic review: association of hypoglycemia with outcomes

	Hazard ratio [95% CI]	*p*-value	Number of patients
Total mortality	1.8 [1.5; 2.2]	0.000	253,390
Cardiovascular mortality	2.2 [2.0; 2.4]	0.000	11,011
Major cardiovascular event	2.3 [1.1; 5.0]	0.026	61,434



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

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Agenda

Sembra, pertanto, ragionevole concludere che è l'ipoglicemia e non l'insulina *per se* ad aumentare il rischio CV

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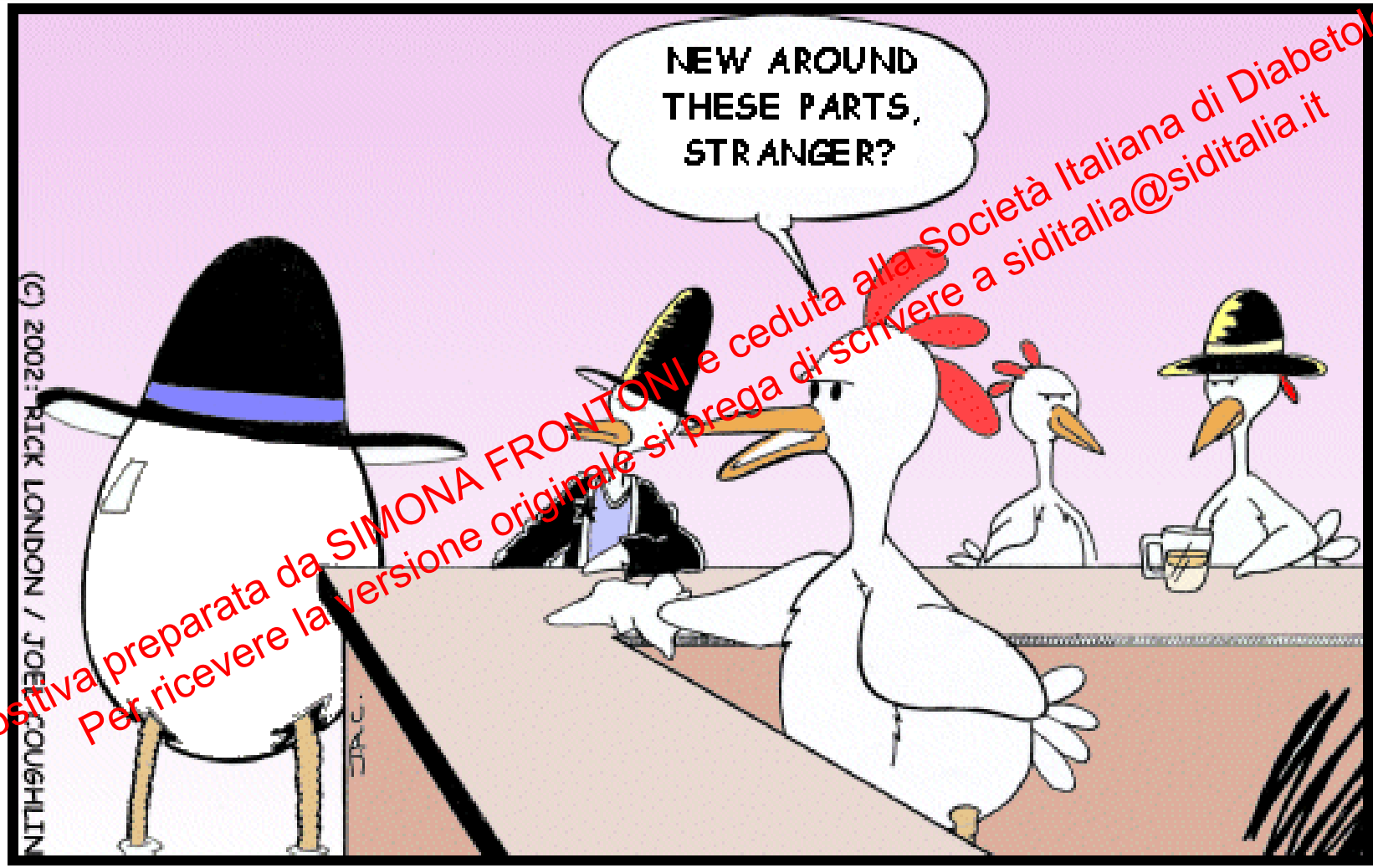
Association of various diabetes treatment with MACE and other endpoint in T2DM

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

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	1.441	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

Currie et al – JCEM 2013; 98: 228

Limiti degli studi osservazionali



AND YET THE QUESTION REMAINED:
"WHO CAME FIRST?"

Limiti degli studi osservazionali

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

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:
  - titrated basal insulin using insulin glargine
  - 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)

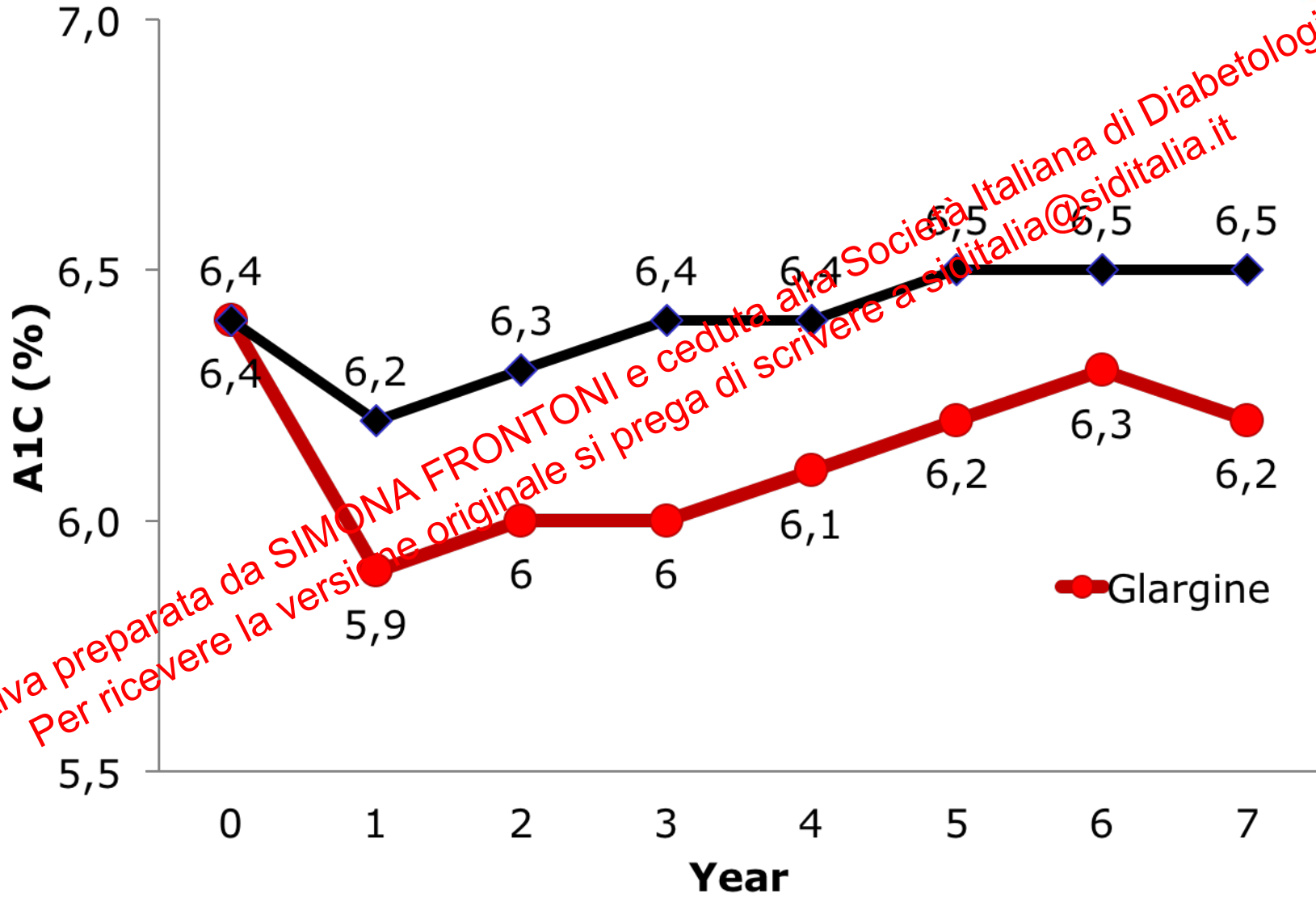
	N	%
Prior Diabetes (for ~ 5.4 y)	10321	82
New Diabetes	760	6
IFG &/or IGT	**1452**	**12**
No G Drug	5052	40
Metformin	3435	27
Sulfonylurea	3711	30
Other G Drug	351	3

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

Baseline Characteristics (Mean Level)

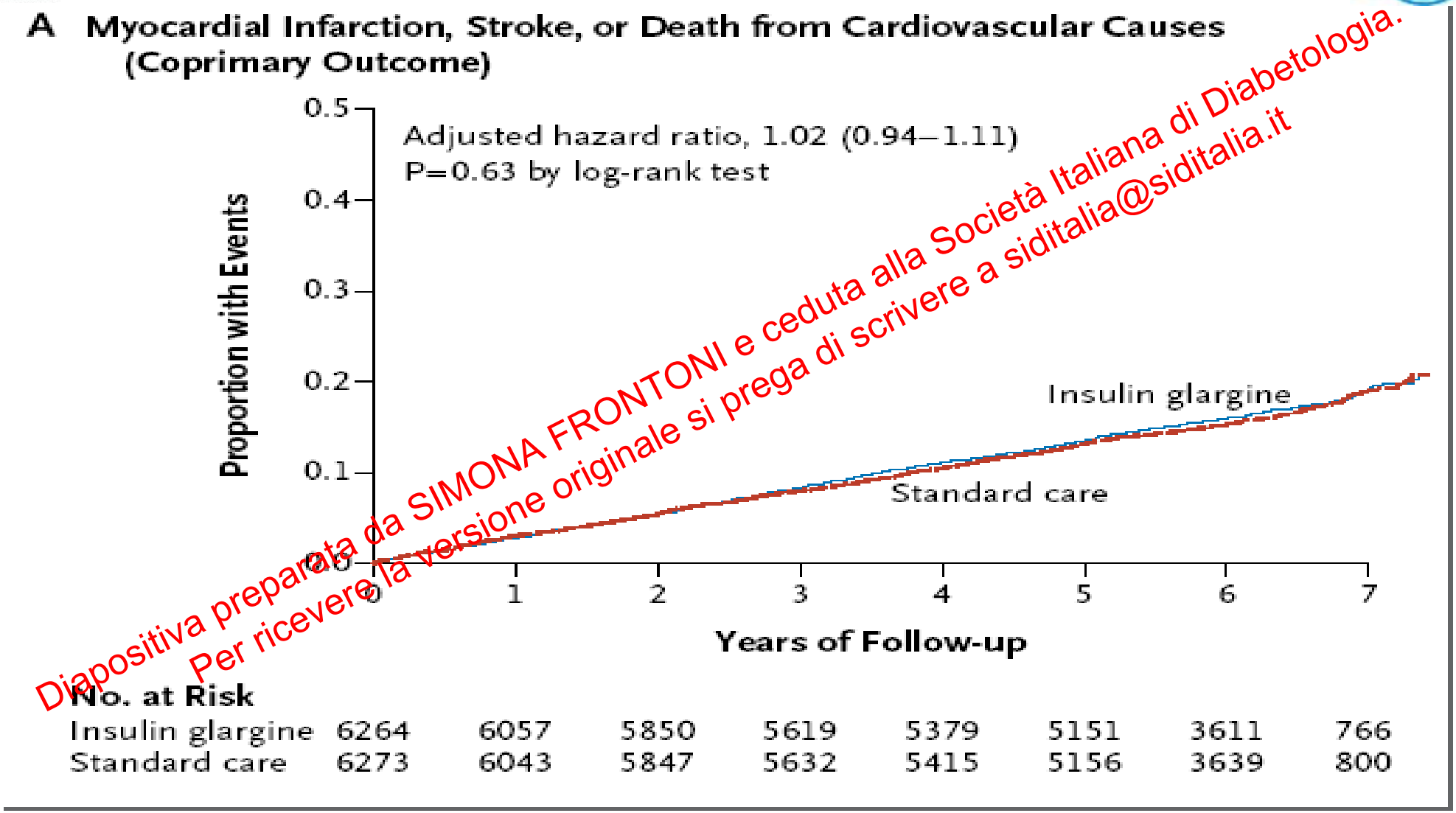
	Conventional Units	SI Units
BMI (kg/m^2)	29.8	29.8
Blood Pressure (mm)	146/84	146/84
Cholesterol (mg/dl or mM)	190	4.9
LDL (mg/dl or mM)	112	2.90
HDL (mg/dl or mM)	46	1.19
TG (Median mg/dl or mM)	140	1.58

ORIGIN – Median HbA1c levels



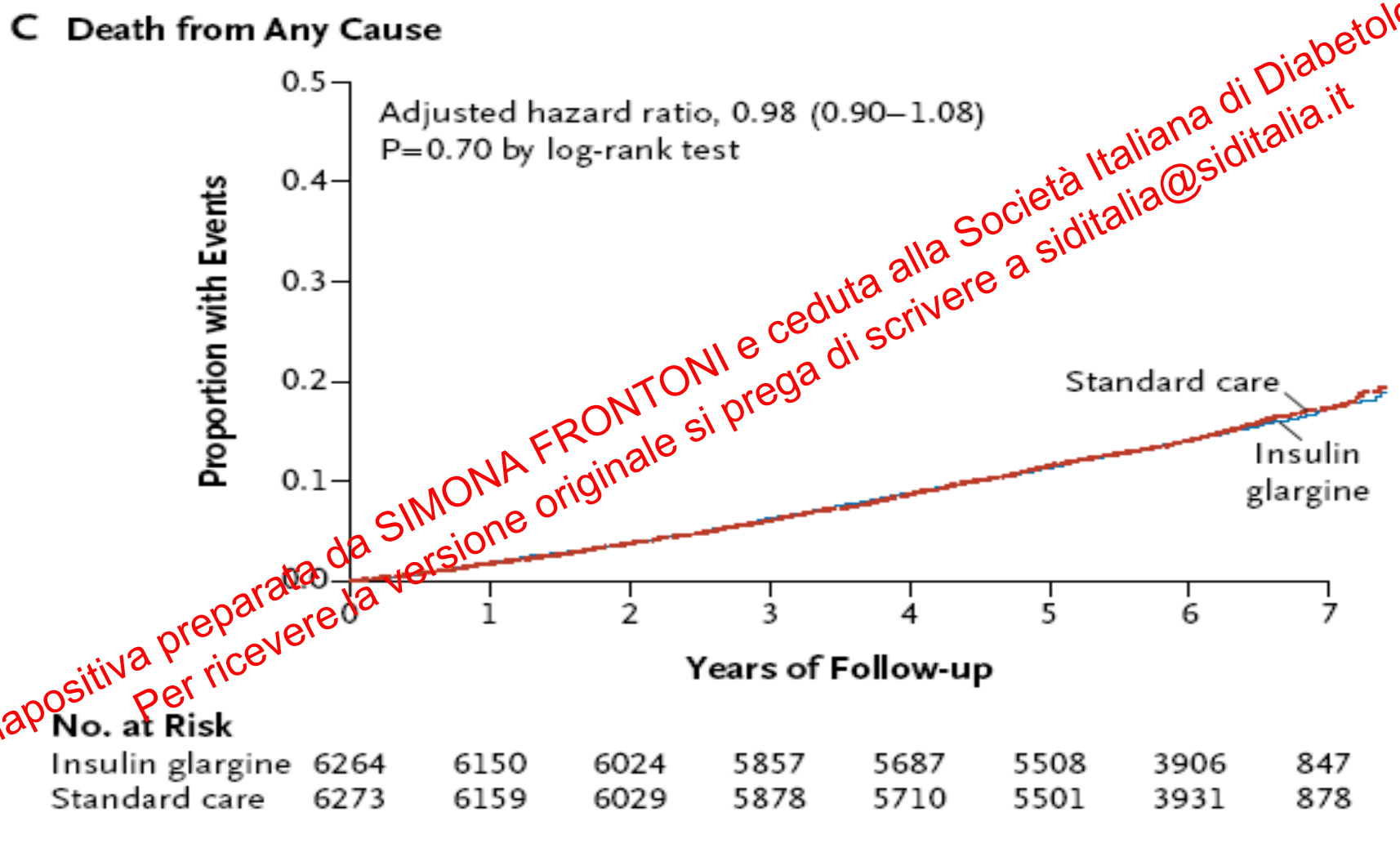
ORIGIN investigators – NEJM June 2012

ORIGIN – Primary outcome



ORIGIN investigators – NEJM June 2012

ORIGIN – Death from Any Cause



ORIGIN investigators – NEJM June 2012

ORIGIN – Severe hypoglycemia

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

ORIGIN investigators – NEJM June 2012

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

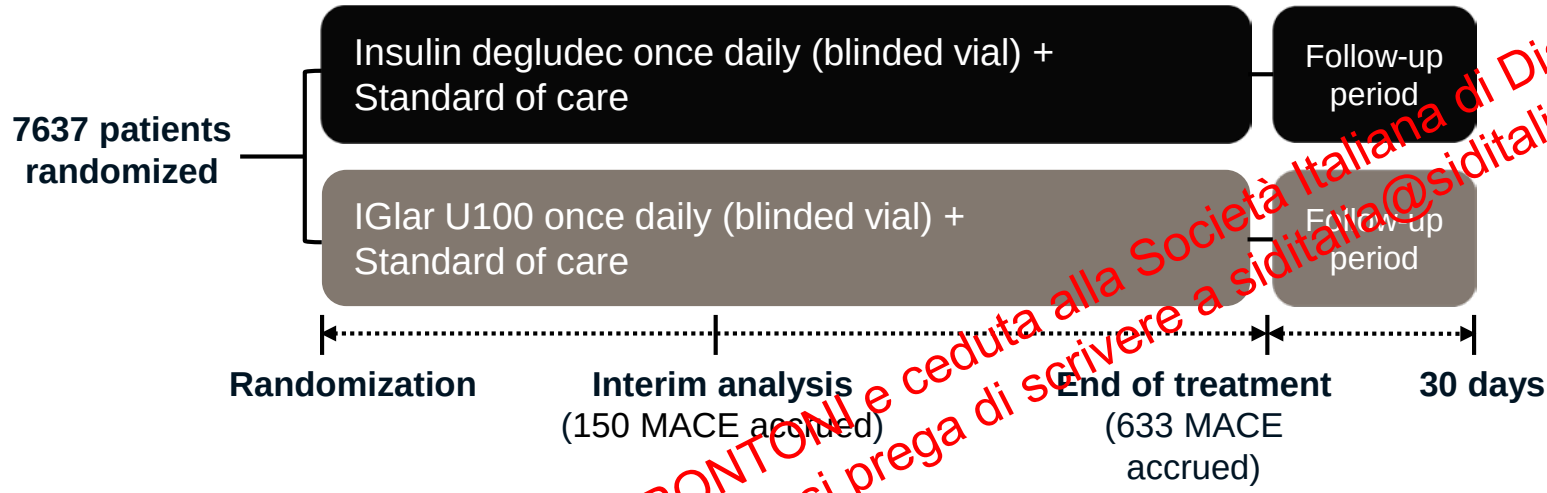
Degludec Cardiovascular Outcomes Trial

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*‡

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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

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Key inclusion criteria: cardiovascular profile

Type 2 diabetes

High cardiovascular risk profile

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

- cardiovascular or chronic kidney disease and aged ≥50

OR

- risk factors for cardiovascular disease and aged ≥60

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DEGLUDEC CARDIOVASCULAR OUTCOMES TRIAL

U, units

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DEVOTE
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

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DEVOTE
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	12.1	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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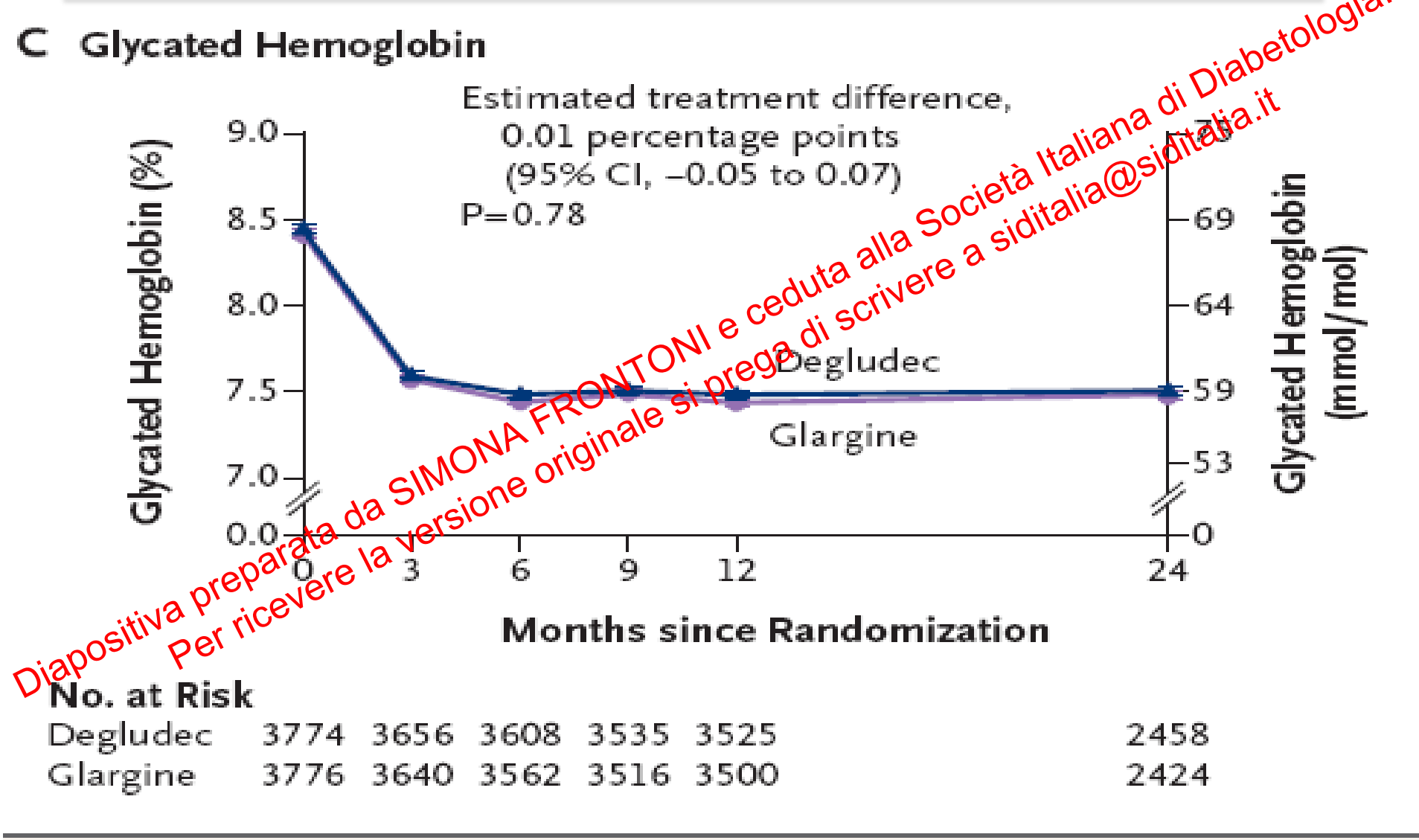
DEVOTE
secondary outcomes



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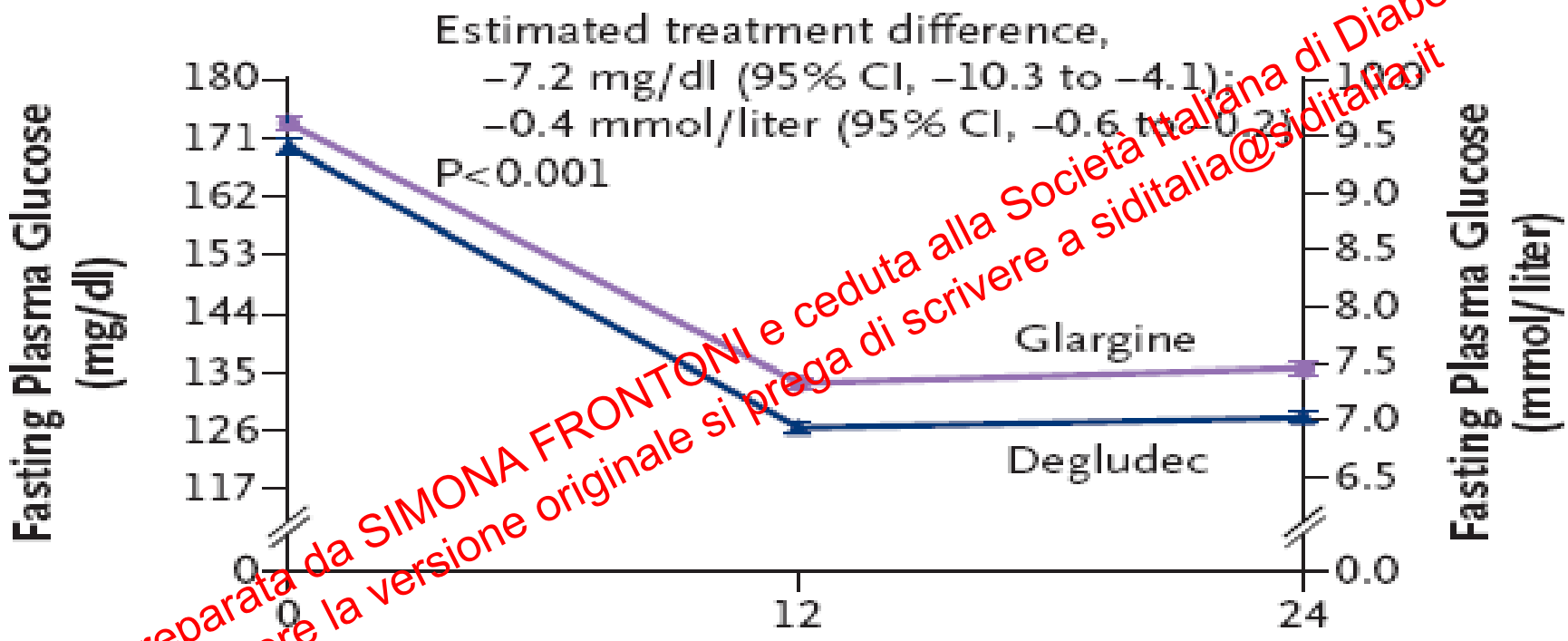
secondary outcomes

D Fasting Plasma Glucose



No. at Risk

Degludec	3757	3521	2457
Glargine	3760	3498	2425

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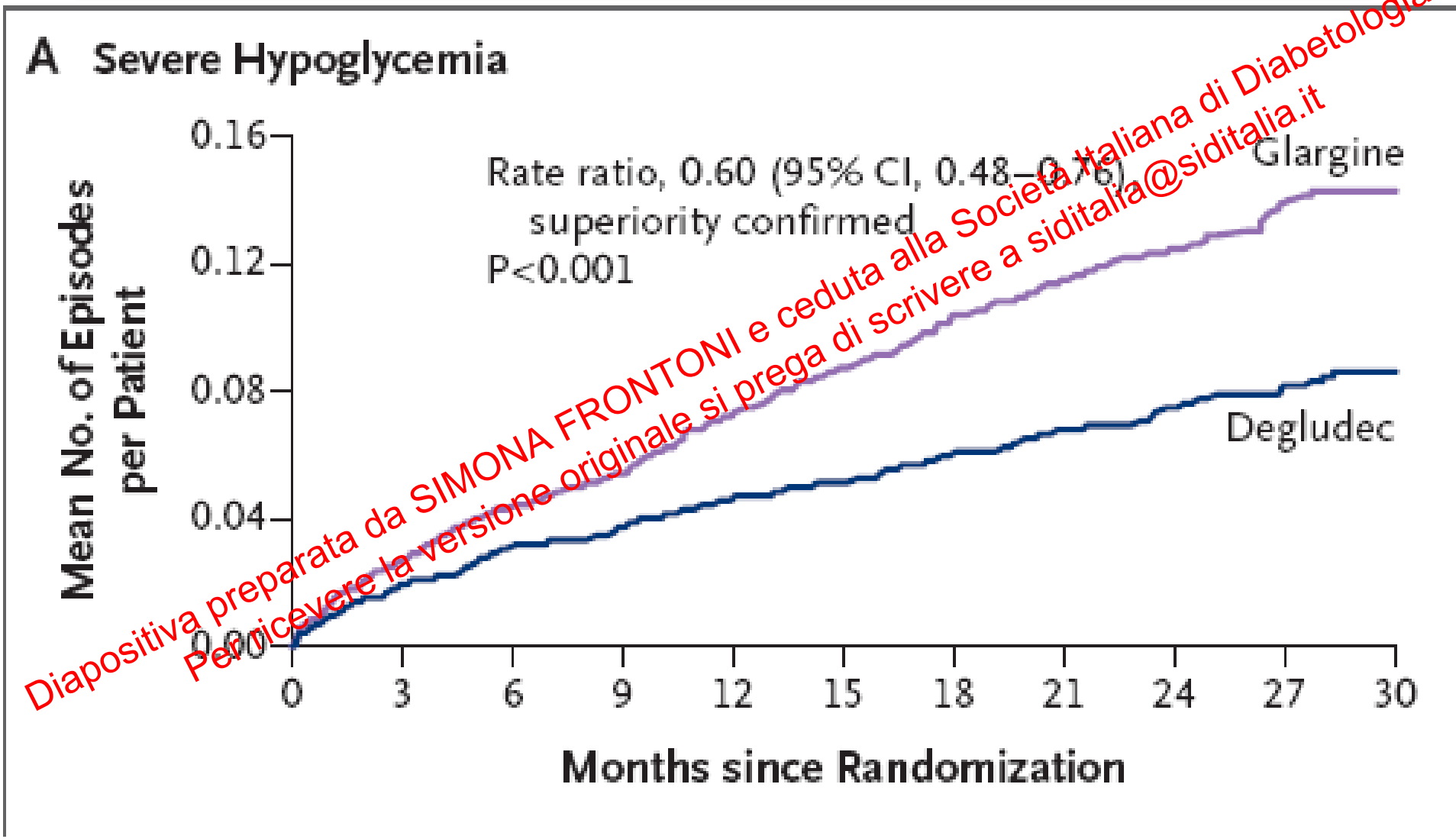
DEVOTE
secondary outcomes



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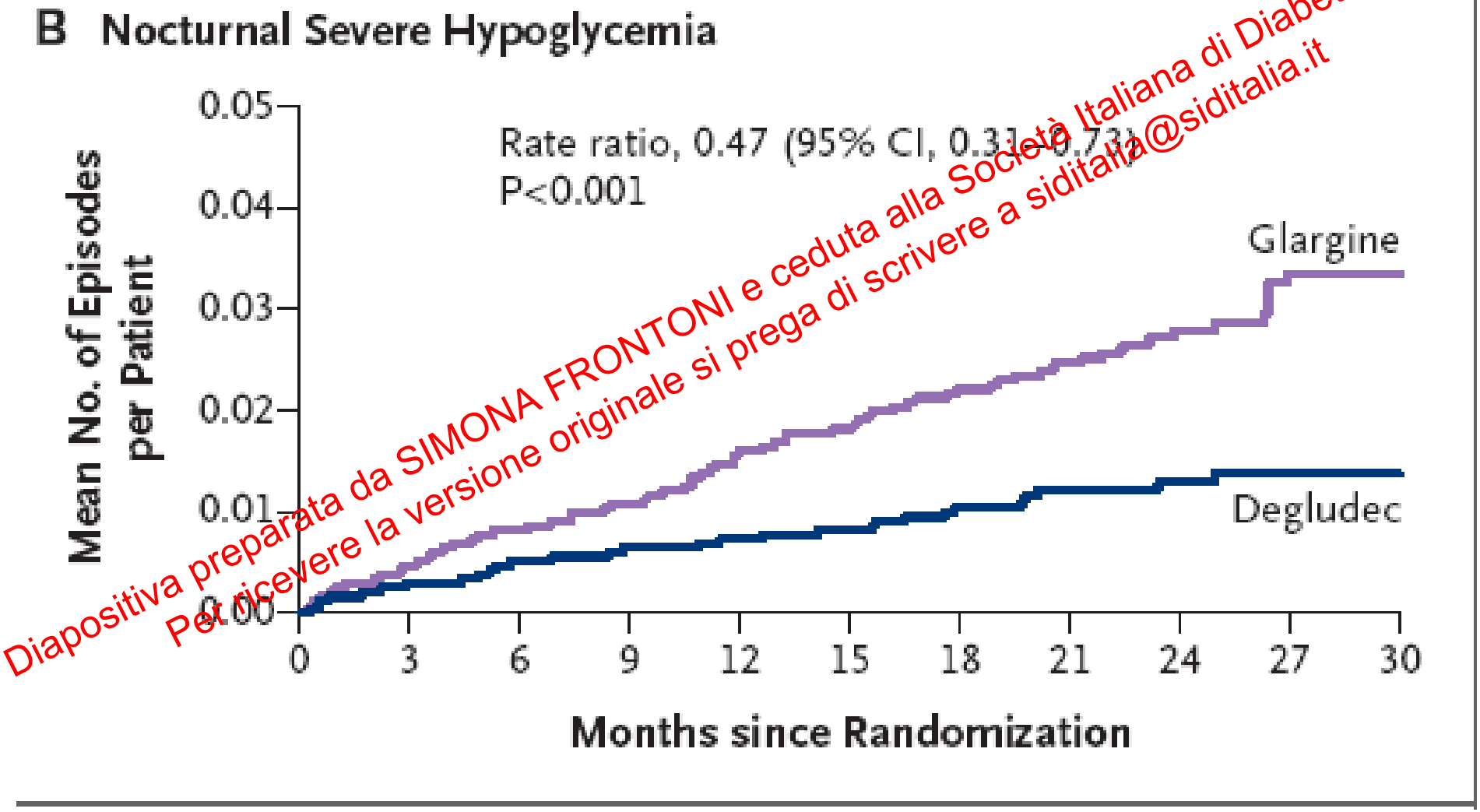
secondary outcomes



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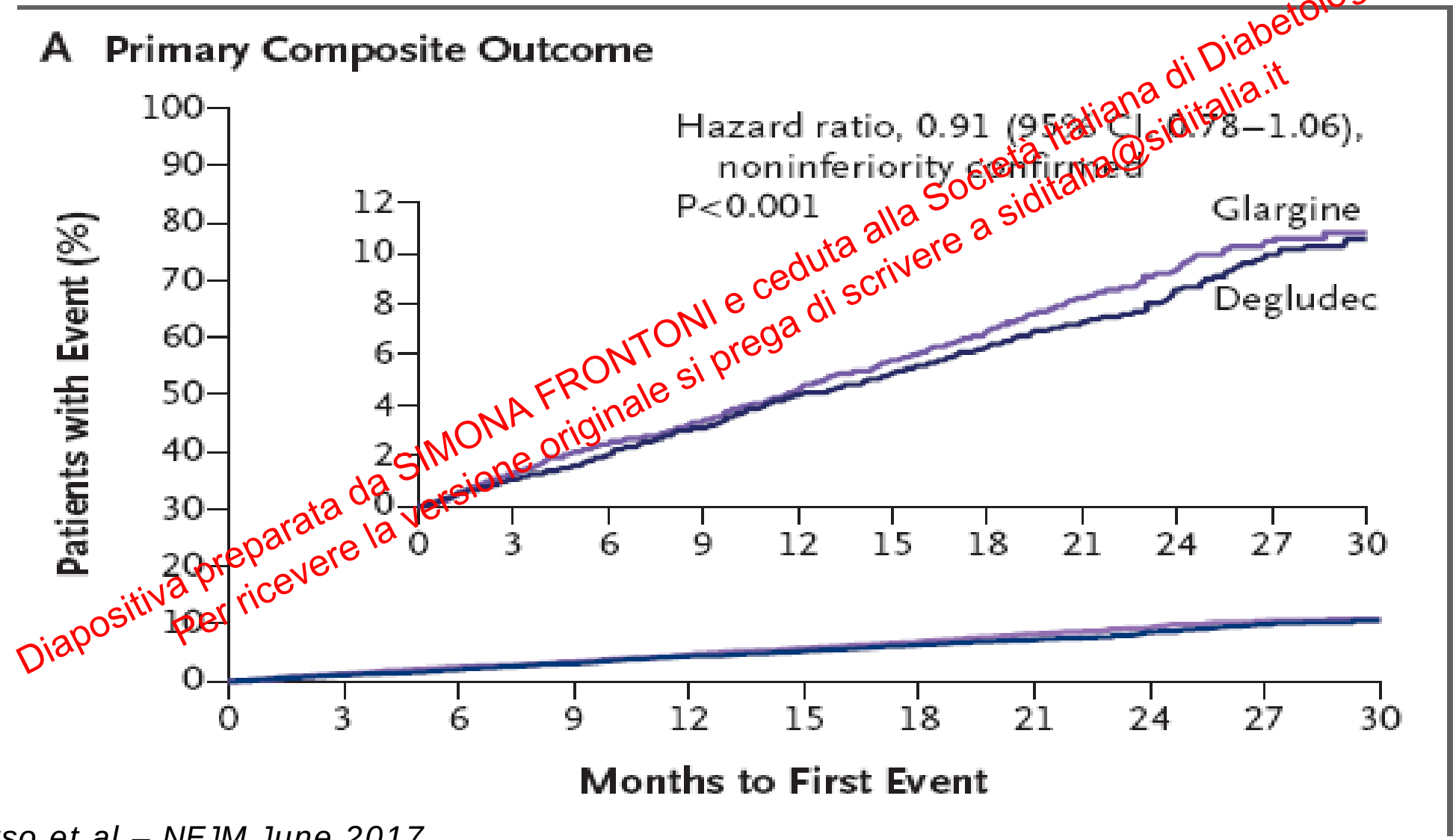
primary composite outcome



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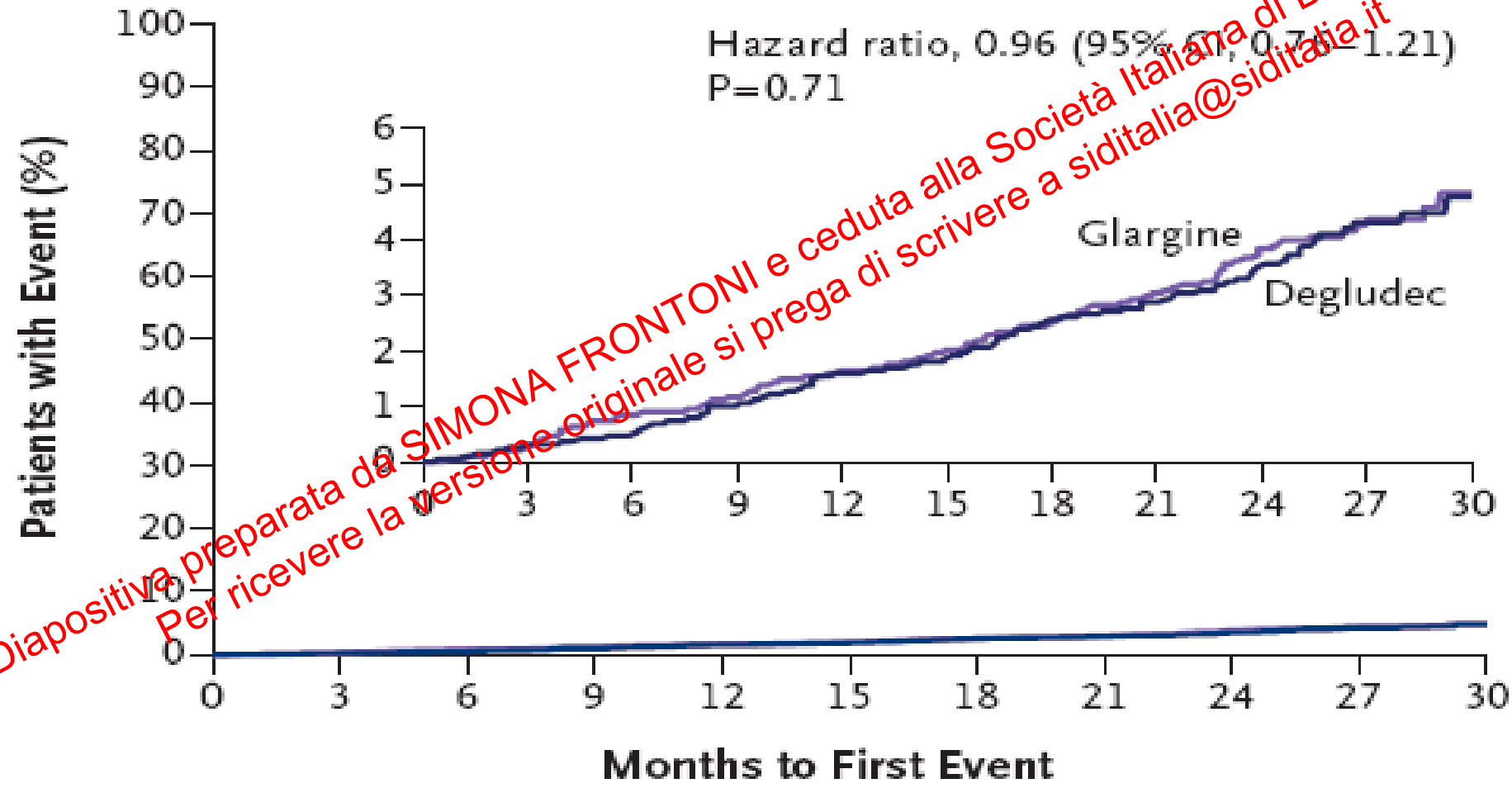
primary outcomes



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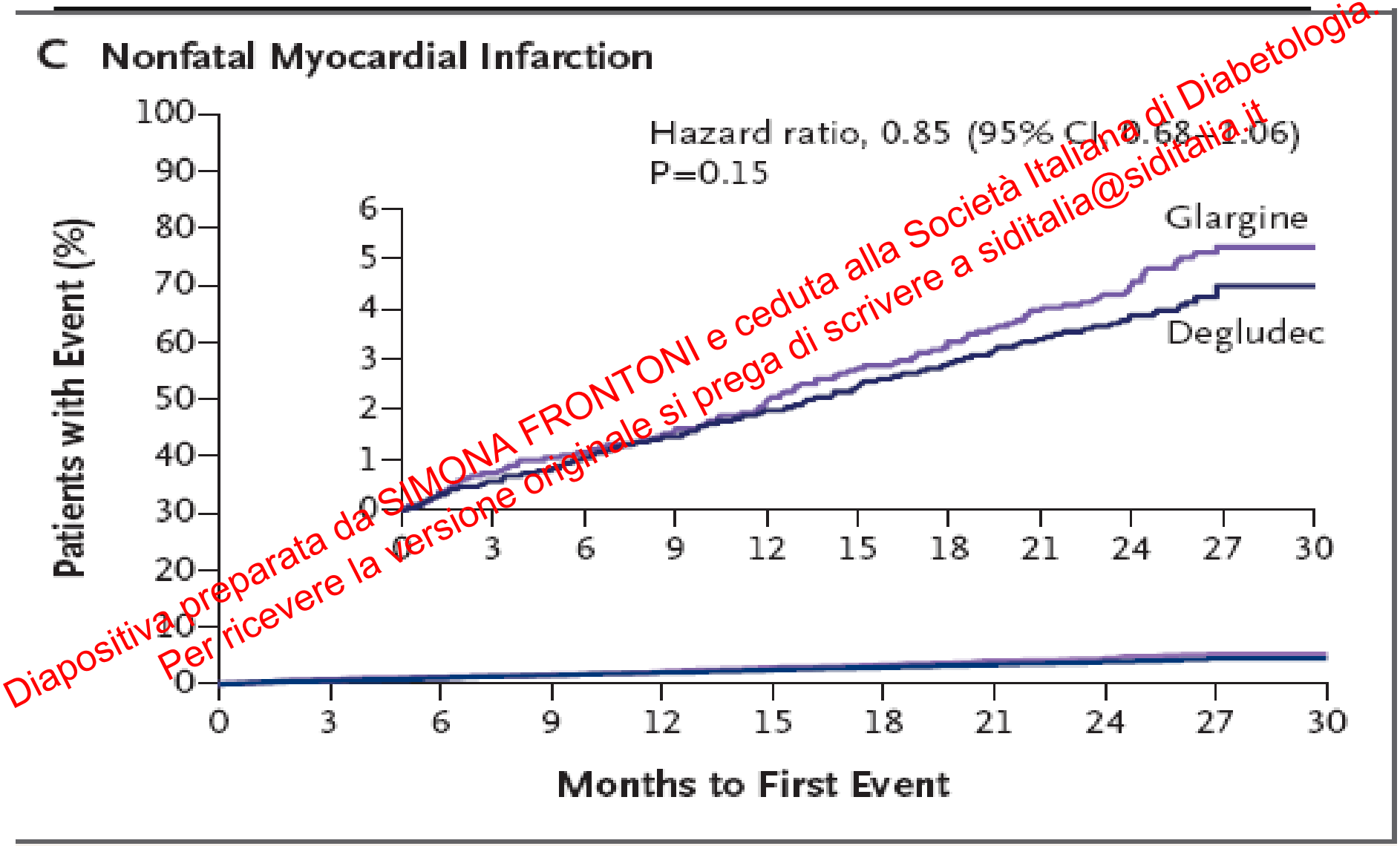
primary outcomes



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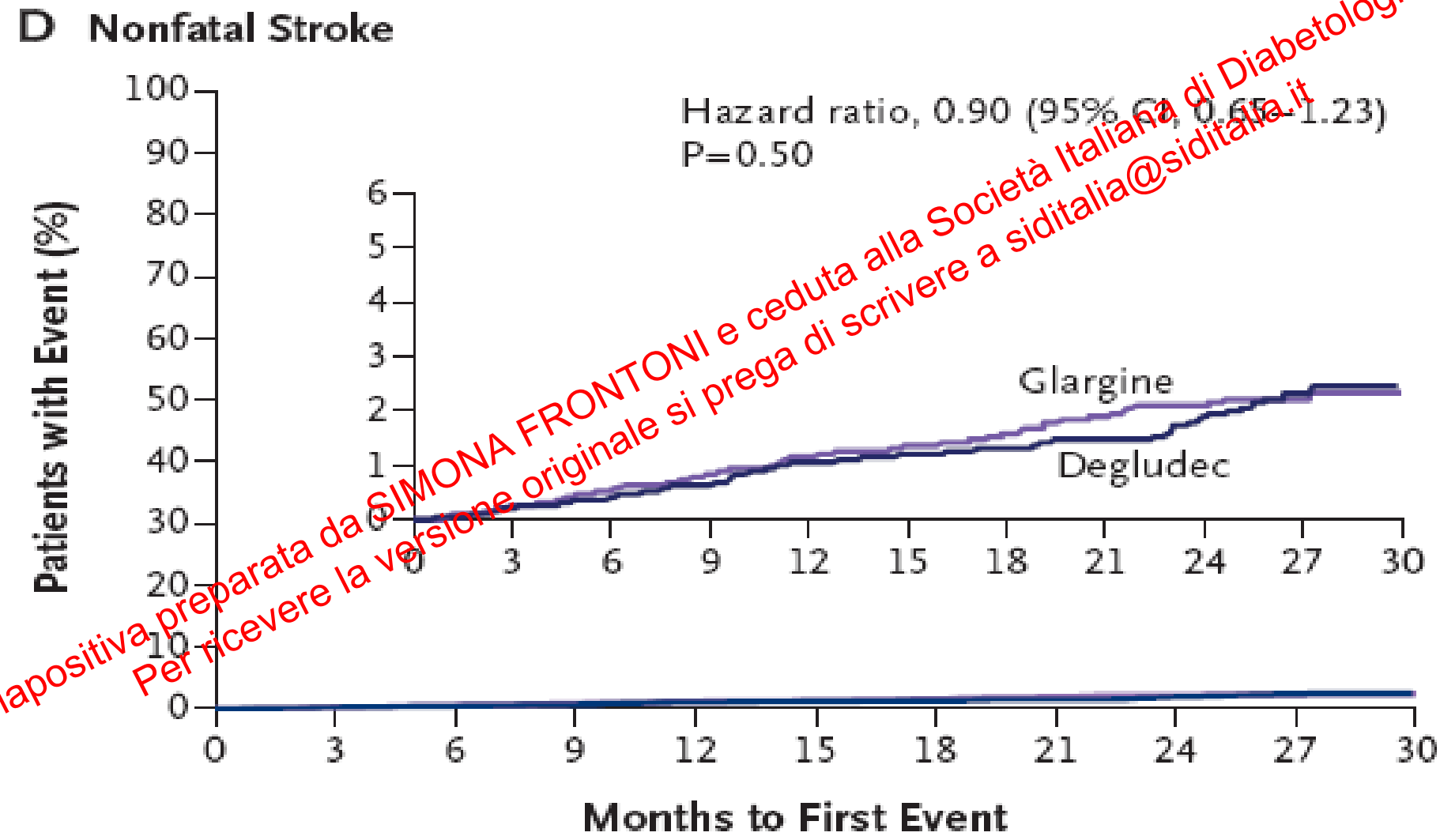
primary outcomes



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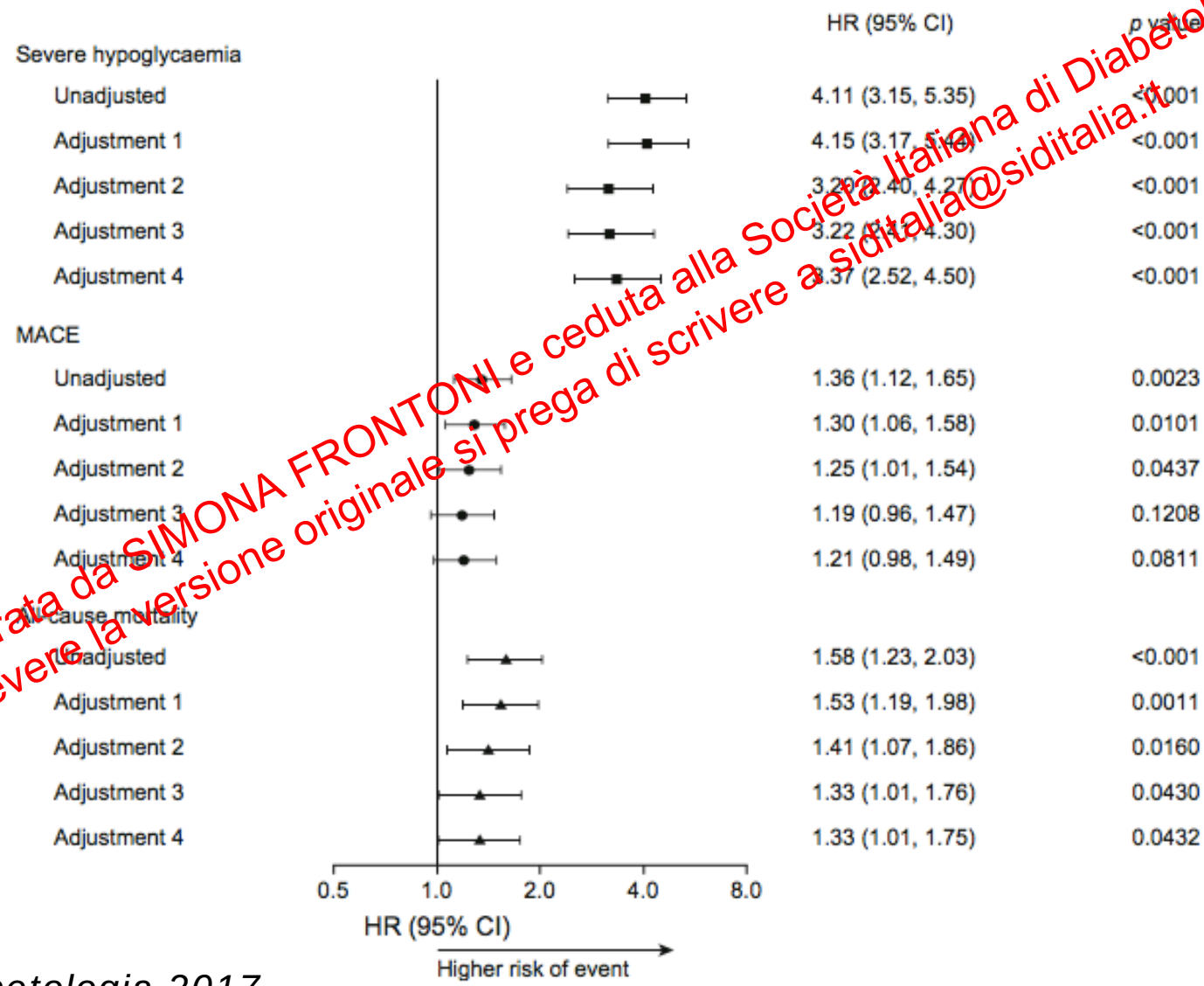
DEVOTE
primary outcomes

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

Marso et al – NEJM June 2017

Day-to-day fasting glycaemic variability DEVOTE 2

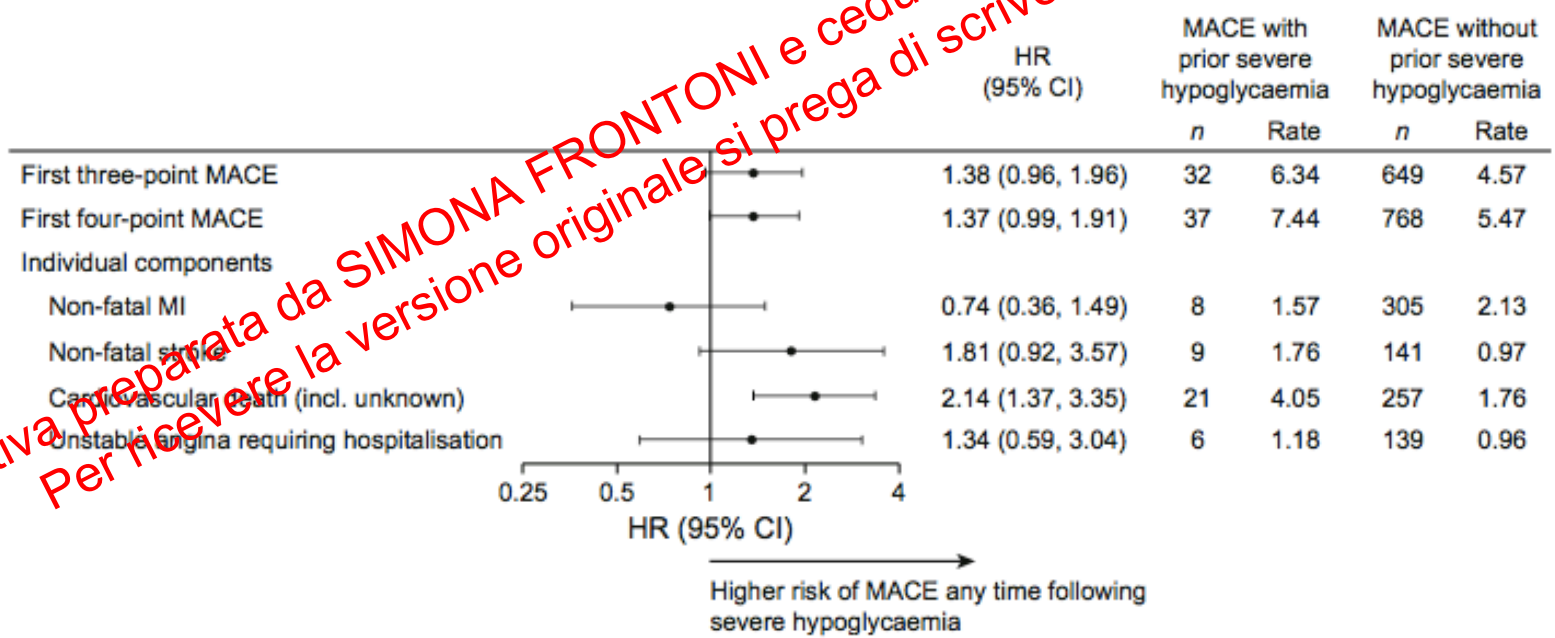


Zinman B et al – Diabetologia 2017

DEVOTE 3: temporal relationships between severe hypoglycaemia, cardiovascular outcomes and mortality

Published online: 15 September 2017

Risk of MACE following a severe hypoglycaemic event



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DEVOTE 3: temporal relationships between severe hypoglycaemia, cardiovascular outcomes and mortality

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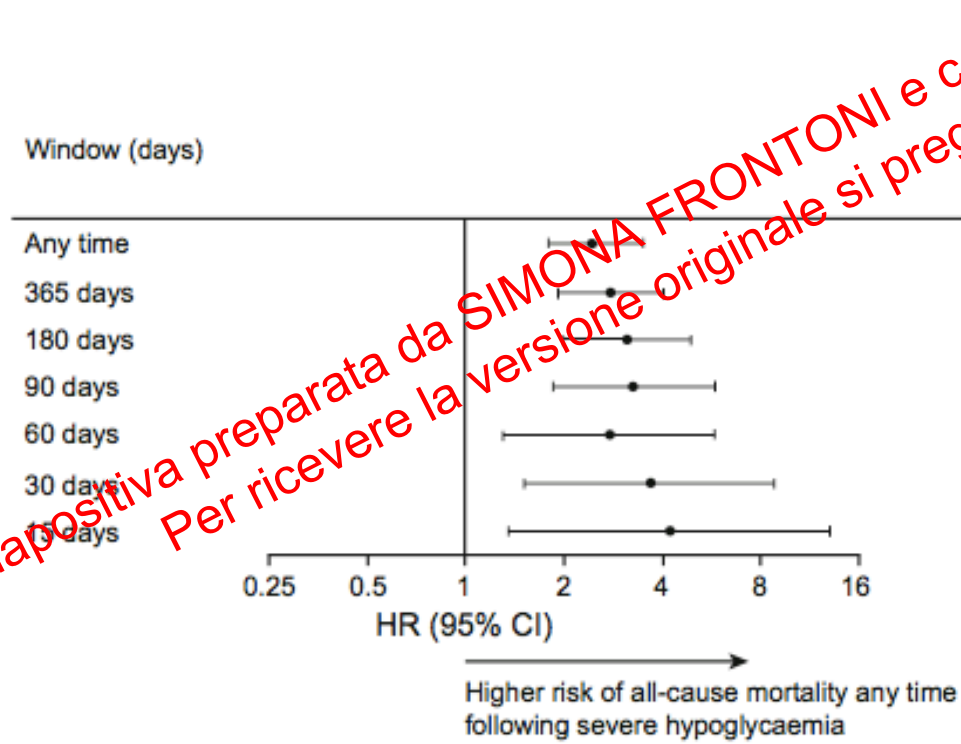
Risk of all-cause death following a severe hypoglycaemic event

by time period. n, number of patients; rate, events per 100 pts-yrs of observation



Pieber TR et al – Diabetologia 2017

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 significativa l'incidenza della ipoglicemia.

3. L'ipoglicemia severa si associa con un aumento della mortalità per tutte le cause, che perdura fino a 1 anno dopo l'episodio ipoglicemico

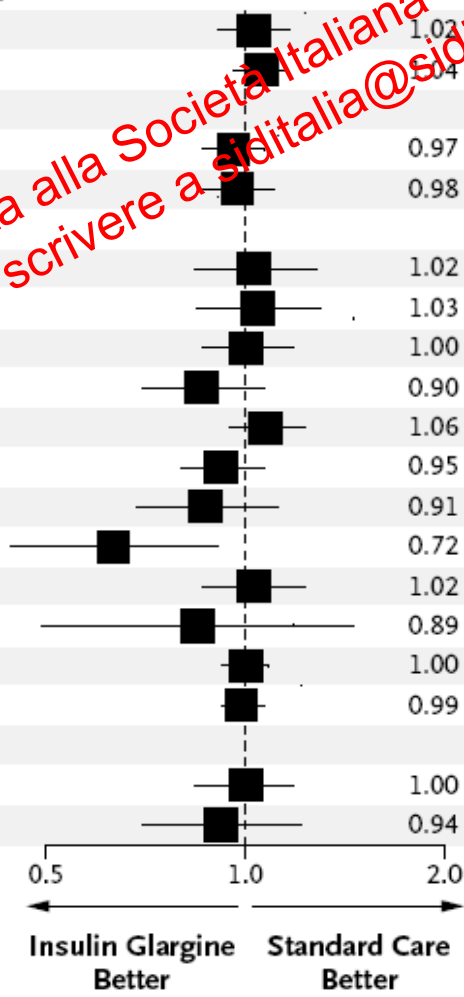
Conclusioni

- Il trattamento insulinico di per sé non determina benefici sul rischio cardiovascolare, ma nemmeno malefici
- E' l'ipoglicemia ad essere SICURAMENTE dannosa in termini di rischio cardiovascolare.
- Una gestione appropriata della terapia insulinica sia da parte del clinico che del paziente (timing, counting CHO, insulina) riduce significativamente il rischio di ipoglicemie
- D'altra parte, l'insulina rimane la terapia più efficace e costo/effettiva per ridurre la glicemia in maniera significativa e in tempi brevi (le sulfoniluree NON devono essere utilizzate)

lunga vita all'insulina

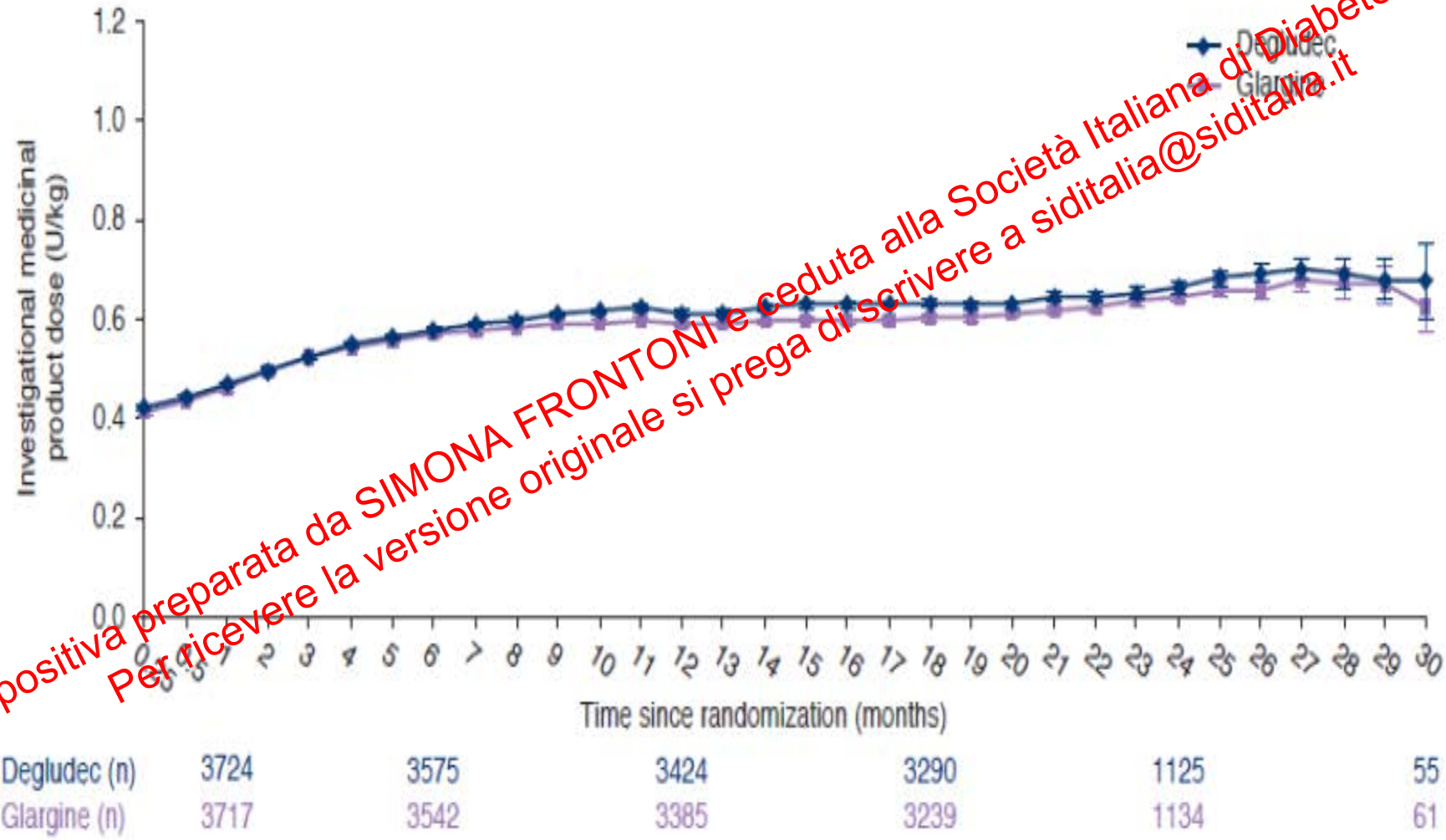
ORIGIN – Primary and secondary outcomes

Outcome	Insulin Glargine (N=6264)		Standard Care (N=6273)		Hazard Ratio (95% CI)	P Value
	no. (%)	*no./100 patient-yr*	*no. (%)*	*no./100 patient-yr*		
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	346 (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	708 (11.3)	2.05	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 investigators – NEJM June 2012

DEVOTE
basal insulin dose



Marso et al – NEJM June 2017