Insulina glargine e diabete di tipo 2: il valore dell'esperienza

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Dipendente: Nessuno

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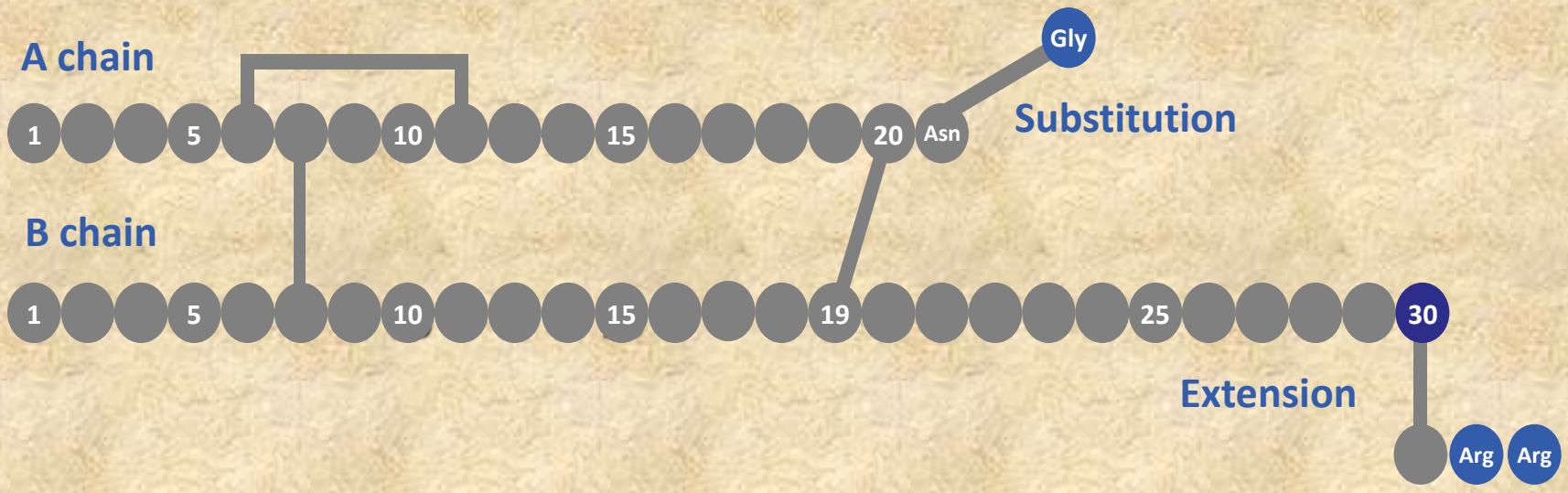
Insulin glargine: a long-acting human insulin analogue designed to have low solubility at neutral pH

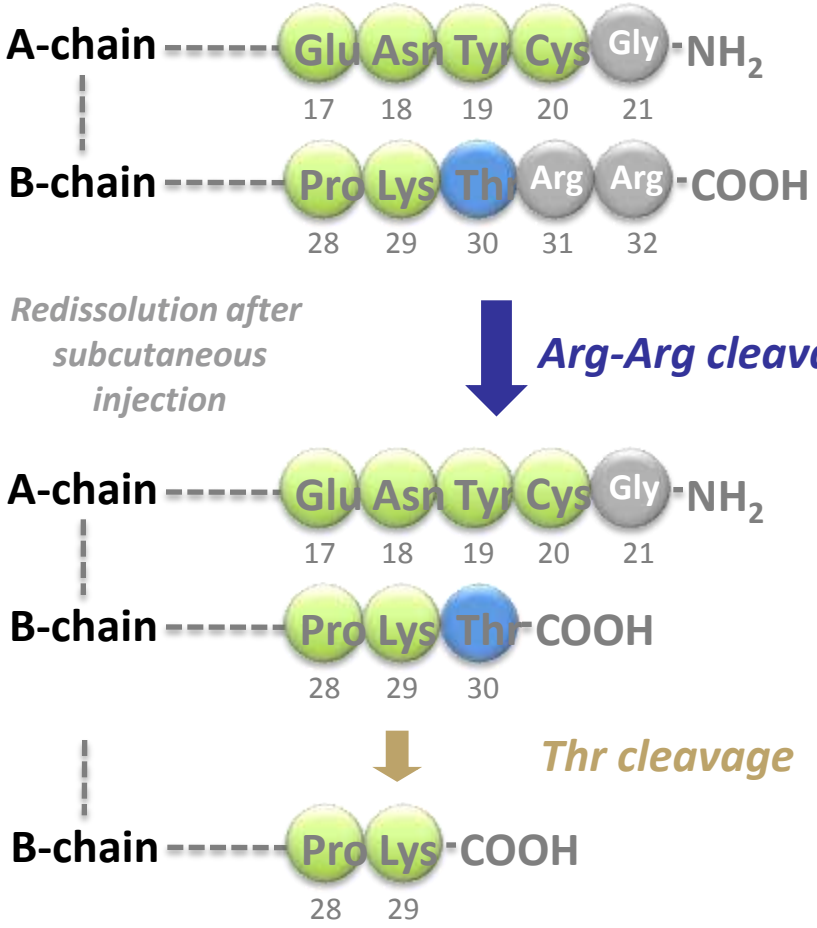


- Asparagine at position A21 replaced by glycine (provides stability)[1,2]
- Addition of 2 arginines at C-terminus of the B chain (soluble at slightly acidic pH)[1,2]

1. Lantus® Summary of Product Characteristics. Available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR__Product_Information/human/000284/WC500036082.pdf (accessed 25 Nov 2013)
2. McKeage K, et al. Drugs. 2001;61:1599–1624

Insulin glargine is a pro-drug of M1

Glargine forms mainly M1 metabolite with biochemical properties of human insulin[1]



21^{A}Gly-31^{B}Arg-32^{B}Arg-human insulin
= Insulin glargine

Not detectable in blood stream

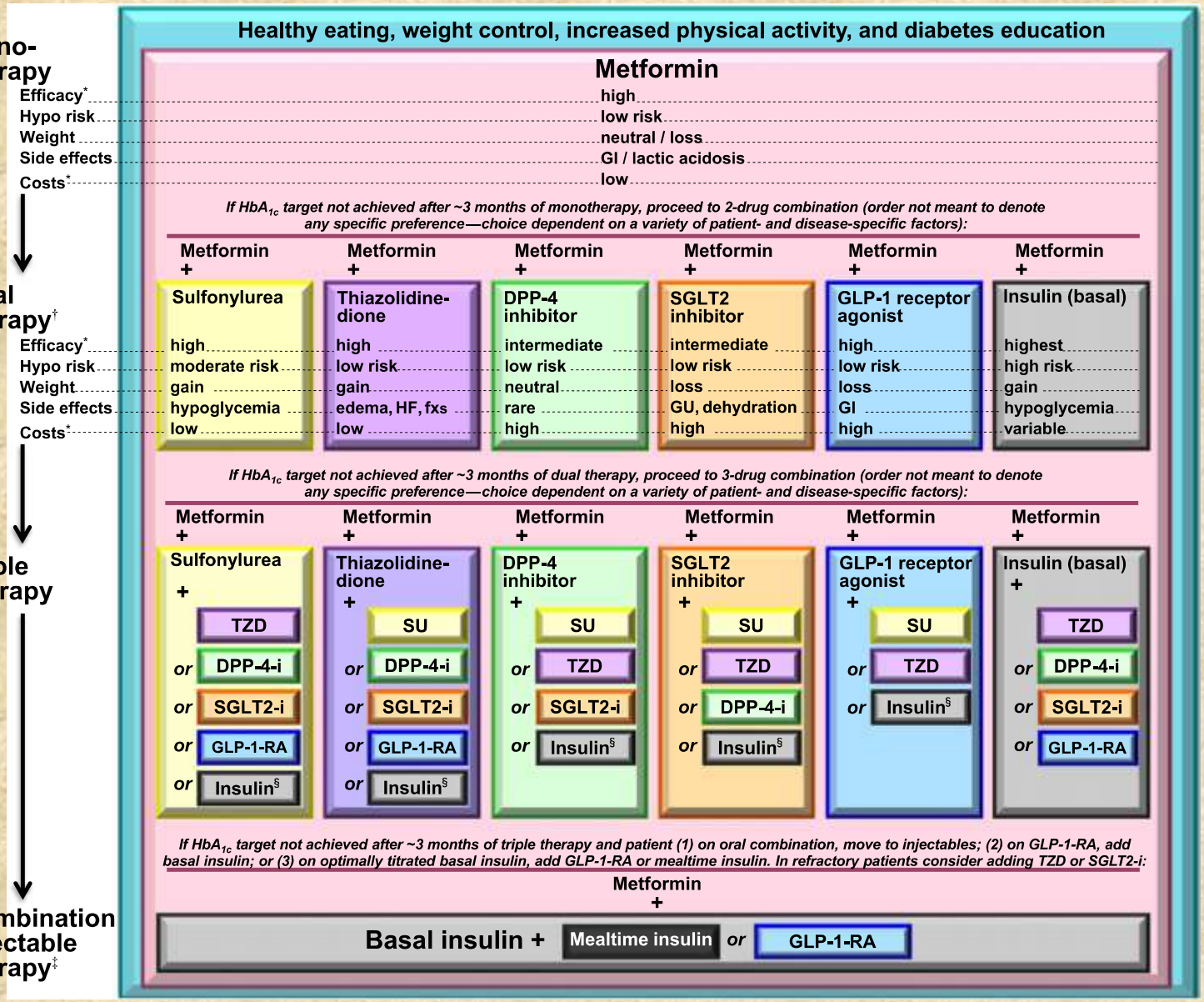
21^{A}Gly-human insulin
M1

Main metabolite with properties comparable to human insulin

21^{A}Gly-des-30^{B}Thr-human insulin
M2

1. Modified from Sommerfeld MR, et al. *PLoS ONE* 2010; 5(3): e9540

EASD-ADA 2015: Recommendations for anti-hyperglycemic therapy in type 2 diabetes



Inzucchi SE et al.; Diabetologia 2015

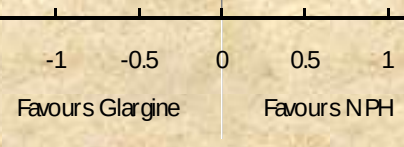
Change in HbA1c in patients with type 2 diabetes: glargine vs NPH

Outcome: 2 Change in HbA1c (pooled SD) - Glargine vs. NPH

Study or subgroup	Glargine N	Mean(SD)	NPH N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Rosenstock 2001	259	-0.41 (1.3)	259	-0.59 (1.3)		17.9 %	0.18 [-0.04, 0.40]
Fritsche 2003	227	-0.96 (1.3)	232	-0.84 (1.3)		15.8 %	-0.12 [-0.36, 0.12]
Eliaschewitz 2006	231	-1.38 (1.3)	250	-1.44 (1.3)		16.6 %	0.06 [-0.17, 0.29]
Yki-Järvinen 2006	61	-1.99 (1.3)	49	-2.1 (1.3)		3.7 %	0.11 [-0.38, 0.60]
Riddle 2003	372	-1.65 (1.3)	392	-1.59 (1.3)		26.3 %	-0.06 [-0.24, 0.12]
Massi 2003	289	-0.46 (1.3)	281	-0.38 (1.3)		19.7 %	-0.08 [-0.29, 0.13]
Total (95% CI)	**1439**		**1463**			**100.0 %**	**0.00 [-0.10, 0.09]**

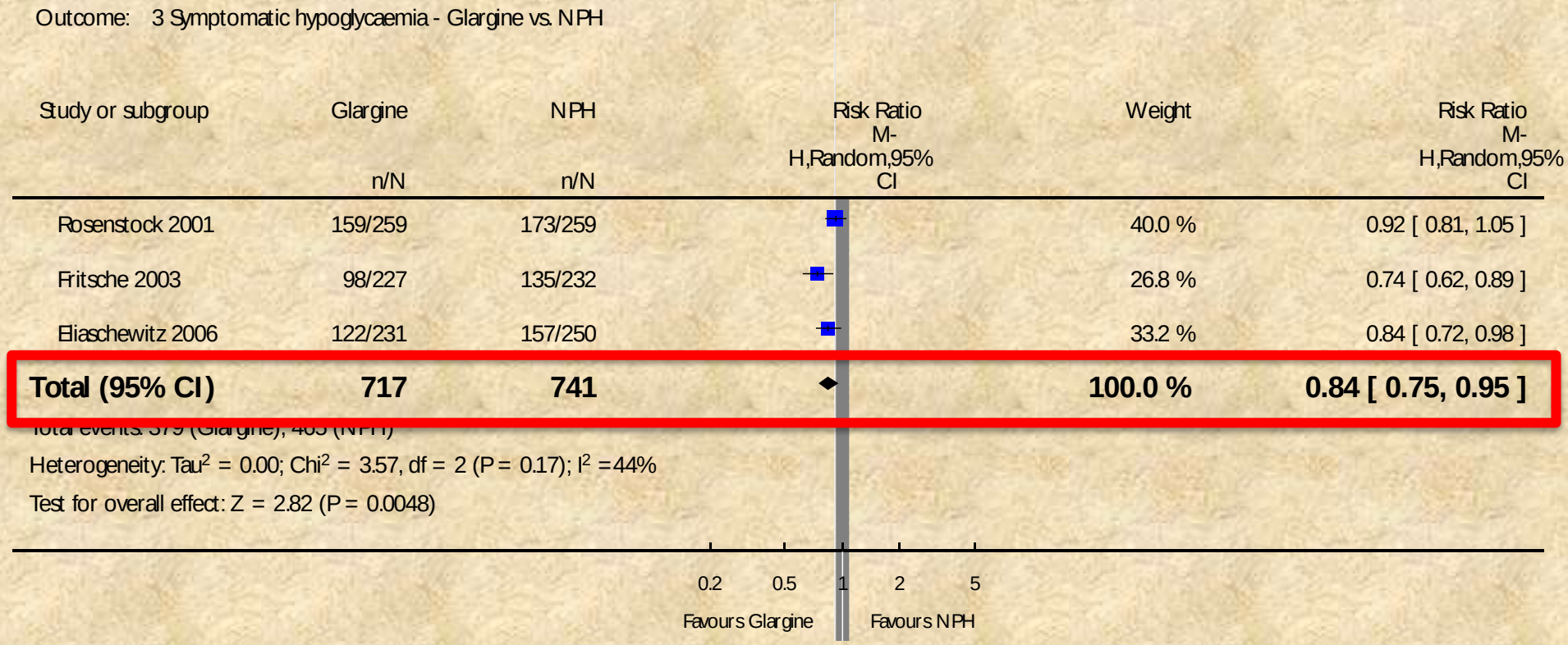
Heterogeneity: Tau² = 0.0; Chi² = 4.85, df = 5 (P = 0.43); I² = 0.0%

Test for overall effect: Z = 0.09 (P = 0.93)



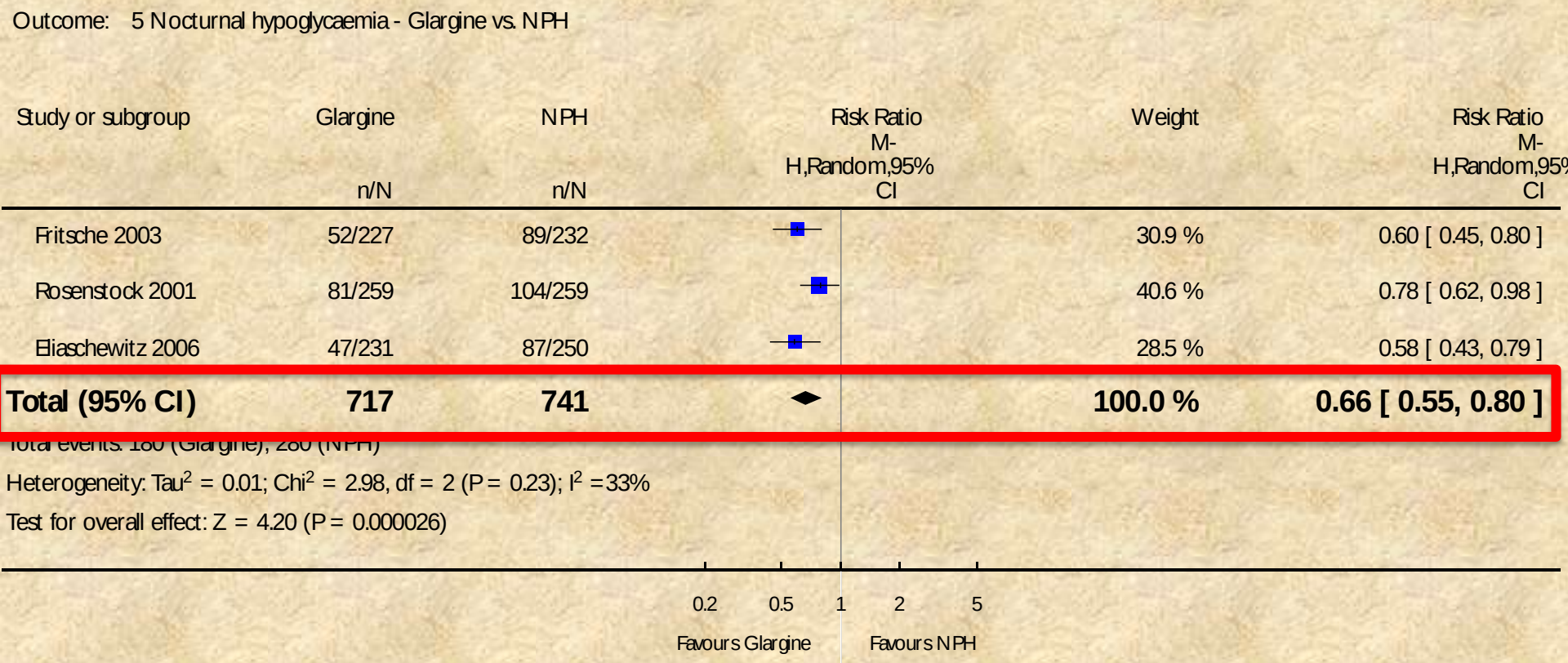
Horvath K et al.; Cochrane Reviews 2009

Symptomatic hypoglycemias in patients with type 2 diabetes: glargine vs NPH



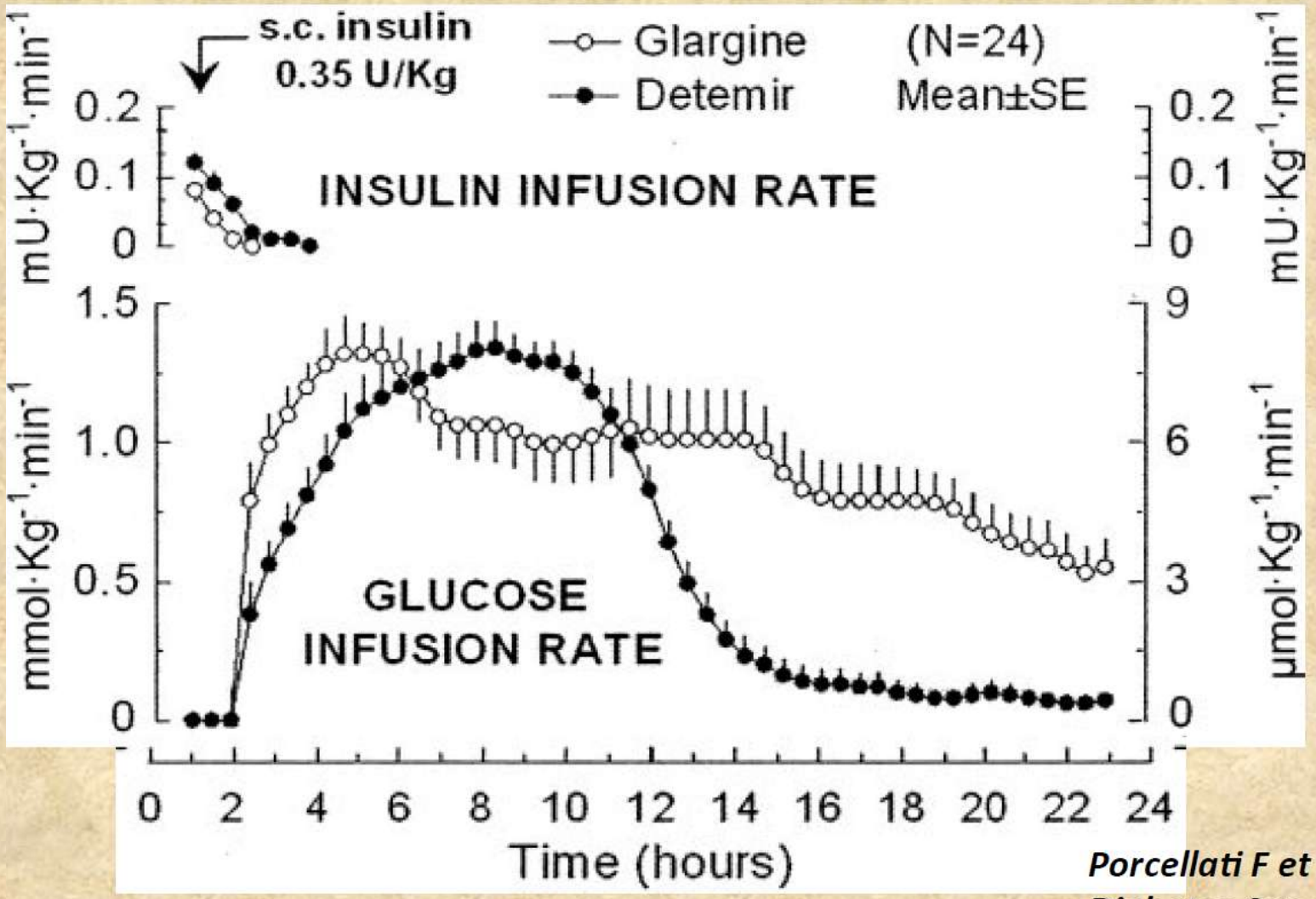
Horvath K et al.; Cochrane Reviews 2009

Nocturnal hypoglycemias in patients with type 2 diabetes: glargine vs NPH



Horvath K et al.; Cochrane Reviews 2009

Glargine vs Detemir: a pharmacodynamic comparison



Porcellati F et al.; Diabetes Care 2007

Efficacy of insulin detemir vs glargine in patients with diabetes. A Cochrane review.

Outcome	Studies (N)	Participants (N)	Mean difference Detemir vs Glargine [95% C.I.]
HbA_{1c}	4	2250	-0.08% [-0.10 , 0.27]
FPG	4	2250	0.34 mmol/L [0.01 , 0.67]

Swinnen SG. et al.; Cochrane Rev 2011

Insulin detemir vs glargine: patients with hypoglycemia. A Cochrane review.

Percent of participants with hypoglycemia			
Episodes	**Studies (N)**	**Participants (N)**	**Rate Ratio [95% C.I.]**
Total	**4**	**2252**	**0.98 [0.92, 1.05]**
Severe	**4**	**2252**	**1.02 [0.90, 1.16]**
Nocturnal	**4**	**2242**	**0.82 [0.51, 1.32]**

Swinnen SG. et al.; Cochrane Rev 2011

Combined outcomes of insulin detemir vs glargine in patients with diabetes. A Cochrane review.

Outcome	Studies (N)	Participants (N)	Risk Ratio Detemir vs Glargine [95% C.I.]
% Pts $HbA_{1c} \leq 7.0\%$	4	2078	0.96 [0.81, 1.14]
% Pts $HbA_{1c} \leq 7.0\%$ without hypos	4	2080	0.87 [0.76 , 1.00]

Swinnen SG. et al.; Cochrane Rev 2011

Insulin detemir vs glargine: other endpoints. A Cochrane review.

Insulin detemir vs glargine			
Endpoint	**Studies (N)**	**Participants (N)**	**Mean difference or Risk ratio [95% C.I.]**
Weight gain	4	2250	-0.91 kg [-1.21, -0.61]
Participants with injection site reaction	4	2252	3.31 [1.13, 9.73]
Daily dose in units per kg	4	2242	+0.26 U/kg [0.11, 0.41]

Swinnen SG. et al.; Cochrane Rev 2011

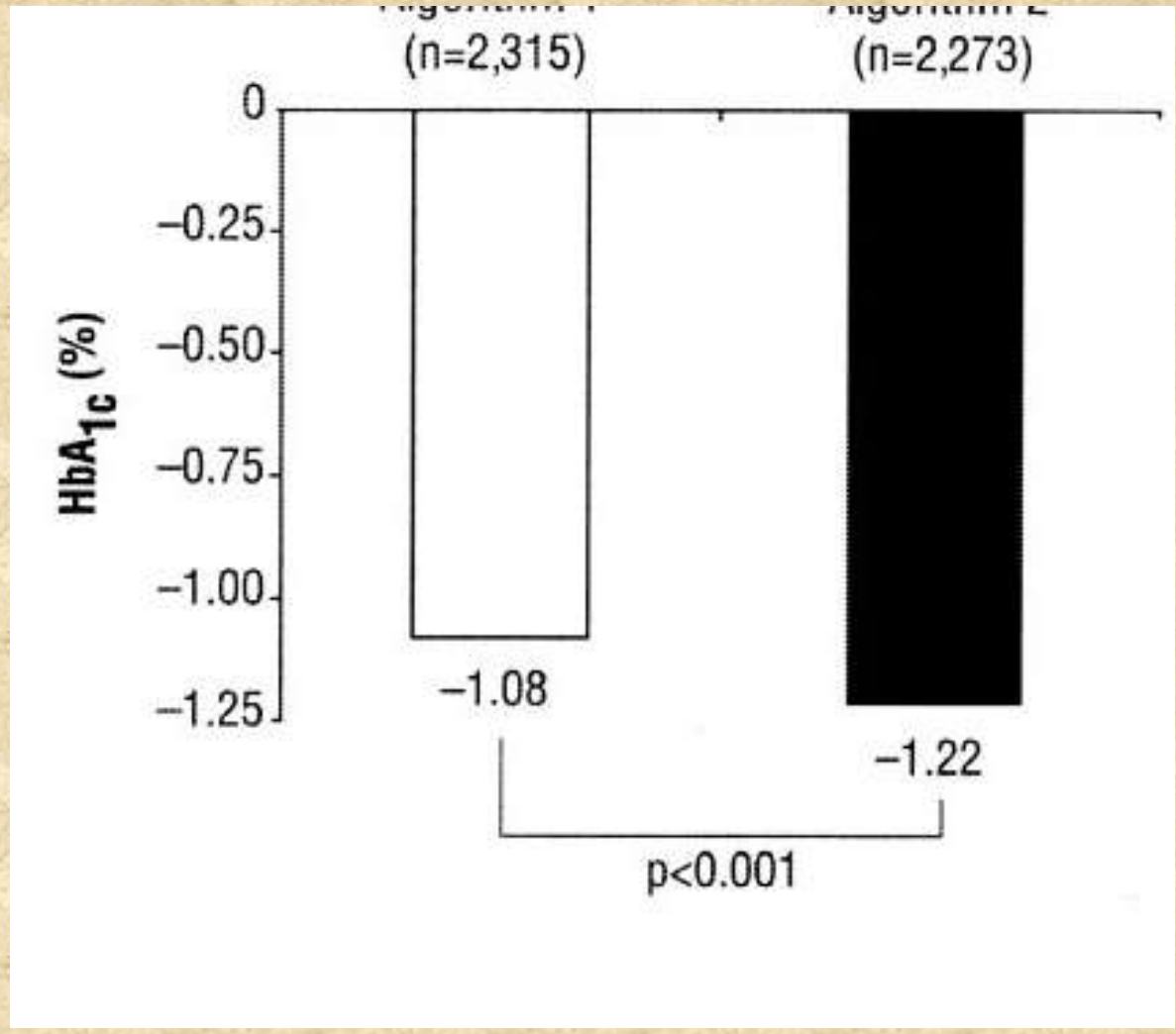
AT-LANTUS: empowering the patient to manage the titration algorIthm of insulin glargine

Mean FBG for the previous 3 consecutive days	Increase in daily basal insulin glargine dose (IU)*	
	Algorithm 1: titration at every visit; managed by physician†	Algorithm 2: titration every 3 days; managed by subject†
≥100 mg/dl and <120 mg/dl (≥5.5 mmol/l and <6.7 mmol/l)	0–2 (at the discretion of the investigator)‡	0–2 (at the discretion of the investigator)‡
≥120 mg/dl and <140 mg/dl (≥6.7 mmol/l and <7.8 mmol/l)	2	2
≥140 mg/dl and <180 mg/dl (≥7.8 mmol/l and <10 mmol/l)	4	2
≥180 mg/dl (≥10 mmol/l)	6–8 (at the discretion of the investigator)‡	2

*Target FBG ≤100 mg/dl (≤5.5 mmol/l). †Reviewed by physician at each visit, either in person or over the telephone; titration occurred only in the absence of blood glucose levels <72 mg/dl (<4.0 mmol/l). ‡Magnitude of daily basal dose was at the discretion of the investigator.

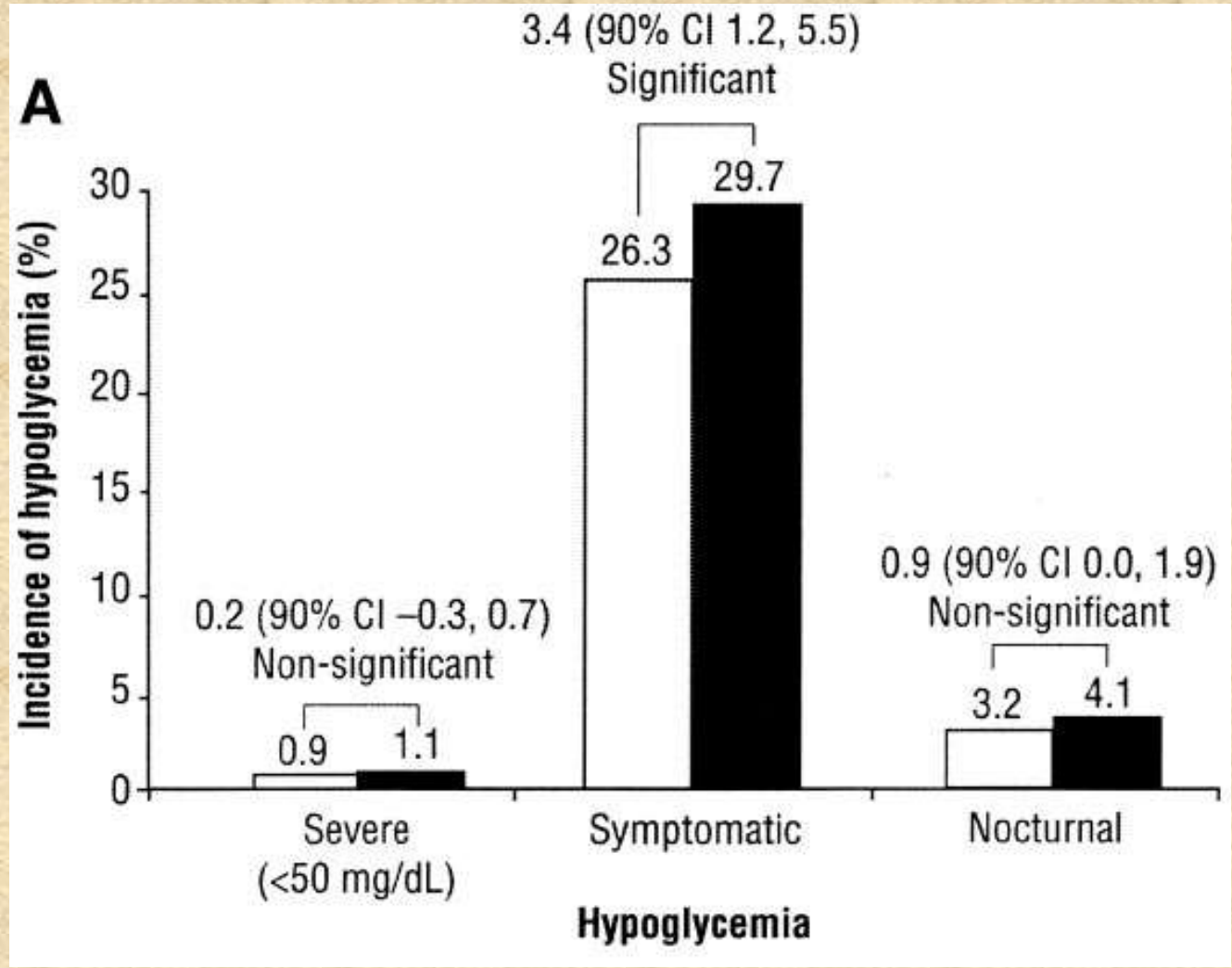
Davies M et al.; Diabetes Care 2005

Patients fare better than physicians in achieving reductions in HbA_{1c}….



Davies M et al.; Diabetes Care 2005

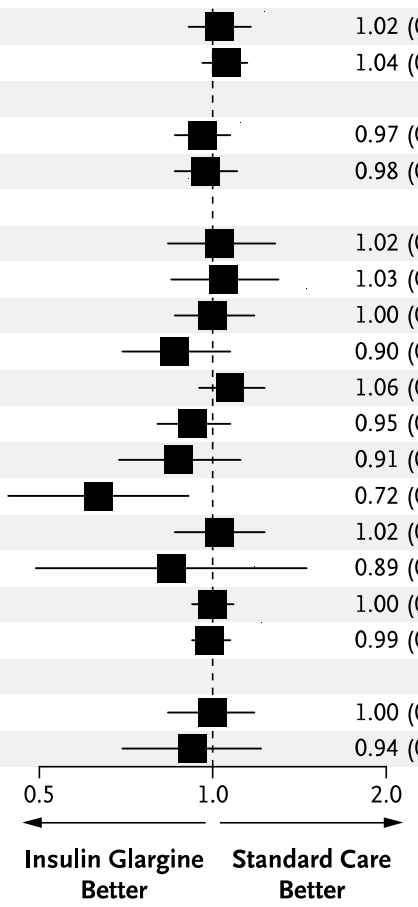
….but they pay a higher toll to hypoglycemia



Davies M et al.; Diabetes Care 2005

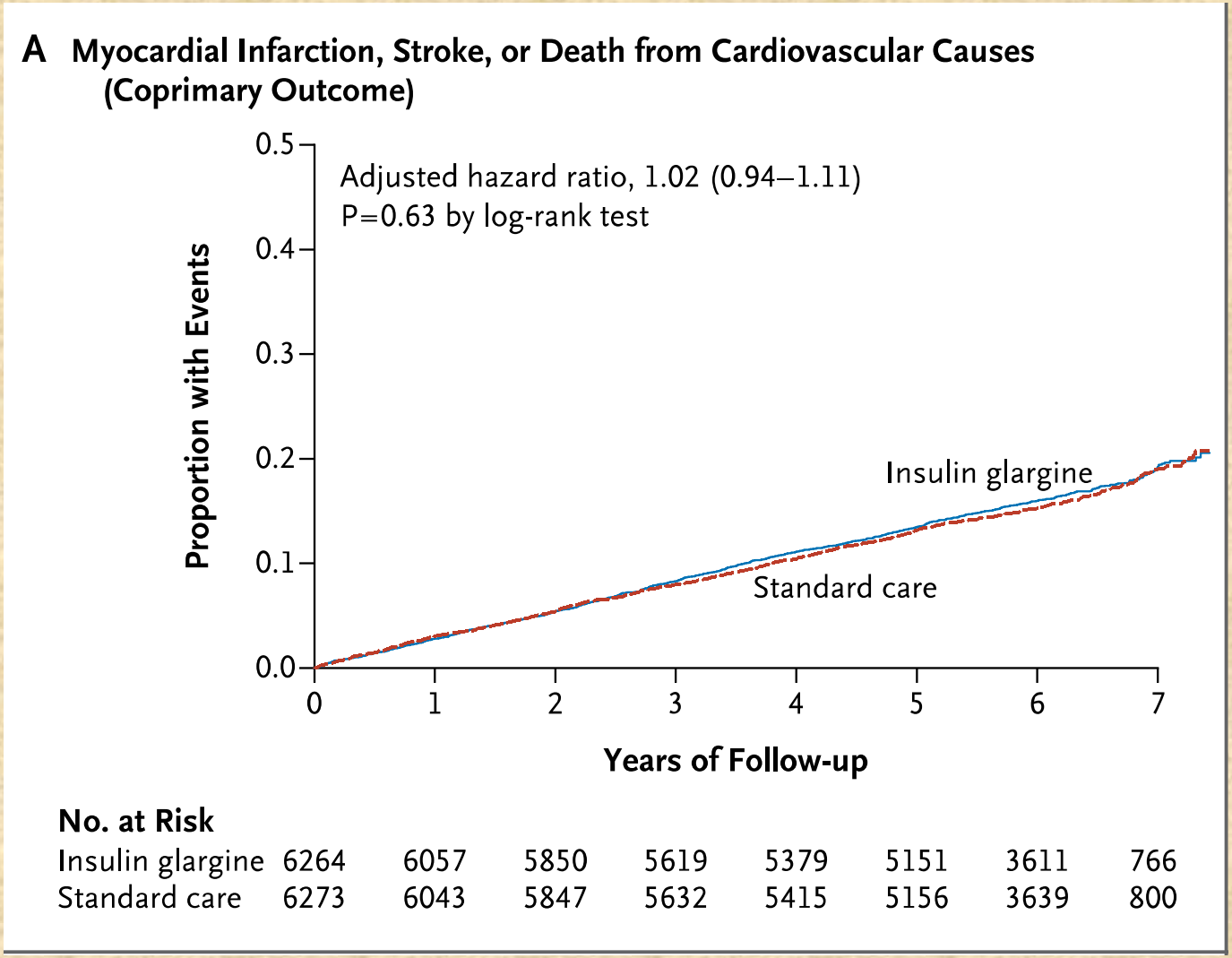
The ORIGIN Study: Hazard Ratios for the coprimary and other outcomes

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	343 (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



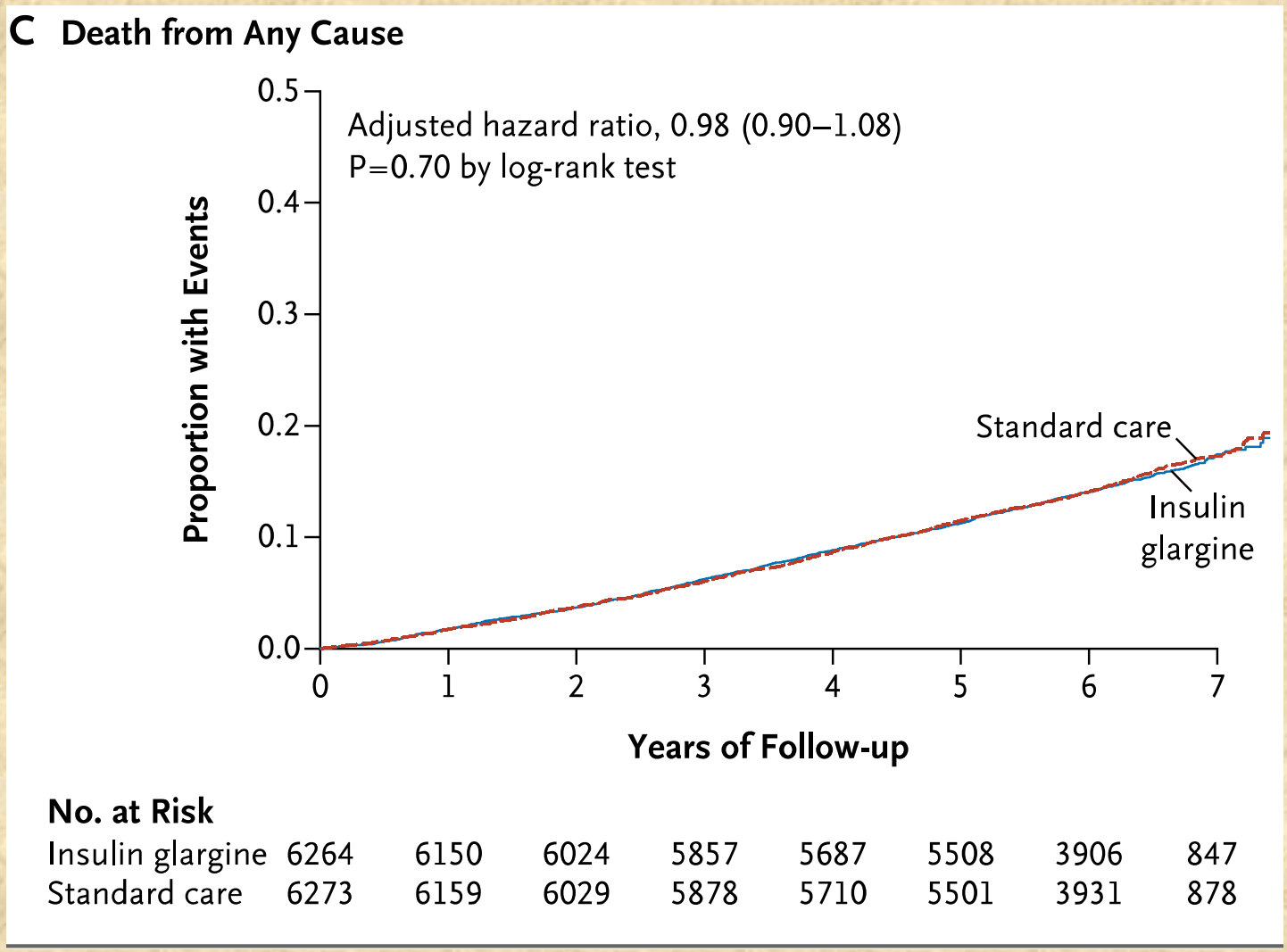
The ORIGIN Trial Investigators; NEJM 2012

The ORIGIN Study: proportion of patients with the coprimary outcome over time



The ORIGIN Trial Investigators; NEJM 2012

The ORIGIN Study: proportion of patients with death from any cause over time



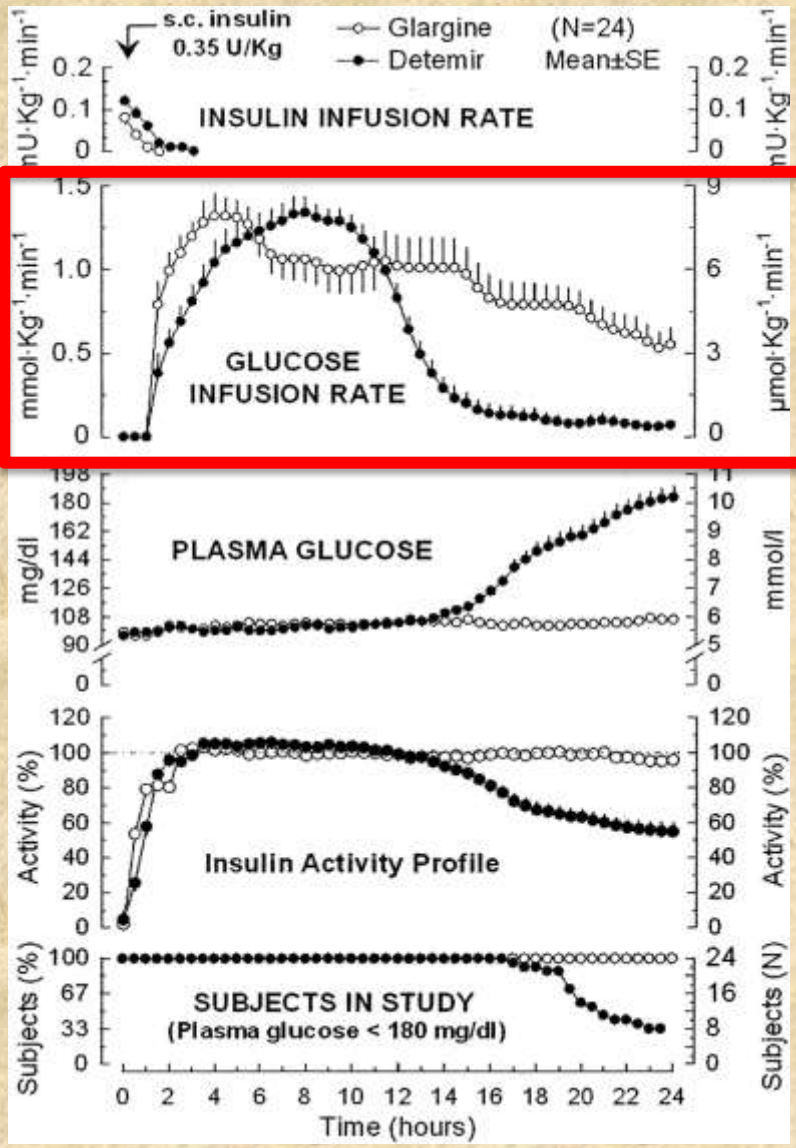
The ORIGIN Trial Investigators; NEJM 2012

Conclusioni

- **L'insulina glargine:**
  - **Ha un profilo farmacodinamico da vera insulina basale**
  - **È altrettanto efficace e induce meno ipoglicemie rispetto alle insuline intermedie**
  - **Ha algoritmi di titolazione semplici ed efficaci**
  - **È stata studiata in combinazione con insuline prandiali e con tutte le classi di farmaci orali anti-diabete**
  - **È l'analogo insulinico con il profilo di sicurezza meglio documentato (ORIGIN trial)**
  - **È il benchmark e comparator di riferimento**
    - **Per le nuove insuline basali**
    - **Per i biosimilari**
    - **Per altri farmaci iniettabili**

Grazie dell'attenzione

Glargine vs Detemir: a pharmacodynamic comparison



Porcellati F et al.; Diabetes Care 2007

Insulin detemir vs glargine: hypoglycemic episodes. A Cochrane review.

Hypoglycemic events per 100 patients' days			
Episodes	**Studies (N)**	**Participants (N)**	**Rate Ratio [95% C.I.]**
Total	**4**	**2252**	**1.00 [0.90, 1.11]**
Severe	**4**	**2252**	**0.88 [0.59, 1.30]**
Nocturnal	**4**	**2242**	**1.0 [0.93, 1.09]**

Swinnen SG. et al.; Cochrane Rev 2011

Efficacy of insulin glargine vs NPH in patients with type 1 diabetes. A Cochrane review.

Outcome	Studies (N)	Participants (N)	Mean difference Glargine vs NPH [95% C.I.]
HbA_{1c}	12	3249	-0.07% [-0.13 , -0.01]
FPG	6	2377	-0.45 mmol/L [-0.73 , -0.16]
Mean SMBG	4	540	-0.49 mmol/L [-0.73 , -0.16]

Vardi M. et al.; Cochrane Rev 2008

Insulin glargine vs NPH in patients with type 1 diabetes: hypoglycemic episodes. A Cochrane review.

Hypoglycemic events per 100 patients' days			
Episodes	Studies (N)	Participants (N)	Mean difference Glargine vs NPH [95% C.I.]
Total	7	1675	-0.41 [-0.54 , -0.27]
Severe	7	1614	-0.00 [-0.02 , +0.02]
Nocturnal	8	1746	-0.14 [-0.21 , -0.07]

Vardi M. et al.; Cochrane Rev 2008

Insulin glargine vs NPH in patients with type 1 diabetes: patients with hypoglycemia. A Cochrane review.

Percent of participants with hypoglycemia			
Episodes	Studies (N)	Participants (N)	Odds Ratio (M-H, Fixed) [95% C.I.]
Total	8	2918	0.96 [0.79, 1.17]
Severe	10	2871	0.76 [0.58, 0.98]
Nocturnal	6	2311	0.84 [0.70, 1.00]

Vardi M. et al.; Cochrane Rev 2008