Vecchie e nuove insuline a confronto

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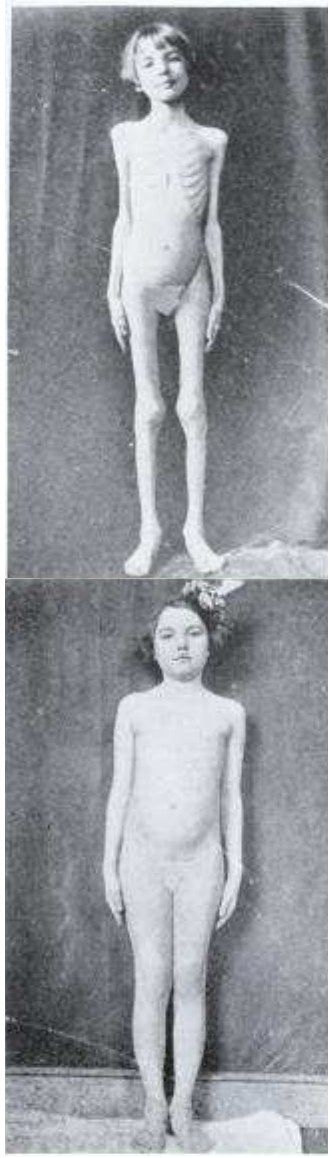
Insulina: breve storia di una scoperta straordinaria

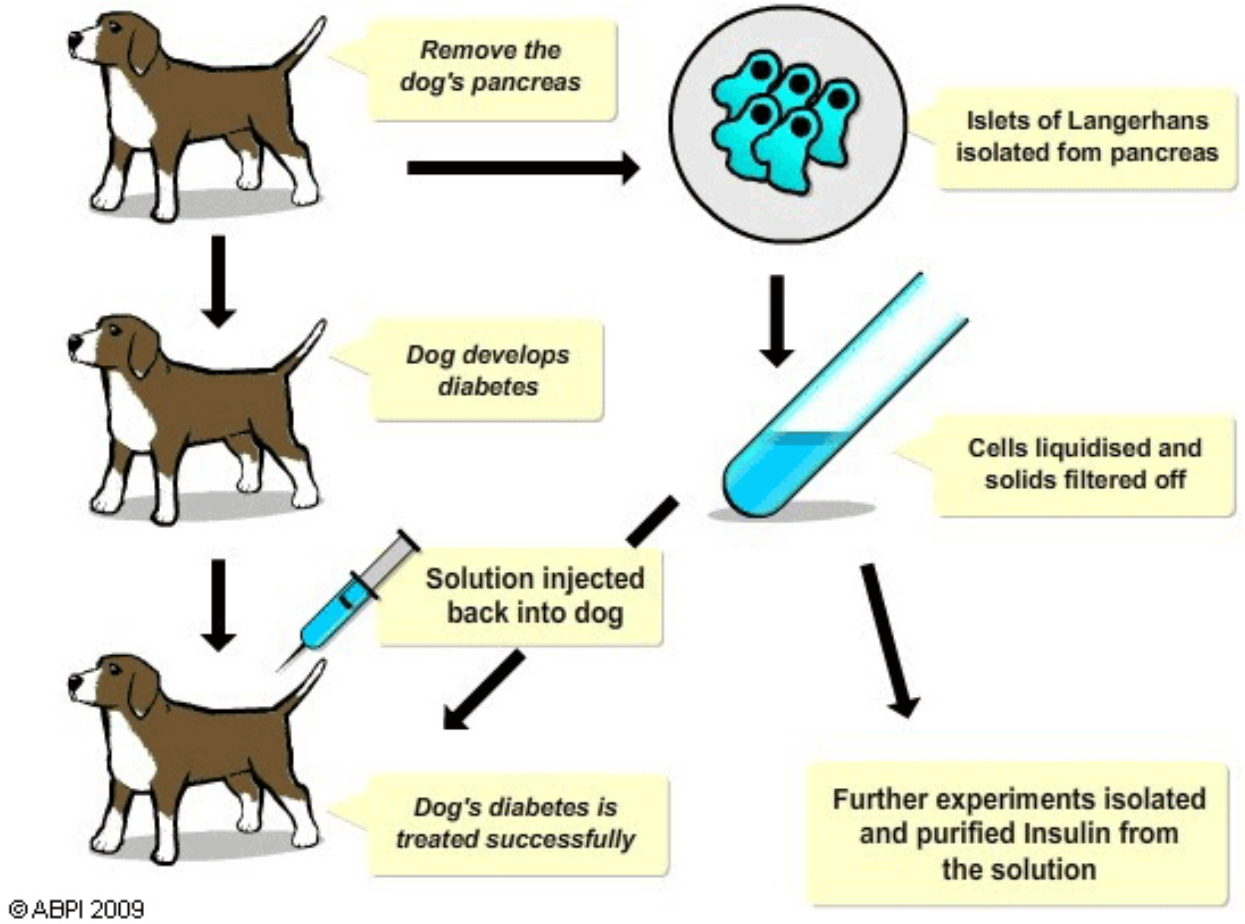


diabetes mellitus

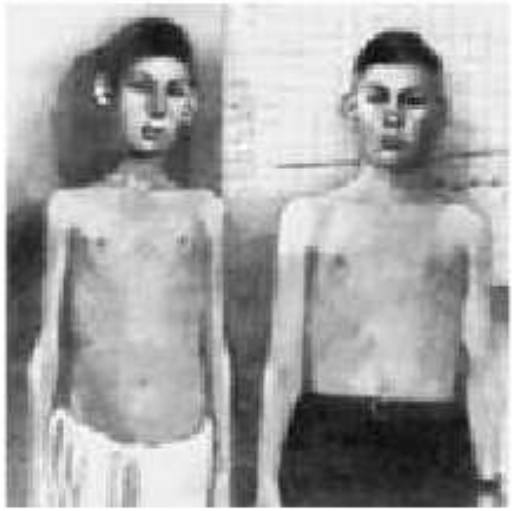
(dia=attraverso; bainein= passare; mellitus= dolce)
(Areteo di Capadocia I secolo d.C)

- Symptoms: always hungry and thirsty, glucose in urine, tired, blurred vision, extreme weight loss.
- Prognosis: slow, painful death

Banting's experiments (oct 1920)



First Human Patient



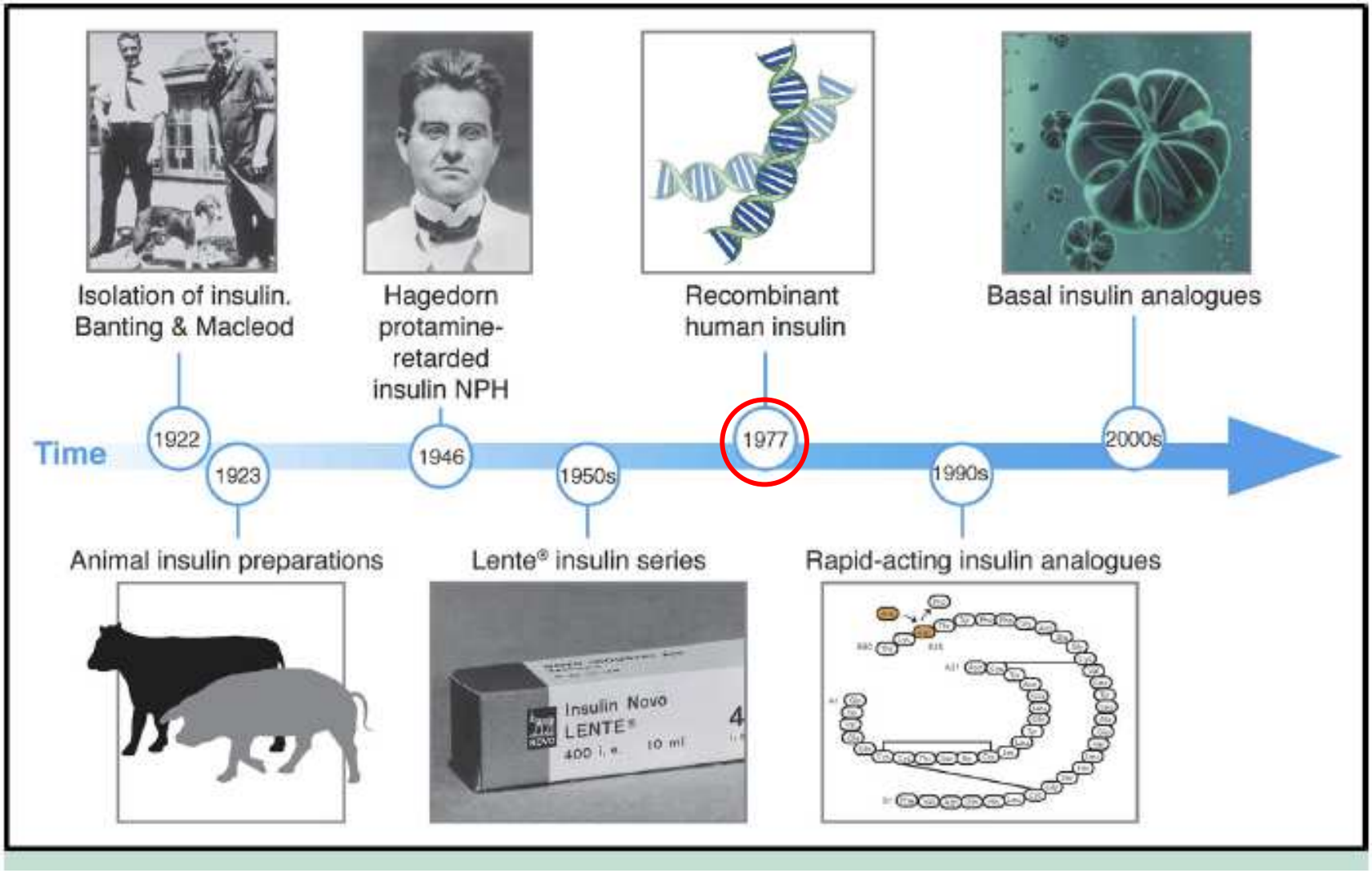
On Jan. 11, 1922, 14-year-old Leonard Thompson was the first human patient to receive insulin made by Banting and Best.

The initial test failed, causing only slight reductions in blood glucose levels.

A second series of "purified" insulin injections, produced by J.B. Collip, achieved the desired results.

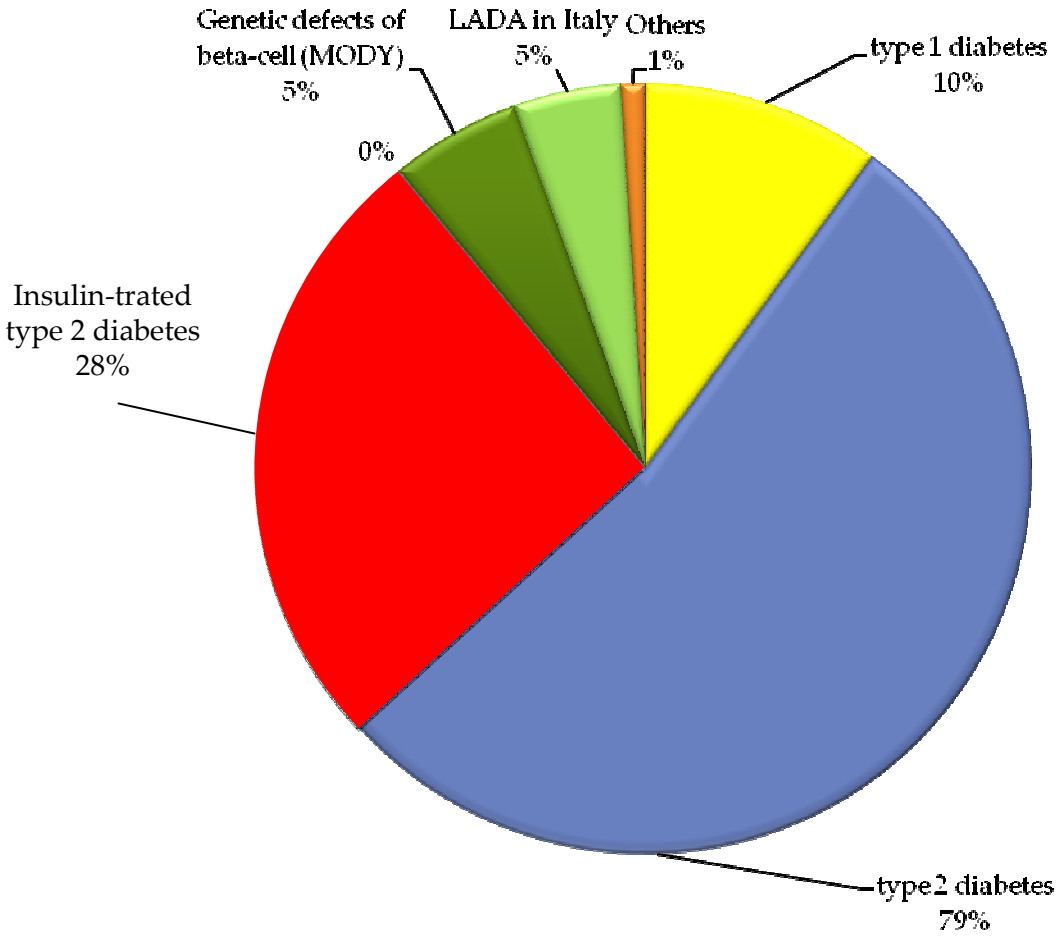
Leonard's blood glucose dropped to normal, and he began to gain weight.

Milestone in the evolution of insulin therapy



Tibaldi J Am J of Medicine 2014

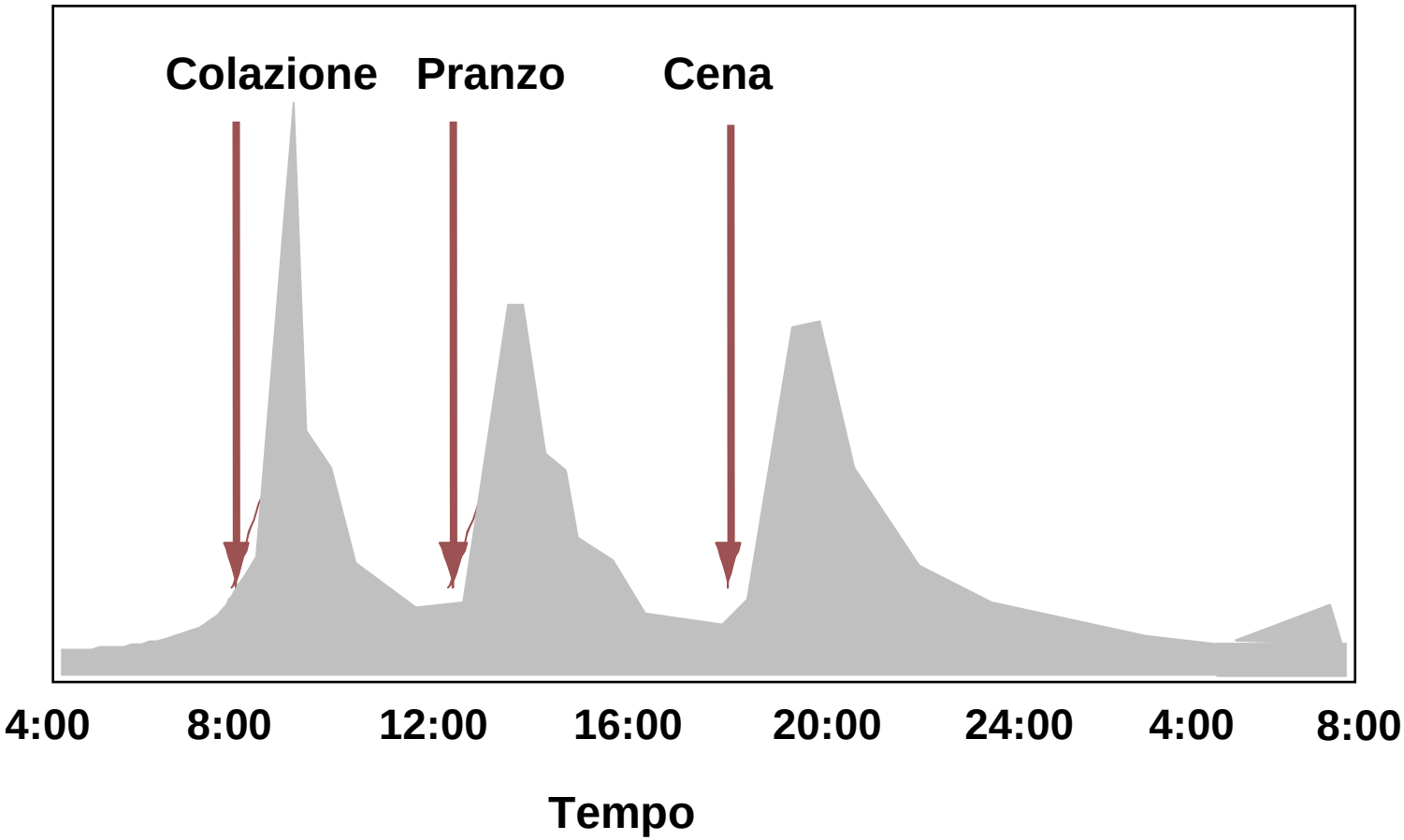
Diabetes Classification



Componenti del fabbisogno insulinico

BASALE:
- ✓controlla gluconeogenesi e la glicogenolisi
- ✓favorisce l'uptake di glucosio nei tessuti
- ✓inibisce la chetogenesi

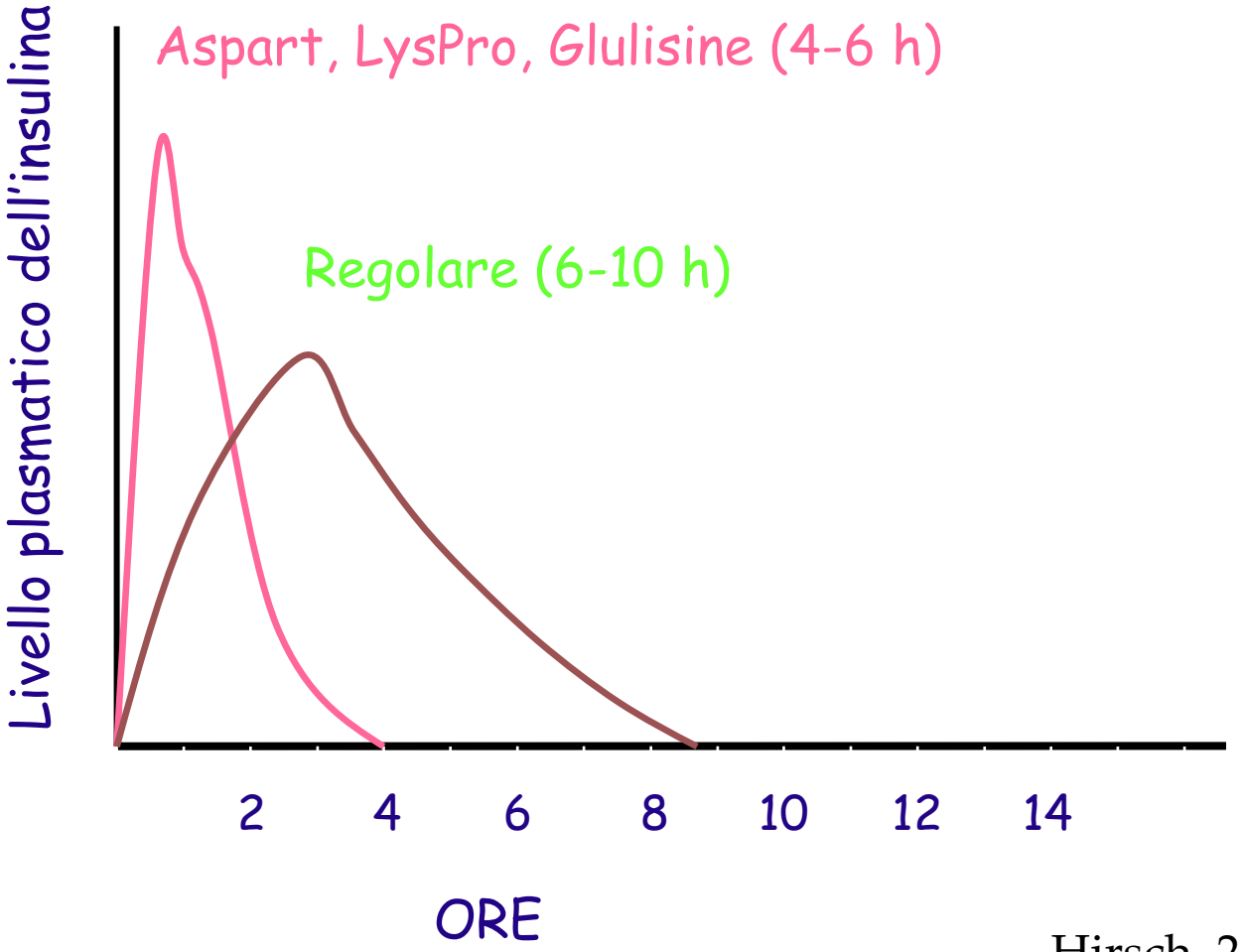
PRANDIALE:
- ✓risponde alla assunzione di CHO del pasto



Fabbisogno prandiale: insuline ad azione rapida/ultrarapida

TIPO	INIZIO	PICCO	DURATA
Insuline Umane REGOLARE (RAPIDA) ACTRAPID/HUMULIN R	30-60 mins	2-3 hrs	4-6 hrs
Analoghi ad azione rapida LISPRO (HUMALOG) ASPART (NOVORAPID) GLULISINA (APIDRA)	<15 mins	30-90 mins	<5 hrs

Profilo farmacocinetico analoghi rapidi/ultrarapidi

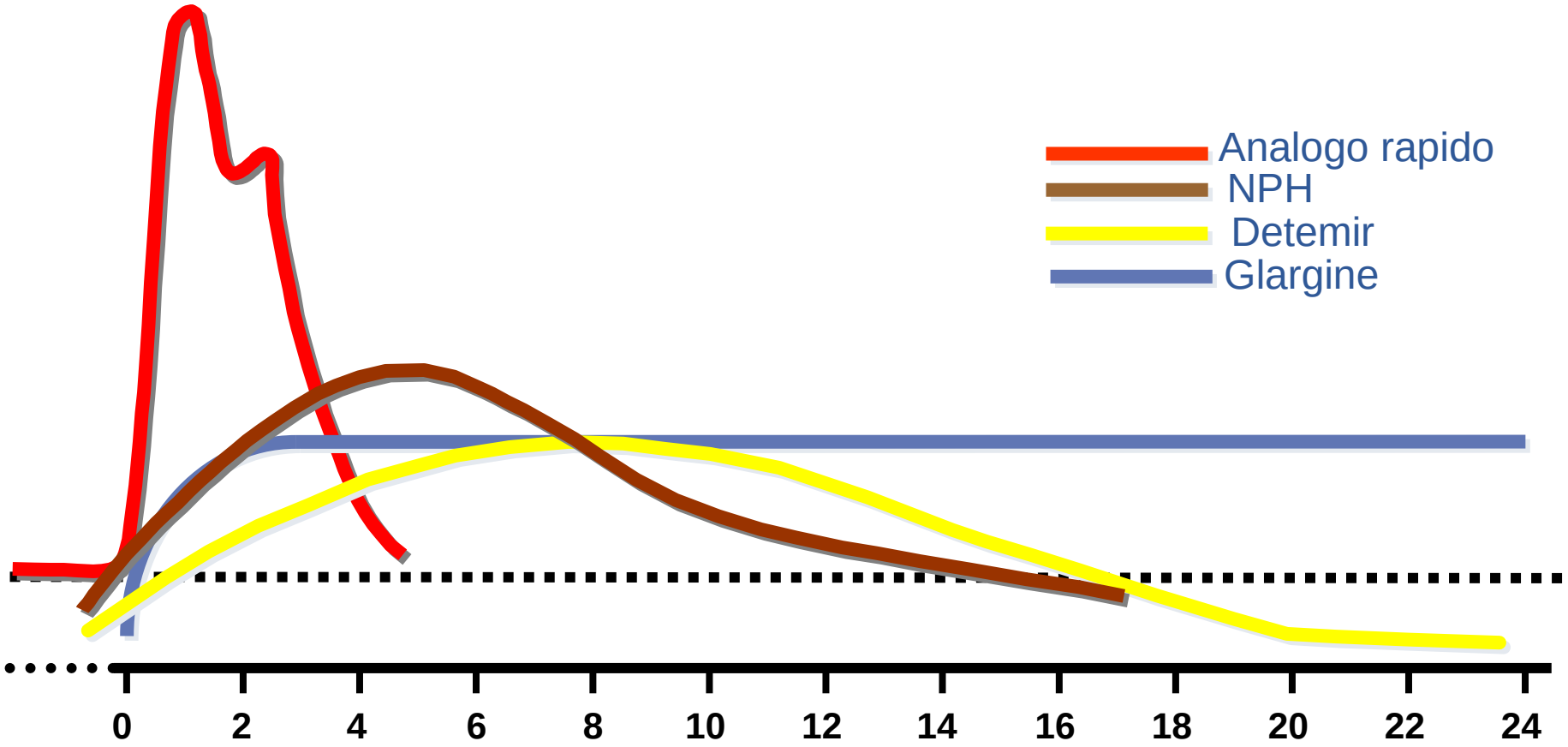


Hirsch, 2005

Fabbisogno basale: insuline lente

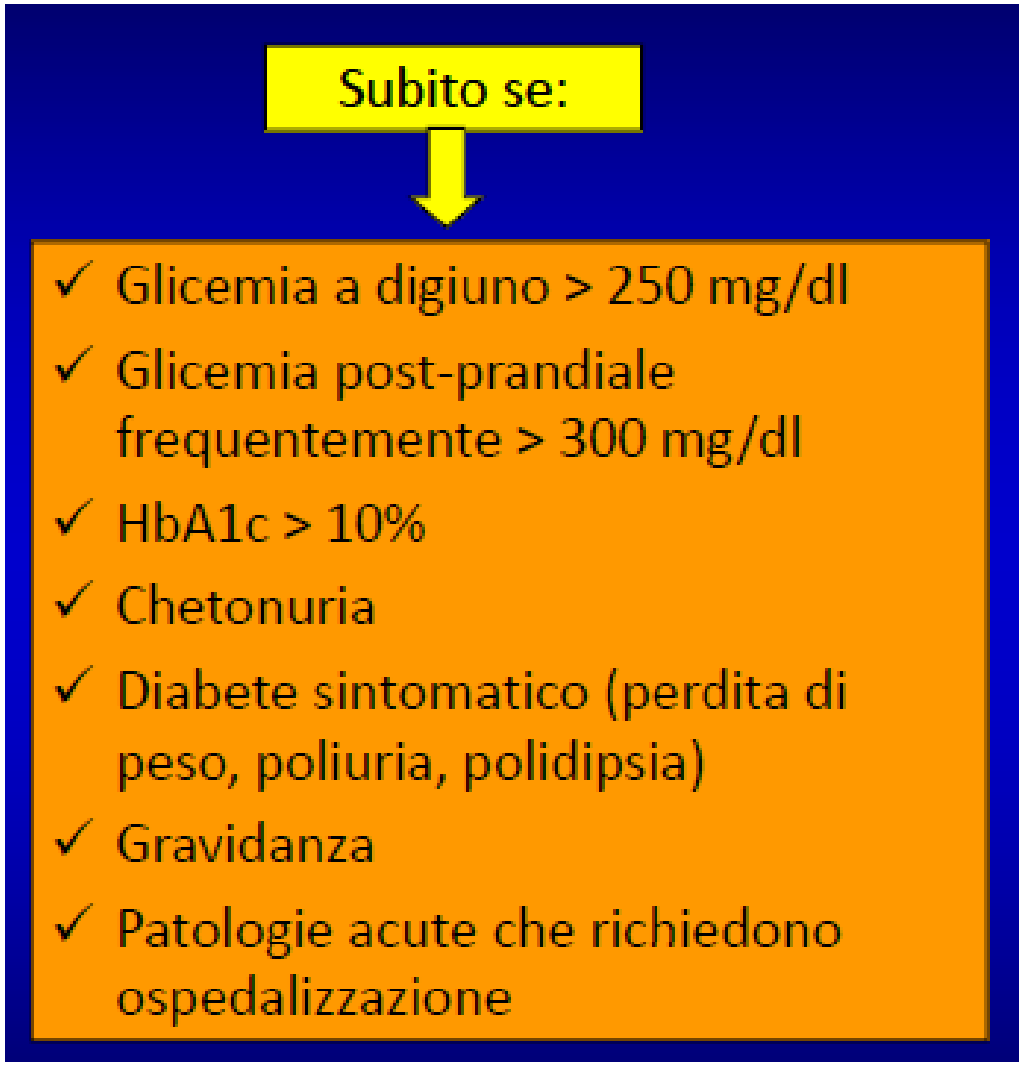
TIPO	INIZIO	PICCO	DURATA
Insuline umane NPH (INTERMEDIA) Protaphane o HUMULIN I	2-4 hrs	6-10hrs	12-18 hrs
GLARGINE (Lantus)	1.5 hours	peakless	18 to 26 hours
DETEMIR (Levemir)	1 hour	peakless	Dose dependent
Lispro Protamina (Humalog Basal)	1 - 4 hrs	6 hrs	15 hrs

Profilo farmacocinetico insulina NPH ed analoghi lenti

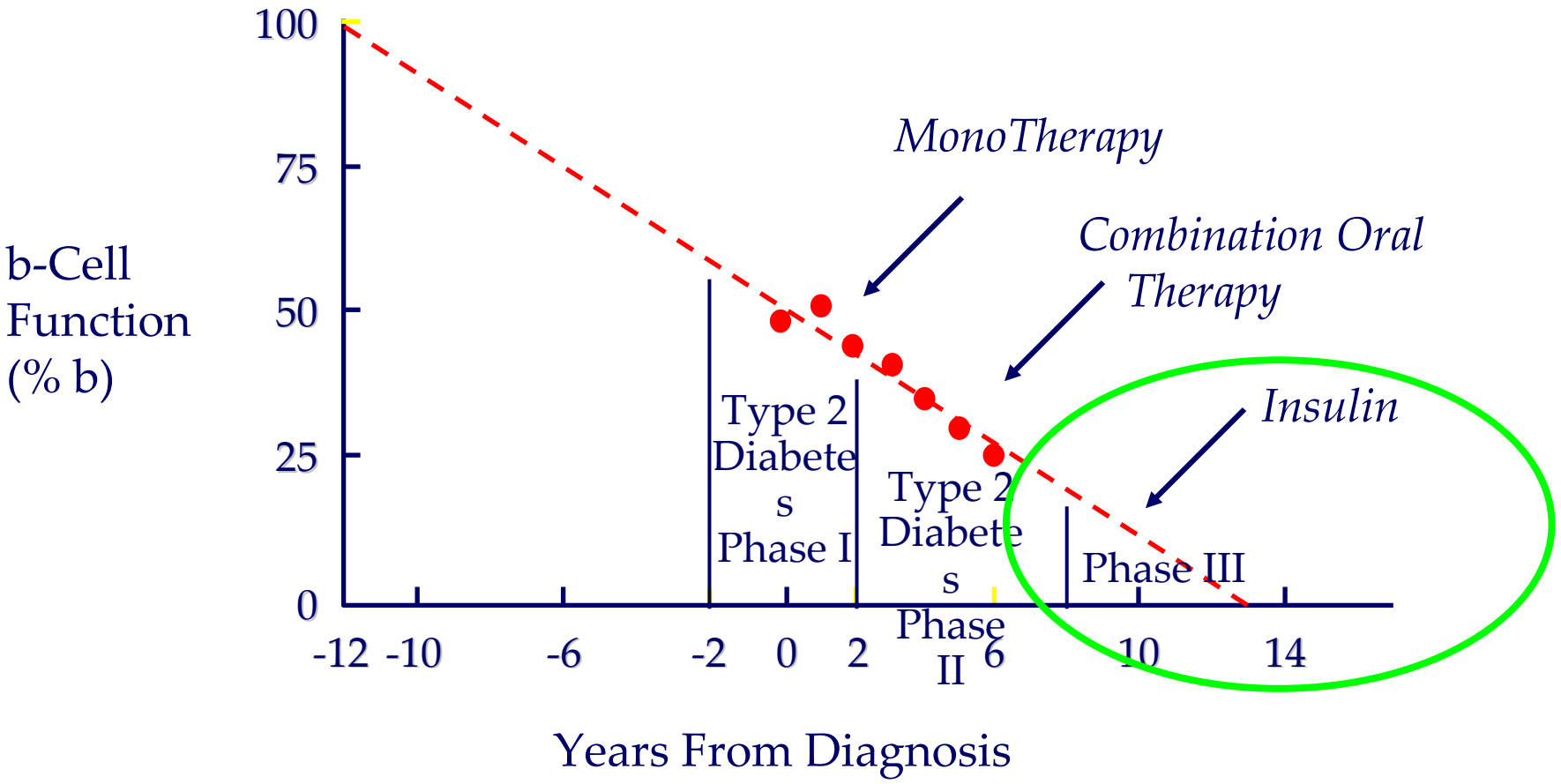


Hirsch IB et al. – NEJM 2005; 352: 174-183

Quando iniziare una terapia insulinica nel diabete tipo 2?


Subito se:
✓ Glicemia a digiuno > 250 mg/dl
✓ Glicemia post-prandiale frequentemente > 300 mg/dl
✓ HbA1c > 10%
✓ Chetonuria
✓ Diabete sintomatico (perdita di peso, poliuria, polidipsia)
✓ Gravidanza
✓ Patologie acute che richiedono ospedalizzazione

Stages of Type 2 Diabetes:

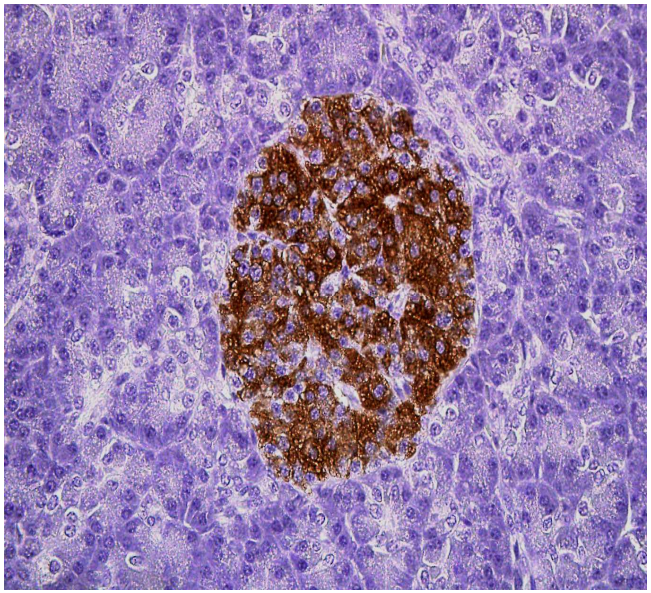


Based on data of UKPDS 16: *Diabetes.* 1995.

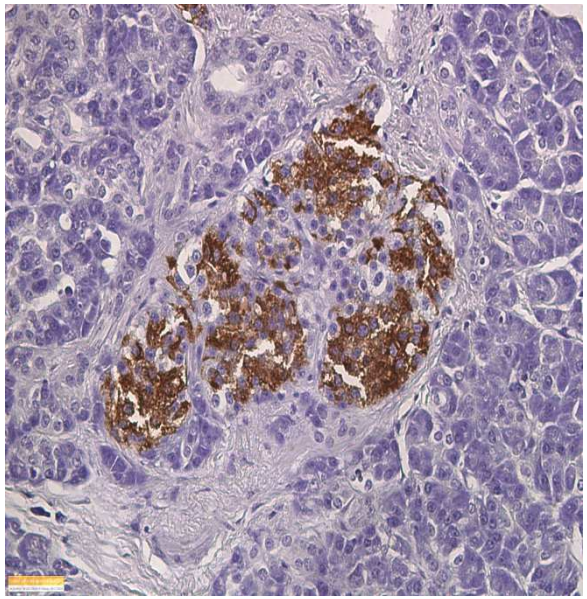
The beta-cell in diabetes

- Decreased islet mass[1–3]
- Decreased beta-cell mass[4–6]

Normal Islet

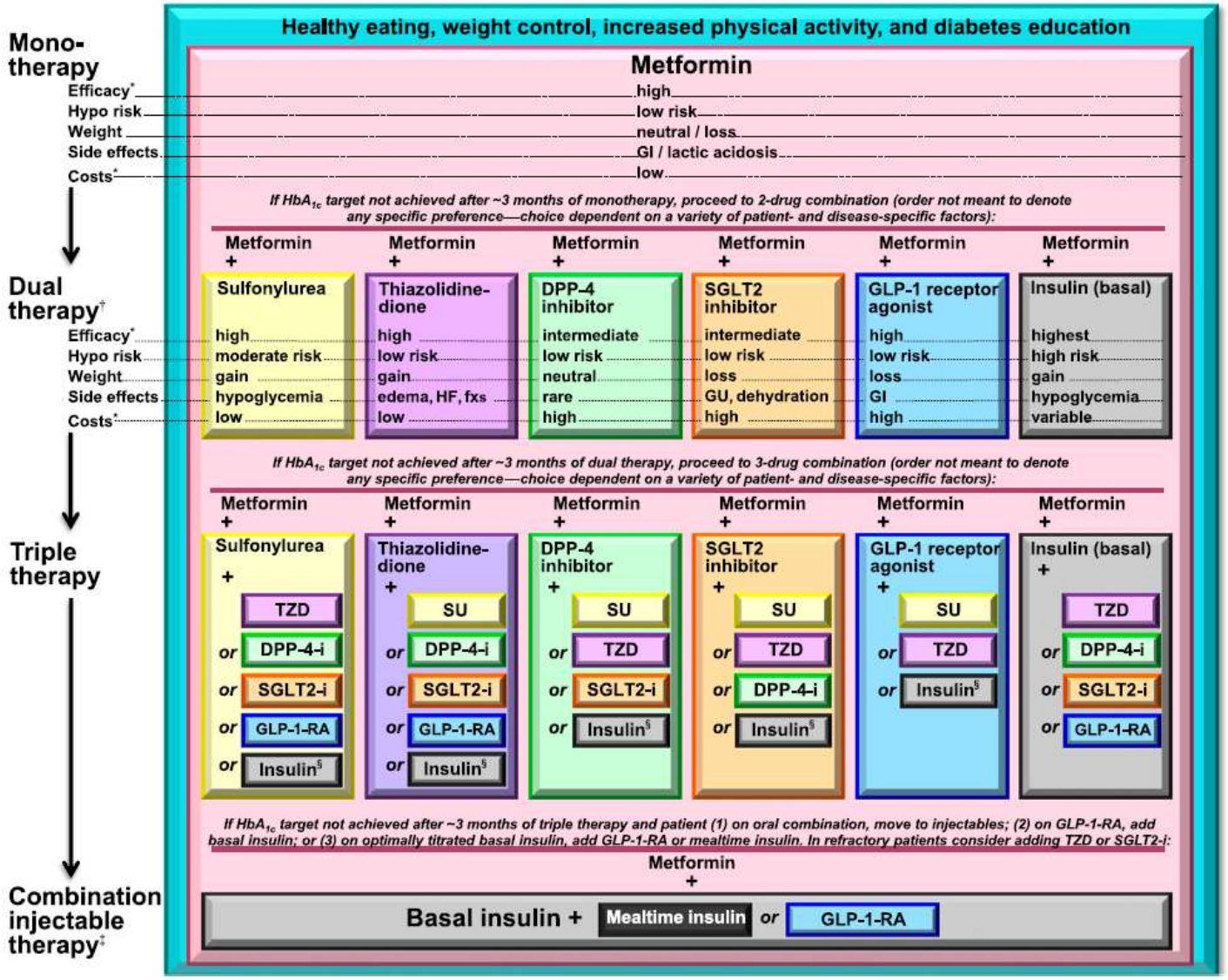


Type 2 Diabetic Islet



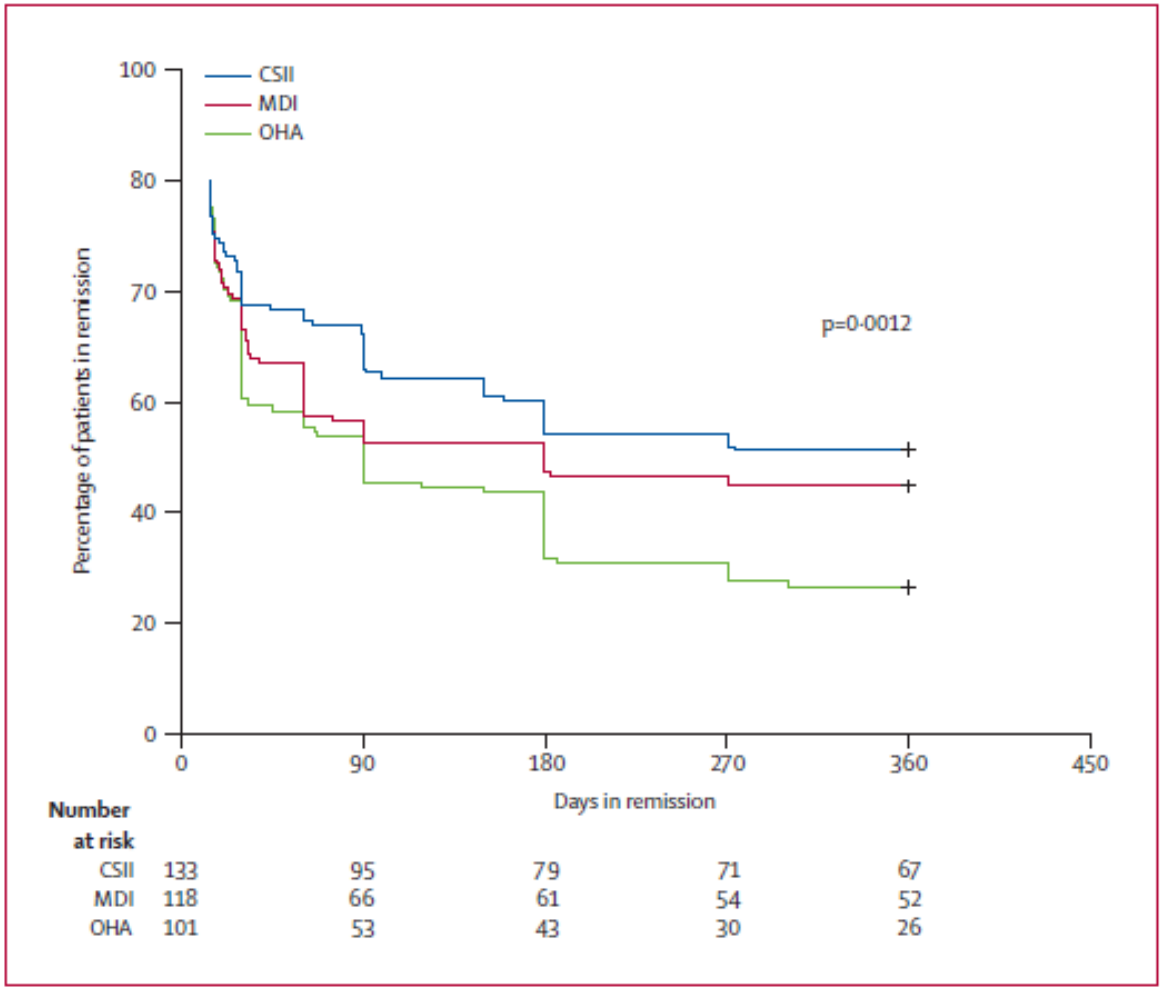
1. Gepts W, et al. Am J Med. 1981;70:105–115
2. Saito K, et al. Tohoku J Exp Med. 1978;125:185–197
3. Westermark P, et al. Diabetologia. 1978;15:417–421
4. Butler AE, et al. Diabetes. 2003;52:102–110;
5. Sakuraba H, et al. Diabetologia. 2002;45:85–96
6. Stefan Y, et al. Diabetes 1982;31:694–700

Management of Hyperglycemia in Type 2 Diabetes, 2015: A Patient- Centered Approach (ADA-EASD)



Diabetes Care 2015

Percentage of newly diagnosed type 2 diabetic patient in remission in 1 year



N=382

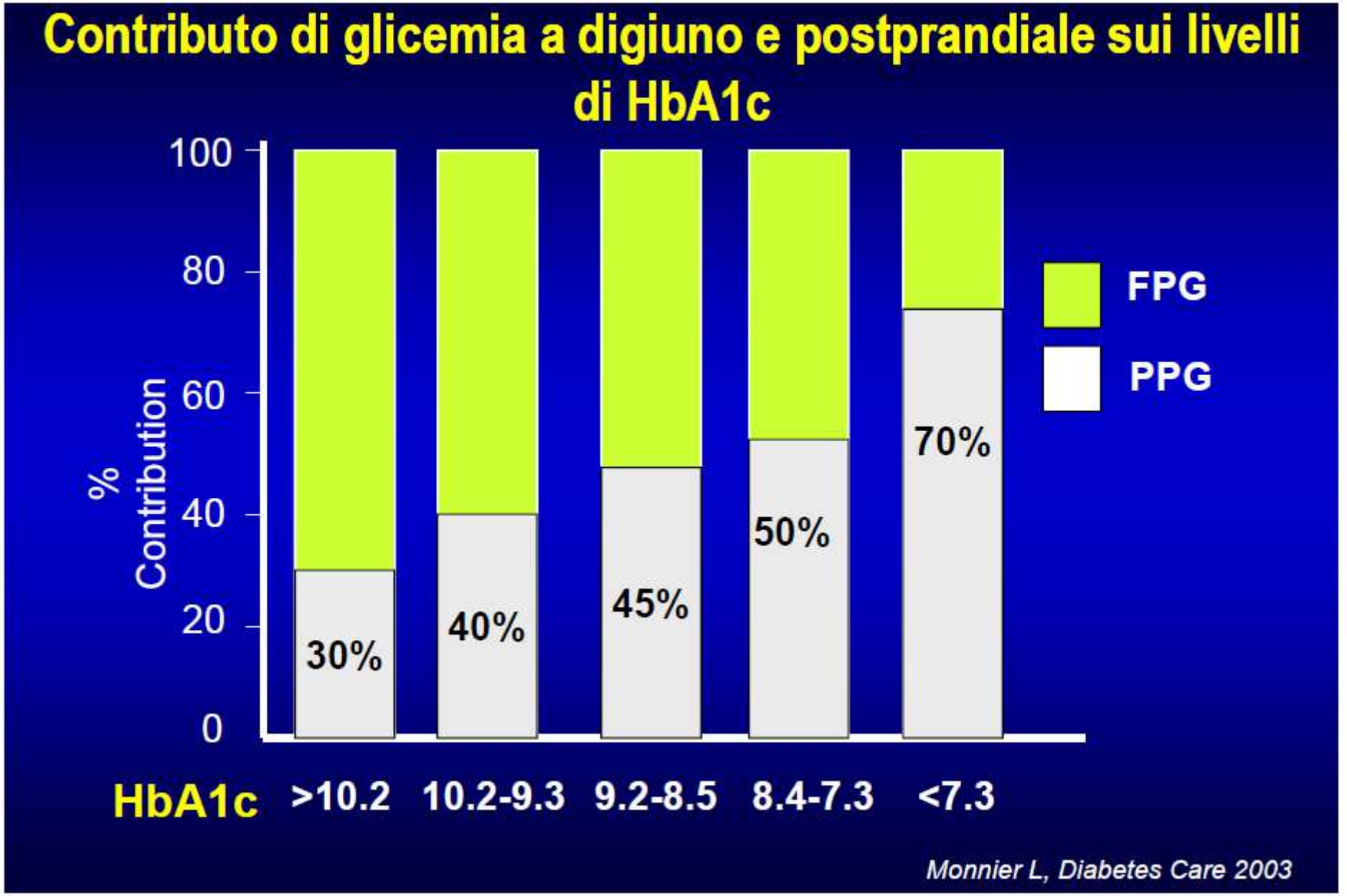
Weng J Lancet 2008

Alterazioni beta-cellulari su cui agisce l'insulina

Alterazioni metaboliche reversibili
Glucotossicità
Lipotossicità
Alterazione di ormoni e citochine
Ridotta azione incretinica
Aumentata secrezione di glucagone
Eccesso di citochine pro-infiammatorie
Alterazioni di proteine beta-cellulari
Recettore insulinico, IRS-1
Riduzione della massa beta-cellulare
Accumulo di amiloide
Apoptosi

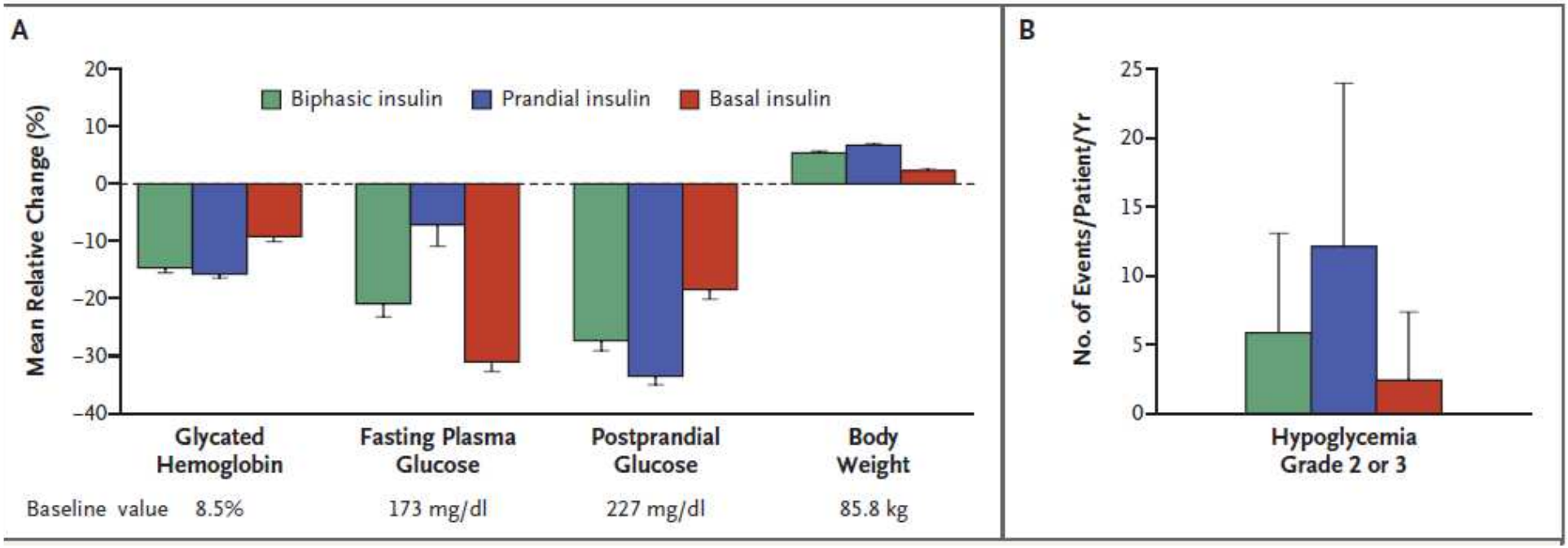
Con che schema iniziare una terapia insulinica nel diabete tipo 2?

Contributo di glicemia a digiuno e postprandiale sui livelli di HbA1c



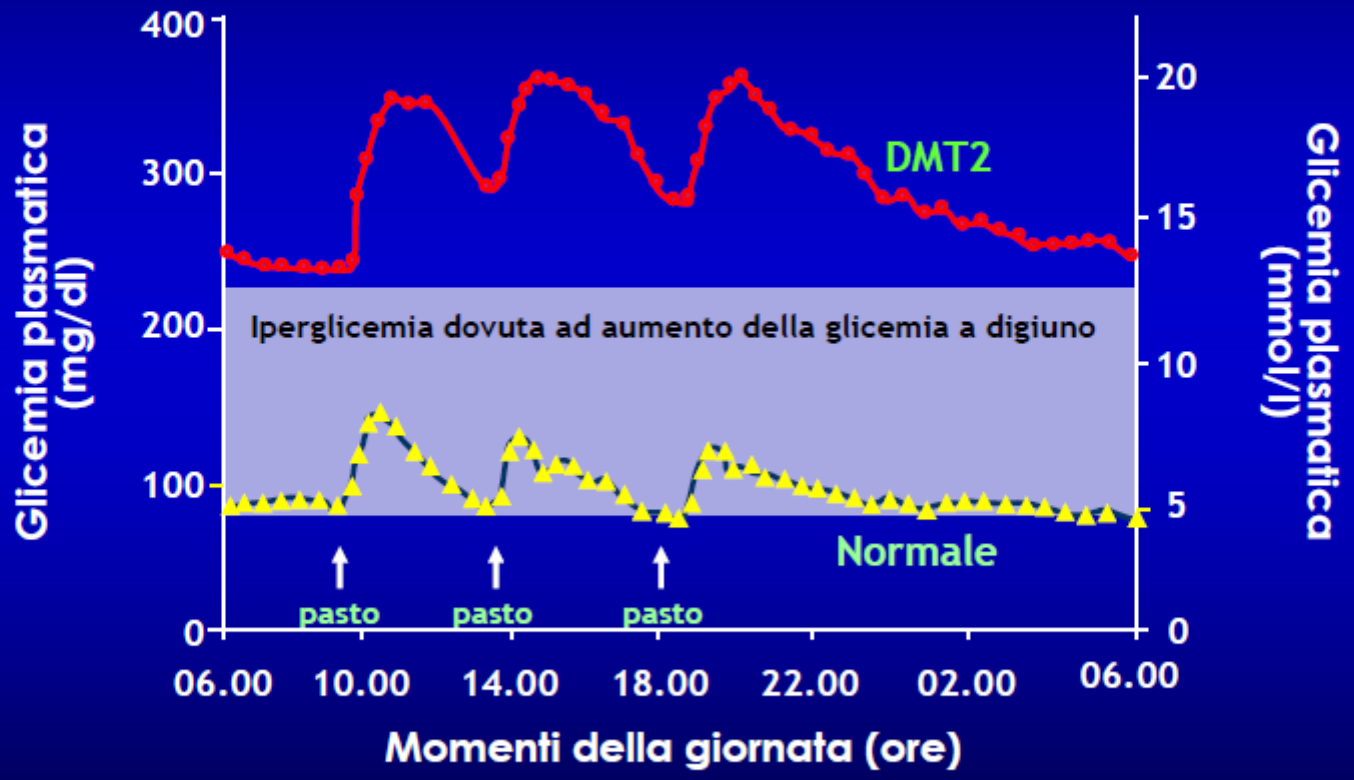
Monnier L, Diabetes Care 2003

Addition of biphasic, prandial or basal insulin to OT in type 2 Diabetes 4-T STUDY



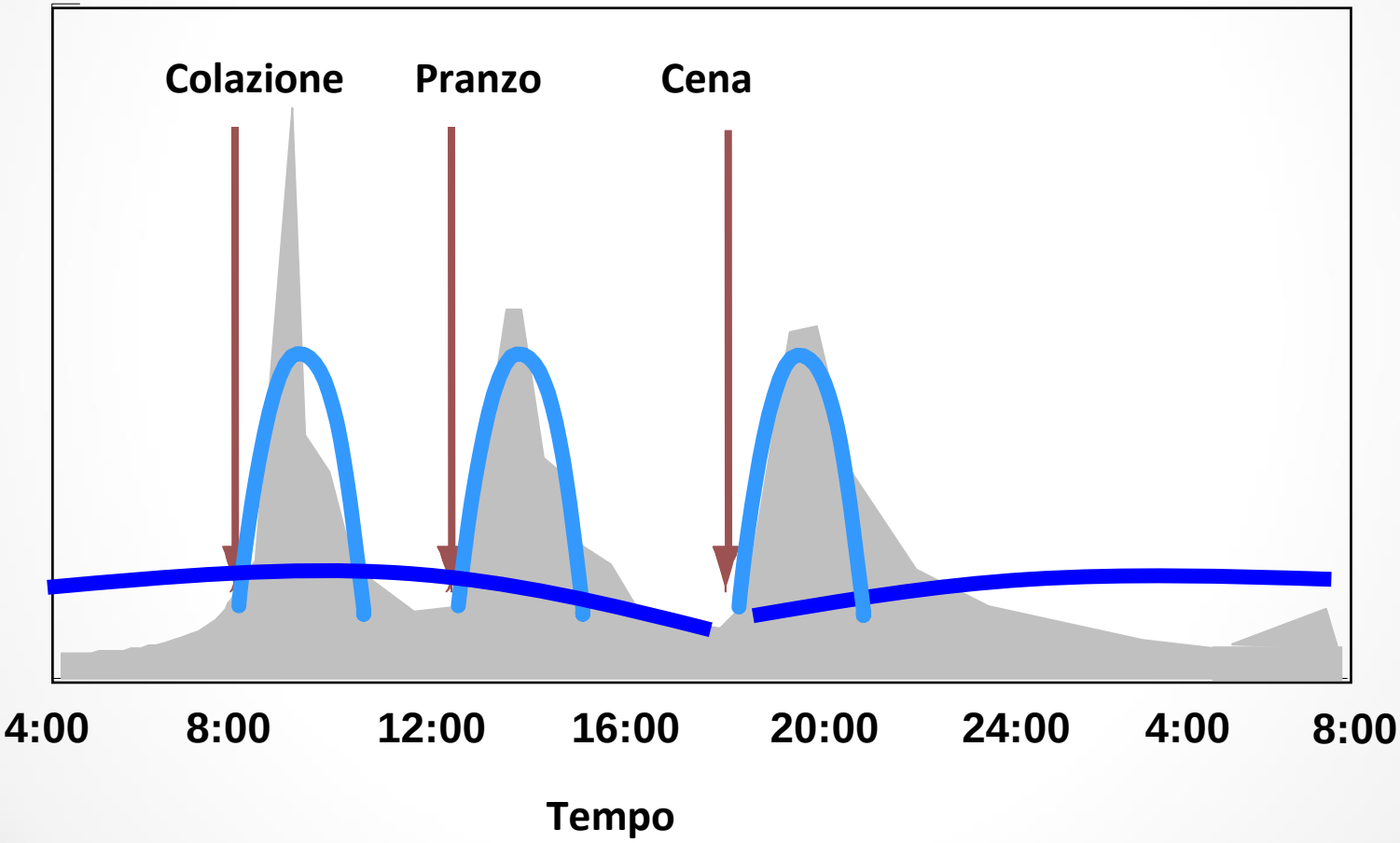
Holman R. NEJM 2007

Il trattamento dell'iperglicemia a digiuno determina un profilo glicemico più basso nelle 24 ore



Llivelli glicemici delle 24 ore in soggetti sani e in pazienti con diabete ($p<0.001$).
Adattato da Hirsch I, et al. Clin Diabetes 2005;23:78–86.

Schemi di terapia insulinica: dal basal plus al basal bolus



Considerazioni nella terapia insulinica

- ✓Efficacia
- ✓Effetti sul peso
- ✓Rischio ipoglicemico
- ✓Safety cardiovascolare
- ✓Safety mitogenica

Considerazioni nella terapia insulinica

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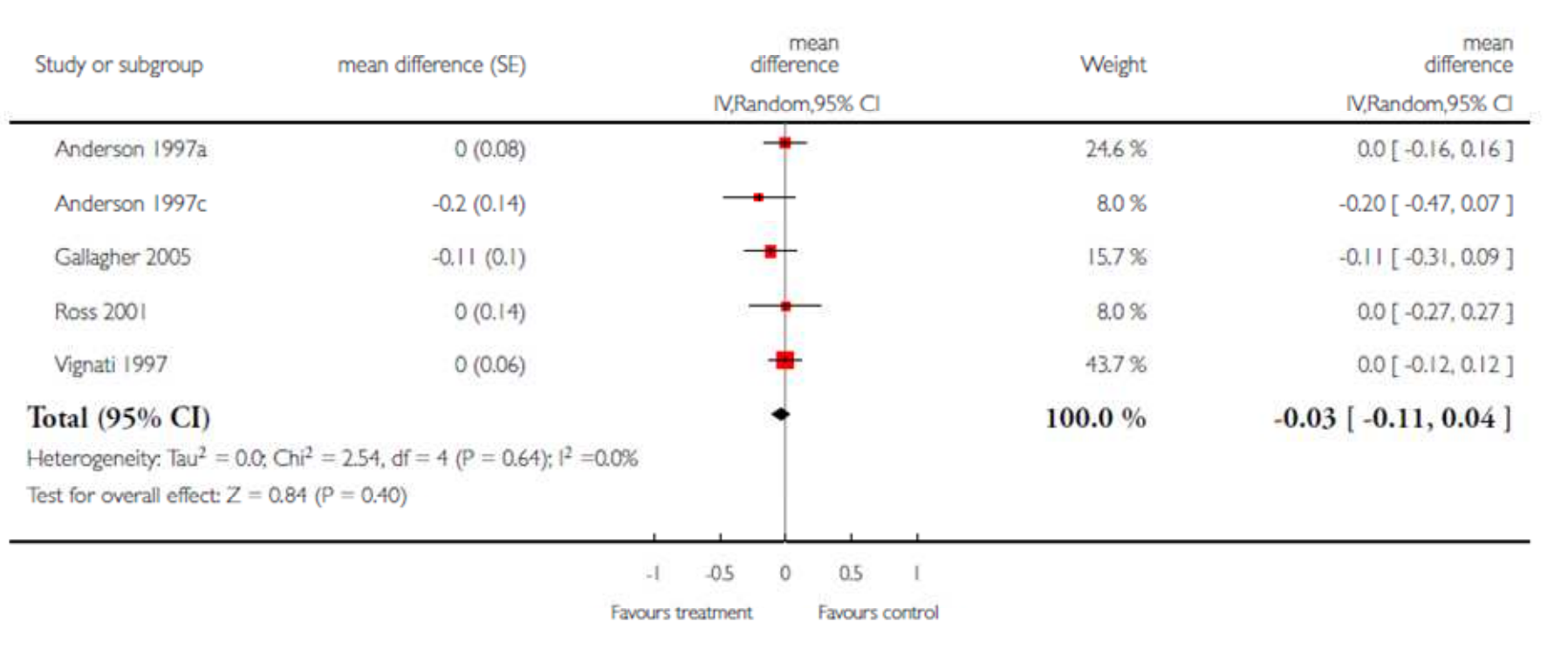
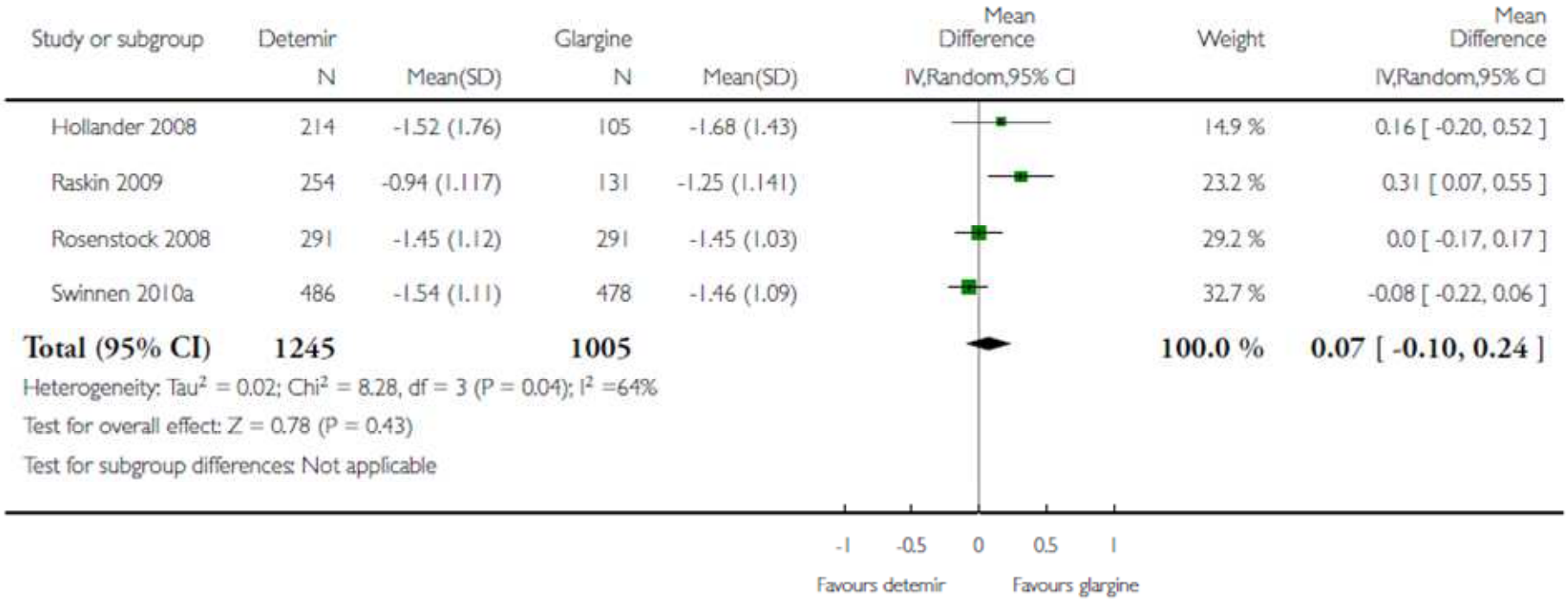
Type 2 diabetes short acting analogues vs structurally unchanged insulin: outcome HbA1C



Insulin detemir vs insulin glargine for type 2 diabetes: Outcome change in HbA1C

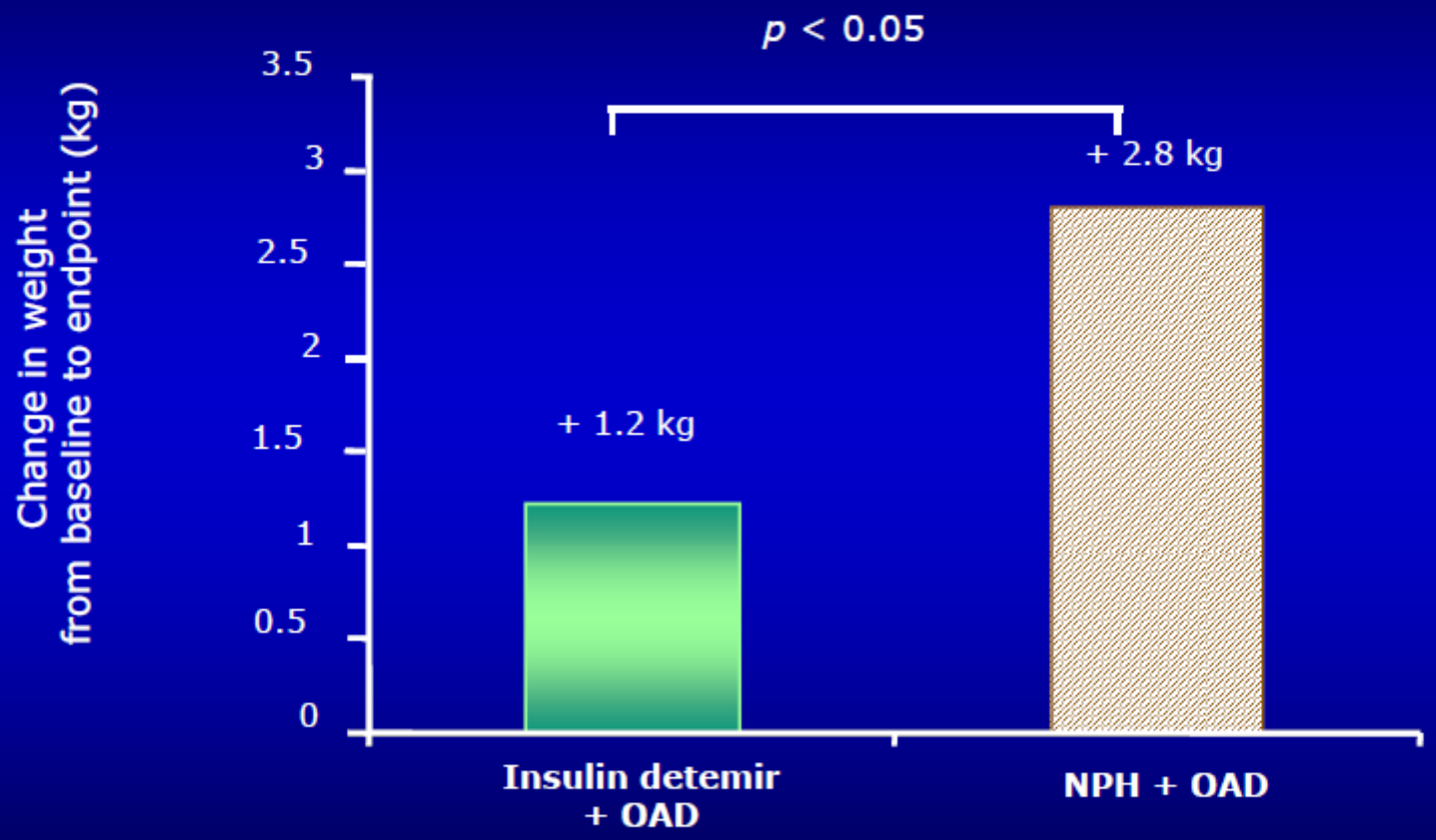


Insulin detemir versus insulin glargine for type 2 diabetes mellitus (Review)

Considerazioni nella terapia insulinica

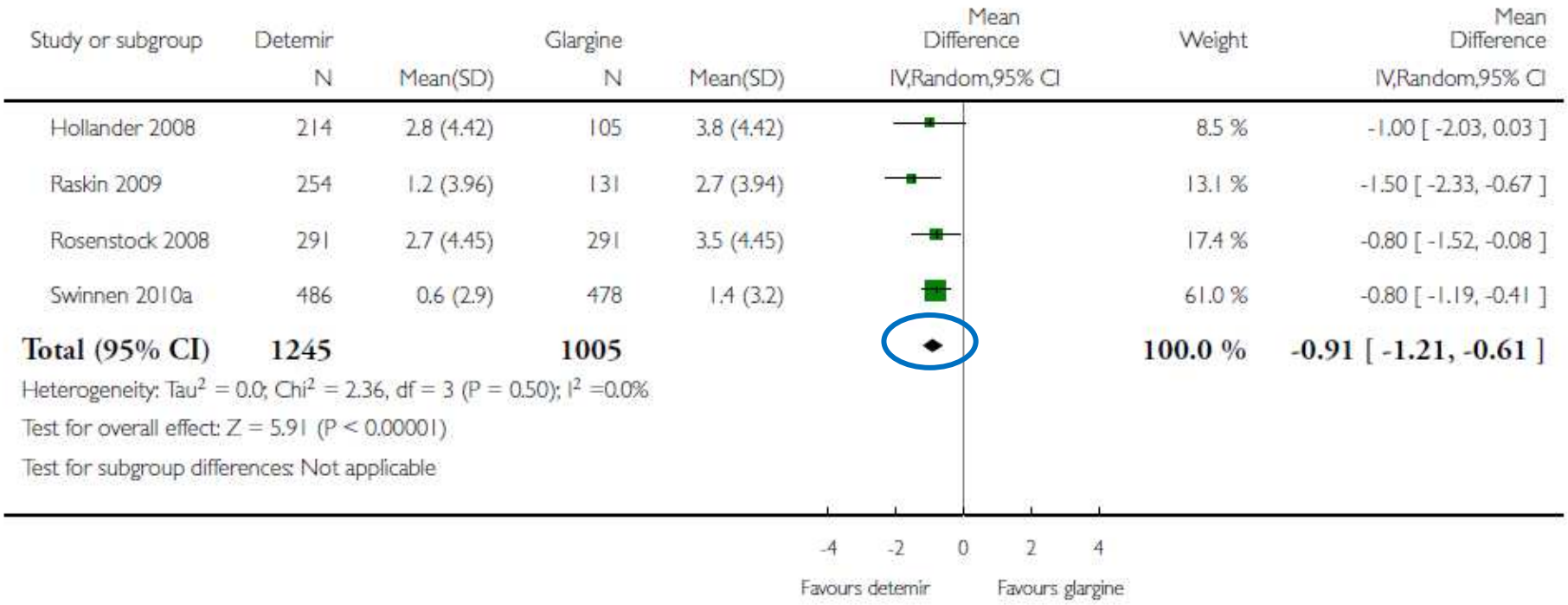
- ✓Efficacia
- ✓Effetti sul peso
- ✓Rischio ipoglicemico
- ✓Safety cardiovascolare
- ✓Safety mitogenica

Insulina Detemir vs. NPH: effetto sul peso



Hermansen *et al. Diabetologia* 2004;47(Suppl. 1):A273

Insulin detemir vs insulin glargine for type 2 diabetes: Outcome weight gain



Considerazioni nella terapia insulinica

- ✓Efficacia
- ✓Effetti sul peso
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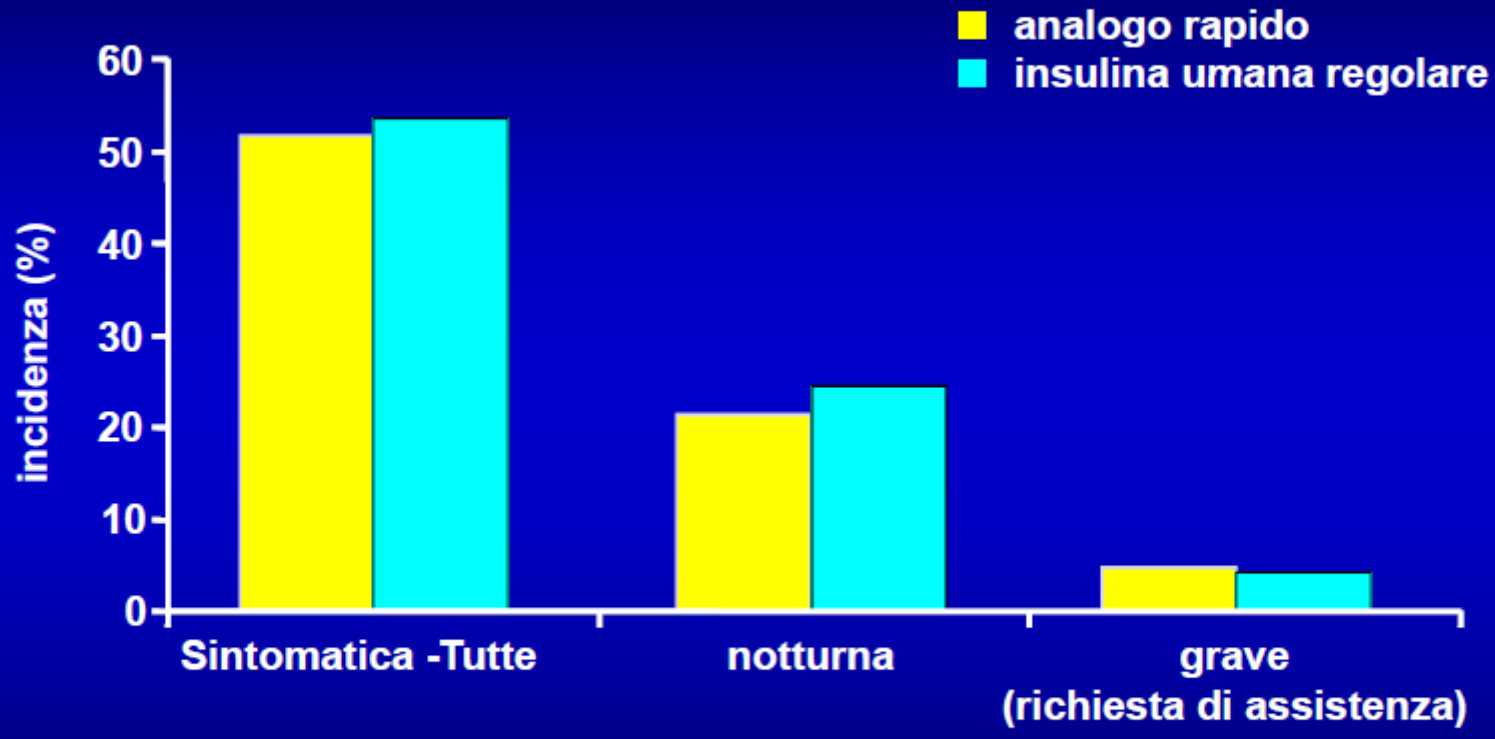
- ✓Safety mitogenica

Incidenza di ipoglicemia sintomatica: confronto tra insulina regolare e analogo rapido

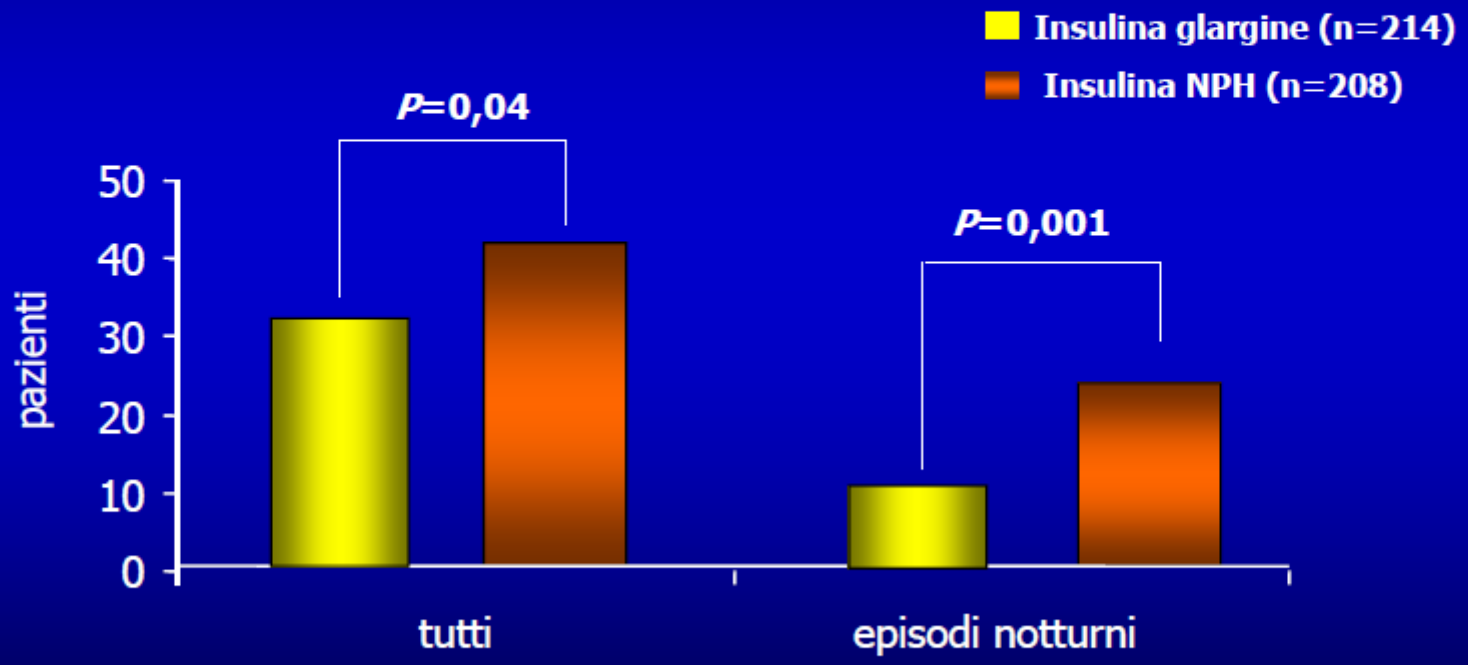


*Proporzione di pazienti con >1 episodio di ipoglicemia dal 4° mese alla fine dello studio.

Dailey G, et al. *Diabetes Care*. 2004;27(10):2363-2368.

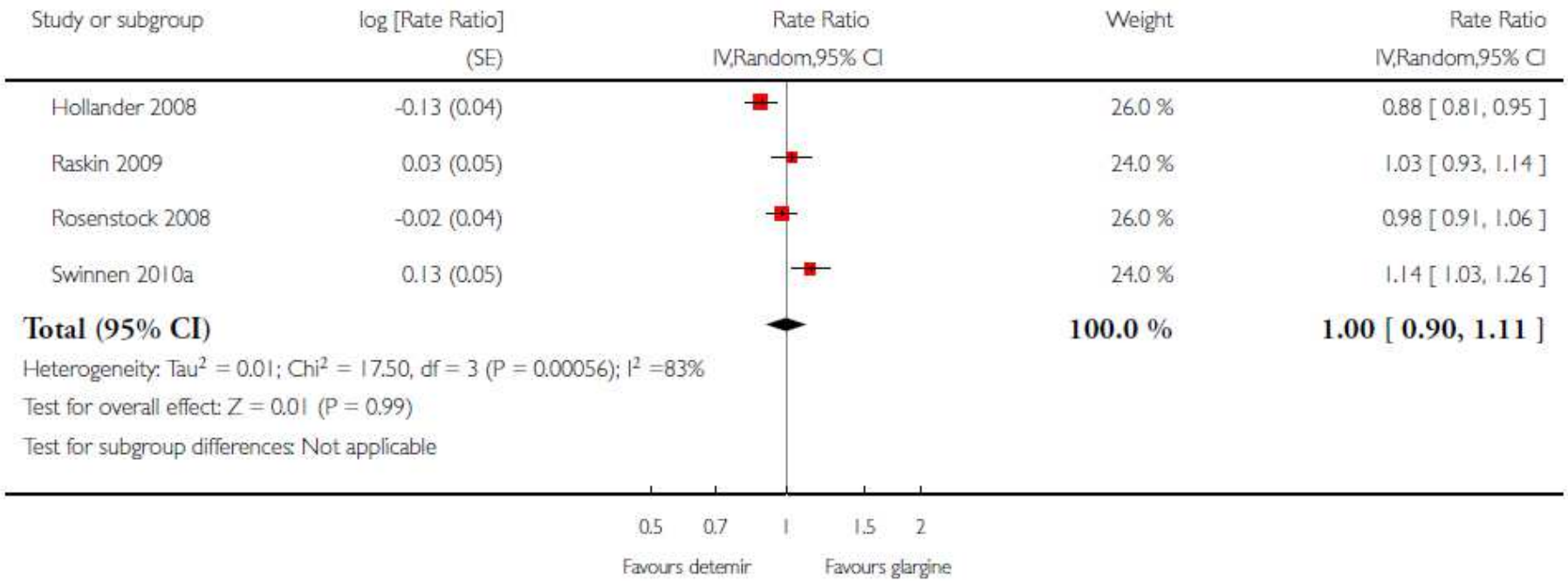
Raggiungimento dell'obiettivo glicemico con minor rischio di ipoglicemia in diabetici di tipo 2

Pazienti che hanno raggiunto l'obiettivo FPG ≤120 mg/dL



Yki-Järvinen H et al. *Diabetes Care*. 2000

Insulin detemir vs insulin glargine for type 2 diabetes: Outcome overall hypoglycemia patient/year



Considerazioni nella terapia insulinica

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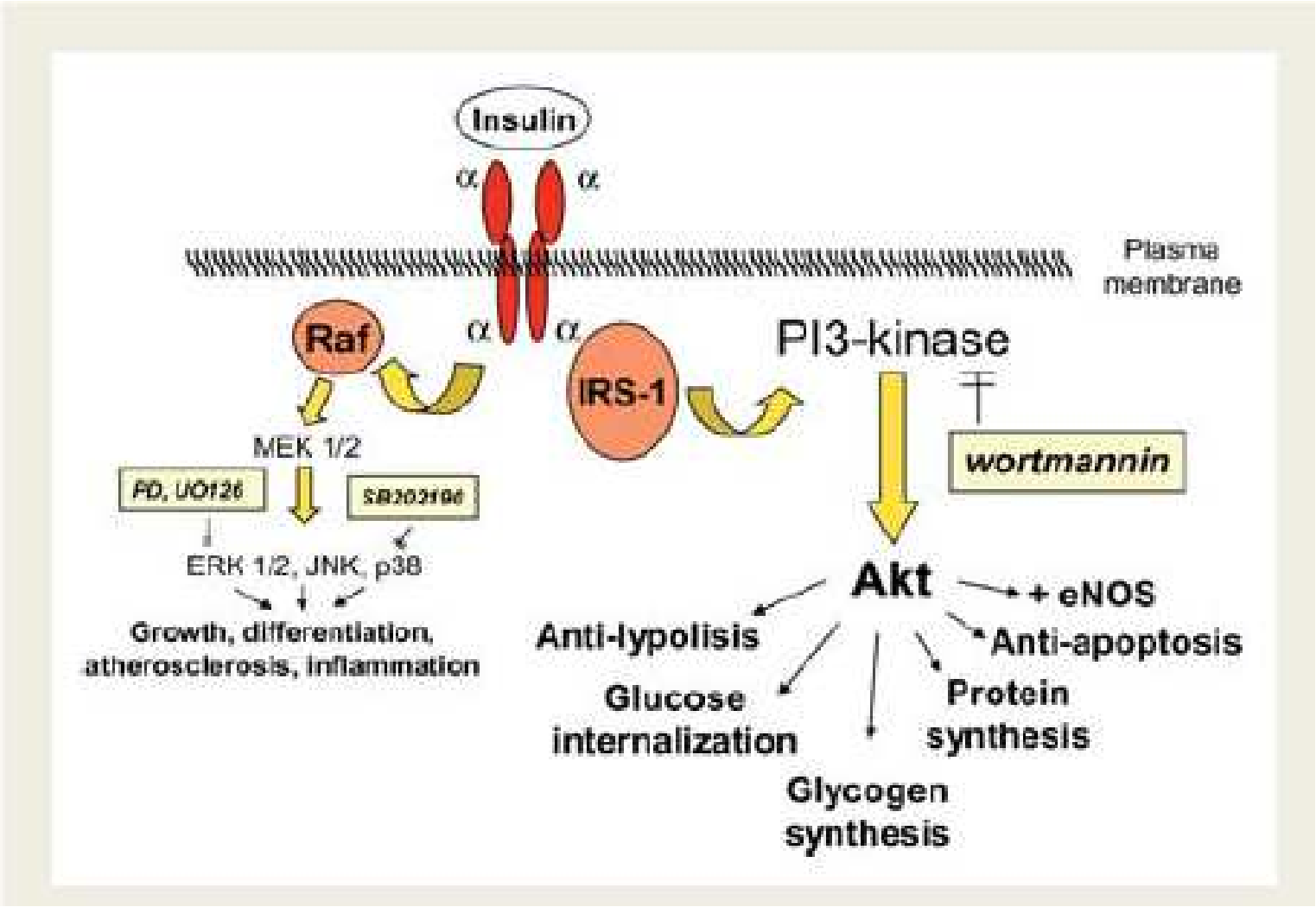
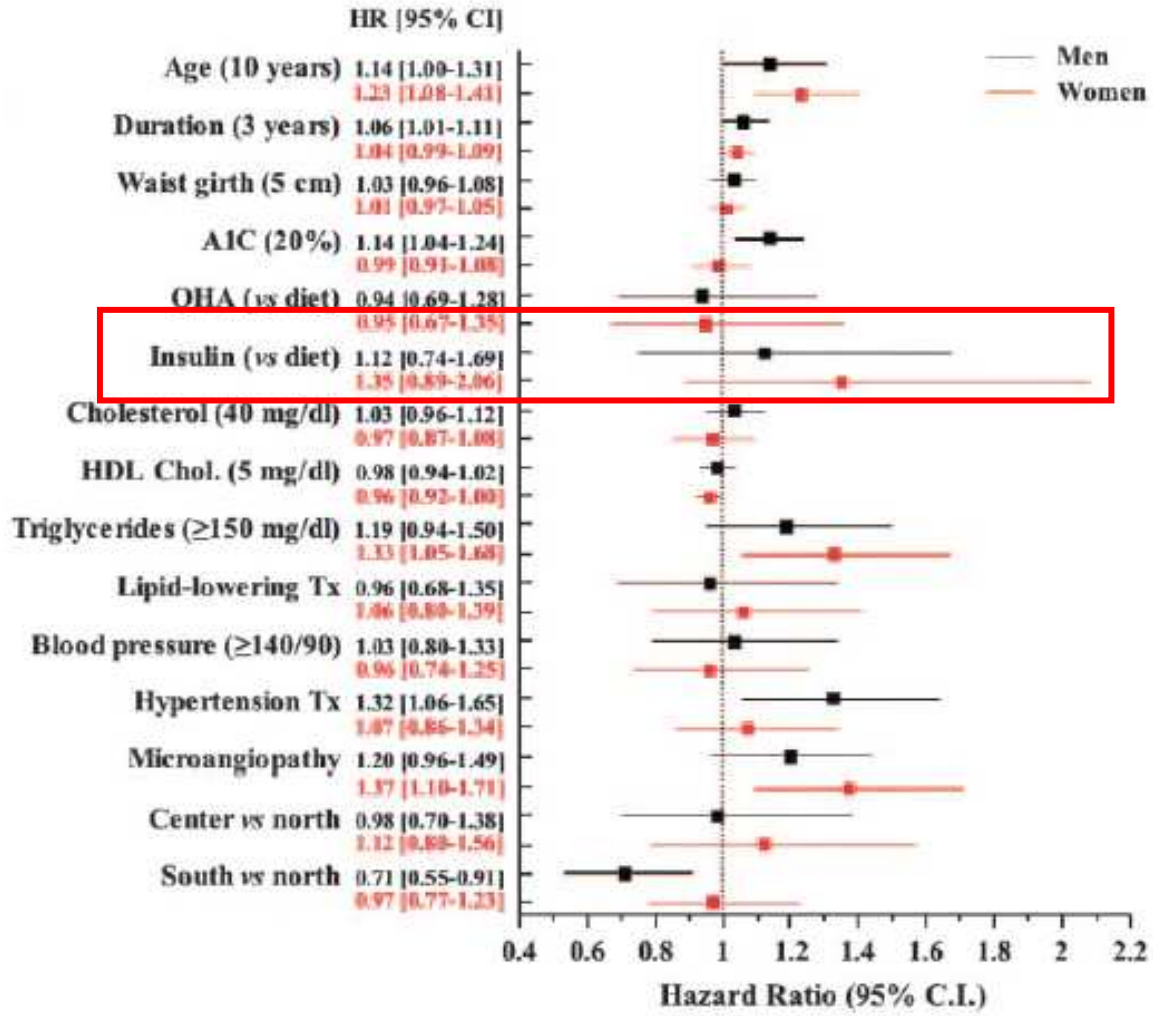
- ✓Safety cardiovascolare
- ✓Safety mitogenica

La terapia insulinica aumenta il rischio cardiovascolare?



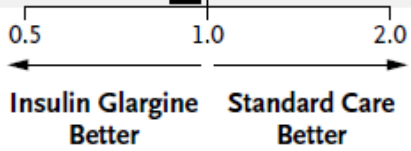
Incidence of coronary heart disease in type 2 diabetic men and women



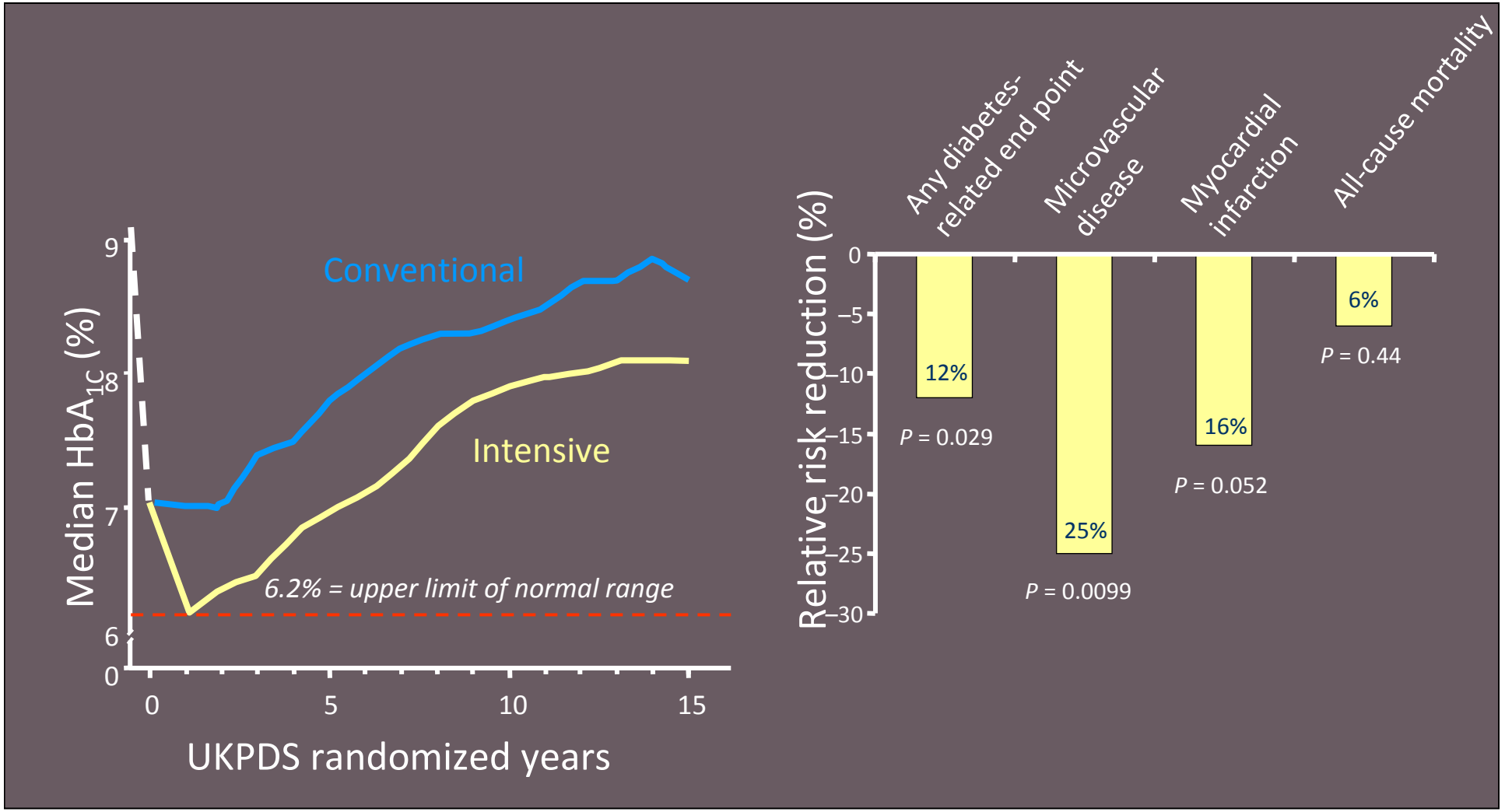
Avogaro A and Diabetes Care 2007

Cardiovascular outcomes in the ORIGIN trial

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

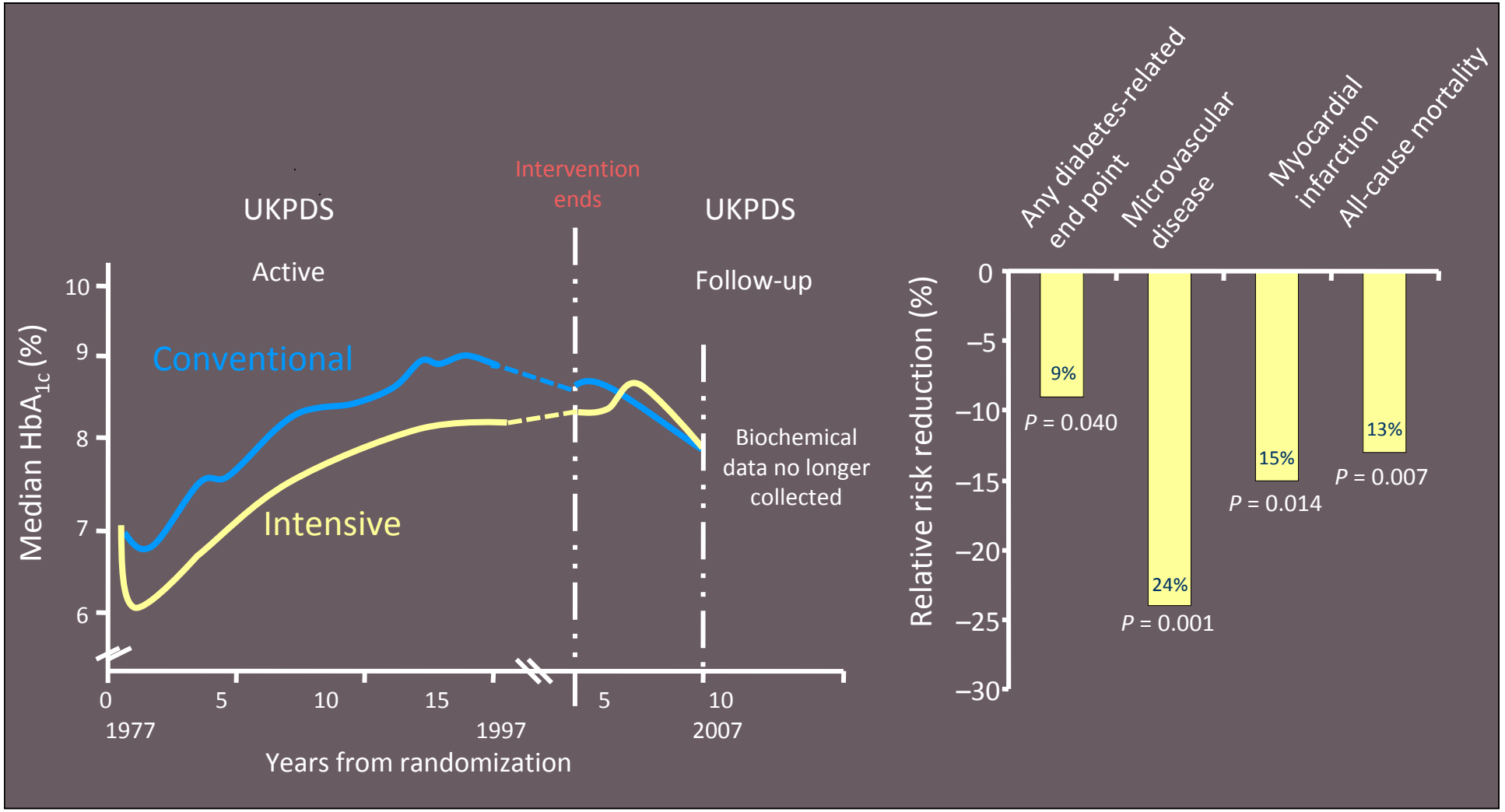


UKPDS: intensive control reduces complications in type 2 diabetes



UKPDS Study Group. *Lancet* 1998; 352:837–853.

UKPDS: long-term follow-up and legacy effect



Bailey CJ & Day C. *Br J Diabetes Vasc Dis* 2008; 8:242–247.
Holman RR, *et al*. *N Engl J Med* 2008; 359:1577–1589.

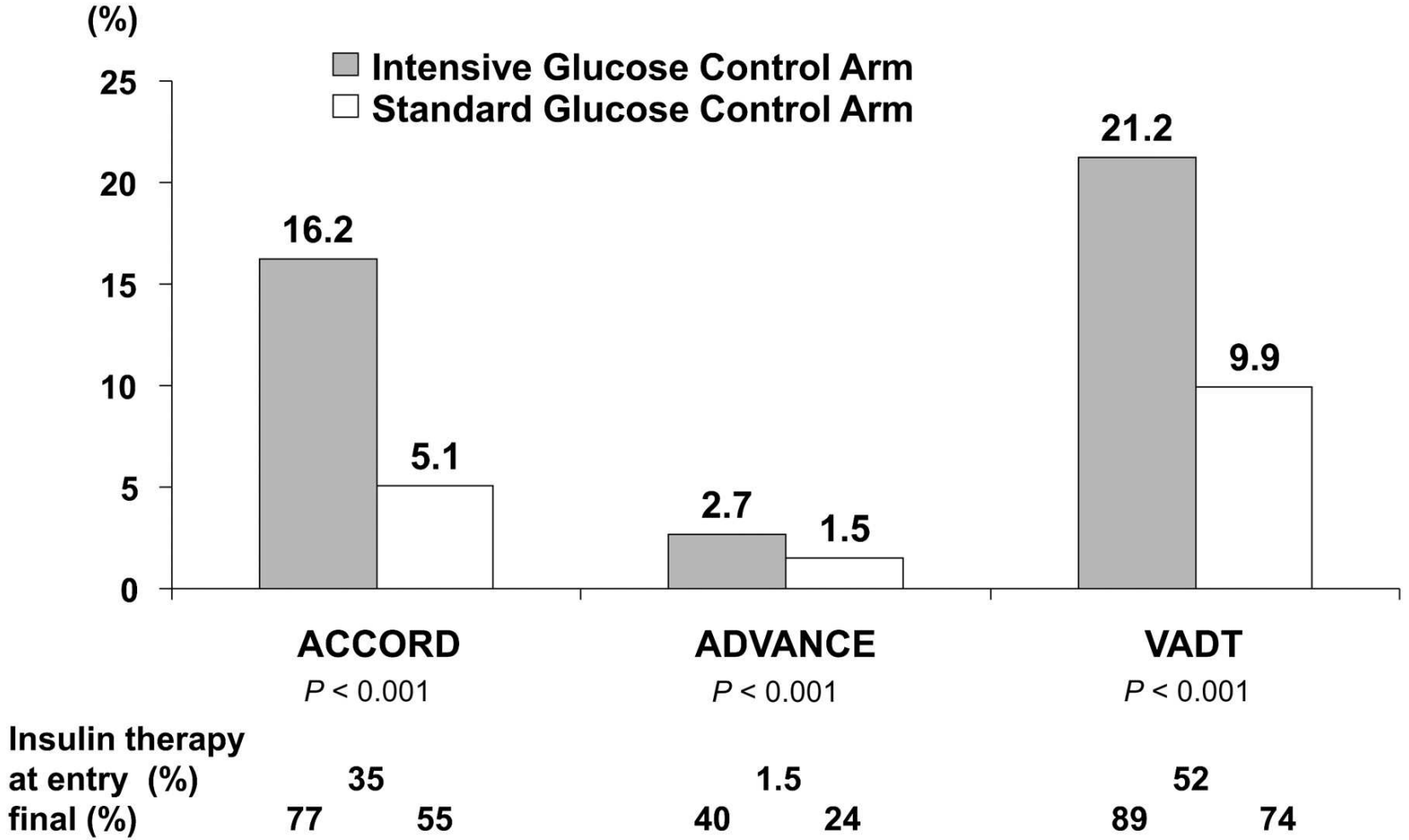
ACCORD, ADVANCE, VADT - Results

	ACCORD	ADVANCE	VADT
Primary outcome	Non-fatal MI Non-fatal stroke CVD death	Non-fatal MI Non-fatal stroke CVD death	Non-fatal MI Non-fatal stroke CVD death Hospitalization for CHF Revascularization
Hazard Ratio for primary outcome (95% CI)	0.90 (0.78 – 1.04)	0.94 (0.84 – 1.06)	0.87 (0.73 – 1.04)
Hazard Ratio for mortality (95% CI)	1.22 (1.01 – 1.46)*	0.93 (0.83 – 1.06)	1.065 (0.80 – 1.42)
Hazard Ratio for CV mortality (95% CI)	1.35 (1.04 – 1.76)**	0.88 (0.74 – 1.04)	1.26 (0.77 – 2.05)

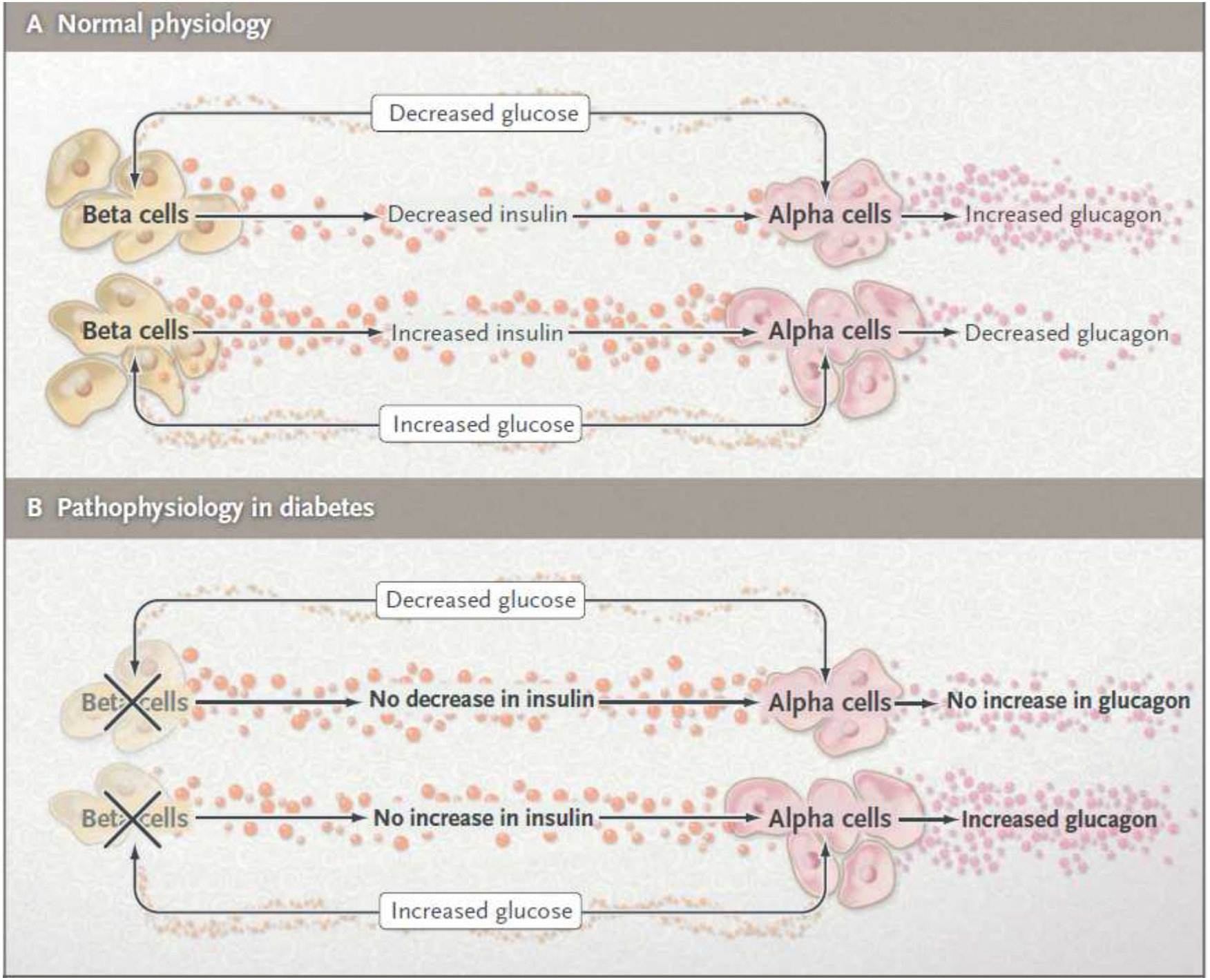
*p=0.04; **p=0.02

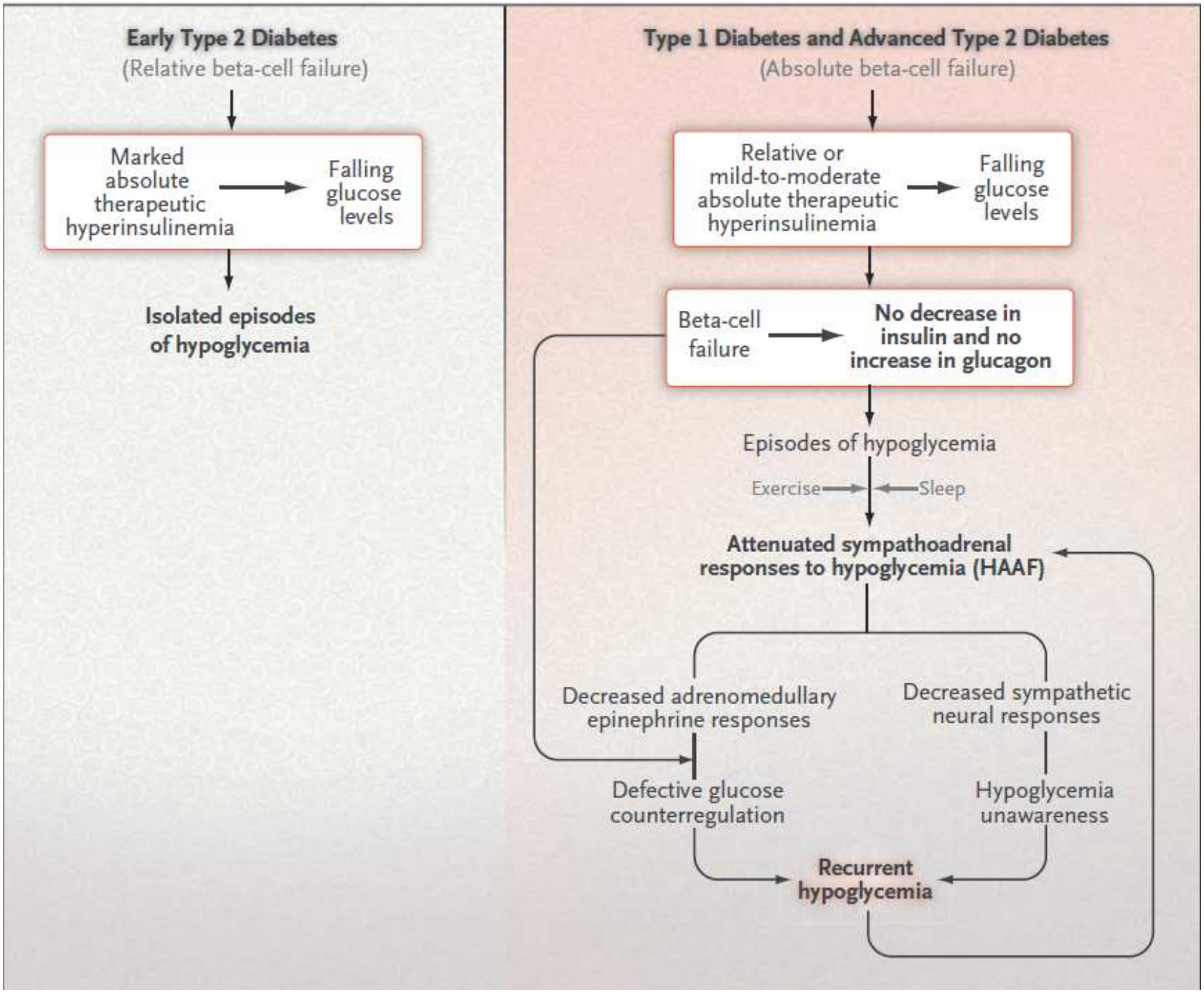
ACCORD, N Engl Med J 2008; 358: 2545-59 - ADVANCE, N Engl Med J 2008; 358: 2560-72
VA-DT, N Engl J Med 2009; 360: 129-139

Percentage of severe hypoglycemic events in ACCORD, ADVANCE, and VADT



Frier B M et al. Dia Care 2011;34:S132-S137

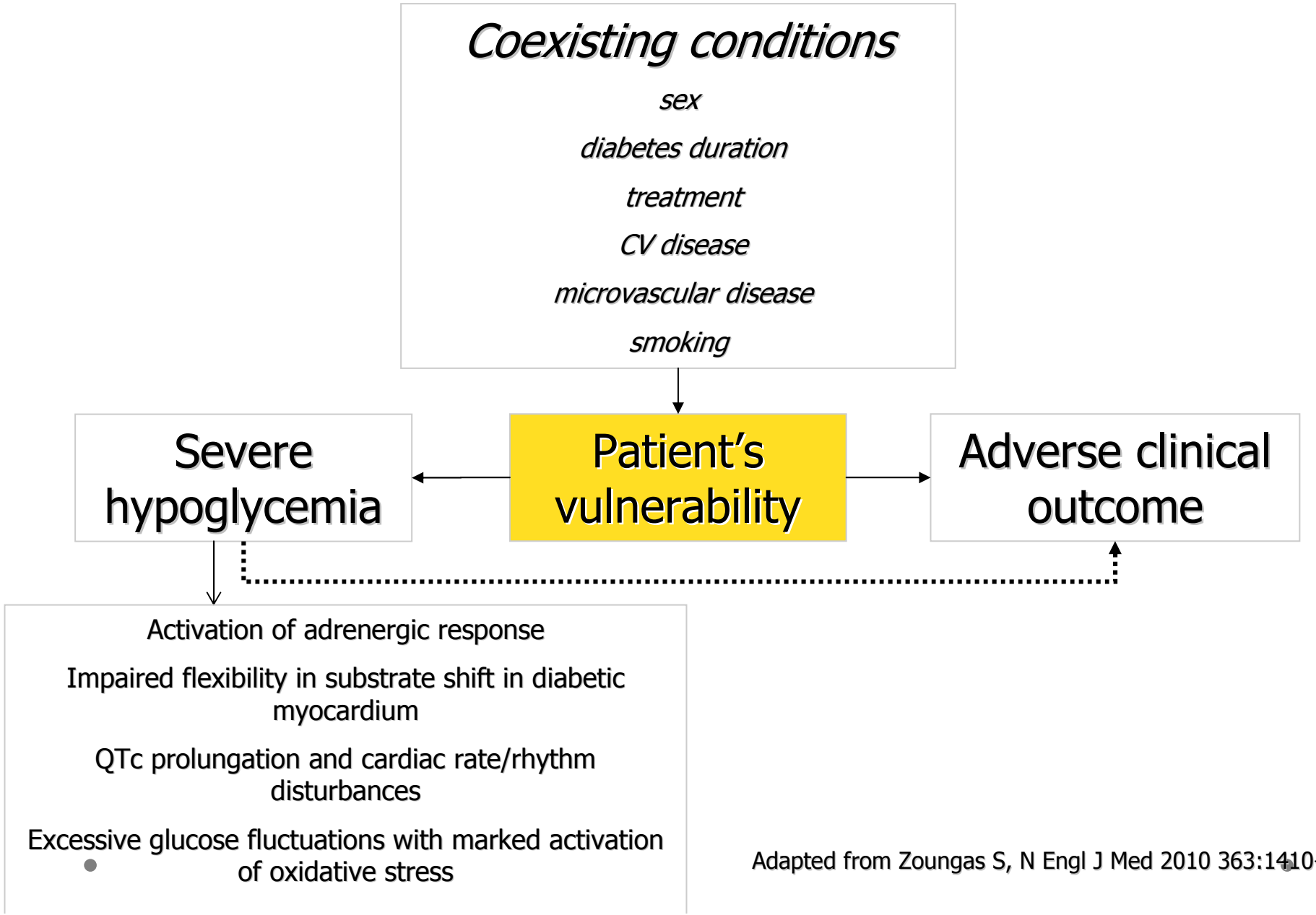

A Normal physiology
Decreased glucose
Beta cells
Decreased insulin
Alpha cells
Increased glucagon
Beta cells
Increased insulin
Alpha cells
Decreased glucagon
Increased glucose
B Pathophysiology in diabetes
Decreased glucose
Beta cells
No decrease in insulin
Alpha cells
No increase in glucagon
Beta cells
No increase in insulin
Alpha cells
Increased glucagon
Increased glucose



Cryer P NEJM 2013

	ACCORD ADVANCE	UKPDS
Age	~60s	53
Diabetes duration	~10yrs	New onset
Macrovascular disease	~1/3	~1/15
Length of follow-up	~5yrs	17yrs

Hypoglycemia CV risk and death



Adapted from Zoungas S, N Engl J Med 2010 363:1410-8.

Considerazioni nella terapia insulinica

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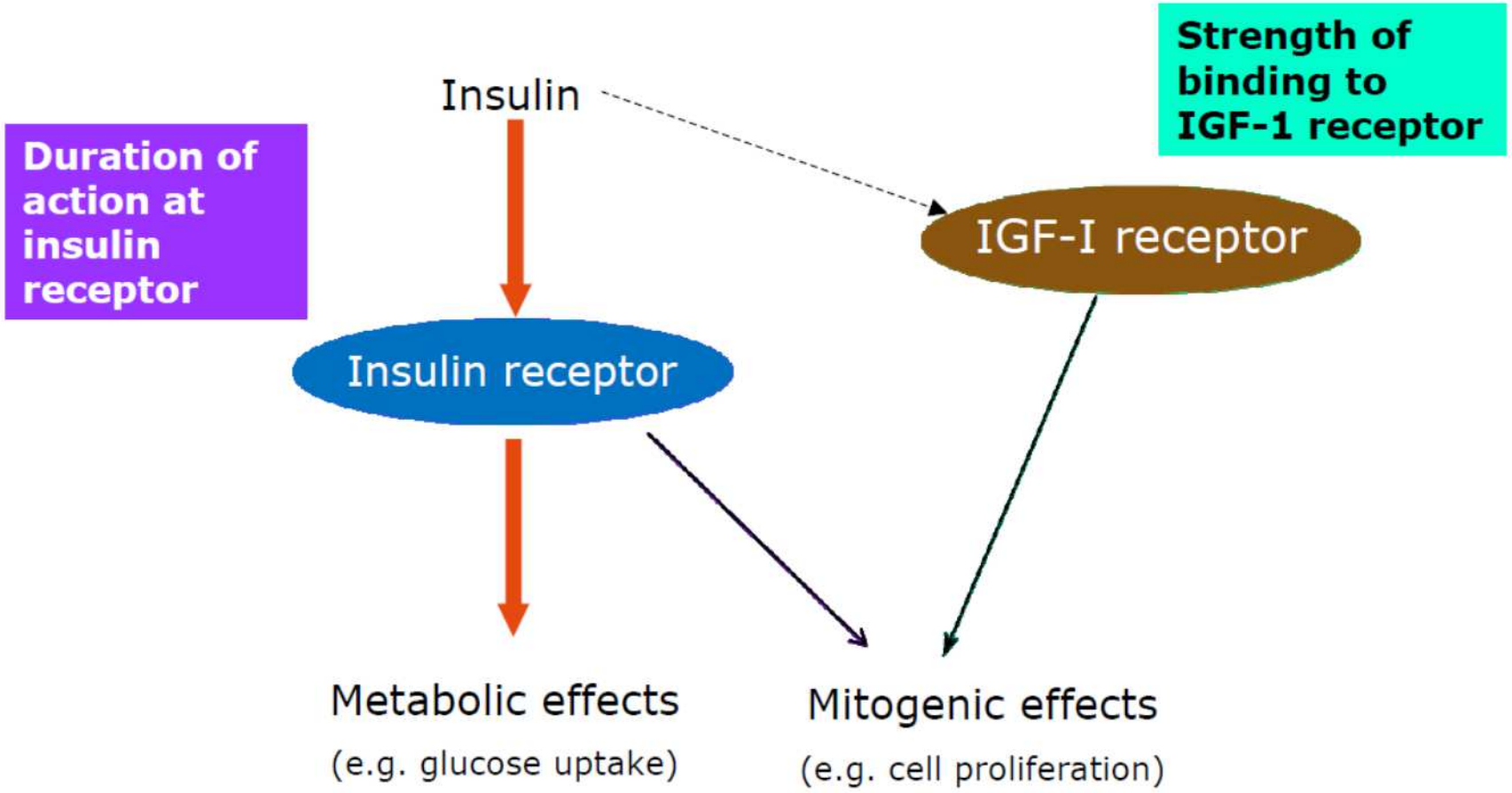
- ✓Effetti sul peso
- ✓Rischio ipoglicemico
- ✓Safety cardiovascolare
- ✓Safety mitogenica

Effetti metabolici e mitogeni dell'insulina



Potenza mitogena degli analoghi dell'insulina *in vitro*

	Insulin receptor affinity	IGF-1R affinity	Insulin receptor off rate	Metabolic potency	Mitogenic potency
Human insulin	=100	=100	=100	=100	=100
Insulin aspart	92 ± 6	81 ± 9	81 ± 8	101 ± 2	58 ± 22
Insulin lispro	84 ± 6	156 ± 16	100 ± 11	82 ± 3	66 ± 10
Insulin glargine	86 ± 3	641 ± 51	152 ± 13	60 ± 3	783 ± 13
Insulin detemir	18 ± 3	16 ± 1	204 ± 9	27	11

Kurtzhals P, et al. Diabetes2000; 49: 999

Potenza mitogena *in vitro* dei metaboliti attivi dell'insulina glargine

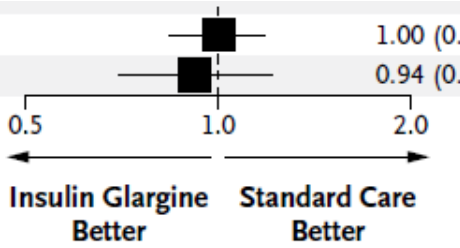
Analog	IGF1R affinity	IGF1R auto-phosphorylation	Mitogenic potency
	IC_{50}	EC_{50}	EC_{50}
	(nmol/L)	(nmol/L)	(nmol/L)
Human insulin	289±53.3	447±38.7	12.25±0.27
Glargine	63.2±19.9	87.5±10	1.61±0.26
Glargine IM	80.0±10.2	179±19.6	3.75±0.31
Glargine M1	649±31.9	644±56.9	16.25±2.35
Glargine M2	427±20.6	485±43.6	17.90±6.50
[Asp^{B10}]insulin	104±12.8	72.7±7.6	1.52±0.15
IGF-1	0.89±0.19	2.9±0.4	0.22±0.05
IGF-2	6.68±2.24	-	-

The lower the E50, the less the concentration of a drug is required to produce 50% of maximum effect and the higher the potency.

Sommerfeld M, PloS ONE 2010

Cancers Overall & by Type (N=953) in the ORIGIN trial

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

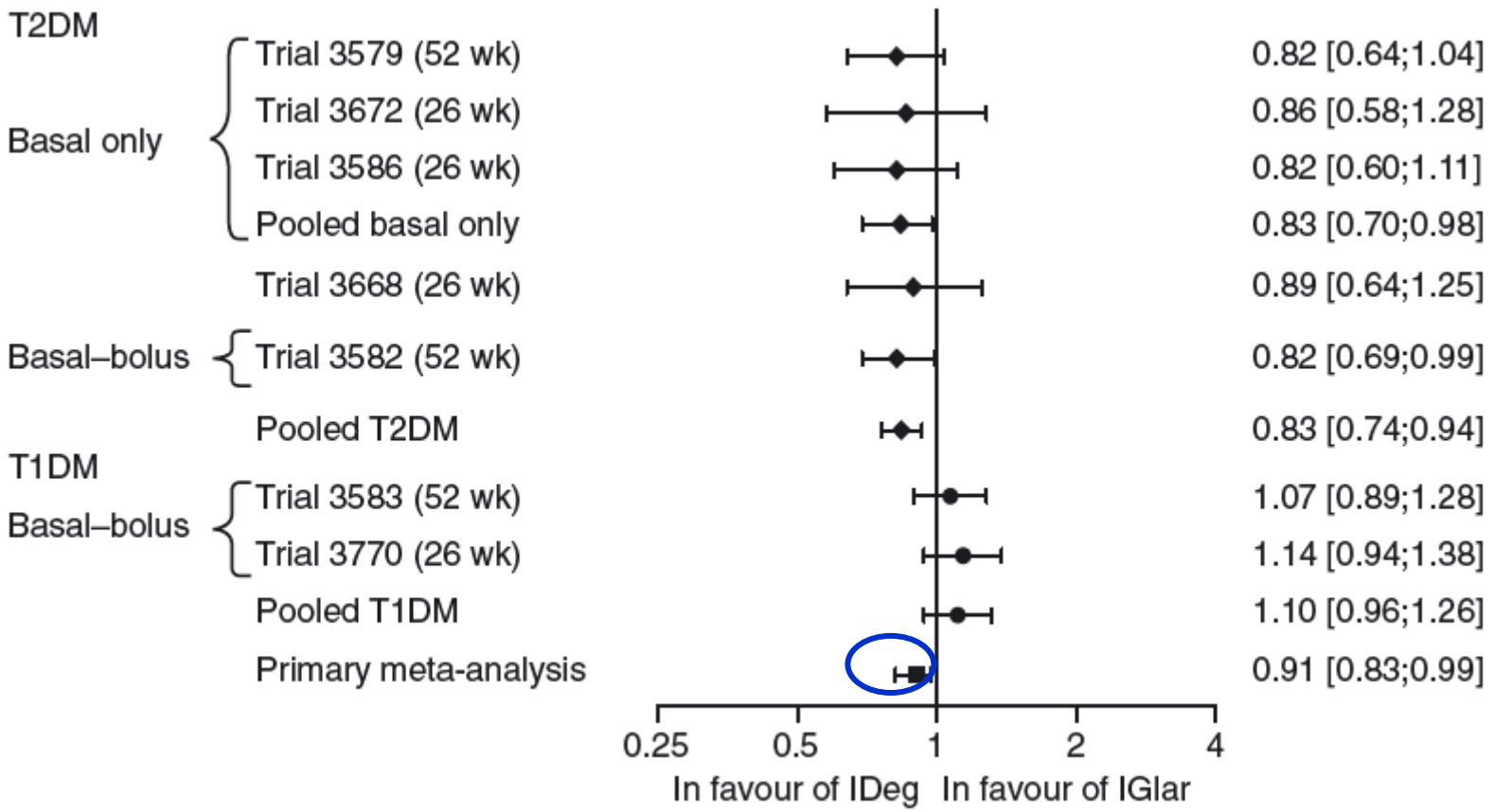


	HR (95%CI)	P	Glargine		Standard	
			N (%)	Rate	N (%)	Rate
Lung	1.21 (0.87, 1.67)	0.27	80 (1.3)	0.22	66 (1.1)	0.18
Colon	1.09 (0.79, 1.51)	0.61	76 (1.2)	0.21	70 (1.1)	0.19
Breast	1.01 (0.60, 1.71)	0.95	28 (0.4)	0.08	28 (0.4)	0.08
Prostate	0.94 (0.70, 1.26)	0.70	88 (2.1)	0.36	89 (2.2)	0.38
Melanoma	0.88 (0.44, 1.75)	0.71	15 (0.2)	0.04	17 (0.3)	0.05
Other	0.95 (0.80, 1.14)	0.59	233 (3.7)	0.64	245 (3.9)	0.67
Any Skin	1.02 (0.78, 1.33)	0.88	110 (1.8)	0.30	108 (1.7)	0.29

Origin Trial, NEJM 2012

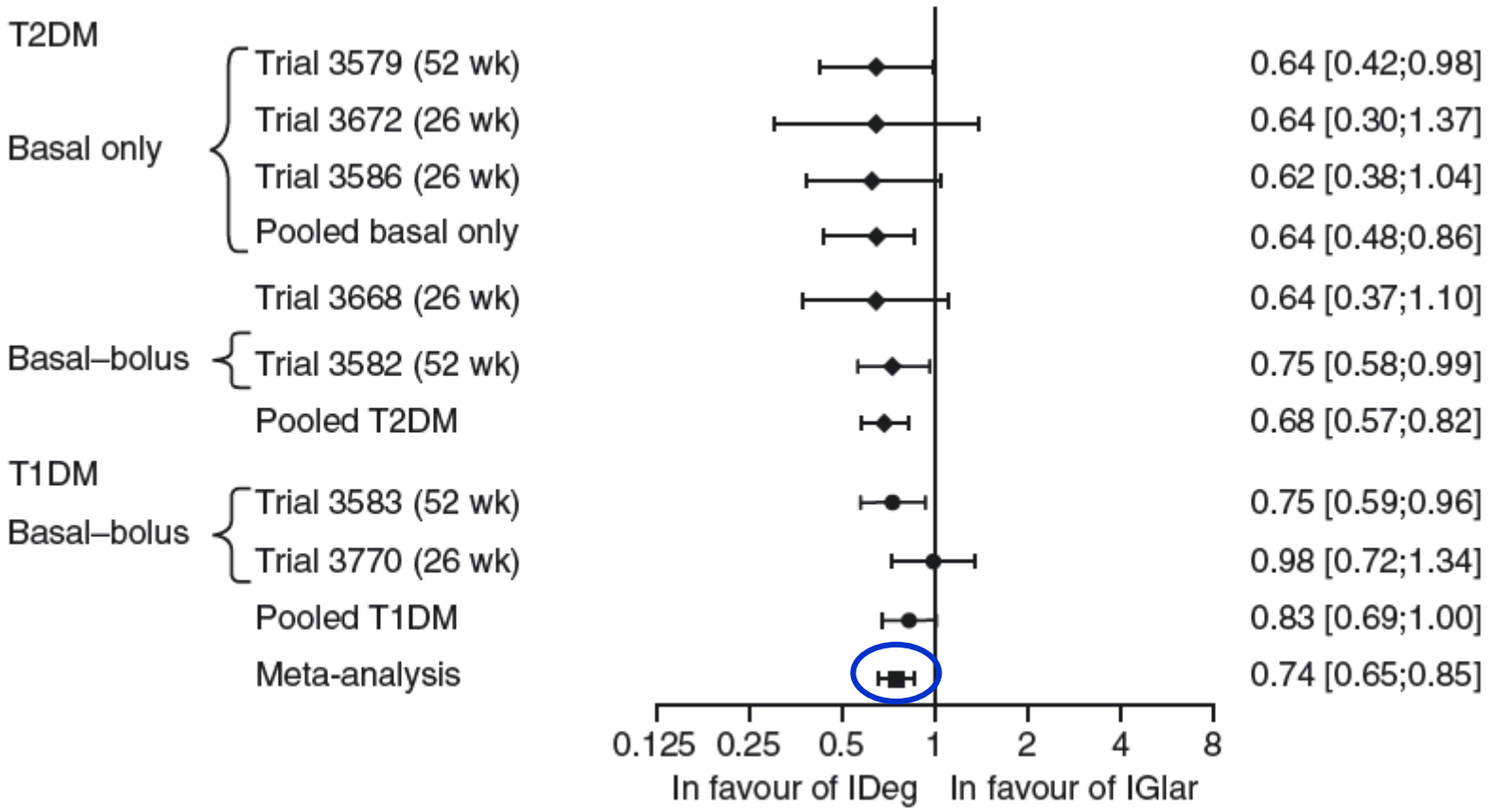
Nuove insuline

Estimated rate ratio (Ideg/IGlar) and 95% confidence intervals of **overall** confirmed hypoglycemic episodes



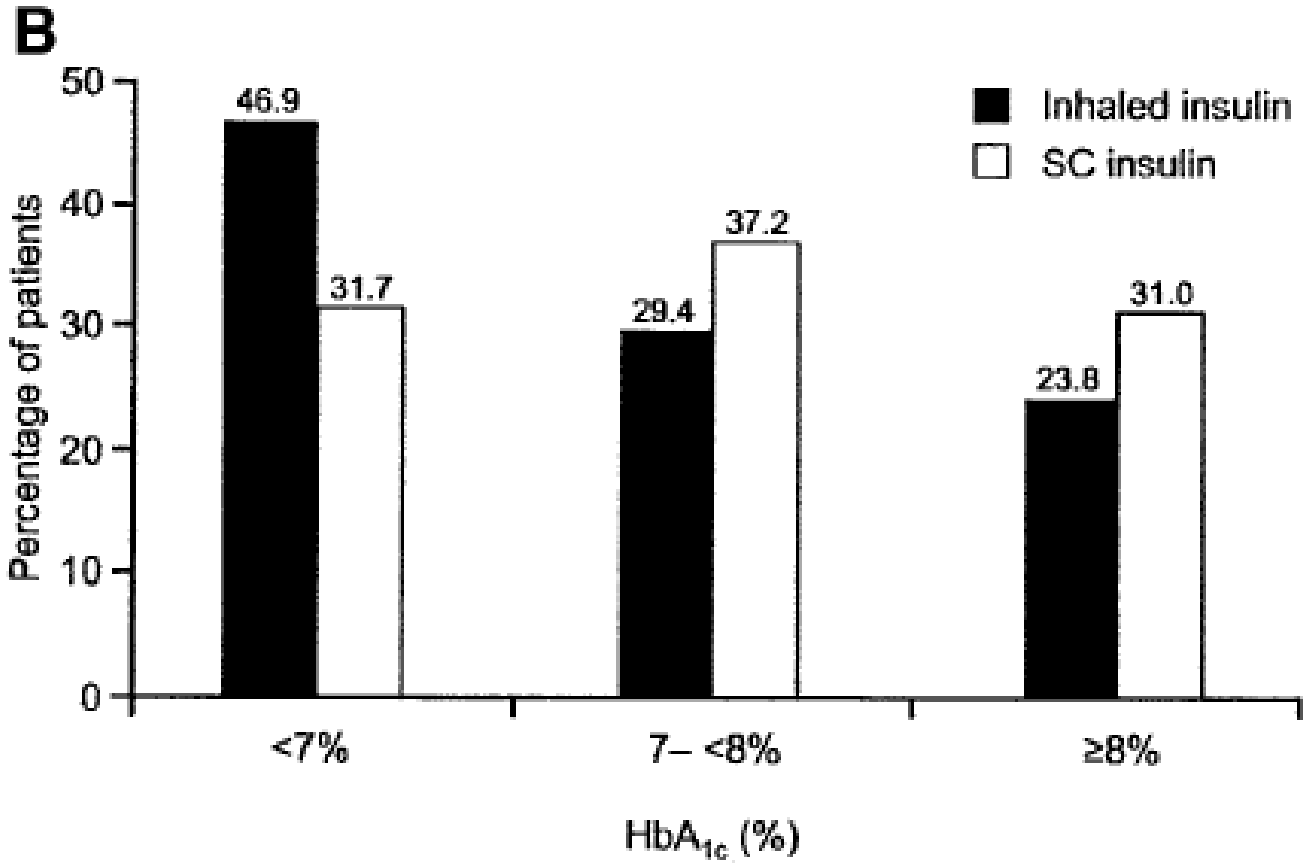
Ratner RE, et al. Diabetes, Obes and Metabolism 2012

Estimated rate ratio (Ideg/IGlar) and 95% confidence intervals of **nocturnal** confirmed hypoglycemic episodes



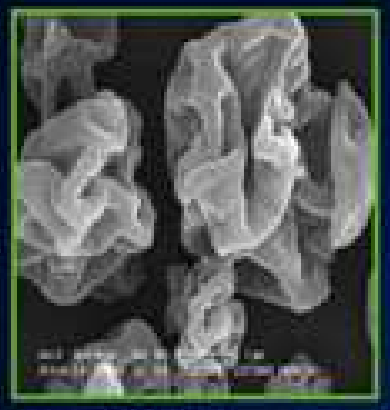
Ratner RE, et al. Diabetes, Obes and Metabolism 2012

Efficacy of inhaled insulin (exubera) compared with sc insulin therapy in patients with type 2 DM (results at 6 months)

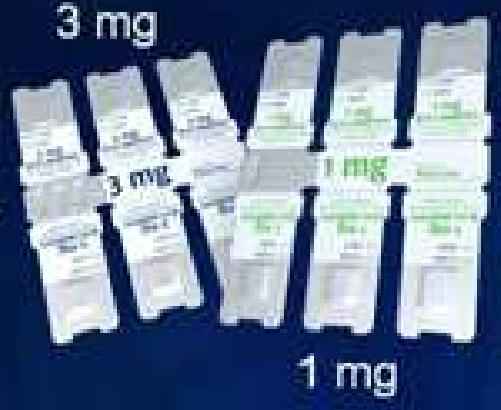


Hollander PA Diabetes Care 2004

Inhaled Insulin: A Novel Delivery System



Dry powder human insulin particles*



Blisters filled with dry powder human insulin

Insulin inhaler in closed position

*The picture on the left (dry powder human insulin particles) is magnified 20,000 times.

Adapted with permission from White S et al. *Diabetes Technol Ther.* 2005;7:896-906.

Joslin Diabetes Center

Insulin pump treatment compared with multiple daily injections for treatment of type 2 diabetes (OpT2mise): a randomised open-label controlled trial

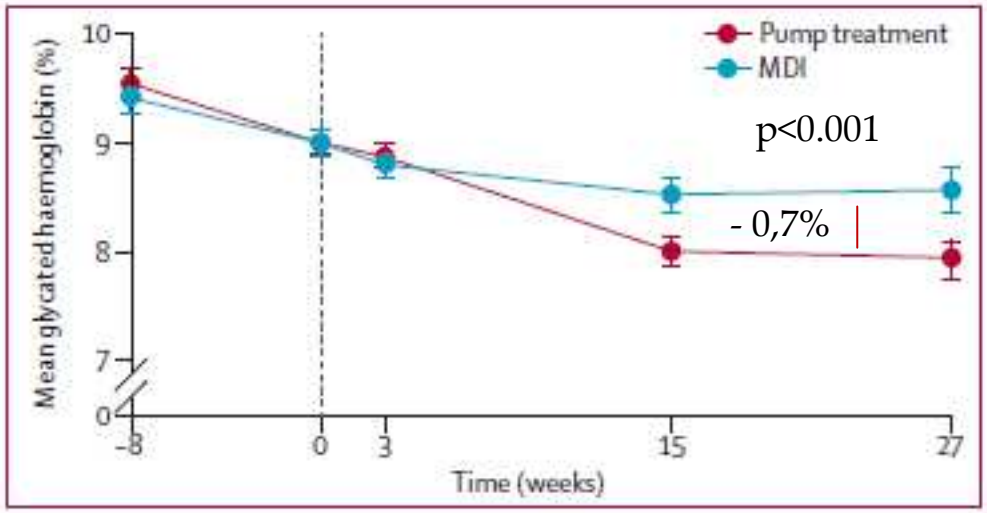
	Pump treatment (n=168)	Multiple daily injection (n=163)
Age (years)	55·5 (9·7)	56·4 (9·5)
Men	94 (56%)	86 (53%)
Ethnic origin		
Black African	6 (4%)	7 (4%)
Other	162 (96%)	156 (96%)
Duration of diabetes (years)	14·9 (8·0)	15·3 (8·0)
Montreal Cognitive Assessment score <26	64 (38%)	64 (39%)
Glycated haemoglobin (%)	9·0% (0·8)	9·0% (0·8)
Weight (kg)	97·3 (22·6)	94·9 (22·0)
Body-mass index (kg/m²)	33·5 (7·5)	33·2 (7·0)
Total daily insulin dose (U/kg per day)	1·1 (0·4)	1·1 (0·4)
Total daily insulin dose (U per day)	112·3 (53·9)	106·2 (49·2)
Total long-acting insulin dose (U per day)	57·4 (30·3)	52·4 (27·7)
Total rapid-acting insulin dose (U per day)	55·6 (31·7)	53·8 (30·8)
History of diabetic complications and comorbidities		
Dyslipidaemia	26 (16%)	16 (10%)
Hypertension, cerebrovascular, and coronary heart diseases	142 (85%)	137 (84%)
Peripheral vascular disease	12 (7%)	7 (4%)
Retinopathy	6 (4%)	3 (2%)
Diabetic nephropathy	22 (13%)	12 (7%)
Peripheral neuropathy	0 (0%)	0 (0%)

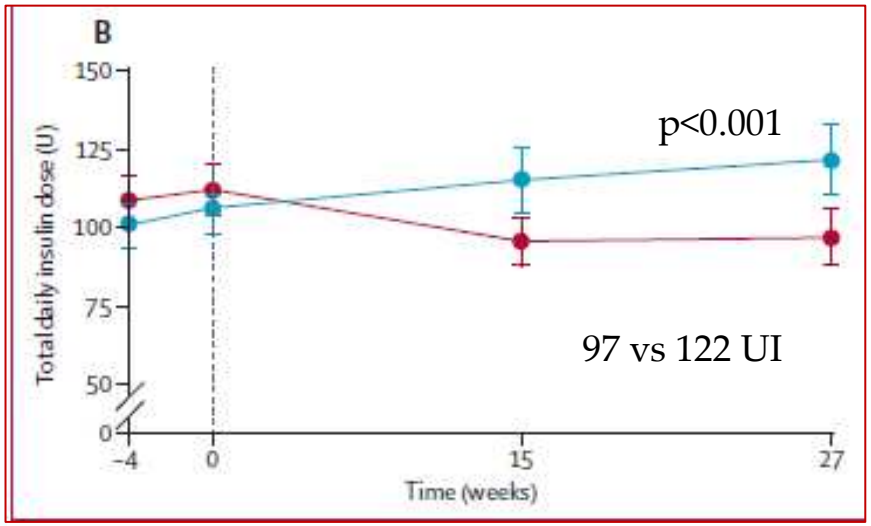
Data are mean (SD) or n (%).

Table 1: **Baseline characteristics**

Reznik. Lancet 2014

Changes in Hb1C and in total insulin dose (results at 6 months)





Reznik. Lancet 2014

Insulin pump treatment compared with multiple daily injections for treatment of type 2 diabetes (OpT2mise): a randomised open-label controlled trial

	Pump treatment	Multiple daily injection	Difference	p value
Change in 24 h mean glucose concentration (mmol/L)	−1·3 (2·4)	−0·3 (1·7)	−1·0	0·0062
AUC change >10 mmol/L (mmol/L × min)	−0·6 (1·4)	−0·1 (0·9)	−0·5	0·0047
Reduction of time spent >10 mmol/L (min)	225·6 (355·9)	56·8 (256·3)	168·7	0·0007
AUC change <3·9 mmol/L (mmol/L × min)	0·0 (0·0)	0·0 (0·1)	0·0	0·4540
Time spent <3·9 mmol/L (min)	8·8 (49·6)	5·1 (71·0)	3·7	0·7669

Data in parentheses are SD. Includes patients with at least 48 h of continuous measurement. AUC=area under the curve.

Table 2: Glycaemic control in each treatment group

Reznik. Lancet 2014

Conclusioni

La terapia insulinica è un'arma efficace, a volte l'unica, per ottenere e mantenere il controllo glicemico

La terapia insulinica mostra un buon profilo di sicurezza cardiovascolare e mitogenico

Il rischio ipoglicemico rimane il principale ostacolo al raggiungimento del target glicemico mediante la terapia insulinica

Le nuove formulazioni e devices a disposizione permettono una maggiore flessibilità d'uso riducendo l'inerzia del clinico e fornendo maggiore accettabilità da parte del paziente