Analoghi dell'insulina prandiale: l'importanza della rapidità di azione

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La dr.ssa Lucia Frittitta dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- AstraZeneca
- Eli-Lilly

Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).

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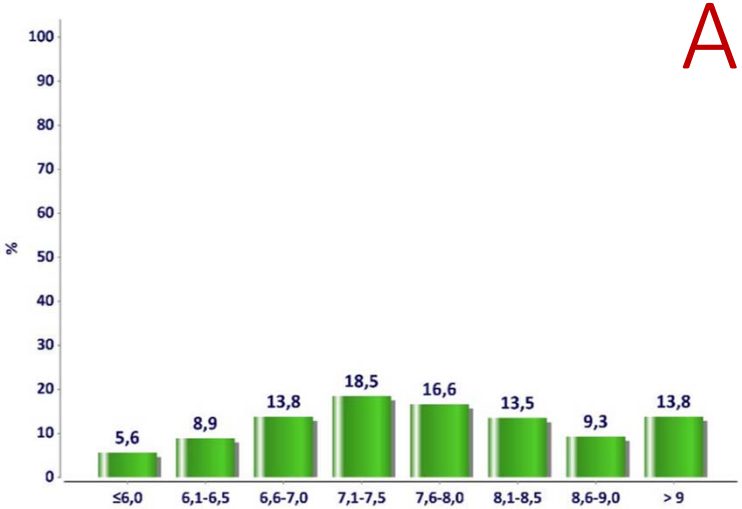

Livelli medi dell'HbA1c (%)

	HbA1c (%)
Tutti	7,8±1,3

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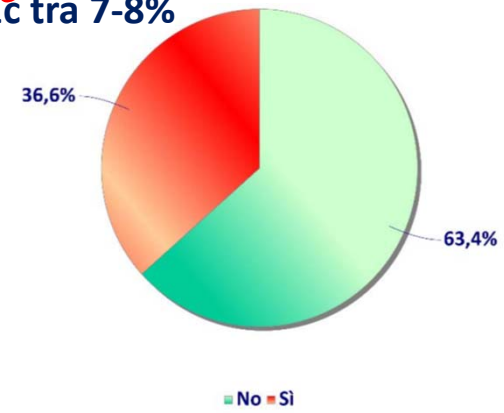
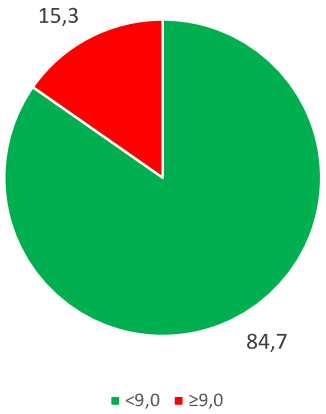
HBA1 ≤7.0 %

HBA1c ≥ 8.0 %

35.1% ha HbA1c tra 7-8%



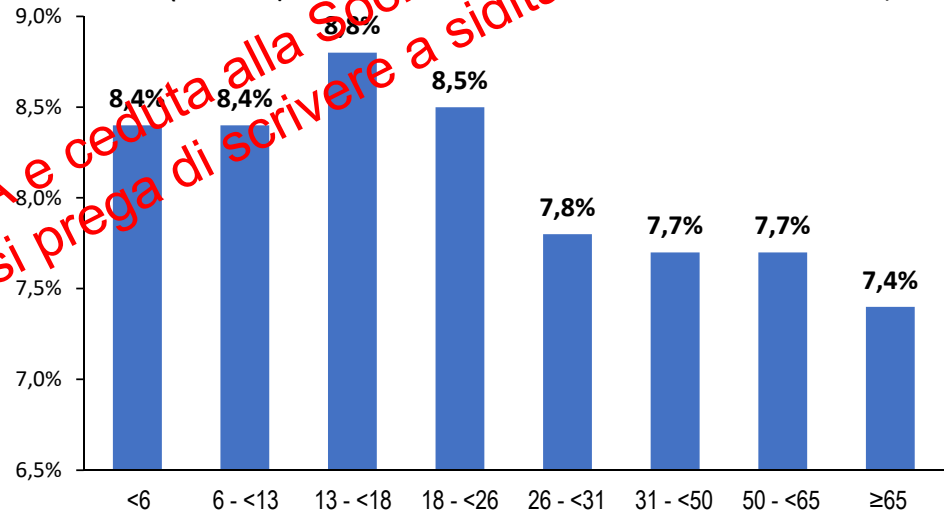
HbA1c ≥9.0%



More than 80% of patients with T1D are not at their glycaemic goal

- Only 8% of patients enrolled in the T1D Exchange Clinic Network had an HbA_{1c} below 6.5%[1]
- The mean HbA_{1c} of a cohort of participants with T1D (n=2764) from 31 centers in 16 European countries enrolled in the EURODIAB study was 8.4%[2]
- Only 11.6% of Brazilian patients studied in a cross-sectional, multicentre study achieved the goal of <7.0% for HbA_{1c}[3]

Mean HbA_{1c} levels from the T1D Exchange Clinic Network[1]*
(25,833 participants from 67 sites in the United States)



Livelli medi dell'HbA1c (%)

	HbA1c (%)
Tutti	7,8±1,3

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1. Beck RW, et al. *J Clin Endocrinol Metab.* 2012;97:4383–4389. **2.** Schoenaker DA, et al. *J Clin Endocrinol Metab*. 2014;99:800–807. **3.** Gomes MB, et al. *Diabetes Res Clin Pract.* 2012;97:63–70. **4.** Danne T, et al. *Diabetes Care.* 2017;40:1631–1640.

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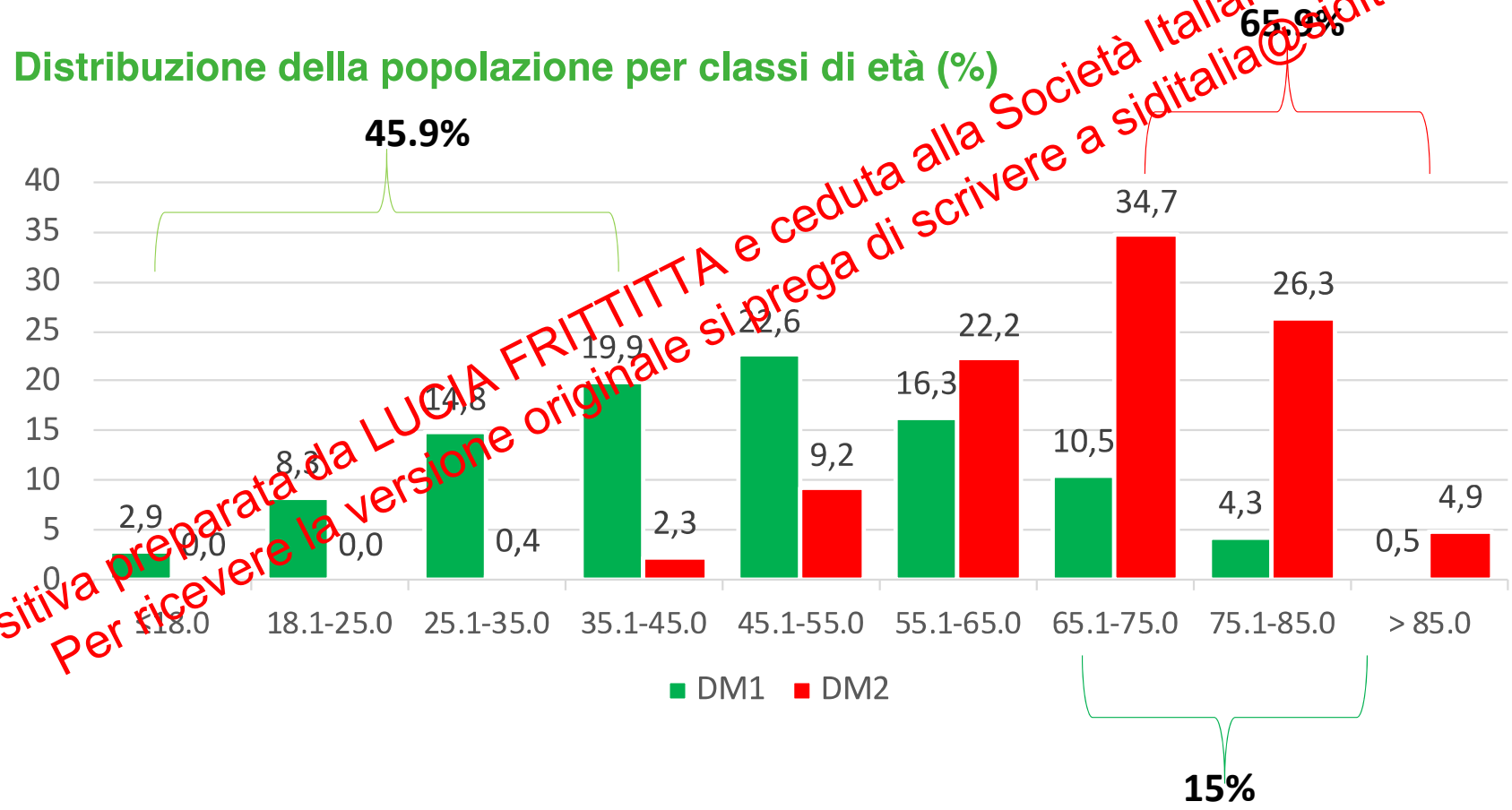

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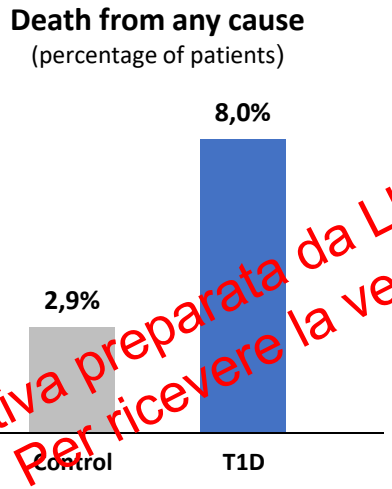
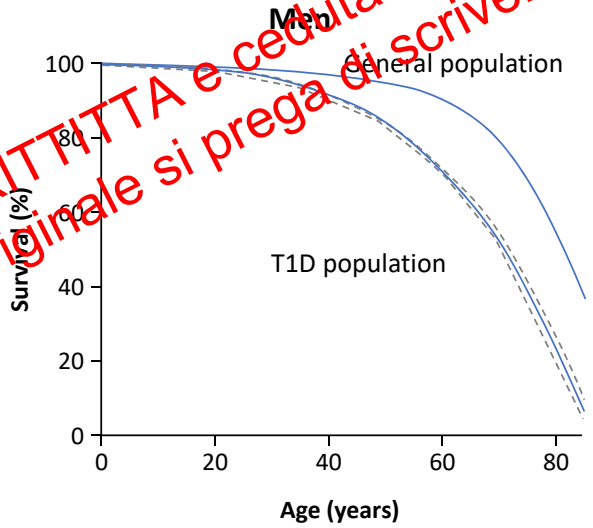
T1D is associated with a significant loss of life expectancy

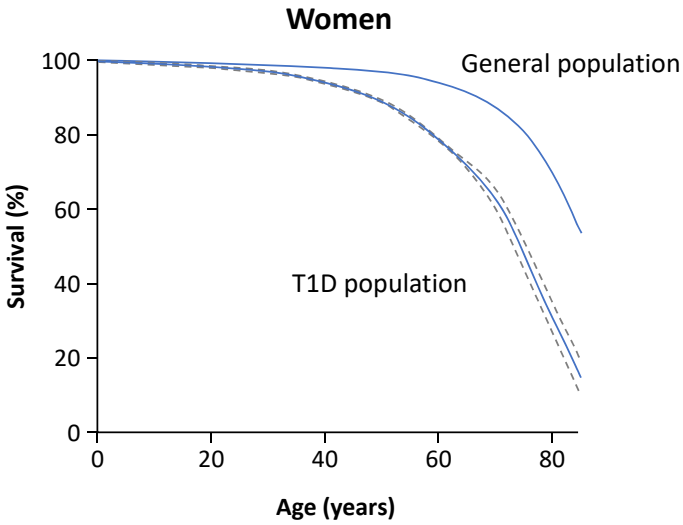
- Patients with T1D are at a 2- to 4-fold increased risk of death[1]
- The estimated life expectancy at birth of patients with T1D is 68.6 years, roughly 12 years less relative to those without diabetes[2]

Mortality among patients with T1D vs control[1]



Estimated life expectancy[2]





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1. Lind M, et al. *N Engl J Med*. 2014;371:1972–1982. **2.** Huo L, et al. *Diabetologia*. 2016;59:1177–1185.

Glycemic Control and Excess Mortality in Type 1 Diabetes: Swedish National Diabetes Register

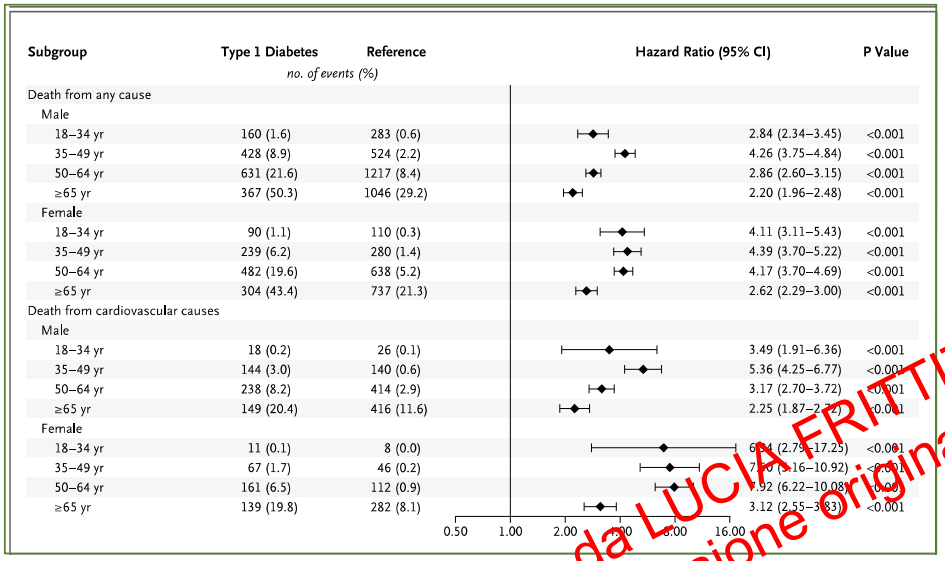

Table 3. Adjusted Hazard Ratios for Death from Any Cause and Death from Cardiovascular Causes among Patients with Type 1 Diabetes versus Controls, According to Time-Updated Mean Glycated Hemoglobin Level and Renal Disease Status, Model 3.*

Variable	Hazard Ratio	
	Death from Any Cause	Death from Cardiovascular Disease
Time-updated mean glycated hemoglobin level — no. of events/total no.	7386/200,539	2326/200,539
Reference group (controls)	1.00	1.00
≤6.9%	2.36 (1.97–2.83)	2.92 (2.07–4.13)
7.0–7.8%	2.38 (2.02–2.80)	3.39 (2.49–4.61)
7.9–8.7%	3.11 (2.66–3.62)	4.44 (3.32–5.96)
8.8–9.6%	3.65 (3.11–4.30)	5.35 (3.94–7.26)
≥9.7%	8.51 (7.24–10.01)	10.46 (7.62–14.37)

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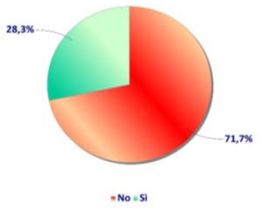
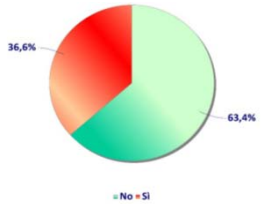
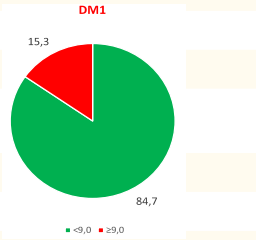
HBA1 > 7.0 %



HBA1c > 8.0 %

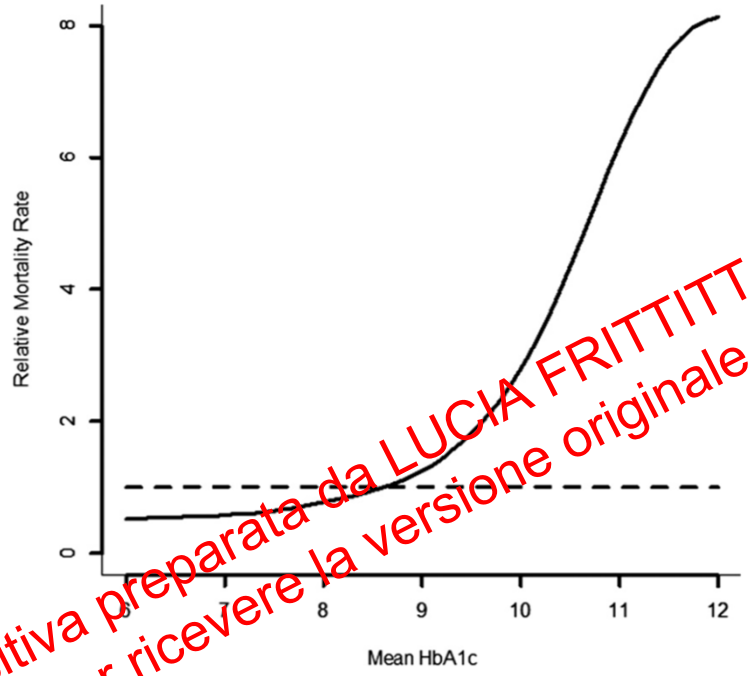


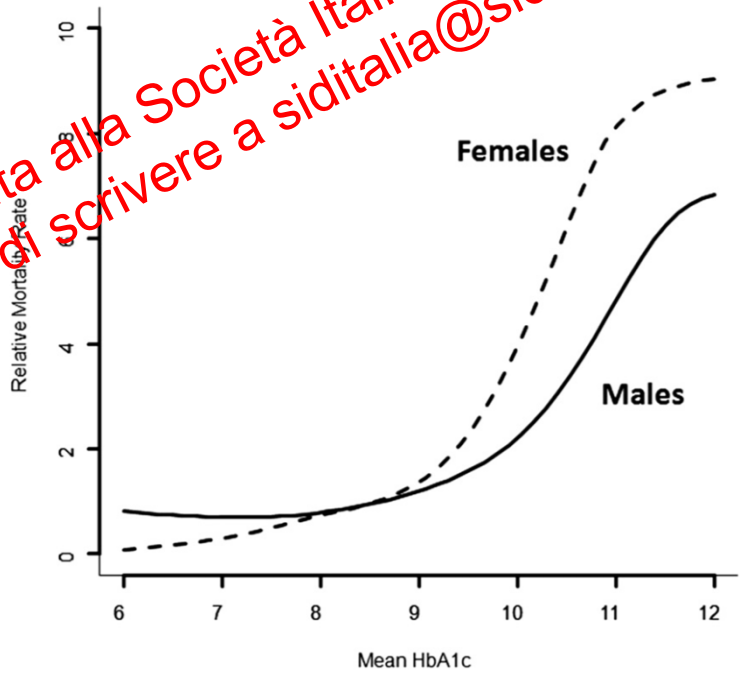
HbA1c ≥9.0%



N Engl J Med 2014;371:1972-82.

DCCT/EDIC study: mortalità e valori di HbA1C





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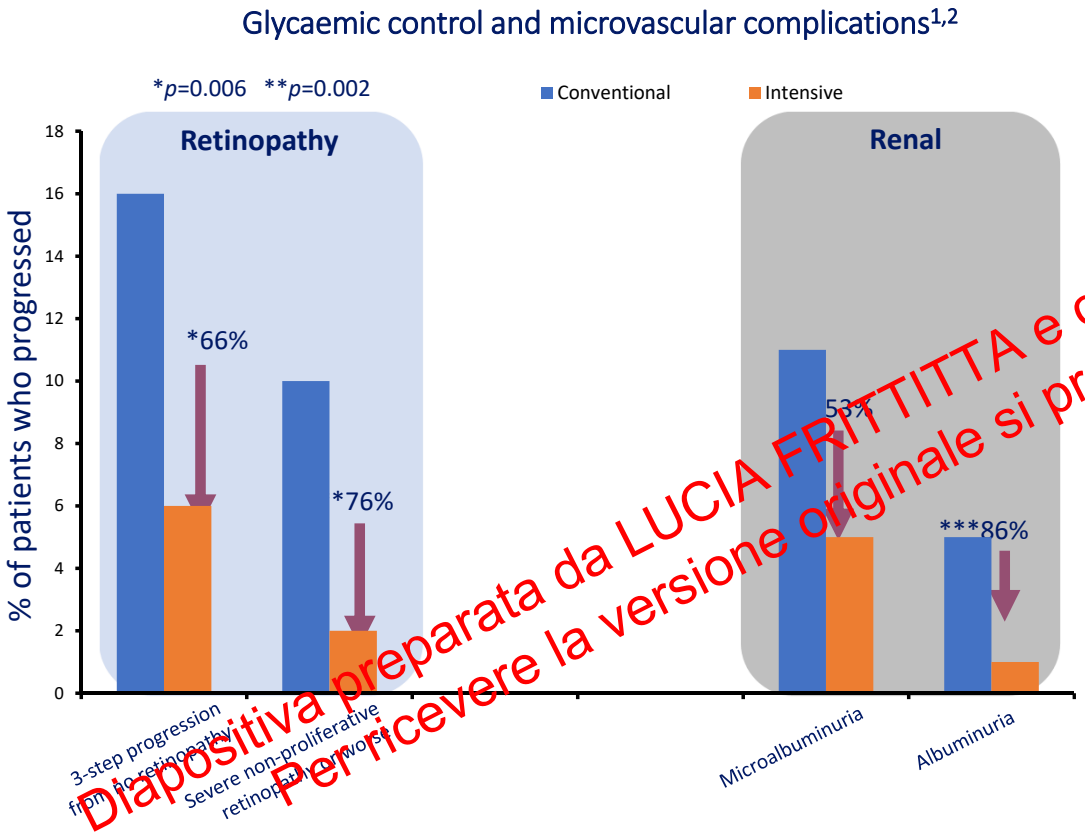
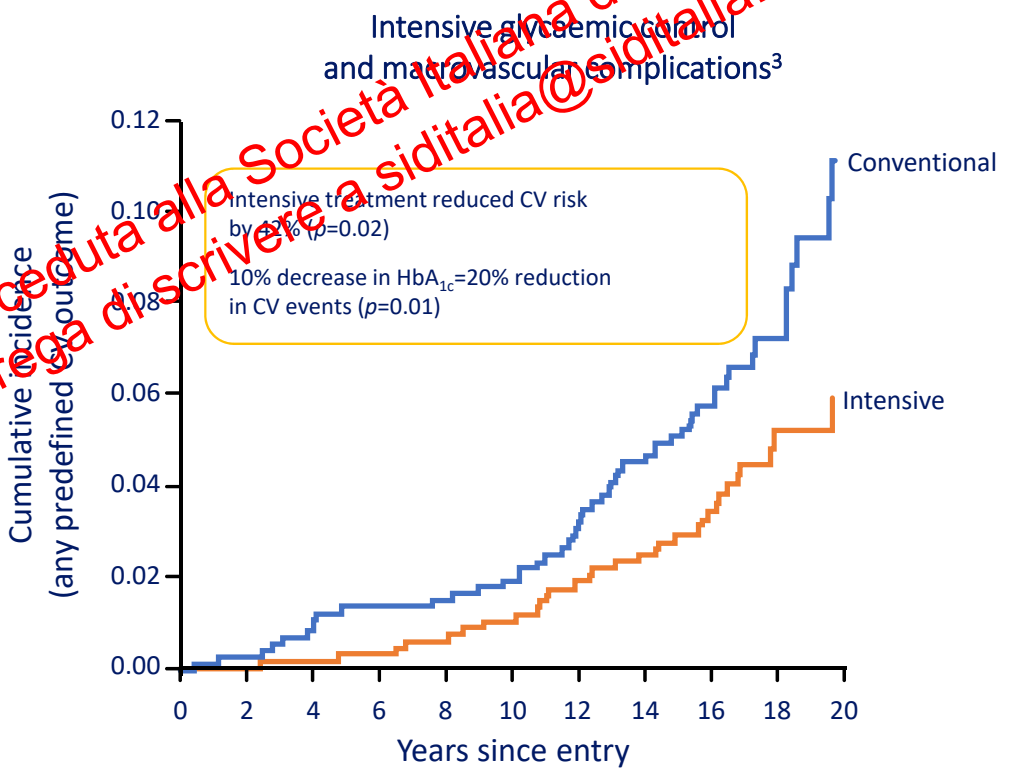
Diabetes Care 2016;39:1378–1383 |

DCCT/EDIC: Intensive vs. conventional treatment in T1D





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CV, cardiovascular; DCCT, Diabetes Control and Complications Trial; EDIC, Epidemiology of Diabetes Interventions and Complications; T1D, type 1 diabetes

1. DCCT/EDIC Group. JAMA 2002;287:2563–9; 2. Martin et al. Diabetes Care 2006;29:340–4; 3. Nathan et al. N Eng J Med 2005;353:2643–53

Standard Italiani SID- AMD

Lo schema di terapia raccomandato è quello basal-bolus da realizzare tramite terapia multiiniettiva o con microinfusore. *I A*

Nella terapia basal-bolus multiiniettiva, si devono usare analoghi a breve durata d'azione per i boli prandiali e analoghi a lunga durata d'azione come insulina basale. *I A*

ADA Standard of care

PHARMACOLOGIC THERAPY FOR TYPE 1 DIABETES

Recommendations

9.1 Most people with type 1 diabetes should be treated with multiple daily injections of prandial and basal insulin, or continuous subcutaneous insulin infusion. **A**

9.2 Most individuals with type 1 diabetes should use rapid-acting insulin analogs to reduce hypoglycemia risk. **A**

9.3 Consider educating individuals with type 1 diabetes on matching prandial insulin doses to carbohydrate intake, premeal blood glucose levels, and anticipated physical activity. **E**

9.4 Individuals with type 1 diabetes who have been successfully using continuous subcutaneous insulin infusion should have continued access to this therapy after they turn 65 years of age. **E**

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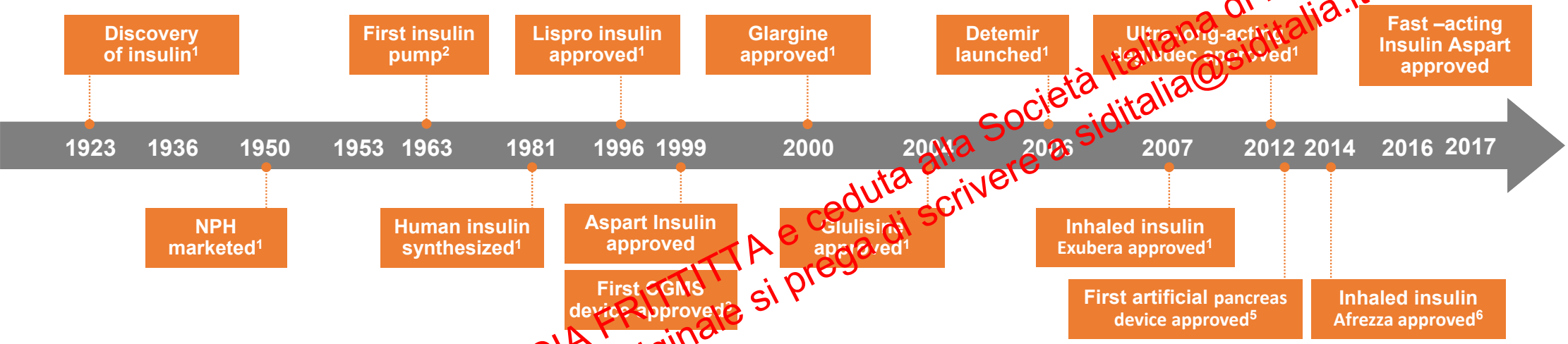
Timeline of insulin and associated modalities for managing T1D



Despite advances for optimising insulin replacement therapy, many patients with T1D struggle to attain glycaemic control

*Approved in USA only.
CGMS=continuous glucose monitoring system; NPH=neutral protamine hagedorn; T1D=type 1 diabetes.

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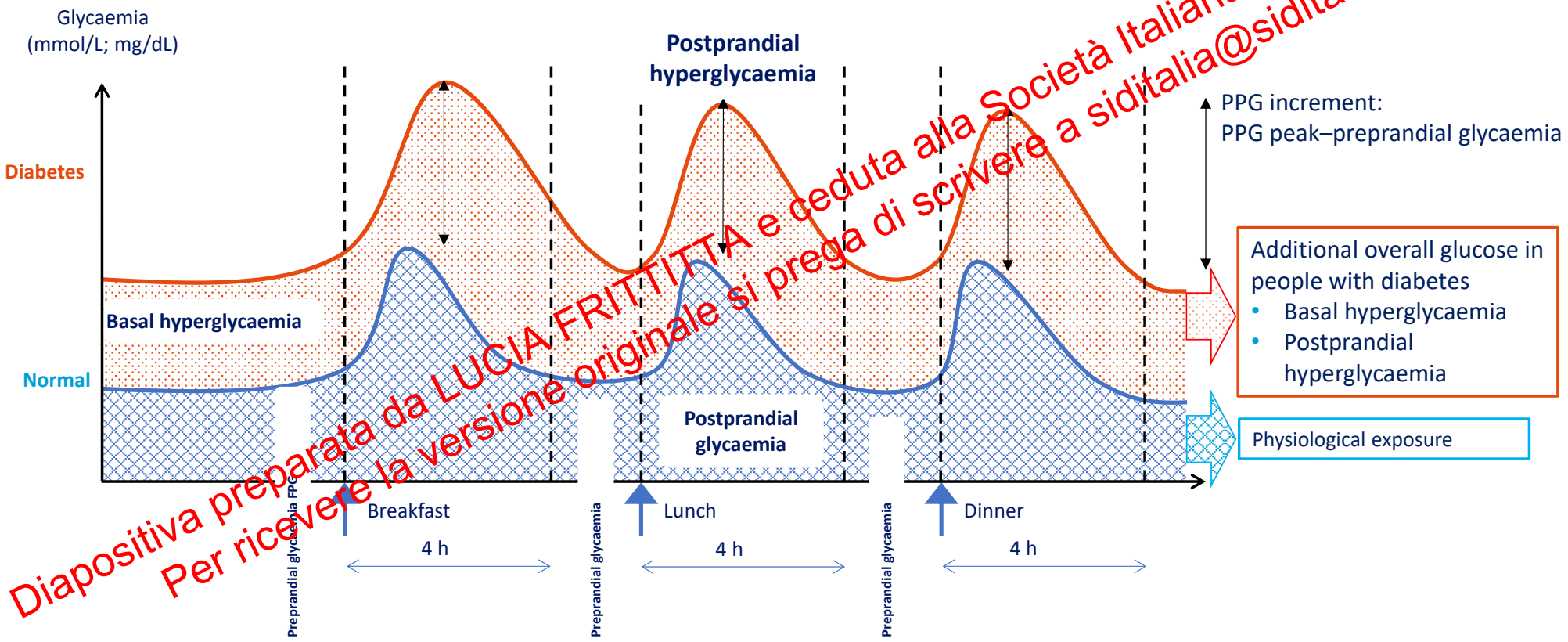
Unmeet needs

Overall glucose exposure is the sum of physiological, basal and postprandial exposures



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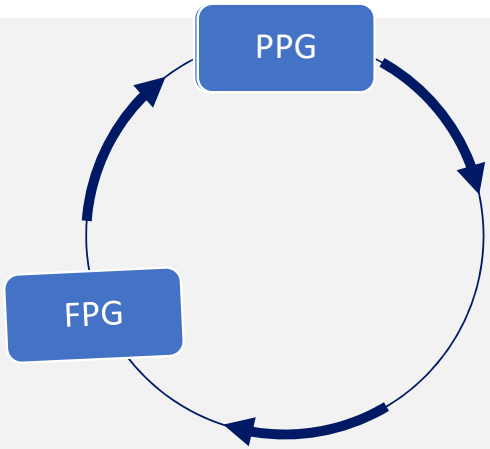
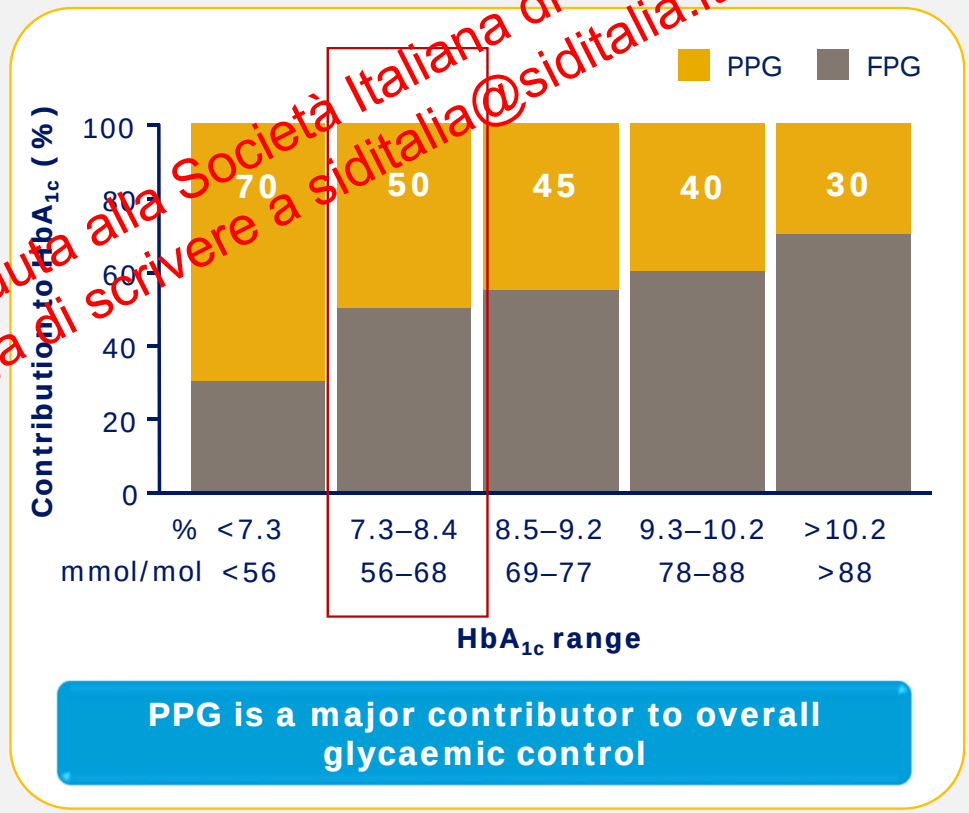
Schematic representation. Adapted from Monnier & Colette. Diabetes Metab 2015;41:179–82

Relationship between FPG and PPG with HbA_{1c} - Why is good PPG control important?



A meta-analysis found that:

- Increased PPG and FPG drive increase in HbA_{1c}[1]
- PPG has a stronger correlation with HbA_{1c} than FPG[3]
- FPG is the predominant contributor in patients with satisfactory to good control of diabetes, whereas the contribution of FPG increases with worsening diabetes[2]



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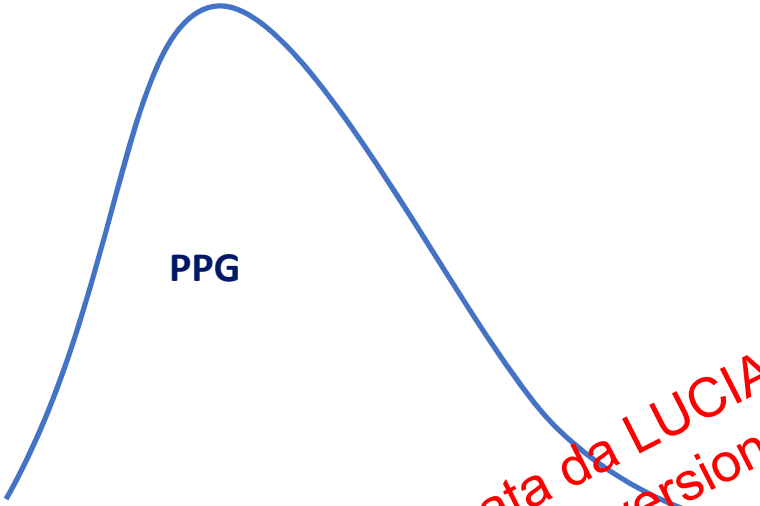
1. Monnier et al. Diabetes Care 2007;30:263–9; 2. Monnier et al. Endocr Pract 2006;12:S1:42–6; 3. Ketema & Kibret. Arch Public Health 2015;73:43; 4. Monnier et al. Diabetes Care 2003;26:881–5;

Relatively complex network controlling postprandial plasma glucose



- **Basal glycaemic level**
- **Insulin secretion and insulin sensitivity**
- **Glucagon and other counter-regulatory hormones**
- **Meal size, content and duration**
- **Gastric emptying and incretin hormones**

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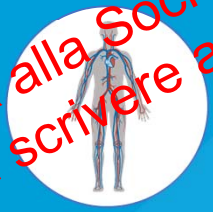
Ceriello. Int J Clin Pract 2010;64:1705–11;

The effect of post-meal hyperglycaemia

Post-meal and post-challenge hyperglycaemia are independent risk factors for macrovascular disease

Post-meal hyperglycaemia is associated with:

- Increased risk of retinopathy
- Increased risk of cancer
- Impaired cognitive function in elderly people with type 2 diabetes



Treatment with agents that target post-meal plasma glucose reduces vascular events in prediabetes

There is a lack of direct RCT evidence showing that correcting post-meal hyperglycaemia improves clinical outcomes

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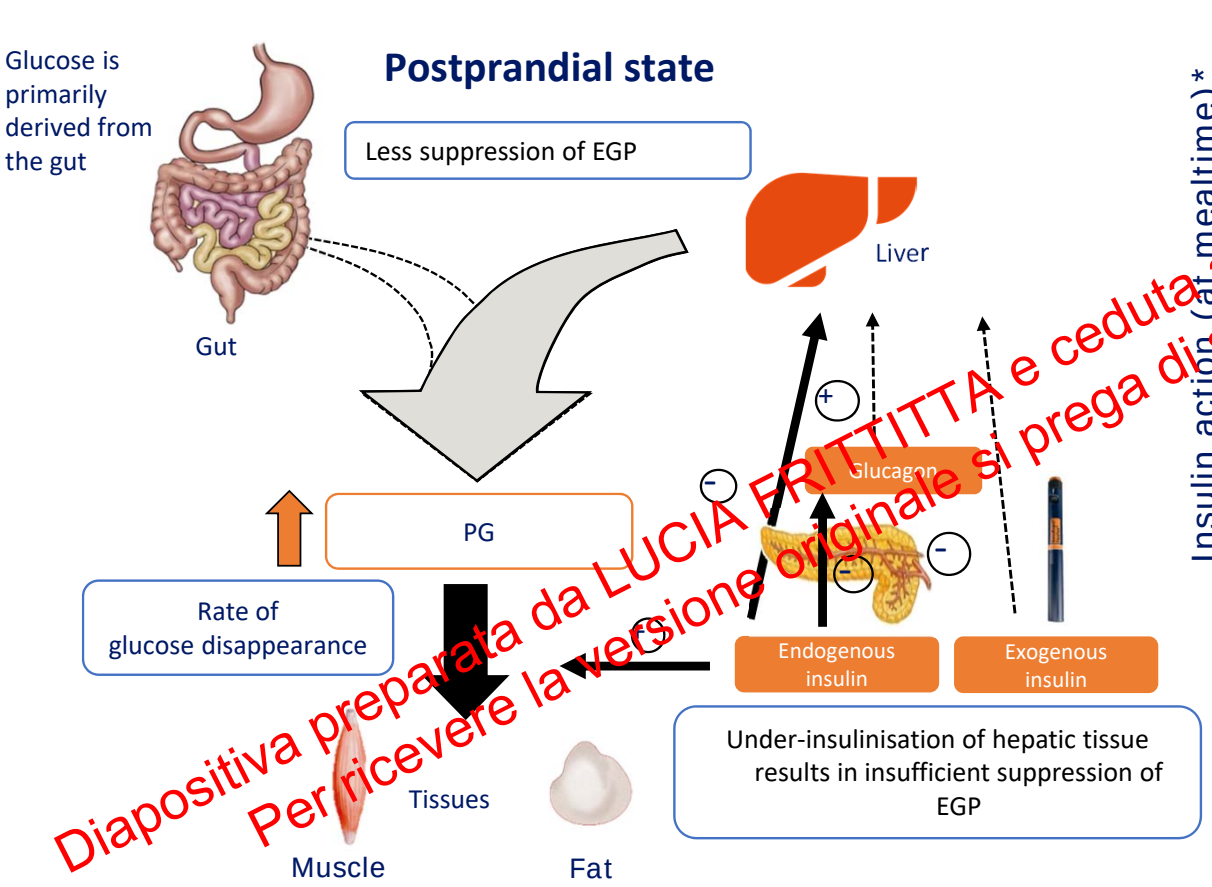
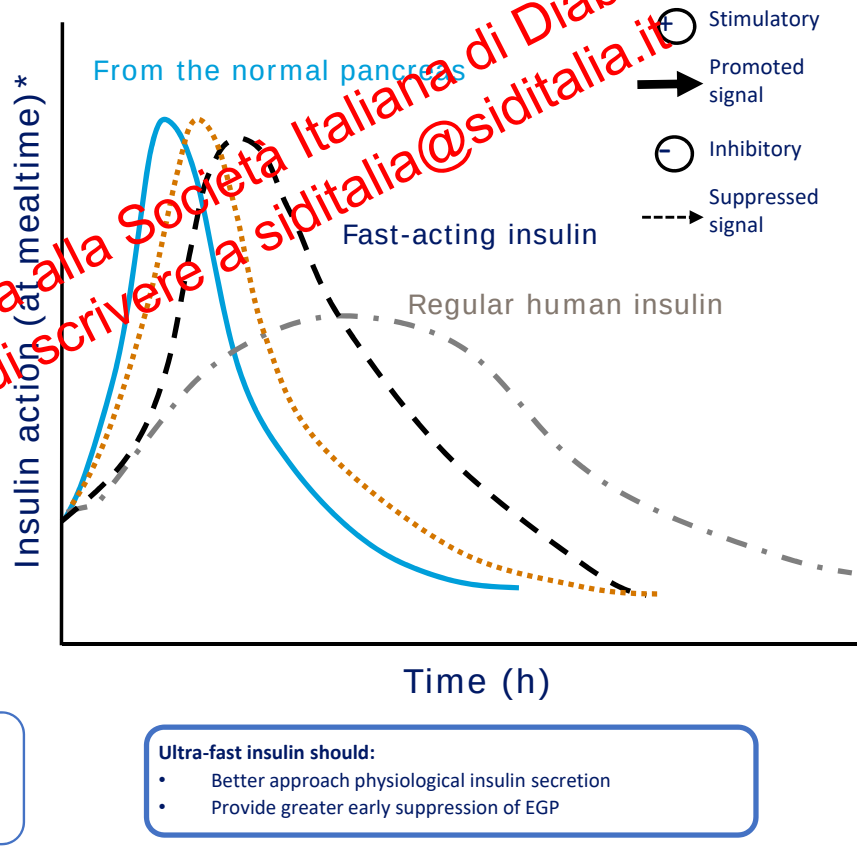
CV, cardiovascular; RCT, randomised controlled trial

Madsbad. J Diabetes Complications 2016;30:374–85; IDF Diabetes Atlas 2019 (9th edition). Available at https://diabetesatlas.org/en/

Approaching the physiological insulin profile could improve PPG control





Ultra-fast insulin should:
- Better approach physiological insulin secretion
- Provide greater early suppression of EGP

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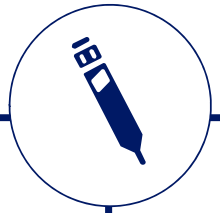
EGP, endogenous glucose production; PG, plasma glucose; PPG, postprandial plasma glucose

Adapted from: Aronoff et al. Diabetes Spectr 2004;17:183–90; Gerich et al. Diabet Med 2010;27:136–42; Home. Diabetes Obes Metab 2015;17:1011–20

Early insulin secretion is important for controlling PPG



Early insulin secretion plays a role in prandial glucoregulation and abolition of this release results in postprandial hyperglycaemia

Early insulin secretion is absent in T1D and blunted early in the development of T2D

In the absence of early insulin secretion, the stimulatory effect of glucagon on EGP is enhanced, thereby contributing to PPG

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1. Firth et al. J Clin Invest 1986;77:1525–32; 2. Luzi et al. Am J Physiol 1989;257:E241–6; 3. Launay et al. Diabetes Care 1998;21:1627–31;
4. Bruttomesso et al. Diabetes 1999;48:99–105; 5. Woerle et al. Am J Physiol Endocrinol Metab 2006;290:E67–77; 6. Basu et al. Clin Endocrinol Metab 2013;98:E409–17

Rapid- acting insulin analogues

TABLE 1. RAPID-ACTING INSULIN ANALOG PRODUCTS

Insulin type	*Product*	*Time to action (min)*	*Time to concentration (min)*	*Duration of action (h)*	*Dosage (U/mL)*	*Vial*	*Pen*
Insulin aspart[46–48]		10–20	40–50	3–5	100	✓	✓
Insulin glulisine[49]		5–15	30–50	3–5	100	✓	✓
Insulin lispro[50]		10–20	55	2–5	100	✓	✓
		15	30–70	2–5	100/200	X	✓

Short acting (regular human)	30-60	2-4 h	6-12

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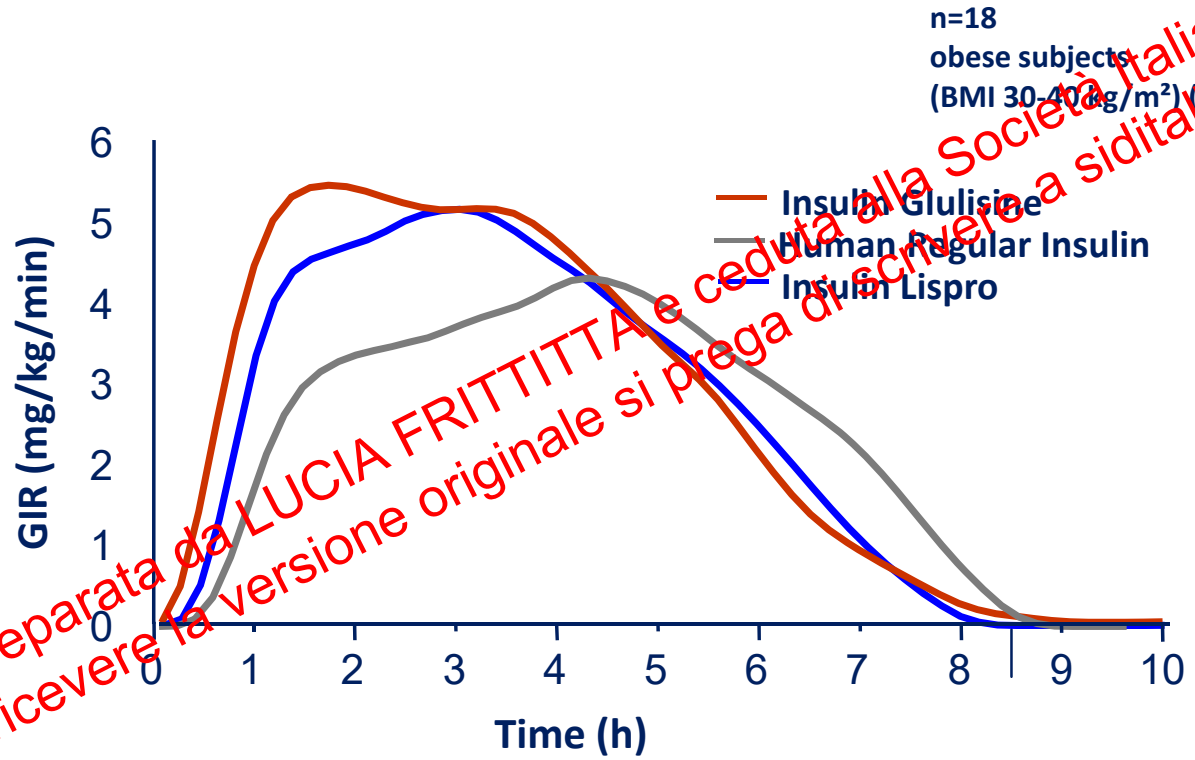
Diab Obesity Metab 22:743, 2020; Diab Tecn & Therap, 22 (5), 2020

PROFILO D'AZIONE GLULISINA, LISPRO, RHI



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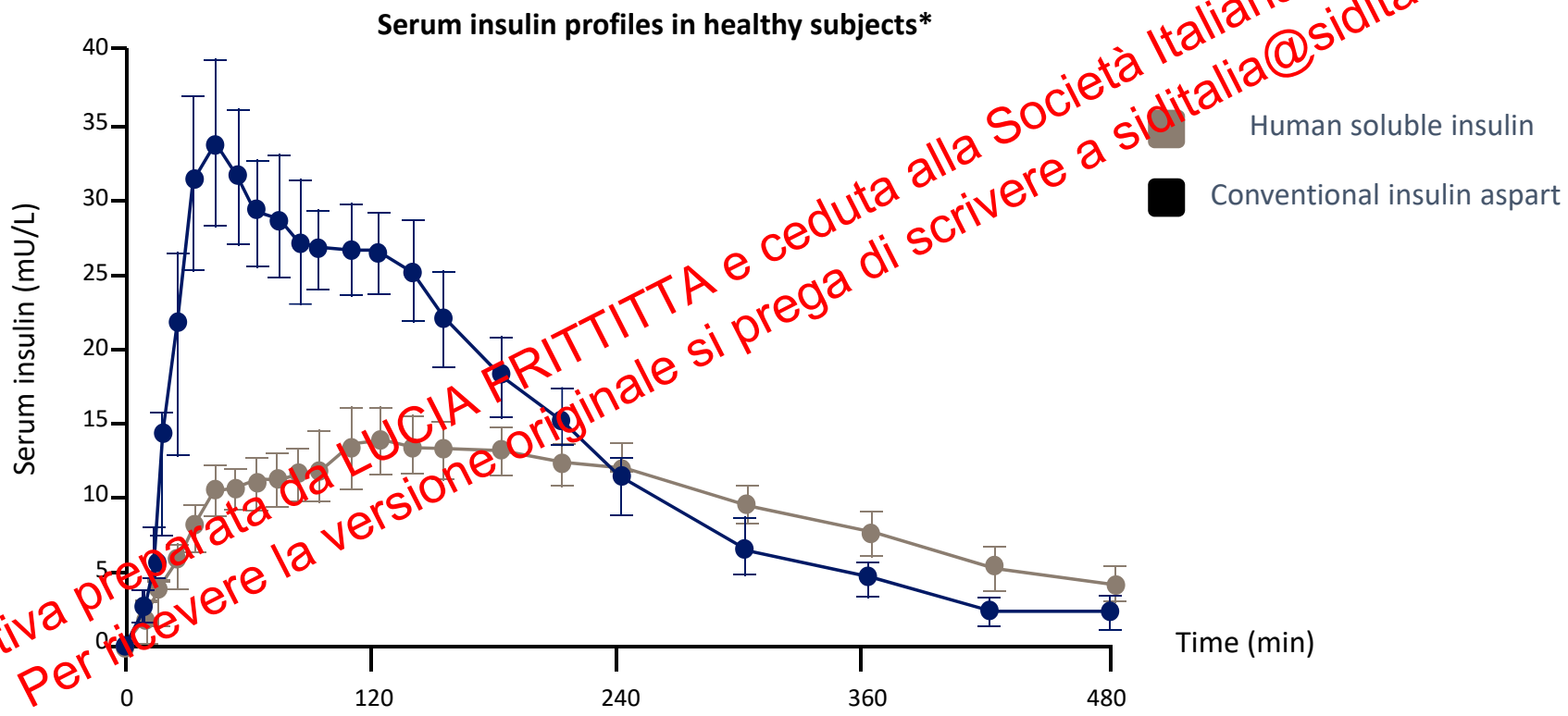
Becker RH et al. Exp Clin Endocrinol Diabetes 113:435-443, 2005

Insulin exposure with conventional insulin aspart compared with human insulin



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*Corrected for endogenous insulin

Home et al. Eur J Clin Pharmacol 1999;55:199–203

Short-acting insulin analogues versus regular human insulin on postprandial glucose in type 1 diabetes mellitus

POSTPRANDIAL GLUCOSE

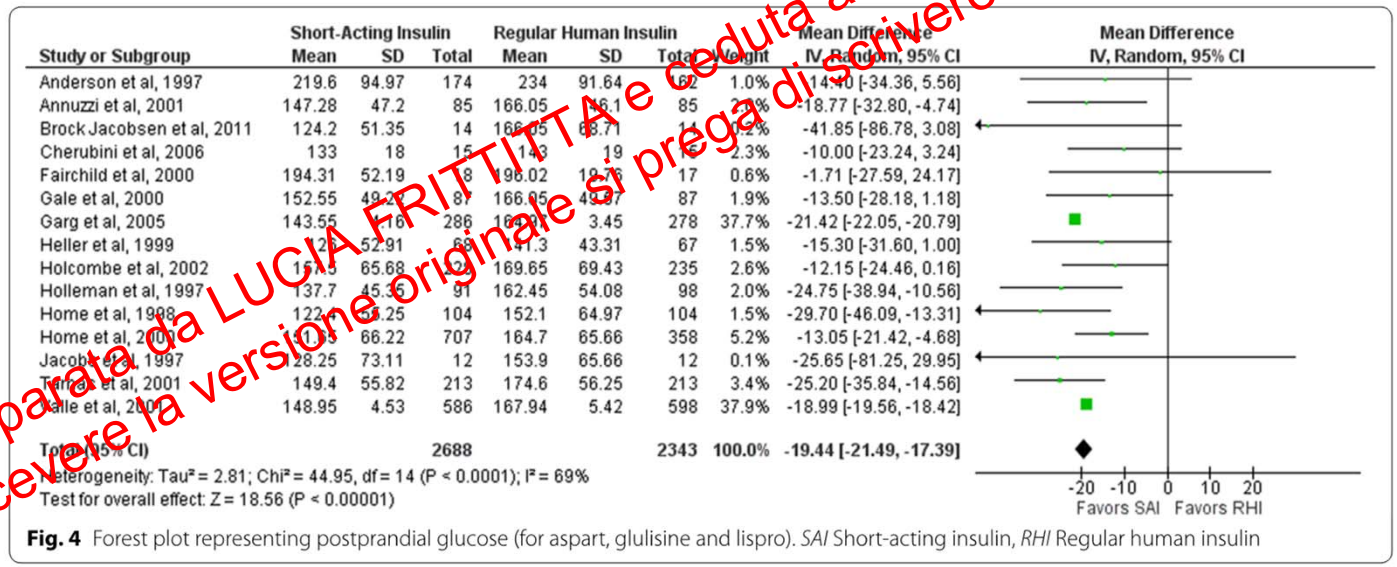

Fig. 4 Forest plot representing postprandial glucose (for aspart, glulisine and lispro). *SAI* Short-acting insulin, *RHI* Regular human insulin

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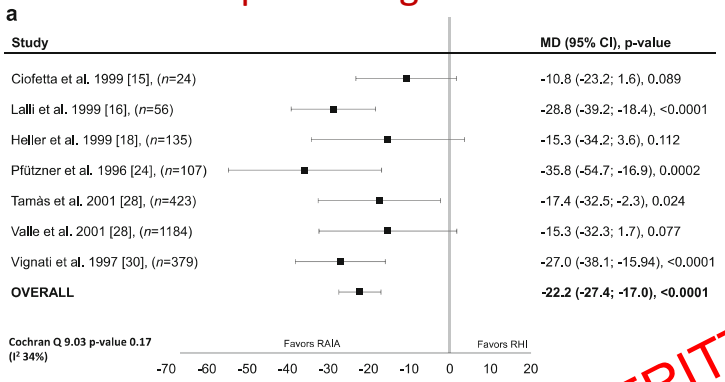
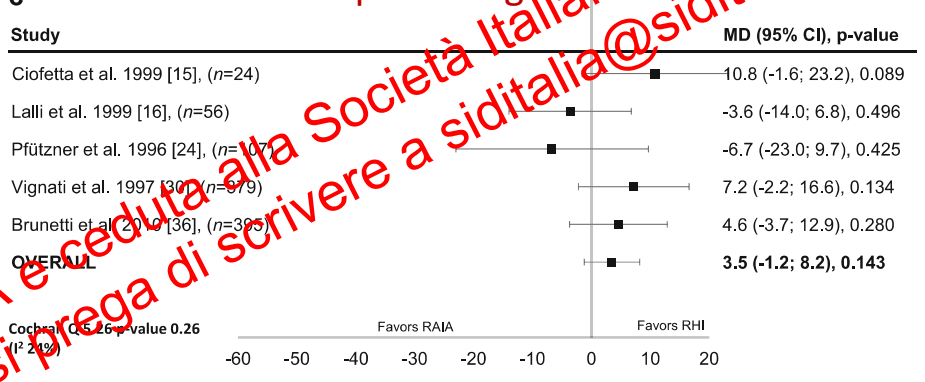
Melo et al. Diabetol Metab Syndr (2019) 11:2

Rapid-Acting Insulin Analogues Versus Regular Human Insulin In T1D

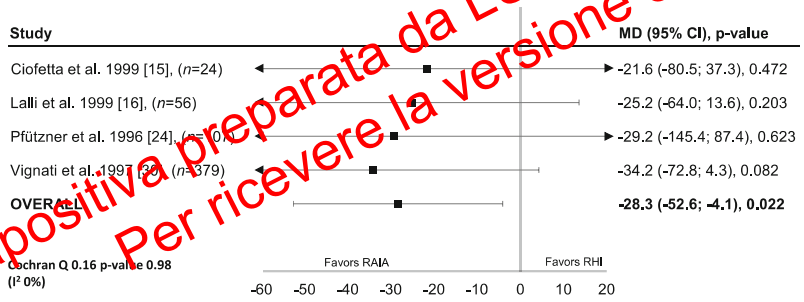
Postprandial glucose



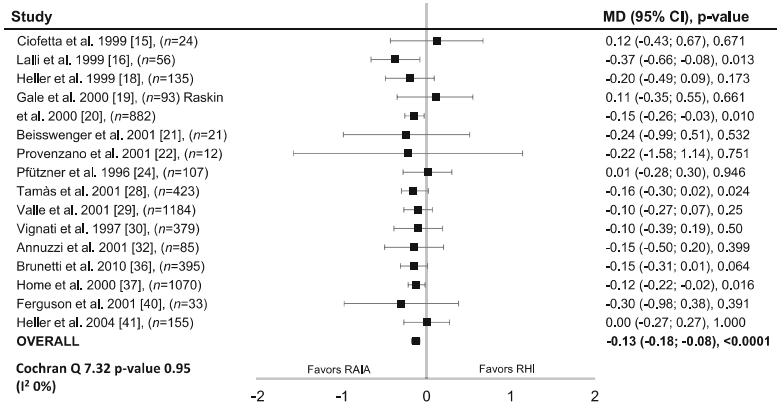
Preprandial glucose



Change in BG following a meal



Glycated Haemoglobin



Nicolucci et al. Diabetes Ther (2020), 11:573

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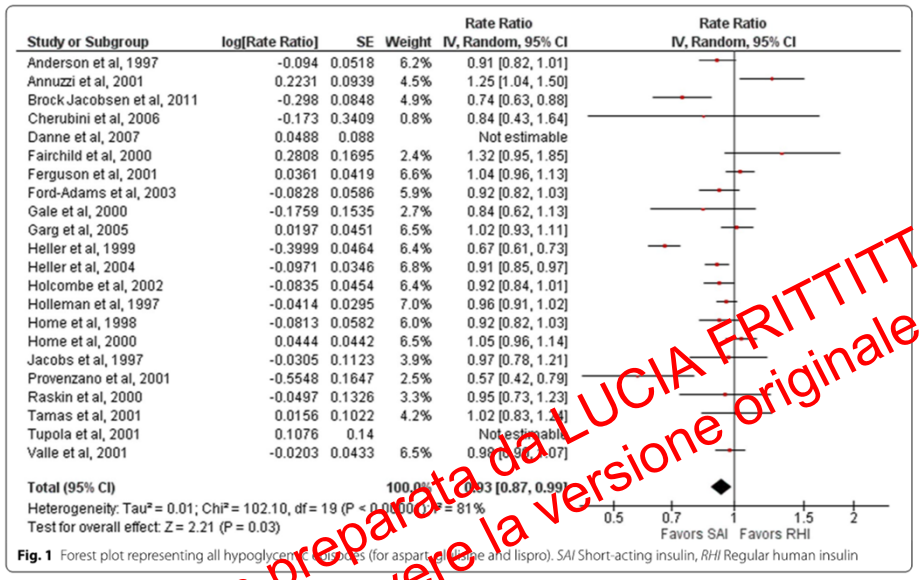
Short-acting insulin analogues versus regular human insulin on hypoglycemia in type 1 diabetes mellitus

HYPOGLYCEMIA



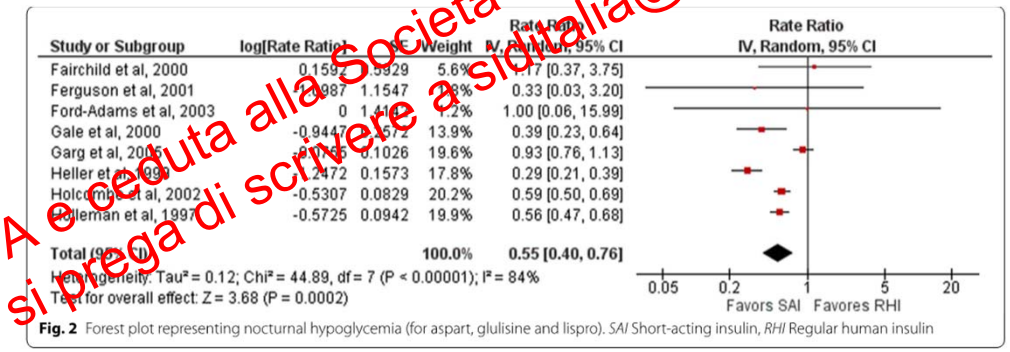
Study or Subgroup	log[Rate Ratio]	SE	Weight	Rate Ratio IV, Random, 95% CI
Anderson et al, 1997	-0.094	0.0518	6.2%	0.91 [0.82, 1.01]
Annuzzi et al, 2001	0.2231	0.0939	4.5%	1.25 [1.04, 1.50]
Brock Jacobsen et al, 2011	-0.298	0.0848	4.9%	0.74 [0.63, 0.88]
Cherubini et al, 2006	-0.173	0.3409	0.8%	0.84 [0.43, 1.64]
Danne et al, 2007	0.0488	0.088		Not estimable
Fairchild et al, 2000	0.2808	0.1695	2.4%	1.32 [0.95, 1.85]
Ferguson et al, 2001	0.0361	0.0419	6.6%	1.04 [0.96, 1.13]
Ford-Adams et al, 2003	-0.0828	0.0586	5.9%	0.92 [0.82, 1.03]
Gale et al, 2000	-0.1759	0.1535	2.7%	0.84 [0.62, 1.13]
Garg et al, 2005	0.0197	0.0451	6.5%	1.02 [0.93, 1.11]
Heller et al, 1999	-0.3999	0.0464	6.4%	0.67 [0.61, 0.73]
Heller et al, 2004	-0.0971	0.0346	6.8%	0.91 [0.85, 0.97]
Holcombe et al, 2002	-0.0835	0.0454	6.4%	0.92 [0.84, 1.01]
Holleman et al, 1997	-0.0414	0.0295	7.0%	0.96 [0.91, 1.02]
Home et al, 1998	-0.0813	0.0582	6.0%	0.92 [0.82, 1.03]
Home et al, 2000	0.0444	0.0442	6.5%	1.05 [0.96, 1.14]
Jacobs et al, 1997	-0.0305	0.1123	3.9%	0.97 [0.78, 1.21]
Provenzano et al, 2001	-0.5548	0.1647	2.5%	0.57 [0.42, 0.79]
Raskin et al, 2000	-0.0497	0.1326	3.3%	0.95 [0.73, 1.23]
Tamas et al, 2001	0.0156	0.1022	4.2%	1.02 [0.83, 1.24]
Tupola et al, 2001	0.1076	0.14		Not estimable
Valle et al, 2001	-0.0203	0.0433	6.5%	0.99 [0.91, 1.07]
Total (95% CI)			100.0%	**0.93 [0.87, 0.99]**

Heterogeneity: Tau² = 0.01; Chi² = 102.10, df = 19 (P < 0.00001); I² = 81%
Test for overall effect: Z = 2.21 (P = 0.03)

Rate Ratio IV, Random, 95% CI
0.5 0.7 1 1.5 2
Favors SAI Favors RHI

Fig. 1 Forest plot representing all hypoglycemic episodes (for aspart, glulisine and lispro). *SAI* Short-acting insulin, *RHI* Regular human insulin

NOCTURNAL HYPOGLYCEMIA



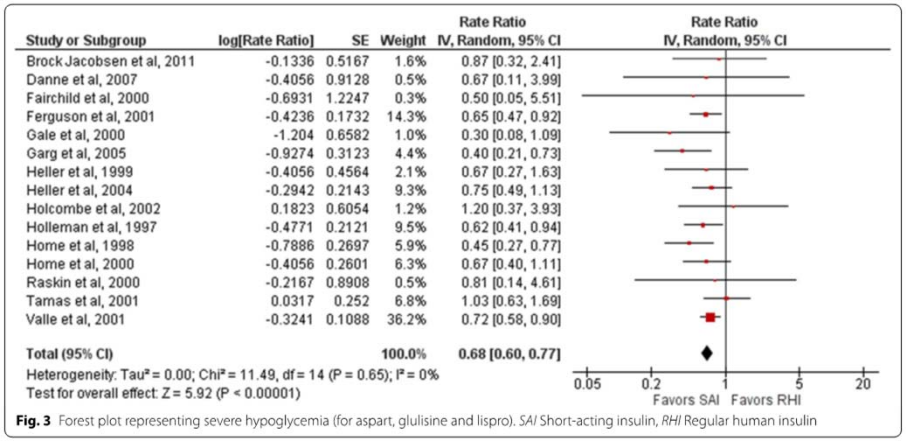
Study or Subgroup	log[Rate Ratio]	SE	Weight	Rate Ratio IV, Random, 95% CI
Fairchild et al, 2000	0.1592	0.5929	5.6%	1.17 [0.37, 3.75]
Ferguson et al, 2001	-1.1087	1.1547	2.8%	0.33 [0.03, 3.20]
Ford-Adams et al, 2003	0	1.4142	1.2%	1.00 [0.06, 15.99]
Gale et al, 2000	-0.9447	0.4572	13.9%	0.39 [0.23, 0.64]
Garg et al, 2005	-0.0645	0.1026	19.6%	0.93 [0.76, 1.13]
Heller et al, 1999	-1.2472	0.1573	17.8%	0.29 [0.21, 0.39]
Holcombe et al, 2002	-0.5307	0.0829	20.2%	0.59 [0.50, 0.69]
Holleman et al, 1997	-0.5725	0.0942	19.9%	0.56 [0.47, 0.68]
Total (95% CI)			100.0%	**0.55 [0.40, 0.76]**

Heterogeneity: Tau² = 0.12; Chi² = 44.89, df = 7 (P < 0.00001); I² = 84%
Test for overall effect: Z = 3.68 (P = 0.0002)

Rate Ratio IV, Random, 95% CI
0.05 0.2 1 5 20
Favors SAI Favores RHI

Fig. 2 Forest plot representing nocturnal hypoglycemia (for aspart, glulisine and lispro). *SAI* Short-acting insulin, *RHI* Regular human insulin

SEVERE HYPOGLYCEMIA



Study or Subgroup	log[Rate Ratio]	SE	Weight	Rate Ratio IV, Random, 95% CI
Brock Jacobsen et al, 2011	-0.1336	0.5167	1.6%	0.87 [0.32, 2.41]
Danne et al, 2007	-0.4056	0.9128	0.5%	0.67 [0.11, 3.99]
Fairchild et al, 2000	-0.6931	1.2247	0.3%	0.50 [0.05, 5.51]
Ferguson et al, 2001	-0.4236	0.1732	14.3%	0.65 [0.47, 0.92]
Gale et al, 2000	-1.204	0.6582	1.0%	0.30 [0.08, 1.09]
Garg et al, 2005	-0.9274	0.3123	4.4%	0.40 [0.21, 0.73]
Heller et al, 1999	-0.4056	0.4564	2.1%	0.67 [0.27, 1.63]
Heller et al, 2004	-0.2942	0.2143	9.3%	0.75 [0.49, 1.13]
Holcombe et al, 2002	0.1823	0.6054	1.2%	1.20 [0.37, 3.93]
Holleman et al, 1997	-0.4771	0.2121	9.5%	0.62 [0.41, 0.94]
Home et al, 1998	-0.7886	0.2697	5.9%	0.45 [0.27, 0.77]
Home et al, 2000	-0.4056	0.2601	6.3%	0.67 [0.40, 1.11]
Raskin et al, 2000	-0.2167	0.8908	0.5%	0.81 [0.14, 4.61]
Tamas et al, 2001	0.0317	0.252	6.8%	1.03 [0.63, 1.69]
Valle et al, 2001	-0.3241	0.1088	36.2%	0.72 [0.58, 0.90]
Total (95% CI)			100.0%	**0.68 [0.60, 0.77]**

Heterogeneity: Tau² = 0.00; Chi² = 11.49, df = 14 (P = 0.65); I² = 0%
Test for overall effect: Z = 5.92 (P < 0.00001)

Rate Ratio IV, Random, 95% CI
0.05 0.2 1 5 20
Favors SAI Favors RHI

Fig. 3 Forest plot representing severe hypoglycemia (for aspart, glulisine and lispro). *SAI* Short-acting insulin, *RHI* Regular human insulin

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Melo *et al. Diabetol Metab Syndr (2019) 11:2*

Conclusion 1: Short-acting vs. regular human insulin

Short-acting insulin analogues are superior to regular human insulin in T1DM patients for the following outcomes:

- postprandial glucose
- HbA1c
- total hypoglycemic episodes
- nocturnal hypoglycemia
- severe hypoglycemia

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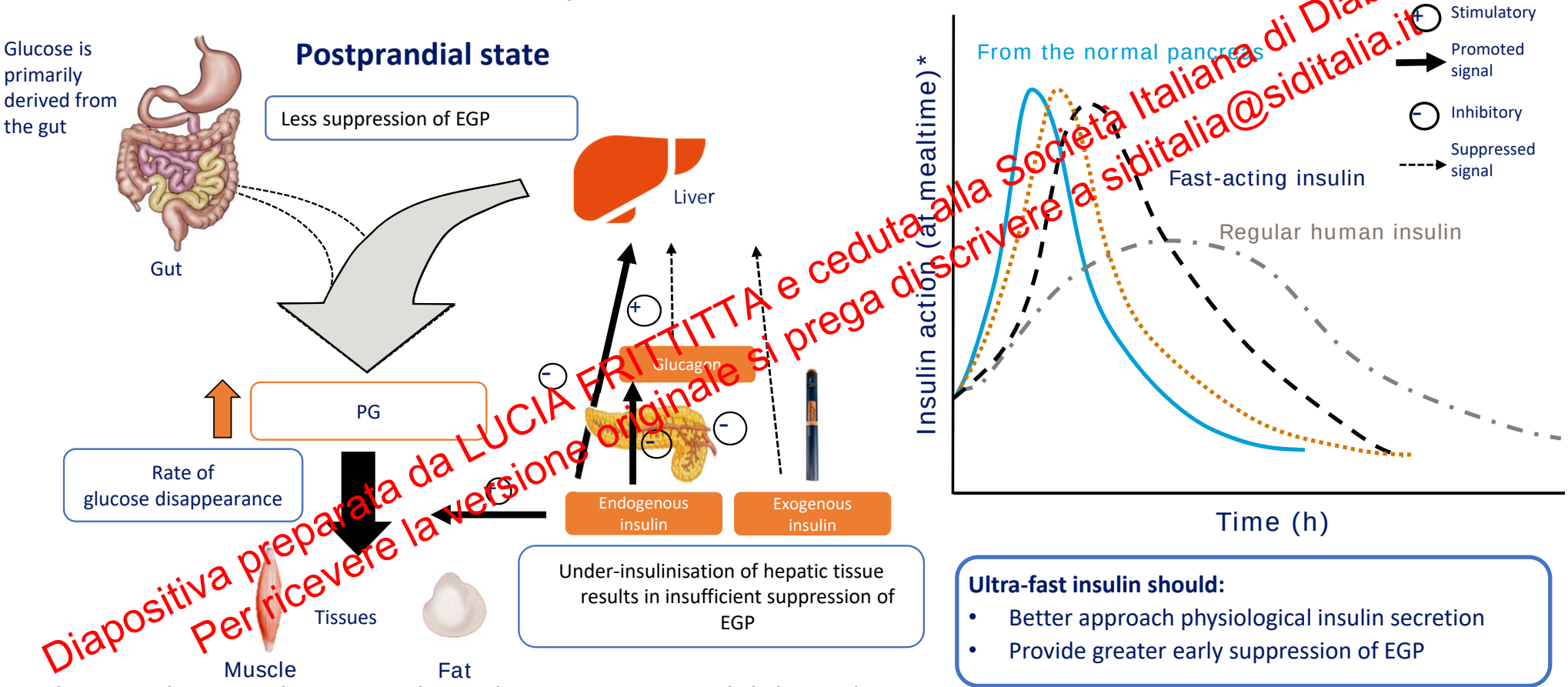
Approaching the physiological insulin profile could improve PPG control



Ultra-fast insulin should:

- Better approach physiological insulin secretion
- Provide greater early suppression of EGP

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EGP, endogenous glucose production; PG, plasma glucose; PPG, postprandial plasma glucose

Adapted from: Aronoff et al. Diabetes Spectr 2004;17:183–90; Gerich et al. Diabet Med 2010;27:136–42; Home. Diabetes Obes Metab 2015;17:1011–20

Rapid- acting insulin analogues

TABLE 1. RAPID-ACTING INSULIN ANALOG PRODUCTS

Insulin type	*Product*	*Onset of action (min)*	*Time to peak insulin concentration (min)*	*Duration of action (h)*	*Dosage strength (U/mL)*	*Vial*	*Pen*
Insulin aspart[46–48]		10–20	40–50	3–5	100	✓	✓
Insulin glulisine[49]		10–20	55	2–5	100	✓	✓
Insulin lispro[50]		15	30–70	2–5	100/200	X	✓
Short acting (regular human)		30-60	2-4 h	6-12			

TABLE 1 Current second-generation rapid-acting insulin analogues in development

Drug	Company	Core insulin structure	Added excipients	Mechanism of action
Faster aspart[27]	Novo Nordisk, Bagsværd, Denmark	Insulin aspart	Niacinamide (vitamin B3), L-arginine	Increased subcutaneous blood flow
Ultra-rapid lispro[28,29]	Eli Lilly, Indianapolis, IN	Insulin lispro	Treprostinil, citrate	Enhanced vascular permeability and increased local vasodilation
BioChaperone Lispro[30]	Adocia, Lyon, France	Insulin lispro	BioChaperone BC222,[a] citrate	Enhanced diffusion

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Second-generation rapid-acting insulins in T1DM

		Faster aspart	Ultra-rapid lispro			BioChaperone Lispro		
Comparator	Administration	Aspart	Lispro	Aspart	Faster aspart	Lispro	Aspart	Faster aspart
Pharmacokinetics								
Onset ($t_{Early50\%Cmax}$)	sc injection	**−9.5 min**[52]	**−8.8**[36] **to −12.5**[43] **min**	**−13.9 min**[43]	**−5.2 min**[43]	**−12.7 min**[a48]	NR	NR
	CSII	**−11.8 min**[55]	**−8.6 min**[40]	NR	NR	NR	**−11.7 min**[30]	−0.7 min[30]
Offset ($t_{Late50\%Cmax}$)	sc injection	**−12.2 min**[52]	**−7.0**[36] **to −13.8**[43] **min**	**−21.1 min**[43]	**−9.5 min**[43]	**−28.2 min**[a48]	NR	NR
	CSII	**−35.4 min**[55]	−12.2 min[40]	NR	NR	NR	NR	NR
Early exposure ($AUC_{30\ min}$)	sc injection	**↑~2-fold**[52]	**↑~2.2**[36] **- to 2.9**[43]**-fold**	**↑2.4-fold**[43]	**↑1.2-fold**[43]	**↑2.5**[a48]**- to 2.7**[49]**-fold**	NR	NR
	CSII	**↑~3-fold**[55]	**↑1.5-fold**[40]	NR	NR	NR	NR	NR
Pharmacodynamic								
Onset ($t_{Early50\%GIRmax}$)	sc injection	**−9.5 min**[52]	**−12.2 min**[b35]	NR	NR	**−10.0 min**[47]	NR	NR
	CSII	**−11.1 min**[55]	NR	NR	NR	NR	**−13.0 min**[30]	+1.3 min[30]
Offset ($t_{Late50\%GIRmax}$)	sc injection	**−14.3 min**[52]	0 min[b35]	NR	NR	NR	NR	NR
	CSII	**−24.0 min**[55]	NR	NR	NR	NR	**−38.2 min**[30]	**−19.6 min**[30]
Early effect ($AUC_{GIR,30\ min}$)	sc injection	**↑~1.7-fold**[52]	NR	NR	NR	**↑>3-fold**[47]	NR	NR
	CSII	**↑~2-fold**[55]	NR	NR	NR	NR	NR	NR

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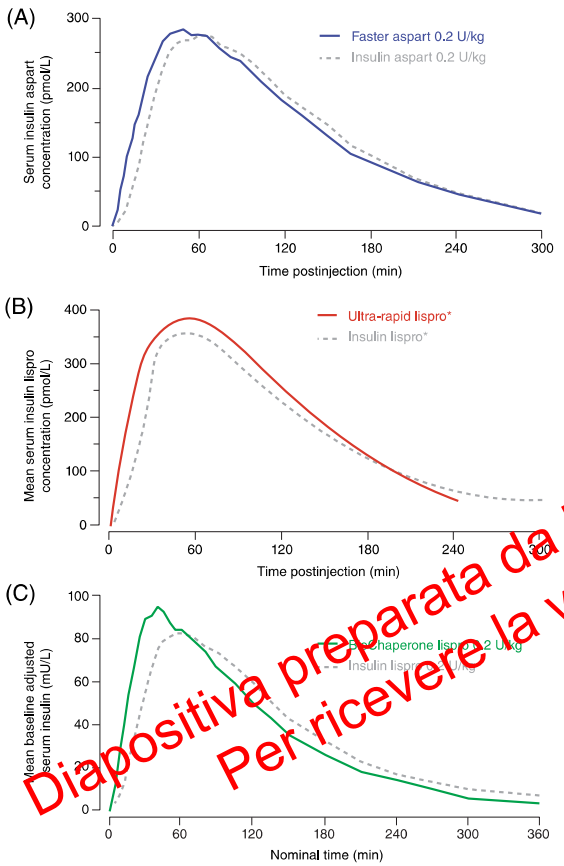
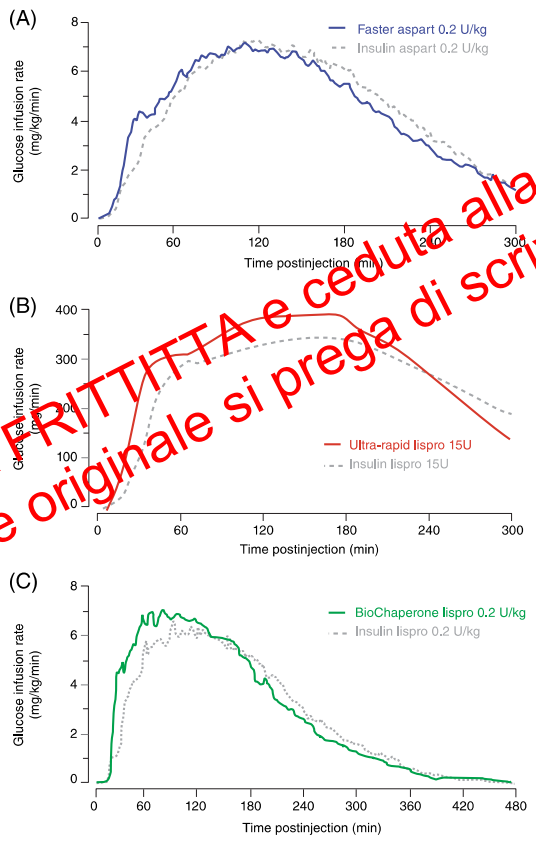
Second-generation rapid-acting insulins in T1DM

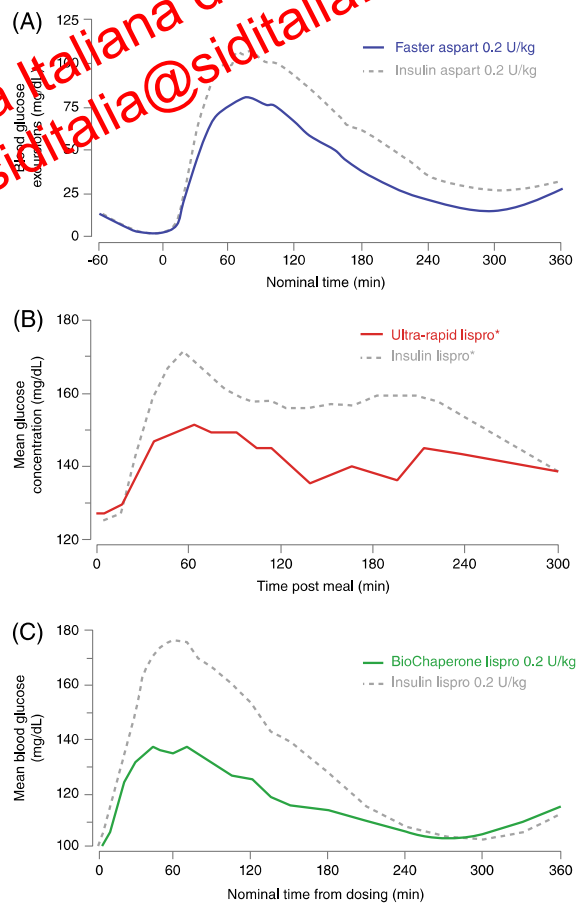
Serum insulin levels after sc injection



Glucose infusion rate in clamp studies after sc injection



Postprandial glucose after sc injection following a liquid meal



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Diab Obesity Metab 22:743, 2020;

TABLE 3A Key features and results of phase 3 trials comparing mealtime faster aspart with different comparators

	T1DM basal-bolus				T2DM basal-bolus			T2DM pump	
Parameter	Onset 1[61,62]		Onset 8[63,64]	Onset 7[65]	Onset 2[66]	Onset 9[70]	Onset 3[67]	Onset 4[68]	Onset 5[69]
Comparator	Aspart		Aspart	Aspart	Aspart	Aspart	Basal insulin only	CSII aspart	CSII aspart
Basal insulin used	IDet		IDeg	IDeg	Gla-100	IDeg	IDet/Gla-100/NPH	–	–
Participants (n)	381 vs. 380	381 vs. 380	342 vs. 342	260 vs. 258	345 vs. 344	546 vs. 545	110 vs. 120	25 vs. 12	236 vs. 236
Duration (weeks)	26	52	26	26	26	52	18	6	16
Glycaemic control									
ΔHbA1c, %	**−0.15**	**−0.10**	−0.02	**−0.17**	−0.02	−0.04	**−0.94**	−0.14	+0.09[a]
HbA1c <7.0%, OR	**1.47**	0.97	0.88	1.33[b]	1.01	NR	**9.31**	NR	0.76
Meal test									
Composition	Liquid[c]	Liquid[c]	Liquid, 78 g CHO	Liquid[d], 75 g CHO/kg	Liquid, ~80 g CHO	Liquid[c]	NA	NA	Liquid[c]
Consumption time	≤12 min	≤12 min	≤12 min	NR	≤12 min	NR	NA	NA	≤12 min
$\Delta PPG_{1\text{-}h}$, mmol/L	**−1.18**	**−0.91**	**−0.90**	NS[d]	**−0.59**	**−0.40**	NA	NA	**−0.91**
$\Delta PPG_{2\text{-}h}$, mmol/L	**−0.67**	−0.42	−0.35	NS[d]	−0.36	−0.30	NA	NA	**−0.90**
SMPG									
$\Delta PPG_{1\text{-}h}$, mmol/L	NR	NR	**−0.68**[e]	**−0.93**[f]	NR	**−0.25**[f]	**−1.14**[e]	NR	**−0.46**[e,f]
$\Delta PPG_{2\text{-}h}$, mmol/L	−0.21[e]	−0.25[e,f]	NR	NR	NR	NR	**−2.48**[e]	−0.77[f,g]	NR
$PPG_{2\text{-}h}$ ≤ 7.8 mmol/L, OR	1.33	1.40	**1.54**[h]	NR	1.18	NR	**41.9**	NR	NR
$PPG_{2\text{-}h}$ ≤ 7.8 mmol/L without SH, OR	NR	**1.47**	NR	NR	1.23	NR	**44.2**	NR	NR
Hypoglycaemia									
Overall[i], RR	1.01	1.01	0.84	1.11	1.09	**0.81**	**8.24**	0.98[j]	1.00
PM within 1 h, RR	**1.48**	**1.37**	1.09	NS	1.29	1.16	NR	NR	**1.78**
PM within 2 h, RR	NR (NS)[k]	NR	0.75[l]	NS	**1.60**	0.97	NR	NR	NR (NS)

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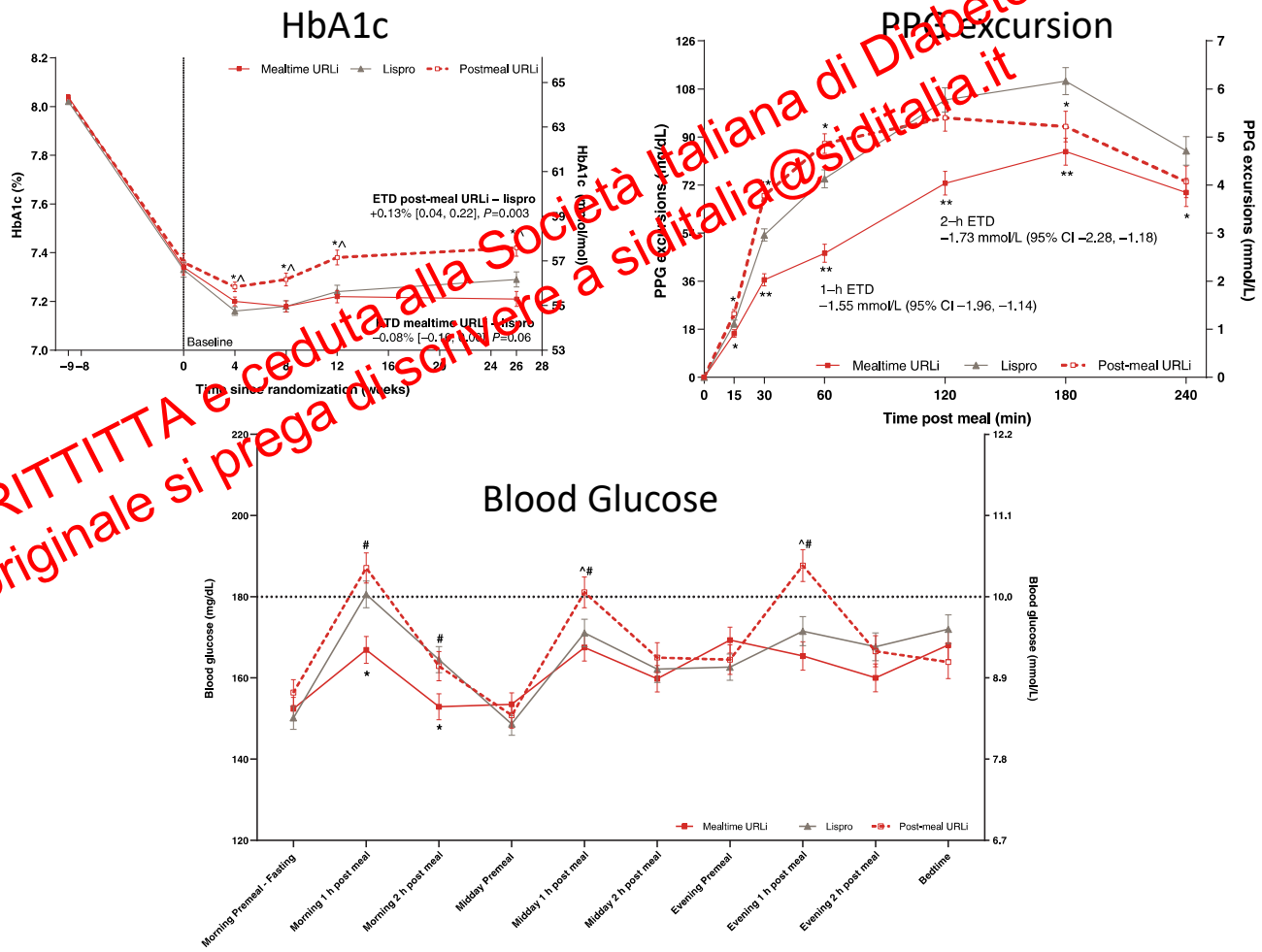
TABLE 3B Key features and results of reported phase 3 trials comparing mealtime ultra-rapid lispro with mealtime lispro

Parameter	T1DM basal-bolus PRONTO-T1D[71,78]	T2DM basal-bolus PRONTO-T2D[76,79]
Comparator	Mealtime lispro	Mealtime lispro
Basal insulin used	Gla-100/IDeg	Gla-100/IDeg
Participants (n)	451 vs. 442	336 vs. 337
Duration (weeks)	26 (52)	26
Glycaemic control		
Δ HbA1c (%)	−0.08	+0.06
Meal test[a]		
Composition	Liquid[a], ~100 g CHO (~57% kcal)	Liquid[a]
Consumption time	NR	NR
$\Delta PPG_{1\text{-}h}$, mmol/L	**−1.55**	**−0.66**
$\Delta PPG_{2\text{-}h}$, mmol/L	**−1.73**	**−0.96**
$\Delta PPG_{3\text{-}h}$, mmol/L	**NR (*P* < 0.001)**	**NR (*P* < 0.001)**
$\Delta PPG_{4\text{-}h}$, mmol/L	**NR (*P* < 0.05)**	**NR (*P* < 0.05)**
Hypoglycaemia rate[b]		
Documented, RR	0.92	1.02
Post-meal ≤1 h, RR	1.16	1.14
Post-meal ≤2 h, RR	1.11	1.33
Post-meal >1 to ≤2 h, RR	1.07	**2.31**
Post-meal >2 to ≤4 h, RR	1.01	**1.44**
Post-meal ≤4 h, RR	1.06	NR
Post-meal >4 h, RR	**0.62 (*P* < 0.001)**	0.95

PRONTO-T1D



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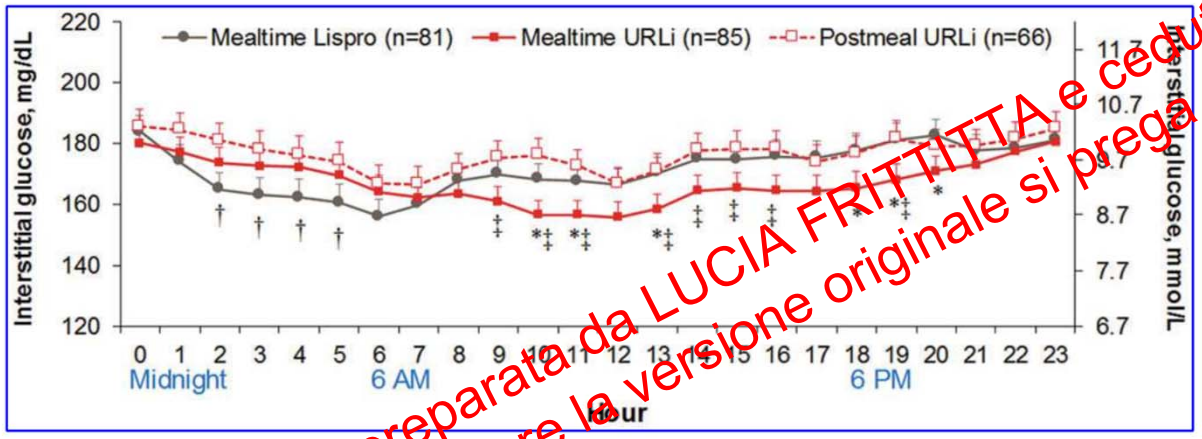
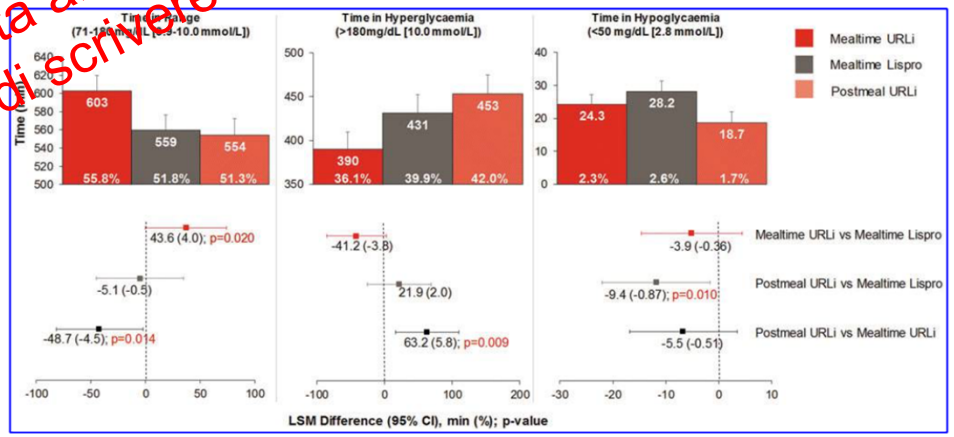
Diab Obesity Metab 22:743, 2020;

Diab Technol Ther (2020: 22:10

Ultra-Rapid Lispro Improves Postprandial Glucose Control and Time in Range in Type 1 Diabetes Compared to Lispro: PRONTO-T1D CGM Substudy

Hourly average glucose during continuous glucose monitoring at week 26.





*P<0.05 for mealtime URLi versus mealtime lispro

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DIABETES TECHNOLOGY & THERAPEUTICS Volume 22, Number 10, 2020

Conclusion 2: second generation rapid-acting insulin

Second generation of rapid acting insulin:

- lesser PPG increment at 1 or 2 hours
- minimal improvement in HbA1c
- similar risk of inter-prandial hypoglycemic episodes
- Additional studies is required for solid meals mimicking real-life conditions

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Postprandial glucose excursions

- Postprandial glucose excursions may be better controlled by adjusting the timing of prandial insulin dose administration.
- The optimal time to administer prandial insulin varies, based on the type of insulin used (regular, rapid-acting analog, inhaled, etc.), measured blood glucose level, timing of meals, and carbohydrate consumption.
- Recommendations for prandial insulin dose administration should therefore be individualized.

Diapedia preparata da LUCIA FRITTITTA e ceduta alla Società Italiana di Diabetologia.
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Assessment of optimal insulin administration timing for standard carbohydrates-rich meals using continuous glucose monitoring in children with type 1 diabetes: A cross-over randomized study

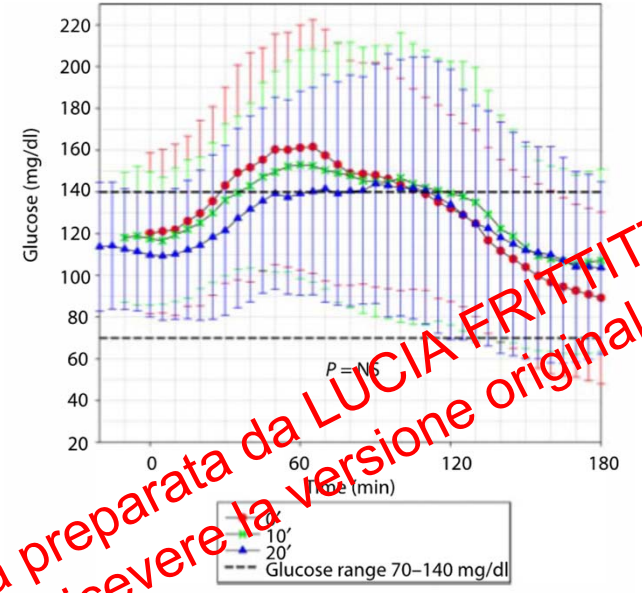

Figure 1 | Profile of mean postprandial glucose concentrations (dots, mean values; whiskers, standard deviation).

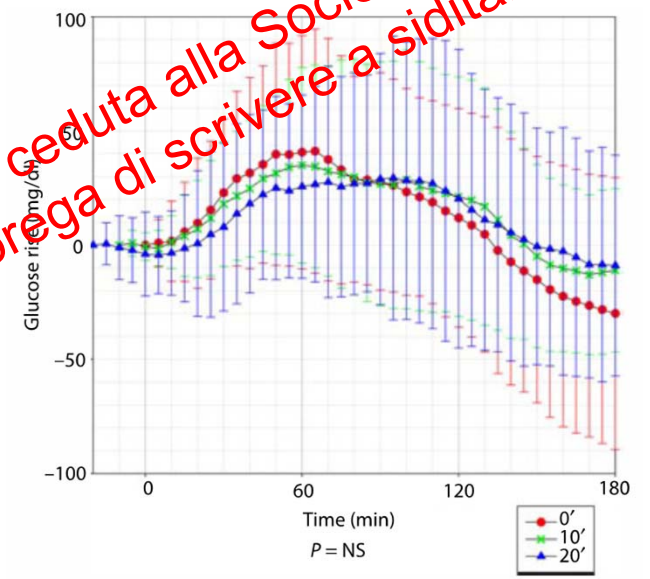

Figure 2 | Profile of mean postprandial glucose concentration rises (dots, mean values; whiskers, standard deviation).

Diapositiva preparata da LUCIA FRITTITTA e ceduta alla Società Italiana di Diabetologia.
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Fattori che influenzano l'attività dell'insulina

- Tipo di insulina
- Spessore del tessuto cutaneo
- Profondità di iniezione
- Zona di iniezione
- Attività fisica
- Iniezione in zone lipoipertrofiche
- Massaggio nella zona di iniezione

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FUTURE TRENDS OF INSULINS

- **Oral administration of basal insulin** would avoid injections and may also deliver the insulin in a more physiologic manner through absorption through the portal vein

- **‘‘Smart’’ or glucose-responsive insulin**, which would help patients avoid hypoglycemic events. This could be accomplished by surrounding the insulin molecules with a matrix that can sense blood glucose concentrations and release the insulin accordingly. In other cases, the insulin molecule itself is modified to allow activation under glucose-replete conditions.

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