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

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- **Astra Zeneca**
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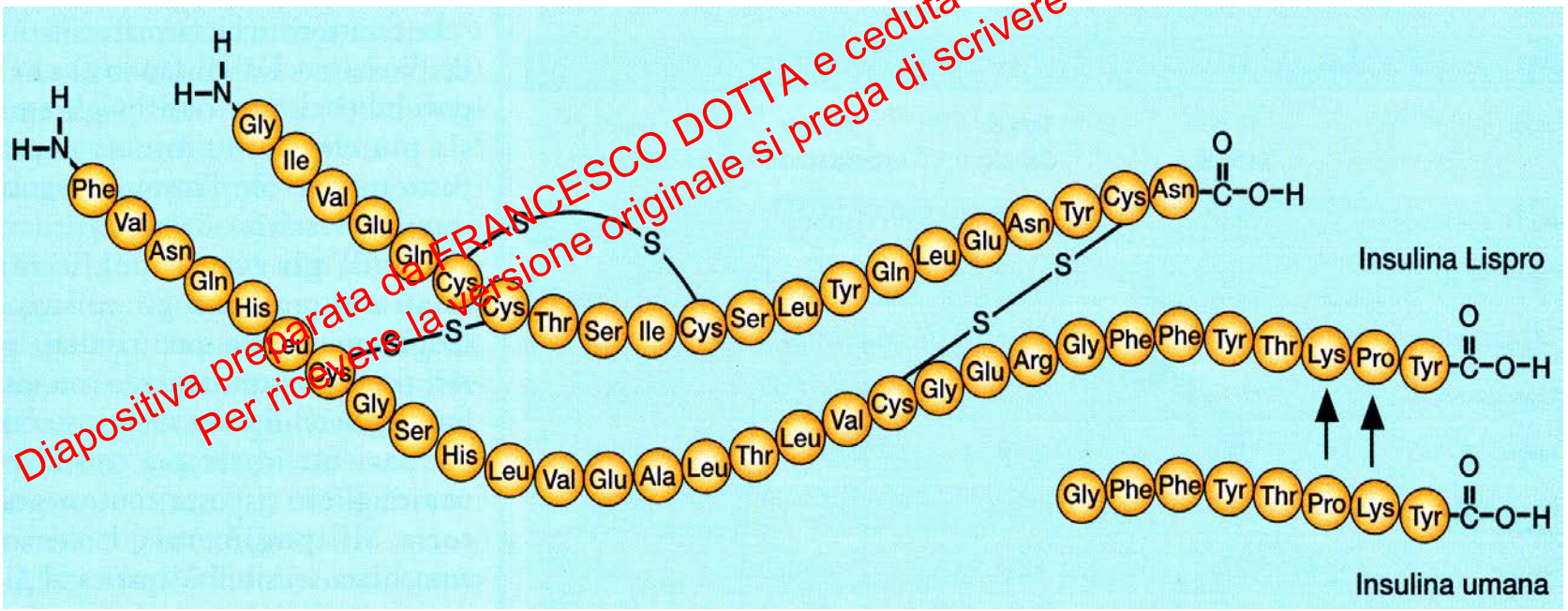
- **GlaxoSmithKline**
- **Johnson & Johnson**
- **Novo Nordisk**
- **Sanofi**

The class of rapid-acting insulin analogues were introduced more than 20 years ago to better control postprandial plasma glucose (PPG) excursions than unmodified regular human insulin (RHI). Insulins lispro, aspart and glulisine all achieved an earlier onset of action, a greater peak effect, and shorter duration of action resulting in lower PPG levels and a reduced risk of late post-prandial hypoglycaemia.

The continuing quest for better subcutaneously administered prandial insulins: a review of recent developments and potential clinical implications

David R. Owens MD1 | Geremia B. Bolli MD

DOI: 10.1111/dom.13963



Insulina Lispro

The class of rapid-acting insulin analogues were introduced more than 20 years ago to better control postprandial plasma glucose (PPG) excursions than unmodified regular human insulin (RHI). Insulins lispro, aspart and glulisine all achieved an earlier onset of action, a greater peak effect, and shorter duration of action resulting in lower PPG levels and a reduced risk of late post-prandial hypoglycaemia.

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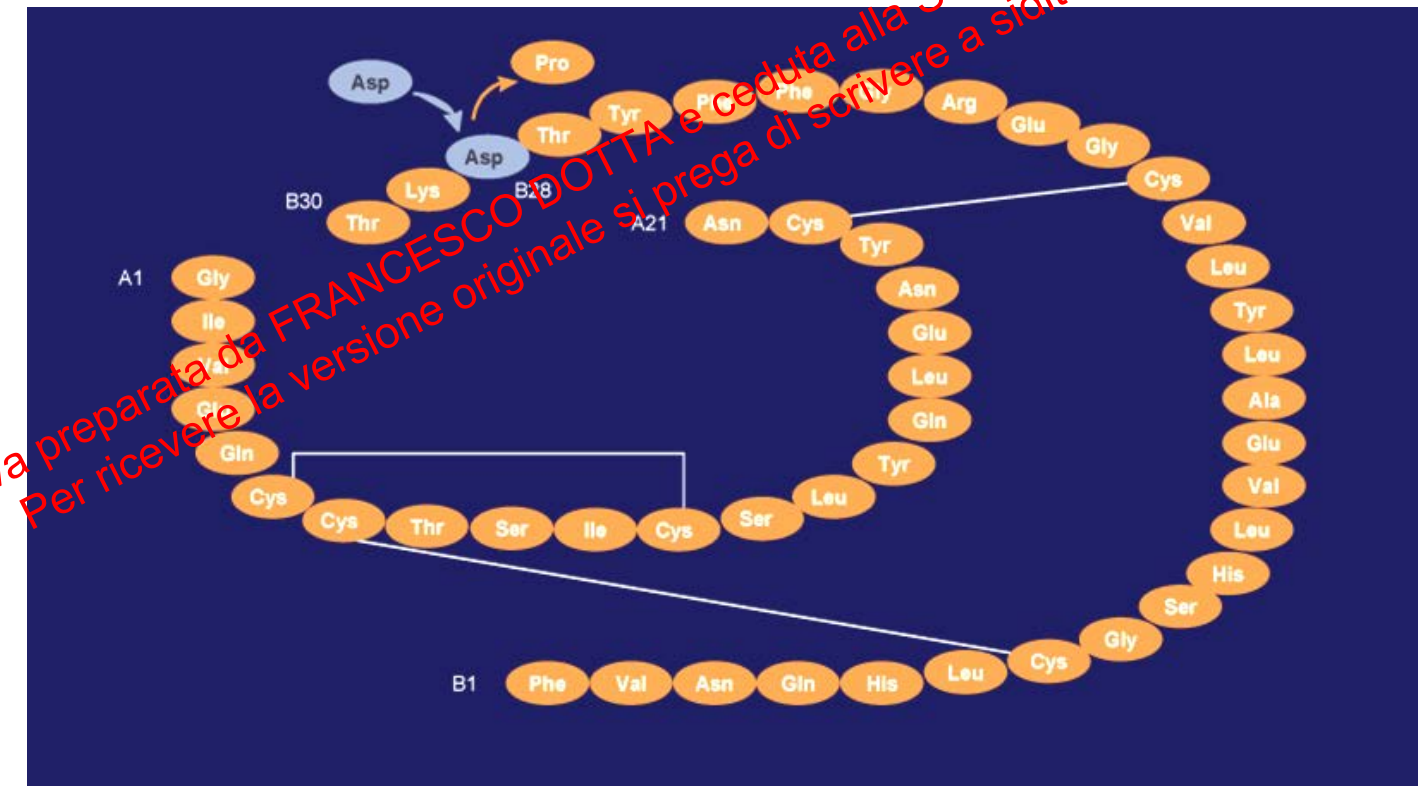

Insulina Aspart

The class of rapid-acting insulin analogues were introduced more than 20 years ago to better control postprandial plasma glucose (PPG) excursions than unmodified regular human insulin (RHI). Insulins lispro, aspart and glulisine all achieved an earlier onset of action, a greater peak effect, and shorter duration of action resulting in lower PPG levels and a reduced risk of late post-prandial hypoglycaemia.

The continuing quest for better subcutaneously administered prandial insulins: a review of recent developments and potential clinical implications

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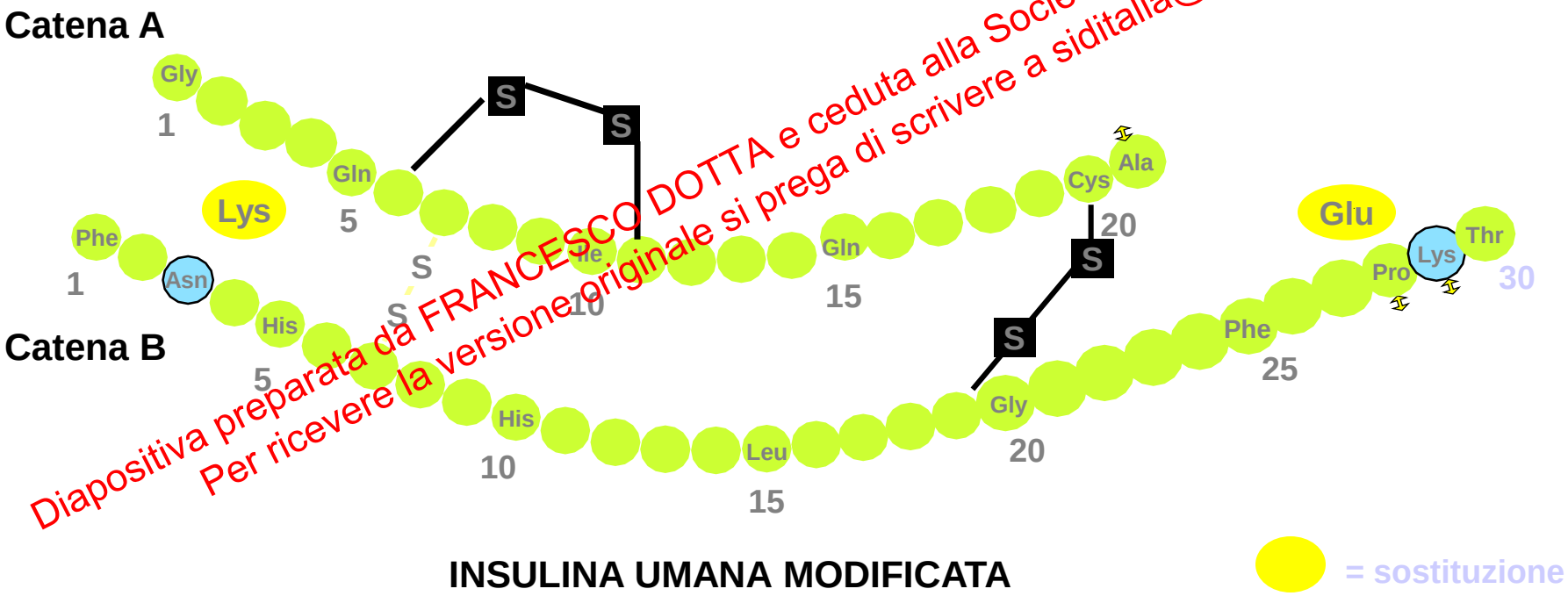


INSULINA UMANA MODIFICATA

Insulina Glulisina

Analoghi Rapidi dell'insulina

NOTA TECNICA

La **Società Italiana di Diabetologia, l'Associazione Medici Diabetologi** e la **Società Italiana di Endocrinologia e Diabetologia Pediatrica** ritengono che non esistano evidenze scientifiche che dimostrino differenze significative in termini di meccanismo d'azione, efficacia, tollerabilità e sicurezza tra le insuline glulisina, lispro e aspart, pur potendo i singoli farmaci diversificarsi per indicazioni terapeutiche aggiuntive.

Melo et al. Diabetol Metab Syndr (2019) 11:2
https://doi.org/10.1186/s13098-018-0397-3

Short-acting insulin analogues versus regular human insulin on postprandial glucose and hypoglycemia in type 1 diabetes mellitus: a systematic review and meta-analysis

Karla F. S. Melo[1,2,3*], Luciana R. Bahia[2,4], Bruna Pasinato[5], Gustavo J. M. Porfirio[6], Ana Luiza Martimbianco[6], Rachel Riera[6,7], Luis E. P. Calliari[8], Walter J. Minicucci[2], Luiz A. A. Turatti[2], Hermelinda C. Pedrosa[2] and Beatriz D. Schaan[5,9]

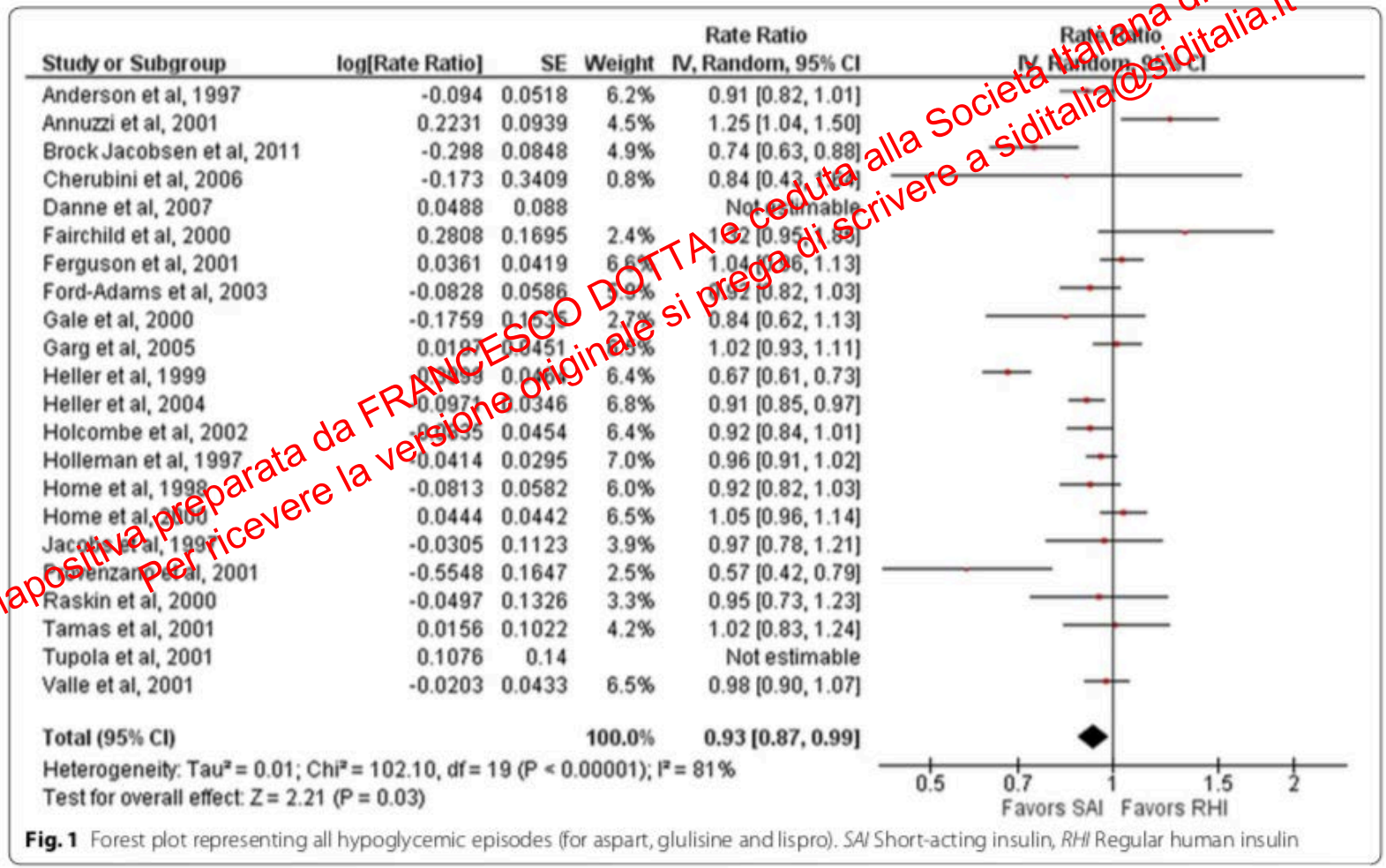


Fig. 1 Forest plot representing all hypoglycemic episodes (for aspart, glulisine and lispro). *SAI* Short-acting insulin, *RHI* Regular human insulin

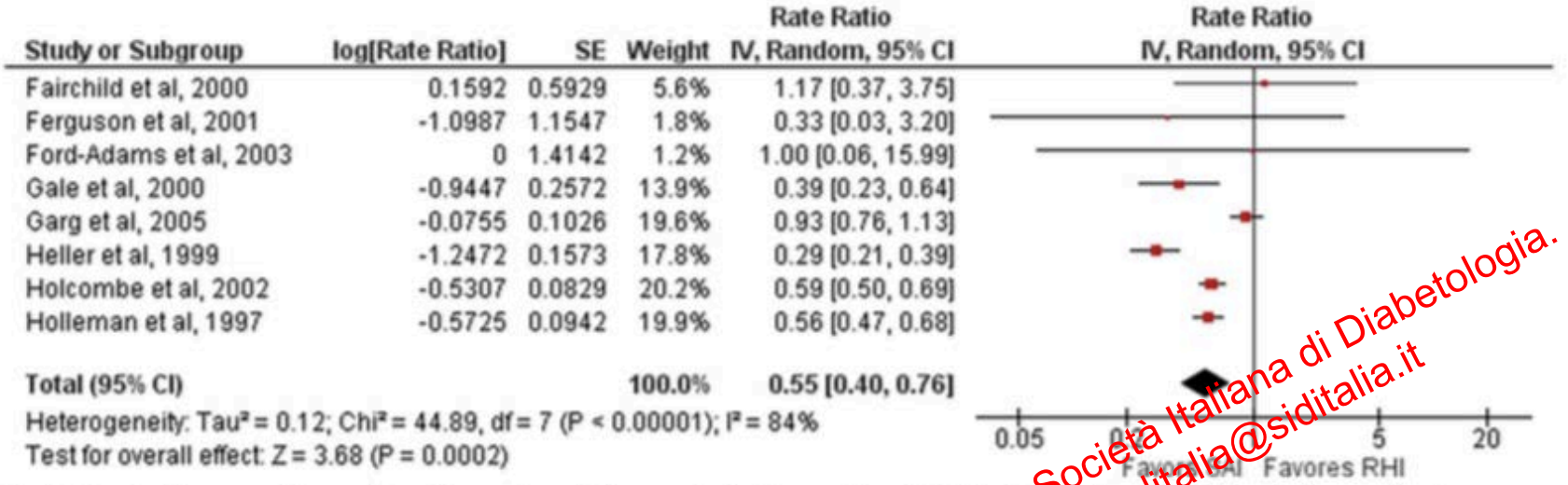


Fig. 2 Forest plot representing nocturnal hypoglycemia (for aspart, glulisine and lispro). *SAI* Short-acting insulin, *RHI* Regular human insulin

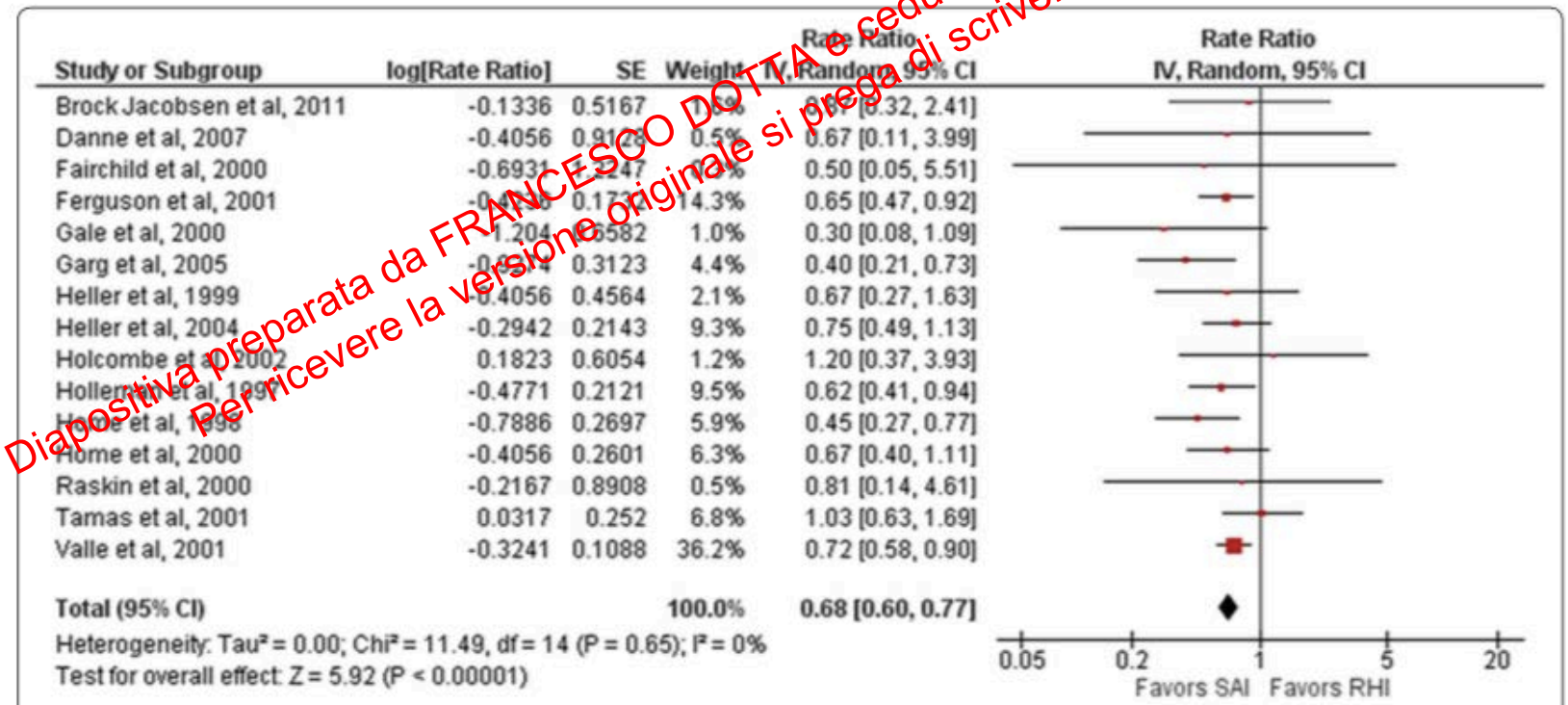


Fig. 3 Forest plot representing severe hypoglycemia (for aspart, glulisine and lispro). *SAI* Short-acting insulin, *RHI* Regular human insulin

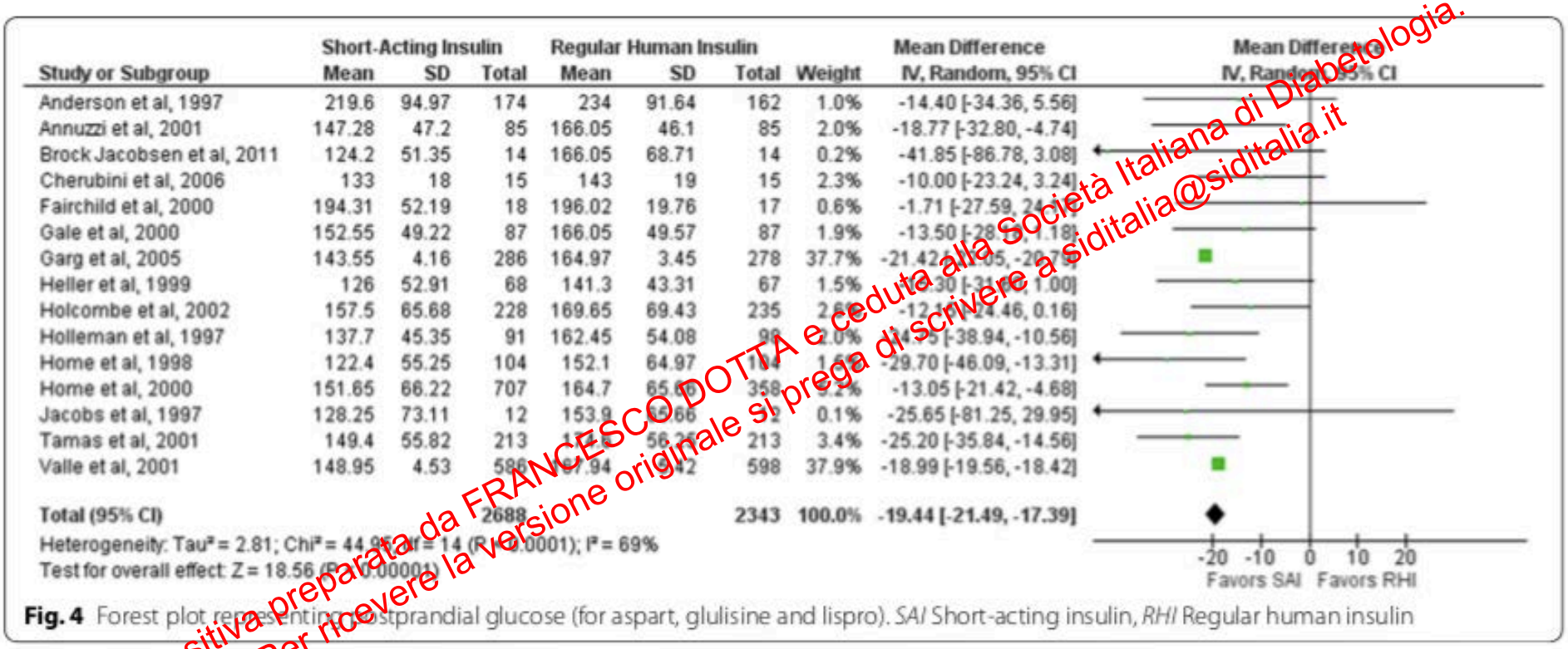


Fig. 4 Forest plot representing postprandial glucose (for aspart, glulisine and lispro). *SAI* Short-acting insulin, *RHI* Regular human insulin

Rapid-Acting Insulin Analogues Versus Regular Human Insulin: A Meta-Analysis of Effects on Glycemic Control in Patients with Diabetes

Antonio Nicolucci · Antonio Ceriello · Paolo Di Bartolo
Antonella Corcos · Marco Orsini Federici

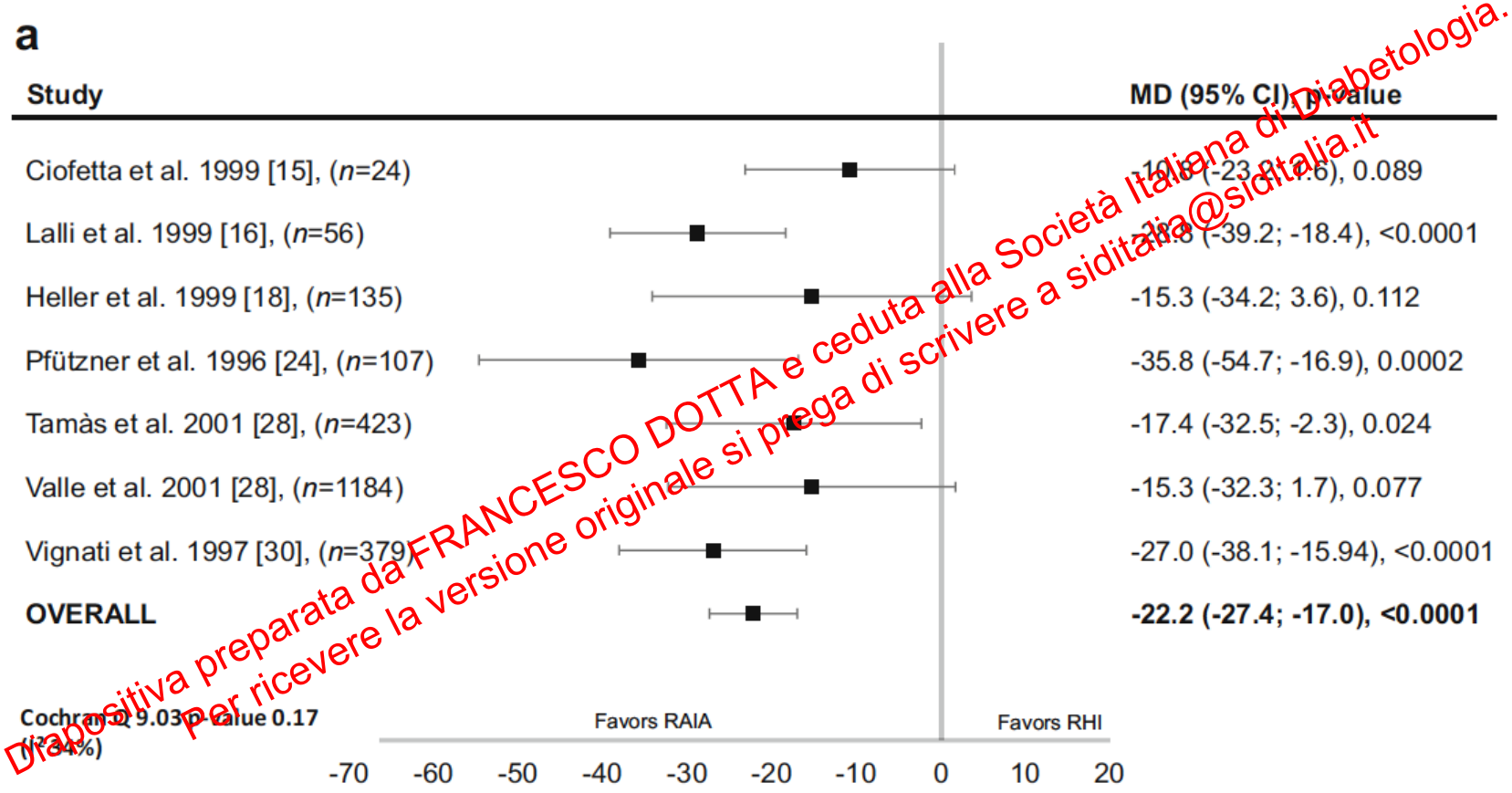
Suboptimal glycemic control and high glycemic variability (GV) are associated with increased risk of complications in patients with diabetes.

The aim of this meta-analysis was to investigate the impact of rapid-acting insulin analogues (RAIAs) and regular human insulin (RHI) on glycemic control, including long- and short-term GV as measured by end-of-treatment glycated haemoglobin (HbA1c) level, change from baseline in HbA1c, pre- and post-prandial glucose levels, and pre- to postprandial change in blood glucose levels.

Twenty-seven studies involving more than 7000 patients were included in the analysis, which found that RAIAs are more effective than RHI at reducing postprandial glucose and improving HbA1c in patients with type 1 diabetes.

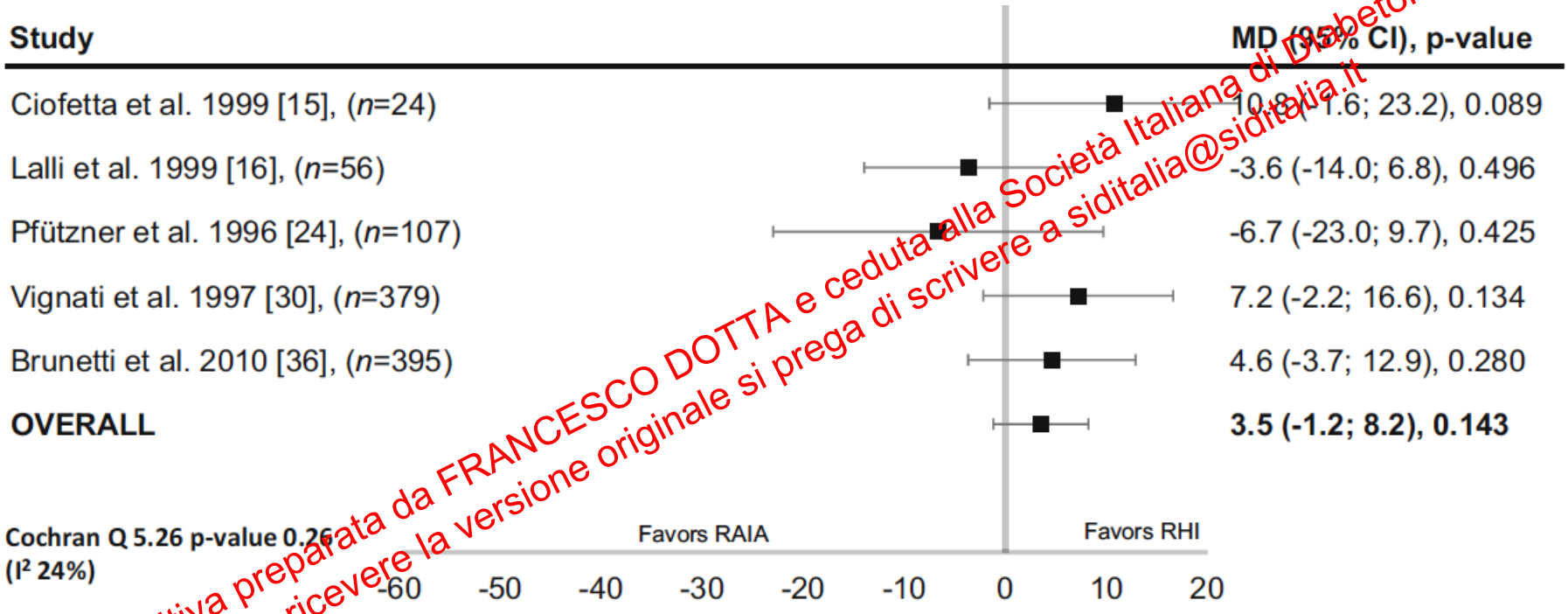
Diabetes Ther
https://doi.org/10.1007/s13300-019-00732-w

Difference in postprandial blood glucose in patients with a type 1 diabetes (mg/dL)



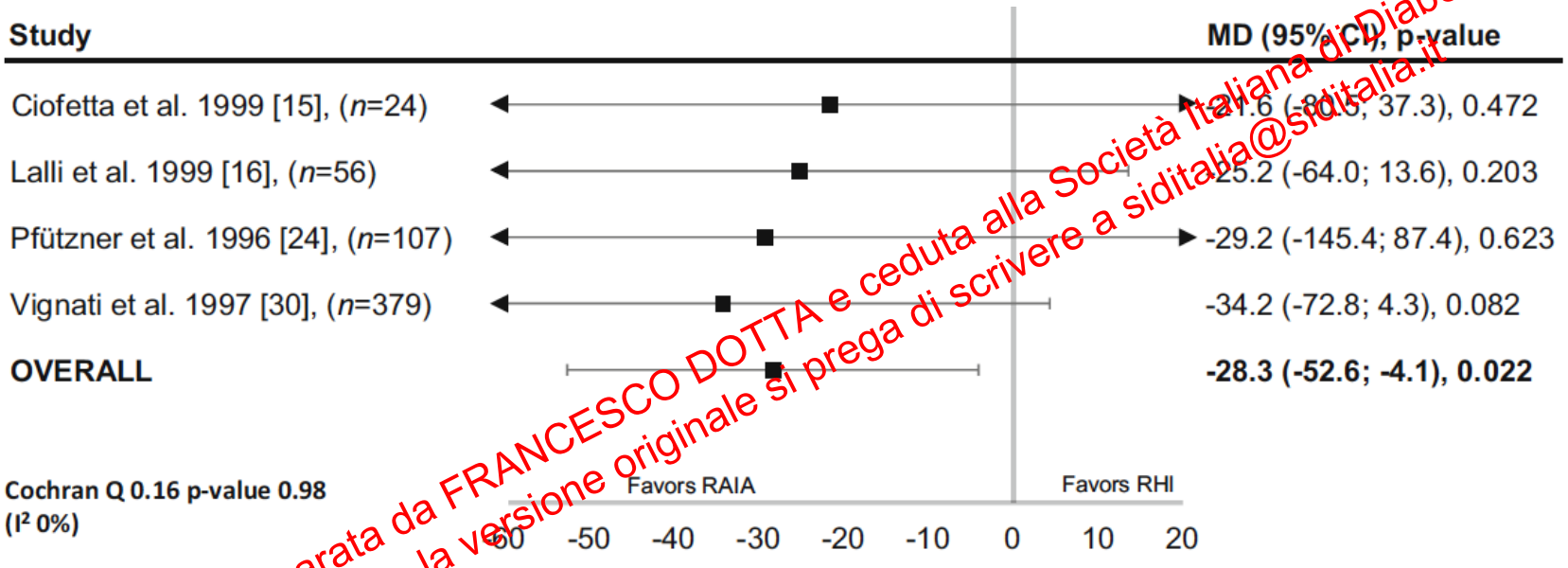
Diabetes Ther
https://doi.org/10.1007/s13300-019-00732-w

Difference in preprandial blood glucose in patients with a type 1 diabetes (mg/dL)



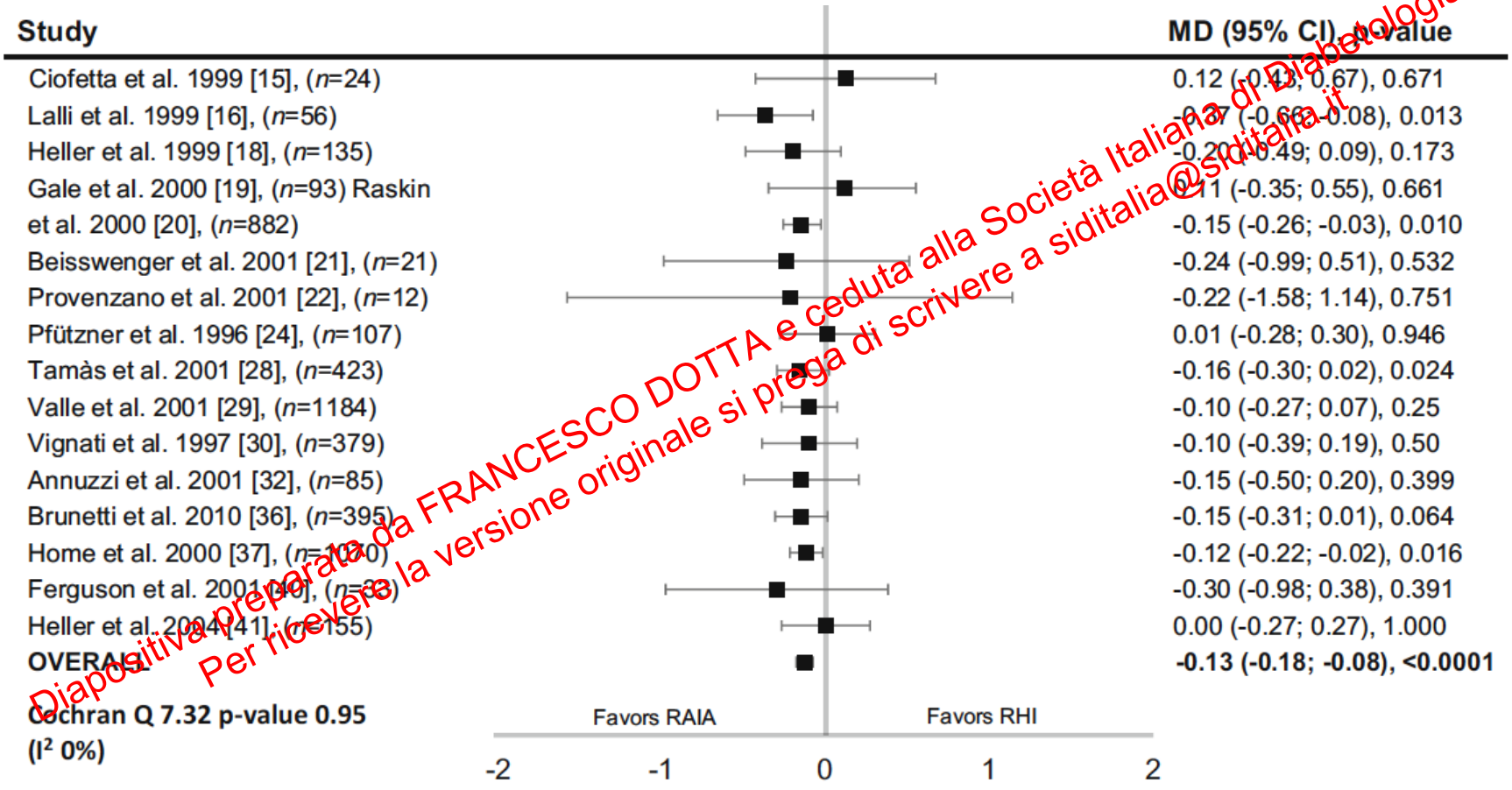
Diabetes Ther
https://doi.org/10.1007/s13300-019-00732-w

Difference in the change in blood glucose following a meal (pre- vs postprandial; mg/dL) with rapid-acting insulin analogues and regular human insulin



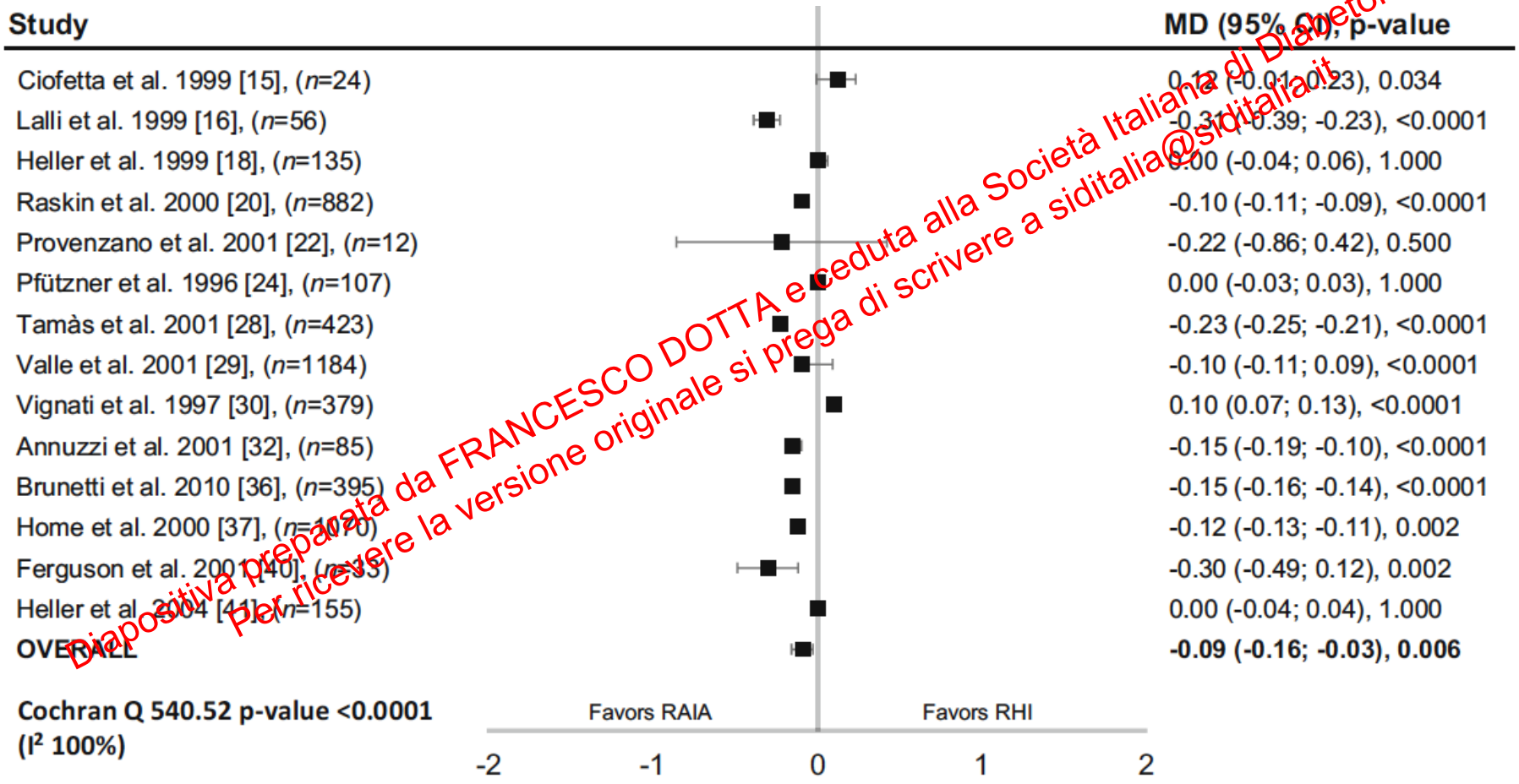
Diabetes Ther
https://doi.org/10.1007/s13300-019-00732-w

Difference in glycated haemoglobin in patients with type 1 diabetes



Diabetes Ther
https://doi.org/10.1007/s13300-019-00732-w

Change from baseline glycated haemoglobin in patients with a type 1 diabetes



Diabetes Ther
https://doi.org/10.1007/s13300-019-00732-w

Fast-Acting Insulin Aspart: The Rationale for a New Mealtime Insulin

Diabetes Ther (2019) 10:1793–1800
https://doi.org/10.1007/s13300-019-00685-0

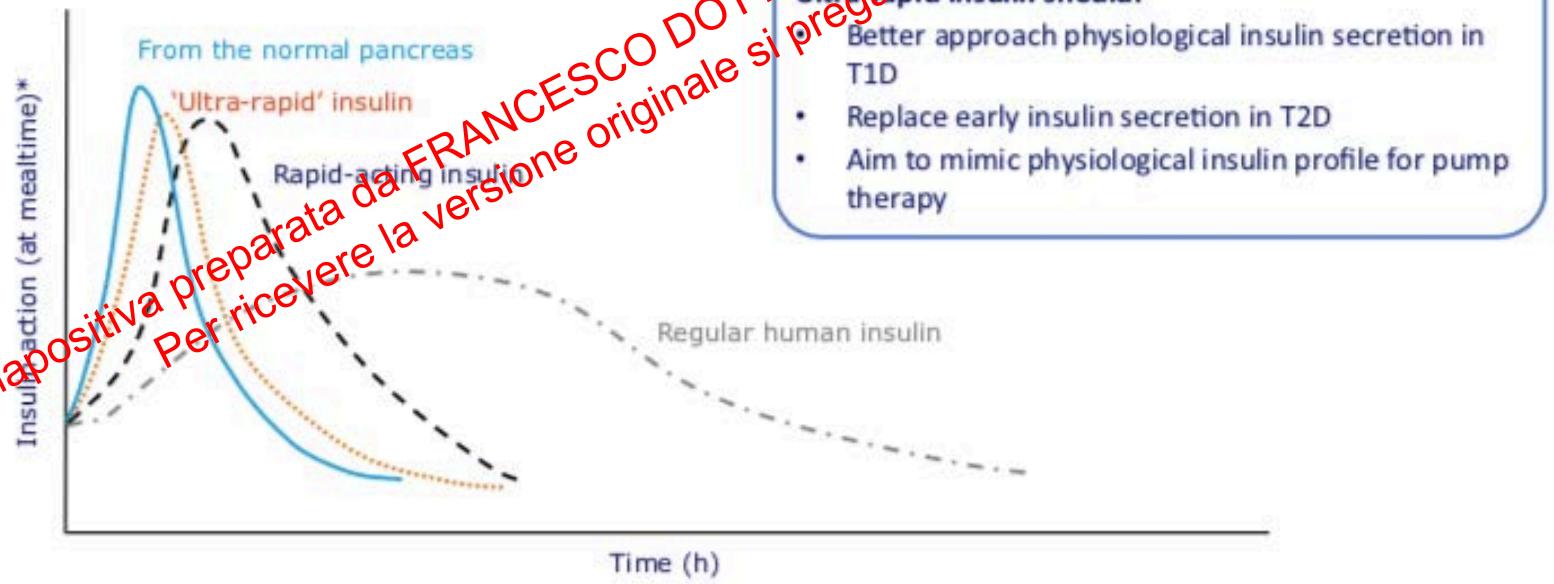
Marc Evans · Mathew Wilkinson · Angeliki Giannpolou

Attenuating postprandial hyperglycaemia is a critical factor in the achievement of optimal glucose control.

Prandial insulin analogues have been developed to limit postprandial glucose excursions.

There is still, however, a significant unmet need, and a considerable focus has been put on attempts to accelerate the time–action profile of prandial insulin.

Ultra-rapid insulin: approaching a physiological insulin profile even further



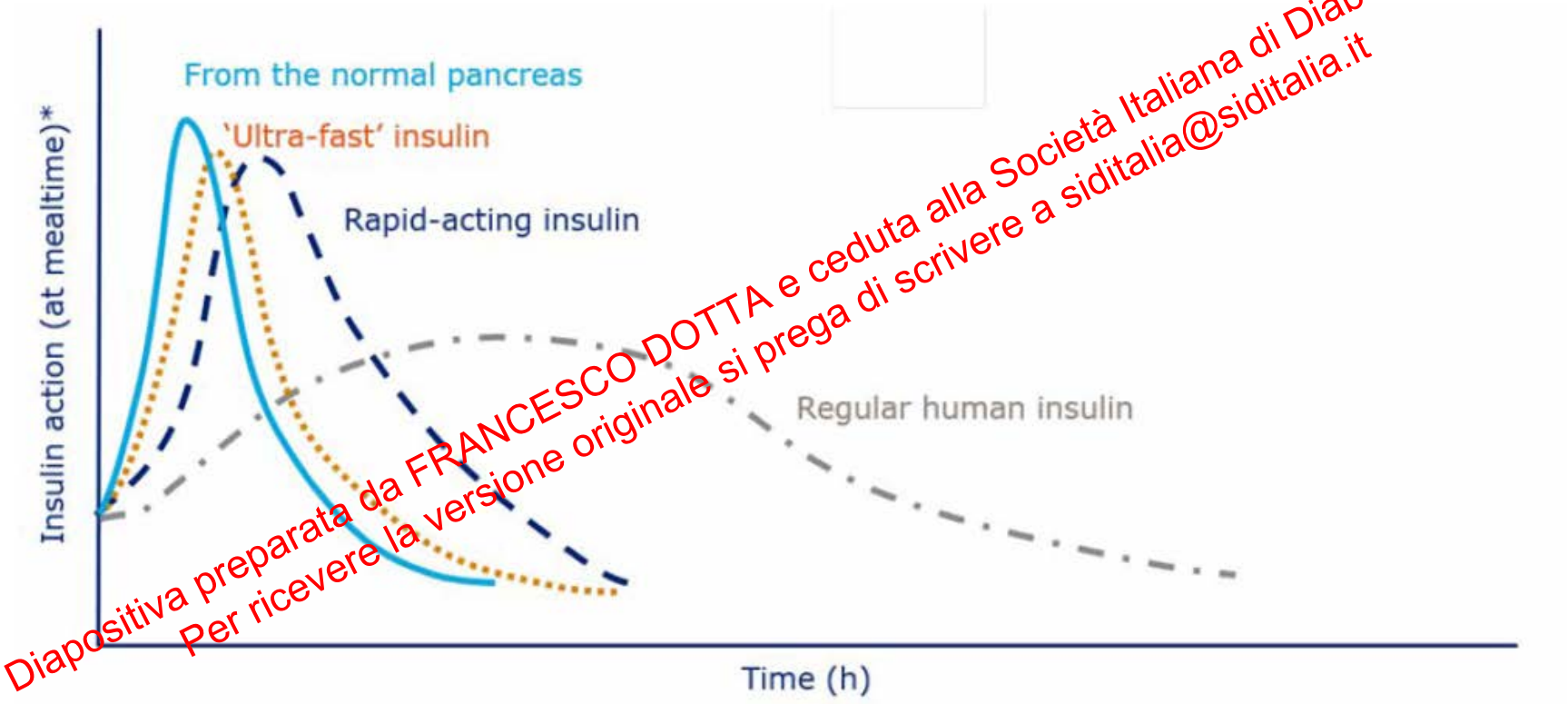
*Schematic representation
T1D, type 1 diabetes; T2D, type 2 diabetes
Adapted from: Home. *Diabetes Obes Metab* 2015;17:1011–20

QUALI SONO I VANTAGGI DELLE INSULINE "ULTRARAPIDE" NEL TRATTAMENTO DEL DIABETE TIPO 1?

il Diabete
Vol. 31, N. 3, settembre 2019
ALLEGATO

Modifiche innovative delle formulazioni di insulina e dei metodi di somministrazione in grado di offrire profili di insulina ultraveloci mirano a migliorare ulteriormente il controllo glicemico della fase post-prandiale, accelerando l'assorbimento dell'insulina e la sua comparsa in circolo.

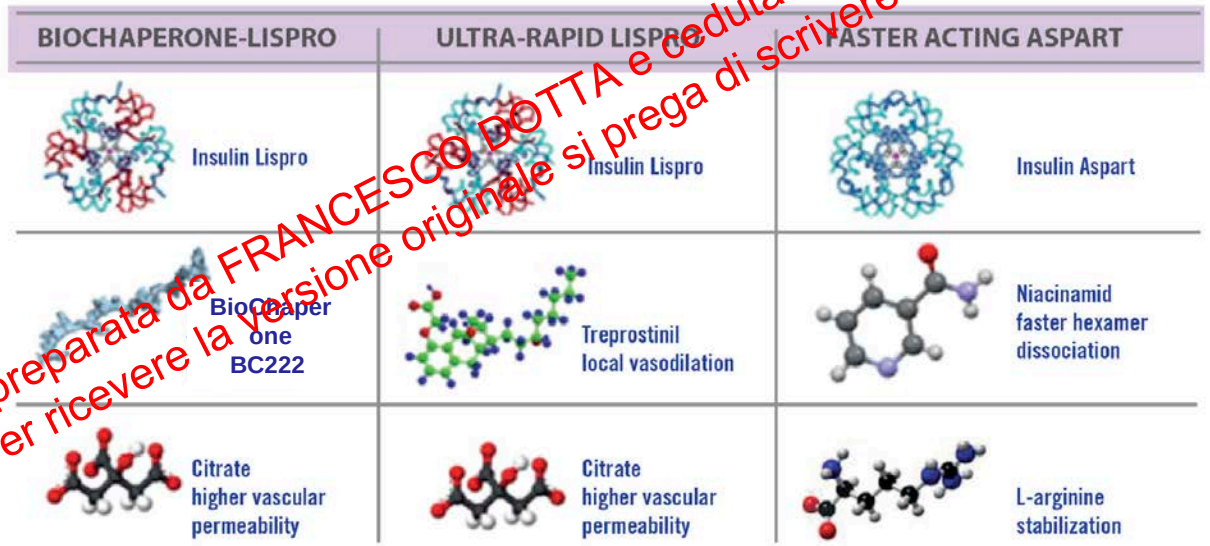
Confronto tra i profili farmacocinetici delle insuline iniettabili, al momento del pasto, rispetto alla fisiologica curva insulinemica del soggetto con normale funzionalità pancreatica



Tra le insuline ultrarapide annoveriamo:

- ***Fast Insulin Aspart*** **(FIASP), una formulazione di insulina Aspart modificata con l'aggiunta degli adiuvanti niacinamide (ammide della vitaminaB3) e L- arginina (aminoacido). La niacinamide permette di ottenere un assorbimento iniziale più rapido dopo l'iniezione sottocutanea, mentre la L-arginina è utilizzata per la stabilizzazione della molecola.**
- **Insulina ultrarapida Lispro, formulata con due nuovi eccipienti: il treprostinil, che favorisce la vasodilatazione locale, e il citrato, che garantisce una maggiore permeabilità vascolare.**
- **BioChaperone Lispro, formulazione che contiene il nuovo eccipiente BioChaperone BC222 (un oligosaccaride modificato con molecole naturali), capace di determinare una più rapida dissociazione dell'esamero, e il citrato per accelerare l'assorbimento dell'insulina Lispro dopo somministrazione sottocutanea.**

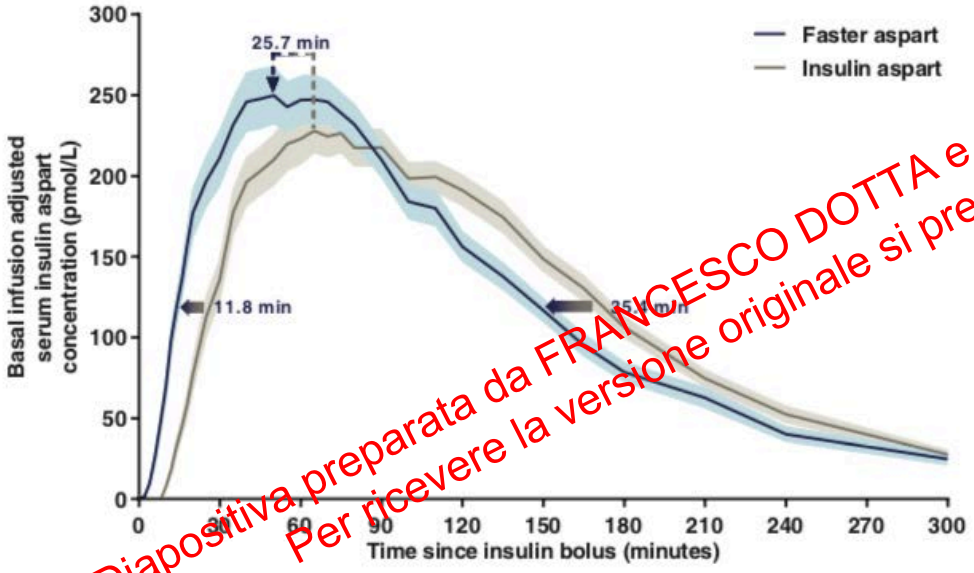
Figura 2. Principali caratteristiche degli analoghi ultrarapidi dell'insulina



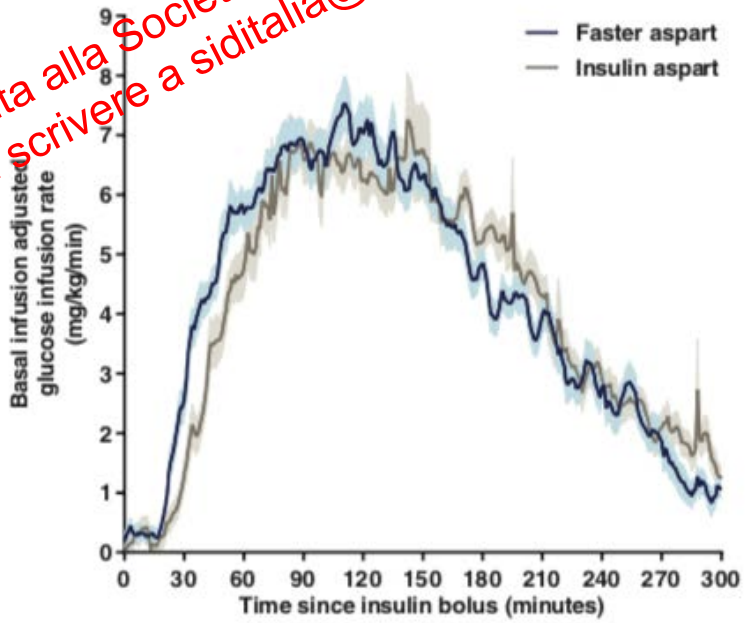
Pharmacological properties of faster-acting insulin aspart vs insulin aspart in patients with type 1 diabetes receiving continuous subcutaneous insulin infusion: A randomized, double-blind, crossover trial

Tim Heise MD[1] | Eric Zijlstra PhD[1] | Leszek Nosek MD[1] | Tord Rikte LicEng[2]
Hanne Haahr PhD[2]

Methods: In this randomized, double-blind, crossover trial, 48 men and women aged 18 to 64 years with type 1 diabetes mellitus (T1DM) received faster aspart and IAsp as a 0.15 U/kg bolus dose via CSII, on top of a basal rate (0.02 U/kg/h), in a glucose clamp setting (target 5.5 mmol/L).

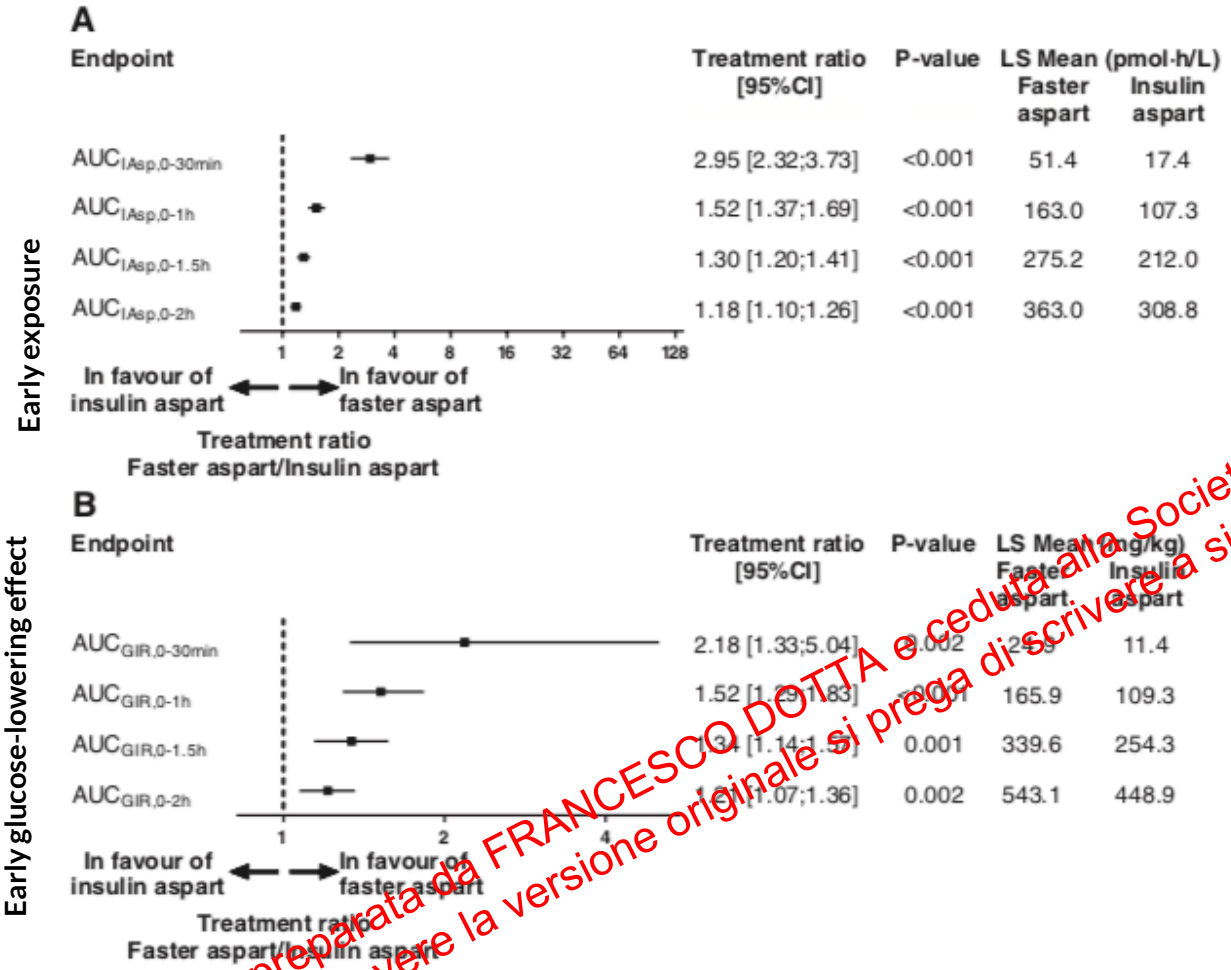


Mean serum insulin aspart concentration after a bolus dose of 0.15 U/kg faster aspart or insulin aspart administered by CSII



Mean glucose-lowering effect after a bolus dose of 0.15 U/kg faster aspart or insulin aspart administered by CSII.

Diabetes Obes Metab 2017; **19(2)**:208–215



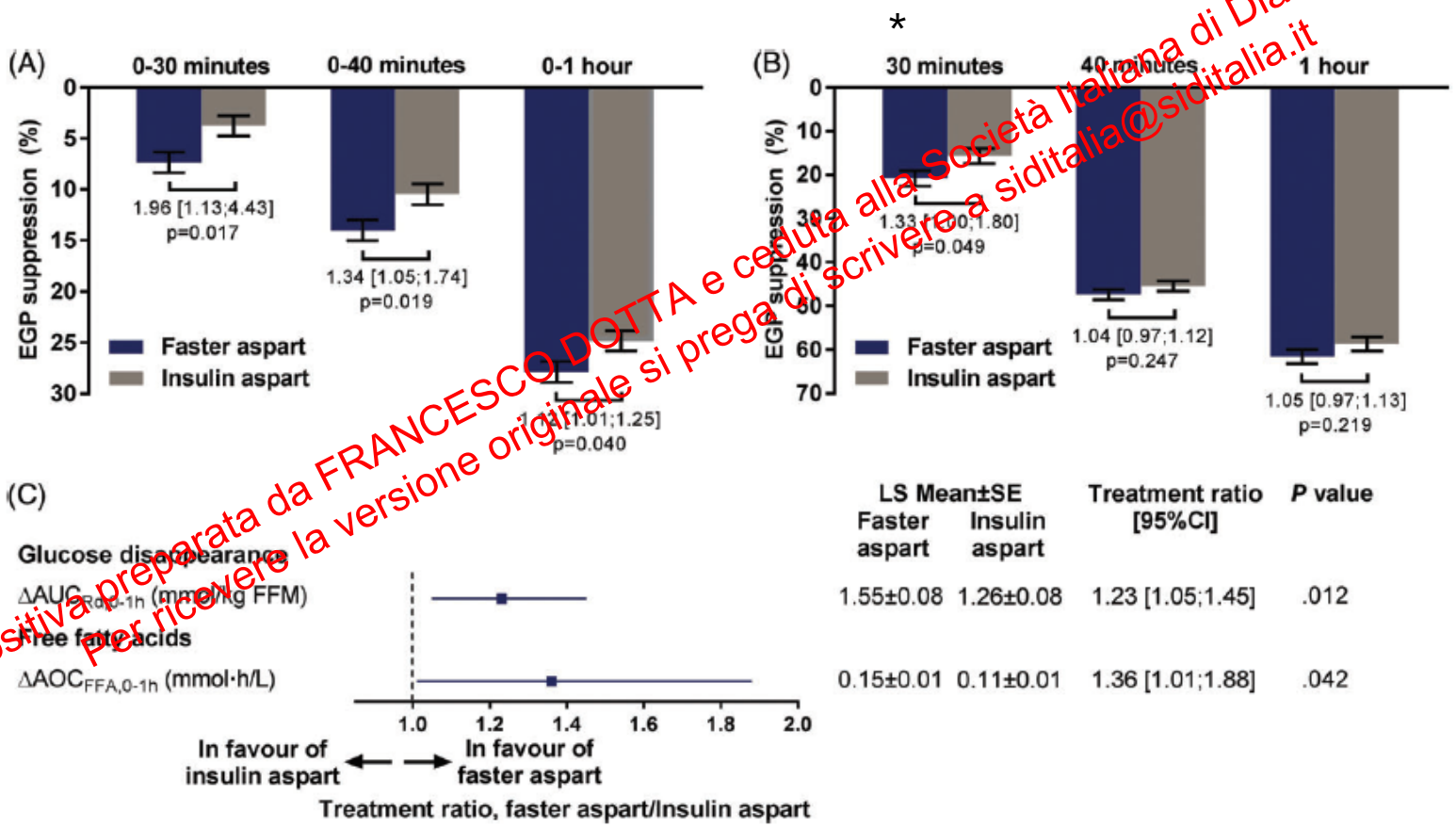
Early exposure (A) and early glucose-lowering effect (B) for faster aspart vs insulin aspart after a bolus dose of 0.15 U/kg administered by CSII.

Both faster aspart and insulin aspart were well tolerated, and no safety issues were identified during the trial.
No confirmed hypoglycaemic episodes occurred during the trial.

Conclusions: In patients with T1DM using CSII, faster aspart better mimics the endogenous prandial insulin secretion and action than does IAsp. Faster aspart therefore has the potential to provide clinical benefits over current rapid-acting insulins in the insulin pump setting.

Greater early postprandial suppression of endogenous glucose production and higher initial glucose disappearance is achieved with fast-acting insulin aspart compared with insulin aspart

Ananda Basu MD[1] | Thomas R. Pieber MD[2] | Ann K. Hansen PhD[3] | Stefanie Sach-Friedl MSc[2] | Lars Erichsen PhD[3] | Rita Basu MD[1] | Hanne Haahr PhD[3]



(Basu A et al. Diabetes, Obes Metab 20: 1615-1622, 2018).

Un'insulina molto rapida potrebbe fornire l'opportunità di somministrare l'insulina dopo l'assunzione del pasto. Nello studio ONSET 8 (FIASP al pasto, Aspart al pasto, FIASP postprandiale), si è osservata una completa sovrapponibilità delle curve glicemiche. Nel momento in cui Aspart e FIASP venivano confrontate durante la somministrazione post- prandiale, la seconda dimostrava una minore escursione glicemica

Figura 3. Effetti sui livelli medi di HbA1c derivanti dall'utilizzo di FIASP al pasto, FIASP postprandiale e insulina Aspart al pasto nello studio ONSET 8 (impiego di Degludec come insulina basale). Differenza in termini di riduzione dei livelli di HbA1c significativa per la non-inferiorità (p<0.001) in entrambi i bracci di trattamento con FIASP

Adattato da Buse JB et al. DOM 2018

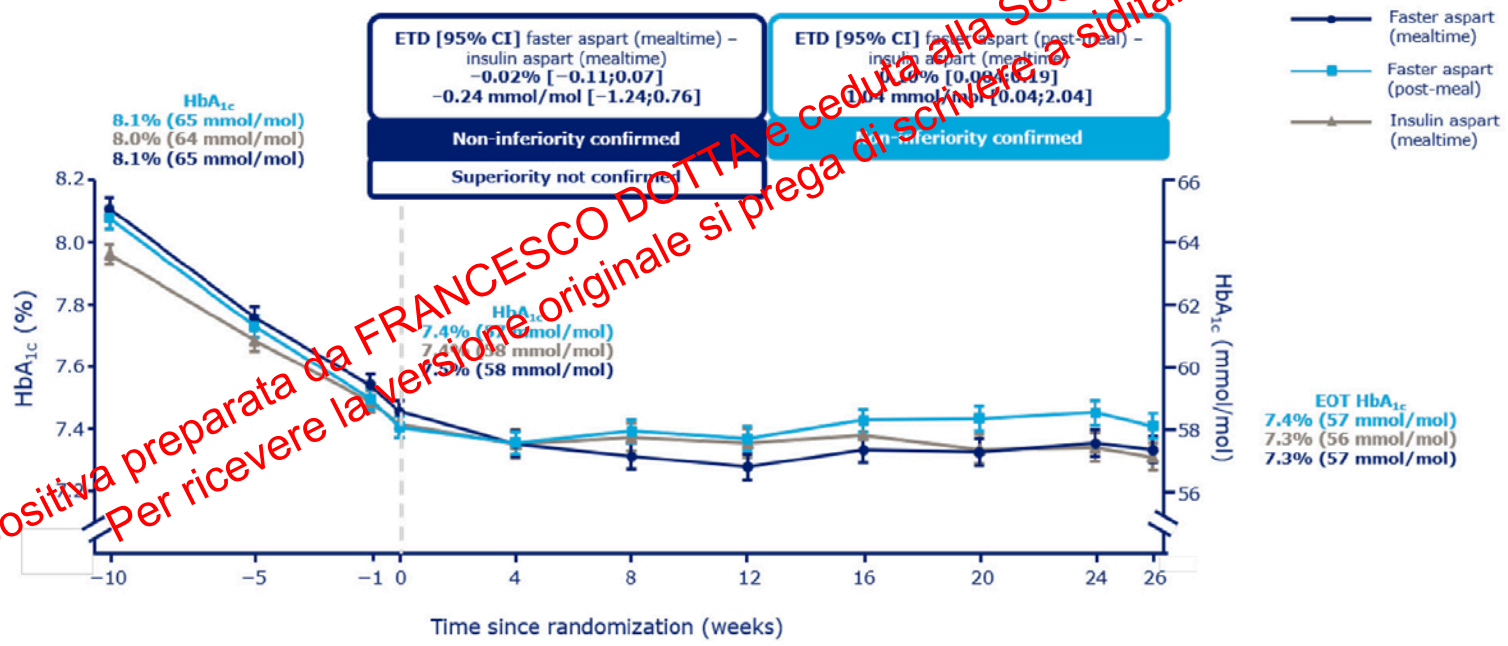
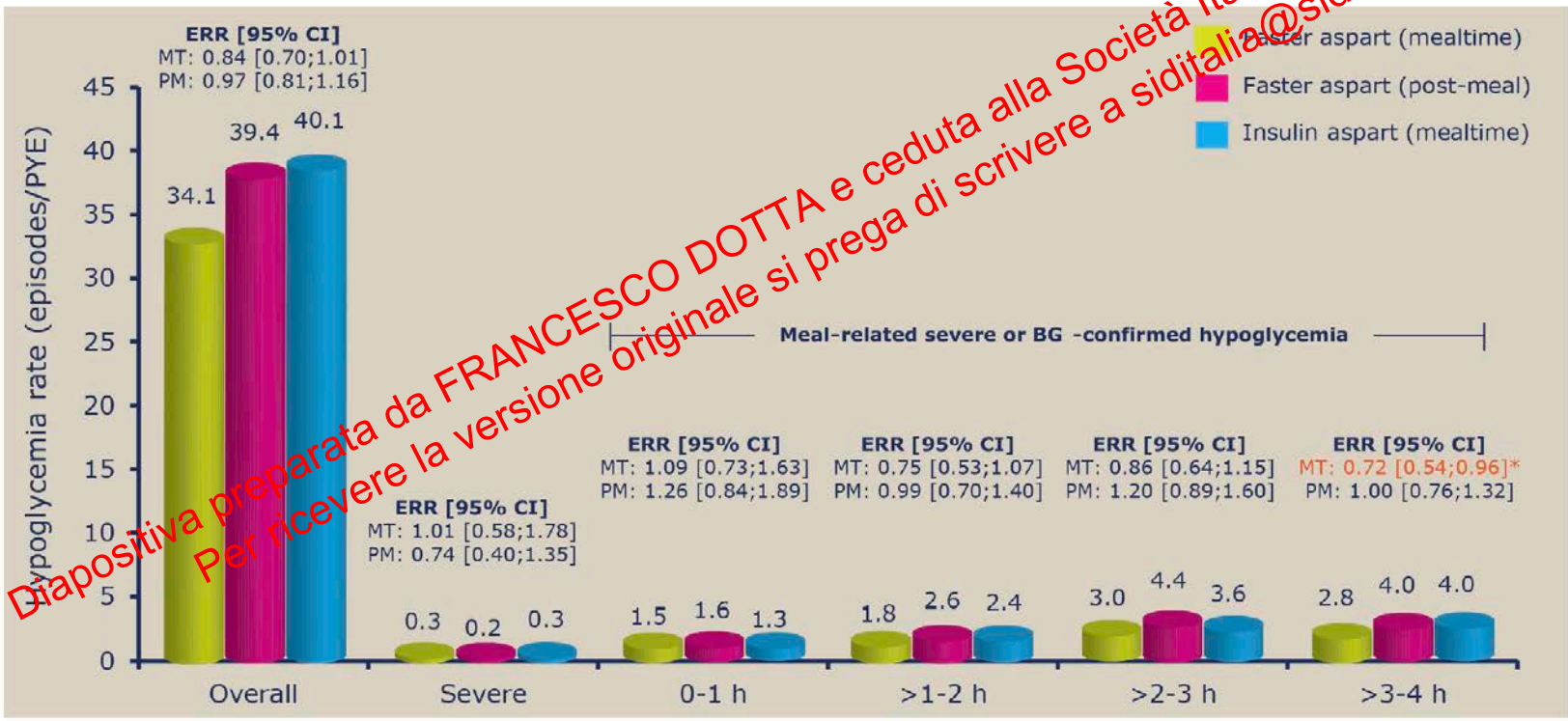


Figura 5. Effetto degli analoghi insulinici ultrarapidi sulle ipoglicemie gravi o confermate con misurazione della glicemia (*BG-confirmed*) durante 26 settimane di trattamento nello studio ONSET 8. (* p=0,024; ipoglicemia confermata con BG: valore PG<3,1 mmol/L (56 mg / dL))

Adattato da Buse JB et al. DOM 2018

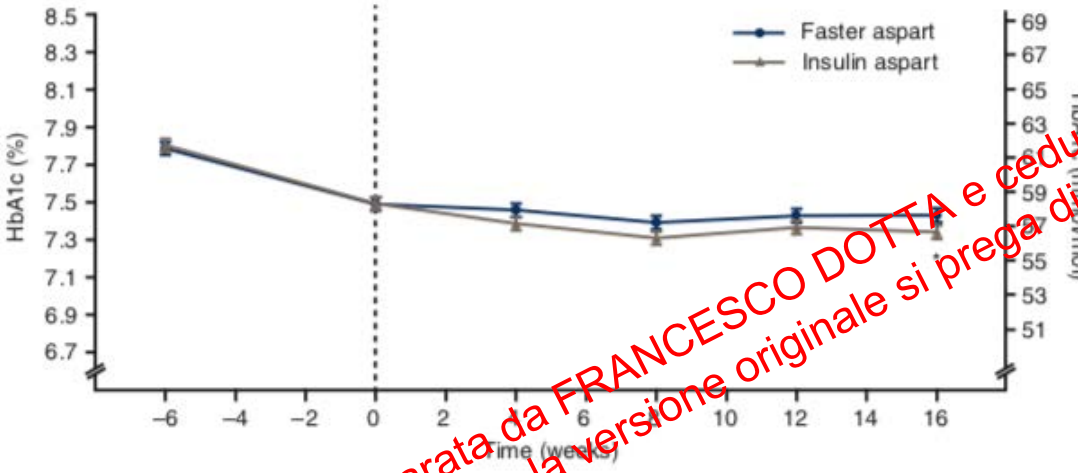


A randomized, multicentre trial evaluating the efficacy and safety of fast-acting insulin aspart in continuous subcutaneous insulin infusion in adults with type 1 diabetes (onset 5)

KLONOFF ET AL.

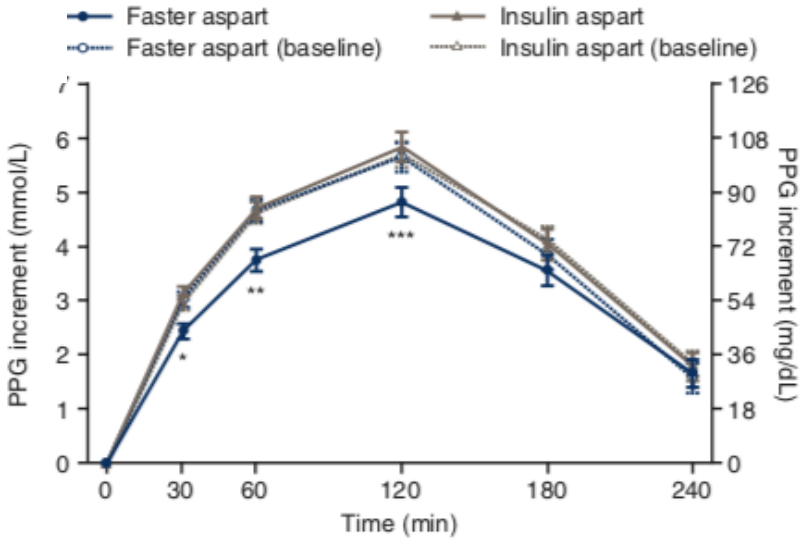
Diabetes Obes Metab. 2019;21:961–967.

Materials and Methods: This was a double-blind, treat-to-target, randomized, 16-week trial investigating CSII treatment with faster aspart (n = 236) or IAsp (n = 236). All available information, regardless of treatment discontinuation, was used for the evaluation of effect.

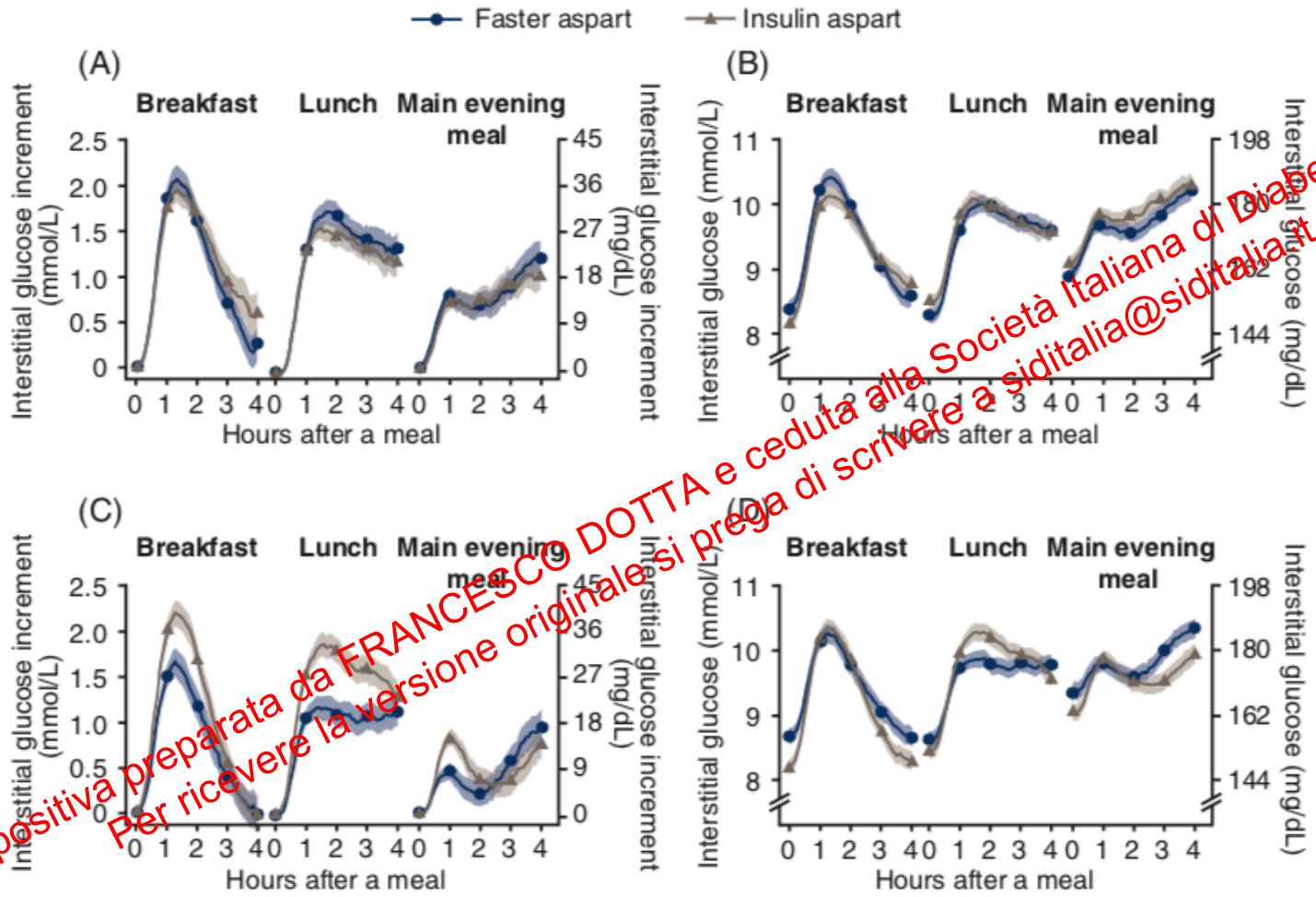


Mean glycated haemoglobin (HbA1c) over time.

Postprandial glucose (PPG) increment after a standardized meal test at baseline and week 16.



Prandial interstitial glucose (IG) profiles, IG increment and IG at baseline (A and B) and at week 16 (C and D). Prandial IG increment is derived as the IG values subtracted by the mean of IG values within 15 minutes before the start of the meal. Meal times during the continuous glucose monitoring period were captured in participants' diaries.



The present trial is the first to evaluate the efficacy and safety of an ultra-fast-acting insulin in CSII therapy in a large number of participants

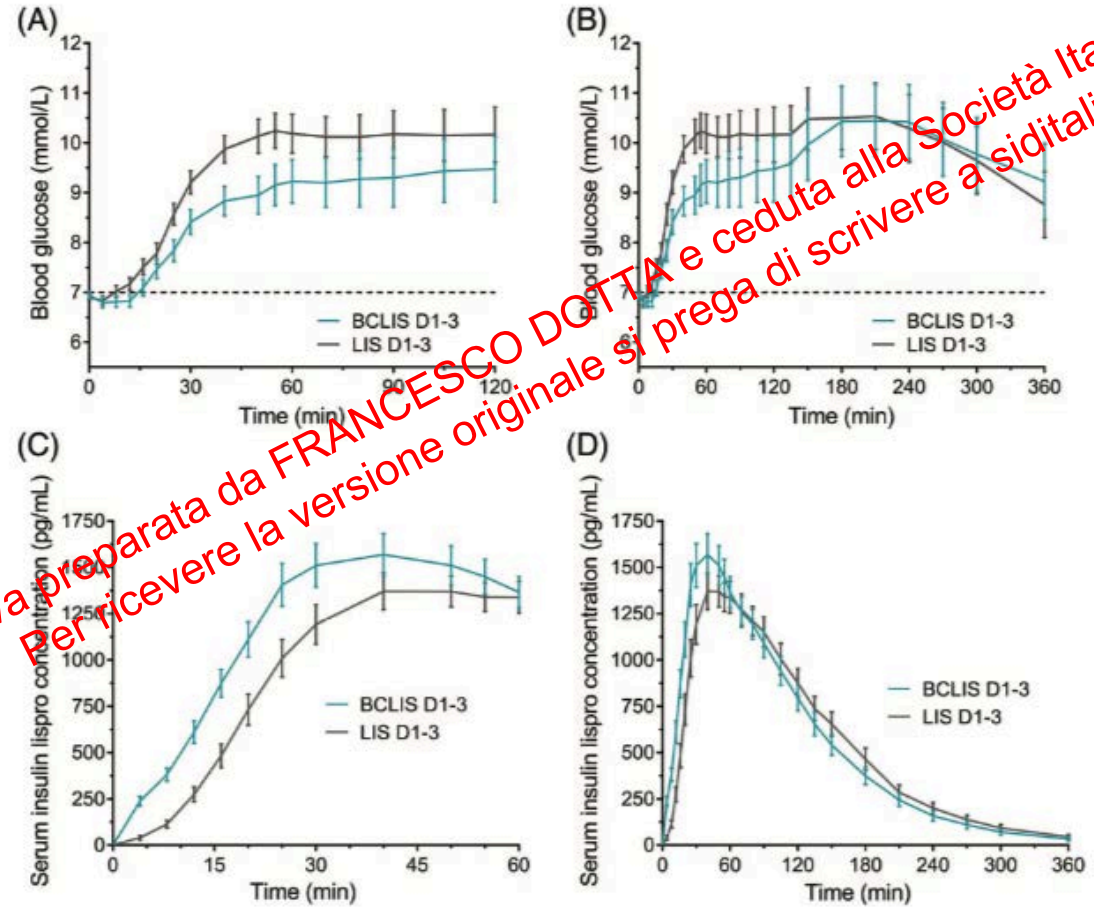
In summary, this trial showed that faster aspart provides an effective and safe option for CSII treatment in people with T1D, with improvements in PPG control reflected in meal-test and CGM results.

Ultra-rapid BioChaperone Lispro improves postprandial blood glucose excursions vs insulin lispro in a 14-day crossover treatment study in people with type 1 diabetes

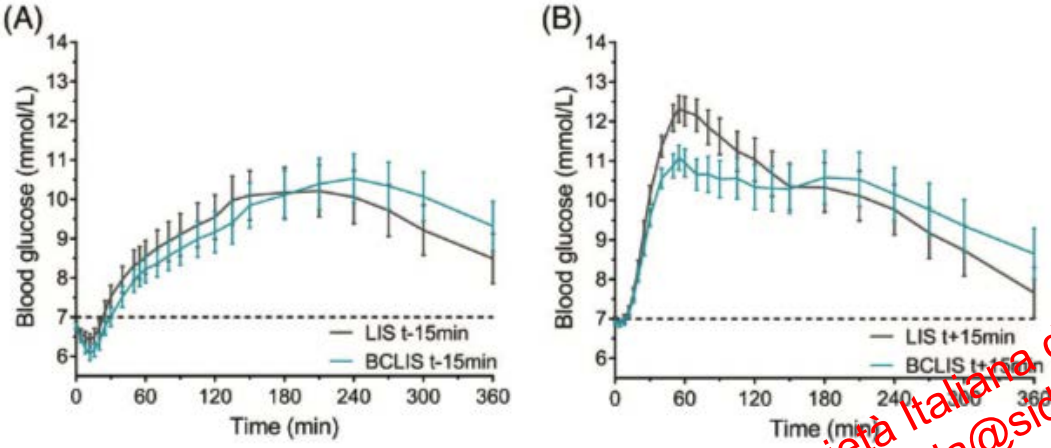
Diabetes Obes Metab. 2018;**20**:2627–2632.

Grit Andersen MD[1] | Grégory Meiffren PhD[2] | Daniela Lamers PhD[1] | J. Hans DeVries MD[1] | Aymeric Ranson MSc[2] | Cyril Seroussi MSc[2] | Bertrand Alluis PhD[2] | Martin Gaudier PhD[2] | Olivier Soula PhD[2] | Tim Heise MD[1]

Materials and Methods: In this randomized, double-blind study, participants self-administered individualized bolus doses of BCLIS or LIS during two 14-day periods in a crossover fashion.



Blood glucose profiles over the first 2 hours (A) and over the 6-hour (B) MMT procedure, and pharmacokinetic profiles over the first hour (C) and 6 hours (D) with insulin injections immediately pre-meal for days 1 to 3

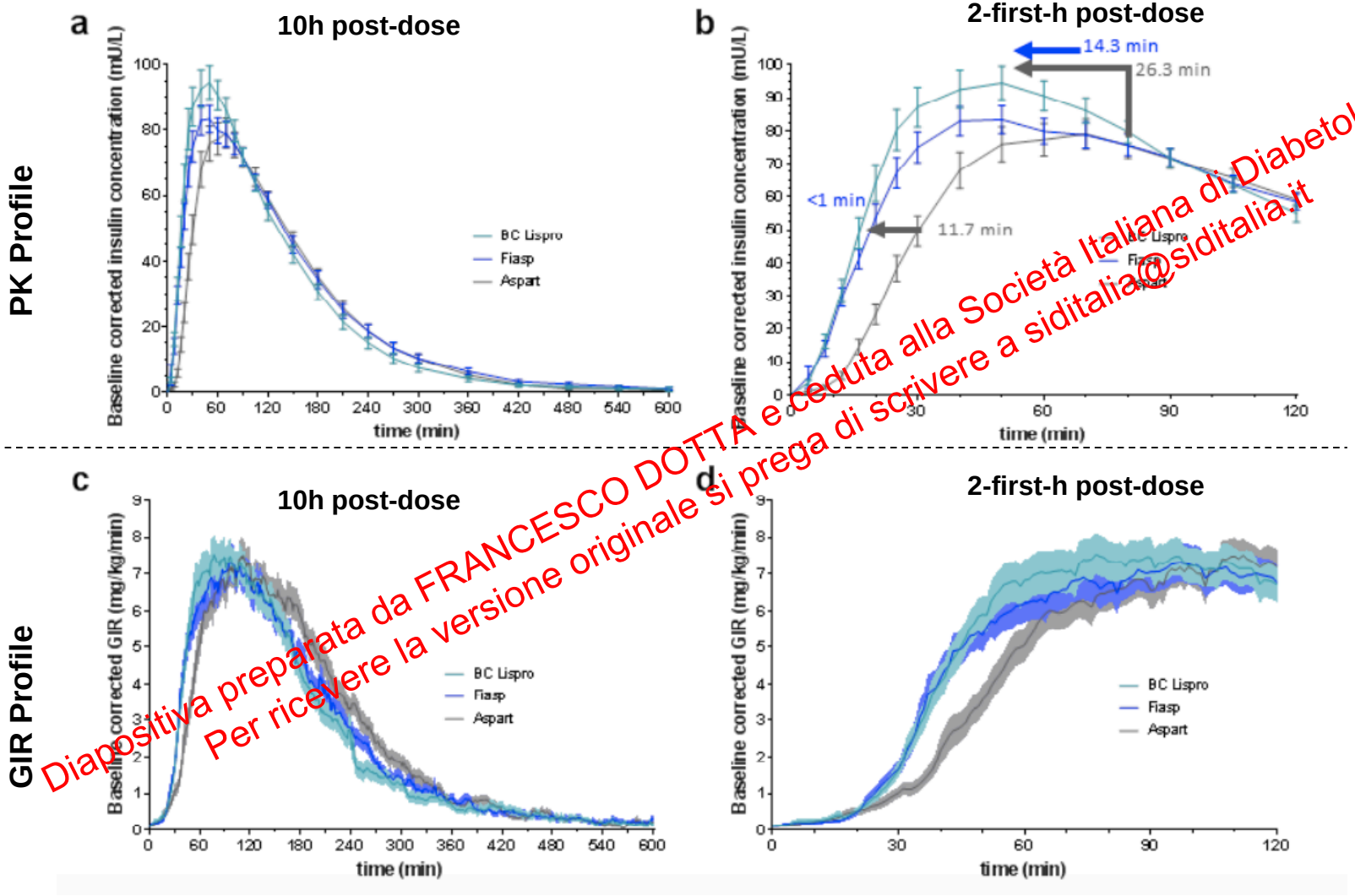


Blood glucose profiles with insulin injections 15 minutes before (A) and 15 minutes after (B) meal start on days 1 to 3

Results: Overall, 35 participants completed both treatment periods. In MMTs with t0 administration, the higher early postprandial PK exposure of BCLIS led to significant reductions in 1- to 2-hour postprandial BG excursions by 30% to 40% vs LIS and the accelerated absorption and action of BCLIS persisted over 14 days. There was no difference in glucose excursion over the full 360-minute postprandial period. Postprandial BG control was similar between BCLIS injected at t + 15 and LIS injected at t0. BCLIS was shown to have safety and tolerability similar to LIS. No injection site reactions occurred with BCLIS.

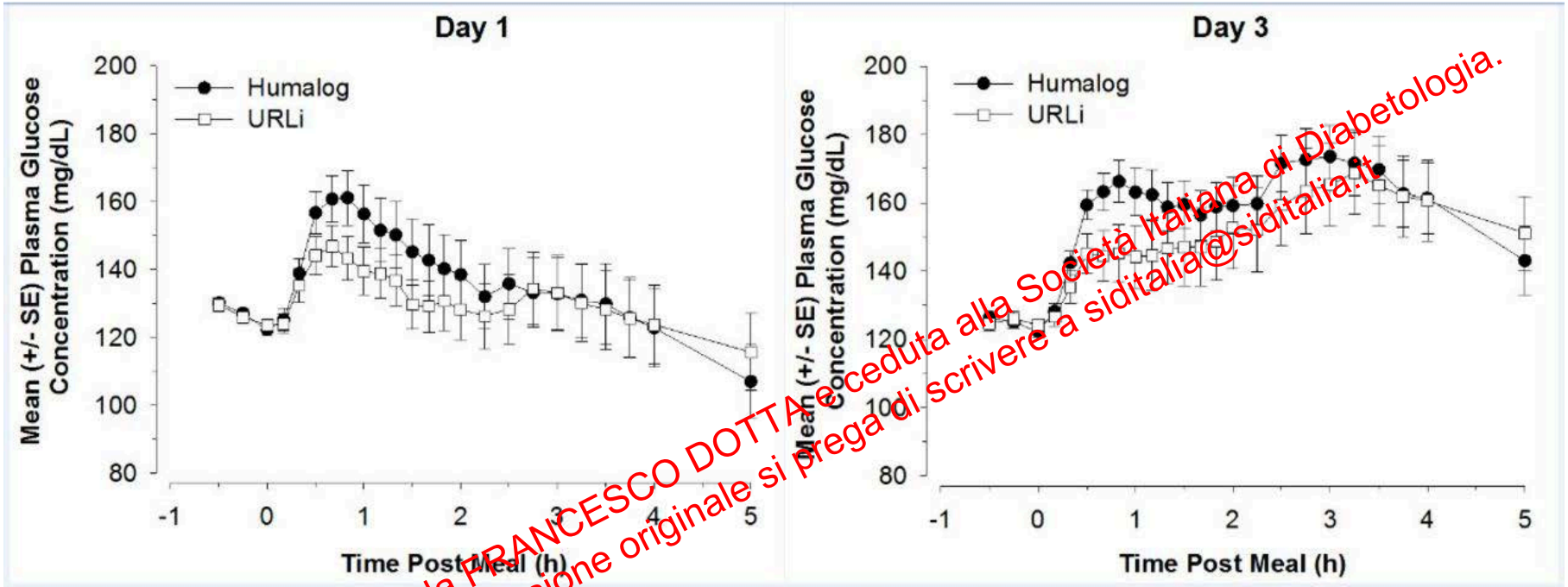
In conclusion, the present study showed improved early PK and PD properties of BCLIS vs LIS, with the potential to reduce the risk of daytime postprandial hypoglycaemia and offering patients flexibility of the insulin administration time. The results of this trial justify further development of BCLIS.

In a head-to-head comparison of BioChaperone insulin Lispro (BCLIS), faster insulin aspart(FIA) and insulin aspart (ASP) in patients with type 1 diabetes using an insulin pump, BCLIS better mimics prandial insulin secretion and action than ASP and shows a faster off-PD than FIA.



BioChaperone Lispro (BCLIS) vs faster aspart (FIA) and insulin aspart (ASP) in patients with type 1 diabetes on continuous subcutaneous insulin infusion: a randomized euglycemic clamp study. Heise T, et al. *Diabetes Obes Metab. 2018 Dec 18. doi: 10.1111/dom.13621. [Epub ahead of print]*

In a double-blind, randomized cross-over study, 24 adult patients with T1D received URLi or insulin lispro for 3 days. MMTT were conducted on Days 1 and 3, using a standard (1.5 U/min) single-wave bolus. URLi showed faster insulin lispro absorption on both days compared to HL. URLi reduced 1-hour postprandial glucose excursion of the MMTT by 45% on Day 1 (p=NS) and 47% on Day 3 (p=0.059) compared with HL.



Abbreviations: H = Hour; SEG = Standard Error; SS = Standard Single-Wave Bolus; URLi = Ultra Rapid Lipsro

Figure: Mean plasma glucose concentration over time for URLi and Humalog® (a trademark of Eli Lilly and Company) on Day 1 (left) vs. Day 3 (right).

No difference was seen in the number or severity of hypoglycemic events or local tolerability between URLi and HL.

Ultra-rapid Lispro (URLi) Shows Faster Absorption of Insulin Lispro vs. Humalog® during Insulin Pump (CSII) Use in Patients with T1D. CHRISTOF M. KAZDA, JENNIFER LEOHR, RONG LIU, THOMAS HARDY, SHOBHAREDDY, SHANE P.C. CHUA, XIAONAN GUO, ULRIKE HOVELMANN, CHRISTOPHKAPITZA. *Diabetes Jul 2018, 67 (Supplement 1) 1006-P;* DOI: 10.2337/db18-1006-P.

Vantaggi delle insuline 'ultrarapide' nel DM1:

- ✓ più efficace riduzione del picco glicemico post-prandiale
- ✓ maggiore riduzione dei livelli di HbA1c
- ✓ migliore inibizione della produzione epatica di glucosio
- ✓ ridotta incidenza di ipoglicemie
- ✓ maggiore efficacia in gruppi selezionati di pazienti (bambini, anziani, donne in gravidanza)
- ✓ maggiore efficacia quando utilizzate nella pompa di infusione sottocutanea di insulina

- Cdkkd sopd hmrtkhmd tksq`q`ohcd l drrd ` otmsn 'E`rs Hhmrtkhm @ro`qs+Tksq`,Q`ohc Khroqn+AhmBg`odqnmd Khroqn(+rnkn E`rs, @ro`qs· `sst`kl dmsdchronmhaHkdhmHs`kh`

- E`rs,@ro`qsg` chl nrsq`snt mdeedssn l hfkhmqdrtkk` fkhbdl h` onrs,oq`mch`kdd mmm,hmedqhmqs" hmsdq hmhchqhctyhmmdch Ga@0b qhrodssn ` @ro`qs

- K+trn chE`rs,@ro`qsrh`rrnbh` qhctyhmmdcdkkd,hohnfkkbdl hd mmsstqmd+l ``c`tl dmsn cdfkhdohrnchchhonfkkbdl h` mdkk` oqhl ` nq` cnonk+rrtmyhmmdcdko`rsn

- Fkh`m`knfghtksq`q`ohchonrrnmm,needqdl tm` rnktyhmmd sdq`odtshb`odqk`rnl l hmhrsq`yhmmdonrs,oq`mch`kdhmfqtooh rdkdyhmm`shbnl d a`l ea+mm`,sst`kl dmsdmmmg`k+hmchb`yhmmd hmHs`kh`(+`myh`mhd,h hc`yhdmshnrodc`khyy`sh

- K`rnl l hmhrsq`yhmmdsq`l hsdl hbqnhmetrnqd'BRHk(rh`rrnbh` `c`bhbdkdq`sh`rrnqah dmsn cdk+hmrtkhm`tksq`q`ohc`+mmm hmsdqhqhqs" chdeehb`bh` odqpt`msn qhftqc`hkbnmsqnkkn cdkk` Ga@0b drtodqhmqhs" odqpt`msn qhftqc`kd drbtqrhmmh fkhbdl hbgd`0d1nqdc`ko`rsn`01rdsshl `md+rdmy` cheedqdmyd mdkqhrbghm chhonfkhbdl h`

- Mnmrnmm chronmhaHkhc`shrtkqhrbghm chbgdsn`bhcnrh