La Terapia Insulinica Sottocutanea in Continuo Mediante Microinfusore

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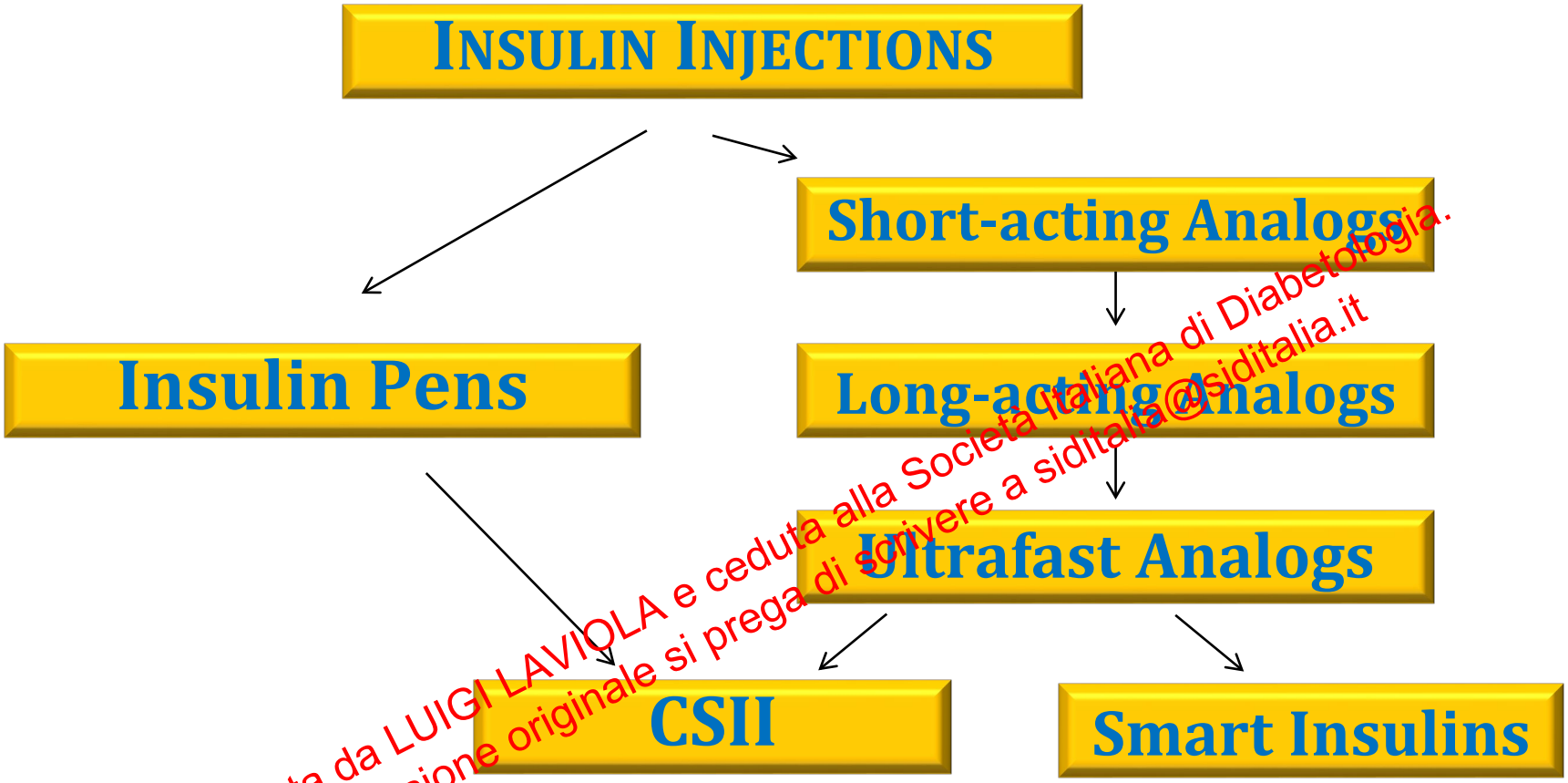
Disclosures

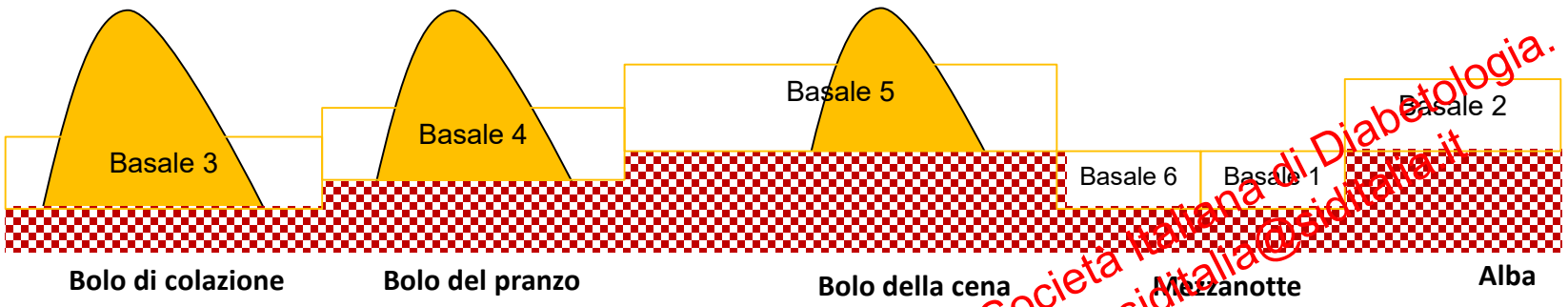
Luigi Laviola dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

Abbott, Boehringer Ingelheim , Astra Zeneca, Lilly Italia, Medtronic, MOVI, Novo Nordisk, Roche, Sanofi Aventis, Takeda (*collaborazione scientifica*)

Abbott, Boehringer Ingelheim, Astra Zeneca, Lilly, Medtronic, Menarini, Movi, MSD, Mundipharma, Novo Nordisk, Roche, Sanofi-Aventis, Takeda (*relazioni a convegni, supporto per partecipazione a congressi*).



CSII: Flessibilità per l'Infusione di Insulina



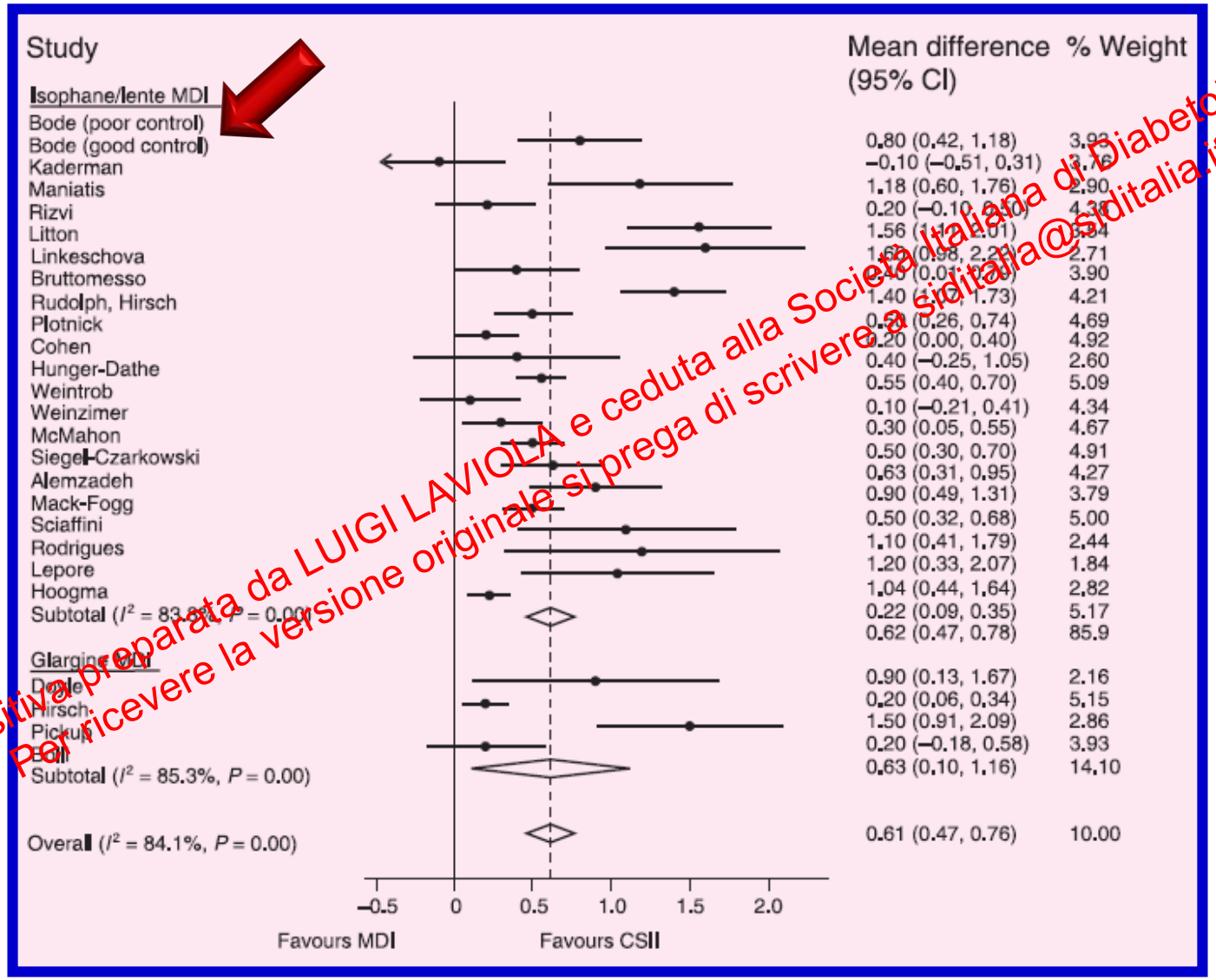
1970s: bassa tecnologia

- Velocità basale unica
- Unica opzione di bolo
- Aggiustamento "manuale"
- del bolo prandiale
- Nessun allarme
- Guidata da SMBG

Attualmente: alta tecnologia

- Velocità basale flessibile
- Diverse opzioni di bolo
- Calcolatore di bolo
- Download dei dati al computer
- Allarmi multipli
- Connessione al CGM
- Funzione "Low Glucose Suspend"
- Funzione "Predictive LGS" → SAP
- Hybrid closed-loop

CSII vs MDI: Effetti sul Compenso Metabolico



Pickup JC et al, Diabet Med 2008

La variazione in HbA1c (MDI vs. CSII) dipende dal valore iniziale di HbA1c

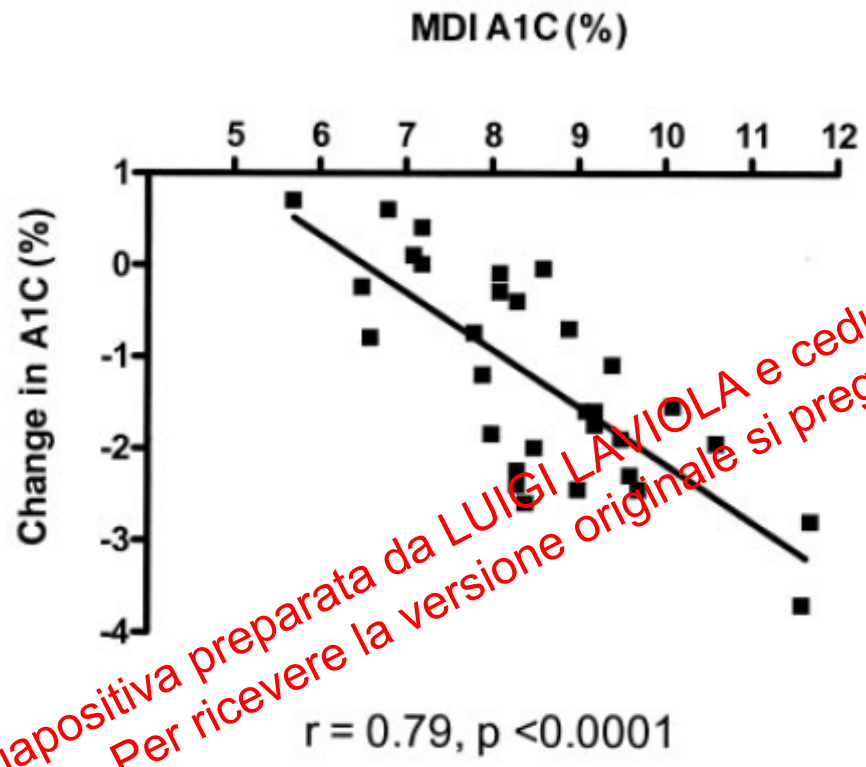
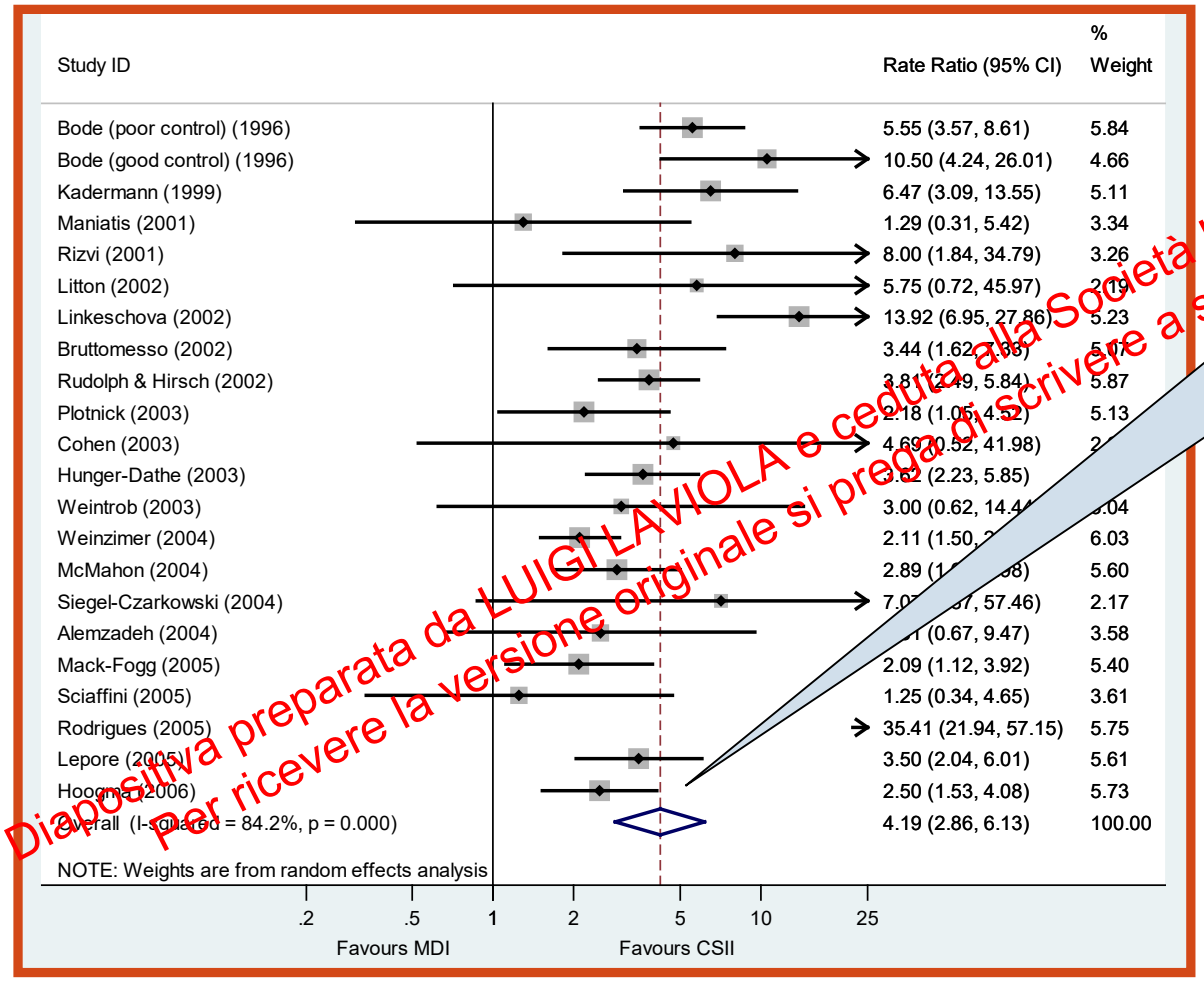


Figure 2—*Correlation in type 1 diabetes between the A1C on MDI and the subsequent change in A1C when patients were switched to CSII. From Pickup et al. (28), with permission.*

La CSII è molto più efficace nei pazienti con peggior controllo durante MDI.

Pickup and Sutton, Diabetic Medicine 2008

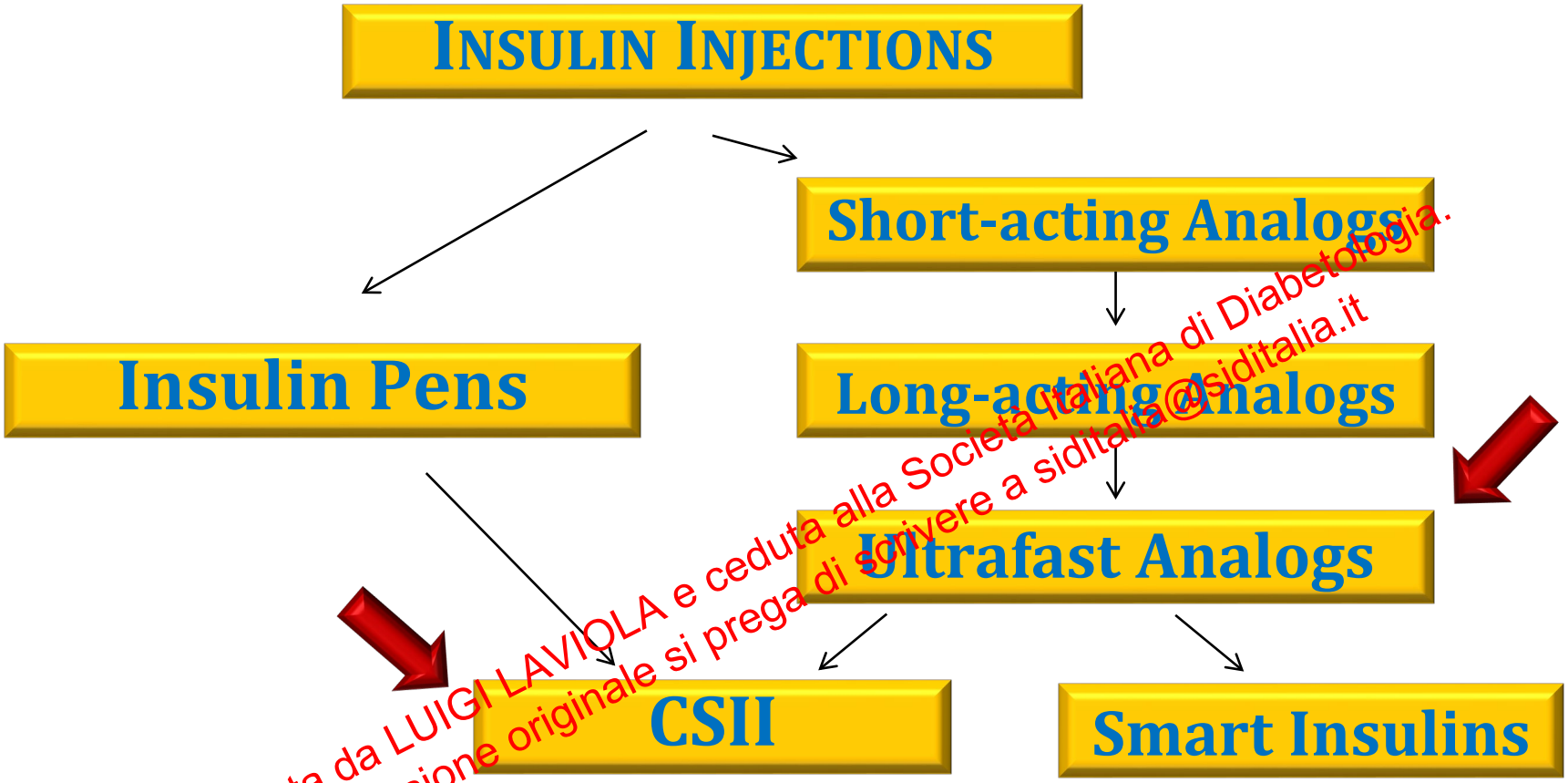
Ipoglicemia severa: MDI vs. CSII



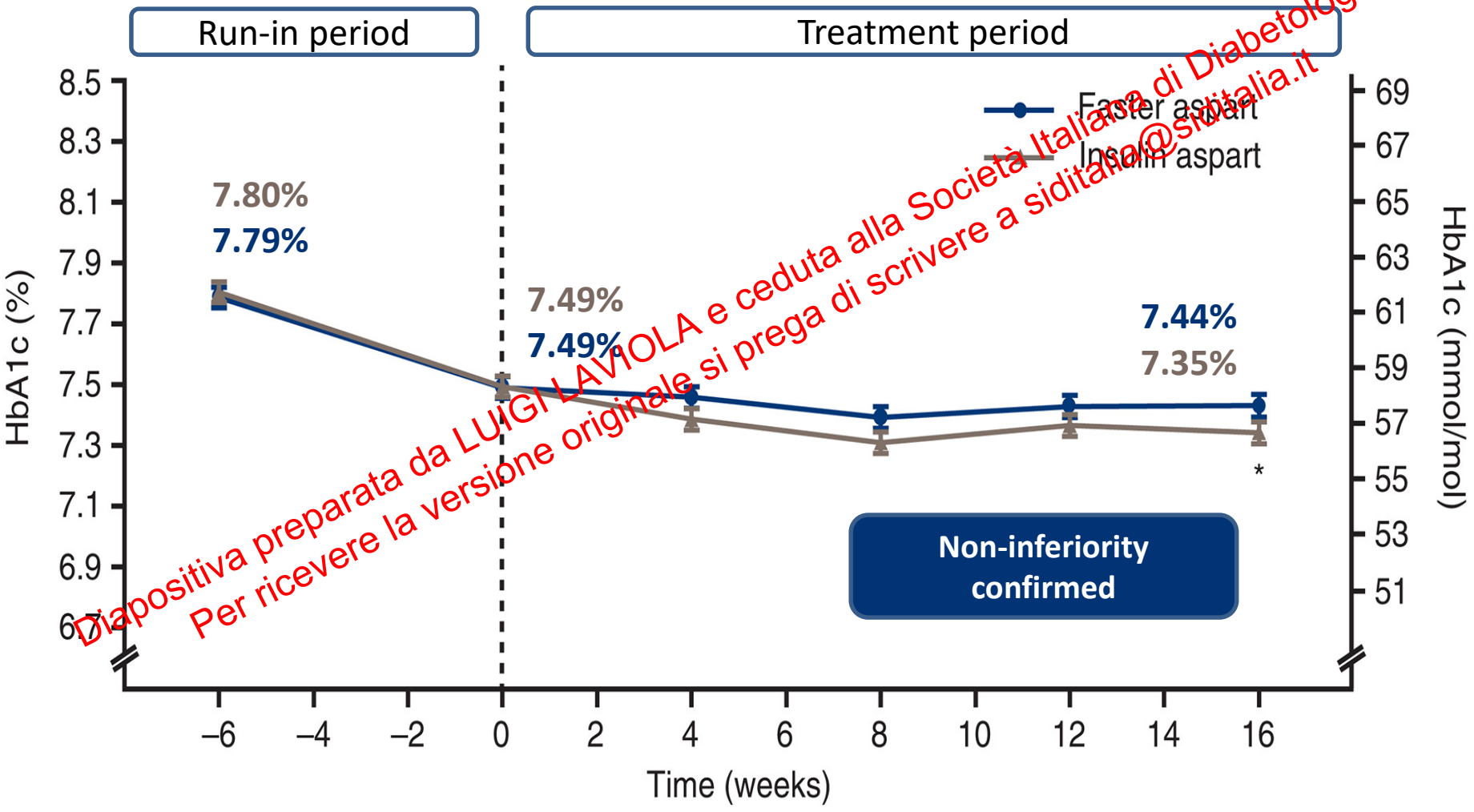
L'ipo severa si riduce di 4 volte passando a CSII

Rate ratio 4.19 [95% CI 2.86 to 6.13])

Pickup and Sutton, Diabetic Medicine 2008

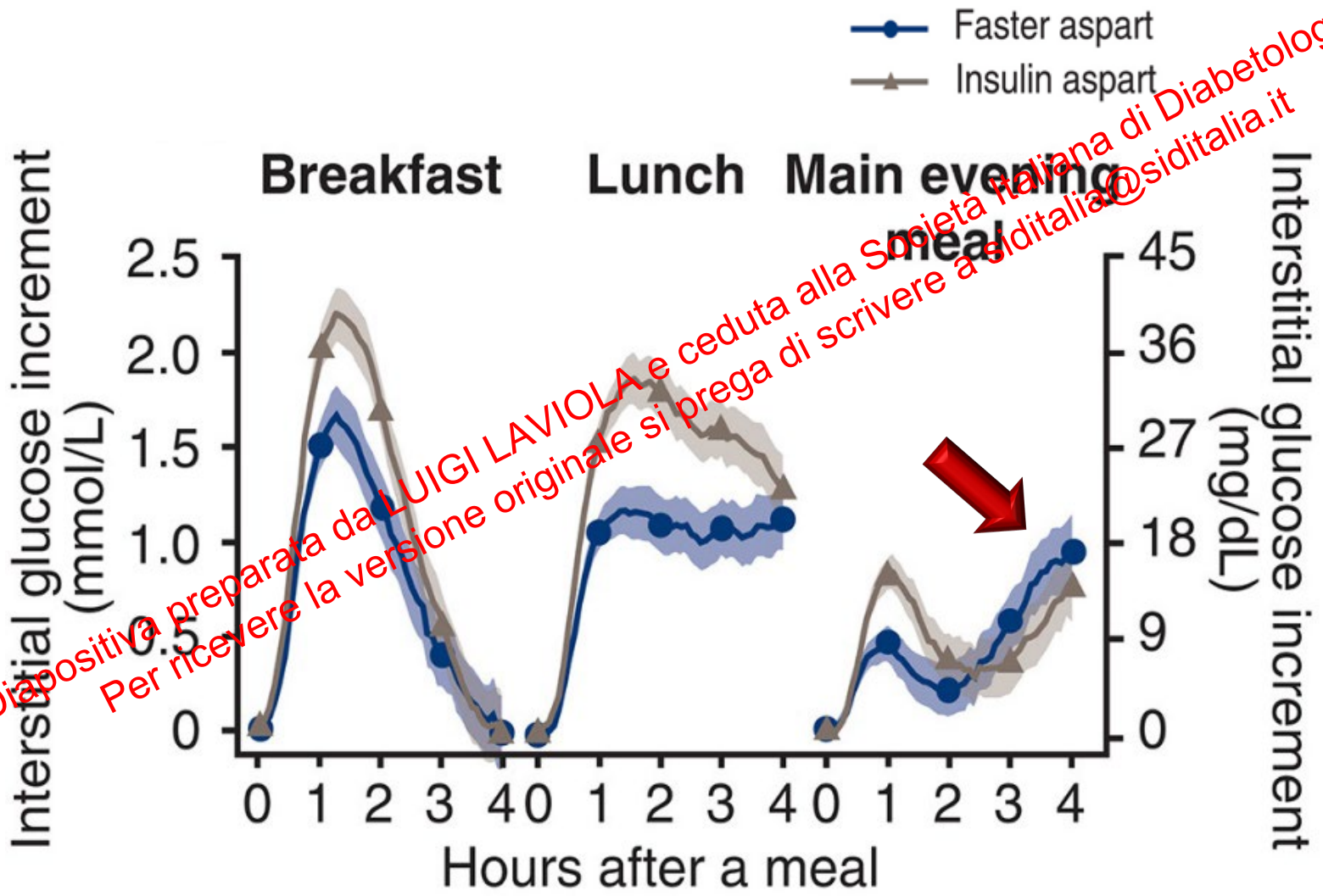


ONSET 5: mean HbA_{1c} over time



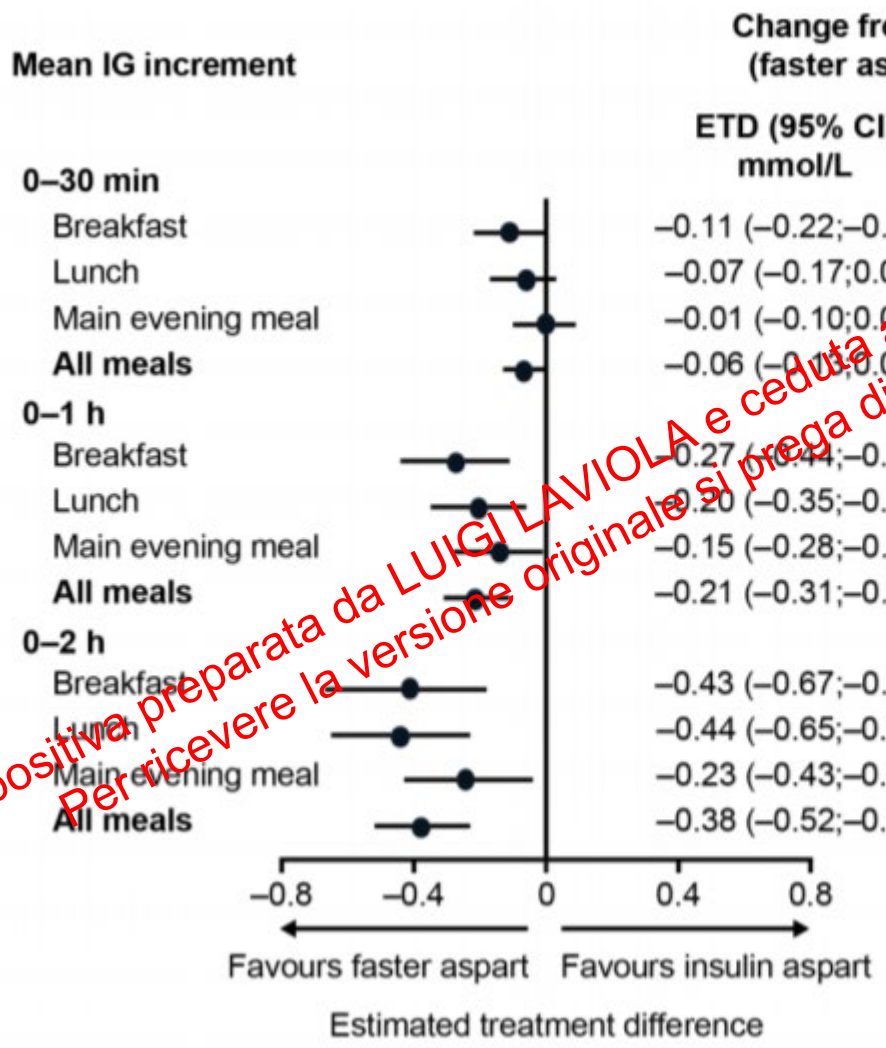
Klonoff et al. Diabetes Obes Metab. 2018

ONSET 5: prandial IG increments at week 16

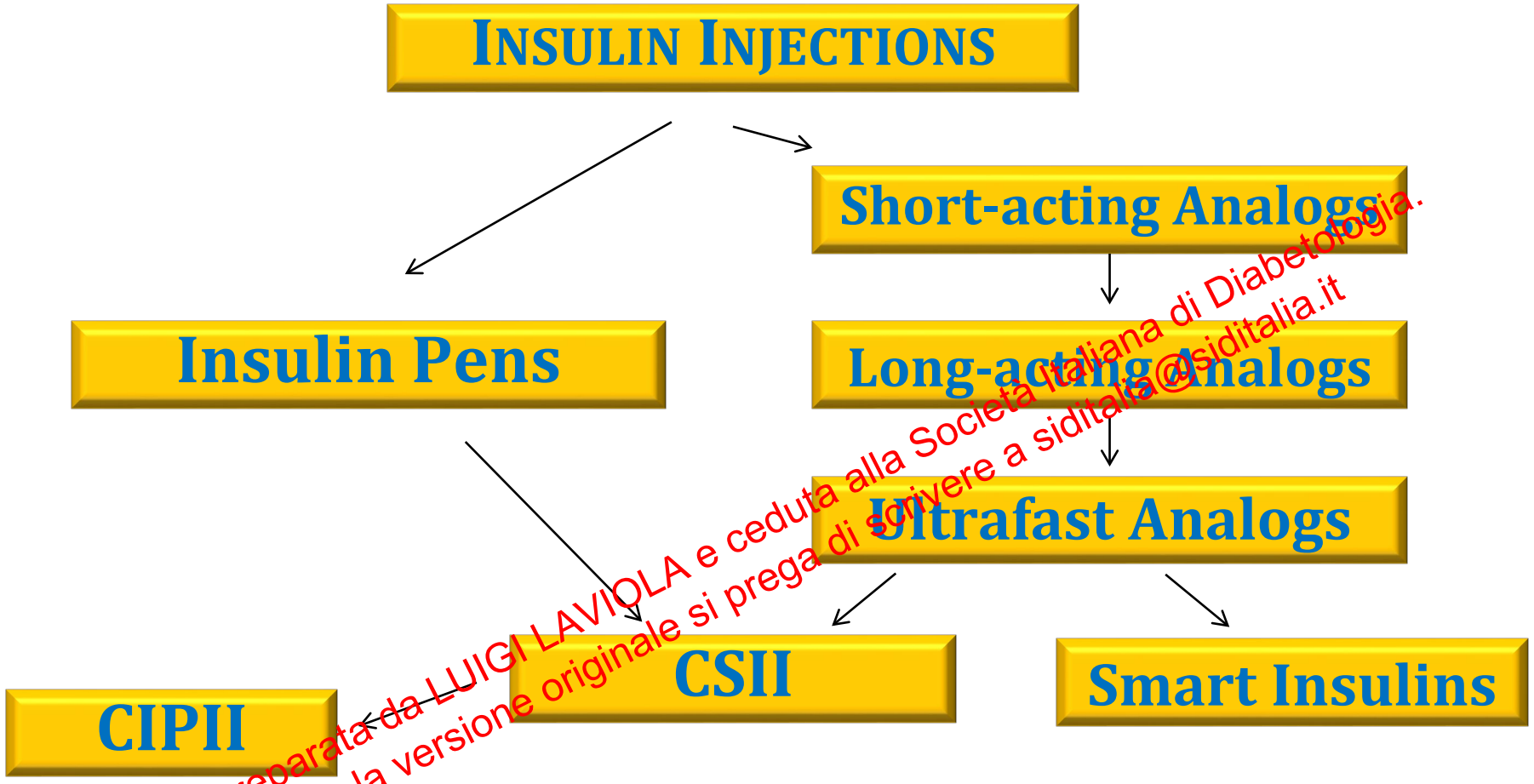


Klonoff et al. Diabetes Obes Metab. 2018

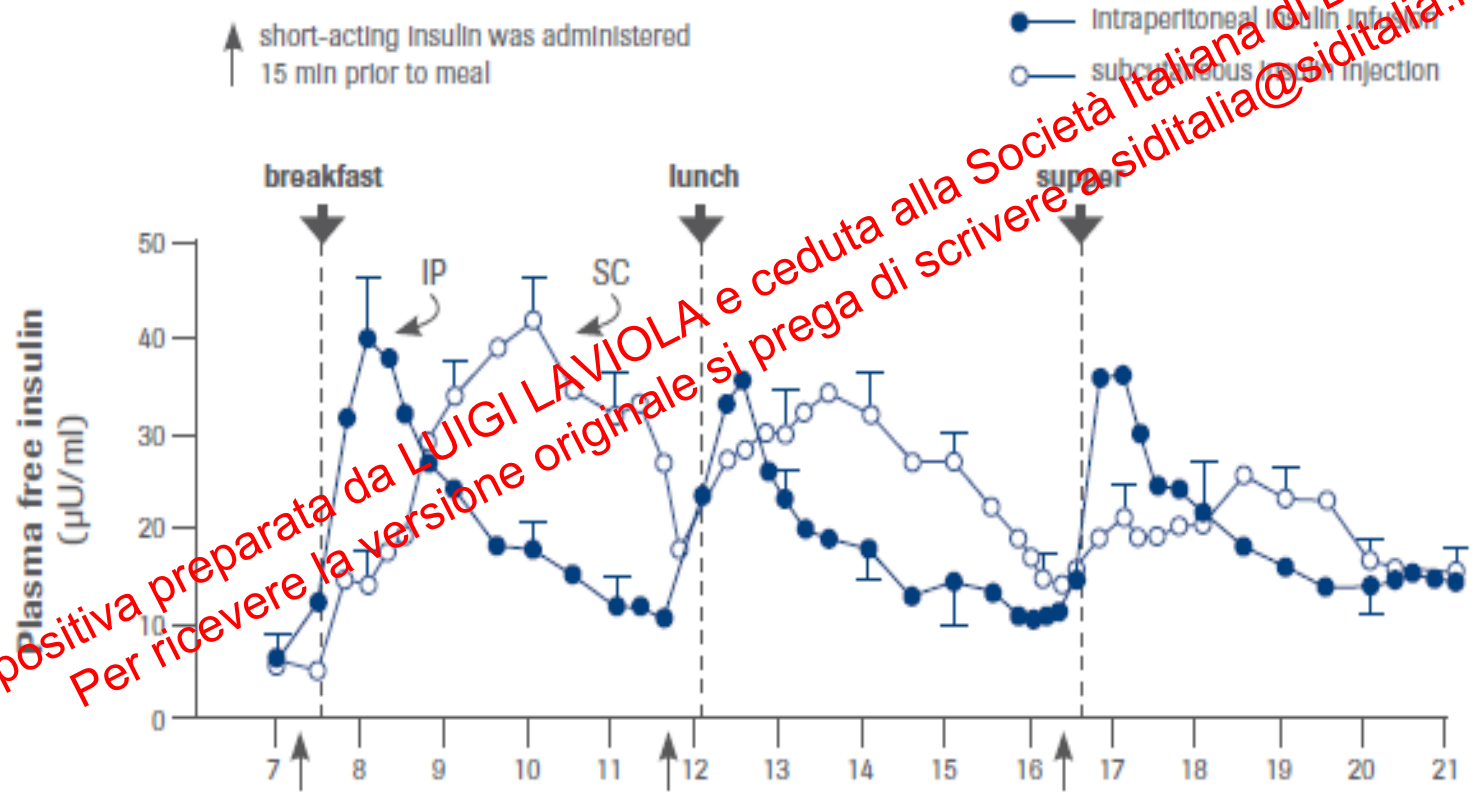
ONSET 5: change from baseline to week 16



Klonoff et al. Diabetes Obes Metab. 2018

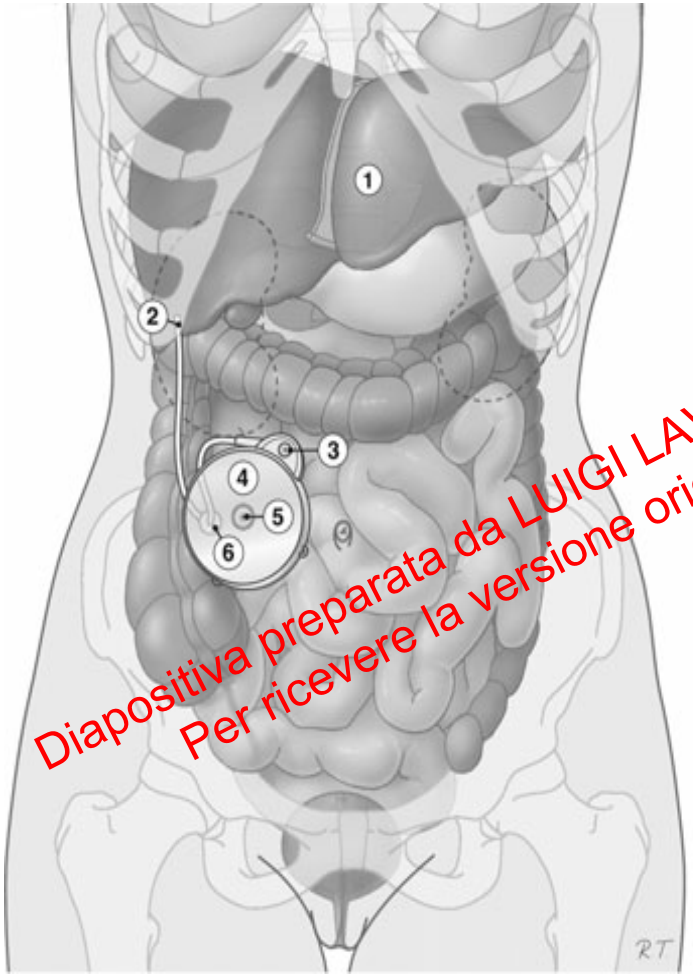


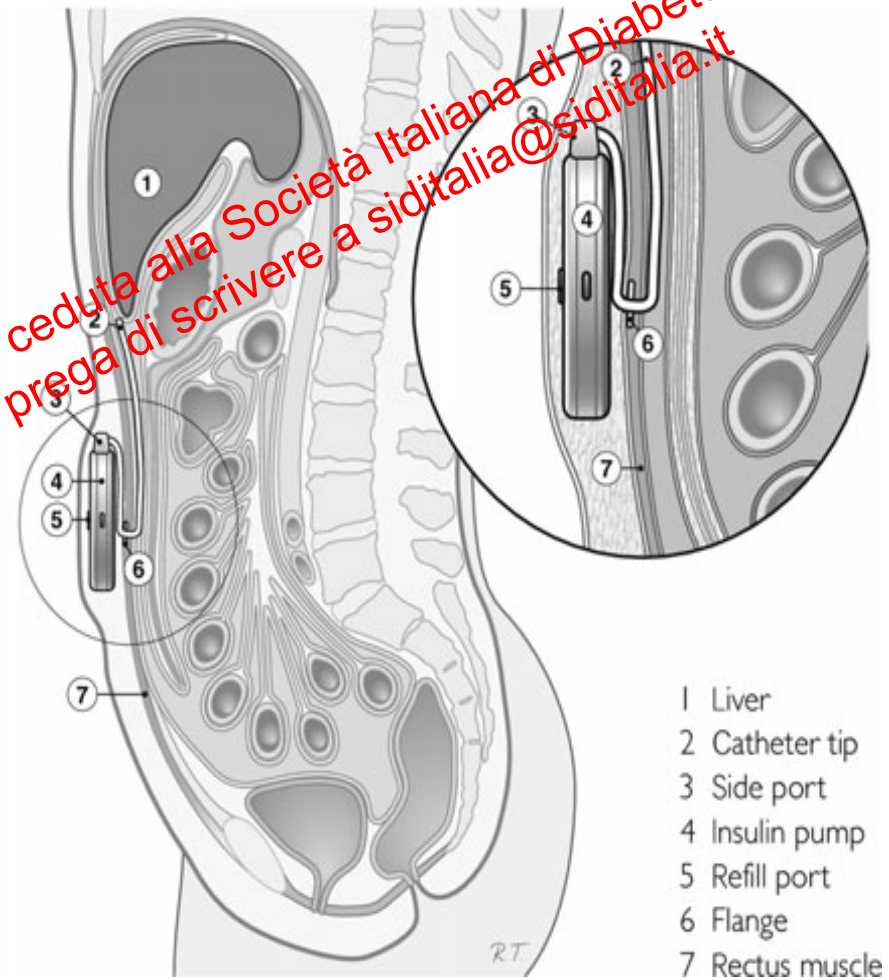
Intra-Peritoneal vs Subcutaneous Insulin Infusion



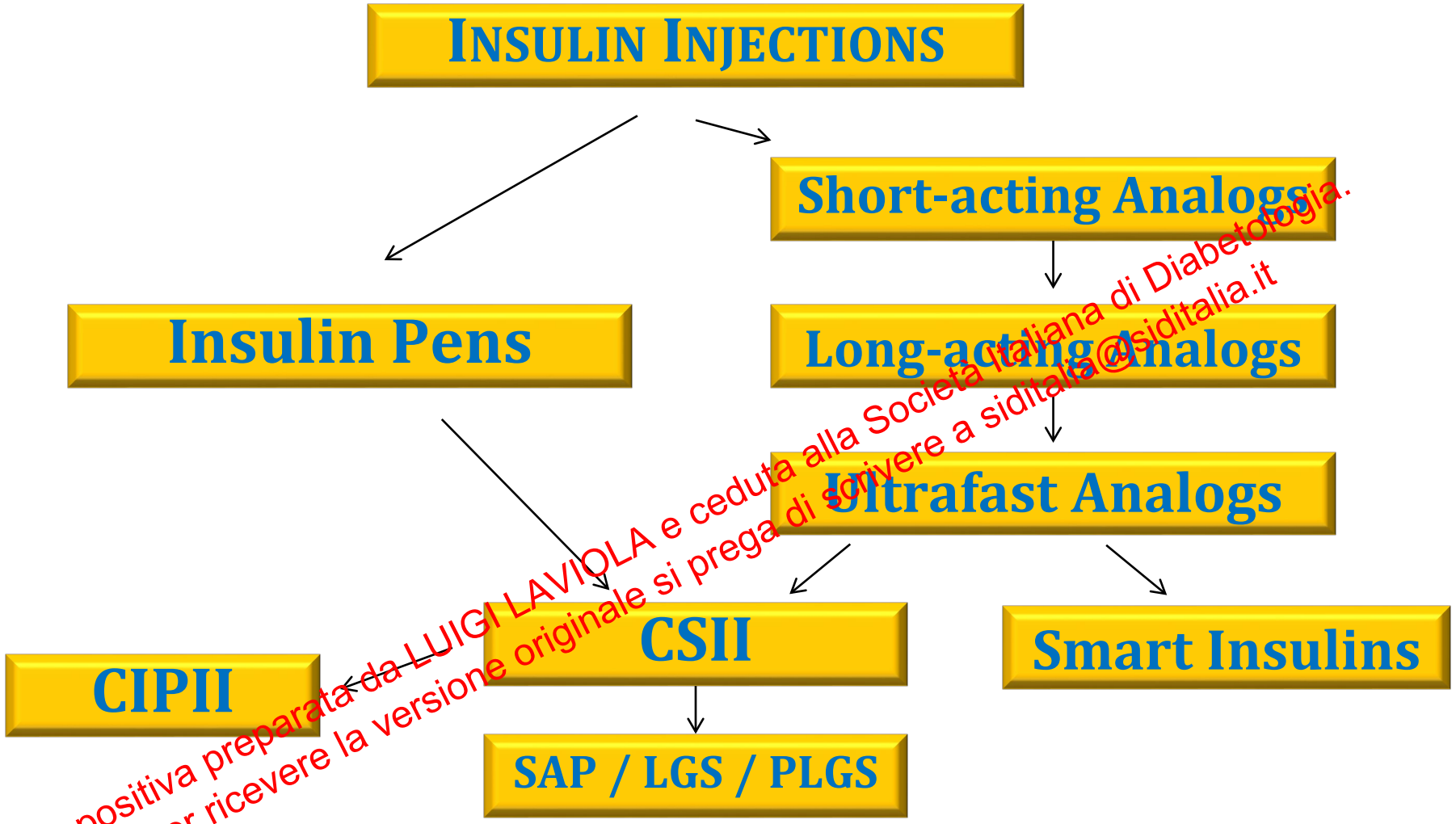
Schade DS et al, Diabetologia 1980

Continuous Intra-Peritoneal Insulin Infusion (CIPII) via Implantable Pump

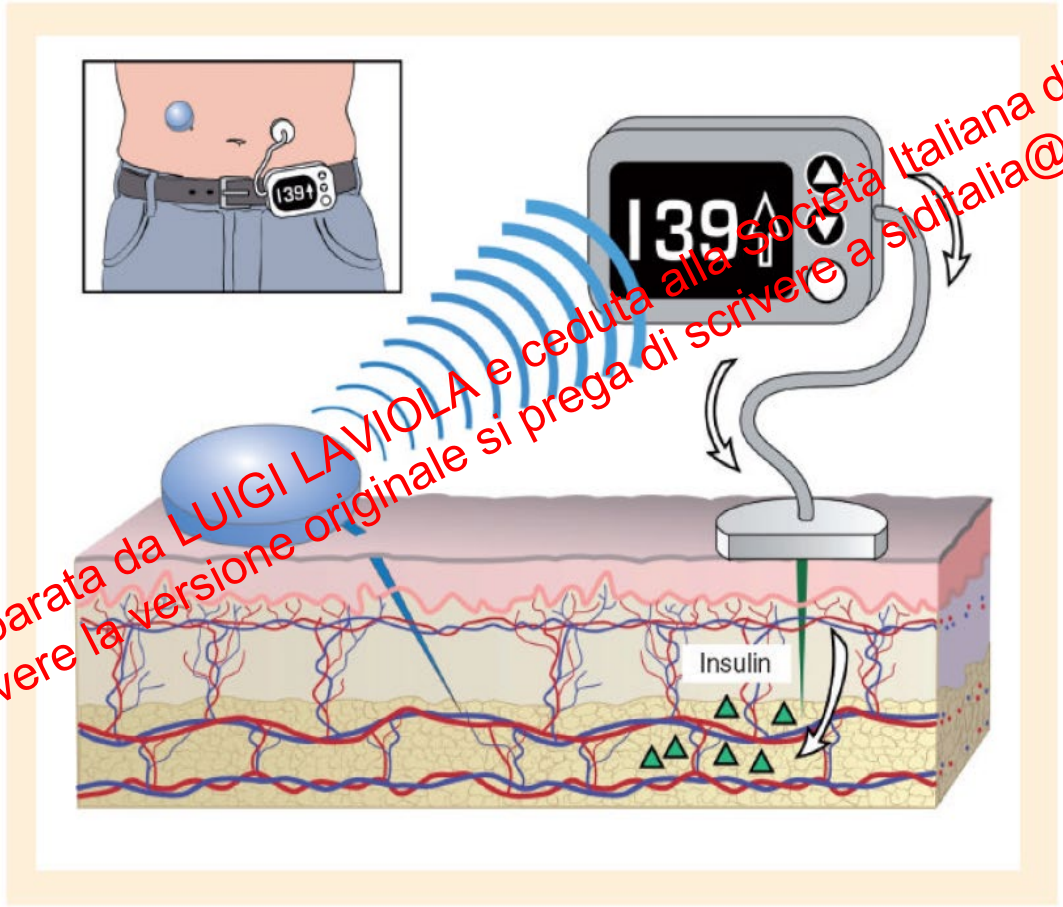




Van Dijk PR et al, Clin End 2014

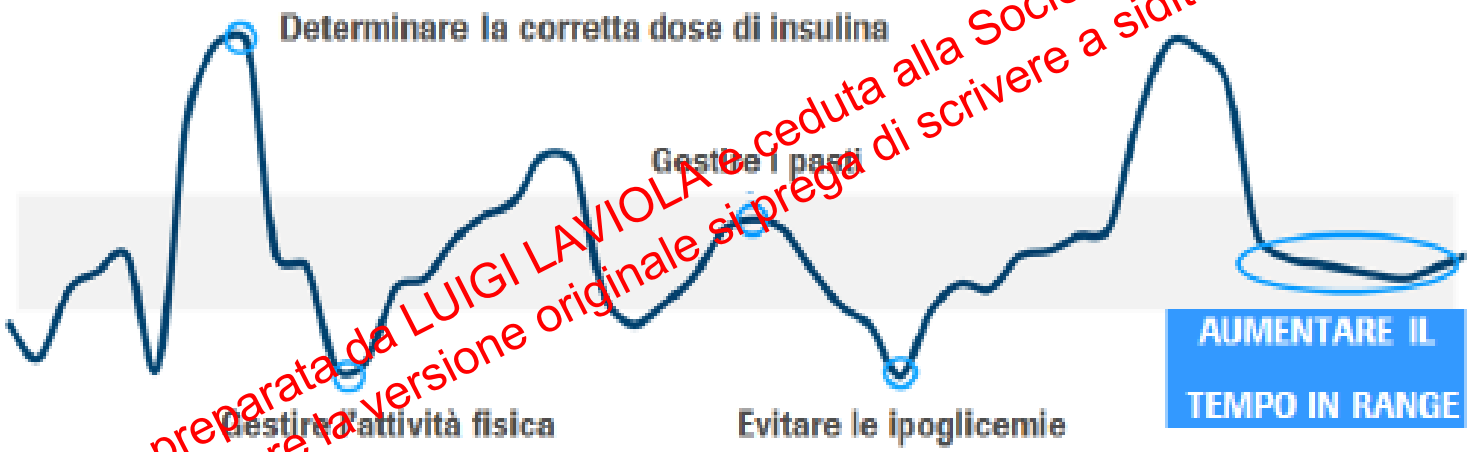


Sensor-Augmented Pump (SAP) Therapy

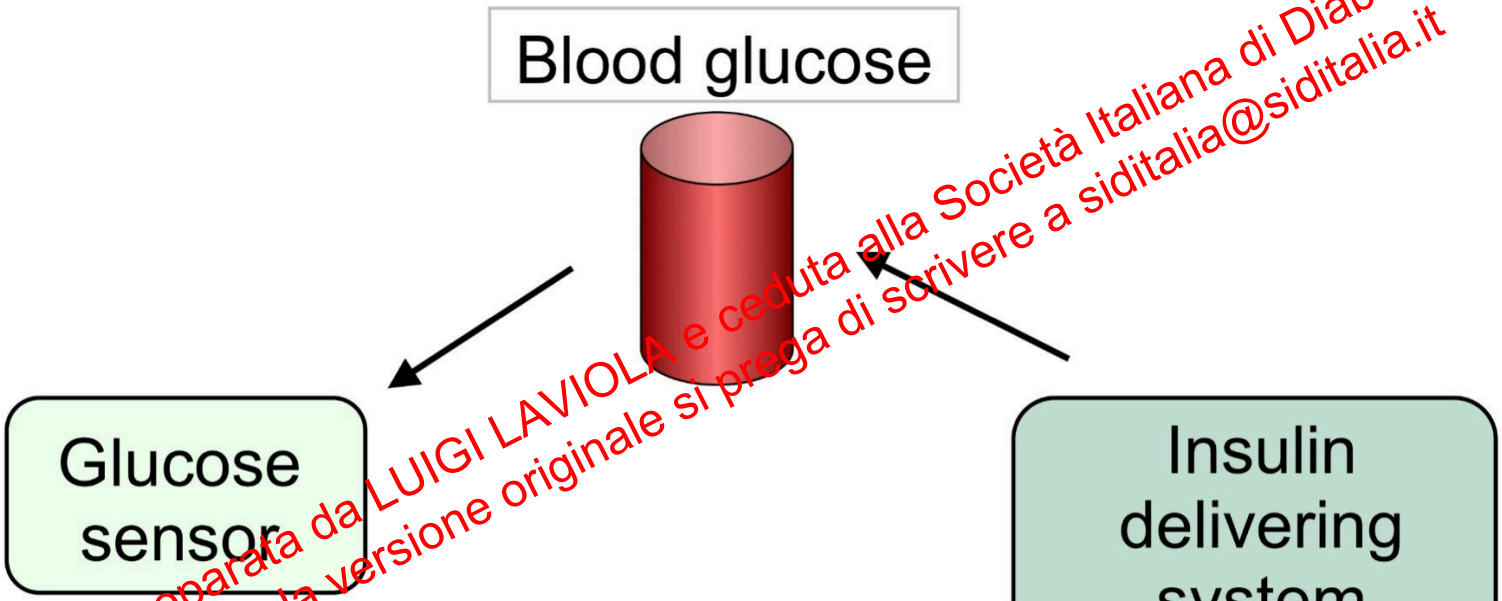


Cengiz et al, Expert Rev Med Devices. 2011 July ; 8(4): 449

Time in Range: l'Impegno di Ogni Giorno

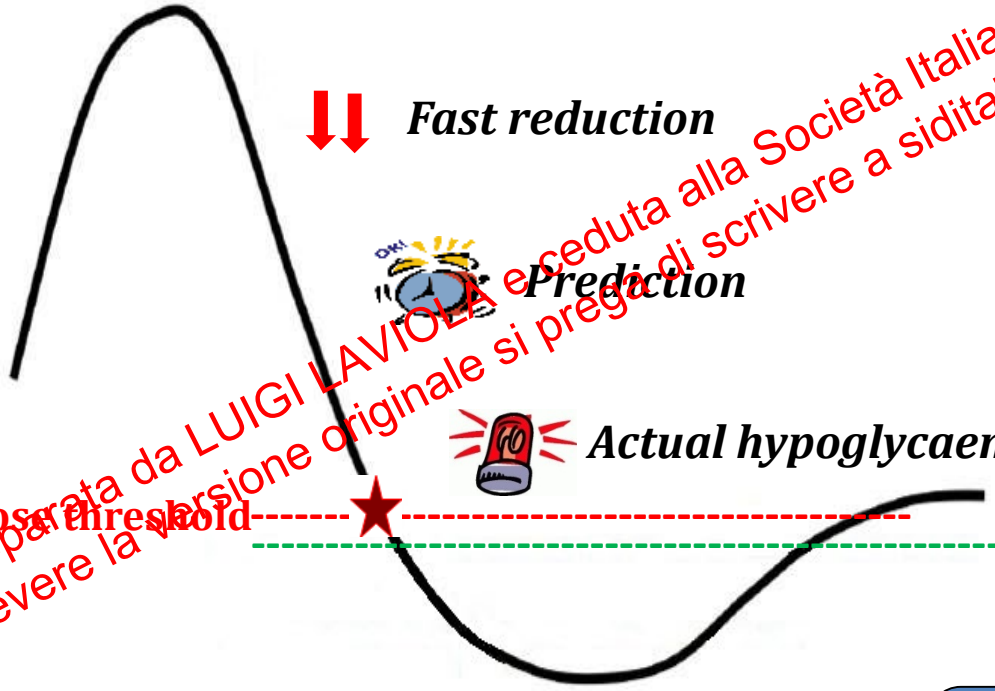


Pancreas Artificiale? È Semplice....



Prevention of/Protection from Hypoglycaemia

SAP with «Low Glucose Suspend (LGS)» Function



Fast reduction

Prediction

Actual hypoglycaemia

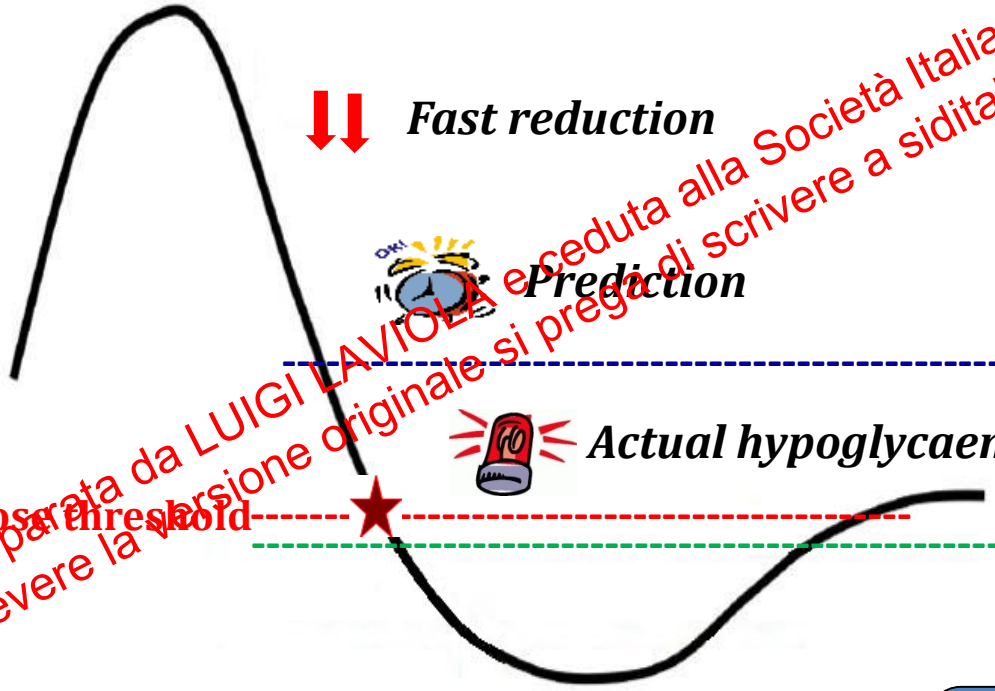
Low glucose threshold

LGS automatic suspension

Insulin pump

PLGS

"Predictive Low-Glucose Suspend System"



Fast reduction

Prediction

Actual hypoglycaemia

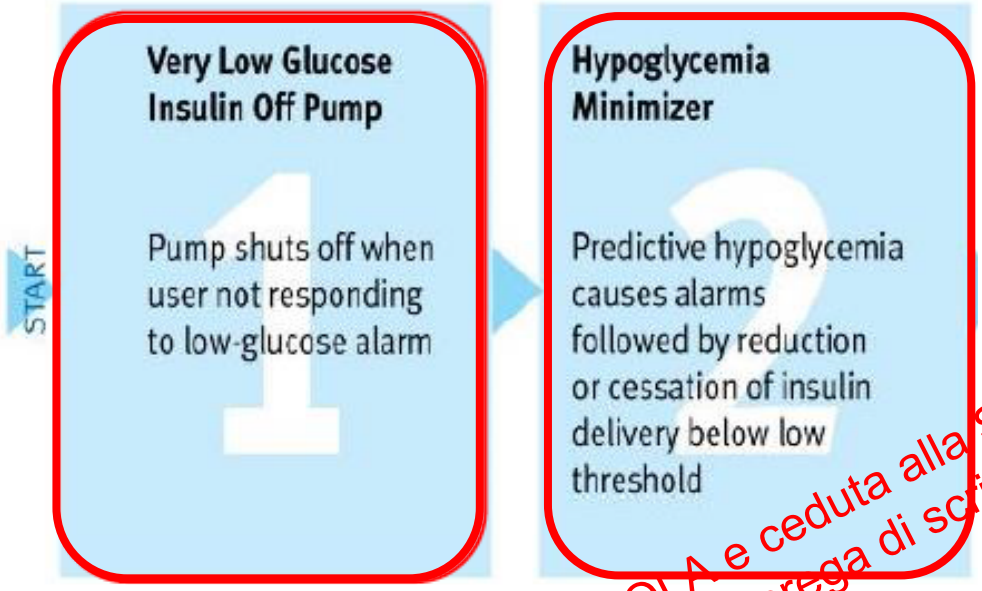
Low glucose threshold

PLGS automatic suspension

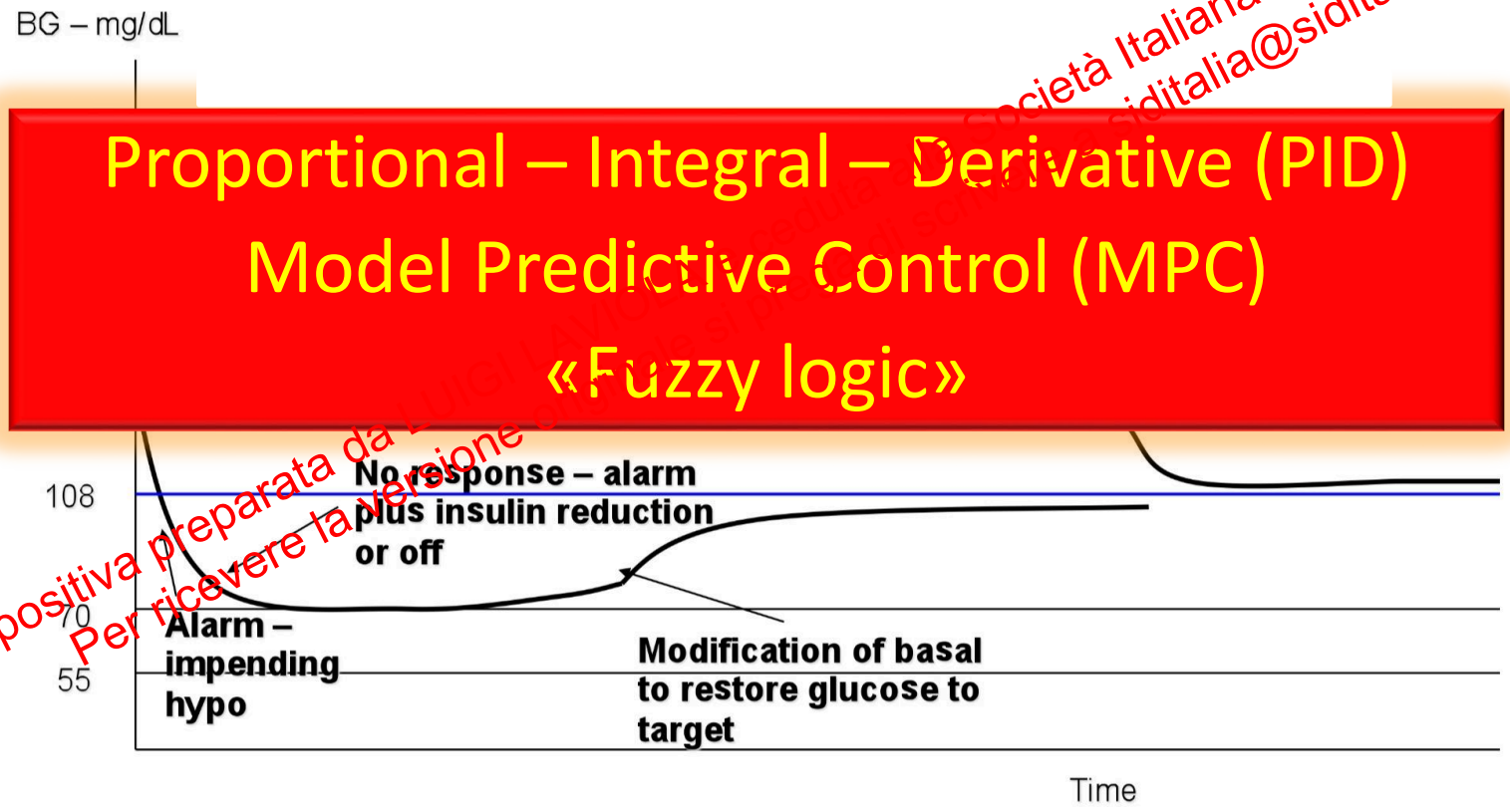
LGS automatic suspension

Insulin pump

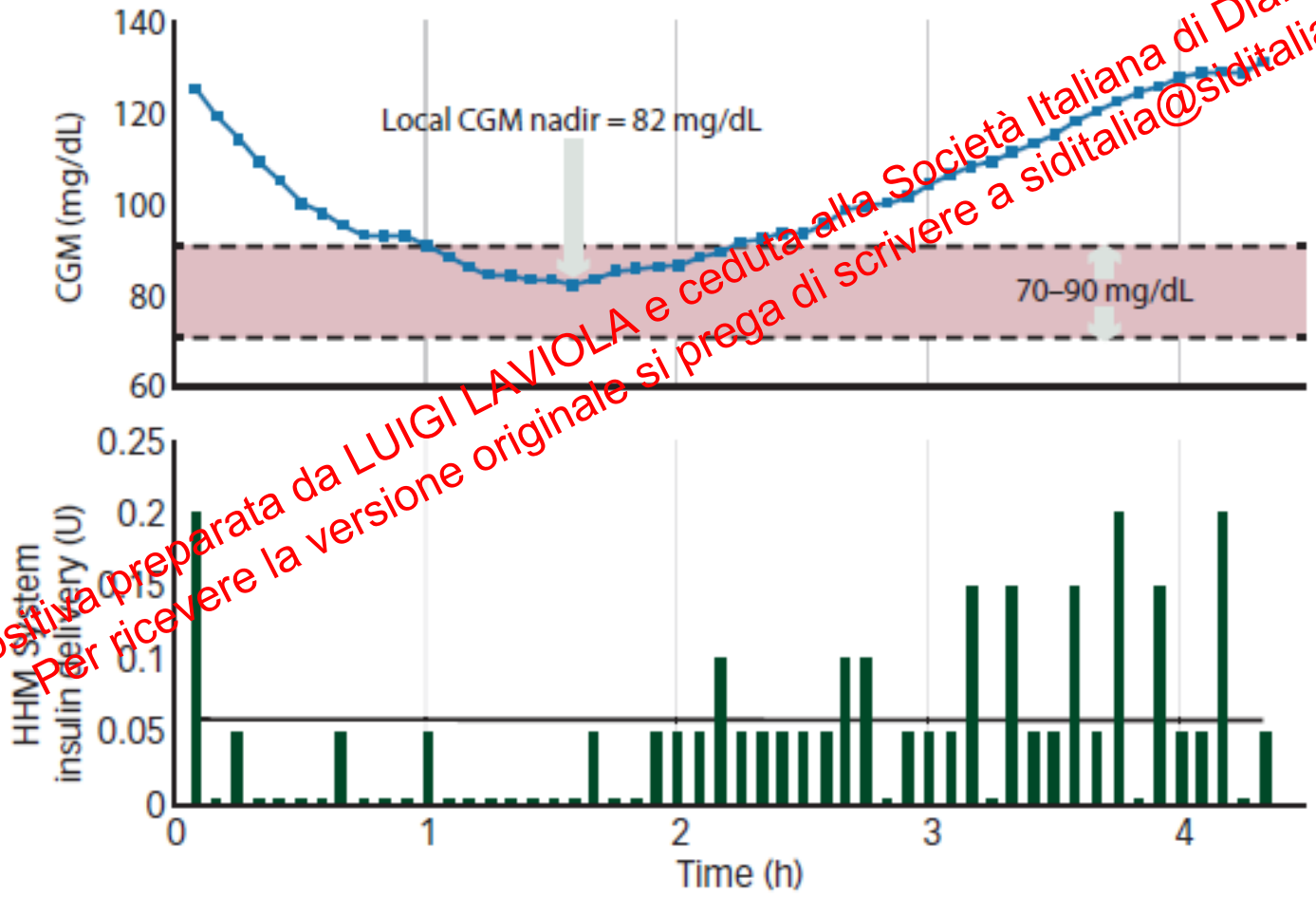
AP Strategy – Iterative Increases in Automation



Pancreas Artificiale:
Molti Algoritmi, tre Approcci

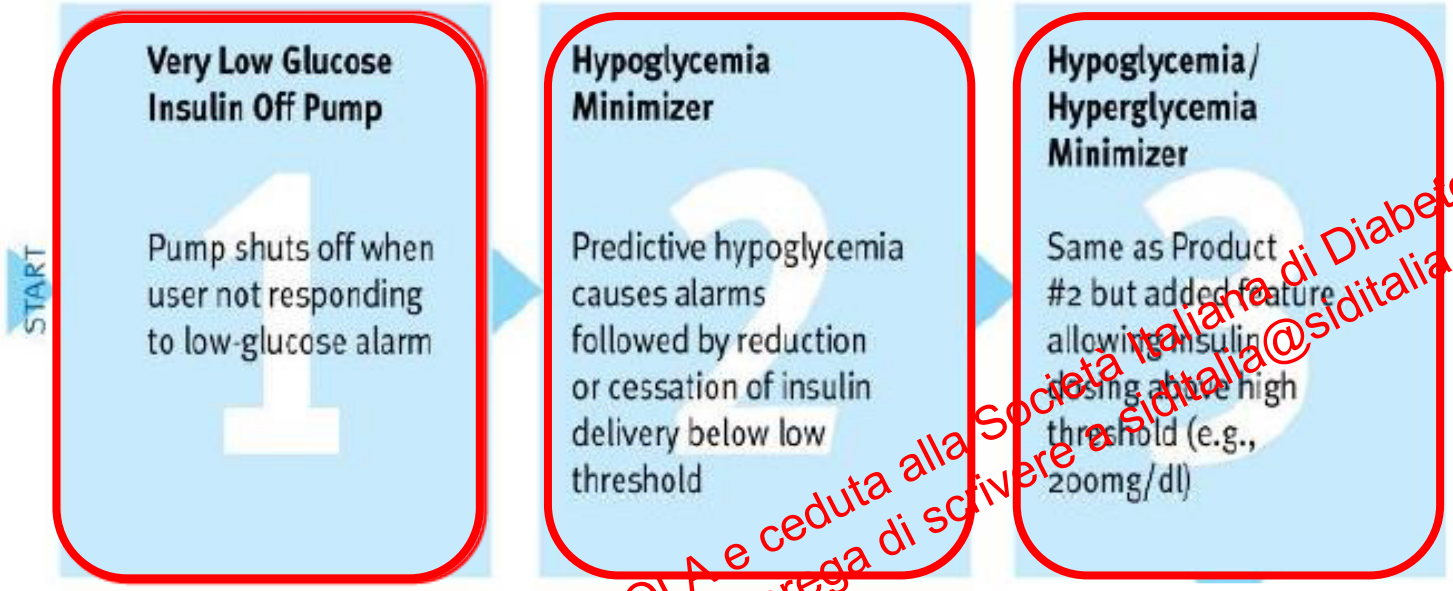


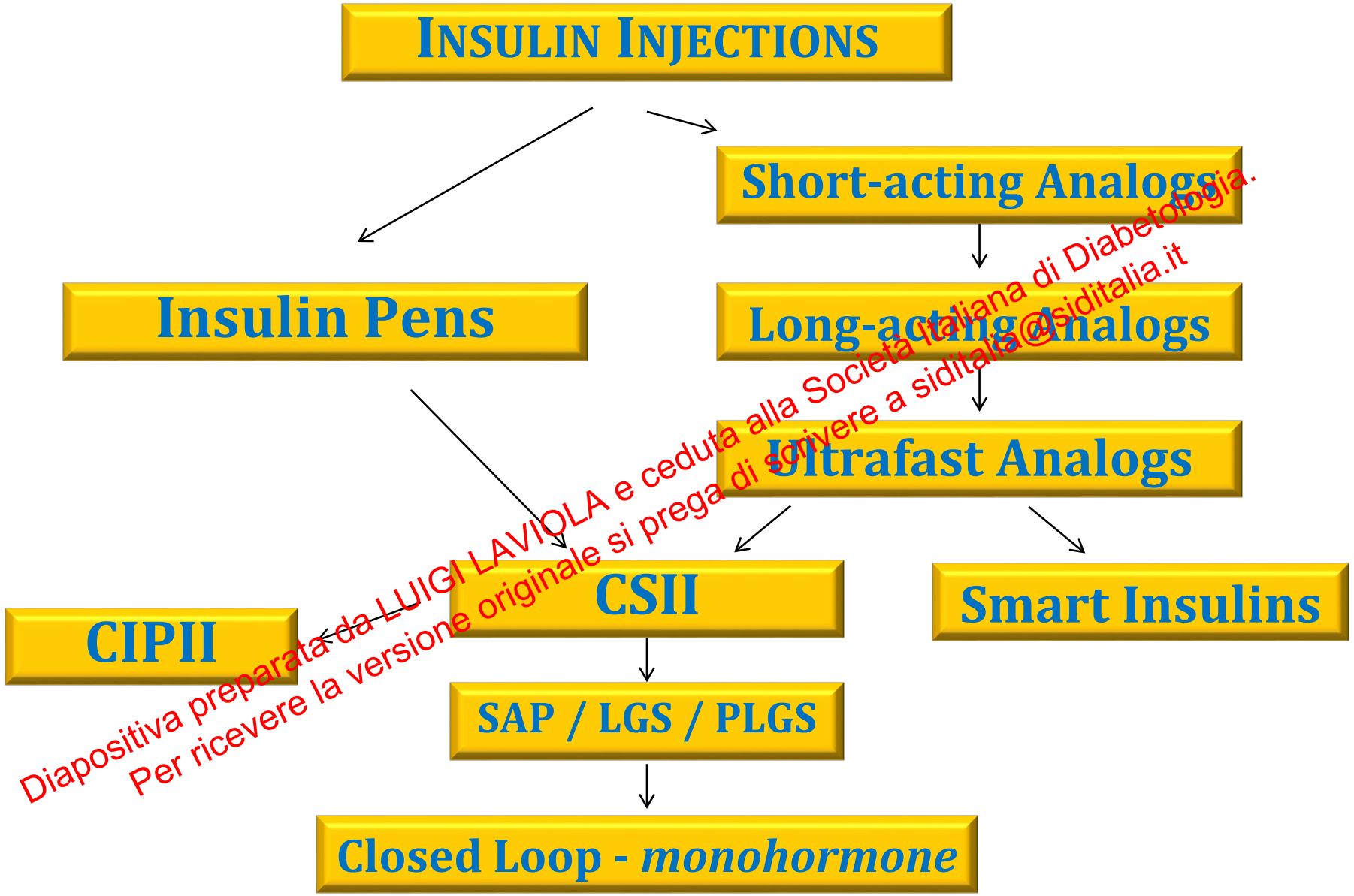
The Hypoglycemia-Hyperglycemia Minimizer (HHM) System



Levy BL et al, Eur Endocrinol 2016

AP Strategy – Iterative Increases in Automation





AP vs CSII/SAP

Study author and year	Trial registration details	Setting	Population	Type of comparator	Intervention duration	Length of follow-up*	No of patients
Bally 2017[25]	NCT02727231	Home	Adults	SAP	24 h	4 weeks	29
Biester 2016[26]	NCT02636491	Home	Adults and adolescents	SAP	24 h	2 days	10
Blauw 2016[27]	NCT02160275	Home	Adults	Insulin pump treatment	24 h	4 days	10
Breton 2017[28]	NCT02604524	Winter camp	Adolescents	SAP	24 h	5 days	32
Brown 2017[29]	NCT02131766, NCT02008188	Hotel or research house	Adults	SAP	Overnight	5 days	40
Chernavvsky 2016[30]	NCT01890954	Research house	Adolescents	Insulin pump treatment	24 h	1 day	16
De Bock 2015[31]	ACTRN12614001005640	Home	Adults and adolescents	SAP+LGS	24 h	5 days	8
De Boer 2017[32]	NCT02750267	Hotel or home	Children	SAP	24 h	4 days	12
Ekhlaspour 2016a[33]	Not reported	Home	Adults	Insulin pump treatment	24 h	3 days	20
Ekhlaspour 2016b[33]	Not reported	Home	Adults	Insulin pump treatment	24 h	3 days	20
El-Khatib 2016[34]	NCT02092220	Home	Adults	Insulin pump treatment or SAP	24 h	2 days	39
Favero 2016[35]	NCT0260878	Diabetes camp	Children	SAP	24 h	3 days	30
Forlenza 2017a[37]	NCT02773875	Home	Adults	SAP	24 h	2 weeks	19
Forlenza 2017b[36]	NCT02714972	Home	Children and adolescents	SAP+LGS	Overnight	21 nights	28
Haidar 2015a[38]	NCT02189694	Diabetes camp	Adolescents	Insulin pump treatment	Overnight	3 days	33
Haidar 2015b[38]	NCT02189694	Diabetes camp	Adolescents	Insulin pump treatment	Overnight	3 days	33
Haidar 2016a[39]	NCT01905020	Home	Adults and adolescents	Insulin pump treatment	Overnight	2 days	28
Haidar 2016b[39]	NCT01905020	Home	Adults and adolescents	Insulin pump treatment	Overnight	2 days	28
Haidar 2017a[40]	NCT01966393	Home	Adults	SAP	24 h	60 hours	23
Haidar 2017b[40]	NCT01966393	Home	Adults	SAP	24 h	60 hours	23
Hovorka 2014[41]	NCT01221467	Home	Adolescents	SAP	Overnight	3 weeks	16
Kingman 2017[42]	Not reported	Outpatient	Adults and adolescents	SAP	24 h	5 weeks	37
Kovatchev 2014[43]	NCT01714505, NCT01727817, NCT01742741	Hotel or guesthouse	Adults	SAP	24 h	40 hours	20
Kropf 2015[44]	NCT02153190	Home	Adults	SAP	Evening and night	8 weeks	32
Leelarantha 2014[45]	NCT01666028	Home	Adults	SAP	24 h	8 days	17
Ly 2014[46]	NCT01973413	Diabetes camp	Adults and adolescents	SAP	Overnight	5-6 days	20
Ly 2015a[48]	NCT02366767	Diabetes camp	Adults and adolescents	SAP+LGS	24 h	6 days	21
Ly 2015b[47]	Not reported	Diabetes camp	Adults and adolescents	SAP	24 h	5 days	16
Ly 2016a[49]	NCT02147860	Diabetes camp	Adolescents	SAP	24 h	5 days	33
Ly 2016b[50]	Not reported	Diabetes camp	Children and adolescents	SAP	Overnight	1 day	21
Nimri 2014[51]	NCT01238406	Home	Adults and adolescents	SAP	Overnight	6 weeks	24
Nimri 2016[52]	NCT0172683	Home	Children, adolescents and adults	SAP	Overnight	4 days	75
Phillip 2013[53]	NCT01238406	Diabetes camp	Adolescents	SAP	Overnight	1 day	54
Renard 2017[54]	Not reported	Outpatient	Children	SAP+LGS	24 h	2 days	24
Russell 2014a[55]	NCT01772199	Home and hotel	Adults	Insulin pump treatment or SAP	24 h	5 days	20
Russell 2016[56]	NCT01933988	Diabetes camp	Adolescents	Insulin pump treatment or SAP	24 h	5 days	32
Russell 2016[56]	NCT02105324	Diabetes camp	Preadolescents	Insulin pump treatment or SAP	24 h	5 days	19
Schmidh 2015[57]	Not reported	Home	Children	SAP	Overnight	4 days	15
Sharifi 2016[58]	Not reported	Home	Adults and adolescents	SAP+LGS	Overnight	4 days	28
Spaic 2017[59]	NCT02438189	Home	Adults and adolescents	SAP+LGS	Overnight	21 nights	30
Tauschmann 2016a[61]	NCT01873066	Home	Adolescents	SAP	24 h	7 days	12
Tauschmann 2016b[60]	NCT01873066	Home	Adolescents	SAP	24 h	3 weeks	12
Thabit 2014[62]	NCT01440140	Home	Adults	SAP	Overnight	4 weeks	24
Thabit 2015a[63]	NCT01961622	Home	Adults	SAP	24 h	12 weeks	33
Thabit 2015b[63]	NCT01778348	Home	Children and adolescents	SAP	Overnight	12 weeks	25

DiAs=Diabetes Assistant; USS=Unified Safety System; SAP=sensor augmented pump treatment; MPC=model predictive control; PID=proportional integral derivative; IFB=insulin feedback; LGS=low glucose suspend; PHHM=predictive hyperglycaemia and hypoglycaemia minimisation; SSM=safety supervision module.
*For crossover trials, length of follow-up refers to the duration of each period, excluding washout period.
†Not included in the meta-analysis.

Bekiari E et al. Artificial pancreas treatment for outpatients with type 1 diabetes: Systematic review and meta-Analysis. BMJ 2018;361.

AP vs CSII/SAP: HbA1c

The Artificial Pancreas:

- ↑ time in range
- ↓ hypoglycaemias
- ↓ mean glucose levels
- ↓ glucose variability

Bekiari E et al. Artificial pancreas treatment for outpatients with type 1 diabetes: Systematic review and meta-Analysis. BMJ 2018;361.

AP Strategy – Iterative Increases in Automation

START

Very Low Glucose Insulin Off Pump

Pump shuts off when user not responding to low-glucose alarm

Hypoglycemia Minimizer

Predictive hypoglycemia causes alarms followed by reduction or cessation of insulin delivery below low threshold

Hypoglycemia/ Hyperglycemia Minimizer

Same as Product #2 but added feature allowing insulin dosing above high threshold (e.g., 200mg/dl)

Automated Basal / Hybrid Closed Loop

Closed loop at all times with meal-time manual assist bolusing

Fully Automated Insulin Closed Loop

Manual meal-time bolus eliminated

Pancreas Artificiale Biormonale in Bambini e Adolescenti

	Conventional pump therapy (96 nights)	Single-hormone artificial pancreas (93 nights)	Dual-hormone artificial pancreas (93 nights)
Number of hypoglycaemic events	15	4	0
Patients with at least one hypoglycaemia event*	11 (33%)	4 (12%)	0
Median time of hypoglycaemia events (h)	0145 (0100–0520)	0025 (0010–0047)	..
Mean total insulin delivery 1 hour before hypoglycaemia events†	1	0·04 (0·06)	..
Mean total insulin delivery 2 h before hypoglycaemia events†	1	0·24 (0·20)	..
Number of hyperglycaemia events	2	2	0
Number of hyperglycaemia events accompanied with ketones	0	0	0
Time of hyperglycaemia events (h)	0340 and 0400	0130 and 0350	..

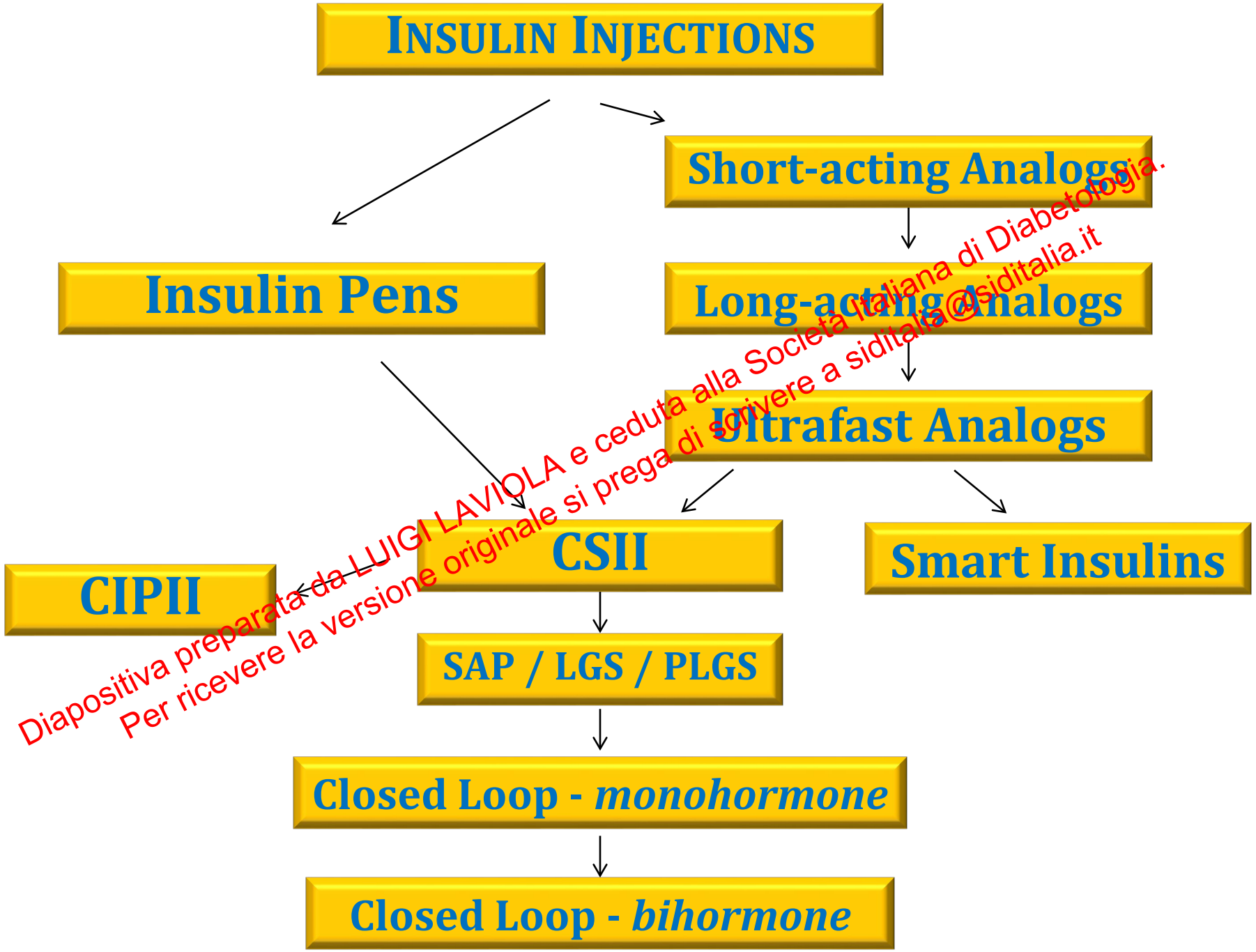
Haidar A et al, Lancet 2015

Dual-hormone vs Single-hormone vs PLGS vs Current Care

4 arms, 3 moderate-intensity aerobic exercise sessions

End point	DH	SH	PLGS	CC	SH-DH	P^1	PLGS-DH	P^1	CC-DH	P^1
% time in hypoglycemia (CGM <70 mg/dL)										
Entire study	1.3 (1.0)	2.8 (1.7)	2.0 (1.5)	3.1 (3.5)	1.5	**<0.001**	0.7	0.044	1.8	**0.007**
Start of exercise in clinic until next meal	3.4 (4.5)	8.3 (12.6)	7.6 (8.0)	4.3 (6.8)	4.9	**0.009**	4.3	**<0.001**	0.9	0.49
% time in range (CGM 70–180 mg/dL)										
Entire study	72.9 (10.8)	74.3 (8.0)	65.2 (13.5)	63.1 (17.3)	2.4	0.44	−6.5	0.036	−8.8	**0.010**
Start of exercise in clinic until next meal	84.3 (16.7)	83.3 (16.7)	78.3 (18.9)	78.2 (26.2)	−0.7	0.85	−5.4	0.24	−5.9	0.30

Jessica R. Castle et al. Diabetes Care 2018



Spunti di riflessione

Complessità vs. semplicità: serve ancora la formazione (del paziente e del medico)?

Come valutiamo il compenso: basta guardare l'HbA1c?

Pancreas artificiale: una risorsa per tutti?

Il futuro… è terminato?

Ipertecnologia: Vantaggi e Limiti

Pro

- Tecnologia più sofisticata = miglior controllo glicemico
- L'automazione rende più libero il paziente
- Una tecnologia flessibile e regolabile risponde a molte esigenze dei pazienti (dieta, attività fisica, etc)

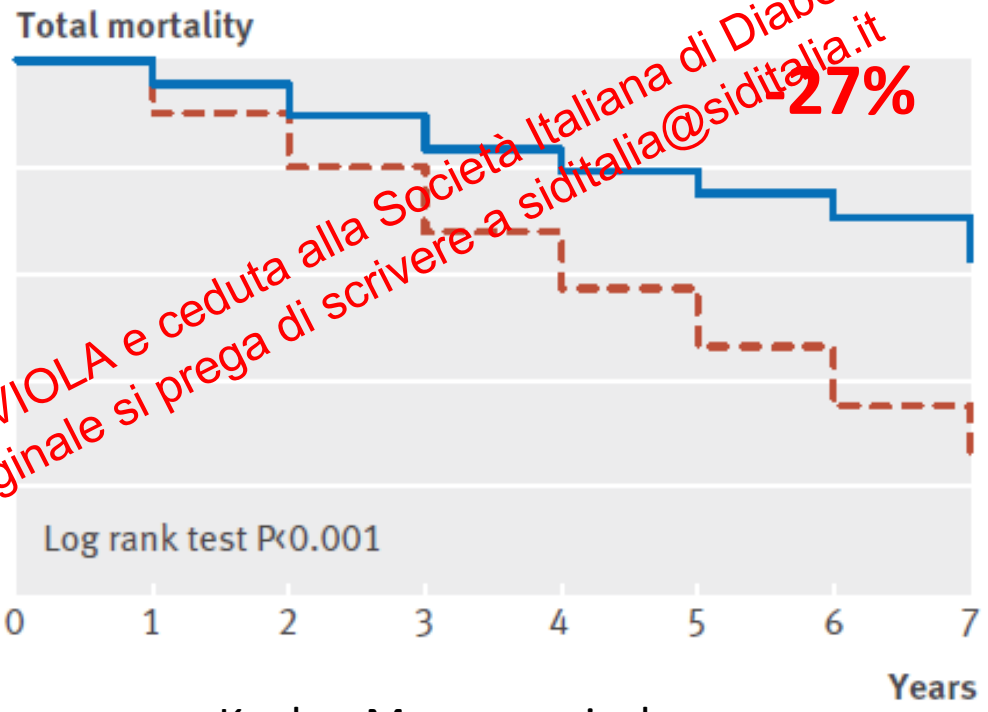
Contro

- Rischio di malfunzionamento
- Complessità di «guida» del sistema
- Ansietà di dipendenza dallo strumento
- Fastidi della tecnologia (es allarmi)
- Problemi di "cybersecurity"
- Non necessaria per alcuni pazienti

Insulin pump therapy, multiple daily injections, and cardiovascular mortality in 18168 people with type 1 diabetes:observational study

- Data from Swedish National Diabetes Registry
- 2441 type 1 DM on CSII
- 15.727 type 1 DM on MDI
- Studied from baseline to first CVD event or death
- Followed up for mean 6.8 Years

- All cause mortality reduced by 27% on CSII
- CHD mortality reduced by 45%
- Stroke and CHD mortality reduced by 42% on CSII



Kaplan-Meyer survival curves
For total mortality

Steineck I et al, BMJ 2015

Possibili ragioni per la ridotta mortalità CVD

Miglioramento della HbA1c: differenza non significativa (HbA1c 7.9±1.3 vs 8.0±1.3% ns, CSII vs MDI)

Riduzione dell'ipoglicemia: numero di pazienti con ≥ 3 eventi ipoglicemici significativamente inferiore con CSII vs MDI (p=0.03)

Riduzione della variabilità glicemica: non misurata

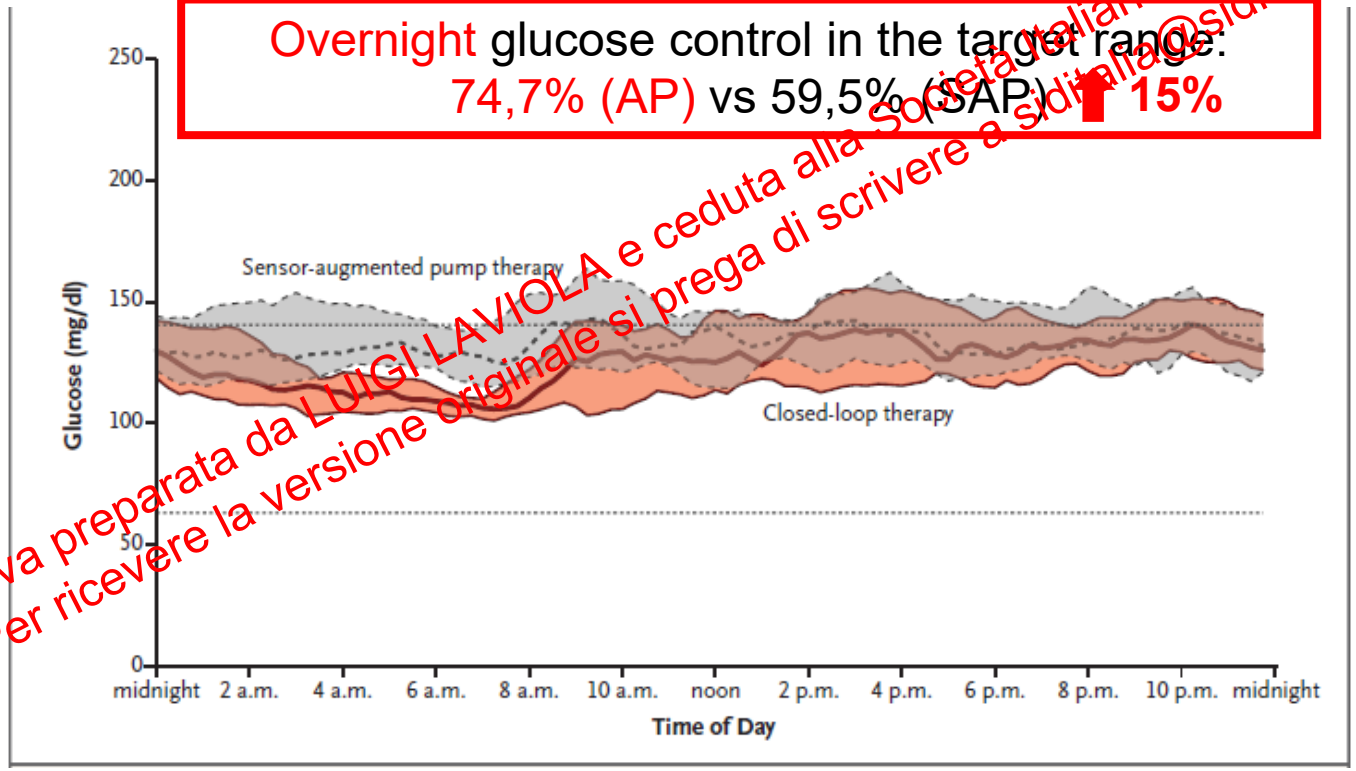
Migliore educazione del paziente in CSII (dieta, esercizio, frequenza di SMBG): non misurata

La ragione esatta per migliori outcomes con CSII non è chiara

Closed-Loop Insulin Delivery during Pregnancy in Women with Type 1 Diabetes

Zoe A. Stewart, M.D., Malgorzata E. Wilinska, Ph.D., Sara Hartnell, B.Sc., Rosemary C. Temple, M.D., Gerry Rayman, M.D., Katharine P. Stanley, M.D., David Simmons, M.D., Graham R. Law, Ph.D., Eleanor M. Scott, M.D., Roman Hovorka, Ph.D., and Helen R. Murphy, M.D.

Overnight glucose control in the target range:
74,7% (AP) vs 59,5% (SAP) ⬆ 15%



No differences in % of time below the target, in insulin doses or in adverse events

N ENGL J MED 375;7 NEJM.ORG AUGUST 18, 2016

Closed-Loop Insulin Delivery during Pregnancy in Women with Type 1 Diabetes

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Continuation phase (day and night CL)

Mean glucose level 126 mg/dl

Glucose level in the target range: 68,7%

Labor and delivery

24 before delivery: median glucose level=110 mg/d

Glucose level in the target: 86,8%; < target 0,5%

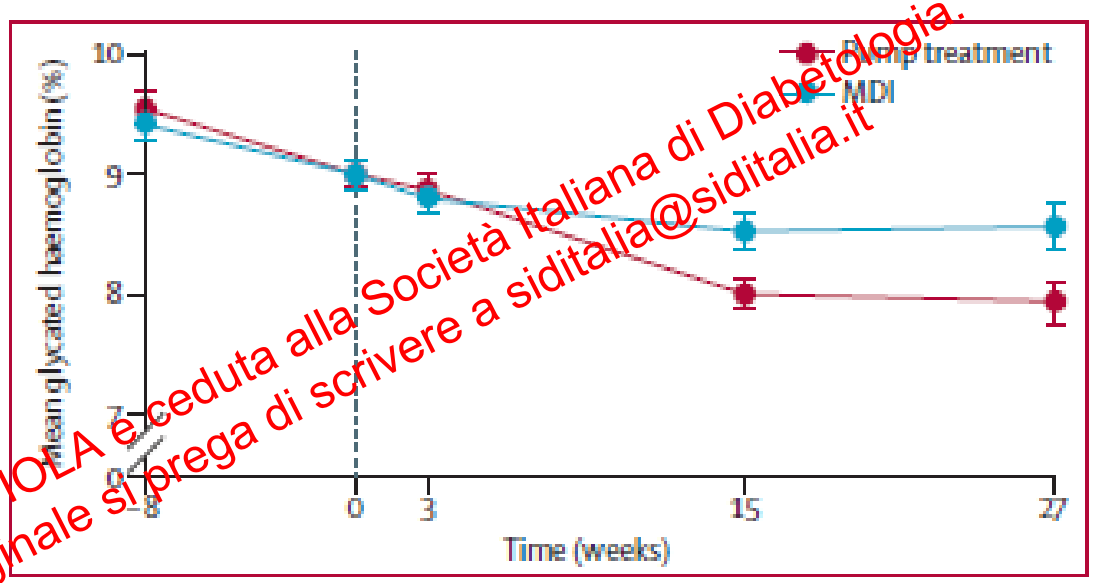
First 48 h after delivery; median glucose level 117 mg/d

Glucose level in the target: 73,7%; <target 0%

I

OpT2mise study: RCT of CSII vs. MDI in type 2 DM

- 331 type 2 DM patients on MDI
- 2-mo run-in to intensify control on MDI using standardised titration protocol
- Those with continued poor control on MDI randomised to continued MDI or CSII for 6 mo

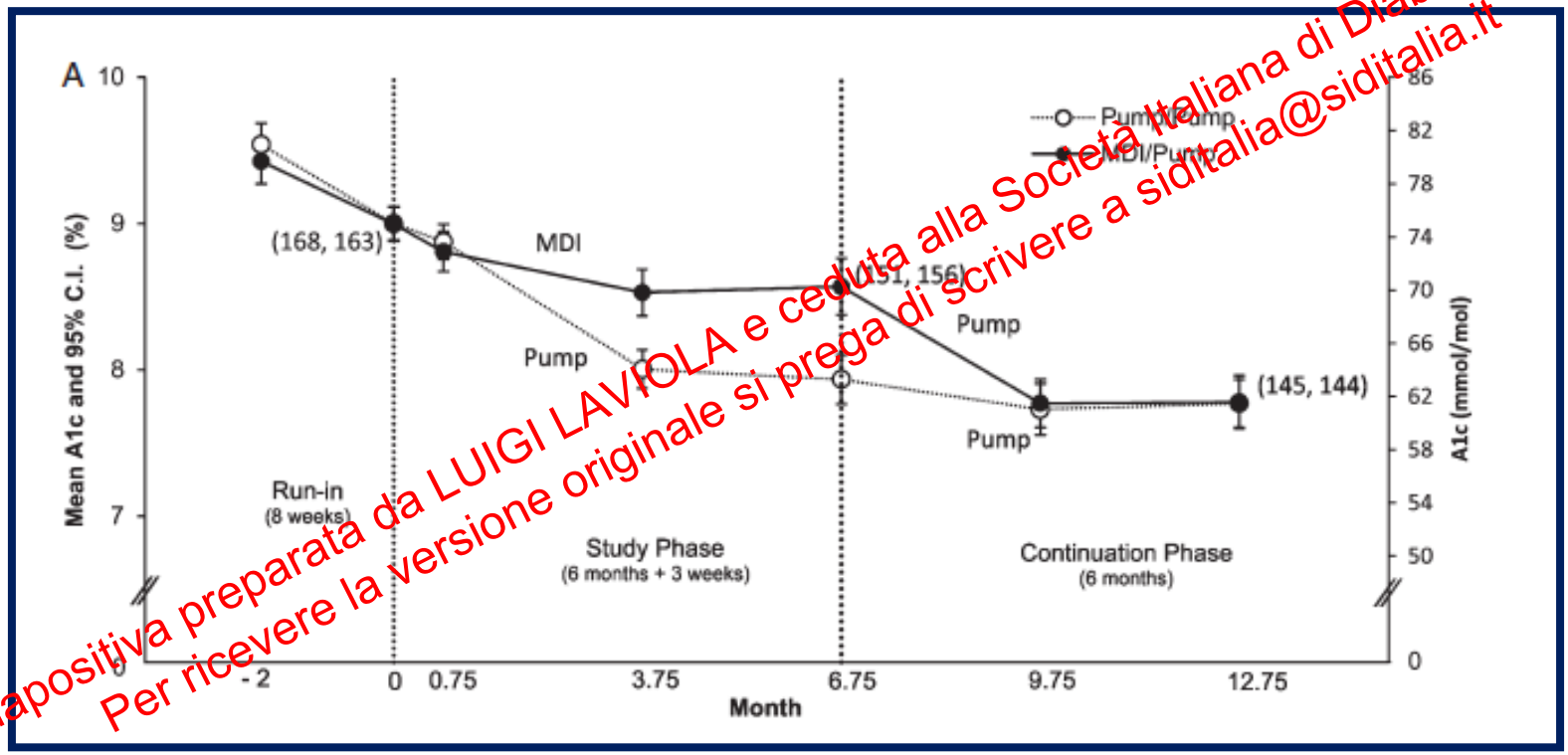


- Baseline HbA1c ≥8.0 and ≤12%
- Baseline insulin dose (0.7-1.8 U/kg)

- Final HbA1c significantly lower on CSII vs. MDI (mean final difference -0.7%, p<0.0001)
- In those with highest baseline (9.3-11.5%) HbA1c difference was -1.1%
- 20% less insulin used on CSII
- No increased hypoglycaemia or weight gain on CSII

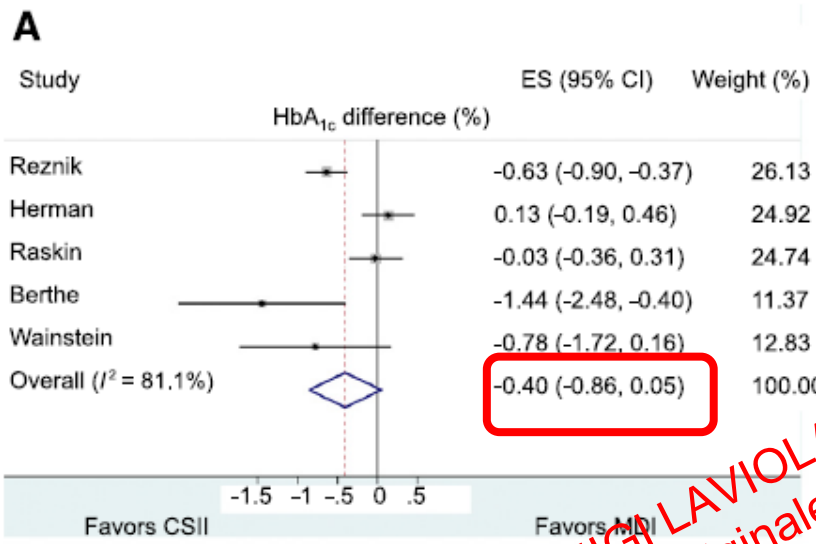
Reznik Y et al ,
Lancet 2014; 384: 1265-72

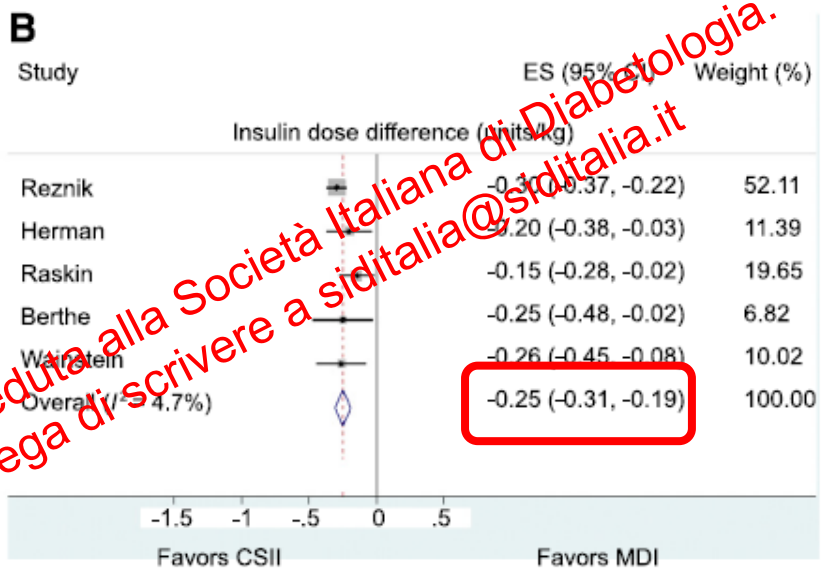
Sustained Efficacy of CSII in Continuation Phase of OpT2mise Trial

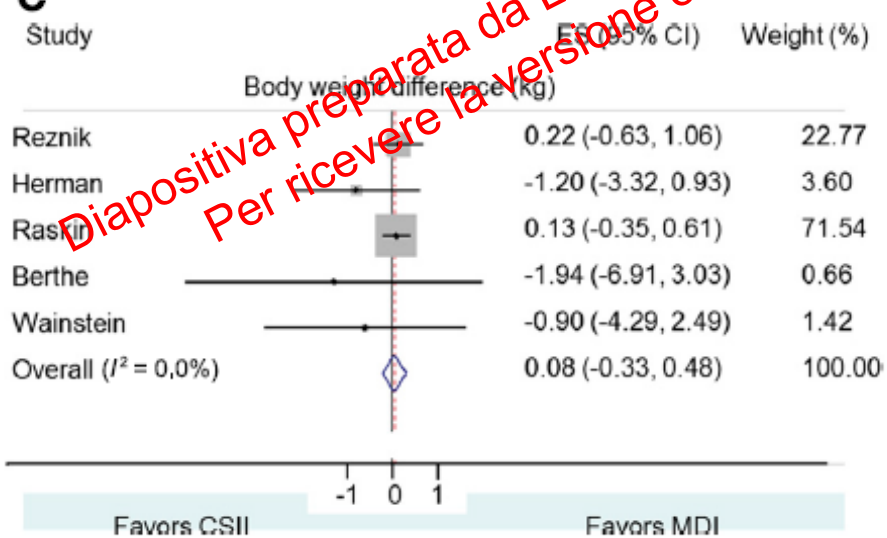


Aronson R et al. Diabet Obes Metab 2016; 18: 500–507.

CSII Versus MDI in T2DM: Individual Patient Data Meta-analysis and Meta-regression of RCTs





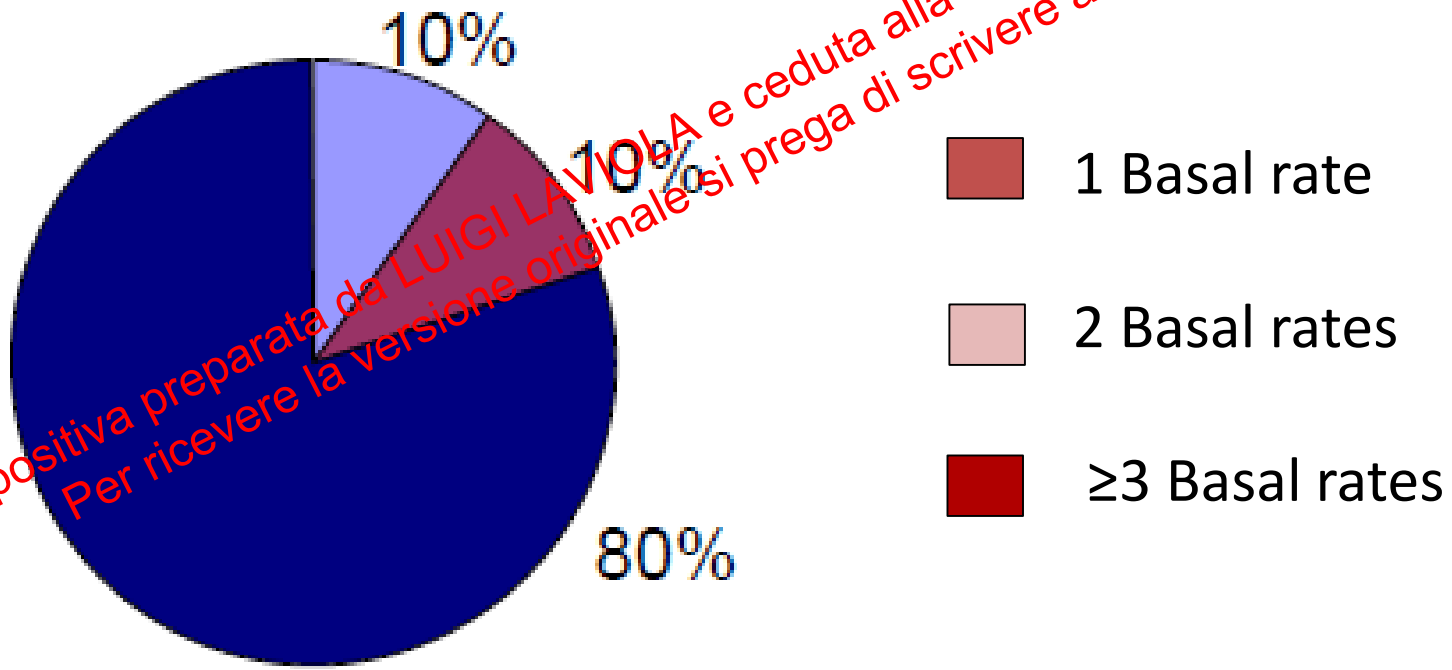


287 MDI
303 CSII

Pickup JC et al, Diabetes Care 2017

Most patients with type 2 diabetes can be managed on CSII with one basal rate throughout the 24 hours

- T2DM switched from MDI to CSII over 16 weeks (n = 21)
- Mean HbA1c: 8.5 → 7.4% (p <0.001)



Edelman SV et al. Diabet Technol Thera 2010; 12: 627-633

Il Futuro della CSII nel Diabete Tipo 2

- **Pompe più piccole e più facili da usare**

- **Procedure della CSII più semplici**
  - velocità basale fissa per ogni persona
  - numero limitato di opzioni di basale tra i pazienti
  - somministrazione semplice del bolo

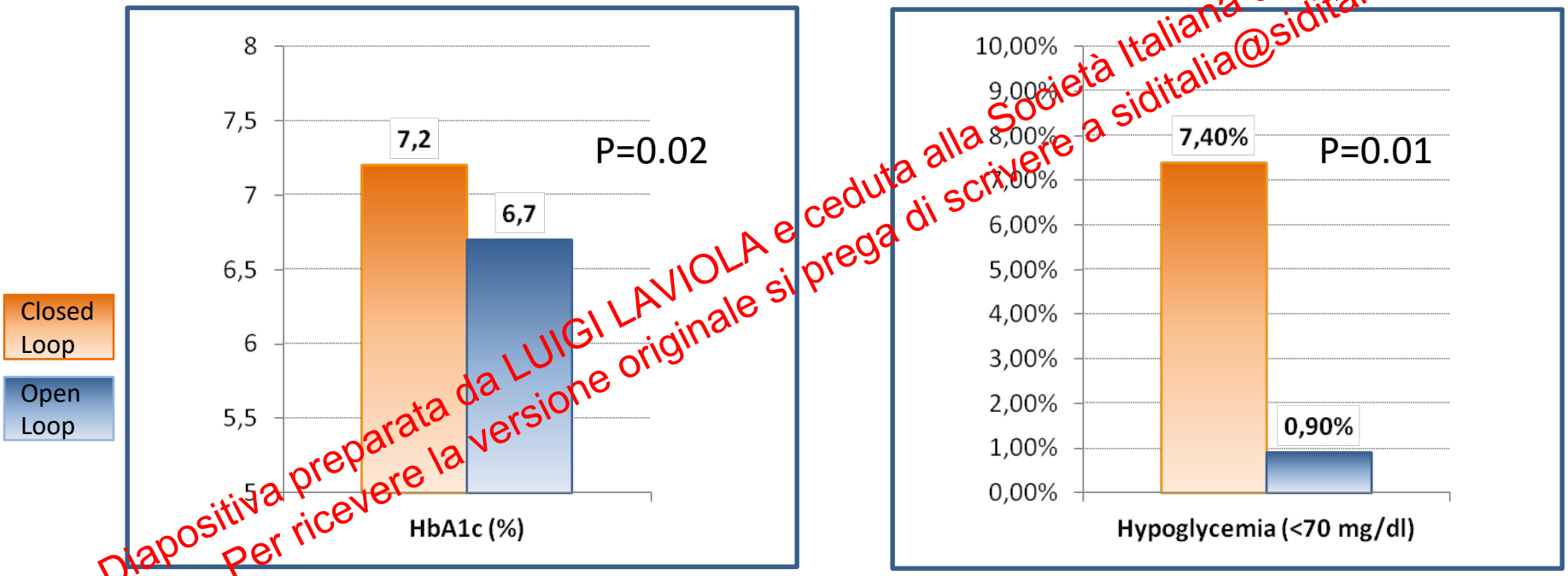
- **Pompe più economiche**

Problemi della CSII nel diabete di tipo 2

- I pazienti possono essere più anziani, con molteplici patologie, minore manualità, visione compromessa, capacità cognitive compromesse (in alcuni), nessun partner disponibile per l'assistenza (in alcuni)
  - –Molti non saranno in grado o non vorranno affrontare la relativa complessità della CSII tradizionale
- Grande numero di potenziali pazienti di tipo 2 come candidati
  - Problemi organizzativi (richiesta di formazione e di personale)
  - -problemi economici (costo elevato delle pompe tradizionali)

Outcomes were Related to System Use

Among those who used the system > 70% of the time



Kovatchev B et al, Diabetes Technol Therap, 2016

Large-Scale Trial

University of Virginia
Harvard University
Mount Sinai School of Medicine
Mayo Clinic
Barbara Davis Diabetes Center
Stanford University
William Sansum Diabetes Center
Academic Medical Center Amsterdam
University of Montpellier
University of Padova
Coordinated by the Jaeb Center for Health Research

Design:

✓ **N=240** participants **in 6-month** RCT comparing Control-to-Range vs. SAP

Outcomes:

✓ HbA1c
✓ Incidence of hypoglycemia

Objectives:

✓ Establish closed-loop control as a viable treatment for type 1 diabetes;
✓ Generate safety and efficacy data satisfying requirements by regulatory agencies;
✓ Demonstrate clinical effectiveness to facilitate reimbursement.

Non-HbA1c Glucose Metrics

Glycemic metrics*,†	
HbA_{1c}	If intervention period ≥3 months
Mean CGM glucose	
% CGM time <50 mg/dL (<2.8 mmol/L)	
% CGM time <60 mg/dL (<3.3 mmol/L)	
% CGM time <70 mg/dL (<3.9 mmol/L)	
% CGM time 70–140 mg/dL (3.9–7.8 mmol/L)	
% CGM time 70–180 mg/dL (3.9–10.0 mmol/L)	
% CGM time >180 mg/dL (>10.0 mmol/L)	
% CGM time >250 mg/dL (>13.9 mmol/L)	
% CGM time >300 mg/dL (>16.7 mmol/L)	
SD and coefficient of variation of CGM values	SD is much more dependent on the mean than coefficient of variation
Fasting blood glucose, mg/dL (mmol/L)	If available, depending on study design; CGM glucose at 06:00 can be taken as proxy

Maahs DM et al. Diabetes Care 2016