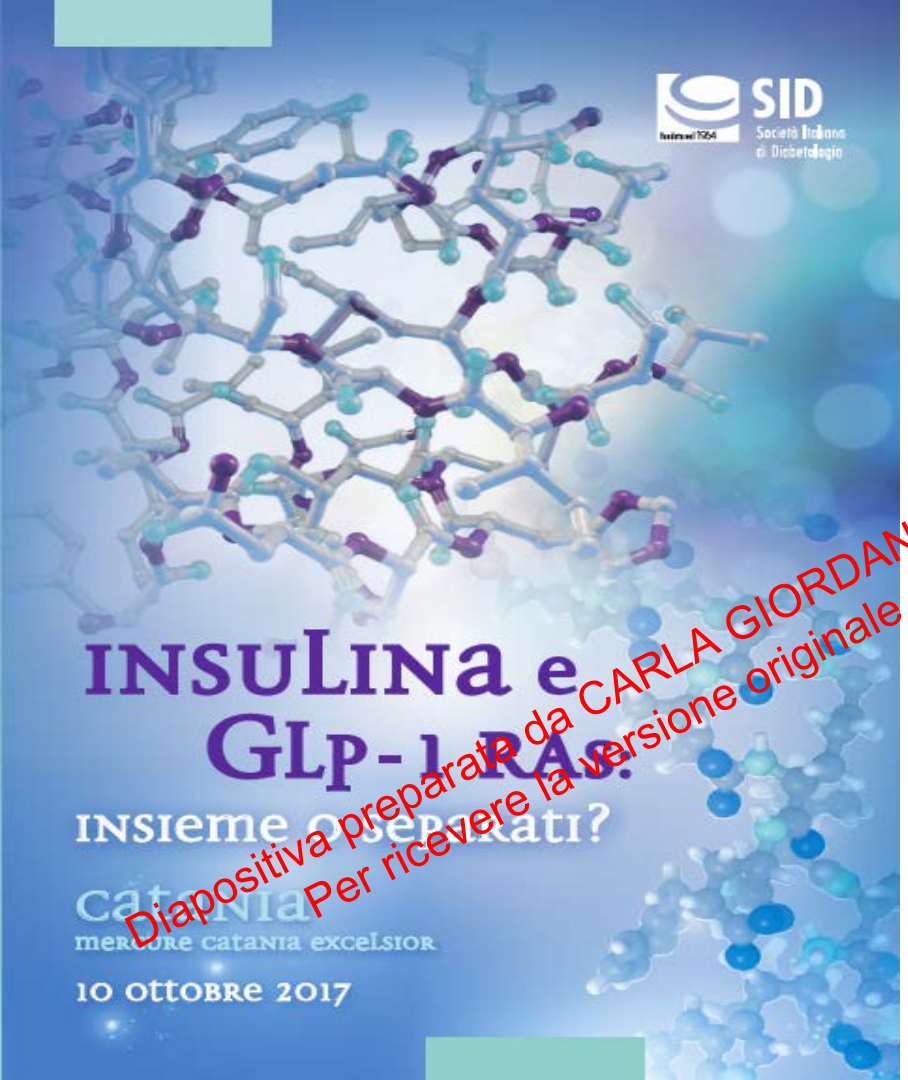



# TERAPIA DI COMBINAZIONE CON INSULINA



**Prof. CARLA GIORDANO**

**Insegnamento di Endocrinologia**

**UOC di ENDOCRINOLOGIA E MM. METABOLICHE, Di.Bi.M.I.S.**

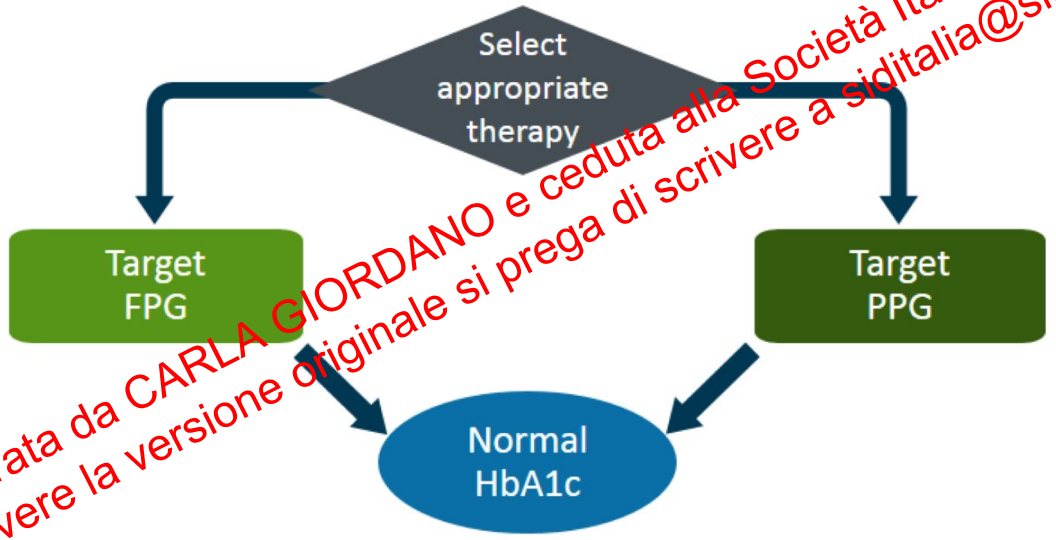
**AOUP PAOLO GIACCONE**

**UNIVERSITÀ DEGLI STUDI DI PALERMO**

azienda ospedaliera universitaria policlinico paolo giaccone di palermo

policlinico.pa.it

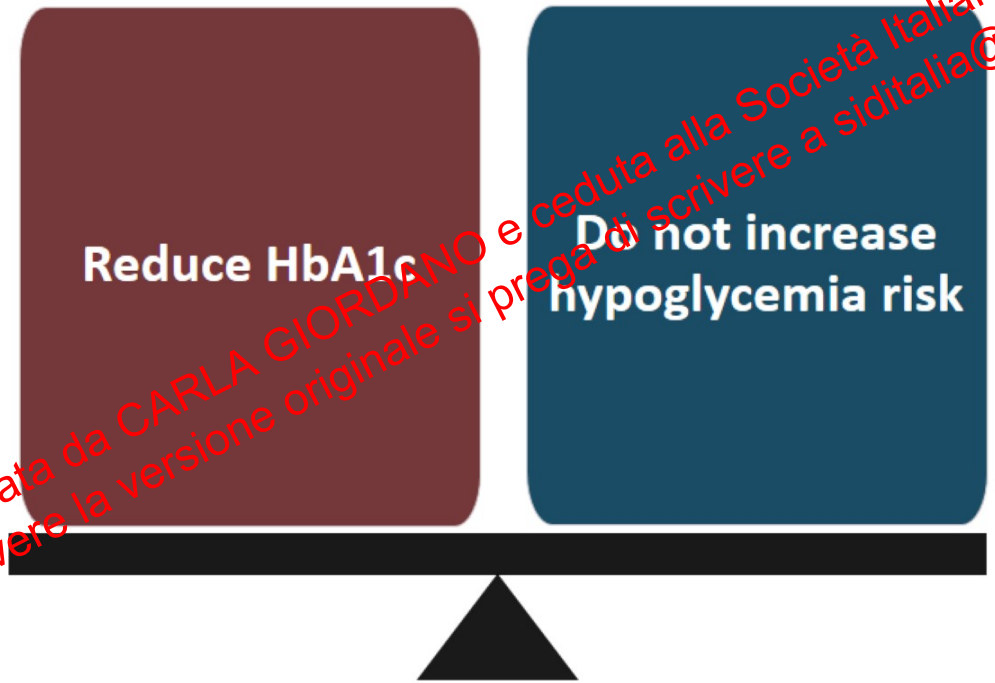
# Personalizing Therapy According to Patient's Glucose Profile






ADA. *Diabetes Care*. 2017;40(Suppl 1):S1-S135.
IDF website.

# Therapeutic Objectives in Diabetes Management



# Biochemical and Physiological Actions of Insulin

## Biochemical Actions

- ↑ Cell permeability to glucose (in muscle and adipose tissue)
- ↑ Glycolysis
- ↑ Glycogen synthesis
- ↑ Triacylglycerol synthesis
- ↓ Gluconeogenesis
- ↓ Lipolysis
- ↓ Protein degradation
- ↑ Protein, DNA, and RNA synthesis

## Physiological Actions

- Signals fed state
- ↓ BG level
- ↑ Fuel storage
- ↑ Cell growth and differentiation



Newsholme EA, et al. *Exp Clin Endocrinol Diabetes*. 2001;109(Suppl 2):S122-S134.
Dimitriadis G, et al. *Diabetes Res Clin Pract*. 2011;93(Suppl 1):S52-S59.

# Good glycaemic control matters

## Impact on diabetes-related complications and treatment cost

**Good glycaemic control**

**UKPDS**

Reduces diabetes-related complications[1]

**1 %** reduction in mean $HbA_{1c}$

**37 %** reduction in microvascular complications

**14 %** reduction in myocardial infarction

**21 %** reduction in diabetes-related mortality

**Retrospective database analysis**

Reduces total diabetes-related costs[2]

Patients with $HbA_{1c}$ ≤7% continuously for 1 year

**25 %** lower overall diabetes-related treatment costs i.e.:

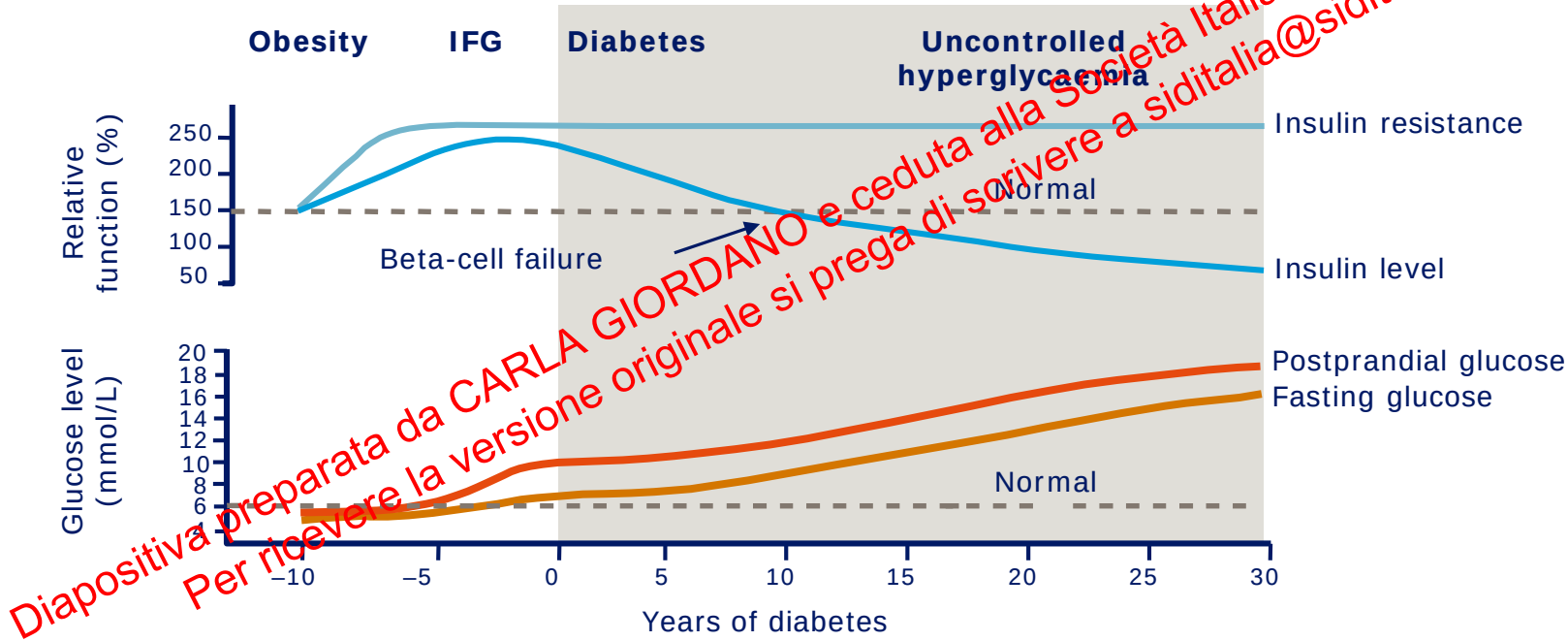
- **22 %** lower diabetes medical costs
- **28 %** lower diabetes pharmacy costs



UKPDS, United Kingdom Prospective Diabetes Study

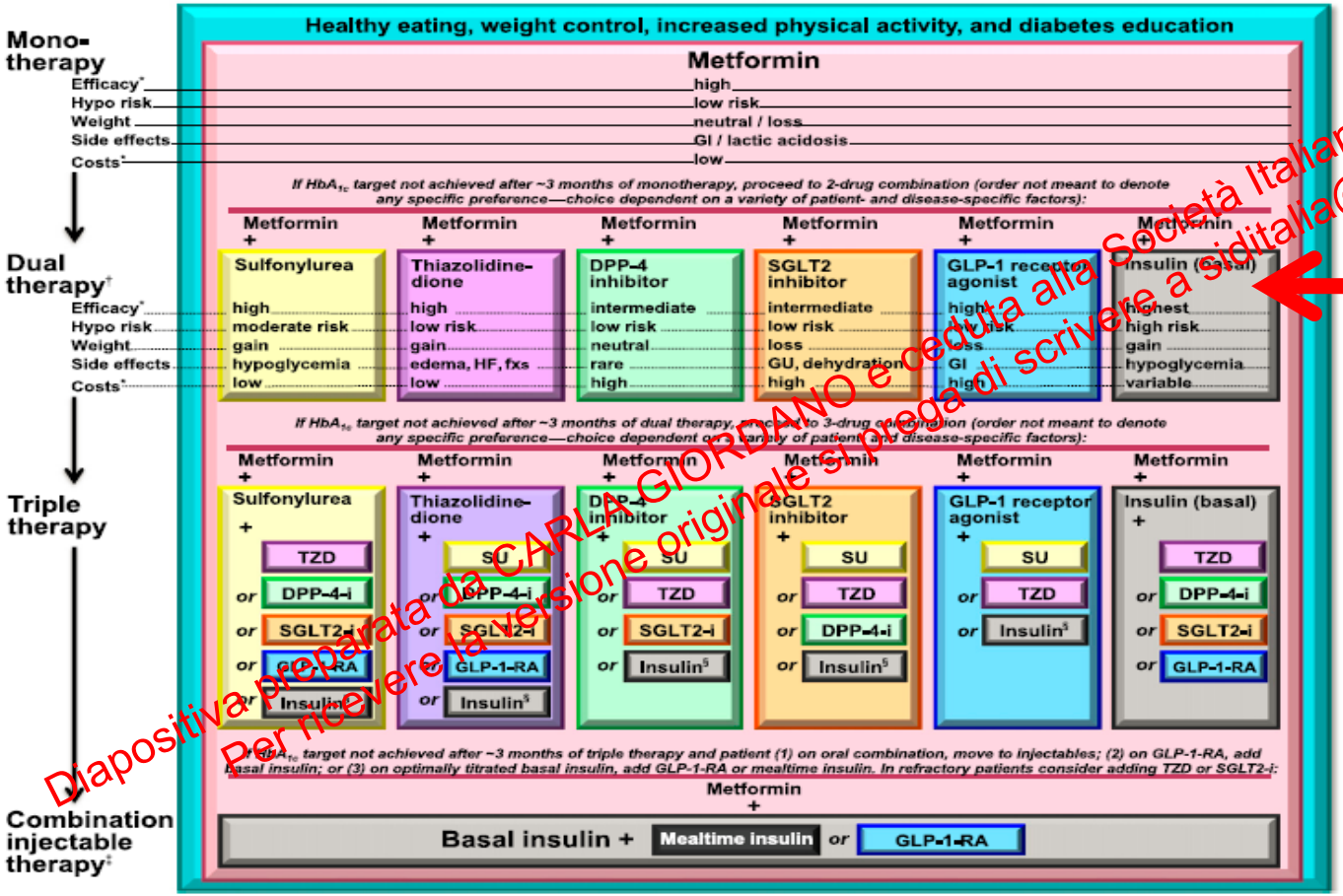
1. Stratton *et al. BMJ* 2000;321:405–12. 2. Shetty *et al. J Manag Care Pharm* 2005;11:559–64

# Disease progression: insulin replacement therapy becomes necessary in type 2 diabetes





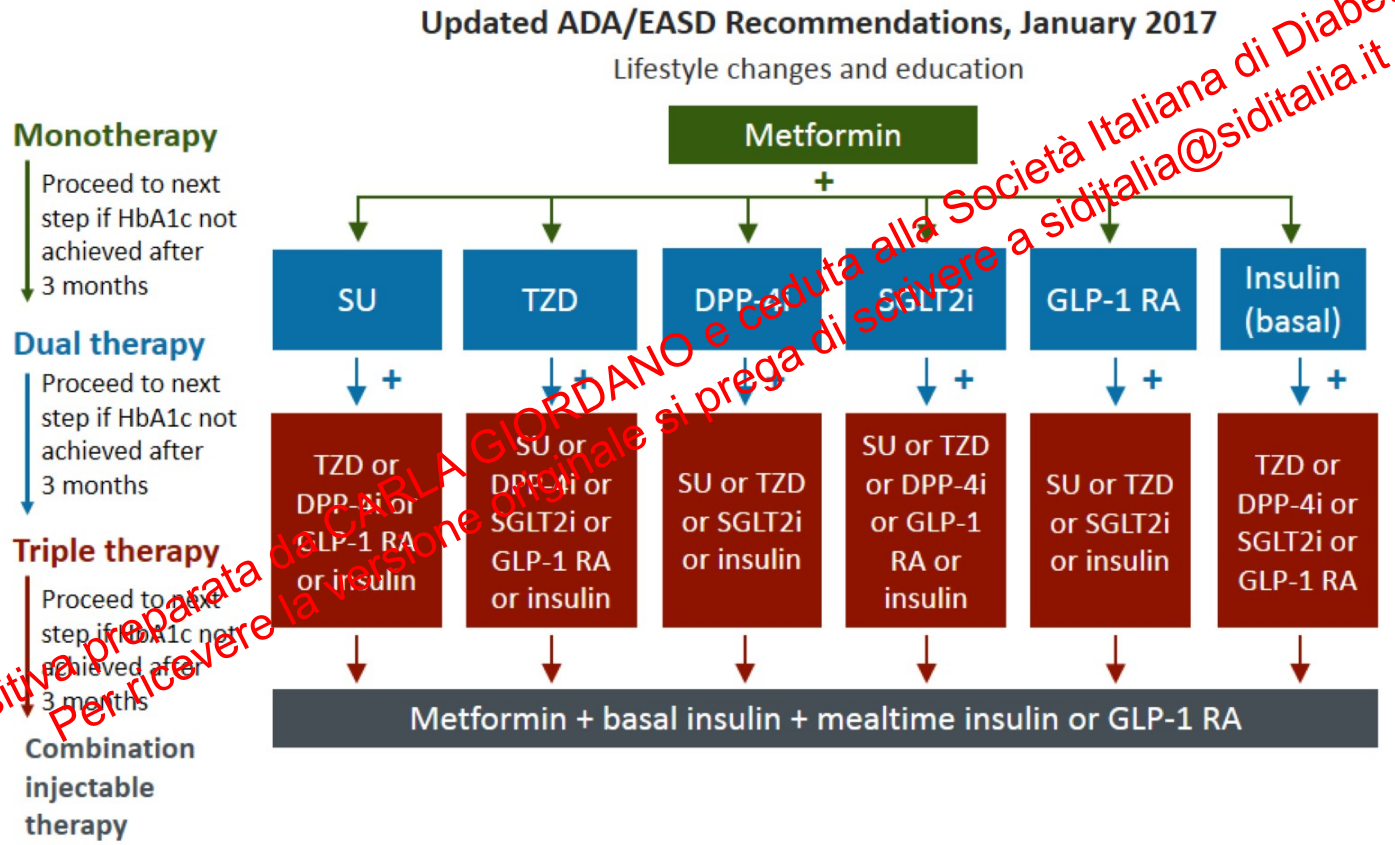

IFG, impaired fasting glucose
Adapted from Bergenstal *et al. Endocrinology.* Philadelphia, PA: WB Saunders Co; 2001:821–35






Diabetes Care 2015;38:140–149 | DOI: 10.2337/dc14-2441

# Glucose-Lowering Therapy Options




ADA. *Diabetes Care*. 2017;40(Suppl 1):S64-S74.

**Table 1** Characteristics of Current Antidiabetes Medications

| Class | Examples | Primary action | Hypoglycemic potential[a] | Weight gain | Adverse events | Cost |
|---|---|---|---|---|---|---|
| *Oral* | | | | | | |
| Biguanide | Metformin | Decrease hepatic glucose production | Low | None | Gastrointestinal symptoms, lactic acidosis | Low |
| Sulfonylurea | Glimepiride, glipizide | Increase insulin secretion | Moderate | Yes | Gastrointestinal symptoms, diarrhea, rashes | Low |
| Meglitinides | Nateglinide, repaglinide | Increase insulin secretion | Moderate | Yes | Respiratory infections, gastrointestinal symptoms | High |
| Thiazolidinedione | Pioglitazone | Increase insulin sensitivity | Low | Yes | Edema, may cause or exacerbate heart failure, bone fractures, bladder cancer | Low |
| α-Glucosidase inhibitor | Acarbose, miglitol | Slow intestinal carbohydrate absorption | Low | None | Gastrointestinal symptoms | Moderate |
| DPP-4 inhibitor | Sitagliptin, saxagliptin, linagliptin, vildagliptin (EU only), alogliptin | Increase insulin secretion<br>Decrease glucagon secretion | Low | None | Upper respiratory tract symptoms, urticaria, angioedema, acute pancreatitis | High |
| SGLT2 inhibitors | Dapagliflozin (EU only), canagliflozin (US only) | Increase urinary excretion of glucose | Low | Reduction | Genital and urinary tract infections | High |
| Bile acid sequestrant | Colesevelam | Unknown | Low | None | Gastrointestinal symptoms | High |
| Dopamine-2 agonist | Bromocriptine (US only) | Modulate central regulation of metabolism<br>Increase insulin sensitivity | Low | None | Dizziness/syncope, nausea, fatigue | High |

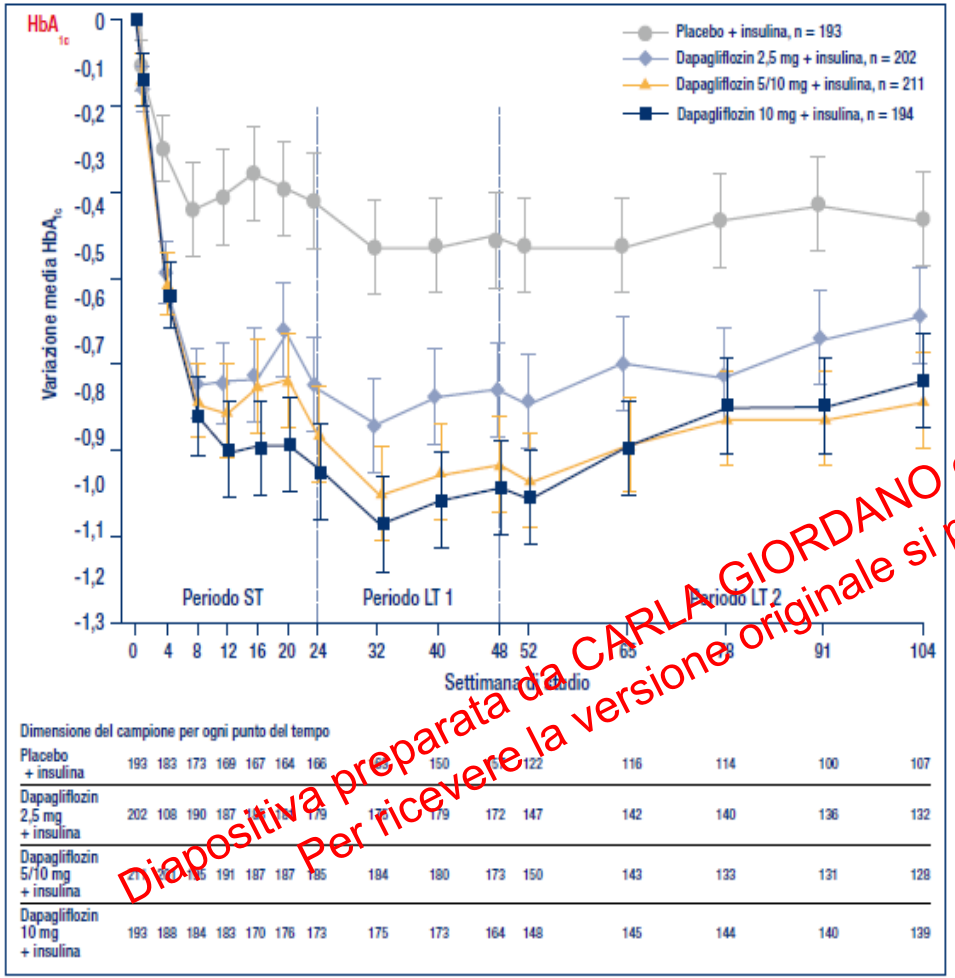
**Table 1** continued

| Class | Examples | Primary action | Hypoglycemic potential[a] | Weight gain | Adverse events | Cost |
|---|---|---|---|---|---|---|
| *Parenteral* | | | | | | |
| GLP-1 receptor agonist | Exenatide, exenatide extended release, liraglutide | Increase insulin secretion<br>Decrease glucagon secretion<br>Slow gastric emptying<br>Increase satiety | Low | Reduction | Gastrointestinal symptoms, acute pancreatitis | High |
| Amylin analogue | Pramlintide | Decrease glucagon secretion<br>Slow gastric emptying<br>Increase satiety | Low | Reduction | Gastrointestinal symptoms, nausea | High |
| Insulin | Insulin, various analogues | Increase glucose disposal<br>Decrease hepatic glucose production | Moderate to severe | Yes | Allergic reaction, hypokalemia, injection site reactions | Low to high |

Data from Inzucchi et al. [32], Rodbard et al. [52] and Whaley et al. [53]

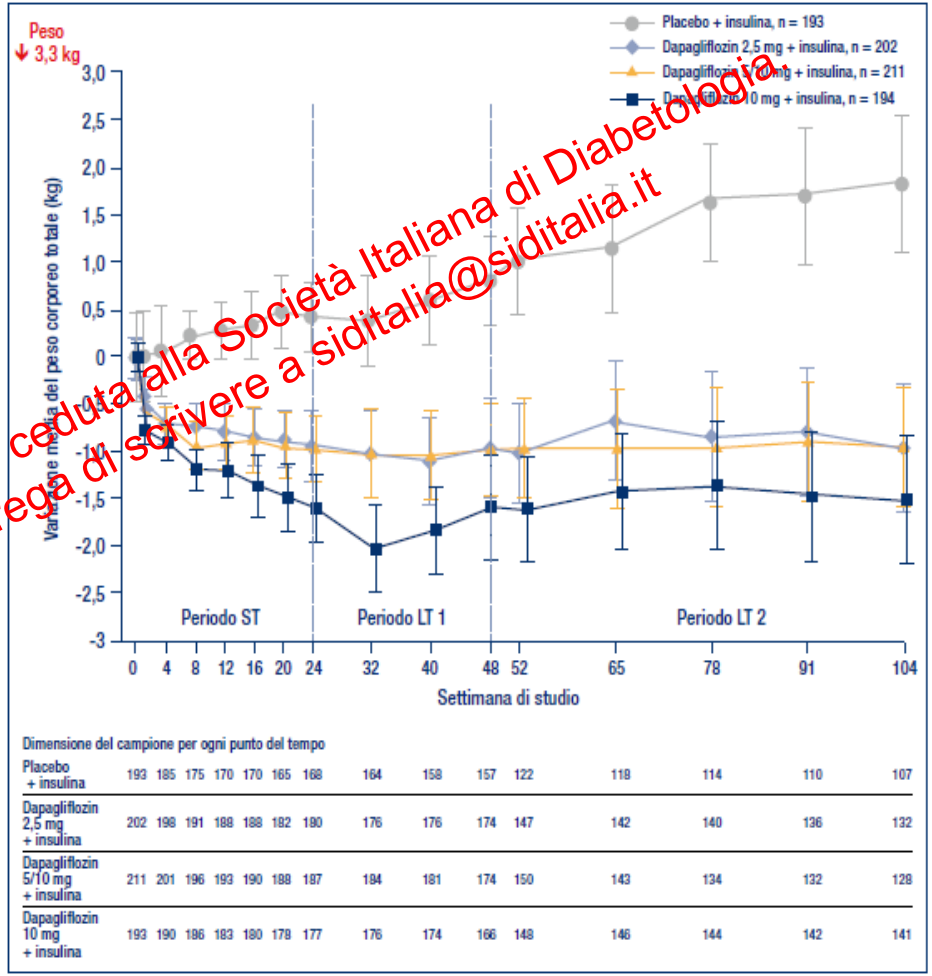
*DPP-4* dipeptidyl peptidase-4, *EU* European Union, *GLP-1* glucagon-like peptide-1, *SGLT2* sodium-glucose cotransporter 2, *US* United States

[a] Hypoglycemic potential when used as monotherapy. Incidence of hypoglycemia may be higher when combined with sulfonylurea or insulin




| Dimensione del campione per ogni punto del tempo | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Placebo + insulina | 193 | 183 | 173 | 169 | 167 | 164 | 166 | | 150 | | 122 | 116 | 114 | 100 | 107 |
| Dapagliflozin 2,5 mg + insulina | 202 | 198 | 190 | 187 | 184 | 181 | 179 | 176 | 179 | 172 | 147 | 142 | 140 | 136 | 132 |
| Dapagliflozin 5/10 mg + insulina | 211 | 201 | 196 | 191 | 187 | 187 | 185 | 184 | 180 | 173 | 150 | 143 | 133 | 131 | 128 |
| Dapagliflozin 10 mg + insulina | 193 | 188 | 184 | 183 | 170 | 176 | 173 | 175 | 173 | 164 | 148 | 145 | 144 | 140 | 139 |

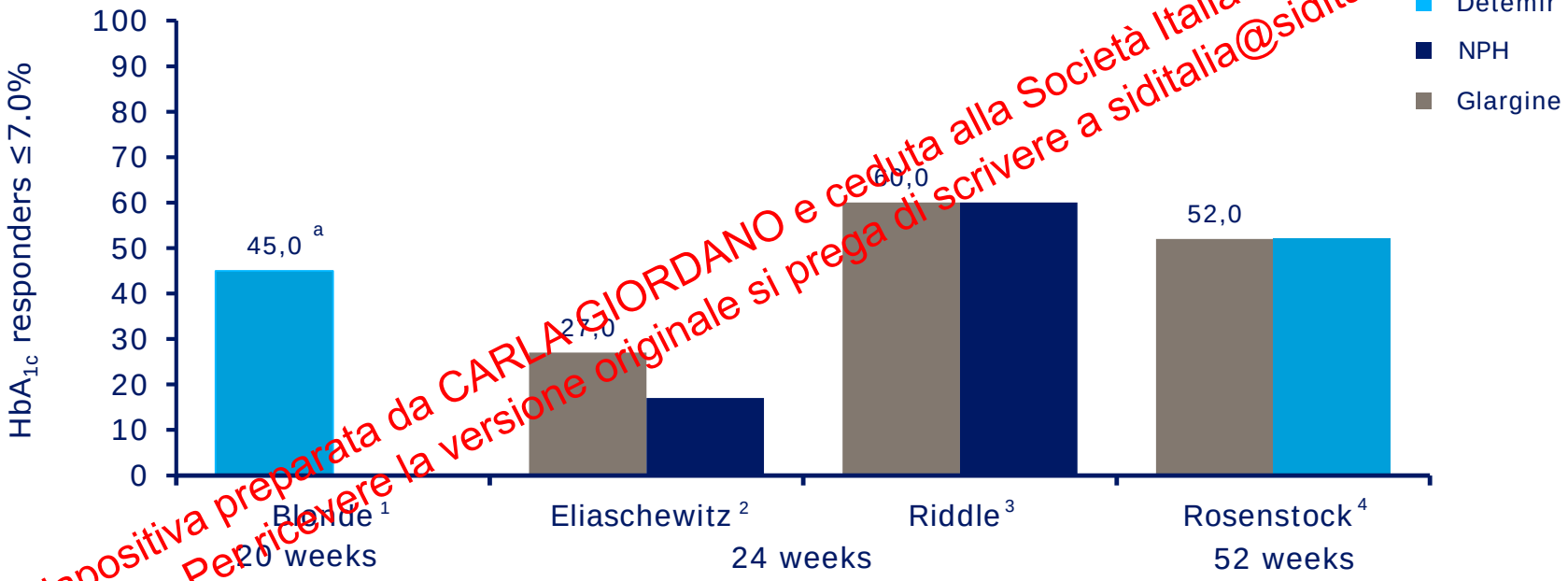
**Figura 4.**
Efficacia di dapagliflozin sull'$HbA_{1c}$ e sul peso corporeo nello studio di add-on a insulina (da Wilding et al., 2014, mod.).




| Dimensione del campione per ogni punto del tempo | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Placebo + insulina | 193 | 185 | 175 | 170 | 170 | 165 | 168 | 164 | 158 | 157 | 122 | 118 | 114 | 110 | 107 |
| Dapagliflozin 2,5 mg + insulina | 202 | 198 | 191 | 188 | 188 | 182 | 180 | 176 | 176 | 174 | 147 | 142 | 140 | 136 | 132 |
| Dapagliflozin 5/10 mg + insulina | 211 | 201 | 196 | 193 | 190 | 188 | 187 | 184 | 181 | 174 | 150 | 143 | 134 | 132 | 128 |
| Dapagliflozin 10 mg + insulina | 193 | 190 | 186 | 183 | 180 | 178 | 177 | 176 | 174 | 166 | 148 | 146 | 144 | 142 | 141 |

**Figura 4.**
Efficacia di dapagliflozin sull'$HbA_{1c}$ e sul peso corporeo nello studio di add-on a insulina (da Wilding et al., 2014, mod.).

# Clinical trials demonstrate that many patients do not achieve glycaemic control despite a treat-to-target approach






[a] HbA$_{1c}$ responders <7% are reported for combined treatment target groups of FPG = 3.9–5.0 mmol/L and FPG = 4.4–6.1 mmol/L

1. Blonde et al. Diabetes Obes Metab 2009;11:623-631
2. Eliaschewitz et al. Arch Med Res 2006;37:495-501
3. Riddle et al. Diabetes Care 2003;26:3080–3086
4. Rosenstock et al. Diabetologia 2008: 51:408-416

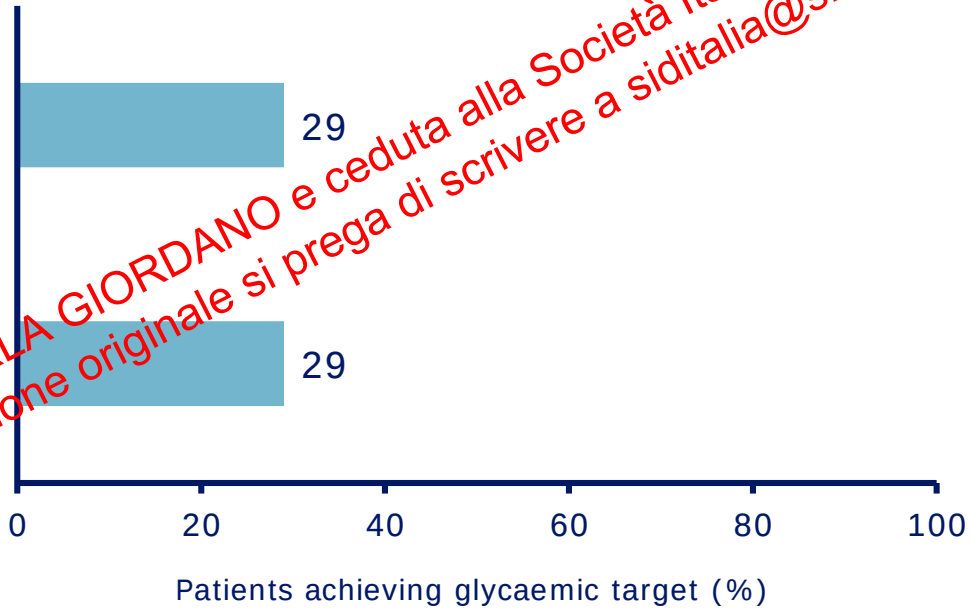
# In clinical practice many patients do not achieve glycaemic target after basal insulin initiation

**2-year retrospective cohort study of basal insulin initiation in the US (n=14,458)[1]**

Baseline $HbA_{1c}$: 8.6%

**3-year retrospective audit of basal insulin initiation in the UK (n=516)[2]**

Baseline $HbA_{1c}$: 8.3%



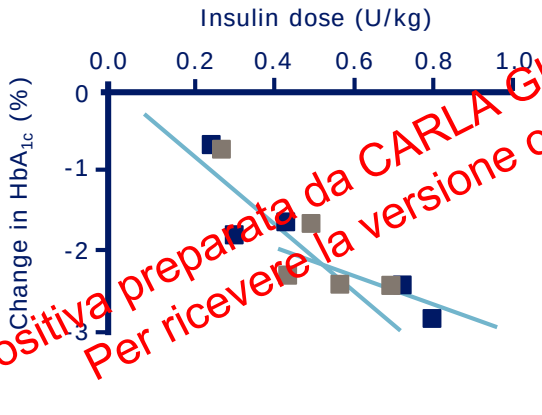



1. Curtis & Lage. J Med Econ 2014;17:21–31
2. Dale et al. Prim Care Diabetes 2010;4:85–9

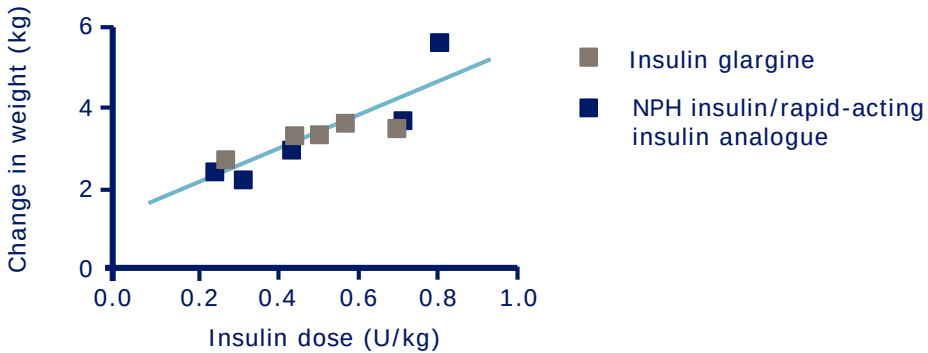
# The effect of high insulin doses on $HbA_{1c}$ reduction and weight gain

- At insulin doses above 0.5 U/kg, the magnitude of the $HbA_{1c}$ reduction decreases and total weight gain continues to increase

**Change in $HbA_{1c}$ by insulin dose**




**Change in body weight by insulin dose**





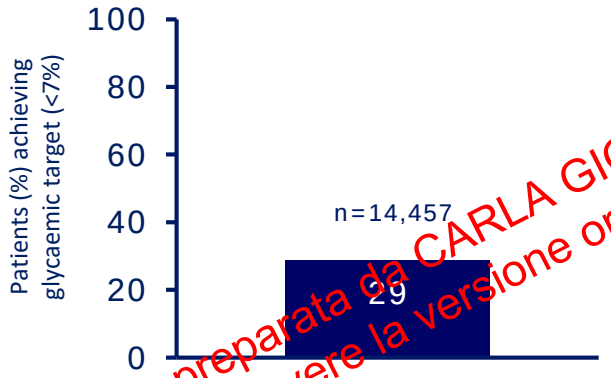

NPH, neutral protamine Hagedorn

Monnier & Colette. Diabetes Metab 2006;32:7–13

# Many patients do not achieve $HbA_{1c}$ <7% after basal insulin initiation and further intensification is often delayed

## Retrospective clinical practice data

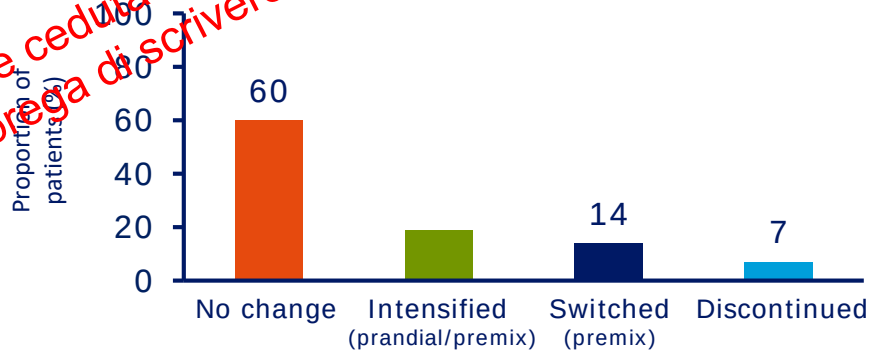
### Patients with $HbA_{1c}$ <7% 2 years following basal insulin initiation in US[1]




| | |
|---|---|
| Baseline $HbA_{1c}$ | 8.6% |
| Follow-up | 2 years |

### Change in basal insulin regimen in UK[2]

3-year follow-up of patients on basal insulin (n=3,185)



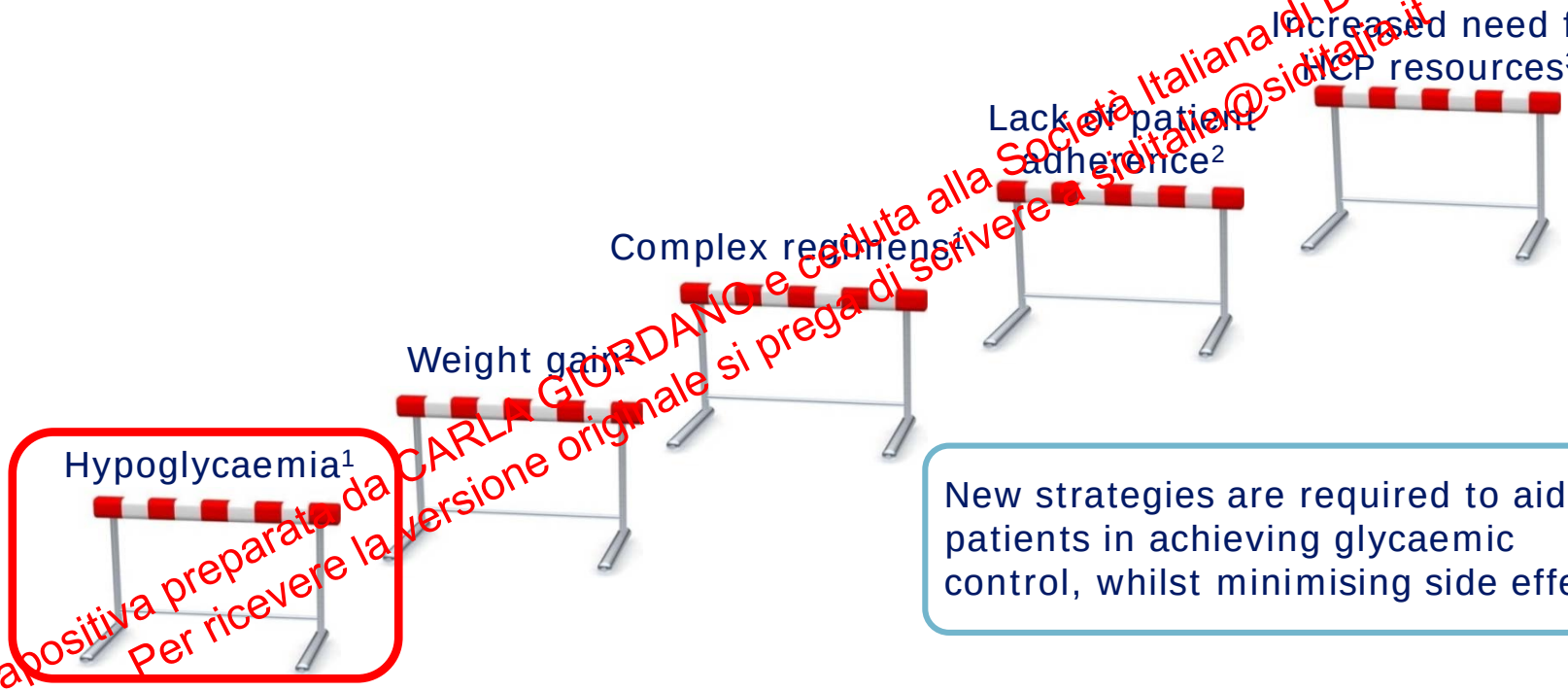

| | | | | |
|---|---|---|---|---|
| $HbA_{1c}$ at therapy change | N/A | 9.2/9.3% | 9.5% | 8.0% |
| 3-year $HbA_{1c}$ | 8.1% | 8.6/8.7% | 8.5% | 7.9% |



N/A, not applicable

1. Curtis & Lage. *J Med Econ* 2014;17:21–31; 2. Blak *et al. Diabet Med* 2012;29:e13–20

# Reasons for lack of insulin intensification




New strategies are required to aid patients in achieving glycaemic control, whilst minimising side effects



HCP, healthcare provider

1. Kunt & Snoek. *Int J Clin Pract* 2009;63(Suppl. 164):6–10; 2. Vijan *et al. J Gen Intern Med* 2005;20:479–82;
3. Cuddihy *et al. Diabetes Educ* 2011;37:111–23

# Glycemic control and microvascular complications in T2DM

## Results of the DCCT

**The Effect of Intensive Treatment of Diabetes on the Development and Progression of Long-Term Complications in Insulin-Dependent Diabetes Mellitus**

*The Diabetes Control and Complications Trial Research Group*

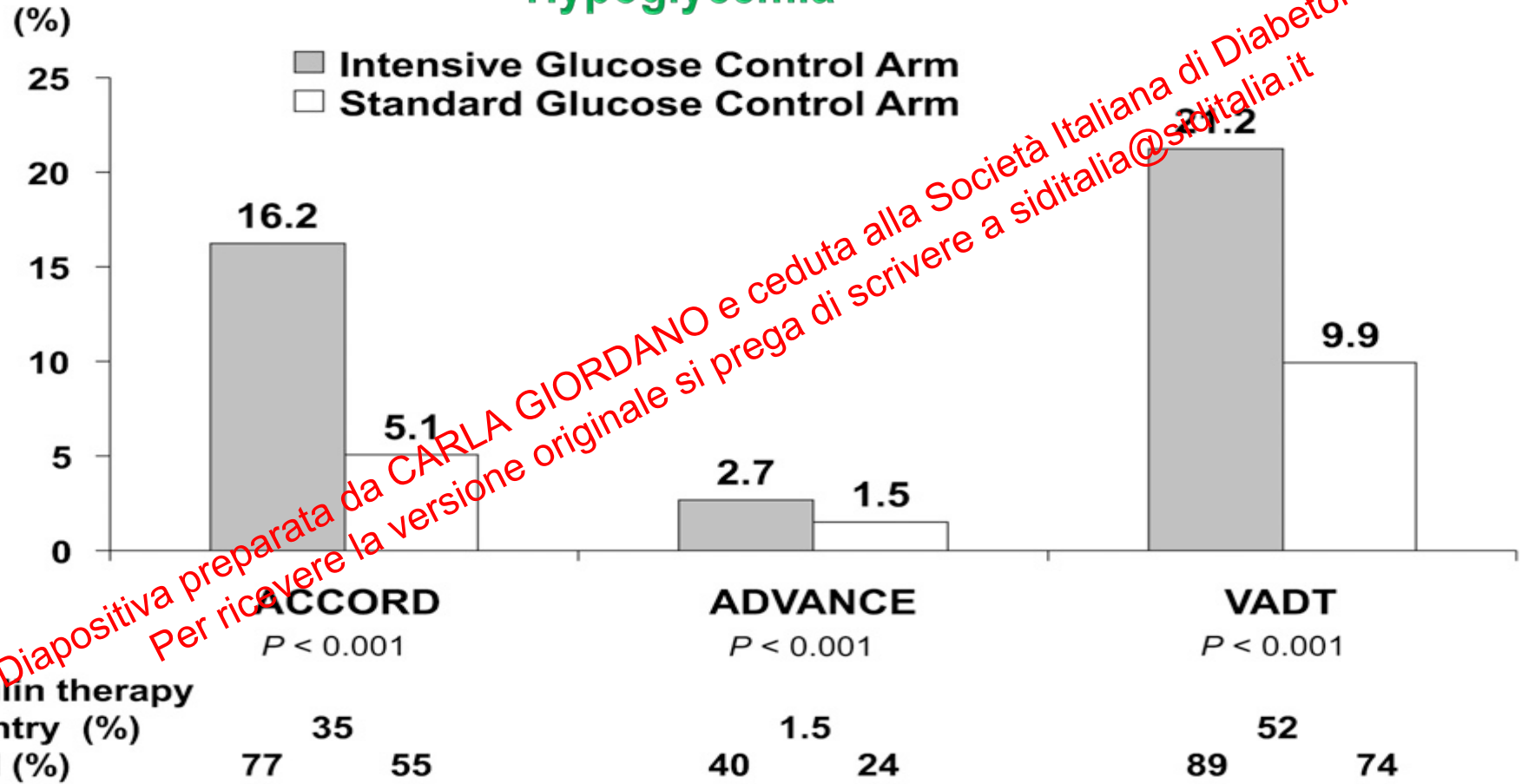
Trattamento insulinico intensivo riduce:

- ✓del 39% l'incidenza di microalbuminuria
- ✓del 75% l'incidenza di retinopatia
- del 60% lo sviluppo di neuropatia
- del 31% l'incidenza di neuropatia vegetativa



DCCT Research Group. Diabetes 1997; 46: 271

# ACCORD, ADVANCE and VADT
## Hypoglycemia



# The relationship between glycaemic variability and hypoglycaemia is established

DIABETES TECHNOLOGY & THERAPEUTICS
Volume 14, Number 11, 2012
© Mary Ann Liebert, Inc.
DOI: 10.1089/dia.2012.0099

DTT
Diabetes Technology & Therapeutics

*ORIGINAL ARTICLE*

## Rate of Hypoglycemia in Insulin-Treated Patients with Type 2 Diabetes Can Be Predicted from Glycemic Variability Data

Yongming Qu, Ph.D.,[1] Scott J. Jacober, D.O.,[1] Qianyi Zhang, Ph.D.,[1] Linda L. Wolka, B.S.,[1]* and J. Hans DeVries, M.D., Ph.D.[2]

PRIMARY CARE DIABETES (2015)


Original research

## Relationships among different glycemic variability indices obtained by continuous glucose monitoring

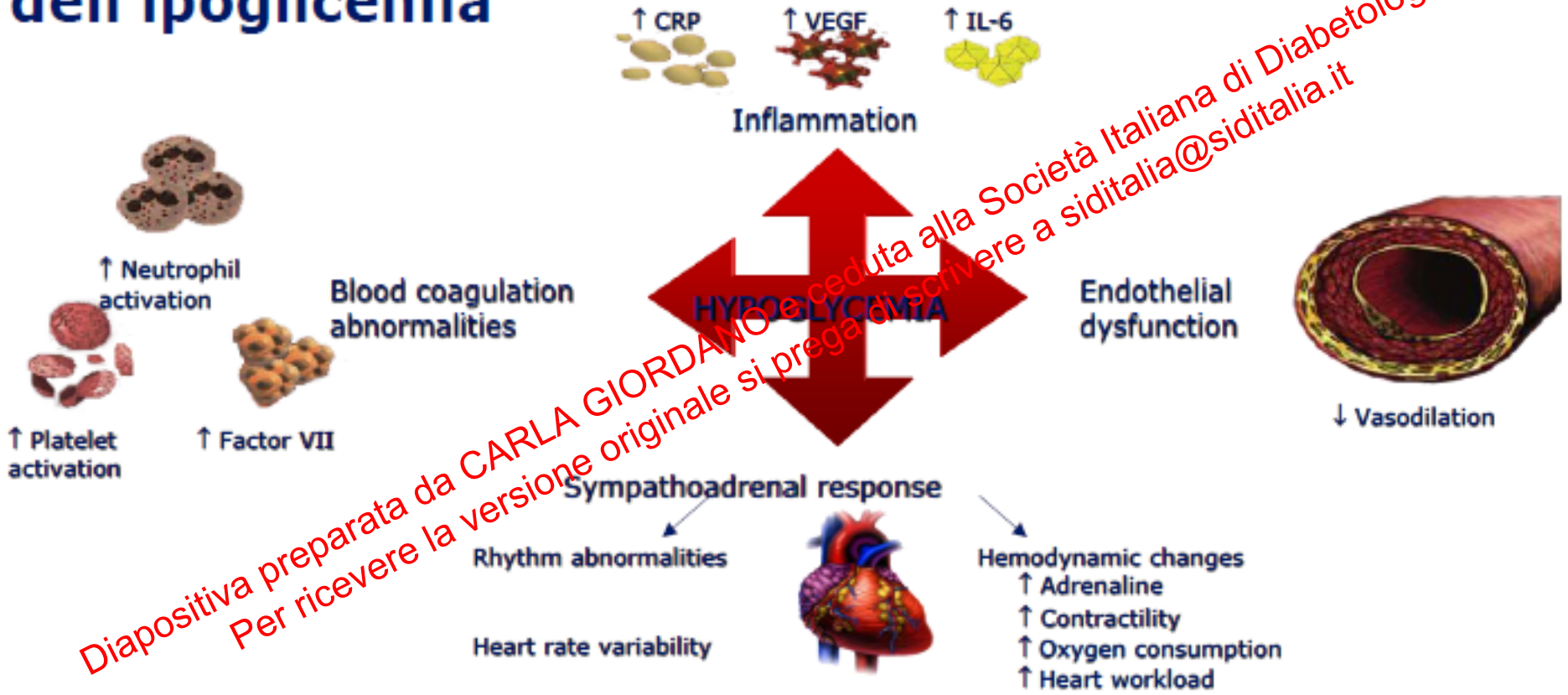
Yoshifumi Saisho[a,*], Chihiro Tanaka[a], Kumiko Tanaka[a], Rachel Roberts[b], Takayuki Abe[b], Masami Tanaka[a], Shu Meguro[a], Junichiro Irie[a], Toshihide Kawai[a], Hiroshi Itoh[a]

[a] Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan
[b] Center for Clinical Research, Keio University School of Medicine, Tokyo, Japan

## Higher rates of confirmed hypoglycaemia are associated with greater within-subject variability in fasting plasma glucose in type 1 and type 2 diabetes: A meta-analysis

Bode *et al. Diabetologia* 2013;56(Suppl. 1):S423

# Conseguenze fisiopatologiche cardiovascolari dell'ipoglicemia

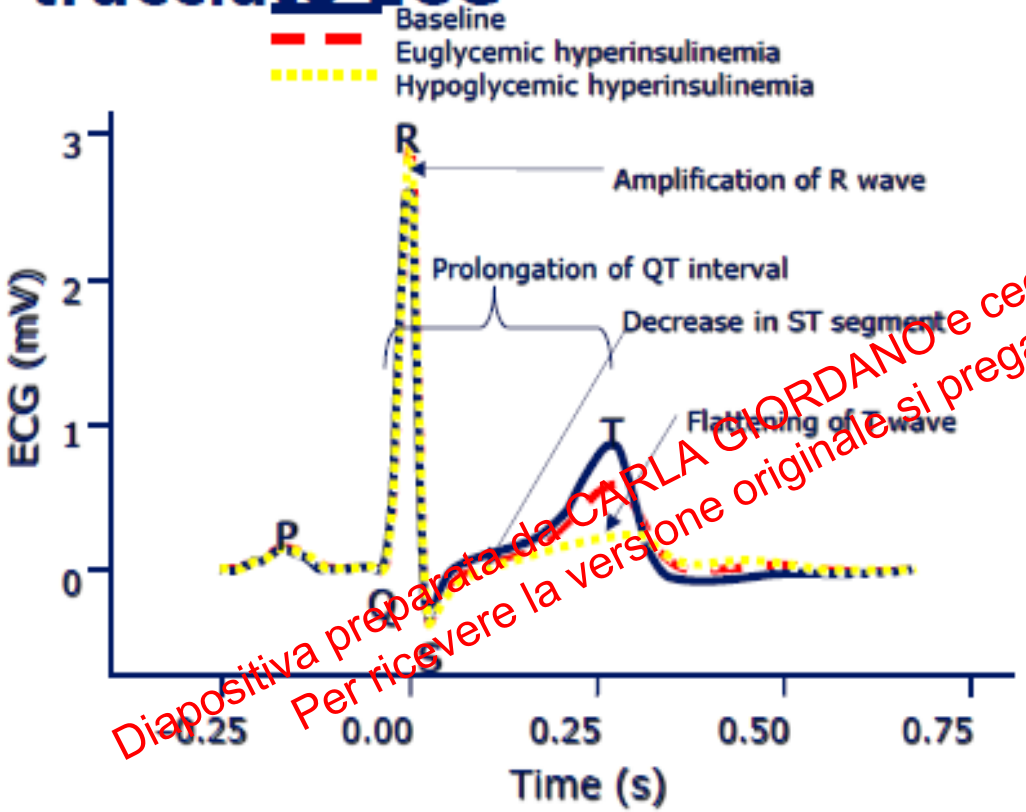





CRP=C-reactive protein; IL-6=interleukin 6; VEGF=vascular endothelial growth factor.

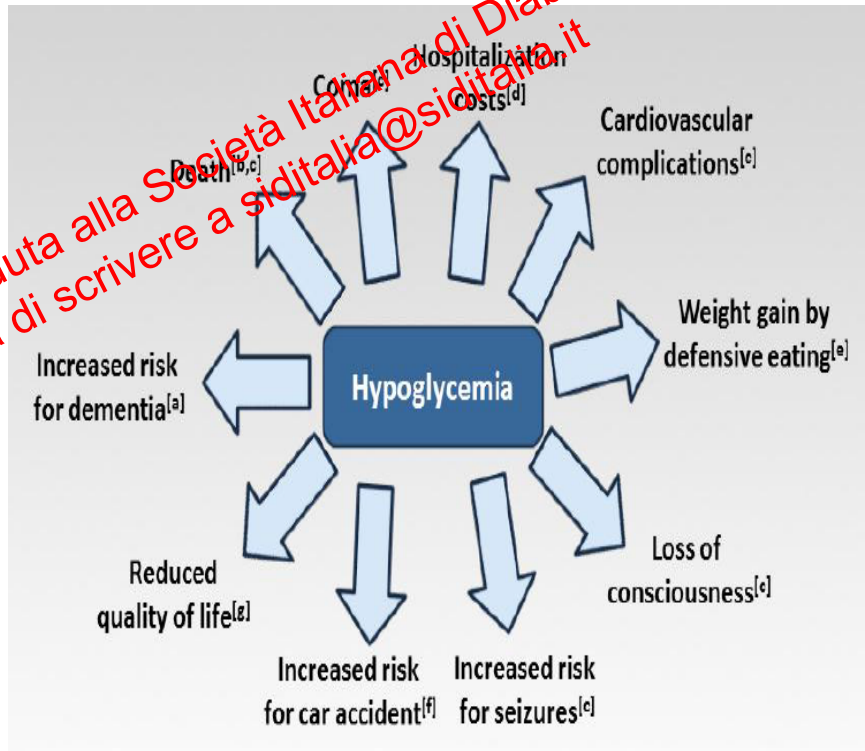
Desouza CV et al. *Diabetes Care*. 2010;33(6):1389-1394.

# L'ipoglicemia risulta in anomalie importanti del tracciato ECG



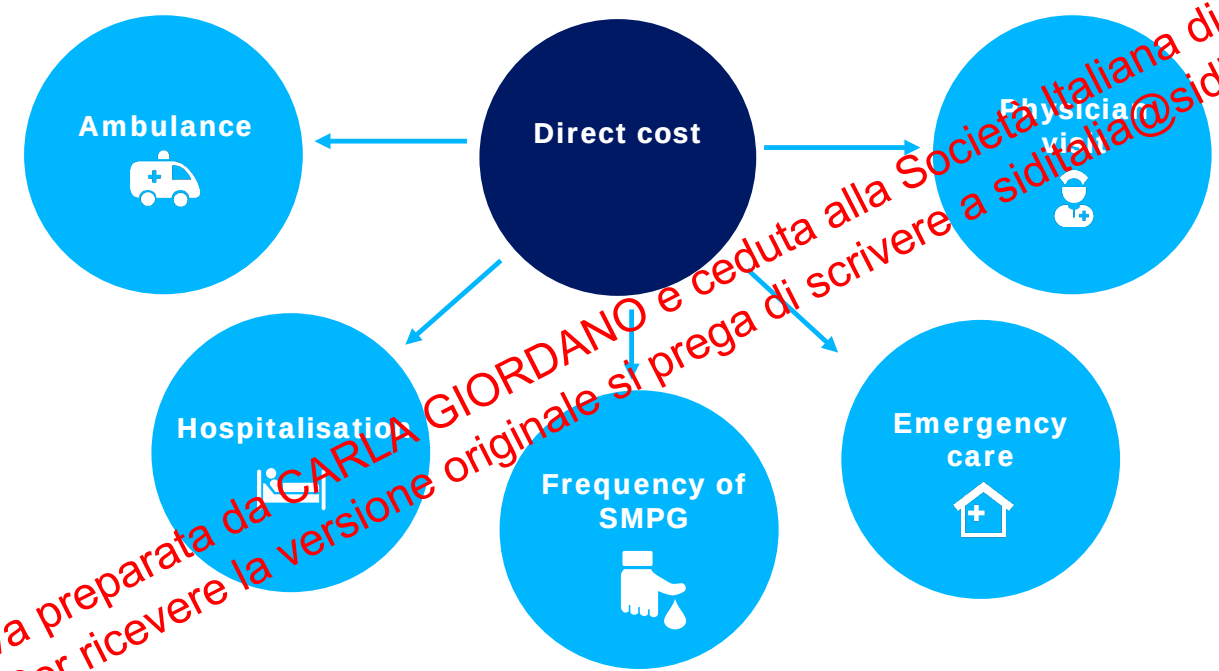

ECG=electrocardiogram.

Laitinen T et al. *Ann Noninvasive Electrocardiol.* 2008;13(2):97-105.




a. Whitmer RA, et al. *JAMA.* 2009;301(15):1565-1572; b. Bonds DE, et al. *BMJ.* 2010;340:b4909; c. Barnett AH. *Curr Med Res Opin.* 2010;26(6):1333-1342; d. Jönsson L, et al. *Value Health.* 2006;9(3):193-198; e.Foley JE, et al. *Vasc Health Risk Manag.* 2010;6:541-548; f. Begg IS, et al. *Can J Diabetes.* 2003;27:128-140; g. McEwan P, et al. *Diabetes Obes Metab.* 2010;12(5):431-436.

# Direct costs associated with hypoglycaemia

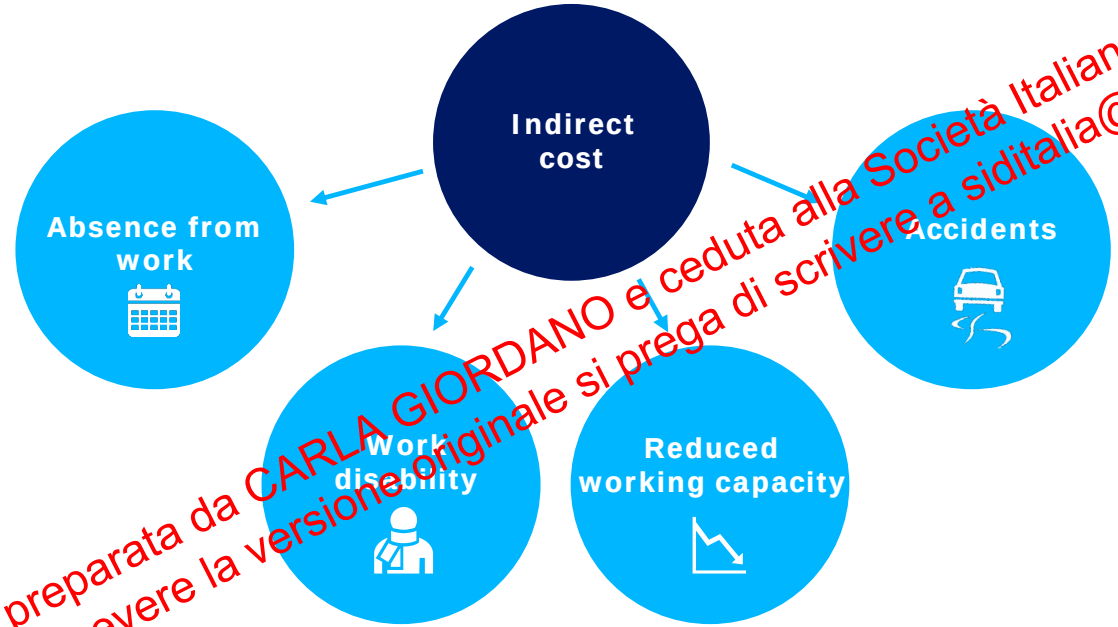





Jönsson, L et al, *J Value Health* 2006;9:193–198. Farmer A et al, *Curr Med Res Op* 2008;24:3097–3104. Amiel, SA et al, *Diabet Med* 2008;25:245–254

SMPG, self-measured plasma glucose

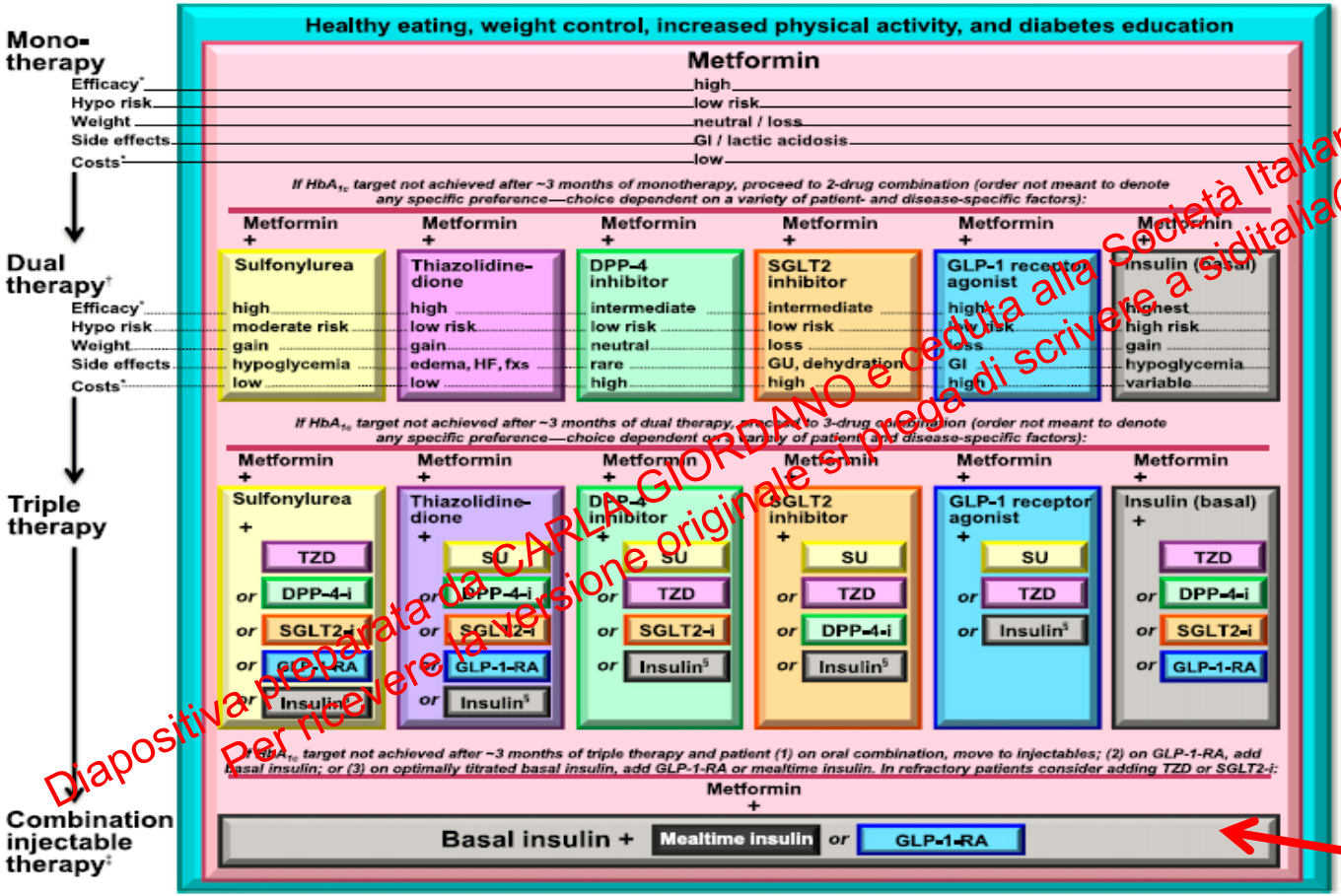
# Indirect costs associated with hypoglycaemia




**In the UK, hypoglycaemic episodes are reported to be associated with five fatal road traffic accidents each year, and 45 serious accidents each month**



Jönsson L et al, *J Value Health* 2006;9:193–198. Farmer A et al, *Curr Med Res Op* 2008;24:3097–3104. Amiel SA et al, *Diabet Med* 2008;25:245–254





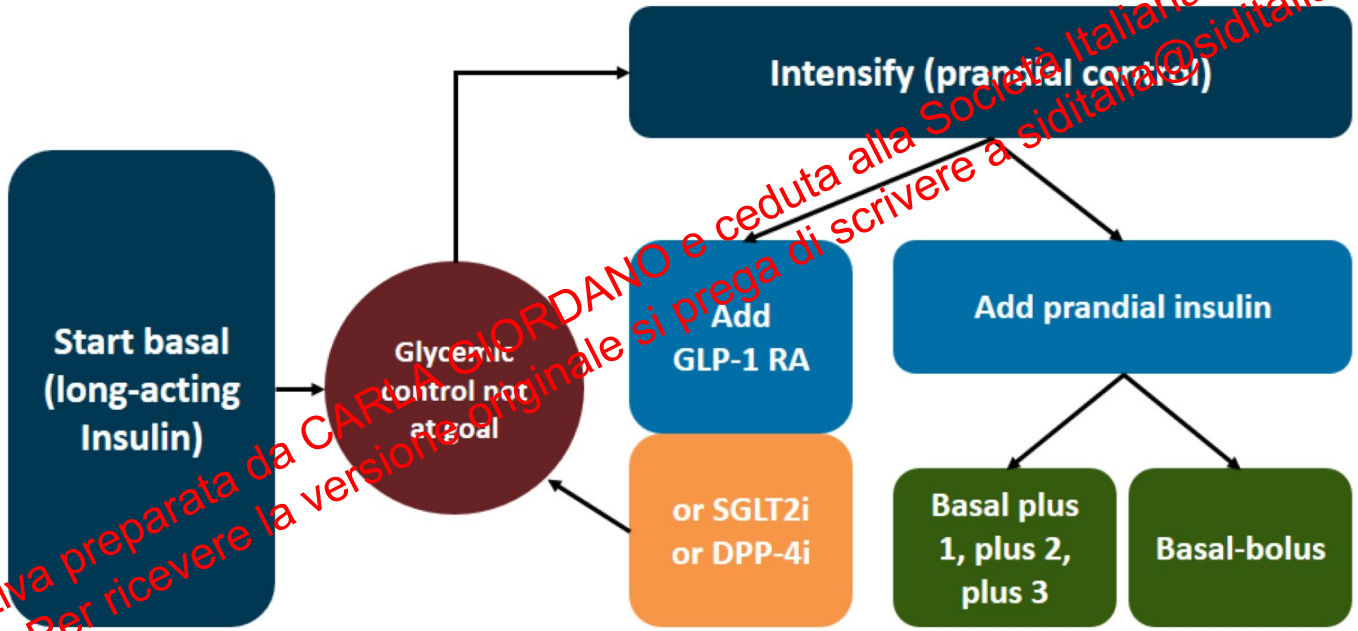

Diabetes Care 2015;38:140–149 | DOI: 10.2337/dc14-2441

# Clinical Features To Consider When Selecting either a GLP-1 RA or Prandial Insulin To Escalate Basal Insulin Therapy

| | Basal insulin plus GLP-1 RA | Basal insulin plus multiple daily insulin doses |
|---|---|---|
| **Body weight** | Overweight/Obese (BMI ≥ 28 kg/m$^2$) | Normal weight/Overweight (BMI < 28 kg/m$^2$) |
| **Duration of disease** | Relatively short (< 10 years) | Relatively long (> 10 years) |
| **Metabolic control** | Closer to target ($HbA_{1c}$ < 8%/8.5%) | Further from target ($HbA_{1c}$ ≥ 8%/8.5%) |
| **Residual β-cell function** | Maintained (C-peptide ≥ 0.6–0.8 ng/mL) | Reduced (C-peptide < 0.6–0.8ng/mL) |

Giorgino F. et al., *DMRR* 2016

# AACE Algorithm for Intensifying Insulin




Garber AJ, et al. *Endocr Pract*. 2017;23:207-238.

# LA TERAPIA DELLA IPERGLICEMIA POSTPRANDIALE: QUANDO AGGIUNGERE L'ANALOGO RAPIDO

# Linee Guida

I soggetti con glicemie non controllate o con iperglicemie sintomatiche e già in trattamento con insulina basale posso beneficiare di un trattamento combinato basale+bolo. L'approccio più semplice è quello di *aggiungere una singola iniezione di analogo rapido al pasto principale* (5 UI o 10% della basale). Il regime basal bolus è più efficace e flessibile (50% della TDD in 3 boli). Le modifiche non devono superare il 10-20%  o 1-2 UI ogni 2-3 giorni. La titolazione si effettua considerando le glicemie postprandiali o le glicemie che precedono il pasto successivo.

*AACE/ACE 2016*

# Standard italiani per la cura del diabete mellito 2014

**5. Quando si avvia la terapia insulinica:**

**5.1.** Iniziare preferibilmente con un'insulina basale come glargine, detemir, ILPS o umana NPH (con umana NPH il rischio di ipoglicemia è tuttavia maggiore), tenendo comunque in considerazione le diverse farmacocinetiche

*oppure, in seconda analisi*

**5.2.** Utilizzare direttamente uno schema basal-bolus

*oppure, in terza analisi*

**5.3.** Utilizzare un analogo rapido ai pasti

*oppure, in casi partico*

**5.4.** In presenza di
somministrazione
paziente verso uno

# Standard Italiani per la Cura del Diabete - 2016

**5.1.** Iniziare preferibilmente con un'insulina basale, tenendo in considerazione le diverse farmacocinetiche delle varie basali disponibili, ma senza dimenticare che ci sono alternative efficaci (terapia orale con 1-2 iniezioni di insulina rapida ai pasti)

*oppure, in seconda analisi*

**5.2.** Utilizzare direttamente uno schema basal-bolus

*oppure, in terza analisi*

**5.3.** Utilizzare schemi alternativi come il basal-plus oppure il basal-plus-plus

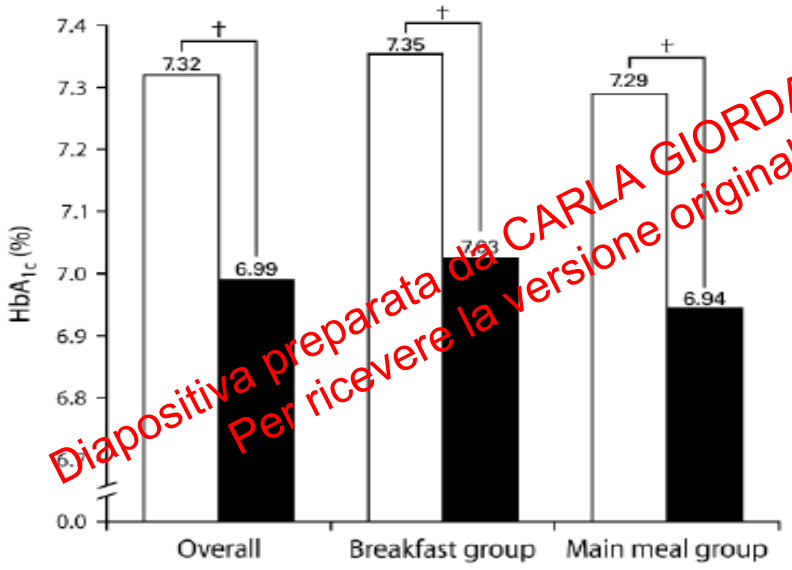
*oppure, in casi particolari,*

**5.4.** In presenza di gravi ed evidenti problemi di compliance, utilizzare una singola o doppia somministrazione di insulina premiscelata (bifasica), tentando comunque di educare il paziente verso uno schema basal-bolus.

# Introducing a simplified approach to insulin therapy in type 2 diabetes: a comparison of two single-dose regimens of insulin glulisine plus insulin glargine and oral antidiabetic drugs

M. R. Lankisch,[1] K. C. Ferlinz,[2] J. L. Leahy[3] and W. A. Scheabauer[4] on behalf of the Orals Plus Apidra and LANTUS (OPAL) study group






Diabetes, Obesity and Metabolism, **10,** 2008, 1178–1185

| | Total | Breakfast injection | Main mealtime injection |
|---|---|---|---|
| Patients with $HbA_{1c}$ >6.5–9.0% at screening (n) | 316 | 162 | 154 |
| Patients who achieved $HbA_{1c} \leq 6.5\%$ at end-point, n (%) | 97 (30.7) | 45 (27.8) | 52 (33.8) |
| Patients with $HbA_{1c}$ >7.0% at baseline (n) | 188 | 96 | 92 |
| Patients with $HbA_{1c}$ >7.0% at baseline achieving $HbA_{1c} \leq 7.0\%$ at end-point, n (%) | 83 (44.1) | 35 (36.5)* | 48 (52.2)* |

$HbA_{1c}$, haemoglobin $A_{1c}$.
*$p = 0.028$ for differences between the two treatment groups.

# Basal–bolus in T2D: study design

## BEGIN BB T2D

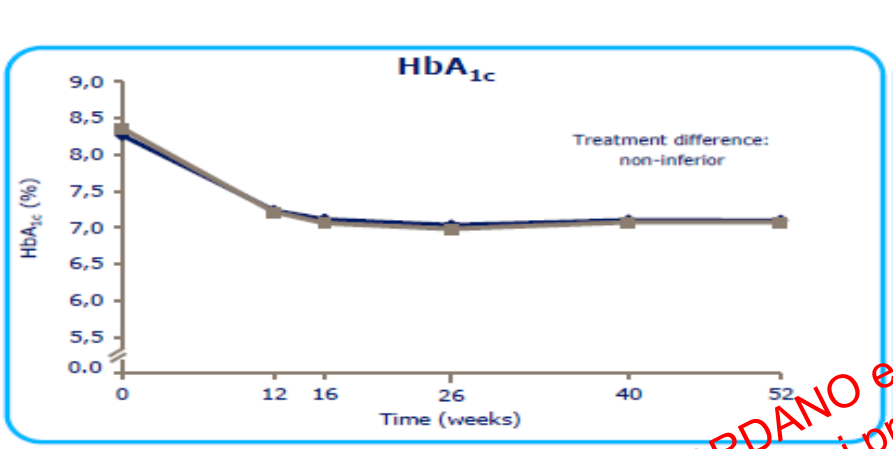

**Inclusion criteria**

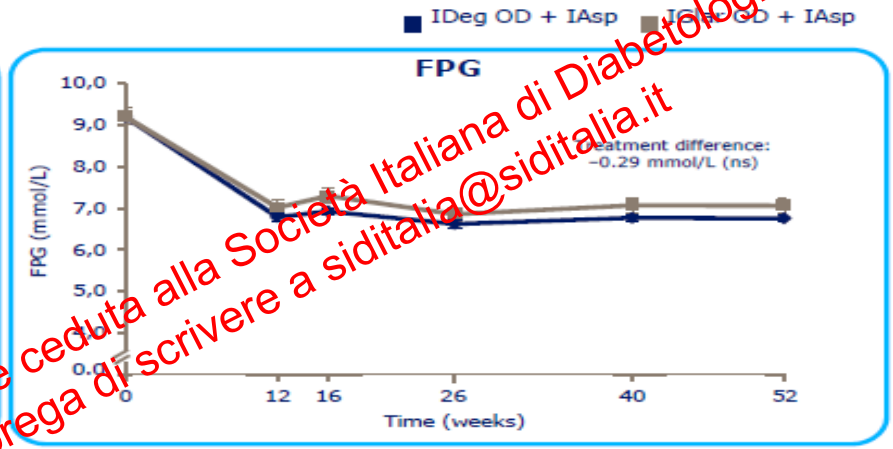
- Type 2 diabetes ≥6 months
- Previously treated with any insulin regimen ≥3 months ±OADs
- $HbA_{1c}$ 7–10%
- BMI ≤40 kg/m²
- Age ≥18 years

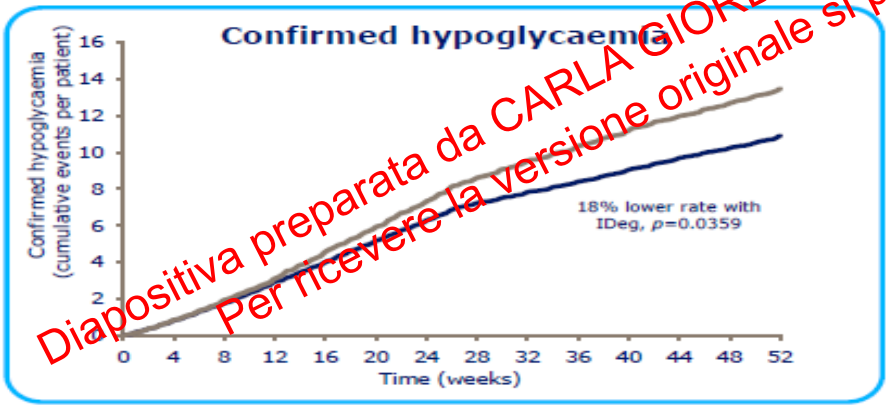
IAsp, insulin aspart
Garber *et al. Lancet* 2012;379:1498–507

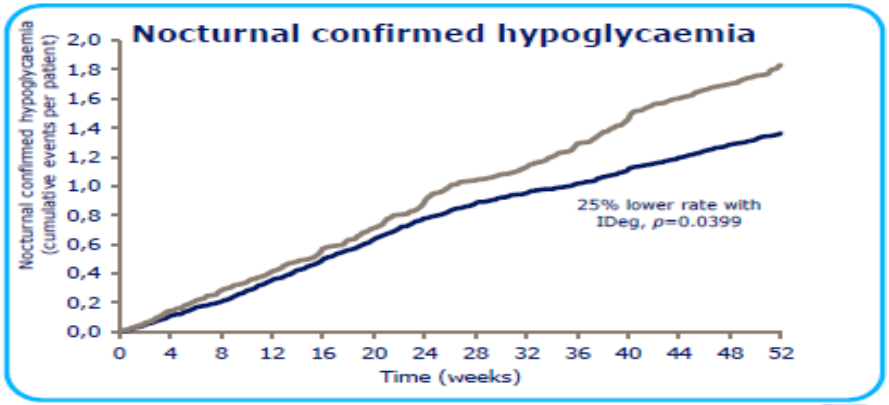
# Basal–bolus in T2D: results

## BEGIN BB T2D






Garber *et al. Lancet* 2012;379:1498–507

# Need for Faster-Acting Insulins

- Current fast-acting insulins
  - Better PPG control vs RHI
  - Less late postprandial hypoglycemic events and early nocturnal hypoglycemia vs RHI
- Start of action is still too slow
  - > 10 minutes before start of glucose-lowering effect
  - > 60 minutes before maximum insulin concentrations are reached
    - Forces patients to wait (15-30 minutes) before starting a meal
    - Affects quality of life; flexibility

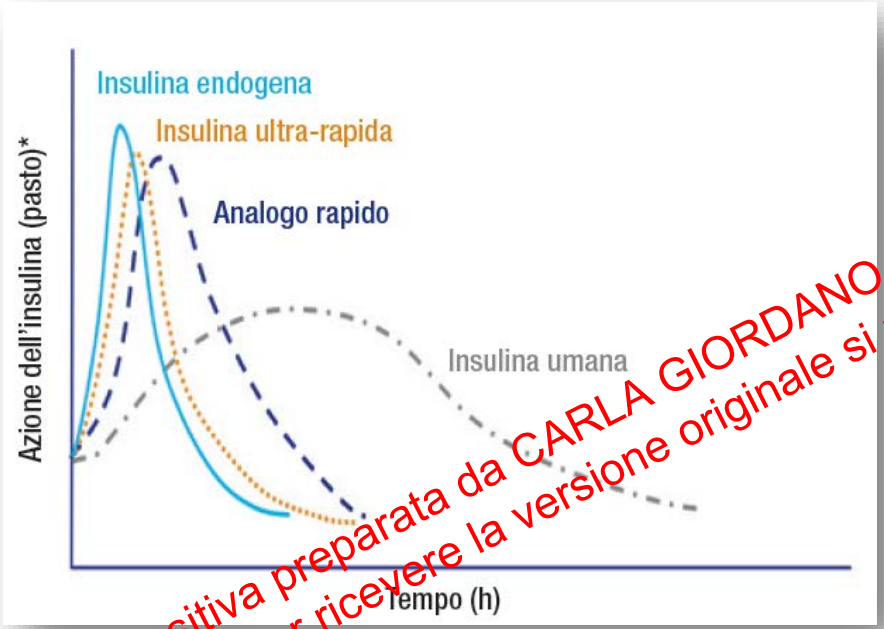
# PPG as a Glycemic Target

- Due to the progressive nature of T2DM, additional treatment intensification may be required when the target HbA1c is not reached
- As the HbA1c levels approach 7%, the dominate contributor to glycemic control becomes PPG[a]
- PPG recommendations
  - ADA: 1- to 2-hour PPG of < 180 mg/dL (10.0 mmol/L)[b]
  - AACE: 2-hour PPG of < 140 mg/dL (7.8 mmol/L)[c]



a. Monnier L, et al. *Diabetes Care*. 2003;26:881-885.
b. ADA. *Diabetes Care*. 2017;40(Suppl 1):S48-S56.
c. Handelsman Y, et al. *Endocr Pract*. 2015;21(Suppl 1):1-87.

# Analogo dell'insulina ad azione ultra-rapida: verso un meccanismo d'azione più simile al profilo fisiologico




**L'insulina ultra-rapida potrebbe:**

- **ottenere un profilo d'azione più fisiologico nel soggetto con DT1**
- **mimare la prima fase di secrezione insulinica nel DT2**
- **avere un profilo d'azione migliore quando utilizzato in pompa**



Irace C. Media 2016; 16:193-200; Home PD. Diabetes Obes Metab 2015;17:1011–20;
Heinemann L. J Diabetes Sci Technol 2012;6(4):728-742

# Diversi approcci sperimentali per ottenere un'insulina ultra-fast

**Administration**

- Sprinkler needle
- Pulmonary

**Formulation**

- Additives, for example:
  - EDTA/citric acid
  - Magnesium
  - Bio-chaperone
  - Niacinamide
  - Other

**Injection site**

- Application of heat
- Hyaluronidase

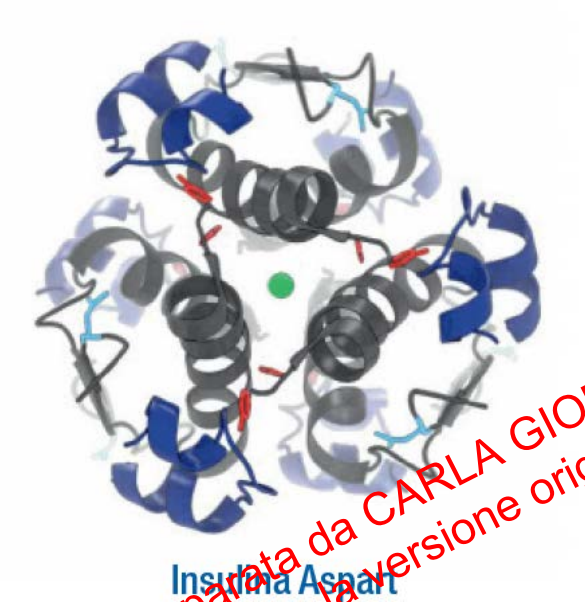




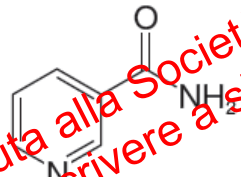
ethylenediamine tetra-acetic acid

## Fast-acting Insulin Aspart

# Nuova formulazione di aspart

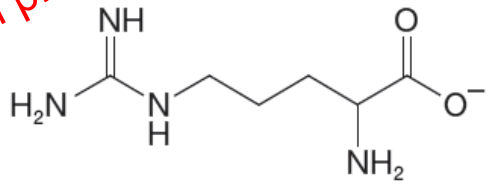



**Niacinamide:** facilitatore dell'assorbimento




Vitamin B3

**L-arginina:** stabilizzatore dell'insulina



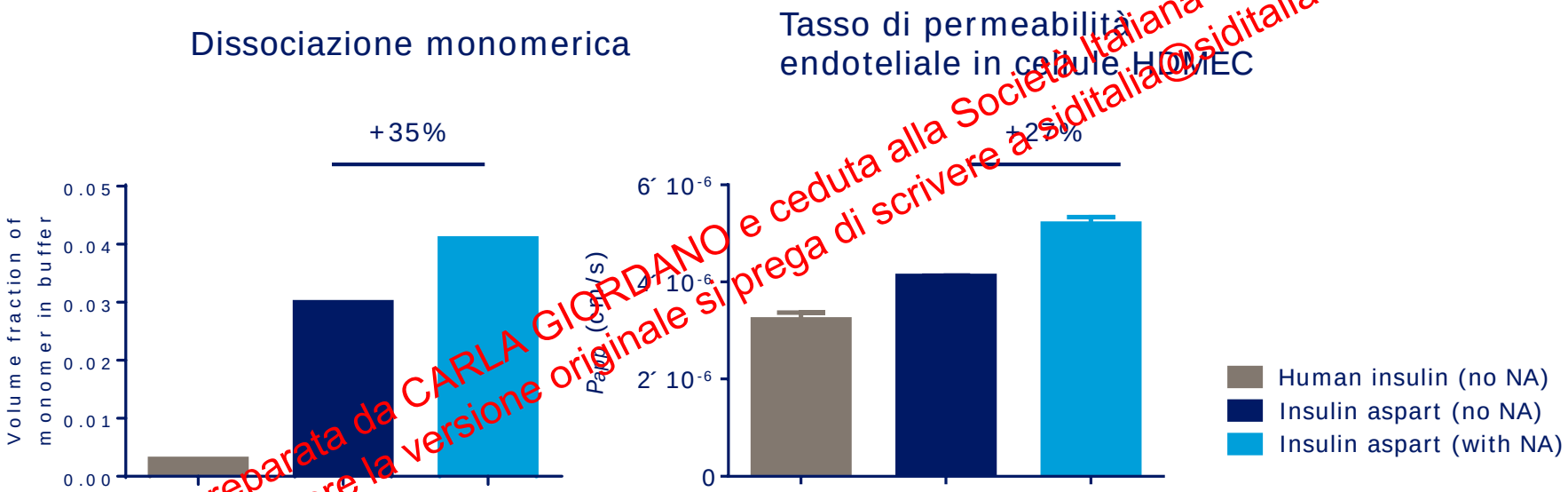

Ammino acido

«Fast-acting Insulin Aspart» è una formulazione di insulina aspart prandiale nella quale l'aggiunta di nicotinamide (vitamina B3) determina un assorbimento iniziale più rapido dell'insulina rispetto alla sola insulina aspart.



Irace C. Media 2016; 16:193-200; RCP Fast- acting Insulin Aspart

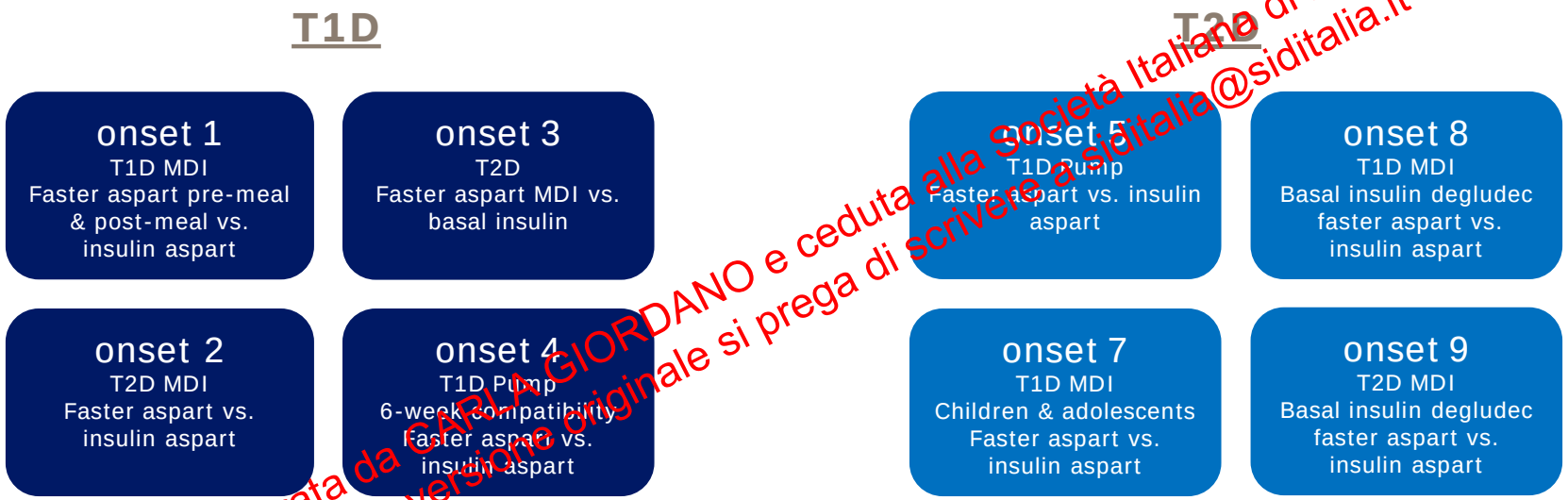
# La vitamina B3 aumenta la dissociazione monomerica e il tasso di permeabilità endoteliale di insulina aspart






NA: niacinamide, HDMEC: human dermal microvascular endothelial cells
Buckley ST *et al.*, ATTD 2016 (ATTD-0083)

# Overview of the onset programme for faster aspart





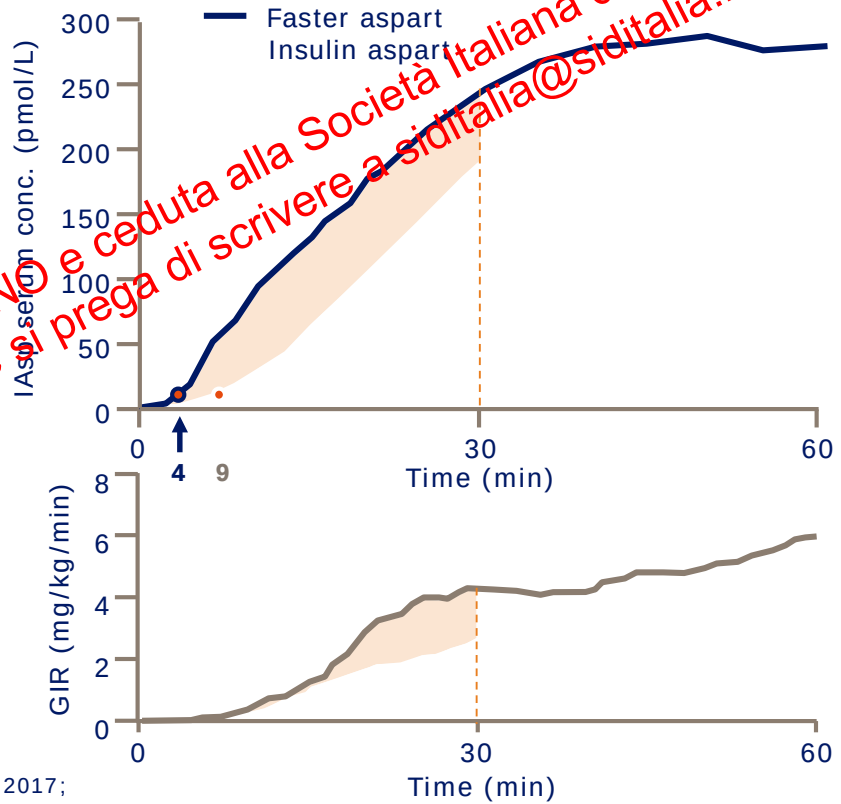

Faster aspart, fast-acting insulin aspart; MDI, multiple daily injections; T1D, type 1 diabetes; T2D, type 2 diabetes

## Fast- acting Insulin Aspart

# Proprietà farmacologiche

**Fast- acting insulin aspart *vs* aspart presenta:**

- Comparsa in circolo 2 volte più veloce
- Quantità di insulina disponibile in circolo due volte maggiore nei primi 30 minuti
- Effetto ipoglicemizzante maggiore del 74% nei primi 30 minuti






GIR, glucose infusion rate; IAsp, insulin aspart; SC, subcutaneous

Heise T et al. *Diabetes* 2016;65(S1):A239; Heise T et al. Clin Pharmacokinet 2017;

## «Fast- acting Insulin Aspart»

- ✓ è stata studiata in più di 2.000 pazienti adulti con diabete
- ✓ è risultata non inferiore ad aspart nel ridurre l'HbA1c nei soggetti DM2 e DM1
- ✓ ha presentato una riduzione dell'HbA1c statisticamente significativa nei DM1 quando somministrata ai pasti e sovrapponibile quando somministrata dopo i pasti
- ✓ è risultata superiore nel ridurre la PPG ad 1h nel DM2 e DM1
- ✓ Profilo di sicurezza sovrapponibile ad aspart

# Complementary actions of GLP-1 and insulin target underlying pathophysiology of type 2 diabetes

## GLP-1 analogue

**Heart**
Cardiac function

**Pancreas**
Glucose-dependent insulin and glucagon secretion
Insulin synthesis

**Liver**
Hepatic glucose output

**GI tract**
Gastric emptying

**Brain**
Energy intake
Satiety
Neuroprotection

## Basal insulin

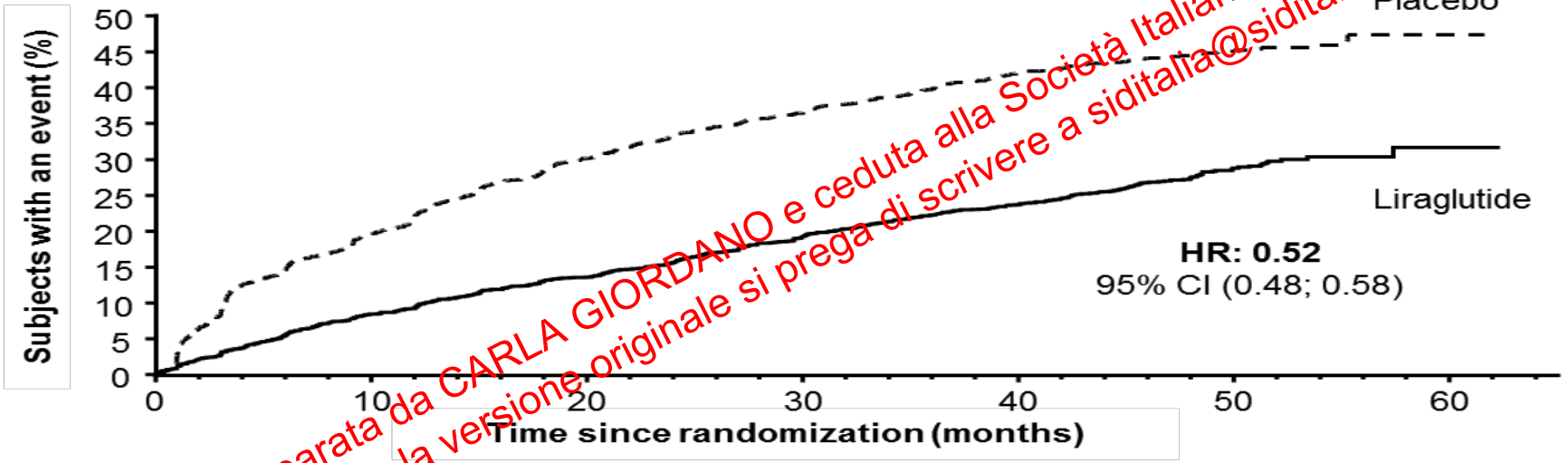
**Skeletal muscle**
Glucose disposal

**Liver**
Hepatic glucose production

**Adipose tissue**
Insulin receptor activation

Baggio, Drucker. Gastroenterol 2007;132:2131–57

# Time to insulin initiation – patients insulin-naïve at baseline




**Subjects at risk**

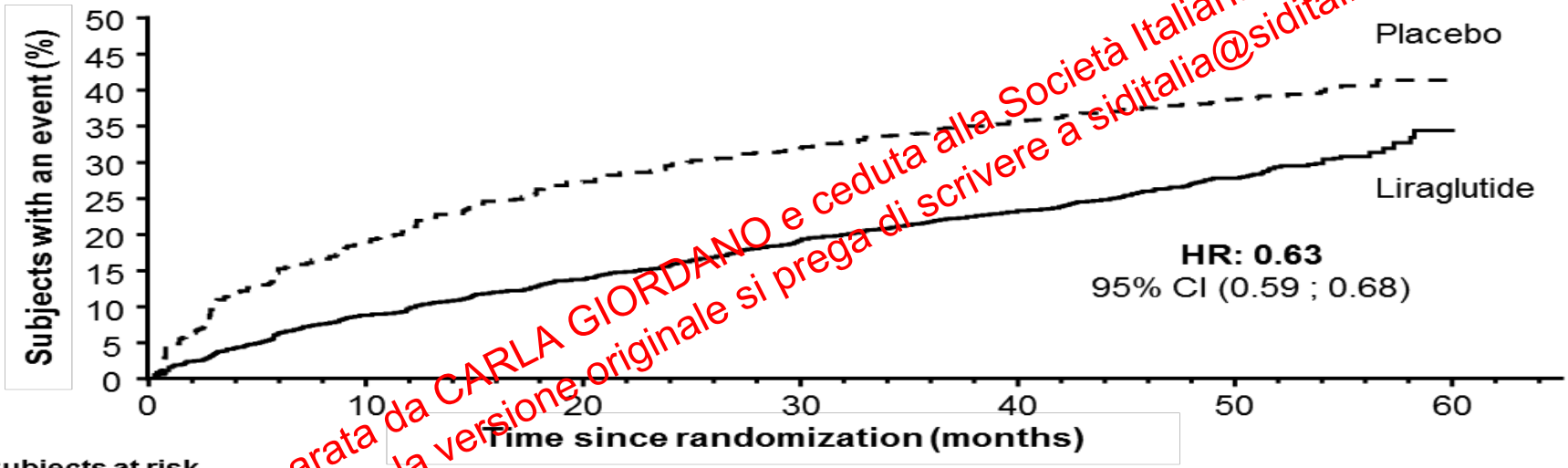
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Liraglutide | 2633 | 2386 | 2238 | 2057 | 1906 | 448 | 3 |
| Placebo | 2648 | 2026 | 1728 | 1534 | 1374 | 336 | 7 |



Kaplan–Meier plot of time to insulin initiation in patients who were insulin-naïve at baseline; Cox proportional-hazards regression model adjusted for treatment; patients without an event are censored at time of last contact (phone or visit)
CI: confidence interval; HR: hazard ratio

Presented at the American Diabetes Association 77th Scientific Sessions, Session 1-AC-SY13. June 11 2017, San Diego, CA, USA

# Time to first initiation of insulin or any new OAD




**Subjects at risk**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Liraglutide | 4668 | 4068 | 3786 | 3452 | 3183 | 705 | 5 |
| Placebo | 4672 | 3575 | 3111 | 2803 | 2548 | 541 | 9 |



Time to first event analyzed using a Cox regression with treatment group as fixed factor. Only events that occurred between randomization date and follow-up date were used for defining first event. Subjects without an event were censored at time of last contact (phone or visit)
CI: confidence interval; HR: hazard ratio; OAD: oral antidiabetic drug

Presented at the American Diabetes Association 77th Scientific Sessions, Session 1-AC-SY13. June 11 2017, San Diego, CA, USA

# Glucagon-like peptide-1 receptor agonist and basal insulin combination treatment for the management of type 2 diabetes: a systematic review and meta-analysis

*Conrad Eng*, Caroline K Kramer*, Bernard Zinman, Ravi Retnakaran*

**Interpretation** GLP-1 agonist and basal insulin combination treatment can enable achievement of the ideal trifecta in diabetic treatment: robust glycaemic control with no increased hypoglycaemia or weight gain. This combination is thus a potential therapeutic strategy that could improve the management of patients with type 2 diabetes.

www.thelancet.com Published online September 12, 2014 http://dx.doi.org/10.1016/S0140-6736(14)61335-0

# Combining therapies offers opportunities to enhance efficacy and diminish side effects


For illustrative purposes only, not meant to quantify or imply magnitude of change in either direction