Diagnosi precoce e trattamento efficace della patologia

CARDIONEFRO METABOLICA

DALLA teoria ALLA pratica

PERCHÉ E QUANDO SERVE L'INSULINA NEL TRATTAMENTO CONTEMPORANEO DEL DIABETE TIPO 2

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MILANO, 4 LUGLIO 2025

Disclosure

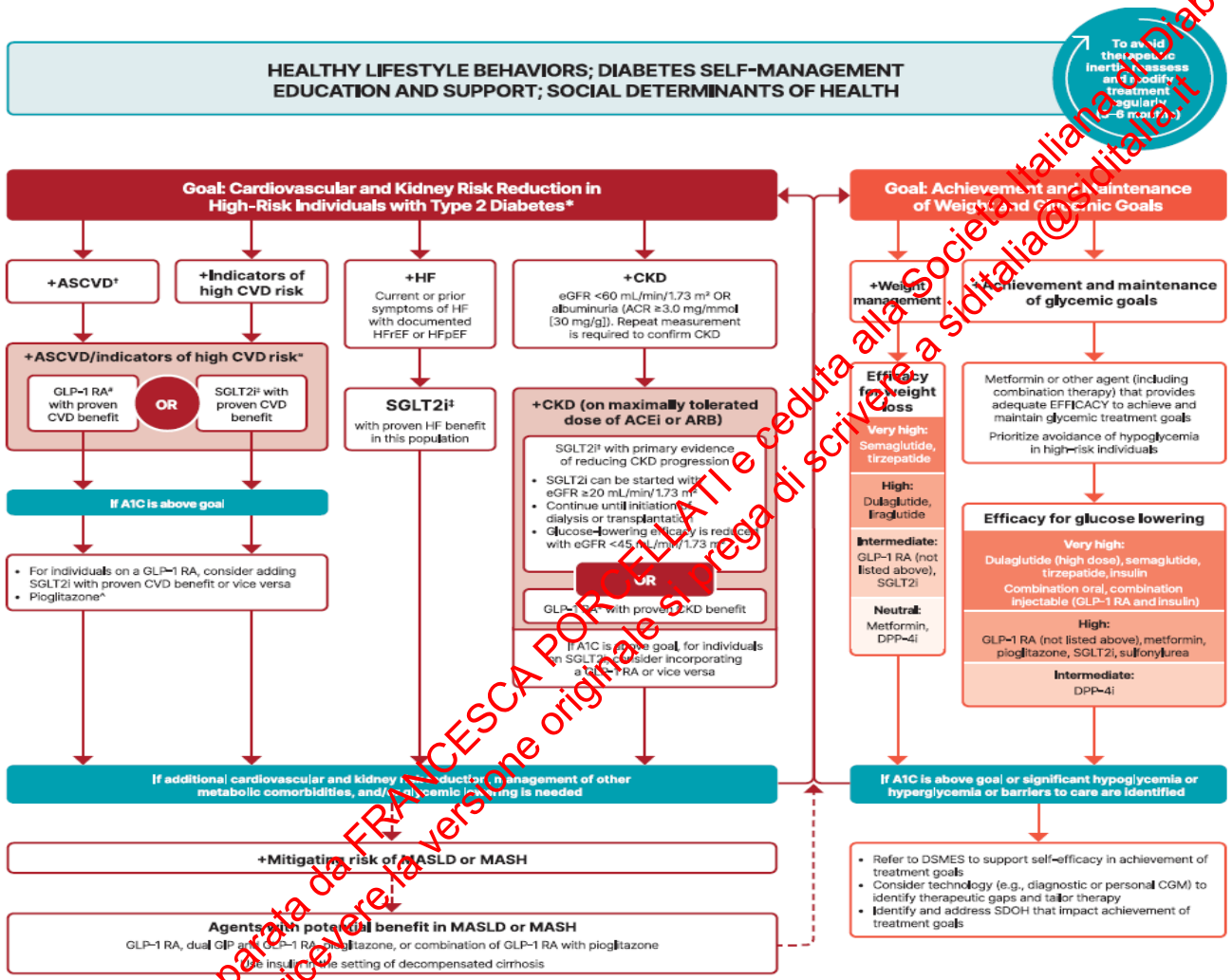
La sottoscritta Dr.ssa Francesca Porcellati dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- Abbott
- AstraZeneca
- Eli-Lilly
- Novo-Nordisk
- Sanofi

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.).

LA "SERENDIPITY" DELLA DIABETOLOGIA

USE OF GLUCOSE-LOWERING MEDICATION IN TYPE 2



* In people with HF, CKD, established CVD, or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be made irrespective of background use of metformin or A1C.

† ASCVD: Defined differently across RCTs but all included individuals with established CVD (e.g., MI, stroke, and arterial revascularization procedure) and variably included conditions such as transient ischemic attack, unstable angina, revascularization, and symptomatic or asymptomatic coronary artery disease. Indicators of high risk: While definitions vary, most comprise ≥55 years of age with two or more additional risk factors (including obesity, hypertension, smoking, dyslipidemia, or albuminuria).

≈ A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high-risk CVD. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen in higher levels of baseline risk and should be factored into the shared decision-making process. See text for details.

For GLP-1 RAs, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke, and kidney end points in individuals with T2D with established or high risk of CVD. One kidney outcome trial demonstrated benefit in reducing persistent eGFR reduction and CV death for a GLP-1 RA in individuals with CKD and T2D.

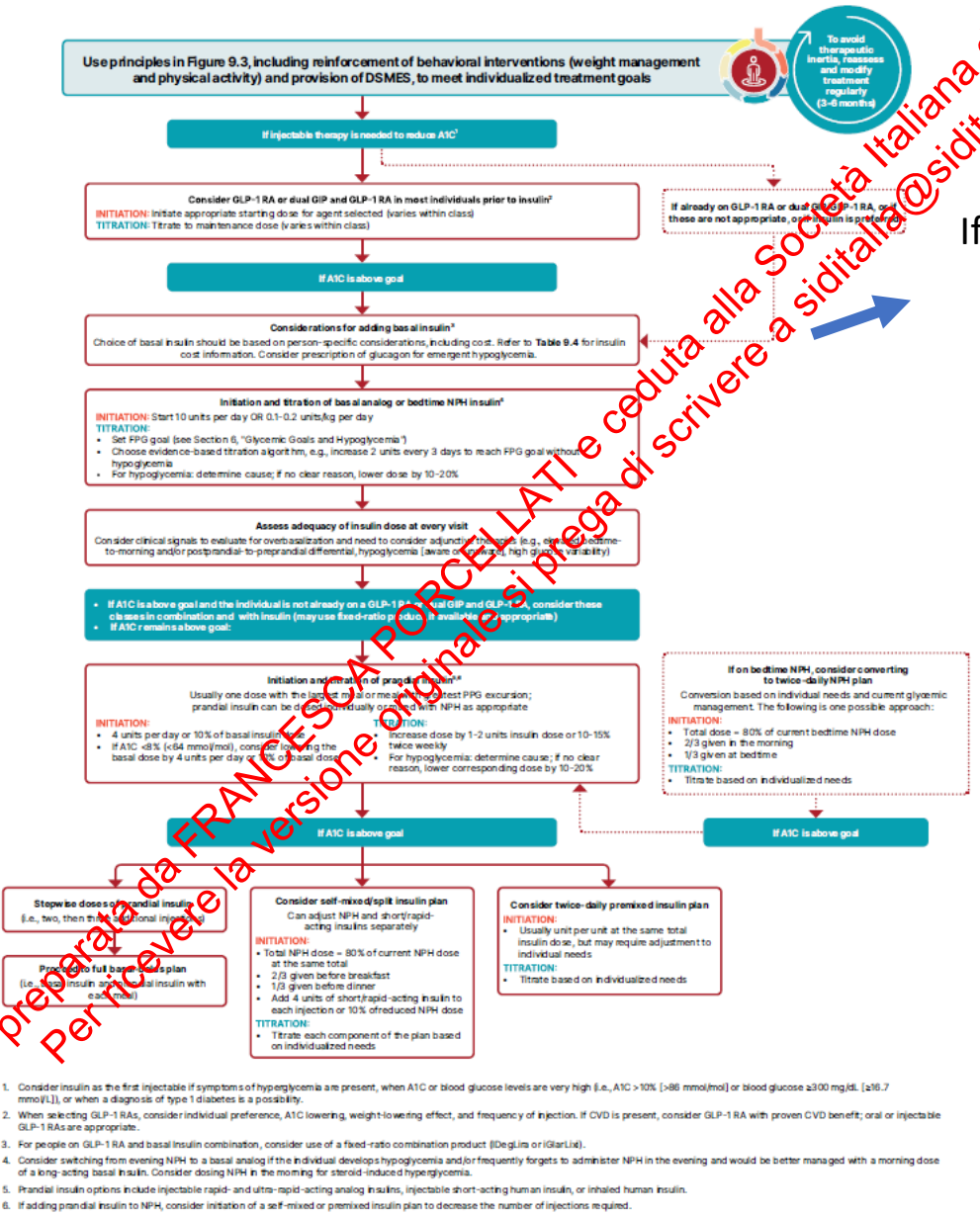
‡ For SGLT2is, CV and kidney outcomes trials demonstrate their efficacy in reducing the risks of composite MACE, CV death, all-cause mortality, MI, HHF, and kidney outcomes in individuals with T2D and established or high risk of CVD.

^ Low-dose pioglitazone may be better tolerated and similarly effective as higher doses.

Diabetes Care 2025;48:S181–S206

INTENSIFYING TO INJECTABLE THERAPY IN TYPE 2 DIABETES

American Diabetes Association



1. Consider insulin as the first injectable if symptoms of hyperglycemia are present, when A1C or blood glucose levels are very high (i.e., A1C >10% [>86 mmol/mol] or blood glucose ≥300 mg/dL [≥16.7 mmol/L]), or when a diagnosis of type 1 diabetes is a possibility.
2. When selecting GLP-1 RAs, consider individual preference, A1C lowering, weight-lowering effect, and frequency of injection. If CVD is present, consider GLP-1 RA with proven CVD benefit; oral or injectable GLP-1 RAs are appropriate.
3. For people on GLP-1 RA and basal insulin combination, consider use of a fixed-ratio combination product (IDegLira or IGlarLixi).
4. Consider switching from evening NPH to a basal analog if the individual develops hypoglycemia and/or frequently forgets to administer NPH in the evening and would be better managed with a morning dose of a long-acting basal insulin. Consider dosing NPH in the morning for steroid-induced hyperglycemia.
5. Prandial insulin options include injectable rapid- and ultra-rapid-acting analog insulins, injectable short-acting human insulin, or inhaled human insulin.
6. If adding prandial insulin to NPH, consider initiation of a self-mixed or premixed insulin plan to decrease the number of injections required.

If injectable therapy is needed to reduce A1C

↓

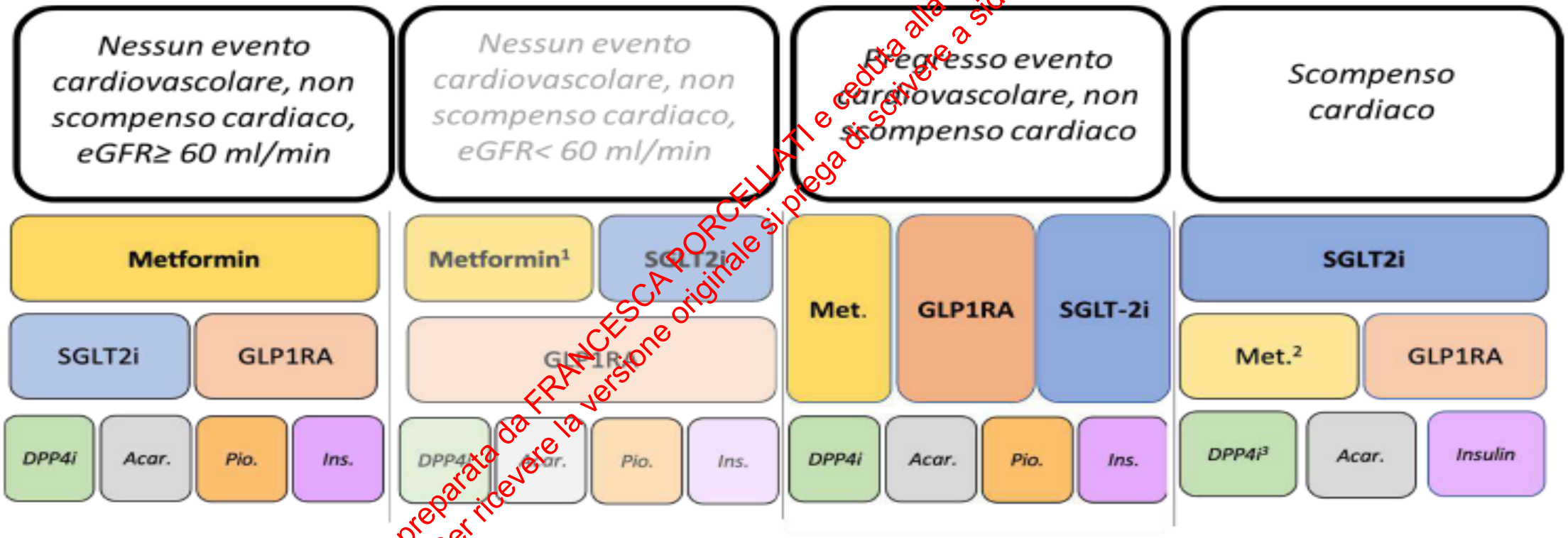
Consider GLP-1 RA or dual GIP and GLP1-RA in most individuals prior to insulin

Consider insulin as the first injectable if symptoms of hyperglycemia are present, when A1C or blood glucose levels are very high (i.e., A1C >10% [>86 mmol/mol] or blood glucose ≥300 mg/dL or when a diagnosis of type 1 diabetes is a possibility.

Diabetes Care 2025;48:S181–S206

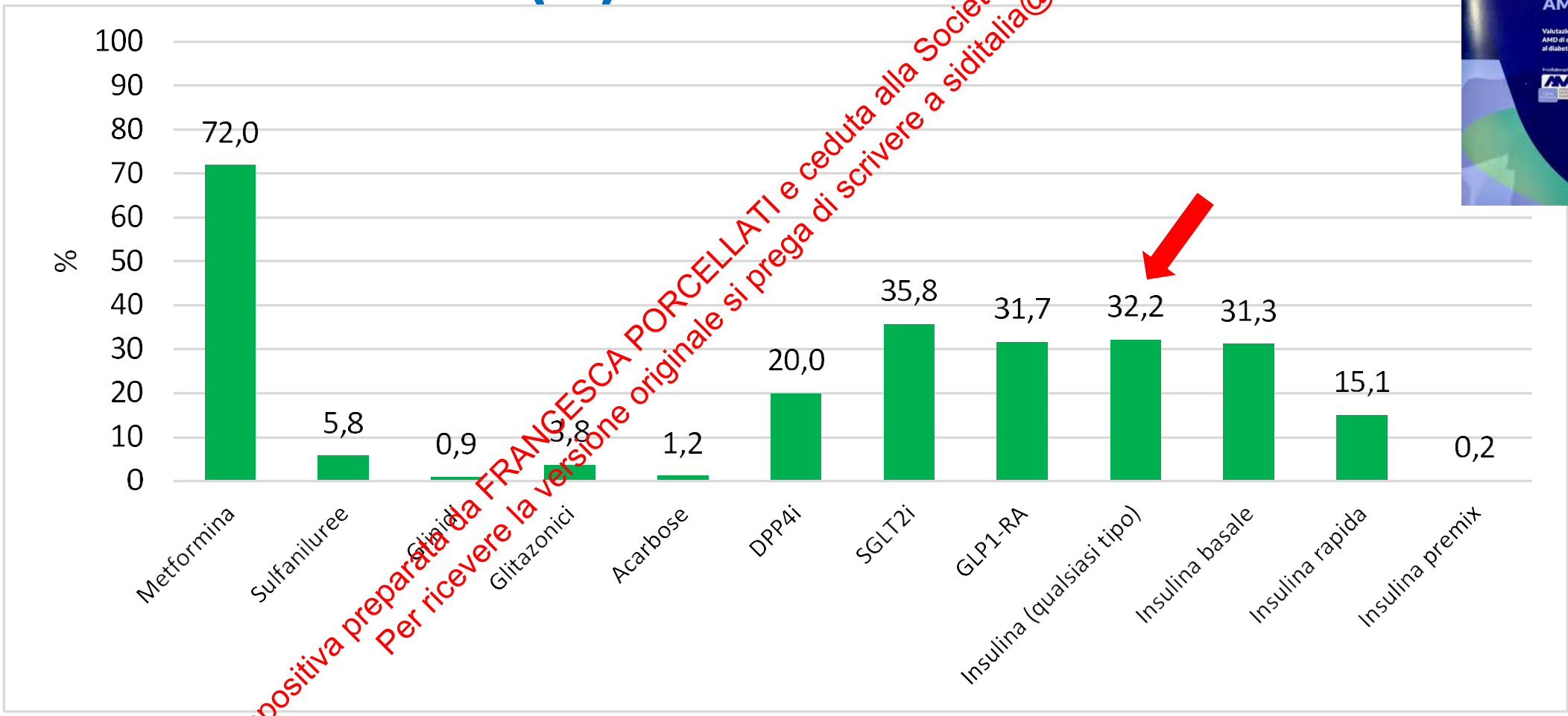
La Terapia del Diabete Mellito di Tipo 2

SISTEMA NAZIONALE LINEE GUIDA DELL'ISTITUTO SUPERIORE DI SANITÀ



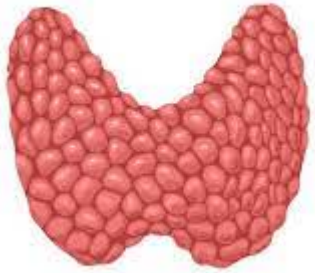
[1]*Se la metformina non è controindicata per ridotto eGFR.*
[2]*Se la metformina non è controindicata per ridotta funzione cardiaca.*
[3]*Eccetto saxagliptin che non è indicato in caso di scompenso cardiaco.*
La raccomandazione sui pazienti con eGFR< 60ml/min è debole per carenza di studi clinici effettuati su questa popolazione
Si raccomanda la deprescrizione di sulfanilurre e glinidi

Distribuzione per classe di farmaco ipoglicemizzante (%) – Annali AMD 2023

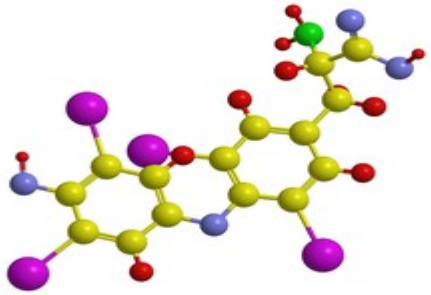


Endocrine Substitute Therapy:
Type 2 Diabetes is an Endocrine Pancreatic Disease

When thyroid fails…….

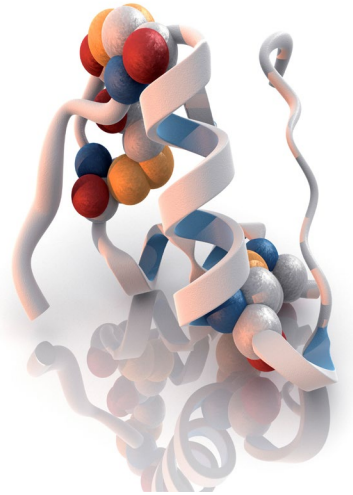


GIVE TYROXINE

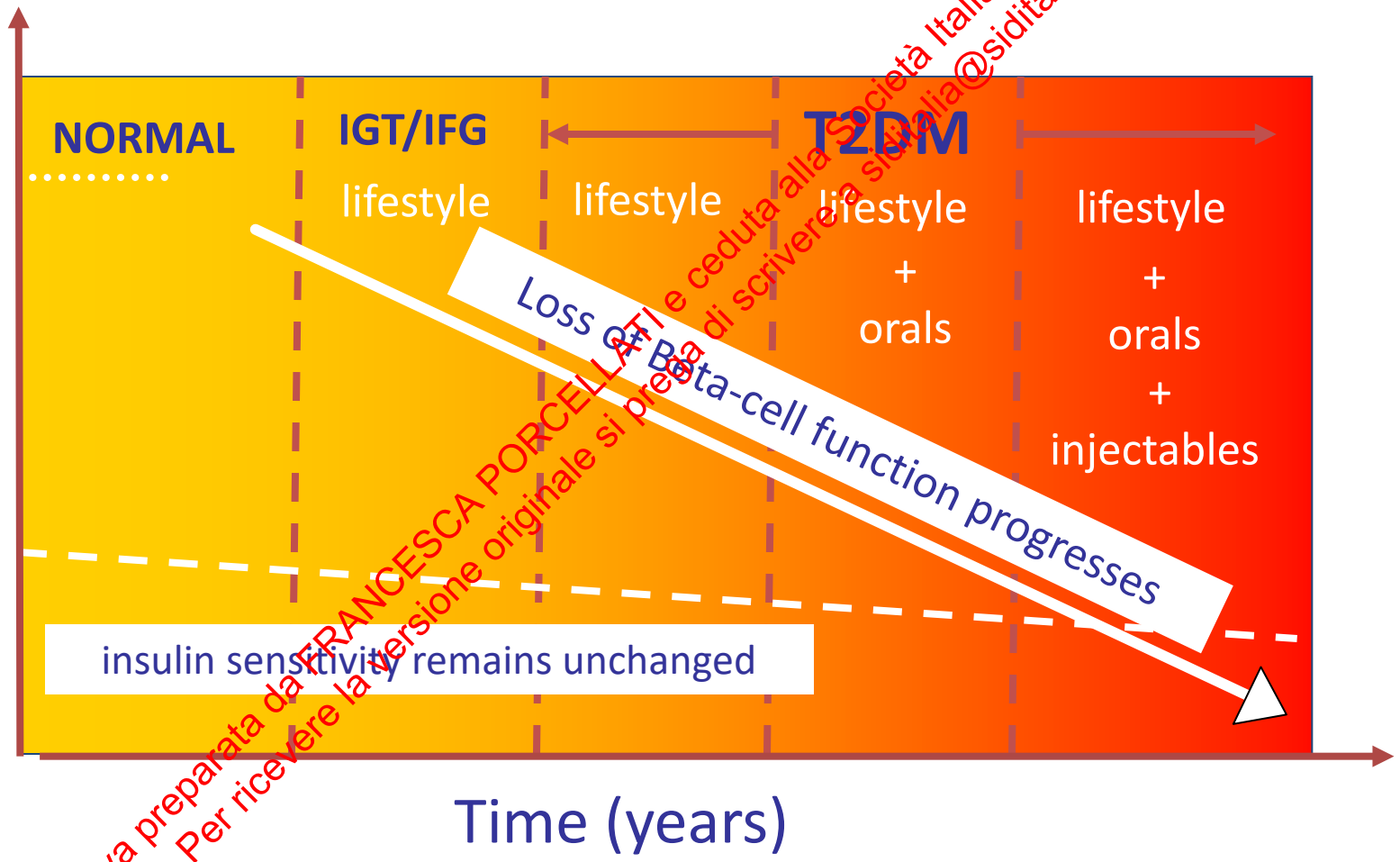


When β-cells fail…….

GIVE INSULIN



Natural history of Type 2 DM based on UKPDS



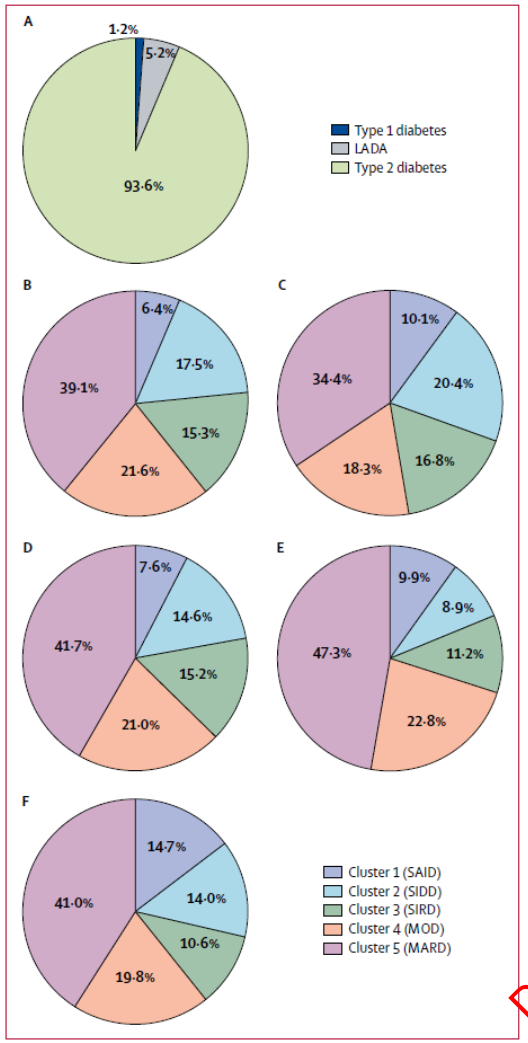
IFG: Impaired fasting glucose; IGT: Impaired glucose tolerance;

UKPDS. Diabetes. 1995;44:1249-58

Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables

Emma Ahlqvist, Petter Storm, Annemari Käräjämäki*, Mats Martinell*, Mozhgan Dorkhan, Annelie Carlsson, Petter Vikman, Rashmi B Prasad, Dina Mansour Aly, Peter Almgren, Ylva Wessman, Nael Shaat, Peter Spégel, Hindrik Mulder, Eero Lindholm, Olle Melander, Ola Hansson, Ulf Malmqvist, Åke Lernmark, Kaj Lahti, Tom Forsén, Tiinamaija Tuomi, Anders H Rosengren, Leif Groop

Lancet Diabetes Endocrinol
2018; 6: 361–69



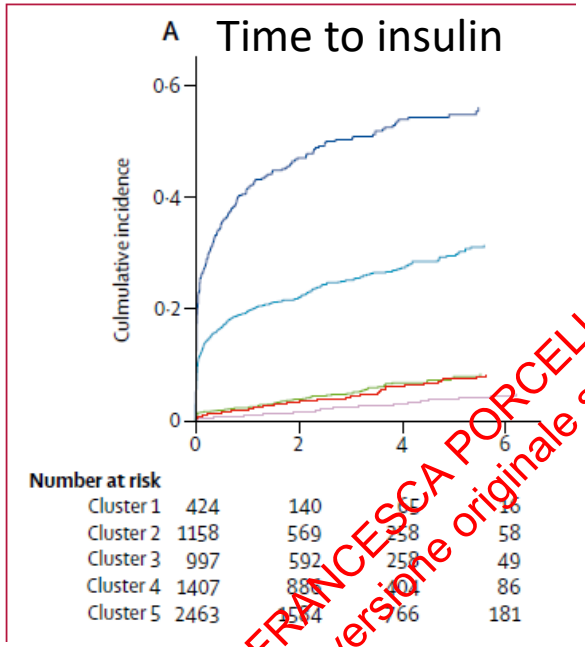


Figure 1: **Patient distribution according to method of classification**
(A) Distribution of ANDIS patients (n=8980) according to traditional classification. (B) Distribution of ANDIS patients (n=8980) according to k-means clustering. (C) Distribution of patients in the Scania Diabetes Registry (n=1466) according to k-means clustering. (D) Distribution of patients in the All New Diabetics in Uppsala cohort (n=844) according to k-means clustering. (E) Distribution of DIREVA patients with newly diagnosed diabetes (n=878) according to k-means clustering. (F) Distribution of DIREVA patients with longer-term diabetes (n=2607) according to k-means clustering. LADA=latent autoimmune diabetes in adults. SAID=severe autoimmune diabetes. SIDD=severe insulin-deficient diabetes. SIRD=severe insulin-resistant diabetes. MOD=mild obesity-related diabetes. MARD=mild age-related diabetes. ANDIS=All New Diabetics in Scania. DIREVA=Diabetes Registry Vaasa.

Heterogeneity of Diabetes, β-Cells, Phenotypes, and Precision Medicine: Proceedings of an International Symposium of the Canadian Institutes of Health Research's Institute of Nutrition, Metabolism and Diabetes and the U.S. National Institutes of Health's National Institute of Diabetes and Digestive and Kidney Diseases

William T. Cefalu,[1] Dana K. Andersen,[2] Guillermo Arreaza-Rubín,[1] Christopher L. Pin,[3] Sheryl Sato,[1] C. Bruce Verchere,[4–6] Minna Woo,[7–9] and Norman D. Rosenblum,[10–12] on behalf of the symposium planning committee, moderators, and speakers*

Diabetes Volume 71, January 2022

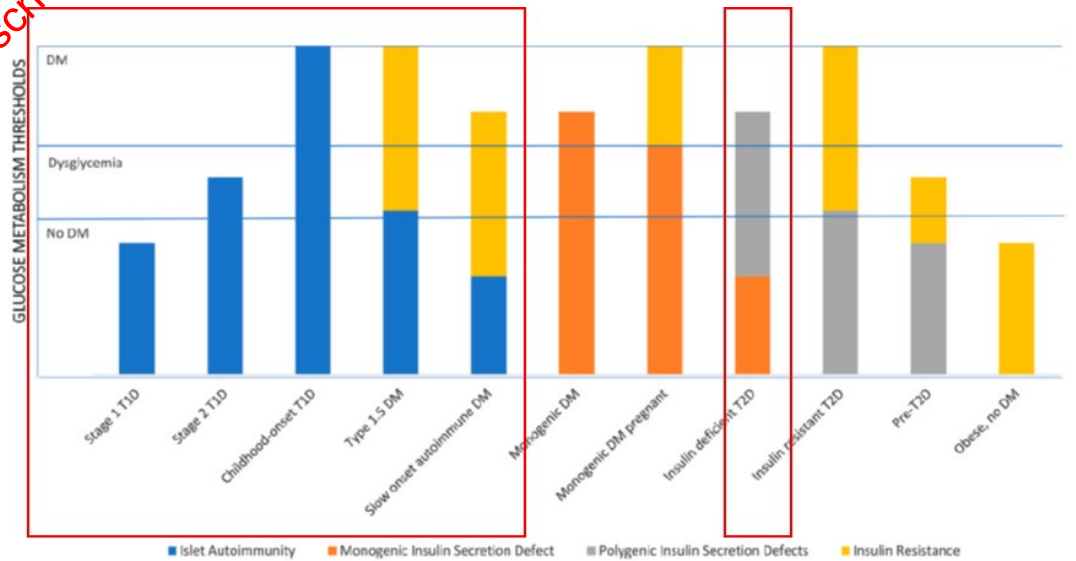


Figure 7—Model of diabetes etiopathogenesis based on the Palette Disease Model (78) and Threshold Hypothesis (79) that explain heterogeneity within diabetes types and overlap between diabetes types. Individuals (represented by bars) may have several diabetogenic mechanisms (represented by different colors) that, in combination, may cause glucose to reach a threshold. DM, diabetes mellitus; T1D, type 1 diabetes; T2D, type 2 diabetes.

Features of Basal Insulin

The Modern Role of Basal Insulin in Advancing Therapy in People With Type 2 Diabetes

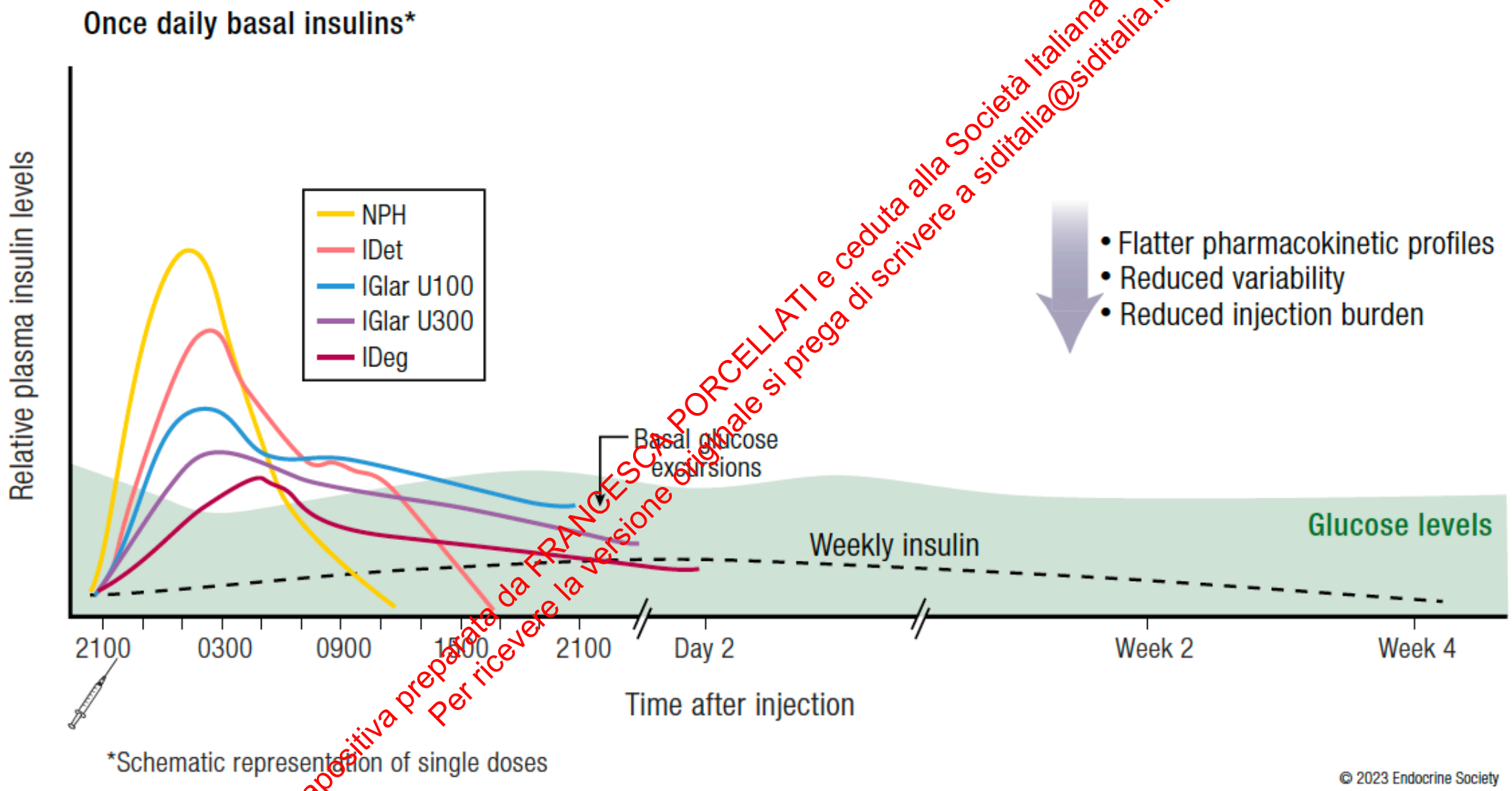
Geremia B. Bolli, Philip D. Home, Francesca Porcellati, Matthew C. Riddle, Hertzel C. Gerstein, Paola Lucidi, Carmine G. Fanelli, and David R. Owens

- Mechanisms of action well established
- Research and clinical experience for > 80 years
- Most efficacious and durable glucose-lowering treatment
- The only treatment with 100% of patients as responders (provided titration is appropriate)
- Most efficient removal of glucotoxicity (improved insulin secretion and action)
- Anti-inflammatory, antiatherogenic, vasodilator, and pro-endothelium effects
- Anabolic effects
- Limited contraindications
- Can be titrated from (very) low to (very) high doses
- Can be used with any other diabetes treatment*
- Long-term protection of ASCVD/CKD risk in people in whom other therapies fail to maintain target HbA1c

* Caution with sulfonylurea (risk of hypoglycemia) and thiazolidinediones (risk of fluid retention and heart failure)

Diabetes Care 2025;48(5):1–11

The Need to Achieve a Favorable Insulin-action Profile



Hypoglycemia with Degludec and Glargine 300 Compared with Glargine 100

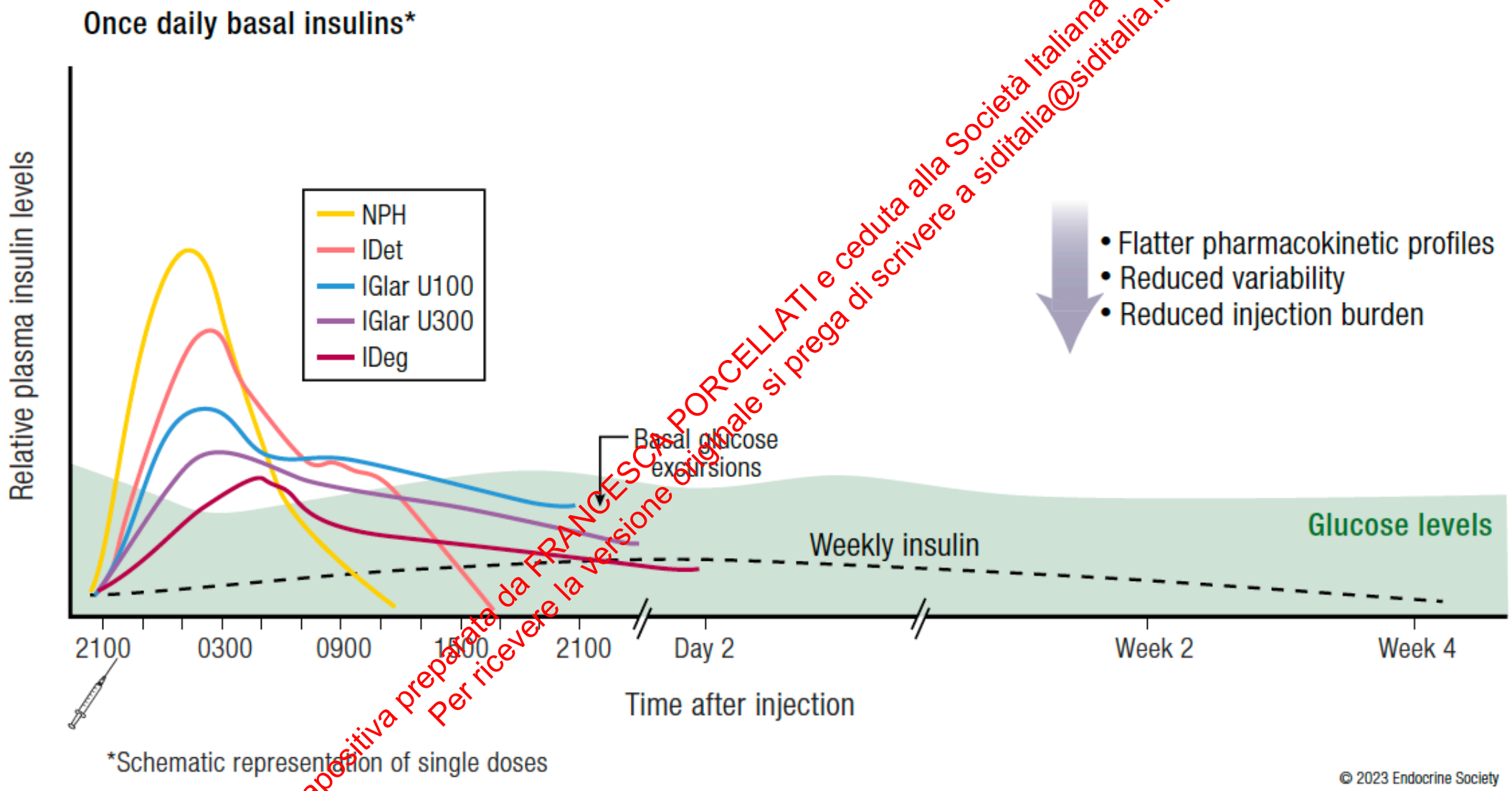
Meta-analyses of phase 3 clinical studies of type 2 diabetes

	Degludec [1]	Glargine 300 [2]
N° of studies	5	3
N° of participants	3372	3496
Definition of confirmed hypoglycemia	<56 mg/dl or severe	≤70 mg/dl or severe
Rate Ratio (95% CI)		
Anytime events	0.83 (0.74-0.94)	0.86 (0.77-0.97)
Nocturnal events	0.68 (0.57-0.82)	0.69 (0.57-0.84)

With both new insulins, ~15% fewer overall and ~30% fewer nocturnal events

[1] Ratner RE et al. Diab Obes Metab 2013;15: 175-184 [2] Ritzel R et al. Diab Obes Metab 2015;17: 859-867

The Need to Achieve a Favorable Insulin-action Profile



diabetesresearchandclinicalpractice 205 (2023) 110984

Once-weekly insulin icodec as novel treatment for type 2 diabetes mellitus: A systematic review and *meta*-analysis of randomized clinical trials

Nanny Natalia Mulyani Soetedjo [a], Hikmat Permana [a,*], Timotius Ivan Hariyanto [b], Marshell Tendean [a,c], Maya Kusumawati [a], Ervita Ritonga [a], Theo Audi Yanto [b], Ketut Suastika [d]

Contents lists available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.journals.elsevier.com/diabetes-research-and-clinical-practice

A total of 9 trials with 3,963 participants were incorporated.

- The results of our meta-analysis showed:
  - No significant difference in the reduction of HbA1c levels between insulin icodec and regular basal insulin (MD 0.11 %; 95 %CI: 0.23, 0.01, p = 0.08, I2 = 91 %).
  - The fasting plasma glucose (FPG) and body weight change from baseline also did not differ significantly between two groups.
  - The total adverse events (TAEs) were shown to be higher in the insulin icodec;
  - The serious AEs (SAEs) and clinically significant hypoglycemia did not differ significantly between insulin icodec and these active controls.

Barriers to Initiating Insulin Therapy

Conditioning factor	Barrier	Strategy
Patient	Adherence Perception of failure	Use of long-acting insulin Dose recall systems Diabetes education program
Social environment	Social rejection	Community education
Treatment	Dosage	Use of simple adjustment guidelines Implementation of FGM/CGM Systems
	Hypoglycemia	Documentation of episodes by the patient Implementation of FGM/CGM systems Education on signs and symptoms Adjustments in physical exercise Instruction in the guidelines for dealing with hypoglycemia
	Method of administration	Simple, intuitive devices adapted to different physical limitations Instructions in management technique.
	Weight Gain	Design of specific devices for patients with needle phobia Healthy eating education Prescription of physical exercise

Galdon Sanz-Pastor A. et al., Front Endocrin 2024, modified

Clinical scenarios in which starting BI may be preferred in the era of GLP-1RAs and SGLT2i

- Metabolic emergencies (hyperosmolality, ketoacidosis)
- Acute or variable hyperglycemia (sick days, steroid therapy, trauma, major surgery, stress)
- Patient preference
- Comorbidities (kidney and liver failure, cancer, chemotherapy)
- Autoimmune pathogenesis (LADA)
- Pregnancy
- Lean, predominantly insulin-deficient T2D
  - including some elderly onset
  - with excessive weight loss on other therapies
- New-onset T2DM with marked hyperglycemia
- HbA1c not at target with other management
- Intolerance of non-insulin therapies (including GLP-1RA, SGLT2i)
- Possibility that patient may have T1DM

Diabetes Care
American Diabetes Association

The Modern Role of Basal Insulin in Advancing Therapy in People With Type 2 Diabetes

Geremia B. Bolli, Philip D. Home, Francesca Porcellati, Matthew C. Riddle, Hertzel C. Gerstein, Paola Lucidi, Carmine G. Fanelli, and David R. Owens

Diabetes Care 2025;48(5):1–11

Glycemic Control Following GLP-1 RA or Basal Insulin Initiation in Real-World Practice

Proportion of all patients achieving HbA_{1c} < 7% by baseline HbA_{1c} (≥7% to <8% vs. ≥ 8% to <9% vs. ≥ 9%) for patients initiated on GLP-1 RAs and for patients initiated on BI

In T2D patients inadequately controlled on oral glucose-lowering drugs, initiation of first injectable therapy (GLP1 RA or BI) did not occur until HbA_{1c} was considerably above target, when control was harder to achieve

Real-world retrospective study using UK CRPD data to evaluate glycemic control with GLP-1 RA (n=5.583) or basal insulin (n=5.606) in type 2DM

Peng XV et al., Diabetes Ther 2020

Basal Insulin Therapy in T2D: a Delphi Consensus

Summary of the statements with high level of consensus (score ≥ 8)

Basal insulin intensification strategies: add-on versus switch

- Insulin therapy should be considered at any stage of the natural history of the disease, if situations such as severe hyperglycemia, symptoms of glycemic decompensation or significant unintentional weight loss are present
- The add-on of basal insulin therapy allows the achievement of optimal metabolic control in most patients on therapy with SGLT2i and/or GLP-1 RA not at target
- In the patient starting basal insulin, it is not appropriate to suspend a pre-existing therapy with SGLT2i and/or GLP-1 RA, unless specific contraindications or tolerability problems are present
- Switching from SGLT2i and/or GLP-1 RA to basal insulin is appropriate in case of specific clinical situations such as contraindications, tolerability issues, unwanted weight loss

Basal insulin intensification strategies: inertia to initiate and inertia to titrate

- Timely titration to an individualized glycemic target is necessary to obtain the full benefits of basal insulin
- Inertia to initiate and titrate basal insulin to personalized glycemic target is often a cause of treatment failure)
- Self-titration of basal insulin should be recommended for all patients, except those who are unable to manage it

Acta Diabetologica (2024) 61:1267–1281

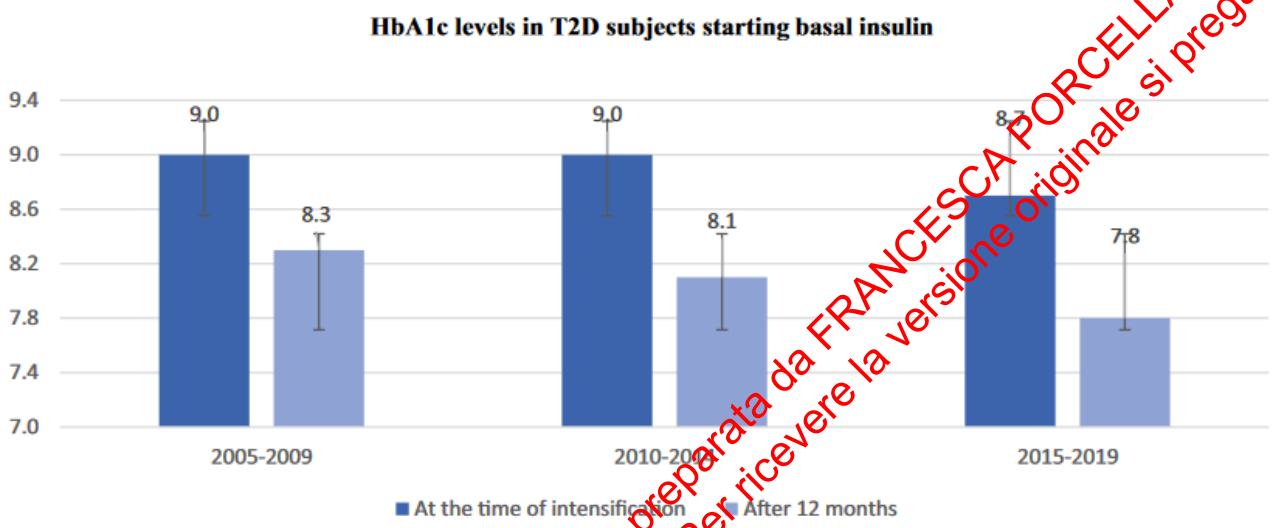
Journal of Endocrinological Investigation
https://doi.org/10.1007/s40618-024-02306-5

ORIGINAL ARTICLE

Temporal trends in the starting of insulin therapy in type 2 diabetes in Italy: data from the AMD Annals initiative

A. Giandalia[1] · A. Nicolucci[2] · M. Modugno[3] · G. Lucisano[2] · M. C. Rossi[2] · V. Manicardi[4] · A. Rocca[5] · G. Di Cianni[6] · P. Di Bartolo[7] · R. Candido[5,8] · D. Cucinotta[1] · G. T. Russo[1]

171.688 T2D subjects who intensified therapy with basal insulin



In this large cohort of T2D subjects, a progressively earlier start of insulin treatment was observed during a long observation period, suggesting a more proactive prescriptive approach.
However, after 12 months from insulin prescription, in many patients, HbA1c levels were still out-of-target

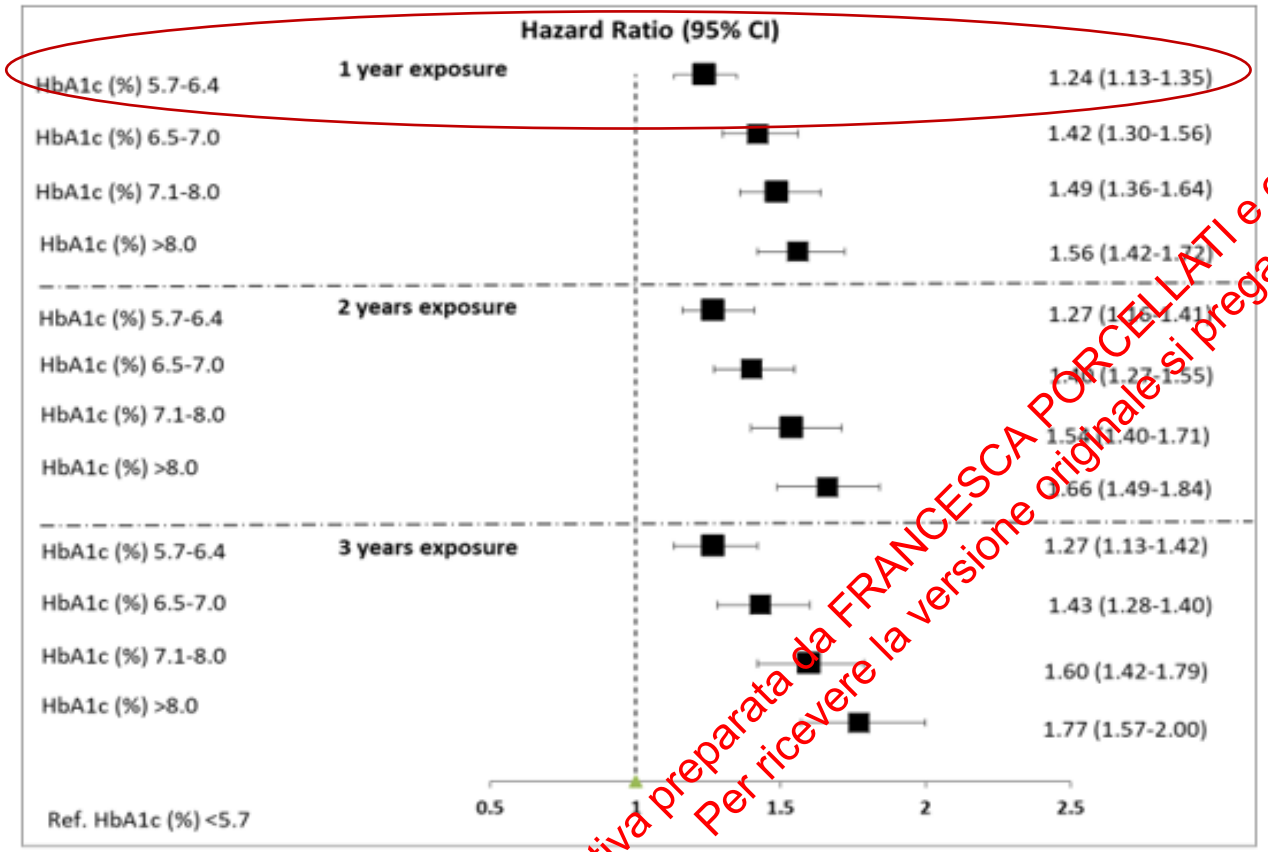
Annali AMD 2024 T2D : Inerzia Terapeutica

Indicatore	Denominatore	%	Gold standard (25° o 75° *percentile*)
Soggetti in sola dieta con HbA1c ≤7,0%	Soggetti in sola dieta (n=15.691)	94,6	100,0
Soggetti in sola dieta nonostante valori di HbA1c >8,0%	Soggetti con valori di HbA1c >8,0% (n=111.072)	0,1	0,0
Soggetti non trattati con insulina nonostante valori di HbA1c ≥9,0%	Soggetti con valori di HbA1c ≥9,0% (n=44.956)	26,5	20,2
Soggetti non trattati con GLP1-RA e/o SGLT2i e/o insulina nonostante valori di HbA1c ≥9,0%	Soggetti con valori di HbA1c ≥9,0% (n=44.956)	7,2	4,0
Soggetti con HbA1c ≥9,0% nonostante il trattamento con insulina	Soggetti trattati con insulina (n=213.268)	15,5	12,8
Soggetti con HbA1c ≥9,0% nonostante il trattamento con GLP1-RA e/o SGLT2i e/o insulina	Soggetti trattati con GLP1-RA e/o SGLT2i e/o insulina (n=408.128)	7,0	5,6
Soggetti con età ≥75 anni e HbA1c <7,0% trattati con secretagoghi e/o insulina	Soggetti con età ≥75 anni e HbA1c <7,0% (n=112.657)	27,7	22,2

Diabetes Volume 74, January 2025 75

When Does Metabolic Memory Start? Insights From the Association of Medical Diabetologists Annals Initiative on Stringent HbA_{1c} Targets

Giuseppina T. Russo,[1] Antonio Nicolucci,[2] Giuseppe Lucisano,[2] Maria Chiara Rossi,[2] Antonio Ceriello,[3] Francesco Prattichizzo,[3] Valeria Manicardi,[4] Alberto Rocca,[5] Paolo Di Bartolo,[6] Salvatore De Cosmo,[7] Graziano Di Cianni,[8] and Riccardo Candido[9]



251.339 pts newly diagnosed with T2D without CVD

Compared with mean HbA1c <5.7% during the first year after diagnosis, the increase in the risk of CVD was 24%, 42%, 49%, and 56% for patients with HbA1c of 5.7–6.4%, 6.5–7.0%, 7.1–8.0%, and >8.0%, respectively.

Pseudo-forest plot showing the adjusted hazard ratios (HR) with the relative 95% confidence interval (CI), derived from the Cox regression analyses exploring the associations between glycemic control and the risk of the CVD at follow-up to the degree of glycemic control in the three exposure periods assessed

The Modern Role of Basal Insulin in Advancing Therapy in People With Type 2 Diabetes

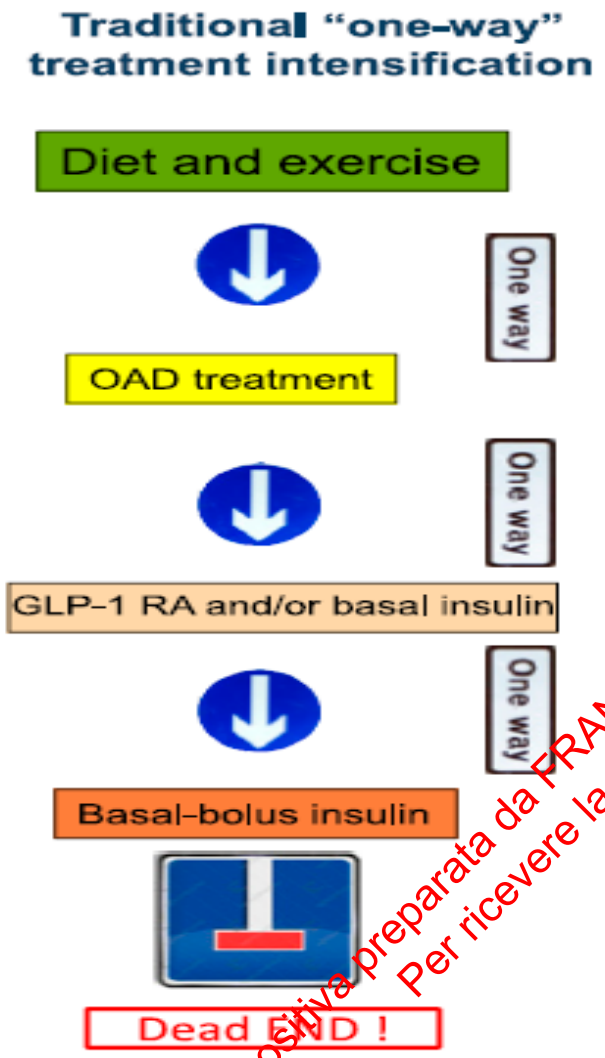
Diabetes Care 2025;48:671–681 | https://doi.org/10.2337/dci24-0104

Geremia B. Bolli,[1] Philip D. Home,[2] Francesca Porcellati,[1] Matthew C. Riddle,[3] Hertzel C. Gerstein,[4] Paola Lucidi,[5] Carmine G. Fanelli,[1] and David R. Owens[6]

Basal Insulin and Mealtime Insulin

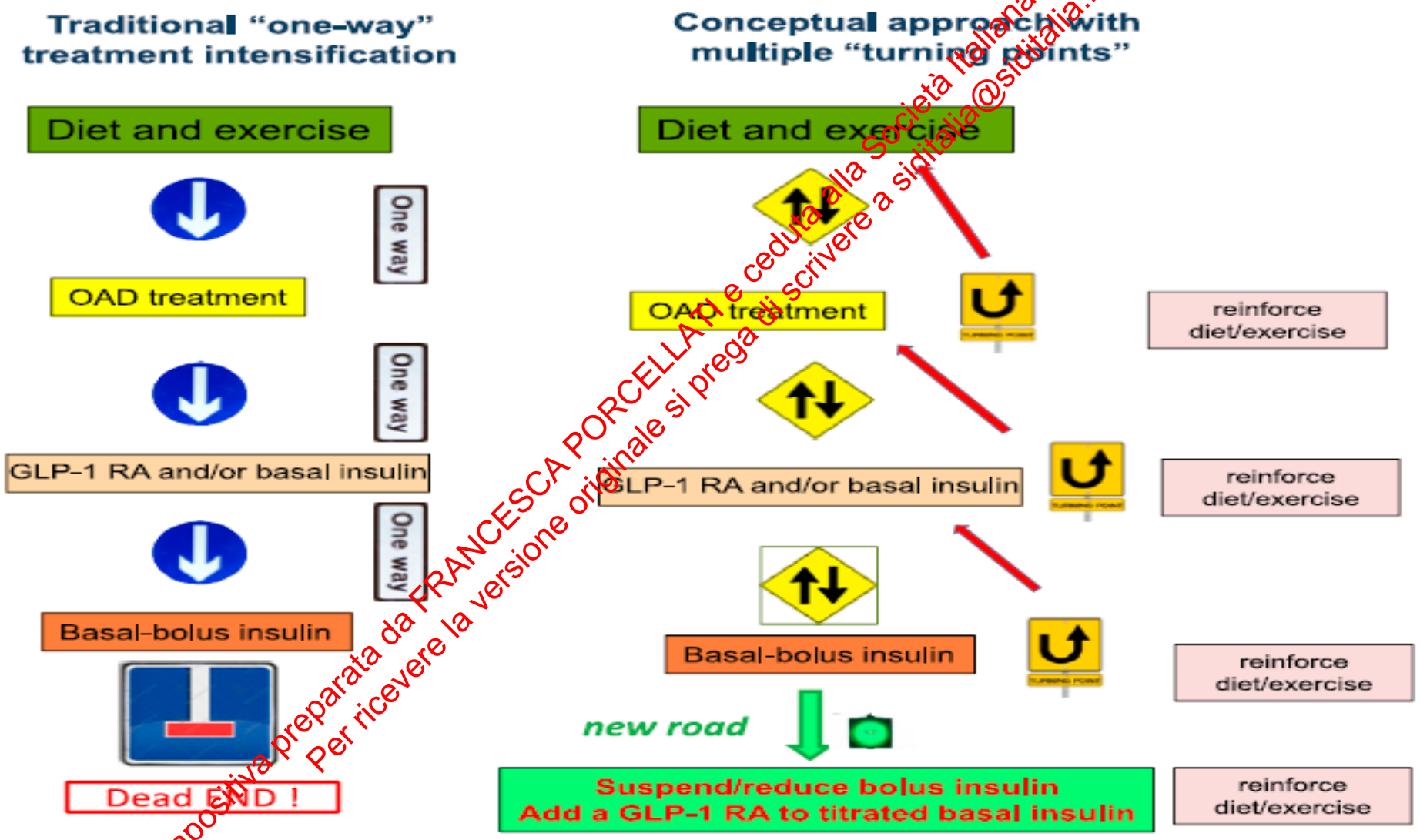
- Traditionally, rapid-acting insulin at mealtimes is added to BI when BI alone can no longer keep HbA1c at target despite FPG at target (inappropriately referred to as “BI failure”). However, beginning rapid-acting insulin is not now recommended in this circumstance unless the options of incretins and/or SGLT2i have already been trialed.

La Terapia del Diabete Mellito di Tipo 2



Geremia B. Bolli et al. Dia Care 2020;43:2333-2335

La Terapia del Diabete Mellito di Tipo 2



G. Bolli et al. Diabetes Care 2020;43:2333-2335

Simplification of Complex Insulin Therapy

Individual on basal (long- or intermediate-acting)* and/or prandial (short- or rapid-acting)† insulins

Individual on premixed insulin†

Basal insulin

Prandial insulin

Use 70% of total dose as basal only in the morning

Change timing from bedtime to morning

Titrate dose of basal insulin based on fasting finger-stick glucose test results over 1 week

Fasting goal: 90–150 mg/dL (5.0–8.3 mmol/L)

- May change goal based on overall health and goals of care

If 50% of the fasting finger-stick glucose values are over the goal:

- Increase dose by 2 units

If >2 fasting finger-stick values/week are <80 mg/dL (<4.4 mmol/L):

- Decrease dose by 2 units

If prandial insulin >10 units/dose:

- Decrease dose by 50% and add noninsulin agent§

Titrate prandial insulin doses down as noninsulin agent doses are increased with aim to discontinue prandial insulin

If prandial insulin ≤10 units/dose:

- Discontinue prandial insulin and add noninsulin agent(s)§

Add noninsulin agents§:

- If eGFR is ≥45 mL/min/1.73 m², start metformin 500 mg daily and increase dose every 2 weeks as tolerated
- If eGFR is <45 mL/min/1.73 m², individual is already taking metformin, or metformin is not tolerated, proceed to second-line agent

Using individual comorbidities (e.g., CKD, ASCVD, low body weight, and risk of dehydration) and drug characteristics to guide decision-making, as depicted in **Fig. 9.3** and **Table 9.2**, select additional agent(s) as needed:

- Every 2 weeks, adjust insulin dose and/or add glucose-lowering medications based on finger-stick glucose testing performed before lunch and before dinner
- Goal: 90–150 mg/dL (5.0–8.3 mmol/L) before meals; may change goal based on overall health and goals of care‖
- If 50% of premeal finger-stick values over 2 weeks are above goal, increase the dose or add another agent
- If >2 premeal finger-stick values/week are <90 mg/dL (<5.0 mmol/L), decrease the dose of medication

Additional Tips

- Do not use rapid- and short-acting insulin at bedtime.
- While adjusting prandial insulin, a simplified sliding scale may be used, for example:
  - For premeal glucose >250 mg/dL (>13.9 mmol/L), give 2 units of short- or rapid-acting insulin.
  - For premeal glucose >350 mg/dL (>19.4 mmol/L), give 4 units of short- or rapid-acting insulin.
- Stop sliding scale when not needed daily

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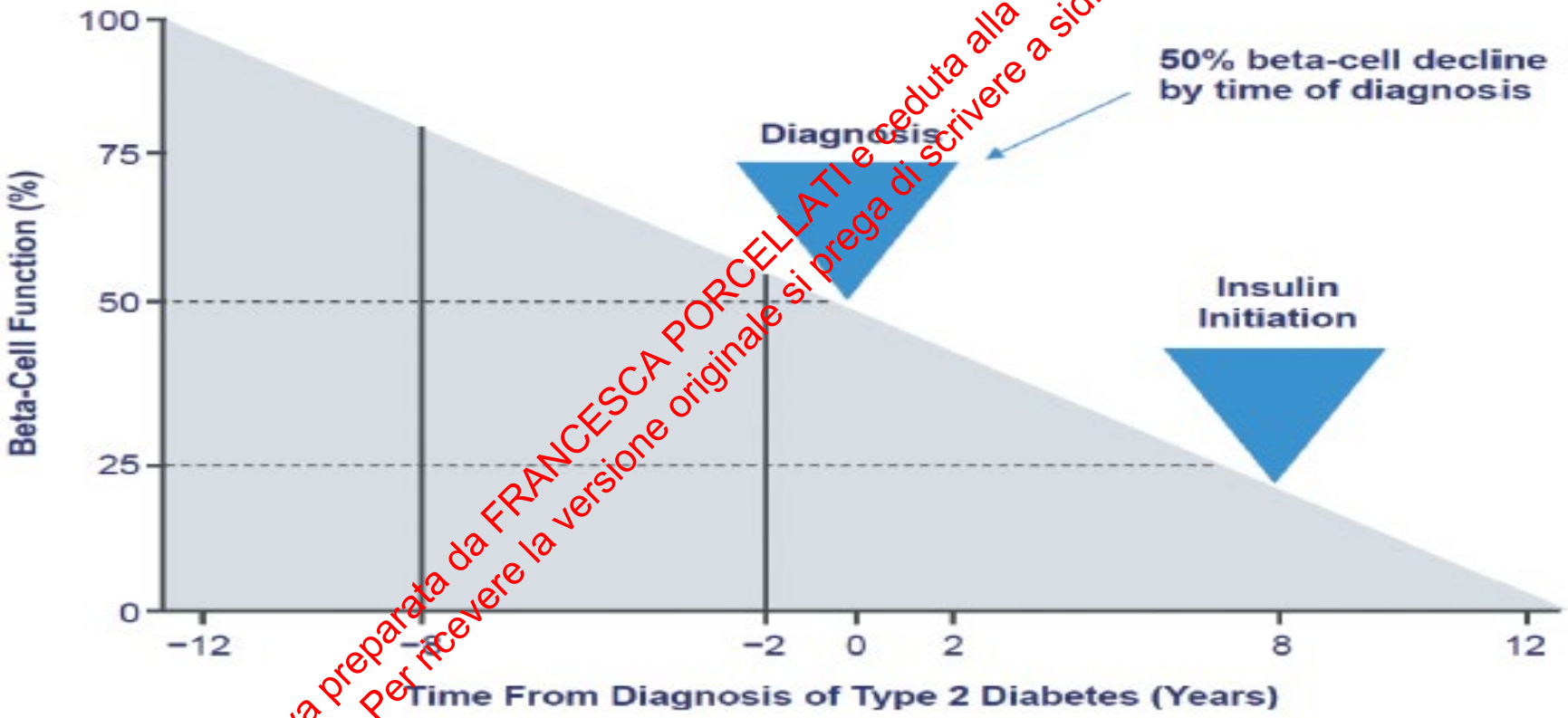
You may delay, but time will not……

"….. medications do not 'fail,' and more importantly, neither do people with T2D……"



Beta-cell modeling suggests that insulin is required approximately 8 years after diagnosis

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INSULIN THERAPY: THE LEARNING CURVE NEVER ENDS

Grazie per l'attenzione!