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

GLORIA FORMOSO

DIPARTIMENTO DI MEDICINA E SCIENZE DELL'INVECCHIAMENTO
CENTRO STUDI E TECNOLOGIE AVANZATE- CAST
UNIVERSITÀ G. D'ANNUNZIO CHIETI-PESCARA

UOC ENDOCRINOLOGIA E MALATTIE METABOLICHE
ASL PESCARA

Dogmi della fede in diabetologia

1. Non può svilupparsi diabete senza un deficit di secrezione insulinica (assoluto, relativo; quantitativo, qualitativo).

2. La terapia insulinica teoricamente non è mai sbagliata ma in moltissimi casi di diabete non è necessaria e quindi è inappropriata.

3. La terapia insulinica è vitale nel diabete tipo 1 classico ed è necessaria anche in molti casi di diabete tipo 2 e di altre varietà della malattia fra cui diabete autoimmune a lenta progressione (LADA), diabete pancreatogenico, diabete monogenico, ecc.

4. In non pochi casi la terapia insulinica, una volta instaurata per motivi contingenti, può (deve) essere poi interrotta.

Bonora E. Expert Opinion 2024

Caratteristiche dell'insulina basale

- Meccanismi d'azione ben consolidati
- Ricerca ed esperienza clinica da oltre 80 anni
- Il trattamento ipoglicemizzante più efficace e duraturo
- L'unico trattamento con il 100% dei pazienti responsivi (se la titolazione è appropriata)
- Rimozione più efficiente della glucotossicità (miglioramento della secrezione e dell'azione dell'insulina)
- Effetti antinfiammatori, antiaterogeni, vasodilatatori e pro-endotelio
- Effetti anabolici
- Controindicazioni limitate
- Può essere titolato da dosi (molto) basse a (molto) alte
- Può essere utilizzato con qualsiasi altro trattamento per il diabete*
- Protezione a lungo termine dal rischio di ASCVD/CKD nelle persone in cui altre terapie non riescono a mantenere l'HbA1c target

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

Diabetes Care
American Diabetes Association

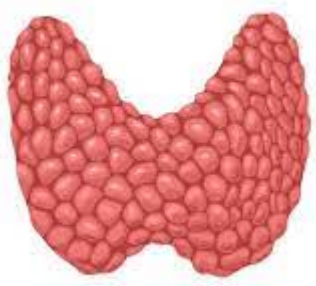
The Modern Role of Basal Insulin in Advancing Therapy in People With Type 2 Diabetes

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

Terapia sostitutiva nelle malattie endocrine: il diabete di tipo 2 è una malattia endocrina di origine pancreatica

Se la tiroide funziona meno....



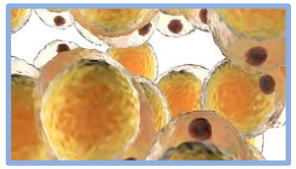
Diamo L-T4

Se la β-cellulla funziona meno.....

Diamo Insulina

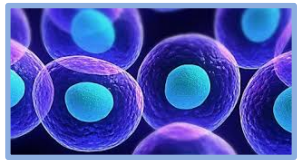
Azioni non glicemiche dell'insulina

Metabolismo lipidico
Inibizione della lipolisi (↓ acidi grassi liberi)
Stimolazione della lipogenesi (↑ sintesi di trigliceridi)
Inibizione della chetogenesi

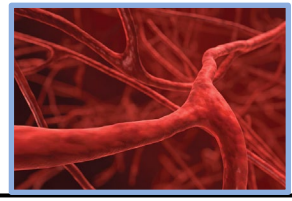


Metabolismo proteico
Stimolazione della sintesi proteica
Inibizione della proteolisi

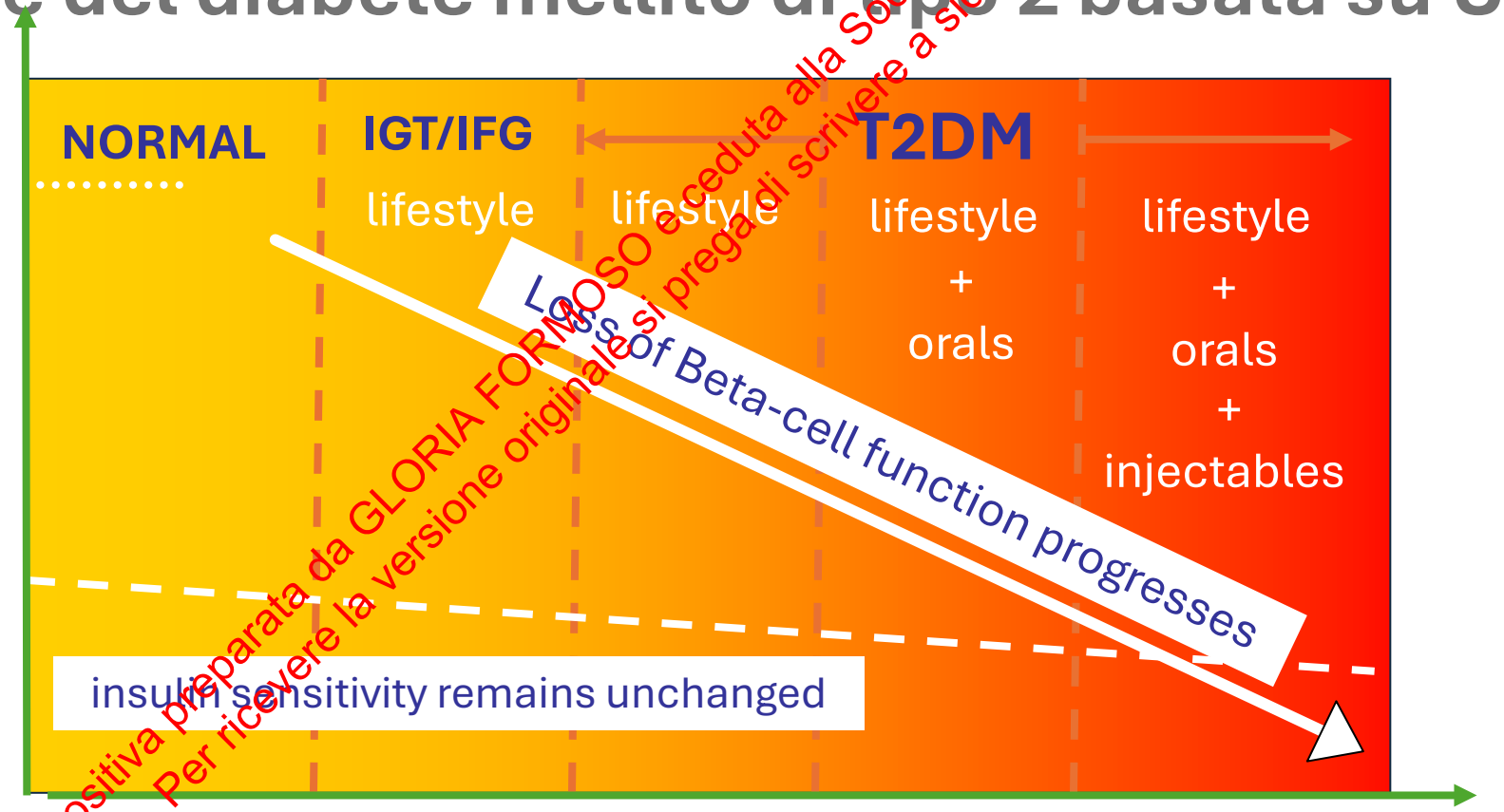
Effetti sugli ioni
Stimolazione del trasporto intracellulare di K^+ (utile nell'iperkaliemia)
Aumento dell'assorbimento di fosfato e magnesio



Effetti vascolari e cellulari
Stimolazione della sintesi di NO → vasodilatazione
Azione anabolica generale (crescita e differenziazione cellulare)



Storia naturale del diabete mellito di tipo 2 basata su UKPDS



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

UKPDS. Diabetes. 1995;44:1249-58

Diagnosi precoce e trattamento efficace della patologia

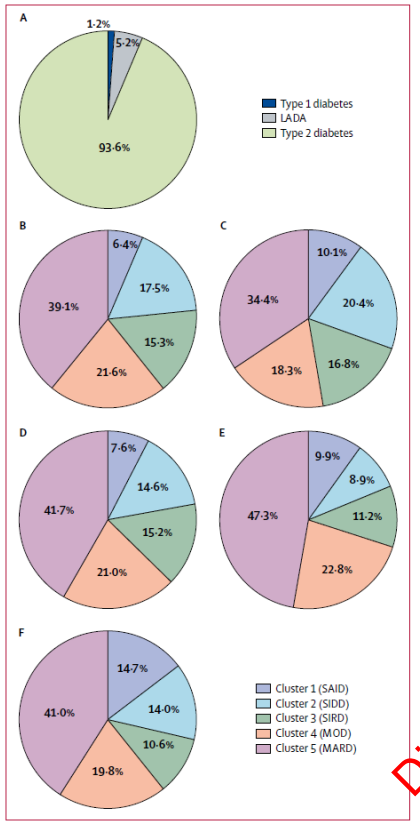
CARDIONEFRO METABOLICA

DALLA teoria ALLA pratica

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



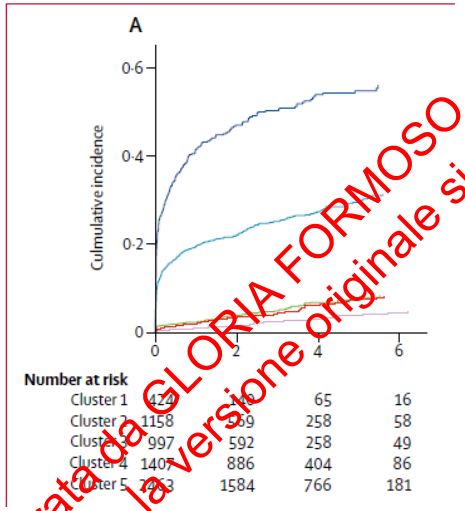


Figure 1: **Patient distribution according to method of classification**
(A) Distribution of ANDIS patients (n=8980) according to traditional classification. (B) Distribution of ANDIS patients (n=8980) according to k-means clustering. (C) Distribution of patients in the Scania Diabetes Registry (n=1466) 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

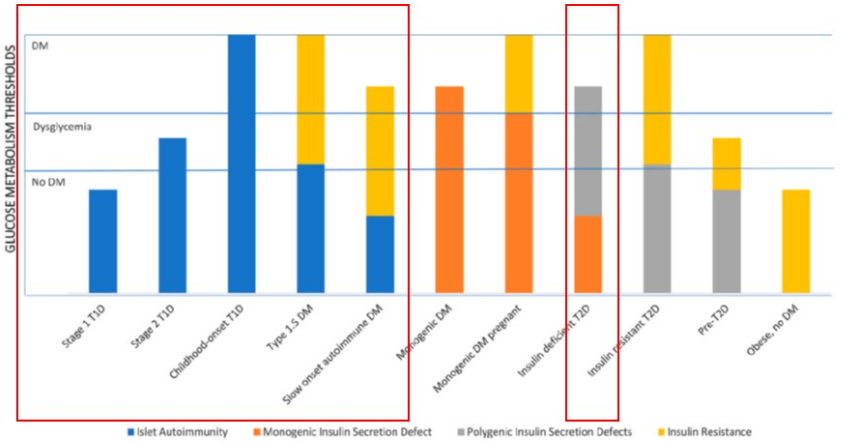
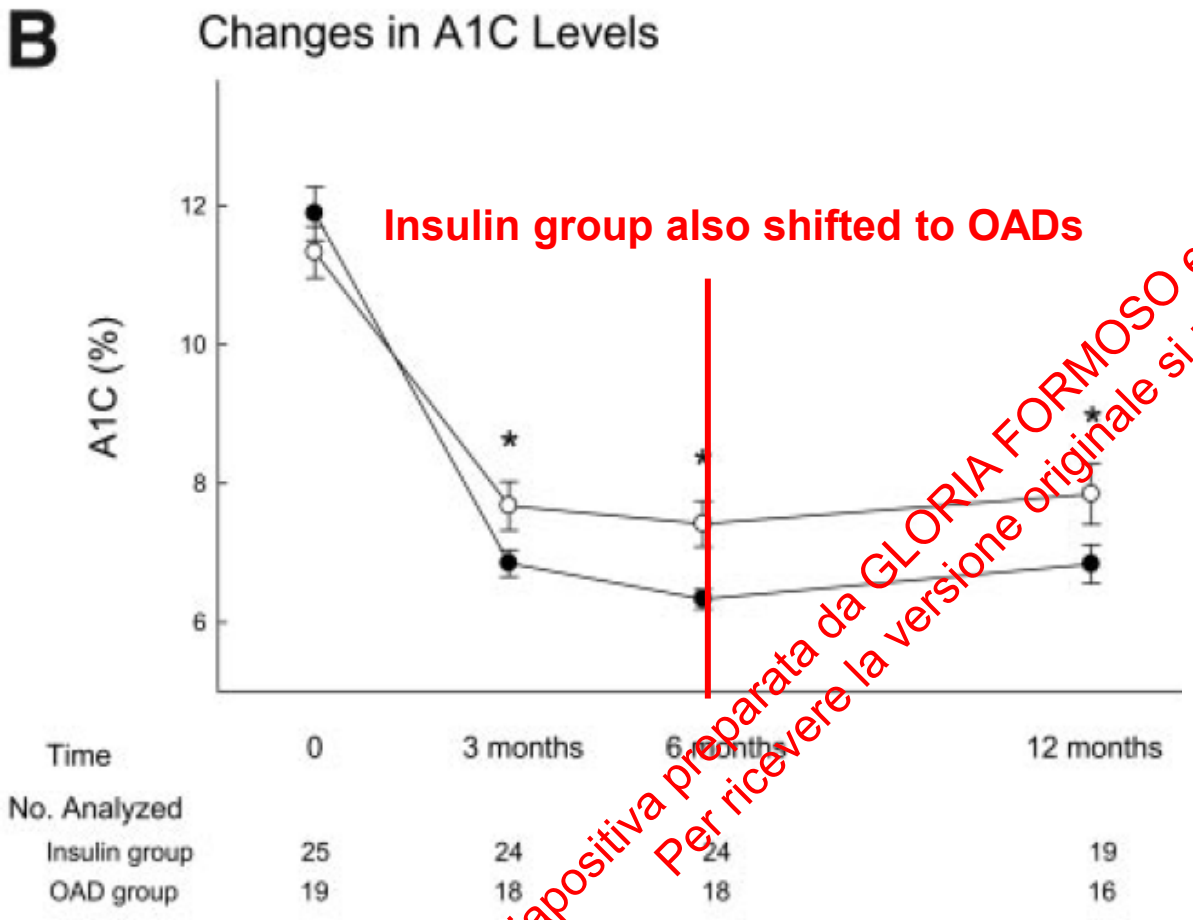


Figure 7—Model of diabetes etiopathogenesis based on the Palette Disease Model (78) and Threshold Hypothesis (79) that explain heterogeneity within diabetes types and overlap between diabetes types. Individuals (represented by bars) may have several diabetogenic mechanisms (represented by different colors)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

Beneficial Effects of Insulin on Glycemic Control and β-Cell Function in Newly Diagnosed Type 2 Diabetes With Severe Hyperglycemia After Short-Term Intensive Insulin Therapy

Chen H-S et al. Diabetes Care 31:1927–1932, 2008



- Insulin group: intensive insulin therapy
- OAD group: mean dose gliclazide-MR 60 mg and metformin 1.200 mg

A 6-month course of insulin therapy, compared with OAD treatment, could more effectively achieve adequate glycemic control and significant improvement of beta-cell function in new-onset type 2 diabetic patients with severe hyperglycemia.

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

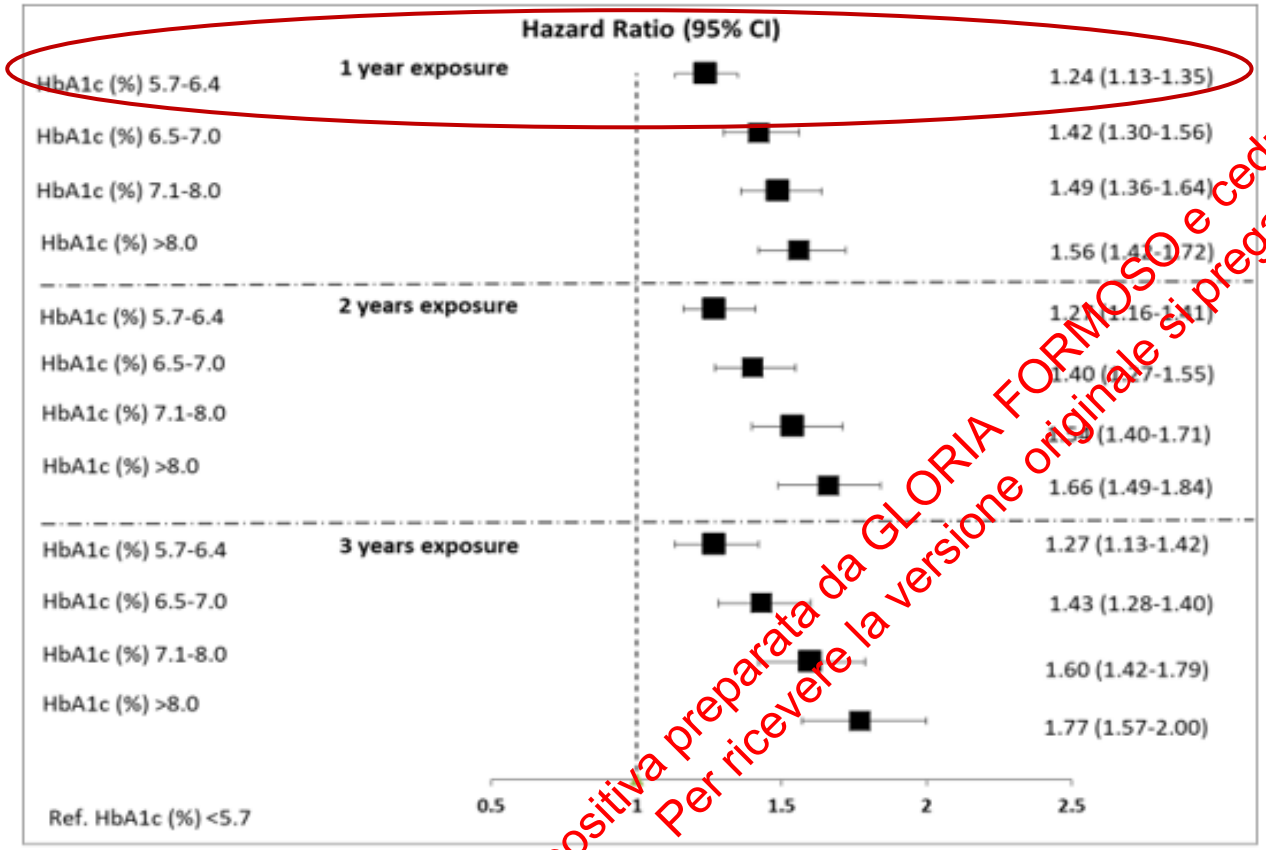
Proportion of all patients achieving HbA_{1c} < 7% by baseline HbA_{1c} (≥7% to <8% vs. ≥ 8% to <9% vs. ≥ 9%) for patients initiated on GLP-1 RAs and for patients initiated on BI

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

At risk						At risk					
≥7–<8%	6844	3126	911	479	274	≥7–<8%	14,323	6378	3837	2712	1984
≥8–<9%	6411	3544	1233	729	439	≥8–<9%	14,025	8115	5624	4228	3231
≥9%	7581	4488	1783	1011	617	≥9%	32,250	19,555	13,840	10,489	7890

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 X. V. Diabetes Ther (2020)



Diabetes Volume XX, 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]

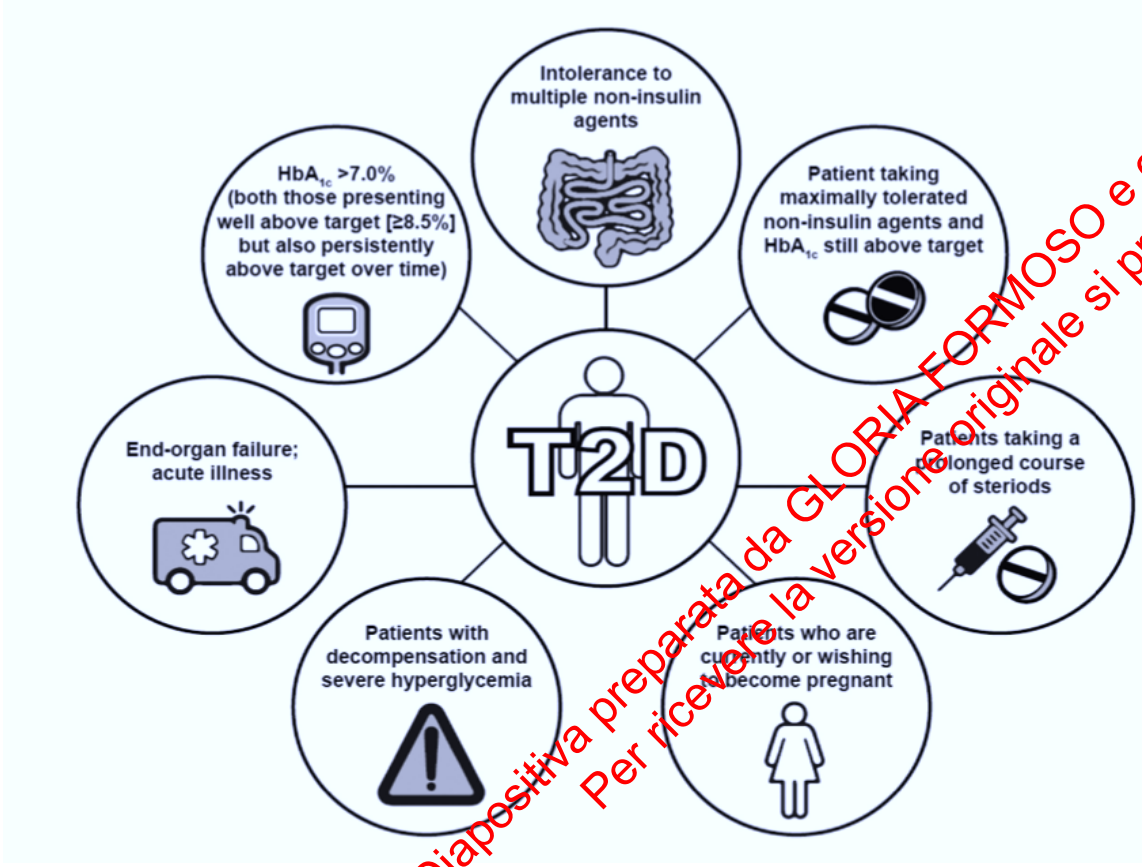
Diabetes 2025;74:75–81 | https://doi.org/10.2337/db24-0166

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

Scenari clinici in cui l'inizio dell'IB può essere preferibile nell'era dei GLP-1RA e degli SGLT2i



Postgraduate Medicine, 2024. 136:2, 150-161, DOI: 10.1080/00325481.2024.2328511

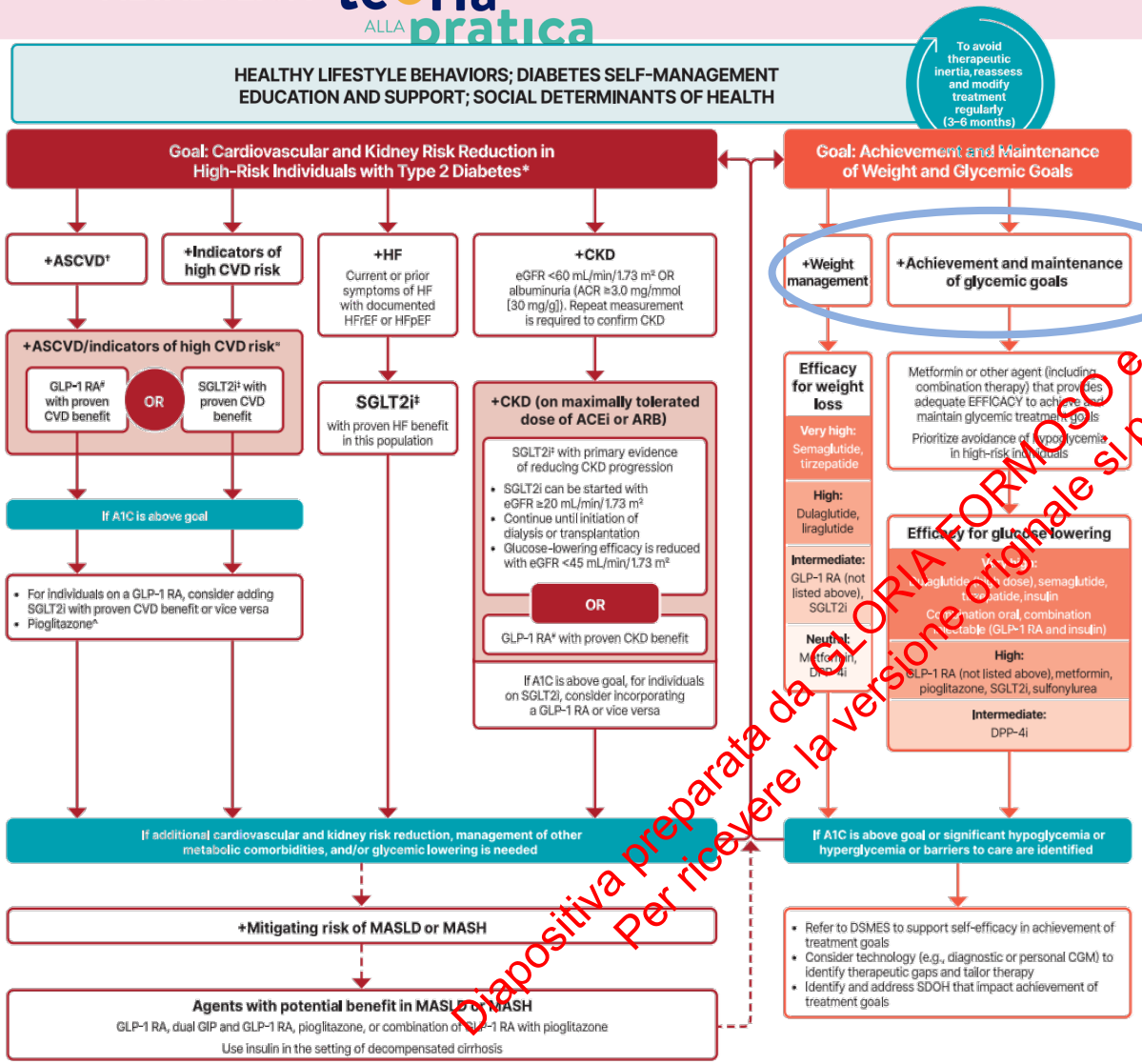
Diabetes Care
American Diabetes Association
The Modern Role of Basal Insulin in Advancing Therapy in People With Type 2 Diabetes 2025;48(5):671–681

- 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

Diagnosi precoce e trattamento efficace della patologia

CARDIONEFRO METABOLICA

DALLA teoria ALLA pratica



L'insulina è un alleata, non una nemica

«I medici dovrebbero **evitare di considerare l'insulina come una minaccia** o descriverla come **un segno di fallimento personale**»

«**L'utilità e l'importanza dell'insulina** per raggiungere e mantenere gli obiettivi glicemici una volta che la progressione della malattia supera l'effetto di altri agenti, così come per l'uso temporaneo in situazioni acute [...] **dovrebbero essere enfatizzate**»

Diabetes Care 2025;48(Suppl. 1):S181–S206 | https://doi.org/10.2337/dc25-S009 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes—2025

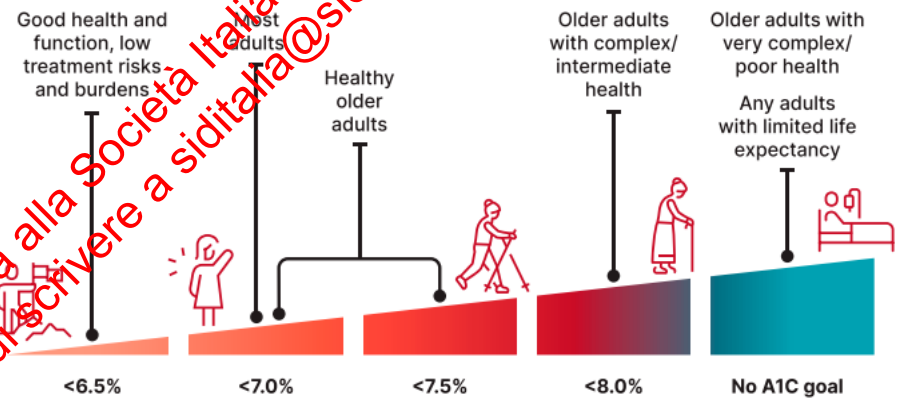
Un obiettivo di HbA1c < 7% è appropriato per gran parte dei pazienti, anche se è raccomandato un approccio personalizzato

Table 6.3—Summary of glycemic goals for many nonpregnant adults with diabetes

A1C	<7.0% (<53 mmol/mol)*†
Preprandial capillary plasma glucose	80–130 mg/dL* (4.4–7.2 mmol/L)
Peak postprandial capillary plasma glucose‡	<180 mg/dL* (<10.0 mmol/L)

*More or less stringent glycemic goals may be appropriate for certain individuals. †CGM may be used to assess glycemic status as noted in Recommendations 6.3b and 6.3c and **Fig. 6.1**. Goals should be individualized based on duration of diabetes, age and life expectancy, comorbid conditions, known cardiovascular disease or advanced microvascular complications, impaired awareness of hypoglycemia, and individual considerations (per **Fig. 6.2**). ‡Postprandial glucose may warrant special attention if A1C goals are not met despite reaching preprandial glucose goals. Postprandial glucose measurements should be made 1–2 h after the beginning of the meal, generally the timing for peak levels in people with diabetes.

Obiettivi più aggressivi possono essere raccomandati se possono essere **raggiunti in sicurezza** e con un carico terapeutico accettabile e se l'aspettativa di vita è sufficiente **per raccogliere i benefici di obiettivi rigorosi.**



Favor more stringent goal	Favor less stringent goal
Short diabetes duration	Long diabetes duration
Low hypoglycemia risk	High hypoglycemia risk
Low treatment risks and burdens	High treatment risks and burdens
Pharmacotherapy with cardiovascular, kidney, weight, or other benefits	Pharmacotherapy without nonglycemic benefits
No cardiovascular complications	Established cardiovascular complications
Few or minor comorbidities	Severe, life-limiting comorbidities

Figure 6.2—Individualized A1C goals for nonpregnant adults. Select the glycemic goal based on individual health and function as described at the top of the figure. Consider modifying to a more or less stringent goal according to the factors listed in the table. Older adults are classified as healthy (few coexisting chronic illnesses, intact cognitive and functional status), as having complex/intermediate health (multiple coexisting chronic illnesses, two or more instrumental impairments to activities of daily living, or mild to moderate cognitive impairment), or as having very complex/ poor health (long-term care or end-stage chronic illnesses, moderate to severe cognitive impairment, or two or more impairments to activities of daily living). Select glycemic goals that avoid symptomatic hypoglycemia and hyperglycemia in all individuals. Consider individuals' resources and support systems to safely achieve glycemic goals. Incorporate the preferences and goals of people with diabetes through shared decision-making.

Diabetes Care 2025;48(Suppl. 1):S128–S145 | https://doi.org/10.2337/dc25-S006 6. Glycemic Goals and Hypoglycemia: Standards of Care in Diabetes—2025

If injectable therapy is needed to reduce A1C[1]

Consider GLP-1 RA or GIP/GLP-1 RA in most individuals prior to insulin[2]
INITIATION: Initiate appropriate starting dose for agent selected (varies within class)
TITRATION: Titrate to maintenance dose (varies within class)

If already on GLP-1 RA or dual GIP and GLP-1 RA or if these are not appropriate OR insulin is preferred

If above A1C target

Add basal insulin[3]
Choice of basal insulin should be based on person-specific considerations, including cost. Refer to **Table 9.4** for insulin cost information. Consider prescription of glucagon for emergent hypoglycemia.

Add basal analog or bedtime NPH insulin[4]

INITIATION: Start 10 units per day OR 0.1–0.2 units/kg per day

TITRATION:

- Set FPG target (see Section 6, "Glycemic Targets")
- Choose evidence-based titration algorithm, e.g., increase 2 units every 3 days to reach FPG target without hypoglycemia
- For hypoglycemia determine cause, if no clear reason lower dose by 10–20%

Assess adequacy of basal insulin dose
Consider clinical signals to evaluate for overbasalization and need to consider adjunctive therapies (e.g., basal dose more than ~0.5 units/kg/day, elevated bedtime–morning and/or post–preprandial differential, hypoglycemia [aware or unaware], high variability)

…nza di iniziare tempestivamente
…i glicemici non vengono
…i del recettore GLP-1

…o gli obiettivi e l'insulina è la …a introduzione non dovrebbe …data'

Table 6.3—Summary of glycemic recommendations for many nonpregnant adults with diabetes

A1C	<7.0% (53 mmol/mol)*#
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*More or less stringent glycemic goals may be appropriate for individual patients. #CGM may be used to assess glycemic target as noted in Recommendation 6.5b and **Fig. 6.1**. Goals should be individualized based on duration of diabetes, age/life expectancy, comorbid conditions, known CVD or advanced microvascular complications, hypoglycemia unawareness, and individual patient considerations (as per **Fig. 6.2**). †Postprandial glucose may be targeted if A1C goals are not met despite reaching preprandial glucose goals. Postprandial glucose measurements should be made 1–2 h after the beginning of the meal, generally peak levels in people with diabetes.

1. Davies MJ, et al. Diabetes Care 2022;45:2753–86; 2. Gonzalez JS, et al. Am Psychol 2016;71:539–51; 3. Adams SK, et al. Practice Innovations 2022;7:85–107; 4. Stratton I, et al. Brit Med J 2000;321:405–12; 5. Hasan R, et al. J Vasc Surg 2016;63:S22–8; 6. Tomic D, et al. Nat Rev Endocrinol 2022;18:525–39; 7. Harding JL, et al. Diabetologia 2019;62:3–16.

Diagnosi precoce e trattamento efficace della patologia

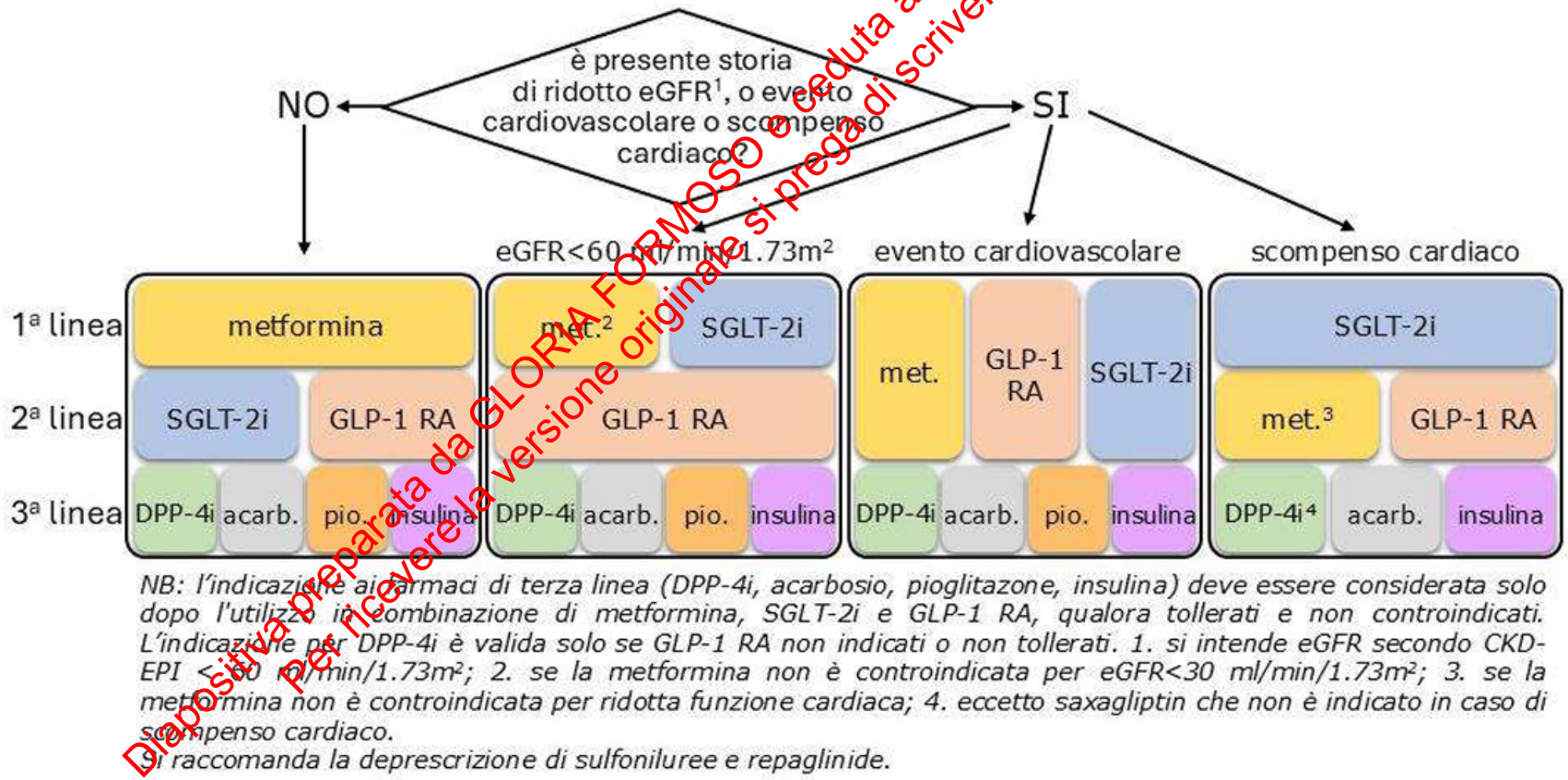
CARDIONEFRO METABOLICA

DALLA teoria ALLA pratica

SID Società Italiana di Diabetologia fondata nel 1964

SISTEMA NAZIONALE LINEE GUIDA DELL'ISTITUTO SUPERIORE DI SANITÀ

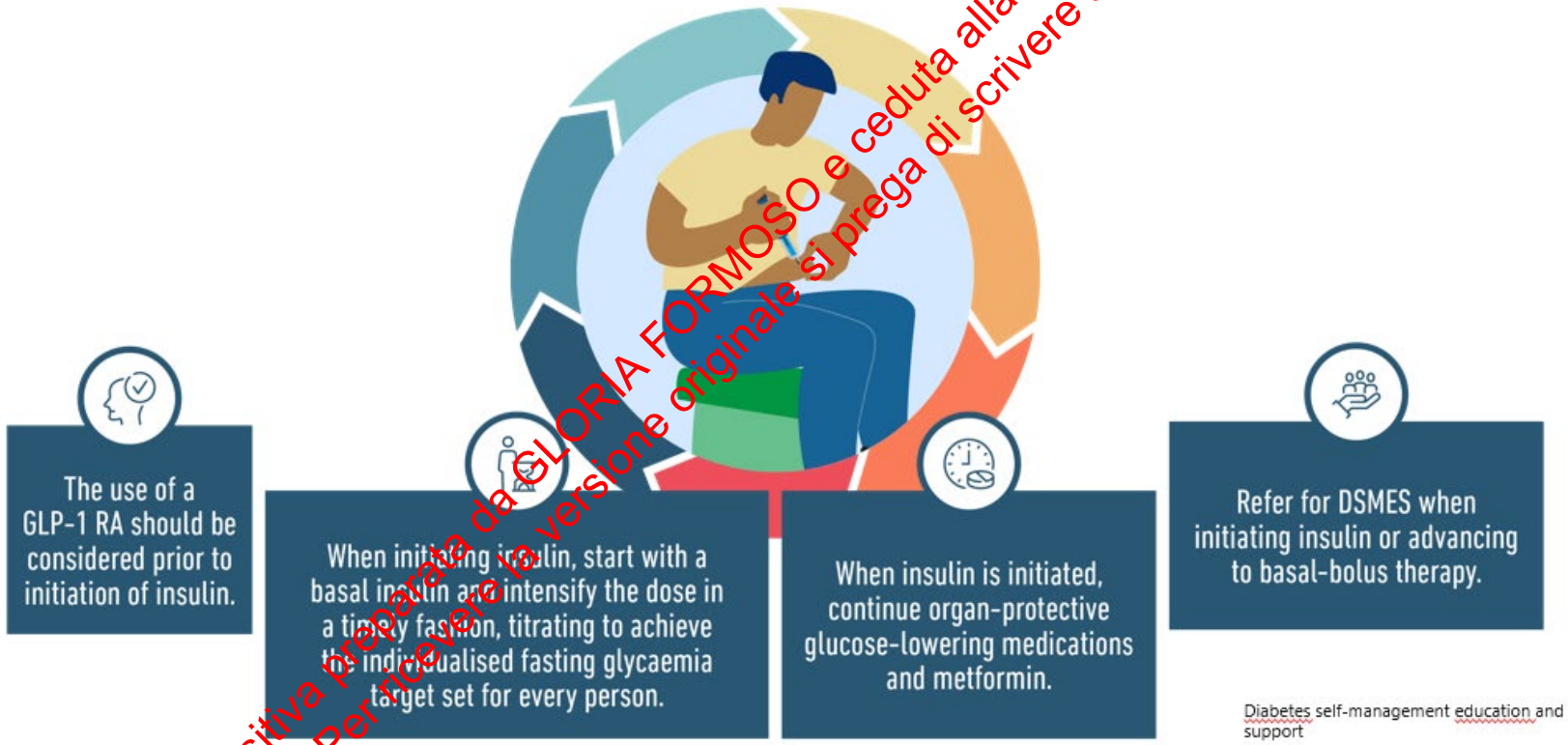
ASSOCIAZIONE MEDICI DIABETOLOGI



NB: l'indicazione ai farmaci di terza linea (DPP-4i, acarbosio, pioglitazone, insulina) deve essere considerata solo dopo l'utilizzo in combinazione di metformina, SGLT-2i e GLP-1 RA, qualora tollerati e non controindicati. L'indicazione per DPP-4i è valida solo se GLP-1 RA non indicati o non tollerati. 1. si intende eGFR secondo CKD-EPI <60 ml/min/1.73m²; 2. se la metformina non è controindicata per eGFR<30 ml/min/1.73m²; 3. se la metformina non è controindicata per ridotta funzione cardiaca; 4. eccetto saxagliptin che non è indicato in caso di scompenso cardiaco.

Si raccomanda la deprescrizione di sulfoniluree e repaglinide.

PLACE OF INSULIN IN TYPE 2 DIABETES



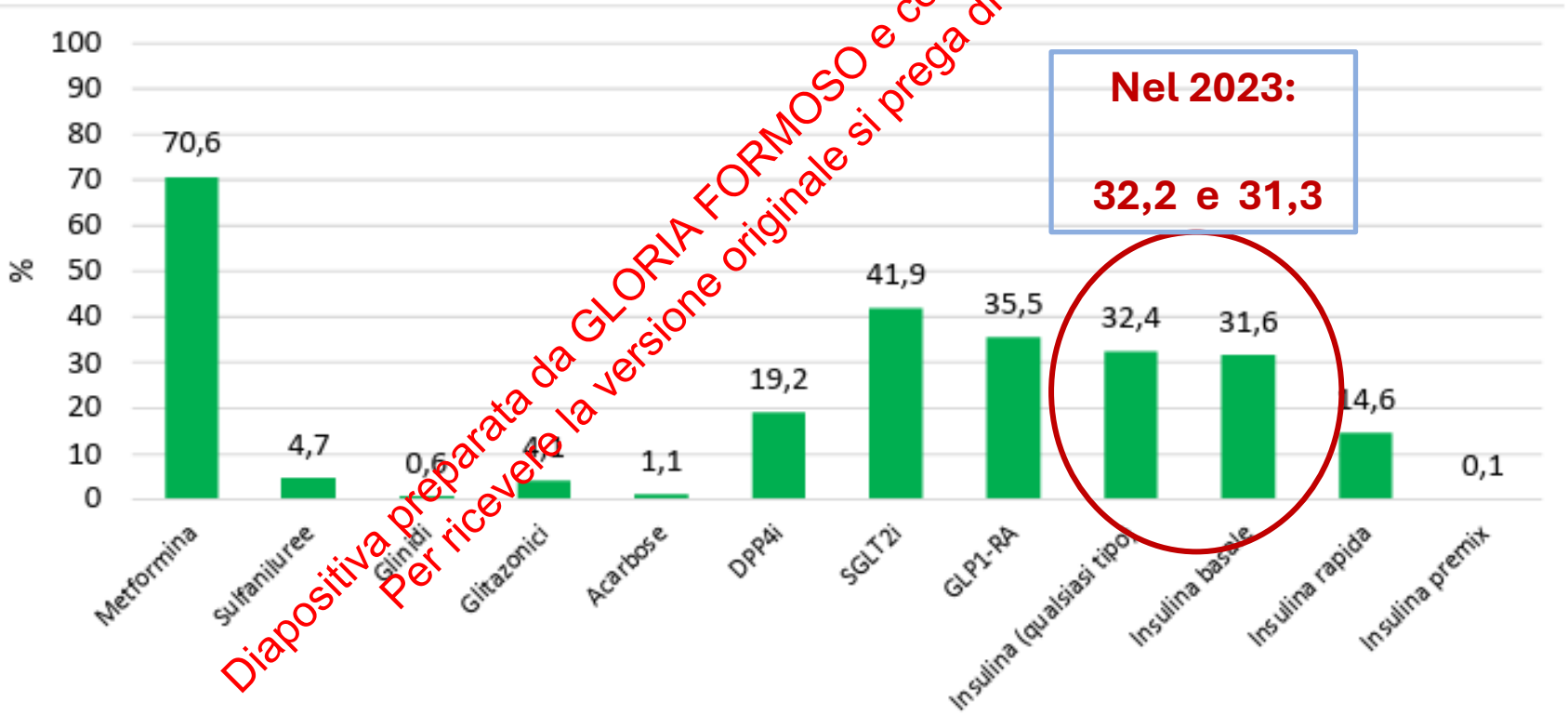
Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, Rosas SE, Del Prato S, Mathieu C, Mingrone G, Rossing P, Tankova T, Tsapas A, Buse JB

Diabetes Care 2022; https://doi.org/10.2337/dci22-0034. *Diabetologia* 2022; https://doi.org/10.1007/s00125-022-05787-2.

Uso dei farmaci (%)

Farmaci per il diabete (%)

Annali AMD 2024
Valutazione degli indicatori AMD di qualità dell'assistenza al diabete in Italia



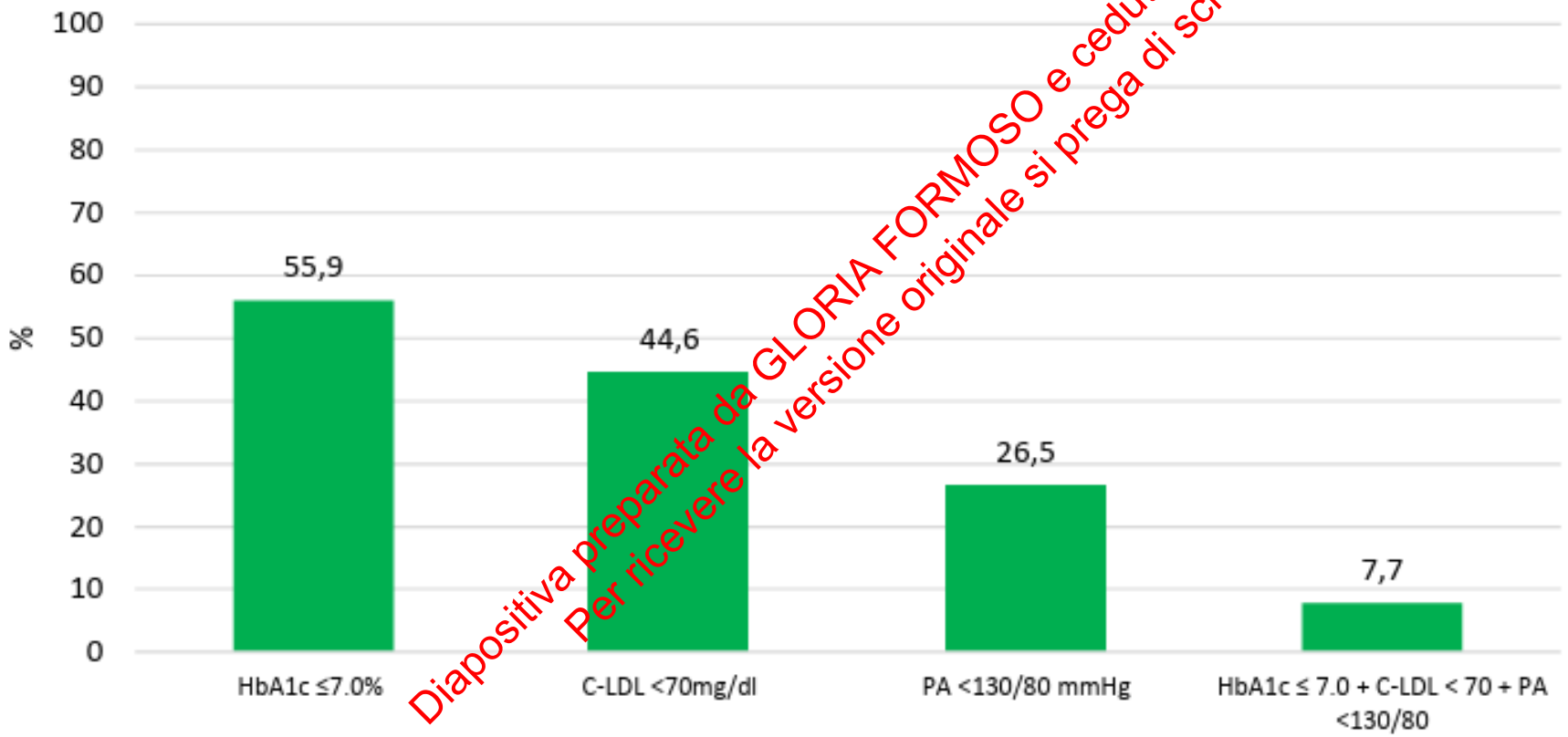
Nel 2023:

32,2 e 31,3

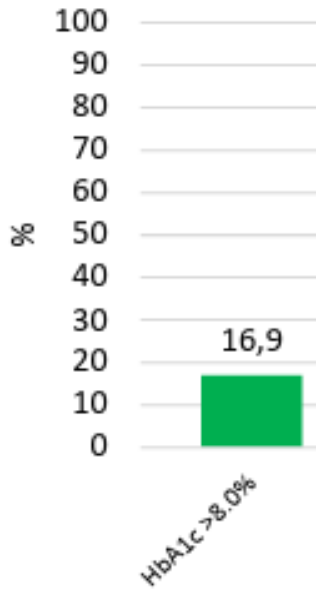
DM2 - Indicatori di esito intermedio

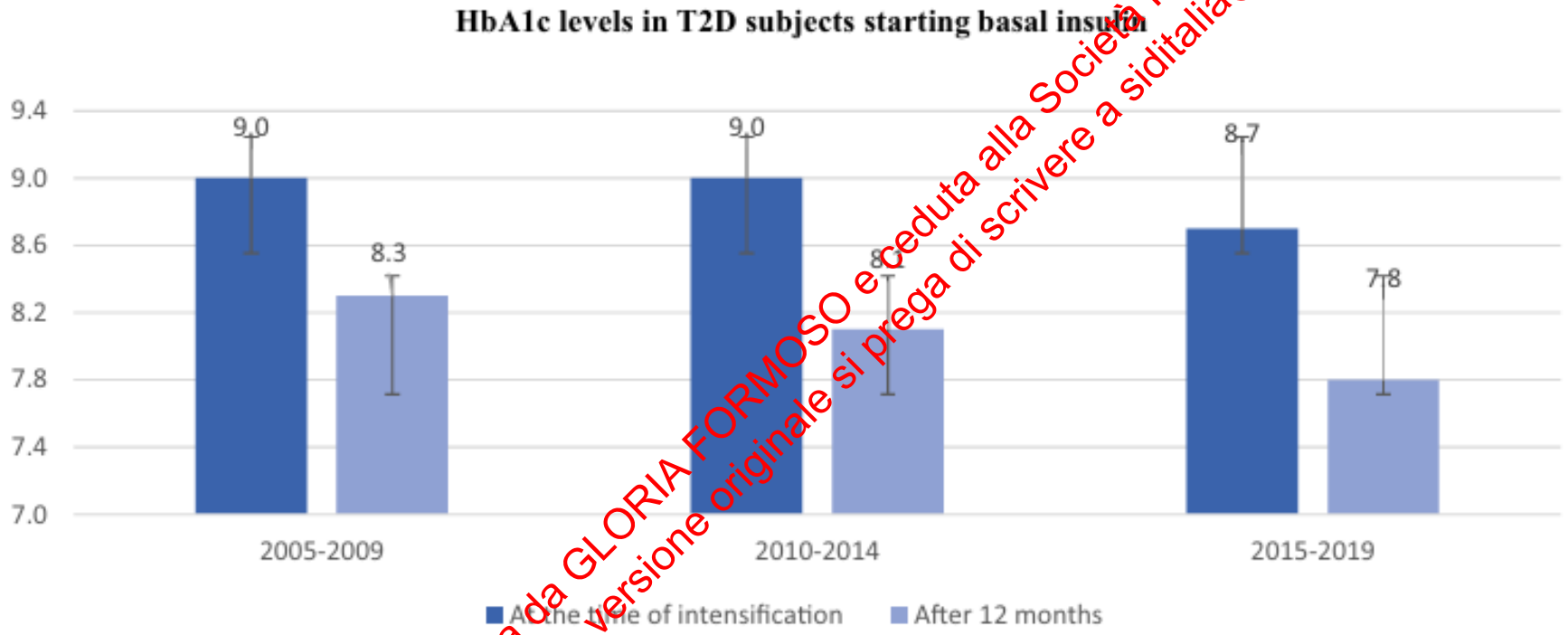
Annali AMD 2024
Valutazione degli indicatori AMD di qualità dell'assistenza al diabete in Italia

Soggetti con esito intermedio favorevole (%)



Soggetti con HbA1c > 8 % (%)





171,588 T2D subjects who intensified therapy with basal insulin

Insulin therapy is still started at high HbA1c values and, after 12 months, mean HbA1c levels are still outof-target, thus documenting the persistence of therapeutic inertia.

Journal of Endocrinological Investigation (2024) 47:2087–2096 https://doi.org/10.1007/s40618-024-02306-5

Diagnosi precoce e trattamento efficace della patologia

CARDIONEFRO METABOLICA

DALLA teoria

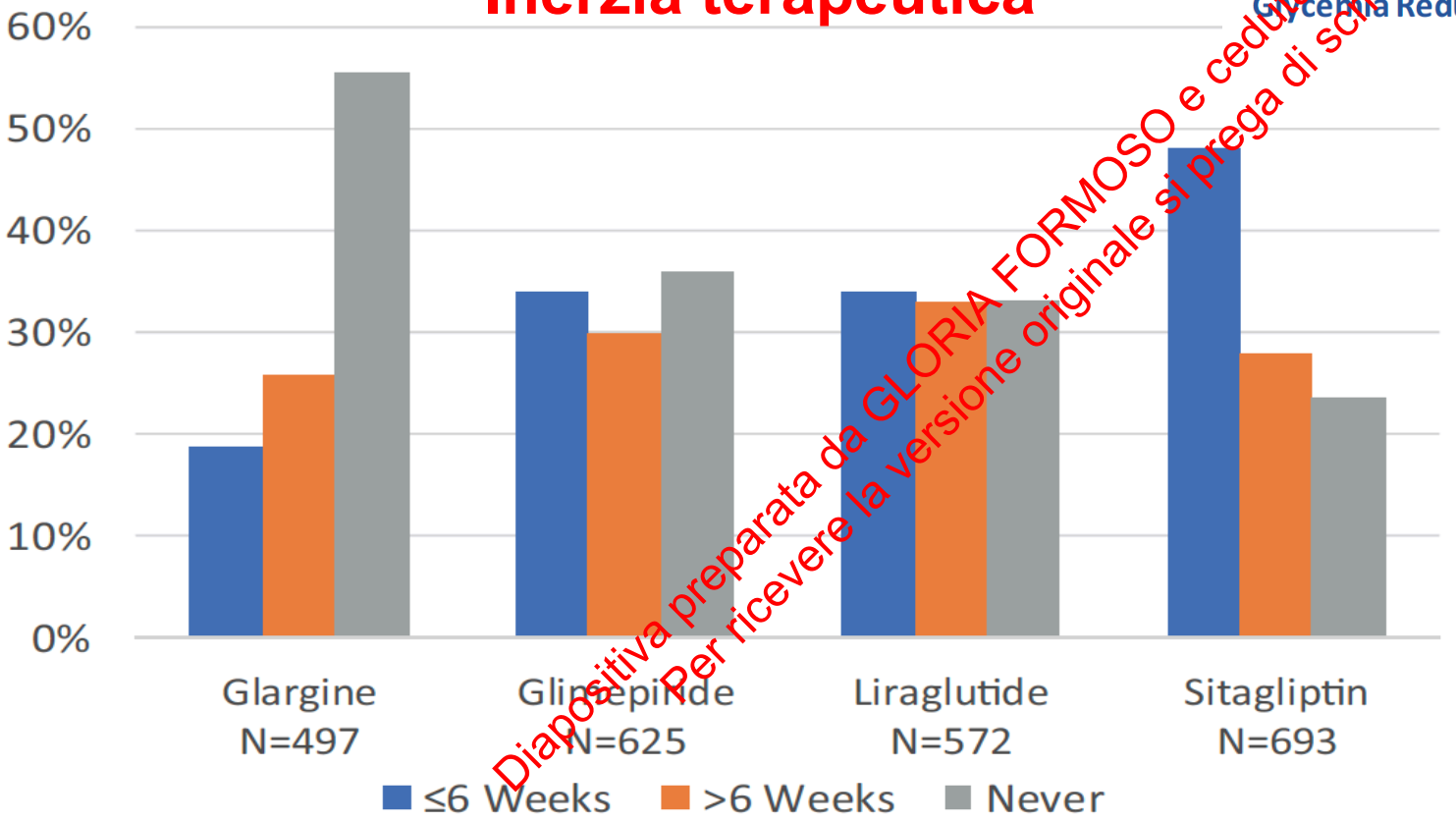
Inerzia Terapeutica

Annali AMD 2024

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

Time to Adding Rescue Insulin by Assigned Treatment Group after Confirmed A1C >7.5% (N=2,387)

Inerzia terapeutica



The Use of Rescue Insulin in GRADE

Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study

Rescue insulin was added to the assigned treatment (glargine, glimepiride, liraglude, sitaglipn),within 6 weeks of confirming A1C >7.5%, by 35% of participants.

Hollander PA et al. Diabetes Care 2024;47(4):638–645

Acta Diabetologica (2024) 61:1267–1281

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