Dibattito

Basal bolus o Insulina long acting + GLP-1RA?

Basal bolus: D. Cucinotta

Insulina long acting + GLP-1RA: A. Ceriello

Terapia insulinica basal/bolus o terapia combinata insulina basale/GLP1-RA?

- Chi?
  - Diabete di tipo 2
- Quando?
  - Fallimento degli ipoglicemizzanti orali

Standard italiani per la cura del diabete mellito 2014

Tabella 15. Terapia con insulina nel diabete tipo 2

1. Iniziare la terapia con insulina quando la terapia ipoglicemizzante non insulinica e l'intervento sullo stile di vita non sono in grado di ottenere il controllo della glicemia. Mantenere tuttavia sempre il supporto per il mantenimento dello stile di vita. Considerare l'inizio o l'aumento dell'insulina ogni 2-6 mesi, con l'obiettivo di raggiungere e mantenere nel tempo valori di HbA_{1c} prestabiliti, in genere <53 mmol/mol o 7%.

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

Management of Hyperglycemia in Type 2 Diabetes, 2015: A Patient-Centered Approach

Update to a Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes

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

Silvio E. Inzucchi,[1] Richard M. Bergenstal,[2] John B. Buse,[3] Michaela Diamant,[4] Ele Ferrannini,[5] Michael Nauck,[6] Anne L. Peters,[7] Apostolos Tsapas,[8] Richard Wender,[9,10] and David R. Matthews[11,12,13]

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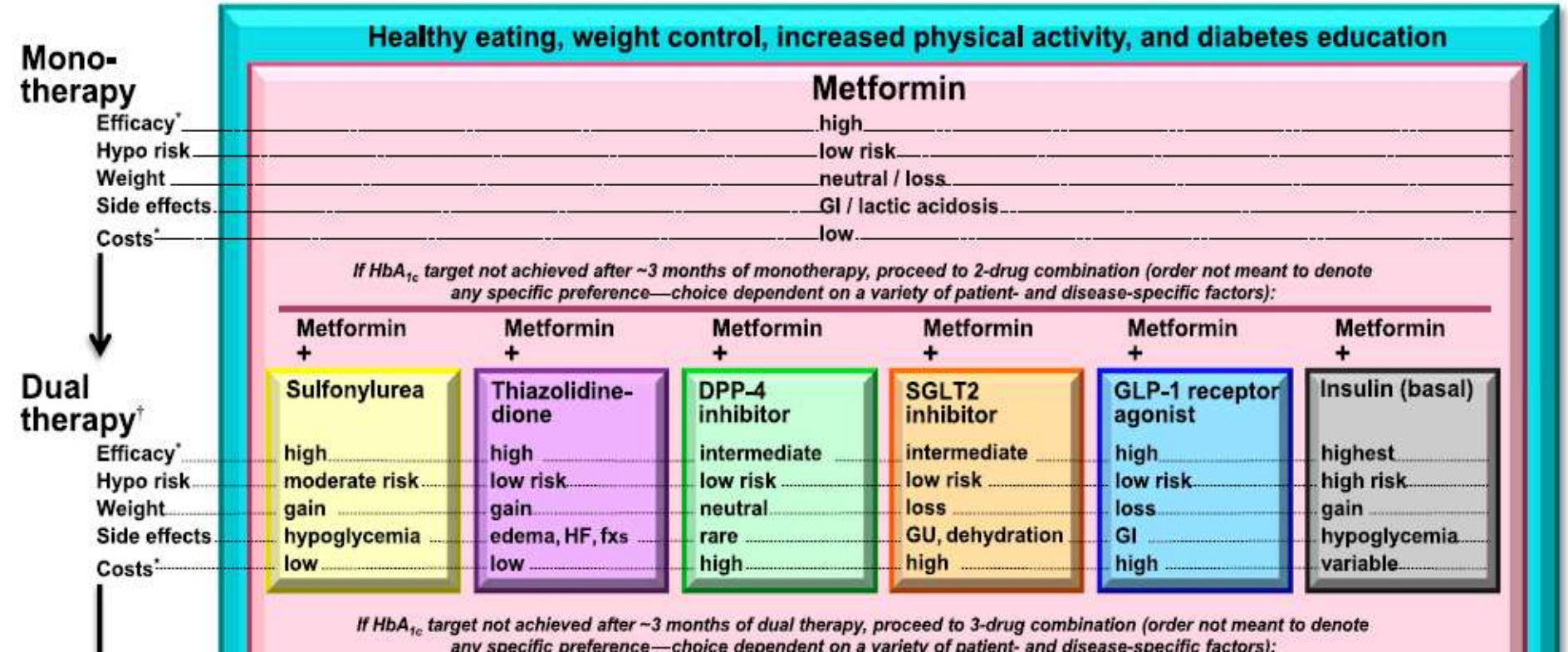
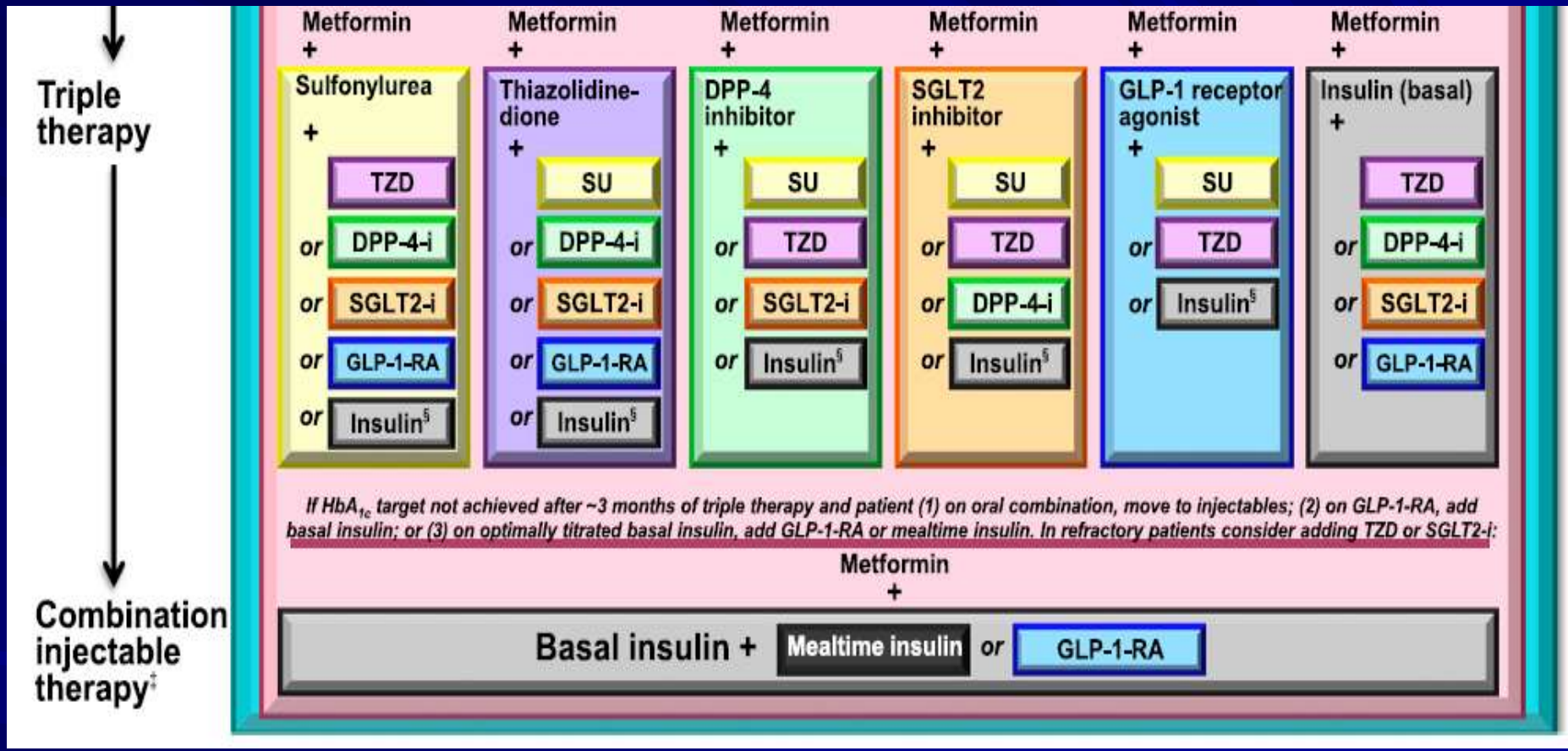



Triple therapy
Metformin + Sulfonylurea + TZD or DPP-4-i or SGLT2-i or GLP-1-RA or Insulin§
Metformin + Thiazolidine-dione + SU or DPP-4-i or SGLT2-i or GLP-1-RA or Insulin§
Metformin + DPP-4 inhibitor + SU or TZD or SGLT2-i or Insulin§
Metformin + SGLT2 inhibitor + SU or TZD or DPP-4-i or Insulin§
Metformin + GLP-1 receptor agonist + SU or TZD or Insulin§
Metformin + Insulin (basal) + TZD or DPP-4-i or SGLT2-i or GLP-1-RA
If HbA1c target not achieved after ~3 months of triple therapy and patient (1) on oral combination, move to injectables; (2) on GLP-1-RA, add basal insulin; or (3) on optimally titrated basal insulin, add GLP-1-RA or mealtime insulin. In refractory patients consider adding TZD or SGLT2-i:
Combination injectable therapy‡
Metformin +
Basal insulin + Mealtime insulin or GLP-1-RA

il Diabete • vol. 24 • n. 4 • Dicembre 2012

RASSEGNA

Incretine e insulina nella terapia del diabete tipo 2

Stefano Del Prato[1], Giorgio Sesti[2], Geremia Bolli[3], Enzo Bonora[4], Emanuele Bosi[5], Agostino Consoli[6], Domenico Cucinotta[7], Andrea Giaccari[8], Francesco Giorgino[9], Davide Lauro[10], Roberto Miccoli[11], Gabriele Perriello[12]

Sulla base delle evidenze disponibili, il trattamento con GLP-1 RA potrebbe rappresentare una nuova opzione terapeutica in soggetti con DMT2 già in terapia con insulina basale e metformina, prima di procedere con l'intensificazione della terapia insulinica. Esso potrebbe essere in particolare indicato nei pazienti con marcati sovrappeso/obesità, con valori di HbA_{1c} non eccessivamente elevati e con prevalente iperglicemia postprandiale, ma sono necessari più ampi studi clinici e una corretta valutazione del rapporto costo/benefici, anche nei confronti delle terapie in atto a disposizione.

Studi di confronto
Basal/bolus vs Basal/GLP1-RA

Diamant M, Nauck MA, Shaginian R, et al. Glucagon-like peptide-1 receptor agonist or bolus insulin with optimized basal insulin in diabetes. *Diabetes Care* 2014; published online July 10. DOI:10.2337/dc14-0876.

Rosenstock J, Fonseca VA, Gross JL, et al. Advancing basal insulin replacement in type 2 diabetes inadequately controlled with insulin glargine plus oral agents: a comparison of adding albiglutide, a weekly GLP-1 receptor agonist, versus thrice-daily prandial insulin lispro. *Diabetes Care* 2014; published June 4. DOI:10.1111/

Shao N, Kuang HY, Hao M, Gao XY, Lin WJ, Zou W. Effects of exenatide on obesity and NAFLD with elevated liver enzymes in patients with type 2 diabetes. *Diabetes Metab Res Rev* 2014; published online May 13. DOI:10.1002/dmrr.2561.

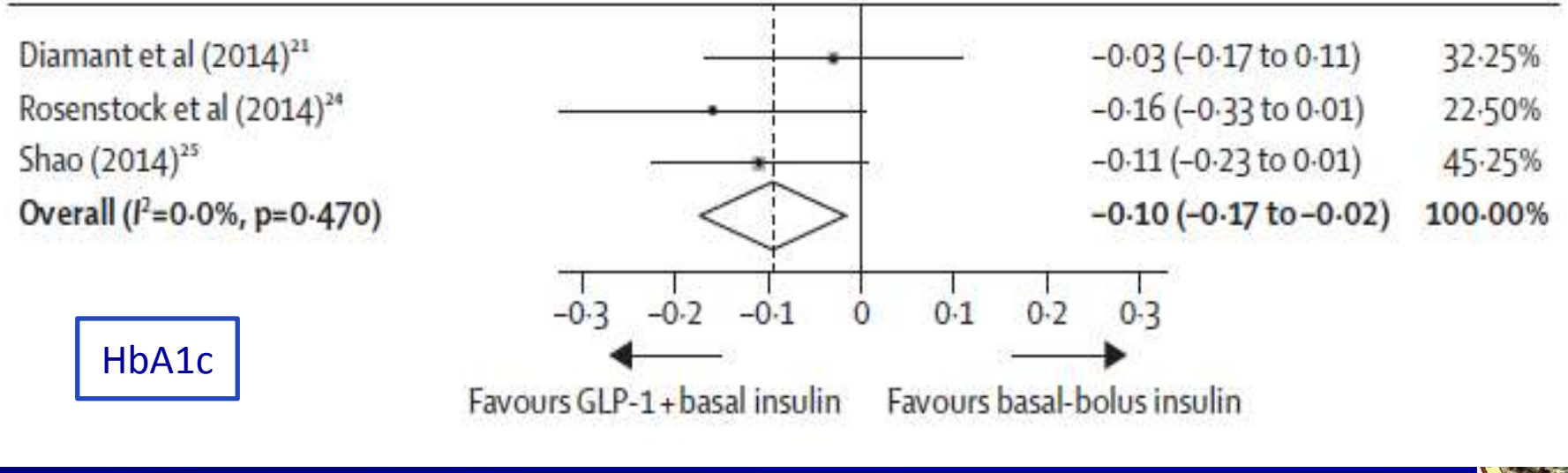
Glucagon-like peptide-1 receptor agonist and basal insulin combination treatment for the management of type 2 diabetes: a systematic review and meta-analysis

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

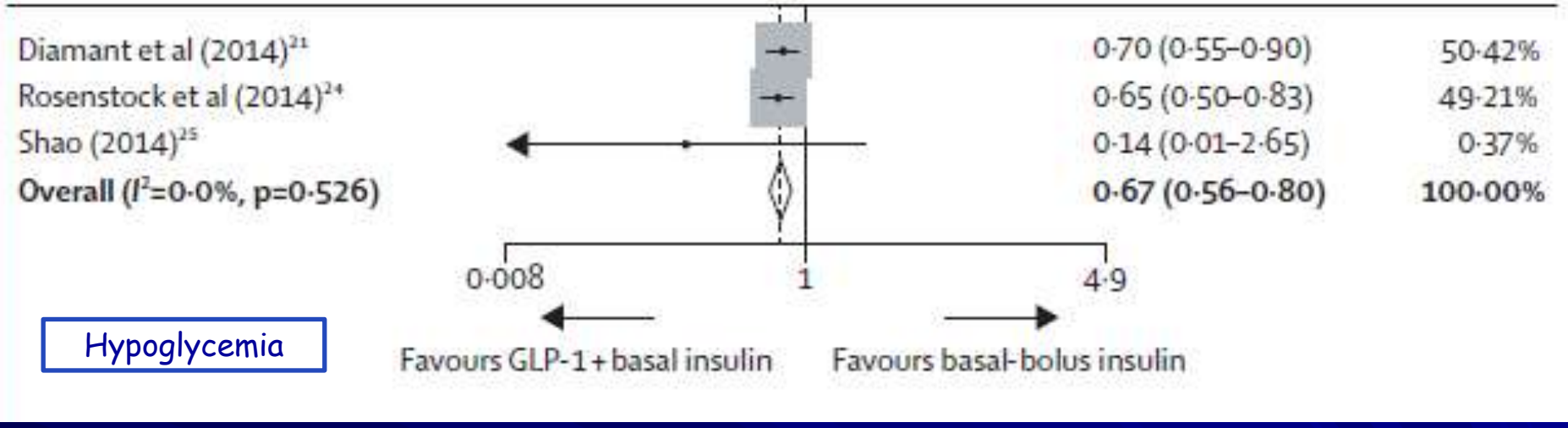
Lancet 2014; 384: 2228–34
Published Online
September 12, 2014
http://dx.doi.org/10.1016/S0140-6736(14)61335-0

Summary

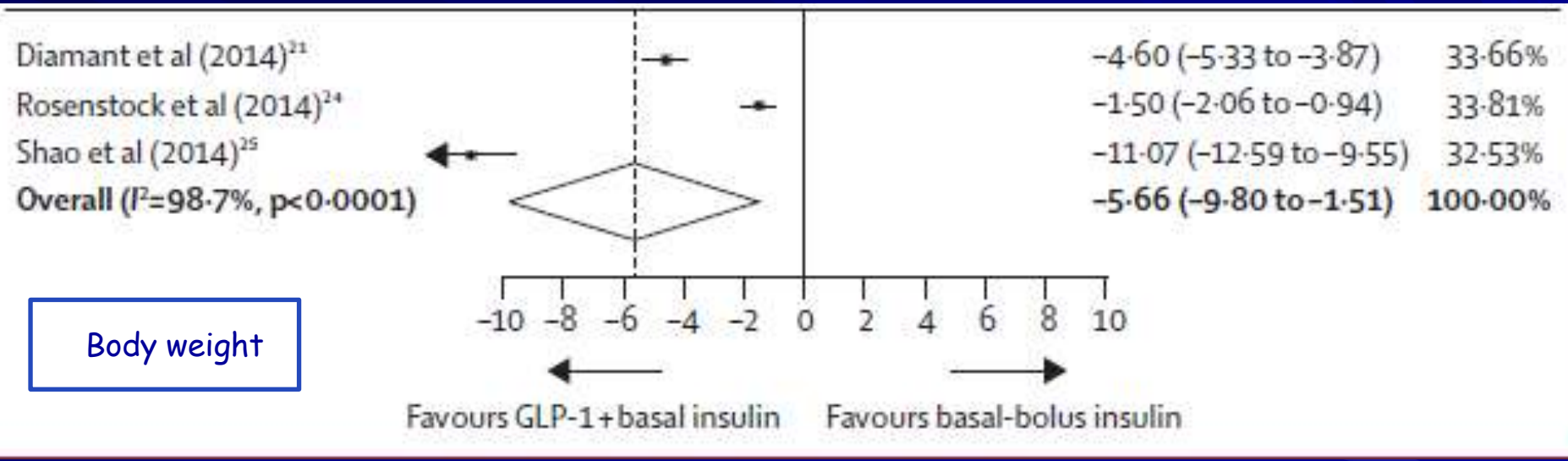
Background Combination treatment with a glucagon-like peptide-1 (GLP-1) agonist and basal insulin has been proposed as a treatment strategy for type 2 diabetes that could provide robust glucose-lowering capability with low risk of hypoglycaemia or weight gain. We thus did a systematic review and meta-analysis of randomised controlled trials to assess the effect of this combination treatment on glycaemic control, hypoglycaemia, and weight gain in patients with type 2 diabetes.



HbA1c



Hypoglycemia



Body weight

Adverse events (except hypoglycemia): significantly more frequent in the GLP-1 + basal insulin group

A limitation of this analysis is that the long-term durability of this treatment is unknown; included trials ranged in duration from 12 weeks to 36 weeks (mean 24·8 weeks). Second, although most of the included studies were published in high-impact journals, there were study features that carry potential risk of bias such as open-label design and pharmaceutical industry funding. Third, there are differences in GLP-1 agonist preparations (which include short-acting, twice-daily formulations, intermediate once-daily versions, and long-acting weekly drugs) that might dictate an optimal choice for combination

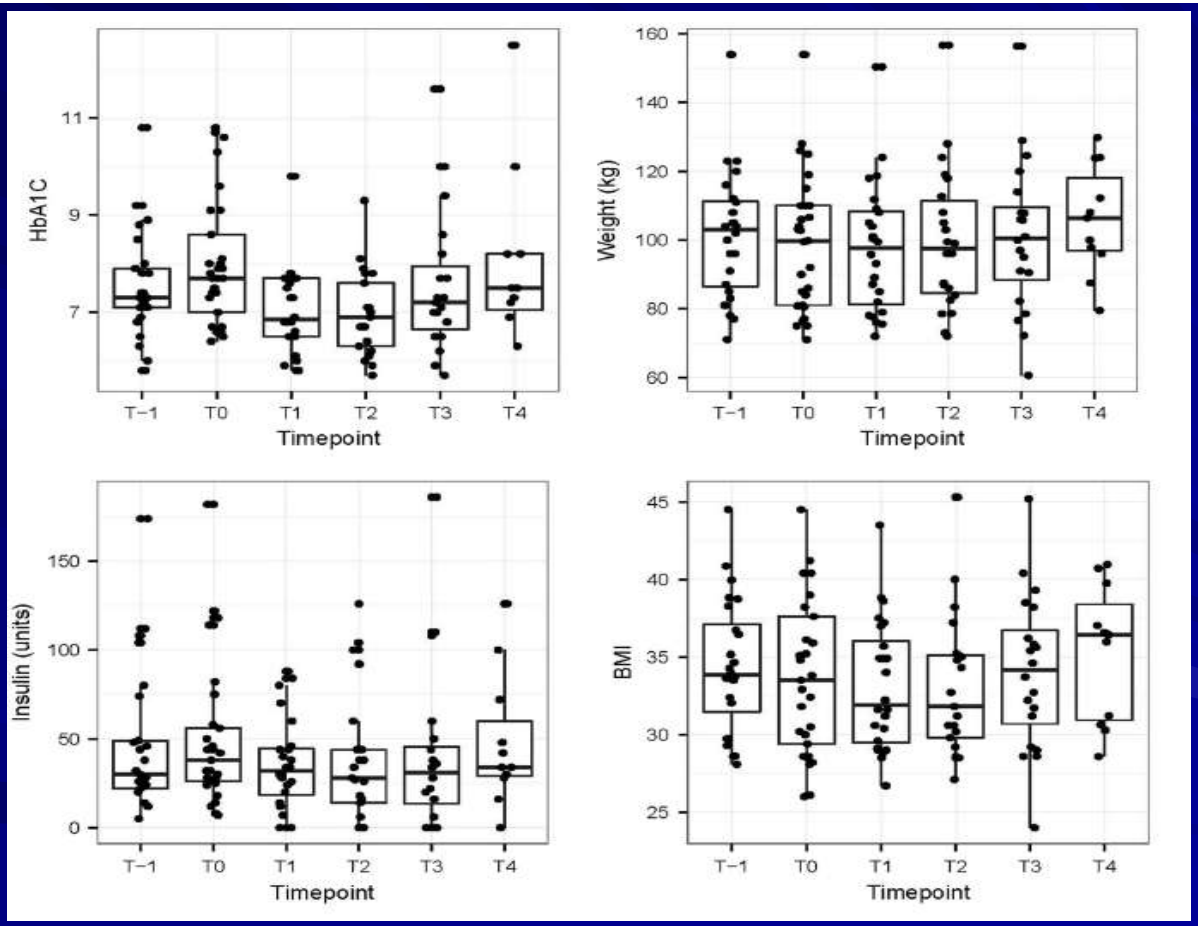
issues such as the long-term durability, safety, and side-effects of GLP-1 agonists have not been established. Finally, the ideal timing for beginning this treatment in the clinical course of the disease is unknown.

Diabetes Ther (2015) 6:41–47
DOI 10.1007/s13300-014-0093-8

ORIGINAL RESEARCH

Liraglutide as Add-On Therapy to Insulin in Type 2 Diabetes Mellitus: A Retrospective, Observational Study From a Daily Clinical Practice Setting in Switzerland

Christof Lipowsky · Lisa Sze · Ina Krull · Michael Brändle

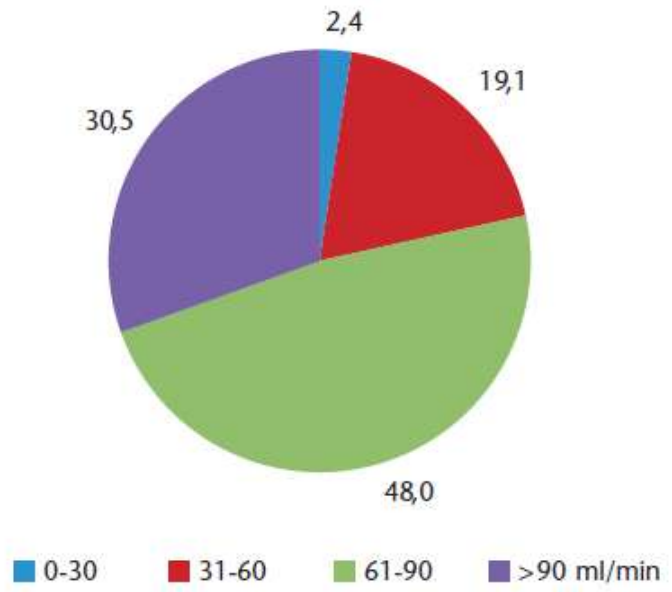


CONCLUSION

Adding liraglutide to pre-existing insulin therapy in T2DM reduces HbA1c and body weight significantly during the initial 6 months of treatment, but there may be a non-sustainable effect during long-term treatment.

Annali AMD Rene

Distribuzione della popolazione divisa per classi di GFR (%)



Circa un paziente si cinque presenta una significativa riduzione del GFR.

	Mild CKD GFR 60-89 ml/min	Moderate CKD GFR 30-59 ml/min	Severe CKD GFR 15-29 ml/min	GFR <15 ml/min o dialysis
Sitagliptin	100 mg/die	50 mg/die	25mg/die	25mg/die
Vildagliptin	50 mg x2/die	50 mg/die	50 mg/die	50 mg/die
Saxagliptin	5 mg/die	2.5 mg/die	2.5 mg/die	2.5 mg/die
Linagliptin	5 mg/die	5 mg/die	5 mg/die	5 mg/die
Alogliptin	25 mg/die	12.5 mg/die	6.25 mg/die	6.25 mg/dl
Exe BID	yes	5 µg x2/die	no	no
Exe LAR	yes	no	no	no
Liraglutide	yes	no	no	no
Lixisenatide	yes	caution	no	no

Insulina basal/bolus vs insulina basale + GLP1-RA

- Contro:
  - Maggior rischio ipoglicemico
  - Maggiore incremento ponderale
  - Regime più complesso
- Pro:
  - Verosimile maggiore efficacia in condizioni di iperglicemia severa o in stadi avanzati di malattia (nessun limite di dosaggio)
  - Regime più flessibile
  - Nessuna controindicazione
  - Costi inferiori (anche calcolando l'autocontrollo)

Chi ***non*** può beneficiare del trattamento insulina basale + GLP1-RA?

- Soggetti con HbA1c>10%
- Soggetti con diabete da >15 anni
- Soggetti con intolleranza gastrointestinale
- Soggetti con insufficienza renale

La maggioranza dei nostri pazienti ?

La progressione della terapia iniettiva nel DM2

Fallimento OHA

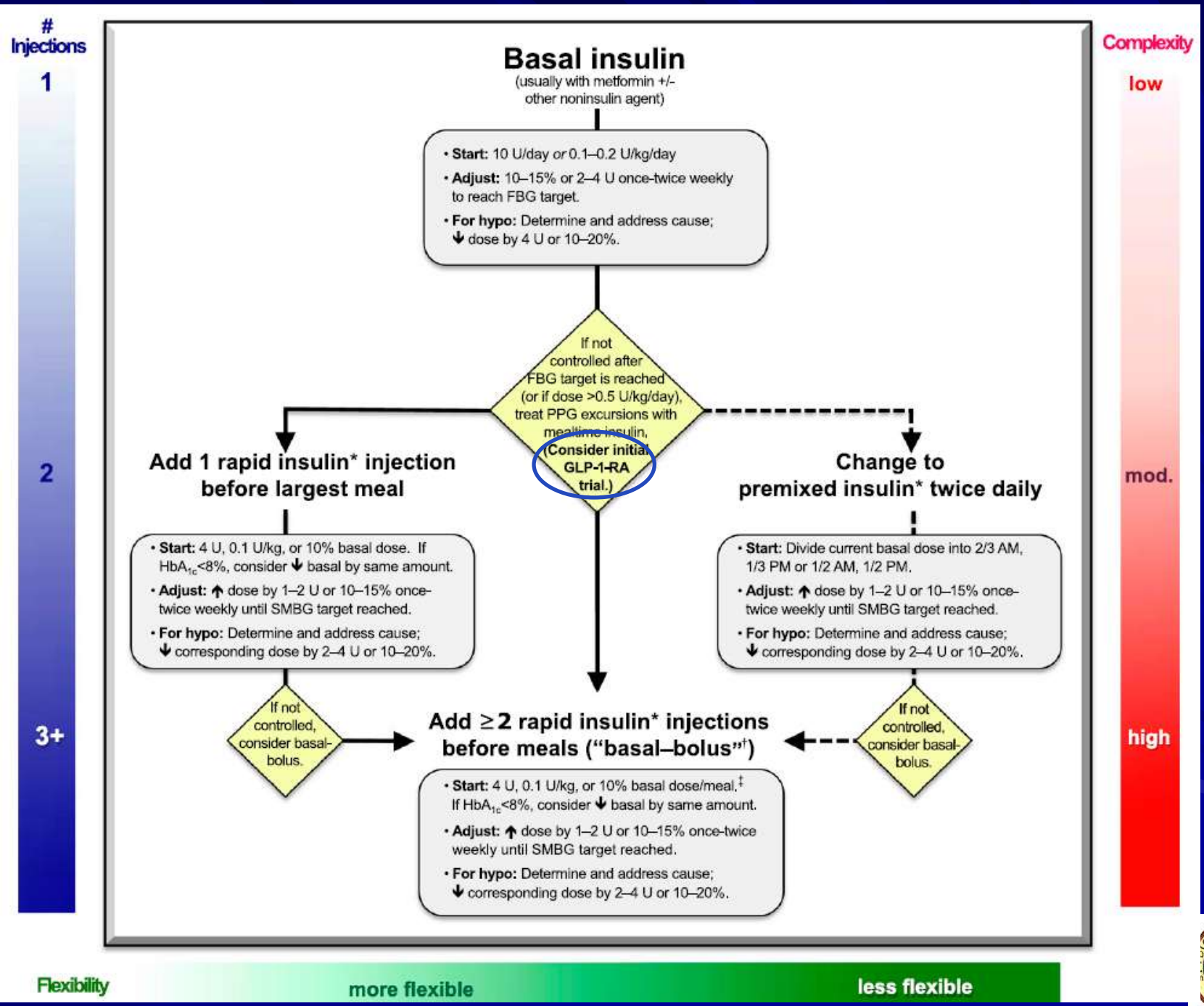
Insulina basale + OHA

Insulina basale + GLP1-RA

(se non controindicati)

Insulina basal-bolus

(se possibile, mantenere sempre metformina)


Injections
1
2
3+
Complexity
low
mod.
high
Basal insulin
(usually with metformin +/- other noninsulin agent)
• Start: 10 U/day or 0.1–0.2 U/kg/day
• Adjust: 10–15% or 2–4 U once-twice weekly to reach FBG target.
• For hypo: Determine and address cause; ↓ dose by 4 U or 10–20%.
If not controlled after FBG target is reached (or if dose >0.5 U/kg/day), treat PPG excursions with mealtime insulin. (Consider initial GLP-1-RA trial.)
Add 1 rapid insulin* injection before largest meal
• Start: 4 U, 0.1 U/kg, or 10% basal dose. If HbA1c<8%, consider ↓ basal by same amount.
• Adjust: ↑ dose by 1–2 U or 10–15% once-twice weekly until SMBG target reached.
• For hypo: Determine and address cause; ↓ corresponding dose by 2–4 U or 10–20%.
If not controlled, consider basal-bolus.
Change to premixed insulin* twice daily
• Start: Divide current basal dose into 2/3 AM, 1/3 PM or 1/2 AM, 1/2 PM.
• Adjust: ↑ dose by 1–2 U or 10–15% once-twice weekly until SMBG target reached.
• For hypo: Determine and address cause; ↓ corresponding dose by 2–4 U or 10–20%.
If not controlled, consider basal-bolus.
Add ≥2 rapid insulin* injections before meals ("basal–bolus"†)
• Start: 4 U, 0.1 U/kg, or 10% basal dose/meal.‡ If HbA1c<8%, consider ↓ basal by same amount.
• Adjust: ↑ dose by 1–2 U or 10–15% once-twice weekly until SMBG target reached.
• For hypo: Determine and address cause; ↓ corresponding dose by 2–4 U or 10–20%.
Flexibility
more flexible
less flexible