Agonisti recettoriali del GPL1 e analoghi dell'insulina

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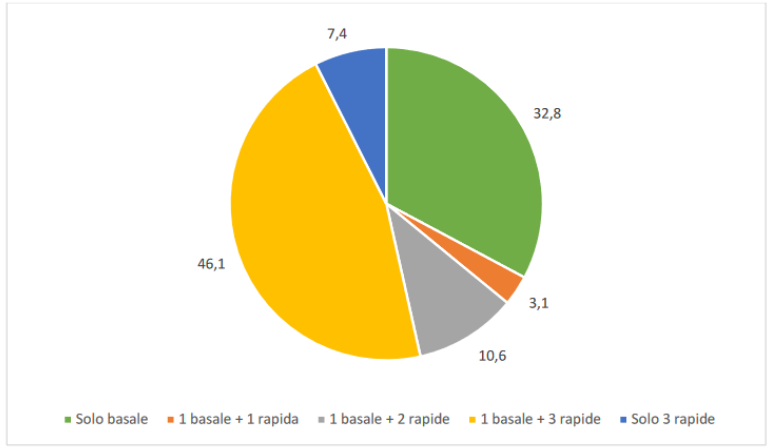
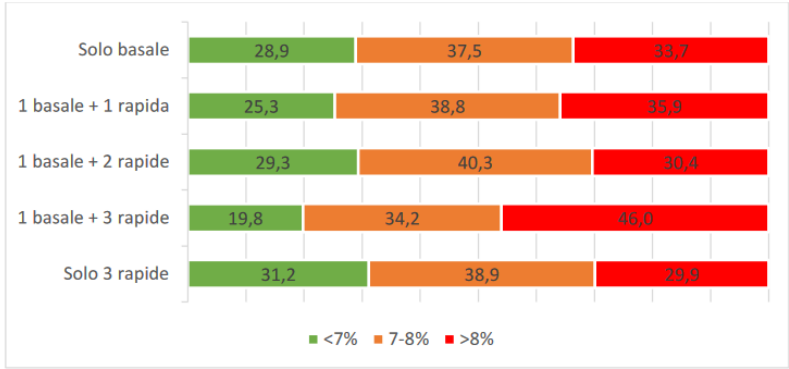
Distribuzione della popolazione per tipo di schema di trattamento



Gli schemi più utilizzati (con o senza l'impiego di altri ipoglicemizzanti diversi dall'insulina) sono rappresentati dal basal-bolus (basale + 3 rapide; 46,1%) e dall'uso della sola insulina basale (32,8%).

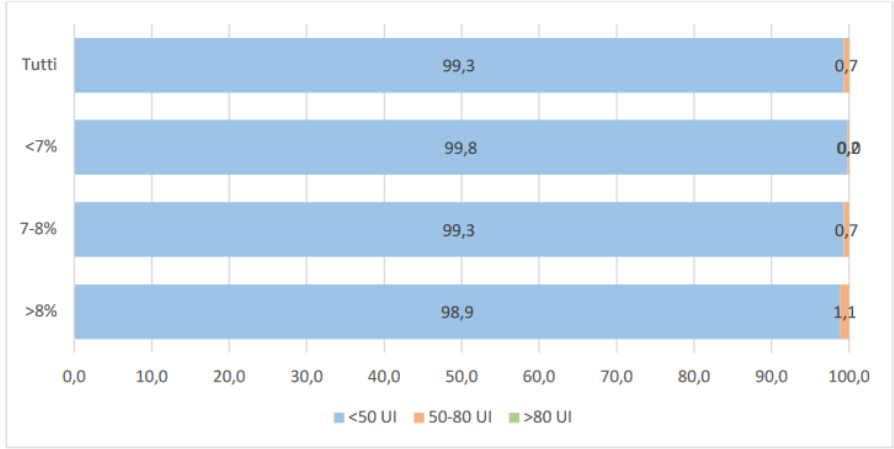


Nei diversi schemi da un quarto ad un terzo circa dei pazienti raggiunge livelli di HbA1c <7,0%, mentre quote rilevanti che oscillano tra il 29,9% ed il 46,0% presentano un controllo metabolico inadeguato nonostante il trattamento con insulina. Il quadro risulta particolarmente sfavorevole per i pazienti in terapia basal-bolus (basale + 3 rapide).

Dosi di insulina (UI totali/die)

Schema di trattamento	Tutti	HbA1c<7%	7%<=HbA1c<=8%	HbA1c >8%
Sola insulina basale	12 (6-32)	10 (5-26)	12 (6-30)	14 (6-36)
1 iniezione di insulina basale + 1 iniezione di insulina rapida	22 (10-49)	19 (10-40)	22 (10-44)	24 (10-63)
1 iniezione di insulina basale + 2 iniezioni di insulina rapida	29 (15-66)	27 (14-60)	29 (16-62)	33 (17-79)
1 iniezione di insulina basale + 3 iniezioni di insulina rapida	53 (26-112)	44 (23-90)	50 (26-103)	60 (28-124)
3 iniezioni di insulina rapida	26 (12-59)	22 (12-50)	24 (12-52)	30 (15-70)

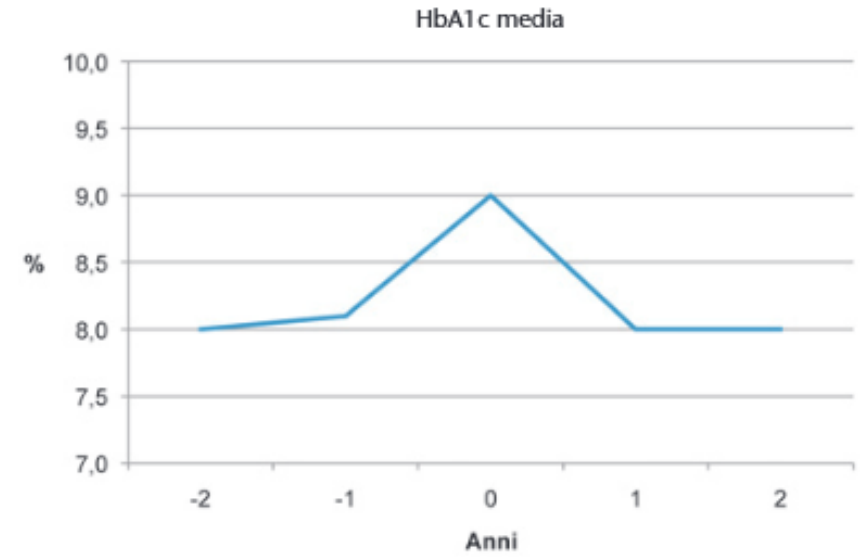
Dati espressi come mediana e 5°-95° percentile.



Fra i soggetti in terapia con sola insulina basale, quasi la totalità è in trattamento con meno di 50 UI, a prescindere dal livello di HbA1c.

Questa sezione mostra le variazioni nei livelli dei principali parametri clinici dai 2 anni precedenti ai 2 anni successivi l'avvio della terapia insulinica.

Figura 11. Analisi longitudinale: trend dei valori medi di HbA1c



Media±ds	8,0±1,4	8,1±1,4	9,0±1,7	8,0±1,3	8,0±1,3

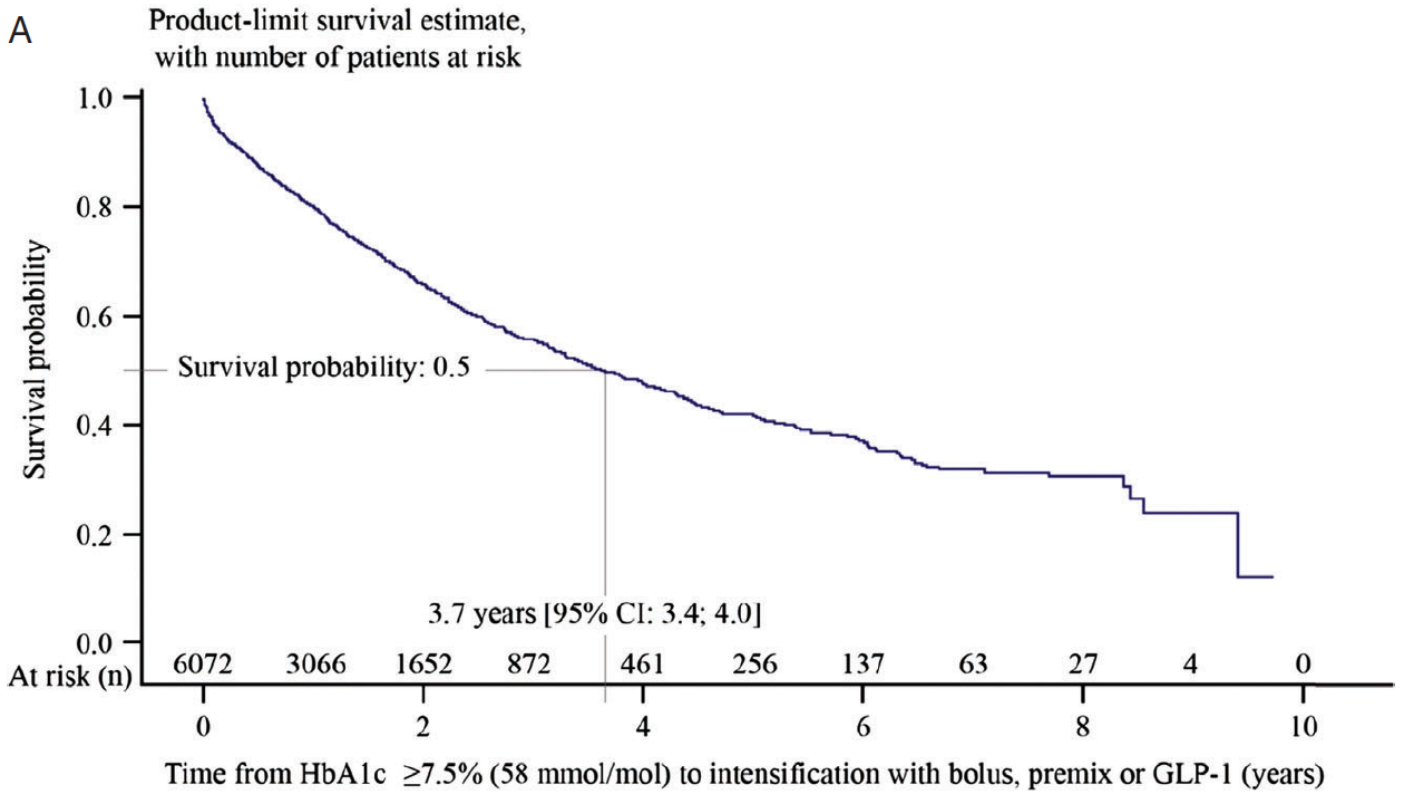
I valori medi di HbA1c erano pari o superiori a 8,0% fin dai 2 anni precedenti l'avvio dell'insulina e, dopo il picco di 9,0% raggiunto in concomitanza con l'intensificazione della terapia, tornano a livelli medi di 8,0% anche nei 2 anni successivi.

original article

Diabetes, Obesity and Metabolism 18: 401–409, 2016.

Clinical inertia with regard to intensifying therapy in people with type 2 diabetes treated with basal insulin

K. Khunti[1,†], A. Nikolajsen[2], B. L. Thorsted[2], M. Andersen[3], M. J. Davies[1] & S. K. Paul[4,†]



In a cohort study evaluating data of 11.696 patients from UK Clinical Practice Research Datalink database, less than a third of BOT patients eligible for treatment intensification (HbA1C > 7.5%) had their treatment regimen intensified, and the median time to intensification was 3.7 years

ORIGINAL ARTICLE

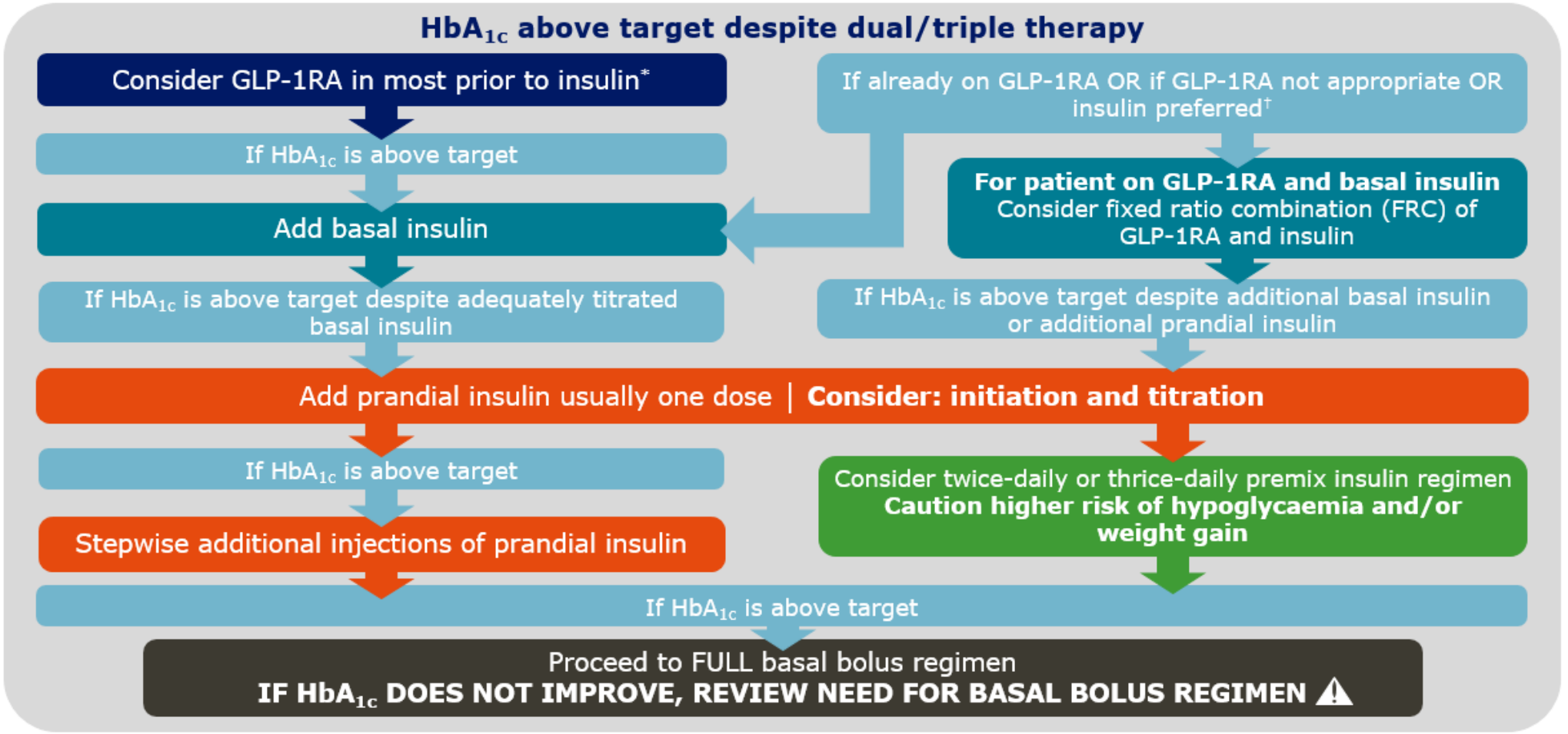
Glycaemic control and hypoglycaemia burden in patients with type 2 diabetes initiating basal insulin in Europe and the USA

Dídac Mauricio MD[1] | Luigi Meneghini MD[2,3] | Jochen Seufert MD[4] | Laura Liao MS[5†] | Hongwei Wang PhD[5] | Liyue Tong MS[5†] | Anna Cali MD[6] | Peter Stella MD[6] | Paulo Carita MS[6] | Kamlesh Khunti MD[7]

Conclusions: Initiating BI with or without OADs is associated with short- and long-term suboptimal glycaemic control; the majority of patients fail to achieve HbA1c target ≤7% in the first 3 months, or after 2 years of BI treatment. Treatment response and hypoglycaemia incidence by 3 months post BI initiation are associated with longer-term glycaemic control and hypoglycaemic risk, respectively. These results support the need for early anti-hyperglycaemic interventions that more effectively control blood glucose levels without increasing the risk of hypoglycaemia.

Diabetes Obes Metab. 2017;19:1155–1164.

Intensifying to injectable therapies




Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)


Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

*Consider choice of GLP-1RA considering patient preference, HbA_{1c} lowering, weight-lowering effect or frequency of injection. If CVD, consider GLP-1RA with proven CVD benefit
†Consider insulin as preferred to GLP-1RA if symptoms of hyperglycaemia are present, or evidence of ongoing catabolism (polyuria, polydipsia or weight loss)
CVD, cardiovascular disease; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycosylated haemoglobin

Fixed-ratio combination of basal insulin and GLP-1 receptor agonist: is two better than one?

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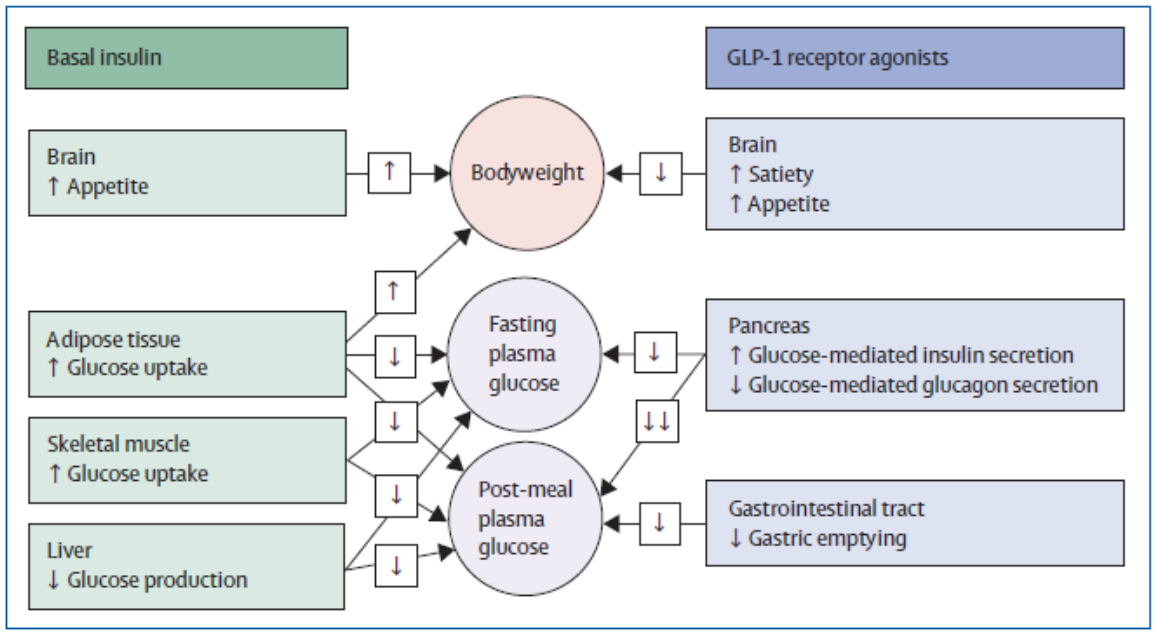

Figure: **Schematic representation of the potential synergistic effects of treatment with basal insulin and a longacting GLP-1 agonist**
Basal insulin suppresses overnight hepatic glucose production, while stimulation of peripheral glucose utilisation is low, meaning that its main effect is to reduce fasting plasma glucose concentrations. Moreover, stimulation of glucose uptake in adipose tissue can sustain lipid synthesis and prevent reductions in bodyweight, an effect insulin also supports via central stimulation of appetite. By contrast, GLP-1 receptor agonists exert an inhibitory effect on appetite while increasing satiety sensation, thus favouring loss of bodyweight. Because of glucose-modulated increases in insulin secretion and suppression of glucagon release, postprandial glucose concentration will be affected more through inhibition of hepatic glucose production. This effect on post-prandial glucose might also be supported by a concomitant slowing effect on gastric emptying.

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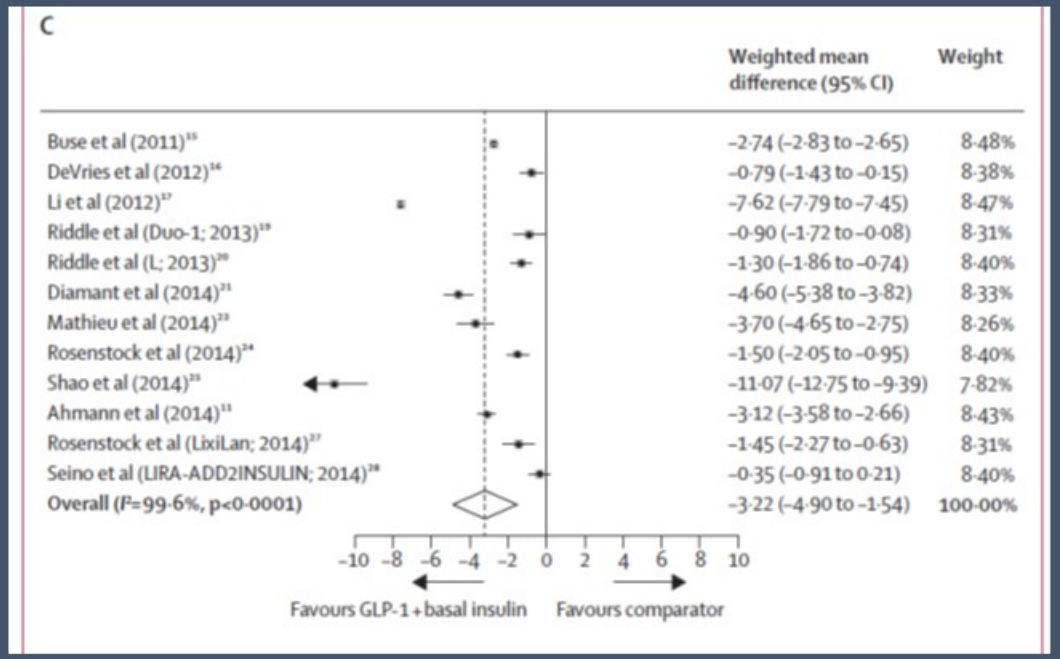
http://dx.doi.org/10.1016/S2213-8587(14)70185-8

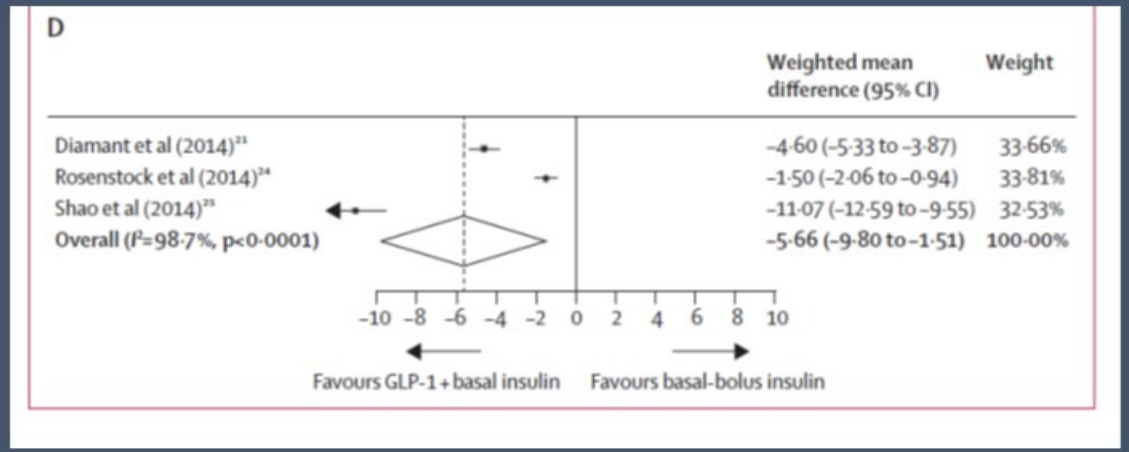
See Articles page 885

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



Weight



Weight Vs Basal Bolus

Lancet 2014; 384: 2228–34

GLP-1 receptor agonist added to insulin versus basal-plus or basal-bolus insulin therapy in type 2 diabetes: A systematic review and meta-analysis

Marco Castellana | Angelo Cignarelli | Francesco Brescia | Luigi Laviola | Francesco Giorgino

Conclusions: The present review supports treatment intensification with GLP-1RA added to insulin versus BP/BB in uncontrolled type 2 diabetes. This could provide similar antihyperglycaemic efficacy while leading to weight loss and sparing of hypoglycaemia and insulin dose. As a consequence, a considerable number of patients with type 2 diabetes could be potentially shifted from BP/BB to GLP-1RA/insulin combinations.

Diabetes Metab
https://doi.org/10.1002/dmrr.3082

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basal insulin should
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079547). PubMed,
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ted with a similar
to 0.02; $P = 0.13$;
−2.95; $P < 0.001$;
e risk [RR] = 0.46;
ong GLP-1RA/insu-
%), lower than with
BP/BB. No difference was found for discontinuation due to lack of efficacy.

Endocrine (2017) 56:485–494
DOI 10.1007/s12020-017-1293-6

META-ANALYSIS

Table 2 Meta-analytic findings for secondary outcomes regarding fixed ratio combinations of basal insulin with GLP-1 RAs

Comparison (references to studies)	Number of studies	Odds ratio (95% CI); I^2			
		Incidence of patients achieving HbA_{1c} < 7%	Incidence of hypoglycaemia	Incidence of nausea	Incidence of vomiting
Fixed ratio combo vs. placebo [19]	1	9.45 (5.98 to 14.93); NA	3.46 (2.12 to 5.64); NA	1.33 (0.47 to 3.81); NA	0.88 (0.25 to 3.07); NA
Fixed ratio combo vs. basal insulin [2, 16, 20, 21]	3	1.97 (1.64 to 2.35); 0%	0.89 (0.74 to 1.06); 53%	3.01 (2.03 to 4.47); 25%	2.57 (1.40 to 4.71); 0%
Fixed ratio combo vs. GLP-1 RA [2, 16, 21]	2	3.58 (2.93 to 4.38); 91%	5.89 (4.23 to 8.21); 0%	0.37 (0.28 to 0.49); 0%	0.45 (0.30 to 0.68); 0%
Switch from basal insulin to fixed ratio combo [14, 15, 17]	3	3.24 (2.65 to 3.97); 57%	0.70 (0.57 to 0.86); 85%	6.89 (3.73 to 12.74); 79%	6.70 (1.50 to 29.92); NA
Switch from GLP-1 RA to fixed ratio combo [18]	1	5.26 (3.43 to 8.08); NA	16.56 (5.95 to 46.09); NA	0.74 (0.26 to 2.12); NA	NR

CI confidence interval, *HbA_{1c}* haemoglobin A_{1c}, *GLP-1 RA* glucagon like peptide 1 receptor agonist, *NA* not applicable, *NR* not reported

Fig. 4 Forest plot for change in body weight (kg). Results are from inverse variance (IV) weighted random effects meta-analysis. *CI* confidence interval, *GLP-1 RA* glucagon like peptide 1 receptor agonist

Moreira et al. Diabetol Metab Syndr (2018) 10:26
https://doi.org/10.1186/s13098-018-0327-4

Diabetology & Metabolic Syndrome

REVIEW Open Access

Combination of basal insulin and GLP-1 receptor agonist: is this the end of basal insulin alone in the treatment of type 2 diabetes?

Rodrigo Oliveira Moreira[1*†], Roberta Cobas[2†] and Raquel C. Lopes Assis Coelho[3†]

Table 1 Studies evaluating the efficacy of IDegLira and IGlarLixi in patients with diabetes mellitus type 2 inadequately controlled with oral medication and insulin naive

Study	DUAL-1			LixiLan-O		
	IDegLira	Degludec	Liraglutide	IGlarLixi	Glargine U100	Lixisenatide
Duration	26 weeks			30 weeks		
Population	1663 T2DM adults, A1c 8.3 ± 0.9; BMI 31.2 ± 4.8 kg/m^2, metformin ± pioglitazone			1170 T2DM adults, A1c 8.2 ± 0.7; BMI 31.7 ± 4.4 kg/m^2; metformin ± pioglitazone		
Mean insulin dose (final)	38 ± 13	53 ± 28		39 ± 14	40 ± 14	
ΔA1c	− 1.9 ± 1.1	− 1.4 ± 1.0	− 1.3 ± 1.1	− 1.6 ± 0.1	− 1.3 ± 0.1	− 0.8 ± 0.1
Final A1c (week 30)	6.4 ± 1.0	6.9 ± 1.1	7.0 ± 1.2	6.5 ± 0.8	6.8 ± 0.8	7.3 ± 0.9
Δ body weight (kg)	− 0.5 ± 3.5	+ 1.6 ± 4.0	− 3.0 ± 3.5	− 0.3 ± 0.2	+ 1.1 ± 0.2	− 2.3 ± 0.3
% A1c < 7%	81	65	60	74	59	33
%A1c < 7% without weight gain	46	21	54	43	25	28
%A1c < 7% without hypoglycemia	60	41	58	53	44	30
%A1c < 7% without weight gain or hypoglycemia	36	14	52	32	19	26
Hypoglycemia (%)[a]	32	39	7	26	24	6

[a] Different definitions for hypoglycaemia were used in the two studies. For the DUAL I trial, confirmed hypoglycaemia was defined as the occurrence of episodes requiring assistance (severe), or episodes in which plasma glucose concentration (determined from self-monitored blood glucose) was less than 56 mg/dL, irrespective of symptoms. For the LixiLan-O trial, documented symptomatic hypoglycemia was defined as typical symptoms of hypoglycaemia accompanied by a measured plasma glucose concentration of #70 mg/dL

Gastrointestinal adverse events with insulin glargine/lixisenatide fixed-ratio combination versus GLP-1 RAs in people with type 2 diabetes mellitus: a network meta-analysis

29 September 2020

DIABETES, OBESITY AND METABOLISM
A JOURNAL OF PHARMACOLOGY AND THERAPEUTICS

Christop
MD[2] | C
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Conclusions: During the first 12 weeks of treatment, iGlarLixi was generally associated with less nausea and vomiting than single-agent GLP-1 RAs. Enhanced gastrointestinal tolerability with fixed-ratio combinations may favour treatment persistence.

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CONCLUSIONS

Findings from this study do not support SU as the second-line treatment choice for patients with type 2 diabetes. Moreover, the results indicate that adding a GLP-1 for people treated with MET and BASAL could be considered, especially if those people suffer from severe hypoglycemia.

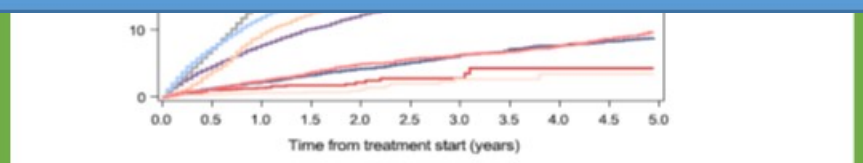

Figure 1—Time to event in a 5-year follow-up after initiation of antihyperglycemic dual and triple type 2 diabetes therapies. *A* is time to MACE, *B* is time to severe hypoglycemia, and *C* is time to death.

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2020

Diabetes Obes Metab. 2019;1–7.

Fixed-ratio combination of insulin degludec and liraglutide (IDegLira) improves cardiovascular risk markers in patients with type 2 diabetes uncontrolled on basal insulin

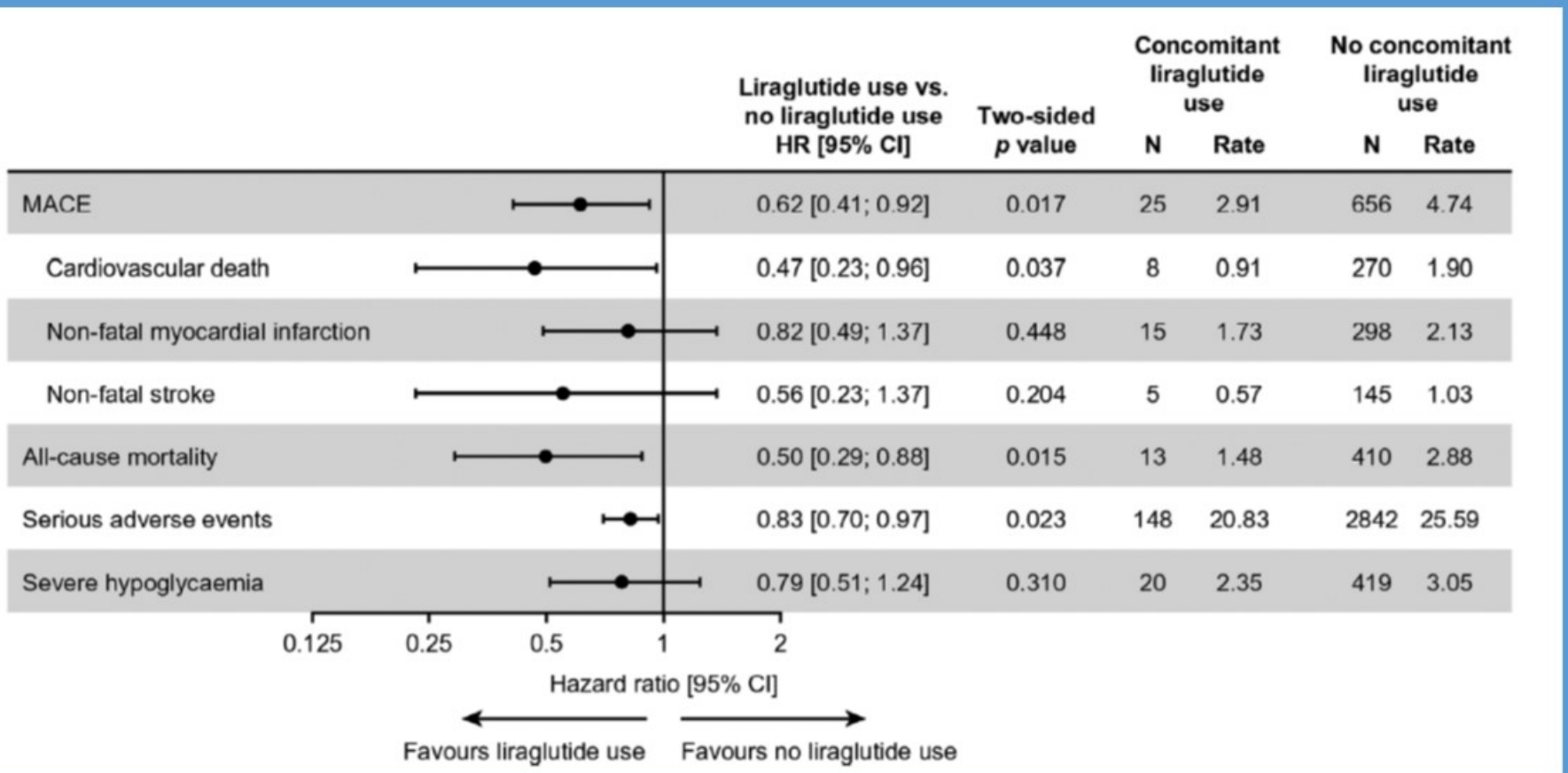
Tina Vilsbøll MD[1] | Thomas C. Blevins MD[2] | Esteban Jodar PhD[3] | Neil Poulter FMed Sci[4] | Nikolaos Tentolouris MD[5] | Bue F. Ross Agner PhD[6] | Lucine Lehmann MD[6] | Lawrence A. Leiter MD[7]

In this post hoc analysis we investigated the effects of insulin degludec/liraglutide fixed-ratio combination (IDegLira) versus comparators on cardiovascular (CV) risk markers in participants in the DUAL II (vs. insulin degludec), DUAL V (vs. insulin glargine 100 units/mL) and DUAL VII (vs. basal–bolus therapy) trials, grouped by sex, age (<65 years, ≥65 years) and diabetes duration (<10 years, ≥10 years). Treatment contrasts were in favour of IDegLira in many subgroups for changes from baseline in glycated haemoblogin (DUAL II, DUAL V), body weight (all three trials), systolic blood pressure (BP; all three trials), HDL cholesterol (DUAL VII) and LDL cholesterol (DUAL II, DUAL V). Higher heart rates were seen with IDegLira versus comparators (all three trials) plus significantly higher diastolic BP in men (DUAL V). Differences in treatment effect were seen between sexes in waist circumference (DUAL II), systolic BP (DUAL II, DUAL V) and triglycerides (DUAL VII), and between diabetes durations in LDL cholesterol (DUAL V). In conclusion, IDegLira is associated with a general improvement in CV risk markers compared with basal insulin or basal–bolus therapy after 26 weeks of treatment.

Lower rates of cardiovascular events and mortality associated with liraglutide use in patients treated with basal insulin: A DEVOTE subanalysis (DEVOTE 10)

Diabetes Obes Metab. 2019;21:1437–1444.

Kirstine Brown-Frandsen MD[1] | Scott S. Emerson MD[2] | Darren K. McGuire MD[3] | Thomas R. Pieber MD[4] | Neil R. Poulter MD[5] | Richard E. Pratley MD[6] | Bernard Zinman MD[7] | Mattis F. Ranthe MD[1] | Randi Grøn PhD[1] | Martin Lange MD[1] | Alan C. Mos
Study Grou



Therapeutic Advances in Endocrinology and Metabolism Review

The role of basal insulin and GLP-1 receptor agonist combination products in the management of type 2 diabetes

Taylor R. Inman, Erika Plyushko, Nicholas P. Austin and Jeremy L. Johnson

Ther Adv Endocrinol Metab

2018, Vol. 9(5) 151–155

DOI: 10.1177/2042018818763698

to

However, some issues remain. For example, the use of a fixed-ratio combination might result in some patients receiving a suboptimum dose of GLP-1 receptor agonist, which could limit some of the beneficial effects such as reduced insulin requirement, reduced risk of hypoglycaemia, and reduced weight gain.
Also unresolved is the therapeutic solution for patients who need more than 50 U of insulin per day.
The bottom-line question remains whether the early introduction of the insulin–GLP-1 receptor agonist combination will result in a more sustained glycaemic control than either component alone.
The answer to this question will be especially important if the combination treatment is more expensive than the individual components, as is expected.
Ultimately, as is often the case, two seems to be better than one and, in this case, the once-daily injection of an insulin–GLP-1 receptor agonist combination, with its easy titration algorithm, improved efficacy, and mitigation of the side-effects of the two components, could offer new potential for treatment of type 2 diabetes.

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insulin regimens.