

Insuline settimanali: dall'innovazione all'applicazione clinica

INNOVAZIONE

Riccardo FORNENGO

S.S.D. di Diabetologia e Malattie Metaboliche
A.S.L. TO4



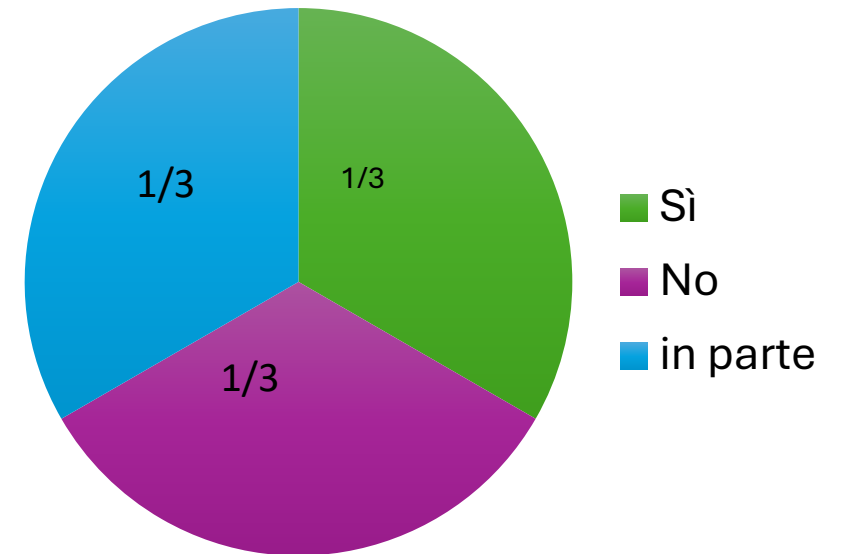
Il dr. RICCARDO FORNENGO dichiara di NON aver ricevuto negli ultimi due anni compensi o finanziamenti da Aziende Farmaceutiche e/o Diagnostiche.

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.).

PREMESSE

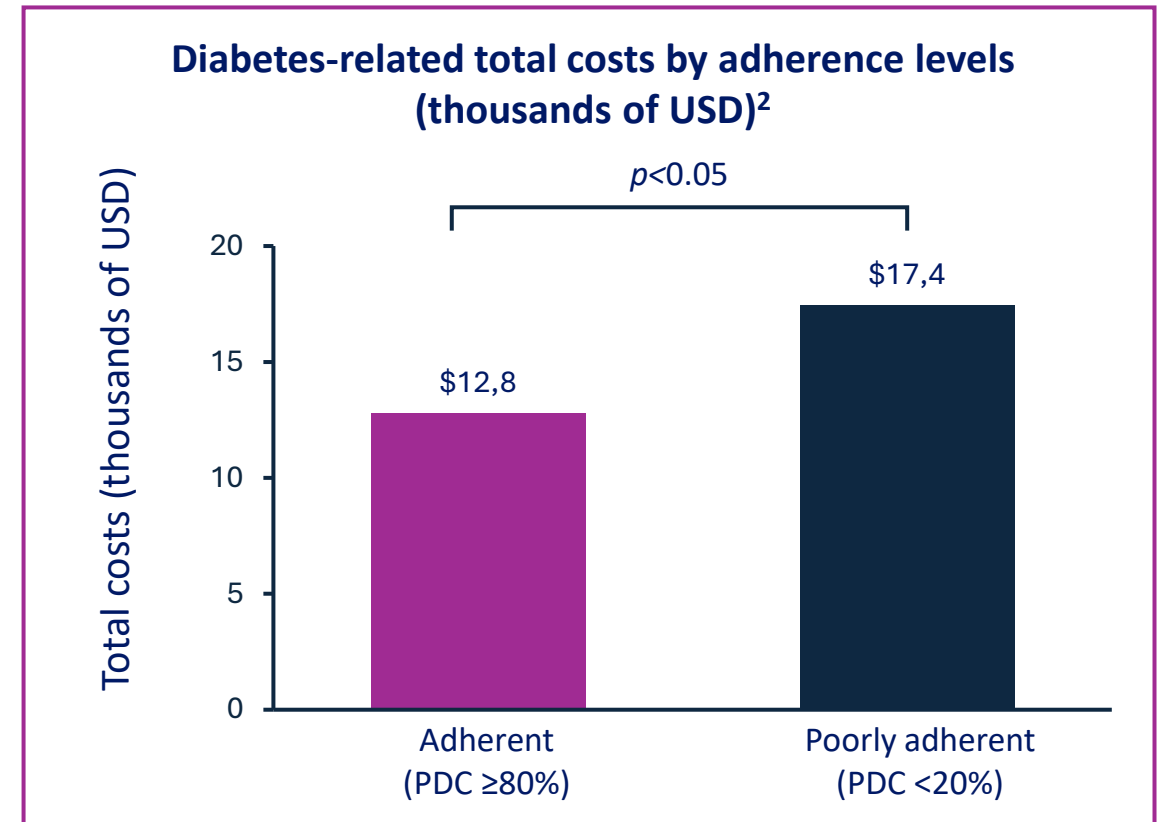
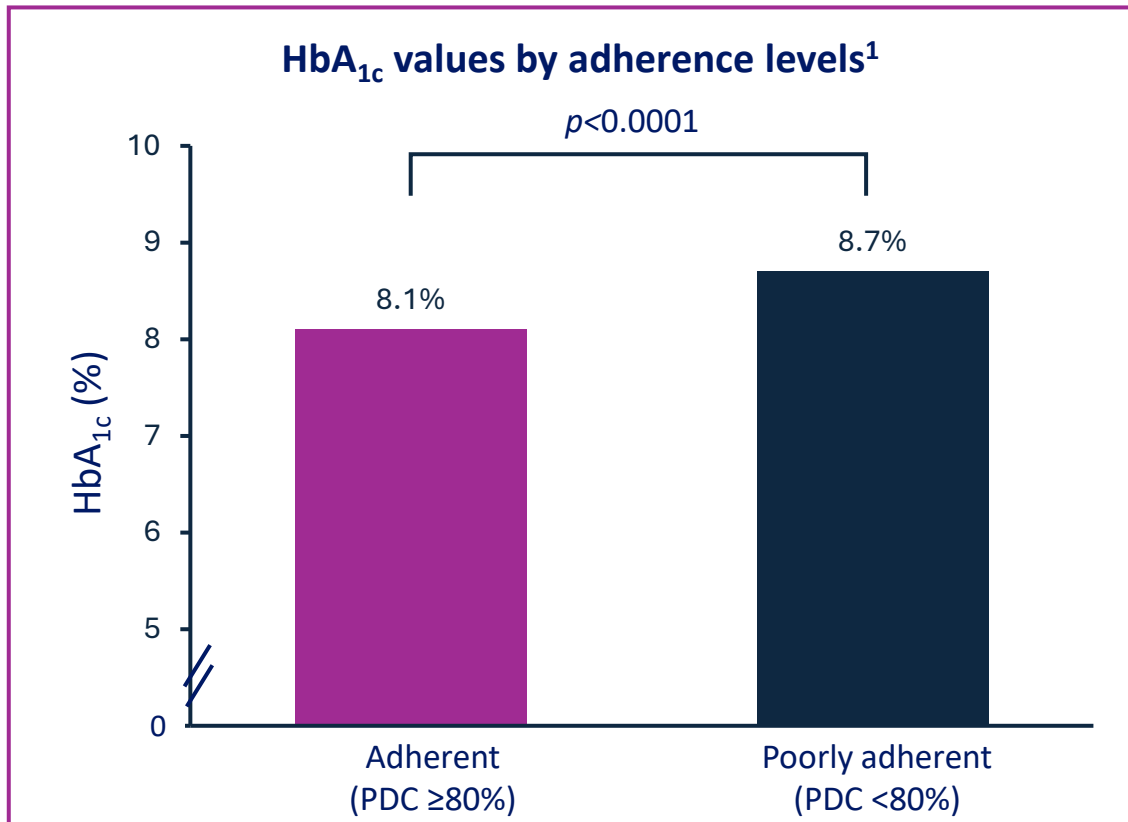
I pazienti assumono i farmaci?

- Solo la metà dei pazienti con patologie croniche assume correttamente i farmaci (dati AIFA).

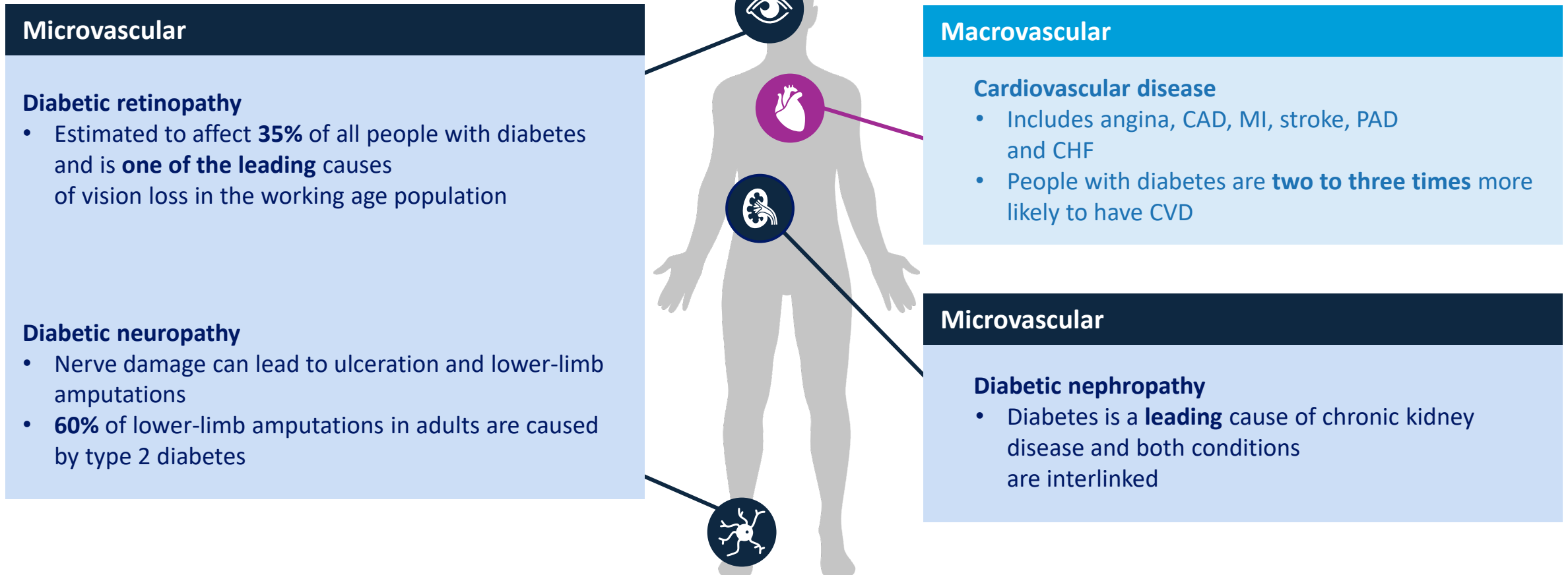


[Fialová D et al, Potentially inappropriate medication use among elderly home care patients in Europe. JAMA 2005; 293: 1348-1358].

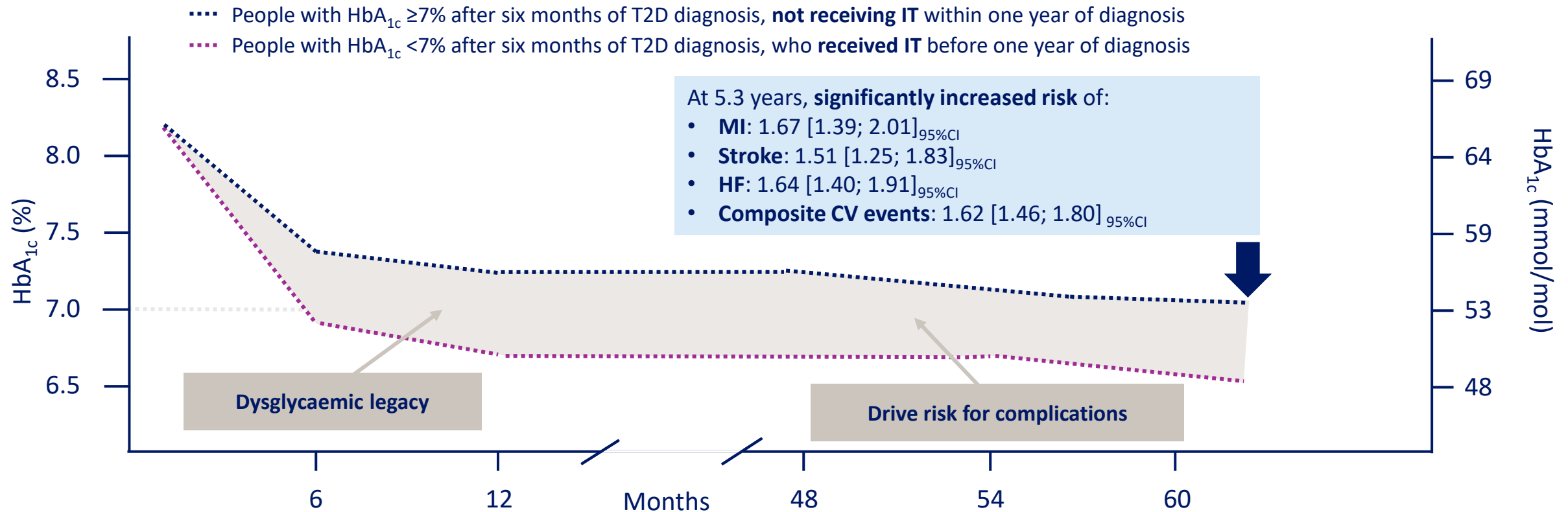
Poor adherence is associated with poor glycaemic control and higher healthcare costs



Poorly controlled diabetes leads to increased risk of developing diabetes-related complications



Consequences of delayed treatment intensification in people with T2D without previous CVD

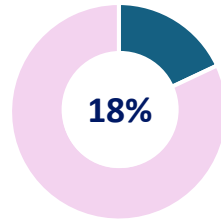


The risk of CVD is shown for people with HbA_{1c} consistently above >7.0% (53 mmol/mol) in the two years following diagnosis for whom treatment intensification is delayed by at least one year versus that of people with HbA_{1c} consistently below <7.0% (53 mmol/mol) in the same period.
CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; HF, heart failure; IT, intensification of treatment; MI, myocardial infarction.
1. Khunti K, Millar-Jones D. *Prim Care Diabetes*. 2017;11(1):3–12; 2. Paul SK et al. *Cardiovasc Diabetol*. 2015;14:100.

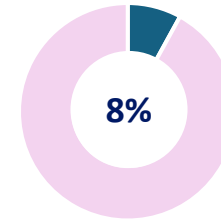


Even one year of poor glycaemic control in people with T2D can result in...

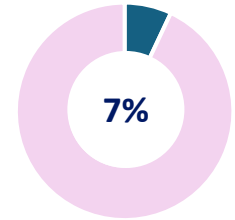
... an increase in the cumulative **incidence** of¹:



Nephropathy

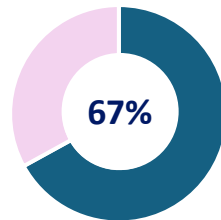


Neuropathy

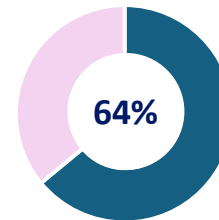


Retinopathy

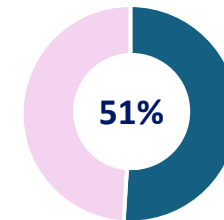
... a significantly increased **risk** of²⁺:



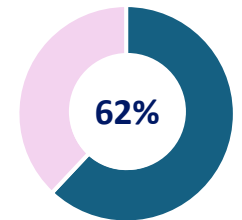
Myocardial infarction



Heart failure



Stroke



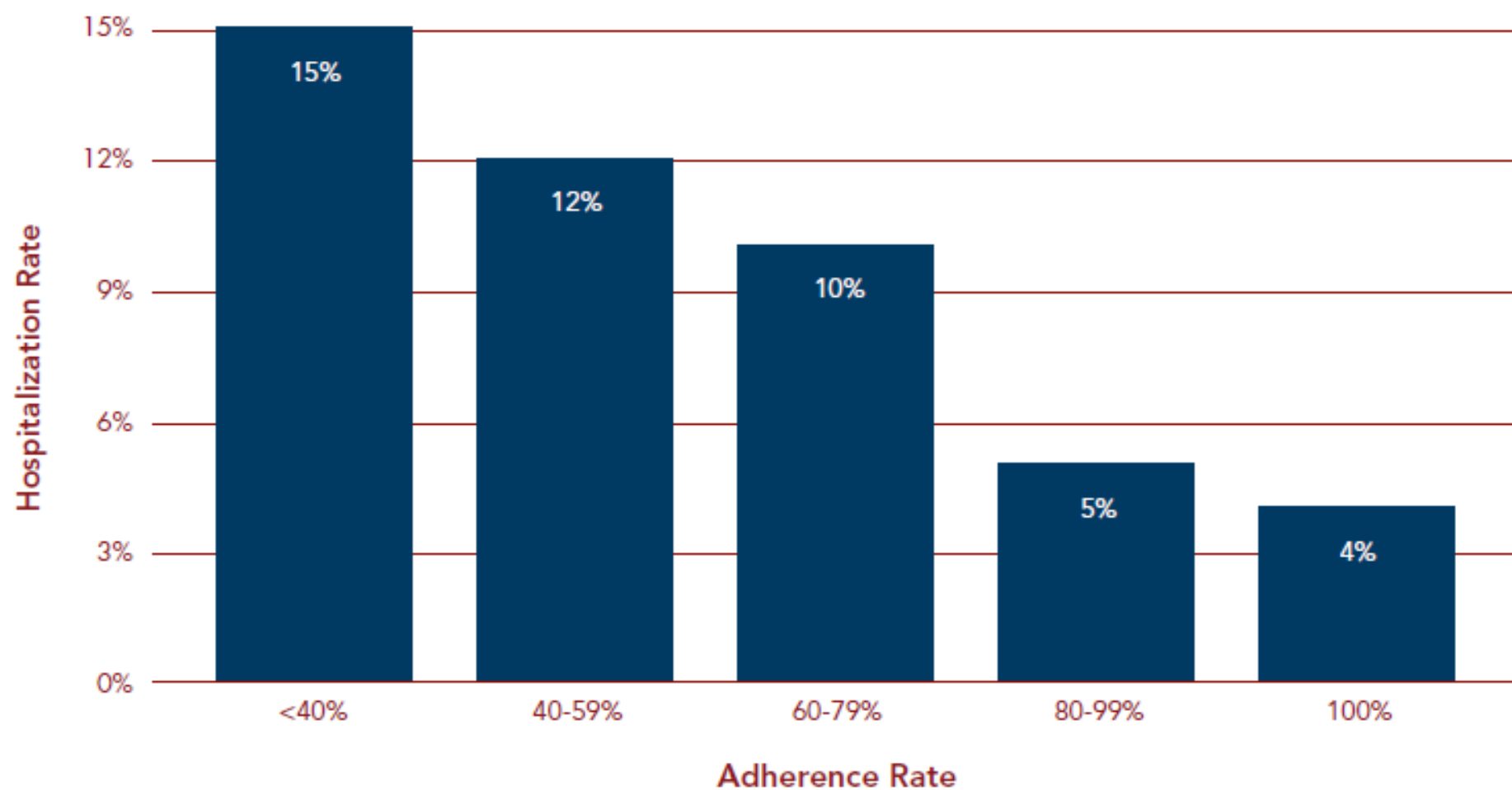
Composite CV events[‡]

[†]compared with patients with HbA1c <7%; [‡]The composite CV events was based on the occurrence of either myocardial infarction, heart failure or stroke.

Abbreviations: CV, cardiovascular; HbA1c, glycated haemoglobin.

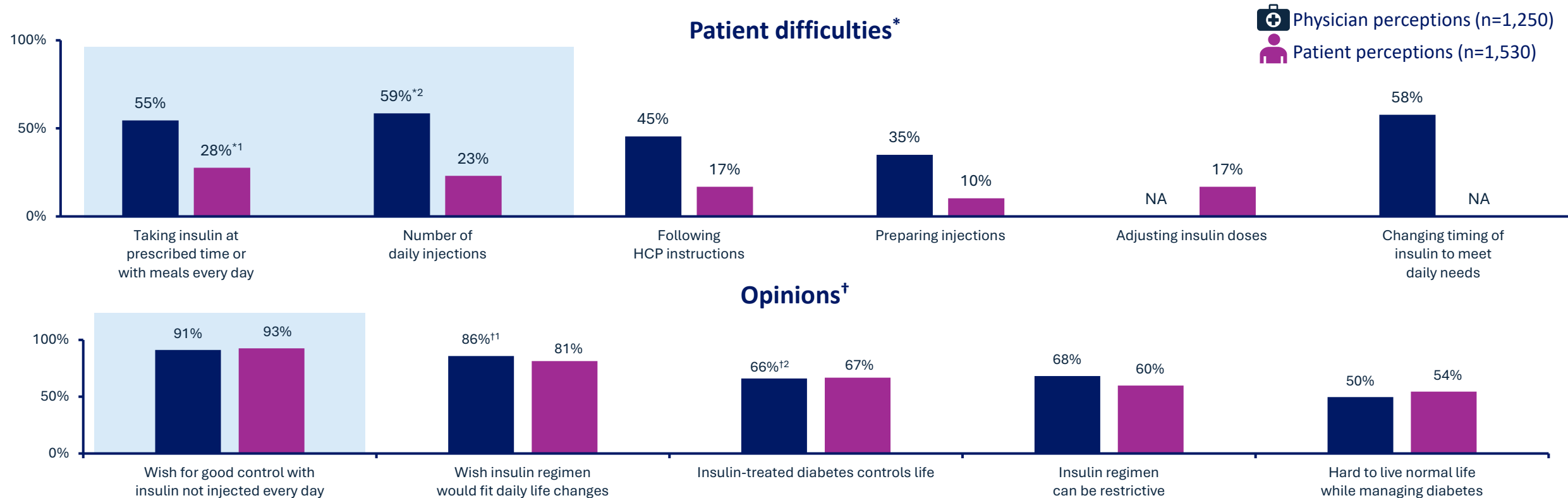
References: 1. Correa et al. J Gen Intern Med. 2019;34(3):372-378. 2. Paul et al. Cardiovascular Diabetology. 2015;14:100.

**FIGURE 2: RELATIONSHIP BETWEEN ADHERENCE AND HOSPITALIZATION
IN PATIENTS WITH DIABETES**



Source: D.T. Lau and D. P. Nau, "Oral Antihyperglycemic Medication Nonadherence and Subsequent Hospitalization Among Individuals with Type 2 Diabetes." *Diabetes Care*, September 2004.

Patients and physicians identify higher frequency of insulin injections as a burden



*Very difficult or somewhat difficult (vs. very easy, somewhat easy, not applicable, 'don't know'). Absolute percentages reported for physicians cannot be compared with percentage of patients for whom this is difficult because physicians report whether this is difficult for their 'typical patient' rather than the percentage of their patients for whom this is difficult; rank order of reasons by patients and physicians can be compared. *¹Average of response for two items (insulin at prescribed times, insulin with each meal). *²Physician item is 'taking insulin frequently'. †Strongly agree or somewhat agree (vs. strongly disagree, somewhat disagree, neither, 'don't know'). †Physician item is 'which insulin treatments could be more flexible'. †²Physician item is if his/her patients feel diabetes controls their lives. HCP, healthcare professional; n, number of subjects; NA, not asked. 1. Peyrot M et al. *Diabet Med.* 2012;29(5):682–689.

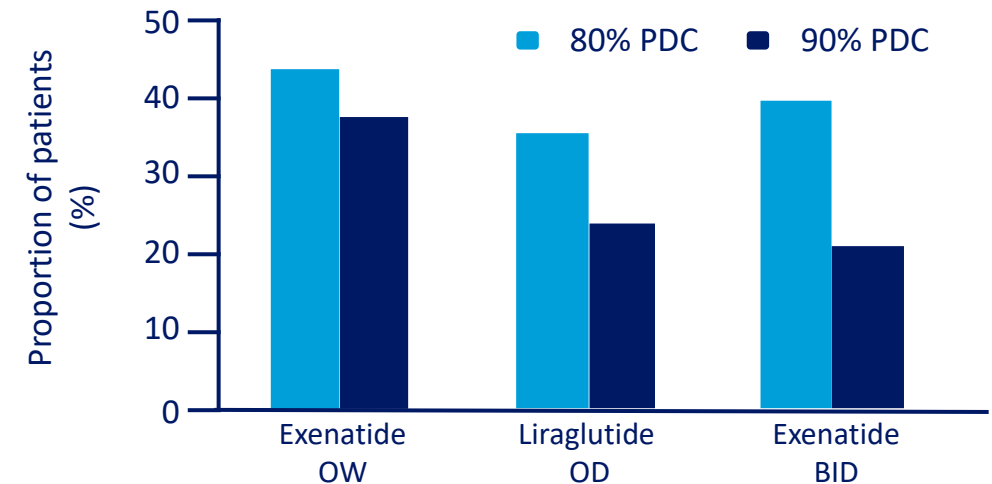


Example: once-weekly GLP-1RAs have improved treatment satisfaction and adherence

Improvement in treatment satisfaction with OW exenatide: results from RCTs¹

	Exenatide BID → OW	
	n*	Change in DTSQ scores
Treatment convenience	123	0.42 ± 1.6 [†]
Satisfaction continuing treatment	123	0.24 ± 1.3 [‡]

Retrospective cohort study of prescription claims data from US Medicare patients²



73.1%

of people receiving injectable anti-diabetes medication would be willing to take a once-weekly injectable medication if it was recommended by their physician³

*Number of subjects with week 30 and week 52 score. [†] $p < 0.01$. [‡] $p \leq 0.05$.

BID, twice-daily; DTSQ, Diabetes Treatment Satisfaction Questionnaire; GLP-1RA, glucagon-like peptide-1 receptor agonist; n, number of subjects; OD, once-daily; OW, once-weekly; PDC, proportion of days covered; RCT, randomised controlled trial.

1. Best JH et al. *Diabet Med*. 2009;26(7):722–728; 2. Nguyen H et al. *Adv Ther*. 2017;34(3):658–673; 3. Polonsky WH et al. *Diabetes Obes Metab*. 2011;13(2):144–149.



Diabetes treatment satisfaction questionnaire

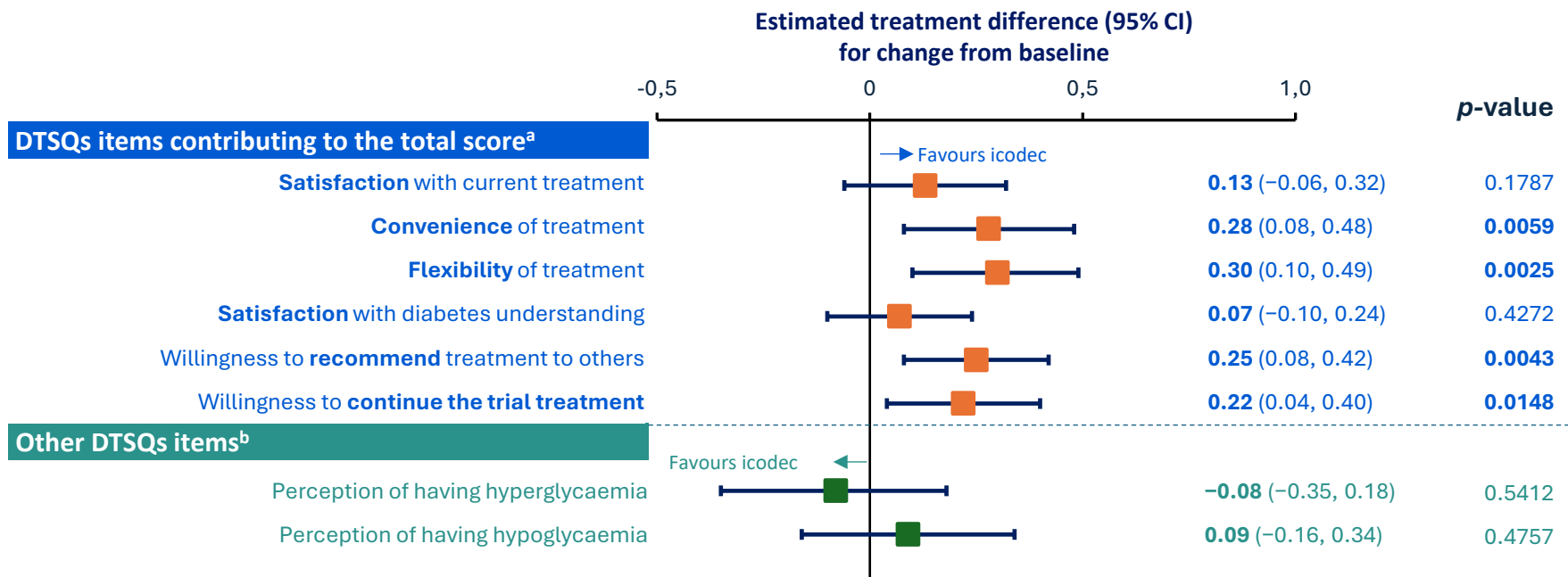
Question		Option range (scored 0–6)	
1	How satisfied are you with your current treatment?*	very dissatisfied	↔ very satisfied
2	How often have you felt that your blood sugars have been unacceptably high recently?	none of the time	↔ most of the time
3	How often have you felt that your blood sugars have been unacceptably low recently?	none of the time	↔ most of the time
4	How convenient have you been finding your treatment to be recently?*	very inconvenient	↔ very convenient
5	How flexible have you been finding your treatment to be recently?*	very inflexible	↔ very flexible
6	How satisfied are you with your understanding of your diabetes?*	very dissatisfied	↔ very satisfied
7	Would you recommend this form of treatment to someone else with your kind of diabetes?*	no, I would definitely not recommend	↔ yes, I would definitely recommend it
8	How satisfied would you be to continue with your present form of treatment?*	very dissatisfied	↔ very satisfied

*Six items (1, 4, 5, 6, 7 and 8) contribute to the overall treatment satisfaction score. DTSQ total treatment satisfaction score can range from 0 to 36, with 0 being the lowest and 36 being the highest score.



Change from baseline in DTSQs scores after 26 weeks

Icodec basal switch in T2D



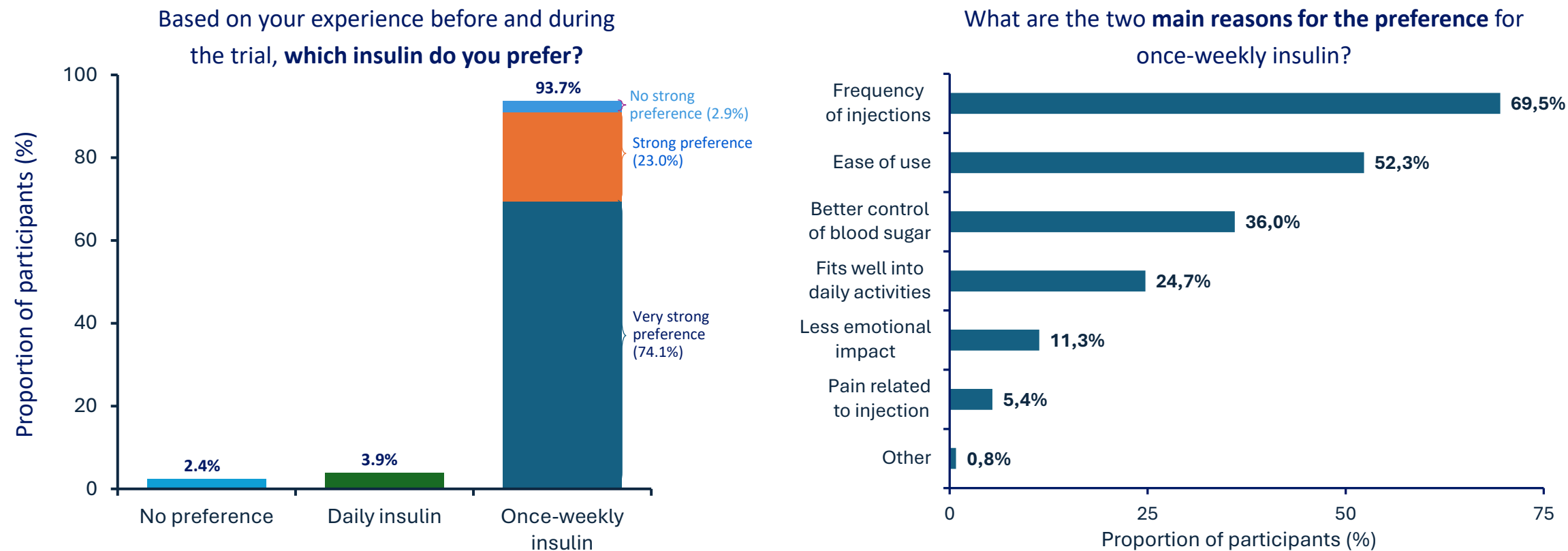
Statistically significantly greater changes with icodec versus degludec were seen in DTSQs total treatment satisfaction score and DTSQs items on convenience, flexibility, willingness to continue trial treatment and to recommend treatment to others

^aETD > 0 favours icodec; ^bETD < 0 favours icodec.
Each item of the DTSQs is scored on a scale from 0 to 6 with higher scores reflecting greater treatment satisfaction. The total treatment score could range from 0 to 36, with 0 being the lowest and 36 being the highest score. In-trial. Full analysis set. No correction for multiplicity. The change from baseline in response after 26 weeks was analysed using an ANCOVA model with treatment, region and personal CGM device use as fixed factors, and baseline response as covariate. Missing values at week 26 were imputed by the baseline value and a random term, using multiple imputation. The random term was normally distributed with mean 0 and standard deviation equal to the estimated residual standard deviation from the ANCOVA model fitted to the LAOT values. The model included the same factors and covariates as the model used for analysis.
p-value: two-sided p-value for test of no treatment difference.
ANCOVA, analysis of covariance; CI, confidence interval; CGM, continuous glucose monitoring; DTSQs, Diabetes Treatment Satisfaction Questionnaire-status; LAOT, last available planned on-treatment.
1. Polonsky W et al. 2023 ESD Annual Meeting. SO-780.



Insulin Preference Questionnaire (icodec participants)

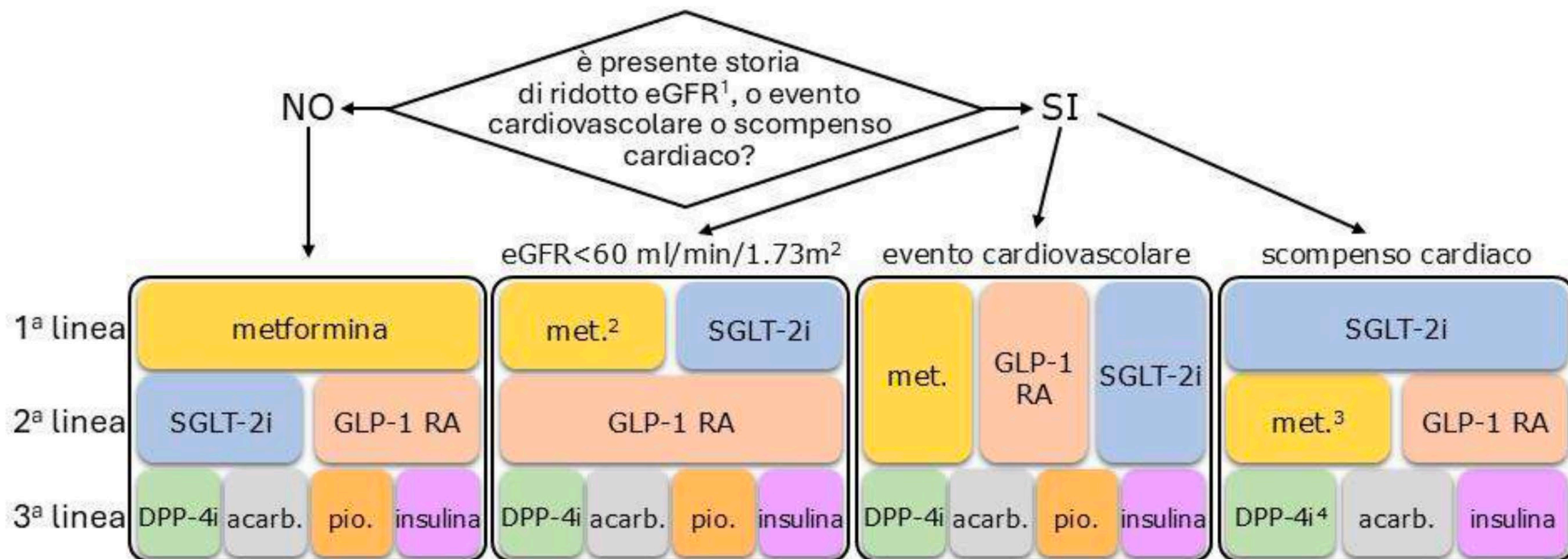
Icodec basal switch in T2D



Majority of the icodec participants had a **very strong preference towards once-weekly insulin icodec** (during the trial) versus their previous daily basal insulin (before the trial)

Pre-trial daily basal insulins were administered once-daily or twice-daily.
Of 263 participants who received insulin icodec, 255 completed the Insulin Preference Questionnaire (239 expressed a preference for once-weekly insulin and provided two reasons each for their preference).
1. Polonsky W et al. 2023 ESD Annual Meeting. SO-780.





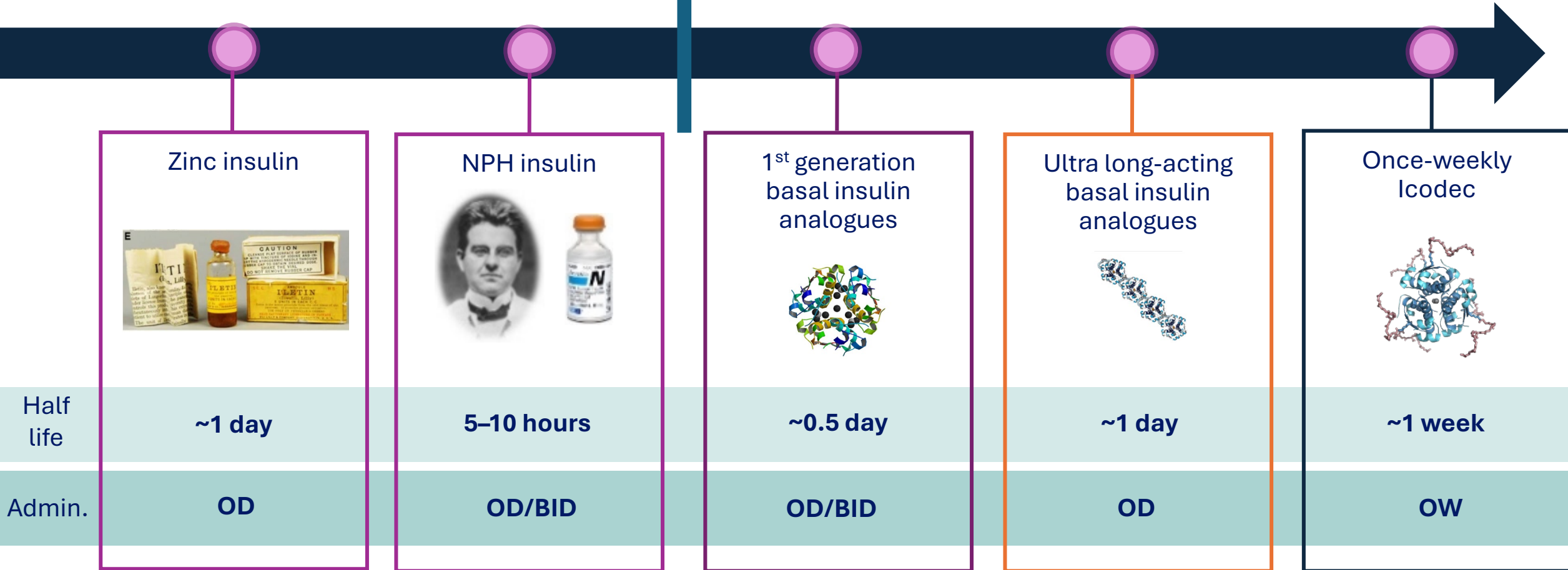
NB: l'indicazione ai farmaci di terza linea (DPP-4i, acarbiosio, pioglitazone, insulina) deve essere considerata solo dopo l'utilizzo in combinazione di metformina, SGLT-2i e GLP-1 RA, qualora tollerati e non controindicati. L'indicazione per DPP-4i è valida solo se GLP-1 RA non indicati o non tollerati. 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.

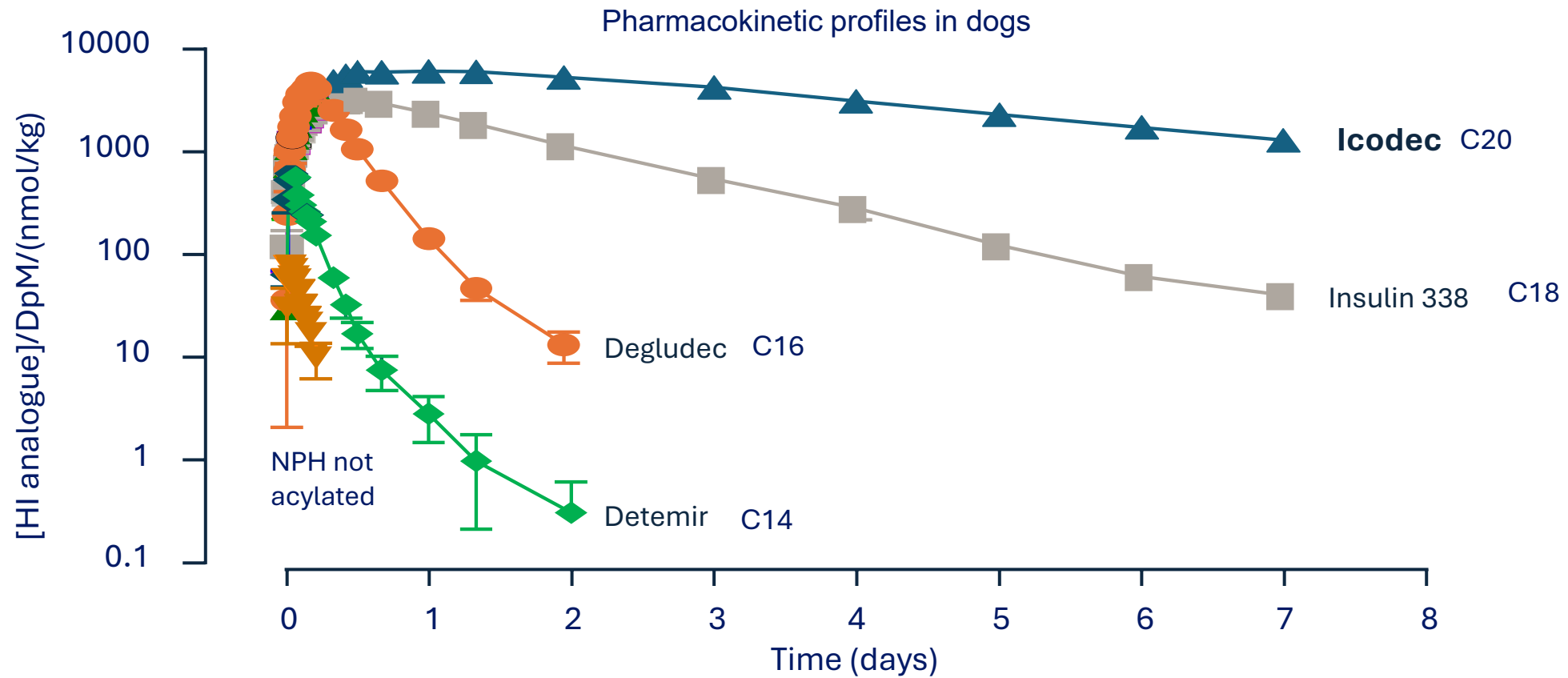
Past and present of basal insulin innovation

Trying to control absorption
of Human Insulin from s.c.

Trying to modify half-life
of Human Insulin Analogue

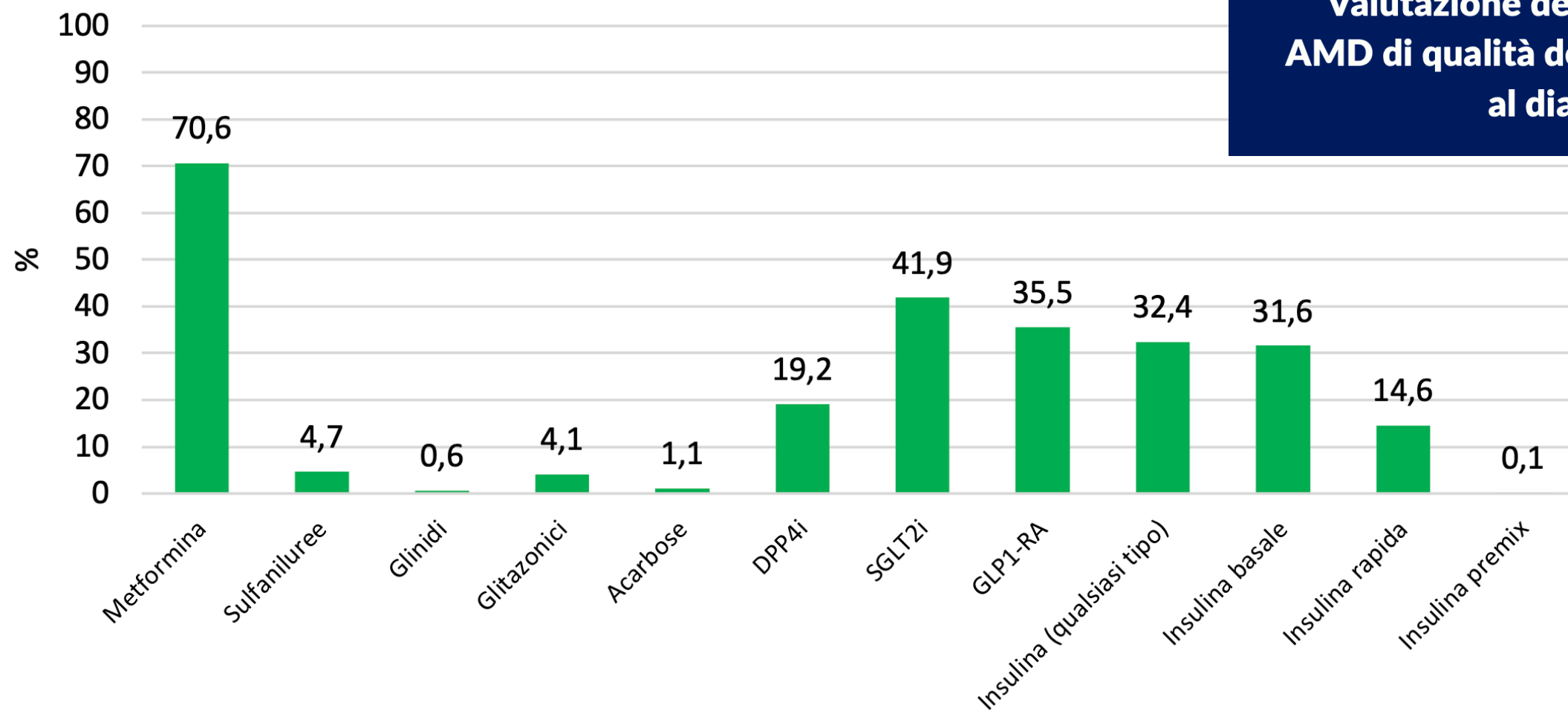


Acylated Insulin analogues: fatty acid affinity with albumin increases half-life



Uso dei farmaci (%)

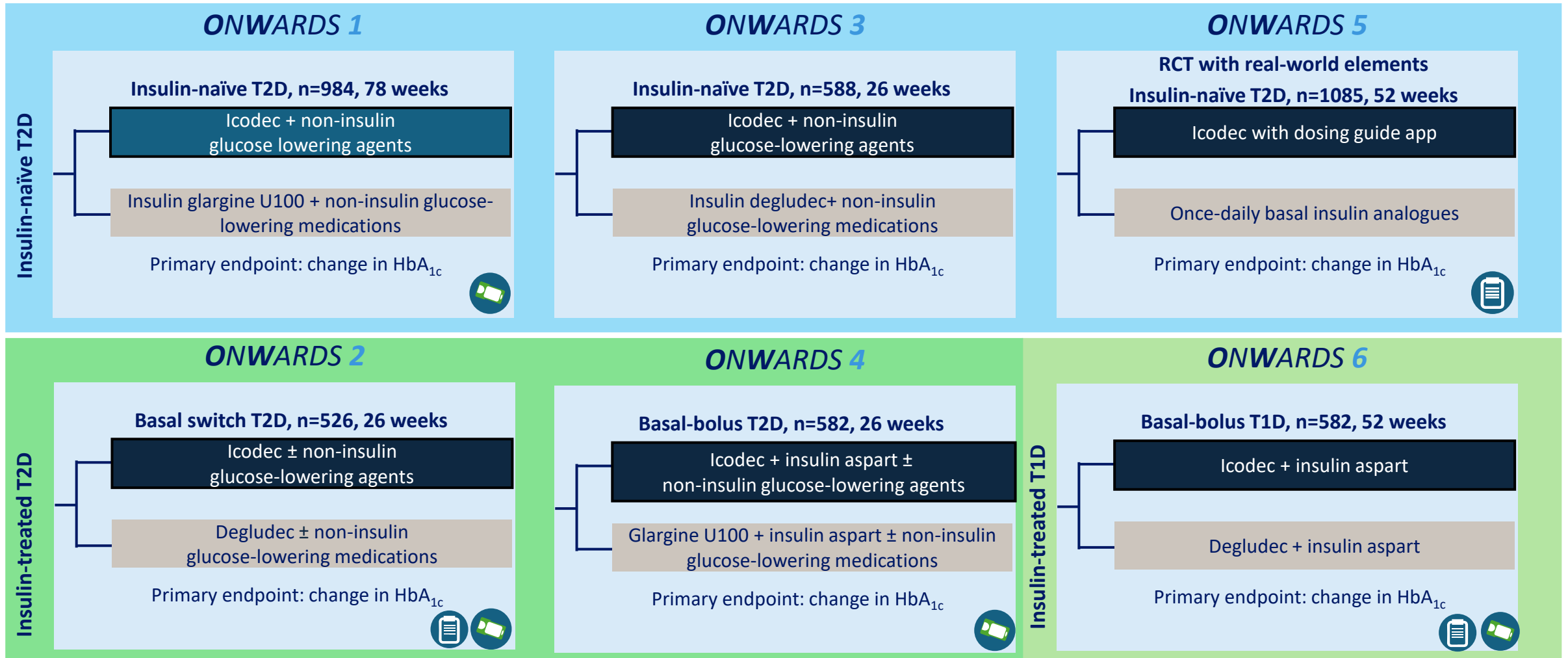
Farmaci per il diabete (%)



ANNALI AMD 2024

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

Summary of the **ONWARDS** programme



PROs collected

CGM



IPOGLICEMIE

CGM metrics in insulin-treated T2D

Post-hoc analyses

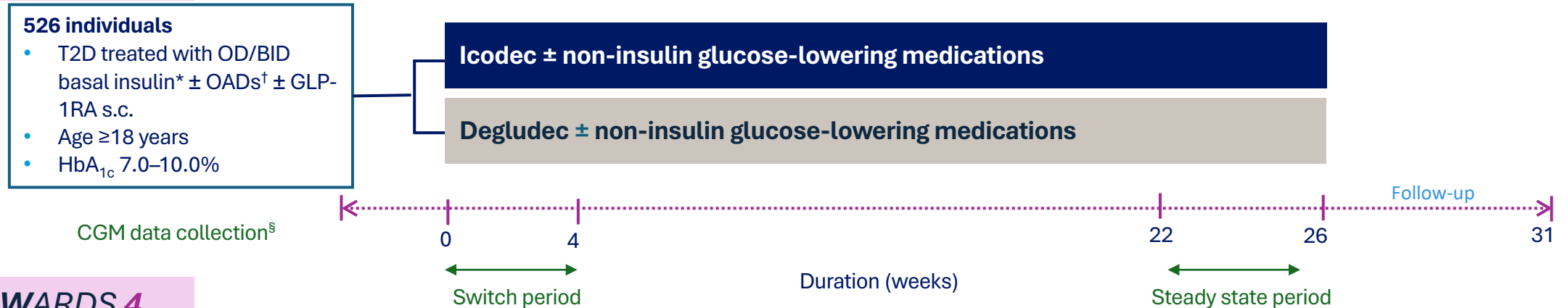
Objective: To investigate the efficacy and safety of once-weekly icodec versus once-daily degludec or glargine U100 in insulin-treated individuals with T2D using CGM-based metrics and CGM-derived hypoglycaemia duration via ***post-hoc analyses from ONWARDS 2 and 4***



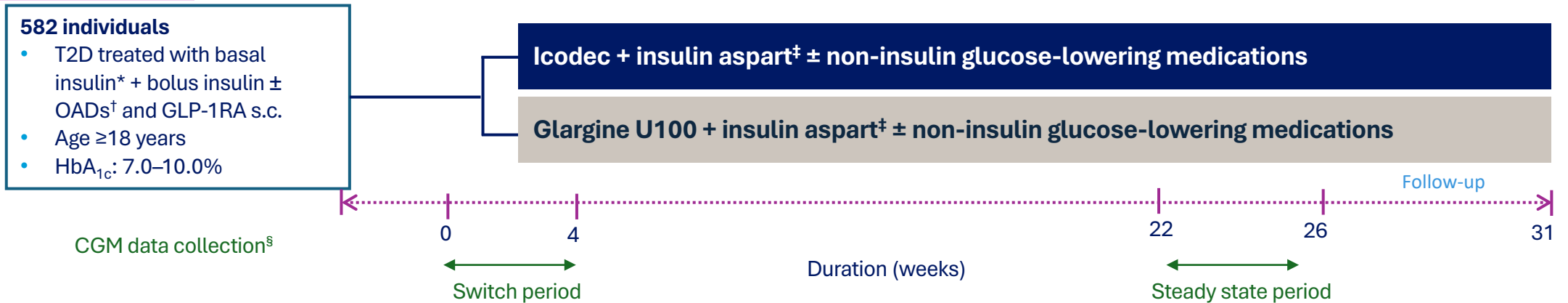
Trial design

CGM metrics in insulin-treated T2D

ONWARDS 2



ONWARDS 4



*Participants treated with OD or BID basal insulin (ONWARDS 2) or OD basal insulin (ONWARDS 4). [†]Sulphonylureas and glinides were discontinued at randomisation to minimise the risk of hypoglycaemia. [‡]2–4 daily injections. [§]Participants were equipped with a CGM device during weeks 0–4 and weeks 22–26

BID, twice daily; CGM, continuous glucose monitoring; GLP-1RA, glucagon-like peptide-1 receptor agonist; OAD, oral glucose-lowering medications; OD, once daily.

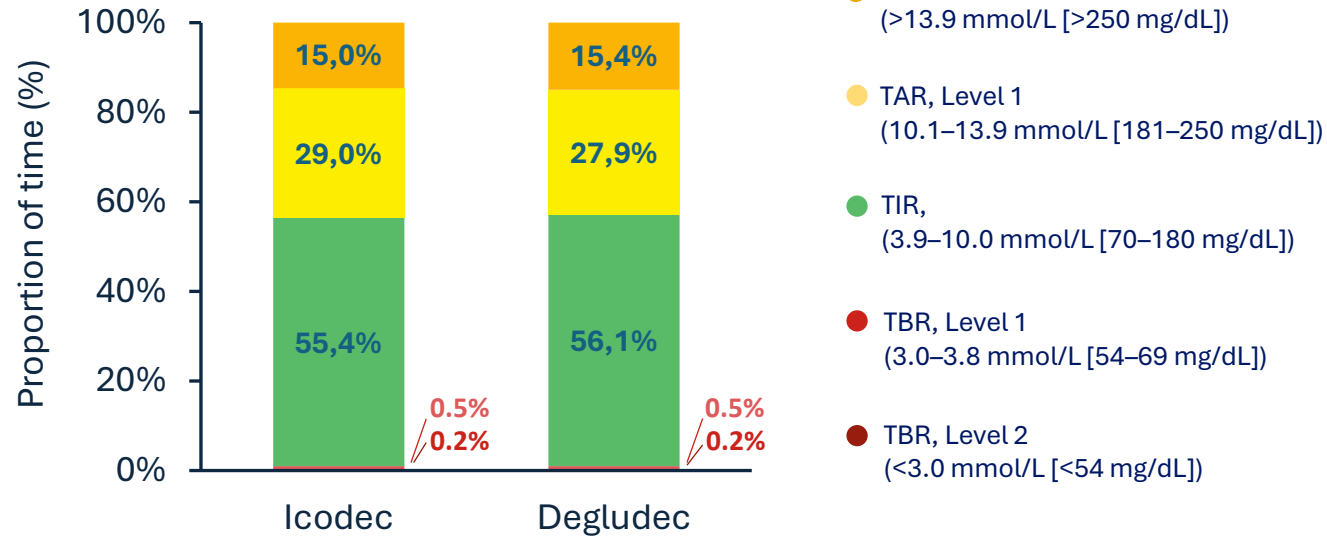
1. Philis-Tsimikas A et al. *Diabetes Obes. Metab.* 2022; doi: 10.1111/dom.14871; 2. Bajaj H et al. *Diabetes Care.* 2024;47(4):1–10; 3. Philis-Tsimikas A et al. *Lancet Diabetes Endocrinol.* 2023;11(6):414–425. 4. Mathieu C et al. *Lancet.* 2023;401(10392):1929–40.



CGM outcomes: Follow-up period (weeks 27–31)

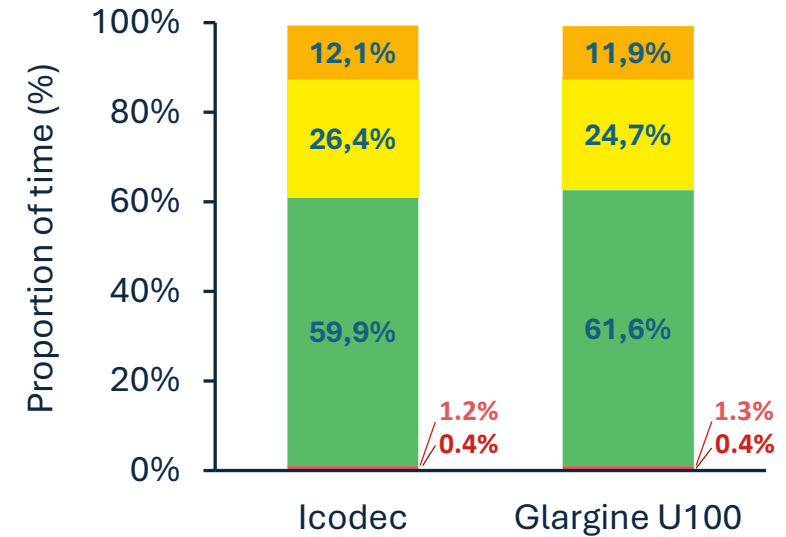
CGM metrics in insulin-treated T2D

ONWARDS 2



	TIR 3.9–10 mmol/L (70–180 mg/dL)	TBR <3.9 mmol/L (<70 mg/dL)	TBR <3.0 mmol/L (<54 mg/dL)	TAR >10 mmol/L (>180 mg/dL)
ERR or ETD [95% CI]	ETD -1.25 [-4.69;2.18]; $p=0.474$	ERR 0.91 [0.67;1.24]; $p=0.548$	ERR 0.85 [0.55;1.31]; $p=0.466$	1.27 [-2.22;4.76]; $p=0.475$

ONWARDS 4



	TIR 3.9–10 mmol/L (70–180 mg/dL)	TBR <3.9 mmol/L (<70 mg/dL)	TBR <3.0 mmol/L (<54 mg/dL)	TAR >10 mmol/L (>180 mg/dL)
ERR or ETD [95% CI]	ETD -1.45 [-4.88;1.97]; $p=0.406$	ERR 0.91 [0.71;1.16]; $p=0.428$	ERR 0.95 [0.69;1.32]; $p=0.776$	ETD 1.56 [-1.94;5.05]; $p=0.382$

CGM, continuous glucose monitoring; CI, confidence interval; ERR, estimated rate ratio; TIR and TAR analysed with an ANOVA model with region, CGM use, and treatment as fixed factors. TBR analysed with a negative binomial model with a log-link function and the logarithm of the total number of recorded measurements as an offset, with region, treatment, and CGM use as fixed factors. ETD, estimated treatment difference; TAR, time-above-range; TBR, time-below-range; TIR, time-in-range.

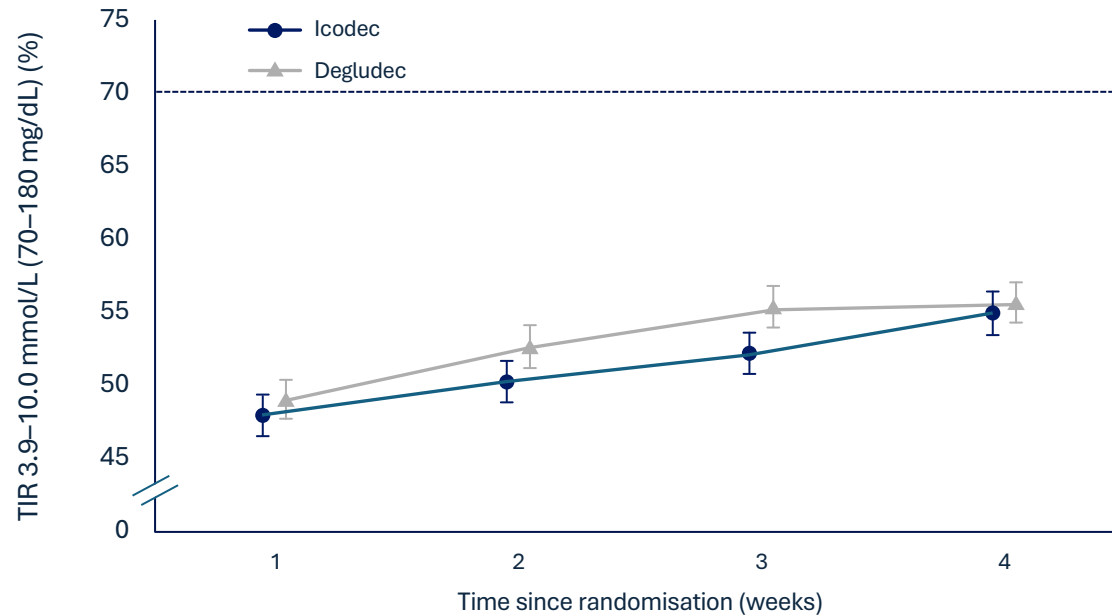
1. Battelino et al. *Lancet Diabetes Endocrinol.* 2023;11(1):42–57; 2. Bajaj H et al. *Diabetes Care.* 2024;47(4):1–10.



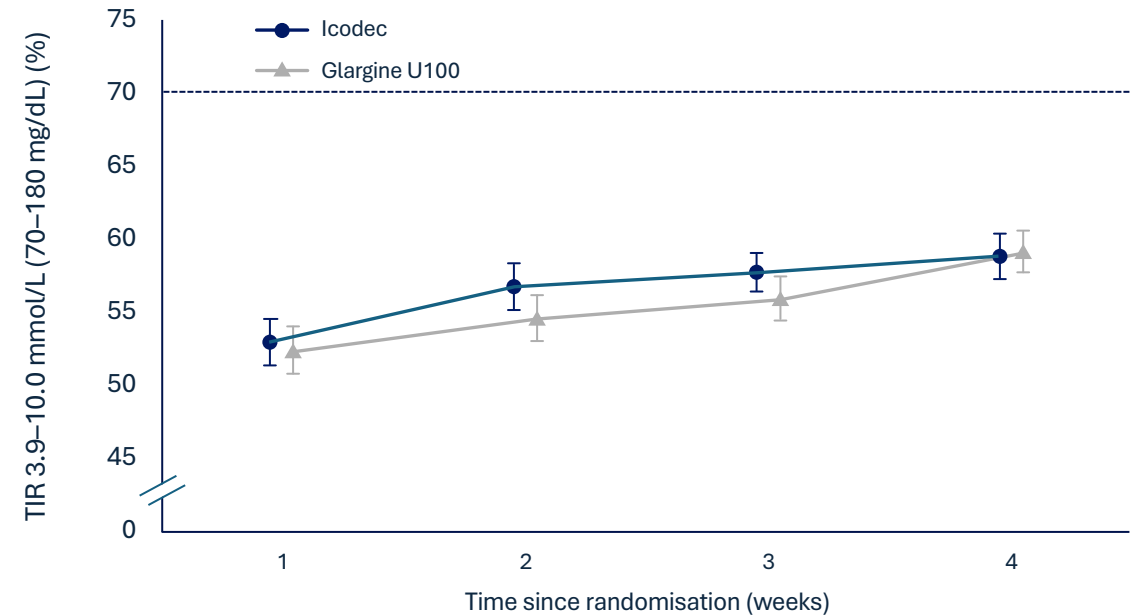
TIR: Switch period (weeks 0–4)

CGM metrics in insulin-treated T2D

ONWARDS 2



ONWARDS 4



Switching to icodec, including a one-time additional 50% icodec dose, **did not compromise glycaemic control (TAR or TIR) versus comparators, and TBR remained within the recommended targets**

Time spent is defined as 100 times the number of recorded measurements in a given range, divided by the number of recorded measurements. Dashed lines indicate recommended glycaemic targets¹

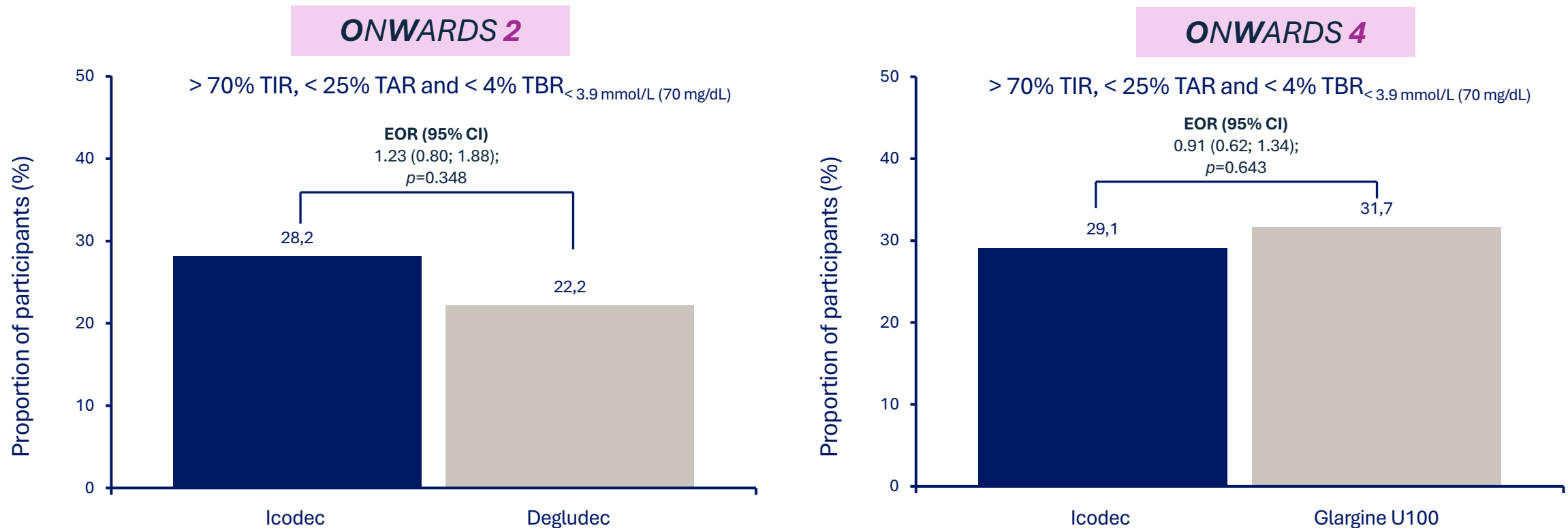
TAR, time-above-range; TBR, time-below-range; TIR, time-in-range.

1. Bajaj H et al. *Diabetes Care*. 2024;47(4):1–10.



Proportion of participants achieving CGM targets during steady state period (weeks 22-26)

CGM metrics in insulin-treated T2D



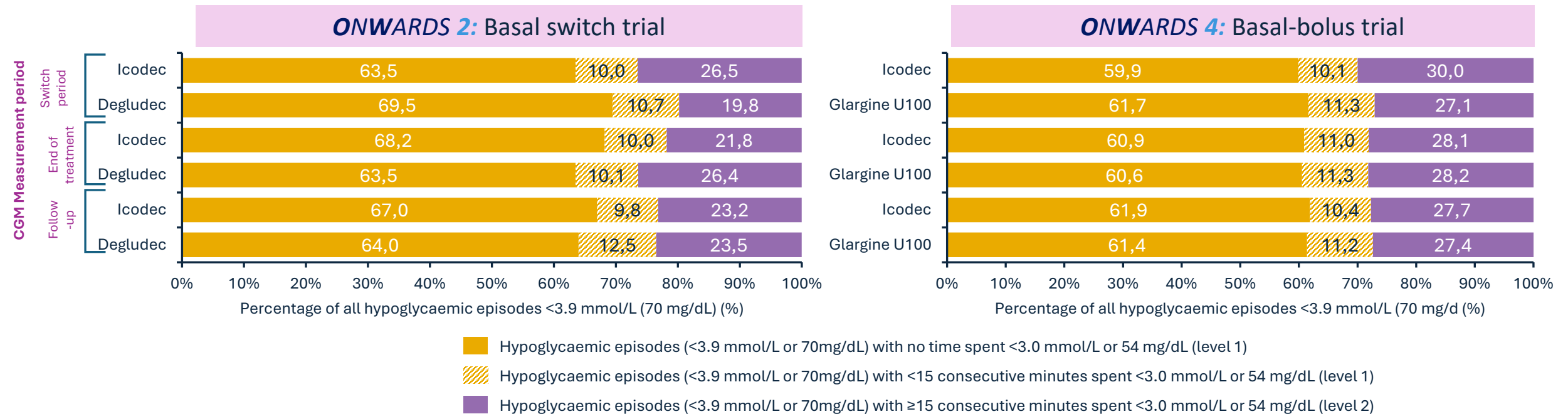
Statistical model: logistic regression. Statistical analysis based on multiple imputed data. Value is the EOR (icodec/degludec [ONWARDS 2]; icodec/glargine U100 [ONWARDS 4]). Statistical model was adjusted for geographic region and use of personal CGM or isCGM device. CGM, continuous glucose monitoring; CI, confidence interval; EOR, estimated odds ratio; isCGM, intermittently scanned CGM; TAR, time-above-range; TBR, time-below-range; TIR, time-in-range.

1. Bajaj H et al. *Diabetes Care*. 2024;47(4):1–10.



Classification of CGM-derived overall hypoglycaemic episodes (<3.9 mmol/L) by time spent <3.0 mmol/L

CGM metrics in insulin-experienced T2D



- During all time periods, most CGM-derived hypoglycaemic episodes <3.9 mmol/L (70 mg/dL) did not include any time spent <3.0 mmol/L (54 mg/dL), or had <15 minutes spent <3.0 mmol/L (54 mg/dL) (level 1)
- There were no substantial differences between icodec and OD comparators in the percentage of CGM-derived hypoglycaemic episodes with time spent <3.0 mmol/L (54 mg/dL) for ≥15 minutes (level 2)



Summary

CGM metrics in insulin-treated T2D

In insulin-treated participants with T2D:

During the switch period, TIR, TAR and TBR were not significantly different between OW icodec and OD comparators

The CGM-derived duration of overall hypoglycaemic episodes <3.9 mmol/L (70 mg/dL) was comparable between OW icodec compared with OD comparators during all three CGM time periods, with all medians ≤ 40 minutes

Switching to once-weekly icodec, with a one-time additional 50% icodec dose, showed:

- No increase in TAR versus once-daily basal insulin comparators
- TBR remained within the international recommended CGM targets in all groups

For individuals receiving icodec, the majority of all hypoglycaemic episodes <3.9 mmol/L (70 mg/dL) did not develop into level 2 hypoglycaemia (<3.0 mmol/L [54 mg/dL] for ≥ 15 minutes) during any of the CGM time periods

During the steady state period, TIR and TAR were not significantly different between once-weekly icodec and once-daily comparators:

- TBR remained within the international recommended CGM targets in all groups



ASSOCIAZIONI CON GLP-1

Efficacy and hypoglycaemia outcomes in T2D according to baseline GLP-1RA use: ONWARDS 1–5

Post-hoc analyses

Aim: This post-hoc analysis of ONWARDS 1–5 assessed the treatment effects of OW icodec versus OD basal insulin comparators according to baseline GLP-1RA use in individuals with T2D



- Pretrial GLP-1RA use was recommended to be continued in all trials, but participants were not stratified by baseline GLP-1RA use upon randomisation
- Per protocol, participants had to be treated with a stable dose of GLP-1RA for at least 90 days prior to screening

Treatment outcomes assessed by trial according to GLP-1RA use at baseline

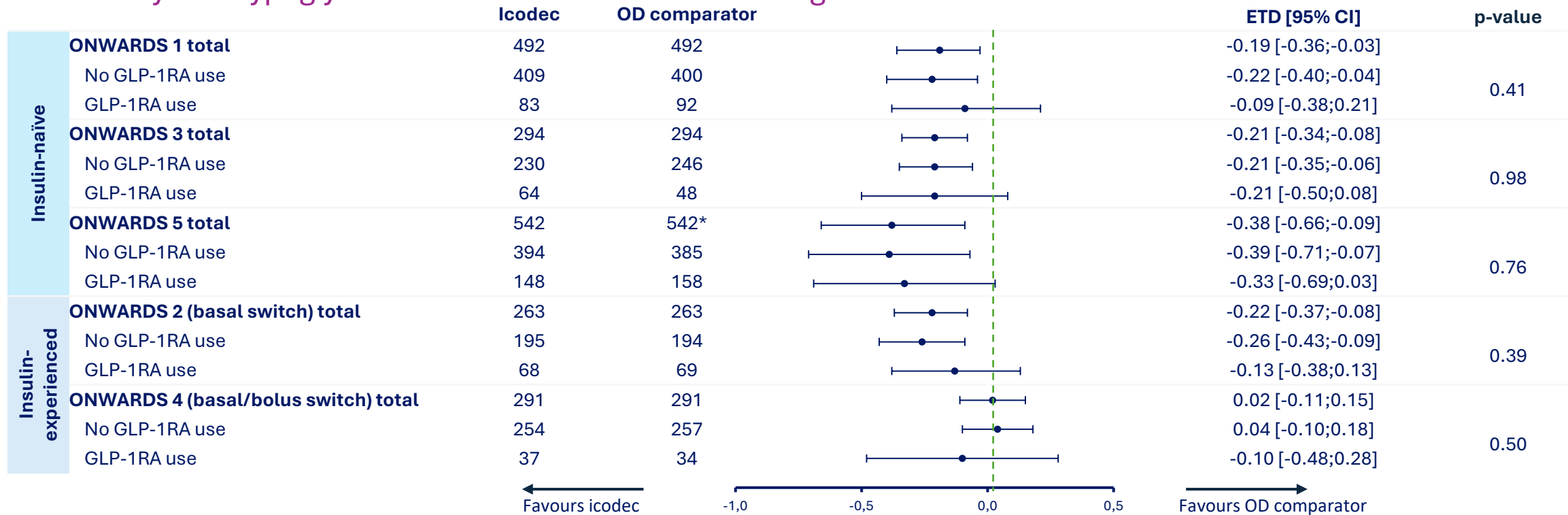
- Estimated treatment difference in change in HbA_{1C} from baseline to EOT^a
- Observed rates of clinically significant or severe hypoglycaemia^b
- Estimated proportion of participants achieving HbA_{1C} <7% at EOT without clinically significant or severe hypoglycaemic episodes in the previous 12 weeks
- Estimated mean weekly basal insulin dose during the last 2 weeks of treatment
- Estimated change in body weight from baseline to EOT

^aONWARDS 1, week 78; ONWARDS 2–4, week 26; ONWARDS 5: week 52. ^bClinically significant hypoglycaemia (level 2): blood glucose level of <54 mg/dL, confirmed by blood glucose meter. Severe hypoglycaemia (level 3): hypoglycaemia associated with severe cognitive impairment requiring external assistance for recovery. HbA_{1C}, glycated haemoglobin; EOT, end of treatment; GLP-1RA, glucagon-like peptide-1 receptor agonist.
1. Vilsbøll T et al. ADA 84th Scientific Sessions. June 21–24, 2024, Orlando Florida. 840-P.



ETD in change in HbA_{1c} from baseline to EOT

Efficacy and hypoglycaemia outcomes in T2D according to baseline GLP-1RA use: ONWARDS 1–5



Across all trials, participants receiving icodec versus OD comparators had larger or similar HbA_{1c} reductions from baseline to EOT irrespective of GLP-1RA use; there was no statistically significant treatment by GLP-1RA subgroup interaction in HbA_{1c} changes



Rates of clinically significant or severe hypoglycaemia

Efficacy and hypoglycaemia outcomes in T2D according to baseline GLP-1RA use: ONWARDS 1–5

Trial		Participants with/without GLP-1RA use, n	With GLP-1RA use at baseline				Without GLP-1RA use at baseline			
			Icodec		OD comparator		Icodec		OD comparator	
			n (%)	E (R)	n (%)	E (R)	n (%)	E (R)	n (%)	E (R)
Clinically significant or severe hypoglycaemia ^a , events/PYE										
Insulin-naive participants	ONWARDS 1	Icodec: 83/409 OD comparator: 92/400	11 (13.3)	22 (0.17)	10 (10.9)	13 (0.09)	50 (12.2)	205 (0.32)	60 (15.0)	108 (0.17)
	ONWARDS 3	Icodec: 64/230 OD comparator: 48/246	7 (10.9)	9 (0.24)	3 (6.2)	4 (0.14)	19 (8.3)	44 (0.33)	15 (6.1)	21 (0.15)
	ONWARDS 5	Icodec: 148/394 OD comparator: 158/385	15 (10.1)	17 (0.11)	9 (5.7)	12 (0.07)	49 (12.4)	87 (0.22)	36 (9.4)	69 (0.17)
Insulin-experienced participants	ONWARDS 2	Icodec: 68/195 OD comparator: 69/194	9 (13.2)	11 (0.27)	3 (4.3)	4 (0.10)	28 (14.4)	102 (0.89)	16 (8.2)	38 (0.34)
	ONWARDS 4	Icodec: 37/254 OD comparator: 34/257	21 (56.8)	122 (5.65)	13 (38.2)	62 (3.12)	129 (50.8)	822 (5.64)	149 (58.0)	876 (5.96)

- Overall rates of clinically significant or severe hypoglycaemia were low across treatment arms in ONWARDS 1, 2, 3 and 5, irrespective of GLP-1RA use (<1 event per PYE)
- In ONWARDS 4, rates of clinically significant or severe hypoglycaemia were similar between GLP-1RA users and non-users in the icodec arm

Clinically significant hypoglycaemia (level 2): blood glucose level of <54 mg/dL, confirmed by blood glucose meter. Severe hypoglycaemia (level 3): hypoglycaemia associated with severe cognitive impairment requiring external assistance for recovery. OD comparators: ONWARDS 1 and 4, glargine U100; ONWARDS 2 and 3, degludec; ONWARDS 5, degludec, glargine U100 or glargine U300.

^aHypoglycaemic episodes that occurred during the on-treatment period (onset date on or after the first dose of trial product and no later than the first date of the follow-up visit, the last date on-trial product +5 weeks for OD insulin and +6 weeks for OW insulin or the end date for the in-trial period).

Deludec, insulin degludec; E, number of hypoglycaemic episodes; glargine U100, insulin glargine U100; glargine U300, insulin glargine U300; GLP-1RA, glucagon-like peptide-1 receptor agonist; icodec, insulin icodec; n, number of participants; OD, once-daily; OW, once-weekly; PYE, patient-year of exposure; R, rate of hypoglycaemia (number of episodes/PYE).

1. Vilsbøll T et al. ADA 84th Scientific Sessions. June 21–24, 2024, Orlando Florida. 840-P.



Summary

Efficacy and hypoglycaemia outcomes in T2D according to baseline GLP-1RA use: ONWARDS 1–5

Overall, the efficacy and safety of OW icodec versus OD comparators were generally consistent among individuals with T2D, regardless of GLP-1RA treatment at baseline

Across GLP-1RA subgroups, there were no statistically significant treatment by GLP-1RA subgroup interaction effects with respect to change in HbA_{1C} from baseline to EOT

Rates (events per PYE) of clinically significant or severe hypoglycaemia were low across the treatment arms of ONWARDS 1, 2, 3 and 5, with an overall numerically lower rate in GLP-1RA users than non-users across all trials (except in ONWARDS 4)

- In ONWARDS 4, the icodec arm had a similar rate of clinically significant or severe hypoglycaemia in GLP-1RA users and non-users

There were no statistically significant treatment by GLP-1RA subgroup interaction effects with respect to the proportion of participants who achieved HbA_{1C} targets without hypoglycaemia and change in body weight from baseline to EOT



ASSOCIAZIONI CON SGLT-2

Efficacy and hypoglycaemia outcomes in T2D according to baseline SGLT2i use: ONWARDS 1–5

Post-hoc analyses

Aim: This post-hoc analysis of the ONWARDS 1–5 trials assessed the treatment effects of OW icodec compared with OD basal insulin comparators according to baseline SGLT2i use in individuals with T2D



- Participants treated with pre-trial SGLT2is were included in the trial, but they were not stratified by baseline SGLT2i use upon randomisation^a
- SGLT2i treatments were continued throughout the trial as recommended by the trial protocols

Treatment outcomes assessed by trial according to SGLT2i use at baseline

- Estimated change in HbA_{1C} from baseline to EOT^b
- Observed rates of clinically significant or severe hypoglycaemia^c
- Estimated proportion of participants achieving HbA_{1C} <7% at EOT without clinically significant or severe hypoglycaemic episodes in the previous 12 weeks
- Estimated mean weekly basal insulin dose during the last 2 weeks of treatment
- Estimated change in body weight from baseline to EOT

^aIn ONWARDS 4, participants also received bolus insulin aspart injections 2–4 times daily.

EOT, end of treatment; HbA_{1C}, glycated haemoglobin; icodec, insulin icodec; OD, once-daily; OW, once-weekly; SGLT2i, sodium-glucose co-transporter-2 inhibitor; T2D, type 2 diabetes.

1. Goldenberg R et al. EASD 60th Annual Meeting, September 9–13, 2024. Madrid, Spain and online.



Baseline characteristics in SGLT2i users and non-users in ONWARDS 1–5

Efficacy and hypoglycaemia outcomes in T2D according to baseline SGLT2i use: ONWARDS 1–5



Of the 3765 participants in the ONWARDS 1–5 trials, 36.9% were treated with SGLT2i (icodec: 37.8%; OD comparator: 36.0%)



In all trials, baseline characteristics (age, BMI, sex, diabetes duration) were broadly similar between treatment arms irrespective of baseline SGLT2i use

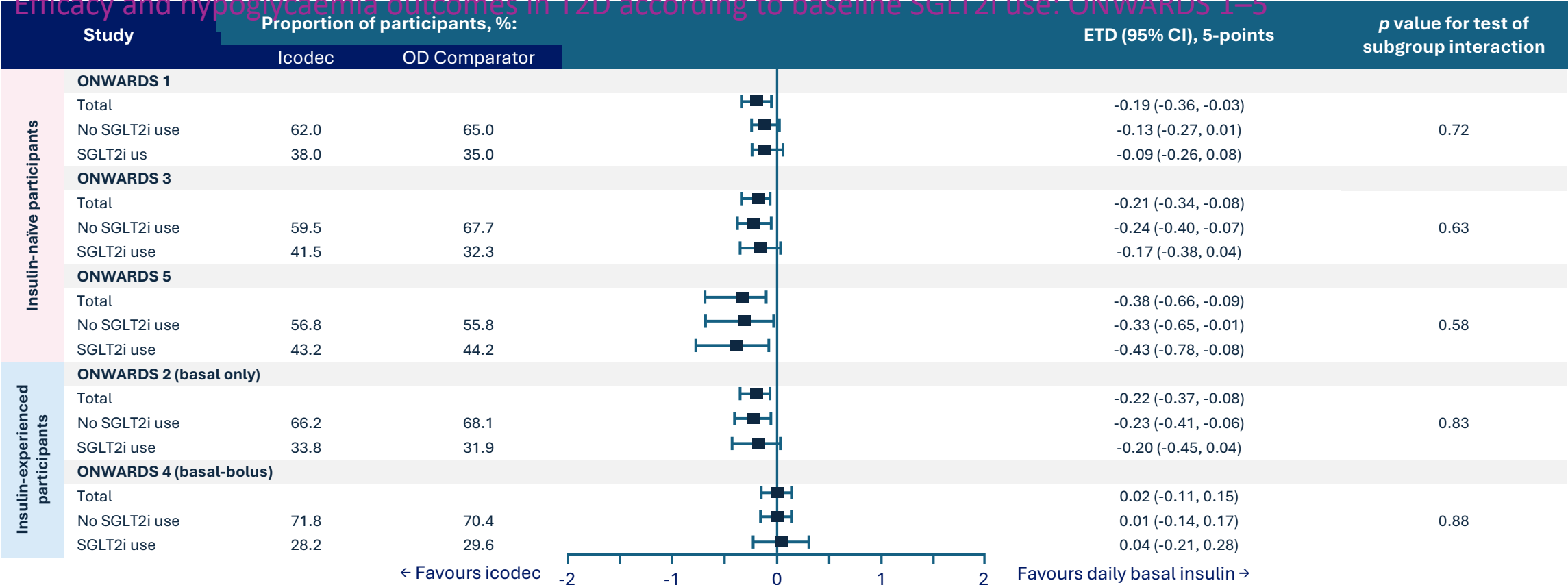


In all trials, except for ONWARDS 2, baseline HbA_{1c} was slightly lower in SGLT2i users compared with non-users between treatment arms



ETD change in HbA_{1c} from baseline to EOT

Efficacy and hypoglycaemia outcomes in T2D according to baseline SGLT2i use: ONWARDS 1–5



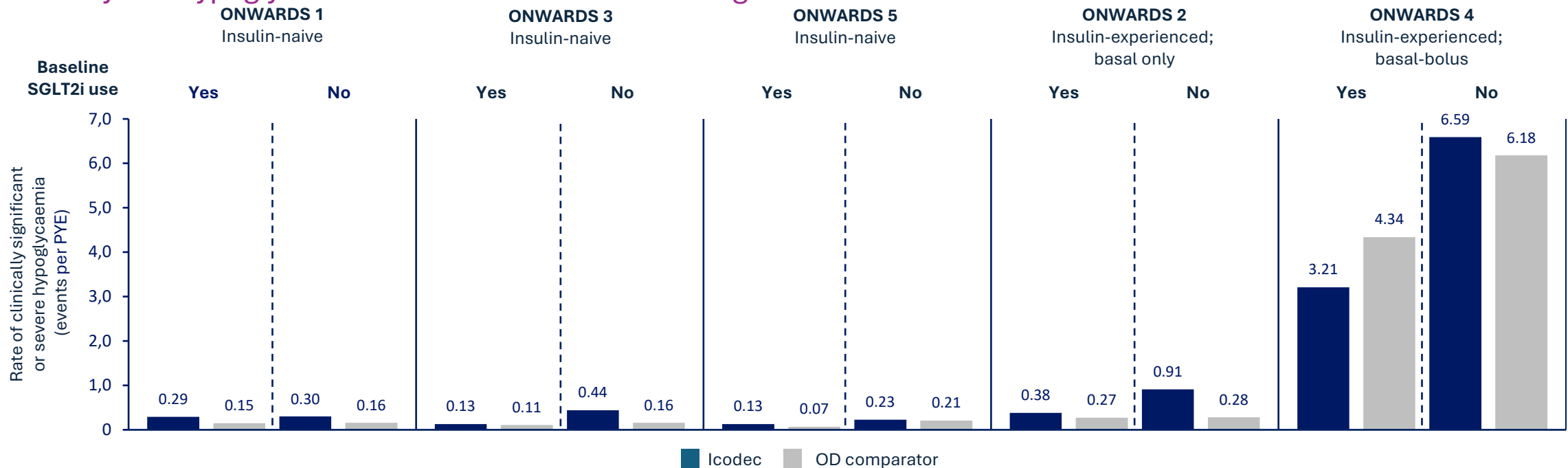
Across all five trials, participants receiving icodec compared with OD comparators had larger or similar HbA_{1c} reductions from baseline to EOT irrespective of SGLT2i use; there was no statistically significant treatment by SGLT2i subgroup interaction in HbA_{1c} changes

EOT: ONWARDS 1, week 78; ONWARDS 2–4, week 26; ONWARDS 5, week 52. ETD: icodec – OD comparator. Participants were not stratified according to their baseline SGLT2i use. Change in HbA_{1c} from baseline to planned EOT was analysed using an ANCOVA model, with treatment, region, treatment by subgroup interactions and, if applicable, additional relevant factors as fixed factors and the baseline response as a covariate. Missing data were imputed using multiple imputation. OD comparators: ONWARDS 1 and 4, glargine U100; ONWARDS 2 and 3, degludec; ONWARDS 5, degludec, glargine U100 or glargine U300. ANCOVA, analysis of covariance; CI, confidence interval; degludec, insulin degludec; EOT, end of treatment; ETD, estimated treatment difference; glargine U100, insulin glargine U100; glargine U300, insulin glargine U300; HbA_{1c}, glycated haemoglobin; icodec, insulin icodec; OD, once-daily; SGLT2i, sodium-glucose co-transporter-2 inhibitor.
1. Goldenberg R et al. EASD 60th Annual Meeting, September 9–13, 2024. Madrid, Spain and online.



Clinically significant or severe hypoglycaemia

Efficacy and hypoglycaemia outcomes in T2D according to baseline SGLT2i use: ONWARDS 1–5



- Overall rates of clinically significant or severe hypoglycaemia were low between treatment arms in ONWARDS 1, 2, 3 and 5, irrespective of SGLT2i use (<1 event per PYE)
- In ONWARDS 4, the rate of clinically significant or severe hypoglycaemia was comparable or numerically lower with icodec compared with the OD comparator across subgroups

Clinically significant hypoglycaemia (level 2): blood glucose level of <3.0 mmol/L, confirmed by blood glucose meter. Severe hypoglycaemia (level 3): hypoglycaemia associated with severe cognitive impairment requiring external assistance for recovery. OD comparators: ONWARDS 1 and 4, glargine U100; ONWARDS 2 and 3, degludec; ONWARDS 5, degludec, glargine U100 or glargine U300. Graph shows the hypoglycaemic episodes that occurred during the on-treatment period (onset date on or after the first dose of trial product and no later than the first date of the follow-up visit, the last date on-trial product +5 weeks for OD insulin and +6 weeks for OW insulin or the end date for the in-trial period). Degludec, insulin degludec; glargine U100, insulin glargine U100; glargine U300, insulin glargine U300; icodec, insulin icodec; OD, once-daily; OW, once-weekly; PYE, patient-year of exposure; SGLT2i, sodium-glucose co-transporter-2 inhibitor.

1. Goldenberg R et al. EASD 60th Annual Meeting, September 9–13, 2024. Madrid, Spain and online.



Summary

Efficacy and hypoglycaemia outcomes in T2D according to baseline SGLT2i use: ONWARDS 1–5

Overall, the efficacy and hypoglycaemia outcomes with OW icodec compared with OD comparators were generally consistent among individuals with T2D, regardless of SGLT2i treatment at baseline

Across the SGLT2i subgroups, there was no statistically significant treatment by SGLT2i subgroup interaction with respect to change in HbA_{1c} from baseline to EOT

Rates of clinically significant or severe hypoglycaemia were low across the treatment arms of ONWARDS 1, 2, 3 and 5, regardless of SGLT2i use at baseline; in ONWARDS 4, the rate was comparable or numerically lower with icodec compared with OD comparator across subgroups

There were no statistically significant treatment by SGLT2i subgroup interaction effects with respect to the achievement of HbA1c targets without clinically significant or severe hypoglycaemia (in all trials), and in the insulin dose and the change in body weight in ONWARDS 1–4

In ONWARDS 5, statistically significant treatment by SGLT2i subgroup interactions were observed for icodec compared with OD comparators in weekly basal insulin dose and change in body weight; specifically, the weight change was most pronounced with icodec compared with OD comparators in SGLT2i users

Clinically significant hypoglycaemia (level 2): blood glucose level of <3.0 mmol/L, confirmed by blood glucose meter. Severe hypoglycaemia (level 3): hypoglycaemia associated with severe cognitive impairment requiring external assistance for recovery. EOT, end of treatment; HbA_{1c}, glycated haemoglobin; insulin icodec; OD, once-daily; OW, once-weekly; SGLT2i, sodium-glucose co-transporter-2 inhibitor; T2D, type 2 diabetes.

1. Goldenberg R et al. EASD 60th Annual Meeting, September 9–13, 2024. Madrid, Spain and online.



ASSOCIAZIONI CON CKD

Efficacy and hypoglycaemia outcomes in individuals with T2D by kidney function: ONWARDS 1–5

Post-hoc analyses

Aim: This post-hoc analysis of ONWARDS 1–5 assessed the efficacy and hypoglycaemia outcomes with once-weekly icodec versus OD basal insulin comparators in insulin-naïve and insulin-experienced adults with T2D by kidney function subgroup



Methods

- ONWARDS 1–5 were multinational, multicenter trials that included insulin-naïve (ONWARDS 1, 3 and 5) and insulin-experienced (ONWARDS 2 and 4) adults (aged ≥ 18 years) with T2D
- Severe kidney function impairment (eGFR < 30 mL/min/1.73 m² at screening) was an exclusion criterion for ONWARDS 1–4; in ONWARDS 5, there were no exclusion criteria for eGFR
- In ONWARDS 5, icodec titration was guided by a dosing guide app; OD comparator doses were titrated at the investigator's discretion as per standard clinical practice

^aIn ONWARDS 4 (basal-bolus trial), participants also received 2–4 daily injections of insulin aspart.

eGFR, estimated glomerular filtration rate; glargine U100, insulin glargine U100; glargine U300, insulin glargine U300; icodec, insulin icodec; OD, once-daily; T2D, type 2 diabetes.

1. Rossing P et al. ADA 84th Scientific Sessions. June 21–24, 2024, Orlando Florida. 826-P.



Post-hoc analysis and trial participants

Efficacy and hypoglycaemia outcomes in individuals with T2D by kidney function: ONWARDS 1–5



ONWARDS 1–5 treatment outcomes were analysed by trial according to kidney function subgroup to assess:

- Change in HbA_{1c}^a
- Observed rates of combined clinically significant or severe hypoglycaemia^b
- Proportion of participants achieving an HbA_{1c} <7% without clinically significant or severe hypoglycaemia^c
- Mean weekly total insulin dose^d



Of the 3765 participants in ONWARDS 1–5, 3763 had eGFR measurements at screening and were included in this analysis:

Normal kidney function

eGFR ≥90
n=1875 (49.8%)

Mild kidney function impairment

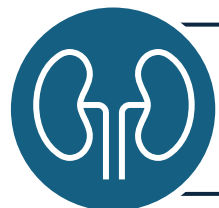
eGFR 60–<90
n=1450 (38.5%)

Moderate kidney function impairment

eGFR 30–<60
n=430 (11.4%)

Severe kidney function impairment

eGFR <30
n=8 (0.2%)

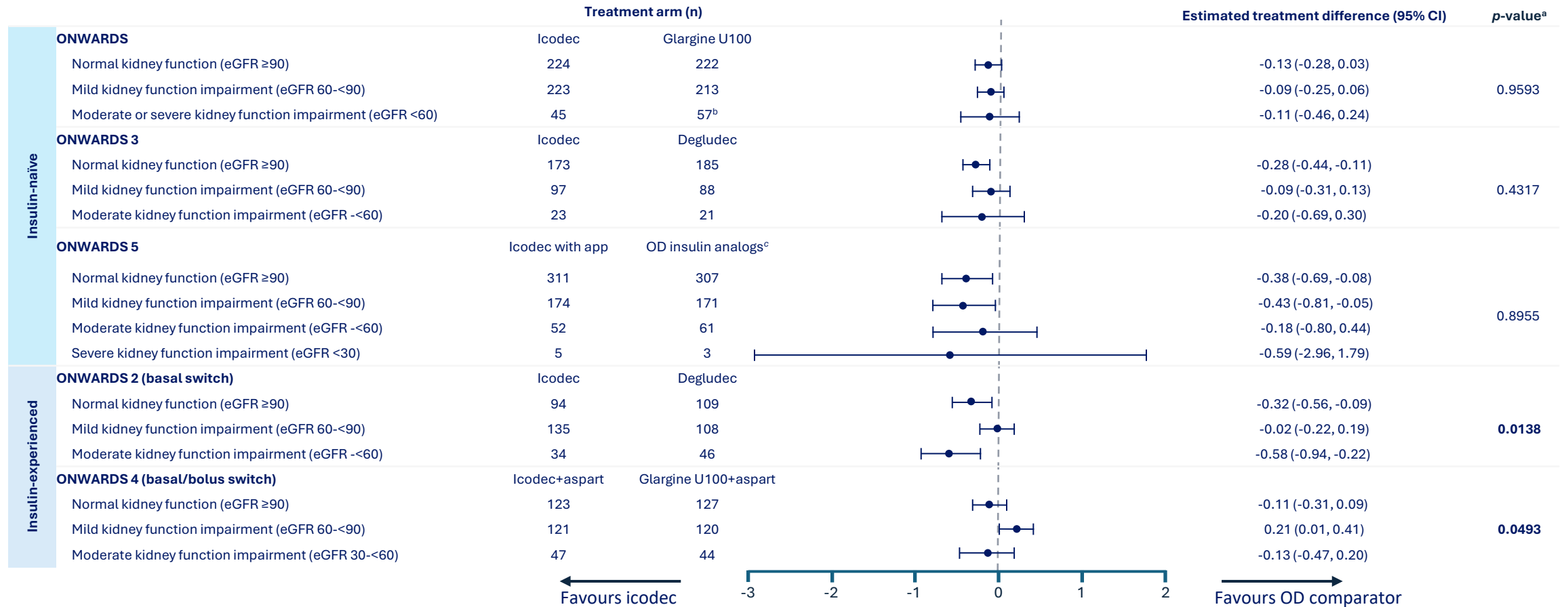


Kidney function subgroups were based on eGFR at screening



Change in HbA_{1c} from baseline to planned EOT

Efficacy and hypoglycaemia outcomes in individuals with T2D by kidney function: ONWARDS 1–5



For two individuals, eGFR was not measured at screening; all eGFR values are presented in mL/min/1.73m². Change in HbA_{1c} from baseline to planned EOT was analysed using an ANCOVA, with treatment, region, treatment by subgroup interactions and, if applicable, additional relevant factors as fixed factors, and the baseline response as a covariate. Bold values denote statistical significance at the p<0.05 level.

^aTwo-sided p value for the test of no treatment by kidney function subgroup interactions.

^bIncludes moderate kidney impairment (n=56) and severe kidney impairment (n=1). In ONWARDS 1, one participant with severe kidney impairment was erroneously randomised to receive treatment.

^cIn ONWARDS 5, participants in the comparator arm received once-daily degludec, glargine U100, or glargine U300 at the investigators' discretion.

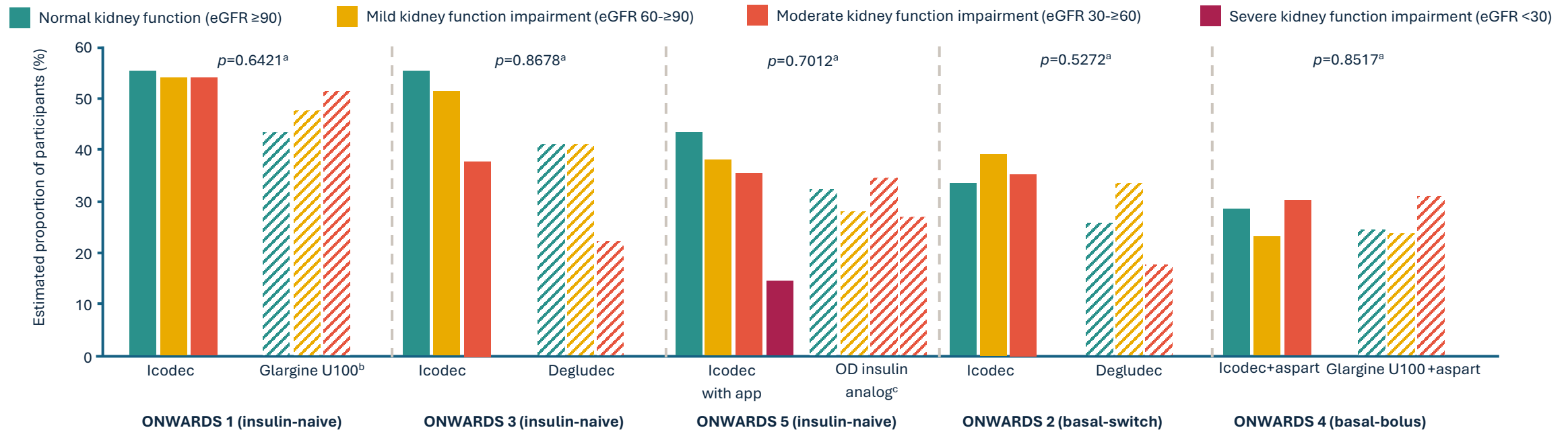
ANCOVA, analysis of covariance; aspart, insulin aspart; degludec, insulin degludec; eGFR, estimated glomerular filtration rate; EOT, end of treatment; glargine U100, insulin glargine U100; glargine U300, insulin glargine U300; icodec, insulin icodec; OD, once-daily.

1. Rossing P et al. ADA 84th Scientific Sessions. June 21–24, 2024, Orlando Florida. 826-P.



Proportion of participants who achieved HbA_{1c} <7% without clinically significant or severe hypoglycaemia

Efficacy and hypoglycaemia outcomes in individuals with T2D by kidney function: ONWARDS 1–5



Across trials, there were no statistically significant treatment interactions by kidney function subgroup for the composite endpoint (all $p > 0.05$)

For two individuals, eGFR was not measured at screening; all eGFR values are presented in mL/min/1.73m². In the severe kidney function impairment subgroup of ONWARDS 5, one of five participants receiving icodec with app and one of three participants receiving an OD comparator achieved HbA_{1c} <7% at EOT without clinically significant or severe hypoglycaemia. Clinically significant hypoglycaemia: blood glucose level of <54 mg/dL, confirmed by blood glucose meter. Severe hypoglycaemia: hypoglycaemia associated with severe cognitive impairment requiring external assistance for recovery. The composite endpoint was analysed using a logistic regression model with log-link function. Treatment, region, and, if applicable, additional relevant factors were used as fixed factors, and the baseline HbA_{1c} value as covariate. Missing HbA_{1c} values were imputed using multiple imputation.

^ap value for treatment by subgroup interaction.

^bIn ONWARDS 1, one participant with severe kidney impairment was erroneously randomised to receive treatment and included in the moderate kidney function impairment subgroup for the purpose of this analysis.

^cIn ONWARDS 5, participants in the comparator arm received once-daily degludec, glargine U100, or glargine U300 at the investigators' discretion.

Aspart, insulin aspart; degludec, insulin degludec; eGFR, estimated glomerular filtration rate; glargine U100, insulin glargine U100; HbA_{1c}, glycated haemoglobin; icodec, insulin icodec; OD, once-daily.

1. Rossing P et al. ADA 84th Scientific Sessions. June 21–24, 2024, Orlando Florida. 826-P.



Summary

Efficacy and hypoglycaemia outcomes in individuals with T2D by kidney function: ONWARDS 1–5

The efficacy and hypoglycaemia outcomes with once-weekly icodec versus OD comparators were generally consistent among insulin-naïve and insulin-experienced adults with T2D, regardless of kidney function

Irrespective of kidney function, overall rates of combined clinically significant or severe hypoglycaemia were comparable between subgroups

Achievement of HbA_{1c} <7% at EOT without clinically significant or severe hypoglycaemia with icodec was similar to or higher than with OD comparators in participants with normal kidney function, or with mild or moderate kidney function impairment (although, across trials, no statistically significant treatment interactions by kidney function subgroup were observed), and consistent with the overall results of the ONWARDS program



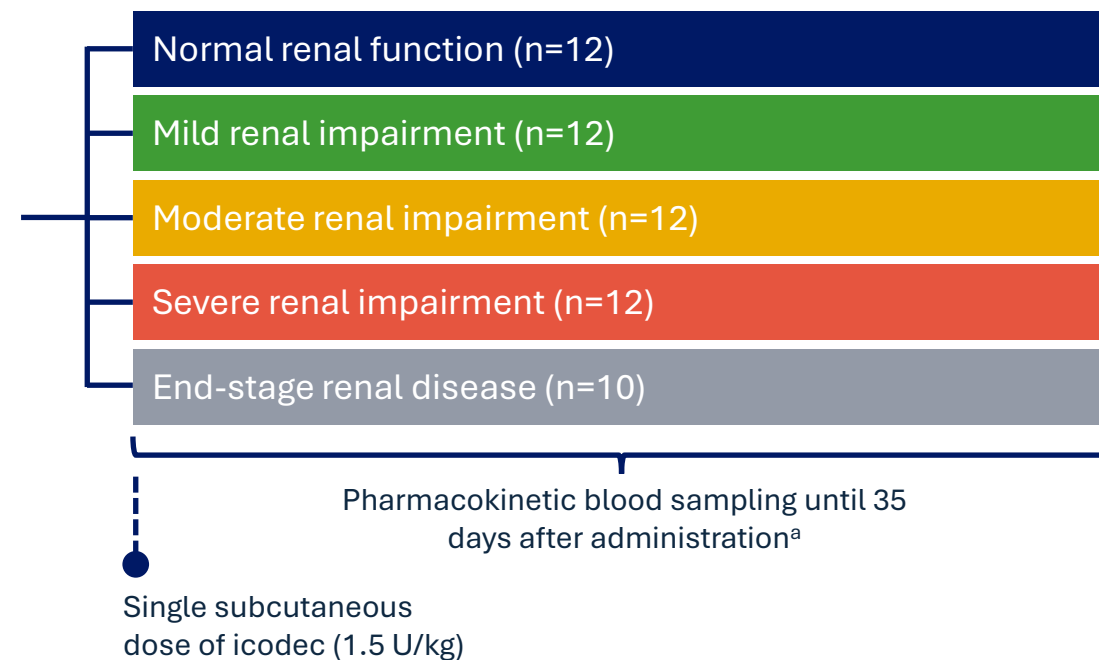
The effect of various degrees of renal impairment on the pharmacokinetic characteristics of once-weekly insulin icodec

Participants

- 58 individuals allocated to five groups based on renal function
- Individuals with renal impairment:
 - Diagnosis of chronic kidney disease
 - mGFR of 60 to <90 mL/min (mild renal impairment), 30 to <60 mL/min (moderate) or <30 mL/min not requiring dialysis (severe), or end-stage renal disease requiring hemodialysis
- Individuals with normal renal function:
 - Generally healthy
 - mGFR ≥ 90 mL/min

Objective:

- To investigate if the pharmacokinetic characteristics of insulin icodec are affected by renal impairment



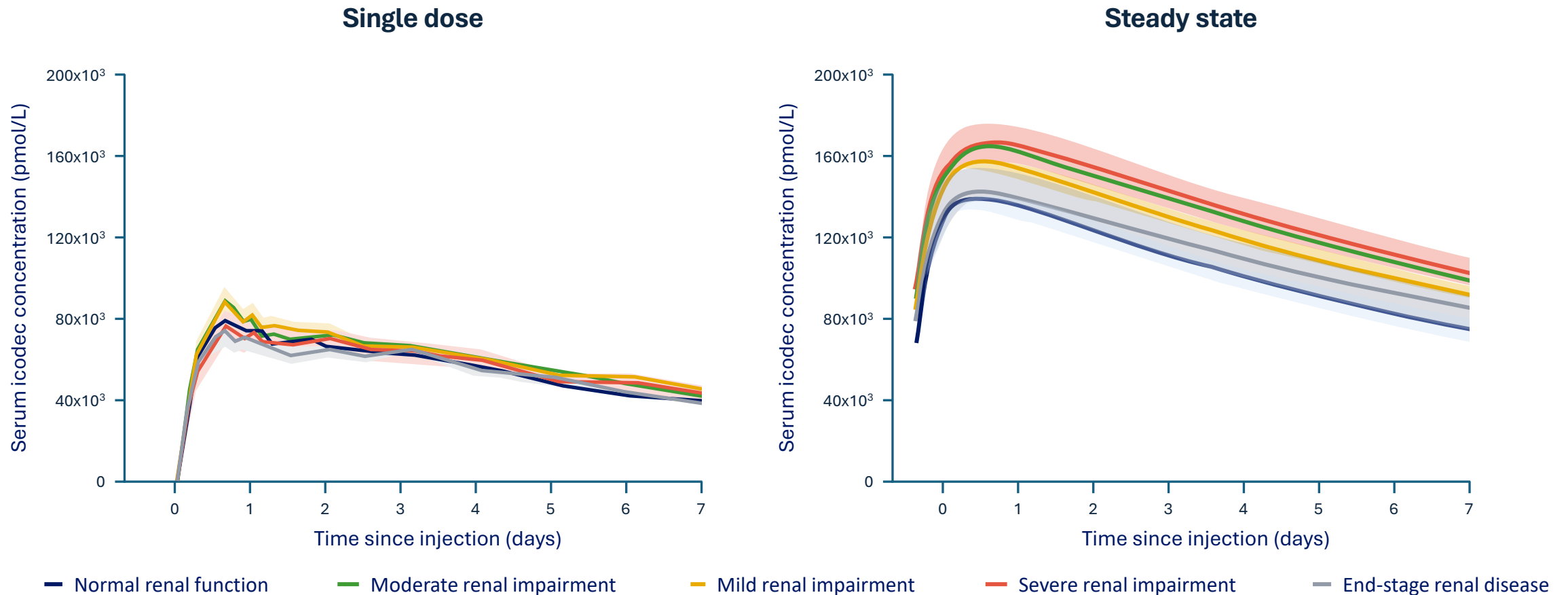
^a In participants with end-stage renal disease, blood for pharmacokinetic analysis was also sampled during a hemodialysis session starting 138-164 hours after administration. Furthermore, in participants without end-stage renal disease, urine was collected before icodec administration and in the first 48 hours after dosing (i.e. around the expected maximum concentration) for analysis of any intact icodec excretion.

mGFR, measured glomerular filtration rate (using iohexol as an external marker).

1. Haahr H. et al, Clin Pharmacokinet 2024, DOI:10.1007/s40262-024-01375-2.



Mean serum insulin icodec concentration during a dosing interval of one week



Insulin icodec dose: 1.5 U/kg. Simulation at steady state: Based on the observed serum icodec concentrations after a single dose, a one-compartment pharmacokinetic model was developed, consisting of parameters to describe absorption, distribution and clearance. Renal function group was included as a covariate on the clearance parameter. The estimated model parameters for each individual were used to simulate the steady-state serum icodec profiles.

1. Haahr H. et al, Clin Pharmacokinet 2024, DOI:10.1007/s40262-024-01375-2.



ASSOCIAZIONI CON EPATOPATIA

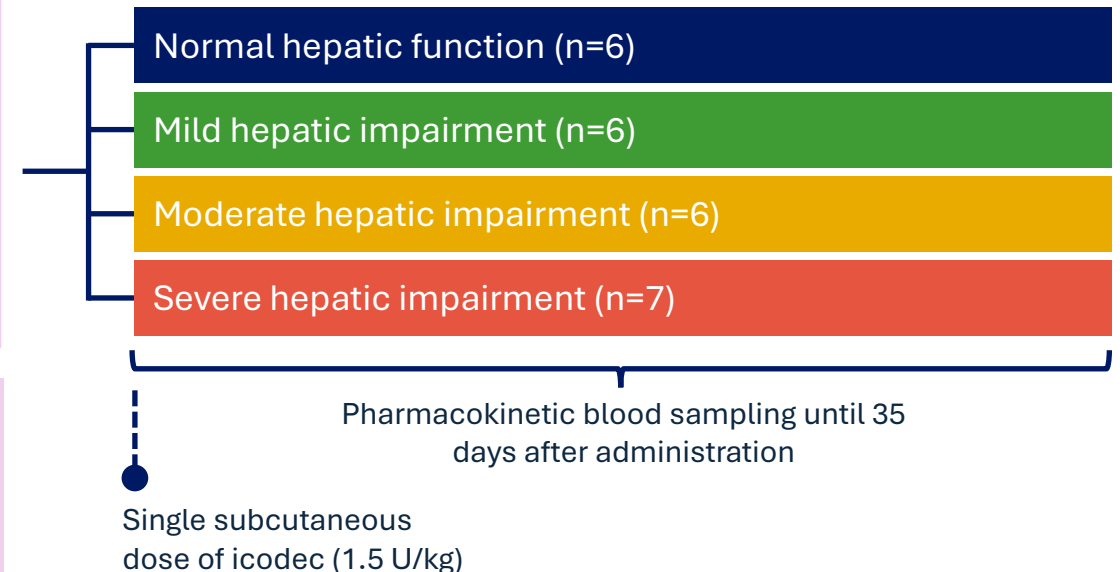
The effect of various degrees of hepatic impairment on the pharmacokinetic characteristics of once-weekly insulin icodec

Participants

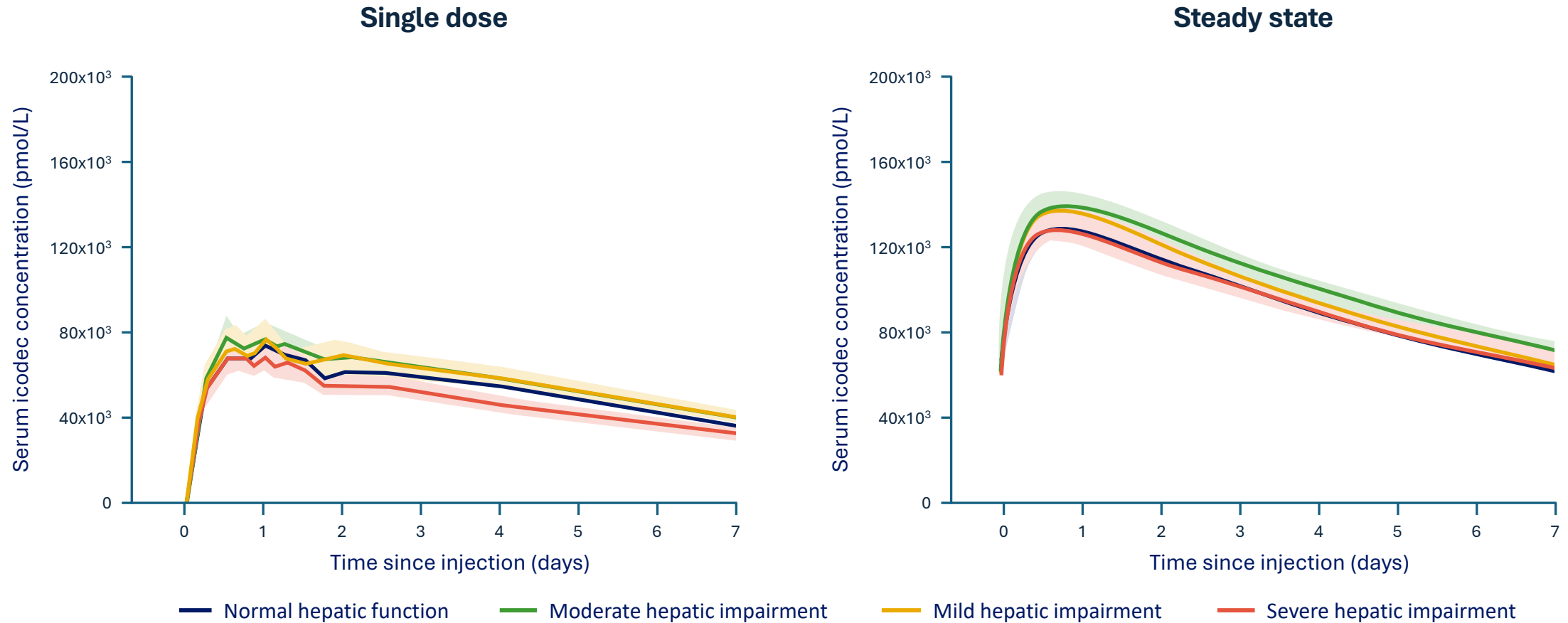
- 25 individuals allocated to four groups based on hepatic function
- Individuals with hepatic impairment:
 - Child–Pugh Classification¹ used to allocate into mild (class A; 5–6 points), moderate (class B; 7–9 points) or severe (class C; 10–15 points)
- Individuals with normal hepatic function:
 - Age- and body weight-matched to the groups of hepatic impairment

Objective:

- To investigate if the pharmacokinetic characteristics of insulin icodec are affected by hepatic impairment



Mean serum insulin icodec concentration during a dosing interval of one week



Insulin icodec dose: 1.5 U/kg.

Simulation at steady state: Based on the observed serum icodec concentrations after a single dose, a one-compartment pharmacokinetic model was developed, consisting of parameters to describe absorption, distribution and clearance. Hepatic function group was included as a covariate on the clearance parameter. The estimated model parameters for each individual were used to simulate the steady-state serum icodec profiles.

1. Haahr H. et al, Clin Pharmacokinet 2024, DOI:10.1007/s40262-024-01375-2.



ATTIVITA' FISICA

*Icodec and **physical activity-related hypoglycaemia**: insights from the ONWARDS 1–5 trials*

Post-hoc analyses

Aim: To assess the proportion and incidence of physical activity-related hypoglycaemic episodes, based on self-reported data, in adults with T2D in ONWARDS 1–5



Methods: ONWARDS 1–5 participants who reported hypoglycaemic episodes were asked whether each episode occurred in relation to physical activity

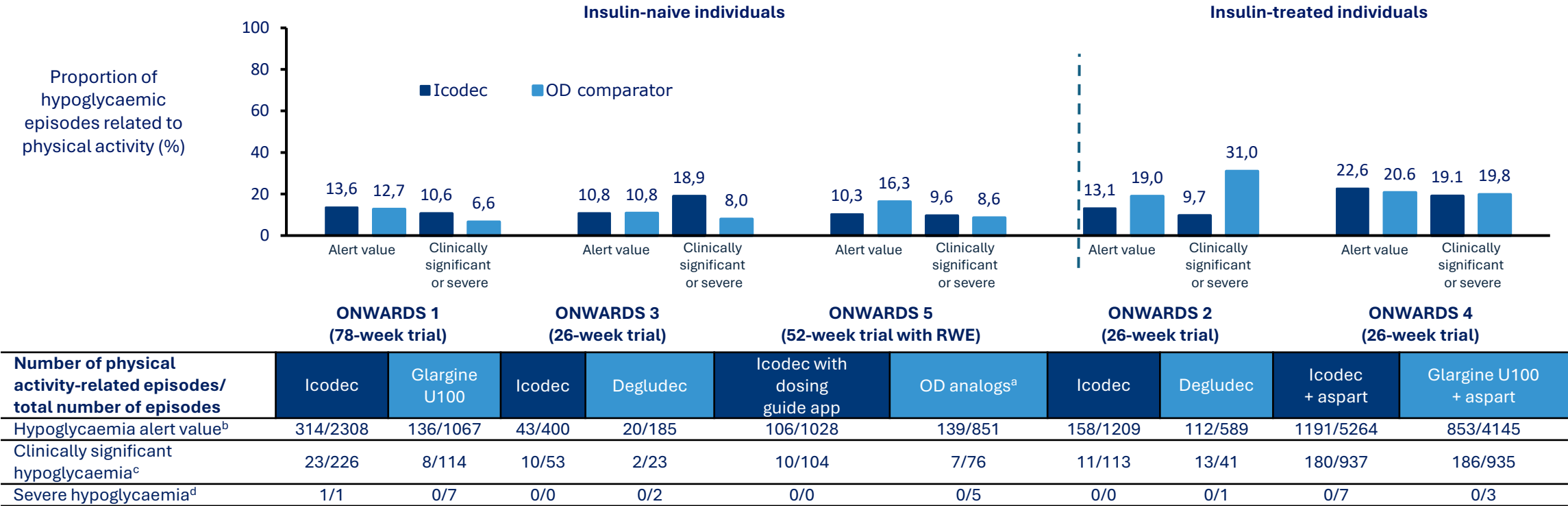
In this post-hoc analysis the following were evaluated the:

- Proportion of hypoglycaemic episodes that were related to physical activity
- Incidence of physical activity-related clinically significant or severe hypoglycaemia
- Proportion of clinically significant or severe hypoglycaemic episodes that were related to physical activity with at least one clinically significant or severe hypoglycaemic episode in the following 24 hours



Proportion of hypoglycaemic episodes related to physical activity during the on-treatment period

Icodec and physical activity-related hypoglycaemia: insights from ONWARDS 1–5

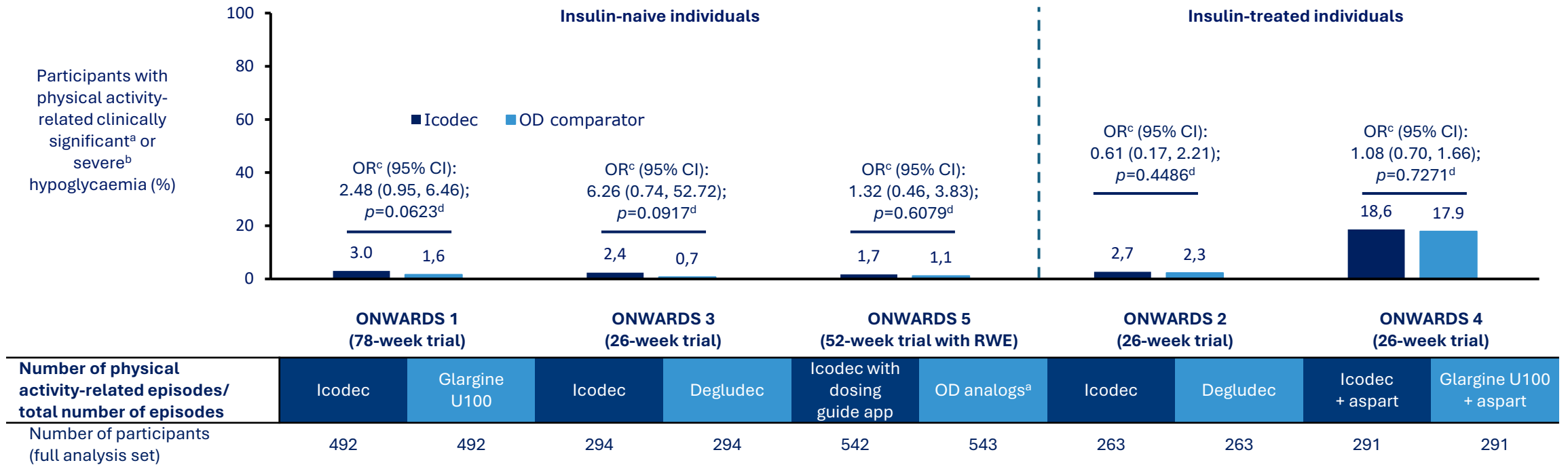


There were no consistent differences in the proportions of physical activity-related hypoglycaemic episodes compared with the total number of hypoglycaemic episodes with icodec versus OD comparators

On-treatment period: onset date on or after the first dose of trial product and no later than the first date of the follow-up visit, the last date on-trial product +5 weeks for OD insulin and +6 weeks for once-weekly insulin or the end date for the in-trial period.
^aThe choice of the OD analog (degludec, glargine U100 or glargine U300) was made at the investigators' discretion. ^bHypoglycaemia alert value: blood glucose value <70 mg/dL (<3.9 mmol/L) but ≥54mg/dL (≥3.0 mmol/L), confirmed by blood glucose meter. ^cClinically significant hypoglycaemia: blood glucose value <54 mg/dL (<3.0 mmol/L), confirmed by blood glucose meter. ^dSevere hypoglycaemia: hypoglycaemia with severe cognitive impairment requiring external assistance for recovery.
OD, once-daily; RWE, real-world elements.
1. Riddell MC et al. ADA 84th Scientific Sessions. June 21–24, 2024, Orlando Florida. 830-P.

Observed incidence of clinically significant or severe hypoglycaemia related to physical activity during the on-treatment period

Icodec and physical activity-related hypoglycaemia: insights from ONWARDS 1–5



There were no statistically significant differences in the odds of experiencing a physical activity-related clinically significant or severe hypoglycaemic episode with icodec versus OD comparators

The incidence of hypoglycaemia was analysed using a binary logistic regression model (logit link) with treatment, region, sulfonylurea/glinides use (ONWARDS 3) and personal continuous glucose monitoring device use (ONWARDS 2 and 4) as fixed factors. Missing data were imputed using multiple imputations. On-treatment period: onset date on or after the first dose of trial product and no later than the first date of the follow-up visit, the last date on-trial product +5 weeks for OD insulin and +6 weeks for once-weekly insulin or the end date for the in-trial period.

^aClinically significant hypoglycaemia: blood glucose value <54 mg/dL (<3.0 mmol/L), confirmed by blood glucose meter. ^bSevere hypoglycaemia: hypoglycaemia with severe cognitive impairment requiring external assistance for recovery. ^cIcodec/OD comparator. ^dTwo-sided p value for the test of no treatment difference (no correction for multiplicity). ^eThe choice of the OD analog (degludec, glargine U100 or glargine U300) was made at the investigators' discretion.

CI, confidence interval; OD, once-daily; OR, odds ratio; RWE, real world evidence.

1. Riddell MC et al. ADA 84th Scientific Sessions. June 21–24, 2024, Orlando Florida. 830-P.

Proportion of clinically significant or severe hypoglycaemic episodes related to physical activity with at least one additional clinically significant or severe hypoglycaemic episode in the following 24 hours

Icodec and physical activity-related hypoglycaemia: insights from ONWARDS 1–5

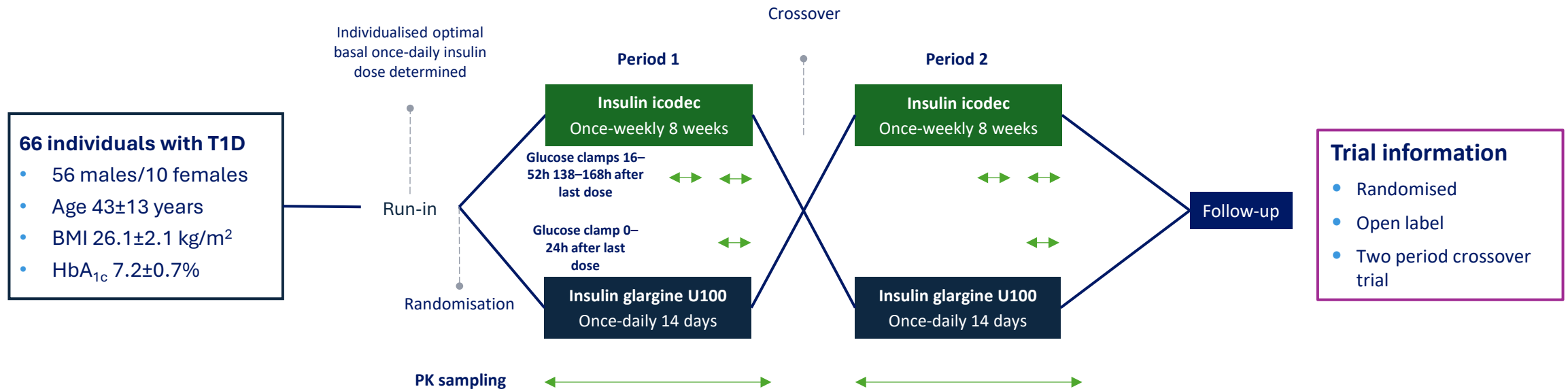
Clinically significant ^a or severe ^b hypoglycaemic episodes related to physical activity (%)	Icodec		OD comparator	
	Clinically significant hypoglycaemia	Severe hypoglycaemia	Clinically significant hypoglycaemia	Severe hypoglycaemia
ONWARDS 1 (basal initiation; 78-week trial)	0	0	0	0
ONWARDS 3 (basal initiation; 26-week trial)	0	0	0	0
ONWARDS 5 (basal initiation; 52-week trial with real-world elements)	0	0	0	0
ONWARDS 2 (basal switch; 26-week trial)	27.3	0	0	0
ONWARDS 4 (basal-bolus; 26-week trial)	15.0	0	8.6	0

The frequency of recurrent clinically significant or severe hypoglycaemic episodes 24 hours after a physical activity-related clinically significant or severe hypoglycaemic episode was low, with no additional severe episodes reported in any participants across the trials

^aClinically significant hypoglycaemia: blood glucose value <54 mg/dL (<3.0 mmol/L), confirmed by blood glucose meter.
^bSevere hypoglycaemia: hypoglycaemia with severe cognitive impairment requiring external assistance for recovery.
OD, once-daily.
1. Riddell MC et al. ADA 84th Scientific Sessions. June 21–24, 2024, Orlando Florida. 830-P.

DMT1

Once-weekly insulin icodec: pharmacokinetic and pharmacodynamic properties in T1D



Trial objectives

- To investigate the pharmacokinetic and pharmacodynamic properties of icodec at steady state in individuals with T1D

Methodology

- Run-in up to 10 weeks: Once-daily glargine U100, fasting SMPG target 4.4–7.2 mmol/L
- Individualised fixed doses of icodec and glargine U100 at equimolar total weekly doses (mean $\pm$ SD 1.91 $\pm$ 0.44 U/kg; range 1.1–3.3 U/kg)
- Insulin aspart as bolus insulin
- Automated glucose clamps after the last insulin dose (ClampArt; target blood glucose 6.7 mmol/L)
- PK-PD modelling to assess the glucose-lowering effect of icodec during a full one-week dosing interval



Hypoglycaemia and other safety information

	Icodec	Glargine U100
Rate of overall clinically significant hypoglycaemic (episodes per PYE)	32.8	23.9
Rate of nocturnal clinically significant hypoglycaemic (episodes per PYE)	5.4	4.4
Duration of clinically significant hypoglycaemic episodes ^a (minutes)	33±25	30±18

Icodec and glargine U100 were both **well tolerated** in this trial

^aData are mean±SD
One level 3 hypoglycaemic episode was reported during icodec treatment. The event occurred 4 days after the 4th weekly icodec dose. The participant remained conscious and showed no signs of disorientation. A relative supplied apple juice (which was the reason for the classification of the event as severe). The participant self-injected glucagon intramuscularly after SMPG values were still below 3.3 mmol/L (60 mg/dL) despite intake of carbohydrates, whereafter the hypoglycaemic episode was resolved after 51 min.
PYE, participant-years of exposure; SMPG, self-measured plasma glucose.
1. Hövelmann U et al. *Diabetes Obes Metab*. 2024. DOI: 10.1111/dom.15510.



NEWS



AME News Farmaci



nr. 49 - mese 2025

Capo-Redattore: Chiara Sabbadin

Redattori: Silvia Briganti, Simona Censi, Carmela Coccaro, Sara De Vincentis, Rita Indirli, Pina Lardo, Alessandro Mondin, Lara Naletto, Valerio Renzelli

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NUOVA FORMULAZIONE PER L'INSULINA ICODEC

Coordinatori

Renato Cozzi & Patrizia Del Monte

Editor

Vincenzo Di Donna & Cecilia Motta

La determina AIFA 1310/2025 autorizza la prossima commercializzazione di una nuova formulazione di insulina Icodec (Awiqli®).

Accanto alla formulazione da 3 mL (700 U/mL in penna pre-riempita da 3 mL), per rispondere all'esigenza dei pazienti che devono somministrare meno di 175 U/settimana, **arriva la formulazione da 1.5 mL** (contiene 1050 U di insulina Icodec in luogo delle 2100 delle formulazioni da 3 mL).

Questa nuova formulazione consentirà di evitare eventuali sprechi di insulina nei soggetti che somministrano un quantitativo ridotto settimanale di unità di insulina. Infatti, dopo la prima apertura, **il medicinale può essere conservato al massimo per 12 settimane alla temperatura di 2-8°C.**

CONCLUSIONI

- Meno iniezioni, meno aghi
- Minor rischio lipodistrofie
- Maggiore accettabilità da parte del paziente
- Maggior compliance con i care giver
- Maggiore aderenza alla terapia
- Possibilità di titolare con un minor consumo di strisce
- Meno ipoglicemie

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