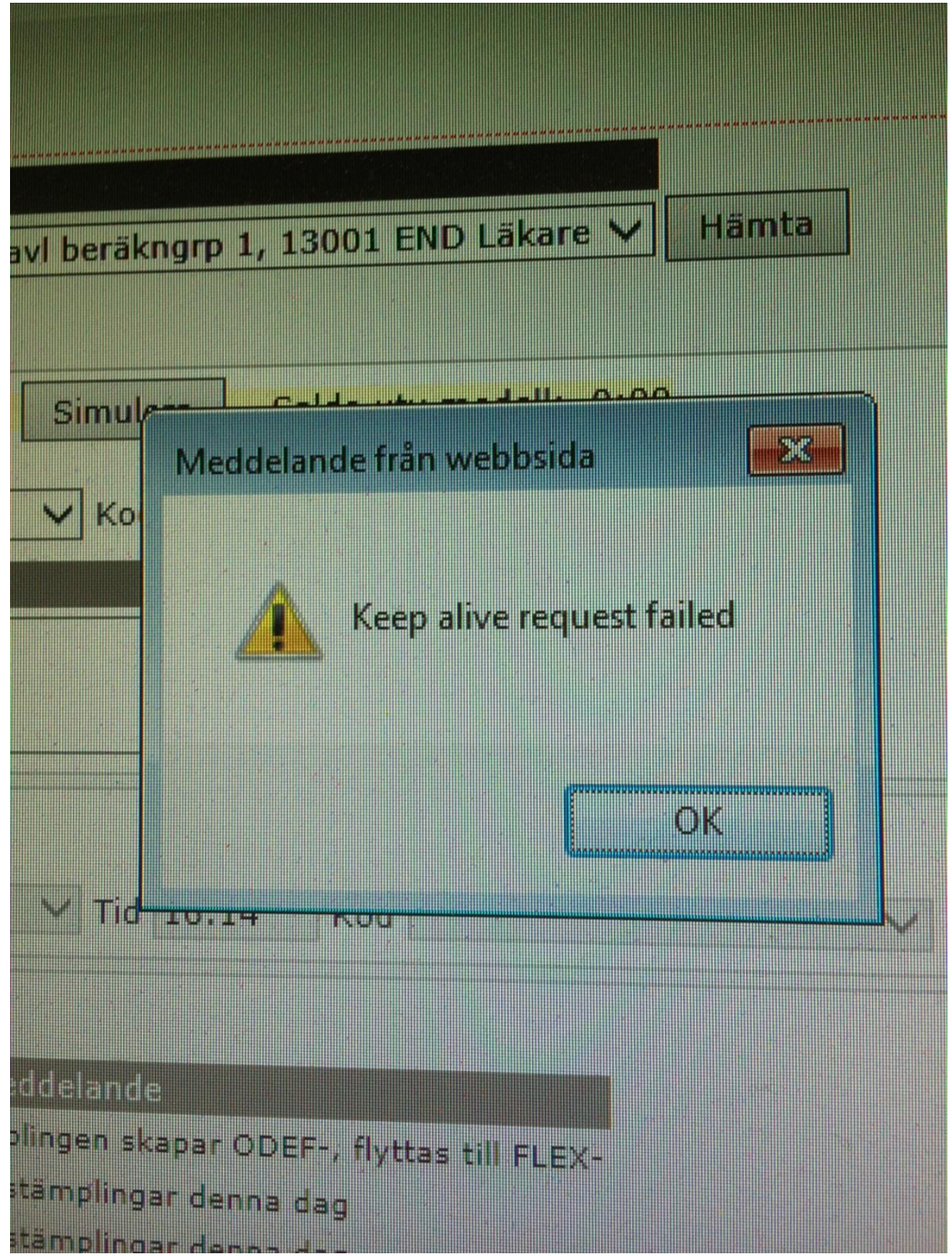
Långverkande insuliner

Anders Frid, Västerås 19 april 2024


avl beräkngrp 1, 13001 END Läkare
Hämta
Meddelande från webbsida
Keep alive request failed
OK
Tid
ddelande
lingen skapar ODEF-, flyttas till FLEX-
tämplingar denna dag

Nobelpriset 1923

Frederick G. Banting

Nobelpriset 1923

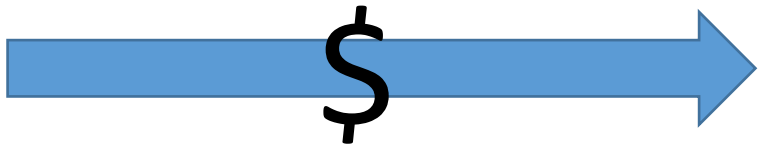
Frederick G. Banting

John MacLeod

Nobelpriset 1923

Frederick G. Banting

John MacLeod

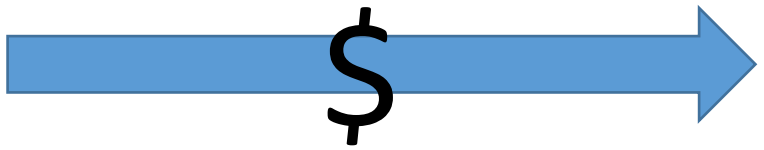


Charles Best

Nobelpriset 1923

Frederick G. Banting

John MacLeod



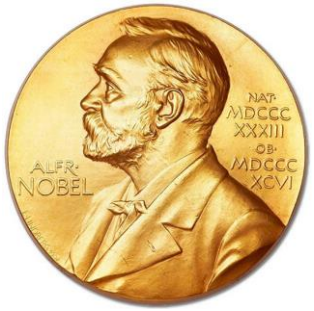
Charles Best

James Collip

Vad tycker jag?

Vad tycker jag?

Frederick G. Banting

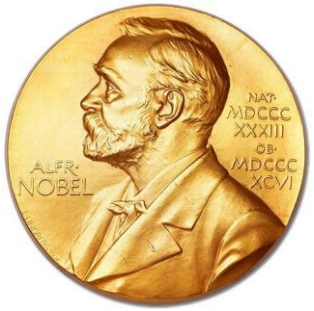


Charles Best

John MacLeod

Vad tycker jag?

Frederick G. Banting

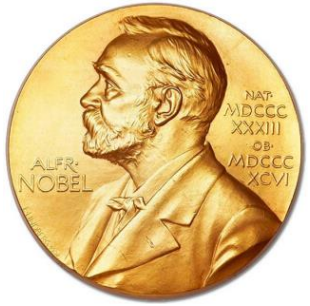


Charles Best

John MacLeod

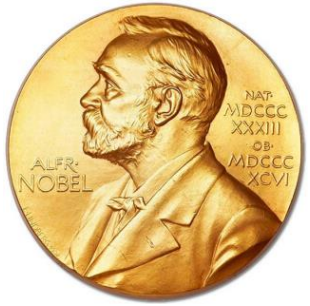
Priset i medicin eller fysiologi

Vad tycker jag?



James Collip

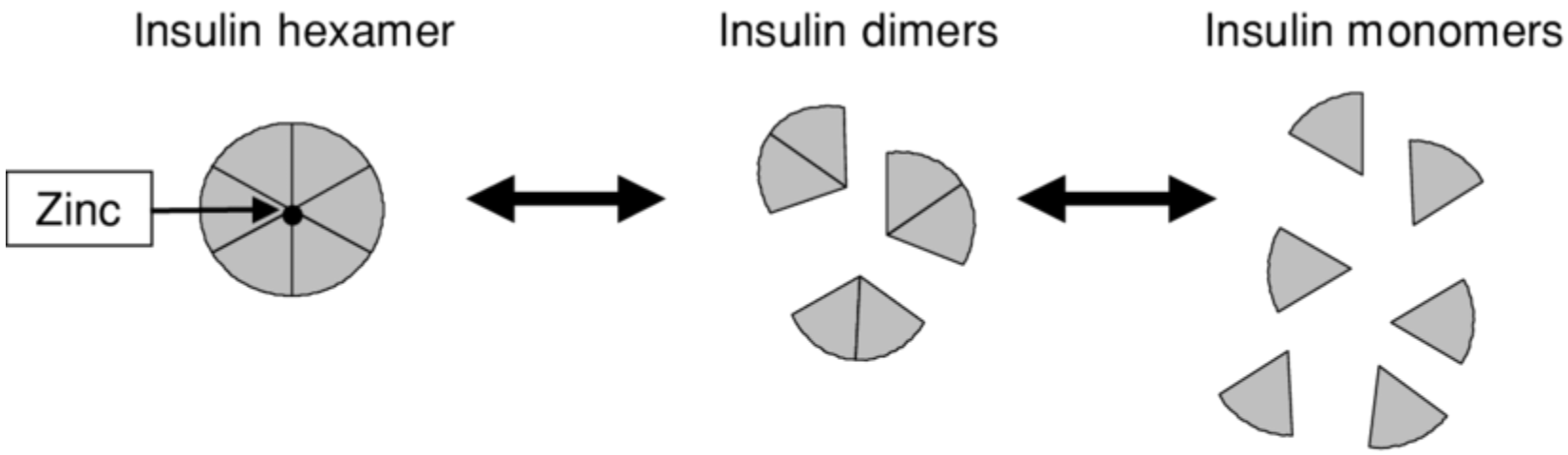
Vad tycker jag?



Priset i kemi

James Collip

Mrs GP *'At 16 years of age, in 1934, I was diagnosed with diabetes by none other than Dr Robin Lawrence of King's College Hospital in London. I was taught how to inject insulin at first into an orange, and then into myself. I used 40-strength soluble insulin twice daily, and I was stabilised at home, returning to hospital each week.'*



Absorberas inte

Absorberas

Hans Christian Hagedorn 1888 - 1971

Hans Christian Hagedorn 1888 - 1971

Sök på Youtube ”kaptajn for livet” Novo Nordisk Foundation 2021

Utveckling av långverkande insuliner

- I Hagedorns lab på Nordisk Insulinlaboratorium upptäcks att protamin från laxmjölke förlänger effekten av insulin
- Upptäckten licensieras till University of Toronto och Eli Lilly (men inte till Novo) som gör ett zink-protamin-insulin (PZI) 1937
- Ett neutralt (isophane) insulin utan zink och protamin i överskott lanseras 1950 under namnet Insulin NPH = Neutral Protamin Hagedorn.

Utveckling av långverkande insuliner

- Novo förlänger absorptionen genom att tillsätta zink i överskott, insulinet Lente lanseras 1952, kompletteras med SemiLente och UltraLente

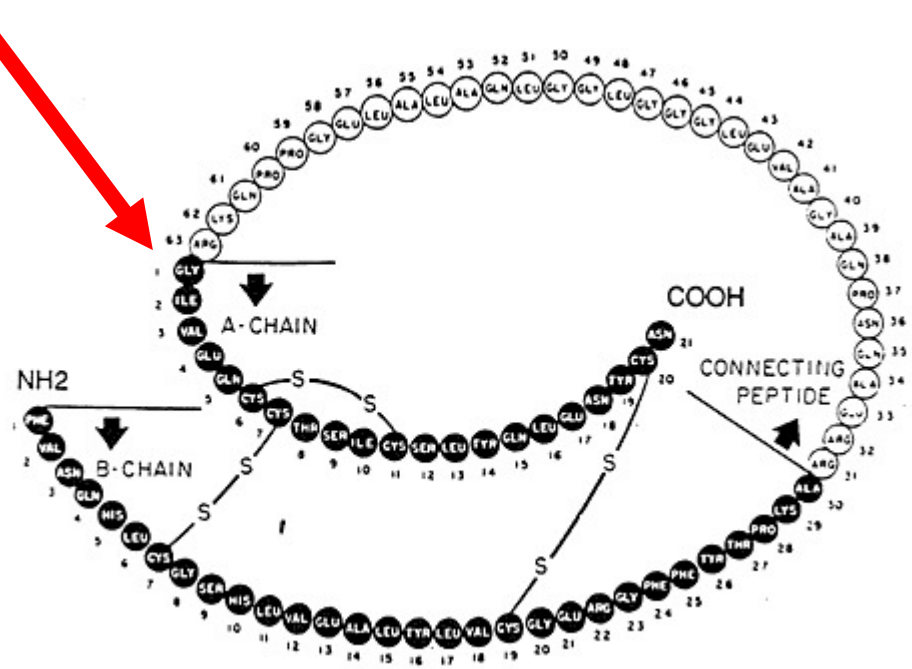
Från humaninsuliner till insulinanaloger

Från humaninsulin till insulinanaloger

- Största behovet: direktverkande insulin
- Nästa behov: långverkande insulin med stabil effekt i ett dygn eller mer.

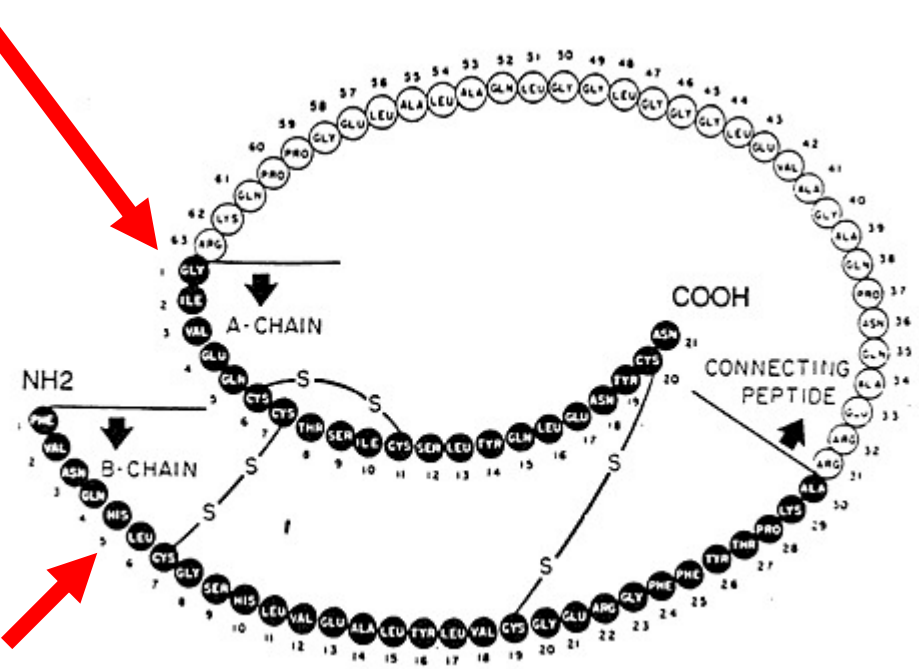
Insulinmolekyl

A-kedja, 21 aminosyror



Insulinmolekyl

A-kedja, 21 aminosyror

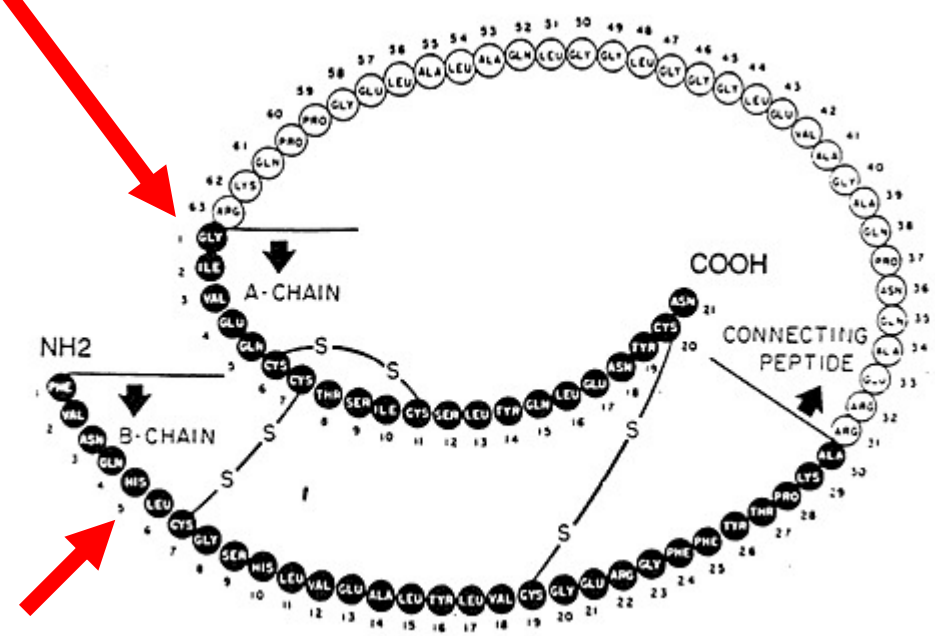


B-kedja, 30 aminosyror

Insulinmolekyl

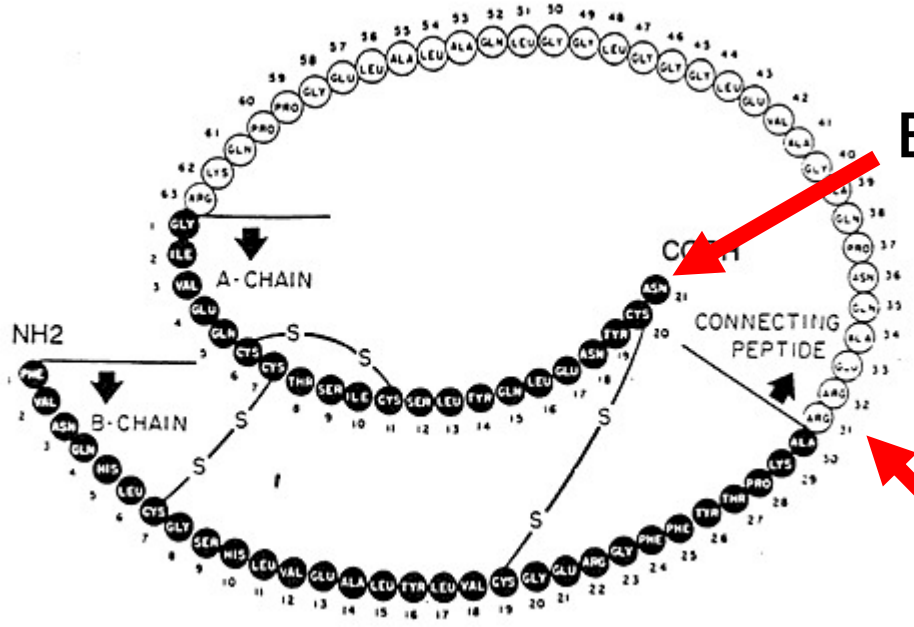
C-peptid, 33 aminosyror

A-kedja, 21 aminosyror



B-kedja, 30 aminosyror

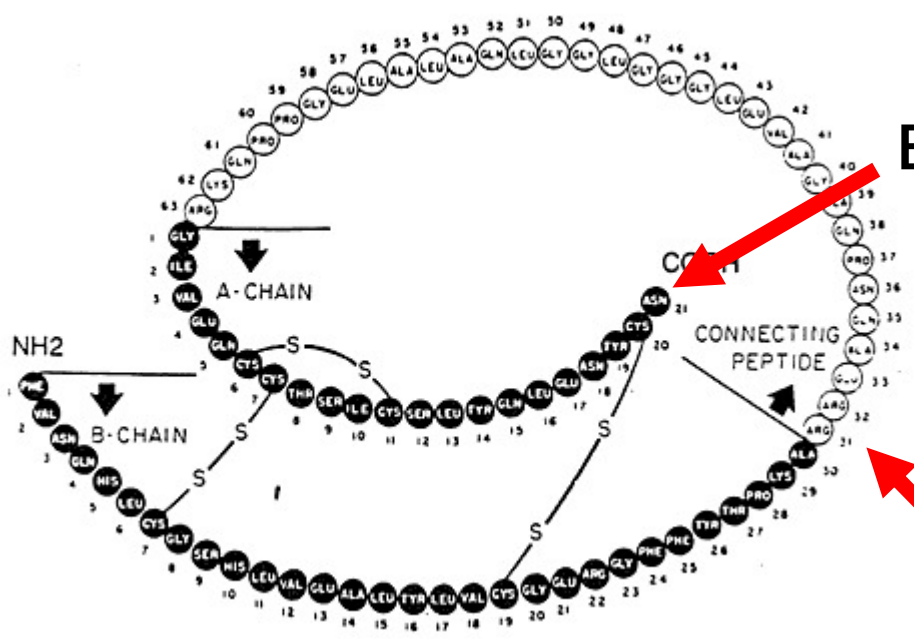
Insulinmolekyl



Byt asparagin mot glysin

Lägg till två arginin

Insulinmolekyl

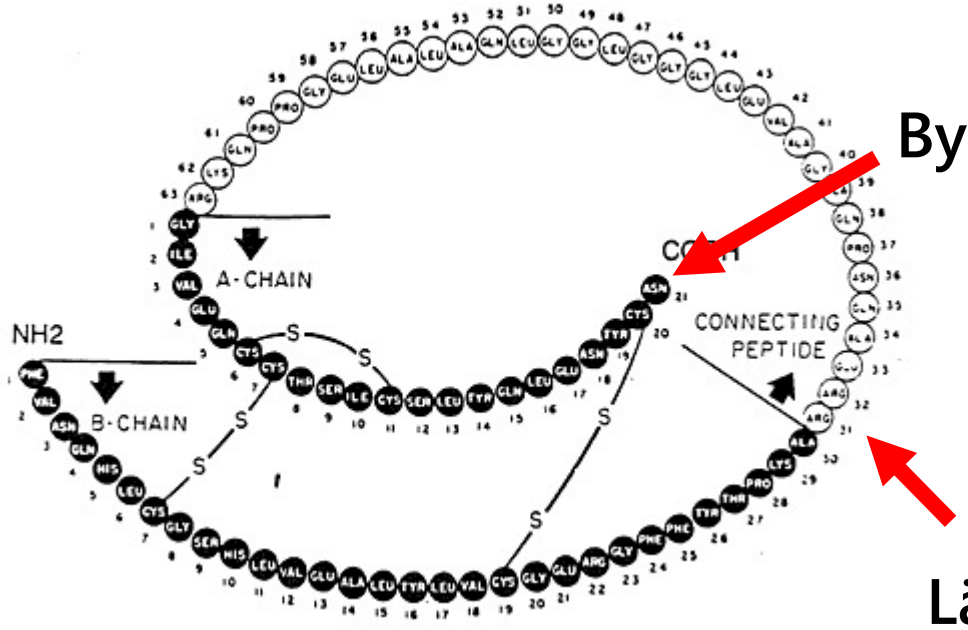


Byt asparagin mot glysin

Lägg till två arginin

= insulin glargin

Insulinmolekyl



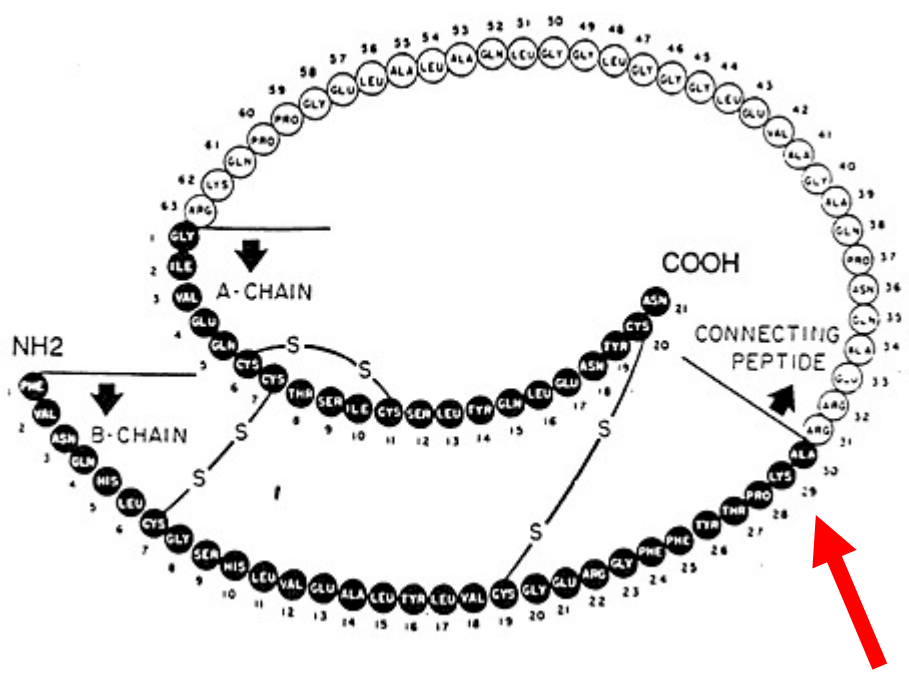
Byt asparagin mot glysin

Lägg till två arginin

= insulin glargin

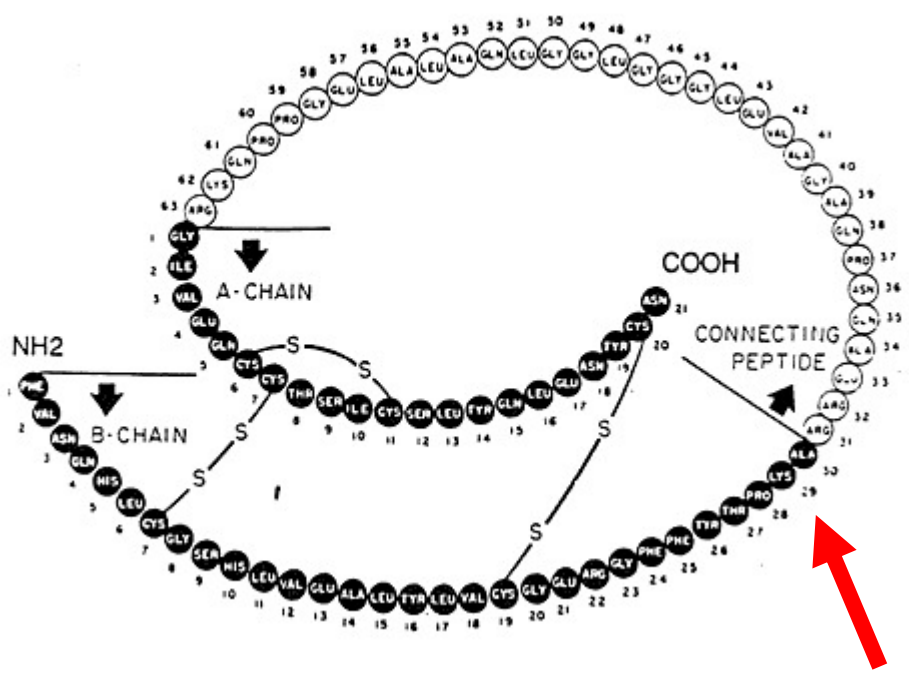
Lantus, godkänt i Europa 2000

Insulinmolekyl



Lägg till en fettsyra, myristinsyra i position B29

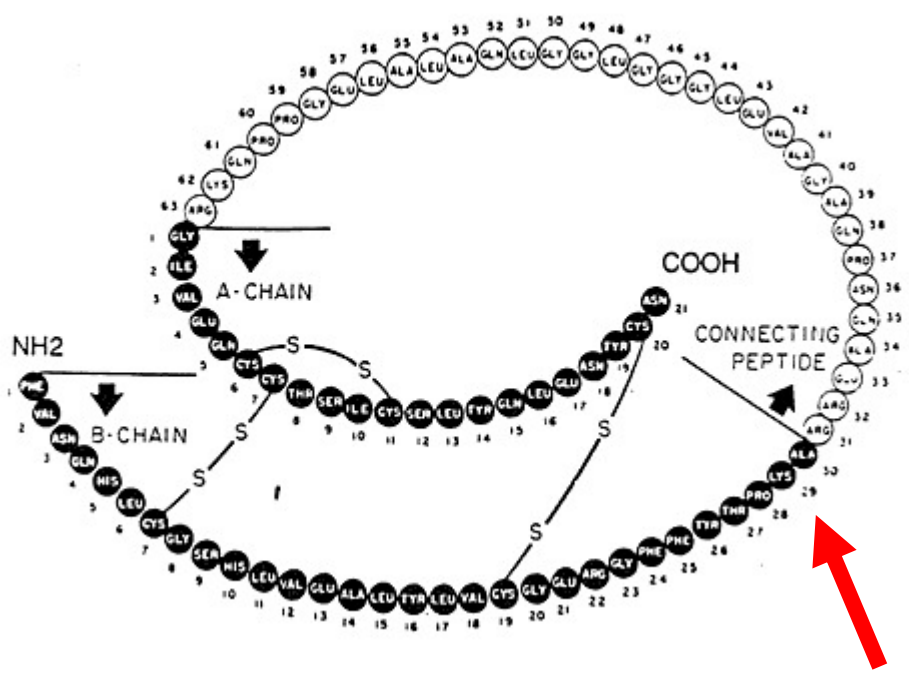
Insulinmolekyl



= insulin detemir

Lägg till en fettsyra, myristinsyra i position B29

Insulinmolekyl

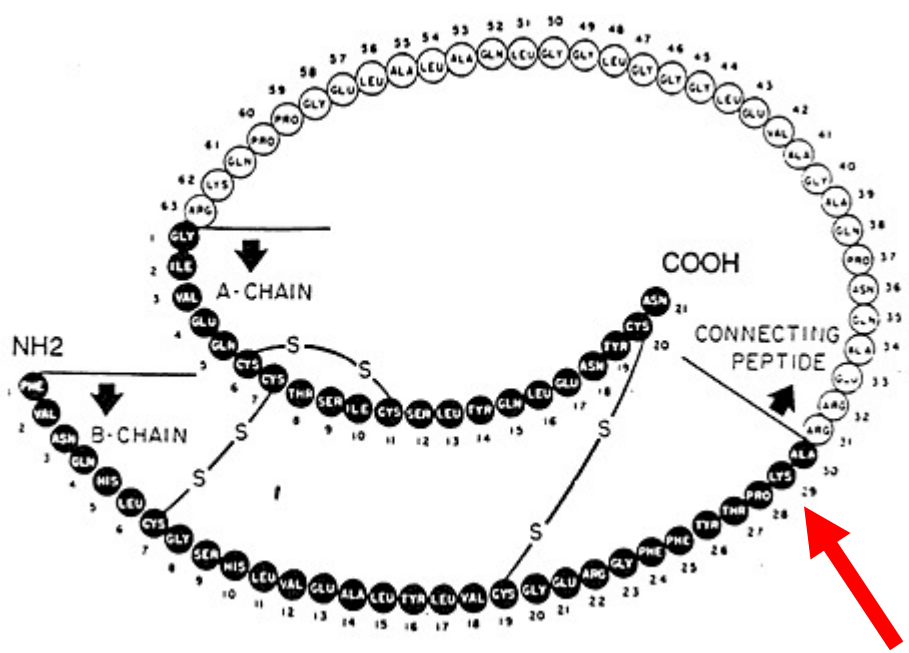


Lägg till en fettsyra, myristinsyra i position B29

= insulin detemir

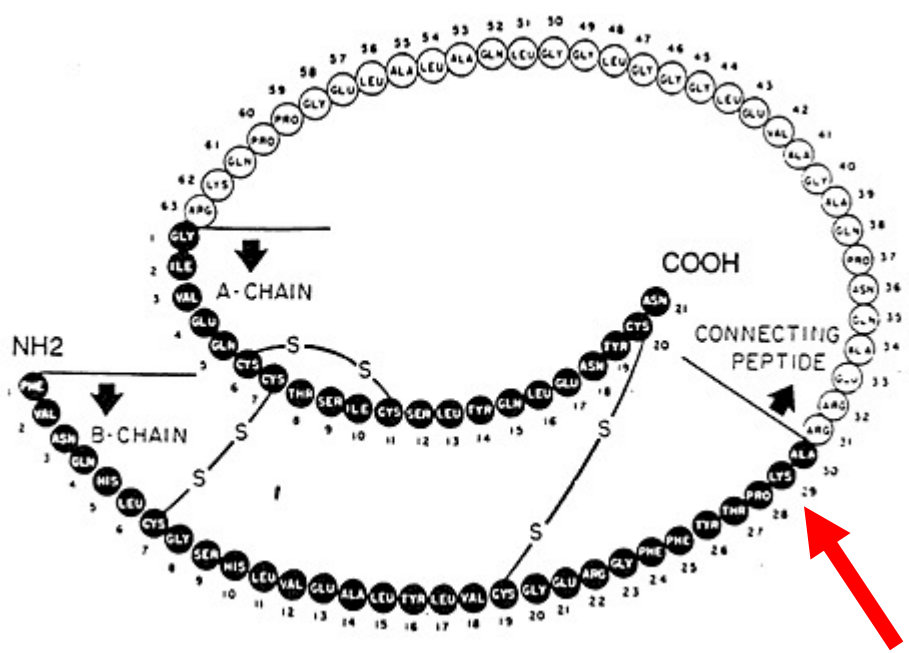
Levemir, godkänt Europa 2004

Insulinmolekyl



Lägg till en annan fettsyra i position B29, ta bort B30

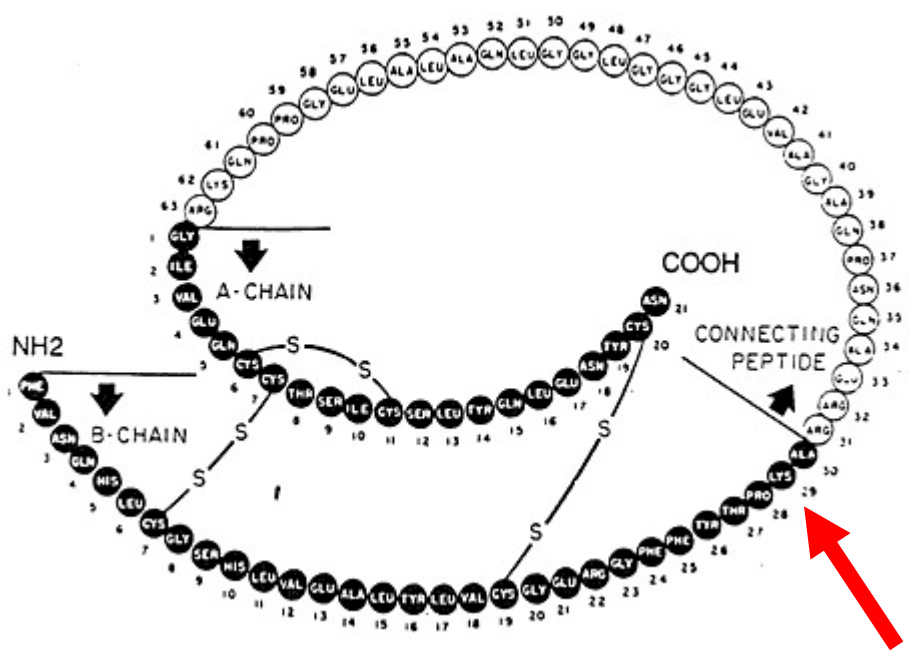
Insulinmolekyl



= insulin degludec, t50 25h

Lägg till en annan fettsyra i position B29, ta bort B30

Insulinmolekyl

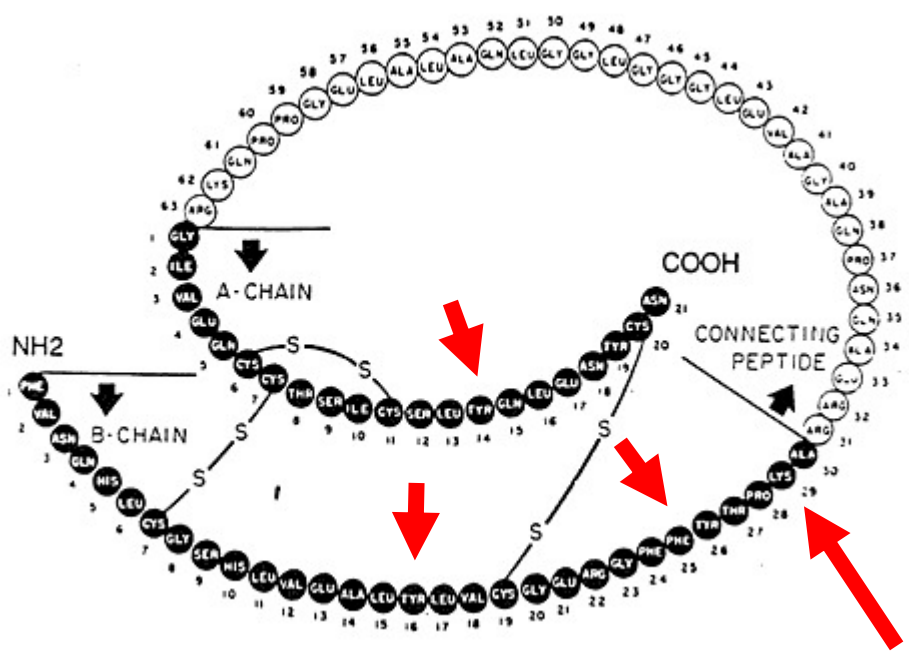


Lägg till en annan fettsyra i position B29, ta bort B30

= insulin degludec, t50 25h

Tresiba, godkänt Europa 2013

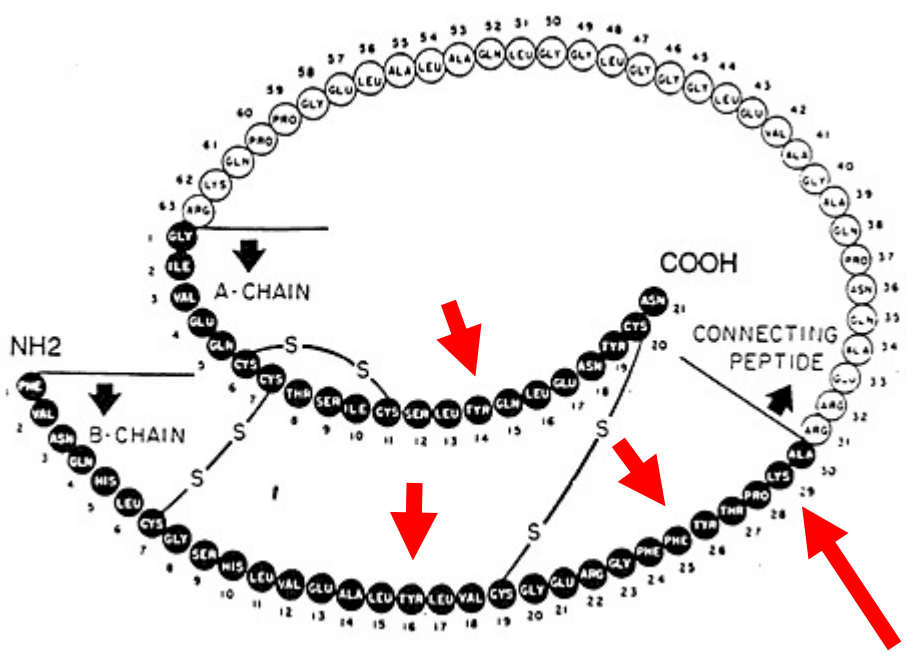
Insulinmolekyl



Lägg till ännu en annan fettsyra i position B29, ta bort B30, byt aminosyror i position A14, B16 och B25

Insulinmolekyl

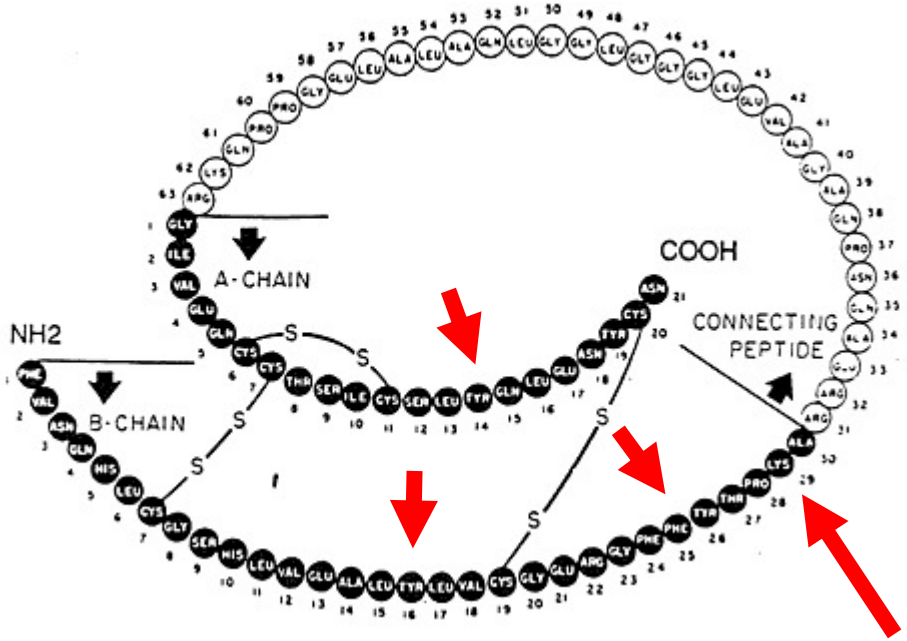
= insulin icodec



Lägg till ännu en annan fettsyra i position B29, ta bort B30, byt aminosyror i position A14, B16 och B25

Insulinmolekyl

= insulin icodec,
t50 7 dygn



Awiqli U700, ”positive opinion” från EMA 21 mars 2024

Lägg till ännu en annan fettsyra i position B29, ta bort B30, byt aminosyror i position A14, B16 och B25

Varför fettsyra?

- För att skapa en reversibel bindning till albumin, både på injektionsstället och i blodet, för icodec är syftet att det mesta av albuminbindningen sker i blodet

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 27, 2023 VOL. 389 NO. 4

Weekly Icodec versus Daily Glargine U100 in Type 2 Diabetes without Previous Insulin

Julio Rosenstock, M.D., Stephen C. Bain, F.R.C.P., Amoolya Gowda, M.D., Esteban Jódar, M.D., Ph.D., Bo Liang, M.D., Ph.D., Ildiko Lingvay, M.D., M.P.H., M.S.C.S., Tomoyuki Nishida, M.Sc, Roberto Trevisan, M.D., Ph.D., and Ofri Mosenzon, M.D., for the ONWARDS 1 Trial Investigators*

JAMA | Original Investigation

Once-Weekly Insulin Icodec vs Once-Daily Insulin Degludec in Adults With Insulin-Naive Type 2 Diabetes
The ONWARDS 3 Randomized Clinical Trial

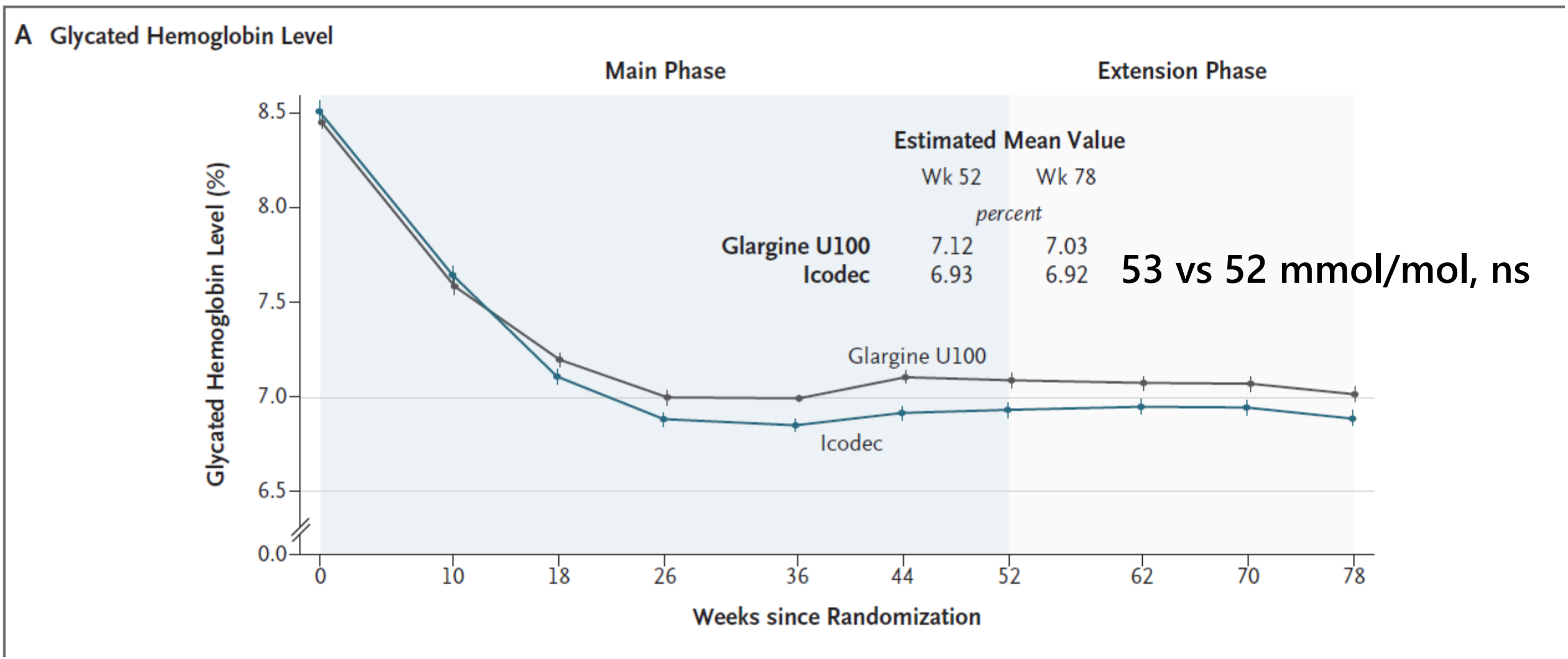
Ildiko Lingvay, MD, MPH, MSCS; Marisse Asong, MD, MSc; Cyrus Desouza, MBBS; Pierre Gourdy, MD, PhD; Soumitra Kar, MSc; André Vianna, MD, PhD; Tina Vilsbøll, MD, DMsc; Siri Vinther, MD, PhD; Yiming Mu, MD

JAMA. 2023;330(3):228-237. doi:10.1001/jama.2023.11313
Published online June 24, 2023. Corrected on October 13, 2023.

Onwards 1

- 492 patienter med DM2, 43% kvinnor, medel 60 år, från Kroatien, Indien, Israel, Italien, Japan, Mexico, Polen, Ryssland, Slovakien, Spanien, UK och USA
- Duration 11,5 år, BMI 30.0 kg/m^2, HbA1c 69 mmol/mol
- Randomisering till insulin icodec 1 gång/v eller glargin 1 gång/dag
- Startdos 70 E icodec/v, 10 E glargin/dag, dosjustering var eller varannan vecka baserat på fasteglukos, SMBG 3 ggr dagl, CGM blindat och utvärderat efter studien
- SU och glinider sätts ut, alla annan behandling behålls
- Observationstid 52 v huvudstudie, 26 v förlängning
- Primärt utfall förändring av HbA1c, ett antal sekundära utfall

ONWARDS 1, HbA1c

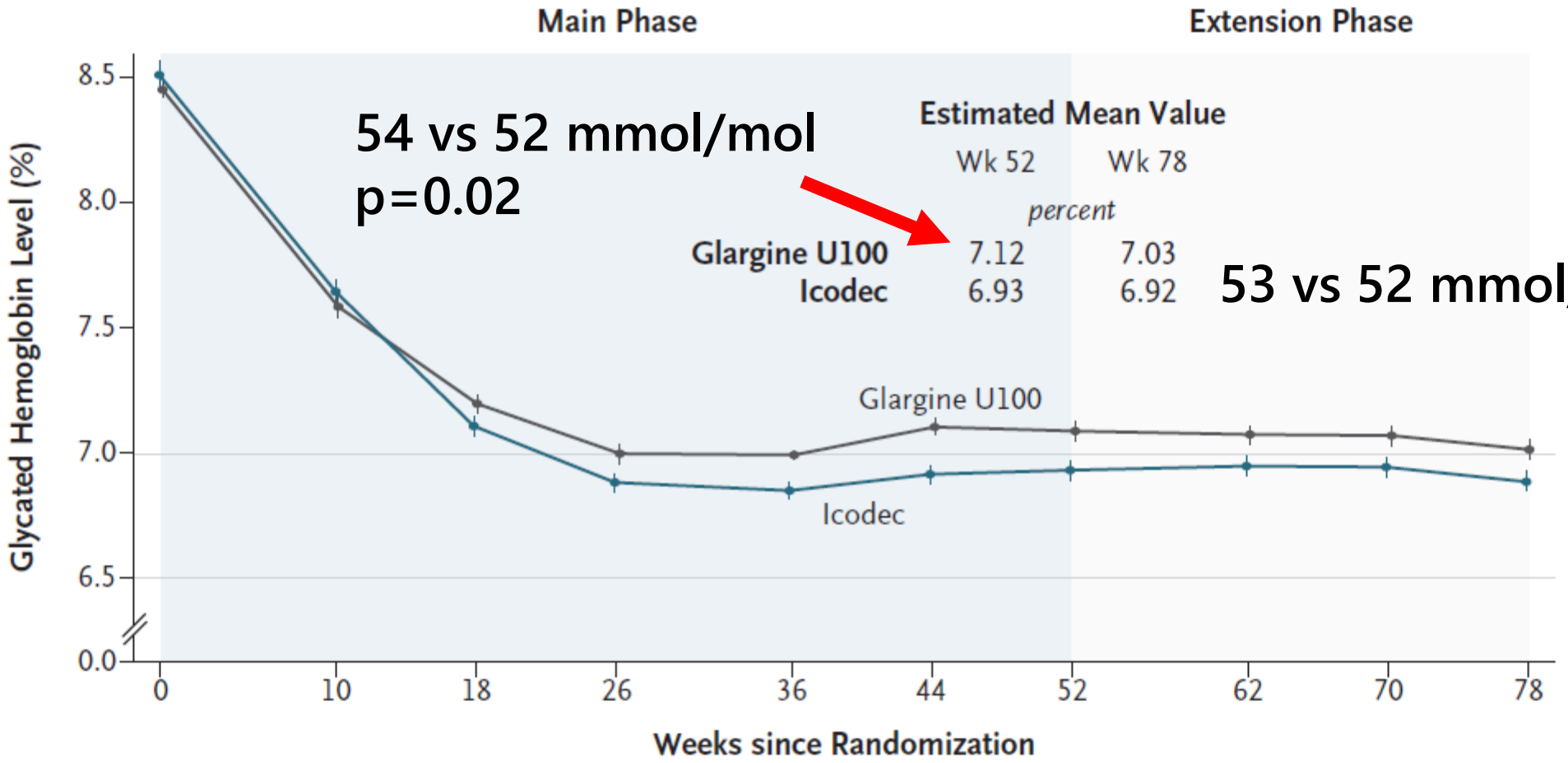


53 vs 52 mmol/mol, ns

This article was published on June 24, 2023, at NEJM.org.

ONWARDS 1, HbA1c

A Glycated Hemoglobin Level



54 vs 52 mmol/mol
p=0.02

53 vs 52 mmol/mol, ns

This article was published on June 24, 2023, at NEJM.org.

ONWARDS 1, insulindoser

	icodec	glargin
Estimated mean weekly insulin dose — U/wk (~U/day)		
Wk 50–52	214 (~31)	222 (~32)
Wk 76–78	224 (~32)	234 (~33)
Post hoc analysis of estimated mean weekly insulin dose — U/kg		
Wk 50–52	2.5	2.6
Wk 76–78	2.6	2.8

This article was published on June 24, 2023,
at NEJM.org.

James Collip 1892 - 1965

ONWARDS 1, hypoglykemier

Overall hypoglycemic episodes, safety analysis, baseline to wk 52 — no. of participants (%) [events data]	icodec	glargin
Hypoglycemia alert value**	232 (47.2) [1447 events; 2.98/PYE]	191 (38.8) [632 events; 1.30/PYE]
Clinically significant hypoglycemia††	48 (9.8) [143 events; 0.29/PYE]	49 (10.0) [75 events; 0.15/PYE]
Severe hypoglycemia‡‡	1 (0.2) [1 event; <0.01/PYE]	3 (0.6) [3 events; 0.01/PYE]
Combined clinically significant or severe hypoglycemia	48 (9.8) [144 events; 0.30/PYE]	52 (10.6) [78 events; 0.16/PYE]
Overall hypoglycemic episodes, safety analysis, baseline to wk 83 — no. of participants (%) [events data]		
Hypoglycemia alert**	278 (56.5) [2308 events; 3.02/PYE]	239 (48.6) [1067 events; 1.39/PYE]
Clinically significant hypoglycemia††	61 (12.4) [226 events; 0.30/PYE]	66 (13.4) [114 events; 0.15/PYE]

This article was published on June 24, 2023,
at NEJM.org.

Onwards 3

- 588 patienter med DM2, 37% kvinnor, medel 58 år från Argentina, Österrike, Brasilien, Kanada, Kina, Tjeckien, Danmark, Frankrike, Mexiko, Taiwan, USA
- Duration 10.6 år, BMI 29.5 kg/m^2, HbA1c 69 mmol/mol
- Randomisering till icodec 1 gång/v + placebo 1 gång/dag eller placebo 1 gång/v + degludec 1 gång/dag
- Startdos 70 E icodec/v, 10 E degludec/dag, dosjustering varje vecka baserat på fasteglukos, SMBG 3 ggr dagl

Onwards 3

- Dos SU och glinider halverades, alla annan behandling behölls oförändrad
- Observationstid 26 veckor
- Primärt utfall förändring av HbA1c, sekundära utfall: insulindos, fasteglukos, viktförändring, hypoglykemier och några till

ONWARDS 3, HbA1c

Table 2. Summary of Key Efficacy and Safety End Points

Outcome	Once-weekly icodec (n = 294)			Once-daily degludec (n = 294)			Estimated treatment difference in icodec vs degludec (95% CI)	*P* value[a]
	Baseline	Week 26	Change from baseline to week 26	Baseline	Week 26	Change from baseline to week 26		
Primary end point								
HbA_{1c}, %	8.6	7.0	−1.6 percentage points	8.5	7.2	−1.4 percentage points	−0.2 (−0.3 to −0.1) percentage points	<.001[b]; .002[c]
mmol/mol	70	53		69	55			
Key secondary end points								
Fasting plasma glucose, mg/dL	187	127	−54	176	127	−54	0 (−6 to 5)	.90
Mean insulin dose from week 24 to 26, U/week	69	204		70	187		Estimated treatment ratio, 1.10 (0.98 to 1.22)	.09
Mean body weight, kg	85.8	87.3	2.8	83.2	86.8	2.3	0.46 (−0.19 to 1.10)	.17

ONWARDS 3, hypoglykemier

	icodec			degludec				
Level 2 or level 3 hypoglycemic episodes								
Baseline to week 31[b]	26 (8.9)	53	0.31	18 (6.1)	25	0.15	1.82 (0.87-3.80)	.11
Baseline to week 26[c]	24 (8.2)	50	0.35	13 (4.4)	17	0.12	3.12 (1.30-7.51)	.01

antal episoder

Once-weekly insulin icodec versus once-daily insulin degludec as part of a basal-bolus regimen in individuals with type 1 diabetes (ONWARDS 6): a phase 3a, randomised, open-label, treat-to-target trial

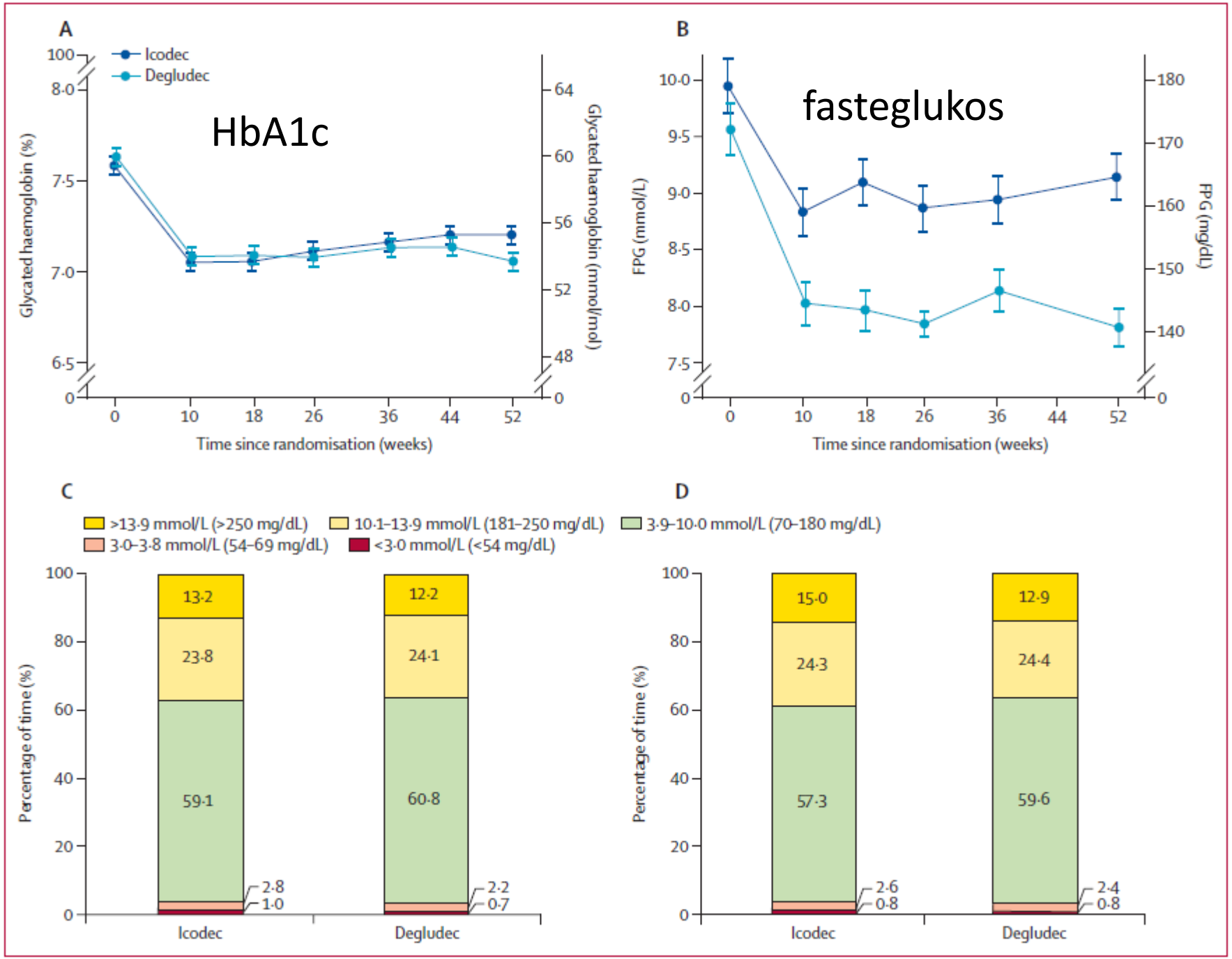
David Russell-Jones, Tetsuya Babazono, Roman Cailleteau, Susanne Engberg, Concetta Irace, Maiken Ina Siegismund Kjaersgaard, Chantal Mathieu, Julio Rosenstock, Vincent Woo, David C Klonoff

Lancet 2023; 402: 1636–47

Published **Online**
October 17, 2023

Onwards 6

- 582 patienter med DM1, 42% kvinnor, medel 44 år, 12 länder
- Duration 19.5 år, BMI 26.5 kg/m², HbA1c 60 mmol/mol
- Basbehandling 40% degludec, 32% glargin U100, 18% glargin U300, 8% detemir, 2% övriga. Alla fick insulin aspart till måltider
- Randomisering till icodec 1 gång/v eller degludec 1 gång/dag
- Observationstid 26 + 26 v, primärt utfall förändring HbA1c, DTSQ med som sekundärt utfall



Lancet 2023; 402: 1636–47

Published Online
October 17, 2023

	Insulin icodec (n=290)		Insulin degludec (n=292)		Insulin icodec *vs* insulin degludec
	Participants	Events (rate)	Participants	Events (rate)	Estimated rate ratio (95% CI), p value
Overall hypoglycaemic episodes (baseline to week 26)					
Hypoglycaemia alert value*	288 (99%)	10799 (75·88)	287 (98%)	7402 (51·36)	..
Clinically significant hypoglycaemia†	246 (85%)	2789 (19·60)	223 (76%)	1478 (10·26)	1·88 (1·53 to 2·32), p<0·0001
Severe hypoglycaemia‡	9 (3%)	47 (0·33)	9 (3%)	17 (0·12)	2·08 (0·39 to 10·96), p=0·39
Combined clinically significant† or severe‡ hypoglycaemia	247 (85%)	2836 (19·93)	223 (76%)	1495 (10·37)	1·89 (1·54 to 2·33), p<0·0001
Overall hypoglycaemic episodes (baseline to week 57)					
Hypoglycaemia alert value*	288 (99%)	20406 (67·98)	289 (99%)	14819 (47·87)	..
Clinically significant hypoglycaemia†	262 (90%)	5047 (16·81)	250 (86%)	2811 (9·08)	1·79 (1·48 to 2·18), p<0·0001
Severe hypoglycaemia‡	13 (4%)	56 (0·19)	12 (4%)	25 (0·08)	1·88 (0·48 to 7·36), p=0·37
Combined clinically significant† or severe‡ hypoglycaemia	263 (91%)	5103 (17·00)	250 (86%)	2836 (9·16)	1·80 (1·48 to 2·18), p<0·0001
Nocturnal hypoglycaemic episodes (baseline to week 26)					
Hypoglycaemia alert value*	214 (74%)	980 (6·89)	171 (59%)	734 (5·09)	..
Clinically significant hypoglycaemia†	135 (47%)	476 (3·34)	98 (34%)	224 (1·55)	2·13 (1·56 to 2·91), p<0·0001
Severe hypoglycaemia‡	2 (1%)	5 (0·04)	3 (1%)	3 (0·02)	..
Combined clinically significant† or severe‡ hypoglycaemia	135 (47%)	481 (3·38)	98 (34%)	227 (1·58)	2·13 (1·56 to 2·91), p<0·0001
Nocturnal hypoglycaemic episodes (baseline to week 57)					
Hypoglycaemia alert value*	237 (82%)	1953 (6·51)	211 (72%)	1523 (4·92)	..
Clinically significant hypoglycaemia†	171 (59%)	861 (2·87)	140 (48%)	458 (1·48)	1·88 (1·43 to 2·47), p<0·0001
Severe hypoglycaemia‡	4 (1%)	9 (0·03)	4 (1%)	4 (0·01)	1·62 (0·22 to 11·86), p=0·63
Combined clinically significant† or severe‡ hypoglycaemia	171 (59%)	870 (2·90)	140 (48%)	462 (1·49)	1·89 (1·44 to 2·48), p<0·0001

Lancet 2023; 402: 1636–47

Published Online October 17, 2023

	Insulin icodec (n=290)		Insulin degludec (n=292)		Insulin icodec *vs* insulin degludec
	Participants	Events (rate)	Participants	Events (rate)	Estimated rate ratio (95% CI), p value
Overall hypoglycaemic episodes (baseline to week 26)					
Hypoglycaemia alert value*	288 (99%)	10799 (75·88)	287 (98%)	7402 (51·36)	..
Clinically significant hypoglycaemia†	246 (85%)	2789 (19·60)	223 (76%)	1478 (10·26)	1·88 (1·53 to 2·32), p<0·0001
Severe hypoglycaemia‡	9 (3%)	47 (0·33)	9 (3%)	17 (0·12)	2·08 (0·39 to 10·96), p=0·39
Combined clinically significant† or severe‡ hypoglycaemia	247 (85%)	2836 (19·93)	223 (76%)	1495 (10·37)	1·89 (1·54 to 2·33), p<0·0001
Overall hypoglycaemic episodes (baseline to week 57)					
Hypoglycaemia alert value*	288 (99%)	20406 (67·98)	289 (99%)	14819 (47·87)	..
Clinically significant hypoglycaemia†	262 (90%)	5047 (16·81)	250 (86%)	2811 (9·08)	1·79 (1·48 to 2·18), p<0·0001
Severe hypoglycaemia‡	13 (4%)	56 (0·19)	12 (4%)	25 (0·08)	1·88 (0·48 to 7·36), p=0·37
Combined clinically significant† or severe‡ hypoglycaemia	263 (91%)	5103 (17·00)	250 (86%)	2836 (9·16)	1·80 (1·48 to 2·18), p<0·0001
Nocturnal hypoglycaemic episodes (baseline to week 26)					
Hypoglycaemia alert value*	214 (74%)	980 (6·89)	171 (59%)	734 (5·09)	..
Clinically significant hypoglycaemia†	135 (47%)	476 (3·34)	98 (34%)	224 (1·55)	2·13 (1·56 to 2·91), p<0·0001
Severe hypoglycaemia‡	2 (1%)	5 (0·04)	3 (1%)	3 (0·02)	..
Combined clinically significant† or severe‡ hypoglycaemia	135 (47%)	481 (3·38)	98 (34%)	227 (1·58)	2·13 (1·56 to 2·91), p<0·0001
Nocturnal hypoglycaemic episodes (baseline to week 57)					
Hypoglycaemia alert value*	237 (82%)	1953 (6·51)	211 (72%)	1523 (4·92)	..
Clinically significant hypoglycaemia†	171 (59%)	861 (2·87)	140 (48%)	458 (1·48)	1·88 (1·43 to 2·47), p<0·0001
Severe hypoglycaemia‡	4 (1%)	9 (0·03)	4 (1%)	4 (0·01)	1·62 (0·22 to 11·86), p=0·63
Combined clinically significant† or severe‡ hypoglycaemia	171 (59%)	870 (2·90)	140 (48%)	462 (1·49)	1·89 (1·44 to 2·48), p<0·0001

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	Insulin icodec (n=290)		Insulin degludec (n=292)		Insulin icodec *vs* insulin degludec
	Participants	Events (rate)	Participants	Events (rate)	Estimated rate ratio (95% CI), p value
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Hypoglycaemia alert value*	288 (99%)	10799 (75·88)	287 (98%)	7402 (51·36)	..
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However, there was a statistically significant treatment difference in favour of degludec in DTSQ total treatment satisfaction score from baseline to weeks 26 and 52

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Hur många har insulinpump idag?

- Alla över 18 åå: 26.1% män, 35.6% kvinnor
- 18-21 åå: 59.5%
- 0-17 åå: 78.6%

Källa: Nationella Diabetesregistret och Swediabkids årsrapporter 2022

Hur många med DM2 insulinbehandlas idag?

- 21.9 % 2022
- 29.9 % 2002

Källa: Nationella Diabetesregistret 2022