Stellenwert der Insulintherapie

Wetzlar, 07. Oktober 2023

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Conflict of Interest Prof. Dr. Thomas Forst

CRS.

Speaker Boards:

Abbott; Amarin; Astra Zeneca; Berlin Chemie; Boehringer Ingelheim, Daiichi-Sankyo, Eli Lilly; Fortbildungskolleg; MSD; Novartis, Novo Nordisk; Sanofi; Santis

Advisory Pannel:

Astra Zeneca; Atrogi, Bayer; Böhringer Ingelheim, Diabetes Acadamy Bad Mergentheim Eli Lilly; Eysense; Fortbildungskolleg; Galapagos, Pfizer; Sanofi; Roche;

Editorial Boards:

Diabetes Science Technology, Diabetes Stoffwechsel & Herz
Associate Editor Endocrinology Diabetes & Metabolism
Editor Diabetes Congress Reports

Pathophysiologisch orientierte Therapie des T2DM

Insulin abhängige Therapie

Insulin Resistenz

- peripher
- hepatisch → ***Metformin***

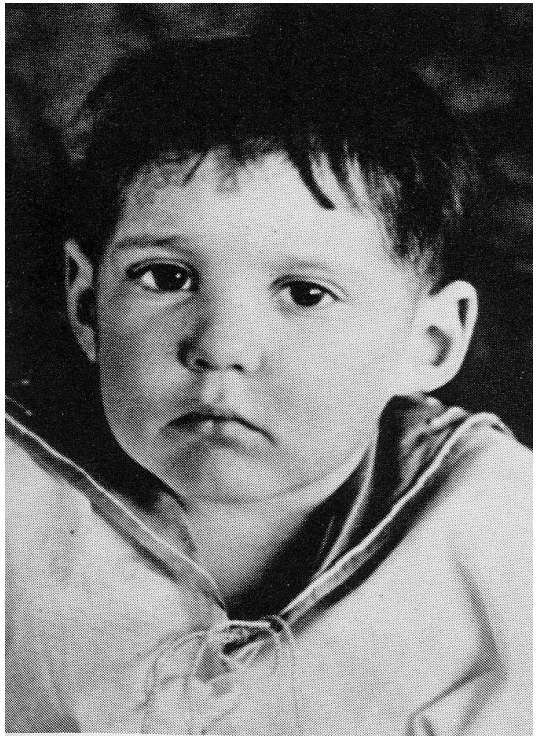
Insel Zell Dysfunktion

- Alpha Zell Dysfunktion
- Beta Zell Dysfunktion → ***SU*** / ***Insulin***

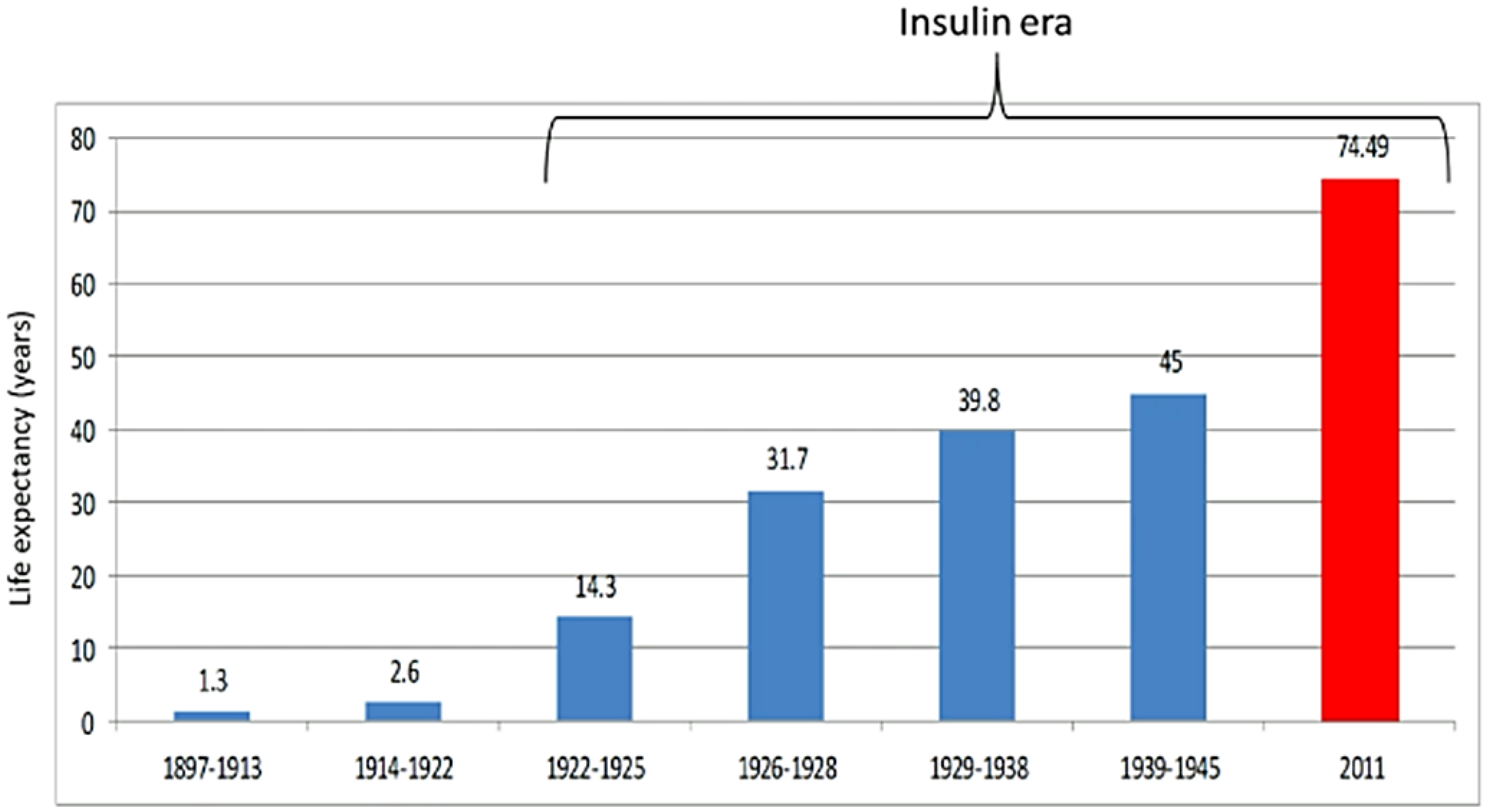
Modified according to: Forst T. et al.; Expert. Rev. Endocrinol. Metab.; 2007 (2) 303-312; Forst T. et al.; Curr. Diabetes Rev.; 2016 (12) 429-439

100 Jahre Insulin

1922-2022



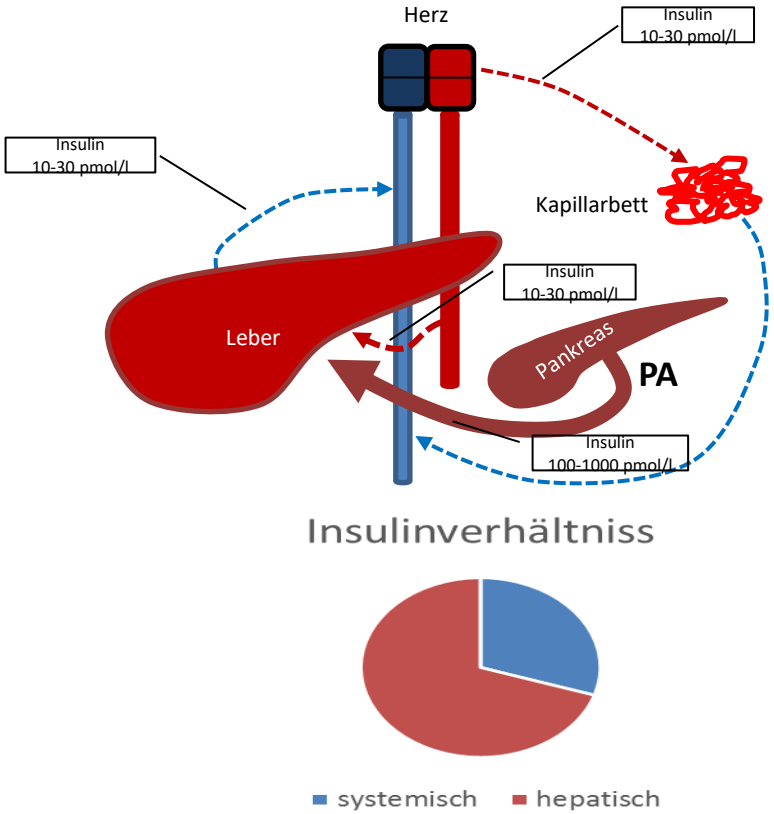
Bedeutung der Insulintherapie für die Lebenserwartung des Patienten mit Diabetes mellitus Typ 1



Gale Lancet 2003; USA Today 2011

Insulinverteilung im Körper nach Freisetzung

A. Nach Freisetzung aus der Betazelle

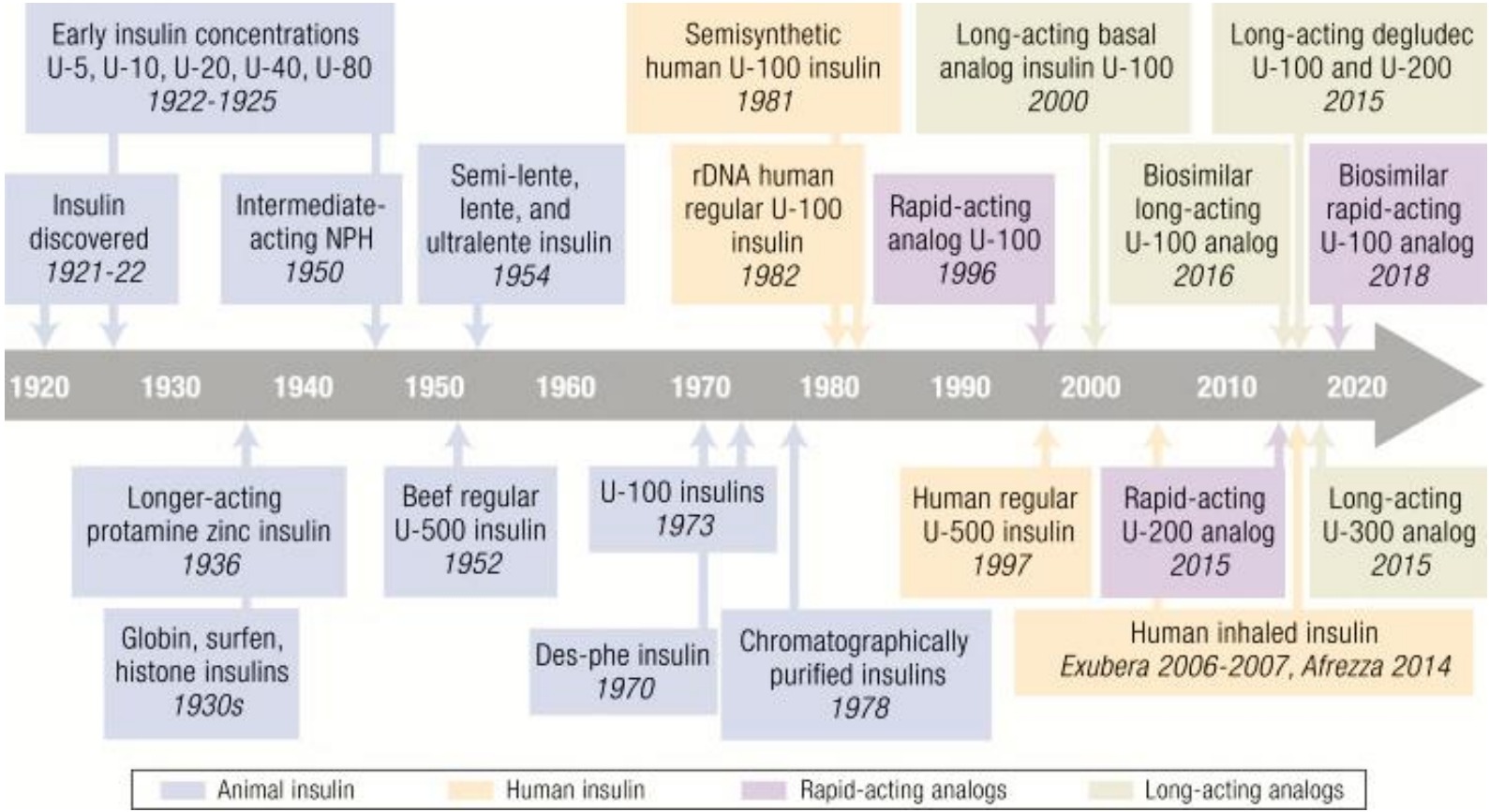


modifiziert nach Forst T., Jahnke J.; Diabetes Stoffwechsel und Herz; 2016

Einschränkungen der subkutanen Insulintherapie

- Unphysiologische Insulinprofile.
- Glukoseunabhängige Insulinwirkung.
- Postprandiale Glukoseexkursionen durch zu langsamen Wirkeintritt.
- Variabilität in der Insulinwirkung in Abhängigkeit von
  - Injektionsort
  - Temperatur
  - Lokaler Durchblutung
- Unphysiologische Verteilung in verschiedenen Körperkompartimenten – Verlust des hepato-peripheren Insulinquotienten -

Entwicklung der Insulintherapie seit 1921



Bajaj H.S.; ADA, New Orleans 6th June 2022

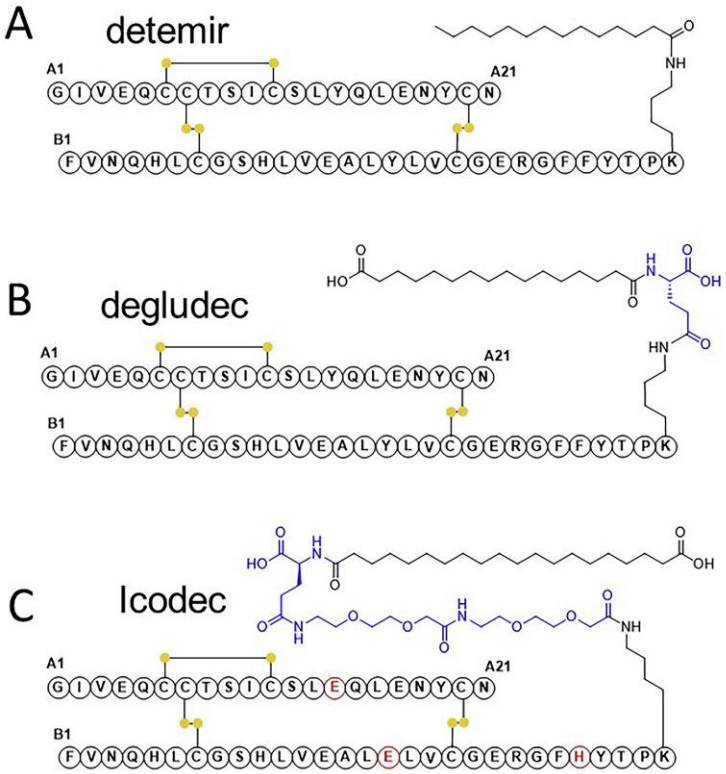
Once Weekly Insuline in der Entwicklung

Molecule	Company	Phase of Development	Diabetes Type	Structular features to prolong activity
Insulin Icodeg	Novo Nordisk	Phase 3	T1D and T2D	Acylation with icosanedioic acid
BIF, LY3209590	Lilly	Phase 3	T1D and T2D	FC-fusion protein
AB 101	Antria /Rezolate	Phase 1	T1D and T2D	Pegylation and microsphere delivery
Insumera, PE0139	Phase Bio	Phase 2 a completed	T2D	ELPylation
AKS-433	Akston Biosciences	Preclinical	T1D and T2D	FC-fusion protein
Single chain insulin FC-fusion variants	Astra Zeneca	Preclinical	Not reported	FC-fusion protein
HM12640A and HM12470	Hamni Pharma Co. Ltd.	Phase 1	T1D and T2D	FC-fusion protein

Rosenstock, Del Prato; Metabolism; 2022; 126: 154924

Bajaj H.S.; ADA, New Orleans 6th June 2022

Verlängerung der Insulinwirkung durch Ankopplung langkettiger Fettsäuren

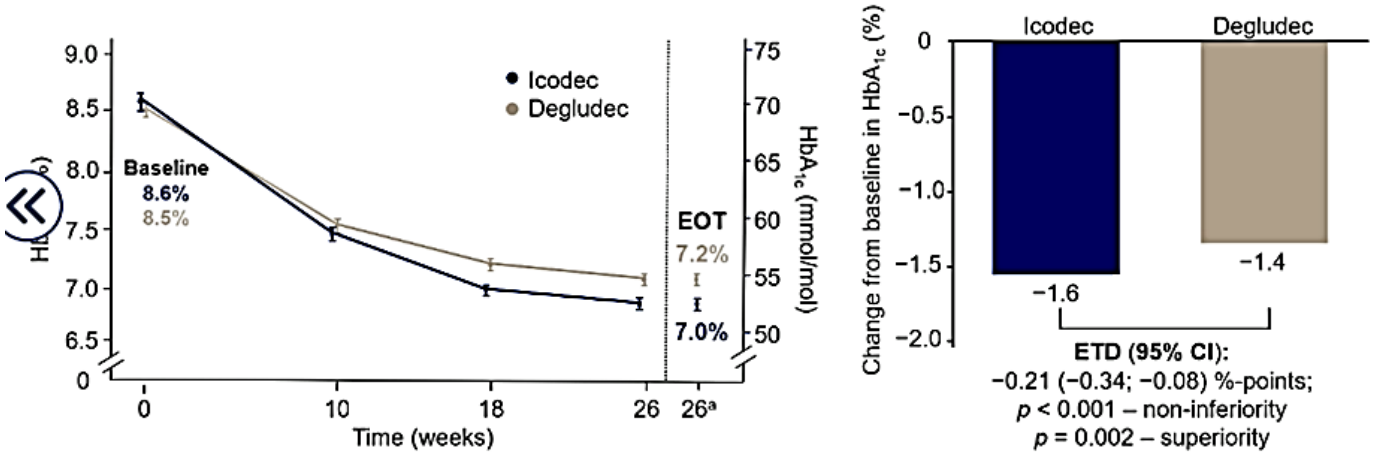


Jarosinski MA et al., Molecular Metabolism, 2021 (52) ; https://doi.org/10.1016/j.molmet.2021.101325

ONWARDS 3: Once weekly Icodec vs. Degludeg in Insulin naiven Patienten mit einem Diabetes mellitus Typ 2

HbA_{1c} change from baseline to week 26

Primary endpoint



Full analysis set. Observed data are shown as mean (symbol) ± SEM (error bars).
[a]Estimated mean HbA_{1c} at week 26 derived based on multiple imputation.
EOT, end of treatment; ETD, estimated treatment difference (icodec – degludec).

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Onwards 3: Once weekly Icodec vs. Degludeg in Insulin naiven Patienten mit einem Diabetes mellitus Typ 2

Overall hypoglycaemia

	Icodec				Degludec				ERR (95% CI)
	n	%	E	R	n	%	E	R	
Weeks 0–31									
Clinically significant	26	8.9	53	0.31	17	5.8	23	0.13	2.09 (0.99; 4.41) $p = 0.054$
Severe	0	–	–	–	2	0.7	2	0.01	–
Clinically significant or severe	26	8.9	53	0.31	18	6.1	25	0.15	1.82 (0.87; 3.80) $p = 0.109$
Weeks 0–26									
Clinically significant	24	8.2	50	0.35	13	4.4	17	0.12	3.12 (1.30; 7.51) $p = 0.011$
Severe	0	–	–	–	0	–	–	–	–
Clinically significant or severe	24	8.2	50	0.35	13	4.4	17	0.12	3.12 (1.30; 7.51) $p = 0.011$

Data were analysed using a negative binomial model with log-link function, with treatment and use of sulphonylureas or glinides (yes/no) as fixed factors and the logarithm of the time period in which a hypoglycaemic episode was considered treatment emergent as offset. ERR = icodec/degludec. R = number of events per PYE (1 PYE = 365.25 days).
E, number of events; ERR, estimated rate ratio; PYE, person-year of exposure; R, rate.

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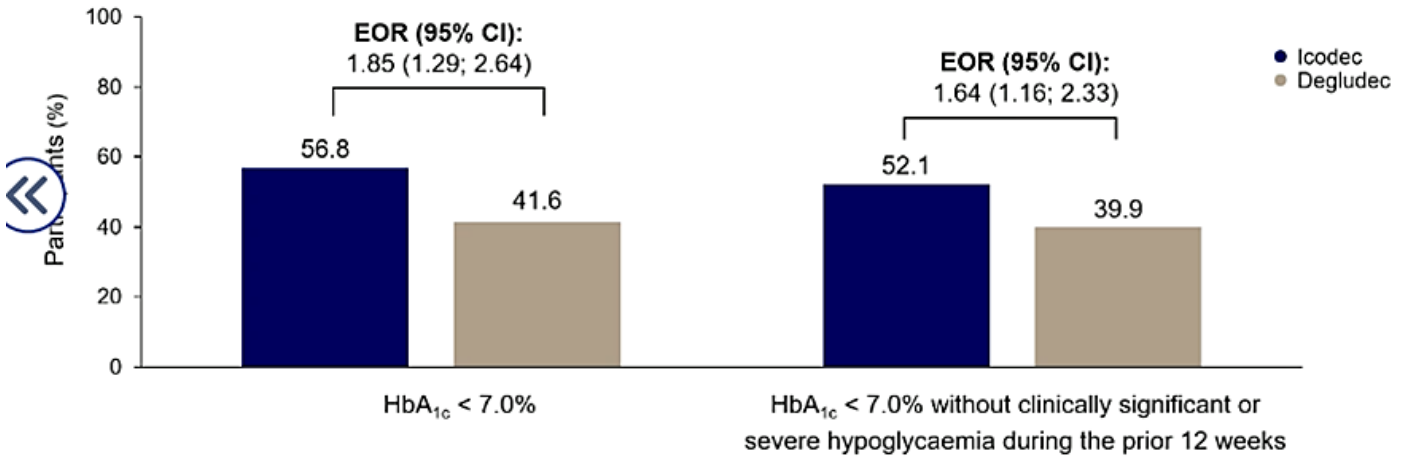
ONWARDS 3: Once weekly Icodec vs. Degludeg in Insulin naiven Patienten mit einem Diabetes mellitus Typ 2

Participants achieving HbA_{1c} targets at week 26

Additional endpoint



Full analysis set. The binary response after 26 weeks was analysed using a binary logistic regression model (logit link) with treatment, region and use of sulphonylureas or glinides (yes/no) as fixed factors, and the baseline HbA_{1c} value as covariate. EOR = icodec/degludec. EOR, estimated odds ratio.

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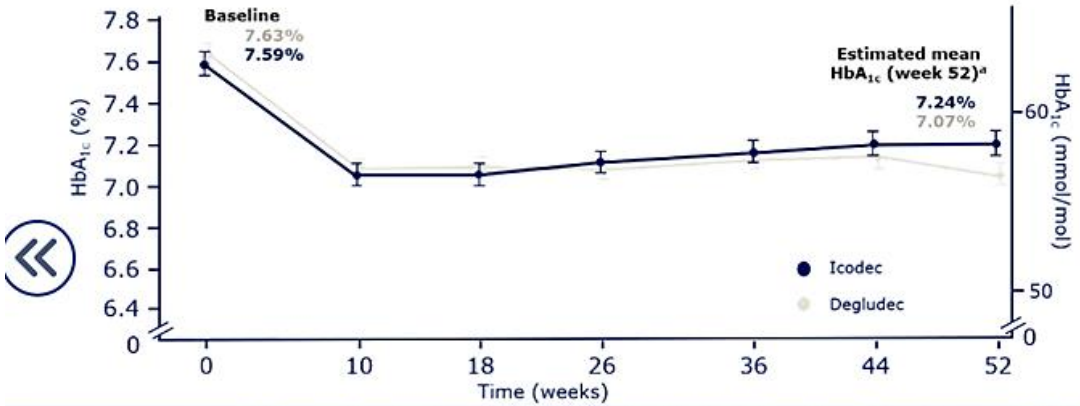
ONWARDS 6: Once weekly Icodec vs. Degludeg bei Patienten mit einem Diabetes mellitus Typ 1

HbA_{1c} over time



Supportive statistical analysis

Estimated mean change from baseline to week 26:

Icodec: −0.37%-points

Degludec: −0.54%-points

ETD (95% CI) at week 52:
0.17%-points
(0.02, 0.31)%-points
$p = 0.0213^c$

The estimated mean change in HbA_{1c} from baseline to week 52 was greater with degludec than with icodec; **there was a statistically significant difference** in favour of degludec

Full analysis set. Observed data are mean (symbol) ± standard error of the mean (error bars) in trial, including data obtained after premature treatment discontinuation. These data were analysed using an ANCOVA model with region, screening HbA_{1c} (< 8.0% or ≥ 8.0%), pre-trial basal insulin treatment and randomised treatment as fixed factors, and baseline HbA_{1c} as a covariate. [a]Estimated mean values at weeks 26 and 52 derived from multiple imputation. [b]p value for test of non-inferiority (0.3%-point margin) of icodec versus degludec. [c]p value for test of no treatment difference. ANCOVA, analysis of covariance; CI, confidence interval; degludec, insulin degludec; ETD, estimated treatment difference (icodec – degludec); HbA_{1c}, glycated haemoglobin; icodec, insulin icodec.

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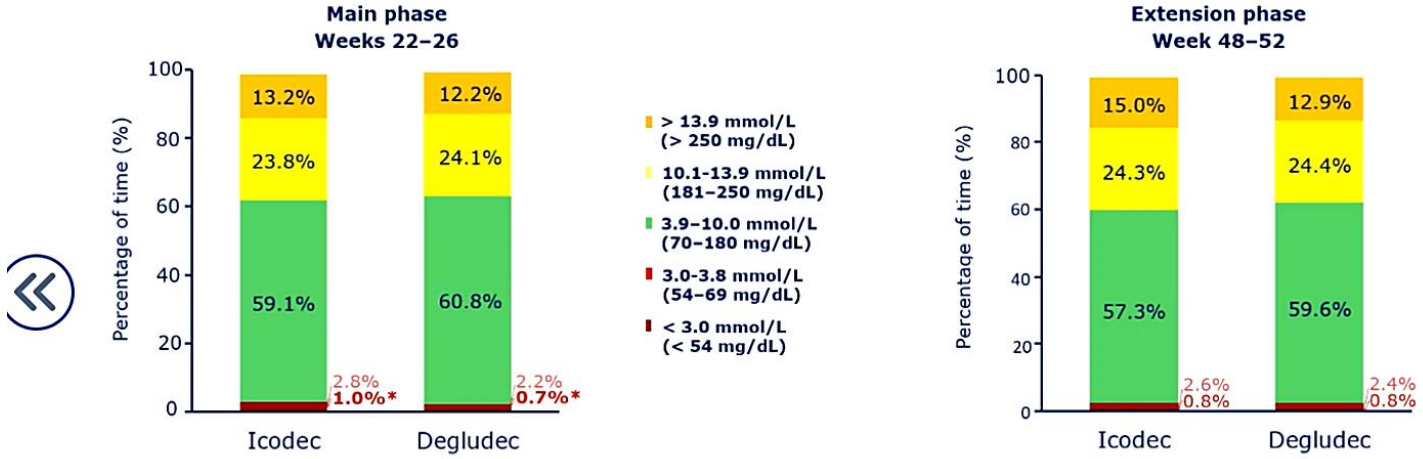
ONWARDS 6: Once weekly Icodec vs. Degludeg bei Patienten mit einem Diabetes mellitus Typ 1

CGM data



Full analysis set. CGM metrics assessed as observed means during weeks 22–26 and weeks 48–52. The percentage of time is defined as 100 times the number of recorded measurements in a given range, divided by the total number of recorded measurements. These data were analysed using an ANOVA model with region, screening HbA_{1c} (< 8.0% or ≥ 8.0%), pre-trial basal insulin treatment and randomised treatment as fixed factors. The percentage of time spent with glucose level below glycaemic range was analysed using a negative binomial model on the number of recorded measurements below range, with a log-link function and the logarithm of the total number of recorded measurements as an offset, and region, screening HbA_{1c} (< 8.0% or ≥ 8.0%), pre-trial basal insulin treatment and randomised treatment as fixed factors.
**Statistically significant difference ($p = 0.0014$) in favour of degludec over icodec in time below 3.0 mmol/L (< 54 mg/dL) during weeks 22–26 (no statistically significant difference was observed during weeks 48–52). ANOVA, analysis of variance; CGM, continuous glucose monitoring; degludec, insulin degludec; HbA_{1c}, glycated haemoglobin; icodec, insulin icodec; TAR, time above range; TIR, time in range.*

ONWARDS 6: Once weekly Icodec vs. Degludeg bei Patienten mit einem Diabetes mellitus Typ 1

Overall hypoglycaemia

From baseline to week 26 and to week 57

	Icodec								Degludec							
	n		%		E		R		n		%		E		R	
Clinically significant	246	262	84.8	90.3	2789	5047	19.60	16.81	223	250	76.4	85.6	1478	2811	10.26	9.08
Severe	9	13	3.1	4.5	47[a]	56	0.33	0.19	9	12	3.1	4.1	17[b]	25	0.12	0.08
Clinically significant or severe	247	263	85.2	90.7	2836	5103	19.93	17.00	223	250	76.4	85.6	1495	2836	10.37	9.16

On treatment	ERR		95% CI		*p* value	
Clinically significant hypoglycaemia	1.88	1.79	(1.53, 2.32)	(1.48, 2.18)	< 0.0001	< 0.0001
Severe hypoglycaemia	2.08	1.88	(0.39, 10.96)	(0.48, 7.36)	0.3889	0.3651
Clinically significant or severe hypoglycaemia	1.89	1.80	(1.54, 2.33)	(1.48, 2.18)	< 0.0001	< 0.0001

There was a **statistically significant** difference in rates of **clinically significant hypoglycaemia** and combined **clinically significant or severe hypoglycaemia in favour of degludec**

Main-on-treatment period (baseline to week 26). On-treatment period (baseline to week 57). Safety analysis set. Clinically significant hypoglycaemia: BG < 3.0 mmol/L (< 54 mg/dL) confirmed by BG meter. Severe hypoglycaemia: hypoglycaemia with severe cognitive impairment requiring external assistance for recovery. Hypoglycaemic episodes were analysed using a negative binomial regression model with log-link function including region, screening HbA_{1c} (< 8.0% or ≥ 8.0%), pre-trial basal insulin treatment and randomised treatment as fixed factors, and the log of the time period for which the hypoglycaemic episodes were considered as an offset. [a]One participant experienced 33 of the 47 reported episodes. [b]One participant experienced seven of the 17 reported episodes. BG, blood glucose; CI, confidence interval; degludec, insulin degludec; E, number of events; ERR, estimated rate ratio; HbA_{1c}, glycated haemoglobin; icodec, insulin icodec; PYE, patient-year of exposure (1 PYE = 365.25 days); R, rate (number of events per PYE).

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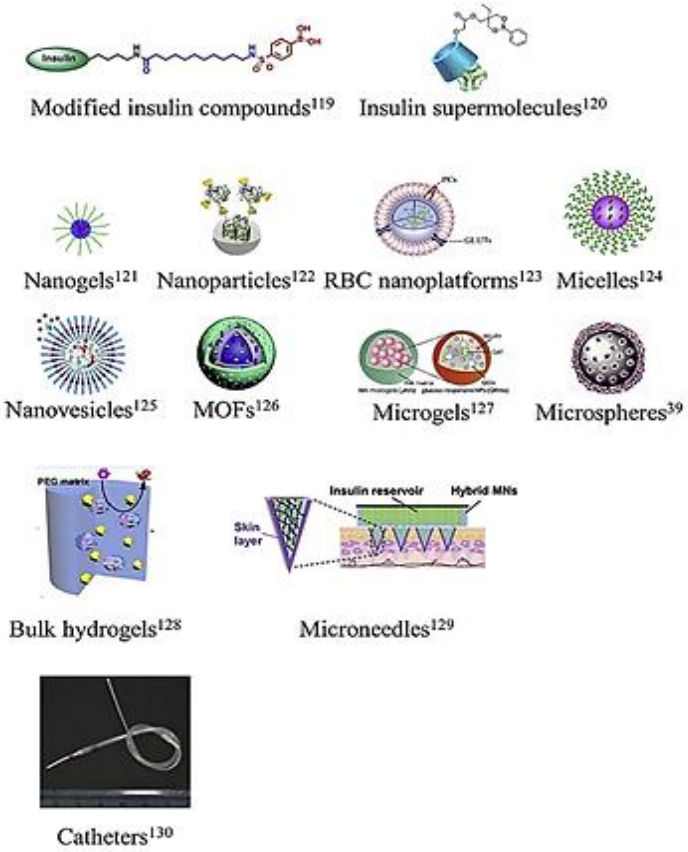
Glukose regulierte Insulinwirkung (GRI)

- Mechanisch: CGM gekoppelte Insulinpumpen
  - Hypoglykämieabschaltung
  - Closed Loop
  - Bihormonale Systeme
- Molekulare Systeme
  - Polymer basiert: Glukoseabhängige Matrixsysteme Lektin
  - Bioinspirierte Carriersysteme: Albumin, GLUT Chanels, Ery
  - Metabolische Clearance: Mannose Rezeptor
  - Unimolekulare GRI

Modifiziert nach: Rege NK: et al., Curr. Opin. Endocrinol Diabetes. Obes. 2017 (24)267; Shen Di et al.. Journal of Controlled Release, 2020 (321) 236

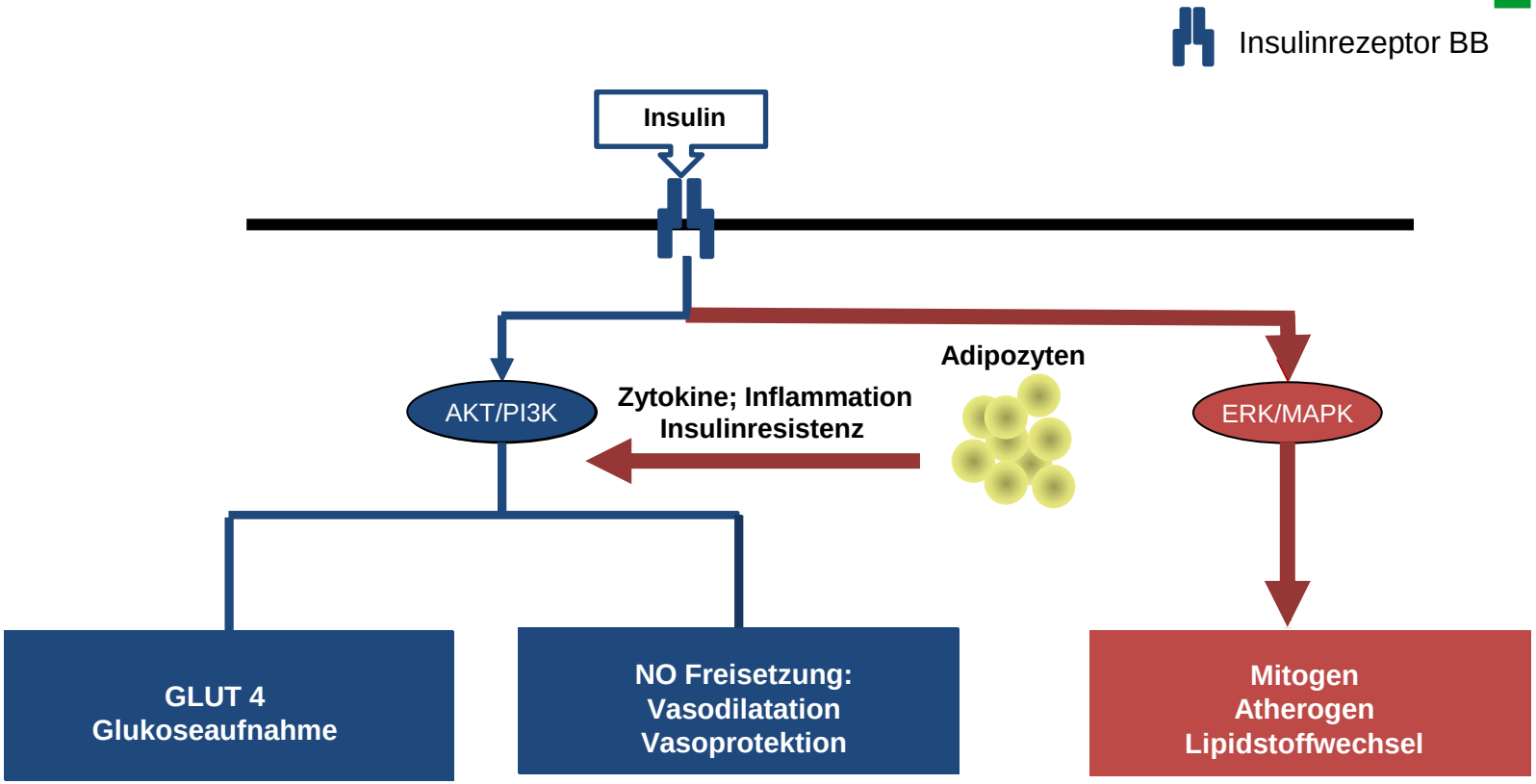
Systeme zur Glukoseregulierten Insulinwirkung

- Glucose responsive Insulins
- Glucose responsive particels
- Glucose responsive macroscopic gels
- Glucose responsive devices



Shen Di et al.. Journal of Controled Release, 2020 (321) 236

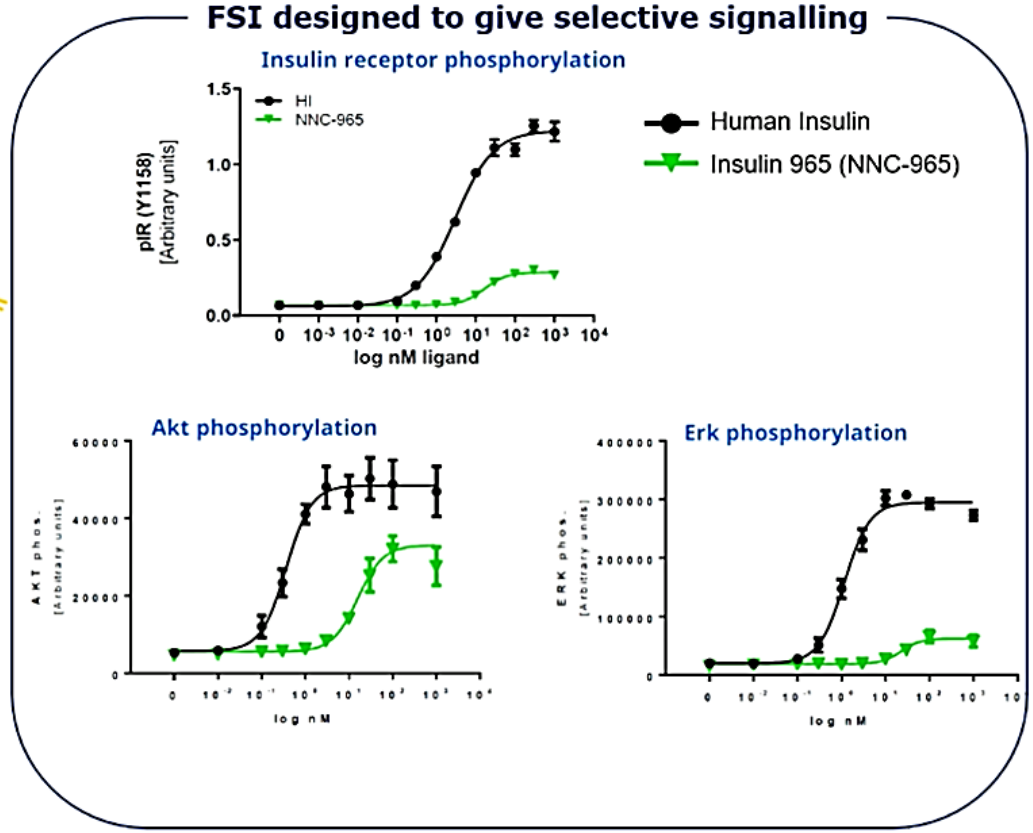
Insulinsignalkaskade Physiologie / Pathophysiologie



Metabolische Effekte **Vaskuläre Effekte**

modifiziert nach: Forst T, DCR (2018) 16-20; Callagher EJ., LeRoith D., Nature Reviews (2020) 20: 629

Effekte und Sicherheit eines funktionell selektiven Insulins (NNC-965)



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Effekte und Sicherheit eines funktionell selektiven Insulins (NNC-965)

Trial Design

PHASE 1B BIOMARKER TRIAL IN T2D ON BASAL INSULIN

86 participants
- T2DM on basal insulin +/- OADs
- HbA1c 6.0-10.0 %
- Insulin dose:
  ≥10U/day if HbA1c>7.5%
  ≥20U/day if HbA1c>6.5% and ≤7.5%
  ≥25U/day if HbA1c≤6.5%
- Age 40-75 years
- eGFR>45 mL/min
- Blood pressure < 160/100 mmHg
- Stable statin dose for past 3 months

Insulin 965 +/- metformin, DPP4i, SGLT2i

Insulin glargine +/- metformin, DPP4i, SGLT2i

Randomisation (1:1) — Duration 26 weeks — End of treatment

Trial information
- 1:1 randomisation, stratified by site and HbA1c (> or ≤ 7.5%)
- Double-blind (double dummy)
- Weekly titration, treat-to-target

Endpoints and Methods

Vascular function
- Flow-mediated dilation | endothelial function **[primary]**
- Pulse wave analysis and velocity | large artery function
- Leg plethysmography | vascular function / tissue circulation
- Retinal flicker | retinal arteriolar dilation response / retinal blood flow

Cardiac function
- Cardiac MRI – EDV strain and ejection fraction

Body composition
- Air displacement plethysmography (BOD POD) | body fat
- Whole body MRI | Visceral and s.c. adipose tissue

Liver fat
- MRI-PDFF

Insulin sensitivity
- Insulin tolerance test

Biomarkers
- Vascular (NT-proBNP, sVCAM-1, ...)
- Glucose / Lipid metabolism (HbA1c, Lp(a), Adiponectin, ...)
- Renal (Albumin excretion)

Safety endpoints
- Adverse events
- Hypoglycaemic episodes

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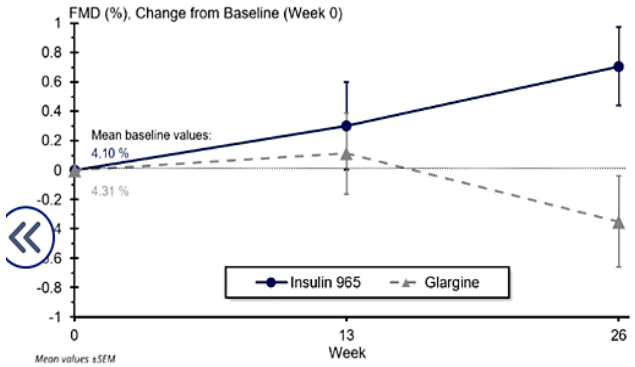
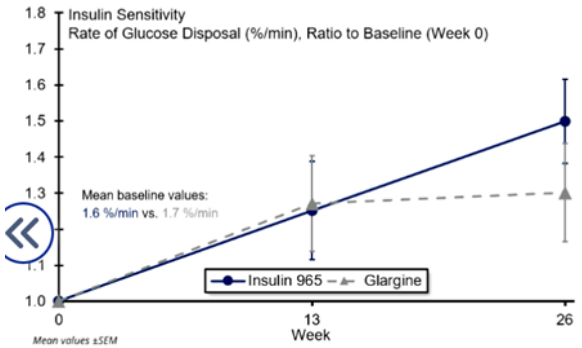
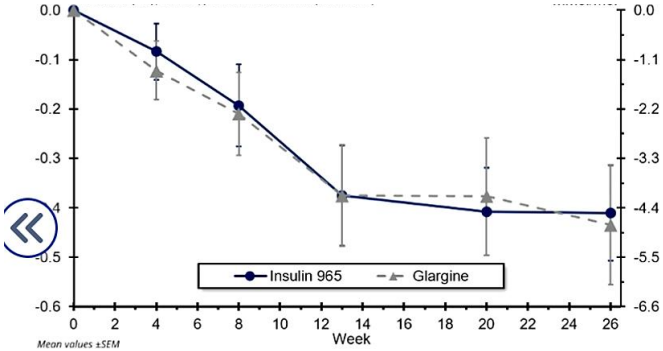
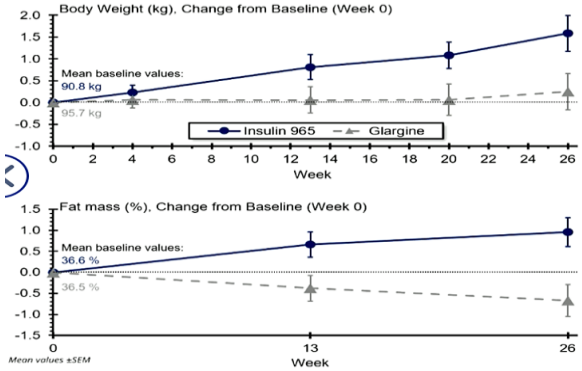
Effekte und Sicherheit eines funktionell selektiven Insulins (NNC-965)









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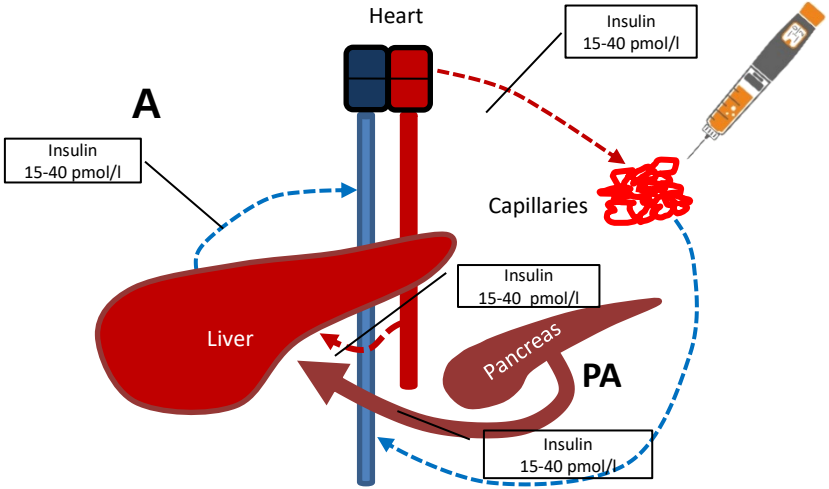
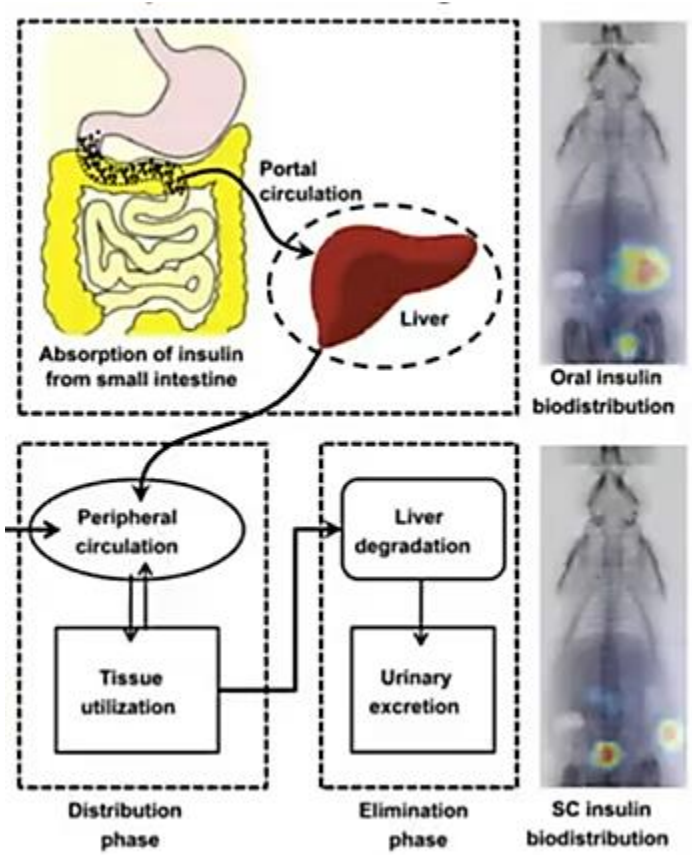
Insulinverteilung nach iv und oraler Insulinapplikation

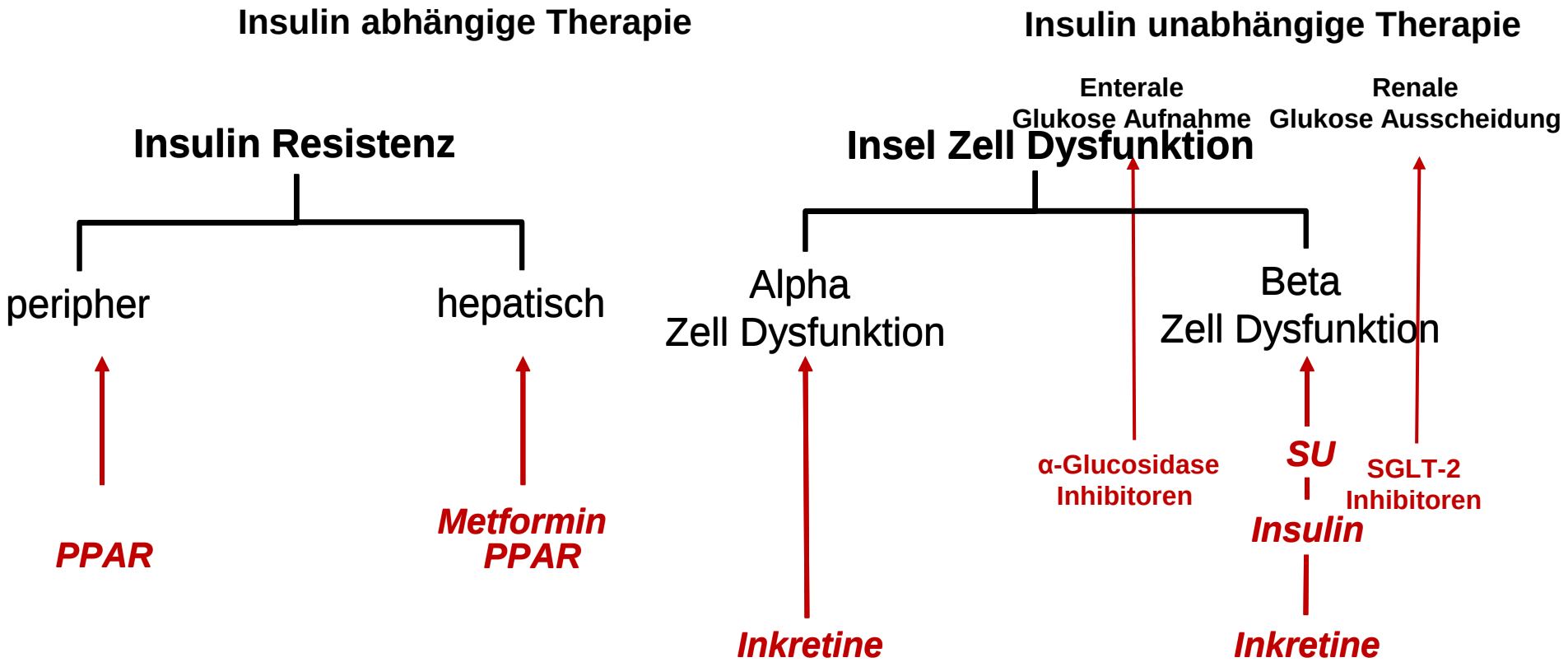




Adapted according to: Forst T., Jahnke J.; Diabetes Stoffwechsel und Herz; 2016

Elcioglu, Seze; Nanoparticle Drug Delivery-Applications and New Aspects; 2014, DOI: 10.577228538

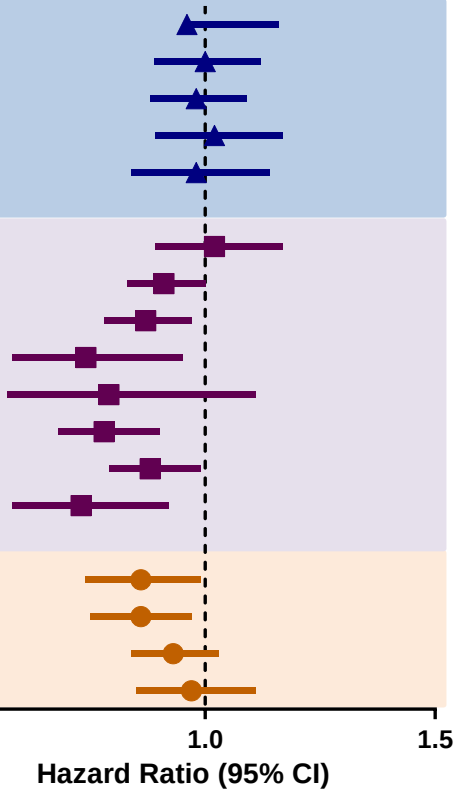
Medikamentöse Therapie des T2DM



Modified according to: Forst T. et al.; Expert. Rev. Endocrinol. Metab.; 2007 (2) 303-312; Forst T. et al.; Curr. Diabetes Rev.; 2016 (12) 429-439

Primärer kombinierter MACE Endpunkt in den bisher abgeschlossenen Studien mit DPP-IV-I, GLP-1-RA und SGLT-2-I

	Study	Investigational Drug/Comparator	Primary Endpoint	HR (95% CI)
DPP-4 Inhibitor	EXAMINE[1]	Alogliptin/Placebo	3-P-MACE	0.96 (≤1.16)*
	SAVOR-TIMI 53[2]	Saxagliptin/Placebo	3-P-MACE	1.00 (0.89-1.12)*
	TECOS[3]	Sitagliptin/Placebo	3-P-MACE[a]	0.98 (0.88-1.09)*
	CARMELINA[4]	Linagliptin/Placebo	3-P-MACE	1.02 (0.89-1.17)*
	CAROLINA[5]	Linagliptin/Glimepiride	3-P-MACE	0.98 (0.84-1.14)*
GLP-1 RA	ELIXA[6]	Lixisenatide/Placebo	3-P-MACE[a]	1.02 (0.89-1.17)*
	EXSCEL[7]	Exenatide/Placebo	3-P-MACE	0.91 (0.83-1.00)*
	LEADER[8]	Liraglutide/Placebo	3-P-MACE	0.87 (0.78-0.97)*
	SUSTAIN 6[9]	Semaglutide/Placebo	3-P-MACE	0.74 (0.58-0.95)*
	PIONEER 6[10]	Oral Semaglutide/Placebo	3-P-MACE	0.79 (0.57-1.11)*
	HARMONY[11]	Albiglutide/Placebo	3-P-MACE	0.78 (0.68-0.90)†
	REWIND[12, $]	Dulaglutide (1,5mg)/Placebo	3-P-MACE	0.88 (0.79-0.99)‡
	AMPLITUDE[13]	Efpeglenatid/Placebo	3-P-MACE	0.73 (0.92-0.58)‡
SGLT-2i	EMPA-REG[14]	Empagliflozin/Placebo	3-P-MACE	0.86 (0.74-0.99)*
	CANVAS[15]	Canagliflozin/Placebo	3-P-MACE	0.86 (0.75-0.97)*
	DECLARE-TIMI 58[16]	Dapagliflozin/Placebo	3-P-MACE	0.93 (0.84-1.03)*
	VERTIS[17]	Ertugliflozin/Placebo	3-P-MACE	0.97 (0.85-1.11)*



Ein direkter Vergleich der Studien ist aufgrund des Studiendesigns, der Population und Methodologie nicht möglich

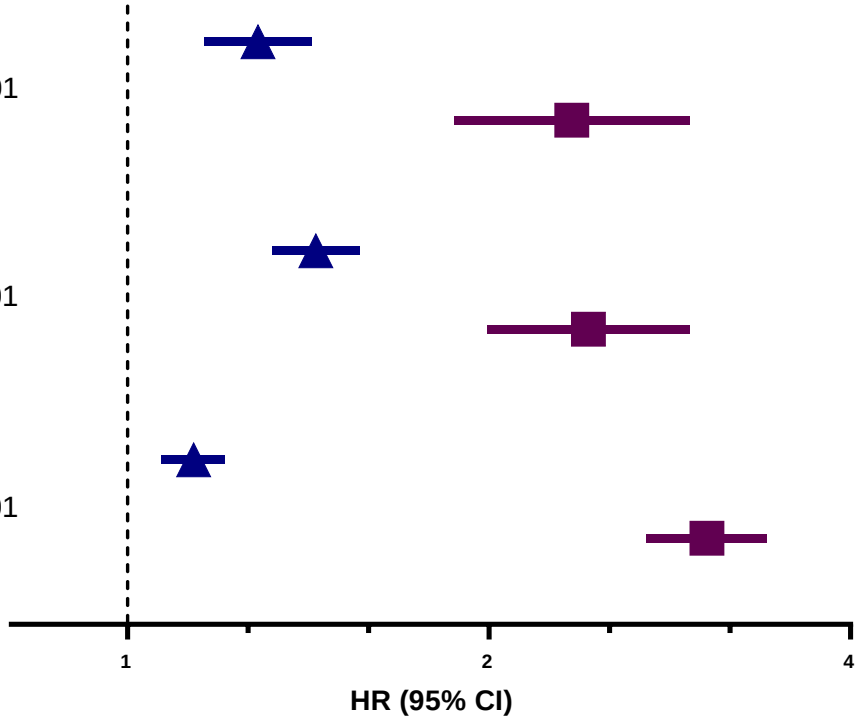
EMPA-REG OUTCOME®-Studienpopulation: erwachsene Patienten mit Typ-2-Diabetes und KHK oder pAVK oder vorangegangenem Myokardinfarkt oder Schlaganfall (Ereignis > 2 Monate)
[$]Belegt durch eine placebokontrollierte, doppelblinde kardiovaskuläre Langzeit-Outcome- Studie REWIND, bei welchem Patienten mit Typ-2 Diabetes und unterschiedlich hohem kardiovaskulären Risiko (Alter ≥ 50 Jahre und klinisch manifeste Gefäßerkrankung, Alter ≥ 55 Jahre und subklinische Gefäßerkrankung; Alter ≥ 60 Jahre und Zutreffen von mind. 2 weiteren Risikofaktoren)1 Dulaglutid 1,5 mg oder Placebo jeweils in Kombination mit einer Standardtherapie verabreicht wurde.
Ein direkter Vergleich der Studien ist aufgrund des Studiendesigns, der Population und Methodologie nicht möglich

Semaglutide SC/Exenatide QW may not be available in some markets.
*P<0.001; †P<0.0001; ‡P=0.026. [a]Hospitalisation for angina.
3-P-MACE=3-point major adverse cardiovascular events; CI=confidence interval, DPP-4=dipeptidyl peptidase-4; GLP-1 RA=glucagon-like peptide-1 receptor agonist; HR=hazard ratio; QW=once weekly; SC=subcutaneous; SGLT-2i=sodium-glucose cotransporter 2 inhibitor.

[1]White WB, et al. New England Journal of Medicine. 2013;369(14): 1327–1335; [2]Scirica BM, et al. New England Journal of Medicine. 2013;369(14): 1317–1326; [3]Green JB, et al. New England Journal of Medicine. 2015;373(3): 232–242; [4]Rosenstock J, et al. Journal of the American Medical Association. 2019;321(1): 69–79; [5]Rosenstock J, et al. Journal of the American Medical Association. 2019;322(12): 1155–1166; [6]Pfeffer MA, et al. New England Journal of Medicine. 2015;373(23): 2247–2257; [7]Holman RR, et al. New England Journal of Medicine. 2017;377(13): 1228–1239; [8]Marso SP, et al. New England Journal of Medicine. 2016;375(4): 311–322; [9]Marso SP, et al. New England Journal of Medicine. 2016;375(19): 1834–1844; [10]Husain M, et al. New England Journal of Medicine. 2019;381(9): 841–851; [11]Hernandez AF, et al. Lancet. 2018;392(10157): 1519–1529; [12]Gerstein HC, et al. Lancet. 2019;394(10193): 121–130; [13]Gerstein HC, et al. 2021; doi 10.1056/NEJMoa2108269; [Epub ahead of print][14]Zinman B, et al. New England Journal of Medicine. 2015;373(22): 2117–2128; [15]Neal B, et al. New England Journal of Medicine. 2017;377(7): 644–657; [16]Wiviott SD, et al. New England Journal of Medicine. 2019;380(4): 347–357; [17]Cannon CP, et al. New England Journal of Medicine. 2020;383(15): 1425–1435.

Retrospektive Kohortenstudie zu kardiovaskulären Endpunkten bei Patienten mit COVID 19 in Patienten mit Diabetes mellitus ohne oder mit Insulintherapie im Vergleich zu Patienten ohne Diabetes mellitus

	n/Events	HR (95% CI)	p
MI			
Diabetes without insulin	14397/445	1.28 (1.16-1.42)	<0.001
Diabetes insulin	1370/81	2.34 (1.87-2.94)	
Stroke			
Diabetes without insulin	14397/673	1.44 (1.32-1.56)	<0.001
Diabetes insulin	1370/110	2.42 (1.99-2.94)	
All cause death			
Diabetes without insulin	14397/1.226	1.16 (1.07-1.21)	<0.001
Diabetes insulin	1370/318	3.04 (2.71-3.41)	



Adjustiert für:Alter, Geschlecht, Monatseinkommen, Charlson Komorbiditätsindex

Lee YB. Et al., Journal of Diabets Invest., 2021 (12) 1855

ORIGIN:
Study Design and Objectives[1,2]

Eligibility Criteria:
- IFG, IGT, or early T2DM with HbA1c <150% of ULN
- Age ≥50 years
- Had established or high risk of CVD

R
1:1

Insulin Glargine (titrated to achieve FPG ≤5.3 mmol/L [95 mg/dL]) N=6264

Standard glycemic care N=6273

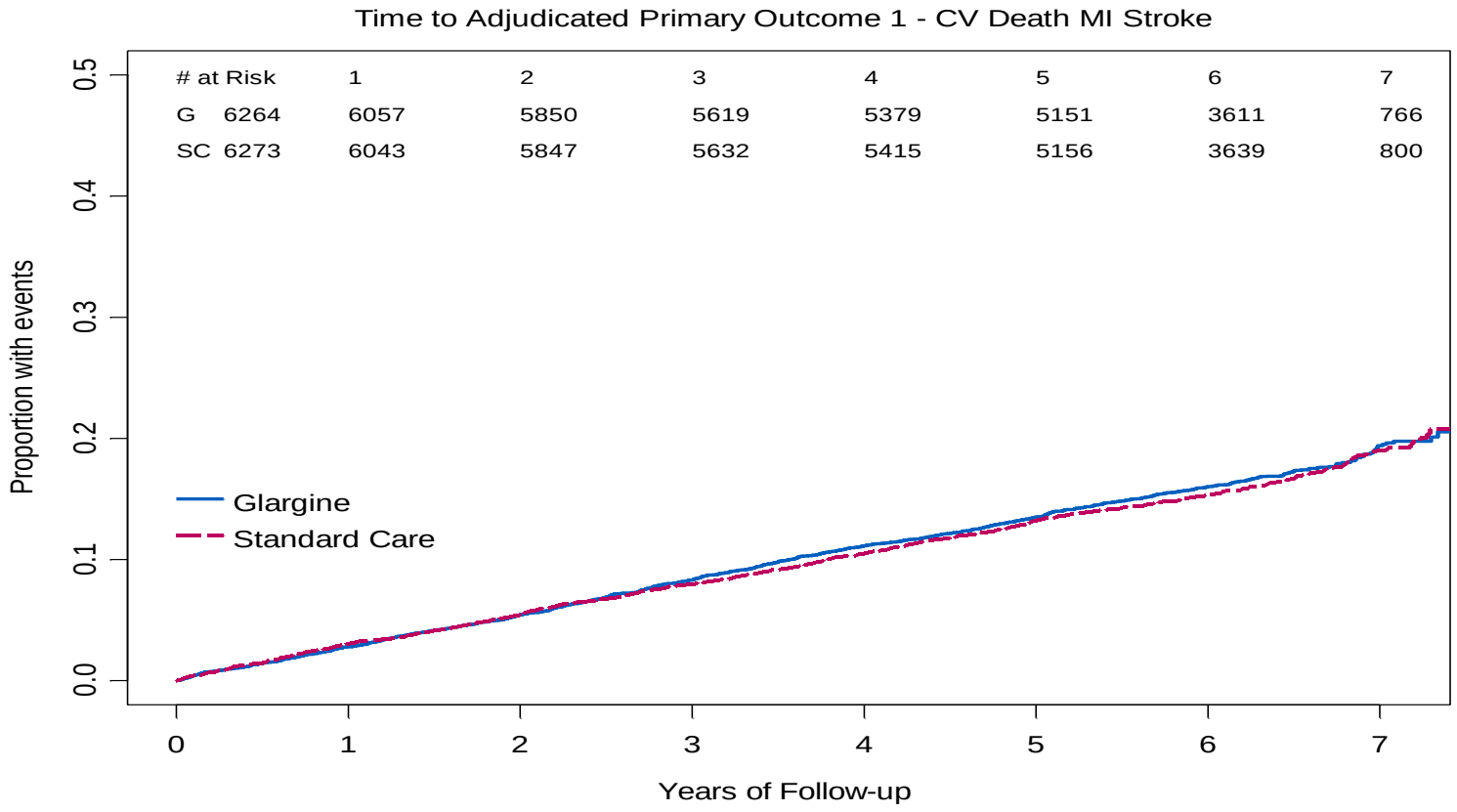
Primary Outcomes:
- Composite of CV death, nonfatal MI, or nonfatal stroke
- Composite of CV death, nonfatal MI, nonfatal stroke, revasularization procedure, or hospitalization for heart failure

Study design: Multicenter, randomized, open-label study

Primary objective: To determine whether insulin glargine-mediated normoglycemia can reduce cardiovascular morbidity and/or mortality in people at high risk for vascular disease with either IFG, IGT or early type 2 diabetes

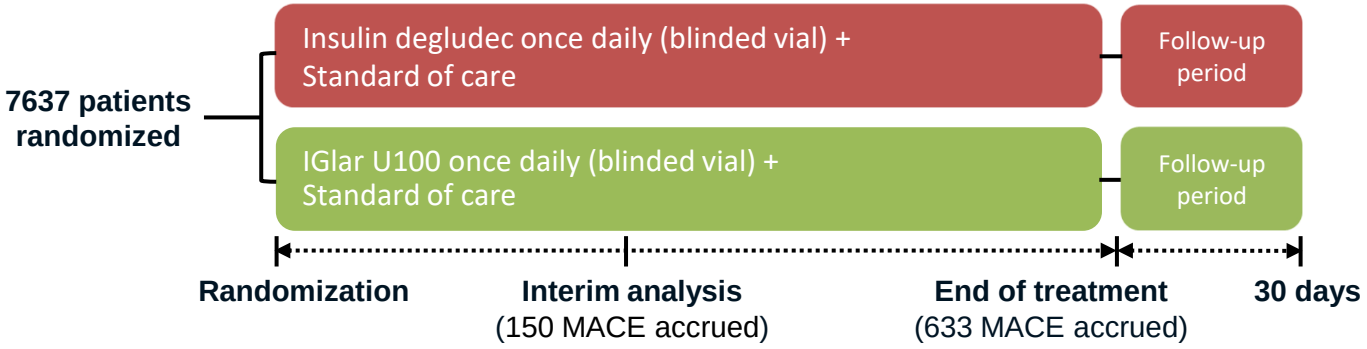
1. ORIGIN Trial Investigators. *Am Heart J* 2008;155:26-32, 32.e1-6
2. ORIGIN Trial Investigators. *N Engl J Med* 2012;367:319-28

Origin Studie: Erster Co-primärer Endpunkt: Myokardinfarkt, Schlaganfall und CV-bedingter Tod



The ORIGIN Trial Investigators. N Engl J Med 2012; published on June 11, 2012, at NEJM.org (10.1056/NEJMoa1203858)

DEVOTE
Trial design

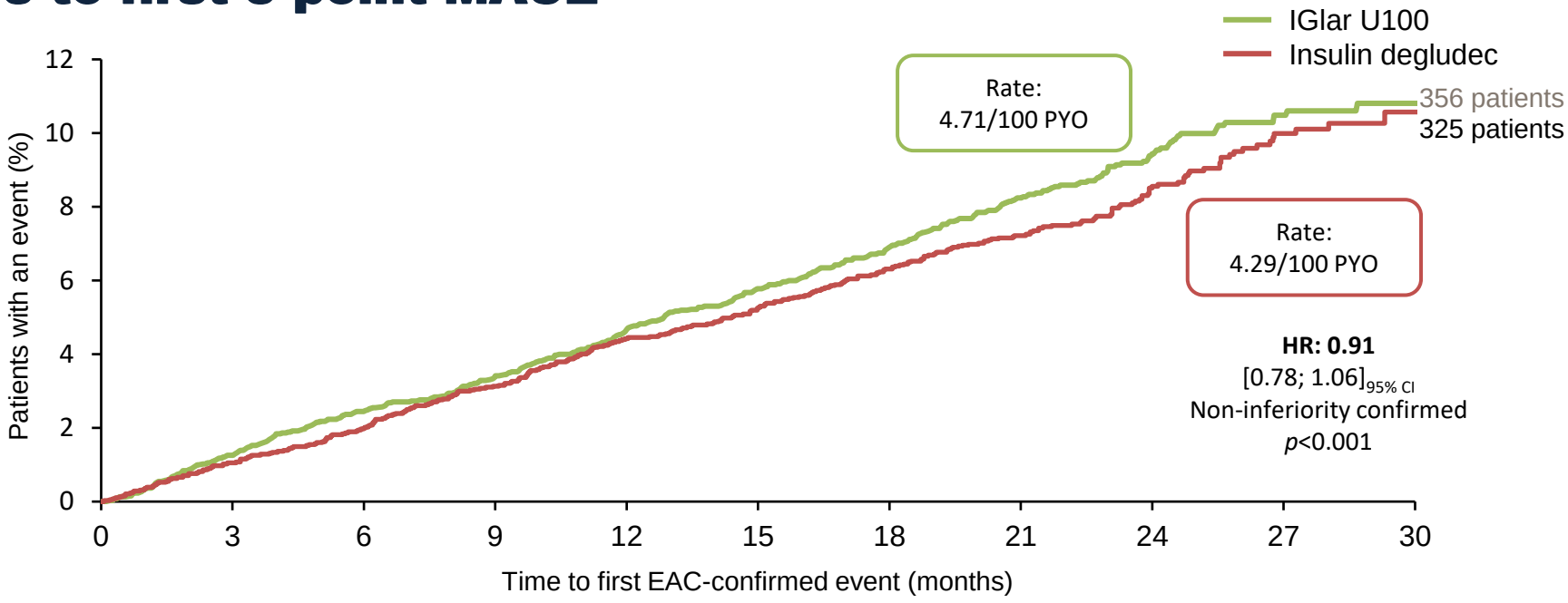


Primary endpoint	Time from randomization to first occurrence of a 3-point MACE: cardiovascular death*†, non-fatal myocardial infarction* or non-fatal stroke*
Secondary endpoints	• Rate of severe hypoglycemic episodes*‡ • Incidence of severe hypoglycemic episodes*‡

*Confirmed by the Event Adjudication Committee; †cardiovascular death includes undetermined cause of death; ‡**severe defined as** an episode requiring the assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions. BG concentrations may not be available during an event, but neurological recovery following the return of BG to normal is considered sufficient evidence that the event was induced by a low BG concentration

BG, blood glucose; MACE, major adverse cardiovascular event

DEVOTE
Time to first 3-point MACE



Insulin degludec (N)	3818	3765	3721	3699	3611	3563	3504	2851	1767	811	217
IGlar U100 (N)	3819	3758	3703	3655	3595	3530	3472	2832	1742	811	205

Full analysis set; Cox regression analysis accounting for treatment. Analysis includes events between randomization date and follow-up date. Patients without an event are censored at the time of last contact (phone or visit)
EAC, Event Adjudication Committee; N, number of patients at risk; PYO, patient-years of observation

GRADE
Study Design and Endpoints

Open, unmasked phase IV parallel study to compare the efficacy of different glucose lowering treatments as add on to metformin

Patients
- T2DM (HbA_{1c} 6,9-10.5%)
- Metformin-Therapy (≥1.000 mg) since more than 8 weeks

Exclusion criteriae
- T1DM
- Other glucose lowering treatments than metformin

R

N=5.047

- **Sulfonylurea (Glimepirid)** + Metformin
- **DPP-4i (Sitagliptin)** + Metformin
- **GLP-1 RA (Liraglutide)** + Metformin
- **Insulin (Insulin glargin)** + Metformin

Screening — *Run-in (4–8 weeks)* — *Study visits every 3 Month* — **April 2021**

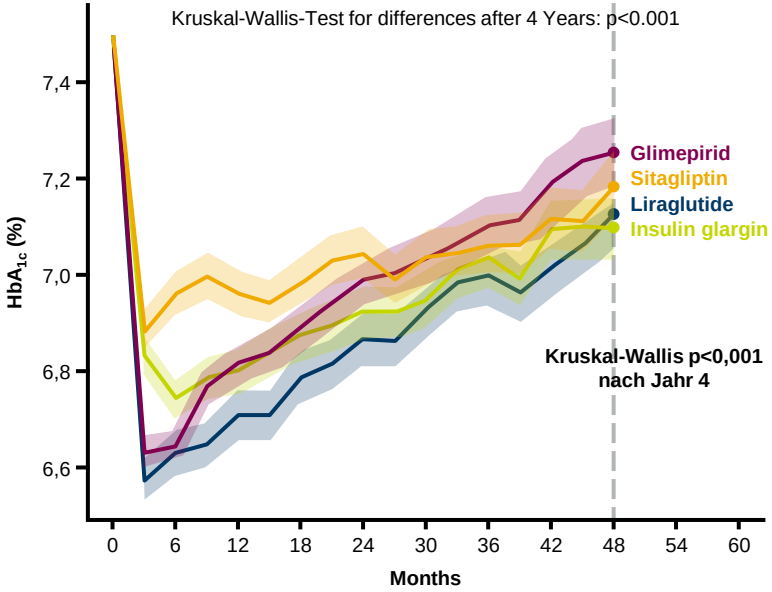
Primary Endpoint
- Time with HbA_{1c} ≥7% (53 mmol/mol) with study medication (+Metformin)

Sekundary Endpoint
- Time with HbA_{1c} <7,5% with study medication (+Metformin)

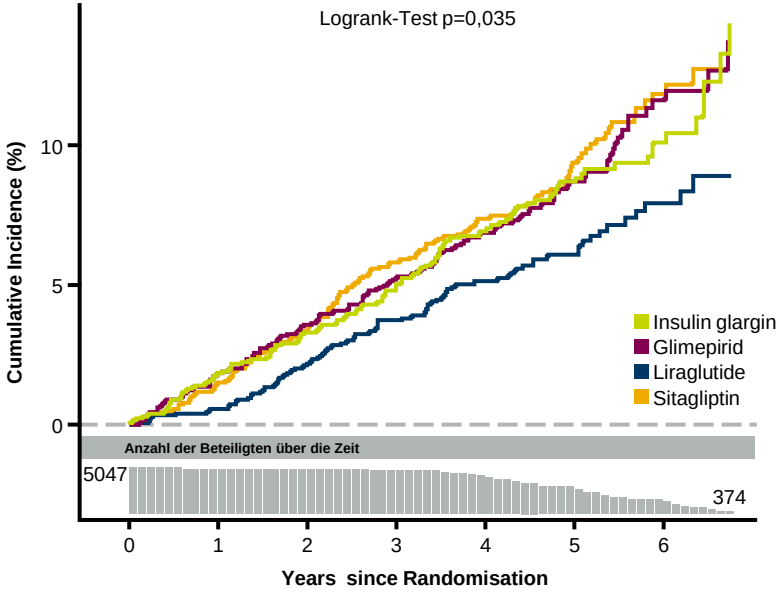
ClinicalTrials.gov https://clinicaltrials.gov/ct2/show/NCT01794143); 07.10.21.

GRADE- Sudie
Hba1c und 3 Punkte MACE

Time course of HbA1c over time



Combined CVD Endpoint *



*MACE, HHI, instabile Angina or Revasczularisation

Buse J, et al. 57th EASD Annual Meeting – Virtual, 27. September – 1. October 2021; S69. [https://www.easd.org/s69.html; abgerufen am: 07.10.21].

Behandlungsintensivierung nach Versagen der oralen Diabetestherapie

CRS.

Versagen der oralen Therapie
Behandlungsintensivierung mit injizierbaren Therapien

Insulin Behandlung:[1]

- Risiko von Hypoglykämien
- Dosistitration
- Gewichtszunahme
- Keine erhöhte Mortalität (Origin Studie[1])

GLP-1 Rezeptor Agonisten:

- Kein erhöhtes Hypoglykämierisiko
- Keine Dosistitration (Dulaglutid)
- Gewichtsreduktion
- Reduktion der Mortalität (LEADER Studie [2], HARMONY Studie [3], REWIND Studie [4], SUSTAIN Studie [5])

1Gerstein HC, et al. N Eng J Med. 2012;367(4):319–328; 2Marso SP, et al. N Engl J Med. 2016;375(4):311–322; 3Hernandez AF, et al. Lancet. 2018;392(10157):1519–1529; 4Gerstein HC, et al. Lancet. 2019;394(10193):131–138; 5Marso SP, et al. N Eng J Med. 2016;375(19):1834–1844

Nationale VersorgungsLeitlinie T2D: Medikamentöse Therapie des T2D

Organprotektion im Fokus - unabhängig vom HbA_{1c}

CRS.

Nach Ausschöpfung der nicht-medikamentösen Basistherapie:
Indikation zur medikamentösen Therapie unter Berücksichtigung individueller Therapieziele
und unter Fortführung der nicht-medikamentösen Therapie

Abschätzung des Risikos für diabetesassoziierte kardiovaskuläre und/oder renale Ereignisse

Kein hohes Risiko

Hohes Risiko
(z. B. klinisch relevante renale Erkrankung)

Klinisch relevante kardiovaskuläre Erkrankung

Individuelle Bewertung und gemeinsame Entscheidungsfindung

Metformin

Individuelles Therapieziel
nach 3-6 Monaten nicht erreicht

Auswahl **eines zweiten Medikaments** entsprechend der Effekte auf priorisierte Endpunkte

Individuelles Therapieziel
nach 3-6 Monaten nicht erreicht

Metformin **plus*** **SGLT2-Inhibitoren**# oder GLP1-RA
(Auswahl entsprechend der Effekte auf priorisierte Endpunkte)

Individuelles Therapieziel
nach 3-6 Monaten nicht erreicht

Ggf. Intensivierung
Auswahl eines zusätzlichen oder alternativen Medikaments entsprechend der Effekte auf priorisierte Endpunkte

NVL: „Die Indikation für die dauerhafte Insulintherapie sieht die Leitliniengruppe daher erst dann gegeben, wenn andere, im Nutzen besser belegte Handlungsoptionen ausgeschöpft sind.“

Überprüfung der Therapiestrategie und des Therapieziels in partizipativer Entscheidungsfindung. *Bei einem HbA_{1c} von ≤ 7% liegen keine Daten für die Wirksamkeit einer Kombinationstherapie bei Menschen mit Typ-2-Diabetes ohne Herzinsuffizienz vor. #Belegter Benefit bedeutet in die Fachinformation aufgenommene Reduktion der jeweiligen Ereignisse in der entsprechenden Population, siehe jeweilige aktuelle Fachinformationen. Referenzen: Bundesärztekammer (BÄK), Kassenärztliche Bundesvereinigung (KBV), Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF). Nationale VersorgungsLeitlinie Typ-2-Diabetes – Teilpublikation der Langfassung, 2. Auflage. Version 1. 2021 [cited: 2022-01-07]. DOI: 10.6101/AZQ/000475 www.leitlinien.de/diabetes

Deeskulation der Insulintherapie bei Patienten mit einem Diabetes mellitus Typ 2

Vertrag über die Vergütung und Abrechnung von Leistungen gemäß § 34 des Vertrags zur Durchführung des Strukturierten Behandlungsprogramms nach § 137f SGB V Diabetes mellitus Typ 2

zwischen

der Kassenärztlichen Vereinigung Berlin
- nachfolgend KV Berlin genannt -

	Deeskalationstherapie Dauerhafte Rückführung von Insulin bei definierten Patienten unter Einsatz moderner Antidiabetika Abrechenbar für Patienten mit mindestens einer der folgenden Voraussetzungen: Insulintherapie seit mindestens 6 Monaten mit Tagesdosierungen > 0,5 IE/Kg Körpergewicht; BMI ≥ 27 Kg/qm; Systolische Herzinsuffizienz (HFrEF < 50%); diastolische Herzinsuffizienz (HFpEF ≥ 50%); chronische Niereninsuffizienz Stad. II – V; Mikroalbuminurie (auch intermittierend); makroangiopathische Endorganschäden (KHK, Apoplex, pAVK).
99134	Ohne Zertifizierung
99134A	Zertifizierung als Diabeteszentrum DDG
99134B	Zertifizierung als Diabetologikum DDG
99135	Ohne Zertifizierung
99135A	Zertifizierung als Diabeteszentrum DDG
99135B	Zertifizierung als Diabetologikum DDG

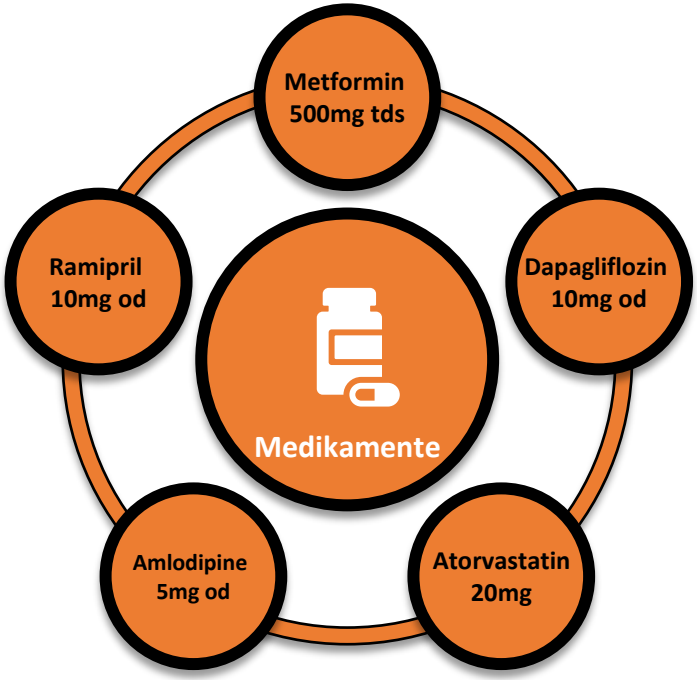
https://www.kvberlin.de/fileadmin/user_upload/vertraege_kv_berlin/disease-management-programme_dmp_/diabetes_mellitus_typ_2/dmp_dm2_allekk_verguetungsvertrag2022.pdf; abgerufen am 12. Mai 2023

Fallbeispiel Frau SW (konstruierter Fall)

- 57 jährige Frau
- Diabetes mellitus Type 2 seit 7 Jahren
- BMI: 36 kg/m²
- HbA1c: 9,3 % 78mmol/mol
- Fettstoffwechselstörung
- Bluthochdruck (BP: 146/94 mmHg)
- Nicht-proliferative diabetische Retinopathie
- Moderate periphere Neuropathie
- eGFR: 66ml/min/173m²

Fallbeispiel Frau SW (konstruierter Fall) Medikation

- Metformin 500 mg bid
- Dapagliflozin 10 mg od
- Ramipril 10 mg od
- Atorvastatin 20 mg od
- Amlodipine 5 mg od



Behandlungsintensivierung nach Versagen der oralen Diabetestherapie

CRS.

Versagen der oralen Therapie
Behandlungsintensivierung mit injizierbaren Therapien

Insulin Behandlung:[1]

- Basal Insulin Behandlung (BOT)
- Mischinsuline
- Basal Bolus Insulintherapie

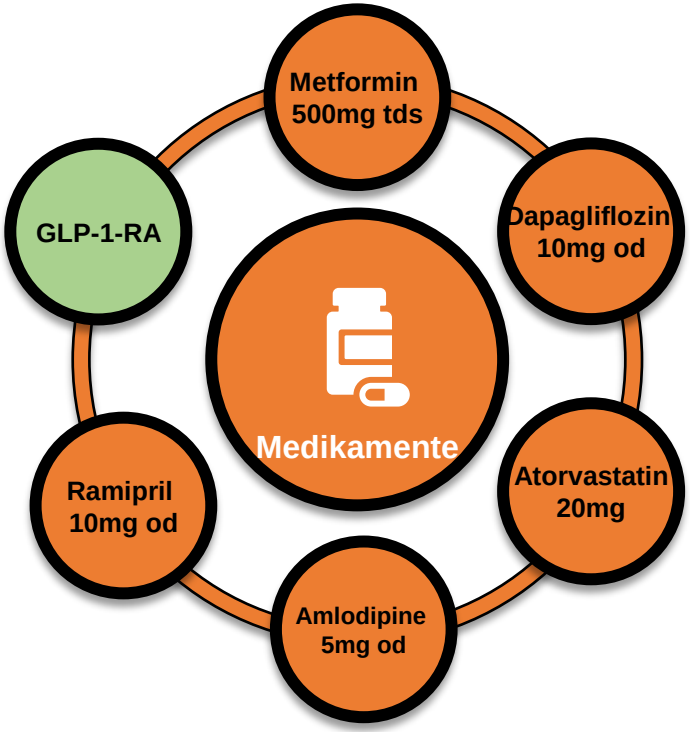
GLP-1 Rezeptor Agonisten:

- Kurz wirksame GLP-1-RA
- Lang wirksamle GLP-1-RA

1Gerstein HC, et al. N Eng J Med. 2012;367(4):319–328; 2Marso SP, et al. N Engl J Med. 2016;375(4):311–322; 3Hernandez AF, et al. Lancet. 2018;392(10157):1519–1529; 4Gerstein HC, et al. Lancet. 2019;394(10193):131–138; 5Marso SP, et al. N Eng J Med. 2016;375(19):1834–1844

Fallbeispiel Frau SW (konstruierter Fall) Medikation

- Metformin 500 mg bid
- Dapagliflozin 10 mg od
- Ramipril 10 mg od
- Atorvastatin 20 mg od
- Amlodipine 5 mg od
- Dulaglutid 1.5 mg einmal wöchentlich



Behandlungsintensivierung nach Versagen der oralen Diabetestherapie

CRS.

Versagen der oralen Therapie
Behandlungsintensivierung mit injizierbaren Therapien

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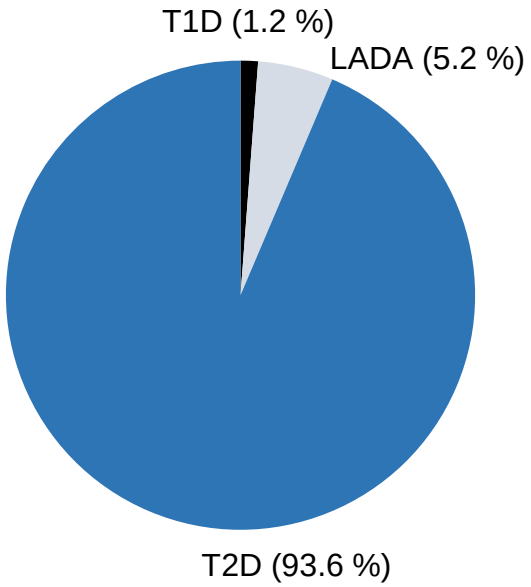
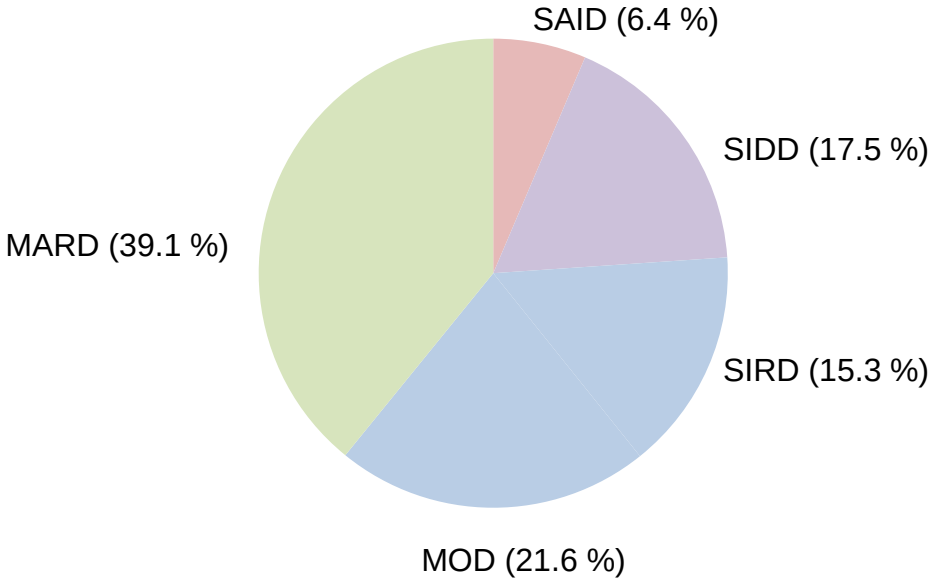
1Gerstein HC, et al. N Eng J Med. 2012;367(4):319–328; 2Marso SP, et al. N Engl J Med. 2016;375(4):311–322; 3Hernandez AF, et al. Lancet. 2018;392(10157):1519–1529; 4Gerstein HC, et al. Lancet. 2019;394(10193):131–138; 5Marso SP, et al. N Eng J Med. 2016;375(19):1834–1844

Neuklassifikation des Diabetes mellitus anhand von Antikörpern, Alter, BMI, HOMA-B und HOMA-IR (ANDIS Patientenregister)





LADA, latent autoimmune diabetes in the adult;
T1D, type 1 diabetes;
T2D, type 2 diabetes

SAID: Severe Autoimmune Diabetes
SIDD: Severe Insulin Deficient Diabetes
SIRD: Severe Insulin Resistant Diabetes
MOD: Mild Obese Diabetes
MARD: Mild age-related Diabetes

Modified according to Ahlqvist E, et al. *Lancet Diabetes Endocrinol* 2018;6(5):361–9

Fallbeispiel Frau SW (konstruierter Fall)

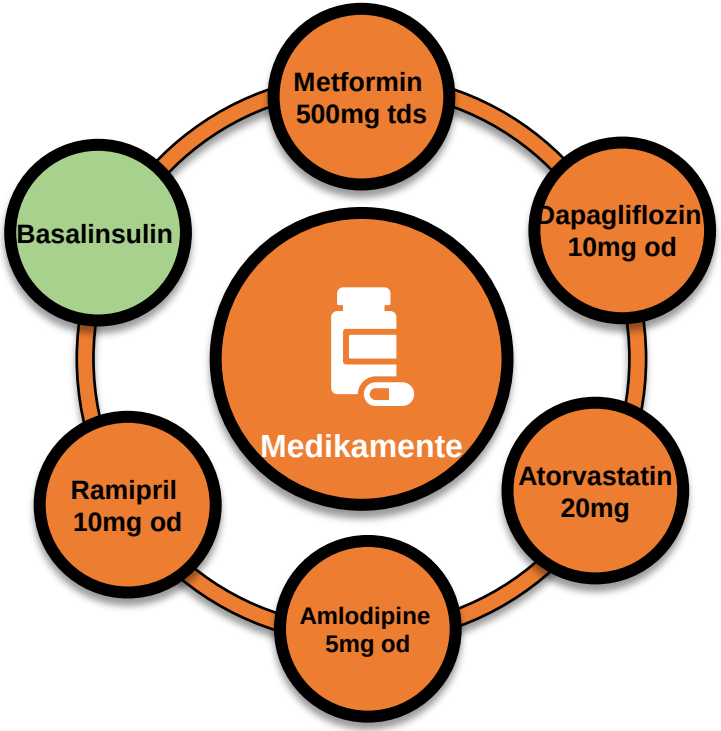
Indikatoren für eine Insulintherapie bei Patienten mit einem Diabetes mellitus Typ 2

Protrahierter Verlust der Betazellfunktion

- Katabole / Ketogene Stoffwechsellage
- Schlanker Patient oder Gewichtsverlust
- Insulin, C-Peptidspiegel
  (nach Stimulation: postprandial, Glukagon, Arginin)

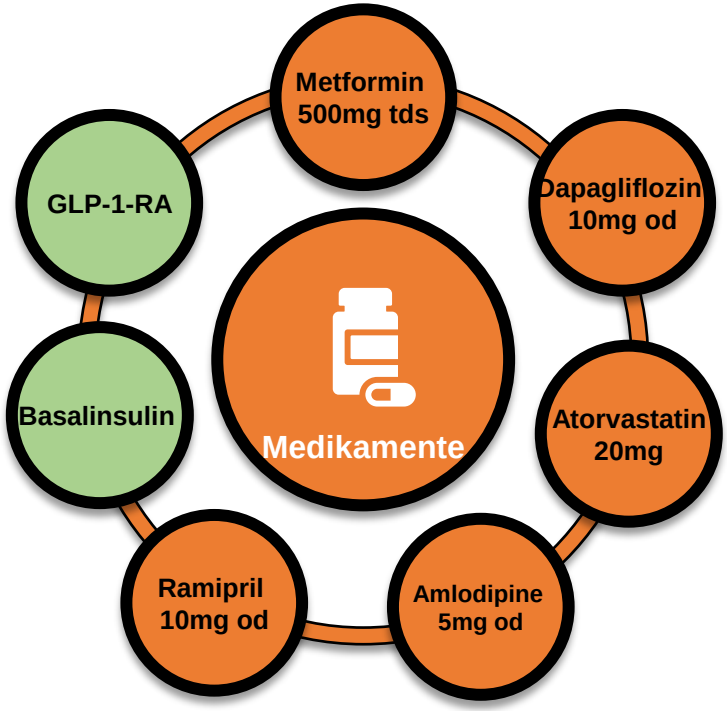
Fallbeispiel Frau SW (konstruierter Fall)
Medikation

- Metformin 500 mg bid
- Dapagliflozin 10 mg od
- Ramipril 10 mg od
- Atorvastatin 20 mg od
- Amlodipine 5 mg od
- Basal Insulin einmal täglich



Fallbeispiel Frau SW (konstruierter Fall)
Medikation

- Metformin 500 mg bid
- Dapagliflozin 10 mg od
- Ramipril 10 mg od
- Atorvastatin 20 mg od
- Amlodipine 5 mg od
- GLP-1-RA einmal wöchentlich
- Basalinsulin einmal täglich

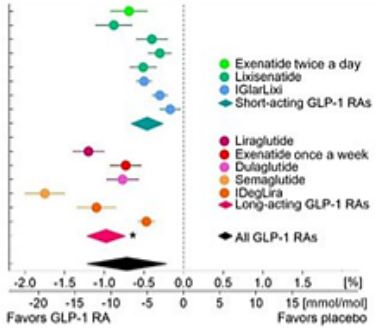


Metaanalyse der Effekte von GLP-1- RA als Zusatztherapie zu Basalinsulin bei Patienten mit einem schlecht kontrollierten T2DM

HbA1c

Study/ publication	Difference in means	95% Confidence interval	Weight [%]	Z-value	P-value
A. HbA_{1c} reduction [%]					
Buse et al. 2011 (13)	-0.69	-0.92; -0.46	11.6	-5.78	< 0.0001
Seino et al. 2012 (14)	-0.88	-1.11; -0.65	11.6	-7.43	< 0.0001
Riddle et al. 2013 a (15)	-0.40	-0.60; -0.20	12.1	-3.93	< 0.0001
Riddle et al. 2013 b (16)	-0.30	-0.45; -0.15	12.7	-3.92	< 0.0001
Yang et al. 2018 (17)	-0.51	-0.68; -0.34	12.5	-5.83	< 0.0001
Aroda et al. 2016 (18)	-0.50	-0.60; -0.40	13.3	-9.82	< 0.0001
Rosenstock at al. 2016 a (19)	-0.30	-0.40; -0.20	13.3	-5.89	< 0.0001
Rosenstock et al. 2016 b (20)	-0.17	-0.30; -0.04	12.9	-2.48	0.013
All short-acting GLP-1 RAs	**-0.46**	**-0.67; -0.26**	-	**-4.42**	**< 0.0001**
Ahmann et al. 2015 (21)	-1.20	-1.40; -1.00	16.8	-11.79	< 0.0001
Guja et al. 2018 (22)	-0.73	-0.93; -0.53	16.8	-7.17	< 0.0001
Pozzilli et al. 2017 (23)	-0.77	-0.97; -0.57	16.7	-7.39	< 0.0001
Rodbard et al. 2018 (24)	-1.75	-2.00; -1.50	15.7	-13.51	< 0.0001
Buse et al. 2014 (25)	-1.10	-1.35; -0.85	15.8	-8.65	< 0.0001
Gough et al. 2014 (26)	-0.47	-0.58; -0.36	18.3	-8.38	< 0.0001
All long-acting GLP-1 RAs	**-0.99**	**-1.23; -0.75**	-	**-8.03**	**< 0.0001**
All GLP-1 RAs	**-0.72**	**-1.23; -0.20**	-	**-2.74**	**0.006**

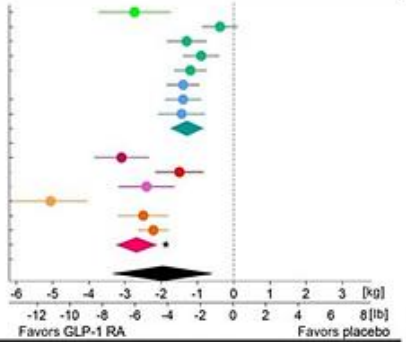
* Difference between short- and long-acting GLP-1 RAs [%]: Δ -0.53, 95% CI: -0.88 ; -0.18 , p= 0.007
Heterogeneity of all GLP-1 RAs: Q-value: 231.98; df (Q): 13; P-value: < 0.0001; I^2: 94.40 %; Tau^2: 0.11



Körpergewicht

Study/ publication	Difference in means	95% Confidence interval	Weight [%]	Z-value	P-value
D. Body weight reduction [kg]					
Buse et al. 2011 (13)	-2.74	-3.74; -1.74	9.0	-5.40	< 0.0001
Seino et al. 2012 (14)	-0.38	-0.87; 0.11	13.2	-1.52	0.13
Riddle et al. 2013 a (15)	-1.30	-1.85; -0.75	12.7	-4.64	< 0.0001
Riddle et al. 2013 b (16)	-0.90	-1.40; -0.40	13.1	-3.54	0.0004
Yang et al. 2018 (17)	-1.20	-1.65; -0.75	13.5	-5.24	< 0.0001
Aroda et al. 2016 (18)	-1.40	-1.85; -0.95	13.5	-6.11	< 0.0001
Rosenstock at al. 2016 a (19)	-1.40	-1.90; -0.90	13.1	-5.50	< 0.0001
Rosenstock et al. 2016 b (20)	-1.44	-2.09; -0.79	11.9	-4.36	< 0.0001
All short-acting GLP-1 RAs	**-1.29**	**-1.74; -0.83**	-	**-5.49**	**< 0.0001**
Ahmann et al. 2015 (21)	-3.10	-3.85; -2.35	16.3	-8.12	< 0.0001
Guja et al. 2018 (22)	-1.50	-2.16; -0.84	17.4	-4.43	< 0.0001
Pozzilli et al. 2017 (23)	-2.41	-3.18; -1.64	16.0	-6.12	< 0.0001
Rodbard et al. 2018 (24)	-5.06	-6.08; -4.04	13.1	-9.77	< 0.0001
Buse et al. 2014 (25)	-2.50	-3.20; -1.80	16.9	-7.02	< 0.0001
Gough et al. 2014 (26)	-2.22	-2.64; -1.80	20.4	-10.37	< 0.0001
All long-acting GLP-1 RAs	**-2.69**	**-3.25; -2.13**	-	**-9.43**	**< 0.0001**
All GLP-1 RAs	**-1.98**	**-3.35; -0.60**	-	**-2.82**	**0.005**

* Difference between short- and long-acting GLP-1 RAs [kg]: Δ -1.40, 95% CI: -2.20 ; -0.60 , p=0.002
Heterogeneity of all GLP-1 RAs: Q-value: 121.25; df (Q): 13; P-value: < 0.0001; I^2: 89.28 %; Tau^2: 0.71



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Zusammenfassung:

- Im Vergleich zur Insulinsekretion durch die Betazelle weist die subkutane Insulinapplikation zahlreiche Limitationen auf.

- Neue Insuline versprechen eine besser an die physiologischen Erfordernisse adaptierte Insulinwirkung.

- Nach Erschöpfung der oralen antidiabetischen Therapie kommt für Patienten mit einem T2DM eine Therapie mit GLP-1 Rezeptoragonisten oder Basalinsulin in Betracht.

- Zahlreiche Fachgesellschaften empfehlen zunächst eine Therapie mit einem GLP-1-RA vor Beginn einer Insulintherapie in Erwägung zu ziehen.

- Patienten mit einem Diabetes mellitus Typ 2 und stark eingeschränkter Betazellfunktion sind weiterhin rechtzeitig auf eine Insulintherapie angewiesen.

- Die Kombination eines GLP-1-RA mit einer Insulintherapie kann den HbA1c verbessern, die Insulindosis und das Körpergewicht reduzieren und möglicherweise die kardiovaskuläre Prognose verbessern.

CRS.
EXPERTS
EARL

Vielen Dank für Ihre Aufmerksamkeit