Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

und

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2022-B-141 Insulin Icodec

Stand: August 2022

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Insulin Icodec **Diabetes mellitus Typ 1 bei Erwachsenen** **Kriterien gemäß 5. Kapitel § 6 VerfO**	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Insuline, *Siehe Übersicht* „II. Zugelassene Arzneimittel im Anwendungsgebiet“.
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	nicht angezeigt

Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	- Beschlüsse über die Nutzenbewertung nach § 35a SGB V
	  o Insulin degludec (Beschluss vom 16.10.2014)
	  o Insulin degludec (Beschluss vom 20.08.2015, neues Anwendungsgebiet)
	- Beschluss des G-BA vom 16.06.2016 über eine Änderung der Richtlinie Methoden vertragsärztliche Versorgung: Kontinuierliche interstitielle Glukosemessung mit Real-Time-Messgeräten (rtCGM) zur Therapiesteuerung bei Patientinnen und Patienten mit insulinpflichtigem Diabetes mellitus

Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche*

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Insulin Icodec A10AE07 Awiqli	**Anwendungsgebiet laut Zulassung** Behandlung des Diabetes mellitus bei Erwachsenen. *[hier zu bewertendes Anwendungsgebiet: Behandlung des Diabetes mellitus Typ 1 bei Erwachsenen.]*
Humaninsulin, biphasisch/ -Isophan (schnell, intermediär, lang wirkend oder Kombination davon) A10AB/AC/AD/AE z.B. Berlinsulin®	Zur Behandlung von Patienten mit Diabetes mellitus, die Insulin für die Aufrechterhaltung einer normalen Glucosehomöostase benötigen. *[FI Berlinsulin, Stand 08/2020]*
Insulin-Analoga	
Langwirksame Insulin-Analoga	
Insulin degludec A10AE06 Tresiba®	Behandlung des Diabetes mellitus bei Erwachsenen, Jugendlichen und Kindern ab dem Alter von 1 Jahr. 4.2 Dosierung und Art der Anwendung Bei Diabetes mellitus **Typ 1** muss Tresiba mit kurz/schnell wirkendem Insulin kombiniert werden, um den mahlzeitenbezogenen Insulinbedarf zu decken. […] *[FI Tresiba, Stand 01/2022]*
Insulin detemir A10AE05 Levemir®	Levemir® wird angewendet zur Behandlung von Diabetes mellitus bei Erwachsenen, Jugendlichen und Kindern ab dem Alter von 1 Jahr. 4.4 Besondere Warnhinweis und Vorsichtsmaßnahmen für die Anwendung Hyperglykämien: Eine unzureichende Dosierung oder das Unterbrechen der Therapie kann, insbesondere bei **Typ 1 Diabetes**, zu Hyperglykämie und diabetischer Ketoazidose führen. […]

II. Zugelassene Arzneimittel im Anwendungsgebiet	
	[FI Levemir, Stand 04/2021]
Insulin glargin A10AE04 z.B. Lantus®	Zur Behandlung von Diabetes mellitus bei Erwachsenen, Jugendlichen und Kindern im Alter von 2 Jahren und älter. *[FI Lantus, Stand 07/2020]*
Kurzwirksame Insulin-Analoga	
Insulin aspart (auch biphasisch) A10AB05 NovoRapid®	NovoRapid® wird angewendet zur Behandlung von Diabetes mellitus bei Erwachsenen, Jugendlichen und Kindern ab dem Alter von 1 Jahr. 4.4 Besondere Warnhinweis und Vorsichtsmaßnahmen für die Anwendung Hyperglykämien: Eine unzureichende Dosierung oder das Unterbrechen der Therapie kann, insbesondere bei **Typ 1 Diabetes**, zu Hyperglykämie und diabetischer Ketoazidose führen. […] *[FI NovoRapid, Stand 09/2020]*
Insulin glulisin A10AB06 Apidra®	Zur Behandlung von Erwachsenen, Jugendlichen und Kindern ab 6 Jahren mit Diabetes mellitus, sofern die Behandlung mit Insulin erforderlich ist. *[FI Apidra, Stand 07/2020]*
Insulin lispro (auch biphasisch) A10AB04 z.B. Humalog®	Zur Behandlung von Erwachsenen und Kindern mit Diabetes mellitus, die Insulin für die Aufrechterhaltung eines normalen Glukosehaushaltes benötigen. Humalog® ist ebenfalls angezeigt bei der Ersteinstellung des Diabetes mellitus. *[FI Humalog, Stand 09/2020]*

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2022-B-141 (Insulin Icodec)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	19. Juli 2022

Inhaltsverzeichnis

Abkürzungsverzeichnis

A1c	Glycated hemoglobin
AE	Adverse events
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
CGM	Continuous glucose monitoring
CSII	Continuous subcutaneous insulin infusion
DM1/2	Diabetes mellitus Type 1/2
ECRI	ECRI Guidelines Trust
FPG	Fasting plasma glucose
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HbA1c	Glycosylated haemoglobin A1c
HR	Hazard Ratio
IDeg	Insulin degludec
IGla	Insulin glargine
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LoE	Level of Evidence
NICE	National Institute for Health and Care Excellence
NMA	Network Meta-Analysis
NPH	Neutral protamine Hagedorn
OR	Odds Ratio
RCT	Randomised controlled trials
RoB	Risk of Bias
RR	Relatives Risiko
SAE	Serious adverse events
SIGN	Scottish Intercollegiate Guidelines Network
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Diabetes mellitus Typ 1 bei Erwachsenen

Hinweis zur Synopse: Informationen hinsichtlich nicht zugelassener Therapieoptionen sind über die vollumfängliche Darstellung der Leitlinienempfehlungen dargestellt.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *Diabetes mellitus Typ 1* durchgeführt und nach PRISMA-S dokumentiert [A]. Die Recherchestrategie wurde vor der Ausführung anhand der PRESS-Checkliste begutachtet [B]. Es erfolgte eine Datenbankrecherche ohne Sprachrestriktion in: The Cochrane Library (Cochrane Database of Systematic Reviews), PubMed. Die Recherche nach grauer Literatur umfasste eine gezielte, iterative Handsuche auf den Internetseiten von Leitlinienorganisationen. Ergänzend wurde eine freie Internetsuche (*https://www.google.com/*) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt.

Der Suchzeitraum wurde auf die letzten fünf Jahre eingeschränkt und die Recherche am 26.06.2022 abgeschlossen. Die detaillierte Darstellung der Recherchestrategie inkl. verwendeter Suchfilter sowie eine Angabe durchsuchter Leitlinienorganisationen ist am Ende der Synopse aufgeführt. Mit Hilfe von EndNote wurden Dubletten identifiziert und entfernt. Die Recherche ergab 1.263 Referenzen.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Referenzen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt 8 Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Hemmingsen B et al., 2021 [3].

(Ultra-)long-acting insulin analogues for people with type 1 diabetes mellitus

Fragestellung

To compare the effects of long-term treatment with (ultra-)long-acting insulin analogues to NPH insulin (neutral protamine Hagedorn) or another (ultra-)long-acting insulin analogue in people with type 1 diabetes mellitus.

Methodik

Population:

- Non-pregnant people withT1DM.

Intervention/Komparator:

- Long-acting insulin analogue or its biosimilar insulin versus human NPH insulin.
- Ultra-long-acting insulin analogue or its biosimilar insulin versus human NPH insulin.
- (Ultra-)long-acting insulin analogue versus another (ultra-)long-acting insulin analogue.

Endpunkte:

- Primary outcomes: All-cause mortality, Health-related quality of life, Severe hypoglycaemia
- Secondary outcomes: Cardiovascular mortality, Non-fatal myocardial infarction, Non-fatal stroke, End-stage renal disease, Blindness, Serious adverse events, Diabetic ketoacidosis, Non-serious adverse events, Nocturnal hypoglycaemia, Mild/moderate hypoglycaemia, Socioeconomic effects, HbA1c levels, Combined HbA1c levels and severe hypoglycaemia

Recherche/Suchzeitraum:

- Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies Online (CRSO) (searched 24 August 2020);
- MEDLINE (Ovid MEDLINE ALL 1946 to Daily Update) (searched 24 August 2020);
- ClinicalTrials.gov (searched 24 August 2020);
- World Health Organization International Clinical Trials Registry Platform (ICTRP) (searched 24 August 2020);
- HTA database (searched 24 August 2020).

Qualitätsbewertung der Studien:

- Cochrane 'Risk of bias 2' (RoB 2) tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 26 studies; A total of 8784 participants were randomised: 2428 participants were randomised to NPH insulin, 2889 participants to insulin detemir, 2095 participants to insulin glargine and 1372 participants to insulin degludec.
- Vergleiche:
  - Nine studies compared insulin detemir with NPH insulin (Bartley 2008; Kobayashi 2007; NCT00595374; NCT00605137; Robertson 2007; Russell-Jones 2004; Standl 2004; Thalange 2013; Vague 2003).
  - Nine studies compared insulin glargine with NPH insulin (Bolli 2009; Chase 2008; Fulcher 2005; Home 2005; Liu 2016; Porcellati 2004; PRESCHOOL; Ratner 2000; Schober 2002).
  - Two studies compared insulin detemir with insulin glargine (Heller 2009; Pieber 2007)
  - and two studies compared insulin degludec with insulin detemir (BEGIN Young; Davies 2014).
  - Finally, four studies compared insulin degludec with insulin glargine (BEGIN Basal-Bolus Type 1; BEGIN Flex T1; SWITCH 1; Urakami 2017).

Charakteristika der Population:

- Eight of the studies included children and randomised 1835 participants, i.e. 21% of all participants. The remaining studies included adults.
- Two studies had a cross-over design (SWITCH 1; Urakami 2017). The remaining studies were parallel-group RCTs. All studies had an open-label design, except for one which was double-blinded (SWITCH 1). The duration of the intervention ranged from 24 weeks to 24 months. Seven studies had an additional extension period.
- Twenty-three studies reported the ethnicity of the participants: 19 studies included mainly white peopleone study mainly Asian people (Davies 2014) and three studies included Asian people only.
- All studies included both genders. The age of the participants varied from 4.2 to 44 years. The duration of T1DM varied from 2.1 to 23.2 years

Qualität der Studien:

- Siehe Cochrane Review: Risk of bias assessments for each outcome are located in the risk of bias table section after the characteristics of studies awaiting assessment and at the side of forest plots

Studienergebnisse:

Insulin detemir vs NPH insulin

SUMMARY OF FINDINGS

Summary of findings 1. Summary of findings: insulin detemir versus NPH insulin

Insulin detemir compared with NPH insulin for T1DM

Patients: people with T1DM

Settings: outpatients

Intervention: insulin detemir

Comparison: NPH insulin

Outcomes	NPH insulin	Insulin detemir	Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
All-cause mortality Follow-up: 24-104 weeks	See comment		**Peto OR 4.97** (0.79 to 31.38)	3334 (9)	⊕⊕⊕⊖ **moderate**[a]	All 5 deaths reported in 2 studies including adults occurred in the insulin detemir group
Health-related quality of life Description: diabetes health profile; insulin therapy-related quality of life at night (scale not specified) Follow-up: 26-48 weeks	See comment			870 (3)	⊕⊕⊖⊖ **low**[b]	No study reported health-related quality of life in a format making it suitable for meta-analysis 1 study including adults reported higher scores in the insulin detemir group vs the NPH insulin group (Kobayashi 2007) 2 studies did not show evidence of a difference between intervention groups (NCT00595374 included children; Standl 2004 included adults)
Severe hypoglycaemia (n/N) Definition: hypoglycaemia requiring third party assistance (Bartley 2008; Kobayashi 2007; NCT00605137; Robertson 2007; Russell-Jones 2004; Standl 2004; Thalange 2013; Vague 2003); episodes where the children were semi-conscious, unconscious or in a coma, with or without convulsions (Thalange 2013) Follow-up: 24-104 weeks	**115 per 1000**	**79 per 1000** (60 to 106)	**RR 0.69** (0.52 to 0.92)	3219 (8)	⊕⊕⊕⊖ **moderate**[c]	The 95% prediction interval ranged between 0.34 and 1.39 5 studies included adults, 3 studies included children (the test for subgroup differences did not indicate interaction)
Non-fatal myocardial infarction/stroke Definition: myocardial infarction Follow-up: 24 months	See comment			495 (1)	⊕⊕⊖⊖ **low**[d]	1/331 participants in the insulin detemir group vs 0/164 participants in the NPH insulin group experienced a non-fatal myocardial infarction (Bartley 2008) Stroke was not reported Study included adults
Severe nocturnal hypoglycaemia (n/N) Definition: severe hypoglycaemia occurring 23:00-06:00 (Bartley 2008; NCT00605137; Russell-Jones 2004; Standl 2004; Vague 2003); occurring 22:00-07:00 (Robertson 2007; Thalange 2013) Follow-up: 24 weeks - 24 months	**54 per 1000**	**36 per 1000** (21 to 64)	**RR 0.67** (0.39 to 1.17)	2925 (7)	⊕⊕⊕⊖ **moderate**[e]	The 95% prediction interval ranged between 0.16 and 2.87 4 studies included adults, 3 studies included children (the test for subgroup differences did not indicate interaction)
Serious adverse events (n/N) Follow-up: 24-104 weeks	**82 per 1000**	**78 per 1000** (62 to 100)	**RR 0.95** (0.75 to 1.21)	3332 (9)	⊕⊕⊕⊖ **moderate**[e]	The 95% prediction interval ranged between 0.71 and 1.27 6 studies included adults, 3 studies included children (the test for subgroup differences did not indicate interaction)
HbA1c (%) Follow-up: 24 weeks - 24 months	The mean HbA1c ranged across the NPH insulin groups from 7.3% to 8.6%	The mean HbA1c in the insulin detemir groups was **0.01% higher** (0.1% lower to 0.1% higher)	—	3122 (8)	⊕⊕⊕⊖ **moderate**[e]	The 95% prediction interval ranged between -0.1% and 0.1% 5 studies included adults, 3 studies included children (the test for subgroup differences did not indicate interaction)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **CSR:** clinical study report; **HbA1c:** glycosylated haemoglobin A1c; **n/N:** number of people experiencing an event; **NPH:** neutral protamine Hagedorn; **OR:** odds ratio **RR:** risk ratio; **T1DM:** type 1 diabetes mellitus.

Insulin glargine vs NPH insulin

Summary of findings 2. Summary of findings: insulin glargine versus NPH insulin

Insulin glargine compared with NPH insulin for T1DM

Patients: people with T1DM

Settings: outpatients

Intervention: insulin glargine

Comparison: NPH insulin

Outcomes	NPH insulin	Insulin glargine	Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
All-cause mortality Follow-up: 24-52 weeks	See comment		**Peto OR 0.14** (0.00 to 6.98)	2175 (8)	⊕⊕⊕⊖ **moderate**[a]	1 study including adults reported 0/1207 participants died in the insulin glargine group vs 1/1068 participants in the NPH insulin group 4 studies included adults, 4 studies included children (the test for subgroup differences could not be performed)
Health-related quality of life Scales: Well-Being Enquiry for Diabetics; General Well-being; Diabetes Quality of Life for Youth and Parents' Diabetes Quality of Life Follow-up: 24-28 weeks	See comment			1013 (4)	⊕⊕⊖⊖ **low**[b]	1 study including adults (Bolli 2009) reported greater improvements in the insulin glargine group compared with NPH insulin in one domain (diabetes-related worries) There was no evidence of a difference in 3 studies (Chase 2008 included children; Home 2005 and Ratner 2000 included adults)
Severe hypoglycaemia (n/N) Definition: symptomatic hypoglycaemia requiring third party assistance, with either a blood glucose level < 2.8 mmol/L or prompt recovery after administration of oral carbohydrate, iv glucose or glucagon (Fulcher 2005; Home 2005; Schober 2002); requiring third party assistance and associated with either blood glucose < 2.0 mmol/L or prompt recovery after oral carbohydrate, iv glucose, or intramuscular or subcutaneous glucagon administration (Chase 2008); hypoglycaemia requiring third party assistance or involving a seizure, coma, unconsciousness or the use of glucagon (Liu 2016); hypoglycaemia requiring third party assistance (Porcellati 2004; PRESCHOOL; Ratner 2000) Follow-up: 24-52 weeks	**125 per 1000**	**105 per 1000** (84 to 130)	**RR 0.84** (0.67 to 1.04)	2350 (9)	⊕⊕⊕⊖ **moderate**[c]	The 95% prediction interval ranged between 0.65 and 1.09 5 studies included adults, 4 studies included children (the test for subgroup differences did not indicate interaction)
Non-fatal myocardial infarction/stroke Definition: myocardial infarction/cerebral ischaemia Follow-up: 28 weeks	See comment			585 (1)	⊕⊕⊖⊖ **low**[d]	No participant experienced a non-fatal myocardial infarction 1 study including adults reported 0/292 participants in the insulin glargine group vs 1/293 participants in the NPH insulin group experienced cerebral ischaemia (Home 2005)
Severe nocturnal hypoglycaemia (n/N)	**87 per 1000**	**72 per 1000** (54 to 97)	**RR 0.83** (0.62 to 1.12)	1893 (6)	⊕⊕⊕⊖ **moderate**[c]	The 95% prediction interval ranged between 0.54 and 1.27

Definition: severe hypoglycaemia occurring 23:00-07:00 (PRESCHOOL); severe hypoglycaemia occurring after the evening insulin injection and before the morning insulin dose (Fulcher 2005); severe hypoglycaemia occurring during sleep between bedtime and rising in the morning, or before the morning pre-breakfast self-blood glucose measurement and the morning insulin injection (Home 2005); severe hypoglycaemia occurring while asleep after the bedtime insulin dose and before the morning insulin dose and before the morning blood glucose measurement (Ratner 2000); severe hypoglycaemia while the participant was sleeping between bedtime and after the evening injection and before getting up in the morning (Schober 2002); severe hypoglycaemia occurring 00:00-06:00 (Chase 2008) Follow-up: 24-28 weeks						3 studies included adults, 3 studies included children (the test for subgroup differences did not indicate interaction)
Serious adverse events (n/N) Follow-up: 24-30 weeks	**100 per 1000**	**108 per 1000** (63 to 184)	**RR 1.08** (0.63 to 1.84)	2229 (8)	⊕⊕⊕⊖ **moderate**[c]	The 95% prediction interval ranged between 0.22 and 5.21 4 studies included adults, 4 studies included children (the test for subgroup differences did not indicate interaction)
HbA1c (%) Follow-up: 24 weeks - 1 year	The mean HbA1c ranged across the NPH insulin groups from 7.1% to 7.3%	The mean HbA1c in the insulin glargine groups was **0.02% higher** (0.1% lower to 0.1% higher)	—	2285 (9)	⊕⊕⊕⊖ **moderate**[c]	The 95% prediction interval ranged between -0.5% and 0.5% 5 studies included adults, 4 studies included children (the test for subgroup differences did not indicate interaction)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
a.m.: ante meridiem; **CI**: confidence interval; **HbA1c**: glycosylated haemoglobin A1c; **iv**: intravenous; **n/N**: number of people experiencing an event; **NPH**: neutral protamine Hagedorn; **RR**: risk ratio; **T1DM**: type 1 diabetes mellitus.

Insulin detemir vs insulin glargine

Summary of findings 3. Summary of findings: insulin detemir versus insulin glargine

Insulin detemir compared with insulin glargine for T1DM

Patients: people with T1DM

Settings: outpatients

Intervention: insulin detemir

Comparison: insulin glargine

Outcomes	Insulin glargine	Insulin detemir	Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
All-cause mortality Follow-up: 26 and 52 weeks	See comment			763 (2)	⊕⊕⊖⊖ **low**[a]	No participant died 2 studies included adults
Health-related quality of life	**Not reported**					
Severe hypoglycaemia (n/N) Definition: hypoglycaemia requiring third party assistance Follow-up: 26 and 52 weeks	**116 per 1000**	**68 per 1000** (15 to 304)	**RR 0.59** (0.13 to 2.63)	763 (2)	⊕⊖⊖⊖ **very low**[b]	2 studies included adults
Non-fatal myocardial infarction/stroke	See comment			443 (1)	⊕⊕⊖⊖ **low**[a]	1 study including adults reported 1/299 participants in the insulin detemir group vs 1/144 participants in

Definition: non-fatal myocardial infarction/stroke Follow-up: 52 weeks						the insulin glargine group experienced a non-fatal myocardial infarction One study including adults reported 2/299 participants in the insulin detemir group vs 0/144 participants in the insulin glargine group experienced a non-fatal stroke
Severe nocturnal hypoglycaemia (n/N) Definition: severe hypoglycaemia occurring from 11 p.m. to 6 a.m. Follow-up: 26 and 52 weeks	**50 per 1000**	**27 per 1000** (3 to 253)	**RR 0.55** (0.06 to 5.12)	763 (2)	⊕⊝⊝⊝ **very low**[b]	2 studies included adults
Serious adverse events (n/N) Follow-up: 26 and 52 weeks	**59 per 1000**	**102 per 1000** (54 to 195)	**RR 1.72** (0.91 to 3.28)	763 (2)	⊕⊕⊝⊝ **low**[c]	The fixed-effect statistical model showed an RR of 1.79 (1.04 to 3.08) in favour of insulin glargine 2 studies included adults
HbA1c (%) Follow-up: 26 and 52 weeks	The mean HbA1c ranged across the insulin glargine groups from 7.6% to 8.2%	The mean HbA1c in the insulin detemir groups was **0.01% lower** (0.1% lower to 0.1% higher)	—	763 (2)	⊕⊕⊝⊝ **low**[c]	2 studies included adults

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
a.m.: ante meridiem; **CI:** confidence interval; **HbA1c**: glycosylated haemoglobin A1c; **n/N**: number of people experiencing an event; **p.m.**: post meridiem; **RR:** risk ratio; **T1DM**: type 1 diabetes mellitus.

Insulin degludec vs insulin detemir

Summary of findings 4. Summary of findings: insulin degludec versus insulin detemir

Insulin degludec compared with insulin detemir for T1DM

Patients people with T1DM

Settings: outpatients

Intervention: insulin degludec

Comparison: insulin detemir

Outcomes	Insulin detemir	Insulin degludec	Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
All-cause mortality Follow-up: 26 weeks	See comment			802 (2)	⊕⊕⊝⊝ **low**[a]	No participant died 1 study included adults, 1 study included children
Health-related quality of life Scale: Short-Form 36 version 2 (higher values mean better health-related quality of life) Follow-up: 26 weeks	**Physical health score**: the mean score in the insulin detemir group was 52.5 **Mental health score**: the mean score in the insulin detemir group was 52.5	**Physical health score**: the mean score in the insulin degludec group was **0.60 points lower** (1.83 points lower to 0.63 points higher) **Mental health score**: the mean score in the insulin degludec group was **3.00 points lower** (4.44 points lower to 1.56 points lower)	—	454 (1)	⊕⊕⊝⊝ **low**[b]	Physical health score: MID is 2-3 points Mental health score: MID is 3 points Study included adults
Severe hypoglycaemia (n/N) Definition: hypoglycaemia requiring third party assistance (Davies 2014) or altered mental status and	**122 per 1000**	**143 per 1000** (99 to 207)	**RR 1.17** (0.81 to 1.69)	802 (2)	⊕⊕⊝⊝ **low**[c]	1 study included adults, 1 study included children (the test for subgroup differences did not indicate interaction)

cannot assist in their own care, is semiconscious or unconscious, or in a coma ± convulsions and may require parenteral therapy (glucagon or iv glucose) (BEGIN Young) Follow-up: 26 weeks						
Non-fatal myocardial infarction/stroke Definition: non-fatal myocardial infarction/stroke Follow-up: 26 weeks	See comment			453 (1)	⊕⊕⊖⊖ **low**[a]	No participant experienced a non-fatal myocardial infarction or stroke Study included adults
Severe nocturnal hypoglycaemia (n/N) Definition: severe hypoglycaemia occurring 00:01-05:59 (Davies 2014) or 23:00-07:00 (BEGIN Young) Follow-up: 26 weeks	**31 per 1000**	**34 per 1000** (16 to 75)	**RR 1.12** (0.51 to 2.46)	802 (2)	⊕⊕⊖⊖ **low**[c]	1 study included children, 1 study included adults (the test for subgroup differences did not indicate interaction)
Serious adverse events (n/N) Follow-up: 26 weeks	**73 per 1000**	**92 per 1000** (56 to 150)	**RR 1.25** (0.76 to 2.05)	802 (2)	⊕⊕⊖⊖ **low**[c]	1 study included children, 1 study included adults (the test for subgroup differences did not indicate interaction)
HbA1c (%) Follow-up: 26 weeks	The mean HbA1c in the insulin glargine groups was 7.3%	The mean HbA1c in the insulin detemir groups was **0.05% lower** (0.1% lower to 0.2% higher)	—	802 (2)	⊕⊕⊖⊖ **low**[c]	1 study included children, 1 study included adults (the test for subgroup differences did not indicate interaction)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
a.m.: ante meridiem; **CI:** confidence interval; **HbA1c**: glycosylated haemoglobin A1c; **iv**: intravenous; **MID:** minimal important difference; **n/N**: number of people experiencing an event; **p.m.**: post meridiem; **RR:** risk ratio; **T1DM**: type 1 diabetes mellitus.

Insulin degludec vs insulin glargine

Summary of findings 5. Summary of findings: insulin degludec versus insulin glargine

Insulin degludec compared with insulin glargine for T1DM

Patients: people with T1DM

Settings: outpatients

Intervention: insulin degludec

Comparison: insulin glargine

Outcomes	Insulin glargine	Insulin degludec	Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
All-cause mortality Follow-up: 26 - 52 weeks	**3 per 1000**	**4 per 1000** (0 to 36)	**Peto OR 1.34** (0.15 to 11.93)	973 (3)	⊕⊖⊖⊖ **very low**[a]	A total of 3/646 participants in the insulin degludec group vs 1/327 participants in the insulin glargine group died 2 studies included adults 1 study included children
Health-related quality of life Scale: Short-Form 36 version 2 (higher values mean better health-related quality of life) Follow-up: 32 and 52 weeks	**Physical health score**: the mean score ranged across the insulin glargine groups from 50.6 to 51.8 **Mental health score**: the mean score ranged across the insulin glargine	**Physical health score**: the mean score in the insulin degludec groups was **0.04 points lower** (1.21 points lower to 1.13 points higher) **Mental health score**: the mean score in the insulin degludec groups was **0.09**	—	1042 (2)	⊕⊖⊖⊖ **very low**[b]	Physical health score: MID is 2-3 points Mental health score: MID is 3 points 2 studies included adults

	groups from 49.9 to 50.4	**points lower** (1.03 points lower to 0.85 points higher)				
Severe hypoglycaemia (n/N) Definition: hypoglycaemia requiring third party assistance (BEGIN Flex T1; BEGIN Young) or an event associated with impaired consciousness or seizure (Urakami 2017) Follow-up: 24 and 52 weeks	**102 per 1000**	**124 per 1000** (83 to 185)	**RR 1.22** (0.82 to 1.82)	970 (3)	⊕⊕⊙⊙ **low**[c]	2 studies included adults 1 study including children reported no child experienced severe hypoglycaemia (Urakami 2017)
Non-fatal myocardial infarction/stroke Definition: non-fatal myocardial infarction/cerebral ischaemia Follow-up: 24 and 52 weeks	See comment			970 (3)/970 (3)	⊕⊕⊙⊙ **low**[d]	2 studies including adults reported 1/637 participants in the insulin degludec group vs 0/315 participants in the insulin glargine group experienced a non-fatal myocardial infarction; there were no events in 1 study including children (Urakami 2017) 2 studies including adults reported 1/637 participants in the insulin degludec group vs 0/315 in the insulin glargine group experienced cerebral ischaemia; there were no events in 1 study including children (Urakami 2017)
Severe nocturnal hypoglycaemia (n/N) Definition: severe hypoglycaemia occurring from 22:00 to 06:59 h Follow-up: 24 - 52 weeks	**25 per 1000**	**35 per 1000** (15 to 83)	**RR 1.39** (0.59 to 3.27)	970 (3)	⊕⊕⊙⊙ **low**[c]	2 studies included adults 1 study include children
Serious adverse events (n/N) Follow-up: 24 and 52 weeks	**77 per 1000**	**71 per 1000** (45 to 113)	**RR 0.92** (0.58 to 1.46)	970 (3)	⊕⊕⊙⊙ **low**[c]	2 studies included adults 1 study including children reported no child experienced a serious adverse event (Urakami 2017)
HbA1c (%) Follow-up: 24 and 52 weeks	The mean HbA1c ranged across the insulin glargine groups from 6.9% to 7.8%	The mean HbA1c in the insulin degludec groups was **0.1% higher** (0% lower to 0.2% higher)	—	1388 (4)	⊕⊕⊙⊙ **low**[c]	The 95% prediction interval ranged between -0.1% and 0.3% 3 studies included adults, 1 study included children (the test for subgroup differences did not indicate interaction)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **CSR:** clinical study report; **HbA1c**: glycosylated haemoglobin A1c; **MID:** minimal important difference; **n/N**: number of people experiencing an event; **OR**: odds ratio; **RR:** risk ratio; **T1DM**: type 1 diabetes mellitus:

Anmerkung/Fazit der Autoren

There was moderate-certainty evidence comparing insulin detemir with NPH insulin for T1DM showing a lower risk of severe hypoglycaemia in favour of insulin detemir. However, the 95% prediction interval indicated inconsistency of this result. Insulin detemir or insulin glargine compared with NPH insulin did not show benefits or harms for severe nocturnal hypoglycaemia. For all other main outcomes, with overall low risk of bias and comparing insulin analogues with each other, there were no clear differences. Data on patient-important outcomes such as health-related quality of life, macrovascular and microvascular diabetic complications were sparse or missing.

Comparing the insulin analogues detemir and glargine with NPH insulin, we are moderately confident about the results for all-cause mortality, severe (nocturnal) hypoglycaemia, SAEs and HbA1c. We are uncertain about the effects on non-fatal myocardial infarction, non-fatal stroke and health-related quality of life, mainly because data were sparse or there were only a few studies which did not last long enough to investigate these outcomes.

3.2 Systematische Reviews

Rezaei S et al., 2022 [5].

Efficacy and safety of insulin detemir versus glargine in patients with diabetes: a systematic review and meta-analysis

Fragestellung

The objective of the current study is to compare the safety and efficacy of insulin glargine and insulin detemir in adults with DM1 and DM2 based on available evidence from RCTs.

Methodik

Population:

- patients diagnosed with DM1 or DM2

Intervention:

- insulin detemir

Komparator:

- insulin glargine

Endpunkte:

- efficacy outcomes namely HbA1c and FPG levels; and safety outcomes including weight gain and hypoglycemia (overall hypoglycemia, nocturnal hypoglycemia, and severe hypoglycemia).

Recherche/Suchzeitraum:

- PubMed, Embase, Scopus, and Cochrane Central Register of Controlled Trials (CENTRAL) up to 18 August 2021

Qualitätsbewertung der Studien:

- JADAD Scale (Oxford quality scoring system) and the Cochrane risk-of-bias tool for randomized trials (RoB 2).

Ergebnisse

Anzahl eingeschlossener Studien:

- Finally, we included 12 RCTs for this systematic review and meta-analysis
- 9 studies in patients with DM2, 3 studies in patients with DM1
- 841 DM1 patients, of which 504 received insulin detemir and 337 received insulin glargine.

Charakteristika der Population:

- In the DM1 studies, the mean age of patients was 43.67 ± 10.20 years, 56.40% were male, and the mean duration of follow-up was 35.33 ± 16.17 weeks.

Table 1. Characteristics of the included studies.

Study	Type of diabetes	Country	Age, years, mean (SD)	Male, n (%)	Mean duration of follow-up, weeks
Meneghini et al., 2020 [20]	2	USA	59.2 (10.9)	1826(55.3)	26
Elisha et al., 2016 [21]	2	Canada	59.7 (2.7)	24 (66.7)	26
Meneghini et al., 2013 [22]	2	USA	57.3 (10.3)	113(56.5)	26
Swinnen et al., 2010 [23]	2	Netherland	58.4 (8.3)	532 (54.7)	24
Raskin et al., 2009 [24]	2	USA	55.8 (10.3)	210 (54.5)	26
Fadini et al., 2011 [25]	2	Italy	66.2 (1.8)	34 (79.1)	26
Rosenstock et al., 2008 [26]	2	UK	58.9 (9.9)	337 (57.9)	26
Hollander et al., 2008 [27]	2	UK	58.5 (11.0)	185 (58.0)	52
Bhosle et al., 2014 [28]	2	India	54.6 (7.7)	28 (70.0)	24
Renard et al., 2011 [29]	1	France	46.8 (13.7)	54 (61.4)	16
Heller et al., 2009 [30]	1	UK	42 (12.0)	248(56.0)	52
Pieber et al., 2007 [31]	1	Germany	40.46 (14.8)	164(51.3)	26

Qualität der Studien:

- Siehe Studienergebnisse für HbA1c (forest plots)

Studienergebnisse:

*Hinweis FBMed: Es werden lediglich Ergebnisse für DM1 Patient*innen dargestellt.*

HbA1c

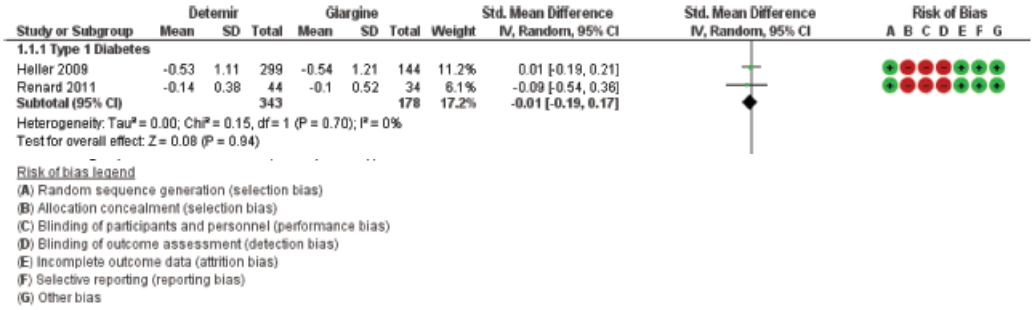


Figure 2. Forest plot of pooled SMD of HbA1c, comparing detemir vs. glargine. SMD, standardized mean difference.

Hypoglycemia

- The pooled RRs of hypoglycemic events were 1.00 (95% CI 0.97 to 1.04; P = 0.78; I2 = 0%). Based on two trials in DM1 patients (involving 763 patients).
- one trial in DM1 patients (involving 320 patients) compared the risk of nocturnal hypoglycemia: The pooled RRs were 0.94 (95% CI 0.75 to 1.17; P = 0.58; I2 = not applicable)
- two trials in DM1 patients (involving 398 patients) compared the risk of severe hypoglycemia: The pooled RRs were 0.28 (95% CI 0.12 to 0.63; P = 0.002; I2 = 0%)

Anmerkung/Fazit der Autoren

Our meta-analysis study shows that insulin detemir and insulin glargine provide similar glycemic control in diabetic patients. We found no statistically significant differences in HbA1c and FPG values between the two insulin treatment groups. Similarly, we observed a not statistically significant difference in the overall incidence of hypoglycemia in DM1 and DM2 patients. The only statistically significant differences between groups were in the weight change in DM2 (P = 0.01) and severe hypoglycemia in DM1 (P = 0.002) variables. According to the results of our sensitivity analysis, DM2 patients achieved the same glycemic control on insulin detemir with less weight gain compared with those on insulin glargine. Collectively, our study suggests that there is no clinically considerable difference in the safety and efficacy outcomes between the two long-acting insulin analogs of detemir and glargine based on the available RCTs.

Yang Y et al., 2022 [8].

Insulin Degludec Versus Insulin Glargine on Glycemic Variability in Diabetic Patients: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Fragestellung

This study aimed to determine whether insulin degludec (IDeg) or insulin glargine (IGla) was more beneficial for reducing glycemic fluctuations.

Methodik

Population:

- All diabetic patients were included, irrespective of the types of diabetes mellitus;

Intervention/Komparator:

- IDeg versus IGla

Endpunkte:

- standard deviation of blood glucose (SDBG), mean amplitude of glycemic excursions (MAGE), mean blood glucose (MBG), time in the range (TIR), mean of daily differences (MODD), the coefficient of variation (CV), area under the glucose curve (AUC), and Mvalue;

Recherche/Suchzeitraum:

- Eight common databases were searched from their inception to 30 November 2021, specifically including the Cochrane Library, PubMed, Embase, Web of Science, Chinese Biomedical Literature Database (CBM), Chinese National Knowledge Infrastructure (CNKI), VIP database, and Wanfang database. Besides, Clinical Trials (ClinicalTrials.gov), unpublished gray literature, and references cited in the eligible studies were also searched.

Qualitätsbewertung der Studien:

- The Cochrane Collaboration tool was used to assess the risk of bias

Ergebnisse

Anzahl eingeschlossener Studien:

- 14 studies involving 8,683 patients were included in this research.

Charakteristika der Population:

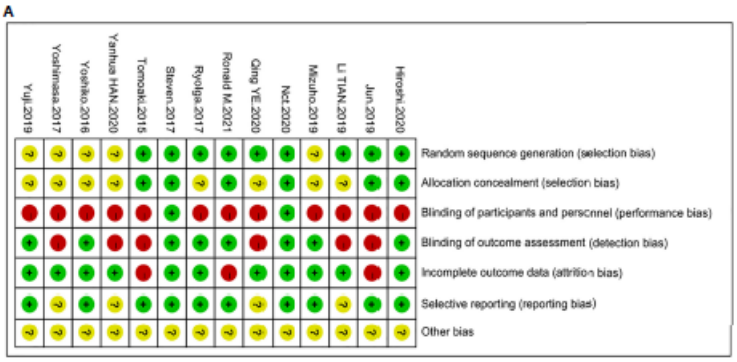
TABLE 1 | Baseline characteristics of included studies.

First author and year	Design	Country	Follow-up	Patients	Male (%)	Total cases	Sample size		Treatment		Age (years)		Disease duration (years)		HbA1c (%)		Outcomes
							IDeg	IGla	Group1	Group2	IDeg	IGla	IDeg	IGla	IDeg	IGla	
Yoshiko, 2016 (13)	RCT, C	Japan	8 weeks	T1DM	54%	13	13☆	13☆	IDeg★	IGla▲	44.9 (7.2)	44.9 (7.2)	15.5 (7.0)	15.5 (7.0)	7.8 (0.54)	7.9 (0.54)	①②④
Ryolga, 2017 (18)	RCT,O,C	Japan	24 weeks	T1DM	55%	20	10	10	IAsp + IDeg★	IAsp + IGla▲	54 (16)	54 (16)	16 (8)	16 (8)	7.1 (0.9)	7.7 (0.6)	②⑤⑦
Yuji, 2019 (28)	RCT,O,C	Japan	10 days	T2DM	60%	30	15	15	IDeg★	IGla300	69.5 (11.3)	69.5 (11.3)	18.3 (11.3)	18.3 (11.3)	8.0 (1.5)	8.5 (2.2)	①②③④⑤⑥⑧
Tomoaki, 2015 (17)	RCT,O,M,C	Japan	8 weeks	T1DM	41%	36	17	19	IDeg★	IGla▲	57 (14)	57 (14)	18 (10)	18 (10)	7.4 (0.8)	7.4 (0.8)	①②
Yoshimasa, 2017 (19)	RCT,O,M,P	Japan	24 weeks	T2DM	45%	43	31	12	IDeg★	IGla▲	64.0 (13.6)	64.7 (15.7)	10 (3.5)	14.5 (5.27)	8.88 (1.48)	8.84 (1.46)	⑥
Hiroshi, 2020 (27)	RCT,M,C	Japan	4 weeks	T1DM	30%	46	23	23	IDeg★	IGla300	53.3 (14.7)	53.3 (14.7)	19.4 (11.6)	19.4 (11.6)	7.6 (0.7)	7.6 (0.7)	①②③④⑤⑥⑧
Jun, 2019 (14)	RCT,O,P	Japan	12 days	T2DM	51%	74	36	38	IDeg100	IGla100	58.9 (10.5)	61.8 (9.4)	3.9 (4.6)	6.6 (8.2)	11.3 (1.4)	10.4 (1.9)	①②③④⑥
Yan.Han, 2020 (31)	RCT,P	China	NR	T2DM	58%	64	32	32	IAsp + IDeg★	IAsp + IGla▲	52.38 (6.29)	52.54 (6.07)	10.34 (1.25)	10.29 (1.54)	9.12 (1.46)	9.07 (1.34)	②⑤
LiTian, 2019 (30)	RCT,P	China	NR	T2DM	67%	86	43	43	IAsp+ IDeg300	IAsp + IGla300	53.3 (8.8)	53.9 (8.5)	NR	NR	11.2 (1.8)	11.4 (1.7)	⑤
Qing, 2020 (29)	RCT,P	China	NR	T2DM	59%	100	30	70	IAsp + IDeg300	IAsp + IGla300	57.96 (8.35)	58.74 (8.41)	4.23 (1.05)	4.12 (1.03)	11.29 (1.74)	11.25 (1.85)	⑤
Ronald, 2021 (26)	RCT,O,M,C	Canada	41 weeks	T2DM	48%	498	249	249	IDeg100	IGla100	62.9 (10.0)	62.7 (9.7)	14.5 (7.0)	15.6 (8.3)	7.6 (1.0)	7.6 (1.0)	⑤
Nct, 2020 (25)	RCT,C	Mexico	6 days	T2DM	67%	12	6	6	IDeg★	IGla▲	44.1 (8.8)	44.1 (8.8)	NR	NR	8.2 (1.4)	8.2 (1.4)	③④
Steven, 2017 (33)	RCT,M,D,P	America	2 years	T2DM	63%	7637	3818	3819	IDeg★	IGla100	64.9 (7.3)	65.0 (7.5)	16.6 (8.8)	16.2 (8.9)	8.4 (1.6)	8.4 (1.7)	②
Mizuho, 2019 (32)	RCT,O,C	Japan	8 weeks	T2DM	50%	24	12	12	IDeg★	IGla300	71.9 (5.2)	69.5 (9.5)	16.5 (9.1)	11.6 (9.1)	6.83 (0.34)	6.78 (0.33)	①②③④⑦

Data are shown as numbers or means (standard deviation) unless otherwise stated.

☆The article did not report sample size of each group. Because it was a crossover study, all participants completed the experiment. So the values in each group are the total sample size; ★These studies did not report the type of insulin degludec; ▲These studies did not report the type of insulin glargine; NR, not report; RCT, randomized controlled trial; O, open-label; M, multicenter; C, crossover; P, parallel; D, double-blind; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; IDeg, insulin degludec; IGla, insulin glargine; IAsp, insulin aspart; IGla300, insulin glargine 300 U/ml; IDeg100, insulin degludec 100 U/ml; IDeg300, insulin degludec 300U/ml; IGla100, insulin glargine 100 U/ml; HbA1c, hemoglobin A1c; ①, SDBG (standard deviation of blood glucose); ②, MBG (mean blood glucose); ③, MAGE (mean amplitude of glycemic excursion); ④, AUC (area under the curve of glucose); ⑤, TIR (time in range); ⑥, CV (coefficient of variation); ⑦, MODD (mean of daily difference); ⑧, M-value.

Qualität der Studien:



Studienergebnisse:

*Hinweis FBMed: Es werden lediglich Ergebnisse für DM1 Patient*innen dargestellt. Es wurde sich auf drei Endpunkte fokussiert.*

Effect of Standard Deviation of Blood Glucose (SDBG)

- Two studies were conducted on patients with T1DM. One study (27) used IGla300 while the other did not specify the type of IGla (13). Patients in these two studies both had a baseline HbA1c of <9%. The pooled result did not show a significant difference between the two treatment groups (MD: 6.43, 95% CI −0.05 to 12.90, P = 0.05), with no heterogeneity (Phe = 0.49, I2 = 0%)

Effect of Mean Blood Glucose (MBG)

- Three studies (13, 18, 27) were undertaken in T1DM patients with a baseline HbA1c of <9%. One study (27) used IGla300, while the other two studies (13, 18) did not report the type of IGla they used. The overall result was similar between the two interventions (MD: 3.68, 95% CI −13.83 to 21.18, P = 0.68), showing no significant heterogeneity (Phe = 0.10, I2 = 57%)
- in the case of the mean of FBG, the meta-analysis of two trials (17, 18) with a baseline HbA1c of <9% in T1DM showed that IDeg was more effective than IGla, which was not unknown for the type (MD: −16.25, 95% CI −29.02 to −3.47, P = 0.01), with no heterogeneity (phe = 0.76, I2 = 0%)

Effect of Time in Range (TIR)

- Two studies with a baseline HbA1c of <9% were undertaken in T1DM. One (27) was compared to IGla300, and the other (18) was unknown for the type of IGla. No difference was observed in the pooled result (MD: −1.28, 95% CI −6.43 to 3.87, P = 0.63) and no heterogeneity was identified (Phe = 0.67, I2 = 0%)

Anmerkung/Fazit der Autoren

In people with T1DM, IDeg was related to a lower mean and SD in FBG compared to IGla. There was comparable efficacy between IDeg and IGla in MAGE, SDBG of 24 h, TIR, MBG of 24 h, CV, MODD, AUC, and M-value. In patients with T2DM, IDeg was associated with a lower mean of FBG versus IGla100. Concerning the CV of FBG, IDeg was also more stable than IGla. Moreover, IDeg achieved TIR longer than IGla100. However, compared with IGla300, IDeg showed similar efficacy in TIR. In terms of MAGE, SDBG, mean of 24 h, CV of 24 h, MODD, AUC, and M-value, there was comparable efficacy between IDeg and IGla.

In conclusion, IDeg was found to be superior to IGla in reducing fasting glucose variability in both T1DM and T2DM, but due to the limitations of the original study, it is still unclear whether IDeg is superior to both IGla100 and IGla300. Moreover, studies comparing the efficacy of IDeg and IGla in fasting glucose fluctuations are still needed. In T2DM, IDeg had a longer TIR than IGla100 but not longer than IGla300. For other indicators of blood glucose variation, including SD of 24 h, MAGE, MBG of 24 h, CV of 24 h, MODD, AUC, and M-value, no significant differences were identified between IDeg and IGla, regardless of T1DM or T2DM.

Tricco AC et al., 2021 [6].

Comparative Efficacy and Safety of Ultra-Long-Acting, Long-Acting, Intermediate-Acting, and Biosimilar Insulins for Type 1 Diabetes Mellitus: a Systematic Review and Network Meta-Analysis

Fragestellung

We aimed to update our prior systematic review including biosimilars to evaluate the comparative efficacy and safety of ultra-long-/long-/intermediate-acting insulin compared to each other and biosimilar insulin.

Methodik

Population:

- Adults (≥ 16 years of age) with T1DM for any duration of time,

Intervention:

- Ultra-long-/long-/intermediate-acting basal/ bolus type of insulin therapy, with basal (taken between meals) and bolus (taken at mealtime) administered separately. […] Bolus insulin included rapid- or short-acting insulin, while basal insulin included ultra-long, long- and intermediate-acting insulin.

Komparator:

- Ultra-long-/long-/intermediate-acting insulin, biosimilar insulin, no treatment

Endpunkte:

- Primary outcomes. *Efficacy*: glycemic control (glycated hemoglobin [A1c], FPG).
- Secondary outcomes. *Efficacy*: all-cause mortality, diabetes-related morbidity (macrovascular, microvascular), health-related quality of life. *Safety*: weight change, hypoglycemia (all-cause, serious, minor, nocturnal), incident cancer, total adverse events (AEs), serious AEs, dropouts due to AEs

Recherche/Suchzeitraum:

- MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) (inception until March 27, 2019)

Qualitätsbewertung der Studien:

- Cochrane ROB tool
- Cochrane EPOC ROB Tool

Ergebnisse

Anzahl eingeschlossener Studien:

- Sixty-five unique studies and 13 companion reports were included 27 and 37 studies were included in the basal insulin class and insulin class/origin/frequency analyses, respectively.

Charakteristika der Population:

- Across the included studies, sample sizes ranged from eight to 749, with a total of 14,200 patients. The proportion of females ranged from 0 to 100%, average age ranged from 23 to 54 years, average baseline A1c ranged from 7 to 10%, average body mass index (BMI) ranged from 22 to 28, and duration of T1DM ranged from 8 to 27 years

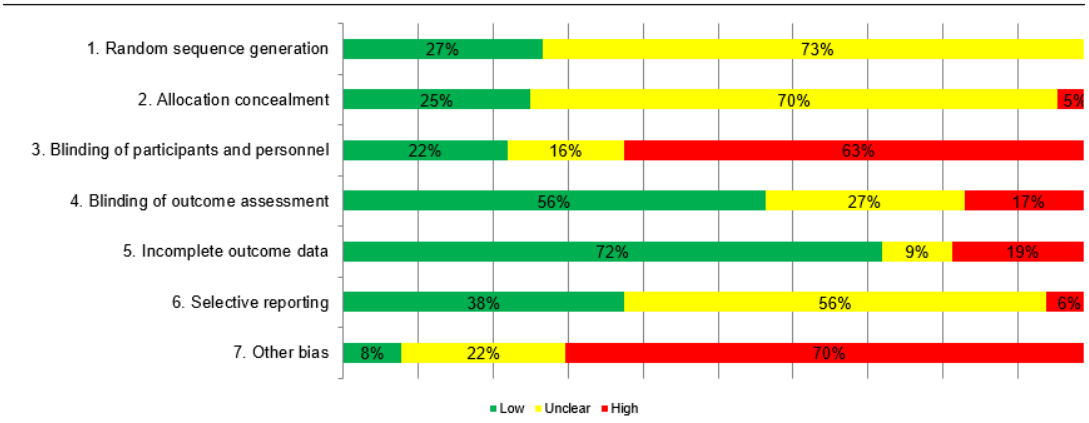
Table 2 Study, Patient, Intervention, and Outcome Characteristics

Characteristics	Number (% out of 65)
Study characteristics	
Setting	
Multi-national	23 (35.4)
Multicenter	14 (21.5)
Single center	17 (26.2)
NR/unclear	11 (16.9)
Continents	
Africa	6 (9.2)
Asia	6 (9.2)
Oceania	6 (9.2)
Europe	54 (83.1)
North America	12 (18.5)
South America	1 (1.5)
Study design	
RCTs	64 (98.5)
Parallel RCTs	41 (64.1)
Cross-over RCTs	23 (35.9)
Non-RCT	1 (1.5)
Year of publication (range)	1984 to 2018
Treatment period (range)	0.14 weeks to 104.36 weeks
Sample size (range)	8 to 749
Patient characteristics	
Mean % female (range)	40.0 (0 to 100)
Mean age, years (range)	38.4 (22.8 to 54.0)
Mean A1c, % (range)	8.0 (6.9 to 10.2)
Mean BMI, kg/m^2 (range)	24.9 (21.8 to 28.0)
Mean duration of T1DM, years (range)	16.0 (8.1 to 26.9)
Intervention characteristics	
Basal class (basal insulin origin), basal frequency	
Intermediate-acting (animal and human) [NPH], bid	1 (1.4)
Intermediate-acting (animal) [NPH], NR	1 (1.4)
Intermediate-acting (human) [NPH], NR	2 (2.9)
Intermediate-acting (animal) [NPH], od	1 (1.4)
Intermediate-acting (human) [NPH], od	13 (18.6)
Intermediate-acting (human) [NPH], bid	21 (30)
Intermediate-acting (human) [NPH], qid	2 (2.9)
Intermediate-acting (animal) [Lente], NR	1 (1.4)
Intermediate-acting (human) [Lente], NR	2 (2.9)
Intermediate-acting (animal) [Lente], bid	2 (2.9)
Intermediate-acting (human) [Lente], bid	3 (4.3)
Long-acting (human) [Detemir], od	15 (21.4)
Long-acting (human) [Detemir], bid	16 (22.9)
Long-acting (human) [Glargine], od	42 (60)
Long-acting (human) [Glargine], bid	2 (2.9)
Long-acting (biosimilar) [Glargine], od	6 (4.3)
Ultra-long-acting (human) [Degludec], od	17 (24.3)
Basal class	
Intermediate-acting	46 (70.8)
Long-acting	78 (120)
Ultra-long-acting	17 (26.2)
Basal insulin type	
NPH	38 (58.5)
Lente	8 (12.3)
Glargine	50 (76.9)
Detemir	28 (43.1)
Degludec	17 (26.2)
Outcome characteristics	
A1c	51 (72.9)
AEs	46 (65.7)
FPG	42 (60)
Hypoglycemia	61 (87.1)
LY	3 (4.3)
Mortality	17 (24.3)
QALY	5 (7.1)
Quality of life	10 (14.3)
Vascular complications	16 (22.9)
Weight change	58 (82.9)

Abbreviations: A1c, glycated hemoglobin; AEs, adverse events; bid, twice a day; BMI, body mass index; FPG, fasting plasma glucose; LY, life years; NPH, neutral protamine Hagedorn; NR, not reported; od, once a day; qid, four times a day; QALY, quality-adjusted life years; RCT, randomized controlled trial; T1DM, Type 1 diabetes mellitus

<u>Qualität der Studien:</u>

- A score of unclear/high ROB was given for the majority of RCTs regarding allocation concealment (75%), blinding of participants and personnel (78%), blinding of outcome assessment (44%), incomplete outcome data (28%), selective reporting (63%), and "other" bias (e.g., funding bias, 92%):



- A single nonrandomized controlled trial was assessed using the Cochrane EPOC ROB Tool, which scored unclear for 7/9 items and high ROB for random sequence generation and incomplete outcome data

<u>Studienergebnisse:</u>

Hinweis FBMed: Bei der Ergebnisextraktion wurde sich auf die Vergleiche zwischen Insulinklassen fokussiert.

Table 1 List of Basal Insulin Analogues Included in the Review

Insulin class	Insulin origin	Insulin class (Origin), frequency	Generic names	Brand names
Intermediate-acting	Animal	Intermediate-acting (animal), od Intermediate-acting (animal), bid Intermediate-acting (animal), NR	NPH (Isophane insulin); Lente (Zinc insulin)	Iletin II, Insulatard MC; Monotard MC
	Animal/ human	Intermediate-acting (animal and human), bid	NPH (isophane insulin)	-
	Human	Intermediate-acting (human), od Intermediate-acting (human), bid Intermediate-acting (human), qid Intermediate-acting (human), NR	NPH (Isophane insulin); Lente (Zinc insulin)	Humulin N, Novolin N, Protaphane HM; Novolin L, Humulin L, Monotard HM
Long-acting	Human	Long-acting (human), od Long-acting (human), bid	Detemir; Glargine	Levemir; Lantus
	Biosimilar	Long-acting (biosimilar), od	Glargine	Basaglar (or Abasaglar), LY2963016, MYL-1501D, Toujeo
Ultra-long-acting	Human	Ultra-long-acting (human), od	Degludec	Tresiba

Abbreviations: bid, twice a day; NPH, neutral protamine Hagedorn; NR, not reported; od, once a day; qid, four times a day

Table 4 Statistically significant treatment comparisons

Comparison description	NMA estimate (CI)
Basal insulin class analysis	
Primary efficacy outcome: A1c -# 8327 patients, # 3 treatment nodes, # 25 RCTs, # 1 treatment comparison	
Long-acting insulin vs. Intermediate-acting insulin	−0.14 (−0.22 to −0.06)
Primary efficacy outcome: Fasting plasma glucose - # 7685 patients, # 3 treatment nodes, # 21 RCTs, #2 treatment comparisons	
Long-acting insulin vs. Intermediate-acting insulin	−1.03 (−1.33 to −0.73)
Ultra-long-acting insulin vs. Intermediate-acting insulin	−1.45 (−2.12 to −0.79)
Secondary safety outcome: Weight change - # 5908 patients, # 3 treatment nodes, # 15 RCTs, # 1 treatment comparison	
Long-acting insulin vs. Intermediate-acting insulin	−0.70 (−1.08 to −0.32)
Secondary safety outcome: Major or serious hypoglycemic episodes - # 6900 patients, # 3 treatment nodes, # 16 RCTs, # 1 treatment comparison	
Long-acting insulin vs. Intermediate-acting insulin	0.63 (0.51 to 0.79)
Secondary safety outcome: Nocturnal hypoglycemic episodes - # 5423 patients, # 3 treatment nodes, # 13 RCTs, # 2 treatment comparisons	
Long-acting insulin vs. Intermediate-acting insulin	0.74 (0.58 to 0.94)
Ultra-long-acting insulin vs. Intermediate-acting insulin	0.64 (0.41 to 0.99)

Primary Outcomes.

A1c.

- For basal insulin class, NMA for the A1c outcome included 25 RCTs and 8327 patients.
- Longacting insulin had a greater A1c reduction compared to intermediate-acting insulin (MD - 0.14, 95% CI: - 0.22 to - 0.06).
- In addition, ultra-long-acting insulin had a greater A1c reduction compared to intermediate-acting insulin (MD - 0.08, 95% CI: - 0.25 to 0.10) but not long-acting insulin (MD 0.06, 95% CI: - 0.10 to 0.22).

Fasting Plasma Glucose (FPG).

- For basal insulin class, NMA for the FPG outcome included 21 RCTs, 7685 patients, and three treatment nodes.
- Long-acting insulin had a greater FPG reduction compared to intermediate-acting insulin (MD - 1.03, 95% CI: - 1.33 to - 0.73) and ultra-longacting insulin had a greater FPG reduction compared to intermediate-acting insulin (MD - 1.45, 95% CI: - 2.12 to - 0.79) and long-acting insulin (MD - 0.42, 95% CI: - 1.02 to 0.18)

Secondary Outcomes.

Weight Change.

- For basal insulin class, NMA was conducted on weight change with 15 RCTs, 5908 patients, and three treatment nodes.
- Long-acting insulin reduced weight gain compared to intermediate-acting insulin (MD - 0.70, 95% CI: - 1.08 to - 0.32).
- Ultra-long-acting insulin reduced weight gain compared to intermediate-acting insulin (MD - 0.53, 95% CI: - 1.25 to 0.18) but not long-acting insulin (MD 0.17, 95% CI: - 0.44 to 0.77).

- Four studies were removed in sensitivity analysis due to the potential for bias associated with smallstudy effects; ultra-long-acting insulin was statistically superior to intermediate-acting insulin (MD - 0.80, 95% CI: - 1.29 to - 0.32)

Major or Serious Hypoglycemia.

- For basal insulin class, NMA was conducted on the major or serious hypoglycemia outcome with 16 RCTs, 6900 patients, and three treatment nodes.
- Long-acting insulin was associated with a reduced incidence of major or serious hypoglycemic episodes compared to intermediate-acting insulin (OR 0.63, 95% CI: 0.51 to 0.79).
- Ultra-long-acting insulin reduced major or serious hypoglycemic episodes compared to intermediate-acting insulin (OR 0.71, 95% CI: 0.43 to 1.17) but not compared to long-acting insulin (OR 1.12, 95% CI: 0.71 to 1.77).

Nocturnal Hypoglycemia.

- For basal insulin class, NMA was conducted for nocturnal hypoglycemia with 13 RCTs, 5423 patients, and three treatment nodes.
- Long-acting insulin (OR 0.74, 95% CI: 0.58 to 0.94) and ultra-long-acting insulin (OR 0.64, 95% CI: 0.41 to 0.99) lowered the incidence of nocturnal hypoglycemic episodes compared to intermediate-acting insulin.
- In addition, ultra-long-acting insulin was associated with a lower risk of nocturnal hypoglycemic episodes compared to long-acting insulin (OR 0.86, 95% CI: 0.60 to 1.24).

Other Secondary Outcomes.

- No statistically significant results were found across treatment comparisons where NMA and or MA was done for the following outcomes: mortality, any vascular complications, microvascular complications, macrovascular complications, quality-of-life, all-cause hypoglycemia, minor or mild hypoglycemia, incident cancers, any AEs, serious AEs, and dropout due to AEs.

Anmerkung/Fazit der Autoren

In conclusion, ultra-long-acting and long-acting insulin were superior to intermediate-acting insulin. Furthermore, long-acting od is more effective than long-acting bid and ultra-long-acting od is more effective than long-acting bid for fasting blood glucose. For weight change, long-acting od was less effective than long-acting bid and long-acting bid was more effective than long-action biosimilar od.

Kommentare zum Review

- Es wurde eine nicht-randomisierte kontrollierte Studie eingeschlossen. Da nur 17 Personen in dieser Studie eingeschlossen wurden, wird das mögliche hieraus resultierende Verzerrungspotential als gering eingeschätzt.
- Bei der Ergebnisextraktion wurde sich auf die Vergleiche zwischen Insulinklassen fokussiert.

3.3 Leitlinien

National Institute for Health and Care Excellence (NICE), 2015 [4].

Type 1 diabetes in adults: diagnosis and management

Zielsetzung/Fragestellung

This guideline covers care and treatment for adults (aged 18 and over) with type 1 diabetes. It includes advice on diagnosis, education and support, blood glucose management, cardiovascular risk, and identifying and managing long-term complications.

Methodik

Grundlage der Leitlinie

Last updated: 29 June 2022

- Repräsentatives Gremium – trifft zu;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt – trifft zu;
- Systematische Suche, Auswahl und Bewertung der Evidenz – trifft zu;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt – trifft zu;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt – trifft zu;
- Regelmäßige Überprüfung der Aktualität gesichert – trifft zu.

Recherche/Suchzeitraum:

- All searches were conducted in Medline, Embase and The Cochrane Library. All searches were updated on 28 August 2014.
- Weitere updates zu späteren Zeitpunkten. Siehe sonstige methodische Hinweise

LoE

- **Table 4: Overall quality of outcome evidence in GRADE**

Level	Description
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low	Any estimate of effect is very uncertain

GoR

- The strength of the recommendation is reflected in the wording (or example the word ‘offer’ was used for strong recommendations and ‘consider’ for weak recommendations)

Sonstige methodische Hinweise

- Die Leitlinie wurde ursprünglich im Juli 2004 publiziert. Updates wurden im August 2015, Dezember 2020, Juli 2021 und im März 2022 durchgeführt.
- “In March 2022, we reviewed the evidence and updated the recommendations on diagnosis and continuous glucose monitoring (CGM), replacing existing recommendations on diagnosis and CGM.”
- “June 2022: We reviewed evidence on periodontitis in people with type 1 diabetes, and made new recommendations. These recommendations are marked [2022] 2022].”

Recommendations: Insulin therapy

Insulin regimens

1.7.1 Offer multiple daily injection basal–bolus insulin regimens as the insulin injection regimen of choice for all adults with type 1 diabetes. Provide guidance on using this regimen. [2015]

1.7.2 Do not offer adults newly diagnosed with type 1 diabetes non-basal–bolus insulin regimens (that is, twice-daily mixed, basal only or bolus only). [2015]

Long-acting insulin

1.7.3 Offer twice-daily insulin detemir as basal insulin therapy for adults with type 1 diabetes. [2021]

1.7.4 Consider 1 of the following as an alternative basal insulin therapy to twice-daily insulin detemir for adults with type 1 diabetes:

- an insulin regimen that is already being used by the person if it is meeting their agreed treatment goals (such as meeting their HbA1c targets or time in target glucose range and minimising hypoglycaemia)
- once-daily insulin glargine (100 units/ml) if insulin detemir is not tolerated or the person has a strong preference for once-daily basal injections
- once-daily insulin degludec (100 units/ml) if there is a particular concern about nocturnal hypoglycaemia
- once-daily ultra-long-acting insulin such as degludec (100 units/ml) for people who need help from a carer or healthcare professional to administer injections.
- There is a risk of severe harm and death due to inappropriately withdrawing insulin from pen devices. See NHS England's patient safety alert for further information. [2021]

1.7.5 When starting an insulin for which a biosimilar is available, use the product with the lowest acquisition cost. [2021]

1.7.6 Ensure the risk of medication errors with insulins is minimised by following Medicines and Healthcare products Regulatory Agency (MHRA) guidance on minimising the risk of medication error with high strength, fixed combination and biosimilar insulin products, which includes advice for healthcare professionals when starting treatment with a biosimilar. [2021]

1.7.7 When people are already using an insulin for which a lower cost biosimilar is available, discuss the possibility of switching to the biosimilar. Make a shared decision with the person after discussing their preferences. [2021]

1.7.8 Consider other basal insulin regimens for adults with type 1 diabetes only if the regimens in recommendations 1.7.3 and 1.7.4 do not meet their agreed treatment goals. When choosing an alternative insulin regimen, take account of:

- the person's preferences
- comorbidities
- risk of hypoglycaemia and diabetic ketoacidosis
- any concerns around adherence
- acquisition cost. [2021]

1.7.9 When prescribing, ensure that insulins are prescribed by brand name. [2021]

Insulin pumps

1.7.10 For guidance on the use of insulin pumps for adults with type 1 diabetes, see NICE's technology appraisal guidance on continuous subcutaneous insulin infusion for the treatment of diabetes mellitus:

> **National Institute for Health and Care Excellence (NICE).** Continuous subcutaneous insulin infusion for the treatment of diabetes mellitus [online]. December 2014. London (GBR): NICE; 2008. [Zugriff: 19.07.2022]. (Technology appraisal guidance; Band TA151). URL: https://www.nice.org.uk/guidance/ta151/resources/continuous-subcutaneous-insulin-infusion-for-the-treatment-of-diabetes-mellitus-pdf-82598309704645.

Rapid-acting insulin

1.7.11 Offer rapid-acting insulin analogues that are injected before meals, rather than rapid-acting soluble human or animal insulins, for mealtime insulin replacement for adults with type 1 diabetes. [2015]

1.7.12 Do not advise routine use of rapid-acting insulin analogues after meals for adults with type 1 diabetes. [2015]

1.7.13 If an adult with type 1 diabetes has a strong preference for an alternative mealtime insulin, respect their wishes and offer the preferred insulin. [2015]

Mixed insulin

1.7.14 Consider a twice-daily human mixed insulin regimen for adults with type 1 diabetes if a multiple daily injection basal–bolus insulin regimen is not possible and a twice-daily mixed insulin regimen is used. [2015]

1.7.15 Consider a trial of a twice-daily analogue mixed insulin regimen if an adult using a twice-daily human mixed insulin regimen has hypoglycaemia that affects their quality of life. [2015]

Optimising insulin therapy

1.7.16 For adults with erratic and unpredictable blood glucose control (hyperglycaemia and hypoglycaemia at no consistent times), consider the following rather than changing a previously optimised insulin regimen:

- injection technique
- injection sites
- self-monitoring skills
- knowledge and self-management skills
- lifestyle
- mental health and psychosocial problems
- possible organic causes, such as gastroparesis. [2004, amended 2015]

1.7.17 Give clear guidelines and protocols ('sick-day rules') to all adults with type 1 diabetes, to help them adjust insulin doses appropriately when they are ill. [2004]

Adjuncts

1.7.18 Consider adding metformin to insulin therapy for adults with type 1 diabetes if:

- they have a BMI of 25 kg/m2 or above (23 kg/m2 or above for people from South Asian and related family backgrounds) and

- they want to improve their blood glucose control while minimising their effective insulin dose. In August 2015, this was an off-label use of metformin. See NICE's information on prescribing medicines. [2015]

Referral for islet or pancreas transplantation

1.9.1 For adults with type 1 diabetes who have recurrent severe hypoglycaemia that has not responded to other treatments (see the section on hypoglycaemia awareness and management), consider referral to a centre that assesses people for islet and/or pancreas transplantation. [2015]

1.9.2 Consider islet or pancreas transplantation for adults with type 1 diabetes with suboptimal diabetes control, if they have had a renal transplant

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Deutsche Diabetes Gesellschaft (DDG), 2018 [1].

S3-Leitlinie Therapie des Typ-1-Diabetes (2. Auflage)

Leitlinienorganisation/Fragestellung

Mit der Erstellung und Aktualisierung dieser Leitlinien verfolgen die Autoren die folgenden Ziele:

1. Die Rate diabetesassoziierter Komplikationen und diabetesassoziierter Folgeschäden zu senken. Hierbei wird erstmals auch die Diagnostik und Behandlung von Lipodystrophien beschrieben.

2. Die Lebensqualität von Menschen mit Typ-1-Diabetes zu verbessern.

3. Zu einer angemessenen Versorgung von Menschen mit Typ-1-Diabetes im Krankenhaus sowohl auf Normalstationen als auch auf Intensivstationen beizutragen. Insbesondere sollte die Implementierung sicherer Protokolle zum Schutz vor Hypoglykämien bei intravenöser Insulintherapie gefördert werden.

4. Eine korrekte Behandlung von Akutkomplikationen sicherzustellen und damit das Risiko von Komplikationen aufgrund der Behandlung zu senken.

5. Die adäquate Schulung von Menschen mit Typ-1-Diabetes besonders im ambulanten Bereich stärker zu verankern.

Methodik

Grundlage der Leitlinie

Die Grundlage für die Aktualisierung der Leitlinie bildete die bestehende Leitlinie sowie insgesamt 6 neue systematische Literaturrecherchen zu priorisierten Themen. Ausführliche Informationen zu den einzelnen Recherchen können dem Methodenreport zu dieser Leitlinie entnommen werden. Weiterhin wurden Publikationen berücksichtigt, die den Autoren und Beteiligten bekannt waren, sowie Publikationen, die in Literaturdatenbanken durch Freihandsuche oder in Literaturverzeichnissen bekannter Publikationen identifiziert wurden. Sowohl die Inhalte der eingeschlossenen Leitlinien als auch die Ergebnisse der berücksichtigten Studien zu den priorisierten Themen wurden in Evidenztabellen extrahiert.

Grundlage der Leitlinie

- Repräsentatives Gremium – trifft zu;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt – trifft zu;
- Systematische Suche, Auswahl und Bewertung der Evidenz – trifft zu;

- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt – trifft zu;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt – trifft zu;
- Regelmäßige Überprüfung der Aktualität gesichert – trifft zu (Die letzte inhaltliche Überarbeitung erfolgte am 28. März 2018. Die Leitlinie behält ihre Gültigkeit bis März 2023).

Recherche/Suchzeitraum:

- Es wurde eine systematische Literaturrecherche nach Primärstudien und systematischen Reviews in den Datenbanken Medline (via Pubmed) und Embase (via Embase) durchgeführt. Außerdem wurde in CENTRAL (Cochrane Central Register of Controlled Trials), CDSR (Cochrane Database of Systemtatic Reviews) und DARE (Database of Abstracts of Reviews of Effects) über die Cochrane Library gesucht.
- Suchzeitraum: bis 09.2016

LoE

Tabelle 1: Bewertung der publizierten Literatur gemäß ihrer wissenschaftlichen Aussagekraft nach Evidenzklassen

Evidenzklassen (EK)	
Ia	Evidenz aufgrund von Metaanalysen randomisierter, kontrollierter Studien
Ib	Evidenz aufgrund mindestens einer randomisierten, kontrollierten Studie
IIa	Evidenz aufgrund mindestens einer gut angelegten, kontrollierten Studie ohne Randomisation
IIb	Evidenz aufgrund mindestens einer gut angelegten, nicht randomisierten und nicht kontrollierten klinischen Studie, z. B. Kohortenstudie
III	Evidenz aufgrund gut angelegter, nicht experimenteller, deskriptiver Studien, wie z. B. Vergleichsstudien, Korrelationsstudien und Fall-Kontroll-Studien
IV	Evidenz aufgrund von Berichten der Experten-Ausschüsse oder Expertenmeinungen und/oder klinischer Erfahrung anerkannter Autoritäten

Die aufgeführte Evidenzklassifizierung wird in den Evidenztabellen als „Evidenzniveau DDG“ geführt.

Tabelle 2: Evidenzbewertung nach SIGN

Grading system for recommendations in evidence based guidelines – Levels of evidence
1++ High quality metaanalyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+ Well conducted metaanalyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1- Metaanalyses, systematic reviews or RCTs, or RCTs with a high risk of bias
2++ High quality systematic reviews of casecontrol or cohort studies or High quality casecontrol or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal
2+ Well conducted casecontrol or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal
2- Casecontrol or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal
3 Nonanalytic studies, eg case reports, case series
4 Expert opinion

GoR

Die Nomenklatur und Graduierung der Empfehlungen wurde entsprechend dem Vorgehen bei Nationalen Versorgungsleitlinien [Bundesärztekammer 2017, EK IV] angewandt.

Tabelle 3: Empfehlungsgraduierung

Nomenklatur	Beschreibung	Empfehlungsgrad
Soll	Starke Empfehlung	**A**
Sollte	Empfehlung	**B**
Kann	offen	**0**

Empfehlungen: Therapie des Typ-1-Diabetes

Insulintherapie

Empfehlungen	Empfehlungsgrad
4-1 Bei Menschen mit Typ-1-Diabetes beeinflussen folgende Faktoren die adäquate Insulinersatztherapie: a. das Ausmaß des Insulindefizits; b. die individuelle Insulinempfindlichkeit unter Berücksichtigung von BMI (Body Mass Index), körperlicher Aktivität, Vorliegen weiterer Erkrankungen und Einnahme von Medikamenten; c. die Pharmakokinetik und -dynamik der verwendeten Insulinpräparate (siehe dort); d. die Nahrungszufuhr. *[Arai 2008, EK III; Muis 2006, EK III] (starker Konsens)*	**Statement**
4-2 Die intensivierte Insulintherapie sollte der Behandlungsstandard bei Menschen mit Typ-1-Diabetes sein. *[Boer 2008, EK Ib und EK IIa; Cleary 2006, EK III; DCCT Research Group 1993, EK Ib; Nathan 2005, EK IIb; Wang 1993, EK Ib; White 2008, EK III] (starker Konsens)*	**B**
4-3 Bei Menschen mit Typ-1-Diabetes soll die Insulintherapie im Rahmen einer strukturierten Diabetesbetreuung erfolgen. Ebenso soll die Schulung strukturiert erfolgen. *[Bundesärztekammer (BÄK) 2012, EK IV; DCCT Research Group 1993, EK Ib] (starker Konsens)*	**A**
4-4 Zur Therapie von Menschen mit Typ-1-Diabetes sollen Humaninsuline (Normalinsulin oder Humaninsuline mit Verzögerungsprinzip) oder Insulinanaloga (kurzwirksame oder langwirksame) eingesetzt werden. *[Ashwell 2008, EK Ib; Bühn 2016; Hermansen 2004, EK Ib; Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen 2010, EK Ia; Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen 2007, EK Ia; Monami 2009, EK Ia; Mullins 2007, EK Ia; Singh 2009, EK Ia] (starker Konsens)*	**A**
4-5 Werden strenge Therapieziele angestrebt, ist der Einsatz kurzwirksamer und langwirksamer Insulinanaloga im Vergleich zu Normalinsulinen mit Vorteilen hinsichtlich HbA1c-Absenkung sowie dem Risiko für Hypoglykämien assoziiert. *[Bühn 2016; Fullerton 2016, EK Ia/LoE 1++; Vardi 2008, EK Ia/LoE 1+] (starker Konsens)*	**Statement**

CSII/rtCGM

Empfehlungen	Empfehlungsgrad
4-10 Bei Menschen mit Typ-1-Diabetes sollte der Einsatz einer Insulinpumpentherapie bei Nichterreichen der individuellen Therapieziele unter intensivierter Insulintherapie überprüft werden. *[Bolli 2009, EK Ib; Fatourechi 2009, EK Ia; Jeitler 2008, EK Ia; Pickup 2008, EK IIb; Retnakaran 2004, EK Ia] (starker Konsens)*	**B**
4-11 Bei Menschen mit Typ-1-Diabetes sollte bei häufigen Hypoglykämien bzw. bei rezidivierenden schweren Hypoglykämien unter intensivierter Insulintherapie der Einsatz einer Insulinpumpentherapie überprüft werden. *[Pickup 2008, EK IIb; Steineck 2015, EK IIb] (starker Konsens)*	**B**
4-12 Menschen mit Typ-1-Diabetes kann eine Insulinpumpentherapie bei folgenden Konstellationen angeboten werden: • bei häufig unregelmäßigem Tagesablauf, z. B. Schichtarbeit, Tätigkeiten mit variierender körperlicher Aktivität, Probleme bei der Durchführung einer klassischen ICT/Spritzentherapie (unter anderem zur Verbesserung der Lebensqualität) *[Barnard 2007, EK Ia; Hoogma 2006, EK Ib];* • bei geplanter Schwangerschaft (Beginn präkonzeptionell) bzw. zu Beginn einer Schwangerschaft; • bei geringem Insulinbedarf *Expertenkonsens EK IV;* • bei unzureichender glykämischer Kontrolle der Stoffwechsellage unter ICT, z. B. Dämmerungsphänomen. *[Chen 2007, EK IIb; Cypryk 2008, EK IIb; Farrar 2007, EK Ia; Gimenez 2007, EK III; Mukhopadhyay 2007, EK Ia] (starker Konsens)*	**0**
4-13 Voraussetzungen für den Beginn einer Insulinpumpentherapie bei Menschen mit Typ-1-Diabetes sind: • Beherrschung einer intensivierten Insulintherapie durch den Patienten; • die Sicherstellung der Betreuung durch eine qualifizierte diabetologische Einrichtung mit entsprechender Erfahrung in der Anwendung von Insulinpumpen; • Schulung zur Insulinpumpentherapie durch ein ausgebildetes Schulungsteam. *Expertenkonsens (starker Konsens)*	**Statement**

Empfehlungen	Empfehlungsgrad
4-14 Selbstmanagement mithilfe rtCGM oder iscCGM (FGM) sollte angeboten werden, wenn individuelle Therapieziele nicht erreicht werden. *Expertenkonsens (starker Konsens)*	**B**
Zu **rtCGM** liegt Evidenz für folgende Endpunkte vor: • Senkung des HbA1c *[Battelino 2012, EK Ia; Battelino 2011, EK Ia; Beck 2017, EK Ia; Langeland 2012, EK Ia; Little 2014, EK Ia; Tumminia 2015, EK Ia];* • Reduktion von Hypoglykämien, insbesondere schwere Hypoglykämien *[Battelino 2012, EK Ia; Battelino 2011, EK Ia; Beck 2017, EK Ia; Langeland 2012, EK Ia; Little 2014, EK Ia; Tumminia 2015, EK Ia];* • Systeme mit Basalratenabschaltung reduzieren die Rate an Hypoglykämien weiter. *[Bergenstal 2013, EK Ib];* • Je größer die Adhärenz zur Nutzung eines solchen Systems, desto größer der Benefit der Anwender. *[Pickup 2011, EK Ia];* • bei Schwangeren: Verbesserung des neonatalen Outcomes *[Feig 2017, EK Ib];* • Verbesserung der Lebensqualität *[Polonsky 2017, EK Ib].* Zu **iscCGM (FGM)** liegt Evidenz für folgende Endpunkte vor: • Reduktion von Hypoglykämien *[Bolinder 2016, EK Ib];* • Verbesserung der Behandlungszufriedenheit *[Bolinder 2016, EK Ib].* Um die Vorteile eines rtCGM/iscCGM-Systems effektiv nutzen zu können, bedarf es einer adäquaten Schulung und regelmäßigen diabetologischen Betreuung durch in der Nutzung dieser Systeme versierte Diabetesteams. *Expertenkonsens (starker Konsens)*	**Statement**

Ernährung

Empfehlungen	Empfehlungsgrad
4-15 Für Menschen mit Typ-1-Diabetes ist weder eine spezifische Ernährungsform oder Diät noch sind spezifische „Diät-Lebensmittel" erforderlich. Für sie gelten die allgemeinen Empfehlungen hinsichtlich einer gesunden Kost. *Expertenkonsens (starker Konsens)*	**Statement**
4-16 Die Beratung von Menschen mit Typ-1-Diabetes soll folgende besondere Komponenten umfassen: • Glukosewirksamkeit von Kohlenhydraten, Fetten und Eiweißen. *Expertenkonsens (starker Konsens)*	**A**
4-17 Zur Begrenzung der Proteinaufnahme bei Menschen mit Typ-1-Diabetes wird auf die entsprechende Leitlinie verwiesen. Zur Begrenzung oder gesteigerten Proteinzufuhr als Teil einer spezifischen Diabetes-Kost liegen widersprüchliche Aussagen hinsichtlich der Nutzen-/Schadensbilanz vor. Allenfalls bei bestehenden Nierenerkrankungen kann unter wenigen spezifischen Umständen eine Beschränkung der täglichen Eiweißzufuhr sinnvoll sein. *[Pfeiffer 2015, EK IV]*	**Statement**
4-18 Menschen mit Typ-1-Diabetes sollten, wie auch für die Allgemeinbevölkerung empfohlen, die Menge des Alkoholgenusses begrenzen (in der Regel Frauen 10 g Alkohol am Tag, Männer 20 g am Tag). Im Besonderen sollte darauf hingewiesen werden, dass bei Genuss größerer Alkoholmengen • das Risiko für schwere, insbesondere nächtliche Hypoglykämien ansteigt und • dieses Risiko durch Nahrungsaufnahme während der Zeit des Alkoholgenusses reduziert wird. *Expertenkonsens (starker Konsens)*	**B**

Schulung/strukturierte Schulungs- und Behandlungsprogramme

Empfehlungen	Emfehlungsgrad
4-19 Jedem Menschen mit Typ-1-Diabetes mellitus sollen strukturierte Schulungs-und Behandlungsprogramme sowie gegebenenfalls wichtigen Bezugspersonen (z. B. An- und Zugehörigen) unmittelbar nach Diagnosestellung des Diabetes und regelmäßig im Verlauf der Erkrankung als unverzichtbarer Bestandteil der Diabetesbehandlung angeboten werden. *[DAFNE Study Group 2002, EK Ib; Ehrmann 2016, EK IIb; Hermanns 2013, EK Ib; McIntyre 2010, EK IIb; Mühlhauser 1987, EK IIa; Plank 2004, EK IIb] (starker Konsens)*	**A**
4-20 Menschen mit Typ-1-Diabetes und Problemen im Zusammenhang mit Hypoglykämien (z. B. Hypoglykämiewahrnehmungsstörung, rezidivierende schwere Hypoglykämien) sollte ein Schulungs- und Behandlungsprogramm zur Verbesserung der Wahrnehmung und des Umgangs mit Hypoglykämien angeboten werden. *[Broers 2002, EK IIb; Cox 1995, EK IIb; Cox 1994, EK IIb; Cox 2001, EK IIb; Hermanns 2010, EK Ib; Hermanns 2007, EK Ib; Kinsley 1999, EK Ib; Schachinger 2005, EK Ib; Yeoh 2015, EK I] (starker Konsens)*	**B**
4-21 Wiederholungs-, Refresher- und Ergänzungsschulungen sowie problemorientierte Schulungen sollten bei Menschen mit Typ-1-Diabetes bei besonderen Problemen bei der Umsetzung der Diabetestherapie, dem Nichterreichen bedeutsamer Therapieziele (z. B. glykämischer Kontrolle, Vermeidung von Hypoglykämien, Ketoazidosen), dem Auftreten von Folge- und Begleiterkrankungen, die besondere Kenntnisse und Fähigkeiten des Patienten erfordern sowie bei bedeutsame Motivationsprobleme bei der Durchführung der Diabetestherapie angeboten werden. *[Bundesärztekammer (BÄK) 2012, EK IV] (starker Konsens)*	**B**

Orale Antidiabetika bei Typ-1-Diabetes

Empfehlungen	Empfehlungsgrad
5-10 Für das alleinige Therapieziel Verbesserung der glykämischen Kontrolle sollte der zusätzliche Einsatz von Metformin bei Menschen mit Typ-1-Diabetes nicht erfolgen. *[Petrie 2017, EK Ib/LoE 1-] (starker Konsens)*	**B**

Empfehlungen	Empfehlungsgrad
5-11 Bei Menschen mit Typ-1-Diabetes, bei welchen kardiovaskuläre Risikofaktoren und ein Übergewicht/Adipositas vorliegen, kann die zusätzliche Gabe von Metformin wegen vorteilhafter Effekte auf das LDL-Cholesterin, das Körpergewicht sowie auf Surrogarparameter der Arteriosklerose erwogen werden. Der Zulassungsstatus von Metformin ist zu beachten. *Expertenkonsens (starker Konsens)*	**0**

Vergleich von Pankreas- und Inseltransplantation

Empfehlungen	Empfehlungsgrad
6-1 Bei allen Patienen mit Typ-1-Diabetes und (prä-)terminaler Niereninsuffizienz sollte die Möglichkeit einer kombinierten Pankreas-Nierentransplantation geprüft werden. *[Gandhi 2008, EK Ia; Gandhi 2008, EK Ia; Huang 2011, EK Ib; Huurman 2007, EK Ib; Pescovitz 2009, EK Ib; Raz 2007, EK Ib; Schloot 2007, EK Ib; Walter 2009, EK Ib; Wiseman 2013, EK Ib] (starker Konsens)*	**B**
6-2 Bei allen Patienten mit Typ-1-Diabetes und schwerer metabolischer Instabilität mit Hypoglykämien und/oder Hypoglykämiewahrnehmungsstörung sollten zunächst die konservativen Möglichkeiten der Therapieoptimierung einschließlich technischer Hilfsmittel ausgeschöpft und bei Versagen die Optionen einer Betazellersatztherapie (Insel- oder Pankreastransplantation) geprüft werden. *[Barrou 1994, EK III; Choudhary 2015, EK IV; Kendall 1997, EK III; Paty 2001, EK III; Pedersen-Bjergaard 2004, EK III; Rickels 2015, EK III] (starker Konsens)*	**B**

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Diabetes Canada, 2018 [2].

Diabetes Canada 2018 clinical practice guidelines for the prevention and management of diabetes in Canada

Zielsetzung/Fragestellung

The guidelines are meant to improve the quality of care and healthcare outcomes of Canadians living with diabetes. A primary purpose is to address clinical care gaps that exist, i.e. discrepancies between evidence-based knowledge and day-to-day clinical practice.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium – trifft zu;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt – trifft zu;
- Systematische Suche, Auswahl und Bewertung der Evidenz – trifft zu;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt – trifft zu;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt – trifft zu;
- Regelmäßige Überprüfung der Aktualität gesichert – unklar.

Recherche/Suchzeitraum:

- MEDLINE, EMBASE, CINAHL, the Cochrane Central Register of Trials, and PsycINFO
- For topics that were covered in the 2013 Clinical Practice Guidelines, the literature searches focused on new evidence published since those guidelines, including literature published in September 2013 or later. For new topics, the search time frame included the literature published since 1990 or earlier where relevant.

LoE

Studies of treatment and prevention	
Level 1A	Systematic overview or meta-analysis of high-quality RCTs a) Comprehensive search for evidence b) Authors avoided bias in selecting articles for inclusion c) Authors assessed each article for validity d) Reports clear conclusions that are supported by the data and appropriate analyses OR Appropriately designed RCT with adequate power to answer the question posed by the investigators a) Patients were randomly allocated to treatment groups b) Follow up at least 80% complete c) Patients and investigators were blinded to the treatment* d) Patients were analyzed in the treatment groups to which they were assigned e) The sample size was large enough to detect the outcome of interest
Level 1B	Non-randomized clinical trial or cohort study with indisputable results
Level 2	RCT or systematic overview that does not meet Level 1 criteria
Level 3	Non-randomized clinical trial or cohort study; systematic overview or meta-analysis of level 3 studies
Level 4	Other

GoR

Table 2
Criteria for assigning grades of recommendations for clinical practice

Grade	Criteria
Grade A	The best evidence was at Level 1
Grade B	The best evidence was at Level 2
Grade C	The best evidence was at Level 3
Grade D	The best evidence was at Level 4 or consensus

Recommendations: Glycemic Management in Adults With Type 1 Diabetes

1. In adults with type 1 diabetes, basal-bolus injection therapy or CSII as part of an intensive diabetes management regimen should be used to achieve glycemic targets [Grade A, Level 1A (2)].

2. In adults with type 1 diabetes using basal-bolus injection therapy or CSII, rapid-acting insulin analogues should be used in place of regular insulin to improve A1C and to minimize the risk of hypoglycemia [Grade B, Level 2 (30,32) for basal-bolus injection therapy; Grade B, Level 2 (66,67) for lispro in CSII; Grade B, Level 2 (65) for aspart in CSII; Grade D, Consensus, for glulisine in CSII] and to achieve postprandial BG targets [Grade B, Level 2 (32) for basal-bolus injection therapy; Grade B, Level 2 (66) for CSII].

3. In adults with type 1 diabetes on basal-bolus injection therapy:

- a. A long-acting insulin analogue may be used in place of NPH to reduce the risk of hypoglycemia [Grade B, Level 2 for detemir (7,50); Grade B, Level 2 for glargine U-100 (4,5,51); Grade D, Consensus for degludec and glargine U-300], including nocturnal hypoglycemia [Grade B, Level 2 (7) for detemir; Grade B, Level 2 (4) for glargine U-100; Grade D, Consensus for degludec, and glargine U-300].
- b. Degludec may be used instead of detemir or glargine U-100 to reduce nocturnal hypoglycemia [Grade B, Level 2 (24) compared to detemir; Grade C, Level 3 (20) compared to glargine U-100].

4. All individuals with type 1 diabetes and their support persons should be counselled about the risk and prevention of hypoglycemia, and risk factors for severe hypoglycemia should be identified and addressed [Grade D, Consensus].

5. In adults with type 1 diabetes and hypoglycemia unawareness, the following nonpharmacological strategies may be used to reduce the risk of hypoglycemia:

- a. A standardized education program targeting rigorous avoidance of hypoglycemia while maintaining overall glycemic control [Grade A, Level 1A (59)]
- b. Increased frequency of SMBG, including periodic assessment during sleeping hours [Grade D, Consensus]
- c. CGM with high sensor adherence in those using CSII [Grade C, Level 3 (98)]
- d. Less stringent glycemic targets with avoidance of hypoglycemia for up to 3 months [Grade C, Level 3 (15,16)].

6. In adults with type 1 diabetes on basal-bolus injection therapy who are not achieving glycemic targets, CSII with or without CGM may be used to improve A1C [Grade B, Level 2 (77,78) with CGM; Grade B, Level 2 (73–75) without CGM].

7. In adults with type 1 diabetes,

- a. CSII may be used instead of basal-bolus injection therapy to improve treatment satisfaction [Grade C, Level 3 (70)]
- b. CSII plus CGM may be used instead of basal-bolus injection therapy or CSII with SMBG to improve quality of life, treatment satisfaction and other health-quality-related outcomes [Grade B, Level 2 (77,84)].

8. Adults with type 1 diabetes on CSII should undergo periodic evaluation to determine whether continued CSII is appropriate [Grade D, Consensus].

9. In adults with type 1 diabetes and an A1C at or above target, regardless of insulin delivery method used, CGM with high sensor adherence may be used to improve or maintain A1C [Grade B, Level 2 (97)] without increasing hypoglycemia [Grade C, Level 3 (97)].

10. In adults with type 1 diabetes experiencing nocturnal hypoglycemia and using CSII and CGM, SAP (sensor augmented pump) with low glucose suspend may be chosen over SAP alone to reduce nocturnal hypoglycemia [Grade B, Level 2 (80)].

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World Health Organization (WHO), 2018 [7].

Guidelines on second-and third-line medicines and type of insulin for the control of blood glucose levels in non-pregnant adults with diabetes mellitus

Leitlinienorganisation/Fragestellung

- To consider the use of DPP-4 inhibitors, SGLT-2 inhibitors, and TZDs as second- and third-line treatment after metformin and sulfonylurea for controlling hyperglycaemia in type 2 diabetes in non-pregnant adults, including whether these oral agents are preferable to insulin.
- To provide guidance regarding the use of insulin analogues for type 1 and type 2 diabetes.
- The scope has been limited to agents for glycaemic control because that field is a dynamic one and has seen more change in evidence and practice in recent years than have other aspects of diabetes management

Methodik

<u>Grundlage der Leitlinie</u>

- Repräsentatives Gremium – trifft zu;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt – trifft zu;
- Systematische Suche, Auswahl und Bewertung der Evidenz – trifft zu;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt – trifft zu;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt – trifft zu;
- Regelmäßige Überprüfung der Aktualität gesichert – trifft zu.

- Update of the WHO PEN recommendations on the choice of second- and third-line treatment for type 2 diabetes based
- WHO established three groups: WHO Guideline Steering Group, Guidelines Development Group and external Peer Review Group

- developed in accordance with the WHO Handbook for Guideline Development. In brief, the WHO Steering Group, in collaboration with the Guideline Development Group developed key questions and rated outcomes to identify those critical for the guideline development
- SR of the evidence were used to build Summary of Findings tables according GRADE
- Outcome rating for recommendations: development of outcome lists, then rating of the Guideline Group if it is critical (rated 7-9), important (rated 4-6) or not important (rated 1-3)
- SR identified in literature search assessment with AMSTAR
- Deciding upon recommendations at Guideline Group met in Geneva in March 2017 on basis of evidence-to-decision tables incorporating Systematic reviews and GRADE tables

Recherche/Suchzeitraum:

- In Pubmed from 2006.
- Es existiert nur ein Datum für den Beginn des Suchzeitraums. Das Ende ist ausschließlich mit „current“ angegeben. Aus den eingeschlossenen Dokumenten kann auf das Jahr 2016 geschlossen werden.

LoE

The following levels of assessment of the evidence were used in the GRADE profiles:

Evidence level	Rationale
High ⊕⊕⊕⊕	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate ⊕⊕⊕O	Further research is likely to have an important impact on our confidence in the effect and may change the estimate.
Low ⊕⊕OO	Further research is very likely to have an impact on the estimate of effect and is likely to change the estimate.
Very low ⊕OOO	Any estimate of effect is very uncertain.

GoR

The recommendations in these guidelines were graded into two categories:

- **A strong recommendation** is one for which the Guideline Group was confident that the desirable effects of adhering to the recommendation outweigh the undesirable effects.
- **A weak** or **conditional recommendation** is one for which the Guideline Group concluded that the desirable effects of adhering to the recommendation probably outweigh the undesirable effects, but the Guideline Group was not confident about these trade-offs.

Recommendations: Insulin

- 4. Use human insulin to control blood glucose levels in adults with type 1 diabetes, and in adults with type 2 diabetes for whom insulin is indicated (strong recommendation, low-quality evidence).
- Remarks: Recommendation 4 covers both short-acting (regular human insulin – RHI) and intermediate-acting human insulin (NPH insulin). The recommendation is strong because evidence of better effectiveness of insulin analogues is lacking and human insulin has a better resource-use profile.

- 5. Consider long-acting insulin analogues to control blood glucose levels in adults with type 1 or type 2 diabetes who have frequent severe hypoglycaemia with human insulin (weak recommendation, moderate-quality evidence for severe hypoglycaemia).
- Remarks: Recommendation 5 is a weak recommendation reflecting the lack of, or very low-quality, evidence for any of the long-term outcomes such as chronic diabetes complications and mortality, and the considerable higher costs for long-acting insulin analogues compared to intermediate-acting human insulin.

Summary of the evidence: Two recent, high-quality systematic reviews and preliminary results from a Cochrane Review update were used to answer the questions. The first systematic review compared long-acting insulin analogues to intermediate-acting human insulin for type 1 diabetes (11) and the second systematic review compared a short-acting insulin analogue to a short-acting human insulin for type 1 diabetes (13). The third systematic review evaluated long-acting insulin analogues versus NPH insulin for type 2 diabetes (42).

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4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 06 of 12, June 2022) am 22.06.2022

#	Suchfrage
1	[mh "Diabetes Mellitus, Type 1"]
2	(diabet* OR dm):ti,ab,kw
3	((type NEXT 1) or (type NEXT i)):ti,ab,kw
4	#2 and #3
5	(t1dm OR tidm OR t1d OR dmt1 OR dmti):ti,ab,kw
6	#1 OR #4 OR #5
7	#6 with Cochrane Library publication date from Jun 2017 to Jun 2022

Systematic Reviews in PubMed am 22.06.2022

verwendete Suchfilter:
Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 02.01.2020.

#	Suchfrage
1	"diabetes mellitus, type 1/therapy"[MeSH Terms]
2	(diabet*[Title/Abstract]) OR dm[Title/Abstract]
3	("type 1"[Title/Abstract]) OR "type I"[Title/Abstract]
4	(#2) AND #3
5	((t1dm[Title/Abstract]) OR tidm[Title/Abstract]) OR t1d[Title/Abstract] OR dmt1[Title/Abstract] OR dmti[Title/Abstract]
6	(#4) OR #5
7	(#6) AND ((treatment*[tiab] OR treating[tiab] OR treated[tiab] OR treat[tiab] OR treats[tiab] OR treatab*[tiab] OR therapy[tiab] OR therapies[tiab] OR therapeutic*[tiab] OR monotherap*[tiab] OR polytherap*[tiab] OR pharmacotherap*[tiab] OR effect*[tiab] OR efficacy[tiab] OR management[tiab] OR drug*[tiab]))
8	(#1) OR #7
9	(#8) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis[pt] OR meta-analysis[ti] OR systematic literature review[ti] OR this systematic review[tw] OR pooling project[tw] OR (systematic review[tiab] AND review[pt]) OR meta synthesis[ti] OR meta-analy*[ti] OR integrative review[tw] OR integrative research review[tw] OR rapid review[tw] OR umbrella review[tw] OR consensus development conference[pt] OR practice guideline[pt] OR drug class reviews[ti] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health technol assess[ta] OR evid rep technol assess summ[ta] OR jbi database system rev implement rep[ta]) OR (clinical guideline[tw] AND management[tw]) OR ((evidence based[ti] OR evidence-based medicine[mh] OR best practice*[ti]

#	Suchfrage
	OR evidence synthesis[tiab]) AND (review[pt] OR diseases category[mh] OR behavior and behavior mechanisms[mh] OR therapeutics[mh] OR evaluation study[pt] OR validation study[pt] OR guideline[pt] OR pmcbook)) OR ((systematic[tw] OR systematically[tw] OR critical[tiab] OR (study selection[tw]) OR (predetermined[tw] OR inclusion[tw] AND criteri* [tw]) OR exclusion criteri*[tw] OR main outcome measures[tw] OR standard of care[tw] OR standards of care[tw]) AND (survey[tiab] OR surveys[tiab] OR overview*[tw] OR review[tiab] OR reviews[tiab] OR search*[tw] OR handsearch[tw] OR analysis[ti] OR critique[tiab] OR appraisal[tw] OR (reduction[tw] AND (risk[mh] OR risk[tw]) AND (death OR recurrence))) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR publication [tiab] OR bibliography[tiab] OR bibliographies[tiab] OR published[tiab] OR pooled data[tw] OR unpublished[tw] OR citation[tw] OR citations[tw] OR database[tiab] OR internet[tiab] OR textbooks[tiab] OR references[tw] OR scales[tw] OR papers[tw] OR datasets[tw] OR trials[tiab] OR meta-analy*[tw] OR (clinical[tiab] AND studies[tiab]) OR treatment outcome[mh] OR treatment outcome[tw] OR pmcbook)) NOT (letter[pt] OR newspaper article[pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))
10	((#9) AND ("2017/06/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))
11	(#10) NOT (retracted publication [pt] OR retraction of publication [pt])

Leitlinien in PubMed am 22.06.2022

verwendete Suchfilter:
Konsentierter Standardfilter für Leitlinien (LL), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 21.06.2017.

#	Suchfrage
1	diabetes mellitus, type 1[MeSH Major Topic]
2	(diabet*[Title]) OR dm[Title]
3	(“type 1”[Title]) OR “type I”[Title]
4	(#2) AND #3
5	((t1dm[Title]) OR tidm[Title]) OR t1d[Title] OR dmt1[Title] OR dmti[Title]
6	(#1 OR #4 OR #5)

#	Suchfrage
7	(#6) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] *OR recommendation*[ti])*
8	(((#7) AND (“2017/06/01”[PDAT] : “3000”[PDAT])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp])) NOT (“The Cochrane database of systematic reviews”[Journal]) NOT ((comment[ptyp]) OR letter[ptyp]))
9	(#8) NOT (retracted publication [pt] OR retraction of publication [pt])

Iterative Handsuche nach grauer Literatur, abgeschlossen am 23.06.2022

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF)
- Nationale VersorgungsLeitlinien (NVL)

- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)

- ECRI Guidelines Trust (ECRI)
- Dynamed / EBSCO
- Guidelines International Network (GIN)
- Trip Medical Database

Referenzen

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[B] **McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C.** PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. J Clin Epidemiol 2016;75:40-46. https://doi.org/10.1016/j.jclinepi.2016.01.021

Beteiligung von AkdÄ und Fachgesellschaften nach §35a Abs. 7 SGB V i.V.m. VerfO 5. Kapitel § 7 Abs. 6

2022-B-141

Kontaktdaten

Deutsche Gesellschaft für Allgemeinmedizin und Familienmedizin (DEGAM), Deutsche Diabetes Gesellschaft (DDG), Deutsche Gesellschaft für Endokrinologie (DGE)

Indikation gemäß Beratungsantrag

Behandlung des Diabetes mellitus Typ 1 bei Erwachsenen

Was ist der Behandlungsstandard in o.g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus?

Der Behandlungsstandard für die Therapie des Typ-1-Diabetes (T1D) ist in der S-3 Leitlinie "Therapie des Typ-1-Diabetes" (AWMF 057-013, 2. Auflage) dargelegt (1) und entspricht weitestgehend den internationalen Empfehlungen der amerikanischen Diabetesgesellschaft (ADA) (2). An der Erstellung der S-3 Leitlinie "Therapie des Typ-1-Diabetes" waren neben der Deutschen Diabetesgesellschaft (DDG) die folgenden medizinischen wissenschaftlichen Fachgesellschaften beteiligt: Deutsche Adipositas Gesellschaft (DAG), Deutsche Gesellschaft für Allgemein- und Familienmedizin (DEGAM), Deutsche Gesellschaft für Anästhesiologie und Intensivmedizin (DGAI), Deutsche Gesellschaft für Innere Medizin (DGIM). Die Leitlinie verfolgt die übergeordneten Ziele: die Rate diabetesassoziierter Komplikationen und Folgeerkrankungen zu senken, die Lebensqualität von Menschen mit Typ-1-Diabetes zu verbessern, die Versorgung und Behandlungssicherheit (in Bezug auf Hypoglykämien und Stoffwechselentgleisungen) der Menschen mit Typ-1-Diabetes im Krankenhaus und in besonderen Situationen zu verbessern, eine korrekte Behandlung von Akutkomplikationen sicherzustellen und eine adäquate Schulung von Menschen mit Typ-1-Diabetes sicherzustellen. Eine aktualisierte Kurzfassung der S-3 Leitlinie "Therapie des Typ-1-Diabetes" wurde als Praxisempfehlung der DDG 2021 publiziert (3).

Generell zielt die Therapie bei Typ-1-Diabetes darauf ab, diabetesbedingte Minderungen der Lebensqualität zu vermeiden. Ebenso gilt es die Akzeptanz für die Erkrankung und die Zufriedenheit mit dem Therapieregime bei den Betroffenen zu erzielen. Um diabetesbedingte Minderungen der Lebensqualität zu vermeiden, soll die Therapie so gestaltet werden, dass das Risiko für schwere Stoffwechselentgleisungen (schwere Hypoglykämien und/oder schwere Hyperglykämien mit Ketoazidose oder Coma diabeticum) möglichst gering ist. Weiterhin soll die Therapie so geführt werden, dass das Risiko für die Entstehung mikroangiopathischer (Retinopathie, Nephropathie) und anderer diabetesassoziierter Folgeschäden (Neuropathie, beschleunigte Makroangiopathie) reduziert wird. Ein weiteres Therapieziel in der Behandlung des Typ-1-Diabetes ist es, zusätzliche Risikofaktoren für Folgeschäden zu vermeiden. Dies erfolgt durch Überwachung und bei Vorliegen durch eine adäquate Therapie von Blutdruck, Lipidprofil sowie einer übergewichtsinduzierten Insulinresistenz. Die Dokumentation im Gesundheitspass Diabetes kann hilfreich sein (3).

Das Therapiekonzept des Typ-1-Diabetes besteht aus den Komponenten Insulintherapie, Ernährungskenntnisse, Schulung, Glukoseselbstkontrolle und psychosoziale Betreuung (1,3). Die Indikation für eine Insulintherapie ist bei Typ-1-Diabetes immer und lebenslang gegeben. Voraussetzung für die Substitution des fehlenden Insulins bei Menschen mit Typ-1-Diabetes sind Kenntnisse über den physiologischen Insulinbedarf sowie die pharmakokinetischen und -dynamischen Eigenschaften der therapeutisch verwendeten Insuline und Kenntnis über die aktuellen Glukosespiegel. Für die Planung der Insulintherapie sind zudem wichtig: (a) die Berücksichtigung der Abhängigkeit des additiven Insulinbedarfs von der Nahrungszufuhr (prandiales Insulin stets zusätzlich zum Basalinsulinbedarf) und (b) das Verhältnis zwischen basalem und prandialem Insulinbedarf. Zur Therapie von

Menschen mit Typ-1-Diabetes sollen Humaninsuline (Normalinsulin oder Humaninsuline mit Verzögerungsprinzip) oder Insulinanaloga (kurzwirksame oder langwirksame) eingesetzt werden (4-11).

Da beim Typ-1-Diabetes ein absoluter Insulinmangel vorliegt, besteht die Insulinsubstitution darin, so gut und für den einzelnen Patienten angemessen wie möglich, die normale Insulinsekretion zu simulieren. Letztere besteht aus einer kontinuierlichen Insulinabgabe (simuliert durch lang wirkende Insuline) und durch nahrungsabhängige pulsatile Insulinfreisetzung (simuliert durch kurz wirkende Insuline) oder durch eine Insulinpumpentherapie (CSII = continuous subcutaneous insulin infusion). Zur Insulintherapie stehen in Deutschland derzeit die folgenden Insuline mit den folgenden Eigenschaften zur Verfügung (3, 12):

Tabelle " Insulinarten – Wirkeigenschaften, unerwünschte Wirkungen, Interaktionen und Kontraindikationen"

	Wirkung			
	Eintritt	**Maximum**	**Dauer**	**Anwendung in der Regel**
Humaninsuline				
NPH-Insulin	1–2 h	6–7 h	14 h	2 × täglich
Normalinsulin	30–60 min	3 h	8 h	0–30 min vor den Mahlzeiten
Mischinsulin NPH (70)/Normal (30)	30–60 min	3–3,5 h	14 h	vor Frühstück und Abendessen
Insulinanaloga				
Degludec	1–2 h[1]	8–14 h geringes Maximum	> 42 h	1 × täglich
Detemir	1 h	7–9 h	19–26 h	1 oder 2 × täglich
Glargin U100	1 h	8–12 h	20–27 h	1 oder 2 × täglich
Glargin U300	1–6 h[1]	12–16 h geringes Maximum	30–32 h	1 × täglich
Aspart	20–25 min	120–150 min	4–5 h	0–15 min vor den Mahlzeiten
Glulisin	20–25 min	120–150 min	4–5 h	0–15 min vor den Mahlzeiten
Lispro	20–25 min	120–150 min	4–5 h	0–15 min vor den Mahlzeiten
ultra rapid lispro	11–13 min	120 min	4–5 h	unmittelbar vor den Mahlzeiten
Faster Aspart	15 min	120 min	4 h	unmittelbar vor den Mahlzeiten
Mischinsulin protamin. Aspart (70)/Aspart (30); protamin. Lispro (70), Lispro (30)	20–25 min	2–3 h	10–14 h	0–15 min vor Frühstück und Abendessen
Kombinationsinsulin Degludec (70)/Aspart (30)	20–25 min	2–3 h	> 30 h	0–15 min vor einer oder vor zwei Hauptmahlzeiten

[1]Unter Steady-State-Bedingungen ist aufgrund der langen Wirkdauer und des flachen Wirkprofils der Zeitpunkt des Wirkeintritts von geringer klinischer Relevanz.

Bei Menschen mit Typ-1-Diabetes sollen in Bezug auf die glykämische Kontrolle individualisierte Therapieziele mit den Patienten vereinbart werden. Die Wahl des HbA1c-Zielwertes soll stets als ein Kompromiss zwischen dem Risiko für Hypo und Hyperglykämien und deren Folgen, dem erwartbaren Nutzen der Risikoreduktion hinsichtlich diabetesbedingter Akut- und Folgekomplikationen, der Patientenpräferenz und den Möglichkeiten des Patienten zur Therapieadhärenz behandelt werden, wobei etwaige Komorbiditäten, das Alter und die Erkrankungsdauer zu berücksichtigen sind (1). Menschen mit Typ-1-Diabetes sollen neben dem Nutzen auch über die Gefahren einer intensiven Insulintherapie aufgeklärt werden. Diese Aufklärung soll insbesondere das Thema der Hypoglykämien und dabei auch das der unbemerkten Stoffwechselentgleisungen beinhalten sowie den dadurch möglichen negativen Einfluss einer intensiven Insulintherapie auf kognitive Fähigkeiten, Wahrscheinlichkeiten für z. B. Herzrhythmusstörungen, Unfälle und Unfalltod umfassen. Diese Aufklärung soll in verständlichen Worten und

ergebnisoffen geschehen (1). Kontinuierliche Glukosemeßsysteme (CGM) mit Alarm- oder Abschaltfunktion eignen sich zur Vermeidung von schweren Hypoglykämien (2,13-15).

Zur Insulintherapie sind einfache und aufwendigere („intensivierte“) Strategien verfügbar. Die intensivierte Insulintherapie ist definiert als Gabe von mindestens drei Insulininjektionen pro Tag. Vor allem aber ist sie gekennzeichnet durch eine Substitution von basalem Insulinbedarf mit langwirkendem "Basalinsulin" und prandialem Insulinbedarf mit kurzwirksamem "Bolusinsulin" zu den Mahlzeiten (Basal-Bolus Prinzip). Synonyme der intensivierten Insulintherapie sind "Funktionelle Insulintherapie" sowie "Flexible Insulintherapie". Diese Therapie kann mit Insulinspritzen, Insulinpens oder Insulinpumpen (siehe Empfehlungen dort) durchgeführt werden (1,3).

In Deutschland sind etwa 32.000 Kinder und Jugendliche sowie 340.000 Erwachsene an einen Typ-1-Diabetes erkrankt, die Inzidenz des Typ-1-Diabetes im Kindes- und Jugendalter nimmt in Deutschland leicht zu (16). Hinsichtlich der Lebenserwartung wurden in den letzten Jahren bei Typ-1-Diabetes Verbesserungen beschrieben. In den Studien nach 1990 lag das relative Mortalitätsrisiko für Menschen mit Typ1-Diabetes im Vergleich zur Allgemeinbevölkerung noch bei etwa 3,0 (16,17). Für Betroffene, bei denen der Typ-1-Diabetes nach 1964 diagnostiziert wurde, konnte ein Trend hin zu einer geringeren Mortalitätsrate identifiziert werden (16,18,19).

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Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen bei der Behandlung des Diabetes mellitus Typ 1 bei Erwachsenen die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?

Die Zielwerte für die durchschnittliche Glykämielage werden individuell festgelegt und sind nach der S3-Leitlinie zur Therapie des Typ-1-Diabetes wie folgt für folgende Situationen definiert (1):

- Bei Erwachsenen mit Typ-1-Diabetes sollte ein HbA1c-Wert ≤ 7,5% (≤ 58 mmol/mol) angestrebt werden, solange keine problematischen Hypoglykämien auftreten (Empfehlungsgrad B)
- Bei Erwachsenen mit Typ-1-Diabetes kann auch ein HbA1c-Wert ≤ 6,5% (≤ 48 mmol/mol) angestrebt werden, wenn ein niedriges intrinsisches Hypoglykämierisiko besteht (z. B. neumanifester Typ-1-Diabetes, stabil geringe glykämische Variabilität) (Empfehlungsgrad 0)
- Bei Erwachsenen mit Typ-1-Diabetes sollte ein weniger strenger HbA1c-Wert < 8,5% (69 mmol/mol) angestrebt werden, wenn die Therapiesicherheit nicht gewährleistet werden kann, gehäuft schwere Hypoglykämien aufgetreten sind, extensive Komorbiditäten oder fortgeschrittene makrovaskuläre Komplikationen vorliegen. (Empfehlungsgrad B)
- Bei Menschen mit Typ-1-Diabetes und schweren Hypoglykämien in den letzten Monaten sollte eine Anhebung des HbA1c-Ziels erfolgen. (Empfehlungsgrad B) bzw. die Anwendung eines CGM-Systems unbedingt in Erwägung gezogen werden (15)
- Bei Menschen mit Typ-1-Diabetes und geringer Lebenserwartung oder bedeutenden Komorbiditäten kann eine Anhebung des Blutzuckers mit dem alleinigen Therapieziel der Symptomfreiheit erwogen werden. (Empfehlungsgrad 0)

<u>Konventionelle Therapie (3)</u>

Die konventionelle Therapie ist charakterisiert durch eine verbindliche Vorgabe sowohl der Insulindosis als auch der Abfolge und Größe der Mahlzeiten (feste Kohlehydratportionen). Eine Blutglukoseselbstmessung wird 3–4 × täglich empfohlen. In der Regel werden fixe Insulinmischungen verwendet, die 2 × täglich zum Frühstück und zum Abendessen verabreicht und, soweit möglich, an das Essverhalten der Patienten angepasst werden. Eine einfache konventionelle Insulintherapie ist nur bei einem festen Kostplan erfolgversprechend.

Diese Form der Insulintherapie kommt bei Menschen mit Typ-1-Diabetes im Gegensatz zu einer intensivierten Therapie als nachrangige Therapieoption in folgenden Konstellationen infrage:

- bei Menschen, die den Anforderungen an eine intensivierte Therapie nicht gerecht werden können (aufgrund von kognitiven Einschränkungen und krankheits- oder altersbedingt),
- bei Menschen, die sich nach ausführlicher Nutzen-Schaden-Aufklärung gegen eine intensivierte Therapie entscheiden,
- bei einer erheblichen Adhärenzproblematik in der Langzeitbetreuung.

Da für die Reduktion des Risikos für diabetesassoziierte Folgekomplikationen die mittel- und langfristige glykämische Kontrolle entscheidend ist, kann eine konventionelle Insulintherapie ausreichend sein, wenn die individuellen HbA1c-Zielwerte erreicht werden, Hypoglykämien vermieden werden und die Lebensqualität durch die Therapie nicht eingeschränkt ist (3).

Kontinuierliche subkutane Insulininfusion (CSII "Insulinpumpentherapie")

Unter den folgenden Voraussetzungen wird in den Leitlinien und Praxisempfehlungen eine "Insulinpumpentherapie" empfohlen (1-3):

Bei Menschen mit Typ-1-Diabetes sollte der Einsatz einer Insulinpumpentherapie bei Nichterreichen der individuellen Therapieziele unter intensivierter Insulintherapie überprüft werden (starker Konsens, Empfehlungsgrad B) (20-24)

Bei Menschen mit Typ-1-Diabetes sollte bei häufigen Hypoglykämien bzw. bei rezidivierenden schweren Hypoglykämien unter intensivierter Insulintherapie der Einsatz einer Insulinpumpentherapie überprüft werden. (starker Konsens, Empfehlungsgrad B) (23,25)

Menschen mit Typ-1-Diabetes kann eine Insulinpumpentherapie bei folgenden Konstellationen angeboten werden (Empfehlungsgrad 0) (3,26-32):

- bei häufig unregelmäßigem Tagesablauf, z. B. Schichtarbeit, Tätigkeiten mit variierender körperlicher Aktivität, Probleme bei der Durchführung einer klassischen ICT/Spritzentherapie (unter anderem zur Verbesserung der Lebensqualität),
- bei geplanter Schwangerschaft (Beginn präkonzeptionell) bzw. zu Beginn einer Schwangerschaft, bei geringem Insulinbedarf, Expertenkonsens EK IV,
- bei unzureichender glykämischer Kontrolle der Stoffwechsellage unter ICT, z. B. Dämmerungsphänomen. (starker Konsens)

Voraussetzungen für den Beginn einer Insulinpumpentherapie bei Menschen mit Typ-1-Diabetes sind: Beherrschung einer intensivierten Insulintherapie durch den Patienten; o die Sicherstellung der Betreuung durch eine qualifizierte diabetologische Einrichtung mit entsprechender Erfahrung in der Anwendung von Insulinpumpen; Schulung zur Insulinpumpentherapie durch ein ausgebildetes Schulungsteam (1)..

Weitere Therapieverfahren in besonderen Situationen (1)

Hospitalisierte Patienten mit Typ-1-Diabetes und akut lebensbedrohlicher Erkrankung sollen kontinuierlich Insulin intravenös (i.v.) erhalten. Dabei soll ein Ziel-Blutglukosewert zwischen 140 und 180 mg/dl (7,8–10,00 mmol/l) angestrebt werden. Die intravenöse Insulintherapie soll nach einem standardisierten, evaluierten Protokoll erfolgen, das hinsichtlich der Hypoglykämievermeidung sicher ist (Empfehlungsgrad A). Die perioperative

Diabeteseinstellung sollte in Absprache mit dem Patienten unter interdisziplinärer Zusammenarbeit von Diabetologe, Operateur und Anästhesist erfolgen (Empfehlungsgrad B).

Bei allen Patienten mit Typ-1-Diabetes und (prä-) terminaler Niereninsuffizienz sollte die Möglichkeit einer kombinierten Pankreas-Nierentransplantation geprüft werden (Empfehlungsgrad B)

Bei allen Patienten mit Typ-1-Diabetes und schwerer metabolischer Instabilität mit Hypoglykämien und/oder Hypoglykämiewahrnehmungs-störung sollten zunächst die konservativen Möglichkeiten der Therapieoptimierung einschließlich technischer Hilfsmittel ausgeschöpft und bei Versagen die Optionen einer Betazellersatztherapie (Insel- oder Pankreastransplantation) geprüft werden. (Empfehlungsgrad B).

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