Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

sowie

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

Vorgang: Insulin degludec

Stand: März 2015

Gemeinsamer Bundesausschuss

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

Insulin degludec
zur Behandlung des Diabetes mellitus bei Erwachsen**, Jugendlichen und Kindern ab 1 Jahr**

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Metformin (bei Kindern ab 10 Jahren) Insulin
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	- Verordnungseinschränkungen schnell wirkende/lang wirkende Insulinanaloga - AM-RL, Anlage III - Festbetrag SH „Antidiabetika vom Sulfonylharnstofftyp“ Gruppe 1 Stufe 2 - Festbetrag Metformin, Stufe 1 - Festbetrag Humaninsulin – „Insuline“, Gruppe 2 Stufe 2
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche*

I. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation/Beratungsanforderung)
Zu bewertendes Arzneimittel:	
Insulin degludec	„Behandlung von Patienten mit Diabetes mellitus bei Erwachsenen, **Jugendlichen und Kindern ab 1 Jahr**“
Metformin A10BA02 z.B. Metformin AbZ	Therapie des Diabetes mellitus Typ 2; insbesondere bei übergewichtigen Patienten, bei denen allein durch Diät und körperliche Betätigung keine ausreichende Einstellung des Blutzuckerspiegels erreicht wurde. - Bei Erwachsenen kann Metformin AbZ 1000 mg in Form einer Monotherapie oder in Kombination mit anderen oralen Antidiabetika bzw. Insulin angewendet werden. - **Bei Kindern ab 10 Jahren und bei Jugendlichen** kann Metformin AbZ 1000 mg in Form einer **Monotherapie oder in Kombination mit Insulin** angewendet werden.
Insulin	
z.B. Humaninsulin	Zur Behandlung des Diabetes mellitus.

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie (zVT):

Inhalt

Indikation für die Recherche bei Insulin degludec:

Behandlung des Diabetes mellitus bei Erwachsenen, **Jugendlichen und Kindern ab dem Alter von 1 Jahr. (neues AWG fett hervorgehoben)**

Berücksichtigte Wirkstoffe/Therapien:

Für das Anwendungsgebiet zugelassenen Arzneimittel, s.: „Übersicht zVT, Tabelle II. Zugelassene Arzneimittel im Anwendungsgebiet“

Systematische Recherche:

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und Evidenz-basierten systematischen Leitlinien zur Indikation ***„Diabetes mellitus bei Kinder und Jugendliche“*** durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 26.02.2015 abgeschlossen. Die Suche erfolgte in folgenden Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database), MEDLINE (PubMed), Leitlinien.de (ÄZQ), AWMF, Clinical Evidence, DAHTA, G-BA, GIN, IQWiG, NGC, NICE, TRIP.

Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Bei der Recherche wurde keine Sprachrestriktion vorgenommen. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 1386 Quellen, die anschließend nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Davon wurden 134 Quellen eingeschlossen. Insgesamt ergab dies **10** Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden. Ergänzend wurden **11** Dokumente anderer Organisationen (AWMSG, NIHR – HSC, Bruno 2011, Szypowska 2011, Garg 2010, CADTH, IQWiG, Copeland 2013) zu möglichen Komparatoren identifiziert und eingeschlossen.

Abkürzungen

ADA	American Diabetes Association
AMD	Associazione Medici Diabetologi;
ÄZQ	Ärztliches Zentrum für Qualität in der Medizin
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
AWMSG	Wales Medicines Strategy Group
CADTH	Canadian Agency for Drugs and Technolog in Health
DAHTA	Deutsche Agentur für Health Technology Assessment
ESMO	European Society for Medical Oncology
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommondation
HbA1c	glykiertes Hämoglobin
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
LoE	Level of Evidnce
NGC	National Guideline Clearinghouse
NHS CRD	National Health Services Center for Reviews and Dissemination
NICE	National Institute for Health and Care Excellence
NIHR - HSC	National Institute for Health Research – Horizon Scanning Center
RCT	randomized controlled trial (randomisierte kontrollierte Studie)
SDI	Societa` Italiana di Diabetologia
T1DM	Diabetes mellitus Typ 1
T2DM	Diabetes mellitus Typ 2
TRIP	Turn Research into Practice Database
WHO	World Health Organization

Teil 1: Diabetes mellitus Typ 1

IQWiG Berichte/ G-BA Beschlüsse

IQWiG, 2009 Kurzwirksame Insulinanaloga bei Kindern und Jugendlichen mit Diabetes mellitus Typ 1 Abschlussbericht (A08-01) [11]	**Fragestellung/Ziele:** Die Ziele der vorliegenden Untersuchung waren • die Nutzenbewertung einer langfristigen Behandlung mit Insulin Aspart, Insulin Glulisin oder Insulin Lispro, jeweils im Vergleich zu einer Behandlung mit kurzwirksamem Humaninsulin und • die vergleichende Nutzenbewertung der 3 o. g. kurzwirksamen Insulinanaloga untereinander jeweils bei Kindern und Jugendlichen mit Diabetes mellitus Typ 1 hinsichtlich patientenrelevanter Therapieziele. Über die Nutzenbewertung hinaus sollten Kurzzeiteffekte der zu untersuchenden Interventionen hinsichtlich der Zielgrößen des Berichts dargestellt werden. Der vorliegende Bericht soll den Nutzen einer Langzeitbehandlung kurzwirksamer Insulinanaloga sowohl im Vergleich zu Humaninsulin als auch untereinander darstellen. Bezüglich mikrovaskulärer Folgekomplikationen sind insbesondere mehrjährige Studien als relevant anzusehen. Hinsichtlich einer Beurteilung der Therapiequalität sind evtl. auch kürzere Studien aussagekräftig, sofern die Blutzucker senkende Wirkung über mehrere Monate hinreichend sicher beurteilt und einem möglichen Effekt auf patientenrelevante Therapieziele (z. B. Hypoglykämien) gegenübergestellt werden kann. In die vorliegende Untersuchung gingen daher nur Studien mit einer Laufzeit von mindestens 24 Wochen ein, um eine hinreichend lange Behandlungs- und

	Beobachtungsdauer nach der Ein- bzw. Umstellungsphase zu gewährleisten. **Population:** Eingeschlossen wurden Studien zu Patienten mit manifestem Diabetes mellitus Typ 1 (laut Studienangabe, z. B. nach Definition der WHO), die zum Zeitpunkt des Studieneinschlusses jünger als 18 Jahre waren. Für Insulin Glulisin ergab sich aus dem Zulassungsstatus darüber hinaus folgende zusätzliche Charakterisierung der Population: Insulin Glulisin ist laut Fachinformation nicht zugelassen bei Kindern unter 6 Jahren. Studien, in die auch Patienten unter 6 Jahren (Insulin Glulisin) oder Patienten ab 18 Jahren (alle Insulinanaloga) eingeschlossen waren, wurden berücksichtigt, sofern • der Anteil der relevanten Patienten (< 18 Jahre; für Insulin Glulisin auch ≥ 6 Jahre) mindestens 80 % betrug oder • entsprechende Subgruppenanalysen mit mindestens 10 Kindern / Jugendlichen in jeder Behandlungsgruppe vorlagen. **Endpunkte**: Für die Untersuchung wurden folgende Zielgrößen verwendet, die eine Bewertung patienten-relevanter Therapieziele ermöglichen: • Erblindung sowie deren Vorstufen (Veränderungen des Augenhintergrundes oder des Visus) • terminale Niereninsuffizienzen mit Dialysenotwendigkeit • Amputationen (Minor- und Majoramputationen) • ketoazidotische Komata • Qualität der Blutzucker senkenden Therapie unter gemeinsamer Betrachtung des HbA1c-Werts und der Hypoglykämierate (schwere

	und nicht schwere Hypoglykämien) • Gesamtmortalität • kardiovaskuläre Morbidität • kardiovaskuläre Mortalität • zerebrovaskuläre Morbidität • zerebrovaskuläre Mortalität • gefäßbedingte nichtkardiovaskuläre und nichtzerebrovaskuläre Morbidität • gefäßbedingte nichtkardiovaskuläre und nichtzerebrovaskuläre Mortalität • körperliche Entwicklungsstörungen • psychosoziale Entwicklungsstörungen • stationäre Behandlungen jeglicher Ursache • durch Hyperglykämie bedingte Symptomatik • unerwünschte Arzneimittelwirkungen • gesundheitsbezogene Lebensqualität • Therapiezufriedenheit **Ergebnis:** 4 relevante Studien: • Lispro vs. Humaninsulin (Studie Z015 [Subgruppe]) n= 38 • Aspart vs. Humaninsulin (Studie 1507) n= 41 • Aspart vs. Humaninsulin vs. Lispro (Studie 2126) n=378

	• Glulisin vs. Lispro (Studie D3001) n=572

Tabelle 2: Operationalisierung der Zielgrößen in den Einzelstudien

Zielgrößen der Nutzenbewertung	**Operationalisierung der Zielgrößen in den Studien**
Erblindung sowie deren Vorstufen	▪ keine relevanten Daten verfügbar
terminale Niereninsuffizienz mit Dialysenotwendigkeit	▪ keine relevanten Daten verfügbar
Amputationen (Minor- und Majoramputationen)	▪ keine relevanten Daten verfügbar
ketoazidotische Komata	▪ in den Studien lediglich im Rahmen der Sicherheitsauswertungen erfasst (auch Ketoazidosen ohne Angabe eines Komas)
Qualität der Blutzucker senkenden Therapie unter gemeinsamer Betrachtung des HbA1c-Werts und der Hypoglykämierate (schwere und nicht schwere Hypoglykämien)	▪ schwere (nächtliche) Hypoglykämien ▪ nicht schwere (nächtliche) Hypoglykämien ▪ HbA1c-Wert
Gesamtmortalität	▪ Todesfälle (lediglich im Rahmen der Sicherheitsauswertungen erfasst)
kardiovaskuläre Morbidität	▪ keine relevanten Daten verfügbar
kardiovaskuläre Mortalität	▪ keine relevanten Daten verfügbar
zerebrovaskuläre Morbidität	▪ keine relevanten Daten verfügbar
zerebrovaskuläre Mortalität	▪ keine relevanten Daten verfügbar
gefäßbedingte nicht kardiovaskuläre und nicht zerebrovaskuläre Morbidität	▪ keine relevanten Daten verfügbar
gefäßbedingte nicht kardiovaskuläre und nicht zerebrovaskuläre Mortalität	▪ keine relevanten Daten verfügbar
stationäre Behandlungen jeglicher Ursache	▪ keine relevanten Daten verfügbar
körperliche Entwicklungsstörungen	▪ keine relevanten Daten verfügbar
psychosoziale Entwicklungsstörungen	▪ keine relevanten Daten verfügbar
durch Hyperglykämie bedingte Symptomatik	▪ keine relevanten Daten verfügbar
unerwünschte Arzneimittelwirkungen	▪ schwerwiegende unerwünschte Ereignisse ▪ Studienabbruch wegen unerwünschter Ereignisse ▪ Gesamtrate unerwünschter Ereignisse
gesundheitsbezogene Lebensqualität	▪ keine relevanten Daten verfügbar
Therapiezufriedenheit	▪ keine relevanten Daten verfügbar

	Langfristige Folgekomplikationen In der Gesamtschau ergab sich hinsichtlich des Auftretens langfristiger Folgekomplikationen kein Beleg für einen Zusatznutzen eines der 3 kurzwirksamen Insulinanaloga im Vergleich zu Humaninsulin oder untereinander. Stationäre Behandlungen Die Häufigkeit von stationären Behandlungen war in keiner Studie als primäre oder sekundäre Zielgröße definiert. Für alle Studien lagen aber im Rahmen der Auswertungen der unerwünschten Ereignisse Angaben zu stationären Behandlungen vor. • Insulinanaloga vs. Humaninsulin Die Notwendigkeit, die Patienten stationär zu behandeln, trat in den Studien zum Vergleich der Insulinanaloga mit Humaninsulin selten auf. In keiner der Studien zeigte sich ein statistisch signifikanter Unterschied zwischen den Behandlungsgruppen. • Insulinanaloga im Direktvergleich: Insgesamt ergab sich hinsichtlich der Häufigkeit stationärer Behandlungen kein Beleg für einen Unterschied zwischen Insulin Aspart bzw. Insulin Glulisin und Insulin Lispro. Ketoazidosen und ketoazidotische Komata • Insulinanaloga vs. Humaninsulin Insgesamt ergab sich hinsichtlich des Auftretens diabetischer Ketoazidosen kein Beleg für einen Unterschied zwischen Insulin Aspart bzw. Insulin Lispro und Humaninsulin. • Insulinanaloga im Direktvergleich Insgesamt ergab sich hinsichtlich des Auftretens von diabetischen Ketoazidosen kein Beleg für einen Unterschied zwischen Insulin Aspart bzw. Insulin Glulisin und Insulin Lispro. Insgesamt waren allerdings nur

	wenige Daten für die Bewertung vorhanden. Gesundheitsbezogene Lebensqualität • Insulinanaloga vs. Humaninsulin Die gesundheitsbezogene Lebensqualität stellte lediglich in 1 Studie zum Vergleich von Insulin Lispro mit Humaninsulin (Z015) eine Zielgröße dar.[…]. Zusammenfassend ergab sich hinsichtlich der Lebensqualität kein Beleg für einen Unterschied zwischen kurzwirksamen Insulinanaloga und Humaninsulin. • Insulinanaloga im Direktvergleich Die Zielgröße gesundheitsbezogene Lebensqualität wurde in den Studien 2126 und D3001 zum Vergleich der Insulinanaloga untereinander nicht untersucht. Es ergab sich somit hinsichtlich dieser Zielgröße kein Beleg für einen Unterschied zwischen den kurzwirksamen Insulinanaloga. Therapiezufriedenheit Insgesamt ergab sich somit hinsichtlich der Therapiezufriedenheit kein Beleg für einen Unterschied zwischen den kurzwirksamen Insulinanaloga und Humaninsulin sowie zwischen den kurzwirksamen Insulinanaloga untereinander. Hypoglykämien unter Berücksichtigung des HbA1c-Werts • Insulinanaloga vs. Humaninsulin Zusammenfassend ergab sich hinsichtlich der Senkung des HbA1c-Werts kein Beleg für einen Unterschied zwischen Insulin Aspart bzw. Insulin Lispro und Humaninsulin. • Insulinanaloga im Direktvergleich Zusammenfassend ergab sich hinsichtlich der Senkung des HbA1c-Werts kein Beleg für einen Unterschied zwischen den kurzwirksamen Insulinanaloga.

	Hypoglykämien • Schwere (nächtliche) Hypoglykämien - Insulinanaloga vs. Humaninsulin Insgesamt ergab sich hinsichtlich der schweren und schweren nächtlichen Hypoglykämien kein Beleg für einen Unterschied zwischen den in den Studien untersuchten kurzwirksamen Insulinanaloga und Humaninsulin. - Insulinanaloga im Direktvergleich Insgesamt ergab sich hinsichtlich der schweren und schweren nächtlichen Hypoglykämien kein Beleg für einen Unterschied zwischen den in den Studien untersuchten kurzwirksamen Insulinanaloga. • Nicht schwere (nächtliche) Hypoglykämien Sämtliche Ergebnisse aus den 4 Studien sind […] als nicht ausreichend messsicher anzusehen und daher ohne Aussagekraft. • Gemeinsame Betrachtung der langfristigen Blutzuckersenkung und der Hypoglykämien - Insulinanaloga vs. Humaninsulin Aus der gemeinsamen Betrachtung aus Blutzuckeränderung und schweren Hypoglykämien (inklusive nächtlichen) ergab sich damit kein Beleg für einen Unterschied zwischen den untersuchten kurzwirksamen Insulinanaloga gegenüber Humaninsulin. - Insulinanaloga im Direktvergleich Aus der gemeinsamen Betrachtung aus Blutzuckeränderung und schweren Hypoglykämien (inklusive nächtlichen) ergab sich insgesamt kein Beleg für einen Unterschied zwischen den untersuchten kurzwirksamen Insulinanaloga. Sonstige unerwünschte Arzneimittelwirkungen

	• <u>Insulinanaloga vs. Humaninsulin</u> Insgesamt ergab sich hinsichtlich des Auftretens schwerwiegender unerwünschter Ereignisse sowie der Rate an Studienabbrechern wegen unerwünschter Ereignisse kein Beleg für einen Unterschied zwischen Insulin Aspart bzw. Insulin Lispro und Humaninsulin. • <u>Insulinanaloga im Direktvergleich</u> Insgesamt ergab sich hinsichtlich des Auftretens schwerwiegender unerwünschter Ereignisse sowie der Rate an Studienabbrechern wegen unerwünschter Ereignisse kein Beleg für einen Unterschied zwischen Insulin Aspart bzw. Insulin Glulisin und Insulin Lispro. **Fazit** Es gibt keinen Beleg für einen Zusatznutzen der kurzwirksamen Insulinanaloga gegenüber Humaninsulin oder im Direktvergleich untereinander. Auch gibt es keinen Beleg für einen höheren oder geringeren Schaden der kurzwirksamen Insulinanaloga gegenüber Humaninsulin oder im Direktvergleich untereinander. Für die Behandlung von Kindern und Jugendlichen mit kurzwirksamen Insulinanaloga lagen ausschließlich Studien mit einer maximalen Behandlungsdauer von 1 Jahr vor. In allen Studien wurden die kurzwirksamen Insulinanaloga im Rahmen einer Basis-Bolus-Therapie untersucht, wobei keine relevanten Studien zur Anwendung in der Pumpentherapie identifiziert wurden. Es lagen keine Langzeitstudien vor, die auf die Untersuchung von mikro- und makrovaskulären Folgeerkrankungen oder von körperlichen oder psychosozialen Entwicklungsstörungen ausgerichtet waren. Es fehlen zudem valide Daten zur gesundheitsbezogenen Lebensqualität und Therapiezufriedenheit.
IQWIG, 2010 Langwirksame Insulinanaloga zur	**Fragestellung/Ziele:** Ziele der vorliegenden Untersuchung waren • die Nutzenbewertung einer langfristigen Behandlung mit einem

Behandlung des Diabetes mellitus Typ 1 [13]	langwirksamen Insulinanalogon im Vergleich zu einer Behandlung mit einem auf Humaninsulin basierenden Verzögerungsinsulin und • die vergleichende Nutzenbewertung langwirksamer Insulinanaloga untereinander jeweils bei Patienten mit Diabetes mellitus Typ 1 hinsichtlich patientenrelevanter Therapieziele. **Population:** Patienten mit manifestem Diabetes mellitus Typ 1 laut Studienangabe, z. B. nach Definition der WHO. **Endpunkte**: Für die Untersuchung wurden folgende Zielgrößen verwendet, die eine Beurteilung patientenrelevanter Therapieziele ermöglichen: • Erblindung sowie deren Vorstufen (Veränderungen des Augenhintergrundes oder des Visus) • terminale Niereninsuffizienz mit Dialysenotwendigkeit • Amputation (Minor- und Majoramputation) • ketoazidotisches Koma • gemeinsame Betrachtung des HbA1c-Wertes und des Auftretens von Hypoglykämien, insbesondere schwerer Hypoglykämien* • Gesamtmortalität • kardiale Morbidität und Mortalität • zerebrale Morbidität und Mortalität • gefäßbedingte nichtkardiale und nichtzerebrale Morbidität und Mortalität

	• stationäre Behandlung jeglicher Ursache • Symptomatik bedingt durch chronische Hyperglykämie • unerwünschte Arzneimittelwirkungen • gesundheitsbezogene Lebensqualität (einschließlich der Berufsfähigkeit und sonstiger Aktivitäten des täglichen Lebens) • Therapiezufriedenheit • Für Kinder und Jugendliche wurden zusätzlich folgende Zielgrößen verwendet: - körperliche Entwicklungsstörungen - psychosoziale Entwicklungsstörungen *Die beiden Zielgrößen HbA1c-Wert und Hypoglykämien können nicht unabhängig voneinander betrachtet werden, da sie in direktem Zusammenhang stehen. Der HbA1c-Wert wird dabei einerseits zur Interpretation der Ergebnisse zu Hypoglykämien herangezogen. Andererseits gilt der HbA1c-Wert bei Diabetes mellitus Typ 1 als Surrogatendpunkt für das Auftreten von mikrovaskulären Komplikationen. Eine Interpretation ist sinnvoll unter gleichzeitiger Berücksichtigung des Auftretens von Hypoglykämien. **Ergebnis /Fazit:** Der Langzeitnutzen und -schaden der langwirksamen Insulinanaloga ist generell nicht ausreichend untersucht. Nur eine der relevanten Studien hatte eine Laufzeit von 24 Monaten, die übrigen Studien liefen nur ca. 6 bis 12 Monate. Ein Großteil der Studien zum Vergleich der Insulinanaloga mit NPH-Insulin war zudem nur eingeschränkt zu verwerten, da das NPH-Insulin nicht optimiert eingesetzt wurde. **Studien mit Kindern und Jugendlichen** • <u>Insulin Glargin vs. NPH-Insulin</u> Es gibt keinen Beleg für einen Zusatznutzen von Insulin Glargin gegenüber NPH-Insulin.

	• <u>Insulin Detemir vs. NPH-Insulin</u> Es gibt keinen Beleg für einen Zusatznutzen von Insulin Detemir gegenüber NPH-Insulin. Unter Insulin Detemir zeigte sich eine geringere Gewichtszunahme, und zwar im Mittel von ca. 0,4 kg/m2 (gemessen am BMI). Die Relevanz des Unterschieds ist unklar. • <u>Insulin Detemir vs. Insulin Glargin</u> Keine Studie evaluierte Insulin Detemir gegenüber Insulin Glargin bei Kindern und Jugendlichen. Daher gibt es keinen Beleg für einen Zusatznutzen eines Insulinanalogons gegenüber dem jeweils anderen.
G-BA, 2014 [8] Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Insulin degludec Siehe auch: **IQWiG, 2014:** Insulin degludec, Bewertungsmodul I, Diabetes mellitus	a) Behandlung des Diabetes mellitus Typ 1 bei Erwachsenen • **Zweckmäßige Vergleichstherapie:** Humaninsulin • **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Humaninsulin:** Ein Zusatznutzen ist nicht belegt.

Typ 1 Nutzenbewertung gemäß § 35a SGB V [14]	

Cochrane Reviews

Es konnten keine relevanten Cochrane Reviews zum Anwendungsgebiet identifiziert.

Systematische Reviews

Es konnten keine relevanten Systematische Reviews zum Anwendungsgebiet identifiziert.

Scottish Intercollegiate Guidelines Network (SIGN). 2010 Management of diabetes. A national clinical guideline [20]	**Fragestellung(en)** 1. In people with type 1 diabetes, which of the following therapies are most beneficial in terms of glycaemic control, hypoglycaemia, diabetic ketoacidosis and quality of life (of patient/parents/carers)? • multiple injection therapy (≥3 injections per day) • insulin pump therapy. 2. Which of the following insulin in people with type 1 diabetes is most beneficial in terms of glycaemic control (HbA1c), hypoglycaemia and quality of life? • analogue (glargine; detemir; aspart; lispro; glulisine) • non-analogue.
	Methodik <u>Grundlage der Leitlinie:</u> systematische Evidenzaufbereitung ohne formalisierte Konsensusprozesse - eigene Checklisten - eigenes Graduierungssystem - repräsentatives Gremium - CoI-Erklärungen auf Anfrage einsehbar - öffentliche Konsultation und Expertenreview • Suchzeitraum: 2003-2009 • Update der SIGN guideline on management of diabetes (SIGN 55) published in 2001 • Weitere Kriterien für die Qualität einer LL:

	- Empfehlungen mit Literaturstellen verknüpft **LoE/GoR:** Siehe Anhang 1 dieser Synopse **Sonstige (methodische) Hinweise:** • Informationen/Empfehlungen zu Kindern und Jugendlichen mit Typ II Diabetes liegen in der LL nicht vor**.**
	Freitext / Empfehlungen / Hinweise 5.3.2 INSULIN REGIMEN **Intensive insulin therapy should be delivered as part of a comprehensive support package. (GoR B)** Evidence: 6. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The **Diabetes Control and Complications Trial Research Group**. N Engl J Med 1993;329(14):977-86. (LoE 1+) 194. Effect of intensive diabetes treatment on the development and progression of long-term complications in adolescents with insulindependent diabetes mellitus: Diabetes Control and Complications Trial. **Diabetes Control and Complications Trial Research Group**. J Pediatr 1994;125(2):177-88. (LoE 1+) • regarding the impact of an intensive insulin regimen upon long term control • also involved a comprehensive patient support element (diet and exercise plans, monthly visits to the healthcare team etc) • did not include children aged less than 13 years • intensive insulin therapy (four injections or more per day or pump insulin) significantly improves glycaemic control over a sustained period compared with conventional insulin therapy (two injections per day) • due to the study design, it is impossible to separate the benefits of

	intensive insulin therapy from intensive support Rapid-acting/basal insulin analogues in children and adolescents **Children and adolescents may use either insulin analogues (rapid-acting and basal), regular human insulin and NPH preparations or an appropriate combination of these. (GoR B)** **The insulin regimen should be tailored to the individual child to achieve the best possible glycaemic control without disabling hypoglycaemia. (GoR C)** Evidence: 195. Singh SR, et al. Efficacy and safety of insulin analogues for the management of diabetes mellitus: a meta-analysis. Can Med Assoc J 2009;180(4):385-97. (LoE 1++) 196. Siebenhofer A, et al. Short acting insulin analogues versus regular human insulin in patients with diabetes mellitus (Cochrane Review). In: The Cochrane Library, Issue 2, 2006. London: Wiley. (LoE 1++) 203. Robertson KJ, et al. Insulin detemir compared with NPH insulin in children and adolescents with Type 1 diabetes. Diabet Med. 2007;24(1):27-34. (LoE 1+) • one systematic review identified four studies in pre-pubertal children and one study involving adolescents o showed no difference in glycaemic control (HbA1c) between rapid-acting insulin analogues and regular human insulin, o overall and nocturnal rates of hypoglycaemia with rapid-acting insulin analogues not significantly different from those using regular human insulin o one study showed reduction in rates of both overall and nocturnal hypoglycaemia when using rapid-acting insulin analogues • a meta-analysis reviewed the same studies as the systematic review with one additional RCT o also showed no significant difference between HbA1c or

	hypoglycaemia between rapid-acting analogues or regular human insulin o compared with NHS insulins, neither of the basal insulin analogues, glargine nor detemir, was associated with a significant difference in HbA1c • one trial comparing detemir with NPH in pre-pubertal children and adolescents o no difference in hypoglycaemia with glargine when compared with NPH insulin o no differences in severe hypoglycaemia observed though minor reductions in nocturnal and overall hypoglycaemia
NICE, 2004 Diagnosis and management of type 1 diabetes in children and young people [17]	**Fragestellung(en)** This guideline addresses the diagnosis and management of children and young people with type 1 diabetes. It has been developed with the aim of providing guidance on: • initial management at diagnosis (including consideration of admission criteria and initial insulin regimens) […]
	Methodik Grundlage der Leitlinie: systematische Evidenzaufbereitung und (fomalisierte) Konsensusprozesse - repräsentatives Gremium - CoI-Erklärungen im Anhang einsehbar – „external review“ • Update: „Review summary: Consultation on review proposal with stakeholders: **01 June 2011 - 14 June 2011,** Review decision date: **August 2011,** Review decision: **Following the recent review recommendation, an** update of this guideline is in progress**“, letzte**

Aktualisierungen in 2014

- Suchzeitraum: bis 2003
- Weitere Kriterien für die Qualität einer LL:
  - Empfehlungen sind indirekt über die Kapitelstruktur mit Literaturstellen verknüpft
  -

LoE:

Ia	Systematic review or meta-analysis of randomised controlled trials
Ib	At least one randomised controlled trial
IIa	At least one well-designed controlled study without randomisation
IIb	At least one well-designed quasi-experimental study, such as a cohort study
III	Well-designed non-experimental descriptive studies, such as comparative studies, correlation studies, case–control studies and case series
IV	Expert committee reports, opinions and/or clinical experience of respected authorities

GoR:
each recommendation graded according to the level of evidence upon which it was based using the established system (siehe oben). For issues of therapy or treatment, the best possible level of evidence (a systematic review or meta-analysis or an individual RCT) would equate to a grade A recommendation. For issues of prognosis, the best possible level of evidence (a cohort study) would equate to a grade B recommendation. However, this should not be interpreted as an inferior grade of

recommendation because it represents the highest level of relevant evidence.

A	Based directly based on level I evidence
B	Based directly on level II evidence or extrapolated from level I evidence
C	Based directly on level III evidence or extrapolated from level I or level II evidence
D	Based directly on level IV evidence or extrapolated from level I, level II or level III evidence
GPP	Good practice point based on the view of the Guideline Development Group
NICE TA	Recommendation taken from a NICE Technology Appraisal

Freitext/Empfehlungen/Hinweise

4.2 Insulin regimens

Pre-school and primary school children with type 1 diabetes should be offered the most appropriate individualised regimens to optimise their glycaemic control. (GoR C)

Young people with type 1 diabetes should be offered multiple daily injection regimens to help optimise their glycaemic control. (GoR A)

Multiple daily injection regimens should be offered only as part of a package of care that involves continuing education, dietary management, instruction on the use of insulin delivery systems and blood glucose monitoring,

	emotional and behavioural support, and medical, nursing and dietetic expertise in paediatric diabetes, because this improves glycaemic control. (GoR C) Children and young people using multiple daily injection regimens should be informed that they may experience an initial increase in the risk of hypoglycaemia and short-term weight gain. (GoR B) Children and young people with type 1 diabetes and their families should be informed about strategies for the avoidance and management of hypoglycaemia. (GoR C) Young people who do not achieve satisfactory glycaemic control with multiple daily injection regimens should be offered additional support and, if appropriate, alternative insulin therapy (once-, twice- or three-times daily mixed insulin regimens or continuous subcutaneous insulin infusion using an insulin pump). (GoR GPP) Young people with type 1 diabetes who have difficulty adhering to multiple daily injection regimens should be offered twice-daily injection regimens. (GoR GPP). Continuous subcutaneous insulin infusion (or insulin pump therapy) is recommended as an option for people with type 1 diabetes provided that: • multiple-dose insulin therapy (including, where appropriate, the use of insulin glargine) has failed;* and • those receiving the treatment have the commitment and competence to use the therapy effectively. (GoR NICE TA) *People for whom multiple-dose therapy has failed are considered to be those for whom it has been impossible to maintain an HbA1c level no greater than 7.5% (or 6.5% in the presence of microalbuminuria or adverse features of the metabolic syndrome) without disabling hypoglycaemia occurring, despite a high level of self care of their diabetes. ‘Disabling

	hypoglycaemia', for the purpose of this guidance, means the repeated and unpredicted occurrence of hypoglycaemia requiring thirdparty assistance that results in continuing anxiety about recurrence and is associated with significant adverse effect on quality of life. (GoR NICE TA) Continuous subcutaneous insulin infusion therapy should be initiated only by a trained specialist team, which should normally comprise a physician with a specialist interest in insulin pump therapy, a diabetes specialist nurse and a dietitian. (GoR NICE TA) All individuals beginning continuous subcutaneous insulin infusion therapy should be provided with specific training in its use. Ongoing support from a specialist team should be available, particularly in the period immediately following the initiation of continuous subcutaneous insulin infusion. It is recommended that specialist teams should agree a common core of advice appropriate for continuous subcutaneous insulin infusion users. (GoR NICE TA) Established users of continuous subcutaneous insulin infusion therapy should have their insulin management reviewed by their specialist team so that a decision can be made about whether a trial or a switch to multiple-dose insulin incorporating insulin glargine would be appropriate. (GoR NICE TA) <u>4.3 Insulin preparations</u> Children and young people with type 1 diabetes should be offered the most appropriate insulin preparations (rapid-acting insulin analogues, short-acting insulins, intermediate-acting insulins, long-acting insulin analogues or biphasic insulins) according to their individual needs and the instructions in the patient information leaflet supplied with the product with the aim of obtaining an HbA1c level of less than 7.5% without frequent disabling hypoglycaemia and maximising quality of life. (LoE GPP) Children and young people with type 1 diabetes using multiple daily insulin

	regimens should be informed that injection of rapid-acting insulin analogues before eating (rather than after eating) reduces postprandial blood glucose levels and thus helps to optimise blood glucose control. (LoE B) For pre-school children with type 1 diabetes it may be appropriate to use rapid-acting insulin analogues shortly after eating (rather than before eating) because food intake can be unpredictable. (LoE GPP) Children and young people with type 1 diabetes who use insulin preparations containing intermediate-acting insulin should be informed that these preparations should be mixed before use according to the instructions in the patient information leaflet supplied with the product. (LoE GPP) <u>4.5 Non-insulin agents (oral antidiabetic drugs)</u> Children and young people with type 1 diabetes should not be offered acarbose or sulphonylureas (glibenclamide, gliclazide, glipizide, tolazamide or glyburide) in combination with insulin because they may increase the risk of hypoglycaemia without improving glycaemic control. (LoE A) Metformin in combination with insulin is suitable for use only within research studies because the effectiveness of this combined treatment in improving glycaemic control is uncertain. (LoE A)

Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren

All Wales Medicines Strategy Group (AWMSG). 2012 Insulin detemir (Levemir®) 100 U/ml solution for injection [2]	Recommendation of AWMSG Insulin detemir (Levemir®) is recommended as an option for use within NHS Wales for the treatment of diabetes mellitus in children aged 2–5 years. Additional notes: AWMSG is of the opinion that insulin detemir (Levemir®) may be appropriate for use within NHS Wales prescribed under specialist recommendation for the indication under consideration. Please refer to the Summary of Product Characteristics for the full licensed indication. In reaching the above recommendation AWMSG has taken account of the AWMSG Secretariat Assessment Report (ASAR), the preliminary appraisal recommendation (PAR) and the applicant company's response to the PAR, clinical expert opinion (where available), the views of patients/patient carers (where available) and the lay member perspective. This recommendation was ratified by the Minister for Health and Social Services in December 2012 and will be considered for review in December 2015.
All Wales Medicines Strategy Group (AWMSG). 2013 Insulin glargine (Lantus®) 100 units/ml solution for injection [3]	Statement of Advice In the absence of a submission from the holder of the marketing authorisation, insulin glargine (Abasria®) cannot be endorsed for use within NHS Wales for the treatment of diabetes mellitus in adults, adolescents and children aged 2 years and above. Advice context: The All Wales Medicines Strategy Group (AWMSG) takes into account the National Institute for Health and Care Excellence (NICE) future work programme when considering whether a product will be appraised. To avoid duplication of effort, AWMSG would not normally consider undertaking an appraisal if NICE intend to publish final technology appraisal advice for the same product within twelve months of the projected Form B

	submission date. AWMSG advice is interim to that of NICE, should NICE subsequently publish guidance. The above medicine cannot be endorsed for use within NHS Wales as a technology appraisal by NICE or AWMSG has not been undertaken. The medicine should NOT be prescribed routinely within NHS Wales for the indication stated above. In the absence of guidance issued by NICE or AWMSG, clinicians should continue to exercise their clinical judgement when providing care for an individual patient. This should be in consultation with the patient and/or guardian or carer, based on the best available evidence. This statement will be removed on receipt of a submission (i.e. the full submission [Forms A and B] or limited submission [Forms A and C]) or when final technology appraisal advice from NICE becomes available.
NIHR Horizon Scanning Centre (NIHR HSC). 2011 Insulin degludec/insulin aspart (DegludecPlus) for type 1 diabetes mellitus [18]	<u>Target group: Type 1 diabetes mellitus.</u> Innovation and/or advantages: If licensed, insulin degludec may provide an additional long-acting treatment option for this patient group who require insulin replacement therapy. NHS or Government priority area: This topic is relevant to The National Service Framework for Children, Young People and Maternity Services (2004) and The National Service Framework for Diabetes (2007). Claimed or potential impact – speculative: Reduction in associated morbidity or Improved quality of life for patients and/or carers
NIHR Horizon Scanning Centre (NIHR HSC). 2011 Insulin degludec/insulin aspart (DegludecPlus) for type 1 diabetes mellitus [19]	<u>Target group: Type 1 diabetes mellitus.</u> Innovation and/or advantages: If licensed, insulin degludec/insulin aspart may provide an additional treatment option for this patient group, combining long-acting and short-duration insulin analogues in a single injectable product. NHS or Government priority area: This topic is relevant to The National Service Framework for Children, Young People and Maternity Services (2004) and The National Service Framework for Diabetes (2007). Claimed or potential impact – speculative: Reduction in associated morbidity or Improved quality of life for patients and/or carers

Bruno, 2011 Highlights from “Italian Standards of Care for Diabetes Mellitus 2009 - 2010” [4]	The Italian Standards for the Treatment of Diabetes Mellitus proposed herein have been drafted by two Italian scientific diabetes societies (AMD and SID) to provide clinicians, patients, researchers and those involved in diabetes care with recommendations for the diagnosis and treatment of diabetes and its complications. The Italian Standards for the Treatment of Diabetes Mellitus can be deemed as a scientific reference for diabetes disease
	Methodik*:* There are many international guidelines for diabetes mellitus: specifically, the Standards of Medical Care published by the American Diabetes Association (ADA) has long been a reference for diabetologists due to its pragmatic nature and systematic updates, together with evidence levels for each recommendation. However, not always treatment standards, which suit other populations and social and healthcare setting, can be applied to the Italian reality; moreover, it is appropriate to provide a national position when differences of opinion circulate in the international diabetes community. […] - Update: Revised document (The document will be revised every two years by a specially appointed Committee.) - Suchzeitraum: Keine Angaben - systematische Recherche: keine Angaben • The project was commissioned by AMD and SID National Steering Committees. They requested a revision of the previous document, which was drafted by experts and discussed by a multidisciplinary panel, and confirmed as official document on the position of scientific societies. • The Editorial Team, composed of 25 diabetologists and a Coordinating Committee of four diabetologists, was responsible for updating or revising specific topics of the text, as well as adding some emerging issues not addressed in the previous version. • A highly interdisciplinary panel of diabetologists and members of other healthcare professions dedicated to diabetes care and lay members was created to guarantee the implementation of the document. • The first draft of the updated text was published online for 20 days, on the AMD and SID websites with an email address made available to members of both societies and anyone who wanted to raise

	criticism, make comments or suggest additions. The suggestions and criticisms of about 30 persons were received, evaluated and largely integrated to those provided by panel members. AMD and SID wish to thank these people for their valuable contribution and suggestions. The Editorial Team analytically and critically evaluated the new contributions within the writing group, and eventually edited the technical version of the final document. • Lastly, the document was approved by AMD and SID National Steering Committees. **LoE und GoR:**

Table 1 Evidence levels and strength of recommendations.

Evidence level	
Type of evidence	
I	Evidence obtained from controlled randomized clinical trials and/or systematic reviews of randomized trials.
II	Evidence obtained from one well-conducted and adequately powered randomized controlled trial.
III	Evidence obtained from non-randomized cohort studies with either concurrent or historical controls or their metanalyses.
IV	Evidence obtained from either retrospective case-control studies or their metanalyses.
V	Evidence obtained from case studies ("series of cases") without a control group.
VI	Expert consensus, as specified in both the guidelines and consensus conferences, or opinions of team members that drafted these guidelines.
Strength of recommendations	
Strength	
A	The performance of a special procedure or diagnostic investigation is highly recommended. This level of strength indicates a special recommendation based upon scientific evidence of good quality, though not necessarily type I or II.
B	There is doubt that the procedure or intervention in question must always be recommended, but it is deemed that its performance must be carefully considered.
C	There is a basic uncertainty either for or against the recommendation to perform the procedure or intervention.
D	Implementation of this procedures is not recommended
E	The implementation of this procedure is strongly advised against.

Sonstige methodische Hinweise:

- Kein systematischer Review

Freitext/Empfehlungen/Hinweise

Diabetes care in children and adolescents - Type 1 Diabetes

<u>Empfehlung 1:</u>

- As with other age groups, the treatment plan of choice for children and adolescents is basal-bolus insulin. In children aged 3 years and less the insulin treatment plan must be customized.
  (Evidence level IV, Recommendation strength B)
- Insulin analogs, rapid and long-acting, can be significantly effective in reducing the frequency of nocturnal hypoglycemia and improving post-prandial glycemic control with benefits on the quality of life.
  (Evidence level VI, Recommendation strength B)
- In selected individuals who, despite an optimal basal-bolus regimen, show poor glycemic control,

	marked metabolic instability with recurrent hypoglycemia, insulin resistance or reduced insulin requirements, the use of a pump may be indicated. *(Evidence level I, Recommendation strength B)*
Szypowska, 2011 Long-acting insulin analogue detemir compared with NPH insulin in type 1 diabetes [21]	**1. Fragestellung** The aim of the study was to compare the effect of treatment with detemir insulin vs. NPH insulin on metabolic control, hypoglycemic episodes, and body weight gain in patients with type 1 diabetes by means of a systematic review and a meta-analysis.
	2. Methodik The systematic review and meta-analysis were performed according to Cochrane Collaboration standards. Studies included in the review had to be randomized controlled trials (RCTs) with a duration of at least 12 weeks, […] In all trials, basal insulin was combined with prandial insulin (human or short-acting analogue). Studies with different prandial insulins (human regular insulin and short-acting analogue) in treatment arms were excluded. Trials which were a follow-up of a previous study, without new randomization, were also excluded. **Population:** Patients with type 1 diabetes. All patients had a history of type 1 diabetes ≥1 year. (Studies with a shorter disease duration were excluded due to there being no relevant information regarding HbA1c values, […] **Intervention:** basal-bolus therapy with long-acting insulin analogue detemir **Komparator:** basal-bolus therapy with NPH human insulin **Endpunkt:** • principle outcome variable used in assessing improvement in diabetes control: HbA1c: • The secondary outcome measures were:

	- changes in fasting plasma glucose (FPG), - weight, severe hypoglycemic episodes (as defined by the investigators), - all‑day hypoglycemic episodes - nocturnal and severe nocturnal hypoglycemic episodes**.** **Suchzeitraum**: bis November 2010 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 10 (n=3825; 3048 adults and 777 children) – Es liegen keine Subgruppenanalysen für Kinder vor. **Qualitätsbewertung der Studien:** We examined the use of the following strategies associated with a good quality trial: a) generation of allocation scheme; b) allocation concealment; c) blinding of participants, outcome assessors and data analysis (yes/no/not reported); d) intention‑to‑treat analysis (yes/no); e) comprehensive follow‑up. Allocation concealment was regarded as adequate when the randomization method used did not allow the investigator or the participant to identify or influence the intervention group before the entry of eligible participants into the study. When randomization was used, but no information about the method of randomization was available, the quality of allocation concealment was considered as unclear, and inadequate when inappropriate methods of randomization (e.g., alternate medical record numbers, unsealed envelopes, coin tossing) were used. In intention‑to‑treat (ITT) analysis, a “yes” response means that the authors had specifically reported undertaking this type of analysis and/or that our own study confirmed this finding. Conversely, “no” means that the authors did not report the use of ITT analysis and/or that we could not confirm its use in the study assessment. The patient follow‑up completeness was assessed by determining the percentage of participants excluded or lost in follow‑up. Only studies with >80% follow‑up were included. All trials contained a sufficient proportion (≥80%) of participants in the final analysis. The duration of the intervention ranged from 4 to 24 months. All included studies were multicenter. One study was crossover,

	the remainder had a parallel-group design. All studies were open-label, as detemir and NPH are visually distinguishable and patients self-administered insulin. A double-dummy technique was considered unnecessary. There was considerable clinical heterogeneity among the trials with regard to the baseline FPG, hypoglycemic episodes (all), nocturnal hypoglycemic episodes (all), and nocturnal hypoglycemic episodes (severe). In all studies except one, aspart insulin was used as prandial insulin. There was unclear allocation concealment in 1 full-length article and in all 3 unpublished studies. In 7 papers, the authors used ITT analysis of categorical data. In 2 other studies the analysis of continuous data was based on the available case analysis. Per protocol analysis was performed in 1 clinical trial. In all unpublished studies, there was no description of randomization. Withdrawals and dropouts were described adequately in all full-length studies, but there was no description of withdrawals in the clinical trial reports. Statistical methods: […] The weighted mean difference (WMD) between the treatment and control groups was selected to represent the difference in continuous outcomes. For the dichotomous measures, the relative risk (RR) between the experimental and the control groups with 95% confidence intervals (CIs) was calculated. The weights given to each study are based on the inverse of the variance. For each total, the extent of inconsistency among the results (I2) was given. In these cases, when significant heterogeneity (I2 >50%) was observed, a random-effects model was used and the sensitivity analysis was conducted.
	3. Ergebnisdarstellung: HbA1c In 5 studies, detemir was significantly better than NPH insulin, and in 5 studies it was not inferior to NPH insulin, in terms of HbA1c improvement. A meta-analysis of data from 3758 participants showed a significant reduction in HbA1c levels (WMD –0.073, 95% CI –0.135 to –0.011, P = 0.021) for patients managed with insulin detemir compared with patients treated with NPH insulin. The included studies were homogenous (I2 = 0%). Statistically significant effect was noticed in adults (7 RCTs; WMD –0.084, 95% CI –0.150 to –0.019, P = 0.011), but not in children (3 RCTs; P = 0.792); in patients with baseline HbA1c ≥8 mg% (7 RCTs; WMD –0.102, 95% CI –0.172 to –0.032, P = 0.004), but not in patients with a better baseline glycemic control (3 RCTs; P = 0.684); in studies lasting not more than 6 months (7 RCTs; WMD –0.076, 95% CI –0.148 to –0.004, P = 0.037), but not in longer studies (3 RCTs,P = 0.603).

	Fasting plasma glucose In 7 studies FPG was significantly lower in the detemir group, in 3 other trials treatment with insulin detemir was no inferior to NPH insulin. Meta-analysis of 10 studies (n = 3748) showed a statistically significant reduction of FPG in the detemir group compared with the NPH group (WMD –0.977 mmol/l, 95% CI –1.395 to –0.558, P <0.001). The included trials were significantly heterogeneous (I2 = 66.5%) and the data were pooled in a random-effects model. We have searched for reasons of heterogeneity between studies, but were not able to identify them. Hypoglycemic episodes All of the studies except 2 reported the number of patients with all-day hypoglycemic episodes and nocturnal hypoglycemic episodes. Meta-analysis of data from 3096 participants showed significant reduction of the number of patients with all-day hypoglycemic episodes in the detemir group compared with the NPH group (RR 0.978, 95% CI 0.961–0.996, P = 0.016), with an estimated risk difference (RD) of –0.02 (95% CI –0.037–0.003, P = 0.02). Pooled results from 3304 patients showed that lower number of participants managed with detemir had nocturnal hypoglycemic episodes, compared with participants treated with NPH (RR 0.877, 95% CI 0.816–0.942, P <0.001), with an estimated RD of –0.076 (95% CI –0.116 to –0.036, P <0.001). Severe hypoglycemic episodes: Data regarding hypoglycemic episodes (24 hours/diurnal) requiring assistance from another person was available from 8 studies. A meta-analysis of data from 3149 participants showed 34% relative risk reduction of severe hypoglycemic episodes inpatients managed with detemir compared with patients treated with NPH (RR 0.665, 95% CI 0.547–0.810, P <0.001), with an estimated RD of –0.028 (95% CI –0.049 to –0.007, P = 0.008). Data for severe nocturnal hypoglycemia were available from 7 studies and included 2642 participants. Results regarding severe nocturnal hypoglycemic episodes in 1 study were not consistent with the outcomes from other studies, which resulted in significant heterogeneity (I2 = 52%). Changing the data model from fixed (RR 0.617, 95% CI 0.430–0.883, P = 0.008) to random effect resulted in a statistically nonsignificant result (RR 0.687, 05% CI 0.392–1.204, P = 0.189). Body weight: Pooled results from 6 trials including 2599 participants showed significantly lower weight gain in the detemir

	group compared with the NPH group (WMD –0.779 kg, 95% CI –0.992 to –0.567, P <0.001;).
	4. Anmerkungen/Fazit der Autoren In conclusion, compared with NPH insulin, the long‑acting insulin analogue detemir used as basal insulin in basal‑bolus therapy, provides a minor benefit in terms of the HbA1c value and significantly reduces FPG in patients with type 1 diabetes. Moreover, treatment with detemir insulin decreases the risk of all‑day, nocturnal, and severe hypoglycemic episodes, and also reduces weight gain. **5. Hinweise durch FB Med)** • Es wurde keine Subgruppenanalyse für Kinder durchgeführt.
Garg, 2010 Clinical Experience with Insulin Glargine in Type 1 Diabetes [7]	**1. Fragestellung** The aim of this review is to provide a descriptive summary of the overall clinical experience with insulin glargine versus neutral protamine Hagedorn (NPH) insulin or continuous subcutaneous insulin infusion (CSII) in adults or children and adolescents with type 1 diabetes as part of a multiple daily injection (MDI) regimen.
	2. Methodik limited to randomized controlled trials **Population:** Adult and pediatric populations utilizing once-daily insulin glargine for a minimum of 12 weeks. **Intervention*:*** insulin glargine **Komparator** NPH insulin; ultralente insulin **Endpunkt** - Change from baseline in glycosylated hemoglobin (A1C), - fasting BG (FBG) or fasting plasma glucose,

	- 2-h postprandial BG (for rapid-acting insulins) **Suchzeitraum (Aktualität der Recherche):** Cutoff date of February 15, 2010 inclusive **Anzahl eingeschlossene Studien/Patienten (Gesamt):** x (n=dddd) Six studies compared insulin glargine with NPH insulin/lente insulin in children and adolescents (Table 2: siehe Anhang 2 dieser Synopse); one of these studies was excluded because the duration of treatment was <12 weeks. **Qualitätsbewertung der Studien:** Keine Angaben
	3. Ergebnisdarstellung The literature search identified six studies (seven publications) in children, ranging in duration from 9 weeks to 32 weeks (Table 2). However, the small sample size (<50 patients) in most of these studies limits their validity. The other two studies enrolled 349 and 175 patients and compared insulin glargine with either NPH insulin (once or twice daily) or NPH insulin/lente insulin. In the study by Schober et al. with children and adolescents 5–16 years of age, insulin glargine was associated with significantly greater improvements in FBG, although this did not translate into improvements in A1C. In the study by Chase et al. in adolescents and teenagers 9–17 years of age, there were no differences in the magnitude of improvement in A1C. However, after adjusting for baseline A1C, the change in A1C was significantly greater with insulin glargine than with NPH insulin/lente insulin. In terms of hypoglycemia, the study by Schober et al. revealed no difference in the rate of hypoglycemia, whereas the study by Chase et al. revealed higher rates of confirmed hypoglycemia with BG <70 mg/dL (116 vs. 94 events/ patient-year, P=0.0298).
	4. Anmerkungen/Fazit der Autoren In conclusion, basal–bolus insulin regimens or CSII should be considered a treatment of choice for type 1 diabetes. The use of long- and short-acting insulin analogs within these regimens offers significant clinical advantages over intermediate-and short-acting human insulins that may enable more patients to reach glycemic targets and reduce the considerable burden of complications associated with poor control in patients with type 1 diabetes.

	5. Hinweise durch FB Med: • Kein systematischer Review.

Primärstudien

Eine systematische Suche nach relevanten Primärstudien im Anwendungsgebiet wurde bisher nicht in Auftrag gegeben.

G-BA, 2014 Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Insulin degludec [8] Siehe auch: **IQWiG, 2014:** Insulin degludec, Bewertungsmodul II, Diabetes mellitus Typ 2 Nutzenbewertung gemäß § 35a SGB V [14]	Insulin degludec (Tresiba®) ist angezeigt zur Behandlung des Diabetes mellitus bei Erwachsenen. a) Monotherapie zur Behandlung des Diabetes mellitus Typ 2 bei Erwachsenen: • **Zweckmäßige Vergleichstherapie:** Humaninsulin • **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Humaninsulin:** Ein Zusatznutzen ist nicht belegt. b) Kombinationstherapie mit einem oder mehreren oralen Antidiabetika zur Behandlung des Diabetes mellitus Typ 2 bei Erwachsenen: • **Zweckmäßige Vergleichstherapie:** Metformin plus Humaninsulin *(Hinweis: Wenn Metformin gemäß Fachinformation nicht geeignet ist, ist Humaninsulin als Therapieoption einzusetzen)* • **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Metformin plus Humaninsulin:** Ein Zusatznutzen ist nicht belegt. c) Kombinationstherapie mit Bolusinsulin (mit oder ohne einem oder mehreren oralen Antidiabetika) zur Behandlung des Diabetes mellitus Typ 2 bei Erwachsenen:

	• **Zweckmäßige Vergleichstherapie:** Humaninsulin plus ggf. Metformin *(Hinweis: In der Kombination mit Bolusinsulin (ohne orales Antidiabetikum) im Rahmen einer ICT ist eine zusätzliche Metformin-Gabe nicht regelhaft indiziert)* • **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Humaninsulin (plus ggf. Metformin):** Ein Zusatznutzen ist nicht belegt.
G-BA, 2014 [9] Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Insulin degludec (neues Anwendungsgebiet)	Insulin degludec (Tresiba®) ist angezeigt zur Behandlung des Diabetes mellitus bei Erwachsenen. *a) Der vorliegende Beschluss bezieht sich ausschließlich auf das neu zugelassene Anwendungsgebiet […], d. h. auf die Kombination von Insulin degludec mit GLP-1-Rezeptor-Agonisten zur Behandlung des Diabetes mellitus Typ 2 bei Erwachsenen.* • **Zweckmäßige Vergleichstherapie:** Die zweckmäßige Vergleichstherapie für Insulin degludec zur Behandlung des Diabetes mellitus Typ 2 in der Kombination mit einem oder mehreren anderen Antidiabetika (außer Insulin) ist: Metformin plus Humaninsulin (Hinweis: Ggf. Therapie nur mit Humaninsulin, wenn Metformin nicht ausreichend wirksam ist oder gemäß Fachinformation nicht geeignet ist) • **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Metformin plus Humaninsulin:** Der Zusatznutzen gilt als nicht belegt.

Cochrane Reviews

Es konnten keine relevanten Cochrane Reviews zum Anwendungsgebiet identifiziert.

Al-Shareef, 2012 Clinical effect of metformin in children and adolescents with type 2 diabetes mellitus: A systematic review and meta-analysis [1]	**1. Fragestellung** This systematic review was carried out to assess the clinical effectiveness of metformin as mono-therapy versus other treatments for T2DM in children and adolescents.
	2. Methodik **Population** Children (2 to 12 years) and adolescents (12 to 18 years) with T2DM, according to the established diagnosis using valid standard criteria, such as WHO 1999 criteria, or the American Diabetes Association (ADA) criteria. Exclusion criteria were: any evidence of one or more positive immune markers for type 1 diabetes mellitus (T1DM) and age above 18 years. **Intervention** Metformin (extended release or immediate release) **Komparator** other treatments of T2DM in children such as diet, exercise, insulin, or other oral hypoglycaemic agent were accepted. **Endpunkt:** <u>Primary outcomes</u> I. Glycaemic control (as measured by glycosylated haemoglobin A1c (HBA1c). II. Diabetes related complications. III. Adverse effects such as lactic acidosis, hypoglycaemia, hyperglycaemia, withdrawal due to adverse effects, and gastrointestinal side effect.

	Secondary outcomes All-cause mortality, compliance, health-related quality of life: physical activity/participation in physical activity, psychological factors/psychological wellbeing, including self-esteem, quality of life, diabetes knowledge, psychosocial factors, school participation/absence. **Hinweis:** Studies using combined drugs treatment in the intervention group and studies with less than four weeks of exposure to treatments (to allow the stabilization of glycaemic control) were excluded. **Suchzeitraum** bis Mai 2008 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 2 (n=347) **Qualitätsbewertung der Studien:** The methodological quality of each randomized controlled trials (RCTs) was assessed independently by two authors using the National Health System Centre for Reviews and Dissemination (NHS CRD) checklist. […] The quality of the included trials was poor. […] In both trial the word‘randomisation’ was used, but without any explanation. Concealment was not mentioned in either trial. Blinding was not mentioned in both trails, probably because the outcomes measured were objective. [...] The two groups in the trials seemed to be treated similarly during the follow-up period. But in the placebo trial more than 50% of the patients in the placebo arm converted to the metformin arm, due to the failure of treatment. Most of them converted before week 6 but their results were analysed according to Intention to treat (ITT) analysis. The glimepiride trial was not conducted according to the ITT analysis. Assessment of heterogeneity:

	Heterogeneity was identified by visual inspection of the forest plots by using a standard χ^2-test and a significance level of a = 0.1, P < 0.1 in view of the low power of such tests. Heterogeneity will also be examined with I^2, where I2 values of 50% and more indicate a substantial level of heterogeneity. When heterogeneity is found, we attempted to determine possible reasons by examining each study characteristics. The main method of synthesis of results was quantitative using Review Manager Software version 5. Both fixed-effect and random-effect analysis were used, however, because of the heterogeneity only the result of random-effect analysis will be reported. Heterogeneity between the results of the trials: From the start and based on a detailed analysis of the characteristics of the placebo trail and glimepiride trail, the authors did not consider that it would be reasonable to get a combined summary estimate. This was mainly because the comparator in the placebo trail was a placebo, which is very different from the comparator in the glimepiride trail which was glimepiride.
	3. Ergebnisdarstellung <u>Glycaemic control</u> <u>Change in HGA1c:</u> Figure 2 shows that in the glimepiride trial, there were significant reductions of mean change of HBA1c from baseline in both arms; it reduced by -0.71% (P = 0.0002) in the metformin group and by -0.54% (P = 0.001) in the other. In addition, more patients (48.1%) in the metformin group had achieved good glycaemic control (<7%) at week 24. In the placebo trial, the metformin group achieved significant improvements in glycaemic control and there was significant reduction in the adjusted mean HBA1c, from baseline 7.5 vs. 8.6 for metformin and placebo, respectively. The mean difference was -1.10 (95%CI of -1.19 to -1.01) which was significant and precise. When the reviewers recalculated the result using the ITT analysis principle and then repeated the meta-analysis for the glimepiride trial, a similar result was attained with same heterogeneity Chi2 = 86.22, I2 = 99% and P value

<0.00001.

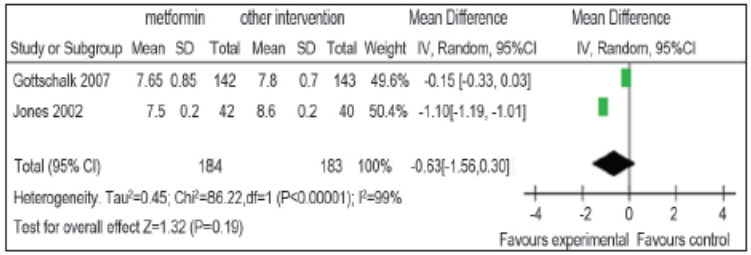


Figure 2: Forest plot of comparison: HBA1C, outcome: mean change in HBA1C from baseline with ITT

<u>Fasting plasma glucose:</u>

In the glimepiride trial, the mean changes in fasting plasma glucose (FPG) from baseline were not significantly different in the glimepiride group; -14.6% and 15.1 % for week 18 and week 24 respectively. In the placebo trial, there was a significant reduction in the adjusted mean of FPG from baseline in the metformin group while there was an increase in the placebo group; -42.9 mg/dl vs. +21.4mg/dl (P value <0.001) with mean difference of -64.80 in favour of the metformin group. Glycaemic control

<u>Weight Change (BMI):</u>

In the glimepiride trial, significant differences at week 12 were 0.07 kg^2 vs. 0.55 kg^2 for metformin and glimepiride respectively (P value < 0.001). These significant differences were also observed at week 24. But, when adjusted, the two groups were comparable. The mean difference was -0.56 with 95%CI of -2.57 to 1.45, which is not significant. In the placebo trial, there was no significant difference between the two groups; the mean difference was -0.2 with 95%CI of -2.33 to 1.44, which is wide and not significant [Figure 3]. After recalculating the result of the glimepiride trial with ITT analysis, the same mean difference was observed, but with a slight change in 95% CI. Overall, there was no significance in the result.

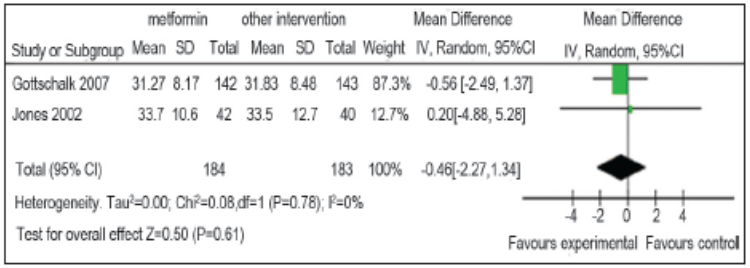


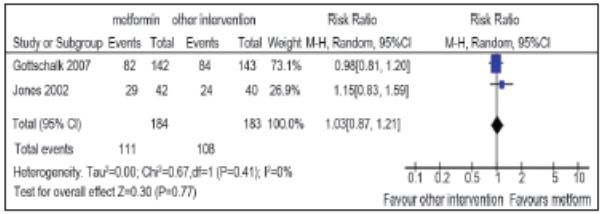
Figure 3: Forest plot of comparison: BMI, outcome: mean change in BMI from baseline with ITT

Lipid profile:

In the glimepiride trial there was no significant difference seen between metformin and glimepiride. In the placebo trial Total Cholesterol decreased from the baseline level in the metformin patients with a slight increase in the placebo group. There was significant decrease in LDL levels in the metformin group. No significant changes were found in the other lipid parameters after adjusting. After recalculating the results using the ITT principle, no change in the results could be detected. The results are heterogeneous, as expected, and at this stage there are not sufficient grounds for using a summary effect estimate obtained by combining the results of the two trails. There was no subgroup analysis in either of trials.

Adverse events

The two trails were of short duration; lasted only from 16 weeks to 24 weeks, therefore it was difficult to assess the adverse events of metformin and the chronic complications of T2DM in children. […] In our included trials there was no death related to the treatment or to the T2DM. In the glimepiride trial, there were two serious adverse events, one in each arm. The incidence of clinical hypoglycaemia was between 10.6% and 8.5%, which is not significant, while in the placebo trial there were five severe adverse events, two in the metformin group and three in the placebo group. None linked to the

	interventions. In the glimepiride trial there was 57.7% of adverse events in the metformin group compared with 59.2% in the glimepiride group. The risk ratio was 0.98 with 95%CI of 0.81 to 1.20, which is a non significant value. In the placebo trial there was 70% of adverse events in the metformin group and 60% in the placebo group. The risk ratio was 1.15 with 95% CI of 0.83 to 1.59, which means that there were 15% more adverse events in the metformin group, but this is still not significant because it can be translated as 17% fewer adverse events in the metformin group compared with as many as 59% more adverse events in the metformin group [Figure 4].  **Figure 4:** Forest plot of comparison of total adverse events in both trails
	4. Anmerkungen/Fazit der Autoren There was limited but not convincing evidence to suggest that metformin can improve the glycaemic control in children and adolescent with type 2 diabetes compared with other interventions. The limited number, poor quality and short duration of the included trials are among limitations of this review.

NICE, 2014 The management of type 2 diabetes [16] [15]	**Fragestellung(en)** Is metformin as monotherapy or in combination with oral antidiabetic drugs effective in the control of blood glucose in people with Type 2 diabetes compared to other oral antidiabetic drugs regimens or placebo? Are the biphasic insulin preparations (premixes) effective in the control of blood glucose compared to NPH in people with Type 2 diabetes? Are the biphasic human insulin preparations effective in the control of blood glucose compared to biphasic analogue preparations in people with Type 2 diabetes? Are multiple analogue insulin injection regimens effective (meal time and basal insulin) compared to basal insulin or biphasic insulin regimes? Are long acting insulin analogues (insulin glargine (LantusR) effective in the control of blood glucose compared to NPH insulin, biphasic insulins or multiple daily injections? Is insulin in combination with oral antidiabetic drugs effective in the control of blood glucose compared to insulin alone in people with Type 2 diabetes?
	Methodik Grundlage der Leitlinie: systematische Evidenzaufbereitung und fomalisierte Konsensusprozesse - GoR schlagen sich in den Formulierungen wider ""To avoid giving the impression that higher

	grade recommendations are of higher priority for implementation, NICE no longer assigns grades to recommendations.“ - repräsentatives Gremium - CoI-Erklärungen im Anhang einsehbar • Update: „Review summary: Consultation on review proposal with stakeholders: **01 June 2011 - 14 June 2011,** Review decision date: **August 2011,** Review decision: **Following the recent review recommendation, an** update of this guideline is in progress**“, letzte Aktualisierungen in 2014** • Suchzeitraum: 2001-2007 • Weitere Kriterien für die Qualität einer LL: - Empfehlungen sind indirekt über die Kapitelstruktur mit Literaturstellen verknüpft **LoE:** nach SIGN (siehe Anhang dieser Synopse) **GoR**: siehe oben **Sonstige (methodische) Hinweise:** The application of the guideline to children has not been excluded. However, we were not able to specifically search for paediatric literature due to the volume of work involved. Healthcare professionals need to use their clinical judgement when applying this guideline to children.
	Freitext/Empfehlungen/Hinweise <u>1.5.1 Metformin</u> 1.5.1.1 Start metformin treatment in a person who is overweight or

	obese (tailoring the assessment of body-weight-associated risk according to ethnic group[4]) and whose blood glucose is inadequately controlled by lifestyle interventions (nutrition and exercise) alone. [4] See Obesity: the prevention, identification, assessment and management of overweight and obesity in adults and children (NICE clinical guideline 43). 1.5.1.2 Consider metformin as an option for first-line glucose-lowering therapy for a person who is not overweight. 1.5.1.3 Continue with metformin if blood glucose control remains or becomes inadequate and another oral glucose-lowering medication (usually a sulfonylurea) is added. 1.5.1.4 Step up metformin therapy gradually over weeks to minimise risk of gastrointestinal (GI) side effects. Consider a trial of extended-absorption metformin tablets where GI tolerability prevents continuation of metformin therapy. 1.5.1.5 Review the dose of metformin if the serum creatinine exceeds 130 micromol/ litre or the estimated glomerular filtration rate (eGFR) is below 45 ml/minute/1.73-m2. • Stop the metformin if the serum creatinine exceeds 150 micromol/litre or the eGFR is below 30 ml/minute/1.73-m2. • Prescribe metformin with caution for those at risk of a sudden deterioration in kidney function and those at risk of eGFR falling below 45 ml/minute/1.73-m2. 1.5.1.6 The benefits of metformin therapy should be discussed with a person with mild to moderate liver dysfunction or cardiac impairment so that: • due consideration can be given to the cardiovascular-

	protective effects of the drug • an informed decision can be made on whether to continue or stop the metformin. 1.7.1 Oral agent combination therapy with insulin 1.7.1.1 When starting basal insulin therapy: • continue with metformin and the sulfonylurea (and acarbose, if used) • review the use of the sulfonylurea if hypoglycaemia occurs. 1.7.1.2 When starting pre-mixed insulin therapy (or mealtime plus basal insulin regimens): • continue with metformin • continue the sulfonylurea initially, but review and discontinue if hypoglycaemia occurs. 1.7.2 Insulin therapy 1.7.2.1 Discuss the benefits and risks of insulin therapy when control of blood glucose remains or becomes inadequate (HbA1c ≥ 7.5% or other higher level agreed with the individual) with other measures. Start insulin therapy if the person agrees. [new 2009] 1.7.2.2 For a person on dual therapy who is markedly hyperglycaemic, consider starting insulin therapy in preference to adding other drugs to control blood glucose unless there is strong justification[7] not to. [new 2009] [7] The recommendations in this section replace 'Guidance on the use of glitazones for the treatment of type 2 diabetes' (NICE technology appraisal guidance 63). 1.7.2.3 When starting insulin therapy, use a structured programme employing active insulin dose titration that encompasses:

	• structured education • continuing telephone support • frequent self-monitoring • dose titration to target • dietary understanding • management of hypoglycaemia • management of acute changes in plasma glucose control • support from an appropriately trained and experienced healthcare professional. 1.7.2.4 Initiate insulin therapy from a choice of a number of insulin types and regimens. • Begin with human NPH insulin injected at bed-time or twice daily according to need. • Consider, as an alternative, using a long-acting insulin analogue (insulin detemir, insulin glargine) if: o the person needs assistance from a carer or healthcare professional to inject insulin, and use of a long-acting insulin analogue (insulin detemir, insulin glargine) would reduce the frequency of injections from twice to once daily, or o the person's lifestyle is restricted by recurrent symptomatic hypoglycaemic episodes, or o the person would otherwise need twice-daily NPH insulin injections in combination with oral glucose-lowering drugs, or o the person cannot use the device to inject NPH insulin.

	• Consider twice-daily pre-mixed (biphasic) human insulin (particularly if HbA1c ≥ 9.0%). A once-daily regimen may be an option. • Consider pre-mixed preparations that include short-acting insulin analogues, rather than pre-mixed preparations that include short-acting human insulin preparations, if: o a person prefers injecting insulin immediately before a meal, or o hypoglycaemia is a problem, or o blood glucose levels rise markedly after meals. [new 2009] 1.7.2.5 Consider switching to a long-acting insulin analogue (insulin detemir, insulin glargine) from NPH insulin in people: • who do not reach their target HbA1c because of significant hypoglycaemia, or • who experience significant hypoglycaemia on NPH insulin irrespective of the level of HbA1c reached, or • who cannot use the device needed to inject NPH insulin but who could administer their own insulin safely and accurately if a switch to a long-acting insulin analogue were made, or • who need help from a carer or healthcare professional to administer insulin injections and for whom switching to a long-acting insulin analogue would reduce the number of daily injections. [new 2009] 1.7.2.6 Monitor a person on a basal insulin regimen (NPH insulin or a long-acting insulin analogue [insulin detemir, insulin glargine]) for the need for short-acting insulin before meals (or a pre-mixed

	insulin preparation). [new 2009] 1.7.2.7 Monitor a person who is using pre-mixed insulin once or twice daily for the need for a further injection of short-acting insulin before meals or for a change to a regimen of mealtime plus basal insulin, based on NPH insulin or longacting insulin analogues (insulin detemir, insulin glargine), if blood glucose control remains inadequate. [new 2009]

Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren

Canadian Agency for Drugs and Technologies in Health (CADTH). 2010 Second-line therapy for patients with diabetes inadequately controlled on metformin: a systematic review and cost-effectiveness analysis [5]	5 RESEARCH QUESTIONS 1. What is the comparative efficacy and safety of second-line antidiabetes drugs in patients with type 2 diabetes inadequately controlled on metformin monotherapy? The populations of interest for this review were adults and children with type 2 diabetes inadequately controlled or intolerant to metformin monotherapy, and requiring a second antidiabetic drug. 6.2.2 study characteristics There was insufficient evidence to conduct the sub-group analyses specified in the project protocol (e.g., patients ≥ 65 years old, First Nations people, and ethnic minorities), nor was there any evidence for children (< 18 years of age) with type 2 diabetes inadequately controlled with metformin monotherapy.
IQWIG, 2006 Kurzwirksame Insulinanaloga zur Behandlung des Diabetes mellitus Typ 2 [10]	**Fragestellung/Ziele:** Ziele der vorliegenden Untersuchung sind • die Nutzenbewertung einer langfristigen Behandlung mit einem kurzwirksamen Insulinanalogon im Vergleich zu einer Behandlung mit kurzwirksamem Humaninsulin und • die vergleichende Nutzenbewertung kurzwirksamer Insulinanaloga untereinander jeweils bei Patienten mit Diabetes mellitus Typ 2 hinsichtlich patientenrelevanter Therapieziele. Unter kurzwirksamen Insulinanaloga sind dabei alle derzeit in Deutschland zugelassenen und erhältlichen Präparate zu verstehen. Dies sind: • Insulin Aspart • Insulin Glulisin • Insulin Lispro **Population:** Eingeschlossen wurden Studien zu Patienten mit manifestem Diabetes mellitus Typ 2 laut Studienangabe, z.B.

	nach Definition der WHO. **Endpunkte**: Als Zielgrößen für die Untersuchung wurden Parameter verwendet, die eine Beurteilung folgender patientenrelevanter Therapieziele ermöglichen: • Reduktion der Gesamtmortalität • Reduktion kardialer Morbidität und Mortalität • Reduktion zerebraler Morbidität und Mortalität • Reduktion gefäßbedingter nichtkardialer und nichtzerebraler Morbidität und Mortalität • Reduktion der Erblindungsrate • Reduktion der Rate terminaler Niereninsuffizienzen mit Dialysenotwendigkeit • Reduktion der Amputationsrate (Minor- und Majoramputationen) • Reduktion der Rate stationärer Behandlungen jeglicher Ursache • Reduktion der Rate hyperosmolarer bzw. ketoazidotischer Komata • Reduktion der durch chronische Hyperglykämie bedingten Symptomatik • Reduktion der Rate an Hypoglykämien, insbesondere schwerer Hypoglykämien • Reduktion sonstiger unerwünschter Arzneimittelwirkungen • Erhalt bzw. Besserung krankheitsbezogener Lebensqualität (einschließlich der Berufsfähigkeit und sonstiger Aktivitäten des täglichen Lebens) und der Therapiezufriedenheit Darüber hinaus wurden Angaben zum HbA1c-Wert als Maß für die langfristige Blutzuckersenkung zur Interpretation der Ergebnisse hinsichtlich der Therapieziele, insbesondere auch bzgl. des Auftretens von Hypoglykämien, dargestellt. **Ergebnis /Fazit:** Es existieren keine überzeugenden Belege für eine Überlegenheit kurzwirksamer Insulinanaloga gegenüber Humaninsulin hinsichtlich patientenrelevanter Therapieziele bei der Behandlung des Typ 2 Diabetes mellitus.

	Hinsichtlich ihrer langfristigen, potenziellen, nützlichen und schädlichen Effekte, sind kurzwirksame Insulinanaloga nicht ausreichend untersucht.
IQWIG, 2009 Langwirksame Insulinanaloga zur Behandlung des Diabetes mellitus Typ 2 [12]	**Fragestellung/Ziele:** Ziele der vorliegenden Untersuchung waren • die Nutzenbewertung einer langfristigen Behandlung mit einem langwirksamen Insulinanalogon (Insulin Glargin oder Insulin Detemir) im Vergleich zu einer Behandlung mit einer Zubereitung eines auf Humaninsulin basierenden Verzögerungsinsulins und • die vergleichende Nutzenbewertung langwirksamer Insulinanaloga untereinander jeweils bei Patienten mit Diabetes mellitus Typ 2 hinsichtlich patientenrelevanter Therapieziele. **Population:** Patienten mit manifestem Diabetes mellitus Typ 2 laut Studienangabe, z. B. nach Definition der WHO. **Endpunkte**: Für die Untersuchung wurden folgende Zielgrößen verwendet, die eine Beurteilung patientenrelevanter Therapieziele ermöglichen: • Gesamtmortalität • kardiale Morbidität und Mortalität • zerebrale Morbidität und Mortalität • gefäßbedingte nichtkardiale und nichtzerebrale Morbidität und Mortalität • Erblindung sowie deren Vorstufen (Veränderungen des Augenhintergrundes oder des Visus) • terminale Niereninsuffizienz mit Dialysenotwendigkeit • Amputation (Minor- und Majoramputationen) • stationäre Behandlung jeglicher Ursache • hyperosmolares bzw. ketoazidotisches Koma • Symptomatik bedingt durch chronische Hyperglykämie

	• Hypoglykämie, insbesondere schwere Hypoglykämie unter Berücksichtigung des HbA1c-Wertes • unerwünschte Arzneimittelwirkungen • gesundheitsbezogene Lebensqualität (einschließlich der Berufsfähigkeit und sonstiger Aktivitäten des täglichen Lebens) • Therapiezufriedenheit **Ergebnis /Fazit:** • <u>Insulin Glargin vs. NPH-Insulin</u> Für die Behandlung im Rahmen einer intensivierten Insulintherapie gibt es keinen Beleg für einen Zusatznutzen von Insulin Glargin gegenüber NPH-Insulin • <u>Insulin Detemir vs. NPH-Insulin</u> Für die Behandlung im Rahmen einer intensivierten Insulintherapie gibt es keinen Beleg für einen Zusatznutzen von Insulin Detemir gegenüber NPH-Insulin. • <u>Insulin Detemir vs. Insulin Glargin</u> Weder für die Behandlung im Rahmen einer basalunterstützten Therapie mit oralen Antidiabetika noch im Rahmen einer intensivierten Insulintherapie gibt es einen Beleg für einen Zusatznutzen eines der Insulinanaloga gegenüber dem jeweils anderen.
Copeland, 2013 Management of Newly Diagnosed Type 2 Diabetes Mellitus (T2DM) in Children and Adolescents [6]	**1. Fragestellung** Specific clinical questions addressed in the evidence review were as follows: (1) the effectiveness of treatment modalities for T2DM in children and adolescents, (2) the efficacy of pharmaceutical therapies for treatment of children and adolescents with T2DM,
	2. Methodik Gundlage: Systematisscher Review und (formalisierter) Konsensusprozess. Gremium: American Academy of Pediatrics (AAP) with the support of the American Diabetes Association, the Pediatric Endocrine Society (PES), the American Academy of Family Physician (AAFP), and the Academy of Nutrition and Dietetics. Conflict of interest – Erklärung im Anhang einsehbar.

Suchzeitraum:
Januar 1990 bis Juni 2008

Population:
Children between the ages of 120 and 215 months with an established diagnosis of T2DM.
Studies in adults were considered for inclusion if >10% of the study population was 45 years of age or younger.

Weitere Kriterien für die Qualität einer LL:

- systematische Recherche in Medline, Cochrane Collaboration and Embase

LoE:

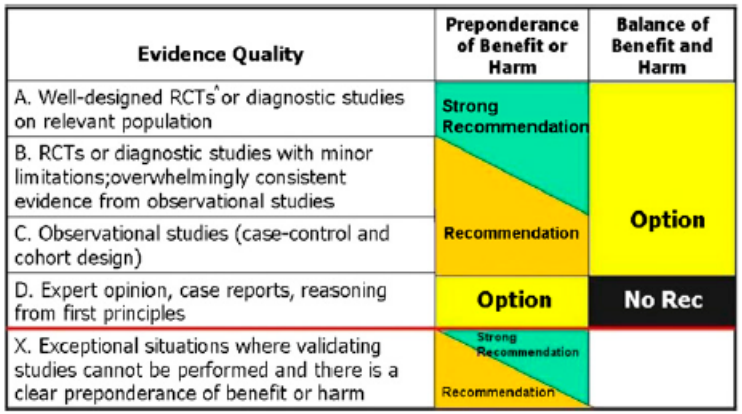


FIGURE 1
Evidence quality. Integrating evidence quality appraisal with an assessment of the anticipated balance between benefits and harms if a policy is carried out leads to designation of a policy as a strong recommendation, recommendation, option, or no recommendation.[32] RCT, randomized controlled trial; Rec, recommendation.

GoR:

Statement	Definition	Implication
Strong recom-mendation	A strong recommendation in favor of a particular action is made when the anticipated benefits of the recommended intervention clearly exceed the harms (as a strong recommendation against an action is made when the anticipated harms clearly exceed the benefits) and the quality of the supporting evidence is excellent. In some clearly identified circumstances, strong recommendations may be made when high-quality evidence is impossible to obtain and the anticipated benefits strongly outweigh the harms.	Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.
Recom-mendation	A recommendation in favor of a particular action is made when the anticipated benefits exceed the harms but the quality of evidence is not as strong. Again, in some clearly identified circumstances, recommendations may be made when high quality evidence is impossible to obtain but the anticipated benefits outweigh the harms.	Clinicians would be prudent to follow a recommendation but should remain alert to new information and sensitive to patient preferences.
Option	Options define courses that may be taken when either the quality of evidence is suspect or carefully performed studies have shown little clear advantage to 1 approach over another.	Clinicians should consider the option in their decision-making, and patient preference may have a substantial role.
No recom-mendation	No recommendation indicates that there is a lack of pertinent published evidence and that the anticipated balance of benefits and harms is presently unclear.	Clinicians should be alert to new published evidence that clarifies the balance of benefit versus harm.

It should be noted that, because childhood T2DM is a relatively recent medical phenomenon, there is a paucity of evidence for many or most of the recommendations provided. In some cases, supporting references for a specific recommendation are provided that do not deal specifically with childhood T2DM, such as T1DM, childhood obesity, or childhood “prediabetes,” or that were not included in the original comprehensive search. Committee members have made every effort to identify those references that did not affect or alter the level of evidence for specific recommendations.

Freitext/Empfehlungen/Hinweise:

Key Action Statement 1

Clinicians must ensure that insulin therapy is initiated for children and adolescents with T2DM who are ketotic or in diabetic ketoacidosis and in whom the distinction between T1DM and T2DM is unclear; and, in usual cases, should initiate insulin therapy for patients:

a) who have random venous or plasma BG concentrations ≥250 mg/dL; or

b) whose HbA1c is >9%.

(Strong Recommendation: evidence quality X, validating studies cannot be performed, and C, observational studies and expert opinion; preponderance of benefit over harm.)

Action Statement Profile KAS 1

Aggregate evidence quality	X (validating studies cannot be performed)
Benefits	Avoidance of progression of diabetic ketoacidosis (DKA) and worsening metabolic acidosis; resolution of acidosis and hyperglycemia; avoidance of coma and/or death. Quicker restoration of glycemic control, potentially allowing islet β cells to "rest and recover," increasing long-term adherence to treatment; avoiding progression to DKA if T1DM. Avoiding hospitalization. Avoidance of potential risks associated with the use of other agents (eg, abdominal discomfort, bloating, loose stools with metformin; possible cardiovascular risks with sulfonylureas).
Harms/risks/cost	Potential for hypoglycemia, insulin-induced weight gain, cost, patient discomfort from injection, necessity for BG testing, more time required by the health care team for patient training.
Benefits-harms assessment	Preponderance of benefit over harm.
Value judgments	Extensive clinical experience of the expert panel was relied on in making this recommendation.
Role of patient preferences	Minimal.
Exclusions	None.
Intentional vagueness	None.
Strength	Strong recommendation.

	Key Action Statement 2 In all other instances, clinicians should initiate a lifestyle modification program, including nutrition and physical activity, and start metformin as first-line therapy for children and adolescents at the time of diagnosis of T2DM. (Strong recommendation: evidence quality B; 1 RCT showing improved outcomes with metformin versus lifestyle; preponderance of benefits over harms.)

Action Statement Profile KAS 2

Aggregate evidence quality	B (1 randomized controlled trial showing improved outcomes with metformin versus lifestyle combined with expert opinion).
Benefit	Lower HbA1c, target HbA1c sustained longer, less early deterioration of BG, less chance of weight gain, improved insulin sensitivity, improved lipid profile.
Harm (of using metformin)	Gastrointestinal adverse effects or potential for lactic acidosis and vitamin B_{12} deficiency, cost of medications, cost to administer, need for additional instruction about medication, self-monitoring blood glucose (SMBG), perceived difficulty of insulin use, possible metabolic deterioration if T1DM is misdiagnosed and treated as T2DM, potential risk of lactic acidosis in the setting of ketosis or significant dehydration. It should be noted that there have been no cases reported of vitamin B_{12} deficiency or lactic acidosis with the use of metformin in children.
Benefits-harms assessment	Preponderance of benefit over harm.
Value judgments	Committee members valued faster achievement of BG control over not medicating children.
Role of patient preferences	Moderate; precise implementation recommendations likely will be dictated by patient preferences regarding healthy nutrition, potential medication adverse reaction, exercise, and physical activity.
Exclusions	Although the recommendation to start metformin applies to all, certain children and adolescents with T2DM will not be able to tolerate metformin. In addition, certain older or more debilitated patients with T2DM may be restricted in the amount of moderate-to-vigorous exercise they can perform safely. Nevertheless, this recommendation applies to the vast majority of children and adolescents with T2DM.
Intentional vagueness	None.
Policy level	Strong recommendation.

Primärstudien

Eine systematische Suche nach relevanten Primärstudien im Anwendungsgebiet wurde bisher nicht in Auftrag gegeben.

Detaillierte Darstellung der Recherchestrategie:

Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database) **am 26.02.2015**

#	Suchfrage
1	MeSH descriptor: [Diabetes Mellitus] explode all trees
2	diabet* mellitus*:ti,ab,kw
3	#1 or #2
4	MeSH descriptor: [Adolescent] explode all trees
5	MeSH descriptor: [Child] explode all trees
6	MeSH descriptor: [Infant] explode all trees
7	#3 or #4 or #5
8	(child* or infant* or adolescent*):ti,ab,kw
9	#7 or #8
10	#3 and #9
11	#10 from 2010 to 2015

SR, HTAs in Medline (PubMed) am 25.02.2015

#	Suchfrage
1	diabetes mellitus[MeSH]
2	(((diabet*[Title/Abstract] AND mellitus*[Title/Abstract])) OR diabetes[Title/Abstract]) OR DM[Title/Abstract]
3	(#1) OR #2
4	Infan* OR newborn* OR new-born* OR perinat* OR neonat* OR baby OR baby*OR babies OR toddler* OR minors OR minors* OR boy OR boys OR boyfriend OR boyhood OR girl* OR kid OR kids OR child OR child* OR children* OR schoolchild* OR schoolchild OR school child[Title/Abstract] OR school child*[Title/Abstract] OR adolescen* OR juvenil* OR youth* OR teen* OR under*age* OR pubescen* OR pediatrics[MeSH] OR pediatric* OR paediatric* OR peadiatric* OR school[Title/Abstract] OR school*[Title/Abstract] OR prematur* OR preterm*
5	(#3) AND #4

6	(#5) AND (Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp])
7	(#5) AND (((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract] OR Medline[Title/Abstract] OR Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR Pubmed[Title/Abstract])) AND systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR ((((((((((HTA[Title/Abstract]) OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR (systematic*[Title/Abstract] AND overview*[Title/Abstract])) OR meta-analy*[Title/Abstract]) OR (meta[Title/Abstract] AND analyz*[Title/Abstract])) OR (meta[Title/Abstract] AND analys*[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract]))) OR (((review*[Title/Abstract]) OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract]) AND based[Title/Abstract]))))
8	(#6) OR #7
9	(#8) AND ("2010/02/01"[PDAT] : "2015/02/25"[PDAT])

Leitlinien in Medline (PubMed) am 25.02.2015

#	Suchfrage
1	diabetes mellitus[MeSH]
2	(((diabet*[Title/Abstract] AND mellitus*[Title/Abstract])) OR diabetes[Title/Abstract]) OR DM[Title/Abstract]
3	(#1) OR #2
4	Infan* OR newborn* OR new-born* OR perinat* OR neonat* OR baby OR baby*OR babies OR toddler* OR minors OR minors* OR boy OR boys OR boyfriend OR boyhood OR girl* OR kid OR kids OR child OR child* OR children* OR schoolchild* OR schoolchild OR school child[Title/Abstract] OR school child*[Title/Abstract] OR adolescen* OR juvenil* OR youth* OR teen* OR under*age* OR pubescen* OR pediatrics[MeSH] OR pediatric* OR paediatric* OR peadiatric* OR school[Title/Abstract] OR school*[Title/Abstract] OR prematur* OR preterm*
5	(#3) AND #4
6	(#5) AND (Guideline[ptyp] OR Practice Guideline[ptyp] or guideline*[Title])

7	(#6) AND ("2010/02/01"[PDAT] : "2015/02/25"[PDAT])

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Gemeinsamer Bundesausschuss

Anhang 1

Tabelle 1: aus SIGN, 2010

LoE	
1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1 -	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++	High quality systematic reviews of case control or cohort studies, high quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2 -	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, eg case reports, case series
4	Expert opinion
GoR	
A	At least one meta-analysis, systematic review, or RCT rated as 1++,and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+
GOOD PRACTICE POINTS	Recommended best practice based on the clinical experience of the guideline development group

Anhang 2

TABLE 2. RANDOMIZED CONTROLLED TRIALS IN CHILDREN/ADOLESCENTS COMPARING INSULIN GLARGINE WITH NPH INSULIN, ULTRALENTE AND CONTINUOUS SUBCUTANEOUS INSULIN INFUSION

					Change from baseline		Frequency of hypoglycaemia (episodes/pt-month, % patients)		
Reference	*Design*	*No. Pts*	*Trial Duration*	*Treatments*	*A1C (%)*	*FBG (mmol/L)*	*Symptomatic*	*Nocturnal*	*Comments*
Schober 2002[66] (Study 3001)	Multicenter, open-label, parallel group in children/ adolescents aged 5–16 years	349	24 weeks	Bedtime Glargine NPH (od or bd)	+0.28% (baseline NR) +0.27% (baseline NR) $P=0.93$	−1.29 mmol/L −0.68 mmol/L $P=0.02$	Severe: 23% Severe: 29% $P=0.22$	Severe 13% Severe: 18% $P=0.19$	Once-daily glargine provides effective glycaemic control and is well tolerated in children and adolescents.
Murphy 2003[64]	Open-label, cross-over study	28	32 weeks	Glargine (pre-bedtime) + lispro	−0.6% (baseline 9.3%)	FBG 8.0 2-h post breakfast 8.1	NR	32% nights	Glargine + lispro reduced nocturnal hypoglycemia and was at least as effective as NPH + RHI in maintaining glycemic control in adolescents on multiple injection regimens.
				NPH (pre-bedtime) + RHI	−0.2% (baseline 9.3%) $P=0.13$	FBG 9.0, 2-h post breakfast 10.7 Both $P<0.0005$	NR NR	56% nights $P<0.05$	
Mianowska 2007[68]	Prospective cross-over study in children aged 6–12 years	14	6 months	Glargine	At 4 months: −0.6% (baseline 7.7%)	−1.8 (baseline 9.8)	NR	No severe hypoglycaemia	Glargine provides better early morning and good glycaemic control, no increase in risk of severe hypoglycaemia.
				NPH	At 4 months: 0.0% (baseline 7.7%) $P=0.007$	−0.5 (baseline 9.8) $P=0.077$	NR	NR	
Chase 2008[62] (Study 4030)	Open-label, multicenter parallel group	175	4 week run in period, 24 weeks	Glargine (od) + lispro ($n=85$)	−0.25% ± 0.14% (baseline 7.8%)	Fasting SMBG: −3.3 mg/dL	Severe: 0.20 events per patient year	Confirmed BG < 70 mg/dL[b]116 events per patient per year	Glargine is well tolerated for pediatric patients and may be more efficacious than NPH/lente in those with elevated A1C
				NPH/lente (bd) ($n=90$)	−0.05% ± 0.13% (baseline 8.0%) $P=0.1725$[a]	Fasting SMBG: + 1.1 mg/dL $P=0.6962$	Severe: 0.09 events per patient year $P=0.1814$	94 events per patient per year $P=0.0298$	
Hassan 2008[67]	Single center, parallel group study	42	3 months	Glargine (bd) + rapid acting insulin mixed in same syringe	−0.1% (baseline 6.8%)	6.0	0 events	NR	Glycemic control with glargine mixed with rapid-acting insulin analog bd was better than standard NPH therapy in newly diagnosed T1DM.
				NPH (bd) + rapid acting insulin	+0.7% (baseline 6.9%) $P<0.029$	10.3 $P<0.008$	7 events	NR	

[a]Analysis of covariance, adjusting for baseline A1C, revealed a strong study arm effect on the slopes of the regression lines, indicating that the reduction in HbA1c was significantly greater with insulin glargine in those patients with higher baseline A1C values; [b]no differences in the occurrence of glucose levels <50 mg/dL ($P=0.82$) or <36 mg/dL ($P=0.32$) were found between the 2 groups. FBG = fasting blood glucose; NS = not significant; NR = not reported; FAA = fast-acting analogue; RHI = regular human insulin; BG = blood glucose; SMBG = self-monitored blood glucose; od = once-daily; bd = twice-daily; NR = not reported; NPH = neutral protamine Hagedorn insulin; glargine = insulin glargine.