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S3-Leitlinie Therapie des Typ-1-Diabetes

2. Auflage

[Leitlinienreport](#)

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Impressum

Die Erstellung der evidenzbasierten Leitlinie erfolgte im Auftrag der Deutschen Diabetes Gesellschaft (DDG)

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Weitere Dokumente zu dieser Leitlinie:

Alle Dokumente zur Leitlinie sind auf den Seiten der AWMF unter der Registernummer 057/013 verfügbar: www.awmf.org/leitlinien/detail/II/057-013.html

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1 Geltungsbereich und Zweck

Die aktuelle Leitlinie Therapie des Typ-1-Diabetes entstand durch die Überarbeitung der Leitlinie aus dem Jahr 2011. Dabei wurde im Jahr 2017 der Inhalt vollständig überarbeitet und dem aktuellen Stand der Wissenschaft und der klinischen Praxis angepasst (siehe auch Leitlinienreport der gleichen Leitlinie aus dem Jahr 2011).

Die Zielsetzung und die Zielgruppe der Leitlinie hat sich dadurch nicht geändert.

Die Leitlinie richtet sich an alle Menschen mit Typ-1-Diabetes sowie alle Berufsgruppen, die Menschen mit Typ-1-Diabetes betreuen, vor allem:

- niedergelassene Diabetologen;
- Allgemeinärzte und Internisten;
- im Krankenhaus tätige Ärzte (Diabetesspezialisten, Anästhesisten, Chirurgen, Radiologen);
- Pflegende (im OP-Bereich, auf den Stationen oder im Bereich der Diagnostik);
- ambulant oder stationär tätige DiabetesberaterInnen.

Darüber hinaus richtet sich die Leitlinie an übergeordnete Institutionen, wie Krankenkassen oder medizinische Dienste.

Durch die vorliegende Leitlinie soll eine adäquate Therapie von Menschen mit Typ-1-Diabetes sichergestellt werden. Ziel ist es, die Rate an diabetesassoziierten Komplikationen und diabetesassoziierten Folgeschäden zu senken und die Lebensqualität und Therapiezufriedenheit zu verbessern. Durch Sicherstellen der korrekten Behandlung von Akutkomplikationen soll das Risiko vermindert werden, durch die Behandlung selbst Komplikationen zu verursachen. Die Leitlinie soll auch zu einer angemessenen Versorgung von Menschen mit Typ-1-Diabetes im Krankenhaus sowohl auf Normalstationen als auch auf Intensivstationen beitragen. Im ambulanten Bereich soll besonders die adäquate Schulung von Menschen mit Typ-1-Diabetes als fester Bestandteil der Therapie verankert werden.

2 Zusammensetzung der Leitliniengruppe

Die Leitliniengruppe setzte sich aus Mitgliedern der Deutschen Diabetes-Gesellschaft (DDG) zusammen, die von der Leitlinienbeauftragten der DDG, Frau Prof. Monika Kellerer, benannt wurden. Um eine repräsentative Interdisziplinarität und Pluralität zu erreichen, wurden weitere Organisationen, die an der Betreuung und Behandlung von Menschen mit Typ-1-Diabetes unmittelbar beteiligt sind, angefragt und soweit von diesen gewünscht in den Erstellungsprozess der Leitlinie eingebunden.

2.1 Leitliniengruppe

Tabelle 1: Experten, die an der Erarbeitung der Leitlinie aktiv mitgearbeitet haben

Benanntes Mitglied der Leitliniengruppe	Beruflicher Hintergrund/Qualifikation
Prof. Dr. med. Thomas Haak	Facharzt für Innere Medizin, Zusatzweiterbildungen: Endokrinologie, Diabetologe DDG, Chefarzt Diabetes Zentrum Mergentheim
Dr. med. Thorsten Siegmund	Facharzt für Innere Medizin, Endokrinologie und Diabetologie, Diabetologe DDG, München
Prof. Dr. med. Andreas Fritzsche, Tübingen	Facharzt für Innere Medizin, Zusatzweiterbildungen: Diabetologie, Ernährungsmedizin, Präventionsmedizin, Diabetologe DDG
PD Dr. med. Martin Füchtenbusch, München	Facharzt für Innere Medizin, Zusatzweiterbildungen: Endokrinologie und Diabetologie, Diabetologe DDG

Benanntes Mitglied der Leitliniengruppe	Beruflicher Hintergrund/Qualifikation
Dr. med. Stefan Gölz, Esslingen	Facharzt für Innere Medizin, Zusatzweiterbildung Diabetologie, Diabetologe DDG
Elisabeth Schnellbächer	Verband der Diabetesberatungs- und Schulungsberufe Deutschlands e.V. (VDBD)
Prof. Dr. Harald Klein Facharzt für Innere Medizin; Zusatzweiterbildung inter-nistische Intensivmedizin, Endokrinologie und Diabetologie, Diabetologe DDG Fachkunde Labor im Gebiet Innere Medizin	Deutsche Gesellschaft für Innere Medizin (DGIM)
Dr. Til Uebel Facharzt für Allgemeinmedizin, Notfallmedizin und Diabetologie kardiovaskuläre Präventivmedizin (DGPR) Sprecher der Arbeitsgruppe Diabetes der DEGAM	Deutsche Gesellschaft für Allgemeinmedizin und Familienmedizin (DEGAM)
Diana Droßel	Gesundheits- und Krankenpflegerin, Deutsche Diabetes Hilfe - Menschen mit Diabetes (DDH-M), Aachen

Tabelle 2: Experten weiterer beteiligter Organisationen

Benanntes Mitglied/Qualifikation	Organisation/Fachgesellschaft
Prof. Dr. Claudia Spies Fachärztin für Anästhesiologie und Intensivmedizin; Zusatzweiterbildung Intensivmedizin	Deutsche Gesellschaft für Anästhesiologie und Intensivmedizin (DGAI)
Corinna Hahn	Deutscher Diabetiker Bund e.V. (DDB)
PD Dr. Susanna Wiegand, Fachärztin für Innere Medizin	Deutsche Adipositas Gesellschaft (DAG)

Methodische Bearbeitung (Literaturrecherche/Evidenzaufarbeitung/Methodenreport/Konsensuskonferenz/Moderation), Edition:

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Dr. Dawid Pieper

Stefanie Bühn, MPH

Arbeitsgemeinschaft Medizinisch Wissenschaftlicher Fachgesellschaften (AWMF):

Dr. Monika Nothacker, MPH

Prof. Dr. Ina Kopp

Editorin:

Andrea Haring, Berlin

3 Patientenbeteiligung

Die vom Deutschen Diabetiker Bund benannte Patientenvertreterin war Corinna Hahn. Weiterhin war Deutschen Diabetes Hilfe - Menschen mit Diabetes (DDH-M) Diana Droßel direkt an der Erstellung der Leitlinie beteiligt.

4 Methodologische Exaktheit

4.1 Formulierung von Schlüsselfragen

Zur Überarbeitung der Leitlinie wurde die Aufteilung der bestehenden Leitlinie im Wesentlichen beibehalten. Die bestehende Leitlinie wurde damit als Basis für die Überarbeitung verwendet und durch neue Erkenntnisse und Evidenzen ergänzt. Insbesondere technische Fortentwicklungen auf dem Gebiet der Therapie des Typ-1-Diabetes wurden in die Leitlinie inkludiert

4.2 Verwendung existierender Leitlinien zum Thema

Eine systematische Recherche nach Leitlinien war nicht Bestandteil der Aktualisierung.

4.3 Systematische Literaturrecherche

Nach dem Auftakttreffen der Leitliniengruppe wurden Rechercheaufträge diskutiert und danach an ein unabhängiges Institut (IFOM, Universität Witten/Herdecke) vergeben. Dort erfolgt nach genau definierten Vorgaben die ausführliche Literaturrecherche für den genau definierten Zeitraum. Die Auswahl der Evidenz und die Bewertung erfolgten ebenfalls extern durch ein neutrales Institut. **Auf diese Weise konnte Verzerrungen durch Interessenskonflikte entgegengewirkt werden.**

Der gesamte Vorgang ist ausführlich im Evidenzbericht, der als Anlage in Kapitel 10 Anhang: Evidenzrecherche beigefügt ist, beschrieben.

Den Mitgliedern der Leitliniengruppe war es gestattet, eigene Literatur vorzustellen. Deren Evidenzstärke wurde innerhalb der Gruppe ausführlich diskutiert. Auf diese Weise konnte auch aktuelle Literatur, die zum Zeitpunkt der Recherche noch nicht publiziert war, berücksichtigt werden.

4.4 Strukturierte Konsensfindung

Die Formulierung der erforderlichen Änderungen wurde in wöchentlichen Telefonkonferenzen der Leitliniengruppe diskutiert und vorbesprochen. Nach Fertigstellung der Entwurfssatzung der Leitlinie wurden die Empfehlungen der Leitlinie nochmals in einer Konsensuskonferenz am 29. November 2017 vorgestellt und strittige Inhalte diskutiert. Die Konsensuskonferenz wurde durch eine externe Moderatorin (Frau Prof. Dr. Ina Kopp, AWMF) im Sinne eines nominalen Gruppenprozesses geleitet. Der nominale Gruppenprozess ist ein von der AWMF empfohlenes Verfahren zur manipulationsfreien und reproduzierbaren Leitlinienerstellung. Er gliedert sich in folgende Schritte:

Ablauf und Bestandteile eines nominalen Gruppenprozesses

- im Vorfeld: Festlegung von Zielen, Vorgehensweise, Abstimmungsverfahren, Tagungsort Einladung aller an der Konsentierung Beteiligten
- unabhängige Moderation
- Tischvorlage: Leitlinienmanuskript, Empfehlungen
- Ablauf
 - Präsentation der zu konsentierenden Aussagen/Empfehlungen
 - Stille Notiz: Welcher Empfehlung/Empfehlungsgrad stimmen Sie nicht zu? Ergänzung, Alternative?
 - Registrierung der Stellungnahmen im Umlaufverfahren und Zusammenfassung von Kommentaren durch den Moderator

- Vorabstimmung über Diskussion der einzelnen Kommentare – Erstellung einer Rangfolge
- Debattieren/Diskussion der Diskussionspunkte
- Endgültige Abstimmung über jede Empfehlung und alle Alternativen
- Schritte werden für jede Empfehlung wiederholt

Die Empfehlungen in der Leitlinie wurden dabei abgestimmt und die Abstimmungsergebnisse protokolliert.

Dabei wurde beachtet, dass auch bei moderaten Interessenskonflikten sich die davon betroffenen Mitglieder der Leitliniengruppe nicht an der Abstimmung beteiligten. Die Abstimmungsergebnisse einschließlich der Anzahl der nicht abstimmender Mitglieder wurden protokolliert.

Für alle abgestimmten Empfehlungen konnte ein Konsens (Zustimmung > 75 %) erreicht werden. Einige Empfehlungen, die aus Zeitgründen nicht abgestimmt werden konnten, wurden mittels schriftlichem Abstimmungsverfahren bearbeitet. Für alle Empfehlungen konnte ein 100 % Konsens erreicht werden.

5 Redaktionelle Unabhängigkeit und Finanzierung der Leitlinie

Finanzierung der Leitlinie erfolgte durch die Deutsche Diabetes Gesellschaft. Hierzu zählte die Übernahme der Kosten für die Literaturrecherche, das Editieren, die Reisekosten der an der Leitlinie beteiligten Mitglieder der Deutschen Diabetes Gesellschaft, Kosten der Telekommunikation sowie die anfallenden Gebühren. Reisekosten von Mitgliedern anderer Organisationen und Fachgesellschaften wurden von den Organisationen getragen. **Die Arbeit der Mitglieder der Leitliniengruppe erfolgte ehrenamtlich.**

6 Darlegung von und Umgang mit potenziellen Interessenkonflikten

Alle Mitglieder der Leitliniengruppe erklärten vor Aufnahme am Ende der Arbeit an der Leitlinie ihre Interessenskonflikte auf dem von der AWMF bereitgestellten Formblatt. Dieses ist als Anhang in Kapitel 11.1 Formular zur Erklärung von Interessen dargestellt.

Bei der Konsensuskonferenz wurden potentielle Interessenskonflikte offengelegt und innerhalb der Gruppe diskutiert. Zusätzlich bewertete die Vertreterin der AWMF, Prof. Dr. Ina Kopp, die Interessenskonflikte bezüglich ihres thematischen Bezugs zur Leitlinie und ihres Ausprägungsgrades.

Dabei wurden moderate Interessenskonflikte nach den Kriterien der AWMF bei einigen Mitgliedern der Leitliniengruppe festgestellt. Mitglieder, auf die dieses zutraf, enthielten sich entsprechend dem thematischen Bezug bei der Abstimmung der Empfehlungen dieser Leitlinie.

Es sei weiterhin darauf hingewiesen, dass Verzerrungen durch Interessenskonflikte durch die pluralistische Zusammensetzung der Leitliniengruppe vor Beginn der aktiven Teilnahme entgegengewirkt worden ist.

Als zusätzlicher protektiver Faktor ist die systematische und unabhängige Eventenzrecherche und -bewertung zu nennen.

7 Externe Begutachtung und Verabschiedung

Nach Fertigstellung der Leitlinie wurde diese den Vorständen der herausgebenden Fachgesellschaften/Organisationen vorgelegt und von diesen wiederum deren Mitgliedern zugänglich gemacht. Nach einer Frist von 4 Wochen wurde die Leitlinie von den Vorständen verabschiedet.

8 Verbreitung und Implementierung

Wie bisher wird auch die überarbeitete Leitlinie in gedruckter Form sowie zum Abruf auf der Homepage der Deutschen Diabetes Gesellschaft (www.deutsche-diabetes-gesellschaft.de) zur Verbreitung und Implementierung zur Verfügung gestellt.

Es wird allen Behandlern von Menschen mit Typ-1-Diabetes mellitus empfohlen, die Empfehlung innerhalb der Leitlinie als Grundlage der Therapie anzuerkennen, ohne dabei für jeden Patienten individualisierte Therapieziele zu formulieren, mit ihm zu besprechen und gemeinsam zu verfolgen.

Beurteilenden Institutionen wie Medizinische Dienste der Krankenversicherungen oder politische Entscheider werden aufgefordert, diese S3-Leitlinie mit als Grundlage für ihre Entscheidung heranzuziehen und zu berücksichtigen.

9 Gültigkeitsdauer und Aktualisierungsverfahren

Die letzte inhaltliche Überarbeitung erfolgte am 28. März 2018. Die Leitlinie behält ihre Gültigkeit bis März 2023.

Ansprechpartner bei Kommentaren ist.

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10 Anhang: Evidenzrecherche

10.1 Einleitung

Im Rahmen der Aktualisierung der S3-Leitlinie „Therapie des Typ-1-Diabetes“ wurden insgesamt 5 Rechercheaufträge durchgeführt. Zusätzlich wurde die aggregierte Evidenz aus den Leitlinien der American Diabetes Association (ADA) und der Canadian Diabetes Association (CDC) aktualisiert (Rechercheauftrag 6).

10.1.1 Rechercheaufträge

1. Rechercheauftrag:

HbA1c, Lipidstatus, Blutdruckwerte und Blutzucker (prä-, postprandial, time in range) als Prädiktoren für Folgeschäden bei Typ 1-Diabetes mellitus. Studientyp Systematische Reviews.

2. Rechercheauftrag:

Vorteile/Nachteile der Therapieform des Typ 1-Diabetes mellitus (intensivierte Insulintherapie, Pumpentherapie; ggf. Therapie mit Mischinsulinen);

Ziel: Erhöhung des Evidenzgrades der ICT von B auf A. Studientyp RCT

3. Rechercheauftrag:

Neue Studien zum Stellenwert der Analoginsuline (Insulin glargin, Insulin detemir, Insulin lispro, Insulin aspart, Insulin glulisin) in der Therapie des Typ 1-Diabetes mellitus. Recherchezeitraum 2008 - 2016. Studientyp RCT

4. Rechercheauftrag:

Insulinresistenz bei Typ 1-Diabetes mellitus, Typ 1- + Typ 2-Diabetes, Typ 1-Diabetes und metabolisches Syndrom; Diagnostik, Therapie (mit Metformin). Recherchezeitraum 2006 – 2016.

5. Rechercheauftrag:

Continuous glucose monitoring systems, Flash glucose monitoring, sensor augmented pump therapy, (Sensor und Pumpe), Recherchezeitraum 2010 - 2016.

6. Rechercheauftrag:

Aktualisierung der alten Zitate der Clinical Recommendations der ADA oder Canadian Diabetes Association durch Zitate neueren Datums (erscheinen wohl jährlich).

10.2 Literaturrecherche

10.2.1 Einschlusskriterien

Die Einschlusskriterien für die einzelnen Fragestellungen gemäß des PICOS-Schemas (Patienten, Intervention, Kontrolle, Endpunkte und Studien) sind in Tabelle 1 bis 5 dargestellt.

Einschlusskriterien Rechercheauftrag 1

E1	<u>Studienpopulation:</u> Erwachsene, nicht schwangere, mit Typ 1-Diabetes mellitus
E2	<u>Prognostische Faktoren:</u> HbA1c, Lipidstatus, Blutdruckwerte und Blutzucker * * Es wurden auch Interventionsstudien eingeschlossen, in denen oben genannte prognostische Faktoren beeinflusst wurden (z.B. Auswirkungen von intensivierter Blutzuckerkontrolle vs. Standard auf den HbA1c-Wert), da unterstellt wurde, dass diese einen Einfluss auf patientenrelevante Folgeschäden haben.
E3	<u>Studentyp:</u> Systematic Reviews
E4	<u>Outcome:</u> patientenrelevante Folgeschäden
E5	<u>Publikationstyp:</u> Studie als Volltext publiziert und beschaffbar
E6	<u>Publikationssprache:</u> Deutsch oder Englisch

Einschlusskriterien Rechercheauftrag 2

E1	<u>Studienpopulation:</u> Erwachsene, nicht schwangere, mit Typ 1-Diabetes mellitus
E2	<u>Intervention:</u> intensivierte, konventionelle Insulintherapie
E3	<u>Kontrolle:</u> konventionelle Therapie
E4	<u>Studentyp:</u> RCTs
E5	<u>Outcome:</u> Patientenrelevante Endpunkte (Mortalität, Morbidität, Lebensqualität)
E6	<u>Publikationstyp:</u> Studie als Volltext publiziert und beschaffbar
E7	<u>Publikationssprache:</u> Deutsch oder Englisch
E8	<u>Publikationsjahr:</u> ab 06.2009

Einschlusskriterien Rechercheauftrag 3

E1	<u>Studienpopulation:</u> Erwachsene, nicht schwangere, mit Typ 1-Diabetes mellitus
E2	<u>Intervention:</u> Therapie mit Analoginsulinen (Insulin glargin, Insulin detemir, Insulin lispro, Insulin aspart, Insulin glulisin) *
E3	<u>Kontrolle:</u> Humaninsulin *
E4	<u>Studentyp:</u> RCTs
E5	<u>Outcome:</u> Patientenrelevante Endpunkte (Mortalität, Morbidität, Lebensqualität)
E6	<u>Publikationstyp:</u> Studie als Volltext publiziert und beschaffbar
E7	<u>Publikationssprache:</u> Deutsch oder Englisch
E8	<u>Publikationsjahr:</u> ab 01/2008 bzw. noch nicht in alter Leitlinie eingeschlossen

* Ebenfalls eingeschlossen: Vergleich Insulin detemir mit Insulin glargin

Einschlusskriterien Rechercheauftrag 4

Diagnose	
E1	<u>Studienpopulation:</u> Erwachsene, nicht schwangere, mit Typ 1-Diabetes mellitus
E2	<u>Indextest:</u> Tests (einschließlich Blutmarker) oder Kriterien zur Diagnose der Insulinresistenz
E3	<u>Referenztest:</u> Anderer Test zur Diagnostik der Insulinresistenz (idealerweise validierter Test)
E4	<u>Studientyp:</u> Diagnostische Güte Studien
E5	<u>Outcome:</u> Diagnostische Güte (Sensitivität, Spezifität)
E6	<u>Publikationstyp:</u> Studie als Volltext publiziert und beschaffbar
E7	<u>Publikationssprache:</u> Deutsch oder Englisch
E8	<u>Publikationsjahr:</u> ab 01/2006
Therapie	
E1	<u>Studienpopulation:</u> Erwachsene, nicht schwangere, mit Typ 1-Diabetes mellitus mit Insulinresistenz
E2	<u>Intervention:</u> Therapie der Insulinresistenz
E3	<u>Kontrolle:</u> Alternative Form der Therapie der Insulinresistenz
E4	<u>Studientyp:</u> RCTs
E5	<u>Outcome:</u> Patientenrelevante Endpunkte (Mortalität, Morbidität, Lebensqualität)
E6	<u>Publikationstyp:</u> Studie als Volltext publiziert und beschaffbar
E7	<u>Publikationssprache:</u> Deutsch oder Englisch
E8	<u>Publikationsjahr:</u> ab 01/2006

Einschlusskriterien Rechercheauftrag 5

E1	<u>Studienpopulation:</u> Erwachsene, nicht schwangere, mit Typ 1-Diabetes mellitus
E2	<u>Intervention:</u> kontinuierliche Glukosemessung (continuous glucose monitoring systems, flash glucose monitoring, sensor augmented pump therapy)
E3	<u>Kontrolle:</u> Selbstmessung des Blutzuckers (z.B. SGBM)
E4	<u>Studientyp:</u> RCTs
E5	<u>Outcome:</u> Patientenrelevante Endpunkte (Mortalität, Morbidität, Lebensqualität)
E6	<u>Publikationstyp:</u> Studie als Volltext publiziert und beschaffbar
E7	<u>Publikationssprache:</u> Deutsch oder Englisch
E8	<u>Publikationsjahr:</u> ab 01/2010

10.2.2 Datenquellen und Suchstrategie

Es wurde eine systematische Literaturrecherche nach Primärstudien und systematischen Reviews in den Datenbanken Medline (via Pubmed) und Embase (via Embase) durchgeführt. Außerdem wurde in CENTRAL (Cochrane Central Register of Controlled Trials), CDSR (**Cochrane Database of Systematic Reviews**) und DARE (Database of Abstracts of Reviews of Effects) über die Cochrane Library gesucht. Tabellen 6-10 enthalten die Suchstrategien für die jeweiligen Fragestellungen, die jeweiligen Suchzeiträume und die Anzahl an Treffern. Zur Identifikation weiterer relevanter Literatur wurden die Referenzen der eingeschlossenen Studien und systematischer Reviews zu verwandten Fragestellungen geprüft.

Recherchestrategie1

Suchzeitraum: bis 08.2016

Suchstrategie Medline (via PubMed)	Treffer
((“Hemoglobin A, Glycosylated” [Mesh] OR (Hemoglobin[tiab] OR Haemoglobin[tiab] OR Hemoglobins[tiab] OR Haemoglobins [tiab] AND (glycated [tiab] OR glycosylated [tiab])) OR Hb A1c [tiab] OR HbA1c [tiab] OR A1C [tiab] OR HbA1[tiab] OR Hb A1 [tiab] OR “Hemoglobin A(1)”[tiab] OR "Blood Pressure"[Mesh] OR (diastolic [tiab] OR pulse [tiab] OR systolic [tiab] AND pressure [tiab]) OR "Cholesterol"[Mesh] OR “Lipid status” [tiab] OR triglyceride [tiab] OR phospholipid [tiab] OR lipoproteins [Mesh] OR Cholesterol [tiab] OR LDL [tiab] OR HDL [tiab] OR “high density lipoprotein cholesterol” [tiab] OR “low density lipoprotein cholesterol” [tiab] OR “dyslipidemia” [tiab] OR “Dyslipidemias”[Mesh] OR “triacylglycerol”[tiab] OR “Postprandial Period” [Mesh] OR “Blood Glucose”[Mesh] OR postprandial [tiab] OR blood glucose [tiab] OR blood sugar [tiab] OR time in range [tiab] Or time-in-range [tiab]) AND (“Diabetes Mellitus, Type 1” [Mesh] OR IDDM [tiab] OR T1DM [tiab] OR T1D [tiab] OR (diabetes [tiab] AND (insulin depend*[tiab] OR insulindepend*[tiab] OR insulin-depend*[tiab])) OR (diabetes [tiab] AND (type 1 [tiab] type I [tiab])) OR (diabetes [tiab] AND (juvenile[tiab] OR britt*[tiab] OR ketosis-prone OR autoimmune)) AND (meta analysis[Publication Type] OR meta analysis[Title/Abstract] OR “systematic review”[tiab] OR meta analysis[MeSH Terms] OR search*[Title/Abstract])))	584
Suchstrategie Embase (via Embase)	Treffer
('hemoglobin a1c'/exp/mj OR hemoglobin AND a1c:ab,ti OR 'hemoglobin a1c' OR glycated OR glycosylated NEXT/1 (haemoglobin OR haemoglobins OR hemoglobin OR hemoglobins OR a1c) OR (haemoglobin OR haemoglobins OR hemoglobin OR hemoglobins OR hb OR hba AND (a:ab,ti AND 1c:ab,ti OR aic:ab,ti OR 1c:ab,ti OR 1:ab,ti)) OR 'lipid blood level'/mj OR (blood:ab,ti OR plasma:ab,ti OR serum:ab,ti AND (fat:ab,ti OR lipid:ab,ti)) OR 'dyslipidemia'/mj OR (lipid:ab,ti AND blood:ab,ti AND level:ab,ti OR fat:ab,ti AND blood:ab,ti AND level:ab,ti) OR cholesterol:ab,ti OR dyslipidemia:ab,ti) OR ('blood pressure' OR (blood:ab,ti AND tension:ab,ti) OR (vascular:ab,ti AND pressure:ab,ti) OR (intravascular:ab,ti AND pressure:ab,ti) OR (systolic:ab,ti AND blood:ab,ti AND pressure:ab,ti) OR ('glucose blood evel'/mj OR blood NEAR/2 (glucose OR serum OR sugar) OR normoglycaemia:ab,ti OR normoglycemia:ab,ti OR (serum:ab,ti OR plasma:ab,ti AND glucose:ab,ti) OR (postprandial:ab,ti AND glucose:ab,ti) OR glucosaemia:ab,ti OR glucosemia:ab,ti OR glycaemia:ab,ti OR glycemia:ab,ti OR (serum:ab,ti AND sugar:ab,ti))) AND ((‘insulin dependent diabetes mellitus’/mj OR (brittle:ab,ti OR juvenile:ab,ti AND onset:ab,ti OR early:ab,ti AND onset:ab,ti OR labile:ab,ti OR ketoacidotic:ab,ti OR type:ab,ti AND 1:ab,ti OR type:ab,ti AND i:ab,ti OR insulin:ab,ti AND dependent:ab,ti AND diabetes:ab,ti AND mellitus:ab,ti) OR (dm:ab,ti AND 1:ab,ti) OR iddm:ab,ti)) AND ('meta	810

analys*:ab,ti OR search:ab,ti OR 'review':it) AND ([embase]/lim NOT ([embase]/lim AND [medline]/lim) AND ([article]/lim OR [article in press]/lim OR [review]/lim))

Suchstrategie CDSR	Treffer
#1 MeSH descriptor: [Diabetes Mellitus, Type 1] this term only #2 MeSH descriptor: [Lipids] this term only #3 MeSH descriptor: [Blood Pressure] this term only #4 MeSH descriptor: [Hemoglobin A, Glycosylated] this term only #5 MeSH descriptor: [Blood Glucose] this term only #6 #2 or #3 or #4 or #5 #7 #1 and #6 #8 "HbA1c":ti,ab,kw or "lipid level":ti,ab,kw or "blood pressure":ti,ab,kw or "blood sugar":ti,ab,kw (Word variations have been searched) #9 #1 and #8 #10 #7 or #9	83

Recherchestrategien 2

Suchzeitraum: bis 06.2009 – 08.2016

Suchstrategie Medline (via PubMed)	Treffer
((randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [mh] NOT humans [mh])) AND (("Insulin"[Mesh] AND "Drug Administration Schedule"[Mesh]) OR (intensive OR intensified OR multiple daily OR supplementary OR continuous subcutaneous OR basal OR bolus OR combined OR functional) AND insulin AND (management OR therapy OR treatment)) AND (once-daily OR conventional) AND insulin AND (therapy OR management OR treatment) OR ((insulin regimen[tiab] OR insulin regimens[tiab])) AND ("Diabetes Mellitus, Type 1" [Mesh]OR IDDM [tiab] OR T1DM [tiab] OR T1D [tiab] OR (diabetes [tiab] AND (insulin depend*[tiab] OR insulinepend*[tiab] OR insulin-depend*[tiab]))) OR (diabetes [tiab] AND (type 1 [tiab] type I [tiab])) OR (diabetes [tiab] AND (juvenile[tiab] OR britt*[tiab] OR ketosis-prone OR autoimmune))) Sort by: Author Filters: Publication date from 2009/06/01 to 2016/08/31	374

Suchstrategie Embase (via Embase)	Treffer
'insulin dependent diabetes mellitus'/mj/exp OR 'insulin dependent diabetes mellitus' OR (brittle:ab,ti OR juvenile:ab,ti AND onset:ab,ti OR early:ab,ti AND onset:ab,ti OR labile:ab,ti OR ketoacidotic:ab,ti OR type:ab,ti AND 1:ab,ti OR type:ab,ti AND i:ab,ti OR insulin:ab,ti AND dependent:ab,ti AND diabetes:ab,ti AND mellitus:ab,ti) OR (dm:ab,ti AND 1:ab,ti) OR iddm:ab,ti AND ('once-daily':ab,ti OR conventional:ab,ti) AND insulin:ab,ti AND (therapy:ab,ti OR management:ab,ti OR treatment:ab,ti) AND (intensive:ab,ti OR intensified:ab,ti OR multiple:ab,ti AND daily:ab,ti OR supplementary:ab,ti OR continuous:ab,ti AND subcutaneous:ab,ti OR basal:ab,ti OR bolus:ab,ti OR combined:ab,ti OR functional:ab,ti AND insulin:ab,ti AND (management:ab,ti OR therapy:ab,ti OR treatment:ab,ti) OR 'insulin regimen':ab,ti OR 'insulin regimens':ab,ti) AND ('crossover procedure':de OR 'double-blind procedure':de OR 'randomized controlled trial':de OR 'single-blind procedure':de OR random*:de,ab,ti OR factorial*:de,ab,ti OR crossover*:de,ab,ti OR (cross NEXT/1 over*):de,ab,ti OR placebo*:de,ab,ti OR (doubl* NEAR/1 blind*):de,ab,ti OR (singl* NEAR/1 blind*):de,ab,ti OR assign*:de,ab,ti OR allocat*:de,ab,ti OR volunteer*:de,ab,ti) AND ([article]/lim OR [article in press]/lim OR [review]/lim) AND [embase]/lim NOT ([em-	61

base]/lim AND [medline]/lim) AND [2009-2016]/py	
CENTRAL/DARE	Treffer

#1 MeSH descriptor: [Diabetes Mellitus, Type 1] this term only
#2 MeSH descriptor: [Insulin] this term only
#3 intensive therapy:ti,ab,kw (Word variations have been searched)
#4 "conventional therapy":ti,ab,kw (Word variations have been searched)
#5 random*:ti,ab,kw (Word variations have been searched)
#6 #1 and #2 and (#3 or #4) and #5 Publication Year from 2009 to 2016

Recherchestrategien 3

Suchzeitraum: bis 01.2008 – 08.2016

Suchstrategie Medline (via PubMed)	Treffer
((("Insulin/analogs and derivatives"[Mesh] OR "Insulin/analogs and derivatives"[Mesh] AND (Long acting [tiab] OR Ultralente [tiab] OR ultralong [tiab] OR semilente [tiab] OR lente [tiab] OR "short acting" [tiab] OR "rapid acting" [tiab]) OR (delayed [tiab] OR slow [tiab] AND acting [tiab]) OR "Insulin Lispro"[Mesh] OR Insulin Lispro [tiab] OR Lyspro [tiab] Insulin-lispro [tiab] OR Lispro [tiab] OR ((Lys[tiab] OR Lysine [tiab])AND ("29(B)"[tiab] OR "28(B)" [tiab])) AND (Pro [tiab] OR Prolineinsulin[tiab])) OR Humalog [tiab] OR Humalog Kwikpen[tiab] OR "Insulin Aspart"[Mesh] OR Insulin Aspart [tiab] OR Aspart [tiab] OR Insulin-Aspart [tiab] OR B28-Asp-Insulin [tiab] OR B28 Asp Insulin [tiab] OR Insulin B28asp [tiab] OR NovoLog[tiab] OR NovoRapid [tiab] OR Novo Nordisk Brand of Insulin Aspart [tiab] OR "Insulin Detemir"[Mesh] OR Insulin Detemir [tiab] OR Detemir [tiab] OR Basal Insulin Detemir [tiab] OR NN304 [tiab] OR NN-304 [tiab] OR NN 304 [tiab] OR Levemir [tiab] OR "Insulin Glargine"[Mesh] OR "LY2963016 insulin glargin" [Supplementary Concept])OR "LY IGLAR"[tiab] OR Insulin Glargine[tiab] OR Glargine[tiab] OR HOE 901 [tiab] OR HOE-901 [tiab] OR HOE901[tiab] OR Lantus[tiab] OR Lantus SoloStar [tiab] OR "insulin glulisine" [Supplementary Concept] OR insulin glulisine [tiab] OR Glulisine [tiab] OR Apidra [tiab])) AND (((Diabetes Mellitus, Type 1" [Mesh] OR IDDM [tiab] OR T1DM [tiab] OR T1D [tiab] OR (diabetes [tiab] AND (insulin depend*[tiab] OR insulin-depend*[tiab] OR insulin-depend*[tiab])) OR (diabetes [tiab] AND (type 1 [tiab] type I [tiab]))) OR (diabetes [tiab] AND (juvenile[tiab] OR britt*[tiab] OR ketosis-prone OR autoimmune)))))) AND (((randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [mh] NOT humans [mh]))) Filters: Publication date from 2008/01/01 to 2016/12/31	479

Suchstrategie Embase (via Embase)	Treffer
'insulin derivative'/mj OR insulin:ab,ti AND (analog:ab,ti OR analogs:ab,ti OR derivative:ab,ti OR derivatives:ab,ti) OR 'insulin lispro'/mj OR insulin:ab,ti AND (lispro:ab,ti OR lyspro:ab,ti) OR lyspro:ab,ti OR lispro:ab,ti OR (lys:ab,ti OR lysine:ab,ti AND (29b:ab,ti OR 28b:ab,ti) AND (pro:ab,ti OR prolineinsulin:ab,ti)) OR (humalog:ab,ti AND (kwikpen:ab,ti OR lispro:ab,ti OR mix:ab,ti OR pen:ab,ti)) OR liprolog:ab,ti OR (ly:ab,ti AND 275585:ab,ti) OR 'insulin aspart'/mj OR (insulin:ab,ti AND (aspart:ab,ti OR aspartic:ab,ti)) OR aspart:ab,ti OR novo AND mix:ab,ti OR novolog:ab,ti OR novomix:ab,ti OR novorapid:ab,ti OR novorapide:ab,ti OR 'insulin detemir'/mj OR (insulin:ab,ti AND detemir:ab,ti) OR determir:ab,ti OR levemir:ab,ti OR (nn:ab,ti AND 304:ab,ti) OR 'insulin glargin'/mj OR (insulin:ab,ti AND glargin:ab,ti) OR glargin:ab,ti OR abasaglar:ab,ti OR abasria:ab,ti OR basagliar:ab,ti OR (hoe:ab,ti	56

AND 901:ab,ti) OR lantus:ab,ti OR (ly:ab,ti AND 2963016:ab,ti) OR optisulin:ab,ti OR toujeo:ab,ti OR 'insulin glulisine':mj OR (insulin:ab,ti AND glulisine:ab,ti) OR glulisine:ab,ti OR apidra:ab,ti OR (hmr:ab,ti AND 1964:ab,ti) AND ('insulin dependent diabetes mellitus':mj OR (brittle:ab,ti OR juvenile:ab,ti AND onset:ab,ti OR early:ab,ti AND onset:ab,ti OR labile:ab,ti OR ketoacidotic:ab,ti OR type:ab,ti AND 1:ab,ti OR type:ab,ti AND i:ab,ti OR insulin:ab,ti AND dependent:ab,ti AND diabetes:ab,ti AND mellitus:ab,ti) OR (dm:ab,ti AND 1:ab,ti) OR iddm:ab,ti) AND ('crossover procedure':de OR 'double-blind procedure':de OR 'randomized controlled trial':de OR 'single-blind procedure':de OR random*:de,ab,ti OR factorial*:de,ab,ti OR crossover*:de,ab,ti OR (cross NEXT/1 over*):de,ab,ti OR placebo*:de,ab,ti OR (doubl* NEAR/1 blind*):de,ab,ti OR (singl* NEAR/1 blind*):de,ab,ti OR assign*:de,ab,ti OR allocat*:de,ab,ti OR volunteer*:de,ab,ti) AND ([article]/lim OR [article in press]/lim OR [review]/lim) AND [embase]/lim NOT ([embase]/lim AND [medline]/lim) AND [2008-2016]/py

CENTRAL/DARE	Treffer
ID Search Hits #1 MeSH descriptor: [Diabetes Mellitus, Type 1] this term only 3589 #2 MeSH descriptor: [Insulin Aspart] this term only 222 #3 MeSH descriptor: [Insulin Lispro] this term only 279 #4 MeSH descriptor: [Insulin Glargine] this term only 381 #5 MeSH descriptor: [Insulin Detemir] this term only 104 #6 insulin and (analog* and derivative*):ti,ab,kw (Word variations have been searched) 179 #7 insulin glulisin:ti,ab,kw (Word variations have been searched) 0 #8 #2 or #3 or #4 or #5 or #7 and #1 and #6 Publication Year from 2008 to 2016	422

Recherchestrategien 4

Suchzeitraum: bis 01.2006 – 09.2016

Suchstrategie Medline (via PubMed) Diagnose	Treffer
((sensitivity*[Title/Abstract] OR sensitivity and specificity[MeSH Terms] OR diagnosis*[Title/Abstract] OR diagnosis[MeSH:noexp] OR diagnostic * [MeSH:noexp])) AND (((("Insulin Resistance"[Majr] OR (insulin [tiab] AND resistance [tiab]))))) AND (((("Diabetes Mellitus, Type 1" [Mesh]OR IDDM [tiab] OR T1DM [tiab] OR T1D [tiab] OR (diabetes [tiab] AND (insulin depend*[tiab] OR insulinepend*[tiab] OR insulin-depend*[tiab]))) OR (diabetes [tiab] AND (type 1 [tiab] type I [tiab]))) OR (diabetes [tiab] AND (juvenile[tiab] OR britt*[tiab] OR ketosis-prone OR autoimmune))))))) Sort by: Author Filters: Publication date from 2006/01/01 to 2016/12/31	462
Suchstrategie Medline (via PubMed) Therapie	Treffer
((((randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [mh] NOT humans [mh])))) AND (((("Insulin Resistance"[Majr] OR (insulin [tiab] AND resistance [tiab]))))) AND (((("Diabetes Mellitus, Type 1" [Mesh]OR IDDM [tiab] OR T1DM [tiab] OR T1D [tiab] OR (diabetes [tiab] AND (insulin depend*[tiab] OR insulinepend*[tiab] OR insulin-depend*[tiab]))) OR (diabetes [tiab] AND (type 1 [tiab] type I [tiab]))) OR (diabetes [tiab] AND (juvenile[tiab] OR britt*[tiab] OR ketosis-prone OR autoimmune))))))) Sort by: Author Filters: Publication date from 2006/01/01 to 2016/12/31	414

Suchstrategie Embase (via Embase) Diagnose	Treffer
('insulin dependent diabetes mellitus'/mj/exp OR 'insulin dependent diabetes mellitus' OR (brittle:ab,ti OR juvenile:ab,ti AND onset:ab,ti OR early:ab,ti AND onset:ab,ti OR labile:ab,ti OR ketoacidotic:ab,ti OR type:ab,ti AND 1:ab,ti OR type:ab,ti AND i:ab,ti OR insulin:ab,ti AND dependent:ab,ti AND diabetes:ab,ti AND mellitus:ab,ti) OR (dm:ab,ti AND 1:ab,ti) OR iddm:ab,ti) AND ('insulin resistance'/mj OR (insulin:ab,ti AND resistance*:ab,ti)) AND (sensitiv:ab,ti OR diagnostic AND accuracy:ab,ti OR diagnostic:ab,ti OR diagnosis:ab,ti) AND ([2006-2016]/py AND ([article]/lim OR [article in press]/lim OR [review]/lim) AND [embase]/lim NOT ([embase]/lim AND [medline]/lim))	238
Suchstrategie Embase (via Embase) Behandlung	Treffer
('insulin dependent diabetes mellitus'/mj/exp OR 'insulin dependent diabetes mellitus' OR (brittle:ab,ti OR juvenile:ab,ti AND onset:ab,ti OR early:ab,ti AND onset:ab,ti OR labile:ab,ti OR ketoacidotic:ab,ti OR type:ab,ti AND 1:ab,ti OR type:ab,ti AND i:ab,ti OR insulin:ab,ti AND dependent:ab,ti AND diabetes:ab,ti AND mellitus:ab,ti) OR (dm:ab,ti AND 1:ab,ti) OR iddm:ab,ti) AND ('crossover procedure':de OR 'double-blind procedure':de OR 'randomized controlled trial':de OR 'single-blind procedure':de OR random*:de,ab,ti OR factorial*:de,ab,ti OR crossover*:de,ab,ti OR (cross NEXT/1 over*):de,ab,ti OR placebo*:de,ab,ti OR (doubl* NEAR/1 blind*):de,ab,ti OR (singl* NEAR/1 blind*):de,ab,ti OR assign*:de,ab,ti OR allocat*:de,ab,ti OR volunteer*:de,ab,ti) AND ('insulin resistance'/mj OR (insulin:ab,ti AND resistance*:ab,ti)) AND ([2006-2016]/py AND ([article]/lim OR [article in press]/lim OR [review]/lim) AND [embase]/lim NOT ([embase]/lim AND [medline]/lim))	596
CENTRAL/DARE	Treffer
#1 MeSH descriptor: [Diabetes Mellitus, Type 1] explode all trees #2 "diabetes mellitus type 1":ti,ab,kw (Word variations have been searched) #3 random*:ti,ab,kw (Word variations have been searched) #4 MeSH descriptor: [Insulin Resistance] this term only #5 "insulin resistance":ti,ab,kw (Word variations have been searched) #6 (#1 or #2) and #3 and (#4 or #5) Publication Year from 2006 to 2016, in Trials	17

Recherchestrategien 5

Suchzeitraum: bis 01.2010 – 09.2016

Suchstrategie Medline (via PubMed)	Treffer
((("Blood Glucose Self-Monitoring"[Mesh] OR "Blood Glucose Self-Monitoring" [tiab] OR "Blood Glucose Self Monitoring" [tiab] OR Home Blood Glucose Monitoring [tiab] OR "Blood Glucose Self-Monitorings" [tiab] OR ((Blood [tiab] OR Glucose [tiab] Blood Sugar [tiab] OR sugar [tiab]) AND (Self-Monitoring [tiab] OR Monitoring [tiab])) OR "flash glucose monitoring" [tiab] OR "sensor augmented pump therapy" [tiab]))) AND (((randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [mh] NOT humans [mh]))) AND ("Diabetes Mellitus, Type 1" [Mesh] OR IDDM [tiab] OR T1DM [tiab] OR T1D [tiab] OR (diabetes [tiab] AND (insulin depend*[tiab] OR insulindepend*[tiab] OR insulin-depend*[tiab]))) OR (diabetes [tiab] AND (type 1 [tiab] type I [tiab]))) OR (diabetes [tiab] AND (juvenile[tiab] OR britt*[tiab] OR ketosis-prone OR autoimmune)))) Sort by: Author Filters: Publication date from 2010/01/01 to 2016/12/31	514

Suchstrategie Embase (via Embase)	Treffer
(('blood glucose monitoring':mj OR 'blood glucose monitoring':ab,ti OR 'blood glucose control':ab,ti OR 'blood glucose self-monitoring':ab,ti OR (glucose:ab,ti OR blood AND sugar:ab,ti AND monitoring:ab,ti)) AND ('insulin dependent diabetes mellitus':mj OR (brittle:ab,ti OR juvenile:ab,ti AND onset:ab,ti OR early:ab,ti AND onset:ab,ti OR labile:ab,ti OR ketoacidotic:ab,ti OR type:ab,ti AND 1:ab,ti OR type:ab,ti AND i:ab,ti OR insulin:ab,ti AND dependent:ab,ti AND diabetes:ab,ti AND mellitus:ab,ti) OR (dm:ab,ti AND 1:ab,ti) OR iddm:ab,ti) AND ('crossover procedure':de OR 'double-blind procedure':de OR 'randomized controlled trial':de OR 'single-blind procedure':de OR random*:de,ab,ti OR factorial*:de,ab,ti OR crossover*:de,ab,ti OR (cross NEXT/1 over*):de,ab,ti OR placebo*:de,ab,ti OR (doubl* NEAR/1 blind*):de,ab,ti OR (singl* NEAR/1 blind*):de,ab,ti OR assign*:de,ab,ti OR allocat*:de,ab,ti OR volunteer*:de,ab,ti) AND ([2010-2016]/py))	244
CENTRAL/DARE	Treffer
#1 MeSH descriptor: [Blood Glucose Self-Monitoring] this term only #2 "continuousglucose monitoring system*" or "Flash glucose monitoring" or "sensor augmented pump therapy":ti,ab,kw (Word variations have been searched) #3 "self-monitor" or "self-monitoring":ti,ab,kw (Word variations have been searched) #4 MeSH descriptor: [Diabetes Mellitus, Type 1] this term only #5 #1 or #2 or #3 #6 #4 and #5 Publication Year from 2010 to 2016 #7 random*:ti,ab,kw (Word variations have been searched) #8 #6 and #7	151

10.3 Studienselektion

Die identifizierte Literatur wurde von zwei Gutachtern unabhängig voneinander selektiert. Zunächst wurden die Abstracts sämtlicher in den Datenbanken erzielten Treffer auf Erfüllung der *a-priori* definierten Einschlusskriterien hin geprüft und anschließend, bei potentieller Relevanz, die Volltexte. Unstimmigkeiten wurden bis zum Konsens diskutiert. Alle Referenzen der eingeschlossenen Primärstudien wurden auf potentiell relevante Literatur hin untersucht und ggf. der Volltext geprüft. Falls zu den Rechercheaufträgen 2, 3, 4 und 5 ein systematischer Review vorlag, so wurden die Primärstudien, die den Einschlusskriterien entsprachen, eingeschlossen und extrahiert.

10.4 Einteilung des Studientyps und Vergabe des Level of Evidence

Für die Evidenzbewertung wurde das der bisherigen Leitlinie zugrunde liegende Evidenz- bewertungssystem weitergeführt, damit die neu identifizierten Studien in die bereits bestehende Evidenz leicht integriert werden können. Es wurde eine Bewertung des Levels of Evidence nach „Evidenzniveau DDG“ durchgeführt (siehe Appendix A) sowie eine Bewertung mit der Evidenzbewertung nach „SIGN“ (siehe Appendix B).

10.5 Studienbewertung (Bewertung des Risikos für systematische Verzerrung)

Für die Studienbewertung von Primärstudien zu Interventionen wurde das „Cochrane Risk of Bias Tool“ verwendet (Appendix C) (1). Jede Frage wurde mit „hohem Risiko für Verzerrung“, „niedrigem Risiko für Verzerrung“, oder „unklarem Risiko für Verzerrung“ bewertet. Da auf Grund der Breite der Fragestellung eine *a-priori* Definition des Items „other source of bias“ nicht möglich erschien, wurde falls dieses Item nicht mit „low risk of bias“ bewertet wurde, der Grund hierfür angegeben. Studien, die

die Effektivität einer diagnostischen Maßnahme bzgl. klinischer und/ oder patientenrelevanter Endpunkte erfassen, wurden ebenfalls mit dem „Cochrane Risk of Bias Tool“ bewertet.

Studien zur diagnostischen Güte wurden mit dem „Quality Assessment for Diagnostic Accuracy (QUADAS-II) Instrument“ bewertet (Appendix D) (2). Jede Frage wurde mit „hohes Risiko für Verzerrung“, „niedriges Risiko für Verzerrung“, oder „unklares Risiko für Verzerrung“ bewertet.

Systematische Reviews (Rechercheauftrag 1) wurden mit „A measurement tool for the assessment of multiple systematic reviews“ (AMSTAR) bewertet (Appendix E) (3). Die einzelnen Fragen wurden mit „ja“, „nein“, „nicht zu beantworten“ und „nicht anwendbar“ beantwortet.

Die Bewertung der Gefahr für systematische Verzerrung bzw. methodologische Qualität wurde unabhängig von zwei Gutachtern vorgenommen. Jegliche Diskrepanz wurde bis zum Konsens diskutiert.

10.6 Datenextraktion

Die gesamte Datenextraktion wurde von einem Gutachter vorgenommen und von einem zweiten Gutachter qualitätsgesichert. Jegliche Unstimmigkeiten wurden bis zum Konsens diskutiert. Mehrere Publikationen die auf derselben Studie bzw. demselben Studienkollektiv basierten wurden zusammengeführt und jeweils durch gestrichelte Linien unterteilt (z.B. weitere Endpunkte, Subgruppenanalysen).

10.6.1 Primärstudien

Es wurden die folgenden Daten in standardisierte vorab getestete Tabellen extrahiert:

- Interventionsstudien
 - Studentyp, Referenz und Ziel der Studie
 - Ein-/Ausschlusskriterien: Alle demografischen und klinischen Ein- und Ausschlusskriterien wurden extrahiert. Formale Einschlusskriterien wurden nicht berücksichtigt (z.B. Einverständniserklärung).
 - Baseline Charakteristika: Alter, Geschlecht und weitere den Schweregrad des Typ 1- Diabetes beschreibende Parameter und/ oder relevante Einflussvariablen.
 - Region: Land in dem die Studie durchgeführt wurde
 - Setting
 - Beschreibung der Interventions-/Kontrollgruppe: Bei Medikamentenstudien wurden der Wirkstoff, die Dosis, die Frequenz, die Applikationsform sowie die Dauer der Therapie extrahiert.
 - Patientenfluss: angegeben wurden die Anzahl an eingeschlossenen und analysierten Patienten sowie Patienten, die die Studie vollständig abgebrochen haben (Drop-Outs + Lost-to-Follow-Ups). Falls diese nicht pro Gruppe angegeben waren, sondern lediglich gruppenbezogene Angaben zum Patientenfluss bezüglich der Analyse gemacht wurden, ist die Differenz zwischen randomisierten/ eingeschlossenen und ausgewerteten Patienten angegeben worden.
 - Ergebnisse zu den Endpunkten der Studien: Für Ereignisse wurde für jeden der Endpunkte die Rate (%) oder für seltene Ereignisse die Anzahl je Gruppe (n) extrahiert und - falls angegeben - die relativen Effektmaße (Odds Ratio, relatives Risiko, Hazard Ratio). Die statistische Signifikanz wurde mit Konfidenzintervallen (KI) und mit p-Werten angegeben. Für kontinuierliche Variablen wurde der Mittelwert bzw. die Mittelwertdifferenz oder das Ratio of Means jeweils mit KI und p-Wert angegeben. Falls kein zweiseitiger Test angewendet wurde, ist dies in Klammern hinter dem p-Wert vermerkt. Bei mehreren Erhebungszeitpunkten wurde auf das letzte Follow-up, beziehungsweise den letzten Erhebungszeitpunkt des Outcomes zurückgegriffen. Falls Behandlungsphase und Follow-up nur separat betrachtet worden sind, wurden die Ergebnisse jeweils für die einzelne Periode angegeben. Für jeden Endpunkt wurde der Erhebungszeitpunkt angegeben. Der Erhebungszeitpunkt des Endpunkts bezieht sich dabei, soweit nicht anders angegeben, auf den Studieneinschluss. Für patientenberichtete Endpunkte wurden Angaben zur Messung des Endpunktes gemacht (z.B. Lebensqualität).
- Studien zur diagnostischen Güte:

- Studientyp, Referenz und Ziel der Studie
- Ein-/Ausschlusskriterien: Alle demografischen und klinischen Ein- und Ausschlusskriterien wurden extrahiert. Formale Einschlusskriterien wurden nicht berücksichtigt (z.B. Einverständniserklärung).
- Indextest, Referenztest, Zeitintervall
- Patientenfluss
- Ergebnisse: Sensitivität, Spezifität und falls möglich der prädiktive Wert, einschließlich zugehöriger Angaben zur statistischen Sicherheit (Konfidenzintervall oder p-Wert)

10.6.2 Systematische Reviews

Die Datenextraktionen für die systematischen Reviews umfassen Angaben zu den Ein- und Ausschlusskriterien für die Studienselektion, den Recherchezeitraum sowie Angaben zum prognostischen Faktor bzw. zu Intervention und Kontrolle. Für die gepoolten Ergebnisse von Metaanalysen wurden die relativen oder die standardisierten Effektmaße extrahiert. Wenn random und fixed effect model berechnet wurden, so wurde das Ergebnis des random effect models berichtet. Zusätzlich wurden für jeden Vergleich die Heterogenität (I^2) sowie die Anzahl der einbezogenen Studien (N) und Patienten angegeben (n). Falls keine Metaanalyse durchgeführt worden ist, wurden die Ergebnisse mittels „modified Vote-Counting“ zusammengefasst. Modified Vote-Counting umfasst die Angabe der Effektrichtung, der Spannbreite der Effektmaße (über die Studien hinweg), die Angabe der Anzahl an Vergleichen, die diese Effektrichtung aufweisen, die Angabe der Anzahl an statistisch signifikanten Vergleichen, die diese Effektrichtung aufweisen und die Anzahl an Vergleichen/ einbezogenen Studien insgesamt für den jeweiligen Endpunkt.

10.7 Ergebnisse der Literaturrecherche

Durch die Recherche in den Datenbanken und durch Prüfung der Referenzen wurden insgesamt 5710 Treffer identifiziert. Bei 237 Publikationen wurden die Volltexte auf Erfüllung der oben genannten Einschlusskriterien geprüft. 29 Publikationen erfüllten alle Einschlusskriterien. Der Selektionsprozess ist in Abbildung 1-5 dargestellt.

Abbildung 1: Flow-chart Rechercheauftrag 1

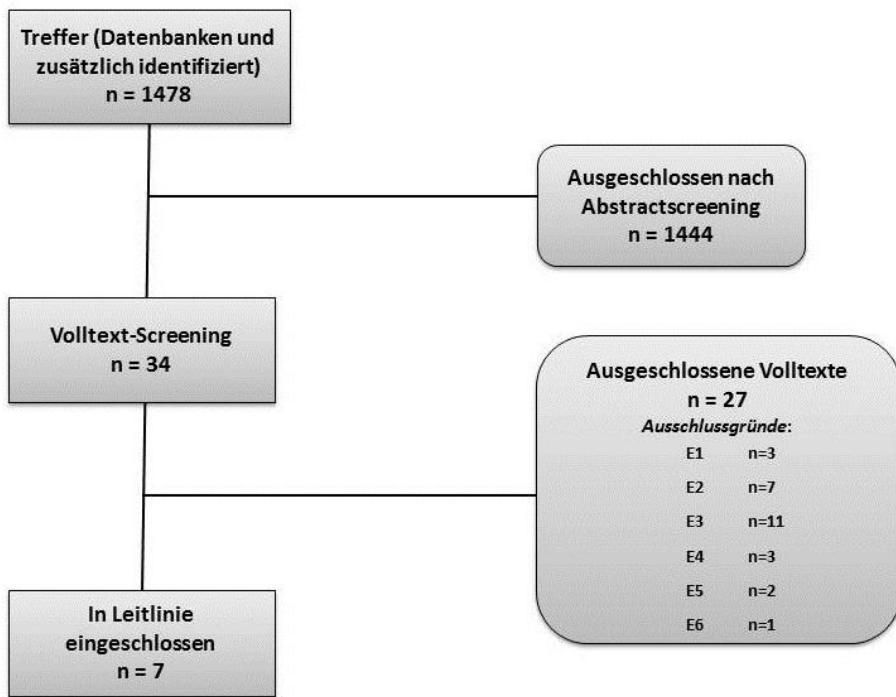


Abbildung 2: Flow-chart Rechercheauftrag 2

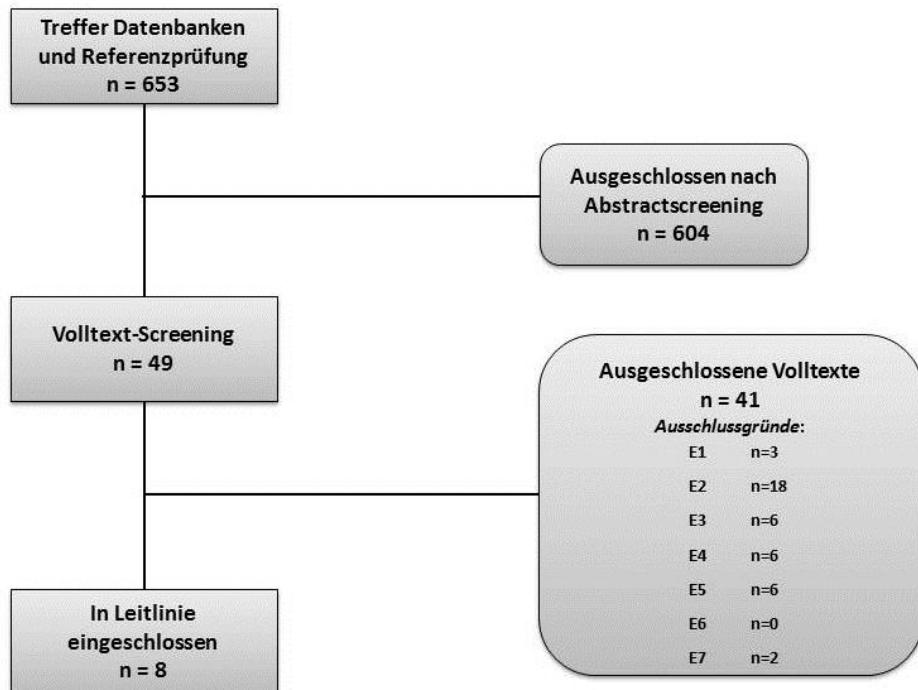


Abbildung 3: Flow-chart Rechercheauftrag 3

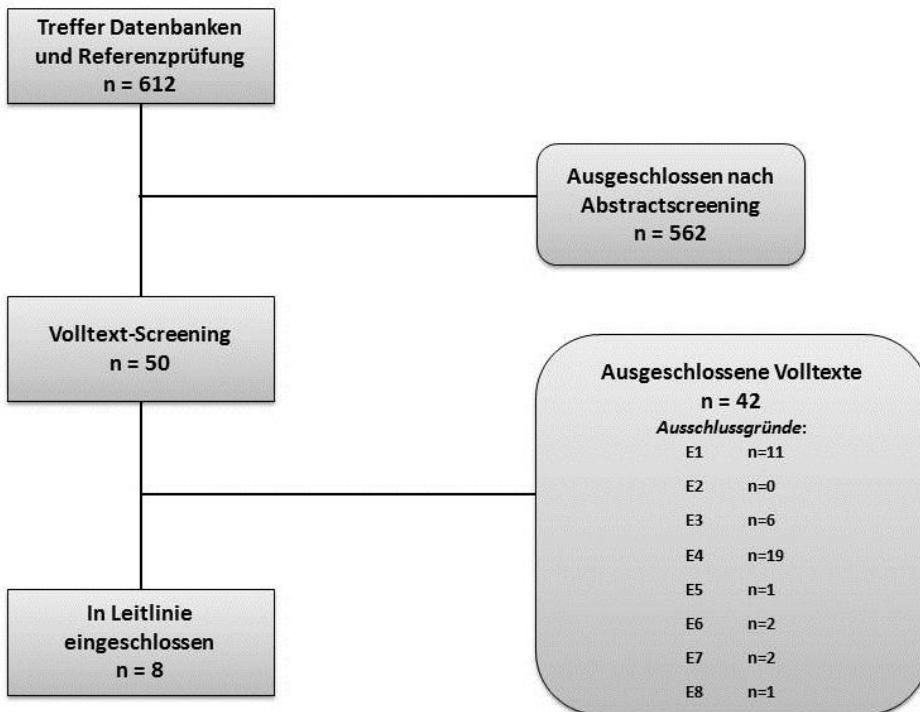


Abbildung 4: Flow-chart Rechercheauftrag 4

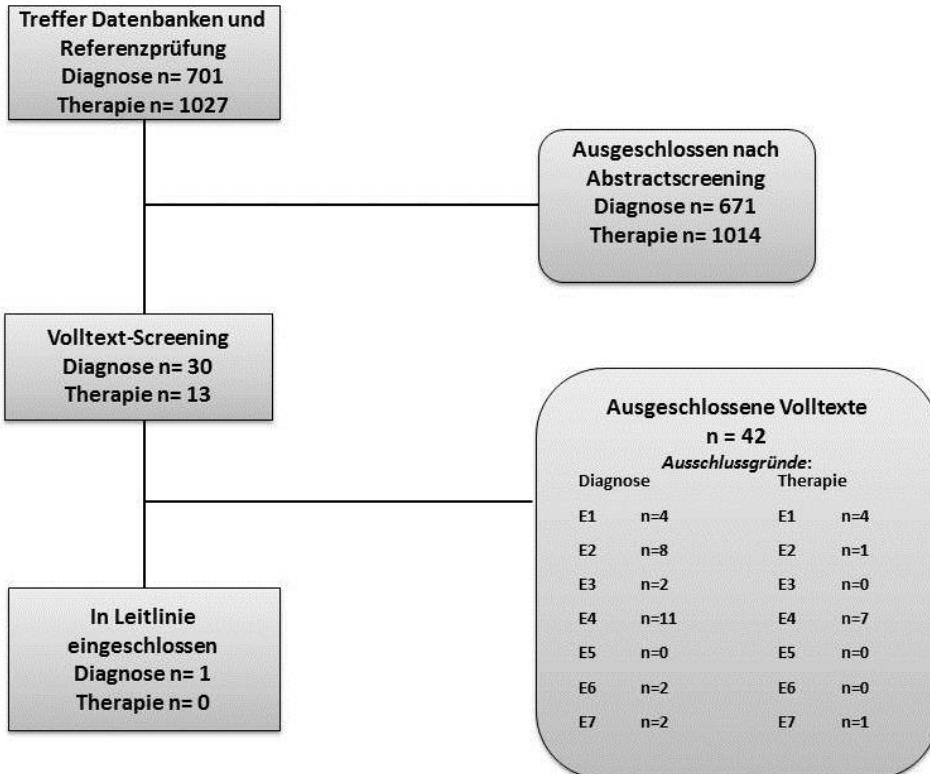
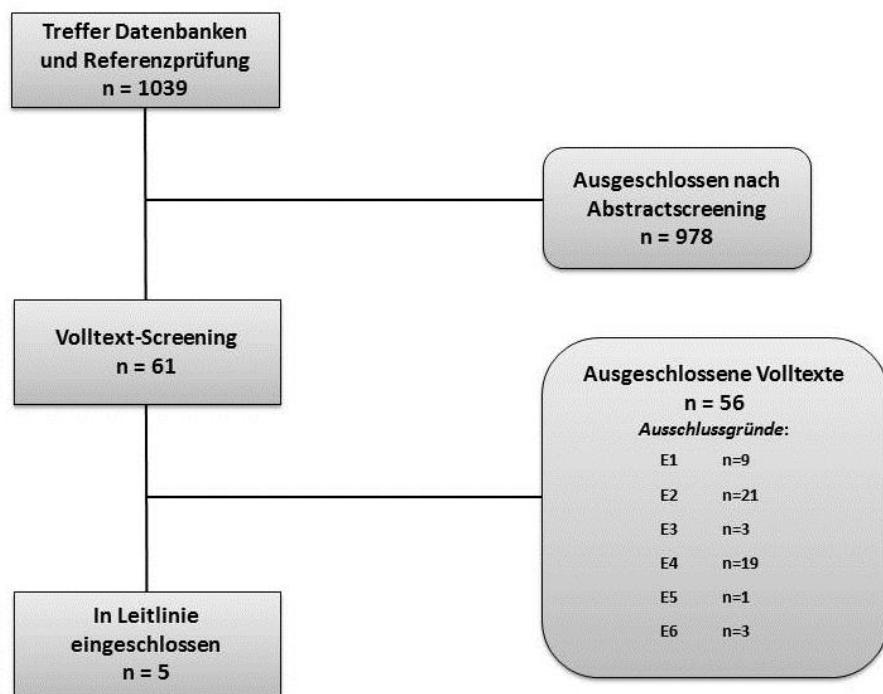


Abbildung 5: Flow-chart Rechercheauftrag 5



10.8 Extraktionstabellen

10.8.1 Rechercheauftrag 1

Review/reference Study type Objective	Inclusion/exclusion criteria search period (patients marked bold)	Prognostic factor	Characteristics of included studies (first author; year; country; follow-up; factor, method of measurement; average in population; outcome evaluated)	Effect (RR /OR/HR/ MD/SDM [CI]; I ² Q; N; n) or (effect direction; number of studies showing effect direction; number of significant studies showing effect direction/ 95% CI; total number of studies)	Level of Evidence, methodological quality and authors conclusion
<p>Adler A.I., et al. 2010, Association between glycated haemoglobin and the risk of lower extremity amputation (LEA) on patients with diabetes mellitus – review and meta-analysis, Diabetologia (2010) 53:840–849.</p> <p>Study type Systematic review</p> <p>Objective “To synthesis available prospective epidemiological data on association between glycaemia measured by HbA_{1c} and the risk of LEA in individuals with diabetes.”</p>	<p>Inclusion criteria</p> <ul style="list-style-type: none"> - measurement of HbA_{1c} at baseline (at least an average of 6 months before occurrence of LEA) and documentation of LEA outcome during follow-up in individuals with diabetes - studies with prospective cohort and nested case-control studies <p>Exclusion criteria</p> <ul style="list-style-type: none"> - cross-sectional and retrospective case-control studies - patients with acute foot ulcers, previous amputation or end-stage renal disease <p>Search period 01.1970 – 07.2009</p> <p>Number of included studies Studies included (N): 14 Studies with Type 1 Diabetes included in analysis (N): 4</p>	HbA _{1c}	<p>Roy (2008); USA; 6 years; HbA_{1c}; HPLC; NR; LEA/ PVD</p> <p>Moss (1999); USA; 14 years; HbA_{1c}; Microcolumn; NR; LEA;</p> <p>Olson (2002); USA; 10 years; HbA_{1c}; Microcolumn, HPLC; NR; LEA/ PVD</p> <p>Mühlhauser (2000); Germany; 10 year; ; HbA_{1c}; Microcolumn, HPLC; NR; LEA</p>	<p><u>Lower extremity amputation RR per 1% increase in HbA_{1c} levels:</u> 1.18 [95% CI 1.02-1.38]; I² = NR; N= 4; n=5509</p>	<p>Level of evidence DDG: 2b SIGN:2+</p> <p>Methodological quality</p> <ul style="list-style-type: none"> A-priori design: - Two reviewers: ? Literature search: + Status of publication: - List of studies: - Study characteristics: + Critical appraisal: + Conclusion: ? Combining findings: ? Publication bias: 0 Conflict of interest: - <p>Authors conclusion: “There is a substantial increase in risk of LEA associated with glycaemia in individuals with diabetes. In the absence of conclusive evidence from trials, this paper provides further epidemiological support for glucose-lowering as a strategy to reduce amputation in a population without acute foot ulceration or former amputation; it also provides disease modellers with estimates to assess the overall burden of hyperglycaemia.”</p>
Cheng, D., et al., HbA1C	Inclusion criteria	glycated hemoglo-	Kilpatrick (2008); USA, Canada; 6.5 years;	Progression of renal status*	Level of evidence

Review/reference Study type Objective	Inclusion/exclusion criteria search period (patients marked bold)	Prognostic factor	Characteristics of included studies (first author; year; country; follow-up; factor, method of measurement; average in population; outcome evaluated)	Effect (RR /OR/HR/ MD/SDM [CI]; I ² / Q; N; n) or (effect direction; number of studies showing effect direction; number of significant studies showing effect direction/ 95% CI; total number of studies)	Level of Evidence, methodological quality and authors conclusion
<p>variability and the risk of renal status progression in Diabetes Mellitus: a meta-analysis. PLoS One, 2014. 9(12): p. e115509</p> <p>Study type Systematic Review</p> <p>Objective “To explore the association between glycated hemoglobin (A1C) variability and renal disease progression in patients with diabetes mellitus.”</p>	<p>- Studies that measured A1C variability, either as the coefficient of variation of A1C (A1C-CV) or standard deviation of A1C (A1C-SD)</p> <p>- Studies that investigated the association between A1C variability and the progression of renal status</p> <p>- Hazard ratios (HRs) and their 95% confidence intervals (CI) could be extracted</p> <p>Exclusion criteria NR</p> <p>Search period studies published before 26.4.2014</p> <p>Number of included studies Studies included (n): 9 Studies with Type 1 Diabetes included in analysis (n): 4</p>	bin (A1C)	<p>A1C variability; mean A1c: 8.5% (aSD: 0.73); microalbuminuria development Waden (2009); Finland; 5.7 years; A1C variability; mean A1C: 8.5% (cSD: 0.78); any increase in albuminuria or progression to ESRD Macovecchio (2011); UK; N.R.; A1C variability; mean A1C: 9.5% (aSD: 0.91); microalbuminuria development Raman (2011); USA; 7 years; A1C variability; N.R.; microalbuminuria development</p>	<p>HR: 1.70 [95% CI 1.41 - 2.05] I²=44.1%; N=4; n=5673</p> <p>Microalbuminuria onset HR: 1.63 [95% CI 1.28 - 2.07], I²=50.2%; N= 3; n=3566</p> <p>Exacerbation of renal function or albuminuria HR: 1.92 [95% CI 1.49 - 2.47], I²= not applicable; N=1; n=2107</p> <p>* defined as microalbuminuria development, any increase in albuminuria, or the progression to chronic kidney disease, which was defined as an estimated glomerular filtration rate (eGFR), 60 ml/min/1.73 m² or the progression to ESRD.</p>	<p>DDG: 2b SIGN: 2+</p> <p>Methodological quality</p> <p>A-priori design: - Two reviewers: ? Literature search: + Status of publication: - List of studies: - Study characteristics: + Critical appraisal: + Conclusion: + Combining findings: + Publication bias: 0 Conflict of interest: -</p> <p>Authors conclusion: “A1C variability is independently associated with the development of microalbuminuria and the progression of renal status in both type 1 and 2 diabetes patients. A standard method for measuring A1C variability is essential for further and deeper analyses. In addition, future studies should assess the effect of reducing A1C variability on nephropathy complication.”</p>
<p>Gorst, C., et al., Long – term Glycemic Variability and Risk of Adverse Outcomes: A Systematic Review and Meta –analysis. Diabetes Care; Vol. 38, 2015</p> <p>Study Type Systematic Review</p> <p>Objective “This systematic review and</p>	<p>Inclusion criteria - Studies of patients with diabetes that evaluated HbA_{1c} variability and adverse outcomes</p> <p>Exclusion criteria - Reviews, editorials and case reports were excluded</p> <p>Search period Articles published between 2004 and September 2014</p>	HbA _{1c} variability	<p>Hermann (2014); Germany and Austria; N.R.; HbA1C CV; N.R.; diabetic retinopathy Hietala (2013); Finland; 5.2 years; HbA1C CV; N.R.; Proliferative retinopathy Kilpatrick (2008); U.S.A. and Canada; 6.5 years; N.R.; Development and progression of diabetic retinopathy and nephropathy Marcovecchio (2011); U.K.; N.R.; N.R.; Microalbuminuria Nazim (2014); 9.2 years; Poland; N.R.; N.R.;</p>	<p>High vs. low HbA_{1c} CV and risk of diabetic retinopathy RR: 1.34 [95% CI 0.89 - 2.04]; I²= 90%; N=2; n=37910</p> <p>Incremental increase in HbA_{1c} CV and risk of microalbuminuria RR: 1.04 [95% CI 1.00 - 1.08]; N.A.; N=1; n= 438</p>	<p>Level of evidence</p> <p>DDG: 2b SIGN: 2+</p> <p>Methodological quality</p> <p>A-priori design: + Two reviewers: + Literature search: - Status of publication: - List of studies: - Study characteristics: -</p>

Review/reference Study type Objective	Inclusion/exclusion criteria search period (patients marked bold)	Prognostic factor	Characteristics of included studies (first author; year; country; follow-up; factor; method of measurement; average in population; outcome evaluated)	Effect (RR /OR/HR/ MD/SDM [CI]; I ² Q; N; n) or (effect direction; number of studies showing effect direction; number of significant studies showing effect direction/ 95% CI; total number of studies)	Level of Evidence, methodological quality and authors conclusion
meta-analysis evaluates the association between HbA _{1c} variability and micro – and macrovascular complications and mortality in type 1 and type 2 diabetes.”	Number of included studies Studies included (N): 20 Studies with Type 1 Diabetes included in analysis (N): 7		Microalbuminuria Raman (2011); U.S.A.; 7 years; N.R.; Micro-albuminuria Waden (2009); Finnland; 5.7 years; N.R.; Cardiovascular event and progression in renal status	<u>High vs. low SD and risk of nephropathy</u> RR: 1.92 [95% CI 1.49 - 2.47]; N.A.; N=1; n=2107 <u>High vs. low SD and risk of CV events</u> RR: 1.98 [95% CI 1.39 - 2.82]; N.A.; N=1; n=2107 <u>Incremental increase in SD and risk of nephropathy</u> RR: 1.86 [95% CI 1.41 - 2.46]; N.A.; N=1; n=1441 <u>Incremental increase in SD and risk of microalbuminuria</u> RR: 1.56 [95% CI 1.08 - 2.25]; I ² = 67%; N=2; n=2125 <u>Incremental increase in SD and risk of retinopathy</u> RR: 2.11 [95% CI 1.54 - 2.89]; N.A.; N=1; n=1441	Critical appraisal: - Conclusion: - Combining findings: + Publication bias: 0 Conflict of interest: - Authors conclusion: “HbA _{1c} variability was positively associated with micro- and macrovascular complications and mortality independently of the HbA _{1c} level and might play a future role in clinical risk assessment.”
Kähler, P., et al., Targeting intensive versus conventional glycaemic control for type 1 diabetes mellitus: a systematic review with meta-analyses and trial sequential analyses of randomised clinical trials. BMJ Open, 2014. 4(8): p. e004806. Study Type Systematic Review Objective “To assess the benefits and harms of targeting intensive versus conventional glycaemic control in patients with type 1 diabetes mellitus.”	Inclusion criteria - Randomized clinical trials - patients with type 1 diabetes mellitus - Inclusion of trials irrespective of duration, language, publication status and predefined outcomes Exclusion criteria - Trials only including pregnant patients Search period Until January 2013 Number of included studies Studies included (N): 18 Studies with Type 1 Diabetes included in analysis (N): 18	intensive glycaemic control (IGC)/conventional glycaemic control (CGC)	DCCT/EDIC; 1983; USA and Canada; 25 years Franklin et al.; 2008; U.K.; 1 year Hvidovre et al.; 1982; Denmark; 180 days Kroc et al.; 1984; North America and England; 2 years Linn et al.; 1996.; Germany; 5 years Linn et al.; 2003.; Germany; 3 years at least Microalbuminuria; 1992/ 1995.; U.K.; 5 years Minnesota DCCT; 1983; USA; 5 years Oslo.; 1986; Norway; 8 years Oxford.; 1983; U.K.; 2 years Perlman et al.; 1984.; Canada; 1 year Service et al.; 1983.; USA; 2.5 years Shah et al.; 1989.; USA; 1 year Steno 1a; 1982; Denmark; 8 years Steno 1b; 1986; Denmark; 5 years	<u>All-cause mortality</u> RR: 1.16 [95% CI 0.65 - 2.08]; I ² = 0%; N=7, n=1971 <u>Cardiovascular mortality</u> RR: 0.49 [95% CI 0.19 - 1.24]; I ² = 0%; N=7, n=1802 <u>Macrovascular complications</u> RR: 0.63 [95% CI 0.41 - 0.96]; I ² = 0%; N=3, n=1577 <u>Severe hypoglycemia</u> RR: 1.40 [95% CI 1.01 - 1.94]; I ² = 46%; N=11, n=1983 <u>Nephropathy</u> RR: 0.37 [95% CI 0.27 - 0.50]; I ² = 5%; N=5, n=1635 <u>End-stage renal disease</u> RR: 0.96 [95% CI 0.13 - 7.05]; I ² = N.R.; N=3,	Level of evidence DDG: 1a SIGN: 1++ Methodological quality A-priori design: + Two reviewers: + Literature search: + Status of publication: - List of studies: + Study characteristics: + Critical appraisal: + Conclusion: + Combining findings: + Publication bias: 0 Conflict of interest: - Authors conclusion: “There was no significant effect towards

Review/reference Study type Objective	Inclusion/exclusion criteria search period (patients marked bold)	Prognostic factor	Characteristics of included studies (first author; year; country; follow-up; factor, method of measurement; average in population; outcome evaluated)	Effect (RR /OR/HR/ MD/SDM [CI]; I ² / Q; N; n) or (effect direction; number of studies showing effect direction; number of significant studies showing effect direction/ 95% CI; total number of studies)	Level of Evidence, methodological quality and authors conclusion
			Stockholm; 1985; Sweden; 14 years Verrillo et al.; 1988; Italy; 5 years Hershey et al.; 1999/ 1994.; USA; 1.5 years	n=124 <u>Adverse events</u> RR: 1.03 [95% CI 0.61 – 1.72]; I ² = 0%; N=2, n=1515 <u>Incidence of cancer</u> RR: 3.12 [95% CI 0.33 – 29.65]; I ² = N.R.; N=2, n=1515 <u>Non-fatal myocardial infarction</u> RR: 0.58 [95% CI 0.26 – 1.32]; I ² = N.R.; N=3, n=1577 <u>Retinopathy</u> RR: 0.74 [95% CI 0.50 – 1.10]; I ² =62%; N=9, n=1605 <u>Retinal photocoagulation</u> RR: 0.41 [95% CI 0.16 – 1.04]; I ² =48%; N=2, n=1238 <u>Congestive heart failure (n)</u> 1/ 1; NR; NR; N=1, n= 1441 <u>Non-fatal stroke (n, during follow-up)</u> 1/ 5; NR; NR; N=1, n= 1441 <u>Amputation of lower extremity (n)</u> 7/ 8; NR; NR; N=1, n= 1441 <u>Peripheral revascularization (n)</u> 0/ 2; NR; NR; N=1, n= 1441 <u>Coronary revascularization (n)</u> 11/ 20; NR; NR; N=1, n= 1441 <u>Health-related quality of life (self-administered multiple choice 46 items specifically for the DCCT, n)</u> NR; NR; NR; p= NS; N=1, n= 1441	improved all-cause mortality when targeting intensive glycaemic control compared with conventional glycaemic control. However, there may be beneficial effects of targeting intensive glycaemic control on the composite macrovascular outcome and on nephropathy, and detrimental effects on severe hypoglycaemia. Notably, the data for retinopathy and ketoacidosis were inconsistent. There was a severe lack of reporting on patient relevant outcomes, and all trials had poor bias control."
Fullerton, B., K. Jeitler, et al. (2014) Intensive glucose control versus conventional glucose control for type 1 diabetes mellitus. <u>Cochrane</u>	Inclusion criteria - all randomised controlled trials (RCTs) that had defined different glycaemic targets in the treatment arms - patients with type 1 diabetes	Intensive glucose control (IGC)/ conventional glucose control (CGC)	Bucharest – Düsseldorf; 1984; Romania, Germany; N.R. DCCT1; 1993; USA.; average follow up of 6.5 years (range: 3 to 9 years) DCCT2; 1993; U.S.A.; average follow up of	<u>Retinopathy</u> RR: 0.71 [95% CI 0.44 - 1.16]; I ² = 79%; N=7, n=1660 <u>Manifestation of retinopathy</u> RR: 0.27 [95% CI 0.18 - 0.42]; I ² = 0%; N=2,	Level of evidence DDG: 1a SIGN:1++ Methodological quality

Review/reference Study type Objective	Inclusion/exclusion criteria search period (patients marked bold)	Prognostic factor	Characteristics of included studies (first author; year; country; follow-up; factor, method of measurement; average in population; outcome evaluated)	Effect (RR /OR/HR/ MD/SDM [CI]; I ² / Q; N; n) or (effect direction; number of studies showing effect direction; number of significant studies showing effect direction/ 95% CI; total number of studies)	Level of Evidence, methodological quality and authors conclusion
<p>Database of Systematic Reviews DOI: 10.1002/14651858.CD009122.pub2</p> <p>Study Type Systematic Review</p> <p>Objective "To assess the effects of intensive versus conventional glycaemic targets in patients with type 1 diabetes in terms of long-term complications and determine whether very low, near normoglycaemic values are of additional benefit."</p>	<p>Exclusion criteria</p> <ul style="list-style-type: none"> - follow up of at least 1 year - non separate analysis of patients with type 1 diabetes - no specified glucose targets in treatment groups - no relevant outcome <p>Search period Until 2012</p> <p>Number of included studies Studies with Type 1 Diabetes included in analyses (N): 11</p>		<p>6.5 years (range: 3 to 9 years)</p> <p>Holman; 1983; U.K.; N.R.</p> <p>Linn; 1996; N.R.; N.R.</p> <p>MCSG; 1995; N.R.; N.R.</p> <p>MDCCT; 1994; N.R.; N.R.</p> <p>Oslo; 1987; Norway; 2 months</p> <p>Steno 1; 1983; N.R.; N.R.</p> <p>Steno 2; 1986; N.R.; N.R.</p> <p>Verrillo; 1988; N.R.; N.R.</p> <p>Wysocki 2003; N.R.; 18 months</p>	<p>n=768</p> <p>Progression of retinopathy RR: 1.10 [95% CI 0.54 - 2.24]; I²= 78%; N=4, n=860</p> <p>Manifestation of Nephropathy RR: 0.56 [95% CI 0.46 - 0.68]; I²= 0%; N=3, n=1475</p> <p>Progression of Nephropathy RR: 0.79 [95% CI 0.37 - 1.70]; I²= 19%; N=3, n=179</p> <p>Manifestation of Neuropathy RR: 0.35 [95% CI 0.23 - 0.53]; I²= 0%; N=3, n=1203</p> <p>Severe hypoglycaemia RR: 1.50 [95% CI 1.17 - 1.91]; I²= 52%; N=11, n=2108</p> <p>Ketoacidosis OR: 1.33 [95% CI 0.95 - 1.86] ; I²= 0%; N=9, n=1924</p> <p>All-cause mortality OR: 1.02 [95% CI 0.48 - 2.19] ; I²= 0%; N=10, n=2039</p> <p>Health-related quality of life (self-administered multiple choice 46 items specifically for the DCCT, n) NR; NR; NR; p= NS; N=1, n= 1441</p> <p>Endstage renal disease (n) 1/0; NR; NR; NR; N=1, n= 70</p>	<p>A-priori design: +</p> <p>Two reviewers: +</p> <p>Literature search: +</p> <p>Status of publication: +</p> <p>List of studies: +</p> <p>Study characteristics: +</p> <p>Critical appraisal: +</p> <p>Conclusion: +</p> <p>Combining findings: +</p> <p>Publication bias: +</p> <p>Conflict of interest: +</p> <p>Authors conclusion: "Tight blood sugar control reduces the risk of developing microvascular diabetes complications. The evidence of benefit is mainly from studies in younger patients at early stages of the disease. Benefits need to be weighed against risks including severe hypoglycaemia, and patient training is an important aspect in practice. The effects of tight blood sugar control seem to become weaker once complications have been manifested. However, further research is needed on this issue. Furthermore, there is a lack of evidence from RCTs on the effects of tight blood sugar control in older patient populations or patients with macrovascular disease. There is no firm evidence for specific blood glucose targets and treatment goals need to be individualised taking into account age, disease progression, macrovascular risk, as well as the patient's lifestyle and disease management capabilities."</p>

Review/reference Study type Objective	Inclusion/exclusion criteria search period (patients marked bold)	Prognostic factor	Characteristics of included studies (first author; year; country; follow-up; factor; method of measurement; average in population; outcome evaluated)	Effect (RR /OR/HR/ MD/SDM [CI]; I ² / Q; N; n) or (effect direction; number of studies showing effect direction; number of significant studies showing effect direction/ 95% CI; total number of studies)	Level of Evidence, methodological quality and authors conclusion
<p>Callaghan Brian, C., et al. Enhanced glucose control for preventing and treating diabetic neuropathy. Cochrane Database of Systematic Reviews, 2012. DOI: 10.1002/14651858.CD007543.pub2.</p> <p>Study Type Systematic Review</p> <p>Objective “To examine the evidence for enhanced glucose control in the prevention of distal symmetric polyneuropathy in people with type 1 and type 2 diabetes.”</p>	<p>Inclusion criteria</p> <ul style="list-style-type: none"> - Males or females of any age with type 1 or type 2 diabetes - randomized, controlled studies investigating enhanced glycemic control - reported neuropathy outcomes after at least one year of intervention <p>Exclusion criteria</p> <ul style="list-style-type: none"> none <p>Search period 1966 – 2012</p> <p>Number of included studies Studies included (N): 17 Studies with Type 1 Diabetes included in analysis (N): 7</p>	<p>Enhanced glucose control*/ standard therapy</p> <p>*Any intervention that enhances glycemic control more than standard care for a period of 12 months or more. Interventions might include more frequent subcutaneous insulin administration, continuous insulin infusion, oral anti-diabetic agents, lifestyle modifications such as diet and exercise, or pancreas transplant.</p>	<p>Dahl – Jorgensen et. al.; 1986; N.R.; N.R. DCCT; 1993a; N.R.; Mfu: 6.5 years DCCT; 1993b; N.R.; Mfu: 6.5 years Jakobsen et. al.; 1988; N.R.; 2 years Lauritzen et. al; 1985; N.R.; N.R. Linn et. al.; 1996; N.R.; Reichard et. al.; 1993; N.R. Holman 1983; N.R.; 2 years</p>	<p><u>Annualized risk difference of developing neuropathy</u> RD= -1.84% [95% CI -2.56, -1.11]; I²=31%; N=3, n=1228</p> <p><u>Incidence of clinical neuropathy after 5 years</u> RR=0.46 [95% CI 0.33 - 0.63]; I²=0.0%; N=3, n=1228</p> <p><u>Annual change in peroneal nerve motor conduction velocity</u> MD= 0.61 [95% CI 0.51 - 0.71]; I²=41%; N=4, n=1371</p> <p><u>Annual change in median nerve motor conduction velocity</u> MD= 0.46 [95% CI 0.36 - 0.57]; I²=0.0%; N=2, n=1241</p> <p><u>Annual change in ulnar nerve motor conduction velocity</u> MD= 1.49 [95% CI -0.74 - 3.71]; I²=81%; N=2, n=134</p> <p><u>Annual change in vibration threshold in the feet</u> SMD= 0.32 [95% CI 0.02 - 0.62]; I²=60%; N=3, n=177</p>	<p>Level of evidence DDG: 1a SIGN: 1+</p> <p>Methodological quality</p> <ul style="list-style-type: none"> A-priori design: + Two reviewers: + Literature search: + Status of publication: + List of studies: - Study characteristics: + Critical appraisal: + Conclusion: + Combining findings: - Publication bias: 0 Conflict of interest: - <p>Authors conclusion: “According to high-quality evidence, enhanced glucose control significantly prevents the development of clinical neuropathy and reduces nerve conduction and vibration threshold abnormalities in type 1 diabetes mellitus. [...]”</p> <p>Importantly, enhanced glucose control significantly increases the risk of severe hypoglycemic episodes, which needs to be taken into account when evaluating its risk/benefit ratio.”</p>
<p>Stettler, C., S. Allemann, et al. (2006) Glycemic control and macrovascular disease in types 1 and 2 diabetes mellitus: meta-analysis of randomized trials (Structured abstract). American Heart</p>	<p>Inclusion criteria</p> <ul style="list-style-type: none"> - randomized controlled trials - target population, general population of patients with either type 1 or type 2 Diabetes mellitus - comparison of regimens aiming to improve glycemic control (subcutane- 	<p>interventions to improve glycemic control/ conventional treatment</p>	<p>Holman et. al.; 1983; N.R.; Mfu: 2.0 Verillo et. al.; 1988; N.R.; Mfu: 5.0 Lauritzen; 1991; N.R.; Mfu: 8.0 Feldt – Ramussen et. al.; 1992; N.R.; Mfu: 5.0 DCCT Primary Prevention; 1993; N.R.; Mfu: 6.5</p>	<p><u>Risk for any macrovascular events</u> IRR= 0.38 [95% CI 0.26 - 0.56]; I²= 0.0%; N= 8, n= 1805</p> <p><u>Risk for cardiac events</u> IRR= 0.41 [95% CI 0.19 - 0.87]; I²= 13.6%; N= 7, n= N.R.</p> <p><u>Risk for peripheral vascular events</u></p>	<p>Level of evidence DDG: 1b SIGN: 1+</p> <p>Methodological quality</p> <ul style="list-style-type: none"> A-priori design: + Two reviewers: + Literature search: +

Review/reference Study type Objective	Inclusion/exclusion criteria search period (patients marked bold)	Prognostic factor	Characteristics of included studies (first author; year; country; follow-up; factor, method of measurement; average in population; outcome evaluated)	Effect (RR /OR/HR/ MD/SDM [CI]; I ² / Q; N; n) or (effect direction; number of studies showing effect direction; number of significant studies showing effect direction/ 95% CI; total number of studies)	Level of Evidence, methodological quality and authors conclusion
<p>Journal 27-38</p> <p>Study Type Systematic Review</p> <p>Objective “The development of macrovascular complications, including cardiac, cerebrovascular, and peripheral vascular complications, is an important concern considering that a substantial proportion of premature deaths in patients with type 1 DM and most deaths in type 2 DM are related to macrovascular disease.”</p>	<p>ous insulin injections, insulin pump, oral antidiabetic agents, or a combination of the previous) with conventional treatments</p> <ul style="list-style-type: none"> - documentation of glycemic control by measurement of glycated hemoglobin (HbA1c) - follow-up of at least 2 years - prospective recording of macrovascular events <p>Exclusion criteria N.R.</p> <p>Search period N.R.</p> <p>Number of included studies Studies included (N): 10 Studies with Type 1 Diabetes included in analysis (N): 8</p>		<p>DCCT Secondary Intervention; 1993; N.R.; Mfu: 6.5 SDIS; 1993; N.R.; Mfu: 7.5 MCSG; 1995; N.R.; Mfu: 5.0</p>	<p>IRR= 0.39 [95% CI 0.25 - 0.62]; I²=0.0%; N= 4, n= N.R. Risk for cerebrovascular events IRR= 0.34 [95% CI 0.05-2.57]; I²=16.9%; N= 2, n= N.R.</p>	<p>Status of publication: - List of studies: - Study characteristics: + Critical appraisal: + Conclusion: + Combining findings: - Publication bias: + Conflict of interest: - Authors conclusion: “Our data suggest that attempts to improve glycemic control reduce the incidence of macrovascular events both in type 1 and type 2 DM. In absolute terms, benefits are comparable, although effects on specific manifestations of macrovascular disease differ.”</p>

IG: intervention group; CG: control group; +: low risk; -: high risk; ?: unclear risk; N.A.: not applicable; CI: confidence interval; NR: not reported; Mfu = Mean follow – up; IRR: incidence rate ratio

Abbildung 6: Überschneidung der eingeschlossenen Primärstudien Rechercheauftrag 1

Primary publication	Systematic review						
	Adler, 2009	Cheng, 2014	Gorsi, 2015	Kähler, 2014	Fullerton, 2014	Callaghan, 2012	Steitler 2006
Moss 1999	x						
Roy 2008	x						
Olson 2002	x						
Mühlhauser 2000	x						
Kilpatrick 2008		x	x				
Wadén 2009		x	x				
Marcovecchio 2011		x	x				
Raman 2011		x	x				
Hermann 2014			x				
Nazim 2014			x				
Hietala 2013		x					
DCCT/EDIC 1983				x	x	x	x
Franklin 2008			x				
Hvidovre 1982			x				
Kroc 1984			x				
Linn 2003			x				
Linn 1996			x	x	x		
Microalbuminuria Collaboration Group.1992/ 1995			x				
Minnesota 1983			x				
Oslo 1986			x	x			
Oxford 1983			x				
Perlman 1984			x				
Service 1983			x				
Shah 1989			x				
Steno 1 1982			x	x			
Steno 1b 1986			x	x			
Stockholm 1985			x				
Verrillo 1988			x	x		x	
Hershey 1999/ White 1994			x				
Feldt-Rasmussen 1992						x	
SDIS 1993						x	
Holman 1983			x	x	x		
Bucharest-Düsseldorf 1984			x				
MSCG 1995			x		x		
MDCCT 1994			x				
Wysocki 2003			x				
Dahl-Jørgensen 1986				x			
Lauritzen 1991						x	
Lauritzen 1985					x		
Reichard 1993					x		
Jakobsen 1988					x		

Abbildung 6 stellt die eingeschlossenen Primärstudien per systematischen Review (SR) dar und in wie vielen SRs sie eingeschlossen sind.

In vier Reviews wurde die DCCT/EDIC -RCT eingeschlossen. In drei Reviews wurden die RCTs von Linn (1996), Verrillo (1988) und Holman (1983) eingeschlossen.

10.8.2 Rechercheauftrag 2

Study / reference/ objective	Region/setting, inclusion criteria, exclusion criteria, baseline characteristics (IG/CG) of study population and patient flow (IG/CG)	Intervention group(s) (IG) / control group (CG)	Outcomes (IG/CG; relative effect measure (RR, OR) or MD; 95% CI and p; primary outcome marked)	Level of evidence / Critical appraisal and authors conclusion
<p>Follow-up study of DCC-trial (RCT) The DCCT/EDIC Research group. Intensive diabetic therapy and ocular surgery in type 1 diabetes, New England journal of medicine 372 (18), 2015</p> <p>Objective “The Diabetes Control and Complications Trial (DCCT) showed a beneficial effect of 6.5 years of intensive glycemic control on retinopathy in patients with type 1 diabetes.”</p>	<p>Region USA/ 29 institutions across the United States and Canada</p> <p>Major inclusion criteria of DCCT</p> <ul style="list-style-type: none"> - insulin dependence, as evidenced by deficient C-peptide secretion - age of 13 to 39 years - absence of hypertension, hypercholesterolemia, and severe diabetic complications or medical conditions <p>Exclusion criteria DCCT</p> <ul style="list-style-type: none"> - centrally measured basal or stimulated C-peptide is greater than .2 pmol/ml - Previous treatment for IDDM with either three or more daily injections of insulin or with an insulin infusion pump except for periods of less than four weeks to manage an intercurrent illness or to determine optimal blood glucose control - Insulin Resistance - Three or more documented episodes of diabetic ketoacidosis requiring hospitalization during the 12 months prior to the time of randomization - Women who are pregnant or who plan or desire a pregnancy - Hypertension - Lipids - Active urinary tract infection - History of alcoholism or drug abuse - Any non-diabetic condition that potentially limits life expectancy - Any form of hemoglobinopathy or hemolytic process 	<p><u>During DCCT:</u> <u>Intensive treatment (INT):</u> Three or more insulin injections daily or continuous subcutaneous insulin infusion, guided by frequent self-monitoring of blood glucose <u>Conventional treatment (CON):</u> One or two insulin injections daily</p>	<p>Diabetes-related ocular surgery <u>(n, median follow-up: 23 years)</u> 63/98; risk reduction*= 48.5% [95% CI 28.8 – 62.7]; p<0.001 <u>All ocular procedures (n, median follow-up: 23 years)</u> 130/ 189; risk reduction*= 37.3% [95% CI 11.9 – 55.4]; p=0.01 * (1 – hazard ratio of intensive versus conventional diabetes therapy) × 100</p>	<p>Level of evidence DDG: 1b SIGN: 1+</p> <p>Risk of bias Generation of allocation sequence + Allocation concealment: + Blinding of participants and personal: - Blinding of outcome assessment: + Incomplete outcome data: + Selective reporting: + Other source of bias: +</p> <p>Authors conclusion: “Intensive therapy in patients with type 1 diabetes was associated with a substantial reduction in the long-term risk of ocular surgery.”</p>

Study / reference/ objective	Region/setting, inclusion criteria, exclusion criteria, baseline characteristics (IG/CG) of study population and patient flow (IG/CG)	Intervention group(s) (IG) / control group (CG)	Outcomes (IG/CG; relative effect measure (RR, OR) or MD; 95% CI and p; primary outcome marked)	Level of evidence / Critical appraisal and authors conclusion
	<ul style="list-style-type: none"> - Diabetic Neuropathy - Previous or current endocrine disorder other than diabetes - Obesity - Chronic disease requiring prescription medication - Major electrocardiographic abnormalities or clinical history of ischemic (coronary) heart disease - History of epilepsy or seizures - Determined psychological and Behavioral Criteria - Any condition or use of any medication which will interfere with the application of treatment - Hypoglycemia - conditions which might confound the assessment of ocular status <p>Baseline characteristics DCCT</p> <p><u>INT/ CON n</u> 711/ 730</p> <p><u>Age [y] mean (SD)</u> 27.1 (7.1)/ 26.5 (7.1)</p> <p><u>Sex: Female (%)</u> 48.5 / 45.9.</p> <p><u>Diabetes duration [y] mean (SD)</u> 6.0 (4.2) / 5.7 (4.1)</p> <p><u>DCCT primary cohort (%)</u> 49 / 51.8</p> <p><u>Hypertension (%)</u> 0 / 0.3</p> <p><u>Hyperlipidemia (%)</u> 22.8 / 23.3</p> <p><u>Current Cigarette smoking (%)</u> 20.5 / 21.6</p> <p><u>BMI [kg/m²] mean (SD)</u> 23.4 (2.7) / 23.5 (2.9)</p>			

Study / reference/ objective	Region/setting, inclusion criteria, exclusion criteria, baseline characteristics (IG/CG) of study population and patient flow (IG/CG)	Intervention group(s) (IG) / control group (CG)	Outcomes (IG/CG; relative effect measure (RR, OR) or MD; 95% CI and p; primary outcome marked)	Level of evidence / Critical appraisal and authors conclusion
	<p><u>Systolic blood pressure [mmHg] mean (SD)</u> 114.5 (11.3) / 114.6 (11.4)</p> <p><u>Diastolic blood pressure [mmHg] mean (SD)</u> 73.1 (8.2) / 72.9 (8.7)</p> <p>Patient flow Included: 1441 Analyzed: 1441</p> <p>Follow-Up Median 23 years</p>			
<p>The DCCT/EDIC Research group. Intensive diabetes therapy and glomerular filtration rate in type 1 diabetes. New England journal of medicine 365 (25), 2011. p:2366-76.</p> <p>Objective “In the current study, we tested the effects of intensive diabetes therapy in the DCCT on the development of an impaired GFR, with a total follow-up period of 22 years.”</p>	<p>Patient flow Included: 1441 Analyzed: 1441</p> <p>Follow-up Median 22 years</p>		<p><u>Impaired GFR* (n, median follow-up: 22 years)</u> 24/ 46; risk reduction**=50% [95% CI 18 - 69]; p=0.006</p> <p><u>End-stage renal disease (n, median follow-up: 22 years)</u> 8/ 16; risk reduction**=51% [95% CI -14 - 79]; p=0.10</p> <p><u>Combined outcome of impaired GFR or death (n, median follow-up: 22 years)</u> 53/ 80; risk reduction**=37% [95% CI 10 - 55]; p=0.01</p> <p>*defined as an estimated GFR <60 ml per minute 1.72 m² at 2 consecutive study visits</p> <p>**(1 – hazard ratio of intensive versus conventional diabetes therapy) × 100</p>	<p>Authors conclusion: “The long-term risk of an impaired GFR was significantly lower among persons treated early in the course of type 1 diabetes with intensive diabetes therapy than among those treated with conventional diabetes therapy.”</p>
<p>EDIC Follow-up study of DCC-trial (RCT) The Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Research Group. Effect of intensive diabetes therapy on the progression of diabetic retinopathy in patients with type 1 diabetes: 18 years of follow-up in the DCCT/EDIC. Diabetes 2015;64, p.:631–642</p> <p>Objective “We now describe the progression of retinopathy over a total of 18 years of EDIC follow-up.”</p>	<p>Region/setting, inclusion criteria, exclusion criteria see above.</p> <p>Baseline characteristics of EDIC at baseline (INT/CON):</p> <p><u>INT/CON n</u> 676/ 673</p> <p><u>Age[y] mean (SD):</u> 34 (7)/ 33 (7)</p> <p><u>Female [%]:</u> 49/ 46</p> <p><u>Diabetes duration [y] mean (SD):</u> 12 (5)/ 12 (5)</p> <p><u>Current cigarette smoking [%]:</u></p>	<p><u>During DCCT:</u></p> <p><u>Intensive treatment (INT):</u> Three or more insulin injections daily or continuous subcutaneous insulin infusion, guided by frequent self-monitoring of blood glucose</p> <p><u>Conventional treatment (CON):</u> One or two insulin injections daily</p>	<p>≥ 3-step or more progression of diabetic retinopathy (%EDIC years 15-18) 41.1/ 58.7; Odds red= 41% [95%CI 25 – 54]; p= 0.0001</p> <p><u>severe nonproliferative diabetic retinopathy (SNPDR) or worse (%EDIC years 15-18)</u> 15.9/ 31.5; Odds red= 42% [95%CI 20 – 58]; p= 0.001</p> <p><u>Proliferative diabetic retinopathy (PDR) or worse (%EDIC years 15-18)</u> 15.7/ 31.5; Odds red= 43% [95%CI 21 – 59]; p= 0.001</p> <p><u>Clinically significant macular edema (%EDIC years 15-18)</u> 17/ 26; Odds red= 23% [95%CI -4 – 44]; p= 0.09</p>	<p>Level of evidence DDG: 1b SIGN: 1+</p> <p>Risk of bias Generation of allocation sequence: + Allocation concealment: + Blinding of participants and personal - Blinding of outcome assessment: + Incomplete outcome data: ? Selective reporting: + Other source of bias: +</p> <p>Authors conclusion: “In conclusion, the initial period of 6.5 years of inten-</p>

Study / reference/ objective	Region/setting, inclusion criteria, exclusion criteria, baseline characteristics (IG/CG) of study population and patient flow (IG/CG)	Intervention group(s) (IG) / control group (CG)	Outcomes (IG/CG; relative effect measure (RR, OR) or MD; 95% CI and p; primary outcome marked)	Level of evidence / Critical appraisal and authors conclusion
	<p>23/ 22</p> <p><u>HbA_{1c} [%] mean (SD):</u> 7.4 (1.1)/ 9.1 (1.6)</p> <p><u>BMI mean (SD):</u> 26.5 (4)/ 25.0 (3)</p> <p>Patient flow</p> <p>Included: 1375</p> <p>Analyzed: 1214</p> <p>Follow-up</p> <p>Total years of follow-up:18</p>		<p><u>Photocoagulation therapy (% EDIC years 15-18)</u> 17.2/ 30.9; Odds red= 33% [95%CI 9 – 51]; p= 0.010</p>	<p>sive therapy during the DCCT has resulted in a sustained beneficial reduction over up to 18 years of extended follow-up during EDIC in the cumulative incidence (total numbers) of subjects showing further retinopathy progression, and progression to more severe levels of retinopathy that require intervention. The benefit (risk reduction), however, is not as great as that observed in prior analyses up to 4 and up to 10 years of EDIC follow-up during which the phenomenon of metabolic memory applied.”</p>
<p>Albers J. et al. Effect of prior intensive insulin treatment during the diabetes control and complications trial (DCCT) on peripheral neuropathy in type 1 diabetes during the epidemiology of diabetes interventions and complications (EDIC) study; Diabetes Care Vol. 22 (5) 2010.</p> <p>Objective</p> <p>“To evaluate the impact of former intensive versus conventional insulin treatment on neuropathy in Diabetes Control and Complications Trial (DCCT) intensive and conventional treatment subjects with type 1 diabetes 13–14 years after DCCT closeout, during which time the two groups had achieved similar A1C levels.”</p>	<p>Patient flow</p> <p>Included (IG/CG): 603/583</p> <p>Analyzed (IG/CG): 505/448</p> <p>Follow-Up</p> <p>13-14 years after DCCT closeout</p>		<p><u>Confirmed clinical neuropathy* (% median follow-up: NR; EDIC years 13-14)</u> 25/35; NR; NR; p<0.001</p> <p><u>Abnormal NCS (% median follow-up: NR; EDIC years 13-14)</u> 54/ 69; NR; [NR; p<0.001</p> <p><u>Clinical neuropathy (% median follow-up: NR; EDIC years 13-14)</u> 55/68; NR; NR; p<0.001</p>	<p>Authors conclusion:</p> <p>“The benefits of former intensive insulin treatment persisted for 13–14 years after DCCT closeout and provide evidence of a durable effect of prior intensive treatment on neuropathy.”</p>
<p>Pop-Busui R. et al. Effects of Prior Intensive Insulin Therapy on Cardiac Autonomic Nervous System Function in Type 1 Diabetes Mellitus. Circulation. 2009;119, p.:2886-2893</p> <p>Objective</p> <p>“Using data obtained during the 13th or 14th year of EDIC follow-up, we evaluated CAN in EDIC participants and asked whether the former DCCT intensive treatment group</p>	<p>Patient flow</p> <p>Included: 1375</p> <p>Analyzed: 1211</p> <p>Follow-Up</p> <p>EDIC year 13/14</p>		<p><u>CAN* (cardiovascular autonomic neuropathy) (n. EDIC years 13-14)</u> 179/ 208; NR; NR; p= 0.018</p> <p>* defined by any one of the following conditions: R-R variation <15; R-R variation <20 in combination with Valsalva ratio ≤1.5 or postural hypotension</p>	<p>Authors conclusion:</p> <p>“Although CAN prevalence increased in both groups, the incidence was significantly lower in the former intensive group compared with the former conventional group. The benefits of former intensive therapy extend to measures of CAN up to 14 years after DCCT closeout.”</p>

Study / reference/ objective	Region/setting, inclusion criteria, exclusion criteria, baseline characteristics (IG/CG) of study population and patient flow (IG/CG)	Intervention group(s) (IG) / control group (CG)	Outcomes (IG/CG; relative effect measure (RR, OR) or MD; 95% CI and p; primary outcome marked)	Level of evidence / Critical appraisal and authors conclusion
continues to experience a lower prevalence and incidence of CAN compared with the former DCCT conventional treatment group despite no differences in levels of glycemic control after the close of the DCCT.”				
<p>Gubitosi-Klug R. et al. Effects of Prior Intensive Insulin Therapy and Risk Factors on Visual Quality-of-Life in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Cohort. JAMA Ophthalmol. 2016 February 1; 134(2). p.:137–145</p> <p>Objective “To assess the effect of prior intensive treatment and risk factors on visual quality of life (VQOL) in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study (DCCT/EDIC) cohort.”</p>	<p>Patient flow Included: 1375 Analyzed: 605/579</p> <p>Follow-up EDIC years 17-20</p>		<p>VQOL* (mean, NEI-VFQ, ,EDIC years 17-20) 92.5/ 90.9; MD= -1.0; [95% CI -1.7 – -0.3]; p=0.0058 Overall QOL** (mean, DQOL, EDIC years 17-20) 90.0/ 88.4; NR; NR; p=0.0052 *average of the 11 vision-related subscale scores **self-administered multiple-choice 46-item questionnaire assessing different aspects of QOL including satisfaction, impact, diabetes worry and social/vocational worry</p>	<p>Authors conclusion: “In the DCCT/EDIC cohort, VQOL remains high in both treatment groups. Intensive diabetes therapy modestly improved VQOL 30 years after the start of the DCCT. VA had the greatest impact on VQOL from among all risk factors.”</p>
<p>Subgroup men Wessels H. et al. Effect of intensive glycemic therapy on erectile function in men with type 1 diabetes in the diabetes control and complication trial/ epidemiology of diabetes interventions and complications study. Journal of Urology 2011, 185 (5) p.: 1828-1834.</p> <p>Objective “To determine whether intensive glycemic therapy reduces the risk of erectile dysfunction (ED) in men with type 1 diabetes enrolled in the Diabetes Control and Complications Trial (DCCT).”</p>	<p>Patient flow Included: 720 Analyzed: 571</p> <p>Follow-Up EDIC year 10</p>		<p>Prevalence of erectile dysfunction (%),EDIC years 10) 26.5/19.6; NR; NR; NR Confidence in erectile function low or very low (%), American Urological Association Symptom Index, EDIC years 10) 11.0/8.5; NR; NR; NR</p>	<p>Authors conclusion: “A period of intensive therapy significantly reduced the prevalence of ED ten years later among those in the secondary intervention cohort, but not the primary prevention cohort; higher HbA1c was significantly associated with risk in both cohorts. These findings provide further support for early implementation of intensive insulin therapy in young men with type 1 diabetes.”</p>
<p>Subgroup women Kim C. et al. Effect of Glycemic Treatment</p>	<p>Patient flow Included: 615</p>		<p>Surgical menopause*(%, mean follow-up: 28 years)</p>	<p>Authors conclusion: “In the DCCT/EDIC, intensive versus conventional</p>

Study / reference/ objective	Region/setting, inclusion criteria, exclusion criteria, baseline characteristics (IG/CG) of study population and patient flow (IG/CG)	Intervention group(s) (IG) / control group (CG)	Outcomes (IG/CG; relative effect measure (RR, OR) or MD; 95% CI and p; primary outcome marked)	Level of evidence / Critical appraisal and authors conclusion
<p>and Microvascular Complications on Menopause in Women With Type 1 Diabetes in the Diabetes Control and Complications Trial/ Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Cohort. Diabetes Care Volume 37, March 2014</p> <p>Objective</p> <p>"We examined the impact of intensive versus conventional diabetes treatment upon menopause among women with type 1 diabetes in the Diabetes Control and Complications Trial (DCCT), a randomized controlled trial of intensive diabetes treatment, and its observational follow-up, the Epidemiology of Diabetes Interventions and Complications (EDIC) study."</p>	<p>Analyzed: 564</p> <p>Follow-Up</p> <p>EDIC year 18 (average of 28 years of follow-up)</p>		<p>NR; RR= 0.84; [95% CI 0.58 – 1.21]; p= 0.34 *defined as cessation of menses if women had undergone bilateral oophorectomy and/or hysterectomy</p>	<p>treatment group and HbA1c level were not associated with menopause risk. Greater insulin dose was associated with lower menopause risk."</p>

+: low risk; -: high risk; ?: unclear risk; N.A.: not applicable, INT/IG: intervention group(s); CON/CG: control group; CI: confidence interval; NR: not reported; y: years; SD: standard deviation; NCS: nerve conduction study; MACE: Major adverse cardiovascular event, CVD: cardiovascular disease, ECG: echocardiogram GFR: glomerular filtration rate HR: Hazard ratio; RAAS: renin-angiotensin-aldosterone system, HR: hazard ratio VQOL: visual quality of life; NEI-VFQ: National Eye Institute Visual Function Questionnaire; MD: mean difference; QOL: quality of life; DQOL: Diabetes Quality of Life; GFR: glomerular filtration rate

10.8.3 Rechercheauftrag 3

Study type / reference/ objective	Region/setting, inclusion criteria, exclusion criteria, baseline characteristics (IG/CG) of study population and patient flow (IG/CG)	Intervention group(s) (IG) / control group (CG)	Outcomes (IG/CG; relative effect measure (RR, OR) or MD; [95% CI]; p; primary outcome marked)	Level of evidence / Critical appraisal and authors conclusion
<p>Study type</p> <p>Double-blinded randomized cross-over study</p> <p>Brock Jacobsen et al., Counter-regulatory hormone response to spontaneous hypoglycaemia during treatment with insulin Aspart or human soluble insulin: a double-blinded randomized cross-over study. Acta Physiologica 2011, 202, p: 337-347.</p>	<p>Region</p> <p>Denmark</p> <p>Inclusion criteria</p> <ul style="list-style-type: none"> -men and women with type 1 diabetes for at least 1 year -age 18-60 years -BMI 18-27,5 kg/m² <p>Exclusion criteria</p>	<p>IG:</p> <p>Drug:</p> <p>Insulin Aspart (B28ASP) plus Neutral Protamine Hagedorn (NPH) insulin twice daily</p> <p>Dosage:</p> <p>Usual (not further explained); adjustment following a predefined algorithm. Further adjustment for patients during condition of</p>	<p><u>HbA1c [%] (mean, 8 weeks)</u> 7.0 / 7.0; NR; NR; NA</p> <p><u>Hypoglycemic events (mean per patient per week, during hospitalization, 8 weeks)</u> 0.9 / 1.1; NR; NR; 0.34</p> <p><u>Unconsciousness due to hypoglycemia IG/ CG (n, during hospitalization)</u> 1/ 0; NR; NR; NR</p>	<p>Level of evidence</p> <p>DDG: 2a</p> <p>SIGN: 2+</p> <p>Risk of bias</p> <p>Generation of allocation sequence: ?</p> <p>Allocation concealment: ?</p>

Study type / reference/ objective	Region/setting, inclusion criteria, exclusion criteria, baseline characteristics (IG/CG) of study population and patient flow (IG/CG)	Intervention group(s) (IG) / control group (CG)	Outcomes (IG/CG; relative effect measure (RR, OR) or MD; [95% CI]; p; primary outcome marked)	Level of evidence / Critical appraisal and authors conclusion
<p>Objective "To compare insulin Aspart and human insulin with respect to glycaemic control, hypoglycaemic frequency and counter-regulatory responses to spontaneous hypoglycaemia."</p> <p>Baseline characteristics of study population (SD)</p> <p>Male n (%) 13 (81)</p> <p>Age [y] mean (SD) 44.4 (8.2)</p> <p>BMI [kg/m²] mean (SD) 24.6 (1.3)</p> <p>HbA1c [%] mean (SD) 7.8 (1.1)</p> <p>Diabetes duration [y] mean (SD) 19 (10)</p> <p>Patient flow Included: 16 Analyzed: 14 excluded from analysis (reasons) n=2 (because of personal reasons)</p>	<p>-pregnancy -impaired vision -impaired renal or hepatic function -cardiac diseases -uncontrolled hypertension -hypoglycaemic unawareness</p> <p>hyperglycemia. NPH dose was divided into 1/3 in the morning (07:00 hours) and 2/3 at bedtime (22:00 hours).</p> <p>Frequency: immediately injected before three mainly meals</p> <p>Mode of application: pen injector</p> <p>How long: 8 weeks then cross-over</p> <p>CG: Drug: Human soluble insulin (Actrapid) Neutral Protamine Hagedorn (NPH) insulin twice daily</p> <p>Dosage: Usual (not further explained); adjustment following a predefined algorithm. Further adjustment for patients during condition of hyperglycemia. NPH dose was divided into 1/3 in the morning (07:00 hours) and 2/3 at bedtime (22:00 hours).</p> <p>Frequency: immediately injected before three mainly meals</p> <p>Mode of application: pen injector</p> <p>How long: 8 weeks then cross-over</p>			<p>Blinding of participants and personal: + Blinding of outcome assessment: ? Incomplete outcome data: ? Selective reporting: + Other source of bias: -</p> <p>Authors conclusion: "Although insulin Aspart treatment was associated with clear postprandial insulin peaks, no improvement in glycaemic control was obtained and no difference in the hypoglycaemic frequency was observed. However, insulin Aspart elicited a slightly different physiological response to spontaneous hypoglycaemia compared with human insulin."</p>
<p>Study type Multicenter, randomized, cross-over study</p> <p>Renard et al., Non-Inferiority of Insulin Glargine Versus Insulin Detemir on Blood Glucose Variability in Type 1 Diabetes Patients: A Multicenter, Randomized, Crossover Study. Diabetic technology & therapeu-</p>	<p>Region France/ 25 diabetes care centers</p> <p>Inclusion criteria</p> <ul style="list-style-type: none"> - duration of diabetes of ≥ 3 years - HbA1c ≤ 8.5% at inclusion visit - intensive insulin therapy treatment for at least 6 months by using basal–bolus regimen 	<p>IG: Drug: Insulin Glargin as basal insulin plus insulin glargin as prandial insulin.</p> <p>Dosage: Titrated for each patient based on the following blood glucose targets:</p>	<p><u>Decrease in HbA1c (%), first period, 16 weeks)</u> 0.19/ 0.20; NR; NR; NR</p> <p><u>Decrease in HbA1c (%), second period, 32 weeks)</u> 0.10/ 0.14; NR; NR; NR</p> <p><u>Severe symptomatic hypoglycemia* (median</u></p>	<p>Level of evidence DDG:2a SIGN: 2+</p> <p>Risk of bias</p> <p>Generation of allocation sequence: ? Allocation concealment:</p>

Study type / reference/ objective	Region/setting, inclusion criteria, exclusion criteria, baseline characteristics (IG/CG) of study population and patient flow (IG/CG)	Intervention group(s) (IG) / control group (CG)	Outcomes (IG/CG; relative effect measure (RR, OR) or MD; [95% CI]; p; primary outcome marked)	Level of evidence / Critical appraisal and authors conclusion
<p>tics, Vol 12 (12) 2011, p: 1213-1218.</p> <p>Objective “This study compared the effects of insulin glargine and insulin detemir on blood glucose variability under clinical practice conditions in patients with type 1 diabetes (T1D) using glulisine as the mealtime insulin.”</p>	<p>with insulin glargin as basal (evening) insulin</p> <ul style="list-style-type: none"> - patients with a more than 50% of pre-dinner blood glucose (PDBG) level of $\leq 8.3 \text{ mmol/L}$ during the last 3 weeks of the initial period <p>Exclusion criteria NR</p> <p>Baseline characteristics of study population (IG/CG)</p> <p><u>Age [y] mean (SD)</u> 48.3 (13.6)/ 46.4 (14.1)</p> <p><u>Male sex [%]</u> 65.9/55.9</p> <p><u>BMI [kg/m^2] mean (SD)</u> 24.6 (3.5)/ 25.3 (3.5)</p> <p><u>Duration of diabetes [y] mean (SD)</u> 17.1 (8.4)/ 18.5 (10.1)</p> <p><u>HbA1c [%] mean (SD)</u> 7.06 (0.69)/ 7.16 (0.71)</p> <p><u>Fasting blood glucose [mg/dL] mean (SD)</u> 140 (68)/ 130 (59)</p> <p><u>Pre-dinner blood glucose [mg/dL] mean (SD)</u> 141 (67)/ 124 (48)</p> <p><u>Complication of diabetes %</u> Retinopathy 20.5/ 26.5 Neuropathy 22.7/ 11.8</p> <p><u>Duration of insulin glargin treatment (months) mean (SD)</u> 35.3 (16.8)/ 32.2 (10.4)</p> <p>Patient flow (IG/CG) Included:50/38 Analyzed: 44/34 (per-protocol) excluded from analysis (reasons) 5/3 (withdrawn)</p>	<p>1) fasting and before meals, $5.0 \text{ mmol/L} < \text{blood glucose} \leq 7.2 \text{ mmol/L}$</p> <p>2) 1–2 h after meal starting, blood glucose $< 9.9 \text{ mmol/L}$</p> <p>3) at bedtime (at least 2.5 h after the last meal), $6.1 \text{ mmol/L} < \text{blood glucose} \leq 8.3 \text{ mmol/L}$</p> <p>The adjustment of insulin doses was performed according to the following protocols.</p> <p><u>Frequency:</u> Once daily injection in the evening.</p> <p><u>Mode of application:</u> Injection</p> <p><u>How long:</u> 16 weeks</p> <p><u>CG:</u></p> <p><u>Drug:</u> Insulin Determir as basal insulin plus insulin glargin as prandial insulin.</p> <p><u>Dosage:</u> Titrated for each patient based on the following blood glucose targets:</p> <p>1) fasting and before meals, $5.0 \text{ mmol/L} < \text{blood glucose} \leq 7.2 \text{ mmol/L}$</p> <p>2) 1–2 h after meal starting, blood glucose $< 9.9 \text{ mmol/L}$</p> <p>3) at bedtime (at least 2.5 h after the last meal), $6.1 \text{ mmol/L} < \text{blood glucose} \leq 8.3 \text{ mmol/L}$</p> <p>The adjustment of insulin doses was performed according to the following protocols.</p> <p><u>Frequency:</u> Once daily injection in the evening. Patients who failed to reach the PDBG target with a single daily (evening) injection of insulin detemir were switched to two daily injections (by adding one prebreakfast injection).</p>	<p><u>monthly rate, NR</u> 10/ 4; NR; NR; N.A.</p> <p><u>Adverse events (%; 32 weeks)</u> 32.9/ 36.0; NR; NR; NR</p> <p><u>Serious adverse events (n. 32 weeks)</u> 4/ 4; NR; NR; NR</p> <p>*(defined as an episode in which the patient's condition requires the indispensable assistance of a third person and is associated with blood glucose of $< 1.98 \text{ mmol/L}$ or a quick recovery after ingestion of sugar or intravenous glucose or glucagon administration)</p>	<p>?</p> <p>Blinding of participants and personal: ?</p> <p>Blinding of outcome assessment: ?</p> <p>Incomplete outcome data: -</p> <p>Selective reporting: +</p> <p>Other source of bias: -</p> <p>Authors conclusion: “In T1D patients under clinical practice conditions, insulin glargin was non-inferior to insulin detemir regarding blood glucose variability, as assessed by CV of FBG.”</p>

Study type / reference/ objective	Region/setting, inclusion criteria, exclusion criteria, baseline characteristics (IG/CG) of study population and patient flow (IG/CG)	Intervention group(s) (IG) / control group (CG)	Outcomes (IG/CG; relative effect measure (RR, OR) or MD; [95% CI]; p; primary outcome marked)	Level of evidence / Critical appraisal and authors conclusion
	2/2 (dropped out) 2/1 (adverse event) 1/0 (protocol violation)	<u>Mode of application:</u> Injection <u>How long:</u> 16 weeks		
Study type Randomized, cross-over study Van Golen, L. et al., Effects of Insulin Detemir and NPH Insulin on Body Weight and Appetite-Regulating Brain Regions in Human Type 1 Diabetes: A Randomized Controlled Trial. <i>POLSone</i> 2014, Vol. 9 (4), e94483. Objective "The aim of this study was to investigate whether insulin detemir treatment differentially modifies brain activation in response to food stimuli as compared to NPH insulin"	Region The Netherlands Inclusion criteria - diabetes duration >1 year - HbA1c < 8.5% (69 mmol/mol) - age 18–60 years - BMI 18–35 kg/m ² Exclusion criteria - history of cardiovascular, renal and liver disease - severe head trauma - neurological or psychiatric disorders - endocrine diseases not well-controlled for the last three months - inability to undergo MRI scanning - substance abuse or the use of anticoagulants, oral steroids or any centrally acting agent - history of or current proliferative retinopathy - history of recurrent severe hypoglycemia (defined as an episode that requires external assistance to aid recovery) - medical history of hypoglycemia unawareness Baseline characteristics of study population <u>Male sex [%]:</u> 100 <u>Age [y] mean (SD):</u> 36.3 (9.4) <u>Body weight [kg] mean (SD):</u> 83.3 (13.9)	IG: <u>Drug:</u> Insulin detemir plus insulin aspart at mealtimes. Dosage: NR Frequency: In the evening <u>Mode of application:</u> Injected <u>How long:</u> 12 weeks CG: <u>Drug:</u> Insulin NPH plus insulin aspart at mealtimes. <u>Dosage:</u> NR <u>Frequency:</u> In the evening <u>Mode of application:</u> Injected <u>How long:</u> 12 weeks	<u>Mean change in HbA1c [mmol/mol] (%.12 weeks)</u> 0.0031/ 0.038; NR; NR; p= 0.8 <u>Perceived hypoglycemia (Diabetes Treatment Satisfaction Questionnaire, NR)</u> No difference between groups; NR; NR, p>0.05 <u>Perceived hyperglycemia (NR, NR)</u> No difference between groups; NR; NR, p>0.05	Level of evidence DDG: 1b SIGN: 1- Risk of bias Generation of allocation sequence: + Allocation concealment: + Blinding of participants and personal: - Blinding of outcome assessment: ? Incomplete outcome data: + Selective reporting: + Other source of bias: + Authors conclusion: "Our findings support the hypothesis that in type 1 diabetic patients, the weight sparing effect of insulin detemir may be mediated by its enhanced action on the central nervous system, resulting in blunted activation in bilateral insula, an appetite-regulating brain region, in response to food stimuli."

Study type / reference/ objective	Region/setting, inclusion criteria, exclusion criteria, baseline characteristics (IG/CB) of study population and patient flow (IG/CB)	Intervention group(s) (IG) / control group (CG)	Outcomes (IG/CG; relative effect measure (RR, OR) or MD; [95% CI]; p; primary outcome marked)	Level of evidence / Critical appraisal and authors conclusion
	<p><u>BMI [kg/m²] mean (SD):</u> 25.2 (3.3)</p> <p><u>HbA1c [%] mean (SD):</u> 7.4 (0.6)</p> <p><u>Diabetes duration [y] mean (SD):</u> 13.0 (8.6)</p> <p>Patient flow (IG/CB) Included 18/18 Analyzed 16/16</p> <p>excluded from analysis (reasons) IG/CG n 0/1 (dropped out) 2/1 (scans excluded)</p>			
<p>Study type prospective, randomized, open-label, blinded-endpoint crossover trial</p> <p>Pedersen-Bjergaard, U., P. L. Kristensen, et al. (2014) Effect of insulin analogues on risk of severe hypoglycaemia in patients with type 1 diabetes prone to recurrent severe hypoglycaemia (HypoAna trial): a prospective, randomised, open-label, blinded-endpoint crossover trial. <i>The lancet. Diabetes & endocrinology</i> 553-561</p> <p>Agesen et al., Effect of insulin analogues on frequency of non-severe hypoglycaemia in patients with type1 diabetes prone to severe hypoglycaemia: The HypoAntrial. <i>Diabetes and Metabolism</i>, 42, 2016; p:249-255.</p> <p>Objective “The HypoAna trial aimed to investigate whether short-acting insulin analogues—specifically insulin aspart and detemir—can reduce the rate of severe hypoglycaemia in comparison with human insulins in patients with type 1 diabetes who are at high risk of</p>	<p>Region Denmark/ outpatients clinics (6 Danish hospital and 1 diabetes centre)</p> <p>Inclusion criteria</p> <ul style="list-style-type: none"> - type 1 diabetes for > 5 years - ≥ 2 episodes of severe hypoglycaemia in the previous year (defined as need for third party assistance to restore blood glucose level) - age > 18 years - negative pregnancy test - following pen-based insulin regimen <p>Exclusion criteria</p> <ul style="list-style-type: none"> - known adrenal or growth hormone insufficiency - untreated hypothyroidism - unstable macrovascular disease - history of malignancy (unless a disease-free period exceeding 5 years) - history of alcohol or drug abuse - pregnancy or lactation - women of childbearing potential who are not using chemical or mechanical contracep- 	<p>IG: <u>Drug:</u> Insulin detemir and Insulin aspart</p> <p>Dosage: Generally four-dose or five-dose basal-bolus regimen.</p> <p>Frequency: Timing or number not specified</p> <p>Mode of application: Injected</p> <p>How long: 1 year</p> <p>CG: <u>Drug:</u> NPH insulin and human regular insulin</p> <p>Dosage: Generally four-dose or five-dose basal-bolus regimen.</p> <p>Frequency: Timing or number not specified</p> <p>Mode of application: Injected</p> <p>How long:</p>	<p>Severe hypoglycaemia, (episodes, during the two 9-month maintenance period) 105/ 136; ARR per patient year=0.51; [95 CI 0.19 – 0.84]; NR</p> <p>HbA1c (%), 24 months) NR; 0.13; [95% CI 0.02-0.24%]; p= 0.020</p> <p>Non-severe hypoglycaemia events (n, 24 month) 4530/ 4819; RRR=6%; [95% CI 2-10%]; p=0.0025</p> <p>Symptomatic hypoglycemia events (n, 24 month) 1666/ 1679; RRR=4%; [95% CI -3-10%]; NR</p> <p>Asymptomatic hypoglycemia events (n, 24 month) 1535/1531; RRR= -4%; [95% CI -11-4%]; NR</p>	<p>Level of evidence DDG: 1b SIGN:1-</p> <p>Risk of bias Generation of allocation sequence: + Allocation concealment: + Blinding of participants and personal: - Blinding of outcome assessment: + Incomplete outcome data: + Selective reporting: + Other source of bias: +</p> <p>Authors conclusion: “No clinically significant differences in hypoglycaemia occurrence were observed between the insulin regimens during the day. The time needed to treat one patient with insulin analogues to avoid one episode (TNT1) of non-severe nocturnal hypoglycaemia was approximately 3 months.”</p>

Study type / reference/ objective	Region/setting, inclusion criteria, exclusion criteria, baseline characteristics (IG/CG) of study population and patient flow (IG/CG)	Intervention group(s) (IG) / control group (CG)	Outcomes (IG/CG; relative effect measure (RR, OR) or MD; [95% CI]; p; primary outcome marked)	Level of evidence / Critical appraisal and authors conclusion
such episodes."	<p>tion</p> <p>Baseline characteristics of study population (total)</p> <p><u>Age [y] mean (SD)</u> 54.1 (13.0)</p> <p><u>Female sex n (%)</u> 44 (38.6)</p> <p><u>Body mass index [kg/m²] mean (SD)</u> 24.8 (3.8)</p> <p><u>Duration of diabetes[y] mean (SD)</u> 30.0 (12.9)</p> <p><u>Glycated haemoglobin [mmol/mol] mean (SD)</u> 64 (11)</p> <p><u>Glycated haemoglobin [%]mean (SD)</u> 8.0 (1.19)</p> <p>Patient flow</p> <p>Included: 149 Analyzed: 149</p>	1 year		
<p>Study type Randomized controlled trial</p> <p>Rosak et al., Insulin Glargine Maintains Equivalent Glycemic Control and Better Lipometabolic Control than NPH Insulin in Type 1 Diabetes Patients Who Missed a Meal, Hormone and Metabolic Research 40, 2008</p> <p>Objective "This study investigated the control of blood glucose (BG) and lipometabolism in patients with type 1 diabetes on basal – bolus regimens with insulin glargine or NPH insulin as the basal insulin, who missed breakfast and the accompanying morning bolus insulin injection."</p>	<p>Region Germany/ 4 study centres</p> <p>Inclusion criteria age ≥ 18 years</p> <ul style="list-style-type: none"> - type 1 diabetes, HbA 1c levels ≤ 11.5 % - BMI ≤ 35 kg/m² - on multiple daily injection basal – bolus insulin regimens, with regular human insulin or a short-acting insulin analogue plus a stable dose of NPH insulin for ≥ 4 weeks prior to study entry <p>Exclusion criteria</p> <ul style="list-style-type: none"> - previous treatment with insulin Glargine - patients with a history of hypersensitivity to the study medication or to excipients - treatment with any investigational drug within 30 days prior to study entry 	<p>IG: Drug: Prandial insulin (NR) plus insulin glargine.</p> <p>Dosage: NR</p> <p>Frequency: Bedtime doses: Blood glucose levels were determined at 22:00 on day 0 and on day 1 at 01:00, 03:00, and 05:00. If FBG levels (06:00 – 07:00) were in the target range (80 – 130 mg / dl [4.4 – 7.2 mmol / l]), patients missed their morning meal and the corresponding insulin injection. All subsequent insulin doses were withheld until 12:00, unless the patient's BG exceeded 220 mg / dl (12.2 mmol / l), in which case a bolus injection of insulin was given for the patient'</p>	<p><u>Hypoglycaemia or hyperglycaemia- related symptoms (%; n.a.)</u> 73.2/ 62.2; NR; NR; p>0.05</p> <p><u>Severe hypoglycaemia (n, follow-up: NR)</u> 1/ 0; NR; NR; NR</p>	<p>Level of evidence DDG: 1b SIGN: 1-</p> <p>Risk of bias Generation of allocation sequence: + Allocation concealment: + Blinding of participants and personal: - Blinding of outcome assessment: ? (not for patients SMBG) Incomplete outcome data: + Selective reporting: + Other source of bias: +</p> <p>Authors conclusion: "For patients who miss a morning meal, glargine is associated with maintained glycemic and lipometabolic control compared with NPH insulin."</p>

Study type / reference/ objective	Region/setting, inclusion criteria, exclusion criteria, baseline characteristics (IG/CB) of study population and patient flow (IG/CB)	Intervention group(s) (IG) / control group (CG)	Outcomes (IG/CG; relative effect measure (RR, OR) or MD; [95% CI]; p; primary outcome marked)	Level of evidence / Critical appraisal and authors conclusion
	<ul style="list-style-type: none"> - clinically relevant cardiovascular, hepatic, neurological, endocrine, or other major systemic disease - history of drug or alcohol abuse - a mental condition rendering the patient unable to understand the nature and possible consequences of the study - patients unlikely to comply with the protocol or to complete the study - women who were breast-feeding <p>Baseline characteristics of study population</p> <p><u>Age [y] mean (SD)</u> 41.6 (10.7)/ 43.3 (14.0)</p> <p><u>Sex: Male [%]</u> 60.7 / 53.1</p> <p><u>Body mass index [kg/m²] mean (SD)</u> 25.0 (3.4)/ 26.1 (4.2)</p> <p><u>Duration of diabetes [y] mean (SD)</u> 14.8 (11.8)/ 14.7 (9.8)</p> <p><u>Glycated haemoglobin [%] mean (SD)</u> 7.7 (1.2)/ 7.4 (1.4)</p> <p>Patient flow (IG/CG)</p> <p>Included 28/ 32 Analyzed 28/ 32</p>	<p>s welfare.</p> <p><u>Mode of application</u> injected</p> <p><u>How long:</u> 24 day observation</p> <p>CG:</p> <p><u>Drug:</u> Prandial insulin (NR) plus NPH insulin</p> <p><u>Dosage:</u> NR</p> <p><u>Frequency:</u> Bedtime doses: Blood glucose levels were determined at 22:00 on day 0 and on day 1 at 01:00, 03:00, and 05:00. If FBG levels (06:00 – 07:00) were in the target range (80 – 130 mg / dl [4.4 – 7.2 mmol / l]), patients missed their morning meal and the corresponding insulin injection. All subsequent insulin doses were withheld until 12:00, unless the patient's BG exceeded 220 mg / dl (12.2 mmol / l), in which case a bolus injection of insulin was given for the patient's welfare.</p> <p><u>Mode of application:</u> Injected</p> <p><u>How long:</u> 24 day observation</p>		
<p>Study type Randomized controlled trial</p> <p>Heller et al., Comparison of Insulin Detemir and Insulin Glargine in a Basal–Bolus Regimen, With Insulin Aspart as the Mealtime Insulin, in Patients with Type 1 Diabetes: A 52-Week, Multinational, Randomized, Open-Label, Parallel-Group, Treat-to-Target Noninferiority Trial, Clinical Therap-</p>	<p>Region multinational</p> <p>Inclusion criteria</p> <ul style="list-style-type: none"> - age ≥18 years - T1DM for at least 12 months - had been taking a basal– bolus insulin regimen for at least 3 months - HbA1c value ≤11.0% <p>Exclusion criteria</p>	<p>IG:</p> <p><u>Drug:</u> Basal insulin detemir plus meal time insulin aspart (based on the previous mealtime insulin dose or on local practice, and was adjusted to achieve a 90-minute postprandial PG target of ≤9.0 mmol/L (≤162 mg/dL))</p> <p><u>Dosage:</u> The mean of each patient's FPG measure-</p>	<p>HbA1c (%; 52 weeks) 7.57/ 7.56; MD= 0.01; [95% CI -0.13 – 0.16]; NR</p> <p><u>Hypoglycaemic episodes (mean, episodes/patient-year, 52 weeks)</u> 53.6/ 57.3; NR; NR; p>0.05</p> <p><u>Risk of hypoglycaemic episodes (n of events, 52 weeks)</u></p>	<p>Level of evidence DDG: 1b SIGN: 1- Risk of bias Generation of allocation sequence: ? Allocation concealment: + Blinding of participants and personal: ? Blinding of outcome assessment: ?</p>

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<p>peutics Vol.31 (10), 2009, p.2086-2095</p> <p>Objective “The primary study objective was to determine whether insulin detemir was noninferior to insulin glargine as the basal insulin in a basal–bolus regimen, with insulin aspart as the mealtime insulin, in terms of glycemic control at the end of 52 weeks in patients with type 1 diabetes mellitus (T1DM).”</p> <p>Baseline characteristics of study population (SD)</p> <p><u>Sex Male, %</u>: 55.9/ 56.3</p> <p><u>Age [y]/ mean (SD)</u>: 42 (13)/ 41 (12)</p> <p><u>Weight [kg] mean (SD)</u>: 79.6 (14.9)/ 78.9 (15.4)</p> <p><u>BMI [kg/m²] mean (SD)</u>: 26.5 (4.0)/ 26.3 (3.9)</p> <p><u>HbA1c [%] mean (SD)</u>: 8.1 (1.1)/ 8.1 (1.2)</p> <p><u>Diabetes duration [y] mean (SD)</u>: 17.2 (11.7)/ 17.3 (10.7)</p> <p>Patient flow (IG/CG) Included: 299/ 144 Analyzed: 299/ 144</p>	<ul style="list-style-type: none"> - proliferative retinopathy or maculopathy requiring acute treatment within 6 months before the study - any recurrent major hypoglycaemia - an anticipated change in any medication known to interfere with glucose metabolism - impaired hepatic or renal function - cardiac problems or uncontrolled hypertension <p>Baseline characteristics of study population (SD)</p> <p><u>Sex Male, %</u>: 55.9/ 56.3</p> <p><u>Age [y]/ mean (SD)</u>: 42 (13)/ 41 (12)</p> <p><u>Weight [kg] mean (SD)</u>: 79.6 (14.9)/ 78.9 (15.4)</p> <p><u>BMI [kg/m²] mean (SD)</u>: 26.5 (4.0)/ 26.3 (3.9)</p> <p><u>HbA1c [%] mean (SD)</u>: 8.1 (1.1)/ 8.1 (1.2)</p> <p><u>Diabetes duration [y] mean (SD)</u>: 17.2 (11.7)/ 17.3 (10.7)</p> <p>Patient flow (IG/CG) Included: 299/ 144 Analyzed: 299/ 144</p>	<p>ments and a predefined algorithm were used to individually titrate the basal insulin doses to achieve and maintain a PG target of ≤6.0 mmol/L (≤108 mg/dL) before breakfast and dinner, with no episodes of significant hypoglycemia. If patients in the detemir arm were achieving the PG target before breakfast but not before dinner, a second daily dose (initially 4 U) administered in the morning was added to the usual evening dose</p> <p>Frequency: Once daily in the evening. If the basal insulin used before the trial had been administered once daily, patients were transferred to an equivalent number of units of the study basal insulin. If the pretrial basal insulin had been administered more frequently, the total daily basal insulin dose was reduced by 30% and given once daily, followed by dose titration.</p> <p>Mode of application: Injected</p> <p>How long: 52 weeks</p> <p>CG:</p> <p>Drug: Basal insulin glargine plus meal time insulin aspart (based on the previous mealtime insulin dose or on local practice, and was adjusted to achieve a 90-minute postprandial PG target of ≤9.0 mmol/L (≤162 mg/dL))</p> <p>Dosage: The mean of each patient's FPG measurements and a predefined algorithm were used to individually titrate the basal insulin doses to achieve and maintain a PG target of ≤6.0 mmol/L (≤108 mg/dL) before breakfast and</p>	<p>14895/ 7501; RR= 0.94; [95% CI 0.74 - 1.18]; NR</p> <p><u>Adverse events (total, 52 weeks)</u>: 1508/ 550; NR; NR; NR</p> <p><u>Serious adverse events (total, 52 weeks)</u>: 35/ 9; NR; NR; NR</p>	<p>Incomplete outcome data: +</p> <p>Selective reporting: +</p> <p>Other source of bias: +</p> <p>Authors conclusion: “During 52 weeks of basal–bolus therapy in patients with T1DM, detemir was noninferior to glargine in terms of overall glycemic control (HbA1c). When used according to the approved labeling, detemir and glargine did not differ in tolerability or in terms of the occurrence of hypoglycemia.”</p>

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		<p>dinner, with no episodes of significant hypoglycemia. In the glargin arm, the dose was administered once daily regardless of the predinner PG measurement, in accordance with its US Food and Drug Administration (FDA)-approved labeling.</p> <p><u>Frequency:</u> Once daily in the evening. If the basal insulin used before the trial had been administered once daily, patients were transferred to an equivalent number of units of the study basal insulin. If the pretrial basal insulin had been administered more frequently, the total daily basal insulin dose was reduced by 30% and given once daily, followed by dose titration.</p> <p><u>Mode of application:</u> Injected</p> <p><u>How long:</u> 52 weeks</p>		
<p>Study type Randomized, parallel-group, open-label, non-inferiority, trial Brunetti P. et al., Incidence of severe nocturnal hypoglycemia in patients with type 1 diabetes treated with insulin lispro or regular human insulin in addition to basal insulin glargin. Nutrition, Metabolism & Cardiovascular Diseases (2010) 20, p.: 519e – 526</p> <p>Objective: The aim of the present study was to further investigate the pairing of insulin glargin with either RHI or lispro in T1DM.</p>	<p>Region Italy/ multicentre (n=47)</p> <p>Inclusion criteria</p> <ul style="list-style-type: none"> - age 18 - 60 years - T1DM > 3 years - multiple daily injections of insulin as basal-bolus regimen with NPH or glargin as the basal insulin - HbA1c value ≤ 9% - fasting C-peptide ≤ 0.1 nmol/l - FBG > 6.9 mmol/l - BMI < 30 kg/m² - ability to perform SMBG - adequate contraception - negative pregnancy test <p>Exclusion criteria</p> <ul style="list-style-type: none"> - total insulin dosage ≥ 1 U/kg/day 	<p>IG: Drug: RHI plus insulin glargin at dinner time was given (titrated to target BG throughout the study). Dose was adjusted to standard algorithms.</p> <p>Dosage: NR</p> <p>Frequency: At each meal time</p> <p>Mode of application: NR</p> <p>How long: 16 weeks</p> <p>CG: Drug: Insulin Lispro plus insulin glargin at dinner</p>	<p>Episodes of severe nocturnal hypoglycaemia (episodes/ patient/ month, 16 weeks) 0.021/ 0.022; NR; NR; p=0.742</p> <p>Episodes of hypoglycaemia (episodes/ patient/ month, 16 weeks) 2.46/ 2.94; NR; NR; p=0.049</p> <p>HbA1c levels (mean: end of study) 7.10/ 6.95; NR; NR; p>0.05</p> <p>Quality of life (mean: Well-being Enquiry for Diabetics* (WED- score); end of study) 2.09/ 2.09; NR; NR; p> 0.05</p> <p>Adverse events (n) 56/ 59; NR; NR; NR</p> <p>*Higher WED scores indicate a better QoL</p>	<p>Level of evidence DDG: 1b SIGN: 1-</p> <p>Risk of bias Generation of allocation sequence: + Allocation concealment: - Blinding of participants and personal: ? Blinding of outcome assessment: ? Incomplete outcome data: + Selective reporting: + Other source of bias: -</p> <p>Authors conclusion: “At the end of the study, both treatments did not differ with respect to glycemic control, as measured by hemoglobin A1c and FBG.”</p>

Study type / reference/ objective	Region/setting, inclusion criteria, exclusion criteria, baseline characteristics (IG/CG) of study population and patient flow (IG/CG)	Intervention group(s) (IG) / control group (CG)	Outcomes (IG/CG; relative effect measure (RR, OR) or MD; [95% CI]; p; primary outcome marked)	Level of evidence / Critical appraisal and authors conclusion
	<ul style="list-style-type: none"> - Serum creatinine >1.5mg/dl - history of renal transplantation or current renal dialysis - congestive heart failure - hypoglycaemia unawareness - concomitant use of β-blockers, thiazides or corticosteroids - <1 episode of severe hypoglycaemia with seizure and coma during past year <p>Baseline characteristics of study population (SD)</p> <p>Sex Male, % 57.9/ 64.8</p> <p>Age [y]/ mean (SD): 35.2 (10.5)/ 35.3 (9.9)</p> <p>Weight [kg] mean (SD): 69.1 (10.8)/ 70.0 (11.1)</p> <p>BMI [kg/m²] mean (SD): 23.8 (2.5)/ 23.7 (2.6)</p> <p>HbA1c [%] mean (SD): 7.39 (0.88)/ 7.39(0.97)</p> <p>Diabetes duration [y] mean (SD): 13.0 (8.8)/ 14.5 (9.4)</p> <p>Patient flow (IG/CG)</p> <p>Included: 202/ 193</p> <p>Analyzed: 202/ 193</p> <p>Follow-Up 2 weeks</p>	<p>time was given (titrated to target BG throughout the study). Dose was adjusted to standard algorithms.</p> <p><u>Dosage:</u> NR</p> <p><u>Frequency:</u> At each meal time</p> <p><u>Mode of application:</u> NR</p> <p><u>How long:</u> 16 weeks</p>		

IG: intervention group; CG: control group; +: low risk; -: high risk; ?: unclear risk; NA: not applicable; CI: confidence interval; NR: not reported; SD: standard deviation ; FBG: fasting blood glucose; RHI: regular human insulin; WED: Well-being Enquiry for Diabetics ;QoL: Quality of Life; T1DM: type 1 diabetes mellitus; BMI: body- mass index; SMBG: self-monitoring of blood glucose; y: years; BG: blood glucose; NPH: neutral protamine Hagedorn

10.8.4 Rechercheauftrag 4

Reference/ Objective	Region/setting, inclusion criteria, exclusion criteria (patients characteristics marked bold) and baseline characteristics of study population	Index test(s), reference standard and patient flow	Diagnostic accuracy (effect size; CI or p)	Study type, level of evidence, risk of bias and authors conclusion
Chillaron J., et al. Estimated glucose disposal rate in assessment of the metabolic syndrome and microvascular complications in patients with Type 1 Diabetes. Journal of clinical endocrinology and metabolism, 2009, 94 (99 p.): 3530-3534. Objective: Thus, the aim of the present study was to quantify insulin resistance in patients with type 1 diabetes by eGDR determination according to the presence or absence of the metabolic syndrome and its relationship with the prevalence of chronic complications, both macro- and microvascular.	<p>Region/setting Spain/ Outpatient endocrinology clinic</p> <p>Inclusion criteria Patients with type 1 immune-mediated diabetes: Diagnostic criteria for type 1 immune-mediated diabetes included past or present positive glutamic acid decarboxylase 65 or tyrosine-nephrophatase-like protein IA2 antibodies and plasma free C-peptide levels lower than 1.1 ng/ml after 6 min of 1 mg glucagon administration.</p> <p>Exclusion criteria - non-Caucasian patients - variation in HbA1c levels greater than 1% in three separate determinations at 2-month intervals - pregnancy - excessive alcohol consumption - presence of end-stage renal disease such - patients undergoing dialysis or who had received a kidney transplant</p> <p>Patient characteristics</p> <p><u>Male/ Female, n</u> 53/ 38</p> <p><u>Age [y] mean (SD)</u> 39.7 (13.2)</p> <p><u>Waist circumference [cm] mean (SD)</u> Men: 92.1 (11.5) Women: 85.5 (11.6)</p> <p><u>BMI [kg/m²] mean (SD)</u> Men: 25.5 (3.1) Women: 25.4 (4.2)</p> <p><u>eGDR [mg/kg⁻¹ * min⁻¹] mean (SD)</u> 8.9 (2.3)</p> <p><u>HbA1c [%] mean (SD)</u> 7.3 (1.4)</p> <p><u>Diabetes duration [y] mean (SD)</u> 16.7 (12.9)</p> <p><u>Insulin dose [IU/kg⁻¹*d⁻¹] mean (SD)</u></p>	<p>Index test(s) Insulin resistance was calculated using the eGDR according to the following equation: $24.31 - (12.22 \times \text{waist to hip ratio}) - (3.29 \times \text{hypertension}) - (0.57 \times \text{HbA1C})$, where the units are milligrams per kilogram⁻¹ per minute⁻¹ and hypertension status was 140/90 mm Hg (or on medications). It should be emphasized that lower eGDR levels indicate greater insulin resistance.</p> <p>Reference standard The metabolic syndrome was defined as a score of 3 or greater according to the modified National Cholesterol Education Program Adult Treatment Panel III by the American Heart Association/ National Heart, Lung, and Blood Institute scientific statement. Because all participants fulfilled the criteria for hyperglycemia, at least two of remaining four criteria were required.</p> <p>Time interval between index and reference test NR</p> <p>Included patients 109</p> <p>Analysed patients 91</p> <p>Attrition 18</p> <p>Excluded from analysis (reason) Did not complete study protocol.</p>	<p>Sensitivity for metabolic syndrome diagnosis <u>eGDR level below 8.77 mg/kg⁻¹ * min⁻¹</u> 100%</p> <p>Specificity 85.2%</p> <p>Positive predictive value NR</p>	<p>Study type Cross-sectional study</p> <p>Level of evidence DDG: 3</p> <p>Risk of bias Selection of patients: - Conduct/interpretation of index test: ? Conduct/interpretation of reference test: ? Patient flow: -</p> <p>Authors conclusion: "Insulin resistance is common in type 1 diabetes patients and is associated with microvascular complications. eGDR, as an insulin resistance marker, provides more useful information than other classical variables such as insulin requirements."</p>

Reference/ Objective	Region/setting, inclusion criteria, exclusion criteria (patients characteristics marked bold) and baseline characteristics of study population	Index test(s), reference standard and patient flow	Diagnostic accuracy (effect size; CI or p)	Study type, level of evidence, risk of bias and authors conclusion
	0.71 (0.3) Prior testing NR			

+ low risk of bias; - high risk of bias, ? unclear risk of bias, CG: control group; CI: confidence interval; IG: intervention groups; NR: not reported

10.8.5 Rechercheauftrag 5

Study / reference/ objective	Region/setting, inclusion criteria, exclusion criteria, baseline characteristics (IG/CB) of study population and patient flow (IG/CB)	Intervention group(s) (IG) / control group (CG)	Outcomes (IG/CB; relative effect measure (RR, OR) or MD; 95% CI and p; primary outcome marked)	Level of evidence / Critical appraisal and authors conclusion
Study type: RCT multicenter 2 x 2 factorial randomized controlled trial Little, S.A., et al., Recovery of hypoglycemia awareness in long-standing type 1 diabetes: a multicenter 2 x 2 factorial randomized controlled trial comparing insulin pump with multiple daily injections and continuous with conventional glucose self-monitoring (Hypo-COMPass). Diabetes Care, 2014. 37 (8), p.: 2114-22. Objective: "To determine whether impaired awareness of hypoglycemia (IAH) can be improved and severe hypoglycemia (SH) prevented in type 1 diabetes, we compared an insulin pump (continuous subcutaneous insulin infusion [CSII]) with multiple daily injections (MDIs) and adjuvant real-time continuous glucose monitoring (RT) with conventional self-monitoring of blood glucose (SMBG)."	Region/ setting UK/ 5 UK tertiary-referral diabetes centers Inclusion criteria - aged between 18 – 74 years - serum C-peptide below the quality assured limit of detection for the assay and laboratory (<50 pmol/L) with simultaneous exclusion of BH (glucose <4.0 mmol/l) by laboratory plasma glucose assay - impaired awareness of hypoglycaemia, as confirmed by a Gold score ≥4 Exclusion criteria - any condition that in the investigator's judgement is likely to cause the participant to be unable to understand the information in the Informed Consent Document or to provide informed consent Baseline characteristics of study population (IG/CB) <u>Age [y] mean (SD):</u> 50.1 (12.6) / 47.1 (11.8) <u>Male sex (%):</u> 48.38 / 47.62 <u>Duration of diabetes [y] mean (SD)(years):</u>	<u>Real time—continuous glucose monitoring group:</u> Real time monitoring, using the CE-marked REAL time continuous glucose monitor (Medtronic). Group was trained on sensor insertion, calibration and use of monitor included trend analysis and hypo- hyperglycemic alerts. Participants will be encouraged to wear the sensor continuously but flexibly with a minimum of 7 days continuous monitoring in the last week of each month and will be advised to re-site the sensor every 7 days. <u>Self Monitoring of Blood Glucose (SMBG):</u> All participants will be required to undertake daily 4-point and weekly 8-point self-monitored capillary glucose profiles. All participants will use the Contour linkW, Bayer Healthcare meter and will undertake this whether or not concurrent RT-CGM is being used.	<u>Severe hypoglycemia [annualized rate events/ patient-year, 24 weeks]</u> 0.8 / 0.9; NR; NR; p=0.95 <u>Hospitalizations due to severe hypoglycemia (rate, 24 weeks)</u> 0/0; NR; NR; NR <u>Fear of hypoglycemia (mean, HFS II-total, 24 weeks)</u> 45/45; NR; NR; p=0.96 <u>Diabetic ketoacidosis requiring hospitalization (n, 24 weeks)</u> 0/3; NR; NR; NR	Level of evidence DDG: 2a SIGN: 2+ Risk of bias Generation of allocation sequence: + Allocation concealment: + Blinding of participants and personal: - Blinding of outcome assessment: - Incomplete outcome data: - Selective reporting: Other source of bias: + Authors conclusion: "Hypoglycemia awareness can be improved and recurrent SH prevented in longstanding type 1 diabetes without relaxing HbA1c. Similar biomedical outcomes can be attained with conventional MDI and SMBG regimens compared with CSII/RT, although satisfaction was higher with CSII."

Study / reference/ objective	Region/setting, inclusion criteria, exclusion criteria, baseline characteristics (IG/C/G) of study population and patient flow (IG/C/G)	Intervention group(s) (IG) / control group (CG)	Outcomes (IG/CG; relative effect measure (RR, OR) or MD; 95% CI and p; primary outcome marked)	Level of evidence / Critical appraisal and authors conclusion
	<p>31.0 (12.2 / 26.7 (12.1) <u>Body mass index [kg/ m²] mean (SD):</u> 26.9 (4.7) / 26.1 (4.3) <u>HbA1c (%) (SD):</u> 8.2 (1.1) / 8.3 (1.3) <u>HbA1c [mmol/mol] mean (SD):</u> 66 (11) / 67 (13) <u>Insulin dose [units/kg/24h]:</u> 0.68 (0.27) / 0.61 (0.19) <u>Current smokers n (N):</u> 10 (21) / 11 (23) <u>Ex – smokers n (N):</u> 12 (26) / 14 (30) <u>Never smoked n (N):</u> 25 (53) / 22 (47) <u>Alcohol consumers n (N):</u> 27 (56) /35 (75) <u>Lipohypertrophy n (N):</u> 17 (38) / 18 (38) <u>Retinopathy n (N):</u> 32 (67) / 29 (62) <u>Laser photocoagulation n (N):</u> 14 (29) / 10 (21) <u>Microalbuminuria n (N):</u> 12 (26) / 10 (22) <u>Creatinine [mmol/L] (SD):</u> 76.5 (21.6) / 72.3 (19.3) <u>Peripheral neuropathy n (N):</u> 10 (21) / 8 (17) <u>Atherosclerotic disease n (N):</u> 5 (10) / 8 (17) <u>Treated thyroid disease n (N):</u> 11 (23) / 17 (35) <u>Postural hypotension n (N):</u> 13 (28) / 13 (27) <u>Mean study visits / person:</u> 6.8 / 6.5</p>			

Study / reference/ objective	Region/setting, inclusion criteria, exclusion criteria, baseline characteristics (IG/CG) of study population and patient flow (IG/CG)	Intervention group(s) (IG) / control group (CG)	Outcomes (IG/CG; relative effect measure (RR, OR) or MD; 95% CI and p; primary outcome marked)	Level of evidence / Critical appraisal and authors conclusion
	<p>Patient flow (IG/CG) Randomized: 48/ 48 Analyzed: 48/48 Follow-Up 18 month</p>			
<p>Study type: cross-over RCT Langeland, L., et. al. Short – term continuos glucose monitoring: effects on glucose and treatment satisfaction in patients with type 1 diabetes mellitus; a randomized controlled trial, The International Journal of Clinical Practice, 2012, 66 (8), p.: 741-747.</p> <p>Objective: “To assess whether 4 week's use of a continuos glucose monitoring (CGM) system improves glucose control, treatment satisfaction or health status; as compared to intensified conventional finger-prick measurements (ICFM) in patients with type 1 diabetes mellitus (DM1).”</p>	<p>Region/ setting Norway/one center study</p> <p>Inclusion criteria</p> <ul style="list-style-type: none"> - HbA1c levels \geq 7% and \leq10% At least one of the following: <ul style="list-style-type: none"> - hypoglycaemic episodes (blood glucose < 3.0 mmol/l, verified by finger-prick measurement) at least once a week - a history of at least one episode with serious hypoglycaemia, defined as need of help from others, during the last 6 months <p>Exclusion criteria</p> <ul style="list-style-type: none"> - patients with untreated hypothyroidism - adrenal gland failure - celiac disease - renal failure - unstable coronary heart disease - serious psychiatric disorder or mental retardation <p>Baseline characteristics of study population (IG/CG)</p> <p><u>Age [y] mean (SD):</u> 34 (9) / 34 (9)</p> <p><u>Weight [kg] (SD):</u> 78 (14) / 84 (15)</p> <p><u>Height [cm] (SD):</u> 169 (8) / 176 (8)</p> <p><u>BMI [kg/m²] (SD):</u> 27.3 (4.6) / 27.3 (5.0)</p> <p><u>Male Sex [%]:</u> 26.7 / 53.3</p>	<p><u>Continuous glucose monitoring (CGM) group:</u> During the intervention period, the patients used the continuous glucose monitor, Guardian REAL-Time device (Medtronic MiniMed) for 4 weeks. All patients were educated in the basic use of the monitor by a specialist diabetes nurse and the principal investigator. Blood glucose values were monitored eight times during the day for four days, and participants were called by the diabetes specialist nurse within the first week to discuss insulin dosage, episodes of hypoglycaemia and other possible problems.</p> <p><u>Intensified conventional finger-prick measurement (ICFM) group:</u> During the ICFM period patients performed intensified conventional finger-prick measurements at least 4 times a day. They were instructed to record these values, as well as episodes of hypoglycaemia, adverse events, and changes in medication. Blood glucose values were monitored eight times during the day for four days, and participants were called by the diabetes specialist nurse within the first week to discuss insulin dosage, episodes of hypoglycaemia and other possible problems.</p>	<p>HbA1c (mean %, 8 weeks) 7.6 / 7.5; NR; NR; p=0.50</p> <p>Hypoglycaemic episodes (mean, mmol/l, 4 weeks) 8.2 / 7.3; NR; NR; p=0.67</p> <p>Quality of health (mean change from baseline, SF-36 - total average) -0.3 / -0.3; NR; NR; p=0.35</p>	<p>Level of evidence DDG: 2b SIGN: 2+</p> <p>Risk of bias Generation of allocation sequence: - Allocation concealment: ? Blinding of participants and personal: - Blinding of outcome assessment: ? Incomplete outcome data: + Selective reporting: + Other source of bias: - (analysis not accounted for correlation)</p> <p>Authors conclusion: “In conclusion the present study found no distinct benefit of short-term continuos glucose monitoring compared to intensified conventional finger-prick measurements on glucose control. It does neither show that CGM increases treatment satisfaction, health status or reduce hypoglycaemic episodes. However, these results are based on evaluation of a limited number of patients.”</p>

Study / reference/ objective	Region/setting, inclusion criteria, exclusion criteria, baseline characteristics (IG/CG) of study population and patient flow (IG/CG)	Intervention group(s) (IG) / control group (CG)	Outcomes (IG/CG; relative effect measure (RR, OR) or MD; 95% CI and p; primary outcome marked)	Level of evidence / Critical appraisal and authors conclusion
	<u>Duration of diabetes [y] (SD)</u> 18 (7) / 19 (9) <u>HbA1c [%] (SD)</u> : 8.1 (1.0) / 7.6 (0.9) <u>Systolic blood pressure [mmHg] (SD)</u> : 116 (14) / 125 (15) <u>Diastolic blood pressure [mmHg] (SD)</u> : 70 (8) / 78 (13) Follow-Up 8 weeks after each intervention period Patient flow (IG/CG) Included: 15/ 15 Analyzed: 27 excluded from analysis (reasons) n=3 (withdrew)			
Study type: cross over RCT Battelino, T., et al., The use and efficacy of continuous glucose monitoring in type 1 diabetes treated with insulin pump therapy: a randomised controlled trial. Diabetologia (2012) 55: p.: 3155-3162. Objective: “The aim of this multicentre, randomised, controlled crossover study was to determine the efficacy of adding continuous glucose monitoring (CGM) to insulin pump therapy (CSII) in type 1 diabetes.”	Region/ setting Slovenia, Spain, Denmark, Austria/ multicenter, randomised controlled crossover study Inclusion criteria - age between 19-70 years (adult group) - type 1 diabetes > 1 year - HbA1c level between 7.5% and 9.5% - eligible participants had been using CSII with rapid-acting insulin analogues > 6 months - were naive to CGM - had successfully completed a five question multiple choice test concerning pump therapy and general understanding of diabetes Exclusion criteria - ≥3 incidents of severe hypoglycaemia in the last 12 months - a history of hypoglycaemia unawareness - concomitant chronic disease known to affect diabetes control - any pharmacological treatment that might modify glycaemic values	Participants used a glucometer (Bayer Ascensia Contour; Bayer Diabetes Care) and an insulin pump system (Mini-Med Paradigm REAL-Time System) able to integrate CGM in the study phase. All participants received structured training on diabetes management and device use and had their knowledge assessed, as previously described IG: Sensor On/Sensor Off (On/Off) treatment sequence CG: Sensor Off/Sensor On (Off/On) treatment sequence	<u>HbA1c (mean, mmol/l, 6 months)</u> NR; NR; -4.4; [95% CI -3.1 – -5.8]; p<0.001	Level of evidence DDG: 2b SIGN: 2+ Risk of bias Generation of allocation sequence: ? Allocation concealment: ? Blinding of participants and personal: + Blinding of outcome assessment: ? Incomplete outcome data: + Selective reporting: + Other source of bias: + Authors conclusion: “Continuous glucose monitoring was associated with decreased HbA1c levels and time spent in hypoglycaemia in individuals with type 1 diabetes using CSII. More frequent self-adjustments of insulin therapy may have contributed to these effects.”

Study / reference/ objective	Region/setting, inclusion criteria, exclusion criteria, baseline characteristics (IG/CB) of study population and patient flow (IG/CB)	Intervention group(s) (IG) / control group (CG)	Outcomes (IG/CG; relative effect measure (RR, OR) or MD; 95% CI and p; primary outcome marked)	Level of evidence / Critical appraisal and authors conclusion
	<p>Baseline characteristics of study population</p> <p><u>Age [y] mean (SD):</u> 42 (10) / 42 (11)</p> <p><u>Male Sex, n [%]:</u> 18 (45) / 20 (49)</p> <p><u>Mean weight [kg]:</u> 77 (15) / 79 (13)</p> <p><u>Mean height [cm]:</u> 174 (10) / 174 (8.8)</p> <p><u>BMI [kg/m²] (SD):</u> 25 (3.3) / 26 (3.2)</p> <p><u>HbA1c [%] (SD):</u> 8.1 (0.5) / 8.4 (0.6)</p> <p><u>HbA1c [mmol/mol] (SD):</u> 65.0 (5.5) / 68.3 (6.5)</p> <p><u>Time since diagnosis of diabetes [y] (SD):</u> 24 (11) / 21 (8.9)</p> <p><u>Time since start of CSII[y] (SD):</u> 6.3 (5.3) / 6.4 (4.8)</p> <p>Patient flow (IG/CB)</p> <p>Included: 40/41</p> <p>Analyzed: NR</p> <p>Follow-Up</p> <p>4 month</p>			
<p>Study type: RCT</p> <p>Battelino, T. et. al., Effect of Continuous Glucose Monitoring on Hypoglycemia in Type 1 Diabetes Diabetes care, 2011, Vol 24, p.: 795-800.</p> <p>Objective: "To assess the impact of continuous glucose monitoring on hypoglycemia in people with type 1 diabetes."</p>	<p>Region/ setting</p> <p>Sweden, Slovenia, Israel / randomized, controlled, multicenter study</p> <p>Inclusion criteria</p> <ul style="list-style-type: none"> - patients aged between 10 and 65 years(adult group: 18-65 years) - type 1 diabetes diagnosed for > 1 year - reasonable metabolic control assessing carbohydrate intake and self-adjusting insulin - an HbA1c level < 7.5% - using intensive insulin treatment with either 	<p>Intervention group:</p> <p>Real-time continuous glucose monitoring, wearing individual sensors for 5 days continuously for 26 weeks (continuous monitoring group)</p> <p>Control group:</p> <p>Home monitoring with a FreeStyle blood glucose meter and a masked continuous glucose monitor to be worn for 5 days every second week</p>	<p>Time spent in hypoglycemia < 63 mg/dL (mean, h/day, 26 weeks)</p> <p>0.59/ 1.27; RM*=54%; NR; NR</p> <p>HbA1c (mean, 6 months)</p> <p>6.51/ 6.83; MD= 0.31; NR; NR</p>	<p>Level of evidence</p> <p>DDG: 2b</p> <p>SIGN: 2+</p> <p>Risk of bias</p> <p>Generation of allocation sequence: +</p> <p>Allocation concealment: +</p> <p>Blinding of participants and personal: -</p> <p>Blinding of outcome assessment: ?</p> <p>Incomplete outcome data: ?</p> <p>Selective reporting: +</p> <p>Other source of bias: +</p>

Study / reference/ objective	Region/setting, inclusion criteria, exclusion criteria, baseline characteristics (IG/CG) of study population and patient flow (IG/CG)	Intervention group(s) (IG) / control group (CG)	Outcomes (IG/CG; relative effect measure (RR, OR) or MD; 95% CI and p; primary outcome marked)	Level of evidence / Critical appraisal and authors conclusion
	<p>an insulin pump or multiple daily injections and not using a real-time continuous glucose monitoring device for at least 4 weeks</p> <p>Exclusion criteria</p> <p>N.R.</p> <p>Baseline characteristics of study population</p> <p><u>Female sex, n [%]:</u> 26 (42) / 19 (33)</p> <p><u>Age [y] (SD):</u> 25.7 (14.1) / 26.0 (14.6)</p> <p><u>Pediatric, n [%]:</u> 27 (44) / 26 (45)</p> <p><u>BMI [kg/m²] (SD):</u> 22.4 (3.8) / 22.0 (3.8)</p> <p><u>Duration of diabetes [y] (SD):</u> 11.6 (11.3) / 11.4 (11.4)</p> <p><u>Insulin administration, pump, n [%]:</u> 47 (76) / 34 (59)</p> <p><u>Insulin administration, MDI, n [%]:</u> 15 (24) / 24 (41)</p> <p><u>Glycated hemoglobin at screening [%]:</u> 6.83 (0.44) / 6.90 (0.47)</p> <p><u>Glycated hemoglobin at baseline [%]:</u> 6.92 (0.56) / 6.91 (0.67)</p> <p><u>Record of severe hypoglycemia in last year, number [%] (N):</u> 5 (8) / 7 (12)</p> <p><u>Diagnosed with hypoglycemia unawareness, number [%] (N):</u> 6 (10) / 4 (7)</p> <p><u>Daily insulin dose [units/kg] (SD):</u> 0.66 (0.25) / 0.67 (0.32)</p> <p><u>Education, number [%], completed further education:</u> 27 (44) / 29 (50)</p> <p><u>Prior use of continuous glucose monitor,</u></p>			<p>Authors conclusion:</p> <p>“Continuous glucose monitoring was associated with reduced time spent in hypoglycemia and a concomitant decrease in HbA1c in children and adults with type 1 diabetes.”</p>

Study / reference/ objective	Region/setting, inclusion criteria, exclusion criteria, baseline characteristics (IG/CG) of study population and patient flow (IG/CG)	Intervention group(s) (IG) / control group (CG)	Outcomes (IG/CG; relative effect measure (RR, OR) or MD; 95% CI and p; primary outcome marked)	Level of evidence / Critical appraisal and authors conclusion
	<p><u>number [%]:</u> 21 (34) / 18 (31)</p> <p><u>Mean blood glucose in 1-month-run-in period [mg/dL] (SD):</u> 147 (23) / 148 (28)</p> <p>Patient flow (IG/CG)</p> <p>Included: 62/ 58</p> <p>Analyzed: 62/ 58</p> <p>Follow-Up</p> <p>NR</p>			
<p>Study type: cross-over RCT</p> <p>Tumminia A. et al., Efficacy of real-time continuous glucose monitoring on glycaemic control and glucose variability in type 1 diabetic patients treated with either insulin pumps or multiple insulin injection therapy: a randomized controlled crossover trial; Diabetes/Metabolism Research and Reviews 2015;31:61-68</p> <p>Objective: "This study aims to determine the efficacy of real-time continuous glucose monitoring in T1D patients treated with insulin pump therapy or multiple daily insulin therapy."</p>	<p>Region/ setting: Italy/ Diabetes Center at the Garibaldi-Nesima Hospital, Catania</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> - age: 18-60 years - similar school education - middle class socio-economic status - diabetes duration > 1 year - HbA_{1c} level > 8.0% (64 mmol/mol) <p>Exclusion criteria:</p> <ul style="list-style-type: none"> - pregnant women and women planning pregnancy - patients with concomitant chronic illness - patients will poor compliance to diet - patients with insulin therapy - patients with glucose monitoring <p>Baseline characteristics of study population (Real-time CGM)/ SMBG):</p> <p>MDI patients</p> <p>HbA_{1c}[%] mean (SD) 8.58 (0.2)/ 8.83 (0.5)</p> <p>AUC>200 [mg/dL/day] mean (SD) 21.34 (7.2)/ 19.03 (13.4)</p> <p>AUC<70 [mg/dL/day] mean (SD) 1.50 (2.4)/ 1.54 (0.5)</p>	<p>IG: Real-time Continuous Glucose Monitoring (RT-CGM)</p> <p>CG: Self-monitoring of blood glucose (SMBG)</p> <p>All of the patients underwent a structured educational programme 1 month before starting the study.</p>	<p>HbA1c (mean %, 6 months) 7.76/ 8.42; NR; NR; NR</p> <p>Ketoacidosis (n) 0/1; NR; NR; NR</p> <p>Severe Hypoglycaemia (n, during study) 0/0; NR; NA</p>	<p>Level of evidence</p> <p>DDG: 2b SIGN: 2+</p> <p>Risk of bias</p> <p>Generation of allocation sequence: ? Allocation concealment: ? Blinding of participants and personal: - Blinding of outcome assessment: - Incomplete outcome data: ? Selective reporting: + Other source of bias: +</p> <p>Authors conclusion:</p> <p>" Appropriate use of real-time continuous glucose monitoring improved glycometabolic control in T1D patients. The effects of continuous glucose monitoring were more evident in patients under multiple daily insulin treatment, compared with insulin pump therapy. Glucose variability, in addition to glycaemic control, was improved in compliant diabetic patients."</p>

Study / reference/ objective	Region/setting, inclusion criteria, exclusion criteria, baseline characteristics (IG/CG) of study population and patient flow (IG/CG)	Intervention group(s) (IG) / control group (CG)	Outcomes (IG/CG; relative effect measure (RR, OR) or MD; 95% CI and p; primary outcome marked)	Level of evidence / Critical appraisal and authors conclusion
	<u>Average glucose [mg/dL] mean (SD)</u> 176 (22)/182 (27) <u>Median glucose [mg/dL] mean (SD)</u> 167 (29)/ 179 (30) <u>MODD mean (SD)</u> 75.88 (30.6)/ 71.13(22.2) <u>SD mean (SD)</u> 75.50 (11.5)/ 63.75 (4.8) <u>CV mean (SD)</u> 43.00 (11.5)/ 35.38 (4.4) <u>MAGE mean (SD)</u> 175.38 (39.2)/ 132.25 (22.5) CSII patients <u>HbA_{1c} [%] mean (SD)</u> 8.50 (0.3)/ 8.22 (0.3) <u>AUC>200 [mg/dL/day] mean (SD)</u> 25.60 (19.4)/ 19.8 (12.9) <u>AUC<70 [mg/dL/day] mean (SD)</u> 1.7 (0.3)/ 1.7 (1.0) <u>Average glucose [mg/dL] mean (SD)</u> 190 (39)/ 164 (16) <u>Median glucose [mg/dL] mean (SD)</u> 186 (41)/ 147 (16) <u>MODD mean (SD)</u> 69.50 (16.9)/ 73.3 (14.2) <u>SD mean (SD)</u> 66.83 (9.2)/ 78.8 (15.5) <u>CV mean (SD)</u> 35.67 (5.3)/ 47.5 (4.6) <u>MAGE mean (SD)</u> 153.5 (29.5)/ 173.5 (29.5) Patient flow (group unclear): Randomized: 10/ 10 Analyzed: 14			

IG: intervention group; CG: control group; SAPT: sensor-augmented pump-therapy; MDI: multiple daily injection; +: low risk; -: high risk; ?: unclear risk; NA: not applicable; CI: confidence interval; NR: not reported; RM: ratio of means; T1D: type 1 diabetes; AUC: area under the curve; CSII: continuous subcutaneous insulin infusion; CV: coefficient of variation; MODD: mean of the daily serum glucose difference; SD: standard deviation; MAGE: mean amplitude of glycaemic excursions.

Study / reference/ objective	Region/setting, inclusion criteria, exclusion criteria, baseline characteristics (IG/CG) of study population and patient flow (IG/CG)	Intervention group(s) (IG) / control group (CG)	Outcomes (IG/CG; relative effect measure (RR, OR) or MD; 95% CI and p; primary outcome marked)	Level of evidence / Critical appraisal and authors conclusion
sion				

10.8.6 Rechercheauftrag 6 – Aktualisierung der aggregierten Evidenz

Aktualisierung der aggregierten Evidenz der Leitlinien der American Diabetes Association (ADA) und der Canadian Diabetes Association (CDC). Die aktualisierten Passagen sind jeweils in rot hinterlegt. Die Literaturangaben entsprechen den Quellen der Originalpublikationen.

Aktualisierung Kapitel: Definition und Klassifikation

Quelle	Text	Evidenz- bzw. Empfehlungsgrad	Literaturbelege	Methodische Bewertung
CDA 2013 [Canadian Diabetes Association 2013] (4)	<p>Definition of Diabetes and Prediabetes Diabetes mellitus is a metabolic disorder characterized by the presence of hyperglycemia due to defective insulin secretion, defective insulin action or both. The chronic hyperglycemia of diabetes is associated with relatively specific long-term microvascular complications affecting the eyes, kidneys and nerves, as well as an increased risk for cardiovascular disease (CVD). The diagnostic criteria for diabetes are based on thresholds of glycemia that are associated with microvascular disease, especially retinopathy. “Prediabetes” is a practical and convenient term referring to impaired fasting glucose (IFG), impaired glucose tolerance (IGT) (1) or a glycated hemoglobin (A1C) of 6.0% to 6.4%, each of which places individuals at high risk of developing diabetes and its complications.</p> <p>Classification of Diabetes The classification of type 1 diabetes, type 2 diabetes and gestational diabetes mellitus (GDM) is summarized in Table 1. Appendix 1 addresses the etiologic classification of diabetes. Distinguishing between type 1 and type 2 diabetes is important be-</p>	n.a.	<p>1. American Diabetes Association. Diagnosis and classification of diabetes mellitus. <i>Diabetes Care</i> 2012;35(suppl 1): S64-71. 2. Patel P, Macerollo A. Diabetes mellitus: diagnosis and screening. <i>Am Fam Physician</i> 2010;81:863-70. 3. Unger RH, Grundy S. Hyperglycemia as an inducer as well as a consequence of impaired islet cell function and insulin resistance: implications for the management of diabetes. <i>Diabetologia</i> 1985;28:119-21. 4. Turner R, Stratton I, Horton V, et al. UKPDS 25: autoantibodies to islet-cell cytoplasm and glutamic acid decarboxylase for prediction of insulin requirement in type 2 diabetes. UK Prospective Diabetes Study Group. <i>Lancet</i> 1997; 350:1288-93.</p>	Die Erstellung der Leitlinie ist gemäß DELBI als methodisch hochwertig zu bewerten. Aussagen zur methodischen Qualität bezüglich spezifischer Aussagen können daraus nicht abgeleitet werden.

Quelle	Text	Evidenz- bzw. Empfehlungsgrad	Literaturbelege	Methodische Bewertung
	<p>cause management strategies differ, but it may be difficult at the time of diagnosis in certain situations. Physical signs of insulin resistance and autoimmune markers, such as anti-glutamic acid decarboxylase (GAD) or anti-islet cell antibody (ICA) antibodies, may be helpful, but have not been adequately studied as diagnostic tests in this setting. While very low C-peptide levels measured after months of clinical stabilization may favour type 1 diabetes (2), they are not helpful in acute hyperglycemia (3). Clinical judgement with safe management and ongoing follow-up is a prudent approach.</p> <p>Table 1. Classification of diabetes (1)</p> <ul style="list-style-type: none"> • Type 1 diabetes* encompasses diabetes that is primarily a result of pancreatic beta cell destruction and is prone to ketoacidosis. This form includes cases due to an autoimmune process and those for which the etiology of beta cell destruction is unknown. • Type 2 diabetes may range from predominant insulin resistance with relative insulin deficiency to a predominant secretory defect with insulin resistance. • Gestational diabetes mellitus refers to glucose intolerance with onset or first recognition during pregnancy. • Other specific types include a wide variety of relatively uncommon conditions, primarily specific genetically defined forms of diabetes or diabetes associated with other diseases or drug use (Appendix 1). <p>* Includes latent autoimmune diabetes in adults (LADA); the term used to describe the small number of people with apparent type 2 diabetes who appear to have immune-mediated loss of pancreatic beta cells (4).</p>			
ADA 2016	Diabetes can be classified into the following general categories:	n.a.	1. American Diabetes Association. Diagno-	Die Erstellung der Leitlinie ist gemäß

Quelle	Text	Evidenz- bzw. Empfehlungsgrad	Literaturbelege	Methodische Bewertung
[American Diabetes Association 2016](5)	<ul style="list-style-type: none"> Type 1 diabetes (due to b-cell destruction, usually leading to absolute insulin deficiency) Type 2 diabetes (due to a progressive loss of insulin secretion on the background of insulin resistance) Gestational diabetes mellitus (GDM) (diabetes diagnosed in the second or third trimester of pregnancy that is not clearly overt diabetes) Specific types of diabetes due to other causes, e.g., monogenic diabetes syndromes (such as neonatal diabetes and maturity-onset diabetes of the young [MODY]), diseases of the exocrine pancreas (such as cystic fibrosis), and drug- or chemical-induced diabetes (such as with glucocorticoid use, in the treatment of HIV/AIDS or after organ transplantation) <p>Type 1 diabetes and type 2 diabetes are heterogeneous diseases in which clinical presentation and disease progression may vary considerably. Classification is important for determining therapy, but some individuals cannot be clearly classified as having type 1 or type 2 diabetes at the time of diagnosis. The traditional paradigms of type 2 diabetes occurring only in adults and type 1 diabetes only in children are no longer accurate, as both diseases occur in both cohorts. Occasionally, patients with type 2 diabetes may present with diabetic ketoacidosis (DKA). Children with type 1 diabetes typically present with the hallmark symptoms of polyuria/polydipsia and approximately one-third with DKA (2). The onset of type 1 diabetes may be more variable in adults, and they may not present with the classic symptoms seen in children. Although difficulties in distinguishing diabetes type may occur in all agegroups at onset, the true diagnosis becomes more obvious over time.</p>		<p>sis and classification of diabetes mellitus. Diabetes Care 2014;37 (Suppl.1):S81–S90.</p> <p>2. Dabelea D, Rewers A, Stafford JM, et al.; SEARCH for Diabetes in Youth Study Group. Trends in the prevalence of ketoacidosis at diabetes diagnosis: the SEARCH for Diabetes in Youth study. Pediatrics 2014; 133:e938-945.</p>	<p>DEBBI von geringer methodischer Qualität. U.a. fehlen Angaben zur Literaturrecherche, Studienbewertung und zur Methodik der Erstellung der Empfehlungen. Aussagen zur methodischen Qualität bezüglich spezifischer Aussagen können daraus nicht abgeleitet werden.</p>

Aktualisierung Kapitel: Therapieziele

Quelle	Text	Evidenz- bzw. Empfehlungsgrad	Literaturbelege	Methodische Bewertung
CDA 2013 (6)	Glycemic targets should be individualized based on age, duration of diabetes, risk of severe hypoglycemia, presence or absence of cardiovascular disease, and life expectancy.	Grade D Consensus	n.a.	Die Erstellung der Leitlinie ist gemäß DELBI als methodisch hochwertig zu bewerten. Aussagen zur methodischen Qualität bezüglich spezifischer Aussagen können daraus nicht abgeleitet werden.
	Therapy in most individuals with type 1 or type 2 diabetes should be targeted to achieve an A1C $\leq 7.0\%$ in order to reduce the risk of micro- vascular	Grade A Level 1A	UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998; 352: 837-53. The Diabetes Control and Complications Trial Research Group. The relationship of glycemic exposure (HbA1c) to the risk of development and progression of retinopathy in the Diabetes Control and Complications Trial. Diabetes 1995; 44: 968-83.	
	and, if implemented early in the course of disease, macrovascular complications	Grade B Level 3	Holman RR, Paul SK, Bethel MA, et al. 10-Year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008; 359: 1577-89. Nathan DM, Cleary PA, Backlund JY, et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Eng J Med 2005; 353: 2643-53.	

Quelle	Text	Evidenz- bzw. Empfehlungsgrad	Literaturbelege	Methodische Bewertung
	An A1C $\leq 6.5\%$ may be targeted in some patients with type 2 diabetes to further lower the risk of nephropathy	Grade A Level 1	The ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008; 358: 2560-72.	
	and retinopathy	Grade A Level 1	The ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008; 358: 2560-72.	
	but this must be balanced against the risk of hypoglycemia	Grade A Level 1	The ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008; 358: 2560-72.	
	Less stringent A1C targets (7.1% - 8.5% in most cases) may be appropriate in patients with type 1 or type 2 diabetes with any of the following: a) Limited life expectancy b) High level of functional dependency c) Extensive coronary artery disease at high risk of ischemic events d) Multiple comorbidities e) History of recurrent severe hypoglycemia f) Hypoglycemia unawareness g) Longstanding diabetes for whom it is difficult to achieve an A1C 7.0% despite effective doses of multiple antihyperglycemic agents, including intensified basal-bolus insulin therapy	Grade D Consensus	n.a.	
	In order to achieve an A1C $\leq 7.0\%$, people with diabetes should aim for: FPG or preprandial PG target of 4.0 – 7.0 mmol/L and a 2-hour PPG target of 5.0 – 10.0 mmol/L			

Quelle	Text	Evidenz- bzw. Empfehlungsgrad	Literaturbelege	Methodische Bewertung
	for type 1;	Grade B Level 2	The Diabetes Control and Complications Trial Research Group. The relationship of glycemic exposure (HbA1c) to the risk of development and progression of retinopathy in the Diabetes Control and Complications Trial. <i>Diabetes</i> 1995; 44: 968-83.	
	for type 2 diabetes	Grade B Level 2	UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). <i>Lancet</i> 1998; 352: 837-53. Ohkubo Y, Kishikawa H, Araki E, et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. <i>Diabetes Res Clin Pract</i> 1995; 28: 103-17.	
	If an A1C target $\leq 7.0\%$ cannot be achieved with a PPG target of 5.0 – 10.0 mmol/L, further PPG lowering to 5.0 – 8.0 mmol/L should be achieved			
	For type 1 diabetes	Grade D Consensus		
	For type 2 diabetes	Grade D Level 4	Monnier L, Lapinski H, Colette C. Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of type 2 diabetic patients:	

Quelle	Text	Evidenz- bzw. Empfehlungsgrad	Literaturbelege	Methodische Bewertung
			variations with increasing levels of HbA1c. Diabetes Care 2003; 26: 881-5. Woele HHJ, Neumann C, Zschau S, et al. Impact of fasting and postprandial glycemia on overall glycemic control in type 2 diabetes. Importance of post-prandial glycemia to achieve target HbA1c levels. Diabetes Res Clin Pract 2007; 77: 280-5.	
ADA 2015 (7)	Lowering A1C to approximately 7% or less has been shown to reduce microvascular complications of diabetes, and, if implemented soon after the diagnosis of diabetes, it is associated with long-term reduction in macrovascular disease . Therefore, a reasonable A1C goal for many nonpregnant adults is <7%.	Level n.a. Grade B	n.a. Hintergrundtext mit Literaturangaben vorhanden	Die Erstellung der Leitlinie ist gemäß DELBI von geringer methodischer Qualität. U.a. fehlen Angaben zur Literaturrecherche, Studienbewertung und zur Methodik der Erstellung der Empfehlungen. Aussagen zur methodischen Qualität bezüglich spezifischer Aussagen können daraus nicht abgeleitet werden.
	Providers might reasonably suggest more stringent A1C goals (such as ,6.5%) for selected individual patients if this can be achieved without significant hypoglycemia or other adverse effects of treatment. Appropriate patients might include those with short duration of diabetes, type 2 diabetes treated with lifestyle or metformin only, long life expectancy, or no significant cardiovascular disease (CVD).	Level n.a. Grade C	n.a. Hintergrundtext mit Literaturangaben vorhanden	
	Less stringent A1C goals (such as <8%) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, or long-standing diabetes in whom the general goal is difficult to attain despite diabetes self-	Level n.a. Grade B	n.a. Hintergrundtext mit Literaturangaben vorhanden	

Quelle	Text	Evidenz- bzw. Empfehlungsgrad	Literaturbelege	Methodische Bewertung
	management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin.			

Aktualisierung Kapitel: Therapiestrategie

Quelle	Text	Evidenz- bzw. Empfehlungsgrad	Literaturbelege	Methodische Bewertung
CDA 2013 (8)	Insulin regimens for type 1 diabetes To achieve glycemic targets in adults with type 1 diabetes, basal-bolus insulin regimens or CSII as part of an intensive diabetes management regimen should be used	Grade A Level 1A	The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-independent diabetes mellitus. N Engl J Med. 1993; 329: 977-986.	Die Erstellung der Leitlinie ist gemäß DELBI als methodisch hochwertig zu bewerten. Aussagen zur methodischen Qualität bezüglich spezifischer Aussagen können daraus nicht abgeleitet werden.
ADA 2015 (9)	The Diabetes Control and Complications Trial (DCCT) clearly showed that intensive insulin therapy (three or more injections per day of insulin) or CSII (insulin pump therapy) was a key part of improved glycemia and better outcomes (10,11)	Level n.a. Grade n.a.	The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993; 329: 977-986 Nathan DM, Cleary PA, Backlund J-YC, et al.; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med 2005; 353: 2643-2653	Die Erstellung der Leitlinie ist gemäß DELBI von geringer methodischer Qualität. U.a. fehlen Angaben zur Literaturrecherche, Studienbewertung und zur Methodik der Erstellung der Empfehlungen. Aussagen zur methodischen Qualität bezüglich spezifischer Aussagen können daraus nicht abgeleitet werden.
	Recommended therapy for type 1 diabetes consists of the	Level n.a.	n.a.	

Quelle	Text	Evidenz- bzw. Empfehlungsgrad	Literaturbelege	Methodische Bewertung
	<p>following:</p> <ol style="list-style-type: none"> 1. Use MDI injections (three to four injections per day of basal and prandial insulin) or CSII therapy. 2. Match prandial insulin to carbohydrate intake, premeal blood glucose, and anticipated physical activity. 3. For most patients (especially those at an elevated risk of hypoglycemia), use insulin analogs. 4. For patients with frequent nocturnal hypoglycemia and/or hypoglycemia unawareness, a sensor-augmented low glucose threshold suspend pump may be considered. 	Grade n.a.		
	Most people with type 1 diabetes should be treated with multiple-dose insulin (MDI) injections (three to four injections per day of basal and prandial insulin) or continuous subcutaneous insulin infusion (CSII).	Level n.a. Grade A	n.a.	
	Most people with type 1 diabetes should be educated in how to match prandial insulin dose to carbohydrate intake, premeal blood glucose, and anticipated activity.	Level n.a. Grade E	n.a.	
	Most people with type 1 diabetes should use insulin analogs to reduce hypoglycemia risk.	Level n.a. Grade A	n.a.	

Aktualisierung Kapitel: Insulinpumpe/Kontinuierliche subkutane Insulininjektion (CSII)

Quelle	Text	Evidenz- bzw. Empfehlungsgrad	Literaturbelege	Methodische Bewertung
CDA 2013 (8)	CSII therapy is a safe and effective method of intensive insulin therapy in type 1 diabetes and has shown improvements in glucose control over NPH-based regimens and, in fewer studies, over long-acting analogue regimens with less severe hypoglycemia .	Level A Grade 1C	2. Hoogma RP, Hammond PJ, Gomis R, et al. Comparison of the effects of continuous subcutaneous insulin infusion (CSII) and NPH-based multiple daily insulin injections	Die Erstellung der Leitlinie ist gemäß DELBI als methodisch hochwertig zu bewerten. Aussagen zur methodischen Qualität bezüglich

Quelle	Text	Evidenz- bzw. Empfehlungsgrad	Literaturbelege	Methodische Bewertung
	mia. Advancements in basal insulins may lessen the value of CSII in type 1 diabetes. CSII may provide some advantages over other methods of intensive therapy, particularly in individuals with higher baseline glycated hemoglobin (A1C).		<p>(MDI) on glycaemic control and quality of life: results of the 5-nations trial. <i>Diabetic Medicine</i> 2005; 23: 141-7.</p> <p>3. Misso ML, Egberts KJ, Page M, et al. Continuous subcutaneous insulin infusion (CSII) versus multiple insulin injections for type 1 diabetes mellitus. <i>Cochrane Database Syst Rev</i> 2010; 1: CD005103.</p> <p>4. Pickup J, Mattock M, Kerry S. Glycaemic control with continuous subcutaneous insulin infusion compared with intensive insulin injections in patients with type 1 diabetes: meta-analysis of randomised controlled trials. <i>BMJ</i> 2002; 324: 705.</p> <p>5. Tsui E, Barnie A, Ross S, et al. Intensive insulin therapy with insulin lispro: a randomized trial of continuous subcutaneous insulin infusion versus multiple daily insulin injection. <i>Diabetes Care</i> 2001; 24: 1722-7.</p> <p>6. DeVries JH, Snoek FJ, Kostense PJ, et al, Dutch Insulin Pump Study Group. A randomized trial of continuous subcutaneous insulin infusion and intensive injection therapy in type 1 diabetes for patients with long-standing poor glycemic control. <i>Diabetes Care</i> 2002; 25: 2074-80.</p> <p>7. Hirsch IB, Bode BW, Garg S, et al, Insulin Aspart CSII/MDI Comparison Study Group. Continuous subcutaneous insulin infusion (CSII) of insulin aspart versus</p>	spezifischer Aussagen können daraus nicht abgeleitet werden.

Quelle	Text	Evidenz- bzw. Empfehlungsgrad	Literaturbelege	Methodische Bewertung
			<p>multiple daily injection of insulin aspart/insulin glargine in type 1 diabetic patients previously treated with CSII. Diabetes Care 2005; 28: 533-8.</p> <p>8. Retnakaran R, Hochman J, DeVries JH, et al. Continuous subcutaneous insulin infusion versus multiple daily injections: the impact of baseline A1c. Diabetes Care 2004; 27: 2590-6.</p> <p>9. Monami M, Lamanna C, Marchionni N, Mannucci E. Continuous subcutaneous insulin infusion versus multiple daily insulin injections in type 1 diabetes: a meta-analysis. Acta Diabetologica 2010; 47(suppl 1): S77-81.</p>	
	In patients using CSII, insulin aspart and insulin lispro have been shown to be superior to regular insulin by improving postprandial glycemic control and reducing hypoglycemia.		<p>10. Zinman B, Tildesley H, Chiasson JL, et al. Insulin lispro in CSII: results of a double-blind crossover study. Diabetes 1997; 46: 440-3.</p> <p>11. Bode B, Weinstein R, Bell D, et al. Comparison of insulin aspart with buffered regular insulin and insulin lispro in continuous subcutaneous insulin infusion: a randomized study in type 1 diabetes. Diabetes Care 2002; 25: 439-44.</p> <p>12. Radermecker RP, Scheen AJ. Continuous subcutaneous insulin infusion with short-acting insulin analogues or human regular insulin: efficacy, safety, quality of life, and cost-effectiveness. Diabetes</p>	

Quelle	Text	Evidenz- bzw. Empfehlungsgrad	Literaturbelege	Methodische Bewertung
			Metab Res Rev 2004; 20: 178-88. 13. Siebenhofer A, Plank J, Berghold A, et al. Meta-analysis of short-acting insulin analogues in adult patients with type 1 diabetes: continuous subcutaneous insulin infusion versus injection therapy. Diabetologia 2004; 47: 1895-905.	
	<p>Recommendation:</p> <p>To achieve glycemic targets in adults with type 1 diabetes, basal-bolus insulin regimens or CSII as part of an intensive diabetes management regimen should be used.</p>	Grade A Level 1A	The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of longterm complications in insulin-dependent diabetes mellitus. N Engl J Med 1993; 329: 977-86.	
ADA 2015 (9)	The Diabetes Control and Complications Trial (DCCT) clearly showed that intensive insulin therapy (three or more injections per day of insulin) or CSII (insulin pump therapy) was a key part of improved glycemia and better outcomes	n.a.	10. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993; 329: 977-986 11. Nathan DM, Cleary PA, Backlund J-YC, et al.; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med 2005; 353:2643-2653	Die Erstellung der Leitlinie ist gemäß DELBI von geringer methodischer Qualität. U.a. fehlen Angaben zur Literaturrecherche, Studienbewertung und zur Methodik der Erstellung der Empfehlungen. Aussagen zur methodischen Qualität bezüglich spezifischer Aussagen können daraus nicht abgeleitet werden.

Aktualisierung Kapitel: Insulinarten

Quelle	Text	Evidenz- bzw. Empfehlungsgrad	Literaturbelege	Methodische Bewertung
ADA 2015 (9)	<p>Since the DCCT, a number of rapid-acting and long-acting insulin analogs have been developed. These analogs are associated with less hypoglycemia in type 1 diabetes, while matching the A1C lowering of human insulins (1,12).</p> <p>Recommended therapy for type 1 diabetes consists of the following:</p> <ol style="list-style-type: none"> 1. Use MDI injections (three to four injections per day of basal and prandial insulin) or CSII therapy. 2. Match prandial insulin to carbohydrate intake, premeal blood glucose, and anticipated physical activity. 3. For most patients (especially those at an elevated risk of hypoglycemia), use insulin analogs. 4. For patients with frequent nocturnal hypoglycemia and/or hypoglycemia unawareness, a sensor-augmented low glucose threshold suspend pump may be considered. 	n.a.	<p>1. DeWitt DE, Hirsch IB. Outpatient insulin therapy in type 1 and type 2 diabetes mellitus: scientific review. JAMA 2003; 289: 2254–2264</p> <p>12. Rosenstock J, Dailey G, Massi-Benedetti M, Fritsche A, Lin Z, Salzman A. Reduced hypoglycemia risk with insulin glargine: a meta-analysis comparing insulin glargine with human NPH insulin in type 2 diabetes. Diabetes Care 2005; 28: 950–955</p>	<p>Die Erstellung der Leitlinie ist gemäß DELBI von geringer methodischer Qualität. U.a. fehlen Angaben zur Literaturrecherche, Studienbewertung und zur Methodik der Erstellung der Empfehlungen. Aussagen zur methodischen Qualität bezüglich spezifischer Aussagen können daraus nicht abgeleitet werden.</p>
CDA 2013 (8)	Rapid-acting bolus insulin analogues, in combination with adequate basal insulin, should be used instead of regular insulin to minimize the occurrence of hypoglycemia, improve A1C	Grade B Level 2	<p>Siebenhofer A, Plank J, Berghold A, et al. Short acting insulin analogues versus regular human insulin in patients with diabetes mellitus. Cochrane Database Syst Rev 2006; 2: CD003287.</p> <p>Plank J, Siebenhofer A, Berghold A, et al. Systematic review and meta-analysis of short-acting insulin analogues in patients with diabetes mellitus. Arch Intern Med 2005; 165: 1337-44.</p> <p>Gough S. A review of human and analogue insulin trials. Diabetes Res Clin Pract 2007; 77: 1-15.</p>	<p>Die Erstellung der Leitlinie ist gemäß DELBI als methodisch hochwertig zu bewerten. Aussagen zur methodischen Qualität bezüglich spezifischer Aussagen können daraus nicht abgeleitet werden.</p>

Quelle	Text	Evidenz- bzw. Empfehlungsgrad	Literaturbelege	Methodische Bewertung
	and achieve postprandial glucose targets	Grade B Level 2	Gough S. A review of human and analogue insulin trials. <i>Diabetes Res Clin Pract</i> 2007; 77: 1-15. DeVries JH, Lindholm A, Jacobsen JL, et al, Tri-Continental Insulin Aspart Study Group. A randomized trial of insulin aspart with intensified basal NPH insulin supplementation in people with type 1 diabetes. <i>Diabet Med</i> 2003; 20: 312-8.	
	Rapid-acting insulin analogues (aspart or lispro) should be used with CSII in adults with type 1 diabetes.	Grade B Level 2	Zinman B, Tildesley H, Chiasson JL, et al. Insulin lispro in CSII: results of a double-blind crossover study. <i>Diabetes</i> 1997; 46: 440-3. Bode B, Weinstein R, Bell D, et al. Comparison of insulin aspart with buffered regular insulin and insulin lispro in continuous subcutaneous insulin infusion: a randomized study in type 1 diabetes. <i>Diabetes Care</i> 2002; 25: 439-44.	
	A long-acting insulin analogue (detemir, glargine) maybe used as the basal insulin	Grade B Level 2	Warren E, Weatherley-Jones E, Chilcott J, et al. Systematic review and economic evaluation of a long-acting insulin analogue, insulin glargine. <i>Health Technol Assess</i> 2004; 8: 1-57. Wang F, Carabino JM, Vergara CM. Insulin glargine: a systematic review of a long-acting insulin analogue. <i>Clin Ther</i> 2003; 25: 1541-77. Dunn CJ, Plosker GL, Keating GM, et al.	

Quelle	Text	Evidenz- bzw. Empfehlungsgrad	Literaturbelege	Methodische Bewertung
			Insulin glargine: an updated review of its use in the management of diabetes mellitus. Drugs 2003; 63: 1743-78. Chapman TM, Perry CM. Insulin detemir: a review of its use in the management of type 1 and 2 diabetes mellitus. Drugs 2004; 64: 2577-95.	
	to reduce the risk of hypoglycemia			
	for detemir;	Grade B Level 2	Goldman-Levine JD, Lee KW. Insulin detemir: a new basal insulin analog. Ann Pharmacother 2005; 39: 502-7.	
	For glargin	Grade C Level 3	Mullins P, Sharplin P, Yki-Jarvinen H, et al. Negative binomial meta-regression analysis of combined glycosylated hemoglobin and hypoglycemia outcomes across eleven phase III and IV studies of insulin glargin compared with neutral protamine Hagedorn insulin in type 1 and type 2 diabetes mellitus. Clin Ther 2007; 29: 1607-19.	
	including nocturnal hypoglycaemia			
	for detemir;	Grade B Level 2	Goldman-Levine JD, Lee KW. Insulin detemir: a new basal insulin analog. Ann Pharmacother 2005; 39: 502-7.	
	for glargin	Grade D Consensus		

Aktualisierung Kapitel: Schulung

Quelle	Text	Evidenz- bzw. Empfehlungsgrad	Literaturbelege	Methodische Bewertung
ADA 2015 (10)	People with diabetes should receive diabetes self management education (DSME) and diabetes self-management support (DSMS) according to the national standards for DSME and DSMS when their diabetes is diagnosed and as needed thereafter.	Grade B Level n.a.	n.a.	Die Erstellung der Leitlinie ist gemäß DELBI von geringer methodischer Qualität. U.a. fehlen Angaben zur Literaturrecherche, Studienbewertung und zur Methodik der Erstellung der Empfehlungen. Aussagen zur methodischen Qualität bezüglich spezifischer Aussagen können daraus nicht abgeleitet werden.
	Effective self-management and quality of life are the key outcomes of DSME and DSMS and should be measured and monitored as part of care.	Grade C Level n.a.	n.a.	
	DSME and DSMS should address psychosocial issues, as emotional well-being is associated with positive diabetes outcomes.	Grade C Level n.a.	n.a.	
	DSME and DSMS programs are appropriate venues for people with prediabetes to receive education and support to develop and maintain behaviors that can prevent or delay the onset of diabetes.	Grade C Level n.a.	n.a.	
	Because DSME and DSMS can result in cost-savings and improved outcomes B,	Grade B Level n.a.	n.a.	
	DSME and DSMS should be adequately reimbursed by third-party payers.	Grade E Level n.a.	n.a.	
CDA 2013 (11)	People with diabetes should be offered timely diabetes education that is tailored to enhance self-care practices and behaviours	Grade A Level 1A	Minet L, Moller S, Lach V, et al. Mediating the effect of self-care management intervention in type 2 diabetes: a meta-analysis	Die Erstellung der Leitlinie ist gemäß DELBI als methodisch hochwertig zu bewerten. Aussagen zur methodi-

Quelle	Text	Evidenz- bzw. Empfehlungsgrad	Literaturbelege	Methodische Bewertung
			<p>of 47 randomised controlled trials. Patient Educ Couns 2010; 80: 29-41.</p> <p>Ellis S, Speroff T, Dittus R, et al. Diabetes patient education: a meta analysis and meta-regression. Patient Educ Couns 2004; 52: 97-105.</p> <p>Norris SL, Engelgau MM, Narayan KMV. Effectiveness of self-management training in type 2 diabetes: a systematic review of randomized controlled trials. Diabetes Care 2001; 24: 561-87.</p>	schen Qualität bezüglich spezifischer Aussagen können daraus nicht abgeleitet werden.
	All people with diabetes who are able should be taught how to self-manage their diabetes	Grade A Level 1A	<p>Norris SL, Engelgau MM, Narayan KMV. Effectiveness of self-management training in type 2 diabetes: a systematic review of randomized controlled trials. Diabetes Care 2001; 24: 561-87.</p>	
	SME that incorporates cognitive-behavioural educational interventions, such as problem solving, goal setting, and self-monitoring of health parameters, should be implemented for all individuals with diabetes	Grade B Level 2	<p>Ellis S, Speroff T, Dittus R, et al. Diabetes patient education: a meta analysis and meta-regression. Patient Educ Couns 2004; 52: 97-105.</p> <p>Kulzer B, Hermanns N, Reinhecker H, et al. Effects of self-management training in type 2 diabetes: a randomized prospective trial. Diabet Med 2007; 24: 415-23.</p> <p>Weinger K, Beverly E, Lee Y, et al. The effect of a structured behavioral intervention in poorly controlled diabetes. Arch Intern Med 2011; 171: 1990-8.</p> <p>Steed L, Cooke D, Newman S. A systemat-</p>	

Quelle	Text	Evidenz- bzw. Empfehlungsgrad	Literaturbelege	Methodische Bewertung
			ic review of psychosocial outcomes following education, self-management and psychological interventions in diabetes mellitus. Patient Educ Couns 2003; 51: 5-15.	
	Interventions that increase patient participation and collaboration in healthcare decision making should be used by providers	Grade B Level 2	Norris SL, Engelgau MM, Narayan KMV. Effectiveness of self-management training in type 2 diabetes: a systematic review of randomized controlled trials. Diabetes Care 2001; 24: 561-87.	
	In both type 1 and 2 diabetes, interventions that target families' ability to cope with stress or diabetes-related conflict should be included in educational interventions when indicated	Grade B Level 2	Armour TA, Norris SL, Jack Jr L, et al. The effectiveness of family interventions in people with diabetes mellitus: a systematic review. Diabet Med 2005; 22: 1295-305.	
	Technologically based home blood glucose monitoring systems may be integrated into SME interventions in order to improve glycemic control	Grade C Level 3	Jaana M, Pare G. Home telemonitoring of patients with diabetes: a systematic assessment of observed effects. J Eval Clin Pract 2007; 13:242-53. Tildesley HD, Mazanderani AB, Ross SA. Effect of internet therapeutic intervention on A1C levels in patients with type 2 diabetes treated with insulin. Diabetes Care 2010; 33: 1738-40.	
	Culturally appropriate SME, which may include peer or lay educators, may be used to increase diabetes-related knowledge and self-care behaviours and to decrease A1C	Grade B Level 2	Whittemore R. Culturally competent interventions for Hispanic adults with type 2 diabetes: a systematic review. J Transcult Nurs 2007; 18: 157-66. Hawthorne K, Robles Y, Cannings-John R, et al. Culturally appropriate health educa-	

Quelle	Text	Evidenz- bzw. Empfehlungsgrad	Literaturbelege	Methodische Bewertung
			<p>tion for type 2 diabetes in ethnic minority groups: a systematic and narrative review of randomized control trials. Diabet Med 2010; 27: 613-23.</p> <p>Babamato K, Sey KA, Karlan V, et al. Improving diabetes care and health measures among Hispanics using community health workers: results from a randomized controlled trial. Health Educ Behav 2009; 36: 113-26.</p>	
	Adding literacy- and numeracy-sensitive materials to a comprehensive diabetes management and education program may be used to improve knowledge, self-efficacy and A1C outcomes for patients with low literacy	Grade C Level 3	<p>Van Scyoc EF, deWalt DA. Interventions to Improve diabetes outcomes for people with low literacy and numeracy: a systematic literature review. Diabetes Spectrum 2010; 23: 228-37.</p>	

Aktualisierung Kapitel: Therapie in Sondersituationen

Quelle	Text	Evidenz- bzw. Empfehlungsgrad	Literaturbelege	Methodische Bewertung
ADA 2015 (12)	Diabetes discharge planning should start at hospital admission, and clear diabetes management instructions should be provided at discharge. E	Grade E	n.a. Hintergrundtext mit Literaturangaben vorhanden	Die Erstellung der Leitlinie ist gemäß DELBI von geringer methodischer Qualität. U.a. fehlen Angaben zur Literaturrecherche, Studienbewertung und zur Methodik der Erstellung der Empfehlungen. Aussagen zur methodischen Qualität bezüglich spezifischer Aussagen können daraus nicht abgeleitet werden.

Quelle	Text	Evidenz- bzw. Empfehlungsgrad	Literaturbelege	Methodische Bewertung
	All patients with diabetes admitted to the hospital should have their diabetes type clearly identified in the medical record. E	Grade E	n.a. Hintergrundtext mit Literaturangaben vorhanden	
	Critically III Patients: Insulin therapy should be initiated for treatment of persistent hyperglycemia starting at a threshold of no greater than 180 mg/dL (10 mmol/L) . Once insulin therapy is started, a glucose range of 140–180 mg/dL (7.8–10 mmol/L) is recommended for the majority of critically ill patients. A	Grade A	n.a. Hintergrundtext mit Literaturangaben vorhanden	
	More stringent goals, such as 110–140 mg/dL (6.1–7.8 mmol/L), may be appropriate for selected patients, as long as this can be achieved without significant hypoglycemia. C	Grade C	n.a. Hintergrundtext mit Literaturangaben vorhanden	
	Critically ill patients require an intravenous insulin protocol that has demonstrated efficacy and safety in achieving the desired glucose range without increasing risk for severe hypoglycemia. E	Grade E	n.a. Hintergrundtext mit Literaturangaben vorhanden	
	Noncritically III Patients: If treated with insulin, generally premeal blood glucose targets of, 140mg/dL (7.8 mmol/L) with random blood glucose, 180 mg/dL (10.0 mmol/L) are reasonable , provided these targets can be safely achieved. More stringent targets may be appropriate in stable patients with previous tight glycemic control. Less stringent targets may be appropriate in those with severe comorbidities. C	Grade C	n.a. Hintergrundtext mit Literaturangaben vorhanden	
	A basal plus correction insulin regimen is the preferred treatment for patients with poor oral intake or who are taking nothing by mouth (NPO). An insulin regimen with basal, nutritional, and correction components is the preferred treatment for patients with good nutritional intake. A	Grade A	n.a. Hintergrundtext mit Literaturangaben vorhanden	

Quelle	Text	Evidenz- bzw. Empfehlungsgrad	Literaturbelege	Methodische Bewertung
	<p>A hypoglycemia management protocol should be adopted and implemented by each hospital or hospital system.</p> <p>A plan for preventing and treating hypoglycemia should be established for each patient. Episodes of hypoglycemia in the hospital should be documented in the medical record and tracked. E</p>	Grade E	n.a. Hintergrundtext mit Literaturangaben vorhanden	
	Consider obtaining an A1C in patients with diabetes admitted to the hospital if the result of testing in the previous 3 months is not available. E	Grade E	n.a. Hintergrundtext mit Literaturangaben vorhanden	
	Consider obtaining an A1C in patients with risk factors for undiagnosed diabetes who exhibit hyperglycemia in the hospital. E	Grade E	n.a. Hintergrundtext mit Literaturangaben vorhanden	
	Patients with hyperglycemia in the hospital who do not have a prior diagnosis of diabetes should have appropriate follow-up testing and care documented at discharge. E	Grade E	n.a. Hintergrundtext mit Literaturangaben vorhanden	
CDA 2013 (13)	<p>Provided that their medical conditions, dietary intake and glycemic control are acceptable, people with diabetes should be maintained on their prehospitalization oral antihyperglycemic agents or insulin regimens.</p>	Grade D Consensus		Die Erstellung der Leitlinie ist gemäß DELBI als methodisch hochwertig zu bewerten. Aussagen zur methodischen Qualität bezüglich spezifischer Aussagen können daraus nicht abgeleitet werden.
	<p>For hospitalized patients with diabetes treated with insulin, a proactive approach that includes basal, bolus and correction (supplemental) insulin, along with pattern management, should be used to reduce adverse events and improve glycemic control, instead of the reactive sliding-scale insulin approach that uses only short- or rapid-acting insulin</p>	Grade B Level 2	<p>Umpierrez GE, Smiley D, Zisman A, et al. Randomized study of basal-bolus insulin therapy in the inpatient management of patients with type 2 diabetes (RABBIT 2 trial). Diabetes Care 2007; 30: 2181-6.</p> <p>Umpierrez GE, Smiley D, Jacobs S, et al. Randomized study of basal-bolus insulin therapy in the inpatient management of</p>	

Quelle	Text	Evidenz- bzw. Empfehlungsgrad	Literaturbelege	Methodische Bewertung
			patients with type 2 diabetes undergoing general surgery (RABBIT 2 surgery). Diabetes Care 2011; 34: 256-61.	
	For the majority of noncritically ill patients treated with insulin, preprandial BG targets should be 5.0 to 8.0 mmol/L in conjunction with random BG values <10.0 mmol/L, as long as these targets can be safely achieved	Grade D Consensus	n.a.	
	For most medical/surgical critically ill patients with hyperglycemia, a continuous IV insulin infusion should be used to maintain glucose levels between 8 and 10 mmol/L	Grade D Consensus	n.a.	
	To maintain intraoperative glycemic levels between 5.5 and 10.0 mmol/L for patients with diabetes undergoing CABG, a continuous IV insulin infusion protocol administered by trained staff should be used.	Grade C Level 3	Furnary AP, Zerr KJ, Grunkemeier GL, et al. Continuous intravenous insulin infusion reduces the incidence of deep sternal wound infection in diabetic patients after cardiac surgical procedures. Ann Thorac Surg 1999; 67: 352-60. Furnary AP, Gao G, Grunkemeier GL, et al. Continuous insulin infusion reduces mortality in patients with diabetes undergoing coronary artery bypass grafting. J Thorac Cardiovasc Surg 2003; 125: 1007-21. Haga KK, McClymont KL, Clarke S, et al. The effect of tight glycaemic control, during and after cardiac surgery, on patient mortality and morbidity: a systematic review and meta-analysis. J Cardiothorac Surg 2011; 6: 3.	
	Perioperative glycemic levels should be maintained between 5.0	Grade D		

Quelle	Text	Evidenz- bzw. Empfehlungsgrad	Literaturbelege	Methodische Bewertung
	and 10.0 mmol/L for most other surgical situations, with an appropriate protocol and trained staff to ensure the safe and effective implementation of therapy and to minimize the likelihood of hypoglycemia	Consensus		
	In hospitalized patients, hypoglycemia should be avoided. Protocols for hypoglycemia avoidance, recognition and management should be implemented with nurse initiated treatment, including glucagon for severe hypoglycemia when IV access is not readily available	[Grade D Consensus].		
	Patients at risk of hypoglycemia should have ready access to an appropriate source of glucose (oral or IV) at all times, particularly when NPO or during diagnostic procedures	Grade D Consensus		
	Healthcare professional education, insulin protocols and order sets may be used to improve adherence to optimal insulin use and glycemic control	Grade C Level 3	Maynard G, Lee J, Phillips G. Improved inpatient use of basal insulin reduced hypoglycemia and improved glycemic control: effect of structured subcutaneous insulin order sets and an insulin management algorithm. J Hosp Med 2009; 4: 3-15.	
	Measures to assess, monitor and improve glycemic control within the inpatient setting should be implemented, as well as diabetes-specific discharge planning	Grade D Consensus		

Aktualisierung Kapitel: Weitere Therapieformen

Quelle	Text	Evidenz- bzw. Empfehlungsgrad	Literaturbelege	Methodische Bewertung
CDA 2013 (14)	Individuals with type 1 diabetes and ESRD who are being considered for kidney transplantation should also be considered for	Grade D Level 4	Ojo AO, Meier-Kriesche HU, Hanson JA, et al. The impact of simultaneous pancre-	Die Erstellung der Leitlinie ist gemäß DELBI als methodisch hochwertig zu

Quelle	Text	Evidenz- bzw. Empfehlungsgrad	Literaturbelege	Methodische Bewertung
	simultaneous pancreas transplantation		as-kidney transplantation on long-term patient survival. Transplantation 2001; 71: 82-90. Weiss AS, Smits G, Wiseman AC. Twelve-month pancreas graft function significantly influences survival following simultaneous pancreas-kidney transplantation. Clin J Am Soc Nephrol 2009; 4: 988-95	bewerten. Aussagen zur methodischen Qualität bezüglich spezifischer Aussagen können daraus nicht abgeleitet werden.
	Individuals with type 1 diabetes with preserved renal function, or who have undergone successful kidney transplantation but have persistent metabolic instability characterized by severe glycemic lability and/or severe hypoglycemia despite best efforts to optimize glycemic control, may be considered for pancreas or islet allotransplantation	Grade D Consensus		
	Individuals undergoing total pancreatectomy for benign pancreatic disease may be considered for islet autotransplantation but only in the context of an experienced islet transplantation centre	Grade D Consensus		

Aktualisierung Kapitel: Akutkomplikationen

Quelle	Text	Evidenz- bzw. Empfehlungsgrad	Literaturbelege	Methodische Bewertung
ADA 2015 (7)	Individuals at risk for hypoglycemia should be asked about symptomatic and asymptomatic hypoglycemia at each encounter. C	Grade C	n.a. Hintergrundtext mit Literaturangaben vorhanden	Die Erstellung der Leitlinie ist gemäß DELBI von geringer methodischer Qualität. U.a. fehlen Angaben zur Literaturrecherche, Studienbewertung und zur Methodik der Erstellung der Empfehlungen. Aussagen zur methodischen Qualität

Quelle	Text	Evidenz- bzw. Empfehlungsgrad	Literaturbelege	Methodische Bewertung
				bezüglich spezifischer Aussagen können daraus nicht abgeleitet werden.
	<p>Glucose (15–20 g) is the preferred treatment for the conscious individual with hypoglycemia, although any form of carbohydrate that contains</p> <p>Glucose may be used. Fifteen minutes after treatment, if SMBG shows continued hypoglycemia, the treatment should be repeated. Once SMBG returns to normal, the individual should consume a meal or snack to prevent recurrence of hypoglycemia. E</p>	Grade E	n.a. Hintergrundtext mit Literaturangaben vorhanden	
	<p>Glucagon should be prescribed for all individuals at an increased risk of severe hypoglycemia, and caregivers or family members of these individuals should be instructed on its administration. Glucagon administration is not limited to health care professionals. E</p>	Grade E	n.a. Hintergrundtext mit Literaturangaben vorhanden	
	<p>Hypoglycemia unawareness or one or more episodes of severe hypoglycemia should trigger reevaluation of the treatment regimen. E</p>	Grade E	n.a. Hintergrundtext mit Literaturangaben vorhanden	
	<p>Insulin-treated patients with hypoglycemia unawareness or an episode of severe hypoglycemia should be advised to raise their glycemic targets to strictly avoid further hypoglycemia for at least several weeks in order to partially reverse hypoglycemia unawareness and reduce risk of future episodes. A</p>	Grade A	n.a. Hintergrundtext mit Literaturangaben vorhanden	
	<p>Ongoing assessment of cognitive function is suggested with increased vigilance for hypoglycemia by the clinician, patient,</p>	Grade B	n.a. Hintergrundtext mit Literaturangaben vorhanden	

Quelle	Text	Evidenz- bzw. Empfehlungsgrad	Literaturbelege	Methodische Bewertung
	and caregivers if low cognition and/or declining cognition is found. B			
CDA 2013 (15)	<p>1. In adult patients with DKA, a protocol should be followed that incorporates the following principles of treatment:</p> <ul style="list-style-type: none"> 1) fluid resuscitation, 2) avoidance of hypokalemia, 3) insulin administration, 4) avoidance of rapidly falling serum osmolality, and 5) search for precipitating cause (as illustrated in Figure 1) [Grade D, Consensus]. <p>2. In adult patients with HHS, a protocol should be followed that incorporates the following principles of treatment:</p> <ul style="list-style-type: none"> 1) fluid resuscitation, 2) avoidance of hypokalemia, 3) avoidance of rapidly falling serum osmolality, 4) search for precipitating cause, and 5) possibly insulin to further reduce hyperglycemia (as illustrated in Figure 1) [Grade D, Consensus]. <p>3. Point-of-care capillary beta-hydroxybutyrate may be measured in the hospital in patients with type 1 diabetes with capillary glucose >14.0 mmol/L to screen for DKA, and a beta-hydroxybutyrate >1.5 mmol/L warrants further testing for DKA [Grade B, Level 2 (10-15)].</p>	<p>LoE: Consensus GoR: D</p> <p>LoE: Consensus GoR: D</p>	<p>n.a.</p> <p>n.a.</p> <p>10. Charles RA, Bee YM, Eng PH, Goh SY. Point-of-care blood ketone testing: screening for diabetic ketoacidosis at the emergency department. Singapore Med J 2007; 48: 986-9. 11. Naunheim R, Jang TJ, Banet G, et al. Point-of-care test identifies diabetic ketoacidosis at triage. Acad Emerg Med 2006; 13: 683-5. 12. Sefedini E, Prasek M, Metelko Z, et al. Use of capillary beta hydroxybutyrate for</p>	<p>Die Erstellung der Leitlinie ist gemäß DELBI als methodisch hochwertig zu bewerten. Aussagen zur methodischen Qualität bezüglich spezifischer Aussagen können daraus nicht abgeleitet werden.</p>

Quelle	Text	Evidenz- bzw. Empfehlungsgrad	Literaturbelege	Methodische Bewertung
			<p>the diagnosis of diabetic ketoacidosis at emergency room: Our one-year experience. Diabetol Croat 2008; 37: 73-8.</p> <p>13. MacKay L, Lyall MJ, Delaney S, et al. Are blood ketones a better predictor than urine ketones of acid base balance in diabetic ketoacidosis? Pract Diabetes Int 2010; 27: 396-9.</p> <p>14. Bektas F, Eray O, Sari R, Akbas H. Point of care blood ketone testing of diabetic patients in the emergency department. Endocr Res 2004; 30: 395-402.</p> <p>15. Harris S, Ng R, Syed H, Hillson R. Near patient blood ketone measurements and their utility in predicting diabetic ketoacidosis. Diabet Med 2004; 22: 221-4.</p>	
	<p>4. In individuals with DKA, IV 0.9% sodium chloride should be administered initially at 500 mL/h for 4 hours, then 250 mL/h for 4 hours [Grade B, Level 2 (32)] with consideration of a higher initial rate (1-2 L/h) in the presence of shock [Grade D, Consensus]. For persons with a HHS, IV fluid administration should be individualized based on the patient's needs [Grade D, Consensus].</p> <p>5. In individuals with DKA, an infusion of short-acting IV insulin of 0.10 U/ kg/h should be used ([Grade B, Level 2 (36, 37)]. The insulin infusion rate should be maintained until the resolution of ketosis [Grade B, Level 2 (42)] as measured by the normalization of the plasma anion gap [Grade D, Consensus]. Once the plasma glucose concentration reaches 14.0 mmol/L, IV dextrose</p>	LoE: 2 GoR: B LoE: Consensus GoR: D	<p>32. Adrogue HJ, Barrero J, Eknayan G. Salutary effects of modest fluid replacement in the treatment of adults with diabetic ketoacidosis. JAMA 1989; 262: 2108-13.</p>	
		LoE: 2 GoR: B LoE: Consensus GoR: D	<p>36. Heber D, Molitch ME, Sperling MA. Low-dose continuous insulin therapy for diabetic ketoacidosis. Prospective comparison with “conventional” insulin therapy. Arch Intern Med 1977; 137: 1377-80.</p> <p>37. Butkiewicz EK, Leibson CL, O'Brien</p>	

Quelle	Text	Evidenz- bzw. Empfehlungsgrad	Literaturbelege	Methodische Bewertung
	should be started to avoid hypoglycemia [Grade D, Consensus].		PC, et al. Insulin therapy for diabetic ketoacidosis. Bolus insulin injection versus continuous insulin infusion. Diabetes Care 1995; 18: 1187-90. 42. Umpierrez GE, Latif K, Stoever J, et al. Efficacy of subcutaneous insulin lispro versus continuous intravenous regular insulin for the treatment of patients with diabetic ketoacidosis. Am J Med 2004; 117: 291-6.	

Aktualisierung Kapitel: Verlaufskontrolle

Quelle	Text	Evidenz- bzw. Empfehlungsgrad	Literaturbelege	Methodische Bewertung
ADA 2015 (7)	When prescribed as part of a broader educational context, self-monitoring of blood glucose (SMBG) results may help to guide treatment decisions and/or self-management for patients using less frequent insulin injections B or noninsulin therapies.	GoR: E	n.a. Hintergrundtext mit Literaturangaben vorhanden	Die Erstellung der Leitlinie ist gemäß DELBI von geringer methodischer Qualität. U.a. fehlen Angaben zur Literaturrecherche, Studienbewertung und zur Methodik der Erstellung der Empfehlungen. Aussagen zur methodischen Qualität bezüglich spezifischer Aussagen können daraus nicht abgeleitet werden.
	When prescribing SMBG, ensure that patients receive ongoing instruction and regular evaluation of SMBG technique, SMBG results, and their ability to use SMBG data to adjust therapy.	GoR: E	n.a. Hintergrundtext mit Literaturangaben vorhanden	
	Most patients on intensive insulin regimens (multiple-dose insulin	GoR: B	n.a. Hintergrundtext mit Literaturangaben	

Quelle	Text	Evidenz- bzw. Empfehlungsgrad	Literaturbelege	Methodische Bewertung
	or insulin pump therapy) should consider SMBG prior to meals and snacks, occasionally postprandially, at bedtime, prior to exercise, when they suspect low blood glucose, after treating low blood glucose until they are normoglycemic, and prior to critical tasks such as driving.		vorhanden	
	When used properly, continuous glucose monitoring (CGM) in conjunction with intensive insulin regimens is a useful tool to lower A1C in selected adults (aged \geq 25 years) with type 1 diabetes.	GoR: A	n.a. Hintergrundtext mit Literaturangaben vorhanden	
	Although the evidence for A1C lowering is less strong in children, teens, and younger adults, CGM may be helpful in these groups. Success correlates with adherence to ongoing use of the device.	GoR: B	n.a. Hintergrundtext mit Literaturangaben vorhanden	
	CGM may be a supplemental tool to SMBG in those with hypoglycemia unawareness and/or frequent hypoglycemic episodes.	GoR: C	n.a. Hintergrundtext mit Literaturangaben vorhanden	
	Given variable adherence to CGM, assess individual readiness for continuing CGM use prior to prescribing.	GoR: E	n.a. Hintergrundtext mit Literaturangaben vorhanden	
	When prescribing CGM, robust diabetes education, training, and support are required for optimal CGM implementation and ongoing use.	GoR: E	n.a. Hintergrundtext mit Literaturangaben vorhanden	
	People who have been successfully using CGM should have continued access after they turn 65 years of age.	GoR: E	n.a. Hintergrundtext mit Literaturangaben vorhanden	
CDA 2013 (16)	For most individuals with diabetes, A1C should be measured every 3 months to ensure that glycemic goals are being met or maintained. Testing at least every 6 months should be performed in adults during periods of treatment and lifestyle stability when glycemic targets have been consistently achieved [Grade D,	LoE: Consensus GoR: D		Die Erstellung der Leitlinie ist gemäß DELBI als methodisch hochwertig zu bewerten. Aussagen zur methodischen Qualität bezüglich spezifischer Aussagen können

Quelle	Text	Evidenz- bzw. Empfehlungsgrad	Literaturbelege	Methodische Bewertung
	<p>Consensus].</p> <p>For individuals using insulin more than once a day, SMBG should be used as an essential part of diabetes self-management [Grade A, Level 1 (21), for type 1 diabetes; Grade C, Level 3 (10), for type 2 diabetes] and should be undertaken at least 3 times per day [Grade C, Level 3 (10,18)] and include both pre- and postprandial measurements [Grade C, Level 3 (18,19,73)]. In those with type 2 diabetes on once-daily insulin in addition to oral antihyperglycemic agents, testing at least once a day at variable times is recommended [Grade D, Consensus].</p>	LoE: 1 GoR: A LoE: 3 GoR: C LoE: Consensus GoR: D	21. Epidemiology of severe hypoglycemia in the Diabetes Control and Complications Trial. The DCCT Research Group. Am J Med 1991; 90: 450-9. 10. Karter AJ, Ackerson LM, Darbinian JA, et al. Self-monitoring of blood glucose levels and glycemic control: the Northern California Kaiser Permanente Diabetes Registry. Am J Med 2001; 111: 1-9. 18. Sheppard P, Bending JJ, Huber JW. Pre- and post-prandial capillary glucose self-monitoring achieves better glycaemic control than pre-prandial only monitoring. A study in insulin treated diabetic patients. Practical Diabetes Int 2005; 22: 15-22. 19. Murata GH, Shah JH, Hoffman RM, et al, Diabetes Outcomes in Veterans Study (DOVES). Intensified blood glucose monitoring improves glycemic control in stable, insulin-treated veterans with type 2 diabetes: the Diabetes Outcomes in Veterans Study (DOVES). Diabetes Care 2003; 26: 1759-63. 73. Rohlfing CL, Wiedmeyer HM, Little RR, et al. Defining the relationship between plasma glucose and HbA(1c): analysis of glucose profiles and HbA(1c) in the Diabetes Control and Complications Trial. Diabetes Care 2002; 25: 275-8.	daraus nicht abgeleitet werden.

Quelle	Text	Evidenz- bzw. Empfehlungsgrad	Literaturbelege	Methodische Bewertung
	<p>For individuals with type 2 diabetes not receiving insulin therapy, SMBG recommendations should be individualized depending on type of antihyperglycemic agents, level of glycemic control and risk of hypoglycemia [Grade D, Consensus].</p> <p>When glycemic control is not being achieved, SMBG should be instituted [Grade B, Level 2 (33, 38)] and should include periodic pre- and postprandial measurements and training of healthcare providers and patients on methods to modify lifestyle and medications in response to SMBG values [Grade B, Level 2 (17)].</p> <p>If achieving glycemic targets or receiving medications not associated with hypoglycemia, infrequent SMBG is appropriate [Grade D, Consensus].</p>	<p>LoE: Consensus GoR: D</p> <p>LoE: 2 GoR: B</p> <p>LoE: Consensus GoR: D</p>	<p>33. Davis WA, Bruce DG, Davis TM. Does self-monitoring of blood glucose improve outcome in type 2 diabetes? The Fremantle Diabetes Study. Diabetologia 2007; 50: 510-5.</p> <p>38. Poolsup N, Suksomboon N, Rattanassookchit S. Meta-analysis of the benefits of self-monitoring of blood glucose on glycemic control in type 2 diabetes patients: an update. Diab Technol Ther 2009; 11: 775-84.</p> <p>17. Polonsky WH, Fisher L, Schikman CH, et al. Structured self-monitoring of blood glucose significantly reduces A1C levels in poorly controlled, noninsulintreated type 2 diabetes: results from the Structured Testing Program study. Diabetes Care 2011; 34: 262-7.</p>	
	In many situations, for all individuals with diabetes, more frequent testing should be undertaken to provide information needed to make behavioural or treatment adjustments required to achieve desired glycemic targets and avoid risk of hypoglycemia [Grade D, Consensus].	LoE: Consensus GoR: D		
	In people with type 1 diabetes, real-time continuous glucose monitoring may be used to improve glycemic control [Grade B, Level 2 (58)] and reduce hypoglycemia [Grade B, Level 2 (65, 69)].	LoE: 2 GoR: B	<p>58. Deiss D, Bolinder J, Riveline JP, et al. Improved glycemic values control in poorly controlled patients with type 1 diabetes using real-time continuous glucose monitoring. Diabetes Care 2006; 29: 2730-2.</p> <p>65. Battelino T, Phillip M, Bratina N, et al.</p>	

Quelle	Text	Evidenz- bzw. Empfehlungsgrad	Literaturbelege	Methodische Bewertung
			<p>Effect of continuous glucose monitoring on hypoglycemia in type 1 diabetes. Diabetes Care 2011; 34: 795-800.</p> <p>69. Garg S, Voelmlle M, Beatson C, et al. Use of continuous glucose monitoring in subjects with type 1 diabetes on multiple daily injections versus continuous subcutaneous insulin infusion therapy. Diabetes Care 2011; 34: 574-9.</p>	
	<p>In order to ensure accuracy of BG meter readings, meter results should be compared with laboratory measurement of simultaneous venous FPG at least annually and when indicators of glycemic control do not match meter readings [Grade D, Consensus].</p> <p>Individuals with type 1 diabetes should be instructed to perform ketone testing during periods of acute illness accompanied by elevated BG, when preprandial BG levels remain >14.0 mmol/L or in the presence of symptoms of DKA [Grade D, Consensus]. Blood ketone testing methods may be preferred over urine ketone testing, as they have been associated with earlier detection of ketosis and response to treatment [Grade B, Level 2 (55)].</p>	<p>LoE: Consensus GoR: D</p> <p>LoE: 2 GoR: B</p>		
			<p>55. Bektas F, Eray O, Sari R, et al. Point of care blood ketone testing of diabetic patients in the emergency department. Endocr Res 2004; 30: 395-402.</p>	

10.9 Appendix Evidenzrecherche

10.9.1 Appendix A: Level of Evidence “Evidenzniveau DGG”

Evidenzklassen (EK) [modifiziert nach AHCPR, 1992; SIGN, 1996]	
Ia	Evidenz aufgrund von Metaanalysen randomisierter, kontrollierter Studien
Ib	Evidenz aufgrund mindestens einer randomisierten, kontrollierten Studie
IIa	Evidenz aufgrund mindestens einer gut angelegten, kontrollierten Studie ohne Randomisation
IIb	Evidenz aufgrund mindestens einer gut angelegten, nicht randomisierten und nicht kontrollierten klinischen Studie, z. B. Kohortenstudie
III	Evidenz aufgrund gut angelegter, nicht experimenteller, deskriptiver Studien, wie z. B. Vergleichsstudien, Korrelationsstudien und Fall-Kontroll-Studien
IV	Evidenz aufgrund von Berichten der Experten-Ausschüsse oder Expertenmeinungen und/oder klinischer Erfahrung anerkannter Autoritäten

10.9.2 Appendix B: Level of Evidence nach “SIGN”

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

10.9.3 Appendix C: Cochrane Risk of Bias

Domain	Description	Review authors' judgement
Sequence generation	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.	Was the allocation sequence adequately generated?
Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.	Was allocation adequately concealed?
Blinding of participants, personnel and outcome assessors <i>Assessments should be made for each main outcome (or class of outcomes)</i>	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Was knowledge of the allocated intervention adequately prevented during the study?
Incomplete outcome data <i>Assessments should be made for each main outcome (or class of outcomes)</i>	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.	Were incomplete outcome data adequately addressed?
Selective outcome reporting	State how the possibility of selective outcome reporting was examined by the review authors, and what was found.	Are reports of the study free of suggestion of selective outcome reporting?
Other sources of bias	State any important concerns about bias not addressed in the other domains in the tool. If particular questions/entries were pre-specified in the review's protocol, responses should be provided for each question/entry.	Was the study apparently free of other problems that could put it at a high risk of bias?

10.9.4 Appendix D: QUADAS II

Domain	Patient Selection	Index Test	Reference Standard	Flow and Timing
Description	Describe methods of patient selection Describe included patients (previous testing, presentation, intended use of index test, and setting)	Describe the index test and how it was conducted and interpreted	Describe the reference standard and how it was conducted and interpreted	Describe any patients who did not receive the index tests or reference standard or who were excluded from the 2 × 2 table (refer to flow diagram) Describe the interval and any interventions between index tests and the reference standard
Signaling questions (yes, no, or unclear)	Was a consecutive or random sample of patients enrolled? Was a case-control design avoided? Did the study avoid inappropriate exclusions?	Were the index test results interpreted without knowledge of the results of the reference standard? If a threshold was used, was it prespecified?	Is the reference standard likely to correctly classify the target condition? Were the reference standard results interpreted without knowledge of the results of the index test?	Was there an appropriate interval between index tests and reference standard? Did all patients receive a reference standard? Did all patients receive the same reference standard? Were all patients included in the analysis?
Risk of bias (high, low, or unclear)	Could the selection of patients have introduced bias?	Could the conduct or interpretation of the index test have introduced bias?	Could the reference standard, its conduct, or its interpretation have introduced bias?	Could the patient flow have introduced bias?
Concerns about applicability (high, low, or unclear)	Are there concerns that the included patients do not match the review question?	Are there concerns that the index test, its conduct, or its interpretation differ from the review question?	Are there concerns that the target condition as defined by the reference standard does not match the review question?	

10.9.5 Appendix E: AMSTAR

AMSTAR – a measurement tool to assess the methodological quality of systematic reviews.

1. Was an 'a priori' design provided?

The research question and inclusion criteria should be established before the conduct of the review.

- Yes
- No
- Can't answer
- Not applicable

Note: Need to refer to a protocol, ethics approval, or pre-determined/a priori published research objectives to score a "yes."

2. Was there duplicate study selection and data extraction?

There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.

- Yes
- No
- Can't answer
- Not applicable

Note: 2 people do study selection, 2 people do data extraction, consensus process or one person checks the other's work.

3. Was a comprehensive literature search performed?

At least two electronic sources should be searched. The report must include years and databases used (e.g., Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.

- Yes
- No
- Can't answer
- Not applicable

Note: If at least 2 sources + one supplementary strategy used, select "yes" (Cochrane register/Central counts as 2 sources; a grey literature search counts as supplementary).

4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?

The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.

- Yes
- No
- Can't answer
- Not applicable

Note: If review indicates that there was a search for "grey literature" or "unpublished literature," indicate "yes." SIGLE database, dissertations, conference proceedings, and trial registries are all considered grey for this purpose. If searching a source that contains both grey and non-grey, must specify that they were searching for grey/unpublished lit.

5. Was a list of studies (included and excluded) provided?

A list of included and excluded studies should be provided.

- Yes
- No
- Can't answer
- Not applicable

Note: Acceptable if the excluded studies are referenced. If there is an electronic link to the list but the link is dead, select "no."

6. Were the characteristics of the included studies provided?

In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g., age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.

- Yes
- No
- Can't answer
- Not applicable

Note: Acceptable if not in table format as long as they are described as above.

7. Was the scientific quality of the included studies assessed and documented?

'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.

- Yes
- No
- Can't answer
- Not applicable

Note: Can include use of a quality scoring tool or checklist, e.g., Jadad scale, risk of bias, sensitivity analysis, etc., or a description of quality items, with some kind of result for EACH study ("low" or "high" is fine, as long as it is clear which studies scored "low" and which scored "high"; a summary score/range for all studies is not acceptable).

8. Was the scientific quality of the included studies used appropriately in formulating conclusions?

The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.

- Yes
- No
- Can't answer
- Not applicable

Note: Might say something such as "the results should be interpreted with caution due to poor quality of included studies." Cannot score "yes" for this question if scored "no" for question 7.

9. Were the methods used to combine the findings of studies appropriate?

For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e., Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e., is it sensible to combine?).

- Yes
- No
- Can't answer
- Not applicable

Note: Indicate "yes" if they mention or describe heterogeneity, i.e., if they explain that they cannot pool because of heterogeneity/variability between interventions.

10. Was the likelihood of publication bias assessed?

An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test, Hedges-Olken).

- Yes
- No
- Can't answer
- Not applicable

Note: If no test values or funnel plot included, score "no". Score "yes" if mentions that publication bias could not be assessed because there were fewer than 10 included studies.

11. Was the conflict of interest included?

Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.

- Yes
- No
- Can't answer
- Not applicable

Note: To get a "yes," must indicate source of funding or support for the systematic review AND for each of the included studies.

Shea et al. BMC Medical Research Methodology 2007 7:10 doi:10.1186/1471-2288-7-10

Additional notes (in italics) made by Michelle Weir, Julia Worswick, and Carolyn Wayne based on conversations with Bev Shea and/or Jeremy Grimshaw in June and October 2008 and July and September 2010.

10.9.6 Appendix E – Liste der ausgeschlossenen Studien mit Gründen

Ausgeschlossene Volltexte - Rechercheauftrag 1

Ausgeschlossene Volltexte	Ausschlussgründe
Erqou, S., et al., Association between glycated haemoglobin and the risk of congestive heart failure in diabetes mellitus: systematic review and meta-analysis. Eur J Heart Fail, 2013. 15(2): p. 185-93.	E1
Yang, Y.F., et al., Elevated glycated hemoglobin levels may increase the risk of atrial fibrillation in patients with diabetes mellitus. International Journal of Clinical and Experimental Medicine, 2015. 8(3): p. 3271-3280.	E1
Monami, M., et al., Fasting and post-prandial glucose and diabetic complication. A meta-analysis. Nutr Metab Cardiovasc Dis, 2013. 23(7): p. 591-8.	E1
Brand-Miller, J., et al., Low-glycemic index diets in the management of diabetes: a meta-analysis of randomized controlled trials. Diabetes Care, 2003. 26(8): p. 2261-7.	E2
Thomas, D. and E.J. Elliott, Low glycaemic index, or low glycaemic load, diets for diabetes mellitus. Cochrane Database Syst Rev, 2009(1): p. CD006296.	E2
Bakris, G.L. and M. Molitch, Microalbuminuria as a risk predictor in diabetes: the continuing saga. Diabetes Care, 2014. 37(3): p. 867-75.	E2
Fernando, M.E., et al., Intensive versus conventional glycaemic control for treating diabetic foot ulcers. Cochrane Database Syst Rev, 2016(1): p. CD010764.	E2
Newman, D.J., et al., Systematic review on urine albumin testing for early detection of diabetic complications. Health Technol Assess, 2005. 9(30): p. iii-vi, xiii-163.	E2
Szypowska, A., et al., Long-acting insulin analogue detemir compared with NPH insulin in type 1 diabetes: a systematic review and meta-analysis. Pol Arch Med Wewn, 2011. 121(7-8): p. 237-46.	E2
Vardi, M., et al. Intermediate acting versus long acting insulin for type 1 diabetes mellitus. Cochrane Database of Systematic Reviews, 2008. DOI: 10.1002/14651858.CD006297.pub2.	E2
Bode, B.W. and S.K. Garg, THE EMERGING ROLE OF ADJUNCTIVE NON-INSULIN ANTIHYPERGLYCEMIC THERAPY IN THE MANAGEMENT OF TYPE 1 DIABETES. Endocr Pract, 2016. 22(2): p. 220-30.	E3
Smith-Palmer, J., et al., Assessment of the association between glycemic variability and diabetes-related complications in type 1 and type 2 diabetes. Diabetes Res Clin Pract, 2014. 105(3): p. 273-84.	E3
Calissi, P.T. and L.A. Jaber, Peripheral diabetic neuropathy: current concepts in treatment. Ann Pharmacother, 1995. 29(7-8): p. 769-77.	E3
Cholesterol Treatment Trialists, C., et al., Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. Lancet, 2008. 371(9607): p. 117-25.	E3
Davidson, J.A., Treatment of the patient with diabetes: importance of maintaining target HbA(1c) levels. Curr Med Res Opin, 2004. 20(12): p. 1919-27.	E3
Jenkins, A.J., W.T. Garvey, and R.L. Klein, Lipoprotein abnormalities in type 1 diabetes. Current Opinion in Endocrinology and Diabetes, 2003. 10(4): p. 245-250.	E3

Ausgeschlossene Volltexte	Ausschlussgründe
Mazzone, T., Intensive glucose lowering and cardiovascular disease prevention in diabetes: reconciling the recent clinical trial data. Circulation, 2010. 122(21): p. 2201-11.	E3
Selvin, E., et al., Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. Ann Intern Med, 2004. 141(6): p. 421-31.	E3
Suh, S. and J.H. Kim, Glycemic variability: How do we measure it and why is it important? Diabetes and Metabolism Journal, 2015. 39(4): p. 273-282.	E3
Teleb, M., et al., Glycemic Control and Excess Cardiovascular Mortality in Type 1 Diabetes. Current Cardiology Reports, 2016. 18(3): p. 1-5.	E3
Nalysnyk, L., M. Hernandez-Medina, and G. Krishnarajah, Glycaemic variability and complications in patients with diabetes mellitus: evidence from a systematic review of the literature. Diabetes Obes Metab, 2010. 12(4): p. 288-98.	E3
Langendam, M., et al. Continuous glucose monitoring systems for type 1 diabetes mellitus. Cochrane Database of Systematic Reviews, 2012. DOI: 10.1002/14651858.CD008101.pub2.	E4
Misso Marie, L., et al. Continuous subcutaneous insulin infusion (CSII) versus multiple insulin injections for type 1 diabetes mellitus. Cochrane Database of Systematic Reviews, 2010. DOI: 10.1002/14651858.CD005103.pub2.	E4
Coster, S., et al., Monitoring blood glucose control in diabetes mellitus: a systematic review. Health Technol Assess, 2000. 4(12): p. i-iv, 1-93.	E4
Achieving and defining HbA1c targets in diabetes management. Diabetic Hypoglycemia, 2010. 3(1): p. 17-20.	E5
Wang, P.H., J. Lau, and T.C. Chalmers, Metaanalysis of the effects of intensive glycemic control on late complications of type I diabetes mellitus. Online J Curr Clin Trials, 1993. Doc No 60: p. [5023 words; 37 paragraphs].	E5
Ufkes, J.G.R., Diabetes mellitus: A review. Pharmaceutisch Weekblad, 1998. 133(1): p. 16-31.	E6

Ausgeschlossene Volltexte - Rechercheauftrag 2

Ausgeschlossene Volltexte	Ausschlussgründe
Hemmati, M., H. Babaei, and M. Abdolsalehei, Survey of the effect of biotin on glycemic control and plasma lipid concentrations in type 1 diabetic patients in Kermanshah in Iran (2008-2009). Oman Medical Journal, 2013. 28(3): p. 195-198.	E1
Kordonouri, O., et al., Sensor augmented pump therapy from onset of type 1 diabetes: late follow-up results of the Pediatric Onset Study. Pediatr Diabetes, 2012. 13(7): p. 515-8.	E1
Sherr, J.L., et al., Safety of nighttime 2-hour suspension of Basal insulin in pump-treated type 1 diabetes even in the absence of low glucose. Diabetes Care, 2014. 37(3): p. 773-9.	E1
Birkeland, K.I., et al., Insulin degludec in type 1 diabetes: a randomized controlled trial of a new-generation ultra-long-acting insulin compared with insulin glargine. Diabetes Care, 2011. 34(3): p. 661-5.	E2
Heller, S., C. Koenen, and B. Bode, Comparison of insulin detemir and insulin glargin in a basal-bolus regimen, with insulin aspart as the mealtime insulin,	E2

Ausgeschlossene Volltexte	Ausschlussgründe
in patients with type 1 diabetes: a 52-week, multinational, randomized, open-label, parallel-group, treat-to-target noninferiority trial. Clin Ther, 2009. 31(10): p. 2086-97.	
Little, S., et al., Comparison of Optimised MDI versus Pumps with or without Sensors in Severe Hypoglycaemia (the Hypo COMPaSS trial). BMC Endocr Disord, 2012. 12: p. 33.	E2
Garg, S.K., et al., Two-year efficacy and safety of AIR inhaled insulin in patients with type 1 diabetes: An open-label randomized controlled trial. Diabetes Technol Ther, 2009. 11 Suppl 2: p. S5-S16.	E2
Laurenzi, A., et al., Effects of carbohydrate counting on glucose control and quality of life over 24 weeks in adult patients with type 1 diabetes on continuous subcutaneous insulin infusion: a randomized, prospective clinical trial (GI-OCAR). Diabetes Care, 2011. 34(4): p. 823-7.	E2
Little, S.A., et al., Recovery of hypoglycemia awareness in long-standing type 1 diabetes: a multicenter 2 x 2 factorial randomized controlled trial comparing insulin pump with multiple daily injections and continuous with conventional glucose self-monitoring (HypoCOMPaSS). Diabetes Care, 2014. 37(8): p. 2114-22.	E2
Mathieu, C., et al., Efficacy and safety of insulin degludec in a flexible dosing regimen vs insulin glargin in patients with type 1 diabetes (BEGIN: Flex T1): a 26-week randomized, treat-to-target trial with a 26-week extension. J Clin Endocrinol Metab, 2013. 98(3): p. 1154-62.	E2
Nakae, R., et al., Medium-term effects of insulin degludec on patients with type 1 diabetes mellitus. Drugs R D, 2014. 14(2): p. 133-8.	E2
Onda, Y., et al., Comparison of glycemic variability in Japanese patients with type 1 diabetes receiving insulin degludec versus insulin glargin using continuous glucose monitoring: A randomized, cross-over, pilot study. Diabetes Res Clin Pract, 2016. 120((Onda Y.; Nishimura R., rimei@jikei.ac.jp; Ando K.; Takahashi H.; Tsujino D.; Utsunomiya K.) Division of Diabetes, Metabolism and Endocrinology, Department of Internal Medicine, Jikei University School of Medicine, Tokyo, Japan): p. 149-155.	E2
Pickup, J.C., Semi-closed-loop insulin delivery systems: early experience with low-glucose insulin suspend pumps. Diabetes Technol Ther, 2011. 13(7): p. 695-8.	E2
Brown, S.A., et al., Multinight "bedside" closed-loop control for patients with type 1 diabetes. Diabetes Technol Ther, 2015. 17(3): p. 203-9.	E2
Davies, M.J., et al., Efficacy and safety of insulin degludec given as part of basal-bolus treatment with mealtime insulin aspart in type 1 diabetes: A 26-week randomized, open-label, treat-to-target non-inferiority trial. Diabetes, Obesity and Metabolism, 2014. 16(10): p. 922-930.	E2
Frandsen, C.S., et al., Twelve-Week Treatment With Liraglutide as Add-on to Insulin in Normal-Weight Patients With Poorly Controlled Type 1 Diabetes: A Randomized, Placebo-Controlled, Double-Blind Parallel Study. Diabetes Care, 2015. 38(12): p. 2250-7.	E2
Haidar, A., et al., Glucose-responsive insulin and glucagon delivery (dual-hormone artificial pancreas) in adults with type 1 diabetes: a randomized crossover controlled trial. CMAJ, 2013. 185(4): p. 297-305.	E2
Hirsch, I.B., et al., Insulin degludec/insulin aspart administered once daily at	E2

Ausgeschlossene Volltexte	Ausschlussgründe
any meal, with insulin aspart at other meals versus a standard basal-bolus regimen in patients with type 1 diabetes: a 26-week, phase 3, randomized, open-label, treat-to-target trial. Diabetes Care, 2012. 35(11): p. 2174-81.	
Hirsch, I.B., et al., Safety and efficacy of insulin degludec/insulin aspart with bolus mealtime insulin aspart compared with standard basal-bolus treatment in people with Type 1 diabetes: 1-year results from a randomized clinical trial (BOOST® T1). Diabetic Medicine, 2016((Hirsch I.B., ihirsch@u.washington.edu) School of Medicine University of Washington Seattle, WA USA).	E2
Heller, S., et al., Insulin degludec, an ultra-longacting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 1 diabetes (BEGIN Basal-Bolus Type 1): a phase 3, randomised, open-label, treat-to-target non-inferiority trial. Lancet, 2012. 379(9825): p. 1489-97.	E2
Rubin, R.R., M. Peyrot, and S.S. Group, Health-related quality of life and treatment satisfaction in the Sensor-Augmented Pump Therapy for A1C Reduction 3 (STAR 3) trial. Diabetes Technol Ther, 2012. 14(2): p. 143-51.	E3
Bolli, G.B., et al., Comparison of a multiple daily insulin injection regimen (basal once-daily glargine plus mealtime lispro) and continuous subcutaneous insulin infusion (lispro) in type 1 diabetes: a randomized open parallel multicenter study. Diabetes Care, 2009. 32(7): p. 1170-6.	E3
Ruiz-De-Adana, M.S., et al., Comparison between a multiple daily insulin injection regimen (basal once-daily glargine plus mealtime lispro) and continuous subcutaneous insulin infusion (lispro) using continuous glucose monitoring in metabolically optimized type 1 diabetes patients: A randomized open-labelled parallel study. Med Clin (Barc), 2016. 146(6): p. 239-246.	E3
Dejgaard, T.F., et al., Efficacy and safety of the glucagon-like peptide-1 receptor agonist liraglutide added to insulin therapy in poorly regulated patients with type 1 diabetes--a protocol for a randomised, double-blind, placebo-controlled study: the Lira-1 study. BMJ Open, 2015. 5(4): p. e007791.	E3
Home, P.D., et al., New Insulin Glargine 300 Units/mL Versus Glargine 100 Units/mL in People With Type 1 Diabetes: A Randomized, Phase 3a, Open-Label Clinical Trial (EDITION 4). Diabetes Care, 2015. 38(12): p. 2217-25.	E3
Kuroda, A., et al., Carbohydrate-to-insulin ratio is estimated from 300-400 divided by total daily insulin dose in type 1 diabetes patients who use the insulin pump. Diabetes Technol Ther, 2012. 14(11): p. 1077-80.	E3
Lachin, J.M., et al., Update on cardiovascular outcomes at 30 years of the diabetes control and complications trial/epidemiology of diabetes interventions and complications study. Diabetes Care, 2014. 37(1): p. 39-43.	E4
de Boer, I.H. and D.E.R. Group, Kidney disease and related findings in the diabetes control and complications trial/epidemiology of diabetes interventions and complications study. Diabetes Care, 2014. 37(1): p. 24-30.	E4
de Boer, I.H., et al., Long-term renal outcomes of patients with type 1 diabetes mellitus and microalbuminuria: an analysis of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications cohort. Arch Intern Med, 2011. 171(5): p. 412-20.	E4
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Berard, L., B. Cameron, and V. Woo, Pen needle preference in a population of Canadians with diabetes: results from a recent patient survey. <i>Can J Diabetes</i> , 2015. 39(3): p. 206-9.	E1
Buse, J.B., et al. The DURAbility of Basal versus Lispro mix 75/25 insulin Efficacy (DURABLE) trial: comparing the durability of lispro mix 75/25 and glargin. <i>Diabetes care</i> , 2011. 249-55 DOI: 10.2337/dc10-1701.	E1
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Otto-Buczkowska, E., P. Jarosz-Chobot, and Ł. Machnica, Diabetes mellitus type 1, type 2 or type 1.5 - Dilemmas in making proper diagnosis. <i>Diabetologia</i>	E1

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Kilpatrick E.S._Insulin Resistance, the Metabolic Syndrome, and Complication Risk_2007	E2
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Altinova, A., et al., Type 1 diabetes mellitus and insulin resistance: Review. Turkiye Klinikleri Journal of Medical Sciences, 2007. 27(2): p. 220-223.	E6
Dib, S.A., [Insulin resistance and metabolic syndrome in type 1 diabetes mellitus]. Arq Bras Endocrinol Metabol, 2006. 50(2): p. 250-63.	E7
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Nwosu, B.U., et al., A Randomized, Double-Blind, Placebo-Controlled Trial of Adjunctive Metformin Therapy in Overweight/Obese Youth with Type 1 Diabetes. PLoS One, 2015. 10(9): p. e0137525.	E1
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Pang, T.T. and P. Narendran, Addressing insulin resistance in Type 1 diabetes. Diabet Med, 2008. 25(9): p. 1015-24.	E4
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Scheen, A.J., [Limited add-on value of oral glucose-lowering agents in type 1 diabetes]. <i>Rev Med Liege</i> , 2013. 68(1): p. 16-21.	E7
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Muller, U., [Care of people with diabetes in the pharmacy]. <i>Pharm Unserer Zeit</i> , 2012. 41(4): p. 313-22.	E1
Nimri, R., et al., The "Glucositter" overnight automated closed loop system for type 1 diabetes: A randomized crossover trial. <i>Pediatr Diabetes</i> , 2013. 14(3): p. 159-167.	E1
Nor Azlin, M.I., et al., Safety and tolerability of once or twice daily neutral protamine hagedorn insulin in fasting pregnant women with diabetes during Ramadan. <i>J Obstet Gynaecol Res</i> , 2011. 37(2): p. 132-7.	E1
Riveline, J.P., et al., Assessment of patient-led or physician-driven continuous glucose monitoring in patients with poorly controlled type 1 diabetes using basal-bolus insulin regimens: A 1-year multicenter study. <i>Diabetes Care</i> , 2012. 35(5): p. 965-971.	E1
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New, J.P., et al., Continuous glucose monitoring in people with diabetes: The randomized controlled Glucose Level Awareness in Diabetes Study (GLADIS). <i>Diabetic Medicine</i> , 2015. 32(5): p. 609-617.	E1
Poolsup, N., N. Suksomboon, and A.M. Kyaw, Systematic review and meta-analysis of the effectiveness of continuous glucose monitoring (CGM) on glucose control in diabetes. <i>Diabetology and Metabolic Syndrome</i> , 2013. 5(1).	E1
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Hermanides, J., et al., Sensor-augmented pump therapy lowers HbA1c in suboptimally controlled Type1 diabetes; a randomized controlled trial. <i>Diabetic Medicine</i> , 2011. 28(10): p. 1158-1167.	E2
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Kamble, S., K.A. Schulman, and S.D. Reed, Cost-effectiveness of sensor-augmented pump therapy in adults with type 1 diabetes in the United States. <i>Value in Health</i> , 2012. 15(5): p. 632-638.	E2
Kamble, S., et al., Patient time costs associated with sensor-augmented insulin pump therapy for type 1 diabetes: results from the STAR 3 randomized trial. <i>Med Decis Making</i> , 2013. 33(2): p. 215-224.	E2
Klonoff, D.C., et al., ASPIRE In-Home: rationale, design, and methods of a study to evaluate the safety and efficacy of automatic insulin suspension for nocturnal hypoglycemia. <i>J Diabetes Sci Technol</i> , 2013. 7(4): p. 1005-10.	E2
Perkins, B.A., et al., Sensor-augmented pump and multiple daily injection therapy in the United States and Canada: post-hoc analysis of a randomized controlled trial. <i>Can J Diabetes</i> , 2015. 39(1): p. 50-4.	E2
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Ausgeschlossene Volltexte	Ausschlussgründe
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Ausgeschlossene Volltexte	Ausschlussgründe
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10.10 Literaturverzeichnis zum Anhang 1

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11 Anhang: Interessenkonflikte

11.1 Formular zur Erklärung von Interessen



Erklärung von Interessen

(Titel, AWMF-Registernummer)

zu Händen

(Leitlinienkoordinator)

Vorbemerkung

Alle Mitglieder der Leitliniengruppe sind gehalten, die nachstehende Erklärung von Interessen auszufüllen. Die Erklärung wird gegenüber dem Leitlinienkoordinator abgegeben. Dies soll bereits zu Beginn des Leitlinienprojekts erfolgen bzw. zu dem Zeitpunkt, an dem die Mitglieder ihre Teilnahme am Leitlinienprojekt gegenüber dem Koordinator bestätigen. Bei länger andauernden Projekten ist eine Erneuerung der Erklärung einmal pro Jahr bis zum Abschluss der Leitlinienentwicklung, zumindest aber vor der Konsensfindung, erforderlich.

In der Erklärung sind alle Interessen aufzuführen, unabhängig davon, ob der/die Erklärende selbst darin einen thematischen Bezug zur Leitlinie oder einen Interessenkonflikt sieht oder nicht. Ob Interessenkonflikte bestehen und ob dadurch die erforderliche Neutralität für die Mitarbeit bei der Leitlinienentwicklung in Frage gestellt ist oder in welchen speziellen Bereichen /Fragestellungen der Leitlinie das professionelle Urteilsvermögen eines Experten durch sekundäre Interessen beeinflusst sein könnte, ist durch einen Dritten zu bewerten und in der Leitliniengruppe zu diskutieren. Die Erklärung betrifft Interessen innerhalb des laufenden Jahres sowie der zurückliegenden 3 Jahre.

Die Originale der Erklärungen verbleiben vertraulich beim Leitlinienkoordinator. Die Inhalte der Erklärungen sind in der Langfassung der Leitlinie bzw. im Leitlinienreport in standardisierter Zusammenfassung offen darzulegen. Ergänzend sind das Verfahren der Sammlung und Bewertung der Erklärungen sowie die Ergebnisse der Diskussion zum Umgang mit Interessenkonflikten darzulegen.

AWMF-Formular zur Erklärung von Interessen im Rahmen von Leitlinienvorhaben
Betaversion für Praxistest, Stand 29.06.2016

Erklärung

1. Allgemeine Angaben

Name, Vorname, Titel		
Arbeitgeber / Institution	Gegenwärtig	Früher(e) innerhalb des laufenden Jahres oder der 3 Kalenderjahre davor
Position / Funktion in der Institution		
Adresse		
e-mail-Adresse		
Bei Rückfragen telefonisch zu erreichen unter		
Funktion in der Leitliniengruppe		
Datum		
Zeitraum, auf den sich die Erklärung bezieht		

2. Direkte, finanzielle Interessen

Hier werden entsprechend §139b SGB V finanzielle Beziehungen zu Unternehmen, Institutionen oder Interessenverbänden im Gesundheitswesen erfasst. Haben Sie oder die Einrichtung, für die Sie tätig sind, innerhalb des laufenden Jahres oder der 3 Kalenderjahre davor Zuwendungen erhalten von Unternehmen der Gesundheitswirtschaft (z.B. Arzneimittelindustrie, Medizinproduktindustrie), industriellen Interessenverbänden, kommerziell orientierten Auftragsinstituten, Versicherungen/Versicherungsträgern, oder von öffentlichen Geldgebern (z.B. Ministerien), Körperschaften/Einrichtungen der Selbstverwaltung, Stiftungen, oder anderen Geldgebern? Machen Sie bitte in folgender Tabelle zu allen zutreffenden Aspekten konkrete Angaben.

Art der Beziehung/Tätigkeit	Name des/der Kooperationspartner/s	Zeitraum der Beziehung/Tätigkeit ¹	Thema, Bezug zur Leitlinie ²	Art der Zuwendung ³	Höhe der Zuwendung ⁴	Empfänger ⁵
Berater-/Gutachtertätigkeit						
Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)						
Vortrags-/oder Schulungstätigkeit						
Autoren-/oder Coautorenschaft						
Forschungsvorhaben/Durchführung klinischer Studien						
Eigentümerinteressen (Patent, Urheberrecht, Aktienbesitz ⁶)						

¹ Innerhalb des Erfassungszeitraums, d.h. im gegenwärtigen und den zurückliegenden 3 Jahren, Angabe: von (Monat/Jahr) bis (Monat/Jahr)

² Angabe des Themas (Freitext), zusätzlich Angabe einer Selbsteinschätzung des Bezugs zur Leitlinie: „Nein“ oder „Ja“

³ Honorar, Drittmittel, geldwerte Vorteile (z.B. Personal- oder Sachmittel; Reisekosten, Teilnahmegebühren, Bewirtung i.R. von Veranstaltungen), Verkaufs Lizenz

⁴ Bitte Schwellenwerte angeben: a) < 1.000 €, b) < 5.000, c) < 10.000 €, d) < 50.000 €, e) < 100.000 €, f) > 100.000 €. Die Angaben beziehen sich auf die Gesamtsumme der Zuwendungen für eine angegebene Tätigkeit über den Erfassungszeitraum, Angabe: von (Monat/Jahr) bis (Monat/Jahr). Diese Angaben werden vertraulich behandelt.

⁵ Bitte angeben: a) wenn Sie persönlich Empfänger der Zuwendung sind oder b) wenn es die Institution ist, für die Sie tätig sind und Sie innerhalb Ihrer Institution direkt entscheidungsverantwortlich für die Verwendung der Zuwendung/Mittel sind. Wenn Sie nicht direkt entscheidungsverantwortlich sind, sind keine Angaben erforderlich.

⁶ Angaben zu Mischfonds sind nicht erforderlich

3. Indirekte, Interessen

Hier werden persönliche Beziehungen zu Interessenverbänden im Gesundheitswesen, „intellektuelle“, akademische, und wissenschaftliche Interessen oder Standpunkte sowie Schwerpunkte klinischer Tätigkeiten/Einkommensquellen erfasst (für den Zeitraum des laufenden Jahres oder der 3 Kalenderjahre davor). Hierunter fallen auch solche, die indirekt mit finanziellen Interessen verbunden sein können.

- Sind oder waren Sie in Wissenschaftlichen Fachgesellschaften, Berufsverbänden, Institutionen der Selbstverwaltung, Patientenselbsthilfegruppen, Verbrauchervertretenen oder anderen Verbänden aktiv? Wenn ja, in welcher Funktion (z.B. Mandatsträger für diese/andere Leitlinien, Vorstand)?
- Können Sie Schwerpunkte Ihrer wissenschaftlichen und /oder klinischen Tätigkeiten benennen? Fühlen Sie sich bestimmten „Schulen“ zugehörig?
- Waren Sie an der inhaltlichen Gestaltung von Fortbildungen federführend beteiligt?
- Haben Sie persönliche Beziehungen (als Partner oder Verwandter 1. Grades) zu einem Vertretungsberechtigten eines Unternehmens der Gesundheitswirtschaft?

Machen Sie bitte in folgender Tabelle zu allen zutreffenden Aspekten konkrete Angaben.

Art der Beziehung/Tätigkeit	Namen / Schwerpunkte (bitte konkret benennen)	Zeitraum der Beziehung/ Tätigkeit ⁷	Themenbezug zur Leitlinie ⁸
Mitgliedschaft /Funktion in Interessenverbänden			
Schwerpunkte wissenschaftlicher Tätigkeiten, Publikationen			
Schwerpunkte klinischer Tätigkeiten			
Federführende Beteiligung an Fortbildungen/Ausbildungsinstituten			
Persönliche Beziehungen (als Partner oder Verwandter 1. Grades) zu einem Vertretungsberechtigten eines Unternehmens der Gesundheitswirtschaft			

⁷ Innerhalb des Erfassungszeitraums, d.h. im gegenwärtigen und den zurückliegenden 3 Jahren, Angabe: von (Monat/Jahr) bis (Monat/Jahr)

⁸ Angabe einer Selbsteinschätzung „Nein“ oder „Ja“

4. Sonstige Interessen

Sehen Sie andere Aspekte oder Umstände, die von Dritten als einschränkend in Bezug auf Ihre Objektivität oder Unabhängigkeit wahrgenommen werden könnten?

Ich erkläre hiermit, dass ich alle mir derzeit bekannten Umstände aufgeführt habe, die gegebenenfalls zu einem persönlichen Interessenkonflikt bei der themenbezogenen Mitwirkung bei der Erstellung der Leitlinie führen können. Ich erkläre weiterhin, dass ich die Diskussion der Erklärungen anderer Mitglieder in der Leitliniengruppe absolut vertraulich behandeln werde. Ich bin darüber informiert, dass die Angaben in standardisierter Zusammenfassung mit der Leitlinie/in einem begleitenden Leitlinienreport veröffentlicht werden, und dass das vorliegende Formular vor der Einsicht unberechtigter Dritter geschützt aufbewahrt wird. Hiermit bin ich einverstanden.

Datum

Unterschrift

Ergänzende Hinweise

- Bitte füllen Sie das Formular vollständig aus.
- Falls Sie zu bestimmten Fragen keine Angaben machen können oder wollen, begründen Sie dies bitte.
- Bitte speichern Sie das ausgefüllte Formular und senden es an das Leitliniensekretariat: xxx@yyy.zz

11.2 Übersicht der Interessenkonflikte

	Berater- bzw. Gutachtertätigkeit ¹	Mitarbeit in einem wissenschaftlichen Beirat (advisory board) ¹	Bezahlte Vor-trags-/oder Schu-lungstätigkeit ¹	Bezahlte Autoren-/oder Coau-torenschaft ¹	Forschungsvorha-ben/Durchführung klinischer Studien ¹	Eigentümerinteres-sen (Patent, Urhe-berrecht, Aktienbe-sitz) ^{1,2}	Indirekte, nicht-finanzielle Interessen ³ (u.a. Mitglied in Fach-gesellschaften, klini-scher Schwerpunkt, pers. Beziehungen)	Von Col betroffene Themen der Leitlinie sowie Einstufung bzgl. der Relevanz
Dr. med. Til Uebel	Nein	Nein, soweit mir bekannt Tätigkeiten für das RKI, den G-BA, BZGA Mitglied der Diabetes-kommision der KVBaEWue Ja: Delegierter bei „Diabetes.de“, die hier vorhandenen multiplen industriellen Verflechtungen von diabetes.de oder zumindest Teile seiner Akteure sind derzeit für mich nicht prüfbar, interne Anfragen wurden nicht beantwortet.	Nein, soweit mir bekannt. Schulungs-/ Vor-trags- Tätigkeiten für die HÄVG, das IHF, die Universitäten Heidelberg und Tübingen, diverse Ärztekammern, DocX, HD-med	Nein	Nein	Nein	Nein Aber Sprecher der AG Diabetes der DEGAM, Mitgliedschaften bei der DDG, DGPR, MEZIS	Keine
Prof. Dr. med. Andreas Fritzsche	Reviews für ver-schiedene diabe-tologische Jour-nals Hypoglykämie Alle Honorare wurden beim Arbeitgeber Uni-versität Tübingen als Nebentätigkeit deklariert. Sie wurden einem un-abhängigen	Tätigkeiten für Novo Nordisk, Lilly 2015-2017 modern insulin advisory board 2015-2017 Diabetes Experten Panel Mün-chen Neue Analoginsuline	Schulungs-/ Vor-trags- Tätigkeiten für MSD und Sano-fi, Insulinanaloga MSD 5/2015 Epi-genetik, kein Bezug zur Leitlinie Sanofi 11/2015 Therapie Typ 2 Diabetes Alle Honorare wur-den beim Arbeitge-ber Universität	Sanofi 2015- 2017 Insulintitration TOP Studie Insulinanaloga Alle Honorare wur-den beim Arbeitge-ber Universität Tü-bingen als Nebentä-tigkeit deklariert. Sie wurden einem un-abhängigen öffentli-chen Genehmi-gungs- verfahren	Sanofi 2015-2017 Insulintitration TOP Studie Insulinanaloga Alle Honorare wur-den beim Arbeitge-ber Universität Tü-bingen als Nebentä-tigkeit deklariert. Sie wurden einem un-abhängigen öffentli-chen Genehmi-gungs- verfahren	Nein	Nein Aber Mitgliedschaft Deutsche Diabetes Gesellschaft, Deut-scher Diabetiker Bund, Diabe-tesDe, EASD 400 Publikationen in peer reviewed Journalen. Relevanter Schwerpunkt Hypoglykämie Behandlung von Patienten mit Typ 1 und Typ 2 Diabetes mellitus	Keine

	Berater- bzw. Gutachtertätigkeit ¹	Mitarbeit in einem wissenschaftlichen Beirat (advisory board) ¹	Bezahlte Vor-trags-/oder Schu-lungstätigkeit ¹	Bezahlte Autoren-/oder Coau-torenschaft ¹	Forschungsvorha-haben/Durchführung klinischer Studien ¹	Eigentümerinteres-sen (Patent, Urheberrecht, Aktienbe-sitz) ^{1,2}	Indirekte, nicht-finanzielle Interessen ³ (u.a. Mitglied in Fach-gesellschaften, klini-scher Schwerpunkt, pers. Beziehungen)	Von Col betroffene Themen der Leitlinie sowie Einstufung bzgl. der Relevanz
	öffentlichen Genehmigungsverfahren unterzogen und auf Zulässigkeit geprüft. Alle Nebentätigkeiten wurden genehmigt. Unterlagen und Honorare können beim Arbeitgeber eingesehen werden.		Tübingen als Nebentätigkeit deklariert. Sie wurden einem unabhängigen öffentlichen Genehmigungsverfahren unterzogen und auf Zulässigkeit geprüft. Alle Nebentätigkeiten wurden genehmigt. Unterlagen und Honorare können beim Arbeitgeber eingesehen werden.		unterzogen und auf Zulässigkeit geprüft. Alle Nebentätigkeiten wurden genehmigt. Unterlagen und Honorare können beim Arbeitgeber eingesehen werden.			
Diana Droßel	Nein	Nationale Diabetes-Surveillance RKI seit 2016	Akademie für Gesundheitsberufe Matthias-Spital Rheine bis 2016 für Diabetiker mit Augenproblemen	Heinemann / Kulzer / Freckmann, keine Aufwandsentschädigung	Nein	Nein Patientenvertreter Diabetesselbsthilfe und Blindensedelbsthilfe	Nein	Keine
Prof. Harald Klein	Nein Mitgliedschaft in Interessenverbänden DDG, DGIM, DGE Schwerpunkte Therapie des Typ 2 Diabetes, Pathogenese Schwerpunkte klinischer Tätigkei-	Astra Zenica bis 2016 ab 01.01.15 bis jetzt Boehringer Ingelheim Bezug zur Leitlinie: Arzneimittel	Berlin Chemie bis 2016 Lilly bis 2017	Nein	TiGenix bis jetzt Kein Bezug zur Leitlinie, Art der Zuwendung: Dritt-mittel	Novo Nordisk Sanofi GSK	Nein	Keine

	Berater- bzw. Gutachtertätigkeit ¹	Mitarbeit in einem wissenschaftlichen Beirat (advisory board) ¹	Bezahlte Vor-trags-/oder Schu-lungstätigkeit ¹	Bezahlte Autoren-/oder Coau-torenschaft ¹	Forschungsvorha-ben/Durchführung klinischer Studien ¹	Eigentümerinteres-sen (Patent, Urhe-berrecht, Aktienbe-sitz) ^{1,2}	Indirekte, nicht-finanzielle Interessen ³ (u.a. Mitglied in Fach-gesellschaften, klini-scher Schwerpunkt, pers. Beziehungen)	Von Col betroffene Themen der Leitlinie sowie Einstufung bzgl. der Relevanz
	ten: Endokrinologie und Diabetologie, Intensivmedizin, Allgemeine Innere Medizin Kongress der Nordrhein-Westfälischen Gesellschaft für Endokrinologie und Diabetologie Diabetes Expertentreffen Kemnade							
PD Dr. Martin Fuechtenbusch	Autor Lilly, Berlin-Chemie, Abbott, Astra, Rocha, Boehringer, MSD 2010 bis 2017 Publikation zu Typ 1 und Typ 2 Diabetes mellitus	Autor Lilly, Berlin-Chemie, Abbott, Astra, Roche, Boehringer, MSD	Lilly, Berlin-Chemie, Abbott, Roche, Astra, Boehringer, Novo, Sanofi, MSD	Lilly zum Bezug Sensor	Nein	Nein Mitgliedschaft in Interessenverbänden: DDG, katholische Akademie Regensburg: ärztlicher Guide der Diabetesberater	Nein	Keine
Dr. Stefan Götz	Mitautor von der DDG berufen Sanofi von 2014 bis 2017	Novo, Nordisk, Novartis, MSD von 2014 bis 2017	Roche, Sanofi, Novo Abbott, Berlin-Chemie, Novartis, MSD, AMGEN, Animas von 2014 bis 2017	Nein	Novo Nordisk Novartis	Nein	Nein Aber Mitgliedschaft in DDG, EASD, BDI, ADBW, Endocrine Society, ADA	Keine
Prof. Dr. med. Thomas Haak	Leitlinienkoordinator Zahlreiche Zeit-	MSD AstraZeneca	Diabetes Akademie Bad Mergentheim e.V.	Nein	Boehringer Ingelheim	Nein	Deutsche Diabetes Gesellschaft, Deutsche Gesellschaft für Innere Medizin, Deutsche	Möglicherweise durch die Beteiligung an der REPLACE-Studie, Vor-

	Berater- bzw. Gutachtertätigkeit ¹	Mitarbeit in einem wissenschaftlichen Beirat (advisory board) ¹	Bezahlte Vor-trags-/oder Schu-lungstätigkeit ¹	Bezahlte Autoren-/oder Coau-torenschaft ¹	Forschungsvorha-haben/Durchführung klinischer Studien ¹	Eigentümerinteres-sen (Patent, Urhe-berrecht, Aktienbe-sitz) ^{1,2}	Indirekte, nicht-finanzielle Interessen ³ (u.a. Mitglied in Fach-gesellschaften, klini-scher Schwerpunkt, pers. Beziehungen)	Von Col betroffene Themen der Leitlinie sowie Einstufung bzgl. der Relevanz
	schriften, darunter Diabetologia, DOM, Diabetes Care seit 2014	Roche Abbott	Abbott		Principal Investigator AstraZeneca Abbott REPLACE-Studie		Gesellschaft für Endokrinologie, EASD, diabetesDE-Deutsche Diabetes Hilfe Vorstand Finanzen und Recht	tragstätigkeit und Beratung von Abbott Col im Kapitel Flash Glucose Monitoring (daher Enthaltung bei der Abstimmung zu diesem Thema)
Dr. med. Thorsten Siegmund	Sozialgericht	Abbott, Ascensia, Boehringer Ingelheim, Eli Lilly, Medtronic, Novo Nordisk	Abbott, Ascensia, Astra Zeneca, Berlin Chemie, Boehringer Ingelheim, Eli Lilly, Medtronic, MSD, Novo Nordisk, Sanofi	Abbott	Astra Zeneca, MSD, NovoNordisk, Sanofi	Nein	Mitglied: DDG, AGDT, DGIM, DGE	Keine
Prof. Dr. med. Ina B. Kopp	Deutsche Akkredi-tierungsstelle (DAkkS) Ludwig Boltzmann Gesellschaft GmbH	AQUA-Institut Wissenschaftlicher Beirat des Instituts für Qualitäts-sicherung und Transparenz im Gesundheitswesen (IQTIG) Ärztliches Zentrum für Qualität in der Medizin (ÄZQ) SCIANA-Netzwerk, gefördert von Robert Bosch Stiftung, Health Foundation, Careum Stiftung	Verband der leiten-den Krankenhaus-ärzte Deutschlands (VLK) Landesärztekam-mere Hessen (LÄK Hessen) Deutsche Gesell-schaft für Innere Medizin (DGIM) Österreichische Gesellschaft für Dermatologie und Venerologie (ÖGDV) Deutsche Gesell-schaft für Implantolo-gie (DG Implant)	Schattauer Verlag	Deutsche Krebshilfe (DKH) Ärztliches Zentrum für Qualität in der Medizin (ÄZQ) Bundesministerium für Gesundheit (BMG) Deutsche For-schungsgemein-schaft (DFG)	Nein	Erweiterte Planungsgruppe für das Programm für Nationale VersorgungsLeitlinien von Bundesärztekammer, Kassenärztlicher Bundesvereinigung und AWMF (Mitglied) Lenkungsausschuss für das Leitlinienprogramm Onkologie von Deutscher Krebsgesell-schaft, Deutscher Krebshilfe und AWMF (Mitglied) Lenkungsausschuss des Ko-operationsverbundes Qualitäts-sicherung durch Klinische Krebsregister (Mitglied) Ständige Kommission Leitlinien der AWMF (Stellv. Vorsitzende) Guidelines International Network	Keine

	Berater- bzw. Gutachtertätigkeit ¹	Mitarbeit in einem wissenschaftlichen Beirat (advisory board) ¹	Bezahlte Vor-trags-/oder Schu-lungstätigkeit ¹	Bezahlte Autoren-/oder Coau-torenschaft ¹	Forschungsvorha-hen/Durchführung klinischer Studien ¹	Eigentümerinteres-sen (Patent, Urhe-berrecht, Aktienbe-sitz) ^{1,2}	Indirekte, nicht-finanzielle Interessen ³ (u.a. Mitglied in Fach-gesellschaften, klini-scher Schwerpunkt, pers. Beziehungen)	Von Col betroffene Themen der Leitlinie sowie Einstufung bzgl. der Relevanz
			Deutsche Veteri-närmedi-zinische Gesell-schaft (DVG) Stiftung Gesund-heits-Wissen Landesärztekam-mer Hessen (LÄK Hessen) Akademie für öffent-liches Gesund-heitwesen Deutscher Schmerzkongress 2017 EBM Frankfurt, Arbeitsgruppe des Instituts für Allge-meinmedizin am FB Medizin der Jo-hann-Wolfgang-Goethe-Universität Frankfurt				Deutsches Netzwerk Evidenz-basierte Medizin (Mitglied) Deutsche Gesellschaft für Chi-rurgie (Mitglied) Fachbeirat für das Programm für Nationale VersorgungsLeit-linien von Bundesärztekammer, Kassenärztlicher Bundesverei-nigung und AWMF (Mitglied)	

	Berater- bzw. Gutachtertätigkeit ¹	Mitarbeit in einem wissenschaftlichen Beirat (advisory board) ¹	Bezahlte Vor-trags-/oder Schu-lungstätigkeit ¹	Bezahlte Autoren-/oder Coau-torenschaft ¹	Forschungsvorha-haben/Durchführung klinischer Studien ¹	Eigentümerinteres-sen (Patent, Urhe-berrecht, Aktienbe-sitz) ^{1,2}	Indirekte, nicht-finanzielle Interessen ³ (u.a. Mitglied in Fach-gesellschaften, klini-scher Schwerpunkt, pers. Beziehungen)	Von Col betroffene Themen der Leitlinie sowie Einstufung bzgl. der Relevanz
Elisabeth Schnellbächer	Becton Dickinson ans Company (BD)	Nein	IhF-Institut für hausärztliche Fortbildung, Wirtschaftsgesellschaft des Hausärzteverbandes RLP, Novo Nordisk, John-son&Johnson, AstraZeneca	Nein	Nein	Nein Mitgliedschaft in Interessenverbänden: VDBD Vorsitzende Pädagogische Leitung VDBD AKADEMIE Pädagogische Leitung VDBD AKADEMIE	Nein	Keine
Haring, Andrea	Nein	Nein	Nein	Nein	Nein	Nein	Nein	Keine
Bühn, Stefanie	Nein	Nein	Nein	Nein	Nein	Nein	Nein	Keine
Dr. Pieper, Dawid	MDS	Nein Evidenzbasierte Medi-zin, klinische Epidemiologie, Evidenzsyn-these, Versorgungs-forschung	Mibeg Institut Methoden EbM „Nein“	Nein	Nein	Nein	Nein	Keine

1 = Hier werden entsprechend §139b SGB V finanzielle Beziehungen zu Unternehmen, Institutionen oder Interessenverbänden im Gesundheitswesen erfasst. Folgende Frage wurde beantwortet: Haben Sie oder die Einrichtung, für die Sie tätig sind, innerhalb des laufenden Jahres oder der 3 Kalenderjahre davor Zuwendungen erhalten von Unternehmen der Gesundheitswirtschaft (z.B. Arzneimittelindustrie, Medizinproduktindustrie), industriellen Interessenverbänden, kommerziell orientierten Auftragsinstituten, Versicherungen/Versicherungsträgern, oder von öffentlichen Geldgebern (z.B. Ministerien), Körperschaften/Einrichtungen der Selbstverwaltung, Stiftungen, oder anderen Geldgebern?

2 = Angaben zu Mischfonds waren nicht erforderlich

3 = Hierzu wurden folgende Aspekte abgefragt: Mitgliedschaft /Funktion in Interessenverbänden; Schwerpunkte wissenschaftlicher Tätigkeiten, Publikationen; Schwerpunkte klinischer Tätigkeiten; Federführende Beteiligung an Fortbildungen/Ausbildungsinstituten; Persönliche Beziehungen (als Partner oder Verwandter 1. Grades) zu einem Vertretungsberechtigten eines Unternehmens der Gesundheitswirtschaft; sonstige relevante Interessen

12 Anhang: Kommentare aus Konsultationsphase

Kommentar	Kommentar Leitliniengruppe
<p>Seiten 9-10; Kapitel 2.1 Aus Gründen der Vollständigkeit sollten die Glykämiekriterien der Diagnose „Diabetes“ aufgezählt werden.</p> <p>Seite 9, Kapitel 2.1, 4. Absatz Ich halte es für sehr problematisch, hier eine neue und m.E. sehr fragwürdige Definition des Begriffs Typ 1-Diabetes unter Einschluß asymptomatischer Vor-/ Risikostadien einzuführen. Auch wenn man von diesen prinzipiellen Bedenken absieht, ist es ja so, daß Sie diesen Krankheitsbegriff im weiteren Verlauf der LL nicht mehr nutzen, Sie müßten ja sonst immer von „Typ 1-Diabetes Stadium 3“ sprechen. Ich würde es für sinnvoll halten, wenn Sie, falls dieser Absatz überhaupt sinnvoll ist, ihn eindeutig als einen Vorschlag der ADA kennzeichnen und vielleicht klein oder kursiv drucken.</p>	<p>Die neue Stadieneinteilung ist zwar von der JDRF und der ADA so vorgenommen worden, die Initiative hierzu war aber eine internationale, nicht zuletzt auch von einer Forschergruppe aus Deutschland initiiert. Wir halten es für wichtig, in dieser neuen LL darauf hinzuweisen, dass sich die Definition des T1D wie hier beschrieben geändert hat um zukünftig den Fokus auf die Bemühungen der Verhinderung oder Verzögerung des Autoimmunprozesses zu legen. Es ist einer der ganz grossen Erkenntnisse der letzten Jahre gewesen, zu sehen, dass bei Nachweis von 2 oder mehr T1D-assoziierten Autoantikörpern in den Folgejahren unausweislich ein klinischer T1D mit Hyperglykämie folgt. Ja es ist ein Perspektiven-Wechsel, den wir explizit begrüßen. Aus unserer Sicht unproblematisch ist, dass wir im weiteren Verlauf im Text der LL nicht konsequent vom T1D Stadium 3 sprechen, da sich diese neue Diagoseeinteilung noch nicht im klinschen Alltag durchgesetzt hat.</p> <p>Modifiziert/ergänzt:</p> <p><i>Die ADA und das JDRF schlagen nunmehr eine neue Stadieneinteilung des Typ-1-Diabetes vor, die es ermöglicht, bereits vor dem Auftreten einer Hyperglykämie, also präsymptomatisch, die Diagnose Typ-1-Diabetes zu stellen [Insel 2015, EK IV/LoE 4]: Das Stadium 1 ist demnach definiert als Nachweis von mindestens zwei persistierenden Autoantikörpern und Normoglykämie. Das präsymptomatische Stadium 2 ist definiert als Nachweis von mindestens zwei Autoantikörpern plus Dysglykämie, also Nachweis entweder einer gestörten Glukosetoleranz oder gestörten Nüchternnglukose (FPG 100-125 mg/dl (5,6-7 mmol/l) oder HbA1c-Werte zwischen 5,7 und 6,4% (39-47 mmol/mol)). Das Stadium 3 des Typ-1-Diabetes ist charakterisiert durch eine Hyperglykämie entsprechend der Glukosekriterien für einen Diabetes [American Diabetes Association (ADA) 2018, EK IV]. Die Glykämiekriterien für die Diagnose Diabetes sind folgende: 1) Nüchtern-Plasmaglucose ≥ 126 mg/dl (7,0 mol/l), dabei ist der Nüchternzustand definiert als eine mindestens 8-stündige Phase ohne Kalorienaufnahme ODER 2) 2-h- postprandiale Plasmaglukose von ≥ 200 mg/dl (11,1 mmol/l) im Rahmen eines OGTT mit 75 g in Wasser gelöster Glukose und vorschriftsmäßiger Anwendung nach den WHO-Standards ODER 3) HbA1c-Wert $\geq 6,5\%$ (48 mmol/mol), wobei die HbA1c-Test-Methode</i></p>

Kommentar	Kommentar Leitliniengruppe
	<p>den NGSP-Kriterien entsprechen und auf den DCCT Assay standardisiert sein sollte ODER 4) ein zufälliger Plasma-Glucose-Wert $\geq 200 \text{ mg/dl}$ ($11,1 \text{ mmol/l}$) mit klassischen Symptomen einer Hyperglykämie [American Diabetes Association (ADA) 2018, EK IV][American Diabetes Association (ADA) 2018, EK IV].</p>
<p>Seite 12, Kapitel 3 - Therapieziele</p> <p>„Lebensqualität“ also Therapieziel ist unstrittig. Die massive Priorsierung dieser Kategorie „Lebensqualität“ ist aber nicht zielführend. Das Ziel einer Reduktion der Exzeßmorbidity und-mortalität durch diabetesbedingte und – assoziierte Komplikationen muß klar benannt werden und nicht nur über die Voraussetzung der „Minderungen der Lebensqualität“ mehr en passant Erwähnung finden. Die sich aus unterschiedlichen Sichtweisen und Prioritäten ergebenden Konflikte im Patienten-Arzt-Verhältnis können dabei thematisiert werden.</p> <p>„Daher gibt es neben den langfristigen Therapiezielen, die in der Regel auf die Reduktion von Folgeerkrankungen fokussiert sind und sich nicht wesentlich von denen von Menschen ohne Diabetes unterscheiden, individuelle unmittelbare Therapieziele.“</p> <p>Dieser Satz ist unverständlich: Typ 1-Diabetiker und Menschen ohne Diabetes haben keine vergleichbaren langfristigen Therapieziele!</p> <p>Seite 13, Empfehlung 3-2</p> <p>„Diese Aufklärung soll in verständlichen Worten und ergebnisoffen geschehen.“</p> <p>Diese Formulierung ist m.E. verzichtbar, weil sie an sich selbstverständlich ist, aber durch ihre explizite Erwähnung nur Unklarheit hervorruft. Was meinen die Autoren mit ergebnisoffen? Dass der Verzicht auf eine intensivierte Insulintherapie eine erwägenswerte Alternative ist? Aus meiner Sicht ist es doch eher so, daß ein Patient über die gesicherten nachteiligen Folgen eines Verzichts auf eine intensivierte Insulintherapie aufzuklären wäre! Unterschwellig könnte man in dem Text die Suggestion entdecken, daß die ICT (im Vergleich zu: ja was eigentlich: CT, kein Insulin?) eigenständige Risiken hätte, die nicht mit den erreichten HbA1c-Werten zusammenhängen</p>	<p>Keine Änderungen, Begründung:</p> <p>Diabetes, nun gleich ob Typ 1 oder Typ 2, lässt grundsätzlich zwei Beratungsbereiche aufkommen: Die Stoffwechselleid kann Maß für eine akute Bedrohung, also eine Krankheit im eigentlichen Sinne sein, verlangt dann eine spezifische Information! Sie kann jedoch auch als Risikofaktor für Folgeerkrankungen gelten und ist dann einer unter anderen. Diese Folgeerkrankungen jedoch treten mit Ausnahme vielleicht der Diabetischen Retinopathie auch ohne Diabetes auf. Aus Sicht der Arbeitsgruppe ist die gewählte Formulierung nicht missverständlich.</p> <p>Die Möglichkeiten einer erfolgreichen Therapie (ICT) sowie des innewohnenden Risikos derselben in verschiedener Stadien einer Diabeteserkrankung zu thematisieren ist eines der wesentlichen Ziele dieser Leitlinie. Wobei die Schärfe der empfohlenen Stoffwechselkontrolle fast regelmäßig der Hypoglykämie-Gefahr entgegensteht. Dies ist kein Widerspruch zu Ihrer berechtigten Forderung, ebenso den Nutzen der Hypoglykämievermeidung gegenüber der Gefahr einer Unterlassung möglicher Stoffwechselziele mit dem Patienten zusammen abzuwegen.</p> <p>Die Leitliniengruppe hatte sich im Rahmen des Entstehungsprozesse entschlossen, der Tatsache, dass sich Chancen wie Risiken in der modernen Diabetologie verändert haben, insofern Rechnung zu tragen, indem sie gängige Forderungen anderer Leitlinienprojekte umsetzt (z.B. das NVL-Programm) bzw. etablierte international gesetzte Standards (z.B. Cochrane) beherzigt, in denen grundsätzlich, aber insbesondere im direkten Patientengespräch die Thematisierung der Absoluten Risikoreduktion und das ist verständlichen Worten verlangt wird.</p> <p>Dazu gehört der von Ihnen hervorgehobene Satz, der spätestens seit Einführung entsprechender Beratungsgesetze auch Patientenrechte geworden ist. Sie finden ihn zum Beispiel wortwörtlich beim Gesetz zur Beratung im Rahmen eines Schwangerschaftskonfliktes oder auch wenn es z.B. um Möglichkeiten und Grenzen des PCA-Screenings geht. Vergleichbare Kern-Aussagen werden künftig auch Teil des sich gerade erneuernden NVL Typ 2 Prozesses.</p>

Kommentar	Kommentar Leitliniengruppe
<p>Seite 55, Empfehlung 5-11 Hier sollte zumindestens darauf hingewiesen werden, dass eine Zulassung nicht vorliegt und es sich damit um einen off-label-use mit allen Problemen handelt (es sei denn, man diagnostiziert einen zusätzlichen Typ 2-Diabetes im Sinnes eines (siehe 2.1. auf Seite 11) „hybriden Doublediabetes“ (könnte man auch auf deutsch ausdrücken).</p>	<p>Wir haben diesen Punkt noch einmal diskutiert und beschlossen, in die Empfehlung den Zusatz mit auf zu nehmen, dass der Zulassungssts berücksichtigt werden muss. Damit bleibt es möglich Metformin innerhalb des labels zu verordnen wenn der Verordner zusätzlich einen Typ 2 Diabetes diagnostiziert.</p> <p>Ergänzt</p> <p><i>Der Zulassungsstatus von Metformin ist zu beachten.</i></p>
<p>Seite 67f, Kapitel 8.1.5., Empfehlung 8-3 und „Hintergrund“ Unter 8-3 werden 50ml 20% Glukose, in der Tabelle 11 20 ml 50% empfohlen. Nach meiner Erfahrung in Klinik und Rettungsdienst sind Ampullen mit Glukose 40% am häufigsten verfügbar.</p>	<p>Die Inkonsistenz zwischen Text und Tabelle wurde korrigiert</p>
<p>Im Titel schon darauf hinweisen, dass es sich alleine um eine LL für den T1D im Erwachsenenalter handelt. Die Besonderheiten der Adoleszenz, wo wir als internistische Diabetologen schon behandeln dürfen, die Transition etc sind in der vorliegenden LL nicht thematisiert.</p>	<p>Keine Änderungen</p>
<p>Seite 62 (...Nierenerkrankungen...) Ich würde auf eine Europäische Clin Pract GL von Nephrologen verweisen, die von 2015 recht neu ist, solange die ältere NVL noch nicht überarbeitet ist.</p>	<p>Keine Änderungen</p>
<p>S. 70: Die obligate stationäre Einweisung bei mittel- bis schwerer diabet. Ketoazidose würde ich härter formulieren, da es immer noch niedergelassene Diabetologen gibt, die sich damit brüsten, dass sie es auch ambulant in den Griff bekommen</p>	<p>Keine Änderungen</p>

Kommentar	Kommentar Leitliniengruppe
<p>Bei der Durchsicht des Leitlinien-Entwurfs „Therapie des Typ-1-Diabetes“ fiel mir auf, dass wie auch in der vorherigen Leitlinie keine Aussage zu den Zielwerten des LDL-Cholesterins getroffen wird (die Suche nach LDL erbrachte 3 Treffer). Dies hätte ich mir sehr gewünscht, da das Thema immer wieder kontrovers diskutiert wird. Zuletzt wurde im Kreis der hamburgischen Diabetologen bei Fortbildungen und Qualitätszirkeln das Thema aufgegriffen ohne dass ein befriedigendes Ergebnis erzielt werden konnte.</p> <p>Aus meiner Sicht geht es nicht um die Hochrisiko-Patienten, da denke ich, ist sich der Großteil der Diabetologen einig. Schwierig ist das Thema bei jungen Typ-1-Diabetikern ohne Folgeerkrankungen, einer Krankheitsdauer von 15-20 Jahren und moderat erhöhtem LDL-Cholesterin. Da taucht immer wieder die Frage auf soll ich dem 32-jährigen Mann ein Statin verordnen oder nicht.</p> <p>Die Typ-2-Diabetes-Leitlinie äußert sich sehr konkret zu dem Thema LDL-Ziel und die Leitlinie der Pädiater hat einen erstaunlich detaillierten Plan zur Therapie der Hypercholesterinämie.</p> <p>Die kardiologischen Leitlinien sehen aus meiner Sicht den Diabetes undifferenziert, da scheint es egal zu sein ob es sich um einen Typ-1- oder Typ-2-Diabetes handelt. Die Hauptsache ist das LDL-Cholesterin unter 100 mg/dl zu senken – aber trifft das auch uneingeschränkt auf den o.g. Beispielpatienten zu?</p> <p>Aus meiner Sicht sollte ein Statement zum LDL-Ziel (und wenn es am Ende offen gehalten wird) ein fester Bestandteil der Leitlinie zur Therapie des Typ-1-Diabetes sein.</p>	<p>Keine Änderungen, Begründung:</p> <p>Da wir eine S3-LL verfasst haben sind wir gehalten offene Kann-Empfehlungen oder aber reine Expertenmeinungen mit geringem evidence-level zu minimieren. Wir haben die wenigen Studien zur Primärprävention CV-Erkrankungen bei T1D angesehen und finden hier keine RCTs. Es gibt zu Ihrer Frage nach unserer Einschätzung als wichtigste Studie lediglich die Arbeit von Frau Hero et al, in Diabetes Care 2016 aus dem schwedischen T1D-Register; hier zeigt sich ein klarer Benefit für Statin-user im Vgl zu nicht-Statinusern für viele CV_Endpunkte inkl CV-death. Jedoch sind hier die non-statin-user im Mittel 36 JAhre alt und die Statin-user 50 JAhre, und die Studie nutzt ein propensity-score-matching um baseline-Risiken auszugleichen. NNTs werden nicht berechnet und man kann hier nicht direkt ableiten, ab welchem LDL-Wert und oder Alter ein Statin sinnvoll wäre. Wir haben deshalb beschlossen keine konkrete Empfehlung in dieser Hinsicht zu geben. Wie gesagt, die Ereignisrate bei den < 40-Jährigen war hier sehr gering, deshalb ist die Datenbasis nicht ausreichend. Auch wissen wir nicht mit welchen Statindosen therapiert wurde. Wir werden aber für die nächste LL-Aktualisierung einen Prüf-Auftrag für eine neue Literatursuche zu dieser Fragestellung geben (wenn es dann hoffentlich mehr Studien gibt).</p> <p>Wie Sie selber schreiben, gibt es nur die bislang gültigen allgm Statements für Diabetes-Patienten die nicht zwischen T1D und T2D unterscheiden: wir haben NICE und wir haben z.B. die ACC-Empfehlungen und die ADA-Standards of Clinical Care, z.B. 2018, die ebenfalls keine neuen speziellen Empfehlungen für T1D geben. Es gibt also zusammenfassend nur die Daten und allgemeinen Überlegungen zur primären Prävention einer CV_Erkrankung.</p> <p>Ein konkretes Statement, dass über die bekannten Empfehlungen von NICE oder ADA oder ACC hinausgeht, können wir aus Mangel an Studien für diese S-3-LL unsere Meinung nach deshalb nicht geben. Leider.</p>
<p>Ich behandle sehr viele Patienten mit CSII und CGM und beim Thema Ketoazidose empfinde ich es als einen sehr großen Vorteil, wenn diese Patienten beim Verdacht auf eine diabetische Ketoazidose den Ketonwert im Blut und NICHT im Urin messen. Zum einen ist die Bereitschaft der Patienten, einen Blutwert zu kontrollieren wie beim Blutzuckermessen, deutlich größer</p>	<p>Ergänzt:</p> <p><i>Es wird empfohlen, dass Patienten mit Typ-1-Diabetes über Teststreifen zur Messung der Ketonkörper im Urin oder im Blut (sofern ein geeignetes Messgerät hierfür vorhanden ist) verfügen und im Umgang mit diesen sowie der</i></p>

Kommentar	Kommentar Leitliniengruppe
und die Genauigkeit ist der Urinmessung deutlich überlegen (besonders bei der Eigentherapie für die Verlaufskontrolle). Außerdem messen wir ja inzwischen mit rtCGM Systemen und Blutzuckermessgeräten, da empfinde ich eine Urinmessung (es wird ja beim Typ 1 auch nicht mehr die Messung von Urinzucker empfohlen) nicht mehr als zeitgemäß.	<i>Interpretation der Messwerte geschult sind.</i>

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