Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2017-B-057 Roxadustat

Stand: Juni 2017

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

Roxadustat
Behandlung der Anämie bei chronischer Niereninsuffizienz

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Antianämika, siehe Anlage II.
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	Erythrozytentransfusion
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Anlage I der AM-RL: - 17. Eisen-(II)-Verbindungen nur zur Behandlung von gesicherter Eisenmangelanaemie - 43. Wasserlösliche Vitamine auch in Kombinationen nur bei der Dialyse. - 44. Wasserlösliche Vitamine, Benfotiamin und Folsäure als Monopräparate nur bei nachgewiesenem, schwerwiegendem Vitaminmangel, der durch eine entsprechende Ernährung nicht behoben werden kann (Folsäure: 5 mg/Dosiseinheit). Anlage III der AM-RL: - 8. Antianaemika-Kombinationen - Verordnungsausschluss Anlage IV der AM-RL: - Erythropoese-stimulierende Wirkstoffe (zur Behandlung der symptomatischen renalen Anämie)
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche*

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Roxadustat	
Darbepoetin alfa B03XA02 z.B. Aranesp®	Zur Behandlung der symptomatischen Anämie bei chronischer Niereninsuffizienz (CNI) bei erwachsenen und pädiatrischen Patienten (siehe Abschnitt 4.2).
Epoetin alfa B03XA01 z.B. Abseamed®	Abseamed® ist angezeigt zur Behandlung der symptomatischen Anämie bei chronischer Niereninsuffizienz: – bei Erwachsenen sowie Kindern und Jugendlichen im Alter von 1 bis 18 Jahren unter Hämodialysebehandlung und bei Erwachsenen unter Peritonealdialysebehandlung (siehe Abschnitt 4.4). – bei Erwachsenen mit Niereninsuffizienz, die noch nicht dialysepflichtig sind, zur Behandlung einer schweren symptomatischen renalen Anämie (siehe Abschnitt 4.4). (…)
Epoetin beta B03XA01 z.B. NeoRecormon®	NeoRecormon wird angewendet zur: – Behandlung der symptomatischen Anämie infolge von chronischer Niereninsuffizienz bei erwachsenen Patienten und Kindern. (…) 4.4: Um eine wirksame Erythropoiese sicherzustellen, sollte bei allen Patienten vor und während der Behandlung der Eisenwert bestimmt werden und gegebenenfalls eine Eisenersatztherapie gemäß den therapeutischen Richtlinien durchgeführt werden.
Epoetin theta B03XA01 z.B. Biopoin®	Behandlung einer symptomatischen Anämie infolge chronischer Niereninsuffizienz bei erwachsenen Patienten. (…)
Epoetin zeta B03XA01 z.B. Retacrit®	Behandlung der symptomatischen Anämie bei chronischer Niereninsuffizienz bei Erwachsenen und pädiatrischen Patienten: • Behandlung der Anämie bei chronischer Niereninsuffizienz bei Erwachsenen und pädiatrischen Patienten unter Hämodialysebehandlung und bei Erwachsenen unter Peritonealdialysebehandlung (siehe Abschnitt 4.4). • Behandlung der schweren symptomatischen renalen Anämie bei Erwachsenen mit Niereninsuffizienz, die noch nicht dialysepflichtig sind (siehe Abschnitt 4.4).
Methoxy-Polyethylenglycol-	Zur Behandlung der symptomatischen Anämie bei erwachsenen Patienten mit chronischer Nierenerkrankung (CKD) (siehe Abschnitt 5.1).

II. Zugelassene Arzneimittel im Anwendungsgebiet

Epoetin beta B03XA03 z.B. MIRCERA®	
Arzneimittel mit Wirkstoffen (wie Eisenverbindungen, Folsäure, Vitamin B) zur Behandlung von Mangelzuständen, die eine dahingehend spezifische Anämie verursachen können, werden nicht aufgelistet.	

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

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

Inhalt

Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und evidenzbasierten systematischen Leitlinien zur Indikation Anämie bei chronischer Niereninsuffizienz durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 20.04.2017 abgeschlossen. Die Suche erfolgte in folgenden Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database), MEDLINE (PubMed), AWMF, Clinical Evidence, DAHTA, G-BA, GIN, IQWiG, NGC, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 256 Quellen, die anschließend in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt ergab dies 14 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Indikation

Behandlung der Anämie bei chronischer Niereninsuffizienz bei erwachsenen Patienten.

Abkürzungen:

ÄZQ	Ärztliches Zentrum für Qualität in der Medizin
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
CKD	Chronic kidney disease
DAHTA	Deutsche Agentur für Health Technology Assessment
DPO	Darbepoetin
EPO	Erythropoetin
ESA	Erythropoiesis Stimulating Agent
G-BA	Gemeinsamer Bundesausschuss
GFR	Glomeruläre Filtrationsrate
GIN	Guidelines International Network
Hb	Hämoglobin
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
NGC	National Guideline Clearinghouse
NHS CRD	National Health Services Center for Reviews and Dissemination
NICE	National Institute for Health and Care Excellence
QoL	Quality of Life
rHuEPO	recombinant human erythropoietin
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
WHO	World Health Organization

G-BA, 2011 [6]. Bekanntmachung eines Beschlusses des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL) in Anlage IV: Therapiehinweis zu Erythropoese-stimulierenden Wirkstoffen (zur Behandlung der symptomatischen renalen Anämie), vom 23. Juni 2011.	**Zugelassene Anwendungsgebiete** Alle Erythropoese-stimulierenden Wirkstoffe (Erythropoiesis Stimulating Agents, ESAs) sind in Deutschland zur Behandlung der symptomatischen Anämie bei chronischer Niereninsuffizienz zugelassen. Arzneimittel, die Epoetin alfa, Epoetin beta, Epoetin theta, Epoetin zeta, Darbepoetin alfa oder Methoxy-Polyethylenglycol-Epoetin beta enthalten, sind bei Patienten mit renaler Anämie zur intravenösen wie auch zur subkutanen Anwendung zugelassen. Epoetin alfa-haltige Biosimilars sind bei Patienten mit renaler Anämie nur für die intravenöse Verabreichung zugelassen, da die Daten für die Sicherheit der subkutanen Anwendung nicht ausreichten. Mit Ausnahme von Methoxy-Polyethylenglycol-Epoetin beta und Epoetin theta bezieht sich die Zulassung auch auf pädiatrische Patienten mit renaler Anämie unter Hämodialysebehandlung. **Empfehlungen zur wirtschaftlichen Verordnungsweise** ESAs werden intravenös oder subkutan (Ausnahme: Biosimilars Epoetin alfa nur intravenös) appliziert und stimulieren wie das körpereigene Hormon Erythropoetin (EPO) die Proliferation, Differenzierung und das Überleben von Vorläuferzellen der Erythropoese im Knochenmark. Die biologischen Wirkungen der gentechnologisch hergestellten ESAs werden ebenso wie die des Glykoproteins EPO durch Bindung an den Erythropoetin-Rezeptor (EPO-R) vermittelt, der spezifisch auf Vorläuferzellen der Erythropoese im Knochenmark exprimiert wird. Für den therapeutischen Einsatz gelten heute alle verfügbaren ESAs als vergleichbar. Für die als sogenannte „Biosimilars“ von der Europäischen Kommission zugelassenen ESAs wurde nachgewiesen, dass ihre Qualität, Wirksamkeit und Sicherheit in den zugelassenen Indikationen ausreichend belegt sind und dem Zulassungsstandard entsprechen. Durch randomisierte kontrollierte Studien (RCT) belegte Therapieziele sind ein Anstieg des Hämoglobin (Hb)-Wertes und eine Verringerung bzw. Vermeidung von Bluttransfusionen. Eine wesentliche Verbesserung der Lebensqualität konnte anhand der vorliegenden Studien bisher nicht eindeutig gezeigt werden. Dem gegenüber stehen RCTs, die belegen, dass ein zu hoher Hämoglobinzielwert (> 12 g/dl) schwerwiegende Risiken (z. B. Erhöhung der Schlaganfallrate, thromboembolische Komplikationen) beinhaltet. Bei der Verordnung von ESAs zur Behandlung der symptomatischen renalen Anämie müssen folgende Punkte berücksichtigt werden: • Vor Verordnung der ESAs müssen andere mögliche Ursachen einer Anämie (siehe Abschnitt Wirkungen) ausgeschlossen und bei labor-chemischen Hinweisen für einen Eisenmangel bzw. leere Eisenspeicher im Knochenmark eine Eisensubstitution parallel zur Gabe von ESAs begonnen werden. Auch während

	der Behandlung mit ESAs sind die Eisen-speicher zu überprüfen und ggf. Eisen zu substituieren. • Vor Verordnung von ESAs sollte unter Einbeziehung der Patienten eine Nutzen-Risiko-Abwägung erfolgen, die unter anderem folgende Faktoren einschließt: Art, Stadium und Prognose der Erkrankung, Schweregrad der Anämie, klinische Situation (z. B. kardiovaskuläre oder pulmonale Begleit-erkrankungen), Behandlungspräferenz der Patienten. Die Patienten müssen über die Risiken bei der Gabe von ESAs (erhöhtes Mortalitäts-risiko bei Patienten mit zu hohen Hb-Werten, thromboembolische Komplikationen, erhöhtes Risiko von Schlaganfällen, mögliche Stimulation des Tumorwachstums) sorgfältig und aktuell informiert werden. • Die Europäische Arzneimittelagentur (European Medicines Agency, EMA) hat nach Abschluss eines Risikobewertungsverfahrens für alle Indikationen einheitliche Therapieziele empfohlen. Danach soll der Zielwert des Hb für Erwachsene zwischen 10 und 12 g/dl (entsprechend 6,2 - 7,45 mmol/l) und für Kinder zwischen 9,5 und 11 g/dl (entsprechend 5,9 - 6,8 mmol/l) liegen und damit den physiologischen Normbereich unterschreiten. • Die Behandlung der symptomatischen renalen Anämie sollte abhängig von der individuellen klinischen Symptomatik ab Hämoglobin-Werten ≤ 10,0 g/dl erwogen werden, nachdem andere Ursachen der Anämie ausgeschlossen wurden. • Bei Hämoglobinwerten < 9 g/dl muss das Risiko vermehrt notwendiger Transfusionen gegenüber einem erhöhten Schlaganfallsrisiko abgewogen werden. Insbesondere bei Patienten, die für eine Transplantation infrage kommen, muss die mögliche Bildung von Alloantikörpern gegen Blut-gruppenantigene durch Erythrozytenkonzentrate berücksichtigt werden. • Ein Anheben des Hb-Wertes über 12 g/dl bringt für den Patienten keine messbaren Vorteile, sondern kann mit erhöhten Risiken verbunden sein. Außerdem wäre dafür eine Erhöhung der Epoetin- bzw. Darbepoetin-Dosis erforderlich. • Die Dosis der ESAs sollte angepasst werden, wenn der Hb-Wert um mehr als 2 g/dl/Monat steigt oder sinkt und/oder wenn der Hb-Wert außerhalb des oben genannten Zielbereichs gerät. • Für die Biosimilars wurden von der EMA im Vergleich zum Referenz-präparat in den Zulassungsstudien keine klinisch relevanten Dosisunterschiede festgestellt. In den der Zulassung entsprechenden Applikationsformen stellen Biosimilars eine kostengünstige Alternative dar. • Für Epoetin alfa und beta wurde gezeigt, dass ein Einsparpotential durch Reduktion der Dosis bei subkutaner im Vergleich zur intravenösen An-wendung besteht.

Cochrane Reviews

Palmer SC et al., 2014 [11]. Darbepoetin for the anaemia of chronic kidney disease	1. Fragestellung To assess the benefits and harms of darbepoetin alfa to treat anaemia in adults and children with CKD (stages 3 to 5, 5D, and kidney transplant recipients).
	2. Methodik **Population**: adults or children with CKD (any stage) **Intervention**: any darbepoetin alfa treatment of at least three months duration **Komparator**: k.A. **Endpunkt:** Patient-centred outcomes (need for blood transfusion, iron therapy, progression of kidney disease, total and cardiovascular mortality, cardiovascular events, cancer, hypertension, seizures, and health-related quality of life) and other outcomes (haemoglobin levels) **Suchzeitraum**: to 13 January 2014 **Anzahl eingeschlossene Studien**/Patienten (Gesamt): 32/9 414 (21/8 328 in meta-analyses) **Qualitätsbewertung der Studien**: risk of bias assessment tool Heterogeneity: Chi² test used on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance and with the I² test; I² values of 25%, 50% and 75% corresponded to low, medium and high levels of heterogeneity
	3. Ergebnisse • studies generally at high or unclear risk of bias for all items (random sequence generation, allocation concealment, incomplete outcome data, blinding of participants and personnel, blinding of outcome assessment, selective outcome reporting, intention to treat analysis and other sources of bias) • studies included in MA: o darbepoetin alfa vs placebo: 1 study (4038 participants) o darbepoetin alfa vs epoetin alfa or beta: 16 studies (2955 participants) o darbepoetin alfa vs methoxy polyethylene glycol-epoetin beta: 4 studies (1198 participants) o more frequent vs less frequent darbepoetin alfa administration: 3 studies (420 participants) o i.v. vs s.c. darbepoetin alfa: 4 studies (303 participants) *Darbepoetin alfa vs. placebo*

	• 1 study (TREAT 2005; 4 038 adults with CKD stage 3 to 5; low risk of bias for most items assessed) • darbepoetin alfa o reduced need for blood transfusion (RR 0.60 [0.53, 0.69])and iron therapy (RR 0.75 [0.73, 0.78]) o improved FACT-Fatigue score (mean difference 1.40 [0.71, 2.09]) o little or no effect on survival o increased risks of hypertension o uncertain effects on quality of life *Darbepoetin alfa vs. epoetin alfa or beta* • 16 studies (2955 participants): data sparse and inconclusive Quellen: Akizawa 2011; Allon 2002; Coyne 2000; Coyne 2006a; Hirakata 2010; Hori 2004; Iwasaki 2008; Li 2008; Locatelli 2001; Nissenson 2002; Smyth 2004; Tessitore 2008; Tolman 2005; Vanrenterghem2002; Warady 2006; Yoon 2004 *Darbepoetin alfa vs. methoxy polyethylene glycol-epoetin beta* • 4 studies (1198 participants): data sparse and inconclusive Quellen: ARCTOS Study 2008; PATRONUS Study 2010; STRIATA Study 2008; TIVOLI Study 2011
	4. Anmerkungen/Fazit der Autoren Data suggest that darbepoetin alfa effectively reduces need for blood transfusions in adults with CKD stage 3 to 5, but has little or no effect on mortality or quality of life. The effects of darbepoetin alfa in adults with CKD stage 5D and kidney transplant recipients and children with CKD remain uncertain as do the relative benefits and harms of darbepoetin alfa compared with other ESAs (epoetin alfa or beta and methoxy polyethylene glycol-epoetin beta). *5. Kommentare zum Review* Einschluss dialysepflichtiger und nicht dialysepflichtiger Patienten Insufficient data were available to generate funnel plots to assess for the potential existence of small study bias
Palmer SC et al., 2014 [12]. Erythropoiesis-stimulating agents for anaemia in adults with chronic kidney disease: a network meta-analysis.	1. Fragestellung To compare the efficacy and safety of ESAs (epoetin alfa, epoetin beta, darbepoetin alfa, or methoxy polyethylene glycol-epoetin beta, and biosimilar ESAs, against each other, placebo, or no treatment) to treat anaemia in adults with CKD.
	2. Methodik **Population**: adults with anaemia due to CKD **Intervention:** ESA (epoetin alfa, epoetin beta, darbepoetin alfa, methoxy polyethylene glycol-epoetin beta, or biosimilar ESA) **Komparato**r: another ESA, placebo or no treatment **Endpunkt:**

	o Preventing blood transfusion o All-cause Mortality o Fatigue, dyspnea o Cardiovascular mortality, MI, stroke, vascular access thrombosis, major adverse cardiovascular events, end-stage kidney disease **Suchzeitraum:** to 11 February 2014 **Anzahl eingeschlossene Studien**/Patienten (Gesamt): 56/15 596 (40/12 103 in meta-analyses) **Qualitätsbewertung der Studien**: Cochrane risk of bias tool for assessing risk of bias in included studies; Assessing the overall evidence quality according to adapted GRADE methodology as very low, low, moderate, or high We assessed for heterogeneity and inconsistency within meta-analyses using standard techniques and planned subgroup and meta-regression to explore for sources of heterogeneity or inconsistency.
	1. Ergebnisdarstellung • risks of bias generally high or unclear for more than half of studies in all of the risk of bias domains • no study was low risk for allocation concealment, blinding of outcome assessment and attrition from follow-up • 40 studies included in meta-analyses: o 7 were placebo controlled (4638 participants) and o 8 compared ESAs with standard care (787participants). o 25 trials were head-to-head studies ▪ epoetin alfa versus darbepoetin alfa (8 studies, 1783 participants), ▪ epoetin beta versus darbepoetin alfa (1 study, 219 participants), ▪ epoetin beta versus methoxy polyethylene glycol-epoetin beta (2 studies, 462 participants), ▪ darbepoetin alfa versus methoxy polyethylene glycol-epoetin beta (5 studies, 1505 participants), ▪ epoetin alfa versus biosimilar ESA (8 studies, 2419 participants) and ▪ epoetin beta versus biosimilar ESA (1 study, 290 participants). <u>network analyses</u> *prevented blood transfusions* • superiority of compared to placebo (moderate to low confidence)

	o epoetin alfa (OR 0.18, 95% CI 0.05 to 0.59), o epoetin beta (OR 0.09, 95% CI 0.02 to 0.38), o darbepoetin alfa (OR 0.17, 95% CI 0.05 to 0.57), o methoxy polyethylene glycol-epoetin beta (OR 0.15, 95% CI 0.03 to 0.70) • very low quality evidence that o biosimilar ESA therapy was possibly no better than placebo (OR 0.27, 95% CI 0.05 to 1.47) with considerable imprecision in estimated effects o . We could not discern whether all ESAs were similar or different • confidence in the comparative effectiveness of different ESAs generally very low *all-cause mortality* • imprecise comparative effects of ESAs compared with another ESA, placebo or no treatment *developing hypertension* • all ESAs increased the odds of hypertension compared to placebo o epoetin alfa OR 2.31, 95%CI 1.27 to 4.23 o epoetin beta OR 2.57, 95% CI 1.23 to 5.39 o darbepoetin alfa OR 1.83, 95% CI 1.05 to 3.21 o methoxy polyethylene glycol-epoetin beta OR 1.96, 95%CI 0.98 to 3.92 • effect of biosimilar ESAs less certain (OR 1.18, 95%CI 0.47 to 2.99) • confidence in comparative effects of ESAs on hypertension low due to considerable imprecision in treatment estimates *cardiovascular mortality, myocardial infarction (MI), stroke, vascular access thrombosis* • comparative effects of all ESAs uncertain • network analyses for major cardiovascular events, end-stage kidney disease (ESKD), fatigue and breathlessness not possible *fatigue* • effects of ESAs described heterogeneously, not useable for analyses
	2. Anmerkungen/Fazit der Autoren In the CKD setting, there is currently insufficient evidence to suggest the superiority of any ESA formulation based on available safety and efficacy data. Directly comparative data for the effectiveness of different ESA formulations based on patient-centred outcomes (such

	as quality of life, fatigue, and functional status) are sparse and poorly reported and current research studies are unable to inform care. All proprietary ESAs (epoetin alfa, epoetin beta, darbepoetin alfa, and methoxy polyethylene glycol-epoetin beta) prevent blood transfusions but information for biosimilar ESAs is less conclusive. Comparative treatment effects of different ESA formulations on other patient-important outcomes such as survival, MI, stroke, breathlessness and fatigue are very uncertain. For consumers, clinicians and funders, considerations such as drug cost and availability and preferences for dosing frequency might be considered as the basis for individualising anaemia care due to lack of data for comparative differences in clinical benefits and harms. *3. Kommentare zum Review* Einschluss dialysepflichtiger und nicht dialysepflichtiger Patienten Untersuchungen und Diskussion der Annahmen bzgl. Transitivität (Ähnlichkeit), Homogenität und Konsistenz innerhalb des Netzwerkes wurden durchgeführt: • important clinical diversity in studies based on the age of the participants, stage of CKD and duration of treatment • Treatment estimates from direct and indirect evidence in networks with closed loops did not show evidence of statistical inconsistency except for three of the five loops for hypertension; results for inconsistency were very imprecise as individual direct and indirect estimates were themselves imprecise and so the possibility of inconsistency in network analyses for other outcomes could not be excluded. • there was an indication that global inconsistency was present within the networks for blood transfusion and hypertension • presence of low to moderate heterogeneity in networks for blood transfusion and hypertension → Limitationen spiegeln sich in der GRADE-Bewertung wider
Cody JD et al., 2016 [3]. Recombinant human erythropoietin versus placebo or no treatment for the anaemia of chronic kidney disease in people not	1. Fragestellung The objective of this review was to ascertain the effects of recombinant human erythropoietin (rHuEPO) treatment in predialysis patients primarily in terms of the timing of the onset of dialysis; but also that predialysis rHuEPO: 1) corrects haemoglobin/haematocrit (markers of anaemia); 2) improves quality of life; and 3) is not associated with an increased incidence of adverse events such as hastening of the onset of dialysis, increased hypertension, clotting of arterio-venous fistulae or seizures.

requiring dialysis.	2. Methodik **Population**: Patients of any age with the anaemia of CKD who have not yet commenced dialysis **Intervention:** rHuEPO irrespective of dose or mode of delivery **Komparato**r: placebo or no rHuEPO **Endpunkt:** correction of anaemia, progression of kidney failure (time from start of rHuEPO to start of dialysis; numbers starting renal replacement therapy; GFR, serum creatinine), QoL, hypertension, safety, mortality **Suchzeitraum:** to 29 June 2015 **Anzahl eingeschlossene Studien**/Patienten (Gesamt): 19 (n=993) **Qualitätsbewertung der Studien:** Cochrane Risk of Bias Tool
	3. Ergebnisse *Risk of Bias* • The risk of bias was reassessed for 13 studies; for the 6 studies only reported as a conference abstract (and therefore the risk of bias was not assessed) • Studies at unclear to high risk of bias *Results* • improvement in haemoglobin (MD 1.90 gm/L, 95% CI -2.34 to -1.47) and haematocrit (MD 9.85%, 95% CI 8.35 to 11.34) with treatment and a decrease in the number of patients requiring blood transfusions (RR 0.32, 95% CI 0.12 to 0.83). • Most of the measures of progression of kidney disease showed no statistically significant difference. • The data from studies reporting quality of life or exercise capacity demonstrated an improvement in the treatment group. • Blood pressure control: no sig. differences in blood pressure detected between groups • No significant increase in adverse events
	4. Fazit der Autoren Treatment with rHuEPO in predialysis patients corrects anaemia, avoids the requirement for blood transfusions and also improves quality of life and exercise capacity. We were unable to assess the effects of rHuEPO on progression of kidney disease, delay in the onset of dialysis or adverse events.
Hahn D et al., 2017 [7]. Short-acting erythropoiesis-stimulating	1. Fragestellung To evaluate the benefits and harms of different routes, frequencies and doses of epoetins (epoetin alpha, epoetin beta and other short-acting epoetins) for anaemia in adults and children with CKD not receiving dialysis.

agents for anaemia in predialysis patients.	2. Methodik **Population**: Patients of any age (adults and children)with anaemia due to CKD (stages 2 to 5) of any severity, who were not receiving dialysis **Intervention:** Short-acting ESAs including epoetins alpha, beta, delta, epoetin theta and biosimilars of epoetin alpha, epoetin zeta including different routes of administration, doses and frequencies **Komparato**r: k.A. **Endpunkte:** death, correction of anaemia, QoL, hypertension and blood pressure outcomes, cardiovascular morbidity, cerebrovascular morbidity, adverse effects, Kidney function measures, need for iron supplementation **Suchzeitraum:** 12 September 2016 **Anzahl eingeschlossene Studien**/Patienten (Gesamt): 14 RCTs (n=2616) **Qualitätsbewertung der Studien:** Cochrane Risk of Bias Tool; GRADE for assessing of overall quality of evidence
	3. Ergebnisse The risk of bias was high in most studies. <u>Comparision of different doses:</u> no significant differences in final haemoglobin (Hb) levels • when dosing every 2 weeks was compared with weekly dosing (4 studies, 785 participants: MD -0.20 g/dL, 95% CI -0.33 to -0.07), • when 4 weekly dosing was compared with 2weekly dosing (three studies, 671 participants: MD -0.16 g/dL, 95% CI -0.43to 0.10) or • when different total doses were administered at the same frequency (4 weekly administration: 1 study, 144 participants: MD 0.17 g/dL 95% CI -0.19 to 0.53). Mortality was only detailed adequately in four studies and only one study included quality of life data (no statistical differences in the final QOL scores and mortality between groups receiving epoetin once weekly or two weekly) <u>Comparison of different EPO</u> Epoetin theta vs epoetin alpha (1 study, 288 participants) • no significant differences in Hb levels (MD -0.02 g/dL, 95% CI -0.25 to 0.21, moderate quality of evidence). • no significant differences in all-cause mortality, transfusions, discontinuation of therapy (all low quality of evidence) and hypertension (moderate quality of evidence)

	Subcutaneous epoetin alpha vs with epoetin beta (1 study, 29 patients) • significantly higher pain scores with subcutaneous epoetin alpha compared with epoetin beta. Epoetin delta vs epoetin alpha (2 studies (165 participants)) • with no results available since the pharmaceutical company withdrew epoetin delta for commercial reasons. BiosimilarHX575 (s.c) vs epoetin alpha (s.c) (1 study) • The study was stopped after patients receiving HX575 subcutaneously developed anti-epoetin antibodies and no results were available. Adverse events were poorly reported in all studies and did not differ significantly within comparisons.
	4. Fazit der Autoren Epoetin alpha given at higher doses for extended intervals (two or four weekly) is non-inferior to more frequent dosing intervals in maintaining final Hb levels with no significant differences in adverse effects in non-dialysed CKD patients. However the data are of low methodological quality so that differences in efficacy and safety cannot be excluded. Further large, well designed, RCTs with patient centred outcomes are required to assess the safety and efficacy of large doses of the shorter acting ESAs, including biosimilars of epoetin alpha, administered less frequently compared with more frequent administration of smaller doses in children and adults with CKD not on dialysis

Systematische Reviews

Collister D et al., 2016 [4]. The Effect of Erythropoietin-Stimulating Agents on Health-Related Quality of Life in Anemia of Chronic Kidney Disease: A Systematic Review and Meta-analysis.	1. Fragestellung To determine the effect of ESAs on HRQOL at different hemoglobin targets in adults with CKD who were receiving or not receiving dialysis.
	2. Methodik **Population**: Adults >18 years of age with predialysis CKD (eGFR<60ml/min/1.7 3m2 for >3 months) or end stage renal disease (hemodialysis or peritoneal dialysis) and anemia of CKD **Intervention:** ESA (erythropoietin, darbopoetin) for the correction of anemia of CKD allowing any concomitant iron supplementation strategy **Komparato**r: placebo /intermediate hemoglobin target versus high hemoglobin target **Endpunkt:** QoL: e.g. SF-36, KDQ, SIP, LASA, others **Recherche:** in PubMed, EMBASE, the Cochrane Library, and ClinicalTrials.gov. from date of their establishment until 1 November 2015. **Anzahl eingeschlossene Studien**/Patienten (Gesamt): 17 **Qualitätsbewertung der Studien:** Cochrane Risk of bias tool
	3. Ergebnisse *Characteristics of the included studies:* Population: • 12 were in the nondialysis CKD population, • 4 were in the dialysis population, • 1 was in a combined sample. Comparisons: • 3 studies on erythropoietin alfa (EPO) vs placebo, • 2 studies on darbepoetin (DPO) vs placebo, • 1 study on EPO vs DPO, • 11 studies on EPO vs EPO. Follow-up ranged from 8 w to 36 mo, with achieved hemoglobin ranging from 7.4 to 12 g/L for the placebo/lower hemoglobin target and 10.2 to 13.6 g/L for the higher hemoglobin target Studies were at unclear or high risk of bias. *Results* <u>SF-36 (13 trials)</u> Randomization to a higher hemoglobin target resulted in no statistically significant improvement in any SF-36 domain

	<u>Kidney Disease Questionnaire (KDQ) (4 trials)</u> Randomization to a higher hemoglobin target resulted in a mean improvement of 0.5 (CI, -2.2 to 1.2) points in the physical symptoms domain, 0.5 (CI, -1.6 to 0.5) points in the fatigue domain, and 0.2 (CI, -1.1 to 0.8) points in the depression domain, but none of these differences were statistically significant <u>Subgroup Analyses</u> • improvement in Physical function in the nondialysis CKD subgroup (3.61 [CI, -6.54 to-0.67]), but this difference was not clinically significant. • no statistically significant differences in the dialysis CKD subgroup; however, only 2 studies reported data on SF-36 domains in patients undergoing dialysis. No other subgroup analyses showed meaningful differences in treatment efficacy
	4. Anmerkungen/Fazit der Autoren ESA treatment of anemia in patients with dialysis-dependent and -independent CKD to higher hemoglobin targets did not result in statistically or clinically significant differences in HRQOL.
Wilhelm-Leen ER, Winkelmayer WC, 2015 [14]. Mortality Risk of Darbepoetin Alfa Versus Epoetin Alfa in Patients With CKD: Systematic Review and Meta-analysis	1. Fragestellung To our knowledge, no study has specifically compared the risks of hard study outcomes between EPO and DPO, such as mortality or cardiovascular events. To fill this evidence gap, we conducted a systematic review and meta-analysis of randomized trials that conducted head-to-head comparisons between EPO and DPO.
	2. Methodik Population: anemia in adults with chronic kidney disease, including those requiring dialysis Intervention/Komparator: DPO versus EPO Endpunkt: all-cause mortality Suchzeitraum: on June 1, 2014; all years Anzahl eingeschlossene Studien/Patienten (Gesamt): 9/2 024 Qualitätsbewertung der Studien: nicht anhand eines Instrumentes bewertet
	3. Ergebnisdarstellung quality of trials (siehe Anhang) • variable: all randomized, 3 double blinded, 6 open label, 5 published in peer reviewed literature, 3 published as

	abstracts, results from 1 trial only on the internet available • studies generally were subject to small enrollment and short follow-up, almost all were funded by industry sponsors results • 126 deaths during follow-up (range from 20 to 52 weeks) • No significant difference in mortality between patients randomly assigned to DPO versus EPO (OR, 1.33; 95% CI, 0.88-2.01) no treatment heterogeneity across studies detected (Q statistic = 4.60; P = 0.8)
	4. Anmerkungen/Fazit der Autoren Few trials directly comparing DPO and EPO have been conducted and follow-up was limited. In aggregate, no effect of specific erythropoiesis-stimulating agent on mortality was identified, but the confidence limits were wide and remained compatible with considerable harm from DPO. Absent adequately powered randomized trials, observational postmarketing comparative effectiveness studies comparing these erythropoiesis-stimulating agents are required to better characterize the long-term safety profiles of these agents. *5. Kommentare zum Review* • Publication bias nicht untersucht • study supported by grant R01DK090181 from the National Institutes of Health, National Institute for Diabetes and Digestive and Kidney Diseases (NIDDK) • Financial Disclosure: Winkelmayer reports having served within the past 36 months as a scientific advisor to and on data safety monitoring boards for different companies. Wilhelm-Leen declares that she had no relevant financial interests.
Covic A et al., 2014 [5]. Erythropoiesis-stimulating agents (ESA) for preventing the progression of chronic kidney disease: a meta-analysis of 19 studies	1. Fragestellung … we decided to perform a systematic analysis of the existing literature in order to establish if different degrees of anemia correction (low or high Hb targets) by ESAs may have different impact on renal function trajectories in CKD patients.
	2. Methodik **Population**: CKD patients stages 1–4 (as defined by the Kidney-Disease Outcomes and Quality Initiative [K-DOQI] guidelines: • stage 1 = GFR $\geq$ 90 ml/min/1.73 m^2 • stage 2 = GFR 60–89 ml/min/1.73 m^2 • stage 3 = GFR 30–59 ml/min/1.73 m^2

	• stage 4 = GFR 15–29 ml/min/1.73 m^2; • stage 5 = GFR <15 ml/min/1.73 m^2 not requiring dialysis) **Intervention:** ESAs (EPO (α or β) or darbepoetin) **Komparator:** lower doses of the same drugs or by a placebo or no treatment or blood transfusion **Endpunkt:** low or high Hb targets **Suchzeitraum:** January 1966 to 1st of January 2014 Anzahl eingeschlossene Studien/Patienten (Gesamt): 19/8 129 **Qualitätsbewertung der Studien:** according to recommendations from the Cochrane Collaboration
	3. Ergebnisdarstellung Study characteristics: • population sample sizes varied between 88 and 4,038 patients • study duration ranged from 12 weeks to 3.3 years • mean of the Glomerular filtration rate at the trial outsets: 16 to 51 ml/min 1.73 m^2 • baseline albuminuria/proteinuria: 0.5 to 3.1 g/day • 2 studies did not include patients with diabetes mellitus • 1 study included only renal transplant recipients • Risk of bias: unclear to high Results: risk of end-stage kidney disease • no difference (RR, 0.97 [CI 0.83–1.20], 17 trials, 8,104 participants), change in GFR • Mean Difference [MD] –0.45 [–2.21, 1.31], 9 trials, 1,848 participants) withdrawal of treatment due to adverse events • RR, 1.18 [CI 0.77–1.81], 10 trials, n = 1,958 participants for patients at higher hemoglobin (Hb) targets Mortality not statistically significant (Risk Ratio [RR] 1.10 [CI 0.90–1.35], 16 trials, n = 8,082 participants)
	4. Anmerkungen/Fazit der Autoren There is no evidence that ESA treatment affects renal function in patients with CKD. Use of these agents should not therefore be influenced by considerations about influencing CKD progression.

	5. Kommentare zum Review • Disclosure Statements: Adrian Covic received speaker honoraria from different companies and is a member of the European Renal Best Practices Board. David Goldsmith received speaker honoraria from different companies. • Role of Funding Source: No funding source was available for this study.
Alsalimy N, Awaisu A, 2014 [1]. Methoxy polyethylene glycol-epoetin beta versus darbepoetin alfa for anemia in non-dialysis-dependent CKD: a systematic review	1. Fragestellung To evaluate the efficacy and tolerability of MPG-EPO compared with other erythropoiesis stimulating agents (in particular darbepoetin alfa) for the treatment of anemia in non-dialysis-dependent CKD patients.
	2. Methodik **Population:** non-dialysis-dependent CKD patients **Intervention:** MPG-EPO **Komparator:** other erythropoiesis stimulating agents (in particular darbepoetin alfa) **Endpunkt:** efficacy and tolerability **Recherche:** in MEDLINE, Cochrane Database of Systematic Reviews, ScienceDirect, ProQuest, clinical trials registries (Clinical-Trials.gov and Roche Trials Database), and Google Scholar.There were no date restrictions placed on the electronic literature searches., Suchzeitraum: k.A. **Anzahl eingeschlossene Studien**/Patienten (Gesamt): 4/1 155 **Qualitätsbewertung der Studien**: using Jadad scale
	3. Ergebnisdarstellung • literature search only found studies comparing MPG-EPO to darbepoetin • no head-to-head studies comparing MPG-EPO with other ESAs • Jadad score ranged between 2 and 3 out of 5, predominantly due to the open-label design of the trials • 3 published in biomedical literature, 1 reported in ClinicalTrials.gov Quellen: 43. Roger SD, Locatelli F, Woitas RP, Laville M, Tobe SW, Provenzano R, et al. C.E.R.A. once every 4 weeks corrects anaemia and maintains haemoglobin in patients with chronic kidney disease not on dialysis. Neph Dial Trans. 2011;26:3980–6. 44. Macdougall IC, Walker R, Provenzano R, de Alvaro F, Locay HR, Nader PC, et al. C.E.R.A. corrects anemia in patients with chronic kidney disease not on dialysis: results of a randomized clinical trial. CJASN. 2008;3:337–47. 45. Kessler M, Martı´nez-Castelao A, Siamopoulos KC, Villa G, Spinowitz B, Dougherty FC, et al. C.E.R.A. once every 4 weeks in patients with chronic kidney disease not on dialysis: The

	ARCTOS extension study. Hemodial Int. 2010;14:233–9. 46. Hoffmann-La Roche. A study of subcutaneous mircera in patients with chronic kidney disease, not on dialysis. 2011. http://clinicaltrials.gov/show/NCT00442702. Results • changes in Hb level from baseline demonstrate that MPG-EPO clinically non-inferior to darbepoetin alfa • MPG-EPO-treated patients experienced a lower rate of Hb level above the target range of 12–13 g/dL than darbepoetin treated patients • proportion of patients requiring RBC transfusion higher among patients who received darbepoetin alfa than those who received MPG-EPO • time to Hb response longer with MPG-EPO than with darbepoetin • incidences of serious adverse events similar between the 2 drugs
	4. Anmerkungen/Fazit der Autoren There are currently only few well-designed head-to-head RCTs investigating the efficacy and safety of MPG-EPO compared with other ESAs in non-dialysis-dependent patients. MPG-EPO therapy compared with darbepoetin alfa has demonstrated favorable effects of increasing and maintaining hemoglobin concentrations to recommended target levels. This mini-review is not conclusive due to limited number of studies. Therefore, the beneficial effects and tolerability of MPG-EPO among non-dialysis-dependent CKD patients should be further investigated, given the economic and clinical benefits of managing anemia in this population. *5. Kommentare zum Review* • study self-initiated and self-supported; no funding obtained • authors have no competing interests to declare
Vinhas J et al., 2012 [13]. Treatment of anaemia with erythropoiesis-stimulating agents in patients with chronic kidney disease does not lower mortality and may increase	1. Fragestellung Evaluation of the benefits and harms of treating anaemia with ESAs in patients with CKD
	2. Methodik **Population:** adults with CKD **Intervention/Komparator**: • different doses of ESAs targeting two different haemoglobin levels • ESAs vs placebo **Endpunkte:** cascular access thrombosis, stroke, risk of ESRD and all-cause mortality

cardiovascular risk: a meta-analysis	**Studiendesign:** RCT, Dauer >= 12 Monate, mit >=500 Patienten **Recherche:** 01/2012 **Anzahl eingeschlossene Studien**/Patienten (Gesamt): 5 (n=7902) **Qualitätsbewertung der Studien**: the adequacy of randomisation, allocation concealment, blinding of patients, blinding of investigators, blinding of outcome assessors, use of intention-to-treat analysis, loss to follow-up, early stopping of trial, funding source, study chair and design, and Jadad score
	3. Ergebnisse • 5 Studien (N=7902) eingeschlossen • Studienqualität gering bis moderat, eine Studie mit geringem Biasrisiko Höhere versus niedrigere Hb-Zielwerte: • All-cause mortality: RR 1.148, 95%CI: 0.977-1.350 • End-Stage Renal Disease: RR 1.089, 95%CI:0.986-1.203 • Stroke: RR 1.735, 95%CI: 1.323-2.275 • Vascular Access Thrombosis: RR 1.343, 95%CI: 1.162-1.554
	4. Fazit der Autoren In CKD patients, treatment of anaemia with ESAs targeting a higher haemoglobin value does not lower mortality or reduce the risk of ESRD, and may increase cardiovascular risk.

Leitlinien

National Institute for Health and Care Excellence (NICE), 2015 [10]. Anaemia management in chronic kidney disease (NG8)	Fragestellung This guideline covers the management of anaemia in adults, children and young people with a clinical diagnosis of anaemia associated with CKD.
	Methodik Grundlage der Leitlinie: The basic steps in the process of producing a guideline are: – developing clinical evidence-based questions – systematically searching for the evidence – critically appraising the evidence – incorporating health economic evidence – distilling and synthesising the evidence and writing recommendations – grading the evidence statements and recommendations – agreeing the recommendations – structuring and writing the guideline – updating the guideline. Update: erste Version von 2006, This is a partial update of the 2011 clinical guideline on Anaemia Management in Chronic Kidney Disease. Suchzeitraum: searches were updated on 14 August 2014 LoE/GoR: siehe Anhang für Empfehlungen aus 2006 (später GRADE angewendet) Sonstige methodische Hinweise • *nur für einige Fragen systematische Literaturrecherchen durchgeführt,* • *unklar, wie die Aktualität der „alten" Empfehlungen überprüft wurde*
	Freitext/Empfehlungen/Hinweise <u>Clinical utility of ESA therapy in iron-replete patients</u> 1.2.3 The pros and cons of a trial of anaemia management should be discussed between the clinician, the person with anaemia of CKD, and their families and carers if applicable. [2006] 1.2.4 ESAs need not be administered where the presence of comorbidities, or the prognosis, is likely to negate the benefits of correcting the anaemia. [2006] 1.2.5 Initiate a trial of anaemia correction when there is uncertainty

over whether the presence of comorbidities, or the prognosis, would negate benefit from correcting the anaemia with ESAs. [2006]

1.2.6 Where a trial of ESA therapy has been performed, assess the effectiveness of the trial after an agreed interval. Where appropriate, a mutual decision should be agreed between the clinician, the person with anaemia of CKD and their families and carers on whether or not to continue ESA therapy. [2006]

1.2.7 Review all people started on ESA therapy after an agreed interval in order to decide whether or not to continue using ESAs. [2006]

Quellen:

A comprehensive literature search did not identify any studies that were suitable to address the clinical or economic aspects of this section, therefore no evidence statements are given.

Benefits of treatment with ESAs

1.3.1 Offer treatment with ESAs to people with anaemia of CKD who are likely to benefit in terms of quality of life and physical function. [2006]

Quellen:

1 Association between recombinant human erythropoietin and quality of life and exercise capacity of patients receiving haemodialysis. Canadian Erythropoietin Study Group. BMJ. 1990; 300(6724):573-578 (LoE 1+)

66 Churchill DN, Muirhead N, Goldstein M, Posen G, Fay W, Beecroft ML et al. Effect of recombinant human erythropoietin on hospitalization of hemodialysis patients. Clinical Nephrology. 1995; 43(3):184-188 (LoE 2+)

67 Cody J, Daly C, Campbell M, Donaldson C, Grant A, Khan I et al. Recombinant human erythropoietin for chronic renal failure anaemia in pre-dialysis patients. Cochrane Database of Systematic Reviews. 2004;(4) (LoE 1+)

256 Nissenson AR, Korbet S, Faber M, Burkart J, Gentile D, Hamburger R et al. Multicenter trial of erythropoietin in patients on peritoneal dialysis. Journal of the American Society of Nephrology. 1995; 5(7):1517-1529 ((insufficient mortality data)

Blood transfusions

1.3.3 In people with anaemia of CKD, there may be situations where a transfusion is indicated clinically. In these cases, follow the relevant national guidance.* [2006, amended 2015]

* NICE is developing the guideline ‘Blood transfusion’ (publication expected November 2015).

Quellen:

77 Crowley JP, Valeri CR, Metzger JB, Pono L, Chazan JA. Lymphocyte subpopulations in long-term dialysis patients: a case-controlled study of the effects of blood transfusion. Transfusion. 1990; 30(7):644-647 (LoE 2+)

Comparisons of ESAs

1.3.4 Discuss the choice of ESA with the person with anaemia of CKD when initiating treatment and at subsequent review, taking into consideration the patient's dialysis status, the route of administration and the local availability of ESAs. There is no evidence to distinguish between ESAs in terms of efficacy. [2006]

Quellen:

257 Nissenson AR, Swan SK, Lindberg JS, Soroka SD, Beatey R, Wang C et al. Randomized,

	controlled trial of darbepoetin alfa for the treatment of anemia in hemodialysis patients. American Journal of Kidney Diseases. 2002; 40(1):110-118 (LoE 1+) 358 Tolman C, Richardson D, Bartlett C, Will E. Structured conversion from thrice weekly to weekly erythropoietic regimens using a computerized decision-support system: a randomized clinical trial. Journal of the American Society of Nephrology. 2005; 16(5):1463-1470 (LoE 1+)
Department of Veterans Affairs, Department of Defense (VA/DoD), 2014 [9]. Clinical practice guideline for the management of chronic kidney disease in primary care	Fragestellung In adult patients with CKD and anemia, are ESAs safe and effective in increasing hemoglobin, improving QoL and slowing the progression of CKD and if so, how should iron be supplemented to optimize ESA effectiveness?
	Methodik The guideline development process for the 2014 CPG update consisted of the following steps: 1. Formulating evidence questions (Key Questions) 2. Conducting the systematic review 3. Convening a face-to-face meeting with the CPG Champions and Work Group members 4. Drafting and submitting a final CPG about the management of CKD to the VA/DoD EBPWG – *Update: Version 3.0 – 2014* – Suchzeitraum: 2007 through December 12, 2013 LoE/GoR: GRADE-Systematik
	Freitext/Empfehlungen/Hinweise <u>Safety and Efficacy of Erythropoiesis-Stimulating Agents</u> *Recommendation* 29 We recommend against offering erythropoietin-stimulating agents (ESAs) to patients with CKD for the purpose of achieving a hemoglobin target above 11.5 g/dL due to increased risk of stroke and hypertension. (Strong Against) 30 We recommend against initiating ESAs at a hemoglobin level greater than 10 g/dL. (Strong Against) *Discussion* The literature search included five systematic reviews, 13 RCTs and one case study which evaluated the safety and/or efficacy of ESA treatment in CKD patients with anemia. Outcomes of interest were all-cause mortality, cardiovascular mortality, stroke, myocardial infarction, worsening hypertension, progression to ESRD, mean decrease in GFR, and quality of life… . None of the drug-specific studies included in the recent literature search were relevant, due to the <u>drugs not being available on the U.S. market</u>. Therefore, the Work

	Group was not able to compare specific ESA drugs against each other or different dosing strategies based on the recent literature review. Quellen: 135. Akizawa T, Gejyo F, Nishi S, et al. Positive outcomes of high hemoglobin target in patients with chronic kidney disease not on dialysis: A randomized controlled study. Ther Apher Dial. Oct 2011;15(5):431-440. 136. Patel M, Thimons DG, Winston JL, Langholff W, McGowan T. An open-label, randomized, multicenter, controlled study of epoetin alfa for the treatment of anemia of chronic kidney disease in the long term care setting. J Am Med Dir Assoc. Mar 2012;13(3):244-248. 137. Villar E, Lievre M, Kessler M, et al. Anemia normalization in patients with type 2 diabetes and chronic kidney disease: Results of the NEPHRODIAB2 randomized trial. J Diabetes Complications. Jul-Aug 2011;25(4):237-243. 138. Pfeffer MA, Burdmann EA, Chen CY, et al. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. N Engl J Med. Nov 19 2009;361(21):2019-2032. 139. Palmer SC, Navaneethan SD, Craig JC, et al. Meta-analysis: Erythropoiesis-stimulating agents in patients with chronic kidney disease. Ann Intern Med. Jul 6 2010;153(1):23-33. 140. Koulouridis I, Alfayez M, Trikalinos TA, Balk EM, Jaber BL. Dose of erythropoiesis-stimulating agents and adverse outcomes in CKD: A metaregression analysis. Am J Kidney Dis. Jan 2013;61(1):44-56. 141. Palmer SC, Saglimbene V, Craig JC, Navaneethan SD, Strippoli GF. Darbepoetin for the anaemia of chronic kidney disease. Cochrane Database Syst Rev. 2014;3:Cd009297. 142. Jing Z, Wei-jie Y, Nan Z, Yi Z, Ling W. Hemoglobin targets for chronic kidney disease patients with anemia: A systematic review and meta-analysis. PLoS One. 2012;7(8):e43655. 143. Solomon SD, Uno H, Lewis EF, et al. Erythropoietic response and outcomes in kidney disease and type 2 diabetes. N Engl J Med. Sep 16 2010;363(12):1146-1155. 144. Skali H, Parving HH, Parfrey PS, et al. Stroke in patients with type 2 diabetes mellitus, chronic kidney disease, and anemia treated with darbepoetin alfa: The trial to reduce cardiovascular events with aranesp therapy (TREAT) experience. Circulation. Dec 20 2011;124(25):2903-2908. 145. Singh AK, Szczech L, Tang KL, et al. Correction of anemia with epoetin alfa in chronic kidney disease. N Engl J Med. Nov 16 2006;355(20):2085-2098. 146. Drueke TB, Locatelli F, Clyne N, et al. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. N Engl J Med. Nov 16 2006;355(20):2071-2084. 147. U.S. Department of Health and Human Services, Food and Drug Administration. FDA drug safety communication: Modified dosing recommendations to improve the safe use of erythropoiesis-stimulating agents (ESAs) in chronic kidney disease. Drug Safety and Availability 2011; http://www.fda.gov/Drugs/DrugSafety/ucm259639.htm. Accessed Aug 1, 2014.
Kidney Disease Improving Global Outcomes (KDIGO) Anemia Work Group 2012, [8]. KDIGO clinical practice guideline for anemia in	Fragestellung Evaluating anemia treatment, including treatment resistance <u>Population</u> Adults and children with CKD, any stage and any comorbidity (including cancer, CVD, etc.) <u>Intervention</u> RBC transfusions; Iron (all forms, routes of administration, dosages), ESA (all forms, dosages, targets, protocols, etc), pharmacological and non-pharmacological adjuvants to ESA including L-carnitine, vitamin C, androgens, pentoxifylline; other interventions used to treat or enhance the treatment of anemia or anemia-related symptoms <u>Comparator</u> Other interventions, ‘‘no’’ interventions, different forms, routes of administration, dosages, targets, protocols, schedules, etc.

chronic kidney disease	Outcomes Death, Cardiac events, Stroke, CKD progression, Quality of life, Thromboembolic events, Pulmonary embolism, Symptomatic deep vein thrombosis, Loss of vascular access, Transfusion requirements, Cognitive function, Sexual function, Other similar quality of life measures, Objective physical function tests, Infections, Loss of transplant eligibility due to antibody sensitization, Antibody sensitization, New cancer or progression of existing cancer, Seizure, Other clinically important adverse events, ESA dose: for comparisons of different ESA regimens and for iron and adjuvant interventions, Achieved Hb/Hb variability for comparisons of different ESA regimens and for iron and adjuvant interventions Study Design RCTs, N≥50 per arm, Minimum follow-up duration: 6 months
	Methodik: The International Society of Nephrology (ISN) aspires towards the elimination of kidney disease worldwide. Guideline development process included the following sequential and concurrent steps: • Appointing Work Group members and Evidence Review Team (ERT). • Discussing process, methods, and results. • Developing and refining topics. • Identifying populations, interventions or predictors, and outcomes of interest. • Selecting topics for systematic evidence review. • Standardizing quality assessment methodology. • Developing and implementing literature search strategies. • Screening abstracts and retrieving full text articles based on predefined eligibility criteria. • Creating data extraction forms. • Data extracting and performing critical appraisal of the literature. • Grading the methodology and outcomes in individual studies. • Tabulating data from individual studies into summary tables. • Grading quality of evidence for each outcome across studies, and assessing the overall quality of evidence across outcomes with the aid of evidence profiles. • Grading the strength of recommendations based on the quality of evidence and other considerations. • Finalizing guideline recommendations and supporting rationale statements. • Sending the guideline draft for peer review to the KDIGO Board of Directors in June 2011, and for public review in September 2011.

	• Publishing the final version of the guideline. – *Update: ältere Versionen von 2006 und 2007* – *Suchzeitraum: last conducted in October 2010, supplemented with additional evidence through March 2012* LoE/GoR: based on GRADE • LoE A: High, • LoE B: Moderate, • LoE C: Low, • LoE D: Very Low • GoR 1: We recommend (The recommendation can be evaluated as a candidate for developing a policy or a performance measure.) • GoR 2: We suggest (The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined) *Sonstige methodische Anmerkungen:* Interessenkonflikterklärungen liegen vor
	Empfehlungen <u>Chapter 3: Use of ESAs and other agents to treat anemia in CKD</u> ESA INITIATION 3.1: Address all correctable causes of anemia (including iron deficiency and inflammatory states) prior to initiation of ESA therapy. (Not Graded) 3.2: In initiating and maintaining ESA therapy, we recommend balancing the potential benefits of reducing blood transfusions and anemia-related symptoms against the risks of harm in individual patients (e.g., stroke, vascular access loss, hypertension). (1B) Quellen: 118. Besarab A, Bolton WK, Browne JK et al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. N Engl J Med 1998; 339: 584–590. 119. Parfrey PS, Wish T. Quality of life in CKD patients treated with erythropoiesis-stimulating agents. Am J Kidney Dis 2010; 55: 423–425. 122. Canadian Erythropoietin Study Group. Association between recombinant human erythropoietin and quality of life and exercise capacity of patients receiving haemodialysis. BMJ 1990; 300: 573–578. 123. Revicki DA, Brown RE, Feeny DH et al. Health-related quality of life associated with recombinant human erythropoietin therapy for predialysis chronic renal disease patients. Am J Kidney Dis 1995; 25: 548–554. 124. Drueke TB, Locatelli F, Clyne N et al. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. N Engl J Med 2006; 355: 2071–2084. 125. Furuland H, Linde T, Ahlmen J et al. A randomized controlled trial of haemoglobin normalization with epoetin alfa in pre-dialysis and dialysis patients. Nephrol Dial Transplant 2003; 18: 353–361. 126. Parfrey PS, Foley RN, Wittreich BH et al. Double-blind comparison of full and partial anemia correction in incident hemodialysis patients without symptomatic heart disease. J Am Soc Nephrol 2005; 16: 2180–2189. 127. Pfeffer MA, Burdmann EA, Chen CY et al. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. N Engl J Med 2009; 361: 2019–2032.

	128. Singh AK, Szczech L, Tang KL et al. Correction of anemia with epoetin alfa in chronic kidney disease. N Engl J Med 2006; 355: 2085–2098. 129. Foley RN, Curtis BM, Parfrey PS. Hemoglobin targets and blood transfusions in hemodialysis patients without symptomatic cardiac disease receiving erythropoietin therapy. Clin J Am Soc Nephrol 2008; 3: 1669–1675. 130. Foley RN, Curtis BM, Parfrey PS. Erythropoietin therapy, hemoglobin targets, and quality of life in healthy hemodialysis patients: a randomized trial. Clin J Am Soc Nephrol 2009; 4: 726–733. 131. FDA presentation at Cardiovascular and Renal Drugs Advisory Committee (CRDAC) meeting, 18 October 2010. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM231978.pdf. 132. Lewis EF, Pfeffer MA, Feng A et al. Darbepoetin alfa impact on health status in diabetes patients with kidney disease: a randomized trial. Clin J Am Soc Nephrol 2011; 6: 845–855. 133. Palmer SC, Navaneethan SD, Craig JC et al. Meta-analysis: erythropoiesisstimulating agents in patients with chronic kidney disease. Ann Intern Med 2010; 153: 23–33. 134. Gandra SR, Finkelstein FO, Bennett AV et al. Impact of erythropoiesisstimulating agents on energy and physical function in nondialysis CKD patients with anemia: a systematic review. Am J Kidney Dis 2010; 55: 519–534. 135. Johansen KL, Finkelstein FO, Revicki DA et al. Systematic review and meta-analysis of exercise tolerance and physical functioning in dialysis patients treated with erythropoiesis-stimulating agents. Am J Kidney Dis 2010; 55: 535–548. 3.3: We recommend using ESA therapy with great caution, if at all, in CKD patients with active malignancy—in particular when cure is the anticipated outcome—(1B), a history of stroke (1B), or a history of malignancy (2C). Quellen: 136. Rizzo JD, Brouwers M, Hurley P et al. American Society of Clinical Oncology/American Society of Hematology clinical practice guideline update on the use of epoetin and darbepoetin in adult patients with cancer. J Clin Oncol 2010; 28: 4996–5010. 137. Rizzo JD, Brouwers M, Hurley P et al. American Society of Hematology/American Society of Clinical Oncology clinical practice guideline update on the use of epoetin and darbepoetin in adult patients with cancer. Blood 2010; 116: 4045–4059. 138. Skali H, Parving HH, Parfrey PS et al. Stroke in patients with type 2 diabetes mellitus, chronic kidney disease, and anemia treated with Darbepoetin Alfa: the trial to reduce cardiovascular events with Aranesp therapy (TREAT) experience. Circulation 2011; 124: 2903–2908. 3.4.1: For adult CKD ND patients with Hb concentration ≥10.0 g/dl (≥100 g/l), we suggest that ESA therapy not be initiated. (2D) 3.4.2: For adult CKD ND patients with Hb concentration <10.0 g/dl (<100 g/l) we suggest that the decision whether to initiate ESA therapy be individualized based on the rate of fall of Hb concentration, prior response to iron therapy, the risk of needing a transfusion, the risks related to ESA therapy and the presence of symptoms attributable to anemia. (2C) 3.4.3: For adult CKD 5D patients, we suggest that ESA therapy be used to avoid having the Hb concentration fall below 9.0 g/dl (90 g/l) by starting ESA therapy when the hemoglobin is between 9.0–10.0 g/dl (90–100 g/l). (2B) 3.4.4: Individualization of therapy is reasonable as some patients may have improvements in quality of life at higher Hb concentration and ESA therapy may be started above 10.0 g/dl (100 g/l). (Not Graded)

	3.4.5: For all pediatric CKD patients, we suggest that the selection of Hb concentration at which ESA therapy is initiated in the individual patient includes consideration of potential benefits (e.g., improvement in quality of life, school attendance/performance, and avoidance of transfusion) and potential harms. (2D) Quellen (s.o. und …): 58. National Kidney Foundation. KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Anemia in Chronic Kidney Disease. Section III. Clinical practice recommendations for anemia in chronic kidney disease in children. Am J Kidney Dis 2006; 47: S86–108. 139. Warady BA, Ho M. Morbidity and mortality in children with anemia at initiation of dialysis. Pediatr Nephrol 2003; 18: 1055–1062. 140. Mitsnefes MM, Kimball TR, Kartal J et al. Progression of left ventricular hypertrophy in children with early chronic kidney disease: 2-year followup study. J Pediatr 2006; 149: 671–675. 141. Schaefer F. Cardiac disease in children with mild-to-moderate chronic kidney disease. Curr Opin Nephrol Hypertens 2008; 17: 292–297. 142. Morris KP, Sharp J, Watson S et al. Non-cardiac benefits of human recombinant erythropoietin in end stage renal failure and anaemia. Arch Dis Child 1993; 69: 580–586. 143. Gerson A, Hwang W, Fiorenza J et al. Anemia and health-related quality of life in adolescents with chronic kidney disease. Am J Kidney Dis 2004; 44: 1017–1023. TYPE OF ESA 3.11.1: We recommend choosing an ESA based on the balance of pharmacodynamics, safety information, clinical outcome data, costs, and availability. (1D) 3.11.2: We suggest using only ESAs that have been approved by an independent regulatory agency. Specifically for ‘copy’ versions of ESAs, true biosimilar products should be used. (2D) Quellen: 158. Boven K, Stryker S, Knight J et al. The increased incidence of pure red cell aplasia with an Eprex formulation in uncoated rubber stopper syringes. Kidney Int 2005; 67: 2346–2353. 159. Casadevall N, Nataf J, Viron B et al. Pure red-cell aplasia and antierythropoietin antibodies in patients treated with recombinant erythropoietin. N Engl J Med 2002; 346: 469–475. 160. Macdougall IC, Ashenden M. Current and upcoming erythropoiesisstimulating agents, iron products, and other novel anemia medications. Adv Chronic Kidney Dis 2009; 16: 117–130. ADJUVANT THERAPIES 3.16.1: We recommend not using androgens as an adjuvant to ESA treatment. (1B) 3.16.2: We suggest not using adjuvants to ESA treatment including vitamin C, vitamin D, vitamin E, folic acid, L-carnitine, and pentoxifylline. (2D) Quellen: 170. Berns JS, Rudnick MR, Cohen RM. A controlled trial of recombinant human erythropoietin and nandrolone decanoate in the treatment of anemia in patients on chronic hemodialysis. Clin Nephrol 1992; 37: 264–267. 171. Gaughan WJ, Liss KA, Dunn SR et al. A 6-month study of low-dose recombinant human erythropoietin alone and in combination with androgens for the treatment of anemia in chronic hemodialysis patients. Am J Kidney Dis 1997; 30: 495–500. 172. Sheashaa H, Abdel-Razek W, El-Husseini A et al. Use of nandrolone decanoate as an adjuvant for erythropoietin dose reduction in treating anemia in patients on hemodialysis.

Nephron Clin Pract 2005; 99: c102–c106.

173. Bridges KR, Hoffman KE. The effects of ascorbic acid on the intracellular metabolism of iron and ferritin. J Biol Chem 1986; 261: 14273–14277.

174. Lipschitz DA, Bothwell TH, Seftel HC et al. The role of ascorbic acid in the metabolism of storage iron. Br J Haematol 1971; 20: 155–163.

175. Deved V, Poyah P, James MT et al. Ascorbic acid for anemia management in hemodialysis patients: a systematic review and meta-analysis. Am J Kidney Dis 2009; 54: 1089–1097.

176. Shahrbanoo K, Taziki O. Effect of intravenous ascorbic acid in hemodialysis patients with anemia and hyperferritinemia. Saudi J Kidney Dis Transpl 2008; 19: 933–936.

177. Attallah N, Osman-Malik Y, Frinak S et al. Effect of intravenous ascorbic acid in hemodialysis patients with EPO-hyporesponsive anemia and hyperferritinemia. Am J Kidney Dis 2006; 47: 644–654.

178. Sezer S, Ozdemir FN, Yakupoglu U et al. Intravenous ascorbic acid administration for erythropoietin-hyporesponsive anemia in iron loaded hemodialysis patients. Artif Organs 2002; 26: 366–370.

Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren

Canadian Agency for Drugs and Technologies in Health (CADTH), 2015 [2]. Erythropoiesis Stimulating Agents in Chronic Kidney Disease: Clinical Effectiveness and Guidelines	1. Fragestellung 1. What are the clinical benefits and harms of erythropoiesis stimulating agents in the treatment of patients with chronic kidney disease and hemoglobin ≥100 g/L? 2. What are the evidence-based guidelines for erythropoiesis stimulating agents in the treatment of patients with chronic kidney disease and hemoglobin ≥100 g/L?
	2. Methodik **Population**: Patients with CKD and Hb ≥100 g/L with no symptoms of anemia **Intervention:** ESAs **Komparator:** Delayed ESAs, Other therapies **Endpunkt:** Clinical effectiveness (benefits [normalize Hb levels, survival] and harms) Guidelines **Suchzeitraum:** between January 1, 2010 and March 4, 2015 **Qualitätsbewertung der Studien**: k.A.
	3. Ergebnisdarstellung • 2 SR, 1 RCT reported in two publications, and 2 evidence-based guidelines identified; no relevant HTA identified • References where it was stated that patients had anemia but where symptom status was unclear were included in this report. One systematic review[1] of randomized trials examined the potential effects of targeted hemoglobin (Hb) levels (high Hb, approximately 13.0 g/dL; low Hb, approximately 10.0 g/dL) on clinical outcomes in CKD patients with anemia who were treated with ESAs. The authors reported a statistically significant increased risk of mortality, hospitalization, stroke, and hypertension with high Hb levels, but no increased risk in non-fatal myocardial infarction and renal replacement therapy. The authors concluded that targeting low Hb levels was beneficial to CKD patients, with this benefit being greater in the pre-dialysis population.[1] Another systematic review and meta-analysis[2] of randomised controlled trials, which allocated patients to different ESA doses, reported that higher Hb targets were associated with increased risk of vascular access thrombosis and stroke. No impacts of higher Hb targets were observed on end-stage renal disease or all-cause mortality.[2]

	The identified RCT[3] examined the effects of maintaining high Hb on renal function in patients with CKD who were not on dialysis. Patients were randomized to either a high Hb group (Hb equal to 11.0 g/dL through 13.0 g/dL) receiving darbepoetin alfa or a low Hb group (Hb equal to 9.0 g/dL through 11.0 g/dL) with epoetin alfa. Three-year cumulative renal survival rates were higher in the high Hb group compared with the low Hb group (39.9% versus 32.4%, respectively) although this difference was not statistically significant. Lower event rates were observed in the high Hb group; however, there were no between-group differences in the incidence of serious adverse cardiovascular events and no safety issues were noted in either group. In a separate publication of the same trial,[4] the authors reported a statistically significantly greater impact on quality of life in the high Hb group. In addition, a statistically significant decrease in the left ventricular mass index was observed in the high Hb group, while this index remained stable in the low Hb group. Quellen: **Systematic Reviews and Meta-analyses** 1. Jing Z, Wei-jie Y, Nan Z, Yi Z, Ling W. Hemoglobin targets for chronic kidney disease patients with anemia: a systematic review and meta-analysis. PLoS ONE [Internet]. 2012 [cited 2015 Mar 11];7(8):e43655. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3431367 PubMed: PM22952731 (→ von dieser Synopse ausgeschlossen aufgrund anderer Fragestellung) 2. Vinhas J, Barreto C, Assuncao J, Parreira L, Vaz A. Treatment of anaemia with erythropoiesis-stimulating agents in patients with chronic kidney disease does not lower mortality and may increase cardiovascular risk: a meta-analysis. Nephron Clin Pract. 2012;121(3-4):c95-101. PubMed: PM23182871 (→Einschluss in Evidenzsynopse) **Randomized Controlled Trial** 3. Tsubakihara Y, Gejyo F, Nishi S, Iino Y, Watanabe Y, Suzuki M, et al. High target hemoglobin with erythropoiesis-stimulating agents has advantages in the renal function of non-dialysis chronic kidney disease patients. Ther Apher Dial. 2012 Dec;16(6):529-40. PubMed: PM23190512 4. Akizawa T, Gejyo F, Nishi S, Iino Y, Watanabe Y, Suzuki M, et al. Positive outcomes of high hemoglobin target in patients with chronic kidney disease not on dialysis: a randomized controlled study. Ther Apher Dial. 2011 Oct;15(5):431-40. PubMed: PM21974695 **Guidelines and Recommendations** 5. National Guideline Clearinghouse [Internet]. Rockville (MD): Agency for healthcare Research and Quality (AHRQ); [1997] -. Guiodeline summary: Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO clinical practice guideline for anemia in chronic kidney disease. 2012 Aug [cited 2015 Mar 4]. Available from: http://www.guideline.gov/content.aspx?id=38245&search=erythropoiesis+stimulating. (siehe unten) *6. Mikhail A, Shrivastava R, Richardson D. Clinical practice guidelines: anaemia of CKD. Draft Version [Internet]. 5th ed., 2009-2012. Petersfield (Hampshire): UK Renal Association; 2010 Feb 15 [cited 2015 Mar 4]. Available from: http://www.renal.org/docs/default-source/guidelines-resources/Anaemia_in_CKD_Draft_Version_-_15_February_2010.pdf?sfvrsn=0*
	4. Anmerkungen/Fazit der Autoren Two systematic reviews, one randomized controlled trial reported in two publications, and two evidence-based guidelines were identified regarding erythropoiesis stimulating agents in chronic kidney disease.

Detaillierte Darstellung der Recherchestrategie

Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database) am 20.04.2017

#	Suchfrage
1	MeSH descriptor: [Renal Insufficiency, Chronic] explode all trees
2	(renal or kidney*):ti,ab,kw (Word variations have been searched)
3	(disease* or failure or insufficien*):ti,ab,kw (Word variations have been searched)
4	#2 and #3
5	ckd:ti,ab,kw (Word variations have been searched)
6	MeSH descriptor: [Renal Dialysis] explode all trees
7	(dialy* or hemodialy* or haemodialy*):ti,ab,kw (Word variations have been searched)
8	#1 or #4 or #5 or #6 or #7
9	MeSH descriptor: [Anemia] explode all trees
10	(anemi* or anaemi*):ti,ab,kw (Word variations have been searched)
11	#9 or #10
12	#8 and #11
13	#12 Publication Year from 2012 to 2017, in Cochrane Reviews (Reviews only) and Technology Assessments

SR, HTAs in Medline (PubMed) am 19.04.2017

#	Suchfrage
1	chronic renal insufficiency[MeSH Terms]
2	(renal[Title/Abstract]) OR kidney*[Title/Abstract]
3	((disease*[Title/Abstract]) OR failure[Title/Abstract]) OR insufficien*[Title/Abstract]
4	(#2) AND #3
5	ckd[Title/Abstract]
6	renal dialysis[MeSH Terms]
7	((dialy*[Title/Abstract]) OR haemodialy*[Title/Abstract]) OR hemodialy*[Title/Abstract]
8	((((#1) OR #4) OR #5) OR #6) OR #7
9	anemia[MeSH Terms]
10	(anemi*[Title/Abstract]) OR anaemi*[Title/Abstract]
11	(#9) OR #10
12	(#8) AND #11
13	(#12) AND ((Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp]) OR (((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract] OR Medline[Title/Abstract] OR Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR Pubmed[Title/Abstract])) AND systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR ((((((((((HTA[Title/Abstract]) OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR

	(systematic*[Title/Abstract] AND overview*[Title/Abstract])) OR meta-analy*[Title/Abstract]) OR (meta[Title/Abstract] AND analyz*[Title/Abstract])) OR (meta[Title/Abstract] AND analys*[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract]))) OR (((review*[Title/Abstract]) OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract]) AND based[Title/Abstract]))))
14	(#13) AND ("2012/04/01"[PDAT] : "2017/04/30"[PDAT])

Leitlinien in Medline (PubMed) am 19.04.2017

#	**Suchfrage**
1	chronic renal insufficiency[MeSH Terms]
2	(renal[Title/Abstract]) OR kidney*[Title/Abstract]
3	((disease*[Title/Abstract]) OR failure[Title/Abstract]) OR insufficien*[Title/Abstract]
4	(#2) AND #3
5	ckd[Title/Abstract]
6	renal dialysis[MeSH Terms]
7	((dialy*[Title/Abstract]) OR haemodialy*[Title/Abstract]) OR hemodialy*[Title/Abstract]
8	((((#1) OR #4) OR #5) OR #6) OR #7
9	anemia[MeSH Terms]
10	(anemi*[Title/Abstract]) OR anaemi*[Title/Abstract]
11	(#9) OR #10
12	(#8) AND #11
13	(#12) AND ((((((Guideline[Publication Type]) OR Practice Guideline[Publication Type]) OR Consensus Development Conference[Publication Type]) OR Consensus Development Conference, NIH[Publication Type]) OR guideline*[Title]) OR recommendation*[Title])
14	(((#13) AND ("2012/04/01"[PDAT] : "2017/04/30"[PDAT]))

Literatur

1. **Alsalimy N, Awaisu A.** Methoxy polyethylene glycol-epoetin beta versus darbepoetin alfa for anemia in non-dialysis-dependent CKD: a systematic review. Int J Clin Pharm 2014;36(6):1115-1125.

2. **Canadian Agency for Drugs and Technologies in Health (CADTH).** Erythropoiesis stimulating agents in chronic kidney disease: clinical effectiveness and guidelines [online]. Ottawa (CAN): CADTH; 2015. [Zugriff: 20.04.2017]. URL: https://www.cadth.ca/sites/default/files/pdf/htis/mar-2015/RB0815%20Erythropoiesis%20stimulating%20agents%20in%20CKD%20Final.pdf.

3. **Cody JD, Hodson EM.** Recombinant human erythropoietin versus placebo or no treatment for the anaemia of chronic kidney disease in people not requiring dialysis. Cochrane Database of Systematic Reviews [online]. 2016(1):Cd003266. URL: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003266.pub3/abstract.

4. **Collister D, Komenda P, Hiebert B, Gunasekara R, Xu Y, Eng F, et al.** The Effect of Erythropoietin-Stimulating Agents on Health-Related Quality of Life in Anemia of Chronic Kidney Disease: A Systematic Review and Meta-analysis. Ann Intern Med 2016;164(7):472-478.

5. **Covic A, Nistor I, Donciu MD, Dumea R, Bolignano D, Goldsmith D.** Erythropoiesis-stimulating agents (ESA) for preventing the progression of chronic kidney disease: a meta-analysis of 19 studies. Am J Nephrol 2014;40(3):263-279.

6. **Gemeinsamer Bundesausschuss (G-BA).** Bekanntmachung eines Beschlusses des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL) in Anlage IV: Therapiehinweis zu Erythropoese-stimulierenden Wirkstoffen (zur Behandlung der symptomatischen renalen Anämie), vom 23. Juni 2011 [online]. Berlin (GER): G-BA; 2011. [Zugriff: 20.04.2017]. URL: https://www.g-ba.de/downloads/39-261-1341/2011-06-23_AM-RL-IV_Erythropoese_BAnz.pdf.

7. **Hahn D, Esezobor CI, Elserafy N, Webster AC, Hodson EM.** Short-acting erythropoiesis-stimulating agents for anaemia in predialysis patients. Cochrane Database of Systematic Reviews [online]. 2017(1):Cd011690. URL: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD011690.pub2/abstract.

8. **Kidney Disease Improving Global Outcomes (KDIGO) Anemia Work Group.** KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. Kidney Int Suppl 2012;2(4):279-335.

9. **Management of Chronic Kidney Disease Working Group.** VA/DoD clinical practice guideline for the management of chronic kidney disease in primary care, Version 3.0 [online]. Washington DC (USA): Department of Veterans Affairs, Department of Defense; 2014. [Zugriff: 20.04.2017]. URL: https://www.healthquality.va.gov/guidelines/CD/ckd/VADoDCKDCPG2014.pdf.

10. **National Clinical Guideline Centre, National Institute for Health and Care Excellence (NICE).** Anaemia management in chronic kidney disease: partial update 2015 [online]. London (GBR): NICE; 2015. [Zugriff: 20.04.2017]. (NICE guideline; Band 8). URL: https://www.nice.org.uk/guidance/ng8/evidence/full-guideline-pdf-70545133.

11. **Palmer SC, Saglimbene V, Craig JC, Navaneethan SD, Strippoli GF.** Darbepoetin for the anaemia of chronic kidney disease. Cochrane Database of Systematic Reviews [online]. 2014(3):Cd009297.
URL: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD009297.pub2/abstract.

12. **Palmer SC, Saglimbene V, Mavridis D, Salanti G, Craig JC, Tonelli M, et al.** Erythropoiesis-stimulating agents for anaemia in adults with chronic kidney disease: a network meta-analysis. Cochrane Database of Systematic Reviews [online]. 2014(12):Cd010590.
URL: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD010590.pub2/abstract.

13. **Vinhas J, Barreto C, Assuncao J, Parreira L, Vaz A.** Treatment of anaemia with erythropoiesis-stimulating agents in patients with chronic kidney disease does not lower mortality and may increase cardiovascular risk: a meta-analysis. Nephron Clin Pract 2012;121(3-4):c95-101.

14. **Wilhelm-Leen ER, Winkelmayer WC.** Mortality risk of darbepoetin alfa versus epoetin alfa in patients with CKD: systematic review and meta-analysis. Am J Kidney Dis 2015;66(1):69-74.

Anhang

Tabelle 1 : aus Wilhelm-Leen ER, Winkelmayer WC. 2015

Table 1. Description of Included Studies and Key Quality Measures

Study	Design and Study Population	N	Double-Blinded	Full-Text Publication	Follow-up Period
Coyne et al[11] (2000) (Amgen #980211)	ESRD- and ESA- naive patients 3:1 randomly assigned to weekly DPO vs 3×/wk EPO	122	No	No	20 wk
Locatelli et al[6] (2001) (Amgen #980202)	Non-ESRD and ESA-naive patients with eGFR ≤ 30 mL/min, 3:1 randomly assigned to DPO weekly vs EPO 2×/wk	166	No	Yes	24 wk
Allon et al[7] (2002) (Amgen #970235)	ESRD patients already on EPO 1:1:1 randomly assigned to DPO weekly, DPO 3×/wk, or EPO 3×/wk	47	No	Yes	52 wk
Nissenson et al[8] (2002) (Amgen #980117)	ESRD patients already on EPO 2:1 randomly assigned to EPO 3×/wk vs DPO weekly	507	Yes	Yes	28 wk
Vanrenterghem et al[9] (2002) (Amgen #980200)	ESRD patients already on EPO 2:1 randomly assigned to DPO weekly or every other week vs epoetin (82% EPO; 18% epoetin beta) 1-3×/wk	522	No	Yes	52 wk
Hori et al[12] (2004) (Kirin Pharma Co)	ESRD patients already on EPO 2-3×/wk 1:1 randomly assigned to continue EPO vs DPO weekly	120	Yes	Yes	28 wk
Amgen #200010125[15] (2005)	African American ESRD patients already on EPO 3×/wk 1:1 randomly assigned to continue EPO vs DPO weekly	407	Yes	No	28 wk
Li et al[10] (2008) (Kirin Pharma Co)	ESRD patients on peritoneal dialysis already on EPO 1:1 randomly assigned to continue EPO either 5 or 10×/mo vs DPO weekly or 2×/mo	45	No	No	24 wk
Jo et al[14] (2010)	Non-ESRD patients with eGFRs of 23 ± 10 mL/min; in first trial period, 1:1 randomly assigned to EPO or DPO weekly for 2 mo; in second trial period, patients who received EPO in the initial arm crossed over to DPO after a washout period; patients who received DPO in the initial arm crossed over to EPO after a washout period	74	No	No	2 mo
Bernieh et al[13] (2014)	ESRD patients already on EPO 1:1 randomly assigned to continue EPO 1-3×/wk y vs DPO weekly or every other week	139	No	Yes	24 wk

Note: All studies were randomized. When applicable, company names and study numbers for sponsors are listed in the first column.
Abbreviations: DPO, darbepoetin alfa; eGFR, estimated glomerular filtration rate; EPO, epoetin alfa; ESA, erythropoiesis-stimulating agent; ESRD, end-stage renal disease.

Tabelle 2: Grading the evidence statements and recommendations, aus National Institute for Health and Care Excellence (NICE). 2015

Levels of evidence			**Classification of recommendations**
Level	**Type of evidence**	**Class**	**Evidence**
1++	High-quality meta-analysis (MA), systematic reviews (SR) of randomised controlled trials (RCTs), or RCTs with a very low risk of bias.	A	Level 1++ and directly applicable to the target population *or* Level 1+ and directly applicable to the target population **AND** consistency of results. Evidence from NICE technology appraisal.
1+	Well-conducted MA, SR or RCTs, or RCTs with a low risk of bias.		

1−	MA, SR of RCTs, or RCTs with a high risk of bias.	Not used as a basis for making a recommendation	
2++	High-quality SR of case-control or cohort studies. High-quality case-control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal.	B	Level 2++, directly applicable to the target population and demonstrating overall consistency of results. *or* Extrapolated evidence from 1++ or 1+.
2+	Well-conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal.		
2−	Case-control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal	Not used as a basis for making a recommendation.	
3	Non-analytic studies (for example case reports, case series).	C	Level 2+, directly applicable to the target population and demonstrating overall consistency of results *or* Extrapolated evidence from 2++.
4	Expert opinion, formal consensus.	D	Level 3 or 4 *or* Extrapolated from 2+ *or* Formal consensus.
		GPP	A good practice point (GPP) is a recommendation based on the experience of the GDG.
Diagnostic study level of evidence and classification of recommendation was also included[242].			

Abbildung 1: Grading the evidence statements and recommendations, aus National Institute for Health and Care Excellence (NICE). 2015