Gemeinsamer Bundesausschuss

# Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

# und

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

## Vorgang: 2018-B-239 Vadadustat

Stand: Januar 2019

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

**Vadadustat**
**zur Behandlung von 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:<br>- 17. Eisen-(II)-Verbindungen nur zur Behandlung von gesicherter Eisenmangelanaemie<br>- 43. Wasserlösliche Vitamine auch in Kombinationen nur bei der Dialyse.<br>- 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).<br>Anlage III der AM-RL:<br>- 8. Antianaemika-Kombinationen - Verordnungsausschluss<br>Anlage IV der AM-RL:<br>- 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**<br>**ATC-Code**<br>**Handelsname** | **Anwendungsgebiet**<br>(Text aus Fachinformation) |
|---|---|
| Zu bewertendes Arzneimittel: | |
| Vadadustat | *Geplantes Anwendungsgebiet laut Beratungsanforderung:*<br>Vadadustat ist angezeigt zur Behandlung der Anämie bei erwachsenen Patienten aufgrund einer chronischen Nierenerkrankung (CKD). |
| Darbepoetin alfa<br>B03XA02<br>z.B. Aranesp® | Zur Behandlung der symptomatischen Anämie bei chronischer Niereninsuffizienz (CNI) bei erwachsenen und pädiatrischen Patienten (siehe Abschnitt 4.2). |
| Epoetin alfa<br>B03XA01<br>z.B. Abseamed® | Abseamed® ist angezeigt zur Behandlung der symptomatischen Anämie bei chronischer Niereninsuffizienz:<br>– bei Erwachsenen sowie Kindern und Jugendlichen im Alter von 1 bis 18 Jahren unter Hämodialysebehandlung und bei Erwachsenen unter Peritonealdialysebehandlung (siehe Abschnitt 4.4).<br>– bei Erwachsenen mit Niereninsuffizienz, die noch nicht dialysepflichtig sind, zur Behandlung einer schweren symptomatischen renalen Anämie (siehe Abschnitt 4.4). (…) |
| Epoetin beta<br>B03XA01<br>z.B. NeoRecormon® | NeoRecormon wird angewendet zur:<br>– Behandlung der symptomatischen Anämie infolge von chronischer Niereninsuffizienz bei erwachsenen Patienten und Kindern. (…)<br>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<br>B03XA01<br>z.B. Biopoin® | Behandlung einer symptomatischen Anämie infolge chronischer Niereninsuffizienz bei erwachsenen Patienten. (…) |
| Epoetin zeta<br>B03XA01<br>z.B. Retacrit® | Behandlung der symptomatischen Anämie bei chronischer Niereninsuffizienz bei Erwachsenen und pädiatrischen Patienten:<br>• Behandlung der Anämie bei chronischer Niereninsuffizienz bei Erwachsenen und pädiatrischen Patienten unter Hämodialysebehandlung und bei Erwachsenen unter Peritonealdialysebehandlung (siehe Abschnitt 4.4).<br>• 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<br>B03XA03<br>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

## Abteilung Fachberatung Medizin

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

## Vorgang: 2018-B-239 (Vadadustat)

| | |
|---|---|
| Auftrag von: | Abt. AM |
| Bearbeitet von: | Abt. FB Med |
| Datum: | 12. November 2018 |

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# Abkürzungsverzeichnis

| | |
|---|---|
| AWMF | Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften |
| CERA | Continuous erythropoiesis receptor activator |
| CKD | Chronic kidney disease |
| DPO | darbopoetin |
| EPO | Erythropoetin |
| ESAs | Erythropoiesis Stimulating Agents |
| ESKD | end-stage kidney disease |
| G-BA | Gemeinsamer Bundesausschuss |
| GFR | glomerular filtration rate |
| GIN | Guidelines International Network |
| GoR | Grade of Recommendations |
| Hb | Hämoglobin |
| HR | Hazard Ratio |
| IQWiG | Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen |
| IV | Intravenous |
| KI | Konfidenzintervall |
| LoE | Level of Evidence |
| MI | myocardial infarction |
| MPG-EPO | Methoxy polyethylene glycol-epoetin |
| n.s. | Not significant |
| NICE | National Institute for Health and Care Excellence |
| OR | Odds Ratio |
| rHuEPO | Recombinant human erythropoietin |
| RR | Relatives Risiko |
| SC | Subkutan |
| SIGN | Scottish Intercollegiate Guidelines Network |
| TRIP | Turn Research into Practice Database |
| WHO | World Health Organization |

# 1 Indikation

zur Behandlung der Anämie bei erwachsenen Patienten aufgrund einer chronischen Nierenerkrankung (CKD).

# 2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation Anämie bei chronischer Nierenerkrankung durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 08.11.2018 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, G-BA, GIN, 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 262 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 15 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

# 3 Ergebnisse

## 3.1 G-BA-Beschlüsse/IQWiG-Berichte

**G-BA, 2013 [7].**

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage I: Zugelassene Ausnahmen zum gesetzlichen Verordnungsausschluss nach § 34 Abs. 1 Satz 2 SGB V (OTC-Übersicht), letzte Änderung in Kraft getreten am 5. Juni 2013

**Fazit / Ausmaß des Zusatznutzens / Ergebnis**

Die Vorschriften in § 12 Abs. 1 bis 10 der Richtlinie in Verbindung mit dieser Anlage regeln abschließend, unter welchen Voraussetzungen nicht verschreibungspflichtige Arzneimittel zu Lasten der gesetzlichen Krankenversicherung verordnungsfähig sind. Insoweit finden die Vorschriften anderer Abschnitte der Arzneimittel-Richtlinie keine Anwendung. Schwerwiegende Erkrankungen und Standardtherapeutika zu deren Behandlung sind:

- 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).

**G-BA, 2017 [8].**

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage III: Übersicht über Verordnungseinschränkungen und -ausschlüsse in der Arzneimittelversorgung durch die Arzneimittel-Richtlinie und aufgrund anderer Vorschriften (§ 34 Absatz 1 Satz 6 und Absatz 3 SGB V), Hinweise zur wirtschaftlichen Verordnungsweise von nicht verschreibungspflichtigen Arzneimitteln für Kinder bis zum vollendeten 12. Lebensjahr und für Jugendliche mit Entwicklungsstörungen bis zum vollendeten 18. Lebensjahr sowie Verordnungseinschränkungen und -ausschlüsse von sonstigen Produkten, letzte Änderung in Kraft getreten am 4. November 2017

**Fazit / Ausmaß des Zusatznutzens / Ergebnis**

8. Antianaemika-Kombinationen:

- Verordnungsausschluss verschreibungspflichtiger Arzneimittel nach dieser Richtlinie. [3]
- Bei nicht verschreibungspflichtigen Arzneimitteln ist eine Verordnung auch für Kinder bis zum vollendeten 12. Lebensjahr und für Jugendliche mit Entwicklungsstörungen bis zum vollendeten 18. Lebensjahr unwirtschaftlich. [6]

**G-BA, 2016 [9].**

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage IV: Therapiehinweise gemäß § 92 Abs. 2 Satz 7 SGB V i. V. m. § 17 AM-RL zur wirtschaftlichen Verordnungsweise von Arzneimitteln, letzte Änderung in Kraft getreten am 21.12.2016

**Fazit / Ausmaß des Zusatznutzens / Ergebnis**

Erythropoese-stimulierende Wirkstoffe (zur Behandlung der symptomatischen renalen Anämie)

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. (…)

Empfehlung 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 laborchemischen 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 Eisenspeicher 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 Begleiterkrankungen), Behandlungspräferenz der Patienten. Die Patienten müssen über die Risiken bei der Gabe von ESAs (erhöhtes Mortalitätsrisiko bei Patienten mit zu hohen Hb-Werten, thromboembolische Kom-

plikationen, 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 Blutgruppenantigene 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 Referenzpräparat 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 Anwendung besteht.

## 3.2 Cochrane Reviews

**Palmer SC et al., 2014 [12].**

Darbepoetin for the anaemia of chronic kidney disease

**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).

**Methodik**

Population:

- Individuals with stage 3, 4, and 5 CKD (including patients on dialysis) as defined by the NKF-KDOQI guidelines
  - Stage 3: glomerular filtration rate (GFR) 30 to 59 mL/ min/1.73 m²
  - Stage 4: GFR 16 to 29 mL/min/1.73 m²
  - Stage 5: GFR < 15 mL/min/1.73 m²
  - Stage 5D: GFR < 15 mL/min/1.73 m² (treated with dialysis)
- Kidney transplant recipients
- Adults and children

Intervention/Komparator:

- Studies of darbepoetin alfa by any route (SC or IV) or dose, compared with epoetin alfa or beta, methoxy polyethylene glycol-epoetin beta, placebo, or no treatment were included.
- The following comparisons were considered for inclusion:
  - Darbepoetin alfa versus placebo or no treatment
  - Darbepoetin alfa versus epoetin alfa or beta
  - Darbepoetin alfa versus methoxy polyethylene glycolepoetin beta
  - Darbepoetin alfa (IV versus SC)
  - Darbepoetin alfa with different strategies of administration (e.g. using higher versus lower doses, targeting higher versus lower Hb levels) and different dosing regimens (frequent versus extended dosing regimens)

Endpunkte:

- 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)

Recherche/Suchzeitraum:

- to 13 January 2014

Qualitätsbewertung der Studien:

- risk of bias assessment tool

**Ergebnisse**

Anzahl eingeschlossener Studien:

- 32/9 414 (21/8 328 in meta-analyses)
- studies included in MA:
  - darbepoetin alfa vs placebo: 1 study (4038 participants)
  - darbepoetin alfa vs epoetin alfa or beta: 16 studies (2955 participants)
  - darbepoetin alfa vs methoxy polyethylene glycol-epoetin beta: 4 studies (1198 participants)
  - more frequent vs less frequent darbepoetin alfa administration: 3 studies (420 participants)
  - i.v. vs s.c. darbepoetin alfa: 4 studies (303 participants)

Qualität der Studien:

- 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)

Studienergebnisse:

- In a single large study, darbepoetin alfa reduced the need for blood transfusion (RR 0.60 [0.53, 0.69]) and iron therapy (RR 0.75 [0.73, 0.78]) compared with placebo in adults with CKD stage 3 to 5, but had little or no effect on survival, increased risks of hypertension, and had uncertain effects on quality of life.
- Data comparing darbepoetin alfa with epoetin alfa or beta or methoxy polyethylene glycol-epoetin beta were sparse and inconclusive.

**Anmerkung/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).

*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

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**Palmer SC et al., 2014 [13].**

Erythropoiesis-stimulating agents for anaemia in adults with chronic kidney disease: a network meta-analysis.

**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.

**Methodik**

Population:

- adults aged 18 years or older with anaemia due to CKD were included. CKD was characterised by clinically relevant proteinuria, haematuria, and/or structural kidney disease with or without estimated glomerular filtration rate (eGFR) < 60 mL/ min/1.73 m², recipients of a kidney transplant, and people with Stage 5 CKD treated with dialysis.

Intervention/Komparator:

- Studies of ESAs (epoetin alfa, epoetin beta, darbepoetin beta, methoxy polyethylene glycol-epoetin beta, biosimilar) to treat or prevent anaemia in CKD administered via any route (IV or SC), compared with each other, placebo or no treatment. Dose adaptation of ESAs and non-randomised iron supplementation depending on haematological response were allowed.
- We coded the comparisons within a study where iron was a randomized co-intervention in all study arms as follows:
  - ESA1 plus iron (any route) versus ESA2 plus iron (any route) = ESA1 versus ESA2
  - ESA plus oral iron versus oral iron = ESA versus no treatment
  - ESA plus oral iron versus oral iron plus placebo injection = ESA versus placebo
  - ESA plus intravenous iron versus intravenous iron plus placebo injection = ESA versus placebo
  - ESA plus intravenous iron versus intravenous iron = ESA versus no treatment.

Endpunkte:

- Preventing blood transfusion
- All-cause Mortality
- Fatigue, dyspnea
- Cardiovascular mortality, MI, stroke, vascular access thrombosis, major adverse cardiovascular events, end-stage kidney disease

Recherche/Suchzeitraum:

- to 11 February 2014

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

**Ergebnisse**

Anzahl eingeschlossener Studien:

- 56 studies involving 15,596 adults with CKD.

Qualität der Studien:

- Risks of bias in the included studies was generally high or unclear for more than half of studies in all of the risk of bias domains we assessed; no study was low risk for allocation concealment, blinding of outcome assessment and attrition from follow-up.

Studienergebnisse:

- In network analyses, there was moderate to low confidence that epoetin alfa (OR 0.18, 95% CI 0.05 to 0.59), epoetin beta (OR 0.09, 95% CI 0.02 to 0.38), darbepoetin alfa (OR 0.17, 95% CI 0.05 to 0.57), and methoxy polyethylene glycol-epoetin beta (OR 0.15, 95% CI 0.03 to 0.70) prevented blood transfusions compared to placebo.
- In very low quality evidence, biosimilar ESA therapy was possibly no better than placebo for preventing blood transfusions with considerable imprecision in estimated effects. We could not discern whether all ESAs were similar or different in their effects on preventing blood transfusions and our confidence in the comparative effectiveness of different ESAs was generally very low.
- Similarly, the comparative effects of ESAs compared with another ESA, placebo or no treatment on all-cause mortality were imprecise.
- All proprietary ESAs increased the odds of hypertension compared to placebo (epoetin alfa: OR 2.31, 95%CI 1.27 to 4.23 / epoetin beta: OR 2.57, 95% CI 1.23 to 5.39 / darbepoetin alfa: OR 1.83, 95% CI 1.05 to 3.21 / methoxy polyethylene glycol-epoetin beta: OR 1.96, 95%CI 0.98 to 3.92), while the effect of biosimilar ESAs on developing hypertension was less certain.
- Our confidence in the comparative effects of ESAs on hypertension was low due to considerable imprecision in treatment estimates.
- The comparative effects of all ESAs on cardiovascular mortality, myocardial infarction (MI), stroke, and vascular access thrombosis were uncertain and network analyses for major cardiovascular events, end-stage kidney disease (ESKD), fatigue and breathlessness were not possible.
- Effects of ESAs on fatigue were described heterogeneously in the available studies in ways that were not useable for analyses.

**Anmerkung/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.

*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

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**Cody JD et al., 2016 [3].**

Recombinant human erythropoietin versus placebo or no treatment for the anaemia of chronic kidney disease in people not requiring dialysis

**Fragestellung**

The objective of this review was to ascertain the effects of 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.

**Methodik**

Population:

- Patients with the anaemia of CKD who have not yet commenced dialysis were included.

Intervention/Komparator:

- Treatment with rHuEPO irrespective of dose or mode of delivery versus placebo or no rHuEPO were included.

Endpunkte:

- 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

Recherche/Suchzeitraum:

- up to 29 June 2015

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias Tool

**Ergebnisse**

Anzahl eingeschlossener Studien:

- 19 studies (enrolling 993 participants)

Qualität der Studien:

- The risk of bias was judged to be unclear in the majority of the studies for most of the domains.

Studienergebnisse:

- There was an 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).
- The data from studies reporting quality of life or exercise capacity demonstrated an improvement in the treatment group. Most of the measures of progression of kidney disease showed no statistically significant difference.
- No significant increase in adverse events was identified.

**Anmerkung/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. Based on the current evidence, decisions on the putative benefits in terms of quality of life are worth the extra costs of predialysis rHuEPO need careful evaluation.

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**Hahn D et al., 2017 [10].**

Short-acting erythropoiesis-stimulating agents for anaemia in predialysis patients

**Fragestellung**

This review aimed 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.

**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, were included. The definitions of CKD and anaemia used in individual studies were used in this review.

Intervention/Komparator:

- Short-acting ESAs including epoetins alpha), beta, delta, epoetin theta and biosimilars of epoetin alpha
- Head-to-head comparisons of different short-acting ESAs.

Endpunkte:

- Death, Measures of correction of anaemia, Quality of Life, Hypertension, Cardiovascular morbidity, cerebrovascular morbidity, adverse events, number of patients developing antibody-mediated pure red cell aplasia, number of patients developing a malignancy, kidney function measures, need for iron supplementation

Recherche/Suchzeitraum:

- to 12 September 2016

Qualitätsbewertung der Studien:

- Cochrane risk of bias too l/ GRADE for assessing of overall quality of evidence

**Ergebnisse**

Anzahl eingeschlossener Studien:

- 14 RCTs (2616 participants)→ 9 studies were multi-centre and 2 studies involved children.
- Four interventions were compared: epoetin alpha or beta at different frequencies using the same total dose (six studies); epoetin alpha at the same frequency and different total doses (two studies); epoetin alpha administered intravenously versus subcutaneous administration (one study); epoetin alpha or beta versus other epoetins or biosimilars (five studies). One study compared both different frequencies of epoetin alpha at the same total dose and at the same frequency using different total doses.

Qualität der Studien:

- The risk of bias was high in most studies; only three studies demonstrated adequate random sequence generation and only two studies were at low risk of bias for allocation concealment. Blinding of participants and personnel was at low risk of bias in one study. Blinding of outcome assessment was judged at low risk in 13 studies as the outcome measures were reported as laboratory results and therefore unlikely to be influenced by blinding. Attrition bias was at low risk of bias in eight studies while selective reporting was at low risk in six included studies.

Studienergebnisse:

- Data from only 7/14 studies could be included in our meta-analyses.
- There were no significant differences in final haemoglobin (Hb) levels when dosing every two weeks was compared with weekly dosing (4 studies, 785 participants), when four weekly dosing was compared with two weekly dosing (three studies, 671 participants) or when different total doses were administered at the same frequency (four weekly administration: one study, 144 participants).
- Five studies evaluated different interventions. One study compared epoetin theta with epoetin alpha and found no significant differences in Hb levels (288 participants).
- One study found significantly higher pain scores with subcutaneous epoetin alpha compared with epoetin beta. The results were provided as median with inter-quartile ranges so could not be included in a meta-analysis.
- Two studies (165 participants) compared epoetin delta with epoetin alpha, with no results available since the pharmaceutical company withdrew epoetin delta for commercial reasons.

- The fifth study comparing the biosimilarHX575 with epoetin alpha was stopped after patients receivingHX575 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.
- Mortality was only detailed adequately in four studies and only one study included quality of life data.

**Anmerkung/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.

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**Saglimbene VM et al., 2017 [14].**

Continuous erythropoiesis receptor activator (CERA) for the anaemia of chronic kidney disease.

**Fragestellung**

To assess benefits and harms of CERA compared with other epoetins (darbepoetin alfa and epoetin alfa or beta) or placebo/no treatment (…)

**Methodik**

Population:

- Studies included people with CKD. People with stage 3 CKD (estimated glomerular filtration rate (eGFR) 30 to 59 mL/ min/1.73 m2), Stage 4 CKD (eGFR 15 to 29 mL/min/1.73 m2) and stage 5 CKD (< 15 mL/min/1.73 m2) were included. Patients who required any form of long-term dialysis were included. We also included people who have a functioning kidney transplant, regardless of their kidney function.

Intervention:

- CERA (also known as methoxy poly ethylene-glycol epoetin beta)

Komparator:

- placebo or no treatment
- darbepoetin alfa
- epoetin alfa or beta

Endpunkte:

- patient-centred outcomes: all-cause and cardiovascular mortality, major adverse cardiovascular events, red cell blood transfusion, iron therapy, cancer, hypertension,

seizures, dialysis vascular access thrombosis, drug injection-related events, hyperkalaemia and health-related quality of life and haemoglobin levels

Recherche/Suchzeitraum:

- to 13 June 2017

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

**Ergebnisse**

Anzahl eingeschlossener Studien:

- 27 studies involving 5410 adults with CKD
- Seven studies (1273 participants) involved people not requiring dialysis, 19 studies (4209 participants) involved people treated with dialysis and one study (71 participants) evaluated treatment in recipients of a kidney transplant

Qualität der Studien:

- Studies were generally at high or unclear risk of bias from allocation concealment and blinding of outcomes. Only two studies masked participants and investigators to treatment allocation
- One study compared CERA with placebo, nine studies CERA with epoetin alfa or beta, nine studies CERA with darbepoetin alfa, and two studies compared CERA with epoetin alfa or beta and darbepoetin alfa.

Studienergebnisse:

- There was low certainty evidence that CERA had little or no effects on mortality (n.s.), major adverse cardiovascular events (n.s.), hypertension (n.s.), need for blood transfusion (n.s.), or additional iron therapy (n.s.) compared to epoetin alfa/beta or darbepoetin alfa respectively.
- There was insufficient evidence to compare the effect of CERA to placebo on clinical outcomes. Only one low quality study reported that CERA compared to placebo might lead to little or no difference in the risk of major cardiovascular events (n.s.) and hypertension (n.s.).
- No studies reported comparative treatment effects of different ESAs on health-related quality of life.

**Anmerkung/Fazit der Autoren**

There is low certainty evidence that CERA has little or no effects on patient-centred outcomes compared with placebo, epoetin alfa or beta or darbepoetin alfa for adults with CKD. The effects of CERA among children who have CKD have not studied in RCTs.

## 3.3 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

**Fragestellung**

To determine the effect of ESAs on HRQOL at different hemoglobin targets in adults with CKD who were receiving or not receiving dialysis.

**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

Komparator:

- placebo /intermediate hemoglobin target versus high hemoglobin target

Endpunkte:

- QoL: e.g. SF-36, KDQ, SIP, LASA, others

Recherche/Suchzeitraum:

- Searches of PubMed, EMBASE, the Cochrane Library, and ClinicalTrials.gov from inception to 1 November 2015

Qualitätsbewertung der Studien:

- Cochrane Risk of bias tool

**Ergebnisse**

Anzahl eingeschlossener Studien:

- 17 studies
- 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.

Charakteristika der Population:

- Population:
  - 12 were in the nondialysis CKD population,

- 4 were in the dialysis population,
- 1 was in a combined sample.

Qualität der Studien:

- Studies were at unclear or high risk of bias.

Studienergebnisse:

- SF-36 (13 trials): Randomization to a higher hemoglobin target resulted in no statistically significant improvement in any SF-36 domain
- Kidney Disease Questionnaire (KDQ) (4 trials): 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.
- Subgroup Analyses
  - improvement in Physical function in the non-dialysis 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

**Anmerkung/Fazit der Autoren**

ESA treatment of anemia to obtain higher hemoglobin targets does not result in important differences in HRQOL in patients with CKD.

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**Wilhelm-Leen ER et al., 2015 [15].**

Mortality risk of darbepoetin alfa versus epoetin alfa in patients with CKD: systematic review and meta-analysis

**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.

**Methodik**

Population:

- anemia in adults with chronic kidney disease, including those requiring dialysis

Intervention/Komparator:

- DPO versus EPO

Endpunkte:

- all-cause mortality

Recherche/Suchzeitraum:

- on June 1, 2014; all years

Qualitätsbewertung der Studien:

- kein spezifisches Instrument genannt

**Ergebnisse**

Anzahl eingeschlossener Studien:

- 9 trials (2024 patients)

Qualität der Studien:

- The quality of trials was variable. While all trials were randomized (per our inclusion criteria), only 3 were double-blinded and the remaining 6 were 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.

Studienergebnisse:

- No significant difference in mortality between patients randomized to DPO versus EPO.
- No treatment heterogeneity across studies was detected (Q-statistic = 4.60; P=0.80).
- In sensitivity analysis, after excluding the 2 trials with zero mortality in one arm, we found a summary odds ratio that was essentially unchanged.

**Anmerkung/Fazit der Autoren**

In summary, we did not detect any significant difference in mortality risk between DPO and EPO using the available evidence from randomized head-to-head trials in patients with CKD, but considerable uncertainty remains. Larger (cluster-) randomized or observational post-marketing comparative effectiveness studies comparing these, and other, erythropoiesis-stimulating agents are required to better characterize the long-term safety profiles of these agents.

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**Covic A et al., 2014 [5].**

Erythropoiesis-stimulating agents (ESA) for preventing the progression of chronic kidney disease: a meta-analysis of 19 studies

**Fragestellung**

(…) 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.

**Methodik**

Population:

- CKD patients stages 1–4 (as defined by the Kidney-Disease Outcomes and Quality Initiative [K-DOQI] guidelines:
  - stage 1 = GFR ≥ 90 ml/min/1.73 m2

- stage 2 = GFR 60–89 ml/min/1.73 m2
- stage 3 = GFR 30–59 ml/min/1.73 m2
- stage 4 = GFR 15–29 ml/min/1.73 m2;
- stage 5 = GFR <15 ml/min/1.73 m2 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

Endpunkte:

- low or high Hb targets

Recherche/Suchzeitraum:

- January 1966 to 1st of January 2014

Qualitätsbewertung der Studien:

- according to recommendations from the Cochrane Collaboration

**Ergebnisse**

Anzahl eingeschlossener Studien:

- 19 studies / 8129 patients
  - 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

Qualität der Studien:

- Risk of bias: unclear to high

Studienergebnisse:

- 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)

**Anmerkung/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.

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**Alsalimy N et al., 2014 [1].**

Methoxy polyethylene glycol-epoetin beta versus darbepoetin alfa for anemia in non-dialysis-dependent CKD: a systematic review

**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.

**Methodik**

Population:

- non-dialysis-dependent CKD patients

Intervention:

- MPG-EPO

Komparator:

- other erythropoiesis stimulating agents (in particular darbepoetin alfa)

Endpunkte:

- hemoglobin response rate and/or difference in mean change in hemoglobin from baseline; blood or red blood cell (RBC) transfusion needs; median time to response; change in QoL including general health, evaluated using generic instrument (the Short Form-36 Health Survey); need for dose adjustments, hemoglobin increase beyond recommended range ([13 g/dL), mortality, and incidence of adverse drug events (AEs) assessed using laboratory safety parameters, history-taking, physical examination and other diagnostic parameters

Recherche/Suchzeitraum:

- 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.

Qualitätsbewertung der Studien:

- Jadad scale

**Ergebnisse**

Anzahl eingeschlossener Studien:

- 4 studies / 1155 patients
- literature search only found studies comparing MPG-EPO to darbepoetin

- no head-to-head studies comparing MPG-EPO with other ESAs

Qualität der Studien:

- Jadad score ranged between 2 and 3 out of 5, predominantly due to the open-label design of the trials

Studienergebnisse:

- 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

**Anmerkung/Fazit der Autoren**

The changes in hemoglobin level from the baseline reported by the reviewed studies demonstrate that MPGEPO was clinically non-inferior to darbepoetin. The incidence of RBC transfusion was higher among patients who received darbepoetin than those who received MPG-EPO. However, the time to hemoglobin response was longer with MPG-EPO than with darbepoetin. Finally, the proportions of serious adverse events were similar between the two therapeutic agents. However, this mini-review is not conclusive due to the limited number of eligible studies. Given the economic and clinical benefits of treating anemia in pre-dialysis patients, the beneficial effects and tolerability of MPG-EPO among non-dialysis CKD patients with anemia should be further investigated using robust landmark clinical trials.

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**Amato L et al., 2018 [2].**

Comparative efficacy and safety in ESA biosimilars vs. originators in adults with chronic kidney disease: a systematic review and meta-analysis

**Fragestellung**

to estimate the comparative efficacy and safety of all ESAs (biosimilars vs. originators) in treating anemia in adults with CKD when used in head-to-head RCTs.

**Methodik**

Population:

- adults aged 18 years or older with anemia due to CKD

Intervention/Komparator:

- effectiveness of different ESAs

Endpunkte:

- Hb level, prevention of blood transfusion, fatigue and dyspnea; and for safety: all-cause mortality; cardiovascular mortality; fatal or nonfatal myocardial infarction; fatal or nonfatal

stroke; vascular access thrombosis; major adverse cardiovascular event; and end-stage renal disease (ESRD).

Recherche/Suchzeitraum:

- PubMed and the Cochrane Library up to July 2015

Qualitätsbewertung der Studien:

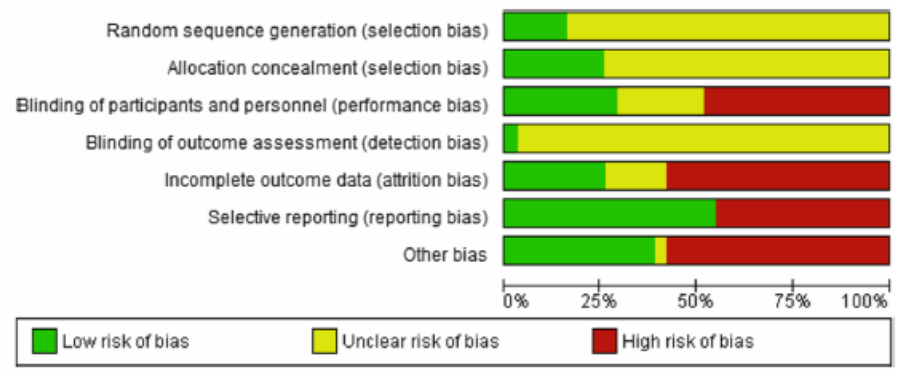
- Bias Assessment tool from the Cochrane Handbook /GRADE system

**Ergebnisse**

Anzahl eingeschlossener Studien:

- 30 eligible studies including 7843 patients with CKD, and 21/30 studies included patients using hemodialysis or peritoneal dialysis.
  - Epoetin α vs. biosimilar: ten studies, 3,160 patients included
  - Epoetin α vs. darbepoetin α: ten studies, 2,338 patients included
  - Epoetin β vs. methoxy polyethylene glycol-epoetin β: three studies, 332 patients included
  - Darbepoetin α vs. methoxy polyethylene glycol-epoetin β: six studies, 1,833 patients included

Qualität der Studien:




Studienergebnisse:

- Compared with ESA biosimilars, epoetin α did not statistically differ for any of the ten measured outcomes. → The quality of evidence varied from low to very low.
- In the comparison between epoetin α vs. darbepoetin α, no differences were observed for all outcomes, but blood transfusions showed favorable results for darbepoetin α: RR 2.18 (1.31–3.62). → The quality of evidence varied from low to very low.
- No differences were observed between epoetin β and methoxy polyethylene glycol-epoetin β, and between darbepoetin α and methoxy polyethylene glycol-epoetin β. → the quality of evidence varied from moderate to very low.

**Anmerkung/Fazit der Autoren**

Data from 31 included studies allowed to pool data in meta-analysis related to four different comparisons and eleven outcome measures. Nevertheless, only one result was statistically significant in favor of darbepoetin α in the comparison with epoetin α concerning blood transfusions. For all the other outcomes and comparisons, we did not find any differences in

terms of efficacy and security between the EPO considered. The quality of evidence is quite low, and further research could change these results. Further high quality studies examining the comparative effectiveness of ESAs need to be conducted.

## 3.4 Leitlinien

**NICE, 2015 [11].**

*National Institute for Health and Care Excellence (NICE)*

Anaemia management in chronic kidney disease, partial update 2015 (Final Version: June 2015)

**Leitlinienorganisation/Fragestellung**

Management of anaemia in adults, children and young people with a clinical 12 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 (formal consensus techniques)
- structuring and writing the guideline
- updating the guideline.

Recherche/Suchzeitraum:

- The information scientist developed a search strategy for each question. Key words for the search were identified by the GDG. In addition, the health economist searched for supplemental papers to inform detailed health economic work (for example modelling). Papers that were published or accepted for publication in peer-reviewed journals were considered as evidence by the GDG. Conference paper abstracts and non-English language papers were excluded from the searches.
- Each clinical question dictated the appropriate study design that was prioritised in the search strategy but the strategy was not limited solely to these study types. The research fellow or health economist identified titles and abstracts from the search results that appeared to be relevant to the question. Exclusion lists were generated for each question together with the rationale for the exclusion.
- All searches were updated on 14 August 2014

LoE/GoR

**Table 5: Grading the evidence statements and recommendations**

| 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<br>*or*<br>Level 1+ and directly applicable to the target population **AND** consistency of results.<br>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.<br>*or*<br>Extrapolated evidence from 1++ or |
| 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. | | |

| | | | |
|---|---|---|---|
| | | | 1+. |
| 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<br><br>*or*<br><br>Extrapolated evidence from 2++. |
| 4 | Expert opinion, formal consensus. | D | Level 3 or 4<br><br>*or*<br><br>Extrapolated from 2+<br><br>*or*<br><br>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]. | | | |

**Table 8: Descriptions of quality elements in GRADE for intervention studies**

| Quality element | Description |
|---|---|
| **Limitations** | Limitations in the study design and implementation may bias the estimates of the treatment effect. Major limitations in studies decrease the confidence in the estimate of the effect. |
| **Inconsistency** | Inconsistency refers to an unexplained heterogeneity of results. |

| Quality element | Description |
|---|---|
| Indirectness | Indirectness refers to differences in study population, intervention, comparator and outcomes between the available evidence and the review question, or recommendation made. |
| Imprecision | Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of the effect relative to the clinically important threshold. |
| Publication bias | Publication bias is a systematic underestimate or an overestimate of the underlying beneficial or harmful effect due to the selective publication of studies. |

**Table 9: Levels for quality elements in GRADE**

| Level | Description |
|---|---|
| None | There are no serious issues with the evidence |
| Serious | The issues are serious enough to downgrade the outcome evidence by one level |
| Very serious | The issues are serious enough to downgrade the outcome evidence by two levels |

**Table 10: Overall quality of outcome evidence in GRADE**

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

Sonstige methodische Hinweise

## Partial update 2015

This is a partial update of the 2011 clinical guideline on Anaemia Management in Chronic Kidney Disease.
The sections new or updated in 2015 are:

- Guideline development group and scope
- Methodology
- Diagnostic tests for the prediction of response to iron therapy
- Concurrent illness
- Iron therapies
- Treatment of ESA resistance

Update 2015

All other sections and recommendations from the 2011 guideline remain unchanged.
The content of other sections has not been amended and we have integrated these new sections into the relevant chapters of the old publication. This has inevitably led to inconsistencies in style of write up for reviews.
New or amended sections of the guideline are highlighted in a pale orange box and have an 'Updated 2015' bar in the left hand margin.

**Recommendations**

→ *Therapiealgorithmus siehe Anhang!*

1. Consider investigating and managing anaemia in people with CKD if:
   - their Hb level falls to 110 g/litre or less (or 105 g/litre or less if younger than 2 years) or
   - they develop symptoms attributable to anaemia (such as tiredness, shortness of breath, lethargy and palpitations). [2011]
2. An estimated glomerular filtration rate (eGFR) of less than 60 ml/min/1.73m² should trigger investigation into whether anaemia is due to CKD. When the eGFR is greater than or equal to 60 ml/min/1.73m² the anaemia is more likely to be related to other causes. [2006]
3. Carry out testing to diagnose iron deficiency and determine potential responsiveness to iron therapy and long-term iron requirements every 3 months (every 1–3 months for people receiving haemodialysis).
   - Use percentage of hypochromic red blood cells (% HRC; more than 6%), but only if processing of blood sample is possible within 6 hours.
   - If using percentage of hypochromic red blood cells is not possible, use reticulocyte Hb content (CHr; less than 29 pg) or equivalent tests – for example, reticulocyte Hb equivalent.
   - If these tests are not available or the person has thalassaemia or thalassaemia trait, use a combination of transferrin saturation (less than 20%) and serum ferritin measurement (less than 100 micrograms/litre). [new 2015]

   Update 2015
4. Do not request transferrin saturation or serum ferritin measurement alone to assess iron deficiency status in people with anaemia of CKD. [new 2015]
5. Do not routinely consider measurement of erythropoietin levels for the diagnosis or management of anaemia in people with anaemia of CKD. [2006]
6. ESA therapy should not be initiated in the presence of absolute iron deficiency without also managing the iron deficiency. [2006]
7. In people treated with iron, serum ferritin levels should not rise above 800 micrograms/litre. In order to prevent this, review the dose of iron when serum ferritin levels reach 500 micrograms/litre. [2006]
8. 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]

9. ESAs need not be administered where the presence of comorbidities, or the prognosis, is likely to negate the benefits of correcting the anaemia. [2006]

10. 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]

11. 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]

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

13. Supplements of vitamin C, folic acid or carnitine should not be prescribed as adjuvants specifically for the treatment of anaemia of CKD. [2006]

14. In people with anaemia of CKD, androgens should not be used to treat the anaemia. [2006]

15. In people with anaemia of CKD, treat clinically relevant hyperparathyroidism to improve the management of the anaemia. [2006]

16. Give people offered ESA therapy, and their GPs information about why ESA therapy is required, how it works, and what benefits and side effects may be experienced. [2006]

17. When managing the treatment of people with anaemia of CKD, there should be agreed protocols defining roles and responsibilities of healthcare professionals in primary and secondary care. [2006]

18. Inform people receiving ESA therapy about the importance of concordance with therapy and the consequences of poor concordance. [2006]

19. When prescribing ESA therapy, take into account patient preferences about supervised- or self-administration, dose frequency, pain on injection, method of supplying ESA and storage. [2006]

20. In order for people to self-administer their ESA in a way that is clinically effective and safe, make arrangements to provide ready, reasonable and uninterrupted access to supplies. [2006]

(…)

22. 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]

23. Avoid blood transfusions where possible in people with anaemia of CKD in whom kidney transplant is a treatment option. [2006]

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

25. 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]

(…)

33. The correction to normal levels of Hb with ESAs is not usually recommended in people with anaemia of CKD.
    - Typically[i] maintain the aspirational Hb range between 100 and 120 g/litre for adults, young people and children aged 2 years and older, and between 95 and 115 g/litre for children younger than 2 years of age, reflecting the lower normal range in that age group.
    - To keep the Hb level within the aspirational range, do not wait until Hb levels are outside the aspirational range before adjusting treatment (for example, take action when Hb levels are within 5 g/litre of the range's limits). [2011, amended 2015]

34. Consider accepting Hb levels below the agreed aspirational range if:
    - high doses[j] of ESAs are required to achieve the aspirational range or
    - the aspirational range is not achieved despite escalating ESA doses. [2011]

35. Optimise iron status before or coincident with the initiation of ESA administration and during maintenance treatment with ESAs. [2006, amended 2011]

36. Use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin type II receptor antagonists is not precluded, but if they are used, an increase in ESA therapy should be considered. [2006]

37. Take into account Hb measurements when determining the dose and frequency of ESA administration:
    - Investigate the cause of an unexpected change in Hb level (that is, intercurrent illness, bleeding) to enable intervention and optimise iron status.
    - Increase or decrease ESA dose and/or frequency when Hb measurements fall outside action thresholds (usually below 105 g/litre or above 115 g/litre), or for example when the rate of change of Hb suggests an established trend (for example, greater than 10 g/litre/month). [2006, amended 2011]

38. Offer people with anaemia of CKD who are receiving ESAs iron therapy to achieve[k]:
    - Percentage of hypochromic red blood cells less than 6% (unless ferritin is greater than 800 micrograms/litre).
    - reticulocyte Hb count or equivalent tests above 29 pg (unless serum ferritin is greater than 800 micrograms/litre).

Update 2015

If the above tests are not available or the person has thalassaemia or thalassaemia trait, iron therapy should maintain transferrin saturation greater than 20% and serum ferritin level greater than 100 micrograms/litre (unless serum ferritin is greater than 800 micrograms/litre).

Most patients will need 500–1000 mg of iron for adults or equivalent doses for children[I], in a single or divided dose depending on the preparation. Intravenous iron should be administered in a setting with facilities for resuscitation. [new 2015]

39. Once percentage of hypochromic red blood cells is less than 6%, reticulocyte Hb count or equivalent tests above 29 pg, or transferrin saturation is greater than 20% and serum ferritin level is greater than 100 micrograms/litre, offer maintenance iron to people with anaemia of CKD who are receiving ESAs.

The dosing regimen will depend on modality, for example haemodialysis patients will need the equivalent of 50–60 mg intravenous iron per week (or an equivalent dose in children[I] of 1 mg/kg/week). [new 2015]

40. Offer iron therapy to people[I] with anaemia of CKD who are iron deficient and who are not receiving ESA therapy, before discussing ESA therapy.

- Discuss the risks and benefits of treatment options. Take into account the person's choice.
- For people who are not receiving haemodialysis, consider a trial of oral iron before offering intravenous iron therapy. If they are intolerant of oral iron or target Hb levels are not reached within 3 months (see recommendation 33), offer intravenous iron therapy.
- For people who are receiving haemodialysis, offer intravenous iron therapy. Offer oral iron therapy to people who are receiving haemodialysis only if:
  - intravenous iron therapy is contraindicated or
  - the person chooses not to have intravenous iron therapy after discussing the relative efficacy and side effects of oral and intravenous iron therapy. [new 2015]

Update 2015

41. Discuss the results of the iron therapy with the person or, where appropriate, with their family or carers and offer ESA therapy if needed (see recommendation 22). [new 2015]

42. Offer iron therapy to people[I] with anaemia of CKD who are iron deficient and who are receiving ESA therapy.

- Discuss the risks and benefits of treatment options. Take into account the person's choice.
- For adults and young people, offer intravenous iron therapy.
- For children who are receiving haemodialysis, offer intravenous iron therapy.
- For children who are not receiving haemodialysis, consider oral iron. If the child is intolerant of oral iron or target Hb levels are not reached within 3 months (see recommendation 33), offer intravenous iron therapy. [new 2015]

43. Offer oral iron therapy to adults and young people who are receiving ESA therapy only if:

- intravenous iron therapy is contraindicated or
- the person chooses not to have intravenous iron therapy after discussing the relative efficacy and side effects of oral and intravenous iron therapy. [new 2015]

44. When offering intravenous iron therapy to people not receiving haemodialysis, consider high-dose low-frequency[m] intravenous iron as the treatment of choice for adults and young people when trying to achieve iron repletion. Take into account all of the following:
    - preferences of the person with anaemia of CKD or, where appropriate, their family or carers
    - nursing and administration costs
    - cost of local drug supply
    - provision of resuscitation facilities.

    Intravenous iron administered at a low dose and high frequency[n] may be more appropriate for all children[o] and for adults who are receiving in-centre haemodialysis. [new 2015]

45. Offer iron therapy to people[o] receiving ESA maintenance therapy to keep their[p]:
    - percentage of hypochromic red blood cells less than 6% (unless serum ferritin is greater than 800 micrograms/litre)
    - reticulocyte Hb count or equivalent tests above 29 pg (unless serum ferritin is greater than 800 micrograms/litre)
    - transferrin saturation level above 20% and serum ferritin level above 100 micrograms/litre (unless serum ferritin is greater than 800 micrograms/litre)

Update 2015

(…)

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**VA/DoD, 2014 [6].**

*Department of Veterans Affairs (VA), Department of Defense (DoD)*

Va/DoD clinical practice guideline for the management of chronic kidney disease in primary care, Version 3.0

**Leitlinienorganisation/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**

Grundlage der Leitlinie

The guideline development process for the 2014 CPG update consisted of the following steps:

- Formulating evidence questions (Key Questions)
- Conducting the systematic review
- Convening a face-to-face meeting with the CPG Champions and Work Group members
- Drafting and submitting a final CPG about the management of CKD to the VA/DoD EBPWG

Recherche/Suchzeitraum:

- Recherche: 2007 through December 12, 2013

LoE/GoR:

- GRADE-Systematik

Sonstige methodische Hinweise

- Update: Version 3.0 – 2014

**Recommendations**

Safety and Efficacy of Erythropoiesis-Stimulating Agents

- 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)
- 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 drugs not being available on the U.S. market. 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.

# 4 Detaillierte Darstellung der Recherchestrategie

**Cochrane Library - Cochrane Database of Systematic Reviews (Issue 11 of 12, November 2018) am 06.11.2018**

| # | 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 | #8 AND #11 with Cochrane Library publication date Between Nov 2013 and Nov 2018 |

**Systematic Reviews in Medline (PubMed) am 06.11.2018**

| # | Suchfrage |
|---|---|
| 1 | renal insufficiency, chronic[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 hemodialy*[Title/Abstract]) OR haemodialy*[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 | (((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 | (#12 AND #13) |
| 15 | (#14) AND ("2013/11/01"[PDAT] : "3000"[PDAT]) |
| 16 | (#15) NOT "The Cochrane database of systematic reviews"[Journal] |
| 17 | (#16) NOT retracted publication[ptyp] |

**Leitlinien in Medline (PubMed) am 06.11.2018**

| # | **Suchfrage** |
|---|---|
| 1 | renal insufficiency, chronic[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 hemodialy*[Title/Abstract]) OR haemodialy*[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 | (((((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 | (#12 AND #13) |
| 15 | (#14) AND ("2013/11/01"[PDAT] : "3000"[PDAT]) |
| 16 | (#15) NOT retracted publication[ptyp] |

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Verordnungsweise von Arzneimitteln; letzte Änderung in Kraft getreten am 21.12.2016 [online]. Berlin (GER): G-BA; 2016. [Zugriff: 08.11.2018]. URL: https://www.g-ba.de/downloads/83-691-436/AM-RL-IV-Therapiehinweise_2016-12-21.pdf.

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# Anhang

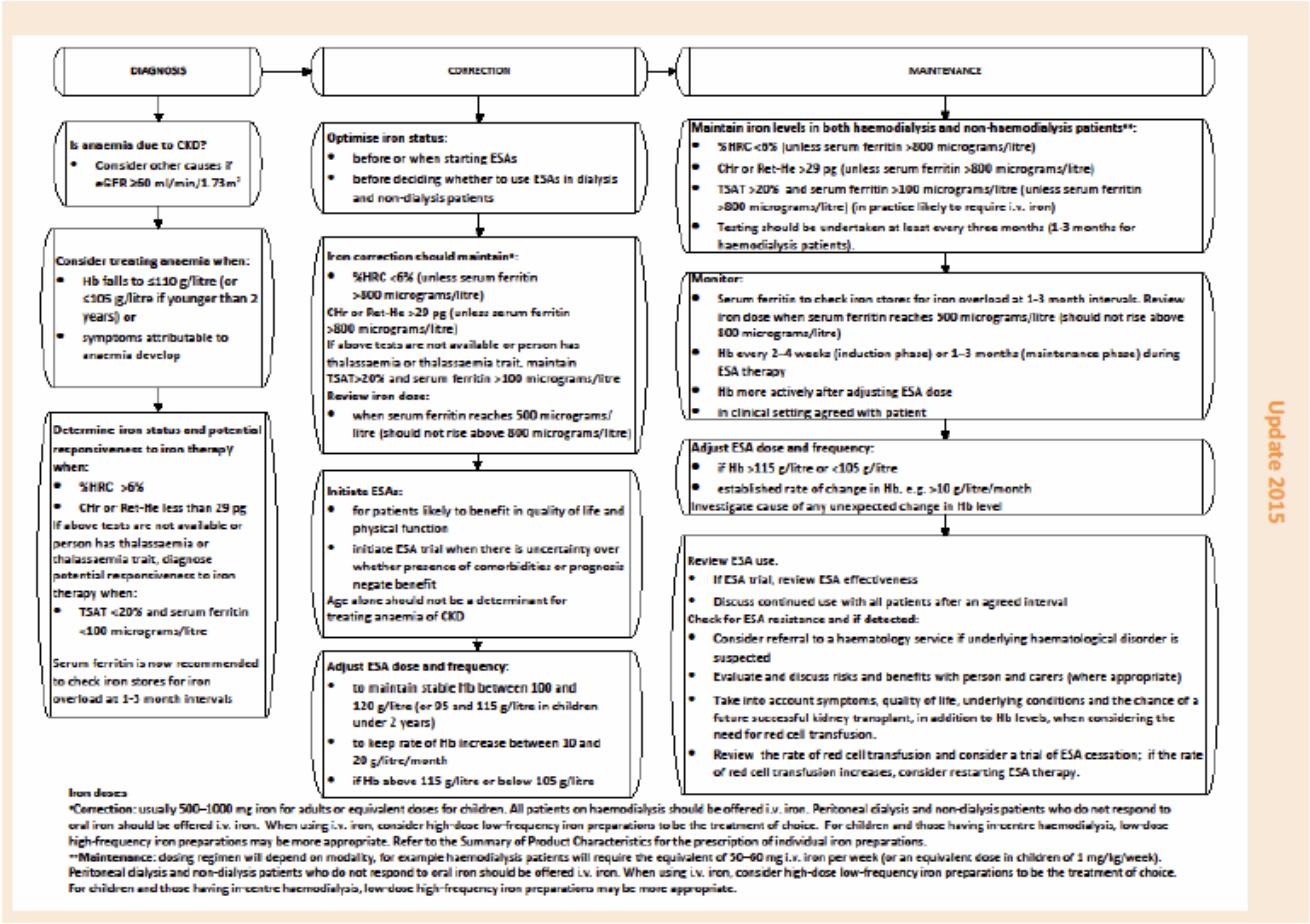


*Abbildung 1: Therapiealgorithmus NICE, 2015 [11]*