# Targeted Literature Review of Patient-Reported Burden of Anemia in Chronic Kidney Disease

Poster #192

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## INTRODUCTION

- Anemia is a common complication in patients with chronic kidney disease (CKD); it is associated with progressive disease severity, poor quality of life (QoL), and increased morbidity and mortality[1-3]
- While the prevalence of anemia is high, the burden of anemia in CKD on patient experience is understudied
- The objective of this study was to summarize the existing evidence relating to the humanistic burden of anemia in CKD and to identify knowledge gaps

## METHODS

- A targeted literature review was conducted between January 1, 2013 and June 27, 2018 to identify studies reporting on humanistic burden of anemia in CKD, specifically on physical function (PF), mental function (MF), fatigue, sleep, caregiver burden, treatment satisfaction, and adherence
- Literature searches were conducted in the electronic databases Embase and PubMed databases
  - Along with searching grey literature including the last two conference proceedings from the Academy of Managed Care Pharmacy, (AMCP), American Society of Nephrology (ASN), European Renal Association-European Dialysis and Transplant Association (ERA-EDTA), International Society of Nephrology (ISN) - World Congress of Nephrology, International Society of Pharmacoeconomics and Outcomes Research (ISPOR)
- Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and the Guidance on the Conduct of Narrative Synthesis in Systematic Reviews were followed (**Figure 1** and **2**); study procedures were outlined in a study protocol
- References of identified papers and related literature reviews were examined
- Predetermined eligibility criteria for article selection included the following: participants diagnosed with anemia in CKD, aged 18 years or older, outcome of interest, US-based, and published in English in the last five years (**Table 1**)

**Table 1. Eligibility Criteria for Study Inclusion**

| PICOS-T | Humanistic outcomes review (RCTs) | Humanistic outcomes review (Observational Studies) |
|---|---|---|
| Population | Adults (aged ≥18 years) with CKD-related anemia | |
| Interventions | Any | NA |
| Comparators | Any | NA |
| Outcomes | • Physical function<br>• Mental function<br>• Fatigue/energy<br>• Adherence | • Sleep<br>• Treatment satisfaction<br>• Caregiver burden |
| Time frame | 2013–2018 | |
| Study design | • RCTs (phase II-IV)<br>• SLRs (for reference checking only) | • Observational cohort studies (retrospective or prospective)<br>• Cross-sectional studies<br>• SLRs (for reference checking only) |
| Geographic region | No restrictions applied | |
| Language of publication | English | |
| Other limits | Humans | |

CKD = Chronic Kidney Disease; NA = Not Applicable; PICOS-T = Population, Interventions and Comparators, Outcomes, Study Design and time frame; RCT = Randomized Controlled Trial; SLR = Systematic Literature Review

**Figure 1. PRISMA Flow Diagram: Literature for observational studies reporting on humanistic outcomes of interest**

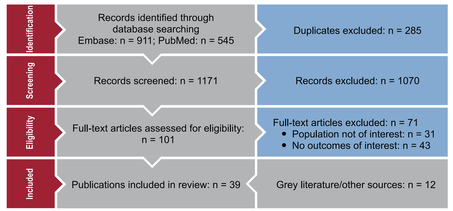
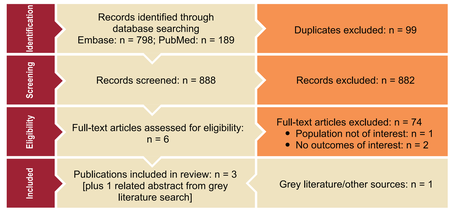


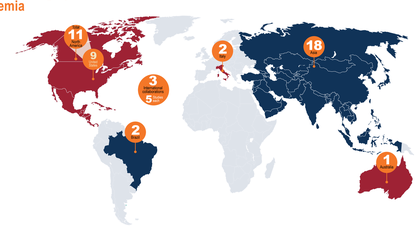

**Figure 2. PRISMA Flow Diagram: Literature for randomized clinical trials reporting on humanistic outcomes of interest**




## RESULTS

- The search strategy retrieved 1171 unique articles and abstracts for observational studies, of which, 39 publications were eligible to be reviewed in the qualitative analysis (**Figure 1**); 888 unique publications for RCTs were identified, and 3 were eligible for full text review and inclusion in the analysis (**Figure 2**)
- Eleven of the observational studies were conducted in North America (of which nine in the US), 18 in Asia, one in Australia, two in Brazil, two in Italy and three studies were international collaborations including at least five studies each (**Figure 3**)
- Two of the randomized clinical trials were conducted in Italy and the 3rd trial was an international study across 20 countries including Australia, Austria, Belgium, Czech Republic, Denmark, France, Germany, Greece, Italy, Netherlands, Norway, Poland, Portugal, Romania, Spain, Sweden, Turkey, United Kingdom, United States

**Figure 3. Geographical distribution of observational studies on humanistic burden of anemia**




## RESULTS

- Study Designs:
  - Observational studies: 22 cross-sectional, 10 retrospective cohort, 4 prospective cohort, 2 reported cross-sectional and prospective cohort results, and 1 with pooled data from two clinical trials
  - RCTs: two open-label RCTs and one post-hoc analysis from a 1-year trial (**Table 2**)

**Table 2. Overview of the RCTs reporting on the humanistic burden of anemia in CKD**

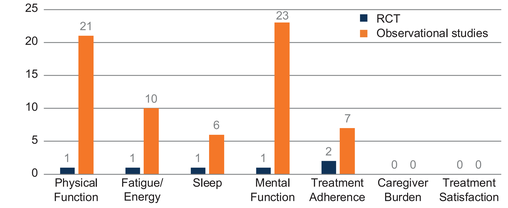
| Trial | Study design and duration | Objective | N | Dialysis status | Age, mean (SD), years | CKD Stage | Mean baseline Hb level |
|---|---|---|---|---|---|---|---|
| Pisani 2015[4] | RCT, OL<br>2 yrs<br>(2011–2013) | To determine if liposomal iron, compared with IV iron, improves anemia in NDD-CKD patients | 99 [OS: 66; IV: 33] | NDD | **OS**: 53.12<br>**IV**: 47.62 | **OS**:<br>III: 43%<br>IV: 49%<br>V: 9%<br>**IV**:<br>III: 48%<br>IV: 43%<br>V: 9% | Hb ≤ 12 g/dL<br>OS: 10.8 (0.6)<br>IV: 10.7 (0.8) |
| MacDougall 2017[5] | RCT<br>(Post-hoc analysis)<br>5 yrs<br>(2009–2014) | To evaluate ESA response rates to oral iron over time in iron-deficient anemic patients with NDD-CKD; compare high vs. low dose ESA | 626 (enrolled)<br>585 (completed)<br>[Oral: 317;<br>IVH: 155;<br>IVL: 154] | NDD | **Mean** (95% CI)<br>**Total** (n=585): 68.8 (67.7–69.9)<br>**Oral** (n=292): 69.0 (67.5–70.6)<br>**IV HD** (n=149): 69.3 (67.3–71.4)<br>**IV LD** (n=144): 67.8 (65.6–70.0) | NR | NR |
| Saglimbene 2017[6] | RCT, OL, blinded-endpoint<br>5 yrs<br>(2009–2014) | To evaluate fixed low-(LD) vs. high-dose (HD) ESA therapy on patient outcomes | 656<br>[HD ESA: 332<br>LD ESA: 324] | DD | **LD ESA**: 65.2 (15.2)<br>**HD ESA**: 66.6 (12.9) | ESRD | >12.5 g/dL |

* 20 countries, including US

CKD, chronic kidney disease; DD, dialysis dependent; ESA, erythropoietin-stimulating agent; ESRD, end-stage renal disease; Hb, hemoglobin; HD, high-dose; IV, intravenous; LD, low-dose; ND, non-dialysis; NDD, non-dialysis dependent; OL, open-label; PO, oral; RCT, randomized controlled trial; CI, confidence interval; IQR, interquartile range; NA, not applicable; SD, standard deviation; IVH, IV ferric carboxymaltose targeting a higher ferritin level (400–600 µg/L); IVL , IV ferric carboxymaltose targe a lower ferritin level (100–200 µg/L); OS= oral supplement.

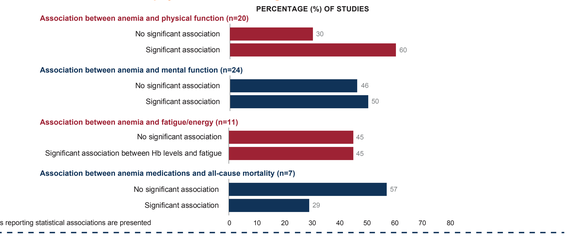
- Populations
  - Observational studies: The size of the 39 non-RCT studies identified was very heterogeneous, ranging between 2,060 and 77,848 study participants, and so was the proportion of female patients, which ranged between 0.6% and 95%
  - Randomized clinical trials: The size of the three RCT studies identified ranged between 99 and 656 participants; study populations were heterogeneous in terms of dialysis status, Hb levels and proportions of female patients
- The number of studies reporting on each of the seven humanistic outcomes of interest across clinical and non-clinical trials was very divergent (**Figure 4**)
  - Most studies described the impact of anemia and its treatment on PF (n=22) and MF (n=24), fewer reported on fatigue/energy (n=11), adherence (n=9) and sleep (n=7); none reported on treatment satisfaction or caregiver burden

**Figure 4. Summary of observational and RCT studies reporting on the humanistic burden of anemia in CKD**




- Results were mixed regarding impact of anemia on mental function (n=24), fatigue/energy (n=10) and generally a non-significant association between with anemia (**Figure 5**)

**Figure 5. Association between anemia and physical function/fatigue***




*Only results for studies reporting statistical associations are presented

- Adherence
  - Two RCTs were identified reporting on adherence to treatment among patients with CKD related anemia; the mean adherence rate to oral iron therapy was high (88.2% [SD 18.4]), regardless of the patients' response to medication in one study and in the second study authors observed that adherence was high and similar in both treatment arms (liposomal iron compared with intravenous (IV) iron)
  - Seven observational studies reported results regarding four retrospective cohorts and three cross-sectional studies. Study designs (adherence targets, Hb & treatment guidelines) and resulting outcomes were highly heterogeneous making it difficult to summarize and draw one main conclusion.

## CONCLUSIONS

- This review identified strong evidence of the burden of anemia on physical function, and mixed results for mental function and fatigue. Limited evidence was available on sleep and treatment adherence, and no literature reported on caregiver burden and treatment satisfaction.
- There is a lack of robust evidence regarding key aspects of the burden associated to CKD related anemia despite availability and use of current treatments.
- To further explore the quality of life burden associated to CKD related anemia, clinician and patient insights could be considered, as well as selective inclusion of patient reported measures in clinical studies.
- This review is subject to several limitations including a selective (though systematic) methods by which pertinent evidence was targeted.
  - Review was limited to evidence available in the past five years (January 1, 2013 to June 27, 2018) and therefore, the findings overlook key studies known to have been published prior to the search cut-off dates.
  - Risk of bias and quality of evidence were not performed for included studies thus study quality may also be heterogenous.

### References

1. Farag YM, Keithi-Reddy SR, Mittal BV, et al. Anemia, inflammation and health-related quality of life in chronic kidney disease patients. *Clin Nephrol.* 2011;75(6):524-533.
2. Smith Jr RE. The clinical and economic burden of anemia. *Am J Manag Care.* 2010;16(Suppl Issues):S59-S66.
3. van Nooten FE, Green J, Brown R, Finkelstein FO, Wish J. Burden of illness for patients with non-dialysis chronic kidney disease and anemia in the United States: review of the literature. *J Med Econ.* 2010;13(2):241-256.
4. Pisani A, Riccio E, Sabbatini M, et al. Effect of oral liposomal iron versus intravenous iron for treatment of iron deficiency anaemia in CKD patients: A randomized trial. *Nephrol Dial Transplant.* 2015;30(4):645-652.
5. MacDougall IC, Bock AH, Carrera F, et al. Erythropoietic response to oral iron in patients with nondialysis-dependent chronic kidney disease in the FIND-CKD trial. *Clin Nephrol.* 2017;88(6):301-310.
6. Saglimbene V, Palmer SC, Craig JC, et al. Low versus high dose erythropoiesis-stimulating agents in hemodialysis patients with anemia: A randomized clinical trial. *PloS one.* 2017;12(3):e0172735.

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### Disclosures

MA, MA, and AB are employees of Evidera. SM and MS are employees of Otsuka Pharmaceutical Development & Commercialization, Inc. GS, AB and YF are employees of Akebia Therapeutics, Inc., where AB was employed during the time the research was completed.

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