Anemia in CKD in Primary Care: Executive Summary

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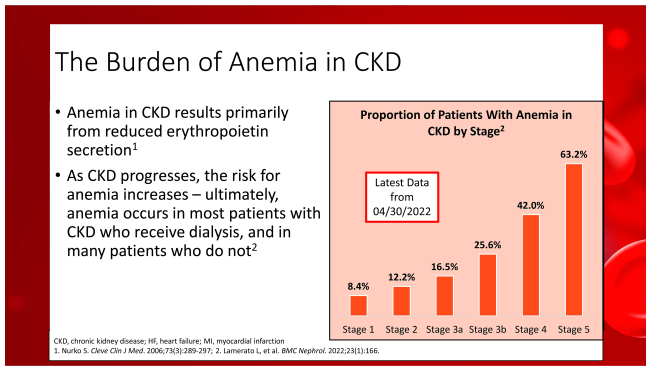

Video 1. Identifying and Managing Anemia in CKD. Available from https://bcove.video/3zxxL2v.

Chronic kidney disease (CKD) is prevalent among people with diabetes. Many people with CKD suffer from anemia as a complication. Despite its prevalence in CKD, anemia tends to be an underrecognized and undertreated condition in this population. Since the 1980s, effective treatments to correct anemia have been available. Additionally, newer treatments are on the horizon that have the potential to provide additional therapy options to improve outcomes for patients with anemia in CKD.

This article is intended to serve as an executive summary for a series of short videos now available on the *Clinical Diabetes* website in which the authors, who each provide care to people with type 2 diabetes, discuss approaches to identifying and managing anemia in CKD and prescribing erythropoiesis-stimulating agents (ESAs) in the primary care setting. They also review novel emerging agents targeting hypoxia-inducible factor (HIF) that are being studied to treat anemia in CKD.

Video Summaries

Identifying and Managing Anemia in CKD (Video 1)

Anemia in people with CKD is primarily a result of decreased secretion of erythropoietin (1). As CKD progresses, anemia becomes more likely to occur. Data from the National Health and Nutrition Examination Survey 2007–2010 (2) indicate the following prevalence rates of anemia by CKD stage: stage 1, 8.4%; stage 2, 12.2%; stage 3, 17.4%; stage 4, 50.3%; and stage 5, 53.4% (2).

Patients with CKD and anemia have a reduced quality of life because of symptoms such as fatigue, reduced exercise capacity, increased ventricular mass, and higher incidence of heart failure and myocardial infarction (3). Identifying anemia in primary care is crucial because primary care practitioners (PCPs) are often the first to encounter this condition. The authors review recommendations for screening, diagnosis, and management of anemia in CKD in primary care settings.

Despite the high prevalence of anemia in CKD, it tends to be underrecognized in clinical settings because it is often asymptomatic, and attention is directed toward other comorbidities of CKD (4,5). PCPs are often hesitant to manage anemia in patients with CKD, often referring these patients to nephrology specialty care even when such a referral is unnecessary (4,5). Because PCPs are more aware of this condition and its basic management recommendations, they can help detect and treat anemia earlier.

Kidney Disease Improving Global Outcomes (KDIGO) guidelines represent the current standard of care for treating anemia in CKD (6). For patients without anemia, KDIGO recommends testing hemoglobin (Hb) at specific frequencies depending on the patient population and clinical conditions (6). Diagnosis of anemia occurs at Hb thresholds of <13.0 g/dL in men and <12.0 g/dL in women (6). The authors discuss how

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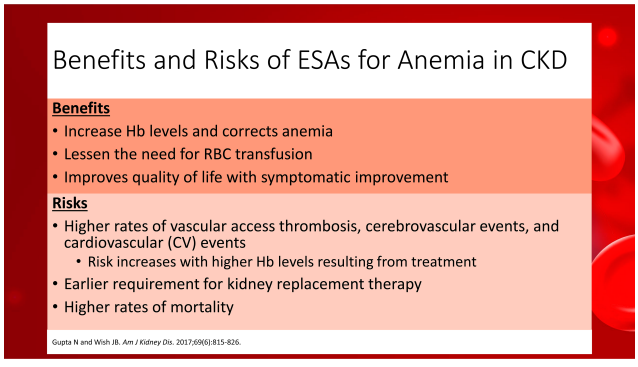
to apply these recommendations in primary care and review additional tests that should be ordered for initial evaluation of anemia.

After establishing a diagnosis of anemia, the next step is to rule out other causes. Treatment of anemia in CKD can be accomplished with iron replacement, use of ESAs, and/or red blood cell (RBC) transfusion (6). In selecting a treatment for anemia, PCPs should consider the patient's severity of anemia, Hb levels, and symptoms. Key considerations for initiating and monitoring treatment of anemia in CKD are also highlighted. For all treatments, the risks and benefits to patients should be considered, and generally the lowest effective dose is recommended to correct anemia.

Although many patients with anemia in CKD can be managed in the primary care setting, some scenarios warrant referral to a nephrologist or hematologist. For patients with severe symptomatic anemia, acutely worsening CKD, or low Hb despite standard treatment, a referral to nephrology is appropriate (7). Additionally, patients with causes of anemia other than CKD who do not improve after addressing the cause should be referred to a hematologist. The authors review some patient case scenarios and discuss how to manage the patients' anemias, including whether they should be referred to a specialist or could be managed in primary care.

How to Prescribe and Monitor ESAs for Anemia in CKD (Video 2)



Video 2. How to Prescribe and Monitor ESAs for Anemia in CKD. Available from https://bcove.video/3P7RvzG.

ESAs have been used to improve production of erythropoietin in patients with anemia and CKD since the 1980s, with the introduction of epoetin alfa (8–10). Initially, ESAs were primarily used in patients on dialysis, but their use has expanded to other stages of CKD over time. Newer ESAs were developed over the years (darbepoetin alfa and methoxy polyethylene glycol-epoetin β) with longer durations of action and less frequent dosing requirements (11,12). In this video, the authors focus on the use of ESAs to treat anemia in CKD.

ESAs are known to increase Hb levels and correct anemia, reduce the need for RBC transfusion, and improve symptoms of anemia (13). However, ESAs also have risks—primarily cardiovascular risks related to thrombosis. Several key studies have highlighted the importance of avoiding overtreatment of anemia and have shown how Hb levels that are too high can increase the risk of cardiovascular events (14–16). The authors review key information from these studies and discuss what clinicians need to know and apply when prescribing ESAs.

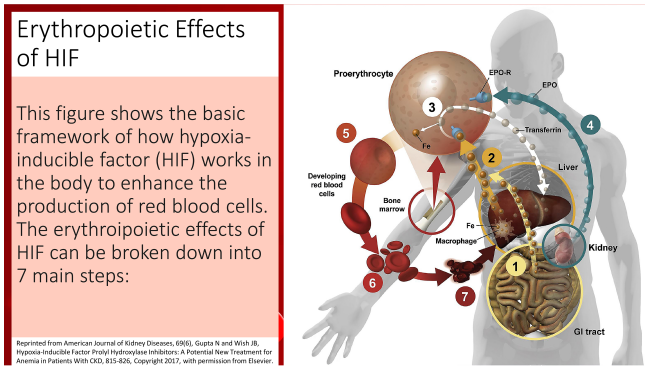
Available ESAs include epoetin alfa, darbepoetin alfa, and methoxy polyethylene glycol-epoetin β (9–12). A biosimilar of epoetin alfa is also available in the United States (17).

Although ESAs have recognized benefits in treating anemia, clinicians must also consider their associated risks when identifying patients who are good candidates for ESA therapy. The authors discuss dosing of ESA agents as well as indications for treatment. ESAs can be initiated when Hb is <10.0 g/dL, and ESA therapy is recommended for patients on dialysis whose Hb is at risk for dropping to <9.0 g/dL (6).

Once patients are initiated on ESA therapy, it is essential to monitor their Hb levels and clinical symptoms to ensure adequate response. Dose adjustment for ESAs is based on the degree of Hb increase, current ESA dose, and clinical circumstances (6). The authors conclude this video by highlighting key considerations for Hb targets and response measures for patients treated with ESAs.

Novel Emerging Agents for Anemia in CKD (Video 3)

In recent years, researchers have focused on developing new agents to treat anemia in CKD because more than a decade has passed since the last U.S. Food and Drug Administration (FDA)-approved treatment for this complication was brought to market. The need for additional therapies is highlighted by challenges and shortcomings of current treatments (13,18). The authors discuss these challenges and the ways in which having new treatment options could benefit patients.



Video 3. Novel Emerging Agents for Anemia in CKD. Available from https://bcove.video/3BI0ioS.

The new class of agents being developed for anemia in CKD works by enhancing the effects of HIF by inhibiting prolyl hydrolase (13). Thus, these agents are collectively termed hypoxia-inducible factor prolyl hydrolase inhibitors (HIF-PHIs). Enhancing the effects of HIF promotes increased production of erythropoietin and improved iron utilization through a variety of mechanisms within RBCs and bone marrow (13). If approved, these oral agents could provide treatment options that offer a more convenient dosage form to patients. The authors review these mechanisms and effects and discuss how they relate to improvement in anemia.

At present, several investigational HIF-PHIs are being studied in late-stage clinical trials for anemia in CKD (19). Daprodustat, roxadustat, and vadadustat are all currently under FDA review. Individual agents are usually studied in two different trials—one for patients with CKD and anemia who are not on dialysis and one for those who are on dialysis. The authors describe key trials for selected HIF-PHIs.

Daprodustat was studied in the ASCEND-ND and ASCEND-D trials and compared with either epoetin alfa or darbepoetin alfa, depending on the trial and subgroup (20,21). Overall, the daprodustat groups demonstrated noninferiority compared with the ESAs for mean change in Hb and incidence of major cardiovascular adverse events (MACE).

Two primary trials evaluating roxadustat, DOLOMITES and SIERRAS, studied roxadustat compared with either epoetin alfa or darbepoetin alfa (22,23). In both trials, roxadustat met noninferiority criteria compared with ESAs for mean change in Hb. Treatment-emergent adverse events were similar between roxadustat and ESAs in both trials.

The authors conclude this video by summarizing two key trials for vadadustat: PRO_2TECT and $INNO_2VATE$ (24,25). Vadadustat was compared with darbepoetin alfa in both trials and demonstrated noninferiority for mean change in Hb. For MACE, vadadustat met noninferiority compared with darbepoetin alfa in $INNO_2VATE$ but not in PRO_2TECT.

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DUALITY OF INTEREST

S.B. serves on an advisory board and/or speakers bureau for Abbott Diabetes Care, AstraZeneca, Bayer, Boehringer Ingelheim, Lilly, Novo Nordisk, Sanofi, and Xeris. He holds stock options with Paracrine. He is also editor-in-chief of *Clinical Diabetes*. S.F. is a consultant and/or researcher for Akebia, AstraZeneca, Fibrogen, and GlaxoSmithKline. J.D.G. serves on an advisory board and/or speakers bureau for Abbott Diabetes Care, Amarin, Bayer, Boehringer Ingelheim, Lilly, Novo Nordisk, Sanofi, and Xeris. E.W. serves as an advisor, consultant, and/or speakers bureau member for Abbott Diabetes Care, Bayer, Boehringer Ingelheim, GlaxoSmithKline, Lilly, and Sanofi.

AUTHOR CONTRIBUTIONS

S.B. and E.W. reviewed and approved the manuscript. S.F. reviewed and provided content for the manuscript. J.D.G. researched data for the manuscript. S.B. is the guarantor of this work and, as such, had full access to all the data included and takes responsibility for the integrity of the data and the accuracy of the data analysis.

REFERENCES

1. Nurko S. Anemia in chronic kidney disease: causes, diagnosis, treatment. Cleve Clin J Med 2006;73:289–297

2. Stauffer ME, Fan T. Prevalence of anemia in chronic kidney disease in the United States. PLoS One 2014;9:e84943

3. Finkelstein FO, Story K, Firanek C, et al. Health-related quality of life and hemoglobin levels in chronic kidney disease patients. Clin J Am Soc Nephrol 2009;4:33–38

4. Schmidt RJ, Dalton CL. Treating anemia of chronic kidney disease in the primary care setting: cardiovascular outcomes and management recommendations. Osteopath Med Prim Care 2007;1:14

5. Fox CH, Brooks A, Zayas LE, McClellan W, Murray B. Primary care physicians' knowledge and practice patterns in the treatment of chronic kidney disease: an Upstate New York Practice-based Research Network (UNYNET) study. J Am Board Fam Med 2006;19:54–61

6. KDIGO. KDIGO clinical practice guideline for anemia in chronic kidney disease. Kidney Int Suppl 2012;2:288–335

7. Cases A, Egocheaga MI, Tranche S, et al. Anemia of chronic kidney disease: protocol of study, management and referral to Nephrology. Nefrologia (Engl Ed) 2018;38:8–12 [in Spanish]

8. Hayat A, Haria D, Salifu MO. Erythropoietin stimulating agents in the management of anemia of chronic kidney disease. Patient Prefer Adherence 2008;2:195–200

9. Amgen. Epogen [prescribing information]. Available from https://www.pi.amgen.com/~/media/amgen/repositorysites/pi-amgen-com/epogen/epogen_pi_hcp_english.pdf. Accessed 4 March 2022

10. Janssen. Procrit [prescribing information]. Available from https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/PROCRIT-pi.pdf. Accessed 4 March 2022

11. Vifor Pharma. Mircera [prescribing information]. Available from https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125164s078lbl.pdf. Accessed 4 March 2022

12. Amgen. Aranesp [prescribing information]. Available from https://www.pi.amgen.com/~/media/amgen/repositorysites/pi-amgen-com/aranesp/ckd/aranesp_pi_hcp_english.pdf. Accessed 4 March 2022

13. Gupta N, Wish JB. Hypoxia-inducible factor prolyl hydroxylase inhibitors: a potential new treatment for anemia in patients With CKD. Am J Kidney Dis 2017;69:815–826

14. Singh AK, Szczech L, Tang KL, et al.; CHOIR Investigators. Correction of anemia with epoetin alfa in chronic kidney disease. N Engl J Med 2006;355:2085–2098

15. Levin NW, Fishbane S, Cañedo FV, et al.; MAXIMA study investigators. Intravenous methoxy polyethylene glycol-epoetin beta for haemoglobin control in patients with chronic kidney disease who are on dialysis: a randomised non-inferiority trial (MAXIMA). Lancet 2007;370:1415–1421

16. Pfeffer MA, Burdmann EA, Chen CY, et al.; TREAT Investigators. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. N Engl J Med 2009;361:2019–2032

17. Pfizer. Retacrit [prescribing information]. Available from https://labeling.pfizer.com/ShowLabeling.aspx?format=PDF&id=10738. Accessed 4 March 2022

18. Dmitrieva O, de Lusignan S, Macdougall IC, et al. Association of anaemia in primary care patients with chronic kidney disease: cross sectional study of quality improvement in chronic kidney disease (QICKD) trial data. BMC Nephrol 2013;14:24

19. Haase VH. Hypoxia-inducible factor-prolyl hydroxylase inhibitors in the treatment of anemia of chronic kidney disease. Kidney Int Suppl (2011) 2021;11:8–25

20. Singh AK, Carroll K, McMurray JJV, et al.; ASCEND-ND Study Group. Daprodustat for the treatment of anemia in patients not undergoing dialysis. N Engl J Med 2021;385:2313–2324

21. Singh AK, Carroll K, Perkovic V, et al.; ASCEND-D Study Group. Daprodustat for the treatment of anemia in patients undergoing dialysis. N Engl J Med 2021;385:2325–2335

22. Barratt J, Andric B, Tataradze A, et al. Roxadustat for the treatment of anaemia in chronic kidney disease patients not on dialysis: a phase 3, randomized, open-label, active-controlled study (DOLOMITES). Nephrol Dial Transplant 2021;36:1616–1628

23. Charytan C, Manllo-Karim R, Martin ER, et al. A randomized trial of roxadustat in anemia of kidney failure: SIERRAS study. Kidney Int Rep 2021;6:1829–1839

24. Chertow GM, Pergola PE, Farag YMK, et al.; PRO2TECT Study Group. Vadadustat in patients with anemia and non-dialysis-dependent CKD. N Engl J Med 2021;384:1589–1600

25. Eckardt KU, Agarwal R, Aswad A, et al. Safety and efficacy of vadadustat for anemia in patients undergoing dialysis. N Engl J Med 2021;384:1601–1612