Improving Detection and Management of Anemia in CKD

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doi: 10.12788/jfp.0411

CONTINUING MEDICAL EDUCATION

LEARNING OBJECTIVES

At the end of the activity, participants will be able to:

- **Describe** approaches to improve recognition of chronic kidney disease (CKD) and anemia in primary care.
- **Explain** the importance of early management of anemia in CKD to reduce adverse outcomes and improve symptoms.
- **Prescribe** evidence-based treatment for patients with anemia in CKD who can be managed in the primary care setting.
- **Discuss** emerging evidence for new agents being studied for treating anemia in CKD.

KEY TAKEAWAYS

- Test hemoglobin (Hb) at least once a year, or more frequently if needed, in patients with CKD to screen for anemia.
- Test Hb at least every 3 months, or more frequently if needed, in patients with CKD and anemia not being treated with an erythropoiesis-stimulating agent (ESA).
- Initial treatment of anemia in CKD can be with oral or intravenous iron if iron deficiency is present; ESAs can be used if the response is inadequate or if Hb remains <10 g/dL.
- Deciding on treatment with ESAs requires balancing risks such as cardiovascular events, and benefits, which include improved symptoms and reduced blood transfusion risk.
- Hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs) are a novel, investigational class of drugs that increase production of erythropoietin and improve iron utilization.

TARGET AUDIENCE

Family physicians and clinicians who wish to gain increased knowledge and greater competency regarding primary care management of anemia in CKD.

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Dr. Austin Ulrich, PharmD, has no disclosures to report.

SPONSORSHIP

This article is sponsored by PCEC and Primary Care Metabolic Group.

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ACKNOWLEDGMENT

Editorial support provided by Austin Ulrich, PharmD, BCACP, of Primary Care Education Consortium.

SUPPORTER

This article is supported by an educational grant from GlaxoSmithKline.

INTRODUCTION

Anemia in patients with chronic kidney disease (CKD) is primarily a result of decreased secretion of erythropoietin (EPO).[1] As CKD progresses, anemia is more likely to occur; based on data from the National Health and Nutrition Examination Survey (NHANES) 2007-2010, anemia is least common in stage 1 CKD and most common in stage 5 CKD (**FIGURE 1**).[2] Patients with CKD and anemia have a reduced quality of life due to symptoms such as fatigue and reduced exercise capacity. Anemia in CKD is also marked by increased ventricular mass and a 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 and can intervene early.

Despite the prevalence of anemia in CKD, it tends to be underrecognized in clinical settings due to its often asymptomatic presentation and attention directed toward other comorbidities in CKD.[4,5] PCPs may be hesitant to manage anemia in patients with CKD and may refer to nephrology, sometimes unnecessarily.[4,5] As PCPs are more aware of this condition and recommended management, they can help detect and treat anemia earlier.

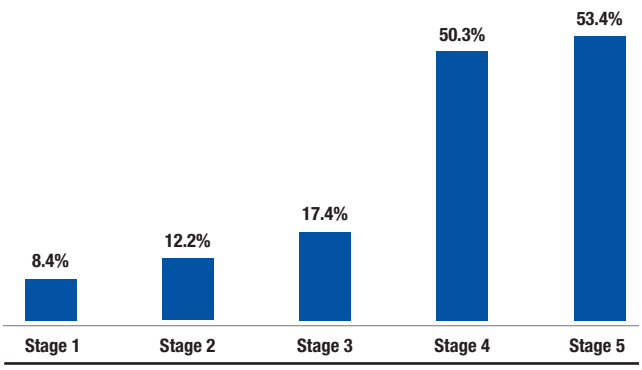
CASE SCENARIO

A 57-year-old man with a history of hypertension, hyperlipidemia, hypothyroidism, and CKD presents to his PCP for an annual office visit. He has not had lab work for the past 6 months. His hemoglobin (Hb) is 9.9 g/dL today, down from 12.2 g/dL 6 months ago. His estimated glomerular filtration rate is 51 mL/min/m^2 today, worsened from 59 mL/min/m^2 6 months ago. He is managed appropriately for his other conditions, and he notes that he takes aspirin 81 mg daily.

IDENTIFICATION OF ANEMIA IN CKD

In this case scenario, the patient can be diagnosed with anemia based on his Hb level and is likely indicated for treatment. Guidelines from Kidney Disease Improving Global Outcomes (KDIGO) represent the current standard of care for identifying and treating anemia in CKD in the United States.[6] However, since the publication of this guideline in 2012, more data are available to help guide clinicians in managing anemia in CKD; some experts have suggested a guideline update is underway and may be published in the near future.[7] Guidelines for anemia in CKD used globally include those from the National Institute for Health and Care Excellence (NICE), as well as those from The Renal Association.[8,9]

FIGURE 1. **Proportion of patients with anemia by CKD stage[2]**



Source: Data from the National Health and Nutrition Examination Survey (NHANES) 2007-2010.

TESTING AND DIAGNOSIS

For patients without anemia, KDIGO recommends testing Hb at specific frequencies depending on the patient population and clinical conditions[6]:

- For CKD patients without anemia, measure Hb:
  - At least annually if stage 3 CKD or higher
  - At least twice per year if stage 4-5 CKD
  - At least every 3 months if on dialysis
- For patients with CKD and anemia not being treated with an erythropoiesis-stimulating agent (ESA):
  - At least every 3 months if stage 3-5 CKD
  - At least monthly if receiving hemodialysis

Diagnosis of anemia occurs at certain Hb thresholds[6]:

- Diagnose in adults and children >15 years with CKD when Hb is <13.0 g/dL (males) and <12.0 g/dL (females)
- Diagnose anemia in children with CKD if Hb concentration is <11.0 g/dL (0.5-5 years), <11.5 g/dL (5-12 years), and <12.0 g/dL (12-15 years)

Furthermore, KDIGO recommends including other laboratory tests for initial evaluation of anemia: complete blood count, absolute reticulocyte count, serum ferritin level, serum transferrin saturation (TSAT), serum vitamin B_{12}, and folate.

MANAGING ANEMIA IN CKD

After establishing a diagnosis of anemia, the next step is to rule out contributing causes. Treatment of anemia in CKD can be accomplished with iron replacement, ESAs, and/or red blood cell (RBC) transfusion.[6] In selecting a treatment for anemia, clinicians should consider the severity of anemia, iron test results, Hb levels, and the patient's symptoms. For all treatments, the risks and benefits to patients should be

TABLE. **Available ESAs and initial dosing**[12,13,15,20]

Drug	Brand name	Approval date	Initial dosing
Epoetin alfa	Epogen/Procrit	6/1/1989	50-100 units/kg IV or SC 3 times a week
	Retacrit	5/18/2018	
Darbepoetin alfa	Aranesp	9/17/2001	0.45-0.75 mg/kg IV or SC every 1-4 weeks, depending on CKD status
Methoxy polyethylene glycol-epoetin beta	MIRCERA	11/15/2007	0.6 mg/kg IV or SC every 2 weeks

Abbreviations: ESA, erythropoiesis-stimulating agents; SC, subcutaneous.

considered, and generally the lowest effective dose is recommended to correct anemia.

Prior to initiating treatment for anemia, clinicians should address any reversible factors, including medications, that can lower Hb. In 1 study, for example, patients with anemia in CKD were often prescribed agents that increase the risk of bleeding.[10] In this study of over 1 million patients, of those with anemia and CKD, 73.0% of patients were prescribed nonsteroidal anti-inflammatory drugs, 61.0% were prescribed aspirin, 14.1% were prescribed warfarin, and 12.4% were prescribed clopidogrel.[10]

In the case scenario described previously, the patient is taking aspirin 81 mg daily, which could be contributing to anemia. If not precluded by other indications, this medication could be stopped to see if it is a primary cause of the anemia.

IRON THERAPY

Oral iron therapy is easily accessible and often is well tolerated; it can be used first to treat a patient with mild anemia with minimal symptoms. KDIGO recommends 65-200 mg of elemental iron taken orally once a day for 1-3 months.[6] Alternatively, intravenous (IV) iron should be considered either as first-line treatment or if oral iron is ineffective.[6]

IV iron is administered as a 1000 mg dose initially, either as a single large dose or repeated smaller doses, depending on the product. This dosage form is often preferred in patients receiving dialysis since IV access is easily attainable and IV iron is more effective at improving anemia.[6] The dose should be repeated if Hb does not increase or if TSAT remains ≤30% and ferritin remains ≤500 mg/dL.[6]

TREATMENT WITH ESAs

ESAs have been used to improve production of erythropoietin in patients with anemia and CKD since the 1980s, with the introduction of epoetin alfa.[11-13] Initially, ESAs were primarily used in patients on dialysis, but their use has expanded to other stages of CKD over time. Newer ESAs have been developed over the years, with longer durations of action and less frequent dosing requirements (**TABLE**).[14,15]

Available ESAs include epoetin alfa, darbepoetin alfa, and methoxy polyethylene-glycol epoetin beta.[12-15] A biosimilar of epoetin alfa is also available in the United States.[16] ESAs have recognized benefits in treating anemia, such as increasing Hb levels, correcting the anemia, improving symptoms, reducing the need for blood transfusion, and improving quality of life.[17] However, ESAs also have risks, primarily cardiovascular (CV) risks related to thrombosis. Several key studies have highlighted the importance of avoiding overtreatment of anemia and that Hb levels that are too high increase risk of CV events (increased cardiovascular risk has only been seen with treatment to Hb targets of ≥13 g/dL).[18-21] In studies with full anemia correction (Hb >13 g/dL), adverse events have included higher rates of vascular access thrombosis, cerebrovascular and CV events, earlier requirement for kidney replacement therapy, and higher mortality.[17] 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 of dropping below 9.0 g/dL.[6]

Once patients are initiated on ESA therapy, it is essential to monitor Hb and clinical symptoms to ensure adequate response. Dose adjustment for ESAs is based on degree of Hb increase, current ESA dose, and clinical circumstances.[6] KDIGO recommends a target ceiling of 11.5 g/dL for Hb, with an absolute ceiling of 13.0 g/dL.[6] Hb monitoring should occur every month during ESA initiation and at least every 3 months thereafter; patients receiving dialysis and treated with an ESA should have Hb checked every month for the duration of therapy.[6] The dose should be lowered rather than withheld if downward adjustment of Hb is needed.[6]

SPECIALIST REFERRAL

While many patients with anemia in CKD can be managed in the primary care setting, some scenarios warrant referral to a nephrologist or hematologist. For a PCP without experience with ESAs or IV iron, a nephrologist could help manage treatment. For patients with more symptomatic anemia,

acutely worsening CKD, or low Hb despite standard treatment, a referral to nephrology is appropriate.[22] Additionally, patients with causes of anemia other than CKD who do not improve after addressing the cause should be referred to a hematologist.

In the patient case scenario, the patient could be treated with iron therapy or ESAs, based on the clinician's judgment. If the anemia did not improve after an adequate trial of standard treatment, or if his CKD was acutely worsening, he could be referred to a specialist.

EMERGING THERAPIES FOR ANEMIA IN CKD

In recent years, research has focused on developing new agents to treat anemia in CKD; it has been over a decade since the last US Food and Drug Administration (FDA)–approved treatment for anemia in CKD was brought to market. The need for additional therapies is highlighted by challenges and shortcomings of current treatments.[10,17] For example, oral iron is often ineffective for treating anemia, IV iron has a relatively high rate of infusion reactions, ESAs have a risk of CV adverse events, and there are risks associated with RBC transfusions.[10,17]

Hypoxia-inducible factor prolyl hydrolase inhibitors (HIF-PHIs) are a new class of agents being developed for anemia in CKD. They work by enhancing the effects of hypoxia-inducible factor (HIF) through inhibiting prolyl hydrolase.[17] Enhancing the effects of HIF promotes increased production of erythropoietin and improved iron utilization through a variety of mechanisms within RBCs and bone marrow (**FIGURE 2**).[17] If approved, these oral agents could provide treatment options that offer a more convenient dosage form to many patients.

At present, several investigational HIF-PHIs are being studied in late-stage clinical trials for anemia in CKD, including daprodustat, roxadustat, vadadustat, molidustat, and enarodustat.[23] Daprodustat, roxadustat, and vadadustat are all under review by the FDA. Each agent is generally studied in 2 different populations: those with CKD and anemia not receiving dialysis and those with CKD and anemia receiving dialysis.

Daprodustat. In the Anemia Studies in Chronic Kidney Disease: Erythropoiesis Via a Novel Prolyl Hydrase Inhibitor Daprodustat-Non-Dialysis (ASCEND-ND) trial, daprodustat was compared with subcutaneous (SC) darbepoetin alfa in 3872 adults with CKD and anemia not on dialysis.[24] This was an open-label, phase 3 randomized trial, and patients had baseline Hb ranging from 8.0-11.0 g/dL, with a target Hb of 10.0-11.0 g/dL. The mean change in Hb was 0.74 g/dL in the daprodustat group and 0.66 g/dL in the darbepoetin alfa group, meeting prespecified noninferiority criteria. After a median of 1.9 years of follow up, major adverse cardiovascular events (MACE) occurred in 19.5% of the daprodustat group and 19.2% of the darbepoetin alfa group, which met the definition of noninferiority.

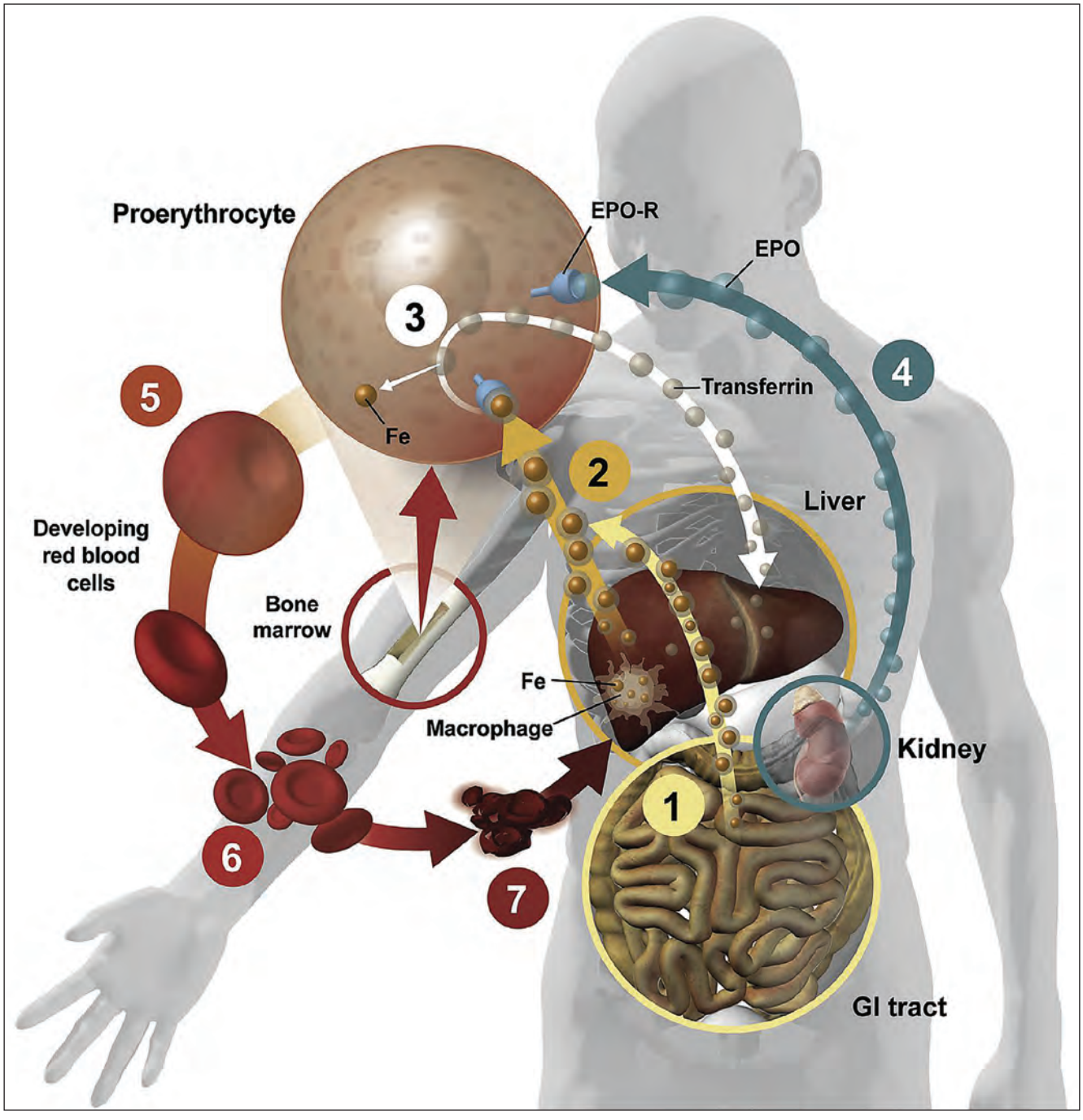
The Anemia Studies in Chronic Kidney Disease: Erythropoiesis Via a Novel Prolyl Hydroxylase Inhibitor Daprodustat–Dialysis (ASCEND-D) trial evaluated daprodustat compared with epoetin alfa (for patients receiving hemodialysis) or darbepoetin alfa (for patients receiving peritoneal dialysis) in 2964 adults with CKD and anemia.[25] In this open-label, phase 3 randomized trial, patients had Hb ranging from 8.0-11.5 g/dL, with a goal to maintain Hb at 10.0-11.0 g/dL. The mean change in Hb was 0.28 g/dL in the daprodustat group and 0.10 g/dL in the ESA group, which met prespecified noninferiority criteria. After a median of 2.5 years of follow up, MACE occurred in 25.2% of the daprodustat group and 26.7% of the darbepoetin alfa group, meeting noninferiority.

Roxadustat. In the Roxadustat in the Treatment of Anemia in Chronic Kidney Disease (CKD) Patients, Not on Dialysis, in Comparison to Darbepoetin Alfa (DOLOMITES) trial, roxadustat was compared with darbepoetin alfa in 616 adults with CKD and anemia not on dialysis.[26] This was an open-label, phase 3 randomized trial, with a target Hb of 10.0-12.0 g/dL. An Hb response was defined as Hb ≥11.0 g/dL and a change from baseline ≥1.0 g/dL if baseline Hb was >8.0 g/dL or change from baseline ≥2.0 g/dL if baseline Hb was ≤8.0 g/dL. There was an Hb response in 89.5% of the roxadustat group and 78.0% of the darbepoetin alfa group, which met prespecified noninferiority criteria. Treatment-emergent adverse events occurred in 91.6% of the roxadustat group and 92.5% of the darbepoetin alfa group; more frequent treatment withdrawal was observed with roxadustat (7.7% vs 3.8%).

The Study to Evaluate the Efficacy and Safety of Roxadustat in the Treatment of Anemia in Participants With ESRD on Stable Dialysis (SIERRAS) trial evaluated roxadustat compared with epoetin alfa in 741 adults with CKD and anemia receiving dialysis and treated with an ESA.[27] In this open-label, phase 3 randomized trial, patients had a mean Hb of 10.3 g/dL (range 9.0-12.0 g/dL) and the goal was to achieve and maintain Hb of 11.0 g/dL. The mean change in Hb was 0.39 g/dL in the roxadustat group and –0.09 in the epoetin alfa group, which met prespecified noninferiority criteria. Treatment-emergent adverse events occurred in 91.6% of the roxadustat group and 91.4% of the epoetin alfa group.

Vadadustat. The PRO_2TECT analysis encompasses 2 clinical trials for vadadustat: 1) the Efficacy and Safety Study to Evaluate Vadadustat for the Correction of Anemia in Subjects With Non-dialysis-dependent Chronic Kidney Disease and 2) the Efficacy and Safety Study to Evaluate Vadadustat for the Maintenance Treatment of Anemia in Subjects With

FIGURE 2. **Erythropoietic effects of HIF**[16]



(1) HIF upregulates divalent metal transporter 1 (DMT1) and duodenal cytochrome B (DcytB) to increase intestinal iron (Fe) absorption; (2) transferrin transports Fe to transferrin receptors in the bone marrow; (3) Fe is released from transferrin into the developing erythrocyte; (4) HIF upregulates the erythropoietin (EPO) receptor (EPO-R) and endogenous EPO production; (5) HIF upregulates transferrin receptor, increasing iron uptake by proerythrocytes; (6) HIF promotes the formation of fully functional mature erythrocytes replete with Hb; (7) after a lifespan averaging approximately 120 days, exhausted erythrocytes are scavenged in the liver and the Fe is returned for reuse.

Abbreviation: GI, gastrointestinal.

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Non-dialysis-dependent Chronic Kidney Disease trials.[28] These trials evaluated vadadustat compared with darbepoetin alfa in a total of 3476 adults with CKD and anemia not receiving dialysis. The trials were open-label, phase 3 randomized trials, and patients had baseline Hb of 8.0-12.0 g/dL in both study arms (eg, those not taking an ESA and those taking an ESA). The mean change in Hb between the 2 groups was 0.05 g/dL (not taking ESA) and –0.01 g/dL (taking ESA) and both met prespecified noninferiority criteria. The MACE hazard ratio between groups for both arms was 1.17 (95% CI 1.01-1.36) and it did not meet the prespecified noninferiority margin of 1.25 for vadadustat.

The INNO$_2$VATE analysis also encompasses 2 clinical trials for vadadustat: 1) the Efficacy and Safety Study to Evaluate Vadadustat for the Correction or Maintenance Treatment of Anemia in Subjects With Incident Dialysis-dependent Chronic Kidney Disease and 2) the Efficacy and Safety Study to Evaluate Vadadustat for the Maintenance Treatment of Anemia in Subjects With Dialysis-dependent Chronic Kidney Disease.[29] These trials compared vadadustat with darbepoetin alfa in a total of 3923 adults with CKD and anemia receiving dialysis. These were open-label, phase 3 randomized trials, and patients had baseline Hb of 8.0-12.0 g/dL, with a goal to achieve and maintain Hb 10.0-12.0 g/dL. There were 2 study arms in each trial, those with incident dialysis-dependent CKD (DD-CKD) and those with prevalent DD-CKD. The mean change in Hb between both groups was –0.31 g/dL (incident DD-CKD) and –0.17 (prevalent DD-CKD), and both arms met prespecified noninferiority criteria. MACE occurred in 18.2% of the vadadustat group and 19.3% of the darbepoetin alfa group; both arms met noninferiority criteria.

SUMMARY

Anemia in CKD is a common condition encountered in primary care that can be successfully managed by PCPs. KDIGO guidelines recommend standards for testing to identify anemia and for treatment with iron, ESAs, and blood transfusions. HIF-PHIs are investigational agents on the horizon that, if approved, will offer patients an oral option to treat anemia in CKD. ●

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