Impact of Erythropoiesis-Stimulating Agents on Energy and Physical Function in Nondialysis CKD Patients With Anemia: A Systematic Review

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Background: Previous analyses report the impact of erythropoiesis-stimulating agents (ESAs) on health-related quality of life across various populations. In this analysis, we review published studies and quantify the effect of ESA therapy on energy/fatigue and physical function in nondialysis patients with chronic kidney disease (CKD) related anemia.

Study Design: Systematic literature search to identify articles (1980-2008) that evaluated effects of ESAs on patient-reported energy and physical function.

Setting & Population: Nondialysis CKD patients with anemia enrolled in prospective trials.

Selection Criteria for Studies: Prospective studies measuring energy or physical function with both baseline and follow-up measurement.

Intervention: ESA treatment.

Outcomes: Improvements in energy and physical function assessed using effect size, a measure of treatment responsiveness.

Results: 14 studies were identified: 11 measured energy and 14 measured physical function. The 36-Item Short-Form Health Survey (SF-36) was the most common instrument used to report energy and physical function. Of 11 studies measuring energy, 2 were double-blind randomized placebo-controlled trials (RCTs), 5 were open-label RCTs, and 4 were single-arm open-label studies. Eight of 11 studies reported statistically significant improvements in energy. Effect size for energy ranged from small (0.24) to large (1.90) in ESA-treated groups and was moderate in each arm of the low- versus high-hemoglobin target RCTs. Of 14 studies measuring physical function, 2 were double-blind RCTs, 6 were open-label RCTs, and 6 were single-arm open-label studies. Ten of 14 studies reported statistically significant improvements in physical function. Effect size for physical function ranged from small (0.37) to large (2.38) in ESA-treated groups and was negligible to moderate in each arm of low- versus high-hemoglobin target studies.

Limitations: Findings and conclusions were limited by the available evidence.

Conclusion: RCTs and single-arm studies indicate that treatment of anemia with ESAs improves energy and physical function in nondialysis CKD patients.

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INDEX WORDS: Nondialysis; chronic kidney disease; erythropoiesis-stimulating agents; energy; physical function; anemia.

Editorial, p. 423

Anemia is one of the most common debilitating complications of chronic kidney disease (CKD) and occurs in ~47% of patients with CKD who are not on dialysis therapy.[1,2] Patients with CKD often develop anemia because of a variety of conditions, including the inability to produce sufficient endogenous erythropoietin to stimulate the production of a normal number of red blood cells.[3] Common symptoms of anemia include low energy, fatigue, weakness, shortness of breath, dizziness, decreased exercise tolerance, impaired cognition, and decreased mental acuity. These symptoms range in severity from mild to debilitating and can significantly limit a patient's ability to function and engage in normal activities.[4] Anemia also has been associated with functional impairment, mobility impairment, increased risk of falls, and diminished health-related quality of life (HRQOL).[5-7] Treatment of anemia with erythropoiesis-stimulating agents (ESAs) increases hemoglobin (Hb) concentra-

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tion in blood, thus potentially relieving symptoms of anemia and improving patients' energy level, fatigue, and physical function.

Previous analyses report the impact of ESAs on HRQOL across various populations with different underlying causes of anemia (CKD [dialysis and nondialysis], cancer, and human immunodeficiency virus [HIV]/acquired immunodeficiency syndrome [AIDS]).[8-12] Although these studies in general suggest that correction of anemia improves HRQOL, the specific domains that are improved and the magnitude of these improvements are less well defined. HRQOL encompasses a variety of domains, of which energy, fatigue, and physical function are important outcomes in studies involving interventions in the care of patients with CKD. Whereas previous analyses measured multiple domains of HRQOL, they did not specifically focus on the effects on energy, fatigue, and physical function in nondialysis CKD patients with anemia.[8-12] The objective of this systematic review is to evaluate published studies and quantify the magnitude of ESA therapy on patient-reported health status, specifically focused on energy, fatigue, and physical function, in nondialysis CKD patients with anemia.

METHODS

Search Strategy

A systematic literature search was performed to identify articles that use patient-reported outcomes to evaluate the effects of ESAs on energy/fatigue and physical function in nondialysis CKD patients with anemia. Searches were conducted in PubMed, EMBASE, and other gray literature sources and were limited to articles published in English (1980-2008). A schematic of the search strategy is shown in Fig 1. Each citation or abstract was screened independently by a subject specialist and 1 other reviewer. Any citation or abstract considered relevant by at least 1 reviewer was retrieved for further review. Bibliographies of included articles were also reviewed for pertinent studies.

Study Selection

The full text of each potentially relevant article was assessed independently by 2 reviewers for inclusion in the review using predetermined eligibility criteria. Articles were eligible for inclusion in the review if they: (1) used patient-reported outcome measures of energy or fatigue and physical function domains as outcome measures in the target population (nondialysis patients with CKD being treated with ESAs, specifically, epoetin alfa and darbepoetin alfa); and (2) had a prospective trial setting with both baseline and follow-up measurement.

Data Extraction

All included articles were grouped by study design: randomized controlled trials (RCTs) or single-arm studies. Data were extracted for trial characteristics (design, sample size, duration of follow-up, sample demographics, funding source, Hb levels at baseline and study end, change in patient-reported outcome, effect size, minimal clinically important difference, etc). If articles presented patient-reported outcome or Hb results in graphs, but did not specify exact values in either the graph or text, values estimated from the graphs were used in this review.

Interpreting the Clinical Significance of Patient-Reported Outcome Data

Translating apparent improvements in patient-reported outcome data into clinically meaningful terms is challenging.[13] In the articles included in this review, changes in energy and physical function for each outcome measure were compared with the published minimal clinically important difference.

Calculating Effect Size

Effect size is a measure of the magnitude of treatment effect or responsiveness, defined as Cohen's d, which is calculated as the difference in means divided by the standard deviation (SD) of the first mean (effect size = $[m_2 - m_1]/SD1$).[14] For studies in which effect-size estimation was not possible because of data limitations, the standardized response mean was calculated (standardized response mean = $[mean_{post} - mean_{pre}]/SD_{change}$).[15,16] The following criteria were used to interpret effect size and standardized response mean: small (effect size, 0.2-0.49), moderate (effect size, 0.5-0.79), and large change (effect size > 0.80).[17]

RESULTS

A total of 14 studies were identified: of these, 11 measured energy/fatigue and all 14 measured physical function, activity, or role limitation. Study design, patient sample, and funding sources for each study included in this review are listed in Table 1.

Energy/Fatigue

Of 11 published studies that met criteria for this review and measured energy/fatigue, 2 were double-blind RCTs,[9,18,19] 5 were open-label RCTs,[20-22,31] and 4 were open-label single-arm studies.[25,26,28,29] Only 1 study included sample size <30,[19] and the remaining studies included sample sizes ranging from 35-1,432. Starting Hb concentration ranged from 8.8-11.9 g/dL. Hb concentration at study end ranged from 8.6-13.9 g/dL. Only 1 study[22] did not report the follow-up period for evaluation of changes in energy/

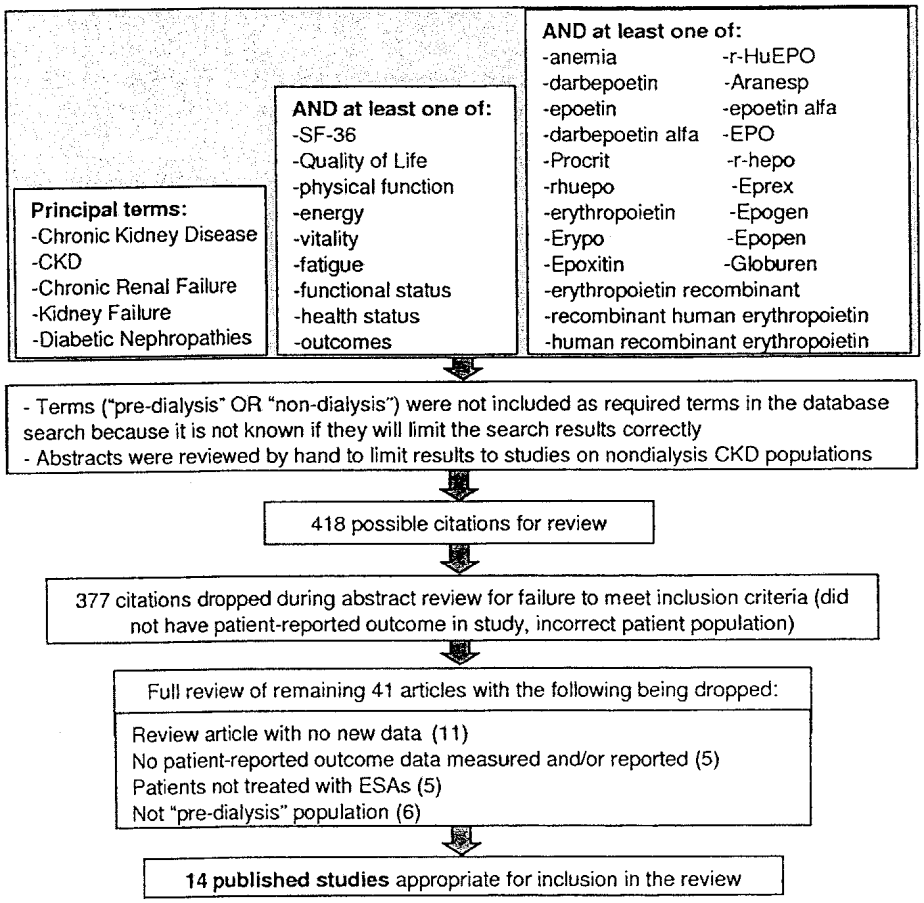

Figure 1. Literature search strategy for the use of the 36-Item Short-Form Health Survey (SF-36) and other patient reported outcomes (PROs) in clinical trials. Abbreviations: CKD, chronic kidney disease; EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; r-HuEPO, recombinant human erythropoietin.

fatigue, and follow-up for the remaining studies ranged from 8 weeks to 12 months.

Of 5 open-label RCTs, 3 were high- versus low-Hb target studies,[21,22,31] 1 was a treatment versus no treatment study,[20] and 1 was a comparison between 2 ESA treatments.[23] Seven studies used the 36-Item Short-Form Health Survey (SF-36) to measure energy and fatigue,[20-23,25,26,31] 4 used the Linear Analogue Scale Assessment (LASA),[22,26,28,29] 2 used an unspecified visual analogue scale or Likert-type items,[18,19] 1 study used the Kidney Disease Questionnaire (KDQ),[28] and 1 used the Functional Assessment of Cancer Therapy (FACT)-Fatigue[25] (Table 2). The minimal clinically important difference values reported in the literature for the SF-36, LASA, and FACT-Fatigue (anchor based) and the KDQ (distribution based) are listed in Table 3. Eight of 11 studies reported statistically significant improvements from baseline. One study reported nonsignificant improvements from baseline,[22] 1 study only reported clinically meaningful improvement,[23] and 1 study did not report results for energy or fatigue as study outcomes.[19]

SF-36 Energy/Vitality

The SF-36 consists of 36 items, of which 35 measure 8 dimensions of health on multi-item scales and an additional single item measures any change in health occurring during the previous year.[38] Table 4 lists the mean change in the SF-36 Energy/Vitality subscale in each of the 7 studies. In all cases, ESA treatment was associated with improved energy/vitality,

Table 1. Demographics of the Patient Sample in PRO Analysis and Funding Source of Clinical Trials

Study	No. of Patients	Design	PRO Follow-up	Demographics of Patient Sample in PRO Analysis: Mean ± SD Age (y)	Women (%)	White (%)	Funding Source
Double-blind Placebo RCTs							
US Recombinant Human Erythropoietin Predialysis Study Group[18] (1991)	110[a]	Anemia corrected (target Hct: ♂, 40%; ♀, 37%) vs not corrected	8 wk	57.1 (24-79)[b]	39	78	Ortho Pharmaceutical Corp
Kleinman et al[19] (1989)	14	Treated (target Hct, 38%-40%) vs placebo	12 wk	NR[c]	NR[c]	NR	Ortho Pharmaceutical Corp
Open-label RCTs							
Revicki et al[20] (1995)	35[a]	Treated (target Hct, 36%) vs untreated	48 wk	Treated, 56.5 ± 11.4; untreated, 58.4 ± 13.2	Treated, 65; untreated, 70	Treated, 70; untreated, 80	R.W. Johnson Pharmaceutical Research Institute & Ortho Biotech Inc
Drueke et al[21] (2006)	603	High (13.0-15.0 g/dL) vs low Hb (10.5-11.5 g/dL) target	12 mo	High, 59.3 ± 14.6; low, 58.8 ± 13.7	High, 57; low, 51	NR	F. Hoffmann-La Roche
Rossert et al[12] (2006)	224[a]	High (13.0-15.0 g/dL) vs low Hb (11.0-12.0 g/dL) target	16 wk	High, 58.5 ± 13.6; low, 57.8 ± 13.6	High, 42; low, 39	High, 94; low, 94	Ortho Biotech Europe
Singh et al[22] (2006)	1,432	High (13.5 g/dL) vs low Hb (11.3 g/dL) target	NR	High, 66.0 ± 14.3; low, 66.3 ± 13.5	High, 56.3; low, 54.1	High, 62.3; low, 61.1	Ortho Biotech Clinical Affairs, LLC
MacDougall et al[23] (2008)	297	DA vs C.E.R.A.	29 wk	DA, 66.9 ± 12.8; C.E.R.A., 63.9 ± 14.1	DA, 51; C.E.R.A., 57	DA, 81; C.E.R.A., 70	Hoffmann-La Roche Ltd
Roger et al[24] (2004)	155	High (12.0-13.0 g/dL) vs low Hb (9.0 – 10.0 g/dL) target	24 mo	High: ♂, 53 ± 13; ♀, 50 ± 14; low: ♂, 54 ± 12 and ♀, 50 ± 15	High, 49; low, 58	NR	Janssen-Cilag Pty Ltd
Open-label Single-Arm or Parallel-Group Studies							
Alexander et al[25] (2007)	48	Open-label single-arm	16 wk	18-64, 43.8; ≥65, 56.3	60.4	52.1	Amgen Inc
Benz et al[26] (2007)	67	Open-label single-arm	16 wk	69.3 ± 14.2	46.3	64.2	Ortho Biotech Clinical Affairs, LLC
Abu-Alfa et al[27] (2008)	277	Open-label single-arm	52 wk	67.1 ± 13.1	54.5	63.2	Amgen Inc
Provenzano et al[28] (2004)	1,184[a]	Open-label single-arm	16 wk	64.7 ± 14.7	58.4	54.6	Ortho Biotech Products LP
	519	Open-label parallel-group	16 wk	68.7 ± 13.2	49.1	66.7	Ortho Biotech Clinical Affairs LLC
Islam et al[30] (2005)	45	Open-label single-arm	6 mo	65 ± 12	45	NR	NR

Note: Conversion factor for hemoglobin in g/dL to g/L, ×10. Locations of sponsoring entities are as follows: Ortho Pharmaceutical Corp and Ortho Biotech Inc, Raritan, NJ; Pharmaceutical Division of F. Hoffmann-La Roche, Basel, Switzerland; Ortho Biotech Europe, Baar, Switzerland; Clinical Affairs LLC, Bridgewater, NJ; Janssen-Cilag Pty Ltd Australia; and Amgen Inc, Thousand Oaks, CA.

Abbreviations: C.E.R.A., methoxy polyethylene glycol-epoetin beta, a continuous erythropoietin receptor activator; DA, darbepoetin alfa; Hb, hemoglobin; Hct, hematocrit; NR, not reported, PRO, patient-reported outcome; RCT, randomized controlled trial; SD, standard deviation.

[a]Demographics were reported for all patients enrolled in the study at baseline, not for the subset of patients completing PRO.

[b]Range, not SD.

[c]Information provided was that the study included men and women aged 38-73 years.

Table 2. Patient-Reported Outcome Measures Used to Measure Energy, Fatigue, and Physical Function in Clinical Trials

Study	Measure of Energy/Fatigue	Measure of Physical Function, Activity, or Role Limitation
Revicki et al[20] (1995)	SF-36[a]	SF-36[b]
Drueke et al[21] (2006)	SF-36[a]	SF-36[b]
Rossert et al[31] (2006)	SF-36[a]	SF-36[b]
Singh et al[22] (2006)	SF-36,[a] LASA-Energy	SF-36,[b] LASA-Activity
Alexander et al[25] (2007)	SF-36,[a] FACT-Fatigue	SF-36[b]
Benz et al[26] (2007)	SF-36,[a] LASA-Energy	SF-36,[b] LASA-Activity
MacDougall et al[23] (2008)	SF-36[a]	SF-36[b]
Provenzano et al[28] (2004)	LASA-Energy, KDQ	LASA-Activity
Provenzano et al[29] (2005)	LASA-Energy	LASA-Activity
The US Recombinant Human Erythropoietin Predialysis Study Group[18] (1991)	5-Point Likert scale (energy)	5-Point Likert scale (ability to do work)
Kleinman et al[19] (1989)	Single-item visual analogue scale (energy)	Single-item visual analogue scale (ability to do work)
Roger et al[24] (2004)	—	SF-36 PCS
Abu-Alfa et al[27] (2008)	—	SF-36 PCS
Islam et al[30] (2005)	—	Not specified

Abbreviations: FACT, Functional Assessment of Cancer Therapy; KDQ, Kidney Disease Questionnaire; LASA, Linear Analogue Scale; SF-36, 36-Item Short-Form Health Survey; SF-36 PCS, SF-36 Physical Component Summary.

[a]SF-36 Energy/Vitality subscale.

[b]SF-36 Physical Function subscale and Role–Physical subscale.

whereas the only RCT with treated and untreated groups showed decreases from baseline in the untreated group; mean changes in Energy/Vitality scores from baseline to follow-up were 5.8 for the treatment group and −3.1 for the untreated group.[20] In 2 open-label single-arm studies, mean change in Energy/Vitality scores from baseline to follow-up ranged from 14.1-14.9 for the SF-36.[25,26] In 1 open-label RCT with low- versus high-Hb targets, there was a statistically significant increase in Energy/Vitality scores from baseline to follow-up (10 in the high-Hb target group and 8.2 in the low-Hb target group; $P < 0.001$).[22] Another open-label RCT with low- versus high-Hb targets did not report information about the statistical significance of the changes from baseline to follow-up (3.8 in the high-Hb target group and −0.5 in the low-Hb target group).[21] Mean changes in Energy/Vitality scores from baseline to follow-up in the open-label RCT with darbepoetin alfa versus C.E.R.A. (continuous erythropoietin receptor activator [methoxy polyethylene glycol–epoetin beta]) groups were 7.5 and 11.2, respectively.[23]

Effect sizes could not be calculated for 3 studies because the baseline or SD values were not reported.[21,23,31] For open-label single-arm studies, the effect size for energy scores ranged from moderate (0.59) to large (5.0).[25,26] In the RCT with treated and untreated groups, the ESA group showed a large positive effect (1.9), whereas the untreated group showed a negative effect (−0.84).[20] One open-label RCT with high- versus low-Hb targets had moderate effect sizes for each group (0.36 and 0.44).[22] In studies with moderate or large effect sizes (0.36-5.0), changes in Hb levels from baseline to follow-up ranged from 1.2-3.5 mg/dL, as well as a change of 4.7% for hematocrit.[20,22,25,26] In the 6 studies for which the change in energy per unit of change in Hb level could be calculated, unit of change ranged from 1.2-7.4 points' improvement in energy for each unit of increase in Hb level.[20-23,25,26,31]

Table 3. Minimal Clinically Important Difference for Measures Included in Review

Patient-Reported Outcome	Minimal Clinically Important Difference
Functional Assessment of Cancer Therapy–Fatigue	3 points[32]
Kidney Disease Questionnaire	Effect size, 0.2-0.5[33]
Linear Analogue Scale Assessment	10-20 points[34-36]
36-Item Short-Form Health Survey	5-10 points[37]

Table 4. Mean Change in 36-Item Short-Form Health Survey Energy/Vitality Subscale

Study	No. of Patients	Design	PRO Follow-up	ΔPRO (mean ± SD)	*P*[a]	Effect Size	MCID	Baseline Hb (g/dL) or Hct (%)	Hb (g/dL) or Hct (%) at Study End	ΔHb (g/dL) or ΔHct (%)	Per Unit Change in Energy/Vitality[b]
					Open-label RCTs						
Revicki et al[20] (1995)	35	Treated (target Hct, 36%) vs untreated	48 wk	Treated, +5.8 ± 3.1[c]; untreated, −3.1 ± 3.7	0.04	Treated, 1.90 (large); untreated, −0.84 (large)	Treated, yes; untreated, nc	Treated, 26.8% ± 4.5%; untreated, 26.8% ± 3.6%	Treated, 31.5%; untreated, 25.8%	Treated, +4.7%; untreated, −1.0%	Treated, 1.2; untreated, 3.1
Rossert et al[31] (2006)	224	High (13.0-15.0 g/dL) vs low Hb (11.0-12.0 g/dL) target	16 wk	NR	0.04	NE	NE	High, 11.5 ± 1.0 g/dL; low, 11.6 ± 0.9 g/dL	High, 13.9 g/dL; low, 11.8 g/dL	High, +2.4 g/dL; low, +0.2 g/dL	NE
Drueke et al[21] (2006)	603	High (13.0-15.0 g/dL) vs low Hb (10.5-11.5 g/dL) target	12 mo	High, +3.8[d]; low, −0.5[d]	<0.001	NE	No	High, 11.6 ± 0.6 g/dL; low, 11.6 ± 0.6 g/dL	High, 13.5 g/dL; low, 11.6 g/dL	High, +1.9 g/dL; low, 0.0 g/dL	High, 2.0; low, NE
Singh et al[22] (2006)	1,432	High (13.5 g/dL) vs low Hb (11.3 g/dL) target	NR	High, +10.0 ± 22.6[c]; low, +8.2 ± 22.4[c]	0.6	High, 0.44 (moderate); low, 0.36 (moderate)	Yes	High, 10.1 ± 0.9 g/dL; low, 10.1 ± 0.9 g/dL	High, 12.6 g/dL; low, 11.3 g/dL	High, +2.5 g/dL; low, +1.2 g/dL	High, 4.0; low, 6.8
MacDougall et al[23] (2008)	297	DA vs C.E.R.A.	29 wk	DA, +7.5[d]; C.E.R.A., +11.2[d]	NR[e]	NE	Yes	DA, 10.2 ± 0.7 g/dL; C.E.R.A., 10.2 ± 0.6 g/dL	DA, 12.2 g/dL; C.E.R.A., 12.3 g/dL	DA, +2.02 g/dL; C.E.R.A., +2.12 g/dL	DA, 3.7; C.E.R.A., 5.3
					Open-label Single-Arm Studies						
Alexander et al[25] (2007)	48	Single arm	16 wk	+14.9 ± 3.2	<0.001	5.0 (large)	Yes	9.1 ± 0.1 g/dL	12.6 g/dL	+3.5 g/dL	4.3
Benz et al[e] (2007)	67	Single arm	16 wk	+14.1 ± 23.9	<0.05	SRM, 0.59 (moderate)	Yes	9.8 ± 0.9 g/dL	11.7 g/dL	+1.9 g/dL	7.4

Note: Conversion factor for Hb in g/dL to g/L, ×10.

Abbreviations: C.E.R.A., methoxy polyethylene glycol-epoetin beta, a continuous erythropoietin receptor activator; DA, darbepoetin alfa; Hct, hematocrit; Hb, hemoglobin; MCID, minimal clinically important difference; NE, not evaluable; NR, not reported; PRO, patient-reported outcome; RCT, randomized controlled trial; SRM, standardized response mean.

[a]Statistical significance reported for RCTs is the between-group comparison of change from baseline.

[b]Change in PRO divided by change in Hb level (or change in Hct).

[c]Represents significant within-group changes from baseline.

[d]SDs were not reported.

[e]MacDougall et al (2008) did not report statistical significance, but instead reported that results were clinically meaningful in both the C.E.R.A. and DA arms.

LASA Energy

The LASA consists of 5 single items. Each item asks respondents to rate their perceived level of functioning on 0-10 scales (0 = as bad as can be, 10 = as good as can be).[39] Interpretation of published data using the LASA is complicated by its single-item nature and questionable ability to reflect multidimensional constructs.[40] Mean changes in the LASA Energy scale are listed in Table 5. In all cases, ESA treatment was associated with improved energy.

In 2 open-label single-arm studies, mean change in Energy scores from baseline to follow-up ranged from 20.6-27.9.[26,28] In the low- versus high-Hb target open-label RCT, mean change in Energy scores from baseline to follow-up ranged from 15.5 (low-target arm) to 16.6 (high-target arm).[22] Effect sizes ranged from small (0.24) to large (1.15) in open-label single-arm studies[26,28,29] and were moderate (0.67 and 0.70) in each arm of the low- versus high-Hb target open-label RCT.[22]

The parallel-group study[29] reported a small improvement in LASA Energy score. The change in energy was 5.4, for an effect size of 0.24. The change in Hb level achieved in this study also was small and ranged from −0.7 to +0.3 across the 4 parallel groups. Studies reporting moderate to large changes in LASA Energy scores (range, 15.5-27.9) achieved larger changes in Hb levels (range, 1.2-2.7 g/dL).[22,26,28] In the 3 studies for which the change in energy per unit of change in Hb level could be calculated, the unit of change ranged from 6.6-12.9 points' improvement in energy for each unit of increase in Hb level.[22,26,28]

Table 5. Mean Change in Linear Analogue Scale Assessment Energy

Study	No. of Patients	Design	PRO Follow-up	ΔPRO (mean ± SD)	*P*[a]	Effect Size	MCID	Baseline Hb (g/dL)	Hb (g/dL) at Study End	ΔHb (g/dL)	Per Unit Change in Energy[b]
Open-label RCT											
Singh et al[22] (2006)	1,432	High (13.5 g/dL) vs low Hb (11.3 g/dL) target	NR	High, +16.6 ± 23.7[c]; low, +15.5 ± 23.1[c]	0.7	High, 0.70 (moderate); low, 0.67 (moderate)	Yes	High, 10.1 ± 0.9; low, 10.1 ± 0.9	High, 12.6; low, 11.3	High, +2.5; low, +1.2	High, 6.6; low, 12.9
Open-label Single-Arm Studies											
Benz et al[26] (2007)	67	Single arm	16 wk	+20.6 ± 21.8	<0.05	SRM, 0.94 (large)	Yes	9.8 ± 0.9 g/dL	11.7	+1.9	10.8
Provenzano et al[28] (2004)	1,184	Single arm	16 wk	+27.9 ± 23.4	<0.001	SRM, 1.15 (large)	Yes	9.1 ± 0.7 g/dL	11.8	+2.7	10.3
Provenzano et al[29] (2005)	519	Parallel group	16 wk	+5.4 ± 22.3	<0.001	0.24 (small)	No	11.8-11.9 g/dL[d]	11.2-12.0[d]	−0.7 to +0.3[d]	NE

Note: Conversion factor for Hb in g/dL to g/L, ×10.

Abbreviations: Hct, hematocrit; Hb, hemoglobin; MCID, minimal clinically important difference; NE, not evaluable; NR, not reported; PRO, patient-reported outcome; RCT, randomized controlled trial; SRM, standardized response mean.

[a]Statistical significance reported for RCTs is the between-group comparison of change from baseline.

[b]Change in PRO divided by change in Hb level (or change in Hct).

[c]Represents significant within-group changes from baseline.

[d]Range.

Other Patient-Reported Outcomes Measuring Energy and Fatigue

An unspecified single-item visual analogue scale and 5-point Likert scale also were used to measure changes in energy after ESA treatment. Fatigue was measured using the KDQ[41,42] and the FACT-Fatigue.[42]

Table 6 lists data from studies that used these other patient-reported outcomes to measure energy and fatigue. Data provided by the 2 double-blind RCTs using the single-item visual analogue scale and Likert scale were not sufficient to calculate effect size.[18,19] Mean changes reported in open-label single-arm studies were 1.4 for the

Table 6. Mean Change in Other Energy/Vitality PRO Measures

Measure	Study	No. of Patients	Design	PRO Follow-up	ΔPRO (mean ± SD)	*P*[a]	Effect Size	MCID	Baseline Hb (g/dL)	Hb (g/dL) at Study End	ΔHb (g/dL) or ΔHct (%)[b]	Per Unit Change In Energy or Fatigue[c]
					Double-blind placebo RCTs							
Energy (5-point Likert scale)	US Recombinant Human Erythropoietin Predialysis Study Group[18] (1991)[d]	110	Anemia corrected (target Hct: ♂, 40%; ♀, 37%) vs not corrected	8 wk	Corrected, +1.45[e]; uncorrected, +0.48[e]	<0.05	NE	NE	Corrected, ♂, 9.3-9.7; ♀, 8.8-9.3[f]; uncorrected, ♂, 9.9 ± 1.6; ♀, 9.4 ± 0.8	NR	NR[g]	NE
Energy (single item VAS)	Kleinman et al[19] (1989)[h]	14	Treated (target Hct, 38%-40%) vs placebo	12 wk	NR	NR[h]	NE	NE	NR	NR	Treated, +7.7%; placebo, −0.1%	NE
					Open-label Single-Arm Studies							
Fatigue (KDQ)	Provenzano et al[28] (2004)	1,184	Single arm	16 wk	+1.4 ± 1.5	<0.001	0.90 (large)	Yes	9.1 ± 0.7	11.8	+2.7 g/dL	0.52
Fatigue (FACT-Fatigue)	Alexander et al[27] (2007)	48	Single arm	16 wk	+6.0 ± 1.6	<0.001	4.3 (large)	Yes	9.1 ± 0.1	12.6	+3.5 g/dL	1.7

Note: Conversion factor for Hb in g/dL to g/L, ×10.

Abbreviations: FACT, Functional Assessment of Cancer Therapy; Hct, hematocrit; Hb, hemoglobin; KDQ, Kidney Disease Questionnaire; MCID, minimal clinically important difference; NE, not evaluable; NR, not reported; PRO, patient-reported outcome; RCT, randomized control trial; VAS, visual analogue scale.

[a]Statistical significance reported for RCTs is the between-group comparison of change from baseline.

[b]Change in Hct is a percentage point change, not a percentage of increase or decrease.

[c]Change in PRO divided by change in Hb level (or change in Hct).

[d]The US Recombinant Human Erythropoietin Predialysis Study Group (1991) randomly assigned patients to 1 of 4 treatment groups, including placebo. Quality-of-life results were reported by 2 groups: anemia corrected and anemia not corrected.

[e]SDs were not reported.

[f]Range.

[g]The US Recombinant Human Erythropoietin Predialysis Study Group (1991) reports the percentage of patients in each arm showing at least 6% change in Hct.

[h]Kleinman et al (1989) reports "quality of life improvement" in treated patients, but not in patients in the placebo group.

KDQ[28] and 6.0 for the FACT-Fatigue.[25] In each of these 2 studies, effect sizes were large (>0.8) and changes in Hb levels from baseline to follow-up were 2.7 and 3.5 g/dL.

Physical Function

A total of 14 published clinical studies used patient-reported outcomes to examine the impact of ESAs on physical function and activity or role limitation in nondialysis CKD patients with anemia. Of these, 2 were double-blind RCTs,[18,19] 6 were open-label RCTs,[20-22,24,31] and 6 were open-label single-arm studies.[25-27,29,20] Only 1 study[19] included a sample size <30, and the remaining studies included sample sizes ranging from 35-1,432. Starting Hb concentration ranged from 8.0-11.9 g/dL. Hb concentration at study end ranged from 8.6-13.9 g/dL. Only 1 study[22] did not report the follow-up period for evaluation of changes in physical function, and the follow-up for the remaining studies ranged from 8 weeks to 24 months.

As listed in Table 3, 9 studies used the SF-36,[20-27,31] 4 studies used the LASA,[22,26,28,29] and 3 studies used other measures.[18,19,30] Statistically significant improvements were reported in 5 of 7 studies measuring physical function using the SF-36,[20-22,25,26] 4 of 7 studies measuring the Role–Physical domain using the SF-36,[21,22,25,26] 4 of 4 studies measuring activity using the LASA,[22,26,28,29] and 3 of 5 studies measuring physical function, activity, or role limitation using other patient-reported outcomes.[18,27,30]

SF-36 Physical Function

Table 7 lists mean changes in the SF-36 Physical Function scale in 7 studies. Both open-label studies had changes in scale scores that were statistically significant and met the minimum clinically important difference.[25,26] Effect sizes for these 2 studies were 2.38 and 0.37. In the RCT with treated versus untreated groups, the treatment arm had a statistically significant improvement that also met the minimum clinically important difference.[20] The effect size of the treatment arm was large (2.52). The 2 high- versus low-Hb target RCTs reporting change in subscale scores had small mean differences (3.2 and 3.3) that were statistically significant improvements in the high-treatment target arms.[21,22] The darbepoetin alfa versus C.E.R.A. study also reported small improvements in physical function in both treatment groups.[23] In the 5 studies for which change in physical function subscale score per unit of change in Hb level could be calculated, the unit of change ranged from 1.3-4.1 points' improvement in physical function for each unit of increase in Hb level.[21-23,25,26]

SF-36 Role–Physical

Table 8 lists mean changes in the SF-36 Role–Physical subscale. Both open-label studies had changes in subscale scores that were statistically significant and met the minimum clinically important difference. One[25] reported a large effect size (3.4), and for the other,[26] effect size could not be evaluated. In the RCT with treated versus untreated groups, the treatment arm had a small improvement in Role–Physical scores.[20] The effect size in the treatment arm was small (0.26). One high- versus low-Hb target RCT had a small improvement in the high-target arm and a decrease in the low-target arm.[21] The second high- versus low-Hb target RCT reporting change in Role–Physical scores had changes in both arms that met the minimum clinically important difference.[22] The darbepoetin alfa versus C.E.R.A. study reported a large (9.5) improvement in the darbepoetin alfa arm and a smaller (3.7) improvement in the C.E.R.A.arm.[23] In the 5 studies for which the change in Role–Physical subscale score per unit of change in Hb level could be calculated, the unit of change ranged from 1.3-7.2 points' improvement in Role–Physical score for each unit of increase in Hb level.[21-23,25,26]

LASA Activity

Each of the 4 studies listed in Table 9 measured activity using the LASA Activity scale and reported statistically significant improvements.[22,26,28,29] Each arm of the high- versus low-Hb target RCT and 2 of the 3 single-arm studies reported changes in activity that met the minimum clinically important difference.[22,26,28] The effect size for the 3 single-arm studies[26,28,29] ranged from 0.19-0.98; it could not be evaluated for the RCT with high- versus low-Hb targets.[22] In the 3 studies for which change in activity score per unit of change in Hb level could be calculated, the unit of change ranged from 6.0-11.1 points' improvement in activity for each unit of increase in Hb level.[22,26,28]

Table 7. Mean Change in 36-Item Short-Form Health Survey Physical Function

Study	No. of Patients	Design	PRO Follow-up	ΔPRO (mean ± SD)	*P*[a]	Effect Size	MCID	Baseline Hb (g/dL) or Hct (%)	Hb (g/dL) or Hct (%) at Study End	ΔHb (g/dL) or ΔHct (%)[b]	Per Unit Change in Physical Function[c]
					Open-label RCTs						
Revicki et al[20] (1995)	35	Treated (target Hct, 36%) vs untreated	48 wk	Treated, +7.8 ± 3.8[d]; untreated, −4.8 ± 2.1[d]	<0.01	Treated, 2.52 (large); untreated, −1.0 (large)	Yes	Treated, 26.8% ± 4.5%; untreated, 26.8% ± 3.6%	Treated, 31.5%; untreated, 25.8%	Treated, +4.7%; untreated, −1.0%	Treated, 1.7; untreated, 4.8
Rossert et al[31] (2006)	224	High (13.0-15.0 g/dL) vs low Hb (11.0-12.0 g/dL) target	16 wk	NR	0.08	NE	NE	High, 11.5 ± 1.0 g/dL; low, 11.6 ± 0.9 g/dL	High, 13.9 g/dL; low, 11.8 g/dL	High, +2.4 g/dL; low, +0.2 g/dL	NE
Drueke et al[21] (2006)	603	High (13.0-15.0 g/dL) vs low Hb (10.5-11.5 g/dL) target	12 mo	High, +3.3[e]; low, −2.2[e]	<0.001	NE	No	High, 11.6 ± 0.6 g/dL; low, 11.6 ± 0.6 g/dL	High, 13.5 g/dL; low, 11.6 g/dL	High, +1.9 g/dL; low, 0.0 g/dL	High, 1.7; low, NE
Singh et al[22] (2006)	1,432	High (13.5 g/dL) vs low Hb (11.3 g/dL) target	NR	High, +3.2 ± 24[d]; low, +2.1 ± 23.2[d]	<0.01	High, 0.11; low, 0.08	No	High, 10.1 ± 0.9 g/dL; low, 10.1 ± 0.9 g/dL	High, 12.6 g/dL; low, 11.3 g/dL	High, +2.5 g/dL; low, +1.2 g/dL	High, 1.3; low, 1.8
MacDougall et al[23] (2008)	297	DA vs C.E.R.A.	29 wk	DA, +3.5[e]; C.E.R.A., +4.2[e]	NR	NE	No	DA, 10.2 ± 0.7 g/dL; C.E.R.A., 10.2 ± 0.6 g/dL	DA, 12.2 g/dL; C.E.R.A., 12.3 g/dL	DA, +2.02 g/dL; C.E.R.A., +2.12 g/dL	DA, 1.7; C.E.R.A., 2.0
					Open-label Single-Arm Studies						
Alexander et al[25] 2007	48	Single arm	16 wk	+9.5 ± 2.9	<0.05	2.38 (large)	Yes	9.1 ± 0.1 g/dL	12.6 g/dL	+3.5 g/dL	2.7
Benz et al[26] (2007)	67	Single arm	16 wk	+7.8 ± 20.9	<0.05	SRM, 0.37 (small)	Yes	9.8 ± 0.9 g/dL	11.7 g/dL	+1.9 g/dL	4.1

Note: Conversion factor for Hb in g/dL to g/L, ×10.

Abbreviations: C.E.R.A., methoxy polyethylene glycol-epoetin beta, a continuous erythropoietin receptor activator; DA, darbepoetin alfa; Hct, hematocrit; Hb, hemoglobin; MCID, minimal clinically important difference; NE, not evaluable; NR, not reported, PRO, patient-reported outcome; RCT, randomized controlled trial; SRM, standardized response mean.

[a]Statistical significance reported for RCTs is the between-group comparison of change from baseline.

[b]Change in Hct is a percentage point change, not a percentage of increase or decrease.

[c]Change in PRO divided by change in Hb level (or change in Hct).

[d]Represents significant within-group changes from baseline.

[e]SDs were not reported.

Table 8. Mean Change in 36-Item Short-Form Health Survey Role–Physical Scores

Study	No. of Patients	Design	PRO Follow-up	ΔPRO (mean ± SD)	*P*[a]	Effect Size	MCID	Baseline Hb (g/dL) or Hct (%)	Hb (g/dL) or Hct (%) at Study End	ΔHb (g/dL) or ΔHct (%)[b]	Per Unit Change in Role–Physical Score[c]
Open-label RCTs											
Revicki et al[20] (1995)	35	Treated (target Hct, 36%) vs untreated	48 wk	Treated, +1.7 ± 6.9; untreated, 0.0 ± 4.0	0.9	Treated, 0.266, SRM, 0.246 (small); untreated, 0, SRM, 0	No	Treated, 26.8% ± 4.5%; untreated, 26.8% ± 3.6%	Treated, 31.5%; untreated, 25.8%	Treated, +4.7 %; untreated, −1.0%	Treated, 0.4; untreated, 0
Rossert et al[31] (2006)	224	High (13.0-15.0 g/dL) vs low Hb (11.0-12.0 g/dL) target	16 wk	NR	<0.05	NE	NE	High, 11.5 ± 1.0 g/dL; low, 11.6 ± 0.9 g/dL	High, 13.9 g/dL; low, 11.8 g/dL	High, +2.4 g/dL; low, +0.2 g/dL	NE
Drueke et al[21] (2006)	603	High (13.0-15.0 g/dL) vs low Hb (10.5-11.5 g/dL) target	12 mo	High, +2.4[d]; low, −5.5[d]	<0.01	NE	High, no; low, yes	High, 11.6 ± 0.6 g/dL; low, 11.6 ± 0.6 g/dL	High, 13.5 g/dL; low, 11.6 g/dL	High, +1.9 g/dL; low, 0.0 g/dL	High, 1.3; low, NE
Singh et al[22] (2006)	1,432	High (13.5 g/dL) vs low Hb (11.3 g/dL) target	NR	High, +6.4 ± 40.7[e]; low, +7.5 ± 43.2[e]	<0.01	High, 0.16; low, 0.23 (small)	Yes	High, 10.1 ± 0.9 g/dL; low, 10.1 ± 0.9 g/dL	High, 12.6 g/dL; low, 11.3 g/dL	High, +2.5 g/dL; low, +1.2 g/dL	High, 2.6; low, 6.3
MacDougall et al[23] (2008)	297	DA vs C.E.R.A.	29 wk	DA, +9.5[d]; C.E.R.A., +3.7[d]	NR	NE	DA, yes; C.E.R.A., no	DA, 10.2 ± 0.7 g/dL; C.E.R.A., 10.2 ± 0.6 g/dL	DA, 12.2 g/dL; C.E.R.A., 12.3 g/dL	DA, +2.02 g/dL; C.E.R.A., +2.12 g/dL	DA, 0.7; C.E.R.A., 1.7
Open-label Single-Arm Studies											
Alexander et al[25] (2007)	48	Single arm	16 wk	+18.1 ± 5.5	<0.001	3.4, SRM, 3.29 (large)	Yes	9.1 ± 0.1 g/dL	12.6 g/dL	+3.5 g/dL	5.2
Benz et al[26] (2007)	67	Single arm	16 wk	+13.6 ± 48.3	<0.05	NE	Yes	9.8 ± 0.9 g/dL	11.7 g/dL	+1.9 g/dL	7.2

Note: Conversion factor for Hb in g/dL to g/L, ×10.

Abbreviations: C.E.R.A., methoxy polyethylene glycol-epoetin beta, a continuous erythropoietin receptor activator; DA, darbepoetin alfa; Hct, hematocrit; Hb, hemoglobin; MCID, minimal clinically important difference; NE, not evaluable; NR, not reported; PRO, patient-reported outcome; RCT, randomized control trial; SRM, standardized response mean.

[a]Statistical significance reported for RCTs is the between-group comparison of change from baseline.

[b]Change in Hct is a percentage point change, not a percentage of increase or decrease.

[c]Change in PRO divided by change in Hb (or change in Hct).

[d]SDs were not reported.

[e]Represents significant within-group changes from baseline.

Table 9. Mean Change in Linear Analogue Scale Assessment Activity

Study	No. of Patients	Design	PRO Follow-up	ΔPRO (mean ± SD)	P[a]	Effect Size	MCID	Baseline Hb (g/dL)	Hb (g/dL) at Study End	ΔHb (mg/dL) OR ΔHct (%)[b]	Per Unit Change in Activity[c]
Open-label RCT											
Singh et al[22] (2006)	1,432	High (13.5 g/dL) vs low Hb (11.3 g/dL) target	NR	High, +15.0 ± 39.9[d]; low, +13.3 ± 29.8[d]	<0.001-0.02	NE	Yes	High, 10.1 ± 0.9; low, 10.1 ± 0.9	High, 12.6; low, 11.3	High, 2.5 g/dL; low, 1.2 g/dL	High, 6.0; low, 11.1
Open-label Single-Arm Studies											
Benz et al[26] (2007)	67	Single arm	16 wk	+17.0 ± 21.9	<0.05	SRM, 0.78 (moderate)	Yes	9.8 ± 0.9	11.7	1.9 g/dL	8.9
Provenzano et al[28] (2004)	1,184	Single arm	16 wk	+24.5 ± 24.9	<0.001	SRM, 0.98 (large)	Yes	9.1 ± 0.7	11.8	2.7 g/dL	9.1
Provenzano et al[29] (2005)	519	Single arm	16 wk	+4.8 ± 27.0	<0.001	0.152, SRM, 0.117	No	11.8 to 11.9[e]	11.2 to 12.0[e]	−0.7 to +0.3 g/dL[e]	NE

Note: Conversion factor for Hb in g/dL to g/L, ×10.

Abbreviations: Hct, hematocrit; Hb, hemoglobin; MCID, minimal clinically important difference; NE, not evaluable; NR, not reported, PRO, patient-reported outcome; RCT, randomized controlled trial; SRM, standardized response mean.

[a]Statistical significance reported for RCTs is the between-group comparison of change from baseline.

[b]Change in Hct is a percentage point change, not a percentage of increase or decrease.

[c]Change in PRO divided by change in Hb (or change in Hct).

[d]Represents significant within-group changes from baseline.

[e]Range.

Other Patient-Reported Outcomes Measuring Physical Function, Activity, or Role Limitation

The 5 studies listed in Table 10 measured physical function, activity, or role limitation using other measures, including a 5-point Likert scale, a single-item visual analogue scale, the Physical Component Summary (PCS) score of the SF-36, and a measure that was not specified. Data provided by the 2 double-blind RCTs using the single-item visual analogue scale and 5-point Likert scale were not sufficient to calculate effect size.[18,19] The high- versus low-Hb target RCT,[24] which measured change in physical health using the SF-36 PCS, reported slight negative effect sizes (−0.18 and −0.09).[24] The open-label single-arm study that used the SF-36 PCS reported a small statistically significant improvement (3.3) and a small effect size (0.3).[27] The change in patient-reported outcome per unit of change in Hb level for this study was 1.8.

DISCUSSION

Findings in the present review provide evidence that ESA therapy may be important in improving energy and physical function reported by nondialysis CKD patients with anemia. Studies examining this topic have used a variety of instruments, including the SF-36, LASA, FACT-Fatigue, and KDQ. The SF-36 was the instrument most commonly used to measure energy and physical function in nondialysis CKD patients with anemia. Although there is considerable variability in study designs and durations of follow-up, correction of anemia was consistently associated with improvements in energy and physical function across the different studies irrespective of the patient-reported outcome instrument used. The magnitude of physical function and energy effect sizes suggests that these are clinically important effects. In the open-label RCT with a treated and untreated arm, the direction of change was negative in the untreated arm for both physical function and energy, with significant increases in the treated arm.[20] One high- versus low-Hb target RCT[21] had a small improvement in the high-target arm and a decrease in the low-target arm for both energy and physical function. This potentially could have been a result of the early (Hb, 11.6 g/dL) versus delayed (Hb < 10.5 g/dL) initiation of treatment in the high- versus low-Hb target groups.

There is a paucity of data using double-blind RCTs evaluating the impact of treatment with ESAs in nondialysis patients with CKD. Two such trials[18,19] used a double-blind randomized placebo-control design to evaluate the effect of treatment of anemia in nondialysis patients with CKD. The US Recombinant Human Erythropoietin Predialysis Study Group[18] randomly assigned 117 individuals to 1 of 3 epoetin alfa groups or placebo. Study duration was 8 weeks. An unspecified questionnaire was used to collect measurements of patient-reported energy and work capacity. More subjects in epoetin-alfa–treated groups reported increased energy or work capacity compared with those in placebo groups. Kleinman et al[19] evaluated changes in patient-reported energy, work capacity, and overall quality of life with epoetin alfa treatment compared with placebo in a small (N = 14) 12-week study using a visual analogue scale. Although the authors did not report changes in energy and work capacity, overall quality of life measured using the visual analogue scale was statistically significantly improved with epoetin alfa treatment compared with placebo. However, it was not possible to estimate the magnitude of effect because of data limitations.

Most RCTs of nondialysis patients with CKD have evaluated the impact of degree of anemia correction by comparing 2 actively treated groups with different Hb targets[22] or the benefits of early versus late correction of anemia.[21] These studies consistently show improvement in patient-reported energy and physical function scores after Hb level correction from baseline (10.1 g/dL) across both high- (>13 g/dL) and low-Hb target (10.5-11.5 g/dL) groups. Furthermore, although these studies have suggested that the higher Hb levels (>13 g/dL) achieved with ESA administration in nondialysis patients with CKD are not associated with an incremental improvement in HRQOL for these patients, they show improvement in patient-reported energy and physical function scores after Hb level correction from baseline (10.1 g/dL) across both high- and low-Hb target groups. These observations support 2 recent articles suggesting that improvements in energy and physical function are maximized in the Hb level range of 10-12 g/dL.[6,43] An ongoing

Table 10. Mean Change in Physical Function, Activity, or Role Limitation Measured Using Other PROs

Measure	Study	No. of Patients	Design	PRO Follow-up	ΔPRO (mean ± SD)	*P*[a]	Effect Size	MCID	Baseline Hb (g/dL) or Hct (%)	Hb (g/dL) or Hct (%) at Study End	ΔHB or ΔHct[b]	Per Unit Change in PRO[c]
					Double-blind Placebo RCTs							
5-Point Likert scale	The US Recombinant Human Erythropoietin Predialysis Study Group[18] (1991)[d]	110	Anemia corrected (target Hct: ♂, 40%; ♀, 37%) vs not corrected	8 wk	Corrected 92[e,f]; uncorrected, 32[f]	<0.05	NE	NE	Corrected[g]: ♂, 93-97 g/L; ♀, 88-93 g/L Uncorrected: ♂, 99 ± 16 g/L; ♀, 94 ± 8 g/L	NR	NR[h]	NE
Single-item VAS	Kleinman et al[19] (1989)	14	Treated (target Hct, 38%-40%) vs placebo	12 wk	NR	NR	NE	NE	NR	NR	Treated, +7.7%; placebo, −0.1%	NE
					Open-label RCT							
SF-36 PCS	Roger et al[24] (2004)	155	High (12.0-13.0 g/dL) vs low Hb (9.0-10.0 g/dL) target	24 mo	High, −2 ± 14; low, −1 ± 13	NR	High, −0.18, SRM, −0.14; low: −0.09, SRM, −0.07	No	High, 112 ± 9 g/L; low, 112 ± 8 g/L	High, 12.1 ± 1.4 g/dL; low, 10.8 ± 1.3 g/dL	High, +0.9 g/dL; low, −0.4 g/dL	High, 2.2; low, 2.5
					Open-label Single-Arm Studies							
SF-36 PCS	Abu-Alfa et al[27] (2008)	277	Single arm	52 wk	+3.3 ± 8.7	<0.001	0.308; SRM, 0.379 (small	No	10 ± 0.9 g/dL	11.8 ± 1.1 g/dL	+1.8 ± 1.3 g/dL	1.8
NR	Islam et al[30] (2005)	45	Single arm	6 mo	+9 ± 68.8	<0.001	0.13	NE	27.86% ± 1.5%	32.81% ± 3.92%	+4.95%	1.8

Note: Conversion factor for Hb in g/dL to g/L, ×10.

Abbreviations: Hct, hematocrit; Hb, hemoglobin; MCID, minimal clinically important difference; NE, not evaluable; NR, not reported; PCS, Physical Component Summary; PRO, patient-reported outcome; RCT, randomized control trial; SRM, standardized response mean.

[a]Statistical significance reported for RCTs is the between-group comparison of change from baseline.

[b]Change in Hct is a percentage point change, not a percentage of increase or decrease.

[c]Change in PRO divided by change in Hb (or change in Hct).

[d]The US Recombinant Human Erythropoietin Predialysis Study Group (1991) randomly assigned patients to 1 of 4 treatment groups, including placebo. Quality-of-life results were reported by 2 groups: anemia corrected and anemia not corrected.

[e]The US Recombinant Human Erythropoietin Predialysis Study Group (1991) measured work capacity on a scale.

[f]SDs were not reported.

[g]Range.

[h]The US Recombinant Human Erythropoietin Predialysis Study Group (1991) reports the percentage of patients in each arm showing at least 6% change in Hct.

double-blind RCT of anemia correction in nondialysis patients with CKD using darbepoetin will provide additional data about the impact of anemia correction on energy and physical function.[44]

Several limitations should be considered when interpreting this review. Study findings and the strength of our conclusions are limited by the available evidence. Few randomized placebo-controlled clinical trials have been completed evaluating the impact of ESA treatment on energy or physical function end points in anemia related to nondialysis patients with CKD. Of studies that measured energy or physical function, selective reporting of results occurred, resulting in an incomplete data set with which to rigorously assess HRQOL. Because patients were not blinded to treatment, this could have affected their response to the self-reported questionnaires. The content validity of these patient-reported instruments has not been established in a nondialysis CKD population. In other words, it has not been determined whether each instrument sufficiently captures the issues within the concept it is measuring that patients in this population indicate are important. Variations in clinical study designs and data collection schedules may impact on outcomes across the different studies reviewed. Finally, there is variability in analyses performed and the way data are presented. In this review, we have made an attempt to standardize the presentation and interpretation of patient-reported data across various studies using effect-size estimates. However, it must be reiterated that effect sizes are simply distribution-based measures driven by both the magnitude of effect and variability within the sample.

In conclusion, the available evidence shows that ESA treatment improves Hb concentrations with accompanying improvements in patient-reported energy and physical function. The effect size, a measure of magnitude of treatment effect, seen with energy and physical function after treatment with ESAs provides further evidence of the beneficial impact of ESA therapy on patient-reported outcomes. Although different instruments were used to measure energy, fatigue, and physical function, there is a remarkable consistency of treatment benefit across different studies.

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