# Systematic Review and Meta-analysis of Exercise Tolerance and Physical Functioning in Dialysis Patients Treated With Erythropoiesis-Stimulating Agents

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**Background:** The role of erythropoiesis-stimulating agents (ESAs) in treating the anemia of chronic kidney disease has been reevaluated in view of recent studies suggesting that the use of these agents may be associated with increased morbidity and mortality. This potential increased risk needs to be weighed against the potential benefit of ESAs in improving various aspects of health-related quality of life, in particular, exercise tolerance and physical functioning.

**Study Design:** A systematic review and meta-analysis of exercise tolerance and physical functioning.

**Setting & Participants:** Adults on maintenance dialysis therapy.

**Selection Criteria for Studies:** Outcomes measured before and after ESA treatment were required. Studies of physical function were required to include at least 25 participants.

**Intervention:** Treatment with any ESA.

**Outcomes:** Exercise tolerance measured using $VO_{2peak}$ (oxygen consumption per minute at the peak workload during the test), duration of exercise, or 6-minute walk distance or physical functioning assessed using $\geq$ 1 patient- or clinician-reported outcome measure that included a physical function domain.

**Results:** 28 articles met criteria for inclusion for evaluation of exercise tolerance, and 14 articles, for physical function. Meta-analysis showed a 23.8% increase in $VO_{2peak}$ from before to after erythropoietin therapy initiation (15 studies) and a nonsignificant 8.2% increase comparing a higher with a lower hemoglobin target (3 studies). For physical functioning, 4 studies met criteria for inclusion in the meta-analysis: there was a 10.5% increase in Karnofsky score from before to after erythropoietin therapy initiation.

**Limitations:** Many studies of exercise tolerance did not include control groups. A wide variety of instruments was used to assess physical function.

**Conclusions:** Partial correction of anemia through ESA treatment has a consistent and positive impact on $VO_{2peak}$. ESA treatment improves patient- and clinician-assessed physical functioning.

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***INDEX WORDS:*** Chronic kidney disease; erythropoiesis-stimulating agents; epoetin alfa; exercise tolerance; quality of life.

**Editorial, p. 423**

Recent studies have focused on health-related quality of life (HRQOL) as an important outcome in patients with chronic kidney disease (CKD). This has occurred in part because HRQOL measures have been associated with hospitalizations and mortality in patients with end-stage renal disease (ESRD) maintained on dialysis therapy.[1,2] However, it also has been recognized that HRQOL measures themselves can be viewed as primary outcome measures in studies involving interventions in the care of patients with CKD.[3,4]

HRQOL measures encompass a variety of domains. Exercise tolerance and physical functioning are important aspects of HRQOL. This is particularly true for patients with CKD, who have been documented to have significant decreases in both these domains. Reasons for these decreases likely are multifactorial. Anemia has been associated with impairment in exercise tolerance and physical functioning and likely contributes, at least in part, to patient difficulties. Other potentially important contributors include

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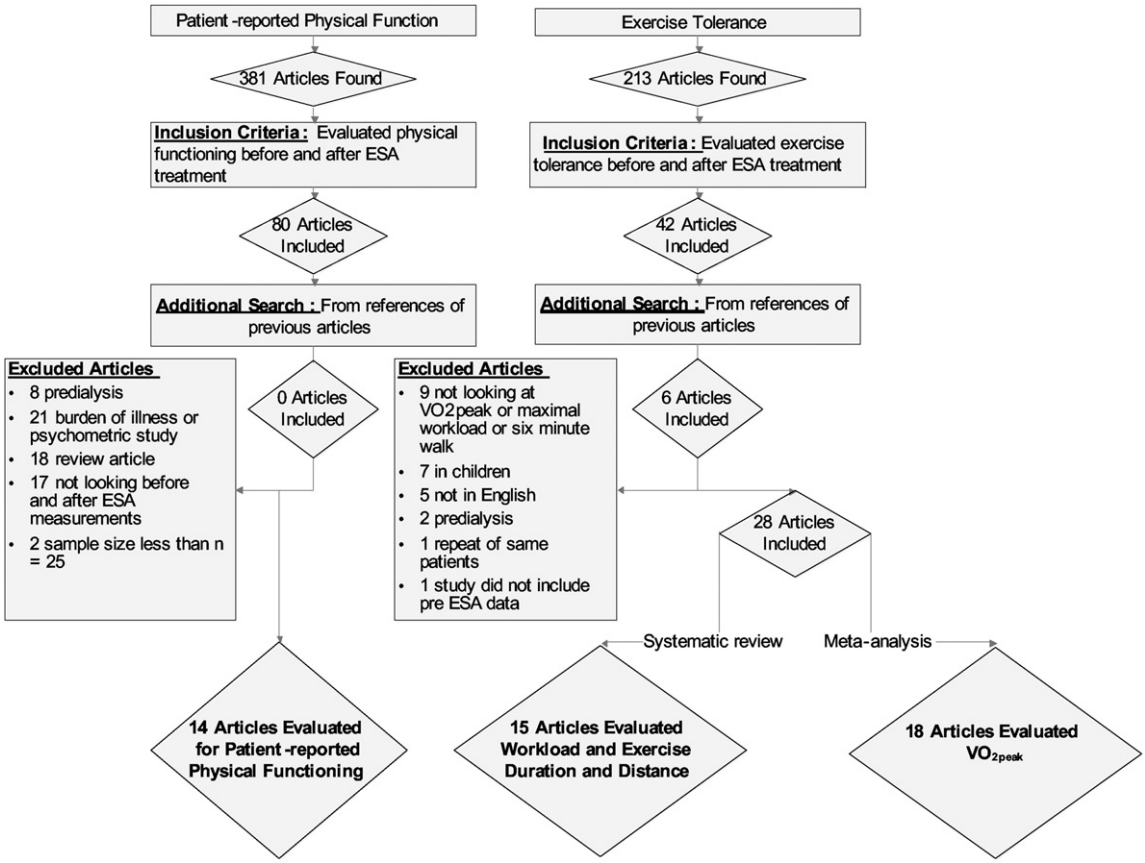


**Figure 1.** Article selection process. Abbreviations: ESA, erythropoiesis-stimulating agent; $Vo_{2peak}$, peak oxygen consumption.

lack of physical conditioning because of sedentary behavior, cardiac dysfunction, abnormalities of bone and mineral metabolism, and various psychosocial factors, such as depression.

The role of erythropoiesis-stimulating agents (ESAs) in treating the anemia of patients with CKD has been reevaluated in view of recent studies suggesting that use of these agents may be associated with increased morbidity and mortality.[5,6] However, several investigators have suggested a benefit of ESAs in improving various aspects of the HRQOL in patients with CKD, particularly in the domains of exercise tolerance and physical functioning.

The purpose of the present study is to review the available published evidence of the effect of ESA treatment on exercise tolerance and physical functioning in patients with CKD maintained on dialysis therapy.

## METHODS

### Review Strategy

We performed a systematic review of the literature for the impact of ESA therapy on exercise tolerance and patient functional outcomes in patients with ESRD. A systematic search was conducted using MEDLINE and EMBASE (Fig 1). The search was limited to articles published in the English language and during the period between 1988 (the first year ESAs were approved by the US Food and Drug Administration for use in the United States) and 2008. Search terms for kidney disease included "chronic renal failure" or "chronic renal insufficiency" or "kidney failure, chronic" (medical subject heading) or "renal insufficiency, chronic" (medical subject heading) or "end stage renal disease" or dialysis or "hemodialysis" or "haemodialysis"; for ESAs, "Epoetin Alfa" or "erythropoietin"; for exercise tolerance, "exercise" or "physical function" or "walking"; and for physical function, "physical functioning" or "physical status" or "physical performance" or "functional status" or "health-related qualify of life" or "HRQL" or "HRQOL" or "quality of life" or "QOL." Articles were identified for the review if they met the following inclusion criteria: (1) adults