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Overview of Erythropoiesis-Stimulating  
Agents for Anemia of Chronic Kidney  
Disease: Systematic Review and  
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**Canadian Agency for Drugs and Technologies in Health**

**Overview of Erythropoiesis-Stimulating Agents  
for Anemia of Chronic Kidney Disease:  
Systematic Review and Economic Evaluation**

March 2008

We thank Eugenia Palylyk-Colwell for her assistance in creating this overview from a longer report authored by Tonelli *et al.*

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## Erythropoiesis-Stimulating Agents for Anemia of Chronic Kidney Disease: Systematic Review and Economic Evaluation

### Technology

Erythropoiesis-stimulating agents (ESA), epoetin alpha (Eprex<sup>®</sup>, Janssen-Ortho), darbepoetin (Aranesp<sup>™</sup>, Amgen), and epoetin beta (NeoRecormon<sup>®</sup>, Roche)

### Condition

Adult patients with anemia of chronic kidney disease (CKD) who need or do not need dialysis.

### Issue

ESAs are routinely used to treat anemia of chronic kidney disease (CKD), especially in patients requiring dialysis. Increasingly, higher doses of ESA are being used to attain higher hemoglobin (Hb) target levels. There is uncertainty about the impact of this approach on the health system.

### Methods and Results

Randomized controlled trials (RCTs) that included anemic adults with CKD receiving epoetin (alpha or beta), darbepoetin or “management without ESA” (no ESA) and compared clinical outcomes and harms on the basis of Hb targets and method of delivery were identified through a systematic review. A cost-utility analysis from the perspective of the Canadian public health care system and a lifetime time horizon was conducted. The budget impact to the provincial health care system was estimated if patients were treated to an intermediate Hb target and if the subcutaneous (SC) rather than the intravenous (IV) route of administration of ESA was used.

### Implications for Decision Making

- **Health outcomes are improved, but some uncertainty remains.** ESA resulted in lower observed cardiovascular mortality, but all-cause mortality was not affected. The impact on health-related quality of life was modest, and most trials did not provide a complete report of these measures.
- **Intermediate and low targets are optimal.** Low (90 to 105 g/L) Hb target strategies represent the least costly and second most effective option. Intermediate Hb target (110 g/L) strategies produce the largest number of quality-adjusted life years (QALYs) at an additional cost per patient lifetime (C\$21,000 to C\$27,000 per patient lifetime compared with the low Hb target in non-dialysis-dependent and dialysis-dependent adult CKD).
- **Route of administration and Hb target will affect health care budgets.** For dialysis-dependent patients, the estimated cost of treating anemia to an intermediate Hb target is C\$9,394 per patient per year on dialysis. If SC epoetin is used instead of IV (or if darbepoetin is used via either route), costs could be reduced to C\$6,577 per patient per year. Altering the Hb target to a low strategy would result in cost savings of C\$35 million to C\$49 million per year compared with the intermediate target.

This summary is based on a comprehensive health technology assessment available from CADTH's web site ([www.cadth.ca](http://www.cadth.ca)): Tonelli M, Klarenbach S, Wiebe N, Shrive F, Hemmelgarn B, Manns B. *Erythropoiesis-Stimulating Agents for Anemia of Chronic Kidney Disease: Systematic Review and Economic Evaluation*

# 1 Introduction

Erythropoiesis-stimulating agents (ESA) raise or maintain red blood cell levels by stimulating red blood cell production. ESA are used for the prevention and treatment of anemia in patients with dialysis-dependent or non-dialysis-dependent chronic kidney disease (CKD). They are administered via the intravenous (IV) or subcutaneous (SC) route. Before ESA, dialysis patients needed frequent blood transfusions, which are costly and can lead to complications. Early studies found that ESA reduced the need for transfusions and improved quality of life (QoL) in patients with CKD when compared with not using ESA.<sup>1,2</sup> Today with ESA being used extensively in patients with CKD, especially for those who are dialysis-dependent, the focus for practitioners has shifted from whether ESA should be used to determine the optimal hemoglobin (Hb) target.

The medication class of ESA includes epoetin alpha, epoetin beta, and darbepoetin. Of these, epoetin alpha (Eprex<sup>®</sup>, Janssen-Ortho) and darbepoetin (Aranesp<sup>™</sup>, Amgen) are currently available in Canada. A third product, epoetin beta (Neorecormon<sup>®</sup>, Roche), which is similar to epoetin alpha and widely used in Europe, may soon be available in Canada. Epoetin alpha is typically administered one to three times weekly. Darbepoetin, because of its longer half-life, is given one to four times monthly. Epoetin alpha and darbepoetin are reimbursed by all Canadian provincial drug programs for patients with anemia of CKD. Continuous erythropoietin receptor activator is being studied in CKD populations, but is unavailable in Canada and is not considered further herein. In this report, we have used the term “epoetin” to refer to either epoetin alpha or epoetin beta. The term “ESA” is used for statements that apply to both epoetins (alpha and/or beta) and darbepoetin.

When they were introduced, ESA were reserved for use in dialysis patients with severe anemia who were often transfusion-dependent. The goals of therapy were to raise Hb levels to 90 g/L to 120 g/L. Today, US clinical practice guidelines (CPGs) advocate dosing ESA to maintain Hb levels of 110 g/L to 120 g/L (but not greater than 130 g/L) in all patients with CKD.<sup>3,4</sup> US and European CPGs are largely based on data from observational studies that support an association of higher Hb targets with better clinical outcomes in CKD. In contrast, trials comparing ESA with no ESA or no treatment have shown similar rates of mortality, cardiovascular morbidity, and hospitalization between comparison groups.<sup>2</sup> Most randomized controlled trial (RCT) data comparing low and high Hb target levels have found no benefit from more intensive therapy. Two large trials (reported in the lay press) on non-dialysis-dependent CKD suggest that higher Hb targets may lead to harm.<sup>5-10</sup> Canadian CPGs are expected to be published by the end of 2008.

The increasing use of ESA and the growing prevalence of CKD in Canada have prompted some jurisdictions to examine the use and clinical impact of these agents. Because ESA are being prescribed to a broader population (i.e., non-dialysis-dependent CKD patients), and higher Hb targets typically require exponential increases in doses of ESA, costs are increasing. These practices are being driven by CPGs as opposed to RCT data, and questions remain as to whether this could result in harm while providing a modest clinical benefit. The examination of these issues will be of benefit to Canadian policy and decision makers, because effective policy development will require the consideration of optimal Hb targets and strategies to achieve maximal clinical benefit and cost-efficiency from ESA use.

## 2 Objectives

The objectives were to perform a systematic review of the clinical efficacy and harms of ESA and to conduct an economic evaluation and budget impact analysis assessing ESA use in adult patients with anemia of CKD. The objectives were achieved by addressing the following research questions:

- What is the direct and indirect evidence for the consequences of treatment with epoetin and darbepoetin on clinically meaningful outcomes [including mortality, cardiovascular morbidity, hospitalization, QoL, red cell transfusions, and adverse events (seizures, intradialytic clotting)] when used to treat anemia of CKD?
- What are the differences between epoetin and darbepoetin in terms of net health impact? In particular, what are the differences in dosing and its impact on the delivery of care between agents?
- What are the cost and consequences of these agents when used to treat anemia of CKD? What is the incremental difference between the two drug products?
- What is the budgetary impact of adopting funding policies that reflect optimal usage?
- What is the optimal Hb target in patients with dialysis-dependent and non-dialysis-dependent CKD? Does this target vary in groups defined by severity of CKD, dialytic modality, or other patient characteristics?

## 3 Clinical Review

### *Methods*

A systematic review was conducted to assess the efficacy and harms of ESA use compared with “management without ESA” (no ESA), a high (more than 120 g/L) Hb target with an intermediate (110 g/L) or low (90 g/L to 105 g/L) Hb target, and epoetin with darbepoetin (i.e., based on dosage, schedule, and route of administration). Published literature was obtained by searching MedLine (from 1966) and EMBASE (from 1988 to December 12, 2006), and all Evidence-Based Medicine (EBM) Reviews. Searches were not restricted by language. Hand-searches of the reference lists of included trials and relevant reviews and searches of grey literature sources were also conducted. Canadian manufacturers of ESA (Amgen and Janssen-Ortho) and the authors of included studies were contacted for information (for example, all-cause mortality and QoL data), if required.

Reviewers independently selected potentially eligible reports if the report was a parallel RCT with 30 or more participants in each treatment group and evaluated epoetin (alpha and beta) or darbepoetin compared with another agent or Hb target, no ESA (for example, placebo), or a different method of delivery (dose, schedule, or route of administration). Outcomes included all-cause or cardiovascular mortality, cardiac events [myocardial infarction (MI), stroke, heart failure, or revascularization], hospitalization, vascular access loss or dialysis dependence, renal function [glomerular filtration rate (GFR), creatinine clearance (CrCl), serum creatinine (SCr)], QoL, red cell transfusions, systolic blood pressure (SBP) and diastolic blood pressure (DBP), left ventricular mass index, and adverse events (AEs).

Reviewers independently extracted data, including information on trial characteristics, study participants, illness severity, therapeutic regimens, control regimens, co-interventions, and outcomes. Trial data were captured for the outcomes of mortality, cardiovascular events, hospitalization, vascular access loss or dialysis dependence, renal function, QoL, red cell transfusions, blood

pressure, left ventricular mass index, and AEs. Data on AEs were extracted as “serious” or “any,” with attention paid to data on the incidence of seizures and intradialytic clotting.

Study quality was independently evaluated by reviewers using a condensed version of the Chalmers Index.<sup>11</sup> The characteristics associated with study quality and information on funding sources were recorded. Any reviewer differences in study selection, data extraction, or quality assessment were resolved with a third party by consensus. Data were analyzed by pooling the results of trials that compared ESA with no ESA, high Hb with intermediate or low Hb protocols, and darbepoetin with epoetin using a random effects model.<sup>12</sup> Relative risk (RR) and the weighted mean difference (WMD) were used to summarize dichotomous and continuous results respectively. Statistical heterogeneity was quantified using the  $I^2$  quantity.<sup>13,14</sup> Regression methods and sensitivity analyses were used to explore the relationships between variables and outcomes. The details are available in the full report.<sup>15</sup>

## **Results**

From a total of 2,289 citations that were identified in the original searches, 2,062 were excluded. Four additional citations were identified from other sources, resulting in 231 potentially relevant reports retrieved for full-text scrutiny. From these, 194 reports were excluded, to yield 37 reports describing 38 trials that met the selection criteria. Sample sizes, study designs, and quality varied between reports. The details of the study characteristics and quality assessments can be found in the full report.<sup>15</sup>

### **a) ESA versus no ESA**

Ten trials<sup>16-25</sup> (n=1,553) of poor to moderate quality compared ESA with no ESA. Four trials were conducted in non-dialysis-dependent patients and six in dialysis-dependent CKD patients. Pooled results from seven trials (n=1,048) found the RR of death (all-cause mortality) was not different between groups, although five of seven trials favoured ESA treatment. Three trials (n=564) reported on cardiovascular mortality, and a lower risk was found with ESA. Two trials (n=445) compared the frequency of MI and heart failure between groups. The RRs were not statistically significant, despite individual trial results favouring ESA. In one trial (n=98) that measured QoL (change in fatigue), the WMD significantly favoured ESA patients. Three trials (n=300) reported the numbers of participants receiving red cell transfusions during follow-up. ESA reduced the transfusion risk by 85%. Three trials (n=246) reported the numbers of participants with non-dialysis-dependent CKD who experienced kidney failure requiring dialysis. Although two trials reported a numerically lower risk of kidney failure with ESA, the pooled result was not significant. Two trials (n=151) supported smaller changes in GFR with ESA. Three trials (n=296) reported a change in SC. The WMD, however, was not significantly different. One trial (n=118) reported the incidence of vascular access thrombosis. Although there were fewer thromboses with ESA, the RR was not significant. Four trials (n=575) reported changes in SBP and DBP. One trial (n=229) showed that ESA recipients were more likely to need antihypertensive therapy, and pooled results from three trials (n=274) revealed a need for new or intensified antihypertensive therapy with ESA. There were no significant differences in withdrawals due to AEs based on three trials (n=343), although all trials favoured no ESA. Serious AEs based on two trials (n=269) were lower with ESA. Based on three trials (n=366), “any” AEs did not differ between groups. There were no significant differences in seizures or clotting events between groups.

## **b) High versus intermediate or low target Hb protocols**

Thirteen trials<sup>5-10,25-31</sup> (n=5,605) of poor to moderate quality compared high with intermediate or low Hb strategies (eight in non-dialysis-dependent, four in dialysis-dependent, and one in both types of CKD patients). The pooled results of 12 trials (n=5,434) found that the RR of death (all-cause mortality) was not different between groups. There were no differences when trials with a follow-up one year more or when stratified by severity of CKD or dialytic modality were considered. The pooled results of six trials (n=3,040) that reported cardiovascular mortality indicated no difference in risk of cardiovascular death between groups. The RRs of MI, stroke, heart failure, and revascularization were not statistically significant when target groups were compared. Four trials (n=3,143) reported numbers of all-cause hospitalizations by treatment group, and pooled results showed an increased risk with high Hb targets. High Hb targets improved the selected measures of QoL in some trials but not others, and the clinical significance of these findings is questionable. Based on four trials (n=2,302), the transfusion risk was significantly reduced in high target Hb groups. Five trials (n=2,741) reported the start of dialysis during follow-up. In four trials, dialysis initiation was more frequent with a high Hb target, but the pooled results were not significant. Seven trials (n=1,367) reported a change in GFR or in CrCl, but the pooled results in each case were not statistically significant. Six trials (n=2,856) reported rates of access thrombosis that were greater in the high target Hb protocol groups. Eight trials (n=3,426) reported changes in SBP and DBP. The WMD for DBP was statistically significant, but that of SBP was not. The pooled results of hypertension risk or need for intensified therapies were non-significant between target groups. Four trials (n=1,067) reported change in left ventricular mass index, which was not significant between groups. Five trials (n=1,391) reported withdrawals due to AEs, and pooled results indicated that the overall RR was not significantly different. Serious AEs were reported in five trials (n=2,529), and the risk was significantly higher for higher target Hb, although all trials tended to favour lower Hb targets. Five trials (n=3,159) reported on “any” AEs, and the pooled risk was significantly greater for higher Hb targets. No significant differences were found in risk of seizure or clotting events between target groups.

## **c) Epoetin versus darbepoetin**

Three trials<sup>32-34</sup> (n=775) of moderate quality compared epoetin and darbepoetin. Two trials (n=670) reported all-cause mortality, one in patients with non-dialysis-dependent CKD and the other in dialysis patients. The pooled results revealed no significant difference between agents. No trials had follow-up for one year or more. One trial (n=166) reported that the risk of cardiovascular death was not significantly different between agents. The pooled results of two trials (n=673) found no difference in transfusion risk between agents, but both trials had fewer darbepoetin patients with transfusions. Two trials (n=612) reported vascular access loss, but the combined results were not significant. One trial (n=166) reported a change in GFR but no difference between agents. One trial (n=166) compared on-treatment changes in SBP and DBP and reported significantly lower SBP with darbepoetin. The changes in DBP were not significantly different. No significant differences were found in one trial (n=105) that reported on the number of patients who had recently started on antihypertensive therapy. Two trials (n=670) reported AEs, and the pooled RR did not significantly differ.

## **d) Supplemental issues and indirect comparisons**

Thirteen articles included supplemental issues, but there was little information to inform optimal dose, schedule, or route of administration of ESA. The SC route of administration was found to require lower doses than IV to achieve the same Hb target in dialysis patients.<sup>35</sup> An indirect comparison technique (random intercept logistic regression) was used to explore the relationships

between Hb target strategies (high, intermediate, low, and no ESA) and all-cause mortality (n=17 trials). The results suggest that high Hb targets are associated with a greater risk of death than combined intermediate and low Hb targets.

## 4 Economic Review

### **Methods**

In addition to the search results from the clinical review, citations from economic searches conducted in MedLine, EMBASE, EconLit, the NHS Economic Evaluation database, and other sources were screened.

Reviewers independently selected eligible studies if they evaluated the incremental impact of an ESA against a comparator group on relevant costs and health benefits and if the comparator group included a placebo, no ESA, different ESA, or same ESA but a varying Hb target, dose, or schedule. Comparisons of agents, route, or schedule to achieve an identical Hb target were included (in a cost-minimization analysis), but only if based on RCT data for effectiveness and if they included other features of an economic evaluation, for example, a sensitivity analysis. Studies were required to examine a cohort of adult patients with stage 3 to 5 CKD not on dialysis or with end-stage renal disease on dialysis. Reviewers independently extracted data that included author, title, intervention, comparators, study population, study design, time horizon, perspective, data sources for effects, data sources for costs, health-related QoL, currency, year, base case incremental cost-effectiveness ratio results or incremental net benefit, sensitivity analysis, and conclusions. The study quality was independently assessed by reviewers using a checklist adapted from the British Medical Journal<sup>36</sup> and the Consensus on Health Economic Criteria.<sup>37</sup> Any disagreements about study selection, data extraction, or quality assessment between reviewers were resolved by consensus. A qualitative synthesis of included studies was conducted as planned.

### **Results**

From a total of 2,289 citations that were identified from the combined searches, 2,230 were excluded, leaving 60 potentially relevant reports retrieved for full-text scrutiny. From these, 54 reports were excluded to yield six reports describing five evaluations<sup>38-43</sup> that met the selection criteria. Study sizes, designs, and quality varied between reports. Details about study characteristics and quality assessments appear in the full report.<sup>15</sup>

A narrative review that focuses on the comparison of ESA with no ESA, route of administration of ESA, and comparison of Hb targets from included studies appears in the full report.<sup>15</sup> Despite the reliance on observational data for estimates of clinical benefit and economic consequences, ESA has become the standard of care for anemia among dialysis patients in Canada and in most developed countries. Two cost-minimization studies<sup>40,41</sup> suggest that SC administration versus IV is preferable because of the lower doses needed to achieve a target Hb. No economic evaluations were identified that compared different agents or use in the non-dialysis CKD population.

## 5 Economic Evaluation

### Methods

Cost-utility and cost-effectiveness analyses were conducted to compare ESA treatment of anemia in CKD patients to a low, intermediate, or high Hb target compared with a strategy of no ESA. Two adult populations of dialysis and non-dialysis-dependent CKD patients were considered separately. It was assumed that epoetin would be administered by IV in dialysis-dependent patients because of theoretical concerns about red cell aplasia and SC in peritoneal dialysis and non-dialysis-dependent patients. Epoetin doses were based on those used in the RCTs to achieve given Hb targets. A decision model<sup>42</sup> was updated for the analysis. Model outputs were quality-adjusted life years (QALYs), life years gained, health care costs, and cost per QALY gained. Base case analyses were performed using Markov cohort analysis, and Monte Carlo simulation was used for probabilistic sensitivity analyses. The target audience was provincial health ministries and regional renal programs. The primary perspective was that of the Canadian publicly funded health care system. A lifetime time horizon was used, and costs and effects were discounted at 5%. Details on the information sources for clinical events, costs, estimates used in the model, assumptions, and potential limitations appear in the full report.<sup>15</sup> Scenario and sensitivity analyses were conducted to explore the assumptions and uncertainties in the model.

### Results

#### a) Dialysis-dependent patients

In the base case analysis, when compared with no ESA, treatment to a low Hb target produced the lowest incremental cost (C\$87,000 per patient lifetime) and the highest incremental effectiveness (4.39 QALYs gained versus 3.49 for no ESA). When compared with no ESA, the cost per QALY gained was C\$138,000 (low), C\$127,000 (intermediate), or \$272,000 (high) for each Hb target. By conventional economic theory, the intermediate strategy is more attractive than the low strategy with the assumptions made in the base case, but it translates into higher incremental costs (i.e., a difference of C\$27,000 per patient lifetime, discounted at 5%).

#### b) Non-dialysis-dependent patients

In the base case analysis, when compared with no ESA, treatment to a low Hb target produced the lowest incremental cost (C\$95,000 per patient lifetime) and the highest incremental effectiveness (3.43 QALYs gained versus 2.73 QALYs for no ESA). When compared with no ESA, the cost per QALY gained was C\$186,000 (low), C\$165,000 (intermediate), and C\$475,000 (high) for each Hb target. The intermediate Hb strategy is more attractive than the low with the assumptions made in the base case, but it translates into higher incremental costs (i.e., a difference of C\$21,000 per patient lifetime, discounted at 5%).

For both patient populations, the results were relatively consistent in all the modelling strategies. If equivalent survival and QoL are assumed between the low and intermediate Hb target strategies, the low strategy is optimal. Treatment to a high Hb target was not cost-effective in any of the models. None of the scenario or sensitivity analyses affected the cost per QALY associated with ESA in any group.

## 6 Limitations

As with all systematic reviews and meta-analyses, the interpretation of the results and strength of the conclusions drawn from the clinical review are limited by the available evidence. Poor trial quality and a lack of RCTs that directly compare low, intermediate, and high Hb targets required the use of indirect comparisons. The selective reporting of QoL domains and a lack of directly measured utility data were found to be weaknesses for reliably informing the analysis. The economic model is limited by the available evidence and the requirement to model all relevant clinical and economic consequences. Other limitations are the use of observational data to assign costs, although it was possible to model dialysis requirements (in the non-dialysis-dependent cohort) and hospitalization (for both cohorts) from available studies. Lastly, no information on indirect and productivity costs could be found.

## 7 Health System Implications

The estimated cost of ESA to treat all dialysis-dependent patients in Canada to an intermediate Hb target is estimated to range from C\$124 million to C\$174 million annually. If the current practice of administering epoetin via the IV route in dialysis-dependent patients is changed to the SC route, immediate cost savings of C\$49 million could result. Available studies suggest that similar costs are incurred for epoetin and darbepoetin to achieve defined Hb targets. Considering ESA costs alone and no potential clinical implications, a low target would lead to annual cost savings of C\$40 million and a high target to additional costs of C\$165 million compared with an intermediate target.

The estimated cost of ESA to treat all non-dialysis-dependent CKD patients to an intermediate Hb target in Canada is estimated to be C\$1.4 million to C\$6.7 million annually. Although a fraction of these patients are currently prescribed ESA, this is likely to increase in the future given the trends in care. It is estimated that a high Hb target would lead to costs that are 6.2 times that of a low target and twice as much as that of an intermediate target.

## 8 Conclusions

In an environment where decision makers are willing to reimburse ESA, the base case analysis suggests that treatment to a target Hb of 110 g/L is most likely to be optimal. This strategy will lead to higher costs (mainly due to ESA acquisition) compared with the low Hb target strategy and is based on the assumption that the intermediate target will improve QoL compared with the low target, which is unproven. Given the generally modest clinical benefit of ESA and the direct relationship between dose and cost, it may be prudent to consider a maximum ESA dose (above which the dose would not be increased further, even if the Hb target is not reached). Future research should focus on this comparison. In the interim, decision makers might reasonably choose to reimburse only the low Hb strategy because of the uncertainty in the QoL gains associated with the intermediate strategy. The route of administration is an important consideration and because of the higher cost of IV epoetin, the merits of reimbursing only SC epoetin (or darbepoetin by either route) should be explored. Lastly, because small differences in potency per unit cost of ESA can translate into large differences in total costs, head-to-head comparisons of epoetin and darbepoetin should be considered.

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