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PERSPECTIVES IN RENAL MEDICINE

Impact of epoetin alfa on clinical end points in patients with chronic renal failure: A meta-analysis

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Impact of epoetin alfa on clinical end points in patients with chronic renal failure: A meta-analysis.

Background. Numerous randomized, controlled trials have demonstrated that recombinant human erythropoietin (rHuEPO, epoetin alfa) significantly raises hemoglobin levels, reduces transfusion requirements, and improves quality of life in anemic patients with chronic renal failure. However, this accumulation of data has yet to be systematically examined. The objectives of this meta-analysis were to quantify the effects of epoetin alfa on clinical efficacy, quality of life, hospitalizations, and transfusions by collecting and analyzing the published body of evidence.

Methods. Sixteen published studies fulfilled all inclusion criteria and were subjected to data extraction. Data specifically related to hemoglobin and/or hematocrit levels, quality-of-life measurements, number and length of hospitalizations, and number of blood transfusions were then pooled across studies using a random effects meta-analysis. Simple combined estimates of the preselected variables were calculated, and adjusted estimates were made using meta-regression.

Results. Baseline hemoglobin levels (<8 g/dL) increased substantially (40% to 50%) after epoetin alfa administration to a nonanemic state (Hb >11 g/dL) for the pooled study group. Substantial improvements (10% to 70%) were observed for all measures of quality of life. In addition, patients who received epoetin alfa had substantial reductions in hospitalization rate, hospital length of stay, transfusion rate, and number of units transfused.

Conclusion. This meta-analysis strongly suggests that epoetin alfa therapy for patients with chronic renal failure provides important clinical and quality-of-life benefits while substantially reducing hospitalizations and transfusions.

Anemia is a nearly inevitable and potentially debilitating consequence of chronic renal failure [1]. Ordinarily, tissue hypoxia leads to an increased production of the hormone erythropoietin within the kidney, which then stimulates the division and differentiation of committed erythroid progenitors in the bone marrow (erythropoiesis). The anemia of chronic renal failure results from inadequate secretion of erythropoietin by the damaged kidney in response to hypoxia. Erythropoietin deficiency leads to diminished red blood cell counts and hemoglobin levels, and lower overall oxygen availability [2]. The consequences for patients include fatigue, loss of energy, and an inability to carry out the activities of daily living, resulting in loss of economic productivity, poor quality-of-life, and increased dependency on others [3].

Recombinant human erythropoietin (rHuEPO, epoetin alfa) has long been accepted as a clinically useful therapy for anemia in patients with chronic renal failure, having been shown to increase hemoglobin levels and decrease transfusion requirements [3–5]. Moreover, published data from rigorous clinical trials, as well as anecdotal reports from patients, indicate that epoetin alfa therapy also provides substantial benefits in quality of life [1, 6, 7]. The most immediate quality-of-life benefits of epoetin alfa therapy described by chronic renal failure patients with anemia appear to be increased energy and resulting increased capacity to function.

Finding and analyzing all relevant therapeutic trials in a given field has become a difficult and specialized task. The systematic aggregation of data from multiple trials using statistically rigorous techniques has thus become an increasingly important aid to achieving meaningful consensus. The meta-analysis reported here analyzes the quantitative outcomes evidence for clinical efficacy, quality of life, hospitalizations (number and length of stay), and transfusions (rate and number) to determine the overall impact of these positive outcomes in patients with chronic renal failure who receive epoetin alfa for anemia. Our objective was to collect, document, and analyze all available data on these variables, and to provide a clear and comprehensive report on the effects of epoetin alfa therapy for this patient population.

Key words: anemia, chronic renal failure, epoetin alfa, hospitalization, meta-analysis, quality of life, transfusion.

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METHODS

Literature search

A critical review of the literature was undertaken, and the published quantitative data were collated and quantitatively synthesized to form balance-of-evidence estimates.

Experienced library staff in the medical library at The Royal North Shore Hospital (Sydney, Australia) employed the Medline database to search for publications relating to epoetin alfa therapy and chronic renal failure. Search parameters included the impact of epoetin alfa on chronic renal failure, with regard to hematocrit and hemoglobin levels, survival, quality of life, hospital admission, transfusion rate, and cost. A combination of a controlled subject heading search and a text/word search was employed to achieve an appropriate trade-off between sensitivity (the likelihood of retrieving relevant items) and specificity (the likelihood of excluding irrelevant items). The staff conducting the literature search for this project regularly performs similar searches for Cochrane groups and used comparable methods for the current study.

Abstracts were sought only for those studies that fit the prespecified inclusion criteria. Studies were included that: (*1*) were published between 1985 and 2000; (*2*) enrolled adult patients ($\geq$18 years of age); (*3*) contained at least 20 patients per study arm; (*4*) recruited patients with a diagnosis of chronic renal failure; (*5*) involved treatment with epoetin alfa; and (*6*) reported on one or more of the chosen variables pertaining to clinical efficacy, quality-of-life, hospitalizations, and/or transfusions. English language was not an inclusion criterion; articles in languages other than English were translated by a qualified translation service.

A question that often arises in a literature search is whether or not any relevant articles may have been missed. Some confidence is gained, however, from the fact that slightly over 1000 abstracts and close to 100 articles in full were reviewed, and a considerable range of journals and articles both in English and in several non-English languages was examined.

Data extraction

An initial review of all articles identified as potentially relevant from the abstract search was conducted to determine which studies met the protocol-defined inclusion criteria, and what pieces of data were sufficiently common across publications to warrant extraction. A computer database was then developed to accept the extracted data.

Data were extracted from each publication by two independent surveyors and entered onto a data extraction form. The surveyors compared extractions and resolved any discrepancies by jointly examining the publication. The data were then entered into the database.

Measurements

All studies used in this meta-analysis were of the "pre/post" design, in that measurements of anemia, quality of life, hospitalizations, and transfusions were taken before and after initiation of epoetin alfa therapy, and any changes in these variables were assumed to be attributable to epoetin alfa. With very few exceptions, all studies reported means and variance estimates pre- and post-therapy; some also reported mean changes or variance estimates of change within subjects. In the former case, it was necessary to calculate the variance estimates of change, assuming independence of the pre- and post-therapy measurements. The approximation method used here works against epoetin alfa, because some of the between-subject variance that is usually removed by calculating pre- to post-therapy changes within each subject remained. Thus, the residual variance was larger than it ought to have been (if individual patient data were available), but the variance attributable to epoetin alfa was not.

A few studies [3, 8, 9] included the means of pre- and post-therapy measurements but lacked measures of variance. To avoid losing such data due to the missing variance estimates, standard errors were imputed, assuming the standard deviation to be equal to the mean of known standard deviations while using the study-specific sample size in the calculation. This approach is the same used by Birks et al [10] of the Cochrane Collaboration in their meta-analyses discussing mild and moderate Alzheimer's disease, and rivastigmine therapy in Alzheimer's disease patients [11].

In accordance with the pre/post design of all studies included in this meta-analysis, the percentage of patients who were hospitalized and/or received transfusions, length of hospital stay; and number of blood units transfused, were calculated both before and after initiation of epoetin alfa therapy, with the exception of deaths. The period over which these variables were recorded generally ranged between 3 and 12 months. In order to standardize the period at risk, all counts were scaled to coincide with a 6-month study period. In doing so, a uniform rate of utilization was assumed (i.e., if 10 transfusions occurred over a 12-month follow-up period, 5 transfusions were assumed for a standard 6-month period).

Where utilization parameters (e.g., total units transfused) were reported for the entire group rather than per patient, the parameter was translated to a per-patient basis by dividing by the number of relevant subjects (e.g., by the total number of transfused patients). The calculation of standard errors for the transformed data assumed that the resulting random variable followed a Poisson distribution. When the sample size pertaining to a particular parameter was unknown, the overall study sample size was assumed.

While epoetin alfa dose has generally been reported as starting dose and final dose in the medical literature, final dose was used for this meta-analysis. Where dosage was reported as units/week rather than units/kg/week, an average 70-kg patient was assumed and the dosage scaled accordingly. In studies that reported dose as a frequency of "three times weekly" or "each dialysis," the dose was multiplied by 3 in order to approximate a weekly dosage.

For analytic purposes, percentages for this meta-analysis were transformed to the logit scale where $\text{logit}(p) = \ln[p/(1-p)]$ and p is the proportion (percent/100). To avoid undefined logits, a constant of 0.01 (1%) was added to all proportions before transformation and subtracted after the analysis. Logits have the desirable properties of asymptotic normal distribution and confidence interval boundaries for proportions that lie within the range $0 \leq P \leq 1$. All percentages of 100% were limited to 99% in order to avoid numerically undefined logits.

Quantitative data analysis

The quantitative analysis had two main components: the formation of simple combined estimates of findings across studies (test of homogeneity [positive result signifies heterogeneity]; significance at $P < .05$), and an analysis of potential publication bias. The simple combined estimates were formed using the DerSimonian and Laird approach [12]. Demographic and clinical history data were extracted, and variation between studies was then analyzed in two primary ways: (*1*) stratification by demographic and clinical characteristics followed by formation of combined estimates within strata and comparison across strata; and (*2*) analysis of demographic, clinical, and study design variables as sources of between-study variance in meta-regression.

Analysis of publication bias was undertaken using the test described by Egger et al [13], and through the creation of funnel plots. This statistical test amounts to a nonparametric correlation of standardized effect size estimates correlated with their variances (significance at $P < .05$).

Quality of life

Quality of life was evaluated using the Karnofsky Performance Scale (KPS), the Kidney Diseases Questionnaire (KDQ), and the Sickness Impact Profile (SIP). The KPS uses 10 steps with scores ranging from 100 (normal, without any limitation) to 10 (moribund) as an overall indicator of functional ability and self-sufficiency, and is considered an objective quality-of-life indicator [14]. The KDQ is specific for patients with end-stage renal disease [15]. It contains 26 questions divided into five sections: patient-specific physical symptoms; fatigue; depression; relationships; and frustration. All questions are scored on a 7-point Likert scale (7 = no problem, 1 = severe problem). The SIP is a behavior-related questionnaire that evaluates non-disease–specific, sickness-related behavioral dysfunction [16]. It is widely used for end-stage renal disease patients and in studies evaluating quality-of-life improvement with epoetin alfa treatment for end-stage renal-disease–related anemia. The SIP includes 136 items grouped into 12 categories of activity in physical and psychologic dimensions. Scores range from 0 (no behavioral dysfunction) to 100 (100% dysfunction in a category or group). Unlike the KPS and the KDQ, lower scores for the SIP indicate better quality of life.

RESULTS

Of the 95 articles that were obtained and assessed for inclusion in this meta-analysis, 22 fulfilled all inclusion criteria. Within this group, another six were determined by the two surveyors to be of inappropriate experimental design because they did not include pre- and post-epoetin alfa therapy measurements.

Quantitative data were, therefore, extracted from a total of 16 published studies [3, 5, 7–9, 17–27]. Five studies were randomized, controlled trials [5, 8, 24, 26, 27]. In two of these 16 studies, epoetin alfa therapy was administered to more than one study group. One study evaluated low-dose versus high-dose epoetin alfa [8], and another included both intravenous and subcutaneous administration [24]. In each of these studies, the two study arms were treated as separate cohorts for this meta-analysis and, hence, data were extracted from a total of 18 separate cohorts (Table 1).

Demographic, clinical, and treatment characteristics

Among all 16 studies included in the quantitative analysis, patients averaged 50 years of age and were comprised of nearly equal proportions of men and women (Table 2). Ninety-four percent of patients were receiving hemodialysis, 5% were in the predialysis category, and the remaining 1% was undergoing peritoneal dialysis. The majority of studies (61%) included the use of supplemental iron. The dose of epoetin alfa was reported generally as a group mean. Among the studies used in this meta-analysis, the mean epoetin alfa starting dosage of 209 U/kg/week was approximately 40% higher than the final dosage of 142 U/kg/week. These data are based on 15 cohorts at baseline and 11 cohorts post-therapy for which dose/kg/week was reported or could be calculated.

Baseline

At baseline, the mean hemoglobin level across all available cohorts for this analysis was less than 8 g/dL, and the mean hematocrit level was less than 30% (Table 3), signifying that the "average patient" was anemic before

Table 1. Graph identifications for primary papers used in meta-analysis

Graph ID	Cohort analyzed	*N*	Design	Authors
A1	Low-dose epoetin alfa	40	C	Canadian Erythropoietin Study Group (1990)
A2	High-dose epoetin alfa	38	U	
B	All patients[a]	23,806	(registry)	Powe et al (1994)
C	All patients	156	U	Moreno et al (2000)
D	All patients	28	U	Harris et al (1991)
E	All patients	22	U	Auer et al (1992)
F	All patients	60	U	Stevens et al (1992)
G	Epoetin alfa study arm[b]	57	C	Moreno et al (1996)
H	Epoetin alfa study arm	42	C	Kuriyama et al (1997)
I1	Intravenous epoetin alfa	38	C	Muirhead, Churchill et al (1992)
I2	Subcutaneous epoetin alfa	45		
J	All patients	142	U	Sundal et al (1991)
K	All patients	37	U	Duff et al (1991)
L	All patients	98	U	Muirhead, Laupacis et al (1992)
M	All patients	58	U	Paganini et al (1989)
N	All patients	333	U	Eschbach et al (1989)
O	All patients	37	U	Delano (1989)
P	Epoetin alfa study arm	43	C	Revicki et al (1995)

Abbreviations are: C, randomized controlled trial; ID, identification; U, uncontrolled trial.
[a]"All patients" for studies B-F and J-O indicates that the study was uncontrolled; all patients received epoetin alfa therapy, and, therefore, all data were extracted.
[b]"Epoetin alfa study arm" for studies G, H, and P indicates that the study was controlled, and, therefore, data were extracted only from the epoetin alfa arm of the trial.

Table 2. Demographic and clinical characteristics

Parameter	Patients (*N*)/cohorts	Mean or %	95% CI(lower–upper)	Homogene
Age	47,695/14	51	48–55	<0.001
% female	47,719/15	49	45–53	0.001
% hemodialysis	48,207/18	94	87–97	<0.001
% peritoneal dialysis	48,207/18	1	0–4	<0.001
% iron use[a]	NA	61 ± 12		
Epoetin alfa dose, baseline *U/kg/week*[b]	NA	209 ± 206		
Epoetin alfa dose, end *U/kg/week*[b]	NA	142 ± 70		

NA is not applicable.
[a]Percentage ± standard error; data available for study sample as a whole, not individuals.
[b]Mean ± standard deviation; data available for study sample as a whole, not individuals.

treatment administration. Additionally, patients' quality of life was poor, with all scores being either depressed in the case of the KPS and the KDQ, or elevated in the case of the SIP, indicating adverse quality of life. Over one quarter of the patients required hospitalization before the onset of epoetin alfa therapy (Table 3). The mean percentage of patients requiring transfusion at baseline among the six cohorts for which that information was available was 87.4%, a figure derived from heterogeneous results, including one randomized controlled trial cohort reporting 15%, and two randomized controlled trial cohorts reporting 100%.

Response to therapy

Anemia. As shown in Table 4, mean hemoglobin increased by >3 g/dL and hematocrit by >9% after the administration of epoetin alfa. Figure 1 shows the individual study findings for hemoglobin and hematocrit response to epoetin alfa, along with the combined estimate, represented by a diamond at the bottom of the graph. The study-specific mean increase in hemoglobin varied from 2 to 5 g/dL, and the mean increase in hematocrit from 5 to almost 15 percentage points among the studies. The between-study variance was significant ($P < 0.001$), as indicated by the test of homogeneity, but the effect of therapy was always positive.

Quality of life. As shown in Table 4, quality of life improved with epoetin alfa, as measured by increases in the KPS and the KDQ and decreases in the SIP. These results are also graphically displayed in Figures 2 and 3. Mean change in KPS was 8.46 points, or approximately 11% of the average baseline score, a statistically significant ($P < 0.001$) improvement in quality of life after epoetin alfa treatment. The physical and fatigue dimensions of the KDQ showed mean increases of approximately one point each, and the relationships and depression dimensions by approximately a half point each. These findings are significant, because the confidence intervals of the combined mean responses do not include the value of zero (Table 4). The positive changes in the physical and fatigue dimensions represent increases between 15% and 30% from baseline, while the scores for the relationships, depression, and global physical dimensions increased between 10% and 15% from baseline. Corresponding quality-of-life changes on the SIP were even greater than those observed for the KDQ, with impact

Table 3. Baseline conditions

Parameter	Patients (*N*)/cohorts	Mean	95% CI (lower–upper)	Homogene
Hematopoietic				
Hemoglobin *g/dL*	780/10	7.48	6.21–8.76	<0.001
Hematocrit %	772/9	24.32	21.11–27.53	<0.001
Quality-of-life				
KPS	201/3	74.50	72.59–76.40	<0.001
KDQ: physical	200/5	4.11	3.82–4.41	0.01
KDQ: fatigue	200/5	4.29	4.10–4.49	0.7
KDQ: relationships	200/5	5.00	4.85–5.15	0.4
KDQ: depression	200/5	4.94	4.74–5.13	0.7
KDQ: frustration	200/5	4.90	4.61–5.19	0.08
KDQ: global physical	117/2	4.45	4.23–4.67	0.7
KDQ: global emotional	117/2	5.06	4.76–5.35	0.2
SIP: global	239/4	12.63	10.31–14.95	<0.001
SIP: physical	239/4	6.61	5.63–7.60	<0.001
SIP: psychologic	239/4	11.70	9.93–13.48	<0.001
Utilization parameters				
Deaths %	NA	NA	NA	NA
Hospitalizations %	23,945/3	27.2	14.90–44.10	<0.001
Hospital days[a]	12,889/3	9.02	5.62–12.42	0.4
Transfusions %	347/6	87.40	55.7–96.8	<0.001
Units transfused[b]	347/3	5.5	0.8–10.3	0.04
Excluding Powe et al study [18][c]				
Hospitalizations %	139/2	21.7	10.9–37.9	0.01
Hospital days[a]	34/2	7.72	3.87–11.58	0.9

Abbreviations are: KDQ, Kidney Disease Questionnaire; KPS, Karnofsky Performance Scale; SIP, Sickness Impact Profile; NA, not applicable/calculable.
[a]Days/hospital patient/6 months.
[b]Units transfused/transfused patient/6 months.
[c]The study conducted by Powe et al [18] is unique with respect to the other 15 trials included in the meta-analysis in that its data were derived from a pre-existing database rather than from a newly designed clinical trial. If this study is removed from the analysis, the mean number of hospitalization days and the percentage of patients hospitalized among those receiving epoetin alfa are reduced slightly from baseline.

Table 4. Response to epoetin alfa therapy (all trials)

Outcome	Patients (*N*)/cohorts	Mean change	95% CI (lower–upper)	*P* values H[a]	*P* values B[b]
Hematopoietic					
Hemoglobin *g/dL*	494/10	3.37	2.82–3.92	<.001	.04
Hematocrit %	493/8	9.10	7.31–10.89	<.001	.5
Quality of life					
KPS	201/3	8.46	2.01–14.92	<.001	.5
KDQ: physical	164/5	1.16	0.88–1.44	.3	.8
KDQ: fatigue	164/5	0.80	0.52–1.09	.7	.4
KDQ: relationships	164/5	0.49	0.24–0.74	.6	.06
KDQ: depression	164/5	0.42	0.14–0.70	.9	.2
KDQ: frustration	164/5	0.21	−0.08–0.50	.9	.4
KDQ: global physical	81/2	0.65	0.31–0.99	.8	NA
KDQ: global emotional	81/2	0.29	−0.04–0.63	.6	NA
SIP: global	239/4	−5.17	−8.62–1.73	<.001	.4
SIP: physical	239/4	−3.29	−5.10–1.48	<.001	.4
SIP: psychologic	239/4	−7.86	−10.47–5.26	<.001	.4
Utilization parameters					
Deaths %	1,136/13	3.3	2.2–4.7	.7	.5
Hospitalizations *odds ratio*	23,945/3	0.62	0.25–1.54	.006	.08
Hospital days[c]	13,824/3	−3.59	−7.77–0.60	.5	.2
Transfusions %	247/4	0.03	0.00–0.24	<.001	.3
Units transfused[d]	247/2	−2.6	−6.7–1.5	.2	NA
Excluding Powe et al study [18][e]					
Hospitalizations *odds ratio*	139/2	0.39	0.20–0.77	.9	NA
Hospital days[c]	17/2	−4.46	−9.03–0.12	.4	NA

Abbreviations are: KDQ, Kidney Disease Questionnaire; KPS, Karnofsky Performance Scale; SIP, Sickness Impact Profile; NA, not applicable/calculable.
[a]Test of homogeneity; $P < 0.05$ = significant.
[b]Publication bias; $P < 0.05$ = significant.
[c]Days/hospital patient/6 months.
[d]Units transfused/transfused patient/6 months.
[e]The study conducted by Powe et al [18] is unique with respect to the other 15 trials included in the meta-analysis in that its data were derived from a preexisting database rather than from a newly designed clinical trial. If this study is removed from the analysis, the mean number of hospitalization days and the percentage of patients hospitalized among those receiving epoetin alfa are reduced slightly from baseline.

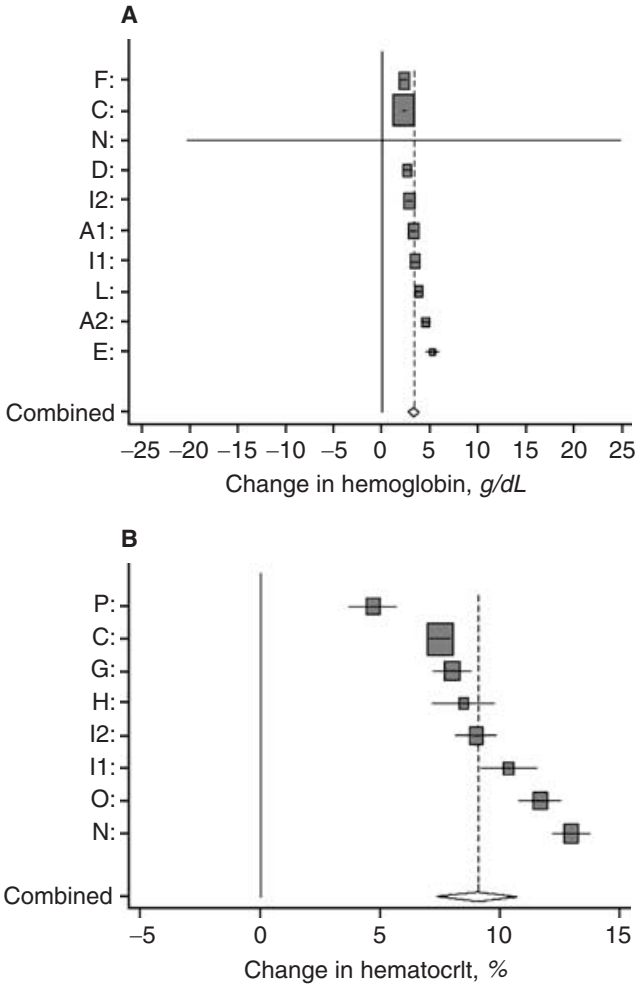

Fig. 1. Effect of epoetin alfa therapy on hemoglobin (*A*) and hematocrit (*B*) across individual studies. The center of the diamond represents the combined mean response, while the tips of the diamond represent the 95% CI. Individual cohorts are similarly labeled with mean response and CI and are sorted by size of response.

scores typically reduced by half after the onset of epoetin alfa therapy. Quality-of-life responses to epoetin alfa therapy, as measured by the SIP scale, suggest improvements of approximately 50% or greater, depending on the subscale analyzed.

Hospitalizations and transfusions. Administration of epoetin alfa therapy substantially reduced the hospitalization rate (Table 4). Also, among those hospitalized, length of stay within the hospital was reduced by over 3 days. The transfusion rate was nearly zero after starting epoetin alfa therapy, and among patients who did receive transfusion, the number of units transfused was reduced by approximately 50%.

Figure 4 displays the impact of epoetin alfa on deaths, hospitalizations, and transfusions. Note that each graph in Figure 4 displays its response axis (x-axis) on a logarithmic scale. Taking log-odds ratios or logits of proportions serves to linearize the scale and improve the resolution for comparing studies. Although data points and/or odds ratios for any one study are more challenging to identify from these logarithmic graphs, between-study relativities are enhanced in regard to interpretability. Increasingly negative values for the logits of death indicate lower death rates; similarly, a log-odds ratio less than zero indicates a decrease in the likelihood of hospitalization or transfusion after commencement of epoetin alfa therapy.

It was deemed appropriate to remove the Powe et al study [18] from the analysis of hospitalization data, because this study does not present a stand-alone clinical trial. Because the Powe et al study found greater-than-average hospitalization rates in comparison to the other studies, the omission of the study from this part of the analysis made the reduction in the hospitalization rate slightly more pronounced than that observed with its inclusion.

Only one aspect of this analysis showed any substantive evidence of potential publication bias; the Egger test for publication bias for change in hemoglobin ($P = .04$; Table 4) achieved statistical significance. At face value, this would imply that the estimate for this parameter presented in Table 4 is biased (in either direction). However, two factors qualitatively argue against this conclusion. First, the P values reported take no account of the number of hypothesis tests conducted; hence, these could be type I errors. In fact, any method of allowing for multiple comparisons would reach this alternative conclusion. Second, there is no suggestion that publication bias affected the measurement of hematocrit level. If there were publication bias operating, one would expect this bias to apply consistently to hemoglobin and hematocrit levels, because these two variables arise from the same measurement domain and also demonstrate a nearly perfect positive correlation. In addition, graphs prepared of the bias (not shown) suggest that the apparent bias in hemoglobin change is the result of a single study (Eschbach et al [19]) with an extremely large standard error. This study also stands out in Figure 1.

Between-study variance

While this meta-analysis clearly demonstrated that epoetin alfa had a substantial and beneficial effect on anemia associated with chronic renal failure, there was considerable evidence of heterogeneity in the extent of the benefit. Statistically significant ($P < .05$) between-study heterogeneity was demonstrated for hemoglobin and hematocrit levels, KPS, the SIP parameters, percent of patients hospitalized, and percent of patients transfused. For example, Figure 3 shows that, with respect to the SIP, all studies yielded improvements in quality of life after the initiation of epoetin alfa therapy, but that the degree of improvement varied. The same situation is true for the changes in transfusion and hospitalization rates

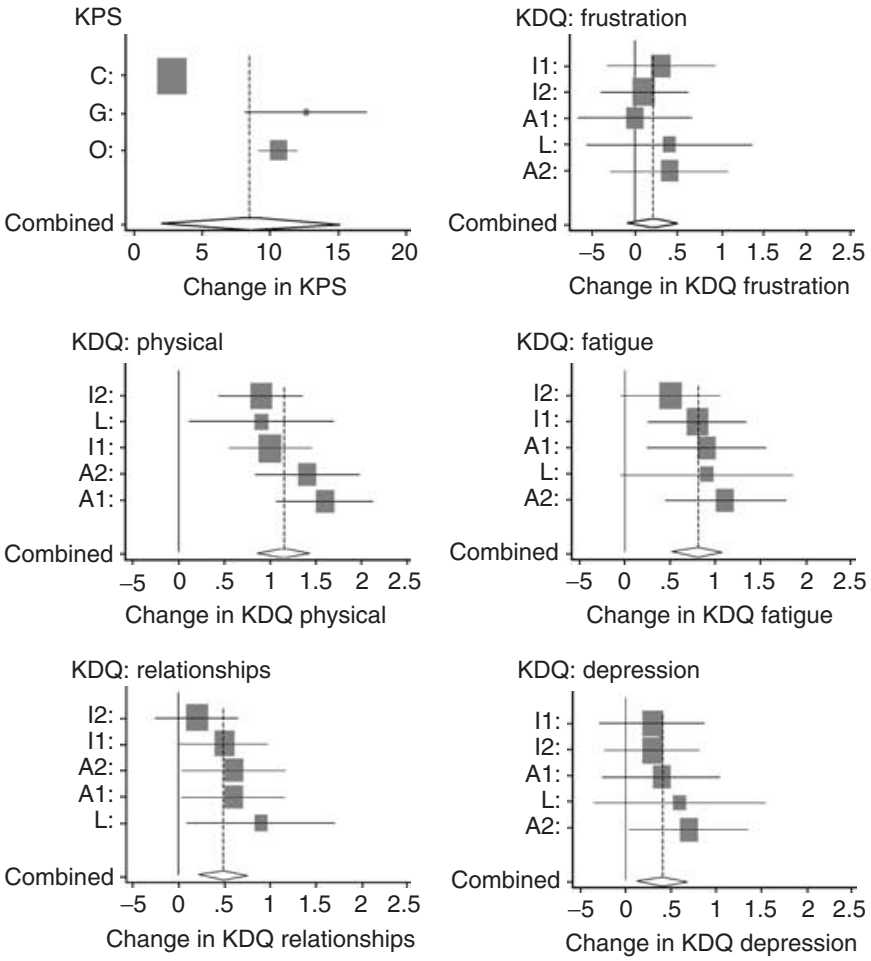

Fig. 2. Effect of epoetin alfa therapy on quality of life as measured by the Karnofsky Performance Scale (KPS) and the Kidney Disease Questionnaire (KDQ) across studies.

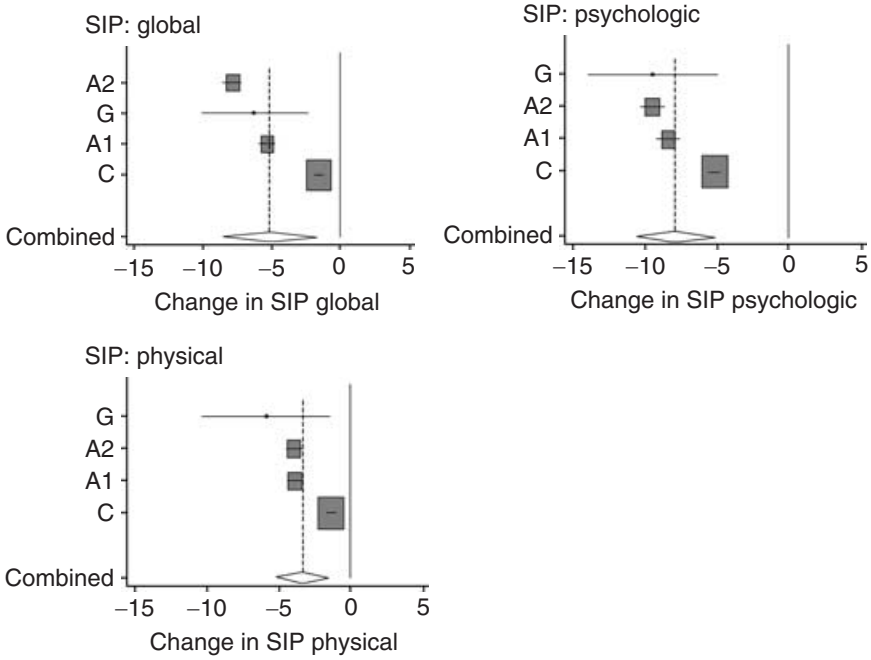

Fig. 3. Effect of epoetin alfa therapy on quality of life, as measured by Sickness Impact Profile (SIP) across studies.

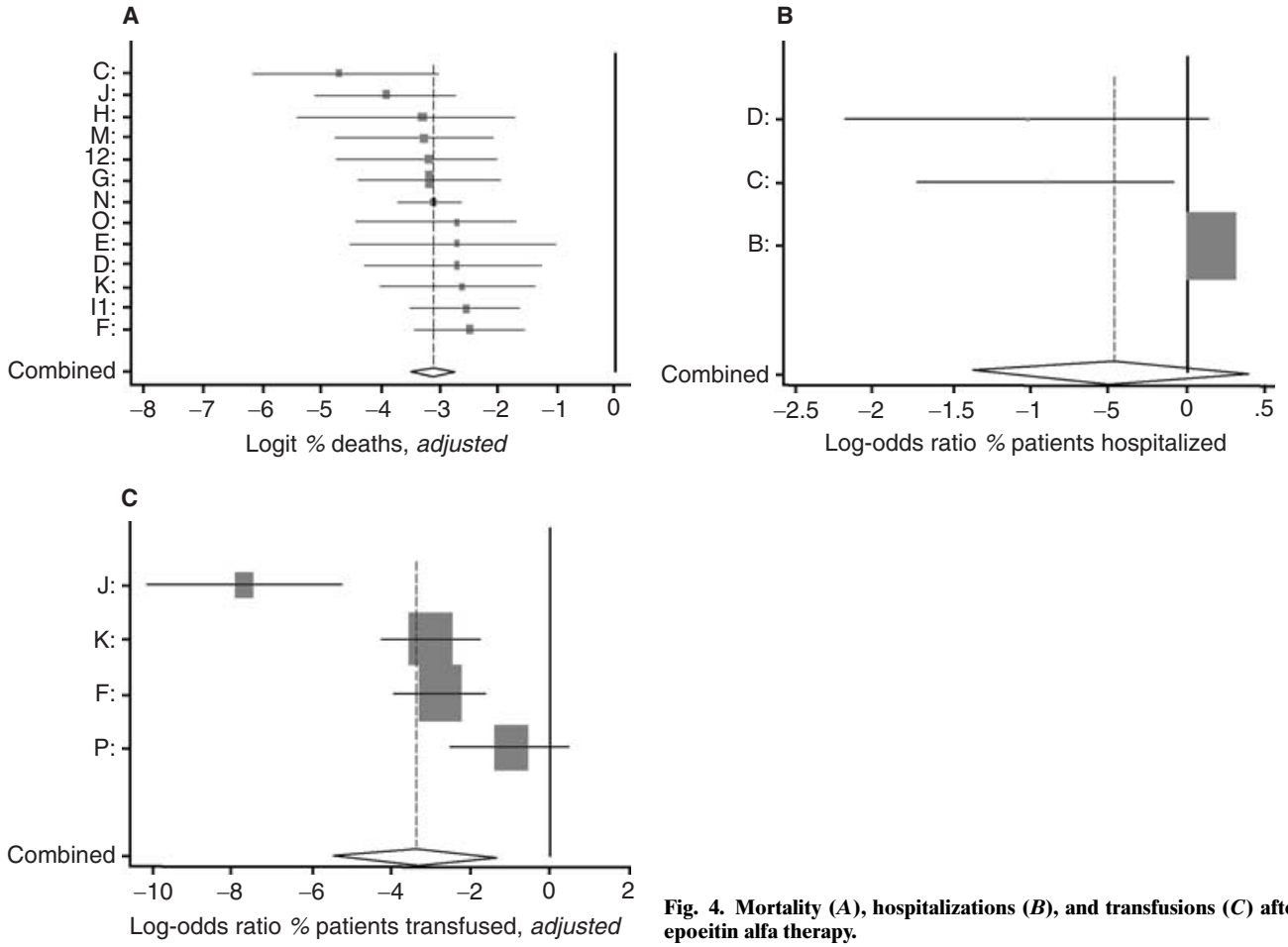

Fig. 4. Mortality (*A*), hospitalizations (*B*), and transfusions (*C*) after epoeitin alfa therapy.

(Fig. 4); only one study with a very small positive odds ratio indicated increased odds of hospitalization [18].

A sensitivity analysis was performed re-examining the clinical response to epoetin alfa using only data from randomized controlled trials. In the sensitivity analysis including randomized controlled trials only, the mean and 95% CI results were similar to those arrived at by the overall meta-analysis for most parameters (Table 5). Positive between-study heterogeneity was demonstrated only for hemoglobin, hematocrit, and SIP: global.

Possible sources of between-study variation were investigated for all parameters for which statistically significant between-study variation was reported in Table 4. The factors considered as potential sources of variation included patient, clinical, and study-design characteristics, including year of publication, experimental design (randomized, controlled trial vs. observational or naturalistic study), treatment duration, mean disease duration, mean age, percentage of females in the sample, and iron supplementation use (allowed vs. disallowed). The independent factors found to have a statistically significant relationship with the change in a given parameter are summarized in Table 6. The entries in parentheses denote the direction of the relationship and the degree of statistical significance (*P* value).

Fewer reductions were noted in the number of transfusions for patients who received epoetin alfa among study populations containing a greater proportion of older patients. In addition, the beneficial effect of epoetin alfa in reducing transfusion requirement was diminished in studies that allowed the use of supplemental iron.

Figure 5 indicates that later publications tended to report a smaller hematologic benefit associated with epoetin alfa than earlier publications, showing a negative directional relationship with anemia and a clear, although not consistent, reduction in the degree of change in hematocrit with later year of publication.

DISCUSSION

Epoetin alfa has long been regarded as effective therapy for anemia associated with chronic renal failure. Of considerable interest are the quality-of-life benefits associated with increased hemoglobin and the impact of

Table 5. Response to epoetin alfa therapy (randomized controlled trials only)

Outcome	Cohorts	Mean change	95% CI (lower–upper)	*P* values H[a]
Hemoglobin *g/dL*	4	3.56	2.94–4.17	<0.001
Hematocrit %	4	8.14	5.63–10.65	<0.001
KPS	0	NA		
KDQ: physical	4	1.20	0.88–1.52	0.2
KDQ: fatigue	4	0.79	0.49–1.09	0.6
KDQ: relationships	4	0.45	0.19–0.71	0.6
KDQ: depression	4	0.40	0.10–0.70	0.8
KDQ: frustration	4	0.19	−0.12–0.49	0.8
KDQ: global physical	2	0.65	0.31–0.99	0.8
KDQ: global emotional	2	0.29	−0.04–0.63	0.6
SIP: global	2	−6.55	−4.10–−5.24	<0.001
SIP: physical	2	−3.85	−4.24–−3.46	0.8
SIP: psychologic	2	−8.85	−9.93–−7.77	0.07

Abbreviations are: KDQ, Kidney Disease Questionnaire; KPS, Karnofsky Performance Scale; SIP, Sickness Impact Profile; NA, not applicable/calculable.
[a]Test of homogeneity; $P < 0.05$ = significant.

Table 6. Effects of patient clinical and experimental factors on changes in selected study variables

Outcome	Clinical/experimental factor(s)
Hemoglobin	No effect
Hematocrit	Year (negative, $P = 0.006$)
KPS	Year (negative, $P < 0.001$)
SIP: global scale	Year (positive, $P = 0.02$)
SIP: physical scale	Year (positive, $P < 0.001$), experimental design (negative, $P < 0.001$), disease duration (positive, $P < 0.001$)
SIP: psychologic scale	Year (positive, $P < 0.001$), experimental design (negative, $P < 0.001$)
OR for transfusions	Age (positive, $P < 0.001$), iron use (positive, $P = 0.001$)

Abbreviations are: KPS, Karnofsky Performance Scale; OR, odds ratio; SIP, Sickness Impact Profile.

epoetin alfa on hospitalizations and transfusions. By analyzing available data for these variables, we have demonstrated that epoetin alfa therapy for anemic patients with chronic renal failure is beneficial for the patient and the health care system.

In every study that has been included in this meta-analysis, epoetin alfa treatment was associated with improvements in patients' clinical state and well-being and with reductions in transfusions. Reductions in hospitalization were associated with epoetin alfa treatment in all studies but one (Powe et al [18]), in which a very small positive odds ratio indicated increased odds of hospitalization. This study did not present a stand-alone clinical trial, and found greater-than-average hospitalization rates in comparison to the other studies in the meta-analysis; notably, it also found significant decreases in readmissions, hospital days, and overall hospital costs per patient.

The increase in hemoglobin/hematocrit levels after epoetin alfa administration was striking, at 40% to 50% relative to baseline scores, across all the studies included in the meta-analysis. We predicted corresponding substantial improvements in quality-of-life and capacity to undertake activities of daily living. As anticipated, the positive response in reduced anemia was matched by positive responses in all quality-of-life measures. The extent of quality-of-life change relative to baseline was universally positive, varying across studies from approximately 10% (KPS) to about 70% (SIP psychologic subscale). Across studies, the hospitalization rate for patients who received epoetin alfa therapy was substantially lowered relative to the pretreatment period, as was the number of days of hospitalization (length of stay) per patient. In addition, both the transfusion rate and the total number of blood units transfused were substantially reduced.

Strong evidence was seen in favor of a benefit from epoetin alfa therapy in reducing the use of hospitalizations and transfusions. Several studies suggest that net costs are reduced with use of epoetin alfa therapy compared with non-use [17]: patients on epoetin alfa therapy require fewer transfusions [8] and fewer hospital admissions [18], and mortality and morbidity associated with epoetin alfa therapy have been consistently reported as low to nonexistent [7, 18]. These results are in keeping with a recent analysis showing that, among patients receiving hemodialysis, the number of hospitalizations and length of stay both decrease as hemoglobin levels increase [28]. The overall cost of transfusion has increased in recent years along with cost per unit of transfused blood, documented blood supply shortages, and newly implemented safety procedures (e.g., leukodepletion), as well as rising acquisition, storage, and administration costs [29, 30]. Meanwhile, the cost and the recommended dose of epoetin alfa for this patient population have both decreased substantially [31]. While a comprehensive analysis of overall cost of care is beyond the scope of this report, the costs associated with hospitalizations and transfusions presently constitute two of the most important elements of resource utilization for patients with chronic renal failure, and any reduction in hospitalizations and transfusions seems likely to lead to an overall lower cost of patient care.

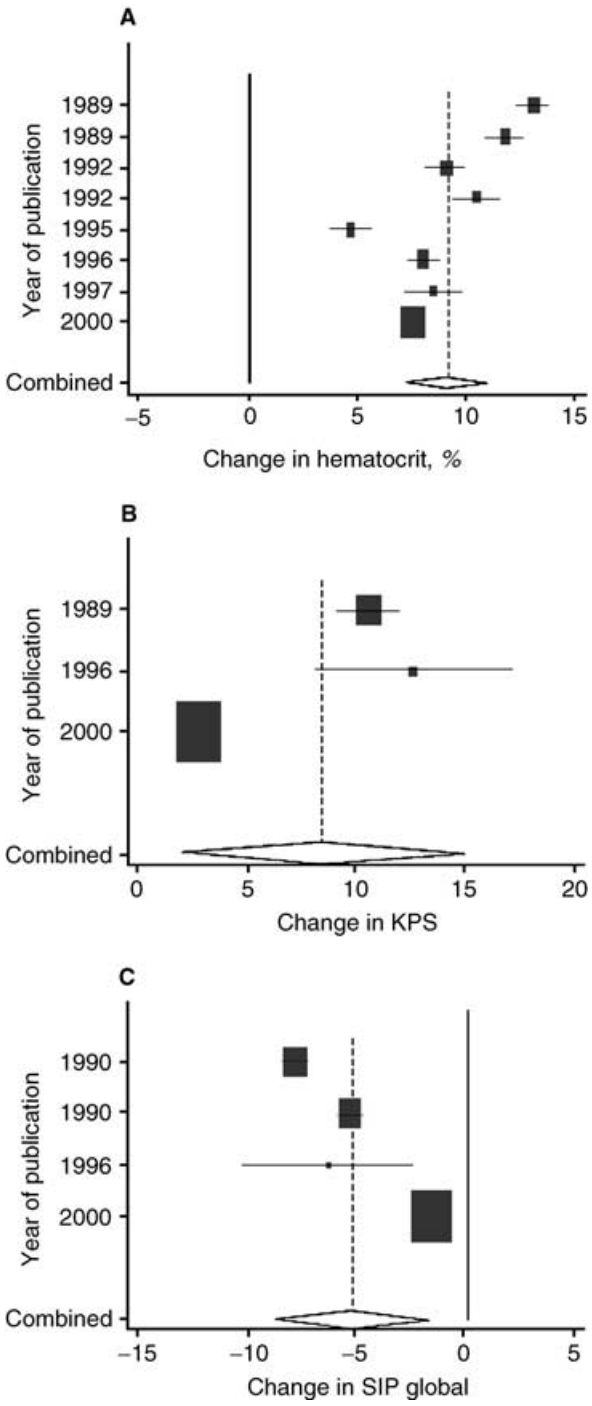

Fig. 5. Impact of study's year of publication on changes in hematocrit (*A*) level, Karnofsky Performance Scale (KPS) score (*B*), and Sickness Impact Profile (SIP) global scale score (*C*) following epoetin alfa therapy.

It should be noted that in many of the studies used in this analysis, the mean baseline hemoglobin level was lower than that generally seen among patients in whom epoetin alfa therapy would normally be initiated now, raising a question as to whether conclusions generalized from these results remain relevant for present purposes. While anemia in patients with chronic renal failure is being treated more aggressively now that epoetin alfa is widely available, trends suggest that a considerable fraction of patients entering dialysis still have significantly lower hematocrit levels than are specified by the recommended targets, with those receiving predialysis erythropoietic therapy having a higher hematocrit at initiation of dialysis than those left untreated [32]. Given that the hemodialysis population reductions in hospitalization continue to appear for incremental increases in hemoglobin levels as high as 13 g/dL ($P < .0001$ for ≥13 g/dL vs. ≤11 but >12 g/dL) [28], it is probable that the potential benefits of optimizing the management of anemia in patients with chronic renal failure have not yet reached a plateau.

The advantages of contemporary meta-analysis include the abilities to elucidate the relationships between variables; increase statistical power by integrating evidence from numerous diverse international studies; detect and explain bias and heterogeneity; identify deficiencies in the design of past and current studies; and generate fruitful new directions for research [33–36]. This meta-analysis has demonstrated consistency of findings across the studies reviewed, despite the fact that these studies differed both in design and in extent of benefit observed. Where statistically significant between-study variance was found, analyses were undertaken to identify possible sources of this variation. Overall, randomized, controlled trials showed epoetin alfa to have a greater positive effect on quality of life than uncontrolled trials. A sensitivity analysis examining the response to epoetin alfa using only data from randomized controlled trials generated efficacy estimates similar to those arrived at by the overall meta-analysis. Notably, while randomized controlled trials represent the gold standard for assessing potential efficacy, the inclusion of uncontrolled trials may ultimately yield better estimates of real-world efficacy. Potential biases and discrepancies, of course, exist within all sorts of individual clinical trials, as well as within meta-analyses [37]. Clinicians must ultimately interpret all reports with caution, since both large randomized controlled trials and meta-analyses report population effects rather than instructing how to treat the individual patient [38].

The present analysis clearly points toward a consensus in favor of an overall hematologic and quality-of-life benefit, plus reductions in hospitalizations and transfusions, for epoetin alfa therapy in anemic patients with chronic renal failure. Additional rigorously controlled, randomized trials, consciously designed to avoid biases and discrepancies, are, as always, desirable to corroborate and substantiate these meta-analytically derived conclusions.

CONCLUSION

Overall, results from this meta-analysis strongly suggest that for patients with anemia associated with chronic

renal failure, epoetin alfa increases hemoglobin and hematocrit levels, with resulting significant and substantial improvements in quality-of-life. In addition, there were major decreases in hospitalizations and transfusions for patients who were treated with epoetin alfa. Further study, using both naturalistic and randomized, controlled designs, should be conducted to investigate and corroborate these relationships.

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