Amgen Inc. v. F. Hoffmann-LaRoche LTD et al Doc. 1106 Att. 2

EXHIBIT B

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DEPARTMENT OF HEALTH & HUMAN SERVICES
PUBLIC HEALTH SERVICE
Food and Drug Administration
Silver Spring, MD 20993

August 14, 2007

Dear Members, Consultants, Speakers and Guests:

Thank you for your willingness to participate in the September 11, 2007 joint meeting of the Cardiovascular and Renal Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee. This meeting will focus upon the safety considerations related to the use of erythropoiesis-stimulating agents (ESAs) to treat the anemia associated with chronic renal failure.

In general, FDA anticipates discussions related to the following topics, especially as they apply to considerations for potential product labeling alterations as well as the design of subsequent clinical studies:

- Considerations related to the use of "target" hemoglobin levels when administering ESAs;

- Identification of patients who may be at increased risk for cardiovascular events as indicated by a suboptimal hemoglobin response to an administered ESA dose.

The supplied briefing materials consist of:
1. Draft topics for the discussion
2. An executive summary
3. Background information
4. Appendices containing FDA review information
5. Copies of relevant publications.

The final questions will be given to you prior to the start of the meeting.

We look forward to your participation and to a productive meeting on September 11, 2007.

Sincerely,

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FDA Advisory Committee Briefing Document
Joint meeting of the
Cardiovascular and Renal Drugs Advisory Committee and the
Drug Safety and Risk Management Committee

September 11, 2007

Prepared by the Division of Medical Imaging and Hematology Products
and Office of Surveillance and Epidemiology (OSE)

Reassessment of the Risks of Erythropoiesis-Stimulating Agents (ESAs) Administered for the Treatment of Anemia associated with Chronic Renal Failure

Table of Contents

Tentative Topics for Discussion

1. Hemoglobin "target" values in ESA dosing:

When using ESAs, the product labels recommend adjustment of ESA dosages to achieve and maintain the lowest hemoglobin level sufficient to avoid the need for red blood cell transfusion and not to exceed 12 g/dL. The strengths and limitations of clinical data supporting a potential change in the ESA product label dosage recommendations will be discussed, with a focus upon the strength and limitations of the data to support the "targeting" of specific hemoglobin values.

2. Identification and management of patients with insufficient responses to ESAs:

Clinical data suggest that "hypo-responders" to ESAs may signal an increased risk for serious cardiovascular events. ESA product labels may be optimized by the inclusion of information that more explicitly describes how to manage patients with insufficient responses to ESAs ("hypo-responders"). The available data and types of additional data necessary to identify and optimize the use of ESAs among "hypo-responders" will be discussed.

EXECUTIVE SUMMARY

Subsequent to the approval of ESAs for use in the treatment of anemia associated with chronic renal failure (CRF), data from randomized, controlled clinical studies showed increased rates of death and serious cardiovascular events when ESAs were administered in an attempt to achieve a higher (relative to lower) hemoglobin concentration. These studies also suggested that the risks for these events were the greatest in patients who had the lowest increase in hemoglobin levels in response to a given ESA dose. The purpose of this advisory committee is to seek advice regarding the available data and the types of clinical data necessary from subsequent studies to support potential changes to the prescribing information pertaining to the use of ESAs among patients with anemia associated with CRF: 1) to achieve specific hemoglobin levels or ranges and 2) to identify and manage patients who have a suboptimal hemoglobin response.

Issue 1) Use of ESAs to achieve specific hemoglobin levels or ranges

The current ESA product labels recommend that prescribers use the lowest ESA dose that will gradually increase the hemoglobin concentration to the lowest level sufficient to avoid the need for red blood cell transfusion. The attainment of a specific hemoglobin level or range is not recommended in the labels.

Randomized, controlled clinical data have not established treatment benefits associated with the differential attainment of specific hemoglobin levels or ranges. However, serious cardiovascular risks have been shown for patients who attain hemoglobin levels in excess of 12 g/dL in two randomized, controlled clinical studies that compared the "targeting" of higher hemoglobin/hematocrit levels to lower levels (see "Normal hematocrit" and CHOIR studies in subsequent information).

In contrast to the lack of randomized, controlled studies showing differential treatment benefits to the attainment of any specific hemoglobin level or ranges, observational clinical data suggest that anemic CRF patients who attain a hemoglobin level of 11 g/dL with ESA therapy may experience greater survival and improved health-related quality of life. Based upon this consideration and the risks associated with "targeting" hemoglobin levels in excess of 12 g/dL, the ESA sponsors propose product label alterations to identify a hemoglobin level of 11 to 12 g/dL as the appropriate target hemoglobin range for anemic CRF patients.

We will seek the committee's advice regarding whether data exist to support a recommendation to dose ESAs to attain and maintain a specific hemoglobin level (or range), and if so, what that level or range should be. We will also seek input regarding the need for additional clinical studies and if so, general study designs to support potential label changes.

Issue 2) Use of ESAs among patients who have minimal hemoglobin responses

Analyses have attempted to correlate the risk for serious cardiovascular events with ESA dosages (see Appendix 2, FDA preliminary review). However, these analyses suggest that the hemoglobin response to an ESA dose, not the dose per se, is the main correlate for the increased cardiovascular risk.

Specifically, analyses of patients' change in hemoglobin level in response to a specific ESA dose in the "Normal hematocrit" and CHOIR study provide a distribution of hemoglobin responses to ESAs. These analyses suggest that patients who have the lowest hemoglobin response to a specific ESA dose are at the greatest risk for serious cardiovascular events. In CHOIR, this risk for these "hypo-responders" was similar among patients randomized to either the high or low hemoglobin target groups.

Although analyses are ongoing, the ESA sponsors have not, to date, proposed a definition of ESA "hypo-responder" for product labeling. We will seek the committee's advice about how to define and identify ESA "hypo-responders" as well as the types of clinical data needed to support labeling alterations to optimize safer use of ESAs in these patients.

BACKGROUND INFORMATION

1. Introduction:

Erythropoietin is a glycoprotein produced predominantly in the kidney whose main function is thought to relate to stimulation of proliferation and differentiation of erythroid precursors in the bone marrow.

Erythropoiesis-stimulating agents (ESAs) were originally developed to replace the deficiency of erythropoiein that frequently develops in patients with CRF. In these CRF patients, ESA administration was shown to increase the red blood cell count (as measured by blood hemoglobin or hematocrit values) and reduce the need for red blood cell transfusion.

Two ESA products are licensed in U.S. and one of these products is marketed under two names, Epogen/Procrit. The other ESA, darbepoetin alfa, is marketed solely under the proprietary name, Aranesp.

Following the initial approval of ESAs, randomized, controlled clinical trials showed that the use of ESAs to attain higher, compared to lower, hemoglobin/hematocrit levels was associated with an increased risk for mortality and serious cardiovascular risks. These risks were shown most notably in two clinical studies, referred to as the "Normal hematocrit" and CHOIR studies and, to a lesser extent in the CREATE study.

The findings from the "Normal hematocrit," CHOIR and CREATE studies, as well as safety findings from studies examining use of ESAs in non-CRF patient populations prompted FDA to reassess the safety of ESAs and, in March, 2007 the ESA product labels were altered to provide new safety and dosage information, including the addition of a boxed warning for this information.

Subsequent portions of this background information will discuss the data and information relevant to:

- the regulatory history for ESAs, including the nature of the clinical data supporting ESA approval
- the March, 2007 ESA label revisions
- the major findings from the "Normal hematocrit," CHOIR and CREATE studies
- considerations in identifying specific hemoglobin goals for ESA dosing
- considerations in the identification and management of patients with minimal hemoglobin responses to ESAs

In part, the identification of specific hemoglobin goals for ESA therapy involve considerations of clinical outcomes apart from the clinical benefit associated with the

avoidance of red blood cell transfusion. The current product label for Epogen/Procrit describes patient-reported and physician-assessed benefits associated with the treatment of anemic CRF patients. Appended to this background information is a summary of FDA's findings from a recent reassessment of the clinical data supporting the inclusion of this information in the product label. This review suggests that the supplied clinical data do not supply sufficient evidence of efficacy to retain the claims, in light of the current regulatory and clinical science expectations for these types of data.

2. Regulatory history:

Epoetin alfa is manufactured, distributed and marketed by Amgen, Inc. under the proprietary name, Epogen. The same epoetin alfa product manufactured by Amgen, Inc. is also marketed and distributed by Ortho Biotech, L.P., a subsidiary of Johnson and Johnson, under the proprietary name, Procrit. Under a contractual agreement with Amgen, Ortho Biotech LP has rights to development and marketing of Procrit for any indication other than for the treatment of anemia associated with chronic renal failure in patients on dialysis or use in diagnostic test kits. Epogen and Procrit have identical labeling information for all approved indications.

Both currently marketed ESAs have been approved for use in the treatment of anemia associated with CRF, as well as other indications. The major regulatory time line for approval actions pertaining to new indications is summarized below:

Epoetin alfa (Epogen/Procrit):

- -1989: approved for use among anemic CRF patients
- -1991: approved for use among zidovudine-treated HIV-infected patients
- -1993: approved for use among chemotherapy- induced anemia in patients with non-myeloid malignancies
- -1996: approved for presurgical use among certain patients undergoing surgery

Darbepoetin alfa (Aranesp):

- -2001: approved for use among anemic CRF patients
- -2002: approved for use among chemotherapy-induced anemia in patients with non-myeloid malignancies

To support the initial FDA approval of Epogen/Procrit, substantial evidence of efficacy was provided predominantly from placebo-controlled and single arm clinical studies that demonstrated the product sufficiently increased and maintained blood hemoglobin levels to reduce the need for red blood cell transfusions. In the clinical development program for Aranesp, evidence of efficacy was provided predominantly from active comparator studies that demonstrated the product increased and maintained hemoglobin concentrations in a manner similar to that of the comparator. In this development paradigm, blood hemoglobin concentration served as a form of surrogate for "reduction in the need for red blood cell transfusions."

In the clinical studies supporting approval, ESAs were administered to achieve and maintain hematocrit values of approximately 32% to 38% (Epogen/Procrit) or hemoglobin concentrations of approximately 9 to 13 g/dL (Aranesp).

The major safety findings detected in the clinical studies supporting Epogen/Procrit approval related predominantly to the occurrence and worsening of hypertension. However, many of these initial clinical studies were of relatively short duration, relatively small sample size and generally did not compare the "targeting" of specific hemoglobin/hematocrit levels. The Aranesp clinical development program showed safety findings similar to that for Epogen/Procrit. This program also did not directly compare the "targeting" of specific hemoglobin/hematocrit levels with respect to safety or efficacy outcomes.

Following the initial licensure of Epogen/Procrit, various small clinical studies suggested that use of the product to "normalize" blood hemoglobin/hematocrit concentrations might result in improved cardiovascular outcomes for anemic CRF patients. However, when tested in large randomized studies, these hypotheses were not confirmed and the results in fact, suggested worse outcomes among patients randomized to "normalize" their hemoglobin/hematocrit levels (see discussion below regarding the "Normal hematrocrit" and CHOIR studies).

In 1996, the Epogen/Procrit label was modified to include the results of the "Normal hematocrit" study that showed a higher mortality rate for anemic dialysis patients randomized to a hematocrit of 42%, compared to a hematocrit of 30%. Ten years later, the CHOIR study reported worse cardiovascular outcomes for anemic CRF patients who were not undergoing dialysis and who were randomized to a hemoglobin of 13.5 g/dL, compared to a hemoglobin of 11.3 g/dL. The CREATE study, also reported in 2006, was a study similar to CHOIR but enrolled much fewer patients. CREATE did not demonstrate statistically significant differences in adverse cardiovascular outcomes for the higher hemoglobin group, but the general trend of the major cardiovascular outcomes was similar to the CHOIR findings.

Shortly following submission of the major CHOIR study findings to the FDA, new study data were also supplied that described adverse cardiovascular or mortality findings for the use of ESAs in the perisurgical setting or in the treatment of chemotherapy-induced anemia among cancer patients. The totality of these data prompted a reassessment of the safety of ESAs and in March, 2007 FDA approved revisions of the ESA product labels to include new safety and dosage information, including a boxed warning for this information.

3. March, 2007 ESA Label Modifications

In November, 2006 FDA issued a Public Health Advisory regarding the serious cardiovascular risks evidenced in the CHOIR study and the "Normal hematocrit" study. Subsequently, FDA received reports of increased risks associated with ESAs used in the treatment of the chemotherapy induced anemia among cancer patients, the use of ESAs

among cancer patients not receiving chemotherapy as well as a report of thrombotic risks among patients receiving an ESA in the perisurgical setting. These data prompted a reassessment of the safety information contained in the ESA product labels and culminated in the approval of revised labels on March 9, 2007.

With respect to dosage information, the reassessment of ESA safety determined that the available clinical data did not support the identification of a specific therapeutic hemoglobin goal, exclusive of the upper hemoglobin limit of 12 g/dL. Consequently, the dosage and administration sections of the label revisions deleted references to any specific therapeutic hemoglobin or hematocrit "target" range for ESAs.

Instead, the label revisions recommended that prescribers use the lowest ESA dose that will gradually increase the hemoglobin concentration to the lowest level sufficient to avoid the need for red blood cell transfusion. This recommendation was based, with respect to the use of ESAs among anemic CRF patients, predominantly upon the "Normal hematocrit" and CHOIR study findings as well as the lack of data to support the safety of any specific hemoglobin or hematocrit level or range under 12 g/dL.

Additionally, clinical data were not available to identify any specific hemoglobin or hematocrit levels that directly correlated with a "reduction in the need for red blood cell transfusion," the main treatment benefit supporting ESA efficacy. Hence, the March, 2007 label revision allowed prescribers to use their clinical judgment in determining the "lowest level sufficient to avoid the need for red blood cell transfusion."

The major components of the 2007 revised labeling consisted of the following:

-A boxed warning that noted:

> -Prescribers should use the lowest ESA dose that will gradually increase the hemoglobin concentration to the lowest level sufficient to avoid the need for red blood cell transfusion.
>
> -ESA increased the risk for death and for serious cardiovascular events when administered to target a hemoglobin of greater than 12 g/dL.
>
> -In cancer patients, ESAs shortened the time to tumor progression in patients with advanced head and neck cancer receiving radiation therapy when administered to target a hemoglobin of greater than 12 g/dL; shortened overall survival and increased deaths attributed to disease progression at four months in patients with metastatic breast cancer receiving chemotherapy when administered to target a hemoglobin of greater than 12 g/dL; increased the risk of death when administered to target a hemoglobin of 12 g/dL in patients with active malignant disease receiving neither chemotherapy nor radiation therapy (ESAs are not indicated for this population).

-In patients receiving ESAs pre-operatively for reduction of allogeneic red blood cell transfusions, a higher incidence of deep venous thrombosis was documented in patients receiving Procrit who were not receiving prophylactic anticoagulation. Antithrombotic prophylaxis should be strongly considered when Procrit is used to reduce allogeneic red blood cell transfusions.

-Additional warning information: to describe the CHOIR study, the perisurgical study and applicable studies conducted among patients with cancer.

-Revised the dosage and administration sections: to cite the recommendation to use the lowest ESA dose that will gradually increase the hemoglobin concentration to the lowest level sufficient to avoid the need for red blood cell transfusion.

-Revised the patient package inserts: to clarify the usage and effects of ESAs.

The major findings from the "Normal hematocrit" and CHOIR studies that importantly supported the label revisions are summarized below, along with a summary of the CREATE study.

4. "Normal Hematocrit," CHOIR and CREATE Study Findings:

a. "Normal Hematocrit" Study:

Following suggestive clinical data in the late 1980's and early 1990's that suggested "normalization" of hematocrit levels might result in better outcomes among anemic dialysis patients, the "Normal hematocrit" study was conducted to rigorously test the potential therapeutic advantages of higher hematocrit levels in certain dialysis patients. The study, conducted between 1993 and 1996, was terminated early due to the detection of important safety considerations. The final study results disclosed that dialysis patients randomized to a hematocrit of 42% ("normal hematocrit") experienced higher mortality and more non-fatal myocardial infarctions than patients randomized to a hematocrit of 30%.

The major study design characteristics and findings are summarized below. The published study report (based, in part, upon interim study findings) is also attached to this document.

Normal Hematocrit Design:

The "Normal hematocrit" study was a prospective, randomized, open label, phase 3 trial consisting of two parallel, relatively equal-sized study arms. A total of 1265 patients with chronic renal disease on maintenance epoetin alfa with a hematocrit of 30 ± 3% were enrolled and randomized into arm A (treatment arm) or arm B (control arm). Arm A patients received additional epoetin alfa during a correction phase to “normalize their hematocrit" to 42 ± 3%, while patients in control arm (B) remained on maintenance epoetin alfa (hematocrit: 30 ± 3%). The publication of the Normal hematocrit study

(attached) is based upon the interim analysis of data available for 1233 patients, not the 1265 ultimately analyzed in the final study report.

The primary objective of the study was to assess the effects of two different hematocrit target levels, 42% and 30%, on mortality and morbidity in hemodialysis patients with documented clinically evident cardiac disease [congestive heart failure (CHF) or ischemic heart disease] who were receiving epoetin alfa therapy. The primary endpoint was a time to death or first non-fatal myocardial infarction comparison between the two study groups.

Eligible patients met the following inclusion criteria:

a) had a diagnosis of end stage renal disease for a minimum of three months;
b) had been undergoing hemodialysis and receiving epoetin alfa treatment for a minimum of at least 4 weeks prior to enrollment;
c) had evidence of pre-existing cardiac disease (documented CHF or ischemic heart disease).

Epoetin alfa was administered intravenously (IV) or subcutaneously (SC). Patients in group A had an initial 1.5-fold increase in epoetin alfa dose. Further increases (by increments of 25% of the original dose) were made at 2-week intervals as needed to achieve 2-4 point increases in hematocrit levels over 2 weeks, to reach the target level. Doses of epoetin alfa were increased or decrease to maintain hematocrit levels within target ranges for both groups throughout the study.

Normal Hematocrit Study Results:

Overall, 634 patients were randomized to the high hematocrit target and 631 to the lower hematocrit target. Baseline characteristics of the two groups were generally similar at study entry.

Table 1. Normal Hematocrit Primary Endpoint Components: Final Study Report

Component	High Hct n = 634	Low Hct n = 631
Primary endpoint deaths	208 (32.8%)	173 (27.4%)
Total deaths	221 (34.9%)	185 (29.0%)
Non-fatal MI	20 (3.2%)	16 (2.5%)

Hct = hematocrit

Twenty-five patients who initially experienced a non-fatal myocardial infarction contributing to the primary endpoint subsequently died, bringing the total number of deaths to 406 [221 (35%) in the high hematocrit group and 185 (29%)] in the low hematocrit group). Overall, the log rank test of event free survival was 0.01, favoring the

low hematocrit group. The relative risk for a primary endpoint event was 1.3 (95% CI of 0.90 to 1.72) for patients in the high hematocrit group compared to those in the low hematocrit group.

The "Normal hematocrit" study publication, based upon analysis of 1233 patients, displayed the primary endpoint time to event curves and is duplicated in Figure 1.

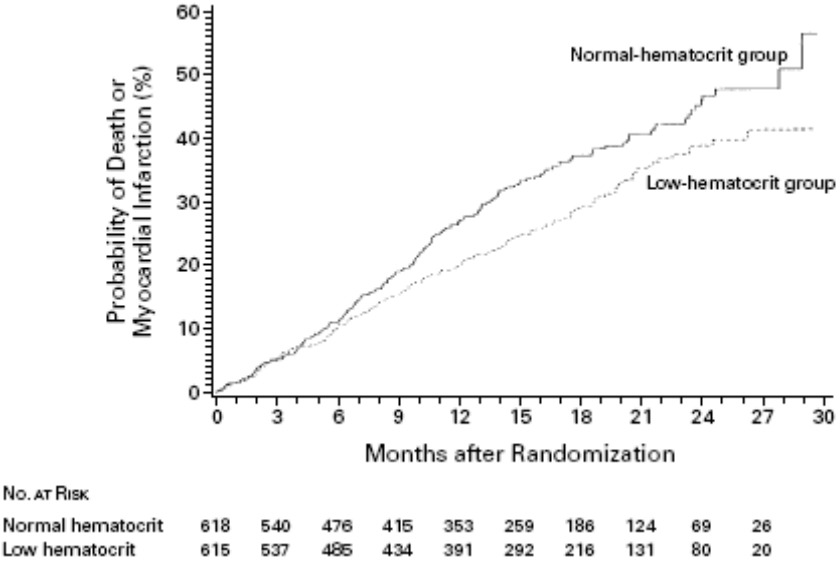


Figure 1. Published time to primary endpoint event curve

The reason for the increased mortality in the study is unknown, however, the incidence of non-fatal myocardial infarction (3.1% versus 2.3%), vascular access thrombosis (39% versus 29%) and all other thrombotic events (22% versus 18%) were also higher in the group randomized to achieve a hematocrit of 42%.

Red blood cell transfusions occurred in 30% of the high hematocrit group and 38% of the low hematocrit group (as indicated in the study report based predominantly upon analyses of 1233 of the 1265 randomized patients).

b. The CHOIR Study:

CHOIR Design:

The objective of the "Correction of hemoglobin and outcomes in renal insufficiency (CHOIR)" study was to compare the composite cardiovascular event rates for CRF patients randomized to a target hemoglobin of 13.5 g/dL (group A; high hemoglobin group) versus a target hemoglobin of 11.3 g/dL (group B; low hemoglobin group). The

main study hypothesis was that the "level of anemia correction with QW dosing would decrease mortality and cardiovascular morbidity." The study was conducted between 2002 and 2005.

CHOIR was a prospective, open-label, randomized, multi-center study conducted among adult CRF patients with baseline hemoglobin levels < 11 g/dL and who were not undergoing dialysis. Patients had to have glomerular filtration rates of more than 15 mL/min/1.73 m^2 but ≤ 50 mL/min/1.73 m^2, adjusted for body surface area.

Patients received epoetin alfa (Procrit) initially at a dose of 10,000 units once a week, subcutaneously (SC). Subsequent epoetin alfa doses were adjusted to achieve and maintain the target hemoglobin levels. However, the maximum dose permitted was 20,000 units/week.

The primary efficacy outcome variable was a time to event comparison for a composite primary endpoint of: mortality (all-cause mortality), CHF hospitalization (not including hospitalizations during which renal replacement therapy occurred), non-fatal stroke, and non-fatal myocardial infarction.

CHOIR Study Results:

Overall, 1432 patients were randomized, 715 to the high hemoglobin group and 717 to the low hemoglobin group. The final study report is described in the publication (attached) and only the major findings are emphasized here. The CHOIR study was terminated early, at the second interim analysis, because the safety monitoring board determined that the study had little or no chance to demonstrate a benefit in the higher hemoglobin group.

Baseline characteristics were generally similar between the two study groups, with the most common etiologies of renal failure relating to diabetes or hypertension.

The study's primary endpoint showed a statistically significant disadvantage for patients in the higher hemoglobin group. Specifically, primary endpoint events occurred among 125 (17.5%) of patients in the higher hemoglobin group and 97 (13.5%) of patients in the lower hemoglobin group, associated with a log rank p-value of 0.03. The time to event curves for the primary endpoint are shown in Figure 2.

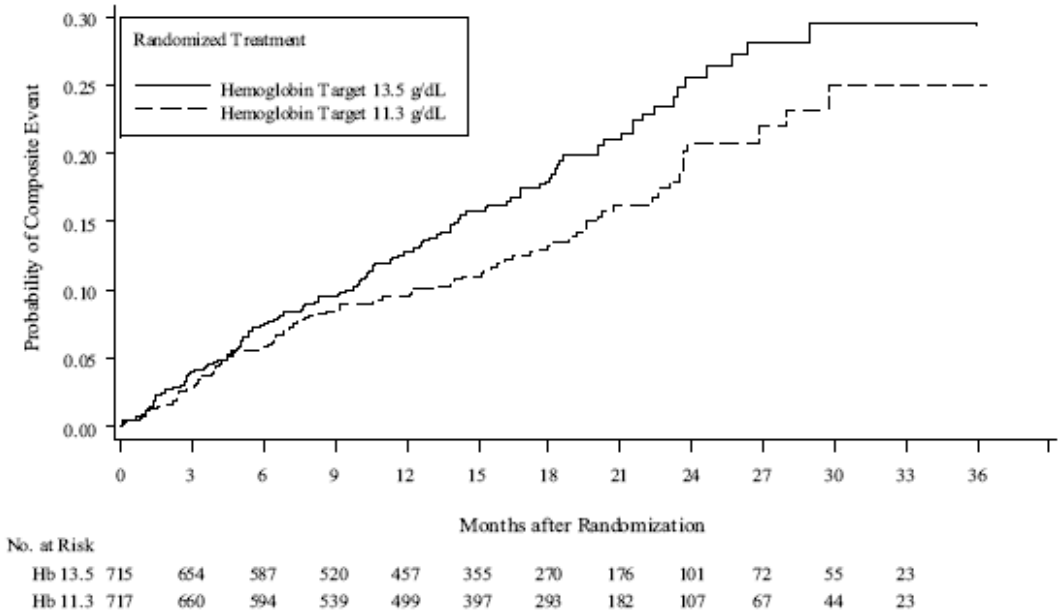


Figure 2. Time to event curves for the CHOIR primary endpoint

The components of the primary endpoint are shown in Table 2 and the overall rates of important cardiovascular outcomes are shown in Table 3.

Table 2. Components of the CHOIR primary endpoint result

Component	Hgb 13.5 g/dL n = 715	Hgb 11.3 g/dL n = 717
Any endpoint component	125 (17.5%)	97 (13.5%)
Death	39 (5.5%)	26 (3.6%)
CHF hospitalization	59 (8.3%)	42 (5.9%)
Non-fatal myocardial infarction	12 (1.7%)	13 (1.8%)
CHF hospitalization & non-fatal myocardial infarction	3 (0.4%)	4 (0.6%)
Non-fatal stroke	12 (1.7%)	11 (1.5%)
Stroke and death	0	1 (0.1%)

Hgb = hemoglobin

Table 3. Overall event rates in CHOIR

Event	Hgb 13.5 g/dL n = 715	Hgb 11.3 g/dL n = 717
All cause mortality	52 (7.3%)	36 (5.0%)
CHF hospitalization	64 (9.0%)	47 (6.6%)
Non-fatal myocardial infarction	18 (2.5%)	20 (2.8%)
Non-fatal stroke	12 (1.7%)	12 (1.7%)
Renal replacement therapy	155 (21.7%)	134 (18.7%)
All cause hospitalization	369 (51.6%)	334 (46.6%)
Hospitalization for vascular access problems	73 (10.2%)	57 (7.9%)

The proportion of patients receiving red blood cell transfusions did not remarkably differ between the groups: 59 patients in group the high hemoglobin group (8.8%) versus 68 patients in the low hemoglobin group (10.0%).

c. CREATE Study

The CREATE Study ("Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta Trial") is briefly cited because it used certain design features that were similar to the CHOIR study. Specifically, CREATE randomized patients who were not undergoing dialysis to either a high hemoglobin target or a low hemoglobin target and also used a time to event analysis for a primary composite cardiovascular endpoint. However, CREATE was conducted entirely in Europe and used epoetin beta, a product not marketed in the United States. The major aspects of the CREATE study are summarized below and described more thoroughly in the attached publication. The study was conducted between 2002 and 2004.

In CREATE, 603 patients with an estimated glomerular filtration rate of 15 to 35 mL per minute per 1.73 m^2 of body-surface area and hemoglobin levels of 11 to 12.5 g/dL were randomized to a high hemoglobin target (13 to 15 g/dL) or a low hemoglobin target (10.5 to 11.5 g/dL). Open label, SC epoetin beta was initiated at randomization (high hemoglobin target group) or only after the hemoglobin level fell below 10.5 g/dL (low hemoglobin target group). The primary endpoint was a composite of eight cardiovascular events: sudden death, myocardial infarction, acute heart failure, stroke, transient ischemic attack, angina pectoris resulting in hospitalization for 24 hours or more or prolongation of hospitalization, complication of peripheral vascular disease (amputation or necrosis), or cardiac arrhythmia resulting in hospitalization for 24 hours or more.

Overall, a primary endpoint event occurred in 58 of 301 (19.3%) patients in the high hemoglobin group and 47 of 302 (15.6%) patients in the low hemoglobin group, with a hazard ratio of 0.78 (95% CI 0.53 to 1.14, p = 0.20). Dialysis was required in more patients in the higher hemoglobin group than in the low hemoglobin group (127 versus 111, p = 0.03).

5. Considerations in identifying specific hemoglobin goals for ESA dosing:

The major considerations for identifying specific hemoglobin goals sufficient to support alteration of the ESA product labeling include:

-the regulatory expectations for "claims" in product labeling;

-the strength and limitations of the available clinical data correlating outcomes with specific hemoglobin levels, including data from randomized, controlled clinical studies as well as observational clinical studies;

a. Regulatory expectations:

The identification of specific hemoglobin goals for ESA usage is, in part, a form of a claim that attainment of these goals will result in treatment benefit. The concept of a "claim" in a product label is generally defined as "a statement of treatment benefit or comparative safety advantage. A claim can appear in any section of a medical product's FDA-approved label or in advertising of prescription drugs."[1] Hence, it is important to first consider the regulatory expectations for a claim prior to summarizing the available clinical data supporting a claim.

In reviewing the clinical data relevant to a claim, special consideration should be given to the regulatory concept of "substantial evidence of effectiveness." Section 505(d) of the Federal Food, Drug and Cosmetic Act establishes "substantial evidence" as the evidence standard for making conclusions that a drug will have a claimed effect and states that reports of adequate and well-controlled investigations provide the basis for determining whether there is "substantial evidence." Biological products, such as the ESAs, are approved under section 351 of the Public Health Service Act that states licenses are issued only once a product has been shown to provide "continued safety, purity and potency." In this context, "potency" for biological products has been interpreted by FDA to include effectiveness, based upon clinical data from adequate and well-controlled clinical studies.[2]

Hence, claims of ESA efficacy sufficient for inclusion of the information within the product labels must be based upon "substantial evidence" from adequate and well-controlled clinical studies. Based upon these regulatory expectations, data from inadequately designed and uncontrolled clinical studies would not support an implicit or explicit product labeling claim.

b. Clinical data correlating specific hemoglobin levels with outcomes:

[1] Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims; see internet web site of: http://www.fda.gov/cder/guidance/5460dft.pdf.
[2] Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products; see internet web site of: http://www.fda.gov/cder/guidance/1397fnl.pdf.

Clinical correlates to the attainment of specific hemoglobin levels may be broadly grouped into efficacy or safety outcomes. The efficacy outcome correlations are summarized below, followed by safety correlations.

Efficacy: As previously noted, the major treatment benefit supporting ESA approval was the demonstration that the products increase blood hemoglobin/hematocrit levels to an extent sufficient to avoid the need for red blood cell transfusion. With respect to other potential benefits of ESAs, the FDA requested the sponsors to supply clinical data supporting any other treatment benefits, specifically regarding survival or improvements in health-related quality of life outcomes. In general,

Regarding potential survival benefits:

ESA sponsors note that, "almost all the clinical trials conducted by the sponsors were not designed to address the specific question regarding ESA use and survival." The sponsors further note that, "As such, the results of individual analyses of the clinical trial data and other analyses using observational data should not be considered definitive because of uncontrolled bias."

Nevertheless, the data in the USRDS (United States Renal Data System) show that all-cause mortality rates in dialysis patients "were high and relatively stable before the introduction of epoetin alfa and declined coincident with epoetin alfa approval in the US." Additionally, observational clinical data suggest improved survival for CRF patients who maintain blood hemoglobin levels > 11 g/dL, compared to patients with lower levels.

In total, no randomized, controlled clinical data have been supplied to establish survival benefits for the attainment of specific hemoglobin levels in association with ESA usage. Observational clinical data are suggestive of survival benefits.

Regarding health-related quality of life considerations:

Appended to this document is a summary of FDA's review of supplied PRO and physician-assessed outcome data. These data were supplied from three relatively small sample size, randomized, double-blind, placebo-controlled clinical studies as well as an open label clinical study. In general, the FDA review found multiple deficiencies within these data.

Overall, FDA has received no randomized, controlled clinical data establishing treatment benefits associated with the attainment of specific hemoglobin levels.

Safety: As previously noted, the "Normal hematocrit" and CHOIR studies showed important safety risks associated with the "targeting" of higher hemoglobin/hematorcrit levels compared to lower levels. The design of these studies used a composite cardiovascular outcome and is somewhat similar to an ongoing clinical study referred to as the TREAT study.

Conceivably, information from the TREAT study may importantly impact the use of ESAs since this study is designed, in part, to compare to the targeting of a higher hemoglobin level to a lower level. TREAT is briefly summarized below.

The TREAT study:

Amgen is currently conducting a study entitled, "Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT)."

This study, conducted among CRF patients with type 2 diabetes mellitus who not undergoing dialysis, randomizes anemic patients to one of two groups:

-treatment with Aranesp to a target hemoglobin level of 13 g/dL

-placebo (with administration of Aranesp to patients whose hemoglobin decreases to less than 9 g/dL)

The study uses a double-blind design and a composite primary endpoint (time to event) of all cause mortality and cardiovascular events (acute myocardial ischemia, congestive heart failure requiring medical attention, myocardial infarction or cerebrovascular accident). The planned sample size is approximately 4000 subjects and the study will conclude when approximately 1203 patients have experienced a primary endpoint event. The sponsor notes that the study's safety monitoring committee continues to monitor the study findings and the study remains active.

6. Considerations in the identification and management of patients with minimal hemoglobin responses to ESAs:

As previously noted, the "Normal hematocrit" and CHOIR studies suggested that a patient's response to a given ESA dose was the most important correlate for increased cardiovascular risks, not the ESA dose itself.

In considering these data, it is important to note that:

-the analyses from the "Normal hematocrit" and CHOIR study are all post-hoc and of a hypothesis-generating nature;

-to date, a well accepted definition of "hypo-responder" does not appear evident in the published literature or information supplied to FDA;

-for inclusion in product labeling, the criteria for identifying a patient as one with a suboptimal hemoglobin response to an ESA dose should be clear, clinically relevant and the consequences of this identification based upon clinical study findings.

APPENDIX 1: FDA SUMMARY REVIEW OF PATIENT-REPORTED AND PHYSICIAN-ASSESSED OUTCOMES

Coincident with the approval of the March, 2007 ESA label alterations, FDA requested Amgen to reassess the data supporting inclusion of the "quality of life" information described within the Clinical Experience section of the Epogen/Procrit label. Specifically, FDA requested that these data be reassessed to determine the extent to which these data met the recommendations described in the 2006 FDA document entitled, "Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims." FDA also requested Amgen to supply information from publications or other sources applicable to these claims.

The current Epogen/Procrit label contains the following information within the Clinical Experience section (within the description of the confirmatory phase 3 clinical study supporting the initial approval):

> "Changes in the quality of life of adult patients treated with PROCRIT were assessed as part of a phase 3 clinical trial. Once the target hematocrit (32% to 38%) was achieved, statistically significant improvements were demonstrated for most quality of life parameters measured, including energy and activity level, functional ability, sleep and eating behavior, health status, satisfaction with health, sex life, well-being, psychological effect, life satisfaction and happiness. Patients also reported improvement in their disease symptoms. They showed a statistically significant increase in exercise capacity (VO2 max), energy, and strength with a significant reduction in aching, dizziness, anxiety, shortness of breath, muscle weakness and leg cramps."

Amgen states that their re-evaluation of these claims does not support retention of several of the "quality of life" claims. Specifically, the following text is proposed for the label:

…Changes in ~~the quality of life~~physician-assessed and patient reported outcomes of adult dialysis patients treated with Epoetin alfa~~EPOGEN®~~ were assessed as part of 2 randomized, placebo-controlled clinical trials and a phase 3 clinical trial.[5,8] Once the target hematocrit (32% to 38%) was achieved, statistically significant improvements were demonstrated for ~~most quality of life parameters measured, including energy and~~ activity level and~~,~~ functional ability, ~~sleep and eating behavior, health status, satisfaction with health, sex life, well-being, psychological effect, life satisfaction, and happiness. Patients also reported improvement in their disease symptoms. They showed a statistically significant increase in~~ exercise capacity ~~(VO$_2$ max)~~, energy, ~~and strength with a significant reduction in aching, dizziness, anxiety,~~ shortness of breath, and muscle weakness~~, and leg cramps~~.[8,21] These results were confirmed in an additional randomized, double-blind, placebo-controlled clinical trial in adult dialysis patients. ...

Importantly, the single phase 3 clinical study supporting the "quality of life" claims in the current Epogen/Procrit label was Study 8601, an open label, single arm study initiated in 1986. It is important to consider that, at the time Study 8601 was designed, the clinical science applicable to the measure of PRO/"quality of life" was evolving, especially with respect to regulatory applications. Indeed, FDA's first guidance upon the quality of data necessary to support PRO claims in labeling was not published until twenty years later.

Based upon the current state of the clinical science pertaining to PRO, the safety risks evidenced for ESAs and the need to update product labeling when important new information becomes available, FDA has reviewed the supplied information and has detected important deficiencies within these data. These deficiencies are described below, following a brief summary of the recommendations from the 2006 PRO guidance document.

PRO Draft Guidance Document Highlights:

A PRO is a measurement of any aspect of a patient's health status that comes directly from the patient (without interpretation of the patient's response). The assessment of PRO within a confirmatory clinical study currently involves many important considerations related predominantly to the specific instruments (such as questionnaire or diary) used in the study, the study design and its analyses.

The FDA PRO guidance makes the following major points regarding the assessment of PRO in confirmatory clinical studies:

- Results of PRO from open-label clinical studies are rarely credible since patients and investigators are aware of the treatment. Hence, PRO should be derived from clinical studies where every effort is made to assure that patients are masked to treatment assignments.

- Missing data within PRO datasets may importantly bias the study results.

- Statistical analytical plans should clearly and appropriately address multiplicity concerns and the impact of missing data upon PRO.

- PRO instrument development is incomplete without patient involvement. FDA will review whether PRO instruments are appropriate, comprehensive and interpretable based upon patient input.

- If documentation exists that a single item is a reliable and valid measure of the concept of interest (e.g., pain severity), a one-item PRO instrument may be a reasonable measure to support a claim concerning that concept. However, if the concept of interest is general (e.g., physical function), a single-item PRO instrument is usually unable to provide a complete understanding of the treatment effect because a single item cannot capture all the domains of the general concept.

- The "recall" period of a PRO instrument is an important consideration because instruments that require patients to rely on memory may threaten the accuracy of the PRO data.

In response to FDA requests, Amgen supplied summaries of observational data, reports from Study 8601 (the open label, single arm study supporting the "quality of life" claims) and study reports for three randomized double blind clinical studies (Studies 8701, 8904 and 8604). All clinical study data pertain to the use of epoetin alfa. The major findings from the FDA review are summarized below:

Regarding Study 8601: This open label, multicenter clinical study provided the supporting evidence for the original symptom efficacy claims in the epoetin alfa label and enrolled 429 patients who were receiving dialysis. Of note, the design of this study had been discussed with the FDA and the single arm design features were chosen due to ethical considerations for use of a placebo as well as the strength of the findings from the previously completed placebo-controlled clinical studies. The major efficacy outcome in Study 8601 was a description of the ability of epoetin alfa to increase the hematocrit six points over baseline or to attain a target hematocrit of 35%. Participants in Study 8601 were "invited" to participate in a prospective survey of "quality of life." The changes in the National Kidney Dialysis and Kidney Transplantation Study (NKDKTS) Symptom List and other instruments were compared between baseline and follow-up (once a hemoglobin of 35% had been achieved) for each participating patient.

Study 8601 PRO deficiencies included:

-use of an open label design
-use of a single arm study design
-no description of missing data or extent of compliance with PRO assessments
-limitation of observations to patients who achieve the target hematocrit, not the entire enrolled population

-use of unvalidated PRO instruments (including NKDKTS, a list of unrelated symptoms which was originally developed to compare the characteristics of end-stage renal disease patients receiving various treatment option, including renal transplantation)

Three randomized, placebo-controlled studies also examined various PRO outcomes and contribute to the sponsor's database, along with Study 8601. Table 4 summarizes the PRO proposed for retention within the Epogen/Procrit label, along with the applicable supportive studies and instruments. This table is followed by a brief summary of the major design and PRO outcome deficiency for each study.

Table 4. Summary of Proposed Labeling Claims/Instruments/Clinical Studies

Study	Functional Ability/Physical Function	Tiredness/Lack of Energy	Weakness	Shortness of Breath	Exercise Capacity
8601	Karnofsky (Physician Assessed)	-NKDKTS item -Single item PRO -NHP Energy Scale	-NKDKTS item -Single item PRO	NKDKTS item	
8701	Karnofsky (Patient Reported)	-NKDKTS item -Single item PRO -NHP Energy Scale	-NKDKTS item -Single item PRO	NKDKTS item	
8904	Karnofsky (Patient Reported)	-NKDKTS item -Single item PRO -NHP Energy Scale	-NKDKTS item -Single item PRO	NKDKTS item	
8604	KDQ Physical SIP -Physical -Body care movement -Home maintenance -Ambulation	-KDQ Fatigue -Patient-generated	Patient-generated	Patient-generated	-Exercise Stress -6-minute Walk

NDKTS = National Kidney Dialysis and Kidney Transplantation Study; PRO =Patient Reported Outcome; NHP = Nottingham Health Profile; KDQ = Kidney Disease Questionnaire; SIP = Sickness Impact Profile

Regarding Study 8701: This double blind, placebo controlled study had a major objective of assessing the ability of epoetin alfa to "ameliorate" the anemia of end stage renal disease and reduce or eliminate the use of red blood cell transfusions. The study consisted of two parts: a 12 week treatment period with either epoetin alfa or placebo and a subsequent 12 week period where all subjects received epoetin alfa. A "quality of life questionnaire" was administered at baseline, week 12 and week 24 (see Table 4). The statistical analytical plan did not describe any specific analyses of the "quality of life" outcomes or plans for the handling of missing data. The final study report cites the enrollment of 106 patients and the finding that hematocrit levels were unchanged at 12 weeks in the placebo group but had increased to an average of 34% (from 22% baseline) in the active treatment group.

Study 8701 major deficiencies include:

-the report finding that "the results here are inconclusive. Patients in the experimental group and those in the control group showed some change (although not statistically significant or consistent) in objective and subjective quality of life between baseline and first follow-up and between first and second follow-up."
-as in Study 8601, use of unvalidated PRO instruments for this patient population
-enrollment of 106 patients but PRO information from only 59 (56%)
-unclear handling of missing data
-lack of prespecified analytical plans specific for PRO

Regarding Study 8904: This randomized, double blind, placebo controlled clinical study enrolled patients undergoing peritoneal dialysis with the major objective to "ameliorate" the anemia of end stage renal disease. Similar to study 8701, this study consisted of two periods, an initial 12 week double blind, placebo controlled period followed by another 12 week period during which all subjects received active treatment. The "quality of life" assessments were similar to those used in Study 8701.

Overall 152 patients were enrolled, 78 (51%) randomized to epoetin alfa and 74 (49%) to placebo. During the blinded period, 16 patients (11%) dropped out of the study.

Study 8904 major deficiencies include;
-as described in the study report, "Sometimes several questionnaires had to be provided with reminders that completing and returning each questionnaire promptly and on schedule was very important to the study. There were still many questionnaires returned late or not returned at all."
-of the 152 enrolled patients, follow-up information is available for only 77 patients (51%), including 38 assigned to epoetin alfa and 40 assigned to placebo
-other deficiencies, as described for Study 8701

Regarding Study 8604: This randomized, double blind, placebo-controlled clinical study was conducted among anemic patients undergoing dialysis in Canada. Subjects were randomized among placebo or one of two active treatment groups (epoetin alfa targeted to either a hemoglobin of 9.5 to 11 g/dL or a hemoglobin of 11.5 to 13 g/dL). The study drugs were administered over a 26 week treatment period. Overall, 118 patients were randomized but 99 (84%) completed the study and these patients supplied the analytical database, as follows:
-placebo, n = 32
-"medium" hemoglobin, n = 34
-high hemoglobin, n = 33

"Quality of life" was assessed using several instruments, including the Sickness Impact Profile, Kidney Disease Questionnaire and a Global Perception of Energy Scale) and two tests of functional capacity (six minute walk and treadmill test). "Quality of life" was assessed at baseline, weeks 9, 17, 23 and "post-study" (see Table 4).

The study report notes that changes in the six minute walk test were not statistically significantly different from placebo at six months. However, the mean time to fatigue (as measured on the treadmill test was reported as significantly different between placebo and the active treatment groups (when combined together) at six months, although information is available for only 76% of the enrolled 118 patients.

Study 8604 major deficiencies include:

-missing information for up to 24% of the enrolled population
-unvalidated PRO instruments
-inconsistent results between the six minute walk and treadmill test
-small sample sizes in treatment groups, such that changes in only a few patients importantly alter the study outcomes
-other deficiencies, as described for the Studies 8701 and 8904

With respect to all three randomized, placebo-controlled studies and the sponsor proposals:

-patients were not enrolled based upon a prespecified degree of anemia symptoms
-all studies were not powered to detect changes in PRO/"quality of life"
-none of the symptom efficacy claims instruments were developed or validated to measure anemia symptoms in the target population; instead, post-hoc selection of specific items and subscales from various instruments were utilized to support symptom claims
-the sponsor's proposed endpoint model does not include a comprehensive list of anemia/physical symptoms, based upon patients' input
-source data are missing for some of the clinical studies
-statistical analytical plans were deficient in description of PRO analyses, especially with respect to multiplicity concerns and the handling of missing data

APPRENDIX 2: FDA PRELIMINARY REVIEW OF ESA RESPONSE-RISK CONSIDERATIONS

OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY
Review Memorandum

Date: 10 August, 2007
From: Ellis F. Unger, M.D.
Deputy Director for Science (Acting)
Office of Surveillance and Epidemiology, CDER

To: Dr. Dwaine Rieves
Acting Director, Division of Medical Imaging and Hematology
Office of New Drugs, CDER

Subject: Consult Review of STN BL 103234/Epogen®/Procrit®

The aim of this review is to consider the risks and benefits of erythropoiesis-stimulating agents (ESAs) (Darbepoetin alfa, marketed as Aranesp® by Amgen, Inc.; and Epoetin alfa, marketed as Epogen® by Amgen, Inc., and as Procrit® by Johnson & Johnson PRD.) when used in the treatment of anemia due to chronic renal disease. Specifically, this review will attempt to characterize the interrelationships between ESA dose, rate of change of ESA dose, ESA responsiveness, hemoglobin target, hemoglobin concentration, and rate of change of hemoglobin concentration.

Background:

In the 1990's, Amgen sponsored the "Normal Hematocrit" study (NHCT), which was designed to test the hypothesis that normalization, versus partial correction of the hematocrit, would improve outcome in hemodialysis patients with a history of chronic heart failure or ischemic heart disease (Besarab et al, 1998[1]). Patients previously receiving Epoetin alfa and maintained at a hematocrit of 30±3% (N = 1233) were randomized to receive protocol-specified increasing doses of Epoetin alfa to achieve and maintain a target "normal" hematocrit of 42±3% (hemoglobin 14±1 g/dL) or to continue to receive Epoetin alfa to maintain a hematocrit of 30±3% (hemoglobin 10±1 g/dL). The primary endpoint was time to death or first non-fatal myocardial infarction. The study was stopped at the third interim analysis, when it was apparent that the results favored the low hematocrit group. The risk ratio for the composite endpoint was 1.3 (95% C.I.: 0.9, 1.9).

The results of the study were incorporated into the Epogen®/Procrit® prescribing information in December, 1998, as well as the original Aranesp® Package Insert (September, 2001). The warning presently reads:

WARNINGS
Adults
Increased Mortality, Serious Cardiovascular and Thromboembolic Events

[1] Besarab A, Bolton WK, Browne JK, et. al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. N Engl J Med. 1998;339:584-590.

> Increased risk for serious cardiovascular events was also reported from a randomized, prospective trial of 1265 hemodialysis patients with clinically evident cardiac disease (ischemic heart disease or congestive heart failure). In this trial, patients were assigned to EPOGEN® treatment targeted to a maintenance hematocrit of either 42 ± 3% or 30 ± 3%.[1] Increased mortality was observed in 634 patients randomized to a target hematocrit of 42% [221 deaths (35% mortality)] compared to 631 patients targeted to remain at a hematocrit of 30% [185 deaths (29% mortality)]. The reason for the increased mortality observed in this study is unknown, however, the incidence of non-fatal myocardial infarctions (3.1% vs. 2.3%), vascular access thromboses (39% vs. 29%), and all other thrombotic events (22% vs. 18%) were also higher in the group randomized to achieve a hematocrit of 42%.

In the exploratory safety analyses of the Aranesp® licensing application performed by the Center for Biologics Evaluation and Research (CBER), an association was observed between hemoglobin rate of rise exceeding 0.5 g/dL/week and risk of cardiovascular and thromboembolic events.

On the basis of the CBER review, a warning was incorporated into the Aranesp® Package Insert, and eventually the Procrit®/Epogen® prescribing information. The current versions of ESA Package Inserts bear this warning (specific text underlined):

> "WARNINGS
>
> Increased Mortality, Serious Cardiovascular and Thromboembolic Events
>
> Aranesp® (Procrit® Epogen®)and other erythropoiesis-stimulating agents (ESAs) increased the risk for death and for serious cardiovascular events in controlled clinical trials when administered to target a hemoglobin of greater than 12 g/dL. There was an increased risk of serious arterial and venous thromboembolic events, including myocardial infarction, stroke, congestive heart failure, and hemodialysis graft occlusion. A rate of hemoglobin rise of greater than 1 g/dL over 2 weeks may also contribute to these risks."

Additional concerns regarding higher hemoglobin targets were raised with publication of the CHOIR Study.[2] CHOIR was an Ortho Biotech-sponsored study, a randomized, open-label trial of 1432 anemic (hemoglobin < 11.0 g/dL) subjects with chronic renal failure who were not undergoing dialysis and had not previously received Epoetin alfa therapy. They were randomly assigned to receive Epoetin alfa treatment to target a maintenance hemoglobin concentration of 13.5 g/dL or 11.3 g/dL. The study was hoped to demonstrate improved outcomes in subjects randomized to the higher hematocrit. The primary endpoint was a composite of death, non-fatal myocardial infarction, hospitalization for congestive heart failure, and stroke. This trial was terminated on the recommendation of the data and safety monitoring board at the second interim analysis. A composite endpoint event occurred in 125 (17.5%) of the 715 patients in the higher hemoglobin group compared to 97 (13.5%) of the 717 patients in the lower hemoglobin group (hazard ratio 1.34; 95% C.I.: 1.03, 1.74; p=0.03). Differences in mortality (7.3% vs. 5.0%) and hospitalization for congestive heart failure (9.0% vs. 6.6%) accounted for the disparity in endpoint events. The relative risks for myocardial infarction and stroke were near unity

[2] Sinhg AK, Szczech L, Kang KL, et. al. Correction of anemia with epoetin alfa in chronic kidney disease. N Engl J Med. 2006;355:2085-2098.

(myocardial infarction: 2.5% vs. 2.8% in higher vs. lower hemoglobin target groups, respectively; stroke: 1.7% in both groups).

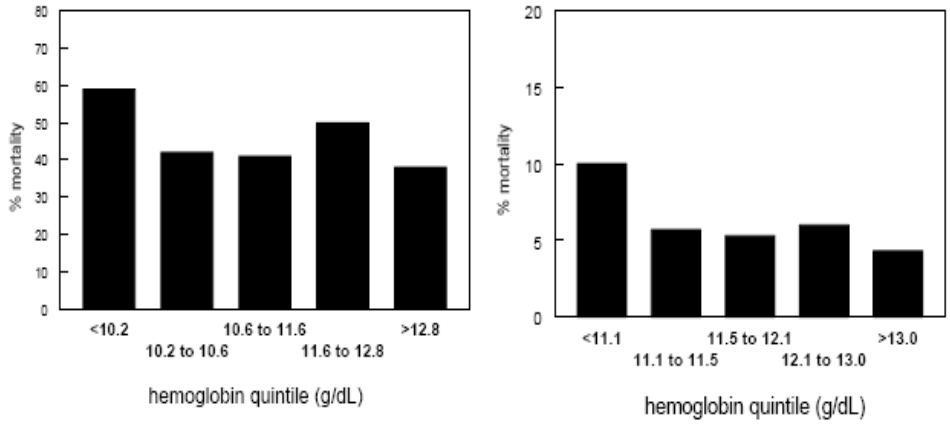
Subsequent to availability of the CHOIR Study results, a black box warning was added to ESA package inserts:

> WARNINGS: Erythropoiesis-Stimulating Agents
>
> Use the lowest dose of Aranesp® that will gradually increase the hemoglobin concentration to the lowest level sufficient to avoid the need for red blood cell transfusion (see DOSAGE AND ADMINISTRATION).
>
> Aranesp® and other erythropoiesis-stimulating agents (ESAs) increased the risk for death and for serious cardiovascular events when administered to target a hemoglobin of greater than 12 g/dL (see WARNINGS: Increased Mortality, Serious Cardiovascular and Thromboembolic Events).

The principle underlying the NHCT and CHOIR Studies was that the optimum hematocrit for a patient with chronic renal failure should be largely no different from than that of healthy individuals. In other words, patients with chronic renal failure would experience improved outcomes with higher, more normal, hemoglobin concentrations. In both studies, subjects were randomized to either a higher or lower hemoglobin target. In both studies, however, randomization to the higher target was associated with increased mortality. These were larger studies that examined a broad spectrum of patients with chronic renal failure: NHCT (n=1233) included patients with a history of ischemic heart disease or chronic heart failure who were on hemodialysis; CHOIR (n=1432) enrolled patients with less advanced kidney disease who were not on dialysis and who were recombinant erythropoietin-naïve. Roughly a quarter of the subjects in CHOIR had a history of congestive heart failure (CHF); and ~35% had a history of myocardial infarction (MI), stroke, coronary artery bypass graft surgery (CABG), percutaneous coronary intervention (PCI), or amputation of a lower extremity.

Running counter to the principal findings of these studies was that higher hemoglobin values, per se, were not associated with increased cardiovascular events. In fact, in both the NHCT and CHOIR Studies, higher mortality tended to be associated with subjects with lower mean hemoglobin concentrations (CDER analysis, Figure 1). Thus, being randomized to a higher hemoglobin target was associated with higher mortality, but having a higher study-average hemoglobin concentration appeared somewhat protective! This counterintuitive finding suggests that some other factor, beyond simple hemoglobin concentration, but associated with randomization to the higher target, was responsible for the excess cardiovascular risk. Possibilities include direct toxic effects of ESAs, conditions that might be brought about by higher ESA doses (e.g., iron deficiency), concomitant medications that might be required to support higher hemoglobin concentrations (e.g., iron), or simply the act of having hemoglobin raised. Is it also possible that expansion of erythropoiesis constitutes a metabolic stress that is deleterious in patients with significant coexisting medical conditions. Although nearly 10 years have passed since publication of the NHCT Study results, the explanation for higher mortality in the "normal" hemoglobin group remains unknown.

Figure 1: Percent Mortality by Average Hemoglobin Concentration Throughout Study: NHCT (left) and CHOIR (right) (CDER analysis)



In part as preparation for this Advisory Committee Meeting, the Division of Medical Imaging and Hematology Products, Office of New Drugs, posed a number of questions to the sponsors. The questions included requests for discussion of:

1) the extent to which ESAs provide a survival advantage for patients with chronic renal failure;

2) a maximum dosage for ESA usage in the treatment of the anemia of chronic renal failure, with supportive data and analyses;

3) ESA dosing considerations, with respect to the concept of a "target hemoglobin"; and

4) comprehensive analyses of the entire controlled clinical database in order to assess the extent to which the cardiovascular risks are directly related to the administered ESA dose and/or the hemoglobin response.

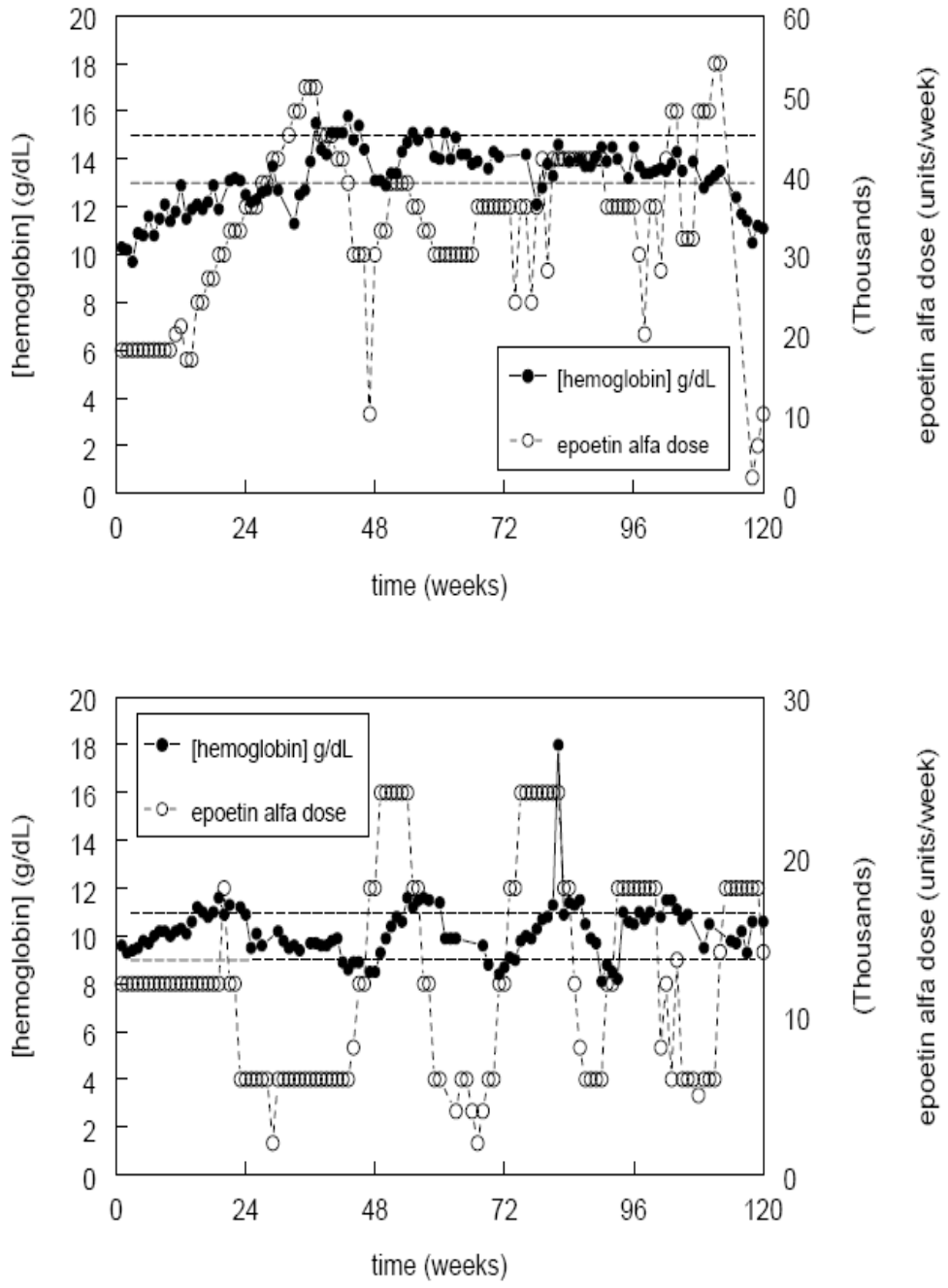
In response, Amgen Inc. and Johnson & Johnson Pharmaceutical Research & Development, LLC submitted the document "Response to Questions Regarding Erythropoiesis-Stimulating Agent (ESA) Administration in Chronic Renal Failure" (June 29, 2007). The sponsors' analyses and recommendations principally consider cardiovascular risk for individual patients to be constant throughout time. However, for a number of reasons pointed out by the sponsor, there are frequent fluctuations in hemoglobin concentration in patients with anemia of chronic renal failure, and this is particularly true in the hemodialysis patient population. Because ESAs are titrated to effect, administered doses often vary widely over time as well.

This reviewer believes that if there are risks associated with higher ESA doses, higher or lower hemoglobin concentrations, excessive rates of hemoglobin change, and/or ESA-responsiveness, these risks are likely to change in any given patient over time. Thus, this review will supplement the sponsors' analyses, and focus on the dynamic nature of ESA dose and hemoglobin response.

Figure 2 shows the hemoglobin concentration and Epoetin alfa dose with respect to time for two unselected subjects entered into the NHCT Study (the subjects with the lowest patient numbers). Hemoglobin concentration is denoted by filled circles and shown on the left *y*-axis. Epoetin alfa dose is denoted by open circles, and shown on the right *y*-axis. In each panel, pairs of parallel horizontal lines mark the hemoglobin target. Excursions in both hemoglobin and dose are evident for both subjects. The subject presented in the top panel (#1001) was randomized to the "normal" hemoglobin target (11-13 g/dL); the subject presented in the lower panel (#1002) was randomized to the lower target (9-11 g/dL). The dose changes in the subject randomized to the lower target are fairly striking, but not unusual. Of note, in order to gain study entry, all subjects had to have been maintained at a hematocrit of 27-33% (corresponding to hemoglobin of 9-11 g/dL) while receiving Epoetin alfa for four weeks prior to enrollment. In other words, the goal for the subject represented in the lower panel was simply to maintain the hemoglobin concentration at the study entry level, yet oscillations in hemoglobin concentration and wide fluctuations in dose are evident.

Thus, when considering the risks of ESA use for patients with chronic renal failure, this reviewer believes that it is important to consider not only overall risk for individual patients, but also how risk may change as hemoglobin concentrations fluctuate and ESA dose is adjusted.

Figure 2: Hemoglobin and Epoetin alfa Dose with Respect to Time: First Two Subjects Enrolled in the Normal Hematocrit Study



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Review of the NHCT and CHOIR Studies

This review document will provide summaries of exploratory analyses of the data from the NHCT and CHOIR Studies. As noted above, these were fairly large studies that enrolled a spectrum of subjects with chronic renal failure, with NHCT including hemodialysis subjects with a history of ischemic heart disease or chronic heart failure, and CHOIR enrolling pre-dialysis subjects who were recombinant erythropoietin-naïve. The basic approach of this review was to analyze serious cardiovascular adverse events by hemoglobin concentration, Epoetin alfa dose, and dose "responsiveness." The data for these analyses were drawn from the SAS transport files supplied under IND 11547, serial number 077 (kae.xpt, kdos01.xpt, kdos2.xpt, khgball.xpt, kprofile.xpt, ksurvall.xpt, and ktte2.xpt) and BLA STN103234\0056, \0063, and \0064 (ae.xpt, basechar.xpt, corevar.xpt, and weekly.xpt).

Analyses of Serious Adverse Events by Hemoglobin Concentration:

Through its impact on rheologic and/or hemodynamic mechanisms, excessive or rapid erythropoiesis is thought to have the potential to precipitate cardiovascular adverse events. These events include accelerated hypertension and congestive heart failure, as well as thrombotic and ischemic events (acute myocardial infarction, stroke, thrombosis of vascular access, peripheral ischemia, and gangrene).

Two basic approaches were used to consider risk by hemoglobin concentration. The first more standard approach considers the risk for each subject to be constant throughout the course of the study, a function of mean hemoglobin concentration. Thus, the cumulative hemoglobin concentration was calculated for each subject, and each subject was then categorized in cumulative dose quintiles. Serious adverse events are presented as frequencies on a per-subject level, by overall hemoglobin quintile (i.e., for hemoglobin quintiles 1 through 5, the percentage of subjects with CHF reported as a serious adverse event, the percentage of subjects with angina, etc.).

For the NHCT Study, hemoglobin values were to be obtained weekly. The hemoglobin quintile ranges for the study as a whole were:

quintile 1: hemoglobin <10.17 g/dL
quintile 2: hemoglobin ≥10.17 and <10.63 g/dL
quintile 3; hemoglobin ≥10.63 and <11.58 g/dL
quintile 4: hemoglobin ≥11.58 and <12.83 g/dL
quintile 5: hemoglobin ≥12.83

For the CHOIR Study, hemoglobin was to be obtained every two weeks until stable, then every four weeks. The hemoglobin quintile ranges over the entire study were:

quintile 1: hemoglobin <11.12 g/dL
quintile 2: hemoglobin ≥11.12 and <11.51 g/dL
quintile 3; hemoglobin ≥11.51 and <12.09 g/dL
quintile 4: hemoglobin ≥12.09 and <13.00 g/dL
quintile 5: hemoglobin ≥13.00

Re-Coding of Cardiovascular Adverse Events:

The adverse event datasets from the NHCT and CHOIR Studies were examined, and all adverse event records were recoded by this reviewer. The records from the two studies were combined prior to recoding to ensure consistency; treatment assignment was masked. Re-coding was accomplished by considering the reported term, preferred term (WHOART; MedDRA); high level term (MedDRA); high level group term (MedDRA); system organ class (both systems); low level term (MedDRA); specific AE group, and AE subgroup.

The adverse events were re-coded under the following terms and groupings: death; acute myocardial infarction; congestive heart failure (CHF) or pulmonary edema (also CHF and pulmonary edema as separate terms); edema (non-pulmonary), fluid retention, fluid overload; left ventricular ejection fraction decreased, left ventricular dysfunction, cardiomyopathy; cardiac arrest, asystole, sudden cardiac death; coronary artery disease, coronary heart disease; coronary artery disease worse/progressive; myocardial ischemia; angina; unstable angina, acute coronary syndrome, rule out myocardial infarction, post-infarction angina; percutaneous coronary intervention; thrombosis of vascular access; ischemia (non-coronary, non-cerebral), thrombophlebitis, thrombosis, phlebitis; arteriosclerosis, peripheral (and non-peripheral) vascular disease; hypertension, blood pressure increased; hypertensive crisis, accelerated hypertension; pulmonary embolism; embolism (all); cerebrovascular accident; transient ischemic attack; subarachnoid hemorrhage; intracerebral hemorrhage (subarachnoid hemorrhage excluded); cerebral ischemia, anoxia (unrelated to cerebrovascular accident); ventricular tachycardia; and ventricular fibrillation. The categorization of serious adverse events was left unchanged, using the regulatory definition of "serious."

Serious, non-serious, and total adverse events were tabulated and considered separately, but the focus of this review is on serious adverse events.

Results:

Tables 1 and 2 show the percentages of subjects in the NHCT and CHOIR Studies, respectively, who experienced serious cardiovascular adverse events.[3] Subjects in the NHCT Study (hemodialysis patient population with overt cardiovascular disease) experienced far more events than subjects in the CHOIR Study (pre-dialysis population). Neither analysis suggests an association between higher hemoglobin concentration (mean throughout the study) and serious cardiovascular adverse events. The lowest hemoglobin quintile in the NHCT Study (hemoglobin concentration <10.17 g/dL) appeared to experience a greater frequency of events than subjects in the higher hemoglobin quintiles. A similar trend was apparent in the CHOIR Study, although the overall event rates were lower. Note that Figure 1 (shown on page 4) displays the results of these analyses for mortality.

[3] Note that the original randomization to hemoglobin target was not included in these analyses. It would be of value to compare frequencies of serious adverse events between treatment groups for a given range of hemoglobin values; however, this was not feasible. The 1st and 2nd hemoglobin quintiles predominantly represented subjects randomized to the lower target; the 4th and 5th quintiles were predominantly subjects randomized to the higher target.

Table 1:
Serious Cardiovascular Adverse Events in the NHCT Study by Mean Hemoglobin Quintile

	Hemoglobin Category (g/dL)				
	<10.17	10.17 to 10.63	10.63 to 11.58	11.58 to 12.83	>12.83
n in quintile	**254**	**251**	**251**	**251**	**252**
any cardiovascular serious adverse event	80%	73%	68%	73%	69%
death	59%	42%	41%	50%	38%
congestive heart failure or pulmonary edema	20%	25%	21%	22%	15%
congestive heart failure	16%	23%	17%	18%	13%
pulmonary edema	6%	6%	5%	7%	4%
edema, non-pulmonary, fluid retention; overload	8%	6%	4%	8%	8%
EF decreased, LV dysfunction, cardiomyopathy	1%	1%	2%	3%	1%
cardiac arrest; asystole, sudden death	14%	8%	12%	9%	6%
acute myocardial infarction	9%	11%	8%	9%	11%
coronary artery disease, coronary heart disease	23%	25%	20%	27%	23%
myocardial ischemia	0%	0%	0%	0%	0%
angina	17%	20%	14%	24%	18%
PTCA or CABG	0%	0%	0%	1%	1%
thrombosis of vascular acsess	22%	21%	21%	30%	23%
ischemia (non-coronary, non-CNS)	3%	1%	1%	3%	1%
thrombophlebitis, thrombosis, phlebitis	23%	22%	22%	31%	26%
deep venous thrombosis	0%	0%	1%	0%	2%
arteriosclerosis, vascular disease, peripheral vascular disease	18%	14%	11%	16%	10%
peripheral vascular disease	17%	12%	10%	14%	10%
hypertension, blood pressure increased	2%	3%	1%	2%	2%
embolism	1%	0%	1%	0%	1%
pulmonary embolus	0%	0%	1%	0%	1%
cerebrovascular accident, transient ischemic attack	8%	7%	6%	7%	10%
cerebrovascular accident	7%	6%	6%	6%	9%
transient ischemic attack	1%	2%	0%	1%	2%

Table 2:
Serious Cardiovascular Adverse Events in the CHOIR Study by Mean Hemoglobin Quintile

	Hemoglobin Category (g/dL)				
	<11.12	11.12 to 11.51	11.51 to 12.09	12.09 to 13.00	>13.00
n in quintile	**281**	**281**	**281**	**281**	**281**
any cardiovascular serious adverse event	30%	22%	23%	23%	17%
death	10%	6%	5%	6%	4%
congestive heart failure or pulmonary edema	17%	9%	7%	9%	7%
congestive heart failure	16%	8%	6%	9%	7%
pulmonary edema	2%	0%	1%	0%	0%
edema, non-pulmonary, fluid retention; overload	3%	1%	1%	1%	1%
EF decreased, LV dysfunction, cardiomyopathy	0%	0%	1%	0%	0%
cardiac arrest; asystole, sudden death	3%	1%	3%	3%	1%
acute myocardial infarction	5%	2%	2%	3%	2%
coronary artery disease, coronary heart disease	6%	5%	4%	5%	2%
coronary artery disease, worse, progressive	1%	1%	2%	1%	0%
myocardial ischemia	1%	0%	0%	0%	1%
angina	1%	3%	1%	3%	1%
angina, unstable, acute coronary syndrome, rule out MI	1%	1%	1%	2%	0%
thrombosis of vascular acsess	0%	0%	1%	0%	0%
thrombophlebitis, thrombosis, phlebitis	0%	0%	1%	0%	0%
deep venous thrombosis	1%	1%	1%	1%	1%
arteriosclerosis, vascular disease, peripheral vascular disease	2%	2%	2%	2%	2%
peripheral vascular disease	1%	0%	2%	1%	1%
hypertension, blood pressure increased	3%	1%	4%	2%	1%
hypertensive crisis, accelerated hypertension	0%	0%	0%	1%	1%
embolism	0%	1%	1%	0%	0%
pulmonary embolus	0%	1%	1%	0%	0%
cerebrovascular accident, transient ischemic attack	1%	4%	4%	4%	3%
cerebrovascular accident	1%	3%	2%	3%	2%
transient ischemic attack	1%	1%	2%	1%	1%
ventricular tachycardia	1%	0%	2%	0%	0%

Methods for "Dynamic" Analyses:

The second approach to the analysis of risk as a function of hemoglobin attempted to consider the dynamic nature of hemoglobin concentrations and cardiovascular risk. Thus, each interval between hemoglobin assessments was viewed as a time-at-risk for adverse events, and each period was associated with a particular hemoglobin value, and a rate of change of hemoglobin concentration preceding each visit. Each subject's hemoglobin data were divided into "periods," separated by dates of visits when hemoglobin was assessed. For each date, the prevailing slope of the hemoglobin-time relation was calculated using linear regression, and the time since the prior hemoglobin assessment represented the time-at-risk, an opportunity for the reporting of a serious adverse event. Thus, a typical subject followed in the NHCT Study for two years would contribute 104 "periods," each with an associated hemoglobin concentration and slope, each 7 days long. For example, consider a patient with hemoglobin values of 10.0 g/dL and 11.0 g/dL on May 1st and May 8th, respectively. An adverse event reported on May 2nd would be associated with a 7-day time-at-risk, during which the prevailing hemoglobin concentration was 11.0 g/dL, and the slope was + 1.0 g/dL/week. The methods are described in some detail, below.

1. Analysis of adverse events by hemoglobin concentration. For each visit date when a hemoglobin assessment was completed or planned ("index date"), the time since the prior hemoglobin assessment was determined. Adverse events that occurred during that interval were linked to that index date, and the length of the interval was used to calculate time at risk. For example (Figure 3), given a subject whose hemoglobin was assessed on 3/15/96 and 3/22/96, adverse events that occurred between 3/16/96 and 3/22/96, inclusive, were associated with the 3/22/96 index date. The length of the interval (7 days) was used to calculate time-at-risk, which served as the denominator for determination of adverse event rates. Had an adverse event occurred on 3/23/96, it would be associated with the subsequent index date, etc. For both studies, periods-at-risk were categorized into quintiles by hemoglobin concentration. Note that the quintiles have somewhat different boundaries than the quintiles for mean study hemoglobin concentrations, used above. Also, transfusions were not considered in these analyses (i.e., hemoglobin concentrations following transfusions were not eliminated).

2. Analysis of adverse events by hemoglobin rate of change. This analyses linked adverse events to the hemoglobin rate of change during the weeks preceding the event. For each visit date where a hemoglobin value was expected (index date), the slope of the preceding hemoglobin-time relation was determined, when possible, using linear regression. In the NHCT Study, hemoglobin values were generally obtained weekly, whereas in CHOIR, hemoglobin was assessed generally every two or four weeks. Thus, different approaches were used to calculate hemoglobin slope in the two studies.

NHCT Study:

a. For each date for which a hemoglobin value was expected, slope was calculated using all hemoglobin values obtained over a two-week period (i.e., 3 hemoglobin values: index date, one week prior to index date, and two weeks prior to index date).

b. If <2 hemoglobin values were reported over a two-week period, such that a slope could not be calculated, an attempt was made to calculate slope over a 4-week period.

c. For calculation of slope, hemoglobin values were construed as having been obtained on the day indicated, i.e., the actual dates were used in calculations.

d. Missing hemoglobin values were not interpolated, and the sponsors' interpolated values were not used.

e. Slopes were expressed as weekly change in hemoglobin concentration. Positive and negative slopes were analyzed separately, with slopes of 0 classified with the positive slopes (quintile 1).

f. Positive slopes (m) were classified into quintiles, as follows:
quintile #1: $m \geq 0$ and < 0.1 g/dL/week
quintile #2: $m \geq 0.1$ and < 0.25 g/dL/week
quintile #3: $m \geq 0.25$ and < 0.35 g/dL/week
quintile #4: $m \geq 0.35$ and < 0.55 g/dL/week
quintile #5: $m \geq 0.55$ g/dL/week

g. Negative slopes (m), corresponding to falling hemoglobin concentrations, were classified as follows:
quintile #1: $m \geq -0.15$ and < 0 g/dL/week
quintile #2: $m \geq -0.33333$ and < -0.15 g/dL/week
quintile #3: $m \geq -0.5$ and < -0.33333 g/dL/week
quintile #4: $m < -0.5$ g/dL/week

CHOIR Study:

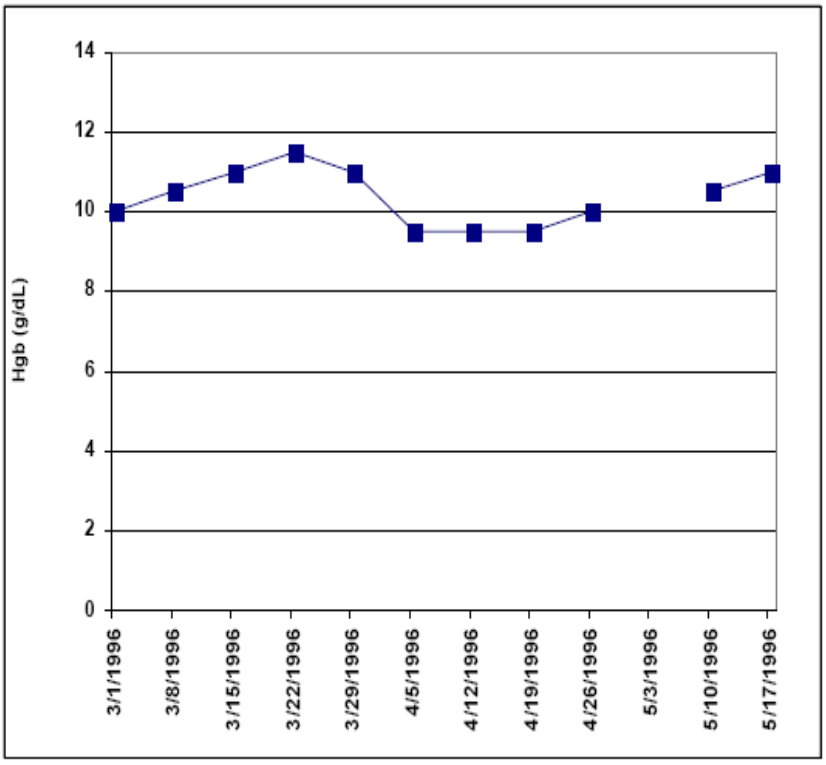
For CHOIR, the general approach was the same, except that all hemoglobin values within 21 days were used for calculation of slope. Sensitivity analyses were conducted using longer and shorter intervals, and the results were substantially the same.

Positive slopes (m) were classified into quintiles, as follows:
quintile #1: $m \geq 0$ and < 0.08232 g/dL/week
quintile #2: $m \geq 0.08232$ and < 0.18669 g/dL/week
quintile #3: $m \geq 0.18669$ and < 0.30002 g/dL/week
quintile #4: $m \geq 0.30002$ and < 0.49413 g/dL/week
quintile #5: $m \geq 0.49413$ g/dL/week

Negative slopes (m), corresponding to falling hemoglobin concentrations, were classified as they were for the NHCT Study.

Figure 3 displays fictitious data from "subject 9999" in the NHCT Study, showing hemoglobin by date. The slopes were calculated using the method, above.

Figure 3: Fictitious data from "Subject 9999"



Subject	line	date	Hgb	slope
1001	1	3/1/96	10	
1001	2	3/8/96	10.5	0.5
1001	3	3/15/96	11	0.5
1001	4	3/22/96	11.5	0.5
1001	5	3/29/96	11	0
1001	6	4/5/96	9.5	-1
1001	7	4/12/96	9.5	-0.75
1001	8	4/19/96	9.5	0
1001	9	4/26/96	10	0.25
1001	10	5/3/96		0.5
1001	11	5/10/96	10.5	0.25
1001	12	5/17/96	11	0.5

3/20/96:
serious adverse event

Notes:
1. No slope can be calculated on line 1.
2. For line 3, the slope is highlighted in gray; only 2 values are available to calculate slope.
3. For line 10, there is no hemoglobin value recorded; slope is calculated from lines 8-9.
4. The serious adverse event on 3/20/96 is attributed to line 4.
5. Most periods have associated hemoglobin concentrations and slopes; in the minority of cases, one or both are missing.

Calculation of Adverse Event Rates:

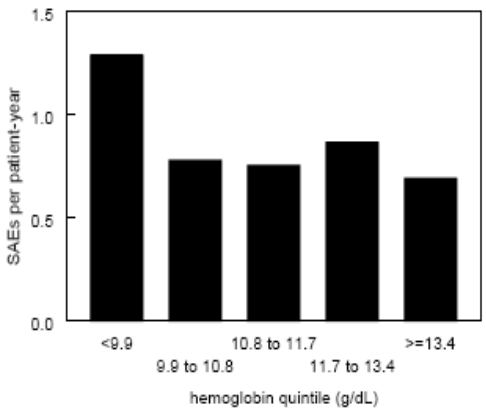
For both studies, rates of adverse events per patient-year were calculated as the number of events for a given hemoglobin/slope category, divided by total time at risk (days) for the category, multiplied by 365.25 days/year.

Results – Adverse Events as a Function of Hemoglobin Concentration:

1. The NHCT Study

The relation between all cardiovascular serious adverse events and *dynamic* serum hemoglobin concentration for the NHCT Study is shown in Figure 4. The rate of serious adverse events was highest in the lowest hemoglobin quintile (hemoglobin <9.9 g/dL); rates were lower and fairly consistent in the four higher hemoglobin quintiles.

Figure 4: NHCT Study – Serious Adverse Events by Hemoglobin Quintile



The relation between all serious adverse events rates and hemoglobin rate of change is shown in Figure 5. There is a clear increase in rates of serious adverse events by increasing negative change in hemoglobin (i.e., greater rates with greater rapidity of hemoglobin decrease). The quintile representing the steepest rate of rise (>0.55 g/dL/week) is also associated with a higher rate of serious adverse events.

Figure 5: NCHT Study – Serious Adverse Events by Hemoglobin Rate of Change Quantile

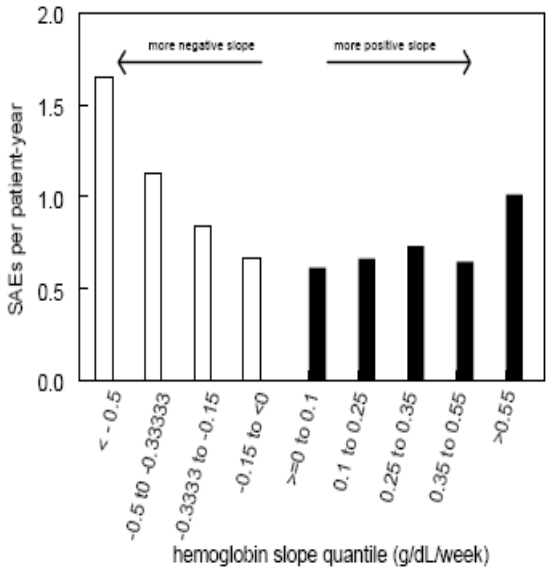
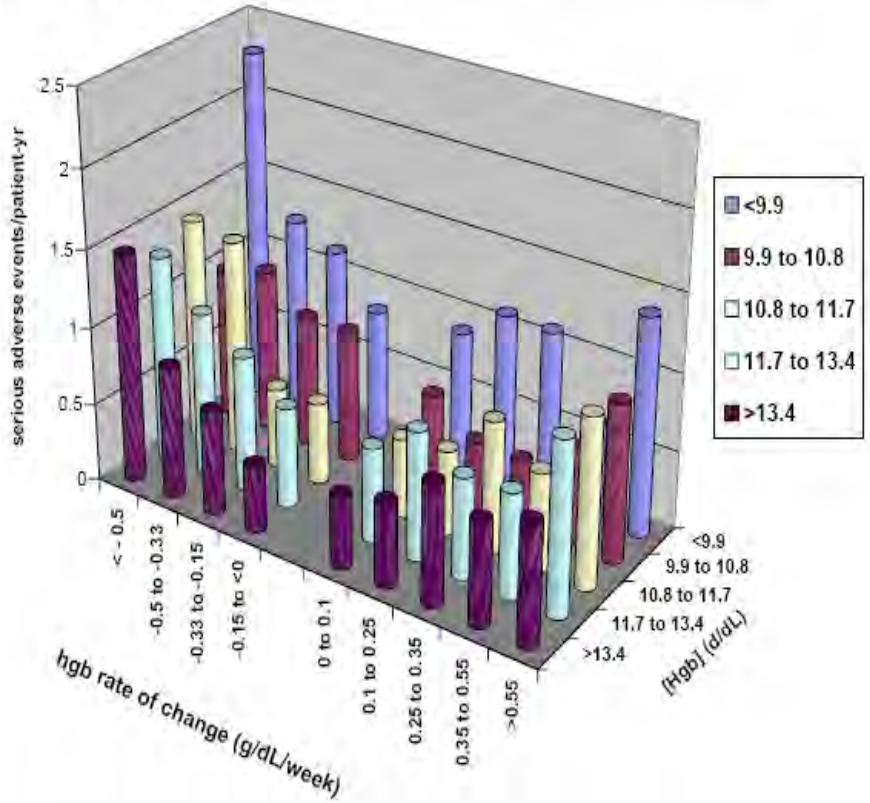


Figure 6 shows the interaction between hemoglobin concentration, hemoglobin rate of change, and cardiovascular serious adverse events in the NHCT Study. The height of each bar represents the annualized rate of cardiovascular serious adverse events per subject. Two trends are apparent: first, hemoglobin concentrations <9.9 g/dL appear to be associated with increased rates of cardiovascular serious adverse events (back row of blue bars). This was evident from Figure 4 as well. More striking, however, are the greater frequencies of events at the extremes of hemoglobin rate of change. In particular, there appears to be a strong relation between rapidity of hemoglobin decrease and adverse events. Rates of adverse events also appear higher with positive hemoglobin/time slope in excess of 0.55 g/dL/week. Of note, the lowest rates of adverse events were associated with higher hemoglobin values and lower rates of change.

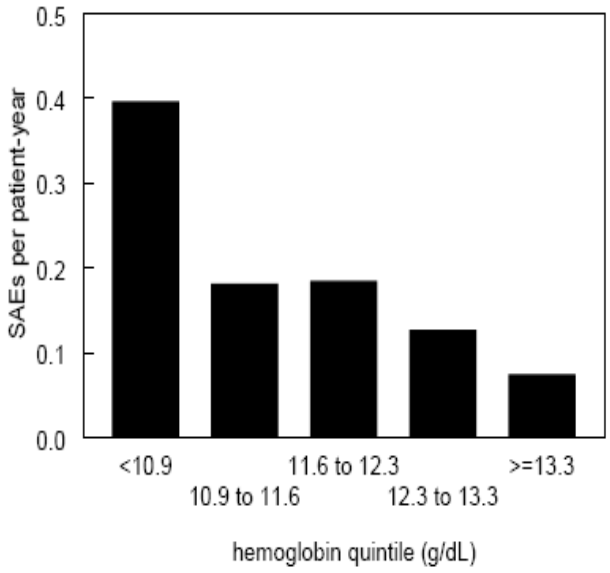
Figure 6: NHCT Study – Rates of Serious Adverse Cardiovascular Events by Hemoglobin and Hemoglobin Rate of Change Categories



2. The CHOIR Study

The relation between hemoglobin concentration and cardiovascular serious adverse events is shown for CHOIR in Figure 7. The rate of serious adverse events was highest in the lowest hemoglobin quintile (hemoglobin <10.9 g/dL); serious adverse event rates tended to decrease with increasing hemoglobin. Note there were fewer serious adverse events in this pre-dialysis patient population (perhaps a third as many per subject-year as there were in the NHCT Study).

Figure 7: CHOIR Study: Serious Adverse Events by Hemoglobin Quintile



The rates of serious cardiovascular adverse events with respect to hemoglobin rate of change are shown in Figure 8. The lowest event rates are associated with the positive slope categories encompassing the range 0.08 to 0.30 g/dL/week. As in the NHCT Study, there is a strong relationship between negative slope and adverse events.

Figure 8: CHOIR Study: Serious Adverse Events by Hemoglobin Rate of Change Quantile

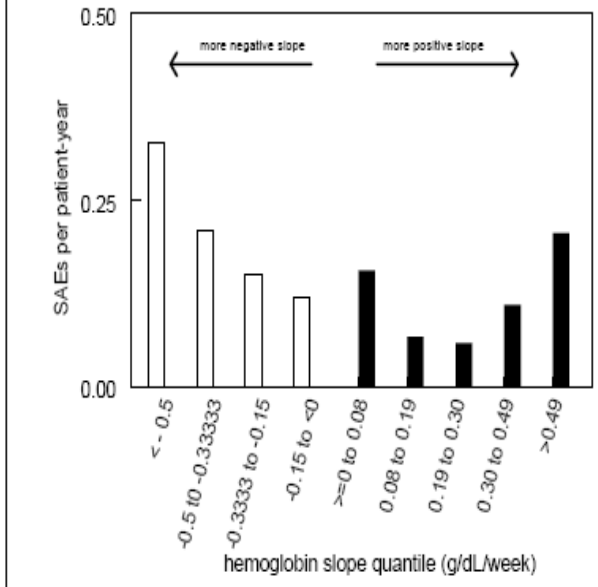
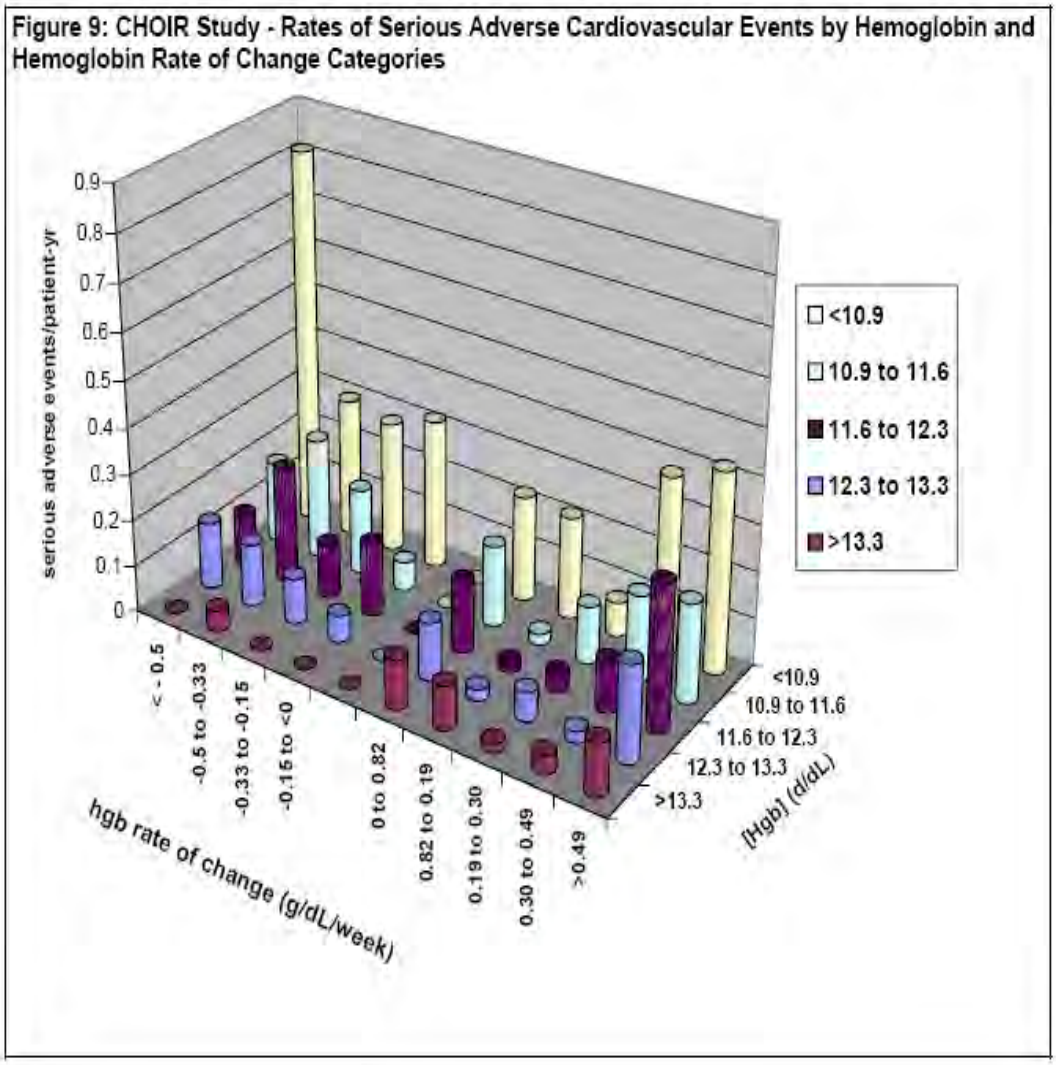


Figure 9 shows rates of cardiovascular serious adverse events for CHOIR by hemoglobin concentration and hemoglobin rate of change. Because there are fewer cardiovascular serious adverse events in this patient population, the analysis is less powerful than the NHCT analysis. Nevertheless, as observed in the NHCT Study, the highest event rates are observed in the lowest hemoglobin quintile (hemoglobin <10.9 g/dL in this study, back row, yellow bars). Also as was seen in NHCT, the highest hemoglobin quintile does not appear to be associated with a particularly high rate of serious cardiovascular adverse events. There was a strikingly high rate of cardiovascular serious adverse events during intervals when patients experienced both lowest hemoglobin values (< 10.9 g/dL) and rapid decline in hemoglobin (rate of decline < -0.5 g/dL/week). In essence, there were patients whose hemoglobin had declined rapidly to a low level. As was noted in the NHCT data, rates of hemoglobin increase > 0.49 g/dL/week are associated with higher rates of cardiovascular serious adverse events.

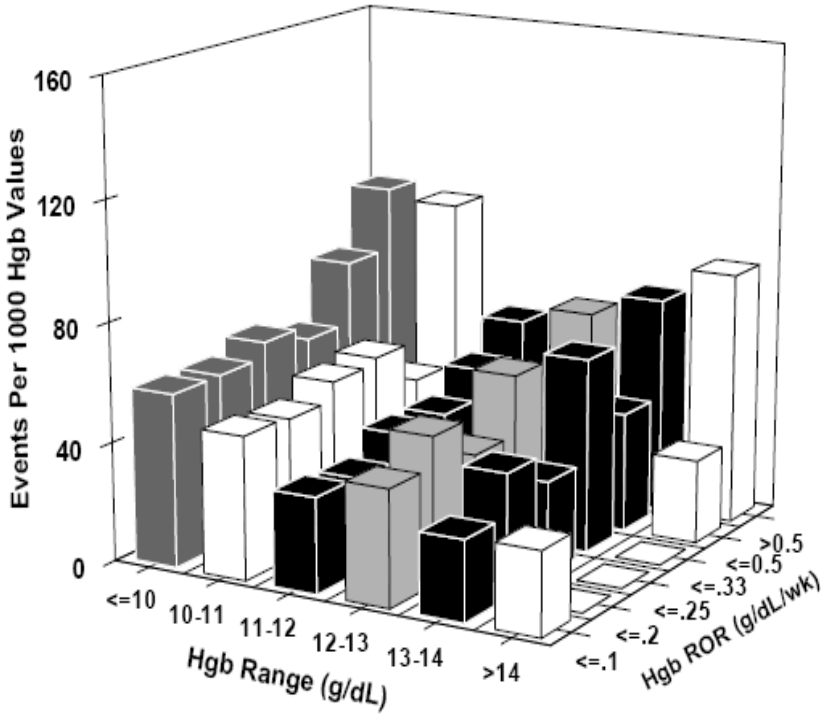
Figure 9: CHOIR Study - Rates of Serious Adverse Cardiovascular Events by Hemoglobin and Hemoglobin Rate of Change Categories



18

These analyses, suggest a strong relation between cardiovascular risk, hemoglobin concentration, and changes in hemoglobin concentration, during treatment with ESAs. The findings are also consistent with exploratory analyses from the Aranesp® (Darbepoetin alfa) registration program. The summary showing the associations between cardiovascular adverse events and hemoglobin changes, reprinted from the Medical Officer's Clinical Review of the Aranesp® development program, is shown in Figure 10. The Aranesp® data, from 1598 subjects with chronic renal failure (a mixture of pre-dialysis, hemodialysis, and peritoneal dialysis patients), show generally decreasing rates of adverse events with increasing hemoglobin concentration, but increasing rates with increasing rates of hemoglobin rise. The Aranesp® analyses also showed increasing rates of events with decreasing hemoglobin concentrations (negative hemoglobin-time slope, data not shown).

Figure 10: Aranesp® Registrational Studies - Rates of Adverse Cardiovascular Events by Hemoglobin and Hemoglobin Rate of Change Categories



Conclusions – Adverse Events as a Function of Hemoglobin:

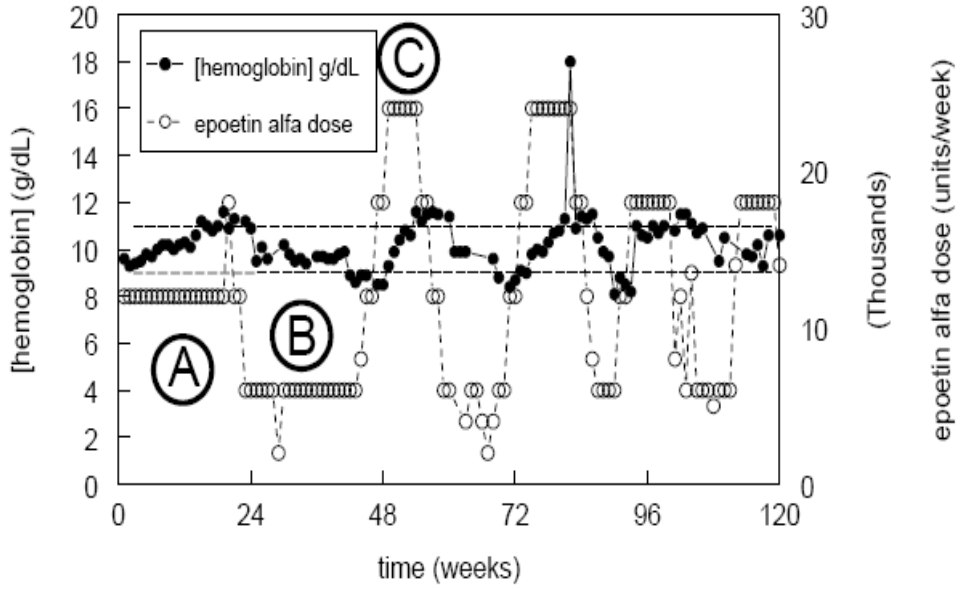
Thus, all three datasets suggest that the extreme hemoglobin rate of rise category (> 0.5 g/dL/week) is associated with excess risk. There is also an important association between decreasing hemoglobin concentrations and cardiovascular risk: the more rapid the hemoglobin decline, the greater the risk. Hemoglobin declines of greater than 0.5 g/dL/week appear to be particularly problematic.

Although these observations are exploratory in nature, they are fairly compelling, given that similar findings have been observed in three discrete data sets obtained from different sources of data obtained over approximately 10 years. Nevertheless, they are only associations. Lower hemoglobin values and falling hemoglobin concentrations tend to be markers of patients with more significant background disease and lower ESA responsiveness, who may be at greater risk of cardiovascular events.

The concern about hemoglobin rates of rise in excess of 0.5 g/dL/week is consistent with a warning in the present ESA labeling. Intuitively, it seems difficult to incriminate ESAs in causing *declines* in hemoglobin. Presumably, rapidly decreasing hemoglobin levels result from coexisting medical conditions that are themselves associated with adverse events. Some of the observed deceases in hemoglobin may be exaggerated, reflecting the fact that patients who undergo hospitalization for adverse events (one of the regulatory definitions of a serious adverse event) are subjected to frequent phlebotomies. On the other hand, neither coexisting disease nor ESA-hyporesponsiveness can be implicated in causing rapid rises in hemoglobin concentration. Rapid rises in hemoglobin concentration are largely the result of ESAs, or more specifically, the way that their doses are determined.

On the whole, the data seem to say that hemoglobin concentrations, and ESA dose, should be maintained at a constant level to the extent possible. *Attempts should be made be to develop better dosing algorithms to help practitioners maintain consistent hemoglobin levels and avoid cycling.*

Figure 11: Hemoglobin and Epoetin alfa Dose with Respect to Time: Subject 1002 in the Normal Hematocrit Study



20

Case in Point:

Consider the patient depicted in the lower panel of Figure 2 (reprinted below as Figure 11). During the initial 22 weeks of the study (circled "A"), the hemoglobin was slowly rising with the subject receiving a constant 12,000 U of Epoetin alfa per week. At week 23, with three hemoglobin values above target, the Epoetin alfa dose was decreased from 12,000 to 6,000 U/week. The hemoglobin then decreased to just below 9 g/dL, slightly below target (circled "B"). Over the next six weeks, the practitioner increased the Epoetin alfa dose to 24,000 U (circled "C"). This was followed by periods of cycling for both hemoglobin concentrations and Epoetin alfa dose, that continued through the end of the study. In retrospect, the cycling might have been avoided had the practitioner waited longer to observe the effect of dose increases between circled "B" and circled "C." Given that the dose of 12,000 U/week the subject had been receiving at study entry caused the subject's hemoglobin to increase beyond the target, it is not surprising that the dose of 24,000 U/week caused overshoot.

Epoetin alfa Dose and Serious Adverse Events:

Subjects randomized to the higher hemoglobin target groups in the NHCT and CHOIR Studies experienced greater mortality than their counterparts randomized to a lower hemoglobin target. The fact that subjects randomized to the higher hemoglobin targets in these studies received generally greater doses of Epoetin alfa raises the possibility that Epoetin alfa is directly deleterious to the cardiovascular system.

The NHCT and CHOIR datasets contain detailed information about Epoetin alfa dose, making exploration of the relation between Epoetin alfa dose and adverse events possible. When considering drugs and therapeutics with dose-related risks, it is important to bear in mind that if they are titrated or administered on a periodic basis, risk is not constant throughout time, but varies with dose or cumulative dose (e.g., adriamycin and cardiac toxicity). In essence, the sponsors' analyses on ESA dose and cardiovascular events evaluate risk as a function of cumulative dose. However, if in fact ESAs pose a direct risk, it is reasonable to consider that risk varies as doses are increased and decreased (see again, Figure 1).

Methods:

The approach used was essentially the same as the one used for the analyses of serious adverse events and dynamic hemoglobin concentrations (above).

For the assessment of adverse events by dose, the cumulative weight-adjusted weekly dose was calculated for each subject, and divided by weeks on study to provide the average Epoetin alfa dose in U/kg/week. In CHOIR, a small number of subjects had no recorded weight, and a weight of 70 kg was used for the purpose of these analyses. Weight-adjusted weekly doses were categorized in quintiles, and frequencies of serious adverse events are presented by dosing quintile.

The calculated quintiles for weight-adjusted weekly Epoetin alfa dose in the NHCT Study were:

quintile 1: dose <83.5 U/kg/week
quintile 2: dose ≥83.5 and <155.4 U/kg/week
quintile 3; dose ≥155.4 and <252.1 U/kg/week

quintile 4: dose ≥252.1 and <423.5 U/kg/week
quintile 5: dose ≥423.5 U/kg/week

The calculated quintiles for weight-adjusted weekly Epoetin alfa dose in the CHOIR Study were:

quintile 1: dose <29.7 U/kg/week
quintile 2: dose ≥29.7 and <63.5 U/kg/week
quintile 3; dose ≥63.5 and <112.9 U/kg/week
quintile 4: dose ≥112.9 and <218.4 U/kg/week
quintile 5: dose ≥218.4 U/kg/week

Method for Calculating Dynamic Dose and Rate of Change of Epoetin alfa Dose over Time:

For the "dynamic" assessment of adverse events by dose (and rate of change of dose), each subject's data were divided into "periods," separated by dates when doses were reported. The NHCT Study datasets contained a record for each week on study, whether or not an Epoetin alfa dose was actually recorded. In the CHOIR dataset, a number of records were separated in time by intervals greater or less than one week, necessitating a slightly different approach for the calculation of slope.

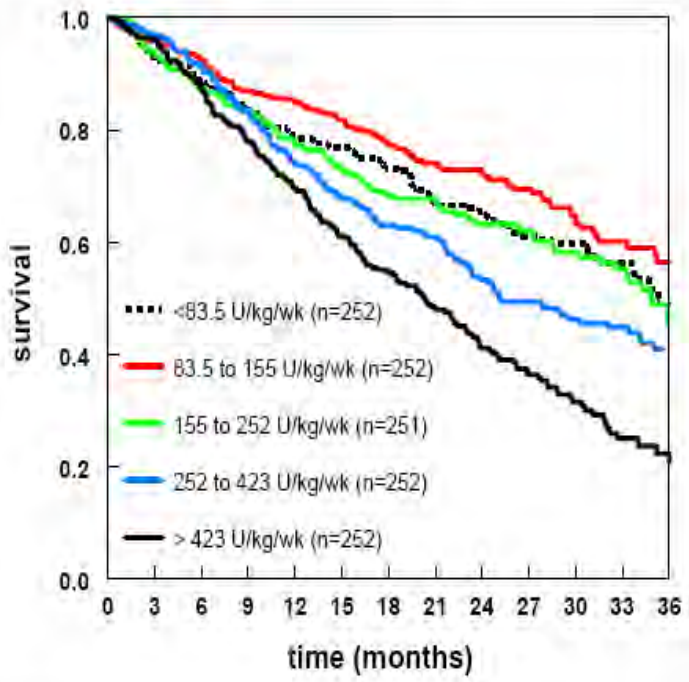
NHCT Study:
For each date for which a dose was recorded or expected, slope was calculated using all hemoglobin values obtained over a two-week period (i.e., 3 dose values: present date, one week prior to date, and two weeks prior to date). If <2 dose values were reported over a two-week period, such that a slope could not be calculated, an attempt was made to calculate slope over a 4-week period. In some cases, missing data precluded calculation of slope (e.g., slope could not be assessed on the date of the initial visit). Negative slopes (decreasing dose) were divided into quintiles separately from positive slopes. Zero slope (constant dose) was considered as a separate category.

CHOIR Study:
All records within 4 weeks of the index date were used to calculate slope, using the actual dates recorded. Missing data were not interpolated.

Results:

Tabulated frequencies of cardiovascular serious adverse events are displayed by mean cumulative weight-adjusted Epoetin alfa dose quintiles for the NHCT Study in Table 3, and for CHOIR in Table 4. The doses were much lower in the CHOIR Study relative to the NHCT Study. Presumably this largely reflects the more advanced renal disease in dialysis patients in the NHCT Study, but other factors may have been operational as well. In the NHCT Study, there was a striking association between cumulative weight-adjusted Epoetin alfa dose and the frequencies of cardiovascular serious adverse events, and importantly, mortality. Figure 12 shows the results of the Kaplan-Meier analysis for mortality by quintiles of weight-adjusted cumulative Epoetin alfa dose. The analysis was not adjusted for underlying cardiovascular risk

Figure 12: The NHCT Study – Relation Between Cumulative Weight-Adjusted Epoetin alfa Dose and Survival



factors, but does seem to contradict the authors of the NHCT Study paper, who commented "A higher Epoetin dose was not associated with increased mortality."[4] The present review included data with slightly longer follow-up and more deaths, which may account for this difference.

By analogy, if an analysis similar to that depicted in Figure 12 were performed to show the relation between furosemide dose and mortality in patients with CHF, it would suggest that furosemide is toxic! Such limitations should be kept in mind when interpreting these data.

Table 3 shows increased frequencies for a number of cardiovascular serious adverse events in subjects who received higher cumulative doses of Epoetin alfa. The risks of intravascular volume-related serious adverse events (CHF or pulmonary edema) as well as some thrombotic events (thrombosis of vascular access, thrombophlebitis, arteriosclerosis, peripheral vascular disease, and cerebrovascular accident) are particularly notable in the higher dose quintiles. Overall event rates were far lower in the pre-dialysis Epoetin alfa patient population in the CHOIR Study (Table 4), and there are no trends suggesting dose-related toxicity in CHOIR.

[4] Besarab A, Bolton WK, Browne JK, et. al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. N Engl J Med. 1998;339:584-590.

Table 3:
Serious Cardiovascular Adverse Events in the NHCT Study by Mean Epoetin Alfa Dose Quintile

	Dose Category (U/kg/week)				
	<83.5	83.5 to <155.4	155.4 to <252.1	252.1 to <423.5	>=423.5
n in quintile	**252**	**252**	**251**	**252**	**252**
any cardiovascular serious adverse event	65%	62%	73%	77%	**85%**
death	40%	34%	42%	50%	**66%**
congestive heart failure or pulmonary edema	17%	18%	19%	21%	**28%**
congestive heart failure	14%	15%	16%	17%	**24%**
pulmonary edema	4%	4%	5%	6%	7%
edema, non-pulmonary, fluid retention; overload	6%	6%	6%	6%	**10%**
EF decreased, LV dysfunction, cardiomyopathy	1%	2%	2%	1%	2%
cardiac arrest; asystole, sudden death	9%	7%	8%	9%	**15%**
acute myocardial infarction	12%	8%	6%	9%	13%
coronary artery disease, coronary heart disease	23%	24%	22%	21%	28%
myocardial ischemia	0%	0%	0%	0%	0%
angina	15%	21%	18%	15%	**25%**
PTCA or CABG	0%	0%	1%	1%	0%
thrombosis of vascular acsess	15%	19%	22%	29%	33%
ischemia (non-coronary, non-CNS)	1%	2%	1%	2%	3%
thrombophlebitis, thrombosis, phlebitis	16%	19%	22%	**31%**	**35%**
deep venous thrombosis	0%	0%	0%	2%	1%
arteriosclerosis, vascular disease, peripheral vascular disease	11%	10%	15%	14%	20%
peripheral vascular disease	10%	8%	14%	13%	**19%**
hypertension, blood pressure increased	1%	1%	1%	3%	3%
embolism	1%	0%	0%	1%	1%
pulmonary embolus	1%	0%	0%	1%	0%
cerebrovascular accident, transient ischemic attack	5%	8%	7%	8%	12%
cerebrovascular accident	5%	7%	6%	5%	11%
transient ischemic attack	1%	1%	1%	2%	1%
cerebral ischemia, anoxia (non-stroke)	0%	0%	0%	1%	2%
ventricular tachycardia	2%	1%	0%	1%	1%
ventricular fibrillation	1%	1%	1%	2%	1%

Table 4:
Serious Cardiovascular Adverse Events in the CHOIR Study by Mean Epoetin Alfa Dose Quintile

	Dose Category (U/kg/week)				
	<29.7	29.7 to <63.5	63.5 to <112.9	112.9 to <218.4	>=218.4
n in quintile	**276**	**275**	**275**	**275**	**276**
any cardiovascular serious adverse event	22%	21%	21%	28%	23%
death	8%	6%	6%	5%	6%
congestive heart failure or pulmonary edema	10%	10%	9%	12%	10%
congestive heart failure	10%	9%	8%	11%	9%
pulmonary edema	0%	1%	0%	1%	0%
edema, non-pulmonary, fluid retention; overload	2%	0%	2%	1%	1%
EF decreased, LV dysfunction, cardiomyopathy	1%	1%	0%	0%	0%
cardiac arrest; asystole, sudden death	3%	2%	1%	1%	3%
acute myocardial infarction	3%	3%	5%	2%	1%
coronary artery disease, coronary heart disease	4%	4%	4%	6%	4%
coronary artery disease, worse or progressive	2%	1%	1%	1%	1%
myocardial ischemia	1%	0%	0%	0%	0%
angina	0%	2%	2%	3%	2%
Angina, unstable, acute coronary syndromw, rule out MI, post-infarction angina	0%	1%	1%	1%	1%
PTCA or CABG	0%	0%	0%	1%	1%
thrombosis of vascular acsess	0%	0%	0%	1%	0%
ischemia (non-coronary, non-CNS)	0%	0%	0%	0%	0%
thrombophlebitis, thrombosis, phlebitis	0%	1%	0%	1%	0%
deep venous thrombosis	1%	1%	0%	2%	1%
arteriosclerosis, vascular disease, peripheral vascular disease	1%	1%	1%	2%	3%
peripheral vascular disease	0%	1%	1%	2%	2%
hypertension, blood pressure increased	3%	1%	1%	3%	4%
embolism	1%	1%	0%	0%	0%
pulmonary embolus	1%	1%	0%	0%	0%
cerebrovascular accident, transient ischemic attack, subarachnoid hemorrhage	3%	3%	3%	5%	3%
cerebrovascular accident	2%	2%	2%	4%	1%
subarachnoid hemorrhage	0%	0%	0%	0%	0%
transient ischemic attack	1%	1%	1%	1%	1%
cerebral ischemia, anoxia (non-stroke)	0%	1%	0%	0%	0%
ventricular tachycardia	0%	1%	0%	0%	1%
ventricular fibrillation	0%	0%	0%	0%	0%

Epoetin alfa Responsiveness and Serious Adverse Events:

The sponsors cite summaries of analyses by Kilpatrick (2007) and Singh (2006) that show, using Cox proportional hazards methodology, associations between ESA responsiveness and risk of cardiovascular events in the NHCT and CHOIR data, respectively. They make the case that the association between ESA dose and outcome is substantially influenced by underlying health status and ESA-responsiveness. The sponsors believe that additional analyses of ESA-hyporesponsiveness might lead to improved dosing guidance in ESA labeling.

Indeed, characterization of ESA-responsiveness for individual patients could provide a means to enhance risk management. Theoretically, ESA-responsiveness would constitute an index that reflects the increase in hemoglobin concentration observed in response to a particular dose of an ESA. This concept of responsiveness is somewhat different, but related to, dosing requirements, which are a measure of the ESA doses needed to maintain a particular hemoglobin concentration. In practice, however, quantification of ESA-responsiveness is difficult. In patients with fluctuations of hemoglobin and frequent dose adjustments, it is difficult to calculate a useful index of responsiveness. Conversely, patients with relatively stable hemoglobin concentrations, in whom few attempts are made to increase hemoglobin, pose another problem. Computation of the ratio of hemoglobin concentration to ESA dose can be used to provide a simple index of ESA-responsiveness; however, the relation between ESA dose and hemoglobin is non-linear, and such an index is primarily driven by the ESA dose.

This reviewer conducted analyses of frequencies of cardiovascular serious adverse events by ESA-responsiveness, where responsiveness was defined for each subject as their cumulative weight-adjusted Epoetin alfa dose divided by their mean on-study hemoglobin concentration, divided into quintiles of relative responsiveness. The results of these analyses for the NHCT Study are shown in Table 5, tabulated by hemoglobin target group. They are not substantially different from frequencies of serious adverse events tabulated by dose quintile alone (Table 3).

The sponsors point out that the NHCT and CHOIR Studies provide unique opportunities to assess ESA-responsiveness. For subjects randomized to the higher hemoglobin target in these studies, attempts were made to increase hemoglobin upon study entry. For example, in the NHCT Study, subjects randomized to "normal" hemoglobin were to have their Epoetin alfa doses increased by a factor of 1.5 on study entry.

Approach to ESA-Responsiveness:

For the NHCT Study, Kilpatrick et al (2007) calculated an EPO response index for each subject, defined as the ratio of weekly hematocrit change per Epoetin alfa dose increase (1000 U/week). The numerator of the index was the slope of each subject's weekly hematocrit over the first 3 study weeks. The denominator was the absolute Epoetin alfa dose increase, calculated as the change in weekly Epoetin alfa dose from the first pre-study week to the first on-study week. Subjects were categorized into EPO response index quartiles to compare outcomes.

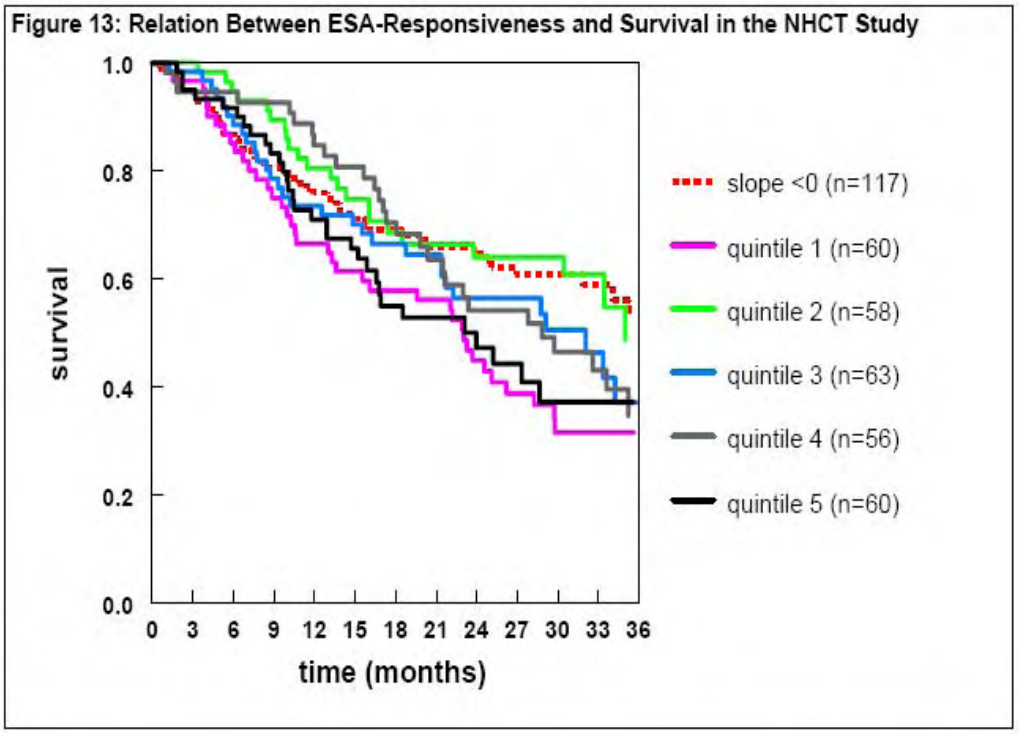
This reviewer took a somewhat different approach to the NHCT data. At the time of enrollment, subjects in the NHCT Study were to have a stable hemoglobin concentration between 27% and 33% for 4 weeks, while receiving Epoetin alfa therapy. Those who were randomized to the "normal" (higher) hemoglobin target were to have their Epoetin alfa doses increased by 50% upon study entry. ESA-responsiveness was calculated for subjects randomized to the higher hemoglobin target, if they received a constant weekly Epoetin alfa dose for two to six weeks following study entry. Responsiveness was calculated as the slope of the hemoglobin-time

relation (using linear regression) throughout the time that a constant Epoetin alfa dose was maintained (but through no more than six weeks). In essence, this assessment of ESA-responsiveness reflects the rapidity of hemoglobin rise in a stable patient, in response to a 50% increase in Epoetin alfa dose.

Results:

Using this definition, ESA-responsiveness could be calculated for 414 subjects out of the total of 618 subjects randomized to a "normal" hematocrit. One hundred seventeen (117) of these subjects had a negative slope (decreasing hemoglobin concentration, despite a 50% increase in Epoetin alfa dose). The remaining 297 subjects with a zero or positive slope were divided into quintiles (quintile 1: lowest responsiveness; quintile 5: highest responsiveness).

Figure 13: Relation Between ESA-Responsiveness and Survival in the NHCT Study



The Kaplan-Meier analysis is shown in Figure 13. There is no consistent pattern suggesting a relation between ESA-responsiveness and survival. Survival in the lowest and highest ESA-responsiveness quintiles tends to be the worst (quintiles 1 and 5, respectively). Moreover, the 117 subjects who experienced a *decline* in serum hemoglobin concentration upon entry into the NHCT Study, despite an Epoetin alfa dose increase (slope <0), fared quite well in this analysis.

The results of this analysis are at apparent odds with the concept that patients who require higher doses of ESAs for a given effect are poor responders with generally compromised health, and are more likely to experience adverse events. It is also contrary to the findings of Kilpatrick and Singh. In light of these questions, and given the importance of this concept, it deserves further study.

Table 5:
Serious Cardiovascular Adverse Events in the NHCT Study by Mean Epoetin Dose/Mean Hgb Quintile

	Lower Hgb Target Quintile (U/kg/wk/g/dL) less responsive →					Higher Hgb Target Category (U/kg/wk/g/dL) less responsive →				
	1	2	3	4	5	10	20	30	40	50
n in quintile	126	125	126	125	126	128	126	125	126	126
any cardiovascular serious adverse event	63%	69%	63%	79%	80%	57%	70%	75%	80%	89%
death	44%	39%	33%	46%	57%	29%	38%	47%	62%	69%
congestive heart failure or pulmonary edema	19%	22%	17%	22%	25%	12%	17%	22%	21%	29%
congestive heart failure	16%	18%	17%	18%	21%	9%	13%	18%	19%	23%
pulmonary edema	5%	6%	3%	6%	7%	2%	5%	6%	3%	10%
edema, non-pulmonary, fluid retention; overload	6%	6%	6%	2%	9%	6%	9%	6%	5%	14%
EF decreased, LV dysfunction, cardiomyopathy	2%	0%	2%	1%	2%	2%	2%	0%	2%	2%
cardiac arrest; asystole, sudden death	9%	10%	6%	12%	12%	4%	6%	10%	14%	14%
acute myocardial infarction	12%	10%	9%	6%	8%	9%	9%	9%	14%	11%
coronary artery disease, coronary heart disease	20%	24%	21%	31%	20%	22%	17%	20%	29%	30%
angina	12%	21%	19%	26%	17%	15%	13%	14%	24%	26%
Angina, unstable, acute coronary syndrome, rule out MI, post-infarction angina	0%	0%	0%	1%	0%	0%	0%	0%	1%	1%
PTCA or CABG	0%	0%	0%	1%	0%	2%	0%	2%	1%	0%
thrombosis of vascular acsess	11%	19%	16%	24%	25%	19%	25%	31%	28%	38%
ischemia (non-coronary, non-CNS)	2%	1%	2%	0%	2%	0%	2%	1%	2%	5%
thrombophlebitis, thrombosis, phlebitis	12%	19%	17%	25%	25%	20%	26%	33%	33%	39%
deep venous thrombosis	0%	0%	1%	1%	1%	1%	1%	2%	0%	2%
arteriosclerosis, vascular disease, peripheral vascular disease	10%	14%	8%	17%	17%	7%	12%	16%	18%	20%
peripheral vascular disease	9%	14%	5%	17%	16%	6%	11%	14%	17%	17%
hypertension, blood pressure increased	2%	1%	1%	2%	2%	0%	4%	2%	4%	2%
embolism	1%	1%	0%	1%	1%	0%	1%	1%	0%	2%
pulmonary embolus	1%	1%	0%	0%	1%	0%	1%	1%	0%	1%
cerebrovascular accident, transient ischemic attack	5%	6%	10%	8%	9%	5%	9%	6%	9%	12%
cerebrovascular accident	5%	6%	8%	7%	6%	4%	7%	6%	7%	11%
transient ischemic attack	1%	1%	1%	1%	2%	1%	2%	0%	2%	0%
cerebral ischemia, anoxia (non-stroke)	0%	0%	0%	0%	2%	1%	0%	2%	1%	1%
ventricular tachycardia	2%	1%	1%	0%	2%	1%	0%	1%	0%	0%
ventricular fibrillation	1%	1%	1%	2%	2%	2%	2%	0%	0%	2%

Discussion:

The most important question regarding ESA-responsiveness can not be addressed through exploratory analyses of existing data. Regardless of whether or not ESA-responsiveness impacts risk, the issue is whether less aggressive ESA dosing, for less responsive patients, would decrease cardiovascular risk.

Conclusions and Issues for Further Consideration:

1. **Given the wide spectrum of chronic renal failure patients, does one target fit all?**

The exploratory analyses of the NHCT and CHOIR Studies, as well as analyses of the Aranesp® registrational studies, show an inverse relation between hemoglobin concentration and cardiovascular risk. Similar trends and associations have been described in observational data as well. However, counter to these findings, the NHCT and CHOIR Studies demonstrated (or strongly suggested) a survival disadvantage for subjects randomized to higher, rather than lower, hemoglobin targets. A finding (or near finding) of increased mortality, in independent studies conducted in somewhat dissimilar patient populations over the span of a decade, is both persuasive and alarming.

Based on these concerns, the ESA package inserts now carry this warning:

> **WARNINGS : Increased Mortality, Serious Cardiovascular and Thromboembolic Events**
>
> "PROCRIT®/ARANESP® and other erythropoiesis-stimulating agents (ESAs) increased the risk for death and for serious cardiovascular events when administered to target a hemoglobin of greater than 12 g/dL….A rate of hemoglobin rise of greater than 1 g/dL over 2 weeks may also contribute to these risks.

Although this warning seems appropriate on its face, the CHOIR hemoglobin target of 13.5 is not much greater than the recommended maximum hemoglobin concentration in labeling (12 g/dL). More importantly, CHOIR enrolled pre-dialysis patients with less advanced disease than many of the patients who receive ESAs. CHOIR tells us that a hemoglobin target 13.5 g/dL is excessive for the pre-dialysis population. The optimum target in a dialysis population is likely less than 13.5 g/dL, but its actual value is unknown. An ESA dosing algorithm that is reasonable and safe for one patient may be overly aggressive for another. A target of 12 g/dL may pose excessive risk to a patient with advanced renal disease and a low hematocrit, who is poorly responsive to ESAs. For such patients, the labeling suggests a search for causative factors, but does not explicitly state a maximum ESA dose, or what constitutes an adequate attempt to raise hemoglobin. The critical, unanswered question is whether poorly responsive patients might incur less cardiovascular risk if attempts were not made to raise their hemoglobin to this "ideal" concentration, and/or if there were a recommendation for a maximum dose.

Recommendation:

Careful, prospective, randomized studies should be conducted to determine the "ideal" hemoglobin target, recognizing that it may differ depending on a number of factors (e.g., chronicity of renal disease; other patient-specific characteristics). Studies should be conducted to determine whether ESA-unresponsive patients can be identified, and, if so, how to best manage their risk.

2. **The ESA package insert suggests avoiding rates of hemoglobin increase exceeding 1 g/dL in any 2-week period, but does it provide adequate advice on how to do that?**

Exploratory analyses from the NHCT and CHOIR Studies, along with analyses from the Aranesp® registrational studies, suggest that increases in hemoglobin concentration exceeding 1 g/dL/ two weeks should be avoided. This information is included as a warning in ESA labeling. However, this reviewer questions whether the package insert provides an optimal strategy for the practitioner to avoid rapid changes in hemoglobin concentration and excursions over target. This is the advice from the ESA package inserts under **DOSAGE AND ADMINISTRATION : Chronic Renal Failure Patients : Dose Adjustment:**

> "The dose should be adjusted for each patient to achieve and maintain a target the lowest hemoglobin level sufficient to avoid the need for RBC transfusion and not to exceed 12 g/dL.
>
> Increases in dose should not be made more frequently than once a month. If the hemoglobin is increasing and approaching 12 g/dL, the dose should be reduced by approximately 25%. If the hemoglobin continues to increase, doses should be temporarily withheld until the hemoglobin begins to decrease, at which point therapy should be reinitiated at a dose approximately 25% below the previous dose. If the hemoglobin increases by more than 1 g/dL in a 2-week period, the dose should be decreased by approximately 25%."

This reviewer is not aware of any data showing that the guidelines are particularly successful in preventing excessive and unnecessary changes in hemoglobin.

Recommendation:

The sponsors should be encouraged to develop safer dosing algorithms. Such algorithms could take into account a patient's present hemoglobin concentration, previous hemoglobin concentrations (i.e., present rate of change), and other parameters as well. The sponsors have available to them a wealth of data that could be used for development of improved dosing paradigms. Once developed, such an algorithm(s) could be tested in a prospective, randomized study against current practice, as directed by the package insert. This reviewer appreciates the value of providing simple and straightforward advice in labeling; however, the goal here is to reduce life- and limb-threatening risks. Though a complex dosing paradigm might be difficult to include in product labeling, it would be feasible in clinical practice, because it could be made available to practitioners using computer software, or through a central website.

3. **Does the package insert explain the undesirable nature of "cycling," and how to avoid it?**

Exploratory analyses of the NHCT and CHOIR Studies show associations between cardiovascular risk, rapid changes in hemoglobin concentration, and rapid changes in ESA dose. Such changes are the hallmark of "cycling." Thus, efforts should be directed to minimize cycling, to maintain a consistent ESA dose and hemoglobin response. The reduction of cycling has the potential to reduce cardiovascular risk.

Recommendation:

Importance of the avoidance of "cycling" should be noted in labeling. By carrying out recommendation #2 (above) to develop better dosing algorithms, cycling might be reduced.

31