# DEVELOPMENT, PREDICTION, AND TREATMENT OF ANEMIA IN PATIENTS WITH LYMPHOMA/MULTIPLE MYELOMA: FINDINGS OF TWO EUROPEAN SURVEYS (ECAS AND BEPOS)

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## ABSTRACT

Quality of life (QOL) in cancer patients is adversely affected by several factors, including disease- or treatment-related anemia. Between January 2001 and February 2002, the European Cancer Anaemia Survey (ECAS) was conducted to provide information on pervasiveness of cancer-related anemia, impact of anemia on World Health Organization (WHO) performance status, risk factors for its development, and anemia treatment practices in Europe. Briefly, a total of 15,367 patients were enrolled, of whom 2360 had lymphoma or multiple myeloma (L/MM). Data analysis showed 53% of L/MM patients were anemic (hemoglobin [Hb] <12 g/dL) at enrollment and 73% were anemic at some time during the survey. Low Hb levels correlated significantly with WHO performance scores of 3 or 4 ($P$ <0.001; R = 0.352).

The ECAS data were additionally analyzed to determine patient and disease characteristics that predicted anemia development and to construct a model for identifying patients at risk. Using logistic regression on the L/MM incidence group (patients who were not anemic and not being treated for cancer at enrollment, started chemotherapy during ECAS, and had at least 2 chemotherapy cycles during the survey),

4 variables were found to significantly predict anemia development. Initial Hb, persistent/recurrent disease, female gender, and treatment with platinum-based chemotherapy were found to independently predict anemia ($P$ <0.001), with an area under the receiver operating characteristic (ROC) curve of 0.821 (95% CI; 0.763–0.878), indicting acceptable predictive accuracy of the model. Three levels of risk (low [24%], moderate [51%], and high [72%]) for developing anemia were calculated from the model ($\chi^2_{(2)} = 112.6$; $P$ <0.001).

Mean time required for anemia development was 9.0 weeks to reach Hb of <12 g/dL, 11.1 weeks to reach Hb of <11 g/dL, and 13.3 weeks to reach Hb of <10 g/dL. Notably, only 46% of anemic L/MM patients received anemia treatment.

Subsequently, a recent (2003) survey, the Belgian Erythropoietin Survey (BEPOS), extended the information gained through ECAS by examining use of recombinant human erythropoietin (rHuEPO) in patients receiving chemotherapy. Specifically, BEPOS documented when rHuEPO treatment was started, dosing schedules and dosage adjustments, length of treatment, impact of iron supplementation on rHuEPO treatment, and outcomes. Patients enrolled had either solid tumors (non–small-cell lung cancer, breast cancer) or hematologic malignancies (MM, Hodgkin's disease [HD], non-Hodgkin's lymphoma [NHL]). Interim results suggest that 72% of BEPOS patients began rHuEPO during the first 2 chemotherapy cycles, with an overall median Hb value of 10.1 g/dL at treatment initiation. For hematologic malignancy patients, the median Hb at treatment initiation was ~10 g/dL for HD; in NHL and MM, the median Hb was >9 g/dL

to <10 g/dL. Mean time for all patients to achieve a 2-g/dL increase in Hb in the absence of transfusion was 6.4 weeks; mean time for NHL patients (6.3 wks) was similar, while mean time for MM patients (9.1 wks) was longer, more in line with that seen in clinical trials.

Achievement of the 2-g/dL increase in Hb after 6.4 weeks determined in BEPOS is consistent with increases of ~1 g/dL after 4 weeks and ~2 g/dL after 8 weeks noted in studies of epoetin alfa.(Demetri, 2001; Littlewood, 2003) Using the large ECAS database, an anemia risk model has been established that should help identify patients at risk for anemia, so that administration of rHuEPO can be initiated expeditiously, before Hb declines to considerably lower levels and/or anemia symptoms, including impaired QOL, develop.

**INTRODUCTION**

- Anemia and its associated symptoms affect all aspects of quality of life (QOL) in hematologic cancer patients(Ludwig, 2001; LaVerde, 2002; Littlewood, 2002); anemia can also have prognostic significance, such as in multiple myeloma (MM), or be a significant indicator of disease stage, such as in chronic lymphocytic leukemia (CLL)(Littlewood, 2002)
- The European Cancer Anaemia Survey (ECAS), a prospective, epidemiological, observational survey, was conducted in cancer treatment centers throughout 24 European countries between January 2001 and February 2002, with patients followed for up to 6 months, to provide information on pervasiveness of cancer-related anemia

(hemoglobin [Hb] <12 g/dL); impact of anemia on World Health Organization (WHO) performance status; risk factors for its development; and anemia treatment practices(Ludwig, 2004a; Ludwig, 2004b)

- Overall findings from ECAS and results from subgroup analysis of patients with lymphoma (L)/MM have been published previously.(Ludwig, 2004a; Birgegard, 2002) A total of 15,367 cancer patients were enrolled in ECAS, of whom 2360 had L/MM. Data analysis showed that 53% of L/MM patients were anemic at enrollment and 73% were anemic at some time during the survey. Low Hb levels correlated significantly with poor WHO performance scores of 3 or 4 ($P$ <0.001; $R$ = 0.352)
- Results from additional analyses of ECAS data to evaluate timing of anemia development in L/MM patients who received chemotherapy, to determine L/MM patient and disease characteristics that predicted anemia development during chemotherapy, and to construct a model for identifying L/MM patients at risk for anemia are reported here. Also reported are interim results from a recent (2003) prospective survey, the Belgian Erythropoietin Survey (BEPOS), conducted to examine the use of recombinant human erythropoietin (rHuEPO; epoetin) in cancer patients receiving chemotherapy

## ECAS METHODS

### Survey Design

- Methods used to conduct ECAS have been previously reported.(Ludwig, 2004a) Briefly, adult patients with solid or hematologic tumors were eligible for enrollment regardless of disease status or cancer treatment. ECAS data were collected for up to

six data points or 6 months of regularly scheduled clinic visits. Enrollment data included age, gender, tumor type (according to ICD-9 code) and stage, disease status, performance status, weight, and hematologic laboratory values. Cancer treatments and anemia therapy within 30 days of survey enrollment and at enrollment were recorded. Malignancies were categorized into 9 groups, one of which was L/MM. Follow-up data included weight, performance status, cancer treatment, number of current cycle for patients receiving chemotherapy, hematologic laboratory values, and anemia treatment. Performance scores throughout the survey were recorded according to the WHO scale of 0 to 4. Anemia was defined as Hb <12 g/dL.

***Patient Populations***

- Mean time to anemia development was calculated using all patients with L/MM who were not anemic at enrollment but developed anemia during ECAS. These patients could have been receiving chemotherapy at enrollment
- Frequency of anemia treatment was calculated using all patients who were ever anemic during ECAS
- The prediction of anemia was calculated using the *chemotherapy incidence population* of patients defined as patients who were not anemic and not receiving chemotherapy or anemia treatment at enrollment, began chemotherapy during ECAS, and had at least 2 chemotherapy cycles during the survey

**Analyses Methods for Anemia Prediction**

- Objectives of these analyses were to determine patient and disease characteristics that predicted anemia development, and to construct a model for identifying patients at risk for anemia
- Potential predictor variables were established a priori and limited to data available at enrollment:
  - tumor characteristics: tumor site, disease status, tumor stage
  - demographics: gender, age group, geographic region of Europe
  - laboratory parameters: ~~high~~ white blood cell (WBC) count, ~~high~~ platelet count, Hb at enrollment
  - other patient attributes: WHO performance score, body mass index ([BMI] = weight [kg] ÷ height $[m]^2$), platinum versus nonplatinum chemotherapy regimen
- Continuous potential predictors (eg, Hb at enrollment, WBC, platelets, BMI) were examined by 10% percentiles for associations with the outcome, and subjectively grouped into categorical strata with a referent category. Ordinal variables (eg, tumor type, WHO performance score, age group) were examined and grouped into fewer variables when initial categories had similar associations with the outcome
- Potential predictors were recorded to be dichotomous, which allowed evaluation of Mantel-Haenszel unadjusted odds ratios (ORs) and 95% confidence intervals (CIs)
- Dichotomized variables were entered into a logistic regression equation to simultaneously evaluate the predictors. Starting with the maximum model, the most parsimonious model was developed with backwards elimination using Wald *P* values for each predictor and maximum likelihood methods (–2 log likelihood ratio tests) to

compare model iterations. Several variables were recharacterized during the modeling process to improve the model's predictive ability (eg, disease status was recharacterized from a trichotomous variable of three categories to one dichotomous variable of persistent/recurrent cancer vs all others)

- The logistic regression model results were transformed into Anemia Risk Scores (ARSs). Individual predictive variables were weighted according to their inherent relationship and given an ARS. ARSs for variables could be added together (plus a constant of 50 to produce a positive number) to attain a Total Anemia Risk Score (TARS)
- Sensitivity, (the percentage of anemic patients correctly identified), specificity (the percentage of nonanemic patients correctly identified), and positive predictive value ([PPV] the percentage of positive anemia predictions that are correct) for all possible values of TARSs were calculated in order to evaluate the overall accuracy of the prediction (area under the receiver operating characteristic [ROC] curve) and to further develop the risk model

**BEPOS Methods**

- BEPOS extended information gained through ECAS by examining epoetin use in patients with varying tumor types and disease stages receiving chemotherapy between January 3, 2003 and June 30, 2003 in participating Belgian centers
- Patients enrolled were adults (age ≥18 years) with solid tumors (non–small-cell lung cancer, breast cancer) or hematologic malignancies (MM, Hodgkin's disease [HD], non-Hodgkin's lymphoma [NHL])

- The following data were collected from the start of epoetin treatment:
  - disease status and anti-cancer treatment
  - when epoetin treatment was initiated and how long it continued
  - epoetin dosing schedules and dosage adjustments
  - laboratory values (Hb levels, iron parameters)
  - impact of iron supplementation on epoetin treatment outcomes
- Interim analysis was conducted

## RESULTS FROM ECAS

### Time to Anemia

- Six hundred seventy-eight patients with L/MM were not anemic at enrollment but became anemic during ECAS
- Mean time required for anemia development in these patients was 9.0 weeks to reach Hb <12 g/dL, 11.1 weeks to reach Hb of <11 g/dL, and 13.3 weeks to reach Hb <10 g/dL

### Anemia Treatment

- Overall 72.9% of patients with L/MM were anemic during ECAS
- Notably, only 46% of anemic L/MM patients received any anemia treatment during ECAS

**Prediction of Anemia**

- One hundred ninety-seven L/MM patients met the criteria for inclusion in the chemotherapy incidence group
- Using logistic regression, 4 variables were found to significantly ($P$ <0.001) and independently predict anemia development: initial Hb, persistent/recurrent disease, female gender, and treatment with platinum-based chemotherapy
- The ARSs assigned to these predictive variables are shown in Table 1. As initial Hb is a continuous variable, not a dichotomous value as with the other risk factors, a constant of 50 was added in order to produce a positive TARS
- Table 2 shows the calculations of sensitivity, specificity, and positive predictive value for all possible values of TARSs
- A tool to calculate TARS for L/MM patients in clinical practice is shown in Figure 1. Figure 2 shows examples of application of this tool to calculate TARSs in L/MM patients and determination of anemia risk based on the model
- Figure 3 shows a plot of sensitivity, specificity, and positive predictive value for all possible values of TARSs. The intersection point of specificity and positive predictive value on this plot determined the pivotal TARS of 45
- An area under the ROC curve of 0.821 (95% CI: 0.763–0.878) indicated acceptable predictive accuracy of the model (Figure 4)
- Three levels of risk for developing anemia were calculated from the model ($\chi^2_{(2)} = 112.6$; $P$ <0.001) (Figure 5)
  - low (24%): TARS ≤40
  - moderate (51%): TARS 41–50

- high (72%): TARS ≥51

**BEPOS Interim Analysis Results**

- Two hundred fourteen patients were included in this interim analysis**.** The majority of patients were female (63%), <70 years of age (76%), being treated for advanced disease (67%), had WHO scores of 0 or 1 (61%), and were receiving nonplatinum-based chemotherapy (71%)
- Seventy-two percent of BEPOS patients began epoetin during their first 2 chemotherapy cycles
- Median Hb level at initiation of epoetin treatment was 10.1 g/dL
  - median Hb at treatment initiation was ~10 g/dL for patients with HD; in patients with NHL and MM, median Hb at initiation was >9 g/dL to <10 g/dL
- Mean Hb increased 1.1 g/dL after 4 weeks of epoetin therapy to 11.1 g/dL (unrelated to transfusion)
- Overall, patients required a mean of 6.4 weeks of epoetin therapy to achieve a 2-g/dL Hb increase unrelated to transfusion
  - by tumor type, NHL patients required a mean of 6.3 weeks of therapy and MM patients required a mean of 9.1 weeks of therapy
- Figure 6 shows Hb category at start of epoetin therapy versus end of survey; at the end of the survey, 63% of patients had Hb ≥11 g/dL versus only 9% before epoetin therapy

## SUMMARY AND CONCLUSIONS

- There is a high frequency (72.5%) of anemia in L/MM patients
- Significant ($P < 0.001$) and independent predictors of anemia in patients with L/MM are:
  - initial Hb, persistent/recurrent disease, female gender, and treatment with platinum chemotherapy
  - TARS can be calculated for individual L/MM patients based on the predictors, and patients could be categorized into 1 of 3 anemia risk groups based on this score (TARS ≤40, low [24%]; TARS 41–50, moderate [51%]; TARS ≥51, high [72%])
- Results of BEPOS interim analysis demonstrated
  - treatment with epoetin resulted in a 1.1-g/dL mean Hb increase after 4 weeks in the overall population and a 2-g/dL Hb increase after a mean of 6.3 weeks and 9.1 weeks in anemic NHL and MM patients, respectively
  - by end of survey, 63% of patients had Hb ≥11 g/dL
  - findings consistent with previous studies indicating mean Hb increases of ~1 g/dL after 4 weeks and ~2 g/dL after 8 weeks of epoetin therapy and correction of mean Hb levels to ~12 g/dL in anemic hematologic cancer patients undergoing chemotherapy(Demetri, 2001; Littlewood, 2003)
- Data from both ECAS and BEPOS suggested that anemia treatment is not optimal in anemic L/MM patients undergoing chemotherapy
  - only 47.4% of anemic L/MM patients received any anemia treatment

  - median Hb at epoetin initiation was ~10 g/dL, suggesting that half of the patients received anemia treatment below the recommended intervention level of 10 g/dL(Rizzo, 2002)

- Development of an anemia risk model helps clinicians predict a patient's risk of developing anemia and initiate effective treatment such as epoetin in a timely manner, before Hb declines to considerably lower levels and/or anemia symptoms, including impaired QOL, develop

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**REFERENCES**

Birgegard G, Ludwig H, Nortier J, Schrijvers D. Despite high prevalence of anemia and impact on performance status (PS), anemia treatment rate is low in multiple myeloma/lymphoma (MM/L) patients according to European Cancer Anaemia Survey (ECAS) [abstract]. *Blood.* 2002;100:18b. Abstract 3521.

Demetri GD, Glaspy J, Gabrilove J. Hematologic and quality of life benefits of epoetin alfa once weekly vs 3 times weekly in patients with hematologic malignancies [abstract]. *Hematol J.* 2001;1:59. Abstract 193.

La Verde G, Arienti D. Cancer-related fatigue in hematological cancer: hematologist's and patient's view. *Recenti Prog Med.* 2002;93:463-469.

Littlewood TJ, Nortier J, Rapoport B, et al, for the Epoetin Alfa Study Group. Epoetin alfa corrects anemia and improves quality of life in patients with hematologic malignancies receiving non-platinum chemotherapy. *Hematol Oncol*. 2003;21:169-180.

Littlewood T, Mandelli F. The effects of anemia in hematologic malignancies: more than a symptom. *Semin Oncol.* 2002;29(3 suppl 8):40-44.

Ludwig H, Strasser K. Symptomatology of anemia. *Semin Oncol.* 2001;28(2 suppl 8):7 14.

Ludwig H, Van Belle S, Barrett-Lee P, et al. The European Cancer Anaemia Survey (ECAS): A large, multinational, prospective survey defining the prevalence, incidence, and treatment of anaemia in cancer patients. *Eur J Cancer.* 2004~~a~~;40:2293-2306.

~~Ludwig H~~, Van Belle S, Ludwig H, Birgegård G, Gascón P~~, Van Belle S, for the ECAS Advisory Board and Participating Centers.~~ Prediction of anemia ~~prediction~~ in cancer patients: results of logistic regression modeling and validation based on the European Cancer Anaemia Survey (ECAS) [abstract]. *Ann Oncol.* 2004~~b~~ 15: 461a **[Citation to be updated after ESMO.]**

Rizzo JD, Lichtin AE, Woolf SH, et al. Use of epoetin in patients with cancer: evidence based clinical practice guidelines of the American Society of Clinical Oncology and the American Society of Hematology. *J Clin Oncol.* 2002;20:4083-4107.

**Table 1. Anemia Risk Scores for Predictive Variables in L/MM Patients**

| Predictive Variable | Anemia Risk Score* |
|---|---|
| Initial Hb† | –8 for each g/dL > 12 at baseline |
| Persistent/recurrent disease | +10 |
| Female gender | +11 |
| Treatment with platinum chemotherapy | +27 |

Hb = hemoglobin; L/MM = lymphoma/multiple myeloma.

*A constant of +50 is added to the sum of the score to produce a positive Total Anemia Risk Score number.

†Continuous variable, not a dichotomous values as with the other risk factors.

**Table 2. Sensitivity, Specificity, and PPV for Total Anemia Risk Scores**

| Total Anemia Risk Scores | Sensitivity | Specificity | PPV |
|---|---|---|---|
| 10 | 0 | 0 | 0.50 |
| 15 | 0 | 0.02 | 0.50 |
| 20 | 0 | 0.05 | 0.51 |
| 25 | 0.01 | 0.10 | 0.52 |
| 30 | 0.04 | 0.22 | 0.54 |
| 35 | 0.09 | 0.36 | 0.57 |
| 40 | 0.15 | 0.52 | 0.62 |
| 45 | 0.24 | 0.66 | 0.67 |
| 50 | 0.41 | 0.80 | 0.70 |
| 55 | 0.59 | 0.88 | 0.74 |
| 60 | 0.77 | 0.94 | 0.75 |
| 65 | 0.87 | 0.97 | 0.80 |
| 70 | 0.93 | 0.99 | 0.85 |
| 75 | 0.96 | 0.99 | 0.86 |
| 80 | 0.98 | 0.99 | 0.78 |
| 85 | 0.99 | 1 | 0.83 |
| 90 | 0.99 | 1 | 0.67 |
| 95 | 1 | 1 | 1 |

PPV = positive predictive value.

**Figure 1.**

**Figure 1. Tool to Calculate L/MM Patient's Total Anemia Risk Score**

| | | Patient Values | Risk Score |
|---|---|---|---|
| Initial Hb (g/dL) | –8 for each g/dL >12 g/dL | _____ | _____ |
| Persistent/recurrent disease | +10 for yes | _____ | _____ |
| Female gender | +11 for yes | _____ | _____ |
| Treat with platinum chemotherapy | +27 for yes | | _____ |
| Subtotal patient anemia risk score | | | _____ |
| Constant | +50 | | +50 |
| **Total Anemia Risk Score** | | | ☐ |

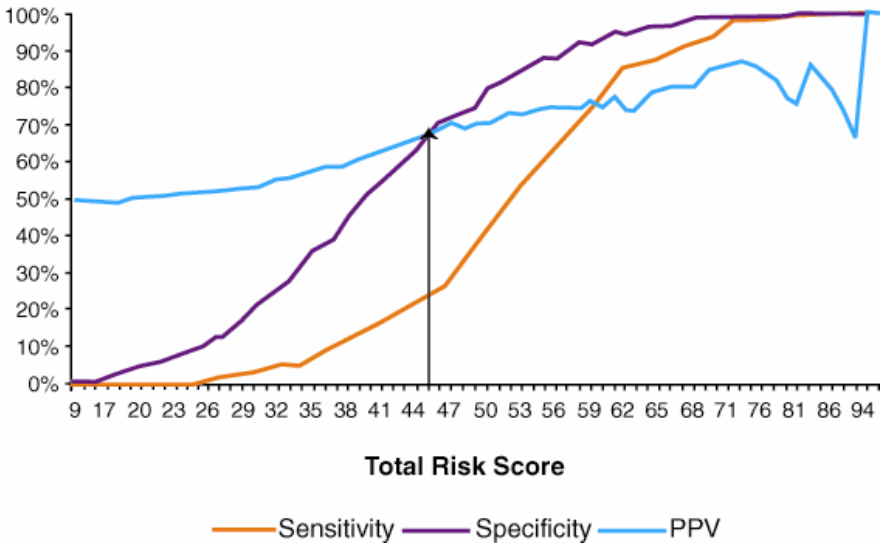
Hb = hemoglobin; L/MM = lymphoma/multiple myeloma.

**Figure 2.**

| Figure 2. Clinical Examples of L/MM Patients' Anemia Risk Using the Model | | | | | | |
|---|---|---|---|---|---|---|
| **Predictive Variable** | **Patient 1** | | **Patient 2** | | **Patient 3** | |
| | **Values** | **Risk Score** | **Values** | **Risk Score** | **Values** | **Risk Score** |
| Initial Hb (g/dL) | 14 | −16 | 14 | −16 | 12 | 0 |
| Persistent/recurrent disease | N | 0 | N | 0 | Y | +10 |
| Female gender | N | 0 | Y | +11 | Y | +11 |
| Treatment with platinum chemotherapy | N | 0 | N | 0 | N | 0 |
| Subtotal patient anemia risk score | | −16 | | −5 | | +21 |
| Constant | | +50 | | +50 | | +50 |
| **Total Anemia Risk Score** | **34 = low risk** | | **45 = moderate risk** | | **71 = high risk** | |

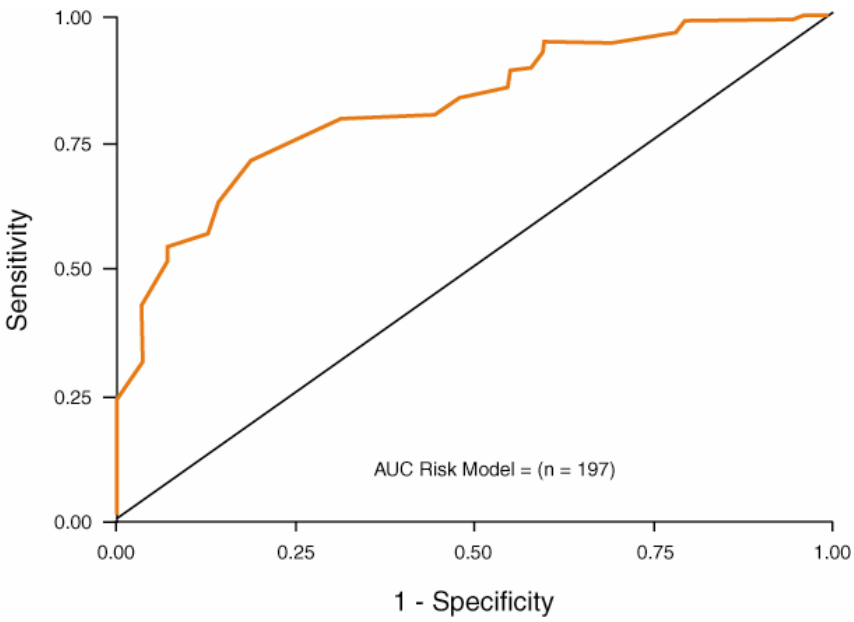
Hb = hemoglobin; L/MM = lymphoma/multiple myeloma.

**Figure 3. Sensitivity, Specificity, and PPV by Total Anemia Risk Score**



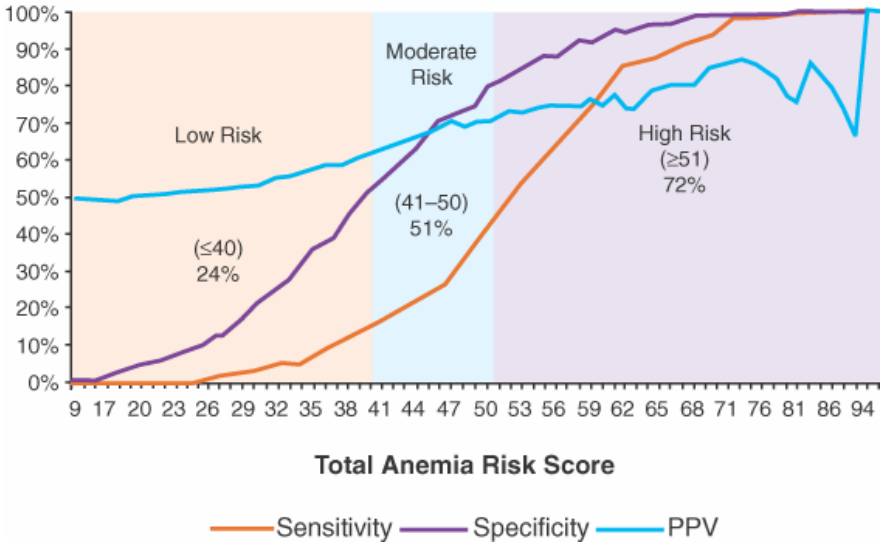

PPV = positive predictive value.

**Figure 4. Area Under the ROC Curve**




ROC = receiver operating characteristic.

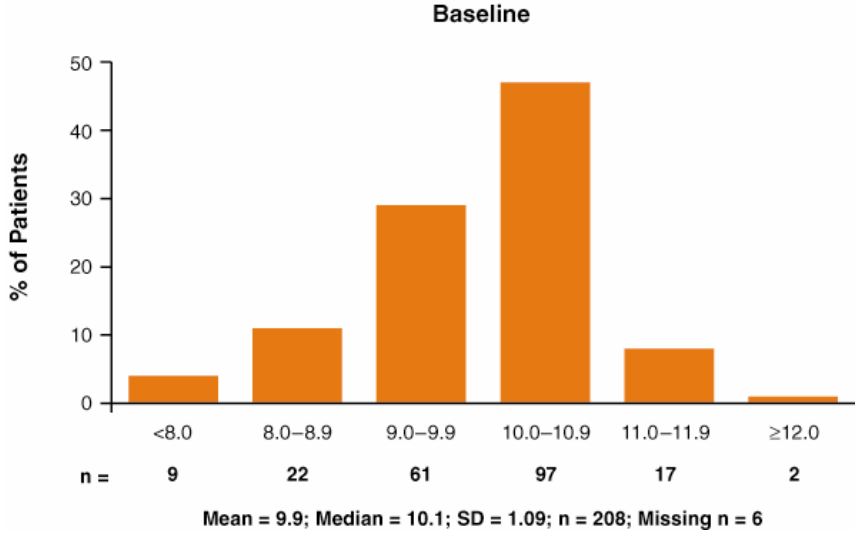
**Figure 5. Levels of Risk for Developing Anemia by Total Anemia Risk Score**



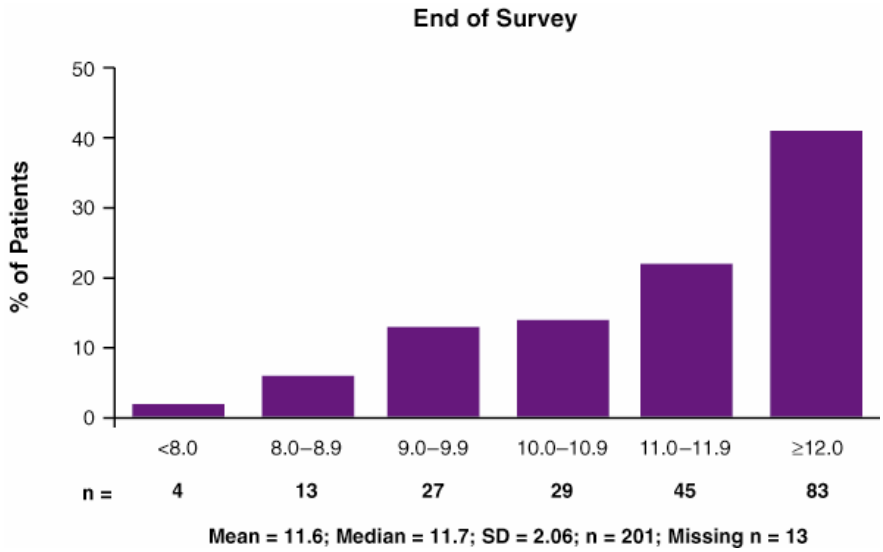

PPV = positive predictive value.

**Figure 6. Hemoglobin Category at Baseline and End of BEPOS Survey (All Patients)**

**A)**




**B)**




BEPOS = Belgian Erythropoietin Survey; Hb = hemoglobin; SD = standard deviation.