Naturally Occurring Higher Hemoglobin Concentration Does Not Increase Mortality among Hemodialysis Patients

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ABSTRACT

A small percentage of hemodialysis patients maintain higher hemoglobin concentrations without transfusion or erythropoietic therapy. Because uncertainty exists regarding the effects of higher hemoglobin concentration on mortality and quality of life among hemodialysis patients, studying this group of patients with sufficient endogenous erythropoietin may provide additional insights. The prospective, observational Dialysis Outcomes and Practice Patterns Study provides an opportunity to investigate this group. Among 29,796 patients in 12 nations, 545 (1.8%) maintained hemoglobin concentrations >12 g/dl for 4 months without erythropoietic support. This subset tended to be male, to have a longer duration of end-stage renal disease, and to not dialyze via a catheter. Cystic disease as the underlying cause of renal failure was over-represented in this group but was present in only 25%. Lung disease, smoking, and cardiovascular disease were associated with increased likelihood of naturally higher hemoglobin concentration. Quality-of-life scores were not higher among this subset compared with the other patients. Unadjusted mortality risk for patients with hemoglobin >12 g/dl and no erythropoietic therapy was lower than for the other patients, but after thorough adjustment for case mix, there was no difference between groups (relative risk, 0.98; 95% CI 0.80 to 1.19). These data show that naturally occurring hemoglobin concentration >12 g/dl does not associate with increased mortality among hemodialysis patients.

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The vast majority of patients who develop advanced chronic kidney disease manifest progressive anemia. It has previously been recognized, however, that a small subset of hemodialysis (HD) patients maintain higher hemoglobin concentrations in the absence of blood transfusions or erythropoiesis-stimulating agent (ESA) therapy, but there is a paucity of literature on the subject. We are aware of only three such papers, describing 11, 78, and 21 patients, respectively.[1–3] The Dialysis Outcomes and Practice Patterns Study (DOPPS)[4,5] follows thousands of HD patients in 12 countries, providing the opportunity to investigate much larger numbers of patients who sustain hemoglobin concentrations in excess of 12 g/dl in the absence of ESA therapy ("Endogenous erythropoietin [EPO]" patients). Uncertainty exists regarding the effects of higher hemoglobin concentration on mortality and

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quality of life among HD patients, and study of this Endogenous EPO group allows additional insights. The detailed collection of demographics, comorbid conditions, laboratory values, and prescriptions in the DOPPS also enables careful consideration of which factors are associated with Endogenous EPO status and adjustments to decipher the influence of Endogenous EPO status *versus* case mix on patient outcomes.

The goals of this report are to (*1*) examine the prevalence of Endogenous EPO status; (*2*) compare the characteristics of the Endogenous EPO patients with the Other group; (*3*) compare mortality between groups; (*4*) compare quality-of-life scores between groups; and (*5*) provide additional perspective to the consideration of hemoglobin concentration and clinical outcomes in HD.

RESULTS

Prevalence of Endogenous EPO Patients

Of the total 29,796 HD patients enrolled during the DOPPS for whom we received hemoglobin concentration and ESA dose at both baseline and 4 months, 545 (1.8%) met the criteria to be included in the Endogenous EPO group (see Concise Methods for group definitions). Considering only the prevalent cross-sections of patients enrolled at the onset of each phase of the study, 483 of 21,185 (2.3%) met the criteria; the significance of this observation will be addressed in the Discussion. The mean hemoglobin concentration ($\pm$ standard deviation) for the Endogenous EPO group was 13.5 $\pm$ 1.1 g/dl, and for the Other group it was 11.1 $\pm$ 1.6 g/dl. Within the Other group, the mean epoetin dose was 10,698 $\pm$ 11,626 units/wk, and the mean darbepoetin dose was 53 $\pm$ 61 μg/wk. Figure 1 shows the prevalence of Endogenous EPO patients across the nations, which varied significantly ($P < 0.0001$, χ^2). Germany had the highest percentage of Endogenous EPO patients (5.1%), whereas Belgium (1.1%), Japan (1.3%), Sweden (1.6%), and the United States (1.6%) had the lowest prevalences.

Sensitivity analyses revealed that 86% of the Endogenous EPO patients also had not received ESA therapy at the next scheduled medication reporting (8 months into the study), and 80% of these patients had also maintained a hemoglobin concentration >12 g/dl. Among the Other patients, 92% had continued to receive ESA therapy at the 8-month time point.

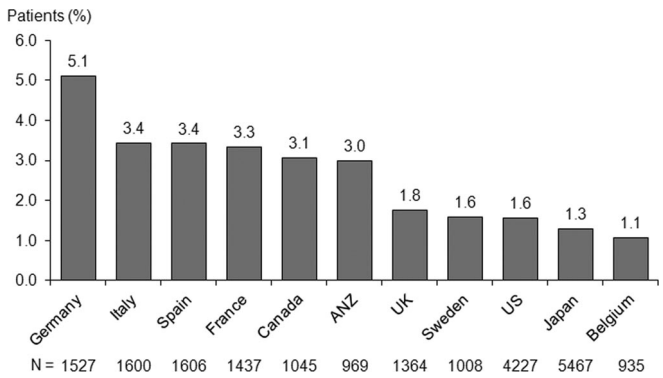

Figure 1. The prevalence of Endogenous EPO patients among the initial study phase samples varies by country (see text). ANZ, Australia/New Zealand. The numbers below figure indicate total denominator for each nation.

Characteristics of Endogenous EPO Patients

Table 1 lists the characteristics of Endogenous EPO and Other patients in each region. Table 2 shows the associations between each characteristic and the likelihood of being in the Endogenous EPO group, after adjustment for the other factors in the table. In all regions, the percentage of male patients was significantly higher among the Endogenous EPO group than among the Other patients; male gender was associated with an adjusted odds ratio (AOR) of being in the Endogenous EPO group of 3.27 (95% confidence interval [CI], 2.59 to 4.14). Mean age was typically lower among Endogenous EPO patients than Other patients. Race was not associated with altered likelihood of Endogenous EPO status. The number of years on HD was longer among the Endogenous EPO patients, and increasing vintage was highly associated with the likelihood of Endogenous EPO status. Smoking was more common among Endogenous EPO patients than among Other patients in all regions except Australia/New Zealand, and being a current smoker was markedly associated with the likelihood of Endogenous EPO status. Use of a percutaneous HD catheter was associated with markedly lower likelihood of Endogenous EPO status (AOR, 0.53; 95% CI, 0.38 to 0.75).

In the adjusted analyses, hypertension was less common among Endogenous EPO patients, whereas the AORs of Endogenous EPO status were positively associated with cardiovascular disease, lung disease, and recurrent cellulitis/gangrene. Diabetes mellitus and cancer were less frequent among the Endogenous EPO patients, but neither diagnosis was significantly associated with Endogenous EPO status in the multivariate analysis.

Cystic disease as a cause of ESRD was associated with a markedly increased likelihood of Endogenous EPO status (AOR, 5.40; 95% CI, 4.02 to 7.25), and cystic disease was notably more prevalent among the Endogenous EPO patients (25.1%) than among the Other patients (5.1%; $P < 0.0001$). However, even within the Endogenous EPO group, cystic disease was the underlying cause of ESRD for only a minority of patients, ranging from 4.1% to 34.7% across the regions.

Serum albumin concentration tended to be higher among the Endogenous EPO patients, and higher values were associated with a significantly increased likelihood of having Endogenous EPO status. Parathyroid hormone (PTH) concentration, transferrin saturation, Kt/V, and prescription of active vitamin D did not appear to be predictive. Additionally assigning nutritional vitamin D products (*e.g.* ergocalciferol and cholecalciferol) to the vitamin D therapy group did not result in a significant association, either. Higher serum ferritin concentration was significantly associated with a lower likelihood of having Endogenous EPO status. Iron prescription was sig-

Table 1. Patient characteristics by endogenous EPO status and region

	Australia-New Zealand		Europe		Japan		North America	
	Endogenous EPO	Other	Endogenous EPO	Other	Endogenous EPO	Other	Endogenous EPO	Other
n	33	1244	323	12,777	73	6453	116	8777
Percent	2.6	97.4	2.5	97.5	1.1	98.9	1.3	98.7
Demographics								
mean age (year)	63.2	61.7	61.5[a]	63.2	55.8[a]	61.5	55.6[a]	62.0
men (%)	90.9[a]	57.4	77.1[a]	58.1	87.7[a]	61.1	83.6[a]	54.8
black (%)	0.0[a]	0.5	0.3[a]	1.7	0.0	0.0	28.4	29.8
mean ESRD vintage (year)	8.7[a]	4.4	7.3[a]	4.2	9.7[a]	7.0	6.6[a]	2.8
current smoker (%)	7.4	12.8	21.2[a]	15.7	40.6[a]	22.9	32.6[a]	19.3
Comorbidities (%)								
coronary disease	45.5	58.1	41.2	41.7	27.4	27.8	62.6	57.3
cancer	9.1	13.5	11.5	13.0	2.7[a]	7.2	5.3[a]	12.4
cardiovascular, other	48.5	33.8	42.4	38.0	34.2	28.1	37.4	32.8
cerebrovascular disease	30.3	16.5	14.9	15.7	9.6	13.5	18.3	18.7
congestive heart failure	27.3	38.3	27.9	31.0	17.8	16.7	37.9	45.7
diabetes mellitus	24.2	40.8	18.9[a]	28.1	23.3	31.0	40.5[a]	52.5
gastrointestinal bleeding	0.0[a]	5.2	3.1[a]	5.6	4.1	4.0	4.3	7.3
HIV/AIDS	0.0	0.1	0.0[a]	0.4	0.0[a]	0.6	1.6	2.3
hypertension	75.8	86.4	68.4[a]	78.4	37.5[a]	66.3	86.7	88.0
lung disease	12.5	14.6	15.2	11.7	1.4	1.9	16.4	15.1
neurological disease	12.1	10.0	7.1	9.5	4.1	6.5	6.1[a]	12.2
psychiatric disorder	18.2	19.5	17.6	17.5	2.7	3.1	15.7[a]	24.5
peripheral vascular disease	27.3	33.3	29.4	26.4	13.7	13.2	31.9	29.0
recurrent cellulitis/gangrene	15.2	11.7	8.7	7.0	5.5	2.7	10.5	10.1
Cause of ESRD (%)[b]								
diabetes mellitus	21.2	26.1	10.8	18.5	19.2	27.0	34.5	37.8
glomerulonephritis	36.4	21.5	19.5	17.8	53.4	48.5	15.5	9.3
hypertension	0.0	10.4	8.1	15.2	0.0	3.8	19.8	26.0
cystic disease	24.2	5.7	34.7	7.2	4.1	3.8	12.1	2.9
other cause	18.2	36.3	26.9	41.3	23.3	17.0	18.1	24.1
Laboratory/treatment measures (mean or %)								
BMI (kg/m^2)	25.6	26.5	25.3[a]	24.7	22.7[a]	20.6	28.6[a]	26.4
albumin (g/dl)	3.71	3.70	3.92[a]	3.76	3.80	3.77	3.83[a]	3.68
PTH (pg/ml)	487	317	316	275	217	206	400[a]	304
Tsat (%)	24.0	27.9	26.8	27.6	26.9	26.1	27.3	27.1
ferritin (ng/ml)	177[a]	517	296[a]	447	233	249	327[a]	467
catheter hemoaccess (%)	6.1	13.2	6.3[a]	18.7	1.4	0.7	16.7[a]	27.5
Kt/V	1.42[a]	1.54	1.38	1.41	1.29[a]	1.34	1.48	1.48
mean (SD) hemoglobin (g/dl)	13.4[a] (± 1.0)	11.6 (±1.5)	13.5[a] (± 1.1)	11.4 (±1.6)	13.1[a] (± 1.0)	10.0 (± 1.3)	13.7[a] (± 1.2)	11.6 (± 1.5)
median (IQR) hemoglobin (g/dl)	13.2 (12.7 to 14.1)	11.6 (10.7 to 12.6)	13.3 (12.6 to 14.1)	11.4 (10.4 to 12.4)	12.8 (12.4 to 13.6)	10.0 (9.2 to 10.8)	13.6 (12.7 to 14.3)	11.6 (10.7 to 12.5)
iron use (%)	32.3[a]	76.1	51.1[a]	73.3	16.7	26.1	53.6[a]	65.0
active vitamin D use (%)	33.3	33.3	39.9	34.9	50.7	45.5	50.9	44.8
mean (SD) epoetin dose (units/wk)		10,250 (±9,073)		9326 (±8497)		4874 (±2967)		16,831 (±15,810)
median (IQR) epoetin dose (units/wk)		8000 (4000 to 12,000)		7000 (4000 to 12,000)		4500 (3000 to 6000)		12,000 (6000 to 22,500)
mean (SD) darbepoetin dose (mcg/wk)		53 (±55)		50 (±54)		23 (±14)		66 (±84)
median (IQR) darbepoetin dose (mcg/wk)		40 (23 to 60)		40 (20 to 60)		20 (13 to 30)		40 (21 to 75)

IQR, interquartile range, 25th to 75th percentile; Tsat, transferrin saturation.

[a]$P < 0.05$ *versus* Other patients within region (*t* test).

[b]Causes of ESRD differed significantly between groups ($P < 0.05$, χ^2 test) in each region, except Japan.

Table 2. Associations between patient characteristics and likelihood of endogenous EPO status

	AOR (95% CI)	*P*
Demographics		
age (per 10 years older)	0.97 (0.89 to 1.05)	0.49
men (*versus* women)	3.27 (2.59 to 4.14)	<0.0001
black (*versus* non-black)	1.07 (0.71 to 1.60)	0.76
ESRD vintage (per year)	1.08 (1.06 to 1.09)	<0.0001
current smoker (*versus* no)	1.42 (1.12 to 1.80)	0.004
Comorbidities (yes *versus* no)		
coronary artery disease	0.97 (0.78 to 1.20)	0.78
cancer	0.89 (0.66 to 1.20)	0.45
cardiovascular disease (other than CAD or CHF)	1.36 (1.12 to 1.66)	0.002
cerebrovascular disease	1.24 (0.96 to 1.61)	0.10
congestive heart failure	0.90 (0.71 to 1.14)	0.36
diabetes mellitus	0.83 (0.57 to 1.21)	0.33
gastrointestinal bleeding	0.68 (0.42 to 1.10)	0.11
HIV/AIDS	0.42 (0.06 to 2.91)	0.38
hypertension	0.58 (0.48 to 0.71)	<0.0001
lung disease	1.39 (1.06 to 1.81)	0.01
neurologic disease	0.75 (0.49 to 1.14)	0.18
psychiatric disorder	0.95 (0.73 to 1.25)	0.72
peripheral vascular disease	1.23 (0.97 to 1.55)	0.09
recurrent cellulitis/gangrene	1.48 (1.04 to 2.10)	0.03
Cause of ESRD (*versus* glomerulonephritis)		
diabetes mellitus	1.01 (0.65 to 1.56)	0.96
hypertension	0.68 (0.48 to 0.96)	0.03
cystic disease	5.40 (4.02 to 7.25)	<0.0001
other	0.82 (0.62 to 1.07)	0.14
Laboratory/treatment measures		
BMI (per 1 kg/m^2)	1.07 (1.05 to 1.09)	<0.0001
albumin (per 0.5 g/dl)	1.22 (1.09 to 1.37)	0.0005
PTH (per 100 pg/ml)	1.02 (1.00 to 1.04)	0.0571
Tsat (per 1%)	1.00 (0.99 to 1.01)	0.91
ferritin (per 100 ng/ml)	0.87 (0.82 to 0.93)	<0.0001
catheter hemoaccess (*versus* other)	0.53 (0.38 to 0.75)	0.0003
Kt/V (per 0.1)	0.99 (0.96 to 1.03)	0.67
iron use (yes/no)	0.42 (0.35 to 0.52)	<0.0001
active vitamin D use (yes/no)	1.04 (0.87 to 1.25)	0.64

AOR was adjusted for all factors listed plus DOPPS phase and region. CAD, coronary artery disease; CHF, congestive heart failure; Tsat, transferrin saturation.

nificantly associated with lower odds of Endogenous EPO status (AOR, 0.42; 95% CI, 0.35 to 0.52).

Mortality

Median time on study was 1.4 years. Crude death rates were 12.6 per 100 patient years for Endogenous EPO patients and 15.4 per 100 patient years for Other patients. As shown in Figure 2, the unadjusted relative risk (RR) of mortality for Endogenous EPO *versus* Other patients was 0.81 (95% CI, 0.66 to 0.98). After adjusting for case mix and region, however, the finding was no longer significant (RR, 0.98; 95% CI, 0.80 to 1.19). A sensitivity analysis looking at group assignment on the basis of a more stringent definition of Endogenous EPO status (no ESA therapy and hemoglobin concentration >12 g/dl at three times: 0, 4, and 8 months) corroborated the primary results: unadjusted RR 0.78 (95% CI, 0.60 to 1.01) and adjusted RR 0.94 (95% CI, 0.72 to 1.22). The adjusted RR comparing mortality among all Endogenous EPO patients with the subset of Other patients whose hemoglobin concentrations were 10 to 12 g/dl was 1.02 (95% CI, 0.83 to 1.25). The adjusted RR comparing mortality among all Endogenous EPO patients with the subset of Other patients whose hemoglobin concentrations were >12 g/dl was 1.03 (95% CI, 0.83 to 1.27).

Within the Endogenous EPO group, the adjusted mortality risks were not statistically significant when patients with baseline hemoglobin concentrations of >14 or 13 to 14 g/dl were compared with those whose hemoglobin concentration was 12 to 13 g/dl. The adjusted mortality risk between Endogenous EPO patients with baseline hemoglobin concentrations >14 g/dl ($n = 137$) and Other patients with baseline hemoglobin concentrations >14 g/dl ($n = 816$) also was NS.

Quality of Life

Adjusted Kidney Disease Quality of Life (KDQOL) scores did not show any significant benefits for the Endogenous EPO patients compared with the Other patients.

DISCUSSION

Nephrologists have long recognized a wide range of ESA dose requirements across HD patients. Doses needed to maintain hematocrit values of 35 ± 3% varied 42-fold in the United States phase 3 registrational trial of epoetin alfa in iron-replete subjects, as published 20 years ago.[6] This is likely related, in part, to variability in the patients' residual capacity to produce EPO. Individuals with polycystic kidney disease, for example, tend to produce more EPO and have been shown to require lower ESA doses.[7] This study examines HD patients at one extreme of the erythropoietic spectrum, those who maintain hemoglobin concentrations >12 g/dl in the absence of ESA prescription. This unusual subset provides a natural opportunity to study the clinical outcomes associated with higher hemoglobin concentrations in the absence of effects of prescribed ESAs.

There are several limitations to our study to acknowledge before discussing the results. First, the potential exists that some individuals were misclassified into the Endogenous EPO or Other group, because ESA doses and hemoglobin concentrations were collected at entry and again at 4 months. The sensitivity analyses adding data from the 8-month time point suggest that group status was reasonably stable. Second, because the DOPPS is an observational study to examine real-world practices, no additional, nonroutine laboratory testing was requested. It would have been informative to consider the associations of inflammatory markers such as C-reactive protein or IL-6 with Endogenous EPO status and mortality, in

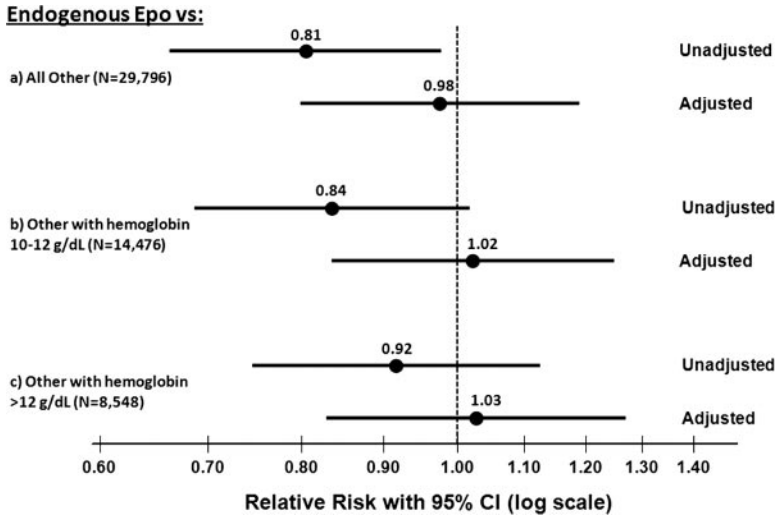

Figure 2. Adjusted risk of mortality does not differ significantly for Endogenous EPO patients compared with Other patients. 545 Endogenous EPO patients were included in each model. The models were stratified by region and study phase, accounted for facility clustering effects, and adjusted for age, sex, black *versus* other race, vintage, smoking, cause of ESRD, catheter hemoaccess, serum PTH and albumin concentrations, Kt/V, and 14 summary comorbid conditions.

addition to serum ferritin. Analysis of serum erythropoietin and leptin concentrations would also likely have proven instructive. Finally, associations with mortality and other outcomes in this observational trial cannot be assumed to prove causality. Although the numerous adjustments accounted for considerable confounding as demonstrated in the mortality analyses, the existence of unmeasured confounding cannot be ruled out.

In 1981, before the availability of recombinant ESA therapies, Charles *et al.*[1] reported that 11 (2.0%) of 549 patients at five HD facilities in Brooklyn, NY, had hematocrit values of ≥40% without transfusion or androgen treatment in the preceding year. In 2002, Iorio and Iodice[2] reported that 78 (2.2%) of 3617 Italian HD patients maintained hemoglobin concentrations >13.5 g/dl for 1 year without epoetin. In 2005, Kuo *et al.*[3] reported that 21 (2.4%) of 888 Taiwanese HD patients were ESA-independent, defined as hemoglobin concentration >12 g/dl and no use of ESA, transfusion, or androgens for 6 months. The study of international HD patients in the DOPPS presented here found that 545 (1.8%) of 29,796 met the criteria for Endogenous EPO status. As explained in the papers that describe the details of the DOPPS design,[4,5] however, each study phase begins with a large prevalent cohort, and as patients exit the study (death, modality change, *etc.*) they are replaced with new, incident HD patients. Because longer duration on dialysis is associated with increased likelihood of Endogenous EPO status (discussed below), enriching the sample with these patients who are new to dialysis will diminish the reported prevalence of Endogenous EPO status. The more germane comparison with historical results is to look only at the prevalent cross-sections, as was done in the past. Within the prevalent-patient DOPPS sample (displayed in Figure 1), 483 (2.3%) of 21,185 patients met the criteria for Endogenous EPO status. Thus, the four studies are remarkably consistent in demonstrating that 2.0 to 2.4% of HD patients independently maintain robust erythropoiesis. Within the DOPPS, there was variation between nations in the prevalence of Endogenous EPO patients. Such patients were found less commonly in Belgium (1.1%), Japan (1.3%), Sweden (1.6%), and the United States (1.6%). DOPPS data have shown that the use of catheters for HD vascular access is considerably higher in Belgium, Sweden, and the United States than in the other nations, potentially explaining the low Endogenous EPO prevalence in these nations, but not in Japan where catheter use is the lowest. The prevalence of polycystic renal disease was considerably lower in the United States (2.4%) and Japan (3.8%) than in the other nations (6.2% to 8.8%). Also, ESAs may be prescribed more liberally in the United States because of favorable federal reimbursement to dialysis facilities for ESA usage. It is unclear why the prevalence of Endogenous EPO patients was high in Germany (5.1%).

The DOPPS data demonstrated that several factors were associated with decreased likelihood of Endogenous EPO status: female gender, fewer years of ESRD, hemoaccess via catheter, and the diagnosis of hypertension. Women were also under-represented among the earlier reported cohorts of patients with naturally higher hemoglobin concentrations.[1–3] Lower androgen levels among women may be associated with diminished erythropoiesis. Inflammation would also be expected to contribute to lower hemoglobin concentrations, which likely explains the relationships between serum albumin concentration, serum ferritin concentration, and catheter hemoaccess with Endogenous EPO status. ESA administration may cause increases in BP,[8] and this may explain the higher likelihood of hypertension among the Other group [although it does not explain the higher likelihood of hypertension as the cause of ESRD among the Other group]. Cardiovascular and lung diseases were associated with increased likelihoods of Endogenous EPO status. Hypoxia resulting from cardiorespiratory disease could stimulate endogenous EPO production from the liver and thereby predispose to Endogenous EPO status. Similarly, smoking was associated with Endogenous EPO status. Cigarette smoke contains carbon monoxide, and inhalation leads to carboxyhemoglobinemia and hypoxemia; in fact, smoking may cause polycythemia.[9] A physiologic link between cellulitis/gangrene and Endogenous EPO status is not readily explained.

It is interesting that increased years on dialysis were associated with greater likelihood of higher hemoglobin concentration in the absence of ESA therapy (8% increased likelihood for

each additional year). This association may be due to simultaneous predispositions for healthier patients to live longer and to require lower, or zero, ESA dose prescriptions. Additionally, the incidence of acquired cystic kidney disease (ACKD) increases over time, and these cysts may produce EPO. The prevalence of ACKD has been stated to reach nearly 100% after 10 years of dialysis.[10] Individual cases of erythrocytosis associated with ACKD have been reported since 1982.[11] Studies assessing a link between cyst extent and higher hematocrits among HD patients have reported contradictory findings, however.[12,13] Kuo *et al.*[3] performed a number of diagnostic tests on their 21 patients who evidenced ESA independence and also on 43 age- and sex-matched HD patients, including renal ultrasonography to evaluate cyst formation, because hemoglobin level strongly correlated with HD duration in their study. They found that comparisons of cyst severity between the two groups failed to reach statistical significance. However, in absolute terms, the severity scores were worse for the ESA-independent group, and it is possible that their sample size was simply too small to reach statistical significance. Increased hepatic production of EPO or increased levels of IGF have also been hypothesized to contribute to higher hemoglobin concentrations with more years of dialysis.[14] Cystic disease as the underlying cause of renal failure was strongly associated with an increased likelihood of Endogenous EPO status in the present study, and cystic disease was more commonly present among this group, although it still accounted for only a minority of the causes of renal failure. Cyst stromal cells have been shown to produce mRNA for EPO, and cysts produce EPO independent of oxygen pressure.[15]

Kuo *et al.*[3] also found that serum EPO concentration was higher among ESA-independent patients (17.8 ± 12.2 milliunits/ml) than among matched controls whose ESA therapy was withheld for 1 week (8.9 ± 3.2 milliunits/ml; $P < 0.05$). Neither serum C-reactive protein nor cortisol levels differed between their groups, whereas both serum ferritin and PTH concentrations were significantly lower among the ESA-independent patients. Elevated PTH levels and bone marrow fibrosis were associated with higher epoetin dose requirements in a small clinical study of HD patients.[16] In our study, however, mean PTH concentrations were nominally higher among the Endogenous EPO patients in each region, significantly so in North America. Leptin has been proposed as a mechanism to explain higher hematocrits among patients with higher body-mass index (BMI),[17] but leptin concentrations did not differ between groups in the study by Kuo *et al.*[3] In our study, a higher BMI was associated with increased likelihood of Endogenous EPO status; leptin concentration was not measured. Small studies have indicated that prescription of vitamin D increases hemoglobin levels and/or decreases ESA dose requirements,[18–20] but vitamin D use was not associated with Endogenous EPO status in this study.

The DOPPS data did not suggest that hemoglobin concentration >12 g/dl increased mortality risk for Endogenous EPO patients compared with Other patients. In fact, the unadjusted RR for mortality was 0.81 (95% CI, 0.66 to 0.98), suggesting a 19% lower risk of death. However, after adjusting for age, sex, race, vintage, smoking status, comorbid diseases, hemoaccess type (catheter *versus* other), cause of ESRD, PTH, albumin, Kt/V, and vitamin D use, the RR increased to 0.98 and was no longer significant (95% CI, 0.80 to 1.19). Clearly, it is necessary to adjust thoroughly for confounding factors such as case mix when investigating associations between hemoglobin and mortality among HD patients. Iorio and Iodice[2] described significantly lower mortality and hospitalization among their high-hemoglobin patients, but they reported only unadjusted comparisons between groups. The adjusted RR comparing mortality among Endogenous EPO patients *versus* a subset of Other patients whose hemoglobin concentrations were within the ESA manufacturers' specified range of 10 to 12 g/dl was 1.02 (95% CI, 0.83 to 1.25), and the RR compared with the subset of Other patients with concentrations >12 g/dl was 1.03 (95% CI, 0.83 to 1.27). Regidor *et al.*[21] studied 58,058 US HD patients and found that, among the subset of patients who maintained hemoglobin concentration ≥12 g/dl, the adjusted risk of mortality was significantly higher for those who did not receive epoetin compared with those who did. Two prospective randomized trials of normalization *versus* partial correction of anemia among CKD patients found adverse outcomes among the normal-hemoglobin-target groups yet also found that higher attained hemoglobin concentrations were not associated with higher risks,[22,23] leading to hypotheses that higher doses of epoetin or intravenous iron may have been deleterious. This observational study found that the adjusted mortality risk is no different between patients who maintain hemoglobin concentrations of >12 g/dl without ESA therapy and other patients, including a comparison with only the subset of other patients whose hemoglobin concentrations were also >12 g/dl.

Randomized clinical trials of normalization of hemoglobin among patients with CKD have yielded inconsistent quality-of-life results, with studies reporting superior scores for the higher hemoglobin group,[24–27] no difference between groups,[22] or inferior scores for the higher hemoglobin group.[28] Adjusted KDQOL scores did not show any significant benefits for the Endogenous EPO patients compared with the Other patients in this study.

The findings from this study show no evidence of increased mortality risk in association with higher hemoglobin values in Endogenous EPO patients. Concerns about high hemoglobin targets for patients with CKD have come to the forefront.[22,26,28] The Kidney Disease Outcomes Quality Initiative and the European Renal Best Practice guidelines recommend a target hemoglobin range of 11 to 12 g/dl when prescribing ESAs.[29,30] Current ESA product labeling specifies a 10 to 12 g/dl maintenance range and cautions against hemoglobin concentration >12 g/dl in CKD. Our results suggest that there are HD patient subgroups for whom hemoglobin concentration >12 g/dl is acceptable and that there is no impetus to phlebotomize an HD patient who maintains hemoglobin values

>12 g/dl without ESA therapy. Determining the appropriate hemoglobin target range and pharmacologic management strategy for HD patients is a very complex endeavor, and the solution remains a work in progress.

CONCISE METHODS

Study Population

Patients were selected randomly from a representative sample of dialysis facilities within each country for enrollment into the DOPPS, as described previously.[4,5] These analyses included 29,796 HD patients enlisted during DOPPS I (1996 through 2001; $n = 9431$), DOPPS II (2002 through 2004; $n = 10,347$), and DOPPS III (2005 to the present; $n = 10,018$) from 12 countries (Australia/New Zealand, Belgium, Canada, France, Germany, Italy, Japan, Spain, Sweden, the United Kingdom, and the United States). Demographic data, detailed comorbidities, laboratory values, medications (including both active and nutritional vitamin D products), hospitalizations, mortality, and vascular access type were abstracted from patient records. Serum erythropoietin, C-reactive protein, and IL-6 concentrations were not measured in this observational study. Demographic factors, comorbidities, and causes of ESRD were determined at study entry, and baseline laboratory and treatment measures were collected from the 4-month data collection. Patients with missing hemoglobin or ESA-dose data at baseline or 4 months were excluded. Quality-of-life scores were collected from administration of the KDQOL (short form) instrument[31] at baseline. The laboratory values were updated at 4-month intervals.

Endogenous EPO patients were defined as those who (*1*) were not receiving ESA treatment when they entered the DOPPS or at the 4-month survey time (it is assumed that these patients did not receive ESA treatment at other times during these 4 months); and (*2*) maintained a hemoglobin concentration >12 g/dl at both time points (hemoglobin values were not uniformly collected at more frequent intervals in the DOPPS). The remaining patients are classified as "Other" in this report. In supplemental analyses, the validity of the definition was considered by additionally examining ESA prescription and hemoglobin level at the next survey (8 months).

Statistical Analyses

Descriptive statistics were compared between the Endogenous EPO group and all Other patients, using *t* tests and χ^2 tests where appropriate. Logistic regression was used to determine the adjusted odds of Endogenous EPO status for each characteristic. Cox models were used to assess the relative mortality risk between the groups. All of the survival analyses started after the time of the 4-month survey, because the criteria for assignment of patients to the Endogenous EPO or Other group required collection of ESA prescription and hemoglobin concentration at baseline and 4 months. Patients were censored at time of moving from the study unit, upon change to peritoneal dialysis, upon renal transplantation, or at study end. Differences in patient quality-of-life scores were assessed using linear mixed models. Models were adjusted for age, sex, race, years of ESRD, cause of ESRD, smoking status, use of catheter for vascular access, serum PTH concentration, serum albumin concentration, single pool Kt/V, vitamin D use, and 14 comorbid conditions that influence mortality among HD patients[32]: coronary artery disease, congestive heart failure, other cardiac disease, cerebrovascular disease, peripheral vascular disease, hypertension, lung disease, cancer, diabetes mellitus, gastrointestinal bleeding, recurrent cellulitis/gangrene, psychiatric disorder, neurologic disease, and HIV/AIDS. Region and DOPPS phase were accounted for by adjustment in logistic regression models and by stratification in Cox models. Analyses were conducted using SAS 9.2 (Cary, NC).

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DISCLOSURES

Dr. Goodkin has consulted for Affymax Inc., AMAG Pharmaceuticals, Amgen Inc., Amira Pharmaceuticals Inc., FibroGen Inc., Keryx Biopharmaceuticals, Seattle Life Sciences Inc., Spectrum Pharmaceuticals Inc., and Xenon Pharmaceuticals Inc. He serves on the Board of Directors of Urodynamix Technologies Ltd. Dr. Robinson has received speaker fees from Kyowa Hakko Kirin. Dr. Combe has received speaker fees from Amgen, Ortho Biotech, Genzyme, Shire, Roche, and Sandoz. He has served on advisory boards for Amgen and Roche and has received research grants from Amgen (site investigator), Ortho Biotech (principal investigator for France), and Roche (site investigator). Dr. Fluck has received consultancy fees, support for attendance at meetings, and honoraria from Amgen, Ortho Biotech, and Roche. Dr. Mendelssohn has received speaker fees from and has served on the advisory boards of Amgen, Ortho Biotech, and Roche and has received research grants from Amgen (site investigator) and Ortho Biotech (principal investigator, multicentre studies). Dr. Akizawa has consulted for Kirin and Chugai and has received grants from Kirin, Chugai, Fresenius, and Tomita. Dr. Pisoni has received speaker fees from Amgen, Kyowa Hakko Kirin, and Vifor, and has served on an advisory panel for Merck. The DOPPS is administered by Arbor Research Collaborative for Health and is supported by scientific research grants from Amgen (since 1996), Kyowa Hakko Kirin (since 1999, in Japan), Genzyme (since 2009), and Abbott (since 2009), without restrictions on publications. Drs. Goodkin, Robinson, Pisoni, and Port are DOPPS investigators.

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See related editorial, "Mortality Risk in Dialysis Patients with Naturally Higher Hemoglobins," on pages 205–206.