# Improving Outcomes for Dialysis Patients in the International Dialysis Outcomes and Practice Patterns Study

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**The international Dialysis Outcomes and Practice Patterns Study (DOPPS) is well suited to evaluate levels of deviation from emerging and established guidelines to clinical practice of hemodialysis, over time and by country. The DOPPS can also evaluate whether the target levels that are chosen in the guidelines are in agreement with outcomes such as elevated risk for mortality, hospitalization, and vascular access failure. At a special DOPPS symposium during the 2004 congress of the American Society of Nephrology, the authors presented such findings; key points from that symposium are presented in this article, focusing on vascular access, mineral metabolism, dialysis dose, and anemia management. Although an observational study cannot prove causality, DOPPS suggests large opportunities to improve care and outcomes of dialysis patients. The international perspective of DOPPS assists in the new efforts for international guidelines. Some encouraging trends in recent years are documented in these areas.**

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The Dialysis Outcomes and Practice Patterns Study (DOPPS) was designed to evaluate practice patterns that can be associated with the improved health and longevity of patients with ESRD. The goals of this large international study of hemodialysis (HD) patients can be summarized as "live longer, live better," which emphasizes its clinical focus. The study enrolls nationally representative samples of dialysis facilities using a stratified random approach and random samples of patients within facilities (1,2). The first phase of the study (DOPPS I, 1996–2001) collected data from France, Germany, Italy, Japan, Spain, the United Kingdom, and the United States. The second phase (DOPPS II, 2002–2004) added five more countries to the original seven: Australia, Belgium, Canada, New Zealand, and Sweden. With assistance from investigators in each of the countries where the study has taken place, the University Renal Research and Education Association selected the dialysis facilities and patients for the study.

Given its large, representative, and international patient sample, this observational study has been able to contribute to many aspects of practice in hemodialysis. It is widely recognized that more randomized, controlled studies are needed as they allow inference of causality and provide the "gold standard" of evidence. However, such studies tend to be rare and often have a limited sample size. If underpowered, then this may lead to negative findings. Furthermore, large and nationally representative HD patient samples such as those in the DOPPS allow results to be pertinent to all types of HD patients and provide a reflection of current national practices. In contrast, randomized, clinical trials often are not performed with a nationally representative sample, potentially limiting the generalizability of study findings. In addition, many components of dialysis therapy do not lend themselves to randomization for ethical reasons; for example, randomization to a high phosphorus level or catheter use would be difficult to justify. Observational studies require experienced and thoughtful adjustments with the goal of simulating randomized, clinical trials (3,4).

As numerous trials and observational studies have provided a growing body of evidence, guidelines have been produced through expert panels in the United States as Dialysis Outcomes Quality Initiative (NKF-DOQI initially, later broadened to Kidney Disease as K/DOQI); in Europe as the European Best Practice Guidelines; and also in Canada, the United Kingdom, Australia, and other regions (5–9). These expert panels conducted extensive literature reviews to define levels of evidence. They often clarify that some guidelines are opinion-based, whereas others are based on various levels of evidence. Evidence is higher for randomized, controlled trials than for observational studies.

It is reassuring to note that recent DOPPS findings are in

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remarkably close agreement with the published regional guidelines regarding the recommended target levels of laboratory values. It has become clear that the science- and evidence-based care of patients with kidney failure should be independent of geographic location or national borders. Therefore, a new initiative was created by international experts to develop truly international guidelines under the new acronym KDIGO, Kidney Disease—Improving Global Outcomes (10,11).

As many of the regional guidelines for HD were published several years ago, it is of interest to study the levels of compliance in representative samples by region and to evaluate time trends from before to after their publication. The DOPPS is ideally suited to evaluate the level of deviation from the guidelines over time and by country. The DOPPS is also in a position to evaluate whether the target levels that are chosen in the guidelines are in agreement with outcomes such as elevated risk for mortality, hospitalization, and vascular access (VA) failure. At a special DOPPS symposium during the 2004 congress of the American Society of Nephrology, the authors presented such findings as DOPPS investigators together with Dr. Eknoyan, who spoke from a KDIGO perspective. The key findings reported at that session are described herein.

## Vascular Access

The type of VA that is used for a cross-section of prevalent HD patients continues to differ substantially from country to country in the DOPPS. As seen in Figure 1, in 2002 to 2003, the percentage of prevalent patients who received dialysis with an arteriovenous fistula (AVF) ranged from 91% in Japan to 31% in the United States. All 12 countries in the study except the United States met the K/DOQI recommendation of having >40% of patients dialyzing *via* AVF. Fortunately, AVF use has increased in the United States from an even lower 24% measured previously (12).

Many factors account for this wide range in AVF use. One important factor is the difference in comorbidity between countries. Several comorbid conditions, such as angina, peripheral vascular disease (PVD), and diabetes, were more prevalent among US HD patients than among European or Japanese HD patients. For prevalent HD patients in the DOPPS, these conditions were significantly associated with not having an AVF (13). Still, DOPPS I data show that the percentage of AVF among nondiabetic young (18 to 54 yr) patients without PVD or coronary artery disease averaged 89 and 76% in men and women in Europe *versus* only 41 and 22%, respectively, in the United States. Furthermore, after adjustment for differences between countries for 14 different classes of comorbidity, the likelihood of patients' using an AVF in the United States was still substantially lower than for HD patients in Europe or Japan (13). The main factor accounting for the much lower percentage of AVF use in the United States may be that some medical directors or nurse managers of HD units in the United States prefer grafts over fistulae; such preferences were not found in other countries (14). Several other factors that may cause international variation in rates of AVF use among incident HD patients may also contribute to AVF use rates among prevalent HD patients: Late referrals to a nephrologist, delays between referral for surgery and creation of AVF, and different lengths of time between AVF creation and first cannulation (13,15).

The percentage of prevalent HD patients who receive dialysis with a catheter is also strikingly different from country to country within the DOPPS. Whereas in six countries catheter use is at most 11% (thus meeting or nearly meeting the K/DOQI recommendation of keeping this rate below 10%), in the other six countries, catheter use ranges from 25 to 38% (Figure 2). Here again, the moderately variable comorbidity from country to country is unlikely to explain fully these substantial differences. Preferences of HD staff and patients are likely major factors. Differences in the time required for first cannulation and removal of catheters in patients with a maturing permanent VA, as demonstrated in DOPPS I, may explain a small part of catheter use in prevalent patients. It is also worth mentioning that the percentage of AV graft use is strikingly different from country to country, exceeding 15% only in the United States (41%) Australia/New Zealand (19%), and Sweden (16%). New results from the DOPPS based on a survey completed by surgeons who create the permanent VA for HD patients indicate that a number of different aspects related to surgical training are strongly associated with the likelihood of patients' receiving an AVF *versus* a graft (16).

The above-mentioned differences in type of VA used are neither trivial nor without consequences for patient health. AVF and graft survival in incident patients has been found to be substantially greater when a patient has not previously used a catheter (13,15). That 50 to 75% of HD patients initiate HD

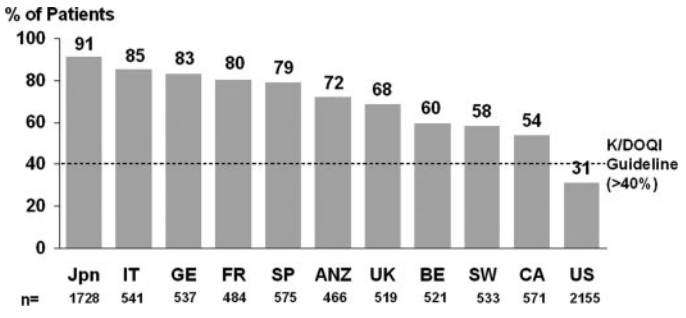



*Figure 1.* Fistula use, by country, in a cross-section of prevalent hemodialysis (HD) patients in Dialysis Outcomes and Practice Patterns Study II (DOPPS II), 2002 to 2003.

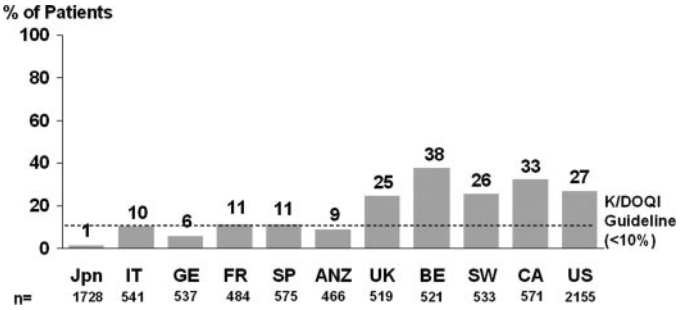



*Figure 2.* Catheter use, by country in a cross-section of prevalent HD patients in DOPPS II, 2002 to 2003.

with a catheter in some countries *versus* 25 to 35% of patients in other countries suggests opportunities for decreasing catheter use that may be helpful for increasing AVF longevity. Figure 3 shows access failure of fistulae (by region) and grafts (United States only). The fraction of those who received dialysis with a fistula and did not have access failure varied by region: Patients in Europe had the best outcomes, and those in the United States had the worst. Access failure for US patients who received dialysis *via* graft was more common than for those who used a fistula in any of the regions examined. After adjustment for many comorbid conditions, the use of a catheter was associated with a substantially higher risk for hospitalization and mortality, when analyzed at both the patient and the facility levels (17,18). In DOPPS I, tunneled and untunneled catheters were shown to be associated with a five-fold and 7.8-fold higher infection rate, respectively, compared with AV fistulae (18). Furthermore, dialysis facilities that had >21% of prevalent patients receiving dialysis with a catheter displayed a 1.6-fold higher risk for hospitalization as a result of infection compared with dialysis units in which only 7% of patients or fewer were using a catheter (17). The risk for death also was 15 to 20% higher at units that had >14% of prevalent patients receiving dialysis with a catheter compared with dialysis units in which 0 to 7% of patients were receiving dialysis with a catheter (17).

Overall, these results underscore a continuing opportunity to improve the care and outcomes of HD patients through concerted efforts to maximize AV fistula use. In recognition of this large opportunity in the United States, the Centers for Medicare and Medicaid instituted a "Fistula First" program in 2004; substantial gains have already been seen in AV fistula use since the program's launch.

## Mineral Metabolism

Abnormal mineral metabolism in patients with ESRD is associated with bone and cardiovascular disease. The serum concentration of calcium, phosphorus, and parathyroid hormone (PTH) provides the most readily available indication of the state of mineral metabolism. Serum measurements of these mineral metabolism indicators are associated directly with bone disease, cardiovascular outcomes, and mortality. Evidence- and consensus-based clinical guidelines for desired serum concentrations of mineral metabolism indicators have been developed and widely disseminated (19,20).

The DOPPS data collection effort included abstraction of serum calcium, phosphorus, and intact PTH values from representative cross-sections of HD patients in all 12 countries. For seven countries (France, Germany, Italy, Japan, Spain, the United Kingdom, and the United States), comparable data were collected during both the first and the second phases of DOPPS. The distributions of patients who fell below, within, and above guideline values were determined at each time point (21). In addition, the prevalence of phosphate binder treatment was determined by categories of guideline ranges and time. It should be noted that the guidelines had not been disseminated at the time the measurements were made.

Figure 4 shows that 41% of DOPPS I patients fell within the currently recommended range for serum phosphorus and 50% fell above the guideline range in 1999. A small but statistically significant improvement occurred as of 2002 using the $\chi^2$ statistic. Modest regional variation was seen with Germany showing the highest percentage of patients above the guideline range but the greatest improvement over time. The percentage of patients who were treated with phosphate binders increased over time (Figure 5). However, among patients with a high serum phosphorus concentration (>5.5 mg/dl), binder therapy was reportedly not prescribed to 21% in 1999 and 12% in 2002.

The serum calcium concentration exceeded the upper limit of the guideline target in a plurality of patients (Figure 6). There was no significant change over time: 43% of patients were within the target range and 48 to 49% were above it at both time points. Modest variation was seen across countries.

In 1999, the serum PTH concentration was above the target range for 29% of patients, within the target range for 25% of patients, and below the target range for 47% of patients (Figure 7). There was a trend away from high PTH concentrations into the normal range by 2002. Again, variation across countries was modest.

These measurements were obtained during the time of initial publication of studies showing adverse cardiovascular associ-

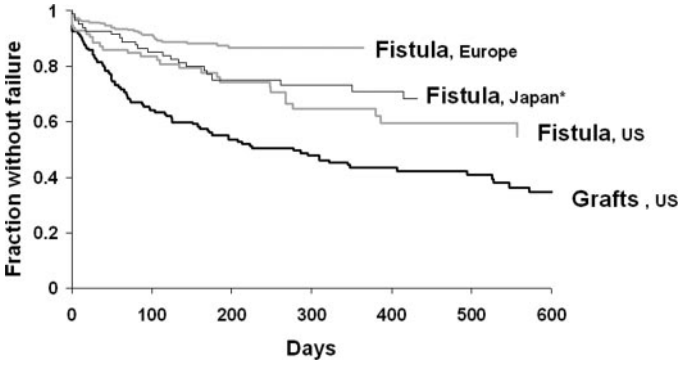
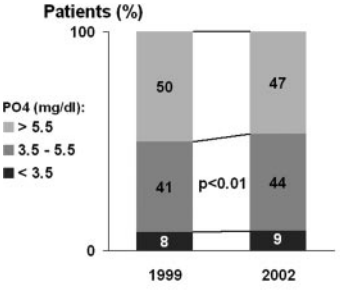


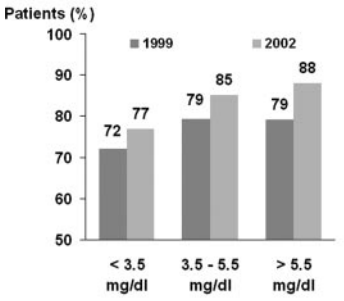

*Figure 3.* Fistula and graft survival in incident patients who started HD with a *permanent* vascular access (VA) in DOPPS I. Adjusted for differences in age, gender, diabetes, and peripheral vascular disease. *In Japan, there were only a small number ($n = 88$) of incident patients for analysis, so confidence interval (CI) at 1 yr is much larger than for other countries; in Japan, 1 yr AV fistula survival CI = 0.60 to 0.87.




| Country ($n_1/n_2$) | Patients above Guidelines (%) | |
|---|---|---|
| | 1999 | 2002 |
| France (635/528) | 44.9 | 40.4 |
| Germany (630/571) | 68.7 | 56.3 |
| Italy (625/576) | 40.7 | 39.7 |
| Japan (2183/1805) | 50.1 | 48.2 |
| Spain (568/613) | 48.0 | 41.3 |
| UK (551/556) | 47.7 | 43.0 |
| US (3532/2246) | 50.8 | 48.3 |
| Overall 7 countries (8724/6904) | 50.4 | 46.6 |

Point prevalent cross-section for DOPPS I (sample size n1) and II (n2)

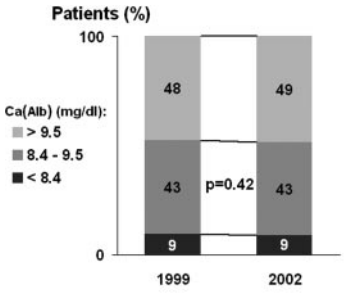
*Figure 4.* Serum phosphorus by guideline categories in 1999 (DOPPS I) and 2002 (DOPPS II).




| Country ($n_1/n_2$) | Patients with Pi >5.5 using Phosphate Binders (%) | |
|---|---|---|
| | 1999 | 2002 |
| France (266/182) | 81.2 | 74.7 |
| Germany (383/277) | 67.6 | 83.0 |
| Italy (246/225) | 79.3 | 88.9 |
| Japan (1088/813) | 79.1 | 85.1 |
| Spain (259/243) | 91.5 | 93.8 |
| UK (224/177) | 80.4 | 88.1 |
| US (1603/1028) | 79.2 | 92.1 |
| Overall 7 countries (4069/2945) | 79.1 | 87.9 |

Point prevalent cross-section for DOPPS I (sample size n1) and II (n2)

*Figure 5.* Percentage of patients who were prescribed phosphate binders, by phosphorus levels.

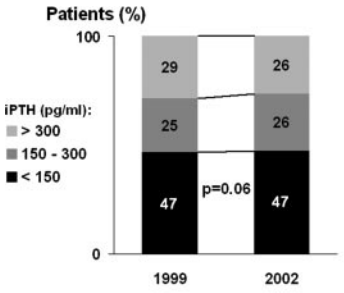



| Country ($n_1/n_2$) | Patients above Guidelines (%) | |
|---|---|---|
| | 1999 | 2002 |
| France (635/528) | 56.8 | 60.1 |
| Germany (630/571) | 40.5 | 34.2 |
| Italy (625/576) | 47.6 | 43.0 |
| Japan (2183/1805) | 45.8 | 42.5 |
| Spain (568/613) | 54.3 | 71.9 |
| UK (551/556) | 64.1 | 65.9 |
| US (3532/2246) | 44.6 | 44.4 |
| Overall 7 countries (8724/6904) | 47.5 | 48.8 |

Corrected for serum albumin concentration

Point prevalent cross-section for DOPPS I (sample size n1) and II (n2)

*Figure 6.* Serum calcium by guideline categories in 1999 (DOPPS I) and 2002 (DOPPS II).




| Country ($n_1/n_2$) | Patients above Guidelines (%) | |
|---|---|---|
| | 1999 | 2002 |
| France (635/528) | 28.9 | 25.7 |
| Germany (630/571) | 33.1 | 22.7 |
| Italy (625/576) | 33.1 | 23.2 |
| Japan (2183/1805) | 20.1 | 19.1 |
| Spain (568/613) | 33.0 | 28.3 |
| UK (551/556) | 32.4 | 30.8 |
| US (3532/2246) | 30.7 | 34.8 |
| Overall 7 countries (8724/6904) | 28.6 | 26.1 |

Point prevalent cross-section for DOPPS I (sample size n1) and II (n2)

*Figure 7.* Intact parathyroid hormone (PTH) by guideline categories in 1999 (DOPPS I) and 2002 (DOPPS II).

ations with calcium and phosphorus concentrations (22–25) but before the release of clinical practice guidelines. The majority of HD patients had high serum concentrations of both phosphorus (Figure 4) and calcium (Figure 6), resulting in an elevated calcium-phosphate product. High levels of phosphorus, calcium, and calcium-phosphate product are strongly and consistently associated with all-cause and especially cardiovascular mortality. A growing body of evidence suggests that altered mineral metabolism among patients with ESRD leads to vascular calcification and predictable adverse consequences. In addition, altered mineral metabolism is associated with metabolic bone disease and attendant complications such as bone pain, fractures, and growth retardation in children.

The high prevalence of hyperphosphatemia is partially explained by suboptimal phosphate binder therapy. A substantial portion of patients with a high serum concentration of phosphorus were reportedly not receiving phosphate binder therapy. The finding suggests that there are important opportunities for improvement with wider usage of currently available treatments. Conversely, the finding that the majority of patients with a serum phosphorus concentration below the target range continue to receive phosphate binders suggests the possibility of overtreatment in some patients.

As seen with serum phosphate, the majority of HD patients had a serum calcium concentration that was outside the target range. As noted, high calcium has been associated with increased mortality (26). Clearly, opportunities exist for improvement through changes in phosphate binder therapy, dietary calcium intake, vitamin D and calcimimetic therapy, and dialysate calcium concentration.

As with serum phosphorus and calcium, the serum intact PTH concentration was outside the target range for a majority of HD patients. Altered PTH contributes to bone disease. Some studies show that high PTH is associated with increased patient mortality. These findings suggest further opportunities for improvement through manipulation of dialysis therapy, diet, phosphate binders, and vitamin D therapy. The large fraction of patients who have PTH levels below the guidelines suggests the need for further study of this group.

Although some differences were found by country, the overall findings are more consistent than different. In general, the DOPPS found that mineral metabolism guideline goals for HD patients are usually not achieved in seven different countries. The guideline levels for PTH seem to be less well supported than others and will need to be revised as new PTH assays are being used. The findings on calcium and phosphorus suggest large opportunities for improvement that could favorably modify the risk for cardiovascular and bone disease.

## Dialysis Dose

The annual reports of ESRD registries in Japan, Europe, and the United States have shown that mortality of patients with ESRD (dialysis and transplant) was higher in the United States and lower in Japan compared with Europe (27). As Kt/V has become accepted as a reliable parameter of dialysis dose for small molecular size (urea), American nephrologists increased the Kt/V steadily from 0.99 in 1986 to 1988 to 1.53 in 2002 (Figure 8) in an effort to improve the quality of dialysis and reduce mortality rates. Concomitant with this tremendous increase in dialysis dose, the comorbidity-adjusted mortality rate improved substantially (28); however, the mortality rate has remained higher in the United States than in Europe or Japan (29).

In 1995, the HEMO Study was started in the United States to determine whether higher-than-average dose of dialysis expressed as Kt/V increases the survival in patients who received long-term HD. The equilibrated (double-pool) Kt/V in this large, randomized, clinical trial averaged 1.16 in the low-dose

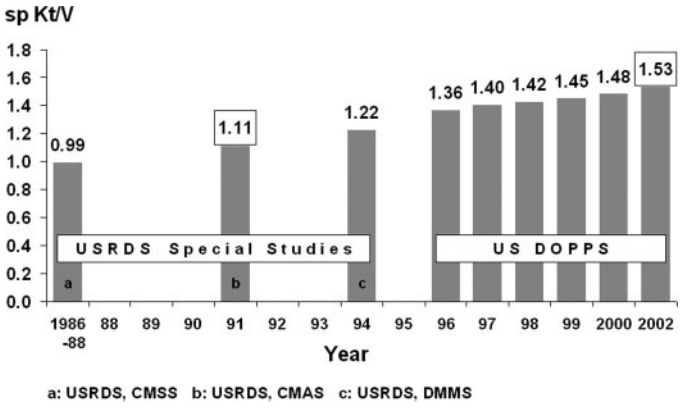



*Figure 8.* Single-pool Kt/V in various cross-sections of the US patients during the past 15 yr.

group and 1.53 in the high-dose group (spKt/V = 1.32 and 1.71). Corresponding urea reduction ratios averaged 66.3 and 75.2 in the two groups. During the mean follow-up time of 2.84 yr, patients who were randomly assigned to the high-dose group had a 4% lower risk for death than those in the low-dose group, which was statistically NS ($P = 0.53$) (30). The HEMO Study finding thus agrees with the null hypothesis of no benefit with higher Kt/V. However, there remains some uncertainty as a result of the wide 95% confidence interval of the estimate (relative risk 0.84 to 1.1), which is also consistent with the significantly lower mortality risk seen in observational studies such as the DOPPS (31). The DOPPS and US national data also confirm the unexplained finding of the HEMO Study showing a significant benefit of higher Kt/V for women but not for men (32,33).

Previous reports of the registries and DOPPS had suggested a nonlinear correlation between morbidity or mortality and Kt/V (34–36). Figure 9 shows that an increase of the average spKt/V from 1.1 in 1991 to approximately 1.3 in the mid-1990s was associated with a steeper decrease of mortality risk, compared with a similar increase of Kt/V during the following years until 2002. This suggests that an increase of Kt/V in its lower range has a larger effect than it does in its higher range.

In DOPPS I, 24 to 42% of HD patients across seven countries received dialysis with Kt/V <1.2; this percentage substantially decreased in DOPPS II, usually to <20%. Despite the consistently improved adherence to the guidelines, international variation in percentages of patients with eKt/V <1.05 (spKt/V <1.2) remains substantial, as shown in Figure 10. Part of this variation may be due to lack of acceptance of the Kt/V concept as a key measure of dialysis adequacy by dialysis units in some countries.

DOPPS data (31,32) and other observational study data (37–39) suggest an increased mortality risk with low dialysis dose; the HEMO Study data are also not inconsistent with the interpretation illustrated in Figure 9. The HEMO Study results do not disagree with the K/DOQI recommendation of a minimum spKt/V of 1.2, as the low-dose group had Kt/V levels *above* this guideline. It remains uncertain whether increasing the Kt/V substantially above this level would reduce the morbidity and mortality in dialysis patients. The DOPPS points to other modifications of dialysis prescription, such as higher blood flow rates, longer dialysis treatment time even at the same Kt/V, and possible survival benefits associated with hemodiafiltration (40–42).

## Anemia and HD

Anemia is increasingly recognized as a major factor among the many others that are associated with mortality and morbidity in the dialysis population and has been the subject of a number of treatment strategies and targets. However, the optimal hemoglobin level for dialysis patients is still a matter of discussion, particularly regarding near-normal levels of hemoglobin. Only a few of the historical prospective and retrospective studies in dialysis patients have analyzed, with adjustments for comorbidities, the association between hemoglobin level and outcome (43–46). These studies have generally shown a strong and consistent association between higher hemoglobin or hematocrit levels and better outcome (43–49).

Unfortunately, results were not consistent for four prospective trials that analyzed all-cause mortality and cardiac events in dialysis patients who were randomly assigned to partial or complete anemia correction (50–53). Some trials reported a

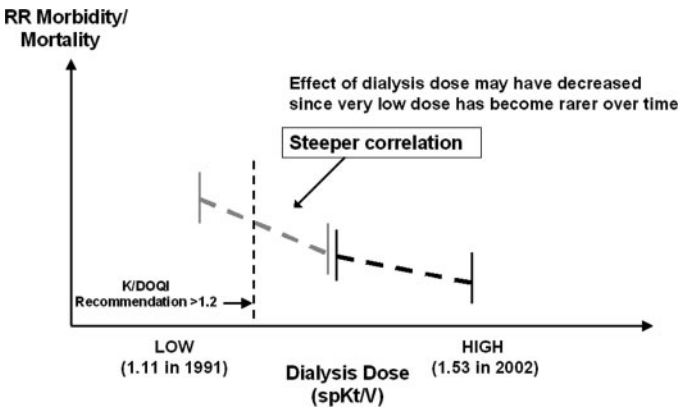



*Figure 9.* Hypothesized diminishing of effect of dialysis dose.

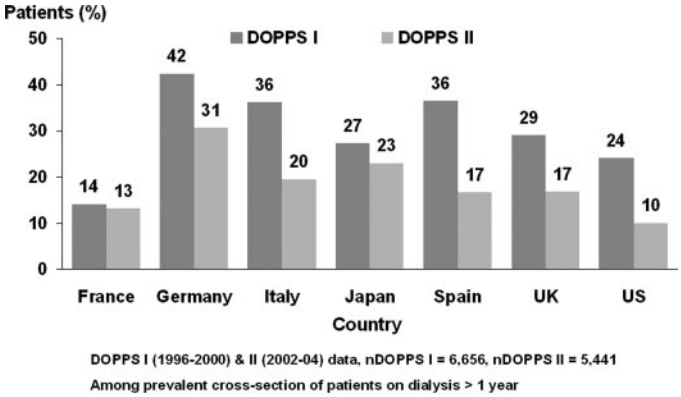



*Figure 10.* Percentage of patients with eKt/V < 1.05 (spKt/V < 1.20), below Kidney Disease Outcomes Quality Initiative guidelines.

significant reduction of left ventricular hypertrophy (LVH) in patients who were randomly assigned to higher hemoglobin levels (54) and the possibility of reducing or reversing LVH by optimizing antihypertensive therapy along with normalizing hemoglobin values (55). A trial of older patients with severe cardiovascular diseases and a high percentage (60%) of grafts suggested a reduced risk with lower-than-normal hemoglobin target (50). Another study (53) was able to demonstrate better quality of life for patients who were randomly assigned to a higher hemoglobin level, confirming the findings of previous studies (56,57).

As shown in Figure 11, DOPPS I and II combined data reveal a strong association between higher hemoglobin levels and improved outcomes. The adjusted relative risk for mortality was on average 6% lower for every 1-g/dl higher hemoglobin concentration ($P < 0.0001$). Although this association does not prove causality, the large sample size and the adjustments for a large number of patient case-mix characteristics (58,59) provide strong support for the validity of the current guidelines for managing anemia (60).

The strength of these correlations is further increased from the results of time-dependent hemoglobin modeling of the association between hemoglobin levels and mortality risk with updated hemoglobin levels at 4-mo intervals. Taking as a reference value the hemoglobin interval of 11 to 11.99 g/dl, the relative risk for mortality was more than two times higher for patients with hemoglobin level <8 ($P < 0.0001$), 35% higher for those with hemoglobin between 8 and 9.99 ($P < 0.0001$), and 11% higher for those with hemoglobin between 10 and 10.99 g/dl ($P = 0.03$), as seen in Figure 12. Hemoglobin levels >12 g/dl were not associated with an increased mortality risk, although half of the values in this category were ≤12.7 g/dl.

It is encouraging that substantial improvement has recently been made in anemia management. The mean hemoglobin of the five European DOPPS I countries increased from 10.8 g/dl in 1998 to 1999 to 11.4 g/dl in 2002. A similar trend in hemoglobin increase has been observed in Japan and the United States (Figure 13). However, DOPPS II findings indicate that

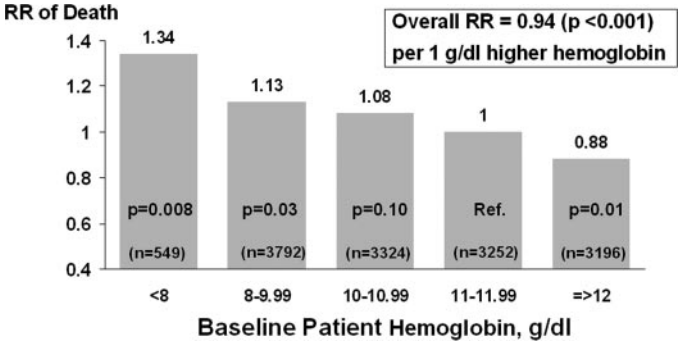



*Figure 11.* Higher baseline hemoglobin levels associated with lower mortality risk. DOPPS I+II: 12 countries, patients on dialysis >180 d, adjusted for age, gender, black race, body mass index, years with ESRD, 14 comorbid classes, spKt/V, serum $PO_4$, serum calcium, albumin, continental region, and facility clustering.

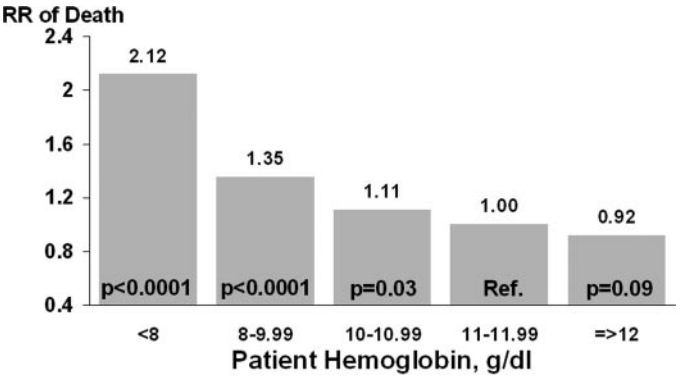



*Figure 12.* Time-dependent hemoglobin modeling: Association of hemoglobin with mortality risk. DOPPS I+II data: 12 countries, adjusted for age, gender, black race, body weight, 15 comorbid classes, serum $PO_4$, serum calcium, albumin, erythropoietin units per week, country, hospitalization during time interval, and facility clustering. Data for incident patients were not used until after 4 mo of dialysis therapy. *Using repeated hemoglobin measurements over course of study participation, excluding hemoglobin measurements within 2 mo of date of death.

| | Japan | | Europe† | | U.S. | |
|---|---|---|---|---|---|---|
| | DOPPS I (n=2055) | DOPPS II (n=1634) | DOPPS I (n=2285) | DOPPS II (n=2505) | DOPPS I (n=3218) | DOPPS II (n=1930) |
| Hgb, mean | 9.7 | 10.1 | 10.8 | 11.4 | 10.8 | 11.7 |
| Epo use, % | 78.8 | 83.1 | 77.5 | 90.3 | 90.4 | 91.7 |
| Epo dose, units per week | - | 5594 | 6486 | 7899 | - | 17238 |
| Epo use prior to ESRD, % | 10.6* | - | 10.8* | 19.2* | 10.4* | 14.9* |
| TSAT, mean | 27.9** | 27.2** | 35.2** | 30.5** | 28.2* | 27.9 |
| % ptnts with TSAT < 20 | 32.6** | 34.1** | 19.2** | 21.6** | 32.1* | 26.6 |
| Ferritin, mean | 185* | 610** | 415* | 551* | 363* | 578* |
| % ptnts with ferritin < 100 | 53.5* | 16.5** | 17.7* | 9.6* | 20.5* | 8.3* |
| % ptnts with ferritin > 800 | 4.5* | 23.1** | 12.7* | 19.2* | 10.2* | 24.3* |
| IV iron use, % | - | 32.3 | 54.8 | 69.0 | 30.3 | 57.7 |

Based on a prevalent cross-section of patients on dialysis > 180 days
† Includes France,Germany, Italy, Spain and the United Kingdom

*15-30% of patients did not have data available
**Greater than 30% of patients did not have data available

*Figure 13.* Anemia management in DOPPS, by phase and region, based on prevalent cross-section of patients who were on dialysis for >180 d. Epo, erythropoietin; TSAT, transferrin saturation.

Japanese patients still have lower hemoglobin levels than their European and US counterparts (10.1, 11.4, and 11.7 g/dl, respectively). Prescriptions of erythropoietin in units per week are higher in the United States than in Europe and Japan (59). This finding can be only partially explained by the relatively small body size of Japanese patients and by the approximately 30% higher burden of severe comorbidities of patients in the United States. The lower mean hemoglobin value in Japan may also reflect the lower guideline target for hemoglobin in Japan. Moreover, hemoglobin concentrations typically are measured on Monday/Tuesday dialysis sessions in Japan, compared with Wednesday/Thursday sessions in most other countries. The greater blood volume dilution that is known to be associated

with Monday/Tuesday dialysis sessions is expected to yield a somewhat lower reported hemoglobin concentration. Finally, the erythropoietin reimbursement policy in Japan and in some European countries likely affects anemia management practices, too.

Data about iron use are more homogeneous among the 12 DOPPS countries, excepting Japan, which displays a substantially lower percentage of patients who receive intravenous iron and consequently a higher proportion with ferritin <100 ng/ml. The mean ferritin value exceeds 500 ng/ml in all of the DOPPS regions (Figure 13). These findings need careful monitoring in the near future, given that the European Best Practice Guidelines (17) have recently revised the higher limit for the serum ferritin target to 500 ng/ml and because iron overload is thought to increase oxidative stress in patients with very high ferritin levels.

Although the majority of prevalent HD patients have a hemoglobin >11g/dl and receive erythropoietin (approximately 90% in Europe, DOPPS II) (59), the same is not true for patients who start HD (Figure 14). Indeed, only 21 to 65% of patients who were new to HD received erythropoietin during the predialysis period. Consequently, the mean hemoglobin concentrations and the percentage of patients who fulfilled present anemia guideline requirements was substantially lower at the start of HD than for HD patients who were on dialysis for >180 d.

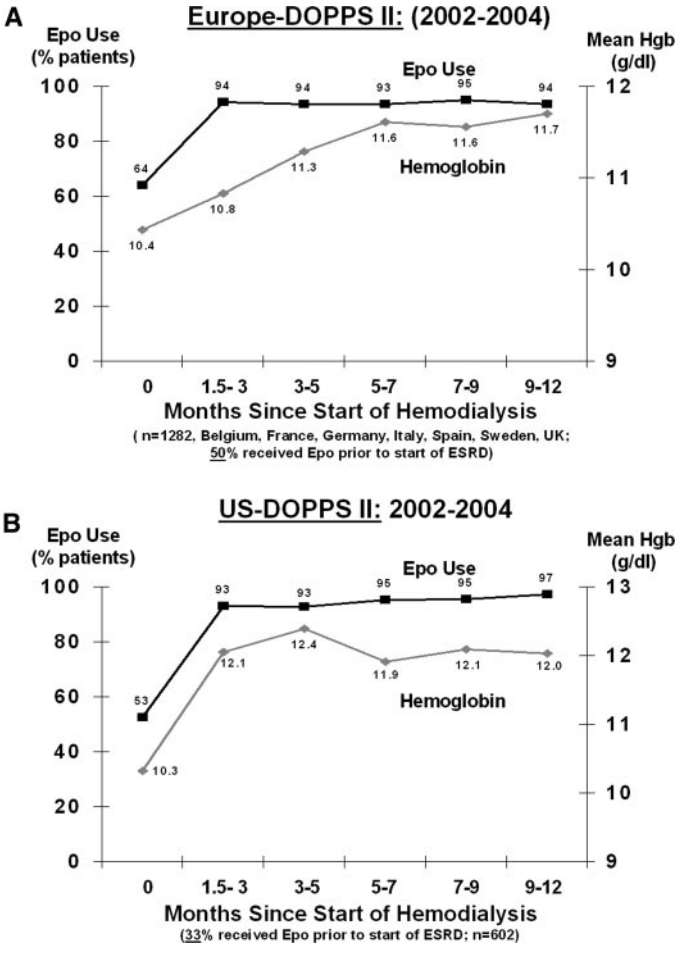



*Figure 14.* Time trend in erythropoietin use and mean hemoglobin for new ESRD patients after initiating HD. Restricted to patients who received long-term dialysis ≤7 d before study entry.

Despite a significant increase in erythropoietin use after the start of HD and a progressive rise in serum hemoglobin, several months are yet required for hemoglobin concentrations to rise to the recommended level (Figure 14). The steeper rise in hemoglobin levels among new HD patients in the US incident patients could conceivably be due to dosing pattern differences between the United States and Europe. Thus, a considerable proportion of patients remain more markedly anemic for a long time after the beginning of dialysis. The same seems to be true in the delicate late phase of chronic kidney disease (CKD), according to the average hemoglobin of 10.3 to 10.4 at the start of HD. Extrapolation from data in dialysis patients suggests that this could increase the risk for mortality and cardiovascular complications and reduce patient quality of life. While awaiting needed randomized, controlled trials, improving the anemia management during this period seems to be indicated. This may be an opportunity to reduce the cardiovascular burden and other clinical problems that are related to the level of predialysis of anemia during CKD stages 4 and 5.

## Limitations

As an observational study, the DOPPS findings of associations cannot prove causative relationships. DOPPS findings point to the need for more randomized, controlled clinical trials. Where this is ethically not feasible (*e.g.*, randomization to high phosphorus levels or catheter use) and until such trials are completed, observational data are of great importance to the practicing physician. The focus here on prevalent patients is relevant to clinical practice, *i.e.*, all patients in a dialysis unit, although such patients are survivors of progressive CKD and of dialysis therapy. Recently, Wolfe *et al.* (61) were able to show that dialysis facilities in the United States that showed greater improvement in meeting guidelines for hemoglobin or Kt/V had a great improvement in their patients' mortality than observed in facilities with smaller or no changes in the adherence to these guidelines. This study, based on 2858 dialysis facilities, reduced the limitations of observational data.

## Conclusion

Because the DOPPS evaluates nationally representative dialysis centers and random samples of patients, it allows comparisons of practices by country and over time. Results on VA, dialysis dose, and anemia show some encouraging trends, although less so regarding indicators of mineral metabolism. Large opportunities to improve care of dialysis patients thus are documented for each of the 12 DOPPS countries. Outcomes findings from the DOPPS largely support the guidelines developed in different regions. The international perspective of DOPPS assists in the new efforts for international evidence-based guidelines (KDIGO).

A third phase of the DOPPS began in 2005. The extension of this study will allow monitoring of responses to the more recently published guidelines. At the same time, DOPPS III

uses refined techniques to evaluate practices that achieve greater compliance with guidelines for improved outcomes of HD patients.

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Functioning vascular access is the lifeline of the hemodialysis patient. Please refer to the Disease of the Month article in the April issue of *JASN* (available online at www.jasn.org) on vascular access to compliment the papers by Nassar *et al*., Asif *et al*., and the access data from DOPPS in this issue of *CJASN*.