International Hemodialysis Patient Outcomes Comparisons Revisited: The Role of Practice Patterns and Other Factors

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The Dallas conference on ESRD in 1989 was a landmark meeting. Among the many presentations, the one by Philip Held stimulated a great deal of discussion. On the basis of data from three registries, the US Renal Data System (USRDS), the European Dialysis and Transplant Association (EDTA), and the Japanese Society of Dialysis and Transplantation (JSDT), he showed higher mortality in the United States than in the other two regions. Categories of age and reported cause of ESRD (diabetes *versus* other) were available in the registries, allowing for descriptions of outcomes by strata of age and diabetes, or adjustment for age and diabetes. The main outcome was 5-yr survival for all patients with ESRD (dialysis and transplantation combined). In virtually each age by diabetes group, a lower percentage of patients survived to 5 years in the US registry than in either the EDTA or the JSDT (1). These results, summarized in Figure 1, were widely quoted for many years. In this article, we (*1*) explore potential explanations for these international outcomes differences using more recent data, (*2*) consider trends in therapy during the past 20 years, and (*3*) describe how study of the associations of practice patterns with outcomes has informed regional differences in survival and can be used to identify opportunities to improve outcomes at the present time.

Potential Explanations for Regional Differences in Survival

The findings of Held *et al.* (1) were considered controversial by many because of the concern that they might reflect or imply poorer care of dialysis patients in the United States. In this section, we consider alternative explanations (*e.g.*, various sources of bias) that may in part explain the findings, and we explore the possible role of differences in dialysis treatment delivery that may account for some of the survival differences.

Regional Differences in Data Quality

The differences in survival could have been due to differences in data completeness and/or event ascertainment, because the USRDS (a mandatory registry) captured all patients and all deaths (supplemented by other sources), whereas the other two registries might have had less complete reporting. The international Dialysis Outcomes and Practice Patterns Study (DOPPS) was begun in 1996 in the United States, in 1999 in Japan, and in 1998 in Europe and was partly motivated to provide insight into the survival differences of hemodialysis (HD) patients by geographic region. The DOPPS provided the opportunity to study case mix, practices, and outcomes using uniform data collection systems and death ascertainment in nationally representative samples from each participating country (2–5). A DOPPS study of mortality risk, with adjustment for very detailed case-mix indicators, allowed Goodkin *et al.* (6) to confirm the original findings of relatively higher mortality in the United States compared with Japan and Europe. Although these differences were somewhat attenuated with case-mix adjustment, mortality risk remained significantly elevated for the United States compared with Europe and Japan (Figure 2).

Regional Differences in Patients Who Start Dialysis

Registry data highlighting differences in new cases of treated ESRD per population (ESRD incidence) provided a suggestion of regional differences in patients who start dialysis. Among patients with terminal kidney failure, differences in acceptance for ESRD therapy (*i.e.*, whether dialysis is started at all) suggests active decision-making about suitability for dialysis. Even without differences in acceptance for dialysis, key clinical and/or socioeconomic characteristics of patients who reach ESRD may differ (*e.g.*, age-matched patients in the United States might reach ESRD with a substantially greater comorbidity burden). As noted already, the DOPPS provided the opportunity to capture uniform, detailed patient data from patients in each participating country and found significant differences in survival even after detailed adjustment for patient characteristics. The possibility cannot be completely excluded that these differences were due in part to "unmeasured confounders" (*e.g.*, regional differences in patient health status that were unrecognized or unmeasured).

Regional Differences in Selection for Transplantation

Because the DOPPS is a study of HD patients and does not include patients who have ESRD with a functioning kidney transplant, the markedly longer survival in Japan may be explained in part by the very low transplantation rate there. Higher transplantation rates in the United States and Europe may deplete the dialysis pool of healthier patients, so the higher mortality in these regions than in Japan is likely explained, at least in part, by differences in transplantation rates. However,

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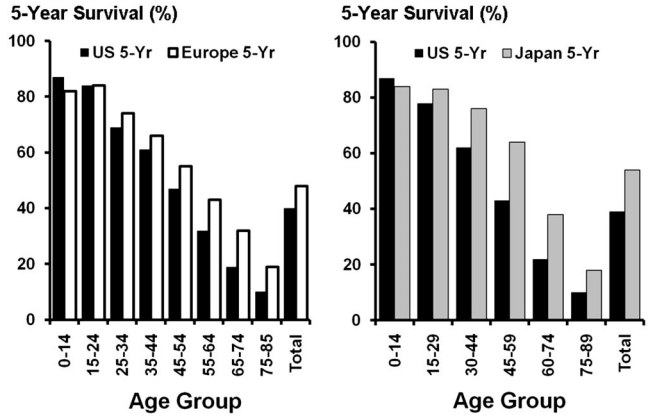

Figure 1. Five-year renal replacement therapy survival by age in the United States *versus* Europe (1982 through 1987) and the United States *versus* Japan (1983 through 1987). US data from the Health Care Financing Administration, European data from EDTA, Japanese data from JSDT (1984 through 1988). European and Japanese age group rates and total rates are standardized to the United States.

the original study by Held *et al.* compared outcomes among all patients with ESRD (dialysis and transplantation). Even though Japan had fewer transplant recipients than the United States, survival was longer there (Figure 1). In addition, because transplantation rates are generally similar for the United States and most European countries in the DOPPS, this explanation does not seem to contribute substantially to the difference in survival between these two regions (7).

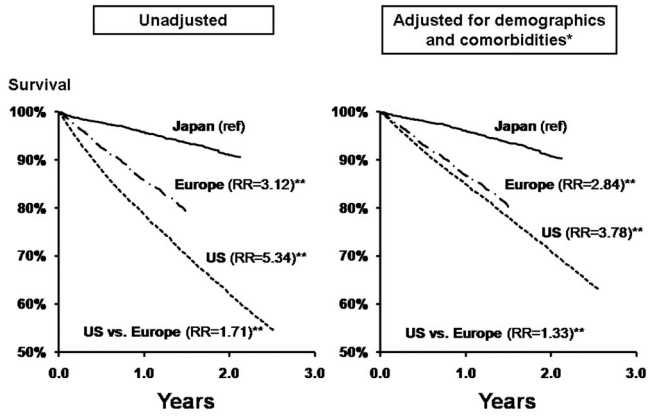

Figure 2. Survival among HD patients in Japan, Europe, and the United States: Data from DOPPS I (1997 through 2001). *Cox proportional hazards model adjusted for age, male gender, black race, coronary artery disease, congestive heart failure, other cardiac disease, left ventricular hypertrophy, cardiomegaly by x-ray, hypertension, cardiovascular disease, peripheral vascular disease, diabetes, lung disease, dyspnea, smoking, cancer, HIV/AIDS, gastrointestinal bleed, peptic ulcer disease, hepatitis B, hepatitis C, neurologic disorder, psychiatric disease, recurrent cellulitis or gangrene, and vision problems. $^{**}P < 0.001$.

Regional Mortality Differences in the General Populations

Another question was whether large differences in the mortality rate in the respective general populations might contribute to the differences in survival for patients with ESRD. Regional US data have shown that mortality for dialysis patients varies by region and correlates with mortality differences in the general population (8); therefore, one may hypothesize that higher mortality in US dialysis patients is partly explained by higher mortality in the general population. Using data from national ESRD registries and DOPPS, Yoshino *et al.* (9) correlated national mortality rates among dialysis patients with national mortality data for the general population from the World Health Organization. A strong association was found, suggesting that countries with relatively high mortality rates in the general population also have relatively high mortality rates in the dialysis population. To consider international differences in treating older dialysis populations, this study also adjusted for age, within the limits of the data, and found an even stronger correlation (Figure 3). In sum, a portion of the observed international differences in mortality among dialysis patients may be explained by international differences in overall health status in the population at large. As noted already, data from countries with very low transplantation rates need to be viewed with caution when analyzing results for dialysis populations.

Regional Differences in Dialysis Care: Vascular Access Practice Differences

The DOPPS has shown large international variations in vascular access (VA) practice. Differences in patient survival by VA type are widely known. Thus, the question arises whether differences in patient survival between regions is in part explained by differences in VA practice. Pisoni *et al.* (10) recently addressed this question in analyses of DOPPS I and II data. US HD patients had 36 to 40% higher adjusted mortality risk than HD patients in five European DOPPS countries; however, when

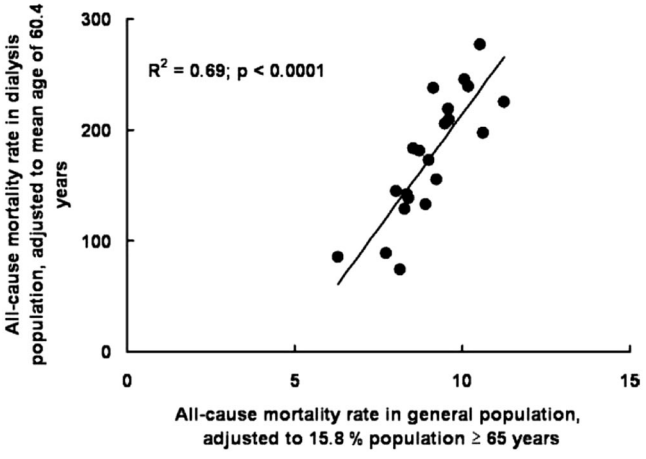

Figure 3. Relationship of all-cause mortality rates (per 1000 population) between general population and dialysis population, by country ($n = 21$). Adjusted for age in the dialysis population and general population. Each dot represents one country. Reprinted from reference 9, with permission.

these survival models were also adjusted for VA use within each facility, the excess mortality risk was attenuated to 6 to 19% (Figure 4). The elevated mortality among HD patients in the United States *versus* Japan was also attenuated somewhat by adjusting for differences in facility VA use. By contrast, the survival differences between regions were not substantially attenuated by adjustment for several other facility practices (treatment time, phosphate, calcium, Kt/V, hemoglobin, and albumin). These results suggest that differences in facility VA use may be one of the main factors explaining the higher mortality risk for HD patients in the United States. Recently, Foley and Hakim (11) suggested several other dialysis treatment practices that differ between regions, are modifiable, and may contribute to international differences in patient outcomes.

Practice Trends in the Past Decade

ESRD care has certainly changed since the 1989 Dallas conference. Among numerous examples, anemia care was revolutionized by the introduction of erythropoietin in the year of the conference. This is exemplified by the observation that the fraction of dialysis patients who receive at least one outpatient blood transfusion per 3 months decreased from 14% before 1989 to <4% as early as 1 year after erythropoietin became available in the United States and has remained very low since (7).

Another example of a dramatic change is the trend in dialysis dosage as estimated by single-pool Kt/V (spKt/V). Nationally representative samples of HD patients in three special studies of the USRDS and subsequent samples from three phases of DOPPS allowed us to describe the average spKt/V in US HD patients over time. As shown in Figure 5, there has been a consistent increase in the dialysis dosage during the past two decades. These examples of dialysis practice could be correlated with improvement in the case-mix adjusted mortality in the United States (12); however, causality of a relationship with mortality cannot be proved. It is interesting that as the mean Kt/V values increased over time, the fraction of patients with spKt/V values <1.2 decreased, which is a range below that studied in the HEMO Trial.

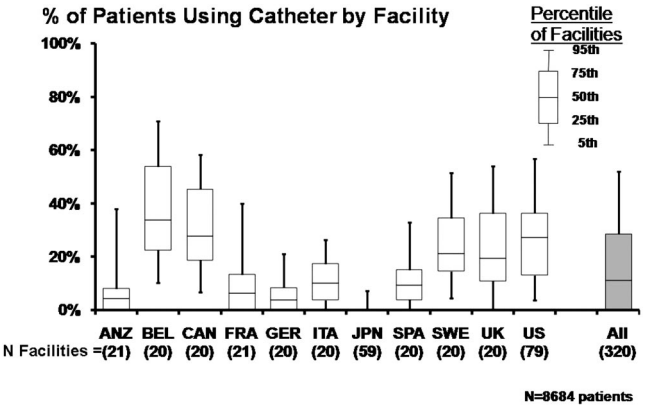

Figure 4. Distributions of percentage of facility patients using a catheter for HD access, by country. DOPPS II (2002 through 2004); $n = 320$ facilities and 8684 patients. Based on the initial prevalent cross-section in facilities with five or more patients with VA data.

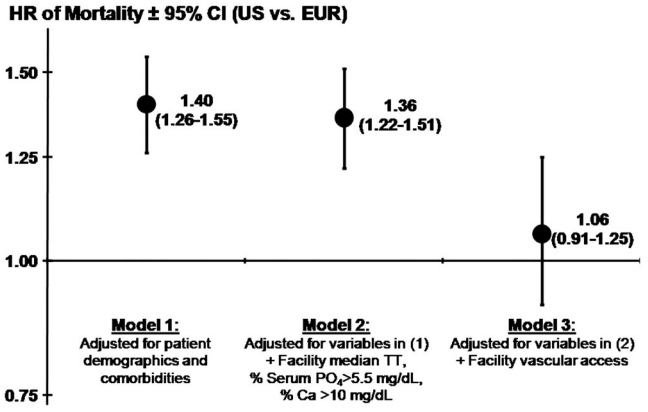

Figure 5. Mortality in the United States *versus* Europe: Influence of adjustment for facility catheter use. Case-mix adjusted hazard ratio (HR) of mortality for HD patients in the United States *versus* five European DOPPS I and II countries ($n = 24{,}398$), with and without adjustment for differences in facility VA use (case-mix adjusted percentage of facility patients using a catheter and the percentage using a graft referenced to the percentage using a native AVF). All Cox models were adjusted for patient age, gender, black race, number of years with ESRD, body weight, 14 summary comorbid conditions, whether treated in a hospital-based unit, stratified by study phase, and accounted for facility clustering effects. Model 2 was additionally adjusted for facility median treatment time (TT) and percentages of patients with serum phosphorus >5.5 mg/dL and serum calcium >10 mg/dL. Model 3 was additionally adjusted for facility VA. Reprinted from reference 10, with permission.

The DOPPS has provided the opportunity to describe trends over the past decade in a wide range of treatments in nationally representative samples of dialysis facilities. Trends in VA, dialysis prescription, laboratory parameters, medication use, and adherence to guidelines have been reported (13–15).

Identifying Opportunities to Improve Practices and Outcomes for HD Patients

When assessing mortality risk by VA use, the usual approach of correlating use with outcomes among individual patients has the potential to provide biased results. Because patients who undergo dialysis by a catheter tend to be sicker than those who undergo dialysis by a fistula, higher mortality among catheter users may be largely because these patients are sicker than those with an arteriovenous fistula (AVF) or graft. Because we observed in the DOPPS that the type of VA use varies widely from one dialysis facility to another, even in the same country (Figure 6) and when adjusting for differences in case mix between facilities, we were able to study the differences in mortality risk by greater *versus* lower facility catheter use (specifically, the percentage of patients who used a catheter in each facility) while adjusting for detailed patient characteristics, country, and year (10). This statistical approach of applying the practice (*e.g.*, facility catheter use) to patient survival models is similar to "instrumental variable analysis," a technique widely

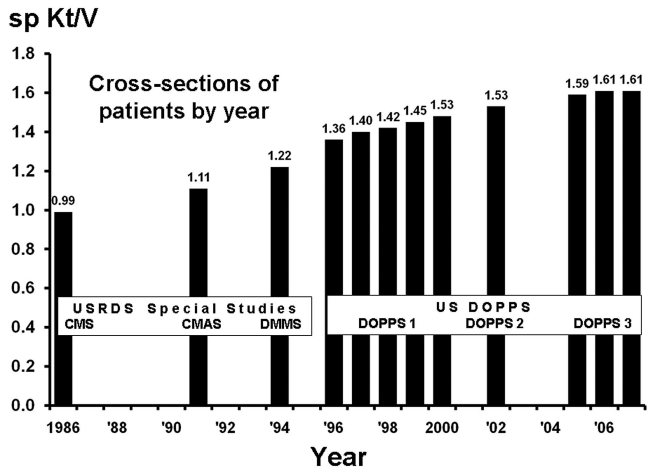

Figure 6. Change over two decades in mean spKt/V among US HD patients. CMS, Centers for Medicare and Medicaid Services; CMAS, Case Mix Adequacy Study; DMMS, Dialysis Morbidity and Mortality Study.

used in economic studies and now more commonly applied to studies of comparative treatment effectiveness in clinical medicine (16–18). The result provides a mortality risk estimate that is based not on the individual patient's use of a catheter, but on the facility practice of greater *versus* lesser catheter use. This analytical approach tends to reduce confounding by indication (*e.g.*, as a result of preferential selection of patients with higher mortality risk for catheter use). DOPPS analyses showed that the overall mortality risk was 20% higher for patients who were treated in facilities with 20% greater case-mix adjusted catheter *versus* AVF use (*e.g.*, 30 *versus* 10% of patients using a catheter, rather than an AVF). In short, patients in facilities with fewer catheters have longer survival.

Although randomized trials provide the strongest evidence to guide clinical medicine, few "gold standard" clinical trials (*i.e.*, multicenter, controlled trials of clinical outcomes) have been completed of dialysis patients. In reality, many (or most) treatment decisions must be made under conditions in which supportive clinical trial data cannot be obtained, including situations in which clinical equipoise is questioned, in which treatment choices are complex, or in populations that may not be readily studied or tend not to participate in clinical trials. Most clinical decisions have to be made before availability of clinical trial results even under the best of circumstances. In dialysis patients, for example, it seems unlikely that patients could ever be randomly assigned to a target phosphate level above 6.0 mg/dL; neither could a clinical trial realistically detect differences in outcomes according to a difference in target phosphate levels as small as 0.5 to 1.0 mg/dL.

Because clinical trial findings cannot inform numerous treatment decisions made in the dialysis unit, we can ask whether the principles of randomization can be applied to analyses of observational data, which are much more readily available. The answer is, in many circumstances, "Yes." Our analysis of facility catheter use, described already, is one example. When differences in facility practices are large, they are likely not explained (or explained only in part) by differences in patient characteristics and are instead due to differences in provider preferences for one treatment over another. Here, one can consider patients as being "randomized" to a practice by factors, such as proximity to home, which are unrelated to health status. This practice-based analytical approach is particularly successful when the average treatment patterns differ substantially among facilities and when case-mix differences can be adjusted. The results assume that provider opinion or preferences are relevant (*i.e.*, that they influence treatment decisions above and beyond differences in patient characteristics alone). In addition, this approach requires the assumption that other practices are not linked with the practice being studied (*i.e.*, a "good" or "bad" practice effect). Although this assumption cannot be completely verified, in DOPPS analyses we adjust simultaneously for other practices (*e.g.*, percentage of patients who achieve clinical practice guidelines) to lessen this concern. In our experience so far, we have been encouraged that adjustments for several other practices have not meaningfully modified the associations seen for practice-based instrumental variable analyses.

Some additional examples of analyses of facility practices and their rationale follow. The first of these is mortality risk by phosphate level. Hyperphosphatemia is associated with elevated mortality, but the utility of this finding for the clinician (*i.e.*, how should this influence practice?) is limited: Patients with very high phosphate levels are often poorly adherent to therapy, and elevated mortality may be due to poor adherence in general rather than hyperphosphatemia itself. Using DOPPS data, Tentori *et al.* (13) observed large differences between dialysis facilities in the percentage of patients with high serum phosphate levels. Marked variation between facilities was observed within, as well as between, countries. For example, 25% of US facilities had ≤26% patients with phosphate levels >6.0 mg/dL (>1.9 mmol/L), whereas 25% had at least 40% of patients >6.0 mg/dL and 5% had at least 53% of patients >6.0 mg/dL. Because this variation remained large after adjustment for case mix, it is reasonable to suspect that it was largely due to practice differences (*e.g.*, opinion regarding the importance of tighter phosphate control and/or preferences for one therapy over another). Applying the practice-based (instrumental variable) approach, we observed that patients who were treated at dialysis facilities with a higher fraction of patients with phosphate levels >6.0 mg/dL had higher mortality risk. It is interesting that the elevation in cardiovascular mortality risk was particularly pronounced, as shown in Figure 7.

As another example, Saran *et al.* (19) found that patients who receive longer treatment time (among patients who receive thrice-weekly dialysis sessions) have longer survival. However, this finding may potentially be biased because patients with shorter life expectancy may receive shorter dialysis sessions. We have therefore applied a practice-based approach, and initial findings indicate that patients who are treated at dialysis facilities that on average provide longer treatment sessions have overall lower mortality risk (20). Again, the patient-based findings are corroborated by these practice-based analyses, pro-

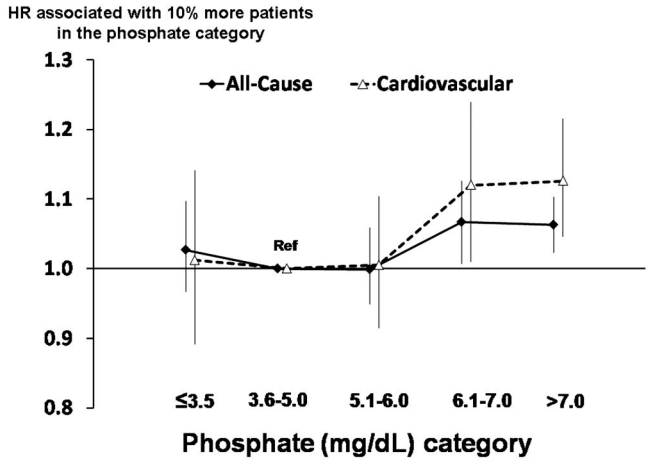

Figure 7. Associations of facility distribution of serum phosphorus levels with all-cause and cardiovascular mortality, among patients on HD >180 d in the DOPPS (n = 20,561). Hazard ratios and 95% confidence intervals (whiskers) for all-cause (events n = 5857) and cardiovascular mortality (events n = 1930). Models were stratified by study phase and region and adjusted for facility clustering effect; baseline patient age, gender, race, body mass index, time on ESRD, 13 comorbid conditions, hemoglobin, albumin, normalized protein catabolic rate, spKt/V, previous parathyroidectomy, and vitamin D prescription; and the percentage of patients at a facility within serum calcium and parathyroid hormone categories. For phosphate, 1 mg/dL = 0.323 mmol/L.

viding an additional level of evidence supporting the importance of the association.

Conclusions

International mortality differences for the United States *versus* Europe and Japan—as reported 20 years ago—have been confirmed with more recent data from DOPPS, using uniform data collection for death ascertainment and detailed case-mix adjustment. Better outcomes for Japanese dialysis patients may be exaggerated to some extent because selection of healthier patients for transplantation is minimal in Japan. Differences in background mortality in the general population, by country or region, seem to explain, in part, differences in dialysis patient outcomes. Differences in VA practice seem to explain a substantial component of the mortality difference between the United States and elsewhere, thus pointing to an opportunity to improve care and outcomes in the United States. Comparing the US with European DOPPS countries, results both without and with adjustment for VA are relevant in that (*1*) mortality is confirmed to be higher for similar patients in the United States than in Europe and (*2*) mortality is nearly equivalent for similar patients in the United States and Europe who undergo dialysis in facilities with similar patterns of VA use.

A variety of aspects in dialysis prescription has changed during the past two decades. Two striking examples include the large increase in average dialysis dosage and the major reduction in blood transfusions since the introduction of erythropoietin.

The DOPPS has shown that dialysis practices vary substantially from one dialysis facility to another, both within and between countries. These differences allow assessment of outcomes by practice pattern, which can lessen in part confounding by indication that may bias patient-based observational analyses. When evaluating practice preferences, our finding that the differences in practice from one dialysis unit to another are often very large may also be persuasive to clinicians, because this large variation strengthens the argument that differences in outcomes may be due in part to differences in provider preferences. Patients in dialysis facilities with greater catheter use or a greater fraction of patients with hyperphosphatemia have significantly higher mortality. These and other findings provide further strong evidence from observational data that may be relevant to improving dialysis practice, patient survival, and quality of life.

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Disclosures

None.

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