The Dialysis Outcomes and Practices Patterns Study (DOPPS): Opportunities to improve health-related outcomes for hemodialysis patients

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The Dialysis Outcomes and Practice Patterns Study (DOPPS) is a large prospective, international cohort study entering its fourth phase, having begun in 1996. Near the start of the DOPPS, the National Kidney Foundation was releasing the Dialysis Outcomes Quality Initiative (DOQI), which subsequently incorporated guidelines for all stages of chronic kidney disease and became the Kidney Disease Outcomes Quality Initiative (KDOQI)¹,². The ultimate objectives of both the DOPPS and KDOQI are similar – that is, the improvement of outcomes in patients with chronic kidney disease. While KDOQI uses a methodology of guideline development to support clinical practice recommendations, the DOPPS uses a research methodology to test hypotheses about patient characteristics, laboratory data, and treatments prescribed at dialysis units to identify practice patterns associated with improved outcomes for patients on maintenance hemodialysis. The DOPPS has also been evaluating the incorporation of clinical practice guidelines into dialysis practice and the impact of adherence on the recommendations concerning morbidity and mortality across countries and dialysis unit settings.

The first phase, DOPPS I, included detailed data from adult hemodialysis patients treated at more than 300 total dialysis units from the United States (initiated in 1996), five European countries (France, Germany, Italy, Spain, and United Kingdom, beginning in 1998), and Japan (1999). DOPPS II started in 2002 and added five more countries (Australia, New Zealand, Belgium, Canada, and Sweden) with enhanced data collection on patients new to dialysis. During 2005-2008, DOPPS III collected additional information on practices and protocols in dialysis facilities as “processes of care” in the same 12 countries. Overall, the DOPPS has provided clinically relevant information based on detailed data gathered from more than 41,000 patients in over 900 dialysis facilities. Data collection for DOPPS IV began in 2009. More than 80 DOPPS publications are listed in MEDLINE. Some DOPPS publications have already been cited in more than 100 articles according to ISI Web of Knowledge³.

This editorial summarizes methodological aspects and selected results from the DOPPS that call attention to patient characteristics and clinical practices found to be associated with outcomes in populations on maintenance hemodialysis.
ASPECTS OF STUDY DESIGN AND STATISTICAL APPROACHES

DOPPS design

The DOPPS is a prospective cohort study, collecting the same data from a random sample of a representative sample of facilities in each country. Details have been published elsewhere on the design. Within each country, the appropriate institutional review boards have approved the study. Informed patient consent has been obtained in accordance with local requirements.

The DOPPS uses a stratified selection process based on facility characteristics (e.g., free-standing, hospital-based, satellites, etc.) and regions within each country. By selecting representative samples, the DOPPS permits description of practice patterns across regions and allows generalization of the findings to national dialysis populations. The large variation in practice patterns among dialysis facilities within and between countries enables the DOPPS to identify significant correlations between practice patterns and patient outcomes.

The DOPPS uses common protocols and standardized data collection instruments across all countries. Detailed patient-level and facility-level information is obtained at study enrollment. Longitudinal detailed data are also collected at subsequent four-month intervals. DOPPS participants are asked to complete validated questionnaires annually on topics such as quality of life, satisfaction with care, depression, sleep disturbance, medication adherence, and nutrition. Additionally, the dialysis facility’s medical director and nurse study manager complete questionnaires annually to provide focused facility-practice information. The latter questionnaires provide a unique opportunity to understand differences in opinions and actual practices that are not available in large administrative or clinical dialysis databases.

DOPPS analytical approaches

DOPPS analyses are performed using both patient-level and facility-level variables. Many DOPPS studies incorporate aspects of both types of analyses that simultaneously account for differences among patients and facilities. Analyses of the patient level variables are used when the main objective is to identify patient characteristics associated with health status (e.g., nutritional status, quality of life, and depression) or with adverse outcomes, such as death and hospitalization. Analyses of facility-level variables are performed to identify practice patterns associated with patient-level hemodialysis outcomes; these can include the health status indicators listed above, as well as mortality, hospitalization, and vascular access failure.

Associations between patient characteristics and health status or subsequent outcomes are assessed by using appropriate statistical methods to account for differences in factors such as socio-demographic attributes, comorbidities, and treatments. Time-to-event models are used to identify prognostic factors captured at the initiation of the follow-up. To investigate changes in laboratory values or health status over time and relate these values to outcomes, time-dependent Cox survival models are used.

To identify which factors account for differences between groups, the DOPPS performs sequential adjustments. An example is DOPPS work developed to assess differences in survival by race/ethnicity among dialysis patients in the United States. The initial results showed survival advantages for each of five racial/ethnic minority categories compared with non-Hispanic white patients. The survival advantages, however, were substantially attenuated or lost in Cox models with progressively more comprehensive adjustment. This suggests that the outcomes differences by race/ethnicity can be explained by a variety of other known factors. From a practical standpoint, the rounding clinician should expect dialysis patients belonging to racial/ethnic minority groups to have survival rates similar to those of white patients with the same demographic and clinical attributes.

One important concern in analyses of associations between treatment and outcomes in observational studies is the influence of uncontrolled confounding by indication. If this confounding stems from differences in treatment of the patients, it may be called treatment-by-indication bias. This type of bias may happen, for example, when the indication to treat a hemodialysis patient with a certain medication is related to the likelihood that
the patient has a higher risk of early death that may, in turn, be prevented by the medication. In this situation not only the effects of the prescribed medication but also differences in the patients according to their indication to receive – or not receive – the medication could account for the risk of death. As these patient characteristics are associated with both the indication to treatment and also with survival, they should be viewed as potential confounders of any association between the treatment and mortality risk. Statistical adjustments control for the confounding effect of measured patient characteristics in order to determine the actual effect of the treatment. However, as many patient characteristics related to the likelihood of death are unknown or not measured, it is not possible to control for the effects of these characteristics on the results by performing analysis of treatment variables at the patient level, that is, analysis based only on patient data.

Analyses of facility level treatment are used in the DOPPS to reduce the influence of unmeasured characteristics (confounders) in the associations between practices and patient outcomes. For these analyses, facility-level measures that represent summaries of practices (such as percentage of patients with prescription of certain medications or having phosphorus within guideline range) are initially determined. In using this statistical method, the summary practice variable is assigned to all patients at the facility as a proxy for the practice. This minimizes treatment-by-indication bias in many situations in which the indication for treatment is associated with prognosis.

The DOPPS approach to analyzing facility-level treatment variables is conceptually similar to instrumental variable analysis, a methodology embraced for decades in econometrics and now used more commonly in clinical studies to address treatment-by-indication bias. The approach seeks to identify natural experiments in which patients are nearly “randomly” assigned to a particular facility practice (and treatment preferences) by factors independent of clinical characteristics, such as proximity to the patient’s residence. Ideally, this mimics randomized treatment assignment in a clinical trial. Recent publications discuss theoretical considerations and provide examples in clinical medicine outside of nephrology.

### SELECTED FINDINGS FROM THE DOPPS

#### Treatment time and ultrafiltration rate

There has been a long debate on whether increasing dialysis treatment time may increase the clearance of middle molecules and provide a better control of blood pressure and volume. DOPPS findings have supported the benefit of longer dialysis sessions in patients on thrice weekly hemodialysis. In this study, DOPPS researchers found that a hemodialysis session longer than 240 minutes was associated with an almost 20% lower risk of death (relative risk (RR)=0.81; P=0.0005). The data also suggest that, overall, an increase of 30 minutes may reduce the mortality risk by 7% (RR=0.93; P<0.0001). By contrast, rapid ultrafiltration above 10 ml/h/Kg was associated with a 30% increase in the odds of intradialytic hypotension (odds ratio =1.3; P=0.045) and with a 9% increase in mortality (RR=1.09; P=0.02). This finding was not explained by higher Kt/V alone. For any level of Kt/V, a longer hemodialysis session was associated with improved survival. Moreover, a statistically significant interaction between treatment time and Kt/V was observed, with the greater benefit of longer treatment time being observed at a higher delivered Kt/V than at lower Kt/V. DOPPS data also show improvement of phosphorus control and appetite among hemodialysis patients receiving longer dialysis sessions. These data supported health policy changes specifically aimed at improving hemodialysis outcomes in Japan. In April 2008, the Japanese reimbursement for dialysis was changed to provide higher pay for longer treatment times (personal communication from Dr. Takashi Akiba, July 16, 2008).

#### Vascular access

**Vascular Access at the Initiation of Maintenance Hemodialysis** – To improve outcomes, KDOQI recommends that at least 50% of patients with newly diagnosed end-stage renal disease (ESRD) who receive hemodialysis have an arteriovenous fistula (AVF) placed and ready for use. DOPPS II data show, however, that the percentage of new ESRD patients initiating hemodialysis with an AVF from 2002 to 2004 was below the KDOQI target in...
several participating countries\textsuperscript{22}. The percentages of patients entering DOPPS II within seven days of first-ever chronic hemodialysis with an AVF as a functioning vascular access was 16% in United States, 26% in Canada and Belgium, 31% in Sweden, and 37% in the United Kingdom. Germany (72%) and Japan (69%) had the highest percentages of new patients receiving hemodialysis by AVF between 2002 and 2004. The DOPPS has shown that late referral to a nephrologist is a major contributing factor to the higher percentages of patients who start hemodialysis with catheters instead of a permanent vascular access\textsuperscript{22}. Other practices associated with hemodialysis by catheter were longer wait times to be seen by a vascular surgeon and longer time between surgical evaluation and vascular access creation\textsuperscript{23,24}.

Arteriovenous Fistula and Patient Survival – KDOQI also recommends that fewer than 10% of patients on chronic hemodialysis be maintained on catheters as a permanent vascular access, defined as the use of a catheter for more than three months without a maturing permanent arteriovenous access\textsuperscript{21}. DOPPS results support K/DOQI recommendations on vascular access practices by showing that mortality is lower at dialysis facilities having a higher percentage of patients with an AVF as the dialysis access\textsuperscript{22}. The DOPPS has shown large variation across regions in the percentage of patients on maintenance hemodialysis by catheter or graft instead of an AVF. In Japan, Italy, Germany, Spain, and France, an AVF is the vascular access used by more than 75% of patients and grafts by 10% or less\textsuperscript{22}. On the other hand, in the United States, the percentage of patients with an AVF has risen to 47% since 1997, with 28% of hemodialysis patients using an arteriovenous graft\textsuperscript{22}. Recently, the DOPPS has found that the much lower use of AVF in the United States (compared with other DOPPS countries) could not be explained by case-mix differences and that the lower percentage of patients with an AVF and larger fractions with a catheter or a graft appear contribute substantially to the lower survival in patients on maintenance hemodialysis in the United States versus Japan and Europe (Fig. 1)\textsuperscript{25}.

Practices Associated with Type of Vascular Access – The DOPPS has analyzed data reported by surgeons affiliated with DOPPS facilities to identify practices associated with greater use of AVF, as well as with lower use of catheters as vascular access. The study found that the average number of vascular accesses created during surgical training varied widely across countries\textsuperscript{26}. The median number of AVF created during surgical training varied markedly, from 16 in the United States to 426 in Germany. Patients were much more likely to receive hemodialysis by an AVF if surgeons had created more AVF during training. Moreover, AVF survival was substantially shorter if surgeons had created fewer than 25 AVF during training. These results strongly suggest that improvements in AVF placement rates and survival may be obtained with greater emphasis on AVF creation during surgical training\textsuperscript{26}.

Recent Changes in Vascular Access Practices in the United States – The DOPPS showed a strong relationship between patient vascular access use and the type of access preferred by the medical director and nurse manager. This work further showed the United States to be the only DOPPS country in 1997-1998 in which a substantial percentage (25%-40%) of medical directors and nurse managers preferred grafts to AVF as the access of first choice for hemodialysis patients. Despite this variation in preference, the use of AVF as a permanent access has been associated with better outcomes even at dialysis facilities where the medical director preferred grafts instead of AVF\textsuperscript{27}. These DOPPS results played an important role in the
development of the Fistula First Initiative in the United States by the Centers for Medicare and Medicaid Services (CMS)\textsuperscript{22,23,28,29}. After publications of the DOPPS results and launch of the Fistula First Initiative, many US medical directors and nurse managers changed their views about vascular access, shifting viewpoint to consider AVF as the access of first choice. The DOPPS showed that, from 1996 to 2007, AVF use increased from 24% to 47% in the United States. However, DOPPS data have shown that the percentage of patients using a catheter in the United States is still high. While the use of AVF increased in the United States, the use of grafts fell from 58% in 1996 to 28% by 2007. DOPPS data support the strategy to use the arteriovenous graft instead of a catheter as vascular access in situations in which an AVF fails or cannot be created\textsuperscript{23}. Thus, the goal should be fistula first and catheter last.

### Anemia management

To improve dialysis outcomes, KDOQI recommends for anemia control a target serum hemoglobin concentration of 11 to 12 g/dL\textsuperscript{30}. The DOPPS has supported KDOQI guidelines by showing that patient mortality risk was 10% lower for every 1 g/dL greater facility mean hemoglobin level\textsuperscript{31}. The DOPPS has also found an independent association between lower serum hemoglobin concentration and lower scores in several components of health-related quality of life (HRQOL) in hemodialysis patients\textsuperscript{32}.

The DOPPS has reported great variation in the percentages of patients within dialysis facilities who achieve and maintain the KDOQI target for anemia control\textsuperscript{31}. The percentages of patients with more than 180 days on maintenance hemodialysis having hemoglobin serum concentration of 111 to 12 g/dL ranged from 23% in Sweden to 77% in Japan. According to the DOPPS, the percentages of patients less likely to reach the KDOQI target for anemia control are greater among younger patients, women, and those using a catheter as vascular access\textsuperscript{31}. The lower concentrations of serum hemoglobin in Japan could be explained, at least partially, by the use of a different target as well as by the restriction of erythropoietin doses to below 9,000 units per week, unless an exception to a written request is granted\textsuperscript{31}.

### Health-Related Quality of Life and Depression

Advances in dialysis have improved survival of ESRD patients. To optimize dialysis care, however, the quality of life of hemodialysis patients also needs to be improved. As recommended by KDOQI, self-report is better than staff report to assess HRQOL, since well-being depends subjectively on the experiences and expectations of the patient. The DOPPS has studied factors associated with HRQOL and the consequences of poorer HRQOL among hemodialysis patients\textsuperscript{32-36}. By using self-report, the DOPPS has identified differences in HRQOL associated with country, race/ethnicity, socio-demographic characteristics, and comorbidities. The importance of self-reported HRQOL as a predictor of adverse clinical outcomes is exemplified by DOPPS results showing that the association between lower scores for the physical component summary (PCS) of HRQOL and higher risk of death was stronger than the corresponding association between serum albumin and death (Fig. 2)\textsuperscript{35}. The DOPPS also found a strong association between lower scores in the mental component summary (MCS) of HRQOL and higher mortality risk\textsuperscript{35}.

Additional analyses using DOPPS data were performed to identify practices related to the diagnosis and treatment of depression. Using a 10-item questionnaire from the Center for Epidemiological Studies Depression Screening Index (CES-D) for symptoms of depression, the DOPPS showed a high percentage of patients in the 12 DOPPS countries (range: 39% – 62%) with scores above the cut-point used to identify those with a high probability of depression (i.e., score $\geq 10$ on a 0 to 30 scale)\textsuperscript{37}. Patients with a CES-D score $\geq 10$ were found to have a higher risk of death by any cause, withdrawal from dialysis, and hospitalizations. Physician diagnosis of depression and treatment with antidepressants also varied widely across countries. Only 25%-50% of patients with a CES-D score $\geq 10$ were diagnosed with depression by a physician in many of the countries\textsuperscript{37}. Patients on antidepressants also varied by country; scored averaged 34.9% among those with physician-diagnosed depression and 17.3% among those with CES-D score $\geq 10$. While the lowest prevalence of physician-diagnosed depression was observed in Japan (2.0%) and France (10.6%), the percentage of patients with CES-D score $\geq 10$ in these counties was similar to the whole sample, i.e., 43%.
Several clinical practice guidelines on serum phosphorus control for patients with stage 5 chronic kidney disease (CKD) have been published. Unfortunately, clinical trials to support recommendations have been largely lacking\textsuperscript{38,39}. Guidelines developed in different countries/regions have not recommended consistent targets for control of the mineral metabolism disturbances in stage 5 CKD. For phosphorus control the recommended targets vary from 2.4 - 3.5 mg/dL for the lower limit to 4.6 - 5.5 mg/dL for the upper limit\textsuperscript{38}.

The DOPPS has shown that there is large variation in mineral metabolism control across hemodialysis units in the 12 DOPPS countries, with large fractions of patients outside recommended guideline targets for serum concentration of calcium, phosphorus, calcium x phosphorus product, and parathyroid hormone (PTH)\textsuperscript{40-42}. Using several survival models with mortality as the outcome and narrow serum concentrations ranges of the laboratory markers of mineral metabolism as predictor variables, the DOPPS has identified ranges of calcium, phosphorus, and PTH associated with the lowest and highest mortality risk among patients on maintenance hemodialysis\textsuperscript{43}. The serum concentrations associated with the lowest mortality risk were for uncorrected calcium 8.6 to 10.0 mg/dL, for calcium corrected for serum albumin 7.6 to 9.5 mg/dL, for phosphorus 3.6 to 5.0 mg/dL, and for PTH 101 to 300 pg/mL (Fig. 3). The serum concentrations associated with the highest mortality risk were >10 mg/dL for calcium (both uncorrected and corrected for albumin), 7.0 mg/dL for phosphorus, and >600 pg/dL for PTH. Additionally, this work demonstrated significantly higher mortality for patients in facilities with a larger percentage of patients with serum phosphorus concentration ≥ 6.0 mg/dL compared with facilities with a larger percentage of patients in the reference category of 3.6 to 5.0 mg/dL. This is an important new finding since the percentage of patients with high phosphorus likely reflects the practices related to phosphorus control in the dialysis facility.

The DOPPS has described strong associations of mineral metabolism control with morbidities among hemodialysis patients\textsuperscript{41,44,45}. The adjusted rate of parathyroidectomy varied fourfold across DOPPS countries and was strongly related to higher patient
baseline serum levels of calcium, phosphorus, calcium x phosphorus product, and PTH. High serum calcium x phosphorus product was strongly associated with subsequent amputation rates in hemodialysis patients with diabetes. High serum calcium levels (>10.2 mg/dl) were strongly associated with hip fractures. The DOPPS has shown a substantial fraction of patients with high PTH levels who have not received prescriptions for phosphate binders, vitamin D, or cinacalcet. Also, prescription of phosphate binders was not observed for a substantial fraction of patients with high serum phosphorus. Thus, DOPPS findings have supported guidelines for serum calcium, phosphorus, and PTH levels and have identified areas within the practice of mineral metabolism control that deserve attention in order to improve facility practices.

**CONCLUSIONS**

The DOPPS sample is representative of a majority of the world’s maintenance hemodialysis population. The main objective of this large prospective cohort study is to identify practice patterns that can improve outcomes, including survival, morbidity, vascular access survival, and HRQOL for patients on maintenance hemodialysis. The results from the DOPPS have been instrumental in guiding health policies and in assessing the impact of compliance with guidelines on hemodialysis outcomes. Because of the sampling methodology used to select dialysis units and patients, DOPPS data may be viewed as representative of the populations of patients on maintenance hemodialysis in each country. The detailed patient characteristics and practices collected across dialysis units, as well as the analytic techniques used, allow the DOPPS to identify possible ways to improve the treatment that is offered to the large population of patients on maintenance hemodialysis.

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References


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