Dialysis Outcomes and Practice Patterns Study (DOPPS): Its Strengths, Limitations, and Role in Informing Practices and Policies

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Introduction
The Dialysis Outcomes and Practice Patterns Study (DOPPS) is a leading source of up-to-date, representative, and comprehensive data on hemodialysis practice and patient outcomes worldwide. Since its inception, the study’s primary aim has been to identify practices that extend survival and improve health-related quality of life (HR-QOL) for hemodialysis patients. The DOPPS has yielded research findings directly relevant to patients, health care providers, and policy makers. The following provides an overview of the study’s design and analytic approach, selected research findings and relevance to policy, new directions, and ways that the study complements other sources of dialysis data.

DOPPS Overview
DOPPS 1 began in 1996 in the United States and in 1998–1999 in Japan, France, Germany, Italy, Spain, and the United Kingdom. In DOPPS 2 (2002–2005), 3 (2006–2008), and 4 (2009–2011), these countries were joined by Australia, New Zealand, Canada, Belgium, and Sweden. The launch of DOPPS 5 is underway in 2012, with new directions and additional countries as detailed later in this article. DOPPS 1–4 followed 300–350 facilities in each study phase, having now collected basic demographic and mortality (census) data for >200,000 patient-years and detailed data for >75,000 patient-years. Additional details are available at http://www.dopps.org.

Funding for the DOPPS was initiated by Amgen in 1996 in support of a “longevity initiative.” Funding for Japan DOPPS has been provided solely by Kyowa Hakko Kirin since 1999. Outside of Japan, funding was provided solely by Amgen through 2008, but since 2009, has been provided by a consortium of sponsors including Amgen as well as Abbott, Baxter, Fresenius Medical Care, Sanofi Renal, and Vifor Fresenius Renal Pharma (current sponsors). Recent expansion of the DOPPS programs (into new countries, CKD, and peritoneal dialysis [PD]) has been made possible by directed sponsor support. All funding support is provided without restrictions on publications and preserves the independence of our scientific research.

DOPPS Goals, Design, and Data
DOPPS research goals are centered on the hypothesis that measurable differences in dialysis facility practices influence patient longevity, morbidity, and HR-QOL. Identifying opportunities for improvement is a primary motivation and guides research priorities (1,2). DOPPS research findings derive logically from key features of the study design. The DOPPS is a prospective cohort study with data from a random sample of patients within a random sample of hemodialysis units in each participating country. We use a stratified selection process to represent the composition of facility types (e.g., free-standing, hospital based, satellite, etc.) and regions within each country. Descriptions of DOPPS sampling and methods have been published (1,3,4).

Random sampling to enroll a representative sample of dialysis units was quite novel among epidemiologic studies at study launch. This approach supports the accurate description of actual practice in national hemodialysis populations and ensures that findings can be generalized to these populations. It also maximizes variation in practices and outcomes in order to enhance the analytic ability to identify important, potentially causal associations. We have learned much from the often surprising differences in practice among participating countries.

The DOPPS captures detailed longitudinal patient- and facility-level information using a common protocol and standardized data collection instruments. With each new phase of the DOPPS, operational flexibility allows questionnaire refinement and new substudies to test new hypotheses and keep the study current. The study collects census data, including demographic and survival data, for all patients in each DOPPS facility. For enrolled patients, detailed longitudinal data are collected that include demographics, numerous comorbidities, medications and dosing, monthly laboratory values, vascular access type and procedures, cause-specific hospitalizations, date and cause of death, and others. The reliability of clinical data abstraction in the DOPPS was confirmed most recently by independent reabstraction from a random selection of participants in our Chinese study, as well as similar data abstraction from European study sites previously.
The DOPPS collects rich data on patient-reported outcomes, with participants completing questionnaires annually on diverse topics such as HR-QOL, recovery time after a dialysis session, satisfaction with care, medication adherence, and others. To provide facility practice information, the unit’s medical director and nurse manager complete questionnaires annually, and surveys can also be collected from other staff. Proposals for new study modules, with collection of novel facility practice data or patient-reported data, preferably with validated survey instruments, are encouraged.

With respect to clinical data, the DOPPS has chosen explicitly not to collect additional biomedical tests (laboratory, radiographic, or other) beyond those ordered for routine clinical care, to avoid biasing the study toward selection of highly motivated (i.e., nonrepresentative) patients or facilities, or to influence practice among participating facilities. Because the DOPPS does not measure bioassays centrally, measurement error may be introduced by nonstandardized measurement. However, the effect is likely small. Even in the case of parathyroid hormone (PTH) assays, most DOPPS facilities use a single assay type (e.g., in the most recent survey: 88% intact PTH, 8% bio-intact PTH, 4% unsure), and we collect data on each laboratory’s reference range, allowing for standardization to this range in sensitivity analyses.

One example of the value of a multinational study is that we have a large amount of data on bioassays measured frequently in some, but not other, countries. For example, serum C-reactive protein (CRP) levels are measured routinely (e.g., monthly) in most DOPPS countries but rarely in the United States. Postdialysis electrolyte levels are measured often in many countries; serum fibrinogen, B-type natriuretic peptide, and troponin levels are common in a few countries. Our large longitudinal database of CRP levels formed the basis for a recent publication describing the range of CRP levels in routine dialysis practice, as well as the added prognostic information gained by CRP even when measured along with inflammatory markers relied on in the United States such as serum albumin and ferritin levels (5). Future analysis will evaluate whether physician responses to elevated CRP levels help to improve clinical outcomes.

DPM for US Trends

The DPM reports detailed, contemporary trends in US dialysis care from the national sample of 120–140 DOPPS facilities. Findings are updated every 4 months, with data lagged by about 4 months. Downloadable slides are also on the website. Publications include analyses of key findings after each major website update, which are accompanied by editorial comment (4,8,9).

The DPM was originally developed to report trends in dialysis care before, during, and after implementation of the new Centers for Medicare and Medicaid Services (CMS) bundled dialysis payment system, the End-Stage Renal Disease Prospective Payment System (ESRD PPS), over January 2011 to January 2014 (10,11). Now in place, the DPM provides a mechanism for public, detailed, and up-to-date reporting of trends in care regardless of cause. An illustrative example is the June 2011 revised US Food and Drug Administration label for prescription of erythropoiesis-stimulating agents (ESAs) to CKD patients, followed in July 2011 by the proposed Quality Incentive Program (QIP) update to remove the hemoglobin floor of 10 g/dl. DPM data indicate dramatic changes in anemia care soon thereafter, with declines in average ESA dose and hemoglobin levels that were larger and more abrupt than after PPS implementation in January 2011. Events now or in the near future also likely to shape clinical practice include roll-out and updates of the QIP in 2012 (based on data from 2010 forward), the anticipated addition to the PPS of oral dialysis-related medications in 2014, and the release of clinical practice recommendations (e.g., Kidney Disease: Improving Global Outcomes anemia in 2012), clinical trial findings (e.g., Evaluation of Cinacalcet HCI Therapy to Lower Cardiovascular Events in 2012), and competitor products (e.g., peginesatide in 2012) (12,13).

In addition to ESA dosing and hemoglobin level, other notable US trends we have reported from 2010 to 2012 include sizeable rises in intravenous iron dosing, ferritin levels, and PTH levels. At the same time, phosphorus levels above recommended targets remain commonplace. By raising public awareness of these findings, the DPM can help inform decisions surrounding calls to introduce QIP measures for these metrics or for consequences such as red blood cell transfusions. This helps assure that financial incentives with the PPS do not remain unchecked.

Advantages over Other Data Sources

Detailed DOPPS data, from a nationally representative sample of dialysis centers, complement data sources that may include more patients but are not representative nationally (e.g., large dialysis organization and other electronic health record data) or are limited in breadth of data (e.g., most registries and administrative data). CMS data also have limited information on incident dialysis patients and the rising percentage of patients covered primarily by private insurance or Medicare Advantage programs, because their care often does not generate Medicare claims. The DOPPS is well suited to study whether differing financial incentives among these patients will translate into differences in care. Prior DOPPS work comparing national financing for dialysis and evaluating links between incentives and patient care across the DOPPS countries has already been detailed and informative (14).
Some Caveats

DOPPS data are reported in aggregate. Facilities and facility groups are not identified individually, and the data are not intended to provide oversight of performance. Because the DOPPS is based on a sample, findings may differ slightly from national census data, and trends reported may merit confirmation with national data, in cases in which those are eventually available. In particular, estimated event rates (e.g., mortality, hospitalizations, transfusions) should be confirmed with national data. Specification of calculated variables also differs slightly from other data sources. For example, our calculation of the percentage of fistula use differs slightly from the Fistula First Initiative using CMS data (e.g., use of a new or marginally functional fistula is incompletely standardized across data sources), as does calculation of hemoglobin levels over time compared with CMS specifications for QIP measures (15,16).

Despite these considerations, we have documented that DOPPS descriptive findings are generally reflective of national dialysis data, because of attention paid to representative cross-sectional sampling and use of sampling weights to report aggregated data. Table 1 demonstrates that data from the DPM sample closely correspond to the national statistics reported by the Elab Project for 97% of US dialysis patients for the quarter of 2010 (17). Similarly, we have shown close correspondence of DOPPS data for the United Kingdom with clinical practice data reported by the UK Renal Registry (18). Such comparisons continue on a regular basis.

Identifying and Understanding International Trends

The DOPPS serves as a resource to monitor and understand temporal trends in dialysis care in each participating country, and to disentangle effects of a policy change in any one country from secular trends internationally. Some policy examples are as follows. In Japan, trends in anemia management from before to after changed ESA reimbursement in 2006, from separately billable (on a per-dose basis) to bundled within the overall dialysis reimbursement (19). This policy change was associated with reduced erythropoietin doses, increased intravenous iron use, and stable hemoglobin levels (19). In Germany, trends in care after the introduction of a weekly dialysis reimbursement rate in 2002–2003, were followed by a quality monitoring system in 2009 based on four parameters (Kt/V ≥1.2, dialysis frequency ≥3 sessions/week, dialysis session length ≥4 hours, hemoglobin ≥10 g/L). Improvements in these metrics occurred before the quality monitoring system; however, the percentage of patients with hemoglobin <10 g/L has increased in recent years (20).

The DOPPS is poised to monitor the effect of future policy changes on dialysis care in its participating countries. In the near term, examples are as follows. In Japan, reimbursement changes were enacted this year in support of hemodialfiltration. In Germany, changes to the weekly dialysis reimbursement rate and its inclusions are under consideration, as are changes to the quality monitoring system (such as adding accountability for hemodialysis catheter use, which is rising). In France, bundling of ESAs
and a reimbursement change for PD are under consideration. In the United Kingdom, a tariff was recently added for hemo-

dialysis via central venous catheter, based in part on DOPPS data demonstrating international variation in vascular access use (Figures 2 and 3). More broadly, economic uncertainty in many DOPPS Europe countries and elsewhere may have unforeseen consequences for dialysis patients. The DPM will expand soon to include Japan, and support for the DPM in Europe is currently sought to provide public reporting of up-to-date trends and international comparisons.

Comparisons of Outcomes Internationally

The DOPPS has been a key resource to directly compare mortality across countries because of representative sampling and uniform data collection methods (1,3). One original motivation for the study was the finding of higher mortality in the United States compared with Japan and Europe based on registry data (21). DOPPS analyses confirmed that this finding persists even after very detailed adjustment for patient characteristics (22), updated with data from 2005 to 2008 in Figure 4. Data from the DOPPS, as well as national ESRD registries and the World Health Organization, indicate that international survival differences among dialysis patients are explained in part by survival differences in the respective general populations (23). More recently, a DOPPS analysis demonstrated a modifiable dialysis practice as a key cause of international variations in outcomes (24). Specifically, regional survival differences (particularly for the United States compared with Europe) were largely explained by differences in facility vascular access use: US and European facilities with similar percentages of fistula, graft, and catheter use have, on average, similar survival. In recent years, with the Fistula First Initiative, there has been a commendable increase in fistula use in the United States, whereas in several other countries, fistula use has fallen and/or catheter use has risen substantially (Figures 2 and 3) (15,25). In the context of these trends, the most recent comparisons of survival internationally will be of great interest.

The DOPPS is not intended to provide precise event rates, which is a mandate of registries collecting national census data (26). As in most studies, sites agreeing to participate in the DOPPS may be somewhat more motivated, and thus have somewhat higher performance on average, than other facilities. Despite this possibility, the annual mortality rates reported by the DOPPS have been similar to, or only slightly lower than, those reported by national registries (4,27–30).

### Analyses of Practice Variation

From its outset, a primary aim of the DOPPS has been to identify facility practices associated with the best patient outcomes, with emphasis on practical findings. Over recent years, we have chosen statistical models that use variations in facility practice as a means to limit bias caused by differences in health status. These biases include treatment-by-indication bias, in which a beneficial treatment (e.g., longer dialysis session length) may appear to “cause” poorer survival because it is often prescribed to sicker patients; and dose-targeting bias, in which a clinical target (e.g., higher hemoglobin levels) may appear beneficial because it is more easily achieved in healthier patients (31,32).

One approach to limit these sources of bias is instrumental variable (IV) analysis, used for decades in econometrics and now increasingly in clinical studies (33–37). DOPPS analyses using IV approaches have been central to the study’s effect on hemo-
dialysis care (38–43). Technically, our analyses utilize group-based IV analysis, which uses aggregate treatment assignments as instruments; past publications used group-treatment analysis, which is not formally an IV analysis but yields very similar, although not mathematically identical, results (44–46). The premise is that patients who are treated by different dialysis facilities, but with the same clinical indications, are “assigned” to receive different levels of treatments due to different treatment preferences, protocols, or policies. For example, facility tendencies to provide dialysis by a catheter or to prescribe a particular dialysate sodium concentration or dialysis session length are based in part on discretionary factors such as training, preference, policy, and/or unit culture. In DOPPS data, we consistently see a wide range of facility practice variation within and

<table>
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<th>Laboratory Results and Demographics</th>
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<th>DPM (%)</th>
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<td>Hemoglobin, g/dl (mean)</td>
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<td>&lt;10</td>
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<td>Transferrin saturation ≥ 20%</td>
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*DOPPS, Dialysis Outcomes and Practice Patterns Study; DPM, DOPPS Practice Monitor; CMS, Centers for Medicare and Medicaid Services.

aElab 2010 and Trends Report (Renal Network of the Upper Midwest, St. Paul, MN; www.esrdnet11.org/Elab); data from the fourth quarter of 2010 for 97% of adult US hemodialysis patients.

bThe DPM is currently increasing this percentage through stratified facility sampling to randomly select facilities with higher prevalence of black patients.

cAscertained diabetes status is different between Elab and DPM; the DPM incorporates use of diabetes-related medications for more complete ascertainment of diabetes.
Figure 2. Distribution of vascular access type (2002–2011) among countries with rising catheter burden over time. Cross-sections of patients on dialysis >90 days at study entry, weighted by facility sampling fraction, in DOPPS 2 (2002–2004), DOPPS 3 (2005–2008), and DOPPS 4 (2009–2011). DOPPS, Dialysis Outcomes and Practice Patterns Study; Aus-NZ, Australia and New Zealand; AV, arteriovenous.

Figure 3. Distribution of vascular access type (2002–2011) among countries with stable or decreasing catheter burden over time. Cross-sections of patients on dialysis >90 days at study entry, weighted by facility sampling fraction, in DOPPS 2 (2002–2004), DOPPS 3 (2005–2008), and DOPPS 4 (2009–2011). DOPPS, Dialysis Outcomes and Practice Patterns Study; AV, arteriovenous.
between countries (Figures 2, 3, and 5). Like all analyses, this analytic approach can be susceptible to bias, and we typically supplement the approach with other techniques when indicated.

Example: Dialysate Composition

Recent DOPPS analyses of dialysate components are illustrative of the study of discretionary practice variation to help inform optimal practice. We have found that many facilities internationally use a single concentration of dialysate sodium, calcium, bicarbonate, or even potassium for nearly all patients, and that this single concentration varies between facilities (i.e., facilities choose one concentration or another). Recent DOPPS publications evaluating dialysate components, by IV analysis and other methods, have questioned the widespread belief that lower dialysate sodium levels are beneficial (47,48), and have raised the possibility that the commonly used dialysate potassium concentration of 2 mEq/L may raise the risk of sudden death compared with higher levels (41,49). Other analyses of dialysate composition are ongoing.

Example: Dialysis Session Length

In recent years, we have seen that dialysis session length has shortened in the United States, whereas it has gotten longer in most other DOPPS countries (Figure 5). By both standard and IV analyses, the DOPPS has found that longer treatment time is associated with lower mortality in
models adjusted for Kt/V, ultrafiltration rate, and other characteristics (Figure 6) (50). Facilities with longer mean treatment time also have better phosphorus and BP control (42).

In the United States, facility performance measures are not tied to dialysis session length, other than urea clearance measures that are usually achieved via high blood flow rate (BFR) and large dialyzer size even with shorter session length. Indeed, average BFR is notably higher in the United States than in Europe and is much higher than in Japan (42). As noted above, a quality monitoring system based on dialysis session length was implemented in Germany in 2009, and average session length in that country is now one of the longest in DOPPS countries (20).

In our opinion, short dialysis session length is now one of the key practice differences between the United States and other DOPPS countries, and its implications merit attention from research and policy perspectives.

**New Directions**

The DOPPS programs have expanded geographically in recent years with the launch of DOPPS in China in 2010 (with a random sample of dialysis facilities in three major cities), in Saudi Arabia in 2011 (with a random sample of facilities selected from the national registry), and in the other Gulf Cooperation Council countries in late 2012, as well as a CKD program in Brazil in late 2012 (51–53). A major goal of international expansion is to provide a detailed description of practice variation in participating nations, which we anticipate will inform allocation of resources to address unwanted practice variation and ultimately improve patient outcomes.

Other additions to the DOPPS programs include the Chronic Kidney Disease Outcomes and Practice Patterns Study (CKDopps) and the Peritoneal Dialysis Outcomes and Practice Patterns Study (P-DOPPS). CKDopps is being launched in five countries, and P-DOPPS data collection will launch internationally in 2013. CKDopps aims to gain understanding of optimal practices, services, and processes of care for advanced CKD patients, including modality choice and the transition to dialysis care, which have been difficult to study to date. We hope CKDopps will be especially relevant because effective integration of care is likely to improve outcomes and may soon be linked to reimbursement (extending from the model of accountable care organizations) in the United States (54). P-DOPPS, launched in partnership with the International Society of Peritoneal Dialysis, will focus on the major causes of PD technique failure to identify approaches to appropriately lengthen time on therapy. The community has indicated need for this collaborative research program because there are vast differences in access to and/or outcomes on this therapy, although rigorous studies to learn about optimal practice are lacking. At the same time, new financial incentives or expected cost savings will likely increase PD use in the coming years (10,55).

The DOPPS continues to yield research findings directly relevant to patients, health care providers, and policy makers. Over 140 DOPPS manuscripts have been published in peer-reviewed journals to date, and invited DOPPS symposia are regularly featured at major national and international renal conferences. DOPPS findings have been used to support and refine clinical practice guidelines (56) and have been presented or reported to government health policy and regulatory agencies around the world.

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**Figure 6.** Associations of dialysis session length with mortality and hospitalizations. Adjusted for age, sex, race, time on dialysis, body mass index, 13 summary comorbid conditions, residual kidney function, prescribed blood flow rate, and catheter use, stratified by country and phase of study, and accounted for facility clustering. In the standard regression model, the patient’s prescribed treatment time is the main predictor of interest. In the instrumental variable analysis, the predictor variable is the expected treatment time for a given patient based on the facility’s treatment time practice and facility case-mix. HF, heart failure; 95% CI, 95% confidence interval.
The topical areas (dialysis treatment time, facility staffing, vascular access, anemia management, dialysis dose measurement, patient-centered outcomes, etc.) have been diverse, but have leveraged our international data and analyses to identify and highlight unwanted practice variation, sharing a focus on practical findings (32,57,58). With the study’s new directions and collaborations, we seek to expand contributions toward improving longevity and quality of life for our patients.

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Disclosures

B.M.K. is principal investigator for the DOPPS, and R.L.P. and F.K.P. are senior investigators with the DOPPS. All coauthors are employees of Arbor Research Collaborative for Health.

References


