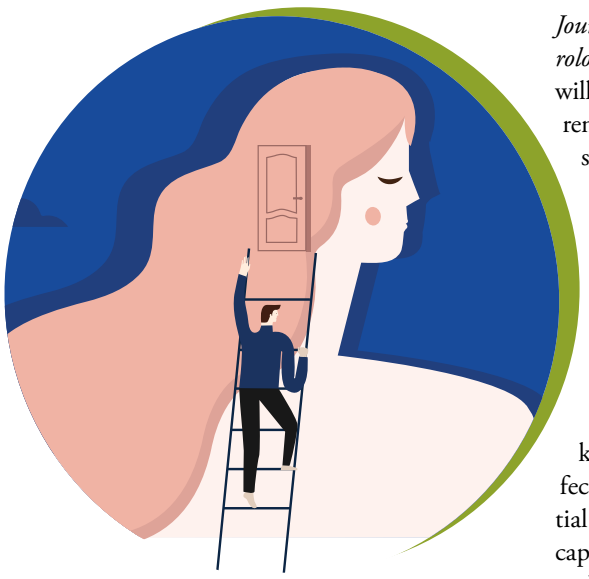
ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

KidneyNews

February 2017 | Vol. 9, Number 2

Depression Undertreated in Patients Receiving Chronic Dialysis

By Tracy Hampton



New research indicates that many patients who are receiving chronic hemodialysis have depressive symptoms but do not wish to receive aggressive treatment to alleviate them. The study, which is published in the *Clinical Journal of the American Society of Nephrology*, also found that when patients are willing to accept treatment for depression, renal providers commonly do not prescribe it.

Depression affects nearly one-quarter of people receiving chronic hemodialysis, compared with an average population lifetime risk of between 8.3% and 9%. These high rates likely reflect the various physiological and psychosocial consequences of living with impaired kidney function—from the adverse effects of frequent treatment to the potential loss of social support and vocational capacity.

Depression in dialysis patients affects not only their mental health and quality of life but has also been linked to missed and abbreviated dialysis treatments, more frequent emergency department visits and hospitalizations, and an increased risk of premature death. To address the negative effects that depression can have on dialysis patients' health and survival, the Centers for Medicare & Medicaid Services Quality Improvement Program (QIP) for end stage renal disease recently mandated that all dialysis facilities report individual patient screening and treatment plans for depression for payment year 2018. Little information, however, is available on the effectiveness of antidepressant therapy in patients on chronic hemodialysis or the acceptance of treatment by patients and clinicians.

To investigate, a team led by Steven Weisbord, MD, MSc, and Julio Pena-Polanco, MD, of the VA Pittsburgh Healthcare System and University of Pittsburgh School of Medicine, asked 101 patients on hemodialysis who were participating in the Symptom Management Involving ESRD (SMILE) trial to complete the Patient Health Questionnaire 9 (PHQ-9) each month. The prospective, multicenter, cluster-randomized SMILE trial compared 2 strategies for the management of 3 common symptoms in cognitively intact adults receiving chronic,

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Why Is Low Blood Pressure Related to Increased Cardiovascular Risk in CKD?

Study Suggests "Reverse Causality" from Subclinical Cardiac Disease

Many studies have noted a U-shaped association between blood pressure and cardiovascular risk in patients with chronic kidney disease (CKD). A report in *Hypertension* suggests a possible explanation for this paradoxical relationship: a confounding effect by subclinical cardiac disease.

"Confounding by disease is the chief explanation for the apparent weakening and reversal of the association between systolic BP and cardiovascular risk in moderate-to-advanced CKD," said William G. Herrington, MD, MRCP(UK) of the Clinical Trial Service Unit & Epidemiological Studies Unit (CTSU), University of Oxford. "Such confounding masks a causal association between blood pressure and risk in patients with CKD with established cardiovascular disease."

Together with other recent evidence, these results add weight to the hypothesis that more-intensive BP reductions might reduce cardiovascular risk in patients with CKD, including those on dialysis.

U-shaped association between BP and mortality in CKD

The researchers analyzed data from The Study of Heart and Renal Protection

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Depression Undertreated

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thrice-weekly outpatient hemodialysis at 9 dialysis units in western Pennsylvania.

For depressed patients (PHQ-9 score ≥10), trained nurses generated treatment recommendations and helped implement therapy if patients and renal providers accepted the recommendations.

Of the 101 patients who were followed for at least 1 year, 39 met criteria for depression based on their PHQ-9 scores. These 39 patients had depression on 147 of 373 (39%) monthly assessments. At 70% of these 147 assessments, patients were receiving anti-depressant therapy. and at 51 of 70 (70%) assessments, patients did not accept nurses' recommendations to intensify treatment. At 44 assessments, patients with depression were not receiving anti-depressant therapy and in 40 instances (91%) did not accept recommendations to start treatment.

In most cases, patients refused the recommendations because they felt their depression was attributable to an acute event, chronic illness, or dialysis. Factors associated with refusal of treatment recommendations were older age, being married, and African American race, although only the association of older age with treatment refusal was statistically significant.

In 11 of 18 instances (61%) in which patients accepted the recommendation related to treatment for depression, renal providers were unwilling to provide treatment. In 8 of these 11 instances, the renal provider offered no explanation for not accepting the recommendation; in 2 instances, the provider deferred treatment recommendations to the patients' primary care provider; and in 1 instance, the provider did not accept the recommendation because the patient was hospitalized.

"We discovered that some patients are on anti-depressant treatment that does not appear to be effective, and most who are not on treatment do not wish to be treated," Weisbord said. "We also noted that when patients do request treatment, renal providers commonly do not prescribe treatment."

Weisbord and his colleagues pointed to past research indicating that 90% of nephrologists provide primary care to their patients who are on dialysis and that as few as 20% of patients on chronic dialysis have a separate primary care provider.

"The apparent unwillingness of renal providers to consider implementing treatment for depression, particularly in the absence of primary providers who might assume this responsibility, represents a major obstacle to the systematic provision of therapy," they wrote.

Considering Medicare's recently released criteria for the end stage renal disease QIP, the authors noted that the implementation of a performance measure based on screening and treatment is logically based on the assumption that patients wish to have the condition treated. Therefore, the results of this study suggest that the requirement to universally document and provide care for depression in dialysis patients may be premature.

In an accompanying editorial, Maree Hackett, PhD, and Meg Jardine, PhD, of the University of Sydney, in Australia, noted that there are many challenges to the detection and treatment of depression in people on dialysis. "The importance of the inner experience may get lost by patients, carers and clinicians in a setting of intensive medical intervention, intercurrent comorbidities, and high rates of unwelcome events," they wrote. They argued that a safe, effective, low-cost treatment for managing depression could help patients live well, rather than just survive, while on dialysis.

Article: "Acceptance of Anti-Depressant Treatment by Patients on Hemodialysis and their Renal Providers." doi: 10.2215/CJN.07720716

Editorial: "We Need to Talk about Depression and Dialysis: But What Questions Should We Ask and Does Anyone Know the Answers?"

Low BP Related to Increased Cardiovascular Risk

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(SHARP)—a seminal trial in which 9270 patients with CKD were randomly assigned to ezetimibe/simvastatin versus placebo. The principal investigators of the SHARP Study (www.sharpinfo.org) were Colin Baigent, FRCP, FFPH, and Martin J. Landray, PhD, FRCP, also of CTSU.

The main SHARP results—published in *The Lancet* in 2011—showed that cholesterol-lowering therapy can substantially reduce the risk of major atherosclerotic events in CKD. Subsequent analyses of the SHARP data have yielded further insights on the outcomes and prognostic factors among people with CKD. In this new analysis, the SHARP investigators explored the paradoxical relationship between BP and cardiovascular risk in patients with CKD.

In apparently healthy adults, as BP increases so does the risk of death from ischemic heart disease, stroke, or heart failure. Risk is approximately doubled for each 20 mm Hg increase in "usual" systolic BP and each 10 mm Hg increase in diastolic BP—there is no threshold below which lower SBP is not associated with lower risk.

However, in CKD, the association curve is often U-shaped—cardiovascular risk is increased at both higher and lower BP values, including low-normal BP. One suggested reason is reverse causality: longstanding hypertension may lead to changes in cardiac structure and function, thus lowering BP while at the same time increasing cardiovascular risk.

Previous studies have found that at least half of patients with stage 4 to 5 CKD show cardiac structural abnormalities, often without signs or symptoms. In the Chronic Renal Insufficiency Cohort (CRIC) study, 75% of patients with an estimated glomerular filtration rate less than 30 mL/min per 1.73 m^2 had left ventricular hypertrophy on echocardiography.

Herrington and colleagues tested the hypothesis that the association between BP and cardiovascular risk might be confounded by the presence of such cardiac damage—patients who have CKD but have not yet developed cardiac disease might exhibit a positive loglinear association similar to that observed in apparently healthy adults.

To do this, the researchers needed a marker of cardiovascular risk. "The investigative trick was to use blood troponin to identify those at lowest risk of subclinical heart disease," Herrington explained. "This was based on several previous studies showing that troponin-I is positively correlated with left ventricular mass and negatively correlated with cardiac function."

In the SHARP cohort, higher baseline troponin-I was associated with male sex, older age, higher systolic BP, a higher prevalence of diabetes, and

worse renal function. During a median follow-up of nearly five years, 2188 subjects had one or more cardiovascular events—a rate of 6.7% per year.

On adjusted analysis, higher baseline troponin-I was a strong predictor of future cardiovascular events. Risk was increased 61% for CKD patients with baseline troponin-I over 0.01 ng/mL and 182% for those over 0.03 ng/mL (compared to the reference value of 0.01 ng/mL or less). This association was apparent in both dialysis and non-dialysis CKD patients.

In the full cohort, the association between systolic BP and cardiovascular risk was U-shaped. However, among the 7278 patients without previous cardiovascular disease, there was a positive loglinear association. On adjusted analysis, each 10 mm Hg increment in usual systolic BP was associated with a 16% increase in cardiovascular risk. This risk increased to 27% per 10 mm Hg when analyses were further restricted to those patients without evidence of subclinical cardiac disease—i.e., baseline troponin of 0.01 ng/mL or less. The association was little affected by adjustment for baseline albumin:creatinine ratio, was about the same for atherosclerotic and nonatherosclerotic events, in dialysis and nondialysis patients, and among patients younger than 62 (the study median age) and those 62 years or older.

In the full cohort, however, there were also U-shaped associations for diastolic BP (but not pulse pressure). Associations with diastolic BP remained U-shaped among patients with a low troponin-I.

Support for studies of lower BP targets in CKD

The findings add to previous data on the complex relationship between BP and cardiovascular risk in CKD. Herrington and coauthors write: "The presence of a clear positive loglinear relationship between SBP (or pulse pressure) and cardiovascular events in patients with CKD at lowest risk of cardiac disease in SHARP suggests that reverse causality is a plausible explanation for previously observed U-shaped associations among patients with moderate-to-advanced CKD."

Herrington commented: "This suggests that guidelines should not be using observational analyses of BP to define optimum BP targets in diseased populations, as such analyses may wrongly conclude that lower BP is dangerous, when the opposite may be the case."

Randomized trials, which control for such confounding, have supported the effectiveness of lowering BP in other population groups where U-shaped associations between BP and cardiovascular risk have been observed, including patients with prior cardiovascular disease and older adults (e.g., the Systolic Blood Pressure Intervention Trial, or SPRINT). The same may therefore be true in CKD.

In the absence of sufficiently large trials, the optimal BP target in CKD remains unknown, and current recommendations vary widely. Recent studies, including SPRINT, "taken together with the evidence of reverse causality in the present analysis in the SHARP trial, suggest that trials of lower BP targets in patients with CKD are indicated," the researchers write. Such studies would also address the potential harms as well as benefits of lower BP targets; in SPRINT, more intensive BP control was associated with an increased risk of acute kidney injury.

"The findings in this paper probably are most applicable to people with CKD not on dialysis," commented Rajiv Agarwal, MBBS, of Indiana University School of Medicine, Indianapolis. In a 2004 review in *Hemodialysis International*, Agarwal hypothesized that reverse causality might account for the U-shaped association between blood pressure and cardiovascular risk in CKD.

To understand the association between BP and cardiovascular risk would require home or ambulatory BP recordings—which weren't available in the SHARP data.

"Nonetheless, observational studies show that low BP associates with higher mortality in dialysis, while meta-analyses of randomized trials suggest the opposite," Agarwal said. "While we don't have a definitive trial on BP level and outcomes in dialysis, I believe that the meta-analyses trump the observational data. Clearly there is room for research in this important area."

Baigent noted: "The observational data in SHARP only appear to show that lower BP associates with higher risk of cardiovascular events. We argue that, if correctly analyzed with due regard to the presence of confounding by subclinical cardiac disease, the true association between BP and risk of major cardiovascular events is positive throughout the range studied."

Suggested Reading

1. Herrington W, et al. Evidence for reverse causality in the association between blood pressure and cardiovascular risk in patients with chronic kidney disease. *Hypertension* 2017; 69:314–322.
2. Agarwal R. Exploring the paradoxical relationship of hypertension with mortality in chronic hemodialysis. *Hemodial Int* 2004; 8:207–213.
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5. The SPRINT Research Group: A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med* 2015; 373:2103–2116.

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KidneyNews

Editorial Staff
Editor-in-Chief: Richard Lafayette, MD
Executive Editor: Dawn McCoy
Design: Lisa Cain Design
Communications Assistant: Sara Leeds

ASN Kidney News is published by the American Society of Nephrology
1510 H Street NW, Suite 800, Washington, DC 20005. Phone: 202-640-4660

www.asn-online.org

Postmaster: Please send address changes to *ASN Kidney News*, c/o Customer Service, American Society of Nephrology 1510 H Street NW, Suite 800, Washington, DC 20005.

Publications mail agreement No. 40624074. Return undeliverable Canadian addresses to PO Box 503, RPO West Beaver Creek, Richmond Hill ON L4B 4R6

ASN Kidney News (ISSN print 1943-8044 and online 1943-8052) is an official publication of the American Society of Nephrology, 1510 H Street NW #800, Washington DC 20005, and is published monthly. Periodicals postage paid at Washington, DC and at additional mailing offices. Subscription rates: $12 per year. To order, please email bhenkel@asn-online.org. Subscription prices subject to change. Annual ASN membership dues include $12 for *ASN Kidney News* subscription.

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Policy Update

GAO Report Reveals Extent of Underfunding of Kidney Disease Research Relative to Health Burden Cost

The American Society of Nephrology (ASN) has repeatedly cautioned health care policymakers that kidney diseases are at staggering levels and, for decades, there have been too few new therapies for treating patients. Now, the US Government Accountability Office (GAO) has conducted a study and published its findings in a new report released January 18, 2017, *National Institutes of Health: Kidney Disease Research Funding and Priority Setting*, that statistically validates these points. The report highlights the inadequacies of federally funded medical research for kidney diseases in the face of a staggering burden on patients and taxpayers.

GAO conducted the study at the request of members of Congress from both the House of Representatives and the Senate. Prior to that request in 2015, ASN had formally requested these members of Congress to call on GAO to conduct the study. GAO is a part of the federal legislative branch, and only members of Congress can direct the agency to undertake studies.

The study, a "performance audit," was conducted from February 2016 to December 2016 and examined two primary factors affecting federally funded kidney disease research: 1) the level of NIH funding for biomedical research on kidney diseases, and for other leading diseases and conditions; and 2) how the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) sets priorities for kidney disease research.

GAO reported that the "NIH, within the Department of Health and Human Services, is the primary federal agency that conducts biomedical research on kidney disease, as well as various other diseases and conditions. NIH's budget—$30 billion in fiscal year 2015—mostly funds extramural research that supports research personnel working at universities, medical schools, and other institutions. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)—one of NIH's 27 institutes and centers (IC)—has primary responsibility for kidney disease research."

GAO began by identifying diseases and conditions with a high disease burden in the United States relative to other conditions based on data from the Centers for Disease Control and Prevention (CDC). Investigators analyzed CDC's national survey data, and interviewed CDC officials to identify conditions that had high mortality, or were chronic conditions with high prevalence, or both. They then matched the diseases and conditions identified with fiscal year 2015 data—the most current available—from NIH's Research, Condition, and Disease Categorization (RCDC) system, which categorizes NIH research projects (and associated funding) into categories.

One unique aspect of kidney diseases in terms of policy is that Medicare covers every American suffering from kidney failure—regardless of age—and guarantees them access to dialysis or kidney transplants through the End-Stage Renal Disease (ESRD) Program. Kidney failure is the only condition covered by Medicare for patients under 65 years of age. More than 20 million Americans have kidney diseases and more than 650,000 have kidney failure.

Despite this commitment to care for patients with kidney diseases, the report demonstrates a significant gap between investment in research and the disease burden. Annually, the federal government spends more on the Medicare ESRD program (nearly $32 billion) than it invests in the entire National Institutes of Health (NIH) budget ($30 billion). With just $564 million dedicated to kidney disease research at NIH, ASN analysis of the report reveals that the equivalent of 1.7% of the annual total cost of care for kidney failure is invested in research to improve therapies and discover cures.

"Kidney diseases are devastating the lives of millions of Americans," said ASN President Eleanor Lederer, MD, FASN. "Innovation has not kept pace with the magnitude of the diseases, and the current underinvestment in kidney research is detrimental to patients and taxpayers. Today's GAO report highlights the extent of the gap between our investment in innovation to treat and cure kidney diseases and the outsized burden they place on every American."

ASN announced at a White House Organ Summit last year its pledge of the first $7 million to launch a prize competition incentivizing the development of novel technologies for renal replacement therapy to improve quality of life for patients with kidney diseases. The society has also pledged to work with Congress to ensure the United States' investment in research to cure kidney diseases is adequate to meet the challenge it poses to patients and taxpayers.

"Despite the federal government's commitment to care for patients with kidney failure, for decades we have seen too few new therapies for kidney patients," said Crystal Gadegbeku, MD, Chair of the ASN Policy and Advocacy Committee. "This report strengthens ASN's resolve to foster innovation that improves patients' lives and extends the value to the Medicare program that has saved so many lives."

Requesters of the GAO report were Congressional Kidney Caucus co-chair Rep. Tom Marino (R-PA), Rep. Barbara Comstock (R-VA), House Science Committee chair Rep. Lamar Smith (R-TX), Sen. Ben Cardin (D-MD), and Sen. Bill Nelson (D-FL).

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Looking Ahead at the Nephrology Workforce

Nephrology workforce research conducted last year by George Washington University–Health Workforce Institute (GWU-HWI) investigators and others revealed some interesting facets of the nephrology workforce that will inform ongoing research activities in 2017. Here's a brief look back at nephrology workforce research in 2016 and trends to watch for in the year ahead.

2016 GWU-HWI report

The most recent report from GWU-HWI investigators led by Edward Salsberg, MPA, uncovered some interesting data points:

- The number of nephrology fellows in training has remained steady, despite a large number of positions going unfilled in the Match.
- University of North Carolina Sheps Center researchers working in collaboration with GWU project the number of adult nephrologists per 10,000 population will grow by 58% between 2016 and 2030.
- Only 64 US MDs matched in nephrology in AY 2017, down 21% from last year and 52% from AY 2009.

Overall, the report details a mixed picture for the specialty. The job market for US medical graduates is improving although it remains challenging for international medical graduates. However, the inflow of new nephrologists is outpacing the rate of retirement for older physicians.

"Our third annual report on the nephrology workforce finds both positive and negative signs," said Salsberg. "For example, while the job market for new nephrologists is still challenging, there were some bright spots especially for US medical school graduates as job prospects improved along with incomes. And a new survey of nephrologists over 55 found that most were satisfied with their specialty, practice, and income."

In addition to surveying nephrologists 55 and older, GWU conducted the annual Nephrology Fellows Survey and outlined the potential of recently introduced ESRD Seamless Care Organization (ESCO) demonstration projects to influence nephrologist demand, which they determined may make the specialty more fulfilling and economically rewarding.

Appointment year (AY) 2017 Match

Results of the AY 2017 nephrology Match released on December 7, 2016, were essentially flat to the previous year. An ASN Data Brief (http://asn.kdny.info/dyo6307Gh2r) highlighted several key points:

- Despite a 4.4% increase in the number of training tracks compared with AY 2016, the number of slots offered was flat, suggesting nephrology training positions may be contracting slightly.

2017 Workforce research portfolio

Nephrology workforce research is one part of ASN's commitment to empower current and future members of the nephrology workforce and advance their professional goals and success. This year's portfolio includes:

GWU-HWI Workforce Surveys

Researchers from GWU-HWI will focus on administering three surveys assessing nephrology fellows and early career nephrologists:

- **2017 Nephrology Fellows Survey**
  4th iteration of the annual fellows survey will capture longitudinal data on job market experiences
- **Survey of Nephrologists One Year Out of Training**
  Assessment of nephrologists' practice and employment settings and experiences 1 year after graduation, conducted in concert with/fulfilling ACGME-required 1-year postgraduate program assessments
- **Survey of Nephrologists Five Years Out of Training**
  Detailed investigation of early career nephrologists, including the first graduating class who completed the ASN Nephrology Fellows Survey assessments of training

Best Practices Project: Internal Medicine Residencies

The Best Practices Project is one of several initiatives designed by the ASN Workforce Committee to assess best practices of institutions that successfully attract trainees, in order to increase interest in nephrology careers among the brightest medical students and residents. The project identified top internal medicine residency producing physicians who subsequently specialize in nephrology and will isolate potentially translatable practices that could be disseminated and implemented at other institutions. Results of the first phase—focusing on medical schools—were presented at ASN Kidney Week 2016.

ASN Data Analytics Program

The Data Analytics Program was created in April 2016 to advance the goals of ASN's new strategic plan. ASN is conducting in-house research and analysis projects, building on collaborations with GWU-HWI and expanding into new areas. The Data Analytics Program will support informed, strategic decision-making and implementation of ASN initiatives and programs by collecting, managing, analyzing, and synthesizing data relevant to nephrology and nephrology professionals.

Data Analytics Program activities in 2016 included:

- *ASN Pediatric Nephrology Fellows Survey Responses*—Brief Analysis Authored for the ASPN Workforce Committee. The full report is available at http://asn.kdny.info/TZpf305BEAy
- *Kidney News Online* ASN Data Bytes Series. Quick takes on items of interest to ASN members. List of current articles available at http://www.kidneynews.org/search/node/Pivert

In 2017, the Program will focus on development of

- *ASN GME Database*
  Allows monitoring of trends among training programs and nephrology fellows
- *Data Collection Efforts*
  Assessing and enumerating knowledge and data resource gaps, as well as potential approaches to address them
- *ASN Data Resource Center*
  A central repository for ASN's ongoing nephrology workforce research and data collection

Workforce, Training, and Career Advancement Department

In April 2016, ASN coalesced its workforce-centered programs into a new Workforce, Training, and Career Advancement Department to foster career development for all kidney health professionals. Among the department's portfolio are Kidney STARS, Kidney TREKS, and the ASN Foundation for Kidney Research grants programs to which ASN commits more than $3 million each year. More than 40 physician volunteers serving on the newly created Career Advancement, Diversity and Inclusion, and Workforce and Training Committees will inform the department's strategic initiatives. Expanding the range of resources available to kidney professionals across the entire career trajectory, from student to senior clinicians and investigators, will advance their professional lives and improve treatment of kidney diseases.

Trends to watch

Among the trends to watch in 2017 are:

- *Shifts in nephrology GME*
  The AY 2017 Match was flat year over year, yet positions have continued to fill. Growing anecdotal evidence demonstrates a shift in reducing the number of fellowship positions.
- *Evolution of the Specialty*
  New training offerings, such as critical care nephrology, could kindle interest in the specialty.
- *A new Congress and administration*
  A new healthcare landscape could result in changing regulations and practice patterns and may influence specialty choice among trainees and future physician demand.

Workforce research reports and other resources are available at http://www.asn-online.org/workforce. If you have questions, concerns, or suggestions for future workforce research, data or knowledge gaps, please contact workforce@asn-online.org.

Delay for CMS Rule on Premium Assistance

By Bridget M. Kuehn

A new CMS regulation that would potentially curtail third party payments for insurance for dialysis patients has been delayed by a U.S. District Court judge in Texas.

Fresenius Medical Care, Davita, U.S. Renal Care, along with Dialysis Patient Citizens, filed a lawsuit to block the CMS rule on Jan. 6, 2017. Issued as an interim rule in August 2016, the regulation was set to go into effect Jan. 13, 2017. The judge's temporary restraining order delaying the rule may stay in place for up to 14 days post-issuance.

In its lawsuit, the groups stated that the rule was pushed through without the proper notice or comment period that usually occurs before a new rule is adopted.

The U.S. District Court judge agreed, stating the organizations likely showed that the Department of Health and Human Services (HHS) implemented the final rule without time for thorough review and comment.

In a statement about the temporary restraining order, Fresenius Medical Care said: "We are pleased that the court has issued a temporary restraining order preventing this improperly issued regulation from going into effect. Today's ruling will help ensure that Americans with kidney failure have the same right as every other American to receive charitable assistance to pay their health insurance premiums. We look forward to working with the new administration on regulations that protect the sustainability of the Medicare program while protecting the ability of Americans to select the health coverage of their choosing, free from discrimination based on their health status or disability."

[The rule requires] that dialysis facilities disclose the risks of various coverage options to their patients, be more transparent about how the provider benefits, and prevent potential disruptions in coverage by seeking insurer approval for coverage.

The rule grew out of a CMS investigation of reports that dialysis companies were paying for private insurance in order to boost their reimbursements. It requires dialysis companies to fully disclose to a patient their insurance options, how the providers would benefit from a patient's receiving private coverage, and would require insurance company approval of coverage for the patient.

In a Jan. 11, 2017, letter to CMS commenting on the rule, the American Society of Nephrology (ASN) urged the agency to take more time and gather more input from stakeholders before finalizing the rule.

"The ASN firmly agrees with CMS that payment of premiums and cost-sharing by third party entities should *only* be used to promote the best interests of the beneficiary," ASN stated in its comment letter. "For many patients in the vulnerable dialysis population, third party assistance currently helps them achieve their goals, be it to work part time, gain access to transplant, or afford medications, and the society is concerned that the proposals in this [rule] would inadvertently jeopardize some individuals' access to care."

Premium support scrutiny

In mid-August 2016, CMS announced it was investigating reports of inappropriate steering of dialysis patients into private insurance by dialysis providers to boost their own reimbursements. According to CMS, the investigation yielded reports of abuse with negative health and financial consequences for patients. This led CMS to issue the interim rule requiring that dialysis facilities disclose the risks of various coverage options to their patients, be more transparent about how the provider benefits, and prevent potential disruptions in coverage by seeking insurer approval for coverage.

Third parties, including nonprofits, have long offered patients who require dialysis help paying for insurance. For example, the American Kidney Fund (AKF) offers such payment assistance for low-income patients to purchase Medicare Part B, Medigap, and private or employer-based insurance. Currently, the organization provides payment assistance to 80,000 patients, including 6400 in Affordable Care Act marketplace plans, according to a press release. The organization runs a health insurance premium assistance program established in 1997 according to guidelines laid out by the US Office of the Inspector General (OIG).

But a *New York Times* investigation, published December 25, 2016, suggested that the AKF had in some instances resisted offering assistance to patients from dialysis clinics not associated with companies that donated to the charity, contrary to OIG guidelines.

In a statement, the AKF argued the article was factually incorrect, that it had "never turned away a patient who was financially qualified," and that 40% of dialysis providers who have patients receiving AKF assistance do not contribute to the fund. But the AKF also expressed concern that social workers from independent dialysis clinics who were interviewed by the *New York Times* believe that the fund is favoring patients from large dialysis companies who donate.

"This is simply not the case, and we want to correct the record, as well as take ownership of any way that AKF itself may have contributed to this misperception," the statement said.

In a fact sheet, CMS noted that in recent years dialysis providers have been offering premium assistance, either directly or through charities, as a way to boost reimbursements. Premiums cost about $6000, but private insurance may pay as much as 4 times more for dialysis care than Medicare, resulting in up to an additional $100,000 to $200,000 in reimbursement.

AKF said in a statement that it supported efforts to stop steering but had urged the agency to withdraw the rule, saying it would leave kidney disease patients with fewer options.

"HHS is irresponsibly upending the entire safety net that exists for dialysis patients who can't afford their health coverage," said Burton. "This cannot be the result that the agency intended to achieve when it set out to protect ESRD patients from improper steering."

Insurance discrimination

The regulation also drew sharp criticism from the patient advocacy group Dialysis Patient Citizens, which said the rule, which requires insurance companies to approve private coverage, allows insurers the chance to "veto" a patient's choice of private coverage.

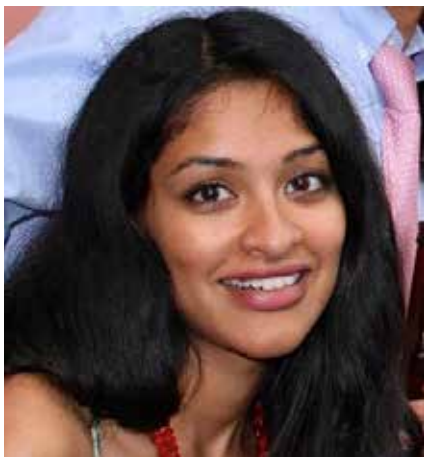
"It basically creates a two-tier system," said Hrant Jamgochian, chief executive officer of Dialysis Patient Citizens, which joined dialysis providers in the lawsuit to block the rule. "If you can afford private coverage, you are protected from discrimination [under ACA], but if you can't afford it [without premium assistance] you aren't."

Patients with HIV are protected from such discrimination, Jamgochian noted, because insurers are required to accept charitable assistance for these patients under the Ryan White Care Act. His organization has proposed similar protection for patients with kidney failure and has urged CMS to crack down on insurance companies steering dialysis patients who could benefit from private insurance into Medicare.

Fellows Corner

Health Literacy in CKD: **A Fellow's Perspective**

By Devika Nair



Devika Nair

Medical students and residents are often intimidated by renal physiology and struggle to understand the many aspects of the kidney's role in medical disease. If trainees have trouble grasping the complexities of the kidney, it should come as no surprise that our patients feel the same way.

Health literacy, or the ability of an individual to be actively engaged in a dialogue about his health, has been linked to patient outcomes. Adequate health literacy is particularly important in chronic kidney disease (CKD), which often requires patients to navigate a complex health system and make drastic lifestyle changes. Patients may be faced with such critical decisions as choosing to begin renal replacement therapy with little to no understanding of its implications.

As a first-year Nephrology fellow, most of the patients I see are new to me as well as new to the clinic. I quickly realized that despite being referred to a clinic that exclusively sees patients with kidney disease, several of my patients were wholly unaware of having renal dysfunction in the first place. When I asked them what they had trouble understanding, they often replied with, "everything," and didn't know where to begin.

Clinical implications of low health literacy

The clinical implications of low health literacy in kidney disease are being recognized by the nephrology community. Lower health literacy has been linked to worsened glomerular filtration rates (1,2). Patients with CKD and poor health literacy tend to access preventive health services less frequently and have poorer self-care methods, all of which can contribute to rising healthcare costs. In addition, one study showed that patients on dialysis with limited health literacy were 78% less likely to be referred for a renal transplant (3).

Further complicating this matter, the Department of Education has reported that 21% of adults in the United States read below a fifth-grade level, and 14% of the population is illiterate. A study of kidney disease–related patient education tools from the United States, Australia, and the United Kingdom revealed that most materials required a ninth-grade reading level for adequate comprehension. In addition, many of these tools were geared toward those who had progressed to hemodialysis with little focus on patients with earlier stages of kidney disease (4). Low health literacy, a high pill burden, and an unfamiliar health system can be an overwhelming combination for a patient with kidney disease.

It is also important to realize that we as providers may fail to recognize existing health literacy issues that are downplayed out of fear or embarrassment. When I asked one of my patients to read back the medication instructions I had written for him, it was only when he held the paper upside down that I realized he could not read.

Table 1 provides a helpful list of patient characteristics that may be associated with low health literacy (5).

How can providers continue to address concerns about patient health literacy? Tools such as the Rapid Estimate of Adult Literacy in Medicine (REALM), Test of Functional Health Literacy in Adults (TOFHLA), and Brief Health Literacy Screen (BHLS) have all been used to successfully screen dialysis patients for poor health literacy (5,6), although studies regarding their effectiveness in earlier stages of kidney disease are lacking. In addition to using these tools, there are simple steps that we can take to help bridge the literacy gap between ourselves and our patients. We can ask open-ended questions, speak slowly with patient-oriented language, and limit the information we discuss at each visit. The "teach-back" method, or asking our patients to repeat back and explain any instructions given to them, can also be a useful tool to help confirm patient comprehension.

Patients with no medical background seem to know what it means to have heart disease and diabetes, but many still struggle with understanding the implications of kidney disease. Not only is it important to collaborate with educators and policy leaders to develop educational tools that provide simple representations of this complex disease process, it is also crucial to support health literacy training in the medical community. It is important that more of these efforts be geared toward patients during earlier stages of kidney disease as well as toward adolescents.

Each of us has a right to knowledge that informs decisions about our own health. It is our responsibility to ensure that this knowledge is delivered in a way that is both understandable and beneficial to our patients. Our health interventions are only as effective as our patients' ability to carry them out—a challenge that we must continue to try to overcome with regard to kidney disease.

Devika Nair, MD, is currently a first-year nephrology fellow at Vanderbilt University. She completed her medical training and chief residency in Internal Medicine at Tulane University and her undergraduate studies at the University of California, Berkeley.

Table 1
Clinical "red flags" for limited health literacy

- Patient registration forms that are incomplete or inaccurately completed
- Non-adherence with medications or treatments
- Frequently missed appointments
- Lack of follow-through with labs, imaging tests, or referrals
- Unable to name medications, explain what medications are for, or explain timing of medication administration
- May offer excuses to deflect reading tasks
- "I forgot my glasses"
- "Let me bring this home so I can discuss it with my children"
- Seldom have questions
- Seek help only when illness is advanced
- Have difficulty explaining medical concerns

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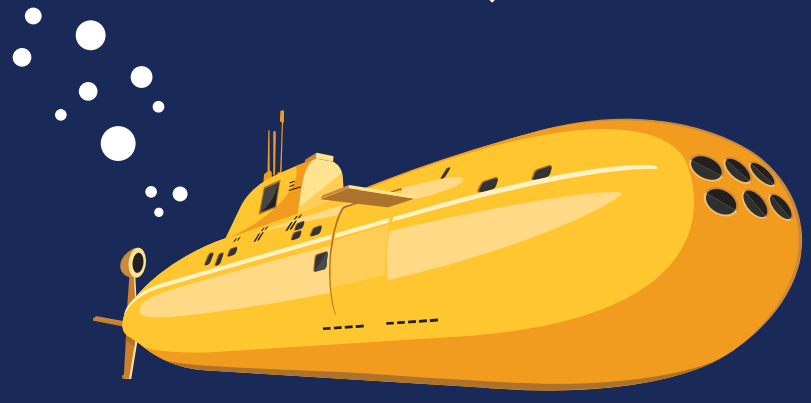

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Findings

Diet Quality Affects Risk of eGFR Decline in Urban Patients

In a diverse urban population, low dietary quality is associated with an increased risk of declining kidney function among adults with hypertension, reports a study in the *Journal of Renal Nutrition*.

The study included data on 1534 participants in the "Healthy Aging in Neighborhoods of Diversity across the Life Span" (HANDLS) study: African Americans and whites, aged 30 to 64 years, with a baseline estimated glomerular filtration rate (eGFR) of 60 mL/min/1.73 m^2 or higher. Mean age was 48 years; 59% of participants were African American.

A Dietary Approaches to Stop Hypertension (DASH) score, based on nine target nutrients, was calculated for each participant. Diet score was evaluated for association with rapid decline in kidney function (greater than 3 mL/min/1.73 m^2 per year), incident chronic kidney disease, and eGFR decline greater than 25%.

Accordance with the DASH diet was "minimal"—median score 1.5 on a 0–8 scale. At a median 5 years' follow-up, rapid eGFR decline occurred in 13.4% of patients overall, 15.2% of those with a DASH score of 1 or less, and 12.0% with a DASH score greater than 1. On adjusted analysis, the association with rapid eGFR decline was significant only for subjects with hypertension: risk ratio 1.68. The DASH score was unrelated to incident chronic kidney disease or eGFR decline greater than 25%.

Previous studies have linked a healthier diet to a lower risk of kidney disease outcomes, but none of these studies have focused on urban populations. The new results show that a low DASH score is associated with an increased risk of rapid decline in eGFR, among urban adults with hypertension. The investigators conclude: "[D]iet quality may play an important role in determining kidney outcomes among individuals with risk factors for CKD" [Liu Y, et al. Dietary habits and risk of kidney function decline in an urban population. *J Renal Nutr* 2017; 27: 6–25].

Mortality Differs by Reason for Starting Dialysis

Among patients initiating dialysis, mortality is higher for those with a primary indication of volume overload or hypertension, suggests a study in the *American Journal of Kidney Diseases*.

The retrospective analysis included 461 patients who initiated hemodialysis or peritoneal dialysis (24 patients) from 2004 through 2012 at 14 facilities. All-cause mortality was analyzed for patients with differing primary indications for dialysis initiation: laboratory evidence of kidney function decline (reference category), uremic symptoms, volume overload, hypertension, or "other/unknown."

At a median follow-up of 2.4 years, 40% percent of patients had died. Crude mortality was 21.7 per 100 patient-years for patients with volume overload or hypertension, compared to 10.0 for those with kidney function decline, 12.7 with uremic symptoms, and 12.2 for the "other/unknown" category.

On adjusted analysis, volume overload or hypertension was the only category associated with increased mortality: hazard ratio 1.69. Among patients using a permanent dialysis access, the risk of death was eight times higher for those in the volume overload/hypertension group, compared to those with decreased kidney function.

The results suggest increased mortality among patients initiating dialysis due to volume overload, relative to those with laboratory evidence of kidney function decline. The researchers write: "Improved understanding of symptoms and clinical decision making at the time of the transition to dialysis therapy has the potential to lead to innovation in identifying the optimal timing for the initiation of maintenance dialysis therapy" [Rivara MB, et al. Indication for dialysis initiation and mortality in patients with chronic kidney failure: a retrospective cohort study. *Am J Kidney Dis* 2017; 69:41–50].

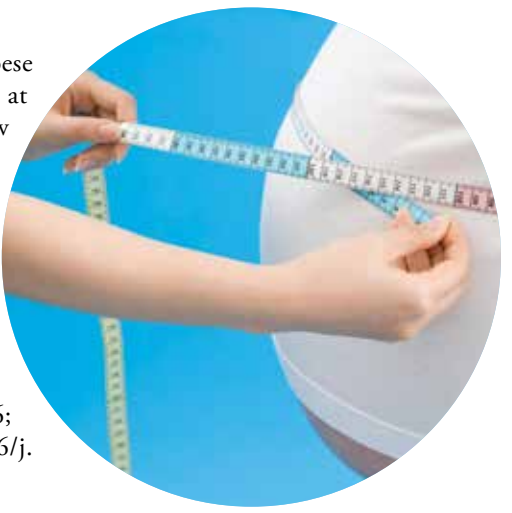
Obese Living Kidney Donors at Increased ESRD Risk

Among living kidney donors, the long-term risk of ESRD is close to doubled for those who are obese, reports a study in *Kidney International*.

The study included data on 119,769 living kidney donors, linked to Centers for Medicare & Medicaid Services data to determine ESRD status. There were 20,588 obese donors, body mass index (BMI) 30 kg/m^2 or higher; and 58,004 nonobese donors. (The remaining 41,177 donors had missing data on BMI.) Postdonation risk of ESRD was compared between groups, with adjustment for potential confounders.

Twenty years after living kidney donation, the cumulative incidence of ESRD was 93.9 per 10,000 for obese donors versus 39.7 per 10,000 for nonobese donors. In adjusted models, obesity was the only potentially modifiable risk factor associated with increased ESRD risk: adjusted hazard ratio 1.86. For each one-unit increase in BMI over 27 kg/m^2, there was a 7% increase in ESRD risk.

While the absolute risk of ESRD after living kidney donation is low, the risk is significantly higher for obese donors. The increase in risk begins at a donor BMI of 27 kg/m^2—below the standard cutoff for obesity. The authors discuss the implications for living donor selection practices, including the possibility of predonation rehabilitation or weight loss programs [Locke JE, et al. Obesity increases the risk of end-stage renal disease among living kidney donors. *Kidney Int* 2016; DOI: http://dx.doi.org/10.1016/j.kint.2016.10.014].



Albuminuria Screening May Predict Rapid eGFR Decline

Screening for elevated albuminuria and hypertension may identify a group of patients at increased risk of faster decline in kidney function, reports a study in *Nephrology Dialysis Transplantation*.

The study included 6471 participants from the population-based Prevention of Renal and Vascular End-stage Disease (PREVEND) study. All had at least two (median four) measurements of estimated glomerular filtration rate (eGFR) over a median 11.3 years' follow-up. Elevated albuminuria was defined as an albumin concentration of 20 mg/L or higher in a first morning urine sample, confirmed by an albumin excretion of 30 mg/d or higher in two 24-hour urine collections. Hypertension was defined as a blood pressure of 140/90 mm Hg or higher or use of antihypertensive drugs.

Participants with elevated albuminuria had a faster rate of decline in eGFR during follow-up. This was so in subjects with known hypertension, −1.84 versus −1.16 mL/min/1.73 m^2 per year; newly diagnosed hypertension, −1.59 versus −1.14 mL/min/1.73 m^2 per year; and normal blood pressure, −1.18 versus −0.81 mL/min/1.73 m^2 per year.

The association was strongest in participants aged 55 or older and in men. Participants with elevated albuminuria had consistently higher blood pressure. Elevated albuminuria and as yet unknown hypertension was associated with the highest blood pressure. This combination was more than twice as common as elevated albuminuria with known hypertension.

Identifying CKD at an early stage might help to prevent ESRD by managing hypertension and albuminuria. Population screening for albuminuria might aid in identifying patients at risk of faster decline in kidney function, who could benefit from treatment. This strategy may be most effective in men and in older patients; the authors suggest the possibility of combining albuminuria screening with colorectal cancer screening [Özyilmaz A, et al. Screening for elevated albuminuria and subsequently hypertension identifies subjects in which treatment may be warranted to prevent renal function decline. *Nephrol Dial Transpl* 2016; doi: 10.1093/ndt/gfw414].

AKI Linked to Unplanned Readmissions

Acute kidney injury (AKI) is strongly associated with an increased risk of unplanned hospital readmissions—especially for acute pulmonary edema, according to a study in *BMC Nephrology*.

The researchers analyzed Scottish population-based data on 16,453 patients who were hospitalized and survived to discharge in 2003. Of these, 2623 patients had AKI, based on KDIGO criteria. AKI and other candidate predictors were analyzed as risk factors for unplanned readmission or death within 90 days.

The main study outcome occurred in 18.6% of patients: readmission in 2701 and death without readmission in 363. On multivariable analysis, AKI was a strong risk factor for the combined outcome: odds ratio 1.50 for stage 1, 2.23 for stage 2, and 2.80 for stage 3. The reason for readmission was acute pulmonary edema in 26.6% of AKI cases, compared to 4.0% of those with no AKI and normal kidney function. Although AKI was a strong predictor, it added little incremental value when added to other predictive models.

Acute kidney injury is a common and serious condition; coordinated care is needed to prevent avoidable complications. The new analysis finds that AKI is a "strong, consistent, and independent risk factor" for unplanned hospital readmissions.

More than one-fourth of readmissions in AKI patients may be related to acute pulmonary edema—a potentially modifiable condition. Some readmissions "may be avoidable by careful pre-emptive planning after AKI to prevent the development of pulmonary edema," the investigators conclude [Sawhney S, et al. Acute kidney injury as an independent risk factor for unplanned 90-day hospital readmissions. *BMC Nephrol* 2017; 18: 9 DOI: 10.1186/s12882-016-0430-4].

No Reduction in AVF Failure with Fish Oil and Aspirin

Treatment with fish oil and/or aspirin does not reduce the risk of arteriovenous fistula (AVF) failure, reports a randomized trial in *JAMA Internal Medicine*.

The "Omega-3 Fatty Acids (Fish Oils) and Aspirin in Vascular Access Outcomes in Renal Disease" (FAVOURED) study included 567 patients at 35 dialysis centers in Australia, Malaysia, New Zealand, and the United Kingdom. All patients had stage 4 or 5 chronic kidney disease and were undergoing surgical AVF creation.

Patients were randomly assigned to receive fish oil, 4 g/d, or placebo. A subset of 406 patients were further assigned to aspirin, 100 mg/d, or placebo. Study treatments began 1 day before surgery and continued for 12 weeks. At 12 months, a composite endpoint of fistula thrombosis or abandonment or cannulation failure was assessed.

The fistula failure rate was 47% in patients assigned to fish oil or placebo, with no difference in the composite outcome or its individual components. There was also no difference between the aspirin and placebo groups: fistula failure rate 45% and 43%, respectively. Adverse events, including bleeding, were similar between groups.

Fish oil and aspirin have differing effects that might make them useful for reducing the high rates of early thrombosis and maturation failure in AVFs. However, the FAVOURED results show no significant difference in AVF failure over 12 months, with either fish oil, aspirin, or the combination of the two. The high failure rate of nearly 50% emphasizes the urgent need to improve AVF outcomes [Irish AB, et al. Effect of fish oil supplementation and aspirin use on arteriovenous fistula failure in patients requiring hemodialysis: a randomized clinical trial. *JAMA Intern Med* 2017; doi:10.1001/jamainternmed.2016.8029].

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Findings

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Worldwide Trends in Hypertension: 40-Year Analysis

More than 1 billion people worldwide now have hypertension, with the highest levels now seen in low-income countries in south Asia and sub-Saharan Africa, according to a report in *The Lancet*.

The NCD Risk Factor Collaboration analyzed pooled data from 1479 studies that had measured blood pressure in 19.1 million adults. The researchers analyzed trends in mean systolic and diastolic blood pressure from 1975 to 2015, as well as the prevalence of raised blood pressure (140/90 mm Hg or higher) in 200 countries.

In 2015, global age-standardized mean blood pressure increased systolic blood pressure was 127.0/78.7 mm Hg in men and 122.3/76.7 mm Hg in women. The age-standardized prevalence of raised blood pressure was 24.1% and 20.1%, respectively.

High-income western and Asia Pacific countries went from having some of the highest measured blood pressure values in the world in 1975 to the lowest in 2015. By 2015, the regions with the highest measured blood pressure levels were central and eastern Europe, sub-Saharan Africa, and south Asia.

The overall number of adults with raised blood pressure increased from 594 million in 1975 to 1.13 billion in 2015, with most of the increase occurring in low- and middle-income countries. The global increase was attributable to population growth and ageing, partly offset by decreases in age-specific prevalence.

Over the past 40 years, the highest measured blood pressure values have shifted from high- to low-income countries, especially in sub-Saharan Africa. The total number of adults with raised blood pressure has increased by 90%. The authors call for multifaceted approaches to address the "large and inequitable burden of cardiovascular diseases and kidney disease associated with high blood pressure" [NCD Risk Factor Collaboration: Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19.1 million participants. *Lancet* 2017; 389:37–55].

How Does Switching to HDHPs Affect Diabetes Care?

For patients with diabetes—including but not limited to low-income patients—switching to high-deductible health plan (HDHPs) leads to major increases in emergency department visits for preventable acute diabetic complications, reports a study in *JAMA Internal Medicine*.

The researchers analyzed the effects of an employer-mandated switch to HDHPs in 12,084 diabetic patients, aged 12 to 64 years. All were enrolled in a low-deductible plan ($500 or less) for 1 year, followed by 2 years in an HDHP ($1000 or higher). The HDHP patients were propensity score-matched to patients who remained on low-deductible plans only.

The effects of switching to an HDHP on diabetes outpatient care and acute complications were assessed, including ED visits for preventable complications. Subgroup analyses focused on 4121 low-income patients and 1899 patients eligible for health savings accounts (HSAs).

Out-of-pocket costs increased for diabetic patients in the year after switching to HDHPs: by 49.4% overall, 51.7% for low-income patients, and 67.8% for HSA-eligible patients. There was no change in high-priority primary care visits or use of disease monitoring tests. However, high-priority specialist visits decreased by 5.5% in the first year and 7.1% in the second year.

After the switch to an HDHP, outpatient visits for acute diabetes complications were delayed in both the overall and low-income cohorts: adjusted hazard ratio 0.94 and 0.89, respectively. Annual ED visits for acute complications increased by 8.0% for all patients, 15.5% in HSA-eligible patients, and 21.7% in low-income patients.

Switching to an HDHP does not appear to affect outpatient visits and disease monitoring for diabetic patients. However, rates of ED visits for preventable acute diabetes complications are substantially increased, particularly for low-income, high-morbidity, and HSA-eligible patients. With the increasing focus on HDHPs in the US healthcare system, the authors discuss implications for preventing adverse effects on diabetes care [Wharam FJ, et al. Diabetes outpatient care and acute complications before and after high-deductible insurance enrollment: a Natural Experiment for Translation in Diabetes (NEXT-D) study. *JAMA Intern Med* 2017; doi:10.1001/jamainternmed.2016.8411].

Better Data on Living Donor Risks Improves Consent

By Bridget M. Kuehn

A growing understanding of the health and psychosocial risks associated with being a living kidney donor is helping drive innovations that will improve the informed consent process, according to recent research.

Receiving a kidney donated by a living donor greatly improves the outcomes of patients with kidney failure. But it also creates risks for the 30,000 otherwise healthy donors around the world who donate kidneys each year. Ensuring that living donors give proper informed consent is essential. Now, a growing body of evidence on the risks associated with living kidney donation and emerging tools to help clinicians and patients assess them are helping to improve the process of informed consent.

"Our ability to walk donors through informed consent has exponentially improved," said Robert S. Gaston, MD, director of the Comprehensive Transplantation Institute at the University of Alabama-Birmingham. "I think we will be able to plug [information] into a calculator really soon and give an absolute risk." Gaston spoke at a Kidney Week 2016 symposium.

Modeling risk

Scientists have created models that can help clinicians assess the risks faced by an individual donor based on several demographic and health characteristics (Grams ME, et al. *N Engl J Med* 2016; 374:411–421). Living donors have about a 3.5- to 5.3-fold higher risk of kidney failure than comparable individuals in the US population, said Robert Foley, MD, associate professor of medicine in the division of renal diseases at the University of Minnesota. Fagan noted that the absolute risks of end stage renal disease (ESRD) are still low.

Among the factors that increase the risk of living donors developing ESRD are the development of postdonation diabetes or hypertension, which boost the risk of proteinuria fourfold and the risk of ESRD by more than twofold, respectively (Ibrahim HN, et al. *J Am Soc Nephrol* 2016; 27:2885–2893).

Even then, predonation factors can help identify individuals at greatest risk.

"What I'd really like to get to is a clinical model that would help donors," Foley said. Ideally, he said such a tool would be very simple and use a spreadsheet program or graphs to explain individual risks and how they might be managed, for example, by keeping blood pressure within the normal range or making lifestyle choices to minimize the risk of diabetes posttransplant.

Pregnancy risks

Emerging data also suggest that women who have donated a kidney may have worse pregnancy outcomes.

Women who donate a kidney have an elevated risk of gestational hypertension compared with those who have never donated a kidney (OR 2.4; 95% confidence interval, 1.2 to 5.0; p=0.01) (Garg AX, et al. *N Engl J Med* 2015; 372:124–133).

Another study that compared donors' pre- and postdonation pregnancies found a higher risk of preterm delivery, fetal loss, gestational diabetes, hypertension, proteinuria, and preeclampsia postdonation (Ibrahim HN, et al. *Am J Transplant* 2009; 9:825–834).

The absolute risks of these outcomes are low, and generally on par with or lower than the risk of this outcome in the general population because donors are healthier than the general population, said Mirna Boumitri, MD, an assistant professor of medicine in the division of renal diseases at the University of Minnesota. Still, "women should be counseled about postdonation risks to pregnancy," Boumitri said.

Paying to donate

Living kidney donors may also face financial or psychosocial consequences of their decision to donate. But better and more consistent screening can help identify donors at risk.

Cheryl Jacobs, MSW, a clinical transplant social worker at the University of Minnesota Medical Center, said her institution has taken steps to ensure that donors are properly screened. They also use a donor advocate who is not involved in the donor's medical care, which is now required by the Centers for Medicare & Medicaid Services.

"We really wanted to make sure we did things consistently," she said.

Many donors report unchanged or even improved quality of life and other psychosocial function after donating a kidney (Clemens KK, et al. *Am J Transplant* 2006; 6:2965–2977). But a small number may face poor psychosocial outcomes, Jacobs noted.

A number of factors, including having good family or other support, viewing the donation process positively, having a higher level of education, and greater comfort with the decision to donate, all appear to protect against poor outcomes, Jacobs said. But other factors, including having poor mental health, limited support, a longer recovery, or financial hardships related to the donation, may lead to poorer outcomes.

Many donors report lost income, dependent care costs, as well as travel and health care costs related to their donation. One study found that 89% of donors suffered a financial loss during the first year after donation, with one-third reporting a loss of more than $2500 (Rodrigue JR, et al. *Am J Transplant* 2016; 16:869–876)

"Donors are paying to donate," Jacobs said.

Donors may also have a harder time accessing health or life insurance, Jacobs said. Some programs have been created to help neutralize the costs to donors. For example, travel grants may be available for some donors. Additionally, the US Living Donor Protection Act, which would prevent insurers from punishing donors, was introduced recently.

"We owe it to donors to advocate where there are gaps," Jacobs said.

Practice Pointers

Pregnancy and End Stage Renal Disease

By Rakhi Khanna

How frequent is pregnancy in ESRD? What are the current outcomes?

Fertility is reduced in dialysis patients. The reasons are multifactorial and include hormonal abnormalities, such as hyperprolactinemia and hypergonadotrophic hypogonadism, anovulatory cycles, and sexual dysfunction (1). In the United States, among women of childbearing age on dialysis, frequency of pregnancy is around 0.5% per year on the basis of survey results (1). Some countries have reported up to 1.4% per year frequency rates. For reasons that are not well understood, patients on hemodialysis have a two to three times greater likelihood of conception than patients on peritoneal dialysis (2). Experts think peritoneal solution may cause interference with implantation and ovum transport.

Approximately 50% of pregnancies result in survival of infants. However, many of these infants are premature and small for gestational age. These infants can have multiple medical and developmental problems (1).

What treatment modalities are best for mother and child? When is fetal monitoring initiated?

Pregnancy requires more aggressive dialysis. This means more frequent dialysis, at least six times a week with a target BUN <45 mg/dL (3). Better outcomes are reported for infants born to pregnant women dialyzed more than 36 hours per week. Intense dialysis improves uremic and maternal volume status. Therefore, these infants have a higher live birth rate compared with those of pregnant women who were dialyzed less frequently (4). Kidney Disease Outcomes Quality Initiative guidelines also recommend long frequent dialysis. However, the standard method to calculate Spkt/V cannot be used, because the equation applies to thrice weekly hemodialysis.

It is also a challenge to adjust the ultrafiltration goal and/or establish a dry weight for the patient. Elevated BP in pregnancy may not always be volume mediated and may be related to preeclampsia. Careful attention is needed to avoid hypotension, which can lead to placental hypoperfusion. Daily dialysis does help in assisting volume balance.

Frequent hemodialysis will mean very careful adjustments in potassium, calcium, and bicarbonate to avoid hypercalcemia and alkalosis (5). A regimen of daily dialysis can lead to alkalosis, and the the bicarbonate bath needs to be adjusted to maintain bicarbonate levels around 20 mEq/L (1). Typical dialysate potassium of 3 mEq/L and bicarbonate concentration of 25 mEq/L are needed.

Peritoneal dialysis may be used and may also be useful in avoiding rapid metabolic changes. However, as pregnancy progresses, it can become difficult to tolerate the exchange volumes (1).

Fetal monitoring is done as per obstetric guidelines using serial ultrasound to examine fetal growth and evaluate the placenta and amniotic fluid. Weekly fetal surveillance is started around 24 to 26 weeks using ultrasound and biophysical profile (6).

What medications are safe?

Antihypertensive medications that are safe and commonly used are methyldopa, labetalol, hydralazine, and dihydropyridine calcium channel blockers. β-blockers other than labetalol can cause fetal bradycardia. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are contraindicated, because they can increase the risk of major congenital malformations (7).

As patients are dialyzed more often, caution and proper medication adjustment are needed to avoid hypotension. Target postdialysis BP should be less than 140/90 mm Hg.

In terms of anticoagulation, heparin can be used in dialysis. It does not cross the placenta, and it is not teratogenic (8). Coumadin cannot be used, and patients who are on Coumadin for access-related clotting problems will have to be changed to subcutaneous heparin (9). Low molecular weight heparins, such as enoxaparin, and novel oral anticoagulants, such as rivoraxaban, dabigatran, and apixaban, are not approved for use in dialysis patients.

Calcium-based phosphorus binders are probably the safest to continue as long as calcium concentration is monitored and maintained within normal limits. Active vitamin D derivatives and vinacalcet are all category C drugs with only case reports of their use. There are not enough reports to show safety. A higher dose of folic acid (at least 5 mg/d) is also needed during pregnancy owing to higher dosage needs and removal of water-soluble vitamins caused by intensive dialysis. The multivitamin dose is also doubled daily.

Is anemia management different? Are there concerns regarding erythropoietin or transfusion?

Anemia, especially hemoglobin levels <8 g/dL, can have adverse effects on the fetus (2). Erythropoietic agents can be used in pregnancy, because there are no reports of teratogenicity (10). Previous studies do not show transfer of epoetin alfa (epogen) across the placenta (11). Multidose formulations containing benzyl alcohol are contraindicated, and single-dose preparations should be used. Dose requirements are 50 to 100% more for pregnant women on dialysis and can be increased right away (1). Intravenous iron preparations can be continued as well, although safety data are lacking. There are sparse reports about packed red blood cell transfusion during pregnancy; therefore, it should be used cautiously following current transfusion guidelines.

What are the postpartum issues for the mother and the baby?

The pregnant dialysis patient requires a highly specialized team, including the nephrologist, a high-risk pregnancy obstetrician, and a neonatologist. The number one issue encountered in pregnant dialysis patients is prematurity, which in turn, is the greatest cause of morbidity and mortality in the infants (1).

Other complications include preeclampsia, polyhydramnios, and premature labor. Most commonly used medicines, such as intravenous magnesium to stop preterm labor, are difficult to use, because they can lead to magnesium toxicity and cause respiratory depression (12). Timing of delivery is usually around 34 to 36 weeks, but the mean gestational age has been noted to be only 32 to 36 weeks. Infants of dialysis patients are born with BUN and creatinine levels similar to the levels of the mother. After birth, these infants can have an osmotic diuresis and develop volume contraction with metabolic alkalosis (13).

Acknowledgments

As a practicing nephrologist, I am indebted to my patients for giving me the opportunity to provide care for them and the inspiration to learn.

Suggestions

Search for this topic revealed multiple review articles but few prospective studies examining management and outcomes of pregnant dialysis patients. I recommend an ongoing registry for pregnant patients on dialysis.

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Rhaki Khanna, DO, is a nephrologist in Gurnee, IL.

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Industry Spotlight

German approval pending for RCC combo therapy benefit

Eisai (Tokyo), a maker of cancer and neurological therapies, is closer to gaining a proven new benefit for its renal cancer treatment, lenvatinib (Kisplyx), in Germany, where 15,000 people develop renal cell carcinoma (RCC) every year.

The German Institute for Quality and Efficiency in Health Care (IQWiG) published conclusions that lenvatinib when delivered in combination with everolimus has additional benefits in patients with RCC. The results of the institute's report were announced by Eisai on Jan. 4, 2017, and will be evaluated by Germany's Federal Joint Committee. A final decision on whether to accept results from the IQWiG report is expected in March 2017.

Eisai submitted phase 2 trial data of 153 people with advanced RCC who had progressed after one previous vascular endothelial growth factor (VEGF) therapy. Patients were randomized to either receive everolimus or lenvatinib monotherapy, or a combination of both. The results showed significant differences in efficacy between the combination treatment and everolimus therapy alone.

When treated with lenvatinib in combination with everolimus, patients experienced a median progression-free survival of 14.6 months compared with 5.5 months for a group of 50 patients who received everolimus alone (p=0.0005). Median overall survival in the study population was 25.5 months in the lenvatinib plus everolimus group compared with 15.4 months in the everolimus group in two update analyses.

The European Commission, as well as the FDA, granted marketing authorization in 2016 for lenvatinib in combination with everolimus for the treatment of adult patients with advanced renal cell carcinoma after one VEGF therapy.

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