New research indicates that many patients who are receiving chronic hemodialysis have depressive symptoms but do not wish to receive aggressive treatment to alleviate it. 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, multi-center, cluster-randomized SMILE trial compared 2 strategies for the management of 3 common symptoms in cognitively intact adults receiving chronic dialysis.
Depression Under-treated

Continued from page 1

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 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.”

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.”

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.

Low BP Related to Increased Cardiovascular Risk

Continued from page 1

(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 Bainton, 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 m² 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 fol-
low-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 tro-
ponin-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 be-
tween systolic BP and cardiovascular risk
was U-shaped. However, among the 7278
patients without previous cardiovascular
disease, there was a positive loglinear asso-
ciation. On adjusted analysis, each 10 mm
Hg increment in usual systolic BP was as-
associated with a 16% increase in cardiovas-
cular risk. This risk increased to 27% per
10 mm Hg when analyses were further re-
stricted to those patients without evidence
of subclinical cardiac disease—i.e., baseline
troponin of 0.01 ng/mL or less. The asso-
ciation was little affected by adjustment for
baseline albumin:creatinine ratio, 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 car-
diovascular 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 asso-
ciations among patients with moderate-to-
advanced CKD.”

Herrington commented: “This suggests
that guidelines should not be using obser-
vational 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 ef-
ectiveness of lowering BP in other popula-
tion groups where U-shaped associations
between BP and cardiovascular risk have
been observed, including patients with pri-
or cardiovascular disease and older adults
(e.g., the Systolic Blood Pressure Interven-
tion Trial, or SPRINT). “The same may
therefore be true in CKD.”

In the absence of sufficiently large tri-
als, the optimal BP target in CKD remains
unknown, and current recommenda-
tions vary widely. Recent studies, includ-
ing 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 po-
tential 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 ac-
count for the U-shaped association be-
 tween 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 de-
finitive 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 cardio-
vascular 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 re-
verse causality in the association be-
 tween blood pressure and cardiovascu-
arisk in patients with chronic kidney
322.
2. Agarwal R. Exploring the paradoxical
relationship of hypertension with mor-
tality in chronic hemodialysis. Hemodi-
alysis Int 2004; 8:207–213.
3. Baigent C, et al. The effects of lower-
ing LDL cholesterol with simvasta-
tin plus ezetimibe in patients with
chronic kidney disease (Study of Heart
and Renal Protection): a randomised
placebo-controlled trial. Lancet 2011;
377:2181–2192.
4. Park M, et al. Associations between
kidney function and subclinical cardiac
abnormalities in CKD. J Am Soc Neph-
5. The SPRINT Research Group: A ran-
domized trial of intensive versus stand-
derd blood-pressure control. N Engl J

THE MORE
DIFFICULT THE CASE,
THE LESS DIFFICULT THE CHOICE OF HOSPITAL.

Ranked No.11 in the nation by U.S. News & World Report, 2016-17, our physicians and scientists at The Mount Sinai Hospital’s Division of Nephrology are internationally recognized as authorities on the causes and treatments of all forms of adult and pediatric kidney diseases. Our kidney transplant specialists are investigating new ways to detect, prevent, and treat rejection that will have a lasting impact on the field. Our physicians are all on the faculty at the Icahn School of Medicine at Mount Sinai, which is ranked among the nation’s top medical schools by U.S. News & World Report.

- Division of Nephrology
- Division of Pediatric Nephrology
- The Recanati/Miller Transplantation Institute
- Hypertension Program
- Glomerular Disease Program
- Mount Sinai Home Dialysis Program
- Mount Sinai Kidney Center (Dialysis)
- Mount Sinai Kidney Stone Center