

- Gilbert RE: The (Pro)renin receptor: Site-specific and functional linkage to the vacuolar H<sup>+</sup>-ATPase in the kidney. *Hypertension* 54: 261–269, 2009
7. Ramkumar N, Stuart D, Calquin M, Quadri S, Wang S, Van Hoek AN, Siragy HM, Ichihara A, Kohan DE: Nephron-specific deletion of the prorenin receptor causes a urine concentration defect. *Am J Physiol Renal Physiol* 309: F48–F56, 2015
  8. Yamaguchi Y, Yonemura S, Takada S: Grainyhead-related transcription factor is required for duct maturation in the salivary gland and the kidney of the mouse. *Development* 133: 4737–4748, 2006
  9. Wang F, Lu X, Peng K, Du Y, Zhou SF, Zhang A, Yang T: Prostaglandin E-prostanoid4 receptor mediates angiotensin II-induced (pro)renin receptor expression in the rat renal medulla. *Hypertension* 64: 369–377, 2014
  10. Gao M, Cao R, Du S, Jia X, Zheng S, Huang S, Han Q, Liu J, Zhang X, Miao Y, Kang J, Gustafsson JA, Guan Y: Disruption of prostaglandin E2 receptor EP4 impairs urinary concentration via decreasing aquaporin 2 in renal collecting ducts. *Proc Natl Acad Sci U S A* 112: 8397–8402, 2015
  11. Morath R, Klein T, Seyberth HW, Nüsing RM: Immunolocalization of the four prostaglandin E2 receptor proteins EP1, EP2, EP3, and EP4 in human kidney. *J Am Soc Nephrol* 10: 1851–1860, 1999
  12. Jensen BL, Stubbe J, Hansen PB, Andreassen D, Skøtt O: Localization of prostaglandin E(2) EP2 and EP4 receptors in the rat kidney. *Am J Physiol Renal Physiol* 280: F1001–F1009, 2001
  13. Breyer MD, Davis L, Jacobson HR, Breyer RM: Differential localization of prostaglandin E receptor subtypes in human kidney. *Am J Physiol* 270: F912–F918, 1996
  14. Nüsing RM, Treude A, Weissenberger C, Jensen B, Bek M, Wagner C, Narumiya S, Seyberth HW: Dominant role of prostaglandin E2 EP4 receptor in furosemide-induced salt-losing tubulopathy: A model for hyperprostaglandin E syndrome/antenatal Bartter syndrome. *J Am Soc Nephrol* 16: 2354–2362, 2005
  15. Pöschke A, Kern N, Maruyama T, Pavenstädt H, Narumiya S, Jensen BL, Nüsing RM: The PGE(2)-EP4 receptor is necessary for stimulation of the renin-angiotensin-aldosterone system in response to low dietary salt intake in vivo. *Am J Physiol Renal Physiol* 303: F1435–F1442, 2012
  16. Li JH, Chou CL, Li B, Gavrilova O, Eisner C, Schnermann J, Anderson SA, Deng CX, Knepper MA, Wess J: A selective EP4 PGE2 receptor agonist alleviates disease in a new mouse model of X-linked nephrogenic diabetes insipidus. *J Clin Invest* 119: 3115–3126, 2009
  17. Olesen ET, Rützler MR, Moeller HB, Praetorius HA, Fenton RA: Vasopressin-independent targeting of aquaporin-2 by selective E-prostanoid receptor agonists alleviates nephrogenic diabetes insipidus. *Proc Natl Acad Sci U S A* 108: 12949–12954, 2011
  18. Zhang MZ, Sanchez Lopez P, McKanna JA, Harris RC: Regulation of cyclooxygenase expression by vasopressin in rat renal medulla. *Endocrinology* 145: 1402–1409, 2004
  19. Yang T, Schnermann JB, Briggs JP: Regulation of cyclooxygenase-2 expression in renal medulla by tonicity in vivo and in vitro. *Am J Physiol* 277: F1–F9, 1999
  20. Wang F, Lu X, Peng K, Zhou L, Li C, Wang W, Yu X, Kohan DE, Zhu SF, Yang T: COX-2 mediates angiotensin II-induced (pro)renin receptor expression in the rat renal medulla. *Am J Physiol Renal Physiol* 307: F25–F32, 2014
  21. Feldt S, Batenburg WW, Mazak I, Maschke U, Wellner M, Kvakan H, Dechend R, Fiebeler A, Burckle C, Contrepas A, Jan Danser AH, Bader M, Nguyen G, Luft FC, Muller DN: Prorenin and renin-induced extracellular signal-regulated kinase 1/2 activation in monocytes is not blocked by aliskiren or the handle-region peptide. *Hypertension* 51: 682–688, 2008
  22. Baggaley E, Nielsen S, Marples D: Dehydration-induced increase in aquaporin-2 protein abundance is blocked by nonsteroidal anti-inflammatory drugs. *Am J Physiol Renal Physiol* 298: F1051–F1058, 2010
  23. Downey P, Sapirstein A, O'Leary E, Sun TX, Brown D, Bonventre JV: Renal concentrating defect in mice lacking group IV cytosolic phospholipase A(2). *Am J Physiol Renal Physiol* 280: F607–F618, 2001
  24. Nørregaard R, Madsen K, Hansen PB, Bie P, Thavalingam S, Frøkiær J, Jensen BL: COX-2 disruption leads to increased central vasopressin

- stores and impaired urine concentrating ability in mice. *Am J Physiol Renal Physiol* 301: F1303–F1313, 2011
25. Jia Z, Liu G, Downton M, Dong Z, Zhang A, Yang T: mPGES-1 deletion potentiates urine concentrating capability after water deprivation. *Am J Physiol Renal Physiol* 302: F1005–F1012, 2012

See related article, "Antidiuretic Action of Collecting Duct (Pro)Renin Receptor Downstream of Vasopressin and PGE<sub>2</sub> Receptor EP<sub>4</sub>," on pages 3022–3034.

## Sex Differences and Renal Protection: Keeping in Touch with Your Feminine Side

Vesna D. Garovic\* and Phyllis August†

\*Division of Nephrology and Hypertension, Mayo Clinic College of Medicine, Rochester, Minnesota; and †Division of Nephrology and Hypertension, Weil Cornell Medicine, New York, New York

*J Am Soc Nephrol* 27: 2921–2924, 2016.  
doi: 10.1681/ASN.2016040454

Recognition of the fundamental roles played by sex-specific factors in health and disease led to the 1993 National Institutes of Health (NIH) Revitalization Act that mandates that National Institutes of Health researchers include women in clinical studies and that results be analyzed by sex or gender.<sup>1</sup> It took another 20 years to advise the implementation of similar policies to preclinical research, such as the equal inclusion of male and female animals and analyses of animal and cell data by sex, suggesting that discovery of key sex differences may inform subsequent clinical studies.<sup>2</sup> Whereas the initial focus of sex differences was on cardiovascular disease, their role in the susceptibility to, and progression of, renal disease has increasingly been recognized, with a growing interest in the possible renal-protective role of female sex and hormones.

Large epidemiologic studies indicate that the incidence of ESRD is higher in men compared with women across the lifespan.<sup>3</sup> In animal models of renal injury, males are commonly affected more than females, thus resulting in male animals being used more often in studies of the mechanisms of renal injury. A recent study has indicated that tolerance to ischemia-reperfusion injury is increased in female compared with male mice, and that female mice receiving supplemental estrogen before ischemia were protected further.<sup>4</sup> Consequently, the possible mechanisms that underlie the renal-protective role of female sex seem to be related to estrogen, and

Published online ahead of print. Publication date available at www.jasn.org.

**Correspondence:** Dr. Vesna D. Garovic, Mayo Clinic, 200 First Street, Rochester, MN 55905, or Dr. Phyllis August, Hypertension Center, 450 East 69th Street, New York, NY 10021. Email: garovic.vesna@mayo.edu or paugust@med.cornell.edu

Copyright © 2016 by the American Society of Nephrology

therefore limited to premenopausal women. This is supported by clinical studies which have demonstrated that premenopausal women, as compared with aged-matched men, are protected from renal and cardiovascular disease; this protective effect seems to be lost with aging and menopause.<sup>5</sup> However, the mechanisms by which estrogen confers protective renal effects are not well understood.

Two studies in this issue extend our knowledge of the renal-protective effects of estrogen, by providing evidence that cyclic changes in female reproductive hormones, including estrogen, in premenopausal women may be protective against renal injury in general,<sup>6</sup> and that estrogen may be a potential therapeutic option for renal injury in diabetic nephropathy, in particular.<sup>7</sup>

Seppi *et al.*<sup>6</sup> investigated the urinary excretion of renal proximal tubular enzymes—fructose-1,6-bisphosphatase (F-1,6-BPase) and glutathione-S-transferase- $\alpha$  (GST $\alpha$ )—during the female reproductive hormone cycle. They found that premenopausal, naturally ovulating women, but not men or postmenopausal women, demonstrated two distinct peaks in the urinary excretion of F-1,6-BPase and GST $\alpha$  that followed the rhythmic hormonal changes of the menstrual cycle, occurring consistently within 7 days after ovulation or the onset of menstrual bleeding. This was not accompanied by changes in the urinary concentrations of the proteins that are reabsorbed by the tubular epithelium (such as albumin), suggesting that enzymuria was not associated with proximal tubular dysfunction. They argue that estrogen exerts proliferative and antiapoptotic effects on proximal tubular cells during the phases of the menstrual cycle characterized by high estrogen levels. In turn, decreases in estrogen, which occur after ovulation and before the onset of menstrual bleeding, may result in proximal tubular cell death, as characterized by urinary F-1,6-BPase and GST $\alpha$  excretion. The authors postulate that the fluctuating levels of female sex hormones translate into transient increases in tubular cell turnover that renders proximal tubular cells more resistant to renal damage, and that the urinary excretion of proximal tubular enzymes reflects this.

Several provocative questions with respect to female renal health and disease can be asked on the basis of the results of this study. First, given the high levels of sex hormones during pregnancy, is it possible that pregnancy-related alterations in renal function, *e.g.*, the increase in GFR, may be, at least in part, related to the estrogen-mediated proliferative and antiapoptotic effects on proximal tubular cells? Second, some, but not all, renal diseases progress during pregnancy, despite the presence of high estrogen levels, raising the possibility that estrogen-protective effects are disease-specific. Alternatively, the protective estrogen effects in pregnancy may be offset by the inflammatory and hypercoagulable milieu that develops as a physiologic adaptation to normal pregnancy and is exaggerated further in pregnancies complicated by renal disease. Third, it is common for women with advanced renal disease to become amenorrheic. Does the absence of normal menstrual cycles/ovulation in CKD patients lead to a vicious cycle of

CKD→ estrogen dysregulation→ CKD, and would hormonal therapy slow the progression of CKD? Finally, the authors suggest that enhanced repair capacity may be potentiated by chronic exposure to cyclic hormonal changes during the premenopausal years. However, several studies have suggested that even temporary, short treatment with estrogen, rather than exposure over the reproductive lifetime, has a renal-protective or therapeutic effect, including the study by Inada *et al.*<sup>7</sup> in this issue.

Inada *et al.*<sup>7</sup> argue that administration of 17 $\beta$ -estradiol (E2) is an effective treatment of diabetic nephropathy, even in the presence of glomerulosclerosis. They used a diabetic transgenic mice model generated by  $\beta$  cell overexpression of inducible cAMP early repressor that has previously been shown to result in severe early-onset diabetes and diabetic renal injury in male, but not female, mice.<sup>8</sup> Citing clinical evidence for a lower risk of diabetic nephropathy in premenopausal compared with postmenopausal women, they hypothesized that female inducible cAMP early repressor transgenic mice were protected from diabetic renal injury by circulating E2 levels. In their study, they treated male mice with E2 pellet implantation in doses that adjusted the E2/androgen ratio to that observed in female transgenic mice. Treatment with E2 ameliorated renal injury, both in early- and late-stage diabetic nephropathy, and was more effective than either orchietomy or islet cell transplantation.

Several epidemiologic and animal studies have confirmed the role of sex and sex hormones in the development of diabetes and progression of diabetic nephropathy. The protective role of female gender parallels estrogen levels, as demonstrated by a steep increase in the incidence of diabetes during the perimenopausal and menopausal years.<sup>9</sup> A study of ovariectomized *db/db* mice, a model of type 2 diabetes mellitus, undergoing an 8-week E2 treatment demonstrated reduced hyperglycemia, reduced albuminuria, and weight gain.<sup>10</sup> Further, the authors of animal studies of castrated and ovariectomized rats have argued that both the absence of estrogens and the presence of androgens are risk factors for glomerular injury.<sup>11,12</sup> Inada *et al.*,<sup>7</sup> investigated the renal effects of E2 with or without orchietomy and concluded that E2 was more effective than orchietomy alone in controlling hyperglycemia, increasing the number of  $\beta$  cells, and reducing glomerular injury. The authors proposed that E2 supplementation that modulates the E2/androgen ratio is a promising therapeutic option for diabetic nephropathy. Their conclusions need to be critically evaluated with respect to E2 safety and efficacy as a therapeutic agent.

The authors of several animal studies have argued that the effects of estrogen on diabetic nephropathy are not always beneficial and that, at least in certain animal strains, estrogen may contribute to the development of glomerulosclerosis.<sup>13,14</sup> The controversy has been fueled further by clinical studies that have argued that exogenous estrogen may be harmful to the kidneys, as suggested by a Canadian study of almost 6000 women, which concluded that estrogen therapy in postmenopausal women was associated with loss of renal function.<sup>15</sup> However, this study had several limitations, including the

failure to control for important confounders, such as hypertension and obesity. More recently, data are becoming available regarding the effects of cross-sex hormone treatment on transgender women (persons who were identified as males at birth, but who identify as females) who receive estrogen in order to develop female secondary sex characteristics. A 6-month course of estrogen therapy in transgender women resulted in significant reductions in BP compared with baseline<sup>16</sup> and decreases in plasma homocysteine levels—a risk factor for atherosclerotic and thrombotic disease.<sup>17</sup> These beneficial estrogen effects on cardiovascular disease risk factors may translate into reduced renal disease risk as well (particularly the favorable BP effects), but may not be clinically useful for the general patient population, due to the unacceptable feminizing side effects in men and the increased breast and uterine cancer risks in women. A safer treatment option would be raloxifene, a selective estrogen receptor modulator. Treatment with raloxifene was proven to be renal-protective, both in a *post hoc* analysis of postmenopausal women with osteoporosis<sup>18</sup> and in a randomized, placebo-controlled trial of postmenopausal women with diabetes and albuminuria.<sup>19</sup> Animal studies have shed light on the possible mechanism of the protective effects of raloxifene in the kidney: in ovariectomized *db/db* mice, raloxifene inhibited TGF  $\beta$ -1-induced fibronectin transcription.<sup>10</sup> Raloxifene, to date, has been used both in men and women for the treatment of neurocognitive deficits in schizophrenia, and has been proven to be safe and effective in improving attention, memory, and learning.<sup>20</sup>

In conclusion, two papers in this issue demonstrate that endogenous estrogen may exert protective renal effects<sup>6</sup> and estrogen supplementation may be an effective treatment strategy for diabetic nephropathy.<sup>7</sup> Additional studies are required to elucidate the clinical importance of these findings. In view of the findings of Seppi *et al.*,<sup>6</sup> consideration should be given to estrogen supplementation in a manner that mimics estrogen variability in premenopausal women. This may be particularly important for proximal cell turnover and repair and, ultimately, increased resistance to renal injury.

## ACKNOWLEDGMENTS

This study was supported by award number P-50 AG44170 from the National Institute on Aging (to V.D.G.).

The contents of this paper are solely the responsibility of the authors and do not necessarily represent the official view of the National Institutes of Health.

## DISCLOSURES

None.

## REFERENCES

1. National Institutes of Health: NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research, 2001. Available at [http://grants.nih.gov/grants/funding/women\\_min/guidelines\\_amended\\_10\\_2001.htm](http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm). Accessed April 9, 2016
2. Clayton JA, Collins FS: Policy: NIH to balance sex in cell and animal studies. *Nature* 509: 282–283, 2014
3. United States Renal Data System: USRDS Annual data Report, 2010. Available at <http://www.usrds.org/2015/view/Default.aspx>. Accessed April 9, 2016
4. Aufhauser DD Jr, Wang Z, Murken DR, Bhatti TR, Wang Y, Ge G, Redfield RR III, Abt PL, Wang L, Svoronos N, Thomasson A, Reese PP, Hancock WW, Levine MH: Improved renal ischemia tolerance in females influences kidney transplantation outcomes [published online ahead of print April 18, 2016]. *J Clin Invest* doi:10.1172/JCI84712
5. Coggins CH, Breyer Lewis J, Caggiula AW, Castaldo LS, Klahr S, Wang SR: Differences between women and men with chronic renal disease. *Nephrol Dial Transplant* 13: 1430–1437, 1998
6. Seppi TPS, Dorler MM, Either O, Hekl D, Nevinny-Stickel M, Skvortsova I, Gstraunthaler G, Lukas P, Lechner J: Sex differences in renal proximal tubular cell homeostasis. *J Am Soc Nephrol* 27: 3051–3062, 2016
7. Inada A, Inada O, Fujii NL, Nagafuchi S, Katsuta H, Yasunami Y, Matsubara T, Arai H, Fukatsu A, Nabeshima YI: Adjusting the 17 $\beta$ -estradiol-to-androgen ratio ameliorates diabetic nephropathy. *J Am Soc Nephrol* 27: 3035–3050, 2016
8. Inada A, Arai H, Nagai K, Miyazaki J, Yamada Y, Seino Y, Fukatsu A: Gender difference in ICER Igamma transgenic diabetic mouse. *Biosci Biotechnol Biochem* 71: 1920–1926, 2007
9. Wild S, Roglic G, Green A, Sicree R, King H: Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care* 27: 1047–1053, 2004
10. Chin M, Isono M, Isshiki K, Araki S, Sugimoto T, Guo B, Sato H, Haneda M, Kashiwagi A, Koya D: Estrogen and raloxifene, a selective estrogen receptor modulator, ameliorate renal damage in *db/db* mice. *Am J Pathol* 166: 1629–1636, 2005
11. Baylis C: Age-dependent glomerular damage in the rat. Dissociation between glomerular injury and both glomerular hypertension and hypertrophy. Male gender as a primary risk factor. *J Clin Invest* 94: 1823–1829, 1994
12. Sakemi T, Ohtsuka N, Shouno Y, Morito F: Effect of ovariectomy on glomerular injury in hypercholesterolemic female Imai rats. *Nephron* 72: 72–78, 1996
13. Rosenmann E, Yanko L, Cohen AM: Female sex hormone and nephropathy in Cohen diabetic rat (genetically selected sucrose-fed). *Horm Metab Res* 16: 11–16, 1984
14. Tomiyoshi Y, Sakemi T, Aoki S, Miyazono M: Different effects of castration and estrogen administration on glomerular injury in spontaneously hyperglycemic Otsuka Long-Evans Tokushima Fatty (OLETF) rats. *Nephron* 92: 860–867, 2002
15. Ahmed SB, Culleton BF, Tonelli M, Klarenbach SW, Macrae JM, Zhang J, Hemmelgarn BR; Alberta Kidney Disease Network: Oral estrogen therapy in postmenopausal women is associated with loss of kidney function. *Kidney Int* 74: 370–376, 2008
16. Deutsch MB, Bhakri V, Kubicek K: Effects of cross-sex hormone treatment on transgender women and men. *Obstet Gynecol* 125: 605–610, 2015
17. Giltay EJ, Verhoef P, Gooren LJ, Geleijnse JM, Schouten EG, Stehouwer CD: Oral and transdermal estrogens both lower plasma total homocysteine in male-to-female transsexuals. *Atherosclerosis* 168: 139–146, 2003
18. Melamed ML, Blackwell T, Neugarten J, Arnsten JH, Ensrud KE, Ishani A, Cummings SR, Silbiger SR: Raloxifene, a selective estrogen receptor modulator, is renoprotective: a post-hoc analysis. *Kidney Int* 79: 241–249, 2011
19. Hadjadj S, Gourdy P, Zaoui P, Guerci B, Roudaut N, Gautier JF, Chabin M, Mauco G, Ragot S; RADIANT Study Group: Effect of raloxifene – a selective oestrogen receptor modulator – on kidney function in post-menopausal women with Type 2 diabetes: results from a randomized, placebo-controlled pilot trial. *Diabet Med* 24: 906–910, 2007

20. Weickert TW, Allen KM, Weickert CS: Potential role of oestrogen modulation in the treatment of neurocognitive deficits in schizophrenia. *CNS Drugs* 30: 125–133, 2016

See related articles, “Adjusting the 17 $\beta$ -Estradiol-to-Androgen Ratio Ameliorates Diabetic Nephropathy,” and “Sex Differences in Renal Proximal Tubular Cell Homeostasis,” on pages 3035–3050 and 3051–3062, respectively.

## ESRD Payment Reform: First Do No Harm

Jenny I. Shen\*<sup>†</sup> and Keith C. Norris<sup>†‡</sup>

\*Department of Medicine, Division of Nephrology, Los Angeles Biomedical Institute at Harbor-University of California, Los Angeles Medical Center, Torrance, California; <sup>†</sup>Division of Nephrology and Hypertension and <sup>‡</sup>Division of General Internal Medicine and Health Services Research, David Geffen School of Medicine at University of California, Los Angeles, Los Angeles, California

*J Am Soc Nephrol* 27: 2924–2926, 2016.  
doi: 10.1681/ASN.2016020153

“Bureaucracy defends the status quo long past the time when the quo has lost its status – Laurence J. Peter (*American educator & writer; 1919–1988*)”

The continued growth of the number of patients receiving RRT levies not only a personal toll on families and communities, but also an increasing financial burden on Medicare. With patients with ESRD accounting for <1% of the total Medicare population but consuming nearly 7% of Medicare costs,<sup>1</sup> there is a crucial need to explore new strategies to advance value-based care. The challenge of balancing cost constraints while maintaining quality of care continuously lingers over the nephrology community. The introduction of new health care policies and regulations are designed to enhance the value of care by improving patient outcomes and/or reducing costs. To ensure there are not unintended consequences of such policies (*Primum non nocere* – first, do no harm), a careful evaluation of their impact is needed. Even if there are formal evaluation strategies in place, it is often incumbent on the medical community to conduct independent analyses, especially when there could be conflicting effects of policies on patient and financial outcomes. In this issue of the *Journal of the American Society of Nephrology (JASN)*, Chertow *et al.* take on such a challenge.<sup>2</sup>

In an effort to balance quality of care and costs to optimize the value of renal health care delivery, the US Congress passed the Medicare Improvements for Patients with Providers Act

(MIPPA HR 6331) in 2008, which mandated reform of Medicare reimbursement policies. The Centers for Medicare and Medicaid Services (CMS) released a final ruling for implementation of the ESRD prospect of payment system in July of 2010<sup>3</sup> that was subsequently implemented in January of 2011.<sup>4,5</sup> This new, bundled payment for ESRD was developed on the same principles that led to the original “Composite Rate” dialysis payment introduced in 1983 and transformed reimbursement to one set payment per dialysis treatment, including ESRD lab tests, intravenous medications (*e.g.*, erythropoiesis stimulating agents [ESAs], vitamin D, and iron), and oral medications with intravenous equivalents.<sup>6</sup> To lower Medicare expenditures, the 2011 bundled payment for ESRD reduced payments to ESRD facilities by 2% overall and eliminated incentives to the overuse of previously profitable, separately billable drugs. In particular, ESAs changed from being separately billable to being part of the bundled payment. This was prompted, in part, due to the high costs of ESA treatment, and in part because controlled trials demonstrated that targeting hemoglobin levels of  $\geq 13$  g/dl led to higher rates of mortality, cardiovascular events, and stroke in patients with CKD.<sup>7–9</sup> These studies also led to the US Food and Drug administration to require a modification of ESA product labels, which were released in June of 2011. This replaced the conventional hemoglobin target of 10–12 g/dl with recommendations to reduce or interrupt dosing as the hemoglobin approaches or exceeds 11 g/dl.<sup>10</sup>

Thus, the combination of the introduction of Medicare ESRD payment reform (in January of 2011) and changes in ESA product labeling (in June of 2011) rapidly led to a 29%–52% reduction in the use of ESAs in dialysis patients across different dialysis organizations.<sup>11</sup> However, the new bundled payment model also raised many concerns about the impact of managing trade-offs that could affect facility and/or provider behaviors and lead to unintended adverse consequences,<sup>12</sup> including worse outcomes for patients with ESRD due to the potential for undertreatment in terms of dialysis time, anemia management, and mineral and bone disorders.<sup>4</sup> In fact, the American Society of Nephrology (ASN) called for close monitoring of not only intermediate quality care outcomes such as lab values, but downstream clinical outcomes such as hospitalizations and mortality.<sup>4</sup> Several studies have subsequently examined the impact of bundled payment on intermediary outcomes and suggest that overall, the nephrology community has done an excellent job in maintaining the quality care for patients with ESRD. A recent analysis by Swaminathan *et al.* found the reduction in ESA use among dialysis patients was limited to those with a hematocrit  $>36\%$ , with little change in use among patients with hematocrit  $\leq 36\%$ , suggesting that the impact on ESA reduction has appropriately been among patients who are least likely to benefit from the use of these agents.<sup>13</sup> In a cross-sectional analysis, Turenne *et al.* reported trends in ESRD quality care measures in 132 facilities in the Dialysis Outcomes and Practice Patterns Study from August of 2010 to December of 2011.<sup>14</sup> Not unexpectedly, they found that not only did mean hemoglobin levels fall from 11.5 to 11.0 g/dl, along with erythropoietin doses falling by  $>25\%$ , but mean serum parathyroid hormone levels rose

Published online ahead of print. Publication date available at www.jasn.org.

**Correspondence:** Dr. Keith C. Norris, Division of General Internal Medicine and Health Services Research, University of California, Los Angeles, 911 Broxton Plaza, Room 103, Los Angeles, CA 90024. Email: kcnorris@mednet.ucla.edu

Copyright © 2016 by the American Society of Nephrology