

# Medication Prescription Patterns for Secondary Hyperparathyroidism

## More Questions than Answers

Harish Seethapathy and Sagar U. Nigwekar

*Clin J Am Soc Nephrol* 14: 178–179, 2019. doi: <https://doi.org/10.2215/CJN.15081218>

Clinical practice patterns provide a real world view of how clinicians deal with the uncertainty of evidence and play an important role in determining outcomes. Study of practice patterns can identify areas for improvement and help design interventions to improve quality of care. For example, a recent study of >370,000 Medicare beneficiaries who had an index emergency department visit and had not received prescriptions for opioids within 6 months before the index emergency room visit identified a wide variation in the rates of opioid prescription among physicians practicing within the same emergency department. By grouping physicians according to opioid prescribing rates as being high-intensity or low-intensity prescribers, the investigators identified treatment by a high-intensity prescriber as an independent risk factor for long-term opioid use (1) and defined a potential target for future interventions aimed at reducing opioid use.

For the nephrology community, the Dialysis Outcomes and Practice Patterns Study (DOPPS) is a concerted effort to identify the best practice patterns relevant to treating patients with kidney disease (2). Beginning in 1996, the DOPPS has tracked >120,000 patients on hemodialysis, patients on peritoneal dialysis, and those with CKD from 20 countries around the world. For the hemodialysis population, the DOPPS collects longitudinal data from a random and representative sample of patients from hemodialysis facilities. In this issue of the *Clinical Journal of the American Society of Nephrology*, Fuller *et al.* (3) evaluate data from the DOPPS to examine variability in the prescription rates of cinacalcet, a calcimimetic agent approved for the treatment of secondary hyperparathyroidism in patients on dialysis. The rationale for their investigation comes from the potential upcoming revisions to the prospective payment system (PPS) to include calcimimetics and thus, the need to identify factors that influence the utilization of calcimimetics among patients on dialysis. Focusing on monthly cross-sectional data collected in the year 2014 from 203 hemodialysis facilities (>10,000 patients) in the United States, the authors characterized the variability in the prescription of cinacalcet in relation to three facility-level exposures of patient percentages—age

<65 years old, dialysis vintage  $\geq 3$  years, and black race. The cinacalcet prescription rates across facilities within each month of the study year were variable (interquartile range, 16%–20% across months during the year 2014). Patients in facilities with the highest quartile compared with the lowest quartile of cinacalcet prescription were significantly younger, had a longer dialysis vintage, and were more frequently of black race. These patient attributes showed monotonic positive associations with cinacalcet prescription, albeit in models adjusted for patient-level covariates corresponding to the facility-level exposure of interest, the associations were attenuated or reversed.

Secondary hyperparathyroidism of CKD is a morbid complication associated with a higher risk for mortality, cardiovascular events, and skeletal fractures. Components of medical management of secondary hyperparathyroidism include dietary phosphate restriction, phosphate binders, vitamin D, and calcimimetics. The average parathyroid hormone (PTH) levels of patients on dialysis have steadily risen over the past decade. In 2002, 13% of patients on hemodialysis had an intact PTH level >600 pg/ml (4). As of December 2017, this number has increased to 24% (2). Blacks fare worse, with the prevalence of intact PTH >600 pg/ml at 33% compared with 22% in nonblacks. The practice patterns for secondary hyperparathyroidism have shifted in recent years, temporally coinciding with the changes in reimbursement policies and guideline statements. Since 2011, the reimbursement for intravenous vitamin D has been incorporated into the bundled payment in the United States, and phosphate binders and calcimimetics are anticipated to follow the suit in future. The average dose of intravenous vitamin D declined among patients on hemodialysis in the United States since 2011 (5). The Kidney Disease Outcomes Quality Initiative 2003 guidelines recommended target PTH levels between 150 and 300 pg/ml for patients on dialysis. These guidelines were subsequently updated (Kidney Disease Improving Global Outcomes [KDIGO] 2009), with a recommendation for a more relaxed target PTH range of two to nine times the upper limit of normal. The recent update (KDIGO 2017) maintained the same target PTH range for patients on dialysis; however,

Division of Nephrology, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts

**Correspondence:**

Dr. Sagar U. Nigwekar, Division of Nephrology, Department of Medicine, Massachusetts General Hospital, 165 Cambridge Street, Suite 302, Boston, MA 02114. Email: [snigwekar@mgh.harvard.edu](mailto:snigwekar@mgh.harvard.edu)

in a departure from the prior version of guidelines, it stated that the optimal PTH level for patients with nondialysis-dependent CKD is unknown. In patients with nondialysis-dependent CKD, the most recent guidelines recommend evaluation and treatment if the PTH elevations are persistent or progressive. Future studies are needed to examine whether the progressively rising PTH levels affect clinical outcomes and how the recent guidelines affect practice patterns.

In a randomized, controlled clinical trial of >3800 patients on hemodialysis with moderate to severe hyperparathyroidism, cinacalcet (compared with placebo) failed to show improvement in mortality or major cardiovascular events over a follow-up of up to 64 months (6). The negative results were likely influenced by the imbalances in baseline characteristics, lower than expected event rates, high dropout rates, and use of clinically prescribed cinacalcet in the placebo arm. The Australian government withdrew funding for cinacalcet after the publication of this large trial, and as a result, most Australian patients on dialysis discontinued cinacalcet therapy. Significant increases in PTH levels (>50% from baseline) over a 12-month period after the withdrawal of cinacalcet among Australian patients on dialysis have been recently noted (7). In the United States, however, cinacalcet prescription rates in patients on hemodialysis have risen (from approximately 20% in 2011 to 30% in 2017) (2,4). However, the average PTH levels for United States patients on hemodialysis continue to rise, and in this complex scenario, the clinical effect of potentially inculcating calcimimetics (cinacalcet and recently approved intravenous etelcalcetide) into the PPS bundle is unclear. The inclusion of calcimimetics into the bundled payment system will affect the selection of other treatments, including vitamin D and surgical parathyroidectomy, and it will likely emphasize a stricter control of hyperparathyroidism before dialysis initiation among patients with CKD.

The expected change to the PPS bundle also raises an important question of whether there will be disparities in care among certain patient populations. Early data suggest that there is no indication of racial disparities resulting from implementation of the PPS (8). The study by Fuller *et al.* (3) prompts us to refocus on these issues and highlights the need for future longitudinal studies to evaluate the effect of bundling on facilities and clinical outcomes among different patient groups. More data regarding comparison of cost-effectiveness between calcimimetic agents and other treatments for secondary hyperparathyroidism are also needed.

In summary, the landscape of secondary hyperparathyroidism has changed—target PTH levels have evolved,

average PTH levels in patients on hemodialysis are higher now than a decade ago, and we have more drugs in our armamentarium, including etelcalcetide and new phosphate binders. The examination of variability in practice patterns and outcomes data as they become available will be an effective way to move the field forward. The clinical and research communities will be looking at databases, like the DOPPS, to identify the best clinical practices.

#### Disclosures

None.

#### References

1. Barnett ML, Olenki AR, Jena AB: Opioid-prescribing patterns of emergency physicians and risk of long-term use. *N Engl J Med* 376: 663–673, 2017
2. Arbor Research Collaborative for Health: DOPPS Practice Monitor. Available at: <https://dopps.org>. Accessed December 20, 2018
3. Fuller D, Xing S, Yehoshua A, Morgenstern H, Robinson B: Variability in cinacalcet prescription across US hemodialysis facilities. *Clin J Am Soc Nephrol* 14: 241–249, 2019
4. Arbor Research Collaborative for Health: 2012 Annual Report of the Dialysis Outcomes and Practice Patterns Study: Hemodialysis Data 1997–2011, Ann Arbor, MI, Arbor Research Collaborative for Health, 2013
5. Spoendlin J, Schneeweiss S, Tsacogianis T, Paik JM, Fischer MA, Kim SC, Desai RJ: Association of Medicare's bundled payment reform with changes in use of vitamin D among patients receiving maintenance hemodialysis: An interrupted time-series analysis. *Am J Kidney Dis* 72: 178–187, 2018
6. Chertow GM, Block GA, Correa-Rotter R, Drüeke TB, Floege J, Goodman WG, Herzog CA, Kubo Y, London GM, Mahaffey KW, Mix TC, Moe SM, Trotman ML, Wheeler DC, Parfrey PS; EVOLVE Trial Investigators: Effect of cinacalcet on cardiovascular disease in patients undergoing dialysis. *N Engl J Med* 367: 2482–2494, 2012
7. Ruderman I, Holt SG, Kirkland GS, Maslen S, Hawley CM, Oliver V, Krishnasamy R, Gray NA, Talaulikar GS, Nelson CL, Rajaram Y, Gock H, Au E, Elder GJ, Mainra R, Toussaint ND: Outcomes of cinacalcet withdrawal in Australian dialysis patients [published online ahead of print July 10, 2018]. *Intern Med J* doi:10.1111/imj.14036
8. Turenne MN, Cope EL, Porenta S, Mukhopadhyay P, Fuller DS, Pearson JM, Dahlerus C, Lantz B, Tentori F, Robinson BM: Has dialysis payment reform led to initial racial disparities in anemia and mineral metabolism management? *J Am Soc Nephrol* 26: 754–764, 2015

Published online ahead of print. Publication date available at [www.cjasn.org](http://www.cjasn.org).

See related article, “Variability in Cinacalcet Prescription across US Hemodialysis Facilities,” on pages 241–249.