Antihypertensive Medication in Patients Pre- and Postdialysis: Still Hazy After All These Years

Jordana B. Cohen and Raymond R. Townsend

Clin J Am Soc Nephrol 11: 1327–1329, 2016. doi: 10.2215/CJN.06130616

Renal, Electrolyte, and Hypertension Division, University of Pennsylvania, Philadelphia, Pennsylvania

Correspondence:
Dr. Jordana B. Cohen, Renal, Electrolyte and Hypertension Division, Hospital of the University of Pennsylvania, 3400 Spruce Street, 1 Founders, Philadelphia, PA 19104. Email: jco@mail.med.upenn.edu

The past few years have witnessed a series of seemingly paradoxical findings in patients on hemodialysis when attempts are made to normalize their hemoglobin (1,2), parathyroid hormone concentrations (3), the amount of vitamin D in their serum (4), or their cholesterol levels (5). Attending the sessions on late-breaking abstracts of clinical trials in nephrology at the annual meeting of the American Society of Nephrology during the last few years has often prompted attendees to reach for citalopram rather than champagne, given the frequently disappointing results of intervention trials in CKD, including ESRD. Obesity and race/ethnicity add more mystery to understanding the patient on dialysis, because those with higher body mass index seem to live longer (6), as do minority patients (7). Perhaps the most bewildering data in the ESRD population is the relationship of BP to outcomes like survival, where there seems to be a wide, shallow U shape with patients with <110 mmHg or >190 mmHg systolic BP faring poorly (8,9). One thing is certain: there is a lot of uncertainty still remaining when trying to determine what BP goal should be pursued, when the BP should be measured, and where the optimal setting to make BP measurements is for any given patient on dialysis. Moreover, the attempt to use existing guidelines for hypertension management in patients on dialysis is hampered by the lack of trials comparing goal BP values (irrespective of the setting). Adding to this, there is a paucity of data on the changes in phenotype that occur as patients enter the late stages of CKD and approach ESRD.

The transition from CKD to ESRD can be impetuous, to say the least. Although CKD in itself is associated with an abundance of morbidities, the added burden of dialysis can be socially, psychologically, and physiologically devastating. Besides the accelerated risk of cardiovascular disease and mortality, the early period after initiation of dialysis is associated with increased rates of hospitalizations and invasive interventions as well as a significant decline in functional status (10–12). Furthermore, patients are often overwhelmed by the increased pill burden, postdialysis fatigue, and newfound social isolation, likely contributing to poor quality of life as well as the high prevalence of depression and anxiety observed among patients on dialysis (13,14). Accordingly, much of the morbidity associated with dialysis initiation cannot be entirely captured by insurance claims and registry data, and is difficult to account for when designing studies. Consequently, there is a scarcity of information on interventions to potentially modify outcomes during the transition period surrounding dialysis initiation.

In this issue of the *Clinical Journal of the American Society of Nephrology*, Chang *et al.* (15) attempted to address the dearth of existing evidence on the management of hypertension during the often tempestuous transition from CKD to dialysis. This retrospective cohort study used Medicare claims data reported to the US Renal Data System to evaluate trends in antihypertensive administration among older adults during the months surrounding the initiation of dialysis. As one would expect, Chang *et al.* (15) found an increase in the number of antihypertensives administered during the period immediately preceding dialysis initiation, which subsequently declined after patients were started on dialysis (patients were on a mean of 2.4 medications 1 year before dialysis, which increased to 3.4 within 3 months before dialysis, and then decreased to 2.2 2 years after dialysis initiation), attributed to likely changes in volume status during the transition to dialysis.

Additionally, Chang *et al.* (15) noted that only 40% of patients were on renin angiotensin system (RAS) blockade, which was persistent before and after initiation of dialysis. Patients with diabetes had a slightly higher rate of RAS blockade use compared with patients without diabetes. During a similar timeframe (mid-2000s), the Chronic Renal Insufficiency Cohort (CRIC) Study examined the use of antihypertensive agent classes in participants with nondialysis CKD at seven regional centers across the United States and observed that the use of RAS blockade in those with a diagnosis of hypertension was 74% (16). Chang *et al.* (15) also observed that β-blocker use was higher among patients with coronary artery disease and systolic heart failure, but there was no difference in use of RAS blockade in these patients compared with patients who did not have increased cardiovascular morbidity. The low rate of use of RAS blockade in these patients suggests that physicians in the community may be hesitant to prescribe RAS blockade because of underlying kidney disease. Nonetheless, RAS blockade use was relatively stable across the peridialysis period in contrast to the other antihypertensive classes (*i.e.*, diuretics, β-blockers, and calcium channel blockers),

the use of which consistently decreased. The stability of RAS blockade use suggests that providers may be less likely to discontinue RAS blockade in patients who are able to tolerate it after they are on dialysis. Of note, there was no difference in Medicare claims for hyperkalemia or AKI in patients who were on RAS blockade compared with patients who were not.

Although other studies have evaluated antihypertensive utilization in the months immediately adjacent to dialysis initiation (17–20), this is the first study to follow patients longitudinally over several months leading up to and after initiation of dialysis, while also taking into account highly relevant comorbidities. However, the study is somewhat limited in its generalizability to the dialysis population as a whole, because patients were required to be eligible for Medicare with low–income medication subsidy 2 years before initiating dialysis. The study is further impaired by the nebulous nature of insurance claims data; as Chang *et al.* (15) noted, they were unable to take into account important confounding information, such as BP or laboratory values (*i.e.*, for corroboration of hyperkalemia or AKI as well as evaluation of residual renal function) (20,21), when interpreting changes in antihypertensive use. Additionally, although pharmacy claims data are likely more reflective of patient medication adherence than, for example, electronic prescribing data (22,23), they may fail to capture actual physician prescribing practices. Correspondingly, there was no correlation made between antihypertensive class and longitudinal cardiovascular outcomes. Unfortunately, the lack of preexisting evidence on optimal treatment of BP in ESRD somewhat limits the applicability of the results with regard to clinical care.

We welcome the efforts of investigators, like Chang *et al.* (15), studying the ESRD population, because this is a group at extreme risk for cardiovascular events; however, precious little is known about how the period leading up to ESRD influences outcomes after dialysis initiation. Their study makes several interesting observations and raises a number of additional questions in addition to underscoring the difficulties and limitations that attend the use of administrative databases. Ongoing CKD cohort studies, like the CRIC Study, although smaller in size than these large databases, have depth in demographics, phenotype, and drug usage along with a follow-up that spans the time period before and after dialysis initiation (24). Among the many questions that still remain in this area, information on antihypertensive drug usage as provided by Chang *et al.* (15), the importance of where and when BP is measured (25), and the role of circumstances, such as an unexpected abrupt decline in kidney function leading to dialysis initiation (26), give hope to those managing patients with ESRD that efforts toward unpacking the mysteries around the peridialysis period will provide more light than heat in this highly vulnerable yet curiously robust population.

Disclosures

R.R.T. is a consultant or on the advisory board of Medtronic (Langhorne, PA), Janssen Biotech (Horsham, PA), GlaxoSmithKline (Brentford, United Kingdom), and Merck GmbH (Darmstadt, Germany).

References

1. Singh AK, Szczech L, Tang KL, Barnhart H, Sapp S, Wolfson M, Reddan D; CHOIR Investigators: Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med* 355: 2085–2098, 2006
2. Besarab A, Bolton WK, Browne JK, Egrie JC, Nissenson AR, Okamoto DM, Schwab SJ, Goodkin DA: The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *N Engl J Med* 339: 584–590, 1998
3. 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
4. Bhan I, Dobens D, Tamez H, Deferio JJ, Li YC, Warren HS, Ankers E, Wenger J, Tucker JK, Trottier C, Pathan F, Kalim S, Nigwekar SU, Thadhani R: Nutritional vitamin D supplementation in dialysis: A randomized trial. *Clin J Am Soc Nephrol* 10: 611–619, 2015
5. Wanner C, Krane V, März W, Olschewski M, Mann JF, Ruf G, Ritz E; German Diabetes and Dialysis Study Investigators: Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med* 353: 238–248, 2005
6. Vashistha T, Mehrotra R, Park J, Streja E, Dukkipati R, Nissenson AR, Ma JZ, Kovesdy CP, Kalantar-Zadeh K: Effect of age and dialysis vintage on obesity paradox in long-term hemodialysis patients. *Am J Kidney Dis* 63: 612–622, 2014
7. Rhee CM, Lertdumrongluk P, Streja E, Park J, Moradi H, Lau WL, Norris KC, Nissenson AR, Amin AN, Kovesdy CP, Kalantar-Zadeh K: Impact of age, race and ethnicity on dialysis patient survival and kidney transplantation disparities. *Am J Nephrol* 39: 183–194, 2014
8. Salem MM: Hypertension in the haemodialysis population: Any relationship to 2-years survival? *Nephrol Dial Transplant* 14: 125–128, 1999
9. Kalantar-Zadeh K, Kilpatrick RD, McAllister CJ, Greenland S, Kopple JD: Reverse epidemiology of hypertension and cardiovascular death in the hemodialysis population: The 58th annual fall conference and scientific sessions. *Hypertension* 45: 811–817, 2005
10. United States Renal Data System: *Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States*, Bethseda, MD, National Institutes of Health: National Institute of Diabetes and Digestive and Kidney Diseases, 2010
11. de Jager DJ, Grootendorst DC, Jager KJ, van Dijk PC, Tomas LM, Ansell D, Collart F, Finne P, Heaf JG, De Meester J, Wetzels JF, Rosendaal FR, Dekker FW: Cardiovascular and noncardiovascular mortality among patients starting dialysis. *JAMA* 302: 1782–1789, 2009
12. Kurella Tamura M, Covinsky KE, Chertow GM, Yaffe K, Landefeld CS, McCulloch CE: Functional status of elderly adults before and after initiation of dialysis. *N Engl J Med* 361: 1539–1547, 2009
13. Jhamb M, Argyropoulos C, Steel JL, Plantinga L, Wu AW, Fink NE, Powe NR, Meyer KB, Unruh ML; Choices for Healthy Outcomes in Caring for End-Stage Renal Disease (CHOICE) Study: Correlates and outcomes of fatigue among incident dialysis patients. *Clin J Am Soc Nephrol* 4: 1779–1786, 2009
14. Alavi NM, Aliakbarzadeh Z, Sharifi K: Depression, anxiety, activities of daily living, and quality of life scores in patients undergoing renal replacement therapies. *Transplant Proc* 41: 3693–3696, 2009
15. Chang TI, Zheng Y, Montez-Rath ME, Winkelmayer WC: Antihypertenseive medication use in older patients transitioning from chronic kidney disease to end-stage renal disease on dialysis. *Clin J Am Soc Nephrol* 11: 1401–1412, 2016
16. Muntner P, Anderson A, Charleston J, Chen Z, Ford V, Makos G, O'Connor A, Perumal K, Rahman M, Steigerwalt S, Teal V, Townsend R, Weir M, Wright JT Jr.; Chronic Renal Insufficiency Cohort (CRIC) Study Investigators: Hypertension awareness, treatment, and control in adults with CKD: Results from the Chronic Renal Insufficiency Cohort (CRIC) Study. *Am J Kidney Dis* 55: 441–451, 2010
17. United States Renal Data System: *Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States*, Bethesda, MD, National Institutes of Health,

National Institute of Diabetes and Digestive and Kidney Diseases, 2013
18. United States Renal Data System: *Annual Data Report: Epidemiology of Kidney Disease in the United States*, Bethesda, MD, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2015
19. St Peter WL, Sozio SM, Shafi T, Ephraim PL, Luly J, McDermott A, Bandeen-Roche K, Meyer KB, Crews DC, Scialla JJ, Miskulin DC, Tangri N, Jaar BG, Michels WM, Wu AW, Boulware LE; DEcIDE Network Patient Outcomes in End-Stage Renal Disease Study Investigators: Patterns in blood pressure medication use in US incident dialysis patients over the first 6 months. *BMC Nephrol* 14: 249, 2013
20. Bragg-Gresham JL, Fissell RB, Mason NA, Bailie GR, Gillespie BW, Wizemann V, Cruz JM, Akiba T, Kurokawa K, Ramirez S, Young EW: Diuretic use, residual renal function, and mortality among hemodialysis patients in the Dialysis Outcomes and Practice Pattern Study (DOPPS). *Am J Kidney Dis* 49: 426–431, 2007
21. Krishnan N, Peixoto AJ: We hold antihypertensives prior to dialysis [published online ahead of print April 26, 2016]. *Semin Dial* doi:10.1111/sdi.12498
22. Bieszk N, Patel R, Heaberlin A, Wlasuk K, Zarowitz B: Detection of medication nonadherence through review of pharmacy claims data. *Am J Health Syst Pharm* 60: 360–366, 2003
23. Grossberg R, Gross R: Use of pharmacy refill data as a measure of antiretroviral adherence. *Curr HIV/AIDS Rep* 4: 187–191, 2007
24. Lash JP, Go AS, Appel LJ, He J, Ojo A, Rahman M, Townsend RR, Xie D, Cifelli D, Cohan J, Fink JC, Fischer MJ, Gadegbeku C, Hamm LL, Kusek JW, Landis JR, Narva A, Robinson N, Teal V, Feldman HI; Chronic Renal Insufficiency Cohort (CRIC) Study Group: Chronic Renal Insufficiency Cohort (CRIC) Study: Baseline characteristics and associations with kidney function. *Clin J Am Soc Nephrol* 4: 1302–1311, 2009
25. Bansal N, McCulloch CE, Rahman M, Kusek JW, Anderson AH, Xie D, Townsend RR, Lora CM, Wright J, Go AS, Ojo A, Alper A, Lustigova E, Cuevas M, Kallem R, Hsu CY; CRIC Study Investigators: Blood pressure and risk of all-cause mortality in advanced chronic kidney disease and hemodialysis: The Chronic Renal Insufficiency Cohort Study. *Hypertension* 65: 93–100, 2015
26. Hsu RK, Chai B, Roy JA, Anderson AH, Bansal N, Feldman HI, Go AS, He J, Horwitz EJ, Kusek JW, Lash JP, Ojo A, Sondheimer JH, Townsend RR, Zhan M, Hsu CY; CRIC Study Investigators: Abrupt decline in kidney function before initiating hemodialysis and all-cause mortality: The Chronic Renal Insufficiency Cohort (CRIC) Study [published online ahead of print January 29, 2016]. *Am J Kidney Dis* doi:10.1053/j.ajkd.2015.12.025

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

See related article, "Antihypertensive Medication Use in Older Patients Transitioning from Chronic Kidney Disease to End-Stage Renal Disease on Dialysis," on pages 1401–1412.