

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

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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),

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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).

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