

Commentary on Pharmacotherapy of Hypertension in Patients on Chronic Dialysis

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Introduction

This comprehensive review by Agarwal and Georgianos summarizes results of numerous clinical trials of antihypertensive medications in patients on chronic dialysis (1). The authors note the unique challenges of such studies in this patient population. For example, the effect of widely used, nonpharmacologic approaches to BP control, such as increased ultrafiltration and dietary sodium restriction, could easily outweigh the more modest effects on BP of pharmacologic treatments. Furthermore, there is enormous variability of BP across the interdialytic period, and uncertainty regarding the most appropriate or optimal timing of BP measurement on which to guide treatment. Acknowledging these challenges and limitations, upon their review the authors note the following key findings:

- Most clinical trials were open-label without blinding of treatment assignment.
- No trials in patients on maintenance dialysis compared different BP goals of antihypertensive pharmacologic treatment.
- Most trials utilized a placebo or “usual care” control comparator group; very few trials directly compared two or more classes of antihypertensive medications.
- Most prior trials involved small samples of patients and examined the effects on change in cardiac structure, vascular function, and/or BP. Only a few trials examined the effects of treatment on cardiovascular morbidity/mortality.
- In some trials of patients on hemodialysis with left ventricular hypertrophy or dilated cardiomyopathy, beta-blockers reduced the incidence of cardiovascular morbidity/mortality.
- Some trials demonstrated a reduction in adverse cardiovascular events with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, but other trials found no such reduction in risk with this class of antihypertensives.
- There is insufficient evidence to support the preferential use of one class of antihypertensive medications over another class.

Evaluating Clinical Trials

One useful systematic approach for evaluating clinical trials is to focus on three characteristics of study

design: the study population, the intervention, and the outcome. The study population in a clinical trial typically balances internal validity (the ability of a study to accurately answer a scientific question), with external validity (the extent to which study results can be applied to other individuals with the same general disease condition). For example, a clinical trial comparing calcium channel blockers to angiotensin-converting enzyme inhibitors might exclude dialysis patients who are obese, have obvious signs of volume overload, or are nonadherent. Such exclusions could improve internal validity by removing extraneous factors to enhance focus on the inherent biologic effects of the medications. However, excluding patients on dialysis who are obese, have clinical edema, or miss some dialysis sessions would preclude understanding of the risks and benefits of the study medications among these relatively common groups, diminishing clinical application. Because large randomized trial designs effectively balance participant characteristics across treatment groups, large pragmatic trials of BP treatments that employ broad entry criteria and simple monitoring strategies would maintain internal validity while providing the greatest impact on clinical care.

Clinical trials of medications must carefully consider the dosage and duration of the intervention to provide clear separation of treatment groups while maintaining patient safety. The numerous trials cited in this review provide ample preliminary data for choosing the correct dose and length of treatment for future large-scale clinical trials.

Ideally, trials assess the impact of a treatment on outcomes that are important to patients, such as the development of major diseases, mortality, symptoms, and quality of life. Surrogate end points are substitutes for direct measurements of how a patient feels, functions, or survives. To qualify as a surrogate end point, a characteristic or measurement must be shown to change in response to treatment in a manner that is consistent with clinical benefit. For example, in the general population, BP is an accepted surrogate end point for cardiovascular disease because antihypertensive medications lower BP while reducing the risks of stroke and heart failure. Simply demonstrating associations of a characteristic with disease risk is not sufficient to establish a surrogate

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end point for the purposes of clinical trials. For example, higher serum phosphate or hemoglobin levels are associated with greater risk of cardiovascular disease and death in patients with CKD; however, they would not be considered surrogate end points for studies of treatment of hyperphosphatemia or anemia with the intention of reducing morbidity/mortality. In fact, there are repeated examples of clinical trials in nephrology and other disciplines that demonstrated beneficial effects of an intervention on a biomarker, only to find null or harmful effects on clinical outcomes (2,3). Uncertainties regarding optimal BP targets and the most accurate methods to measure BP in patients on dialysis temper the use of BP as a surrogate end point in studies of ESRD. Future BP trials that directly assess clinical outcomes among patients on chronic dialysis would have the greatest impact on clinical care.

Disclosures

None.

References

1. Georgianos PI, Agarwal R: Pharmacotherapy of Hypertension in Chronic Dialysis Patients. *Clin J Am Soc Nephrol* 11: 2062–2075, 2016
2. Echt DS, Liebson PR, Mitchell LB, Peters RW, Obias-Manno D, Barker AH, Arensberg D, Baker A, Friedman L, Greene HL, Huther ML, Richardson DW and CAST Investigators: Mortality and morbidity in patients receiving encainide, flecainide, or placebo. The Cardiac Arrhythmia Suppression Trial. *N Engl J Med* 324: 781–788, 1991
3. Pfeffer MA, Burdmann EA, Chen C-Y, Cooper ME, de Zeeuw D, Eckardt K-U, Feyzi JM, Ivanovich P, Kewalramani R, Levey AS, Lewis EF, McGill JB, McMurray JJV, Parfrey P, Parving H-H, Remuzzi G, Singh AK, Solomon SD, Toto R; TREAT Investigators: A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. *N Engl J Med* 361: 2019–2032, 2009

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