Hypertension 2022: Nephrologists in Charge

By Kenar Jhaveri

The knowledge and understanding of hypertension (HTN) have always been cornerstones of nephrology, and over the last 3 decades, nephrologists have emerged at the forefront of HTN management. As we look back over the last few years, several major trials and findings have emerged, leading to some changes in our ways of thinking and practice. I'll highlight the top 10 major findings and studies that are making an impact in HTN management. In 2022, we need to continue to take ownership of HTN as nephrologists.

10. ***Managing hyperkalemia when using anti-HTN agents.*** Chronic kidney disease (CKD) and HTN are common in heart failure (HF). Use of renin-angiotensin-aldosterone system inhibitors (RAASi) is frequently underused in HF and even in CKD due to hyperkalemia risk. The advent of patiromer and sodium zirconium cyclosilicate has made practice changes in nephrology. A much-awaited trial will be the LIFT (Lokelma for RAAS Maximisation in CKD & Heart Failure) trial (1), which will randomize 130 patients with CKD and HF (HFrEF [HF with reduced ejection fraction]; i.e., ejection fraction <40%) to novel potassium-lowering binders or placebo and allow for maximizing RAASi use. The primary outcome will be the proportion of participants who achieve maximum RAASi dose while maintaining normokalemia using sodium zirconium cyclosilicate. I believe this study and similar studies can change the way we practice nephrology and manage HTN, CKD, and HF with agents we once avoided due to hyperkalemia.

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9. ***Renal denervation trials—are we done yet?*** Why use an invasive procedure in management of HTN? The basis of this approach comes from the fact that increased renal sympathetic activity results in the following: 1) increased renin secretion mediated by direct adrenergic innervation of the juxtaglomerular apparatus; 2) increased tubular sodium reabsorption and sodium retention mediated by direct contact between nerve endings and basolateral membranes of the tubular epithelial cell throughout the nephron; and 3) renal vasoconstriction, resulting in decreased glomerular filtration rate and renal blood flow. Although renal denervation has been available in Europe, the US Food and Drug Administration (FDA) has not yet approved it. Trials, to date, have been inconsistent, without showing many long-term benefits. The SYMPLICITY HTN-3 (Renal Denervation in Patients with Uncontrolled Hypertension) trial, which enrolled more than 500 participants with resistant HTN, demonstrated no difference in blood pressure (BP) reduction with renal denervation compared with sham-control procedures. SYMPLICITY HTN-3 was criticized by denervation enthusiasts for several study-design limitations, including a variable number of ablations and the enrollment of a heterogeneous patient population (2). More recently, three randomized, multi-center, single-blinded, sham-controlled trials have reported results using improved approaches: SPYRAL HTN OFF-MED, SPYRAL HTN ON-MED, and RADIANCE-HTN SOLO (A Study of the ReCor Medical Paradise System in Clinical Hypertension) (3–5). All three trials reported consistent reductions in ambulatory and office BP in the short (2–3 months) and medium (6 months) term post-procedure with radiofrequency (SPYRAL trials) or highly focused ultrasound-based (RADIANCE-HTN SOLO) denervation. Hence, the story continues. Will we consider such procedures for our patients with resistant HTN? We need to wait to learn more about the long-term risks and benefits of these approaches. Time will tell.

8. ***Do we intensify HTN management in the elderly?*** Do we control BP similarly in the elderly (>60 years of age) as we do in the general population? Or is there an increased risk of falls, acute kidney injury (AKI), etc.? Improving BP control in this population may require a better understanding of the specific challenges for BP control at an older age. A recent study published in 2021 answered this question (6). A Chinese cohort of 8000 patients was randomly assigned to intensive arm (110 to <130 mm Hg) versus standard treatment arm (130 to <150 mm Hg). At the 1-year follow-up, the intensive arm had a mean systolic BP (SBP) of 127 mm Hg, and the standard arm had 135 mm Hg, with fewer cardiovascular (CV) events in the intensive arm. The results for safety and kidney outcomes did not differ significantly between the two groups, except for the incidence of hypotension, which was higher in the intensive-treatment group. Although this study was performed in a Chinese population, this may be something we need to consider in the general US and European populations.

7. ***CLICK on the thiazides for CKD-related HTN.*** Traditionally, loop diuretics have been preferred in later-stage CKD-related HTN. Use of thiazides has been considered but never well studied. In this recent CLICK (Chlorthalidone in Chronic Kidney Disease) trial (7), patients with CKD stage 4 and HTN were randomly assigned to receive chlorthalidone from a 12.5-mg dose to a maximum of 50 mg per day or placebo. To my surprise, the thiazide arm had better BP control at 12 weeks with a change of ~11 mm

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Table 1. Key takeaways from the KDIGO 2021 HTN guidelines

Standardized BP measurement. The importance of appropriate preparations and the measurement technique, not the type of device, is emphasized with standardized BP measurement. The relationship between routine office BP and standardized office BP is highly variable; therefore, it is not possible to apply a correction factor to translate a given routine BP value to a standardized BP value.
Home BP monitoring (HBPM). When a clinic visit is not practical, HBPM may be particularly important for the management of BP. However, at present, HBPM should only be used to complement standardized office measurement.
CKD patients not on dialysis. Adults with high BP and CKD should be treated to a target SBP <120 mm Hg. Targeting SBP <120 mm Hg reduces the risks of CV events and all-cause mortality in CKD; however, the effects on progression of kidney disease are uncertain.
BP in CKD subgroups. The SBP target of <120 mm Hg also applies to the subgroups of older adults and those with increased albuminuria. The balance of benefits and harms is less certain in people with CKD G5 and in those with severely increased albuminuria.
BP in diabetic CKD. The benefits of intensive BP lowering are less certain among patients with concomitant CKD and diabetes, compared to patients with CKD without diabetes.
Anti-HTN agents in CKD. RAASi (angiotensin-converting enzyme inhibitor [ACEi] or angiotensin-receptor blocker [ARB]) should be used in patients with CKD and increased albuminuria, with or without diabetes. The evidence for use of RAASi in patients with moderately increased albuminuria is lower in quality than in severely increased albuminuria.
Lifestyle changes. Low sodium intake (<2 g/day) and moderate-intensity physical activity (≥150 minutes/week) are suggested in accordance with recommendations for the general population.
Kidney transplant patients. For adult kidney transplant recipients, a target of <130/<80 mm Hg is still a reasonable goal. A lower SBP goal (<120 mm Hg) for kidney transplant recipients would require additional data on the risks and benefits in this population. Dihydropyridine calcium channel blocker (CCB) or ARB should be used as the first-line anti-hypertensive agent in adult kidney transplant recipients, given their efficacy and the importance of preventing graft loss.
BP in children. BP target in children with high BP and CKD should be lowered to less than or equal to the 50th percentile for age, sex, and height, according to 24-hour mean arterial pressure (MAP) by ambulatory BP monitoring (ABPM). When ABPM is not available, a standardized auscultatory office measurement should be used to target SBP less than the 90th percentile. The best agents for treatment are ACEi/ARBs.
Accurate reading of BP in the office/home. Steps include the following: quiet room (no talking by patient or observer); no smoking, caffeine, or exercise for <30 minutes before measurement; and empty bladder. Relax for >5 minutes. Do not talk during rest period and between measurements. Pick appropriate cuff size for the patient. The arms should be bare and resting. The BP should be at level of mid-arm at midpoint of the sternum. Feet should be on the floor. Finally, a validated oscillometric or manual auscultatory device that is calibrated periodically should be used.

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Hg in SBP compared to placebo. The percent change in the urinary albumin/creatinine ratio was improved as well. There was more hypokalemia, hyperuricemia, dizziness, and hypercreatinemia with the thiazide arm. The change in SBP is really dramatic. This is a practice-changing study and may lead to more use of chlorthalidone in 2022. As we prescribe more of this, monitoring for electrolyte changes is essential.

6. ***More and more guidelines and ever-changing target for BP control.*** 2021 saw the final report of the SBP intervention trial (Systolic Blood Pressure Intervention Trial [SPRINT]), which assessed additional primary outcome events adjudicated after data lock for the primary analysis and included a post-trial observational period for 1 year (8). The report had concluded that among patients who were at increased CV risk, targeting a SBP of less than 120 mm Hg resulted in lower rates of major adverse CV events and lower all-cause mortality than targeting a SBP of less than 140 mm Hg—both during receipt of the randomly assigned therapy and after the trial. The Kidney Disease: Improving Global Outcomes (KDIGO) revised 2021 guidelines propose a SBP target of less than 120 mm Hg using standardized office reading for most people with CKD not receiving dialysis, the exception being children and kidney transplant recipients (Table 1). These guidelines simplify things a bit for us as we move into 2022.

5. ***Potassium is important in HTN management.*** 2021 taught us, via two trials, that potassium is an important player in HTN management. A salt-substitute study (9), performed in China, randomly assigned participants with HTN to a salt substitute that had 75% sodium chloride and 25% potassium chloride or a control group of 100% sodium chloride. Among people who had a history of stroke or were 60 years of age or older and had HTN, the rates of stroke, major CV events, and death from any cause were lower with the salt substitute than with regular salt. Another study published online in 2021 showed that higher sodium and lower potassium intakes, as measured in multiple 24-hour urine samples, were associated in a dose-response manner with a higher CV risk (10). The role of potassium in HTN management continues to gain momentum. This may be something to watch out for in 2022 as we understand this story better.

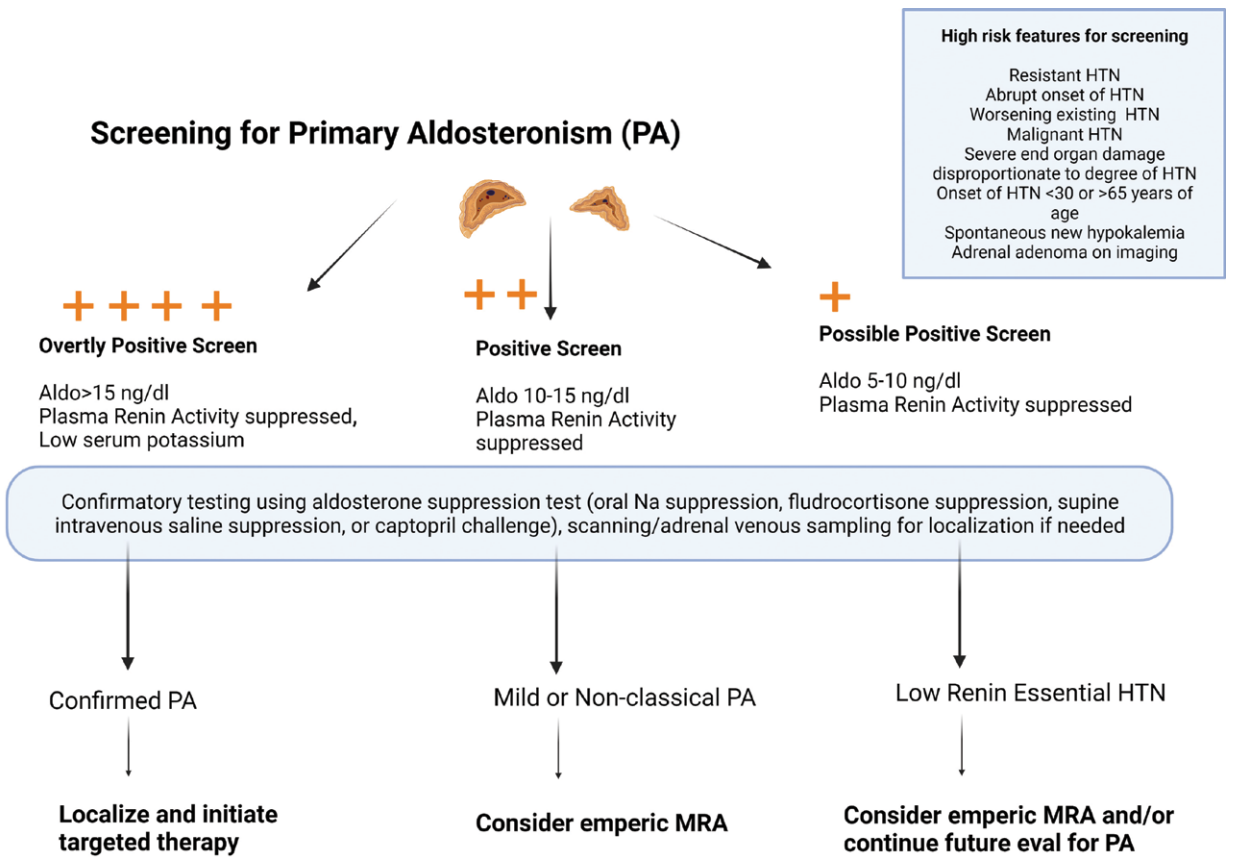
4. ***Quartet may be the magic pill.*** The multi-center Australian clinical trial of a potential future "quadpill" dose of four medications, termed Quadruple Ultra-Low-Dose Treatment for Hypertension (QUARTET) (11), demonstrated that a single pill containing an ultra-low quadruple combination is much more effective than the traditional approach of starting with monotherapy (single drug). The pill contained irbesartan at 37.5 mg, amlodipine at 1.25 mg, indapamide at 0.625 mg, and bisoprolol at 2.5 mg. The primary outcome was the significantly reduced BP in the group starting on the quadpill at 12 weeks. These differences were sustained, with BP control still better with the quadpill approach compared to the standard approach at 12 months and no differences in side effects. This was the first study to show that the benefits are maintained long term without any reduction over time. Although I am not a fan of multiple pills in one, this may help change the polypharmacy we see in medicine. Will something similar be in the making for diabetic nephropathy in 2022?

3. ***Inequalities exist in HTN management.*** COVID-19 has exacerbated the preexisting inequities in HTN management and control in the United States (12). Virtual healthcare is now widespread because of COVID-19, and this may widen the divide in healthcare access across race/ethnicity, wealth, geography, and education levels. BP control rates are declining, especially among communities of color and those without access to healthcare or health insurance (13). Bress et al. (13) performed a qualitative study that underscored environmental and socioeconomic factors that are deeply embedded in US healthcare and research that impact inequities in HTN. As suggested by the authors, there is an urgent need to improve the implementation of community-based interventions and BP self-monitoring, which can help build patient trust and increase healthcare engagement in all communities.

2. ***Rise of the MRAs.*** Resistant HTN is not uncommon in the world of nephrology. The PATHWAY 2 trial showed us that the mineralocorticoid receptor antagonist (MRA) spironolactone is a clear winner in the treatment of resistant HTN (14). The superiority of spironolactone supports a primary role of sodium retention in this condition. More recently (15), another MRA (finerenone), when used in patients with CKD and type 2 diabetes, resulted in lower risks of CKD progression and CV events than placebo. Interestingly, the impact of finerenone in BP control was minimal, hinting at direct kidney anti-fibrotic effects. Although we worry about potassium increases and hypercreatinemia, the use of MRAs in HTN management has been limited (16).

1. ***Rise of the "aldo"—missed aldosteronism.*** We need to recognize and treat more primary aldosteronism. A 2021 multi-center study found that only 1.6% of patients with treatment-resistant HTN were appropriately tested for primary aldosteronism (16). A nephrology or endocrinology visit was associated with a higher likelihood of diagnosis, and testing and diagnosis increased the likelihood of therapy with MRA and better BP control over time. Another recent study found a similarly low rate of screening for primary aldosteronism as well (17). A prior study found that adjusted prevalence estimates for biochemical-overt primary aldosteronism were close to 11% in resistant HTN (18)—a very high number—indicating that we are missing the opportunity to treat many patients with the most appropriate medication. The aldo/renin ratio has a poor sensitivity and negative-predictive value. Low plasma renin activity should prompt a diagnosis of primary aldosteronism (and most cases will not have an adenoma but will still respond well to MRAs). Our threshold criteria for defining aldosterone levels may also not be accurate. Figure 1 suggests that the diagnosis of primary aldosteronism need not rely on binary thresholds; rather, it may exist across a continuum of severity, whereby mild and non-classical cases may be detected as well. It is time that we redefine primary aldosteronism, as it may have a role in what we keep calling "essential HTN." The rise of aldo has begun. In 2022, let's all start blocking its untoward effect. ■

Figure 1.



Proposed modifications to the diagnostic approach to detect overt and milder forms of primary aldosteronism. Biochemical screening for primary aldosteronism is generally pursued when classical indications are observed, as recommended by the Endocrine Society. A positive screen for primary aldosteronism should suggest renin-independent aldosterone secretion, whereby aldosterone levels are relatively high in the context of a suppressed renin. In the absence of overt evidence for renin-independent aldosteronism on screening, confirmatory testing can be used to affirm the diagnosis. Failure or relative failure to suppress aldosterone on dynamic testing may confirm the diagnosis, whereas marked suppression of aldosterone may instead suggest a diagnosis of low-renin hypertension. Modified from Vaidya et al. (19). Created using BioRender.com.

Kenar D. Jhaveri, MD, is Professor of Medicine at the Donald and Barbara Zucker School of Medicine at Hofstra/Northwell and an attending nephrologist at Northwell Health, Long Island, NY, and is editor-in-chief of ASN Kidney News.

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