Editorial Commentary

Hypertension monitoring on cardiac health outcomes

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Introduction

When treating children with chronic kidney disease (CKD), blood pressure (BP) management is a significant aspect of any prolonged treatment plan. The study by Sinha *et al.* examining the Hypertension Optimal Treatment in Children with Chronic Kidney Disease (HOT-KID) trial provides critical evidence demonstrating the positive effects of hypertension monitoring on cardiac health outcomes (1). Previous clinical studies have outlined the role of elevated BP in CKD progression, such as how elevated oxidative metabolism contributes to renal hypoxia and subsequent exacerbation of BP and CKD (2). CKD progression can lead to an increase in fatal cardiovascular events such as sudden cardiac death and is also associated with CKD-related cardiomyopathy through elevated left ventricular mass (LVM) and subsequent left ventricular hypertrophy (LVH) (3). Pediatric CKD treatment is often complicated, requiring specialized attention due to added comorbidities such as seizure disorder, congenital heart disease, and neurocognitive delay (4). Amidst these varied treatment challenges, Sinha *et al.* contributes a valuable resource displaying how the supervised reduction of BP can reduce LVH while also presenting further areas for research in terms of long-term effectiveness, cost considerations, and potential confounding effects of the antihypertensive drugs and BP monitoring methods utilized.

BP management at the 50th percentile is optimal for reducing LVH

In the HOT-KID randomized, controlled trial, the percentile benchmark of BP was analyzed for the effectiveness of treatment, and the outcome favoring reducing BP past the 50th percentile reflects similar research within the field and sets a standard for future treatment. Sugianto *et al.* conducted a longitudinal analysis of pediatric CKD patients with an estimated glomerular filtration rate below 60 mL/min/1.73 m^2 between 2009 and 2011, stratifying patients according to their BP percentile (5). Their findings demonstrated that systolic BP (SBP) below the 75th percentile was correlated with a left ventricular mass index (LVMI) reduction compared to SBP exposure in the 75th to 90th percentile range, which had no significant alterations to

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Table 1 Blood pressure and associated cardiac outcomes

Studies	Sample size	Intervention			Control		
		Blood pressure	Cardiac outcomes	Age (years), mean ± SD or median (IQR)	Blood pressure	Cardiac outcomes	Age (years), mean ± SD or median (IQR)
Sugianto *et al.* 2023, (5)	96	50th to ≤75th percentile	Resulted in a LVMI decrease of −5.24 g/m$^{2.16}$ (P=0.007)	15.3±3	75th to ≤90th percentile	No LVMI decrease	15.3±3
do Val *et al.* 2019, (10)	102	122/76 mmHg	LVMZ was 0.48 (SD =1.75) for the CKD patients	13.1±4.6	99/59 mmHg	LVMZ was −0.94 (SD =1.00) for the patients in the control group	13.0±3.7
Greiner *et al.* 2023, (7)	48	Mean ± SD: 113.2±10.5 mmHg	The mean ± SD of LVMI was 38.3±11.0 g/m$^{2.16}$	13.5±4.2	N/A	N/A	N/A
Sinha *et al.* 2023, (1)	124	107/62 mmHg	Variation in average LVMI over treatment duration: −1.9 (95% CI: −2.4 to −1.3)	9.4 (6.2–12.4)	108/64 mmHg	Variation in average LVMI over treatment duration: −1.2 (95% CI: −1.5 to 0.8)	10.3 (7.3–12.8)

SD, standard deviation; IQR, interquartile range; LVMI, left ventricular mass index; LVMZ, left ventricular mass z-score; CKD, chronic kidney disease; N/A, not applicable; CI, confidence interval.

LVMI. Overall, this study supported previous findings that the lowest LVMI levels were correlated with an SBP less than the 60th percentile (5). Establishing this baseline treatment value was a key goal for the two studies, both of whom examine hypertension and its resulting impact on left ventricular development within pediatric patients. In the HOT-KID study, Sinha *et al.* expanded upon the results of the ESCAPE trial, a randomized controlled trial of 385 pediatric patients with CKD in 2009 that led to the current standard practice targeting the 50th–75th BP percentile for hypertension patients as opposed to the 50th–90th BP percentile, while also drawing from Sugianto *et al.*'s findings describing lower LVH at sub 75th percentile BP values (5,6). Through Sinha *et al.*'s work, a more intensive treatment method targeting below the 40th percentile BP has been ruled out, as there was not a significant reduction in LVMI compared to the 50th percentile (1). Furthermore, addressing hypertension and other adverse health conditions in pediatric patients is critical for their future health, such as successful detection of LVH, an indicator of early cardiac restructuring, which is predictive for future cardiovascular events (7). Another study by Flynn *et al.* also supports the connection between BP and LVH by demonstrating that consistent hypertensive states from ambulatory BP monitoring (ABPM) is associated with an increase in LVM (8). A systematic review conducted by Taddei *et al.* also discussed the importance of adult hypertension management in controlling adverse cardiac outcomes, as both BP and fluid overload contribute to LVH in CKD patients (9). Do Val *et al.* also emphasizes hypertension's role in unfavorable cardiovascular outcomes in children with CKD and the importance of strict control of SBP in these situations, and the comparative outcomes of these studies are summarized within *Table 1* (10). Sinha *et al.*'s study shows the relationship between hypertension and cardiac remodeling and reflects the continuing theme in CKD research connecting BP targets to left ventricular outcomes, providing evidence and treatment guidelines to better support pediatric CKD patients.

Comparison of the efficacy and utilization of various BP monitoring methods

A broader point of comparison in Sinha *et al.*'s research is regarding the type of BP measurement employed for the study's data collection, specifically focusing on their use of office auscultatory BP measurement. According to Sinha *et al.*, ambulatory BP is not recommended in certain guidelines due to United Kingdom programs finding it too intensive for continuous monitoring in children (1,11). In other studies, examining the impact of BP monitoring on LVH and other related cardiac outcomes, several other measures of BP have been utilized, including central BP, peripheral BP, ambulatory BP, and casual BP. Greiner *et al.* investigated the differences in central and peripheral BP measurements in accurately identifying high-risk patients

and predicting potential cardiovascular alterations and future mortality in 48 pediatric CKD patients (7). Their study concluded that peripheral BP levels were inferior to central BP levels in predicting LVMI and pulse wave velocity, both markers suggesting cardiovascular organ dysfunction (7). A literature review by Boonyasai noted a discrepancy in auscultatory BP measurement from guidelines to practice, resulting in less accurate estimations of adult cardiovascular outcomes compared to automated office BP (AOBP) (12). Furthermore, Krmar and Ferraris argue for the accuracy of ambulatory BP measurements in diagnostic and research purposes, suggesting it is superior to measurements obtained in the clinical setting and thus detection of candidates for antihypertensive therapy and prediction of cardiovascular outcomes (13). Another factor to consider is the cost benefit of ABPM (up to 14% savings in treatment and testing costs and 23% decrease in days of care necessary) when incorporated in the diagnosis and management of hypertension in adults (13,14). Despite any differences in the sensitivity or broader accuracy of the measurement methods utilized to record patient data, Sinha *et al.*'s results have shown to be statistically significant (P=0.01) when looking at the secondary outcome of relative wall thickness between intensive (BP less than 40th percentile) versus standard BP reduction (BP reduced to within 50th to 75th percentile) (1).

Connection between CKD and hypertension

Analyzing the fundamental connection between CKD and hypertension is a key aspect underpinning Sinha *et al.*'s finding on the impact of BP monitoring at a target percentile on preventing adverse cardiac outcomes. Sinha *et al.* references the pioneering ESCAPE trial when discussing modern treatment recommendations, but it is important to note that there are several factors contributing to the relationship between CKD and increased BP. For example, immunosuppressive regimens involving calcineurin inhibitors (CNI) can lead to hypertension by constriction of the afferent arteriole of the glomerulus, stimulation of the renin-angiotensin-aldosterone system, and the release of reactive oxygen species (15). Furthermore, pediatric CKD patients are increasingly affected by hypertension, especially following renal transplantation (15). This reaffirms the need for specialized pediatric CKD care methods, especially within the broader scope of reducing adverse heart outcomes, as there remains uncertainty in terms of optimal treatment procedures and potential causal effects of medication. The pathophysiology connecting hypertension and CKD is multi-faceted, but research has shown that pediatric hypertensive outcomes in CKD can have continuing effects into adulthood, and work remains to be done in elucidating the best treatment modality for patient success (8).

The effect of anemia on LVH as a potential confound

A potential confounding variable within the methodology of Sinha *et al.*'s study and an area of future research to be pursued is the effect of anemia due to CKD on LVH, especially in pediatric patients with late-stage CKD. In a cross-sectional study of 69 children with CKD conducted in Brazil, the investigators observed a relationship between LVM and hemoglobin levels, supporting previous literature that LVMI is associated with anemia (10). CKD impacts cardiovascular outcomes in a variety of ways, including hemodynamic (anemia, arteriovenous fistula, and fluid overload), metabolic (free radical damage), hyperhomocysteinemia, inflammation, and proteinuria, highlighting the complex ways LVH can be affected in the body (10). The relationship between anemia and adverse cardiac outcomes goes beyond CKD, as a Korean group study analyzing a large 48,000 adult patient population demonstrated that decreased hemoglobin levels are associated with a higher probability of LVH (16). Thus, when evaluating Sinha *et al.*'s trial, there remains further analysis to be completed in interpreting how hemodynamic and metabolic factors independently affect observed outcomes, and the studies demonstrating this potential association between anemia and LVH outcomes are outlined in *Table 2*. In fact, although angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) were used as first-line therapies within the trial, a retrospective case study examining 701 patients with diabetes mellitus, congestive heart failure, and/or hypertension reported an association between their use and anemia development (1,19). Despite this potential confound, Sinha *et al.*'s work demonstrates how BP may have the most significant effect on LVH, as the results of reducing BP to the 50th percentile was positively correlated with reduced LVH. Sinha *et al.*'s hypertension research provides treatment guidelines and clinical evidence supporting the association between BP and LVH, but there remains a need for further investigation into understanding the connection between anemia and LVH and creating potential treatments

Table 2 Association between anemia and left ventricular hypertrophy

Studies	Anemia analysis, mean ± SD	Cardiac outcomes	Sample size	Therapies provided & comorbidities
Park *et al.* 2020, (16)	Men and women were separated into different test groups, and results showed that in patients with and without CKD, there was a statistical association between decreased hemoglobin levels and LVH outcomes	The chance of having LVH in males with a hemoglobin concentration ≥14.9 g/dL and women with ≥13 g/dL was decreased by more than 50% compared to men with hemoglobin <13 g/dL and women having hemoglobin <12 g/dL. This provides evidence connecting reduced hemoglobin levels to adverse LVH outcomes	48,034	161 arrythmia 1,448 cancer medical history 1,017 cancer or COPD 386 previous issues with myocardial infarction or angina 58 systolic left ventricular dysfunction No therapies provided
Matteucci *et al.* 2006, (17)	Average blood hemoglobin (g/dL): 12.1±1.6	Through the study analysis, a decreased blood hemoglobin was associated with increased LVMI	156	Antihypertensive treatment, including ACE inhibition, was provided to 70 out of 156 study participants
Canpolat *et al.* 2012, (18)	Anemia contributed to issues in insulin secretion within dialysis patients Blood hemoglobin (pre-dialysis) (g/dL): 12.3±2.2 Blood hemoglobin (post-dialysis) (g/dL): 9.9±1.3	Anemia was shown to be an indicator for LVH within adolescents and children diagnosed with CKD	66	Antihypertensive treatment, including ACE inhibition, was provided to 26 out of 66 study participants 21 patients were considered underweight and 3 patients were classified as overweight
Ajmal *et al.* 2013, (19)	Average blood hemoglobin (g/dL): 14.58±1.43	Examined how the utilization of common antihypertensive drugs could contribute to anemia, and describes how treating anemia reduced LVMI	701	47 out of 701 patients had CHF 657 out of 701 patients were diagnosed with hypertension 263 out of 701 patients had diabetes mellitus

CKD, chronic kidney disease; LVH, left ventricular hypertrophy; COPD, chronic obstructive pulmonary disease; LVMI, left ventricular mass index; ACE, angiotensin-converting enzyme; CHF, congestive heart failure.

to address both hemodynamic and metabolic factors influencing adverse heart health outcomes.

Secondary hyperparathyroidism (SHP) and its association with LVH

The incidence of SHP in pediatric patients with CKD is another potential contributor to LVH and presents another avenue for future research. CKD reduces vitamin D activation in the kidneys, resulting in hypocalcemia, hyperphosphatemia, and prompting increased parathyroid hormone (PTH) production, causing SHP (20). A cross-sectional study of 106 pre-dialysis pediatric patients by Ehsan *et al.* found an elevated percentage of increased PTH levels in patients with cardiac abnormalities, noting that increased PTH levels may contribute to LVH progression in pediatric CKD patients (21). Another analysis of 70 pediatric patients with late stages of CKD saw increased levels of PTH as CKD progressed and labeled hyperparathyroidism [intact PTH (iPTH) >88 pg/mL] as a non-traditional risk factor for adverse cardiac outcomes (22). Sinha *et al.* does mention the scientific discussion regarding the impact of thyroid hormones on cardiac remodeling and notes normal ranges for serum iPTH levels in the baseline measurements for the intensive and standard treatment group. However, Sinha *et al.* does not provide information regarding SHP for the longitudinal cohort and there is a need for additional research examining the relationship between SHP and LVH to determine optimal treatment guidelines for pediatric CKD patients. PTH and SHP have been shown to be associated with CKD and adverse cardiac outcomes in pediatric patients, and SHP is to be considered when examining LVH results in Sinha *et al.*'s study.

Study limitations

When addressing the effectiveness of Sinha *et al.*'s trial, it is important to recognize potential limitations for treatment applications, as the length of the trial follow-up period was capped at 3 years. Sinha *et al.* cites the ESCAPE trial, which had a 5-year follow-up with patients, as the general resource for physicians treating hypertension in pediatric CKD patients and modifies the existing auscultatory BP recommendations based on the data they collected in the HOT-KID trial (1, 6). Since both the ESCAPE and HOT-KID studies deal with pediatric patients, it's reasonable to question the ability of these trials to establish recommendations for these patients as they age into adults, and whether the positive impact of reducing LVH would continue with age. Additionally, Oh and Hong discuss the importance of altering parameters for measuring BP as children age due to a variety of factors affecting body habits and subsequent BP (23). CKD studies examining adults with hypertension have demonstrated that anemia, BP control, and SHP management are all key factors in the therapy of LVH in CKD (24,25). Even as pediatric patients grew older in both the ESCAPE and HOT-KID trials, the same BP management strategies had a positive impact on LVH outcomes. Without a clear consensus on the optimal BP target for the treatment of adults and kids with CKD, Sinha *et al.*'s guidelines at the 50th percentile for optimal reduction of LVH can be used as a template for future adult research and longitudinal studies in pediatric patients.

Sinha *et al.*'s randomized, controlled trial evaluated the impact of intensive BP treatment on LVH and demonstrated that the 50th percentile, office auscultatory BP benchmark is optimal for the reduction of adverse cardiac remodeling outcomes, providing treatment guidelines and potential avenues for future research. The trial built upon previous research in the field, including the ESCAPE trial and other studies analyzing the connection between CKD and hypertension in adults and children, and reinforced their conclusion emphasizing the importance of BP monitoring on LVH. However, both the standard and intensive treatment groups within the trial had BP measurements near the 50th percentile, showing a potential limitation of the study with only a modest BP change between cohorts. Additionally, although various BP measurement tools exist, Sinha *et al.*'s use of auscultatory BP was shown to be significant and allows for the broader application of study results. Sinha *et al.*'s research highlights the need for specialized pediatric care amidst the larger relationship between childhood and adult hypertension outcomes in CKD patients, and the results show a clear correlation between BP reduction and lowered LVH despite potential hemodynamic confounds, which present opportunities for future research. Potential directions for additional research could involve expanding the study to encompass a more diverse population, extending the longitudinal follow-up duration, analyzing the impact of anemia and SHP in conjunction with hypertension on LVH, and considering stratification of treatment groups based on different CKD stages. Finally, based on literature illustrating the similarities between adult and child hypertension care in CKD patients, Sinha *et al.*'s work can be used as a basic template for future work in the field. The HOT-KID study further delineated the connection between BP and LVH while also establishing recommendations for the most effective LVH reduction through medicated BP treatment, constructing a framework for further research and clinical care.

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Footnote

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