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# Combination therapy and formulation challenges in paediatric hypertension: an unmet need

Emre Leventoğlu and Sevcan A. Bakkaloğlu

Department of Pediatric Nephrology, Faculty of Medicine, Gazi University, Ankara, Türkiye

## Editorial

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**Corresponding author:**
Emre Leventoğlu;
Email: dremrelevent@gmail.com

**Abstract**

Hypertension is an increasingly prevalent condition in both adults and children and is associated with significant long-term cardiovascular and renal morbidity. Current paediatric guidelines recommend a stepwise pharmacological approach, initiating treatment with a single antihypertensive agent at a low dose, followed by gradual titration up to the maximum tolerated dose and the addition of a second agent only if blood pressure control is not achieved. In contrast, adult hypertension guidelines increasingly support early combination therapy, particularly in patients with stage 2 hypertension, to achieve faster and more consistent blood pressure control and improve medication adherence. Given that blood pressure regulation involves multiple physiological systems, combining agents with complementary mechanisms of action may enhance antihypertensive efficacy while reducing dose-dependent adverse effects. Although the use of fixed-dose combination therapies is well established in adults, their application in paediatric populations remains limited due to regulatory-, clinical-, and formulation-related challenges. We propose that, in selected paediatric patients with an anticipated inadequate response to monotherapy, early combination therapy may be considered as an alternative to strict stepwise escalation. Expanding paediatric clinical research and developing age-appropriate formulations are essential to optimise hypertension management and improve long-term outcomes in this population.

Hypertension is a significant public health issue due to its increasing prevalence in both adults and children; if not diagnosed early and managed appropriately, it can lead to morbidity in many organs, particularly the cardiovascular system. Given the long-term effects of hypertension that begin in childhood and extend into adulthood, the adoption of timely, effective treatment approaches is of great importance.[1]

Blood pressure is tightly regulated by multiple biological systems that interact with one another. The primary regulators include the renin–angiotensin–aldosterone system, the sympathetic nervous system, the kidneys' effects on sodium and water balance, and mediators derived from the vascular endothelium. These systems dynamically modulate vascular tone, cardiac output, and intravascular volume to maintain blood pressure within physiological limits in both the short- and long-term.[2] First-line agents used in the treatment of hypertension primarily exert their effects through these systems.[3] Angiotensin-converting enzyme inhibitors reduce levels of angiotensin II—a potent vasoconstrictor—by blocking the conversion of angiotensin I to angiotensin II. Additionally, they increase vasodilation by inhibiting the breakdown of bradykinin. At the renal level, angiotensin-converting enzyme inhibitors preferentially dilate the efferent arteriole, leading to a reduction in intraglomerular pressure and providing renoprotective effects. As a result, systemic vascular resistance decreases and blood pressure declines. Angiotensin II receptor blockers competitively inhibit the binding of angiotensin II to angiotensin I receptors. Consequently, vasoconstriction, aldosterone release, and sodium retention are reduced. Similar to angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers also promote efferent arteriolar dilation, thereby decreasing intraglomerular pressure and contributing to kidney protection. Calcium channel blockers reduce calcium influx into vascular smooth muscle cells by inhibiting L-type voltage-dependent calcium channels. This leads to arteriolar vasodilation, lowering peripheral vascular resistance and producing an antihypertensive effect. Thiazide and thiazide-like diuretics, on the other hand, increase sodium and water excretion by inhibiting the sodium-chloride cotransporter in the distal tubule. While they initially lower blood pressure due to a decrease in intravascular volume, they maintain their effects in the long term through a reduction in peripheral vascular resistance.[3] In addition, although they are not recommended as first-line therapy for uncomplicated primary hypertension in current guidelines, β-blockers, loop diuretics, and α-blockers are also used in the treatment of paediatric hypertension in certain clinical situations. β-blockers exert an antihypertensive effect by reducing heart rate and cardiac output while suppressing renin release.[4] Loop diuretics are preferred, particularly in cases accompanied by chronic kidney disease, severe loss of kidney function, or volume overload.[5] Alpha-blockers, on

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