Cardiology in the Young

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

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Editorial

Cite this article: Leventoğlu E and Bakkaloğlu SA (2026) Combination therapy and formulation challenges in paediatric hypertension: an unmet need. *Cardiology in the Young*, page 1 of 3. doi: 10.1017/S1047951126124007

Received: 6 July 2026 UTC
Revised: 27 July 2026 UTC
Accepted: 29 July 2026 UTC

Keywords:
paediatric hypertension; combination therapy; antihypertensive agents; medication adherence; fixed-dose combination

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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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the other hand, have a limited role in routine antihypertensive therapy and are used in selected conditions such as pheochromocytoma or resistant hypertension.[6]

In guidelines for paediatric hypertension, the pharmacological treatment approach is based on a stepwise strategy. In children with persistent hypertension despite lifestyle modifications, those with symptomatic hypertension, those with stage 2 hypertension without a modifiable cause, or those with chronic kidney disease or diabetes, treatment is recommended to begin with a single antihypertensive agent at a low dose. Treatment is continued with dose titration of the initial agent at 2–4 week intervals based on blood pressure response, with escalation towards the maximum tolerated dose if adequate control is not achieved.[7,8] Although approximately 28% of children with hypertension require more than one antihypertensive medication, initiating treatment with combination therapy in the early stages is not recommended in paediatric patients.[9] However, in cases of suboptimal response, partial dose up-titration followed by the early addition of a second antihypertensive agent—rather than waiting to reach the maximal dose—may be considered to achieve more effective blood pressure control. As mentioned earlier, blood pressure is regulated by multiple biological systems. Therefore, combining antihypertensive agents with complementary mechanisms of action may improve blood pressure control while reducing certain adverse effects. For example, the combination of angiotensin II receptor blockers with thiazide-type diuretics may reduce electrolyte imbalances compared to using these medications alone at maximum doses. In another example, the combined use of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers with a calcium channel blocker may reduce the frequency and severity of peripheral oedema.[10]

Fixed-dose combination formulations, which exert their effects through different mechanisms, are widely used in the treatment of hypertension in adults, and it is well established that this approach positively impacts treatment success and improves medication adherence.[11] However, the direct application of this strategy to paediatric patients is currently limited due to various structural and regulatory constraints. The primary reason for this is regulatory requirements that mandate the collection of separate efficacy and safety data for each combination in the paediatric age group. Since the approval of such formulations is not possible without sufficient paediatric clinical trial data, the routine use and widespread adoption of fixed-dose combinations in children cannot yet be considered a recommended strategy. However, even in the absence of ready-to-use fixed-dose paediatric formulations, we propose that in selected patients with an anticipated inadequate initial response to monotherapy, early combination therapy with two agents with relatively low/moderate doses acting via distinct mechanisms may be considered rather than relying solely on stepwise dose escalation of a single drug. This approach may enhance treatment response while potentially reducing the risk of dose-dependent adverse effects associated with high-dose monotherapy.[12]

When fixed-dose combination therapies are evaluated from an economic perspective, existing evidence from adult populations shows that they are not always more expensive than equivalent single-component medications. A case study conducted in India found that the procurement and retail prices of fixed-dose combination antihypertensive therapies were comparable to—and in some cases lower than—the total prices of separate single-component tablets.[13] Furthermore, a systematic review has shown that polypill strategies improve treatment adherence and are generally cost-effective—and even cost-saving—compared to multiple monotherapies.[14] However, there is no comparable pharmacoeconomic data available for paediatric hypertension; therefore, clinical and economic evaluations specific to this population are necessary before the widespread implementation of paediatric fixed-dose combination therapies.

The lack of appropriate pharmaceutical forms of antihypertensive medications for paediatric patients is another notable issue. Particularly given the difficulties in using tablet formulations in younger age groups, the inadequacy of liquid (syrup/suspension) formulations stands out as a significant inequity that negatively impacts treatment adherence. This deficiency not only complicates clinical practice but also limits paediatric patients' access to optimal treatment.[15] In this context, developing age-appropriate pharmaceutical formulations and strengthening paediatrics-specific treatment approaches are of critical importance for addressing existing disparities.

Disparities in paediatric participation in clinical trials during the antihypertensive era remain a major and concerning challenge in patient care. Children are consistently underrepresented in antihypertensive drug trials, despite the high burden of disease and the frequent need for pharmacological treatment in this population. As a result, clinicians are often compelled to rely on off-label use of these medications in routine practice.[16] This limited evidence base poses a significant challenge for both physicians and families in making evidence-based decisions and underscores the need for targeted strategies to improve paediatric trial participation and representation.

In conclusion, childhood hypertension requires unique and targeted treatment approaches due to its increasing prevalence and long-term effects. Despite treatment successes in adults, the lack of clinical trials in paediatric patients, the scarcity of appropriate pharmaceutical formulations, and the limited use of combination therapies create a significant gap. Addressing these disparities requires an increase in paediatric research and the development of age-appropriate treatment options.

Financial support. This research received no specific grant from any funding agency, commercial, or not-for-profit sectors.

Competing interests. The authors have no conflicts of interest to disclose.

Ethical standard. Not applicable.

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