

Fixed-dose combinations: A valuable tool to improve adherence to antihypertensive treatment

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Hypertension is a major modifiable cardiovascular risk factor.^{1–3} Several studies have shown that management of hypertension with all five main classes of blood pressure (BP)-lowering drugs (diuretics, β -blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers) substantially reduces cardiovascular morbidity and mortality.⁴ However, only a minority of patients with hypertension achieve BP targets.^{5–7} An important contributor to these low rates of BP control is poor adherence to treatment.⁸ Indeed, a substantial proportion of patients do not adhere to antihypertensive treatment.^{8,9} In turn, poor adherence increases the risk for cardiovascular and all-cause mortality.^{10,11}

Several predictors of nonadherence to antihypertensive treatment have been identified, including older age, belonging to a racial/ethnic minority, male sex, and depression.^{8,12} Moreover, several studies have shown that an increase in the number of antihypertensive agents is associated with reduced adherence to treatment.^{8,12} This observation is particularly pertinent for the management of hypertension, since most patients with hypertension require more than one agent to achieve BP targets.^{13,14}

In this context, a meta-analysis by Du and colleagues¹⁵ offers valuable information in the effort to improve adherence to antihypertensive treatment. The authors analyzed nine studies in 62 481 patients with hypertension and report that the mean difference of medication adherence for fixed-dose combination (FDC) vs free-equivalent combination therapies was 14.92% (95% confidence interval, 7.38%–22.46%).¹⁵ Moreover, patients in the FDC group were nearly two times more likely to adhere to their antihypertensive treatment (risk ratio, 1.84, 95% confidence interval, 1.00–3.39).¹⁵

Despite the important findings reported in this meta-analysis, there are still unanswered questions regarding the role of FDCs in the management of hypertension. First, eight of nine studies included in the meta-analysis by Du and coworkers¹⁵ were retrospective. More prospective studies are needed to clearly define the benefits of FDCs. Moreover, this meta-analysis did not evaluate whether different types of FDCs (eg, renin-angiotensin system inhibitors combined

with diuretics vs renin-angiotensin system inhibitors combined with calcium channel blockers) have the same impact on adherence.¹⁵ It appears that adherence to diuretics is lower than with other antihypertensive agents.¹² On the other hand, calcium channel blocker use was reported to be independently associated with lower risk for decline in adherence.¹⁶ This question has particular importance, since in the ACCOMPLISH (Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension) trial, combining an angiotensin-converting enzyme inhibitor with a calcium channel blocker reduced cardiovascular events more than the combination with a diuretic, despite a similar reduction in BP.¹⁷ Third, only fixed combinations of two agents were evaluated in the meta-analysis by Du and colleagues.¹⁵ Thus, the incremental benefit of using a triple-agent fixed combination remains unclear.

It should be emphasized that FDCs are not a panacea in patients receiving multiple antihypertensive agents. Indeed, a recent study has suggested that switching to a single-pill combination in patients who are highly adherent to free-combined antihypertensive regimens might paradoxically decrease adherence.¹⁸ In contrast, in patients receiving a single antihypertensive agent, switching to a fixed-dose combination improves adherence more than switching to a different single agent.¹⁹ Moreover, among patients with poor adherence who are treated with a single antihypertensive agent, adherence to fixed-dose combinations is higher than to alternative strategies of either switching to another agent or titration of the same agent.¹⁹ Therefore, FDCs should be combined with other interventions to further enhance adherence. Several other relevant strategies have been proposed, including prescription of a once-daily regimen, provision of adherence-related awards to patients, and text messaging.^{20,21} The use of a combination of these strategies appears to be more effective than a single intervention.²⁰ Interestingly, the use of standardized hypertension treatment protocols and the routine recommendation of home BP monitor use appear to be associated with wider implementation of adherence-promoting strategies.²⁰

In conclusion, FDCs are a valuable tool to improve adherence in patients with hypertension. The combination of FDCs with other strategies that have also been shown to be effective should be promoted. In addition, given the high rates of poor adherence in patients with hypertension, these patients should be routinely questioned about the consistency of use of their antihypertensive medications. In selected cases, biochemical confirmation of adherence might offer additional benefits in achieving BP targets.²²

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