

# Initial Single-Pill Blood Pressure–Lowering Therapy: Should It Be for Most People?

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The importance of lowering blood pressure (BP) to reduce cardiovascular risk and progression of chronic kidney disease is well established. Furthermore, clinical trials that randomized various monotherapies to evaluate outcomes ultimately required an average of 2 or more medications to achieve BP goals (Figure).<sup>1–14</sup> This was also true in trials involving elderly people.<sup>15</sup>

The concept of initiating 2 different BP-lowering medications that have complementary mechanisms of action is not novel. Use of combination BP-lowering therapies started in the 1950s, when the single-pill, triple combination of hydralazine, hydrochlorothiazide, and reserpine was introduced.<sup>1</sup> This was then followed by several other formulations in the 1960s and 1970s, containing thiazide diuretics, including combinations with potassium-sparing diuretics,  $\beta$ -blockers, and clonidine.<sup>1</sup>

In this issue of *JAHA*, the efficacy of initial combination antihypertensive therapy versus either of its individual components to achieve a BP goal was assessed by MacDonald and colleagues.<sup>16</sup> They evaluated 605 untreated hypertensive patients in a double-blind, randomized, controlled trial to see if combination therapy with losartan plus hydrochlorothiazide would result in better BP control compared with the individual monotherapies. The authors evaluated differences from baseline in home systolic BP, averaged over different durations of the study. The authors noted that monotherapy had a 4.9-mm Hg higher systolic BP compared with the combination group at 16 weeks, but by 32 weeks this effect dissipated once all patients crossed over to combination therapy. Differences in BP lowering were noted

on the basis of plasma renin activity. Predictably, those with low renin levels had a greater BP-lowering response to hydrochlorothiazide, whereas the converse was true for losartan. The response to BP lowering by renin levels was prospectively tested in a trial in which renin levels were used to predict therapy response versus routine care; the primary end point was BP goal achievement.<sup>17</sup> The study showed results similar to what was observed by the investigators. The authors also note no differences in withdrawals attributable to adverse events among the groups. They conclude that many combination tablets cost no more than the single components but assert they offer no advantage for BP control in the long-term. Although this is true based on this and other observations, having BP better controlled for 4 months over the monotherapy groups does provide at least a theoretical advantage.

The authors should be commended for using home BP as the primary end point rather than office BP. They have previously published studies that support the observation that combination antihypertensive agents effectively lower BP.<sup>18,19</sup> The STITCH (Simplified Treatment Intervention to Control Hypertension) study supports the authors' findings of earlier achievement of BP targets with combination therapy.<sup>20</sup> STITCH used a cluster randomization of an initial single-pill combination, similar to MacDonald et al,<sup>16</sup> and compared it with the Canadian Hypertension Education Program guidelines monotherapy approach. The primary end point was the proportion of patients treated to <140/90 mm Hg at 6 months. More patients achieved the BP target in the combination group versus the monotherapy approach (64.7% versus 52.7%;  $P=0.026$ ).<sup>20</sup>

The authors take data from a controlled trial and try to extrapolate them to the general population. The question is not so much the speed with which BP control is achieved, although this remains an important factor for patients' perception of therapy. Many other factors are important to sustain adherence.<sup>21</sup> Single-pill combinations of BP-lowering agents improve adherence and have fewer adverse effects when compared with doubling the dose of a single medication to achieve the BP goal.<sup>22,23</sup> This study argues there was no need to double the dose because ultimately BP level was achieved over time, but other variables that could have

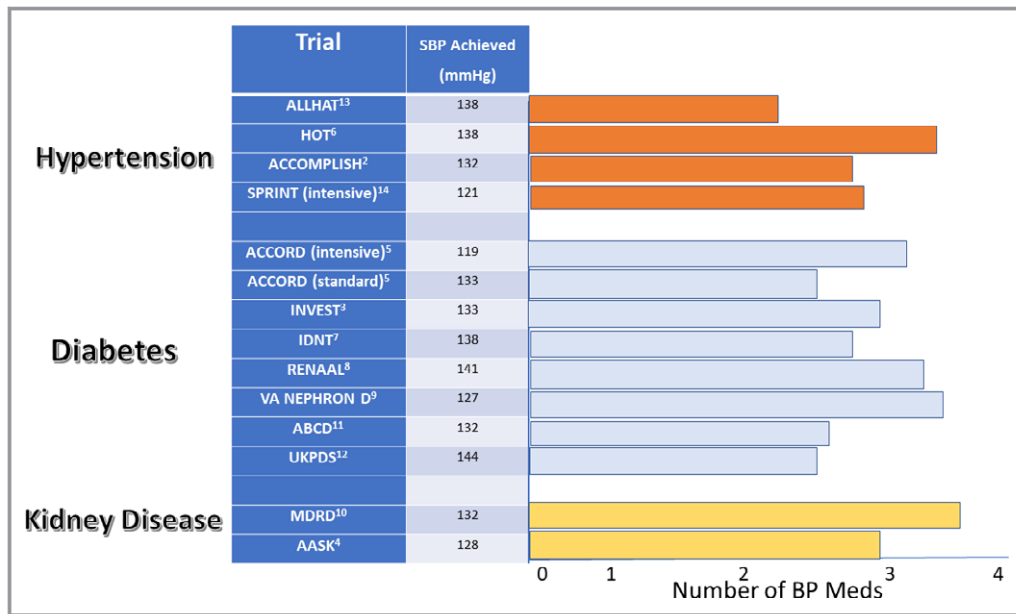
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**Figure.** Medications required to achieve blood pressure (BP) control in clinical trials. AASK indicates African American Study of Kidney Disease and Hypertension; ABCD, Appropriate Blood Pressure Control in Diabetes; ACCOMPLISH, Avoiding Cardiovascular Events in Combination Therapy in Patients Living With Systolic Hypertension; ACCORD, Action to Control Cardiovascular Risk in Diabetes; ALLHAT, Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial; HOT, Hypertension Optimal Treatment; IDNT, Irbesartan Diabetic Nephropathy Trial; INVEST, International Verapamil-Trandolapril Study; MDRD, Modification of Diet in Renal Disease; RENAAL, Reduction in Endpoints in Patients With Non-Insulin-Dependent Diabetes Mellitus With the Angiotensin II Antagonist Losartan; SBP, systolic BP; SPRINT, Systolic Blood Pressure Intervention Trial; UKPDS, UK Prospective Diabetes Study; and VA Nephron D, Veterans Affairs Nephropathy in Diabetes.

contributed to this were not assessed, like dietary sodium restriction or weight loss. In addition, initial single-pill combination treatment avoids therapeutic inertia or physician inaction in the face of a BP that is higher than target.<sup>1,24</sup> More than 7200 patients studied demonstrated that physicians only made medication changes in 13.1% of visits where BP was higher than the guideline goal, although more recent studies show this has been improving.<sup>1,24</sup>

The authors assert that neither the STITCH trial nor the meta-analyses evaluating adverse events on combination therapy have changed practice patterns. MacDonald and colleagues<sup>16</sup> should appreciate, however, that most guidelines around the world advocate for initial combinations of BP-lowering therapies when BP is >20/10 mm Hg higher than the goal or  $\geq 160/100$  mm Hg.<sup>25-27</sup> In addition, initial single-pill combinations in hypertensive patients at high cardiovascular risk have demonstrated cardiovascular outcome benefits in randomized trials.<sup>2</sup> Many physicians practice what they were taught in training. Most are not exposed to initial single-pill combination therapy because their choice of therapy is based on hospital or clinic formularies, which often lack or have limited options of BP-lowering combination medications, mainly because of their higher cost.<sup>28</sup>

Paradoxically, one of the major reasons they are taught to avoid combination medications is their potential for adverse events. Although there are no differences in adverse events if single and combination therapy are similar doses, similar to the authors' findings, if BP was not controlled by monotherapy and dosage increased, all classes have increased adverse effects over the combinations in almost all published data.<sup>25,29</sup>

All single-pill combinations available and approved by the Food and Drug Administration have demonstrated added BP-lowering efficacy with fewer adverse events compared with individual higher-dosed components of the combination.<sup>1</sup> A detailed discussion of initial single-pill combinations and their efficacy for reduction of BP and cardiovascular events is presented in the American Society of Hypertension Consensus Report.<sup>25</sup> Combinations of renin-angiotensin system blockers with either thiazide-like diuretics or calcium channel blockers are preferred initial therapy if BP is >20/10 mm Hg higher than the goal BP. These specific combinations were chosen because they have good evidence for cardiovascular risk reduction and data on slowed progression of chronic kidney disease, while providing fewer adverse events compared with high doses of individual monotherapy approaches.<sup>25</sup>

## Disclosures

None.

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