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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).[1–14] This was also true in trials involving elderly people.[15]

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.[1] This was then followed by several other formulations in the 1960s and 1970s, containing thiazide diuretics, including combinations with potassium-sparing diuretics, β-blockers, and clonidine.[1]

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.[16] 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.[17] 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.[18,19] The STITCH (Simplified Treatment Intervention to Control Hypertension) study supports the authors' findings of earlier achievement of BP targets with combination therapy.[20] STITCH used a cluster randomization of an initial single-pill combination, similar to MacDonald et al,[16] 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).[20]

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.[21] 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.[22,23] 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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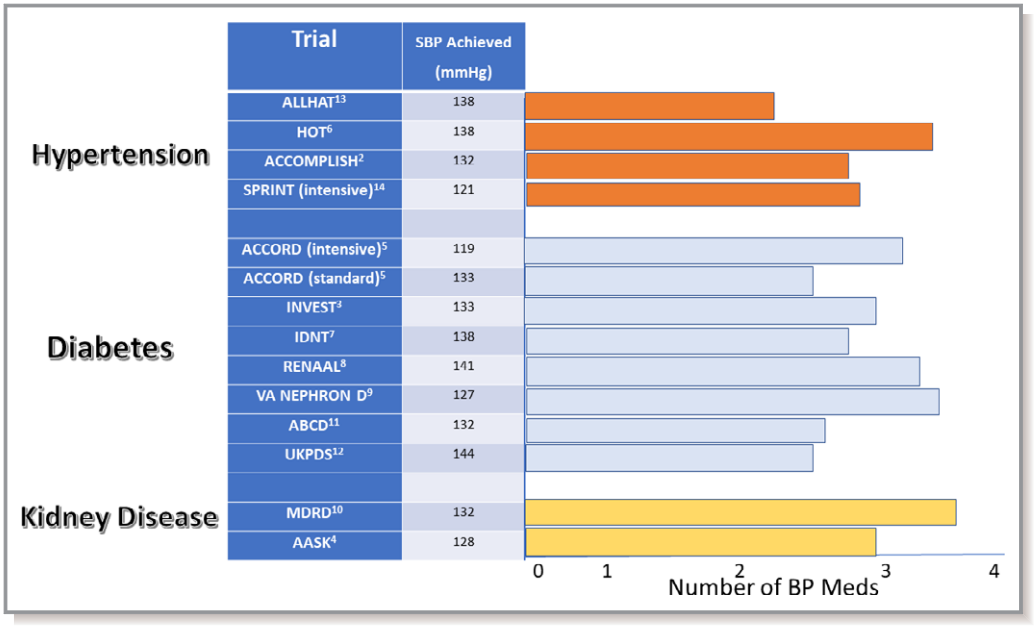

Figure. Medications required to achieve blood pressure (BP) control in clinical trials. AASK indicates African American Study of Kidney Disease and Hypertension; ABCD, Appropriate Blood Pressure Control in Diabetes; ACCOMPLISH, Avoiding Cardiovascular Events in Combination Therapy in Patients Living 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.[1,24] 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.[1,24]

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[16] 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 ≥160/100 mm Hg.[25–27] In addition, initial single-pill combinations in hypertensive patients at high cardiovascular risk have demonstrated cardiovascular outcome benefits in randomized trials.[2] 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.[28]

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.[25,29]

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.[1] 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.[25] 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.[25]

Disclosures

None.

References

1. Yamout H, Bakris GL. Use of combination therapy. In: Bakris GL, Sorrentino M, eds. *Hypertension: A Companian to Braunwald's the Heart*. Philadelphia, PA: Elsevier; 2017:261–269.
2. Jamerson K, Weber MA, Bakris GL, Dahlof B, Pitt B, Shi V, Hester A, Gupte J, Gatlin M, Velazquez EJ; ACCOMPLISH Trial Investigators. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *N Engl J Med*. 2008;359:2417–2428.
3. Cooper-DeHoff RM, Gong Y, Handberg EM, Bavry AA, Denardo SJ, Bakris GL, Pepine CJ. Tight blood pressure control and cardiovascular outcomes among hypertensive patients with diabetes and coronary artery disease. *JAMA*. 2010;304:61–68.
4. Appel LJ, Wright JT Jr, Greene T, Agodoa LY, Astor BC, Bakris GL, Cleveland WH, Charleston J, Contreras G, Faulkner ML, Gabbai FB, Gassman JJ, Hebert LA, Jamerson KA, Kopple JD, Kusek JW, Lash JP, Lea JP, Lewis JB, Lipkowitz MS, Massry SG, Miller ER, Norris K, Phillips RA, Pogue VA, Randall OS, Rostand SG, Smogorzewski MJ, Toto RD, Wang X; AASK Collaborative Research Group. Intensive blood-pressure control in hypertensive chronic kidney disease. *N Engl J Med*. 2010;363:918–929.
5. Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME, Byington RP, Goff DC Jr, Bigger JT, Buse JB, Cushman WC, Genuth S, Ismail-Beigi F, Grimm RH Jr, Probstfield JL, Simons-Morton DG, Friedewald WT. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med*. 2008;358:2545–2559.
6. Hansson L, Zanchetti A, Carruthers SG, Dahlof B, Elmfeldt D, Julius S, Menard J, Rahn KH, Wedel H, Westerling S; HOT Study Group. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the hypertension optimal treatment (HOT) randomised trial. *Lancet*. 1998;351:1755–1762.
7. Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, Ritz E, Atkins RC, Rohde R, Raz I; Collaborative Study Group. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med*. 2001;345:851–860.
8. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, Remuzzi G, Snapinn SM, Zhang Z, Shahinfar S; RENAAL Study Investigators. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med*. 2001;345:861–869.
9. Fried LF, Emanuele N, Zhang JH. Combined angiotensin inhibition in diabetic nephropathy. *N Engl J Med*. 2014;370:779.
10. Klahr S, Levey AS, Beck GJ, Caggiula AW, Hunsicker L, Kusek JW, Striker G. Modification of Diet in Renal Disease Study Group. The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. *N Engl J Med*. 1994;330:877–884.
11. Estacio RO, Jeffers BW, Gifford N, Schrier RW. Effect of blood pressure control on diabetic microvascular complications in patients with hypertension and type 2 diabetes. *Diabetes Care*. 2000;23(suppl 2):B54–B64.
12. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ*. 1998;317:703–713.
13. ALLHAT Collaborative Research Group. Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlorthalidone: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). *JAMA*. 2000;283:1967–1975.
14. Wright JT Jr, Whelton PK, Reboussin DM. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med*. 2016;374:2294.
15. Aronow WS, Fleg JL, Pepine CJ, Artinian NT, Bakris G, Brown AS, Ferdinand KC, Forciea MA, Frishman WH, Jaigobin C, Kostis JB, Mancia G, Oparil S, Ortiz E, Reisin E, Rich MW, Schocken DD, Weber MA, Wesley DJ, Harrington RA; ACCF Task Force. ACCF/AHA 2011 expert consensus document on hypertension in the elderly: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. *Circulation*. 2011;123:2434–2506.
16. MacDonald T, Williams B, Webb DJ, Morant S, Caulfield M, Cruickshank JK, Ford I, Sever P, Mackenzie IS, Padmanabhan S, McCann GP, Salsbury J, McInnes G, Brown MJ; for The British Hypertension Society Programme of Prevention And Treatment of Hypertension With Algorithm-based Therapy (PATHWAY). Combination therapy is superior to sequential monotherapy for the initial treatment of hypertension: a double-blind randomised controlled trial. *J Am Heart Assoc*. 2017;6:e006986. DOI: 10.1161/JAHA.117.006986.
17. Egan BM, Basile JN, Rehman SU, Davis PB, Grob CH III, Riehle JF, Walters CA, Lackland DT, Merali C, Sealey JE, Laragh JH. Plasma renin test-guided drug treatment algorithm for correcting patients with treated but uncontrolled hypertension: a randomized controlled trial. *Am J Hypertens*. 2009;22:792–801.
18. Brown MJ, McInnes GT, Papst CC, Zhang J, MacDonald TM. Aliskiren and the calcium channel blocker amlodipine combination as an initial treatment strategy for hypertension control (ACCELERATE): a randomised, parallel-group trial. *Lancet*. 2011;377:312–320.
19. Brown MJ, Williams B, Morant SV, Webb DJ, Caulfield MJ, Cruickshank JK, Ford I, McInnes G, Sever P, Salsbury J, Mackenzie IS, Padmanabhan S, MacDonald TM; British Hypertension Society's Prevention and Treatment of Hypertension With Algorithm-Based Therapy (PATHWAY) Studies Group. Effect of amiloride, or amiloride plus hydrochlorothiazide, versus hydrochlorothiazide on glucose tolerance and blood pressure (PATHWAY-3): a parallel-group, double-blind randomised phase 4 trial. *Lancet Diabetes Endocrinol*. 2016;4:136–147.
20. Feldman RD, Zou GY, Vandervoort MK, Wong CJ, Nelson SA, Feagan BG. A simplified approach to the treatment of uncomplicated hypertension: a cluster randomized, controlled trial. *Hypertension*. 2009;53:646–653.
21. van der Laan DM, Elders PJM, Boons C, Beckeringh JJ, Nijpels G, Hugtenburg JG. Factors associated with antihypertensive medication non-adherence: a systematic review. *J Hum Hypertens*. 2017;31:687–694.
22. Wald DS, Law M, Morris JK, Bestwick JP, Wald NJ. Combination therapy versus monotherapy in reducing blood pressure: meta-analysis on 11,000 participants from 42 trials. *Am J Med*. 2009;122:290–300.
23. Law MR, Wald NJ, Morris JK, Jordan RE. Value of low dose combination treatment with blood pressure lowering drugs: analysis of 354 randomised trials. *BMJ*. 2003;326:1427.
24. Escobar C, Barrios V, Alonso-Moreno FJ, Prieto MA, Valls F, Calderon A, Llisterri JL; Working Group of Arterial Hypertension of the Spanish Society of Primary Care Physicians; PRESCAP 2010 Investigators. Evolution of therapy inertia in primary care setting in Spain during 2002–2010. *J Hypertens*. 2014;32:1138–1145; discussion 1145.
25. Gradman AH, Basile JN, Carter BL, Bakris GL; American Society of Hypertension Writing Group. Combination therapy in hypertension. *J Clin Hypertens (Greenwich)*. 2011;13:146–154.
26. Whelton PK, CR AW, Casey DE Jr, Collins KJ, Dennison-Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, MacLaughlin EJ, Muntner P, Ovbiagele B, Smith SC, Spencer CC, Stafford RS, Taler SJ, Thomas RJ, Williams KA Sr, Williamson JD, Wright JT Jr. ACC/AHA/AAPA/ABC/ACPM/AGS/APHA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association and Task Force on Clinical Practice Guidelines. *Hypertension*. 2017. In Press.
27. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, Christiaens T, Cifkova R, De Backer G, Dominiczak A, Galderisi M, Grobbee DE, Jaarsma T, Kirchhof P, Kjeldsen SE, Laurent S, Manolis AJ, Nilsson PM, Ruilope LM, Schmieder RE, Sirnes PA, Sleight P, Viigimaa M, Waeber B, Zannad F; Task Force Members. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens*. 2013;31:1281–1357.
28. Majumdar SR, Soumerai SB. Why most interventions to improve physician prescribing do not seem to work. *CMAJ*. 2003;169:30–31.
29. Gradman AH, Parise H, Lefebvre P, Falvey H, Lafeuille MH, Duh MS. Initial combination therapy reduces the risk of cardiovascular events in hypertensive patients: a matched cohort study. *Hypertension*. 2013;61:309–318.

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