Hypertension

REVIEW

# Starting Antihypertensive Drug Treatment With Combination Therapy

## *Controversies in Hypertension* - Pro *Side of the Argument*

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One of the highlights of the current recommendations of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH) for the management of arterial hypertension published in 2018[1] is the strong position in favor of a single-pill combination (SPC) comprising 2 antihypertensive drugs as first-line treatment in most hypertensive patients. The scope of this article is to summarize the background and evidence supporting this recommendation. First, we review the recommendation in detail and show that it did not come out of the blue but rather reinforces strategies already proposed in the 2013 guidelines[2] and is consistent with other major current guidelines.[3–5] Second, we summarize the evidence supporting dual therapy per se compared with other therapeutic strategies to achieve blood pressure (BP) goals, as well as the evidence supporting the specific use of SPC instead of prescribing 2 antihypertensive drugs in free combination. Third, we discuss the advantages of this strategy as a pragmatic approach to improve BP control and, therefore, to decrease cardiovascular risk.

## WHAT DO THE 2018 ESC/ESH GUIDELINES SAY?

The 2018 ESC/ESH guidelines recommend to initiate an antihypertensive treatment with a 2-drug combination, preferably in a SPC in most hypertensive patients. The exceptions are (1) frail older patients/patients ≥80 years in whom, due to baroreflex impairment, the risk of hypotension may be higher, (2) patients with grade 1 hypertension at low or moderate risk (particularly if systolic BP is <150 mm Hg) and, possibly, (3) patients with high normal BP and high cardiovascular risk because only a small BP reduction is required to achieve the BP target.[1]

## FIRST-LINE SPC—A REVOLUTION IN THE 2018 ESC/ESH GUIDELINES?

As acknowledged by the writing committee, this recommendation is not a revolution but rather normalizes the concept of initial dual therapy expressed in the 2013 guidelines,[2] which already showed a preference for two-drug combination in patients with marked BP elevation or with grade 1 hypertension at high/very high cardiovascular risk. However, in contrast with the 2013 guidelines,[2] in the 2018 guidelines,[1] initial dual therapy is the object of a strong recommendation rather than an advice and applies to a wider spectrum of hypertensive patients, thus becoming the standard approach.





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## IS TREATMENT INITIATION WITH DUAL THERAPY SUPPORTED BY OTHER HYPERTENSION GUIDELINES?

The American College of Cardiology/American Heart Association hypertension guidelines[3] recommend treatment initiation with dual antihypertensive therapy in adults with stage 2 hypertension (corresponding to grade 1 and 2 in the ESH classification)[1] (Table) and an average BP >20/10 mm Hg above target. Although the use of SPCs is left to the decision of the physician, its potential usefulness to improve drug adherence compared to free-drug equivalents is acknowledged.[3] Similarly, but without specification of BP level, the Japanese Hypertension Guidelines[4] recommend outright use of combination therapy when a BP decrease of ≥20/10 mm Hg is targeted. Finally, the optimal treatment strategy advocated by the International Society of Hypertension Global Guidelines[5] includes dual SPC combination as first choice in all hypertensive patients, with possible exception of grade 1 hypertension, frail or very old (≥80 years) patients, while leaving the door open to use equivalent free-drug combinations in case SPCs are unavailable or unaffordable. There is thus a wide worldwide consensus on the use of dual antihypertensive therapy as initial drug treatment, preferably in the form of SPC, in most antihypertensive patients.

## WHAT IS THE EVIDENCE SUPPORTING TREATMENT INITIATION WITH A DUAL THERAPY?

The strong position of the writing committee of the 2018 ESC/ESH guidelines[1] in favor of first-line dual therapy needs to be interpreted in the context of the lower BP goals proposed in this document, that is, diastolic BP <80 mm Hg for all patients and systolic BP <130 mm Hg in most patients below the age of 65 years and within the range of 130 to 139 mm Hg in patients 65 years and older. Randomized controlled studies show that 2 or more antihypertensive drugs are needed to reach even less strict BP goals in the majority of hypertensive patients.[6] Furthermore, the French randomized controlled trial STRATHE (Strategies of Treatment in Hypertension: Evaluation)[7] has shown a higher rate of success in achieving target BP after 3, 6, and 9 months in previously untreated hypertensive patients prescribed a low-dose combination (62%) compared with sequential monotherapy (49%, P=0.02) or stepped-care strategies (47%, P=0.005). These results were confirmed and further expanded in large observational studies.[8,9] Along the same lines, a meta-analysis including 11 000 participants from 42 trials has shown that adding a drug from another class to an initial monotherapy at standard dose is more efficient to reduce BP than doubling the dose of the same drug, irrespective of the initial drug class.[10] Finally, in a retrospective analysis including 1700 patients, the median time to BP control was significantly shorter (9.7 versus 11.9 months, p=0.004) in patients initially treated with a drug combination compared with those who were shifted to a combination after an initial monotherapy.[11] These findings are relevant in view of the importance of early achievement of BP target, especially in at-risk patients, as clearly shown in the Valsartan Antihypertensive Long-term Use Evaluation trial (VALUE).[12] A subanalysis of this trial based on a technique of serial median matching[13] indeed showed that the hazard ratios of fatal and nonfatal cardiovascular events (cardiac: −25%; stroke: −45%) and all-cause death (−21%) were substantially decreased in patients who reached BP control at 6 months compared with uncontrolled patients, irrespective of the treatment arm in the trial. The crucial role of achieving BP control early after diagnosis is further supported by a large retrospective study (n=88 756) in which delays in BP treatment intensification of 1.4 to 4.7 months were associated with a progressive increase in the hazard ratio of a combined end point including cardiovascular events and all-cause death from any cause from 1.12 to 1.2.[14] The option for selection of the more adequate dual therapy in individual patients is extended by the availability of multiple large randomized trials comparing different drug strategies (Anglo-Scandinavian

**Table. Classification of Hypertension Based on Office Blood Pressure Current Guidelines**

| Categories | | | | | |
|---|---|---|---|---|---|
| ESC/ESH 2018* | ISH 2020† | ACC/AHA 2017‡ | Systolic, mm Hg | | Diastolic, mm Hg |
| Normal | Normal | Elevated | 120–129 | and/or | 80–84 |
| High normal | High normal | Stage 1 hypertension | 130–139 | and/or | 85–89 |
| Grade 1 hypertension | Grade 1 hypertension | Stage 2 hypertension | 140–159 | and/or | 90–99 |
| Grade 2 hypertension | Grade 2 hypertension | | 160–179 | and/or | 100–109 |
| Grade 3 hypertension | | | ≥180 | and/or | ≥110 |

ACC indicates American College of Cardiology; AHA, American Heart Association; ESC, European Society of Cardiology; ESH, European Society of Hypertension and ISH, International Society of Hypertension.

*Williams et al.[1]

†Unger et al.[5]

‡Whelton et al.[3]

Cardiac Outcomes Trial [ASCOT];ONgoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial [ONTARGET])[15,16] or fixed-dose combinations (Avoiding Cardiovascular Events in Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH)).[17]

## WHAT IS THE EVIDENCE IN FAVOR OF SPC VERSUS FREE-DRUG DUAL THERAPY?

Although initial treatment with dual drug therapy is superior to other treatment strategies in terms of rate and timing of BP achievement, why shall we use SPC instead of free-drug dual therapy? The main argument is that SPC improves treatment adherence, which is a key factor for BP control and subsequent prevention of BP-related cardiovascular complications. In a widely quoted systematic review including patients with various clinical conditions, Claxton et al[18] have shown an inverse relation between the number of daily doses of drugs and drug adherence. Evidence directly supporting the use of SPC as a tool to improve drug adherence in hypertensive patients is summarized in the meta-analysis of Gupta et al.[19] This analysis demonstrated that the use of SPCs in 17 999 patients enrolled in 5 different studies was associated with improved drug adherence assessed by indirect methods (drug pill count or medication possession ratio) compared with corresponding free-drug combinations (odds ratio, 1.21, p=0.02). Finally, several other meta-analysis indicated shifting from free-drug combinations to SPC as being one of the most effective ways to improve drug adherence.[20] More recently, Salam et al[21] conducted a systematic review and meta-analysis of 33 randomized controlled trials comparing initial monotherapy with dual therapy. Compared with standard-dose monotherapy, initiating treatment with low-to-standard-dose dual combination therapy proved more efficacious in terms of BP control, without increasing withdrawals due to adverse events.

Notably, the favorable impact of reducing pill burden in clinical studies may be underestimated compared to real life due to the known positive impact of participation in a study on patients behavior (Hawthorne effect), including individual drug adherence and persistence.[22] All investigators involved in recruitment in renal denervation trials have experienced the high number of patients with difficult to treat hypertension who suddenly reached BP control during the run-in period, either spontaneously or after a shift to a standardized fixed-dose triple therapy.[23–25]

## WHICH IS THE AVAILABILITY OF SPCS WORLDWIDE?

We checked databases listing information about medications authorized in different countries around the world (drugs.com [the Drugs.com International Drug Name Database], drugbank.com, ema.europa.eu [Public data from Article 57 database] and fda.gov [Orange Book: approved drug products with therapeutic equivalence evaluations]) for the availability of ACE (angiotensin-converting enzyme) inhibitors and angiotensin receptor blockers in dual SPCs, in combination with either a thiazide/thiazide-like diuretic or a calcium channel blocker. Research of available drug combinations for these drug classes was based on the corresponding Anatomical Therapeutic Chemical (ATC) codes provided by the World Health Organization–ATC and defined daily dose (DDD) index (https://www.whocc.no/atc_ddd_index/). This analysis showed that at least 9 different ACE inhibitors/calcium channel blockers, 12 different ACE inhibitors/diuretics, 8 different angiotensin receptor blockers/calcium channel blockers, and 8 different angiotensin receptor blockers/diuretic SPCs, many of which are marketed in different dosing levels, are potentially available globally. However, there are significant regional differences. Indeed, although these SPCs are widely available in some countries in Europe, North America (Canada and United States), and in Asia (China, Japan, India, and South Korea), fewer SPCs are available in countries in the Middle East and Australia, particularly those including a renin angiotensin system-blocker and a calcium channel blocker, and information for Africa is difficult to retrieve.

Accordingly, as already mentioned, the recent International Society of Hypertension Global Guidelines[5] distinguish between essential and optimal measures. In this perspective, although the use of first-line SPC is considered as optimal in most hypertensive patients, the essential is to use dual therapy, even as combination of free drugs if SPCs are unavailable or unaffordable (see higher). Such 2-level recommendations have the advantage to propose widely applicable measures, including in low-resource countries, while setting ambitious standards likely to encourage local initiatives to reach such standards.

## BEYOND EVIDENCE-BASED MEDICINE, WHICH ARE THE TENTATIVE ADVANTAGES OF COMBINATION THERAPY TO IMPROVE OVERALL BP CONTROL?

We are well aware that most studies mentioned in favor of combination therapy in hypertension have limitations and that evidence is often somewhat weak and contradictory. Furthermore, randomized studies directly comparing the benefit of treatment strategies based on first-line SPC versus initial monotherapy-based strategies on prevention of cardiovascular events are lacking. However, such studies are very difficult to conduct and they may nevertheless not capture the full benefits of combination therapy in real-life medical practice. The fact that drug companies are actively promoting SPCs which allow them capitalizing on already existent drugs beyond

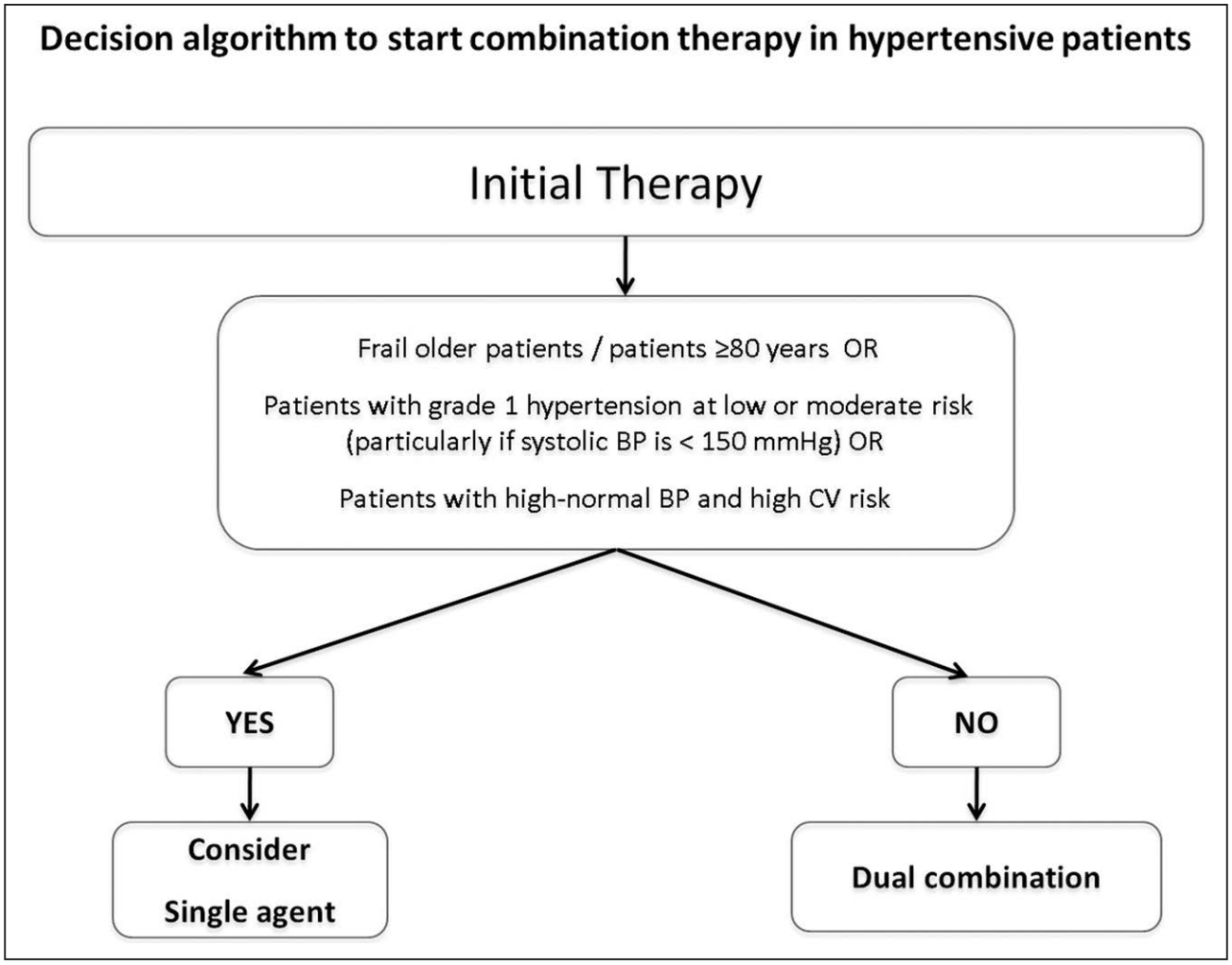


**Figure. Decision algorithm to start combination therapy in hypertensive patients.**
BP indicates blood pressure; CV, cardiovascular; and OR, odds ratio.

patent expiration raises further suspicion on this strategy, which sometimes elicits visceral reactions. Nevertheless, very recently, the World Health Organization added for the first time SPC (or fixed-dose combination) comprising 2 antihypertensive medications to the World Health Organization Essential Medicines List[26] and thereby acknowledges that the use of SPC is the emerging best practice for safe, effective, rapid, and convenient hypertension control worldwide.[27]

We are in full agreement with this recognition because many reasons based on common sense and medical experience support this strategy. In contrast with stepped-care therapy, which was still supported by several hypertension specialists until recently, the use of validated low-dose antihypertensive combinations does not require a specific expertise and should allow to control ≈80% of hypertensive patients (Avoiding Cardiovascular Events in Combination Therapy in Patients Living with Systolic Hypertension [ACCOMPLISH])[17] without increasing or even reducing the number of adverse events.[19] Timely achievement of BP with few or no adverse events is important not only to decrease cardiovascular risk[13] but also to avoid discouragement in patients already reluctant to initiate antihypertensive drug treatment who may escape medical follow-up after a few unsuccessful attempts. In contrast, quick therapeutic success using a well-tolerated SPC may strengthen physician-patient relationship, reinforce drug adherence, and decrease the risk of treatment discontinuation.[28,29] It is also well known that once a monotherapy is prescribed with some improvement in BP, both patients and physicians will be tempted to delay shift to a combination therapy.[30] Standard use of initial combination therapy may therefore be effective to prevent not only poor drug adherence but also therapeutic inertia.[1] Finally, decreasing pill burden is critical because as shown already many decades ago, 75% of patients with hypertension have at least another risk factor.[31] Thus, many hypertensive patients are candidates not only to antihypertensive treatment but also to lipid-lowering[32] or antidiabetic drugs, providing the rationale for the use of a polypill including drugs targeting the main cardiovascular risk factors.[33] Still, the discussion of pros

and cons of polypill, particularly as a way to decrease cardiovascular risk in entire populations partly differs from that of SPCs, and is beyond the scope of this article.

## IMPORTANCE OF ACCURATE BP MEASUREMENT AT AND OUTSIDE THE PHYSICIAN'S OFFICE

Safe and efficient implementation of the first-line SPC strategy based on the 2018 ESC/ESH recommendation[1] requires accurate evaluation of BP level in the individual patient according to repeated office BP measurements, ideally complemented by out-of-office BP measurements, also strongly advocated by the 2018 ESC/ESH guidelines.[1] In particular, patients with grade 2 to 3 hypertension at the office but who have mild hypertension at ambulatory blood pressure measurement are not necessarily candidates to a first-line SPC, especially if they are frail, very old, have orthostatic hypotension, or are at low cardiovascular risk.[1] These exceptions have been clearly listed in the 2018 ESC/ESH guidelines[1] and pointed out at the beginning of this article.

## CONCLUSIONS

In conclusion, the use of dual therapy as first-line antihypertensive treatment in most hypertensive patients, preferably in the form of SPCs, appears as a pragmatic and effective means to improve BP control and thus decrease the associated cardiovascular burden worldwide. A simple algorithm based on the ESC/ESH 2018[1] recommendation is shown in Figure. Still, medicine remains an art, and treatment approach needs to be tailored to the individual patient.

## ARTICLE INFORMATION

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## REFERENCES

1. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, Clement DL, Coca A, de Simone G, Dominiczak A, et al; ESC Scientific Document Group. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J*. 2018;39:3021–3104. doi: 10.1093/eurheartj/ehy339
2. Mancia G, Fagard R, Narkiewicz K, Redón J, Zanchetti A, Böhm M, Christiaens T, Cifkova R, De Backer G, Dominiczak A, et al; 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. doi: 10.1097/01.hjh.0000431740.32696.cc
3. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, et al. 2017 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 Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2018;71:e127–e248. doi: 10.1016/j.jacc.2017.11.006
4. Umemura S, Arima H, Arima S, Asayama K, Dohi Y, Hirooka Y, Horio T, Hoshide S, Ikeda S, Ishimitsu T, et al. The Japanese Society of hypertension guidelines for the management of hypertension (JSH 2019). *Hypertens Res*. 2019;42:1235–1481. doi: 10.1038/s41440-019-0284-9
5. Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D, Ramirez A, Schlaich M, Stergiou GS, Tomaszewski M, et al. 2020 International society of hypertension global hypertension practice guidelines. *Hypertension*. 2020;75:1334–1357. doi: 10.1161/HYPERTENSIONAHA.120.15026
6. Bakris G, Sarafidis P, Agarwal R, Ruilope L. Review of blood pressure control rates and outcomes. *J Am Soc Hypertens*. 2014;8:127–141. doi: 10.1016/j.jash.2013.07.009
7. Mourad JJ, Waeber B, Zannad F, Laville M, Duru G, Andréjak M; investigators of the STRATHE trial. Comparison of different therapeutic strategies in hypertension: a low-dose combination of perindopril/indapamide versus a sequential monotherapy or a stepped-care approach. *J Hypertens*. 2004;22:2379–2386. doi: 10.1097/00004872-200412000-00021
8. Mourad JJ, Nguyen V, Lopez-Sublet M, Waeber B. Blood pressure normalization in a large population of hypertensive patients treated with perindopril/indapamide combination: results of the OPTIMAX trial. *Vasc Health Risk Manag*. 2007;3:173–180.
9. Egan BM, Bandyopadhyay D, Shaftman SR, Wagner CS, Zhao Y, Yu-Isenberg KS. Initial monotherapy and combination therapy and hypertension control the first year. *Hypertension*. 2012;59:1124–1131. doi: 10.1161/HYPERTENSIONAHA.112.194167
10. 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. doi: 10.1016/j.amjmed.2008.09.038
11. Gradman AH, Parisé 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. doi: 10.1161/HYPERTENSIONAHA.112.201566
12. Julius S, Kjeldsen SE, Weber M, Brunner HR, Ekman S, Hansson L, Hua T, Laragh J, McInnes GT, Mitchell L, et al; VALUE trial group. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. *Lancet*. 2004;363:2022–2031. doi: 10.1016/S0140-6736(04)16451-9
13. Weber MA, Julius S, Kjeldsen SE, Brunner HR, Ekman S, Hansson L, Hua T, Laragh JH, McInnes GT, Mitchell L, et al. Blood pressure dependent and independent effects of antihypertensive treatment on clinical events in the VALUE Trial. *Lancet*. 2004;363:2049–2051. doi: 10.1016/S0140-6736(04)16456-8
14. Xu W, Goldberg SI, Shubina M, Turchin A. Optimal systolic blood pressure target, time to intensification, and time to follow-up in treatment of hypertension: population based retrospective cohort study. *BMJ*. 2015;350:h158. doi: 10.1136/bmj.h158
15. Dahlöf B, Sever PS, Poulter NR, Wedel H, Beevers DG, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT, et al; ASCOT Investigators. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a

multicentre randomised controlled trial. *Lancet*. 2005;366:895–906. doi: 10.1016/S0140-6736(05)67185-1
16. Yusuf S, Teo KK, Pogue J, Dyal L, Copland I, Schumacher H, Dagenais G, Sleight P, Anderson C. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med*. 2008;358:1547–1559.
17. Jamerson K, Weber MA, Bakris GL, Dahlöf 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. doi: 10.1056/NEJMoa0806182
18. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. *Clin Ther*. 2001;23:1296–1310. doi: 10.1016/s0149-2918(01)80109-0
19. Gupta AK, Arshad S, Poulter NR. Compliance, safety, and effectiveness of fixed-dose combinations of antihypertensive agents: a meta-analysis. *Hypertension*. 2010;55:399–407. doi: 10.1161/HYPERTENSIONAHA.109.139816
20. Conn VS, Ruppar TM, Chase JA, Enriquez M, Cooper PS. Interventions to improve medication adherence in hypertensive patients: systematic review and meta-analysis. *Curr Hypertens Rep*. 2015;17:94. doi: 10.1007/s11906-015-0606-5
21. Salam A, Kanukula R, Atkins E, Wang X, Islam S, Kishore SP, Jaffe MG, Patel A, Rodgers A. Efficacy and safety of dual combination therapy of blood pressure-lowering drugs as initial treatment for hypertension: a systematic review and meta-analysis of randomized controlled trials. *J Hypertens*. 2019;37:1768–1774. doi: 10.1097/HJH.0000000000002096
22. Kjeldsen SE, Fadl Elmula FE, Os I, Persu A, Jin Y, Staessen JA. Renal sympathetic denervation after Symplicity HTN-3 and therapeutic drug monitoring in patients with resistant hypertension to improve patients' adherence. *Eur Heart J Cardiovasc Pharmacother*. 2015;1:48–56. doi: 10.1093/ehjcvp/pvu009
23. Kandzari DE, Böhm M, Mahfoud F, Townsend RR, Weber MA, Pocock S, Tsioufis K, Tousoulis D, Choi JW, East C, et al; SPYRAL HTN-ON MED Trial Investigators. Effect of renal denervation on blood pressure in the presence of antihypertensive drugs: 6-month efficacy and safety results from the SPYRAL HTN-ON MED proof-of-concept randomised trial. *Lancet*. 2018;391:2346–2355. doi: 10.1016/S0140-6736(18)30951-6
24. Fengler K, Rommel KP, Blazek S, Besler C, Hartung P, von Roeder M, Petzold M, Winkler S, Höllriegel R, Desch S, et al. A three-arm randomized trial of different renal denervation devices and techniques in patients with resistant hypertension (RADIOSOUND-HTN). *Circulation*. 2019;139:590–600. doi: 10.1161/CIRCULATIONAHA.118.037654
25. Persu A, Kjeldsen S, Staessen JA, Azizi M. Renal denervation for treatment of hypertension: a second start and new challenges. *Curr Hypertens Rep*. 2016;18:6. doi: 10.1007/s11906-015-0610-9
26. Salam A KR, Esam H, Bahiru E, Sharma A, Heller D, Huffman M, Vedanthan R, Agarwal A, Jaffe MG, Frieden T, Kishore SP, Rodgers A. An application to include blood pressure lowering drug fixed dose combinations to the model list of essential medicines lists for the treatment of essential hypertension in adults. *World Health Organisation*. 2020:1–63.
27. Benjamin IJ, Kreutz R, Olsen MH, Schutte AE, Lopez-Jaramillo P, Frieden TR, Sliwa K, Lackland DT, Brainin M. Fixed-dose combination antihypertensive medications. *Lancet*. 2019;394:637–638. doi: 10.1016/S0140-6736(19)31629-0
28. Corrao G, Parodi A, Zambon A, Heiman F, Filippi A, Cricelli C, Merlino L, Mancia G. Reduced discontinuation of antihypertensive treatment by two-drug combination as first step. Evidence from daily life practice. *J Hypertens*. 2010;28:1584–1590. doi: 10.1097/HJH.0b013e328339f9fa
29. Corrao G, Parodi A, Nicotra F, Zambon A, Merlino L, Cesana G, Mancia G. Better compliance to antihypertensive medications reduces cardiovascular risk. *J Hypertens*. 2011;29:610–618. doi: 10.1097/HJH.0b013e328342ca97
30. Redon J, Erdine S, Böhm M, Ferri C, Kolloch R, Kreutz R, Laurent S, Persu A, Schmieder RE; SHARE Steering Committee. Physician attitudes to blood pressure control: findings from the Supporting Hypertension Awareness and Research Europe-wide survey. *J Hypertens*. 2011;29:1633–1640. doi: 10.1097/HJH.0b013e328348c934
31. Kannel WB. Risk stratification in hypertension: new insights from the Framingham Study. *Am J Hypertens*. 2000;13(1 pt 2):3S–10S. doi: 10.1016/s0895-7061(99)00252-6
32. Yusuf S, Lonn E, Pais P, Bosch J, López-Jaramillo P, Zhu J, Xavier D, Avezum A, Leiter LA, Piegas LS, et al; HOPE-3 Investigators. Blood-Pressure and cholesterol lowering in persons without cardiovascular disease. *N Engl J Med*. 2016;374:2032–2043. doi: 10.1056/NEJMoa1600177
33. Coca A, Kreutz R, Manolis AJ, Mancia G. A practical approach to switch from a multiple pill therapeutic strategy to a polypill-based strategy for cardiovascular prevention in patients with hypertension. *J Hypertens*. 2020;38:1890–1898. doi: 10.1097/HJH.0000000000002464

REVIEW



## Response to Starting Antihypertensive Treatment With Combination Therapy: Controversies in Hypertension - Pro Side of the Argument

*Jan A. Staessen, Zhen-Yu Zhang, Yu-Ling Yu, Kei Asayama, Tine W. Hansen, Gladys E. Maestre*

What is being debated is the strong recommendation—not just advice—to start antihypertensive treatment in most patients with single-pill combinations (SPCs). Dr Persu correctly states that most studies in favor of SPCs are weak. Indeed, these studies were observational with follow-up typically below 3 months. They were written under the auspices of SPC-marketing companies. In the scarce randomized trials, SPCs, after 3 months of follow-up, did not provide better hypertension control than free single-drug combinations. Application of the ESH and ISH guidelines will compel billions of patients, most living in middle- or low-resource countries, to resort to expensive SPCs, thereby straining scarce health care resources, whereas in over one-third of patients, hypertension can be controlled with cheap long-acting drugs, such as chlorthalidone or generic amlodipine. Furthermore, SPCs lack flexibility in combining and dosing drug classes and spreading doses over the day. Patients value minimizing side effects, more likely to occur under exposure to multiple agents at the same time, over simple dosing, an observation that challenges the concept that SPCs might enhance adherence. In view of these arguments, the strong recommendation to start antihypertensive drug treatment with SPCs should be modified.