

481. Chow CK, Thakkar J, Bennett A, Hillis G, Burke M, Usherwood T, et al. Quarter-dose quadruple combination therapy for initial treatment of hypertension: placebo-controlled, crossover, randomised trial and systematic review. *Lancet* 2017;**389**: 1035–42. [https://doi.org/10.1016/s0140-6736\(17\)30260-x](https://doi.org/10.1016/s0140-6736(17)30260-x)
482. Chow CK, Atkins ER, Hillis GS, Nelson MR, Reid CM, Schlaich MP, et al. Initial treatment with a single pill containing quadruple combination of quarter doses of blood pressure medicines versus standard dose monotherapy in patients with hypertension (QUARTET): a phase 3, randomised, double-blind, active-controlled trial. *Lancet* 2021;**398**:1043–52. [https://doi.org/10.1016/s0140-6736\(21\)01922-x](https://doi.org/10.1016/s0140-6736(21)01922-x)
483. Webster R, Salam A, de Silva HA, Selak V, Stepien S, Rajapakse S, et al. Fixed low-dose triple combination antihypertensive medication vs usual care for blood pressure control in patients with mild to moderate hypertension in Sri Lanka: a randomized clinical trial. *JAMA* 2018;**320**:566–79. <https://doi.org/10.1001/jama.2018.10359>
484. MacDonald TM, Williams B, Webb DJ, Morant S, Caulfield M, Cruickshank JK, et al. Combination therapy is superior to sequential monotherapy for the initial treatment of hypertension: a double-blind randomized controlled trial. *J Am Heart Assoc* 2017;**6**: e006986. <https://doi.org/10.1161/jaha.117.006986>
485. Salam A, Kanukula R, Atkins E, Wang X, Islam S, Kishore SP, et al. 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**:1768–74. <https://doi.org/10.1097/hjh.0000000000002096>
486. Zhang ZY, Yu YL, Asayama K, Hansen TW, Maestre GE, Staessen JA. Starting antihypertensive drug treatment with combination therapy: controversies in hypertension—con side of the argument. *Hypertension* 2021;**77**:788–98. <https://doi.org/10.1161/hypertensionaha.120.12858>
487. Kahan T. Low-dose combination of blood pressure-lowering medicines. *Lancet* 2021;**398**:1022–3. [https://doi.org/10.1016/s0140-6736\(21\)01964-4](https://doi.org/10.1016/s0140-6736(21)01964-4)
488. Rea F, Corrao G, Merlino L, Mancía G. Initial antihypertensive treatment strategies and therapeutic inertia. *Hypertension* 2018;**72**:846–53. <https://doi.org/10.1161/hypertensionaha.118.11308>
489. 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**:1124–31. <https://doi.org/10.1161/hypertensionaha.112.194167>
490. Sundström J, Lind L, Nowrouzi S, Hagström E, Held C, Lytys P, et al. Heterogeneity in blood pressure response to 4 antihypertensive drugs: a randomized clinical trial. *JAMA* 2023;**329**:1160–9. <https://doi.org/10.1001/jama.2023.3322>
491. Tsioufis K, Kreutz R, Sykara G, van Vugt J, Hassan T. Impact of single-pill combination therapy on adherence, blood pressure control, and clinical outcomes: a rapid evidence assessment of recent literature. *J Hypertens* 2020;**38**:1016–28. <https://doi.org/10.1097/hjh.0000000000002381>
492. Parati G, Kjeldsen S, Coca A, Cushman WC, Wang J. Adherence to single-pill versus free-equivalent combination therapy in hypertension: a systematic review and meta-analysis. *Hypertension* 2021;**77**:692–705. <https://doi.org/10.1161/hypertensionaha.120.15781>
493. Egan BM, Kjeldsen SE, Narkiewicz K, Kreutz R, Burnier M. Single-pill combinations, hypertension control and clinical outcomes: potential, pitfalls and solutions. *Blood Press* 2022;**31**:164–8. <https://doi.org/10.1080/08037051.2022.2095254>
494. Yusuf S, Joseph P, Dans A, Gao P, Teo K, Xavier D, et al. Polypill with or without aspirin in persons without cardiovascular disease. *N Engl J Med* 2021;**384**:216–28. <https://doi.org/10.1056/NEJMoa2028220>
495. Roshandel G, Khoshnia M, Poustchi H, Hemming K, Kamangar F, Gharavi A, et al. Effectiveness of polypill for primary and secondary prevention of cardiovascular diseases (PolyIran): a pragmatic, cluster-randomised trial. *Lancet* 2019;**394**:672–83. [https://doi.org/10.1016/s0140-6736\(19\)31791-x](https://doi.org/10.1016/s0140-6736(19)31791-x)
496. Joseph P, Roshandel G, Gao P, Pais P, Lonn E, Xavier D, et al. Fixed-dose combination therapies with and without aspirin for primary prevention of cardiovascular disease: an individual participant data meta-analysis. *Lancet* 2021;**398**:1133–46. [https://doi.org/10.1016/s0140-6736\(21\)01827-4](https://doi.org/10.1016/s0140-6736(21)01827-4)
497. van Vark LC, Bertrand M, Akkerhuis KM, Bruggs JJ, Fox K, Mourad JJ, et al. Angiotensin-converting enzyme inhibitors reduce mortality in hypertension: a meta-analysis of randomized clinical trials of renin-angiotensin-aldosterone system inhibitors involving 158 998 patients. *Eur Heart J* 2012;**33**:2088–97. <https://doi.org/10.1093/eurheartj/ehs075>
498. Parving HH, Brenner BM, McMurray JJ, de Zeeuw D, Haffner SM, Solomon SD, et al. Cardiac end points in a trial of aliskiren for type 2 diabetes. *N Engl J Med* 2012;**367**: 2204–13. <https://doi.org/10.1056/NEJMoa1208799>
499. Fried LF, Emanuele N, Zhang JH, Brophy M, Conner TA, Duckworth WW, et al. Combined angiotensin inhibition for the treatment of diabetic nephropathy. *N Engl J Med* 2013;**369**:1892–903. <https://doi.org/10.1056/NEJMoa1303154>
500. Yusuf S, Teo KK, Pogue J, Dyal L, Copland I, Schumacher H, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med* 2008;**358**:1547–59. <https://doi.org/10.1056/NEJMoa0801317>
501. 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. <https://doi.org/10.1161/hypertensionaha.109.139816>
502. Gnanenthiran SR, Wang N, Di Tanna GL, Salam A, Webster R, de Silva HA, et al. Association of low-dose triple combination therapy vs usual care with time at target blood pressure: a secondary analysis of the TRIUMPH randomized clinical trial. *JAMA Cardiol* 2022;**7**:645–50. <https://doi.org/10.1001/jamacardio.2022.0471>
503. Tam TS, Wu MH, Masson SC, Tsang MP, Stabler SN, Kinkade A, et al. Eplerenone for hypertension. *Cochrane Database Syst Rev* 2017;**2**:CD008996. <https://doi.org/10.1002/14651858.CD008996.pub2>
504. Pedersen ME, Cockcroft JR. The vasodilatory beta-blockers. *Curr Hypertens Rep* 2007;**9**:269–77. <https://doi.org/10.1007/s11906-007-0050-2>
505. Sica DA. Minoxidil: an underused vasodilator for resistant or severe hypertension. *J Clin Hypertens (Greenwich)* 2004;**6**:283–7. <https://doi.org/10.1111/j.1524-6175.2004.03585.x>
506. Muñoz D, Uzoije P, Reynolds C, Miller R, Walkley D, Pappalardo S, et al. Polypill for cardiovascular disease prevention in an underserved population. *N Engl J Med* 2019;**381**:1114–23. <https://doi.org/10.1056/NEJMoa1815359>
507. Castellano JM, Pocock SJ, Bhatt DL, Quesada AJ, Owen R, Fernandez-Ortiz A, et al. Polypill strategy in secondary cardiovascular prevention. *N Engl J Med* 2022;**387**: 967–77. <https://doi.org/10.1056/NEJMoa2208275>
508. González-Juanatey JR, Cordero A, Castellano JM, Masana L, Dalmau R, Ruiz E, et al. The CNIC-polypill reduces recurrent major cardiovascular events in real-life secondary prevention patients in Spain: the NEPTUNO study. *Int J Cardiol* 2022;**361**:116–23. <https://doi.org/10.1016/j.ijcard.2022.05.015>
509. Jowett S, Barton P, Roalfe A, Fletcher K, Hobbs FDR, McManus RJ, et al. Cost-effectiveness analysis of use of a polypill versus usual care or best practice for primary prevention in people at high risk of cardiovascular disease. *PLoS One* 2017;**12**:e0182625. <https://doi.org/10.1371/journal.pone.0182625>
510. McManus RJ, Mant J, Bray EP, Holder R, Jones MI, Greenfield S, et al. Telemonitoring and self-management in the control of hypertension (TASMINH2): a randomised controlled trial. *Lancet* 2010;**376**:163–72. [https://doi.org/10.1016/s0140-6736\(10\)60964-6](https://doi.org/10.1016/s0140-6736(10)60964-6)
511. Clark CE, Smith LF, Taylor RS, Campbell JL. Nurse led interventions to improve control of blood pressure in people with hypertension: systematic review and meta-analysis. *BMJ* 2010;**341**:c3995. <https://doi.org/10.1136/bmj.c3995>
512. Mackenzie IS, Rogers A, Poulter NR, Williams B, Brown MJ, Webb DJ, et al. Cardiovascular outcomes in adults with hypertension with evening versus morning dosing of usual antihypertensives in the UK (TIME study): a prospective, randomised, open-label, blinded-endpoint clinical trial. *Lancet* 2022;**400**:1417–25. [https://doi.org/10.1016/s0140-6736\(22\)01786-x](https://doi.org/10.1016/s0140-6736(22)01786-x)
513. Conn VS, Ruppert 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. <https://doi.org/10.1007/s11906-015-0606-5>
514. Corrao G, Parodi A, Zambon A, Heiman F, Filippi A, Cricelli C, et al. Reduced discontinuation of antihypertensive treatment by two-drug combination as first step. Evidence from daily life practice. *J Hypertens* 2010;**28**:1584–90. <https://doi.org/10.1097/HJH.0b013e328339f9fa>
515. Krieger EM, Drager LF, Giorgi DMA, Pereira AC, Barreto-Filho JAS, Nogueira AR, et al. Spironolactone versus clonidine as a fourth-drug therapy for resistant hypertension: the ReHOT randomized study (resistant hypertension optimal treatment). *Hypertension* 2018;**71**:681–90. <https://doi.org/10.1161/hypertensionaha.117.10662>
516. Williams B, MacDonald TM, Morant SV, Webb DJ, Sever P, McInnes GT, et al. Endocrine and haemodynamic changes in resistant hypertension, and blood pressure responses to spironolactone or amiloride: the PATHWAY-2 mechanisms substudies. *Lancet Diabetes Endocrinol* 2018;**6**:464–75. [https://doi.org/10.1016/s2213-8587\(18\)30071-8](https://doi.org/10.1016/s2213-8587(18)30071-8)
517. Mann JF, Schmieder RE, McQueen M, Dyal L, Schumacher H, Pogue J, et al. Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial. *Lancet* 2008;**372**:547–53. [https://doi.org/10.1016/s0140-6736\(08\)61236-2](https://doi.org/10.1016/s0140-6736(08)61236-2)
518. Jones DW, Whelton PK, Allen N, Clark D III, Gidding SS, Muntner P, et al. Management of stage 1 hypertension in adults with a low 10-year risk for cardiovascular disease: filling a guidance gap: a scientific statement from the American Heart Association. *Hypertension* 2021;**77**:e58–67. <https://doi.org/10.1161/hyp.0000000000000195>
519. Ali DH, Kiliç B, Hart HE, Bots ML, Biemans MCJ, Spiering W, et al. Therapeutic inertia in the management of hypertension in primary care. *J Hypertens* 2021;**39**:1238–45. <https://doi.org/10.1097/hjh.0000000000002783>
520. Appel LJ, Champagne CM, Harsha DW, Cooper LS, Obarzanek E, Elmer PJ, et al. Effects of comprehensive lifestyle modification on blood pressure control: main results of the PREMIER clinical trial. *JAMA* 2003;**289**:2083–93. <https://doi.org/10.1001/jama.289.16.2083>
521. Appel LJ, Sacks FM, Carey VJ, Obarzanek E, Swain JF, Miller ER, et al. Effects of protein, monounsaturated fat, and carbohydrate intake on blood pressure and serum lipids: results of the Omni-Heart randomized trial. *JAMA* 2005;**294**:2455–64. <https://doi.org/10.1001/jama.294.19.2455>
522. Thomopoulos C, Parati G, Zanchetti A. Effects of blood-pressure-lowering treatment on outcome incidence. 12. Effects in individuals with high-normal and normal blood pressure: overview and meta-analyses of randomized trials. *J Hypertens* 2017;**35**: 2150–60. <https://doi.org/10.1097/hjh.0000000000001547>
523. Williamson JD, Supiano MA, Applegate WB, Berlowitz DR, Campbell RC, Chertow GM, et al. Intensive vs standard blood pressure control and cardiovascular disease