

treating resistant hypertension but one that acknowledges some uncertainty of outcomes benefit. Future outcome trials of MRAs, perhaps including finerenone,^{460–462} are encouraged in patients with hypertension.

Clinical outcome evidence from trials for other BP-lowering drug classes, such as alpha-blockers, hydralazine, minoxidil, other potassium-sparing diuretics, and centrally acting agents, is less compelling and caution regarding adverse effects is warranted. However, they may be a final addition if all other therapeutic efforts are insufficient to decrease BP. Of note, in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack (ALLHAT) trial, the alpha-blocker arm was stopped early due to futility of benefit for the CVD outcome.⁴⁶³

8.3.3. New therapies with blood pressure-lowering properties that await supportive evidence from cardiovascular outcomes trials prior to guideline endorsement and routine use in hypertension

A few other drug classes with indication in heart failure have emerged that also have BP-lowering properties. For example, the angiotensin receptor–neprilysin inhibitor (ARNi) sacubitril/valsartan, which was initially developed for hypertension,⁴⁶⁴ reduces CVD mortality and morbidity in patients with heart failure, an effect that may have been mediated, in part, by superior BP lowering compared with enalapril alone.^{465,466} In a *post hoc* subgroup analysis, sacubitril/valsartan lowered BP in adults with both heart failure with preserved ejection fraction (HFpEF) and resistant hypertension.⁴⁶⁷ In the context of research studies, sacubitril/valsartan has been used in higher doses (200 mg or 400 mg once daily) for treating hypertension.^{464,466,468,469}

SGLT2 inhibitors have shown favourable effects on CVD events and renal haemodynamics in patients with and without type 2 diabetes, and in heart failure trials.⁴⁷⁰ In these trials, SGLT2 inhibitors did lower BP, though only modestly.⁴⁷¹ Small trials among adults with hypertension have confirmed the potential for BP lowering with this drug class.^{472,473}

Other new drugs with preliminary data include GLP-1 agonists and the new non-steroidal MRAs, e.g. finerenone, in managing hypertension.^{415,460,461} In addition, novel aldosterone synthase inhibitors (baxdrostat and lorundrostat) have significantly lowered BP in patients with uncontrolled hypertension in phase 2 trials.^{474,475}

The dual endothelin-A and -B receptor antagonist apocritentan also reduced office and 24 h BP compared with placebo at 4 weeks in patients with resistant hypertension in a phase 3 trial.⁴⁷⁶ Zilebesiran, an investigational RNA interference agent administered subcutaneously, inhibits hepatic angiotensinogen synthesis and a single dose reduced 24 h BP over approximately 6 months.⁴⁷⁷

8.3.4. Drug combinations and up-titrating strategies

To treat hypertension, many patients will require more than one BP-lowering medication. Combining drugs from different drug classes can have additive or synergistic effects and lead to greater BP reduction than increasing the dose of one drug.^{478–483} The superior BP-lowering efficacy of combination therapy is mediated, at least in part, by the potential of combination therapy to target multiple pathophysiological pathways contributing to perturbed BP in each patient.⁴⁸⁴ A further benefit of combination therapy is the potential to use lower doses of each individual BP-lowering agent, which may reduce side effects and improve adherence and persistence,⁴⁸⁵ though the evidence for this hypothesis has been questioned.⁴⁸⁶

Upfront low-dose combination therapy is therefore recommended in persons with hypertension, with the potential advantages of fewer side effects and swifter BP control being important for long-term adherence.^{487–489} If combination BP-lowering therapy is pursued, single-pill combinations are preferred. For those with elevated BP who have

an indication for BP-lowering treatment, monotherapy is recommended in the first instance.

One caveat to combination therapy in hypertension is that patient-level response to individual BP-lowering drug classes can be heterogeneous (suggesting some patients may benefit from more personalized treatment compared with routine combinations).⁴⁹⁰ This is relevant also with respect to race/ethnicity (see Section 9). Another caveat is that the evidence for reduced CVD outcomes with BP-lowering drugs in combination therapy is based on observational studies.^{491–493} There are no outcomes data from prospective trials that prove superiority of upfront combination therapy (either as single-pill combinations or as separate pills) over upfront monotherapy in the isolated treatment of hypertension.⁴⁸⁶ Therefore, we considered giving upfront combination therapy (either as separate pills or as single-pill combinations) a Class IIa recommendation in these guidelines. However, given the totality of evidence for outcomes benefit in observational studies, randomized trial data for better BP control and adherence, and importantly, also given CVD outcomes benefit for polypills (a form of single-pill combination) in randomized trials,^{494–496} we chose to provide a Class I recommendation for upfront combination therapy in adults with confirmed hypertension, in agreement with 2018 ESC recommendations.

The major four drug classes (ACE inhibitors, ARBs, dihydropyridine CCBs, and thiazide or thiazide-like diuretics) are recommended as first-line BP-lowering medications, either alone or in combination.^{122,447,484,497} An exception is the combination of two RAS blockers, which is not recommended.^{498–500} For most hypertensive patients, a single-pill combination, initially containing two of these major drug classes, and initially at low dose, is recommended.^{489,501,502} Doses of BP-lowering drugs are presented in the [Supplementary data online, Tables S7 and S8](#).

When BP is still uncontrolled under maximally tolerated triple-combination (RAS blocker, CCB, and diuretic) therapy, and after adherence is assessed, the patient should be considered resistant and referred to an expert centre for appropriate work-up (see Section 7.5). At the same time, the addition of spironolactone should be considered.⁴⁵⁹ If spironolactone is not tolerated, eplerenone or other MRA, or beta-blockers (if not already indicated), should be considered. Eplerenone may need to be dosed higher (50–200 mg) for effective BP lowering. In a meta-analysis, eplerenone 25 mg did not lower BP.⁵⁰³ Due to the shorter time of action than spironolactone, eplerenone may need to be administered twice daily for treating hypertension. An alternative to MRA as fourth-line treatment for BP lowering is the use of beta-blockers for persons who do not already have a compelling indication. A vasodilating beta-blocker (e.g. labetalol, carvedilol, or nebivolol) is preferred when a beta-blocker is chosen.⁵⁰⁴ However, we note that the BP-lowering effects of beta-blockade appears to be less potent than spironolactone in the setting of resistant hypertension.⁴⁵⁹

Only thereafter should hydralazine, other potassium-sparing diuretics (amiloride and triamterene), centrally acting BP-lowering medications, or alpha-blockers be considered. Given multiple side-effects, minoxidil should only be considered if all other pharmacological agents prove ineffective in resistant hypertension.⁵⁰⁵

As noted above, polypills combining fixed doses of BP-lowering treatment, lipid-lowering therapy and, if indicated, aspirin are effective in more general CVD prevention.^{496,506–509} However, the polypill is not available for routine clinical use in many European countries.

8.3.5. A practical algorithm for intensive, effective, and tolerable blood pressure lowering with drug therapy, including considerations around single-pill combinations

The aim of the algorithm in [Figure 18](#) is to introduce a low-dose double- and then triple-combination strategy while monitoring tolerance