Treatment algorithms for hypertension: a practical approach



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Practice Points

- The majority of patients with hypertension will require more than one drug to reach their blood pressure (BP) goal, and combination therapy is recommended as a first-line therapy when BP is 20/10 mmHg above target, or in high-risk patients.
- Dual combinations are recommended as first-line treatment in patients less likely to achieve BP goal and those at particularly high cardiovascular risk. Guidelines emphasize that physicians should ensure dual treatment is administered at optimal doses.
- Patients who require triple therapy may have significant additional comorbidities; these should influence the careful selection of add-on therapies.
- If triple therapy is required, a renin–angiotensin system inhibitor with a calcium channel blocker and a thiazide diuretic is one rational combination, supported by clinical evidence.
- Although single-pill combinations of three different antihypertensive medications are emerging, offering convenience and reducing pill burden, they may not be suitable for all patients.
- The management of patients who need multiple therapies requires the balance of convenience against the clinical indications for specific drug classes.
- Patient-centered guidance for the use of antihypertensive combinations is needed, and future guidelines should offer clear and practical treatment algorithms to aid physicians in the selection of appropriate treatment regimens according to individual patient characteristics.

SUMMARY Renin–angiotensin system inhibitors, calcium channel blockers and diuretics are the mainstay of current antihypertensive therapy. Patient characteristics are likely to influence the individual response to these agents, although the majority of patients require dual therapy to meet blood pressure goals and some require triple therapy. Combination therapies offer effective blood pressure reductions, particularly when combining therapies

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with complementary modes of action, and may reduce side-effect burden. Typically, patients who require combination therapy will have comorbidities that influence the preferred antihypertensive class for their treatment. Single-pill combinations can offer practical benefits, but lack dose flexibility and may not comprise drug classes that are optimal for a specific patient. The management of patients who require multiple therapies, therefore, involves weighing the benefits of convenience against the need to select therapies based on a consideration of therapeutic indications.

It is widely accepted that hypertension is associated with very significant increases in cardiovascular (CV) and renal risk, and that effective blood pressure (BP) lowering reduces fatal and nonfatal CV events [1,2]. International guidelines strongly recommend target goals for office systolic BP (SBP)/diastolic BP (DBP) of <140/90 mmHg. In patients with an added risk of CV complications, such as diabetes, renal disease or for those with high CV risk associated with clinical conditions (e.g., stroke or myocardial infarction [MI]), current guidelines recommend a BP goal of <130/80 mmHg [1,3]. However, recent evidence suggests that, in patients with diabetes, a reduction below 130/80 mmHg confers no additional clinical benefit and, with the exception of diabetes patients at high risk of stroke, the more conservative target of 140/90 mmHg may be sufficient [4].

International hypertension guidelines favor three major classes of antihypertensive agents: renin-angiotensin system (RAS) blockers (comprising angiotensin-converting enzyme [ACE] inhibitors and angiotensin II receptor blockers [ARBs]), calcium channel blocker (CCBs) and diuretics for the treatment of hypertension. The direct renin inhibitors, although not included in major guidelines, are suggested as an alternative RAS inhibitor by the European Society of Hypertension (ESH) [5]. In addition to the three major classes, other antihypertensive agents such as β -blockers, aldosterone antagonists and mineralocorticoid-blocking agents (spironolactone and eplerenone) are also used [6,7]. These agents are used either as monotherapy or in combination therapy, although optimal reduction of BP requires combination therapy in most patients with hypertension. Importantly, the ESH/European Society of Cardiology, NICE (UK), Japanese Society for Hypertension and Canadian Hypertension Education Program guidelines generally do not stipulate which drug classes should be used universally as first-,

second- or third-line options, instead identifying those that are preferred in specific conditions and patient subtypes [2,5,8,201].

Practical treatment algorithms will enable practitioners in the selection of antihypertensive agents from the wide variety available, to provide the best possible treatment for their patients. This review will discuss the effect of patient comorbidities and other risk factors on the choice of antihypertensive therapy, with reference to existing treatment algorithms and clinical data. The particular focus will be on combination therapy, especially triple combination therapy, as it is patients who require multiple medications who are also most likely to have additional risk factors, and for whom the choice of therapy can be particularly problematic.

Selection of antihypertensive therapy in clinical practice

Monotherapy: effectiveness & selection based on clinical setting

In most regions and clinical settings, monotherapy is currently considered the first line of treatment, with combination therapy considered only after monotherapy fails. Monotherapy may provide BP reductions in the region of approximately 5–11/3–8 mmHg. However, only a limited number of patients achieve adequate BP control with monotherapy [1,9,10].

For uncomplicated hypertension without a clear indication for other drug choices, the Joint National Committee (JNC) guidelines from 2003 [1] favor the use of a thiazide/thiazide-like diuretic either alone or combined with drugs from other classes as first-line therapy. The more recent 2011 NICE guidelines suggest that a CCB should be considered as first-line therapy in older and black patients [11,201]. Where a CCB is contraindicated, it is suggested to offer a thiazide-like diuretic (such as chlorthalidone or indap-amide). These guidelines are likely to continue to evolve based on emerging evidence and new

compounds. Large meta-analyses indicate that the major antihypertensive drug classes (ACE inhibitors, ARBs, CCBs, diuretics and β-blockers) do not significantly differ in their overall BPlowering efficacy and may each be considered for the initiation of antihypertensive treatment [3,5]. Specific antihypertensive drugs may be favored depending on the clinical setting, since the different classes, and sometimes different agents within the class, have features that make them more or less suitable in older patients, in specific ethnicities or in patients with certain conditions [5,12,201]. This was summarized in the ESH/European Society of Cardiology Practice Guidelines 2007 (Box 1) [3]. Additionally, the contraindications for each class within specific clinical settings should be considered when selecting monotherapy [3]. Moreover, too much emphasis on a preferred first drug may not be meaningful, since most patients will require more than one drug for effective BP control [3,13].

Treatment discontinuation in antihypertensive monotherapy is high, with 41% of patients abandoning therapy within 1 year, with the number increasing to 50% after 5 years. Treatment adherence rates differ between the respective antihypertensive classes. The adherence rate is highest with ARBs followed by ACE inhibitors, CCBs, α -blockers, β -blockers and diuretics [14–18]. Poor adherence is inevitably a major determinant of poor BP control.

Initial monotherapy may fail to effectively address the cause of elevated BP in many patients since multiple mechanisms are involved in the pathogenesis of hypertension and pathophysiologic characteristics differ among individuals [19]. Effectiveness of monotherapy may be limited due to the stimulation of counter-regulatory mechanisms that compensate for the effect of a single agent on a particular pathophysiologic mechanism [20]. Furthermore, both effectiveness and adverse effects of most antihypertensives are dose dependent, and so increasing the dose of an agent typically increases the risk of side effects [21].

Combination therapy: when to consider it & which combinations?

Due to the aforementioned factors, including the complex pathophysiology underlying hypertension and the activation of compensatory mechanisms, control of BP is often better achieved with a combination of complementary antihypertensive agents than with monotherapy. In hypertensive

Box 1. Specific antihypertensive drugs may be favored in certain conditions.

Thiazide diuretics

- ISH (elderly)
- Heart failure
- Hypertension in black patients
- β-blockers
- Angina pectoris
- Post-MI
- Heart failure
- Tachyarrhythmias
- Glaucoma
- Pregnancy
- Calcium antagonists (dihydropyridines)

ISH (elderly)

- Angina pectoris
- LVH
- Carotid/coronary atherosclerosis
- Pregnancy
- Hypertension in blacks

Calcium antagonists (verapamil/diltiazem)

- Angina pectoris
- Carotid atherosclerosis
- Supraventricular tachycardia

ACE inhibitors

- Heart failure
- LVD
- Post-MI
- Diabetic nephropathy
- Nondiabetic nephropathy
- LVH
- Carotid atherosclerosis
- Proteinuria/microalbuminuria
- AF
 - Metabolic syndrome

Angiotensin receptor antagonists

- Heart failure
- Post-MI
 - Diabetic nephropathy
- Proteinuria/microalbuminuria
- LVH
- AF
- Metabolic syndrome
- ACE inhibitor-induced cough
- **Diuretics (anti-aldosterone)**
- Heart failure
- Post-MI
- Loop diuretics

ESRD

Heart failure

ACE: Angiotensin-converting enzyme; AF: Atrial fibrillation; ESRD: End-stage renal disease; ISH: Isolated systolic hypertension; LVD: Left ventricular dysfunction; LVH: Left ventricular hypertrophy; MI: Myocardial infarction. Reproduced with permission from [3]. patients who are poorly controlled by low-dose monotherapy, low-dose combination therapy is a more rational therapeutic strategy than high-dose monotherapy [9,22]. For example, it has been estimated that the additional BP reduction achieved by combining drugs from two different and complementary classes is approximately fivefold that of doubling the standard dose of one drug [23]. When an appropriate combination is selected, there may certainly be an additive effect.

Current guidelines acknowledge that the majority of patients will require more than one drug to successfully achieve their BP goal [1,3,5,24]. Accordingly, they recommend that two-drug combinations are considered as firstline treatment in patients who have a high initial BP markedly above the hypertension threshold (e.g., 20/10 mmHg above target) and are therefore less likely to achieve target BP, or in those who are classified as being at high/very high CV risk due to the presence of organ damage, diabetes, renal disease or a history of CV disease [2,5]. The early use of combination therapy in such patients may help them to achieve their BP goal more promptly and allows protective effects to manifest as soon as possible [5]. Early treatment success could also motivate both the patient and the physician and help to improve treatment compliance and adherence. The current European guidelines feature a helpful decision algorithm for selecting a strategy based on combination therapy versus one based on monotherapy [3,5].

In chronic conditions that require life-long treatment, such as hypertension, treatment adherence is crucial, but may be compromised by medication side effects and dosing complexity [25]. A low-dose combination of two different agents may reduce dose-related adverse events [2,20,21,26-29], which could in turn improve treatment adherence. Furthermore, the potential for one agent to offset some of the deleterious effects of the other is a useful phenomenon. For example, the risk for peripheral edema associated with CCB monotherapy may be reduced by adding on a RAS blocker [30-33]. Single-pill combinations (SPCs) help to simplify the treatment schedule, reducing the pill burden and favoring compliance still further [3,5,34].

Selecting an appropriate dual combination therapy

A number of suitable combinations between the classes of antihypertensive drugs are available

(Figure 1) [3,15]. Two antihypertensive agents of the same class should not be given simultaneously, instead two complementary drugs should be selected [12]. Since RAS blockade is effective in combination with CCB and thiazide diuretics, SPCs to treat hypertension typically include a RAS inhibitor with either a CCB or diuretic. Diuretics or CCBs appear to have an additive BPreducing effect in combination with most other antihypertensive agents [12]. Choosing a diuretic for add-on therapy may be desirable in patients who require volume depletion (e.g., in those with reduced estimated glomerular filtration rate [eGFR]), or in individuals in whom edema is a major barrier to tolerability. The selection of a suitable diuretic will be discussed later in more detail.

Dual therapy using an ACE inhibitor combined with a CCB is associated with a reduction in CV events, as demonstrated by the ACCOMPLISH and ASCOT studies [35-38]. In the context of chronic kidney disease (CKD), a RAS/CCB combination also slowed progression of nephropathy to a greater extent than RAS/diuretic [35,36,38]. Combination of RAS blockade with a CCB is therefore a strong candidate for dual therapy in patients at high CV and renal risk. Although amlodipine has been the most commonly used CCB in combination therapy, other CCBs such as lercanidipine [39-41] and manedipine [42-46] in combination with ACE inhibitors or ARBs have also been shown to provide additional BP lowering and benefits beyond BP lowering. The combination of an ACE inhibitor plus a diuretic, compared with ACE inhibitor alone, provides greater BP reductions and may have a greater preventive effect on stroke [47].

Combining an ARB with a diuretic or CCB also provides an effective reduction of BP and a high rate of BP control in a variety of clinical settings. The use of an ARB (e.g., telmisartan, valsartan or olmesartan) in combination with a CCB (amlodipine) provides superior BP reduction compared with full-dose monotherapy with the CCB alone, including in high-risk patients and those with severe hypertension [27,48-51]. The combination of an ARB plus a CCB has demonstrated efficacy in a wide range of patients with moderate-to-severe hypertension, in older patients and in those at added risk (e.g., diabetes, obesity or renal impairment) [52-56]. This dual combination has good tolerability with a reduced risk of peripheral edema compared



Figure 1. Possible combinations of classes of antihypertensive agents, as supported by 2007 European guidelines and recent clinical trial evidence. The thick lines indicate preferred combinations in the general hypertensive population. Dashed lines indicate combinations also shown to be beneficial in controlled intervention trials.

ACE: Angiotensin-converting enzyme; ARB: Angiotensin II receptor blocker; CCB: Calcium channel blocker.

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with CCB monotherapy and a low incidence of cough compared with ACE inhibitor combinations [51,57-61]. The combination of an ARB plus a diuretic, compared with ARB alone, provides significantly greater BP reductions, and is effective and well tolerated in a broad spectrum of patients with mild to severe hypertension [62-66].

Less commonly used dual combinations include the combination of CCB with a diuretic, which provides greater BP reductions than increasing the dose of a CCB as monotherapy [23,67]. The dual combination of an ACE inhibitor plus an ARB is not recommended for general use; although this combination may decrease proteinuria in patients with diabetes or renal disease, this is not necessarily accompanied by a decline in renal or CV end points and this combination may increase serious side effects [5,8,68,69]. In the ALTITUDE study, patients taking aliskiren 300 mg added to a background ACE inhibitor or ARB experienced an increased incidence of nonfatal stroke, renal complications, hyperkalemia and hypotension during 18-24 months of follow-up, leading to early termination of the study [70,71]. Consequently, dual aliskiren with ACE inhibitor/ARB therapy

is now contraindicated in patients with diabetes and should be avoided in patients with moderate renal impairment (GFR <60 ml/min) [202].

• Considerations for triple/multiple combination therapy

Although the majority of hypertensive patients achieve BP control with monotherapy or dual combination therapy, some patients need three or more antihypertensive drugs to achieve effective BP control [3,5,35,72,73]. There was, however, relatively scant advice to encompass triple combination therapy in the 2007 European Guidelines or the Seventh Report of the JNC on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) [1-3]; however, the revised European guidelines of 2009 recommend a RAS inhibitor, a calcium antagonist and a thiazide diuretic as a rational three-drug combination [5,72]. The recent NICE guidelines emphasize the importance of reviewing medication to ensure that two-drug treatment is at optimal doses, but if treatment with three drugs is required, the combination of a RAS inhibitor plus a CCB and thiazide diuretic is also recommended [201].

The STITCH algorithm, reviewed by Epstein [29], guides the physician through the decisions that need to be made for the individual patient (Figure 2). If a diuretic is already being used in dual therapy, a calcium antagonist may be added if triple therapy is required. Clinical trials have demonstrated a beneficial effect with triple therapy of a RAS inhibitor, calcium antagonist and a diuretic; for example, in the TRINITY study [29,73–77]. Triple combination regimens

have demonstrated clinically relevant increases in BP goal attainment and BP control compared with dual therapies, where BP targets had not previously been reached [73].

A number of triple SPCs are emerging; some that have received recent approval for hypertension in patients who have not responded to initial therapy include: valsartan/amlodipine/ hydrochlorothiazide (HCTZ) [73,75,76,78]; olmesartan/amlodipine/HCTZ [73]; and aliskiren/



Figure 2. A proposed algorithm to guide selection of antihypertensive therapy for patients with stage 2 hypertension or stage 1 hypertension warranting combination therapy. CV events include coronary artery disease and metabolic syndrome.

BP: Blood pressure; CCB: Calcium channel blocker; CV: Cardiovascular events; RAS: Renin–angiotensin system.

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amlodipine/HCTZ. Triple SPC therapy can provide the benefits of three drugs with complementary modes of action, plus simplification of the regimen, leading to a reduced pill burden and improved adherence. Triple SPCs may increase the rate of side effects such as dizziness, but may produce less peripheral edema compared with dual therapies [75,76]. There are some disadvantages to a single-pill dosing of triple combination therapy, including an inevitable lack of dose flexibility and an increased risk of dose-independent drug-drug interactions [28,29,74,78-80].

Considerations in choice of third antihypertensive drug

For patients receiving dual therapy with two vasodilator drugs, such as a RAS inhibitor plus a CCB, the typical third agent of choice would be a thiazide diuretic [81]. In patients in whom one of these drug classes is contraindicated, alternative configurations may include β -blockers or other diuretics.

The pivotal registration trial for valsartan/ amlodipine/HCTZ, which was a randomized, double-blind, 8-week study in 2271 patients with moderate-to-severe hypertension (mean SBP $\geq 145 \text{ mmHg}$; mean DBP $\geq 100 \text{ mmHg}$), showed that SBP/DBP reduction was greater with triple combination (-39.7/-24.7 mmHg) than any dual combination (valsartan/HCTZ: -32.0/-19.7 mmHg; amlodipine/valsartan: -33.5/-21.5 mmHg; amlodipine/HCTZ: -31.5/-19.5 mmHg), although a number of patients still failed to reach BP control [74]. At the end of the study, 70.8% of patients in the triple combination group achieved BP control (<140/90 mmHg). Previous authors have argued that this could highlight those patients, approximately 30% in this study, with resistant hypertension (i.e., the inability to achieve BP <140/90 mmHg or <130/80 mmHg in patients with CV or CKD) [78].

The VALUE study, in which 15,245 patients were randomized to stepwise treatment with valsartan 80–160 mg/day or amlodipine 5–10 mg/day plus HCTZ 12.5–25 mg/day plus other antihypertensive treatment as needed, showed that BP reduction and stroke risk was greater with amlodipine-based than valsartanbased regimens during the first 3 months [82]. After the addition of HCTZ plus other antihypertensive medications, there was no significant difference in stroke rate between the two groups. However, Black has queried the design of this trial for supporting the triple-dose combination, emphasizing the need for closer examination of SBP [28]. Furthermore, the 25-mg/day dose of HCTZ was not maximal in either valsartan study [74,82], leading to arguments about the degree of resistant hypertension versus inadequate dosing. Manidipine added as the third drug to a RAS inhibitor plus a low dose of diuretic was observed to significantly reduce BP, improve renal function, reduce microalbuminuria and have favorable effects on the lipid and glucose profiles in uncontrolled hypertensive patients with Type 2 diabetes [83]. Triple-combination treatment with olmesartan/amlodipine/HCTZ was observed to provide greater BP reductions than dual-combination treatments, regardless of race [84-86].

While HCTZ is the common choice as the third agent, other types of diuretics may be more appropriate for some patients, including the thiazide-like diuretics, indapamide and chlorthalidone [87,88] or aldosterone antagonists (potassium-sparing diuretics, such as spironolactone). Thiazide and thiazide-like diuretics should be considered when edema or congestive heart failure is present, and are most effective in older patients and black patients [12,89,90]. Thiazide diuretics are effective in the presence of obesity or diabetes mellitus and may decrease the risk of CV events in patients with pre-existing diabetes mellitus [12,91]. However, thiazide diuretics have been associated with an increased risk of new-onset diabetes, and so should be used with caution, close monitoring and possibly in combination with a RAS inhibitor, in patients who are at high risk for developing diabetes mellitus [13]. Thiazide diuretics at doses higher than 25 mg/day are also associated with an increased risk of hyperuricemia and gout [92-95]. Thiazide diuretics are not effective when eGFR is less than 30 ml/min; in such patients, a more potent thiazide-like diuretic, such as indapamide, may be preferred [12]. Loop diuretics (e.g., furosemide) have a short duration of action but are more suitable for use in the presence of CKD and an eGFR <30 ml/min/1.73 m²[96]. In patients with normal renal function, loop diuretics are less effective than thiazide diuretics [12]. Potassiumsparing diuretics should be used with caution in the presence of renal failure, or in combination with RAS inhibitors or direct renin-inhibitors, due to the increased risk of hyperkalemia.

Patients who need triple antihypertensive therapy may have significant additional comorbidities, such as renal disease [2]. In the presence of concomitant medical conditions, the patient's individual characteristics should influence the careful choice of the third drug, because a triple combination of a RAS blocker with a CCB and thiazide diuretic may not be appropriate [72]. Although many guidelines do not address the issue of triple combinations in detail, the compelling indications for the selection of monotherapy classes provide useful guidance for shaping an appropriate combination therapy (Box 1) [3].

Selective endothelin-A receptor antagonists used as the third agent may confer benefits in patients with CKD. A recent study of 22 patients with CKD showed that BQ-123 (a selective endothelin-A receptor antagonist) significantly reduced proteinuria compared with active placebo (-26/-4%; p < 0.01) [97]. In clinical trials, the administration of selective endothelin-A receptor antagonists was occasionally associated with an increase in heart rate [98], marked elevation of liver enzymes in patients with chronic heart failure [99] and edema, which may be limited by combining with diuretics [100].

In patients with heart failure, previous MI or angina, β -blockers may be an appropriate choice as the third agent [3], since they may help to reduce recurrent MI and mortality through protective actions on the ischemic myocardial tissue and antiarrhythmic properties [101]. CCBs, on the other hand, should be avoided in patients with congestive heart failure unless they are required to control the symptoms of angina [3,5,102].

The choice of the third antihypertensive agent should also take into account factors such as age. For example, isolated systolic hypertension and atrial fibrillation are common in elderly patients and may warrant special consideration. Nondihydropyridine CCBs (verapamil and diltiazem) and β -blockers may help to control ventricular rate [3]. Additionally, α -blockers have a specific indication in the presence of benign prostatic hyperplasia [3].

The NICE 2011 guidelines advise that, in patients with resistant hypertension, if a fourth drug is needed, then further diuretic therapy with low-dose spironolactone (25 mg once a day) should be considered if blood potassium levels are <4.5 mmol/l and eGFR is >60 ml/min/1.73 m² [201]. In a study of 304 patients whose baseline

BP was 158/89 mmHg despite treatment, the addition of spironolactone further reduced the BP by 24.1/9.2 mmHg [103]. Resistant hypertension is commonly linked to hyperaldosteronism [104]. In fact, primary aldosteronism may be an underestimated culprit, affecting around 20% of patients with resistant hypertension [105]. For patients with primary aldosteronism or severe secondary aldosteronism, especially in heart failure, spironolactone and eplerenone (either with or without a thiazide-type diuretic) may be an appropriate component of combination therapy to address this issue [6,12,106,107]. When blood potassium levels are higher than 4.5 mmol/l, the NICE guidelines recommend a higher-dose thiazide-like diuretic treatment as a fourth option (e.g., indapamide). If further diuretic therapy as a fourth drug for treating resistant hypertension is not tolerated, contraindicated or ineffective, an α - or β -blocker may be appropriate [201]. Renal sympathetic denervation is an interventional minimally invasive procedure that has, in recent years, been shown to be effective in reducing BP in treatment refractory patients who do not reach sufficient BP control despite antihypertensive combination therapy of significant duration [108,109].

Conclusion

The vast majority of patients with hypertension will require combination therapy to meet target BP goals. The use of a RAS inhibitor and either a CCB or a diuretic has become a popular strategy for dual combination therapy since they are likely to offer beneficial CV and renal protective effects in addition to reductions in BP, and this is reflected in the international guidelines. These combinations demonstrate superior efficacy to the individual agents alone, and can circumvent the side effects associated with using high-dose monotherapy. SPCs are available in a range of dual-agent combinations, which can help to reduce the pill burden and are therefore of value in increasing adherence.

A smaller proportion of patients require three or more antihypertensive agents to achieve successful BP control. However, these patients typically have existing comorbidities in addition to resistant hypertension, and so the selection of addon agents should be carefully considered. When necessitated, triple therapy typically includes a diuretic with two vasodilating drugs (e.g., RAS inhibitor and a CCB) but the composition of therapy should be tailored to the individual. Currently available triple SPCs (combining a RAS blocker with a CCB and a thiazide diuretic) are useful for many patients, but may not be optimal for the safe and efficacious treatment of all patients with hypertension resistant to treatment with dual therapy. Optimal management of patients who need multiple therapies therefore requires the physician to weigh the benefits of convenience with SPCs against indications for specific drug classes on the basis of therapeutic indications.

Future perspective

The majority of patients with hypertension will require more than one drug to reach their BP goal, and combination therapy is recommended as first-line therapy when BP is 20/10 mmHg above target, or in high-risk patients. More frequently in clinical practice, hypertensive patients have additional CV risk factors. Furthermore, the global prevalence of diabetes and obesity is rising, and so this situation is predicted to worsen. Patient-centered guidance for the use of antihypertensive combinations is needed, and

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future guidelines should offer clear and practical treatment algorithms to aid physicians in the selection of appropriate treatment regimens according to individual patient characteristics.

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