

The 2018 European guidelines: tailoring treatment to new hypertension goals

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Abstract: The 2018 European hypertension guidelines recognize poor patient adherence, physician inertia, and secondary hypertension as main causes of unsatisfactory blood pressure (BP) control. While the definition and classification of hypertension remained unchanged, the blood pressure targets are more stringent. The guidelines recommend preferred use of two-drug combination therapy for the initial treatment of most patients and the preferred use of single-pill combination (SPC) therapy in hypertension management. The new strategy is based on simplified drug treatment algorithms, with the preferred use of an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) combined with a calcium channel blocker (CCB) or/and diuretic as the core treatment strategy for most patients, with β -blockers used for specific indications. Despite the increased efficacy provided by combining agents from two different classes, more than 20% of patients do not achieve BP goals even with two-agent SPCs, and require the use of a three-drug SPC comprising an RAS blocker + CCB + diuretic. Ideal core components of the SPC should be tailored to both the clinical condition and the patient's age, necessitating combinations of several drugs as double and triple SPCs. Furthermore, these combinations need to be supported by randomized clinical trials. The perindopril-based family of SPCs (dual combinations with indapamide, amlodipine, or bisoprolol, and triple combinations of perindopril, amlodipine, and indapamide) offer a wide range of opportunities to individualize treatment and control blood pressure with one tablet in the vast majority of our patients. ■ *Heart Metab.* 2019;79:15-19

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Introduction

Despite enormous progress in cardiovascular pharmacotherapy and well-documented benefits of blood-pressure lowering,^{1,2} the management of hypertension remains challenging and blood pressure control is far from satisfactory.^{3,4} After the publication of the 2013 European

guidelines,⁵ several important clinical studies gave us new insights into critical aspects of hypertension management, including blood pressure goals and the benefits of combination treatment. These issues were addressed in the 2018 guidelines,⁶ which identified key barriers in hypertension management, lowered BP targets, and proposed novel treatment strategies.

Key barriers to success

The 2018 guidelines recognize poor patient adherence, physician inertia, and secondary hypertension as main causes of unsatisfactory BP control.

Patient adherence

Low adherence to the prescribed medications can concern up to 50% of patients with apparently resistant hypertension,⁷ and has been consistently linked to higher risk of cardiovascular events.⁸ Early recognition of poor adherence to treatment might reduce the number of costly investigations and procedures, including interventional treatment.⁹ Nonadherence is related to several factors including the fact that hypertension is chronic and generally symptom-free, the side effects associated with certain drugs, pill burden, and the complexity of some treatment regimens.⁷ There is a close inverse relationship between compliance and pill burden; compliance decreases as the number of daily doses increases.¹⁰ Importantly, patient adherence can be improved by an appropriate therapeutic and follow-up regimen.¹¹

Physician inertia

There is overwhelming evidence that failure to diagnose hypertension or to reveal uncontrolled treated hypertension (diagnostic inertia) and failure to initiate or escalate treatment (therapeutic inertia) contribute to poor BP control.¹² An important factor that plays a role in the suboptimal rate of BP control is the frequent utilization of monotherapy. It has been well demonstrated that combination of two drugs from different classes with complementary mechanisms of action provides greater BP-lowering efficacy, compared with increasing the dose of monotherapy.^{13,14} Combination therapy has been estimated to have an additional BP-lowering efficacy, approximately five times greater than that obtained by doubling the dose of monotherapy.

Secondary hypertension

If inadequate control of BP is confirmed by the out-of-the office measurement, and nonadherence is ruled out, patients should be screened for a secondary cause of hypertension, especially primary aldoste-

ronism and renal artery stenosis. The new guidelines stress that early detection of secondary causes of hypertension is important because interventions may be curative or at least improve blood pressure control.

2018 guidelines: unchanged definition, but lower blood pressure targets

The 2018 guidelines reaffirmed the validity of the previous hypertension definition and classification. Hypertension is defined as office SBP values ≥ 140 mm Hg, and/or diastolic BP (DBP) values ≥ 90 mm Hg. The same definition and three-grade classification are used in younger, middle-aged, and older subjects.

The 2013 hypertension guidelines recommended an office BP treatment target of $<140/90$ mm Hg, regardless of the number of risk factors, comorbidities and level of CV risk. The 2018 Task Force recommends that when BP-lowering drugs are initiated, the first objective should be to lower BP to $<140/90$ mm Hg in all patients. However, if the treatment is well tolerated, treated BP values should be targeted to $130/80$ mm Hg or—in subjects younger than 65—lower to values between 120 and 130 mm Hg. The optimal treated DBP range is between 70 and 80 mm Hg. Importantly, the new recommendations stress that BP control should be achieved within 3 months.

New strategy – central place of SPCs

More stringent BP targets make achievement of BP control more challenging. Consequently, our approach to hypertension management had to be changed. The 2018 ESH/ESC guidelines presented a new SPC treatment strategy (*Figure 1*) to improve BP control including: (i) preferred use of two-drug combination therapy for the initial treatment of most people with hypertension; (ii) the preferred use SPC therapy for most patients; (iii) simplified drug-treatment algorithms with the preferred use of an ACE inhibitor or ARB combined with a CCB or/and diuretic as the core treatment strategy for most patients, with β -blockers used for specific indications.

The major differences between the 2013 and 2018 guidelines are summarized in *Table 1*. The 2013 guidelines recommended that low-dose combination therapy be used as a first-line treatment only in patients with marked BP elevation (grades 2 and 3) and high/very high CV risk, but not in grade 1 hyperten-

sion. Furthermore, the level of recommendation for SPC use was weak (class IIb “might be considered”).

The new guidelines recommend (class I) the initiation of treatment with a SPC comprising two drugs in most patients in order to improve the speed, efficiency, and predictability of BP control. While the preferred two-drug combinations are an RAS blocker with a CCB or a diuretic, a β -blocker in combination is an alternative when there is a specific indication for its use, such as angina, in the first year post-myocardial infarction, heart failure with an ejection fraction <40%, or heart-rate control.

Thus, initial therapy for most patients with hypertension should be with a combination of two drugs, not a single drug. The only exception would be in a limited number of low-risk patients with stage 1 hypertension whose SBP is <150 mm Hg or older, especially frail, patients, in whom more gentle reduction of BP may be desirable.

Despite the increased efficacy provided by combining agents from two different classes, more than 20% of patients do not achieve BP goals with two-agent SPCs and require the use of a three-drug SPC comprising an RAS blocker + CCB + diuretic (Figure 1–step 2).

RAS blockade is a cornerstone of combination therapy. Importantly, increasing the dosages of ACEIs and ARBs appears to have a less marked effect on adverse events in comparison to CCBs, diuretics and β -blockers.¹⁵ Therefore, the use of RAS blocker combinations is logical because these agents can be

used at higher doses in combination therapy without increasing treatment-related adverse events.

As outlined above, there are several reasons explaining the dominant position of SPCs in management of hypertension such as faster and better BP control, less variability in response, safety, and better tolerability and better adherence to therapy. In other words, SPCs in hypertension management meet the challenge, takes into account the human factors, and minimizes the risk of treatment failure.

Looking for optimal SPCs

Ideal core components of SPCs should be useful in various clinical conditions and in different age groups, available in combination with several drugs in double and triple SPCs, and supported by randomized clinical trials (evidence-based medicine).

The perindopril-based family of SPCs (dual combinations with amlodipine, indapamide or bisoprolol, and triple combination of perindopril, amlodipine,

	2013 guidelines ⁵	2018 guidelines ⁶
Initial combination therapy in stage 1	Not recommended	Strong recommendation (class I)
Initial combination therapy in stages 2 and 3	Weak recommendation (class IIb)	Strong recommendation (class I)
SPC preferential use	Weak recommendation (class IIb)	Strong recommendation (class I)

Table 1 Positioning of combination therapy in 2013 and 2018 European hypertension guidelines.

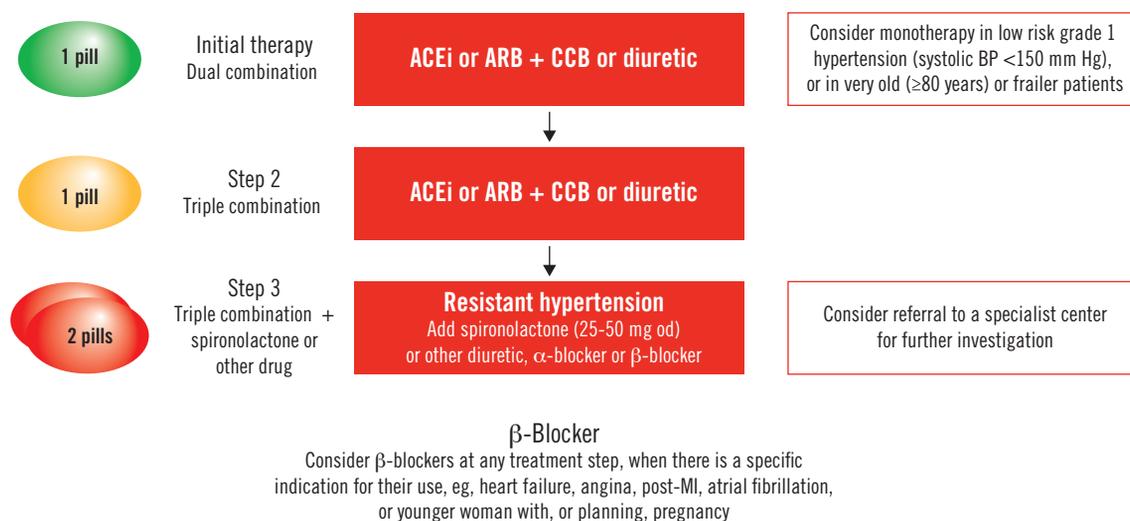


Figure 1 Core drug treatment strategy for uncomplicated hypertension according to the 2018 ESC/ESH hypertension guidelines.⁶ ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; HMOD, hypertension-mediated organ damage; MI, myocardial infarction; o.d., once daily; PAD, peripheral artery disease

and indapamide) offer opportunities to individualize treatment and control blood pressure with one tablet in the vast majority of our patients.

Among ACE inhibitors, perindopril (used as monotherapy or in combination) has strong evidence of cardiovascular protection in different clinical high-risk conditions including hypertension (ASCOT-BPLA study),¹⁶ diabetes (ADVANCE trial),¹⁷ coronary artery disease (EUROPA trial),¹⁸ post-stroke patients (PROGRESS¹⁹) and hypertension in the very elderly (HYVET).²⁰ Importantly, treatment with perindopril, in contrast to the ARBs, results in a significant further reduction in all-cause mortality.^{21,22}

The new guidelines⁶ stress that most randomized clinical trials demonstrating the benefits of CCBs in outcomes have used dihydropyridines (especially amlodipine). Finally, there is growing evidence²³ that the long-term risk:benefit ratio of thiazide-like diuretics, such as indapamide, is more favorable than that of thiazides.

Putting guidelines into practice

There is a clear-cut gap between the potential of modern antihypertensive therapy and actual blood pressure control in real life. Therefore, the guidelines identify interventions that may facilitate drug adherence and consequently improve prevention of hypertension-mediated cardiovascular events. Key interventions include counselling and empowerment of the patient, motivational strategies, self-monitoring of BP, and accessibility to drugs including reimbursement of SPC pills.

For many years SPCs were considered an option in hypertension treatment. In 2019, routine SPC use, including initiation of treatment, is becoming a new standard of hypertension management replacing the previous strategy. In accordance with the new European guidelines,⁶ SPCs based upon RAS blockers have the greatest potential to deliver strong antihypertensive efficacy with excellent tolerability, improve compliance through reduced pill burden, and provide optimal cardiovascular protection. ■

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