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REVIEW ARTICLE

Achieving Goal Blood Pressure

Stéphane Laurent[1]

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Abstract Both monotherapy and combination therapy options are appropriate for antihypertensive therapy according to the 2013 European Society of Hypertension (ESH)/European Society of Cardiology (ESC) guidelines. Most patients require more than one agent to achieve blood pressure (BP) control, and adding a second agent is more effective than doubling the dose of existing therapy. The addition of a third agent may be required to achieve adequate BP reductions in some patients. Single-pill fixed-dose combinations (FDCs) allow multiple-drug regimens to be delivered without any negative impact on patient compliance or persistence with therapy. FDCs also have documented beneficial clinical effects and use of FDCs containing two or three agents is recommended by the 2013 ESH/ESC guidelines.

Keywords Hypertension · Angiotensin II receptor antagonist · Combination therapy · Organ damage

1 Introduction

The 2013 ESH/European Society of Cardiology (ESC) guidelines state that monotherapy and combination therapy can be used as appropriate and propose the treatment algorithm shown in Fig. 1 [1]. The first step in pharmacological therapy is the choice of antihypertensive drugs. Diuretics, β-blockers, calcium channel blockers (CCBs), angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs) are all suitable and recommended [1]. Clinical trials show that the majority of patients require at least two agents to achieve goal BP and that two drugs are five times more effective than one [2–4]. It is important to note that, for the major drug classes, the incremental effect of doubling the monotherapy dose on systolic BP (SBP) is only about 20 % of that achieved by adding a drug from another class [5]. As a result, the use of combination therapy has been recommended by guidelines since 2003. In addition to efficacy gains, some combinations can also reduce drug-related side effects, such as CCB-induced ankle oedema [6, 7], and are recommended by ESH/ESC 2013 guidelines. In a randomised, double-blind, parallel group, multicentre study, adding olmesartan (OLM) to amlodipine (AML) significantly improved antihypertensive efficacy in patients with an inadequate response to monotherapy (Fig. 2) [8].

2 Strategies to improve adherence

When needed, efficacy can be improved by adding a third agent to a two-drug combination regimen [9]. A triple combination therapy, with hydrochlorothiazide (HCTZ) added to OLM/AML, was evaluated in a randomised, double-blind, parallel group, multicentre study, and was superior to the two-drug combination across a range of doses (Fig. 3) [10]. More recently, the BP-CRUSH study, a multicentre, prospective, open-label, single-arm, dose-titration trial, showed that nearly all patients achieved BP <140/90 mmHg with stepwise OLM/AML/HCTZ therapy [11].

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✉ Stéphane Laurent
stephane.laurent@egp.aphp.fr

[1] Department of Pharmacology, Hôpital Européen Georges Pompidou, INSERM U 970 and Paris Descartes University, Paris, France

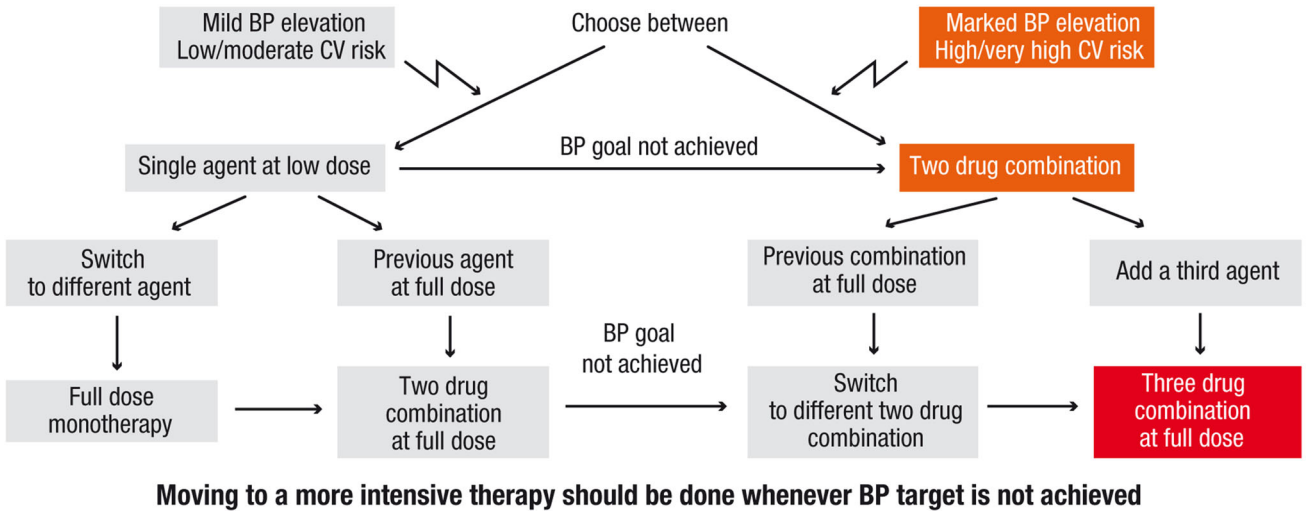

Fig. 1 Hypertension treatment algorithm (modified from Mancia et al. [1])

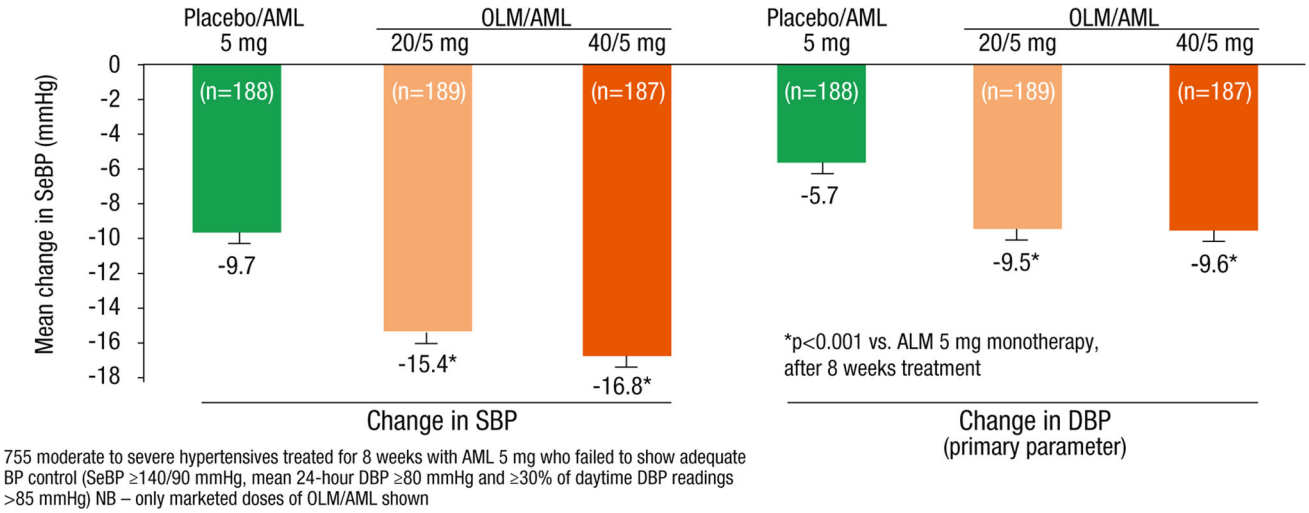

Fig. 2 Blood pressure reduction with amlodipine (AML) alone and in combination with olmesartan (OLM) (modified from Volpe et al. [8])

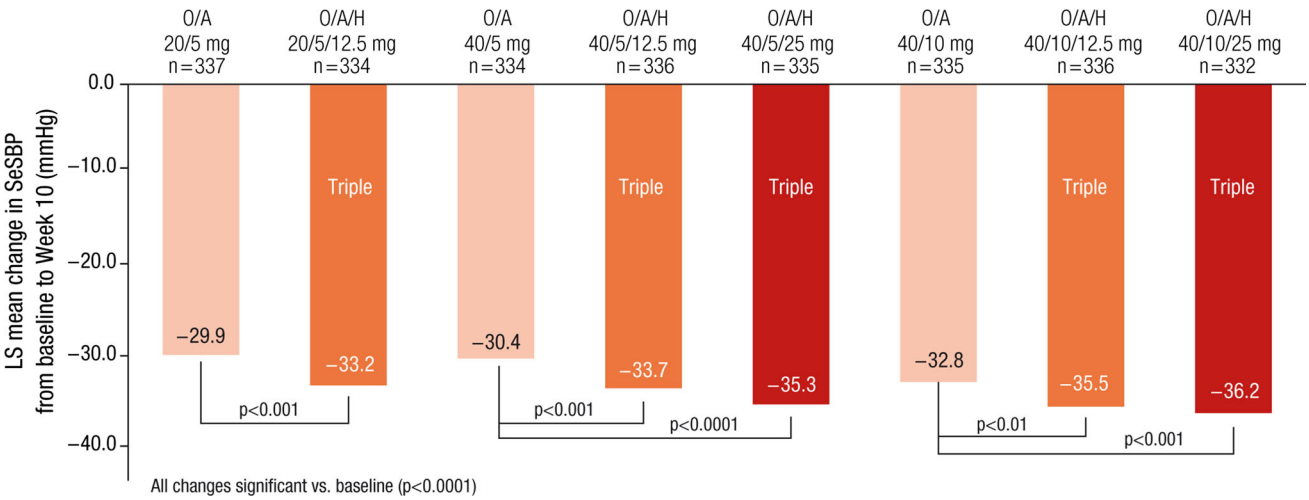

Fig. 3 Blood pressure reductions during treatment with olmesartan (O)/amlodipine (A) alone and with the addition of hydrochlorothiazide (H) (modified from Volpe et al. [10])

Table 1 ARB-based strategy: treatment algorithm for patients with HTN and specific risk factors and subclinical (A) or overt (B) organ damage (reproduced with permission from Volpe et al. [22])

A: Risk factor/subclinical organ damage	Grade 1 SBP 140–159 or DBP 90–99	Grade 2 SBP 160–179 or DBP 100–109	Grade 3 SBP ≥180 or DBP ≥110
No risk factors	OLM 10–20 mg	OLM/AML 20/5 mg[a,b]	OLM/AML 20–40/10 mg[a,b]
		OLM/HCTZ 20/12.5 mg[a,b]	OLM/HCTZ 20–40/25 mg[a,b]
Dyslipidaemia, hyperuricemia, obesity, or metabolic syndrome	OLM 10–20 mg	OLM/AML 20/5 mg[a]	OLM/AML 20–40/5–10 mg[a]
Fit elderly, <80 years old	OLM 10–20 mg if well-tolerated	OLM/HCTZ 20/12.5 mg[a]	OLM/HCTZ 20–40/25 mg[a]
Frail elderly, >80 years old, SBP >160[c]	Consider OLM 10–20 mg	OLM/HCTZ 10–20/12.5 mg[a]	OLM/HCTZ 20–40/25 mg[a]
Atherosclerosis, arteriosclerosis, or PAD[d,e]	Consider OLM 10–20 mg	OLM/AML 20–40/5 mg	OLM/AML 20–40/10 mg
LV hypertrophy	OLM 20–40 mg	OLM/HCTZ 20–40/12.5 mg[a]	OLM/HCTZ 20–40/25 mg[a]
Microalbuminuria/proteinuria (CKD stage <3)[f]	OLM 20–40 mg[g]	OLM/AML 40/5 mg[g]	OLM/AML 40/10 mg[g]
Diabetes[h]	OLM 20–40 mg	OLM/AML 40/5 mg[a]	OLM/AML 40/10 mg[a]
B: Overt organ damage	**Grade 1 SBP 140–159 or DBP 90–99**	**Grade 2 SBP 160–179 or DBP 100–109**	**Grade 3 SBP ≥180 or DBP ≥110**
Atrial fibrillation[i]	OLM 20–40 mg	OLM/HCTZ 20–40/12.5 mg	OLM/HCTZ 20–40/25 mg
Nephropathy (CKD stage >3)[j] eGFR <30 ml/min/1.73 m^2	OLM 20–40 mg[o,p]	OLM/AML 40/5 mg[o,p]	OLM/AML 40/10 mg[o,p]
Coronary artery disease[k]	OLM 10–20 mg	OLM/AML 20–40/5 mg[l]	OLM/AML 40/10 mg[l]
Previous stroke or transient ischemic attack[m]	OLM 10–20 mg	OLM/AML 20–40/5 mg[l]	OLM/AML 40/10 mg[l]
Heart failure with reduced EF[n]	OLM/HCTZ 10–20/12.5 mg[q]	OLM/HCTZ 20–40/25 mg[l,q]	OLM/HCTZ 40/25 mg[l,q]

Patients continue to receive treatment for underlying conditions according to guidelines. Avoid dual RAS therapy. Change therapy if ineffective or not tolerated

AML amlodipine, *HCTZ* hydrochlorothiazide, *LVEF* left ventricular ejection fraction, *OLM* olmesartan medoxomil

[a] Consider single-pill triple combination if BP is not at target

[b] Use HCTZ in elderly patients or AML in young patients

[c] In patients >80 years, consider a systolic BP target of 150 mmHg; continue therapy only if well-tolerated, monitor for postural hypotension

[d] ESC Guidelines on the diagnosis and treatment of peripheral artery diseases

[e] Calcium channel blockers and ACE-inhibitors are recommended in the ESH/ESC 2013 Guidelines for the management of arterial hypertension if carotid atherosclerosis is present

[f] European Renal Best Practice (ERBP) position statement on Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for the Management of Blood Pressure in Non-dialysis-dependent Chronic Kidney Disease: an endorsement with some caveats for real-life application

[g] Consider the use of loop diuretics, especially in patients with CKD stage G3b (eGFR <45 ml/min/1.73 m^2)

[h] Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

[i] Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC)

[j] A European Renal Best Practice (ERBP) position statement on the Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for the Management of Blood Pressure in Nondialysis-dependent Chronic Kidney Disease: an endorsement with some caveats for real-life application

[k] 2013 ESC guidelines on the management of stable coronary artery disease

[l] Consider single-pill triple combination treatment if BP is not at target

[m] ESO Guidelines for management of ischaemic stroke and transient ischaemic attack 2008

[n] ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012

[o] Initiate OLM at low doses (10 mg) and uptitrate only with close monitoring of serum potassium

[p] Consider adding loop diuretics for volume overload

[q] Consider replacing HCTZ with a loop diuretic for symptoms of volume overload

Moreover, single-pill fixed-dose combinations (FDCs) can reduce pill burden and simplify treatment regimens [1]. Adherence/compliance in hypertensive (HTN) patients typically falls over time and tolerability has been shown to affect drug use [12]. According to Italian Health Service data, ARBs were the most well-tolerated drug class, with the lowest rate of discontinuation; within this, the discontinuation rate was lowest for OLM [13]. Good adherence to antihypertensive therapy decreases cardiovascular (CV) risk. Compared to patients with low (<80 %) adherence, those with high (≥80 %) adherence were less likely to develop chronic heart failure [14], coronary artery disease [15] and cerebrovascular disease [16].

FDCs have other important benefits over giving the same individual agents separately: improved BP control and normalisation rates [17]; increased compliance (particularly in older patients) [18, 19]; improved persistence on treatment [20]; and reduced total and CV-related hospitalisation costs [21]. These are all reasons underlying the 2013 ESH/ESC guideline recommendation for the use of FDCs containing two or three agents [1].

Very recently, Volpe et al. [22] proposed an ARB-based single pill strategy that includes an ARB alone or in combination with AML and/or HCTZ. The strategy outlines appropriate therapy for patients with varying characteristics and needs, based on clinical evidence, guidelines, best practice and clinical experience. Efficacy should be assessed after 2–4 weeks and treatment intensified if required. To improve adherence, the use of a FDC is recommended. Essentially, this strategy is based on OLM, which is available as monotherapy and in FDCs with AML and/or HCTZ. In addition, the triple OLM/AML/HCTZ single-pill combination is the only ARB-based triple combination with an add-on indication in Europe. The ARB platform recommends specific treatment algorithms for patients with specific risk factors or subclinical organ damage (OD) and patients with overt OD (Table 1A, B), and outlines how the majority of patients with HTN can be effectively treated in general practice with an ARB like OLM, combined with AML and/or HCTZ.

3 Conclusions

Monotherapy and combination antihypertensive therapy can be used to effectively treat patients with hypertension in clinical practice. The majority of people with hypertension will require two or three antihypertensive agents to achieve optimal BP. The ESH/ESC guidelines recommend the use of FDCs of two or three agents in clinical practice to effectively achieve goal BP in patients with hypertension, as single-pill FDCs have been shown to improve adherence to medication as well as BP control.

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Conflict of interest Prof. Laurent states that he has conducted clinical advisory activities and that he has received honoraria from Daiichi Sankyo. The activities conducted with the support of the Menarini group do not constitute a conflict of interest in relation to the contents of this article.

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