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REVIEW ARTICLE

Single-Pill Combination with Three Antihypertensive Agents to Improve Blood Pressure Control in Hypertension: Focus on Olmesartan-Based Combinations

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Abstract
Blood pressure control remains an unmet clinical need. Only about half of patients achieve their blood pressure (BP) targets and of these, the majority require combination and double or triple therapies. International guidelines recommend the association of drugs with complementary mechanisms of action and, in particular, the combination of renin-angiotensin system (RAS) inhibitors, calcium channel blockers (CCBs), and diuretics. Among the various angiotensin receptor blockers, olmesartan (OM) is available as a monotherapy and in dual and triple single-pill combinations (SPCs) with amlodipine (AML) and/or hydrochlorothiazide (HCTZ). Several phase III and IV studies, together with real-world studies, have demonstrated the additional benefits of combining OM either with AML or with HCTZ in terms of BP control and target BP achievements both in the general population and in special subgroups of hypertensive patients, such as the elderly, diabetic, chronic kidney disease or obese patients. Ambulatory BP monitoring studies assessing 24h BP have also demonstrated that dual, as well as triple, OM-based SPCs induce a more sustained and smoother BP reduction than placebo and monotherapy. Furthermore, triple OM-based SPC has been shown to improve therapeutic adherence in hypertensive patients compared to free combinations. The availability of OM combined with HCTZ, AML or both at different dosages makes it a valuable option to customize therapy based on the levels of BP and the clinical characteristics of hypertensive patients.

Keywords Olmesartan · Single pill combination · Adherence · Blood pressure control · Diabetes · Obesity · Elderly

1 Introduction

Hypertension is the leading preventable risk factor for cardiovascular disease (CVD) and for all-cause mortality worldwide [1]. Estimates predict that in 2025 hypertension will affect 1.56 billion people [2]. In the last decades, blood pressure (BP) and the prevalence of raised BP have declined substantially in high-income regions but have continued to rise in low- and middle-income countries [3]. Yet, even in high income countries, BP control among treated hypertensive adults remains poor with less than 50% of them having BP values at or below recommended targets [4]. More worrisome are recent observations indicating a recent decline in BP control in some patient groups such as the elderly, women and non-Hispanic blacks in the US [5] or women in France [6]. Thus, despite great efforts to improve the detection of subjects with elevated BP around the world [7] and to promote the health benefits of a good BP control at all ages [8], hypertension remains not only a major health burden leading to disabilities and deaths but also a significant financial burden that includes direct costs (drugs, laboratory tests, clinical visits, hospitalization for complications related to hypertension) and indirect costs (loss of productivity due to sick leave, premature mortality and disability for hypertension and related diseases) [1].

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2 Rationale for the Use of Single Pill Combinations

Several reasons have been brought forth to explain why treated hypertensive patients do not have an adequately controlled BP. These include low patient adherence to prescribed medications, clinical inertia and factors related to the health care system, such as lack of access and cost of medication, or to the patient, as low socioeconomic status [9]. Among the barriers to hypertension control, suboptimal adherence, which includes failure to initiate pharmacotherapy, to take medications as often as prescribed, and to persist with therapy long-term is of high relevance [10]. Another issue that can contribute to poor control of hypertension is therapeutic inertia, identified as the failure of the physician to treat one or more conditions and to adjust the pharmacological therapy of patients who do not respond adequately to treatment adopting a "wait and see at next appointment" approach. Therapeutic inertia is frequent in hypertension but factors leading to this are not well understood [11, 12]. Therapeutic inertia in hypertension is thought to contribute to the development of cardiovascular events [13].

Since polypharmacy and the complexity of treatments are two determining factors of poor adherence, simplifying drug regimens by using a single pill combination (SPC) has been proposed as a therapeutic strategy in hypertension to improve drug adherence [14–16], a strategy which has now been included in the most recent guidelines as will be discussed below [9, 17, 18]. Indeed, there is now strong evidence that the use of SPCs improves adherence [19] and that a better adherence to therapy translates into better clinical outcomes, both in terms of blood pressure control [20] and in terms of cardiovascular risk reduction [21, 22]. A recent review and meta-analysis of 44 studies that have investigated the clinical impact of using SPCs have demonstrated that the use of SPCs is associated with significant reduction in systolic and diastolic BP, in higher rates of patients achieving BP targets and most importantly a significant increase in drug adherence and persistence [23]. Additionally, the use of SPCs can also be associated with cost saving over using free combinations for many reasons, including fewer follow-up visits, and fewer hospitalizations for uncontrolled hypertension and cardiovascular events [15]. The availability of SPCs may also address some of the common misconceptions thought to promote clinical inertia [24]. Indeed, with the use of SPCs a greater percentage of patients will be controlled, more patients will stay on therapy and the tolerability profile is often improved [25–27]. Taken together, these factors should facilitate the management of hypertension by practitioners.

In addition to simplifying the therapy and increasing drug adherence and persistence, there are several other pharmacological and clinical reasons to use SPCs. Combining drugs with different and complementary modes of action has been shown to provide synergistic effects on BP and consequently greater antihypertensive efficacy than monotherapies, increasing the likelihood to reach BP targets in a newly treated hypertensive patients from ~ 30 to 50–60% [14, 28, 29]. Furthermore, the combination of three antihypertensive drugs, each at half the standard dose, further reduces the risk of coronary heart disease and stroke compared to standard doses of the single drugs alone and a reduction in adverse events can also be observed using specific combination strategies [28, 30, 31]. The combination of a diuretic with a blocker of the renin-angiotensin system (RAS) is associated with a lower rate of diuretic-induced adverse metabolic effects and the combination of RAS blocker with a dihydropyridine calcium channel blocker (CCB) such as amlodipine significantly reduces the frequency of peripheral edema due to the CCB [28]. In general, adverse events with CCB and thiazides are strongly dose related [28], therefore their use at low doses in combination therapies can improve their tolerability profile. On the other hand, RAS blocker such as angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs) do not have a dose-related tolerability profile, which allows them to be used at full dosage in combination therapies. Also, recent data from a large-scale, observational network study confirm ARBs effectiveness complemented by an excellent safety profile [32].

On these bases, recent guidelines recommend as a first-line therapy for the majority of patients in uncomplicated hypertension, a single-pill dual combination therapy based on an ACEi or an ARB and a calcium channel blocker (CCB) or a diuretic [9, 17, 18]. The ISH guidelines also state that the first step is a low-dose dual combination, followed by a dose increase in case of insufficient response [18]. Regarding the choice between ACEi and ARB, the guidelines do not give preferential indications. In case of insufficient response with a dual combination, a triple SPC is now recommended whenever available [9].

3 Olmesartan Medoxomil-Based Combinations

Among the various angiotensin receptor blockers, olmesartan medoxomil (OM) is available as a monotherapy and in dual and triple SPCs with amlodipine (AML) and/or hydrochlorothiazide (HCTZ). The triple SPC OM/AML/HCTZ is available in 5 different dosages: 20 mg/5 mg/12.5 mg, 40 mg/5 mg/12.5, 40 mg/10 mg/12.5 mg, 40 mg/5 mg/25 mg, 40 mg/10 mg/25 mg.

Numerous phase III and phase IV studies have demonstrated the additional benefits of combining OM either with AML or with HCTZ in terms of BP control and target BP achievements [33–37]. The ability of OM to lower BP has been documented in patients poorly controlled on OM alone as well as in patients uncontrolled on AML or HCTZ alone. Dual OM-based SPCs have been effective in various subgroups of hypertensive patients including the elderly, diabetics, patients with chronic kidney diseases or obese subjects. Studies performed using 24 h ambulatory BP monitoring have also demonstrated that dual as well as triple OM-based SPCs induce a more sustained and smoother BP reduction than placebo and monotherapies [34].

In addition to their efficacy on BP, the OM-based combinations have demonstrated a positive impact on the reduction of vascular hypertrophy, carotid intima-media thickness and atherosclerotic plaque volume [38, 39] (Fig. 1). In this regard, 1-year treatment with OM led to a significant reduction in the arteriolar wall–lumen ratio (from 14.9 to 11.1%; $P < 0.01$), with the achievement of values similar to those of normotensive controls (11%). However, no significant change was observed in arteries from atenolol-treated patients. Thus, the blockade of angiotensin type 1 (AT1) receptors showed a structural improvement in the resistance arteries in essential hypertension, an effect independent of the extent of the reduction in blood pressure [38]. The Multicentre Olmesartan atherosclerosis Regression Evaluation (MORE) study, conducted in patients with hypertension at increased cardiovascular risk, demonstrated the efficacy of OM not only in reducing the wall thickness but also in reducing the volume of larger atherosclerotic plaques [39].

In a prospective, double-blind, placebo-controlled, multicenter study, Fliser et al. [40] have evaluated the anti-inflammatory effect of OM, alone or in combination with pravastatin, in patients with essential hypertension and signs of microinflammation (i.e. highly-sensitivity C-reactive protein (hsCRP) > 3 mg/L). OM monotherapy and the OM/pravastatin combination therapy resulted in a reduction in hsCRP (− 21.1%; $P < 0.02$), high tumor necrosis factor, sensitivity-tumor necrosis factor-α (− 13.6%; $P < 0.01$) and interleukin-6 (− 18.0%; $P < 0.01$), while pravastatin alone did not significantly alter inflammation markers.

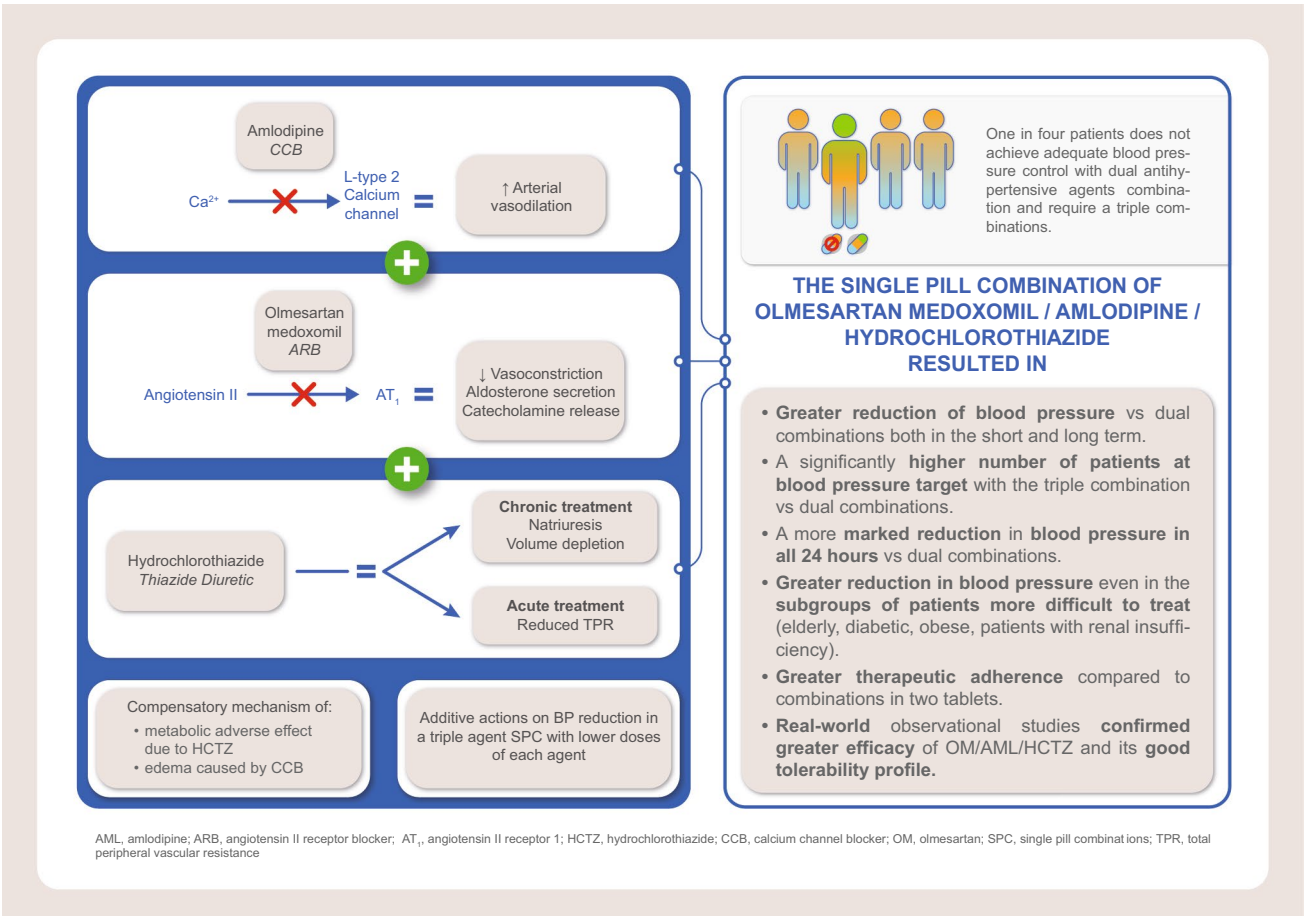

Fig. 1 Olmesartan ancillary effects on microinflammation, vascular abnormalities and atherosclerosis in hypertensive patients. *OM* olmesartan medoxomil, *AML* amlodipine, *HCTZ* hydrochlorothiazide, *BP* blood pressure

4 Olmesartan-Based Available Combinations: Focus on Triple SPCs

4.1 Up-Titration Open-Label Studies

The clinical evidence on the SPC of OM/AML/HCTZ starts from small studies with up-titration design and continues with randomized controlled trials. The main features of the studies analyzed are summarized in Table 1.

A 24-week open-label practice-based trial assessed the effectiveness of an antihypertensive treatment algorithm with OM as the initial agent [41]. The 201 patients enrolled received OM 20 mg/day for 4 weeks after a run-in period with placebo. At subsequent 4-week intervals, the treatment regimen was titrated by first increasing OM to 40 mg/day, then adding increasing doses of HCTZ first, and then AML until reaching a treatment based on OM 40 mg/HCTZ 25 mg/AML 10 mg, in those with BP > 130/85 mmHg,. At week 24, SBP/DBP reductions from baseline were 33.7/18.2 mmHg. Overall, 87.7% of patients achieved a target BP of ≤ 130/85 mmHg and 93.3% achieved BP levels of ≤ 140/90 mmHg [41].

In the 44-week open-label extension of the 8-week, double-blind Combination of Olmesartan Medoxomil and Amlodipine Besylate in Controlling High Blood Pressure (COACH) study conducted in 1684 patients, OM-based combination therapy was titrated as needed up to OM/

Table 1 Characteristics and main results of trials assessing olmesartan-based triple combination

Study, year	Patients (n)	Duration (weeks)	OM/AML/HCTZ (mg)	SBP/DBP change vs baseline (mmHg)	P value	Target to be achieved (mmHg)	Proportion of patients achieving target (%)
Neutel, 2004	71	24	40/5/25 and 40/10/25	− 33.7/− 18.2	NA	≤ 130/85	96.1 (week 16)
Chrysant, 2009	287 419	52	40/10/12.5 40/10/25	− 34.8/− 21.2 − 36.1/− 19.8	NA	< 140/90 or < 130/80 in T2D	66.6 46.3
Volpe, 2009	68 27	28	40/10/12.5 40/10/25	NA NA	NA	< 140/90 or < 130/80 in T2D	47.1 33.3
Weir, 2011	671 484	12	40/10/12.5 40/10/25	− 23.8/− 13.3 − 25.1/− 13.7	All P values < 0.0001 vs baseline	SeSBP < 140 or < 130 in T2D	86.7 90.3
Oparil, 2010	627	12	40/10/25	− 37.1/− 21.8	All P values < 0.001 vs baseline All P values < 0.001 vs each double combination	< 140/90 or < 130/80 in T2D, CKD and CVD	69.9
Volpe 2012	335 336 336 336 336	10	20/5/12.5 40/5/12.5 40/5/25 40/10/12.5 40/10/25	− 33.2*/− 22.5‡ − 33.7*/− 22.5‡ − 35.3**/− 23‡ − 35.5‡/− 23.9‡ − 36.2*/− 23.8‡	*P < 0.001 **P < 0.0001 ‡P < 0.01 ‡P < 0.05 For comparison between triple and dual treatments	< 140/90 or < 130/80 in T2D, CKD and CVD	66.2 66.4 72.8 71.7 72.6
Volpe, 2014	1447 272 480 146 164	44	20/5/12.5 40/5/12.5 40/5/25 40/10/12.5 40/10/25	− 42.8/− 26.7 − 40.1/− 24.9 − 39.9/− 25.7 − 39.4/− 24.6 − 36.5/− 21.6	NA	< 140/90 or < 130/80 in T2D, CKD and CVD	89.4 73.2 68.2 55.1 35.6
Punzi, 2014	40	4	40/10/25	NA	NA	< 140/90	90
Sohn, 2016	167	8	20/5/12.5	− 16.3/− 9.5	P < 0.0001 vs. baseline; P < 0.0001 between triple combination and OM/HCTZ	< 140/90 or < 130/80 in T2DCKD and CVD	65.3

OM olmesartan medoxomil, *AML* amlodipine besylate, *HCTZ* hydrochlorothiazide, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *NA* not available, *CKD* chronic kidney disease, *CVD* cardiovascular disease, *T2D* type 2 diabetes, *NA* not available

AML/HCTZ 10/40/12.5 and then to 10/40/25 mg in those patients who did not reach the BP target (< 140/90 mmHg or < 130/80 mmHg in patients with diabetes) [42]. This extension study demonstrated that patients titrated to AML 10 mg/day + OM 40 mg/day + HCTZ 25 mg/day achieved the greatest reduction from baseline in systolic BP (SBP) (− 36.1 mmHg). These patients had the highest mean baseline BP (172.9/103.2 mmHg) and 46.3% of them met the BP treatment goal. Therefore, the addition and up-titration of HCTZ allowed a higher percentage of patients to reach the BP goal while maintaining good tolerability [42].

Another up-titration long term open-label study assessed a treatment algorithm based on OM, AML and HCTZ. Six hundred ninety-two patients with moderate to severe hypertension inadequately controlled on AML 5 mg/day alone and then treated for 16 weeks with combined OM/AML treatment, entered an open-label 28-week phase in which they received OM/AML 40/5 mg/day. After 4, 10 and 19 weeks, therapy was progressively increased in a step-wise manner to OM/AML 40/10 mg; OM/AML/HCTZ 40/10/12.5 mg and OM/AML/HCTZ 40/10/25 mg, in patients with inadequately controlled hypertension. Approximately 70% of patients reached the target BP recommended by the guidelines (SBP < 140 mmHg and DBP < 90 mmHg for patients without diabetes mellitus, and SBP < 130 mmHg and DBP < 80 mmHg for patients with diabetes), confirming that a treatment algorithm based on OM/AML/HCTZ provides a high degree of BP control in these patients. All the combinations tested were generally well tolerated, with no unexpected safety concerns [43].

With a similar design, the BP-CRUSH (Blood Pressure Control in All Subgroups With Hypertension) titration study evaluated 999 patients with uncontrolled hypertension, demonstrating that adding HCTZ to the OM/AML titration regimen enabled a higher proportion of patients to achieve the seated office BP goal of < 140/90 mmHg (< 130/80 mmHg for patients with diabetes) while showing a good tolerability. Moreover, the BP-CRUSH study evaluated the 24-h ambulatory blood pressure (ABPM). The reduction from baseline in the mean 24-h ABPM were statistically significant at both weeks 12 and 20. The mean daytime (8 AM–4 PM) ABPM target of < 135/85 mmHg was achieved by 72.9% and 88.4% of patients at weeks 12 and 20, respectively, and the mean night-time (10 PM–6 AM) ambulatory BP target of < 120/70 mmHg was achieved by 62.0% of patients at week 12 and 78.9% of patients at week 20 [44].

Concerning special populations, a meta-analysis of 25 studies compared the efficacy and safety of OM alone with active control (AC) (non-OM) monotherapy with either an ARB, ACE inhibitor, β-blocker, CCB, or a diuretic, in 4487 elderly patients (aged 60–79 years) demonstrating greater efficacy of OM in reducing BP levels and achieving BP targets in all patients and in particular in those with impaired renal function [45]. Concerning the association with AML, the safety and efficacy of an AML/OM-based titration regimen was also assessed in patients with type 2 diabetes mellitus and hypertension. After a 2–3-week placebo run-in period, 207 patients received AML 5 mg and were up-titrated to AML/OM 5/20, 5/40, and 10/40 mg and then AML/OM 10/40 mg plus HCTZ 12.5 and 25 mg in a step-wise approach at 3-week intervals if the seated BP remained >120/70 mmHg. At the end of 18 weeks of active treatment in patients up-titrated to AML/OM 10/40 mg plus HCTZ 25 mg, the change from baseline in the mean ± SEM seated BP was − 28.0 ± 1.5/− 13.7 ± 1.0 mmHg (P < 0.0001 vs baseline), with 62% of patients reaching the guideline-recommended seated BP goal of < 130/80 mmHg [46]. Finally, the fixed combination OM/AML was compared with perindopril (PER)/AML in a non-inferiority trial with a randomized, double-blind, double-dummy parallel group, controlled design in hypertensive patients with diabetes mellitus and with a missed dose. The two combinations were equally effective and tolerated even in the case of a missed dose. However, the OM/AML combination showed faster control with a smaller dose increase [47].

4.2 Randomized Clinical Trials on OM/AML/HCTZ and Other Evidence

The pivotal study evaluating the benefits of OM, AML, and HCTZ-based triple SPC therapy is the TRINITY (Triple Therapy with OM, AML, and HCTZ in the Hypertensive Patient Study) trial [48], a 12-week, multicenter, randomized, double-blind, parallel-group study, that randomized 2492 patients with moderate to severe hypertension. The TRINITY study was the first study that compared triple combination therapy with dual combination therapies of the individual components in fixed-dose formulations, including OM/AML 40/10 mg, OM/HCTZ 40/25 mg, and AML/HCTZ 10/25 mg.

After a 3-week washout period, patients were randomized to receive dual combination treatment or placebo. All patients assigned to a dual combination treatment group continued the assigned treatment through week 4, while patients assigned to placebo were switched at week 2 to one of the dual combination treatments through week 4. At week 4, patients continued on dual combination treatment or switched to triple combination treatment through week 12. The primary endpoint was the change in seated office diastolic BP from baseline to week 12. At the end of the study, triple combination treatment was associated with significantly greater least-squares mean reduction in seated BP compared with the dual combinations (DBP: − 21.8 vs − 15.1 to − 18.0 mmHg, respectively [$P < 0.001$]; SBP: − 37.1 vs − 27.5 to − 30.0 mmHg [$P < 0.001$]) and a significantly higher proportion of patients receiving triple

combination treatment reached BP targets compared with the dual combinations ($P < 0.001$).The proportion of patients reaching the BP target of < 140/90 mmHg at week 12 was 69.9% in the triple combination treatment group and 52.9%, 53.4%, and 41.1% in the treatment groups receiving OM 40 mg/AML 10 mg, OM 40 mg/HCTZ 25 mg, and AML 10 mg + HCTZ 25 mg, respectively ($P < 0.001$, triple combination vs each dual combination) [48] (Fig. 2).

An ABPM sub-study of TRINITY was conducted in some centers selected for their specific experience and in patients who voluntarily joined this roll-over study. In this study, 440 patients randomized to the 4 treatment groups were included in the ABPM analysis. ABP measurements were acquired at baseline and after 12 weeks of treatment. Blood pressure reduction was more marked in all 24 h with triple SPC (− 30.3/− 18.0 mmHg) compared to double combinations (OM 40 mg/AML 10 mg: − 23.5/− 13.9, OM 40 mg/HCTZ 25 mg: − 23.9/− 14.5, and AML 10 mg/HCTZ 25 mg: − 18.5 mmHg/− 10.7 mmHg; P < 0.0001 each). Greater efficacy was also confirmed in the average of day and night measurements and during the last 6, 4, and 2 h of the interval between doses [49].

An article by Volpe et al. [50] extended these observations and showed significantly increased BP reductions and goal rate achievement following the addition of HCTZ to a range of OM/AML doses in patients with moderate-to-severe hypertension. This phase III randomized trial enrolled 2690 patients and compared triple combination therapy with double combinations. Patients treated with the OM/AML/HCTZ combination had significantly greater mean reduction in DBP (P < 0.032 for each comparison) and systolic blood pressure (SBP) (P < 0.0034 for each comparison), compared to patients in the OM/AML combination group. In three of the OM/AML/HCTZ groups (40 mg/5 mg/25 mg, 40 mg/10 mg/12.5 mg and 40 mg/10 mg/25 mg), BP < 140/90 mmHg threshold achievement by week 10 was over 70%. At the end of the follow-up period, all triple combination therapies induced significantly greater reduction in systolic and diastolic blood pressure levels and significantly improved blood pressure control rate compared to double combinations [51].

The study reported by Volpe et al. contained an extension phase that involved open-label treatment designed to reflect real-life clinical practice and in which a high level of BP control and a substantial reduction in the level of hypertension severity were achieved. Significant reductions from baseline were observed in each group after 36 weeks (37–43 mmHg seated SBP and 22–27 mmHg DBP) and 78.1% of patients overall achieved the blood pressure goal. As expected, BP reduction correlated with BP level at baseline, with reductions of 34.3 mmHg and 59.4 mmHg for patients in the lowest (150–159 mmHg) and highest category (190–200 mmHg), respectively [50].

A small randomized single-center study assessed the efficacy and safety of once-daily OM/AML/HCTZ 40/10/25 mg in patients with hypertension not at goal with mono, dual or triple-drug therapy. Treatment with OM/AM/HCTZ resulted in a significant reduction from baseline in ambulatory PAS

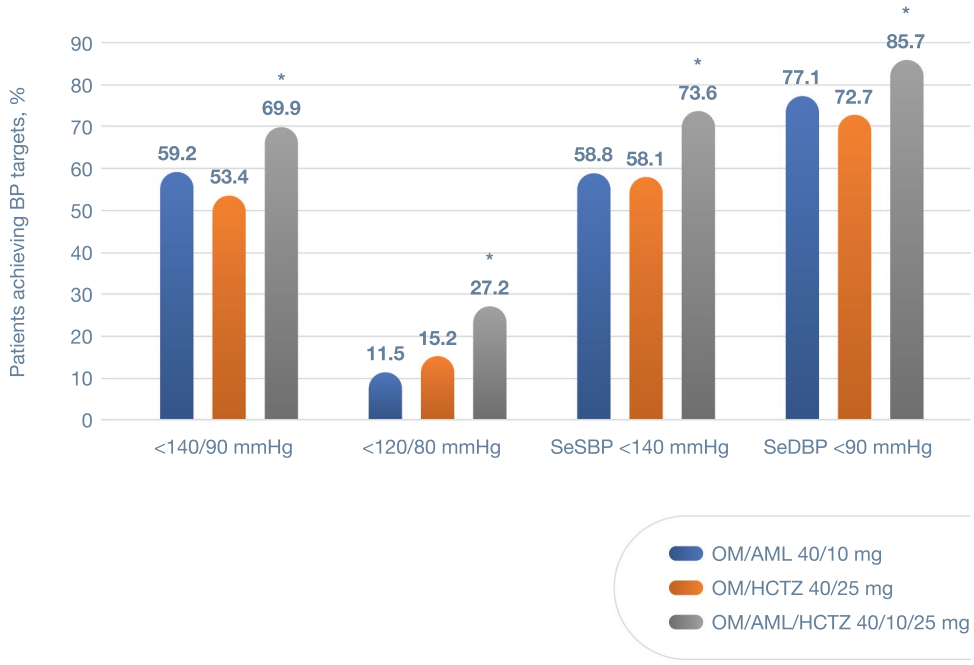

Fig. 2 Percentages of patients reaching blood pressure (BP) targets at week 12 in the TRINITY study. *P ≤ 0.003 for all comparisons. *OM* olmesartan medoxomil, *AML* amlodipine, *HCTZ* hydrochlorothiazide, *SeSBP* seated systolic blood pressure, *SeDBP* seated diastolic blood pressure. *P < 0.001, triple combination treatment versus each dual combination treatment

reduction of 5.55 ± 1.3 mmHg (P < 0.0001). A significant proportion of patients (90%) treated with OM/AM/HCTZ achieved BP < 140/90 mmHg at week 4, with 97% achieving less than 140 mmHg. The antihypertensive effect began with the first dose. Blood pressure control continued to improve between the first and fourth week of therapy. No patient experienced hypotensive episodes [52].

More recently, another randomized clinical trial was conducted in Korea to evaluate the efficacy and safety of OM/AML/HCTZ in 264 Korean patients. The study demonstrated that in Korean patients with uncontrolled moderate hypertension treated first-line with the double combination (OM/HCTZ 20/12.5), the triple SPC (OM/AML/HCTZ 20/5/12.5) was associated with significant blood pressure reductions and greater achievement of blood pressure goals and was well tolerated [25, 26]. Finally, triple OM/AML/HCTZ SPC efficacy has been analyzed also in a primary care setting. In this study 139 eligible patients, with uncontrolled BP > 140/90 mmHg, were enrolled by 20 general practitioners (GPs) [53]. After enrollment, GPs were randomized into two treatment groups: interventional care and standard care. In the interventional therapy group, which included 54 patients), antihypertensive therapy was augmented using an SPC (OM, AML, and HCTZ) at 4-week intervals. In the standard care group, GPs treated patients according to ESH/ESC 2013 guidelines. After 6 months, in the interventional care group, a greater percentage of patients achieved their blood pressure goal than those in standard care. Moreover, although statistically and clinically significant reductions in blood pressure were observed in both groups, the respective reductions in blood pressure were achieved with a significantly lower medication burden in the interventional care group [53].

4.3 Special Patient Populations: Subgroup Analyses on Obese, Diabetic, and CKD Patients

Patients with diabetes mellitus (DM), chronic kidney disease (CKD) and obesity, have a high prevalence of hypertension and at the same time less control of blood pressure (BP) and an increased CV risk. For these reasons, international guidelines recommend more stringent blood pressure control in these patients; the treatment should therefore have the possibility of being individualized.

Predefined analyses of the TRINITY population evaluated the efficacy and safety of OM/AML/HCTZ SPC in hypertensive patients with diabetes, CKD or CVD; in different ethnic groups, including black and non-black individuals, as well as in patients aged ≥ 65 years and in those with obesity [54]. The main results of the special population analyzed are summarized in Table 2. In more detail, triple OM-based combination treatment resulted in significant mean reduction in seated diastolic and systolic BP (P < 0.0001 vs each dual-combination treatment) with a greater proportion of participants reaching BP goal compared with dual-combination treatments, regardless of race (black and non-black participants) [55]. Moreover, triple-combination treatment with OM/AML/HCTZ 40/10/25 mg was well tolerated and more effective in lowering BP than the component dual-combination treatments both in the elderly and non-elderly subgroups [56] and irrespective of BMI [57]. The TRINITY subgroup analysis demonstrated the effectiveness of this triple-combination also in difficult-to-treat participants with hypertension and diabetes, CKD, or chronic CVD. BP reductions with triple-combination treatment in these subgroups at week 12 were comparable to those for the overall study cohort (− 37/22 mmHg) [58, 59] (Table 2). In all the studies analyzed, the treatment with OM-based combination was well tolerated, both in the general population and in the patients involved in the subgroup analysis. As for the triple SPC, the incidence of adverse events related to hypotension was 0.7% in the TRINITY study.

4.4 Real-World Studies on OM/AML/HCTZ Single-Pill Combination

The clinical studies presented so far have shown that the triple combination of OM/AML/HCTZ is effective, safe, and well-tolerated both when given as an extemporaneous combination of the separate tablets for each drug and as an SPC. The first real-world analysis was performed by Bramlage in 2015 which included 5831 patients followed in a primary-care setting [60]. The main objective was to obtain further information on the safety profile of SPC OM/AML/HCTZ. The secondary goal was the assessment of blood pressure-reduction efficacy. The results of this real-world analysis confirmed those collected in the randomized controlled clinical trials and demonstrated that the SPC OM/AML/HCTZ tablet is associated with very few adverse drug reactions (ADRs), in all patients including the elderly, those with diabetes mellitus or other cardiovascular risk factors, and those receiving concomitant medications. Furthermore, this study demonstrated that, in clinical practice reflecting real-life practice, treatment with SPCs led to high rates of responders and patients reaching the BP target. Moreover, contrary to the TRINITY study in which co-medications were not allowed, in these real-world studies 35–39% of patients were receiving antihypertensive concomitant medications, and about 66% were receiving concomitant non-antihypertensive medications; this data is significant because concomitant drugs could affect the efficacy and safety of SPCs. The ADR rate found in this study in patients with concomitant therapies was only 0.5% higher than in those taking SPC alone. This suggests that OM-based SPCs can

Table 2 Main results of subanalysis of the TRINITY study conducted in patients with comorbidities

Study, year	Duration (weeks)	OM/AML/HCTZ (mg)	Comorbidity	SBP/DBP change vs baseline (mmHg)	BP target to be achieved (mmHg)	Proportion of patients achieving target (%)
Kereiakes, 2012	12	40/10/25	CKD Chronic CVD	− 44.3/− 25.5 − 37.8/− 20.6	< 130/80	55 38.9
Chrysant, 2012	12	40/10/25	Diabetes	− 37.9/− 22	< 130/80	41.1
Roth, 2013	12	40/10/25	Obesity (BMI ≥ 30 kg/m^2)	− 37.9/− 21.1	< 140/90 or < 130/80 in diabetes or CKD or CVD	61.6

OM olmesartan medoxomil, *AML* amlodipine besylate, *HCTZ* hydrochlorothiazide, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *CKD* chronic kidney disease, *CVD* cardiovascular disease, *BMI* body mass index

be safely administered in combination with a variety of other medications [60].

Recently, due to the lack of Asian population in the TRINITY studies, two observational real-world studies in Korea added evidence of safety and efficacy for OM/AML/HCTZ in more than 10,000 hypertensive patients [61, 62]. The RESOLVE study [61] was a large, observational, retrospective cohort study that analyzed the medical records of 9749 patients with essential hypertension who had been prescribed OM/AML/HCTZ in the year before the analysis. Mean BP was significantly reduced from baseline at all visits (all P < 0.0001) and the overall patient target rate was 82.56%. Similarly, the RESOLVE-PRO study [62] demonstrated that OM/AML/HCTZ triple SPC treatment has significant efficacy in reducing BP and achieving BP control over the 1-year observation period in 3752 Korean hypertensive patients and it was well tolerated.

5 Olmesartan-Based Triple SPC: Impact on Adherence and Health-Related Quality of Life

The simplicity of a regimen is known to be an important driver capable to improve adherence. More commonly adherence studies are conducted on an observational basis, while randomized controlled trial on medication adherence are rare. Among them, the AMTRAC study is an open-label RCT performed in China with 145 patients randomized to receive OM/AML/HCTZ or the equivalent combination of two pills [27]. The objective of this study was to investigate whether a triple-component SPC improved medication adherence. Adherence was measured with the Medication Event Monitoring System (MEMS), long considered the gold standard for measuring therapeutic adherence [27, 63]. It is a specially designed medicine container that records the date and time of its opening and from which the data can be transferred to a computer and analyzed later. In particular, the difference in the percentage of doses taken (PDT) and percentage of days with the prescribed dose taken correctly (PDTc) between the single-and two-pill therapy groups were the primary outcomes. Results from this study confirmed a better adherence of triple-SPC versus the equivalent two-pill combinations; the single-pill group had significantly higher PDT and PDTc than the two-pill group: median (25–75 percentile) PDT 95.1 (86.7–100.0) versus 92.1 (73.0–97.3); and PDTc 91.0 (79.4–96.5) versus 88.6 (69.2–96.3%), $P = 0.04$ for both [27].

The observational, retrospective cohort study, RESOLVE-PRO, conducted in more than 3500 hypertensive patients treated with OM/AML/HCTZ SPC for 1 year, confirmed the finding of a high percentage of days covered by the drug over 1 year with an SPC treatment. In the RESOLVE-PRO study, the adherence was assessed using medication possession rate (MPR) [62]. The MPR was calculated as a proportion, representing the number of days covered by prescription of OM/AML/HCTZ, divided by the number of days between the date of the first prescription and the date for the last prescription. The mean MPR during the observation period was 0.96. Moreover, patients' and physicians' satisfaction were assessed through a numeric rating scale (NRS) ranging from 0 (= 'not satisfied at all') to 10 (= 'completely satisfied'). NRS scores of patients' and physicians' satisfaction with the use of the SPC of OM/AML/HCTZ were 8.2 and 8.2 points at month 6; and 8.6 and 8.4 points at month 12, respectively [62].

The SPC of OM/AML/HCTZ contributes to the improvement of Health-related quality of life, as demonstrated by a post-hoc analysis that was performed on the data from a 54-week phase III study to measure changes in the health-related quality of life (HRQoL) of 2,690 patients with moderate-to-severe hypertension who received OM/AML/HCTZ SPC [64]. HRQoL was measured by MINICHAL (Mini-questionnaire of Quality of Life in Hypertension) and EQ-5D (European Quality of life instrument 5 Dimensions) tools. The MINICHAL tool consists of 16 items and measures the impact of hypertension on a patient's HRQoL. The EQ-5D is a generic tool that measures patients' responses across 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort,

and anxiety/depression). Each dimension has 3 answers to choose from, which can be generally classified as no problems, moderate problems, or significant problems on the specific dimension. In addition, the EQ-5D also includes a visual analog scale (VAS) describing the patient's own health state with scores ranging from 0 (worst state) to 100 (best state). Patients' baseline MINICHAL mood and somatic domains scores were 5.5 and 2.6. Over the study period, HRQoL improved as both EQ-5D and MINICHAL scores, decreased by 31–33%. Patients' baseline EQ-5D index and VAS scores were 0.9 and 73.4 respectively, increasing by 6% and 12% over the study period. In summary, this study showed that triple OM/AML/HCTZ SPC reduced BP and significantly increased BP control whilst improving patients' HRQoL.

6 OM-Based SPCs for a Patient-Oriented Therapy

Given the availability of several fixed-dose combinations of OM, in the perspective of personalized treatment, Volpe et al. proposed a platform to summarize the differential use and targeting of the OM-based combinations [65]. This platform can help to identify patients that can benefit from the different available combinations, in the context of a personalized therapeutic approach. The platform is a practical tool that aims to apply guidelines to clinical practice. It helps physicians to match the appropriate SPC of 2/3 drugs to the various situations encountered in the treatment of hypertension. Patients with specific risk factors,

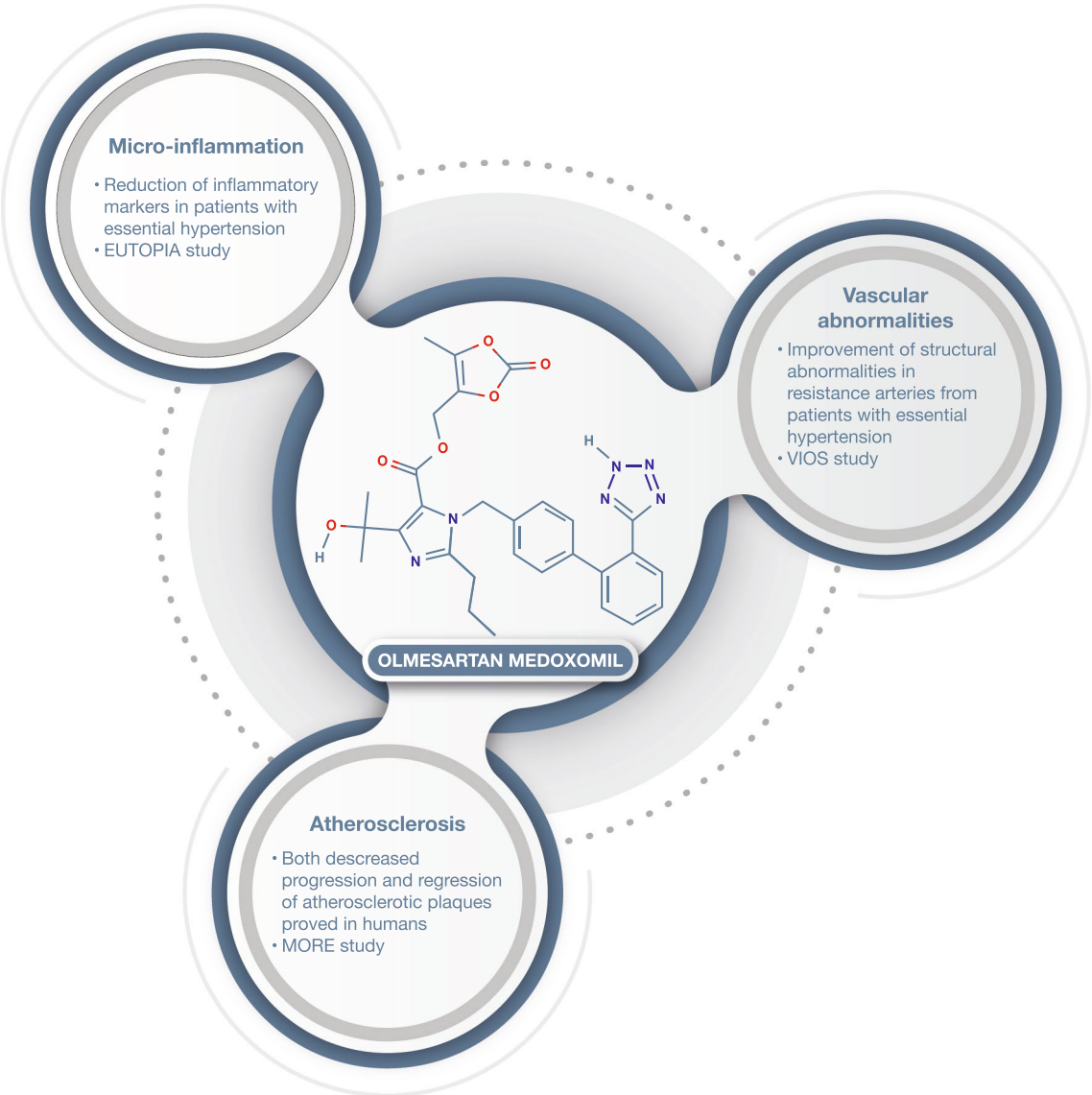

Fig. 3 Mechanisms of action of the components of the SPC based on olmesartan and summary of the main findings highlighted in this review

subclinical or overt organ damage could receive the right combination on the basis of clinical trials, guidelines, best practices and clinical experience, following an approach aimed at determining the appropriate therapeutic intensity based on concomitant conditions and thereby help physicians to tailor treatment strategies on an individual basis.

The platform is organized to match the intensity of therapy (defined as the recommended dose range and type of association) with the appropriate grade of hypertension and the overall cardiovascular risk profile of an individual patient (which is achieved by assessing risk factors, subclinical organ damage or clinical conditions). For example, the need to achieve BP control is more urgent in patients with higher cardiovascular risk. Therefore, such patients may benefit from higher doses and/or from combination therapy, potentially as first-line treatment [65, 66].

7 Conclusion and Future Perspective

BP control remains an unmet clinical need. Only about half of patients achieve their BP targets [10] and of these, the majority require combination with double or triple therapy [28]. International guidelines recommend the association of drugs with different and complementary mechanisms of action and, in particular, the combination of RAS inhibitors, CCBs, and diuretics. Furthermore, to reduce the complexity of therapies and thus improve therapeutic adherence, they recommend that these combinations be administered as SPCs [9, 17, 18]. Among RAS blockers, the evidence presented indicates ARBs, alone or in combination, as appropriate in the treatment of hypertension [32]. Long lasting ARBs, such as OM, are more suitable for the purpose of SPCs which need to control BP over the 24 h [49]. The availability of OM combined with HCTZ, AML or both at different dosages makes it a valuable option to individualize therapy based on the levels of BP and the clinical characteristics of different hypertensive patients [65, 66] (Fig. 3). The use of these combinations in a single pill provides benefits in terms of therapeutic adherence and quality of life and should simplify the management of hypertension by physicians. In this respect, SPCs represent an important therapeutic tool. In the future, although some studies suggest that SPCs have a favorable impact on cardiovascular endpoints [22], these benefits could be further expanded by trials on morbidity/mortality and cardiovascular risk prevention.

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Declarations

Conflict of Interest M. Burnier received speaker fees, honorarium and research grants from Menarini, Servier, Bayer and Idorsia. J. Redon received speaker fees from Menarini, Daichi-Sankyo, Boehringer Ingelheim and Ferrer. M. Volpe has received honoraria for speakers' bureau or consulting in AB from Menarini Int., Bayer, Servier, Astra Zeneca, Amgen Zentiva.

Ethical Approval No ethical approval was necessary for this review.

Data availability No data availability from this review.

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