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REVIEW

Triple-combination therapy in the treatment of hypertension: a review of the evidence

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Hypertension is a serious public health concern with inadequate control of blood pressure (BP) worldwide. Contributing factors include low efficacy of drugs, underuse of combination therapies, irrational combinations, physicians' therapeutic inertia and poor adherence to treatment. Current guidelines recommend the use of initial (dual) combination therapy in high-risk patients for immediate BP response, better short- and long-term BP control, and continued/improved patient adherence. This article aims to review the existing evidence of triple-combination therapies with respect to efficacy, safety and adherence to treatment. It is estimated that three drugs are required to achieve BP control in approximately one-fourth to one-third of patients. Randomised controlled trials (RCTs) have shown that triple combinations of amlodipine/valsartan/hydrochlorothiazide, amlodipine/olmesartan/hydrochlorothiazide and amlodipine/telmisartan/hydrochlorothiazide produce greater BP reductions, with greater proportions of patients achieving BP control compared with dual therapies. Further evidence also demonstrates that triple-combination therapy is efficacious for moderate to severe hypertension, with substantial additional BP reduction over dual regimens. Both RCTs and post-marketing observational studies have shown consistent and comparable efficacy in both the general population and high-risk hypertensive subgroups. Triple therapies are generally well tolerated with adverse event profiles similar to dual regimens. In addition, fixed-dose combinations used as single pill improve patient adherence leading to better long-term BP control. Depending on regional circumstances, they may also be cost effective. Thus, single-pill triple combinations of different classes of drugs with complementary mechanisms of action help to treat patients to goal with improved efficacy and better adherence to treatment.

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INTRODUCTION

Hypertension is a serious public health concern worldwide, and due to population growth and ageing, the number of people with uncontrolled hypertension continues to rise. Data from the National Health and Nutrition Examination Survey (NHANES) from 2011 to 2014 indicate that among 29% of adults with hypertension in the US, only 53% had their hypertension under control, and the situation is even more alarming in other countries. A large, cross-sectional, multicentre study in 153 996 patients from high-, middle- and low-income countries has shown that of 40.6% patients treated for hypertension, blood pressure (BP) control was observed in only 13.2% patients (32.5% of those receiving treatment).[1] Furthermore, recent data from a large cohort in China revealed that of 500 223 adults aged 35–74 years, 32.5% had hypertension, of which $<5\%$ achieved BP control. Uncontrolled hypertension accounted for about one-third of deaths due to cardiovascular (CV) disease (CVD).[2]

Hypertension is a multifactorial disease and it is estimated that approximately one-third of patients require two drugs to achieve BP control, defined as $<140/90$ mm Hg, and one-third require three or more anti-hypertensive agents.[3] Despite availability of several anti-hypertensive classes of drugs, hypertension remains poorly controlled in a majority of patients worldwide. Various reasons for poor BP control include low efficacy of hypertensive agents in monotherapy, underuse of combination therapies, irrational combinations, therapeutic inertia among doctors and non-adherence with anti-hypertensive treatment from patients.[4]

COMBINATION THERAPY AS AN INITIAL APPROACH AND AS A STEP-UP STRATEGY TO REACH BP GOALS

Present guidelines recommend the use of initial combination therapy in high-risk patients for immediate BP response, improved tolerability and possibly improved patient adherence.[5] The beneficial effect of early and effective BP control on the CV outcome was shown in the Valsartan Antihypertensive Long Term Use Evaluation (VALUE) trial that included hypertensive patients at high CV risk.[6] Furthermore, in the Anglo-Scandinavian Cardiac Outcomes Trial—Blood Pressure Lowering Arm (ASCOT-BPLA) study, early intensive BP lowering was also associated with a reduced CV event rate in such treated patients.[7]

One crucial aspect for the need of combination therapy is the question of how far BP should be lowered by anti-hypertensive treatment. Data suggest that CV morbidity and mortality are rising progressively starting at systolic BP (SBP) values as low as 115 mm Hg.[8] It would therefore seem appropriate and logical to aim for such low BP values when managing hypertensive patients. However, based on available evidence, current guidelines recommend a general target BP of $<140/90$ mm Hg with goal BP values slightly higher or lower in elderly patients or special subgroups.[5,9]

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Table 1. RCTs with triple-combination therapy for the treatment of hypertension

Study	*Study design*	N	*Triple combination*	*Dual comparator in the studies*	*BP reductions with triple vs dual therapies*
Triple antihypertensive therapy with Aml, Val and HCTZ: a randomised clinical trial[20]	Multicentre, randomised, double-blind, parallel-group, 8-week study in patients with moderate to severe hypertension	2271	Aml/Val/HCTZ (10/320/ 25 mg)	Aml/Val (10/320 mg) Val/HCTZ (320/25 mg) Aml/HCTZ (10/25 mg)	Change (LS mean) from baseline to week 8 for triple vs respective dual combinations in SBP: – 39.7 vs – 32.0, – 33.5 and – 31.5 mm Hg DBP: – 24.7 vs – 19.7, – 21.5 and – 19.5 mm Hg
Triple therapy with Olm, Aml and HCTZ in adult patients with hypertension[21]	Multicentre, randomised, double-blind, parallel-group, 12-week study in patients with moderate to severe hypertension	2492	Aml/Olm/ HCTZ (10/40/ 25 mg)	Olm/Aml (40/10 mg) Olm/HCTZ (40/25 mg) Aml/HCTZ (10/25 mg)	Change from baseline (LS mean) to week 12 for triple vs respective dual combinations in SBP: – 37.1 mm Hg vs – 30.0, – 29.7 and – 27.5 mm Hg DBP: – 21.8 vs – 18.0, – 16.9, and – 15.1 mm Hg
Triple-drug combination of Tel, Aml and HCTZ in the treatment of essential hypertension[22]	Randomised, single-blind, 12-week study in patients with moderate to severe hypertension	220	Aml/Tel/HCTZ (5/40/12.5 mg)	Tel/HCTZ (40/12.5 mg)	Reduction in mean sitting SBP/DBP from baseline to end of week 12 from 166.84/103.62 to 123.05/81.17 mm Hg for triple vs 168.89/105.43 to 130.93/84.24 mm Hg with dual therapy
Efficacy and safety of aliskiren-based dual and triple-combination therapies in US minority patients with stage 2 hypertension[60]	Randomised, double-blind, active-controlled, parallel-group, forced-titration 8-week study in patients with stage 2 hypertension	412	Aml/Ali/HCTZ (5/150/ 12.5 mg)	Aml/Ali (5/150 mg)	Change (LS mean) from baseline to week 8 for triple vs dual combination in SBP: – 36.5 vs – 29.5 mm Hg DBP: – 15.1 vs – 12.0 mm Hg

Abbreviations: Aml, amlodipine; Ali, aliskiren; BP, blood pressure; DBP, diastolic blood pressure; HCTZ, hydrochlorothiazide; LS, least square; Olm, olmesartan; RCTs, randomised controlled trials; SBP, systolic blood pressure; Tel, telmisartan; Val, valsartan.

The present consensus on these 'conservative' BP goals in the treatment of hypertension has recently been questioned, based on the results from a randomised trial of intensive vs standard BP control (Systolic Blood Pressure Intervention Trial (SPRINT)), in which a BP goal of < 140 mm Hg was compared with a target BP of < 120 mm Hg in 9361 individuals at increased CV risk but without diabetes.[10] The primary composite endpoint was myocardial infarction, other acute coronary syndromes, stroke, heart failure or death from CV causes. The intervention was discontinued early after a median follow-up of 3.26 years owing to lower rates of CV morbidity and mortality in patients on the intensive treatment.[10] However, the generalizability of the SPRINT results has been questioned on the basis of patients selected, BP values achieved, BP measurement procedure used and other considerations.[11] Interestingly, the benefit of intensive BP lowering in SPRINT was almost entirely due to a reduction in the new onset of heart failure.[11]

In this context, a recent meta-analysis has reported significant reductions in the risk of major CVD events, stroke, coronary heart disease, heart failure and all-cause mortality, with every 10 mm Hg reduction in SBP to an on-treatment BP < 130 mm Hg.[12] In contrast, in the HOPE-3 trial, treatment with candesartan/hydrochlorothiazide (HCTZ) 16/12.5 mg vs placebo over a period of 5.6 years in a population with a baseline mean BP 138.1/81.9 mm Hg lowered SBP to 128.2 mm Hg (vs 133.9 mm Hg in the placebo group) but did not result in a significantly lower risk of major CV events in an intermediate-risk population without CVD and with a low rate of diabetes.[13] These conflicting data on the important question of target BP to aim for in a given patient, may at least in part, be due to the variations in patient characteristics, baseline BP, low or high total CV risk, diabetes and so on. With more information available, this will eventually result in recommendations for a more individualised treatment strategy. Taken together, however, at least in certain subgroups, hypertension treatment will probably be more intense than it is recommended today, and this would also have marked consequences for the need of combination treatment strategies.

HISTORICAL ASPECTS OF SPC DEVELOPMENT

Dual and triple single-pill combinations (SPC) were available from the 1960s, mostly combining reserpine with a diuretic and (di) hydralazine. At that time, the term generally used was 'fixed-dose combinations' since the possibility to change doses of one or more combination partners was rather limited when 'single-pill combinations' were introduced on the market. The success of these combinations was based on the evidence from the Veterans Administration studies 1 and 2, indicating that they were highly effective in lowering BP and markedly reduced CV events and mortality.[14,15] After several such SPCs gaining market access in the 1960s, no triple SPCs containing more modern anti-hypertensive agents were approved for approximately three decades owing to growing restrictions from government agencies. Essentially, it was required that when two or more drugs were to be combined in a single dosage form, each component (in the chosen dosage) had to contribute to the claimed effect.

With the need for SPC in various indications becoming more obvious and also with the growing knowledge about clinical trial methodology over the following decades, the requirements for the approval of SPC slowly changed. In the US, a factorial design comparing the highest triple dose to the highest dose of each of the dual combinations was required for the approval of a triple SPC as second-line therapy, wherein the triple combination must be superior to all three dual therapies. In Europe, approval of the triple SPC as second-line therapy requires conducting studies that randomise non-responders to dual therapy, to receive triple therapy. However, for a combination of drugs where a wide therapeutic experience is available, a study showing bioequivalence to the components in free combination with the fixed-dose combination is acceptable for approval as substitution or replacement therapy. With this renewed approval policy, amlodipine (Aml), valsartan (Val) and HCTZ was the first modern triple anti-hypertensive SPC to become available in 2009, followed by olmesartan (Olm), Aml and HCTZ, and aliskiren (Ali), Aml and HCTZ in 2010.

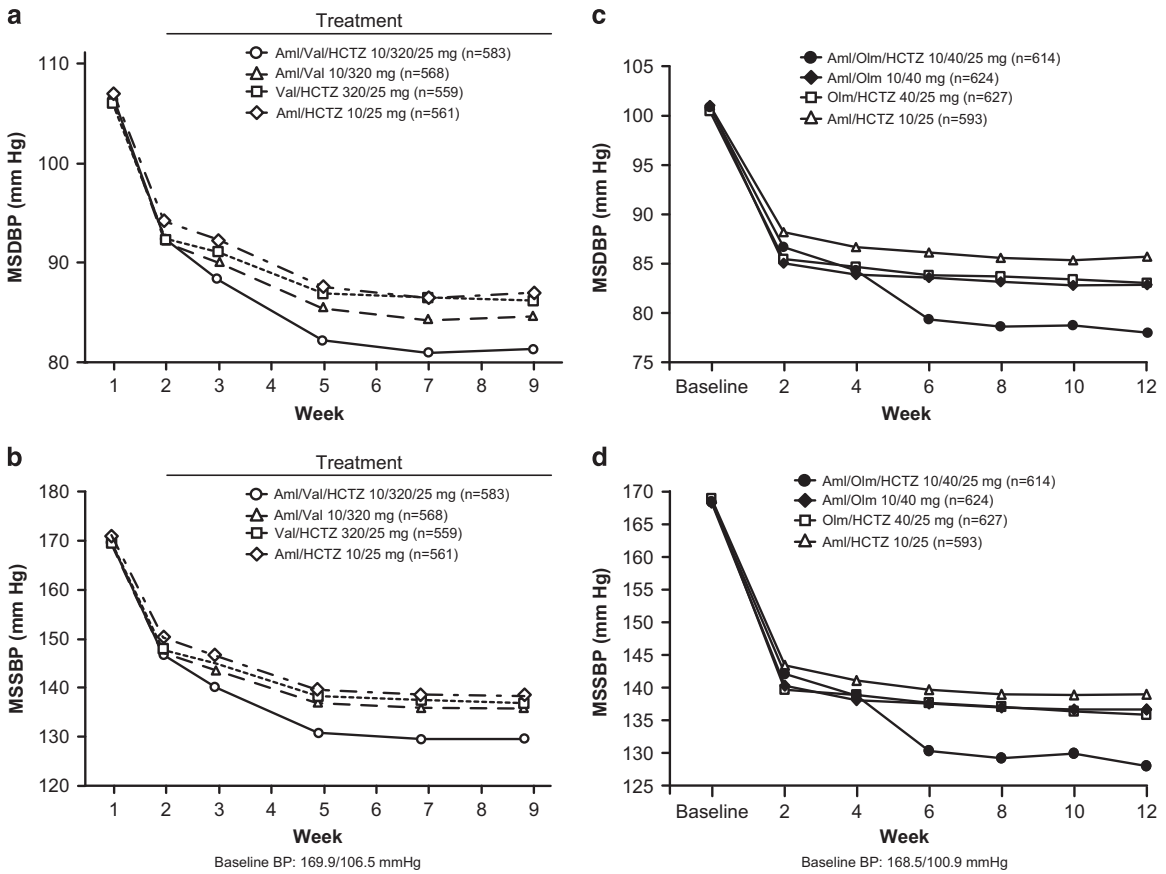


Figure 1. Triple-combination therapies with Aml/Val/HCTZ[20] and Aml/Olm/HCTZ[21] provide early reductions in DBP (**a**,**c**) and SBP (**b**,**d**) from baseline compared with dual therapies. MSDBP, mean sitting diastolic blood pressure; MSSBP, mean sitting systolic blood pressure.

RATIONALE FOR THE USE OF MULTIPLE AGENTS IN A COMBINATION THERAPY IN THE TREATMENT OF HYPERTENSION

Dual combinations fail to achieve BP control in a significant proportion of patients. It has been estimated that three and more anti-hypertensive agents are required in approximately one-fourth to one-third of patients.[3,16] Combining anti-hypertensive agents from two different classes has been shown to result in an approximately five-fold greater BP reduction vs doubling the dose of a single agent.[17] In addition, combining drugs with complementary mechanisms of action may provide benefit beyond BP lowering, such as improving tolerability, and thus higher rates of adherence with the prescribed medication as compared with increasing the dose of a single agent.[18]

Commonly used classes of drugs for hypertension include angiotensin receptor blockers (ARBs), such as Val or Olm; angiotensin-converting enzyme inhibitors (ACEIs); thiazides (HCTZ and bendroflumethiazide), and thiazide-like diuretics (chlorthalidone and indapamide (Ind)), and calcium channel blockers (CCBs), such as Aml. Other effective anti-hypertensive agents are α- and ß-receptor blockers and centrally acting agents.

Combining drugs from different classes may provide inherent advantages. Addition of an inhibitor of the renin–angiotensin–aldosterone system (RAAS) to a thiazide or a thiazide-like diuretic has an additive effect on BP reduction and also improves the safety profile by countering the diuretic-induced adverse impact on electrolytes (hypokalaemia), uric acid and glucose metabolism.[19] Combining RAAS inhibitors with a CCB improves the tolerability profile by reducing the incidence of peripheral oedema, an important adverse event (AE) observed with CCBs and also blunts the heart rate acceleration occasionally observed with a dihydropyridine CCB.[19] Further, CCBs and diuretics are known to activate the RAAS, and this may act as a counter regulatory mechanism, limiting the BP-lowering efficacy of these drugs. By this mechanism, combination with a RAAS inhibitor will markedly enhance the anti-hypertensive efficacy of both diuretics and CCBs.

Table 1 lists randomised trials with triple SPC therapies in patients with hypertension. A large, double-blind, parallel-design trial in 2271 patients with BP ⩾ 145/100 mm Hg showed that triple therapy with Aml/Val/HCTZ at a dose of 10/320/25 mg produced significantly greater reductions in SBP of 39.7 mm Hg compared with 31.5–33.5 mm Hg on the three dual combinations contained in the triple SPC (Aml/Val 10/320 mg, Val/HCTZ 320/25 mg and Aml/HCTZ 10/25 mg). In all treatment groups, the full BP-lowering effect was seen after 2 weeks at maximal dose. At the end of the study (week 8), a significantly greater proportion of patients (70.8%) achieved BP control with triple therapy, compared with 48.3% for Val/HCTZ, 54.1% for Aml/Val and 44.8% for Aml/HCTZ.[20] A 12-week, randomised, double-blind, parallel-group trial, 'Triple Therapy with Olmesartan Medoxomil, Amlodipine and Hydrochlorothiazide in Hypertensive Patients Study' (TRINITY) conducted in 2492 patients with BP ⩾ 140/100 or ⩾ 160/90 mm Hg, showed that Aml/Olm/HCTZ (10/40/25 mg) lead to significantly greater reductions in sitting BP compared with the dual combinations Aml/Olm 10/40 mg, Aml/HCTZ 10/25 mg and Olm/HCTZ 40/25 mg. Accordingly, the proportion of patients reaching BP target at study end was significantly higher with triple combination (69.9%) compared with the dual therapies (52.9, 53.4 and 41.1% respectively).[21] Figure 1 depicts BP reductions from baseline in patients with moderate to severe hypertension with both the triple combinations Aml/Val/HCTZ and Aml/Olm/HCTZ. In a third albeit much smaller randomised, single-blind study in 220 patients, a triple SPC

containing telmisartan (Tel) reported that SBP and diastolic BP (DBP) reductions were superior with Aml/Tel/HCTZ (5/40/12.5 mg) at the end of a 12-week treatment period compared with dual therapy with Tel/HCTZ (40/12.5 mg).[22]

Aml/Val/HCTZ was found to reduce mean 24-h ambulatory BP, daytime and night time mean ambulatory BP by 30.3/19.7, 31.2/20.5 and 28.0/17.8 mm Hg, respectively, consistently more effective compared with the respective dual-combination

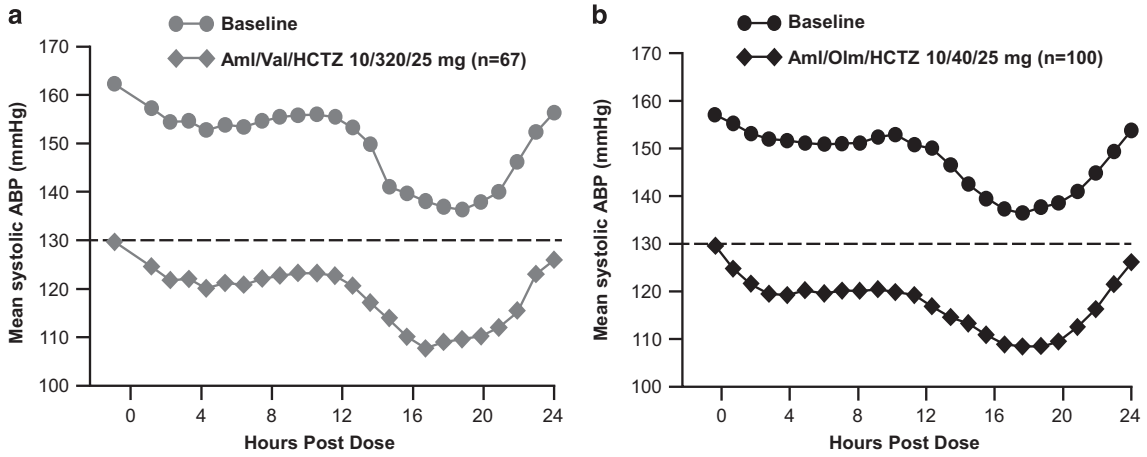


Figure 2. Reduction of mean ambulatory SBP through 24 h with the triple-combination therapies Aml/Val/HCTZ[23] (**a**) and Aml/Olm/HCTZ[24] (**b**). ABP, ambulatory blood pressure.

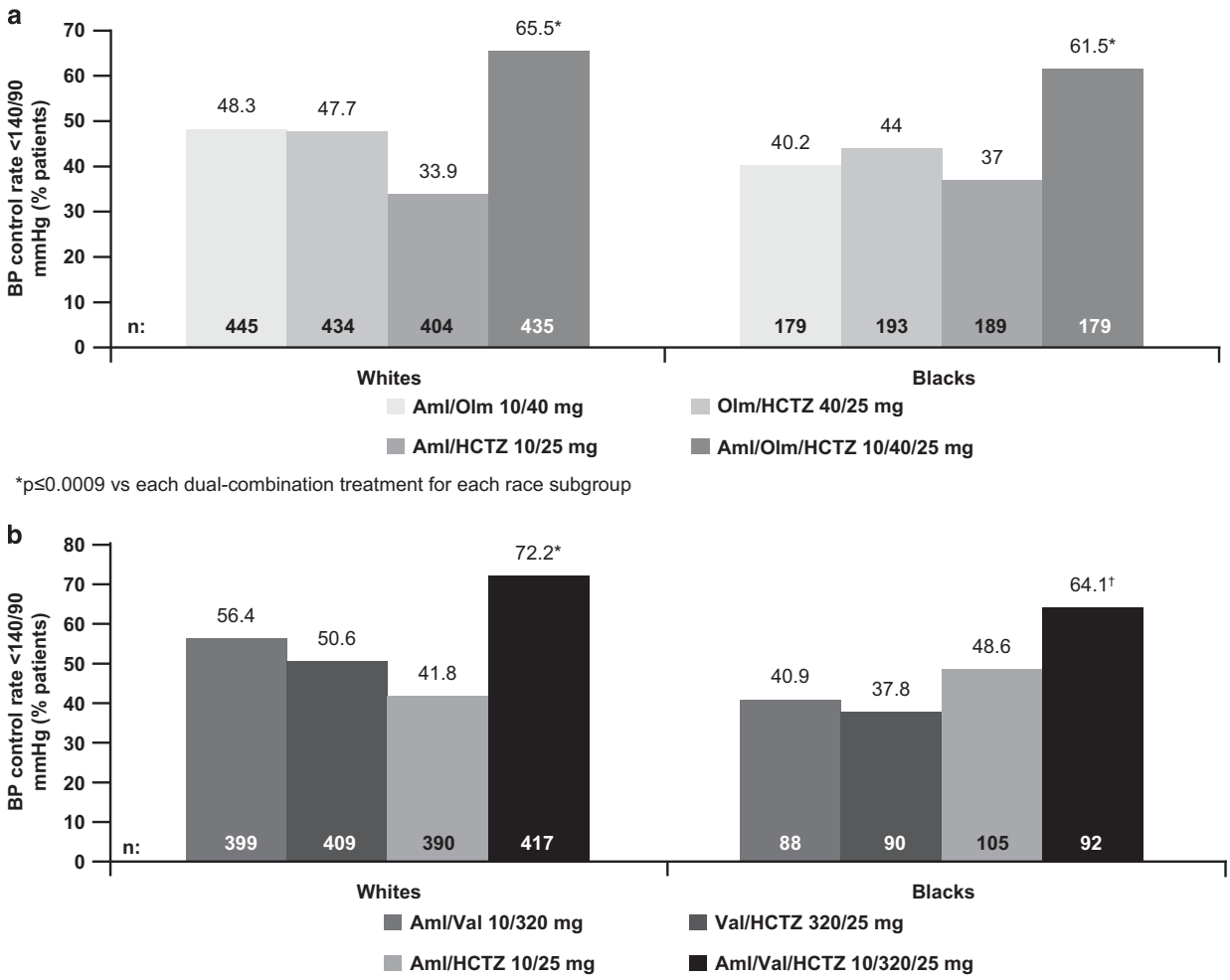


Figure 3. Triple-combination therapy with Aml/Olm/HCTZ[29] (**a**) and Aml/Val/HCTZ[28] (**b**) enabled better BP control compared with dual therapies, independent of race.

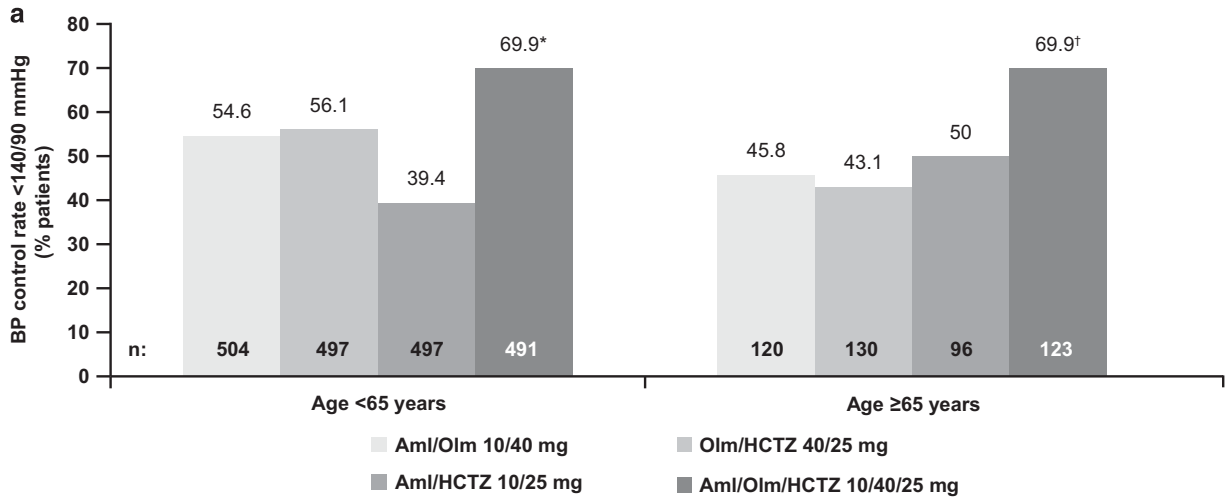
therapies[23] (Figure 2). The TRINITY ambulatory BP monitoring sub study, a randomised, double-blind study conducted in 440 patients with moderate to severe hypertension, also showed that once-daily Aml/Olm/HCTZ resulted in greater reductions in the mean 24-h SBP and DBP compared with the dual-combination regimens.[24]

Similar safety and tolerability profiles were reported with triple therapies compared with dual regimens in the aforementioned studies. In a systematic review and meta-analysis of 11 studies and 7563 patients, based on the evaluable results of 10 studies, it was shown that triple combinations with CCB/ARB/HCTZ, at any dose, provided more BP control than dual combinations and significantly decreased BP more than any dual combination of these agents (5.8/3.5 mm Hg in SBP/DBP (for both $P < 0.0001$)).[25] Similarly, based on the results of four studies with ambulatory BP measurements, triple combinations decreased 24-h ambulatory SBP/DBP by 7.1/4.5 mm Hg more than dual combinations (for both $P < 0.0001$).[25] These BP-associated benefits with triple therapy vs dual therapy were not seen at the expense of increased risk of AEs.[25]

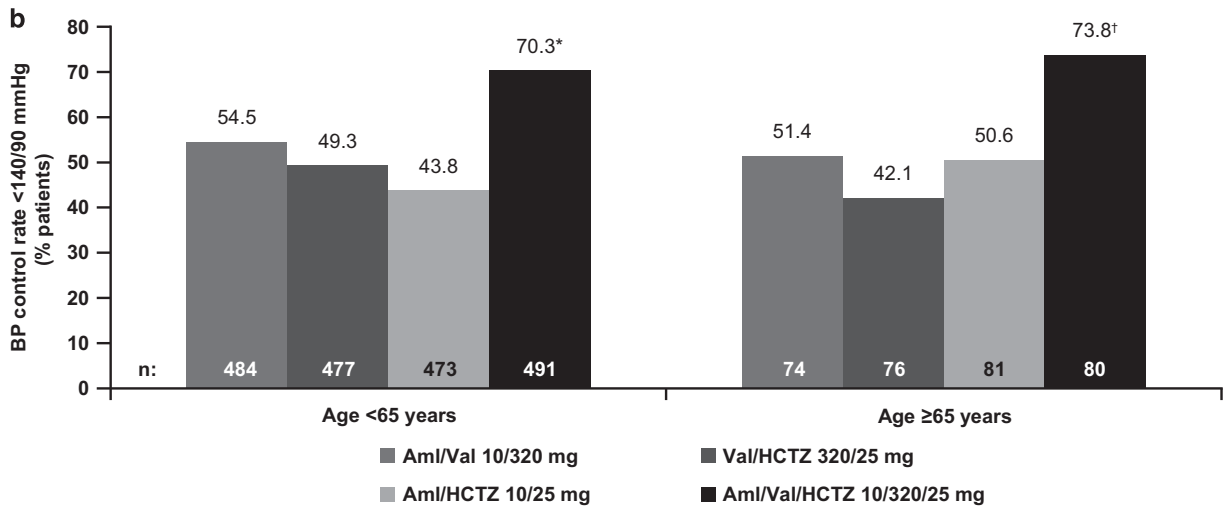
All recent national and international guidelines to date agree that the main classes of anti-hypertensives to be used in the management of hypertension should be RAAS blockers, CCB and diuretics.[5,9] There is a minor disagreement with respect to the recommendations of dual combinations with RAAS blockers plus either diuretics or CCB playing an outstanding role. In contrast to the fact that there are several choices both for initial monotherapy and dual combinations, all guidelines recommend the combination of a RAAS blocker plus CCB and diuretic whenever triple therapy is required.[5,9,26] Currently the ARBs Val and Olm are approved as triple SPC by the regulatory institutions in the US (Food and Drug Association (FDA)) and Europe (European Medical Agency (EMA)). The direct renin inhibitor aliskiren (in combination with Aml and HCTZ) is also approved by the FDA, while the ARB Tel plus Aml and HCTZ and the ACEI perindopril plus Aml and Ind are available in some regions.[5,9,26]

TRIPLE THERAPY IN HIGH-RISK PATIENT GROUPS AND FACTORS AFFECTING BP LOWERING

RAAS blockers, CCBs and diuretics are recommended for the treatment of hypertension in high-risk individuals, such as patients with CVD, chronic kidney disease, stroke etc.[5,9] A TRINITY subgroup analysis in patients with diabetes, chronic kidney disease or chronic CVD showed that both short-term (12 weeks) and long-term treatment with Aml/Olm/HCTZ was well tolerated,

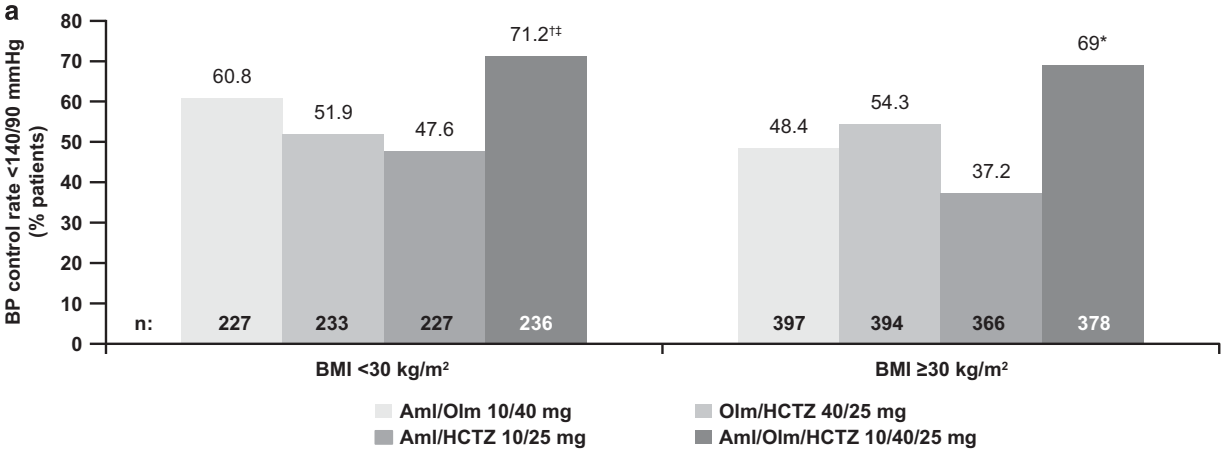


*p<0.0001, †p≤0.005 vs each dual-combination treatment within age subgroup

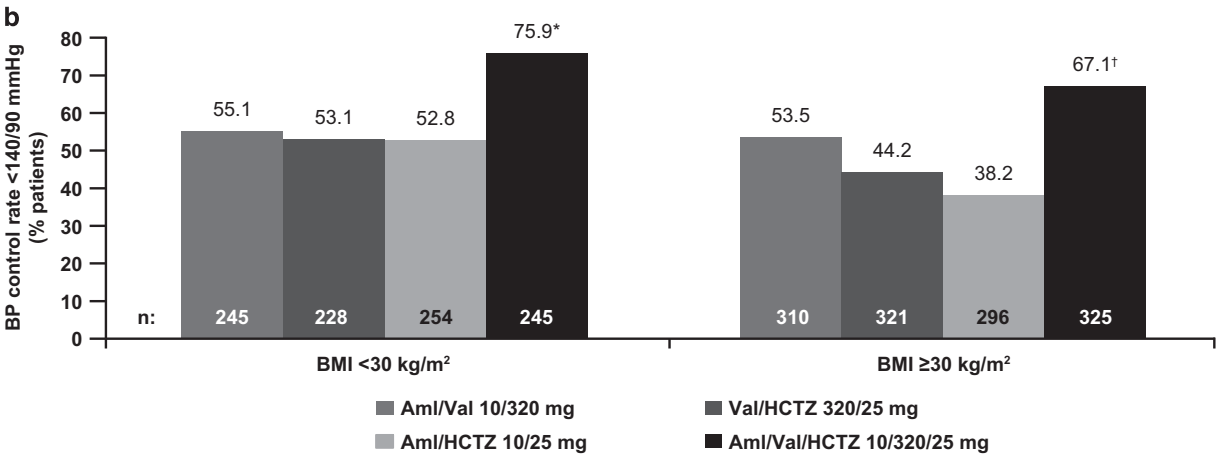


*p<0.0001 vs. each dual therapy; †p<0.01 vs. each dual therapy

Figure 4. Triple-combination therapy with Aml/Olm/HCTZ[31] (**a**) and Aml/Val/HCTZ[28] (**b**) enabled better BP control compared with dual therapies, independent of age.



*p<0.0001 vs each dual therapy; †p<0.05 vs Aml/Olm; ‡p<0.0001 vs Olm/HCTZ and Aml/HCTZ



*p<0.0001 vs. each dual therapy; †p<0.001 vs. each dual therapy

Figure 5. Triple-combination therapy with Aml/Olm/HCTZ[32] (**a**) and Aml/Val/HCTZ[28] (**b**) enabled better BP control compared with dual therapies, independent of BMI.

lowered BP more effectively, and enabled more patients to reach BP goal than the corresponding dual regimens.[27]

Demographic factors and patient characteristics, such as age, race, ethnicity, gender and body mass index (BMI) are known to affect the response to anti-hypertensive agents.[5] In the study by Calhoun *et al.*,[28] Aml/Val/HCTZ produced significantly greater reductions in SBP and DBP, and significantly better SBP control in black patients than dual therapies (Aml/Val and Aml/HCTZ). In a subgroup analysis of black and non-black populations in the TRINITY trial, Aml/Olm/HCTZ provided greater BP reductions, with higher proportions of patients achieving BP control than those on the component dual therapies, regardless of race[29] (Figure 3). Subgroup analysis of a 12-week, double-blind, randomised, active-controlled, parallel-group, international, multicentre study (Exforge Evaluation in Stage Two Hypertensives of African Descent (EX-STAND)) showed that in black patients with stage 2 hypertension, Aml/Val produced a significantly greater change in SBP than Aml monotherapy from baseline to week 12. Addition of HCTZ to existing dual therapy further reduced SBP by 8.9 mm Hg, producing greatest reductions from baseline.[30]

Hypertension prevalence markedly increases with age. At present, on-treatment goal BP in elderly patients remains a matter of controversy with two guidelines recommending a target BP of $<150/90$ mm Hg (instead of $<140/90$ mm Hg) in adults, aged $\geqslant 60$ years.[5,9] A subgroup analysis of the TRINITY trial showed that Aml/Olm/HCTZ combination was more effective than dual therapies in patients with moderate to severe hypertension aged $\geqslant 65$ years[31] (Figure 4). Also, in the pivotal trial of Aml/Val/HCTZ SPC, this triple combination produced significantly higher BP control rates and was more effective than dual therapies, independent of gender, age (<65 or $\geqslant 65$ years), BMI (<30 or $\geqslant 30$ kg m^{-2}) or ethnicity (Hispanic/Latinos or Non-Hispanic/Latinos).[28]

Obesity (defined as BMI $\geqslant 30$ kg m^{-2}) is another important risk factor for the development of hypertension, and prompt adequate control of BP in obese individuals is important. A pre-specified subgroup analysis of the TRINITY trial showed that the Aml/Oml/HCTZ combination was efficacious and safe in obese patients providing greater mean BP reductions and enabling larger proportions of study participants to achieve BP goal compared with the component dual-combination treatments.[32] Higher BP control rates were also achieved with Aml/Val/HCTZ compared with the respective dual combinations, independent of BMI <30 or $\geqslant 30$ kg m^{-2} [28] (Figure 5).

TRIPLE-COMBINATION THERAPY IN A REAL-WORLD SETTING

Randomised controlled trials (RCTs) are essential and remain the gold standard to determine the efficacy, safety and tolerability of a drug in a controlled clinical setting, in particular towards the registration of a new drug. Although 'real-world evidence' studies may not be as effective as RCTs in collecting efficacy data, they are

Table 2. Comparison of real-world evidence studies of triple-combination therapies

	Aml/Val/HCTZ (EXCITE study)[34] N = *9794*	*Aml/Olm/HCTZ*[35] N = *5831*	*Aml/Per/Ind (PAINT study)*[36] N = *6088*	*Aml/Per/Ind (PIANIST study)*[37] N = *4731*
Countries where the study was conducted	Middle East (Egypt, Lebanon, UAE, Oman, Kuwait, Qatar and Bahrain) Asia (The Philippines, Indonesia, Pakistan, Taiwan and South Korea)	Austria and Germany	Hungary	Hungary
Baseline BP	166.0/97.7 mm Hg	162.1/93.6 mm Hg	158.1/92.6 mm Hg	160.5/90.8 mm Hg
Mean SBP reduction from baseline	− 36.6/ − 17.8 mm Hg (week 26)	− 28.8/ − 13.9 mm Hg (week 24)	− 26.7/ − 12.9 mm Hg (month 4)	− 28.3/ − 13.8 mm Hg (month 4)
Patients achieving BP goal (%)	70.9	67.5	80, 77, 73 and 71% for Per/Aml/Ind 5/5/1.5, 5/10/1.5, 10/5/1.5 and 10/10/1.5 mg, respectively	72
24-hour BP-lowering efficacy	NA	NA	Baseline: 138.7/77.5 mm Hg Month 4: 125.5/70.4 mm Hg	Baseline: 147.4/82.1 mm Hg Month 4: 122.6/72.8 mm Hg
Dose and administration	Aml/Val/HCTZ: 5/160/12.5, 5/160/25, 10/160/12.5, 10/160/25, and 10/320/25 mg OD	Aml/Olm/HCTZ: 5/20/12.5, 5/40/12.5, 10/40/12.5, and 10/40/25 mg OD	Aml/Per/Ind: 5/2.5/1.25, 5/5/1.25, 10/5/1.25, 5/10/2.5, and 10/10/2.5 mg OD	

Abbreviations: Aml, amlodipine; BP, blood pressure; HCTZ, hydrochlorothiazide; Ind, indapamide; NA, not available; OD, once daily; Olm, olmesartan; Per, perindopril; SBP, systolic blood pressure; Val, valsartan.

capable of providing data from large patient populations beyond the inclusion and exclusion criteria of a clinical trial in an observational, non-interventional setting and thus may provide proof of the generalizability of the results of the respective RCTs.[33]

In four observational studies of real-world clinical experience, SPC therapy with Aml/Val/HCTZ, Aml/Olm/HCTZ or Aml/Per/Ind was associated with significant reductions in BP, achievement of BP goals and improved control rates[34] (Table 2). Treatment effects were observed in large groups of patients with hypertension, including different ethnicities, and in patients inadequately controlled with initial monotherapy or dual combination therapy. The 'Experience of Amlodipine and Valsartan in Hypertension' (EXCITE) study, a large, multinational, prospective, non-interventional study in 9794 hypertensive patients from 13 countries in the Middle East and Asia showed that Aml/Val/HCTZ SPC provided meaningful SBP and DBP reductions from baseline across all severities of hypertension. Similarly, in a subgroup analysis of the EXCITE study that included elderly, obese patients, and patients with diabetes or isolated systolic hypertension, significant and clinically relevant BP reductions were observed with Aml/Val/HCTZ SPC. Triple combinations enabled ~70% of patients to achieve a BP target of $< 140/90$ mm Hg.[34]

In another multicentre, prospective, non-interventional study, Aml/Olm/HCTZ SPC provided meaningful BP reductions in 5831 patients. Following ~24 weeks of treatment, the target BP of $< 140/90$ mm Hg was attained in 67.5% of patients.[35] In the 'Perindopril-Amlodipine plus Indapamide Combination for Controlled Hypertension—Non-Intervention Trial' (PAINT), a 4-month, multicentre, prospective, observational, open-label study, 6088 patients not controlled with previous anti-hypertensive treatment were switched to triple therapy with Aml/Per/Ind sustained-release single-pill triple-combination therapy. Meaningful BP reductions were achieved in this real-world setting. The Aml/Per/Ind combination was also effective in reducing ambulatory BP in hypertensive patients uncontrolled on previous therapy.[36] The 'Perindopril-Indapamide plus Amlodipine in High Risk Hypertensive Patients' (PIANIST) study conducted in 4731 adult patients at high or very high CV risk demonstrated that Aml/Per/Ind was effective in reducing both office BP and ambulatory BP in a large population of high- and very high-risk hypertensive patients with uncontrolled BP on previous therapy in a real-life setting.[37] Thus, these real-world studies confirm the reliability of RCTs and strengthen the applicability of the RCT data in an actual clinical setting.

SAFETY AND TOLERABILITY OF A TRIPLE THERAPY

Triple combinations of ARBs or ACEIs, Aml and diuretics are generally well tolerated, and randomised trials have shown that the two triple combinations Aml/Val/HCTZ and Aml/Olm/HCTZ are associated with similar rates of AEs in patients with stage 2 hypertension.[38] Further studies could demonstrate that on both triple therapies, the rates of AE are similar to those on the respective dual combinations[20,21] (Table 3). Most reported AEs were mild to moderate in intensity, and no additional risks other than those previously identified were observed with long-term treatment. The most frequently reported AEs with the triple combination were generally dizziness, peripheral oedema and headache. The incidence of AEs reported in different clinical studies cannot be directly compared because of differences in study populations and conduct and also may not reflect the incidence in clinical practice. In real-world studies, similar tolerability profiles were reported with low incidence of AEs related to low BP.[34–36] In general, all combinations with ARBs have similar safety and tolerability, although recently some concern was raised with Olm, wherein an increased risk of serious enteropathies was reported, though very rare ($< 1/10\,000$). Sprue-like enteropathy may be associated with symptoms including severe or chronic diarrhoea and substantial weight loss and may require hospitalisation.[39] Of note, while efficacy in terms of BP reductions, morbidity and mortality is well studied with Val in various indications (hypertension, heart failure, post myocardial infarction),[6,40,41] similar data are not available with Olm.

It is important to emphasise here that the use of SPCs in everyday practice is no longer hampered by the loss of dosing flexibility. Even for triple combinations, a choice between different doses of the components is available. Thus, in the available single-pill triple (and dual) combinations, both Aml and the respective ARB can be employed up to their maximal doses. In contrast, the choice of HCTZ in all SPC is restricted to either 12.5 or 25 mg. In this context, it is interesting to note that HCTZ doses of 50–100 per day mg are markedly more effective in lowering BP[42] and have successfully

Table 3. Tolerability profile with triple-combination therapies in patients with moderate to severe hypertension from independent studies

	Aml/Val/HCTZ[20] *10/320/25 mg*	*Aml/HCTZ 10/325 mg*	*Val/HCTZ 320/25 mg*	*Aml/Val 10/320 mg*
All AEs	263 (45.2)	271 (48.3)	253 (45.3)	254 (44.9)
Discontinuation due to AE	Dizziness (1.0%), hypotension (0.7%) and peripheral oedema (0.2%)	Dizziness (0.2%), hypotension (0%) and peripheral oedema (0.9%)	Dizziness (1.1%), hypotension (1.1%) and peripheral oedema (0%)	Dizziness (0.4%), hypotension (0%) and peripheral oedema (0.4%)
AEs occurring in ⩾2% of any treatment group				
Peripheral oedema	26 (4.5)	50 (8.9)	5 (0.9)	48 (8.5)
Headache	25 (4.3)	39 (7.0)	30 (5.4)	28 (4.9)
Dizziness	45 (7.7)	22 (3.9)	39 (7.0)	13 (2.3)
Nasopharyngitis	12 (2.1)	12 (2.1)	13 (2.3)	13 (2.3)
Nausea	12 (2.1)	12 (2.1)	7 (1.3)	10 (1.8)
Back pain	12 (2.1)	12 (2.1)	13 (2.3)	5 (0.9)
Fatigue	13 (2.2)	8 (1.4)	15 (2.7)	12 (2.1)
Muscle spasms	13 (2.2)	5 (0.9)	7 (1.3)	7 (1.2)
Dyspepsia	13 (2.2)	2 (0.4)	5 (0.9)	6 (1.1)

	Aml/Olm/HCTZ[21] *10/40/25 mg*	*Aml/Olm 10/40 mg*	*Olm/HCTZ 40/25 mg*	*Aml/HCTZ 10/25 mg*
All AEs	335 (58.4)	308 (51.7)	319 (55)	325 (58.9)
Discontinuation due to AE	23 (4.0)	6 (1)	12 (2.1)	11 (2)
AEs occurring in ⩾2% of any treatment group				
Dizziness	57 (9.9)	29 (4.9)	58 (10)	17 (3.1)
Peripheral oedema	44 (7.7)	42 (7.0)	6 (1.0)	46 (8.3)
Headache	37 (6.4)	42 (7.0)	38 (6.6)	33 (6.0)
Fatigue	24 (4.2)	34 (5.7)	31 (5.3)	36 (6.5)
Nasopharyngitis	20 (3.5)	11 (1.8)	20 (3.4)	16 (2.9)
Muscle spasms	18 (3.1)	12 (2.0)	14 (2.4)	13 (2.4)
Nausea	17 (3.0)	12 (2.0)	22 (3.8)	12 (2.2)
Upper respiratory tract infection	16 (2.8)	26 (4.4)	18 (3.1)	14 (2.5)

	Aml/Tel/HCTZ[22] *5/40/12.5 mg (%)*	*Tel/HCTZ 40/12.5 mg (%)*
Nausea	3.77	5.88
Vomiting	4.72	4.9
Tiredness	3.77	6.86
Gastrointestinal distress	3.77	–
Headache	–	4.9

	Aml/Ali/HCTZ[60] *5/150/12.5 mg*	*Ali/Aml 150/5 mg*
All AEs	69 (34.2)	84 (40.2)
Discontinuation due to AE	7 (3.5)	4 (1.9)
Treatment emergent AE	21 (10.4)	23 (11)
Most frequent AEs (⩾2% patients)		
Headache	22 (10.9)	18 (8.6)
Dizziness	8 (4.0)	6 (2.9)
Diarrhoea	3 (1.5)	10 (4.8)
Peripheral oedema	4 (2.0)	6 (2.9)
Muscle spasms	5 (2.5)	4 (1.9)
Cough	2 (1.0)	6 (2.9)
Nasopharyngitis	3 (1.5)	5 (2.4)
Palpitations	5 (2.5)	0

Abbreviations: Aml, amlodipine; AE, adverse event; Ali, aliskiren; HCTZ, hydrochlorothiazide; Olm, olmesartan; Tel, telmisartan; Val, valsartan. Values are presented as n (%) unless otherwise specified.

been used in the past, such as in the Veterans Administration trials 1 and 2.[14,15] However, in recent years, these higher doses of HCTZ have disappeared in order to avoid dose-dependent biochemical and metabolic adverse events such as hypokalemia, hyponatremia, hyperuricemia and possibly insulin resistance.[43]

This restriction of HCTZ to a maximum dose of 25 mg both in monotherapy and also in combination therapy including SPC has implications for the efficacy of both dual and triple SPC. Patients without normalisation of their BP in spite of triple therapy containing a diuretic have been described as being drug-resistant and it is estimated that ~5–10% of all hypertensive patients may be resistant by this definition (excluding non-adherence).[5] It can thus be concluded that stepping up therapy to the available SPC with high doses of Aml and ARB and 25 mg HCTZ may allow BP control in ~90% of the hypertensive population. Intensification of diuretic therapy by the use of adding spironolactone has recently been

shown to be more effective in lowering BP in such drug-resistant patients than adding doxazosin or bisoprolol[44]. However, spironolactone use is limited by hormonal side effects in men and by the risk of hyperkalemia, especially in patients with impaired renal function. It is therefore interesting to speculate that increasing the dose of HCTZ in triple combinations will also markedly enhance the BP lowering efficacy and will thus, without adding a fourth antihypertensive agent, reduce the number of 'drug-resistant' patients.

ADHERENCE, COST EFFECTIVENESS AND HEALTH ECONOMIC BENEFITS

As a chronic disease, hypertension requires long-term treatment; it is therefore important to ensure treatment adherence and consider the cost effectiveness of the long-term therapy. Furthermore, non-adherence or poor adherence to treatment has been shown to predict higher BP levels compared with adherence to the treatment regimen in some but not all studies.[45] In this context, it is important to note that patient adherence has been shown to be high at the time of a doctor's visit, a phenomenon named white coat compliance.[46] It is therefore that office or clinic BP may not correlate closely with the degree of adherence to a prescribed drug regimen.

Among the multifactorial origin of non-adherence, therapy itself may be a crucial factor involved. An early retrospective study could show that the total number of daily pills may be a critical factor for adherence with newly prescribed BP or lipid-lowering treatment.[47] Also, a Cochrane analysis concluded that reducing the number of daily doses appears to be effective in increasing adherence to BP lowering medication and should be tried as a first line strategy.[48]

SPCs simplify anti-hypertensive regimens by reducing the daily pill burden and result in improved patient adherence compared with multiple-pill/free combination regimens. The availability of SPC that leads to a more rapid achievement of BP goals may positively affect clinical inertia, which may also act to ultimately improve BP control.[49] Improved adherence may finally translate into better outcome which has been demonstrated in several studies in patients with coronary heart disease.[50–52] This is in line with European Society of Cardiology/European Society of Hypertension (ESC/ESH) 2013 guideline recommendations for SPC to achieve better adherence and thereby BP control.[5] SPCs have also been recommended by other guidelines, such as the American Society of Hypertension/International Society of Hypertension, Canadian, and Japanese hypertension guidelines.[26,53,54]

Several studies have shown that SPC with three antihypertensive agents are advantageous for the patient and clinician to ensure patient compliance and adherence to treatment compared with multiple single drug or free-pill combinations.[45,55] Meta-analyses comparing dual combination therapy provided either as SPC or as two separate pills have reported that SPCs resulted in significant improvement in compliance and persistence compared with free-drug combinations in patients with hypertension.[56,57]

A German non-interventional study with Aml/Val/HCTZ involving 7101 patients and 905 physicians showed that approximately half of the patients were willing to make an out-of-pocket payment for reducing the number of pills to half. Furthermore, physicians were also willing to prescribe combination products to reduce pill burden.[58] Finally, real-world data indicate that Aml/Val/HCTZ SPC combination is associated with reduced health resource utilisation compared with free combinations.[59]

In conclusion, combination therapy including drugs from classes having complementary action is advantageous in terms of BP reduction and control, particularly in high-risk patients, and may be associated with improved tolerability. Administration of combination therapy as SPC is capable of enhancing adherence to treatment. With the goal of long-term BP reduction, prevention of end-organ damage, and a reduction in CV morbidity and mortality, triple-combination therapy as SPC may be beneficial in patients not controlled on dual therapy. This is in line with major hypertension guidelines that recommend two or more hypertensive agents with complementary mechanisms of action to control BP administered as SPC to improve adherence to treatment.

CONFLICT OF INTEREST

RD has received honoraria for scientific lectures and financial support for conducting clinical studies from Novartis, Servier, Berlin Chemie and UCB Pharma. MD has received consulting and lecture fees and research grants from Boehringer Ingelheim, AstraZeneca, Servier, Menarini IFR, Schering-Plough, Guidotti, Pfizer, Knoll, Bayer, Chiesi, Daiichi-Sankyo, Merck Sharpe & Dohme and Malesci. MD has also received research support as a study investigator from Novartis Pharma AG and has been a speaker at scientific meetings organised by Novartis. BW has received consulting and lecture fees from Novartis, Pfizer, Menarini and Servier. PB is an employee of Novartis Pharma are thus eligible for Novartis stocks and stock options. CSM was an employee of Novartis at the time of manuscript preparation.

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