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Aliskiren, amlodipine and hydrochlorothiazide triple combination for hypertension

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Abstract

Cardiovascular-related morbidity and mortality is linked to hypertension with proportional gains in cardiovascular risk factor reduction with the lowering of blood pressure. Clinical trial data has shown that attaining goal blood pressure requires, for most patients, at least two antihypertensive medications, with a significant proportion requiring regimens of three or more medications. Single-pill triple combinations have returned to the market following results of increased efficacy and adherence over dual- and mono-therapy. The combination of aliskiren, amlodipine and hydrochlorothiazide is a rational choice for combination therapy and recent studies suggest that it is safe and effective in lowering blood pressure in patients who fail dual combination therapy.

Keywords

Aliskiren; amlodipine; angiotensin II; antihypertensive medications; cardiovascular disease; combination therapy; hypertension; renin

Hypertension (HTN) remains a major risk factor for cardiovascular disease (CVD) that affects over 65 million individuals in the USA [1] and nearly 1.5 billion individuals worldwide [2]. The relationship between blood pressure (BP) and risk of CVD is continuous and consistent, with each increment of 20 mmHg in systolic BP (SBP) or 10 mmHg in diastolic BP (DBP) doubling the risk of CVD [3–5]. A series of large-scale studies [6–10] have demonstrated that a combination of two or more antihypertensive medications is generally required to meet the HTN guidelines [4, 11]. Combining drug therapy to target multiple regulatory mechanisms offers the potential for improved BP control given the multifactorial pathogenesis of HTN [7, 12 – 14].

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••of considerable interest

Fixed-dose, triple-combination therapy has recently returned to the market showing improved efficacy and tolerability [15, 16]. Following the Veteran Affairs Cooperative Study in 1967 and 1970 of the triple drug combination reserpine, hydralazine and hydro-chlorothiazide (HCT), triple-combination therapy fell out of use in favor of a stepped-care approach [17, 18]. However, in May 2009 the US FDA approved a single-pill, triple combination of amlodipine (AML), valsartan (VAL) and HCT. In 2010, two more triple combinations were approved: AML, olmesartan (OM) and HCT; and aliskiren (ALI), AML and HCT. However, availability of these combinations is still limited to the USA and select European countries. All three formulations are consistent with guideline recommendations that a combination of a renin–angiotensin–aldosterone system (RAAS) blocker, a calcium channel blocker (CCB) and a diuretic be used when three drugs are required [11].

AML and HCT are popular choices for a CCB and diuretic, respectively, in single-pill combinations given their proven efficacy and tolerability [19]. RAAS blockers are widely used in combination therapies due to the life-saving evidence from landmark trials in patients with diabetes and cardio–renal risk [20–25]. ALI, a direct renin inhibitor, falls into the class of RAAS blockers with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (ARBs), and studies have shown similar efficacy and benefit [26–30]. Furthermore, drug combinations with ALI and AML or HCT have improved tolerability. For example, ALI reduces the incidence of CCB-related vasodilatory edema [31, 32] and diuretic-related hypokalemia [33–36].

The two prior triple-combination drug formulations (AML/VAL/HCT and OM/AML/HCT) have been previously reviewed [37, 38]. The aim of this article is to review the pharmacologic properties, efficacy and tolerability of the fixed-dose triple combination of ALI, AML and HCT.

Introduction to the drug

Amturnide (ALI/AML/HCT) is a single tablet of ALI hemifumarate, AML besylate and HCT. It is available in the following dosages: 150/5/12.5 mg, 300/5/12.5 mg, 300/5/25 mg, 300/10/12.5 mg and 300/10/25 mg [101].

Pharmacologic properties of ALI, AML & HCT: mechanisms of action

ALI is a nonpeptide piperidine with high affinity and specificity for human renin [39, 40]. It is the first available direct renin inhibitor and acts at the rate-limiting step of angiotensin II synthesis, inhibiting the conversion of angiotensinogen to angiotensin I [41]. Unlike angiotensin-converting-enzyme inhibitors or ARBs, ALI does not cause a compensatory increase in plasma renin activity (PRA) [30, 41, 42]. The BP-lowering effects of ALI are mediated through decreased angiotensin II-related vasoconstriction and sodium retention. AML is a dihydropyridine CCB that blocks the contractile effects of calcium on cardiac and vascular smooth muscle cells, causing a reduction in peripheral vascular resistance [37]. HCT is a thiazide diuretic with inhibition of the sodium chloride cotransporter in the renal distal convoluted tubule and its mechanism for lowering BP is still not completely understood [43]. Combining the different mechanisms of action of ALI, AML and HCT may provide synergistic efficacy in BP reduction by lessening compensatory physiologic changes seen with mono- or dual-therapy. Specifically, the renin-raising effects of HCT and AML are reduced by ALI, which would lead to less generation of angiotensin I [31, 32, 44].

Pharmacokinetics & pharmacodynamics

The pharmacokinetics of ALI, AML and HCT are not altered during coadministration (Table 1) [101, 102].

Aliskiren—ALI is poorly absorbed with an oral bioavailability of only approximately 2.5% [45]. Peak plasma concentrations ($C_{\max}$) are reached within 1–3 h of oral administration with wide interindividual variability in $C_{\max}$ [41, 46]. There is a large effect of food on the pharmacokinetics of ALI. Area under the plasma concentration–time curve is decreased by 71% and $C_{\max}$ by 85% when ALI is taken 30 min following a high-fat meal; however, these decreases are not considered clinically relevant because peak and trough plasma ALI concentrations exceed those needed for 50% inhibition of renin (0.6 nmol/l) after a single 150-mg dose [47]. Steady-state blood levels are achieved in 5–8 days with once-daily dosing. The terminal elimination half-life is 23–70 h (median 40 h) [46]. ALI is 47–51% protein-bound with a volume of distribution of approximately 135 l [46, 47]. Only a small portion of the active form of ALI (Figure 1) is metabolized via CYP450-3A4. The most important elimination route of ALI is via feces in its unmetabolized form. Because ALI is largely not metabolized and does not undergo significant renal excretion, no dose adjustment is required for patients with hepatic or renal impairment [101]. As with all RAAS blockers, ALI carries a black box warning for fertile women because it can cause injury and death to a developing fetus.

Amlodipine—The pharmacodynamics of AML have been extensively reviewed [48, 49]. Peak plasma concentrations of AML are reached 6–12 h after oral administration. Bioavailability is 64–90% and not altered by food. Steady-state levels are achieved in approximately 7 days with once-daily dosing, though peak biologic effect on BP may not be achieved for 4–6 weeks. AML undergoes extensive hepatic metabolism (~90%) to inactive metabolites. Excretion is primarily renal (60% metabolites and 10% unchanged), yet no dose adjustments are necessary in patients with renal impairment. Plasma concentrations rise with severe hepatic impairment (area under the plasma concentration–time curve: 40–60% increase) and caution is advised with administration in this patient population [50].

Hydrochlorothiazide—The pharmacodynamics of HCT have been previously reviewed [51]. Peak plasma concentrations of HCT are seen approximately 1–2.5 h following oral administration. Bioavailability is 60–80% and not altered by food. HCT has a half life of 6–19 h and is excreted in the urine unchanged. Diuresis begins within 2 h of oral administration, peaks at approximately 4 h, and is maintained for 6–12 h [103]. The diuretic effects of HCT are usually ineffective with severe renal impairment (creatinine clearance: <30 ml/min).

Clinical efficacy & tolerability

The efficacy and tolerability of the combination ALI, AML and HCT has been investigated in several clinical trials (Table 2) [52–56]. Most of these trials were open-label, step-up therapy studies where ALI, AML and HCT were not combined in a single pill. The ASCENT study is the only published randomized trial involving the single-pill formulation ALI, AML and HCT [53]. The studies described in this section include adult patients with mild-to-moderate HTN.

ACCELERATE—The ACCELERATE study was a Phase III trial for the combination ALI/AML and included titration to ALI/AML plus HCT or ALI/AML plus placebo (PL) for patients remaining uncontrolled after 24 weeks [52]. A total of 1254 adults with mild-to-moderate HTN (SBP 150–180 mmHg and DBP <110 mmHg) entered the 32-week, multicenter, double-blind, randomized, parallel-group superiority trial.

Following a 2–4 week PL run-in, patients were randomized in a 1:1:2 ratio to treatment with ALI 150 mg plus PL, AML 5 mg plus PL, or ALI/AML 150/5 mg. At week 8 an uptitration was forced with ALI 300 mg plus PL, AML 10 mg plus PL, and ALI/AML 300/10 mg.

From weeks 16–24 all patients received the same combination pill ALI/AML 300/10 mg. In the final phase (weeks 24–32) patients received an add-on HCT 12.5 mg or PL if their BP was above goal (140/90 mmHg).

Of the 1254 patients enrolled, 316 patients received AML/PL combination, 318 patients received ALI/PL combination, and 620 patients the ALI/AML combination. A total of 326 patients (26%) received ALI/AML 300/10 plus HCT 12.5mg at week 24. The overall efficacy of ALI/AML with or without HCT was 71.9%, with 901 of 1254 considered BP responders (SBP <140 mmHg or >20 mmHg reduction in SBP from baseline). Similar proportions of patients received the add-on therapy HCT or PL in each group; however, BP reductions comparing combination therapy with HCT and combination therapy with PL were not reported.

The study design allowed for comparing the lasting effects of initial BP therapy as all three groups converge to the same treatment at week 16. The authors hypothesized that initial combination therapy reduces compensatory effects associated with monotherapy. By week 32 there was no difference between the ALI/AML combination group and the ALI monotherapy group (SBP difference: $-0.7 \text{ mmHg} \pm -2.6 \text{ to } 1.2 \text{ mmHg}$; DBP difference: $0 \text{ mmHg} \pm -1.1 \text{ to } 1.1 \text{ mmHg}$), yet ALI/AML combination in comparison with the AML monotherapy showed a small BP difference (SBP difference: $-2.1 \text{ mmHg} \pm -4.0 \text{ to } -0.2 \text{ mmHg}$; DBP difference: $-1.3 \text{ mmHg} \pm -2.5 \text{ to } -0.2 \text{ mmHg}$).

Regarding tolerability, the cumulative withdrawal rate due to adverse events (AEs) was 13.8% in the initial combination group and 16.3% in the monotherapy groups. The withdrawal rate for ALI/AML compared with AML alone (18.4%) was statistically significant with a p-value of 0.04. Peripheral edema remained the most common AE, reported in 261 patients (20.8%). There were 32 serious AEs and six were potentially study drug related (angioedema cardiac failure, hypertensive crisis, peripheral edema and sigmoiditis).

ASCENT—The efficacy and tolerability of the triple-combination treatment with ALI/AML/HCT was compared to the dual combination ALI/AML in an 8 week double-blind, randomized, parallel-group, forced-titration, multicenter study in self-identified minorities [53]. The ASCENT study included 412 minority adults (62.3% African-American and 28.2% Hispanic/Latino) with stage 2 HTN (mean seated SBP: 160–200 mmHg). After a 1–4-week washout period, patients were randomized (1:1) to combination therapy ALI/AML 150/5 mg or monotherapy AML 5 mg. At week 1 therapy increased to ALI/AML/HCT 150/5/12.5 mg and ALI/AML 150/5 mg. At week 2 uptitration began and the two treatment groups received ALI/AML/HCT 300/5/25 mg and ALI/AML 300/5 mg. At week 4 the AML was doubled in both treatment groups, setting the two groups at ALI/AML/HCT 300/10/25 mg and ALI/AML 300/10 mg by the 8-week conclusion of the trial. In addition to obtaining office BP and safety data, ambulatory BP monitoring was conducted in 226 patients and biomarker (PRA, plasma renin concentration [PRC], plasma asymmetric dimethylarginine, serum cystatin C and urinary F2-isoprostanes) analysis performed.

A total of 203 patients (49.3%) received ALI/AML/HCT and in this group mean BP was reduced from 167.1/95.3 mmHg at baseline to 130.7/80.1 mmHg at the end of week 8. In total, 72.6% of patients receiving triple combination versus 53.2% of patients receiving dual therapy achieved BP <140/90 mmHg ($p < 0.0001$) (Figure 2). Notably, BP reduction was minimal in both groups between weeks 4 and 8 when AML was doubled (mean BP change of $-1.8/-1.3 \text{ mmHg}$ ALI/AML/HCT and $-2.6/-2.2 \text{ mmHg}$ ALI/AML). In the subset of patients with ambulatory BP monitoring, BP control was sustained over a 24-h period for both dual and triple-combination therapy. However, BP reductions with ALI/AML/HCT

approached those of ALI/AML after treatment dose after 15 h. Changes in PRA and PRC were consistent with known effects of ALI in both triple and dual therapy.

Cumulative AEs were less common in the triple-therapy group when compared with the dual-therapy group (34.2 vs. 40.2%), although seven of the 11 AEs that led to study discontinuation were in the ALI/AML/HCT group. The most commonly reported AEs were headache (10.9% ALI/AML/HCT vs. 8.6% ALI/AML), dizziness (4.0 vs. 2.9%) and peripheral edema (2.0 vs. 2.9%). Headache (n = 3), hypotension (n = 2) and upper abdominal pain (n = 2) were the only AEs resulting in study discontinuation for more than one patient, and were all seen in the triple-therapy group. The only AE report of abnormal serum potassium was mild hypokalemia (dual-therapy group).

ALI stepped-care treatment—Richter *et al.* assessed the efficacy and tolerability of an ALI-based, stepped-care treatment regimen where HTN treatment was incrementally increased up to ALI 300 mg plus HCT 25 mg plus AML 10 mg [54]. A total of 256 adults with mild-to-moderate HTN (mean seated SBP: 140–180 mmHg and DBP: 90–110 mmHg) were enrolled in the 24-week, open-label, multi center study. Following a 0–2-week optional washout period, patients underwent a 3-week PL run-in period to establish baseline BP and eligibility for treatment assignment. The study consisted of six sequential 4-week treatment periods. Patients progressed through the study receiving uptitration or addition of new medication until their BP was controlled (<140/90 mmHg or <130/90 mmHg for diabetics). Therapy was initiated with AML 150 mg daily followed by up-titration of ALI to 300 mg daily, addition of HCT 12.5 mg daily, uptitration of HCT to 25 mg daily, addition of AML 5 mg daily and finally uptitration of AML to 10 mg daily. The primary efficacy end point was the estimated cumulative probability of patients achieving BP target. Of the 256 active participants, 232 completed the study with 86.1% achieving BP control (mean seated BP < 140/90 mmHg or <130/80 mmHg for diabetics). In total, 46% (119 out of 265) of patients required ALI plus HCT plus AML and showed mean reductions in BP of –27.0/–13.7 mmHg. The three serious AEs (myocardial infarction, arterial HTN with noncardiac chest pain, and renal neoplasm) were not considered to be related to the study medication, and overall the discontinuation rate was low (9.4%).

Notably, the study population was predominantly Caucasian (99.2%) middle-aged (79.3% <65 years) men (55.9%), with a higher prevalence of diabetes mellitus (34.4%) than the general population. Within the diabetic subset, the majority (72.6%) achieved the stricter BP target of <130/80 mmHg.

Long-term safety, tolerability & efficacy of ALI/AML

Littlejohn *et al.* assessed the long-term efficacy and tolerability in a Phase IV trial for the ALI/AML combination with the option to add HCT if BP remained uncontrolled [55]. A total of 556 adults (predominately Caucasian [86%] middle-aged [81.8% <65 years] men [59.4%]) with an average BMI of 30.6 kg/m² with mean sitting DBP 90–110 mmHg were enrolled in the 54-week, open-label, multicenter study. Following a 2–4-week washout period, patients were given ALI/AML 150/5 mg combination pill for 2 weeks and then underwent forced titration to ALI/AML 300/10 mg to continue for 52 weeks. If BP was above goal of 140/90 mmHg at two consecutive visits, HCT 12.5 mg daily was added starting at week 10 with titration to 25 mg daily at week 14. Other antihypertensive medications and potassium supplements were prohibited.

Of the 556 patients that entered the study, 452 (81.3%) completed the 12 months of treatment. The primary reasons for discontinuation was AEs (n = 67; 12.1%), lost to follow-up (n = 9; 1.6%), and unsatisfactory therapeutic effect (n = 3; 0.5%). Eighty six (15.5%) of

the treated patients received at least one dose of HCT 12.5 mg, and the dose was titrated to 25 mg in 38 patients (6.8%). In the 86 patients who received ALI/AML + HCT the mean reduction in BP was 23.7/14.2 mmHg. The overall BP control (<140/90 mmHg) rate was 74.3% with a mean reduction in BP of 24.2/15.5 mmHg with or without HCT.

Regarding safety and tolerability, 424 patients (76.3%) reported at least one AE, yet the majority were mild or moderate in intensity. Fifteen patients (2.7%) reported serious AEs (none suspected to be related to the study drug); there were no deaths during the study. The most frequently reported AEs were peripheral edema (22.7%), upper respiratory tract infection (7.2%), headache (6.8%) and bronchitis (6.1%). The frequency of peripheral edema was decreased in the 86 patients receiving ALI/AML plus HCT (14.0 vs. 20.5%). Edema was reported as severe in nine patients (7.1%). Sixty six patients (11.9%) discontinued the study due to AEs, of which peripheral edema was the most common (36 patients).

ALI/HCT with or without AML when uncontrolled on candesartan/HCT

Schweizer *et al.* assessed the efficacy and tolerability of the combination pill ALI/HCT with the option to add AML in patients who remained uncontrolled after 4 weeks on candesartan/HCT [56].

A total of 186 adults with moderate HTN (DBP: 100–109 mmHg) participated in the open-label, multicenter study consisting of three 4-week phases. After a washout period (2 weeks), 186 patients entered Phase I where they received candesartan 32 mg plus HCT 25 mg. After 4 weeks 123 patients were nonresponders (mean DBP: 90 mmHg) and entered Phase II, where therapy was changed to ALI/HCT 300/25 mg. At the conclusion of Phase II, the first 61 patients who were eligible entered the extension phase where AML 5 mg was added.

The 61 patients who received ALI/HCT 300/25 mg plus AML 5 mg were predominately middle-aged (58.9 years) Caucasian (100%) males (60.7%) with mean baseline sitting BP of 149.4/96.5 mmHg. Changing from candesartan 32 mg plus HCT 25 mg to ALI/HCT 300/25 mg resulted in 23.6% more patients achieving a BP of <140/90 mmHg. The addition of AML 5 mg to ALI/HCT 300/25 mg further normalized 36.1% more BPs.

AEs were reported in 9.8% of the ALI/HCT phase and 13.1% of the ALI/HCT + AML phase. The majority were rated mild-to-moderate in severity (91.7% of ALI/HCT and 87.5% of the ALI/HCT + AML phase). Suspected drug-related AEs were seen in 3.3% of the ALI/HCT phase (two gastrointestinal disorders, one diabetes mellitus conversion and one hyperhidrosis) and in 1.6% of the ALI/HCT + AML phase (one hepatobiliary disorder).

Conclusion

Antihypertensive therapy has expanded in attempts to control BP to guideline levels with lower cardiovascular risk. Triple-combination pills have followed dual combinations in the search for improved efficacy and tolerability. The data reviewed in this article demonstrate that the combination of ALI, AML and HCT does show both improved efficacy and tolerability in a variety of patient populations with mild-to-moderate HTN including ethnic minorities, the elderly, those with controlled diabetes mellitus, and the obese.

Expert commentary

In the largest prospective randomized BP trial to date with 33,357 patients with stage 1 HTN (mean baseline BP 144.8/83.3 mmHg), BP control of <140/90 mmHg required an average of

2.0 medications at 5 years and 27.3% required three or more antihypertensive medications [10]. In the stepped-care study by Richter *et al.* [54], which included patients with stage 1 and 2 HTN, more than 50% required at least three medications for BP control. In a growing population of people with mild and moderate HTN, the need for multiple antihypertensive medications is evident.

Triple-fixed dose combination therapy has many potential advantages, as outlined in a recent editorial by Black [17]. Proposed advantages of multidrug therapy for HTN include a synergistic increase in efficacy by combining complementary mechanisms of action, more prompt achievement of goal BP, and reduced AEs when combining agents with offsetting adverse effects. Advantages of single-pill combinations include simplification of regimen, improved adherence, reduced pill burden and potential for reduced cost. The cost of the ALI/AML/HCT fixed-dose combination is similar to the ALI/AML or ALI/HCT combinations, and has the advantage of both a reduced copayment and lower individual drug costs when compared with adding the third agent outside of the combination. However, ALI/AML/HCT remains more expensive than the other two available fixed-dose triple combinations.

The advantages of prompt BP control are supported by data from the reviewed clinical trials with ALI/AML/HCT. In the ASCENT trial the mean BP was at goal by week 2 of therapy in the ALI/AML/HCT arm after only 1 week of the triple combination [53]. Furthermore, the Systolic Hypertension in Europe trial showed that lowering BP early can reduce clinical events (cerebrovascular and cardiovascular) compared with delayed treatment [57].

Improved efficacy of triple combinations over dual therapies has been established in a randomized trial by Calhoun *et al.* [15] and these results are similar to those of ASCENT, where BP reduction was greater with ALI/AML/HCT when compared with ALI/AML (−36.5/−15.1 mmHg vs. −29.5/−12.0 mmHg). However, both of these trials were only 8 weeks long and separation of BP reduction may not persist in the long term, as evident by the study by Littlejohn *et al.* [55], in which the 54-week study triple-combination ALI/AML + HCT did not show improved BP reduction compared with the dual combination ALI/AML (−23.7/−14.2 mmHg vs. −24.2/−15.7 mmHg).

Important limitations to the clinical trials on ALI/AML/HCT include the exclusion of patients with severe cardiovascular or cerebrovascular disease and severe HTN. Selected patients also had normal serum potassium levels (3.5–5.5 mEq/l), and patient populations were predominately Caucasian (77.6–100%) in every study except ASCENT.

Diabetic patients were well-represented (12.4–34.4%), while other subgroups, including patients with chronic kidney disease and older patients (> 65 years old), were less commonly studied or not isolated as a subgroup. The study by Richter *et al.* is the only one that reported chronic kidney disease prevalence in the study population (7.4% with a baseline-estimated glomerular filtration rate of <60 ml/min/1.73 m²) [54]. Primarily due to the small number of study patients receiving the combination of ALI/AML/HCT (46–326 patients), subgroup analyses were not performed.

Another important limitation of the reviewed trials is the choice of primary end points. To date there is no trial assessing morbidity or mortality of any fixed-dose triple-combination therapy. Furthermore, there are no data for making comparisons between the available fixed-dose triple-combination therapies. ALI has shown similar tolerability and efficacy as ARBs, which comprise the other two triple combinations. However, ALI has yet to show superiority over an ARB in either efficacy or tolerability by clinical trial data.

The study by Littlejohn *et al.* was best suited to evaluate the safety and tolerability of ALI/AML/HCT since it lasted 54 weeks [55]. In that study peripheral edema was the most frequent AE, yet the incidence of peripheral edema seen with ALI/AML combination was not higher than that observed in previous studies of angio-tensin-converting enzyme inhibitor or ARB combinations with AML 10 mg [58, 59]. In fact, both the study by Littlejohn *et al.* and ACCELERATE showed less peripheral edema when ALI is added to AML. These results are supported by a study of 545 patients with mild-to-moderate HTN and uncontrolled on AML 5-mg daily, the combination ALI/AML 150/5 mg provided similar BP-lowering efficacy to AML 10-mg daily with markedly lower incidence of peripheral edema (2.1 vs. 11.2%) [31]. Overall, ALI/AML/HCT was well tolerated without any shared severe AEs between the five clinical trials (Table 3). In addition, when in combination ALI appears to reduce the individual AEs of AML and HCT [31–36].

One potential benefit of adding ALI to combination therapies is its ability to attenuate increases in PRA caused by HCT and AML [31, 59, 60]. The reactive rise in PRC seen with ALI is similar to other RAAS blockers and has not been associated with increases in BP [61]. Findings from ASCENT and ACCELERATE show similar drops in the level of PRA and rises in the level of PRC previously seen with ALI combination therapy.

The studies reviewed in this article illustrate that uptitration to a triple-combination regimen of ALI/AML/HCT results in additional BP reduction with increased number of patients reaching goal BP and comparable or improved tolerability relative to dual therapies. These findings support the use of ALI/AML/HCT in patients unable to achieve goal BP on dual combination therapy.

Five-year view

New HTN guidelines (JNC 8) will set the tone for HTN treatment in the next 5 years. Emphasis on the longer-acting thiazide diuretic chlorthalidone as well as the use of aldosterone antagonists in resistant HTN may slow the use of triple-combination products. In addition, new pill-reducing therapies (renal denervation) may emerge as an effective BP-lowering therapy for a subset of patients with resistant HTN. Overall, as new therapies emerge and known effective therapies become more widely implemented, the use of fixed-dose triple combination therapy may decline. However, the available data does support ALI/AML/HCT as a safe and effective option for patients remaining uncontrolled on dual therapy.

Information resources

- American Heart Association patient education on hypertension: www.heart.org/HEARTORG/Conditions/HighBlood-Pressure/High-Blood-Pressure_UCM_002020_Sub-HomePage.jsp
- Thomson Reuters Micromedex 2.0 Mobile Application: www.micromedex.com
- Novartis. Amlturnide (aliskiren, amlodipine, and hydrochlorothiazide) tablets: US prescribing information. Novartis Pharmaceuticals Corporation (NJ, USA): www.pharma.us.novartis.com/product/pi/pdf/amlturnide.pdf

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Key issues

- Lowering blood pressure proportionally reduces cardiovascular-related morbidity and mortality.
- Clinical trial data shows that attaining goal blood pressure usually requires at least two antihypertensive medications and a significant proportion require regimens of three or more medications.
- Potential advantages of single-pill triple combinations are improved efficacy, tolerability and adherence.
- Data with aliskiren, amlodipine and hydrochlorothiazide illustrate improved efficacy when dual combination therapy fails to achieve goal blood pressure.
- Triple-combination aliskiren/amlodipine/hydrochlorothiazide 300/10/25 mg was well tolerated and effective; in the ASCENT study the most common adverse events were headache and dizziness.

Figure 1. Chemical structure of aliskiren with a condensed scheme of metabolism

M1 is the primary metabolite (3% of plasma radioactivity at time of C_{max}). Reproduced with permission from [63].

Figure 2. Proportion of treatment responders (mean sitting systolic blood pressure <140 mmHg or reduction from baseline of ≥ 20 mm Hg) and patients achieving blood pressure goal during double-blind treatment of the ASCENT study

A: Aliskiren; AML: Amlodipine; BP: Blood pressure; HCTZ: Hydrochlorothiazide; MSSBP: Mean sitting systolic blood pressure. Reproduced with permission from [53].

Table 1

Pharmacology of aliskiren, amlodipine and hydrochlorothiazide.

Pharmacology	Aliskiren	Amlodipine	Hydrochlorothiazide
Molecular weight (Da)	609.8	567.1	297.7
Pharmacokinetics			
<i>Absorption</i>			
Bioavailability (%)	2.5	64–90	60–80
C _{max} (h)	1–3	6–12	1–4
Effects of food	AUC decreased by 78%; C _{max} decreased by 89%	No effect	No effect
<i>Distribution</i>			
V _D	135 l/kg	21 l/kg	3–4 l/kg
Plasma protein binding (%)	47–51	93	40
<i>Elimination</i>			
Half-life (h)	40	30–50	5.8–18.9
Excretion	Bile/fecal: 91/77.5% unchanged	Renal: 60% metabolites and 10% unchanged Fecal: 20–25%	Renal: 61% unchanged
<i>Metabolism</i>			
	Hepatic: minor via CYP3A4	Hepatic: extensive (~90%)	Not metabolized
<i>Drug interactions</i>			
	Coadministration with potent P-gp inhibitors (cyclosporine, quinidine, verapamil) is contraindicated in the EU. Caution advised with coadministration of moderate P-gp inhibitors (ketoconazole, itraconazole, clarithromycin, erythromycin, amiodarone). Grapefruit, orange and apple juice should not be taken together with aliskiren.	Caution advised with coadministration of CYP3A4 inhibitors and inducers.	Reported interactions with: alcohol, barbiturates, narcotics, antidiabetic agents, cholestyramine, colestipol, corticosteroids, ACTH, lithium and NSAIDs.
<i>Effects of renal impairment</i>			
	No significant effect on pharmacokinetics, yet caution advised in severe renal impairment.	No significant effect on pharmacokinetics.	Avoid use in patients with CrCl <10 ml/min; usually ineffective with CrCl <30 ml/min.
<i>Effects of hepatic impairment</i>			
	No significant effect on pharmacokinetics.	40–60% increase in AUC; caution advised in severe hepatic impairment.	No significant effect on pharmacokinetics, yet caution advised in impaired hepatic function.
<i>Effects of age</i>			

Pharmacology	Aliskiren	Amlodipine	Hydrochlorothiazide
	AUC and C _{max} increased by 57 and 28% for those aged >65 years	40–60% increase in AUC	No significant effect on pharmacokinetics

ACTH: Adrenocorticotrophic hormone; AUC: Area under the curve; CrCl: Creatinine clearance; P-gp: P-glycoprotein; V_D: Volume of distribution. Data taken from [45–51, 62, 101, 102].

Table 2

Summary of clinical trials with aliskiren, amlodipine and hydrochlorothiazide.

Study (year)	Design	Patient population	Treatment [†]	Key findings	Ref.
ACCELERATE	Double-blind, randomized, parallel-group, 32-week, multicenter, superiority trial	1254 patients with mild-to-moderate HTN Mean baseline SeBP: 161.5/92.5 mmHg Mean age: 58.2 years Diabetes: 12.4% Caucasian: 77.6% Male: 50.6%	AML/PL5 → AML/PL 10 ALI/PL 150 → ALI/PL 300 ALI/AML 150/5 ALI/AML 300/10 ALI/AML 300/10 + (HCT 12.5 or PL)	326 patients (26%) received ALI/AML 300/10 mg + HCT 12.5 mg The overall efficacy of ALI/AML with or without HCT was 71.9%, with 901 out of 1254 achieving target BP Most common AEs were peripheral edema (20.8%) and dizziness (4.2%)	[52]
ASCENT	Double-blind, randomized, parallel-group, forced-titration, 8-week, multicenter efficacy and safety study	412 patients with stage 2 HTN Mean baseline SeBP: 167.3/95.3 mmHg Mean age: 55.2 years Age >65 years: 16.3% Diabetes: 28.7% African-American: 62.3% Hispanic/Latino: 28.2% Male: 49.6%	AML 5 ALI/AML 150/5 ALI/AML 300/5 ALI/AML 300/10 ALI/AML/HCT 150/5/12.5 ALI/AML/HCT 300/5/25 ALI/AML/HCT 300/10/25	203 patients (49.3%) received ALI/AML/HCT and in this group mean BP was reduced from 167.1/95.3 mmHg at baseline to 130.7/80.1 mmHg at the end of week 8 72.6% of patients receiving triple-combination therapy achieved BP <140/90 mmHg AEs reported in 34.2% of triple-therapy group with most common being headache (10.9%), dizziness (4%), muscle spasms (2.5%), palpitations (2.5%) and peripheral edema (2.0%)	[53]
Aliskiren stepped-care treatment Richter <i>et al.</i> (2011)	Open-label, 24-week, multicenter, step-up therapy study	256 patients with mild-to-moderate hypertension Mean baseline SeBP: 155.7/91.7 mmHg Mean age: 55.4 years Age >65 years: 20.7% Age >75 years: 4.7% Diabetes: 34.4% Caucasian: 99.2% Male: 55.9%	ALI 150 ALI 300 ALI 300 + HCT 12.5 ALI 300 + HCT 25 ALI 300 + HCT 25 + AML 5 ALI 300 + HCT 25 + AML 10	46% (119 out of 265) of patients received ALI + HCT + AML and showed mean reductions in BP of 27.0/13.7 mmHg Most common AE was upper respiratory infection (3.1 %)	[54]
Long-term safety, tolerability, and efficacy of ALI/AML Littlejohn <i>et al.</i> (2009)	Open-label, 54-week, multicenter, long-term safety and tolerability study	556 patients with mild-to-moderate HTN Mean baseline SeBP: 153.5/97.6 mmHg Mean age: 54.4 years Age >65 years: 18.2% Diabetes: 16% Caucasian: 86% Male: 59.4%	ALI/AML 150/5 ALI/AML 300/10 ALI/AML 300/10 + HCT 12.5 ALI/AML 300/10 + HCT 25	86 patients (15.5%) received ALI/AML + HCT with a mean BP reduction of 23.7/14.2 mmHg Overall BP control rate was 74.3% with a mean reduction in BP of 24.2/15.5 mmHg with or without HCT Most frequent AEs were peripheral edema (22.7%), upper respiratory infection (7.2%), headache (6.8%) and bronchitis (3.4%)	[55]
ALI/HCT with or without AML when uncontrolled on CAN/HCT Schweizer <i>et al.</i> (2011)	Open-label, single-arm, 12-week, multicenter, nonresponder designed, efficacy and tolerability study	186 patients with moderate HTN Mean baseline SeBP [‡] : 149.4/96.5 mmHg Mean age*: 58.9 years Caucasian [‡] : 100% Male [‡] : 60.7%	CAN 16 + HCT 12.5 CAN 32 + HCT 25 ALI/HCT 300/25 ALI/HCT 300/25 + AML 5	61 patients received ALI/HCT + AML and 36.1 % more patients achieved BP normalization (<140/90 mmHg) with the addition of AML to ALI/HCT Suspected drug-related AEs were seen in 3.3% of the ALI/HCT phase (two GI disorders, one DM2 conversion, one hyperhidrosis) and in 1.6% of the ALI/HCT + AML phase (one hepatobiliary disorder)	[56]

[†] All unspecified doses are in milligrams.

[‡] Data from ALI/HCT 300/25 + AML 5 phase of the study.

AE: Adverse event; ALI: Aliskiren; AML: Amlodipine; BP: Blood pressure; CAN: Candesartan; DM2: Type 2 diabetes mellitus; GI: Gastrointestinal; HCT: Hydrochlorothiazide; HTN: Hypertension; PL: Placebo; SeBP: Seated blood pressure.

Table 3

Summary of adverse events with aliskiren, amlodipine and hydrochlorothiazide in fixed-dose combination[†].

Adverse event	Patient reporting an event, n (%)
Headache	22 (10.9)
Dizziness	8 (4.0)
Diarrhea	3 (1.5)
Peripheral edema	4 (2.0)
Muscle spasms	5 (2.5)
Cough	2 (1.0)
Nasopharyngitis	3 (1.5)
Palpitations	5 (2.5)

[†] ASCENT [53] is the only available clinical trial with single-pill dosing of aliskiren/amlodipine/hydrochlorothiazide.