Aliskiren/Amlodipine (TEKAMLO®)
National PBM Drug Monograph
Abbreviated Review
November 2011

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The PBM prepares abbreviated reviews to compile information relevant to making formulary decisions. VA clinical experts may provide input on the content. Wider field review is not sought. Documents no longer current will be placed in the Archive section of the PBM INTRAnet (http://vaww.pbm.va.gov).

Introduction[1,2]

On August 26, 2010, the Food and Drug Administration approved the fixed-dose combination of aliskiren and amlodipine (TEKAMLO®) for the treatment of hypertension (HTN).[1] The product is approved as initial therapy for patients who require multiple medications to control blood pressure (BP), add-on therapy in individuals who are not controlled with monotherapy, and a substitute for the use of the individual components, amlodipine and aliskiren.[2] TEKAMLO includes the direct renin inhibitor, aliskiren, and a dihydropyridine calcium channel blocker, amlodipine. Amlodipine is available on the VA National Formulary; aliskiren is available non-formulary, restricted to criteria for use.

For detailed information on the pharmacology, pharmacokinetics, efficacy, adverse events, precautions/warnings, drug interactions, and look alike/sound alike error risk potential of aliskiren, and therapeutic alternatives on the VA National Formulary for the treatment of hypertension, refer to the VA National drug monograph for aliskiren located on the PBM Web sites (at www.pbm.va.gov and http://vaww.pbm.va.gov). The respective manufacturer's product information for aliskiren or amlodipine should be consulted for additional prescribing information for these agents.

Summary of Clinical Trial Data[3-5]

The fixed-dose combination of aliskiren/amlodipine was studied for efficacy in reducing BP in over 5000 patients prior to receiving FDA approval. A search of PubMed was completed using the search words amlodipine and aliskiren, with inclusion limited to published clinical trials of the medications used in combination. Unpublished information was obtained from Novartis to obtain pivotal clinical trial data. The pivotal trial (unpublished) involved 1,688 patients who were randomized to receive aliskiren 150-300 mg/amlodipine 5-10 mg, monotherapy with individual components of the combination therapy, or placebo for eight weeks. The primary endpoint was the change from baseline to week eight in mean sitting diastolic blood pressure (MSDBP). The secondary endpoints included the change from baseline to week eight in mean sitting systolic blood pressure (MSSBP), the percent of patients obtaining controlled BP (MSSBP <140 mmHg and MSDBP <90 mmHg), the percent of patients obtaining a MSDBP <90 mmHg or a 10 mmHg or greater reduction from baseline, and the percent of patients obtaining a MSSBP <140 mmHg or a 20 mmHg or greater reduction in baseline[3] (see Appendix for more details).

Treatment at 8 weeks	Δ MSDBP[a,b] (mm Hg)	Δ MSSBP[b] (mm Hg)
Aliskiren 150 mg/amlodipine 5 mg	-13.98[c]	-20.64[c]
Aliskiren 150 mg/amlodipine 10 mg	-16.16[c]	-23.87[d,e,f]
Aliskiren 300 mg/amlodipine 5 mg	-14.99[c]	-21.82[c]
Aliskiren 300 mg/amlodipine 10 mg	-16.45[c]	-23.19[d,e,f]
Amlodipine 5 mg	-11[d]	-15.82[d]
Amlodipine 10 mg	-13.82[d]	-21.04[d]
Aliskiren 150 mg	-7.99[d]	-10.67[d]
Aliskiren 300 mg	-10.19[d]	-15.37[d]
Placebo	-5.35	-6.79

[a] Primary endpoint
[b] Compared to baseline
[c] P<0.05 vs. respective aliskiren monotherapy, amlodipine monotherapy, and placebo
[d] P<0.05 vs. placebo
[e] P<0.05 vs. respective aliskiren monotherapy only
[f] P=0.143 vs. respective amlodipine monotherapy

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The combination of aliskiren/amlodipine resulted in statistically significant decreases in MSDBP when compared to the respective doses of aliskiren and amlodipine monotherapy and placebo. When aliskiren 150-300 mg/amlodipine 5 mg were compared to the respective monotherapies, a statistically significant decrease was observed in MSSBP. This was also observed when aliskiren 150-300 mg/amlodipine 10 mg was compared to aliskiren monotherapy; however, when compared to amlodipine 10 mg, there was no statistically significant difference in MSSBP.[3]

A subgroup analysis in 819 patients was also conducted as part of the trial to evaluate the change from baseline to eight weeks in ambulatory blood pressure monitoring (ABPM). All patients receiving the aliskiren/amlodipine fixed-dose combinations experienced a statistically significant decrease in mean ambulatory diastolic blood pressure (MADBP) and mean ambulatory systolic blood pressure (MASBP) when compared to the respective amlodipine and aliskiren monotherapies.[3]

Aliskiren/amlodipine was also compared to amlodipine and aliskiren monotherapy in Aliskiren and the Calcium Channel Blocker Amlodipine Combination as an Initial Treatment Strategy for Hypertension Control (ACCELERATE) trial. This 32-week, double-blind, randomized, parallel-group, superiority trial randomly assigned patients to aliskiren 150 mg/amlodipine 5 mg or the individual components as monotherapy for the first eight weeks of the trial. At week eight, the dose of the study medication was doubled, and at week 16, all therapies were changed to aliskiren 300 mg/ amlodipine 10 mg. Prior to the medication change at week 16, patients who initially started on the combination therapy experienced a statistically significant average reduction in systolic blood pressure of 6.5 mmHg more than those on monotherapy. From week 16 to 24, patients initiated on aliskiren/amlodipine combination therapy experienced a 1.4 mm Hg greater decrease in systolic blood pressure when compared to those switched to combination therapy from monotherapy, which was not statistically significant.[4]

The Aliskiren Amlodipine Combination in African Americans with Stage 2 Hypertension (AACESS) trial compared the combination of aliskiren 300 mg/amlodipine 10 mg to amlodipine 10 mg monotherapy. At the end of the study at week eight, patients taking the combination therapy experienced a greater decrease in mean systolic blood pressure compared to the patients taking amlodipine alone (-34.1 vs. -28.9 mm Hg, P<0.001). During the mid-point of the study at week 4, more patients in the combination group met the blood pressure goal of <140/<90 mm Hg (54.5% vs. 43.5%), which was statistically significant (P=0.022); however at the end of the study, there was no statistically significant difference between the groups. At week 8, 57.3% of patients in the aliskiren/amlodipine group and 48% of patients in the amlodipine group met blood pressure goal (P=0.051).[5]

Safety [2,3,6]

Aliskiren/amlodipine was studied for safety in more than 2800 patients. During the pivotal trial, more patients discontinued amlodipine 10 mg monotherapy than the other medications evaluated in the trial (3.9% vs. 0.5-2.2%). The aliskiren 300 mg/ amlodipine 10 mg group experienced the greatest incidence of side effects (44% vs. 31.4-37.4%). Peripheral edema was the most common side effect with the patients taking medications containing amlodipine 10 mg experiencing the greatest amount of peripheral edema. The incidence of edema in the amlodipine 10 mg monotherapy group was 13.8%, 13.6% in the aliskiren 300 mg/amlodipine 10 mg group, and 7.7% in the aliskiren 150 mg/amlodipine 10 mg group. Headache was the second most common side effect, but the highest incidence occurred in the placebo group (10.1%). The incidence of diarrhea was greatest in the aliskiren 150 mg group (3.6%), followed by the aliskiren 300 mg/amlodipine 5 mg group (2.8%). The incidence of diarrhea was 1.1% or less in the other study groups. No patients experienced angioedema, and only one patient who was in the amlodipine 5 mg group had an elevated potassium concentration. [2,3]

The Long-term Safety, Tolerability, and Efficacy of Combination Therapy with Aliskiren and Amlodipine in Patients with Hypertension trial studied aliskiren/amlodipine at various doses in 556 patients. The trial lasted 54 weeks. The study reported peripheral edema as the most common side effect, occurring in 22.7% of patients treated with aliskiren/amlodipine. The incidence of an upper respiratory tract infection was the second most common side effect (7.2% of patients), followed by bronchitis (6.1%), and headache (6.8%). Thirteen patients receiving aliskiren 300 mg/amlodipine 10 mg experienced serious adverse effects, while two patients experienced serious adverse effects in the aliskiren 300 mg/amlodipine 10 mg and hydrochlorothiazide treatment group.[6]

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This fixed-dose combination contains a boxed warning regarding the use in pregnant patients due to the aliskiren component. This medication should not be used in pregnant patients due to the increased risk for fetal injury or mortality.

Concomitant use of cyclosporine and itraconazole should also be avoided with aliskiren/amlodipine as the concentration of aliskiren may be increased.

Look-alike/Sound-alike (LA/SA) Error Risk Potential

As part of a Joint Commission standard, LA/SA names are assessed during the formulary selection of drugs. Based on clinical judgment and an evaluation of LA/SA information from four data sources (Lexi-Comp, USP Online LASA Finder, First Databank, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion:

NME Drug Name	Lexi-Comp	First DataBank	USP	ISMP	Clinical Judgment
Aliskiren/amlodipine 150/5, 150/10, 300/5, 300/10 mg tablets	None	Amlodipine-amiloride	None	Amlodipine-amiloride	Aliskiren/amlodipine/hydrochlorothiazide Aliskiren/hydrochlorothiazide Aliskiren/valsartan Amlodipine/atorvastatin ALKERAN
TEKAMLO	None	None	None	None	TEKTURNA®

Dosage

The recommended starting dose of aliskiren/amlodipine for the treatment of hypertension is aliskiren 150 mg/amlodipine 5 mg once daily. If blood pressure remains uncontrolled after two to four weeks of therapy, the dose may be titrated to a maximum of aliskiren 300 mg/amlodipine 10 mg daily.

The fixed-dose combination of aliskiren/amlodipine is available in the following tablet strengths: aliskiren 150 mg/amlodipine 5 mg; aliskiren 150 mg/amlodipine 10 mg; aliskiren 300 mg/amlodipine 5 mg; aliskiren 300mg/amlodipine 10 mg. It is administered once daily without regard to meals.

Price Comparison

VA Price

Dose/Regimen	Price/Tablet	Price/Patient/Month	Annual Price/Patient
Aliskiren 150 mg/Amlodipine 5 mg once daily	$1.7957	$53.87	$646.45
Aliskiren 150 mg/Amlodipine 10 mg once daily	$1.7957	$53.87	$646.45
Aliskiren 300 mg/Amlodipine 5 mg once daily	$2.2707	$68.12	$817.45
Aliskiren 300 mg/Amlodipine 10 mg once daily	$2.2707	$68.12	$817.45

Note: VA prices current as of 10242011 per Low2000. Check VA pricing resources for updated information.

Price Comparison of Fixed-Dose Combination vs. Individual Components

Aliskiren/Amlodipine	Price/Dose	vs. Price of Individual Components	Annual Price Difference/Patient
Fixed-Dose Combination Aliskiren/Amlodipine			
150 mg/5 mg	$1.7957	$0.6329	$418.65
150 mg /10 mg	$1.7957	$0.6464	$413.75
300 mg/5 mg	$2.2707	$0.6929	$568.01
300 mg/10 mg	$2.2707	$0.7064	$563.15
Aliskiren			
150 mg	$0.63		
300 mg	$0.69		
Amlodipine			
5 mg	$0.0029		
10 mg	$0.0164		

Note: VA prices current as of 10242011 per Low2000. Check VA pricing resources for updated information.

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Conclusions

The fixed-dose combination of aliskiren/amlodipine appears to be effective, safe, and well-tolerated in patients with hypertension. Amlodipine is available on the VA National Formulary; aliskiren is available non-formulary, restricted to criteria for use. Although aliskiren/amlodipine was approved for use as an initial therapy in the treatment of hypertension, it should be reserved for individuals who do not achieve adequate blood pressure control with VA National Formulary agents and with treatment as recommended in national clinical practice guidelines for the management of hypertension. Due to the availability of individual drug therapy options and the higher cost of the fixed-dose combination aliskiren/amlodipine in comparison to the individual components, the combination of individual drug therapy options should be maximized prior to considering the fixed-dose combination product. In a patient who is receiving aliskiren and amlodipine as individual components, where it is felt tablet burden is impeding the patient's ability to adhere to the medication regimen, the fixed-dose combination at the comparable strengths, if available, may be considered.

References

1. U.S. Food and Drug Administration. TEKAMLO. Drugs @ FDA. Available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails Accessed August 30, 2011.
2. TEKAMLO® (aliskiren/amlodipine) package insert. East Hanover, NJ: Novartis Pharmaceuticals Corp.; Mar 2011.
3. Data on File. Study SPA1000A2305, CSR. Novartis Pharmaceutical Corporation. 2009 Sep.
4. Brown MJ, McInnes GT, Papst CC, Zhang J, MacDonald TM. Aliskiren and the calcium channel blocker amlodipine combination as an initial treatment strategy for hypertension control (ACCELERATE): a randomised, parallel-group trial. Lancet 2011;377:312-20.
5. Black HR, Weinberger MH, Purkayaastha D, et al. Comparative efficacy and safety of combination aliskiren/amlodipine and amlodipine monotherapy in African Americans with stage 2 hypertension. J Clin Hypertens 2011;13:571-81.
6. Littlejohn TW, Trenkwalder P, Hollanders G, Zhao Y, Liao W. Long-term safety, tolerability and efficacy of combination therapy with aliskiren and amlodipine in patients with hypertension. Curr Med Res Opin 2009:25:951-9.

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Contact Person: Elaine M. Furmaga, PharmD, Clinical Pharmacy Specialist, VA National PBM Services

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Appendix: Evidence Table (Monotherapy and Combination Therapy Trials)

<table>
<tr><th>Citation</th><th>Eligibility Criteria</th><th>Interventions/Endpoints</th><th>Efficacy Results/Author's Conclusions</th><th>Safety/Study Analysis</th></tr>
<tr>
<td>Data on File[3]

MC, R, DB, PC

n=1688; 819 (ABPM sub-study)

8 wks

Funded by Novartis</td>
<td>Inclusion
Men and women ≥ 18 yrs, essential HTN (MSDBP ≥ 95 mm Hg and < 110 mm Hg)

Exclusion
Severe hypertension (MSDBP > 110 mm Hg and/or MSSBP > 180 mm Hg), secondary HTN, uncontrolled diabetes, hx of hypertensive encephalopathy or CVA, hx of TIA, MI, coronary bypass surgery or PCI, or previous or current diagnosis of HF</td>
<td>Primary
Δ MSDBP from baseline to wk 8

Secondary
Δ MSSBP from baseline to wk 8; percent of patients achieving BP control (MSSBP <140 mm Hg and MSDBP <90 mm Hg), percent of patients achieving DBP response (MSDBP <90mm Hg or at least 10 mm Hg reduction from baseline), percent of patients achieving SBP response (MSSBP <140 mm Hg or at least 20 mm Hg reduction from baseline)

Sub-study
Δ 24hr ABPM from baseline to wk 8

Wash-out
W/D HTN Rx

Run-in
SB placebo

Tx Phase
Aliskiren 150 mg/amlodipine 5 mg, aliskiren 150 mg/amlodipine 10 mg, aliskiren 300 mg/amlodipine 5 mg, aliskiren 300 mg/amlodipine 10 mg, aliskiren 150 mg, aliskiren 300 mg, amlodipine 5 mg, amlodipine 10 mg, or placebo for 8 wks. Those randomized to aliskiren 150-300 mg/amlodipine 10 mg or amlodipine 10 mg started with aliskiren 150-300 mg/amlodipine 5 mg, or amlodipine 5 mg and forced titrated after one week.</td>
<td>Baseline characteristics
Mean age: 54.1 yrs; 50.8% male; 62.1% Caucasian; MSSBP/MSDBP 157.3/99.7 mm Hg.

<table>
<tr><th>Tx</th><th>Δ MSDBP (mm Hg)</th><th>Δ MSSBP (mm Hg)</th></tr>
<tr><td>Aliskiren150 mg/amlodipine 5 mg</td><td>-13.98[a]</td><td>-20.64[a]</td></tr>
<tr><td>Aliskiren 150 mg/amlodipine 10 mg</td><td>-16.16[a]</td><td>-23.87[b,c]</td></tr>
<tr><td>Aliskiren 300 mg/amlodipine 5 mg</td><td>-14.99[a]</td><td>-21.82[a]</td></tr>
<tr><td>Aliskiren 300 mg/amlodipine 10 mg</td><td>-16.45[a]</td><td>-23.19[b,c]</td></tr>
<tr><td>Aliskiren 150 mg monotherapy</td><td>-7.99[c]</td><td>-10.67[c]</td></tr>
<tr><td>Aliskiren 300 mg monotherapy</td><td>-10.19[c]</td><td>-15.37[c]</td></tr>
<tr><td>Amlodipine 5 mg monotherapy</td><td>-11[c]</td><td>-15.82[c]</td></tr>
<tr><td>Amlodipine 10 mg monotherapy</td><td>-13.82[c]</td><td>-21.04[c]</td></tr>
<tr><td>Placebo</td><td>-5.35</td><td>-6.79</td></tr>
</table>
[a]p<0.05 vs. respective aliskiren monotherapy, amlodipine monotherapy, and placebo
[b]p<0.05 vs. respective aliskiren monotherapy only
[c]p<0.05 vs. placebo only

BP Response
All patients taking the fixed-dose combinations of aliskiren/amlodipine had a greater and statistically significant DBP response compared to the respective monotherapies and placebo.
Aliskiren 300 mg/amlodipine 10 mg gave the greatest effect on DBP, with an 84.7% response rate.
Patients taking aliskiren 150-300 mg/amlodipine 5 mg showed a statistically significant response in SBP compared to monotherapy, but the difference was not statistically significant between those taking aliskiren 150-300 mg/amlodipine 10 mg and amlodipine 10 mg monotherapy.

Δ 24hr ABPM (n=819)
All combinations of aliskiren/amlodipine provided patients with a statistically significant lowering of MASBP and MADBP when compared to the respective monotherapies (p<0.05).

Study Conclusions
The fixed-dose combination of aliskiren/amlodipine was more effective in lowering MSDBP than the respective dose aliskiren and amlodipine monotherapy. The fixed-dose combination appears to be relatively well-tolerated compared to placebo and the respective monotherapies.</td>
<td>Adverse Events
-Discontinuation due to AE: highest in amlodipine 10 mg group (3.9%) versus other groups (0.5-2.2%)
-Total AEs were highest in the aliskiren 30 mg/amlodipine 10 mg group (44.6% vs 31.4-37.4% in other groups)
-Peripheral edema was greatest in the amlodipine 10 mg (13.8%) and aliskiren 300 mg/amlodipine10 mg (13.6%) groups
-1 patient had hypotension, 1 patient had syncope, 1 patient had presyncope
-Orthostatic hypotension was not experienced in any group
-Deaths: 0

Study Analysis
Strengths:
-Over 1,000 patients were studied
-The number of men and women in the study was approximately equal
-ABPM was used in the sub-study which can be more accurate than measuring BP during clinic visits

Limitations:
-Unpublished data
-Over 60% of patients were Caucasian, which makes it difficult to determine external validity
-The trial only lasted 8 weeks, which makes it difficult to assess the long-term benefits and adverse events of the fixed-dose combination
-Surrogate endpoints were used which makes it difficult to assess if the fixed-dose combination prevents clinically relevant events related to HTN</td>
</tr>
</table>

ABPM=ambulatory blood pressure monitoring; AE=adverse event; BP=blood pressure; CV=cardiovascular; CVA= cerebrovascular accident; d=day; DB=double-blind; HA=headache; DBP= diastolic blood pressure; HF= heart failure; hr=hour; hx= history; HTN=hypertension; MADBP=mean ambulatory diastolic blood pressure; MASBP=mean ambulatory systolic blood pressure; MC=multicenter; MI=myocardial infarction; MSDBP= mean sitting diastolic blood pressure, MSSBP= mean sitting systolic blood pressure, n=number of patients; PC=placebo-controlled; PCI= percutaneous coronary intervention; R=randomized; SB= single blind; SBP= systolic blood pressure; sCr=serum creatinine; TIA= transient ischemic attack; tx=treatment; W/D=withdrawal; wk=week; yrs=years

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<table>
<tr><th>Citation</th><th>Eligibility Criteria</th><th>Interventions/Endpoints</th><th>Efficacy Results/Author's Conclusions</th><th>Safety/Study Analysis</th></tr>
<tr>
<td>Brown et al[4].

MC, R, DB, PG

n=1254

32 wks

Funded by Novartis</td>
<td>Inclusion
Men and women ≥ 18 yrs, seated SBP 150-180 mmHg at time of randomization and seated DBP <110 mmHg

Exclusion
SBP <150 mmHg or >180mm and DBP >100 mmHg at time of randomization</td>
<td>Primary
-Mean adjusted reduction from baseline in SBP over weeks 8 to 24
-Second primary endpoint tested only if primary endpoint met: reduction MSSBP baseline vs. week 24

Secondary
-Reduction in MSDBP at weeks 16 and 24 weeks from baseline
-Reduction in MSSBP and MSDBP at 32 weeks
-Effect of baseline variables on BP at the end of each phase
-Analysis of initial combination therapy vs. monotherapy reduction in SBP and DBP
-Percentage of patients achieving target BP (<140/<90 mmHg)
-Number of patients achieving SBP <140 mm Hg or experiencing >20 mmHg reduction in SBP
Wash-out
W/D HTN Rx during run-in period with placebo
Run-in
SB placebo x 2 weeks minimum Further 2 weeks if SBP did not meet inclusion criteria or changed by >20 mm Hg at time of initial screening
Tx Phase
Weeks 0-16: Phase I
-Patients randomized 1:1:2 ratio to aliskiren 150 mg plus placebo, amlodipine 5 mg plus placebo, or aliskiren 150 mg/amlodipine 5 mg
-At week 8, the dose was doubled
Weeks 16-24: Phase II
-All patients received aliskiren 300 mg/amlodipine 10 mg
Weeks 24-32 Phase III
-Patients received hydrochlorothiazide 12.5 mg if SBP >140 mmHg or DBP >90 mmHg
-Other patients received placebo</td>
<td>Baseline characteristics
Mean age: 58 years; 51% men, 77.6% Caucasian; Mean BP range: 161.1-161.8/92-93

<table>
<tr><th>Initial Tx</th><th>Δ MSSBP (mm Hg) from baseline to weeks 8-24</th><th>Δ MSSBP (mm Hg) baseline vs. week 24</th><th>ΔMSDBP (mm Hg) from baseline to weeks 8-24</th></tr>
<tr><td>Aliskiren 150 mg/amlodipine 5 mg</td><td>-25.3[a]</td><td>-27.4[b]</td><td>-12.4[c]</td></tr>
<tr><td>Aliskiren 150 mg monotherapy or amlodipine 5 mg monotherapy</td><td>-18.9</td><td>-25.9</td><td>-8.7</td></tr>
</table>
[a] P<0.0001 compared to aliskiren monotherapy and amlodipine monotherapy
[b] P= 0.059 compared to patients initiated on aliskiren monotherapy or amlodipine monotherapy
[c] P<0.0001 compared to aliskiren monotherapy and amlodipine monotherapy

Week 24 (after 8 weeks aliskiren 300 mg/amlodipine 10 mg)
Initial aliskiren/amlodipine: 133.5/78.8 mm Hg
Initial aliskiren: 134.4/78.8 mm Hg
Initial amlodipine: 134.9/80.6 mm Hg

Percent of patients achieving SBP <140 mm Hg or experiencing >20 mm Hg reduction in BP
<table>
<tr><th>Initial Tx</th><th>Week 4</th><th>Week 8</th><th>Week* 16</th><th>Week 32</th></tr>
<tr><td>Aliskiren 150 mg/amlodipine 5 mg</td><td>62.7%[a]</td><td>79.1%[a]</td><td>77%[b,d]</td><td>77%[c,e]</td></tr>
<tr><td>Aliskiren 150 mg monotherapy</td><td>33%</td><td>47.8%</td><td>74.4%</td><td>73.7%</td></tr>
<tr><td>Amlodipine 5 mg monotherapy</td><td>40.9%</td><td>59.4%</td><td>70.9%</td><td>65.8%</td></tr>
</table>
*At week 16, all patients received aliskiren 300 mg/amlodipine 10 mg
[a] P<0.0001 compared to initial aliskiren monotherapy and amlodipine monotherapy
[b] P=0.47 compared to initial aliskiren monotherapy
[c] P=0.35 compared to initial aliskiren monotherapy
[d] P=0.05 compared to initial amlodipine monotherapy
[e] P=0.0004 compared to initial amlodipine monotherapy

Study Conclusions
Combination therapy with aliskiren/amlodipine lowers BP to a greater extent compared to monotherapy. Initial treatment with combination therapy reduced SBP by 1.4 mm Hg compared to titration of monotherapy.</td>
<td>Adverse Events
-Peripheral edema was the most common AE, affecting 21.4% in the combination therapy group, 16.8% in the aliskiren group, and 24.1% in the amlodipine group
- 7.1% of patients in the initial combination therapy group, 6.3% in the aliskiren group, and 11.4% in the amlodipine group discontinued the study drugs due to peripheral edema
-14 significant AEs occurred in the initial combination therapy group, and 9 each occurred in the aliskiren and amlodipine groups, but the study investigators only deemed 6 to be due to the study treatment (angioedema, cardiac failure, hypertensive crisis, peripheral edema, and sigmoiditis)
-5 patients experienced hypotension in the combination therapy group, 1 in the aliskiren group, and 2 in the amlodipine group
Deaths: 0

Study Analysis
Strengths:
-The study lasted 32 weeks, which is longer than the others used to gain approval for the fixed-dose combination
-Investigators studied the early and late effects of combination therapy versus monotherapy for HTN, which is not extensively studied

Limitations:
-Surrogate endpoints were used, which limits external validity
-Target BP was <140/<90 mm Hg for all patients, but patients with CKD or DM required a lower goal
-Over 77% of the patients were Caucasian
-Patients with severe HTN were excluded, which lessens external validity
-The study lasted 32 weeks, but the primary endpoints only examined the change in MSSBP from baseline to week 24</td>
</tr>
</table>

AE=adverse event; BP=blood pressure; CKD= chronic kidney disease; CV=cardiovascular; CVA= cerebrovascular accident; d=day; DB=double-blind; DBP= diastolic blood pressure; DM= diabetes mellitus; HA=headache; HF= heart failure; hr=hour; hx= history; HTN=hypertension; MC=multicenter; MI=myocardial infarction; MSDBP= mean sitting diastolic blood pressure, MSSBP= mean sitting systolic blood pressure, n=number of patients; PC=placebo-controlled; PCI= percutaneous coronary intervention; PG=parallel group; R=randomized; SB= single blind; SBP= systolic blood pressure; sCr=serum creatinine; TIA= transient ischemic attack; tx=treatment; W/D=withdrawal; wk=week; yrs=years

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<tr>
<td>Black HR et al[5].
MC, R, DB, AC, PG

n=443; 147 (ABPM sub-study)

8 wks

Funded by Novartis</td>
<td>Inclusion
African American men and women ≥ 18 yrs, newly diagnosed w/ HTN and tx naïve or taking ≤ 3 antihypertensive medications, MSSBP ≥ 160 mm Hg and < 200 mm Hg

Exclusion
MSSBP ≥ 200 mm Hg, MSDBP ≥110 mm Hg, taking ≥ 4 antihypertensive medications, refractory HTN (BP >140/90 despite triple-drug therapy that includes a diuretic), severe uncontrolled BP (MSSBP ≥180 mm Hg while taking >1 antihypertensive agent at screening), type 1 diabetes or uncontrolled type 2 diabetes, hx of encephalopathy, CVA, TIA, HF, coronary bypass graft surgery, PCI, unstable angina, or MI within past 12 months, serum sodium level <130 mEq/L, serum potassium level <3.5 mEq/L or ≥ 5.5mEq/L, pregnant or nursing women, or women not using contraception</td>
<td>Primary
∆ MSSBP from baseline to wk 8

Secondary
∆ MSDBP from baseline to wk 8; percent of patients achieving BP goal (MSSBP <140 mm Hg and MSDBP <90 mm Hg), ∆ PRA, PRC, UACR, and safety, tolerability, and incidence of peripheral edema

Sub-study
∆ 24hr ABPM from baseline to wk 8

Wash-out
W/D HTN Rx x 1-4 wks

Tx Phase
-Patients randomized to receive aliskiren 150 mg/amlodipine 5 mg or amlodipine 5 mg alone.
-After week 1, doses titrated to aliskiren 300 mg/amlodipine 10 mg or amlodipine 10 mg</td>
<td>Baseline (mean)
Mean age: 52.8 yrs; 46.2% male; 100% African American; MSSBP/MSDBP 167/96 mm Hg

Change in BP from baseline to week 8
<table>
<tr><th>Initial Tx</th><th>∆ MSSBP (mm Hg)</th><th>∆ MSDBP (mm Hg)</th></tr>
<tr><td>Aliskiren/amlodipine</td><td>-34.1[a]</td><td>-14.3[a]</td></tr>
<tr><td>Amlodipine</td><td>-28.9</td><td>-10.5</td></tr>
</table>
[a]P<0.001 compared to amlodipine monotherapy

Percent of patients obtaining BP goal (<140/<90 mm Hg)
<table>
<tr><th>Tx</th><th>Percent at Week 4</th><th>Percent at Week 8</th></tr>
<tr><td>Aliskiren/amlodipine</td><td>54.5%[a]</td><td>57.3%[b]</td></tr>
<tr><td>Amlodipine</td><td>43.5%</td><td>48%</td></tr>
</table>
[a] P=0.022 compared to amlodipine monotherapy group
[b] P=0.051 compared to amlodipine monotherapy group

∆ 24hr ABPM (n=819)
The combination aliskiren/amlodipine provided patients with a statistically significant lowering of MADBP when compared to amlodipine monotherapy (P=0.032); however there was no statistically significant difference between the two groups in lowering MASBP (P=0.086).

∆ PRA, PRC, UACR
PRA decreased by 61.7% from baseline in the aliskiren/amlodipine group compared to a 50% increase from baseline in the amlodipine group (P<0.001).
PRC increased by 495.4% from baseline in the aliskiren/amlodipine group and 34.8% in the amlodipine group (P<0.001).
There was no significant change in UACR from baseline in either treatment group.

Study Conclusions
The combination of aliskiren/amlodipine was more effective than amlodipine monotherapy in lowering MSDBP and MSSBP in African American patients. The incidence of AEs were similar among the two groups, and the combination of aliskiren/amlodipine appears to be well-tolerated.</td>
<td>Withdrawal
-33 patients discontinued the study
-9 patients in aliskiren/amlodipine group and 3 in the amlodipine group withdrew due to AEs
-The AEs for the aliskiren/amlodipine group were unstable angina, vertigo, peripheral edema, chest pain, rash, and hypotension
-The AEs in the amlodipine group were peripheral edema, pruritis, and increased BP
-4 patients in the aliskiren/amlodipine group and 5 in the amlodipine group withdrew their consent
-1 patient in the aliskiren/amlodipine group and 6 in the amlodipine group were lost to follow-up
-2 patients withdrew due to a lack of therapeutic effect in the amlodipine group
-3 patients in the amlodipine group were withdrawn due to noncompliance with the study protocol

Adverse Events
-35% of patients in the aliskiren/amlodipine group and 32.7% of patients in the amlodipine group experienced at least one side effect
-Peripheral edema was the most common side effect, occurring in 7.7% of patients in the combination therapy group and 9% in the monotherapy group
-1 patient in each group suffered a SAE; in the aliskiren/amlodipine group a patient experienced unstable angina and in the amlodipine monotherapy group, a patient experienced pneumonia and back pain

Study Analysis

Strengths:
-All patients studied were African Americans; other trials contained a majority of Caucasian patients
-ABPM was utilized in a sub-group of patients

Limitations:
-The trial only lasted 8 weeks, which makes it difficult to determine the safety and continued efficacy of the fixed-dose combination over an extended period of time
-Surrogate endpoints were used
-The majority of patients were under the age of 65 which makes it difficult to determine how an older population would respond to the fixed-dose combination</td>
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ABPM=ambulatory blood pressure monitoring ; AC= active control; AE=adverse event; BP=blood pressure; CV=cardiovascular; CVA= cerebrovascular accident; d=day; DB=double-blind; DBP= diastolic blood pressure; HA=headache; HF= heart failure; hr=hour; hx= history; HTN=hypertension; MC=multicenter; MI=myocardial infarction; MSDBP= mean sitting diastolic blood pressure, MSSBP= mean sitting systolic blood pressure, n=number of patients; PC=placebo-controlled; PCI= percutaneous coronary intervention; PRA= plasma renin activity; PRC= plasma renin concentration; R=randomized; SB= single blind; SBP= systolic blood pressure; sCr=serum creatinine; TIA= transient ischemic attack; tx=treatment; UACR= urine albumin: creatinine ratio; W/D=withdrawal; wk=week; yrs=years

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Safety Study

Citation	Eligibility Criteria	Interventions/Endpoints	Efficacy Results/Author's Conclusions	Safety
Littlejohn et al.[6] OL, MC n=556 54 wks Funded by Novartis	**Inclusion** Men and women ≥ 18 yrs, essential hypertension (MSDBP ≥ 90 mm Hg and < 110 mm Hg) **Exclusion** Severe hypertension (MSDBP > 110 mm Hg and/or MSSBP > 180 mm Hg), secondary HTN, hx of hypertensive encephalopathy, CVA, previous or current dx of heart failure NYHA class III-IV, serum potassium ≥ 5.3 mEq/L, or TIA, MI, coronary bypass surgery, PCI within 12 months, uncontrolled diabetes, heart block, atrial fibrillation, potentially life-threatening arrhythmia	**Primary** Long-term safety of aliskiren 300 mg/amlodipine 10 mg **Secondary** Long-term blood pressure efficacy (Δ from baseline in MSBDP and MSSBP), percent of patients achieving BP control (MSSBP <140 mm Hg and MSDBP <90 mm Hg), percent of patients achieving DBP response (MSDBP <90mm Hg or at least 10 mm Hg reduction from baseline) **Wash-out** W/D HTN Rx over 1-4 weeks Additional 2 weeks of wash-out if patients did not meet BP eligibility criteria **Tx Phase** -Aliskiren 150 mg/amlodipine 5 mg x 2 weeks, then all patients titrated to aliskiren 300 mg/amlodipine 10 mg -Patients returned to clinic every 2 weeks for first month, then monthly for 2 months, then every 3 months -Patients with MSSBP <100 mmHg did not undergo dose titration and were withdrawn from the study -Hydrochlorothiazide 12.5 mg was added to patients with MSSBP ≥ 140 mm Hg and /or MSDBP ≥ 90 mmHg for 2 consecutive visits and titrated to 25 mg daily if necessary	**Baseline (mean)** Mean age: 54.4 yrs; 59.4% male; 80.6% Caucasian **Reduction in MSSBP/MSBDP** -MSSBP decreased from 153 mmHg at baseline to 138 mmHg at week 2 in patients taking aliskiren 150 mg/amlodipine 5 mg -At the end of the trial, MSSBP was 128 mmHg on aliskiren 300 mg/amlodipine 10 mg -The maximum mean decrease in MSSBP (-23.5 mm Hg) and MSDBP (-15.1 mm Hg) were seen at week 10 **Study Conclusions** Aliskiren/amlodipine appears to be a safe and efficacious option in patients with hypertension.	**Adverse Events: Primary endpoint** -Infectious and infestations occurred in 36.3% of patients -Peripheral edema was reported in 22.7% of patients -6.5% of patients discontinued the study drug due to peripheral edema -Diarrhea occurred in 3.2% of patients and was considered mild in most patients. Diarrhea was not attributed to the study medication in two patients who experienced a severe case. -Mild to moderate orthostatic hypotension was reported in 3 patients -15 patients experienced SAE -13 patients taking aliskiren 300 mg/amlodipine 10 mg experienced acetabulum fracture, acute renal failure, amebiasis, asthma, atrial fibrillation, deep vein thrombosis, depression, diabetes mellitus, diarrhea, fall, gastroenteritis, hypovolemia, intestinal ischemia, ligament injury, metastatic prostate cancer, malignant melanoma, osteoarthritis, post-procedural infection, pubic rami facture, pulmonary embolism, respiratory tract infection, rotator cuff syndrome, and attempted suicide -2 patients taking aliskiren 300 mg/amlodipine 10 mg plus hydrochlorothiazide experienced gangrene and hypotension. -Deaths: 0

AE=adverse event; BP=blood pressure; CV=cardiovascular; CVA= cerebrovascular accident; d=day; DB=double-blind; DBP= diastolic blood pressure; HA=headache; HF= heart failure; hr=hour; hx= history; HTN=hypertension; MC=multicenter; MI=myocardial infarction; MSDBP= mean sitting diastolic blood pressure, MSSBP= mean sitting systolic blood pressure, n=number of patients; OL= open label; PC=placebo-controlled; PCI= percutaneous coronary intervention; SAE= serious adverse event; SBP= systolic blood pressure; sCr=serum creatinine; TIA= transient ischemic attack; tx=treatment; W/D=withdrawal; wk=week; yrs=years

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