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ORIGINAL ARTICLE

Efficacy, safety and tolerability of aliskiren, a direct renin inhibitor, in women with hypertension: a pooled analysis of eight studies

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Hypertension is a major risk factor for cardiovascular disease, which is the leading cause of mortality in women in developed countries. This pooled analysis assessed the antihypertensive efficacy, safety and tolerability of monotherapy with the direct renin inhibitor aliskiren (150 mg and 300 mg) over 8–12 weeks in women with mild-to-moderate hypertension (mean sitting diastolic blood pressure (msDBP) $\geqslant$ 95 and $<$ 110 mm Hg) across eight randomized and double-blind trials. Safety and tolerability were assessed in the five placebo-controlled trials in the analysis. In the 1527 women enrolled in these studies, aliskiren 150 mg and 300 mg produced significantly greater blood pressure (BP) reductions (14.1/11.0 and 16.1/12.3 mm Hg, respectively) compared with placebo (7.2/7.6 mm Hg; $P<0.0001$). BP reductions with aliskiren monotherapy in women were similar to those observed in men, and consistent across subgroups of age, metabolic syndrome and obesity. The overall incidence of adverse events in women was similar with aliskiren treatment (150 mg, 42.3%; 300 mg, 46.0%) and placebo (39.0%); adverse events with aliskiren were more frequent in women than in men, consistent with previous studies of gender differences in drug tolerability. In conclusion, aliskiren monotherapy at 150 mg and 300 mg doses provided effective, dose-dependent BP-lowering in women with mild-to-moderate hypertension, and it was well tolerated.
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Introduction

Although cardiovascular disease (CVD) is often perceived as being a 'male' disease because of its high incidence in middle-aged men, it is the leading cause of mortality and morbidity in women in developed countries. Worldwide, almost half of all deaths from coronary heart disease occur in women[1] and in the United States of America, more women than men die from CVD each year.[2] Despite this, many women remain unaware of the risk posed by CVD. In a 2006 survey, only 57% of women identified heart disease as the leading cause of death among women.[3]

Hypertension, diabetes, obesity and hypercholesterolaemia are major risk factors for CVD in both men and women. However, evidence suggests that these factors may make a greater contribution to cardiovascular risk in women than in men.[4–6] Hypertension is an important risk factor for CVD in women and it is more prevalent in women than men in people aged 55 years and above.[2] Furthermore, there is an age-dependent increased prevalence of hypertension in postmenopausal compared with pre-menopausal women corresponding to a fourfold greater risk of coronary heart disease.[7]

Well-controlled clinical trials have shown that effective antihypertensive treatment improves cardiovascular outcomes similarly in women and men, irrespective of age.[8,9] Moreover, in developed countries, awareness of hypertension is generally higher among women than men, as are treatment rates. However, rates of blood pressure (BP) control remain low; overall, only about one-third of women with hypertension achieve BP control in the United States of America, with lower rates reported in some European countries.[10–12] Findings from the Women's

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Health Initiative study suggest that inadequate intensity of antihypertensive therapy could account for these poor BP control rates.[13]

Taken together, these findings point to a need for more effective treatment options for women with hypertension. Aliskiren, the first in a new class of oral direct renin inhibitors, is approved for the treatment of hypertension at once-daily doses of 150 mg and 300 mg. In a large clinical trial programme involving approximately 5500 women with hypertension, aliskiren demonstrated effective BP lowering and was generally well tolerated in short- and long-term (up to 52 weeks) studies, both as monotherapy and in combination with other antihypertensive agents.[16] This pooled analysis of eight clinical trials assessed the antihypertensive efficacy, safety and tolerability of aliskiren 150 mg and 300 mg monotherapy in women with mild-to-moderate hypertension.

Patients and methods

Study design

This pooled analysis evaluated efficacy data from eight randomized, double-blind, multicentre studies of aliskiren monotherapy in patients with mild-to-moderate hypertension (Table 1).[14,15,17–22] Data were analysed for aliskiren 150 mg and 300 mg (the US Food and Drug Administration and European Union approved doses for the treatment of hypertension) and placebo after 8 or 12 weeks of treatment for the subgroups of women and men. All of the trials were 8 weeks in duration, except for the aliskiren vs ramipril (6 months) and aliskiren vs HCT (12 months) studies.[19,22] In these two long-term trials, the effects of aliskiren monotherapy were assessed after 12 weeks, before the optional addition of HCT (aliskiren vs ramipril study) or amlodipine (aliskiren vs HCT study) was permitted for BP control. Patients in the aliskiren vs ramipril study started treatment with aliskiren 150 mg, with optional dose titration to 300 mg allowed for BP control after 6 weeks.[19] Patients in the aliskiren vs HCT study underwent forced titration from aliskiren 150 mg to 300 mg after 3 weeks.[22]

Patients

All eight studies enrolled patients $\geqslant$18 years of age with mild-to-moderate hypertension (mean sitting diastolic BP (msDBP) $\geqslant$95 mm Hg and $<$110 mm Hg). For inclusion in the aliskiren/ramipril study,[21] patients also had to have type I or type II diabetes mellitus. In all of the studies, patients with severe hypertension (msDBP$\geqslant$110 mm Hg and/or mean sitting systolic BP (msSBP) $\geqslant$180 mmHg), a history or evidence of secondary hypertension, or a history of severe cerebrovascular or CVD were excluded. Pregnant or nursing women were also excluded from these studies.

All studies were conducted according to the ethical principles of the Declaration of Helsinki. Study protocols and any amendments were reviewed and approved by the independent ethics committee or institutional review board for each study centre, and patients provided written informed consent before participating in any of the studies.

Assessments

The efficacy of aliskiren 150 mg or 300 mg monotherapy was assessed in eight double-blind,

Table 1 Summary of aliskiren clinical trials enrolling patients with mild-to-moderate hypertension

Study	*Number of randomized patients*	*Maximum active treatment duration assessed (weeks)*	*Placebo group*	*Aliskiren monotherapy treatment (mg)*[a]	*Number of randomized patients included in pooled efficacy analysis*					
					Women			*Men*		
					PBO	*ALI 150*	*ALI 300*	*PBO*	*ALI 150*	*ALI 300*
Aliskiren monotherapy study 1	455	8	Yes	75, 150 and 300	25	31	33	90	81	80
Aliskiren monotherapy study 2	652	8	Yes	150, 300 and 600	67	54	55	64	73	75
Aliskiren monotherapy study 3	672	8	Yes	150, 300 and 600	61	65	63	104	107	106
Aliskiren/valsartan multifactorial	1123	8	Yes	75, 150 and 300	80	77	75	97	101	100
Aliskiren/HCT multifactorial	2776	8	Yes	75, 150 and 300	86	73	84	109	112	99
Aliskiren/ramipril[b]	837	8	No	300	—	—	125	—	—	157
Aliskiren vs ramipril	842	12[c]	No	150 and 300	—	196[d]		—	224[d]	
Aliskiren vs HCT	1124	12[c]	No	150 and 300	—	260[e]		—	307[e]	

Abbreviations: ALI 150, aliskiren 150 mg; ALI 300, aliskiren 300 mg; HCT, hydrochlorothiazide; PBO, placebo.
[a]All doses indicated were taken once daily.
[b]All patients enrolled in this study had type I or type II diabetes.
[c]The aliskiren vs ramipril and aliskiren vs HCT studies were long-term trials (6 and 12 months, respectively) with dose titrations. Short-term blood pressure reductions with aliskiren monotherapy at week 12 were assessed for the pooled analysis.
[d]Randomized to aliskiren 150 mg with optional titration to aliskiren 300 mg for blood pressure control at week 6.
[e]Randomized to aliskiren 150 mg and force titrated to aliskiren 300 mg at week 3.

parallel-group, placebo- and/or active-controlled studies (Table 1). The pooled efficacy analysis assessed the mean change in msSBP and msDBP from baseline, and BP control (msSBP/DBP $<140/90$ mm Hg) and responder rates (msDBP <90 mm Hg and/or $\geqslant 10$ mm Hg reduction from baseline), at the end of the monotherapy treatment period (week 8 for six studies and week 12 for two studies; Table 1).

The safety and tolerability of aliskiren monotherapy was assessed in the five double-blind, parallel-group, placebo-controlled studies (Table 1). Adverse events were recorded at each study visit and assessed by study investigators for severity and likely relationship to study medication. Standard laboratory analyses were carried out during each study and the proportions of patients meeting pre-defined laboratory safety parameters (serum potassium concentrations <3.5, >5.5 and $\geqslant 6.0$ mmol l^{-1}, serum creatinine >176.8 μmol l^{-1} and blood urea nitrogen levels >14.28 mmol l^{-1}) were recorded.

Statistical analysis

Data from the male and female subgroups were analysed separately. Changes in msSBP from baseline to study endpoint were analysed using an analysis of covariance model with treatment as a factor and baseline msSBP as a covariate. A similar analysis was carried out for change in msDBP from baseline to endpoint. Responder and BP control rates at study endpoint were analysed using a logistic regression model with treatment as a factor and baseline msDBP as a covariate. Endpoint was defined as the last postrandomization measurement collected during the monotherapy treatment period (week 8 for six studies and week 12 for two studies; Table 1).

Further analyses were carried out for the following subgroups of female patients (which were defined using data collected at baseline): non-elderly (<65 years) or elderly ($\geqslant 65$ years); pre-menopausal (<50 years), menopausal (50–55 years inclusive) or postmenopausal (>55 years); non-obese (body mass index <30 kg m^{-2}) or obese (body mass index $\geqslant 30$ kg m^{-2}); without metabolic syndrome or with metabolic syndrome (defined according to NCEP ATP III criteria[23]). For each subgroup the changes from baseline in msSBP and msDBP and the BP control rates were analysed as described above.

Results

Patient demographics

The pooled analysis involved a total of 3591 patients with hypertension. In all, 1527 women were included (42.5%), and the proportion of women was similar across the three treatment groups analysed (aliskiren 150 mg, 41.6%; aliskiren 300 mg, 44.1%; and placebo, 40.7%). Within the gender subgroups, patient demographics were generally similar across the three treatment groups (Table 2). Women participating in the studies tended to be slightly older than men (range of means 55.1–57.3 years vs 52.9–55.3 years), with a longer duration of hypertension (7.8–8.2 years vs 6.5–7.8 years).

Table 2 Patient demographics and baseline characteristics (pooled safety population)

Parameter	*Female patients*			*Male patients*		
	Placebo (n = 318)	*Aliskiren 150 mg (n = 496)*	*Aliskiren 300 mg (n = 713)*	*Placebo (n = 463)*	*Aliskiren 150 mg (n = 697)*	*Aliskiren 300 mg (n = 904)*
Age (years)	56.0 ± 11.8	55.1 ± 10.7	57.3 ± 10.9	53.3 ± 11.1	52.9 ± 11.7	55.3 ± 11.1
Age ⩾65 years, *n* (%)	71 (22.3)	91 (18.3)	189 (26.5)	69 (14.9)	116 (16.6)	174 (19.2)
Race, n (%)						
Caucasian	227 (71.4)	339 (68.3)	601 (84.3)	292 (63.1)	498 (71.4)	746 (82.5)
Asian	33 (10.4)	44 (8.9)	55 (7.7)	118 (25.5)	117 (16.8)	116 (12.8)
Black	39 (12.3)	88 (17.7)	36 (5.0)	30 (6.5)	59 (8.5)	20 (2.2)
Other	16 (5.0)	19 (3.8)	16 (2.2)	19 (4.1)	20 (2.9)	19 (2.1)
BMI (kg m^{-2})	29.8 ± 6.6	29.7 ± 6.5	29.6 ± 6.1	28.7 ± 5.0	28.9 ± 4.8	29.3 ± 4.9
Obesity (BMI ⩾30 kg m^{-2}), *n* (%)[a]	136 (42.8)	205 (41.3)	291 (40.8)	144 (31.1)	231 (33.1)	341 (37.7)
Metabolic syndrome, *n* (%)[b]	81 (25.5)	166 (33.5)	241 (33.8)	109 (23.5)	202 (29.0)	305 (33.7)
Diabetes, *n* (%)[c]	11 (3.5)	27 (5.4)	162 (22.7)	21 (4.5)	51 (7.3)	214 (23.7)
Duration of hypertension (years)	7.8 ± 7.7	7.9 ± 7.4	8.2 ± 7.6	6.5 ± 6.4	7.1 ± 6.9	7.8 ± 7.5
msSBP (mm Hg)	153.7 ± 11.9	153.1 ± 12.4	154.9 ± 11.5	151.9 ± 12.0	152.3 ± 11.7	154.0 ± 11.6
msDBP (mm Hg)	98.6 ± 3.2	98.7 ± 3.3	98.6 ± 3.1	99.5 ± 3.7	99.3 ± 3.6	99.4 ± 3.7

Abbreviations: BMI, body mass index; msDBP, mean sitting diastolic blood pressure; msSBP, mean sitting systolic blood pressure.
Data are presented as mean ± s.d. unless otherwise stated.
[a]Data not available: female subjects: aliskiren 150 mg, $n = 1$; and aliskiren 300 mg, $n = 7$; male subjects: placebo, $n = 1$; aliskiren 150 mg, $n = 6$; and aliskiren 300 mg, $n = 4$.
[b]Metabolic syndrome was defined according to NCEP ATP III guidelines. Data not available: female subjects: aliskiren 300 mg, $n = 2$ and male subjects: aliskiren 300 mg, $n = 2$.
[c]Diabetes diagnosis from medical history. Data not available: female subjects: placebo, $n = 147$; aliskiren 150 mg, $n = 131$; and aliskiren 300 mg, $n = 151$; male subjects: placebo, $n = 161$; aliskiren 150 mg, $n = 174$; and aliskiren 300 mg, $n = 156$.

There was a higher proportion of Black women (5.0–17.7%) than Black men (2.2–8.5%); conversely, the proportion of Asian women (7.7–10.4%) was lower than the proportion of Asian men (12.8–25.5%). Slightly more women than men were obese (40.8–42.8% vs 31.1–37.7%). Baseline BP was similar in women and men.

Few patients in this analysis discontinued aliskiren treatment and the incidence was similar in women (150 mg, 7.3%; 300 mg, 5.8%) and men (150 mg, 6.8%; 300 mg, 6.6%). Discontinuation rates with placebo were higher than with aliskiren therapy for both women (12.5%) and men (12.9%), primarily because of the higher numbers of discontinuations due to unsatisfactory therapeutic effect with placebo (5.0–5.6%) than with active therapy (1.5–2.3%). The reasons for discontinuation from aliskiren treatment were similar across doses and genders, with adverse events (0.8–2.7%) and withdrawal of consent (0.9–2.3%) being the most commonly reported reasons.

Efficacy

Aliskiren 150 mg and 300 mg provided significantly greater, dose-dependent reductions from baseline in msSBP and msDBP compared with placebo in women with hypertension (all $P<0.0001$; Figure 1). Mean BP reductions at endpoint with both aliskiren doses were slightly larger in women than in men, although the placebo-adjusted changes were similar in women and men for the 150 mg and 300 mg doses.

Blood pressure control rates in women were significantly higher with aliskiren 150 mg (42.3%) and 300 mg (46.4%) monotherapy than with placebo (26.7%; both $P<0.0001$) (Figure 2). Control rates with aliskiren treatment were higher in women than in men, although placebo-adjusted rates were similar in both genders. In women, responder rates were also significantly higher with aliskiren 150 mg (62.6%) or 300 mg (72.5%) than with placebo (47.6%; both $P<0.0001$); similar responder rates were observed in men (150 mg, 56.3%; 300 mg, 67.3%; placebo, 35.6%; $P<0.0001$).

Subgroup analyses in women showed that BP reductions with aliskiren monotherapy were similar in elderly and younger patients, in patients with and without metabolic syndrome and in obese and non-obese patients (Table 3). Although reductions from baseline in msSBP with aliskiren 300 mg tended to be larger in the subgroups of elderly women and those without metabolic syndrome or obesity, there were no notable differences for placebo-corrected BP changes. In all of these subgroups, BP reductions from baseline with aliskiren 150 mg and 300 mg were significantly greater than with placebo (all $P\leqslant 0.0009$).

Subgroup analysis by age (<50, 50–55 and >55 years) was used to assess the effects of menopausal status on the response to aliskiren monotherapy. Baseline msSBP increased with increasing

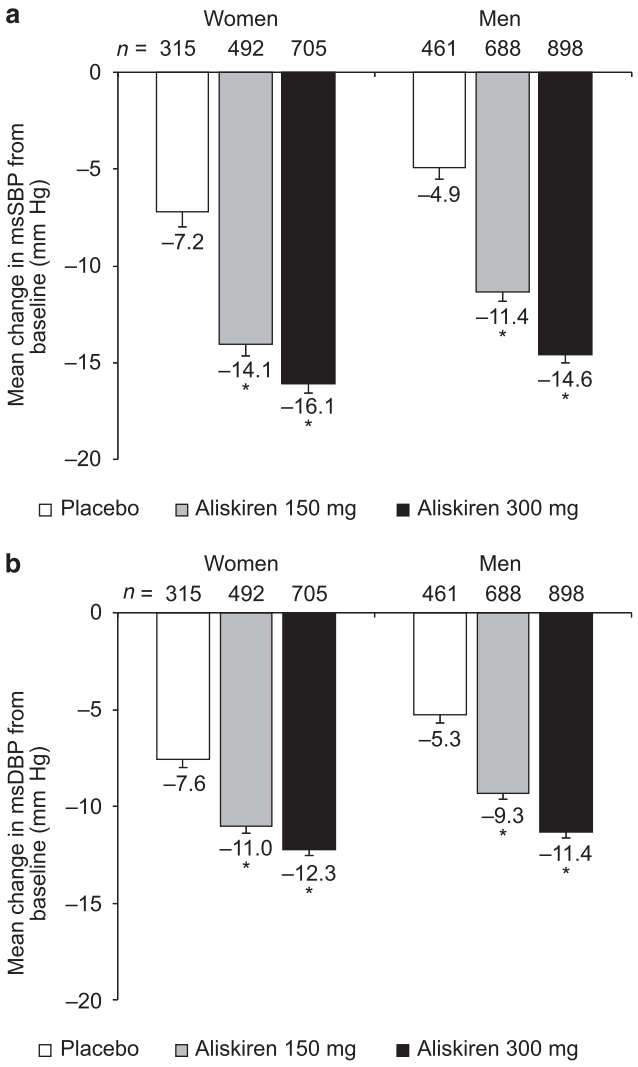

Figure 1 Change in (**a**) mean sitting systolic BP (msSBP) and (**b**) mean sitting diastolic BP (msDBP) from baseline with aliskiren monotherapy, analysed by gender. *$P<0.0001$ vs placebo.

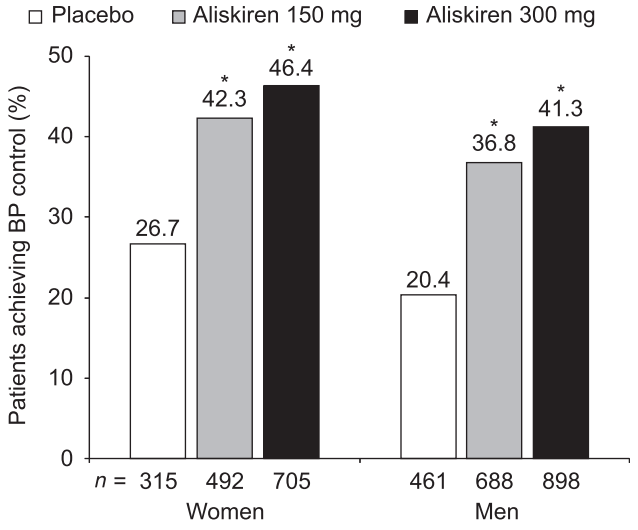

Figure 2 Proportion of patients achieving BP control (BP<140/90 mm Hg) by gender with aliskiren monotherapy. *$P<0.0001$ vs placebo.

Table 3 Subgroup analyses of least squares mean changes in mean sitting systolic and diastolic blood pressure (msSBP and msDBP) from baseline with aliskiren monotherapy in women

	Placebo		*Aliskiren 150 mg*		*Aliskiren 300 mg*	
	n	*msSBP/msDBP*	*n*	*msSBP/msDBP*	*n*	*msSBP/msDBP*
Age (years)						
Elderly (⩾65)	70	–3.2/–8.3	90	–15.0/–12.8	186	–15.4/–12.7
Younger (<65)	245	–8.6/–7.4	402	–13.9/–10.7	519	–16.6/–12.2
Metabolic syndrome[a]						
Present	81	–5.0/–5.9	166	–15.0/–11.4	238	–15.1/–11.7
Not present	234	–8.2/–8.2	326	–13.9/–10.9	465	–16.9/–12.6
Obesity (BMI⩾30 kg m^{-2})						
Obese	133	–6.0/–6.9	205	–13.7/–10.9	290	–14.1/–11.3
Non-obese	182	–8.6/–8.2	286	–14.7/–11.2	409	–17.8/–12.9

Abbreviation: BMI, body mass index.
[a]Metabolic syndrome was defined according to NCEP ATP III guidelines.

age; reductions in BP with aliskiren 150 mg or 300 mg were generally similar across age groups (Figure 3). In addition, the effect of oestrogen therapy was assessed by subgroup analysis in the five placebo-controlled studies, although only small numbers of women received oestrogen in these trials (150 mg, $n=35$ (out of 298); 300 mg, $n=27$ (out of 326)). There was no consistent effect of oestrogen therapy on the BP-lowering efficacy of aliskiren 150 mg or 300 mg (data not shown).

Safety and tolerability

Aliskiren 150 mg and 300 mg showed a similar tolerability profile to placebo in women with hypertension. The overall incidence of adverse events in women was similar in both aliskiren groups (150 mg, 42.3%; 300 mg, 46.0%) and in the placebo group (39.0%). The majority of adverse events were transient and either mild or moderate in intensity and few women discontinued because of adverse events (2.0–2.8%). The most frequently reported adverse events in all the three treatment groups were headache and nasopharyngitis.

The overall incidence of adverse events in both the aliskiren 150 mg and 300 mg groups was higher in women than in men (Table 4). However, the most frequently reported adverse events were the same for both genders, and there were no notable differences in either the type of adverse events or their frequency that would account for the overall difference in incidence seen between the genders. Some small differences in incidence were observed between genders. Headache was reported less frequently with aliskiren 150 mg and 300 mg therapy than with placebo by both women and men, although the difference was more marked in men. Diarrhoea showed a larger difference in incidence between aliskiren 300 mg and placebo in women (3.0 vs 1.3%) than in men (1.8 vs 1.1%), but rates

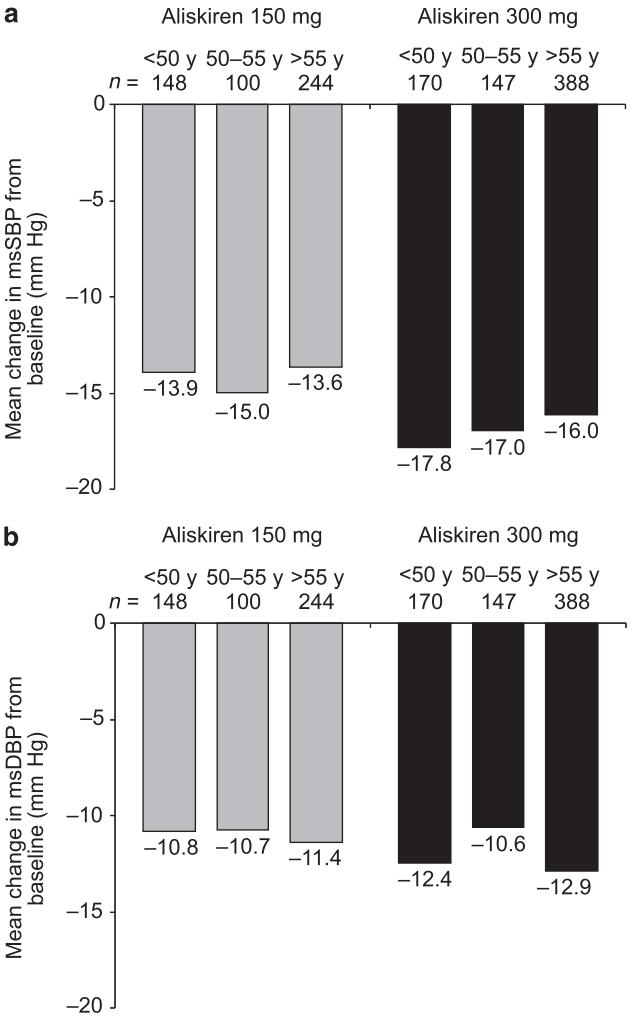

Figure 3 Change in (**a**) mean sitting systolic BP (msSBP) and (**b**) mean sitting diastolic BP (msDBP) from baseline with aliskiren monotherapy in women, analysed by age. Baseline BP (<50; 50–55; >55 years): aliskiren 150 mg; 147.3/99.0, 152.1/98.9 and 157.0/98.5 mm Hg; aliskiren 300 mg; 149.5/99.0, 154.1/98.5 and 157.6/98.4 mm Hg.

Table 4 Number (%) of patients reporting adverse events or with predefined abnormal laboratory values in placebo-controlled trials

Adverse event	*Women*			*Men*		
	Placebo (n = 318)	*Aliskiren 150 mg (n = 300)*	*Aliskiren 300 mg (n = 328)*	*Placebo (n = 463)*	*Aliskiren 150 mg (n = 474)*	*Aliskiren 300 mg (n = 440)*
Any AE	124 (39.0)	127 (42.3)	151 (46.0)	190 (41.0)	163 (34.4)	158 (35.9)
Discontinuations because of AE	9 (2.8)	6 (2.0)	9 (2.7)	16 (3.4)	4 (0.8)	11 (2.5)
Most frequent AEs (>2.0% in any treatment group)						
Diarrhoea	4 (1.3)	5 (1.7)	10 (3.0)	5 (1.1)	4 (0.8)	8 (1.8)
Dizziness	9 (2.8)	5 (1.7)	8 (2.4)	8 (1.7)	4 (0.8)	11 (2.5)
Fatigue	5 (1.6)	2 (0.7)	2 (0.6)	7 (1.5)	3 (0.6)	11 (2.5)
Headache	28 (8.8)	21 (7.0)	24 (7.3)	40 (8.6)	21 (4.4)	20 (4.5)
Nasopharyngitis	16 (5.0)	13 (4.3)	11 (3.4)	29 (6.3)	20 (4.2)	18 (4.1)
Nausea	8 (2.5)	3 (1.0)	9 (2.7)	3 (0.6)	0	3 (0.7)
Urinary tract infection	7 (2.2)	6 (2.0)	4 (1.2)	2 (0.4)	1 (0.2)	2 (0.5)
URTI	6 (1.9)	0	8 (2.4)	6 (1.3)	7 (1.5)	5 (1.1)
Other AEs						
Cough	0	5 (1.7)	6 (1.8)	5 (1.1)	6 (1.3)	1 (0.2)
Peripheral oedema	2 (0.6)	3 (1.0)	3 (0.9)	3 (0.6)	3 (0.6)	4 (0.9)
Laboratory abnormalities						
Serum potassium ($mmol\,l^{-1}$)	$n = 284$	$n = 279$	$n = 296$	$n = 418$	$n = 424$	$n = 406$
<3.5	11 (3.9)	3 (1.1)	3 (1.0)	12 (2.9)	6 (1.4)	4 (1.0)
>5.5	2 (0.7)	2 (0.7)	4 (1.4)	2 (0.5)	3 (0.7)	3 (0.7)
$\geqslant 6.0$	0	0	1 (0.3)	1 (0.2)	1 (0.2)	0
BUN ($mmol\,l^{-1}$)	$n = 304$	$n = 292$	$n = 323$	$n = 449$	$n = 462$	$n = 431$
>14.28	0	0	0	0	0	1 (0.2)
Creatinine ($\mu mol\,l^{-1}$)	$n = 304$	$n = 292$	$n = 323$	$n = 449$	$n = 462$	$n = 431$
>176.8	0	0	0	0	0	1 (0.2)

Abbreviations: AE, adverse event; BUN, blood urea nitrogen; URTI, upper respiratory tract infection.

remained low. The incidence of cough was low (<2%) in both women and men in all three treatment groups; the incidence was similar in women and men with aliskiren 150 mg, although cough was more frequent in women than in men at the 300 mg dose.

The incidence of abnormal laboratory values during the study was low and similar in women and men (Table 4). Serum potassium levels $<3.5\,mmol\,l^{-1}$ were more frequent with placebo in both women (3.9%) and men (2.9%) than with aliskiren therapy (1.0–1.4%). Serum potassium elevations $>5.5\,mmol\,l^{-1}$ occurred infrequently across genders and treatment groups (0.5–1.4%), and only three patients (two male and one female) exhibited serum potassium levels $\geqslant 6.0\,mmol\,l^{-1}$.

Discussion

Our pooled analysis shows that once-daily treatment with aliskiren monotherapy at doses of 150 mg and 300 mg provides effective, dose-dependent BP-lowering in women with mild-to-moderate hypertension, similar to the effects observed in men. The antihypertensive effects of aliskiren monotherapy in women were consistent across subgroups of age, metabolic syndrome and obesity. Both doses of aliskiren showed a similar tolerability profile to placebo in women and men.

Aliskiren 150 mg and 300 mg produced significantly greater reductions in BP than placebo in women after 8–12 weeks' treatment. BP control rates and responder rates were also significantly greater with aliskiren treatment than placebo. Subgroup analyses in women showed that aliskiren therapy provided effective BP lowering in elderly patients ($\geqslant$65 years), obese patients and those with metabolic syndrome. The decreases in BP seen with aliskiren therapy in elderly women were similar to those seen in younger individuals. Effective antihypertensive treatment in older women is important in reducing the burden of hypertension, as the prevalence of hypertension in the elderly is higher in women than men,[2] and the proportion of women achieving BP control decreases with age.[11,12]

The subgroup analysis also showed that aliskiren monotherapy was effective in hypertensive women with metabolic syndrome and those with obesity. Previous studies of aliskiren in both men and women with hypertension have shown similar BP reductions in patients with and without metabolic syndrome,[24] and in obese and non-obese patients.[25] Metabolic risk factors for cardiovascular morbidity and mortality, particularly obesity, are common in women with hypertension. In a recent survey of patients with diagnosed hypertension, central obesity was significantly more prevalent in women than men (79 vs 64%), as were elevated total cholesterol (61 vs 48%) and low HDL cholesterol (40 vs 36%).[26] Furthermore, significantly more women than men had three or more cardiovascular risk factors (53 vs

41%), underlining the importance of effective BP control in women with hypertension and metabolic disorders.

Subgroup analysis by age (used as a surrogate for menopausal status) suggested that menopausal status had little effect on the BP-lowering efficacy of aliskiren, Although there is a clear age-dependent increase in the prevalence of hypertension in women,[2] the relationship between menopausal status and hypertension is uncertain; some studies report an increase in BP related to menopause, whereas others suggest that factors such as age, weight and physical activity can account for this apparent relationship.[27,28] The findings from this analysis suggest that aliskiren provides effective BP reductions in women, irrespective of menopausal status. The effects of oestrogen use on aliskiren therapy were unclear, probably reflecting the small numbers of women receiving oestrogen in these clinical trials. Studies examining the effects of hormone-replacement therapy on antihypertensive treatments are limited, although an observational study in postmenopausal women with hypertension showed that the antihypertensive efficacy of candesartan (alone or in combination with HCT) was similar with or without hormone replacement therapy.[29]

The antihypertensive efficacy of aliskiren in women was similar to that observed in men. This is consistent with findings with other antihypertensive agents, although analyses examining effects of antihypertensive medications by gender in hypertension are limited.[30] Some studies have reported differences between genders. In the HANE (hydrochlorothiazide, atenolol, nitrendipine and enalapril) study in patients with mild-to-moderate hypertension, the overall response rate (DBP <90 mm Hg) was higher in women (55%) than men (48%), and enalapril provided significantly higher response rates in women than in men.[31]

In this pooled analysis, both the 150 mg and 300 mg doses of aliskiren were generally well tolerated in women. The type, severity and overall incidence of adverse events reported for aliskiren 150 mg and 300 mg were similar to those observed with placebo, and there were no clear differences in the types of adverse events between genders. Adverse events on aliskiren treatment were more frequently reported in women than in men. This is consistent with the previous studies that suggest that women tend to experience more adverse events with drug treatment than men.[32,33] The underlying reasons are not fully understood, although gender-related differences in pharmacokinetics and pharmacodynamics, hormonal factors and medication use may all play a role.[34,35] Differences in the incidence of adverse events between genders have been observed in some studies in patients with hypertension. In the TOMHS (Treatment Of Mild Hypertension Study), adverse events were reported more frequently by women than men, although the incidence was similar in the treatment and placebo groups.[36]

Gender-based differences in tolerability have been observed with some antihypertensive treatments, although the reasons for these differences have yet to be elucidated. ACE-inhibitor-induced cough and lower extremity oedema with calcium-channel blockers have been reported more frequently in women than in men.[37–41] In this analysis, the incidence of cough with aliskiren monotherapy was low ($<2\%$) in both women and men; the incidence of peripheral oedema in women in the aliskiren groups was also low (0.9–1.0%) and similar to that observed in men (0.6–0.9%).

Changes in biochemical parameters with antihypertensive medication may also show differences between genders. Both hyponatraemia and hypokalaemia associated with diuretic therapy are more frequent in women than in men.[42–45] In the current study, the incidence of serum potassium levels $<3.5\,\text{mmol}\,\text{l}^{-1}$ with aliskiren therapy was low (1.0–1.4%) and did not differ between genders. Similarly, few women or men experienced serum potassium elevations $>5.5\,\text{mmol}\,\text{l}^{-1}$ with aliskiren therapy (0.7–1.4%).

In conclusion, aliskiren monotherapy at doses of 150 mg and 300 mg provided effective, dose-dependent BP-lowering in women with mild-to-moderate hypertension, and was generally well tolerated. Aliskiren treatment showed similar antihypertensive efficacy and tolerability in both women and men. Furthermore, aliskiren treatment demonstrated effective BP lowering in women who were elderly, obese or had metabolic syndrome. These results suggest that aliskiren offers an effective and well-tolerated option for the treatment of hypertension in women.

What is known about this topic

- Cardiovascular disease is often perceived as being a 'male' disease because of its high incidence in middle-aged men, but it is also the leading cause of mortality and morbidity in women in developed countries.
- Effective blood pressure (BP) control is important to reduce the risk of cardiovascular disease in men and women, but relatively few studies have specifically evaluated the BP-lowering effects of antihypertensive therapy in women.
- The direct renin inhibitor (DRI) aliskiren is approved for the treatment of hypertension at once-daily doses of 150 mg and 300 mg, and has been shown to provide highly effective BP reduction with good tolerability across a broad range of patients with hypertension.

What this study adds

- Aliskiren 150 and 300 mg monotherapy provided effective BP reductions in women similar to those observed in men, and these were consistent across subgroups of age (menopausal status), metabolic syndrome and obesity.
- The overall incidence of adverse events in women was similar with aliskiren treatment (150 mg, 42.3% and 300 mg, 46.0%) and placebo (39.0%), and there were no notable differences between genders.
- Aliskiren therefore provides an effective and well-tolerated option for the treatment of hypertension in women.

Conflict of interest

AHG has received research grants from Novartis; served on speakers' bureaus for Novartis, Merck, Daiichi-Sankyo, AstraZeneca, Pfizer, Boehringer-Ingelheim and Forest Laboratories; and as a consultant/on advisory boards for Novartis, Daiichi-Sankyo, Forest Laboratories, Merck and AstraZeneca. MRW has served as a scientific advisor for Novartis, Daiichi-Sankyo, Boehringer-Ingelheim and MSD. MW is an employee of Novartis Pharma AG, Basel, Switzerland; and CAB and DLK are employees of Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; all three are thus eligible for Novartis stock and stock options.

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References

1 World Health Organization. *Preventing chronic diseases: a vital investment: WHO global report*. World Health Organization: Geneva, 2005.
2 Lloyd-Jones D, Adams R, Carnethon M, De Simone G, Ferguson TB, Flegal K *et al.* Heart disease and stroke statistics—2009 update. A report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2009; **119**: e21–e181.
3 Christian AH, Rosamond W, White AR, Mosca L. Nine-year trends and racial and ethnic disparities in women's awareness of heart disease and stroke: an American Heart Association national study. *J Womens Health (Larchmt)* 2007; **16**: 68–81.
4 Huxley R, Barzi F, Woodward M. Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies. *BMJ* 2006; **332**: 73–78.
5 Huxley R, Woodward M, Barzi F, Wong JW, Pan WH, Patel A. Does sex matter in the associations between classic risk factors and fatal coronary heart disease in populations from the Asia-Pacific region? *J Womens Health (Larchmt)* 2005; **14**: 820–828.
6 Polk DM, Naqvi TZ. Cardiovascular disease in women: sex differences in presentation, risk factors, and evaluation. *Curr Cardiol Rep* 2005; **7**: 166–172.
7 Franklin SS. Definition and epidemiology of hypertensive cardiovascular disease in women: the size of the problem. *J Hypertens Suppl* 2002; **20**: S3–S5.
8 Gueyffier F, Boutitie F, Boissel JP, Pocock S, Coope J, Cutler J *et al.* Effect of antihypertensive drug treatment on cardiovascular outcomes in women and men. A meta-analysis of individual patient data from randomized, controlled trials. The INDANA Investigators. *Ann Intern Med* 1997; **126**: 761–767.
9 Quan A, Kerlikowske K, Gueyffier F, Boissel JP. Efficacy of treating hypertension in women. *J Gen Intern Med* 1999; **14**: 718–729.
10 Wolf-Maier K, Cooper RS, Kramer H, Banegas JR, Giampaoli S, Joffres MR *et al.* Hypertension treatment and control in five European countries, Canada, and the United States. *Hypertension* 2004; **43**: 10–17.
11 Lloyd-Jones DM, Evans JC, Levy D. Hypertension in adults across the age spectrum: current outcomes and control in the community. *JAMA* 2005; **294**: 466–472.
12 Wassertheil-Smoller S, Anderson G, Psaty BM, Black HR, Manson J, Wong N *et al.* Hypertension and its treatment in postmenopausal women: baseline data from the Women's Health Initiative. *Hypertension* 2000; **36**: 780–789.
13 Oparil S. Women and hypertension: what did we learn from the Women's Health Initiative? *Cardiol Rev* 2006; **14**: 267–275.
14 Oh BH, Mitchell J, Herron JR, Chung J, Khan M, Keefe DL. Aliskiren, an oral renin inhibitor, provides dose-dependent efficacy and sustained 24-h blood pressure control in patients with hypertension. *J Am Coll Cardiol* 2007; **49**: 1157–1163.
15 Gradman AH, Schmieder RE, Lins RL, Nussberger J, Chiang Y, Bedigian MP. Aliskiren, a novel orally effective renin inhibitor, provides dose-dependent antihypertensive efficacy and placebo-like tolerability in hypertensive patients. *Circulation* 2005; **111**: 1012–1018.
16 Frampton JE, Curran MP. Aliskiren: a review of its use in the management of hypertension. *Drugs* 2007; **67**: 1767–1792.
17 Pool JL, Schmieder RE, Azizi M, Aldigier JC, Januszewicz A, Zidek W *et al.* Aliskiren, an orally effective renin inhibitor, provides antihypertensive efficacy alone and in combination with valsartan. *Am J Hypertens* 2007; **20**: 11–20.
18 Villamil A, Chrysant SG, Calhoun D, Schober B, Hsu H, Matrisciano-Dimichino L *et al.* Renin inhibition with aliskiren provides additive antihypertensive efficacy when used in combination with hydrochlorothiazide. *J Hypertens* 2007; **25**: 217–226.
19 Andersen K, Weinberger MH, Egan B, Constance CM, Ali MA, Jin J *et al.* Comparative efficacy and safety of aliskiren, an oral direct renin inhibitor, and ramipril in hypertension: a 6-month, randomized, double-blind trial. *J Hypertens* 2008; **26**: 589–599.
20 Kushiro T, Itakura H, Abo Y, Gotou H, Terao S, Keefe DL. Aliskiren, a novel oral renin inhibitor, provides dose-dependent efficacy and placebo-like tolerability in Japanese patients with hypertension. *Hypertens Res* 2006; **29**: 997–1005.
21 Uresin Y, Taylor A, Kilo C, Tschoepe D, Santonastaso M, Ibram G *et al.* Efficacy and safety of the direct renin inhibitor aliskiren and ramipril alone or in combination in patients with diabetes and hypertension. *J Renin Angiotensin Aldosterone Syst* 2007; **8**: 190–198.
22 Schmieder RE, Philipp T, Guerediaga J, Gorostidi M, Smith B, Weissbach N *et al.* Long-term antihypertensive efficacy and safety of the oral direct renin inhibitor aliskiren: a 12-month randomized, double-blind comparator trial with hydrochlorothiazide. *Circulation* 2009; **119**: 417–425.

23 NCEP. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002; **106**: 3143–3421.
24 White WB, Anderson DR, Arora V, Bush C, Keefe DL. Antihypertensive effectiveness of the direct renin inhibitor aliskiren in patients with metabolic syndrome: a comparative analysis of 7219 patients from 10 randomized trials. *Eur Heart J* 2007; **28**: 868 P4845.
25 Schmieder RE, Philipp T, Gueredíaga J, Gorostidi M, Bush C, Keefe DL. Aliskiren-based therapy lowers blood pressure more effectively than hydrochlorothiazide-based therapy in obese patients with hypertension: sub-analysis of a 52-week, randomized, double-blind trial. *J Hypertens* 2009; **27**: 1493–1501.
26 Ong KL, Tso AW, Lam KS, Cheung BM. Gender difference in blood pressure control and cardiovascular risk factors in Americans with diagnosed hypertension. *Hypertension* 2008; **51**: 1142–1148.
27 August P, Oparil S. Hypertension in women. *J Clin Endocrinol Metab* 1999; **84**: 1862–1866.
28 Coylewright M, Reckelhoff JF, Ouyang P. Menopause and hypertension. An age-old debate. *Hypertension* 2008; **51**: 952–959.
29 Fernandez-Vega F, Abellan J, Vegazo O, De Vinuesa SG, Rodriguez JC, Maceira B *et al.* Angiotensin II type 1 receptor blockade to control blood pressure in postmenopausal women: Influence of hormone replacement therapy. *Kidney Int* 2002; **62**(Suppl 82): 36–41.
30 Lewis CE. Characteristics and treatment of hypertension in women: a review of the literature. *Am J Med Sci* 1996; **311**: 193–199.
31 Philipp T, Anlauf M, Distler A, Holzgreve H, Michaelis J, Wellek S. Randomised, double blind, multicentre comparison of hydrochlorothiazide, atenolol, nitrendipine, and enalapril in antihypertensive treatment: results of the HANE study. HANE Trial Research Group. *BMJ* 1997; **315**: 154–159.
32 Kando JC, Yonkers KA, Cole JO. Gender as a risk factor for adverse events to medications. *Drugs* 1995; **50**: 1–6.
33 Rademaker M. Do women have more adverse drug reactions? *Am J Clin Dermatol* 2001; **2**: 349–351.
34 Anderson GD. Sex and racial differences in pharmacological response: where is the evidence? Pharmacogenetics, pharmacokinetics, and pharmacodynamics. *J Womens Health (Larchmt)* 2005; **14**: 19–29.
35 Miller MA. Gender-based differences in the toxicity of pharmaceuticals—the Food and Drug Administration's perspective. *Int J Toxicol* 2001; **20**: 149–152.
36 Lewis CE, Grandits A, Flack J, McDonald R, Elmer PJ. Efficacy and tolerance of antihypertensive treatment in men and women with stage 1 diastolic hypertension. Results of the Treatment of Mild Hypertension Study. *Arch Intern Med* 1996; **156**: 377–385.
37 Taler SJ. Hypertension in women. *Curr Hypertens Rep* 2009; **11**: 23–28.
38 Os I, Bratland B, Dahlof B, Gisholt K, Syvertsen JO, Tretli S. Female preponderance for lisinopril-induced cough in hypertension. *Am J Hypertens* 1994; **7**: 1012–1015.
39 Gibson GR. Enalapril-induced cough. *Arch Intern Med* 1989; **149**: 2701–2703.
40 Yeo WW, Foster G, Ramsay LE. Prevalence of persistent cough during long-term enalapril treatment: controlled study versus nifedipine. *Q J Med* 1991; **80**: 763–770.
41 Hammond JJ, Cutler SA. A comparison of isradipine and felodipine in Australian patients with hypertension: focus on ankle oedema. The Physician's Study Group. *Blood Press* 1993; **2**: 205–211.
42 Sharabi Y, Illan R, Kamari Y, Cohen H, Nadler M, Messerli FH *et al.* Diuretic induced hyponatraemia in elderly hypertensive women. *J Hum Hypertens* 2002; **16**: 631–635.
43 Sonnenblick M, Friedlander Y, Rosin AJ. Diuretic-induced severe hyponatremia. Review and analysis of 129 reported patients. *Chest* 1993; **103**: 601–606.
44 Clark BG, Wheatley R, Rawlings JL, Vestal RE. Female preponderance in diuretic-associated hypokalemia: a retrospective study in seven long-term care facilities. *J Am Geriatr Soc* 1982; **30**: 316–321.
45 Toner JM, Ramsay LE. Thiazide-induced hypokalaemia; prevalence higher in women. *Br J Clin Pharmacol* 1984; **18**: 449–452.