Aliskiren vs. Angiotensin Receptor Blockers in Hypertension: Meta-Analysis of Randomized Controlled Trials

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BACKGROUND

Aliskiren, a newly discovered renin inhibitor, blocks the renin–angiotensin system (RAS) from the top of the enzyme cascade and therefore, might provide comparable or even superior clinical efficacy of blood pressure (BP) control than angiotensin receptor blockers (ARBs). With this meta-analysis, we aimed to compare the efficacy and tolerability of aliskiren and ARBs in the treatment of hypertension in the short-term treatment period.

METHODS

Reports of randomized controlled trials (RCTs) comparing aliskiren and ARBs in patients with hypertension were selected by a search of the Cochrane Central Register of Controlled Trials, MEDLINE, and EMBASE. The main outcome measures were reduction in diastolic BP (DBP) and systolic BP (SBP) and rates of therapeutic response and BP control. We also compared the tolerability of aliskiren and ARBs. Revman v5.0 was used to obtain the pooled estimates.

RESULTS

We analyzed data from 10 reports of trials involving 3,732 participants. DBP and SBP reduction did not differ between aliskiren and ARBs (weighted mean difference (WMD), −0.18; 95% confidence interval (CI), −1.07 to 0.71, and WMD, 0.15; 95% CI, −1.38 to 1.69, respectively). Aliskiren and ARB treatment did not differ in rates of BP control or therapeutic response. Moreover, aliskiren and ARB treatment led to a similar number of adverse events, severe adverse events, and withdrawal due to adverse events.

CONCLUSION

Aliskiren is as effective as ARBs (losartan, valsartan, and irbesartan) in controlling BP and does not differ from ARBs in risk of adverse events.

Keywords: *angiotensin receptor blockers; blood pressure; hypertension; meta-analysis; renin inhibitor*

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Hypertension is a major risk factor leading to development of cardiovascular disease. Elevated blood pressure (BP) is consistently found associated with stroke, cardiovascular events, and renal failure.[1] Patients with persistent hypertension are at high risk of cardiovascular morbidity and mortality,[2] and the benefits of reducing BP in terms of preventing end-organ damage are well established.[3]

The renin–angiotensin system (RAS) plays a key role in BP regulation, acting primarily via the effects of the octapeptide hormone angiotensin II. Excessive RAS activity is a major underlying cause of many pathological states because angiotensin II increases BP and exerts direct growth-promoting effects on tissues that lead to organ damage.[4] Indeed, RAS inhibitors such as angiotensin-converting enzyme inhibitors and angiotensin AT1 receptor blockers (ARBs) have been highly successful in hypertension, heart failure and related cardiovascular disorders.[5]

Because renin catalyzes the first and rate-limiting step of the RAS and has high specificity for the substrate angiotensinogen, renin inhibitors have the potential to supersede traditional RAS blockers as the preferred inhibitors of the cascade in patients with hypertension,[6] and might have comparable or even superior clinical efficacy in BP control than are ARBs or angiotensin-converting enzyme inhibitors.[7]

Aliskiren is the first of a new class of renin inhibitors taken orally. It was approved for treating hypertension by the US Food and Drug Administration in 2007 and was found efficacious in BP control as compared with placebo.[8] Several studies evaluating aliskiren included arms with ARBs as active controls, but whether aliskiren is superior to traditional RAS inhibitors such as ARBs in control of BP is still controversial. To determine whether aliskiren has any advantages over ARBs in BP control in terms of enhanced efficacy and fewer adverse events, we undertook a systematic review and meta-analysis of all relevant randomized controlled trials (RCTs) comparing aliskiren and ARBs in patients with hypertension.

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METHODS

Search strategy. We searched for articles in MEDLINE via PubMED (articles published from 1966 to June 2010), EMBASE (articles published from 1980 to June 2010), and the Cochrane Central Registry of Clinical Trials (using the OVID interface for articles published before the second quarter of 2010), with no restriction on language. The search combined the terms related to "renin inhibitor," "aliskiren" ("Tekturna," "Rasilez") with the terms related to ARBs ("losartan,*" "irbesartan,*" "valsartan,*" "telmisartan,*" "Olmesartan,*" "Candesartan,*" "Eprosartan*"). We also searched the Clinical Trials (http://clinicaltrials.gov/) and the Novartis Clinical Trials Results Database (http://www.novctrd.com/ctrdWebApp/clinicaltrialrepository/public/main.jsp) for other unpublished data and reviewed the reference lists of included RCTs and review articles to identify otherwise unrecognized or unpublished reports of RCTs.[9]

Selection of articles. We included articles with the following criteria: (i) a prospective RCT; (ii) involving patients with hypertension, with or without other diseases such as metabolic syndrome or diabetes; (iii) subjects receiving aliskiren or ARBs; and (iv) studying mean BP reduction, therapeutic BP response rate (defined as the percentage of patients with a mean diastolic BP (mDBP) <90 mm Hg and/or at least 10 mm Hg reduction from baseline) or BP control rate (defined as the percentage of patients with a mDBP <90 mm Hg and mean systolic BP (mSBP) <140 mm Hg), adverse events, severe adverse events, and withdrawal due to adverse events. Two reviewers (D.G., N.N.) independently assessed the eligibility of articles, which was checked by another author (X.N.). To avoid duplication, only the data from the latest series were included, if the same group of patients were involved in different reports.

Outcome measures. The primary efficacy outcome was the reduction from baseline to the end of treatment in mean clinic or 24-h ambulatory DBP and SBP. Secondary efficacy outcomes were rates of therapeutic response and of DBP and SBP control. We also assessed the tolerability of the drugs by considering overall rates of adverse events, severe adverse events, and withdrawal from a study due to adverse events.

Data abstraction. The quality of the included RCTs was assessed by the Jadad scale.[10] Data were independently abstracted for each identified article by two researchers (D.G., N.N.) who used a predesigned review form, and any disagreement was resolved by discussion. The following data were abstracted: authors; year of publication; trial design; duration of the study; number, age, and sex of participants; baseline SBP and DBP values; endpoint SBP and DBP values; changes from baseline in SBP and DBP; and rates of therapeutic response and of SBP and DBP control. In addition, we retrieved the number or proportion of adverse events, severe adverse events, withdrawals due to adverse events, and death. When the report did not contain sufficient details to evaluate the validity of the study or outcome data were missing, we attempted to contact the authors by e-mail and in writing. The study complied with the recently reported Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISRMA) statement.[11]

Missing data. We abstracted the mean ± s.d. BP reduction from baseline to the end of treatment directly from reports if available. If authors reported s.e. instead of s.d., we calculated s.d. by the formula s.d. = s.e. × $(N)^{1/2}$. If the s.d. of the change in BP was missing, the s.d. was imputed as described in The Cochrane Handbook for Systematic Reviews of Interventions.[12] Briefly,

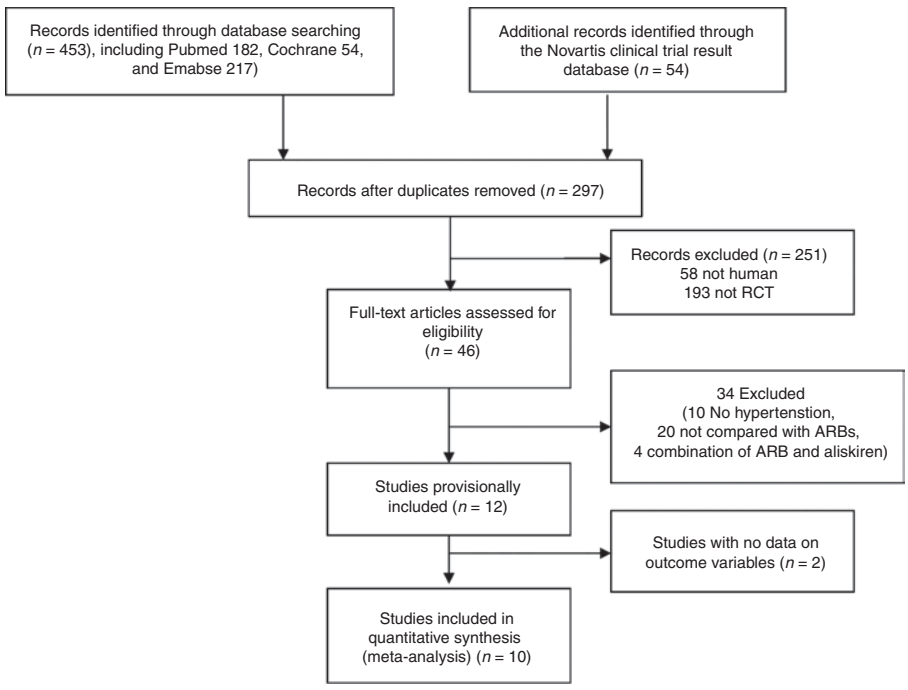

Figure 1 | Flow diagram of the selection of articles in the study. ARB, angiotensin receptor blockers; RCT, randomized controlled trials.

t value was calculated from *P* value that was reported. s.e. was calculated by the formula s.e. = mean difference (MD)/*t*. s.d. was imputed by the formula s.d. = s.e./1/$\left(\frac{1}{Ne}+\frac{1}{Nc}\right)^{1/2}$ (Ne = numbers in the experimental group, Nc = numbers in the control group).

Statistical analysis. We undertook separate meta-analyses for each comparison and outcome. For dichotomous outcomes, results are expressed as relative risk (RR) with 95% confidence intervals (CIs). For continuous outcomes, pooled data are described with the weighted mean difference (WMD) and 95% CIs. Heterogeneity of results across trials was assessed with a standard χ^2-test with significance set at $P < 0.10$ and an I^2 statistic with significance set at $I^2 > 50\%$. Subgroup analysis was performed in order to evaluate effect size differences between different ARBs. Publication bias was evaluated by the funnel plot. We also performed the sensitivity analysis to evaluate the effect of methodological characteristics of RCTs on the results of this meta-analysis. All analyses involved use of Review Manager version 5.02 (Revman; The Cochrane Collaboration, Oxford, UK).

RESULTS

Study characteristics

We identified 507 reports; 46 full-text articles were retrieved for in-depth review. In total, 10 studies[13–22] enrolling 3,732 participants fulfilled all eligibility criteria. **Figure 1** shows the selection of articles for the study. All 10 articles were available as full reports (all in English). The quality assessments are in **Table 1**. The patient and trial characteristics are shown in **Table 2**. Aliskiren was compared with losartan in two trials,[13,14] valsartan in three trials,[15–17] and irbesartan in five trials.[18–22] In one trial,[13] in which the patients were randomized to receive aliskiren, 37.5, 75, 150, 300 mg, or losartan, 100 mg, we did not extract the data for 37.5, 75, and 150 mg aliskiren to avoid potential duplication. One trial[15] included active treatment arms of 75, 150, 300 mg aliskiren compared to 80, 160, 320 mg valsartan; data were extracted as three different trials separately labeled as a, b, and c. One report of unpublished data was checked with the Novartis Clinical Trials Results Database and was named CSPP100A1301.[14]

The manufacturer Novartis sponsored all 10 included RCTs. We contacted the manufacturer by e-mail for any additional information on ongoing studies and for missing data from the published reports meeting our inclusion criteria but did not receive a response.

A funnel plot for the studies comparing the effects of aliskiren and ARBs in terms of DBP reduction is in **Figure 2**. The funnel plot results were asymmetric and may have been due to retention of results by Krone *et al.*,[20] which involved true heterogeneity. The funnel plot indicated the absence of publication bias.

Efficacy

Reduction in clinic BP. Nine trials[5,12–17,19–22] (n = 3,292) described evaluation of changes in clinic BP. Considering overall efficacy, we found no difference between aliskiren and ARBs in the reduction of both mDBP (ΔmDBP) and mSBP (ΔmSBP) (WMD, −0.18; 95% CI, −1.07 to 0.71, and WMD, 0.15; 95% CI, −1.38 to 1.69, respectively) (**Figures 3** and **4**).

Aliskiren vs. losartan. Two trials[13,14] involving 681 patients compared aliskiren with losartan. We found no difference between aliksiren and losartan in ΔmDBP (WMD, −0.20; 95% CI, −1.52 to 1.12; $P = 0.77$) or ΔmSBP (WMD, 0.16; 95% CI, −1.76 to 2.09; $P = 0.87$). Results were homogenous ($P = 1$, $I^2 = 0\%$, and $P = 0.88$, $I^2 = 0\%$, respectively).

Aliskiren vs. valsartan. Three trials[15–17] involving 1,919 patients compared aliskiren with valsartan. We found no difference between aliskiren and valsartan in ΔmDBP (WMD, 0.68; 95% CI, −0.21 to 1.57; $P = 0.13$) or ΔmSBP (WMD, 1.49; 95% CI, −0.28 to 3.26; $P = 0.10$). Results were homogenous for ΔmDBP and ΔmSBP ($P = 0.48$, $I^2 = 0\%$ and $P = 0.14$, $I^2 = 42\%$, respectively).

Table 1 | Quality features of 10 reports of randomized controlled trials (RCTs) assessed in the meta-analysis

Study	Year	Design	Multicenter	Randomization	Intent-to-treat analysis	Generation of random sequence	Completeness of follow-up	Description of withdrawals	Quality score
CSPP100A1301	2007	DB-P	Yes	Yes	Yes	IVRS	Y	Y	5
Stanton *et al.*[13]	2003	DB-P	Yes	Yes	Yes	NA	Y	Y	4
Geiger *et al.*[17]	2009	DB-P	Yes	Yes	Yes	IVRS	Y	Y	5
Pool *et al.*[15]	2007	DB-P	Yes	Yes	Yes	IVRS	Y	Y	5
Oparil *et al.*[16]	2007	DB-P	Yes	Yes	Yes	IVRS	Y	Y	5
Palatini *et al.*[18]	2010	DB-P	Yes	Yes	Yes	IVRS	Y	Y	5
Krone *et al.*[20]	2010	DB-P	Yes	Yes	Yes	IVRS	Y	Y	5
Gradman *et al.*[19]	2005	DB-P	Yes	Yes	Yes	IVRS	Y	Y	5
Jordan *et al.*[21]	2007	DB-P	Yes	Yes	Yes	IVRS	Y	Y	5
Persson *et al.*[22]	2009	DB-C	No	Yes	Yes	NA	Y	Y	3

DB-C, double-blind crossover; DB-P, double-blind parallel; IVRS, interactive voice response systems; NA, unable to assess.

Table 2 | Patient and trial characteristics of randomized controlled trials included in the meta-analysis

Study	Number of subjects Total (Aliskiren/ARB)	Mean age Aliskiren/ARB	Sex (M) Aliskiren/ARB	Dose Aliskiren	Dose ARBs	Follow-up	BP stage	Comorbidities
Aliskiren vs. losartan								
CSPP100A1301	761 (302/303)	52.0 ± 10.24/ 52.1 ± 10.25	220/221	150 mg	50 mg	8 weeks	Mild-to-moderate	No
Stanton *et al.*[13]	226 (47/44)	51.8 ± 10.5/ 55.9 ± 8.9	23/23	300 mg	100 mg	4 weeks	Mild-to-moderate	No
Aliskiren vs. valsartan								
Geiger *et al.*[17]	641 (166/155)	52.3 ± 10.9/ 55.0 ± 11.4	74/67	150–300 mg	160–320 mg	8 weeks	Mild-to-moderate	No
Pool *et al.*[15,a]	1,123 (179/58)	55.4 ± 13.1/ 56.0 ± 13.0	80/20	75 mg	80 mg	8 weeks	Mild-to-moderate	No
Pool *et al.*[15,b]	1,123 (178/59)	56.2 ± 12.4/ 55.1 ± 11.8	77/53	150 mg	160 mg	8 weeks	Mild-to-moderate	No
Pool *et al.*[15,c]	1,123 (178/59)	56.7 ± 11.9/ 56.8 ± 10.7	75/29	300 mg	320 mg	8 weeks	Mild-to-moderate	No
Oparil *et al.*[16]	1,797 (437/455)	51.9 ± 10.4/ 52.4 ± 10.4	255/281	150–300 mg	160–320 mg	8 weeks	Mild-to-moderate	No
Aliskiren vs. irbesartan								
Palatini *et al.*[18]	654 (218/222)	53.5 ± 10.71/ 53.4 ± 9.69	81/80	150–300 mg	150–300 mg	7 weeks	Mild-to-moderate	No
Krone *et al.*[20]	141 (75/66)	58.6 ± 8.9/ 59.2 ± 9.1	48/43	150–300 mg	150–300 mg	12 weeks	Mild-to-moderate	Metabolic syndrome
Gradman *et al.*[19]	652 (127/134)	55.0 ± 12.5/ 56.1 ± 11.8	54/68	150 mg	150 mg	8 weeks	Mild-to-moderate	No
Jordan *et al.*[21]	560 (122/119)	53.1 ± 11.9/ 53.0 ± 11.0	66/48	150–300 mg	150–300 mg	12 weeks	Mild-to-moderate	Obese
Persson *et al.*[22]	26 (26/26)	59.8 ± 9.2	20	300 mg	300 mg	2 months	Mild-to-moderate	Diabetes

ARB, angiotensin receptor blocker; BP, blood pressure.

Aliskiren vs. irbesartan. Four trials[19–22] involving 692 patients compared aliskiren and irbesartan, with no difference in ΔmDBP (WMD, −1.38; 95% CI, −3.31 to 0.55; $P = 0.16$) and ΔmSBP (WMD, −1.83; 95% CI, −5.30, 1.64, $P = 0.30$). However, results were significantly heterogenous ($P = 0.06$ and $P = 0.008$; $I^2 = 59\%$ and 75%, respectively). After excluding the data for the Krone *et al.*,[20] study resulted in no significant heterogeneity ($P = 0.53$, $I^2 = 0\%$, and $P = 0.69$, $I^2 = 0\%$, respectively) and showed no significant difference in ΔmDBP (WMD, −0.43; 95% CI, −1.79 to 0.93; $P = 0.53$) or ΔmSBP (WMD, −0.06; 95% CI, −1.91 to 1.79; $P = 0.95$).

Sensitivity analysis. We conducted a sensitivity analysis to evaluate the effect of methodological characteristics on the analysis of clinic DBP reduction. After excluding data for three trials[20–22] of patients with coexisting metabolic syndrome, obesity, or diabetes that received aliskiren and ARBs (all in the irbesartan subgroup), we still found no significant difference overall in clinic BP reduction between aliskiren and ARBs (six trials, 2,861 patients, WMD 0.31, 95% CI −0.38 to 1.01, $P = 0.37$). Trial results for comparing aliskiren and ARBs (losartan, valsartan, and irbesartan) used as monotherapy[12,13,15,16,19,20,22] ($n = 7$) showed no difference in BP reduction (**Tables 3–5**). We then divided the studies into three groups according to comparable drug doses: initial dose (aliskiren 150 mg compared to 50 mg losartan, 160 mg valsartan, and 150 mg irbesartan), high dose (aliskiren 300 mg compared to 100 mg losartan, 320 mg valsartan, and 300 mg irbesartan) and initial to high dose (aliskiren 150–300 mg compared to 50–100 losartan, 160–320 mg, and 150–320 mg irbesartan). As seen in **Table 5**, we still found no significant difference overall in clinic BP reduction between aliskiren and ARBs in different comparable drug doses.

Reduction in ambulatory BP. Four trials[13,16,18,22] (one compared with losartan, one with valsartan, and two with irbesartan, $n = 762$) compared the effects of treatments with aliskiren and ARBs in terms of reduction in ambulatory BP. There was no significant reduction in mDBP (WMD, 0.26; 95% CI, −0.59 to 1.12; $P = 0.55$) and SBP (WMD, −1.69; 95% CI, −4.88 to 1.50; $P = 0.30$). A significant heterogeneity was found in the analysis on DBP ($P = 0.002$, $I^2 = 79\%$).

Therapeutic response and control rate of BP. Therapeutic response rate was reported in four trials[14–16,21] (n = 1,416). Considering overall therapeutic response rate (**Figure 5**), no difference between aliskiren and ARBs was found (RR, 0.98; 95% CI, 0.92 to 1.05; P = 0.59). As compared with losartan, rates of therapeutic response (RR, 1.12; 95% CI, 0.91 to 1.37; P = 0.3) were reported for only one trial,[14] with no difference between each drug at the initial recommended dose (aliskiren, 150 mg, and losartan, 50 mg). As compared with valsartan, a therapeutic response rate was reported for two trials,[15,16] with no difference between aliskiren and valsartan (RR, 0.99; 95% CI: 0.99–1.08; P = 0.8). Only one article[21] described the effect of aliskiren and irbesartan on therapeutic response rate and reported no difference between the two groups (RR, 1.04; 95% CI: 0.88–1.22, P = 0.67).

BP control rate was described in seven trials[14–17,19–21] (n = 3,142). Considering overall BP control rate **Figure 6**), no difference between aliskiren and ARBs was found (RR, 1.01; 95% CI: 0.89–1.14; P = 0.89). As compared with losartan, BP control rate was reported only in one trial,[14] with no difference between each drug (RR, 1.12; 95% CI: 0.91–1.38, P = 0.29). Reports for three trials[15–17] gave a BP control rate but with no difference between aliskiren and valsartan (RR, 0.92; 95% CI: 0.77–1.11; P = 0.37). Three trials[19–21] compared BP control rate between aliskiren and irbesartan, with no significant difference between aliskiren and irbesartan and BP control (RR, 1.12; 95% CI: 0.91–1.38; P = 0.29).

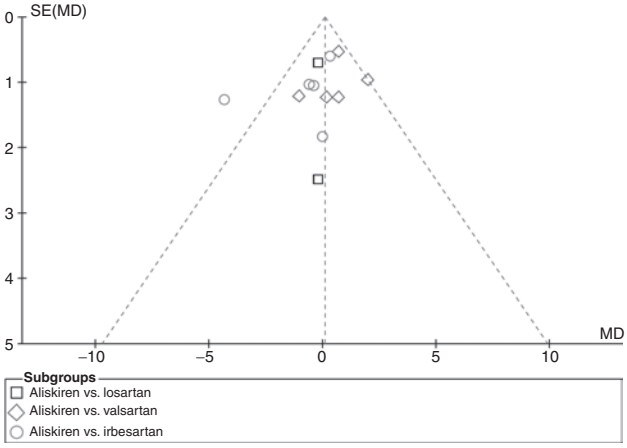

Figure 2 | Funnel plot of the studies comparing the effects of aliskiren and angiotensin receptor blockers (ARBs) on diastolic blood pressure reduction. MD, mean difference.

Tolerability

As shown in **Table 6**, considering overall tolerability, aliskiren treatment did not differ from the three ARBs in number or proportion of adverse events, severe adverse events, or withdrawal due to adverse events. For the aliskiren and ARB groups, the overall rate of adverse events was 36 and 37%, severe adverse events 9.5 and 15%, and withdrawal due to adverse events 2.3 and 2.7%, respectively.

Aliskiren vs. losartan. Adverse events, severe adverse events, and withdrawal from a study due to adverse events did not differ between aliskiren and losartan treatment (**Table 6**). One death (due to ruptured aneurysm of the left common iliac artery) and one cerebro-cardiovascular event (brain stem infarction) was reported in the losartan group.

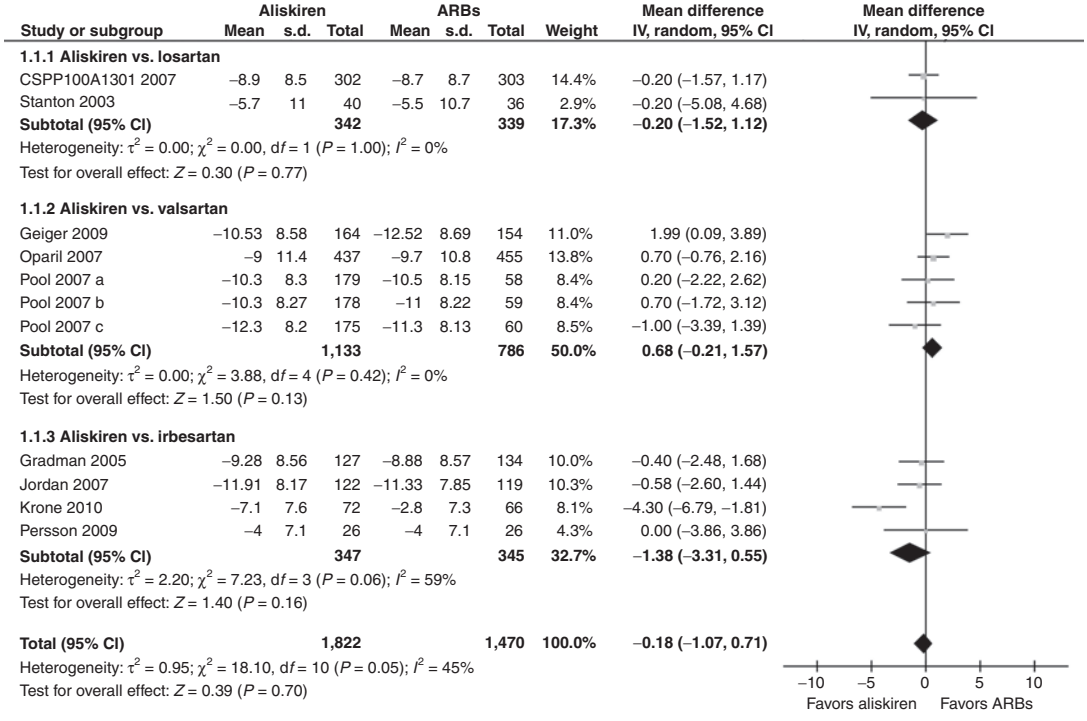

Figure 3 | Diastolic blood pressure-lowering effect of aliskiren vs. angiotensin receptor blockers (ARBs). CI, confidence interval; IV, inverse variance.

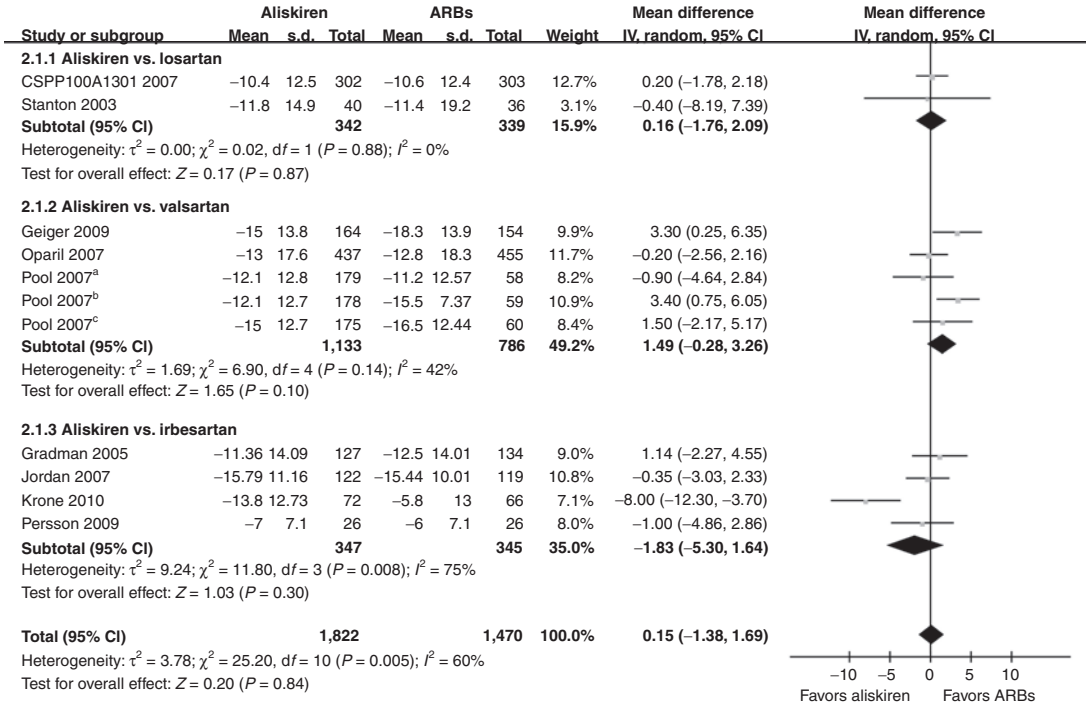

Figure 4 | Systolic blood pressure-lowering effect of aliskiren vs. angiotensin receptor blockers (ARBs). CI, confidence interval; IV, inverse variance.

Table 3 | Sensitivity analysis

		Krone *et al.*[20] excluded		As monotherapy		Clinical BP reduction		With no comorbidities	
	Interventions	WMD (95% CI)	*P* value	WMD (95% CI)	*P* value	WMD (95% CI)	*P* value	WMD (95% CI)	*P* value
ΔmDBP	Aliskiren vs. ARBs	0.29 (−0.24, 0.83)	*P* = 0.28	−0.22 (−1.01,0.58)	*P* = 0.59	−0.15 (−1.02 0.72)	*P* = 0.73	0.37 (−0.19,0.93)	*P* = 0.20
	Aliskiren vs. losartan	−0.20 (−1.52, 1.12)	*P* = 0.77	−0.20 (−1.52, 1.12)	*P* = 0.77	−0.20 (−1.52, 1.12)	*P* = 0.77	−0.20 (−1.52, 1.12)	*P* = 0.77
	Aliskiren vs. valsartan	0.68 (−0.09, 1.46)	*P* = 0.08	0.42 (−0.43, 1.27)	*P* = 0.33	0.68 (−0.09, 1.46)	*P* = 0.08	0.68 (−0.09, 1.46)	*P* = 0.08
	Aliskiren vs. irbesartan	0.01 (−0.88, 0.89)	*P* = 0.99	−1.02 (−3.08, 1.05)	*P* = 0.33	−1.36 (−3.27,0.55)	*P* = 0.43	0.16 (−0.87,1.19)	*P* = 0.76

95% CI, 95% confidence interval; ARBs, angiotensin receptor blockers; BP, blood pressure; WMD, weighted mean difference; ΔmDBP, mean diastolic blood pressure reduction.

Aliskiren vs. valsartan. Aliskiren and valsartan treatment did not lead to differences in number or proportion of adverse events, severe adverse events, or withdrawal due to adverse events. Two deaths (one sudden death and one not explained) were reported in the valsartan group and one in the aliskiren group (myocardial infarction).

Aliskiren vs. irbesartan. Aliskiren and irbesartan treatment did not lead to differences in number or proportion of adverse events, severe adverse events, or withdrawal due to adverse events. No death or cardio-cerebrovascular event was reported in either treatment group.

DISCUSSION

We performed a meta-analysis of 10 reports of RCTs comparing the efficacy of aliskiren, a direct renin inhibitor, and ARBs in reducing BP in patients with hypertension. Our results do not show a superiority of aliskiren over ARBs such as losartan, valsartan, and irbesartan in BP control. Moreover, adverse events did not differ with aliskiren or ARB treatment.

The goal in the management of hypertension is to reduce the incidence of morbidity and mortality due to cardiovascular events. Although the importance of reducing BP is well known and a reduction in BP of 2–3 mm Hg should translate into a risk reduction of 4–5%,[23] only 34% of hypertensive patients showed adequate control of BP to ≤140/90 mm Hg.[24] Therefore, despite the number of drugs available for treating hypertension, adequate control of BP has yet to be achieved in most hypertensive patients.

Renin inhibitors have been suggested to have comparable or even superior clinical efficacy in BP control than is possible with traditional RAS blockers such as ARBs.[7] Our meta-analysis pooling the results of 10 high-quality RCTs focused on direct comparisons of treatment with aliskiren and ARBs such

Table 4 | Sensitivity analysis (difference of each effect model on the pooled results)

	ΔmDBP WMD (95% CI)		ΔmSBP WMD (95% CI)		Therapeutic response rate RR (95% CI)		BP control rate RR (95% CI)	
Interventions	Random effect	Fixed effect	Random effect	Fixed effect	Random effect	Fixed effect	Random effect	Fixed effect
Aliskiren vs. ARBs	0.21 (−0.43, 0.86) $P = 0.52$	−0.07 (−0.70, 0.55) $P = 0.82$	0.15 (−1.38,1.69) $P = 0.84$	0.37 (−0.54,1.29) $P = 0.43$	0.98 (0.92,1.05) $P = 0.59$	0.98 (0.92,1.05) $P = 0.51$	1.01 (0.89,1.14) $P = 0.89$	1.03 (0.94,1.13) $P = 0.51$
Aliskiren vs. losartan	−0.20 (−1.52, 1.12) $P = 0.77$	−0.20 (−1.52, 1.12) $P = 0.77$	0.16 (−1.76,2.09) $P = 0.87$	0.16 (−1.76,2.09) $P = 0.87$	0.92 (0.80,1.07) $P = 0.27$	0.92 (0.80,1.07) $P = 0.27$	1.12 (0.91,1.37) $P = 0.30$	1.12 (0.91,1.37) $P = 0.30$
Aliskiren vs. valsartan	0.68 (−0.21, 1.57) $P = 0.13$	0.68 (−0.21, 1.57) $P = 0.13$	1.49 (−0.28, 3.26) $P = 0.10$	1.48 (0.16, 2.79) $P = 0.03$	0.99 (0.90,1.08) $P = 0.80$	0.99 (0.90,1.08) $P = 0.80$	0.92 (0.77,1.11) $P = 0.37$	0.97 (0.86,1.09) $P = 0.57$
Aliskiren vs. irbesartan	−0.43 (−1.79, 0.93) $P = 0.53$	−1.32 (−2.51, −0.13) $P = 0.03$	−1.83 (−5.30, 1.64) $P = 0.30$	−1.30 (−3.00, 0.40) $P = 0.13$	1.04 (0.88,1.22) $P = 0.67$	1.04 (0.88,1.22) $P = 0.67$	1.12 (0.91,1.38) $P = 0.29$	1.14 (0.94,1.13) i = 0.51

95% CI, 95% confidence interval; ARBs, angiotensin receptor blockers; RR, relative risk; WMD, weighted mean difference; ΔmDBP, mean diastolic blood pressure reduction; ΔmSBP, mean systolic blood pressure reduction.

Table 5 | Sensitivity analysis of the pooled result of ΔmDBP based on the different dose level

Interventions	Initial dose WMD (95% CI)	High dose WMD (95% CI)	Initial to high dose WMD (95% CI)
Aliskiren vs. ARBs	−0.08 (−1.08,0.92), $P = 0.88$	−0.20 (−5.08,4.68), $P = 0.94$	−0.42 (−2.70,1.87), $P = 0.72$
Aliskiren vs. losartan	−0.20 (−1.57,1.17), $P = 0.77$	−0.20 (−5.08,4.68), $P = 0.94$	NA
Aliskiren vs. valsartan	0.70 (−1.72,3.12), $P = 0.57$	−1.00 (−3.39,1.39), $P = 0.41$	1.20 (−0.03,2.43), $P = 0.06$
Aliskiren vs. irbesartan	−0.31 (−2.14,1.52), $P = 0.74$	0.00 (−3.86,3.86), $P = 0.50$	−2.37 (−6.01,1.28), $P = 0.20$

95% CI, 95% confidence interval; ARBs, angiotensin receptor blockers; WMD, weighted mean difference; ΔmDBP, mean diastolic blood pressure reduction.

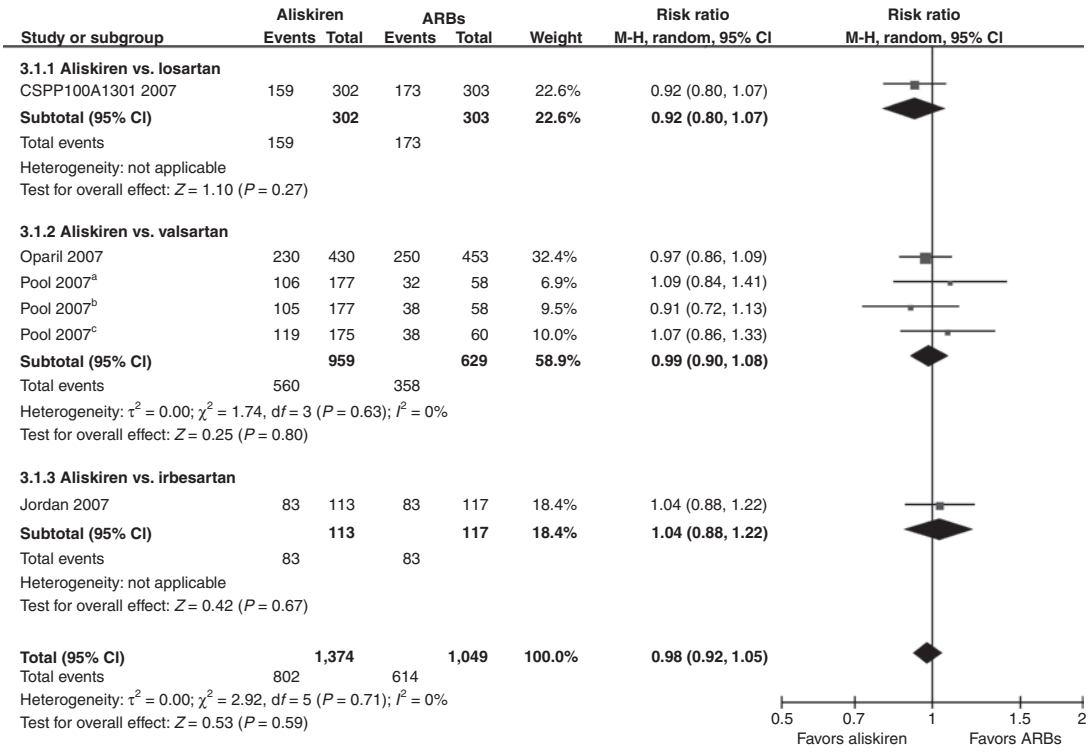

Figure 5 | Effect of aliskiren and angiotensin receptor blockers (ARBs) on blood pressure control. 95% CI, 95% confidence interval; M-H, Mantek-Haenzel.

as losartan, valsartan, and irbesartan. We found that aliskiren was comparable but not superior to ARBs in reducing BP. Moreover, the two drug types did not differ in rates of therapeutic response or BP control rate. However, the 10 pivotal RCTs were of limited size and duration and were not designed to demonstrate the effect on objective clinical outcomes such as cardiovascular events. The BP-lowering effect of aliskiren appeared to be comparable only to that seen with ARBs that

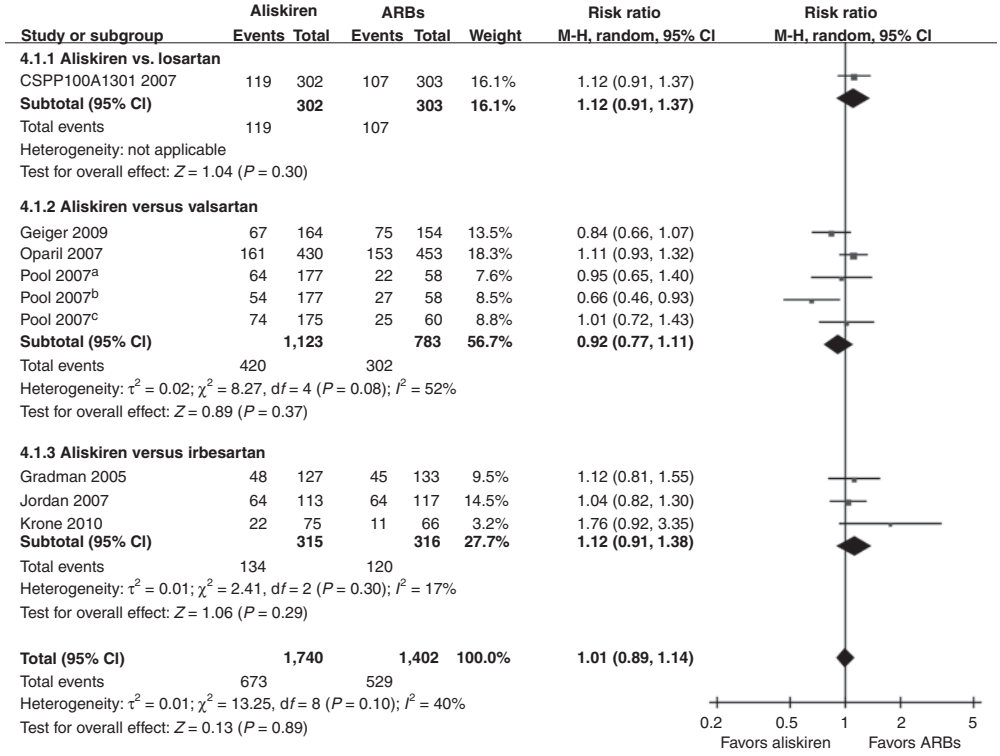

Figure 6 | Effect of aliskiren and angiotensin receptor blockers (ARBs) on therapeutic response. 95% CI, 95% confidence interval; M-H, Mantek-Haenzel.

Table 6 | Tolerability of aliskiren vs. angiotensin receptor blockers

	Adverse events (any reason) RR (95% CI)		Severe adverse events (any reason) RR RR (95% CI)		Withdrawal (adverse events) RR (95% CI)	
Interventions	**Random effect**	**Fixed effect**	**Random effect**	**Fixed effect**	**Random effect**	**Fixed effect**
Aliskiren vs. ARBs	0.98 (0.89,1.08) $P = 0.68$	0.98 (0.90,1.07) $P = 0.62$	0.72 (0.36,1.46) $P = 0.36$	0.65 (0.34,1.24) $P = 0.19$	0.82 (0.54,1.25) $P = 0.35$	0.84 (0.56,1.27) $P = 0.41$
Aliskiren vs. losartan	1.03 (0.79,1.35) $P = 0.83$	1.06 (0.90,1.24) $P = 0.51$	0.33 (0.01,8.18) $P = 0.5$	0.33 (0.01,8.18) $P = 0.5$	0.76 (0.28,2.08) $P = 0.60$	0.77 (0.29,2.05) $P = 0.60$
Aliskiren vs. valsartan	0.92 (0.81,1.05) $P = 0.20$	0.93 (0.82,1.05) $P = 0.24$	0.63 (0.09,4.43) $P = 0.65$	0.83 (0.35,1.96) $P = 0.67$	0.89 (0.50,1.58) $P = 0.69$	0.94 (0.54,1.64) $P = 0.83$
Aliskiren vs. irbesartan	1.00 (0.81,1.23) $P = 0.99$	1.00 (0.81,1.23) $P = 0.62$	0.55 (0.18,1.67) $P = 0.29$	0.52 (0.18,1.45) $P = 0.21$	0.73 (0.33,1.61) $P = 0.43$	0.72 (0.56,1.27) $P = 0.41$

ARBs, angiotensin receptor blockers; 95% CI, 95% confidence interval; RR, relative risk.

have been shown to reduce cardiovascular events. Recently, some publication of results gave us the hope that aliskiren may possibly be considered effective in preventing end-organ damage in hypertensive patients. Aliskiren in Left Ventricular Hypertrophy (ALLAY) trial[25] showed that aliskiren alone reduces left ventricular hypertrophy as effectively as ARB (losartan). Aliskiren in the eValuation of prOteinuria In Diabetes (AVOID) trial[26] compared aliskiren vs. placebo in diabetic patients treated with losartan. This study used albumin/protein ratio as the endpoint and found combination therapy with aliskiren lowered the ratio more than placebo. However, BP reduction was of borderline greater magnitude in the aliskiren group, potentially confounding the interpretation regarding a specific effect of aliskiren on renal target organ injury. Pending studies have been designed to evaluate the relative effects of angiotensin-converting enzyme inhibitors and ARBs on cardiac and renal endpoints.[27,28] But until now, in the absence of definitive outcome data and/or more substantial reductions in pressure, aliskiren might only be prescribed when less expensive blockers of the RAS such as ARBs, with established effects on morbidity and mortality, are not tolerated or have failed to reduce BP effectively.

We did not find any differences between aliskiren and ARB treatment in number or proportion of adverse events. Some trial reports listed only a few events, generally those with an incidence >1–2.5% in any group. The most common adverse events were headache, nasopharyngitis, diarrhea, and back pain, which were similar between aliskiren and ARB groups.

We found no differences between the drug types in adverse events, severe adverse events, or withdrawal due to adverse events. Three deaths were reported in ARB groups and one death in aliskiren groups. Thus, aliskiren might provide the same tolerability as ARBs in controlling BP.

Our meta-analysis contains some limitations. First, we did not have access to individual patient data. Second, the follow-up times of studies in this meta-analysis were short, and the analyses deal only with surrogate endpoints and with short-term effects of BP control and we did not evaluate the incidence of cardiovascular events or mortality due to the short study periods. Other potential sources of heterogeneity in the results are the population of patients studied, comorbidities, and doses of drugs.

In conclusion, our meta-analysis of RCTs of aliskiren and ARBs (losartan, valsartan, and irbesartan) currently used for BP control showed that in hypertensive patients, the renin inhibitor aliskiren is not superior to ARBs in BP control. Some comparative data from this study may be helpful for clinical practice. However, because of the lack of key comparative data such as rates of mortality and cardiac-cerebrovascular events, physicians, administrators, and the public may be confused about how to use this new drug in the context of standard clinical practice. Pragmatic RCTs lasting at least 12 months (preferably even ≥5 years) are needed to compare the effects of aliskiren and ARBs in adults with hypertension. The outcome data should include BP reduction (both clinical and 24-h ambulatory), mortality, cardiovascular events, and adverse events. In particular, studies should investigate how well aliskiren works in patients with inadequate response to ARBs, because aliskiren might be a replacement for ARBs.

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1. Kannel WB, Schwartz MJ, McNamara PM. Blood pressure and risk of coronary heart disease: the Framingham Study. 1969. *Chest* 2009; 136:e23.
2. Vongpatanasin W. Cardiovascular morbidity and mortality in high-risk populations: epidemiology and opportunities for risk reduction. *J Clin Hypertens (Greenwich)* 2007; 9:11–15.
3. Wang JG, Staessen JA, Franklin SS, Fagard R, Gueyffier F. Systolic and diastolic blood pressure lowering as determinants of cardiovascular outcome. *Hypertension* 2005; 45:907–913.
4. Probstfield JL, O'Brien KD. Progression of cardiovascular damage: the role of renin-angiotensin system blockade. *Am J Cardiol* 2010; 105:10A–20A.
5. Mancia G, Giannattasio C, Seravalle G, Quarti-Trevano F, Grassi G. Protective effects of renin-angiotensin blockade beyond blood pressure control. *J Hum Hypertens* 2009; 23:570–577.
6. Fisher ND, Hollenberg NK. Renin inhibition: what are the therapeutic opportunities? *J Am Soc Nephrol* 2005; 16:592–599.
7. Kelly DJ, Wilkinson-Berka JL, Gilbert RE. Renin inhibition: new potential for an old therapeutic target. *Hypertension* 2005; 46:471–472.
8. Musini VM, Fortin PM, Bassett K, Wright JM. Blood pressure lowering efficacy of renin inhibitors for primary hypertension. *Cochrane Database Syst Rev* 2008: CD007066.
9. Hopewell S, McDonald S, Clarke M, Egger M. Grey literature in meta-analyses of randomized trials of health care interventions. *Cochrane Database Syst Rev* 2007: MR000010.
10. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996; 17:1–12.
11. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009; 339:b2535.
12. Higgins JPT, Green S, Cochrane Collaboration. *Cochrane Handbook for Systematic Reviews of Interventions*. Wiley-Blackwell: Chichester, England; Hoboken, NJ, 2008.
13. Stanton A, Jensen C, Nussberger J, O'Brien E. Blood pressure lowering in essential hypertension with an oral renin inhibitor, aliskiren. *Hypertension* 2003; 42:1137–1143.
14. A randomized, double-blind, placebo and active-controlled, multicenter, parallel-group study comparing SPP100(Aliskiren) 150 mg to placebo and to Losartan 50 mg to evaluate efficacy, safety and pharmacokinetics in patients with mild to moderate essential hypertension. <http://www.novctrd.com/ctrdWebApp/clinicaltrialrepository/displayFile.do?trialResult=2494>.
15. Pool JL, Schmieder RE, Azizi M, Aldigier JC, Januszewicz A, Zidek W, Chiang Y, Satlin A. Aliskiren, an orally effective renin inhibitor, provides antihypertensive efficacy alone and in combination with valsartan. *Am J Hypertens* 2007; 20:11–20.
16. Oparil S, Yarows SA, Patel S, Fang H, Zhang J, Satlin A. Efficacy and safety of combined use of aliskiren and valsartan in patients with hypertension: a randomised, double-blind trial. *Lancet* 2007; 370:221–229.
17. Geiger H, Barranco E, Gorostidi M, Taylor A, Zhang X, Xiang Z, Zhang J. Combination therapy with various combinations of aliskiren, valsartan, and hydrochlorothiazide in hypertensive patients not adequately responsive to hydrochlorothiazide alone. *J Clin Hypertens (Greenwich)* 2009; 11:324–332.
18. Palatini P, Jung W, Shlyakhto E, Botha J, Bush C, Keefe DL. Maintenance of blood-pressure-lowering effect following a missed dose of aliskiren, irbesartan or ramipril: results of a randomized, double-blind study. *J Hum Hypertens* 2010; 24:93–103.
19. 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.
20. Krone W, Hanefeld M, Meyer HF, Jung T, Bartlett M, Yeh CM, Rajman I, Prescott MF, Dole WP. Comparative efficacy and safety of aliskiren and irbesartan in patients with hypertension and metabolic syndrome. *J Hum Hypertens* 2010.
21. Jordan J, Engeli S, Boye SW, Le Breton S, Keefe DL. Direct Renin inhibition with aliskiren in obese patients with arterial hypertension. *Hypertension* 2007; 49:1047–1055.
22. Persson F, Rossing P, Reinhard H, Juhl T, Stehouwer CD, Schalkwijk C, Danser AH, Boomsma F, Frandsen E, Parving HH. Renal effects of aliskiren compared with and in combination with irbesartan in patients with type 2 diabetes, hypertension, and albuminuria. *Diabetes Care* 2009; 32:1873–1879.
23. Yusuf S, Teo KK, Pogue J, Dyal L, Copland I, Schumacher H, Dagenais G, Sleight P, Anderson C; ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med* 2008; 358:1547–1559.
24. Jackson JH, Sobolski J, Krienke R, Wong KS, Frech-Tamas F, Nightengale B. Blood pressure control and pharmacotherapy patterns in the United States before and after the release of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) guidelines. *J Am Board Fam Med* 2008; 21:512–521.
25. Solomon SD, Appelbaum E, Manning WJ, Verma A, Berglund T, Lukashevich V, Cherif Papst C, Smith BA, Dahlöf B; Aliskiren in Left Ventricular Hypertrophy (ALLAY) Trial Investigators. Effect of the direct Renin inhibitor aliskiren, the Angiotensin receptor blocker losartan, or both on left ventricular mass in patients with hypertension and left ventricular hypertrophy. *Circulation* 2009; 119:530–537.
26. Parving HH, Persson F, Lewis JB, Lewis EJ, Hollenberg NK; AVOID Study Investigators. Aliskiren combined with losartan in type 2 diabetes and nephropathy. *N Engl J Med* 2008; 358:2433–2446.
27. Efficacy and Safety of Aliskiren and Aliskiren/Enalapril Combination on Morbi-mortality in Patients With Chronic Heart Failure (ATMOSPHERE). Identifier: NCT00853658. <http://www.clinicaltrials.gov>. Accessed 20 May 2010.
28. Parving HH, Brenner BM, McMurray JJ, de Zeeuw D, Haffner SM, Solomon SD, Chaturvedi N, Ghadanfar M, Weissbach N, Xiang Z, Armbrecht J, Pfeffer MA. Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints (ALTITUDE): rationale and study design. *Nephrol Dial Transplant* 2009; 24:1663–1671.