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ORIGINAL ARTICLE

Aliskiren *vs.* other antihypertensive drugs in the treatment of hypertension: a meta-analysis

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To investigate the antihypertensive effects and tolerability of aliskiren in comparison with other antihypertensive drugs and placebo in patients with hypertension, a meta-analysis was performed of studies published between 1950 and 2012. A systematic literature search of MEDLINE and the Cochrane Library was conducted for randomized controlled trials. Weighted mean differences and relative risk with 95% confidence intervals were calculated for continuous and dichotomous data, respectively. In all, 14 studies with 6741 participants were included in the present meta-analysis. Nine studies included trial arms with placebo, four included angiotensin (Ang) AT1 receptor blockers (ARBs), three included Ang-converting enzyme inhibitors (ACEIs), two included calcium channel blockers (CCBs), one included a β-blocker, and one included hydrochlorothiazide (HCTZ). We found that aliskiren, which lowered blood pressure (BP) effectively in patients with mild-to-moderate hypertension, was similar to HCTZ but inferior to CCBs in BP reduction, response rates and control rates. Furthermore, aliskiren was superior to ACEIs in lowering diastolic BP (DBP), while it had similar effects to ACEIs on systolic BP (SBP) reduction, response rates and control rates. Additionally, the present meta-analysis showed the superiority of atenolol over aliskiren in DBP reduction and BP response but showed that atenolol was inferior in SBP reduction and BP control. No difference was found in the rates of therapeutic response between aliskiren and ARBs, while more patients achieved BP control with aliskiren. Further studies will be needed to determine the antihypertensive effects and tolerability of aliskiren in comparison with other antihypertensive drugs.
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Keywords: aliskiren; efficacy; hypertension; meta-analysis; safety

INTRODUCTION

Hypertension is an important public health problem worldwide. The estimated total number of adults with hypertension in 2000 was 972 million (957–987 million): 333 million (329–336 million) in economically developed countries and 639 million (625–654 million) in economically developing countries.[1] The number of adults with hypertension in 2025 is predicted to increase by ~60%, to a total of 1.56 billion (1.54–1.58 billion).[1] In addition to its high frequency, hypertension has been identified as the leading risk factor for cardiovascular and kidney diseases[2,3] and for mortality.[4]

The renin–angiotensin (Ang)–aldosterone system (RAAS) has a crucial role in volume regulation and the maintenance of blood pressure (BP), acting primarily through Ang II. Ang-converting enzyme inhibitors (ACEIs) and Ang AT1 receptor blockers (ARBs) reduce the effects of Ang II, either by reducing its production or by directly blocking its interaction with the Ang-1 receptor, respectively.[5] Although ACEIs and ARBs have been proven effective, suppression of RAAS remains incomplete with these agents because of their disruption of the negative feedback effects of Ang II on renin release, with a consequent increase in plasma renin activity and the reactive activation of the RAAS.[6] As renin catalyzes the conversion of angiotensinogen into Ang I, the initial and rate-limiting step of the RAAS, it has been suggested that renin inhibitors offer the potential to optimize suppression of the RAAS by interrupting the system at its first regulated step.[7,8]

Aliskiren is the first orally effective direct renin inhibitor,[9] and it has recently been approved by the US Food and Drug Administration and the European Medicines Agency for the treatment of hypertension. It inhibits the activity of renin, controlling the renin system at the rate-limiting step. Some clinical trials have studied its efficacy in hypertension;[10,11] however, there have been no meta-analyses that have examined the effects of aliskiren and other antihypertensive agents on BP.

Therefore, we performed a meta-analysis to investigate the anti-hypertensive effects and tolerability of aliskiren, in comparison with other antihypertensive drugs and placebo, in patients with hypertension.

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MATERIALS AND METHODS

Search strategy

We developed a protocol for the review and followed standard QUOROM reporting guidelines.[12] We searched online databases, including MEDLINE (1950–2012) and the Cochrane Library (Issue 5, 2012), using the following terms: aliskiren, renin inhibitor, hypertension and BP, without restrictions on language. We also searched the Clinical Trials (http://clinicaltrials.gov/) Web site and the Novartis Clinical Trials Results Database (http://www.novctrd.com/ctrdWebApp/clinicaltrialrepository/public/main.jsp) for unpublished data and reviewed the reference lists of the included randomized controlled trials (RCTs) and review articles to identify other unrecognized or unpublished reports of RCTs.[13,14]

Inclusion criteria

Studies were eligible for inclusion if they met the following criteria: (1) double-blind, prospective, randomized, controlled trials of antihypertensive treatment with aliskiren; (2) enrolled patients $\geqslant$18 years of age with mild-to-moderate hypertension (systolic BP (SBP) 140–179 mm Hg and/or diastolic BP (DBP) 90–109 mm Hg, as defined in current international guidelines);[15,16] (3) study treatments had to have been taken for at least 4 weeks with aliskiren at 300 mg per day and other active comparators at the maximum commonly used dose; (4) only monotherapy treatment arms were included in the meta-analysis; and (5) assessment of the effectiveness of aliskiren *vs.* placebo or other classes of drugs for hypertension.

Exclusion criteria

The exclusion criteria pertained to studies that recruited participants with secondary hypertension, severe hypertension (DBP$\geqslant$110 mm Hg and/or SBP$\geqslant$180 mm Hg), poorly controlled diabetes mellitus, a history of severe cardiovascular or cerebrovascular disease, severe chronic kidney disease (stage 4–5), other severe life-threatening medical conditions, unavailable data or no quantitative data and that had cohorts of $<$25 patients. Studies that only enrolled patients in a specific subgroup (for example, based on ethnicity or diabetes mellitus) and that used aliskiren for indications other than hypertension were also excluded.

Data extraction

The quality of each included study was assessed on the Jadad quality scale,[17] with a score of 0–2 reflecting low quality, a score of 3–4 indicating moderate quality and a score of 5 representing a high-quality study. All of the data were extracted by two independent authors. The following information was abstracted from each trial: number, age and sex of participants; intervention strategies; baseline SBP and DBP values; duration; and measures of end points (that is, changes from baseline in SBP and DBP, rates of therapeutic response and of SBP and DBP control; proportion of adverse events; and the number of drop-outs). Disagreements were resolved by discussion between the authors.

Statistical analysis

The meta-analysis was performed using the Cochrane RevMan software, version 5.02 (Cochrane Library, UK). For continuous data, the results were expressed as weighted mean differences (WMDs) with 95% confidence intervals (CIs). For dichotomous data, pooling data were described as relative risks (RRs) with 95% CIs. Subgroup analysis was conducted between different comparators. We assessed heterogeneity with a standard χ^2-test, with significance set at $P<0.10$, and with the I^2 statistic, with significance set at $I^2>50\%$.[18] The fixed-effects model was employed in the absence of between study heterogeneity; otherwise, the random-effects model was used.

RESULTS

Study characteristics

After screening the titles and abstracts of all of the studies identified by the search strategy, 491 potentially relevant articles were selected and reviewed for more detailed information. We excluded 30 duplicate articles, 35 non-related articles and 46 preclinical studies. Of the 380 reports selected for detailed evaluation, 359 studies were excluded, predominantly for study type (open-label, cross-over), study duration and article type (reviews, letters, comments, and interviews). Of the 21 full-text articles selected for assessing for eligibility, seven studies were not RCTs. Therefore, a total of 14 studies,[10,11,19–30] enrolling 6741 participants, fulfilled all of the inclusion criteria. All 14 articles were available as full reports (all in English). Table 1 describes the baseline characteristics of all of the eligible studies. The 14 studies included in this meta-analysis were short-term (4–16 weeks), randomized, double-blind clinical trials with similar designs and comparable primary end points and secondary efficacy measures. The patient demographics and baseline characteristics were also similar in all of the included studies, except that two studies that included patients aged older than 65 years old,[27,29] and one study included patients aged between 21 and 70 years old.[26]

Aliskiren was compared with ARBs (losartan, irbesartan and valsartan) in four trials,[21,23,24,26] ACEIs (ramipril, lisinopril) in two trials,[10,27] calcium channel blocker (CCB) (amlodipine) in two trials,[19,30] a β-blocker (atenolol) in one trial,[20] a thiazide diuretic (hydrochlorothiazide, HCTZ)[28] in one trial, and placebo in nine trials.[11,21–25,28–30] Two reports of unpublished data were checked with the Novartis Clinical Trials Results Database and the Clinical Trials Web site, and they were designated CSPP100A2405[29] and CSPA100A2305.[30] According to the Jadad quality scale, our quality assessment scores ranged from 3 to 5 for all of the studies included. These studies were considered to be of good quality, with six of them having excellent quality.

Outcome characteristics

Sitting clinic BP was used for all of the trials. The primary outcome of most of the trials was the change from baseline in mean sitting DBP, except for the studies by Verdecchia (2007)[27] and by Stanton (2003),[26] the primary outcomes of which were the change from baseline in mean 24 h ambulatory SBP, and for the study by Brown (2011)[19] and for CSPP100A2405,[29] the primary outcomes of which were the change from baseline in mean sitting SBP (msSBP). Secondary variables included the following: the change from baseline in msSBP, diastolic responder rates (defined as mean sitting DBP $<$90 mm Hg or equal to 10 mm Hg reduction in mean sitting DBP) or systolic responder rates (defined as msSBP $<$140 mm Hg or equal to 20 mm Hg reduction in msSBP); BP control rates (defined as a BP $<$140/90 mm Hg); number of patients with adverse events and withdrawals due to adverse effects.

Efficacy

Aliskiren vs. placebo. Nine trials[11,21–25,28–30] involving 3541 patients compared the effects of treatments with aliskiren and placebo in terms of reduction in BP. Aliskiren was significantly superior to placebo in lowering DBP and SBP (WMD −4.75, 95% CI −5.59 to −3.92, P$<$0.00001; WMD −8.12, 95% CI −9.61 to −6.63, $P<0.00001$, respectively); Figures 1 and 2. Seven trials[11,23–25,28–30] ($n=2915$) reported statistically significant improvements in responder rates (RR 1.65, 95% CI 1.52–1.80, $P<0.00001$); Figure 3. Six trials[21,23–25,28,30] ($n=2577$) reported that aliskiren led to significantly greater control rates than placebo (RR 1.96, 95% CI 1.73–2.23, $P<0.00001$); Figure 4.

Aliskiren vs. ARBs. Four trials[21,23,24,26] involving 1467 patients compared the effects of treatments with aliskiren and ARBs in terms of reduction in BP. No significant differences were found in the reduction of DBP and SBP of the two groups (WMD −0.83, 95% CI −2.79 to −1.13, $P=0.40$; WMD −0.57, 95% CI −2.40 to

Table 1 The baseline characteristics of all eligible studies included in the meta-analysis

Study	*Design and treatment duration*	*Sample size*	*Dosage (mg d^{-1})*	Male/n(%)	Age (mean ± s.d.)	*Baseline BP (mm Hg)*		*BP change from baseline (mm Hg)*		*Inclusion criteria*	*Jadad score*
						DBP	SBP	DBP	SBP		
Stanton 2003[26]	r, db, ac, pg, 4 weeks	226	Aliskiren 300	23/40(57.5)	51.8 ± 10.5	94.1 ± 11.1	157.6 ± 16.8	−5.7 ± 11.0	−11.8 ± 14.9	DASBP: ⩾140	3
			Losartan 100	23/36(63.9)	55.9 ± 8.9	95.0 ± 8.1	159.0 ± 15.5	−5.5 ± 10.7	−11.4 ± 19.2		
Gradman 2005[21]	r, mc, db, pg, pc, ac, 8 weeks	652	Aliskiren 300	55/130(42.3)	56.0 ± 10.2	98.8 ± 3.4	152.1 ± 10.2	−11.77 ± 8.56	−15.76 ± 14.02	DBP:95–110	5
			Placebo Irbesartan 150	64/131(48.9)	57.1 ± 12.0 56	98.9 ± 3.3	152.3 ± 12.1	−6.34 ± 8.56	−5.29 ± 14.02		
				66/134(49.3)	1 ± 11.8	99.4 ± 4.0	152.8 ± 11.2	−8.88 ± 8.53	−12.50 ± 13.95		
Oh 2007[22]	r, mc, db, pg, pc, 8 weeks	672	Aliskiren 300	106/169(62.7)	54 53	99.7 99.4	153.1 151.0	−11.1 ± 8.32	−14.7 ± 13.26	DBP:95–110	3
			Placebo	104/165(63.0)				−4.9 ± 8.22	−3.8 ± 13.10		
Oparil 2007[23]	r, mc, db, pg, pc, 8 weeks	1797	Aliskiren 300	255/437(58%)	51.9 ± 10.4	100.2 ± 3.9	153.9 ± 11.7	−9.0 ± 8.71	−13.0 ± 13.89	DBP:95–110	5
			Placebo	281/459 (61%)	52.6 ± 10.4	100.4 ± 4.2	154.1 ± 12.8	−4.1 ± 8.75	−4.6 ± 13.86		
			Valsartan 320	281/455 (62%)	52.4 ± 10.4	100.3 ± 3.8	154.2 ± 12.7	−9.7 ± 8.73	−12.8 ± 13.83		
Dietz 2008[20]	r, mc, db, 12 weeks	694	Aliskiren 300	134/	55.8 ± 11.9	99.7 ± 3.8	157.6 ± 12.3	−11.26 ± 9.08	−14.34 ± 16.14	DBP:95–110	4
			Atenolol 100	231(58.0%)	54.7 ± 11.5	99.4 ± 3.8	155.9 ± 12.9	−13.66 ± 9.07	−14.26 ± 16.14		
				113/							
				231(48.9%)							
Kushiro 2006[11]	r, mc, db, pc, pg, 8 weeks	455	Aliskiren 300	80/113(70.8%)	51.6 ± 9.9	99.6 ± 4.4	155.0 ± 11.7	−10.72 ± 7.97	−14.09 ± 12.54	DBP:95–110	5
			Placebo	90/115(78.3%)	52.7 ± 9.5	99.4 ± 3.9	155.4 ± 10.7	−3.26 ± 8.04	−2.85 ± 12.55		
Puig 2009	r, mc, db, pc, pg, 8 weeks	642	Aliskiren 300	91/158(57.6)	52.1 ± 11.01	100.3 ± 3.96	152.9 ± 12.73	−8.43 ± 7.99	−9.90 ± 13.74	DBP:95–110	5
			Placebo	93/160(58.1)	51.9 ± 11.06	100.1 ± 4.23	153.6 ± 13.03	−3.95 ± 7.94	−5.25 ± 13.77		
Andersen 2008[25]	r, mc, db, ac, 26 weeks	842	Aliskiren 300	224/420/53.3%)	53.4 ± 10.8	98.8 ± 3.4	151.3 ± 11.7	−11.3 ± 8.14	−14.0 ± 12.2	DBP:95–110	3
			Ramipril 10	256/422/60.7%)	53.1 ± 11.2	98.9 ± 3.5	151.5 ± 11.7	−9.7 ± 8.18	−11.3 ± 12.3		
Villamil 2007[10]	r, mc, db, pc, pg, 8 weeks	2776	Aliskiren 300	99/183(54.1%)	54.2	99.3	154.4	−10.3 ± 8.05	−15.7 ± 12.75	DBP:95–110	3
			Placebo	109/	54.4	99.3	152.7	−6.9 ± 8.04	−7.5 ± 12.75		
			HCTZ 25	195(55.9%)	55.1	99.1	154.5	−9.4 ± 8.02	−14.3 ± 12.76		
				92/176(52.3%)							
Pool 2007[24]	r, mc, db, pc, pg, ac, 8 weeks	1123	Aliskiren 300	100/	56.7 ± 11.9	99.1 ± 3.41	152.9 ± 12.20	−12.3 ± 8.20	−15.0 ± 12.70	DBP:95–110	4
			Placebo	175(57.1%)	55.2 ± 12.2	98.7 ± 3.03	152.6 ± 11.80	−8.6 ± 8.23	−10.0 ± 12.74		
			Valsartan 320	97/177(54.8%)	56.8 ± 10.7	98.9 ± 3.49	153.4 ± 9.73	−11.3 ± 8.13	−16.5 ± 12.55		
				31/60(51.7%)							
Verdecchia 2007[27]	r, mc, db, pg, ac, 8 weeks	355	Aliskiren 300	35/94(37.2%)	73.0 ± 5.6	90.1 ± 8.2	160.7 ± 8.9	−6.4 ± 7.85	-14.5 ± 14.06	SBP:140–180	5
			Lisinopril 10	29/86(33.7%)	74.2 ± 6.1	88.1 ± 8.6	161.4 ± 9.2	−5.4 ± 8.02	−14.9 ± 14.29		
Brown 2011[19]	r, mc, db, pg, ac, 32 weeks	1254	Aliskiren 300	164/318(51.6)	58.4 ± 10.8	92.1 ± 10.5	161.0 ± 8.0	NR	NR	SBP:150–180	5
			Amlodipine 10	156/316(49.4)	58.1 ± 10.9	93.0 ± 9.1	161.2 ± 8.2				
CSPP100A2405	r, mc, db, pc, pg, 8 weeks	755	Aliskiren 300	84/186(45.2)	72.1 ± 5.47	NR	NR	−6.66 ± 7.90	−14.14 ± 14.22	SBP:150–180 DBP: <110	
			Placebo	89/187(47.6)	72.3 ± 5.25			−3.50 ± 7.85	−7.97 ± 14.15		
CSPA100A2305	r, mc, db, ac, pg, pc, 8 weeks	1688	Aliskiren 300	95/203(46.8)	54.0 ± 9.99	NR	NR	−10.19 ± 8.98	−15.37 ± 14.04	DBP:95–110	
			Placebo	90/198(45.5)	53.7 ± 10.32			−5.35 ± 8.72	−6.79 ± 14.07		
			Amlodipine 10	87/181(48.1)	55.0 ± 10.34			−13.82 ± 8.83	−21.04 ± 14.05		

Abbreviations: ac, active comparator; BP, blood pressure; DASBP, daytime ambulatory SBP; db, double-blind; DBP, diastolic BP; HCTZ, hydrochlorothiazide; mc, multicenter; NR, not reported; pc, placebo-controlled; pg, parallel group; r, randomized; SBP, systolic BP.
Age, SBP and DBP are expressed as mean ± s.d. unless otherwise indicated.

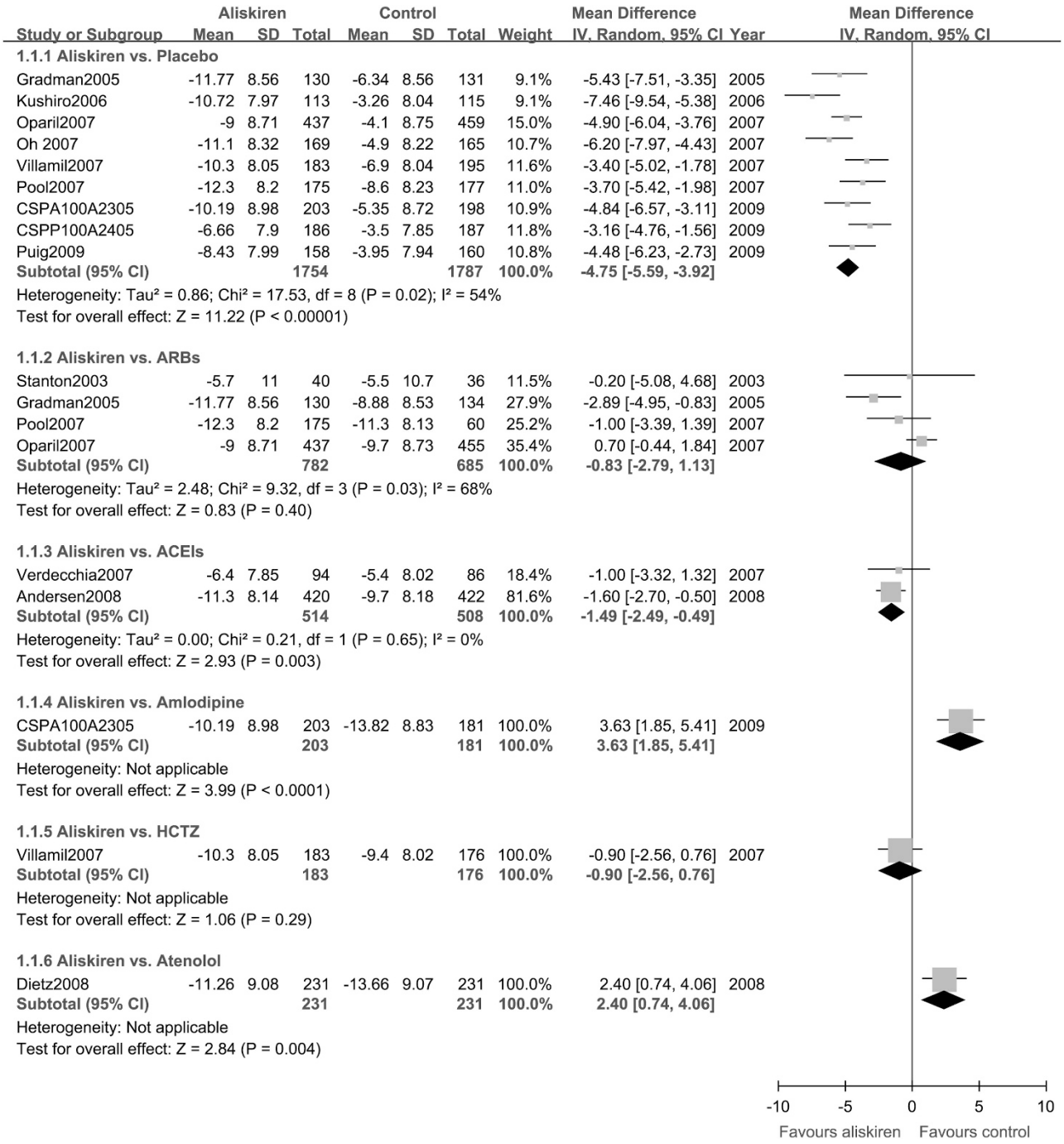

Figure 1 Change (mm Hg) from baseline in mean sitting diastolic BP at end point following treatment with aliskiren or other antihypertensive drugs and placebo during monotherapy. ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; CI, confidence interval; HCTZ, hydrochlorothiazide; IV, inverse variance. Control, antihypertensive drug used as comparator drug in that study. 'Total' indicates the total number of individuals.

−1.25, $P=0.54$, respectively); Figures 1 and 2. Two trials[23,24] ($n=1118$) compared BP responder rates between aliskiren and ARBs, with no significant difference between the two groups (RR 0.99, 95% CI 0.89–1.10, $P=0.84$); see Figure 3. Three trials[21,23,24] ($n=1381$) reported that more patients achieved BP control with aliskiren than with ARBs (RR 1.16, 95% CI 1.01–1.34, $P=0.03$); Figure 4. Additionally, Stanton (2003)[26] showed that the reductions in daytime and nighttime ambulatory SBP and DBPs were of a similar magnitude with aliskiren and losartan.

Aliskiren vs. ACEIs. Two trials[10,27] involving 1022 patients compared the effects of treatments with aliskiren and ACEIs in terms of reduction in BP. Aliskiren significantly reduced DBP compared with ACEIs (WMD −1.49, 95% CI −2.49 to −0.49, $P=0.003$), while no

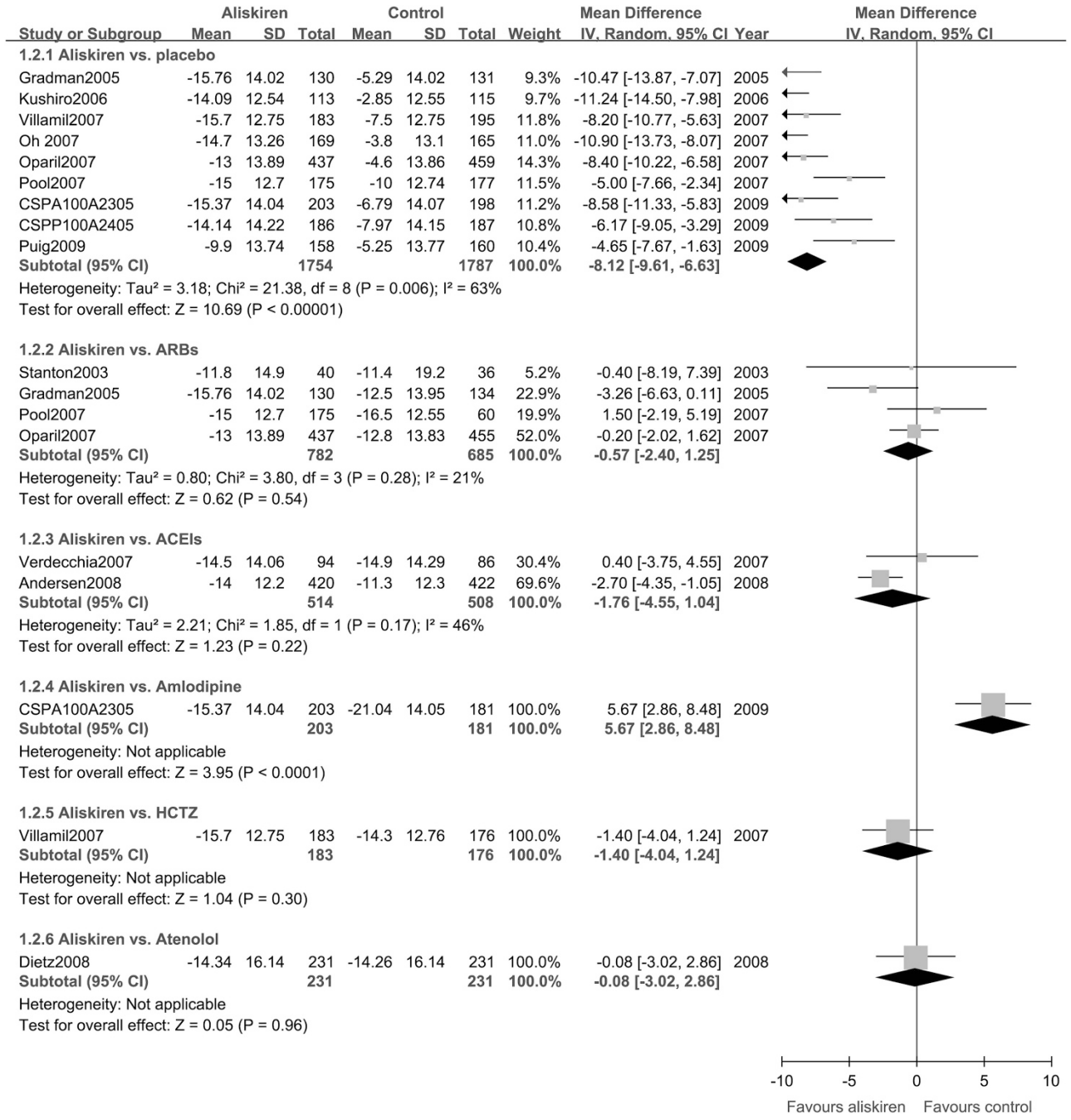

Figure 2 Change (mm Hg) from baseline in mean sitting systolic BP at end point following treatment with aliskiren or other antihypertensive drugs and placebo during monotherapy. ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; CI, confidence interval; HCTZ, hydrochlorothiazide; IV, inverse variance. Control, antihypertensive drug used as comparator drug in that study. 'Total' indicates the total number of individuals.

difference was found in the reduction of SBP of the two groups (WMD −1.76, 95% CI −4.55 to −1.04, $P=0.22$); Figures 1 and 2. Only one trial[10] ($n=832$) compared BP responder rates between aliskiren and ACEIs, with no significant difference between the two groups (RR 1.10, 95% CI 0.99–1.24, $P=0.09$); Figure 3. There was no significant difference in BP control rates between the two groups (RR 1.12, 95% CI 0.96–1.30, $P=0.15$); Figure 4. In addition, Verdecchia[27] found that both aliskiren and lisinopril groups produced significant decreases in mean 24 h ambulatory SBP and ambulatory DBP from baseline to end point.

Aliskiren vs. amlodipine. Only one study[30] involving 384 patients reported the effects of treatments with aliskiren and amlodipine in terms of reduction in BP. Aliskiren was inferior to amlodipine

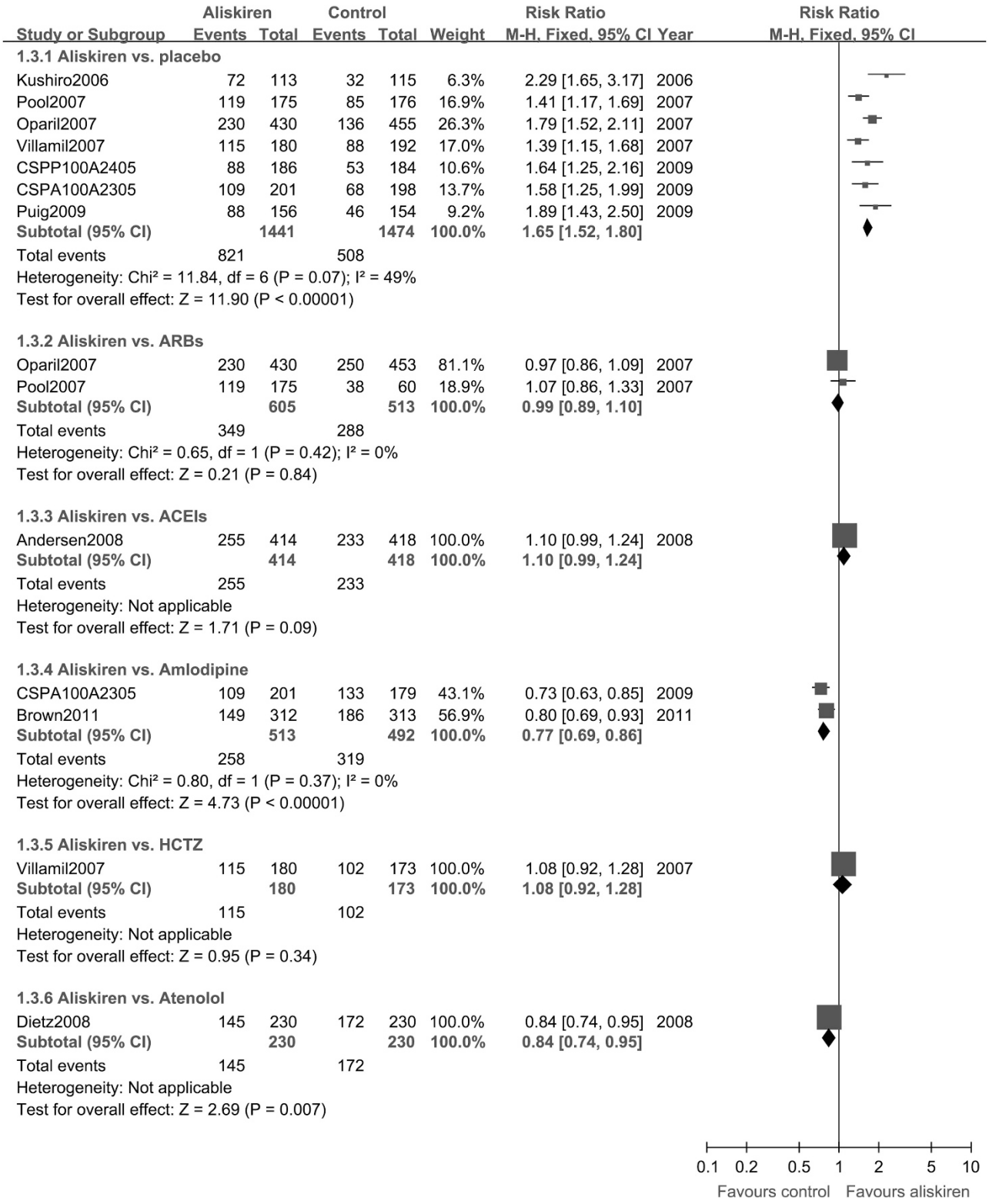

Figure 3 BP response rates of patients to aliskiren compared with other antihypertensive drugs and placebo. A successful response to treatment was defined as a mean sitting diastolic BP <90 mm Hg or a 10 $\geqslant$ mm Hg reduction from baseline or a mean sitting systolic BP (msSBP) <140 mm Hg or a 20 $\geqslant$ mm Hg reduction from baseline. 'Events' indicate number of patients with a successful response. 'Total' indicates the total number of individuals. ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; BP, blood pressure; CI, confidence interval; HCTZ, hydrochlorothiazide; RR, relative risk; M-H, Mantek-Haenzel.

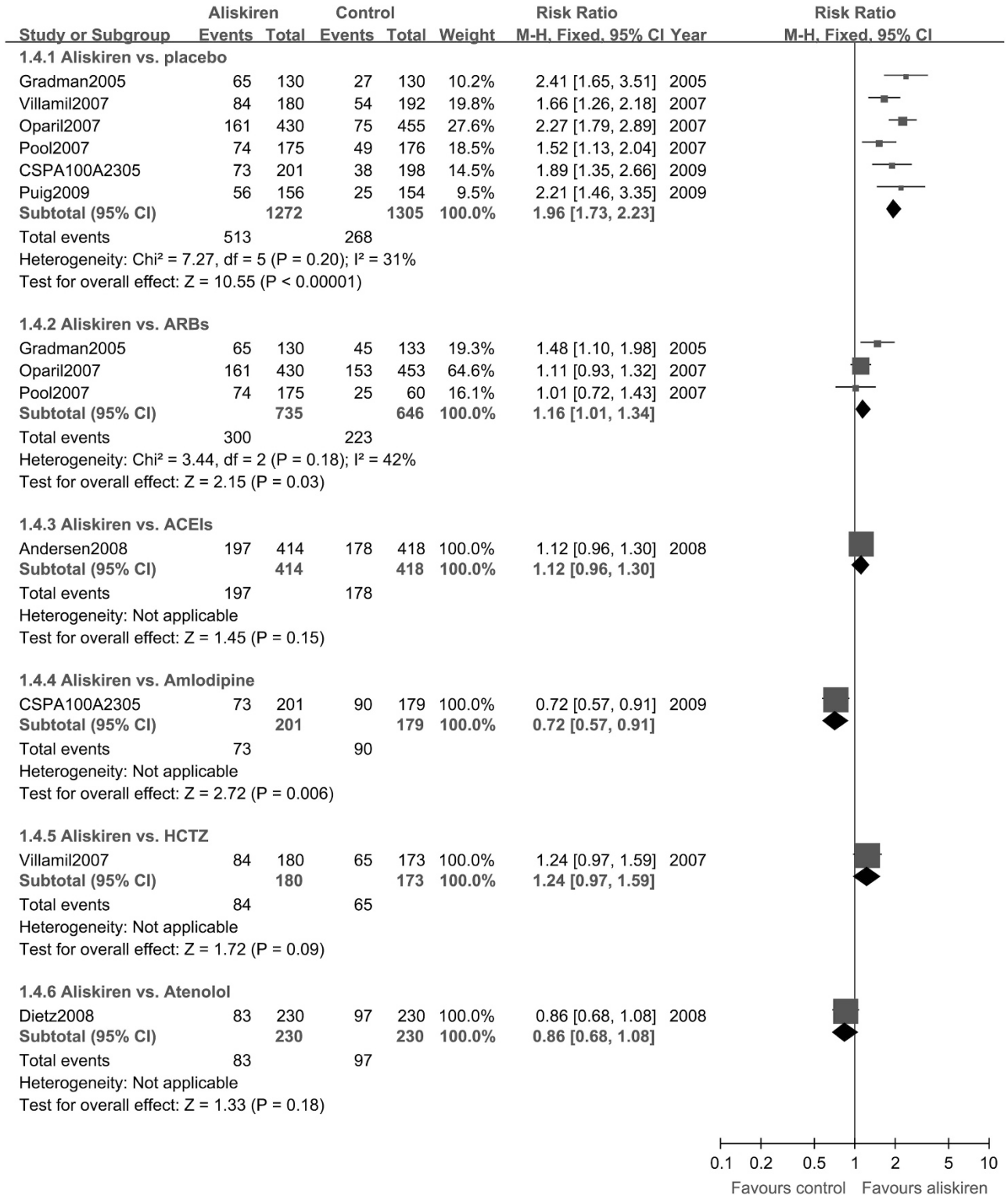

Figure 4 BP control rates of patients to aliskiren or other antihypertensive drugs and placebo. Control rate was defined as mean sitting diastolic BP <90 mm Hg and mean sitting systolic BP < 140 mm Hg. 'Events' indicate number of patients with a successful control. 'Total' indicates the total number of individuals. ACEIs. angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; BP, blood pressure; CI, confidence interval; HCTZ, hydrochlorothiazide; RR, relative risk; M-H, Mantek-Haenzel.

in lowering DBP and SBP (WMD 3.63, 95% CI 1.85–5.41, $P<0.0001$; WMD 5.67, 95% CI 2.86–8.48, $P<0.0001$, respectively); Figures 1 and 2. Two trials[19,30] ($n=1005$) reported the response rates. Response rates were significantly higher with amlodipine than with aliskiren (RR 0.77, 95% CI 0.69–0.86, $P<0.00001$); Figure 3. Only one trial[30] ($n=380$) reported the control rates. The control rates were significantly higher with amlodipine than with aliskiren (RR 0.72, 95% CI 0.57–0.91, $P=0.006$); Figure 4.

Aliskiren vs. HCTZ. Only one study[28] involving 359 patients reported the effects of treatments with aliskiren and HCTZ in terms of reduction in BP. No difference was found in the reduction of DBP and SBP of the two groups (WMD −0.90, 95% CI −2.56–0.76, $P=0.29$; WMD −1.40, 95% CI −4.04–1.24, $P=0.30$, respectively); Figures 1 and 2. The trial[28] ($n=353$) compared BP responder rates between aliskiren and HCTZ, with no significant difference between the two groups (RR 1.08, 95% CI 0.92–1.28, $P=0.34$); Figure 3. There was no significant difference in BP control rates between the two groups (RR 1.24, 95% CI 0.97–1.59, $P=0.09$); Figure 4.

Aliskiren vs. atenolol. Only one study[20] involving 462 patients reported the effects of treatments with aliskiren and atenolol in terms of reduction in BP. DBP changes were larger with atenolol than with aliskiren (WMD 2.40, 95% CI 0.74–4.06, $P=0.004$), while there was no significant difference between the msSBP reductions of the two groups (WMD −0.08, 95% CI −3.02–2.86, $P=0.96$); Figures 1 and 2. Only one trial[20] ($n=460$) reported response rates. Response rates were significantly higher with atenolol than aliskiren (RR 0.84, 95% CI 0.74–0.95, $P=0.007$); Figure 3. There was no significant difference in BP control rates between the two groups (RR 0.86, 95% CI 0.68–1.08, $P=0.18$) of the trial;[20] Figure 4.

Safety and tolerability

The safety population comprised all of the patients randomized in the 14 trials included in this analysis ($n=7879$). The most common adverse events included headache, dizziness, diarrhea, nasopharyngitis, fatigue and nausea. There were no significant differences in number of adverse events between aliskiren and placebo or other active comparators (Table 2). Similarly, there were no significant differences in withdrawals due to adverse events between aliskiren and placebo or other active comparators (Table 2).

Table 2 Safety and tolerability of aliskiren *vs.* other antihypertensive drugs

Interventions	*Adverse events (any reason) RR (95% CI)*	I^2	P	*Withdrawals due to adverse effects RR (95% CI)*	I^2	*P*
Aliskiren *vs.* placebo	0.96 (0.88,1.05)	0%	0.34	0.83 (0.54,1.27)	0%	0.39
Aliskiren *vs.* ARBs	0.93 (0.81,1.08)	0%	0.33	0.91 (0.50,1.67)	0%	0.76
Aliskiren *vs.* ACEIs	1.00 (0.89,1.11)	0%	0.93	0.62 (0.11,3.70)	65%	0.60
Aliskiren *vs.* Amlodipine	0.99 (0.89,1.11)	37%	0.92	0.42 (0.08,2.30)	65%	0.32
Aliskiren *vs.* HCTZ	0.95 (0.74,1.22)	NA	0.68	1.92 (0.59,6.27)	NA	0.28
Aliskiren *vs.* Atenolol	0.88 (0.72,1.08)	NA	0.23	0.60 (0.22,1.62)	NA	0.31

Abbreviations: ACEIs: Angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; CI, confidence interval; HCTZ: hydrochlorothiazide; NA, not applicable; RR, relative risk.

DISCUSSION

The present study evaluated the antihypertensive efficacy, safety, and tolerability of the novel, orally effective direct renin inhibitor aliskiren in comparison with other antihypertensive agents, in a total of 6741 patients with mild-to-moderate hypertension.

The results of our study suggest that aliskiren, which lowered BP effectively in patients with mild-to-moderate hypertension, was similar to HCTZ but inferior to CCBs in BP reduction, response rates and control rates. Furthermore, aliskiren was superior to ACEIs in lowering DBP, while it had similar effects to ACEIs on SBP reduction, response rates and control rates. Additionally, the present meta-analysis showed the superiority of atenolol over aliskiren in DBP reduction and BP response and atenolol's inferiority in SBP reduction and BP control. No difference was found in rates of therapeutic response between aliskiren and ARBs; these findings are consistent with the results from two previous studies,[31,32] which demonstrated that aliskiren and ARBs have comparable efficacy, while we found that more patients achieved BP control with aliskiren. The most obvious difference between the two studies[31,32] and ours is that they only assessed the antihypertensive efficacy and safety of aliskiren in comparison with ARBs in mild-to-moderate hypertensive patients, while our study included other antihypertensive drugs, apart from ARBs, for analysis. The two other meta-analyses[31,32] included study treatments with aliskiren at doses of 150 and 300 mg, drug combinations, and specific groups, such as obese patients. Zheng *et al.*[31] found that aliskiren monotherapy at 150 mg per day provided comparable antihypertensive efficacy to ARBs at half of the recommended maximum dose; moreover, aliskiren and ARB combination therapy provided more effective BP reduction than each respective monotherapy, without increasing adverse events, and this combination might have organ-protective effects.

Aliskiren provides highly effective BP reduction independent of age or sex in patients with hypertension. In a pooled analysis by Weir,[33] aliskiren demonstrated comparable efficacy in patients aged $\geqslant 65$ years old or <65 years old, in men and women, and it lowered BP effectively in all racial subgroups, consistent with previous studies.[34,35]

In addition to its antihypertensive effects, some recent publications have published findings regarding aliskiren's protective profile on the organs. Aliskiren has been shown to induce reductions in plasma levels of B-type natriuretic peptide in heart failure[36] and in left ventricular mass in hypertensive patients with left ventricular hypertrophy.[37] In addition, the AVOID trial showed that aliskiren has renoprotective effects that are independent of its BP lowering effects in hypertensive type 2 diabetic patients with nephropathy who are receiving the recommended maximal renoprotective treatment.[38]

Our meta-analysis indicates that aliskiren is associated with a similar incidence of adverse events and discontinuation due to adverse events to placebo and that it has similar tolerability with other antihypertensive drug classes. A pooled analysis of $>12\,000$ patients confirmed our results, which demonstrate that aliskiren at doses of 150 mg or 300 mg exhibits an excellent safety profile in patients with hypertension.[39] These findings suggest that aliskiren could be widely used for the treatment of hypertension because tolerability is an important factor in patient non-compliance and quality of life.[40]

We analyzed the short-term antihypertensive effects and tolerability of aliskiren in patients with mild-to-moderate hypertension. The longest-duration randomized, controlled trial, Brown (2011),[19] was 32 weeks, while the most common trial length was eight weeks. Nevertheless, White's Pooled Analysis found that more than 750 patient-years of aliskiren exposure confirmed the tolerability of aliskiren in long-term studies.[39] A pooled analysis reported that rates of discontinuation due to adverse events were low (1.7%–2.6%); the most frequently reported adverse events with aliskiren were headache (5.7%), nasopharyngitis (4.4%), diarrhea (2.6%), dizziness (1.8%) and fatigue (1.6%).[33]

A meta-analysis of the result of serious adverse events was not conducted because of the lack of effective data in Villamil[28] and in Pool.[24] However, the incidence of serious adverse events was very low: three trials[10,23,26] reported one case of death in each in the losartan,[26] aliskiren,[23] and valsartan[23] and ramipril group.[10] Although aliskiren has shown a good safety and tolerability profile, we should note that the Food and Drug Administration has recently issued a warning about combining aliskiren with ACEIs and ARBs in patients diagnosed with diabetes or renal impairment. The ALTITUDE study, which was recently terminated, found an increased risk of adverse events in patients considered high-risk and who were taking direct renin inhibitors as an add-on to other antihypertensive medications, such as ARBs and ACEIs. The Food and Drug Administration said in a safety announcement that diabetic patients who combine the drugs are at risk of renal impairment, hypotension and hyperkalemia, although the combination showed similar safety and tolerability in patients with uncomplicated hypertension.

Change from baseline in mean sitting DB was the primary outcome in most of the trials included in our analysis, while two trials[27,29] with population aged older than 65 years used change from baseline in SBP as the primary outcome. Usually, diastolic hypertension predominates before age 50, and systolic hypertension represents the most common form of hypertension in patients older than 50 years of age;[41] therefore, SBP is the main efficacy variable for the diagnosis and treatment of hypertension in the elderly.[42]

To the best of our knowledge, this is the only systematic review summarizing the antihypertensive effects and tolerability of aliskiren in comparison with other antihypertensive drugs. There are still some limitations to our meta-analysis. First, each result of our meta-analysis was based only on limited trials with limited sizes; in particular, there was only one single study comparing aliskiren with atenolol and one comparing HCTZ and amlodipine. The results should be interpreted cautiously, and more RCTs are necessary to support our findings. Actually, there are some ongoing trials with large-scale populations that will provide further data on the efficacy and tolerability of aliskiren.[43–45] Second, the duration of the trials in our analysis was relatively short. Third, we dealt with surrogate end points, instead of direct clinical outcomes, such as the incidence of cardiovascular disease or morbidity and mortality.

CONCLUSION

Our meta-analysis indicates that the direct renin inhibitor aliskiren, at doses of 300 mg, provided good antihypertensive efficacy that was at least as effective as that provided by ACEIs, ARBs and HCTZ at the recommended daily doses. However, aliskiren might not be as effective as CCBs and β-blockers, although it has similar safety and tolerability in patients with hypertension. Additional large-scale, well-controlled trials, preferably with clinical end points, are warranted.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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