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RESEARCH

Efficacy and safety of dual blockade of the renin-angiotensin system: meta-analysis of randomised trials


OPEN ACCESS

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Abstract

Objective To compare the long term efficacy and adverse events of dual blockade of the renin-angiotensin system with monotherapy.

Design Systematic review and meta-analysis.

Data sources PubMed, Embase, and the Cochrane central register of controlled trials, January 1990 to August 2012.

Study selection Randomised controlled trials comparing dual blockers of the renin-angiotensin system with monotherapy, reporting data on either long term efficacy (≥1 year) or safety events (≥4 weeks), and with a sample size of at least 50. Analysis was stratified by trials with patients with heart failure versus patients without heart failure.

Results 33 randomised controlled trials with 68 405 patients (mean age 61 years, 71% men) and mean duration of 52 weeks were included. Dual blockade of the renin-angiotensin system was not associated with any significant benefit for all cause mortality (relative risk 0.97, 95% confidence interval 0.89 to 1.06) and cardiovascular mortality (0.96, 0.88 to 1.05) compared with monotherapy. Compared with monotherapy, dual therapy was associated with an 18% reduction in admissions to hospital for heart failure (0.82, 0.74 to 0.92). However, compared with monotherapy, dual therapy was associated with a 55% increase in the risk of hyperkalaemia (P<0.001), a 66% increase in the risk of hypotension (P<0.001), a 41% increase in the risk of renal failure (P=0.01), and a 27% increase in the risk of withdrawal owing to adverse events (P<0.001). Efficacy and safety results were consistent in cohorts with and without heart failure when dual therapy was compared with monotherapy except for all cause mortality, which was higher in the cohort without heart failure (P=0.04 *v* P=0.15), and renal failure was significantly higher in the cohort with heart failure (P<0.001 *v* P=0.79).

Conclusion Although dual blockade of the renin-angiotensin system may have seemingly beneficial effects on certain surrogate endpoints, it failed to reduce mortality and was associated with an excessive risk of adverse events such as hyperkalaemia, hypotension, and renal failure compared with monotherapy. The risk to benefit ratio argues against the use of dual therapy.

Introduction

The concept of dual blockade of the renin-angiotensin system originated from an experimental model[1] purporting to show a "synergistic" effect between angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers. The concept seemed so logical and appealing that seemingly beneficial changes in surrogate endpoints such as blood pressure, proteinuria, and endothelial dysfunction became accepted as a free pass for dual blockade having cardioprotective and nephroprotective effects. Despite a lack of solid evidence on the safety and efficacy of dual blockade of the renin-angiotensin system this type of therapy has been mentioned in several sets of guidelines.[2-4] Thus dual therapy was commonly used in patients with hypertension and with diabetes or proteinuria, or both and also to a lesser extent in those with heart failure resistant to treatment. Even patients with uncomplicated essential hypertension were not entirely able to escape this fashionable trend. In the United States more than 200 000 patients are currently treated with dual blockade of the renin-angiotensin system, most of them by the combination of an angiotensin receptor blocker and ACE inhibitor (70%).[5 6] Some other combinations are also used, such as two ACE inhibitors (15%), two angiotensin receptor blockers (5%), and ACE inhibitors or

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Additional tables and figures
Full title of studies included in table 1

angiotensin receptor blockers in combination with a direct renin inhibitor (8%).[5] The long term efficacy and safety of dual blockade is not, however, well defined.

We compared the long term efficacy of dual blockade of the renin-angiotensin system (any two of ACE inhibitors, angiotensin receptor blockers, or aliskiren) with monotherapy and evaluated adverse events in patients receiving dual therapy compared with monotherapy.

Methods

We systematically searched PubMed, Embase, and the Cochrane central register of controlled trials (Cochrane Library Issue 6, June 2012) using the key terms "ACE inhibitors", "angiotensin receptor blockers", "direct renin inhibitors" and using the names of individual drugs (see supplementary table 1). The search was restricted to randomised controlled trials in humans and in peer reviewed journals from 1990 to August 2012. No language restriction was applied. We checked the reference lists of the reviewed articles and original studies identified by the electronic search for other potentially eligible articles.

Study selection and data extraction

Two authors (KD and AS) searched the data independently and in duplicate. Disagreements were resolved by consensus. For this analysis we extracted the year of publication, baseline characteristics of the study population, sample size, type of drug, mean age, study duration, percentage of men, long term efficacy (all cause mortality, cardiovascular mortality, and admissions to hospital for heart failure), and safety events (hyperkalaemia, hypotension, renal failure, and withdrawal owing to drug related adverse events). Hyperkalaemia was defined in the included studies as a serum concentration of potassium greater than 5.5 mmol/L and renal failure as a serum creatinine concentration greater than 176.8 μmol/L (>2.0 mg/dL) or a doubling of baseline serum creatinine level. The definition of hypotension in the studies varied from symptomatic hypotension to evidence of low blood pressure. Withdrawal owing to drug related adverse events was defined as withdrawal by a patient as a result of any of the clinical or biochemical adverse events.

Selection criteria

We screened the trials for eligibility using the following criteria: randomised clinical trials comparing individual blockers with a combination of blockers (ACE inhibitor, angiotensin receptor blocker, or direct renin inhibitor), data on either long term efficacy (duration ≥1 year) or safety events (duration ≥4 weeks), and a sample size of at least 50. Given the limited number of trials reporting data on stroke and myocardial infarction, these outcomes were not evaluated in the study.

Quality assessment

The criteria used for quality assessment were sequence generation of allocation; allocation concealment; masking of participants, staff, and outcome assessors; incomplete outcome data; selective outcome reporting; and other sources of bias, as recommended by the Cochrane Collaboration.[7] We classed studies with high or unclear risk of bias for any of the first three components to be of low quality.

Statistical analysis

The statistical analysis was done in line with recommendations from the Cochrane Collaboration and the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines[8] using Review Manager (RevMan), version 5.1.7 (Cochrane Collaboration, 2012). Heterogeneity was assessed using the I^2 statistic. I^2 is the proportion of total variation observed between the trials attributable to differences between trials rather than to sampling error (chance), and we considered I^2 <25% as representing low heterogeneity and I^2 >75% as representing high heterogeneity. We used the random effects model of DerSimonian and Laird[9] to calculate the effect sizes because of known clinical and methodological heterogeneity of the studies. All analyses were performed using the intention to treat principle. Results were calculated by relative risk ratio and 95% confidence intervals using the Mantel-Haenszel method. We carried out head to head comparisons between individual blockers and the combination of blockers for both long term efficacy and safety data. Analysis was stratified by patient cohorts with and without heart failure. Analysis was also done to evaluate the safety outcomes between dual blockers (ACE inhibitors+angiotensin receptor blockers, angiotensin receptor blockers+aliskiren, ACE inhibitors+aliskiren) and individual blockers.

Publication bias was estimated visually by funnel plots[10] or by Begg's test and the weighted regression test of Egger.[11] If there was evidence of publication bias, we applied the trim and fill method to adjust the results of the meta-analysis.[12]

Sensitivity analysis

Sensitivity analysis was performed for safety outcomes based on the cohort of patients with heart failure versus the cohort without, risk of bias in the trial (low *v* high), duration of follow-up (<1 year *v* ≥1year), and number of patients (<500 *v* ≥500). We used a test for interaction to estimate differences between the subgroups.[13] Sensitivity analysis was not done for long term efficacy outcomes because of the limited number of studies available.

Results

A total of 138 full text articles were assessed for eligibility, of which 33 met the inclusion criteria (fig 1⇓). The 33 trials[14-46] enrolled 68 405 patients with a mean age of 61 (SD 4) years, 71% men, followed-up for a mean duration of 52 weeks (table 1⇓). A combination of an ACE inhibitor and angiotensin receptor blocker was used in 22 trials,[14-35] an ACE inhibitor and aliskiren in three trials,[36-38] an angiotensin receptor blocker and aliskiren in seven trials,[39-45] and an ACE inhibitor or angiotensin receptor blocker with aliskiren in one trial.[46]

Efficacy data were available from seven trials with a total of 56 824 patients (mean age 65 (SD 2) years, 72% males) and mean duration of 2.7 years. Safety data were available from all of the included trials.

Of the 33 trials, 18 reported adequate generation of allocation sequence and adequate allocation concealment and 24 reported adequate masking of participants, staff, and outcome assessors. On the basis of quality assessment, 18 were deemed to be at low risk of bias and the remainder to be at high risk.

Dual therapy versus monotherapy: efficacy outcomes

All cause mortality

Data were available from seven trials with a total of 56 824 patients. Overall, 3314 of 21 638 patients (15.3%) died in the dual therapy group compared with 5286 of 35 186 patients (15.0%) in the monotherapy group. When compared with

monotherapy alone, dual therapy had no benefit on all cause mortality (relative risk 0.97, 95% confidence interval 0.89 to 1.06, P=0.50, I^2=69%, fig 2⇓).

In subgroup analysis, dual therapy showed no benefit for all cause mortality in the cohort with heart failure (0.92, 0.82 to 1.03, P=0.15), however mortality was increased in the cohort without heart failure (1.07, 1.00 to 1.14, P=0.04, fig 2). The difference between these two subgroups was significant (P=0.02).

Cardiovascular mortality

In six trials 2812 of 19 127 patients (14.7%) died of cardiovascular causes in the dual therapy group compared with 5128 of 32 687 patients (15.7%) in the monotherapy group. Dual therapy had no significant benefit on cardiovascular mortality (0.96, 0.88 to 1.05, P=0.38, I^2=59%, fig 3⇓) compared with monotherapy.

In subgroup analysis, dual therapy had no benefit on cardiovascular mortality in the cohorts both with heart failure (P=0.14) and without (P=0.61).

Admissions to hospital for heart failure

In five trials 1825 of 16 728 patients (10.9%0 in the dual therapy group were admitted to hospital for heart failure compared with 2604 of 25 343 patients (10.3%) in the monotherapy group. Dual therapy was associated with a 18% reduction in admissions to hospital for heart failure compared with monotherapy (0.82, 0.74 to 0.92, I^2=68%, P=0.0003, fig 4⇓). This was largely driven by a benefit in the cohort with heart failure (0.77, 0.68 to 0.88, P=0.0001), although there was a trend towards benefit in the cohort without heart failure (0.91, 0.82 to 1.01, P=0.07).

Dual therapy versus monotherapy: safety outcomes

Hyperkalaemia

In 23 trials 2188 of 22 717 patients (9.6%) had hyperkalaemia in the dual therapy group compared with 1887 of 37 921 patients (4.9%) in the monotherapy group. Dual therapy was associated with a 55% increased risk of hyperkalaemia (1.55, 1.32 to 1.82, I^2=50%, P<0.001, fig 5⇓) compared with monotherapy.

In subgroup analysis, the risk of hyperkalaemia increased significantly in both the cohort with heart failure (P=0.02) and the cohort without (P<0.001).

Hypotension

In 18 trials 2042 of 23 572 patients (8.7%) had hypotension in the dual therapy group compared with 2227 of 37 680 patients (5.9%) in the monotherapy group. Dual therapy was associated with a 66% increased risk of hypotension (1.66 1.38 to 1.98, I^2=66%, P<0.001, fig 6⇓) compared with monotherapy.

In subgroup analysis, the risk of hypotension increased significantly in the cohorts both with heart failure (P<0.001) and without (P=0.002).

Renal failure

In 20 trials 2026 of 24 536 patients (8.3%) had renal failure in the dual therapy group compared with 2551 of 39 784 patients (6.4%) in the monotherapy group. Dual therapy was associated with a 41% increased risk of renal failure (1.41, 1.09 to 1.84, I^2=83%, P=0.01, fig 7⇓) compared with monotherapy.

In subgroup analysis, the risk of renal failure increased significantly in the cohort with heart failure (2.19, 1.82 to 2.65, P<0.001) but not in the cohort without (1.04, 0.80 to 1.35, P=0.76). The difference between these two subgroups was significant (P<0.001).

Withdrawal owing to drug related adverse events

In 26 trials 4265 of 24 994 patients (17.1%) had withdrawal owing to drug related adverse events in the dual therapy group compared with 5825 of 40 247 patients (14.5%) in the monotherapy group. Dual therapy was associated with a 27% increase in the risk of withdrawal owing to drug related adverse events (1.27, 1.21 to 1.32, I^2=2%, P<0.001, fig 8⇓) compared with monotherapy.

In subgroup analysis, the risk of withdrawal owing to drug related adverse events increased significantly in the cohort both with heart failure (P<0.001) and without (P=0.0003).

Subgroup analysis of safety outcomes

Comparing the combination of ACE inhibitors and angiotensin receptor blockers with ACE inhibitors alone, the risk of all safety outcomes (hyperkalaemia, hypotension, renal failure, and withdrawal owing to drug related adverse events) increased significantly with combination treatment: (table 2⇓). Comparing the combination of ACE inhibitors and angiotensin receptor blockers with angiotensin receptor blockers alone, the risk of hypotension and withdrawal owing to drug related adverse events increased significantly but not the risk of hyperkalaemia and renal failure with combination treatment (table 2). Comparing the combination of ACE inhibitors and aliskiren with ACE inhibitors alone, the risk of hyperkalaemia and hypotension increased significantly but there was no difference in the risk of renal failure and withdrawal owing to drug related adverse events with combination treatment (table 2). Comparing the combination of ACE inhibitors and aliskiren with aliskiren alone, the risk of hyperkalaemia, hypotension, renal failure, and withdrawal owing to drug related adverse effects did not differ with combination treatment (table 2). Comparing the combination of angiotensin receptor blockers and aliskiren with angiotensin receptor blockers alone, the risk of hyperkalaemia was increased significantly but there was no difference in the risk of other adverse events (table 2). Comparing the combination of angiotensin receptor blockers and aliskiren with aliskiren alone, none of the adverse events differed significantly between the two groups (table 2). These subgroup analyses are presented as forest plots in supplementary figures 1-4.

Sensitivity analyses did not show any significant difference in the groups for hyperkalaemia, hypotension, or withdrawal owing to drug related adverse effects. The risk of renal failure was significantly higher in the cohort of patients with heart failure compared with the cohort without heart failure (P<0.001, see supplementary table 2).

Significant heterogeneity was present in most of the analyses. Thus a random variance model was used. No evidence of publication bias was suggested by visual inspection of funnel plots or by Egger's test. The results were not significantly different after applying the trim and fill method all cause mortality (relative risk 0.94, 95% confidence interval 0.86 to 1.03), cardiovascular mortality (0.96, 0.86 to 1.04), admissions to hospital for heart failure (0.82, 0.74 to 0.91), hyperkalaemia (1.44, 1.22 to 1.70), hypotension (1.59, 1.33 to 1.91), renal failure (1.47, 1.13 to 1.92), and withdrawal owing to drug related adverse events (1.27, 1.20 to 1.34) (see supplementary figure 5).

Discussion

The present analysis evaluating the long term efficacy and safety of dual blockade of the renin-angiotensin system failed to show any benefit for all cause mortality and cardiovascular mortality with dual therapy compared with monotherapy. This is the most comprehensive review of literature evaluating both the safety and outcomes of dual therapy. Although compared with monotherapy dual therapy was associated with a reduction in admissions to hospital for heart failure mainly in the cohort with heart failure, the risks of hyperkalaemia, hypotension, renal failure, and withdrawal owing to drug related adverse events were significantly increased. Given these facts it may appropriately be asked why dual therapy was and still is extensively used to treat many patients with hypertension and heart failure. With the exception of the CHARM Added trial,[18] most if not all data making dual therapy attractive are based on evidence from surrogate endpoints.

One meta-analysis[47] reported "encouraging" evidence that dual therapy reduced proteinuria by an incremental 20-25% compared with monotherapy. The COOPERATE study[48] even showed that dual therapy with trandolapril and losartan reduced the risk of the primary endpoint (time to doubling of serum creatinine level or end stage renal disease) by 60% better than monotherapy, thereby becoming one of the most widely quoted studies by the *Lancet*.[49] After such seemingly robust evidence many physicians accepted that reduction of albuminuria or proteinuria was synonymous with nephroprotection. In the CHARM Added trial,[18] in a cohort of 2548 patients with heart failure, dual blockade of the renin-angiotensin system (candesartan and ACE inhibitor) significantly reduced the primary outcome of cardiovascular death or admission to hospital for worsening of heart failure. As a consequence, dual therapy became more and more used in patients with hypertension, diabetes, and heart failure resistant to treatment.

The importance of dual therapy began to change with publication of the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET).[50] Similar to other studies, in this study the surrogate endpoint albuminuria was reduced with dual therapy compared with monotherapy. However, a significant doubling of creatinine level and dialysis in the combination arm (despite less albuminuria) argued against a nephroprotection by dual therapy. More recently, authors[51] found several inconsistencies in COOPERATE, eventually leading to retraction of the study by the *Lancet*.[52]

In heart failure, the safety issue remained a major concern with dual therapy. In the CHARM Added trial, hyperkalaemia was almost five times more common and increased creatinine levels twice as common with dual therapy than with monotherapy. A meta-analysis[53] in over 18 000 patients with left ventricular dysfunction showed a significantly increased risk of adverse events of dual therapy compared with monotherapy, leading to the discontinuation of dual therapy. Given the adverse effects and lack of consistent survival benefits, the addition of an angiotensin receptor blocker to ACE inhibitor therapy in patients with heart failure should perhaps be reserved only for selected patients who continue to have symptoms while receiving monotherapy and cannot tolerate mineralocorticoid antagonists.

Several trials have shown a beneficial effect of aliskiren in combination with ACE inhibitors or angiotensin receptor blockers in patients with heart failure or diabetic nephropathy on surrogate endpoints, such as in proteinuria,[41] left ventricular hypertrophy,[39] and neurohormonal changes.[36] Our analysis showed a significantly increased risk of hyperkalaemia with combination therapy with aliskiren compared with monotherapy. Similar results were also found in a recent meta-analysis of 10 studies with over 4800 patients.[54] The ALTITUDE trial[46] was terminated early because of an increased risk of adverse outcomes (stroke, hypotension, and hyperkalaemia) when aliskiren was combined with ACE inhibitors or angiotensin receptor blockers. As to the mechanism of hypotension, one author suggested that blockade of the renin-angiotensin-aldosterone system could trigger the Bezold-Jarisch reflex sensitised by withdrawal of the effect of angiotensin II.[55] More extensive blockade of the renin-angiotensin system with two drugs could lead to a reduction in sympathetic outflow from the brainstem and excessive vagal tone causing prolonged hypotension and bradycardia. Conceivably this mechanism might account for the higher incidence of stroke and hypotension in patients receiving dual therapy.[55] Regulatory agencies such as the Food and Drug Administration and European Medicines Agency[56] recommended avoiding aliskiren in patients with diabetes or moderate to severe renal dysfunction who are already taking ACE inhibitors or angiotensin receptor blockers. Of note, the VA NEPHRON-D multicentre trial[57] to assess the effect of combination of losartan and lisinopril compared with losartan alone, on the progression of kidney disease in 1850 patients with diabetes and overt proteinuria was terminated recently for similar reasons to those of ALTITUDE.

The present data evolving from studies with dual blockade of the renin-angiotensin system should be a reminder hat many purported benefits of such therapy was solely based on data using surrogate endpoints. Surrogate endpoints not uncommonly fail to emulate hard outcomes endpoints and leapfrogging from surrogate data cannot substitute for the exposure of patients in clinical outcome studies.

Strengths and limitations of this meta-analysis

Our paper had several limitations. As with other meta-analyses, given the lack of data in each trial, we did not adjust our analysis for adherence to therapy. Also, the results are subject to limitations inherent to any meta-analysis based on pooling of data from different trials with different duration, doses of drugs, definitions for safety outcomes, and patient groups. Analysis of safety events is also prone to several biases since the data vary in each study for quality, incidence, severity, and adjudication. The reporting may also be influenced by expectations of the investigators, sponsors, and patients. Despite all the limitations, this is the most comprehensive analysis evaluating the safety and efficacy of dual blockade of the renin-angiotensin system. Despite significant heterogeneity among the studies, there was no evidence of publication bias visually and by Egger's test. The results were fairly consistent among various subgroups.

Conclusion

Although dual blockade of the renin-angiotensin system may have seemingly beneficial effects on certain surrogate endpoints, it failed to reduce mortality and was associated with an excessive risk of adverse events such as hyperkalaemia, hypotension, and renal failure when compared with monotherapy. The overall risk to benefit ratio argues against the use of dual therapy.

Contributors: HM supervised the study, had full access to all the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis. He is the guarantor. HM, SB, and FHM conceived and designed the study, acquired the data, drafted the

What is already known on this topic

Dual blockade of the renin-angiotensin system (RAS) is extensively used for treatment of resistant forms of heart failure, hypertension, diabetic nephropathy, and proteinuria

The efficacy and safety of dual RAS blockade, however, remains controversial

What this study adds

Although dual RAS blockade reduced admissions to hospital for heart failure (mainly in patients with heart failure), it had no effect on all cause or cardiovascular mortality

Compared with monotherapy, dual therapy was associated with a significant increase in adverse events such as hyperkalaemia, hypotension, and renal failure

These considerations of risk-benefit argue against the routine use of dual therapy

manuscript, and critically revised the manuscript for important intellectual content. KAD and AS analysed and interpreted the data. All authors carried out the statistical analysis and had full access to all the data in the study.

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Ethical approval: Not required.

Data sharing: No additional data available.

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Tables

Table 1| Characteristics of included studies

Trial name, year	Patient cohort	No of patients	Mean age (years)	Men (%)	Follow-up (weeks)	RAS blocker monotherapy	RAS blocker combination	Risk of bias	Data available
ACE inhibitor/ARB combination *v* RAS blocker monotherapy:									
AMAZE[14] 2004	Essential hypertension	1096	54	58	8	Lisinopril	Lisinopril+candesartan	High	Safety
Azizi et al[15] 2000	Mild to moderate hypertension	177	NR	64	6	Enalapril or losartan	Enalapril+losartan	High	Safety
CALM[16] 2001	Diabetes, hypertension and microalbuminuria	197	60	65	24	Lisinopril or candesartan	Lisinopril+candesartan	High	Safety
CALM II[17] 2005	Hypertension and diabetes	75	55	75	52	Lisinopril	Lisinopril+candesartan	High	Safety
CHARM Added[18] 2003	Heart failure and ejection fraction ≤40%	2548	64	79	178	Any ACE inhibitor	ACE inhibitor+candesartan	Low	Efficacy and safety
Cice et al[19] 2010	Haemodialysis, heart failure with ejection fraction ≤40%	332	63	54	156	Any ACE inhibitor	ACE inhibitor+telmisartan	Low	Efficacy and safety
IMPROVE[20] 2007	High risk cardiovascular disease and microalbuminuria	405	66	61	20	Ramipril	Ramipril+irbesartan	High	Safety
Kanno et al[21] 2006	Hypertension and chronic kidney disease	90	60	40	156	Any ACE inhibitor	ACE inhibitor+candesartan	Low	Safety
Kum et al[22] 2008	Chronic systolic heart failure with ejection fraction <50%	50	66	72	52	Any ACE inhibitor	ACE inhibitor+irbesartan	High	Efficacy and safety
Mehdi et al[23] 2009	Diabetes, hypertension, and albuminuria	81	50	48	48	Lisinopril	Lisinopril+losartan	High	Safety
Ogawa et al[24] 2007	Hypertension and diabetic nephropathy	164	62	48	96	Temocapril, candesartan	Temocapril+candesartan	High	Safety
ONTARGET[25] 2008	High risk cardiovascular disease	25 620	67	73	243	Ramipril or telmisartan	Ramipril+telmisartan	Low	Efficacy and safety
RESOLVD[26] 1999	Heart failure with ejection fraction <40%	768	64	83	43	Enalapril or candesartan	Enalapril+candesartan	Low	Safety
Ruilope et al[27] 2000	Hypertension, chronic kidney disease with or without proteinuria	108	57	70	4	Valsartan	Benazepril+valsartan	High	Safety
Titan et al[28] 2011	Diabetic nephropathy	56	58	63	16	Enalapril	Enalapril+losartan	High	Safety
Tonkon et al[29] 2000	Chronic heart failure	109	64	76	12	Any ACE inhibitor	ACE inhibitor+irbesartan	High	Safety
VALERIA[30] 2008	Hypertension and microalbuminuria	133	59	69	30	Lisinopril or valsartan	Lisinopril+valsartan	Low	Safety
Val-HeFT[31] 2001	NYHA class II-IV heart failure	5010	63	80	100	Any ACE inhibitor	ACE inhibitor+valsartan	Low	Efficacy and safety
V-HeFT[32] 1999	Symptomatic NYHA class II-IV heart failure	83	64	100	4	Any ACE inhibitor	ACE inhibitor+valsartan	High	Safety
VALIANT[33] 2003	Acute myocardial infarction complicated by heart failure	14 703	65	69	107	Captopril or valsartan	Captopril+valsartan	Low	Efficacy and safety
White et al[34] 2007	Symptomatic heart failure with ejection fraction ≤40%	80	62	90	26	Any ACE inhibitor	ACE inhibitor+candesartan	High	Safety
Yasamura et al[35] 2004	Mild to moderate chronic heart failure	106	65	80	26	Any ACE inhibitor	ACE inhibitor+ARB	High	Safety
ACE inhibitor/aliskiren combination *v* RAS blocker monotherapy:									
ALOFT[36] 2008	Hypertension and NYHA class II-IV heart failure	302	67	78	12	Any ACE inhibitor	ACE inhibitor+aliskiren	Low	Safety
ASPIRE[37] 2011	Post-myocardial infarction with systolic dysfunction	820	60	82	36	Any ACE inhibitor	ACE inhibitor+aliskiren	Low	Safety

Table 1 (continued)

Trial name, year	Patient cohort	No of patients	Mean age (years)	Men (%)	Follow-up (weeks)	RAS blocker monotherapy	RAS blocker combination	Risk of bias	Data available
Uresin et al[38] 2007	Diabetes mellitus and hypertension	837	59	59	8	Ramipril or aliskiren	Ramipril+aliskiren	Low	Safety
ARB/aliskiren combination *v* RAS blocker monotherapy:									
ALLAY[39] 2009	Hypertension and left ventricular hypertrophy	460	59	76	36	Losartan or aliskiren	Losartan+aliskiren	Low	Safety
AVANTE GARDE[40] 2010	Acute coronary syndrome without heart failure, raised natriuretic peptide	1101	63	68	8	Valsartan or aliskiren	Valsartan+aliskiren	Low	Safety
AVOID[41] 2008	Hypertension and diabetic nephropathy	599	62	71	24	Losartan	Losartan+aliskiren	Low	Safety
Drummond et al[42] 2011	Diabetes mellitus and hypertension	363	57	54	12	Valsartan	Valsartan+aliskiren	Low	Safety
Oparil et al[43] 2007	Hypertension	1797	52	61	8	Valsartan or aliskiren,	Valsartan+aliskiren	Low	Safety
Pool et al[44] 2007	Mild to moderate hypertension	1123	56	56	8	Valsartan or aliskiren	Valsartan+aliskiren	Low	Safety
VANTAGE[45] 2010	Stage 2 hypertension	451	57	51	8	Valsartan	Valsartan+aliskiren	High	Safety
ACE inhibitor or ARB/aliskiren combination *v* RAS blocker monotherapy:									
ALTITUDE[46] 2012	Diabetic nephropathy	8561	65	68	139	Aliskiren	ACE inhibitor or ARB+aliskiren	Low	Efficacy and safety

ACE=angiotensin converting enzyme; ARB=angiotensin receptor blocker; RAS=renin-angiotensin system; NR=not recorded; NYHA=New York Heart Association.

Table 2| Safety outcomes between different drug combinations for dual blockade of the renin-angiotensin system (RAS) compared with monotherapy

RAS blocker combination *v.* monotherapy	Relative risk (95% CI), P value		Interaction P value
ACE inhibitors+angiotensin receptor blockers:	ACE inhibitors	Angiotensin receptor blockers	
Hyperkalaemia	1.83 (1.35 to 2.50), 0.0001	1.34 (0.86 to 2.09), 0.19	0.26
Hypotension	2.02 (1.46 to 2.80), <0.001	1.44 (1.04 to 2.01), 0.03	0.15
Renal failure	1.55 (1.23 to 1.96), 0.0002	1.15 (0.92 to 1.43), 0.22	0.07
Withdrawal owing to drug related adverse events	1.21 (1.16 to 1.26), <0.001	1.39 (1.14 to 1.70), 0.001	0.18
ACE inhibitors+aliskiren:	ACE inhibitors	Aliskiren	
Hyperkalaemia	1.70 (1.11 to 2.58), 0.01	2.55 (1.00 to 6.46), 0.05	0.44
Hypotension	1.97 (1.17 to 3.30), 0.02	No studies available	NA
Renal failure	1.75 (0.92 to 3.34), 0.09	0.34 (0.04 to 3.24), 0.35	0.16
Withdrawal owing to drug related adverse events	0.97 (0.34 to 2.74), 0.95	0.56 (0.21 to 1.48), 0.24	0.45
Angiotensin receptor blockers+aliskiren:	Angiotensin receptor blockers	Aliskiren	
Hyperkalaemia	1.40 (1.02 to 1.91), 0.04	1.49 (0.83 to 2.68), 0.18	0.86
Hypotension	1.62 (0.70 to 3.74), 0.26	1.02 (0.66 to 1.56), 0.94	0.34
Renal failure	1.13 (0.52 to 2.47), 0.76	1.02 (0.36 to 2.93), 0.97	0.88
Withdrawal owing to drug related adverse events	1.06 (0.79 to 1.43), 0.70	1.19 (0.54 to 2.66), 0.67	0.79

ACE=angiotensin converting enzyme; NA=not applicable.

Figures

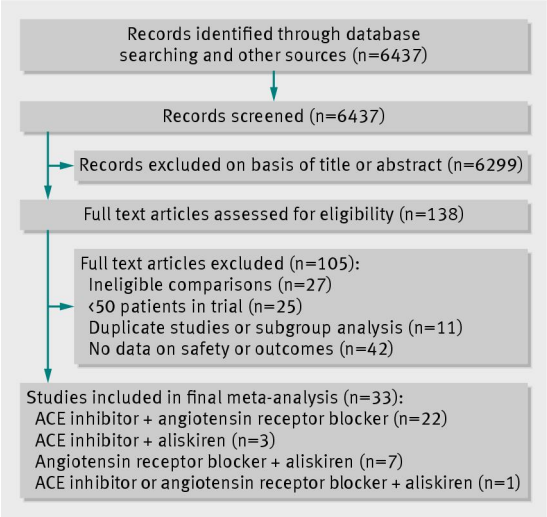

Fig 1 Selection of studies. ACE=angiotensin converting enzyme inhibitor

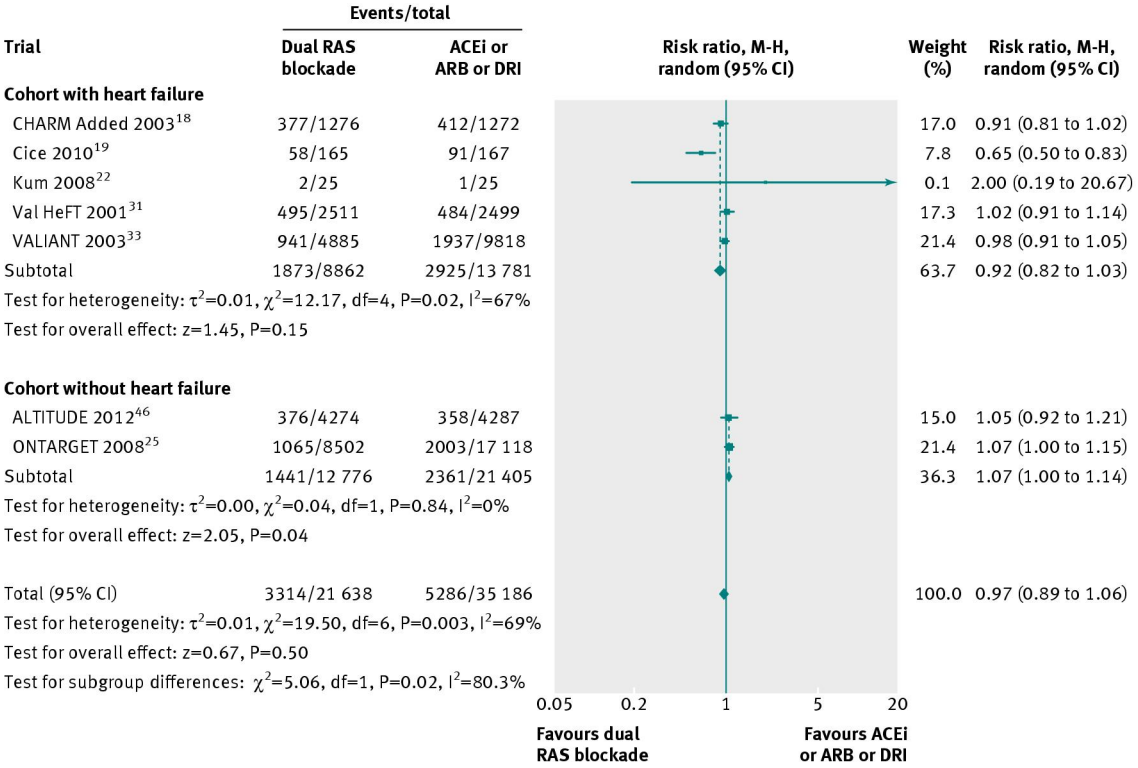

Fig 2 Comparison of dual blockade of the renin-angiotensin system (RAS) with monotherapy for all cause mortality. Error bars represent 95% confidence intervals and data marker sizes indicate sample sizes of cohorts. ACEi=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker; DRI=direct renin inhibitor, M-H=Mantel-Haenszel

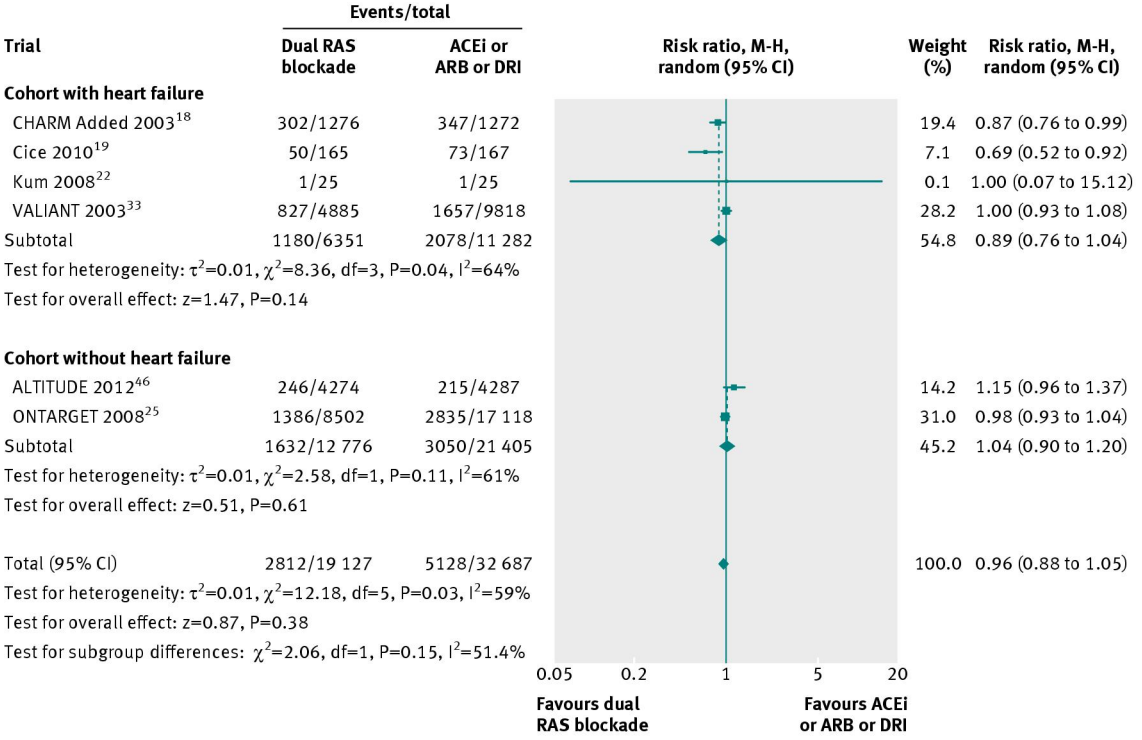

Fig 3 Comparison of dual blockade of the renin-angiotensin system (RAS) with monotherapy for cardiovascular mortality. ACEi=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker; DRI=direct renin inhibitor, M-H=Mantel-Haenszel

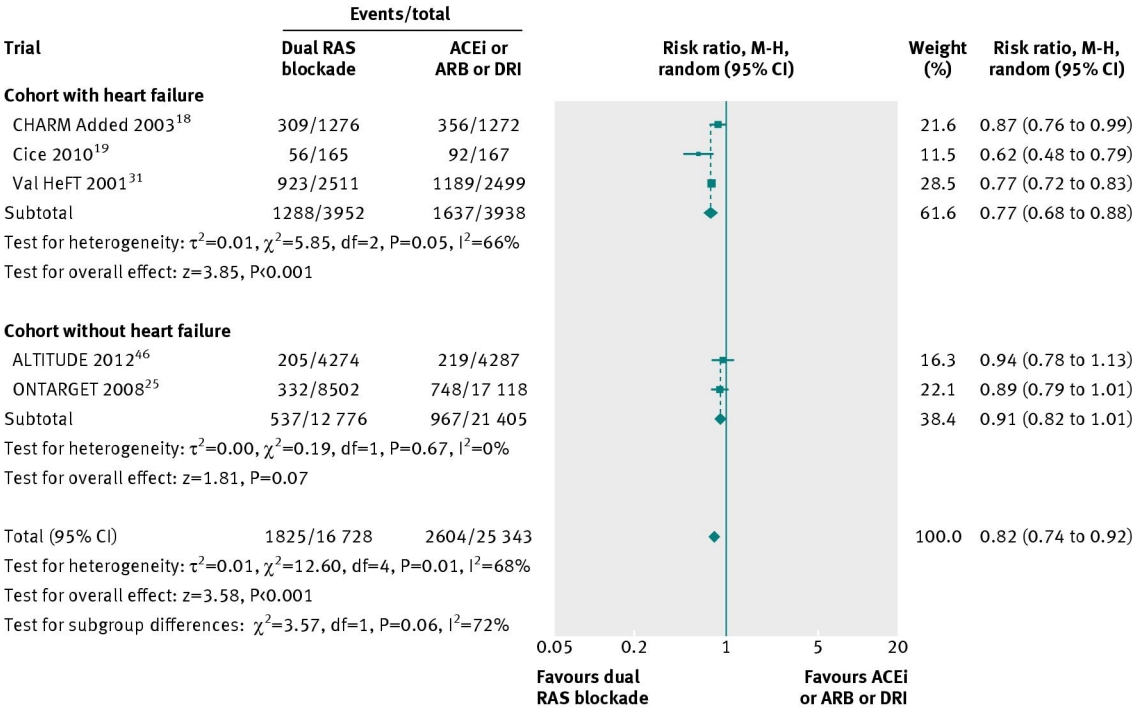

Fig 4 Comparison of dual blockade of the renin-angiotensin system (RAS) with monotherapy for admissions to hospital for heart failure. ACEi=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker; DRI=direct renin inhibitor, M-H=Mantel-Haenszel

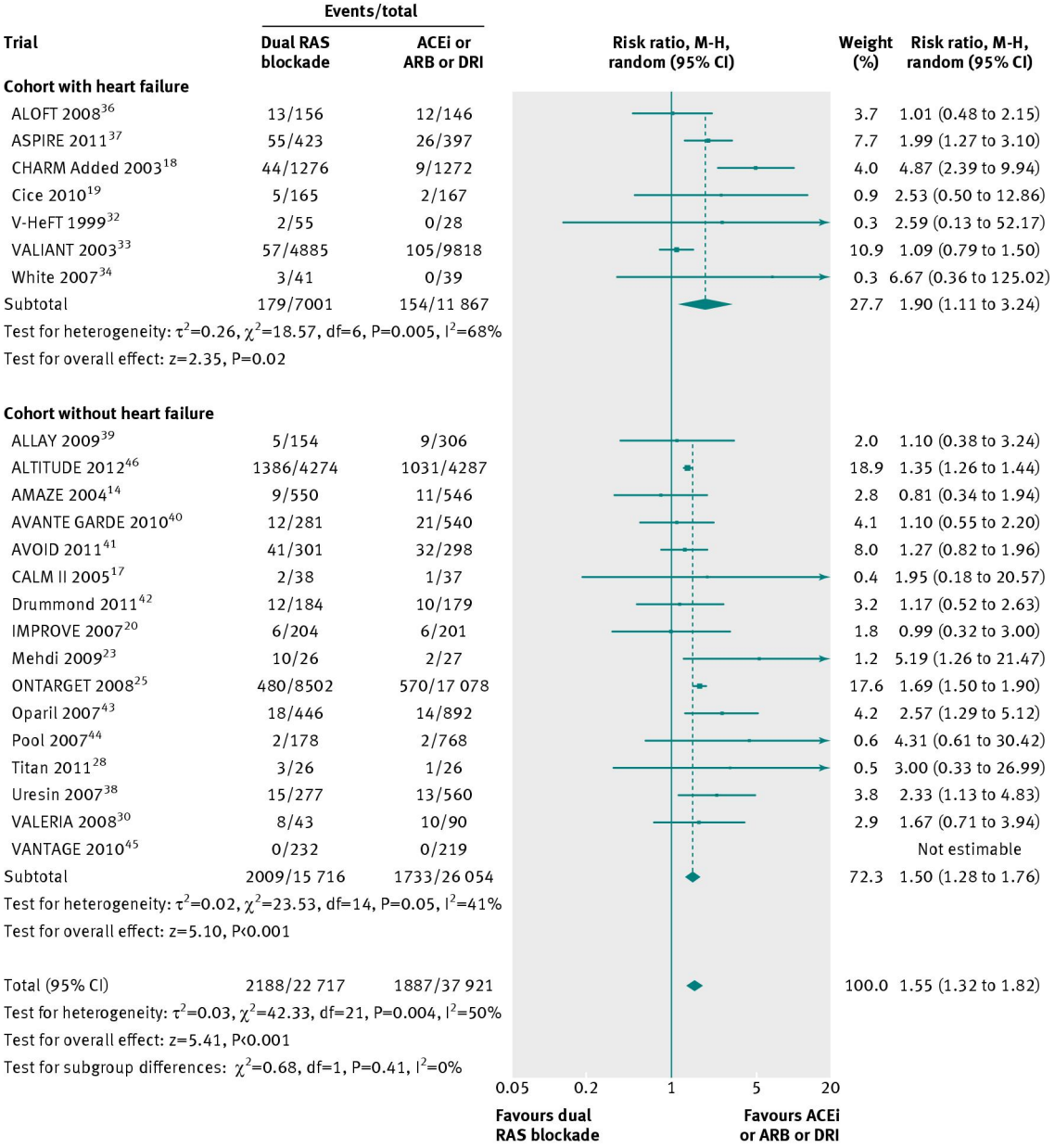

Fig 5 Comparison of dual blockade of the renin-angiotensin system (RAS) with monotherapy for hyperkalaemia. ACEi=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker; M-H=Mantel-Haenszel

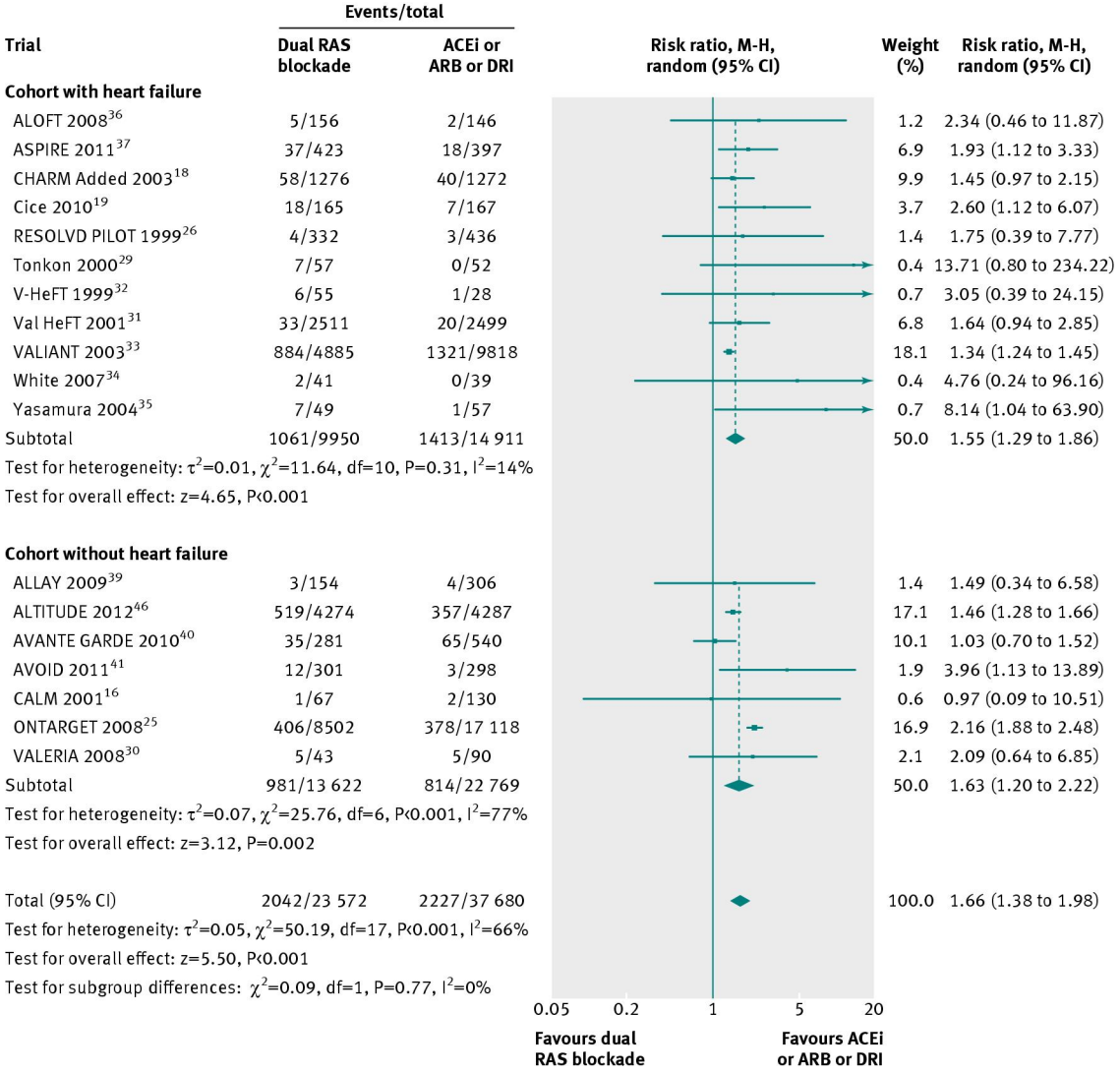

Fig 6 Comparison of dual blockade of the renin-angiotensin system (RAS) with monotherapy for hypotension, ACEi=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker; DRI=direct renin inhibitor, M-H=Mantel-Haenszel

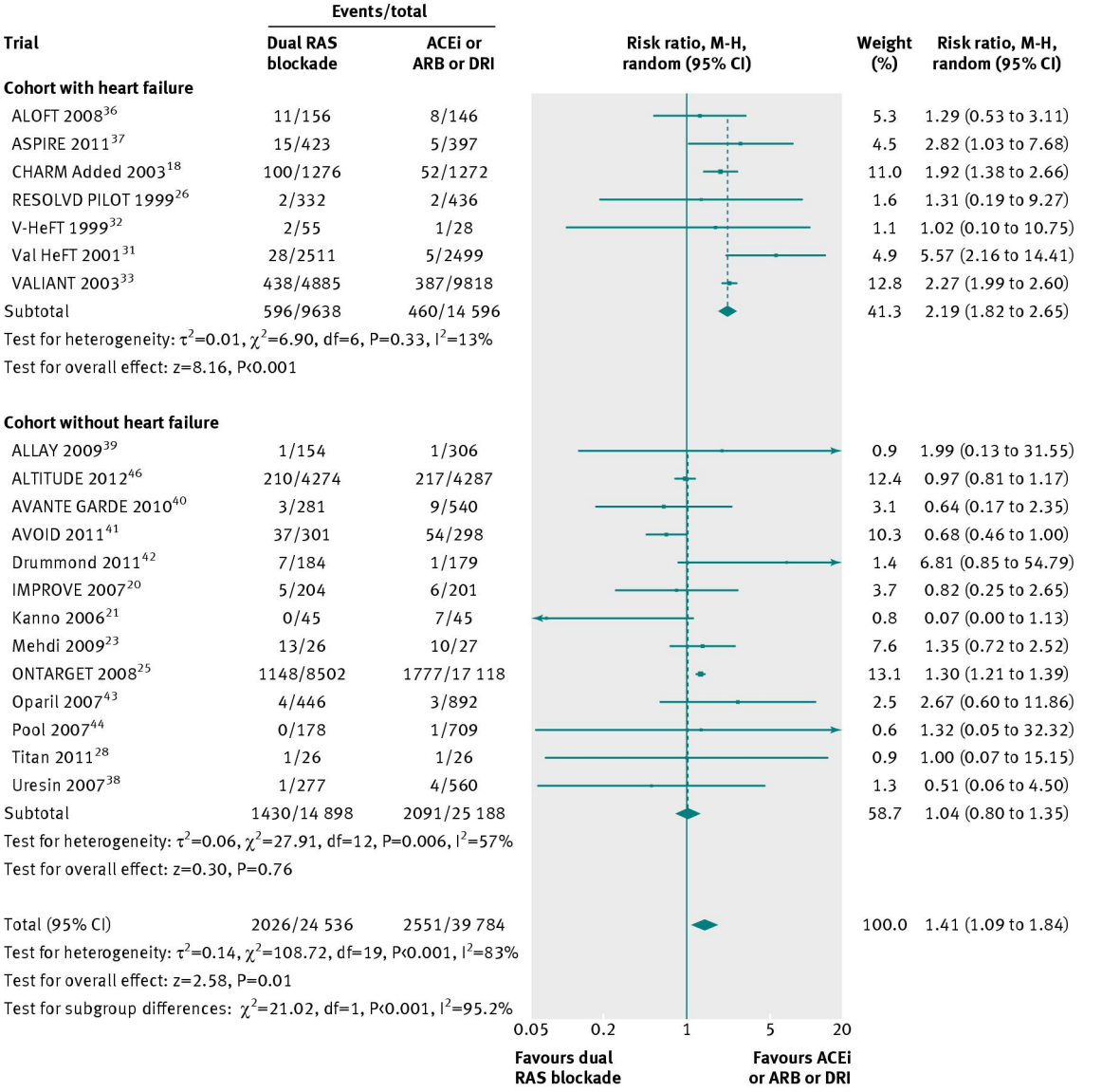

Fig 7 Comparison of dual blockade of the renin-angiotensin system (RAS) with monotherapy for renal failure. ACEi=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker; DRI=direct renin inhibitor, M-H=Mantel-Haenszel

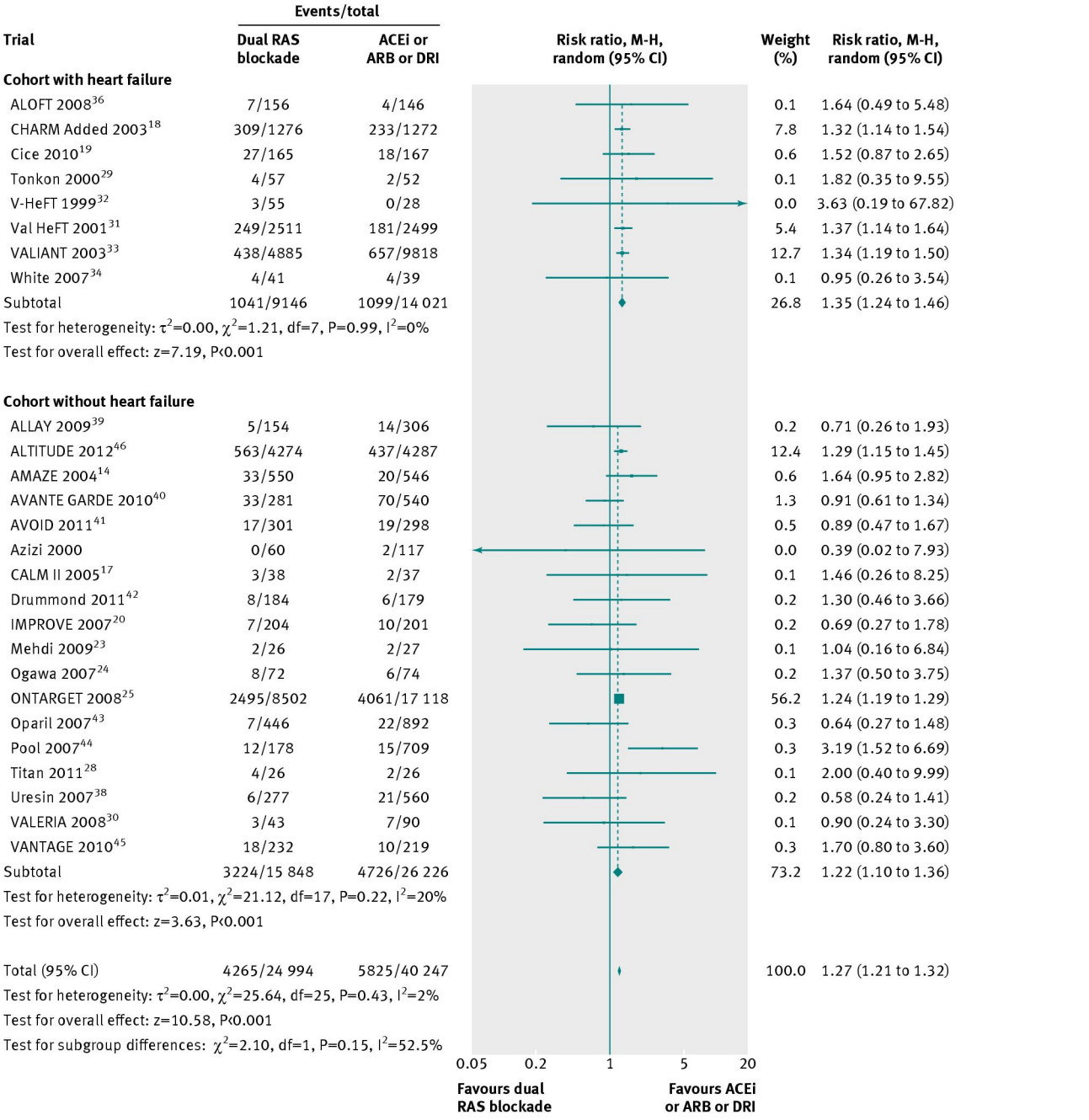

Fig 8 Comparison of dual blockade of the renin-angiotensin system (RAS) with monotherapy for withdrawal owing to drug related to adverse events