

## Supplementary Online Content

Makani H, Bangalore S, Desouza K, et al. Efficacy and Safety of Dual Renin-Angiotensin System Blockade – A Meta-Analysis of Randomized Trials.

**Table 1:** Details of MeSH search terms

**Table 2:** Sensitivity Analyses

**Figure 1. Forest plot showing risk of hyperkalemia comparing RAS blocker combination to monotherapy**

- A. Comparison of ACEi + ARB combination to ACEi monotherapy
- B. Comparison of ACEi + ARB combination to ARB monotherapy
- C. Comparison of ACEi + Aliskiren combination to ACEi monotherapy
- D. Comparison of ACEi + Aliskiren combination to Aliskiren monotherapy
- E. Comparison of ARB + Aliskiren combination to ARB monotherapy
- F. Comparison of ARB + Aliskiren combination to Aliskiren monotherapy

**Figure 2. Forest plot showing risk of hypotension comparing RAS blocker combination to monotherapy**

- A. Comparison of ACEi + ARB combination to ACEi monotherapy
- B. Comparison of ACEi + ARB combination to ARB monotherapy
- C. Comparison of ACEi + Aliskiren combination to ACEi monotherapy
- D. Comparison of ACEi + Aliskiren combination to Aliskiren monotherapy
- E. Comparison of ARB + Aliskiren combination to ARB monotherapy
- F. Comparison of ARB + Aliskiren combination to Aliskiren monotherapy

**Figure 3. Forest plot showing risk of renal failure comparing RAS blocker combination to monotherapy**

- A. Comparison of ACEi + ARB combination to ACEi monotherapy
- B. Comparison of ACEi + ARB combination to ARB monotherapy
- C. Comparison of ACEi + Aliskiren combination to ACEi monotherapy
- D. Comparison of ACEi + Aliskiren combination to Aliskiren monotherapy
- E. Comparison of ARB + Aliskiren combination to ARB monotherapy
- F. Comparison of ARB+ Aliskiren combination to Aliskiren monotherapy

**Figure 4. Forest plot showing risk of withdrawal due to DRAE comparing RAS blocker combination to monotherapy**

- A. Comparison of ACEi + ARB combination to ACEi monotherapy
- B. Comparison of ACEi + ARB combination to ARB monotherapy
- C. Comparison of ACEi + Aliskiren combination to ACEi monotherapy
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- E. Comparison of ARB + Aliskiren combination to ARB monotherapy
- F. Comparison of ARB+ Aliskiren combination to Aliskiren monotherapy

**Figure 5. Funnel plot showing relationship between log risk ratio and standard error of relative risk for comparison of RAS blocker combination to monotherapy**

- A. All-cause mortality
- B. Cardiovascular mortality
- C. Heart failure hospitalization
- D. Hyperkalemia
- E. Symptomatic hypotension
- F. Renal failure
- G. Withdrawal due to DRAE

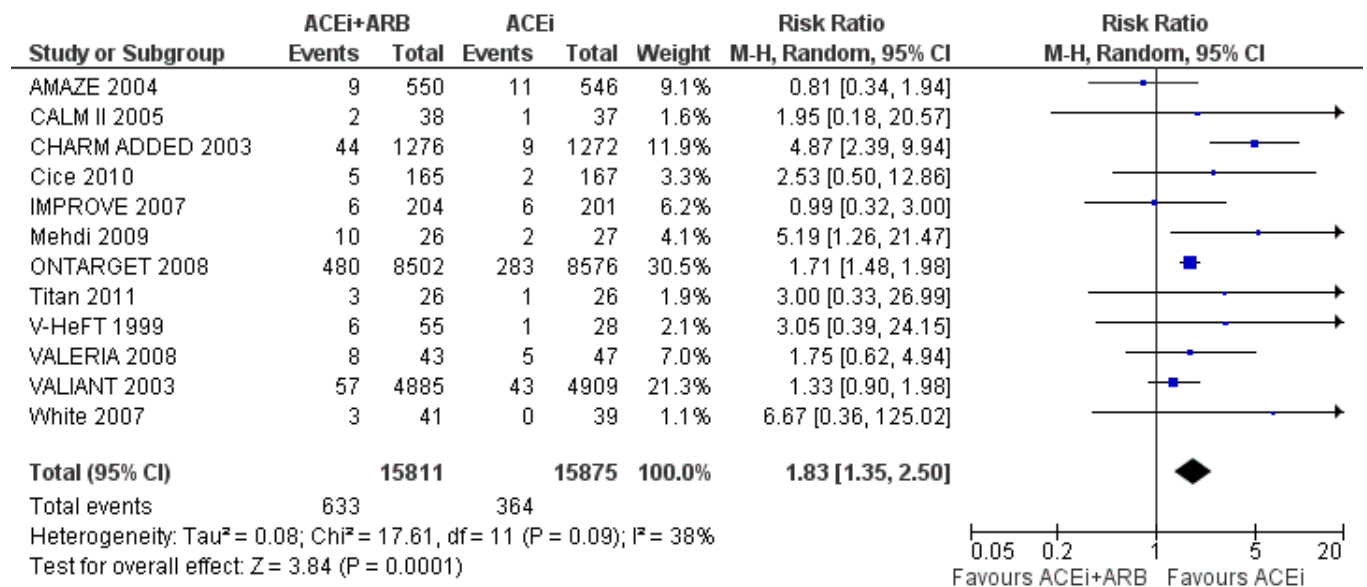
**Table 1.** Details of MeSH Search Terms

<b>Category</b>	<b>MeSH terms</b>
Angiotensin Converting Enzyme Inhibitor (ACEi)	Randomized controlled trial, Human, Angiotensin converting enzyme inhibitor, Angiotensin converting enzyme inhibitors, Benazepril, Captopril, Enalapril, Cilazapril, Delapril, Fosinopril, Imidapril, Lisinopril, Moexipril, Perindopril, Quinapril, Ramipril, Spirapril, Temocapril, Trandolapril, Zofenopril
Angiotensin Receptor Blocker (ARB)	Randomized controlled trial, Human, Angiotensin receptor blocker, Angiotensin receptor blockers, Angiotensin receptor antagonist, Angiotensin receptor antagonists, Angiotensin II receptor antagonist, Angiotensin II receptor blocker, Candesartan, Irbesartan, Losartan, Telmisartan, Valsartan, Olmesartan, Eprosartan
Direct Renin Inhibitors (DRI)	Randomized controlled trial, Human, Direct renin inhibitors, DRI, Aliskiren

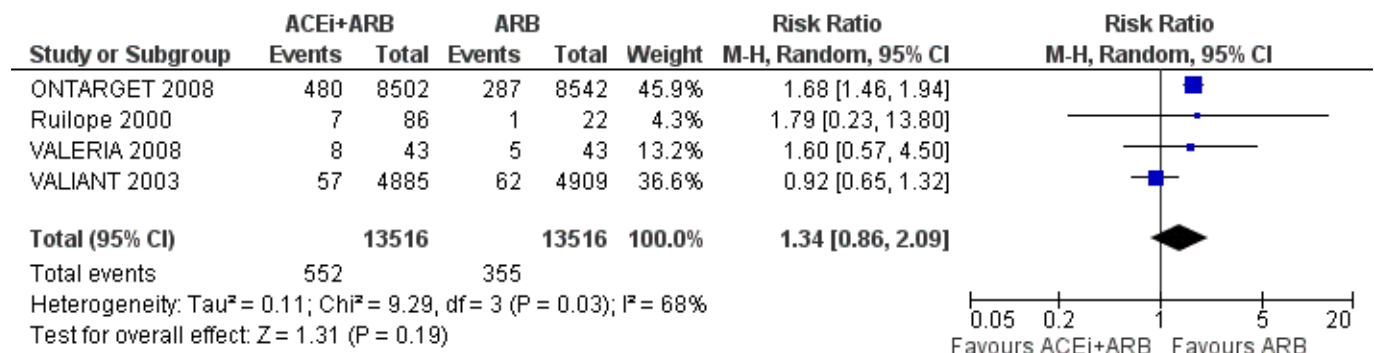
**Table 2. Sensitivity Analyses**

<b>Dual RAS blockade vs. Monotherapy</b>	<b>No. of studies</b>	<b>No. of patients</b>	<b>Relative risk (95% CI)</b>	<b>P Value</b>	<b>Interaction p-value</b>
<b>Hyperkalemia</b>					
HF cohort	7	18868	1.9 (1.1-3.2)	0.02	0.41
Non-HF cohort	16	41770	1.5 (1.3-1.8)	<0.00001	
<b>Risk of bias</b>					
Low	15	58343	1.6 (1.3-1.9)	<0.00001	1.00
High	8	2295	1.6 (0.8-3.0)	0.16	
<b>Duration</b>					
< 1 year	17	8831	1.6 (1.3-1.9)	<0.0001	1.00
≥ 1 year	6	51807	1.6 (1.3-2.0)	0.0001	
<b>No. of pts</b>					
< 500	12	2789	1.5 (1.01-2.1)	0.04	0.76
≥ 500	11	57849	1.6 (1.3-1.9)	<0.00001	
<b>Hypotension</b>					
HF cohort	11	24861	1.6 (1.3-1.9)	<0.00001	0.73
Non-HF cohort	7	36391	1.7 (1.2-2.1)	0.008	
<b>Risk of bias</b>					
Low	13	60677	1.6 (1.4-2.0)	<0.0001	0.09
High	5	575	4.1 (1.4-11.9)	0.009	
<b>Duration</b>					
< 1 year	11	3710	1.9 (1.3-2.9)	0.003	0.63
≥ 1 year	7	57542	1.7 (1.3-2.0)	<0.0001	
<b>No. of pts</b>					
< 500	9	1802	2.6 (1.5-4.3)	0.0003	0.09
≥ 500	9	59450	1.6 (1.3-1.9)	<0.00001	
<b>Renal failure</b>					
HF cohort	7	24234	2.2 (1.8-2.7)	<0.00001	<0.0001
Non-HF cohort	13	40086	1.04 (0.8-1.4)	0.79	
<b>Risk of bias</b>					
Low	15	62959	1.5 (1.1-2.0)	0.01	0.45
High	5	1361	1.2 (0.7-2.0)	0.49	
<b>Duration</b>					
< 1 year	14	7110	1.1 (0.8-1.7)	0.57	0.10
≥ 1 year	6	57210	1.7 (1.2-2.4)	0.003	
<b>No. of pts</b>					
< 500	9	2695	1.2 (0.8-1.9)	0.33	0.40
≥ 500	11	61625	1.5 (1.1-2.0)	0.01	
<b>Withdrawal due to DRAE</b>					
HF cohort	8	23167	1.4 (1.2-1.5)	<0.00001	0.22
Non-HF cohort	17	33513	1.2 (0.9-1.4)	0.12	
<b>Risk of bias</b>					
Low	14	53953	1.3 (1.2-1.4)	<0.00001	0.66
High	11	2727	1.4 (1.01-1.9)	0.04	
<b>Duration</b>					
< 1 year	19	8392	1.1 (0.9-1.4)	0.26	0.24
≥ 1 year	6	48288	1.26 (1.2-1.3)	<0.00001	
<b>No. of pts</b>					
< 500	15	3221	1.3 (0.96-1.7)	0.10	1.00
≥ 500	10	53459	1.3 (1.1-1.4)	<0.00001	

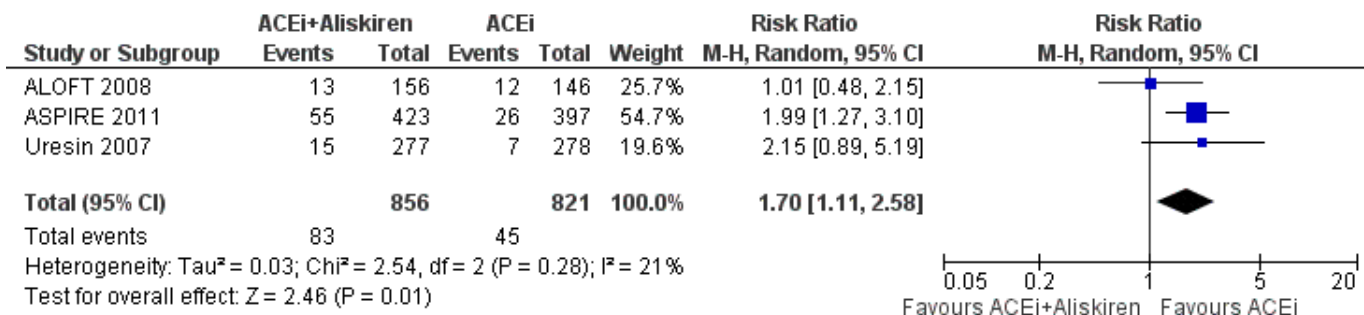
**Figure 1A. Risk of hyperkalemia comparing ACEi+ARB vs. ACEi**



**Figure 1B. Risk of hyperkalemia comparing ACEi+ARB vs. ARB**



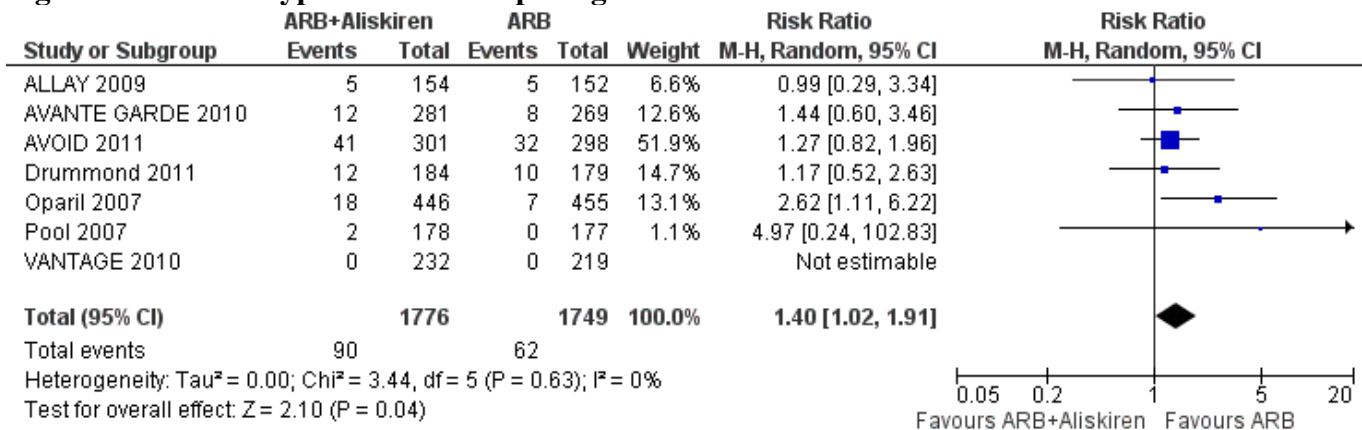
**Figure 1C. Risk of hyperkalemia comparing ACEi+Aliskiren vs. ACEi**



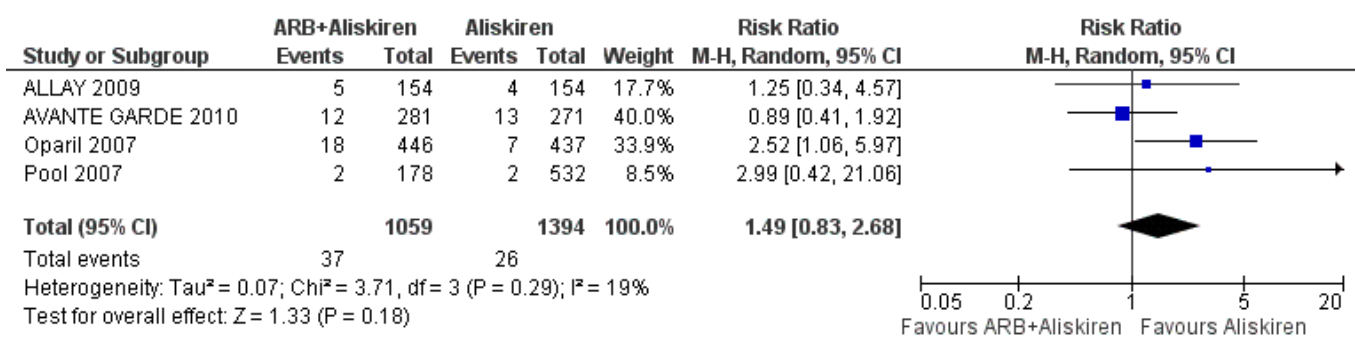
**Figure 1D. Risk of hyperkalemia comparing ACEi+Aliskiren vs. Aliskiren**



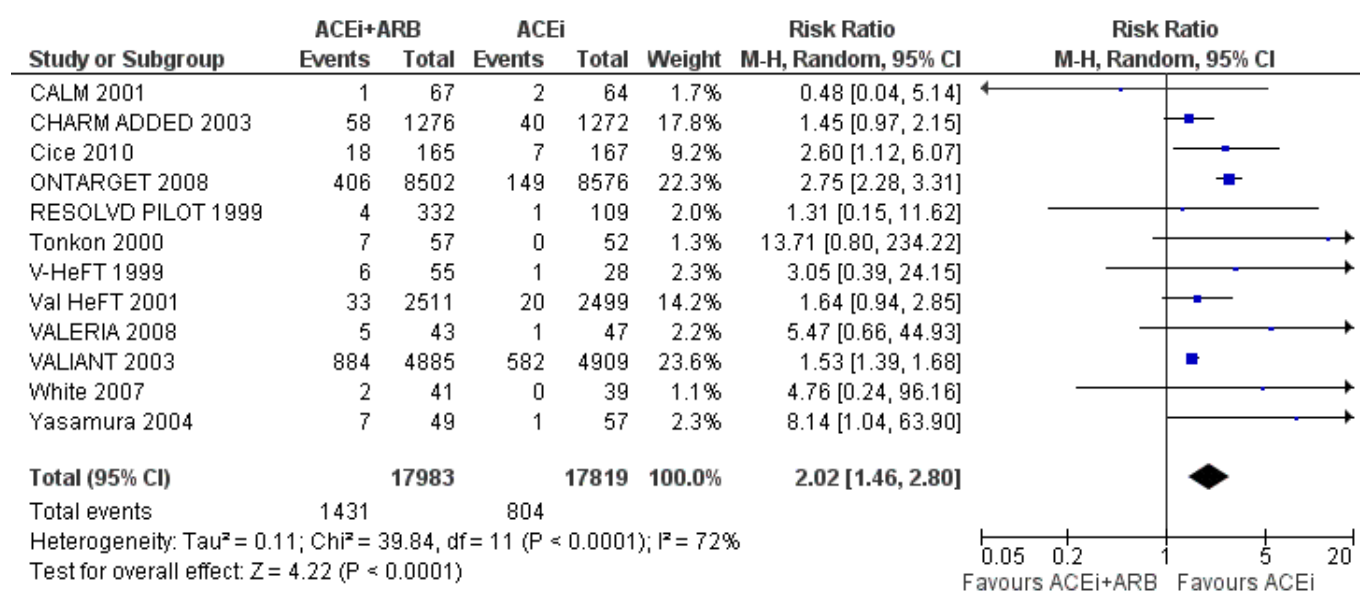
**Figure 1E. Risk of hyperkalemia comparing ARB+Aliskiren vs. ARB**



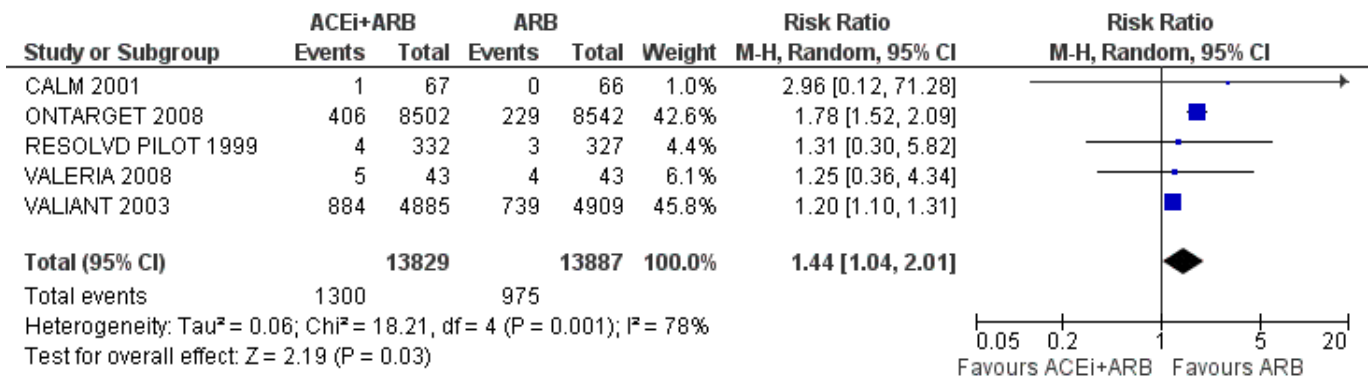
**Figure 1F. Risk of hyperkalemia comparing ARB+Aliskiren vs. Aliskiren**



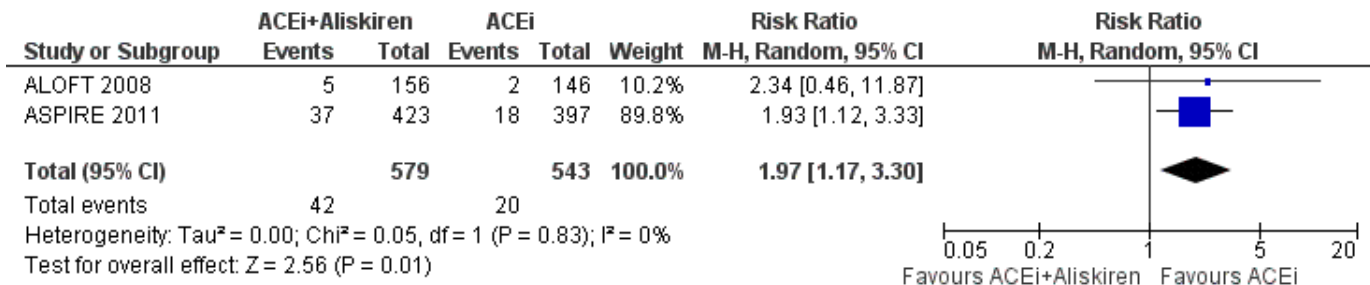
**Figure 2A. Risk of hypotension comparing ACEi+ARB vs. ACEi**



**Figure 2B. Risk of hypotension comparing ACEi+ARB vs. ARB**



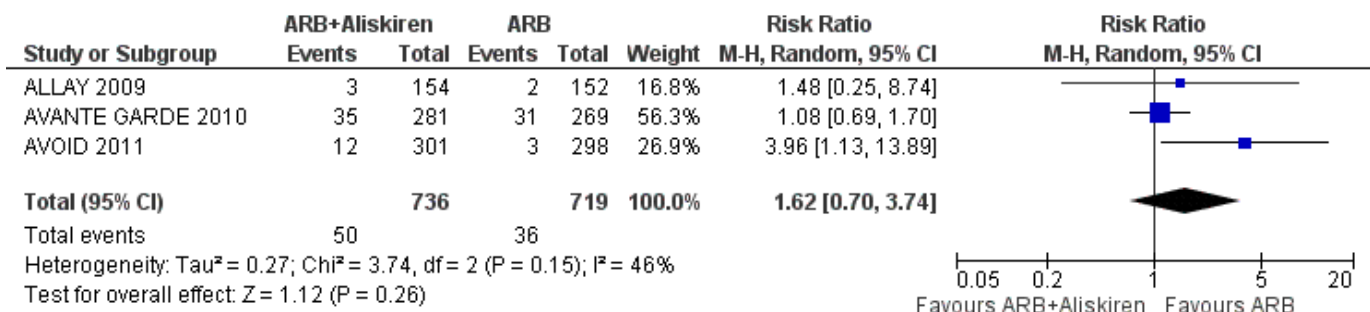
**Figure 2C. Risk of hypotension comparing ACEi+Aliskiren vs. ACEi**



**Figure 2D. Risk of hypotension comparing ACEi+Aliskiren vs. Aliskiren**

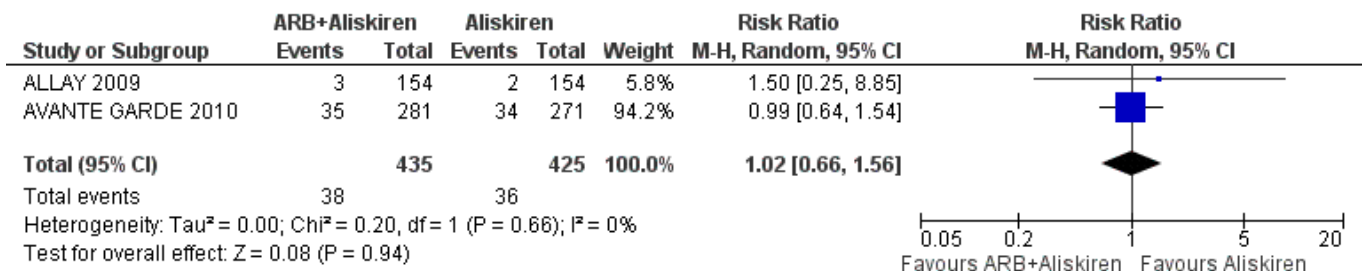
No studies available.

**Figure 2E. Risk of hypotension comparing ARB+Aliskiren vs. ARB**

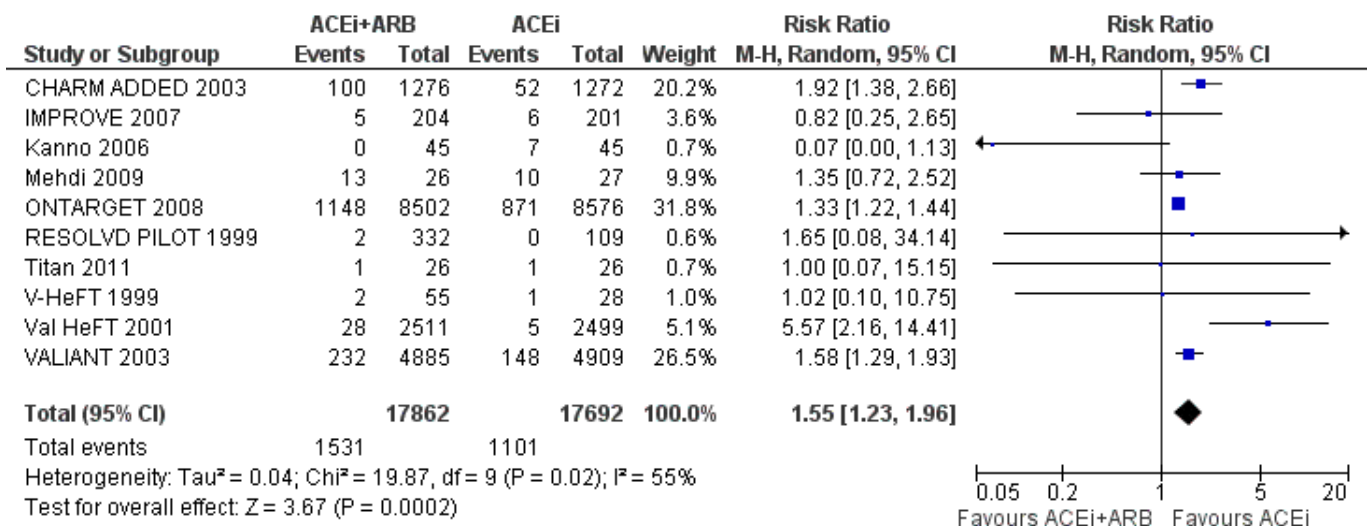


**Figure 2F. Risk of hypotension comparing ARB+Aliskiren vs. Aliskiren**

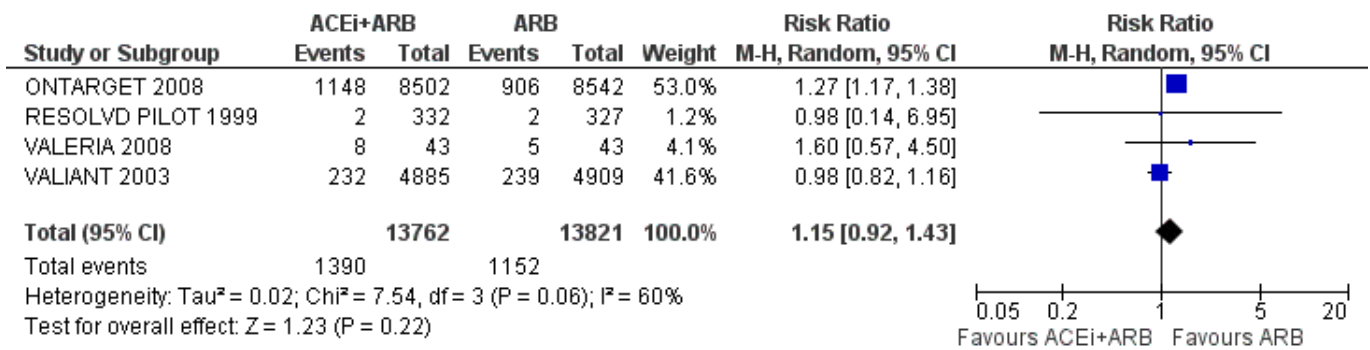




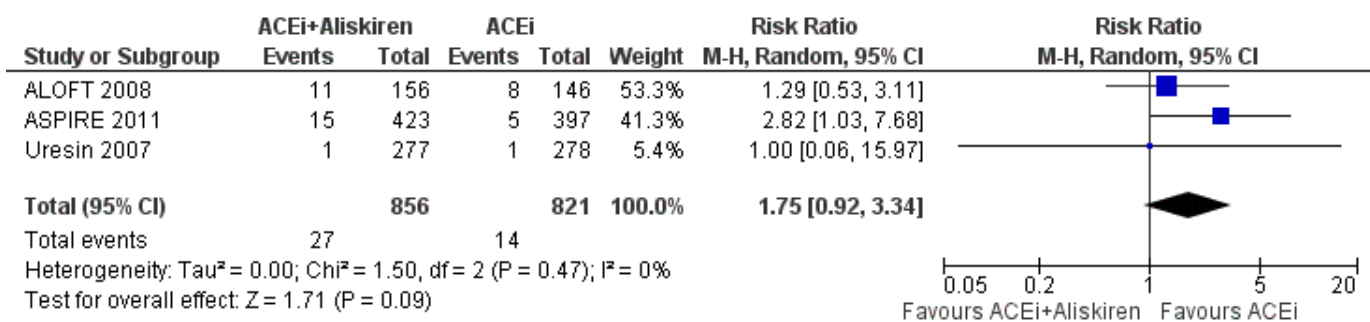
**Figure 3A. Risk of renal failure comparing ACEi+ARB vs. ACEi**



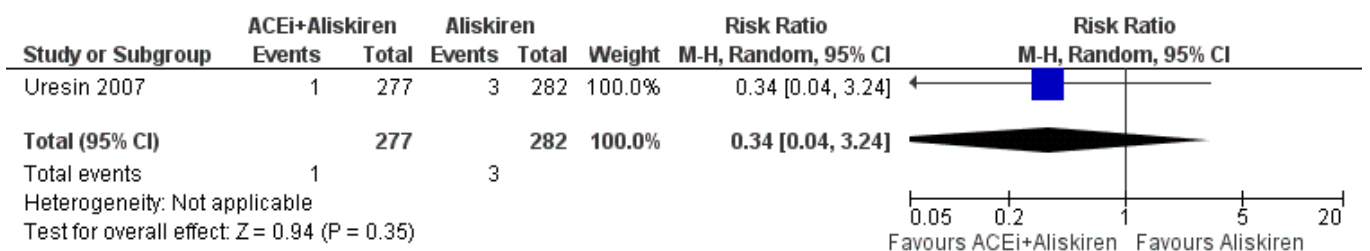
**Figure 3B. Risk of renal failure comparing ACEi+ARB vs. ARB**



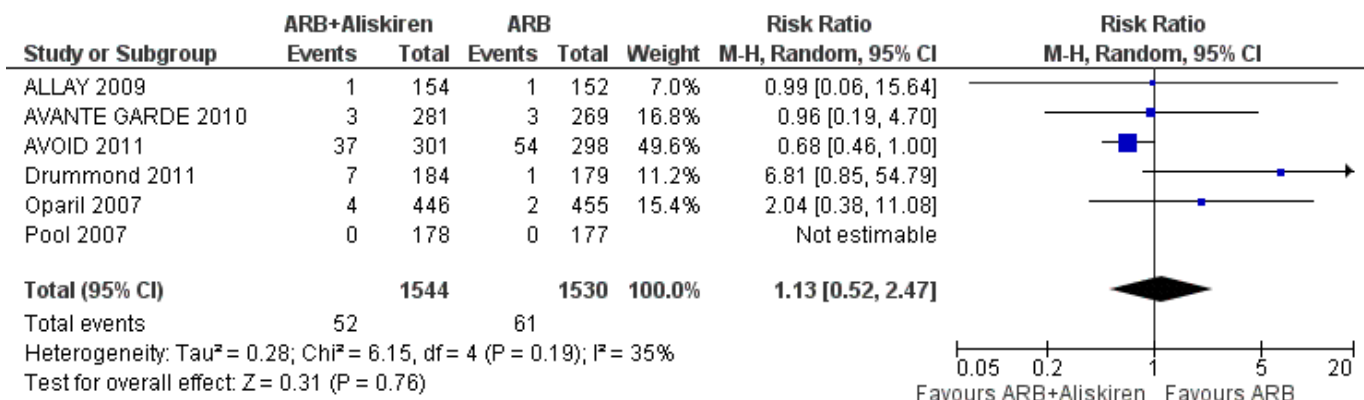
**Figure 3C. Risk of renal failure comparing ACEi+Aliskiren vs. ACEi**



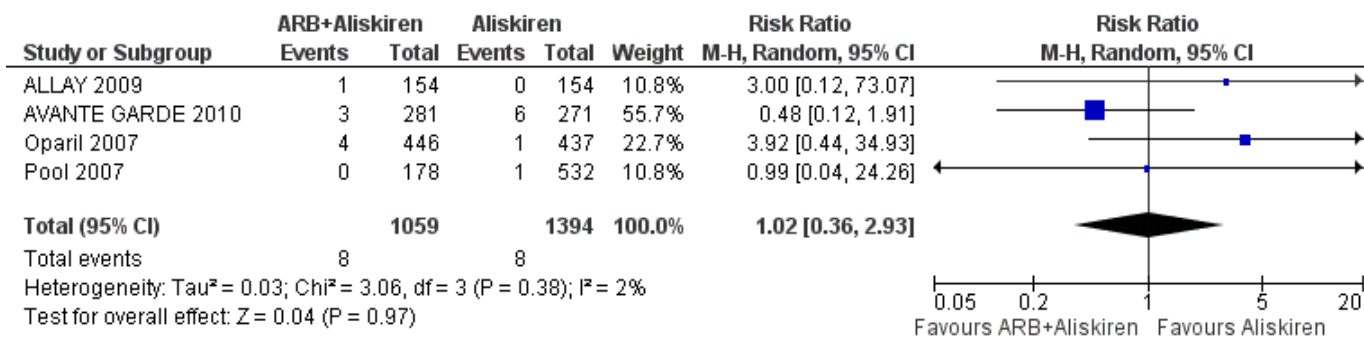
**Figure 3D. Risk of renal failure comparing ACEi+Aliskiren vs. Aliskiren**



**Figure 3E. Risk of renal failure comparing ARB+Aliskiren vs. ARB**



**Figure 3F. Risk of renal failure comparing ARB+Aliskiren vs. Aliskiren**



**Figure 4A. Risk of withdrawal due to DRAE comparing ACEi+ARB vs. ACEi**

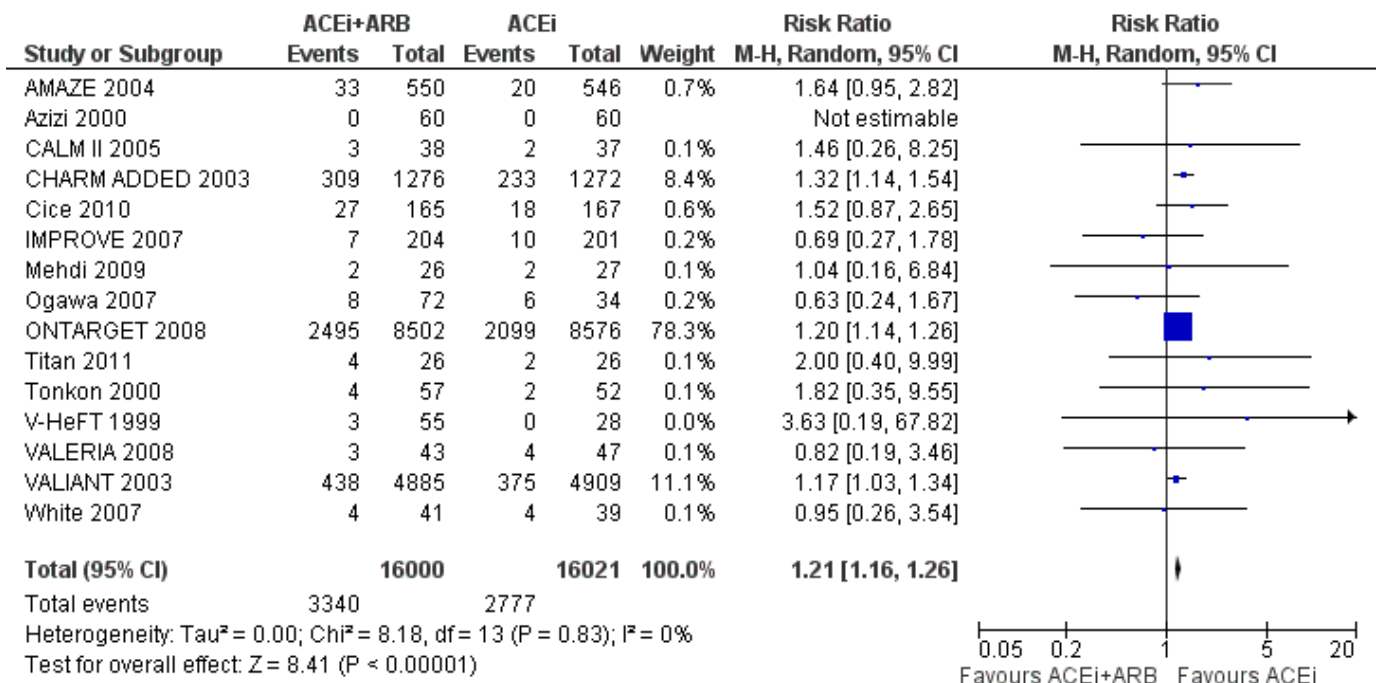


Figure 4B. Risk of withdrawal due to DRAE comparing ACEi+ARB vs. ARB

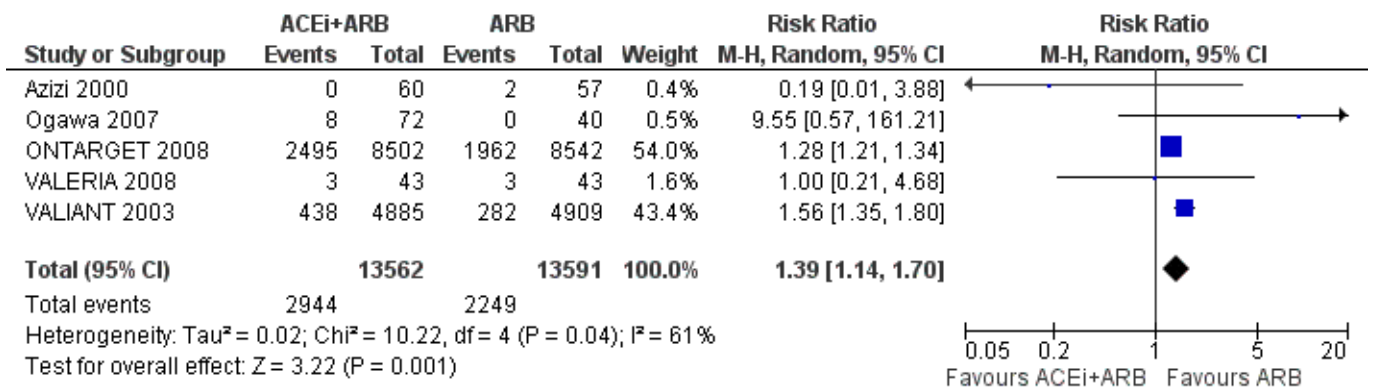


Figure 4C. Risk of withdrawal due to DRAE comparing ACEi+Aliskiren vs. ACEi

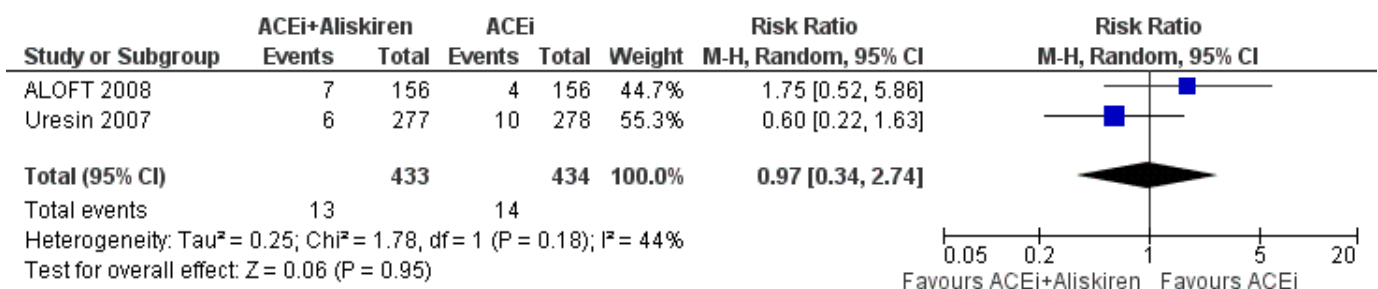


Figure 4D. Risk of withdrawal due to DRAE comparing ACEi+Aliskiren vs. Aliskiren

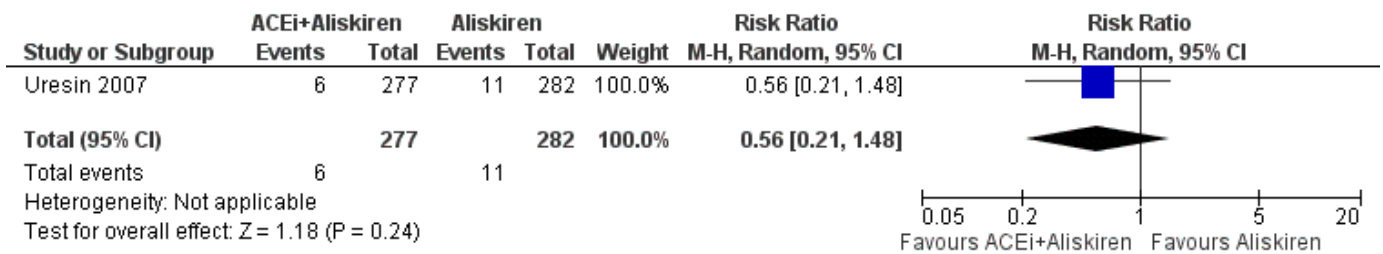


Figure 4E. Risk of withdrawal due to DRAE comparing ARB+Aliskiren vs. ARB

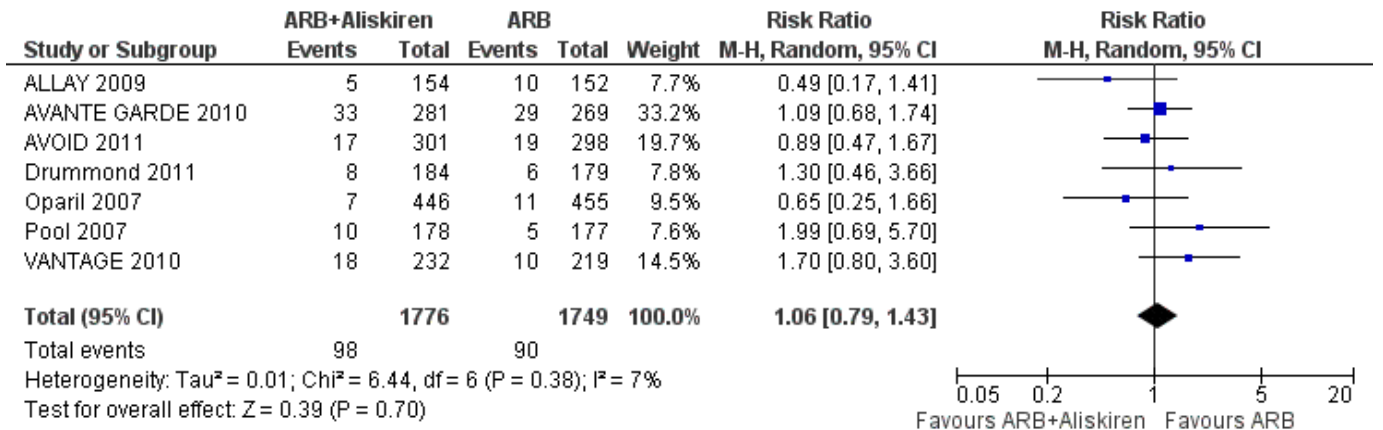
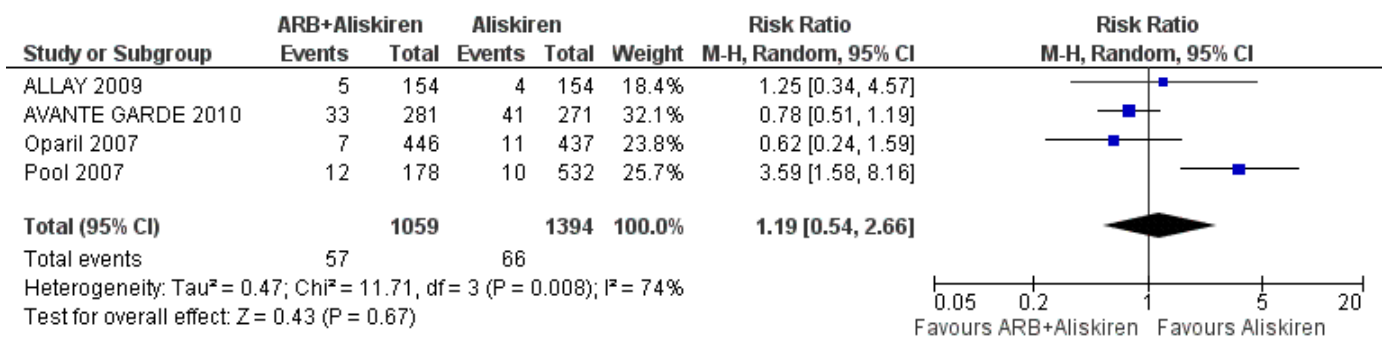
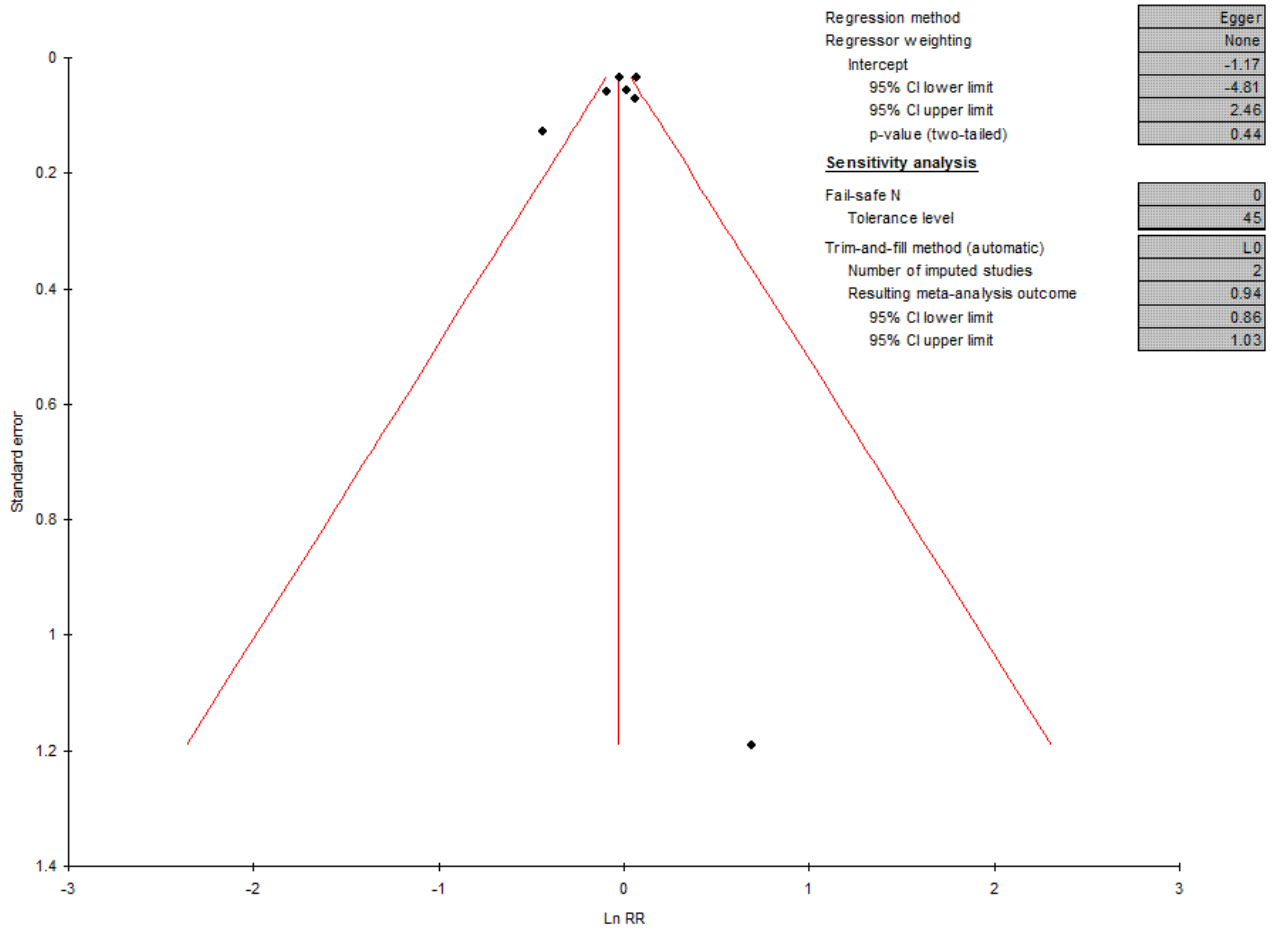


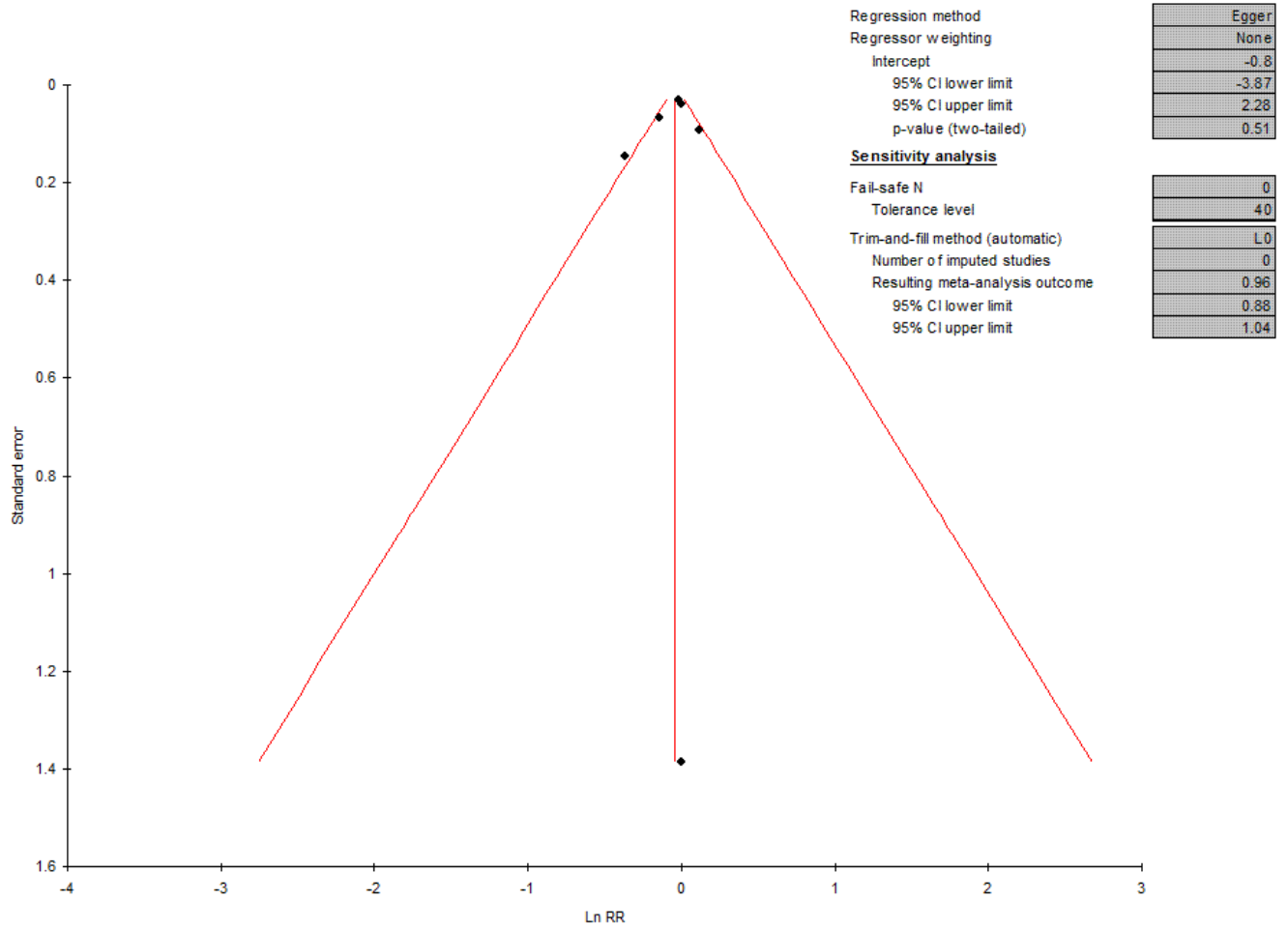
Figure 4F. Risk of withdrawal due to DRAE comparing ARB+Aliskiren vs. Aliskiren



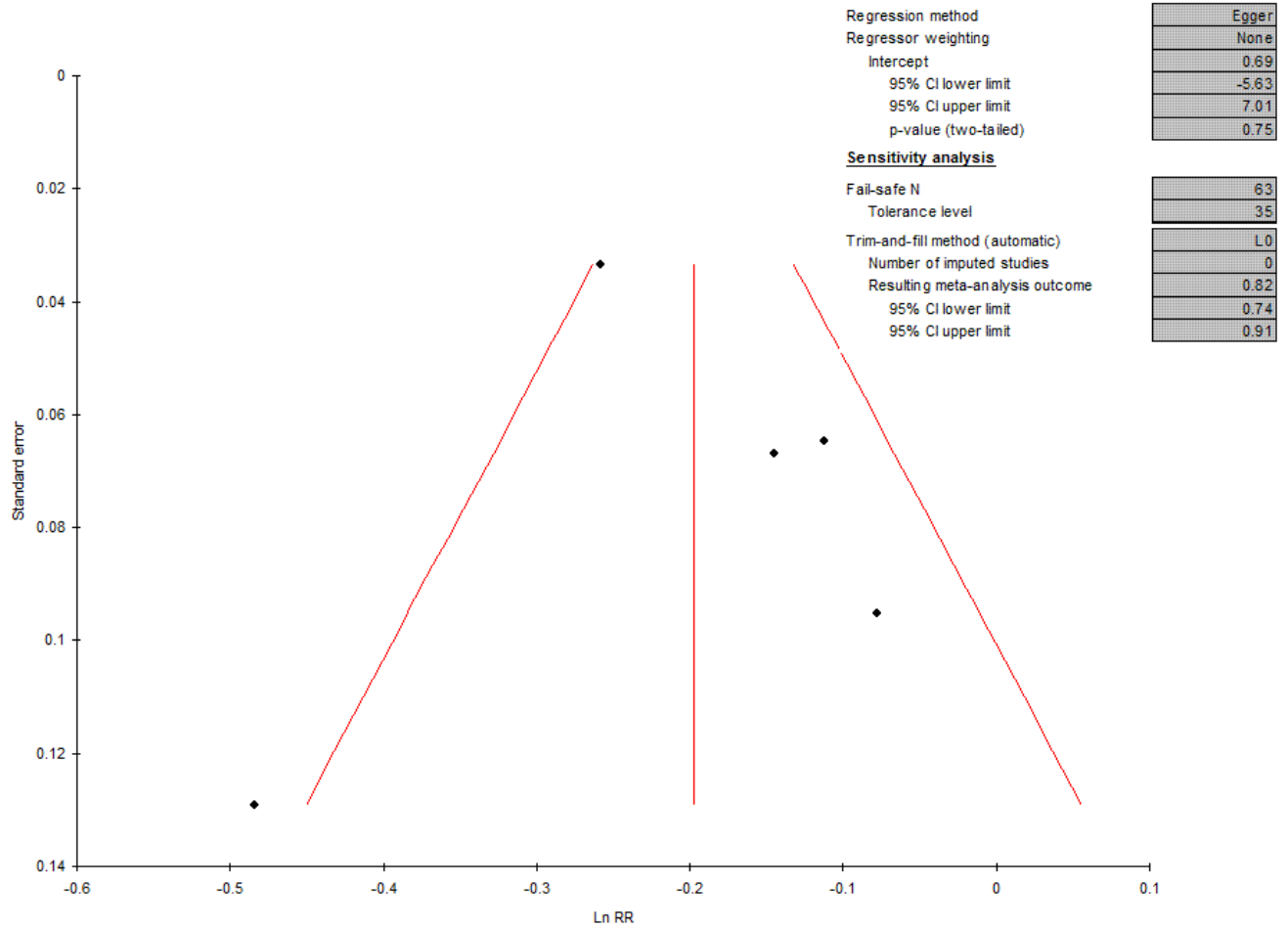
**Figure 5A. Funnel plot comparing RAS blocker combination to monotherapy for All-cause mortality**



**Figure 5B. Funnel plot comparing RAS blocker combination to monotherapy for Cardiovascular mortality**

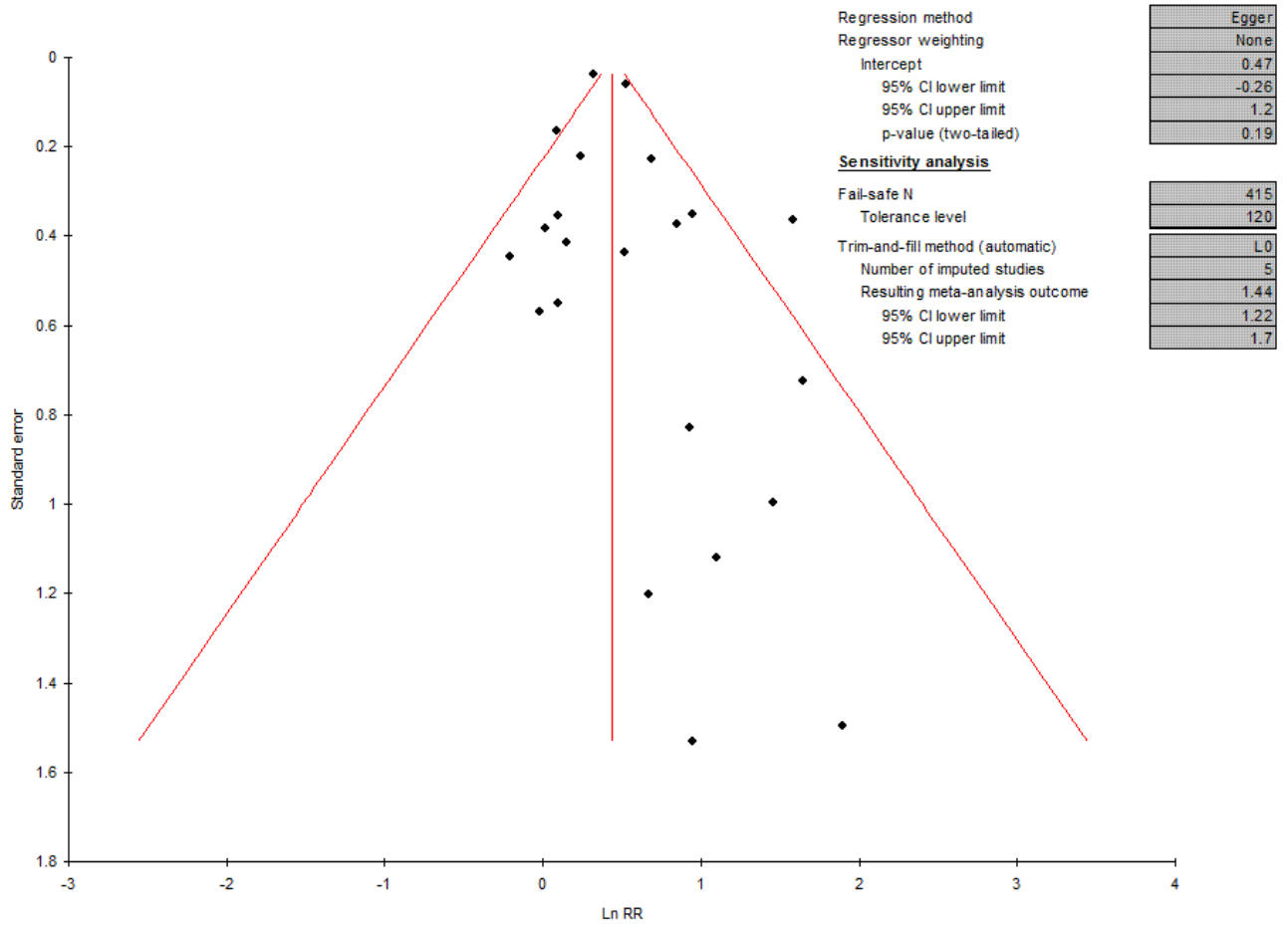


**Figure 5C. Funnel plot comparing RAS blocker combination to monotherapy for Heart failure hospitalization**

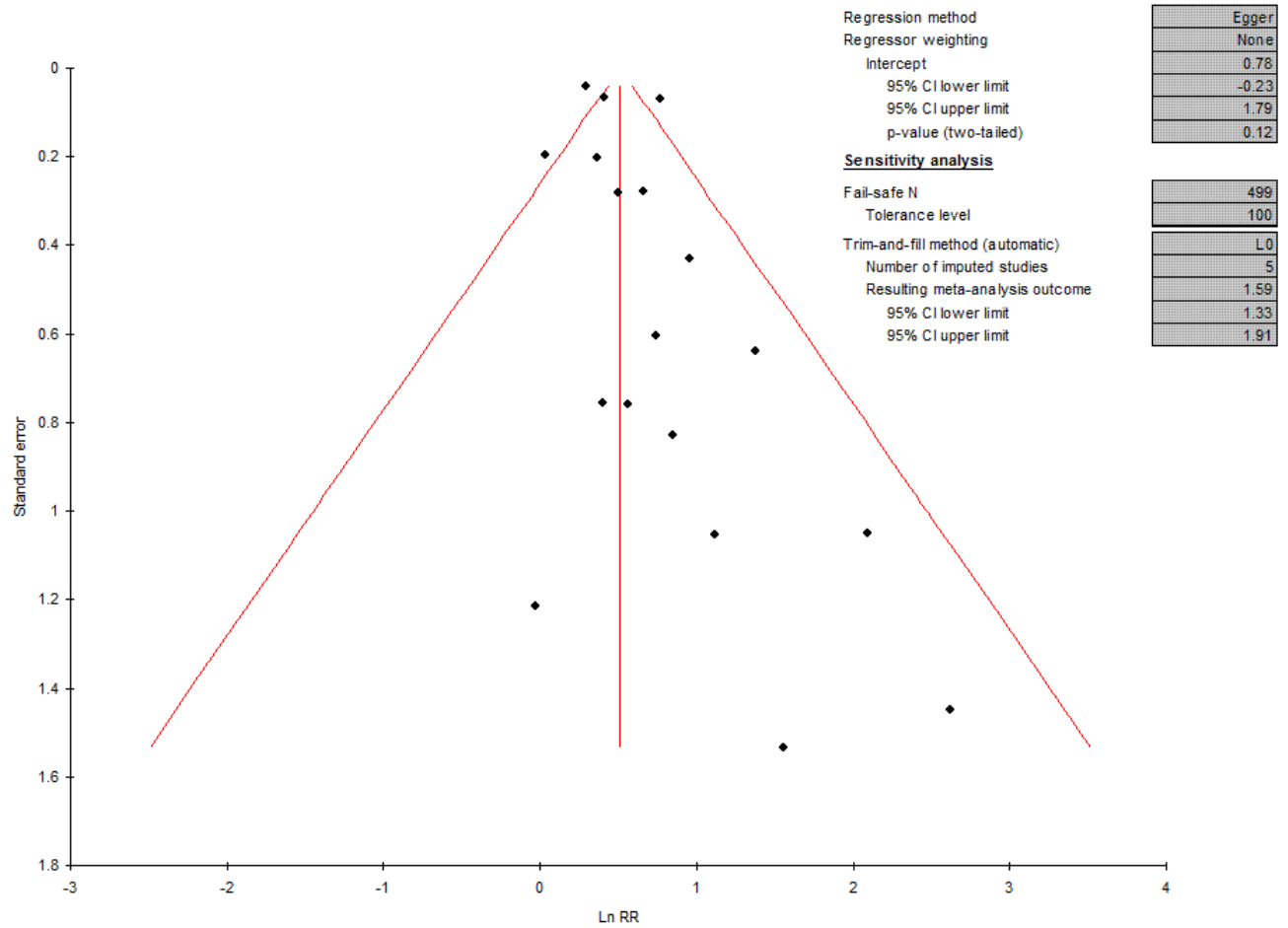




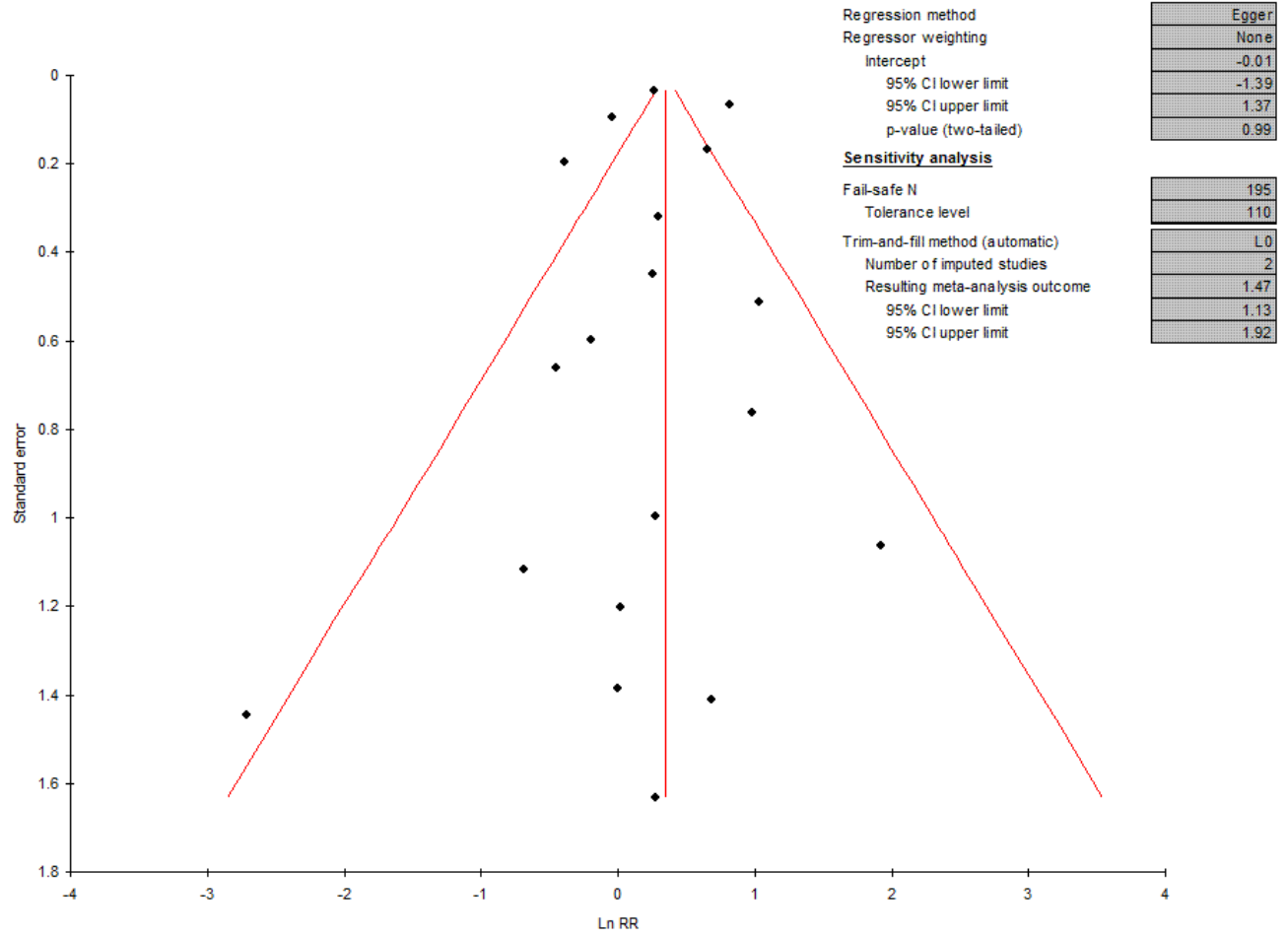
**Figure 5D. Funnel plot comparing RAS blocker combination to monotherapy for hyperkalemia**



**Figure 5E. Funnel plot comparing RAS blocker combination to monotherapy for hypotension**



**Figure 5F. Funnel plot comparing RAS blocker combination to monotherapy for renal failure**



**Figure 5G. Funnel plot comparing RAS blocker combination to monotherapy for Withdrawal due to DRAE**

