

Supplementary Appendix

Should Diabetes Mellitus be a Compelling Indication for Renin Angiotensin System Blockers?

Insights from a Systematic Review and Meta-Analysis of Randomized Trials

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This appendix has been provided by the authors to give readers additional information about their work.

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Figure S1. Study selection

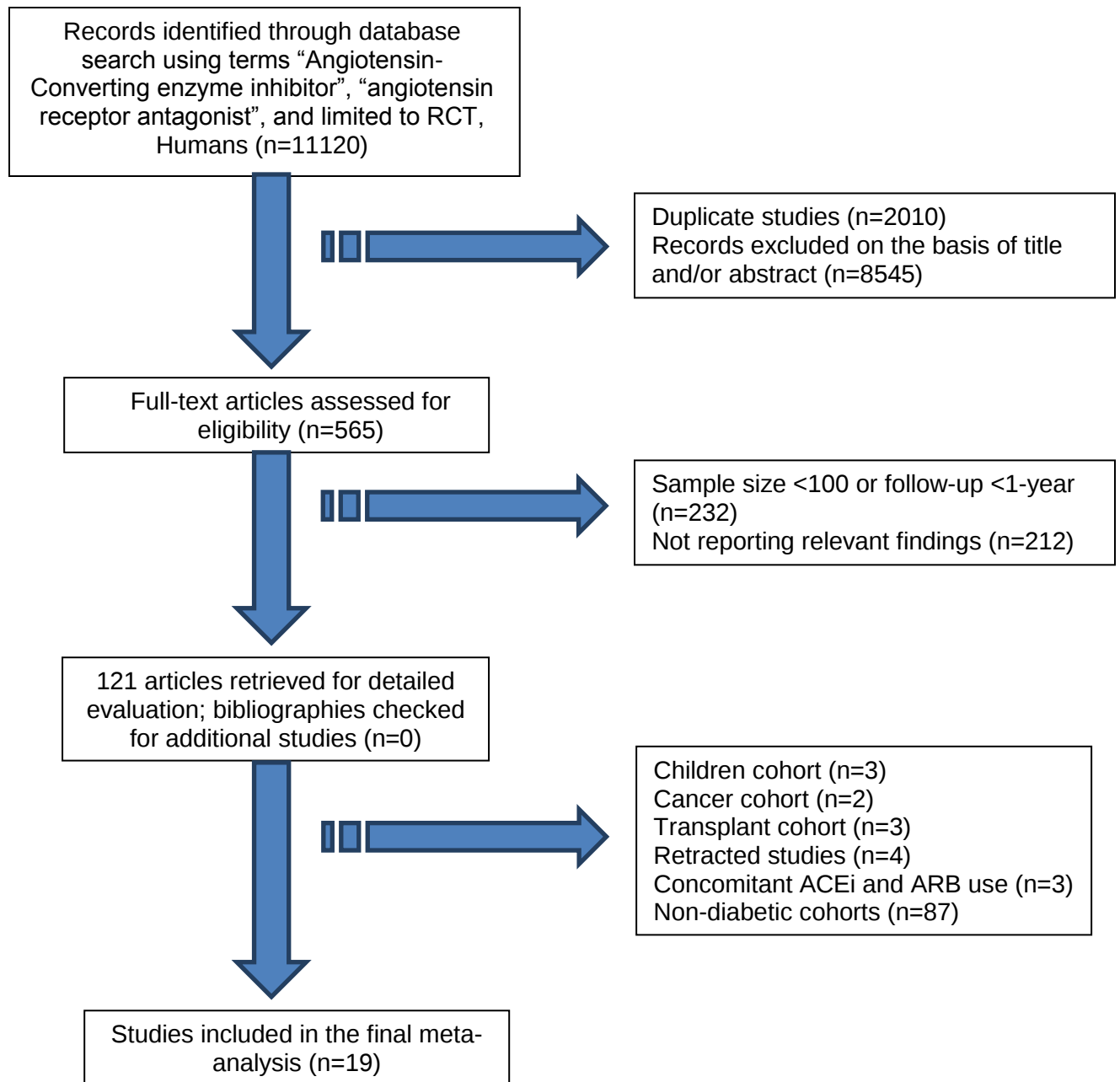


Figure S2. Funnel Plot: RAS blockers versus other antihypertensive agents for the outcome of death

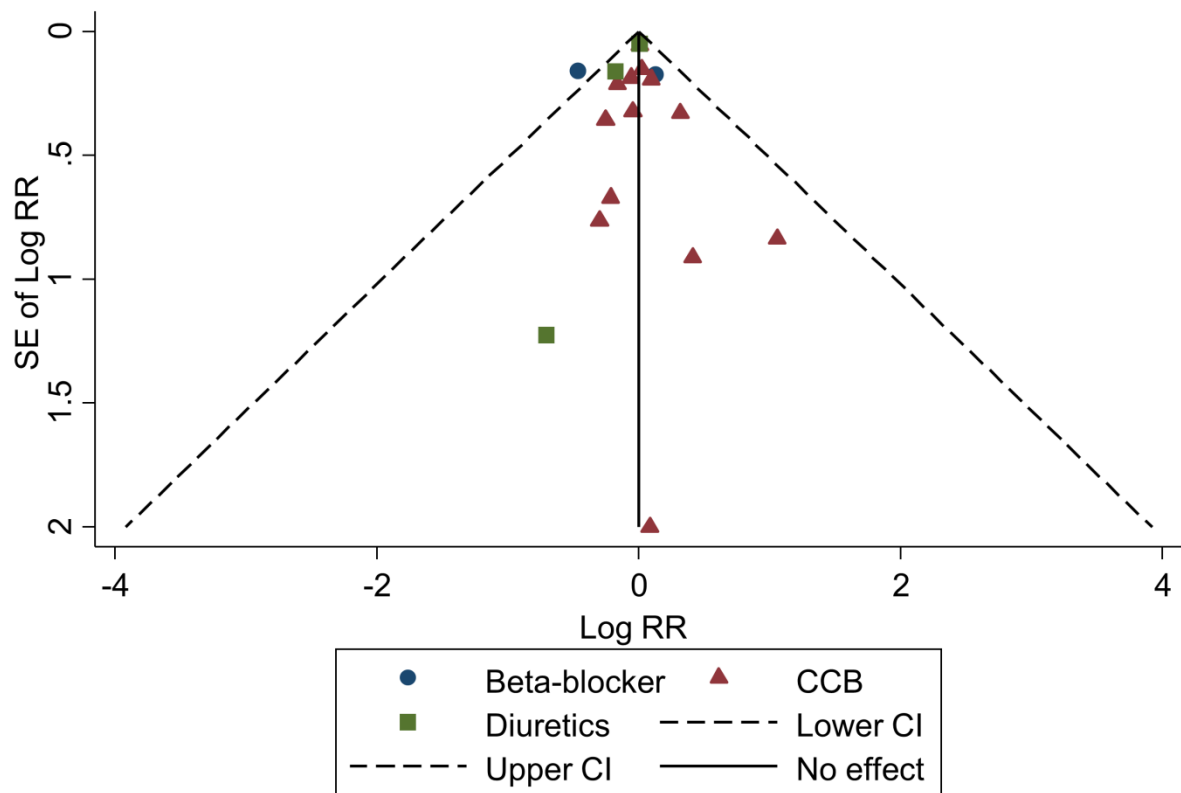


Figure S3. Funnel Plot: RAS blockers versus other antihypertensive agents for the outcome of cardiovascular death

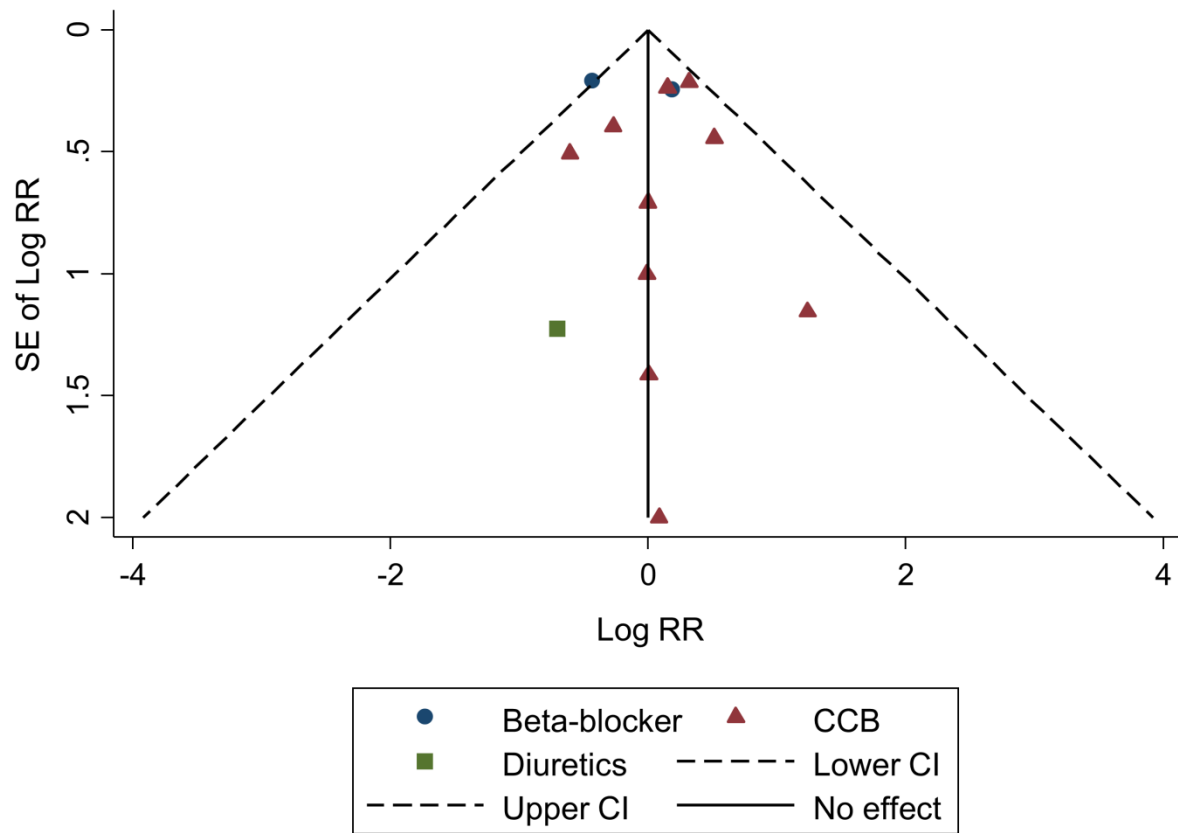


Figure S4. Funnel Plot: RAS blockers versus other antihypertensive agents for the outcome of myocardial infarction

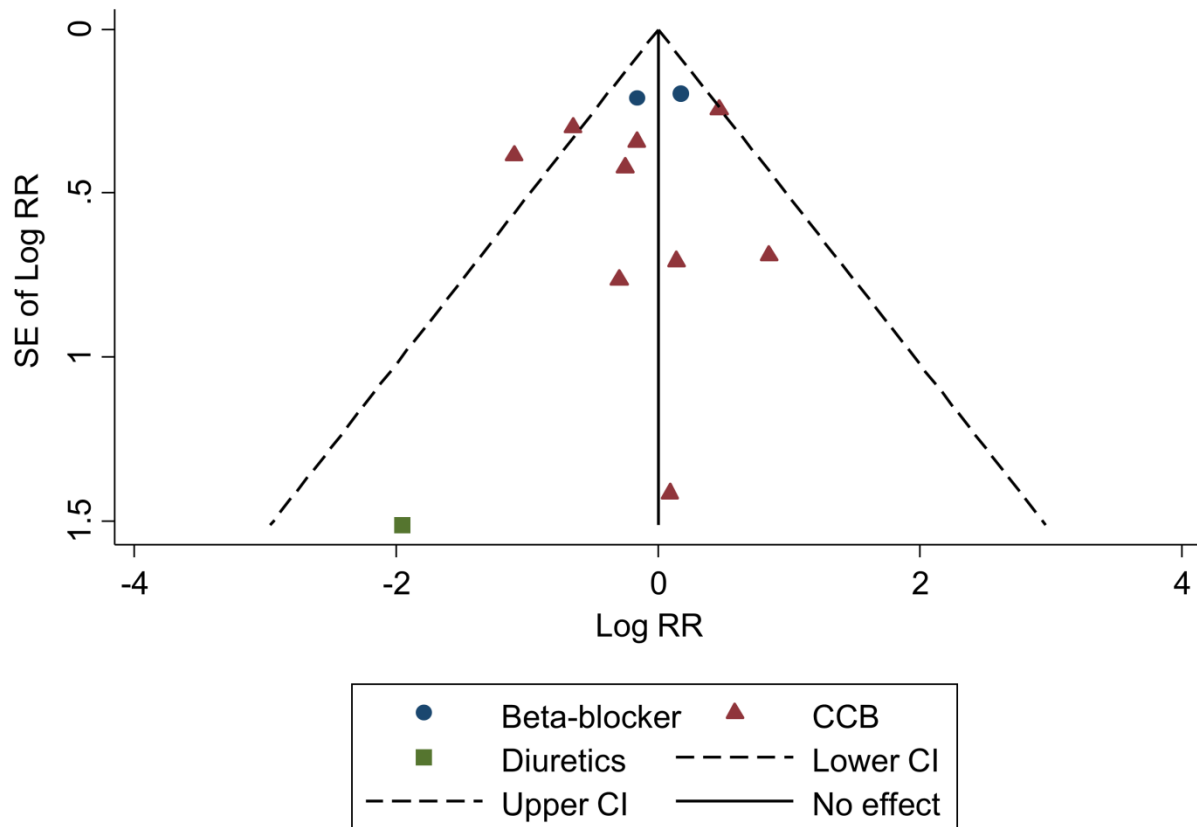


Figure S5. Funnel Plot: RAS blockers versus other antihypertensive agents for the outcome of angina pectoris

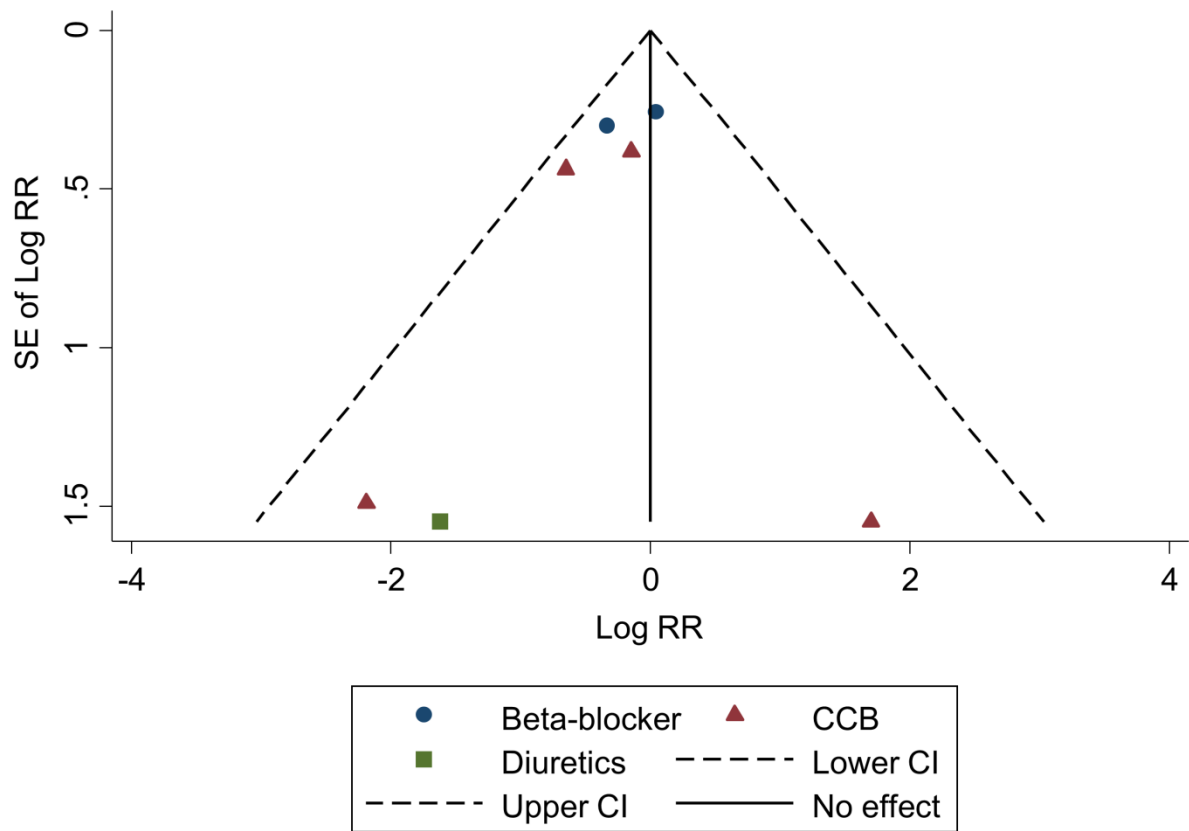


Figure S6. Funnel Plot: RAS blockers versus other antihypertensive agents for the outcome of stroke

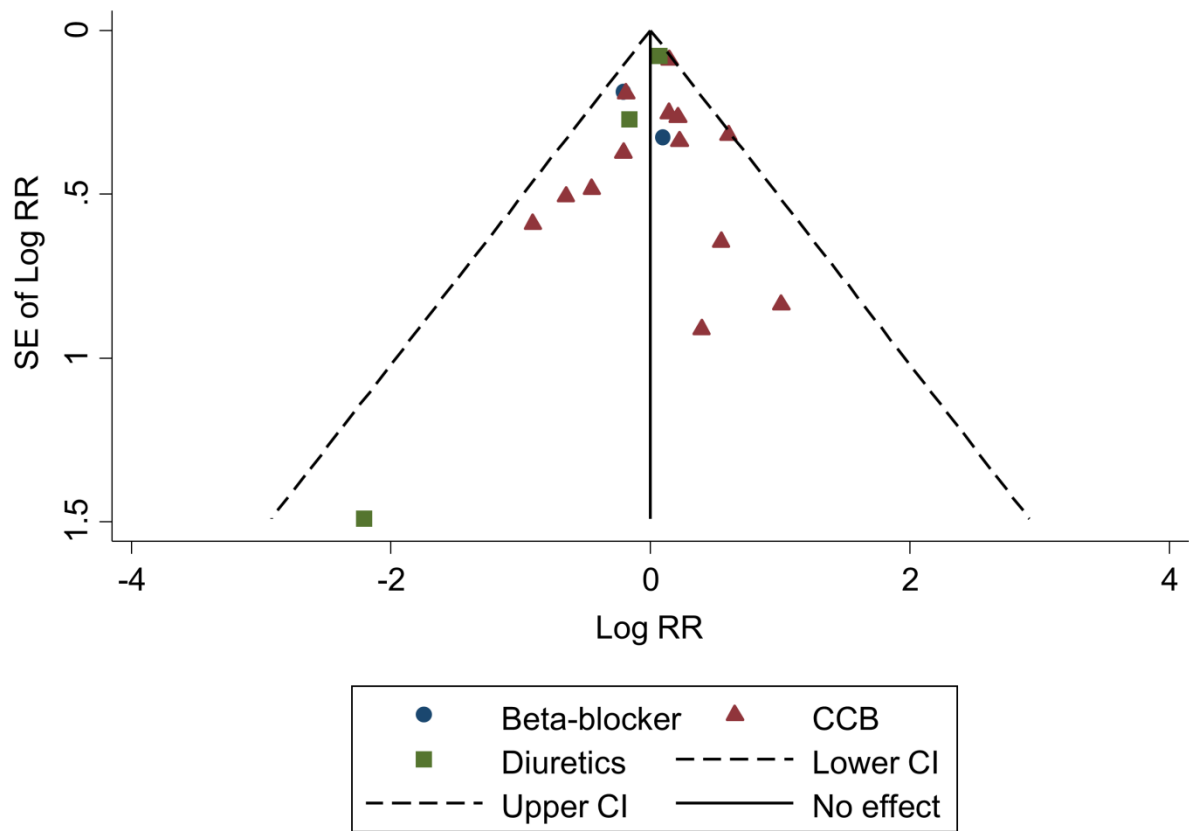


Figure S7. Funnel Plot: RAS blockers versus other antihypertensive agents for the outcome of heart failure

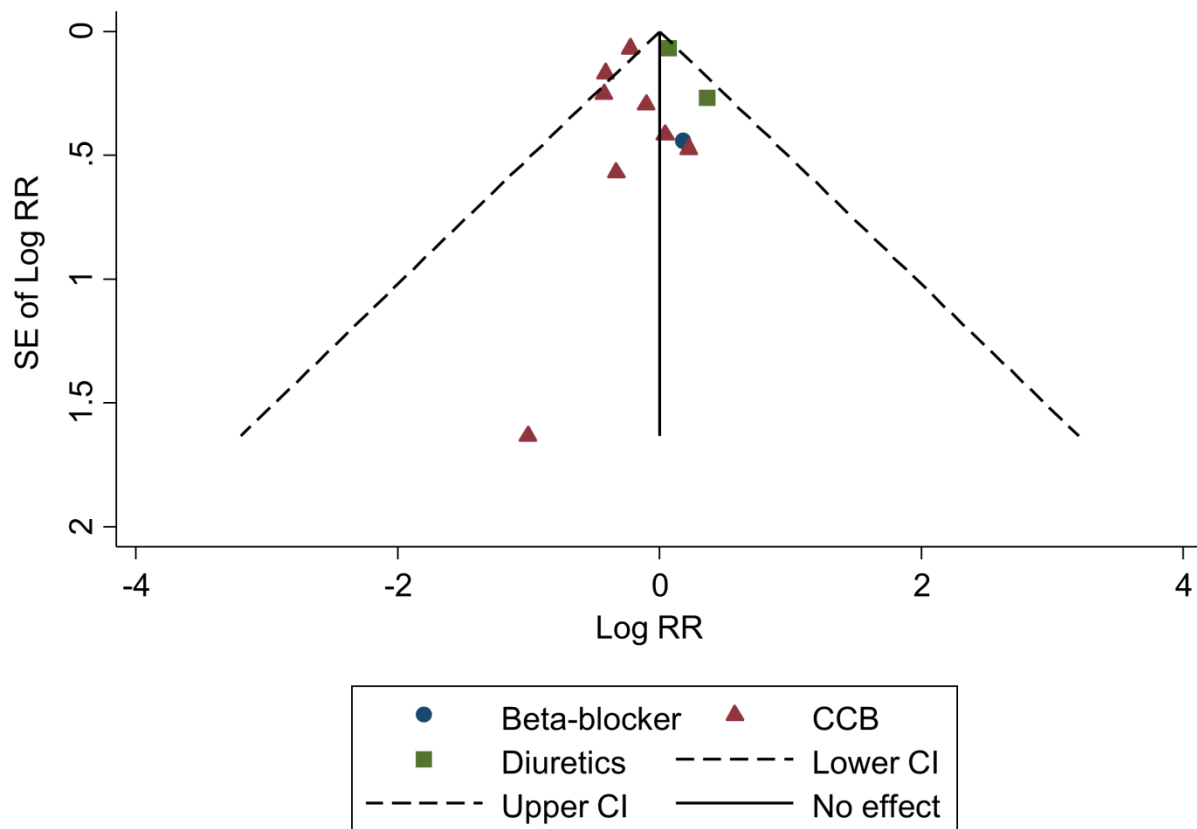


Figure S8. Funnel Plot: RAS blockers versus other antihypertensive agents for the outcome of death

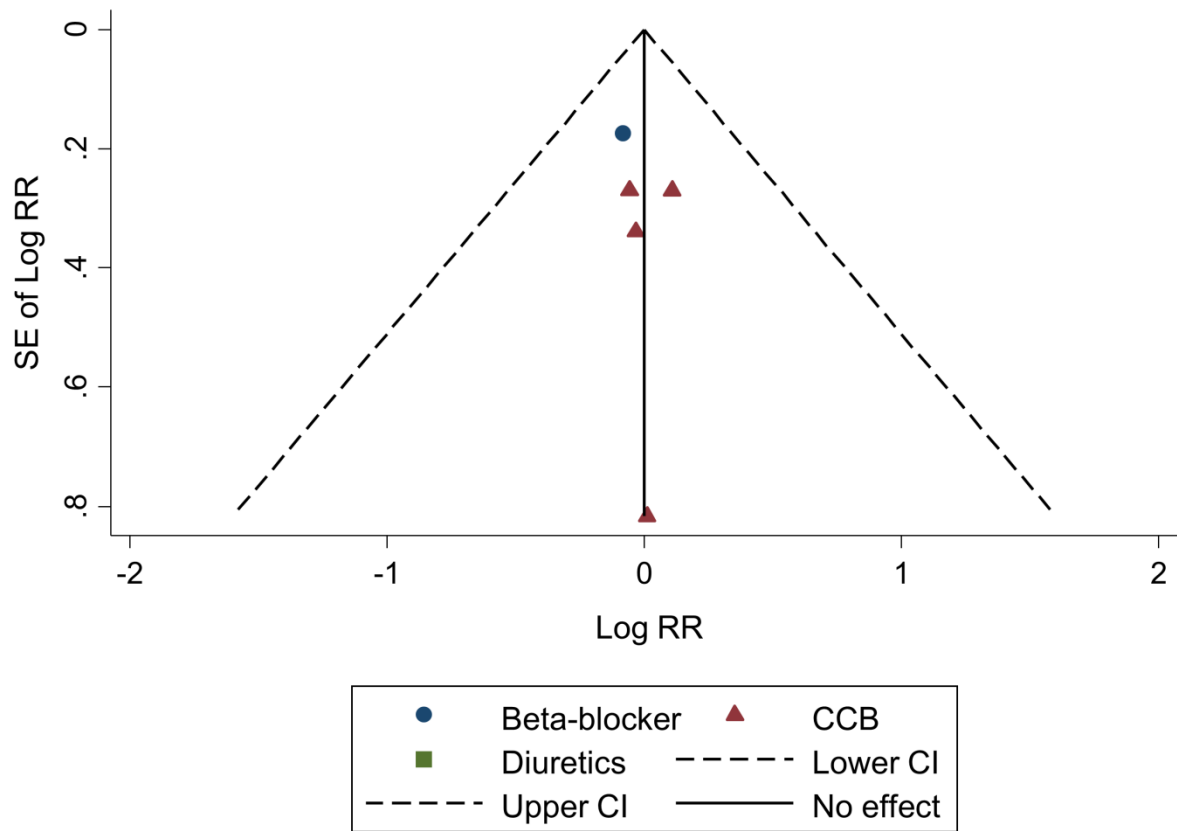


Figure S9. Funnel Plot: RAS blockers versus other antihypertensive agents for the outcome of end stage renal disease

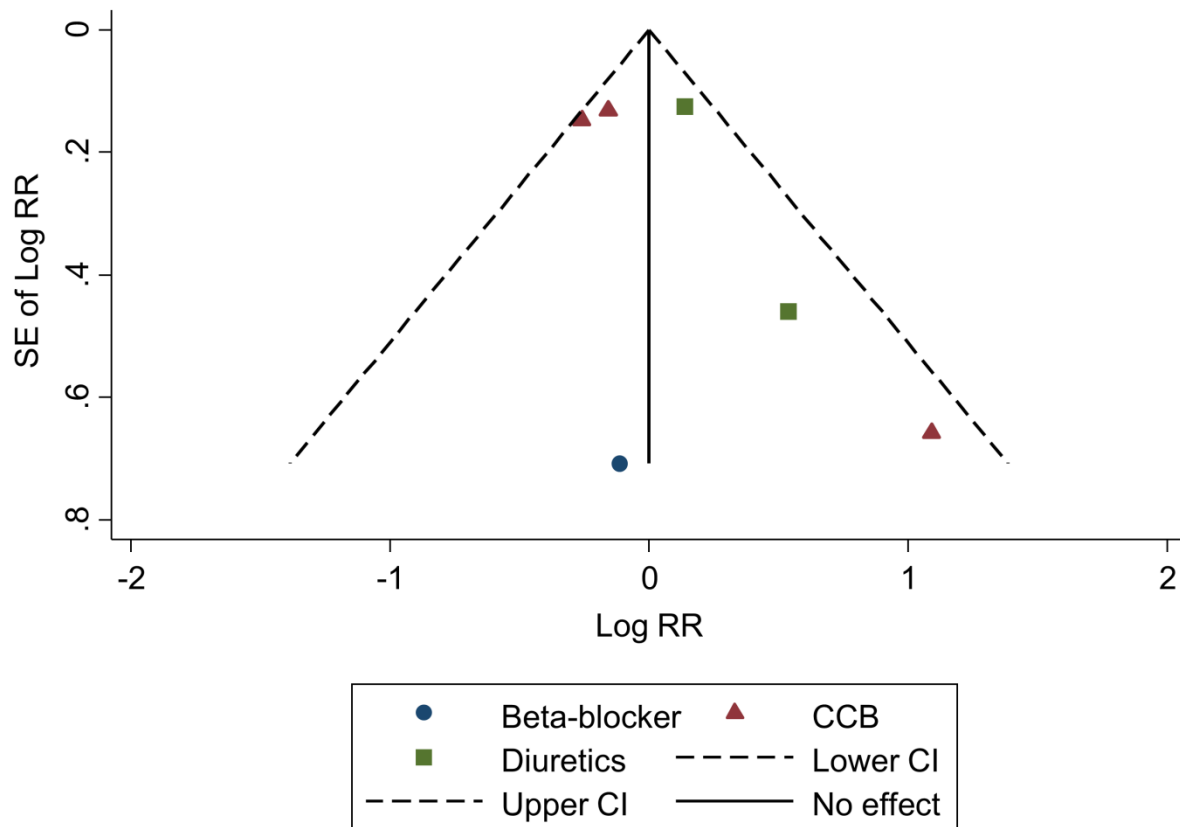


Figure S10. Funnel Plot: RAS blockers versus other antihypertensive agents for the outcome of drug withdrawal due to adverse effects

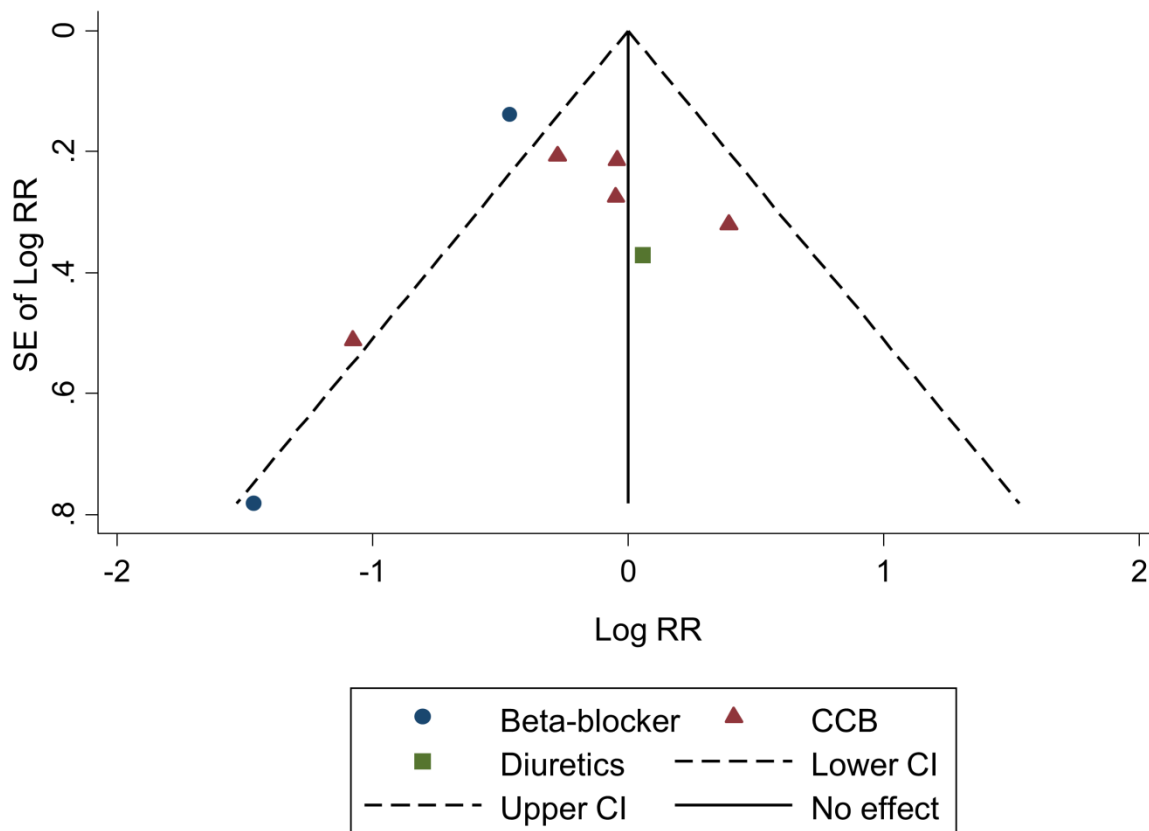


Table S1. Details of Search Terms

Search terms used
Candesartan or Irbesartan or Losartan or Telmisartan or Valsartan or Olmesartan or Eprosartan or Azilsartan or Fimasartan or Benazepril or Captopril or Enalapril or Cilazapril or Delapril or Fosinopril or Imidapril or Lisinopril or Moexipril or Perindopril or Quinapril or Ramipril or Spirapril or Temocapril or Trandolapril or Zofenopril
Angiotensin-Converting Enzyme Inhibitor; Angiotensin-Converting Enzyme Inhibitors; angiotensin receptor antagonist; angiotensin receptor antagonists; angiotensin receptor blocker; angiotensin receptor blockers

Table S2. Baseline Characteristics of the Clinical Trials included in the Meta-analysis

Trial	Treatment	Comparison	Nephropathy (treatment vs comparison)	Primary Endpoint
ABCD (Hypertensive) ^{1,2}	Enalapril	Nisoldipine	18% vs 19%	Change in 24h CrCl
ABCD (Normotensive) ³	Enalapril	Nisoldipine	34% vs 34%	Change in 24h CrCl
ALLHAT ⁴⁻⁶	Lisinopril	Amlodipine	NR	Combined fatal coronary heart disease or non-fatal MI
BENEDICT ⁷	Trandalopril	Verapamil	None	Persistent microalbuminuria
CAMELOT ⁸ (DM subgroup)	Enalapril	Amlodipine	NR	CV events
CASE-J ⁹⁻¹¹ (DM subgroup)	Candesartan	Amlodipine	23% vs 22%	CV events
FACET ¹²	Fosinopril	Amlodipine	None	Lipid profile and glucose metabolism
Fogari et al ¹³	Fosinopril	Amlodipine	100% vs 100%	Urinary albumin excretion
IDNT ¹⁴⁻¹⁶	Irbesartan	Amlodipine	100% vs 100%	Composite endpoint of a doubling of serum Cr, development of ESRD, or death
JMIC-B ^{17,18} (DM subgroup)	Enalapril, Imidapril, Lisinopril	Nifedipine	NR	Cardiac events
J-MIND ¹⁹	Enalapril	Nifedipine	36% vs 38%	Macroalbuminuria
MITEC ²⁰	Candesartan	Amlodipine	NR	Common carotid artery intima- media thickness
MOSES ^{21,22} (DM subgroup)	Eprosartan	Nitrendipine	6% vs 8%	Composite of total mortality and all cardiovascular events
NAGOYA HEART ²³	Valsartan	Amlodipine	NR	Composite of MI, stroke, coronary revascularization, admission for CHF, or sudden cardiac death
STOP-Hypertension- 2 ²⁴ (DM subgroup)	Enalapril, Lisinopril	Felodipine, Isradipine	NR	Fatal CV disease
ALLHAT ⁴⁻⁶	Lisinopril	Chlorthalidone	NR	Combined fatal coronary heart disease or non-fatal MI
ANBP2 ^{25,26} (DM subgroup)	Enalapril	HCTZ	13%	Any CV event or death
NESTOR ²⁷	Enalapril	Indapamide	100% vs 100%	Microalbuminuria
UKPDS 39 ²⁸	Captopril	Atenolol	16% vs 20%	(1) first clinical endpoint related to DM; (2) death related to DM; and (3) death from all causes (three separate endpoints)
LIFE ²⁹⁻³² (DM subgroup)	Losartan	Atenolol	11% vs 12%	Composite endpoint of CV death, MI and stroke

ABCD=Appropriate Blood Pressure Control in Diabetes; ALLHAT=Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ANBP2= Second Australian National Blood Pressure Study; BENEDICT=Bergamo Nephrologic Diabetes Complications Trial; β -blocker=Beta-blocker; CAD=Coronary artery disease;

CAMELOT=Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis; CASE-J= Candesartan Antihypertensive Survival Evaluation in Japan; CCB=Calcium channel blocker; CVA=Cerebrovascular accident; DM=Diabetes mellitus; FACET= Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial; HTN=Hypertension; IDNT=Irbesartan Type II Diabetic Nephropathy Trial; IFG=Impaired fasting glucose; JMIC-B=Japan Multicenter Investigation for Cardiovascular Diseases-B; J-MIND=Japan Multicenter Investigation of Antihypertensive Treatment for Nephropathy in Diabetics; LIFE=Losartan Intervention For Endpoint reduction; LVH=Left ventricular hypertrophy; MITEC=Media Intima Thickness Evaluation with Candesartan cilexetil; MOSES=Morbidity and Mortality After Stroke, Eprosartan Compared With Nitrendipine for Secondary Prevention; NAGOYA HEART=Comparison between valsartan and amlodipine regarding morbidity and mortality in patients with hypertension and glucose intolerance; NESTOR=Natrilix SR versus Enalapril Study in Type 2 diabetic hypertensives with microalbuminuria; NR=not reported; RAS-inh=Renin-Angiotensin System inhibitor; STOP-Hypertension=Swedish Trial in Old Patients with Hypertension; UKPDS=UK Prospective Diabetes Study Group.

*Represents risk of bias based on: sequence generation of allocation; allocation concealment and blinding. '+' represents low bias risk, '-' high bias risk, and "±" unclear bias risk.

Table S3. RAS blockers vs. other antihypertensive agents: Sensitivity analysis excluding impaired fasting glucose cohorts

Outcome	RR (95% CI) (Random-effects)	RR (95% CI) (Fixed-effect)
Death	0.99 (0.93-1.06)	0.99 (0.93-1.06)
Cardiovascular death	1.02 (0.83-1.24)	1.02 (0.83-1.23)
Myocardial Infarction	0.87 (0.64-1.18)	0.93 (0.76-1.12)
Angina Pectoris	0.80 (0.58-1.11)	0.81 (0.59-1.10)
Stroke	1.04 (0.91-1.19)	1.06 (0.96-1.17)
Heart Failure	0.89 (0.75-1.06)	0.91 (0.84-1.00)
Revascularization	0.97 (0.77-1.22)	0.97 (0.77-1.22)
End Stage Renal Disease	0.92 (0.75-1.13)	0.93 (0.80-1.08)
Withdrawal due to adverse events	0.80 (0.61-1.05)	0.77 (0.65-0.92)

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