SUPPLEMENTAL MATERIAL

Data S1. Trials that contributed grouped tabular data

Trial Name	Trial Team
ACEI-COVID	Team: Bauer A, Sappler N, Dolejsi T, Tilg H, Aulinger BA, Weiss G, Bellmann-Weiler R, Adolf C, Wolf D, Pirklbauer M, Graziadei I, Gänzer H, von Bary C, May AE, Wöll E, von Scheidt W, Rassaf T, Duerschmied D, Brenner C, Kääb S, Metzler B, Joannidis M, Kain HU, Kaiser N, Schwinger R, Witzenbichler B, Alber H, Straube F, Hartmann N, Achenbach S, von Bergwelt-Baildon M, von Stülpnagel L, Schoenherr S, Forer L, Embacher-Aichhorn S, Mansmann U, Massberg S Funding: Austrian Science Fund and German Center for Cardiovascular Research.
RAAS-COVID	Team: Elharram M, Ni J, Afilalo J, Flannery A, Ezekowitz JA, Cheng MP, Ambrosy AP, Zannad F, Brophy J, Giannetti N, Bessissow A, Kronfli N, Marelli A. Aziz H, Alqahtani M, Aflaki M, Craig M, Lopes RD, Ferreira JP Funding: McGill Interdisciplinary Initiative in Infection and Immunity (MI4) and the Division of Cardiology at McGill University.
REPLACE-COVID	Team: Hanff TC, William P, Sweitzer N, Rosado-Santander NR, Medina C, Rodriguez-Mori JE, Renna N, Chang TI, Corrales-Medina V, Andrade-Villanueva JF, Barbagelata A, Cristodulo-Cortez R, Díaz-Cucho OA, Spaak J, Alfonso CE, Valdivia-Vega R, Villavicencio-Carranza M, Ayala-García RJ, Castro-Callirgos CA, González-Hernández LA, Bernales-Salas EF, Coacalla-Guerra JC, Salinas-Herrera CD, Nicolosi L, Basconcel M, Byrd JB, Sharkoski T, Bendezú-Huasasquiche LE, Chittams J, Edmonston DL, Vasquez CR Funding: REPLACE COVID Investigators, REPLACE COVID Trial Social Fundraising Campaign, and FastGrants.
SWITCH-COVID	Team: Girardi ACC, Tavares CAM, Cardozo FAM, Betonico GN, de Almeida L Funding: University of Sao Paulo
ALPS-COVID IP	Team: Ingraham NE, Merck LH, Driver BE, Wacker DA, Black LP, Jones AE, Fletcher CV, South AM, Nelson AC, Lewandowski C, Farhat J, Benoit JL, Biros MH, Cherabuddi K, Chipman JG, Schacker TW, Guirgis FW, Voelker HT, Koopmeiners JS, Tignanelli CJ Funding: Bill and Melinda Gates Foundation, NIH
ALPS-COVID OP	Team: Cummins NW, Ingraham NE, Wacker DA, Reilkoff RA, Driver BE, Biros MH, Bellolio F, Chipman JG, Nelson AC, Beckman K, Langlois R, Bold T, Aliota MT, Schacker TW, Voelker HT, Koopmeiners JS Funding: Minnesota Partnership for Biotechnology and Medical Genomics
COVERAGE-France	Team: Malvy D, Anglaret X, Richert L, Wittkop L, Lhomme E, Sitta R, Gelley A, Hardel L, Wallet C, Schwimmer C, Thiebaut R, Onaisi R, Saint-Lary O, Joseph JP, Dupouy J, Gimenez L, Boucaut A, Chastang J, Naccache JM, Piroth L, Binquet C, Lefèvre B, Makinson A, Picot MC, Montoya A, Crantelle L, Molimard M, Bouchet S, de Lamballerie X, Roussillon C, Landman R Funding: Ministère des Solidarités et de la Santé, Agence Nationale de la Recherche, ANRS | Maladies Infectieuses Emergentes, University of Bordeaux
COVID MED	Team: Victory J, Jenkins P, Krupa N, Wheeler J, Vail GM, Riesenfeld E, Cross P, Gilmore C, Huckabone M, Schworm A, Boregowda U, Deshmukh F, Choi Y, Khan A, Gadomski A Funding: Bassett Healthcare, Reid Health, Goshen Health System
PRAETORIAN-COVID	Team: Aarts GWA, Konijnenberg LSF, Mensink FB, Herrmann JJ. Funding: NLHI, the Dutch Heart Foundation, Novartis Pharma and ZonMW grant 10430012010020
STAR-COVID	Team: Ángeles-Duran GY, Flores-Gómez IR, Flores-Martínez E, Valdin-Orozco TI, Pedraza-Hervert C Funding: National Polytechnic Institute, Mexico
Telmisartan for treatment of patients with COVID-19	Team: Duarte M, Nicolosi LN, Salgado MV, Vetulli H, Aquieri A, Azzato F, Castro M, Coyle J, Davolos I, Criado IF, Gregori R, Mastrodonato P, Rubio MC, Sarquis S, Wahlmann F Funding: Facultad de Medicina (Universidad de Buenos Aires, Argentina), Hospital Espa~nol de Buenos Aires (Argentina) and Laboratorio Elea (Argentina)

Table S1. Quality assessment of RCTs – Cochrane Collaboration Risk of Bias Tool.

Trial Name	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and researchers (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other
ACEI-COVID	Low risk	High risk	High risk	Low risk	Low risk	Low risk	Open label trial
BRACE-CORONA	Low risk	High risk	High risk	Low risk	Low risk	Low risk	Open label trial
RAAS-COVID	Low risk	High risk	High risk	Unclear risk	Low risk	Low risk	Open label trial
REPLACE-COVID	Low risk	High risk	High risk	Low risk	Low risk	Low risk	Open label trial
SWITCH-COVID	Low risk	High risk	High risk	Low risk	Low risk	Low risk	Open label trial
ALPS-COVID IP	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Placebo controlled
ALPS-COVID OP	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Placebo controlled
ARB use to minimize progression to respiratory failure	Low risk	High risk	High risk	Unclear risk	Low risk	Low risk	Open label trial
COVERAGE-France	Low risk	High risk	High risk	Low risk	Low risk	Low risk	Open label trial
COVID MED	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Placebo controlled
Evaluation of the effect of losartan in COVID-19	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Comparator amlodipine rather than placebo
PRAETORIAN-COVID	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Placebo controlled
STAR-COVID	Low risk	High risk	High risk	Low risk	Low risk	Low risk	Open label trial
Telmisartan for treatment of patients with COVID-19	Low risk	High risk	High risk	Unclear risk	High risk	Unclear risk	Open label trial loss to follow-up:>10%

Table S2. Sensitivity analyses to account for small counts in trials*

	Original analyses RR, 95%CI	Sensitivity analyses* RR, 95%CI
Mortality	RR 0.95 (0.69-1.30), p=0.73	RR 0.95 (0.69-1.30), p=0.73
Myocardial infarction	RR 0.59 (0.33-1.06), p=0.08	RR 0.60 (0.24-1.06), p=0.08
Intensive care admission	RR 1.00 (0.77-1.30), p=0.98	RR 1.02 (0.78-1.32), p=0.90
Mechanical ventilation	RR 1.00 (0.76-1.31), p=0.99	RR 1.02 (0.77-1.35), p=0.90
Hypotension requiring inotropes	RR 1.01 (0.73-1.41), p=0.93	RR 1.01 (0.73-1.41), p=0.93
Acute kidney injury	RR 1.82 (1.05-3.16), p=0.03	RR 1.82 (1.05-3.14), p=0.03
Acute kidney injury requiring dialysis	RR 1.15 (0.60-2.21), p=0.67	RR 1.15 (0.60-2.19), p=0.68

RR relative risk, CI confidence interval

*Sensitivity analysis using the reciprocal of the sample size of the opposite arm to the cells in tables with zeroes

Figure S1. Quality assessment of RCTs – Cochrane Collaboration Risk of Bias Tool.

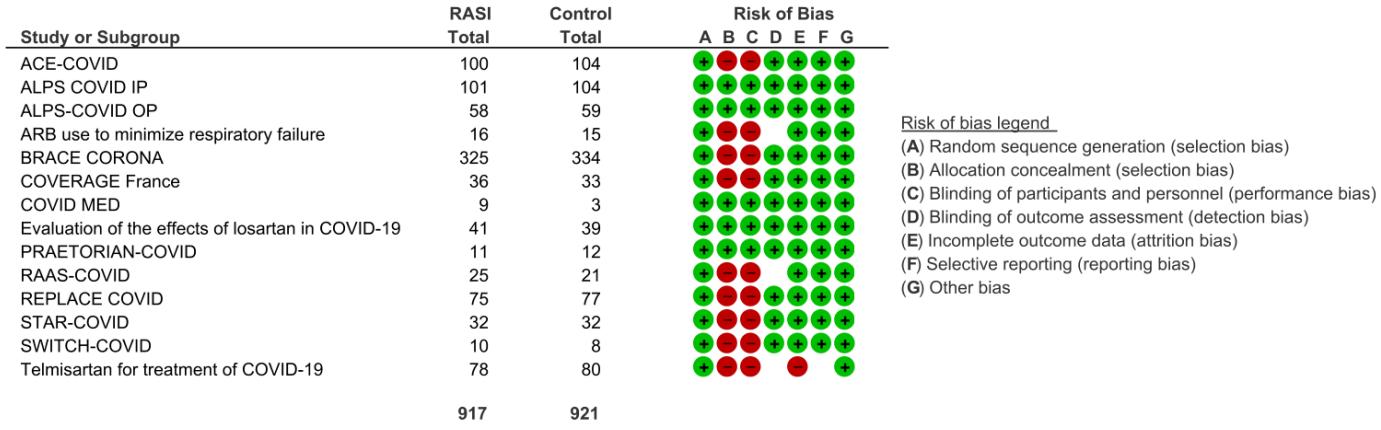


Figure S2: All-Cause Mortality – Start vs Continue/Discontinue Trials

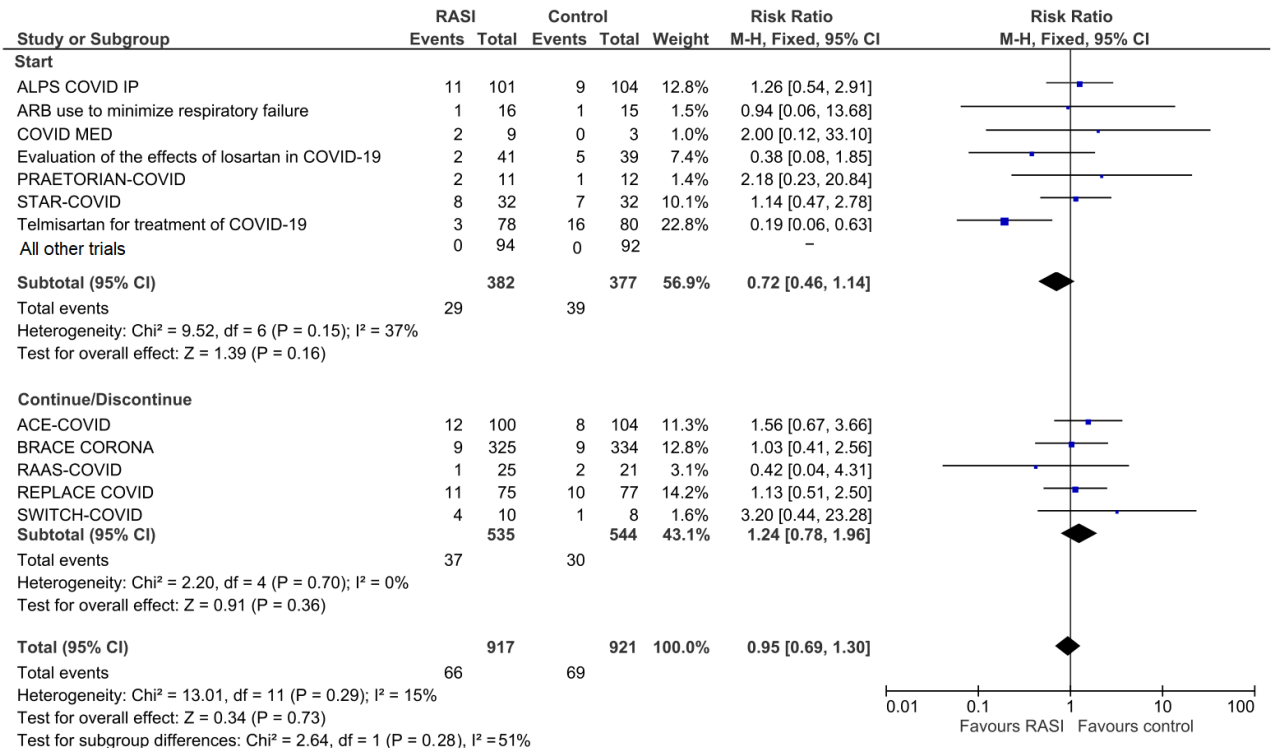


Figure S3: All-Cause Mortality – Placebo Control vs Open Label Trials

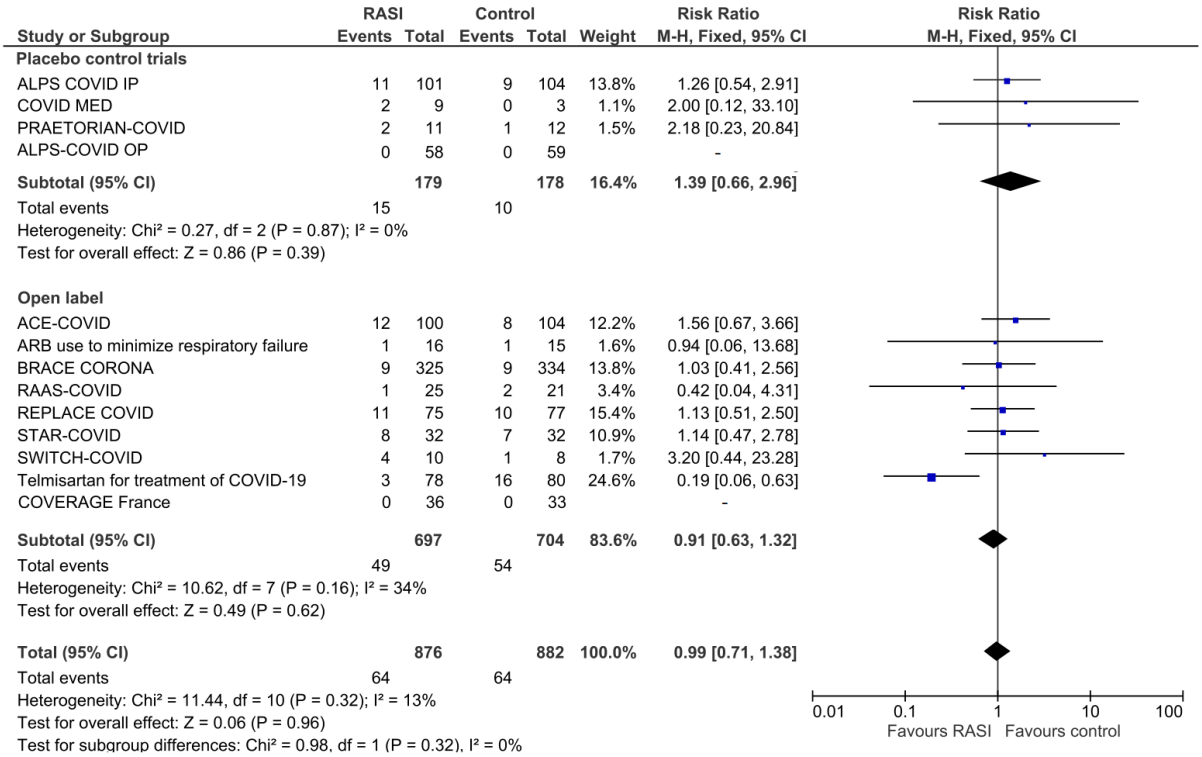
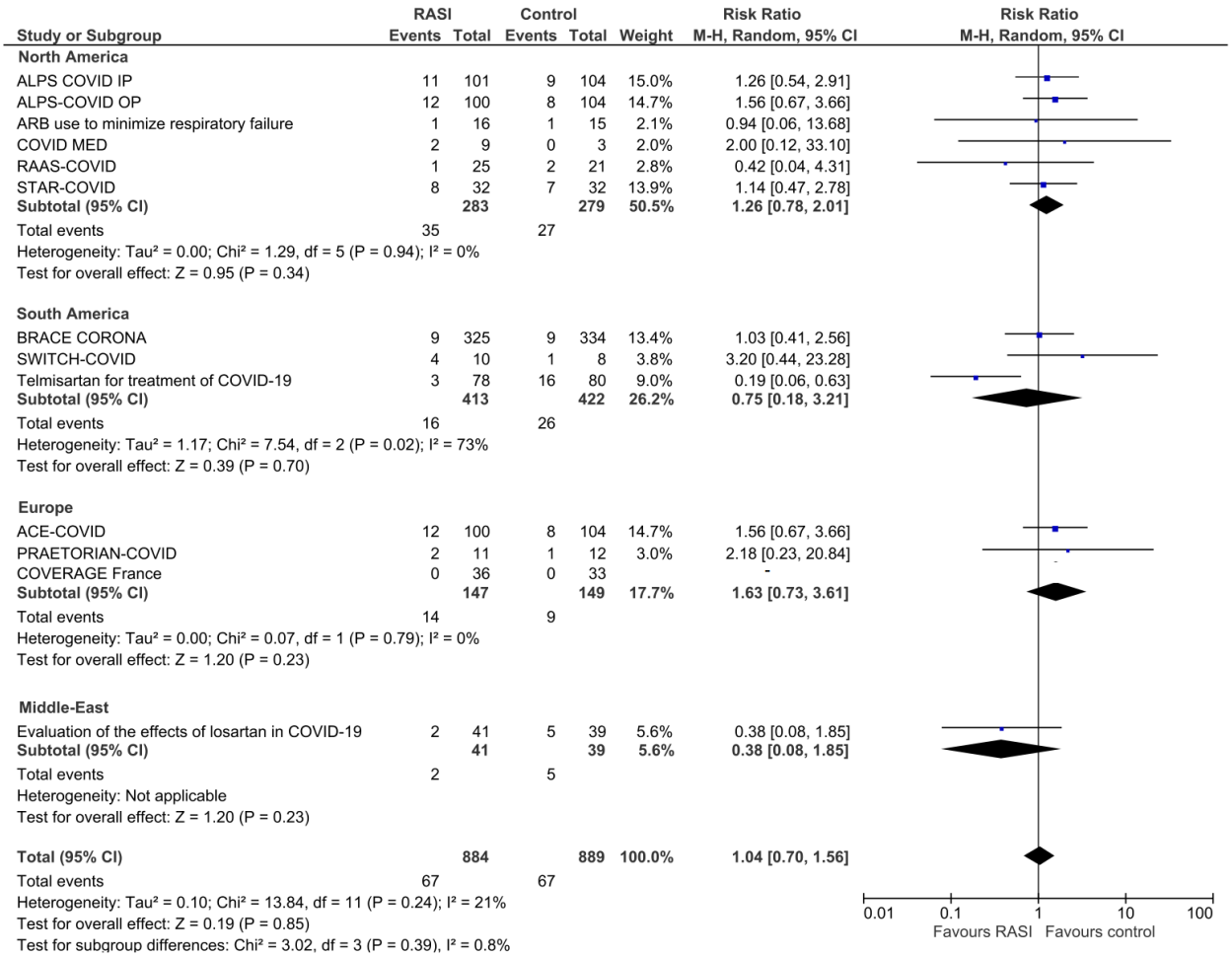


Figure S4: All-Cause Mortality – Trial Location

(A) Random Effect



(B) Fixed Effects

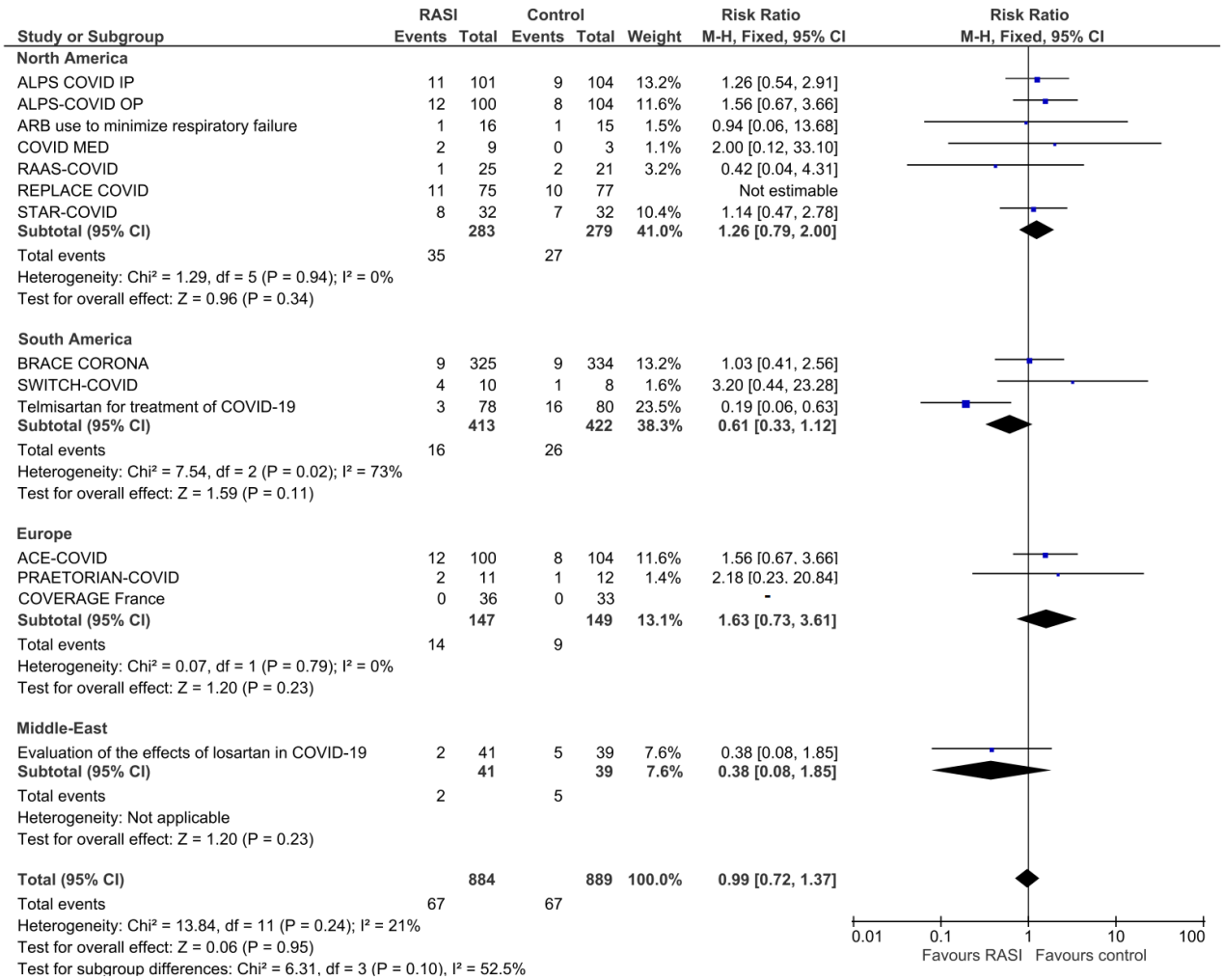


Figure S5: All-Cause Mortality – Severity of COVID-19

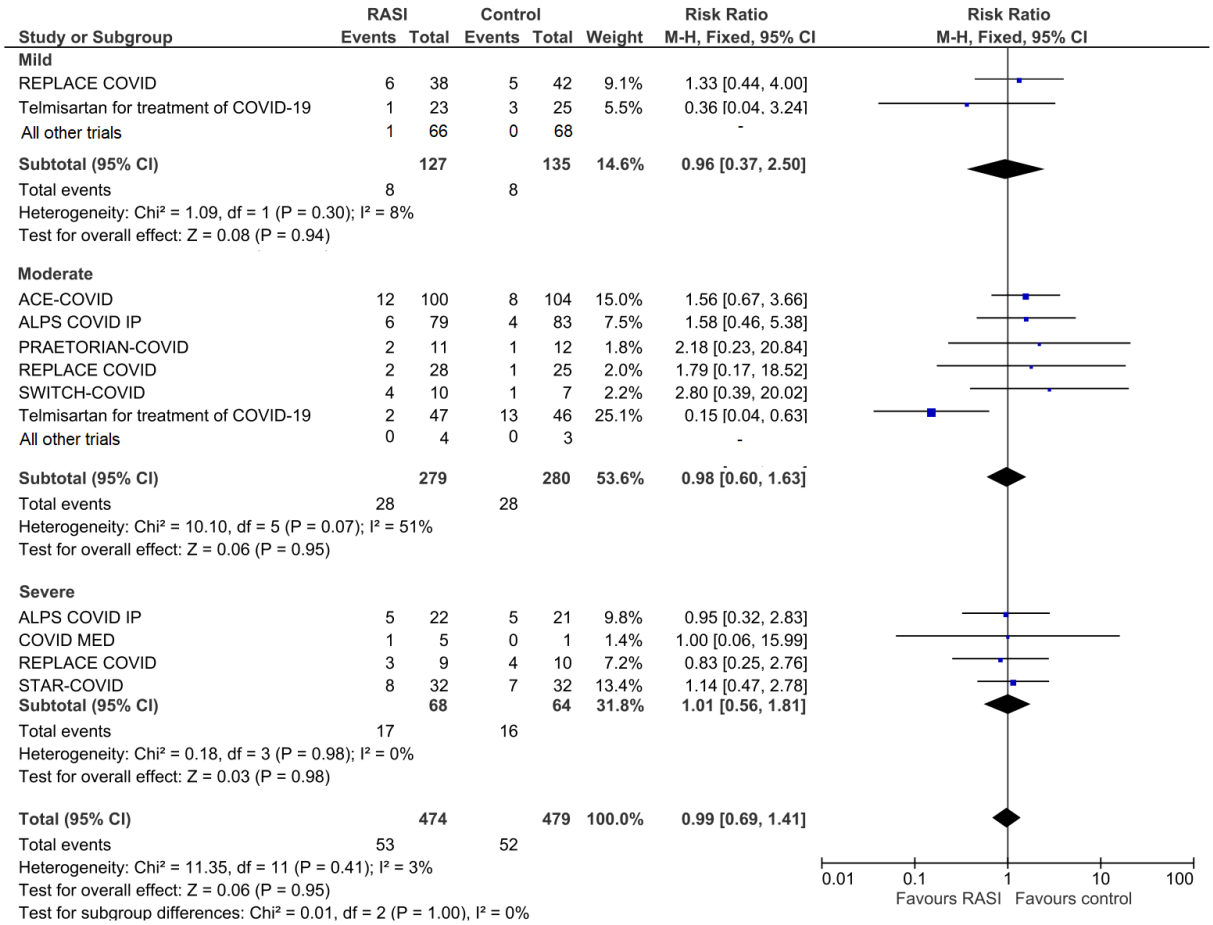
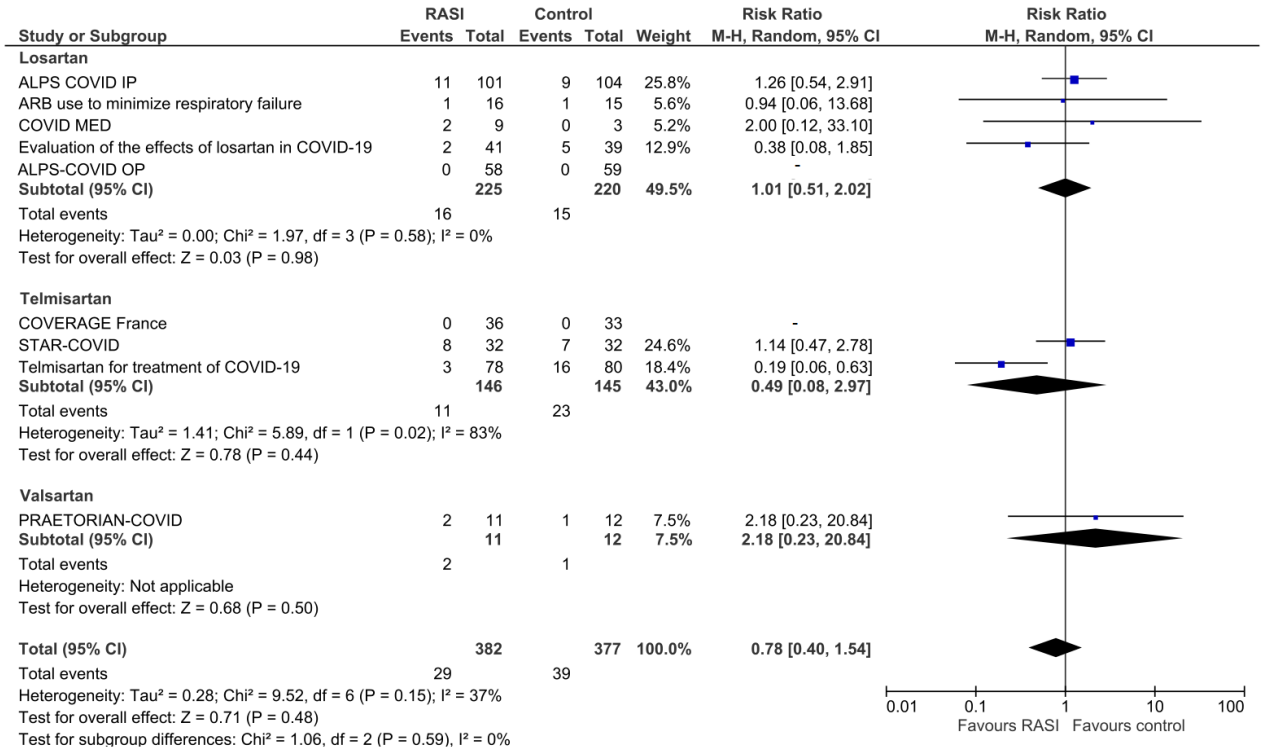


Figure S6: All-Cause Mortality by Angiotensin II type 1 Receptor Blocker

(A) Random Effects



(B) Fixed Effects

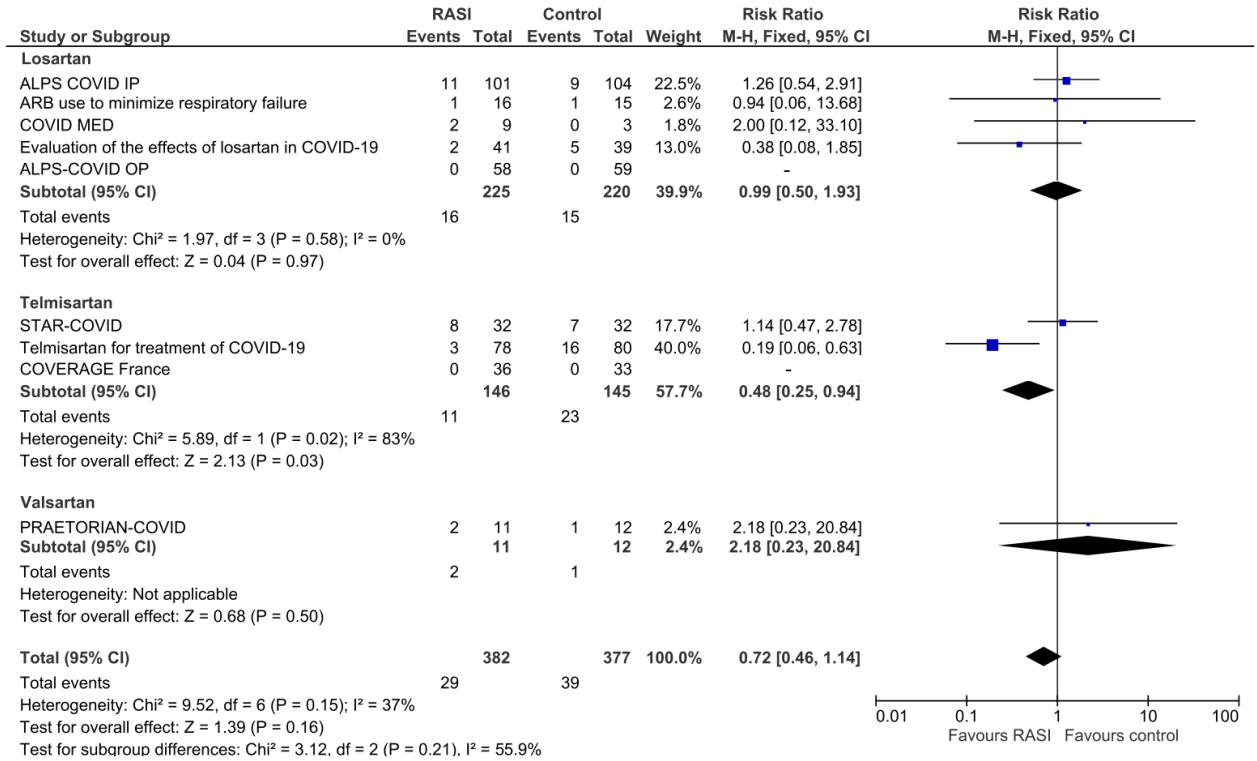
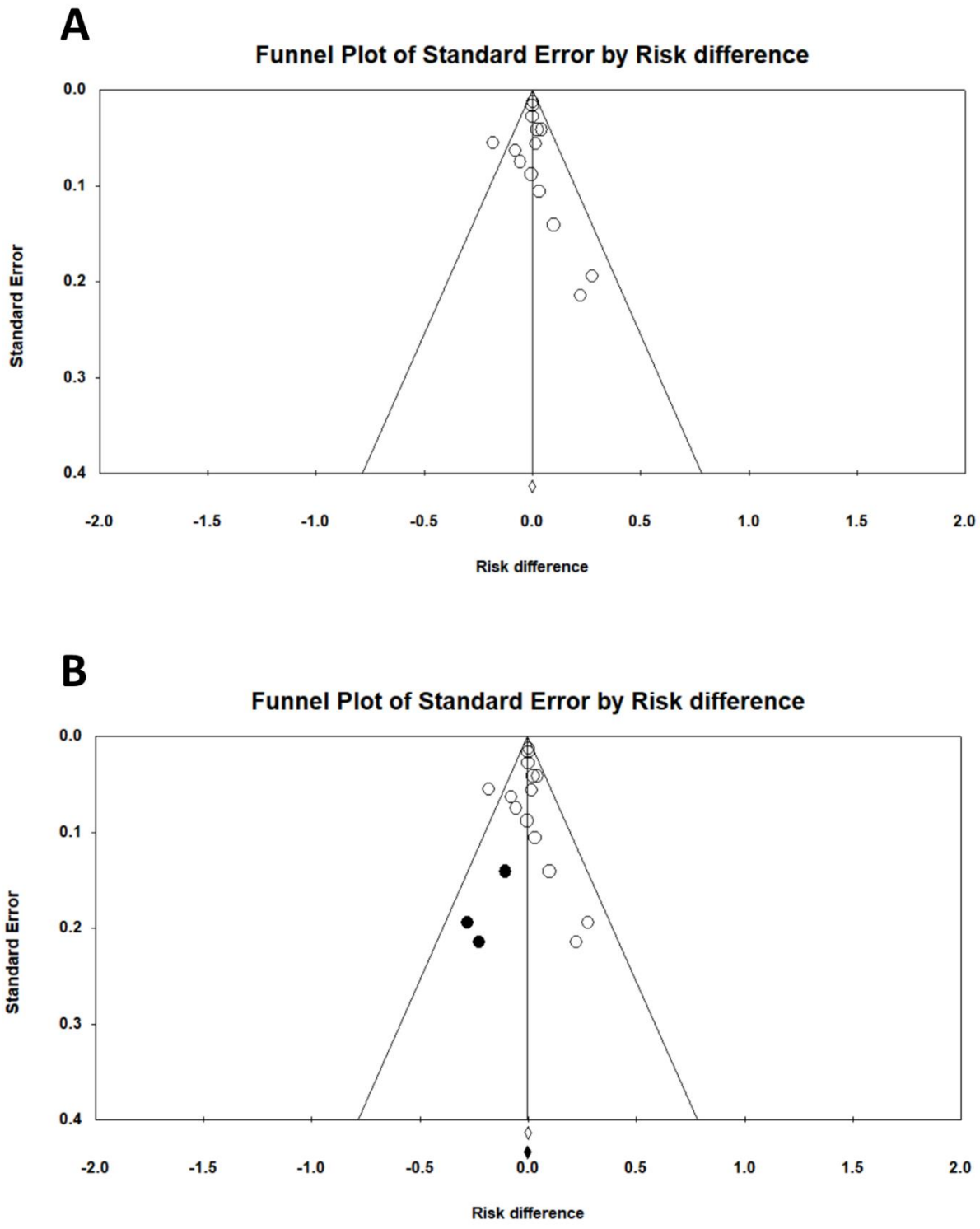


Figure S7: Publication bias and all-cause mortality

(A) Observed trials; (B) Observed and imputed trials.



Open circles: observed trials; closed black circles: imputed trials

Figure S8: All-Cause Mortality – Age subgroups

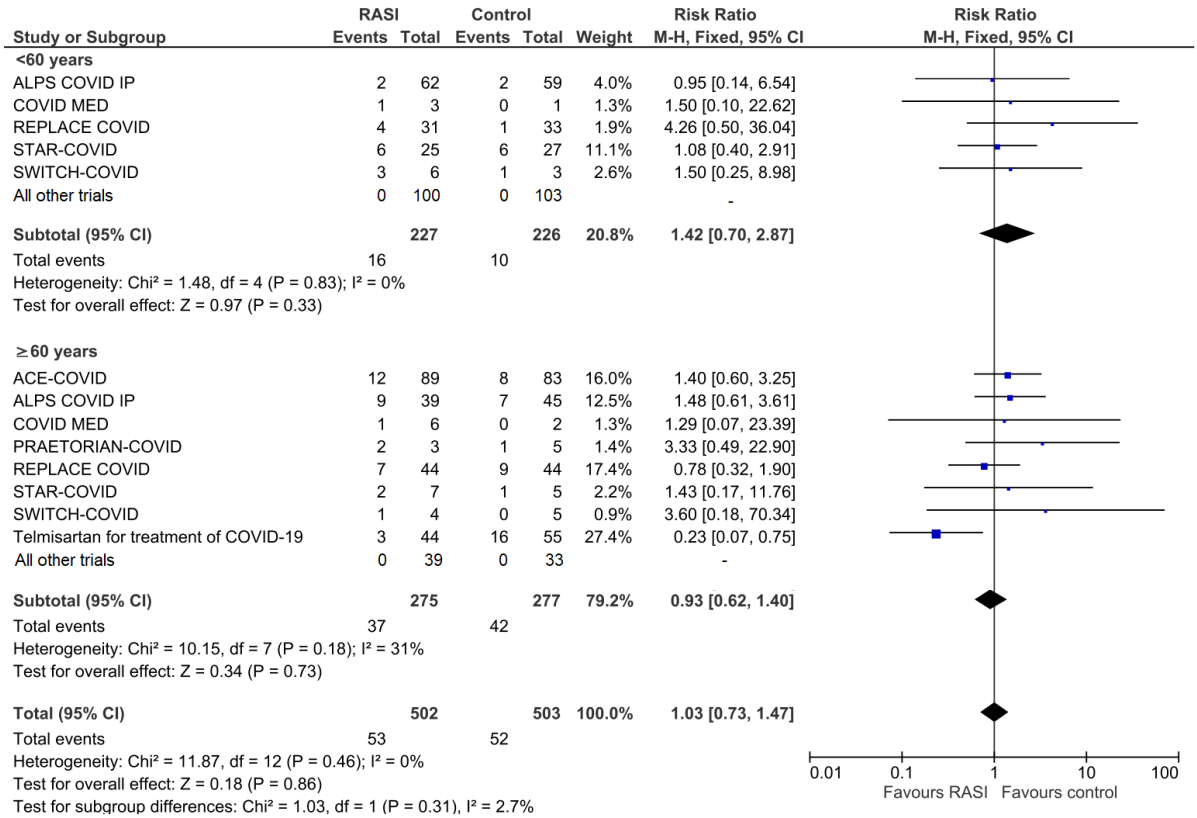


Figure S9: All-Cause Mortality – Sex

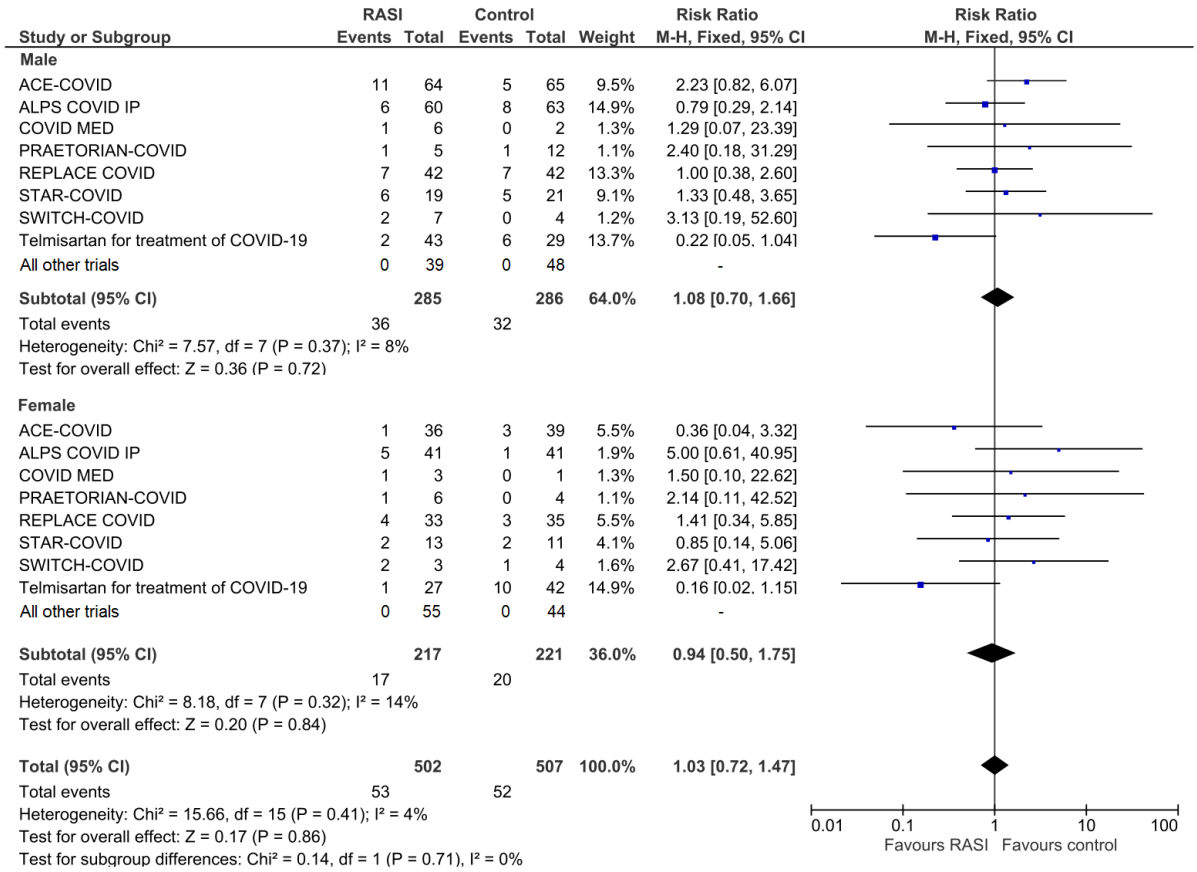


Figure S10: All-Cause Mortality – Ethnicity

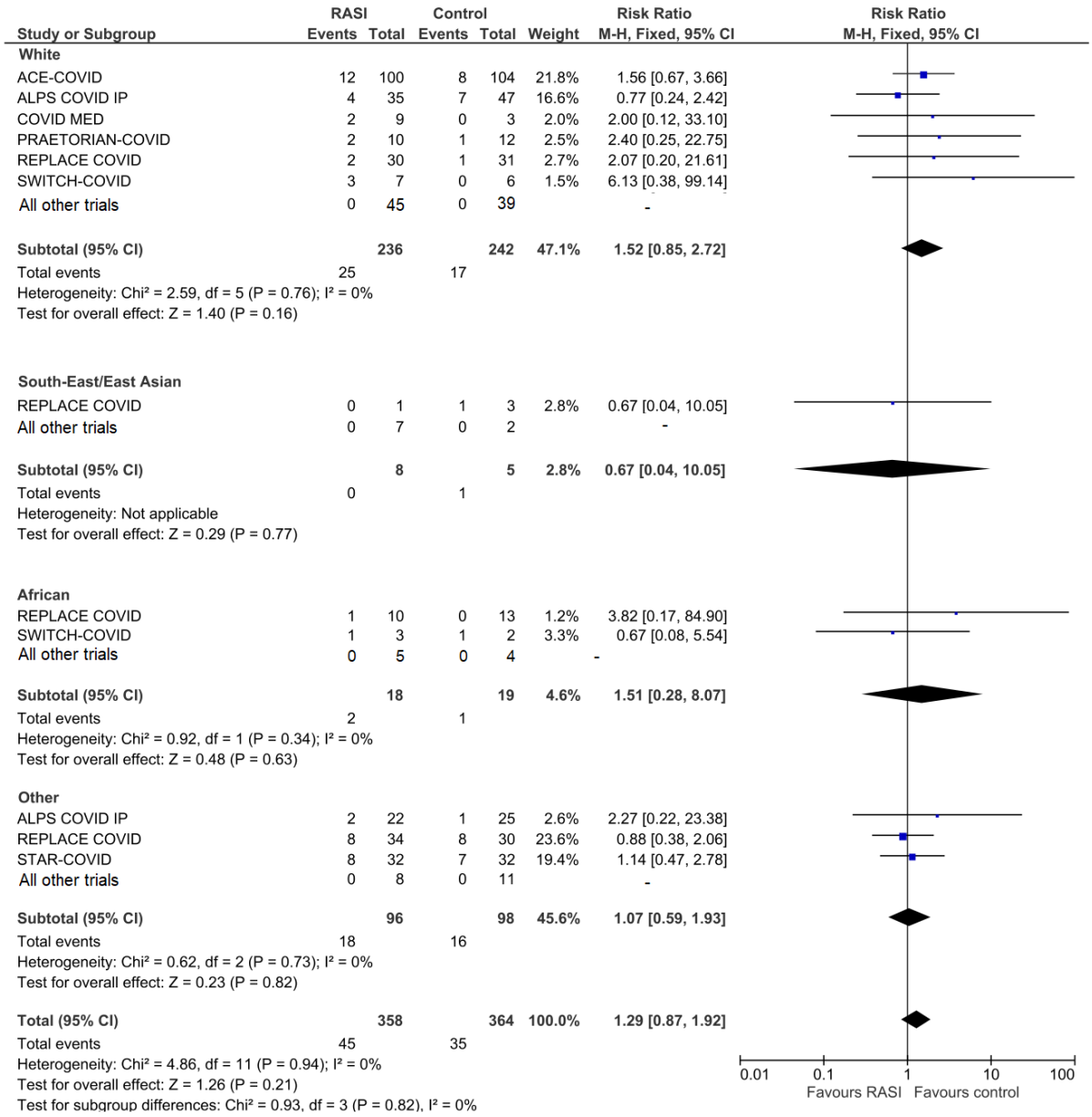
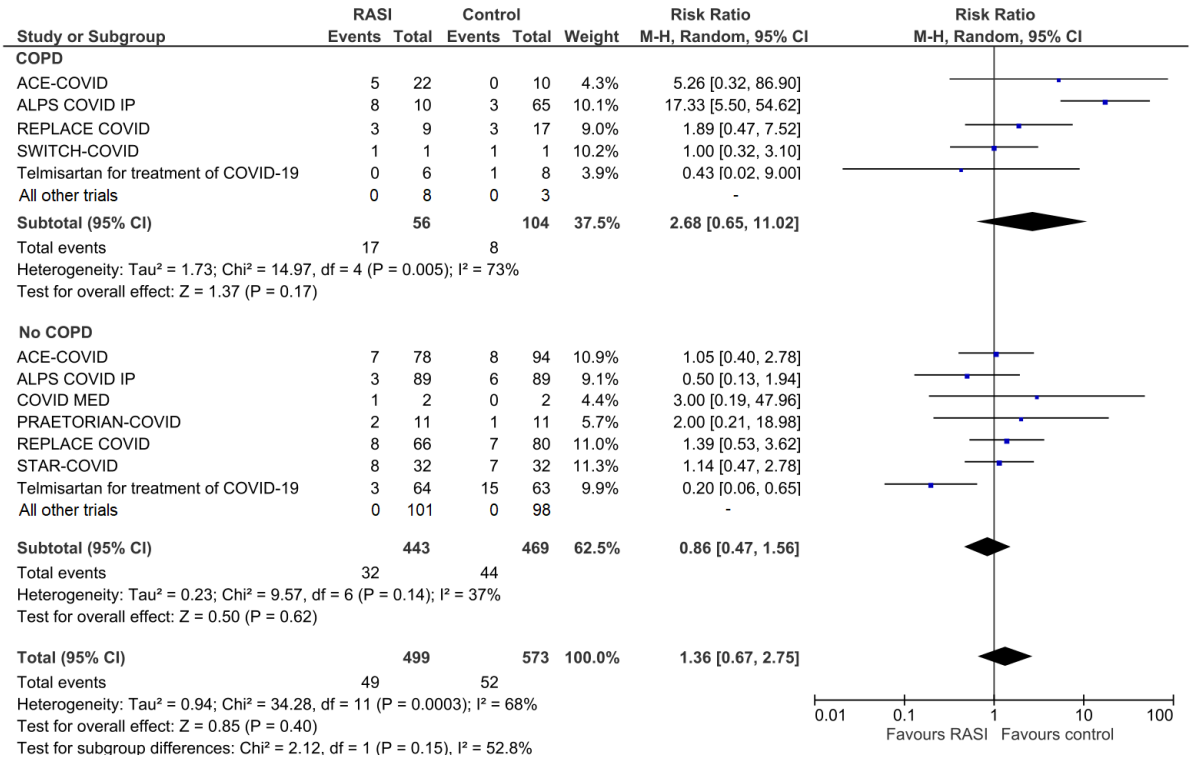


Figure S11: All-Cause Mortality – COPD vs no COPD

(A) Random Effects



(B) Fixed Effects

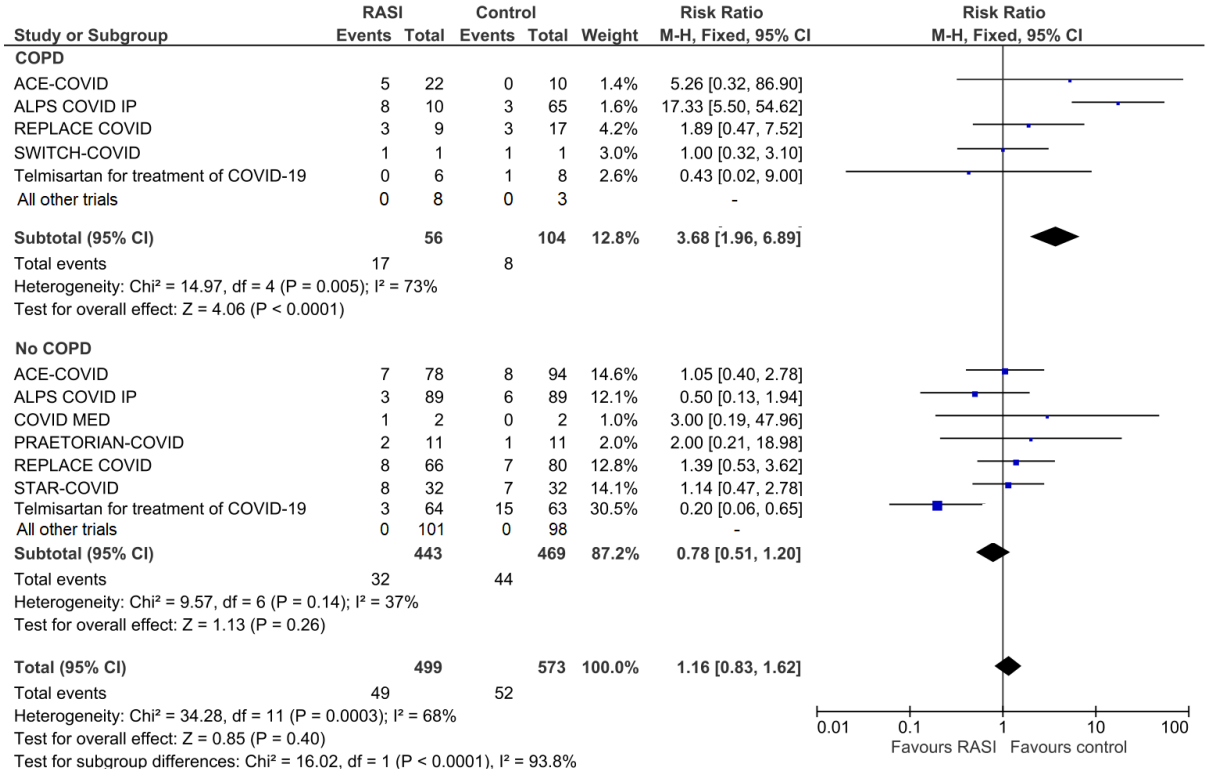


Figure S12: All-Cause Mortality – Hypertension vs no Hypertension

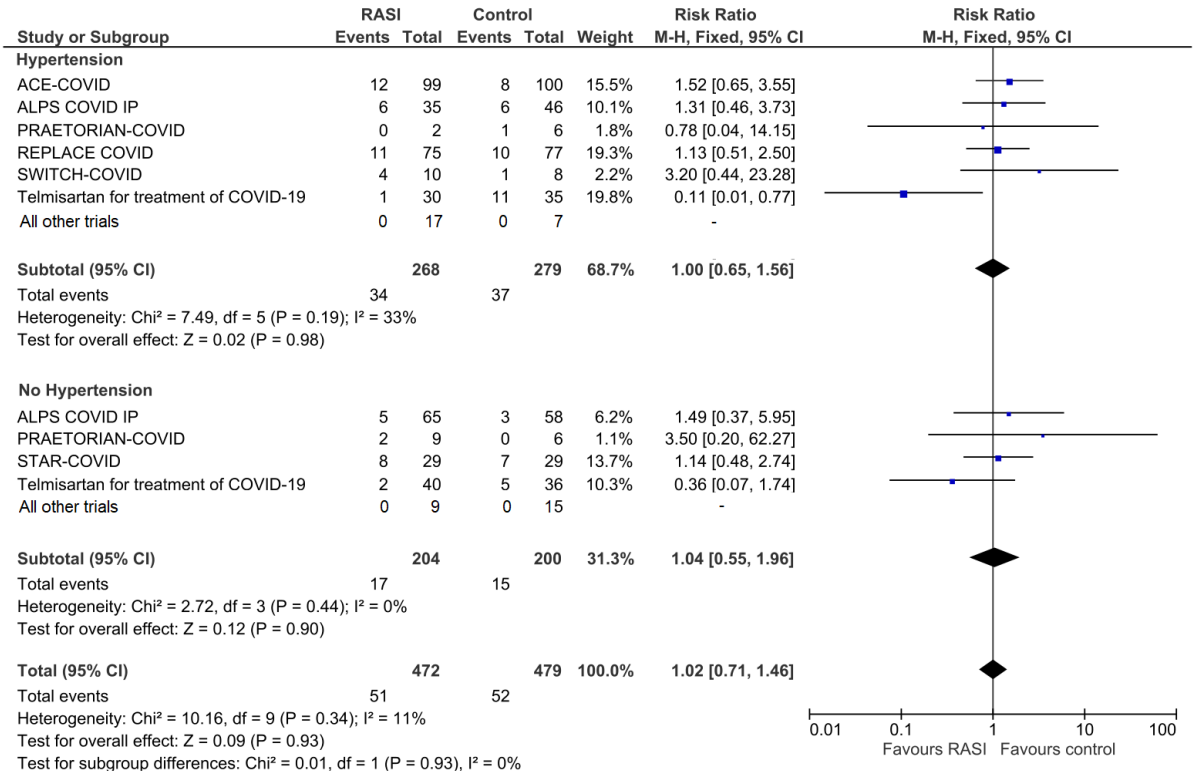


Figure S13: All-Cause Mortality – Diabetes Mellitus vs no Diabetes

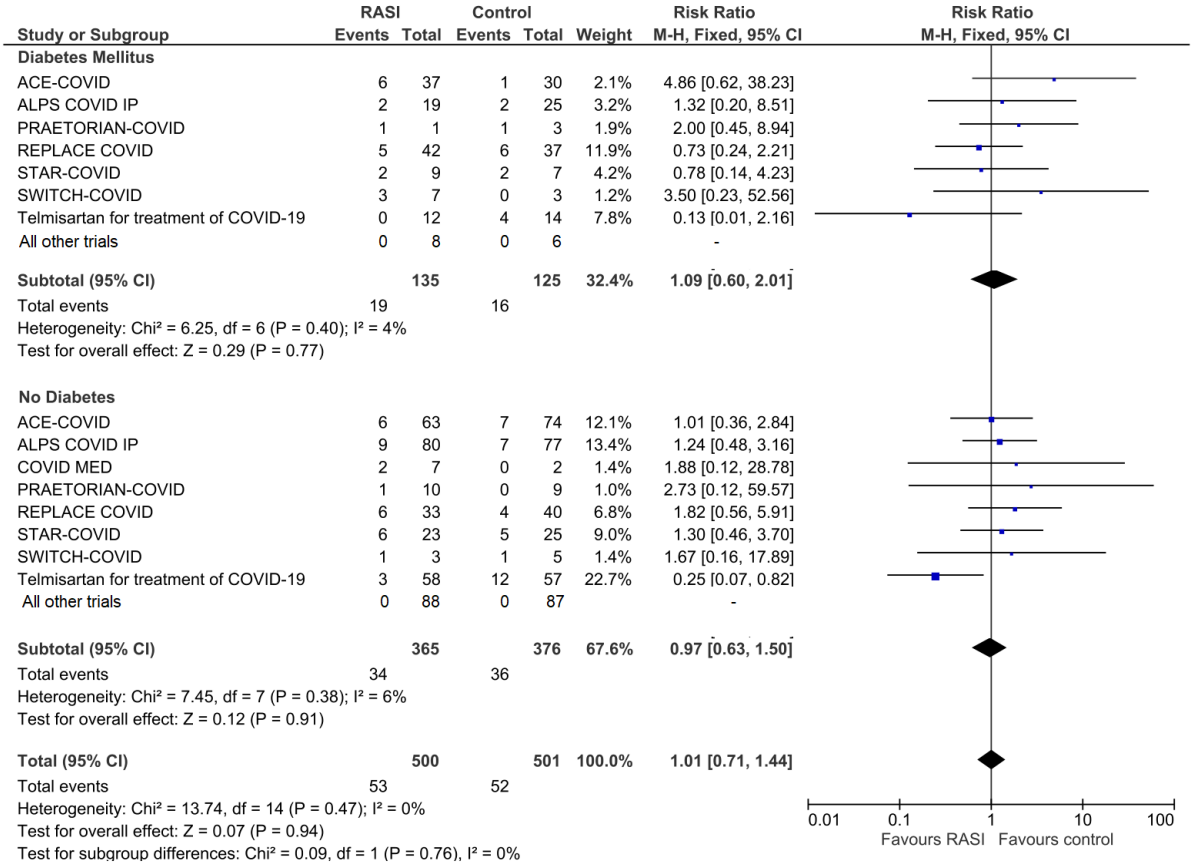


Figure S14: All-Cause Mortality – Obesity vs No Obesity

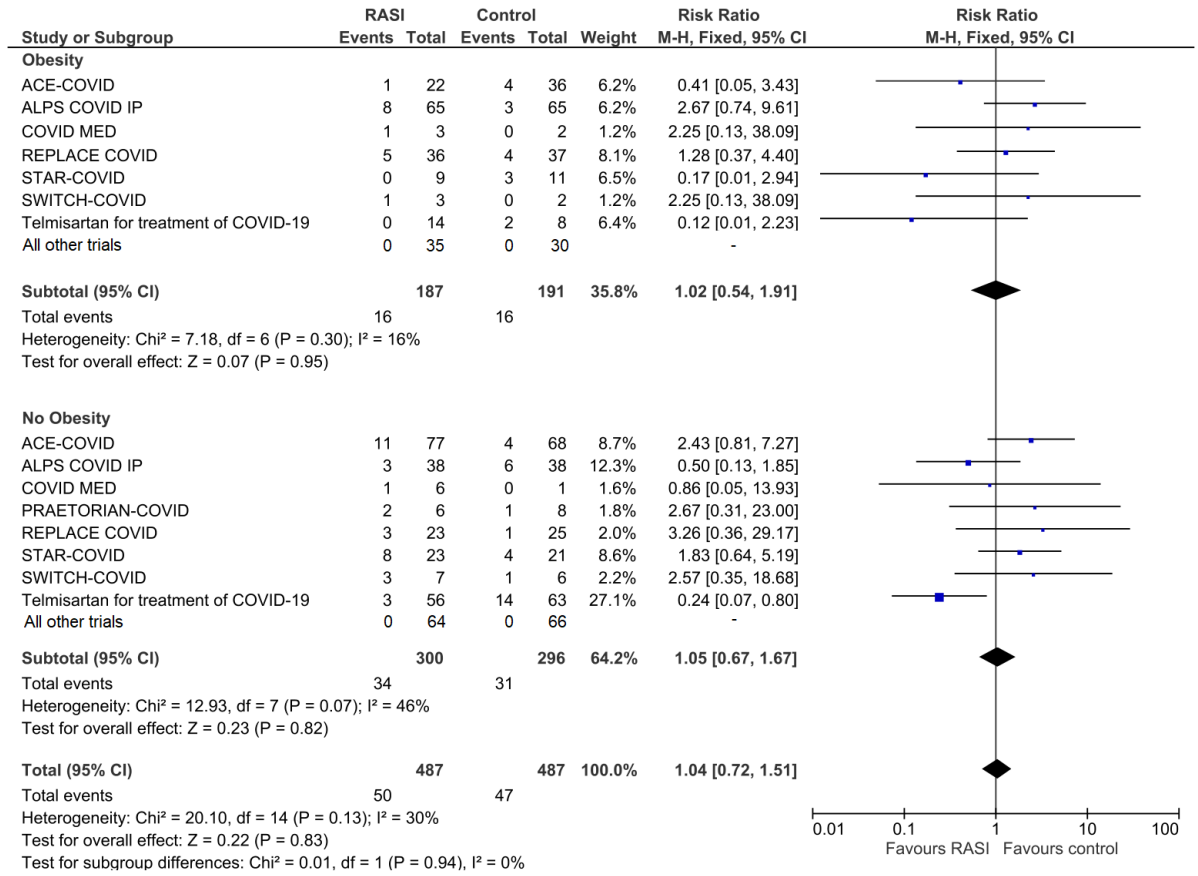


Figure S15: All-Cause Mortality – CVD vs no CVD

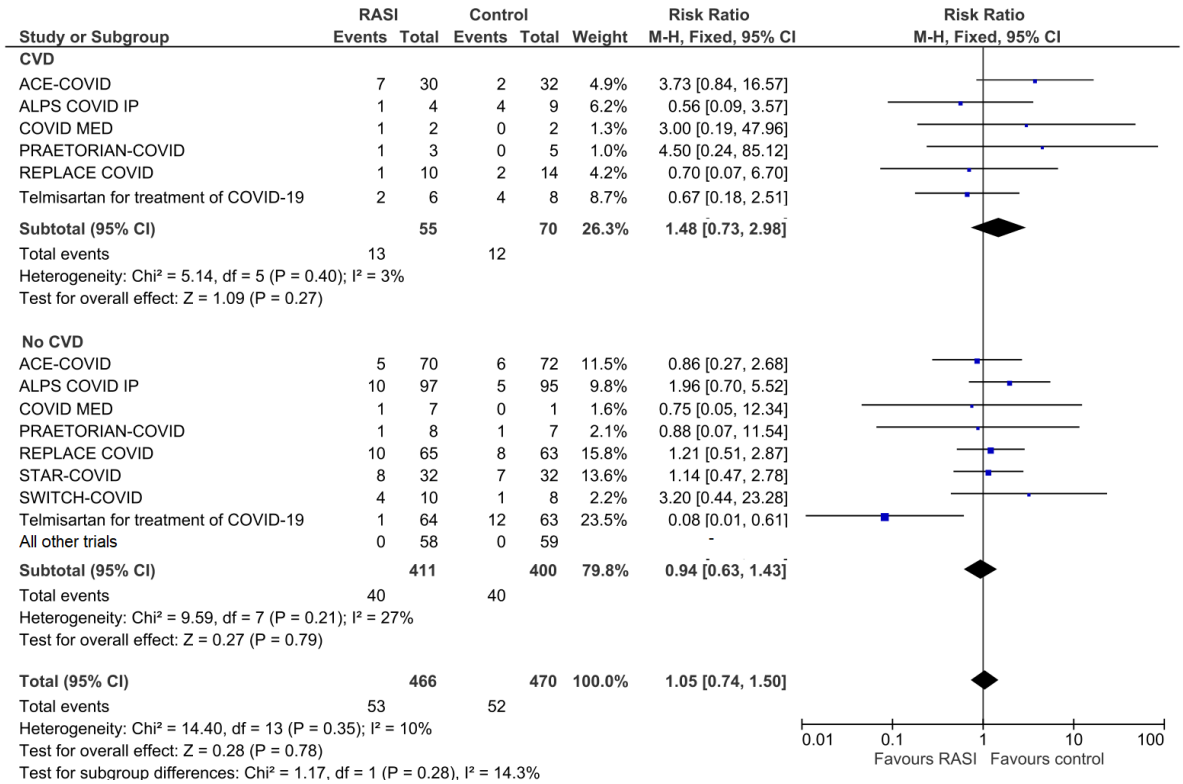


Figure S16: All-Cause Mortality – CKD vs no CKD

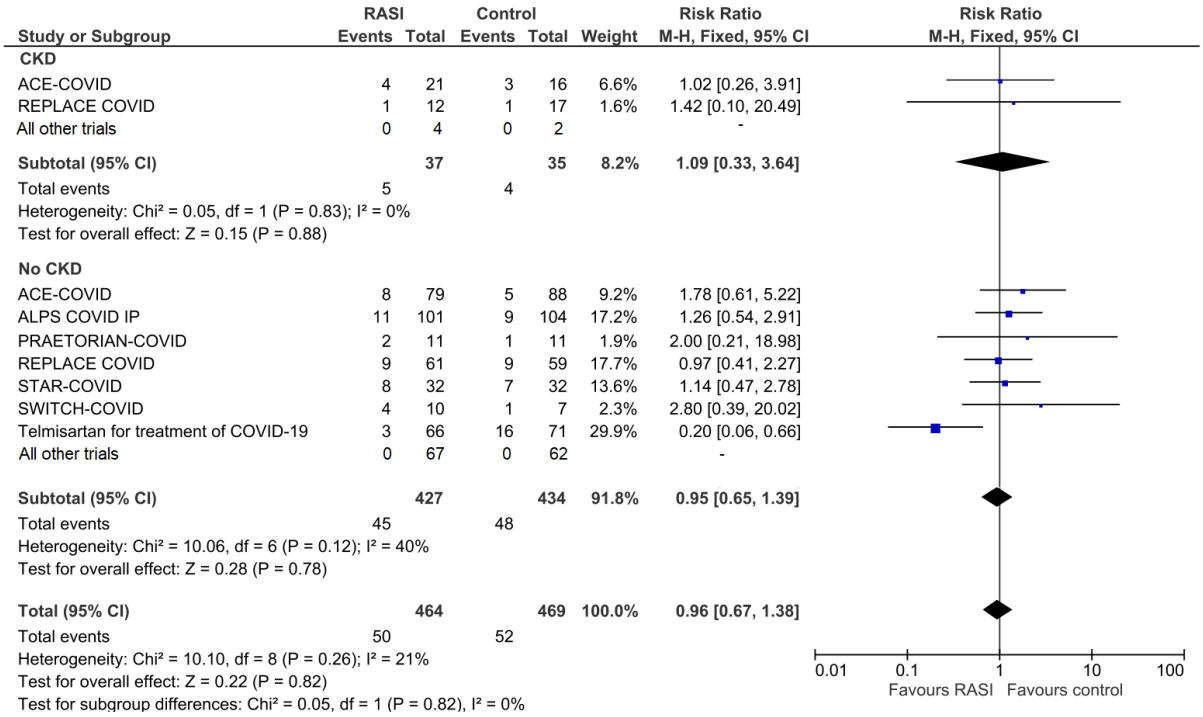


Figure S17: All-Cause Mortality - Smoker vs Non-Smoker

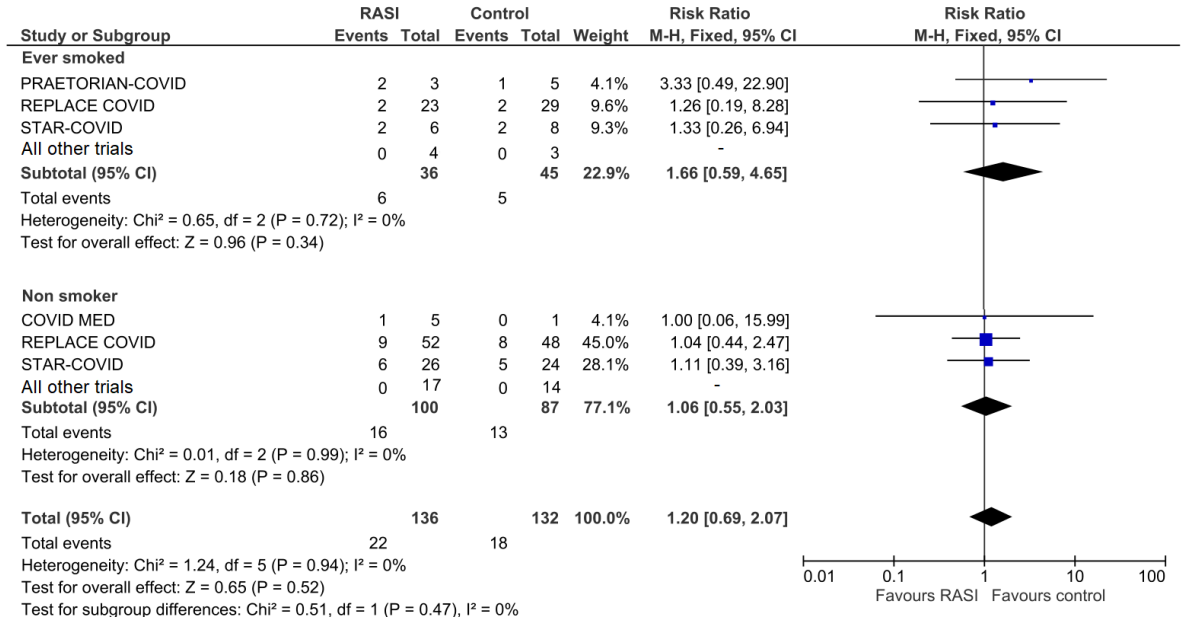


Figure S18: Meta-regression of loss to follow-up versus all-cause mortality

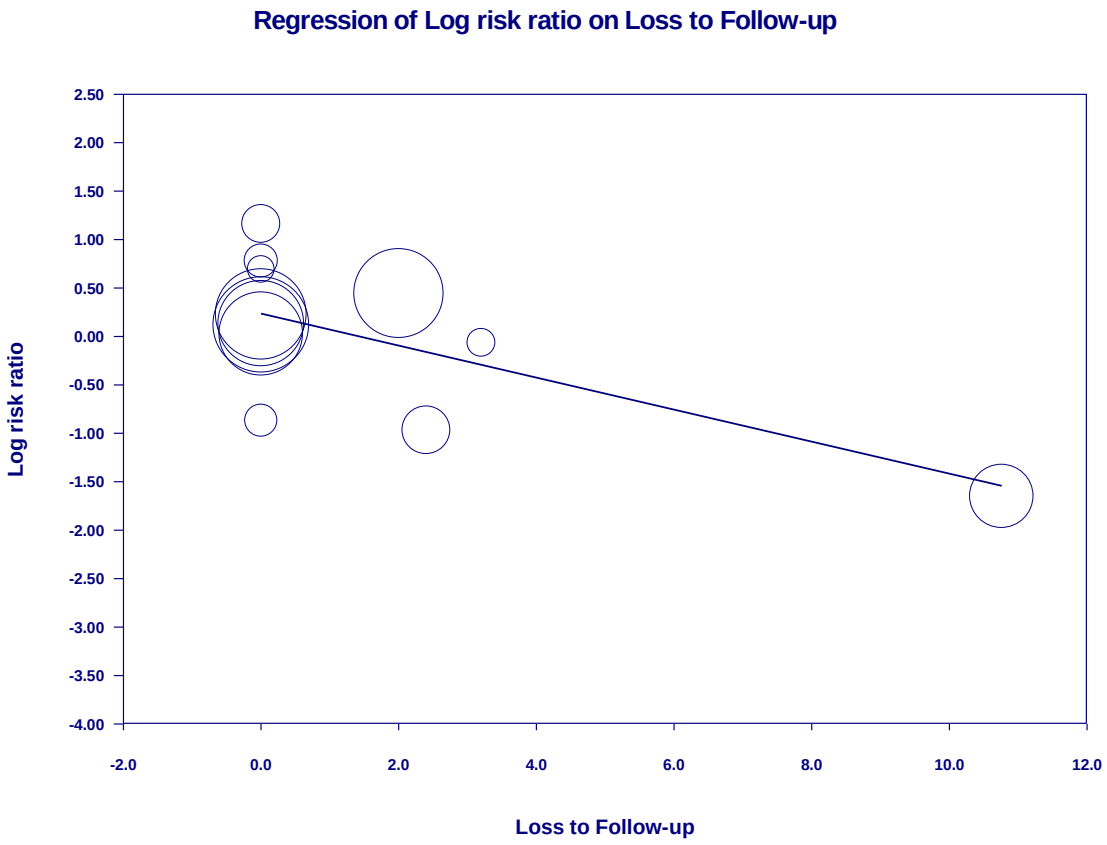


Figure S19: Network Meta-analysis comparing control vs ACEi or ARB – Mortality Risk Ratio with 95%CI.

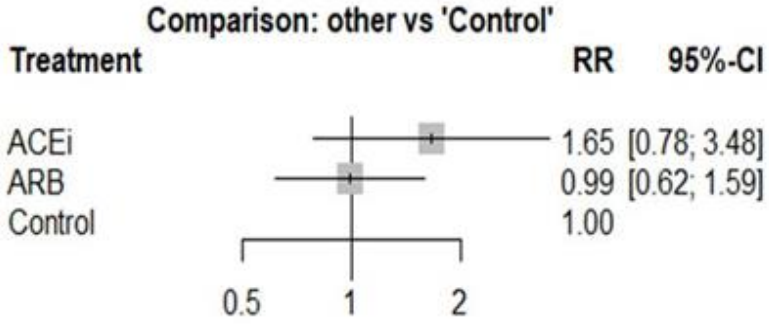


Figure S20: Network Meta-analysis comparing control, ACEi and ARB Rankogram Plot - Probability of having a specific rank.

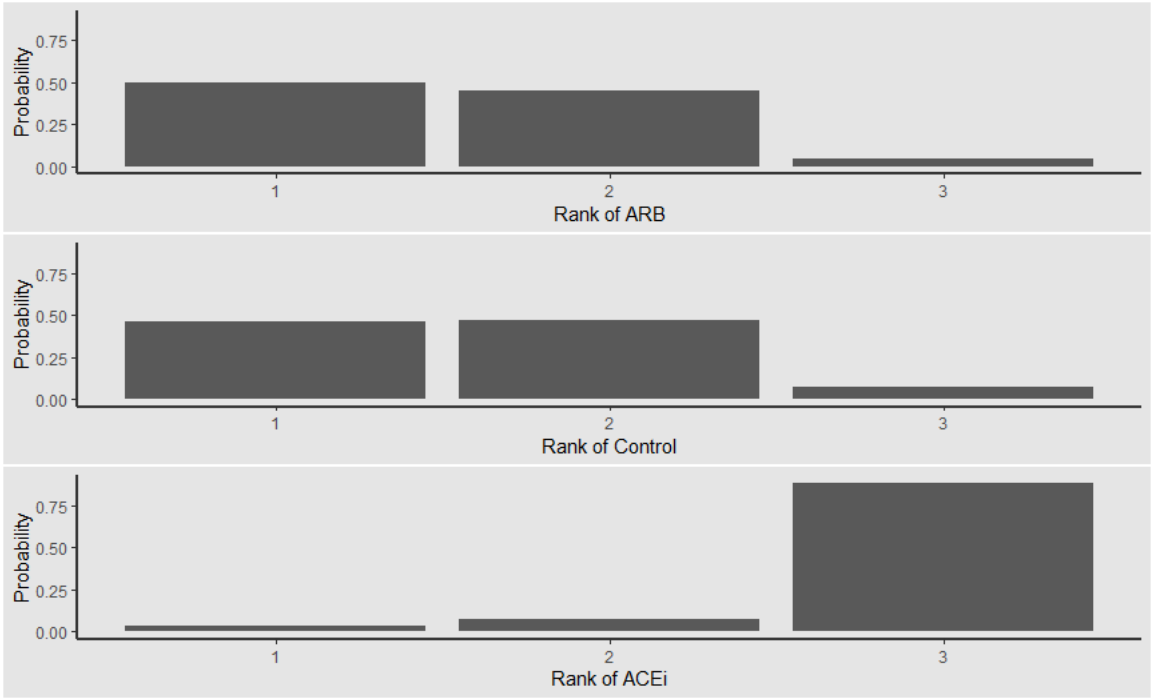


Figure S21: Cerebrovascular Events

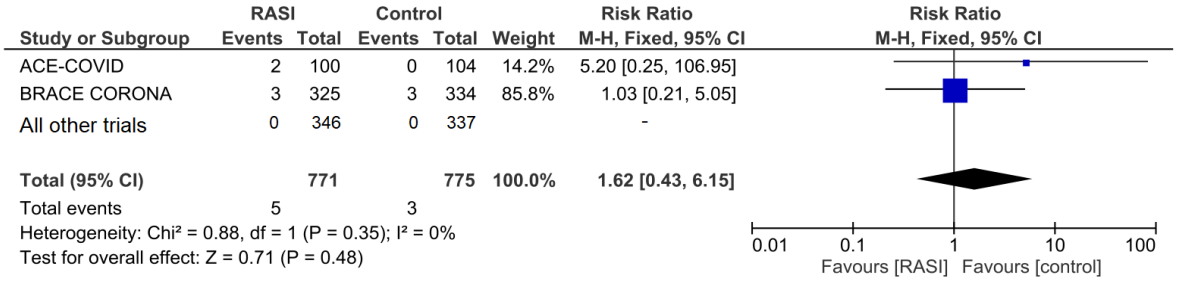
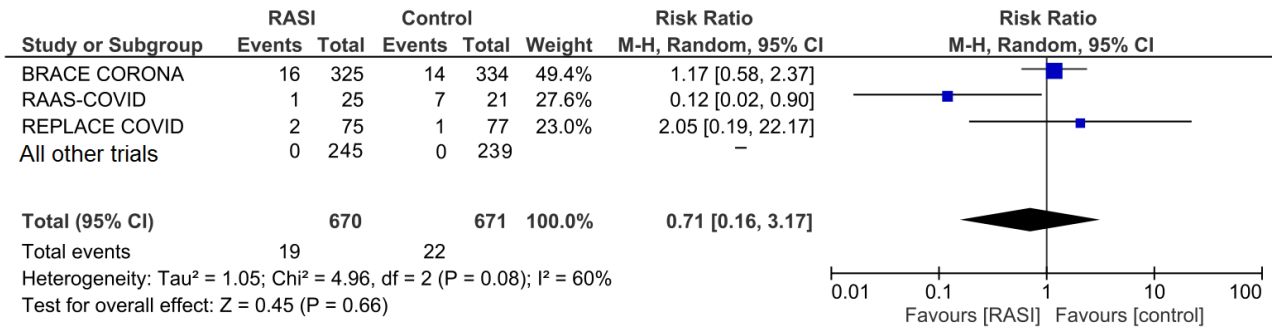


Figure S22: Congestive Cardiac Failure

(A) Random Effects



(B) Fixed Effects

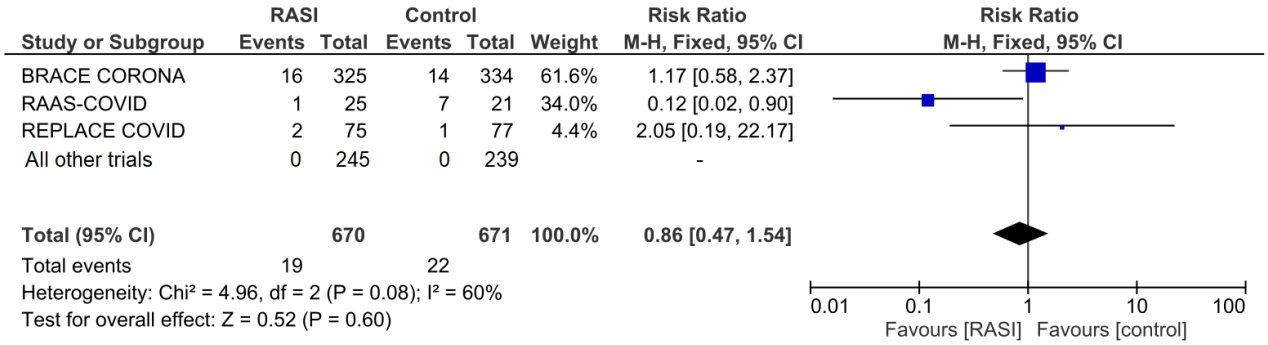


Figure S23: Venous Thromboembolism

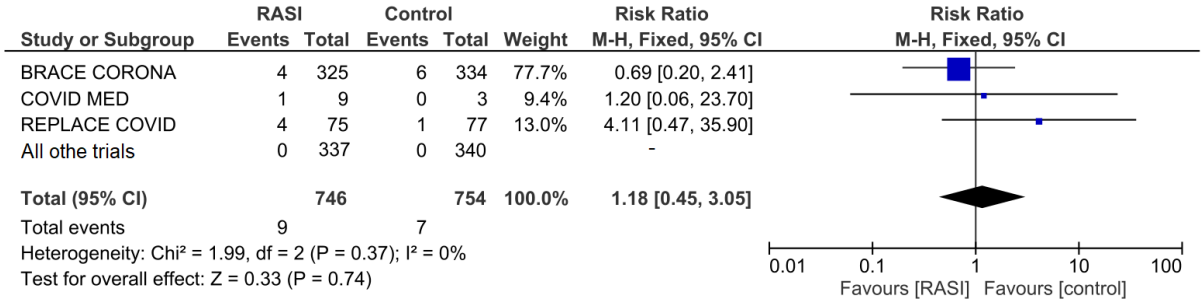


Figure S24: Hospitalisation

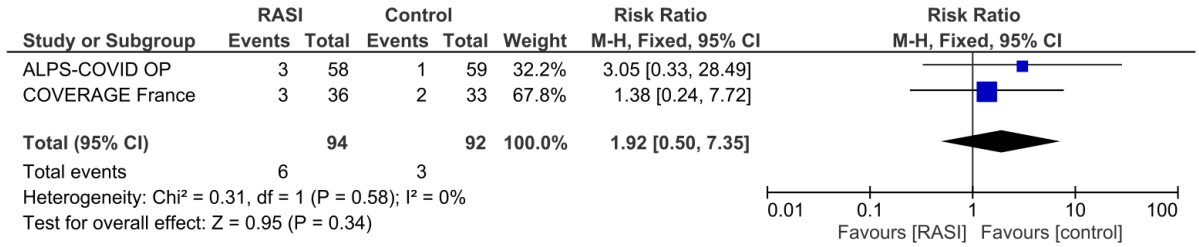


Figure S25: ICU admission –Start vs Continue/Discontinue Trials

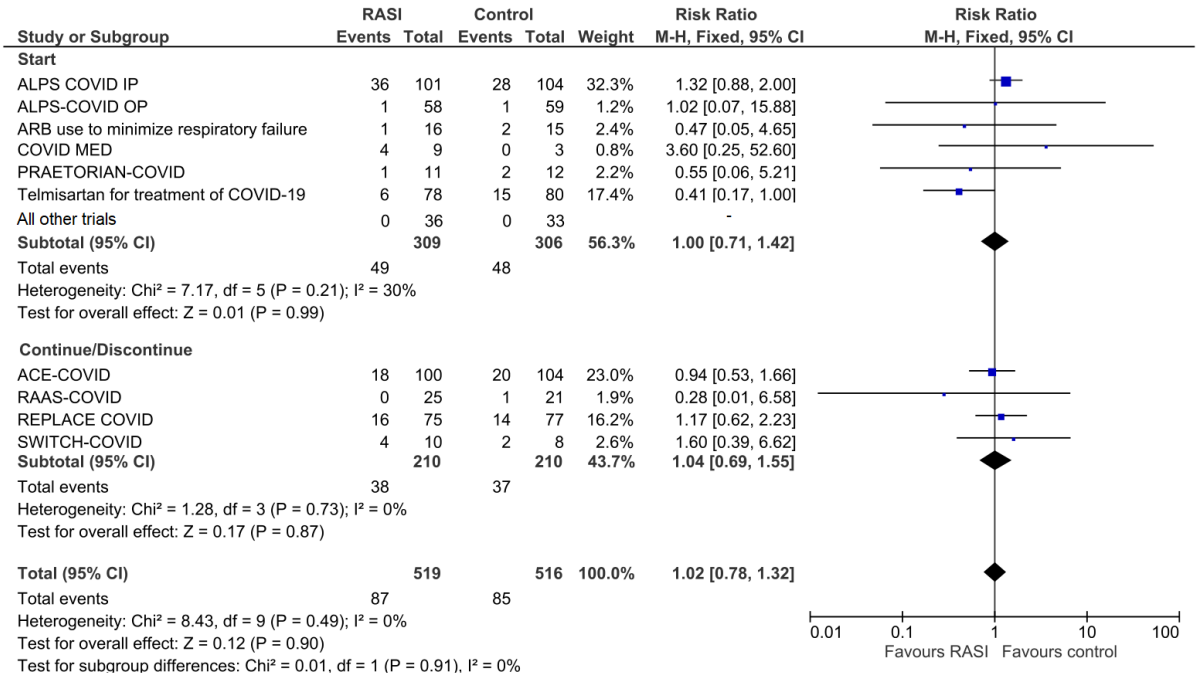


Figure S26: Mechanical Ventilation –Start vs Continue/Discontinue Trials

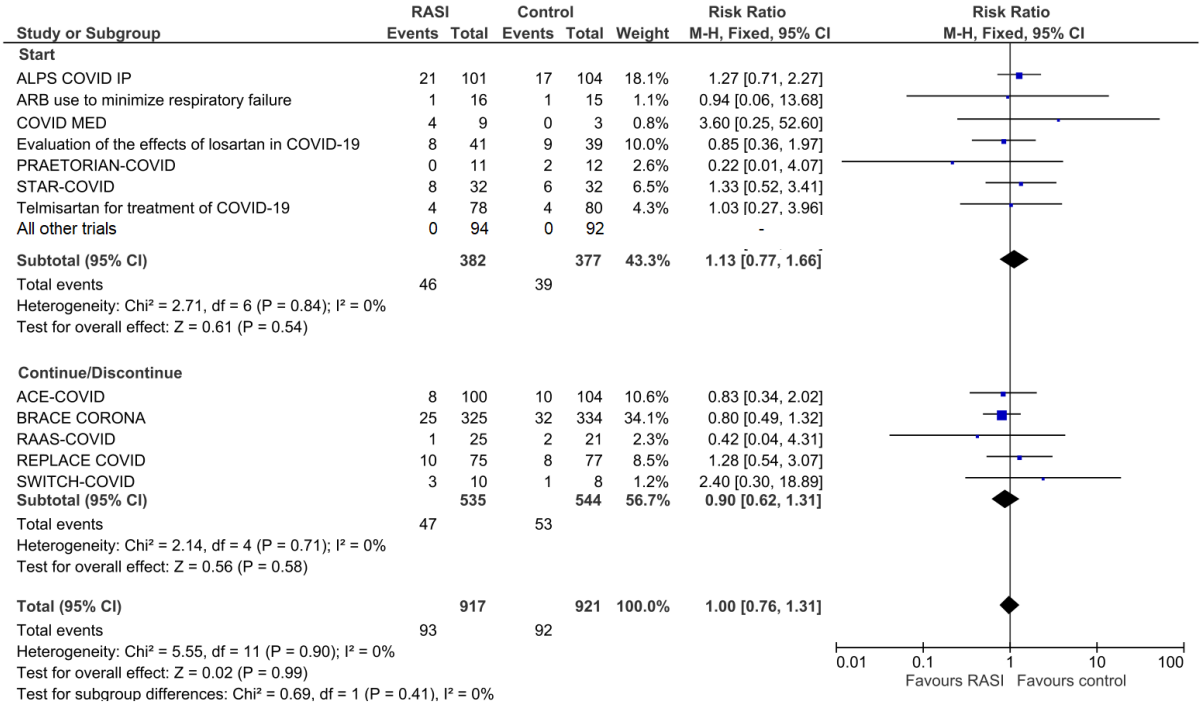


Figure S27: Hypotension requiring Inotropes by COVID-19 severity

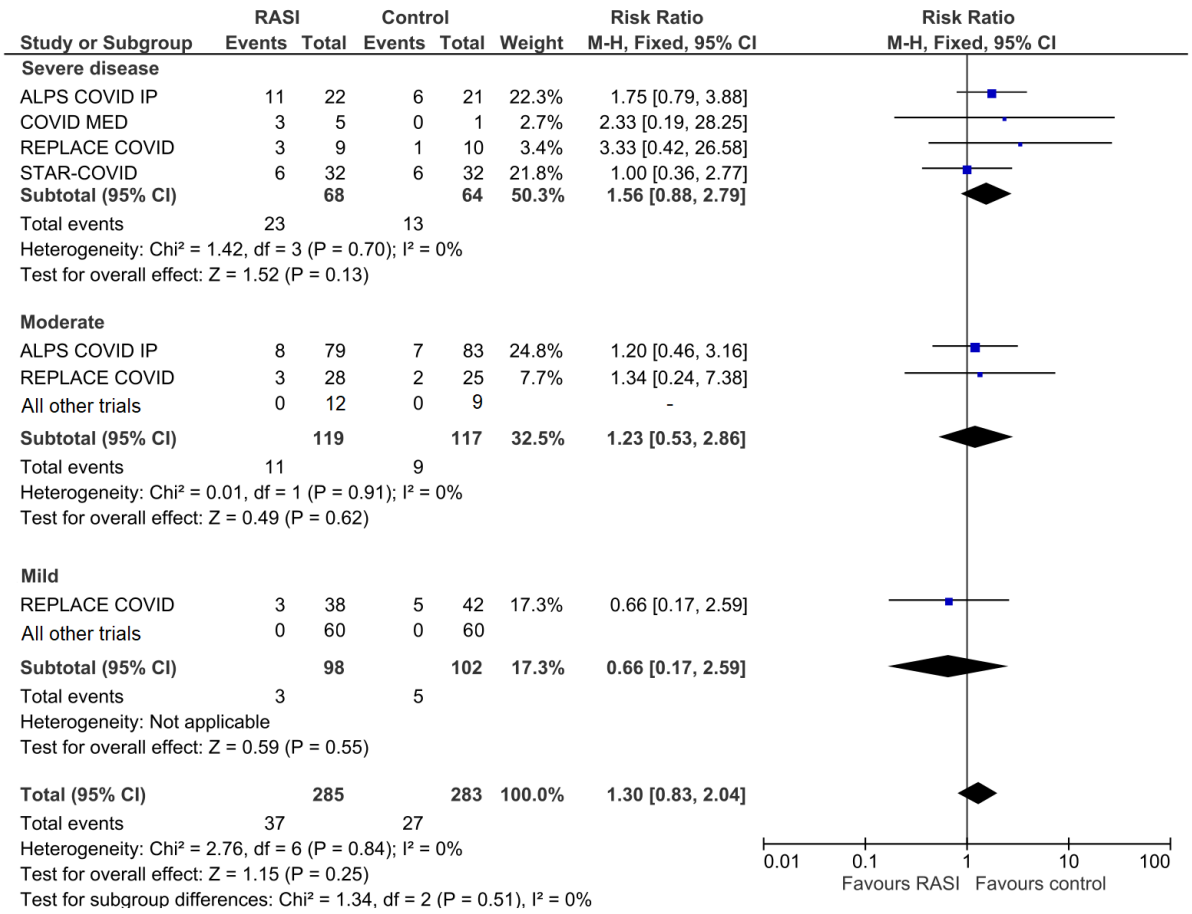


Figure S28: Inotropes – Start vs Continue/Discontinue Trials

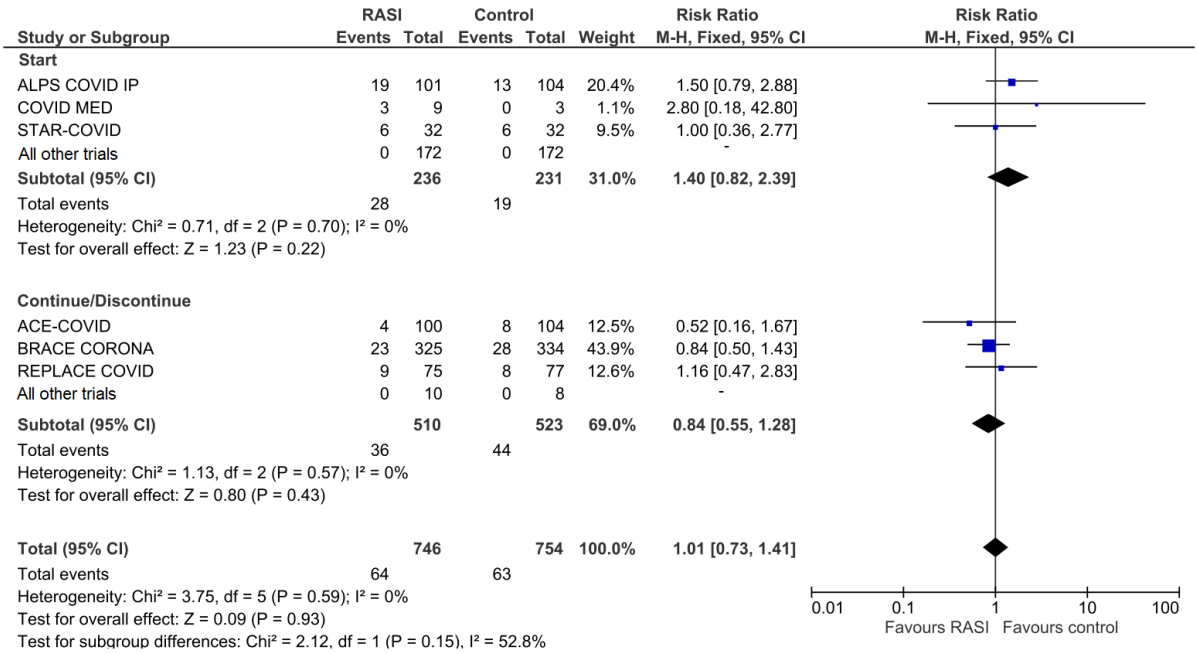


Figure S29: Acute Kidney Injury – Start vs Continue/Discontinue Trials

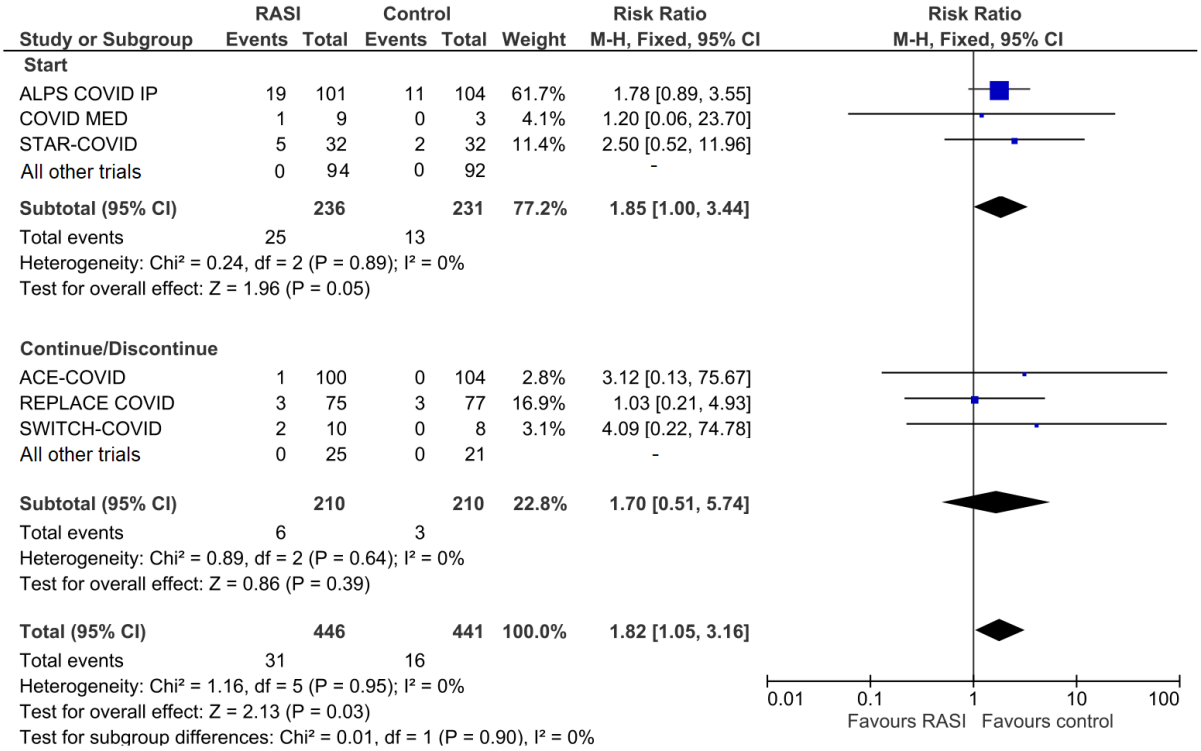


Figure S30: Acute Kidney Injury – Severity of COVID-19