

Supplementary Materials

Supplementary Figures

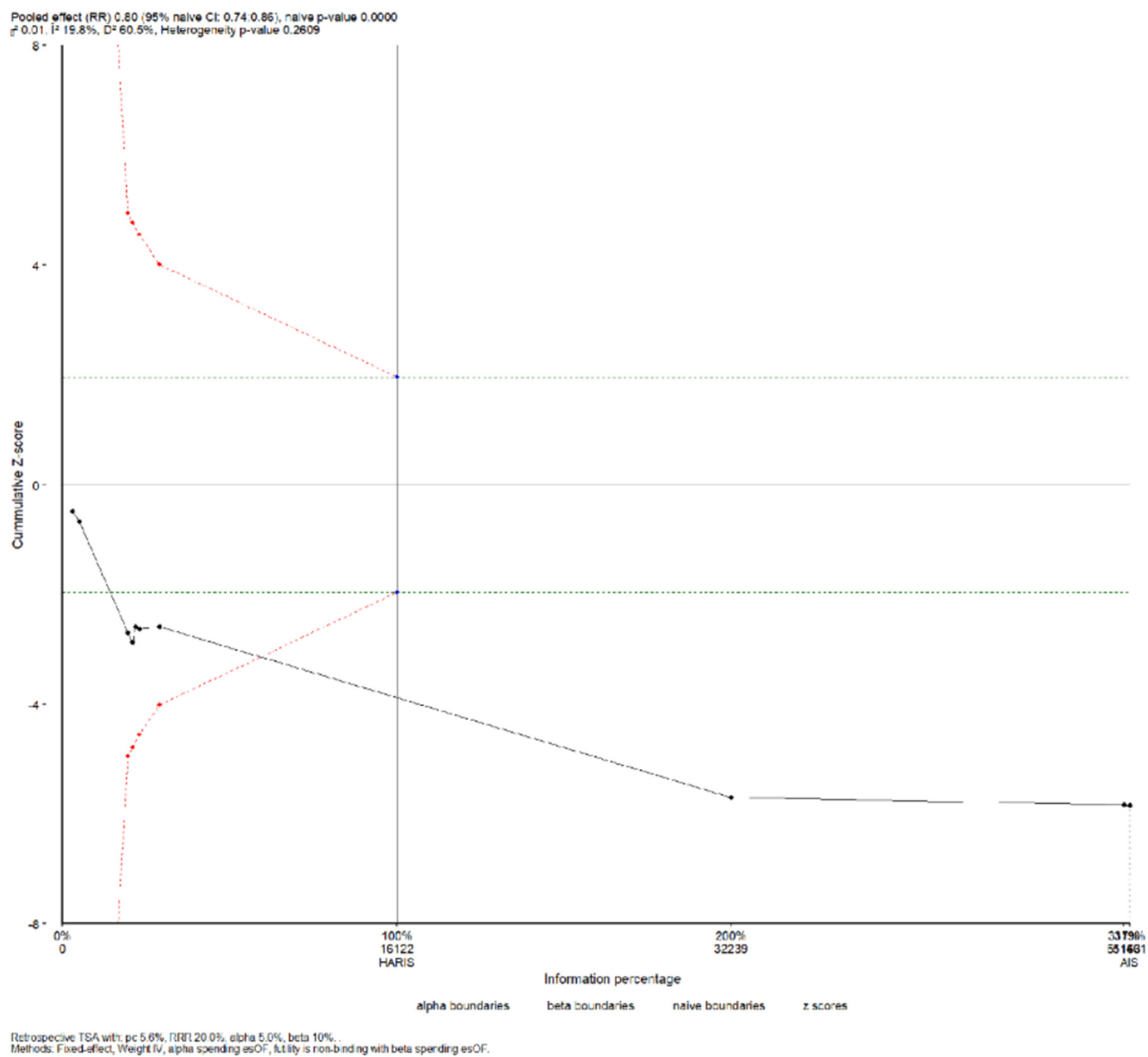


Figure S1. Trial Sequential Analysis for Myocardial Infarction.

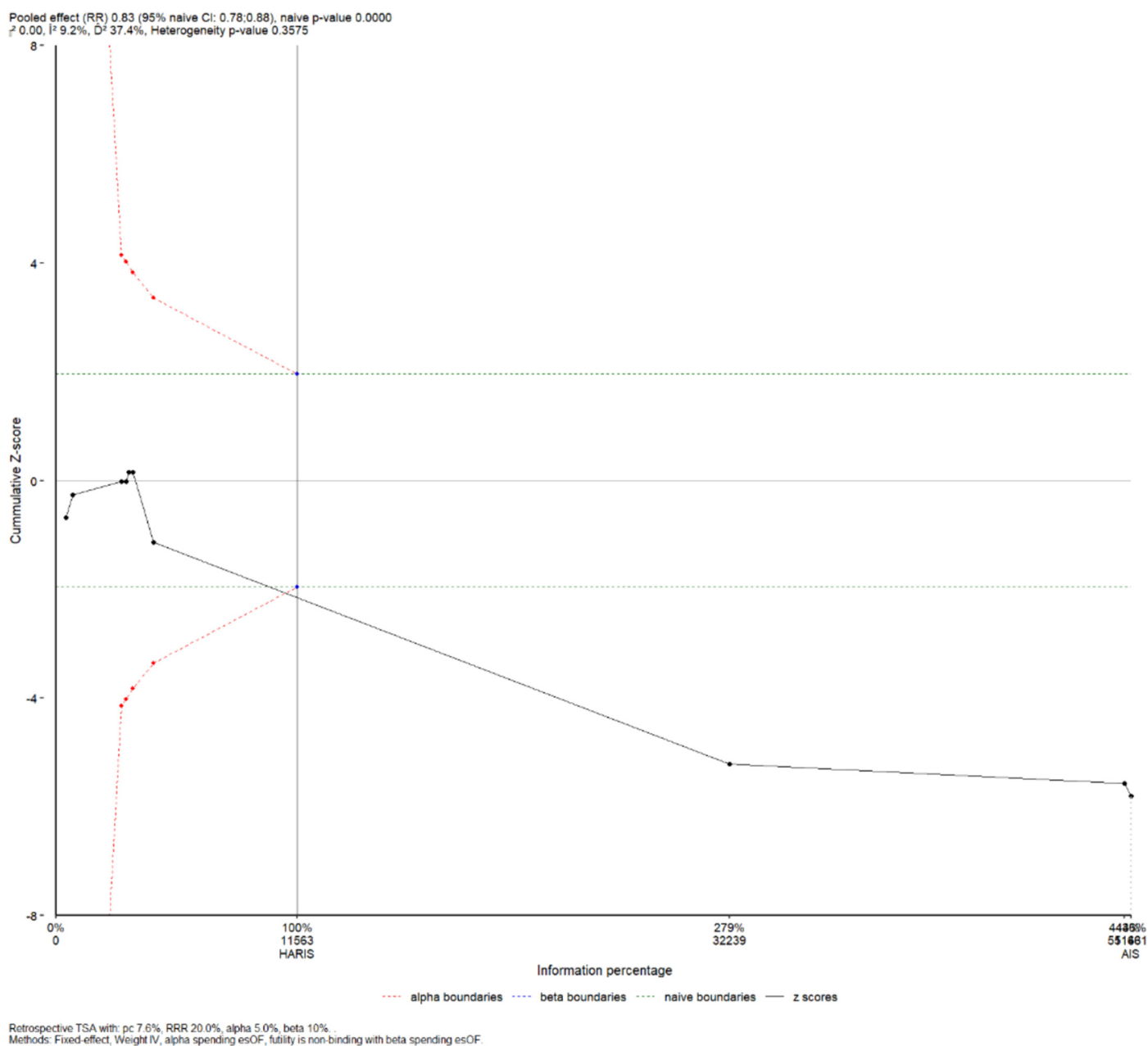


Figure S2. Trial Sequential Analysis for Coronary Revascularisation.

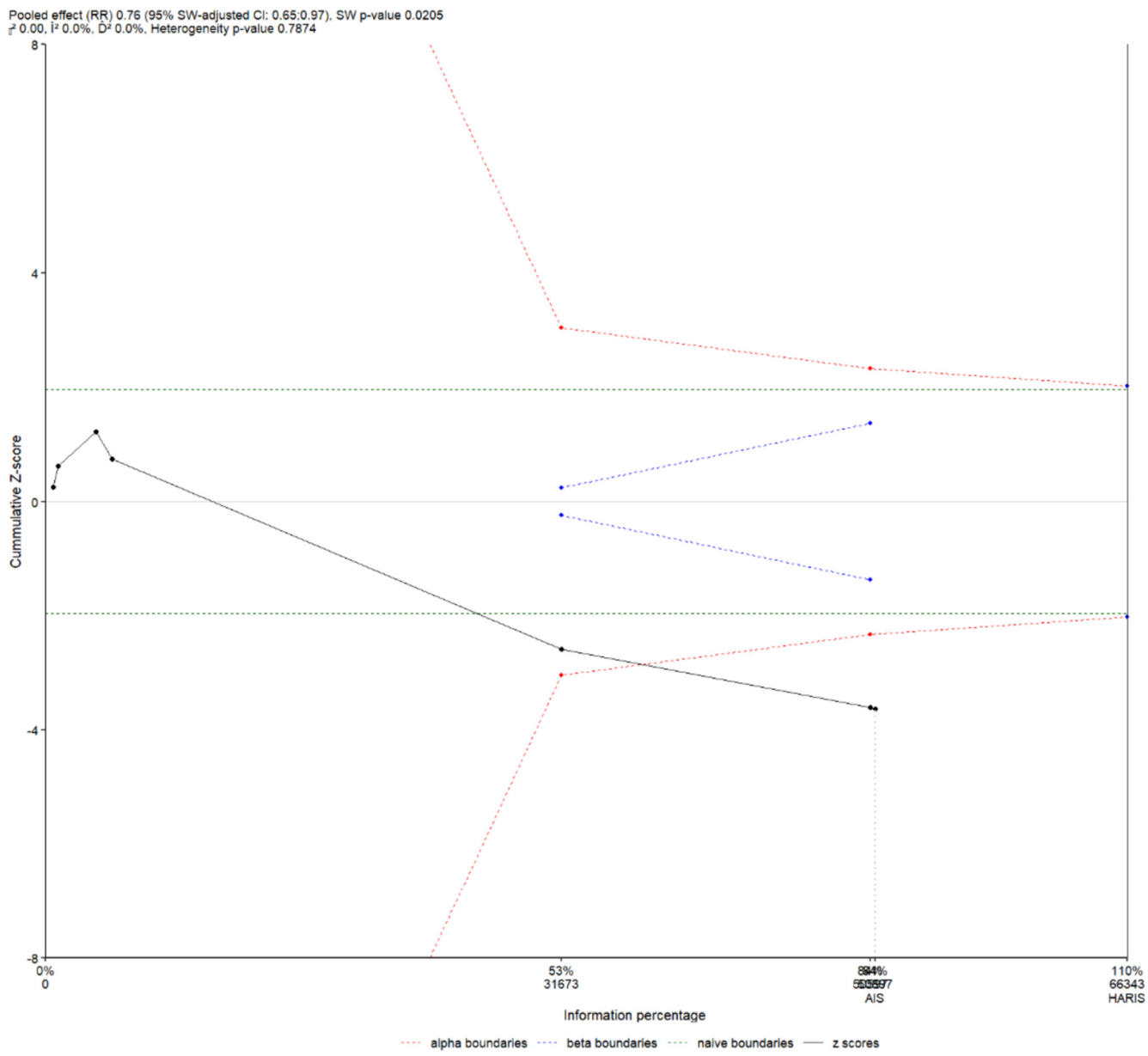
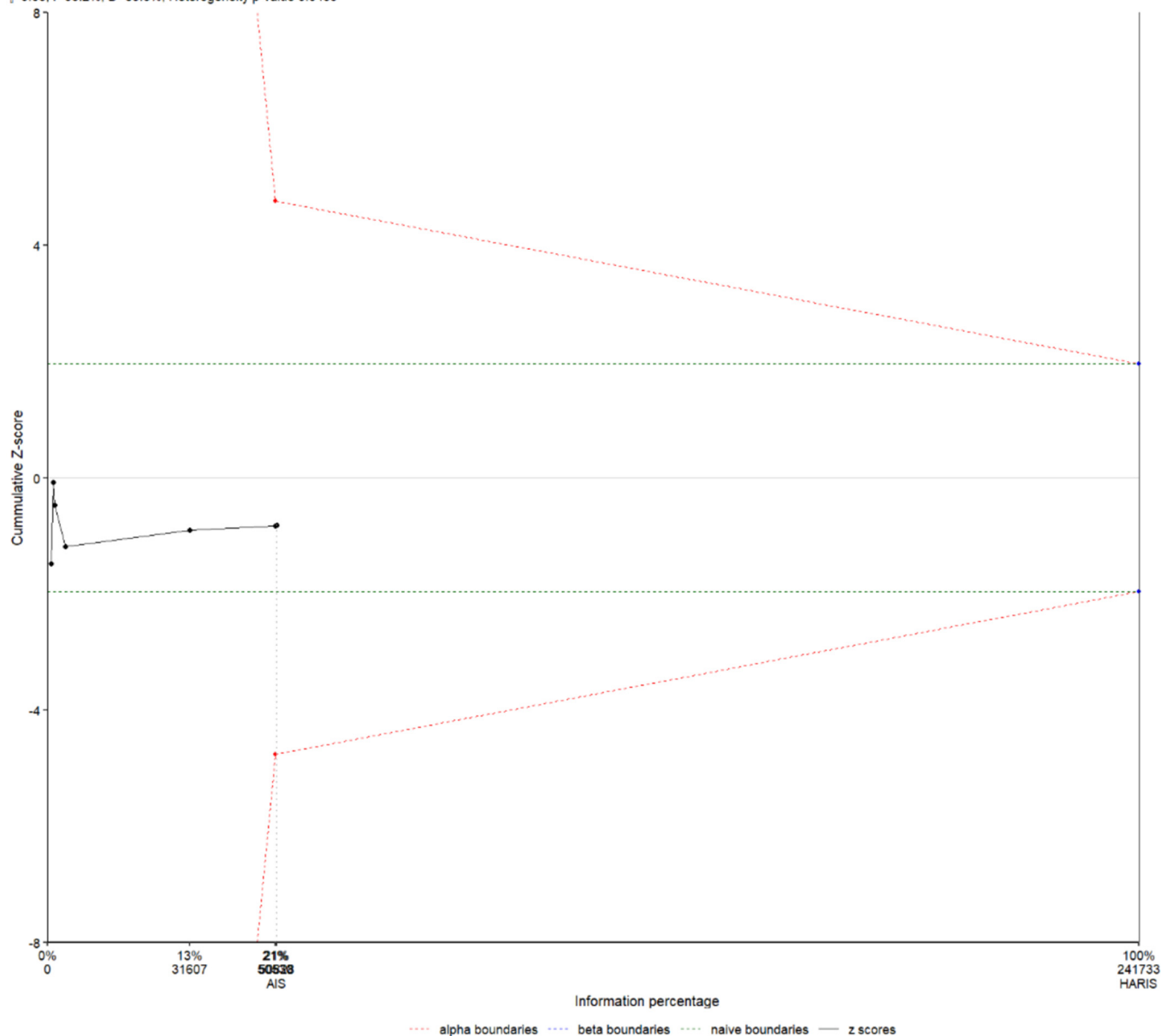


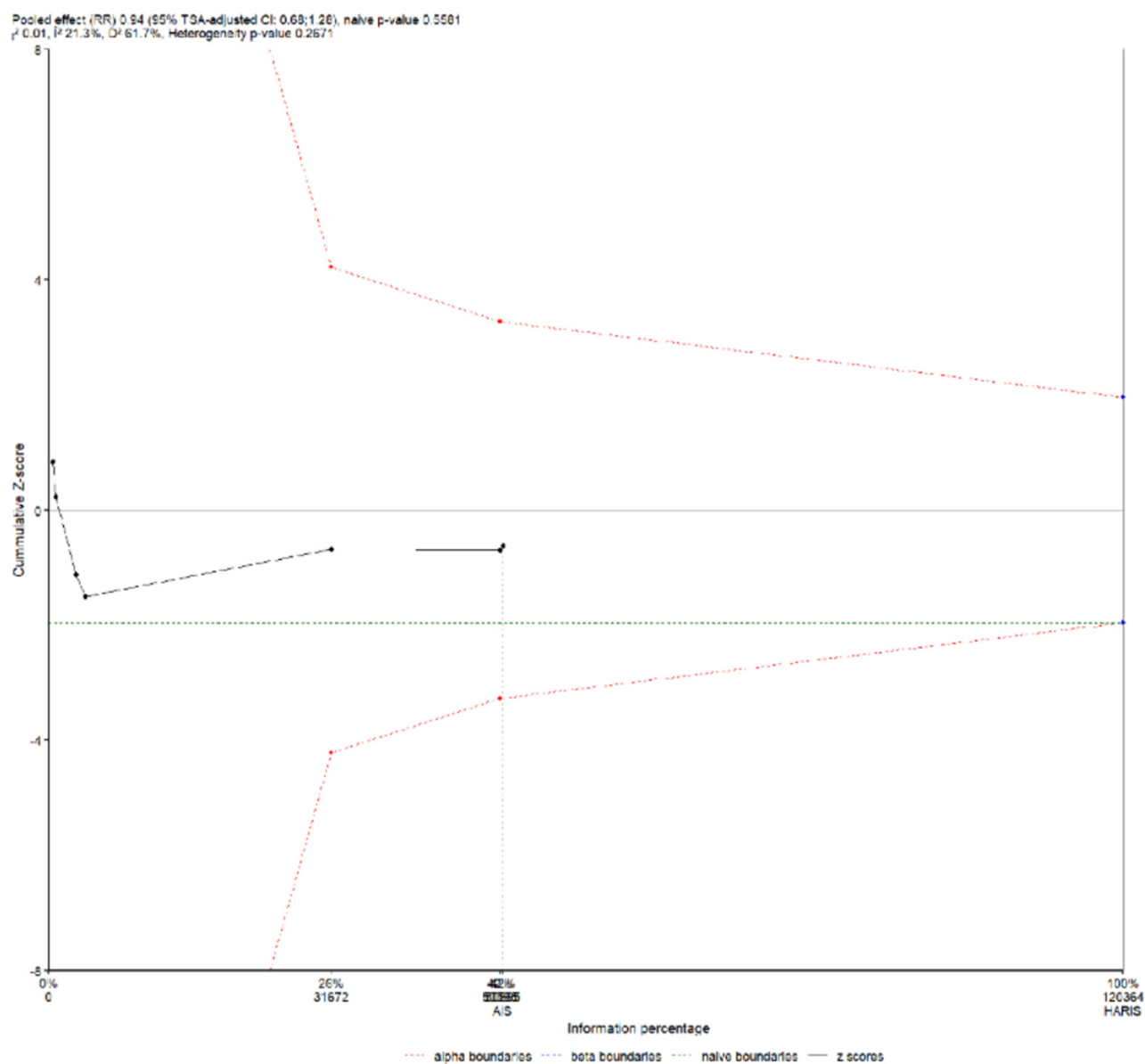
Figure S3. Trial Sequential Analysis for Ischemic Stroke.

Pooled effect (RR) 0.88 (95% TSA-adjusted CI: 0.39;1.93), naive p-value 0.4463
 τ^2 0.03, I^2 53.2%, D^2 89.6%, Heterogeneity p-value 0.0459



Retrospective TSA with: pc 3.4%, RRR 20.0%, alpha 5.0%, beta 10%. Sample size is adjusted by tau2 and assuming 7 additional trials.
 Methods: Random-effects, DL_HKSJ, Weight IV, alpha spending esOF, futility is non-binding with beta spending esOF.

Figure S4. Trial Sequential Analysis for All-cause Mortality.



Retrospective TSA with: ρ 2.1%, RRR 20.0%, alpha 5.0%, beta 10%. Sample size is adjusted by τ^2 and assuming 3 additional trials.
 Methods: Random-effects, DL_HKS; Weight IV, alpha spending esOT , futility is non-binding with beta spending esOT .

Figure S5. Trial Sequential Analysis for Cardiovascular Death.

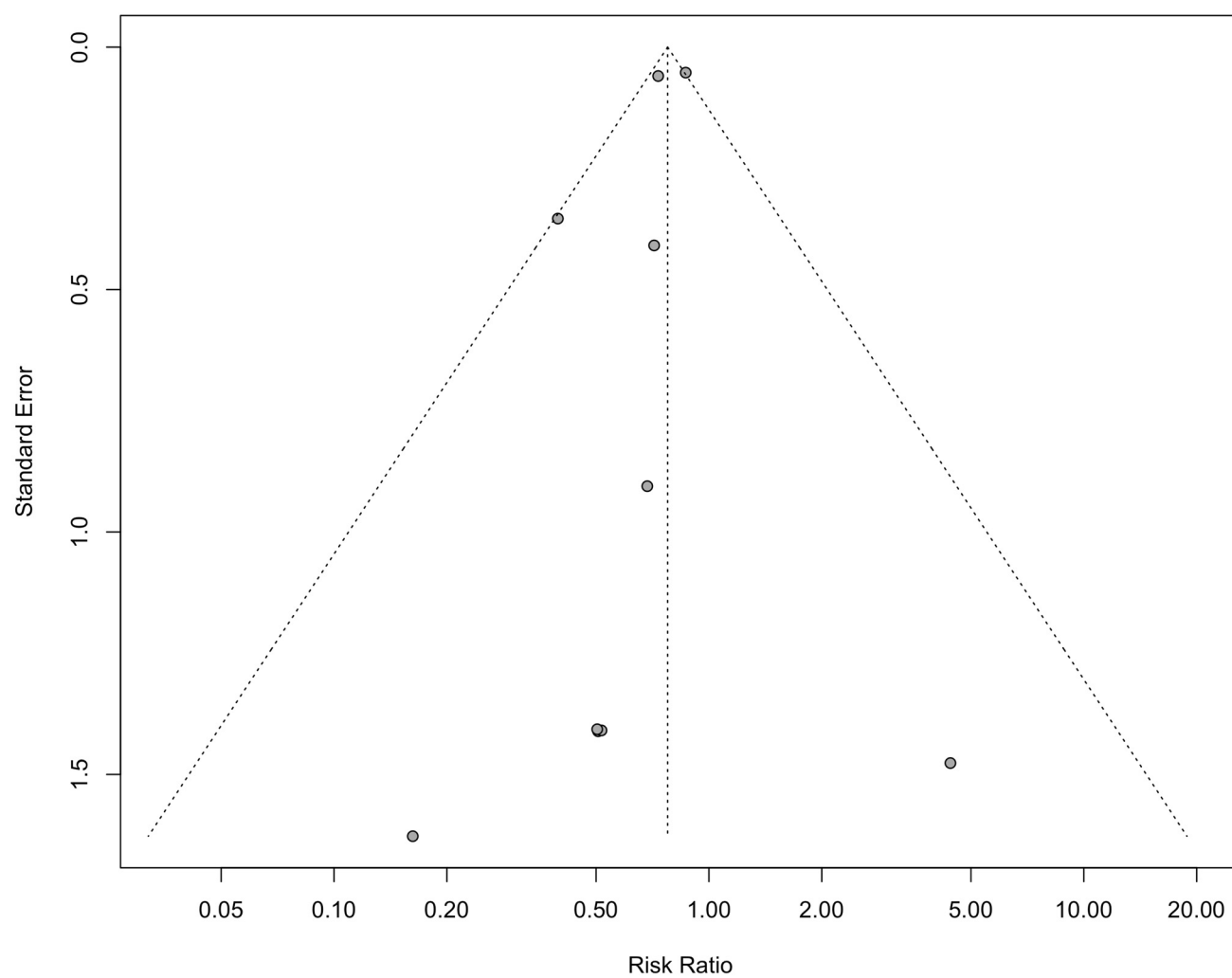


Figure S6. Funnel Plot for Myocardial Infarction.

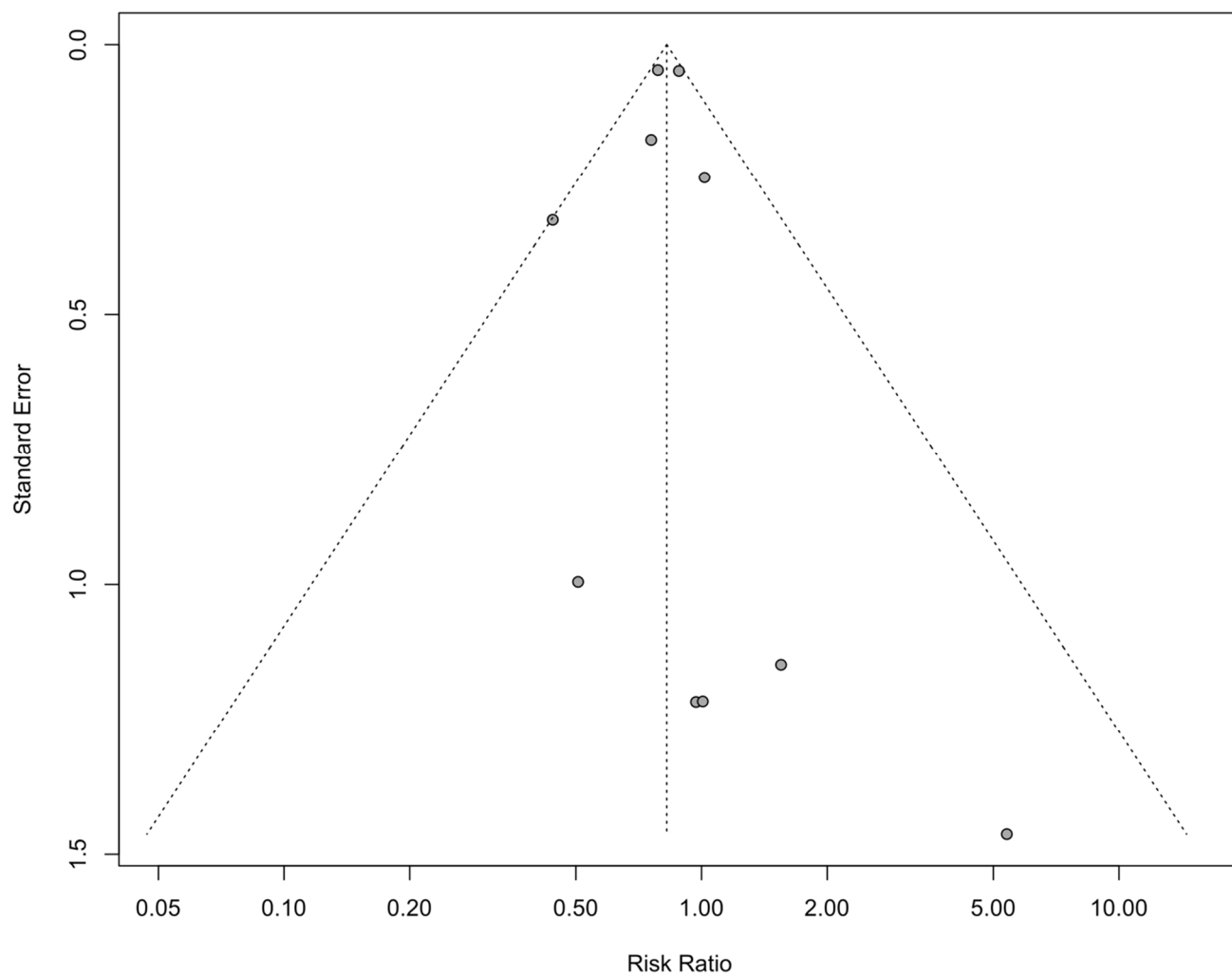


Figure S7. Funnel Plot for Coronary Revascularisation.

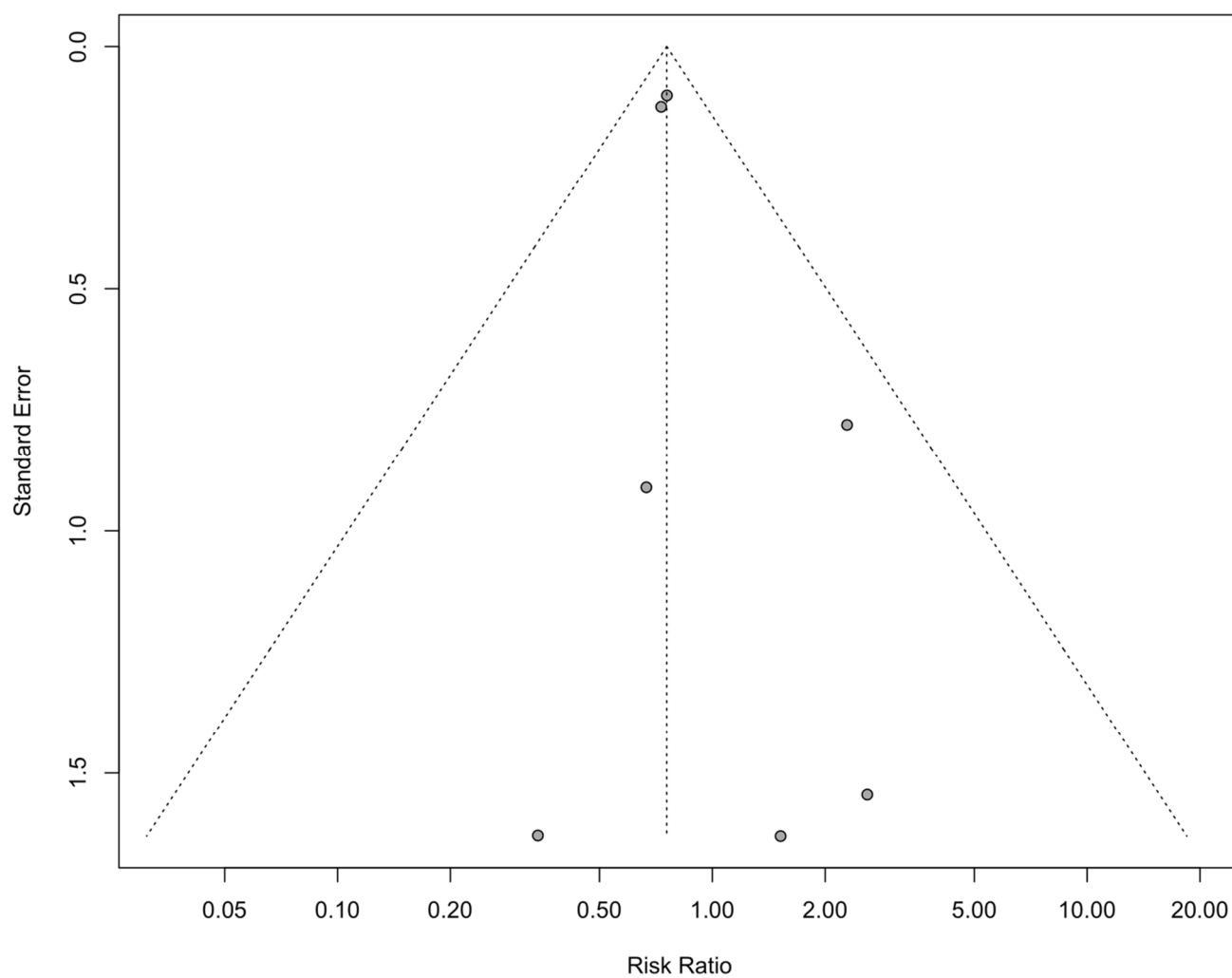


Figure S8. Funnel Plot for Ischaemic Stroke.

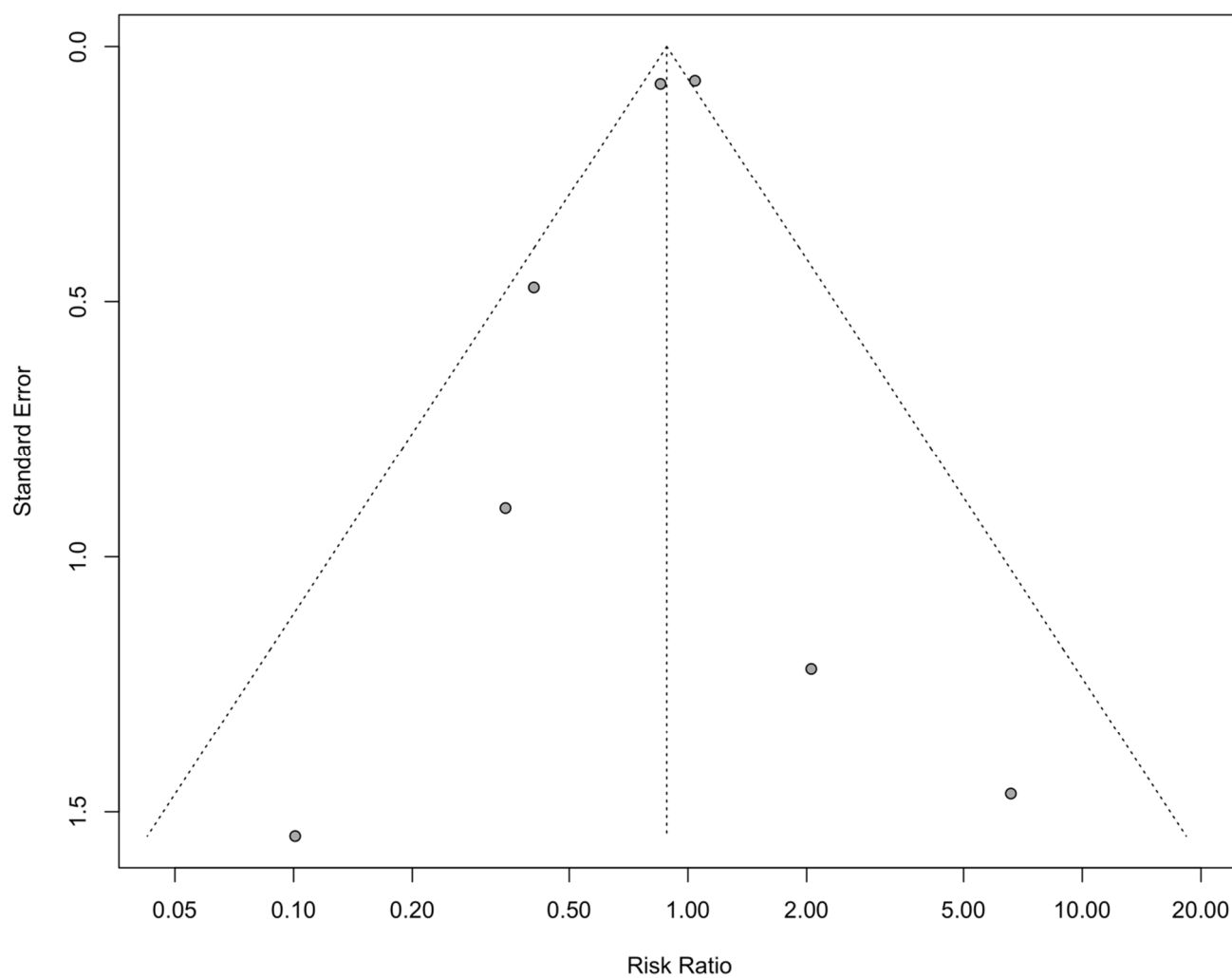


Figure S9. Funnel Plot for All-cause Mortality.

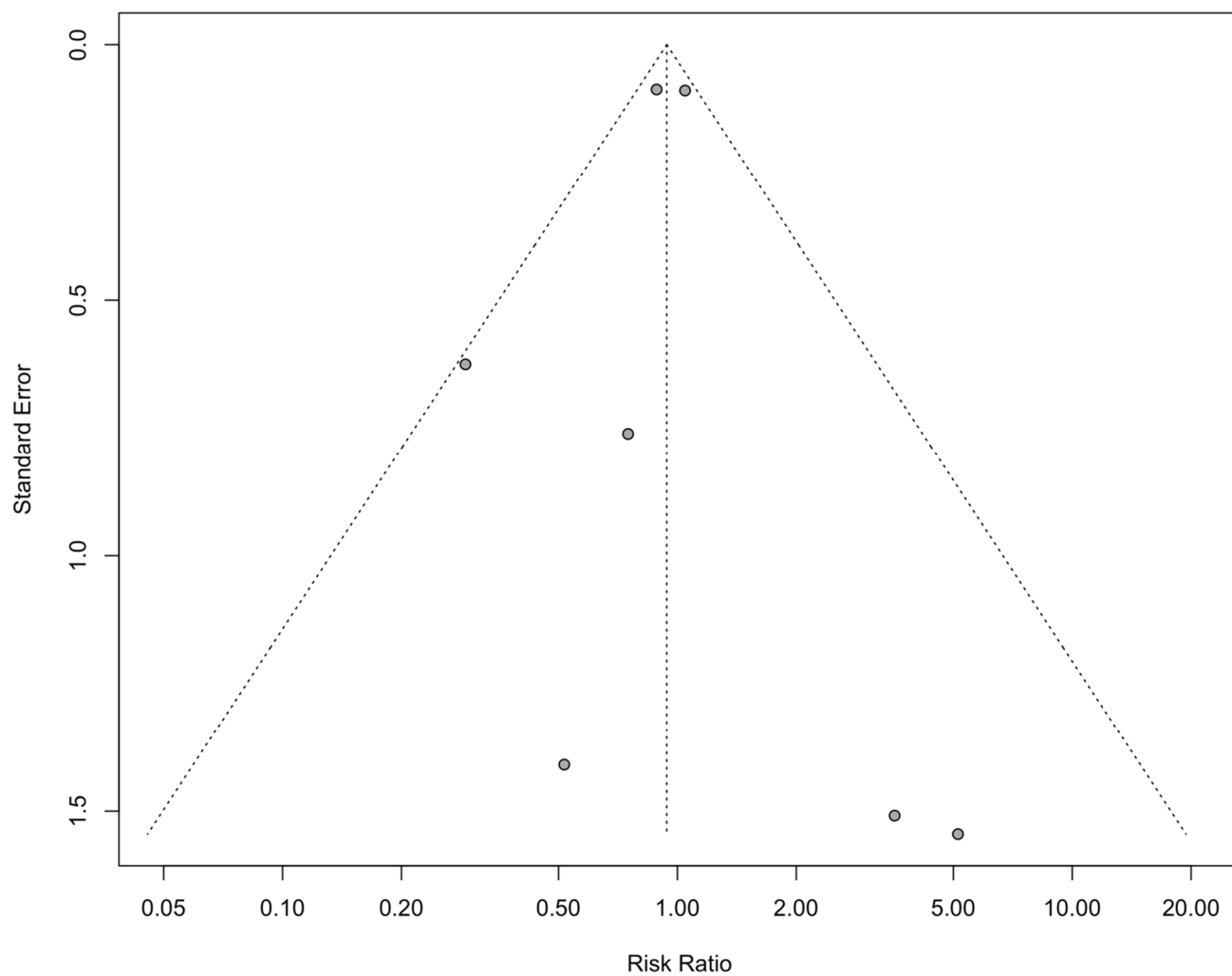


Figure S10. Funnel Plot for Cardiovascular Death.

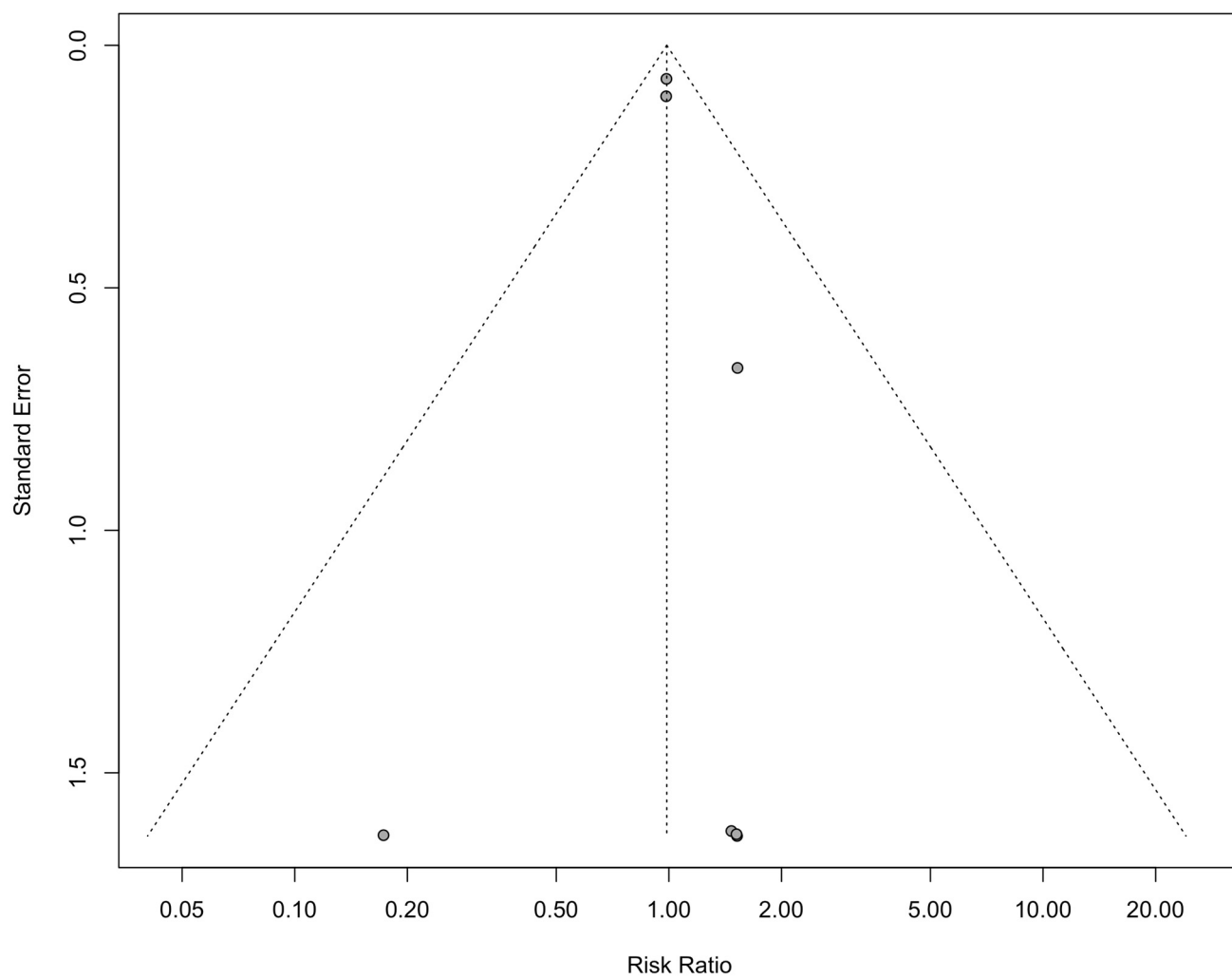


Figure S11. Funnel Plot for Hospitalisation for Heart Failure.

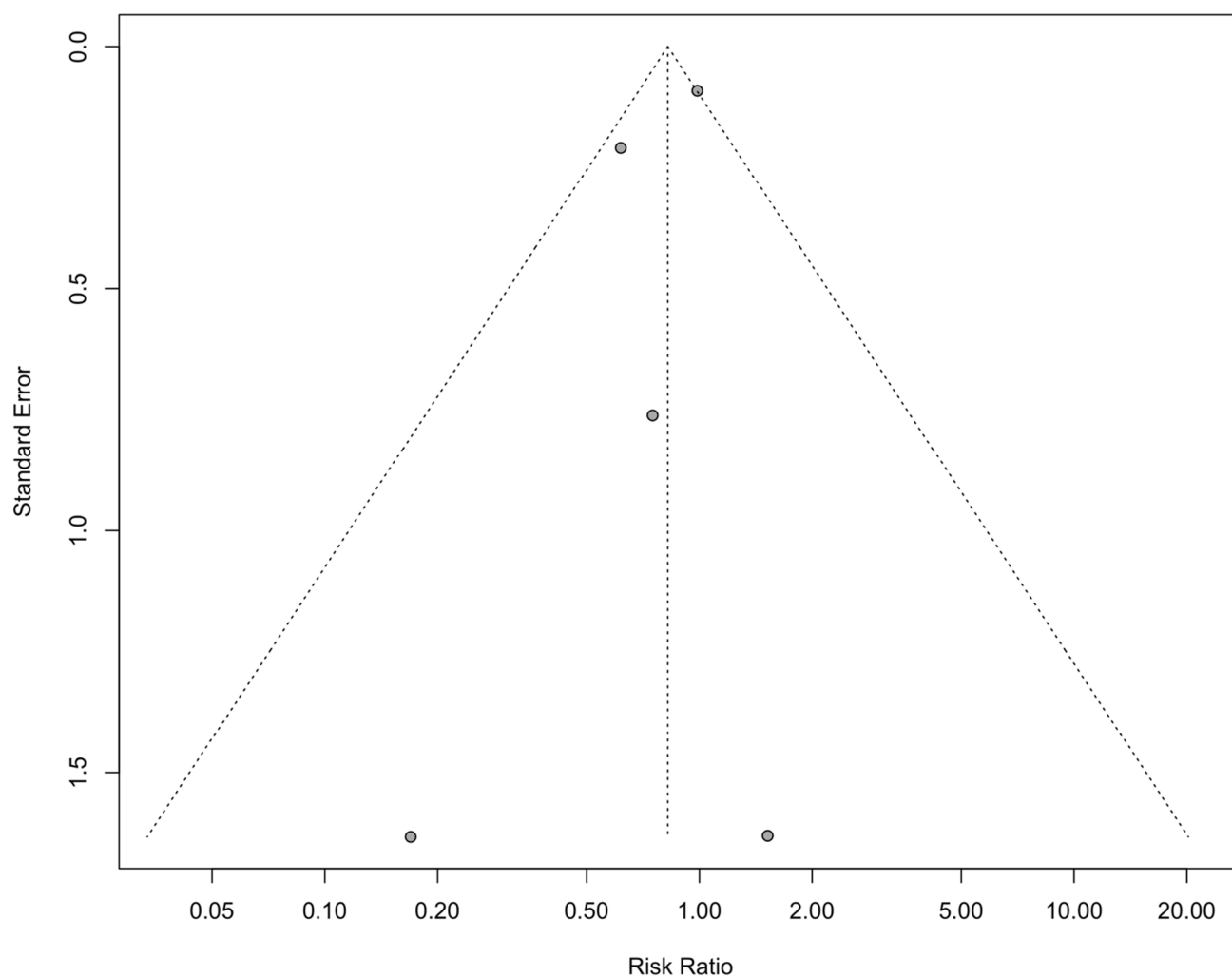


Figure S12. Funnel Plot for Hospitalisation for Unstable Angina.

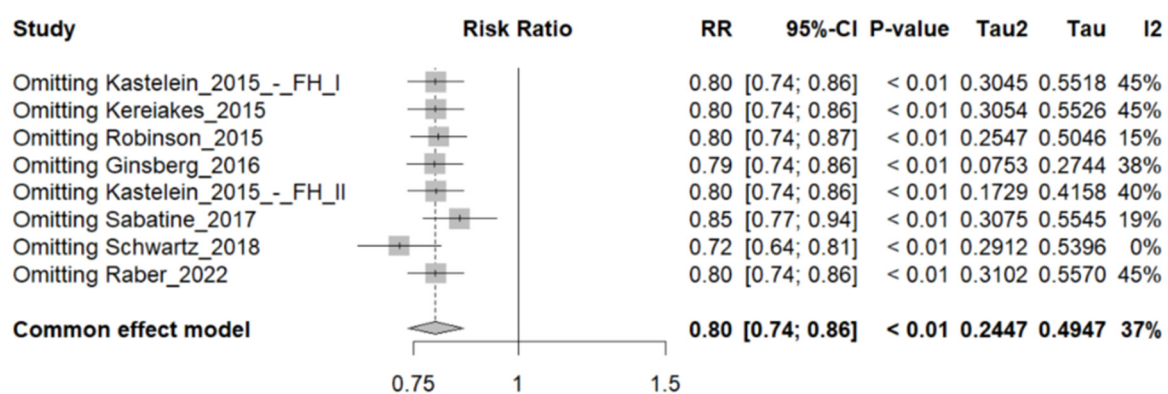


Figure S13. Leave one out Analysis for Myocardial Infarction.

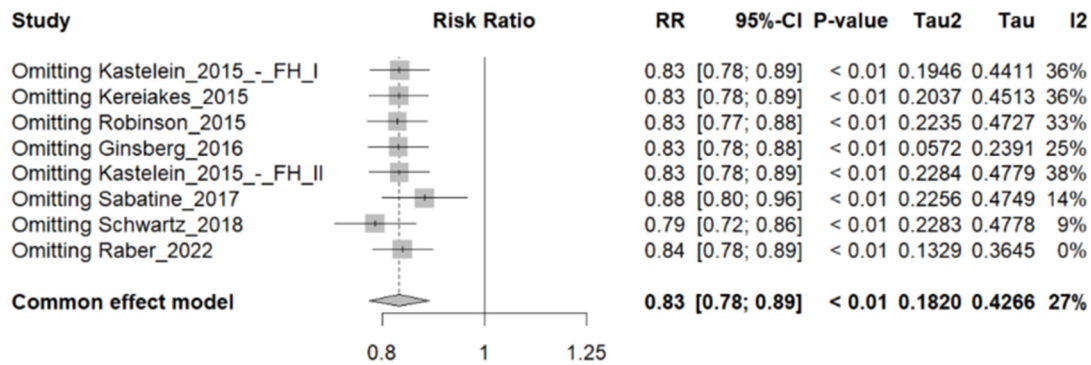


Figure S14. Leave one out Analysis for Coronary Revascularisation.

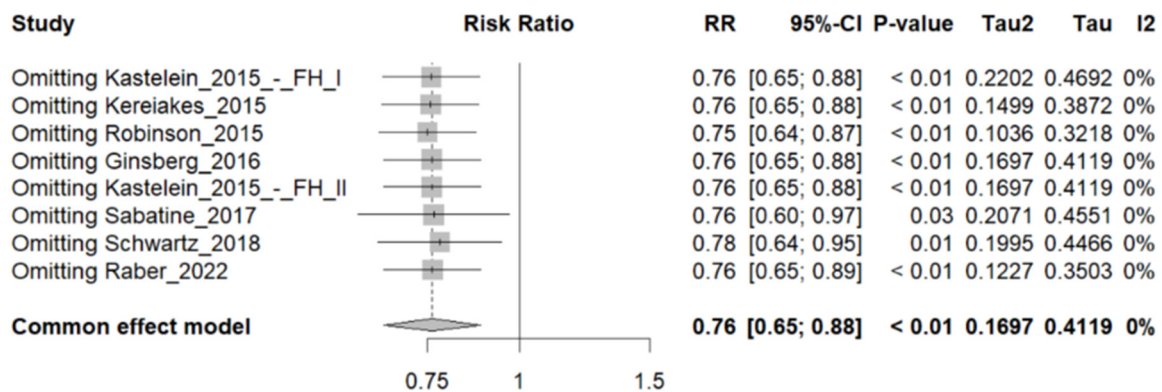


Figure S15. Leave one out Analysis for Ischemic Stroke.

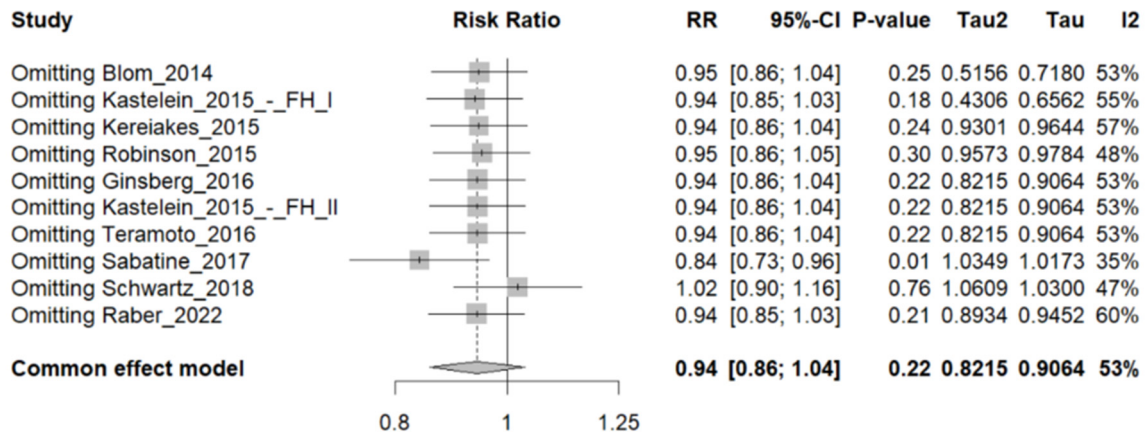


Figure S16. Leave one out Analysis for All-cause Mortality.

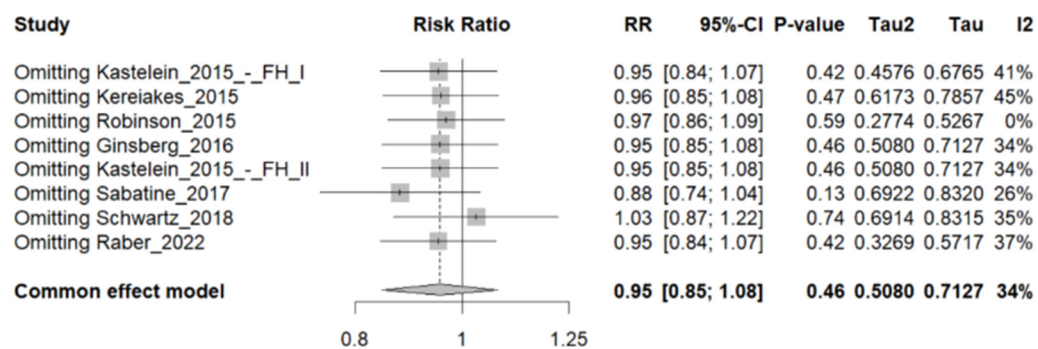


Figure S17. Leave one out Analysis for Cardiovascular Death.

Supplementary Tables

Table S1. Search Strategy.

	Adults AND
Population	Cardiovascular disease OR CVD OR ASCVD OR atherosclerotic cardiovascular disease OR dyslipidaemia OR dyslipidemia OR hyperlipidaemia OR hyperlipidemia OR hypercholesterolaemia OR hypercholesterolemia
Intervention	PCSK9 inhibitor OR PCSK9 monoclonal antibodies OR alirocumab OR evolocumab OR Repatha OR bococizumab OR Proprotein convertase subtilisin kexin type 9 OR proprotein convertase 9 OR Anticholesteremic Agents OR inhibit Proprotein Convertase Subtilisin OR inhibit Kexin Type 9 OR Ralpancizumab OR RN317 OR SAR236553 OR AMG145 OR Praluent
Comparator	Placebo
Outcomes	MACE OR Major Adverse Cardiovascular Events OR Cardiac Events OR Adverse Cardiac Event OR coronary disease OR Coronary Occlusion OR coronary revascularisation OR coronary revascularization OR Mortality OR Heart Failure OR Sudden Cardiac Death OR Arrhythmia OR Stroke OR cerebrovascular accident OR Myocardial Infarction OR MI OR AMI OR Infarction OR cardiovascular mortality OR cardiovascular death OR unstable angina OR HFrEF OR HFpEF OR Atrial Fibrillation OR SCD OR AF OR Atrial Flutter OR SVT OR PSVT OR VT OR VF Or Supraventricular Tachycardia OR Ventricular Tachycardia OR Ventricular Fibrillation OR Atrial Flutter OR Wolff-Parkinson-White OR WPW OR Torsades de Pointes

Table S2. Summary of studies that met inclusion criteria.

Author Year	Study Period	Country	Study Design	Sample Size (n)	Intervention	PCSK9i (n)	Placebo (n)	Length of Follow-up	Mean Age: PCSK9i	Mean Age: Placebo	Men–n (%) PCSK9i	Men–n (%) Placebo
Blom et al. 2014	January 2012–November 2013	Multinational	Randomised controlled trial	901	Evolocumab 420 mg every 4 weeks	599	302	52 weeks	55.9 ± 10.8	56.7 ± 10.1	290 (48.4)	140 (46.4)
Kastelein et al. 201–FH I 5	July 2012–December 2014	Multinational	Randomised controlled trial	486	Alirocumab 75 mg every 2 weeks	323	163	78 weeks	52.1 ± 12.9	51.7 ± 12.3	180 (55.7)	94 (57.7)
Kastelein et al. 2015–FH II	December 2012–January 2015	Multinational	Randomised controlled trial	249	Alirocumab 75 or 150 mg every two weeks	167	82	78 weeks	53.2 ± 12.9	53.2 ± 12.5	86 (51.5)	45 (54.9)
Kereiakes et al. 2015	July 2012–April 2014	United States	Randomised controlled trial	316	Alirocumab 75 or 150 mg every 2 weeks	209	107	52 weeks	63.0 ± 9.5	63.0 ± 8.8	131 (62.7)	77 (72.0)
Robinson et al. 2015		Multinational	Randomised controlled trial	2341	Alirocumab 150 mg every 2 weeks	1553	788	78 weeks	60.4 ± 10.4	60.6 ± 10.4	983 (63.3)	474 (60.2)
Ginsberg et al. 2016	June 2012–January 2015	Multinational	Randomised controlled trial	107	Alirocumab 150 mg every two weeks	72	35	78 weeks	49.8 ± 14.2	52.1 ± 11.2	35 (48.6)	22 (62.9)
Nicholls et al. 2016	May 2013–January 2015	Multinational	Randomised controlled trial	968	Evolocumab 420 mg every 4 weeks	484	484	78 weeks	59.8 ± 9.6	59.8 ± 8.8	349 (72.1)	350 (72.3)
Sabatine et al. 2017	February 2013–June 2015	Multinational	Randomised controlled trial	27,564	Evolocumab 140 mg every 2 weeks	13,784	13,780	113 weeks	62.5 ± 9.1	62.5 ± 8.9	10,397 (75.4)	10,398 (75.5)
Schwartz et al. 2018	November 2012–November 2017	Multinational	Randomised controlled trial	18,924	Alirocumab 75 mg every two weeks	9462	9462	146 weeks	58.5 ± 9.3	58.6 ± 9.4	7072 (74.7)	7090 (74.9)
Raber et al. 2022	May 2017–October 2021	Multinational	Randomised controlled trial	300	Alirocumab 150 mg every two weeks	148	152	52 weeks	58.4 ± 10.0	58.6 ± 9.4	124 (83.8)	119 (78.3)
Teramoto et al. 2016	March 2014–September 2015	Japan	Randomised controlled trial	215	Alirocumab 75 mg every two weeks	143	72	52 weeks	60.3 ± 9.7	61.8 ± 9.0	84 (58.3)	47 (65.3)

Note: PCSK9i, proprotein convertase subtilisin kexin 9 inhibitor; mg, milligrams.

Table S3. Risk of Bias—Joanna Briggs Institute Tool for Randomised Controlled Trials.

[illegible]

Table S4. Bayesian Meta-analysis Results for Myocardial Infarction.

Prior Belief for θ		Posterior Median OR (95% Credible Interval)	Posterior Probability for True RR (%)		
Prior Belief for τ^2			RR < 1.0	RR < 0.9	RR < 0.8
Non-informative	Uniform	0.730 (0.383–1.179)	94.2	88.8	71.4
	Half-normal	0.741 (0.456–1.045)	96.8	91.8	71.8
	Tibshirani	0.752 (0.462–1.039)	97.1	92.6	70.6
Sceptical	Uniform	0.817 (0.628–1.144)	89.5	75.7	42.5
	Half-normal	0.808 (0.634–1.074)	93.6	81.7	46.1
	Tibshirani	0.805 (0.641–1.054)	94.7	84.6	47.4
Optimistic	Uniform	0.729 (0.528–0.934)	99.2	96.1	78.6
	Half-normal	0.736 (0.546–0.921)	99.5	96.8	78.2
	Tibshirani	0.745 (0.559–0.915)	99.6	97.2	77.1

Table S5. Bayesian Meta-analysis Results for Coronary Revascularisation.

Prior Belief for θ Prior Belief for τ^2		Posterior Median RR (95% Credible Interval)	Posterior Probability for True RR (%)		
			RR < 1.0	RR < 0.9	RR < 0.8
Non-informative	Uniform	0.824 (0.562–1.192)	91.4	79.4	38.0
	Half-normal	0.824 (0.606–1.094)	94.1	82.4	36.8
	Tibshirani	0.825 (0.627–1.060)	95.6	84.9	34.5
Sceptical	Uniform	0.852 (0.693–1.127)	89.5	70.9	21.6
	Half-normal	0.848 (0.700–1.083)	92.3	74.5	21.8
	Tibshirani	0.844 (0.709–1.051)	94.4	78.5	21.3
Optimistic	Uniform	0.801 (0.608–0.977)	98.6	91.5	49.4
	Half-normal	0.805 (0.627–0.966)	98.9	92.1	47.2
	Tibshirani	0.809 (0.646–0.957)	99.2	93.0	43.8

Table S6. Bayesian Meta-analysis Results for Ischemic Stroke.

Prior Belief for θ Prior Belief for τ^2		Posterior Median RR (95% Credible Interval)	Posterior Probability for True RR (%)		
			RR < 1.0	RR < 0.9	RR < 0.8
Non-informative	Uniform	0.783 (0.471–1.635)	83.8	75.0	55.0
	Half-normal	0.774 (0.542–1.245)	90.4	82.0	59.6
	Tibshirani	0.777 (0.525–1.317)	89.3	80.5	58.0
Sceptical	Uniform	0.850 (0.656–1.240)	80.6	63.3	33.2
	Half-normal	0.831 (0.656–1.166)	86.4	70.5	37.8
	Tibshirani	0.837 (0.654–1.176)	85.7	68.8	36.0
Optimistic	Uniform	0.750 (0.573–0.979)	98.2	93.0	72.1
	Half-normal	0.750 (0.591–0.954)	98.7	94.3	73.2
	Tibshirani	0.750 (0.587–0.960)	98.7	93.8	72.3

Table S7. Bayesian Meta-analysis Results for All-cause Mortality.

Prior Belief for θ Prior Belief for τ^2		Posterior Median RR (95% Credible Interval)	Posterior Probability for True RR (%)		
			RR < 1.0	RR < 0.9	RR < 0.8
Non-informative	Uniform	0.840 (0.401–1.393)	82.9	63.4	42.2
	Half-normal	0.864 (0.504–1.237)	84.7	60.2	34.9
	Tibshirani	0.874 (0.490–1.253)	84.5	58.0	31.8
Sceptical	Uniform	0.916 (0.679–1.215)	77.1	44.1	15.7
	Half-normal	0.916 (0.697–1.171)	79.8	43.5	13.8
	Tibshirani	0.918 (0.706–1.163)	80.3	42.3	12.2
Optimistic	Uniform	0.777 (0.540–1.036)	96.4	82.6	56.7
	Half-normal	0.800 (0.568–1.037)	96.3	79.6	50.1
	Tibshirani	0.813 (0.573–1.041)	96.0	77.4	46.0

Table S8. Bayesian Meta-analysis Results for Cardiovascular Death.

Prior Belief for θ Prior Belief for τ^2		Posterior Median RR (95% Credible Interval)	Posterior Probability for True RR (%)		
			RR < 1.0	RR < 0.9	RR < 0.8
Non-informative	Uniform	0.915 (0.414–1.788)	69.4	46.5	28.1
	Half-normal	0.924 (0.551–1.383)	72.3	42.7	20.9
	Tibshirani	0.925 (0.521–1.448)	71.7	42.5	20.5
Sceptical	Uniform	0.951 (0.710–1.276)	66.8	31.8	9.6
	Half-normal	0.949 (0.732–1.222)	69.3	30.5	7.8
	Tibshirani	0.950 (0.735–1.220)	69.0	30.6	7.5
Optimistic	Uniform	0.815 (0.554–1.079)	93.1	73.4	46.1
	Half-normal	0.844 (0.591–1.080)	92.3	68.1	37.3
	Tibshirani	0.847 (0.591–1.084)	92.1	67.7	36.1