Supplemental Material

Table S1. Study Characteristics

Study	Year	Phase	Treatment duration, weeks	Investigational drug and dose	Control	Population	Statin	clinicaltrials.gov ID
DESCARTES [1]	2014	3	48	Evolocumab 420 mg Q4W	Placebo	HC	Both	NCT01516879
FOURIER[2]	2017	3	113	Evolocumab 420 mg Q4W/140 mg Q2W	Placebo	HC	Both	NCT01764633
GAUSS [3]	2012	2	12	Evolocumab 420 mg Q4W ± Ezetimibe 10 mg	Ezetimibe	HC - Statin intolerant	Non-intensive	NCT01375764
GAUSS-2 [4]	2014	3	12	Evolocumab 420 mg/140 mg Q2W	Ezetimibe	HC - Statin intolerant	Non-intensive	NCT01763905
GAUSS-3 [5]	2016	3	24	Evolocumab 420 mg Q4W	Ezetimibe	HC - Statin intolerant	None	NCT01984424
GLAGOV [6]	2016	3	76	Evolocumab 420 mg Q4W	Placebo	HC - CAD	Both	NCT01813422
LAPLACE-2 [7]	2014	3	12	Evolocumab 420 mg Q4W/140 mg Q2W	Ezetimibe/ placebo	HC	Both	NCT01763866
LAPLACE-TIMI57 [8]	2012	2	12	Evolocumab 420 mg Q4W/140 mg Q2W	Placebo	HC	Both	NCT01380730
McKenney et al. [9]	2012	2	12	Alirocumab 150 mg Q2W/300 mg Q4W	Placebo	HC	Both	NCT01288443
MENDEL[10]	2012	2	12	Evolocumab 420 mg Q4W/140 mg Q2W	Ezetimibe/ placebo	HC	None	NCT01375777
MENDEL-2 [11]	2014	3	12	Evolocumab 420 mg Q4W/140 mg Q2W	Ezetimibe/ placebo	HC	None	NCT01763827

ODYSSEY								
ALTERNATIVE [12]	2015	3	24	Alirocumab 75 mg Q2W with potential up-titration to 150 mg Q2W	Ezetimibe	HC - Statin intolerant	None	NCT01709513
CHOICE I [13]	2016	3	48	Alirocumab 75 mg Q2W/ 300 mg Q4W with potential up-titration to 150 mg Q2W	Placebo	HC	Both	NCT01926782
CHOICE II [14]	2016	3	24	Alirocumab 75 mg Q2W/150 mg Q4Wwith potential up-titration to 150 mg Q2W	Placebo	HC - Statin intolerant	None	NCT02023879
COMBO I [15]	2015	3	52	Alirocumab 75mg Q2W, increased to 150mg Q2W prn	Placebo	HC	Both	NCT01644175
COMBO II [16]	2015	3	104*	Alirocumab 75mg Q2W with potential up-titration to 150 mg Q2W	Ezetimibe	HC	Both	NCT01644188
ESCAPE [17]	2016	3	18	Alirocumab 150mg Q2W	Placebo	HeFH	Both	NCT02326220
FH I [18]	2015	3	78	Alirocumab 75mg Q2W with potential up-titration to 150 mg Q2W	Placebo	HeFH	Both	NCT01623115
FH II [18]	2015	3	78	Alirocumab 75mg Q2W with potential up-titration to 150 mg Q2W	Placebo	HeFH	Both	NCT01709500

HIGH FH [19]	2016	3	78	Alirocumab 150mg Q2W	Placebo	HeFH	Both	NCT01617655
JAPAN [20]	2016	3	52	Alirocumab 75mg Q2W with potential up-titration to 150 mg Q2W	Placebo	HC	Both	NCT02107898
LONG TERM [21]	2015	3	78	Alirocumab 150mg Q2W	Placebo	HC	Both	NCT01507831
MONO [22]	2014	3	24	Alirocumab 75mg Q2W with potential up-titration to 150 mg Q2W	Ezetimibe	HC	None	NCT01644474
OPTIONS I [23]	2015	3	24	Alirocumab 75mg Q2W with potential up-titration to 150 mg Q2W	Ezetimibe/ double statin	HC	Both	NCT01730040
OPTIONS II [24]	2015	3	24	Alirocumab 75mg Q2W with potential up-titration to 150 mg Q2W	Ezetimibe/ double statin	HC	Both	NCT01730053
OSLER 1 and 2 [25]	2015	OL	48	Evolocumab 420 mg Q4W/140 mg Q2W	Standard therapy	HC	Both	NCT01439880, NCT01854918
Roth et al. [26]	2012	2	8	Alirocumab 150mg Q2W	Placebo	HC	Both	NCT01288469
RUTHERFORD [27]	2012	2	12	Evolocumab 420 mg Q4W	Placebo	HeFH	Both	NCT01375751
RUTHERFORD 2 [28]	2015	3	12	Evolocumab 420 mg Q4W/140 mg Q2W	Placebo	HeFH	Both	NCT01763918
Stein et al. [29]	2012	2	12	Alirocumab 150 mg Q2W/300 mg Q4W	Placebo	HeFH	Both	NCT01266876
Teramoto et al. [30]	2016	2	12	Alirocumab 150 mg Q2W	Placebo	HC	Both	NCT01812707
TESLA PART B [31]	2015	3	12	Evolocumab 420 mg Q4W	Placebo	HoFH	Both	NCT01588496

YUKAWA [32]	2014	2	12	Evolocumab 420 mg Q4W/140 mg Q2W	Placebo	HC	Both	NCT01652703
YUKAWA II [33]	2016	3	12	Evolocumab 420 mg Q4W/140 mg Q2W	Placebo	HC	Both	NCT01953328

CAD, coronary artery disease; HC, hypercholesterolemia; HeFH, heterozygous familial hypercholesterolemia; HoFH, homozygous familial hypercholesterolemia; Q2W, every four weeks; Q2W, every two weeks. * Results reported up to week 52.

Expanded trial names: DESCARTES = Durable Effect of PCSK9 Antibody Compared with Placebo Study; FOURIER = Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk; GAUSS = Goal Achievement after Utilizing an anti-PCSK9 antibody in Statin Intolerant Subjects; GLAGOV = Global Assessment of Plaque Regression With a PCSK9 Antibody as Measured by Intravascular UltrasoundLAPLACE-2 = LDL-C Assessment with PCKS9 Monoclonal Antibody Inhibition Combined With Statin Therapy-2; LAPLACE-TIMI 57 = LDL-C Assessment with PCKS9 Monoclonal Antibody Inhibition Combined With Statin Therapy = Thrombosis in Myocardial Infarction 57; MENDEL = Monoclonal Antibody Against PCSK9 to Reduce Elevated LDL-C in Patients Currently Not Receiving Drug Therapy For Easing Lipid Levels; OSLER = Open-Label Study of Long-term Evaluation Against LDL-C; RUTHERFORD = The Reduction of LDL-C With PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder; TESLA = Trial Evaluating PCSK9 Antibody in Subjects with LDL Receptor Abnormalities; YUKAWA = Study of LDL-Cholesterol Reduction Using a Monoclonal PCSK9 Antibody in Japanese Patients With Advanced Cardiovascular Risk.

Table S2. Baseline patient characteristics

Study	Participants, n	Age, years	Male, %	CAD, %	HTN, %	DM2, %	BMI, kg/m^2	LDL-C, mean	Statin, %	Intensive statin, %
DESCARTES [1]	901	55.4	47.7%	15.1%	48.8%	12.2%	30.2	100.3	87.7%	45.2%
FOURIER[2]	27,654	62.5	75.4%	NA	80.1%	36.6%	NA	93.7†	100.0%	69.3%
GAUSS [3]	94	61.5	35.1%	20.2%	48.9%	11.7%	28.1	192.3	16.0%	0.0%
GAUSS-2 [4]	307	61.7	54.0%	29.0%	59.0%	20.2%	NA	193.0	17.9%	0.0%
GAUSS-3 [5]	218	58.8	51.4%	31.7%	51.4%	11.9%	28.0	219.8	0.0%	0.0%
GLAGOV [6]	968	59.8	72.2%	100.0%	83.0%	20.9%	29.5	92.5	98.6%	58.9%
LAPLACE-2 [7]	1896	59.9	54.2%	22.5%	NA	15.5%	NA	109.1	100.0%	40.8%
LAPLACE-TIMI57 [8]	315	62.6	45.4%	32.1%	70.2%	16.5%	29.4	121.8	99.2%	29.3%
McKenney et al. [9]	92	56.2	43.5%	5.4%	41.3%	14.1%	28.8	128.6	100.0%	NA
MENDEL[10]	225	51.2	36.4%	0.0%	32.9%	0.0%	32.8	142.3	0.0%	0.0%
MENDEL-2 [11]	614	53.2	31.1%	0.0%	28.7%	0.2%	NA	142.9	0.0%	0.0%
ODYSSEY										
ALTERNATIVE [12]	251	63.5	54.6%	47.0%	64.6%	23.9%	29.0	191.3	0.0%	0.0%
CHOICE I [13]	803	60.8	57.5%	52.4%	NA	27.0%	31.1	122.1	68.1%	NA

CHOICE II [14]	233	63.1	55.8%	49.8%	60.9%	16.3%	28.9	157.9	0.0%	0.0%
COMBO I [15]	316	63.0	65.8%	78.2%	NA	43.1%	32.3	102.2	99.7%	62.7%
COMBO II [16]	720	61.6	73.6%	90.1%	NA	30.9%	30.2	107.0	99.9%	66.7%
ESCAPE [17]	62	58.7	58.1%	NA	NA	NA	30.4	180.7	51.6%	40.3%
FH I [18]	486	52.0	56.4%	46.3%	43.2%	11.7%	29.3	144.6	100.0%	83.5%
FH II [18]	249	53.2	52.6%	35.7%	32.5%	4.0%	28.3	134.4	100.0%	88.4%
HIGH FH [19]	107	50.6	53.3%	49.5%	57.0%	14.0%	28.9	197.8	100.0%	72.9%
JAPAN [20]	216	60.8	60.6%	NA	NA	68.5%	25.5	141.2	100.0%	NA
LONG TERM [21]	2341	60.5	62.2%	68.6%	NA	34.6%	30.3	122.4	99.9%	46.8%
MONO [35]	103	60.2	53.4%	NA	NA	3.9%	29.3	139.7	0.0%	0.0%
OPTIONS I [23]	355	62.9	65.1%	56.3%	78.3%	49.9%	31.0	105.1	100.0%	68.5%
OPTIONS II [24]	305	60.9	61.3%	58.0%	72.5%	41.3%	31.3	111.3	100.0%	68.2%
OSLER 1 and 2 [25]	4465	57.9	50.5%	20.1%	52.0%	13.4%	NA	122.3†	70.1%	27.1%
Roth et al. [26]	92	56.9	40.2%	3.3%	51.1%	15.2%	29.4	122.6	100.0%	66.3%
RUTHERFORD [27]	112	50.6	52.7%	21.5%	NA	NA	NA	152.7	100.0%	87.5%
RUTHERFORD 2 [28]	329	51.2	57.8%	31.3%	NA	NA	NA	156.0	100.0%	87.0%
Stein et al. [29]	46	54.2	63.0%	39.1%	NA	0.0%	29.5	146.1	100.0%	78.3%

Teramoto et al. [30]	75	57.7	52.0%	0.0%	34.7%	14.7%	24.8	120.8	100.0%	NA
TESLA PART B [31]	49	31.0	51.0%	43.0%	NA	NA	NA	348.0	100.0%	93.9%
YUKAWA [32]	207	60.8	67.6%	27.1%	72.9%	35.3%	NA	140.2	100.0%	23.7%
YUKAWA II [33]	404	61.5	60.4%	12.9%	73.5%	48.8%	NA	106.0	100.0%	50.7%
Overall	45,520	61.0	67.6%	39.2%	73.1%	30.6%	30.0	106.0	91.8%	58.4%

BMI, body mass index; CAD, coronary artery disease; DM2, diabetes mellitus type 2; HTN, hypertension; LDL-C, low-density lipoprotein cholesterol; NA, not available.

See Table S1 for trial name abbreviations

[†]Estimated from median and interquartile range

Table S3. Random effects meta-regression analysis showing the study-level association between baseline low-density lipoprotein cholesterol (left) and treatment difference vs. control in percent LDL-C reduction from baseline (right) and cardiovascular/safety end points

End point	Moderator variable					
	Baseline LDL-C		Treatment difference vs. control in % LDL-C reduction from baseline		PCSK9i treatment duration	
	Regression coefficient (95% CI)	p	Regression coefficient (95% CI)	p	Regression coefficient (95% CI)	p
All-cause mortality	-0.02 (-0.05, 0.00)	0.038	-0.02 (-0.07, 0.02)	0.358	0.01 (0.00, 0.02)	0.012
CV mortality	-0.02 (-0.05, 0.01)	0.196	-0.01 (-0.06, 0.03)	0.621	0.00 (0.00, 0.01)	0.197
Myocardial infarction	0.00 (-0.01, 0.01)	0.976	0.03 (0.00, 0.06)	0.075	0.00 (-0.01, 0.01)	0.943
Stroke	0.02 (-0.01, 0.05)	0.166	0.00 (-0.06, 0.06)	0.954	-0.01 (-0.02, 0.01)	0.414
Coronary revascularization	0.00 (0.00, 0.01)	0.281	0.04 (0.01, 0.06)	0.012	0.00 (-0.01, 0.00)	0.487
Unstable angina	-0.01 (-0.05, 0.03)	0.487	0.03 (-0.08, 0.14)	0.612	0.01 (-0.01, 0.02)	0.480
CHF exacerbation	0.00 (-0.02, 0.02)	0.873	-0.03 (-0.11, 0.04)	0.400	0.00 (-0.01, 0.02)	0.674
Neurocognitive adverse events	0.00 (-0.01, 0.02)	0.862	-0.03 (-0.07, 0.01)	0.201	0.00 (-0.01, 0.01)	0.903
Diabetes mellitus	0.00 (-0.01, 0.01)	0.938	-0.02 (-0.06, 0.02)	0.236	0.00 (-0.01, 0.01)	0.824

CHF, congestive heart failure; CV, cardiovascular; LDL-C, low-density lipoprotein cholesterol; PCSK9i, PCSK9inhibitor

Table S4. Subgroup analyses for cardiovascular/safety end points stratified by familial hypercholesterolemia, and background statin therapy

End point	Population: FH vs. Non-FH/mixed, OR (95% CI)			Statin intolerant/PCSK9i monotherapy, OR (95% CI)		
	Non-FH/mixed	FH	p	No	Yes	p
All-cause mortality	0.99 (0.87, 1.13)	6.72 (0.38, 119.95)	0.194	1.00 (0.88, 1.14)	0.79 (0.07, 8.79)	0.846
CV mortality	1.00 (0.84, 1.19)	3.58 (0.18, 69.77)	0.401	1.01 (0.85, 1.19)	-*	-
Myocardial infarction	0.72 (0.64, 0.81)	0.99 (0.25, 3.99)	0.999	0.72 (0.64, 0.81)	0.62 (0.19, 2.00)	0.999
Stroke	0.81(0.68, 0.97)	1.53 (0.06, 37.66)	0.695	0.80 (0.67, 0.96)	4.54 (0.18, 112.74)	0.290
Coronary revascularization	0.78 (0.72, 0.86)	1.35 (0.39, 4.64)	0.842	0.78 (0.72, 0.86)	1.48 (0.46, 4.75)	0.346
Unstable angina	0.97 (0.81, 1.16)	1.53 (0.06, 37.66)	0.783	0.97 (0.82, 1.16)	-*	-
CHF exacerbation	0.98 (0.86, 1.13)	1.51 (0.16, 14.65)	0.711	0.99 (0.86, 1.13)	0.19 (0.02, 2.16)	0.185
Neurocognitive AEs	1.14 (0.95, 1.36)	0.38 (0.09, 1.56)	0.160	1.11 (0.93, 1.33)	1.45 (0.16, 13.17)	0.809
Diabetes mellitus	1.05 (0.95, 1.17)	0.78 (0.30, 2.03)	0.532	1.05 (0.95, 1.16)	3.43 (0.38, 31.41)	0.278

AE, adverse event; CHF, congestive heart failure; CV, cardiovascular; FH, familial hypercholesterolemia; PCSK9i, proprotein convertase subtilisin-kexin type 9 inhibitor, * There were no studies reporting events in these subgroups

Table S5. Random- and fixed-effects models for cardiovascular/safety end points

End point	Meta-analysis model			
	Fixed-effects		Random effects	
	OR (95% CI)	p	OR (95% CI)	p
All-cause mortality	1.00 (0.88, 1.14)	0.999	0.71 (0.47, 1.09)	0.119
CV mortality	1.01 (0.85, 1.19)	0.936	1.01 (0.85, 1.19)	0.954
Myocardial infarction	0.72 (0.64, 0.81)	<0.001	0.72 (0.64, 0.81)	<0.001
Stroke	0.81 (0.68, 0.97)	0.02	0.80 (0.67, 0.96)	0.017
Coronary revascularization	0.79 (0.72, 0.86)	<0.001	0.78 (0.71, 0.86)	<0.001
Unstable angina	0.97 (0.82, 1.16)	0.762	0.97 (0.82, 1.16)	0.767
CHF exacerbation	0.98 (0.86, 1.13)	0.8	0.98 (0.86, 1.13)	0.789
Neurocognitive adverse events	1.12 (0.94, 1.33)	0.218	1.12 (0.88, 1.42)	0.366
Diabetes mellitus	1.05 (0.95, 1.16)	0.337	1.05 (0.95, 1.17)	0.32

CHF, congestive heart failure; CV, cardiovascular

Table S6. Egger's regression test for cardiovascular/safety endpoints

End point	p
All-cause mortality	0.131
Cardiovascular mortality	0.268
Myocardial infarction	0.937
Unstable angina	0.393
Stroke	0.186
CHF exacerbation	0.734
Coronary revascularization	0.098
Neurocognitive adverse events	0.549
Diabetes mellitus	0.856

CHF, congestive heart failure

Figure S1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) meta-analysis flowchart

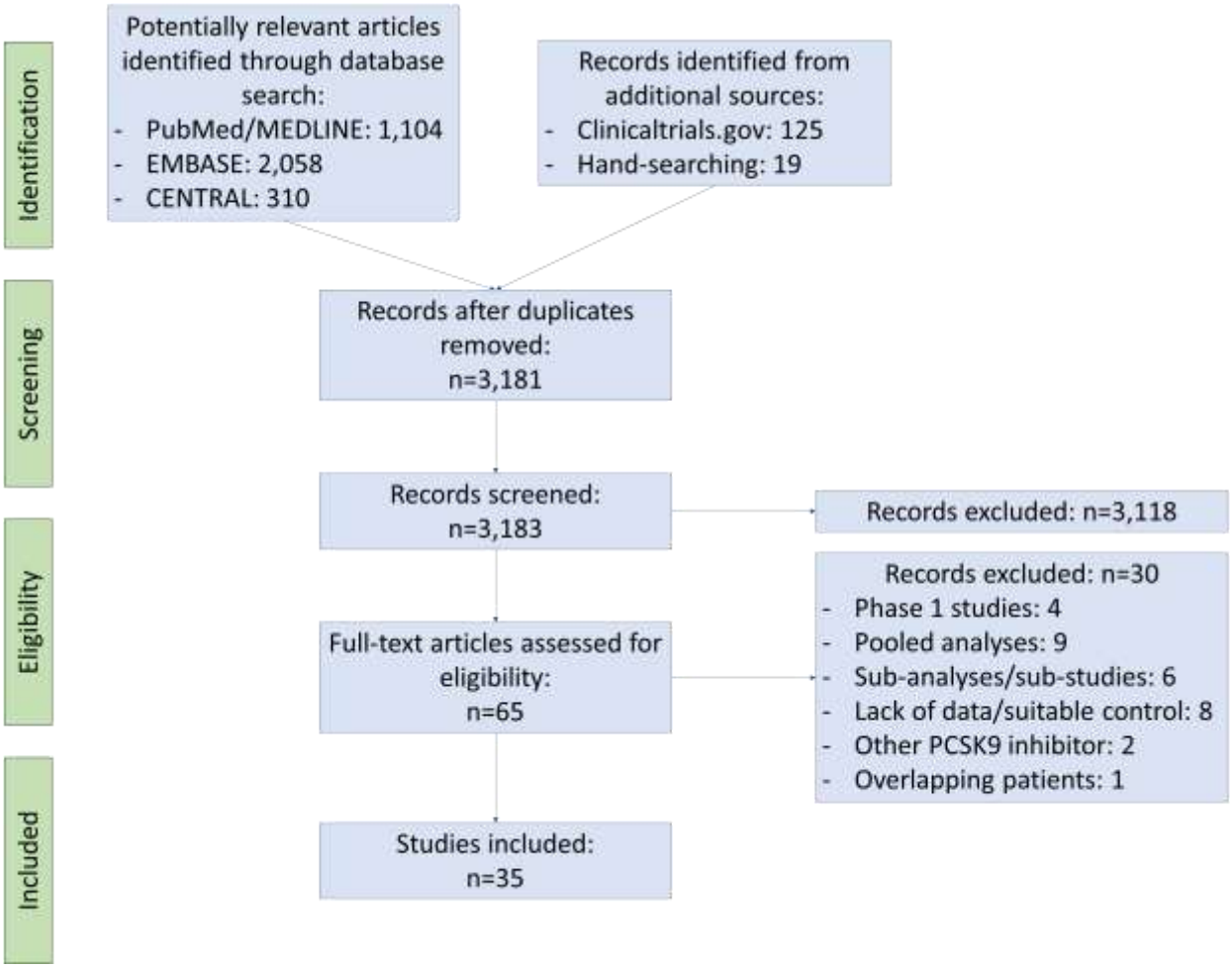


Figure S2. Risk of bias assessment of included studies

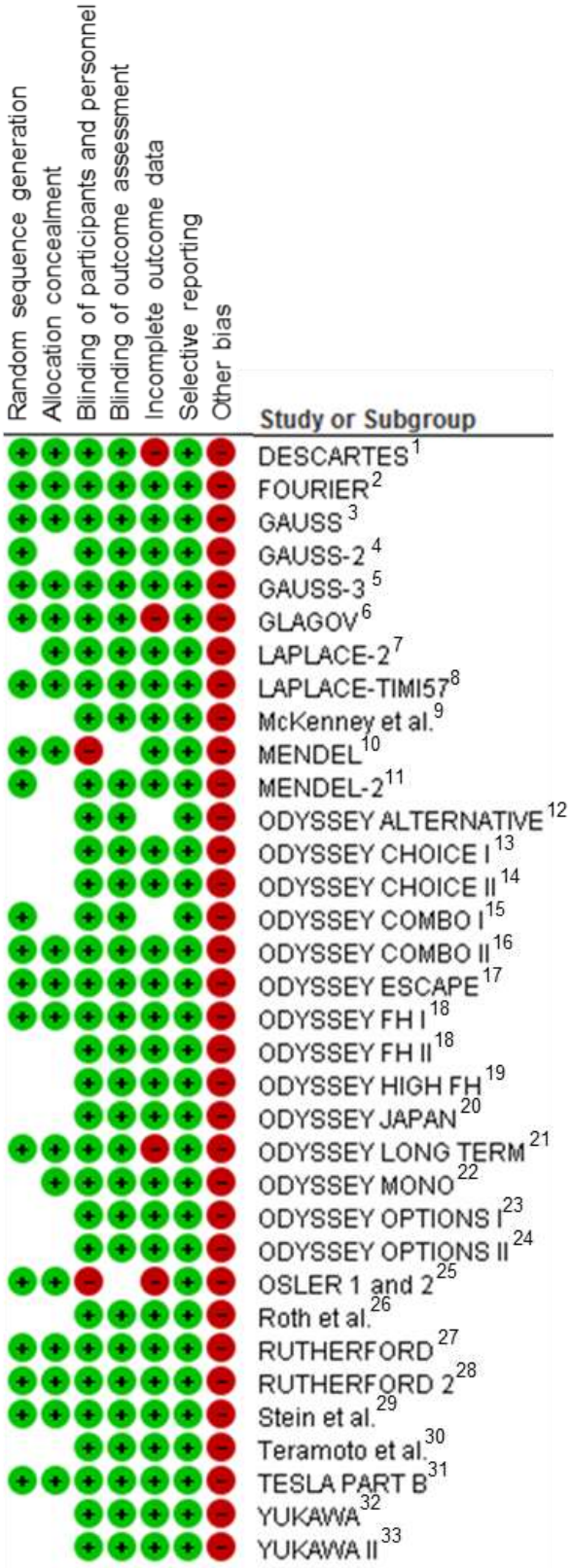


Figure S3. Unstable angina

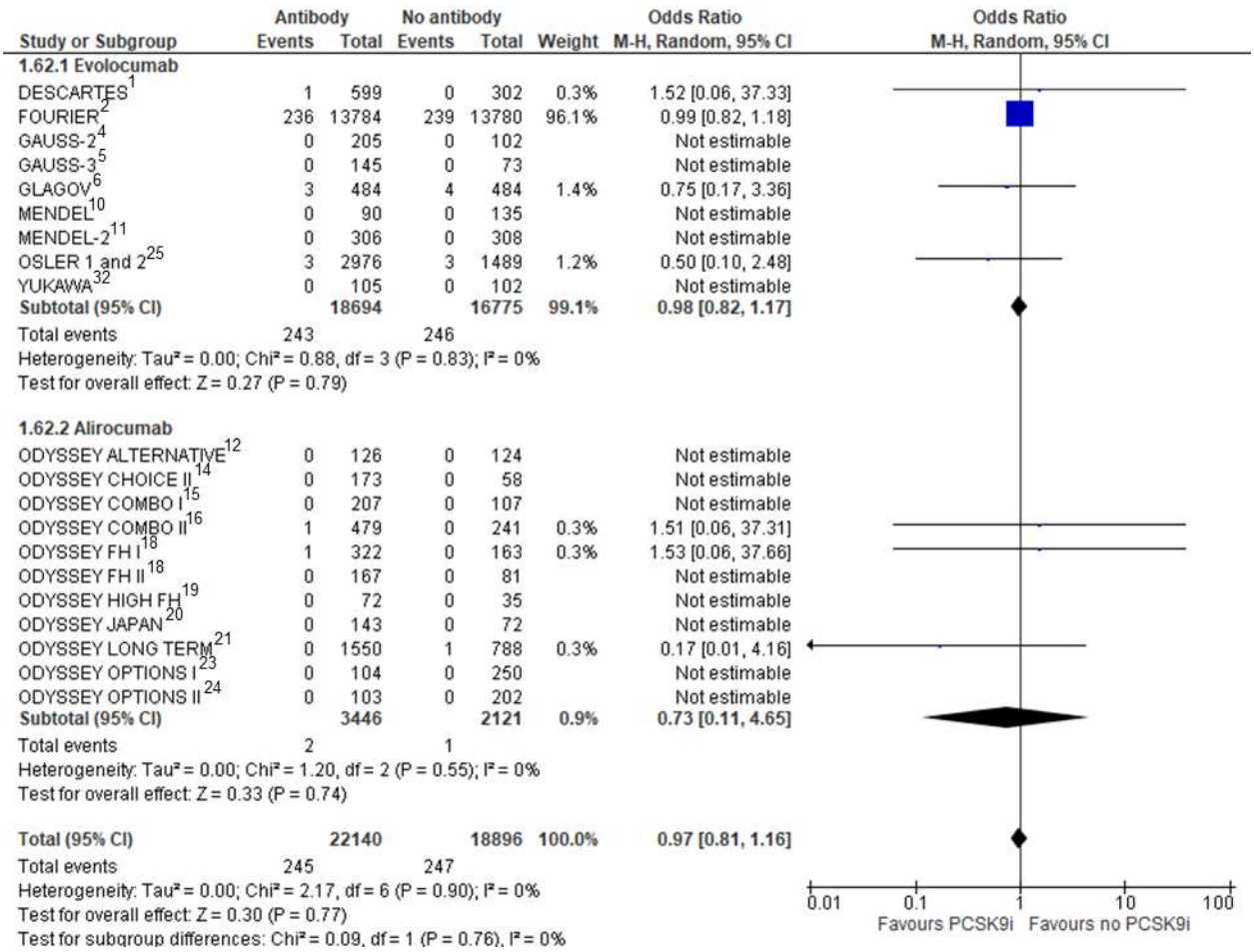


Figure S4. Congestive heart failure exacerbation

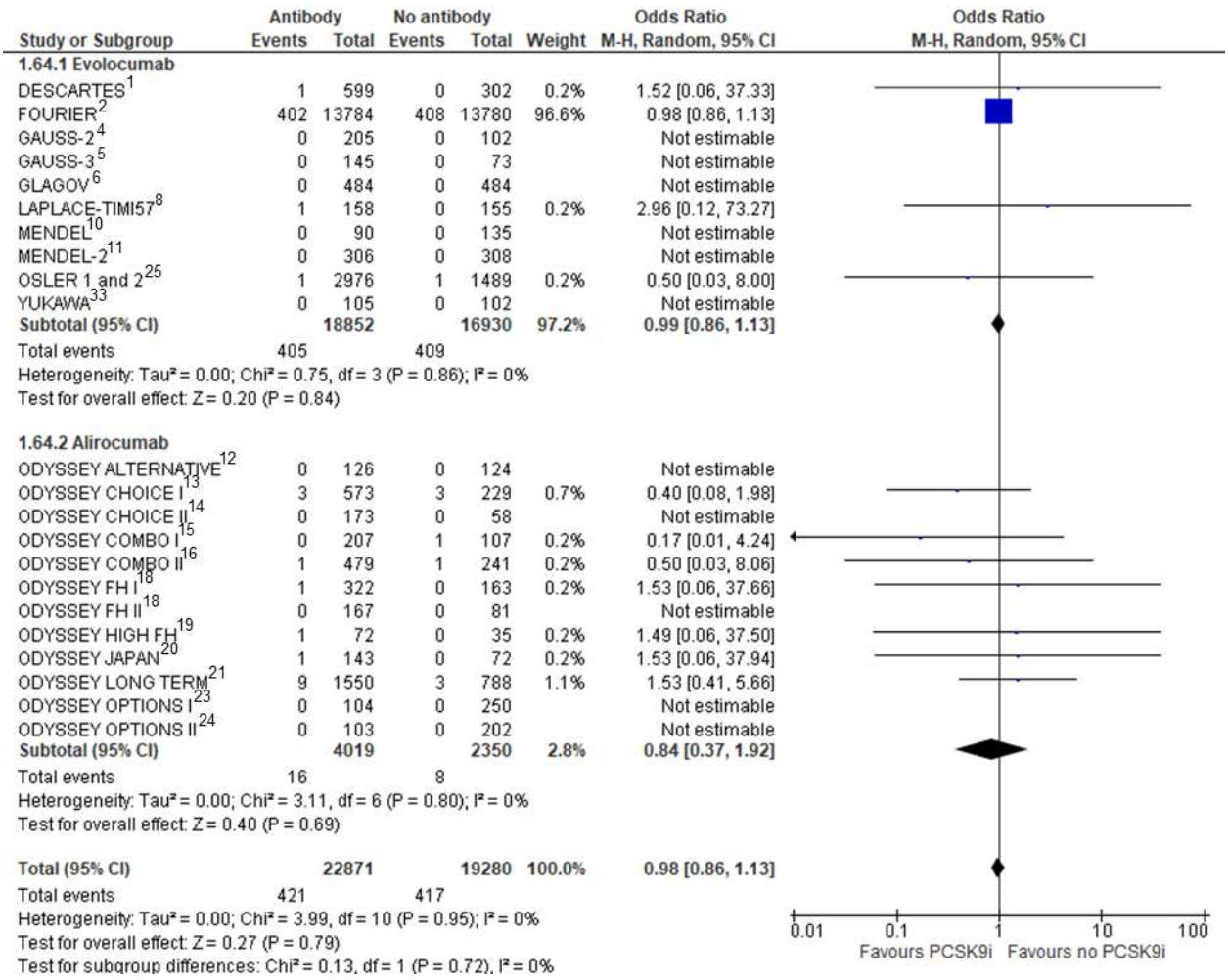


Figure S5. Diabetes mellitus

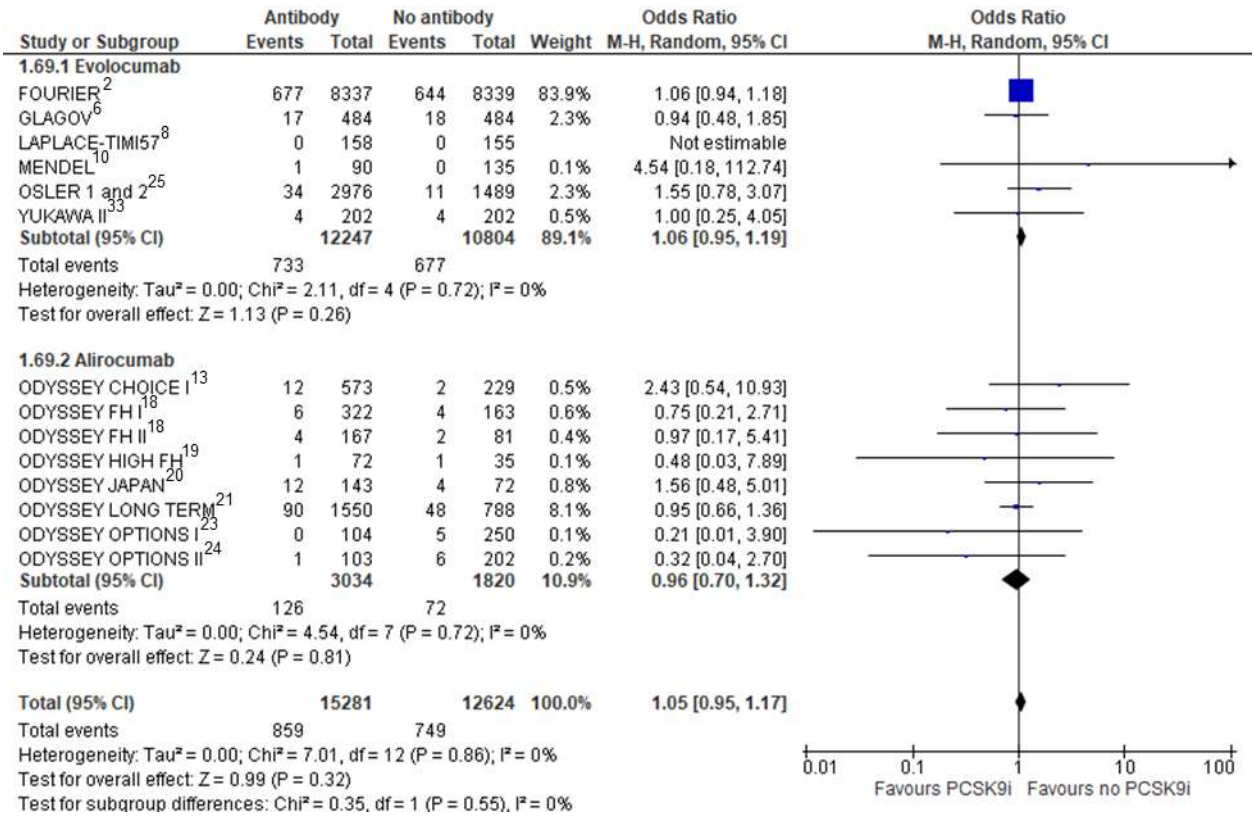


Figure S6. Increase in creatine kinase

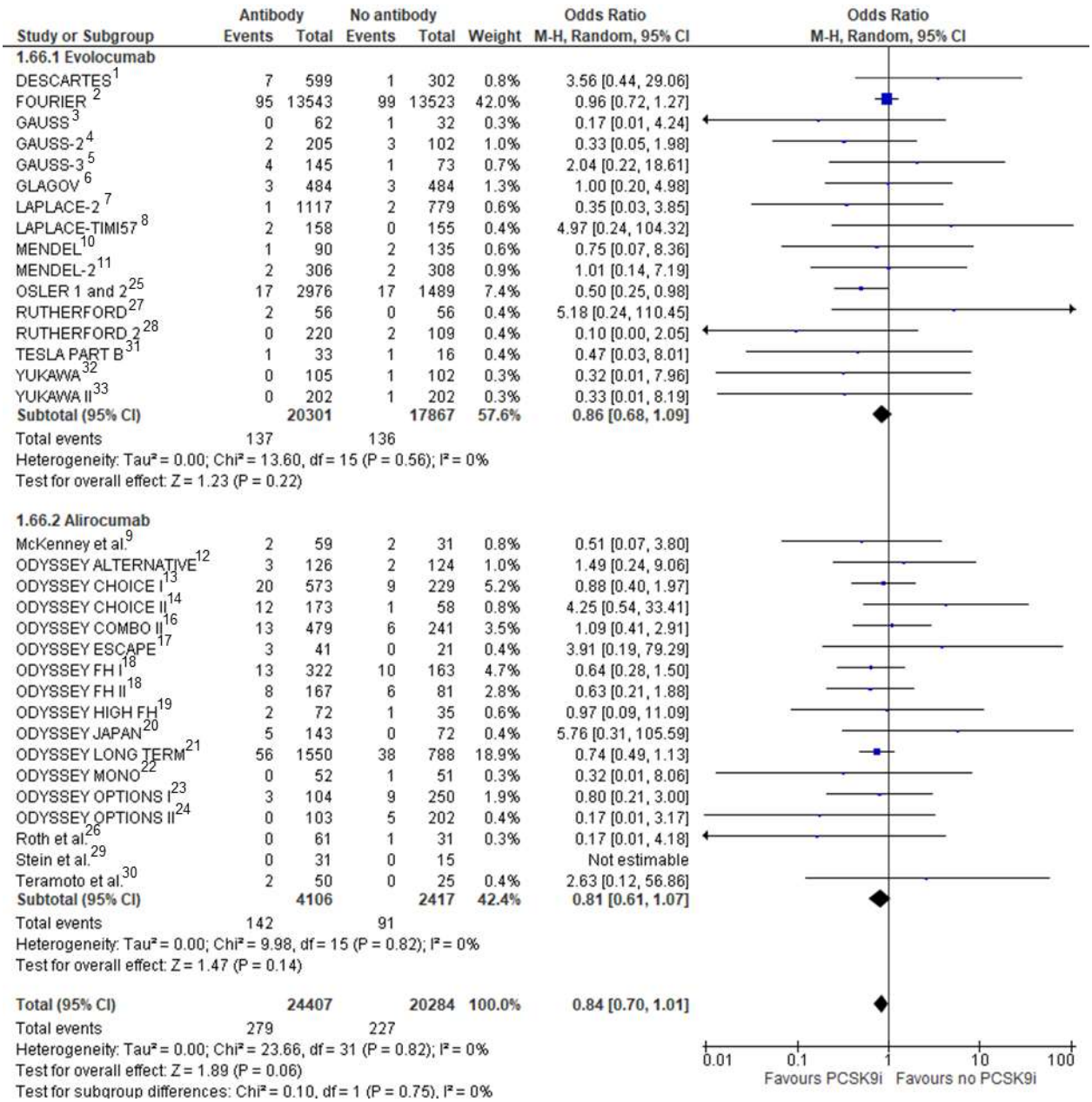


Figure S7. Myalgia

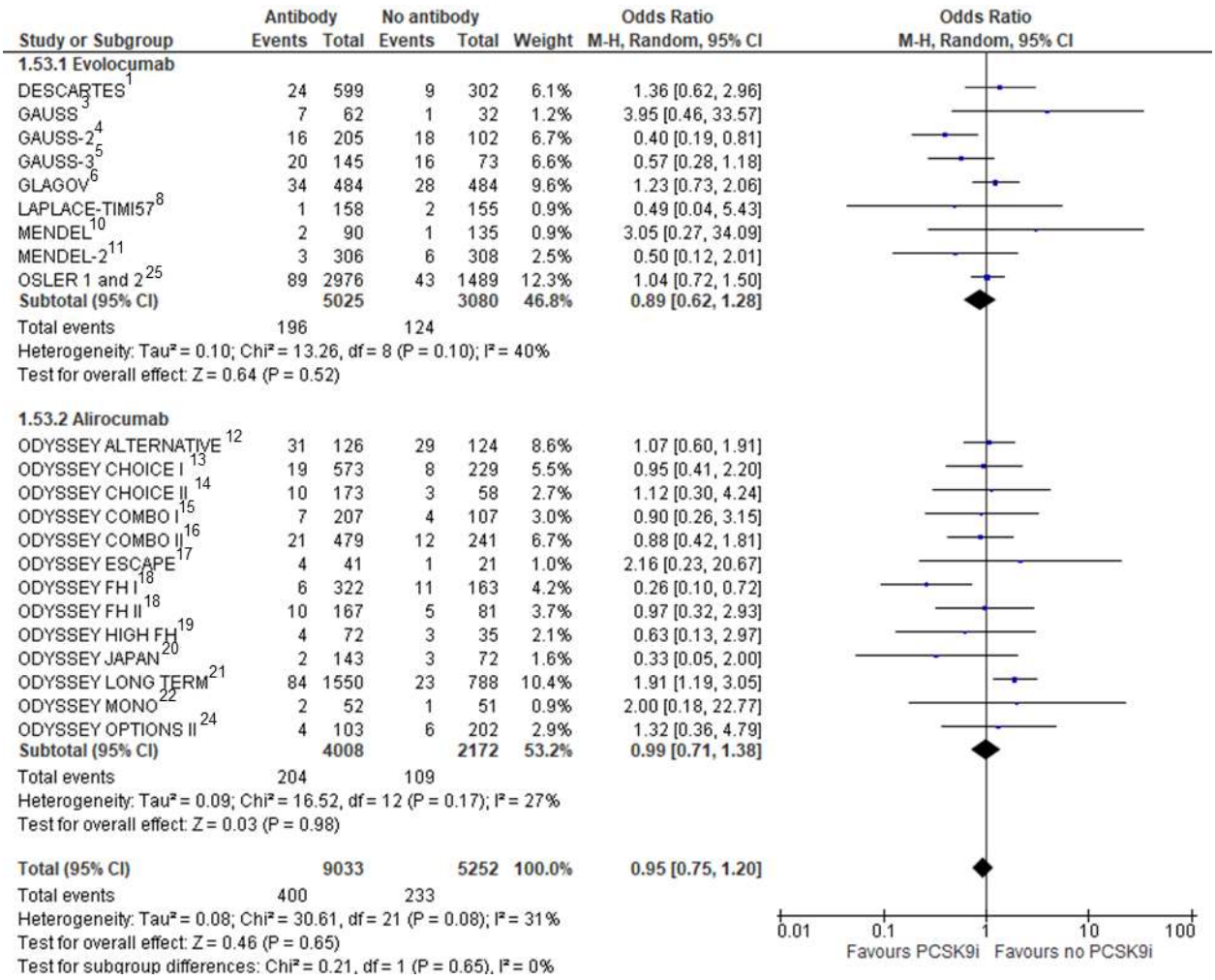


Figure S8. Alanine/aspartate aminotransferase increase

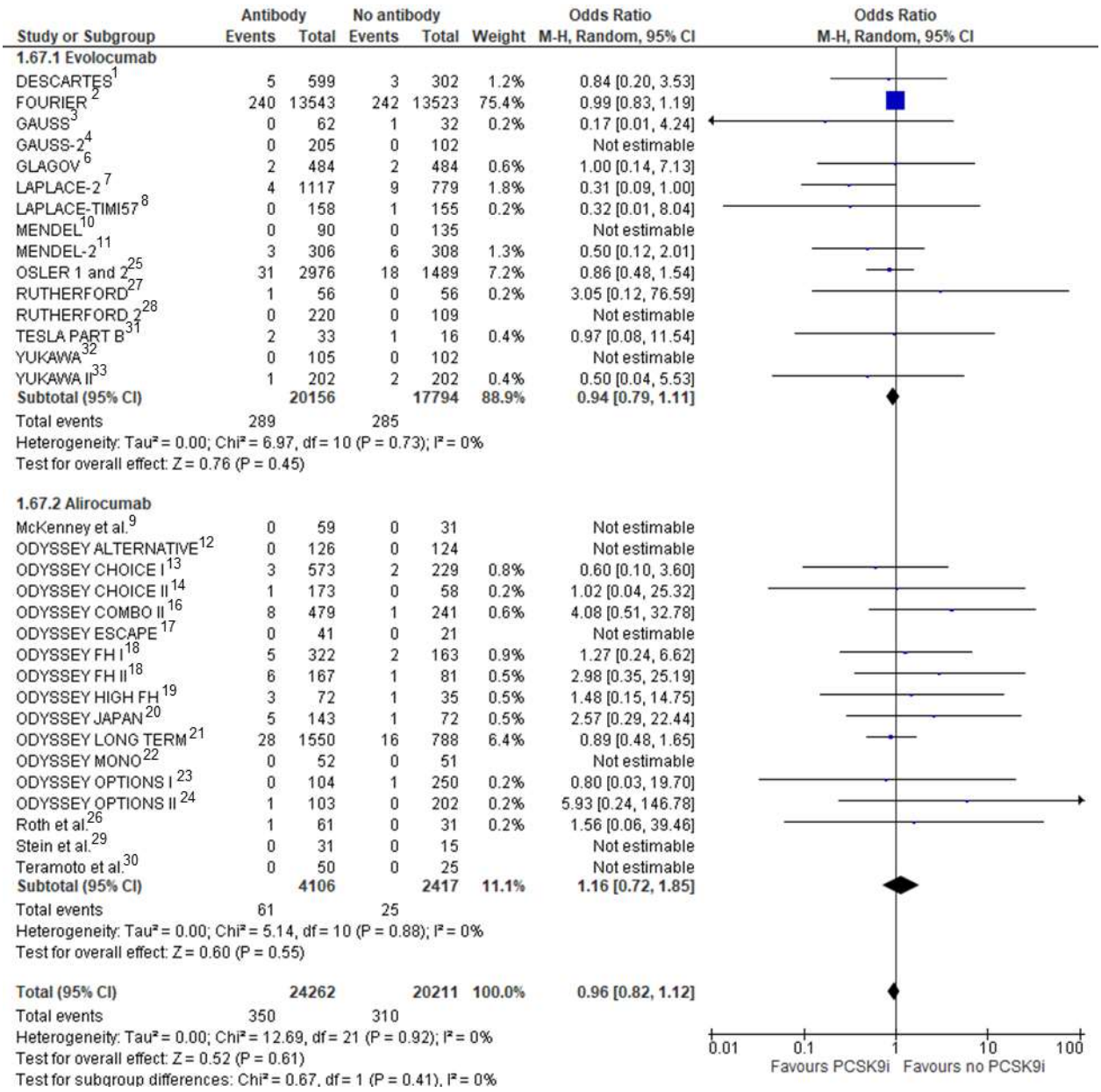


Figure S9. Treatment emergent serious adverse events

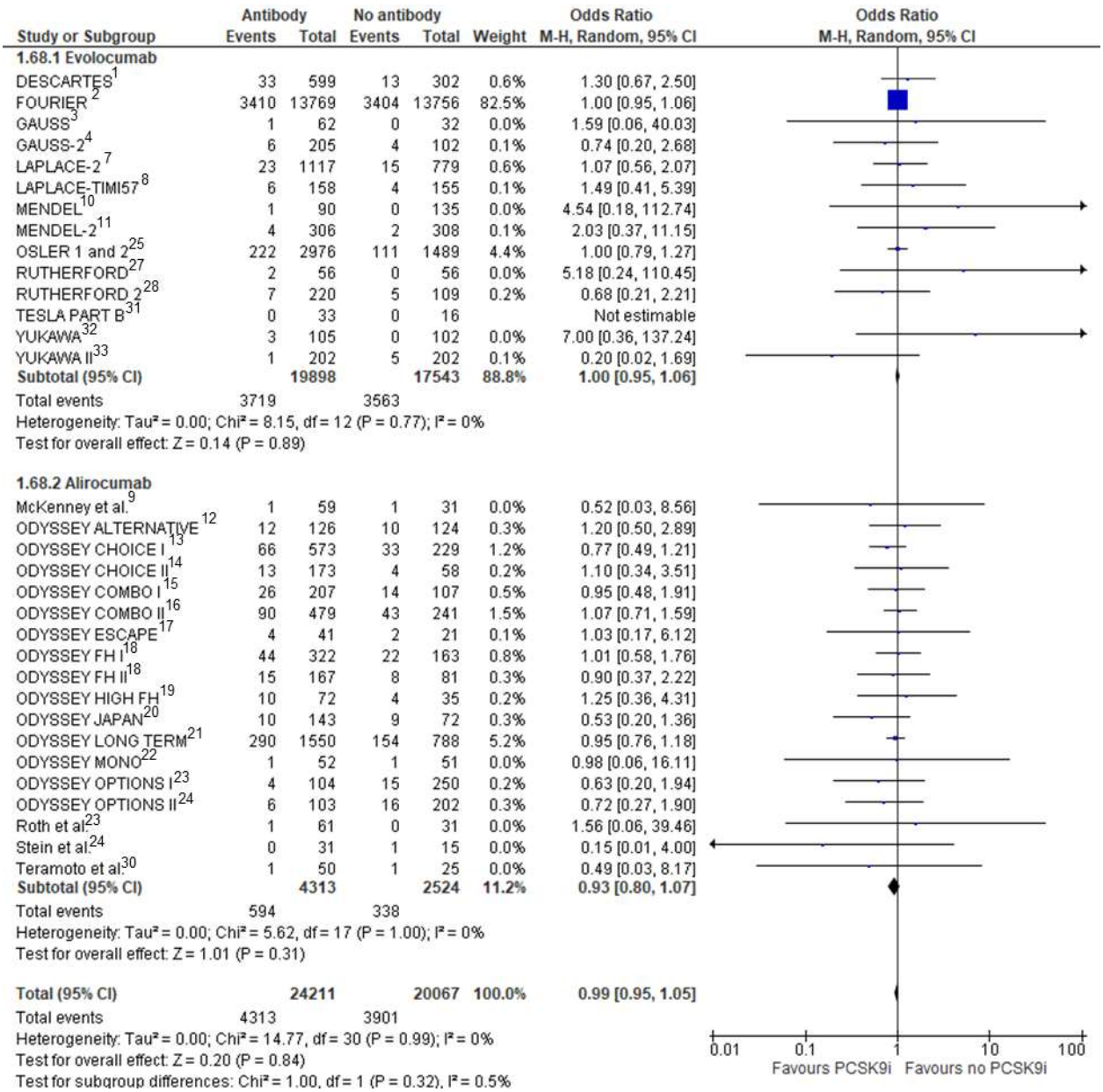


Figure S10. Low-density lipoprotein cholesterol % change from baseline

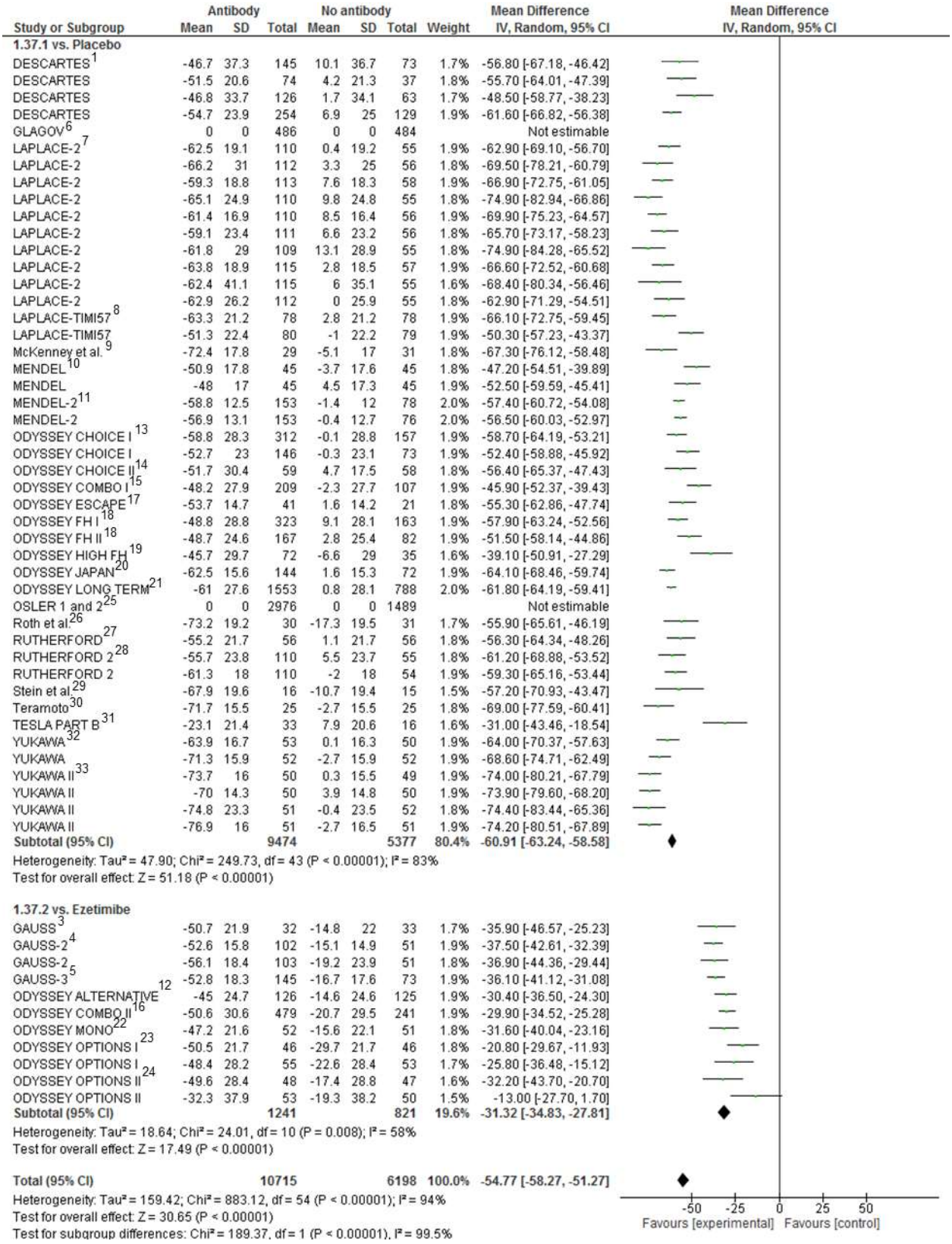


Figure S11. High-density lipoprotein cholesterol % change from baseline

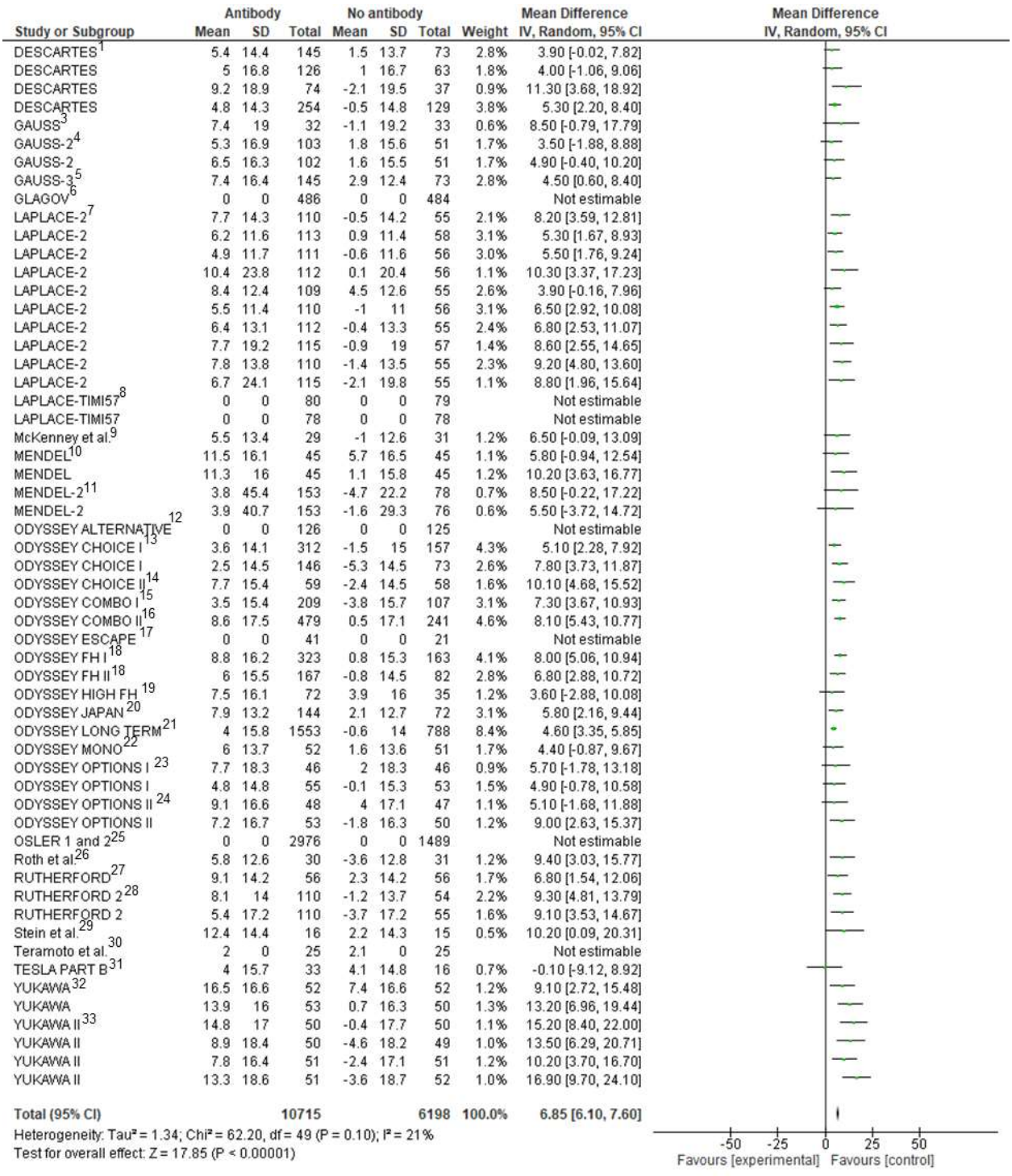


Figure S12. Total cholesterol % change from baseline

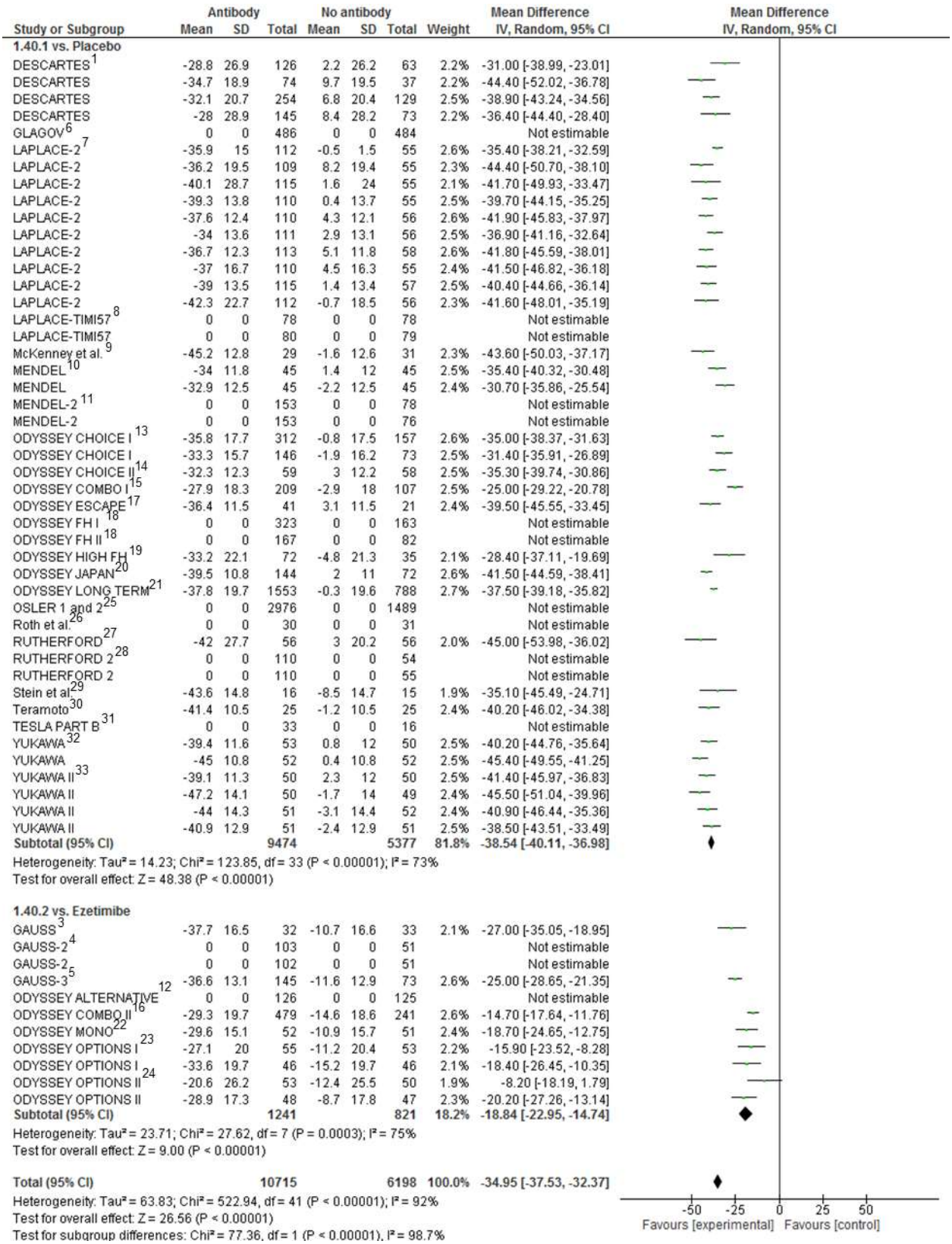


Figure S13. Lipoprotein(a) % change from baseline

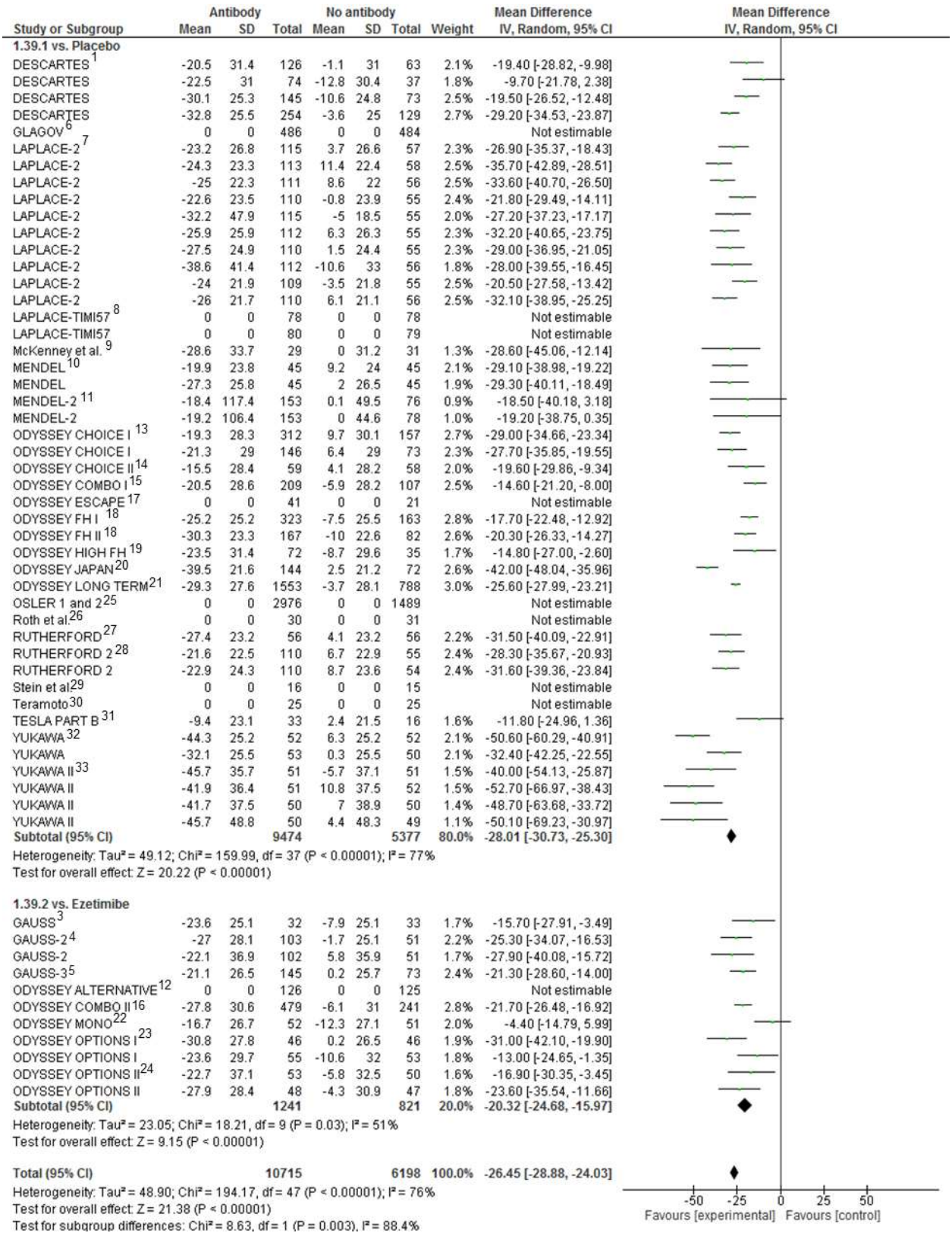


Figure S14. Apolipoprotein B % change from baseline

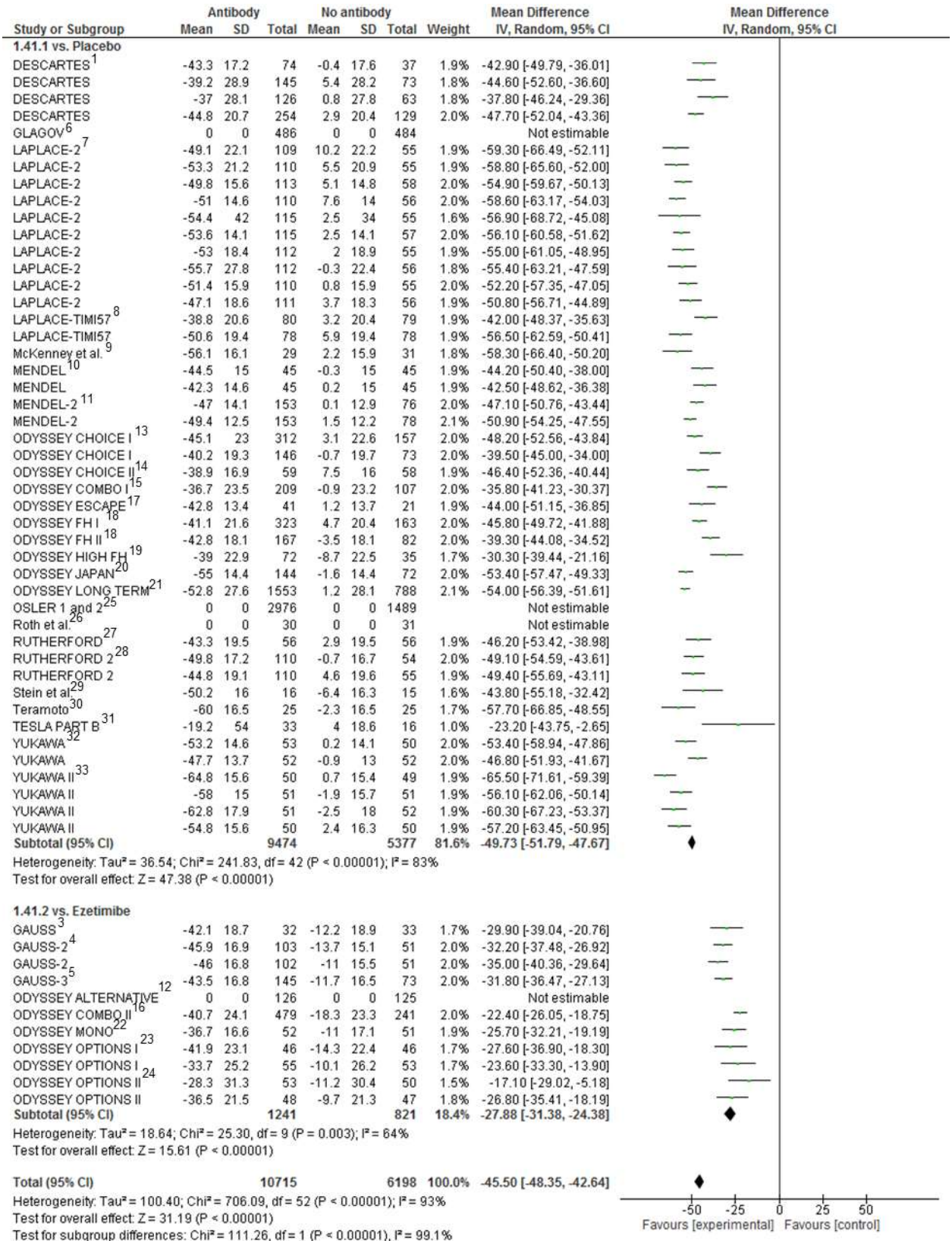


Figure S15. Funnel plot: all-cause mortality

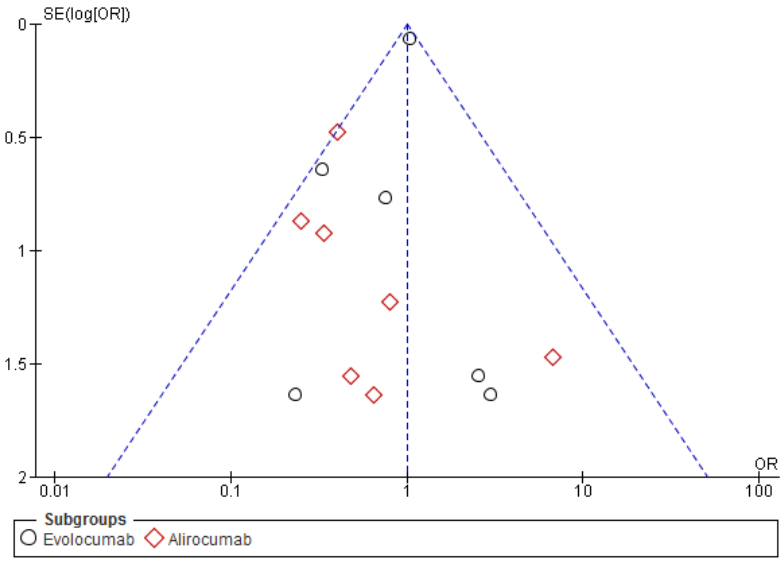


Figure S16. Funnel plot: cardiovascular mortality

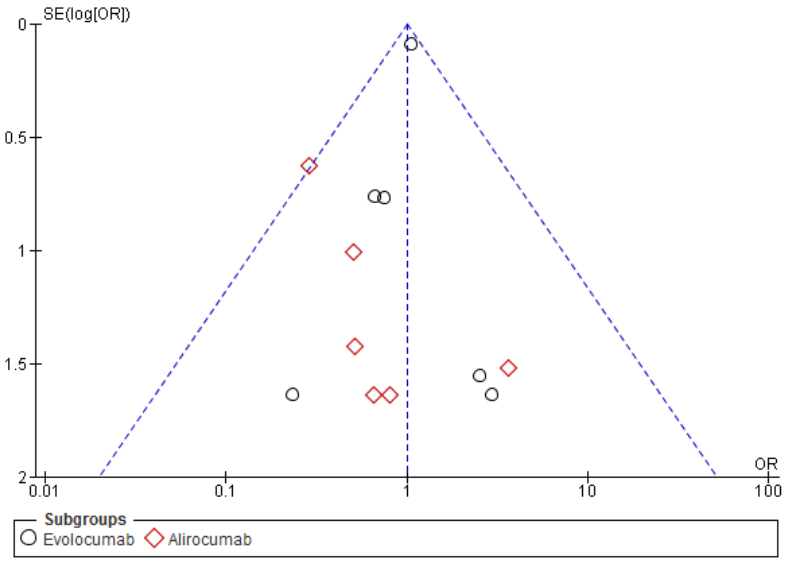


Figure S17. Funnel plot: myocardial infarction

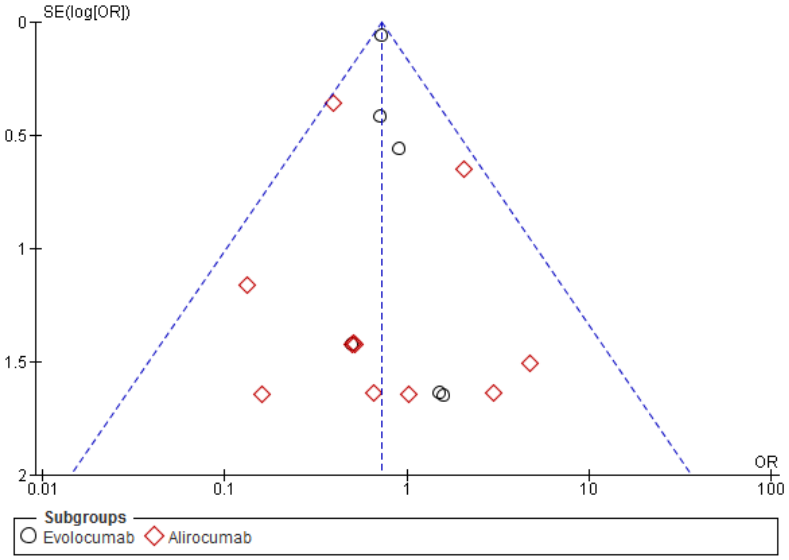


Figure S18. Funnel plot: stroke

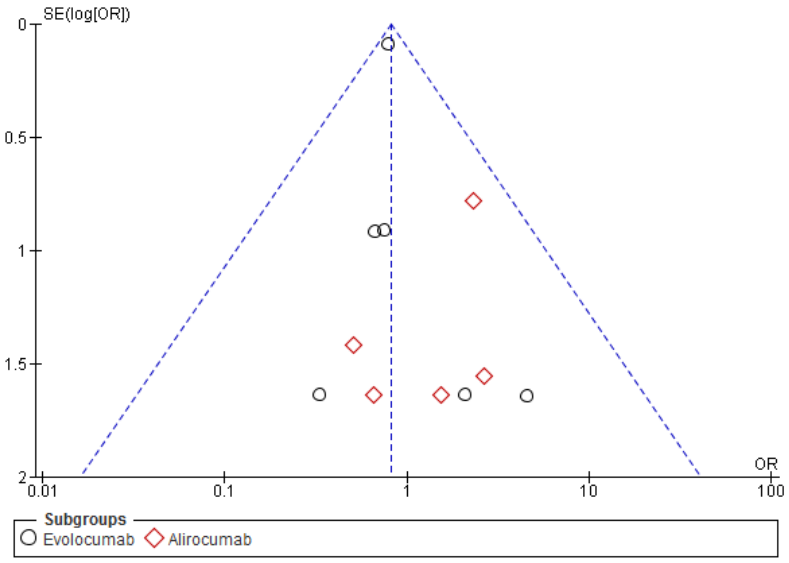


Figure S19. Funnel plot: coronary revascularization

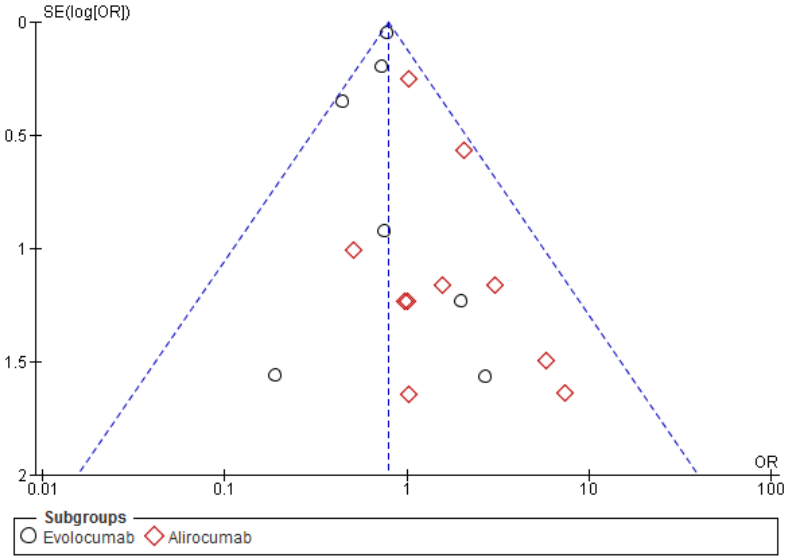


Figure S20. Funnel plot: unstable angina

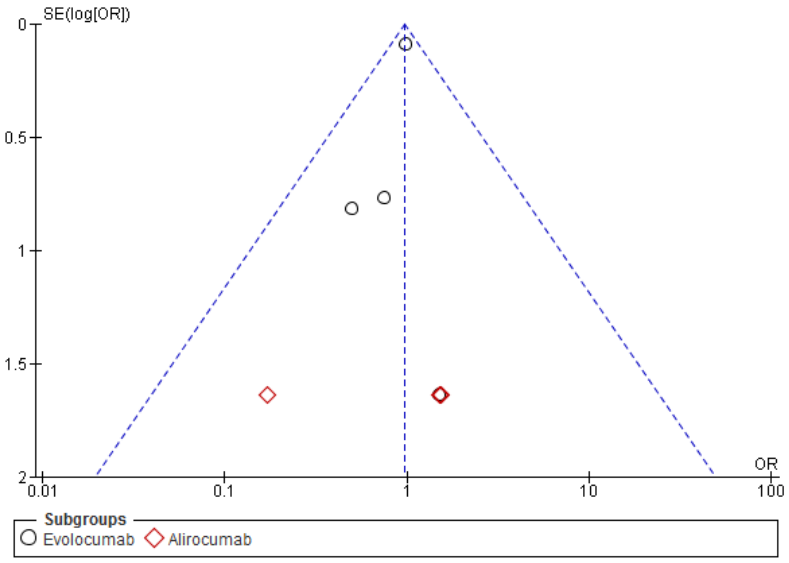


Figure S21. Funnel plot: congestive heart failure exacerbation

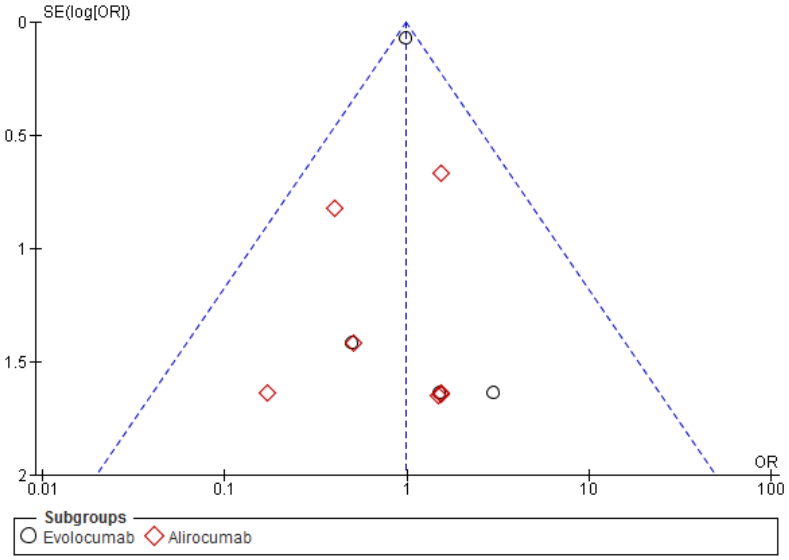


Figure S22. Funnel plot: neurocognitive adverse events

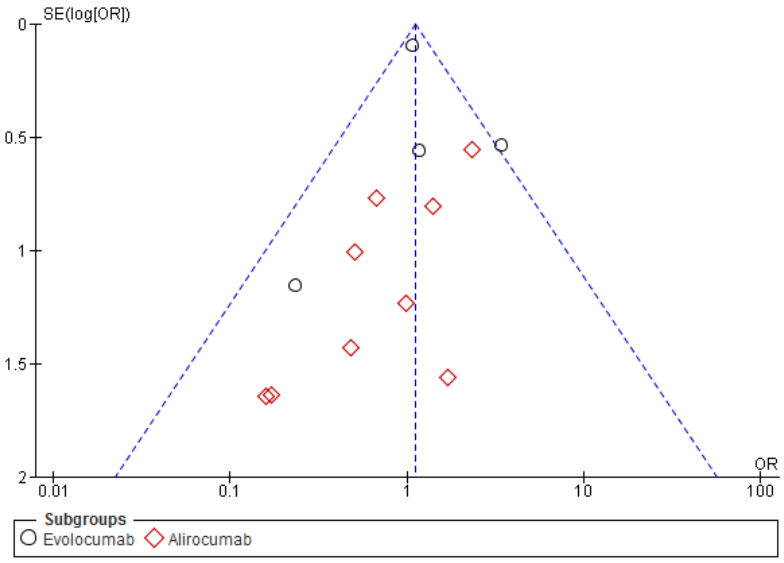


Figure S23. Funnel plot: diabetes mellitus

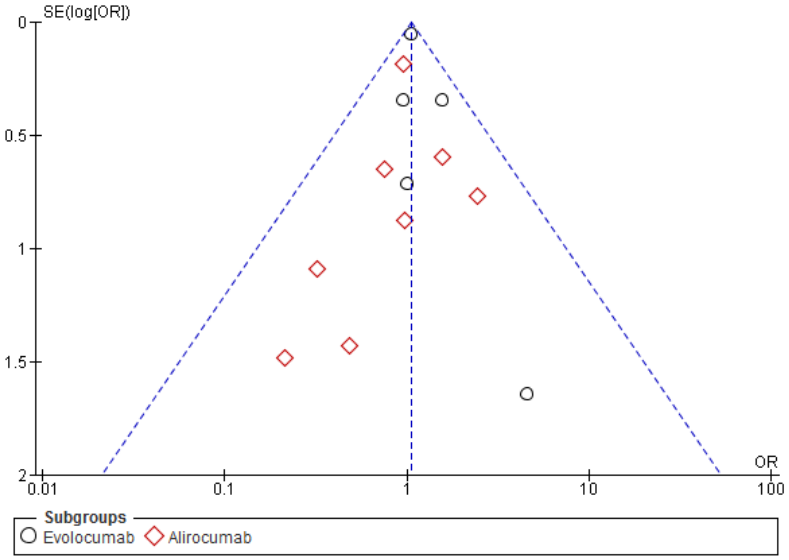


Figure S24. Funnel plot: increase in creatine kinase

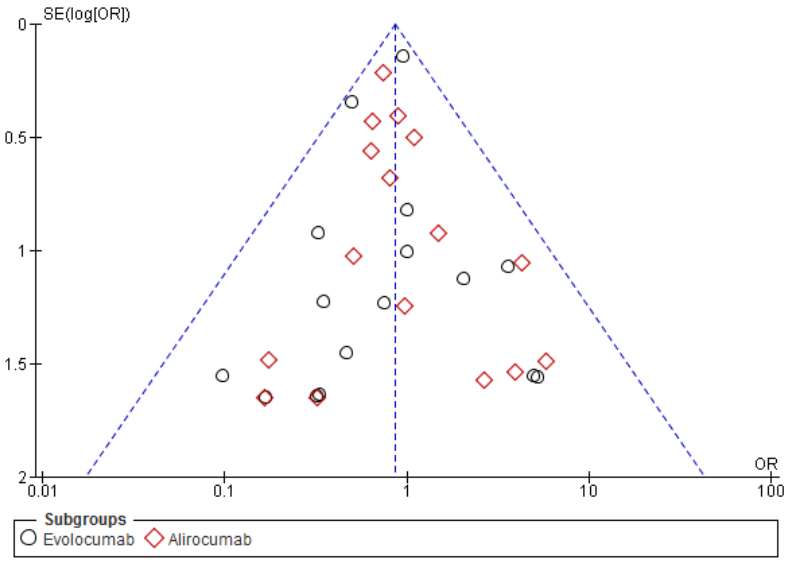


Figure S25. Funnel plot: myalgia

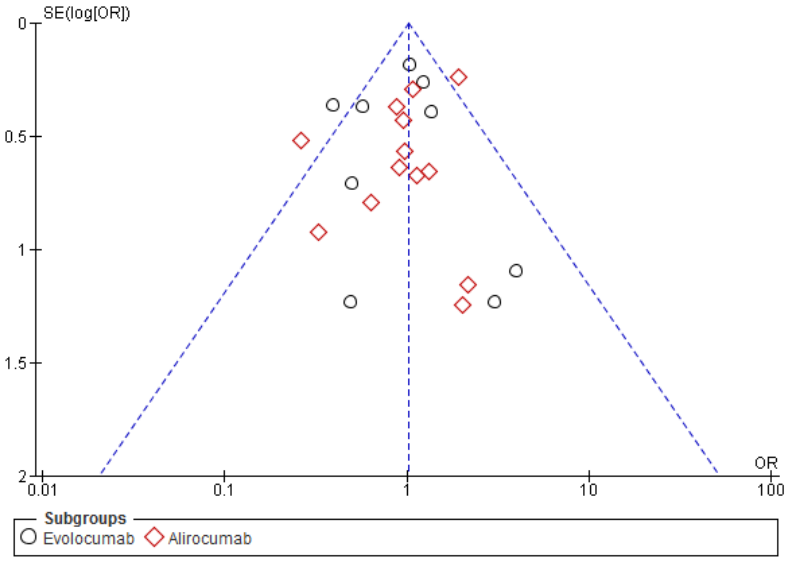


Figure S26. Funnel plot: increase in alanine/aspartate aminotransferase

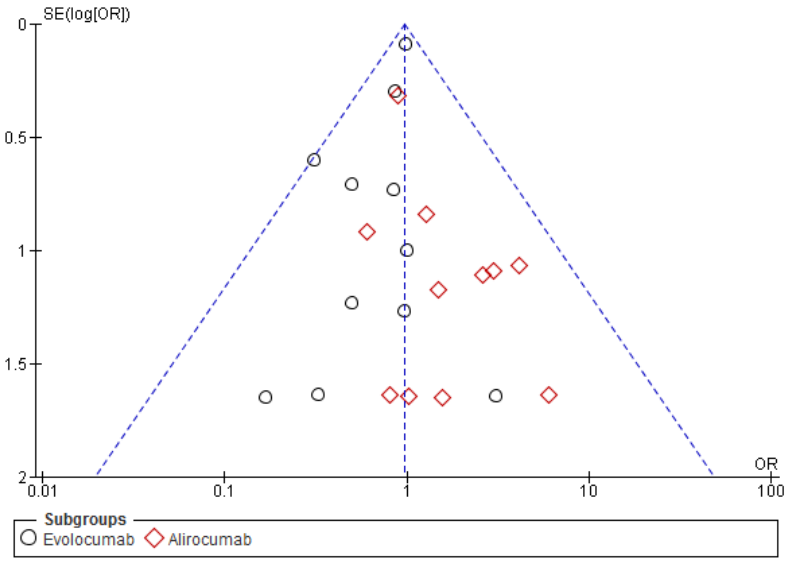


Figure S27. Funnel plot: treatment emergent serious adverse events

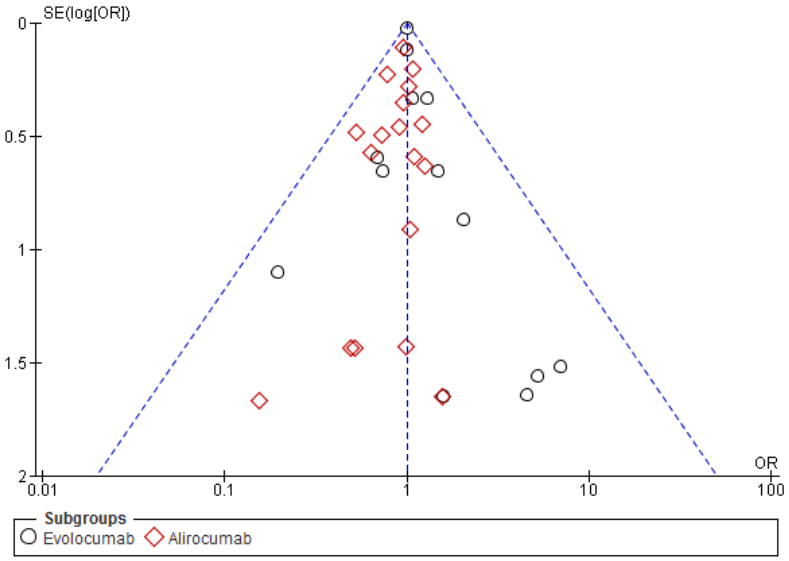


Figure S28. Funnel plot: LDL- Cholesterol

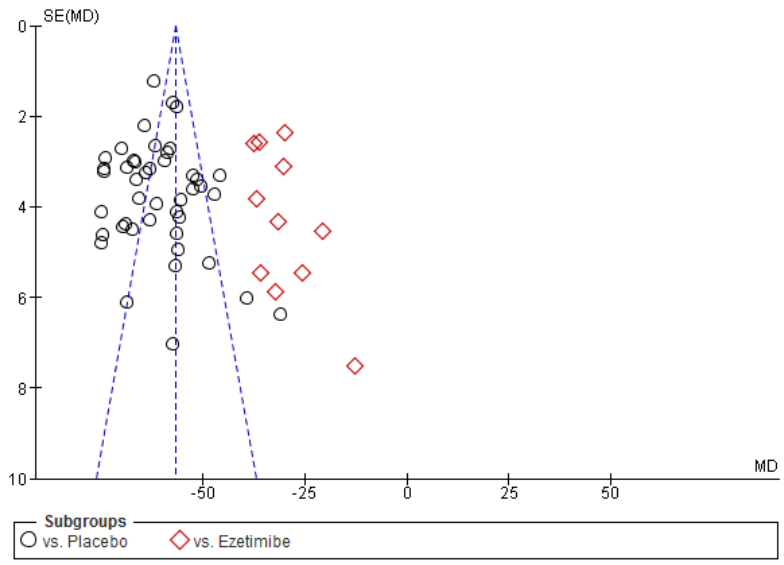


Figure S29. Funnel plot: HDL- cholesterol

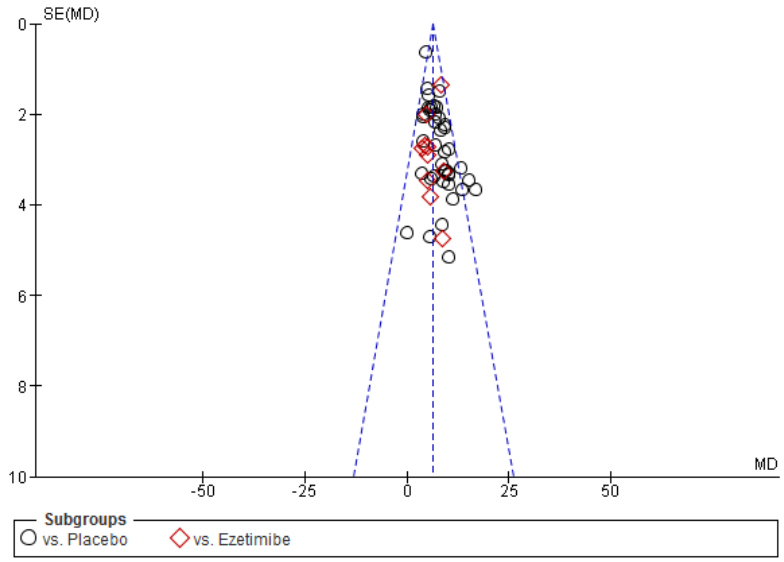


Figure S30. Funnel plot: total cholesterol

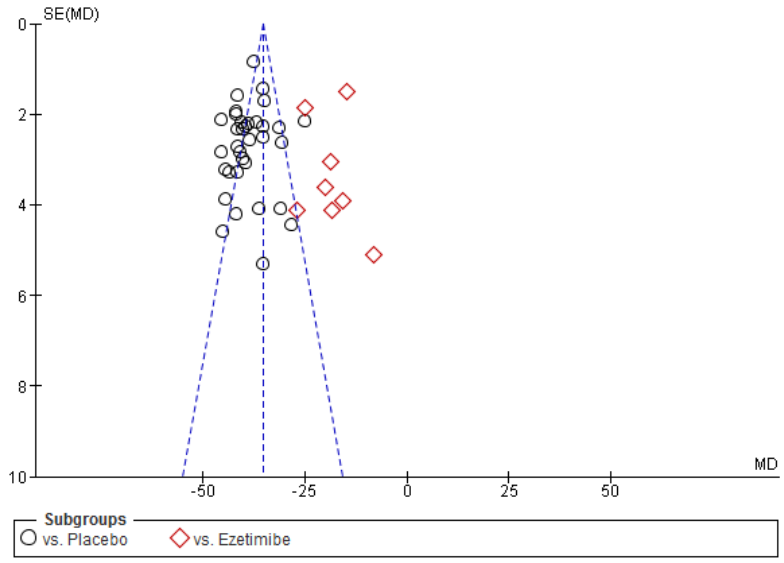


Figure S31. Funnel plot: lipoprotein(a)

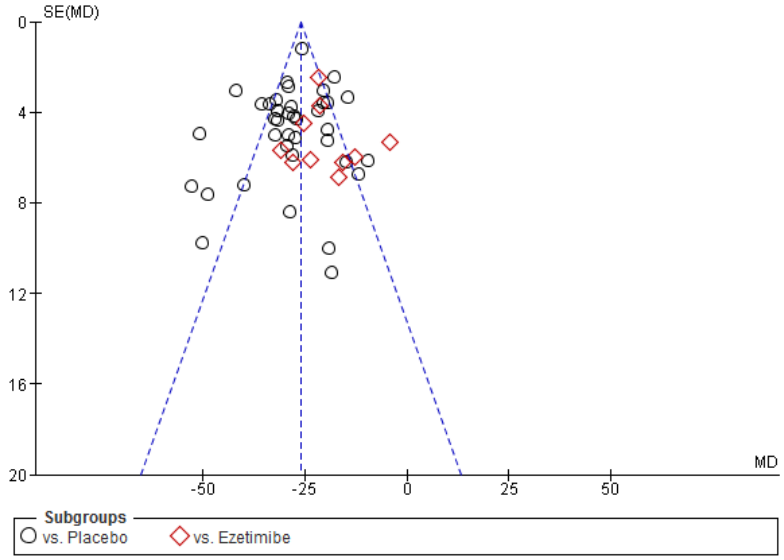
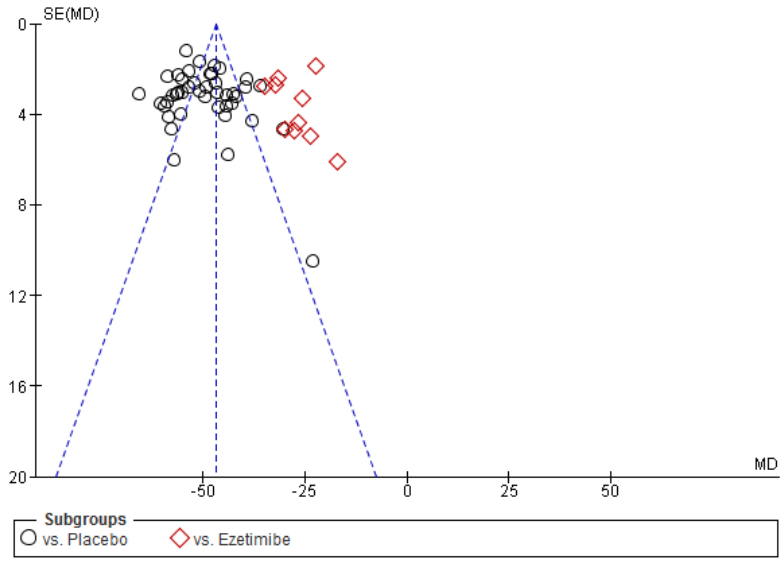


Figure S32. Funnel plot: apolipoprotein B



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