Online Supplemental Material

e Table 1. PubMed search strategy

N	Search Terms	Records
1	Lipid AND Lowering	4809
2	LDL AND Lowering	2491
3	Cholesterol AND Lowering	3663
4	Statin AND Cholesterol	4139
5	Statin AND LDL	3152
6	Statin AND Lipid	5022
7	Ezetimibe AND Cholesterol	471
8	Ezetimibe AND LDL	423
9	Ezetimibe AND Lipid	493
10	Proprotein convertase subtilisin/kexin type 9 AND Cholesterol	102
11	Proprotein convertase subtilisin/kexin type 9 AND LDL	96
12	Proprotein convertase subtilisin/kexin type 9 AND Lipid	97

e Table 2. Risk of bias in the included trials as assessed by the Cochrane risk of bias assessment scale

Studies	Randomization	Allocation concealment	Blinding (Physician/Patient)	Adjudication of outcomes	Selective outcome reporting	Incomplete data reporting addressed ?	Free of other bias ?
STATIN							
4S							
WOSCOPS[1]							
CARE[2]							
AFCAPS/TexCAPS[3]							
GISSI-P[4]							
ALLHAT-LLT[5]							
GREACE[6]							
HPS[7]							
PROSPER[8]							
ALERT[9]							
ASCOT-LLA[10]							
PROVE-IT TIMI 22[11]							
CARDS[12]							
IDEAL[13]							
TNT[14]							
MEGA[15]							
ASPEN[16]							
SPARCL[17]							
JUPITER[18]							
SEARCH[19]							
HOPE 3[20]							
EZETIMIBE + STATIN							
SEAS[21]							

SHARP[22]							
IMPROVE IT[23]							
PCSK9 INHIBITOR							
ODYSSEY LONG TERM[24]							
SPIRE 1[25]							
SPIRE 2[25]							
FOURIER[26]							
ODYSSEY OUTCOMES[27]							

Green (low risk); yellow (unclear risk); Red (high risk); 4S (SSSS), Scandinavian Simvastatin Survival Study; ALLHAT-LLT, AFCAPS-TexCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study; ALERT, Assessment of LEscol in Renal Transplantation Study; ASCOT-LLA, Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm; ASPEN, Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus; CARE, Cholesterol And Recurrent Events; CARDS, Collaborative Atorvastatin Diabetes Study; FOURIER, Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk; GISSI-P, Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico; HOPE-3, Heart Outcomes Prevention Evaluation; GREACE, The GREek Atorvastatin and Coronary-heart-disease Evaluation Study; HPS, Heart Protection Study; IDEAL, Incremental Decrease in End Points Through Aggressive Lipid Lowering Study Group; IMPROVE-IT, Improved Reduction of Outcomes: Vytorin Efficacy International Trial; JUPITER, Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin study group; LIPID, Long–term Intervention with Pravastatin in Ischaemic Disease; MEGA, Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese Study Group; ODYSSEY LONG TERM, Long-term Safety and Tolerability of Alirocumab in High Cardiovascular Risk Patients with Hypercholesterolemia Not Adequately Controlled with Their Lipid Modifying Therapy; ODYSSEY Outcomes, Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab; ; PROVE IT-TIMI 22, the Pravastatin or Atorvastatin Evaluation and Infection Therapy; PROSPER, SEARCH, Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine; SEAS, Simvastatin and Ezetimibe in Aortic Stenosis; SHARP, Study of Heart and Renal Protection; SPARCL, The Stroke Prevention by Aggressive Reduction in Cholesterol Levels; SPIRE 1 & 2, Studies of PCSK9 Inhibition and the Reduction of Vascular Events 1 & 2; TNT, Treating to New Targets; WOSCOPS, West of Scotland Coronary Prevention Study

e Table 3. Definition of cerebrovascular events

Trial name	Setting	Year	Definition
STATIN			
4S[28]	Secondary	1994	Any cerebrovascular event
WOSCOPS[1]	Primary	1995	Fatal or non fatal stroke
AFCAPS-TexCAPS[3]	Primary	1997	Total stroke
GISSI-P[4]	Secondary	2000	Fatal or non fatal stroke
ALLHAT-LLT[5]	Primary	2002	Fatal or non fatal stroke
HPS[7]	Secondary	2002	Any stroke
PROSPER[8]	Primary	2002	Fatal or non fatal stroke
ALERT[9]	Primary	2003	Fatal or nonfatal stroke or transient ischemic attack
ASCOT-LLA[10]	Primary	2003	Fatal or non fatal stroke
PROVE IT-TIMI 22[11]	Secondary	2004	Stroke
CARDS[12]	Primary	2004	Stroke
IDEAL[13]	Secondary	2005	Fatal or nonfatal stroke
TNT[14]	Secondary	2005	Fatal or nonfatal stroke or transient ischemic attack
MEGA[15]	Primary	2006	Any stroke
ASPEN[16]	Primary	2006	Fatal or non fatal stroke
SPARCL[17]	Secondary	2006	Fatal or nonfatal stroke
JUPITER[18]	Primary	2008	Any stroke
SEARCH[19]	Secondary	2010	Total Stroke
HOPE 3[20]	Primary	2016	Stroke
EZETIMIBE + STATIN			
SEAS[21]	Primary	2008	Nonhaemorrhagic stroke
SHARP[22]	Primary	2011	Haemorrhagic or nonhaemorrhagic stroke
IMPROVE IT[23]	Secondary	2015	Any stroke
PCSK9 INHIBITOR			
ODYSSEY LONGTERM[24]	Secondary	2015	Fatal or nonfatal ischemic stroke
FOURIER[26]	Secondary	2017	Total Stroke

SPIRE 1[25]	Secondary	2017	Nonfatal Stroke
SPIRE 2[25]	Secondary	2017	Nonfatal Stroke
ODYSSEY OUTCOMES[27]	Secondary	2018	Fatal or nonfatal ischemic stroke

e Table 4. Definition of major adverse cardiovascular events (MACE)

Trial name	Setting	Year	Definition
STATIN			
4S[28]	Secondary	1994	Coronary death, nonfatal definite or probable MI, silent MI, or resuscitated cardiac arrest
WOSCOPS[1]	Primary	1995	Cardiovascular death, nonfatal myocardial infarction, readmission for ACS, and stroke
AFCAPS-TexCAPS[3]	Primary	1997	Fatal or nonfatal MI, unstable angina, or sudden cardiac death
GISSI-P[4]	Secondary	2000	Cumulative rate of total mortality, non-fatal MI, and stroke
HPS[7]	Secondary	2002	Coronary death, nonfatal MI, stroke, revascularization
PROSPER[8]	Primary	2002	Death from CHD or nonfatal MI or fatal or non-fatal stroke
ALERT[9]	Primary	2003	Cardiac death, non-fatal MI, or coronary revascularization procedure, including coronary-artery bypass graft or percutaneous coronary intervention
ASCOT-LLA[10]	Primary	2003	Total cardiovascular events and procedures
PROVE IT-TIMI 22[11]	Secondary	2004	Death from any cause, myocardial infarction, documented unstable angina requiring rehospitalization, revascularization (performed at least 30 days after randomization), and stroke
CARDS[12]	Primary	2004	Acute coronary heart disease events, coronary revascularization, or stroke
IDEAL[13]	Secondary	2005	CHD death, nonfatal MI, cardiac arrest with resuscitation and stroke
TNT[14]	Secondary	2005	Death from CHD, nonfatal non–procedure related myocardial infarction, resuscitation after cardiac arrest, or fatal or nonfatal stroke
MEGA[15]	Primary	2006	Coronary heart disease
ASPEN[16]	Primary	2006	Cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, recanalization, coronary artery bypass surgery, resuscitated cardiac arrest, and worsening or unstable angina requiring hospitalization
SPARCL[17]		2006	Death from cardiac causes, nonfatal MI, resuscitation after cardiac arrest, nonfatal or fatal stroke
JUPITER[18]	Primary	2008	Myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina, or death from cardiovascular causes

SEARCH[19]		2010	Coronary death, myocardial infarction, stroke, or arterial revascularization
HOPE 3[20]	Primary	2016	Death from cardiovascular causes, nonfatal MI, or nonfatal stroke
EZETIMIBE + STATIN			
SEAS[21]	Primary	2008	Death from cardiovascular causes, aortic-valve replacement, nonfatal myocardial infarction, hospitalization for unstable angina pectoris, heart failure, CABG, PCI, and non-hemorrhagic stroke.
SHARP[22]	Primary	2011	Non-fatal myocardial infarction or coronary death, non-haemorrhagic stroke, or any arterial revascularisation procedure
IMPROVE IT[23]	Secondary	2015	
PCSK9 INHIBITOR			
ODYSSEY LONGTERM[24]	Secondary	2015	Death from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, and unstable angina requiring hospitalization
FOURIER[26]	Secondary	2017	Cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization
SPIRE 1[25]	Secondary	2017	Nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina requiring urgent revascularization, or cardiovascular death
SPIRE 2[25]	Secondary	2017	Nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina requiring urgent revascularization, or cardiovascular death
ODYSSEY OUTCOMES[27]	Secondary	2018	Death from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization.

e Table 5. Multivariate meta-regression models for the associations of BMI with cardiovascular outcomes

Outcome	Studies	Patients	BMI (Kg/m^2)	Multivariate Models			
				Adjusted for Baseline LDL-C, mg/dL	Adjusted for Absolute LDL-C Reduction, mg/dL	Adjusted for Percentage Reduction in LDL-C, mg/dL	Adjusted for Age, Gender and Risk Profile
Cardiovascular mortality	29	265766	1.07 [1.02-1.13]	1.04 [0.99-1.10]	1.05 [1.01-1.11]	1.09 [1.04-1.14]	1.06 [1.01-1.12]
All-cause mortality	29	265766	1.03 [0.99-1.06]	1.00 [0.97-1.04]	1.02 [0.97-1.05]	1.03 [1.00-1.07]	1.02 [0.98-1.05]
Myocardial infarction	29	265766	1.06 [1.02-1.09]	1.04 [0.99-1.09]	1.04 [1.01-1.08]	1.07 [1.03-1.10]	1.06 [1.02-1.09]
Revascularization	29	265766	1.08 [1.03-1.12]	1.07 [1.01-1.13]	1.07 [1.03-1.11]	1.10 [1.05-1.14]	1.07 [1.02-1.12]
Cerebrovascular events	29	265766	0.99 [0.94-1.03]	0.98 [0.93-1.03]	0.97 [0.93-1.02]	0.99 [0.94-1.03]	0.98 [0.93-1.03]
MACE	29	265766	1.04 [1.01-1.07]	1.02 [0.98-1.06]	1.03 [1.00-1.06]	1.05 [1.02-1.08]	1.02 [1.00-1.05]

Absolute reduction in low-density lipoprotein cholesterol (LDL-C) refers to between-group differences achieved in LDL-C (each 38.7 mg/dL). Percentage reduction refers to 10% reduction in active arm compared with control. Risk profile was categorized as low/moderate risk vs high risk defined as diabetes, chronic kidney disease, recent acute coronary syndrome or revascularization or C- reactive protein ≥ 2 mg/L.

e Table 6. Meta-regression models for the associations of LDL-C parameters with cardiovascular outcomes

Outcome	Studies	Patients	Baseline LDL-C, mg/dL	Absolute Reduction in LDL-C, mg/dL
Cardiovascular mortality	29	265766	0.87 [0.81-0.94]	0.79 [0.72-0.87]
All-cause mortality	29	265766	0.92 [0.88-0.97]	0.90 [0.83-0.98]
Myocardial infarction	29	265766	0.92 [0.87-0.97]	0.83 [0.77-0.90]
Revascularization	29	265766	0.90 [0.84-0.97]	0.83 [0.74-0.94]
Cerebrovascular events	29	265766	1.01 [0.93-1.08]	0.89 [0.79-0.99]
MACE	29	265766	0.92 [0.87-0.97]	0.88 [0.81-0.96]

Absolute reduction in low-density lipoprotein cholesterol (LDL-C) refers to between-group differences achieved in LDL-C (each 38.7 mg/dL). Baseline LDL-C represents change in RR for every 38.7 mg/dL increase in baseline LDL-C values.

e Table 7: Analysis stratified according to baseline LDL-C, absolute LDL-C reduction and percentage reduction in LDL-C in relation to BMI

			HAZARD RATIO [95% CI]					
Baseline LDL-C, mg/dL								
BMI, Kg/m^2		**No. of Studies (Patients)**	**Cardiovascular mortality**	**All-cause mortality**	**Myocardial infarction**	**Revascularisation**	**Cerebrovascular events**	**MACE**
<25	<100	0	NA	0	NA	0	NA	0
	100-129	0	NA	0	NA	0	NA	0
	130-159	1 (7832)	0.63 [0.30-1.33]	0.72 [0.51-1.01]	0.52 [0.29-0.94]	0.60 [0.41-0.88]	0.83 [0.57-1.21]	0.67 [0.49-0.91]
	≥160	1 (1600)	0.54 [0.32-0.90]	0.58 [0.36-0.96]	0.43 [0.27-0.69]	0.50 [0.31-0.81]	0.54 [0.25-1.17]	0.48 [0.34-0.67]
25-29.9	<100	5 (86697)	0.97 [0.90-1.04]	0.98 [0.93-1.04]	0.82 [0.77-0.88]	0.86 [0.77-0.95]	0.82 [0.76-0.89]	0.88 [0.83-0.94]
	100-129	7 (58078)	0.84 [0.70-1.00]	0.92 [0.83-1.01]	0.75 [0.64-0.89]	0.78 [0.69-0.87]	0.77 [0.66-0.89]	0.79 [0.70-0.88]
	130-159	10 (70741)	0.84 [0.79-0.90]	0.93 [0.89-0.98]	0.77 [0.69-0.84]	0.76 [0.69-0.83]	0.84 [0.76-0.92]	0.82 [0.78-0.87]
	≥160	2 (11039)	0.67 [0.56-0.80]	0.74 [0.64-0.86]	0.68 [0.60-0.77]	0.66 [0.57-0.76]	0.75 [0.54-1.03]	0.71 [0.64-0.80]
≥30	<100	1 (16817)	1.20 [0.74-1.95]	1.12 [0.79-1.59]	1.11 [0.83-1.48]	0.82 [0.49-1.37]	0.52 [0.30-0.91]	0.99 [0.80-1.22]
	100-129	1 (2341)	0.58 [0.18-1.89]	0.80 [0.32-2.02]	0.78 [0.39-1.56]	1.95 [1.23-3.09]	3.57 [1.10-11.64]	1.04 [0.61-1.78]
	130-159	1 (10621)	0.82 [0.50-1.35]	0.91 [0.63-1.32]	0.76 [0.58-1.00]	0.95 [0.62-1.46]	0.66 [0.40-1.09]	0.79 [0.65-0.97]
	≥160	0	NA	0	NA	0	NA	0
Absolute Reduction in LDL-C, mg/dL								
<25	<35	1 (7832)	0.63 [0.30-1.33]	0.72 [0.51-1.01]	0.52 [0.29-0.94]	0.60 [0.41-0.88]	0.83 [0.57-1.21]	0.67 [0.49-0.91]
	35-65	0	NA					
	≥65	1 (1600)	0.54 [0.32-0.90]	0.58 [0.36-0.96]	0.43 [0.27-0.69]	0.56 [0.41-0.76]	0.54 [0.25-1.17]	0.48 [0.34-0.67]
25-29.9	<35	10 (92270)	0.96 [0.91-1.02]	0.99 [0.95-1.03]	0.86 [0.82-0.90]	0.85 [0.79-0.92]	0.85 [0.80-0.92]	0.89 [0.85-0.93]
	35-65	12 (127968)	0.80 [0.72-0.88]	0.91 [0.86-0.96]	0.73 [0.67-0.79]	0.74 [0.68-0.80]	0.78 [0.71-0.85]	0.78 [0.73-0.82]
	≥65	2 (6317)	0.70 [0.58-0.84]	0.85 [0.59-1.23]	0.67 [0.58-0.77]	0.65 [0.56-0.76]	0.82 [0.48-1.40]	0.83 [0.62-1.10]
≥30	<35	0						
	35-65	2 (27438)	1.00 [0.69-1.45]	1.01 [0.79-1.31]	0.92 [0.63-1.33]	0.89 [0.64-1.24]	0.59 [0.41-0.86]	0.88 [0.71-1.10]
	≥65	1 (2341)	058 [0.18-1.89]	0.80 [0.32-2.02]	0.78 [0.39-1.56]	1.95 [1.23-3.09]	3.57 [1.10-11.64]	1.04 [0.61-1.78]
Percentage Reduction in LDL-C								
<25	<25	1 (7832)	0.63 [0.30-1.33]	0.72 [0.51-1.01]	0.52 [0.29-0.94]	0.60 [0.41-0.88]	0.83 [0.57-1.21]	0.67 [0.49-0.91]
	25-50	1 (1600)	0.54 [0.32-0.90]	0.58 [0.36-0.96]	0.43 [0.27-0.69]	0.50 [0.31-0.81]	0.54 [0.25-1.17]	0.48 [0.34- 0.67]
	>50	0						
25-29.9	<25	7 (65825)	0.98 [0.92-1.05]	0.99 [0.94-1.03]	0.86 [0.81-0.91]	0.89 [0.82-0.97]	0.91 [0.83-0.99]	0.93 [0.89-0.97]
	25-50	15 (115364)	0.83 [0.79-0.88]	0.91 [0.85-0.96]	0.76 [0.71-0.82]	0.76 [0.71-0.81]	0.77 [0.73-0.82]	0.80 [0.76-0.83]
	>50	2 (45366)	0.78 [0.49-1.22]	0.95 [0.79-1.14]	0.63 [0.46-0.85]	0.64 [0.46-0.88]	0.76 [0.54-1.08]	0.78 [0.61-0.99]
≥30	<25	0						
	25-50	2 (27438)	1.00 [0.69-1.45]	1.01 [0.79-1.31]	0.92 [0.63-1.33]	0.89 [0.64-1.24]	0.59 [0.41-0.86]	0.88 [0.71-1.10]
	>50	1 (2341)	0.58 [0.18-1.89]	0.80 [0.32-2.02]	0.78 [0.39-1.56]	1.95 [1.23-3.09]	3.57 [1.10-11.64]	1.04 [0.61-1.78]

e Table 8: Sensitivity analysis stratified for agent used in active treatment group

		STATIN			EZETIMIBE + STATIN			PCSK9 INHIBITOR		
OUTCOME	**BMI**	**Studies**	**Patients**	**HR [95% CI]**	**Studies**	**Patients**	**HR [95% CI]**	**Studies**	**Patients**	**HR [95% CI]**
Cardiovascular mortality	<25	2	9432	0.57 [0.37-0.86]	0	0	NA	0	0	NA
	25-29.9	19	150780	0.82 [0.76-0.89]	3	29287	0.96 [0.88-1.05]	2	46488	0.96 [0.81-1.14]
	≥30	0	0	NA	0	0	NA	3	29779	0.96 [0.68-1.33]
All-cause mortality	<25	2	9432	0.67 [0.51-0.89]	0	0	NA	0	0	NA
	25-29.9	19	150780	0.92 [0.88-0.96]	3	29287	1.01 [0.95-1.07]	2	46488	0.94 [0.77-1.15]
	≥30	0	0	NA	0	0	NA	3	29779	1.00 [0.78-1.12]
Myocardial infarction	<25	2	9432	0.47 [0.32-0.67]	0	0	NA	0	0	NA
	25-29.9	19	150780	0.76 [0.71-0.81]	3	29287	0.88 [0.81-0.95]	2	46488	0.79 [0.68-0.93]
	≥30	0	0	NA	0	0	NA	3	29779	0.89 [0.67-1.19]
Revascularisation	<25	2	9432	0.56 [0.41-0.76]	0	0	NA	0	0	NA
	25-29.9	19	150780	0.76 [0.72-0.82]	3	29287	0.86 [0.71-1.05]	2	46488	0.83 [0.73-0.93]
	≥30	0	0	NA	0	0	NA	3	29779	1.15 [0.69-1.94]
Cerebrovascular events	<25	2	9432	0.76 [0.54-1.07]	0	0	NA	0	0	NA
	25-29.9	19	150780	0.81 [0.75-0.87]	3	29287	0.86 [0.77-0.97]	2	46488	0.77 [0.66-0.89]
	≥30	0	0	NA	0	0	NA	3	29779	0.89 [0.40-2.00]
MACE	<25	2	9432	0.57 [0.41-0.79]	0	0	NA	0	0	NA
	25-29.9	19	150780	0.80 [0.75-0.84]	3	29287	0.92 [0.86-0.97]	2	46488	0.85 [0.80-0.90]
	≥30	0	0	NA	0	0	NA	3	29779	0.89 [0.75-1.06]

e Table 9: Sensitivity analysis stratified according to primary prevention trials versus secondary prevention trials

		PRIMARY PREVENTION			*SECONDARY PREVENTION		
OUTCOME	**BMI (Kg/m^2)**	**Studies**	**Patients**	**HR [95% CI]**	**Studies**	**Patients**	**HR [95% CI]**
Cardiovascular mortality	<25	1	7832	0.63 [0.30-1.33]	1	1600	0.54 [0.32-0.90]
	25-29.9	12	88667	0.81 [0.72-0.91]	12	137888	0.89 [0.82-0.96]
	≥30	0	0	NA	3	29779	0.96 [0.68-1.33]
All-cause mortality	<25	1	7832	0.72 [0.51-1.01]	1	1600	0.58 [0.36-0.96]
	25-29.9	12	88667	0.95 [0.90-1.01]	12	137888	0.93 [0.88-0.99]
	≥30	0	0	NA	3	29779	1.00 [0.78-1.28]
Myocardial infarction	<25	1	7832	0.52 [0.29-0.94]	1	1600	0.43 [0.32-0.67]
	25-29.9	12	88667	0.74 [0.66-0.83]	12	137888	0.79 [0.74-0.84]
	≥30	0	0	NA	3	29779	0.89 [0.67-1.19]
Revascularisation	<25	1	7832	0.60 [0.41-0.88]	1	1600	0.50 [0.31-0.81]
	25-29.9	12	88667	0.75 [0.67-0.83]	12	137888	0.80 [0.74-0.87]
	≥30	0	0	NA	3	29779	1.15 [0.69-1.94]
Cerebrovascular events	<25	1	7832	0.83 [0.57-1.21]	1	1600	0.54 [0.25-1.17]
	25-29.9	12	88667	0.84 [0.74-0.94]	12	137888	0.80 [0.75-0.84]
	≥30	0	0	NA	3	29779	0.89 [0.40-2.00]
MACE	<25	1	7832	0.67 [0.49-0.91]	1	1600	0.48 [0.34-0.67]
	25-29.9	12	88667	0.79 [0.72-0.86]	12	137888	0.84 [0.80-0.89]
	≥30	0	0	NA	3	29779	0.89 [0.75-1.06]

*Secondary prevention trials were defined as having patients with history of known atherosclerotic cardiovascular disease (coronary artery disease or cerebrovascular disease or peripheral artery disease) or at least 60% secondary prevention population.

e Table 10: Analysis stratified according to weighted mean values for LDL-C parameters, mg/dL

					HAZARD RATIO [95% CI]					
BMI (Kg/m^2)	Trials	Baseline LDL-C, mg/dL	Absolute LDL-C reduction, mg/dL	Percentage reduction in LDL-C	Cardiovascular mortality	All-cause mortality	Myocardial infarction	Revascularisation	Cerebrovascular events	MACE
<25	GREACE[6]	179.5	72.9	40.6	0.54 [0.32-0.90]	0.58 [0.36-0.96]	0.43 [0.27-0.69]	0.50 [0.31-0.81]	0.54 [0.25-1.17]	0.48 [0.34-0.67]
	MEGA[15]	156.6	20.4	13.0	0.63 [0.30-1.33]	0.72 [[0.51-1.01]	0.52 [0.29-0.94]	0.60 [0.41-0.88]	0.83 [0.57-1.21]	0.67 [0.49-0.91]
		168.0	**46.6**	**26.8**	**0.57 [0.37-0.86]**	**0.67 [0.51-0.89]**	**0.47 [0.32-0.67]**	**0.56 [0.41-0.76]**	**0.76 [0.54-1.07]**	**0.57 [0.41-0.79]**
25-29.9	4S[28]	188.3	67.6	35.9	0.66 [0.53-0.82]	0.71 [0.59-0.86]	0.67 [0.58-0.78]	0.66 [0.57-0.77	0.65 [0.47-0.89]	0.72 [0.63-0.82]
	WOSCOPS[1]	192	49.9	26	0.69 [0.48-0.98]	0.79 [0.61-1.01]	0.70 [0.57-0.87]	0.64 [0.46-0.90]	0.90 [0.61-1.34]	0.70 [0.58-0.85]
	CARE[2]	139	40.3	29	0.81 [0.62-1.05]	0.92 [0.75-1.12]	0.76 [0.62-0.93]	0.75 [0.65-.088]	0.70 [0.49-0.98]	0.77 [0.65-0.93]
	AFCAPS/TexCAPS[3]	150	41.7	27.8	0.68 [0.37-1.25]	1.04 [0.76-1.42]	0.61 [0.44-0.83]	0.68 [0.53-0.88]	0.82 [0.41-1.67]	0.64 [0.51-0.80]
	GISSI-P[4]	151.6	17.9	11.8	0.80 [0.56-1.15]	0.82 [0.60-1.12]	0.88 [0.59-1.32]	0.90 [0.72-1.11]	1.05 [0.56-1.97]	0.88 [0.69-1.13]
	ALLHAT-LLT[5]	145.5	17.4	12	0.98 [0.84-1.15]	0.98 [0.88-1.10]	0.90 [0.79-1.04]	0.88 [0.76-1.03]	0.90 [0.75-1.09]	0.90 [0.79-1.04]
	HPS[7]	131.5	38.7	29.4	0.83 [0.76-0.92]	0.88 [0.82-0.95]	0.74 [0.68-0.81]	0.78 [0.72-0.85]	0.76 [0.67-0.86]	0.79 [0.74-0.83]
	PROSPER[8]	147	50	34	0.76 [0.58-0.99]	0.97 [0.83-1.14]	0.86 [0.72-1.03]	0.82 [0.54-1.25]	0.98 [0.76-1.26]	0.85 [0.74-0.97]
	ALERT[9]	158.5	38.1	24	0.67 [0.44-1.01]	1.04 [0.82-1.31]	0.70 [0.48-1.01]	0.89 [0.61-1.28]	1.17 [0.84-1.64]	0.84 [0.65-1.07]
	ASCOT-LLA[10]	133	37.2	28	0.90 [0.66-1.23]	0.87 [0.71-1.06]	0.82 [0.40-1.67]	0.63 [0.45-0.89]	0.73 [0.56-0.96]	0.79 [0.69-0.90]
	CARDS[12]	117	46.4	39.7	0.68 [0.41-1.12]	0.73 [0.52-1.02]	0.55 [0.37-0.83]	0.69 [0.41-1.16]	0.52 [0.31-0.88]	0.63 [0.48-0.83]
	PROVE IT-TIMI22[11]	106	32.9	31	0.79 [0.46-1.37]	0.70 [0.48-1.01]	0.91 [0.72-1.14]	0.88 [0.76-1.02]	1.00 [0.55-1.83]	0.87 [0.77-0.98]
	IDEAL[13]	121.4	21.7	17.9	1.03 [0.85-1.24]	0.98 [0.85-1.13]	0.83 [0.71-0.98]	0.77 [0.69-0.86]	0.87 [0.70-1.08]	0.89 [0.78-1.01]
	TNT[14]	97.5	24	24.6	0.80 [0.62-1.04]	1.01 [0.85-1.20]	0.78 [0.66-0.93]	0.74 [0.67-0.82]	0.77 [0.64-0.93]	0.78 [0.69-0.89]
	ASPEN[16]	113.5	33.8	29.8	1.03 [0.65-1.61]	1.03 [0.74-1.44]	0.74 [0.52-1.07]	0.98 [0.73-1.31]	0.89 [0.56-1.42]	0.92-0.75-1.14]
	SPARCL[17]	132.7	55.3	41.7	0.78 [0.58-1.05]	1.00 [0.82-1.21]	0.51 [0.35-0.74]	0.55 [0.43-0.71]	0.77 [0.67-0.88]	0.80 [0.69-0.92]
	JUPITER[18]	108	54.9	50.8	0.53 [0.40-0.70]	0.80 [0.66-0.96]	0.46 [0.30-0.70]	0.54 [0.41-0.72]	0.52 [0.34-0.79]	0.56 [0.46-0.69]
	SEARCH[19]	96.7	13.5	14	0.99 [0.88-1.11]	0.99 [0.91-1.09]	0.85 [0.76-0.95]	0.93 [0.83-1.05]	0.91 [0.77-1.08]	0.95 [0.89-1.02]
	HOPE-3[20]	127.8	34.4	26.9	0.89 [0.72-1.11]	0.93 [0.80-1.08]	0.65 [0.44-0.95]	0.68 [0.48-0.96]	0.70 [0.52-0.95]	0.76 [0.64-0.91]
	FOURIER[26]	92	54.1	58.8	1.05 [0.88-1.25]	1.04 [0.91-1.19]	0.73 [0.65-0.82]	0.78 [0.71-0.86]	0.79 [0.66-0.95]	0.85 [0.79-0.92]
	ODYSSEY OUTCOMES[27]	92	38.7	42.1	0.88 [0.74-1.05]	0.85 [0.73-0.98]	0.86 [0.77-0.96]	0.88 [0.79-0.98]	0.73 [0.57-0.93]	0.85 [0.78-0.93]
	SEAS[21]	139.5	69	49.5	0.83 [0.56-1.23]	1.04 [0.79-1.36]	0.64 [0.35-1.17]	0.46 [0.20-1.06]	1.12 [0.68-1.85]	0.96 [0.83-1.12]
	SHARP[22]	107.3	29.3	27.3	0.93 [0.81-1.07]	1.02 [0.94-1.11]	0.93 [0.77-1.12]	0.81 [0.69-0.94]	0.83 [0.68-1.02]	0.85 [0.76-0.95]
	IMPROVE IT[23]	93.8	12.8	13.7	1.00 [0.89-1.13]	0.99 [0.91-1.07]	0.87 [0.80-0.95]	0.96 [0.90-1.02]	0.86 [0.73-1.01]	0.93 [0.87-0.99]
		128.4	**38.3**	**30.2**	**0.86 [0.80-0.92]**	**0.94 [0.90-0.98]**	**0.78 [0.74-0.82]**	**0.78 [0.74-0.83]**	**0.81 [0.77-0.86]**	**0.82 [0.78-0.86]**
≥30	ODYSSEY LONG TERM[24]	122.3	70.8	57.9	0.58 [0.18-1.89]	0.80 [0.32-2.02]	0.78 [0.39-1.56]	1.95 [1.23-3.09]	3.57 [1.10-11.64]	1.04 [0.61-1.78]
	SPIRE 1[25]	93.8	44.9	47.9	1.20 [0.74-1.95]	1.12 [0.79-1.59]	1.11 [0.83-1.48]	0.82 [0.49-1.37]	0.52 [0.30-0.91]	0.99 [0.80-1.22]
	SPIRE 2[25]	133.6	58	43.4	0.82 [0.50-1.35]	0.91 [0.63-1.32]	0.76 [0.58-1.00]	0.95 [0.62-1.46]	0.66 [0.40-1.09]	0.79 [0.65-0.97]
		116.5	**57.9**	**49.7**	**0.96 [0.68-1.33]**	**1.00 [0.78-1.28]**	**0.89 [0.67-1.19]**	**1.15 [0.69-1.94]**	**0.89 [0.40-2.00]**	**0.89 [0.75-1.06]**
	Total	**129.9**	**40.9**	**32.0**	**0.85 [0.80-0.91]**	**0.93 [0.90-0.97]**	**0.77 [0.73-0.82]**	**0.78 [0.73-0.83]**	**0.81 [0.77-0.86]**	**0.82 [0.79-0.86]**

Bold indicates weighted mean values

e Table 11. Sensitivity analysis by excluding individual trials

		HAZARD RATIO [95% CI]					
BMI (Kg/m^2)	**Trials Excluded**	**Cardiovascular mortality**	**All-cause mortality**	**Myocardial infarction**	**Revascularisation**	**Cerebrovascular events**	**MACE**
<25	GREACE[6]	0.63 [0.30-1.33]	0.72 [0.51-1.01]	0.52 [0.29-0.94]	0.60 [0.41-0.88]	0.83 [0.57-1.21]	0.67 [0.49-0.91]
	MEGA[15]	0.54 [0.32-0.90]	0.58 [0.36-0.96]	0.43 [0.27-0.69]	0.50 [0.31-0.81]	0.54 [0.25-1.17]	0.48 [0.34-0.67]
25-29.9	4S[28]	0.87 [0.82-0.93]	0.95 [0.92-0.99]	0.79 [0.74-0.83]	0.79 [0.74-0.84]	0.82 [0.77-0.86]	0.83 [0.79-0.86]
	WOSCOPS[1]	0.86 [0.81-0.92]	0.94 [0.90-0.98]	0.78 [0.74-0.83]	0.79 [0.74-0.84]	0.81 [0.77-0.86]	0.83 [0.79-0.86]
	CARE[2]	0.86 [0.80-0.92]	0.94 [0.90-0.98]	0.78 [0.73-0.83]	0.78 [0.74-0.84]	0.82 [0.77-0.86]	0.82 [0.78-0.86]
	AFCAPS/TexCAPS[3]	0.86 [0.80-0.92]	0.94 [0.90-0.98]	0.78 [0.74-0.83]	0.79 [0.74-0.84]	0.81 [0.77-0.86]	0.83 [0.79-0.86]
	GISSI-P[4]	0.86 [0.80-0.92]	0.94 [0.90-0.98]	0.78 [0.73-0.82]	0.78 [0.73-0.83]	0.81 [0.77-0.86]	0.82 [0.78-0.86]
	ALLHAT-LLT[5]	0.85 [0.79-0.91]	0.93 [0.89-0.98]	0.77 [0.73-0.82]	0.78 [0.73-0.83]	0.81 [0.76-0.85]	0.82 [0.78-0.86]
	HPS[7]	0.86 [0.80-0.92]	0.94 [0.91-0.99]	0.78 [0.74-0.83]	0.78 [0.73-0.84]	0.82 [0.77-0.87]	0.82 [0.78-0.86]
	PROSPER[8]	0.86 [0.81-0.92]	0.94 [0.90-0.98]	0.77 [0.73-0.82]	0.78 [0.73-0.83]	0.81 [0.76-0.85]	0.82 [0.78-0.86]
	ALERT[9]	0.86 [0.81-0.92]	0.94 [0.90-0.98]	0.78 [0.74-0.83]	0.78 [0.73-0.83]	0.80 [0.77-0.85]	0.82 [0.78-0.86]
	ASCOT-LLA[10]	0.86 [0.80-0.92]	0.94 [0.90-0.98]	0.77 [0.73-0.82]	0.79 [0.74-0.84]	0.82 [0.77-0.86]	0.82 [0.78-0.86]
	CARDS[12]	0.86 [0.81-0.92]	0.94 [0.90-0.98]	0.78 [0.74-0.83]	0.78 [0.74-0.84]	0.82 [0.77-0.86]	0.83 [0.79-0.86]
	PROVE IT-TIMI22[11]	0.86 [0.80-0.92]	0.94 [0.90-0.98]	0.77 [0.73-0.82]	0.78 [0.73-0.83]	0.81 [0.77-0.86]	0.82 [0.78-0.86]
	IDEAL[13]	0.85 [0.79-0.91]	0.93 [0.90-0.98]	0.77 [0.73-0.82]	0.78 [0.73-0.84]	0.81 [0.76-0.86]	0.82 [0.78-0.86]
	TNT[14]	0.86 [0.80-0.92]	0.93 [0.90-0.98]	0.78 [0.73-0.82]	0.79 [0.74-0.84]	0.82 [0.77-0.87]	0.82 [0.78-0.86]
	ASPEN[16]	0.85 [0.80-0.91]	0.94 [0.90-0.98]	0.77 [0.74-0.82]	0.78 [0.73-0.83]	0.81 [0.77-0.86]	0.82 [0.78-0.86]
	SPARCL[17]	0.86 [0.80-0.92]	0.94 [0.90-0.98]	0.79 [0.75-0.83]	0.79 [0.75-0.84]	0.82 [0.77-0.87]	0.82 [0.78-0.86]
	JUPITER[18]	0.88 [0.83-0.93]	0.94 [0.91-0.98]	0.79 [0.75-0.83]	0.79 [0.75-0.84]	0.82 [0.78-0.86]	0.83 [0.80-0.87]
	SEARCH[19]	0.85 [0.79-0.91]	0.93 [0.89-0.97]	0.77 [0.73-0.82]	0.77 [0.73-0.83]	0.80 [0.76-0.85]	0.81 [0.78-0.85]
	HOPE-3[20]	0.85 [0.80-0.92]	0.94 [0.90-0.98]	0.78 [0.74-0.83]	0.79 [0.74-0.84]	0.82 [0.77-0.86]	0.82 [0.79-0.86]
	FOURIER[26]	0.85 [0.79-0.91]	0.93 [0.89-0.97]	0.78 [0.74-0.83]	0.78 [0.73-0.84]	0.81 [0.77-0.86]	0.82 [0.78-0.86]
	ODYSSEY OUTCOMES[27]	0.85 [0.80-0.92]	0.94 [0.90-0.98]	0.77 [0.73-0.82]	0.78 [0.73-0.83]	0.82 [0.77-0.86]	0.82 [0.78-0.86]
	SEAS[21]	0.86 [0.80-0.92]	0.94 [0.90-0.98]	0.78 [0.74-0.83]	0.79 [0.74-0.84]	0.81 [0.77-0.86]	0.82 [0.78-0.85]
	SHARP[22]	0.85 [0.79-0.91]	0.93 [0.89-0.97]	0.77 [0.73-0.82]	0.78 [0.73-0.83]	0.81 [0.76-0.86]	0.82 [0.78-0.86]
	IMPROVE IT[23]	0.85 [0.79-0.91]	0.93 [0.89-0.97]	0.77 [0.73-0.82]	0.78 [0.73-0.82]	0.81 [0.77-0.86]	0.81 [0.78-0.85]
≥30	ODYSSEY LONG TERM[24]	1.00 [0.69-1.45]	1.01 [0.79-1.31]	0.92 [0.63-1.33]	0.89 [0.64-1.24]	0.59 [0.41-0.86]	0.88 [0.71-1.10]
	SPIRE 1[25]	0.78 [0.49-1.23]	0.89 [0.63-1.26]	0.76 [0.59-0.98]	1.35 [0.67-2.73]	1.41 [0.27-7.28]	0.82 [0.68-0.99]
	SPIRE 2[25]	1.03 [0.57-1.84]	1.07 [0.77-1.49]	1.05 [0.81-1.38]	1.27 [0.55-2.97]	1.27 [0.19-8.32]	1.00 [0.82-1.21]

e Table 12. Baseline Characteristics of the Trials and Participants

			No. (%)					Interventions							
Study (Year)	**N**	**Age**	**Women**	**CAD**	**Vascular Disease**	**Diabetes**	**CKD (%)**	**Active Agent**	**No.**	**Control**	**No.**	**BMI (Kg/m^2)**	**Baseline LDL-C (mg/dL)**	**Between-Group Difference Achieved LDL-C (mg/dL)**	**Follow-up, Yrs**
STATIN															
4S (1994)[28]	4444	58.6	827 (19)	4444 (100)	4444 (100)	202 (5)	505 (11)	Simvastatin (20-40mg)	2221	Placebo	2223	26.0	188.3	67.6	5.4
WOSCOPS (1995)[1]	6595	55	0	338 (5)	531 (8)	76 (1)	NA	Pravastatin (40 mg)	3302	Placebo	3293	25.9	192	49.9	4.9
CARE (1996)[2]	4159	59	576 (14)	4159 (100)	4159 (100)	586 (14)	NA	Pravastatin (40 mg)	2081	Placebo	2078	28.0	139	40.3	5.0
AFCAPS/TexCAPS (1998)[3]	6605	58.2	997 (15)	<1	<1	155 (2)	304 (5)	Lovastatin (20-40 mg)	3304	Placebo	3301	26.7	150	41.7	5.2
GISSI-P (2000)[4]	4271	59.9	587 (14)	4271 (100)	4271 (100)	582 (14)	NA	Pravastatin (20 mg)	2138	Usual care	2133	26.3	151.6	17.9	2.0
ALLHAT-LLT (2002)[5]	10355	66	5051 (49)	1475 (14)	NA	3638 (35)	NA	Pravastatin (20 mg)	5170	Usual care	5185	29.0	145.5	17.4	4.8
GREACE (2002)[6]	1600	58.5	344 (22)	1600 (100)	1600 (100)	313 (20)	NA	Atorvastatin (10-80 mg)	800	Usual care	800	24.0	179.5	72.9	3.0

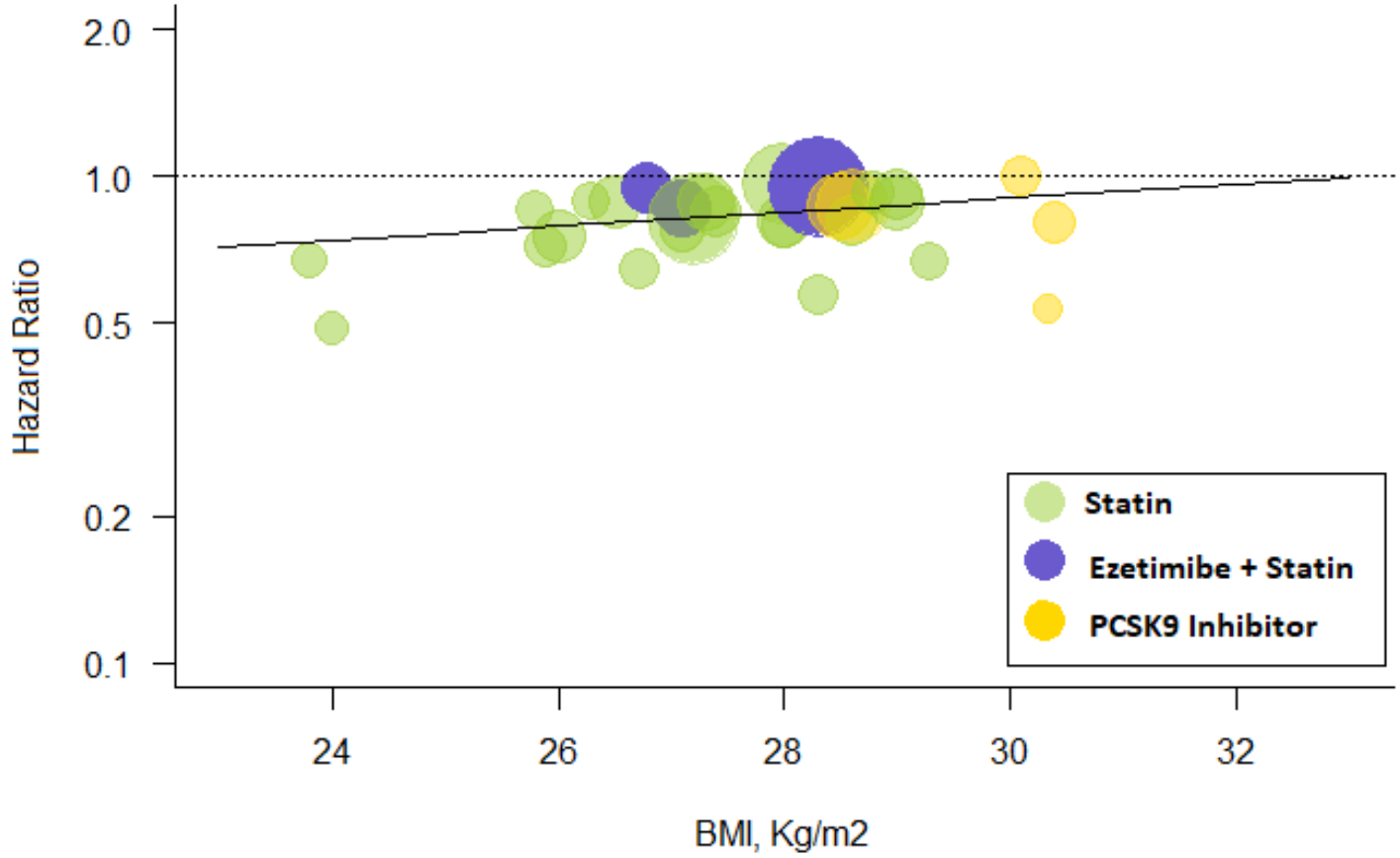
HPS (2002)[7]	20536	63.4	5082 (25)	13386 (65)	17907 (87)	5963 (29)	1329 (6)	Simvastatin (40mg)	10269	Placebo	10267	27.2	131.5	38.7	5
PROSPER (2002)[8]	5804	75	3000 (52)	2335 (40)	2565 (44)	623 (11)	3077 (53)	Pravastatin (40 mg)	2891	Placebo	2913	26.5	147	50	3.2
ALERT (2003)[9]	2102	49.8	715 (34)	148 (7)	158 (8)	396 (19)	NA	Fluvastatin (40 mg)	1050	Placebo	1052	25.8	158.5	38.1	5.4
ASCOT-LLA (2003)[10]	10305	63.0	1942 (19)	<1	1515 (15)	2527 (25)	6517 (63)	Atorvastatin (10 mg)	5168	Placebo	5137	28.6	133	37.2	3.3
PROVE IT-TIMI 22 (2004)[11]	4162	58.2	911 (22)	4162 (100)	4162 (100)	734 (18)	NA	Atorvastatin (80 mg)	2099	Pravastatin (40mg)	2063	29.0	106	32.9	2.0
CARDS (2004)[12]	2841	61.6	909 (32)	<1	<1	2838 (100)	970 (34)	Atorvastatin (10 mg)	1429	Placebo	1412	29.3	117	46.4	3.9
IDEAL (2005)[13]	8888	61.7	1702 (19)	8888 (100)	8888 (100)	1069 (12)	NA	Atorvastatin (80mg)	4439	Simvastatin (20mg)	4449	27.3	121.4	21.7	4.8
TNT (2005)[14]	10001	61.0	1902 (19)	10001 (100)	10001 (100)	1501 (15)	NA	Atorvastatin (80mg)	4995	Atorvastatin (10mg)	5006	28.0	97.5	24	4.9
MEGA (2006)[15]	8214	58.3	5547 (68)	<1	<1	1686 (21)	2978 (38)	Pravastatin (10-20 mg)	3866	Usual care	3966	23.8	156.6	20.4	5.3
ASPEN (2006)[16]	2410	61.0	811 (34)	790 (33)	1121 (47)	2410 (100)	NA	Atorvastatin (10 mg)	1211	Placebo	1199	28.8	113.5	33.8	4.0
SPARCL (2006)[17]	4731	62.7	1908 (40)	0	4731 (100)	794 (17)	NA	Atorvastatin (80mg)	2365	Placebo	2366	27.4	132.7	55.3	4.9
JUPITER (2008)[18]	17802	66.0	6801 (30)	0	0	76 (<1)	3267 (18)	Rosuvastatin (20 mg)	8901	Placebo	8901	28.3	108	54.9	1.9

SEARCH (2010)[19]	12064	64.2	2052 (17)	12064 (100)	12064 (100)	1267 (11)	1686 (14)	Simvastatin (80mg)	6031	Simvastatin (20mg)	6033	28.0	96.7	13.5	6.7
HOPE 3 (2016)[20]	12705	65.7	5874 (46)	0	0	731 (6)	NA	Rosuvastatin (10 mg)	6361	Placebo	6344	27.1	127.8	34.4	5.6
EZETIMIBE + STATIN															
SEAS (2008)[21]	1873	67.5	723 (39)	0	0	0	NA	Simvastatin (40 mg) + ezetimibe (10 mg)	944	Placebo	929	26.8	139.5	69	4.4
SHARP (2011)[22]	9270	62.0	3470 (37)	0	1393 (15)	2094 (23)	9270 (100)	Simvastatin (20 mg) + ezetimibe (10 mg)	4650	Placebo	4620	27.1	107.3	29.3	4.9
IMPROVE IT (2015)[23]	18144	63.6	4416 (24)	18144 (100)	18144 (100)	4933 (27)	NA	Simvastatin (40mg) + Ezetimibe (10mg)	9067	Simvastatin (40mg)	9077	28.3	93.8	12.8	6.0
PCSK9 INHIBITOR															
ODYSSEY LONGTERM (2015)[24]	2341	60.5	884 (38)	1607 (69)	2341 (100)	809 (35)	NA	Alirocumab (150mg every 2 weeks)	1553	Placebo	788	30.4	122.3	70.8	1.5
FOURIER (2017)[26]	27564	62.5	6769 (25)	22351 (81)	27564 (100)	10081 (37)	NA	Evolocumab (140mg every 2 weeks or	13784	Placebo	13780	28.6	92	54.1	2.2

								420mg every month)							
SPIRE 1 (2017)[25]	16817	63.3	4439 (26)	NA	14563 (87)	8047 (48)	NA	Bococizumab (150 mg every 2 weeks)	8408	Placebo	8409	30.1	93.8	44.9	0.6
SPIRE 2 (2017)[25]	10621	62.4	3675 (35)	NA	8635 (81)	4986 (47)	NA	Bococizumab (150mg every 2 weeks)	5312	Placebo	5309	30.4	133.6	58	1.0
ODYSSEY OUTCOMES (2018)[27]	18,924	58.5	4762 (25)	18924 (100)	759 (4)	5444 (29)	NA	Alirocumab (75-150 mg every 2 weeks)	9462	Placebo	9462	28.5	92	38.7	2.8

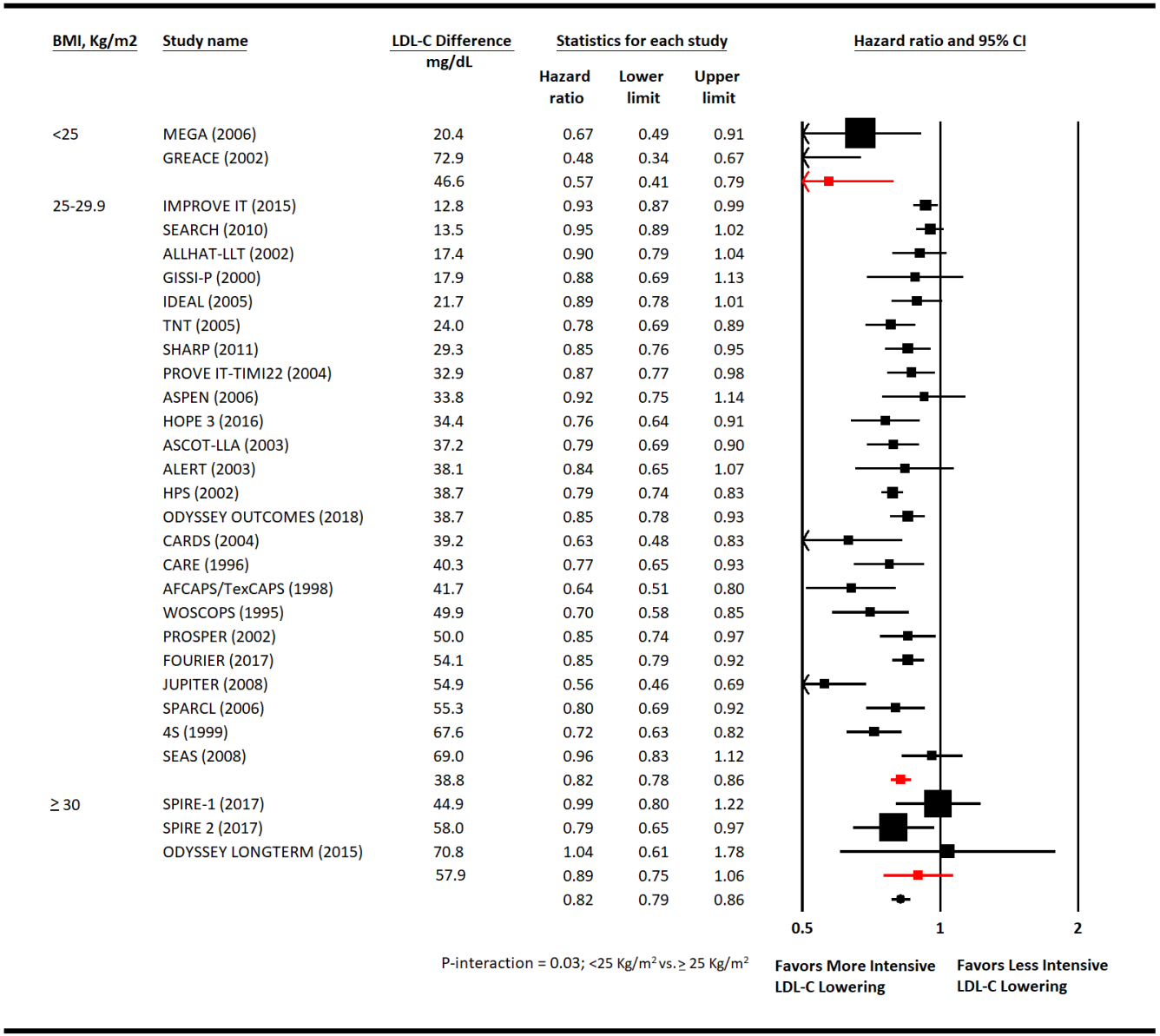
Values are mean or median, which ever was available; 4S (SSSS), Scandinavian Simvastatin Survival Study; ALLHAT-LLT, AFCAPS-TexCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study; ALERT, Assessment of LEscol in Renal Transplantation Study; ASCOT-LLA, Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm; ASPEN, Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus; CARE, Cholesterol And Recurrent Events; CARDS, Collaborative Atorvastatin Diabetes Study; FOURIER, Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk; GISSI-P, Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico; HOPE-3, Heart Outcomes Prevention Evaluation; GREACE, The GREek Atorvastatin and Coronary-heart-disease Evaluation Study; HPS, Heart Protection Study; IDEAL, Incremental Decrease in End Points Through Aggressive Lipid Lowering Study Group; IMPROVE-IT, Improved Reduction of Outcomes: Vytorin Efficacy International Trial; JUPITER, Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin study group; LIPID, Long–term Intervention with Pravastatin in Ischaemic Disease; MEGA, Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese Study Group; ODYSSEY LONG TERM, Long-term Safety and Tolerability of Alirocumab in High Cardiovascular Risk Patients with Hypercholesterolemia Not Adequately Controlled with Their Lipid Modifying Therapy; ODYSSEY Outcomes, Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab; ; PROVE IT-TIMI 22, the Pravastatin or Atorvastatin Evaluation and Infection Therapy; PROSPER, SEARCH, Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine; SEAS, Simvastatin and Ezetimibe in Aortic Stenosis; SHARP, Study of Heart and Renal Protection; SPARCL, The Stroke Prevention by Aggressive Reduction in Cholesterol Levels; SPIRE 1 & 2, Studies of PCSK9 Inhibition and the Reduction of Vascular Events 1 & 2; TNT, Treating to New Targets; WOSCOPS, West of Scotland Coronary Prevention Study

e Figure 1: Meta-Regression for BMI Effect on MACE

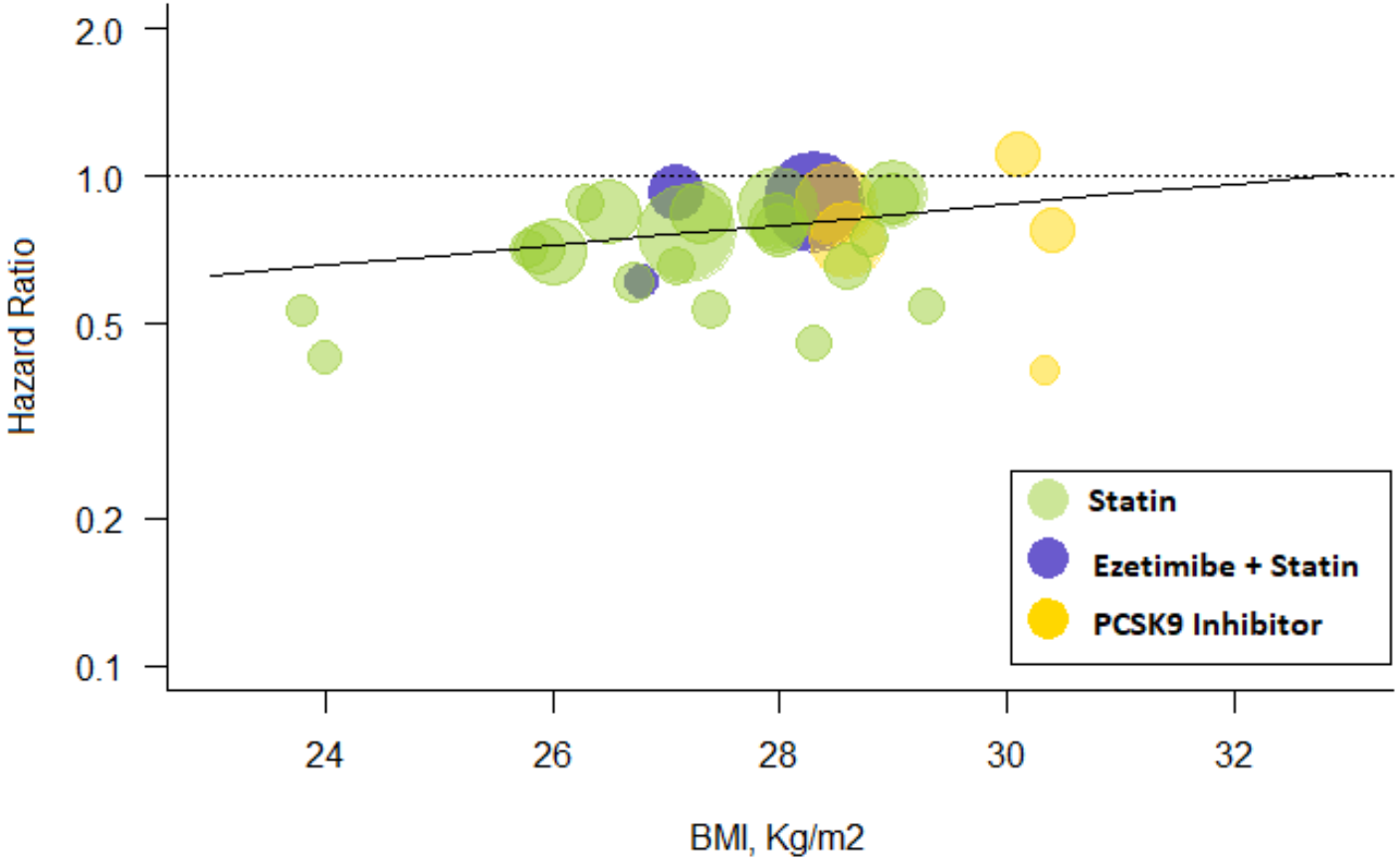


Change in hazard ratios and 95% confidence intervals for MACE plotted against body mass index (BMI, Kg/m^2). Size of the data marker is proportional to the weight in the meta-regression. Data marker colors represent the classes of lipid-lowering agents used in the active treatment group as per trial randomization design. The solid line represents the meta-regression slope of the change in hazard ratio for treatment across BMI values.

e Figure 2: Meta-Analysis for MACE

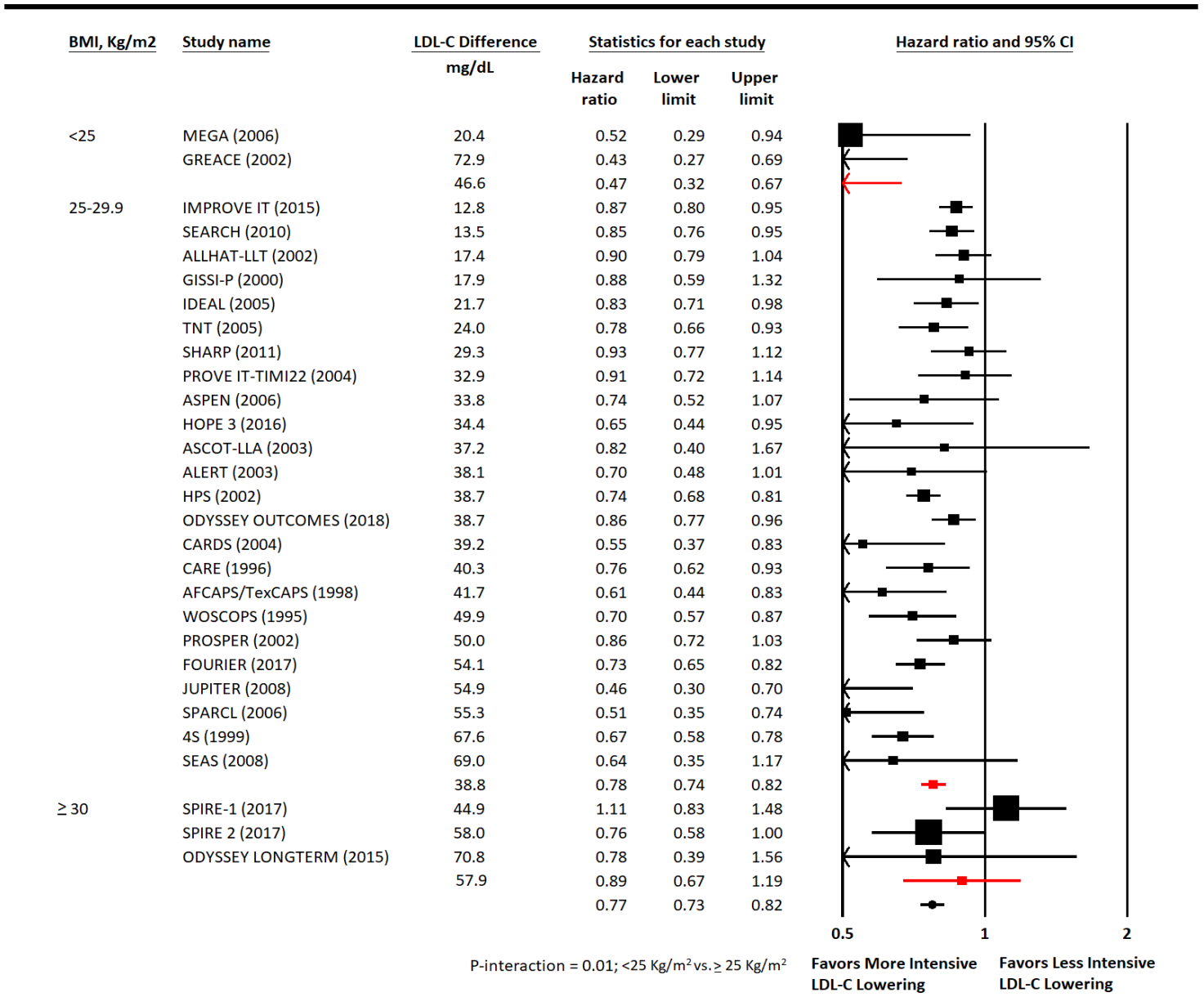


e Figure 3. Meta-Regression for BMI Effect on Myocardial Infarction

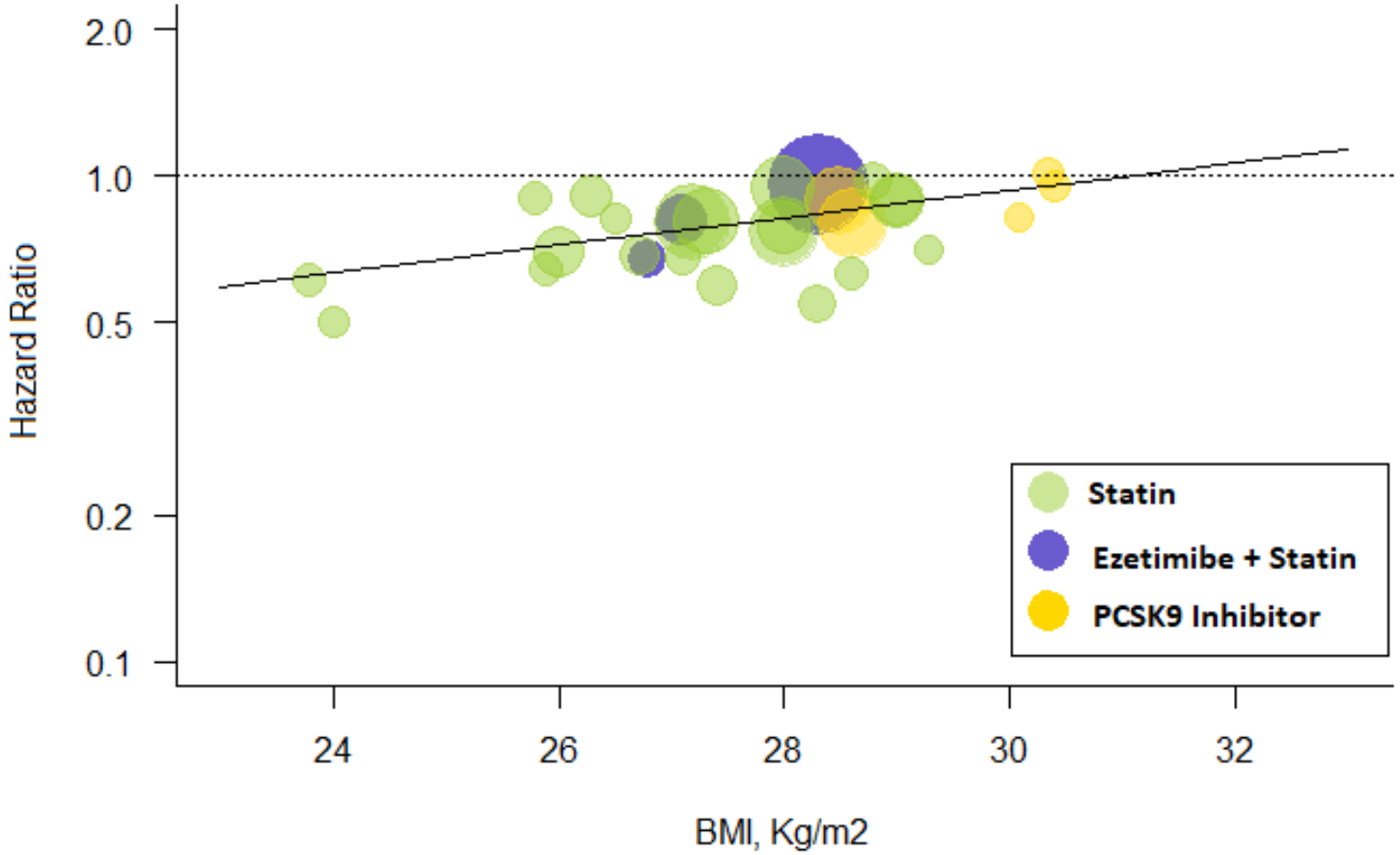


Change in hazard ratios and 95% confidence intervals for myocardial infarction plotted against body mass index (BMI, Kg/m^2). Size of the data marker is proportional to the weight in the meta-regression. Data marker colors represent the classes of lipid-lowering agents used in the active treatment group as per trial randomization design. The solid line represents the meta-regression slope of the change in hazard ratio for treatment across BMI values.

e Figure 4. Meta-Analysis for Myocardial Infarction

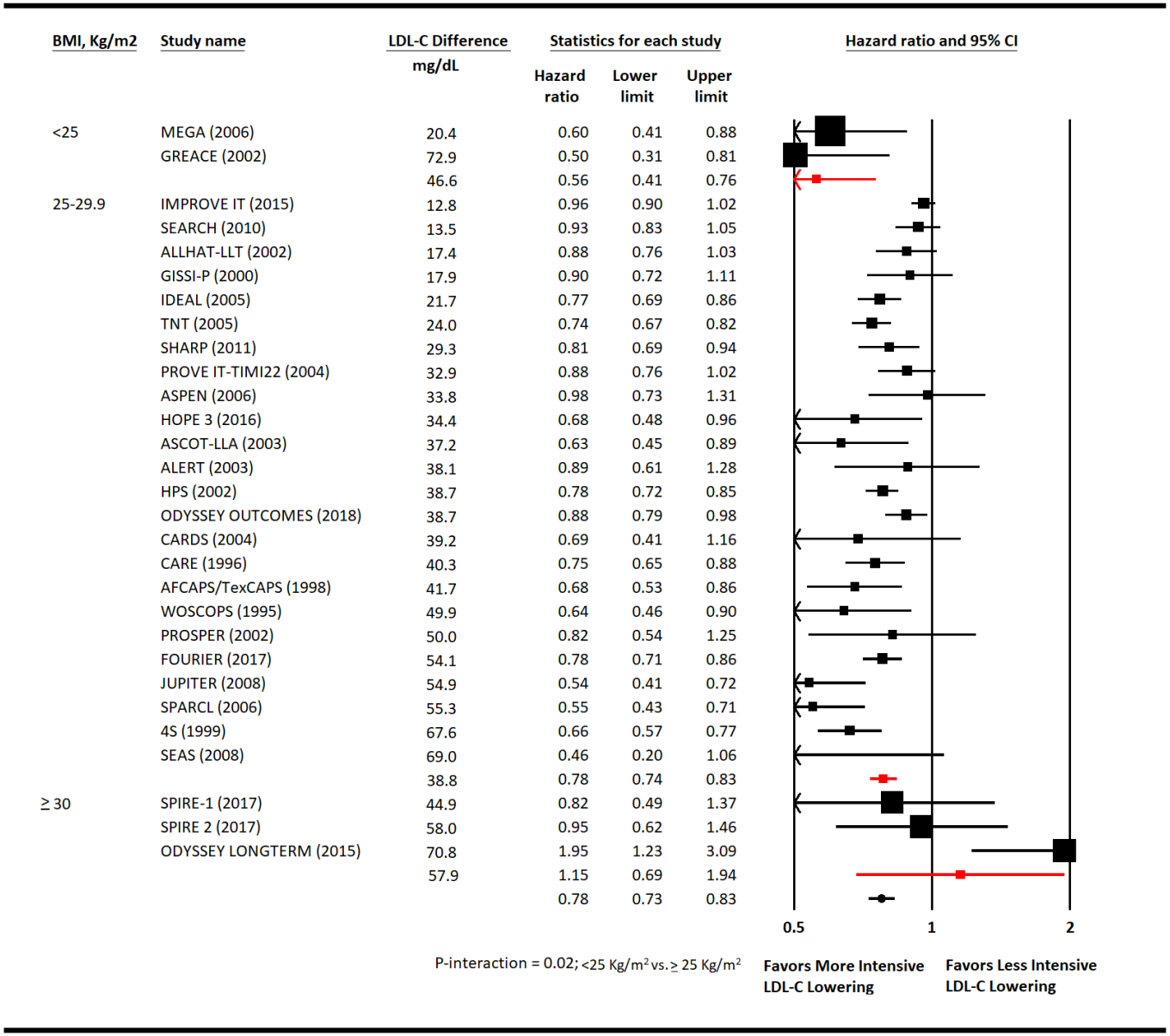


e Figure 5. Meta-Regression for BMI Effect on Revascularization

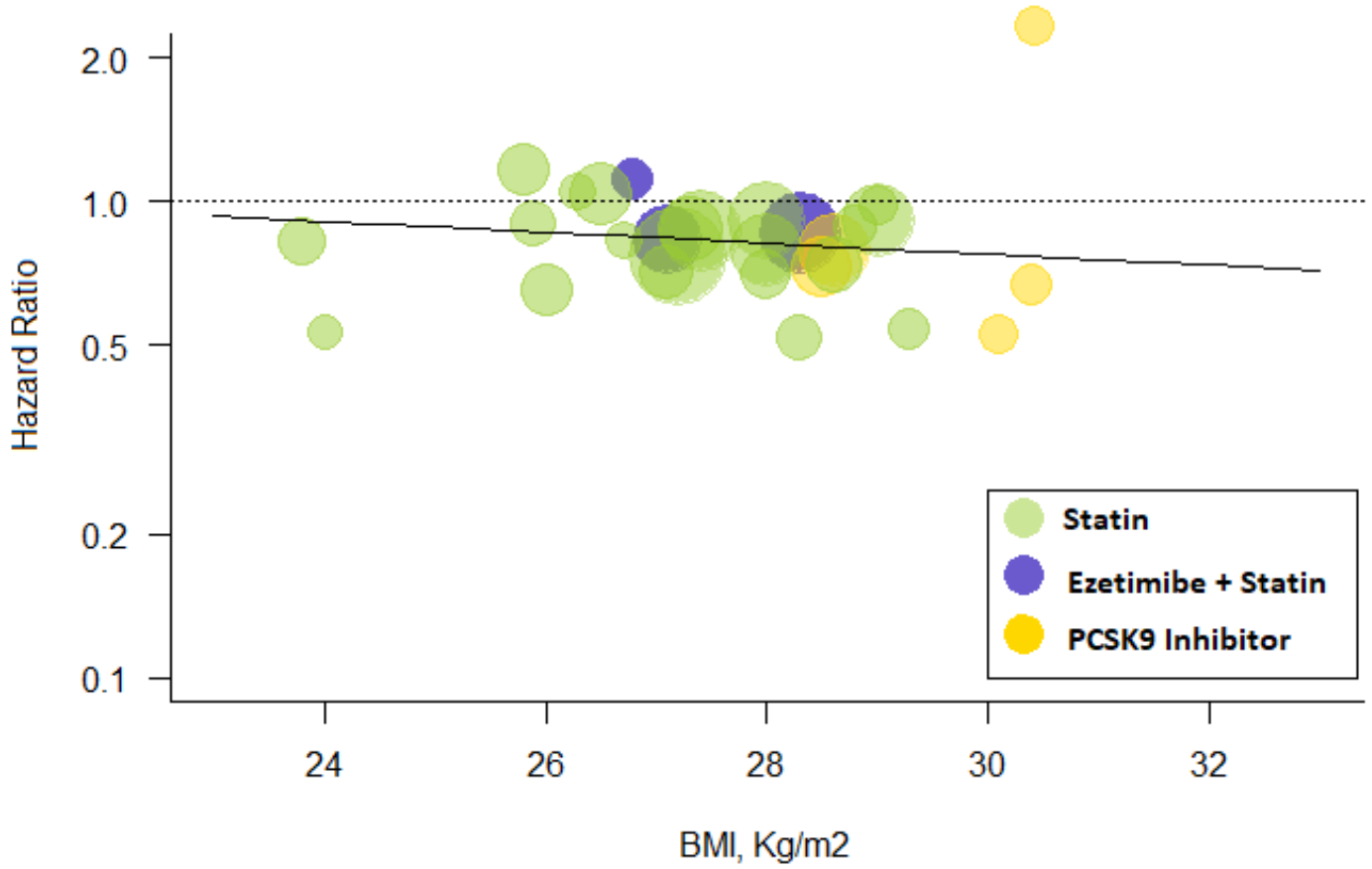


Change in hazard ratios and 95% confidence intervals for revascularization plotted against body mass index (BMI, Kg/m^2). Size of the data marker is proportional to the weight in the meta-regression. Data marker colors represent the classes of lipid-lowering agents used in the active treatment group as per trial randomization design. The solid line represents the meta-regression slope of the change in hazard ratio for treatment across BMI values.

e Figure 6. Meta-Analysis for Revascularization

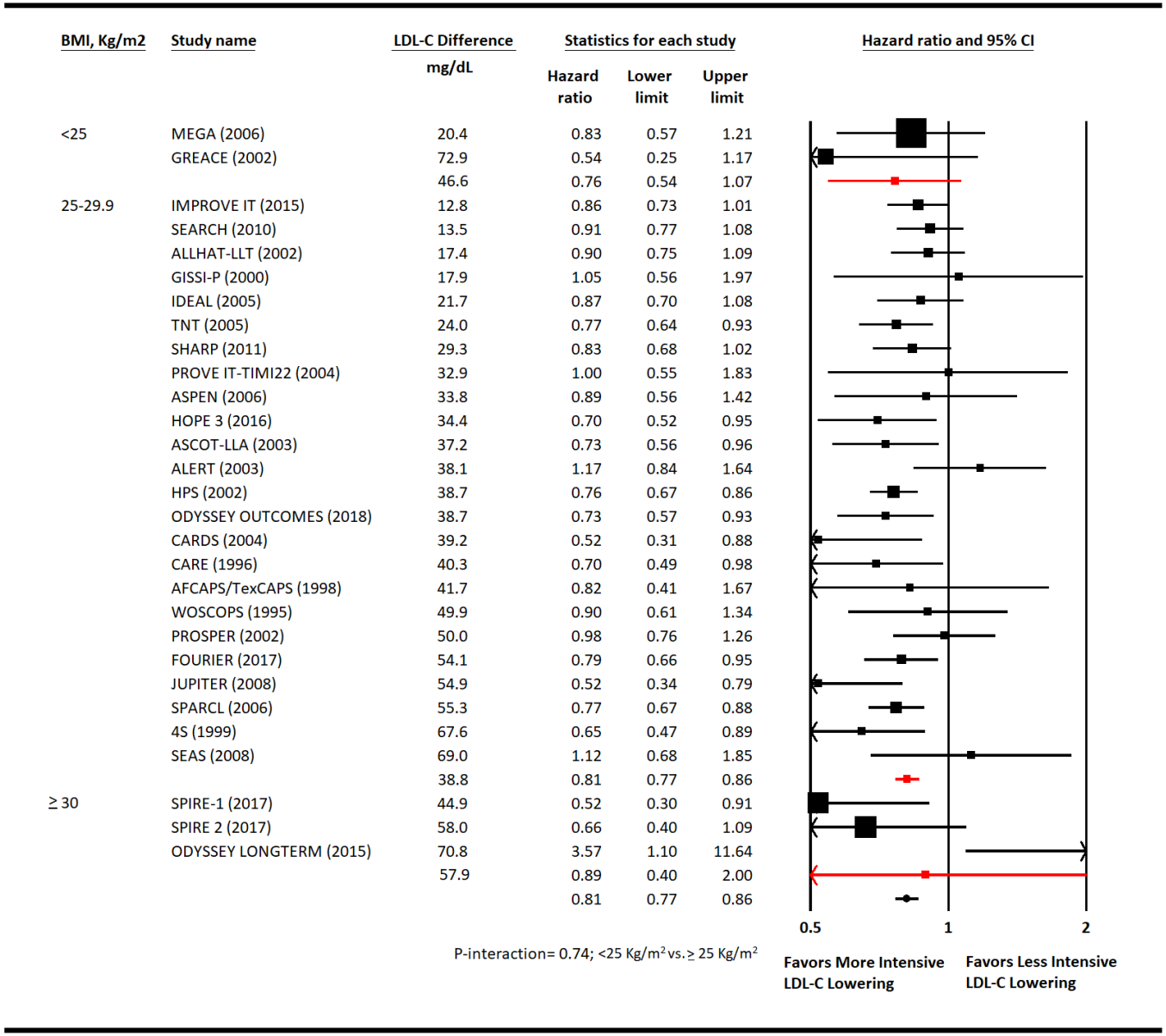


e Figure 7. Meta-Regression for BMI Effect on Cerebrovascular Events

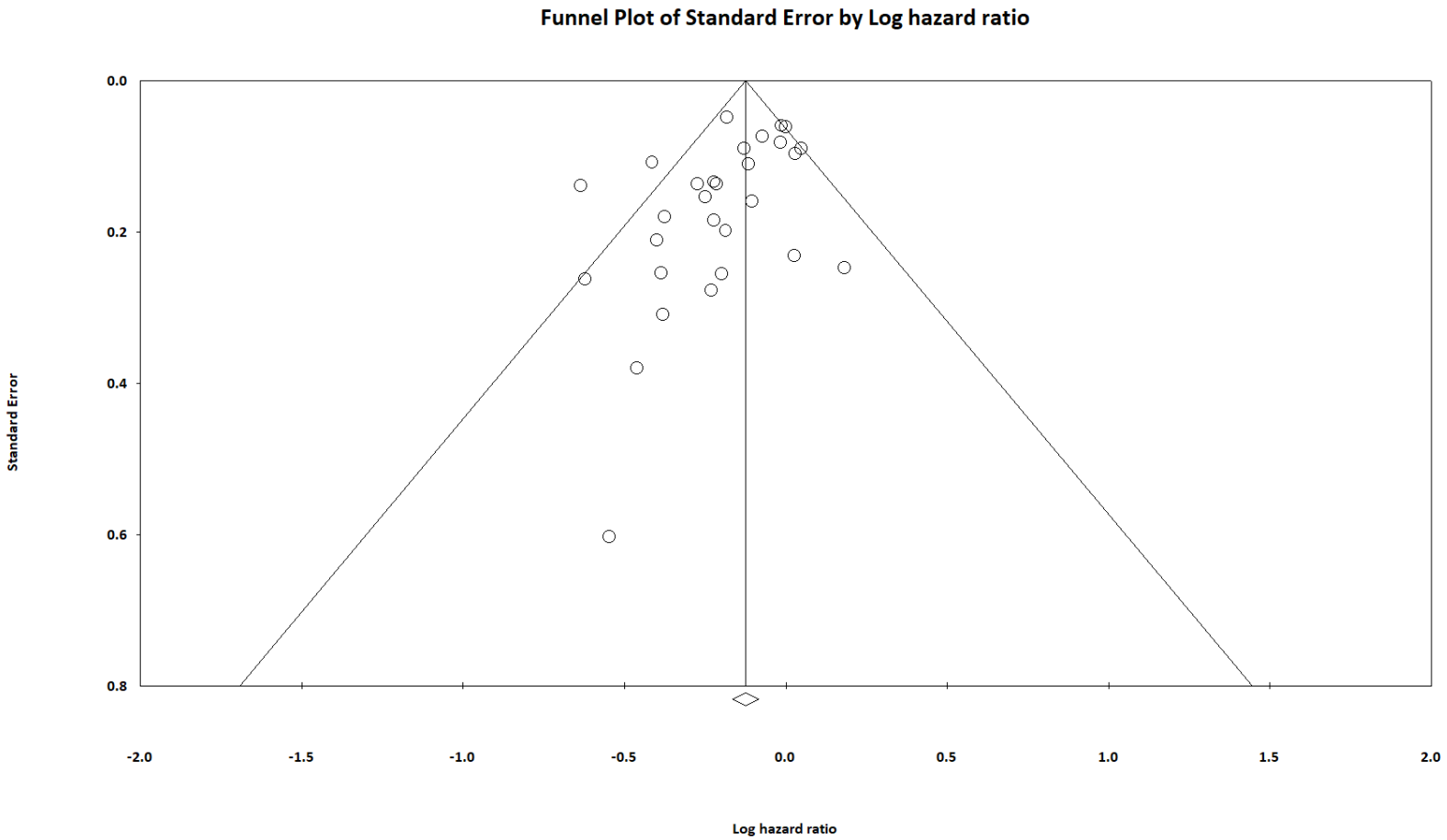


Change in hazard ratios and 95% confidence intervals for cerebrovascular events plotted against body mass index (BMI, Kg/m^2). Size of the data marker is proportional to the weight in the meta-regression. Data marker colors represent the classes of lipid-lowering agents used in the active treatment group as per trial randomization design. The solid line represents the meta-regression slope of the change in hazard ratio for treatment across BMI values.

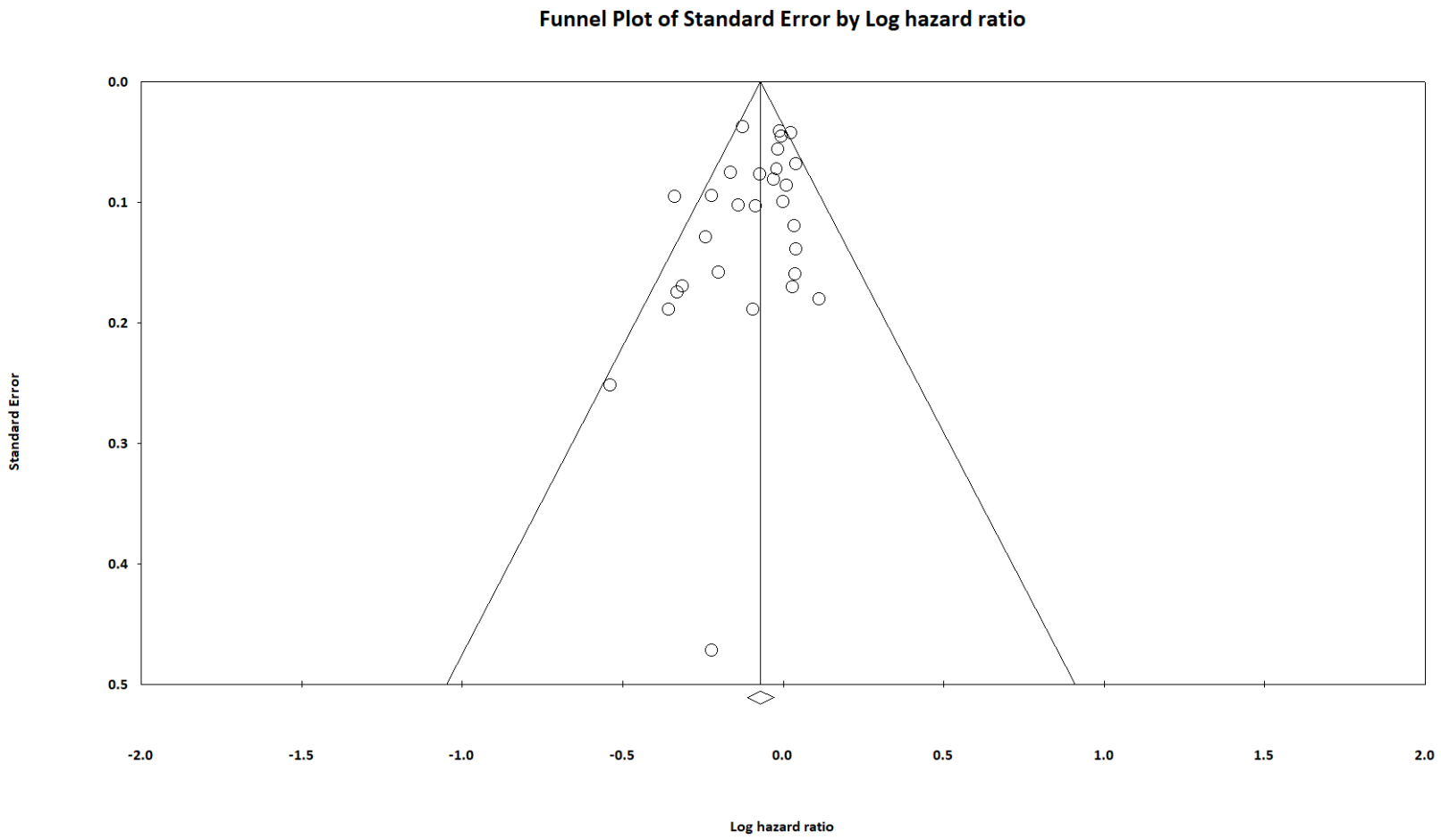
e Figure 8. Meta-Analysis for Cerebrovascular Events



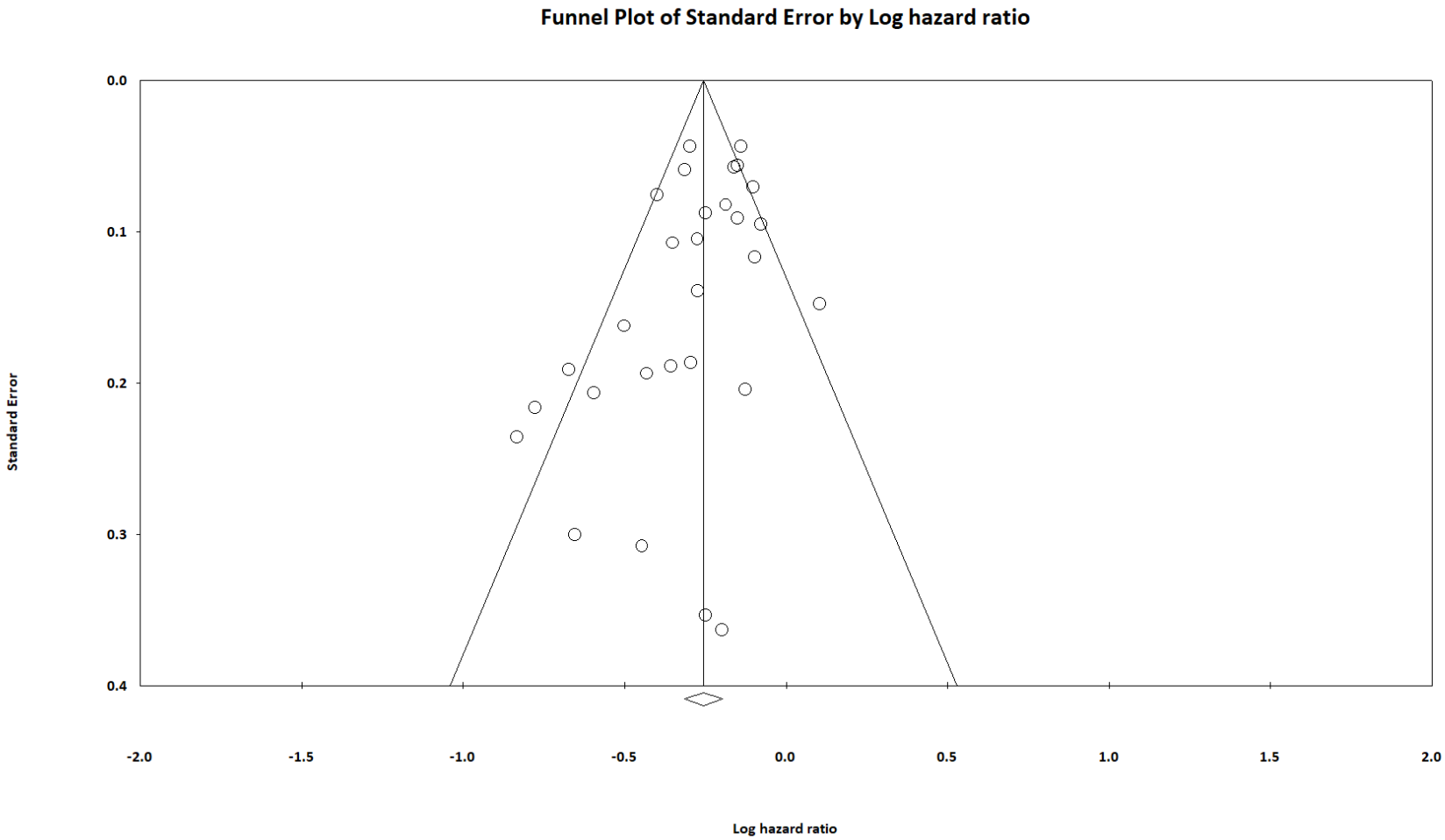
e Figure 9. Funnel plot for assessment of publication bias: cardiovascular mortality



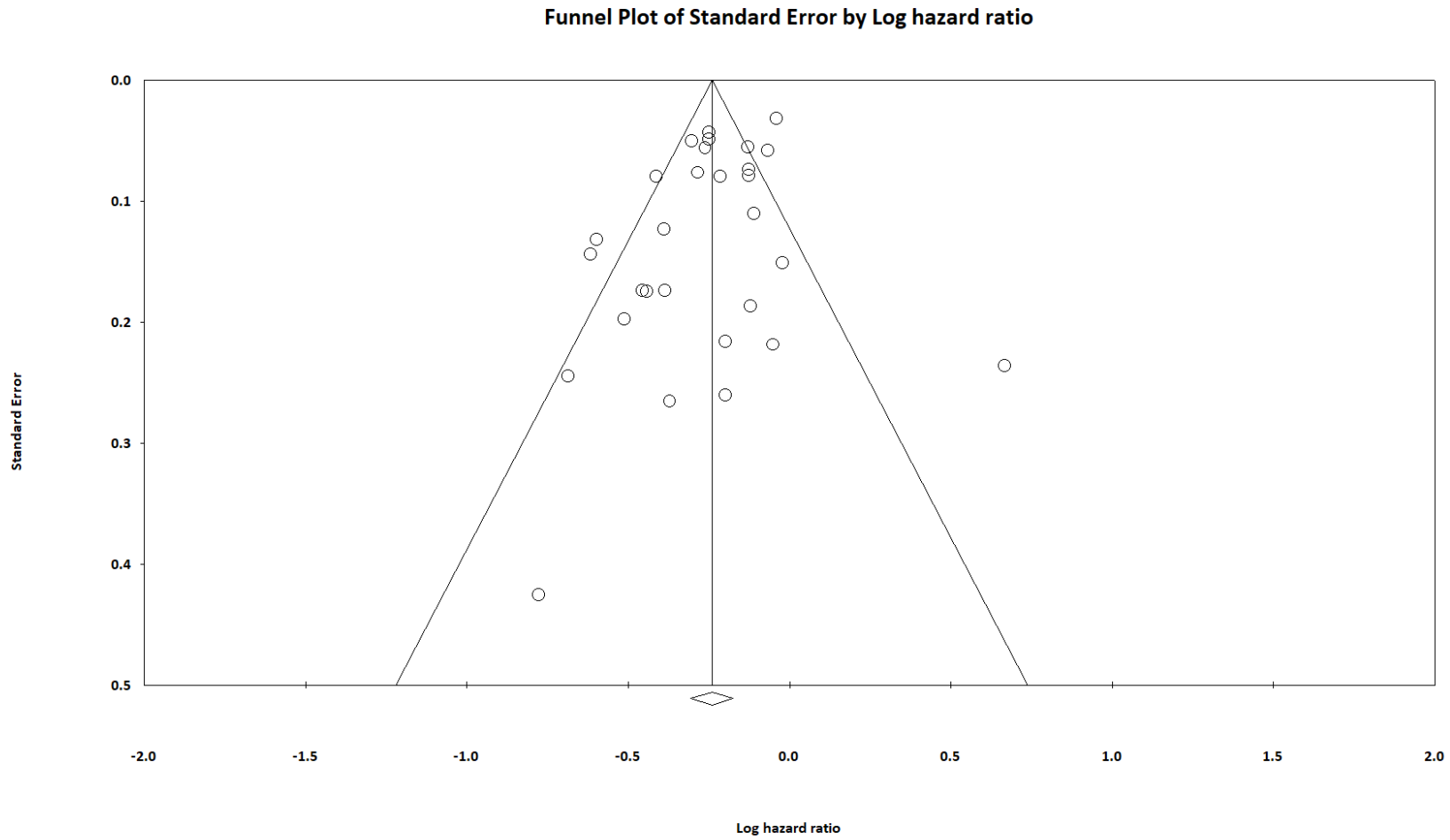
e Figure 10. Funnel plot for assessment of publication bias: all- cause mortality



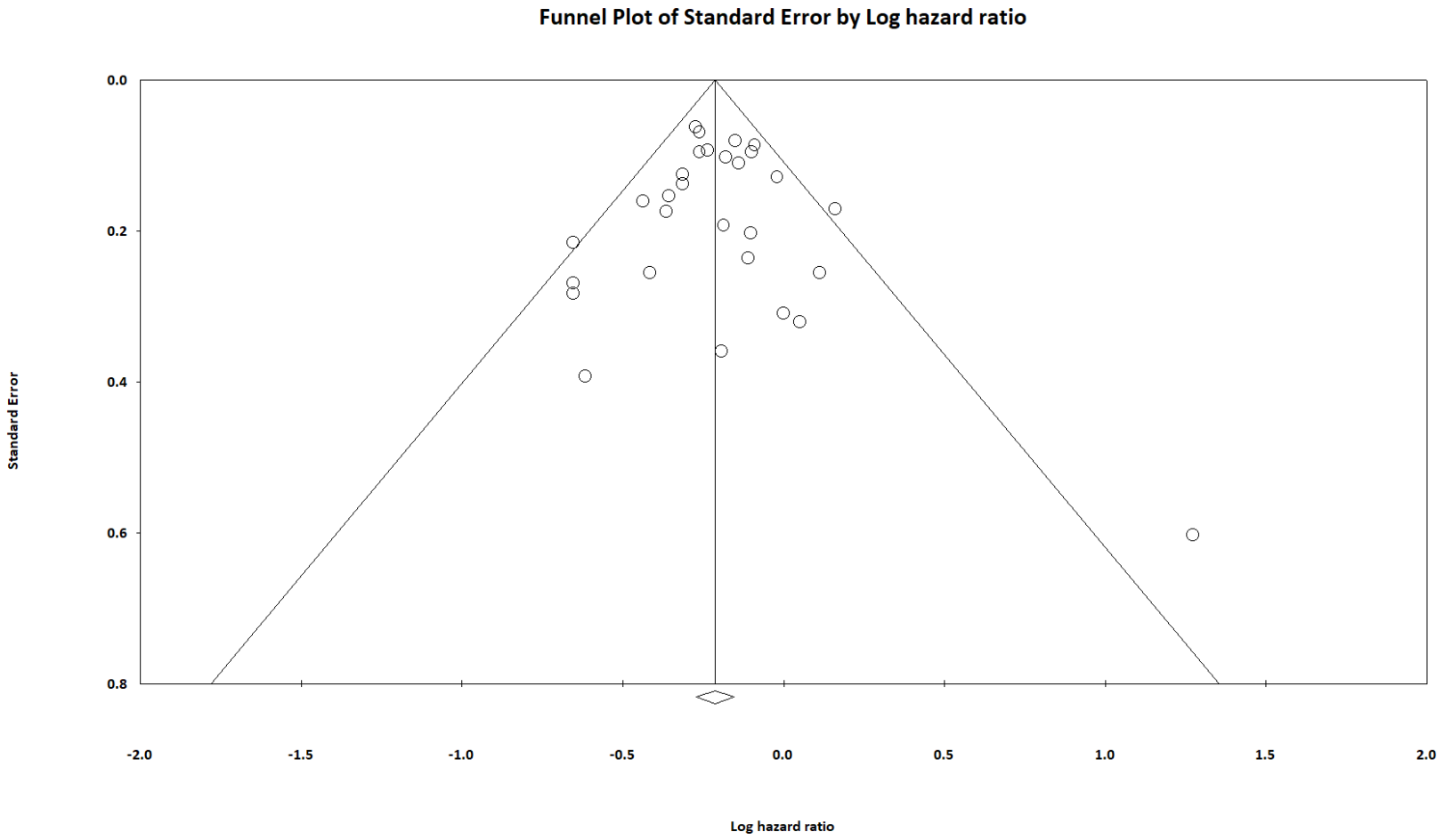
e Figure 11. Funnel plot for assessment of publication bias: myocardial infarction



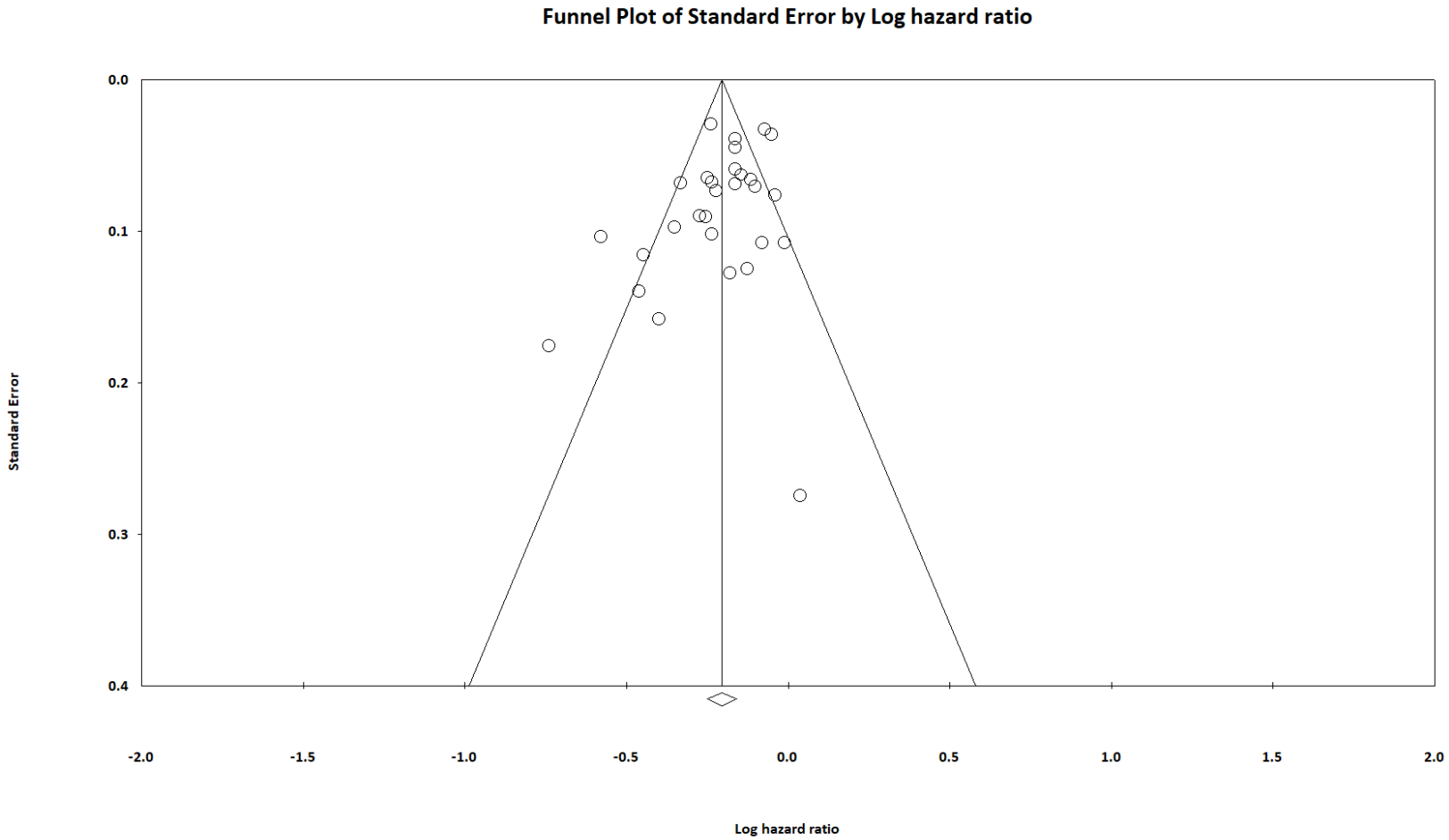
e Figure 12. Funnel plot for assessment of publication bias: revascularization



e Figure 13. Funnel plot for assessment of publication bias: cerebrovascular events



e Figure 14. Funnel plot for assessment of publication bias: major adverse cardiovascular events



REFERENCES

1. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, McKillop JH and Packard CJ. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med*. 1995;333:1301-7.
2. Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, Brown L, Warnica JW, Arnold JM, Wun CC, Davis BR and Braunwald E. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. *N Engl J Med*. 1996;335:1001-9.
3. Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, Langendorfer A, Stein EA, Kruyer W and Gotto AM, Jr. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *Jama*. 1998;279:1615-22.
4. Results of the low-dose (20 mg) pravastatin GISSI Prevenzione trial in 4271 patients with recent myocardial infarction: do stopped trials contribute to overall knowledge? GISSI Prevenzione Investigators (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico). *Italian heart journal : official journal of the Italian Federation of Cardiology*. 2000;1:810-20.
5. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). *Jama*. 2002;288:2998-3007.
6. Athyros VG, Papageorgiou AA, Mercouris BR, Athyrou VV, Symeonidis AN, Basayannis EO, Demitriadis DS and Kontopoulos AG. Treatment with atorvastatin to the National Cholesterol Educational Program goal versus 'usual' care in secondary coronary heart disease prevention. The GREek Atorvastatin and Coronary-heart-disease Evaluation (GREACE) study. *Current medical research and opinion*. 2002;18:220-8.
7. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet*. 2002;360:7-22.
8. Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobbe SM, Ford I, Gaw A, Hyland M, Jukema JW, Kamper AM, Macfarlane PW, Meinders AE, Norrie J, Packard CJ, Perry IJ, Stott DJ, Sweeney BJ, Twomey C and Westendorp RG. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet*. 2002;360:1623-30.
9. Holdaas H, Fellstrom B, Jardine AG, Holme I, Nyberg G, Fauchald P, Gronhagen-Riska C, Madsen S, Neumayer HH, Cole E, Maes B, Ambuhl P, Olsson AG, Hartmann A, Solbu DO and Pedersen TR. Effect of fluvastatin on cardiac outcomes in renal transplant recipients: a multicentre, randomised, placebo-controlled trial. *Lancet*. 2003;361:2024-31.
10. Sever PS, Dahlof B, Poulter NR, Wedel H, Beevers G, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E and Ostergren J. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial--Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet*. 2003;361:1149-58.
11. Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, Joyal SV, Hill KA, Pfeffer MA and Skene AM. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med*. 2004;350:1495-504.
12. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ, Thomason MJ, Mackness MI, Charlton-Menys V, Fuller JH and investigators C. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet*. 2004;364:685-96.

13. Pedersen TR, Faergeman O, Kastelein JJ, Olsson AG, Tikkanen MJ, Holme I, Larsen ML, Bendiksen FS, Lindahl C, Szarek M and Tsai J. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. *Jama*. 2005;294:2437-45.
14. LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart JC, Gotto AM, Greten H, Kastelein JJ, Shepherd J and Wenger NK. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med*. 2005;352:1425-35.
15. Nakamura H, Arakawa K, Itakura H, Kitabatake A, Goto Y, Toyota T, Nakaya N, Nishimoto S, Muranaka M, Yamamoto A, Mizuno K and Ohashi Y. Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA Study): a prospective randomised controlled trial. *Lancet*. 2006;368:1155-63.
16. Knopp RH, d'Emden M, Smilde JG and Pocock SJ. Efficacy and safety of atorvastatin in the prevention of cardiovascular end points in subjects with type 2 diabetes: the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in non-insulin-dependent diabetes mellitus (ASPEN). *Diabetes care*. 2006;29:1478-85.
17. Amarenco P, Bogousslavsky J, Callahan A, 3rd, Goldstein LB, Hennerici M, Rudolph AE, Sillesen H, Simunovic L, Szarek M, Welch KM and Zivin JA. High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med*. 2006;355:549-59.
18. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM, Jr., Kastelein JJ, Koenig W, Libby P, Lorenzatti AJ, MacFadyen JG, Nordestgaard BG, Shepherd J, Willerson JT, Glynn RJ and Group JS. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med*. 2008;359:2195-207.
19. Armitage J, Bowman L, Wallendszus K, Bulbulia R, Rahimi K, Haynes R, Parish S, Peto R and Collins R. Intensive lowering of LDL cholesterol with 80 mg versus 20 mg simvastatin daily in 12,064 survivors of myocardial infarction: a double-blind randomised trial. *Lancet*. 2010;376:1658-69.
20. Yusuf S, Bosch J, Dagenais G, Zhu J, Xavier D, Liu L, Pais P, Lopez-Jaramillo P, Leiter LA, Dans A, Avezum A, Piegas LS, Parkhomenko A, Keltai K, Keltai M, Sliwa K, Peters RJ, Held C, Chazova I, Yusoff K, Lewis BS, Jansky P, Khunti K, Toff WD, Reid CM, Varigos J, Sanchez-Vallejo G, McKelvie R, Pogue J, Jung H, Gao P, Diaz R, Lonn E and Investigators H-. Cholesterol Lowering in Intermediate-Risk Persons without Cardiovascular Disease. *N Engl J Med*. 2016;374:2021-31.
21. Rossebo AB, Pedersen TR, Boman K, Brudi P, Chambers JB, Egstrup K, Gerdts E, Gohlke-Barwolf C, Holme I, Kesaniemi YA, Malbecq W, Nienaber CA, Ray S, Skjaerpe T, Wachtell K and Willenheimer R. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. *N Engl J Med*. 2008;359:1343-56.
22. Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, Wanner C, Krane V, Cass A, Craig J, Neal B, Jiang L, Hooi LS, Levin A, Agodoa L, Gaziano M, Kasiske B, Walker R, Massy ZA, Feldt-Rasmussen B, Krairittichai U, Ophascharoensuk V, Fellstrom B, Holdaas H, Tesar V, Wiecek A, Grobbee D, de Zeeuw D, Gronhagen-Riska C, Dasgupta T, Lewis D, Herrington W, Mafham M, Majoni W, Wallendszus K, Grimm R, Pedersen T, Tobert J, Armitage J, Baxter A, Bray C, Chen Y, Chen Z, Hill M, Knott C, Parish S, Simpson D, Sleight P, Young A and Collins R. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet*. 2011;377:2181-92.
23. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, Darius H, Lewis BS, Ophuis TO, Jukema JW, De Ferrari GM, Ruzyllo W, De Lucca P, Im K, Bohula EA, Reist C, Wiviott SD, Tershakovec AM, Musliner TA, Braunwald E and Califf RM. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. *N Engl J Med*. 2015;372:2387-97.

24. Robinson JG, Farnier M, Krempf M, Bergeron J, Luc G, Averna M, Stroes ES, Langslet G, Raal FJ, El Shahawy M, Koren MJ, Lepor NE, Lorenzato C, Pordy R, Chaudhari U and Kastelein JJ. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. *N Engl J Med*. 2015;372:1489-99.
25. Ridker PM, Revkin J, Amarenco P, Brunell R, Curto M, Civeira F, Flather M, Glynn RJ, Gregoire J, Jukema JW, Karpov Y, Kastelein JJP, Koenig W, Lorenzatti A, Manga P, Masiukiewicz U, Miller M, Mosterd A, Murin J, Nicolau JC, Nissen S, Ponikowski P, Santos RD, Schwartz PF, Soran H, White H, Wright RS, Vrablik M, Yunis C, Shear CL and Tardif JC. Cardiovascular Efficacy and Safety of Bococizumab in High-Risk Patients. *N Engl J Med*. 2017;376:1527-1539.
26. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, Kuder JF, Wang H, Liu T, Wasserman SM, Sever PS, Pedersen TR, Committee FS and Investigators. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. *N Engl J Med*. 2017;376:1713-1722.
27. Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, Edelberg JM, Goodman SG, Hanotin C, Harrington RA, Jukema JW, Lecorps G, Mahaffey KW, Moryusef A, Pordy R, Quintero K, Roe MT, Sasiela WJ, Tamby JF, Tricoci P, White HD, Zeiher AM, Committees OO and Investigators. Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. *N Engl J Med*. 2018;379:2097-2107.
28. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet*. 1994;344:1383-9.