Electronic Supplementary Material

American Journal of Cardiovascular Drugs

Lipid-Lowering Efficacy of Ezetimibe in Patients with Atherosclerotic Cardiovascular Disease: A Systematic Review and Meta-Analyses

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Systematic literature review

Specific congress proceedings searched

- AACE – American Association of Clinical Endocrinology
- AANP – American Association of Nurse Practitioners
- AAPA – American Association of Physician Assistants
- ACC – American College of Cardiology
- ADA – American Diabetes Association
- AHA – American Heart Association
- AMCP/AMCP Nexus – Academy of Managed Care Pharmacy
- DGK – German Society of Cardiology (Deutsche Gesellschaft für Kardiologie)
- EAS – European Atherosclerosis Society
- EASD – European Association for the Study of Diabetes
- ESC – European Society of Cardiology
- EuroPCR – Annual Meeting of the European Association of Percutaneous Cardiovascular Interventions (EAPCI)
- ICAAC – Interscience Conference on Antimicrobial Agents and Chemotherapy
- IDF – International Diabetes Federation
- ISA – International Atherosclerosis Society
- ISPOR – International Society of Pharmacoeconomics and Outcomes Research
- ISPOR-EU – International Society of Pharmacoeconomics and Outcomes Research – EU
- NLA – National Lipid Association
- QCOR – Council on Quality Care and Outcomes Research
- TCT – Transcatheter Cardiovascular Therapeutics

Supplemental Table S1 Search strategy for MEDLINE® via PubMed (date of search: August 27, 2018)

#	Search string	Results
1	"Ezetimibe"[Mesh] OR Ezetimibe[tiab] OR Absorcol[tiab] OR ezetib[tiab] OR ezetimibe[tiab] OR ezetrol[tiab] OR sch 58235[tiab] OR sch58235[tiab] OR viemm[tiab] OR zetia[tiab] OR zient[tiab]	2989
2	"Ezetimibe, Simvastatin Drug Combination"[Mesh] OR Inegy[tiab] OR Vytorin[tiab] OR Zetsim[tiab] OR Zintrepid[tiab]	176
3	"liptruzet" [Supplementary Concept] OR liptruzet[tiab]	3
4	"Hydroxymethylglutaryl-CoA Reductase Inhibitors"[Mesh]	26885
5	"Hydroxymethylglutaryl-CoA Reductase Inhibitors" [Pharmacological Action]	37424
6	Hydroxymethylglutaryl-CoA Reductase Inhibit* [tiab] OR Statin[tiab] OR Statins[tiab] OR HMG-CoA [tiab]	39749
7	"lovastatin-niacin combination" [Supplementary Concept] OR Advicor[tiab] OR ("Niacin"[Mesh] OR niacin[tiab]) AND ("Lovastatin"[Mesh] OR Mevacor[tiab] OR Lovastatin[tiab] OR Mevinolin[tiab] OR Monacolin K[tiab] OR 6-Methylcompactin[tiab] OR MK-803[tiab] OR MK803[tiab])	278
8	Altoprev[tiab]	4
9	("Amlodipine"[Mesh] OR Amlodipine[tiab] OR Amlodis[tiab] OR Astudal[tiab] OR Norvasc[tiab] OR Istin[tiab] OR Amlor[tiab]) AND ("Atorvastatin Calcium"[Mesh] OR Atorvastatin[tiab] OR Cardyl[tiab] OR CI 981[tiab] OR CI981[tiab] OR lipibec[tiab] OR Lipitor[tiab] OR liprimar[tiab] OR liptonorm[tiab] OR lowlipen[tiab] OR sortis[tiab] OR storvas[tiab] OR tahor[tiab] OR torvast[tiab] OR totalip[tiab] OR xarator[tiab] OR ym 548[tiab] OR ym548 [tiab] OR zarator[tiab]) OR amlodipine, atorvastatin drug combination [Supplementary Concept] OR Caduet[tiab]	213
10	Rosuvastatin[tiab] OR Crestor[tiab] OR ZD4522[tiab] OR ZD 4522[tiab]	3038
11	Juvisync[tiab] OR ("Sitagliptin Phosphate"[Mesh] OR Sitagliptin[tiab] OR MK0431 MK-0431 OR Januvia[tiab]) AND ("Simvastatin"[Mesh] OR Simvastatin[tiab] OR denan[tiab] OR Epistatin[tiab] OR Synvinolin[tiab] OR l 644128[tiab]	22

	OR l644128[tiab] OR Lipex[tiab] OR Lipovas[tiab] OR Lodales[tiab] OR Medipo[tiab] OR MK-733[tiab] OR MK733[tiab] OR Sinvacor[tiab] OR Vasilip[tiab] OR Zocor[tiab] OR Zocord[tiab])	
12	"fluvastatin" [Supplementary Concept] OR Lescol[tiab] OR Fluvastatin[tiab] OR Fluindostatin[tiab] OR XU 62-320[tiab] OR XU-62320[tiab] OR XU 62320[tiab]	1968
13	Atorvastatin Calcium[Mesh] OR Atorvastatin[tiab] OR Cardyl[tiab] OR CI 981[tiab] OR CI981[tiab] OR lipibec[tiab] OR Lipitor[tiab] OR liprimar[tiab] OR liptonorm[tiab] OR lowlipen[tiab] OR sortis[tiab] OR storvas[tiab] OR tahor[tiab] OR torvast[tiab] OR totalip[tiab] OR xarator[tiab] OR ym 548[tiab] OR ym548 [tiab] OR zarator[tiab]	8707
14	“pitavastatin" [Supplementary Concept] OR Livalo[tiab] OR Pitavastatin[tiab] OR itavastatin[tiab] OR nisvastatin[tiab] OR NK-104[tiab] OR P-872441[tiab]	841
15	“Lovastatin”[Mesh] OR Mevacor[tiab] OR Lovastatin[tiab] OR Mevinolin[tiab] OR Monacolin K[tiab] OR 6-Methylcompactin[tiab] OR MK-803[tiab] OR MK803[tiab]	11816
16	Pravachol[tiab] OR Pravastatin[tiab] OR Eptastatin[tiab] OR Vasten[tiab] OR CS-514[tiab] OR CS514[tiab] OR Lipemol[tiab] OR Liplat[tiab] OR Prareduct[tiab] OR Mevalotin[tiab] OR Pravachol[tiab] OR Elisor[tiab] OR Selektine[tiab] OR Lipostat[tiab] OR Pravasin[tiab] OR RMS-431[tiab] OR RMS431[tiab] OR SQ-31000[tiab] OR SQ31000[tiab] OR SQ-31,000[tiab] OR SQ31,000[tiab] OR Bristacol[tiab]	3935
17	(((“Niacin”[Mesh] OR niacin[tiab]) AND (“Simvastatin”[Mesh] OR Simvastatin[tiab] OR denan[tiab] OR Epistatin[tiab] OR Synvinolin[tiab] OR l 644128[tiab] OR l644128[tiab] OR Lipex[tiab] OR Lipovas[tiab] OR Lodales[tiab] OR Medipo[tiab] OR MK-733[tiab] OR MK733[tiab] OR Sinvacor[tiab] OR Vasilip[tiab] OR Zocor[tiab] OR Zocord[tiab]))) OR (“Simcor” [Supplementary Concept] OR Simcor[tiab])	217
18	Simvastatin[Mesh] OR Simvastatin[tiab] OR denan[tiab] OR Epistatin[tiab] OR Synvinolin[tiab] OR l 644128[tiab] OR l644128[tiab] OR Lipex[tiab] OR Lipovas[tiab] OR Lodales[tiab] OR Medipo[tiab] OR MK-733[tiab] OR MK733[tiab] OR Sinvacor[tiab] OR Vasilip[tiab] OR Zocor[tiab] OR Zocord[tiab])	10045
19	OR/4-18	57412
20	1 AND 19	2279
21	2 OR 3	179

22	20 OR 21	2285
23	(“Animals”[Mesh]) NOT ((“Animals”[Mesh]) AND “Humans”[Mesh])	
24	22 NOT 23	
25	English[Language]	
26	24 AND 25	
27	(((((((“Clinical Study” [Publication Type] OR “Cohort Studies”[Mesh] OR “Multicenter Study” [Publication Type] OR “Clinical Trials as Topic”[Mesh] OR “Randomized Controlled Trials as Topic”[Mesh] OR “Random Allocation”[Mesh] OR “Double-Blind Method”[Mesh] OR “Single-Blind Method”[Mesh] OR “Placebos”[Mesh])) OR (placebo*[tiab] OR dumm*[tiab] OR mock[tiab] OR sham[tiab])) OR ((singl*[tiab] OR doubl*[tiab] OR treb*[tiab] OR tripl*[tiab]) AND (blind*[tiab] OR mask*[tiab]))) OR (clinical[tiab] AND trial*[tiab])) OR ((random*[tiab] OR RCT[tiab] OR RCTs[tiab]))) OR (prospective*[tiab] OR retrospective*[tiab])	
28	26 AND 27	1254

Supplemental Table S2 Search strategy for EMBASE via OvidSP (date of search: August 30, 2018; EMBASE segment used: 1974 to August 28, 2018)

#	Search string	Results
1	exp Ezetimibe/ or (Ezetimibe or ezetib or ezetimibe or ezetrol or sch 58235 or sch58235 or viemm or zetia or zient).ti,ab,kw.	9307
2	exp ezetimibe plus simvastatin/ or (Inegy or Vytorin or Zetsim or Zintrepid).ti,ab,kw.	1311
3	exp atorvastatin plus ezetimibe/ or liptruzet.ti,ab,kw.	71
4	exp ezetimibe plus rosuvastatin/	37
5	exp hydroxymethylglutaryl coenzyme A reductase inhibitor/ or (Hydroxymethylglutaryl-CoA Reductase Inhibit$ or Statin or Statins or HMG-CoA).ti,ab.	142372
6	exp rosuvastatin/ or (Rosuvastatin or Crestor or ZD4522 or ZD 4522).ti,ab,kw.	13372
7	exp lovastatin plus nicotinic acid/ or Advicor.ti,ab,kw.	151
8	((niacin or nicotinic acid) and (lovastatin or Mevacor or Mevinolin or Monacolin K or 6-Methylcompactin or MK-803 or MK803)).ti,ab,kw.	207
9	exp amlodipine plus atorvastatin/ or Caduet.ti,ab,kw.	255
10	((Amlodipine or Amlodis or Astudal or Norvasc or Istin or Amlor) and (Atorvastatin or Cardyl or CI 981 or CI981 or lipibec or Lipitor or liprimar or liptonorm or lowlipen or sortis or storvas or tahor or torvast or totalip or xarator or ym 548 or ym548 or zarator)).ti,ab,kw.	382
11	exp simvastatin plus sitagliptin/ or Juvisync.ti,ab,kw.	26

12	((Sitagliptin or MK0431 MK-0431 or Januvia) and (Simvastatin or denan or Epistatin or Synvinolin or l 644128 or l644128 or Lipex or Lipovas or Lodales or Medipo or MK-733 or MK733 or Sinvacor or Vasilip or Zocor or Zocord)).ti,ab,kw.	50
13	exp nicotinic acid plus simvastatin/ or Simcor.ti,ab,kw.	112
14	((niacin or nicotinic acid) and (Simvastatin or denan or Epistatin or Synvinolin or l 644128 or l644128 or Lipex or Lipovas or Lodales or Medipo or MK-733 or MK733 or Sinvacor or Vasilip or Zocor or Zocord)).ti,ab,kw.	352
15	exp mevinolin/ or (Altoprev or Mevacor or Lovastatin or Mevinolin or Monacolin K or 6-Methylcompactin or MK-803 or MK803).ti,ab,kw.	15621
16	exp rosuvastatin/ or (Rosuvastatin or Crestor or ZD4522 or ZD 4522).ti,ab,kw.	13372
17	exp fluindostatin/ or (Lescol or Fluvastatin or Fluindostatin or XU 62-320 or XU-62320 or XU 62320).ti,ab,kw.	8973
18	exp atorvastatin/ or (Atorvastatin or Cardyl or CI 981 or CI981 or lipibec or Lipitor or liprimar or liptonorm or lowlipen or sortis or storvas or tahor or torvast or totalip or xarator or ym 548 or ym548 or zarator).ti,ab,kw.	34087
19	exp pitavastatin/ or (Livalo or Pitavastatin or itavastatin or nisvastatin or NK-104 or P-872441).ti,ab,kw.	2782
20	exp pravastatin/ or (Pravachol or Pravastatin or Eptastatin or Vasten or CS-514 or CS514 or Lipemol or Liplat or Prareduct or Mevalotin or Pravachol or Elisor or Selektine or Lipostat or Pravasin or RMS-431 or RMS431 or SQ-31000 or SQ31000 or Bristacol).ti,ab,kw.	19272
21	exp simvastatin/ or (Simvastatin or denan or Epistatin or Synvinolin or l 644128 or l644128 or Lipex or Lipovas or Lodales or Medipo or MK-733 or MK733 or Sinvacor or Vasilip or Zocor or Zocord).ti,ab,kw.	35662
22	or/5-21	143668
23	1 and 22	7888
24	or/2-4	1390
25	23 or 24	8365

26	(exp animal/ or nonhuman/) not exp human/	5873750
27	25 not 26	8246
28	english.lg.	26219773
29	27 and 28	7655
30	(book or chapter or “conference review” or editorial or note or press or “review” or short or short survey or survey).pt.	4225835
31	29 not 30	4604
32	exp case report/ or exp *practice guideline/ or (review or meta-analysis or meta-analyses or metaanalysis or metaanalyses or case report or systematic review).ti.	2769453
33	31 not 32	4028
34	(article or article in press or conference paper).pt.	20646523
35	33 and 34	2842
36	exp Comparative study/ or exp Controlled study/ or exp Clinical study/ or "clinical trial (topic)"/ or "multicenter study (topic)"/	12800633
37	exp randomization/ or exp double blind procedure/	227262
38	exp placebo/ or (placebo$ or dumm$ or mock or sham).ti,ab.	533433
39	((singl$ or doubl$ or treb$ or tripl$) and (blind$ or mask$)).ti,ab.	241545
40	(clinical and trial$).ti,ab.	652072
41	(random$ or RCT or RCTs).ti,ab.	1330744

42	(prospective$ or retrospective$).ti,ab.	1814539
43	or/36-42	13833697
44	35 and 43	2344
45	(aace or american college of cardiology or american diabetes or american heart or amcp or aha or Deutsche Gesellschaft or European Atherosclerosis Society or eas or easd or European Association for the Study of Diabetes or European Society of Cardiology or EuroPCR or International Diabetes Federation or idf or ispor or nla or national lipid or tct or Transcatheter Cardiovascular Therapeutics).cf.	194460
46	33 and 45	560
47	limit 46 to yr=”2015 -Current”	239
48	44 or 47	2583
49	remove duplicates from 48	2548

RCT randomized controlled trial

Supplemental Table S3 Search strategy for The Cochrane Library (date of search: August 30, 2018)

#	Search string	Results
1	MeSH descriptor: [Ezetimibe] explode all trees	603
2	(Ezetimibe or ezetib or ezetimibe or ezetrol or sch 58235 or sch58235 or viemm or zetia or zient):ti,ab,kw	1261
3	#1 OR #2	1261
4	MeSH descriptor: [Ezetimibe, Simvastatin Drug Combination] explode all trees	74
5	(Inegy or Vytorin or Zetsim or Zintrepid OR liptruzet):ti,ab,kw	67
6	#4 OR #5	118
7	MeSH descriptor: [Hydroxymethylglutaryl-CoA Reductase Inhibitors] explode all trees	3179
8	(Hydroxymethylglutaryl-CoA Reductase Inhibit$ or Statin or Statins or HMG-CoA):ti,ab,kw	6744
9	(Rosuvastatin or Crestor or ZD4522 or ZD 4522):ti,ab,kw	1902
10	(Altoprev or Mevacor or Lovastatin or Mevinolin or MK-803 or MK803):ti,ab,kw	920
11	(Lescol or Fluvastatin or Fluindostatin):ti,ab,kw	670
12	(Atorvastatin or Cardyl or lipibec or Lipitor or liprimar or liptonorm or lowlipen or sortis or storvas or tahor or torvast or totalip or xarator or zarator):ti,ab,kw	4314
13	(Livalo or Pitavastatin or itavastatin or nisvastatin):ti,ab,kw	339
14	(Pravachol or Pravastatin or Eptastatin or Vasten or CS-514 or CS514 or Lipemol or Liplat or Prareduct or Mevalotin or Pravachol or Elisor or Selektine or Lipostat or Pravasin or Bristacol):ti,ab,kw	1723

15	(Simvastatin or denan or Epistatin or Synvinolin or l644128 or Lipex or Lipovas or Lodales or Medipo or MK-733 or MK733 or Sinvacor or Vasilip or Zocor or Zocord):ti,ab,kw	3190
16	MeSH descriptor: [Lovastatin] explode all trees	1948
17	MeSH descriptor: [Rosuvastatin Calcium] explode all trees	885
18	MeSH descriptor: [Atorvastatin Calcium] explode all trees	2028
19	MeSH descriptor: [Pravastatin] explode all trees	957
20	MeSH descriptor: [Simvastatin] explode all trees	1604
21	(Advicor or Caduet or Juvisync or Simcor):ti,ab,kw	24
22	[1-#21]	12948
23	#3 AND #22	1100
24	#6 OR #23	1104
25	#24 in Trials (Word variations have been searched)	1102
26	#25 NOT (embase or medline or pubmed or clinicaltrials.gov)	67

MeSH Medical Subject Heading

Supplemental Table S4 Two-arm studies identified from the literature review and justification recorded for inclusion/exclusion in analyses

Study reference (trial name)	Ezetimibe group	Comparator	Analysis intervention	Analysis comparator	Included in analyses?
Cannon CP et al. *N Engl J Med*. 2015;372:2387–2397. (IMPROVE-IT)	EZE 10 mg QD + SIM 40–80 mg QD	SIM 40–80 mg QD	EZE + SIM	SIM	Yes
Farnier M et al. *Int J Cardiol*. 2005;102:327-332.	EZE 10 mg QD + SIM 2 mg QD	SIM 2 mg QD	EZE + SIM	SIM	No: % change in LDL-C reported; not compatible with mean change in LDL-C
Hibi K et al. *Circ J*. 2018;82:757–766.	EZE 10 mg QD + PITA 2 mg QD	PITA 2 mg QD	EZE + PITA	PITA	Yes
Joshi S et al. *J Clin Diagn Res*. 2017;11:OC28–OC31.	EZE 10 mg QD + ROSU 10 mg QD	ROSU 10 mg QD	EZE + ROSU	ROSU	Yes
Masuda J et al 2015. *Int Heart J*. 2015;56:278–285.	EZE 10 mg QD + ROSU 5 mg QD	ROSU 5 mg QD	EZE + ROSU	ROSU	Yes
Ren Y et al. *Exp Ther Med*. 2017;14:4942–4950.	EZE 10 mg QD + ROSU 10 mg QD	ROSU 10 mg QD	EZE + ROSU	ROSU	Yes
Ueda Y et al. *Circ J*. 2017;81:1611–1619. (ZIPANGU)	EZE 10 mg QD + ATOR 10–20 mg QD	ATOR 10–20 mg QD	EZE + ATOR	ATOR	Yes
Wang J et al. *Int Angiol*. 2017;36:467–473.	EZE 10 mg QD + ATOR 20 mg QD	ATOR 20 mg QD	EZE + ATOR	ATOR	Yes

Wang X et al. *Heart Lung Circ*. 2016;25:459–465.	EZE 10 mg QD + ROSU 10 mg QD	ROSU 10 mg QD	EZE + ROSU	ROSU	Yes
Zou YC et al. *J Am Geriatr Soc*. 2016;64:S328.	EZE 10 mg QD + ATOR 10 mg QD	ATOR 10 mg QD	EZE + ATOR	ATOR	Yes

ALI alirocumab, *ATOR* atorvastatin, *EZE* ezetimibe, *MTD* maximum tolerated dose, *NA* not applicable, *PBO* placebo, *PITA* pitavastatin, *PRA* pravastatin, *QD* daily, *ROSU* rosuvastatin, *SIM* simvastatin

Supplemental Table S5 Multi-arm studies identified from the literature review and justification recorded for inclusion/exclusion in analyses

Study reference (study name)	Group name	Analysis name	Included in analyses?
Brohet C et al. *Curr Med Res Opin*. 2005;21:571–578.	EZE 10 mg QD + SIM 10/20 mg QD	EZE + SIM	Yes
	SIM 10/20 mg QD	SIM	
	EZE 10 mg QD + SIM 10 mg QD	EZE + SIM	No: outcome not reported
	SIM 10 mg QD	SIM	
	EZE 10 mg QD + SIM 20 mg QD	EZE + SIM	
	SIM 20 mg QD	SIM	
Cruz-Fernández JM et al. *Int J Clin Pract*. 2005;59:619–627.	EZE 10 mg QD + ATOR 10 mg QD	EZE + ATOR	No: % change in LDL-C reported; not compatible with mean change in LDL-C
	ATOR 10 mg QD	ATOR	
	EZE 10 mg QD + ATOR 20 mg QD	EZE + ATOR	
	ATOR 20 mg QD	ATOR	
Ran D et al. *Int J Cardiol*. 2017;235:49–55.	EZE 10 mg QD + ROSU 10 mg QD	EZE + ROSU	Yes
	ROSU 10 mg QD	ROSU	
	ROSU 20 mg QD	ROSU	No: incomparable intervention

West AM et al. *Atherosclerosis*. 2011;218;156–162.	EZE 10 mg QD + SIM 40 mg QD	EZE + SIM	Yes
	SIM 40 mg QD	SIM	
	EZE 10 mg QD	EZE	No: incomparable intervention

ATOR atorvastatin, *EZE* ezetimibe, *NA* not applicable, *QD* daily, *PS* plant sterols, *ROSU* rosuvastatin.

Supplemental Table S6 Cardiovascular history as defined within each included study

Study reference	Cardiovascular inclusion criterion	Study definition
Brohet C et al. *Curr Med Res Opin*. 2005;21:571–578.	CHD	NR
Cannon CP et al. *N Engl J Med*. 2015;372:2387–2397.	ACS	ST-segment elevation myocardial infraction; non-ST-segment elevation myocardial infarction, unstable angina
Hibi K et al. *Circ J*. 2018;82:757–766.	ACS	Unstable angina pectoris, non-ST-segment elevation myocardial infarction, ST-segment elevation myocardial infarction
Joshi S et al. *J Clin Diagn Res*. 2017;11:OC28–OC31.	CAD	CAD was diagnosed on the basis of clinical history and electrocardiography (ECG) changes (ST depression/elevation, T wave inversion)
Masuda J et al 2015. *Int Heart J*. 2015;56:278–285.	CAD	Clinically stable angina pectoris undergoing elective PCI
Ran D et al. *Int J Cardiol*. 2017;235:49–55.	ACS	Non-ST-segment elevation ACS (including unstable angina and non-ST-elevation myocardial infarction) undergoing PCI
Ren Y et al. *Exp Ther Med*. 2017;14:4942–4950.	AMI	Hospitalized within preceding 24 hours for AMI, including ST-segment elevation myocardial infarction (STEMI) with or without non-ST-segment elevation myocardial infarction (NSTEMI). STEMI was defined as an AMI with dynamic changes in the electrocardiogram and at least one instance of elevated levels of cardiac enzymes or myocardial necrosis biomarkers, defined as total creatine phosphokinase or creatine kinase major basic fraction >2‑fold the upper limit of the normal range and/or positive troponin I or troponin T
Ueda Y et al. *Circ J*. 2017;81:1611–1619.	CAD	Patients with stable CAD who underwent elective PCI and had yellow plaques (≥1 yellow plaque of grade ≥2)

Wang J et al. *Int Angiol*. 2017;36:467–473.	CAS, CHD	Patients with CAS confirmed by ultrasound and with type 2 diabetes mellitus and CHD. CHD defined as at least one major coronary artery stenosis rate heavier than 50% in coronary angiography
Wang X et al. *Heart Lung Circ*. 2016;25:459–465.	CHD	Atherosclerotic lesions identified by coronary angiography near the middle of the coronary arteries (borderline lesions, 40–70% stenosis; severe lesions, >75% stenosis)
West AM et al. *Atherosclerosis*. 2011;218;156–162.	PAD	NR
Zou YC et al. *J Am Geriatr Soc*. 2016;64:S328.	CAS and CHD	NR

ACS acute coronary syndrome, *AMI* acute myocardial infarction, *CAS* carotid atherosclerosis, *CAD* coronary artery disease, *CHD* coronary heart disease, *NR* not reported, *PAD* peripheral arterial disease, *PCI* percutaneous coronary intervention

Supplemental Table S7 LDL-C outcomes reported in included studies

Study reference trial name (trial number)	Treatment arms	Number of patients	Timepoint	LDL-C outcome	LDL-C value
Brohet C et al. *Curr Med Res Opin*. 2005;21:571–578.	EZE 10 mg QD + SIM 10/20 mg QD	204	Baseline to 6 weeks	% change from baseline	−27.1
			6 weeks	Mean (SD)	88.6 (19.7) mg/dL
	SIM 10/20 mg QD	207	Baseline to 6 weeks	% change from baseline	−4.1
			6 weeks	Mean (SD)	117.2 (17.8) mg/dL
Cannon CP et al. *N Engl J Med*. 2015;372:2387–2397. IMPROVE-IT (NCT00202878)	EZE 10 mg QD + SIM 40–80 mg QD	9067	1 year	Mean	53.2 mg/dL
	SIM 40–80 mg QD	9077	1 year	Mean	69.9 mg/dL
Hibi K et al. *Circ J*. 2018;82:757–766. (NCT00549926)	EZE 10 mg QD + PITA 2 mg QD	50	Baseline to 10 months	Mean (SD) change from baseline	−58 (27) mg/dL
				% change from baseline	−45.7
			10 months	Mean (SD)	64 (18) mg/dL
	PITA 2 mg QD	53	Baseline to 10 months	Mean (SD) change from baseline	−40 (31) mg/dL
				% change from baseline	−28.8

			10 months	Mean (SD)	87 (21) mg/dL
Joshi S et al. *J Clin Diagn Res*. 2017;11:OC28–OC31.	EZE 10 mg QD + ROSU 10 mg QD	40	Baseline to 12 weeks	% change from baseline	−53.7
			12 weeks	Mean (SD)	76.8 (10.1) mg/dL
			Baseline to 24 weeks	% change from baseline	−57.4
			24 weeks	Mean (SD)	70.6 (9.0) mg/dL
	ROSU 10 mg QD	40	Baseline to 12 weeks	% change from baseline	−41.1
			12 weeks	Mean (SD)	90.4 (17.9) mg/dL
			Baseline to 24 weeks	% change from baseline	−45.5
			24 weeks	Mean (SD)	83.2 (14.0) mg/dL
Masuda J et al 2015. *Int Heart J*. 2015;56:278–285. (UMIN000010323)	EZE 10 mg QD + ROSU 5 mg QD	21	Baseline to 6 months	% (SD) change from baseline	–55.8 (18.9)
			Baseline to 6 months	Mean (SD) change from baseline	–74.5 (23.4) mg/dL
			6 months	Mean (SD)	57.3 (20.2) mg/dL
	ROSU 5 mg QD	19	Baseline to 6 months	% (SD) change from baseline	–36.8 (18.9)
			Baseline to 6 months	Mean (SD) change from baseline	–47.9 (24.7) mg/dL
			6 months	Mean (SD)	75.1 (21.4) mg/dL
Ran D et al. *Int J Cardiol*.	EZE 10 mg QD + ROSU 10 mg QD	42	Baseline to 4 weeks	% change from baseline (adjusted mean)	–50.3

2017;235:49–55.			Baseline to 4 weeks	Mean (SD) change from baseline	–72 (23.5) mg/dL
			4 weeks	Mean (SD)	69 (16) mg/dL
			Baseline to 12 weeks	% change from baseline (adjusted mean)	–67.3
			Baseline to 12 weeks	Mean (SD) change from baseline	–95 (23.5) mg/dL
			12 weeks	Mean (SD)	46 (17) mg/dL
	ROSU 10 mg QD	42	Baseline to 4 weeks	% change from baseline (adjusted mean)	–29.0
			Baseline to 4 weeks	Mean (SD) change from baseline	–43 (28.9) mg/dL
			4 weeks	Mean (SD)	98 (21) mg/dL
			Baseline to 12 weeks	% change from baseline (adjusted mean)	–43.9
			Baseline to 12 weeks	Mean (SD) change from baseline	–64 (28.6) mg/dL
			12 weeks	Mean (SD)	77 (17) mg/dL
	ROSU 20 mg QD	41	Baseline to 4 weeks	% change from baseline (adjusted mean)	–37.9
			Baseline to 4 weeks	Mean (SD) change from baseline	–56 mg/dL

			4 weeks	Mean (SD)	85 (21) mg/dL
			Baseline to 12 weeks	% change from baseline (adjusted mean)	–52.8
			Baseline to 12 weeks	Mean (SD) change from baseline	–77 mg/dL
			12 weeks	Mean (SD)	64 (15) mg/dL
Ren Y et al. *Exp Ther Med*. 2017;14:4942–4950.	EZE 10 mg QD + ROSU 10 mg QD	54	Baseline to 1 month	Mean (SD) change from baseline	−59.2 (38.3) mg/dL
		53	Baseline to 3 months	Mean (SD) change from baseline	−63.8 (33.6) mg/dL
		51	Baseline to 6 months	Mean (SD) change from baseline	−68.1 (34.4) mg/dL
		50	Baseline to 1 year	Mean (SD) change from baseline	−70.0 (34.0) mg/dL
		54	1 month	Mean (SD)	57.1 (27.0) mg/dL
		53	3 months	Mean (SD)	52.2 (23.6) mg/dL
		51	6 months	Mean (SD)	48.0 (18.6) mg/dL
		50	1 year	Mean (SD)	46.0 (16.6) mg/dL
	ROSU 10 mg QD	57	Baseline to 1 month	Mean (SD) change from baseline	−45.6 (25.9) mg/dL
		55	Baseline to 3 months	Mean (SD) change from baseline	−51.8 (31.3) mg/dL

		54	Baseline to 6 months	Mean (SD) change from baseline	−54.5 (32.1) mg/dL
		53	Baseline to 1 year	Mean (SD) change from baseline	−55.7 (37.9) mg/dL
		57	1 month	Mean (SD)	68.1 (30.2) mg/dL
		55	3 months	Mean (SD)	61.9 (19.7) mg/dL
		54	6 months	Mean (SD)	58.8 (16.2) mg/dL
		53	1 year	Mean (SD)	57.6 (19.7) mg/dL
Ueda Y et al. *Circ J*. 2017;81:1611–1619. ZIPANGU (UMIN000006971)	EZE 10 mg QD + ATOR 10–20 mg QD	54	1 month	Mean (SD)	61 (16) mg/dL
			3 months	Mean (SD)	63 (14) mg/dL
			9 months	Mean (SD)	61 (17) mg/dL
	ATOR 10–20 mg QD	54	1 month	Mean (SD)	81 (19) mg/dL
			3 months	Mean (SD)	77 (19) mg/dL
			9 months	Mean (SD)	75 (16) mg/dL
Wang J et al. *Int Angiol*. 2017;36:467–473.	EZE 10 mg QD + ATOR 20 mg QD	51	Baseline to 12 months	Mean (SD) change from baseline	−71.9 (29.0) mg/dL
			12 months	Mean (SD)	64.6 (16.6) mg/dL
	ATOR 20 mg QD	49	Baseline to 12 months	Mean (SD) change from baseline	−54.5 (25.9) mg/dL
			12 months	Mean (SD)	78.9 (20.9) mg/dL

Wang X et al. *Heart Lung Circ*. 2016;25:459–465.	EZE 10 mg QD + ROSU 10 mg QD		Baseline to 1 month	Mean (SD) change from baseline	−22.0 (40.2) mg/dL
			Baseline to 6 months	Mean (SD) change from baseline	−64.6 (39.4) mg/dL
		50	Baseline to 12 months	Mean (SD) change from baseline	−87.0 (40.6) mg/dL
			1 month	Mean (SD)	117.9 (30.5) mg/dL
			6 months	Mean (SD)	75.4 (23.6) mg/dL
			12 months	Mean (SD)	53.0 (32.1) mg/dL
	ROSU 10 mg QD		Baseline to 1 month	Mean (SD) change from baseline	−14.3 (43.3) mg/dL
			Baseline to 6 months	Mean (SD) change from baseline	−42.5 (43.7) mg/dL
		48	Baseline to 12 months	Mean (SD) change from baseline	−63.0 (42.5) mg/dL
			1 month	Mean (SD)	120.3 (33.3) mg/dL
			6 months	Mean (SD)	92.0 (35.2) mg/dL
			12 months	Mean (SD)	71.5 (30.5) mg/dL
West AM et al. *Atherosclerosis*. 2011;218;156–162. (NCT00587678)	EZE 10 mg QD	33	1 year	Mean (SD)	79 (33) mg/dL
			2 years	Mean (SD)	78 (27) mg/dL
	EZE 10 mg QD +	18	1 year	Mean (SD)	67 (31) mg/dL

	SIM 40 mg QD		2 years	Mean (SD)	68 (49) mg/dL
	SIM 40 mg QD	16	1 year	Mean (SD)	91 (32) mg/dL
			2 years	Mean (SD)	85 (29) mg/dL
Zou YC et al. *J Am Geriatr Soc*. 2016;64:S328.	EZE 10 mg QD + ATOR 10 mg QD	40	Baseline to 12 months	Mean (SD) change from baseline	−114.0 (21.6) mg/dL
	ATOR 10 mg QD	40	Baseline to 12 months	Mean (SD) change from baseline	−78.5 (21.6) mg/dL

ATOR atorvastatin, *EZE* ezetimibe, *LDL-C* low-density lipoprotein cholesterol, *NR* not reported, *QD* daily, *PITA* pitavastatin, *ROSU* rosuvastatin, *SD* standard deviation, *SIM* simvastatin

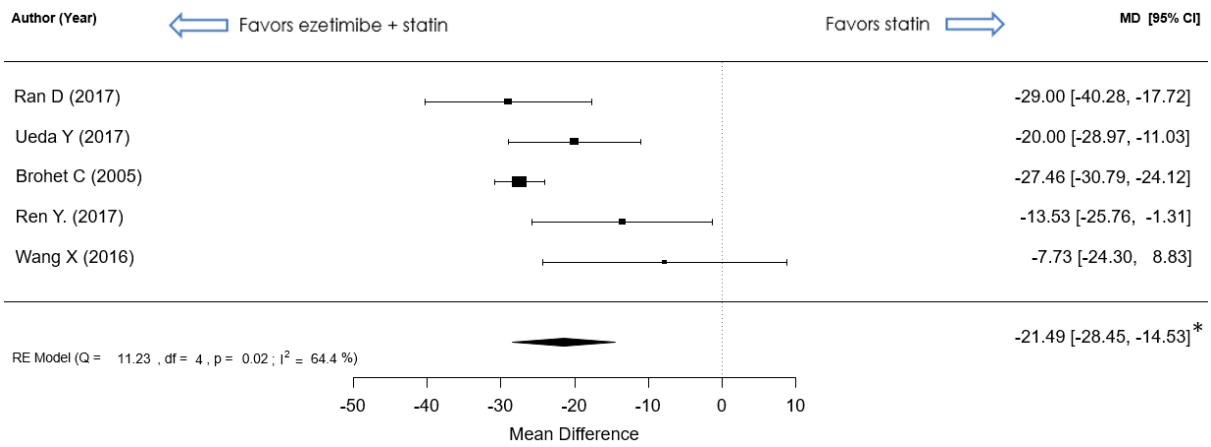
Supplemental Table S8. Quality appraisal checklist[a]

	Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias
Study reference (trial name)	**Random sequence generation**	**Allocation concealment**	**Blinding of participants and personnel**	**Blinding of outcome assessment**	**Incomplete outcome data**	**Selective reporting**	**Other sources of bias**
Brohet C et al. *Curr Med Res Opin*. 2005;21:571–578.	Low	Unclear	Low	Unclear	Unclear	Low	Unclear
Cannon CP et al. *N Engl J Med*. 2015;372:2387–2397. (IMPROVE-IT)	Unclear	Unclear	Unclear	Unclear	Low	Low	Low
Hibi K et al. *Circ J*. 2018;82:757–766. (NCT00549926)	Low	Unclear	High	Low	High	Low	Unclear
Joshi S et al. *J Clin Diagn Res*. 2017;11:OC28–OC31.	Low	Unclear	Unclear	Unclear	Unclear	High	Unclear
Masuda J et al 2015. *Int Heart J*. 2015;56:278–285. (NR)	Low	Low	High	High	Low	Low	Low
Ran D et al. *Int J Cardiol*. 2017;235:49–55.	Low	Unclear	High	Unclear	Unclear	Low	Unclear
Ren Y et al. *Exp Ther Med*. 2017;14:4942–4950.	Low	Unclear	Unclear	Unclear	Low	Low	Unclear

Ueda Y et al. *Circ J*. 2017;81:1611–1619. ZIPANGU (UMIN000006971)	Low	Unclear	High	Low	Low	High	High
Wang J et al. *Int Angiol*. 2017;36:467–473.	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Wang X et al. *Heart Lung Circ*. 2016;25:459–465.	Low	Unclear	Unclear	Unclear	Low	Unclear	Unclear
West AM et al. *Atherosclerosis*. 2011;218;156–162. (NCT00587678)	Low	Unclear	Low	Low	Low	Low	Unclear
Zou YC et al. *J Am Geriatr Soc*. 2016;64:S328.	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear

[a]The Cochrane Collaboration Risk of Bias Assessment Tool for systematic reviews [13] to evaluate seven domains of bias was used

Supplemental Fig. S1 Treatment difference in LDL-C change (mg/dL) from baseline between combination ezetimibe plus statin therapy and statin monotherapy comparator at 1 month[a]

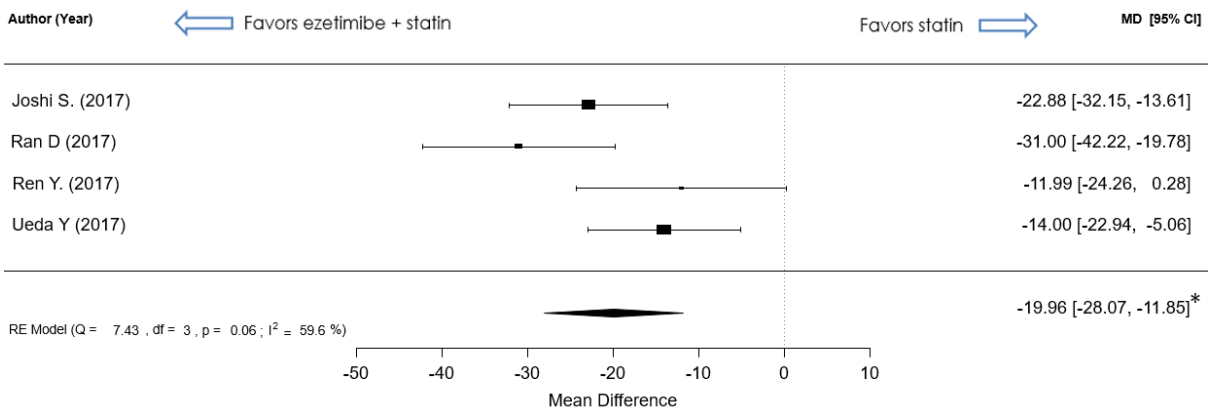


CI confidence interval, *LDL-C* low-density lipoprotein cholesterol, *MD* mean difference, *RE* random effects

[a]Meta-analysis included 812 participants from five studies, who received treatment (ezetimibe + statin vs statin) for a mean duration of 1.18 months

*$p < 0.0001$

Supplemental Fig. S2 Treatment difference in LDL-C change (mg/dL) from baseline between combination ezetimibe plus statin therapy and statin monotherapy comparator at 3 months[a]

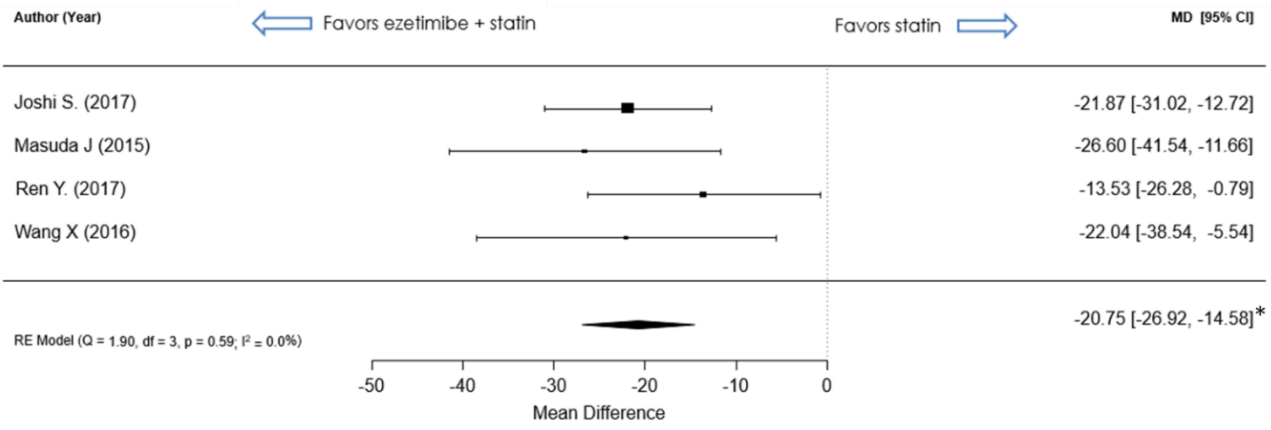


CI confidence interval, *LDL-C* low-density lipoprotein cholesterol, *MD* mean difference, *RE* random effects

[a]Meta-analysis included 380 participants from four studies, who received treatment (ezetimibe plus statin vs statin) for a mean duration of 2.90 months

*$p < 0.0001$

Supplemental Fig. S3 Treatment difference in LDL-C change (mg/dL) from baseline between combination ezetimibe plus statin therapy and statin monotherapy comparator at 6 months[a]

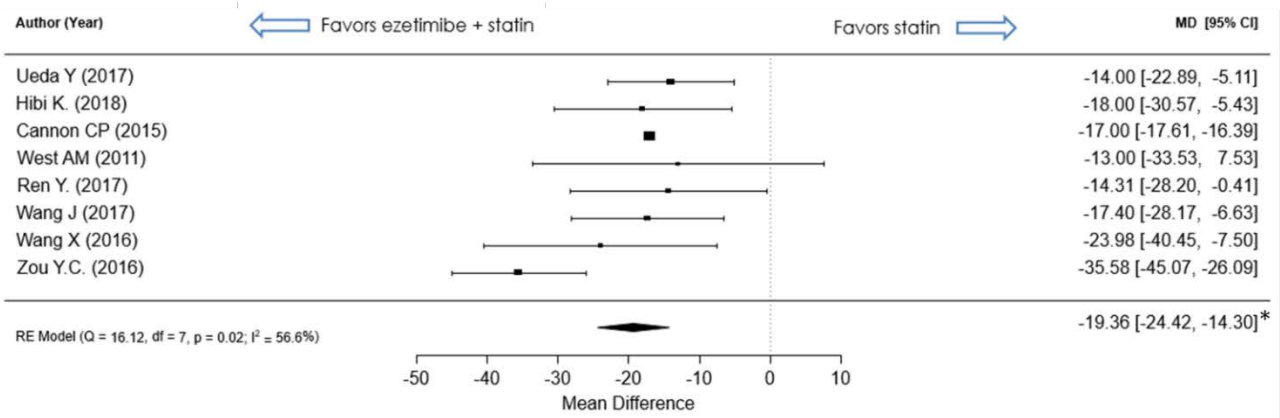


CI confidence interval, *LDL-C* low-density lipoprotein cholesterol, *MD* mean difference, *RE* random effects

[a]Meta-analysis included 323 participants from four studies, who received treatment (ezetimibe plus statin vs statin) for a mean duration of 5.88 months

*$p < 0.0001$

Supplemental Fig. S4 Treatment difference in LDL-C change (mg/dL) from baseline between combination ezetimibe plus statin therapy and statin monotherapy comparator at 9–12 months[a]

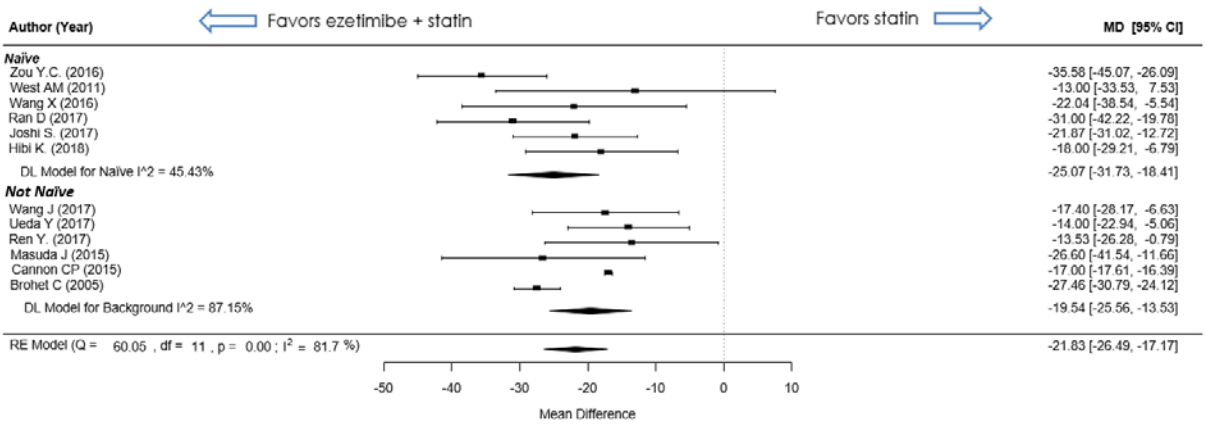


CI confidence interval, *LDL-C* low-density lipoprotein cholesterol, *MD* mean difference, *RE* random effects

[a]Meta-analysis included 18,787 participants from eight studies, who received treatment (ezetimibe plus statin vs statin) for a mean duration of 11.96 months

*$p < 0.0001$

Supplemental Fig. S5 Sub-analysis of LDL-C change (mg/dL) from baseline at 6 months, or at the reported time point closest to 6 months, in statin-naïve patients and in patients with prior statin therapy[a]



CI confidence interval, *LDL-C* low-density lipoprotein cholesterol, *MD* mean difference, *RE* random effects

[a]Statin-naïve meta-analysis included 496 participants from six studies, who received treatment (ezetimibe plus statin versus statin) for a mean duration of 7.79 months. In patients with a history of statin therapy, meta-analysis included 18,908 participants from six studies, who received treatment (ezetimibe plus statin versus statin) for a mean duration of 11.66 months. There is no statistically significant difference between the two groups (p = 0.2462)

1. Writing Committee, Lloyd-Jones DM, Morris PB, Ballantyne CM, Birtcher KK, Daly DD, Jr., et al. 2016 ACC Expert Consensus Decision Pathway on the role of non-statin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular disease risk: a report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. J Am Coll Cardiol. 2016;68(1):92-125.