

Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. PubMed Search Strategy

N	Search Terms	Records
1	*Lipid AND *Lowering	4841
2	*LDL AND *Lowering	2507
3	*Cholesterol AND *Lowering	3685
4	*Statin AND *Cholesterol	4161
5	*Statin AND *LDL	3169
6	*Statin AND *Lipid	5052
7	*Ezetimibe AND *Cholesterol	475
8	*Ezetimibe AND *LDL	424
9	*Ezetimibe AND *Lipid	496
10	*Proprotein convertase subtilisin/kexin type 9 AND *Cholesterol	104
11	*Proprotein convertase subtilisin/kexin type 9 AND *LDL	98
12	*Proprotein convertase subtilisin/kexin type 9 AND *Lipid	100
13	*Bile acid sequestrants AND *Cholesterol	27
14	*Bile acid sequestrants AND *LDL	20
15	*Bile acid sequestrants AND *Lipid	25
16	*Fibrates AND *Cholesterol	951
17	*Fibrates AND *LDL	601
18	*Fibrates AND *Lipid	1223
19	*Niacin AND *Cholesterol	273
20	*Niacin AND *LDL	187
21	*Niacin AND *Lipid	345
22	*Omega 3 fatty acid AND *Cholesterol	700
23	*Omega 3 fatty acid AND *LDL	418
24	*Omega 3 fatty acid AND *Lipid	3252

eTable 2. Estimation of Percentage of Women in Disease Populations

Disease	Region	% in disease population	Source
Acute Coronary Syndrome	USA	43	Mozaffarian D, Benjamin EJ, Go AS, et al. Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. <i>Circulation</i> . 2016 Jan 26;133(4):e38-e360, p. 296.
	Asia	45.9	Greenslade JH, Cullen L, Parsonage W, et al. Examining the signs and symptoms experienced by individuals with suspected acute coronary syndrome in the Asia-Pacific region: a prospective observational study. <i>Ann Emerg Med</i> . 2012;60:777-785 e3
	Europe	30.5	Andre R, Bongard V, Elosua R, et al. International differences in acute coronary syndrome patients' baseline characteristics, clinical management and outcomes in Western Europe: the EURHOBOP study. <i>Heart</i> . 2014;100:1201-1207
Coronary Heart Disease	Global	48.7	Roth GA, Johnson C, Abajobir A, et al. Global, Regional, and National Burden of Cardiovascular Diseases for 10 Causes, 1990 to 2015. <i>J Am Coll Cardiol</i> . 2017;70(1):1-25
Heart Failure	USA	53	Mozaffarian D, Benjamin EJ, Go AS, et al. Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. <i>Circulation</i> . 2016 Jan 26;133(4):e38-e360, p. e274
	China	42.5	Yu SB, Cui HY, Qin M, et al. [Characteristics of in-hospital patients with chronic heart failure in Hubei province from 2000 to 2010]. <i>Zhonghua Xin Xue Guan Bing Za Zhi</i> . 2011;39:549-552.10

Disease	Region	% in disease population	Source
	Japan	30.2	Shiba N, Nochioka K, Miura M, Kohno H, Shimokawa H and Investigators C-. Trend of westernization of etiology and clinical characteristics of heart failure patients in Japan-- first report from the CHART-2 study. <i>Circ J</i> . 2011;75:823-833.11
	Europe	32.5	Maggioni AP, Dahlstrom U, Filippatos G, Chioncel O, Leiro MC, Drozd J, Fruhwald F, Gullestad L, Logeart D, Metra M, Parissis J, Persson H, Ponikowski P, Rauchhaus M, Voors A, Nielsen OW, Zannad F, Tavazzi L and Heart Failure Association of ESC. EURObservational Research Programme: the Heart Failure Pilot Survey (ESC-HF Pilot). <i>Eur J Heart Fail</i> . 2010;12:1076-1084.
Diabetes Mellitus	Global	48	GBD Compare IHME Viz Hub. Vizhub.healthdata.org. https://vizhub.healthdata.org/gbd-compare/ . [Accessed January 9, 2020.]
Hypercholesteremia	Global	35.8	Venkitachalam L, Wang K, Porath A, et al. Global variation in the prevalence of elevated cholesterol in outpatients with established vascular disease or 3 cardiovascular risk factors according to national indices of economic development and health system performance. <i>Circulation</i> . 2012;125(15):1858-1869.

eTable 3. List of Randomized Clinical Trials Included in Systematic Review

Trial Name	Participants
STATIN	
PMSGCRP ¹	1062
4S ²	4444
WOSCOP ³	6595
CARE ⁴	4159
POST CABG ⁵	1351
AFCAPS-TexCAPS ⁶	6605
LIPID ⁷	9014
GISSI-P ⁸	4271
MIRACL ⁹	3086
ALLHAT-LLT ¹⁰	10355
GREACE ¹¹	1600
HPS ¹²	20536
LIPS ¹³	1677
PROSPER ¹⁴	5804
ALERT ¹⁵	2102
ASCOT-LLA ¹⁶	10305
A to Z ¹⁷	4497
ALLIANCE ¹⁸	2442
CARDS ¹⁹	2838
PROVE-IT TIMI 22 ²⁰	4162
TNT ²¹	10001
4D ²²	1255
IDEAL ²³	8888
ASPEN ²⁴	2410
MEGA ²⁵	7832
SPARCL ²⁶	4731
CORONA ²⁷	5011
JUPITER ²⁸	17802
GISSI-HF ²⁹	4574
AURORA ³⁰	2773
SEARCH ³¹	12064
HOPE-3 ³²	12705
EZETIMIBE	
SEAS ³³	1873
SHARP ³⁴	9270
IMPROVE-IT ³⁵	18144
PCSK9 INHIBITOR	
ODYSSEY LONGTERM ³⁶	2341
OSLER ³⁷	4465

FOURIER ³⁸	27564
SPIRE 1 ³⁹	16817
SPIRE 2 ³⁹	10564
ODYSSEY OUTCOMES ⁴⁰	18924
FIBRATES	
BIP ⁴¹	3090
LEADER ⁴²	1568
FIELD ⁴³	9795
ACCORD ⁴⁴	5518
VA-HIT ⁴⁵	2531
NIACIN	
AIM-HIGH ⁴⁶	3414
HPS2-THRIVE ⁴⁷	25673
OMEGA 3 FATTY ACID	
AREDS-2 ⁴⁸	4203
SU.FOL.MO3 ⁴⁹	2501
JELIS ⁵⁰	18645
ALPHA OMEGA ⁵¹	4837
OMEGA ⁵²	3851
R&P ⁵³	12505
GISSI-HF ⁵⁴	6975
ORIGIN ⁵⁵	12536
GISSI-P ⁵⁶	11324
VITAL ⁵⁷	25871
ASCEND ⁵⁸	15480
REDUCE-IT ⁵⁹	8179

eTable 4. Women Representation in Lipid-Lowering Therapy Randomized Clinical Trials

	No. of Trials	Overall Population	Women, No. (%)	P-value
Publication Year				
1990-1994	2	5506	1074 (19.5)	0.01
1995-1998	5	27724	3200 (11.5)	
1999-2002	11	65842	17339 (26.3)	
2003-2006	13	71258	21943 (30.7)	
2007-2010	12	86424	31379 (36.3)	
2011-2014	6	67601	22878 (33.8)	
2015-2018	11	161054	54224 (33.6)	
Therapy				
Statins	32	196951	55940 (28.4)	0.04
Ezetimibe	3	29287	8609 (29.3)	
PCSK9 inhibitors	6	80675	22696 (28.1)	
Fibrates	5	22502	5634(25.0)	
Niacin	2	29087	4948 (17.0)	
Omega 3 fatty acids	12	126907	54210 (42.7)	
Setting				
Primary prevention	28	224494	94662 (42.2)	0.02
Secondary prevention	32	260915	57375 (22.0)	
Target population/indication				
Aortic stenosis	1	1873	723 (38.6)	0.08
Chronic kidney disease	4	15400	5813 (37.7)	
Diabetes mellites	6	48577	17271 (35.6)	
Hypercholesterolemia	7	70175	31875 (45.4)	
Hypercholesterolemia with risk factors for ASCVD	5	36541	19018 (52.0)	
Risk factors for ASCVD without hypercholesteremia	3	40379	17414 (43.1)	
Acute coronary syndrome	16	113339	23039 (20.3)	
Stable coronary heart disease	15	142565	33156 (23.3)	

Heart failure	3	16560	3728 (10.6)	
Location				
North America	13	93317	35526 (38.1)	0.35
Western Europe	21	142034	39791 (28)	
Multiregional	20	190358	53457 (28)	
Rest of the world	6	59700	25263 (42)	
Funding				
Industry	35	267631	82673 (31)	0.14
Government	3	35592	17166 (48.2)	
University/organization	5	22071	5660 (26)	
Other/combined	17	160115	46538 (29)	

eTable 5. Inclusion/Exclusion Criteria Focusing on Women and Older Participants in Randomized Clinical Trials

Inclusion/Exclusion criteria	Percentage [95% CI]
Women	
All women excluded	5.0% (1.7% to 13.7%)
Pregnant women excluded	23.3% (14.4% to 35.4%)
Lactating women excluded	16.6% (9.3% to 28.1%)
Only postmenopausal women or surgically sterile women included	28.3% (18.5%to 40.7%)
Only women >55 years included	3.3% (0.9% to 11.3%)
Only women >60 years included	5.0% (1.7% to 13.7%)
Only >65 years included	1.6% (0.2% to 8.8%)
Older participants (inclusion criteria)	
<65 years	1.6% (0.2% to 8.8%)
<70 years	3.3% (0.9% to 11.3%)
<75 years	20.0% (11.8% to 31.7%)
<79 years	1.6% (0.2% to 8.8%)
<80 years	15.0% (8.0% to 26.1%)
<82 years	1.6% (0.2% to 8.8%)
<85 years	1.6% (0.2% to 8.8%).

eTable 6. Mean Age of Enrolled Patients Within Lipid-Lowering Therapy Randomized Clinical Trials

	No. of Trials	Total Population	Mean age (SD)	P-value
Publication Year				<0.001
1990-1994	2	5506	56.8 (2.5)	
1995-1998	5	27724	59.1 (2.8)	
1999-2002	11	65842	64.1 (5.1)	
2003-2006	13	71258	60.6 (3.7)	
2007-2010	12	86424	65.6 (3.6)	
2011-2014	6	67601	65.4 (4.5)	
2015-2018	11	161054	62.6 (2.8)	
Therapy				0.41
Statins	32	196951	62.1 (5)	
Ezetimibe	3	29287	64.4 (2.8)	
PCSK9 inhibitors	6	80675	60.9 (2.2)	
Fibrates	5	22502	63.4 (3.2)	
Niacin	2	29087	64.3 (0.8)	
Omega 3 fatty acids	12	126907	64.8 (4.1)	
Setting				0.66
Primary Prevention	28	224494	63.1 (5.4)	
Secondary Prevention	32	260915	62.6 (3.3)	
Target population/indication				0.03
Aortic stenosis	1	1873	67.5 (NA)	
Chronic kidney disease	4	15400	60.5 (7.1)	
Diabetes mellites	6	48577	62.3 (1)	
Hypercholesterolemia	7	70175	60.8 (4.2)	
Hypercholesterolemia with risk factors for ASCVD	5	36541	63.6 (7.9)	
Risk factors for ASCVD without hypercholesteremia	3	40379	68.2 (5.7)	
Acute coronary syndrome	16	113339	61.8 (2.9)	
Stable coronary heart disease	15	142565	62.6 (2.5)	
Heart failure	3	16560	69.3 (3.2)	

Location				
North America	13	93317	63.3 (4.4)	0.24
Western Europe	21	142034	64.1 (4.5)	
Multiregional	20	190358	62.0 (4.6)	
Rest of the world	6	59700	60.5 (1.5)	
Funding				
Industry	35	267631	62.4 (4.6)	0.16
Government	3	35592	67.9 (6.1)	
University/organization	5	22071	64.6 (5.1)	
Other/combined	17	160115	62.3 (2.8)	

eTable 7. Representation of Older (≥ 65 years) Participants in Lipid-Lowering Therapy Randomized Clinical Trials

	No. of Trials	Overall Population	Older participants, No. (%)	P-values
Publication Year				
1990-1994	NR	NR	NR	0.43
1995-1998	2	15619	4930 (31.6)	
1999-2002	4	37693	19082 (50.6)	
2003-2006	3	16367	6055 (37.0)	
2007-2010	3	26093	12479 (47.8)	
2011-2014	4	54128	28102 (51.9)	
2015-2018	7	113728	52589 (46.2)	
Therapy				
Statins	10	90633	42112 (46.5)	0.49
Ezetimibe	1	18144	7971(43.9)	
PCSK9 inhibitors	3	48829	18187 (37.2)	
Fibrates	3	17844	7079 (39.7)	
Niacin	2	29087	14323 (49.2)	
Omega 3 fatty acids	4	59091	33565 (56.8)	
Setting				
Primary Prevention	12	121216	61723 (50.9)	0.81
Secondary Prevention	11	142412	61514 (43.2)	
Target population/indication				
Aortic stenosis	0	0	0	0.14
Chronic kidney disease	1	2773	1360 (49.0)	
Diabetes mellitus	4	30259	13923 (46.0)	
Hypercholesterolemia	4	37103	17233 (46.4)	
Hypercholesterolemia with risk factors for ASCVD	2	25210	13184 (52.3)	
Risk factors for ASCVD without hypercholesterolemia	1	25871	16023 (61.9)	
Acute coronary syndrome	5	54515	19211 (35.2)	
Stable coronary heart disease	6	87897	42303 (48.1)	

Heart failure	0	0	0	
Location				
North America	8	71161	35727 (50.2)	0.82
Western Europe	3	37312	18648 (50.0)	
Multiregional	10	136346	61393 (45.0)	
Rest of the world	2	18809	7469 (39.7)	
Funding				
Industry	12	123940	51863 (41.8)	0.32
Government	2	31389	17881 (57.0)	
University/organization	2	14066	5367 (38.2)	
Other/combined	7	94233	48126 (51.1)	

ASCVD, Atherosclerotic Cardiovascular Disease; NR, Not Reported

eTable 8. Trends in Randomized Clinical Trials Reporting Outcomes Based on Sex and Age

Characteristics	1990-1994	1995-1998	1999-2002	2003-2006	2007-2010	2011-2014	2015-2018	P-value
Trials reporting outcomes in women, No. (%)	NR	3 (60)	5 (45.5)	5 (38.5)	7 (58.3)	4 (66.7)	8 (72.7)	0.42
Women participants, No. (%)	NR	3095 (15.6)	14064 (33)	12985 (35.5)	26617 (39.9)	16105 (31.7)	43943 (34)	0.39
Trials reporting outcomes in participants ≥ 65 yrs., No. (%)	NR	1 (25)	5 (50)	3 (25)	3 (30)	4 (80)	6 (60)	0.20
Participants age ≥ 65 yrs., No. (%)	NR	3514 (39)	19082 (48.6)	5185 (28.1)	12479 (47.8)	28102 (51.9)	36566 (41.6)	0.81
Women								
Therapy, No (%)								
Statins	NR	3 (17.6)	5 (29.4)	4 (23.5)	4 (23.5)	NR	1(5.9)	0.01
Ezetimibe	NR	NR	NR	NR	NR	1 (50)	1 (50)	
PCSK9 inhibitors	NR	NR	NR	NR	NR	NR	3 (100)	
Fibrates	NR	NR	NR	1 (50)	1 (50)	NR	NR	
Niacin	NR	NR	NR	NR	NR	2 (100)	NR	
Omega 3 fatty acids	NR	NR	NR	NR	2 (33.3)	1 (16.7)	3 (50)	
Indication or baseline population, No. (%)								0.82
Aortic stenosis	NR	NR	NR	NR	NR	NR	NR	
Chronic kidney disease	NR	NR	NR	NR	1 (50)	1 (50)	NR	
Diabetes mellitus	NR	NR	NR	1 (33.3)	1 (33.3)	NR	1 (33.3)	
Hypercholesterolemia	NR	1 (16.7)	1 (16.7)	1 (16.7)	2 (33.3)	NR	1 (16.7)	
Hypercholesterolemia with risk factors for ASCVD	NR	NR	1 (33.3)	NR	NR	1 (33.3)	1 (33.3)	
Risk factors for ASCVD without hypercholesterolemia	NR	NR	NR	1 (50)	NR	NR	1 (50)	
Acute coronary syndrome	NR	2 (22.2)	1 (11.2)	2 (22.2)	2 (22.2)	NR	2 (22.2)	
Stable coronary heart disease	NR	NR	2 (33.3)	NR	NR	2 (33.3)	2 (33.3)	
Heart failure	NR	NR	NR	NR	1 (100)	NR	NR	
Setting, No. (%)								
Primary prevention	NR	1 (6.3)	2 (12.5)	3 (18.8)	4 (25)	2 (12.5)	4 (25)	0.97

Secondary prevention	NR	2 (12.5)	3 (18.8)	2 (12.5)	3 (18.8)	2 (12.5)	4 (25)	
Location, No. (%)								
North America	NR	2 (25)	1 (12.5)	1 (12.5)	1 (12.5)	1 (12.5)	2 (25)	0.15
Western Europe	NR	NR	4 (40)	1 (10)	2 (20)	2 (20)	1 (10)	
Multiregional	NR	NR	NR	1 (10)	3 (30)	1 (10)	5 (50)	
Rest of the world	NR	1 (25)	NR	2 (50)	1 (25)	NR	NR	
Funding, No (%)								
Industry	NR	1 (6.7)	1 (6.7)	3 (20)	4 (26.7)	1 (6.7)	5 (33.3)	0.55
Government	NR	NR	NR	NR	1 (50)	NR	1 (50)	
University/organization	NR	NR	2 (50)	1 (25)	1 (25)	NR	NR	
Other/combined	NR	2 (18.2)	2 (18.2)	1 (9.1)	1 (9.1)	3 (27.3)	2 (18.2)	
Age ≥ 65 years								
Therapy, No (%)								
Statins	NR	1 (11.1)	3 (33.3)	2 (22.2)	2 (22.2)	NR	1 (11.1)	0.11
Ezetimibe	NR	NR	NR	NR	NR	NR	1 (100)	
PCSK9 inhibitors	NR	NR	NR	NR	NR	NR	3 (100)	
Fibrates	NR	NR	2 (50)	1 (25)	1 (25)	NR	NR	
Niacin	NR	NR	NR	NR	NR	2 (100)	NR	
Omega 3 fatty acids	NR	NR	NR	NR	NR	2 (66.6)	1 (33.3)	
Indication or baseline population, No. (%)								
Aortic stenosis	NR	NR	NR	NR	NR	NR	NR	0.50
Chronic kidney disease	NR	NR	NR	NR	1 (100)	NR	NR	
Diabetes mellitus	NR	NR	NR	1 (33.3)	1 (33.3)	1 (33.3)	NR	
Hypercholesterolemia	NR	NR	1 (33.3)	NR	1 (33.3)	NR	1 (33.3)	
Hypercholesterolemia with risk factors for ASCVD	NR	NR	NR	NR	NR	1 (50)	1 (50)	
Risk factors for ASCVD without hypercholesterolemia	NR	NR	NR	NR	NR	NR	NR	
Acute coronary syndrome	NR	1 (16.7)	1 (16.7)	2 (33.3)	NR	NR	2 (33.3)	
Stable coronary heart disease	NR	NR	3 (42.9)	NR	NR	2 (28.6)	2 (28.6)	
Heart failure	NR	NR	NR	NR	NR	NR	NR	
Setting, No. (%)								

Primary prevention	NR	NR	1 (11.1)	1 (11.1)	3 (33.3)	2 (22.2)	2 (22.2)	0.28
Secondary prevention	NR	1 (7.7)	4 (30.8)	2 (15.4)	NR	2 (15.4)	4 (30.8)	
Location, No. (%)								
North America	NR	NR	2 (33.3)	1 (16.7)	1 (16.7)	1 (16.7)	1 (16.7)	0.04
Western Europe	NR	NR	3 (75)	NR	NR	1 (25)	NR	
Multiregional	NR	NR	NR	1 (10)	2 (20)	2 (20)	5 (50)	
Rest of the world	NR	1 (50)	NR	1 (50)	NR	NR	NR	
Funding, No (%)								
Industry	NR	NR	1 (9.1)	2 (18.2)	2 (18.2)	1 (9.1)	5 (45.5)	0.12
Government	NR	NR	NR	NR	1(100)	NR	NR	
University/organization	NR	NR	2 (66.6)	1 (33.3)	NR	NR	NR	
Other/combined	NR	1 (14.3)	2 (28.6)	NR	NR	3 (42.9)	1 (14.3)	

ASCVD, Atherosclerotic Cardiovascular Disease; NR, Not Reported; NA, Not Applicable

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