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Review Article
Bayesian Meta-Analysis: The Effect of Statins on the Treatment of Hypercholesterolemia

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Abstract

Statins inhibit cholesterol synthesis by blocking 3-hydroxy-3-methylglutaryl coenzyme A reductase in the liver, thereby ameliorating hypercholesterolemia. Thus, to determine statins with the best efficacy, a meta-analysis was performed to compare the effects of statins against hypercholesterolemia. Comprehensive literature searches were established, from Cochrane library, Pubmed, Embase. The studies were performed to randomize controlled trials (RCTs), cohort studies or case-control studies about efficacy of different statin drugs and dose against hypercholesterolemia published between 1997 and 20 February, 2017. Study qualities were assessed according to Cochrane collaboration recommendations. The non-programming software Aggregate Data Drug Information System (ADDIS) (version 1.16.5) was used to perform Bayesian network meta-analysis and compare treatments using the Markov Chain Monte Carlo (MCMC) method. Overall, 28 RCTs studies, including 12855 patients, met the inclusion criteria. Total cholesterol (TC) levels significantly reduced ($p<0.05$) using 2 mg Pitavastatin (Pit) than those using 20 mg Pravastatin (Pra), 10 mg Simvastatin (Sim) or 10 mg Atorvastatin (Ato). Similarly, triglyceride (TG) levels reduced using 2 mg Pit than those using 20 mg Pra ($p<0.05$), 10 mg Sim ($p<0.05$) or 20 mg Sim ($p<0.05$) and reduced apolipoprotein B (Apo B) levels were observed than those using 10 mg Ato or 20 mg Pra ($p<0.05$). Rosuvastatin (Ros) significantly reduced TC and TG levels ($p<0.05$) when administered at 20 and 10 mg Ros treatments ameliorated percentage changes in low-density lipoprotein cholesterol more than the other drugs ($p<0.05$) and increased high-density lipoprotein cholesterol levels more effectively than 10 mg Ato ($p<0.05$), 20 mg Pra ($p<0.05$) or 10 mg Sim ($p<0.05$). Increases in Apo A1 levels did not differ between treatments ($p>0.05$). Among the present statin drug regimens, 2 mg Pit and 10 or 20 mg Ros had the highest efficacy against hypercholesterolemia.

Key words: Statins, hypercholesterolemia, Bayesian meta-analysis, Cochrane collaboration, randomized controlled trial

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Hypercholesterolemia is a lipid metabolism disorder that is characterized by very high cholesterol levels in the blood and increased risks of coronary heart disease (CHD)[1]. Approximately 1 in 300-500 people in most countries carry inherited familial hypercholesterolemia, which can result in extremely high cholesterol levels (above 300 mg dL^{-1})[2,3]. Multiple studies show decreased the risks of CHD in patients with hypercholesterolemic receiving treatments with statins[4,5], which are 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) inhibitors[6].

Because HMG-CoA reductase is necessary for the production of cholesterol[7], the statins can block HMG-CoA rosuvastatin (Ros), atorvastatin (Ato), simvastatin (Sim), pravastatin (Pra), lovastatin (Lov) and pitavastatin (Pit) inhibit cholesterol synthesis and increase low-density lipoprotein (LDL) uptake in the liver[8,9]. At doses of 5, 10 and 20 mg, Ros significantly reduces LDL and improves flow-mediated dilation as well as reduces adiponectin levels and insulin sensitivity in patients with hypercholesterolemia after 2 months[10,11]. In contrast, Ato inhibits calcification of the aortic valves by inhibiting the LRP5 receptor (murine LDL receptor homologue) pathway in hypercholesterolemia mice[12]. Sim is an effective lipid-lowering drug that can decrease LDL levels by up to 50%[13,14]. Pit decreases the levels of serum lectin-like oxidized LDL receptor 1 ligand and membrane-type 1 matrix metalloproteinase expression in CD14+mononuclear cells in patients with hypercholesterolemia[15]. In addition, in a previous dose specific meta-analysis, statins acted as anti-hypercholesterolemia agents by reducing the total cholesterol (TC) and LDL cholesterol (LDL-C)[16,17]. However, the relative efficacy of these statins remains unclear.

In this study, a comprehensive literature search was conducted from the Cochrane Library, Pubmed, Embase databases upto 20 February, 2017. These studies were included in the present study, such as randomized controlled trials (RCTs), cohort studies or case-control studies on statin drug and dose effects in patients with hypercholesterolemia. Subsequently, the quality of studies was assessed and aggregate data drug information system software was used to compare treatments in a Bayesian meta-analysis. This Cochrane systematic review provides high-level comparisons of the effects of various statins and provides essential guidance for the treatment of hypercholesterolemia.

MATERIALS AND METHODS

Search strategy: The Cochrane Library, Pubmed, Embase databases were comprehensively searched for literature published before 20 February, 2017 using the key search terms "statin", "rosuvastatin", "atorvastatin" or "atorvastatine", "simvastatin" or "simvastatine", "pravastatin" or "pravachol", "lovastatin", "pitavastatin", "hypercholesteremia" or "hypercholesterolemia" or "hypercholesteroli" and "randomized controlled trial (RCT)". Only studies published in English were retrieved.

Selection criteria: Included studies met the following inclusion and exclusion criteria for the meta-analysis: (1) They reported the efficacy of statins as hypercholesterolemia treatments and were published in English language journals and (2) Their design included RCTs, cohort studies or case-control studies on the efficacy of varying doses of statin drugs and determination of TC, LDL-C, high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), apolipoprotein B (Apo B) and Apo A1 (% change). Reviews, reports, letters and comments were excluded.

Study characteristics: In the initial network meta-analysis, screened 2384 relevant studies from the database searches. 972 duplicated articles and 1249 articles that did not completely meet the inclusion criteria. These were excluded without retrieving full papers (Fig. 1). Subsequently, from the remaining 135 articles, review articles (30), letters/editors/comments (29), case series/reports (19), articles in the same area (11) and data from a total of 12855 patients with hypercholesterolemia from different countries in 28 RCT studies. Among these patients, 3732 were treated with Ato, 1246 were treated with Pra, 6207 patients treated with Ros, 386 were treated with Pit, 1284 were treated with Sim. As shown in Table 1, these studies were published between 1997 and 2015, included patients groups that did not differ in ages, sex or BMI, were followed for 6-12 weeks and were treated with drugs at dose of 1-40 mg. TC, LDL-C, HDL-C, TG, Apo B and Apo A1 (change %) levels were reported in all included studies (Table 2).

Data extraction and quality evaluation: To reduce bias, three investigators independently reviewed and extracted the information from all enrolled studies and reached a consensus on all items during discussion with an additional investigator. The following data were extracted from each eligible study:

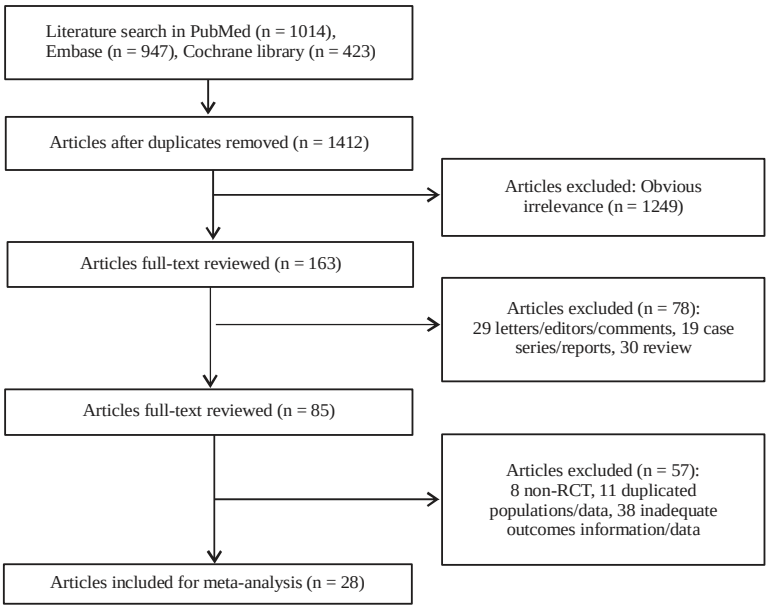

Fig. 1: Diagram of the study screening protocol

Table 1: Characteristics of included studies from online literature databases (1997-2017)

Authors	Public year	Follow-up	Groups	Dose (mg)	No. of patients	Males	Age (years)	BMI (kg m^{-2})
BertoliniS	1997	16 weeks	Ato	10	227	47	56 (0.7)	26 (0.2)
			Pra	20	78	41	57 (1.2)	25 (0.3)
			Ros	5	394	205	59.0±11	28.0±4.0
BlasettoJW1	2003	12 weeks	Ros	10	392	221	59.0±10	28.0±4.0
			Ato	10	396	211	59.0±12	28.0±5.0
			Ros	5	243	110	57.0±11	28.0±5.0
			Ros	10	231	92	59.0±10	29.0±6.0
BlasettoJW2	2003	12 weeks	Sim	10	250	109	59.0±12	28.0±5.0
			Pra	20	255	113	59.0±11	27.0±4.0
BotsAFE	2005	12 weeks	Ros	10	621	366	61.0±9.7	27.9±4.0
			Ato	10	189	110	62.0±9.9	27.7±3.9
			Sim	20	194	109	62.0±9.3	27.7±4.1
			Pra	40	211	127	60.0±9.3	27.8±4.0
			Ros	5	123	49	57.2±10.4	29.1±5.1
			Ros	10	116	43	58.4±10.2	29.8±6.5
BrownWV	2002	52 weeks	Pra	20	118	50	60.0±11.0	28.0±4.4
			Sim	20	120	44	59.4±12.1	28.8±5.8
			Ros	10	521	NA	NA	NA
			Ato	10	240	NA	NA	NA
CheungRC	2005	16 weeks	Ato	20	299	NA	NA	NA
			Sim	20	250	NA	NA	NA
			Pra	40	253	NA	NA	NA
DartA	1997	16 weeks	Ato	10	132	NA	NA	26 (0.3)
			Sim	10	45	NA	NA	27 (0.4)
			Ros	5	132	54	57.9±10.8	28.3±4.8
DavidsonM	2002	12 weeks	Ros	10	129	59	57.2±10.4	28.6±4.6
			Ato	10	130	61	56.4±12.7	29.6±6.4
			Ros	10	189	121	56.8±11.4	27.0±4.0
			Ros	20	182	136	55.6±10.9	26.9±4.0
DeedwaniaPC	2007	6 weeks	Ato	10	185	125	55.8±11.1	27.5±4.3
			Ato	20	184	120	55.2±10.6	27.0±4.5
			Ato	10	109	64	50.0±11	25.0±3.0

Table 1: Continue

Authors	Public year	Follow-up	Groups	Dose (mg)	No. of patients	Males	Age (years)	BMI (kg m^{-2})
FarnierM	2000	6 weeks	Sim	10	54	62	51.0±10	26.0±3.0
			Ato	10	35	11	53.0±9	NA
KadikoyluG	2003	24 weeks	Sim	10	26	7	54.0±10	NA
KurabayashiM	2008	8 weeks	Ato	10	207	78	64.4±10.3	NA
			Ros	5	208	95	66.7±9.6	NA
			Ros	10	334	134	62.9±9.4	29.6±4.7
LaksT	2008	12 weeks	Sim	20	170	71	63.9±9.7	28.8±4.7
			Pra	40	21	15	55.9±9.5	26.4±3.4
LeeWJ	2008	8 weeks	Pra	10	19	10	61.3±8.3	25.9±2.8
			Pit	2	112	69	58.7±9.3	26.6±3.6
LiuPY	2013	12 weeks	Ato	10	113	70	58.7±7.9	26.2±3.4
			Ros	10	184	89	58.0±10.8	30.0±5.3
			Ros	20	173	84	57.8±10.9	29.7±5.4
LloretR	2006	6 weeks	Ato	10	168	84	56.7±11.7	30.7±5.7
			Ato	20	171	88	59.0±9.8	29.6±4.9
			Ros	5	159	79	63.9±8.9	NA
NoharaR	2012	16 weeks	Pra	10	155	76	63.3±9.1	NA
			Ros	5	138	72	56.3±10.1	26.7±3.9
OlssonAG	2002	12 weeks	Ros	10	134	81	57.8±10.0	26.2±3.1
			Ato	10	140	80	58.2±10.6	26.5±3.5
			Ros	5	119	NA	NA	NA
			Ros	10	111	NA	NA	NA
PaolettiR	2001	12 weeks	Pra	20	136	NA	NA	NA
			Sim	20	129	NA	NA	NA
			Pit	2	49	18	59.90±7.8	24.9±2.3
ParkS	2005	8 weeks	Sim	20	46	18	56.40±9.5	24.9±2.9
			Pit	1	50	16	59.20±9.04	24.55±3.39
SansanayudhN	2010	8 weeks	Ato	10	50	24	58.28±10.98	24.34±3.66
			Pit	2	88	NA	62.90±8.8	NA
SasakiJ	2008	52 weeks	Ato	10	85	NA	63.70±9.5	NA
			Ros	5	127	80	62.00±10	29.0±5
SchwartzGG	2004	12 weeks	Ros	10	128	81	62.00±10	28.0±4
			Ato	10	127	71	62.00±11	29.0±5
			Ros	5	45	NA	56.20±6.4	28.1±4.2
ShepherdJ	2004	6 weeks	Ros	10	44	NA	57.40±8.1	27.5±5.2
			Pit	2	52	36	59.20±13	24.2±4.6
TaniS	2014	6 months	Ato	10	52	29	60.50±13	24.9±3.5
			Ros	10	40	17	57.18±1.48	25.53±3.39
WongwiwatthananukitS	2006	8 weeks	Ros	5	40	15	62.10±1.57	25.85±4.02
			Pit	2	21	7	59.7±8.7	24.6±2.9
YoshidaH	2013	12 weeks	Ato	10	21	9	61.5±7.9	23.8±3.9
			Ros	10	950	492	60.3±10.3	25.7±3.7
ZhuJR	2007	12 weeks	Ato	10	472	235	60.8±10.1	25.5±3.6
			Pit	1	7	7	12.0±1.4	19.0±4.4
HaradaShiba M	2015	52 weeks	Pit	2	7	7	11.6±1.8	18.3±2.2

m(se)/m±sd: Mean (standard error)/mean±standard deviation, Ato: Atorvastatin, Ros: Rosuvastatin, Pit: Pitavastatin, Pra: Pravastatin, Sim: Simvastatine, NA: Not available

name of the first author, year of publication, case number, age, sex and body mass index (BMI), follow-up time, methods of intervention, kinds of statin, dose, TC, LDL-C, HDL-C, TG, Apo B and Apo A1 (change %). Subsequently, the risk of bias was assessed according to the recommendations of the Cochrane collaboration.

Statistical analysis: The non-programming software Aggregate Data Drug Information System (ADDIS) (version 1.16.5), was used to perform Bayesian network meta-analysis and compare treatments using the Markov Chain Monte Carlo (MCMC) method[18,19]. All data are presented as Means±Standard Deviation (M±SD) or 95% confidence interval (CIs). A random-effects model was used in all test and node-splitting analyses were used to assess inconsistencies in network meta-analysis[20]. The model was considered consistent when $p>0.05$ and convergence in the model was identified according to Potential Scale Reduction Factor (PSRF) using Brooks-Gelman-Rubin method. In general, PSRF that are close to 1 indicate good convergence[21]. Finally, it is evaluated ranking probabilities of drugs to identify the best therapy for hypercholesterolemia.

Table 2: Indices of hypercholesterolemia are listed with drug names and doses

Authors	Groups	Dose (mg)	N	TC change (%)	LDL-C change (%)	HDL-C change (%)	TG change (%)	Apo B change (%)	Apo A1 change (%)
BertoliniS	Ato	10	222	-25 (0.7)	-35 (0.9)	6 (0.9)	-17 (1.9)	-27 (0.9)	7 (0.9)
	Pra	20	77	-17 (1.1)	-23 (1.4)	8 (1.5)	-9 (3.1)	-16 (1.4)	11 (1.4)
	Ros	5	390	-29.6 (0.5)	-41.9 (0.7)	8.2 (0.6)	-16.4 (1.3)	-32.7 (0.6)	6.0 (0.6)
BlasettoJW1	Ros	10	389	-33.0 (0.5)	-46.7 (0.7)	8.9 (0.6)	-19.2 (1.3)	-36.5 (0.6)	7.3 (0.6)
	Ato	10	393	-26.7 (0.5)	-36.4 (0.7)	5.5 (0.6)	-17.6 (1.3)	-29.0 (0.6)	4.1 (0.6)
	Ros	5	243	-29.1 (0.7)	-40.6 (0.9)	6.9 (0.8)	14.9 (1.8)	-32.3 (0.8)	5.4 (0.8)
	Ros	10	231	-34.0 (0.7)	-48.1 (0.9)	9.1 (0.8)	-20.2 (1.9)	-37.9 (0.8)	5.3 (0.9)
BlasettoJW2	Sim	10	250	-25.1 (0.6)	-35.7 (0.9)	6.2 (0.8)	-12.2 (1.8)	-28.0 (0.8)	4.8 (0.8)
	Pra	20	255	-19.2 (0.6)	-27.1 (0.9)	6.2 (0.8)	-12.4 (1.8)	-20.6 (0.8)	4.2 (0.8)
	Ros	10	482	NA	NA	6.3 (0.7)	-18.3 (1.6)	NA	NA
	Ato	10	140	NA	NA	5.1 (1.3)	-16.4 (2.7)	NA	NA
BotsAFE	Sim	20	156	NA	NA	3.7 (1.2)	-15.9 (2.6)	NA	NA
	Pra	40	169	NA	NA	2.4 (1.1)	-7.3 (2.4)	NA	NA
	Ros	5	121	-28.0 (1.0)	-39.1 (1.3)	8.2 (1.2)	-17.6 (2.5)	-31.1 (1.2)	4.2 (1.2)
	Ros	10	115	-33.4 (1.0)	-47.4 (1.3)	11.9 (1.2)	-21.5 (2.5)	-37.3 (1.2)	5.9 (1.2)
BrownWV	Pra	20	116	-18.5 (1.0)	-26.5 (1.3)	8.3 (1.2)	-11.4 (2.5)	-20.3 (1.2)	4.6 (1.2)
	Sim	20	120	-23.8 (1.0)	-34.6 (1.3)	8.8 (1.2)	-10.2 (2.5)	-26.7 (1.2)	5.2 (1.2)
	Ros	10	521	-32.6 (11.7)	-47.5 (15.2)	10.3 (15.7)	NA	-37.4 (13.1)	6.4 (13.8)
	Ato	10	240	-26.6 (0.7)	-38.5 (0.9)	8.0 (1.0)	NA	-30.4 (0.8)	3.7 (1.0)
CheungRC	Ato	20	299	-30.8 (0.8)	-44.0 (1.0)	5.7 (1.0)	NA	-30.4 (0.8)	2.6 (0.8)
	Sim	20	250	-25.6 (0.8)	-37.4 (1.0)	8.4 (1.2)	NA	-28.9 (0.9)	5.6 (1.0)
	Pra	40	253	-21.9 (0.7)	-32.4 (0.9)	7.3 (1.0)	NA	-25.2 (0.9)	4.6 (0.9)
	Ato	10	132	-29 (0.9)	-37 (1.1)	7 (1.2)	-23(2.1)	-34 (1.0)	NA
DartA	Sim	10	45	-24 (1.4)	-30 (1.7)	7 (1.8)	-15(3.3)	-30 (1.6)	NA
	Lov	10	167	-15.0±9.2	-21.6±12.3	4.9±12.3	-6.4±28.4	NA	NA
	Lov	20	164	-19.1±8.6	-27.3±10.7	5.7±12.0	-5.7±29.7	NA	NA
DavidsonMH	Lov	40	169	-22.4±9.1	-31.8±12.2	6.1±10.4	-11.3±25.3	NA	NA
	Flu	20	170	-13.2±9.9	-18.8±12.7	3.5±11.0	-3.3±25.4	NA	NA
	Flu	40	167	-16.5±9.7	-22.6±12.9	4.3±13.4	-11.4±28.2	NA	NA
DavidsonM	Ros	5	129	-28 (1.0)	-40 (1.3)	13 (1.0)	-17 (2.4)	-31 (1.2)	7 (1.1)
	Ros	10	130	-30 (1.0)	-43 (1.3)	12 (1.0)	-19 (2.4)	-33 (1.2)	7 (1.1)
	Ato	10	128	-25 (1.0)	-35 (1.3)	8 (1.0)	-19 (2.4)	-26 (1.2)	3 (1.1)
	Ros	10	183	-31 (1)	NA	NA	-19 (2)	-34 (1)	NA
DeedwaniaPC	Ros	20	171	-35 (1)	NA	NA	-22 (2)	-38 (1)	NA
	Ato	10	180	-28 (1)	NA	NA	-20 (2)	-30 (1)	NA
	Ato	20	175	-33 (1)	NA	NA	-19 (2)	-37 (1)	NA
	Ato	10	109	-30.1±9.7	-37.0±11.3	5.7±13.0	NA	-37.7±12.0	NA
FarnierM	Sim	10	54	-23.0±8.1	-28.9±9.2	2.2±15.3	NA	-31.9±9.8	NA
	Ato	10	35	-27.5±13.9	-38.6±19.6	12.6±59.4	-15.8±41.9	NA	NA
KadikoyluG	Sim	10	26	-24.6±16.8	-33.6±22.3	-0.6±18.0	2.0±56.7	NA	NA
KurabayashiM	Ato	10	205	-2.2±10.3	-1.2±14.7	-1.7±11.7	5.2±43.5	NA	NA
	Ros	5	198	-3.3±11.6	-6.0±17.0	0.1±12.2	12.9±48.2	NA	NA
LaksT	Ros	10	334	-30.41 (0.88)	-38.79 (1.27)	0.66 (1.14)	-14.47 (1.86)	NA	NA
	Sim	20	170	-25.27 (1.09)	-32.03 (1.37)	2.26 (1.47)	-14.43 (2.45)	NA	NA
	Pra	40	21	-21.5±11.5	-29.1±13.4	7.7±15.4	-20.5±30.5	NA	NA

Table 2: Continue

Authors	Groups	Dose (mg)	N	TC change (%)	LDL-C change (%)	HDL-C change (%)	TG change (%)	Apo B change (%)	Apo A1 change (%)
LeeWJ	Pra	10	19	-9.4±15.2	-14.4±19.2	8.8±13.4	-11.8±37.2	NA	NA
LiuPY	Pit	2	112	-27.3±10.0	-35.0±14.1	1.7±11.9	-18.1±32.9	-26.1±11.9	0.6±14.3
	Ato	10	113	-28.7±9.1	-38.4±12.8	1.8±11.5	-19.1±26.4	-30.1±14.0	-0.2±9.4
	Ros	10	174	-32 (1)	NA	NA	-20 (2)	-36 (1)	4 (1)
	Ros	20	167	-35 (1)	NA	NA	-18 (2)	-40 (1)	4 (1)
LloretR	Ato	10	161	-26 (1)	NA	NA	-14 (2)	-29 (1)	4 (1)
	Ato	20	161	-31 (1)	NA	NA	-22 (2)	-36 (1)	2 (1)
	Ros	5	159	NA	-47.8±15.5	7.2±20.7	-13.0±41.6	NA	NA
NoharaR	Pra	10	155	NA	-21.2±14.1	5.9±16.9	-7.8±53.7	NA	NA
	Ros	5	135	-32 (1.0)	-46 (1.3)	6 (1.3)	-15 (2.5)	NA	NA
OlssonAG	Ros	10	132	-35 (1.0)	-50 (1.3)	8 (1.3)	-19 (2.5)	NA	NA
	Ato	10	139	-28 (0.9)	-39 (1.2)	6 (1.2)	-16 (2.4)	NA	NA
	Ros	5	119	-30 (0.9)	-42 (1.3)	6 (1.2)	-12 (2.9)	-33 (1.2)	7 (1.3)
	Ros	10	111	-34 (1.0)	-49 (1.3)	7 (1.3)	-18 (3.0)	-40 (1.2)	5 (1.3)
PaolettiR	Pra	20	136	-20 (0.9)	-28 (1.2)	4 (1.2)	-13 (2.7)	-21 (1.1)	4 (1.2)
	Sim	20	129	-26 (0.9)	-37 (1.2)	4 (1.2)	-14 (2.8)	-30 (1.1)	4 (1.2)
	Pit	2	49	-26.9±8.9	-38.2±11.6	8.3±13.4	-29.8±20.6	NA	NA
ParkS	Sim	20	46	-28.5±8.7	-39.4±12.9	3.6±16.2	-17.4±36.9	NA	NA
SansanayudhN	Pit	1	50	-27.55±8.06	-37.37±11.37	2.76±17.94	-10.37±38.92	NA	NA
	Ato	10	50	-32.31±8.37	-45.75±10.60	-0.41±11.41	-7.06±36.33	NA	NA
	Pit	2	88	NA	-33.0±16.1	8.2±17.1	-7.1±40.4	-28.2±13.9	5.1±13.2
SasakiJ	Ato	10	85	NA	-40.1±13.5	2.9±14.6	-14.6±49.2	-35.1±12.1	0.6±11.4
SchwartzGG	Ros	5	127	29.1 (0.8)	39.8 (1.1)	6.6 (1.0)	17.4 (2.2)	31.5 (1.1)	5.5 (1.2)
	Ros	10	128	-33.9 (0.8)	-47.1 (1.1)	7.7 (1.0)	-19.8 (2.2)	-36.4 (1.0	7.0 (1.2)
	Ato	10	127	-26.8 (0.8)	-35.0 (1.1)	2.7 (1.0)	-17.8 (2.2)	-28.3 (1.1)	3.6 (1.2)
	Ros	5	45	-25.0 (1.6)	-37.6 (2.1)	11.0 (1.7)	-12.6 (3.7)	-32.5 (2.0)	9.4 (1.6)
ShepherdJ	Ros	10	44	-31.3 (1.6)	-49.3 (2.1)	7.9 (1.7)	-8.9 (3.7)	-37.8 (1.9)	8.2 (1.5)
	Pit	2	52	-25.7±10.4	-36.8±14.9	0.43±13.1	NA	-32.4±13.4	-0.7±10.1
TaniS	Ato	10	52	-26.5±10.1	-36.6±15.6	2.7±11.2	NA	-29.5±11.9	7.2±10.8
	Ros	10	40	-36.76±13.49	-48.22±19.06	8.60±18.42	-20.95±18.03	NA	NA
WongwiwatthananukitS	Ros	5	40	-28.08±10.65	-38.83±12.42	5.79±18.73	-8.59±26.80	NA	NA
	Pit	2	21	-30.4±8.5	-42.8±10.9	9.2±13.5	-12.6±31.4	-35.0±9.8	8.5±13.3
YoshidaH	Ato	10	21	-32.0±6.5	-44.1±8.7	3.8±10.7	-20.2±32.9	-38.9±6.8	3.1±10.8
	Ros	10	515	-34.2 (0.66)	-47.5 (0.90)	0.7 (0.88)	-13.5 (1.60)	NA	NA
ZhuJR1	Ato	10	267	-29.6 (0.87)	-40.2 (1.18)	-1.6 (1.15)	-11.8 (2.11)	NA	NA
	Ros	10	433	-23.1 (1.07)	-33.9 (1.51)	1.3 (1.23)	-1.2 (2.94)	NA	NA
ZhuJR2	Ato	10	204	-16.3 (1.29	-24.0 (1.83)	1.5 (1.49)	0.4 (3.55)	NA	NA
Harada-Shiba M	Pit	1	7	-17.6±9.7	-24.3±10.3	4.9±10.0	3.5±34.0	NA	NA
	Pit	2	7	-27.3±4.3	-32.2±5.9	-3.8±7.5	-18.5±28.4	NA	NA

1: Lipid-lowering therapy, 2: Switched, Change (%): Percent change from base line, Values obtained by Mean±Standard deviation (M±SD)

RESULTS

Quality evaluation displayed that all 28 studies were of relatively high quality (Fig. 2a). However, blinding of participants and personnel (performance bias) and blinding of outcome assessments (detection bias) were not mentioned in many studies, potentially introducing a source of bias (Fig. 2b).

Comparative effects of statins on TC levels: Node-splitting analysis indicated sufficient consistency (p>0.05) and PSRF ranged from 1.00-1.02. Thus, a consistency model was used for meta-analysis. As shown in Fig. 3a, regiments of Pit at 2 mg doses had the highest probability of reducing TC levels followed by those of Ros at 20 mg doses. The effects of 2 mg Pit regimens differed significantly from those of 20 mg Pra (p = 0.003), 10 mg Sim (p = 0.020), 10 mg Ato (p = 0.006). 20 mg Ros were significantly different from those of 20 mg Praregimens (p = 0.040).

Comparative effect of statins on TG levels: Treatments with Pit at 2 mg doses had the highest probability of reducing TG levels (Fig. 3b), followed by those with Pit at 1 mg and then Ros at 20 mg. The effects of 2 mg Pit regimens were significantly superior to those of 20 mg Pra (p = 0.006), 10 mg Pra (p = 0.048), 40 mg Pra (p = 0.002), 10 mg Sim (p = 0.008) and Sim 20 mg (P = 0.049). No significant differences were identified between the effects of 1 mg Pit and those of other drugs. However, 20 mg Ros regimens had significantly greater efficacy than40 mg Pra (p = 0.001), Ros 5 mg (p = 0.040), Sim 10 mg (p = 0.002) and Sim 20 mg (p = 0.030).

Comparative effects of statins on percent changes in LDL-C levels: In assessments of consistency, node-splitting analysis was used. p>0.05 and PSRF ranged from 1.00-1.01, warranting use of the consistency model. As shown in Fig. 3c, 10 mg Ros regimens had the highest probability of reducing percent changes in LDL-C levels and were significantly superior to the drug regimens (p<0.05).

Comparative effects of statins on percent changes in HDL-C levels: As shown in Fig. 3d, 1 mg Pit had the highest probability of increasing changes in HDL-Clevels followed by 10 mg Ros regimens. In addition, the efficacy of 1 mg Pit significantly differed from that of 20 mg Ato (p = 0.020) and that of 10 mg Ros doses significantly differed from that of 10 mg Ato (p<0.001), 20 mg Ato (p = 0.001), 20 mg Pra (p = 0.004), 40 mg Pra (p = 0.001), 10 mg Sim (p = 0.002) and 20 mg Sim regimens (p = 0.006).

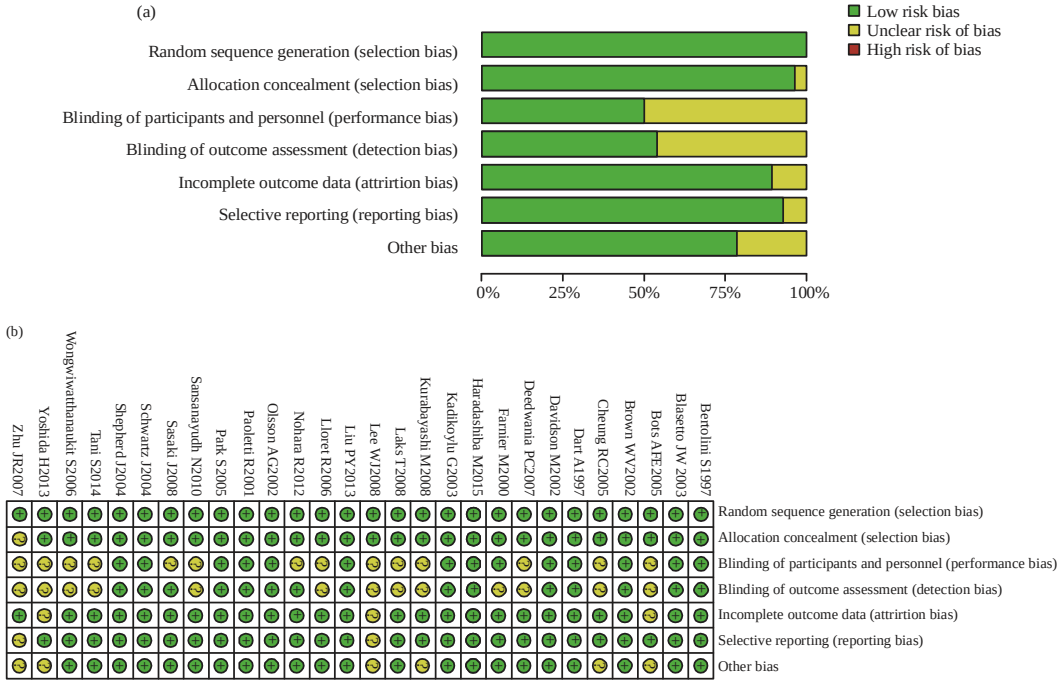

Fig. 2(a-b): (a) Quality evaluation of included studies was performed according to the recommendations of the Cochrane collaboration (b) Blinding of participants and personnel (performance bias) and blinding of outcome assessments (detection bias), introducing a source of bias

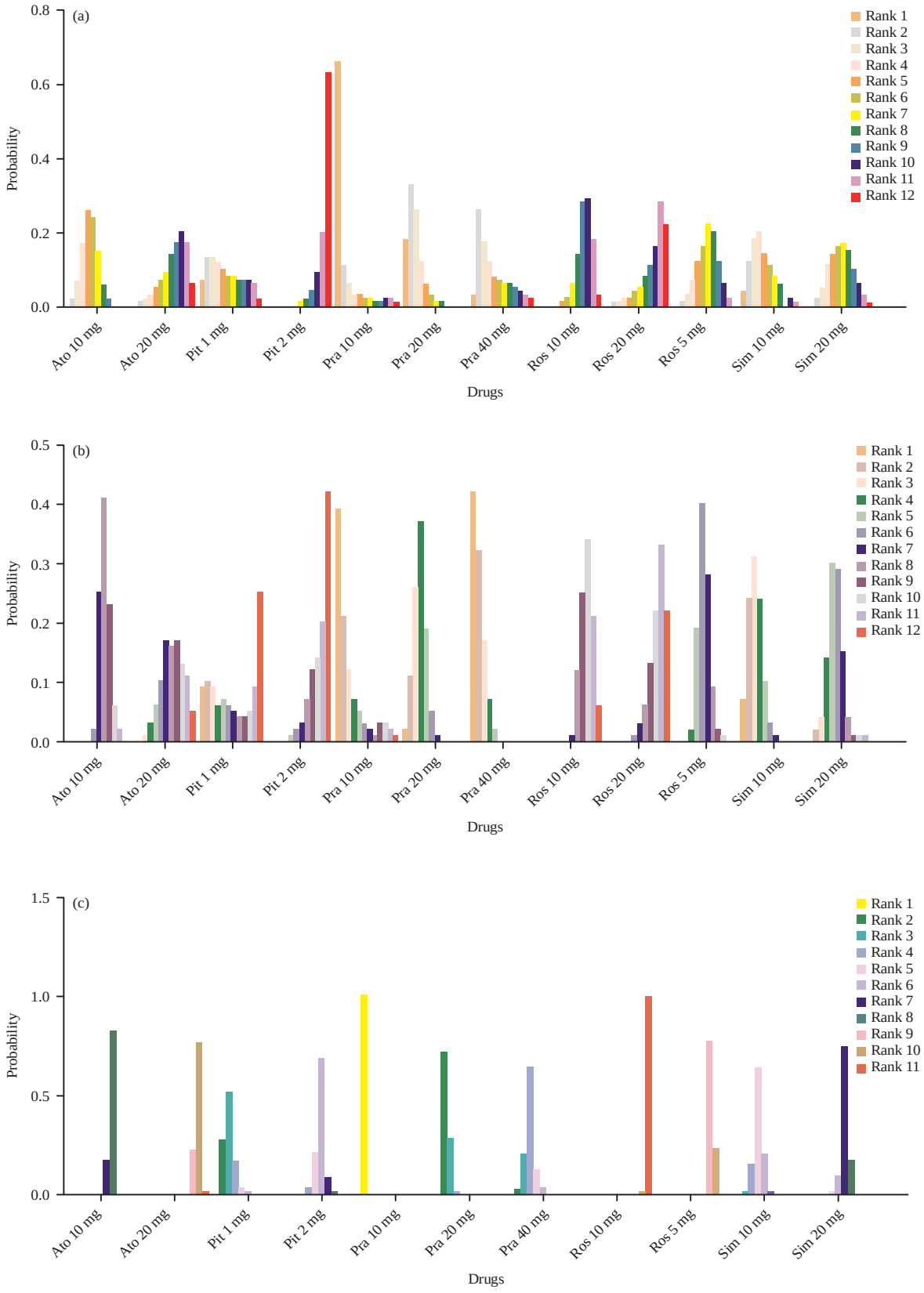

Fig. 3(a-f): Continue

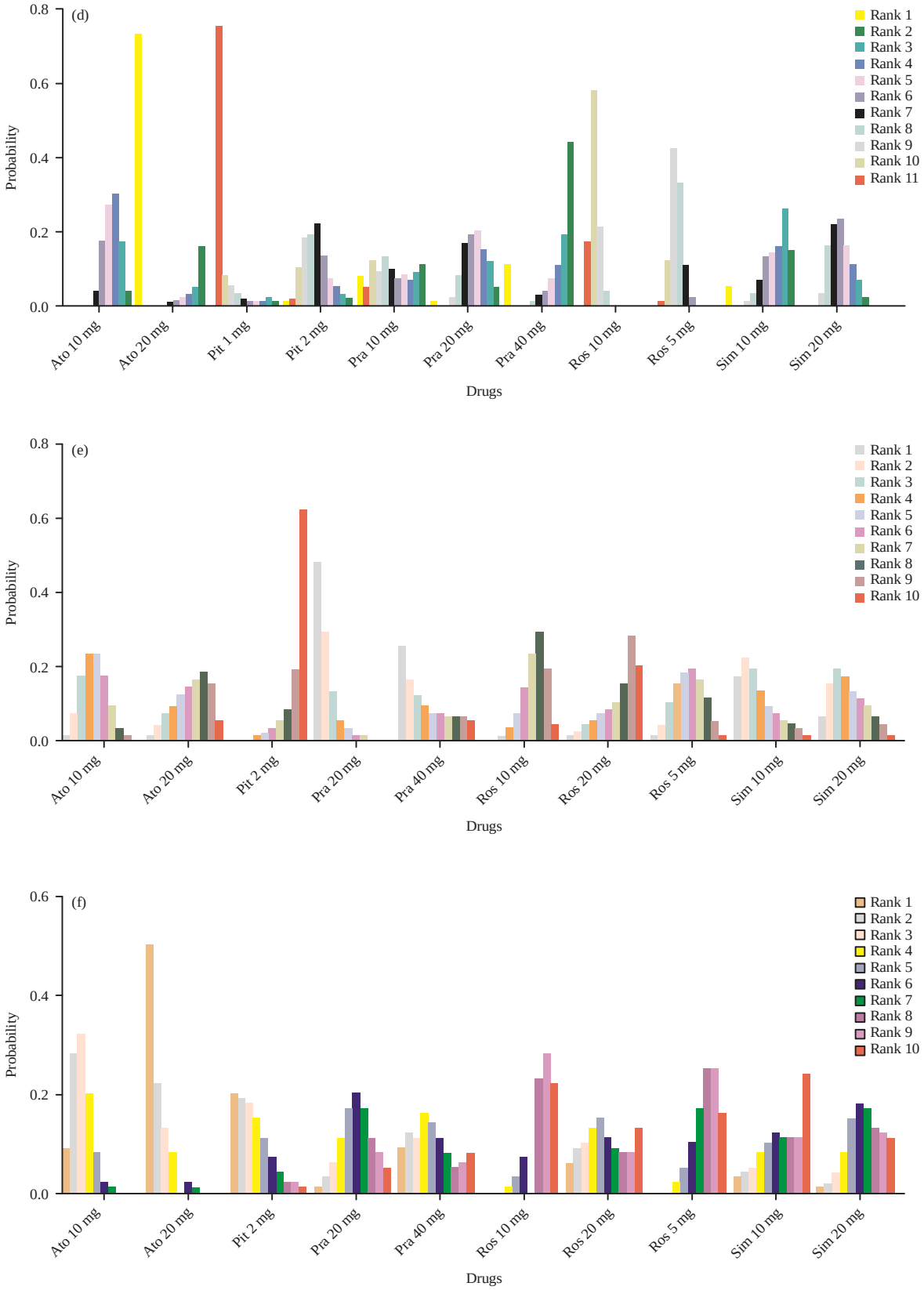

Fig. 3(a-f): Statins were ranked according to the probability of efficacy as treatments for hypercholesterolemia on (a) TC, (b) TG, (c) LDL-C, (d) HDL-C, (e) Apo B and (f) Apo A1

Comparative effects of statins on Apo B levels: Among the present statins, regimens of 2 mg Pit had the highest probability of reducing changes in Apo B levels followed by regimens of 20 mg Ros (Fig. 3e). Moreover, the effects of 2 mg Pit were significantly different f rom those of 10 mg Ato ($p = 0.030$) and Pra 20 mg ($p = 0.010$). However, no significant differences were identified between the effects of 20 mg Ros and other drugs ($p>0.05$).

Comparative effects of statins on Apo A1 levels: Although the highest probability of increasing changes in Apo A1 levels were achieved with 10 mg Ros followed by 10 mg Sim (Fig. 3f).

DISCUSSION

In the present systematic review, 28 studies from global databases met the inclusion criteria and contained data from a total of 12855 patients with hypercholesterolemia. Subsequent network meta-analysis showed that TC levels are significantly reduced in patients with hypercholesterolemia receiving 2 and 20 mg doses of Pit and Ros, ($p<0.05$), respectively. However, although 2 mg Pit, 1 mg Pit and 20 mg Ros regimens reduced TG levels. 10 mg Ros regimens had the highest probability of reducing the changes in LDL-C levels. Moreover, the probability of increasing changes in HDL-C levels was greater with 1 mg Pit and 10 mg Ros regimens, whereas 2 mg Pit and 20 mg Ros had the highest probability of reducing the changes of Apo B. However, although 10 mg Ros and 10 mg Sim regimens were more likely to increase Apo A1 levels, no significant differences in the levels with other drugs were identified.

Multiple studies show that statins decreased the levels of TC, TG, LDL-C and Apo B levels and significantly increase HDL-C and Apo A1 levels in patients with hypercholesterolemia[22-49]. In a study by Avis[50], the efficacy and safety of statin therapies were assessed in children with heterozygous familial hypercholesterolemia but the reported effects were inconsistent with the findings of the present meta-analysis. For example, at doses of 10-20 mg Ato reduced the levels of LDL-C by 39%, TC by 30% and Apo B by 34%, whereas, at doses of 40 mg, Pra only increased HDL-C levels by 9% and Apo A1 levels by 5%[50]. In contrast, significantly reduced TC, TG and Apo B levels following treatments with 2 mg Pit or 20 mg Ros and 10 mg Ros treatments had the highest probability of reducing changes in LDL-C levels and increasing HDL-C and Apo A1 levels. These discrepancies likely reflect differing patients groups in the present studies compared with those in the study by Avis[50], which only included children with heterozygous familial hypercholesterolemia. Additionally, Yokote *et al.*[51] found that 2 mg Pit and 10 mg Ato regimens reduced TC, TG and LDL-C in Japanese patients with hypercholesterolemia. In particular, 2 mg Pit decreased Apo B levels with an efficacy equal to that of 10 mg Ato in patients with primary hypercholesterolemia[52,53]. Treatments with 10 mg Ros significantly decreased LDL-C levels and increased HDL-C levels comparison with those with 20 mg Sim 20 and 40 mg Pra[54]. Moreover, treatments with 10 mg Ros reduced LDL-C levels more than those with 20 mg Ato, whereas, HDL-C levels were similarly increased by both treatments[55]. These data were similar to the findings of the present meta-analysis, which indicated that treatments with10 mg Ros show the highest chances of reducing the percent changes of LDL-C levels and increasing HDL-C levels. Previously, treatments with Ros at 10 or 20 mg were effective and safe in patients at high risks of CHD and acted by reducing TC, LDL-C and Apo B levels[56]. Ros also reduced TC with significantly greater efficacy than the other statins and reduced TG levels significantly more than 10-80 mg treatments with Sim and Pra[57]. The present meta-analysis provides strong evidence of the relative efficacies of statins types and doses and could be used to inform future selections were helpful for patients statin drugs patients with hypercholesterolemia. However, (1) The subgroup analyses were not performed due to the absence of relevant data lacked in some included studies, (2) Numbers eligible studies were low and other indexes were insufficiently reported to form a closed cycle network meta-analysis, (3) ADDIS is a non-programming software with limited facilities and (4) 'No' safety data for statins were investigated.

CONCLUSION

Based on the present data from 28 studies, 2 mg Pit or 10 and 20 mg Ros ameliorated hypercholesterolemia with greater efficacy than those with other statin drugs. The present evidence will inform further investigations and clinical selections of statins for the treatment of patients with hypercholesterolemia.

SIGNIFICANCE STATEMENTS

The results of meta-analysis show that 2 mg Pit and 10 and 20 mg Ros produce better outcomes than other statin drugs in patients with hypercholesterolemia. These findings provide important information for the selection of statin drugs for the treatment of the patients with hypercholesterolemia.

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