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Secondary prevention of major cerebrovascular events with seven different statins: a multi-treatment meta-analysis

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Background: Statins have been recommended for the use in atherosclerotic cardiovascular diseases, but different statins have distinct pharmacological characteristics. This multi-treatment meta-analysis aimed to evaluate the efficacy of seven statins in the secondary prevention of major cerebrovascular events (CVEs).

Methods and analyses: The PubMed, Embase, Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials were searched to identify studies published between January 1, 2011, and June 30, 2016. The included randomized controlled trials investigated the efficacy of lovastatin, atorvastatin, fluvastatin, simvastatin, pitavastatin, pravastatin or rosuvastatin in the secondary prevention of CVEs. The primary outcomes were CVEs; the secondary outcomes were all-cause death, fatal stroke and nonfatal stroke. Meta-analysis and network meta-analysis were used for data synthesis.

Results: A total of 42 studies with 82,601 patients were included for analysis. In the secondary prevention of cardiovascular diseases, the major CVEs in pravastatin (risk ratio [RR] 0.87, 0.76–0.99)- and atorvastatin (RR 0.59, 0.49–0.72)-treated patients reduced significantly compared with controls. Indirect comparisons with network meta-analysis showed that RR was 0.60 (0.40–0.92) for atorvastatin compared with rosuvastatin. Compared to controls, the all-cause death was reduced by 12% in statins-treated patients (RR 0.88, 0.81–0.96). Indirect comparisons with network analysis showed a significant difference in the nonfatal stroke between fluvastatin-treated patients and lovastatin-treated patients (RR 0.28, 0.07–0.95).

Conclusion: Different statins have distinct pharmacological characteristics, and there are differences in statistical and clinical outcomes among several statins.

Keywords: atherosclerotic cardiovascular disease, cerebrovascular event, randomized, controlled trial, primary outcome

Introduction

In the past century, the disease profile changed significantly worldwide. Atherosclerotic cardiovascular disease (ASCVD) accounted for 1/10 of causes of death in early 1900s, but it has been the leading cause of death worldwide so far, accounting for one-third of causes of death. The prevalence of ASCVD increases with age. In addition, its prevalence further elevates in late life with the reduced mortality related to infection and malnutrition. Thus, ASCVD is affecting the decision making of world public health policy. Ischemic stroke is one of the most important clinical types of ASCVD and has a high recurrence rate. The ischemic stroke-related neurological impairment and subsequent emotional dysfunction and social dysfunction bring a great burden to the society and the families of these patients. Currently, controlling the serum lipid

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marker (low-density lipoprotein cholesterol [LDL-C]) is crucial to reduce the recurrence rate of transient ischemic attack (TIA) or ischemic stroke.[1]

To date, statins (3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor) have been widely used in the lipid-lowering therapy. On the basis of findings from randomized controlled trials (RCTs), statins have been a major strategy in reducing the risk for ASCVD.[2] Several clinical trials have shown that statins can significantly reduce serum LDL-C and effectively decrease the risk for stroke.[3] Statins can reduce the incidence of major cardiovascular events, and thus, they have been recommended for the secondary prevention of ischemic stroke.[1,4,5] In addition, there is evidence showing that high-dose statins are better to reduce the risk for stroke compared to standard-dose statins.[6] However, there is still controversy on the clinical effects of different statins on the outcomes of ASCVD. A study indirectly compared influence of atorvastatin, pravastatin and simvastatin on the cerebrovascular events (CVEs), but it was a placebo-control study with a small sample size and there were active comparator trials in this study.[7] The network meta-analysis was conducted to evaluate the RCT that investigated the effects of primary and secondary prevention with atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin or simvastatin in CVD patients, but it excluded head–head evaluation of different statins. Although another network meta-analysis used head–head evaluation, but pitavastatin was not investigated.[8] Moreover, the incidence of cerebrovascular diseases was not a primary outcome in previous head–head network meta-analysis.[9–12]

Different statins have distinct pharmacological characteristics. As the number of patients in need for statin therapy continues to increase, information regarding the relative efficacy of statins is needed for better decision making. Meta-analysis with a large amount of updated data may provide true and strict clinical evaluation and accurately assess the therapeutic efficacy. This meta-analysis aimed to systemically evaluate the efficacy of statins in clinical studies that were conducted between statins-treated patients and routine controls or placebo controls and different statin-treated patients. In addition, the role of different statins in the secondary prevention of major CVEs was evaluated in patients with cardiovascular diseases.

Methods and analyses

Systematic review methods

We searched PubMed, Embase, Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials to identify studies published between January 1, 2011, and June 30, 2016. We identified the studies prior to January 2011 from the bibliography of previously published systematic literature reviews and meta-analyses. We used the search terms "lovastatin", "atorvastatin", "fluvastatin", "simvastatin", "pitavastatin", "pravastatin", "rosuvastatin", "cardiovascular disease" and "HMG-CoA reductase inhibitors/therapeutic use". Two reviewers (PZ and DW) independently performed abstract, title and full-text screening and entered data into a data extraction form. A third reviewer (YW) approved the study selection.

The inclusion criteria were as follows: 1) open and double-blind RCTs were included; 2) head–head studies or those with placebo, diet or routine therapy as a control were included; 3) patients had cardiovascular diseases; 4) the number of patients was >60; 5) atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin or simvastatin was used for >4 weeks and 6) the primary outcomes were major CVEs, and the secondary outcomes were all-cause death, fatal stroke and nonfatal stroke. The major CVEs in this study included fatal stroke, nonfatal stroke and TIA; the nonfatal stroke did not include TIA. In addition, clinical studies in which there were patients with renal dysfunction were excluded. The study characteristics, including methods, participants, interventions and outcomes, were extracted from each study (Supplementary material).

Statistical analysis

To summarize all available evidence, we conducted both direct and network meta-analyses. First, we did traditional pairwise meta-analysis for direct comparisons between two treatment arms by Review Manager 5.1. In the conventional direct meta-analysis, two or more studies that compared two interventions of interest were statistically combined. We calculated the pooled risk ratio (RR) with a 95% CI. Heterogeneity was assessed using the Cochran's Q and I^2 statistics. For the Q statistic, a P-value >0.10 and for the χ^2 test and for the I^2 statistic, an I^2 value <25% were interpreted as low-level heterogeneity. A pooled effect was calculated with a fixed-effect model when there was no statistically significant heterogeneity; otherwise, a random-effect model was used.

A network meta-analysis was conducted using a Bayesian Markov Chain Monte Carlo method and fitted in R package. Analytical results are presented as RR with 95% credible intervals (CrIs). The RR was estimated using the median of the posterior distribution, and 95% CrIs were obtained based on the 2.5th and 97.5th percentiles of the

posterior distribution, which can be interpreted in the same way as conventional 95% CIs. Rankings for the treatment efficacy of the interventions were originally derived from Monte Carlo simulations and presented as the probability of possessing a specific ranking; the probabilities of different rankings of the same treatment were summed to 100%. Pooled results were considered as statistically significant for $P<0.05$ or if the 95% CI (CrI) did not contain the value 1. In this study, the patient samples from different statins were weighted in both pairwise meta-analysis and network meta-analysis.

Results

General data

A total of 20,770 studies potentially related to the topic were identified, of which 607 studies were included for final analysis and 20,163 unrelated studies that did not meet the inclusion criteria were excluded (Figure 1). In addition, 42 clinical trials published between 1994 and 2016 were included for network meta-analysis. The general information of these studies is presented in Table 1. In the studies included for network meta-analysis, 82,601 subjects received treatment with one of seven statins and 24.1% subjects were female. Of these studies, treatment with one statin was compared with control (placebo treatment, routine treatment or diet treatment) in 32 studies. Of these 32 studies, pravastatin was evaluated in 13 studies,[13–25] atorvastatin in seven,[26–32] lovastatin in three,[33–35] simvastatin in three,[36–38] fluvastatin in three,[39–41] rosuvastatin in two[42,43] and pitavastatin in one.[44] In 10 studies, the treatment with one statin was compared with therapy of another statin.[45–54] In these 10 studies, a statin was used at two doses in one study,[54] the head–head study of atorvastatin and pravastatin was found in four studies,[45,46,48,51] head–head study of atorvastatin and rosuvastatin was found in three studies[49,50,54] (rosuvastatin at two doses was used in one study), head–head study of atorvastatin and simvastatin was found in two studies[52,53] and head–head study of rosuvastatin and simvastatin was found in one study.[47] The follow-up period ranged from 143 weeks to 317 weeks. In five studies, the follow-up period was <24 weeks. Figure 2 shows the meta-analysis of seven statins in the prevention of major CVEs.

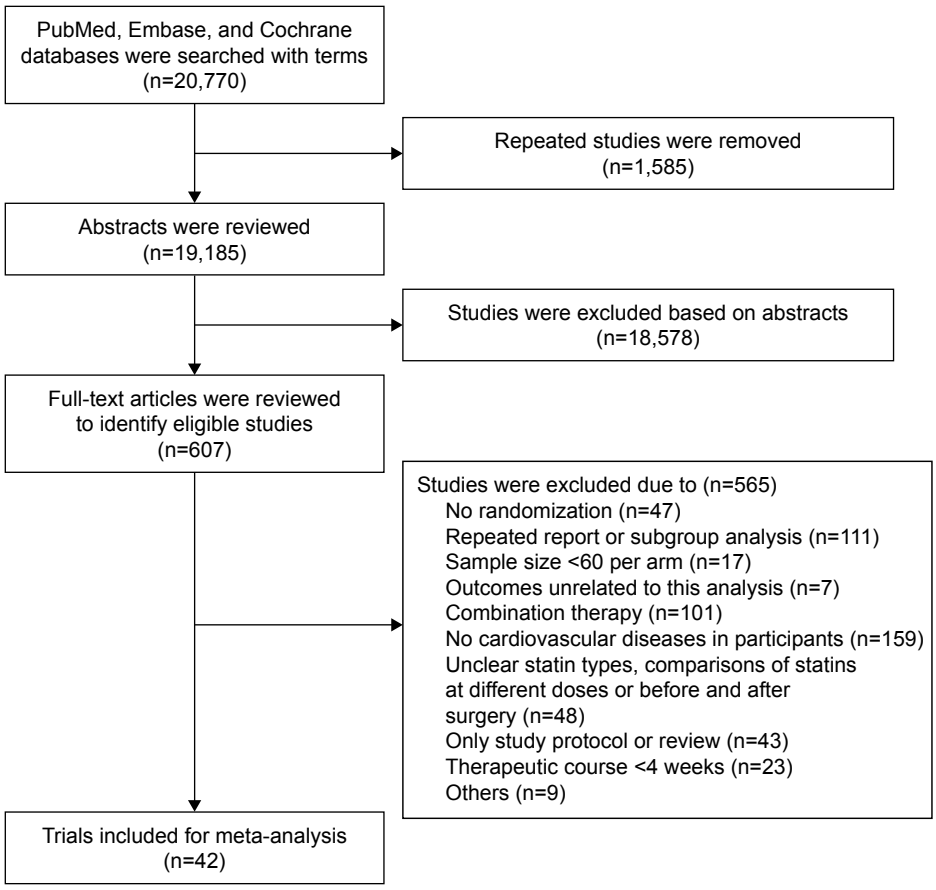

Figure 1 Flowchart of study inclusion.

Table 1 Characteristics of studies included

Year	Trial name	Mean age, years	% woman	Treatment	Number randomized	Major cerebrovascular events, n	All-cause death, n	Fatal stroke, n	Nonfatal stroke, n	TIA, n
1993	MARS[33]	58	9	Lovastatin	123	NR	2	NR	NR	NR
		58	9	Placebo	124	NR	1	NR	NR	NR
1994	4S[36]	58.6	19	Simvastatin	2,221	124	182	14	95	19
		58.6	18	Placebo	2,223	102	256	12	61	29
1994	MAAS[37]	54.9	12	Simvastatin	193	NR	4	NR	NR	NR
		55.6	11	Placebo	188	NR	11	NR	NR	NR
1994	CCAIT[34]	53	18	Lovastatin	165	0	2	0	NR	NR
		53	19	Placebo	166	0	2	0	NR	NR
1994	LRTS[35]	62	28	Lovastatin	203	0	3	NR	0	NR
		62	29	Placebo	201	1	1	NR	1	NR
1995	PLAC-II[16]	63	15	Pravastatin	75	NR	3	NR	NR	NR
		63	15	Placebo	76	NR	5	NR	NR	NR
1995	REGRESS[17]	56.5	0	Pravastatin	450	NR	5	0	NR	NR
		55.9	0	Placebo	434	NR	7	0	NR	NR
1995	PLAC-I[20]	57	62	Pravastatin	206	0	4	0	0	NR
		57	62	Placebo	202	2	6	0	2	NR
1996	CARE[21]	59	14	Pravastatin	2,081	54	NR	NR	54	NR
		59	14	Placebo	2,078	78	NR	NR	78	NR
1997	PREDICT[15]	58.5	17	Pravastatin	347	1	4	1	NR	NR
		58.2	15.6	Placebo	348	0	1	0	NR	NR
1998	LIPID[13]	62	17	Pravastatin	4,512	169	498	NR	NR	NR
		62	17	Placebo	4,502	204	633	NR	NR	NR
2000	GISSP-P[14]	59.7	13.3	Pravastatin	2,138	20	72	4	16	NR
		60	14.2	Placebo	2,133	19	88	4	15	NR
2000	SCAT[38]	61	13	Simvastatin	230	4	13	NR	4	NR
		61	9	Placebo	230	2	6	NR	2	NR
2001	MIRACL[31]	65	35.5	Atorvastatin	1,538	12	64	3	9	NR
		65	34.1	Placebo	1,548	24	68	2	22	NR
2002	GREACE[27]	58	22	Atorvastatin	800	9	23	NR	9	NR
		59	21	Usual care	800	17	40	NR	17	NR
2002	FLORIDA[39]	61	19	Fluvastatin	265	2	7	2	NR	NR
		60	15	Placebo	275	1	11	1	NR	NR
2002	LIPS[41]	60	15.8	Fluvastatin	844	2	36	2	NR	NR
		60	16.6	Placebo	833	1	49	1	NR	NR
2002	PROSPER – secondary[23]	75.3	51.7	Pravastatin	2,891	135	298	22	116	77
		75.4	51.7	Placebo	2,913	131	306	14	119	102
2003	TREAT TO TARGET[52]	63	24.3	Atorvastatin	556	0	0	0	NR	NR
		62.5	24.8	Simvastatin	537	0	0	0	NR	NR
2004	PROVE IT-TIMI[45]	58.1	22.2	Atorvastatin	2,099	21	46	NR	21	NR
		58.3	21.6	Pravastatin	2,063	21	66	NR	21	NR
2004	PACT[24]	NR	23.5	Pravastatin	1,710	NR	24	NR	NR	NR
		NR	24.3	Placebo	1,698	NR	37	NR	NR	NR
2004	Bae et al[28]	60	37	Atorvastatin	105	1	0	0	1	NR
		60	27	Usual care	100	1	0	0	1	NR
2004	ALLIANCE[30]	61.1	17.8	Atorvastatin	1,217	35	121	35	NR	NR
		61.3	17.7	Usual care	1,225	39	127	39	NR	NR
2004	PCS[19]	59.2	91	Pravastatin	54	3	5	0	3	NR
		59.9	92	Diet	66	4	3	0	4	NR
2004	REVERSAL[51]	NA	NA	Atorvastatin	327	1	1	NR	1	NR
		NA	NA	Pravastatin	327	1	1	NR	1	NR
2005	PCABG[18]	59.6	19.7	Pravastatin	152	1	6	0	1	0
		58.2	11.9	Placebo	151	6	11	1	5	1
2005	IDEAL[53]	61.6	19.2	Atorvastatin	4,439	NR	366	NR	NR	NR
		61.8	19.1	Simvastatin	4,449	NR	374	NR	NR	NR

(*Continued*)

Table 1 (*Continued*)

Year	Trial name	Mean age, years	% woman	Treatment	Number randomized	Major cerebrovascular events, n	All-cause death, n	Fatal stroke, n	Nonfatal stroke, n	TIA, n
2005	Stone et al[32]	NR	14	Atorvastatin	96	1	1	NR	1	NR
		NR	12	Placebo	103	0	0	NR	0	NR
2005	ATHEROMA[25]	NA	NA	Pravastatin	186	5	1	NR	5	NR
		NA	NA	Diet	187	4	2	NR	4	NR
2006	SPARCL[26]	63	39.7	Atorvastatin	2,365	165	216	24	247	153
		62.5	41	Placebo	2,366	311	211	41	280	208
2006	ASPEN – secondary[29]	60.5	38	Atorvastatin	252	7	26	NR	NR	NR
		60.4	37	Placebo	253	9	27	NR	NR	NR
2007	SAGE[46]	72.4	31.2	Atorvastatin	446	NR	6	NR	NR	NR
		72.6	29.9	Pravastatin	445	NR	18	NR	NR	NR
2007	CORONA[42]	73	24	Rosuvastatin	2,514	103	728	14	89	NR
		73	24	Placebo	2,497	115	759	11	104	NR
2008	GISSI-HF[43]	68	23.8	Rosuvastatin	2,285	82	657	38	44	NR
		68	21.4	Placebo	2,289	66	644	29	37	NR
2008	OACIS-LIPID[22]	63.6	26.7	Pravastatin	176	0	3	NR	0	NR
		62.9	19.8	Usual care	177	2	2	NR	2	NR
2009	SPACE	62.1	20.7	Rosuvastatin	633	2	11	NR	2	1
	ROCKET[47]	62.5	20.5	Simvastatin	630	0	16	NR	0	2
2010	FACS[40]	60.9	29.5	Fluvastatin	78	1	1	NR	1	NR
		63.2	34.6	Placebo	78	3	4	NR	3	NR
2010	CENTAURUS[49]	NA	NA	Rosuvastatin	406	3	2	0	3	NR
		NA	NA	Atorvastatin	423	0	4	NR	0	NR
2011	SATURN[50]	57.4	27.1	Rosuvastatin	520	3	NR	NR	3	NR
		57.9	25.6	Atorvastatin	519	2	NR	NR	2	NR
2012	LUNAR[54]	52.9	11.2	Atorvastatin	278	NR	1	NR	NR	NR
		53	15.3	20 rosuvastatin	277	NR	0	NR	NR	NR
		52.8	15.9	40 rosuvastatin	270	NR	2	NR	NR	NR
2013	PEARL[44]	62.9	19.1	Pitavastatin	289	8	27	NR	8	NR
		62.2	17.8	Control	288	9	37	NR	9	NR
2015	ALPS-AMI[48]	65.7	19	Pravastatin	261	10	14	5	5	NR
		66.3	19.6	Atorvastatin	264	5	9	4	1	NR

Abbreviations: TIA, transient ischemic attack; NR, not reported; NA, not applicable.

Comparative benefits of statins on major CVEs: findings of the multiple-treatment meta-analyses

In 32 studies comparing statins treatment and control treatment, major CVEs were reported in 27 studies[13–15,18–23,25–32,34–36,38–44] in which there were 66,007 patients and a total of 2,057 major CVEs. In the secondary prevention of cardiovascular diseases, results showed that pravastatin and atorvastatin could reduce the incidence of major CVEs by 13% and 41%, respectively, compared with the control group, but there was no significant difference between other statins and control (Table 2). In 10 head–head studies,[45–54] the influence of statins on the major CVEs was reported in seven studies,[45,47–52] in which there were 9,565 patients and a total of 69 major CVEs. Paired comparison in network meta-analysis showed a significant difference only between atorvastatin and rosuvastatin (RR 1.7,1.10-2.50).

Comparative benefits of statins on all-cause mortality: findings of the multiple-treatment meta-analyses

The all-cause death was investigated in 40 studies,[13–20,22–49,51–54] in which there were 76,483 patients and 7,328 deaths. Of included studies, statin treatment was compared with control treatment in 31 studies, in which there were 6,391 deaths occurring in 57,354 patients; comparison between two statin treatments was found in 10 studies,[42,45–49,51–54] in which there were 937 deaths occurring in 19,133 patients. Direct meta-analysis showed that the mortality of any cause in statin-treated patients was reduced by 12% compared to the control group (RR 0.88, 0.81–0.96), and a significant

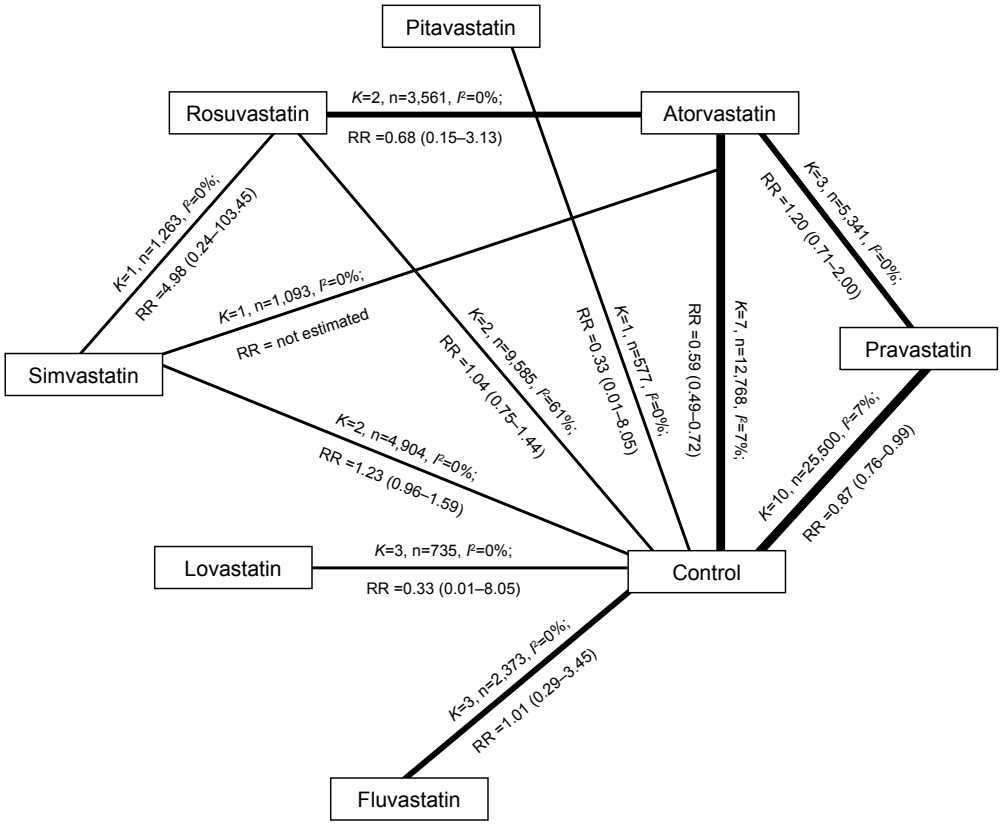

Figure 2 Meta-analysis of seven statins in the prevention of major CVEs.
Notes: Rosuvastatin vs atorvastatin: *K*=2, n=3,561, I^2=0%; RR =0.68 (0.15–3.13); atorvastatin vs simvastatin: *K*=1, n=1,093, I^2=0%; RR = not estimated; rosuvastatin vs control: *K*=2, n=9,585, I^2=61%; RR =1.04 (0.75–1.44); atorvastatin vs pravastatin: *K*=3, n=5,341, I^2=0%; RR =1.20 (0.71–2.00) and atorvastatin vs control: *K*=7, n=12,768, I^2=7%; RR =0.59 (0.49–0.72).
Abbreviations: CVE, cerebrovascular event; RR, risk ratio.

difference was only noted between the pravastatin group and the control group (RR 0.84, 0.76–0.94). Comparison between two treatments showed significant difference between pravastatin and atorvastatin (RR 1.60, 1.17–2.19), but network meta-analysis showed a marked difference only between fluvastatin and lovastatin (RR 3.60, 1.10–14.00; Table 3).

Table 2 Network meta-analysis of prevention of major CVEs: direction comparisons between statin treatment and control treatment as well as different statin treatments

Treatment comparison	RR (95% CI)
Stain treatment vs control treatment	
Pravastatin vs control	0.87 (0.76–0.99)
Atorvastatin vs control	0.59 (0.49–0.72)
Fluvastatin vs control	1.01 (0.29–3.45)
Simvastatin vs control	1.23 (0.96–1.59)
Lovastatin vs control	0.33 (0.01–8.05)
Rosuvastatin vs control	1.04 (0.75–1.44)
Pitavastatin vs control	0.89 (0.35–2.26)
All statins vs control	0.88 (0.71–1.10)
Two different statin treatments	
Pravastatin vs atorvastatin	1.20 (0.71–2.00)
Atorvastatin vs rosuvastatin	0.68 (0.15–3.13)
Rosuvastatin vs simvastatin	4.98 (0.24–103.45)

Abbreviations: CVEs, cerebrovascular events; RR, risk ratio.

Comparative benefits of statins on nonfatal and fatal strokes: findings of the multiple-treatment meta-analyses

Of the studies on pitavastatin, fatal stroke had never been reported. In 19 studies with 41,144 patients,[14,15,17–20,23,26,28,30,31,34,36,39,41–43,48,52] the fatal stroke was reported in 323 patients. In 26 studies,[14,18–23,25–28,31,32,35,36,38,40,42–45,47–51] nonfatal stroke was reported as an outcome, and it was found in 1,529 patients among 49,710 patients included in these studies. Direct meta-analysis showed no significant difference between statin treatment and control treatment as well as between two statin treatments. Table 4 summarizes the results of network meta-analysis of fatal stroke and nonfatal stroke. Our results showed that significant difference was observed in the nonfatal stroke only between atorvastatin and simvastatin (RR 1.9, 1.1–3.7).

Table 3 Network meta-analysis of prevention of major CVEs and death of any cause with seven different statins

Pravastatin	0.73 (0.55–1.0)	1.1 (0.38–3.3)	1.2 (0.82–1.90)	1.3 (0.75–2.10)	2.8 (0.22–93.00)	1.8 (0.55–6.30)	1.1 (0.88–1.40)
1.10 (0.91–1.50)	Atorvastatin	1.5 (0.51–4.5)	1.7 (1.10–2.50)	1.8 (0.97–2.80)	3.8 (0.29–1.3×10^{2})	2.4 (0.73–8.50)	1.5 (1.10–1.90)
1.30 (0.70–2.50)	1.1 (0.61–2.10)	Pitavastatin	1.1 (0.36–3.30)	1.2 (0.36–3.70)	2.5 (0.17–95.0)	1.6 (0.33–7.8)	1.0 (0.35–2.90)
1.00 (0.79–1.60)	0.92 (0.70–1.30)	0.81 (0.43–1.60)	Rosuvastatin	1.10 (0.57–1.80)	2.3 (0.18–7.7)	1.5 (0.44–5.3)	0.92 (0.63–1.3)
1.10 (0.84–1.60)	1.00 (0.75–1.30)	0.88 (0.45–1.70)	1.10 (0.73–1.50)	Simvastatin	2.2 (0.16–72.0)	1.4 (0.40–5.0)	0.85 (0.56–1.4)
0.37 (0.098–1.20)	0.33 (0.09–1.00)	0.29 (0.07–1.10)	0.35 (0.09–1.20)	0.33 (0.09–1.10)	Lovastatin	0.62 (0.02–11.0)	0.39 (0.01–5.0)
1.30 (0.82–2.30)	1.20 (0.72–2.00)	1.00 (0.49–2.20)	1.30 (0.74–2.10)	1.20 (0.70–2.00)	3.60 (1.10–14.00)	Fluvastatin	0.62 (0.18–2.0)
0.96 (0.82–1.20)	0.86 (0.71–1.00)	0.75 (0.41–1.40)	0.93 (0.68–1.20)	0.84 (0.66–1.10)	2.60 (0.83–9.80)	0.72 (0.45–1.10)	Control

Notes: RR is from the comparison of drugs in the rows and lines. The upper data refer to the influence of statins on major CVEs; the lower data refer to the influence of statins on the death of any cause. The underline indicates RR of comparison between drugs in the row and the line has statistical significance.
Abbreviations: CVEs, cerebrovascular events; RR, risk ratio.

Table 4 Network meta-analysis of prevention of fatal stroke and nonfatal stroke with seven different statins

Pravastatin	0.50 (0.24–1.10)	–	0.76 (0.28–1.70)	0.63 (0.16–1.90)	9.3×10^{3} (0.20–2.5×10^{18})	1.9 (0.32–14.0)	0.57 (0.27–1.0)
0.84 (0.53–1.2)	Atorvastatin	–	1.5 (0.57–3.10)	1.3 (0.33–3.40)	1.9×10^{4} (0.36–5.2×10^{18})	3.8 (0.66–26.0)	1.1 (0.57–1.7)
1.1 (0.36–3.3)	1.3 (0.43–4.0)	Pitavastatin	–	–	–	–	–
1.2 (0.73–2.0)	1.4 (1.10–3.70)	1.0 (0.35–3.4)	Rosuvastatin	0.83 (0.23–2.5)	1.3×10^{4} (0.21–3.4×10^{18})	2.5 (0.45–19.0)	0.73 (0.39–1.4)
1.6 (0.85–2.9)	1.9 (1.10–3.7)	1.5 (0.45–4.9)	1.4 (0.67–2.5)	Simvastatin	1.5×10^{4} (0.27–4.3×10^{18})	3.1 (0.46–29.0)	0.90 (0.35–2.6)
1.0 (0.02–58.0)	1.2 (0.02–65.0)	0.95 (0.02–48.0)	0.86 (0.02–51.0)	0.62 (0.01–35.0)	Lovastatin	0.0002 (–1.0×10^{18}–13)	–5.9×10^{5} (–2.1×10^{19}–3.2)
0.65 (0.08–4.5)	0.79 (0.09–5.5)	0.59 (0.06–5.4)	0.56 (0.07–3.9)	0.40 (0.05–3.0)	0.61 (0.006–43.0)	Fluvastatin	3.4 (0.67–24.0)
1.1 (0.81–1.5)	1.3 (0.98–1.9)	0.99 (0.35–2.9)	0.96 (0.60–1.4)	0.67 (0.41–1.2)	1.1 (0.02–58.0)	1.7 (0.25–14.0)	Control

Notes: RR is from the comparison of drugs in the rows and lines. The upper data refer to the influence of statins on fatal stroke; the lower data refer to the influence of statins on the nonfatal stroke. The underline indicates RR of comparison between drugs in the row and the line has statistical significance.
Abbreviation: RR, risk ratio.

Discussion

This meta-analysis was based on 42 studies in which a total of 82,601 subjects randomly received treatment with seven different statins. Statistical and clinical differences were found in several statins. Our results showed that, in the secondary prevention of cardiovascular diseases, the mortality of any cause was reduced by 12% after statin treatment compared to the control treatment; the incidence of major CVEs was reduced by 13% and 41% after treatment with pravastatin and atorvastatin, respectively, compared with the control treatment. Indirect comparison with network meta-analysis showed that rosuvastatin was better than atorvastatin in the prevention of major CVEs and fluvastatin was better than lovastatin in the prevention of nonfatal stroke when statins were used in the secondary prevention of cardiovascular diseases.

Statins have pleiotropic effects, including the lipid-lowering, vasodilation, anti-thrombotic, anti-inflammatory and anti-oxidative effects.[55–62] Animal experiments and clinical studies have shown that statins may exert neuroprotective effects after acute cerebral infarction.[63–65] Our results further confirmed and expanded previous results from meta-analysis. Clinical guideline recommends the use of statins in the secondary prevention of noncardiac stroke.[66] To reduce LDL-C has been one of important strategies in the clinical prevention of cardiovascular events, and undoubtedly statins, are the most effective drugs used to reduce LDL-C. Statins may competitively inhibit hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase, which is a rate-limiting enzyme in the endogenous cholesterol synthesis, and then block the metabolism of intracellular hydroxymaleic acid and reduce the endogenous production of cholesterol, exerting lipid-lowering effect. Although different statins have the identical mechanism in their lipid-lowering effect, the difference in the chemical structure among these statins makes their physical characteristics and internal pharmacokinetics different. SPARCL was the only one study that investigated the influence of statins used for secondary prevention on the TIA and stroke,[26] but we could not expand their results to the use of other statins. In this study, meta-analysis was conducted in the population with cardiovascular diseases who were medicated with statins for the secondary prevention, and results showed difference among several statins. Probably, the actual difference among other statins might not be identified by this meta-analysis.

In this study, the majority of clinical trials included did not fully report the information about the randomization and allocation concealment, which may compromise the overall validity. Of note, the studies on different statins had similarities on the study design and implementation, and the lack of information about the quality assessment might be ascribed to the manuscript drafting but not to the actual defect in study design as shown in other systemic reviews.[67] In our study, new network meta-analysis was used, and placebo-controlled and active comparator trials were merged to investigate the head–head studies of statins. Our study was different from previous network analysis: 1) not only placebo-controlled trials but also active comparator trials were included for analysis; 2) our study was an update of previous studies, and studies investigating seven commercially available statins (cerivastatin is not commercially available due to adverse effects) were included for analysis, which was not found in previous meta-analysis of stroke and 3) in this study, the major CVEs served as the main outcomes, but cardiovascular events were used as main outcomes in previous meta-analyses.

There were limitations in this study. First, this was a meta-analysis based on previous studies, and the number of studies included was limited. Only a few prospective, head–head clinical trials with clinical outcome were identified in the available studies. Second, the meta-analysis based on the data from published studies was limited by the quality of these studies. For example, the included studies that reported major CVEs might not report the fatal stroke. Third, there was a difference in the results of direct and indirect analyses, but direct comparison would make the results be more likely to be true. This difference might be related to the small sample size and the conservative nature of the Bayesian hierarchical random-effects model.

Conclusion

Different statins have distinct pharmacological characteristics and there are differences of statistical and clinical outcome among several statins.

Disclosure

The authors report no conflicts of interest in this work.

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