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The Many Roles of Statins in Ischemic Stroke

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Abstract: Stroke is the third leading cause of human death. Endothelial dysfunction, thrombogenesis, inflammatory and oxidative stress damage, and angiogenesis play an important role in cerebral ischemic pathogenesis and represent a target for prevention and treatment. Statins have been found to improve endothelial function, modulate thrombogenesis, attenuate inflammatory and oxidative stress damage, and facilitate angiogenesis far beyond lowering cholesterol levels. Statins have also been proved to significantly decrease cardiovascular risk and to improve clinical outcome. Could statins be the new candidate agent for the prevention and therapy in ischemic stroke? In recent years, a vast expansion in the understanding of the pathophysiology of ischemic stroke and the pleiotropic effects of statins has occurred and clinical trials involving statins for the prevention and treatment of ischemic stroke have begun. These facts force us to revisit ischemic stroke and consider new strategies for prevention and treatment. Here, we survey the important developments in the non-lipid dependent pleiotropic effects and clinical effects of statins in ischemic stroke.

Keywords: Clinical effects, endothelial dysfunction, inflammation, ischemic stroke, oxidative stress, statins, thrombogenesis.

INTRODUCTION

Despite considerable advances in the understanding of the pathophysiology of ischemic stroke, therapeutic options, particularly pharmacological agents for prevention and treatment are still limited. Stroke is still the third leading cause of death and the most frequent cause of permanent disability in adults worldwide [1]. Systemic and local processes of endothelial dysfunction, thrombogenesis, inflammatory and oxidative stress damage, and angiogenesis play an important role in cerebral ischemic pathogenesis and may represent strategic targets for prevention and treatment of ischemic stroke [2].

Statins lower serum cholesterol level by inhibiting hydroxymethylglutaryl-coenzymeA (HMG-CoA) reductase [3]. Statins have been found to improve endothelial function, modulate thrombogenesis, attenuate inflammatory and oxidative stress damage, and facilitate angiogenesis far beyond lowering cholesterol levels [4-7]. Statins have also been proved to significantly decrease cardiovascular risk and to improve clinical outcome [8]. Could statins be the new candidate agents for the prevention and treatment of ischemic stroke?

In recent years, a vast expansion in the understanding of the pathophysiology of ischemic stroke and the pleiotropic effects of statins has occurred. Clinical trials involving statins for prevention and treatment of ischemic stroke have begun. Treatment with statins either before, or early after cerebral arterial occlusion has been proved to associate with reduced infarct volume and improved neurological function in animal models [9-11]. In several large clinical trials, the effects of statins on stroke prevention and treatment have also been well established [12-14]. Statins may have surpassed other pharmacologic medicine in the reduction of the incidence of stroke and total mortality [15, 16]. These facts force us to revisit ischemic stroke and consider new strategies for prevention and treatment.

In this review, we survey recent important developments in the pleiotropic anti-inflammatory, antioxidative, antithrombotic and endothelial protective effects of statins (Fig. **1**) and the data from the prospective and observational studies of statins focused on their preventive and therapeutic effects in ischemic stroke (Tables **1** and **2**).

MAIN PLEIOTROPIC EFFECTS OF STATINS BEYOND LOWERING CHOLESTEROL

It has been known that statins exert lipid dependent effects on atherosclerosis by lowering the generation of serum low density lipoprotein (LDL), oxidized LDL and cholesterol [17]. Statins inhibit HMG-CoA reductase, ultimately leading to a reduction not only of cholesterol but also of a range of other intermediate metabolites, among which the formation of isoprenoids plays a key role in cellular signaling and control of cell functions such as proliferation, differentiation and migration [18]. It is not surprising that, other than reducing cholesterol, statins

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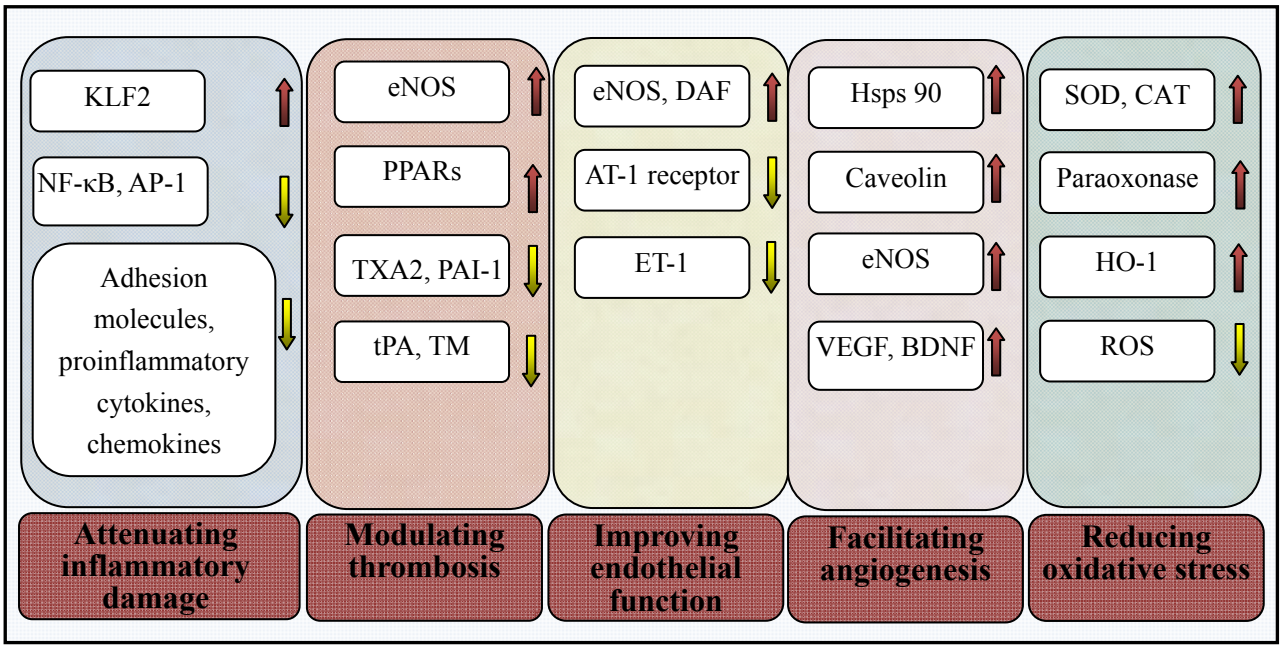

Fig. (1). Many roles of statins beyond lowering cholesterol. The pleiotropic effects and the underlying associated mechanisms of statins beyond lowering cholesterol, including improving endothelial function, modulating thrombogenesis, attenuating inflammatory and oxidative stress damage, and facilitating angiogenesis. NF-κB = nuclear factor-κB; AP-1 = activatorprotein-1; PPARs = peroxisome proliferator-activated receptors; KLF2 = Kruppel-like factor-2; TXA2 = thromboxane A2; PAI-1 = plasminogen activator inhibitor-1; tPA = tissue plasminogen activator; TM = thrombomodulin; ET-1 = endothelin-1; AT-1 = angiotensin II type 1; eNOS = endothelial nitric oxide synthase; VEGF = vascular endothelial growth factor; BDNF = brain-derived neurotrophic factor; Hsp90 = heat-shock protein 90; ROS = reactive oxygen species.

Table 1. Summary of the statins clinical trials: effects on stroke prevention with or without ischemic heart disease.

Trials [Reference]	Inclusion Criteria	Statins	Dose (mg/d)	RRR for Stroke	*P* value	Follow-up
4S [16]	MI, UA	Simvastatin	10 - 40	30%	0.024	5.4 years
WOSCOP [66]	Hypercholesteremia, without IHD	Pravastatin	40	11%	NS	4.9 years
CARE [65]	MI	Pravastatin	40	31%	0.03	5.8 years
LIPID [12]	MI, UA, without hypercholesteremia	Pravastatin	40	19%	0.048	6.1 years
A-Z [76]	IHD	Simvastatin	40/80	30%	NS	6 - 24 months
PROSPER [13]	Vascular risk factors or MI, stroke	Pravastatin	40	3%	NS	3.2 years
HPS [75]	CHD, DM, stroke, other vascular diseases	Simvastatin	40	25%, (2% for previous stroke)	0.0001, (NS)	5.0 years
SPARCL [73]	Stroke, TIA without IHD	Atorvastatin	80	16%	0.03	4.9 years
GREACE [70]	CHD	Atorvastatin	10 - 80	47%	0.0034	3.0 years
ASCOTLLA [69]	Hypertension with at least three other risk factors, without hypercholesterolemia and CHD	Atorvastatin	10	27%	0.024	5.0 years
ALLIANCE [71]	CHD	Atorvastatin	10 - 80	13%	NS	4.3 years
ALLHAT-LLT [67]	Hypertension	Pravastatin	40	9%	NS	4.8 years
MEGA [68]	Hypercholesterolemia	Pravastatin	10 - 20	17%	NS	5.3 years
ASPEN [72]	DM	Atorvastatin	10	11%	NS	4.0 years
JUPITER [77]	CRP > 2.0 mg/l	Rosuvastatin	20	48%	0.002	1.9 years

Note: MI = myocardial infarction; CHD = coronary heart disease; DM = diabetes mellitus; HR = hazard ratio; IHD = ischemic heart disease; NS = not significant; RRR = relative risk reduction; TIA = transient ischemic attack; UA = unstable angina.

Table 2. Summary of statins clinical trials in stroke severity and functional outcomes.

Trials [Reference]	Inclusion Criteria	Statins	Dose (mg/d)	Control Group	Evaluation Criteria	Efficiency	Administration Time
MISTICS [83]	Cortical stroke	Simvastatin	40	Placebo	NIHSS	(46.4% vs. 17.9%, $P = 0.022$) by the third day	3 - 12 h from symptom onset
North Dublin Study [84]	Acute ischemic stroke	Atorvastatin Pravastatin	10 - 80 10 - 40	Statins-untreated	Decreased fatality	OR = 0.48; $P = 0.05$ at 1 year, OR = 0.23; $P = 0.002$ at 90 days, OR = 0.04; $P = 0.003$ at 7 days	Pre-stroke
						OR = 0.26; $P < 0.001$ at 1 year, OR = 0.19; $P < 0.001$ at 90 days, OR = 0.12; $P = 0.006$ at 7 days	Acute post-stroke (< 72 h)
					Functional outcome (mRS 0 - 2)	OR = 1.41; $P = 0.37$ at 1 year, OR = 2.21; $P = 0.05$ at 90 days, OR = 2.15; $P = 0.07$ at 7 days	Pre-stroke
						OR = 1.69; $P = 0.14$ at 1 year, OR = 1.88; $P = 0.09$ at 90 days, OR = 2.06; $P = 0.06$ at 7 days	Acute post-stroke (< 72 h)
Statins withdrawal for functional outcome [87]	Hemispheric ischemic stroke within 24 h	Statins withdrawal group	---	Atorvastatin 20mg/d	mRS > 2	OR = 4.66; $P < 0.05$	Withdrawal for first 3 days after admission
						END	OR = 8.7; $P = 0.002$
						Mean infarct volume	63 ml (SE 10.01; $P < 0.001$)
Statins withdrawal for poststroke survival [88]	Acute ischemic stroke	Statins prescription	---	Statins use both before and during hospitalization	Poststroke survival	HR = 2.5; $P < 0.001$	Withdrawal in hospital
				No statins use before and during hospitalization		HR = 0.55; $P < 0.001$	Initiation in the hospital
				No statins use before hospitalization		HR = 0.85; $P < 0.001$	Before ischemic stroke
				No statins use before and during hospitalization		HR = 0.59; $P < 0.001$	Before and during hospitalization
Prestroke statins for initial severity [81]	Ischemic stroke	High dose (rosuvastatin; any other statins)	40 80	No statins use	Mild stroke severity (NIHSS ≤ 5)	OR = 3.297; 95% CI: 1.480 - 7.345	Pre-stroke
				Low to moderate dose	Stroke severity (NIHSS)	Median [interquartile range]: 2 [4] $P = 0.010$	
		Low to moderate dose (rosuvastatin; any other statins)	0 - 40 0 - 80	No statins use	Mild stroke severity (NIHSS ≤ 5)	OR = 1.637; 95% CI: 1.156 - 2.319	

Table 2. contd….

Trials [Reference]	Inclusion Criteria	Statins	Dose (mg/d)	Control Group	Evaluation Criteria	Efficiency	Administration Time
				High dose	Stroke severity (NIHSS)	Median [interquartile range]: 4 [9] $P = 0.010$	
Prestroke statins on severity and outcome [82]	First-ever ischemic stroke	Statins users		Non-statins users	Functional outcome (mRS)	OR = 0.76; $P = 0.221$	Use before onset
					Initial severity (NIHSS)	Median[interquartile range]4 [7] versus 4 [9] $P = 0.104$	

Note: HR = hazard ratio; ND = early neurological deterioration; mRS = modified Rankin Scale; NIHSS = national institute of health stroke scale; OR = odds ratio.

appear to lead to the non-lipid dependent, pleiotropic effects on ischemic stroke [19].

Inhibition of Isoprenoids Formation

There is growing evidence indicating that some of the lipid-independent effects are mediated by interruption of isoprenoids biosynthesis [19]. Isoprenoids, such as indicates isopentyl pyrophosphate (IPP); 3, 3-dimethylallyl pyrophosphate (DPP), geranyl pyrophosphate (GPP), farnesyl pyrophosphate (FPP), geranylgeranyl pyrophosphate (GGPP) are important intermediate metabolites in cholesterol biosynthesis pathway. Prenylation (isoprenylation), such as farnesylation and geranylgeranylation, is critical for the insertion and anchorage of proteins to cell membranes and for their full biological functionality [19]. The translocation of Ras and Ras-like proteins (Rho and Rac) to the membrane is dependent on farnesylation and geranylgeranylation, respectively [20]. Statins block the transformation of HMG-CoA into L-mevalonate, the formation of isoprenoids such as FPP and GGPP, and subsequent translocation of Ras and Ras-like proteins to the membrane (Fig. **2**). Statins increase the production and bioavailability of endothelium-derived nitric oxide (NO) through reducing the Rho GTPase [21]. By inhibiting Rac prenylation, statins lead to a reduction in nicotinamide adenine dinucleotide phosphate oxidase (NOX) assembly and consequent generation of reactive oxygen species (ROS) [22]. Statins activate endothelial Ras which is associated with cellular proliferation and lead to proangio-genic effects [23].

Improvement of Endothelial Function and Vasomotor Reactivity

Endothelial dysfunction is one of the earliest manifestations of atherosclerosis and is strongly related to stroke occurrence [24]. Statins improve endothelial function through non-lipid dependent effect at least in part mediated by upregulating endothelial nitric oxide synthase (eNOS) [4]. Endothelium-derived NO may mediate vasodilation and decrease vascular smooth muscle cells (VSMCs) proliferation [25]. Parts of eNOS-induced effects on vascular wall are attributed to the inhibition of the Rho/Rho kinase (ROCK) pathway (Fig. **2**). Inhibition of Rho/ROCK activates PI3K/Akt/eNOS pathway and increases the eNOS mRNA stability *via* changes in actin cytoskeleton and extension in eNOS mRNA half-life, which are reversed by GGPP [26, 27].

Statins protect vascular endothelium against complement-mediated injury through decay-accelerating factor (DAF) upregulation, which are mediated by inhibiting RhoA, independent of NO [28]. Statins reduce angiotensin II type 1 (AT-1) receptor gene expression with subsequent alleviation of vasoconstrictive angiotensin II (AT-II) effects through a Rho-dependent manner to promote vasorelaxation [29]. Statins also inhibit the expression of endothelin-1 (ET-1) in a Rho-dependent pathway, to limit vasoconstriction and VSMCs proliferation [30].

Giannopoulos *et al*. believed that statins pretreatment significantly improved cerebral vasomotor reactivity through the upregulation of eNOS in patients with severe small vessel disease [31]. Endres *et al*. thought that prophylactic treatment with statins augmented cerebral blood flow and reduced brain injury during cerebral ischemia by upregulating eNOS [32]. Combination of simvastatin and dipyridamole may have greater benefits in stroke protection than statin alone through NO- dependent vascular protection [33].

Modulation of Thrombogenesis

Thrombosis superimposed on atherosclerosis plays an important role during ischemic stroke. Statins reduce the production of thromboxane A2 (TXA2) in platelet and erythrocyte membranes, resulting in a decrease in thrombogenic potential of these cells [34]. Acute intravenous administration of lovastatin is associated with favorable alterations in platelet function including impaired aggregation, reduced dense granule release, and reduction in subsequent platelet-mediated thrombus formation in an animal study [5]. Statins reduce platelet activation and thrombus formation partly mediated by decreased Rho-GTPase prenylation and subsequent increased eNOS expression [35]. Peroxisome proliferator-activated receptor-α (PPAR-α) and peroxisome proliferator-activated receptor-γ (PPAR-γ) stimulation in platelets surface have been suggested as additional mechanisms to reduce platelet activation [36].

Statins increase Thrombomodulin (TM) expression and function through a NO-dependent mechanism *in vitro* [37].

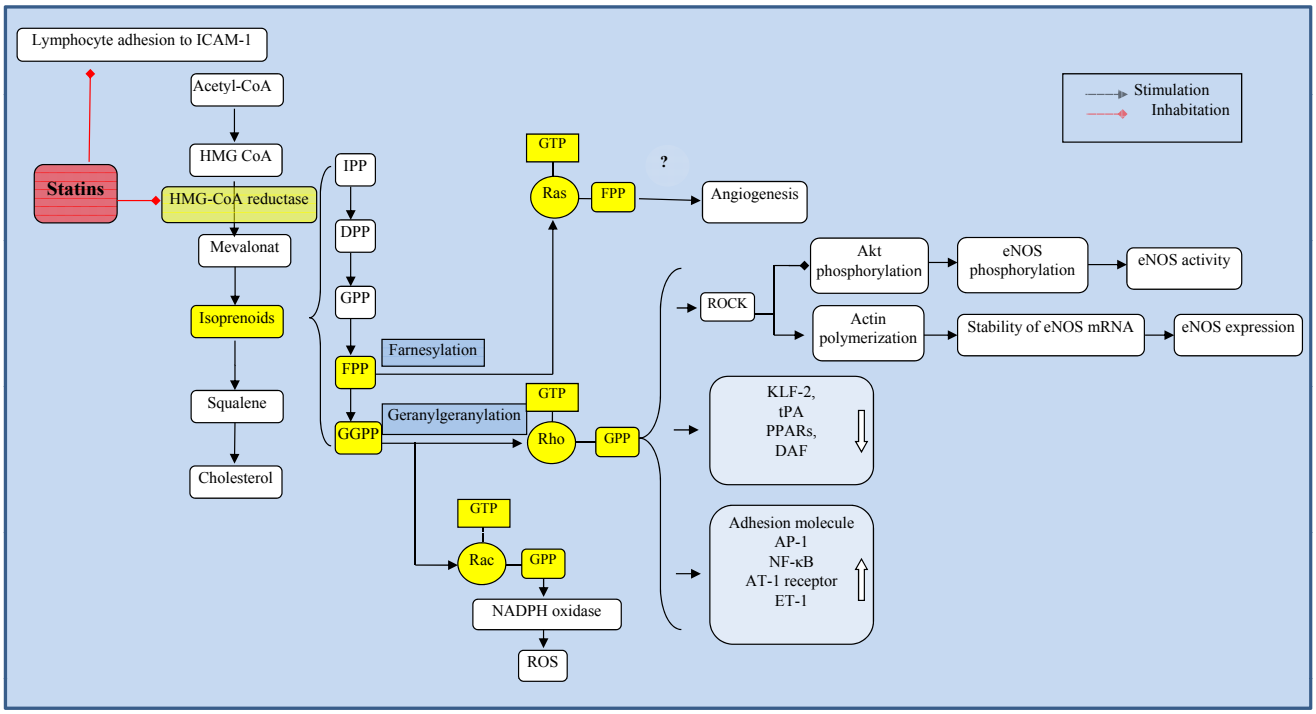

Fig. (2). Isoprenoids-related mechanisms. Statins inhibit HMG-CoA reductase and decrease isoprenoids intermediates such as FPP and GGPP, which leads to an inhibition of isoprenylation of small GTPases such as Ras, Rho, and Rac. The many roles of statins in ischemic stroke may be due to the interruption of isoprenoid biosynthesis. IPP = isopentyl pyrophosphate; DPP = 3,3-dimethylallyl pyrophosphate, GPP = geranyl pyrophosphate, FPP = farnesyl pyrophosphate, GGPP = geranylgeranyl pyrophosphate, ROCK = Rho kinase, eNOS = endothelial nitric oxide synthase, NF-κB = nuclear factor-κB, KLF2 = Kruppel-like factor-2, tPA = tissue plasminogen activator, AT-1 = angiotensin II type 1, ET-1 = endothelin-1, DAF = decay-accelerating factor, AP-1 = activatorprotein-1, PPARs = peroxisome proliferator-activated receptors, ROS = reactive oxygen species, LFA-1 = lymphocyte function-associated antigen-1.

Fu *et al*. provided the novel mechanisms for statins-induced TM upregulation that heat-shock factor-1 (HSF-1) dissociated from HSP-90 and activated Kruppel like factor (KLF)-2, subsequently both of the transcription factors translocating to the nucleus where they binded to promoter regions of TM involving heat shock element (HSE)-1 and -3 and Sp1/KLF [38]. Lovastatin increase tPA activity in rat aortic endothelial cells involving Rho proteins [39]. The signaling pathways by which statins induce downregulation of PAI-1 are still unclear.

Attenuation of Inflammatory Damage

Inflammatory processes have a key role in the pathophysiology of ischemic stroke [40]. Statins have been proved to inhibit inflammatory cell recruitment, adhesion and migration. Statins inhibit the expression of adhesion molecules such as vascular adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1) and E-selectin, thereby reducing inflammatory cell recruitment [6]. Statins reduce macrophage receptor-1 (MAC1) (CD11b/CD18) expression and CD11b dependent monocyte adhesion to endothelium [41], probably mediated by reducing isoprenylation of leukocyte G-proteins [42]. Statins also inhibit leukocyte adhesion by direct interactions with the leukocyte-function antigen-1 (LFA-1) (CD11a/CD18), rather than targeting HMG-CoA reductase [43]. (Fig. **2**). Statins reduce expression of the chemokine such as monocyte chemoattractant protein-1 (MCP-1), interleukin (IL)-8, and regulated on activation normally T-cell expressed and secreted (RANTES) *in vitro* [44, 45].

Statins are associated with reductions in inflammatory biomarkers, referring to c-reactive protein (CRP), cytokines (IL-1, IL-6, IL-12, tumour necrosis factor-α (TNF-α), IFN-γ), lipoprotein-associated phospholipase A2 [45-47]. Statins inhibit the activation of inflammatory transcription factors activating protein-1 (AP-1) and NF-κB in human endothelial cells and VSMCs [48], probably mediated by Rho and Rac proteins [49, 50]. Further study shows that statins suppress the activation of NF-κB probably through inducing the expression of a novel transcriptional regulator Kruppel-like factor-2 (KLF2) [51], which can be abolished by GGPP, involving the Rho pathway [52].

Reduction of Oxidative Stress

The release and production of ROS is thought to be a key event in the pathogenesis of endothelial dysfunction and atherosclerosis [53]. Statins confer a reduction of AT-II-induced release of ROS by two important mechanisms involved in decreased geranylgeranyl-dependent activation of Rac1 GTPase and reduced AT-1 receptor expression mediated by destabilization of AT1 mRNA [7]. Activation of NOX is a major source of ROS during ischemic stroke [54]. NOX subunit nox1 and p22phox expression were found to

decrease from an in-vitro and in-vivo study of atorvastatin [22].

Antioxidative defense systems are equally important for oxidative stress besides inhibiting ROS generation. The antioxidant effects of statins may attribute to increased heme oxygenase-1 (HO-1) expression and paraoxonase activity [55, 56]. Statins also produce broader antioxidant defenses by increasing radical-scavenging enzymes activity [57]. De Oliveira *et al*. proved that atorvastatin withdrawal led to oxidative/nitrosative damage in the rat cerebral cortex, and that mitochondrial superoxide dismutase (SOD) activities played a part in such harmful condition [58]. However, Wassmann *et al*. demonstrated that atorvastatin did not significantly alter the mRNA expression of SOD isoforms and glutathione peroxidase (GSH-Px), in addition to catalase [22].

Facilitation of Angiogenesis

The key role of angiogenesis is an unresolved issue in the understanding of recovery mechanisms after stroke. Atorvastatin promotes angiogenesis and enhances functional recovery after stroke through a mechanism involving an increase of vascular endothelial growth factor (VEGF), brain-derived neurotrophic factor (BDNF), cGMP, synaptic protein and synaptophysin in the rodent middle cerebral artery occlusion model [59, 60]. Statins increase bone marrow-derived endothelial progenitor cell (EPC) levels, which play a role in neovascularization after vascular injury, probably through NO-related mechanisms [61]. Phosphatidyl inositol 3-kinase (PI3K)/Akt/eNOS, caveolin/eNOS and Hsp90/Akt/eNOS are identified as key targets of statins to modulate NO-mediated angiogenesis [26, 62].

After initial reports on angiogenesis effects of statins, subsequent studies imply inhibition of angiogenesis by statins [63]. Disparities of angiogenesis may result from different statins concentrations. Low concentrations of atorvastatin or mevastatin activated endothelial Ras and promoted Akt and eNOS phosphorylation, leading to proangiogenic effects, while high concentrations resulted in anti-angiogenic effects through inhibiting Ras and RhoA without upregulating eNOS [23]. However, simvastatin of the same dose promoted angiogenesis in response to hypoxic conditions and inhibited angiogenesis during inflammation [64], which implies that the effect on angiogenesis also change according to the inner environment and underlying disease. More trials are needed to illuminate the complex relationship between statins and angiogenesis.

CLINICAL PREVENTIVE EFFECTS OF STATINS IN ISCHEMIC STROKE

Statins have emerged as guideline therapy for primary and secondary stroke prevention. The results from several large randomized, double-blind trials have firmly established that statins use in ischemic stroke is associated with reduced risk of incident and recurrent stroke (Table **1**).

Pravastatin

The CARE study demonstrated that pravastatin (40 mg/day) significantly decreased incidence of stroke by 31% in patients with myocardial infarction (MI) (P = 0.03) [65]. The LIPID study demonstrated that pravastatin (40 mg/day) in patients with MI or unstable angina (UA) resulted in a 19% relative risk reduction (RRR) in stroke [12]. However, PROSPER, ALLHAT-LLT and WOSCOP study failed to demonstrate significant reduction in stroke incidence among patients taken pravastatin (40 mg/day) [13, 66, 67]. No significant difference was found in stroke RRR in MEGA study, in which people took pravastatin (10 to 20 mg/day) [68].

Atorvastatin

In the trial of ASCOTLLA, atorvastatin (10 mg/day) was associated with a 27% reduction in fatal or nonfatal stroke (P = 0.02) [69]. In the GREACE study, atorvastatin (10 to 80mg/day) was proved to reduce stroke incidence by 47% (P = 0.03) [70]. There was no significant difference of stroke RRR between atorvastatin group and control group in the trial of ALLIANCE and ASPEN [71, 72].

The SPARCL trial provided the best evidence to support the role of atorvastatin for the secondary stroke prevention. Atorvastatin 80 mg/day reduced the incidence of recurrent ischemic stroke versus placebo (RRR: 16%; P = 0.03) [73].

Simvastatin

The Scandinavian Simvastatin Survival Study (4S) showed that simvastatin 40 mg/day given in population with prior MI or UA reduced the incidence of stroke and TIA by 30% over the follow-up period of 5.4 years [16]. The Heart Protection Study (HPS) firmly established the efficacy of simvastatin in reducing stroke and other vascular events among 20, 536 adults with cerebrovascular and other occlusive arterial disease or diabetes. Simvastatin (40 mg/day) reduced the incidence of ischemic stroke by 25%, and statins therapy was beneficial for people with preexisting cerebrovascular disease, in consideration of the reduction by 20% (8% - 29%) in major vascular events (nonfatal myocardial infarction, stroke of any type, *et al*). However, there was no obvious reduction in stroke incidence and severity among those with previous cerebrovascular disease [74, 75]. In the phase Z of A to Z trial of patients with acute coronary syndrome, 2,232 patients received placebo for 4 months followed by simvastatin (20 mg/day) and 2,265 patients received simvastatin (40 mg/day) for 1 month followed by 80 mg thereafter, no significant differences were observed in stroke incidence [76].

Rosuvastatin

From the JUPITER trial, rosuvastatin was demonstrated to significantly reduce not only major cardiovascular events but also stroke risk (RRR: 48%; P = 0.002) in those apparently looked healthy individuals but with elevated high-sensitivity CRP levels. However, due to the low number of stroke events and the fact that JUPITER included individuals without a specific condition placing them at risk of stroke, the relevance for primary stroke prevention was limited [77].

Meta-analysis of the Preventive Effects

In consideration of above contradictory results, a large meta-analysis of 38 trials including 83,161 patients with a

mean follow-up of 4.7 years showed that pre-stroke statins use was associated with a stroke RRR of 26% ($P < 0.001$) [78]. Another meta-analysis of 121,000 patients concluded that statins provided an obvious protection against all-cause mortality and non-hemorrhagic stroke [79]. Results from a meta-analysis of more than 170,000 participants showed a positive overall effect of statins treatment in all types of adults, even those with a relatively low risk for major vascular events [14].

CLINICAL THERAPEUTIC EFFECTS OF STATINS IN ISCHEMIC STROKE

In addition to the stroke risk reduction with pre-stroke statins therapy, evidences from clinical trials demonstrated that statins may also improve stroke prognosis (Table **2**), even when administered after the event onset, but the effect of statins on stroke initial severity and subsequent functional outcomes is still controversial.

Improved Stroke Functional Outcome with Pre-stroke Therapy

Statins pretreatment improved clinical outcomes with a significant improvement in neurological deficit scores (NIHSS) over 1-month follow-up [80]. Patricia concluded that pretreatment with statins, at high (40 mg of rosuvastatin or 80 mg of any other statins) as well as at low to moderate (< 40 mg of rosuvastatin or < 80 mg of any other statins) doses, was associated with lower stroke severity (NIHSS ≤ 5) on admission among 969 ischemic stroke patients [81]. However, among 953 patients with first-ever ischemic stroke (127 with previous statins administration), prestroke statins therapy did not affect initial clinical severity and the association between prestroke statins treatment and better early functional outcomes after ischemic stroke was non-significant [82].

Improved Functional Outcome with Acute Post-stroke Therapy

In the MISTICS trial, simvastatin (40 mg/day) was given at 3-12 h from symptom onset. Patients treated with simvastatin had better functional outcomes at 3 days compared with placebo group ($P = 0.02$), but no neurological functional improvement was observed at 90 days [83]. Of the 448 ischemic stroke patients in North Dublin Study, modified Rankin Scale (mRS) score and fatality were assessed from 7 days to 1 year. Post-stroke statins therapy (within 72 h from stroke onset) was independently associated with improved survival and functional outcomes [84]. However, Insufficient data were available from randomized trials to indicate that statins were effective and safe in acute ischemic stroke and TIA, through analyzing eight randomized controlled trials - comparing statins of different type and dosage versus placebo or no treatment, administered within two weeks from stroke or TIA onset [85].

Meta-analysis of the Therapeutic Effects in Acute Stroke

Because the association between statins therapy and outcomes recovery after acute ischemic stroke from clinical studies is conflicting, the meta-analysis of observational and randomized trials by Danielle *et al*. investigated the relationship between statins therapy and outcome after acute ischemic stroke. They concluded that pre-stroke statins use was associated with improved functional outcomes (mRS score 0 to 2) at 90 days but not 1 year, and with reduced fatality at 90 days and 1 year among observational studies, In the single randomized controlled trial (SPARCL trial), statins treatment was associated with good 90-day functional outcomes. However, this association was not observed in thrombolysis-treated patients. Randomized controlled trials of acute post-stroke statins therapy in acute ischemic stroke were still needed [86].

Continuous Therapy in Acute Stroke

Although we still don't have convincing data to support statins therapy for acute ischemic stroke, but it seems harmful to discontinue statins if the patient is already taking them before acute cerebral ischemic stroke. From 215 patients admitted within 24 hours of a hemispheric ischemic stroke, 89 patients with chronic statins treatment were randomly assigned within 24 hours of onset either to statins withdrawal for the first 3 days (n = 46) or to immediately receiving atorvastatin 20 mg/day (n = 43). This trial emphasized that statins treatment should be continued in the acute phase of ischemic stroke in consideration of increased brain damage and worsened functional outcomes with statins withdrawal during acute period [87]. Records from 12,689 patients admitted with ischemic stroke demonstrated that statins withdrawal even for a brief period was associated with worsened survival [88]. The guideline for the early management of patients with acute ischemic stroke from the American Heart Association/American Stroke Association (AHA/ASA) recommends that among patients already taking statins at the time of onset of ischemic stroke, continuation of statins therapy during the acute period is reasonable (Class IIa; Level of Evidence B) in 2013 [89].

DISCUSSION

In this review we have outlined the theoretical and clinical benefits of statins in ischemic stroke. The pleiotropic effects of statins offer new opportunity for the prevention and treatment of ischemic stroke. The guideline for the management of patients with acute ischemic stroke from the AHA/ASA recommended continuous statins therapy in the acute period of ischemic stroke among patients with pre-stroke statins therapy in 2013 [89]. Statins should be dubbed the most important medicines in ischemic stroke prevention and therapy since the introduction of aspirin.

Much effort has been taken to clarify the pleiotropic effect of statins, but the precise mechanisms responsible for these effects are still unclear. Further preclinical experimental data are required for better evaluation of statins. More experimental work is needed to illuminate the complex relationship between statins and angiogenesis in stroke recovery process, the mechanism of statins to facilitate EPC increment in acute stroke, and effective signaling pathways for antithrombotic effects of statins.

An increasing amount of clinical trials suggest that statins improve functional outcomes after ischemic stroke, but most are observational studies or sample sizes are limited. The potential bias from limited clinical trials is considered likely to reduce the estimated effect of statins.

Therefore, we still need larger, randomized, placebo-controlled clinical trials to completely prove efficacy and safety of statins in acute ischemic stroke, especially the duration of pre-stroke and post-stroke statins therapy, as well as the effects of different doses and types on initial stroke severity and functional outcomes. Ongoing studies such as NeuSTART II, EUREKA may provide more valuable safety and efficacy information of statins therapy in acute ischemic stroke [90, 91]. However, we cannot neglect a fact that a large proportion of stroke patients survive stroke but die later of myocardial infarction rather than another stroke, or more stroke patients die from IHD than those from stroke. Consequently, it will be advisable to use statins therapy for stroke patients in consideration of these reasons.

In conclusion, new knowledge about statins has provided surprising insights into their pleiotropic beneficial effects in ischemic stroke, has offered new opportunities for prevention and treatment, and may lead to new candidate agents after aspirin for treatment of this life-threatening disease.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interests.

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