

# Statins for aneurysmal subarachnoid haemorrhage: Another loss in translation

Matthew T. V. Chan

## Abstract

Experimental evidence suggests that statin attenuates inflammation, oxidation, platelet aggregation and excitotoxicity. In brain ischemic models, statin administration produces vasodilatation and reduces neuronal apoptosis. It was hypothesized that statin administration may improve outcome by reducing delayed ischemic neurological deficit after aneurysmal subarachnoid haemorrhage. Earlier pilot trials suggested demonstrated encouraging results but the recent Simvastatin in Aneurysmal Subarachnoid Haemorrhage Trial, using simvastatin 40 mg per day, failed to demonstrate a benefit. Even at larger doses, simvastatin 80 mg per day did not reduce delayed ischemic neurological deficit. In common with many other interventions, statin represents another translational failure of presumed neuroprotective agents.

**Key words:** Aneurysmal subarachnoid haemorrhage, delayed ischaemic neurological deficit, statin

## INTRODUCTION

Aneurysmal subarachnoid haemorrhage affects 2–22/100,000 persons every year and is associated with high morbidity and mortality rate.<sup>[1,2]</sup> The reported 30-day case fatality rate was between 32% and 42%.<sup>[3,4]</sup> Among patients who survived the initial insult, 30%–50% of patients were severely disabled and required life-long assistance.<sup>[1–4]</sup> Early mortality of aneurysmal subarachnoid haemorrhage is due to re-bleeding, intracranial hypertension and cerebral oedema. Subsequent causes of death are related to sepsis, pulmonary aspiration, metabolic derangement, myocardial infarction, heart failure and thromboembolism.<sup>[2,5]</sup> In addition, a substantial proportion (18%–56%) of patients suffers secondary

ischaemia, 3–10 days after aneurysmal subarachnoid haemorrhage. Delayed ischaemic neurological deficit due to cerebral vasospasm is currently considered as an important cause of poor outcome after subarachnoid haemorrhage.<sup>[6,7]</sup>

Biologically, the presence of deoxy (ferrous)-haemoglobin in the basal subarachnoid space and the initial insult from early cerebral hypoxia and ischaemia trigger a wide range of damages. These include release of oxygen free radicals, depletion of nitric oxide in the endothelium and initiation of spreading depression [Figure 1].<sup>[5–9]</sup> Each of these processes contributes to spasm and thrombosis in the microcirculation and may result in delayed ischaemic neurological deficits.

## STATINS TO IMPROVE NEUROLOGICAL OUTCOME AFTER SUBARACHNOID HAEMORRHAGE

Statins are competitive inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase,

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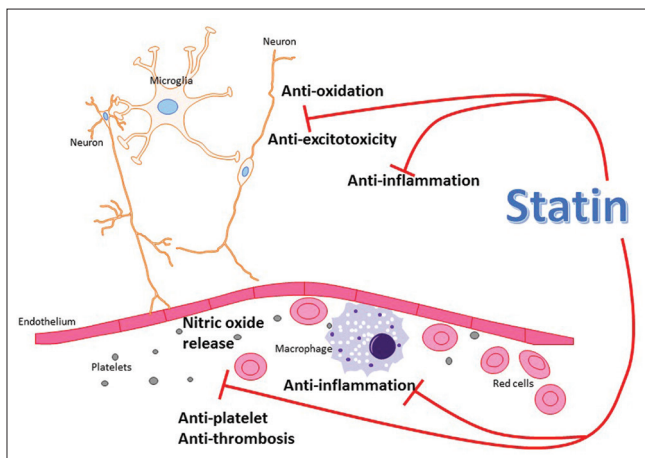
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a rate-limiting enzyme of the mevalonate pathway, which is pivotal for the production of cholesterol and mevalonate. Experimentally, statins produce a number of cholesterol-independent effects.<sup>[9]</sup> These include as follows:

- Anti-inflammation<sup>[10,11]</sup> – Statin inhibits intracellular cholesterol synthesis such that neuro-inflammation is attenuated after focal cerebral ischaemia. This is dependent on CD11b expression and inhibition of monocyte adhesion to endothelium<sup>[12]</sup>
- Anti-oxidation – This is a dose-dependent effect primarily due to a decrease in oxidase activity and suppression of free oxygen radical production<sup>[13]</sup>
- Anti-platelet – There is a direct inhibitory effect on platelet. In addition, there is a decrease in platelet response to thrombin and platelet disposition to the exposed and damaged endothelium<sup>[14]</sup>
- Anti-excitotoxicity<sup>[15]</sup> – This is associated with N-methyl-d-aspartate receptor antagonism and a decrease in calcium influx with glutamate stimulation
- Anti-apoptosis – Statins are known to inhibit caspase 3-dependent apoptotic pathway and thus reduce neuronal apoptosis. Statins have also been shown to induce neurogenesis and synaptogenesis after ischaemic brain injury<sup>[16]</sup>
- Vasodilatation<sup>[17]</sup> – Statin inhibits Rho GTPase and activates protein kinase B. The end result is an increase in endothelial-derived nitric oxide synthase activity, resulting in cerebral vasodilatation and restoration of auto-regulation.

These effects, working individually or in combination, may exert neuro-protection to subarachnoid haemorrhage by limiting neuronal damage during initial impact and prevent subsequent vasospasm [Figure 1]. It should



**Figure 1:** Mechanisms of statin-induced neuro-protection. In the blood stream, statin prevents macrophage adhesion, increases nitric oxide bioavailability, reduces thrombus formation and promotes endothelial vasomotor function. In the brain side, statin possesses antioxidant properties and suppresses cytokine responses during cerebral ischaemia

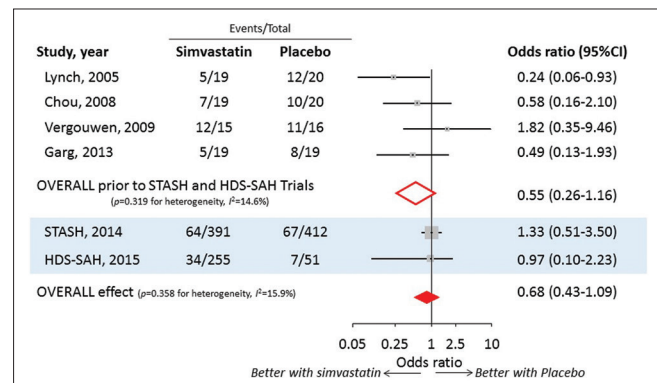
be noted that only simvastatin and lovastatin cross the blood–brain barrier,<sup>[18]</sup> and the current research has focussed on the use of simvastatin to improve neurological outcome after aneurysmal subarachnoid haemorrhage.

In experimental models, simvastatin treatment before and after subarachnoid haemorrhage attenuated cerebral vasospasm and significantly improved neurological outcomes.<sup>[16,19-21]</sup> Similarly, in a meta-analysis of animal stroke models, treatment with simvastatin decreases infarct volume by 25%–30% and improves neurological outcome scores by 20%.<sup>[22]</sup>

Given these encouraging results, a few pilot trials have been performed to test the feasibility of large randomised trial.<sup>[20,23-27]</sup> Figures 2 and 3 show the pooled effect of high-dose simvastatin, 80 mg/day, given for 14–21 days after subarachnoid haemorrhage. Compared with placebo, the rates of delayed ischaemic deficit tended to be lower with simvastatin treatment (40.3% vs. 54.7%),<sup>[23,24,26,27]</sup> odds ratio (95% confidence intervals): 0.54 (0.27–1.08),  $P = 0.083$ . More importantly, simvastatin treatment was well tolerated. Neurological recovery was not improved. The odds ratio (95% confidence intervals for unfavourable neurological outcome at 6 months after subarachnoid hemorrhage 1.18 (0.90–1.55).

## SIMVASTATIN IN ANEURYSMAL SUBARACHNOID HAEMORRHAGE TRIAL

Based on the potential benefits of simvastatin highlighted in pilot trials, an international randomised controlled trial was conducted. The simvastatin in aneurysmal subarachnoid haemorrhage (STASH) trial randomised 803 patients presented within 96 h from onset of symptoms to receive either simvastatin 40 mg or matched placebo tablets for 3 weeks.<sup>[28]</sup> The primary end-point was functional performance measured by



**Figure 2:** Forrest plot of odds ratios to measure the effect of simvastatin on the prevention of delayed neurological ischaemic deficit before and after reporting of the simvastatin in aneurysmal subarachnoid haemorrhage trial and high-dose simvastatin for aneurysmal subarachnoid haemorrhage trial

the modified Rankin scale score at 6 months after randomisation. Throughout the study, the rate of cerebral vasospasm was similar (simvastatin 16% vs. placebo 16%). At 6 months after randomisation, there was no difference in neurological recovery (modified Rankin score scale  $\leq 2$ : Simvastatin 72% vs. placebo 72%) between groups. These findings suggest that simvastatin 40 mg/day had no measurable effect of neurological recovery after aneurysmal subarachnoid haemorrhage.

It should be noted that STASH trial used lower dose than previous trials and may have led to limited efficacy. In this respect, simvastatin 80 mg/day is the largest dose approved clinically. It is therefore unclear whether high-dose regimen (simvastatin 80 mg/day) would produce superior neurological recovery compared with the lower dose (simvastatin 40 mg/day).

### HIGH-DOSE SIMVASTATIN FOR ANEURYSMAL SUBARACHNOID HAEMORRHAGE TRIAL

We have recently reported the high-dose simvastatin for aneurysmal subarachnoid haemorrhage (HDS-SAH) trial.<sup>[29]</sup> A total of 255 patients who presented within 96 h of aneurysmal subarachnoid haemorrhage were randomised to receive simvastatin 80 or 40 mg/day for 21 days. Delayed ischaemic deficit was recorded as the primary outcome and neurological recovery at 3 months after subarachnoid haemorrhage was the secondary end-point.

In the HDS-SAH trial, there was no difference in the rate of delayed ischaemic neurological deficit between groups (simvastatin 80 mg – 27% vs. simvastatin 40 mg – 32%). Neurological recovery was also similar between groups. When compared with another cohort of patients who have not been exposed to simvastatin treatment ( $n = 51$ ), neurological recovery or delayed ischaemic neurological deficit was similar to patients receiving simvastatin treatment. The findings were not changed substantially after adjustment for severity of subarachnoid haemorrhage, gender, age and location of aneurysm.<sup>[30]</sup> Cognitive performance also did not differ between groups.

### CONCLUSIONS

The current data suggest that simvastatin, regardless of dose regimens, given after subarachnoid haemorrhage does not affect the rate of delayed ischaemic neurological deficit or functional neurological recovery. Similar to many other agents, such as magnesium<sup>[31-33]</sup> and clazosentan,<sup>[34-36]</sup> statin fails to translate laboratory results to clinical success. This is not surprising given the

### Table 1: Important differences between animal and human research

#### Heterogeneity in subjects

##### Comorbidity

Age (older in human research vs. younger animals in laboratory research)

#### Animal model does not represent human disease

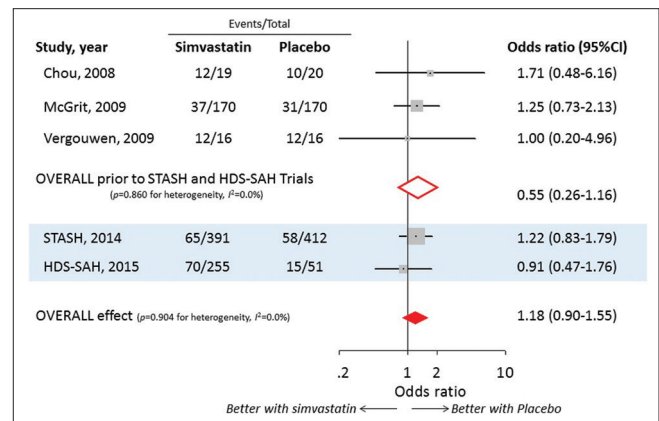
Severity in subarachnoid haemorrhage

Differences in aetiology

Treatment window – delayed treatment in human research

#### Endpoint differences

Infarct volume, surrogate markers in animal research versus neurological (functional) recovery in human trials



**Figure 3:** Forrest plot of odds ratios to measure the impact of simvastatin on the unfavourable neurological outcome before and after reporting of the simvastatin in aneurysmal subarachnoid haemorrhage trial and high-dose simvastatin for aneurysmal subarachnoid haemorrhage trial

heterogeneity of aneurysmal subarachnoid haemorrhage in humans compares with purposely designed animal models. There are also issues of treatment time window when a delay of 96 h may be too long in humans [Table 1]. More importantly, the current literature shows that results from small clinical trials are generally fragile and that adequately powered trial will be required to inform clinical care.<sup>[37]</sup>

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### Conflicts of interest

There are no conflicts of interest.

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