Table 2: Summary of the published clinical studies for statin with intracranial hemorrhage						
Study	Study type	Size (s:n)	Statin therapy	Outcome		
				Timing	Good outcome (OR, 95% CI)	Mortality (OR, 95% CI)
Leker *et al.*[33]	Observation	312 (89:223)	Any	At discharge	2.97, 1.25-7.35 ($P = 0.015$)	0.25, 0.09-0.63 ($P = 0.004$)
Biffi *et al.*[28]	Observation	699 (238: 461)	Any	90 days	2.08, 1.37-3.17 ($P = 0.004$)	0.47, 0.32-0.70 ($P = 0.005$)
Biffi *et al.*[28]	Meta-analysis (6 obs + 1 RCT)	2521 (698: 1,823)	Any	90 days	1.91, 1.38-2.65 ($P < 0.0001$)	0.55, 0.42-0.72 ($P < 0.0001$)

Observed outcome with pretreatment of statin. s:n: statin: no statin; obs: observation; RCT: randomized controlled trial; ICH: intracerebral hemorrhage

Table 3: Risk of ICH with statin treatment					
Study	Study type	Population	Size	Statin therapy	Risk of ICH
Goldstein *et al.*[34]	RCTs	Treatment after stroke (include TIA)	88 (s55: n33)	Atorvastatin 80 mg	OR 1.68 (95% CI 1.09-2.59, $P = 0.02$)
Hackam *et al.*[35]	Meta-analysis	Statin with various cause		Any	
	23 RCTs	526, 518 patients-years (median 3.9 years),497 ICH			RR 1.10 (95% CI 0.86-4.14)
	19 Obs	219,459 patients-years (median 3.0 years),14280 ICH			RR 0.94 (95% CI 0.81-1.10) for 12 observational cohort RR 0.60 (95% CI 0.41-0.88) for 6 case control study

RCTs: randomized controlled trials; TIA: transient ischemia attach; OR: odds ratio; CI: cerebral ischemia; ICH: intracerebral hemorrhage; RR: relative risk; Obs: observation

hemorrhage (ICH), cerebral infarction, traumatic brain injury (TBI), status epilepticus and meningitis. Studies were identified by performing a PubMed search using following key words: "statin" and each disease which was discussed in this review. Study selection was performed by two reviewers independently and the third reviewer would step in if there were any disagreement. The studies only published in English were selected. Discussion between reviewers was made to get a final consensus. The results were described in Figure 1. The main focus was the evidence for timing of statin initiation as well as specific agent and doses in the patient presenting to the emergency department and acute care unit.

SAH

Symptomatic cerebral vasospasm and delayed cerebral ischemia (DCI) is a major source of disability, unfavorable outcome and cause of death after aneurysmal SAH. Although the exact mechanism of SAH associated vasospasm and DCI are not well known, experimental studies suggest multifactorial pathogenesis involving inflammation, No depletion, endothelial injury, free radical and microvascular by autoregulation.[9-11] The pleiotropic effects of statin may be beneficial in attenuation of SAH associated vasospasm and DCI via inhibit the underlying mechanism of vasospasm and DCI. The results from 3 different animal models (mice, rabbits and dogs), have supported this hypothesis.[12-14]

Clinical evidence suggesting benefits in by reducing DCI and possibly vasospasm and early in-hospital mortality that has come from 6 randomized controlled trials (RCTs)[15-20] (two of which have only published as abstracts[19,20]), four observational cohort studies[21-24] [Table 1] and two case-control studies.[25,26]

All 6 RCT were phase II, single-center trials and none of which enrolled more than 100 patients.[15-20] One RCT[17] focused on patents with Fisher grade 3 and the other RCTs[15,16,18-20] included all grades. The statins used in these trials were either pravastain 40 mg[15,19] or simvastatin 80 mg[16-18,20] administrated within 96 h (range from 24-96 h) following aneurysmal SAH. Three RCTs administered statin for 2 weeks,[15,16,18] two used statin for 3 weeks,[17,20] and the other prescribed statins when patients were admitted to the intensive care unit.[19] Because the definition of vasospasm varied between trials, the effects of statins on vasospasm were inconsistent. Vasospasm-related DCIs was based on both neurological deterioration and neuroimaging findings in all trials. Statin therapy reduced the incidence of DCI in three trials,[15,16,18] but showed a non-significant trend to reduce the DCI in two trials[17,20] and was neutral in one trial.[18] None of these trials showed significant benefits of early statin therapy on functional outcomes by modified Rankin Scale or Glasgow Outcome Score.[15,17-20] Mortality was reduced by statin therapy in three RCTs,[15,17,20] but not in others.[18,19]

A meta-analysis with high quality four RCTs[15-18] showed that use of statin after SAH significantly reduced both DCI [odd ratios (OR) 0.41, 95% confidence interval (CI) 0.20-0.82, $P < 0.001$] and mortality (OR 0.29, 95% CI 0.09-0.93, $P = 0.04$).[27] When data from non-published

Table 4: Summary the published clinical studies for statin with acute cerebral infarct

Study	Study type	Size (s:n)	Outcome	
			Result	Definition
Aboa-Eboulé *et al.*[42]	Observation	953 (127:826)	OR 0.76 (95% CI 0.53-1.09, $P = 0.134$)	Good outcome
Marti-Favregas *et al.*[8]	Observation	167 (30:137)	OR 5.55 (95% CI 1.42-0.80, $P = 0.012$)	Good outcome at 3 months
Elkind *et al.*[43]	Observation	650 (57:593)	1.8% *vs.* 10.6% ($P = 0.04$)	Mortality at 3 months
Greisenegger *et al.*[44]	Observation	1,691 (152:1,539)	6% *vs.* 14%, OR 0.37 (95% CI 0.19-0.74, $P = 0.004$)	Severe stroke (mRS 5-6)
Flint *et al.*[45]	Observation Treatment pre- or during hospitalization	12,689 (6,294:6,395)	22.1% *vs.* 33.8%, HR 0.59 (95% CI 0.53-0.65, $P < 0.001$)	Mortality at 1 year

Pretreatment of statin and associated outcome. s:n: statin: no statin; OR: odds ratio; CI: cerebral ischemia; HR: heart rate

Table 5: Outcome after in-hospital cessation of statin therapy

Study	Study type	Size	Outcome	
			Result	Definition
Flint *et al.*[45]	Observation	468 of 3,749	46.2% *vs.* 22.1%, HR 2.5 (95% CI 2.1-2.9, $P < 0.001$)	Mortality at 1 year
Blanco *et al.*[46]	Randomized controlled	46 of 89	65.2% *vs.* 20.9%, OR 8.67 (95% CI 3.05-24.63, $P < 0.0001$)	Early neurologic deterioration
			60.0% *vs.* 39.0%, OR 4.66 (95% CI 1.46-14.91, $P = 0.043$)	Death or dependency

OR: odds ratio; CI: cerebral ischemia; HR: Heart rate

Table 6: Outcome after statin initiation in acute phase of ischemic stroke

Study	Study type	Size (s:n)	Outcome	
			Result	Definition
Flint *et al.*[45]	Observation	8,940 (2,545:6,395)	19.4 % *vs.* 33.8%, HR0.55 (95% CI 0.50-0.61, $P < 0.001$)	Mortality at 1 year
Kennedy *et al.*[47]	Randomized controlled	199:193	10.6% *vs.* 7.3%, RR 1.3 (95% CI 0.7-2.4, $P = 0.25$)	Stroke within 90 days
Squizzato *et al.*[48]	Meta-analysis of 7 RCTs	Total 431	OR 1.51 (95% CI 0.60-3.81)	Mortality

s:n: statin: no statin; OR: odds ratio; CI: cerebral ischemia; HR: heart rate; RR: relative risk; RCTs: randomized controlled trials

RCTs[19,20] was included in the analysis, statin therapy significantly reduced DCI (fixed model, OR 0.38, 95% CI 0.23-0.65, $P < 0.001$) and was associated with a trend toward reduced mortality (fixed model, OR 0.51, 95% CI 0.25-1.02, $P = 0.06$).[27]

Four single centers reported observation from cohorts that ranged from 49 to 170 patients of statin therapy following aneurysmal SAH.[21-24] These observational studies were considered to low quality because of relatively small sample sizes, heterogeneity in baseline, clinical management and definition of clinical outcome. A meta-analysis was performed using these 4-observation cohort studies, one case control study[25] and 6 RCTs which included 1,542 patients, whom 385 received statin.[27] Statin use after aneurysmal SAH was not significant associated with reduced DCI (OR 0.96, 95% CI 0.71-1.31, $P = 0.80$) or mortality (OR 1.16, 95% CI 0.78-1.73, $P = 0.47$). A more recent case-control study with atorvastatin suggested that the atorvastatin may have an anti-ischemic effect on imaging, but no clinical benefit after aneurysmal SAH.[26]

Consistent across all studied, there were no significant adverse effects associated with statin use after aneurysmal SAH. Asymptomatic elevation of liver enzyme within unexpected range was reported in 3 RCTs[15,17,18] with only 1 patient having to discontinue statin because of myalgia.[18]

ICH

Although case-control studies of statin use before ICH has demonstrated an association with favorable outcomes and reduced mortality after ICH,[28] there are no clinical studies of early initiation after ICH onset. Preclinical studies have shown beneficial effects on functional outcome in several animal models of ICH.[29-31] Pleiotropic effects of statin such as neuroprotection and stimulation of neurogenesis and synaptogenesis might be contributed to this benefit.[32] A multicenter observational cohort study in Israel, including 89 patients with statin from a total of 312 ICH patients, showed that the prior use of statins was associated with good neurologic outcome at discharge of the patients (OR 2.97, 95% CI 1.25-7.35, $P = 0.015$) and reduced mortality or discharge to a nursing facility (OR 0.25, 95% CI 0.09-0.63, $P = 0.004$) [Tables 2 and 3].[33] Another single center study compared 90-day functional outcome in 238 pre-ICH statin cases and 461 statin-free cases.[28] In this study, statin therapy was associated with improved functional outcome (OR 2.08, 95% CI 1.37-3.17, $P = 0.004$) and reduced mortality (OR 0.47, 95% CI 0.32-0.70, $P = 0.005$) without an effect on hematoma expansion. A meta-analysis was performed of 6 trials that usedstatins before ICH and the data showed a increased associationwith favorable outcomes (OR 1.19, 95% CI 1.38-2.65, $P < 0.0001$) and reduced mortality (OR 0.55, 95% CI