Simvastatin in aneurysmal subarachnoid haemorrhage (STASH): a multicentre randomised phase 3 trial

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Summary

Background The benefit of statins in patients with acute aneurysmal subarachnoid haemorrhage is unclear. We aimed to determine whether simvastatin 40 mg could improve the long-term outcome in patients with this disorder.

Methods In this international, multicentre, randomised, double-blind trial, we enrolled patients aged 18–65 years with confirmatory evidence of an aneurysmal subarachnoid haemorrhage and presenting less than 96 h from ictus from 35 acute neurosurgical centres in nine countries. Patients were randomly allocated (1:1) to receive either simvastatin 40 mg or placebo once a day for up to 21 days. We used a computer-generated randomisation code to randomise patients in every centre by blocks of ten (five simvastatin, five placebo). Participants and investigators were masked to treatment assignment. The primary outcome was the distribution of modified Rankin Scale (mRS) score obtained by questionnaire at 6 months. Analyses were done on the intention-to-treat population. This trial has been completed and is registered with Current Controlled Trials, number ISRCTN75948817.

Findings Between Jan 6, 2007, and Feb 1, 2013, apart from the period between May 15, 2009, and Feb 8, 2011, when recruitment was on hold, 803 patients were randomly assigned to receive either simvastatin 40 mg (n=391) or placebo (n=412). All patients were included in the intention-to-treat population. 782 (97%) patients had outcome data recorded at 6 months, of whom 560 (72%) were classed as having a favourable outcome, mRS 0–2 (271 patients in the simvastatin group *vs* 289 in the placebo group). The primary ordinal analysis of the mRS, adjusted for age and World Federation of Neurological Surgeons grade on admission, gave a common odds ratio (OR) of 0·97, 95% CI 0·75–1·25; p=0·803. At 6 months, we recorded 37 (10%) deaths in the simvastatin group compared with 35 (9%) in the placebo group (log-rank p=0·592). 70 (18%) serious adverse events were reported in the simvastatin group compared with 74 (18%) in the placebo group. No suspected unexpected serious adverse reactions were reported.

Interpretation The STASH trial did not detect any benefit in the use of simvastatin for long-term or short-term outcome in patients with aneurysmal subarachnoid haemorrhage. Despite demonstrating no safety concerns, we conclude that patients with subarachnoid haemorrhage should not be treated routinely with simvastatin during the acute stages.

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Introduction

Subarachnoid haemorrhage from a ruptured intracranial aneurysm remains a somewhat common subtype of cerebral haemorrhagic stroke and is of substantial clinical and socioeconomic importance, affecting about 600 000 patients worldwide[1] and 7000 patients within the UK[2] every year. Subarachnoid haemorrhage causes a high level of death and disability, particularly since it affects a younger age group than do other stroke subtypes.[3] Combined morbidity and mortality reaches up to 50%, with a third of survivors remaining dependent,[2] and 20–30% of patients admitted to hospital initially with good clinical grade can have poor outcomes.[4] In the UK, this equates to 3500 patients either dying or with severe disability every year.[5] Death and disability relate largely to the extent of the bleed and secondary complications, including hydrocephalus, sepsis, and cerebral infarction.[6]

Pharmacological attempts to improve outcome have been largely disappointing.[7–11] Nimodipine, a selective calcium-channel blocker, remains the only specifically applied pharmacological intervention in the acute management of subarachnoid haemorrhage population.[12] Despite this isolated therapeutic advance, delayed ischaemic deficits remain a source of disability after subarachnoid haemorrhage, and prevention of cerebral artery vasospasm remains a key target for new pharmacological treatments.[13] Candidate drugs include statins,[14–16] which have an excellent safety record as well as several potential beneficial effects after subarachnoid haemorrhage, such as cerebral blood flow enhancement, anti-inflammation, and upregulation of the endothelial nitric oxide synthase (eNOS) pathway. Statins inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase and block the formation of mevalonate, an important precursor for both cholesterol and other non-sterol products.[17] This inhibitory mechanism might underpin some of the known neuroprotective properties of statins: improved endothelial vasomotor function, increased endothelial cell fibrinolytic activity, reduced thrombogenic potential, inhibition of platelet activation, and suppression of cytokine response during cerebral

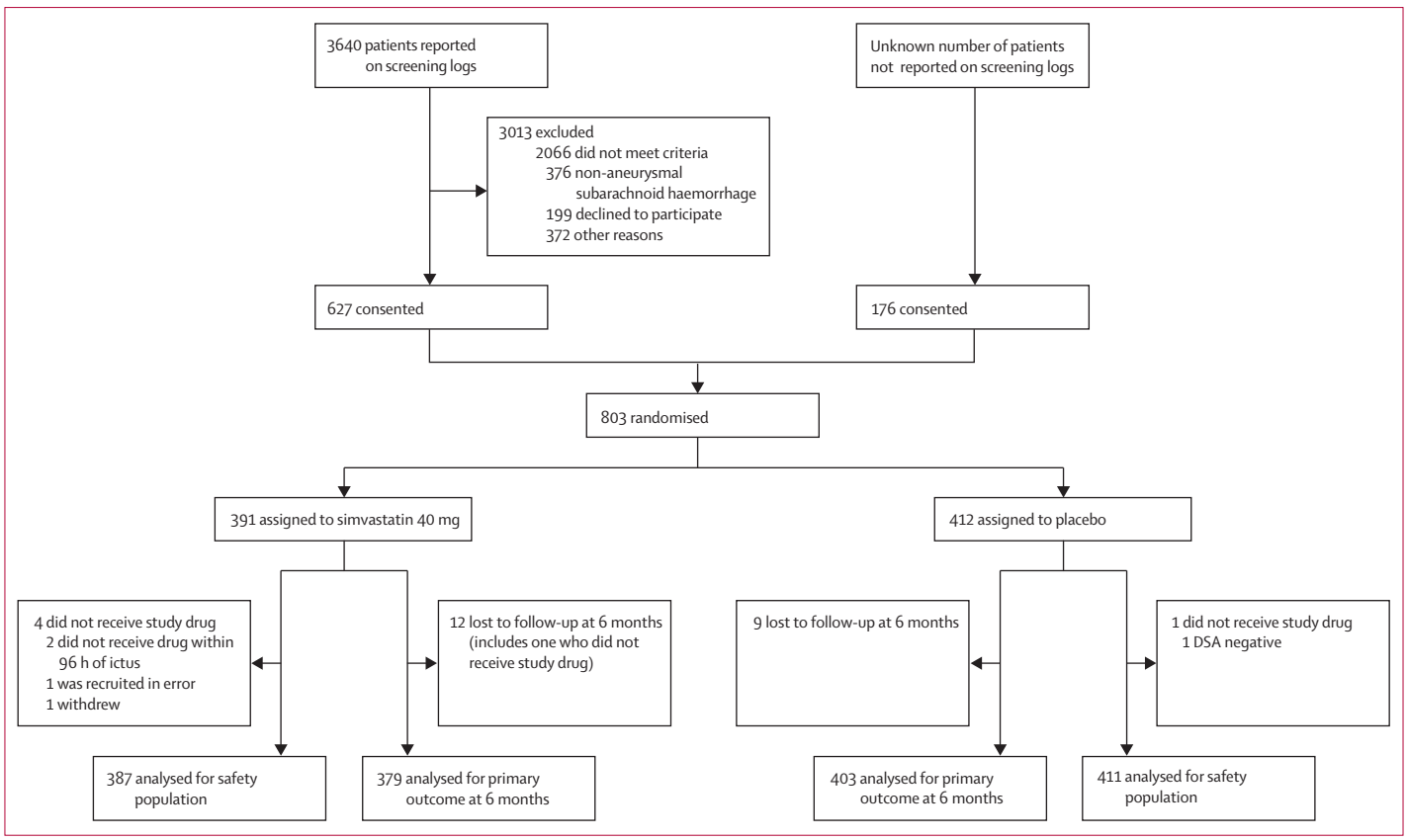

Figure 1: **Trial profile**
DSA=digital subtraction angiography. A screening log is a document that records all patients who enter the screening process before consent.

ischaemia.[18] Statins also improve cerebral blood flow through other properties that are of particular relevance to subarachnoid haemorrhage in view of low cerebral blood flow and impaired autoregulation. The timing for these effects is clearly important given that, in the experimental setting, statins take 24 h to affect enhanced cerebral blood flow in the ischaemic brain.[19]

See Online for appendix

Results from phase 2 randomised trials have shown a potential role for statin therapy in subarachnoid haemorrhage.[15,20–22] For example, pravastatin (40 mg per day) ameliorated cerebral vasospasm, maintained autoregulation, and reduced the incidence of vasospasm-related delayed ischaemic deficit after subarachnoid haemorrhage.[15] The need for inotropic support therapy and intensive care units, and incidence of unfavourable outcomes also showed improvements.

We aimed to investigate the effect of statins on the clinical outcome of patients with aneurysmal subarachnoid haemorrhage.

Methods

Trial design and participants

For the **STASH** protocol see http://www.stashtrial.com

STASH is an international, multicentre, parallel group, double-blind, randomised phase 3 trial. Patients were recruited from 35 neurosurgical units (23 in the UK and 12 non-UK sites: in Canada, Colombia, Italy, Russia, Singapore, Sweden, Uruguay, and USA; appendix).

For UK sites, we obtained ethics approval from the Berkshire Research Ethics Committee (06/MRE12/26) and regulatory approval from the Medicines and Healthcare products Regulatory Agency, MHRA (2006-000277-30). Appropriate ethics and regulatory approvals were sought for non-UK participating sites, in accordance with the International Conference on Harmonisation guidelines for good clinical practice (ICH GCP). We obtained informed written consent from all patients or their legal representative.

Recruitment took place between Jan 6, 2007, and Feb 1, 2013, with a period of 20 months between May 15, 2009, and Feb 8, 2011, when recruitment was on hold. This break was needed to address trial drug dispensing and labelling regulatory issues. On resolution it was no longer feasible to recruit from non-UK sites.

Inclusion criteria were radiological confirmatory evidence of an aneurysmal subarachnoid haemorrhage (by digital subtraction angiography [DSA], CT angiography [CTA], or magnetic resonance angiography [MRA]), age 18–65 years, and presentation less than 96 h from ictus.

Exclusion criteria were patient taking statin therapy at presentation, pregnancy, no reasonable prospect of

survival, known renal or hepatic impairment, patient not fully independent before bleed, strong suspicion of drug or alcohol misuse, patient unlikely to be amenable to follow-up, patient taking warfarin-type drugs, patient taking contraindicated medication (amiodarone, amlodipine, verapamil, or potent CYP3A4 inhibitors), or suspected additional life-threatening disease.

Randomisation and masking

Patients were randomly assigned (1:1) to receive either simvastatin 40 mg or placebo. Coded bottles containing either 21 tablets of simvastatin 40 mg or placebo were assigned a number (Ipswich Pharmacy Manufacturing Unit, UK). A computer-generated randomisation code was used to randomise patients by blocks of ten (five simvastatin, five placebo). Equal numbers of active and placebo bottles in batches of ten were distributed to every study centre. Each bottle was identified by a code number specific to the centre and subsequently selected for distribution in ascending numerical order. The solution to each code was kept secure within the Ipswich Pharmacy Manufacturing Unit and the Clinical Trial Pharmacy Department in the Study Coordinating Centre (Cambridge University Hospitals NHS Foundation Trust). To preserve masking, the placebo and simvastatin pills were identical white tablets with no identifiable markings.

Procedures

Patients started treatment as soon as possible within 96 h of the ictus, for a period of up to 3 weeks. Trial medication consisted of one tablet a day, given orally or ground by pestle and mortar and then via a nasogastric tube. The study drug was stopped on discharge from the neurosurgical unit. Because patients were believed to be at very low risk of subsequent vasospasm at discharge, we deemed continuation of trial medication thereafter unnecessary. Commencement of study drug was not dependent on aneurysm treatment, which was standard for each recruiting centre.

Outcomes

The primary outcome was the distribution of modified Rankin Scale (mRS) scores assessed at 6 months by means of a standardised questionnaire. Secondary outcomes were death at 6 months, delayed ischaemic deficits, delayed ischaemic deficit requiring rescue therapy, requirement for intensive care, incidence of sepsis, discharge destination, and quality of life as measured by the SF-36 (short form health survey questionnaire at 6 months). These secondary outcomes were preselected to provide supportive evidence related to the primary outcome. We defined delayed ischaemic deficit as a deterioration of two or more points on the Glasgow Coma Scale that could not be attributed to any other cause including sepsis. We defined sepsis when clinical symptoms (eg, raised temperature, raised white cell count, tachycardia, or raised respiratory rate) had microbiological confirmation. Use of hypervolaemic and inotropic rescue treatment was that adopted by every centre and did not follow any prescribed definition.

Previous data showed no safety concerns.[16] We confined reporting of adverse events in this study to serious adverse events and those that we deemed to be related to trial medication.

Statistical analysis

We did the analysis of outcome measures on the intention-to-treat population (namely, all patients who were randomly assigned to treatment and had any post-randomisation data recorded). Accordingly, we included all those discharged before completion of the 21-day treatment period or who died during these first 21 days. For the primary outcome measure alone, we did a secondary analysis on the per-protocol population. The per-protocol population included all patients who were randomly assigned to treatment and who received at least

	Simvastatin 40 mg (n=391)	Placebo (n=412)
UK participants	332 (85%)	344 (83%)
Non-UK participants	59 (15%)	68 (17%)
Mean age, years (range; SD)	51 (20–65; 9·5)	49 (20–69; 9·8)
Male sex	131 (34%)	121 (29%)
Ethnic origin*		
White	360 (92%)	363 (88%)
Asian	12 (3%)	25 (6%)
Black	6 (2%)	7 (2%)
Hispanic	10 (3%)	14 (3%)
Other	3 (<1%)	2 (<1%)
WFNS SAH grade		
I	198 (51%)	192 (47%)
II	90 (23%)	108 (26%)
III	8 (2%)	23 (6%)
IV	56 (14%)	51 (12%)
V	39 (10%)	38 (9%)
Motor deficit	36 (9%)	62 (15%)
Cranial nerve deficit	31 (8%)	40 (10%)
Ventilated	84 (22%)	81 (20%)
Fisher grade†		
1	7 (2%)	8 (2%)
2	47 (12%)	64 (16%)
3	135 (35%)	132 (32%)
4	200 (51%)	206 (50%)
Intraparenchymal haemorrhage	53 (14%)	58 (14%)
Intraventricular haemorrhage	136 (35%)	146 (35%)
Subdural haemorrhage	8 (2%)	9 (2%)
Cerebral infarct	3 (<1%)	2 (<1%)
Hydrocephalus (requiring external ventricular drain)	55 (14%)	59 (14%)

Data are number of patients (%) unless otherwise indicated. WFNS=World Federation of Neurosurgical Societies. SAH=subarachnoid haemorrhage. *Data were missing for one patient in the placebo group. †Data were missing for two patients in each group.

Table 1: **Baseline clinical and demographic characteristics of participants**

one dose of study medication or placebo, did not have a major protocol violation, and completed a 6-month mRS. We based the reporting of data for biochemistry and adverse events on the safety population (ie, all patients who received at least one dose of study medication or placebo). We defined major protocol violations in the statistical analysis plan, which was completed before database lock. Likewise, we predetermined evaluable patients during a review of blinded data.

	Simvastatin 40 mg (n=391)	Placebo (n=412)
Imaging modality*		
MRA	4 (1%)	6 (2%)
CTA	299 (76%)	314 (76%)
DSA	123 (31%)	135 (33%)
Location of aneurysm		
Anterior communicating	145 (37%)	117 (28%)
Posterior communicating	88 (23%)	97 (24%)
Internal carotid	32 (8%)	39 (10%)
Middle cerebral	77 (20%)	95 (23%)
Posterior circulation	37 (10%)	37 (9%)
Other	9 (2 %)	21 (5%)
Not recorded	3 (<1%)	6 (2%)
Mean time from ictus to treatment, days (range; SD)	1·7 (0–10; 1·3)	1·7 (0–17; 1·6)
Mean time from ictus to first dosing, days (range; SD)	2·1 (0–5; 1·0)	2·2 (0–4; 1·0)
Treatment modality		
Clipping only	119 (30%)	135 (33%)
Coiling only	258 (66%)	255 (62%)
Clipping and coiling	2 (<1%)	12 (3%)
Other	0	2 (<1%)
No treatment	12 (3%)	8 (2%)

Data are number of patients (%) unless otherwise indicated. MRA=magnetic resonance angiography. CTA=computed tomography angiography. DSA=digital subtraction angiography. *Some patients had more than one type of imaging to confirm aneurysm.

Table 2: **Inpatient investigational variables and treatment profile**

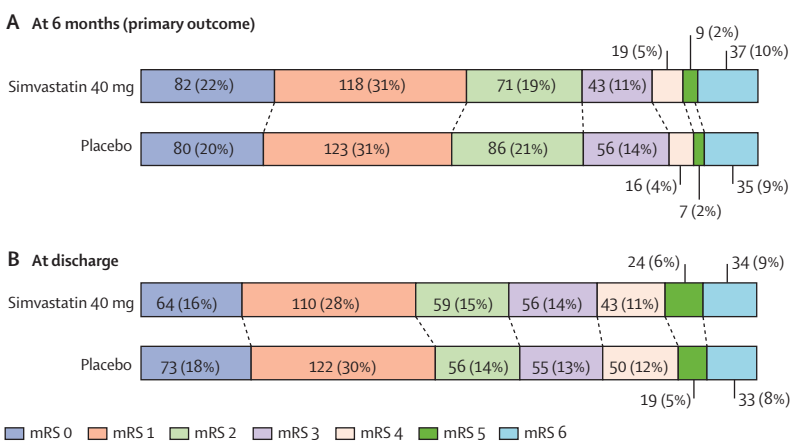

Figure 2: **Distribution of scores on the mRS scale**
(A) At 6 months. (B) At discharge. mRS=modified Rankin Scale.

All data were obtained and assessed locally. A selection of patient case notes and laboratory data was reviewed for accuracy by one study monitor who visited as many sites as was feasible throughout the trial.

We estimated the sample size of 800 randomised patients to give 90% power at the 5% significance level (two-sided) to detect a treatment effect equivalent to an absolute increase of 7% in the proportion of patients with a favourable outcome. This calculation was based on an ordinal analysis of the 6-month mRS (the primary outcome) assuming that the treatment effect follows a proportional odds model.[23]

We included presenting WFNS grade and age as covariates along with the treatment allocation. Results are presented as an adjusted common odds ratio (OR) with the corresponding 95% CI, with values of the common OR of less than 1 indicating a treatment effect in favour of simvastatin. Additionally, a sensitivity analysis using binary logistic regression was done with the same covariates as specified above, adopting the conventional dichotomy of favourable mRS (0–2) versus unfavourable mRS (3–6). An exploratory analysis examined all other potential splits of the mRS. We repeated the ordinal and binary logistic analyses using the per-protocol population.

We did all analyses of secondary outcome measures on the intention-to-treat population, using χ^2 test or two-sample t tests as appropriate. Mortality after randomisation is shown with Kaplan-Meier survival estimates and we compared the groups formally using a log-rank test. We deemed adjustment for multiplicity unnecessary because the trial has a single pre-specified primary outcome measure. We examined the influence of key pre-randomisation characteristics of patients and treatment type on favourable or unfavourable outcome by means of a post-hoc forest plot analysis.

For the biochemical profiles, we reported percentage changes from baseline to accommodate potentially highly skewed data making absolute changes inappropriate.[24] The lipid profiles were sought to show whether the trial statin treatment was having an expected and appropriate physiological effect. This trial is registered with Current Controlled Trials, number ISRCTN75948817 and ClinicalTrials.gov (NCT00731627).

Role of the funding source

The funders of the study had no role in the study design, data collection, data analysis, data interpretation, nor writing of the report. Following completion of recruitment, the corresponding author had full access to all the data in the study and final responsibility for the decision to submit for publication.

Results

We randomly assigned 803 patients from 35 neurosurgical units (appendix) to receive either simvastatin 40 mg (391 patients) or placebo (412 patients) between Jan 6, 2007, and Feb 1, 2013, except from the period between May 15,

2009, and Feb 8, 2011 when recruitment was on hold. 782 (97%) patients had outcome data recorded at 6 months, with 379 allocated to the simvastatin group and 403 to the placebo group (figure 1).

Baseline characteristics were balanced between the two groups with respect to age, sex, ethnic origin, and neurological status on admission (table 1). Although about 73% of both groups had a good WFNS grade on admission (WFNS 1 or 2), a high proportion of patients had heavy blood load determined by Fisher grades 3 and 4 (335 [86%] of 391 patients given simvastatin, 338 [82%] of 412 patients given placebo).

Imaging modality was well matched, with most intracranial aneurysms identified with CTA (76% for both groups; table 2). Groups were also matched with respect to aneurysm location, although the simvastatin group had a slightly higher percentage of anterior communicating aneurysms than did the placebo group (table 2). Time from ictus to treatment of aneurysm (surgical or endovascular), or from ictus to randomisation did not differ between groups. Surgical clipping occurred in about a third of patients in each group.

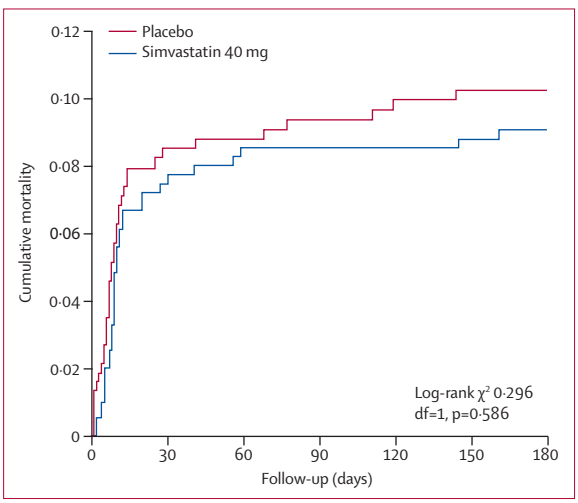

Figure 3: **Kaplan-Meier survival curve**

	Adjusted* OR (95% CI)
0 *vs* 1–6	0·89 (0·62–1·27)
0–1 *vs* 2–6	0·91 (0·68–1·22)
0–2 *vs* 3–6	1·01 (0·73–1·41)
0–3 *vs* 4–6	1·27 (0·86–1·89)
0–4 *vs* 5–6	1·22 (0·80–1·92)
0–5 *vs* 6	1·22 (0·77–1·93)

OR=odds ratio. mRS=modified Rankin Scale. *Adjusted common OR for the primary ordinal analysis was 0·97 (95% CI 0·75–1·25, p=0·809). Analyses were adjusted for age and baseline World Federation of Neurosurgical Societies subarachnoid haemorrhage grade. ORs of less than 1 indicate a treatment effect in favour of simvastatin.

Table 3: **Logistic regression analysis for all potential splits of the mRS**

At 6 months' follow-up, 560 (72%) patients were classed as having a favourable outcome, mRS 0–2 (271 patients in the simvastatin group *vs* 289 patients in the placebo group [adjusted for age and WFNS grade on admission common OR 0·97, 95% CI 0·75–1·25; p=0·809]; figure 2). The proportion recorded with a favourable outcome at

	Simvastatin 40 mg (n=391)	Placebo (n=412)	p value
Suspected delayed ischaemia			
Proven radiological infarct	61 (16%)	71 (17%)	0·5328
Clinical delayed ischaemic deficits	64 (16%)	67 (16%)	0·9675
Other causes of deterioration			
Sepsis	96 (25%)	99 (24%)	0·8628
Epilepsy	7 (2%)	12 (3%)	0·2956
Hypoxia	7 (2%)	5 (1%)	0·5008
Rebleed	8 (2%)	10 (2%)	0·7153
Hydrocephalus (requiring external ventricular drain)	69 (18%)	76 (18%)	0·7685
Other	35 (9%)	44 (11%)	0·4111
Suspected statin-related deterioration			
Raised liver function tests	15 (4%)	27 (7%)	0·0839
Interstitial lung disease	0	0	
Rhabdomyolysis	0	0	
Rescue therapy			
Extended hypervolaemic therapy	81 (21%)	118 (29%)	0·0093
Inotropic support	112 (29%)	123 (30%)	0·7064
Angioplasty	10 (3%)	11 (3%)	0·9206
Intrarterial papaverine or nimodipine	7 (2%)	10 (2%)	0·5309
Steroids	27 (7%)	36 (9%)	0·3344
ITU or HDU stay	212 (54%)	227 (55%)	0·8029
ITU or HDU mean stay, days (range; SD)	10·7 (1–68; 8·8)	12·8 (1–151; 13·4)	..
Mean length of hospital stay (range; SD)	20 (1–160; 17·5)	20 (4–120; 16·5)	..
Discharge destination			0·1547
Home	235 (60%)	236 (57%)	..
Non-neurosurgical ward	71 (18%)	63 (15%)	..
Rehabilitation	41 (10%)	61 (15%)	..
Other	10 (3%)	19 (5%)	..
Died	34 (9%)	33 (8%)	..
Modified Rankin Scale score at discharge			0·9181
mRS 0	64 (16%)	73 (18%)	..
mRS 1	110 (28%)	122 (30%)	..
mRS 2	59 (15%)	56 (14%)	..
mRS 3	56 (14%)	55 (13%)	..
mRS 4	43 (11%)	50 (12%)	..
mRS 5	24 (6%)	19 (5%)	..
mRS 6	34 (9%)	33 (8%)	..
SF-36 at 6 months			..
Number of patients	315	341	..
Physical score mean (range; SD)	57·6 (2–100; 25·4)	57·2 (4–100; 25·5)	0·8479
Mental score mean (range; SD)	58·4 (2–100; 25·6)	59·2 (5–100; 25·3)	0·7135
Overall score mean (range; SD)	59·0 (4–100; 25·8)	59·0 (4–100; 25·5)	0·9880

ITU=intensive therapy unit. HDU=high dependency unit.

Table 4: **Secondary outcome measures**

discharge was also similar between groups: 233 (60%) in the simvastatin group compared with 251 (62%) in the placebo group (OR 1·08, 0·81–1·43, p=0·608; figure 2). At 6 months, 37 (10%) patients in the simvastatin group had died compared with 35 (9%) in the placebo group (log-rank p=0·592, figure 3). Binary logistic regression exploring all potential splits for the mRS at 6 months (table 3) failed to show a difference for any level examined. We could not detect any major violations of the proportional odds assumption and this was confirmed by a formal goodness of fit test.

For the secondary outcomes, clinical deterioration thought to be related to delayed ischaemic deficit, statin-related deterioration, or other possible causes did not differ between groups (table 4). Length of hospital stay (mean 20 days in both groups) and mortality at discharge did not differ between groups.

Use of extended hypervolaemic therapy differed between groups (table 4), although the duration of extended hypervolaemic therapy was the same (8 days in both groups). The need for hypertensive inotropic support showed no differences between groups.

We recorded biochemical markers at baseline and between days 9 and 12. A recording for total cholesterol at baseline and at follow-up was available in 503 (63%) of 803 patients (245 in the statin group, 258 in the placebo group). Total cholesterol, low-density lipoprotein (LDL), and LDL/high-density lipoprotein (HDL) ratio were lower in the simvastatin group than in the placebo group (table 5).

44 patients were reported to have an adverse event of raised liver function tests (23 in the statin group, 21 in the placebo group), 18 patients had rebleeds (11 in the statin group, seven in the placebo group), of which four were intraoperative and five occurred before securing the aneurysm. 64 patients had a cerebral infarction (31 in the statin group, 33 in the placebo group). We could not detect any differences in adverse events between the two groups.

62 patients were withdrawn from study medication before completing the course (26 in the statin group, 36 in the placebo group). 16 patients chose to withdraw (eight in each group), and 18 were withdrawn because of prescription of contraindicated drugs (three in the statin group, 15 in the placebo group). In 13 cases it was not possible to determine whether changes in liver function tests were related to the trial drug (seven in the statin group, six in the placebo group). Six patients missed several doses and were withdrawn by the local clinician (four in the statin group, two in the placebo group), two patients had an unexplained rash (both in the statin group), one from the statin group chose to withdraw because of excess nausea, and six were withdrawn for undetermined causes (one in the statin group, five in the placebo group).

No suspected unexpected serious adverse reactions were reported. 18% of patients in both the simvastatin group (n=70) and the placebo group (n=74) had a serious adverse event. Of these, there were 72 deaths (37 in the statin group *vs* 35 in the placebo group), nine patients in each group had a significant infarction, 28 patients (11 statin, 17 placebo) were readmitted, and the remainder (13 in both groups) had a range of events including myocardial infarction, sepsis, infarction, rebleed and pulmonary embolus. The appendix shows all serious adverse events.

A post-hoc analysis of the primary outcome was undertaken to assess the influence of trial drug compliance. Distribution of mRS scores did not differ between groups in patients who were recorded as being fully trial drug compliant (documented as having taken all the allocated medication prescribed; n=496; adjusted for age and WFNS grade on admission OR 1·13, 95% CI 0·82–1·56; p=0·4465; figure 4).

	Baseline	Day 9–12	Percent change from baseline to day 9–12	p value comparing treatment groups*
Total cholesterol (mmol/L)				<0·0001
Placebo	4·4 (3·7 to 5·2)	4·5 (3·7 to 5·2)	0 (–13 to 18)	
Simvastatin 40 mg	4·4 (3·7 to 5·3)	3·6 (3·0 to 4·1)	–21 (–35 to –8)	
LDL (mmol/L)				<0·0001
Placebo	2·7 (2·0 to 3·2)	2·8 (2·1 to 3·5)	8 (–12 to 38)	
Simvastatin 40 mg	2·6 (2·0 to 3·3)	1·8 (1·4 to 2·3)	–28 (–46 to 7)	
HDL (mmol/L)				0·4910
Placebo	1·2 (1·0 to 1·5)	1·0 (0·8 to 1·2)	–22 (–36 to –8)	
Simvastatin 40 mg	1·2 (1·0 to 1·5)	0·9 (0·8 to 1·2)	–22 (–34 to –8)	
LDL/HDL ratio				<0·0001
Placebo	2·1 (1·6 to 2·8)	2·8 (2·2 to 3·8)	36 (5 to 90)	
Simvastatin 40 mg	2·2 (1·6 to 3·0)	2·0 (1·4 to 2·6)	–8 (–38 to 37)	
Triglycerides (mmol/L)				0·0070
Placebo	1·2 (0·9 to 1·7)	1·6 (1·2 to 2·2)	32 (0 to 85)	
Simvastatin 40 mg	1·2 (0·9 to 1·6)	1·4 (1·1 to 1·9)	21 (–10 to 61)	
C-reactive protein (mg/L)				0·9663
Placebo	16 (6 to 45)	16 (7 to 38)	0 (–67 to 133)	
Simvastatin 40 mg	18 (6 to 50)	16 (7 to 39)	–15 (–63 to 143)	
Muscle creatine kinase (U/L)				0·9077
Placebo	112 (65 to 268)	56 (38 to 99)	–54 (–77 to –6)	
Simvastatin 40 mg	114 (68 to 244)	58 (38 to 97)	–50 (–78 to –16)	

Data are median (IQR). LDL=low-density lipoprotein. HDL=high-density lipoprotein. *p values are based on Mann-Whitney tests.

Table 5: **Biochemical markers**

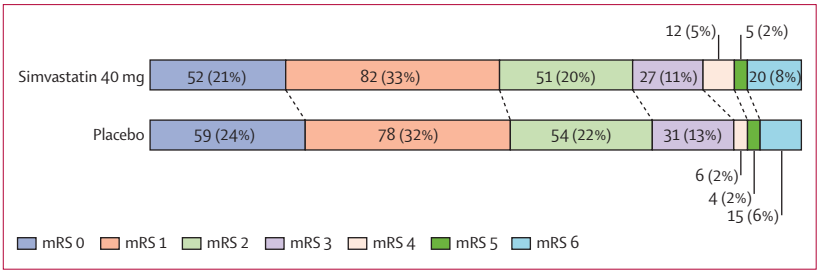

Figure 4: **Distribution of scores on the mRS scale at 6 months for patients who were fully compliant to study medication**

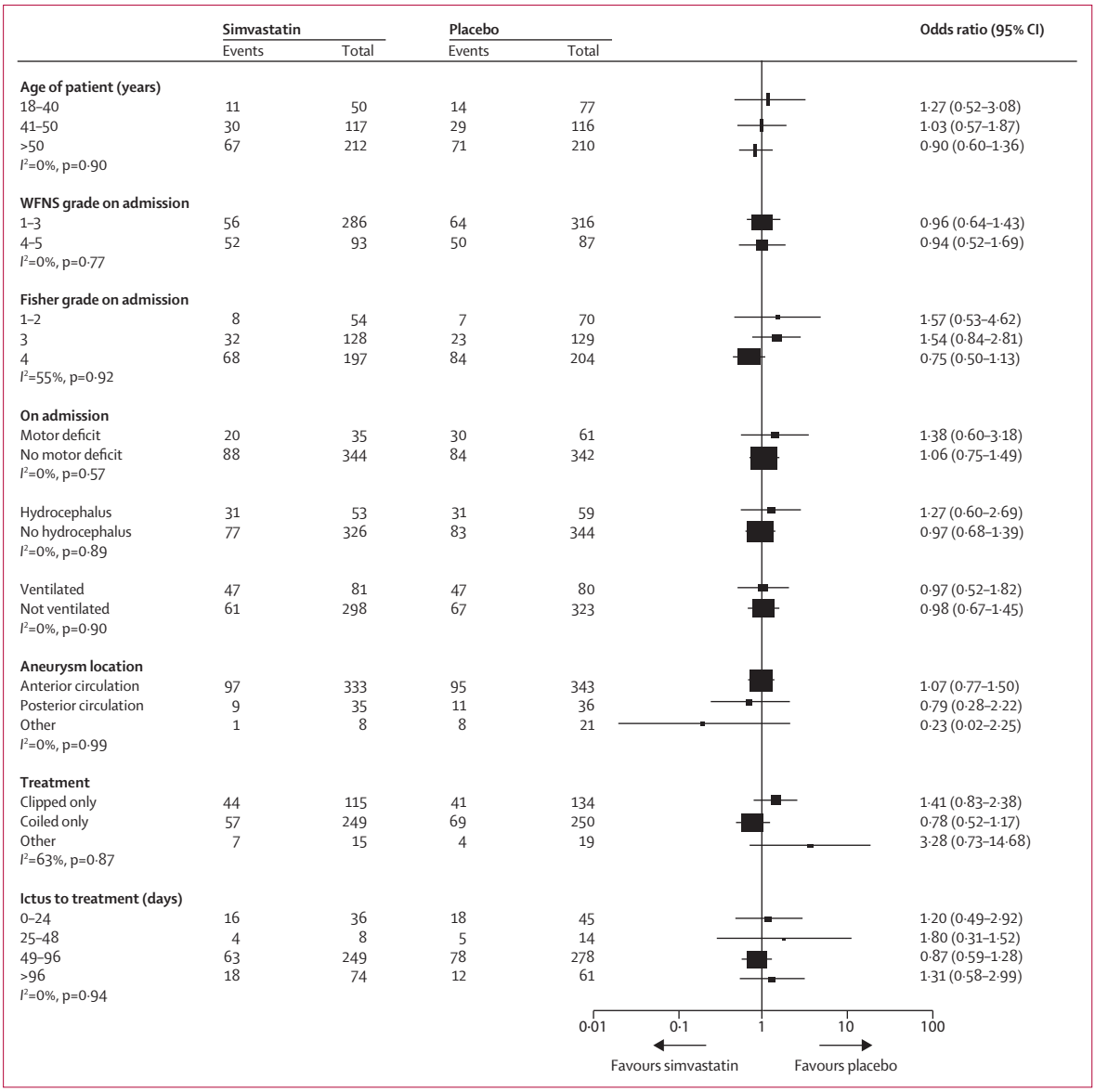

Figure 5: **Influence of key pre-randomisation characteristics of patients and treatment type on favourable or unfavourable outcome, post-hoc analysis**
WFNS=World Federation of Neurosurgical Societies.

Analysis of pre-randomisation prognostic variables (age, WFNS grade, ventilation status, CT findings, aneurysm location) and the timing and mode of treatment failed to show any benefit for treatment with simvastatin according to each variable examined (figure 5). I^2 estimates the percentage of the observed differences between subgroups which cannot be explained by chance.[25]

Discussion

The STASH study conclusively shows that 40 mg of simvastatin, although safe, affords no significant benefit in clinical outcome after acute aneurysmal subarachnoid haemorrhage. All primary outcome measures were neutral between treatment groups for all potential splits of mRS in the logistic regression analysis. Outcome was also neutral for all secondary endpoints except for the need for extended hypervolaemic therapy. This need for extended hypervolaemic treatment did not translate into a reduction in the length of intensive-care facility stay or overall hospital stay, nor reduce the need for inotropic hypertensive support. In the context of the other primary and secondary outcomes, we consider this finding most likely to be spurious, and of little clinical relevance, particularly since the degree of hypervolaemic therapy might not be quantified accurately.

Why has STASH not shown any effect in light of positive phase 2 studies (panel, figure 6)?[15,20] The study did

well in selection and follow-up of an appropriate target population, with only nine (1%) of 803 patients proving angiogram negative, and 21 (3%) not having a 6-month outcome assessment. Loss of follow-up of only 3% of the cohort is unlikely to have influenced our results, and hence a worst case scenario analysis was considered futile. The angiogram-negative population (which on the whole do not develop delayed ischaemic deficit) has been a substantial degrading factor in previous studies of this type.[12] As such, we do not consider that patient selection has influenced our results. The great improvement in the selection of a pure population of aneurysm-positive patients indicates rapid access to CT scanning and angiography, allowing a positive aneurysm diagnosis in advance of assessment for study eligibility.

Study drug compliance is of concern, with only 496 (62%) of 803 patients taking full trial medication according to the protocol. However, the key biochemical profiles did show the expected responses, with substantial falls in serum total cholesterol and LDL in the simvastatin group only. Additionally, a post-hoc analysis restricting the outcome comparisons to those who took all prescribed medications according to protocol showed complete neutrality in the primary outcome measure. Therefore, we do not feel that STASH missed an effect due to incomplete dispensing. Likewise, the trial drug was dispensed at an early stage in most cases (mean of 2 days, table 2).

The use of simvastatin 40 mg (as opposed to pravastatin 40 mg) is an unlikely explanation for the differences seen between phase 2 studies[15] and the outcome of STASH. The phase 2 studies explored physiological variables (cerebral arterial flow velocity and autoregulation) related to delayed ischaemic deficit, which showed improvements. However, most patients with disturbed autoregulation still remained clinically well. Simvastatin 40 mg has twice the LDL reducing properties of pravastatin 40 mg; hence insufficient dose is an unlikely explanation.[15] Whether pravastatin has a unique effect in enhancing cerebral blood flow not noted with simvastatin is a possibility, but does not explain the equally positive phase 2 studies reported for simvastatin in subarachnoid haemorrhage.[20] A positive effect with a higher dose of simvastatin (80 mg once daily) cannot be excluded, especially for certain subgroups, but at this juncture we feel this effect is unlikely given the totally flat response irrespective of how much trial medication was actually taken.

The rate of clinically diagnosed delayed ischaemic deficit was low in both groups (about 16%), reflecting a high proportion of good grade (WFNS 1 and 2) patients at recruitment (about 73%). A study powered to detect a 7% improvement in favourable outcome based on reductions in events related to delayed ischaemic deficit might therefore have proven ambitious. The higher rate for observed delayed ischaemic deficit (30%) in the phase 2 pravastatin study[15] is a clear example of how small studies can be misleading when powering phase 3 studies. However, a high percentage of patients did show dense bleeds (over 80% had Fisher grade 3 and 4) on the presenting CT scan, a feature usually associated with delayed ischaemic deficit and poor outcome. In view of the proposed effect of simvastatin in reducing delayed ischaemic deficit,[6] the small proportion of poor grade patients and related delayed ischaemic deficit might have been important factors in explaining the outcome of STASH. Previously reported prevalence rates for delayed ischaemic deficit of up to 40%[6] probably reflect several mechanisms, including technical difficulties in aneurysm treatment leading to obstruction of key associated vessels, impairments of cerebral blood flow, and delayed clinical manifestations, all indistinguishable from vasospasm-related delayed ischaemic deficit. Such technical difficulties have reduced with improved neurovascular and interventional treatments; hence, the low rate of delayed ischaemic deficit in our study is likely to represent the current true incidence of vasospasm-related delayed ischaemic deficit.[34]

Panel: Research in context

Systematic review

We searched the Cochrane, Medline, Embase, and PubMed databases for randomised trials and meta-analyses up to December, 2013. We identified four meta-analyses[26–29] and one Cochrane review.[30] Two of the meta-analyses[27,29] could not identify a benefit to the use of statins in aneurysmal subarachnoid haemorrhage, one supported their routine use,[28] and a further meta-analysis,[26] along with the Cochrane review,[30] concluded that there was insufficient evidence to conclusively determine their benefit. The STASH trial is to our knowledge the largest trial completed to date in patients with subarachnoid haemorrhage. Some heterogeneity exists between the trials with respect to type of statin (pravastatin and simvastatin), statin dose (40 mg and 80 mg), and length of treatment. Outcome measures vary between trials and are therefore difficult to compare. Figure 6 shows randomised trials assessing neurological outcome at discharge.[15,31,32] The largest study before STASH, published by McGirt and colleagues[33] with a cohort of 340 patients, concluded that simvastatin did not reduce the incidence of symptomatic cerebral vasospasm, death, or poor outcome in patients with subarachnoid haemorrhage; however, this was a prospective observational study.

Interpretation

Before this trial, the largest randomised blinded trials investigating the effects of statins in subarachnoid haemorrhage included 80,[15] 39,[20] and 32 patients.[32] There has been a need for a large randomised trial to definitively answer the question as to the effectiveness of statins in this population. Findings from the STASH trial show that statins have no measurable effect on the short-term or long-term outcome in these patients.

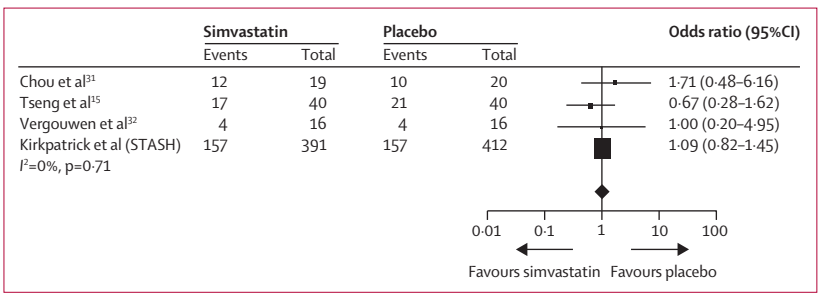

Figure 6: **Randomised trials measuring neurological outcome at discharge**

Other causes of deterioration were also equally represented between treatment groups, including sepsis, epilepsy, rebleeding, and hydrocephalus. The fibrinolytic properties of statins[2] did not seem to alter the rate of re-bleeding, notably low, nor the chances of developing acute hydrocephalus. Of some interest was the absence of an effect on sepsis given the positive findings for statins in intensive care septic complications.[16] The very low rates of epilepsy seen in this study undoubtedly show the overall improvement in the treatment of this disorder and parallel the low rates of delayed ischaemic deficit and ischaemic-related morbidity.

In summary, despite showing no safety concerns, results from the STASH study have shown that the generalised treatment of patients with subarachnoid haemorrhage with simvastatin during the acute stages has no place in clinical practice. The study limitations, including trial drug errors and non-compliance, early withdrawals, and dose limitation to 40 mg simvastatin, do not seem to account for our neutral findings.

Contributors

PJK, ADM, PJH, and CLT conceived the study. PJK, CLT, GDM, PJH, MT, and ADM designed and wrote the study protocol with input from all listed contributors. GDM is the study statistician who prepared the analysis for the report. All authors commented on the drafts and approved the final version. All listed investigators contributed to enrolment of patients and interpretation of data.

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Declaration of interests

We declare competing interests.

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