Fast assessment of stroke and transient ischaemic attack to prevent early recurrence (FASTER): a randomised controlled pilot trial

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Summary

Background Patients with transient ischaemic attack (TIA) or minor stroke are at high immediate risk of stroke. The optimum early treatment options for these patients are not known.

Methods Within 24 h of symptom onset, we randomly assigned, in a factorial design, 392 patients with TIA or minor stroke to clopidogrel (300 mg loading dose then 75 mg daily; 198 patients) or placebo (194 patients), and simvastatin (40 mg daily; 199 patients) or placebo (193 patients). All patients were also given aspirin and were followed for 90 days. Descriptive analyses were done by intention to treat. The primary outcome was total stroke (ischaemic and haemorrhagic) within 90 days. Safety outcomes included haemorrhage related to clopidogrel and myositis related to simvastatin. This study is registered as an International Standard Randomised Controlled Trial (number 35624812) and with ClinicalTrials.gov (NCT00109382).

Findings The median time to stroke outcome was 1 day (range 0–62 days). The trial was stopped early due to a failure to recruit patients at the prespecified minimum enrolment rate because of increased use of statins. 14 (7·1%) patients on clopidogrel had a stroke within 90 days compared with 21 (10·8%) patients on placebo (risk ratio 0·7 [95% CI 0·3–1·2]; absolute risk reduction −3·8% [95% CI −9·4 to 1·9]; p=0·19). 21 (10·6%) patients on simvastatin had a stroke within 90 days compared with 14 (7·3%) patients on placebo (risk ratio 1·3 [0·7–2·4]; absolute risk increase 3·3% [−2·3 to 8·9]; p=0·25). The interaction between clopidogrel and simvastatin was not significant (p=0·64). Two patients on clopidogrel had intracranial haemorrhage compared with none on placebo (absolute risk increase 1·0% [−0·4 to 2·4]; p=0·5). There was no difference between groups for the simvastatin safety outcomes.

Interpretation Immediately after TIA or minor stroke, patients are at high risk of stroke, which might be reduced by using clopidogrel in addition to aspirin. The haemorrhagic risks of the combination of aspirin and clopidogrel do not seem to offset this potential benefit. We were unable to provide evidence of benefit of simvastatin in this setting. This aggressive prevention approach merits further study.

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See Reflection and Reaction page 941

See Articles page 953

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Introduction

Time is crucial to the treatment of patients with cerebrovascular disease. Systems of care have been forced to become more responsive with the evidence that selected patients who receive thrombolysis with alteplase (recombinant tissue plasminogen activator, rt-PA) within 3 h of the onset of ischaemic stroke have an increased chance of excellent functional outcome.[1] However, the introduction of alteplase has also indicated those populations of patients for whom alternative treatment strategies need to be found, analogous to cardiology in which different treatments have evolved for ST elevation and non-ST elevation myocardial infarction.[2,3]

Patients have an unstable clinical course in the immediate aftermath of transient ischaemic attack (TIA) and minor stroke and have a high risk of recurrent stroke, most of which accrues in the initial 48 h after symptom onset.[4–7] Patients who substantially recover from their initial deficit are at the greatest risk of deterioration.[8,9] Alteplase is contraindicated in patients who recover, particularly those either rapidly improving or with a mild deficit,[10] but those patients excluded from alteplase treatment for these reasons are at a high subsequent risk of death or dependence at hospital discharge.[11] Secondary stroke prevention trials have either not focused on this period of

***Panel:* Stroke trial acronyms:**

CAPRIE—Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events

CARESS—Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic carotid Stenosis

CHARISMA—Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilisation, Management and Avoidance

ESPRIT—European/Australasian Stroke Prevention in Reversible Ischaemia Trial

MATCH—Management of Atherothrombosis with clopidogrel in high-risk patients with recent Transient ischaemic attack or isCHaemic stroke

MIRACL—Myocardial Ischemia Reduction and Aggressive Cholesterol Lowering

PRoFESS—Prevention Regimen For Effectively avoiding Second Strokes

SPARCL—Stroke Prevention by Aggressive Reduction in Cholesterol Levels

TOAST—Trial of Org 10172 in Acute Stroke Treatment

immediate high risk (eg, MATCH [within 3 months of symptom onset] and ESPRIT [within 6 months] trials, trial acronyms defined in panel),[12,13] or actively excluded such patients from randomisation (eg, SPARCL [patients not eligible for randomisation within 1 month of symptoms] and CAPRIE [not within 1 week of symptoms] trials).[14,15] Only the International Stroke Trial and Chinese Acute Stroke Trial have previously concentrated on enrolling patients with acute stroke within 48 h to an antiplatelet trial, both of which showed a reduction in the risk of recurrent stroke with the use of aspirin.[16–18]

The Fast Assessment of Stroke and TIA to prevent Early Recurrence (FASTER) trial was designed to assess, in a factorial design, whether clopidogrel and simvastatin, if started within 24 h of symptom onset and continued for 90 days, would reduce the risk of stroke after TIA or minor stroke.

Methods

Participants

Between May, 2003, and December, 2006, patients aged 40 years or older with a minor stroke, as defined by a US National Institutes of Health stroke scale (NIHSS) score of 3 or less at the time of randomisation, or TIA within 24 h of onset were eligible for enrolment. In addition, weakness or speech disturbance, dysarthria or dysphasia, had to be part of the symptom complex for greater than 5 min for patients to be eligible. The institutional review boards of each of the participating hospitals provided ethics approval for the study protocol and all patients provided written informed consent. The trial was administered from the FASTER Coordinating Centre in Calgary, Canada. All sites were monitored in person and all charts were reviewed, with in-depth review of 10% of all charts. This study is registered as an International Standard Randomised Controlled Trial (number 35624812) and with ClinicalTrials.gov (NCT00109382).

	Patients excluded (% of total screened)
Inclusion criteria	
Age ≥40 years	66 (2·1%)
Weakness or speech disturbance for >5 min	125 (4·0%)
Written informed consent	97 (3·1%)
Exclusion criteria	
Pure sensory, vertigo or dizziness, ataxia or visual disturbance symptoms without speech disturbance or weakness	263 (8·5%)
Indication for alteplase or other acute intervention	144 (4·6%)
Currently on a statin, antiplatelet therapy (but not aspirin), anticoagulation or long-term non-steroidal anti-inflammatory drugs (but not COX2 inhibitors)	851 (27·4%)
Should be started on a statin (in the opinion of the site investigator)	54 (1·7%)
Cause for their neurological deficit other than acute brain ischaemia (ie, intracranial haemorrhage or migraine)	544 (17·5%)
Presumed cardiac source of embolus	146 (4·7%)
Concomitant acute coronary syndrome	17 (0·5%)
Pre-morbid modified Rankin score ≥3	137 (4·4%)
Event secondary to a procedure (ie, carotid stenting)	8 (0·3%)
Uncontrolled or malignant hypertension	28 (0·9%)
Pregnant or breastfeeding	5 (0·2%)
Clear contraindication to use of the study medication (ie, known bleeding diathesis or hepatic dysfunction)	80 (2·6%)
Limited life expectancy	20 (0·6%)
Geographic or other factor that may interfere with trial follow-up	67 (2·2%)
Participation in another clinical trial concurrently or within 30 days	53 (1·7%)
Total	2705 (87·2%)

Data shown are the numbers (%) of patients who either did not meet the inclusion criteria, or met the exclusion criteria.

Table 1: **Reasons for screening failure**

Procedures

All patients were given 81 mg aspirin daily for the study duration, with a loading dose of 162 mg if they were naive to aspirin before study enrolment. In addition, patients were randomly assigned in a 2×2 factorial design to either placebo or 300 mg clopidogrel loading dose immediately followed by 75 mg clopidogrel daily, and to placebo or 40 mg simvastatin immediately followed by 40 mg daily in the evening. A patient was considered as randomised the moment that the loading doses were taken. A blocked randomisation procedure generated by the trial biostatistician was used by the central trial pharmacist to produce identical numbered study-treatment kits containing active drug or matched placebo. These were supplied to each site and were used sequentially, ensuring balanced numbers of patients in each group of the trial at any given time. The original trial protocol only allowed enrolment within 12 h of symptom onset. This was increased to 24 h in March, 2004, in an attempt to increase the enrolment rate. However, the focus on early enrolment was maintained by each site having a quota to enrol one patient within 12 h of symptom onset for every three patients enrolled within 12–24 h. The trial was blinded (patients, treating physicians, nurses, and study site coordinators). The central pharmacist, who played no role in the care of the patients, was the only person aware of treatment allocation.

Data collected at baseline included patients' demographics, vascular risk factors, pre-morbid modified Rankin scale (mRS) and Barthel index scores, history of the event leading to randomisation and clinical examination at the time of randomisation, including the NIHSS, and blood pressure. All patients had baseline brain imaging, with either CT or MRI, and an electrocardiogram before randomisation. In addition, blood was taken at baseline to identify patients with a clear contraindication to the trial medication, and to provide a benchmark to monitor the safety profile of the medication over the course of the trial.

Patients were followed for 90 days, with telephone contact made at 2, 30, and 60 days, and clinic visits at 10 and 90 days. If a patient had a stroke outcome, an additional clinic visit was made for 90 days after the stroke event to assess stroke severity. During telephone

contact, the questionnaire for verifying stroke-free status was administered,[19] with additional questions aimed to assess safety and other efficacy outcomes. If any outcomes were identified over the telephone, the patient was brought to clinic for review as soon as was practical. The clinic visits also involved the administration of the stroke-free-status questionnaire. Each patient was examined to provide NIHSS, mRS, and Barthel index scores. Stroke scales were scored by clinical nursing staff and physicians certified in the NIHSS. Blood was taken to monitor the safety of the medication.

The only brain imaging required by the trial protocol was done at baseline and after a stroke outcome, to ensure that no symptomatic intracranial haemorrhage was missed. All original copies were read centrally by the trial neuroradiologist. Other investigations were left to the site investigator's discretion, but copies of the reports of all investigations done during the study follow-up period were provided to the trial coordinating centre. At the clinic visit on day 90, the site investigators determined the mechanism of the event leading to randomisation by use of the TOAST trial classification.[20]

Patients' outcomes were adjudicated centrally by the outcomes committee, who were blinded to treatment allocation. The primary efficacy outcome was any stroke (ischaemic or haemorrhagic) within 90 days of randomisation. Stroke severity was measured by NIHSS, mRS, and Barthel index scores 90 days after stroke. The secondary outcome was the combination of any stroke, myocardial infarction, and vascular death. The tertiary outcome was the combination of any stroke, TIA, acute coronary syndrome, or all-cause death. We used the WHO definitions of TIA and stroke. Haemorrhagic events were reviewed and assigned into intracranial and extracranial groups (determined by the source of bleeding). The extracranial group was further divided as follows: severe—defined as life threatening, resulting in haemodynamic compromise or hypovolaemic shock, requiring inotropic support or other means to maintain cardiac output, requiring blood transfusion of more than 2 units of packed red blood cells, or associated with a fall in haemoglobin greater than or equal to 5 g/L; moderate—defined as requiring a transfusion of 2 units of packed red blood cells or less, not severe as

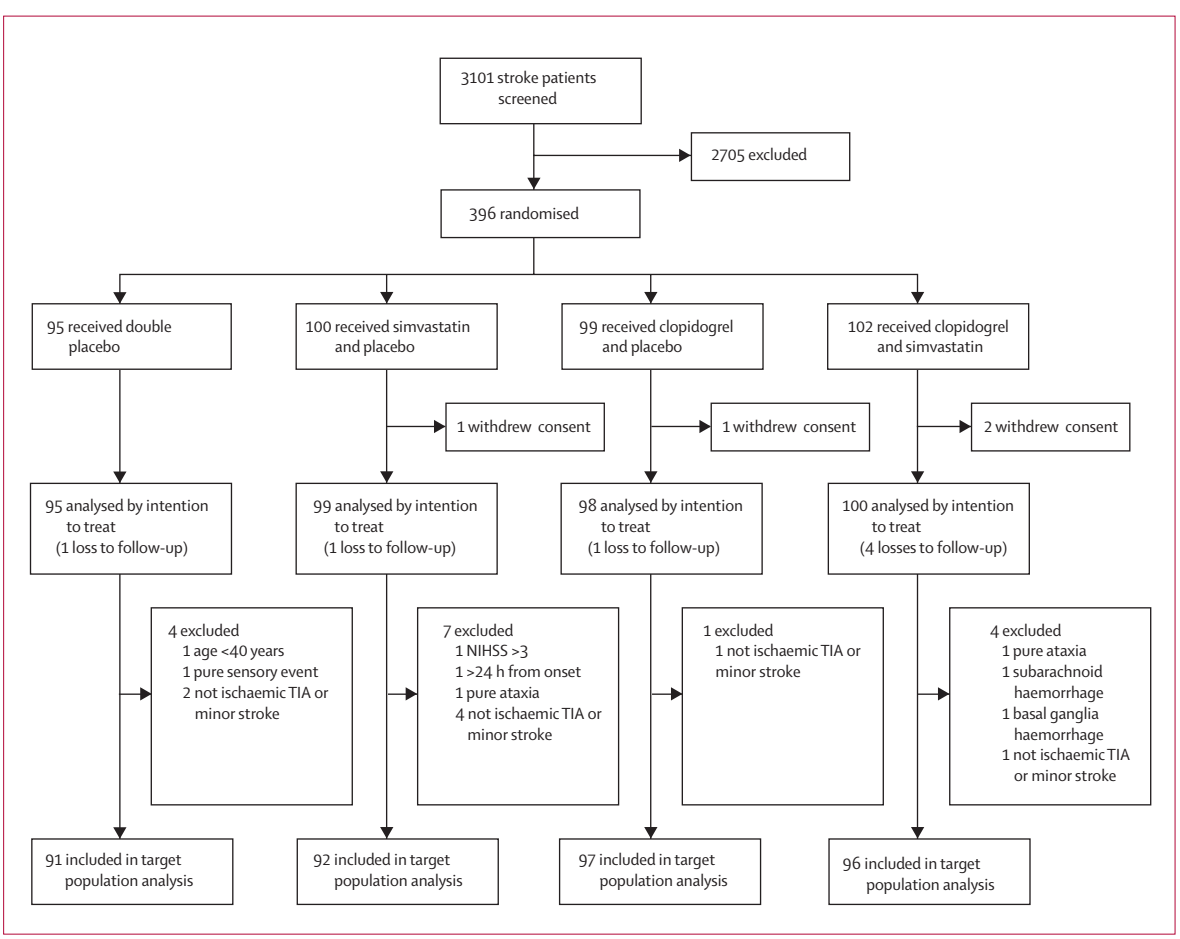

Figure 1: **Trial profile**
Losses to follow-up were included in the analyses, but were assumed not to have any outcome events. NIHSS=National Institutes of Health stroke scale; TIA=transient ischaemic attack.

defined above, or associated with a fall in haemoglobin of less than 5 g/L; mild—defined as bleeding not requiring transfusion, not causing haemodynamic compromise, usually including haematoma, subcutaneous bleeding, oozing from puncture sites, and may require modification of drug regimen; and asymptomatic—defined as bleeding that results in no symptoms.

Other safety outcomes were those known to be associated with the trial medication. Clopidogrel-specific safety outcomes were the incidence of bleeding at all sites, thrombotic thrombocytopenic purpura, and granulocytopenia. Simvastatin-specific safety outcomes were muscle pain, myositis, rhabdomyolysis, liver dysfunction, and renal failure.

Statistical analysis

We report the results from the feasibility study, as mandated by the peer review committee. There were two reasons for showing feasibility. First, at the time of study inception, there was scepticism as to the proposed event rate in the study, modelled on the data from three studies on early stroke after TIA.[4,6,7] The second reason was to determine whether the aggressive approach to enrolment was pragmatic and, to that end, enrolment success was defined as more than one patient per 4 weeks per centre. In addition, the feasibility study was to collect sufficient data to estimate the level of safety and efficacy of the two interventions for the planning of a larger trial. The two components of trial feasibility were assessed by calculating the rate of enrolment compared eith the prespecified enrolment success rule, and by calculating the overall event rate. The projected event rate for a future randomised clinical trial was 10%. The medication-specific safety outcomes were compared between the respective allocations to clopidogrel or placebo, and simvastatin and placebo, by use of the chi-squared test. The trial had a prespecified safety failure criterion if the rate of symptomatic intracranial haemorrhage was greater than 2%.

In the absence of a CONSORT statement on trials of factorial design, the efficacy outcomes are presented in a format recommended for factorial trials.[21] The degree to which clopidogrel and simvastatin acted independently as treatments was assessed by presenting risk estimates "inside the table" and "at the margin" in conjunction with the interaction ratio between clopidogrel and simvastatin.[21] All analyses are done on the intention-to-treat population, which was defined as all patients randomised in the trial who did not subsequently withdraw their consent. The primary efficacy outcome was also analysed in the target population, defined as only those patients enrolled in the study who met all the inclusion criteria.

The feasibility study had a sample of convenience of 500 patients. No interim analyses were planned. The data monitoring committee were to be given the data at the completion of the pilot trial. The committee chair was able to request access to the data at any time during the trial.

On completion of the study, a comprehensive literature search was done to identify randomised trials of either the combination of clopidogrel and aspirin, or any statin, that enrolled patients with stroke or TIA within 24 h of symptom onset. The prespecified outcome of interest was the tertiary outcome used in the FASTER trial: stroke, TIA, acute coronary syndromes, and all-cause mortality. The broadest outcome was chosen because of the lack of emphasis on early enrolment in these trials. The intent was to do a meta-analysis of those trials identified to determine the effect of early initiation of each strategy. All analyses were done using Stata 9 (StataCorp, College Station, TX, USA).

	Double placebo (n=95)	Simvastatin only (n=99)	Clopidogrel only (n=98)	Simvastatin and clopidogrel (n=100)
Demographics				
Age (years)	69·8 (12·3)	66·6 (14·2)	68·9 (13·0)	67·1 (12·9)
Female	53 (55·8%)	47 (47·5%)	46 (46·9%)	39 (39%)
White	82 (86·3%)	93 (93·9%)	92 (93·9%)	93 (93%)
Medical history				
Hypertension	55 (57·9%)	51 (51·5%)	46 (46·9%)	46 (46%)
Diabetes mellitus	6 (6·3%)	12 (12·1%)	9 (9·2%)	15 (15%)
Hypercholesterolaemia	6 (6·3%)	9 (9·1%)	5 (5·1%)	8 (8%)
Peripheral vascular disease	2 (2·1%)	1 (1·0%)	2 (2·0%)	3 (3%)
Known carotid disease at baseline	3 (3·2%)	1 (1·0%)	2 (2·0%)	2 (2%)
Smoking within the past year	23 (24·2%)	25 (25·3%)	26 (26·5%)	28 (28%)
Previous stroke	9 (9·5%)	8 (8·1%)	7 (7·1%)	5 (5%)
Previous TIA	17 (17·9%)	14 (14·1%)	14 (14·3%)	18 (18%)
Previous myocardial infarction	6 (6·3%)	2 (2·0%)	3 (3·1%)	8 (8%)
Previous coronary artery disease	3 (3·2%)	5 (5·1%)	6 (6·1%)	10 (10%)
Known atrial fibrillation/flutter	1 (1·1%)	1 (1·0%)	1 (1·0%)	2 (2%)
Other cardiac arrhythmias	8 (8·4%)	3 (3·0%)	3 (3·1%)	4 (4%)
Congestive heart failure	2 (2·1%)	0	0	1 (1%)
Valvular heart disease	1 (1·1%)	2 (2·0%)	0	0
Surgical history				
CABG/PTCA	2 (2·1%)	0	2 (2·0%)	3 (3%)
Valvular surgery	0	0	0	0
Peripheral vascular surgery	1 (1·1%)	2 (2·0%)	1 (1·0%)	1 (1%)
Radiotherapy to neck	1 (1·1%)	1 (1·0%)	1 (1·0%)	0
Carotid endarterectomy	0	0	1 (1·0%)	0
Carotid stenting/angioplasty	0	0	0	0

Data are means (SD) or numbers (%), unless otherwise indicated. CABG/PTCA=coronary artery bypass graft/percutaneous transluminal coronary angioplasty. TIA=transient ischaemic attack.

Table 2: **Baseline characteristics of patients by treatment allocated**

Role of the funding source

The clopidogrel placebo was provided by Sanofi-Aventis; both simvastatin and placebo were provided by Merck-Frosst Canada. Peer review by the Canadian Institutes of

Health Research mandated the pilot phase of this trial design to determine feasibility. Other than this aspect of the trial design, none of the trial sponsors played any role in the trial design, data collection, analysis, interpretation, or in the writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit it for publication.

Results

3101 patients with suspected TIA or ischaemic stroke presenting within 24 h of symptom onset were screened at 18 centres for study enrolment, among which 288 (9·3% of the screened population) were excluded for failure to meet an inclusion criterion and 2417 (77·9%) were excluded for meeting an exclusion criterion (table 1). 396 (12·8%) patients took the trial medication and were thus enrolled into the trial. However, four patients withdrew consent from involvement in the trial within 24 h of randomisation, and only data from the remaining 392 patients are included in the intention-to-treat analysis. Figure 1 describes the patient flow and randomisation into the four groups, and also identifies the reasons for excluding patients for the target population analysis of the primary outcome. Tables 2 and 3 show baseline characteristics and presenting features of the patients, which were similar in the four groups. Table 4 shows the mechanism of the event that led to each patient's randomisation. The high number of patients with an unknown mechanism was expected and was mainly due to the inability of the site investigators to ascribe a mechanism to those events that had resolved by the time of randomisation.

Seven patients (1·8%) were lost to follow-up and are assumed not to have had outcome events for the purposes of the analysis. Sites and their enrolment numbers are shown in the list of investigators. At the day 90 visit, 40 patients (20·2%) had stopped active clopidogrel and 45 patients (23·2%) had stopped the clopidogrel placebo (p=0·47). The corresponding numbers for simvastatin were as follows: 37 patients (18·6%) in the active simvastatin group compared with 38 (19·7%) patients in the placebo group (p=0·78). The most common reasons for stopping medication were as follows: having an adverse event, including outcome and safety events (17 [8·6%] in the active clopidogrel group *vs* 20 [10·3%] in the placebo group [p=0·56]; 16 [8·0%] in the active simvastatin group *vs* 18 [9·3%] in the placebo group [p=0·65]); or commencement of an indicated treatment precluding continuation of trial medication, typically warfarin in the case of the clopidogrel group for a cardioembolic source identified after randomisation (6 [3·0%] in the active clopidogrel group *vs* 10 [5·2%] in the placebo group [p=0·32]) and use of open-label statin for those patients with raised cholesterol (7 [2·3%] in the active simvastatin group *vs* 7 [3·6%] in the placebo group [p=1·0]).

	Double placebo (n=95)	Simvastatin only (n=99)	Clopidogrel only (n=98)	Simvastatin and clopidogrel (n=100)
Clinical presentation				
Systolic blood pressure (mm Hg)	148·9 (20·2)	149·3 (20·8)	146·0 (18·7)	147·8 (20·1)
Diastolic blood pressure (mm Hg)	81·5 (13·4)	80·0 (12·2)	80·5 (11·0)	82·0 (12·7)
Body-mass index (kg/m^2)	27·6* (6·4)	26·9* (4·7)	26·5 (4·7)	27·2* (4·5)
Symptoms				
Symptoms present at randomisation	57 (60·0%)	56 (56·6%)	52 (53·1%)	61 (61%)
If symptoms resolved, duration of symptoms (mins)	52·5 (20–120)	60 (20–180)	55 (15–135)	45 (20–120)
Loss of consciousness	3 (3·2%)	2 (2·0%)	1 (1·0%)	0
Monocular blindness	1 (1·1%)	0	1 (1·0%)	0
Hemianopia	4 (4·2%)	3 (3·0%)	4 (4·1%)	0
Diplopia	1 (1·1%)	5 (5·1%)	4 (4·1%)	1 (1%)
Aphasia	25 (26·3%)	26 (26·3%)	25 (25·5%)	31 (31%)
Expressive	22	25	21	28
Receptive	0	0	0	1
Global	3	1	4	2
Dysarthria	31 (32·6%)	32 (32·3%)	35 (35·7%)	39 (39%)
Speech (aphasia/dysarthria)	53 (55·8%)	49 (49·5%)	57 (58·2%)	61 (61%)
Weakness/paralysis	86 (90·5%)	84 (84·9%)	86 (87·8%)	84 (84%)
Paraesthesia/anaesthesia	42 (44·2%)	46 (46·5%)	41 (41·8%)	39 (39%)
Hemi-neglect	5 (5·3%)	4 (4·0%)	4 (4·1%)	1 (1%)
Gait ataxia	8 (8·4%)	10 (10·1%)	14 (14·3%)	13 (13%)
Headache	15 (15·8%)	11 (11·1%)	13 (13·3%)	12 (12%)
Baseline scales (median [range])				
Premorbid modified Rankin scale	0 (0–2)	0 (0–3)	0 (0–2)	0 (0–3)
Premorbid Barthel index	100 (85–100)	100 (80–100)	100 (85–100)	100 (65–100)
NIHSS at randomisation	1 (0–5)	1 (0–4)	0·5 (0–3)	1 (0–3)
Process measures				
Time to imaging (h)	3·9 (1·9–6·7)	3·5 (2·2–6·3)	4·0 (2·5–8·1)	3·5 (2·5–6·7)
Time to randomisation (h)	8·5 (5·1–13·8)	8·2 (5·0–17·1)	9·1 (5·0–16·5)	8·4 (5·3–14·7)

*Single missing value for body-mass index due to no height measured (three in total). Data are means (SD), numbers (%), or medians (IQR), unless otherwise indicated (ie, baseline scales). NIHSS=National Institutes of Health stroke scale.

Table 3: **Baseline presenting features by treatment allocated**

	Double placebo (n=95)	Simvastatin only (n=99)	Clopidogrel only (n=98)	Simvastatin and clopidogrel (n=100)
Cardioembolic	10 (10·8%)	7 (7·4%)	5 (5·2%)	4 (4·1%)
Lacunar	26 (28·0%)	24 (25·3%)	28 (28·9%)	35 (36·1%)
Large artery	27 (29·0%)	21 (22·1%)	25 (25·8%)	21 (21·2%)
Other	2 (2·2%)	1 (1·1%)	1 (1·0%)	1 (1·0%)
Unknown	28 (30·1%)	42 (44·2%)	38 (39·2%)	36 (37·1%)

Only patients with an ischaemic cerebrovascular event are included in this table.

Table 4: **Mechanism of event leading to randomisation by treatment allocated**

As of Dec 31, 2006, the trial had failed to recruit above its prespecified enrolment success rate for 12 months (0·35 patients per 4 weeks per centre in 2006). This led to the steering committee's decision to close the trial to

	With simvastatin	Without simvastatin	With or without simvastatin (total)
Primary efficacy outcomes			
With clopidogrel	9/100 (9·0%)	5/98 (5·1%)	14/198 (7·1%)
Without clopidogrel	12/99 (12·1%)	9/95 (9·5%)	21/194 (10·8%)
With or without clopidogrel (total)	21/199 (10·6%)	14/193 (7·3%)	..
Secondary efficacy outcomes			
With clopidogrel	11/100 (11·0%)	6/98 (6·1%)	17/198 (8·6%)
Without clopidogrel	12/99 (12·1%)	11/95 (11·6%)	23/194 (11·9%)
With or without clopidogrel (total)	23/199 (11·6%)	17/193 (8·8%)	..
Tertiary efficacy outcomes			
With clopidogrel	17/100 (17·0%)	12/98 (12·2%)	29/198 (14·7%)
Without clopidogrel	21/99 (21·2%)	21/95 (22·1%)	42/194 (21·7%)
With or without clopidogrel (total)	38/199 (19·1%)	33/193 (17·1%)	..

Primary efficacy outcome: 90 day risk of stroke; secondary efficacy outcome: 90 day risk of stroke, myocardial infarction, and vascular death; tertiary efficacy outcome: 90 day risk of stroke, transient ischaemic attack, acute coronary syndrome, and all-cause death.

Table 5: **2×2 tables of primary, secondary, and tertiary outcomes**

	Risk difference (95% CI)	Risk ratio (95% CI)	p
Primary efficacy outcomes			
Clopidogrel *vs* placebo			
At the margins	−3·8% (−9·4 to 1·9)	0·7 (0·3–1·2)	0·19
Inside the table	−4·4% (−11·7 to 3·0)	0·5 (0·2–1·5)	0·24
Simvastatin *vs* placebo			
At the margins	3·3% (−2·3 to 8·9)	1·5 (0·8–2·8)	0·25
Inside the table	2·6% (−6·1 to 11·4)	1·3 (0·6–2·9)	0·55
Secondary efficacy outcomes			
Clopidogrel *vs* placebo			
At the margins	−3·3% (−9·3 to 2·7)	0·7 (0·4–1·3)	0·28
Inside the table	−5·5% (−13·5 to 2·5)	0·5 (0·2–1·4)	0·18
Simvastatin *vs* placebo			
At the margins	2·7% (−3·2 to 8·7)	1·3 (0·7–2·4)	0·37
Inside the table	0·5% (−8·5 to 9·6)	1·0 (0·5–2·3)	0·91
Tertiary efficacy outcomes			
Clopidogrel *vs* placebo			
At the margins	−7·0% (−14·6 to 0·6)	0·7 (0·4–1·2)	0·07
Inside the table	−9·8% (−20·4 to 0·7)	0·6 (0·3–1·1)	0·07
Simvastatin *vs* placebo			
At the margins	1·9% (−5·6 to 9·6)	1·1 (0·7–1·7)	0·61
Inside the table	−0·1% (−12·5 to 10·7)	1·0 (0·6–1·6)	0·88

Primary efficacy outcome: 90 day risk of stroke (interaction ratio 1·39 [95% CI 0·36–5·24]; p=0·64); secondary efficacy outcome: 90 day risk of stroke, myocardial infarction, and vascular death (interaction ratio 1·72 [0·50–5·85]; p=0·39); tertiary efficacy outcome: 90 day risk of stroke, transient ischaemic attack, acute coronary syndrome, and all-cause death (interaction ratio 1·45 [0·61–3·45]; p=0·40). "At the margins" refers to the margins of the 2×2 tables, and "inside the table" refers to the body of the 2×2 tables (see table 5).

Table 6: **Intention-to-treat analysis of primary, secondary, and tertiary efficacy outcomes**

enrolment. There were a total of 35 (8·9%) adjudicated stroke outcomes in the trial: 33 were ischaemic and two were haemorrhagic. One of the haemorrhages was fatal. The median time to stroke outcome was 1 day (range 0–62 days). The mechanism of the 33 ischaemic strokes by the TOAST classification was as follows: four were cardioembolic, nine were lacunar, 10 were large artery, nine were unknown in origin, and one was classified as "other". 12 of the 34 non-fatal strokes were disabling, as defined by an mRS score of greater than 1. The intention-to-treat analysis is described in tables 5 and 6. The estimates of effect were unchanged when the analysis was restricted to the target population. Tables 5 and 6 also show the analyses for the secondary and tertiary outcomes. Active clopidogrel was associated with a consistent point-estimate reduction (approximate absolute risk reduction 4%) across all outcomes when compared with placebo. However, active simvastatin was associated with an increase in the primary outcome of stroke when compared with placebo, and this difference narrowed across the other outcomes. Although there was no evidence of a significant interaction between clopidogrel and simvastatin across the three outcomes, the effect of clopidogrel was diluted in the presence of active simvastatin across all three outcomes.

The comparison of the clopidogrel-specific safety outcomes is summarised in table 7, which showed a significant increase in the number of bleeding outcomes on active clopidogrel when compared to placebo. Most outcomes were judged to be asymptomatic, consisting of increased bruising only; six extracranial haemorrhages were symptomatic. There were no outcomes of thrombotic thrombocytopenic purpura or granulocytopenia. The simvastatin-specific safety outcomes were not different between the two groups: 15 (7·5%) in the active simvastatin group (four abnormal creatine kinase, nine muscle ache, two worsening liver function) and 19 (9·8%) outcomes (four abnormal creatine kinase, 14 muscle ache, one worsening liver function) in the placebo groups (p=0·42). There were no episodes of rhabdomyolysis in the trial. All the simvastatin safety outcomes were adjudicated as mild by the outcomes committee.

For the meta-analysis, no other trials were identified that enrolled patients within 24 h of stroke or TIA onset to statin treatment. Three trials were found to have studied the combination of clopidogrel and aspirin in this population of patients: CHARISMA,[22] MATCH,[12] and CARESS trials.[23] A further 35 patients' data and three outcomes were included in the meta-analysis (personal communications from D L Bhatt and E J Topol on behalf of the CHARISMA Investigators; H C Diener on behalf of the MATCH Investigators; and H J Markus on behalf of the CARESS Investigators). No further analysis of the statin data is presented; however, the combination of aspirin and clopidogrel was associated with a reduction in the combined tertiary outcome (risk ratio 0·66 [95% CI 0·43–1·0]; figure 2).

Discussion

The FASTER trial underscores the high risk of stroke in the immediate aftermath of symptom onset in patients with acute ischaemic cerebrovascular events, whose symptoms have either completely recovered or are too mild, precluding them from treatment with alteplase. Early aggressive antiplatelet therapy may be associated with a reduction in these events, although at the cost of slightly increased haemorrhagic complications. Early simvastatin use does not seem to have a similar effect, and may attenuate the effect of the antiplatelet strategy. Although it was possible to enrol patients within 24 h of symptom onset into a prevention trial, the trial failed to meet its recruitment rate target and was stopped prematurely. The investigators felt that the main reason for this was that it had become increasingly difficult over the course of the study to identify eligible patients previously not on statin therapy. There are no routinely collected Canadian federal or provincial statistics to confirm this assertion, but given the positive results of the Heart Protection Study,[24] and, particularly relevant to this population, the SPARCL trial,[14] the previously identified increase in statin prescription in Canada is likely to have continued during the course of the trial.[25]

The pleiotropic effects of statins have raised much interest in their potential role in stroke prevention, with mechanisms such as plaque stabilisation, inhibition of the inflammatory response, and increased nitric oxide bioavailability improving cerebral blood flow proposed as the means by which statins may improve outcome.[26,27] However, the results of the FASTER trial do not support the hypothesis that immediate simvastatin use prevents early stroke recurrence. The 95% CIs for the risk ratios of the primary outcome only just included the proposed clinically meaningful relative risk reduction of 20% for a larger clinical trial. The point estimate of excess risk diminishes across the three outcomes, suggesting that it is an effect of the small number of stroke outcomes. This finding is compatible with the cardiac literature. The MIRACL study, with a similar emphasis on early statin initiation (80 mg atorvastatin *vs* placebo) in patients with acute coronary syndrome, was only borderline significant for its primary outcome at 16 weeks, driven by the relatively soft outcome of recurrent symptoms leading to readmission to hospital.[28] This trial did not reduce its equivalent outcome, myocardial infarction, but did have the unexpected finding of a reduction in stroke outcomes.[29] A meta-analysis of the short-term effects of statins after acute coronary syndromes, which included the MIRACL data, concluded that statin therapy started within 14 days of symptom onset did not reduce the occurrence of death, myocardial infarction, or stroke up to 4 months.[30]

By contrast, there was a consistent point estimate across the three outcomes for an absolute reduction of 3·8%, 3·3%, and 7·0% over 90 days for the primary (all stroke), secondary (all stroke, myocardial infarction, and vascular death), and tertiary outcomes (all stroke, TIA, acute coronary syndrome, and all-cause death), respectively, for the combination of aspirin and clopidogrel over aspirin use alone. The complementary meta-analysis showed borderline significant risk reduction of 34% of using the combination of aspirin and clopidogrel over either drug used as monotherapy for the combined outcome of all stroke, TIA, acute coronary syndrome, and all-cause death. The MATCH trial did not show a significant reduction in its primary outcome with combination treatment over clopidogrel in a similar population of patients; however, the differences between the two trials are important. First, as can be seen from the meta-analysis, the MATCH trial did not focus on the period of high early risk, with only 13 patients enrolled within 24 h. Second, the patient eligibility criteria for the MATCH trial skewed enrolment towards those with small-vessel disease. A higher proportion of patients with large-artery disease were enrolled into the FASTER trial because it did not focus so specifically on those with hypertension and diabetes. Large-artery disease has a higher rate of early recurrence,[31,32] and the combination of aspirin and

	n (%)		Risk difference (95% CI)	p*
	No clopidogrel (n=194)	Clopidogrel (n=198)		
Intracranial haemorrhage	0	2 (1·0%)	1% (−0·4 to 2·4)	0·5
Extracranial haemorrhage				
Severe	0	1 (0·5%)	0·5% (−0·5 to 1·5)	1·0
Moderate	0	2 (1·0%)	1% (−0·4 to 2·4)	0·5
Mild	0	1 (0·5%)	0·5% (−0·5 to 1·5)	1·0
Total symptomatic	0	6 (3·0%)	3·0% (0·6 to 5·4)	0·03
Total asymptomatic	27 (13·9%)	61 (30·8%)	16·9% (8·8 to 25·0)	0·0001

*Fisher's exact test. 94 patients had 124 bleeding events. One patient had two mild events and one severe extracranial bleeding event and was classified as severe for the purposes of the analysis. The other events were all asymptomatic and if a patient had more than one asymptomatic event it was classified as a single event.

***Table 7*: Site and severity of bleeding outcomes**

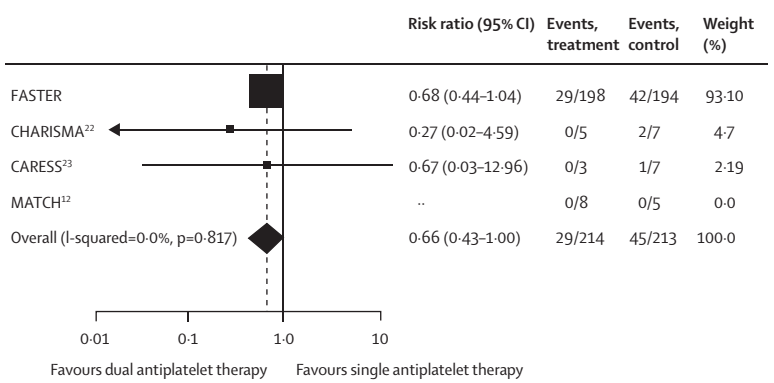

***Figure 2*: Fixed-effects meta-analysis of 90-day risk of tertiary efficacy outcome**
Tertiary outcome was combined outcome of stroke, transient ischaemic attack, acute coronary syndrome, and all-cause death in patients enrolled within 24 h of onset of stroke or transient ischaemic attack. Note that x-axis is a logarithmic scale.

clopidogrel has been shown to modify the continuing asymptomatic embolisation from recently symptomatic carotid plaque.[23] This latter effect may explain why the combination of aspirin and clopidogrel was able to modify risk so quickly after treatment initiation compared with the combination of aspirin and dipyridamole, which in the ESPRIT trial required 2 years of treatment before the treatment curves diverged.[13] A better understanding of the modification of early risk given by aspirin and dipyridamole may arise from the ongoing PRoFESS trial.[33] However, in common with the MATCH trial, patients seem to be at an increased of risk of intracranial haemorrhage. In both trials, the risk was 1%, but was realised over 90 days in the FASTER trial, compared with 18 months in the MATCH trial.

One of the strengths of a factorial design is that it allows an understanding of any interaction between the two medications. The FASTER trial was underpowered to show an interaction and consequently the 95% CIs were wide with a non-significant p value across the three outcomes. However, the point estimate for the interaction ratio is consistently above 1·25, the upper limit proposed by McAlister and colleagues,[21] and thus the possible beneficial effect of clopidogrel is attenuated across the three outcomes if the patients were also randomised to receive active simvastatin. Clopidogrel is an inactive pro-drug, which requires activation through the cytochrome P450 isoenzymes, particularly CYP3A4.[34,35] This metabolic pathway is shared by some (eg, simvastatin and atorvastatin) but not all (eg, pravastatin and fluvastatin) of the statins.[36] Some laboratory studies have shown a significant reduction in ADP-induced platelet aggregation,[37,38] but these are countered by retrospective analyses of clinical trials, which have as yet failed to show an effect on the clinical event rate.[39,40] No study to date (including this one) has either had the correct study design or the statistical power to unequivocally answer this clinically important question, which, given its public-health implications, deserves proper assessment.

In conclusion, there is no current evidence to define the optimum early treatment for this group of patients. It is not unusual in clinical routine for indicated treatments and investigation to be delayed until the period of highest risk has passed,[41] and therefore the patients at highest risk have typically been overlooked in previous clinical trials. This study complements those from Rothwell and colleagues and Lavallée and colleagues, but is distinctly different because it focuses only on patients who present immediately for medical attention, most of whom have ongoing symptoms.[42,43] Extrapolating evidence from previous trials is not valid because of the increased magnitude of stroke risk and potential haemorrhage risk in these patients. The FASTER pilot trial points to the need for further concerted study of TIA and minor stroke patients in the hyperacute phase of their illness to quantify the risk-benefit profile and to look at the potential interaction between preventive strategies.

Contributors

JK wrote the first draft of the paper. ME supervised the data analysis done by JK and MDH. AMB and JK obtained the funding. JK, MDH, KJR, ME, AMD, and AMB conceived, designed, and supervised the study, and contributed to subsequent versions of the manuscript. All members of the writing committee approved the final report.

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Conflicts of interest

JK and AMD have been consultants and speakers for Sanofi-Aventis. MDH and AMB have been consultants for Sanofi-Aventis. KJR and ME report no conflicts of interest.

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