Title

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Reduction in early stroke risk in carotid stenosis with transient ischemic attack associated with statin treatment

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Abstract

Background and Purpose—Statins reduce stroke risk when initiated months after TIA/stroke and reduce early vascular events in acute coronary syndromes, possibly via pleiotropic plaque-stabilisation. Few data exist regarding acute statin use in TIA. We aimed to determine if statin pre-treatment at TIA onset modified early stroke risk in carotid stenosis.

Methods—We analyzed data from 2770 TIA patients from 11 centres, 387 with ipsilateral carotid stenosis. ABCD2 score, abnormal DWI, medication pre-treatment, and early stroke were recorded.

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Conflict of interest:

AM has received unrestricted educational grants from Lundbeck, Pfizer and Boehringer Ingelheim to attend conferences. PJK has received speakers' honoraria from Boehringer Ingelheim, Pfizer, and Bristol Myer Squibb. Pfizer and Servier have provided unrestricted educational grants to the Neurovascular Unit for Translational and Therapeutics Research towards stroke education and research. JLS has been an advisory board member of AGA Medical, Boehringer Ingelheim, Bristol Myer Squibb, CoAxia, Fibro Gen, and Sanofi Aventis, he has performed consultancy work for ImaRx and received honoraria from Concentric Medical. SBC has been an advisory board member for Bristol Myer Squibb. JLM has been an advisory board member of Bayer, Boehringer Ingelheim, Bristol Myer Squibb, Daiichi-Sankyo and Sanofi Aventis and has received speaker fees from Astra-Zeneca, Pfizer and Takeda. The other authors have no conflicts of interest.

Results—In patients with carotid stenosis, 7-day stroke risk was 8.3% (95% confidence interval [CI] 5.7–11.1) compared with 2.7% [CI 2.0–3.4%] without stenosis (p<0.0001) (90-day risks 17.8% and 5.7% [p<0.0001]). Among carotid stenosis patients, non-procedural 7-day stroke risk was 3.8% [CI 1.2–9.7%] with statin treatment at TIA onset, compared to 13.2% [CI 8.5–19.8%] in those not statin pre-treated (p=0.01) (90-day risks 8.9% versus 20.8% [p=0.01]). Statin pre-treatment was associated with reduced stroke risk in carotid stenosis patients (OR for 90-day stroke 0.37, CI 0.17–0.82), but not non-stenosis patients (OR 1.3, CI 0.8–2.24) (p for interaction 0.008). On multivariable logistic regression, the association remained after adjustment for ABCD2 score, smoking, antiplatelet treatment, recent TIA, and DWI hyperintensity (adjusted p for interaction 0.054).

Conclusion—In acute symptomatic carotid stenosis, statin pre-treatment was associated with reduced stroke risk, consistent with findings from randomized trials in acute coronary syndromes. These data support the hypothesis that statins started acutely after TIA symptom onset may also be beneficial to prevent early stroke. Randomized trials addressing this question are required.

Keywords

Transient ischaemic attack; carotid stenosis; statin

Introduction

Patients with TIA and carotid stenosis are at high risk of early stroke, independently of abnormal acute DWI, ABCD2 score, and vascular risk factors, with highest risk observed in the first days after symptom onset and in patients with hemispheric TIA, greater lumen stenosis, and ulcerated plaque on angiography.[1–3] In randomized trials, carotid endarterectomy (CEA) is highly beneficial for secondary stroke prevention, with maximum benefit observed in those who underwent surgery within 2 weeks of symptom onset.[4] However, despite greatest recurrent stroke risk within the first days after initial symptoms, the safety of very early CEA remains to be established. For example, in the Swedish Vascular Registry the combined rate of stroke and death in patients who underwent CEA within 48 hours was 11.5%, with a 4-fold increase in the odds of poor outcome compared to 3–7 days. [5] Available data indicate that about half of recently-symptomatic patients do not undergo CEA, and only a minority have CEA within the recommended 14-day period.[6–9] For these reasons, improved medical treatments are needed within the first days after symptoms for patients before revascularization and in those not selected for revascularization.

In randomized trials, statins begun within days of acute coronary syndromes were beneficial for secondary vascular event prevention as early as 30 days, possibly due to plaque stabilization independently of lipid-lowering.[10,11] While statins have proven benefit for late stroke prevention when begun months after TIA or stroke[12], few data exist in patients with unstable carotid stenosis on the effects on early stroke recurrence of statin pre-treatment at the time of symptom onset or statins begun acutely after symptoms. We hypothesized that statin pre-treatment at TIA onset would be associated with reduced early stroke risk in TIA patients with carotid stenosis, including those awaiting CEA. In the absence of randomized trial data, we investigated this hypothesis in an international multi-centre pooled dataset of individual TIA patients.

Methods

Study Population

Centers with large TIA patient cohorts were identified from published studies and invited to include data. Eleven centers from Europe, Asia and North America contributed data from 2,770 individual patients. Study settings were hospital-based stroke specialist services (stroke-specialist treated hospitalized and TIA clinic patients, 9 centers), and population-based settings (2 centers, specialist and non-specialist care). Cohorts were recruited and prospectively followed for recurrent stroke at each center.

Inclusion criteria and definitions

Pre-specified inclusion criteria were: (1) TIA verified by a stroke specialist (2) Data available on presence/absence of ipsilateral carotid stenosis (3) Medication data at time of TIA onset available (4) Outcome non-procedural stroke data available at 7 or 90 days. Patients were excluded if an alternative diagnosis other than TIA was reached, if peri-procedural stroke occurred following CEA/stenting, or if medical attention and/or brain imaging was first sought for a stroke recurrence rather than the index TIA. Medication treatment at TIA onset (i.e. prescribed before the onset of TIA symptoms) and post-TIA (including continuing treatment with pre-TIA medications, and newly-prescribed medications) were recorded based on data obtained at each individual site.

Data was abstracted from existing TIA registries at each individual center using a standardized electronic template, de-identified, and collated centrally. As the study was observational, patient treatment at each center was at the discretion of the treating clinician.

Standardized definitions of all variables were applied by all centers as previously described.[3] Because the American Stroke Association proposed tissue-based definition was not used uniformly in the USA, Europe, and Asia, and because all included cohorts had applied the traditional time-based definition, TIA was defined clinically as an acute loss of focal cerebral or ocular function lasting less than 24 hours, attributed to embolic or thrombotic vascular disease. The index TIA for study inclusion was defined as that most recently preceding stroke specialist assessment. For standardisation and generalisability stroke was defined as a new neurological deficit according to the WHO definition, which occurred after complete resolution of symptoms of the preceding TIA.

ABCD2 score was trichotomized into low (0–3), medium (4–5) and high-risk (6–7) categories. Carotid stenosis was defined as ≥50% non-occlusive narrowing of the internal carotid artery (ICA) lumen on carotid imaging (duplex ultrasound, computerized tomography, magnetic resonance, or invasive angiogram), as interpreted by the reporting physician using the NASCET method. Dual TIA was defined as the occurrence of at least one earlier TIA within 7 days of presentation with the index TIA. DWI hyperintensity (DWI<72 hours of TIA) was defined as lesion(s) consistent with acute cerebral ischemia determined by the treating neuroradiologist and/or stroke physician at each centre, supported by apparent diffusion coefficient and FLAIR/T2 sequences.

Stroke recurrence

Stroke status at 7 and 90 days was determined at each site by in-person assessment, and/or telephone interview and medical file review. Peri-procedural stroke was defined as stroke occurring within 48 hours after the day of carotid revascularization (CEA or stenting).

Ethics committee approval was provided per local site procedures, and patients provided informed consent for participation in research into stroke prevention following TIA.

Statistical analysis

Statistical analysis was performed using Stata 9.0. Parametric and non-parametric comparisons of categorical and continuous variables were made using chi-squared, Fisher's exact, t-test and Mann-Whitney tests, as appropriate. All significance tests were two-sided. Analyses for interaction between statins at TIA onset, carotid stenosis, and early stroke were performed by inclusion of interaction terms in logistic regression models. Forward stepwise multivariable logistic regression was performed to adjust for other independent variables associated with outcome at the p<0·05 level on univariate analysis. A case deletion strategy was applied for patients where key data variables were unavailable. Data from patients with peri-procedural stroke were excluded from analysis and all outcomes reported describe nonprocedure related stroke.

Results

Patient characteristics

Of 2,770 patients with TIA from 11 centers, carotid imaging data was available in 98.2% (2,721 patients), 387 (14.2%) of whom had ipsilateral carotid stenosis. Of the 387 patients with carotid stenosis, statin pre-treatment data were available in 68% (262 patients). Of these, follow-up was complete in 95% (249 patients) at 7 days, and 94% (245 patients) at 90 days.

Patients with stenosis were more frequently male (p=0.04), and were older, with higher prevalence of hypertension, hyperlipidaemia, prior stroke, recent TIA, coronary disease, and diabetes (p<0.0001 for all) (Table 1). In the carotid stenosis patients 39.1% underwent carotid revascularization (35.8% CEA, 3.3% carotid artery stenting [CAS], median presentation-revascularization interval 7 days [interquartile range 4–14 days]). Of the 387 carotid stenosis patients, statin data at TIA onset was available in 262 (Figure 1, Table 2 and supplementary table I). In these, 43.5% were prescribed a statin prior to the index TIA, rising to 87.7% after the index TIA. Anti-platelet medication was highly associated with statin treatment (p<0.0001). Despite higher rates of preventive medications in carotid stenosis patients, non-procedural 7-day stroke risk was 8.3% compared to 2.7% in patients without stenosis (p<0.001) (17.8% versus 5.7% at 90 days, p<0.001) (Table 1). Carotid revascularization was more common in patients with acute DWI hyperintensity (p=0.01), but was not associated with other vascular risk factors (Supplementary-table 2). No interaction was observed between statin pre-treatment, carotid revascularization, and early stroke risk (p for interaction 0.8).

Early stroke risk factors stratified by carotid stenosis

Among carotid stenosis patients, non-procedural 7-day stroke risk was 3.8% (4/105) in those pre-treated with statins compared to 13.2% (19/144) in non-statin pre-treated patients (p=0.01). Corresponding risks at 90 days were 8.9% (statin-treated, 9/101) and 20.8% (statin-untreated, 30/144) (p=0.01) (Figure 2). In TIA patients with carotid stenosis, the OR of stroke at 7 days associated with statin pre-treatment was 0.26 (95% confidence interval [CI] 0.09–0.79), indicating reduced stroke risk. The OR for 90-day stroke was 0.37 (CI 0.17–0.82). No such benefit was observed in non-stenosis TIA (Figure 3).

A significant interaction was observed between statin pre-treatment at TIA onset and carotid stenosis for early recurrent stroke (p for interaction 0.03 for 7-day stroke, 0.008 for 90-day stroke) (Figure 3, supplementary table 3). Smoking at symptom onset was associated with higher risk of 7-day stroke in patients with carotid stenosis (p for interaction 0.04) with a protective influence of antiplatelet treatment at TIA onset (p for interaction 0.02) (Figure 3). Higher stroke risk was observed with higher ABCD2 score, acute DWI hyperintensity, and

dual TIA in carotid stenosis and non-stenosis patients, and with atrial fibrillation in non-stenosis patients only (Figure 3, supplementary table 3).

On multivariable logistic regression analysis (adjusting for ABCD2 score, smoking, and antiplatelet treatment), the statin/carotid stenosis interaction remained significant for early stroke (adjusted p for interaction 0.01 for stroke at 90 days, n=1339). When DWI hyperintensity and dual TIA were added to the model, the statin/carotid stenosis adjusted p-value for interaction was 0.054 (n=438 due to unavailable DWI or dual TIA data in 901 patients).

Discussion

Few randomized trials investigating the benefit of acute statin therapy for early stroke prevention after TIA have been performed and none have selected patients with recently-symptomatic carotid stenosis deemed unsuitable for, or who are awaiting, carotid revascularization. In the absence of 'gold-standard' randomized data, we examined early stroke risk in patients with carotid stenosis who were on statin treatment at TIA onset (ie. statin pre-treatment) in our large observational TIA database. We sought to provide data which might support the rationale for randomized trials of acute statin therapy begun after symptoms have occurred.

Our main finding was of a substantial reduction in non-procedural early stroke risk in patients with carotid stenosis who were pre-treated with statins at the time of TIA onset. In contrast, no such risk reduction associated with statin pre-treatment was observed in TIA patients without carotid stenosis. A significant interaction was observed between the protective association with statins for early recurrent stroke in carotid stenosis patients, which remained after adjustment for confounding variables.

Evidence indicates that an unmet need exists for improved treatment to prevent early recurrent stroke in patients with recently-symptomatic carotid stenosis. First, in population studies, carotid stenosis is associated with 3-fold increase in early stroke recurrence risk compared with other subtypes.[6,13] When combined with acute DWI hyperintensity, recent earlier TIA ('dual TIA'), and ABCD2 score in the ABCD3-I score, the addition of carotid stenosis significantly improved the c-statistic for early stroke discrimination after TIA, compared to the ABCD2 score.[3]

Second, although recurrent stroke risk after symptomatic carotid stenosis is highest in the first days, the safety of very early CEA remains unclear. In a large study from the Swedish Vascular Registry, the combined stroke and death rate after CEA within 2 days of symptoms was 11.5%, greatly exceeding procedural event rates associated with benefit in randomized trials.[5] On multivariate analysis, time was an independent risk factor, with a 4-fold increase in adjusted OR for peri-operative complications for CEA within 48 hours compared with 3–7 days. Supporting these data, a recent meta-analysis has reported a pooled OR of stroke and death of 4.6 with emergency CEA in unstable patients (stroke-in-evolution and crescendo TIA).[14]

Third, in clinical practice many patients with symptomatic carotid stenosis are not selected for carotid revascularization, due to disabling stroke or other factors resulting in a perceived unfavourable risk-benefit assessment by treating clinicians. In the Canadian Stroke Network Registry, only 17.5% of patients with symptomatic carotid stenosis had CEA within 6 months[7]. In the Californian Kaiser-Permanente network, only 36% of women and 54% of men with TIA and severe carotid stenosis had CEA.[8] Similar rates have been reported from population studies in Ireland and United Kingdom.[6,9] In our pooled analysis, the rate of carotid revascularisation was 39.1%, consistent with earlier reports. CEA was performed

more frequently in TIA patients with acute DWI hyperintensity, suggesting that early DWI findings may influence physicians' perception of surgical risk-benefit. For patients who do not have CEA or in those for whom revascularization is delayed, improved acute medical treatments are needed.

Inflammation is a central biological process involved in atherosclerotic plaque rupture and thrombo-embolic stroke. In the PROVE-IT and MIRACL randomized trials in patients with acute coronary syndromes, early statin treatment (within 10 and 4 days of symptoms) was associated with reduced rates of early recurrent vascular events, possibly mediated by stabilization of symptomatic plaque.[10,11] In PROVE-IT, benefit of intensive statin therapy (atorvastatin 80mg) was observed as early as 15 days, becoming statistically-significant at 30 days, despite coronary revascularization in 70% of included patients. [10]

In cerebrovascular disease, no large studies have investigated the benefit of early statins in patients with acutely-symptomatic carotid atherosclerosis. A positron-emission tomography (PET) study showed that inflammation-related carotid plaque flurodeoxyglucose (FDG) uptake predicted early stroke recurrence, independently of stenosis severity. [15] Others have reported dose-dependent reduction of carotid FDG uptake with statins. Statins may also improve cerebral vasomotor reactivity and collateralization.[16] In the FASTER trial, patients with TIA/minor stroke were randomized to clopidogrel/placebo and simvastatin/placebo.[17] However, FASTER was discontinued due to sub-optimal recruitment and no clear benefit of simvastatin was apparent. The non-randomized SOS-TIA, EXPRESS, and TWO-ACES studies have reported reduced early stroke risk with intensive acute treatment, including statins in patients with all TIA mechanisms.[18–20] The SPARCL trial demonstrated the benefit of atorvastatin begun weeks or months after TIA/stroke in patients with carotid stenosis for reduction of late recurrent stroke and coronary events.[12,21]

Strengths of our analysis include the availability of DWI and outcome data in a large patient sample assessed acutely after TIA. We adjusted for known confounders and measured the clinically-important outcome of recurrent stroke in the early phase after TIA, when stroke risk is known to be highest. We acknowledge several limitations. Although data were available on whether or not patients were treated with statins at discharge from hospital evaluation for their TIA, the time interval between TIA onset and prescribing of new statin was unavailable. Therefore, we were unable to distinguish patients who received emergency statin treatment immediately (within 24 hours) after TIA onset from those that received new statin treatment days or weeks later. Statin dose was unavailable, precluding analysis of the relationship of dose-response on early stroke events. Therefore we conducted our primary analysis in patients prescribed statins before and at the time of TIA onset. Low stroke event rates (reflecting early stroke specialist treatment) limited statistical power for multivariable analysis within the first week after TIA. As pre-event statin data was unavailable for some patients and centres, we cannot exclude the possibility that this may have influenced our findings. Patients with carotid stenosis had were more likely to be treated with statins, antiplatelet, or antihypertensive therapy at TIA onset, but also were older and had higher rates of risk factors for recurrent stroke (acute DWI hyperintensity, diabetes, and greater ABCD2 score). Thus it is possible that residual confounding by these factors may have contributed to our findings. We also cannot exclude the possibility that statin pre-treatment at TIA onset may have been a marker for unmeasured factors associated with lower risk of early stroke (confounding by indication), or that residual confounding may exist from plaque-related factors (such as degree of stenosis or plaque morphology) or other unmeasured variables. However, our findings remained after adjusting for other significant predictors of early stroke after TIA, including smoking, ABCD2 score, and antiplatelet treatment.

Current clinical trials are investigating emergency combination anti-platelet treatment after TIA, and carotid revascularization compared to best medical therapy in symptomatic patients stratified by the Oxford risk prediction score. We emphasize that we do not advocate delaying CEA or replacing CEA with statin therapy in patients eligible for revascularization. Neither does our paper provide data to support routine emergency treatment with statins in TIA. Rather, we believe that our study provides preliminary hypothesis-generating data suggesting that emergency treatment with statins may further reduce stroke risk in symptomatic patients with carotid disease after TIA, who are particularly high risk of recurrent stroke. Future randomized trials should investigate this question.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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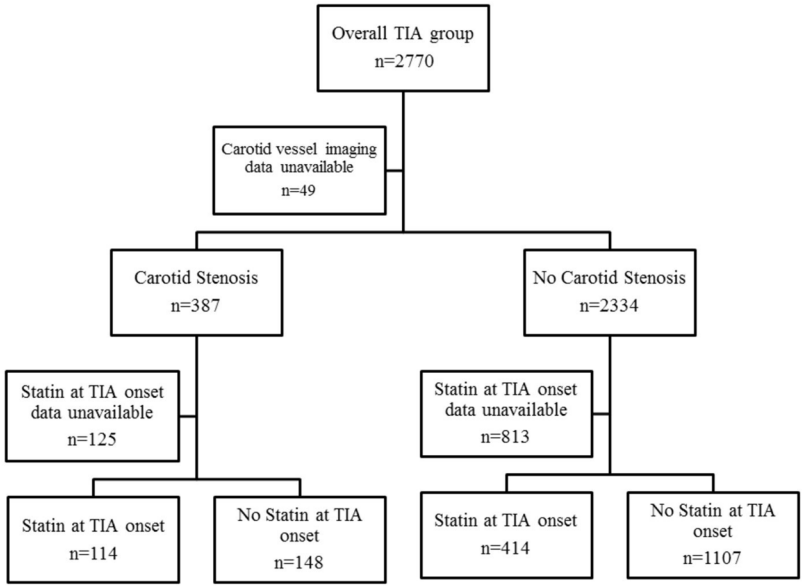

Figure 1.
Flow diagram of patients included in study.

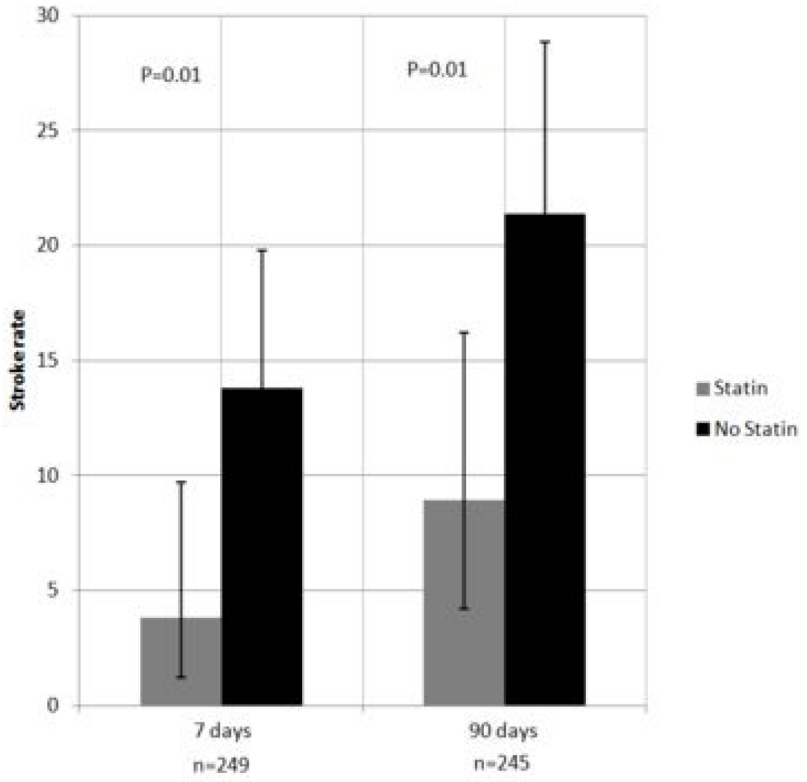

Figure 2.
Non procedural early stroke rates after TIA in patients with carotid stenosis, stratified by statin treatment at TIA onset. 7 days (n=249) statin and 90 days (n=245).

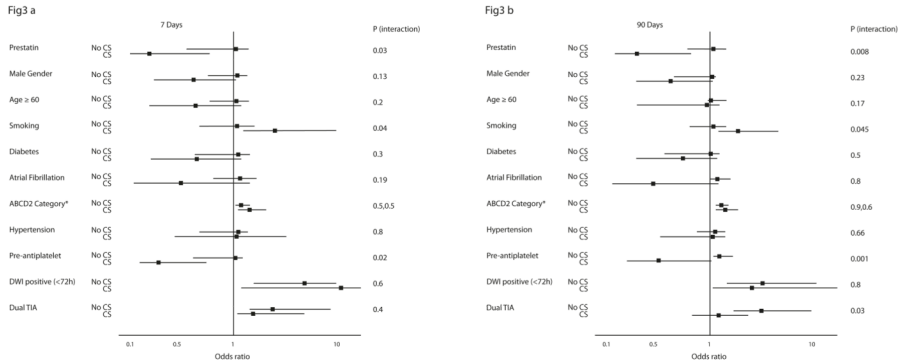

Figure 3.

Risk (odds ratio) factors for stroke at 7 and 90 days after TIA, stratified by presence or absence of carotid stenosis. CS= carotid stenosis *= p value for moderate and high ABCD2 scores, with reference category ABCD2 0–3

Table 1

Characteristics of patients stratified by carotid stenosis. (Includes patients not incorporated in subsequent analyses due to unavailable data).

		Carotid stenosis (n=387)	No carotid stenosis (n=2,334)	p
Gender (% Male, n)		58·4 (223)	52.8(1232)	0.04
Age (mean, SD)		71·1 (10·6)	65.3 (14.9)	<0.0001
Hypertension (%, n)		71·2 (235)	60.3(1099)	<0.0001
Hyperlipidaemia (%, n)		54·5(145)	41.8(640)	<0.0001
Atrial fibrillation (%, n)		11·1 (41)	14.3(307)	0.1
Prior stroke(%, n)		14·7 (38)	7.8(120)	<0.0001
Dual TIA (%, n)		30·5 (89)	15.7(264)	<0.0001
Current smoker (%, n)		25·4(63)	22.2(313)	0.3
Coronary artery disease (%, n)		27·4(104)	16.6(374)	<0.0001
Diabetes mellitus (%, n)		25·8(100)	16.8(393)	<0.0001
ABCD2 score (%, n)	0–3	31·1 (120)	37.6(875)	<0.0001
	4–5	46·9 (181)	48.5(1129)	
	6–7	22·0(85)	13.9(323)	
Acute DWI abnormality (%, n)	<24 hours	42·0(60)	28.7(288)	0.001
	<72 hours	45·2(90)	32.0(419)	<0.0001
Medications at TIA onset (%, n)	Statin	43.5 (114)	27.2(414)	<0.0001
	Antiplatelet	57.8 (214)	48.7(1048)	0.001
	Antihypertensive	65.2(163)	49.1(723)	<0.0001
Recurrent stroke (%, n)	7 days	8·3(31)	2.7(61)	<0.0001
	90 days	17·8 (48)	5.7(94)	<0.0001

Table 2

Clinical features of TIA patients included in the study, stratified by carotid stenosis and statin treatment at TIA onset. (Proportions describe patients for whom data were available).

	Carotid stenosis			No carotid stenosis		
	Statin n=114	**No statin n=148**	**p**	**Statin n=414**	**No statin n=1107**	**p**
Gender (% male, n)	52.6(60)	64.9(96)	0.05	55.5 (229)	51.5(570)	0.2
Age (mean, SD)	71.6 (9.7)	70.4(11.3)	0.3	62.4(0.46)	69.9(0.55)	<0.001
Hypertension* (%, n)	73.6(67)	62.3(76)	0.08	78(241)	52.6(412)	<0.001
Hyperlipidaemia (%, n)	80.4(86)	38.6(56)	<0.001	83.5(313)	28.1(285)	<0.001
Atrial Fib. † (%, n)	13.2(14)	13.0 (18)	1.0	19.4(71)	13.6(131)	0.009
Prior Stroke (%, n)	23.4(25)	9.0(13)	0.002	14.5(57)	4.5(52)	<0.001
Dual TIA ‡	25(22)	27.1(23)	0.8	11.0(32)	11.0(72)	1
Current Smoker §, (%, n)	18.0(18)	31.5(41)	0.02	18.9(63)	25.9(229)	0.01
CAD (%, n)	39.5(45)	12.8(19)	<0.001	37.2(154)	7.4(82)	<0.001
Diabetes Mellitus (%, n)	28.1(32)	19.6(29)	0.1	29(120)	12.9(143)	<0.001
ABCD2≥ 4 (%, n)	65.8(75)	66.9(99/148)	0.9	65.4(270)	56.6(624)	0.002
CEA (%, n)	42.4(45)	30.6(42)	0.06			
CAS (%, n)	4.7(5)	2.2(3)	0.3			
Acute DWI abnormality ||, (%, n)	45.9(17)	52.2(24)	0.6	31.9(44)	35.9(139)	0.4

Atrial Fib= atrial fibrillation. CEA= carotid endarterectomy, CAS= carotid artery stenting.

*data missing for 26.8% patients

†data missing for 11.5% patients

‡data missing for 38.4% patients,

§data missing for 18.9%,

||data missing for 65.9%.