Acta Neurol. Belg., 2011, **111**, 261-267

Review article

Pre-stroke use of statins on stroke outcome: a meta-analysis of observational studies

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Abstract

Background: Animal pre-clinical studies suggest that statins may have neuroprotective effects in acute ischaemic stroke. Statins might also increase the risk of developing haemorrhagic transformation after thrombolytic treatment.

Methods: We performed a systematic review and included studies that compared good functional outcome, defined as a modified Rankin Scale (mRS) score ≤ 2 at 3 months, in-hospital mortality and risk of symptomatic haemorrhagic transformation, between pre -stroke statin users and non users with acute ischaemic stroke.

Results: Eleven studies met our predefined inclusion criteria. Statin therapy before stroke-onset was associated with a lower risk of in-hospital mortality (OR 0.56; 95% CI: 0.40 to 0.78, P < 0.0006). There was no difference between the two groups for good functional outcome at 3 months (OR 1.01; 95% CI: 0.64 to 1.61, P = 0.96). Statin use was associated with an increased risk of developing symptomatic haemorrhagic transformation after thrombolytic therapy (OR 2.34; 95% CI 1.31 to 4.17, P = 0.004).

Conclusions: Our meta-analysis suggests that pre-treatment with statins does not improve 3 months functional outcome, defined as independence on mRS, but decreases in-hospital mortality and increases the risk of developing a symptomatic haemorrhagic transformation in patients treated with thrombolysis.

Key words: Ischaemic stroke; statins; outcome; neuroprotection; thrombolysis; ICH; meta-analysis.

Introduction

Because of their vasoprotective actions, statins (hydroxymethyl-glutaryl-CoA reductase inhibitors) are widely used for the primary and secondary prevention of cardiovascular events, including stroke (1-3). In addition to their cholesterol lowering, antithrombotic and atherosclerotic plaque stabilising effects, statins may also have a neuroprotective effect in ischaemic stroke. Potential neuroprotective mechanisms include an up-regulation of endothelial NO synthase, which may increase blood flow in the ischaemic penumbra, antioxidant effects, and inhibition of inflammatory processes (4, 5). After induced focal brain ischaemia in rats, statin treatment reduced infarct volume up to 46% (6).

Several studies reported that low cholesterol levels and the use of statins in patients with ischaemic stroke may increase the risk of haemorrhagic transformation (1, 7, 9). However, a large prospective study could not demonstrate an increase in haemorrhagic stroke occurrence in statin users (8).

We undertook a meta-analysis to assess whether pre-stroke use of statins influences stroke mortality, functional outcome and the risk of symptomatic haemorrhagic transformation in patients with acute ischaemic stroke.

Methods

Search strategy

Two reviewers independently performed the search. The MEDLINE database was searched between 1966 and December 2010, using different MeSH terms: "*stroke*", "*stroke outcome*", "*statins*", "*hydroxymethyl-glutaryl-CoA reductase inhibitors*". The search was limited to English studies in humans. We reviewed title, abstract and selected relevant studies for further examination. We also screened

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bibliographies of selected articles for additional relevant articles.

Selection of studies

Two reviewers independently applied inclusion criteria for articles. Disagreements were resolved by discussion. To be eligible a study had to meet the following criteria: (1) patients aged 18 years or older with acute ischaemic stroke (confirmed by neuroimaging) with or without intravenous or intra-arterial thrombolytic treatment; (2) comparing patients who used statins with those who didn't use statins at the time of their stroke; (3) reporting either functional outcome assessed by the modified Rankin Scale (mRS) at 3 months, risk of symptomatic haemorrhagic transformation, or in-hospital mortality. We defined good functional outcome as a mRS score ≤ 2 (independency), and symptomatic haemorrhagic transformation as a neurological deterioration within 48 hours following thrombolysis with a haematoma on brain CT.

Data extraction

All data were abstracted using a standardised reporting form. Two reviewers independently abstracted data from included articles. Disagreements were resolved through discussion.

Statistics

Data were processed using review manager 5.1. All analyses were performed using a random effects model. Effect sizes were expressed in pooled odds ratio (OR) estimates. Statistical uncertainty was expressed in 95% confidence intervals (CIs). Significance level was set at $P < 0.05$. Heterogeneity was examined by using the χ^2 distribution, with (n-1) degrees of freedom. The overall heterogeneity was assessed by calculation of I^2. Significance level was set at $P < 0.01$ or $I^2 > 0.20$.

Two studies did not report patient numbers; we calculated them from reported percentages.

Results

Six-hundred forty-one publications met the search criteria and were evaluated. Of these, 8 met the inclusion criteria (10-17). Three further studies were identified from reference lists (18-20) (Fig. 1). Eleven studies were excluded because the outcome parameters did not meet our predefined inclusion criteria. In four studies patients were treated with IV or IA-thrombolysis (10-13). In two studies some patients received thrombolytic treatment (19, 20) in five studies we found no information on whether or not patients were treated with a thrombolytic drug (14-18). Characteristics of the included studies are shown in table 1.

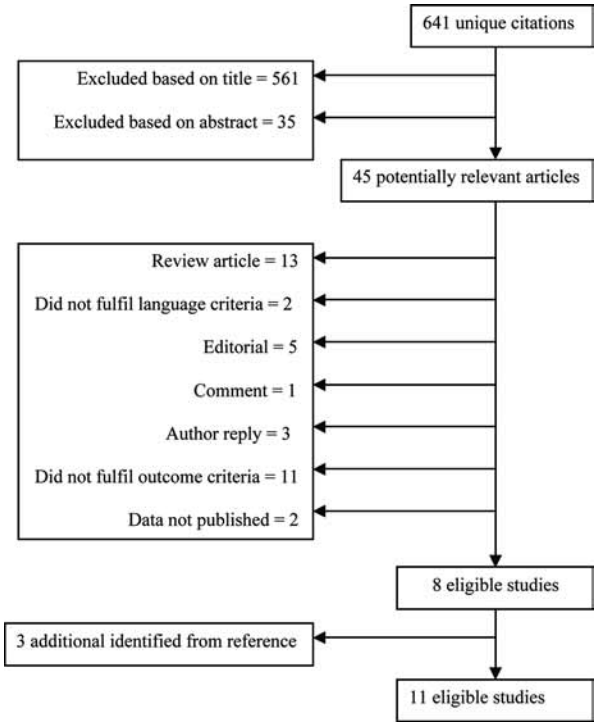

Fig. 1. — Study selection for inclusion in systematic review

In-hospital mortality

Eight studies reported data on in-hospital mortality (10, 14-20). In one study all patients were treated with IV tPA (10), in two studies a number of patients received thrombolytic treatment (19, 20), and in five studies thrombolytic treatment was not mentioned (14-18). Data on 9,337 patients were available. In total, 1,518 patients used statins prior to stroke onset. In the statin group 78 (5.1%) patients died before discharge, compared with 685 (8.8%) patients in the non-statin group (OR 0.56; 95% CI: 0.40 to 0.78, $P < 0.0006$) (Fig. 2).

We indentified minor between-study heterogeneity of effect-sizes. The heterogeneity probability value was 0.15 with I^2 35%.

Functional outcome: mRS ≤ 2 after 3 months

Four studies reported on functional outcome using the mRS after 3 months (10-13). In all studies,

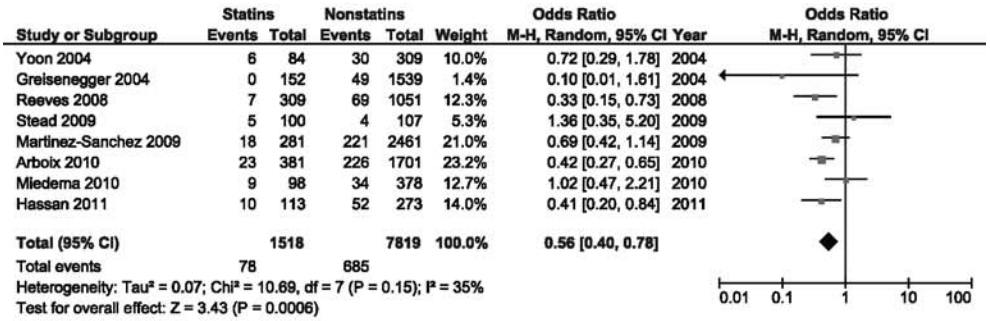

FIG. 2. — Forest plot: In-hospital mortality. In the statin group 78 (5.1%) patients died before discharge, compared with 685 (8.8%) patients in the non-statin group (OR 0.56; 95% CI: 0.40 to 0.78, P < 0.0006). The result shows a lower risk of in-hospital mortality following ischaemic stroke in statin users.

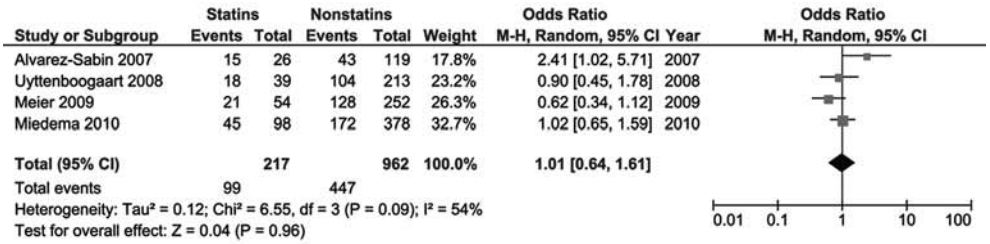

FIG. 3. — Forest plot: Functional outcome. Among the statins users 99 (45%) had a mRS ≤ 2 after 3 months, compared with 447 (46%) in the non-statin group (OR 1.01; 95% CI: 0.64 to 1.61, P = 0.96). The result suggests that statins do not influence the 3 months functional outcome as measured with the mRS.

patients received thrombolytic treatment (three with IV-tPA (10-12), one with IA-tPA (13)). Data on 1,179 patients were available, of which 217 used statins. Among the statins users 99 (45%) had a mRS ≤ 2 after 3 months, compared with 447 (46%) in the non-statin group (OR 1.01; 95% CI: 0.64 to 1.61, P = 0.96) (Fig. 3).

HAEMORRHAGIC TRANSFORMATION

Three studies were included (10, 11, 13), and all reported data on patients who had thrombolytic treatment (two IV-tPA (10, 11), one IA-tPA) (13). Data of 1,039 patients were available. One-hundred ninety-two patients were in the statin-group, 847 patients in the non-statin group. Nineteen (9.9%) patients who used statins developed a symptomatic haemorrhagic transformation, compared with 38 (4.5%) in the non-statin group. The results show a significant increase in the risk of developing a symptomatic haemorrhagic transformation after thrombolytic therapy in the statin users (OR 2.34; 95% CI 1.31 to 4.17, P = 0.004) (Fig. 4).

Discussion

In this meta-analysis we evaluated the effect of pre-stroke treatment with statins on in-hospital mortality, the risk of developing symptomatic haemorrhagic transformation after thrombolytic therapy, and 3 months functional outcome in patients with acute ischaemic stroke.

Statins did not influence the 3 months functional outcome as measured with the mRS.

This is in contrast with a systematic review of Lakhan *et al.* (21) and a recently published meta-analysis of Biffi *et al.* (22), who suggested that ischaemic stroke patients using statins may have a more favourable outcome. The discrepancy with our results may be explained by the fact that these studies included different endpoints at different follow-up times, whereas we only included studies reporting a good functional outcome defined by a mRS ≤ 2 at 3 months.

In animal models of ischaemic stroke, statins appear to be neuroprotective, but as in other studies using neuroprotective drugs, animal models do not

Table 1

Characteristics of included studies

	Subjects, n		tPA	Age, mean, Y		Men %		NIHSS (mean)		Arterial hypertension %		Diabetes %		Dyslipidaemia %		Atrial fibrillation %	
	Statin	No statin		Statin	No statin	Statin	No statin	Statin	No statin	Statin	No statin	Statin	No statin	Statin	No statin	Statin	No statin
Miedema 2010	98	378	Yes	71	67	54	54	12	13	60	43	23	10	65	36	...	...
Uytenboogaart 2008	39	213	Yes	68		54		12		44		12		31		25	
Alvarez-Sabin 2007	26	119	Yes	71	72	54	52	18	17	69	49	35	16	96	18	35	38
Meier 2009	54	252	Yes	67	62	67	54	14	14	93	56	20	13	...	...	33	33
Arboix 2010	381	1701	?	72	76	51	47	...	...	...	...	...	...	...	...	...	...
Reeves 2008	309	1051	?	...	...	51	46	...	...	27	73	33	67	61	39	24	76
Martinez-Sanchez 2009	281	2461	Both	70	69	61	56	...	...	75	60	41	28	89	19	17	17
Hassan 2010	113	273	?	64	65	69	59	...	...	94	81	55	46	64	33	7	7
Yoon 2004	95	338	?	75	75	55	46	...	...	77	67	28	17	80	25	19	18
Greisnegger 2004	152	1539	Both	70	71	46	52	...	...	80	61	36	22	...	...	17	22
Stead 2009	100	107	?	72	72	7	54	4	4	...	...	...	...	...	...	...	...

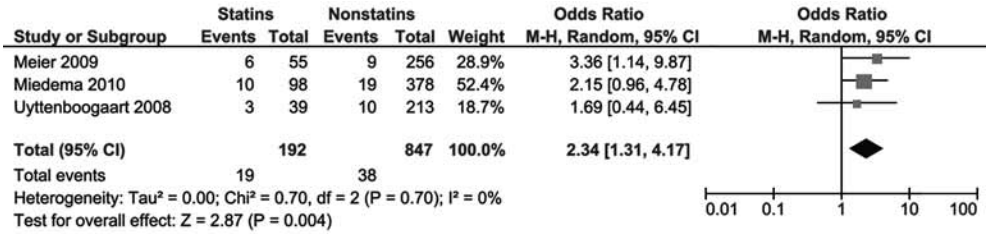

FIG. 4. — Forest plot: Haemorrhagic transformation. 9.9% of the patients who used statins developed a symptomatic haemorrhagic transformation, compared with 4.5% in the non-statin group. The results show a significant increase in the risk of developing a symptomatic haemorrhagic transformation after thrombolytic therapy in the statin users (OR 2.34; 95% CI 1.31 to 4.17, P = 0.004).

mimic the clinical situation (23), and positive results cannot simply be extrapolated to the situation in patients. Many complications associated with stroke, such as for example an increased body temperature, may counteract a possible beneficial effect of a neuroprotective compound (23).

Our meta-analysis suggests that pre-treatment with statins significantly lowers the risk of in-hospital mortality after ischaemic stroke. Infections and myocardial infarction are common causes of mortality after stroke (24, 25). Statins have cardioprotective effects and may prevent infections, and hence may reduce mortality associated with these complications (26-28). Unfortunately, we have no information on the causes of death in the studies included in this meta-analysis, and it is also unclear whether this effect is related to prior use of statins or their continuation after stroke.

This meta-analysis also shows that pre-stroke use of statins significantly increases the risk of developing symptomatic intracranial haemorrhage in patients treated with thrombolysis.

A randomised trial of secondary prevention with atorvastatin after stroke showed a higher incidence of haemorrhagic stroke (1). It remains controversial whether this effect can be explained by a cholesterol lowering effect of statins. Some reports suggest a relationship between low cholesterol levels and intracerebral haemorrhages (29-31), but others did not find such an association (32). A possible explanation could be that cholesterol plays a role in maintaining the integrity of small cerebral vessels (33). Cerebral microbleeds are also more prevalent in ischaemic stroke patients with low cholesterol levels (34).

We realise that our study has limitations. All studies are observational, and thus susceptible to bias, especially when other risk factors between statin users and non-statin users are unbalanced. Aspects such as negative publication bias, selection bias (we excluded several studies that did not met our predefined inclusion criteria) are potential sources of false results. Numbers were too small to assess the effect of publication bias using the Egger method.

Since some studies included few patients, especially in the statin group, there could be a possible small study effect. This could under- or over estimate our results. Since we did not have individual patient data, we could not perform multivariate analyses, to adjust for potential confounders. It can be expected that pre-stroke use of antiplatelets, admission NIHSS score, high glucose level at entry could influence mortality, functional outcome and risk of developing haemorrhagic transformation. Miedema *et al.* (10) found in the multivariable analysis that statin use was not independently associated with the occurrence of hemorrhagic transformation. Antiplatelet therapy, higher NIHSS score at presentation, higher serum glucose levels and a hypodensity of more than 33% on CT scan were independent predictors of hemorrhagic transformation.

The most important finding of our study is a lower risk of in-hospital mortality following ischaemic stroke in statin users. This supports other studies in different other conditions that statin use is associated with reduced mortality. Soyseth *et al.* showed that treatment with statins was associated with improved survival after chronic obstructive pulmonary disease exacerbation (35). In a study of 1,674 patients undergoing aortic reconstruction pre-statin use significantly reduced the risk of death (36). Further studies are needed to fully understand how statins may prevent mortality in acute stroke. Our findings also bring up the question whether starting statins immediately after acute stroke may reduce mortality and whether this potential benefit may outweight the risk of haemorrhagic transformation in patients receiving thrombolytic therapy.

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