Research Article

Do statins reduce the mortality rate in stroke patients treated with systemic thrombolysis in a 5-year single-center study?

https://doi.org/10.4103/1673-5374.306088

Date of submission: August 23, 2020

Date of decision: November 3, 2020

Date of acceptance: November 30, 2020

Date of web publication: January 25, 2021

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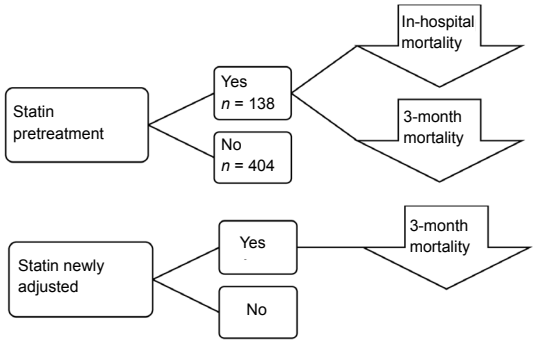
Graphical Abstract *Do statins reduce the mortality rate in stroke patients treated with systemic thrombolysis in a mono-center study?*



Abstract

The present study investigated the association between pre-treatment with a cholesterol-lowering drug (statin) or new setting hereon and the effect on the mortality rate in patients with acute ischemic stroke who received intravenous systemic thrombolysis. During a 5-year period (starting in October 2008), 542 consecutive stroke patients who received intravenous systemic thrombolysis with recombinant tissue plasminogen activator (rt-PA) at the Department of Neurology, University Hospital Schleswig-Holstein, Campus Lübeck, Germany, were included. Patients were characterized according to statins. The primary endpoint was mortality; it was assessed twice: in hospital and 3 months after discharge. The secondary outcome was the rate of symptomatic intracerebral hemorrhage. Of the 542 stroke patients examined (mean age 72 ± 13 years; 51% women, mean National Institutes of Health Stroke Scale (NIHSS) score 11), 138 patients (25.5%) had been pre-treated with statin, while in 190 patients (35.1%) statin therapy was initiated during their stay in hospital, whereas 193 (35.6%) never received statins. Patients pre-treated with statin were older and more frequently had previous illnesses (arterial hypertension, diabetes mellitus and previous cerebral infarctions), but were comparably similarly affected by the stroke (NIHSS 11 *vs*. 11; $P = 0.76$) compared to patients who were not on statin treatment at the time of cerebral infarction. Patients pretreated with statin did not differ in 3-month mortality from those newly treated to a statin (7.6% *vs*. 8%; $P = 0.9$). Interestingly, the group of patients pretreated with statin showed a lower rate of in hospital mortality (6.6% *vs*. 17.0; $P = 0.005$) and 3-month mortality (10.7% *vs*. 23.7%; $P = 0.005$) than the group of patients who had no statin treatment at all. The same effect was seen for patients newly adjusted to a statin during the hospital stay compared to patients who did not receive statins (3-month mortality: 7.1% *vs*. 23.7%; $P < 0.001$). With a good functional outcome (mRS ≤ 2), 60% of patients were discharged, the majority (69.6%; $P < 0.001$) of whom received a statin at discharge. The rate of symptomatic intracerebral hemorrhages in the course of cranial computed tomography was independent of whether the patients were pretreated with a statin or not (8.8% *vs*. 8.7%, $P = 0.96$). Pre-treatment with statin as well as new adjustment could reveal positive effect on prognosis of intravenous thrombolyzed stroke patients. Further investigations are required. The study was approved by the Ethic Committee of the University of Lübeck (approval No. 4-147).

Key Words: acute ischemic stroke; hemorrhage; mortality; outcome; secondary prophylaxis; statins; stroke; systemic thrombolysis

Chinese Library Classification No. R453; R741

Introduction

Stroke is one of the most common diseases in developed countries and one of the leading causes of morbidity and mortality worldwide (Kim et al., 2020). The only evidence-based and approved drug therapy option is the intravenous application of rtPA (Hacke et al., 2008) within the first 4.5 hours after onset of symptoms. Numerous studies have shown that patients with ischemic stroke benefit from secondary prophylaxis with platelet aggregation inhibitors such as acetylsalicylic acid (ASA) or clopidogrel as well as from therapy with a statin (Vergouwen et al., 2008; Amarenco and Labreuche, 2009; Manktelow and Potter, 2009). In the last four decades, numerous randomized controlled trials investigated the impact of lipid-lowering medication on cardiovascular disease risk. Pre-statin age/the age before the widespread use of statins, the Lipid Research Clinics trial showed a benefit

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How to cite this article: *Brüning T, Al-Khaled M (2021) Do statins reduce the mortality rate in stroke patients treated with systemic thrombolysis in a 5-year single-center study? Neural Regen Res 16(9):1807-1812.*

associated with a rather moderate cholesterol reduction induced by cholestyramine (1984). Ten years later for the first time the Scandinavian Survival Simvastatin Study (4S) revealed a significant impact of simvastatin on global mortality and hence changed the approach to cardiovascular prevention (1994). Ever since, statins have been mandatory in patients at high cardiovascular risk. The main effect of the HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme-A) reductase inhibitors is achieved by a significant reduction of low-density lipoprotein (LDL) cholesterol and apolipoprotein B (apoB)-containing lipoproteins in the arterial wall as the key initiating event in atherogenesis. In addition to this cholesterol-lowering effect, so-called pleiotropic effects are also believed to be responsible for the therapeutic benefits of statins. These include potential effects of statins on plaque stabilization, endothelial function, cell adhesion and inflammation. Statin therapy is frequently associated with changes in HDL-C levels that are inversely proportional to the progression of coronary atherosclerosis, even in patients with low levels of LDL-C (Lin et al., 2018). The CAPITAIN study (Chronic and Acute Effects of Pitavastatin on Monocyte Phenotype, Endothelial Dysfunction and HDL Atheroprotective Function in Subjects With Metabolic Syndrome) revealed that pitavastatin progressively normalized the triglycerides-to-cholesterol ratio within 6 months of treatment, without modifying glucose metabolism or significantly changing HDL levels (Chapman et al., 2014). Furthermore, this study suggested that pitavastatin enhances plasmalogen production, this might be clinically relevant in reducing oxidative stress and inflammation, although the biochemical mechanism is not yet fully understood (Chapman et al., 2014). Moreover, it could be shown that statin treatment resulted in a significant decrease of high-sensitivity C reactive protein levels in patients with metabolic syndrome, whereas high-molecular-weight adiponectin levels did not change (Matsubara et al., 2012). A recent systematic review and meta-analysis showed that treatment with a statin leads to a significant reduction in the plasma concentration of vascular endothelial growth factor, the main vascular growth factor with pro-inflammatory and atherogenic properties (Sahebkar et al., 2015).

This raises the possibility that statins might have an effect on the course and outcome of stroke patients. It has been shown recently that statins play an important role in the treatment of ischemic stroke, preventing stroke recurrence and cardiovascular events, and in improving functional performance (Vitturi and Gagliardi, 2020). Our clinical practice is permeated by doubts regarding the evidence of the use of statins in the acute stroke phase. Despite numerous studies (Cappellari et al., 2011; Fang and Wu, 2012), one of these questions is about WHEN prescribing a statin to take advantage of the best effectiveness. The aim of the present study was therefore to investigate the association between treatment with statins and the outcome and mortality rate after intravenous systemic thrombolysis with rtPA in patients with acute ischemic stroke.

Subjects and Methods

Subjects

Over a 5-year period (2008–2013), 542 consecutive patients with acute ischemic stroke (mean age 72 ± 13 years; 51% women, mean National Institutes of Health Stroke Scale (NIHSS) score 11 [IQR, 7-15]) admitted to the Department of Neurology at the University Medical Center Schleswig-Holstein, Campus Lübeck and received intravenous systemic thrombolysis with rtPA were recruited. In our study, we included 25 patients (4.6%) who received intravenous injection of rt-PA and additional mechanical thrombectomy. Baseline and sociodemographic data such as gender, age, comorbidities, neurological deficit at admission, and clinical and laboratory findings were taken from the patient records and the hospital information system (**Table 1**).

Outcomes

The primary Outcome was determined using the modified Rankin Scale (mRS), which is an assessment score for disability and functional status in stroke ranging from 0 (no symptoms) to 6 points (death) (van Swieten et al., 1988).

Primary Outcome data were collected by telephone interviews with patients, and general practitioners. Mortality was evaluated at the time of discharge from hospital and after 3 months. The secondary outcome was the occurrence of intracerebral hemorrhage after the systemic thrombolysis with rt-PA during the hospitalization.

Study design

All patients included in the study were admitted to the

Table 1 | **Baseline data**

		Statin pretreatment			Statin new treatment		
Characteristics	***N* = 542**	**No (*n* = 385)**	**Yes (*n* = 138)**	***P***	**No (*n* = 342)**	**Yes (*n* = 190)**	***P***
Age[a] (yr)	71.9±12.8	70.8±13.4	73.7±10.0	0.02	72.5±12.8	70.3±12.7	0.05
Female[b] [*n*(%)]	274(51)	203(53)	59(43)	0.04	166	101	0.3
NIHSS score[c]	11(7–15)	11(6–16)	10(7–15)	0.8	11(7–16)	9.5(6–15)	0.02
Pre-existing conditions[b] [*n*(%)]							
Previous stroke	194(37)	128(33)	66(48)	0.003	125	72	0.8
Atrial fibrillation	229(44)	171(44)	58(42)	0.6	166	65	0.001
Arterial hypertension	404(77)	276(72)	128(93)	< 0.001	267	143	0.4
Diabetes mellitus	142(27)	94(25)	48(35)	0.02	102	45	0.1
Premedication[b] [*n*(%)]							
Secondary prevention	270(50)	154(41)	111(82)	< 0.001	194	71	< 0.001
Beta blocker	283(52)	178(48)	102(76)	< 0.001	198	82	< 0.001
ACE inhibitors	211(39)	132(35)	77(57)	< 0.001	143	67	0.08
Laboratory findings[a]							
Total cholesterol (mM)	4.70±1.13	4.88±1.11	4.22±0.98	< 0.001	4.39±1.08	5.17±1.02	< 0.001
HDL (mM)	1.16±0.34	1.18±0.34	1.12±0.30	0.1	1.14±0.33	1.18±0.33	0.1
LDL (mM)	2.91±0.98	3.09±0.96	2.45±0.82	< 0.001	2.62±0.92	3.34±0.88	< 0.001
Door-to-needle time[a] (min)	67±43	66±42	60±36	0.1	68±43	65±41	0.4
Time from symptom to start of therapya (min)	153±72	154±74	153±68	0.9	153±71	152±75	0.9

[a]Data are expressed as the mean ± SD; [b]Data are expressed as number (percentage); [c]Data are expressed as median (IQR). IQR: Interquartile rank; NIHSS: National Institutes of Health Stroke Scale.

stroke unit or to the intensive care unit and were treated by neurologists specializing in stroke treatment. Statins were administered in accordance with the guidelines of the German Society for Neurology for therapy and secondary prevention of stroke. The data acquisition was part of the ongoing stroke registry of the Department of Neurology (AZ: 4-147). The approval for the stroke registry was granted by the Ethics Committee of the University of Lübeck. The entry in the stroke registry was mandatory as part of the benchmarking project, for the inclusion the follow up questionnaire an informed consent was obtained from patients or caregivers.

Statistical analysis

For data analysis, we used SPSS version 22.0.0.2 (IBM, Armonk, NY, USA). The data were described with mean and standard deviation for continuous variables, median and interquartile rank (IQR) for scores, and absolute numbers and percentages for nominal and categorical variables. We performed chi-square tests for categorical variables, Student's *t*-tests for continuous variables, and Mann-Whitney *U* tests for scores. The multivariate logistic regression was performed to determine the odds ratio. All variables in univariate analysis with a *P*-value < 0.1 were entered in the logistic regression model (**Table 1**). A *P*-value less than 0.05 was assumed to be significant.

Results

Baseline characteristics

Of the 542 patients with acute ischemic stroke examined, 138 patients (25.5%) were pretreated with a statin. In another 190 patients (35.1%), statin treatment was initiated during their stay in hospital, whereas 193 patients (35.6%) did not receive statins at all.

The patients pre-treated with a statin were older (74 *vs*. 71 years; *P* = 0.02), more frequently male (57% *vs*. 47%; *P* = 0.04), and similarly affected by the stroke (NIHSS 11.1 ± 5.2 *vs*. 11.3 ± 5.3; *P* = 0.76). Moreover, they were also more likely to have a history of previous stroke (48% *vs*. 33%; *P* = 0.003), arterial hypertension (93% *vs*. 72%; *P* < 0.001) and diabetes mellitus (35% *vs*. 25%; *P* = 0.02). They were also more likely to having received medication for stroke secondary prophylaxis, beta-blockers and ACE inhibitors (all *P* < 0.001). In patients pretreated with statins markedly lower serum levels of both total cholesterol and LDL were observed, while there were no relevant differences in HDL levels. Atrial fibrillation was not different in the two groups. They also did not differ with regard to door-to-needle time and the time from the onset of symptoms to the start of therapy. The etiology of stroke was cardio-embolic in 47% of cases, 13.5% atherothrombotic, 3.5% microangiopathic and 36% unknown or reasons.

Outcomes

If we draw a direct comparison between the group of patients pretreated with a statin and the group of patients who had not received a statin either before or after the cerebral infarction and during the phase of the inpatient stay or at the time of discharge, it was found a lower rate of hospital mortality (17.0% *vs*. 6.6%; *P* = 0.005) and lower mortality rates after 3 months (23.7% *vs*. 10.7%; *P* = 0.005). Of the 482 patients who left the hospital alive, 315 were on a statin at the time of discharge (65.4%). Patients who were newly adjusted to a statin had significantly lower mortality rates at 3 months (23.7% *vs*. 7.1%; *P* < 0.001) than those who did not receive a statin at all.

Outcome data were available for 522 patients. It was found that 313 patients (60%) left the clinic with a good outcome (mRS ≤ 2), the majority (69.6%; *P* < 0.001) of whom were treated with a statin at discharge. With regard to a good functional outcome, it did not matter whether the patients were already pretreated with a statin at admission or were adjusted to it during their stay in hospital. Only when looking at the patient groups at discharge a significant difference could be observed. The frequency of good functional outcome was significantly higher in patients discharged with statin than in patients discharged without (70.8% *vs*. 44.4%; *P* < 0.001). The majority of patients with poor functional outcome were not treated with a statin at discharge (56.9%).

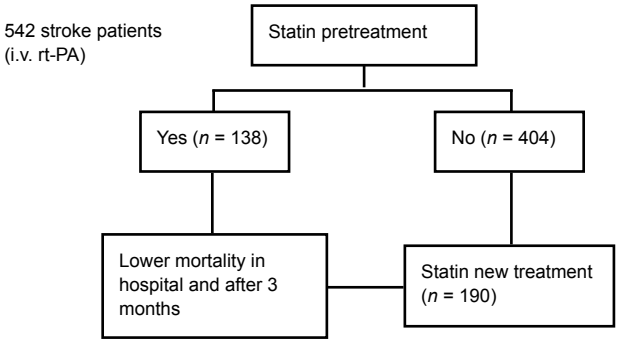

Figure 1 | **Study flow chart.**
rt-PA: Recombinant tissue plasminogen activator.

The rate of symptomatic intracerebral hemorrhage on follow-up CT was independent of whether the patients were pretreated with a statin or not (8.8% *vs*. 8.7%, *P* = 0.96).

Discussion

While a causal relationship between hyperlipidemia and atherosclerosis is undoubted, the significance of hypercholesterolemia for brain infarction has long been disputed, as numerous studies have failed to demonstrate a consistent relationship between cholesterol levels and stroke frequency (Endres et al., 2011). The SPARCL study was the first to demonstrate an absolute risk reduction for the common vascular endpoint of 3.5% in patients with post-stroke or TIA conditions without other vascular comorbidities, corresponding to a relative risk reduction of 20% when treated with atorvastatin 80 mg *versus* placebo, although the reduction in ischemic stroke is at least partially offset by an increased risk of cerebral hemorrhage (Amarenco et al., 2006).

A comparable relative risk reduction of 20% for an ischemic stroke could also already be shown by a systematic review, but an increased risk for hemorrhagic strokes was also found here (Vergouwen et al., 2008). A large network meta-analysis summarized a total of 170.255 patients with vascular risk from 76 randomized controlled treatment studies with different statins, in which, however, only one study (SPARCL) included patients with stroke, whereas the large majority of the studies (*n* = 42) included patients with CHD. In addition to a reduction in overall and cardiovascular mortality, a significant reduction in the combined stroke endpoint was also shown (Mills et al., 2011).

HMG-CoA reductase inhibitors are recommended as the first-line of lipid-lowering drug therapy in the primary and secondary prevention of cardiovascular events (Jellinger et al., 2017).

The influence of statins on the atherosclerotic process has little influence on reducing mortality in the acute phase of stroke. Several studies have demonstrated the beneficial effects of pre-stroke and post-stroke statin use in ischemic stroke (Robinson et al., 2005; Cholesterol Treatment Trialists et al., 2010).

In the observation period of our study, about a quarter of the patients had already been pre-treated with a statin at the time of the index event, in a good third of the patients medication was initiated during the inpatient stay. Different reasons

may have played a role in why a higher number was not achieved. The spectrum ranges from contraindications and incompatibilities to a lack of patient consent to treatment with a statin. The treating physicians might also be inclined not to have treated severely affected patients with a presumably unfavourable outcome with a statin. We were unable to establish a correlation between the severity of the patient's functional impairment and whether a statin treatment existed at the time of discharge from hospital. Lower mortality rates and better outcome of stroke patients treated with statin were also found in other studies (Al-Khaled et al., 2014).

It is interesting to note that in our study the patients pre-treated with statin generally showed a higher rate of pre-existing conditions.

Adherence to statins in real-world clinical practice is known to be suboptimal; reported numbers fluctuate between 35–70% (Rannanheimo et al., 2015; Chen et al., 2016). The reason for lack of adherence might be an exaggerated fear of side-effects among doctors and patients.

In the recent past, concerns have repeatedly been raised that statin therapy carries the risk of increased cerebral hemorrhage rates. And indeed, it has been shown that low cholesterol levels increase the risk of hemorrhagic stroke, while on the other hand, an association, albeit weak, between elevated cholesterol and ischemic stroke has been shown (Endres et al., 2011). Patients with cerebral hemorrhages should therefore only be treated with a statin after considering the risks and benefits. Although the concern regarding the association of statin use with the risk of cerebral hemorrhage remains, in a recent meta-analysis of 1.652 cerebral hemorrhage patients exposed to statins and 5.309 cerebral hemorrhage patients without statin use, prior statin use was not associated with an increase in the short-term mortality, an unfavorable functional outcome, or post-cerebral hemorrhage hematoma volume at admission (Lei et al., 2014).

In a recently published large nationwide Danish population-based, propensity score matched cohort study including 519,894 stroke-free individuals initiating statins statin users and non-users had similar symptomatic intracerebral hemorrhage (sICH) risk during the first 6 months after statin initiation. Hereafter, statin users had an even lower risk throughout the study period (follow up to 10 years) (Ribe et al., 2019).

Our findings regarding risk of sICH are in line with recently published data that does not show any significant association between risk of sICH and poor outcome after IVT for patients on prior statin therapy (Mowla et al., 2020).

However, this observation can be distorted by a "healthy initiator bias", that might arise through two different paths: a selective initiation of preventive treatment with statin e.g. among healthy and health-conscious patients and a treatment selection away from frail individuals at increased risk of adverse outcome (Lund et al., 2015). We cannot exclude that stroke patients initiating statins in our study display a selected group of more healthy individuals with a lower risk of sICH. A confounding by indication could arise from the fact that statins are given to patients at higher cardiovascular risk. Furthermore, in observational studies there is usually a risk of confounding. Despite all efforts to avoid or minimize baseline confounding, we cannot conclude that time-varying confounding, such as a "healthy adherer bias", is non-existent. The group of statin users could become healthier over time if statin adherence is a proxy for beneficial lifestyle and health behavior at the patient level and for selective discontinuation of treatment at the healthcare provider level. Therefore, the positive effect of statins on the risk of sICH could possibly be exaggerated. The lower risk of bleeding associated with statins might be falsified by simultaneous treatment with other drugs that reduce the risk of sICH, such as antihypertensive drugs. Hypertension is known to be closely associated with risk of sICH (Ariesen et al., 2003), and antihypertensive agents are likely to be initiated concurrently with statins in populations with high cardiovascular risk (Sever et al., 2003).

The reduction of cardiovascular events under statin therapy, which has long been clearly demonstrated by several large intervention studies, is currently attributed to a LDL cholesterol-lowering effect. While our patients pre-treated with statin showed highly significant reductions in total cholesterol and LDL cholesterol, a causal attribution to the lower LDL levels is not possible. Remarkably, favorable statin effects are also found at relatively low LDL cholesterol initial values. This has drawn attention to special properties of statins, which are presumably primarily related to effects on the intermediate metabolism of cholesterol. In addition to the cholesterol-lowering effect, the statins are therefore attributed therapeutically relevant indirect side effects, so-called pleiotropic effects, which possibly enhance the cholesterol-lowering effect of the statins and can thus contribute to success in therapy and prevention. A large number of studies have focused on possible effects of statins on endothelial function in patients with hypercholesterolemia, since disturbed endothelial function is considered an early indicator of vascular damage. Here it could be shown that statins quickly lead to an improvement in endothelial function, which cannot be explained by the reduction of endothelial toxic LDL alone. Various working groups were able to prove in patients with hyperlipidemia that statins also lead to a significant reduction in C reactive protein concentration (Ridker et al., 1999; Strandberg et al., 1999). However, it is not yet clear whether the results of these investigations in patients with coronary events can also be transferred to patients with cerebral ischemia. The effects of statins on the release of mediators and chemokines, which play a role at both T-lymphocyte and monocyte level, may contribute to their antiatherogenic effect (Thiery and Brugel, 2003). In more advanced stages of atherogenesis, fibroblasts and smooth muscle cell proliferation are of great relevance. Statins have been shown to block platelet derived growth factor-induced smooth muscle cell proliferation by inhibiting DNA synthesis, and this antiproliferative effect is likely to be due to inhibition of cholesterol synthesis intermediates (Braun-Dullaeus et al., 1998). In addition, statins can induce apoptosis in phagocytes, smooth muscle cells and tumor cells. By means of these significant effects on cell proliferation and apoptotic processes, statins are able to have a decisive influence on the progression and plaque rupture of atherosclerotic lesions (Braun-Dullaeus et al., 1998). The role of macrophages is also relevant in the context of plaque stabilization or destabilization. Unstable atherosclerotic lesions are characterized by a large lipid core and a thin fibrotic cap. Activated macrophages secrete proteolytic enzymes such as metalloproteinases, which weaken the fibrous cap of atherosclerotic lesions. The cap loses collagen, ruptures and thrombogenic material is released from the lipid core. Statins are believed to contribute to plaque stabilization by inhibiting the uptake of aggregated or modified LDL by smooth muscle cells and macrophages, resulting in a decrease of the lipid core is coming. By inhibiting macrophage activation, statins lead to a reduced expression of metalloproteinases, which in turn leads to a possible accumulation of collagen and reinforcement of the fibrotic cap (Luan et al., 2003). Another important association is the one between hypercholesterolemia and increased platelet activity and their significant reduction by statins (Opper et al., 1995). A reduced production of thromboxane A2 and an increase in the synthesis of prostacyclin are discussed as possible mechanisms. A modification of the cholesterol content in the platelet membrane and thus a reduction of its thrombogenic potential is also conceivable. Statins reduce platelet attachment to damaged vessel areas and reduce thrombus

formation (Opper et al., 1995; Thiery and Brugel, 2003). It is conceivable that statins can prevent the fatal outcome by the prevention of other subsequent fatal thrombotic events.

Several experimental studies have shown that statin pretreatment increases cerebral blood flow and reduces cerebral infarction size during cerebral ischemia (Endres et al., 1998; Aboa-Eboule et al., 2013). In accordance with these animal studies, several clinical studies have reported an association between pre-stroke statin use and more collaterals or a smaller infarction size in patients with acute cerebral ischemia (Shook et al., 2006; Ovbiagele et al., 2007). Increasing evidence has shown that pre-stroke statin use reduces the risk of initial and recurrent stroke and evokes beneficial effects on the severity, functional outcome, and mortality in patients with ischemic stroke (Sacco et al., 2011). Therefore, the beneficial effects of statin therapy may be due to the reduction of cerebral infarction by enhancing early reperfusion.

Our work has the usual limitations of a registry study, but we were able to show that both pre-treatment and new treatment with a statin are positively correlated with the prognosis of intravenous thrombolysed patients with brain infarction.

There is a potential bias, as our study included patients newly treated with a statin, some of whom were discharged after 2 days and others after 36 days. There was no specification in the data collection as to when statin treatment was started (< 72 hours or < 7 days or later). Further studies should illuminate this issue to improve the impact and the clinical usefulness regarding the question if there is a net benefit of early statin prescription. Another major limitation of our study is that it cannot be used to derive any statement on long-term outcome. Most comparable studies have also only investigated the effect of pre-stroke statin use on short-term functional outcome at discharge, 7 days, or 90 days after stroke using the modified Rankin scale (Goldstein et al., 2009; Sacco et al., 2011; Flint et al., 2012).

Although most of these studies found that pre-stroke statin use was associated with favorable functional outcome some studies also reported no significant improvement of functional outcome in ischemic stroke patients.

There is another important bias of our study. Statin prescription is usually highly prescribed according to stroke etiology and evidence of its benefits is lacking for some Trial of Org 10172 in Acute Stroke Treatment (TOAST) subtypes (Vitturi and Gagliardi, 2020). Looking at the stratification of patients after TOAST, statins showed positive results in the majority of patients: in cases of major arterial atherosclerosis, small vessel occlusion and stroke of unknown cause. However, in contrast to other studies our study also suggests that cardioembolic stroke and stroke of other determinate cause may benefit equally from statin therapy (Vitturi and Gagliardi, 2020). The role of the inherent heterogeneity of these groups of stroke patients has not yet been finally clarified. Furthermore, in anticoagulated patients, the question arises as to the additional benefit of statins.

It is not really surprising that the initiation of statins during hospitalization could lead to reduced mortality. This could be an artifact of patient selection. Physicians in the clinic might instinctively have stopped giving statins to those patients with a poor prognosis or dysphagia.

The beneficial effects of statin therapy initiated after stroke during hospitalization have been reported in patients with ischemic stroke. Post-stroke statin use has been found to be associated with good functional outcome (mRS 0–2) in patients with ischemic stroke (Al-Khaled et al., 2014). Further especially prospective and randomized studies are necessary.

In conclusion, pre-treatment with statin as well as new adjustment could reveal positive effect in patients with acute ischemic stroke who received an intravenous systemic thrombolysis with rt-PA. The mortality as well as the functional outcomes may benefit from the medical treatment with statins. An effect on the occurrence of intracerebral hemorrhage after thrombolysis was not found. Further investigations are required.

Author contributions: *TB designed the study, collected the data, interpreted the results and wrote the manuscript. MAK designed the study, interpreted the results and wrote the manuscript. Both authors approved the final manuscript.*
Conflicts of interest: *The authors declare that they have no conflicts of interest.*
Financial support: *The authors received no funding for the research reported in this paper.*
Institutional review board statement: *The study was approved by the Ethic Committee of the University of Lübeck (approval No. 4-147).*
Declaration of patient consent: *The authors certify that they have obtained all appropriate patient consent forms. In the forms the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.*
Reporting statement: *This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.*
Biostatistics statement: *The statistical methods of this study were reviewed by the biostatistician of University Medical Center Schleswig-Holstein, Campus Lübeck in Germany.*
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Data sharing statement: *The study was part of the department own bench marking project, the data used in this study cannot be shared.*
Plagiarism check: *Checked twice by iThenticate.*
Peer review: *Externally peer reviewed.*

References

(1984) The Lipid Research Clinics Coronary Primary Prevention Trial results. II. The relationship of reduction in incidence of coronary heart disease to cholesterol lowering. JAMA 251:365-374.

(1994) Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 344:1383-1389.

Aboa-Eboule C, Binquet C, Jacquin A, Hervieu M, Bonithon-Kopp C, Durier J, Giroud M, Bejot Y (2013) Effect of previous statin therapy on severity and outcome in ischemic stroke patients: a population-based study. J Neurol 260:30-37.

Al-Khaled M, Matthis C, Eggers J (2014) Statin treatment in patients with acute ischemic stroke. Int J Stroke 9:597-601.

Amarenco P, Labreuche J (2009) Lipid management in the prevention of stroke: review and updated meta-analysis of statins for stroke prevention. Lancet Neurol 8:453-463.

Amarenco P, Bogousslavsky J, Callahan A, 3rd, Goldstein LB, Hennerici M, Rudolph AE, Sillesen H, Simunovic L, Szarek M, Welch KM, Zivin JA, Stroke Prevention by Aggressive Reduction in Cholesterol Levels I (2006) High-dose atorvastatin after stroke or transient ischemic attack. N Engl J Med 355:549-559.

Ariesen MJ, Claus SP, Rinkel GJ, Algra A (2003) Risk factors for intracerebral hemorrhage in the general population: a systematic review. Stroke 34:2060-2065.

Braun-Dullaeus RC, Mann MJ, Dzau VJ (1998) Cell cycle progression: new therapeutic target for vascular proliferative disease. Circulation 98:82-89.

Cappellari M, Deluca C, Tinazzi M, Tomelleri G, Carletti M, Fiaschi A, Bovi P, Moretto G (2011) Does statin in the acute phase of ischemic stroke improve outcome after intravenous thrombolysis? A retrospective study. J Neurol Sci 308:128-134.

Chapman MJ, Orsoni A, Robillard P, Hounslow N, Sponseller CA, Giral P (2014) Effect of high-dose pitavastatin on glucose homeostasis in patients at elevated risk of new-onset diabetes: insights from the CAPITAIN and PREVAIL-US studies. Curr Med Res Opin 30:775-784.

Chen PS, Cheng CL, Kao Yang YH, Li YH (2016) Statin adherence after ischemic stroke or transient ischemic attack is associated with clinical outcome. Circ J 80:731-737.

Cholesterol Treatment Trialists C, Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, Peto R, Barnes EH, Keech A, Simes J, Collins R (2010) Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet 376:1670-1681.

Endres M, Heuschmann PU, Laufs U, Hakim AM (2011) Primary prevention of stroke: blood pressure, lipids, and heart failure. Eur Heart J 32:545-552.

Endres M, Laufs U, Huang Z, Nakamura T, Huang P, Moskowitz MA, Liao JK (1998) Stroke protection by 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase inhibitors mediated by endothelial nitric oxide synthase. Proc Natl Acad Sci U S A 95:8880-8885.

Fang S, Wu J (2012) Does statin in the acute phase of ischemic stroke improve outcome after intravenous thrombolysis? J Neurol Sci 312(1-2):196.

Flint AC, Kamel H, Navi BB, Rao VA, Faigeles BS, Conell C, Klingman JG, Hills NK, Nguyen-Huynh M, Cullen SP, Sidney S, Johnston SC (2012) Inpatient statin use predicts improved ischemic stroke discharge disposition. Neurology 78:1678-1683.

Goldstein LB, Amarenco P, Zivin J, Messig M, Altafullah I, Callahan A, Hennerici M, MacLeod MJ, Sillesen H, Zweifler R, Michael K, Welch A, Stroke Prevention by Aggressive Reduction in Cholesterol Levels I (2009) Statin treatment and stroke outcome in the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial. Stroke 40:3526-3531.

Hacke W, Kaste M, Bluhmki E, Brozman M, Davalos A, Guidetti D, Larrue V, Lees KR, Medeghri Z, Machnig T, Schneider D, von Kummer R, Wahlgren N, Toni D, Investigators E (2008) Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med 359:1317-1329.

Jellinger PS, Handelsman Y, Rosenblit PD, Bloomgarden ZT, Fonseca VA, Garber AJ, Grunberger G, Guerin CK, Bell DSH, Mechanick JI, Pessah-Pollack R, Wyne K, Smith D, Brinton EA, Fazio S, Davidson M (2017) American Association of Clinical Endocrinologists and American College of Endocrinology Guidelines for Management of Dyslipidemia and Prevention of Cardiovascular Disease. Endocr Pract 23:1-87.

Kim J, Thayabaranathan T, Donnan GA, Howard G, Howard VJ, Rothwell PM, Feigin V, Norrving B, Owolabi M, Pandian J, Liu L, Cadilhac DA, Thrift AG (2020) Global Stroke Statistics 2019. Int J Stroke 15:819-838.

Lei C, Wu B, Liu M, Chen Y (2014) Association between statin use and intracerebral hemorrhage: a systematic review and meta-analysis. Eur J Neurol 21:192-198.

Lin HP, Baghdasarian S, Singer MR, Mott MM, Bradlee ML, Pickering RT, Moore LL (2018) Dietary cholesterol, lipid levels, and cardiovascular risk among adults with diabetes or impaired fasting glucose in the framingham offspring study. Nutrients 10:770.

Luan Z, Chase AJ, Newby AC (2003) Statins inhibit secretion of metalloproteinases-1,-2,-3, and-9 from vascular smooth muscle cells and macrophages. Arterioscler Thromb Vasc Biol 23:769-775.

Lund JL, Richardson DB, Sturmer T (2015) The active comparator, new user study design in pharmacoepidemiology: historical foundations and contemporary application. Curr Epidemiol Rep 2:221-228.

Manktelow BN, Potter JF (2009) Interventions in the management of serum lipids for preventing stroke recurrence. Cochrane Database Syst Rev 2009:CD002091.

Matsubara T, Naruse K, Arakawa T, Nakao M, Yokoi K, Oguri M, Marui N, Amano T, Ichimiya S, Ohashi T, Imai K, Sakai S, Sugiyama S, Ishii H, Murohara T (2012) Impact of pitavastatin on high-sensitivity C-reactive protein and adiponectin in hypercholesterolemic patients with the metabolic syndrome: the PREMIUM Study. J Cardiol 60:389-394.

Mills EJ, Wu P, Chong G, Ghement I, Singh S, Akl EA, Eyawo O, Guyatt G, Berwanger O, Briel M (2011) Efficacy and safety of statin treatment for cardiovascular disease: a network meta-analysis of 170,255 patients from 76 randomized trials. QJM 104:109-124.

Mowla A, Shah H, Lail NS, Vaughn CB, Shirani P, Sawyer RN (2020) Statins use and outcome of acute ischemic stroke patients after systemic thrombolysis. Cerebrovasc Dis 49:503-508.

Opper C, Clement C, Schwarz H, Krappe J, Steinmetz A, Schneider J, Wesemann W (1995) Increased number of high sensitive platelets in hypercholesterolemia, cardiovascular diseases, and after incubation with cholesterol. Atherosclerosis 113:211-217.

Ovbiagele B, Saver JL, Starkman S, Kim D, Ali LK, Jahan R, Duckwiler GR, Vinuela F, Pineda S, Liebeskind DS (2007) Statin enhancement of collateralization in acute stroke. Neurology 68:2129-2131.

Rannanheimo PK, Tiittanen P, Hartikainen J, Helin-Salmivaara A, Huupponen R, Vahtera J, Korhonen MJ (2015) Impact of statin adherence on cardiovascular morbidity and all-cause mortality in the primary prevention of cardiovascular disease: a population-based cohort study in Finland. Value Health 18:896-905.

Ribe AR, Vestergaard CH, Vestergaard M, Fenger-Gron M, Pedersen HS, Lietzen LW, Brynningsen PK (2019) Statins and risk of intracerebral haemorrhage in a stroke-free population: a nationwide Danish propensity score matched cohort study. EClinicalMedicine 8:78-84.

Ridker PM, Rifai N, Pfeffer MA, Sacks F, Braunwald E (1999) Long-term effects of pravastatin on plasma concentration of C-reactive protein. The Cholesterol and Recurrent Events (CARE) Investigators. Circulation 100:230-235.

Robinson JG, Smith B, Maheshwari N, Schrott H (2005) Pleiotropic effects of statins: benefit beyond cholesterol reduction? A meta-regression analysis. J Am Coll Cardiol 46:1855-1862.

Sacco S, Toni D, Bignamini AA, Zaninelli A, Gensini GF, Carolei A, Group SS (2011) Effect of prior medical treatments on ischemic stroke severity and outcome. Funct Neurol 26:133-139.

Sahebkar A, Ponziani MC, Goitre I, Bo S (2015) Does statin therapy reduce plasma VEGF levels in humans? A systematic review and meta-analysis of randomized controlled trials. Metabolism 64:1466-1476.

Sever PS, Dahlof B, Poulter NR, Wedel H, Beevers G, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Ostergren J, investigators A (2003) Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial--Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. Lancet 361:1149-1158.

Shook SJ, Gupta R, Vora NA, Tievsky AL, Katzan I, Krieger DW (2006) Statin use is independently associated with smaller infarct volume in nonlacunar MCA territory stroke. J Neuroimaging 16:341-346.

Strandberg TE, Vanhanen H, Tikkanen MJ (1999) Effect of statins on C-reactive protein in patients with coronary artery disease. Lancet 353:118-119.

Thiery J, Brugel M (2003) Is LDL reduction the only effect of statins? Pleiotropic effects of statins. Pharm Unserer Zeit 32:472-478.

van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J (1988) Interobserver agreement for the assessment of handicap in stroke patients. Stroke 19:604-607.

Vergouwen MD, de Haan RJ, Vermeulen M, Roos YB (2008) Statin treatment and the occurrence of hemorrhagic stroke in patients with a history of cerebrovascular disease. Stroke 39:497-502.

Vitturi BK, Gagliardi RJ (2020) Effects of statin therapy on outcomes of ischemic stroke: a real-world experience in Brazil. Arq Neuropsiquiatr 78:461-467.

C-Editors: Zhao M, Li CH; T-Editor: Jia Y