DOI:
10.1159/000501543

Document Version
Peer reviewed version

The impact of pre and post-stroke statin use on stroke severity and long-term outcomes: A population-based cohort study

Short Title: Impact of statins on stroke severity and survival

First Author: Clare Flach[1], PhD

Maria Elstad[1], MSc

Walter Muruet[1], MD

Charles DA Wolfe[1 2], MD

Anthony G Rudd[1 2], FRCP

Abdel Douiri[1 2], PhD

1 King's College London, School of Population Health and Environmental Sciences, London, United Kingdom;

2 National Institute for Health Research Biomedical Research Centre, Guy's and St Thomas' NHS Foundation Trust and King's College London, London, United Kingdom

Keywords: Stroke, recurrence, survival, statin

Word count: 3,707, Tables 4, Figures 1

Correspondence to: clare.flach@kcl.ac.uk

4.07 Addison House, Guy's Campus,

King's College London

SE1 1UL

Tlf: 020 7848 8229

Email addresses (in order of authors list):

maria.elstad@kcl.ac.uk

walter.muruet_gutierrez@kcl.ac.uk

charles.wolfe@kcl.ac.uk

anthony.rudd@kcl.ac.uk

abdel.douiri@kcl.ac.uk

Abstract

Background: The benefit of statins on stroke incidence is well known. However, data on the relationship between pre and post stroke statin use, recurrence and survival outcomes are limited. We aim to investigate the short-term and long-term relationship between statin prescription, stroke recurrence and survival in patients with first-ever ischemic stroke.

Methods: Data were collected from the population-based South London Stroke Register for the years 1995-2015. Patients were assessed at time of first ever stroke, three months and annually thereafter. Data on vascular risk factors, treatments prescribed, socio-demographic characteristics, stroke subtype, survival and stroke recurrence were collected. Cox proportional hazard analyses were used to assess the relationship of statin prescriptions pre- and post-stroke on stroke severity, and long-term recurrence and survival.

Results: Patients prescribed statins both pre- and post-stroke showed a 24% reduction in mortality (adjusted Hazard Ratio aHR=0.76, 0.60-0.97), those who were prescribed statins pre-stroke and then stopped post stroke showed greater risk of mortality (aHR=1.85, 1.10-3.12) and stroke recurrence (aHR=3.25, 1.35-7.84) compared to those that were not prescribed statins at any time. No associations were observed between pre-stroke statin and severity of the initial stroke overall, though a protective effect against moderate/severe stroke (Glasgow Coma Scale≤12) was observed in those aged 75y+ (aOR=0.70, 0.52-0.95)

Conclusions: Statins play a significant role in improving survival rates after a stroke. Adherence to the National Guidelines that promote statin treatment primary and secondary prevention of stroke should be monitored and a focus for quality improvement programs.

Background and purpose

The association between total cholesterol levels and ischemic stroke risk is well established[1-4]. Decreasing LDL-Cholesterol levels is associated with significant reductions in stroke/TIA incidence [5-9] and low HDL-Cholesterol is associated with higher risk of ischemic stroke/TIA [1,4,10,11]. Statins reduce low-density lipoprotein cholesterol (LDL-C) levels[12] and have been shown to increase HDL-C levels and functioning[13]. Their ability to reduce stroke incidence is well known [7,14-17] but the evidence on the effect of statin use on stroke severity is mixed; some finding a reduction in stroke severity[18,19] but others finding no impact[20]. A systematic review of observational studies report an improved functional outcome at 90 days in those already on statins but this is not maintained to one year[21].

There is only one prospective randomised trial of statins after stroke and this provides evidence of a benefit in statin use for stroke recurrence and other cardiovascular events but no impact on overall mortality[22]. Observational studies have provided some evidence that statin use is associated with a reduction in both recurrence and mortality after stroke[23,24] and a detrimental impact of statin withdrawal after stroke[23,25]

In randomized control trials, pre-intervention treatment and long-term effect of statins are not well investigated due to the lack of long-term studies and insufficient patient medication history. In the present study, we aim to investigate the relationship between pre-stroke statin use on stroke severity and both pre- and post-stroke statin use on two major outcomes after acute ischaemic stroke in patients registered on the South London Stroke Register (SLSR): stroke recurrence and survival.

Methods

Data for the present study were obtained from the South London Stroke Register (SLSR), a prospective population-based stroke register of first strokes recorded in an inner area of South London comprising 22 electoral wards in Southwark and Lambeth. This study includes individuals diagnosed with their first stroke between January 1995 and December 2015. Follow-up data were collected prospectively by specially trained field workers and nurses at three months after the patient's first stroke and annually thereafter via validated postal or face-to-face interviews with patients and/or their carers. A capture-recapture analysis was undertaken to establish completeness of stroke incidence data and estimates that the register coverage is 88%[26]. Details of the stroke register methodology have been published elsewhere,[27] a short summary of key elements for this analysis is provided here.

All first strokes according to the World Health Organisation definition of stroke were included (fatal and non-fatal). Diagnosis was verified by a medical doctor. Neuroradiology reports, cerebrospinal fluid analysis and necropsy findings were used to classify strokes into ischemic stroke, primary intracerebral haemorrhage or subarachnoid haemorrhage.

Vascular risk factors for stroke were either self-reported or extracted from medical notes. These included transient ischaemic attack, atrial fibrillation, ischemic heart disease (history of angina or myocardial infarction), hypertension, diabetes mellitus, hypercholesterolemia and smoking status. Pre-morbid disability was measured using Barthel Index scores. A cut-off of 15 was used to classify patients by mild disability/independent, disabled or unknown. Severity of the initial stroke was assessed using Glasgow Coma Scores (lower and higher than 13), urinary incontinence, dysphagia (failure of swallow test) and motor deficits.

At each follow-up details including date of new strokes were recorded. In addition, all strokes occurring within the SLSR area were reported to the register including recurrent strokes. The definition of stroke recurrence was by the same WHO criteria, only recurrences that had

taken place more than 21 days post-stroke or in a different vascular area were counted. Death was confirmed by the Office for National Statistics. Information on death and recurrence is assumed to be complete for all individuals.

Medication prior to the initial stroke and at discharge were recorded as free text reported by the individual and from clinic notes, prescriptions at three months were by self-report. Medications were grouped by indication using the British National Formulary coding. It is assumed that if a medication is not recorded but the interview was conducted then it was not prescribed.

The impact of pre-stroke medications and medications given within the first three months (including at discharge) are investigated.

Statistical methods

Socio-demographic characteristics, stroke subtype, pre-stroke vascular risk factors, disability status and living conditions of the study population were described. The proportion of patients on different pre-stroke medication (cholesterol-lowering, antihypertensive, antithrombotic) were calculated. Associations between pre-stroke statin use and initial stroke severity were assessed using Poisson regression adjusting for demographic factors (age, sex, ethnicity, socio-economic status), pre-stroke vascular risk factors (TIA, atrial fibrillation, ischemic heart disease, smoking, hypertension, diabetes), other pre-stroke medications (antihypertensive, antiplatelet, anticoagulant) and year of stroke. Subgroup analyses were conducted for those under 55yrs at time of first stroke, in the elderly (75+yrs) and in those who had a diagnosis of atrial fibrillation prior to stroke. Due to changes in recording of prior diagnosis of ischaemic heart disease over the course of the register this is calculated as a combination of previous MI, angina or ischaemic heart disease.

Event rates for death and recurrence were calculated for:

1. Patients who have never been treated with a statin (our baseline for comparison)

2. Patients who have had statin treatment prior to their stroke but have discontinued treatment since.
3. Patients who have only had statin treatment after their stroke (within first 3 months)
4. Patients who have been treated with a statin before and after their stroke

Patients were excluded from the analysis comparing pre- and post-stroke statin use if they died before discharge, did not have discharge information or did not have a three-month follow-up interview. The relationship between these different groups and long-term survival and recurrence was first determined on a univariate level using Cox proportional hazards model. This same model was used in a multivariate analysis, where we adjusted for potential confounding factors. Year of first stroke is grouped into 5-year bands. An interaction between statin effects and year of first stroke is assessed in the fully adjusted model using a likelihood ratio test.

Analyses were not adjusted for pre-stroke hypercholesterolemia as it is highly correlated with statin use.

Results

A total of 3,803 individuals were diagnosed with an ischaemic stroke between 1st January 1995 and 31st December 2015 and registered on the SLSR. The study population consisted of 1,923 (51%) males, 1,690 (45%) were over 75 years with only 171 (5%) under 45 and 1061 (27%) of non-white ethnicity. The majority (2,432, 64%) had a previous diagnosis of hypertension, further details are provided in table 1.

Prior to their first stroke 2,009 (53%) of individuals were on antihypertensive medication, only around a fifth (742, 20%) were on cholesterol lowering medication (738, 99% of these were statin) (table 2).

Of the 2,006 that had both discharge and three month information 1,015 (51%) individuals were prescribed cholesterol lowering medication (1000, 99% of these were statin) within the first three months of their initial stroke. This has increased from 7% in 1995-1999 to 87% in 2010-2015. Overall, this resulted in 967 (48%) having never received statin treatment, 372 (19%) having a statin both pre- and post- their initial stroke and 1,039 (52%) at some point. After accounting for demographic differences, pre-stroke vascular risk factors and other medications there was no association between having a prescription for a statin prior to the initial stroke and any stroke severity outcome (table 3). In subgroup analyses of the participants by age group statin use showed a statistically significant protective effect against stroke severity measured by the GCS in those aged 75y+ (OR=0.70, 0.52-0.95) a similar effect size was observed in the <55yr age group but this was not statistically significant (OR=0.70, 0.29-1.69). We saw no associations within either age group between statin use and other severity measures. We analysed the subgroup of patients with a diagnosis of AF and found similar results to those in table 3 with no association between pre-stroke statin use and stroke severity in this subgroup (supplementary table 1).

There were 1,173 deaths in 12,763 person years giving a mortality rate of 91.9/1000pys (95% confidence interval 86.8 – 97.3). The maximum follow-up time was 19.6 years with median 5.0 years. Those included in the analysis were more likely to be economically active, have previous hypercholesterolemia or TIA and have a more severe stroke by Glasgow coma scale compared to those who did not have both pieces of data but had not died before discharge, we adjust for these in the analysis.

In a cox proportional hazards model (table 4) statin use pre-stroke had no impact on risk of death. A statin prescription only after stroke shows a 31% reduction in mortality compared to

never using a statin (aHR=0.69, 0.57 – 0.83). Having a statin both before and after the stroke reduces mortality by 24% (aHR=0.76, 0.60-0.97). However, statin use before stroke that is then stopped results in an increased risk of dying compared to never having a statin prescription (aHR=1.85, 1.10-3.12). Survival curves by statin prescription are presented in figure 1a.

255 individuals had at least one recurrence in 11,668 person years of time giving a recurrence rate of 21.9/1000pys (95% confidence interval 19.3 – 24.7). The maximum follow-up time was 19.6 years with median 4.4 years.

No benefit of statin use was found on the incidence of recurrence after adjustment for baseline risk factors, demographics and prescription of other medications (table 4). However, there is a suggestion that risk of recurrence is decreased in those that were prescribed statins at discharge compared to never having a statin prescription (adjusted hazard ratio=0.66, 95% confidence interval 0.43 – 1.01). As with survival there is evidence that having a statin prescribed prior to the stroke which is then stopped is detrimental resulting in increased risk of a stroke recurrence (aHR=3.25, 95% CI 1.35 – 7.84). However, this is based on very few events.

There was no interaction between year of first stroke and effect of pre- and post-stroke statin use on recurrence (p-value=0.891) or survival (p-value=0.159).

Discussion

We have demonstrated that statin use prior to a stroke is not associated with a reduction in the severity of the resulting neurological deficit in the overall population, although our subgroup analysis did find a significant protective effect in those 75+years old. It is possible that the reason we failed to detect a significant overall effect is because we used the GCS to measure

the degree of stroke severity. Studies reporting reduction of the neurological deficits in the statin group have used the NIHSS score, a more sensitive tool. However, the reported differences in median NIHSS between groups in these studies is around 1 point[28-30]. This suggest that the protective effect of pre-stroke statins may be clinically insignificant for younger patients, and only clinically relevant for elderly ones.

Statins prescribed in the first few months after a stroke are associated with a reduction in mortality. This agrees with other observational studies that have found a similar mortality reduction with post-stroke statin use[23,24,29-32]. Although improved survival associated with statin use was not seen on a previous prospective randomised trial[22], the authors acknowledged that the study was not powered enough to assess reduction in all-cause mortality.The trial did show a beneficial impact of statin use on recurrence, which is supported by the observational studies. This decrease in recurrence is not shown in our data where the impact of statin prescription at discharge does not quite reach statistical significance. However, it is likely this is due to the distribution of stroke aetiological subtypes in our population, where only 9.3% of strokes where due to large artery atherothrombosis, while 27.8% were cardioembolic and 24.2% were undetermined[33].

Statin use pre-stroke which is then discontinued is associated with an increased risk of both recurrence and mortality, a finding supported by other studies[23,25,34]. It is difficult to disentangle cause and effect in this scenario, those that were on statins prior to their stroke may have been more unwell and therefore at higher risk of a poor outcome anyway. However, pre-stroke statin use was not associated with outcomes in our data. It may also be that the decision to stop statins is taken as part of the end of life pathway.

We have adjusted for conditions prior to the stroke; atrial fibrillation, diabetes, hypertension, TIA and ischaemic heart disease but there may be others. In future studies it would be beneficial to look at the impact of comorbidities in this group.

As this is an observational study it is not possible to account for all possible confounding factors and so we can only infer associations rather than any causative effect of statin use. Medication prescriptions are taken from self-report or medical notes however this is only an indication of prescription, not necessarily usage, additionally dose is not recorded. The impact of any medications on outcomes may be diluted through non-adherence to treatment or differing prescriptions. We expect to have complete data for the recurrence and survival outcomes. In addition to patient reports recurrences are monitored through the register which uses several sources to identify strokes within the register area. The only loss of information may be if individuals move out of the area but these are still followed-up in annual interviews and so will be kept to a minimum. Death reports are linked through the Office for National Statistics and are therefore complete.

Acknowledgements: We thank patients, their families, and the fieldworkers who have collected data for the South London Stroke Register since 1995.

Funding: We would like to acknowledge the support and funding from the National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care South London at King's College Hospital NHS Foundation Trust and the Royal College of Physicians, as well as the support from the NIHR Biomedical Research Centre based at Guy's and St Thomas' NHS Foundation Trust and King's College London.

Disclosures: No competing interests declared.

Ethics approval: The SLSR design was approved by the ethics committees of Guys and St Thomas NHS Foundation Trust, Kings College Hospital, Queens Square and Westminster Hospitals (London).

Author contributions: CW, AR and AD designed the original study and conceptualised the paper. CF analysed the data. CF, ME, WM, AD, CW, AR all contributed to writing the paper.

References

1 Koren-Morag N, Tanne D, Graff E, Goldbourt U: Low- and high-density lipoprotein cholesterol and ischemic cerebrovascular disease: the bezafibrate infarction prevention registry. Arch Intern Med 2002;162:993-999.

2 Iso H, Jacobs DR, Wentworth D, Neaton JD, Cohen JD: Serum cholesterol levels and six-year mortality from stroke in 350,977 men screened for the multiple risk factor intervention trial. N Engl J Med 1989;320:904-910.

3 Lindenstrøm E, Boysen G, Nyboe J: Influence of total cholesterol, high density lipoprotein cholesterol, and triglycerides on risk of cerebrovascular disease: the Copenhagen City Heart Study. BMJ 1994;309:11-15.

4 Tirschwell DL, Smith NL, Heckbert SR, Lemaitre RN, Longstreth WT, Psaty BM: Association of cholesterol with stroke risk varies in stroke subtypes and patient subgroups. Neurology 2004;63:1868-1875.

5 Amarenco P, Lavallée P, Touboul PJ: Statins and stroke prevention. Cerebrovasc Dis 2004;17 Suppl 1:81-88.

6 Amarenco P: Atorvastatin in prevention of stroke and transient ischaemic attack. Expert Opin Pharmacother 2007;8:2789-2797.

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

8 Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, Kirby A, Sourjina T, Peto R, Collins R, Simes R, Collaborators CTTC: Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 2005;366:1267-1278.

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

10 Zhang Y, Tuomilehto J, Jousilahti P, Wang Y, Antikainen R, Hu G: Total and high-density lipoprotein cholesterol and stroke risk. Stroke 2012;43:1768-1774.

11 Amarenco P, Goldstein LB, Callahan A, Sillesen H, Hennerici MG, O'Neill BJ, Rudolph AE, Simunovic L, Zivin JA, Welch KM, Investigators S: Baseline blood pressure, low- and high-density lipoproteins, and triglycerides and the risk of vascular events in the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial. Atherosclerosis 2009;204:515-520.

12 Gazzerro P, Proto MC, Gangemi G, Malfitano AM, Ciaglia E, Pisanti S, Santoro A, Laezza C, Bifulco M: Pharmacological actions of statins: a critical appraisal in the management of cancer. Pharmacol Rev 2012;64:102-146.

13 Yamashita S, Tsubakio-Yamamoto K, Ohama T, Nakagawa-Toyama Y, Nishida M: Molecular mechanisms of HDL-cholesterol elevation by statins and its effects on HDL functions. J Atheroscler Thromb 2010;17:436-451.

14 Blauw GJ, Lagaay AM, Smelt AH, Westendorp RG: Stroke, statins, and cholesterol. A meta-analysis of randomized, placebo-controlled, double-blind trials with HMG-CoA reductase inhibitors. Stroke 1997;28:946-950.

15 Bushnell CD, Newby LK, Goldstein LB, Lin F, Yaffe K, Simon JA: Statin use and stroke outcomes in the Heart and Estrogen-Progestin Replacement Study (HERS). Neurology 2004;62:968-970.

16 Straus SE, Majumdar SR, McAlister FA: New evidence for stroke prevention: scientific review. JAMA 2002;288:1388-1395.

17 O'Regan C, Wu P, Arora P, Perri D, Mills EJ: Statin therapy in stroke prevention: a meta-analysis involving 121,000 patients. Am J Med 2008;121:24-33.

18 Marti-Fabregas J, Gomis M, Arboix A, Aleu A, Pagonabarraga J, Belvis R, Cocho D, Roquer J, Rodriguez A, Garcia MD, Molina-Porcel L, Diaz-Manera J, Marti-Vilalta JL: Favorable outcome of ischemic stroke in patients pretreated with statins. Stroke 2004;35:1117-1121.
19 Choi JC, Lee JS, Park TH, Cho Y-J, Park J-M, Kang K, Lee KB, Lee S-J, Ko Y, Lee J, Kim J-T, Yu K-H, Lee B-C, Cha J-K, Kim D-H, Lee J, Kim D-E, Jang MS, Kim BJ, Han M-K, Bae H-J, Hong K-S: Effect of pre-stroke statin use on stroke severity and early functional recovery: a retrospective cohort study. BMC Neurology 2015;15:120.
20 Aboa-Eboule C, Binquet C, Jacquin A, Hervieu M, Bonithon-Kopp C, Durier J, Giroud M, Bejot Y: Effect of previous statin therapy on severity and outcome in ischemic stroke patients: a population-based study. Journal of neurology 2013;260:30-37.
21 Chróinín DN, Asplund K, Åsberg S, Callaly E, Cuadrado-Godia E, Díez-Tejedor E, Di Napoli M, Engelter ST, Furie KL, Giannopoulos S: Statin therapy and outcome after ischemic stroke. Stroke 2013:STROKEAHA. 112.668277.
22 Amarenco P, Bogousslavsky J, Callahan A, Goldstein LB, Hennerici M, Rudolph AE, Sillesen H, Simunovic L, Szarek M, Welch KM, Zivin JA, Investigators SPbARiCLS: High-dose atorvastatin after stroke or transient ischemic attack. N Engl J Med 2006;355:549-559.
23 Flint AC, Kamel H, Navi BB, Rao VA, Faigeles BS, Conell C, Klingman JG, Sidney S, Hills NK, Sorel M, Cullen SP, Johnston SC: Statin Use During Ischemic Stroke Hospitalization Is Strongly Associated With Improved Poststroke Survival. Stroke 2012;43:147-154.
24 Milionis HJ, Giannopoulos S, Kosmidou M, Panoulas V, Manios E, Kyritsis AP, Elisaf MS, Vemmos K: Statin therapy after first stroke reduces 10-year stroke recurrence and improves survival. Neurology 2009;72:1816-1822.
25 Blanco M, Nombela F, Castellanos M, Rodriguez-Yáñez M, García-Gil M, Leira R, Lizasoain I, Serena J, Vivancos J, Moro MA, Dávalos A, Castillo J: Statin treatment withdrawal in ischemic stroke. A controlled randomized study 2007;69:904-910.
26 Tilling K, Sterne JAC, Wolfe CDA: Estimation of the incidence of stroke using a capture-recapture model including covariates. International Journal of Epidemiology 2001;30:1351-1359.
27 Stewart JA, Dundas R, Howard RS, Rudd AG, Wolfe CDA: Ethnic differences in incidence of stroke: prospective study with stroke register. BMJ 1999;318:967-971.
28 Ishikawa H, Wakisaka Y, Matsuo R, Makihara N, Hata J, Kuroda J, Ago T, Kitayama J, Nakane H, Kamouchi M, Kitazono T: Influence of Statin Pretreatment on Initial Neurological Severity and Short-Term Functional Outcome in Acute Ischemic Stroke Patients: The Fukuoka Stroke Registry. Cerebrovascular Diseases 2016;42:395-403.
29 Chróinín DN, Callaly EL, Duggan J, Merwick Á, Hannon N, Sheehan Ó, Marnane M, Horgan G, Williams EB, Harris D, Kyne L, McCormack PME, Moroney J, Grant T, Williams D, Daly L, Kelly PJ: Association Between Acute Statin Therapy, Survival, and Improved Functional Outcome After Ischemic Stroke. Stroke 2011;42:1021-1029.
30 Tsivgoulis G, Katsanos AH, Sharma VK, Krogias C, Mikulik R, Vadikolias K, Mijajlovic M, Safouris A, Zompola C, Faissner S, Weiss V, Giannopoulos S, Vasdekis S, Boviatsis E, Alexandrov AW, Voumvourakis K, Alexandrov AV: Statin pretreatment is associated with better outcomes in large artery atherosclerotic stroke. Neurology 2016;86:1103-1111.
31 Palnum KH, Mehnert F, Andersen G, Ingeman A, Krog BR, Bartels PD, Johnsen SP: Use of secondary medical prophylaxis and clinical outcome among patients with ischemic stroke: a nationwide follow-up study. Stroke 2012;43:802-807.
32 Kim J, Lee HS, Nam CM, Heo JH: Effects of Statin Intensity and Adherence on the Long-Term Prognosis After Acute Ischemic Stroke. Stroke 2017;48:2723-2730.
33 Hajat C, Heuschmann PU, Coshall C, Padayachee S, Chambers J, Rudd AG, Wolfe CDA: Incidence of aetiological subtypes of stroke in a multi-ethnic population based study: the South London Stroke Register. Journal of Neurology, Neurosurgery & Psychiatry 2011;82:527-533.
34 Endres M, Laufs U: Discontinuation of Statin Treatment in Stroke Patients. Stroke 2006;37:2640-2643.

Index of tables

Index of figures