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STATINS ARE ASSOCIATED TO DECREASED MORTALITY RISK AFTER STATUS EPILEPTICUS

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Vincent Alvarez participated in the acquisition of data, worked in the results interpretation and collaborated in the elaboration of the manuscript.

Mohamed Faouzi was responsible for the statistical analysis.

Bernard Burnand gave technical support for the elaboration of the manuscript and collaborated in the analysis and interpretation of data.

Andrea O. Rossetti participated in the acquisition of data, worked in the analysis and interpretation of data, and was responsible for the supervision and coordination of the manuscript.

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ABSTRACT

Objective: Statins display anti-inflammatory and antiepileptogenic properties in animal models, and may reduce the epilepsy risk in elderly humans; however, a possible modulating role on outcome in patients with status epilepticus (SE) has not been assessed.

Methods: This cohort study was based on a prospective registry including all consecutive adults with incident SE treated in our center between April 2006 and September 2012. SE outcome was categorized at hospital discharge into “return to baseline”, “new disability”, and “mortality”. The role of potential predictors, including statins treatment on admission, was evaluated using a multinomial logistic regression model.

Results: Among 427 patients identified, information on statins was available in 413 (97%). Mean age was 60.9 [\pm 17.8] years; 201 (49%) were women; 211 (51%) had a potentially fatal SE etiology; and 191 (46%) experienced generalized-convulsive or non-convulsive SE in coma. Statins (simvastatin, atorvastatin, or pravastatin) were prescribed prior to admission in 76 (18%) subjects, mostly elderly. While 208 (50.4%) patients returned to baseline, 58 (14%) died. After adjustment for established SE outcome predictors (age, etiology, SE severity score- STESS), statins correlated significantly with lower mortality (related risk ratio=0.38, p=0.046),.

Conclusion: This study shows for the first time that exposure to statins before a SE episode is related to its outcome, suggesting a possible antiepileptogenic role. Other studies are needed to confirm this intriguing finding.

Introduction

Status epilepticus represents an acute neurological condition with considerable morbidity and an estimated short-term mortality of up to 22%^{1,2}. Several studies have shown that outcome is independently related to increasing age, underlying etiology, and SE severity³⁻⁶, while the specific impact of antiepileptic treatment is debated⁷. Moreover, the role of medications not related to seizure suppression has received scarce attention so far.

Statins are competitive inhibitors of 3-hydroxy-3-methylglutaryl co-enzyme A (HMG-CoA) reductase, the key enzyme in cholesterol biosynthesis. They are usually prescribed in hypercholesterolemia, atherosclerosis diseases, and for secondary prevention of cardiovascular disease⁸⁻¹⁰. Recently, statins potential neuroprotective, anti-inflammatory and antiexcitotoxic effects have been described in animal models of different neurological processes, such as multiple sclerosis, Parkinson's and Alzheimer's diseases, traumatic brain injury (TBI), and, particularly, epilepsy¹¹⁻¹⁵, where these compounds seem to decrease seizures severity and related hippocampal cell death in rodent models¹⁶⁻¹⁹.

Despite the wide prescription of statins, their potential effect in human epilepsy has been addressed in only two observational studies, which showed a protective role for the risk of developing epilepsy in elderly patients^{20, 21}. Nevertheless, to the best of our knowledge, their role in status epilepticus (SE) prognosis in humans has not been studied so far. The present analysis was designed to investigate the relationship of statins with SE outcome.

PATIENTS AND METHODS

Patients

This observational cohort study enrolled consecutive adults with an incident episode of SE, treated at our tertiary care center between April 1, 2006 and September 1, 2012 (77 months) and prospectively included in our registry²². Subjects younger than 16 years, with post-anoxic SE, or with previous SE episodes were excluded. We retrospectively collected information (assessed through charts review) regarding different types and doses of statins administered on a daily basis before admission for the incident SE episode. This study was fully approved by the research ethics committee of the Canton of Vaud.

Definition of variables

As detailed previously²², demographic data, time to treatment institution, and occurrence of previous seizures were prospectively collected at each SE admission for our SE registry. SE was defined as the occurrence of continuous epileptic seizures or recurrent seizures without recovery of consciousness, for >30 min (until 2008), and >5 min (since 2008), according to the operational definition²³. Seizure semiology was classified as simple partial, absence, generalized myoclonic, complex partial, generalized convulsive, or nonconvulsive SE in coma, defined by the worst clinical seizure type in a given SE episode. SE was diagnosed clinically, but in nonconvulsive episodes EEG confirmation was formally required. We further classified etiologies as «potentially fatal» if potentially leading to death independently of SE (e.g., acute large vessel ischemic stroke, acute cerebral hemorrhage, acute central nervous system (CNS) infection, severe systemic infection, malignant brain tumor, acquired immunodeficiency

syndrome (AIDS) with CNS complications, chronic renal failure requiring dialysis, systemic vasculitis, metabolic disturbance or acute intoxication sufficient to cause coma in the absence of SE, eclampsia). This approach has been shown by our and other groups to better account for outcome than the classical etiological categorization into acute symptomatic, remote symptomatic, progressive symptomatic, and idiopathic/cryptogenic^{5, 24, 25}. The validated prognostic score “STESS” (Status Epilepticus Severity Score), relying on age, previous seizure history, seizure type, and degree of consciousness impairment⁶, was prospectively categorized as 0-2 (favorable outcome) vs. 3-6 (unfavorable outcome). At hospital discharge, we assessed three outcomes: return to baseline clinical conditions, survival with residual disability, or death.

Procedures

All subjects underwent electrolytic, metabolic, and hematologic work-up. Brain imaging (computed tomography scan and/or magnetic resonance imaging) and lumbar puncture were performed as needed. All patients had at least one EEG recording in the first 12-24 h after hospitalization. Follow-up studies were performed as clinically required. Patients were treated first-line with benzodiazepines, most frequently with 0.5-2 mg intravenous clonazepam. Second-line treatment included intravenous phenytoin (typical loading dose of 20 mg/kg), valproate (20 mg/kg), or levetiracetam (20-30 mg/kg). When the patient did not respond to the first and second line treatment, SE was considered as refractory, and its management was performed according to the predominant seizure type and the general clinical situation of the patient, ranging from controlled antiepileptic treatment escalation (both in dosage and number of compounds) without coma induction, to tracheal intubation and coma induction targeting electrographic burst-

suppression for at least 24 h before weaning the anesthetic medication over 12-24 h. In these cases, propofol, midazolam, and thiopental were used alone or in combination.

Statistical analyses

Data analysis was performed using STATA 12.1 (College Station, TX, USA). Data were summarized as mean (\pm sd) for continuous variables and as numbers (percentages) for categorical data. Univariate multinomial logistic regression was performed to assess the association of potential outcome predictors (age, gender, SE semiology, occurrence of previous seizures, potentially fatal etiology, STESS, SE duration shorter than 30 minutes, and previous statin treatment) to the SE outcome. The strength of the associations was measured using the RRR (Relative Risk Ratio), where the “return to baseline” group was fixed as the reference. Significant predictors at the level of 20% were used in a backward procedure to fit a multivariate model.

RESULTS

From a total of 515 SE episodes recorded during the study period, we identified 427 incident patients. In 413 of them (80% of total, 97% of the incident episodes), data regarding statin treatment on admission were available: mean age was 60.9 [\pm 17.8] years; 201 (49%) were women; 172 (42%) had a previous diagnosis of epilepsy; 249 (60%) presented an acute symptomatic etiology, and 211 (51%) a potentially fatal etiology. The duration of the episode was between 5-29 minutes in 37 (9%) patients. Regarding semiology, 5 (1%) experienced

absence SE, 1 (0.2%) myoclonic SE (in the context of genetic generalized epilepsy), 81 (20%) simple-partial SE, 135 (33%) complex-partial SE, 170 (41%) generalized-convulsive SE, and 21 (5%) nonconvulsive SE in coma. Statins (simvastatin, atorvastatin and pravastatin) were prescribed before admission in 76 (18%) subjects. For details, see **Figure 1**. Regarding SE outcome, 208 (50%) patients returned to baseline clinical conditions, whereas 58 (14%) died. **Table 1** illustrates the univariable analyses of potential outcome predictors: older age, the presence of previous seizures, a potentially fatal etiology, and STESS \geq 3 were significantly related to outcome (both new disability and mortality; $p < 0.001$); while gender, SE semiology, and duration of the episodes (categorized at 30 minutes) were not. Of note, previous treatment with statins was not associated with a different outcome in univariable analysis. Older patients were clearly more likely to receive this type of drugs ($p < 0.001$). After adjustment for age, previous seizures, potentially fatal etiology, and STESS, statins use was independently associated with a lower risk of mortality (RRR= 0.38, 95% Confidence interval (CI) [0.15-0.98], $p=0.046$), but not of new disability (RRR= 0.72, 95% CI [0.4-1.36], $p=0.29$) (**Table 2**). Older age and potentially fatal etiology were independent predictors for both outcomes, while previous seizures were only related to a lower risk of new disability. A high STESS score was independently related to a higher mortality, but it was not associated to a lower disability. Of note, there was no interaction between statins and stroke as regards SE outcome. **Figure 2** illustrates that the association between age and mortality after a first episode of SE was maintained in patients exposed to statins, however at a lower occurrence rate.

DISCUSSION

This study provides Class III evidence that statins, usually prescribed for reducing cardiovascular risk, are significantly correlated with a lower risk of mortality after SE, following adjustment for the most important outcome predictors^{3-5,24}.

Only two human studies have examined the possible benefits of HMG-CoA inhibitors in modifying the risk of epilepsy so far. The rate of new-onset epilepsy in older veterans was lowered by statin prescription (OR 0.64, 95% CI 0.56–0.73), suggesting a possible target for prevention of geriatric epilepsy²⁰. Among a large cohort of cardiovascular patients who received a revascularization procedure, 217 cases with a diagnosis of epilepsy were matched to 2170 controls by age and admission time; the adjusted risk ratio for epilepsy among statin users was 0.65 (95% CI 0.46–0.92), whereas no benefit was found for non-statin cholesterol-lowering drugs, β -blockers, or angiotensin-converting enzyme inhibitors²¹. Overall, these two congruent findings suggest a protective effect of statins for the risk of developing epilepsy. Our results therefore expand these observations in adults with incident SE. Statins use was only related to mortality but not to new disability: mortality after SE mostly relates to etiology and complications, and not to SE itself³⁻⁵, it is therefore possible that statins also impacted on the the global health of acutely admitted patients. Furthermore, disability is not as a robust outcome as mortality, and is assessed at a variable time (hospital discharge), likely influencing the strengths of the found relationships.

Several experimental studies have supported the antiepileptogenic properties of statins. Simvastatin, lovastatin and atorvastatin reduced the severity of kainite-induced-seizures and excitotoxicity in the hippocampus and limbic structures^{16, 17}, and atorvastatin also attenuated

kainate-induced hippocampal cellular death involving the Akt-phosphorylation pathway and glutamate transport modulation¹⁸. An additive anticonvulsant effect of simvastatin, fluvastatin, lovastatin and atorvastatin, when co-administered with some antiepileptic compounds in the DBA/2 mice model of generalized tonic-clonic seizure has been reported¹⁹. Our findings suggest a possible anti-epileptogenic mechanism of statins also in humans, which might be the consequence of anti-inflammatory properties^{26, 27}, in light of the increasing evidence of a link between inflammation and the epileptogenicity²⁸⁻³⁰.

This study has some limitations. Although our SE database is prospective, ensuring the best possible data quality for variables assessed acutely, data collection regarding previous statin treatment was retrospective; however, we were able to find detailed information for the vast majority of patients. The predictive models were not adjusted for medical comorbidities, although these show only a marginal added value in outcome prognostication²⁴. Indeed, our statistical model controlled for potential confounding by the most robust prognostic factors. We did not analyze antiepileptic treatment, since on a subgroup of patients of the present cohort we recently showed that treatment appropriateness does not significantly influence clinical outcome⁷. Finally, statins were not analyzed separately regarding type and dose, due to the relatively low numbers in each group. Conversely, this study includes a large number of patients with SE diagnosis, and to the best of our knowledge it is the first addressing this question. Further studies are needed to confirm this potentially important clinical observation.

TABLES:

Table 1. Summary description of potentially outcome predictors of disability or death in SE patients; univariable analyses (statistically significant factors in bold). (Abbreviations: N: Number of patients, RRR: Relative risk ratio, RRR-1: New disability vs. Return to baseline, RRR-2: Mortality vs Return to baseline, SD: standard deviation, F: female).

	Return to baseline N (%)	New disability N (%)	Mortality N (%)	RRR-1	RRR-2	P value-1	P value-2
Total	208 (50)	147 (36)	58 (14)	--	--	--	--
Age, mean (SD)	56.1 (18)	65.2 (16)	67.7 (16)	1.03	1.04	<0.001	<0.001
Gender (F)	95 (46)	75 (51)	31 (53)	1.24	1.37	0.320	0.290
Previous seizures	124 (60)	34 (23)	14 (24)	0.21	0.22	<0.001	<0.001
Semiology (Generalized convulsive or non-convulsive SE in coma)	100 (46)	66 (45)	25 (43)	0.88	0.82	0.550	0.500
Potentially fatal etiology	68 (33)	96 (65)	47 (81)	3.87	8.79	<0.001	<0.001
STESS, median (range)	2 (0-5)	3 (0-6)	3 (1-6)	1.66	2.12	<0.001	<0.001
SE Duration <30'	20 (10)	13 (9)	4 (7)	0.91	0.69	0.810	0.520
Statins treatment on admission	42 (20)	27 (18)	7 (12)	0.89	0.54	0.670	0.160

Table 2. Potential predictors of new disability or death in SE patients; results of the multinomial logistic model (statistically significant factors in bold). (Abbreviations: RRR: Relative risk ratio, RRR-1: New disability vs. Return to baseline, RRR-2: Mortality vs. Return to baseline, CI: Confidence interval).

	RRR-1 [95% CI]	RRR-2 [95% CI]	P value-1	P value-2
Age	1.02 [1.01-1.04]	1.04 [1.01-1.06]	0.001	0.001
Previous seizures	0.33 [0.19-0.58]	0.54 [0.25-1.18]	<0.001	0.120
Potentially fatal etiology	3.38 [2.08-5.51]	8.7 [4.02-18.78]	<0.001	<0.001
STESS ≥ 3	1.45 [0.82-2.56]	3.1 [1.31-7.3]	0.200	0.010
Statins previous treatment	0.73 [0.4-1.36]	0.38 [0.15-0.98]	0.300	0.046

REFERENCES

1. Koubeissi M, Alshekhlee A. In-hospital mortality of generalized convulsive status epilepticus: a large US sample. *Neurology* 2007;69:886-893.
2. Chin RF, Neville BG, Scott RC. A systematic review of the epidemiology of status epilepticus. *Eur J Neurol* 2004;11:800-810.
3. Towne AR, Pellock JM, Ko D, DeLorenzo RJ. Determinants of mortality in status epilepticus. *Epilepsia* 1994;35:27-34.
4. Logroscino G, Hesdorffer DC, Cascino G, Annegers JF, Hauser WA. Short-term mortality after a first episode of status epilepticus. *Epilepsia* 1997;38:1344-1349.
5. Rossetti AO, Hurwitz S, Logroscino G, Bromfield EB. Prognosis of status epilepticus: role of aetiology, age, and consciousness impairment at presentation. *J Neurol Neurosurg Psychiatry* 2006;77:611-615.
6. Rossetti AO, Logroscino G, Milligan TA, Michaelides C, Ruffieux C, Bromfield EB. Status Epilepticus Severity Score (STESS): a tool to orient early treatment strategy. *J Neurol* 2008;255:1561-1566.
7. Rossetti AO, Alvarez V, Januel JM, Burnand B. Treatment deviating from guidelines does not influence status epilepticus prognosis. *J Neurol* 2013;260:421-428.
8. Shitara Y, Sugiyama Y. Pharmacokinetic and pharmacodynamic alterations of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors: drug-drug interactions and interindividual differences in transporter and metabolic enzyme functions. *Pharmacol Ther* 2006;112:71-105.
9. Veillard NR, Mach F. Statins: the new aspirin? *Cell Mol Life Sci* 2002;59:1771-1786.
10. Endres M. Statins and stroke. *J Cereb Blood Flow Metab* 2005;25:1093-1110.

11. Vollmer T, Key L, Durkalski V, et al. Oral simvastatin treatment in relapsing-remitting multiple sclerosis. *Lancet* 2004;363:1607-1608.
12. Zacco A, Togo J, Spence K, et al. 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors protect cortical neurons from excitotoxicity. *J Neurosci* 2003;23:11104-11111.
13. Kumar A, Sharma N, Gupta A, Kalonia H, Mishra J. Neuroprotective potential of atorvastatin and simvastatin (HMG-CoA reductase inhibitors) against 6-hydroxydopamine (6-OHDA) induced Parkinson-like symptoms. *Brain Res* 2012;1471:13-22.
14. Kirsch C, Eckert GP, Koudinov AR, Muller WE. Brain cholesterol, statins and Alzheimer's Disease. *Pharmacopsychiatry* 2003;36 Suppl 2:S113-119.
15. Lu D, Goussev A, Chen J, et al. Atorvastatin reduces neurological deficit and increases synaptogenesis, angiogenesis, and neuronal survival in rats subjected to traumatic brain injury. *J Neurotrauma* 2004;21:21-32.
16. Ramirez C, Tercero I, Pineda A, Burgos JS. Simvastatin is the statin that most efficiently protects against kainate-induced excitotoxicity and memory impairment. *J Alzheimers Dis* 2011;24:161-174.
17. Lee JK, Won JS, Singh AK, Singh I. Statin inhibits kainic acid-induced seizure and associated inflammation and hippocampal cell death. *Neurosci Lett* 2008;440:260-264.
18. Piermartiri TC, Vandresen-Filho S, de Araujo Herculano B, et al. Atorvastatin prevents hippocampal cell death due to quinolinic acid-induced seizures in mice by increasing Akt phosphorylation and glutamate uptake. *Neurotox Res* 2009;16:106-115.
19. Russo E, Donato di Paola E, Gareri P, et al. Pharmacodynamic potentiation of antiepileptic drugs' effects by some HMG-CoA reductase inhibitors against audiogenic seizures in DBA/2 mice. *Pharmacol Res* 2012;70:1-12.

20. Pugh MJ, Knoefel JE, Mortensen EM, Amuan ME, Berlowitz DR, Van Cott AC. New-onset epilepsy risk factors in older veterans. *J Am Geriatr Soc* 2009;57:237-242.
21. Etminan M, Samii A, Brophy JM. Statin use and risk of epilepsy: a nested case-control study. *Neurology* 2010;75:1496-1500.
22. Novy J, Logroscino G, Rossetti AO. Refractory status epilepticus: a prospective observational study. *Epilepsia* 2010;51:251-256.
23. Lowenstein DH, Bleck T, Macdonald RL. It's time to revise the definition of status epilepticus. *Epilepsia* 1999;40:120-122.
24. Alvarez V, Januel JM, Burnand B, Rossetti AO. Role of comorbidities in outcome prediction after status epilepticus. *Epilepsia* 2012;53:e89-92.
25. Tsai MH, Chuang YC, Chang HW, et al. Factors predictive of outcome in patients with de novo status epilepticus. *Qjm* 2009;102:57-62.
26. Stuve O, Youssef S, Dunn S, Slavin AJ, Steinman L, Zamvil SS. The potential therapeutic role of statins in central nervous system autoimmune disorders. *Cell Mol Life Sci* 2003;60:2483-2491.
27. Willey JZ, Elkind MS. 3-Hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors in the treatment of central nervous system diseases. *Arch Neurol* 2010;67:1062-1067.
28. Vezzani A, French J, Bartfai T, Baram TZ. The role of inflammation in epilepsy. *Nat Rev Neurol* 2011;7:31-40.
29. Vezzani A, Granata T. Brain inflammation in epilepsy: experimental and clinical evidence. *Epilepsia* 2005;46:1724-1743.

30. Jiang J, Quan Y, Ganesh T, Pouliot WA, Dudek FE, Dingledine R. Inhibition of the prostaglandin receptor EP2 following status epilepticus reduces delayed mortality and brain inflammation. *Proc Natl Acad Sci U S A* 2013.

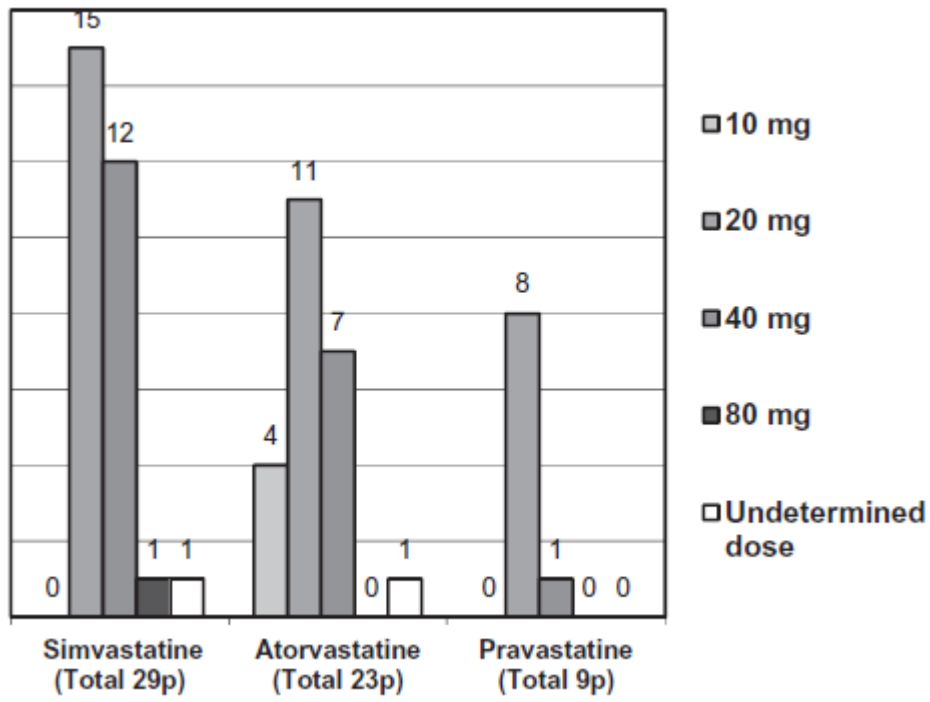


Figure 1

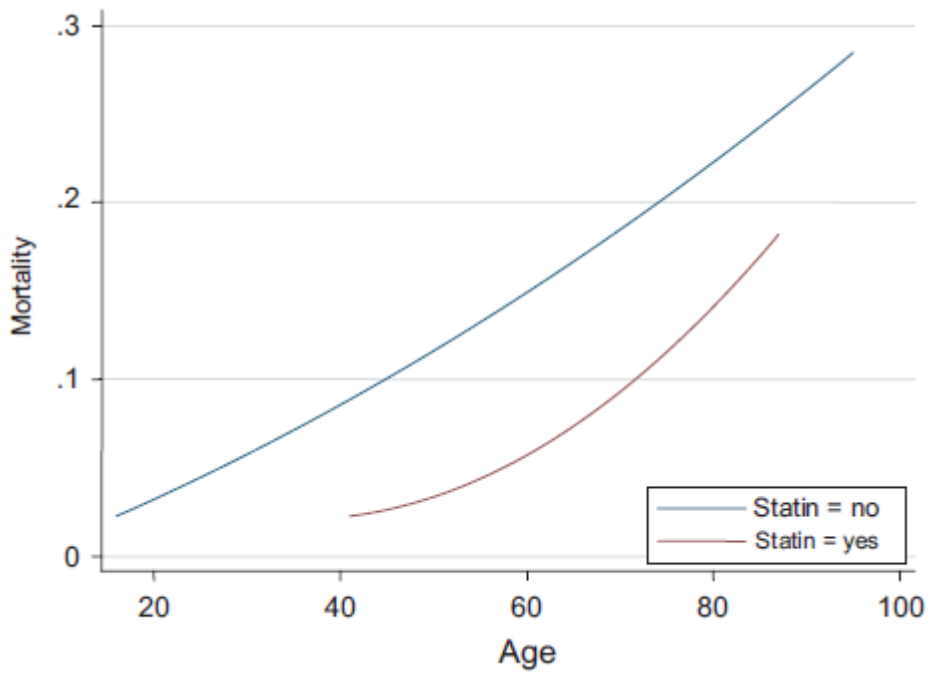


Figure 2