

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	A register based cohort study of the association of pre-stroke medicine use and health outcomes after ischemic stroke in Sweden
AUTHORS	Ingrid, Lekander; von Euler, Mia; Sunnerhagen, Katharina

VERSION 1 – REVIEW

REVIEWER	Timothy Kleinig Royal Adelaide Hospital, Port Road, Adelaide, South Australia 5000
REVIEW RETURNED	27-Dec-2019

GENERAL COMMENTS	<p>In this study the association between pre-stroke medications and post-stroke health outcome was assessed in a large stroke registry population, with links to national death databases and stroke outcome assessments.</p> <p>The major shortcoming of this study is that of significance. The authors do appropriately address the shortcomings entailed by the analysis they perform, particularly the confounding by indication entailed, and the missing data on stroke impact if the stroke is survived. But it is not clear that the findings have any practical implications. That said, the study is comprehensive, large and thought provoking.</p> <p>It is not clear whether statistical analyses were performed with or without adjustment for multiple comparisons, and this should be explicitly stated.</p> <p>Other minor comments</p> <p>1) Page 13 “The literature is more scares” should be scarce</p> <p>2) The last sentence is a little unclear: “In the event of an ischemic stroke, attention should be given to the management of these risks patients to potentially improve health outcomes post stroke.” Do the authors suggest only patients on such medications should be given attention? Or do they mean something like “Pre-stroke treatment with oral anticoagulants, antihypertensives, hypoglycaemic medications and antidepressants are all associated with worse outcomes post-stroke, and may serve as a special prompt to ensure acute and preventative stroke treatments are thoroughly applied.”</p>
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REVIEWER	Hai Sun Rutgers Robert Wood Johnson Medical School New Brunswick, Neurosurgery
REVIEW RETURNED	19-Jan-2020

GENERAL COMMENTS	In this study, the authors retrospectively reviewed a regional stroke registry and performed univariate and multivariate analyses on the
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	<p>factors associated with the outcomes of the stroke interventions. The factors the authors were interested in are the usage of oral medications including antihypertensives, anticoagulants, antidepressants and those treating diabetes. Adult patients were identified using ICD-10 codes that included both hemorrhage and ischemic stroke. If a patient had several stroke diagnosis during the initial inpatient admission, a hierarchy was applied where hemorrhagic type is considered the final type and therefore was excluded from the study. All classes of medications in each of pharmaceutical groups aforementioned were considered. A patient is considered being on a treatment if he or she received two prescriptions in a pharmaceutical group within one year prior to stroke. The health outcome variables were estimated at one and two years after stroke. They included patients' survival and functional status (ADL independent or estimated mRS 0-2 1 year after stroke). Logistic univariate regression analyses were first performed for each pharmaceutical group and each respective health outcome. The authors then performed a multivariate analysis of usage of each pharmaceutical group while adjusting factors shown previously to have impact on health outcomes including sex, age, ADL dependency prior to stroke, accommodate prior to stroke, consciousness at arrival and level of education. 35913 patients with ischemic stroke between 2009-2011 were included in the study. The patients characteristics, neurological status at the arrival, and overall outcomes were in line with the similar studies reported in the literature. The authors also found that there is increase in the usage of antihypertensive, anticoagulants, antidepressants and medications for treating diabetes after the stroke and the use of NSAIDs is decreased however.</p> <p>The univariate analysis revealed that patients on anticoagulants, antihypertensives, antidepressants or drugs for diabetes had worse health outcomes compared to those with any of these medications. Patients on statins or NSAIDs had higher survival. In the multivariate analysis, after adjusting confounding factors, patients taking antihypertensives and drugs for diabetes had less favorable outcomes compared to those who don't. The same trend was detected for patients on anticoagulants and antidepressants although it didn't reach statistical significance. The same protective trend were detected for patients on statin and NSAIDs.</p> <p>This study was conducted in a large registry, which is the strength of this study. The statistical analysis was done rigorously. The limitation of this study, as the authors correctly pointed out, is the retrospective nature and some inherent bias associated with patient selection in this registry and follow up. Also the study only demonstrated the association of these factors with the outcomes and the association is a complex phenomenon that cannot be interpreted as a prediction. For example, the group of patients on antihypertensives prior to stroke is a heterogeneous group and the study such as this one doesn't provide answers to the effect of antihypertensives on stroke outcome, which the author may want to emphasize. Here are some of my additional comments and suggestions:</p> <p>The authors excluded patients with multiple strokes during the initial inpatient admission of any of stroke turned out to be hemorrhagic. Ischemic stroke can have hemorrhagic transformation especially with surgical intervention, which has become more common. This criterion may have potential to exclude some patient ischemic stroke that may have worse outcome. Can the authors comment on this?</p>
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	On page 12, line 20, the authors use acronym NOAC without provide the full phase. Since oral anticoagulants were used elsewhere without using NOAC, it might be better not to use the acronym.
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REVIEWER	Tom Moullaali University of Edinburgh, UK
REVIEW RETURNED	22-Jan-2020

GENERAL COMMENTS	<p>1. Research question: your research question is broad. What is your primary hypothesis? With a clearer hypothesis, you could then define a hierarchy to your analyses (see below)</p> <p>2. Abstract: I think you could show some statistics in the abstract</p> <p>3. Design: is there a way to access more information about SVUES in English language?</p> <p>6. Outcomes: you define a number of outcomes without a clear hierarchy. What is your primary hypothesis? And how might your analyses be designed to show this?</p> <p>9 and 10. Results:</p> <p>Please check STROBE checklist #14-16 carefully: I don't think you show enough data for the reader to easily understand your cohort, data availability and sources of bias.</p> <p>Table 2 I think table 2 could be more complete by showing mean (SD) for continuous variables, and N (%) for categorical variables. It would also be nice to see information on pre-stroke drug use here too (again, show N (%) using anticoagulants, statins etc), as this gives the reader important information on the population you are analysing. If you have information on ethnicity, and medical comorbidities, you could also show this in Table 2.</p> <p>Results text In the text, please give N (%) for descriptive statistics for completeness, and show some statistics for your results of the multivariable analyses: you don't show adjusted OR (95%CI) in text or figure, only in the supplementary table.</p> <p>You use the term 'significant effects' to describe the results of the multivariable analyses: you are not reporting effects, rather associations.</p> <p>Figure 2 is of poor resolution: make it larger and adjust the page layout to landscape to improve readability.</p> <p>11. Use of 'effects' in the discussion is incorrect: associations only! I agree that there is confounding by indication here: think about the meaning of your results with this in mind - is it the drug or the indication driving the associations? Overall, I think the flow of the discussion could be improved with the following structure: https://www.bmj.com/content/318/7193/1224 (see attached document)</p> <p>15. There are a number of grammatical errors</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewers' Comments to Author:

Reviewer: 1

Reviewer Name: Timothy Kleinig

Institution and Country: Royal Adelaide Hospital, Port Road, Adelaide, South Australia, Australia
Please state any competing interests or state 'None declared': None declared

In this study the association between pre-stroke medications and post-stroke health outcome was assessed in a large stroke registry population, with links to national death databases and stroke outcome assessments.

The major shortcoming of this study is that of significance. The authors do appropriately address the shortcomings entailed by the analysis they perform, particularly the confounding by indication entailed, and the missing data on stroke impact if the stroke is survived. But it is not clear that the findings have any practical implications. That said, the study is comprehensive, large and thought provoking.

It is not clear whether statistical analyses were performed with or without adjustment for multiple comparisons, and this should be explicitly stated.

We have added a comment in the methods-section that we have not performed adjustment for multiple comparisons. Please come back to us if you see this as a necessity for interpreting the results. We do not believe that it will alter the overall conclusions.

Other minor comments

- 1) Page 13 "The literature is more scares" should be scarce

Thank you, this is amended.
- 2) The last sentence is a little unclear: "In the event of an ischemic stroke, attention should be given to the management of these risks patients to potentially improve health outcomes post stroke." Do the authors suggest only patients on such medications should be given attention? Or do they mean something like "Prestroke treatment with oral anticoagulants, antihypertensives, hypoglycaemic medications and antidepressants are all associated with worse outcomes poststroke, and may serve as a special prompt to ensure acute and preventative stroke treatments are thoroughly applied."

Thank you, we have tried to clarify accordingly.

Reviewer: 2

Reviewer Name: Hai Sun

Institution and Country: Dept of Neurosurgery, Robert Wood Johnson Medical School, Rutgers University, United States Please state any competing interests or state 'None declared': None

In this study, the authors retrospectively reviewed a regional stroke registry and performed univariate and multivariate analyses on the factors associated with the outcomes of the stroke interventions. The factors the authors were interested in are the usage of oral medications including antihypertensives, anticoagulants, antidepressants and those treating diabetes. Adult patients were identified using ICD-10 codes that included both hemorrhage and ischemic stroke. If a patient had several stroke diagnosis during the initial inpatient admission, a hierarchy was applied where hemorrhagic type is considered the final type and therefore was excluded from the study. All classes of medications in each of pharmaceutical groups aforementioned were considered. A patient is considered being on a treatment if he or she received two prescriptions in a pharmaceutical group within one year prior to stroke. The health outcome variables were estimated at one and two years after stroke. They included patients' survival and functional status (ADL independent or estimated mRS 0-2 1 year after stroke). Logistic univariate regression analyses were first performed for each pharmaceutical group and each respective health outcome. The authors then performed a multivariate analysis of usage of each pharmaceutical group while adjusting factors shown previously to have impact on health outcomes including sex, age, ADL dependency prior to stroke, accommodation prior to stroke, consciousness at arrival and level of education.

35913 patients with ischemic stroke between 2009-2011 were included in the study.

The patients characteristics, neurological status at the arrival, and overall outcomes were in line with the similar studies reported in the literature. The authors also found that there is increase in the usage of antihypertensive, anticoagulants, antidepressants and medications for treating diabetes after the stroke and the use of NSAIDs is decreased however.

The univariate analysis revealed that patients on anticoagulants, antihypertensives, antidepressants or drugs for diabetes had worse health outcomes compared to those with any of these medications. Patients on statins or NSAIDs had higher survival. In the multivariate analysis, after adjusting confounding factors, patients taking antihypertensives and drugs for diabetes had less favorable outcomes compared to those who don't. The same trend was detected for patients on anticoagulants and antidepressants although it didn't reach statistical significance. The same protective trend were detected for patients on statin and NSAIDs.

This study was conducted in a large registry, which is the strength of this study. The statistical analysis was done rigorously. The limitation of this study, as the authors correctly pointed out, is the retrospective nature and some inherent bias associated with patient selection in this registry and follow up. Also the study only demonstrated the association of these factors with the outcomes and the association is a complex phenomenon that cannot be interpreted as a prediction. For example, the group of patients on antihypertensives prior to stroke is a heterogeneous group and the study such as this one doesn't provide answers to the effect of antihypertensives on stroke outcome, which the author may want to emphasize. Here are some of my additional comments and suggestions:

The authors excluded patients with multiple strokes during the initial inpatient admission of any of stroke turned out to be hemorrhagic. Ischemic stroke can have hemorrhagic transformation especially with surgical intervention, which has become more common. This criterion may have potential to exclude some patient ischemic stroke that may have worse outcome. Can the authors comment on this?

Thank you for this suggestion, we have added a comment in the methods section about this criteria being aligned with the Swedish quality register, as well as a comment in the limitations section of the discussion relating to the point raised by the reviewer.

On page 12, line 20, the authors use acronym NOAC without provide the full phrase. Since oral anticoagulants were used elsewhere without using NOAC, it might be better not to use the acronym.

Thank you for this comment, we have clarified but kept the reference to NOACs where it refers to another study.

Reviewer: 3

Reviewer Name: Tom Moullaali

Institution and Country: University of Edinburgh, UK Please state any competing interests or state 'None declared': None declared

1. Research question: your research question is broad. What is your primary hypothesis? With a clearer hypothesis, you could then define a hierarchy to your analyses (see below) 6. Outcomes: you define a number of outcomes without a clear hierarchy. What is your primary hypothesis? And how might your analyses be designed to show this?

We have chosen to have a broad questions for giving a more holistic view than in many other studies. It is part of our chosen study design.

2. Abstract: I think you could show some statistics in the abstract

It has been added.

3. Design: is there a way to access more information about SVUES in English language? **There are unfortunately not so much written about Sveus in English.**

9 and 10. Results:

Please check STROBE checklist #14-16 carefully: I don't think you show enough data for the reader to easily understand your cohort, data availability and sources of bias.

We have added some more details of the patient population which we hope will improve the understanding of the cohort. Please advise on what other information you feel is missing.

Table 2

I think table 2 could be more complete by showing mean (SD) for continuous variables, and N (%) for categorical variables. It would also be nice to see information on pre-stroke drug use here too (again, show N (%) using anticoagulants, statins etc), as this gives the reader important information on the population you are analysing. If you have information on ethnicity, and medical comorbidities, you could also show this in Table 2.

More statistics have been added to Table 2. Information on ethnicity is not available. As drug use is such a big part of the study, we have chosen to report it instead in Figure 1. Do you still think that the numbers are needed in Table 2?

Results text

In the text, please give N (%) for descriptive statistics for completeness, and show some statistics for your results of the multivariable analyses: you don't show adjusted OR (95%CI) in text or figure, only in the supplementary table.

We have added some statistics in the text of the results-section.

You use the term 'significant effects' to describe the results of the multivariable analyses: you are not reporting effects, rather associations.

Thank you, we have changed the wording.

Figure 2 is of poor resolution: make it larger and adjust the page layout to landscape to improve readability.

For the final submission, resolution has been improved.

11. Use of 'effects' in the discussion is incorrect: associations only! I agree that there is confounding by indication here: think about the meaning of your results with this in mind - is it the drug or the indication driving the associations? Overall, I think the flow of the discussion could be improved with the following structure: <https://www.bmj.com/content/318/7193/1224> (see attached document)

Thank you, we have changed the wording.

15. There are a number of grammatical errors

We have done another read-through. Please indicate if you think of any specific grammatical errors.

VERSION 2 – REVIEW

REVIEWER	Timothy Kleinig Royal Adelaide Hospital Australia
REVIEW RETURNED	26-Feb-2020
GENERAL COMMENTS	Thankyou for these revisions. I have no further comments.
REVIEWER	Hai Sun Rutgers Robert Wood Johnson Medical School New Brunswick, Neurosurgery
REVIEW RETURNED	08-Mar-2020
GENERAL COMMENTS	The authors have adequately addressed my questions and concerns. I recommend the paper for publication.
REVIEWER	Tom Moullaali University of Edinburgh, UK
REVIEW RETURNED	08-Mar-2020
GENERAL COMMENTS	The authors have considered reviewer comments and improved the paper. Thank you for addressing my comments.