PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Characteristics, risk factors and mortality of stroke patients in Kyoto, Japan
AUTHORS	Shigematsu, Kazuo; Nakano, Hiromi; Watanabe, Yoshiyuki; Sekimoto, Tatsuyuki; Shimizu, Kouichiro; Nishizawa, Akihiko; Makino, Masahiro; Okumura, Atsushi; Bando, Kazuhiko; Kitagawa, Yasushi

VERSION 1 - REVIEW

REVIEWER	Tanvir Chowdhury University of Calgary Calgary Alberta Canada
REVIEW RETURNED	08-Nov-2012

THE STUDY	The authors need to cite / refer / discuss the studies from Japan who have reported on the incidence of stroke (and sub-types) in Japanese population using stroke registry.
GENERAL COMMENTS	In this manuscript the authors have analyzed data from Kyoto Stroke Registry to present the stroke patient characteristics, prevalence of risk factors, and acute-fatality. Kyoto Stroke Registry registers all incidence stroke patients in Kyoto prefecture (catchment area population about 2,630,000). A well-executed stroke registry has the potential of capturing the information on stroke incidence trends in a population with greater precision. The authors used the information of 14.268 stroke patients enrolled during the period of 1999 -- 2009.

The most important aspect of the usage of registry data would be the information on incidence and trends of incidence over time. The authors did not report these. Only giving the proportions of stroke subtypes are not adequate. The incidence information (age-adjusted gender specific incidence) is crucial and also comparing the Kyoto-incidence with other similar stroke registries is necessary.

The authors mentioned that they have data on CT / MRI, angiography and scintigraphy for the stroke patients. That will give the authors the capability to identify the ischemic stroke subtypes (lacunar, cardioembolic, etc). This information will be important from Japanese population as the proportion of subtypes differ from the Western population.

Regarding the risk factor of stroke, the data in fact, does not add any information on the effect of risk factors on stroke occurrence (the registry data is not meant to do that type of study) – rather the data is appropriate to present the prevalence of different risk factors among the stroke patients. The authors have compared the risk factors across the subtypes and provided the pair-wise comparison |

	for them. But they did not mention if they have accounted for the multiple comparisons.
	While estimating the hazard ratios for mortality, the model included SBP and DBP both. Were not these two variables correlated? Due to the existing correlation, conventionally, either SBP or DBP is considered for modeling purpose – what was the rationale of the authors for including both these variables in their model.
	The authors mentioned that cox model hazard ration was adjusted for age, sex, SBP, DBP, and JCS levels – why not the other variables, which showed significant, difference across the subtypes (Table 1). Not using those also variables will not be appropriate.
	The Hazard Ratios in Table 2 – might consider presenting only two decimal place.

REVIEWER	Shigenobu Nakamura, MD, PhD, Emeritus Professor Director, Rakuwakai Clinical Trial Centre, Japan
REVIEW RETURNED	27-Nov-2012

THE STUDY	1. Incidence of stroke in Kyoto calculated from this study was turned out to be 0.49/1,000 inhabitants /year, if all cases were registered. The incidence in Hisayama-cho Kyushu has been reported to be around 5, suggesting that all cases do not seem to be registered in the present study. However, the number of cases are so large that some characteristics are worth reporting in this journa after a major revisionl. 2. Two references are necessary to be added; a. incidence of stroke in Japan such as those conducted in Hisayama, Japan b. mortality rate of CH
RESULTS & CONCLUSIONS	Low incidence of stroke and low mortality of CH should be discussed in more detail. In contrst, CT or MRI is equipped in almost all hospitals and many clinics in Kyoto prefecture. The advantage of equipment should be stressed in Discussion.

REVIEWER	Yoshitaka Murakami Associate Professor Shiga University of Medical Science, Japan There is no competing interests.
REVIEW RETURNED	05-Dec-2012

THE STUDY	1. The registry system was not fully described. In this paper, we did only find the brief description of the Kyoto stroke registry in the Method section. This description was not adequate for understanding the details of the system, such as their size (how many hospitals are there?), the system (who collected the data?) and the methods they use (is this web-based registry system? how to find the incidence cases ?). This cohort study is based on the registry and the quality of the system is important for

	interpreting the study results.
	2. Period effect
	The data collection periods in this registry covered the long time, from year 1999 to the end of 2009. We suppose that the medical technology, environments, and related factors have been improved during this long period. The authors should consider this period effect in their analysis.
RESULTS & CONCLUSIONS	3. Discussion
	Several stroke registry systems for both the patients and the general population are found in Japan and other developed nations. They might conduct the similar investigation like the authors' did. The comparison between their results and those of other registration system are essential in the discussion section.
GENERAL COMMENTS	This study described the characteristics, risk factors and mortality of stroke patients in a certain district of Japan. The sample size of the cohort is in the middle level and the findings are not novel in stroke. We can find many bullet points in your manuscript. We never use such bullet point so often in the scientific paper. We usually write down the contents using a paragraph, not a sentence itself which will leads an ambiguous expression. We can find many bullet points in the Methods section, Results section, Discussion section and the Limitation in your manuscript, and should be changed in a paragraph.
	Major comments;
	1. The registry system was not fully described.
	In this paper, we did only find the brief description of the Kyoto stroke registry in the Method section. This description was not adequate for understanding the details of the system, such as their size (how many hospitals are there?), the system (who collected the data?) and the methods they use (is this web-based registry system? how to find the incidence cases ?). This cohort study is based on the registry and the quality of the system is important for interpreting the study results.
	2. Period effect
	The data collection periods in this registry covered the long time, from year 1999 to the end of 2009. We suppose that the medical technology, environments, and related factors have been improved during this long period. The authors should consider this period effect in their analysis.
	3. Discussion
	Several stroke registry systems for both the patients and the general population are found in Japan and other developed nations. They might conduct the similar investigation like the authors' did. The comparison between their results and those of other registration system are essential in the discussion section.
	Minor points;
	1. Though the article focus and the key messages are the essential and the important parts for paper writing, you only wrote down few sentences with ambiguous expression. You should write these parts (Article focus and Key messages) accurately and precisely.
	2. In the results section in the abstract, the percentage of cerebral infraction was wrong. The right number should be 65.4%, not 86.3%.

	3. We found many grammatical errors in this manuscript. We want the authors to have an English editing service of a native speaker.

REVIEWER	Tetsuya Ohira, MD, PhD, Associate Professor, Osaka University Graduate School of Medicine, Department of Social and Environmental Medicine, Japan.
REVIEW RETURNED	13-Dec-2012

| THE STUDY | The design of this study is not described adequately. Representativeness of the patients, inclusion and exclusion criteria should be presented in more detail in the methods section.

Since mean age and sex ratio are very differenct among stroke subtypes, stroke risk factors presented in Table 1 should be compared after adjustment for age and sex.

The mortality rate of ischemic stroke and risk characteristics must vary by its subtypes, such as embolic stroke and lacunar stroke. The authors should discuss it in the discussion section.

Generally, J- or U-shaped association was observed between alcohol intake and stroke incidence. Why the authors did not analyse the association between amount of alcohol intake and stroke prognosis?

Minor comments-

In Abstract, in the results section,

A total of 13,788 confirmed stroke patients in the study cohort comprised 9,011 (86.3%) CI, 3,549 (25.7%) CH and 1,197 (8.7%) SAH cases.

I think that "86.3%" is incollect.

Concerning the hazard ratios (HR), two places of decimals must be enough, not three. |
|---|---|

<div align="center">

VERSION 1 – AUTHOR RESPONSE

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Reviewer: Tanvir Chowdhury
University of Calgary
Calgary, Alberta, Canada

Thank you very much for your comments and suggestions.

Your comments

The authors need to cite / refer / discuss the studies from Japan who have reported on the incidence of stroke (and sub-types) in Japanese population using stroke registry. In this manuscript the authors have analyzed data from Kyoto Stroke Registry to present the stroke patient characteristics, prevalence of risk factors, and acute-fatality. Kyoto Stroke Registry registers all incidence stroke patients in Kyoto prefecture (catchment area population about 2,630,000). A well-executed stroke registry has the potential of capturing the information on stroke incidence trends in a population with greater precision. The authors used the information of 14.268 stroke patients enrolled during the

period of 1999 -- 2009. The most important aspect of the usage of registry data would be the information on incidence and trends of incidence over time. The authors did not report these. Only giving the proportions of stroke subtypes are not adequate. The incidence information (age-adjusted gender specific incidence) is crucial and also comparing the Kyoto-incidence with other similar stroke registries is necessary.

Response

1. We summarized incidence information based on Kyoto Stroke Registry (KSR) in supplementary Tables 2 (A, B, C). Japan has 47 prefectures. To our knowledge, there are five stroke registries based on a population in the entire prefecture in recent years; Akita Stroke Registry (ASR) [1 2], Iwate Stroke Registry (ISR) [3], Tochigi Stroke Registry (TSR)   [4 5], Miyazaki Stroke Registry (MSR) [6] and KSR. ASR has been published age-adjusted gender specific incidence. Although we could not find age-adjusted gender specific incidence among the other prefectural stroke registries, TSR and MSR reported data on numbers of patients they registered. We calculated age-adjusted gender specific incidence in TSR and MSR based on their annual report and summarized them in supplementary Tables 2 (D, E, F, G, H, I). ISR says that their reports will be ready [7].

Supplementary Tables:

Supplementary Table 2-A. Age and Sex Distribution of Strokes in Kyoto Stroke Registry
Supplementary Table 2-B. Population by Sex and Age, Kyoto Prefecture, Japan
Supplementary Table 2-C. Annual Monitoring Rates of Subtypes in Stroke per 10,000 Populations in Kyoto Prefecture
Supplementary Table 2-D. Age and Sex Distribution of Strokes in Tochigi Stroke Registry
Supplementary Table 2-E Population by Sex and Age, Tochigi Prefecture, Japan
Supplementary Table 2-F. Annual Monitoring Rates of Subtypes in Stroke per 10,000 Populations in Tochigi Prefecture
Supplementary Table 2-G. Age and Sex Distribution of Strokes in Miyazaki Stroke Registry
Supplementary Table 2-H. Population by Sex and Age, Miyazaki Prefecture, Japan
Supplementary Table 2-I. Annual Monitoring Rates of Subtypes in Stroke per 10,000 Populations in Miyazaki Prefecture

One of the major purposes of these prefectural stroke registries is to clarify the current situation of stroke events in order to maintain and improve health care system in the prefecture. In Japan, health care systems largely depend on each prefectural government, and therefore information on each prefecture is important.

To our knowledge, all the prefectural registries ask as many hospitals and facilities to register all the stroke events as possible. Registration, however, is not mandatory but depends on voluntary contributions of hospitals. Some hospitals might be difficult to undertake this social work. Therefore, registries by a fewer hospitals on a more restricted area may be suitable to clarify stroke incidence in a community. The incidence rates of stroke reported from the Takashima Stroke Registry [8-14] and the Hisayama Study [15-17] are higher than those from the prefectural stroke registries. The Hisayama study is reported to examine about 80 % residents (at age of 40 or over) of the area, which has a population of about 8,400 (http://www.med.kyushu-u.ac.jp/envmed/about/index.html). Nevertheless, inherent limitation to clarify the precise incidence is unavoidable for any registries in Japan.

2. In order to clarify trends over time, we divided the study cohort into two groups, Group-A and Group-B, according to the date of onset of the event. Group-A comprises patients who developed stroke between January 1999 and June 2004, and Group-B comprises patients who developed stroke

between July 2004 and December 2009. We showed differences between the two groups and, using multivariate analyses, calculated hazard ratios for death comparing the two groups.

We added Table 2 A, Table 2 B and Supplementary Table 3.

Table 2 A Temporal trends of characteristics of stroke patients, comparing Group-A and Group-B

Supplementary Table 3 Characteristics of stroke patients in Group-A and in Group-B

Table 2 B. Hazard Ratios for death, comparing Group-A and Group-B

The characteristics significantly different between Group-A and Group-B were age, diastolic blood pressure, histories of hypertension and hyperlipemia, tobacco and alcohol use, delay time and surgery. Hazard ratio for death in cerebral infarction was significantly higher in Group-B than that in Group-A after adjustments for age, sex, histories of risk factors and use of tobacco and alcohol.

Your comments

The authors mentioned that they have data on CT / MRI, angiography and scintigraphy for the stroke patients. That will give the authors the capability to identify the ischemic stroke subtypes (lacunar, cardioembolic, etc). This information will be important from Japanese population as the proportion of subtypes differ from the Western population.

Response

One of the strengths of a stroke registry in Japan is a high availability of CT and MRI. As you cited in your article, Japan has the most MRI units (40 U per million population) and CT scanners (93 U per million populations) per capita among the developed countries [18]. However, also as you mentioned in your another article, "community-based surveillance studies for stroke also have been initiated for the purpose of disease detection, assessment of trends, identification of service needs for program and policy development, or research in specific populations. These studies use existing administrative health service data for their purposes, and thus detailed information on the stroke events in these circumstances are often somewhat limited" [19].

Your comments

Regarding the risk factor of stroke, the data in fact, does not add any information on the effect of risk factors on stroke occurrence (the registry data is not meant to do that type of study) – rather the data is appropriate to present the prevalence of different risk factors among the stroke patients. The authors have compared the risk factors across the subtypes and provided the pair-wise comparison for them. But they did not mention if they have accounted for the multiple comparisons.

Response

We agree with your opinion that the registry data are appropriate to present the prevalence of different risk factors among the stroke patients. The higher prevalence of a factor in a certain group, however, may support the higher association between the factor and the group.

Our data added information on the prevalence of risk factors among stroke patients and clarified the differences among stroke subtypes. We can compare such prevalence in stroke patients with that in general population.

We also added multivariate analyses. Using a logistic regression model, we estimated odds ratios (and 95% CI) for the prevalence of these risk factors comparing each stroke subtype after adjusted for age and sex.

We added Table 4.

Table 4 Odds ratios for the prevalence of each risk factors among stroke subtypes, adjusted for age and sex

Your comments

While estimating the hazard ratios for mortality, the model included SBP and DBP both. Were not these two variables correlated? Due to the existing correlation, conventionally, either SBP or DBP is considered for modeling purpose – what was the rationale of the authors for including both these variables in their model.

The authors mentioned that cox model hazard ration was adjusted for age, sex, SBP, DBP, and JCS levels – why not the other variables, which showed significant, difference across the subtypes (Table 1). Not using those also variables will not be appropriate.

Response

We showed hazard ratios adjusted for age, sex, past history, and uses of tobacco and alcohol.

Table 5 Hazard Ratios for death, comparing stroke subtypes

Your comments

The Hazard Ratios in Table 2 – might consider presenting only two decimal place.

Response

We presented two decimal places.

Reviewer: Shigenobu Nakamura, MD, PhD, Emeritus Professor
Director,
Rakuwakai Clinical Trial Centre,
Japan

We deeply appreciate the time and effort that you have put into assessing our manuscript. We thank you very much for your precious comments and kind advice.

Your comments

1. Incidence of stroke in Kyoto calculated from this study was turned out to be 0.49/1,000

inhabitants /year, if all cases were registered. The incidence in Hisayama-cho Kyushu has been reported to be around 5, suggesting that all cases do not seem to be registered in the present study. However, the number of cases is so large that some characteristics are worth reporting in this journal after a major revision.

Response

We totally agree with you. Like other prefectural stroke registries in Japan, we have tried to capture all stroke events occurred in the entire Kyoto Prefecture by asking virtually all hospitals in the prefecture. We keep sending letters, registration forms, and annual reports regularly to all hospitals belong to Kyoto Medical Association. However, prefectural registries in Japan are not mandatory but depend on voluntary contributions of physicians and hospitals. The Hisayama study is one of the best population-based studies in Japan. It is reported to register about 80 % residents (at age of 40 or over) of the area, which has a population of about 8,400 [15]. In respect to incidence rate of stroke, the Hisayama study should be more suitable than other studies based on prefectural registries, although the area covered by the Hisayama study is rather small. Registries of smaller areas covered by a fewer hospitals may show incidences of stroke more accurately. Age-standardized incidence rates (per 10,000 person-years) of stroke in the 3rd cohort (1988-2000) of the Hisayama Study are 529 in men and 388 in women [17]. Among subtypes of stroke, they are 357:77, 130:21 and 42:13 (men: women) in cerebral infarction, cerebral hemorrhage and subarachnoid hemorrhage, respectively [17].

A prefectural registry is, however, important for each prefecture, because a local government is largely responsible to establish their own health care systems for the residents. In KSR, voluntary contribution mentioned above has built up a registry of 14,268 stroke patients over 11 years, which could add valuable information to understand the facts about stroke patients in Kyoto Prefecture better. To be compared with the other prefectural registries, one of the outstanding strengths of KSR is that it has information on survival days up to 30 days after the onset in 13,735 patients out of 13,788 patients of this study cohort (99.6%). KSR makes it possible to analyse relationships between a certain factor and early mortality.

Your comments

2. Two references are necessary to be added;
a. incidence of stroke in Japan such as those conducted in Hisayama, Japan
b. mortality rate of CH
Low incidence of stroke and low mortality of CH should be discussed in more detail.

Response

Age-standardized incidence rates (per 10,000 person-years) of stroke in the 3rd cohort (1988-2000) of the Hisayama Study are 529 in men and 388 in women [17]. Among subtypes of stroke, they are 357:77, 130:21 and 42:13 (men: women) in cerebral infarction, cerebral hemorrhage and subarachnoid hemorrhage, respectively [17].

The average annual mortality of cerebral hemorrhage is 3.9 per 1,000 PYE whereas that of cerebral infarction is 6.5 in Hisayama population aged 40 and over [20]. Some prefectural stroke registries reported mortality rates. In TSR, they were 10%, 16% and 29% in CI, CH and SAH, respectively [4]. According to ASR, survival rates were 94%, 92%, 83%, 84%, 70% and 70% in CI-men, CI-women, CH-men, CH-women, SAH-men and SAH-women, respectively [21 22], which generally agrees with the results of KSR. The present study added the age, sex, histories of hypertension, arrhythmia, diabetes and hyperlipemia, and uses of tobacco and alcohol adjusted hazard ratios for death in each

stroke subtype. In KSR, voluntary contribution mentioned above has built up a registry of 14,268 stroke patients over 11 years. To be compared with the other prefectural registries, one of the outstanding strengths of KSR is that it has information on survival days up to 30 days after the onset in 13,735 patients out of 13,788 patients of this study cohort (99.6%). KSR makes it possible to analyse relationships between a certain factor and early mortality.

Your comments

In contrast, CT or MRI is equipped in almost all hospitals and many clinics in Kyoto prefecture. The advantage of equipment should be stressed in Discussion.

We deeply appreciate your kind suggestion.

Japan has the most MRI units (40 U per million population) and CT scanners (93 U per million populations) among the developed countries. In the study cohort, 12,365 patients (89.7%) had CT examination and 8,891 patients (64.5%) had MRI examination. The study added the information on recent trends on usage of these examinations. As expected, but interestingly, the usage CT declined whereas the usage of MRI increased with time during the study period of 11 years.

Reviewer: Yoshitaka Murakami
Associate Professor
Shiga University of Medical Science, Japan
There is no competing interests.

Your comments

1. The registry system was not fully described.
In this paper, we did only find the brief description of the Kyoto stroke registry in the Method section. This description was not adequate for understanding the details of the system, such as their size (how many hospitals are there?), the system (who collected the data?) and the methods they use (is this web-based registry system? how to find the incidence cases ?). This cohort study is based on the registry and the quality of the system is important for interpreting the study results.

Response

The Kyoto Medical Association distributed the registration forms to the affiliated medical institutions and collected the data. A total of 151 hospitals have registered patients.

We supplied the summary of Kyoto Stroke Registry Program in supplementary Table 1.
This summary has been distributed to all hospitals affiliated to the Kyoto Medical Association and to public health centers in Kyoto Prefecture. It is also attached to the annual reports published by Kyoto Prefecture.

Supplementary Table1: The Summary of the Kyoto Stroke Registry Program

1. Purpose
The purpose of this registry is to register and analyze all stroke patients in Kyoto prefecture with cooperation of the affiliated medical institutions to better understand the facts about stroke patients and to identify effective countermeasures against stroke including prevention, rehabilitation, and

home care.

2. Implementation body
Kyoto prefecture entrusts the program to the Kyoto Medical Association. The Kyoto Medical Association conducts the registry with cooperation of affiliated medical associations.

3. Registry Committee
The Committee of the Kyoto Medical Association Stroke Registry Program supervises and advises the program for smooth conduction.

4. Subjects
The residents of Kyoto prefecture who consult medical institutions that belong to the Kyoto Medical Association are subjected to registration.

5. Methods
(1) The Kyoto Medical Association distributes the stroke patients registration forms to the affiliated medical institutions
(2) The medical institutions fill in and submit the registration forms when their patients apply to the following criteria.
1 Patients diagnosed with stroke
2 Patients diagnosed with stroke who were treated for stroke or had been treated for stroke and the treatment was discontinued in the past
3 Patients who were once enrolled in the registry and had stroke again
4 Patients whose diagnoses were confirmed as stroke after they were registered with suspected stroke
(3) The Kyoto Medical Association computerizes the registration forms and registers, stores and analyzes patients information
(4) The Kyoto Medical Association inquires the medical institutions if crucial information such as patients' address and their dates of birth is missing
(5) The Kyoto Medical Association informs the medical institutions results of its registry

6. Death records
The registry is referred with death records

7. Follow-up study
Supplementary study and follow-up study are conducted by the Kyoto Medical Association with cooperation of attending physicians if needed

8. Cooperation of related associations and organizations
This project is conducted with cooperation of medical institutions and related associations, organizations, research organizations and expert meetings.

9. Privacy policy
Doctors and any other participants in this registry must protect patients' privacy

10. Contact with patients
Patients must not be contacted without any permission from attending physicians

Your comments

2. Period effect

The data collection periods in this registry covered the long time, from year 1999 to the end of 2009. We suppose that the medical technology, environments, and related factors have been improved during this long period. The authors should consider this period effect in their analysis.

Response

In order to clarify period effects, we divided the study cohort into two groups, Group-A and Group-B, according to the date of onset of the events. Group-A comprises patients who developed stroke between January 1999 and June 2004, and Group-B comprises patients who developed stroke between July 2004 and December 2009. We showed differences between the two groups and calculated hazard ratios for death, comparing the two groups.

We added Table 2, Supplementary Table 2 and Table 3.

Table 2 Temporal trends of characteristics of stroke patients, comparing Group-A and Group-B

Supplementary Table 2 Characteristics of stroke patients in Group-A and Group-B

Table 3 Hazard ratios for death, comparing Group-A and Group-B

Your comments

3. Discussion
Several stroke registry systems for both the patients and the general population are found in Japan and other developed nations. They might conduct the similar investigation like the authors' did. The comparison between their results and those of other registration system are essential in the discussion section.
This study described the characteristics, risk factors and mortality of stroke patients in a certain district of Japan. The sample size of the cohort is in the middle level and the findings are not novel in stroke.

Response

To our knowledge, there are five prefectural stroke registries in Japan. Although each prefectural registry reported the result annually to the local government, to health care centers, and to the public, most of them are not available in English literature. A larger registry, such as a national registry has not been done yet.

The ratio of stroke subtypes, men and women ratio among stroke subtypes, prevalence of risk factors and early mortality are similar among those prefectural registries. The present study added odds ratios of prevalence of risk factors in each subtype with adjustments for age and sex, hazard ratios with adjustments for age, sex and risk factors, and analyses on period effects.

Although there are some excellent stroke registries for general population, such as Takashima Stroke Registry [11-14 18 19 23 24] and the Hisayama study [17 25], they are based on rather restricted areas, and prefectural registries are also necessary to understand current situations of stroke patients in corresponding prefectures. Each prefecture is responsible to provide appropriate health care systems.

Prefectural registries in Japan depend on voluntary contribution of a large number of hospitals and their staff. To understand existing circumstances about stroke registries at the prefectural levels may

also be important to establish better registry systems and, eventually, should help prefectures to improve their health care systems.

Based on such voluntary contribution of hospitals, KSR has accumulated information on 14,268 stroke patients. One of the strengths of this registry is that it has data on clinical outcome 30 days after the onset. In cases patients died within 30 days, survival days were also recorded. Multivariate analyses to estimate hazard ratio for death should provide some important information on current stroke situation. We report the study hoping that 14,268 stroke victims and immeasurable efforts to register them do not remain totally in vain.

Your comments

We can find many bullet points in your manuscript. We never use such bullet point so often in the scientific paper. We usually write down the contents using a paragraph, not a sentence itself which will leads an ambiguous expression. We can find many bullet points in the Methods section, Results section, Discussion section and the Limitation in your manuscript, and should be changed in a paragraph.

Response

As you have pointed out, bullet points can sometimes lead to ambiguous expressions. In this case however, I used bullet points to make points more clear and simple. I'd like to leave the sentences as they are as those were read and edited by an ex-editor in chief of an international scientific journal.

I made some corrections following your advice not to use bullet points and the corrected sentences in Limitations section.

I asked professors and friends in North America to proofread our article. I added more to the article after it was proofread. If there are grammatical mistakes in my sentences, they are all my mistakes.

I will carefully proofread my article again. If there are any more mistakes, I'm more than pleased to be advised.

Your comments

Minor points;
1. Though the article focus and the key messages are the essential and the important parts for paper writing, you only wrote down few sentences with ambiguous expression. You should write these parts (Article focus and Key messages) accurately and precisely.

Response

We rewrote Article focus and Key messages trying to be more accurate and precise.
If there are still ambiguous expressions, we are more than pleased to be advised.

Your comments

2. In the results section in the abstract, the percentage of cerebral infraction was wrong. The right number should be 65.4%, not 86.3%.

Response

I am terribly sorry for this and thank you very much for your correction.

Your comments

3. We found many grammatical errors in this manuscript. We want the authors to have an English editing service of a native speaker.

Response

I asked professors and friends in North America to proofread our article. I added more to the article after it was proofread. If there are grammatical mistakes in my sentences, they are all my mistakes.

I will carefully proofread our article again. If there are any more mistakes, I'm more than pleased to be advised.

Reviewer: Tetsuya Ohira, MD, PhD, Associate Professor, Osaka University Graduate School of Medicine,
Department of Social and Environmental Medicine, Japan

Your comments

The design of this study is not described adequately. Representativeness of the patients, inclusion and exclusion criteria should be presented in more detail in the methods section.

Response

The Kyoto Medical Association distributed the registration forms to the affiliated medical institutions and collected the data. A total of 151 hospitals have registered patients.

The Kyoto Stroke Registry Program has been distributed to all hospitals affiliated to the Kyoto Medical Association and to public health centers in Kyoto Prefecture. It is also attached to the annual reports published by Kyoto Prefecture.

The summary of the Kyoto Stroke Registry Program are presented in supplementary Table 1 A.

Supplementary Table1 A: The Summary of the Kyoto Stroke Registry Program (This Table is shown previously in this letter)

Inclusion and exclusion criteria for KSR are presented in supplementary Table 1 B.

Supplementary Table 1B Inclusion and Exclusion criteria for KSR

[Inclusion criteria]
1 Patients are registered when they have acute clinical symptoms arising from cerebrovascular disorders that last for more than 24 hours or lead to death.
2 Patients are registered regardless to their age.
3 Patients are registered regardless to their sex.
4 Patients must have lived in Kyoto Prefecture.
5 Conditions such as shock, Adam-Strokes Syndrome or hypertensive encephalopathy are excluded as they are not caused directly by cerebrovascular events.

6 TIA is also excluded as the symptoms cease within 24 hours after onset.
7 Differential diagnoses are made by attending physicians based on CT/MRI images and other clinical examinations.

[Exclusion criteria]
1 When patients are diagnosed with some other disorder than stroke
2 When patients move out of Kyoto prefecture
3 When patients have symptomatic stroke (stroke-like symptoms but caused by non cerebrovascular origins)
Caused by head trauma
Developed during pregnancy, parturition and puerperal periods
Caused by drugs and toxins
Caused by cancer
Caused by hematologic disease
Caused by encephalitis or meningitis

Your comments

Since mean age and sex ratio are very different among stroke subtypes, stroke risk factors presented in Table 1 should be compared after adjustment for age and sex.

Response

We deeply appreciate your kind advice.
According to your suggestion, we calculated odds ratios for the prevalence of risk factors after adjustment for age and sex, using a logistic regression model.

It is noteworthy that history of hypertension is more strongly associated with cerebral hemorrhage and less strongly associated with subarachnoid hemorrhage when compared with cerebral infarction.

We added Table 4.

Table 4 Odds Ratios for the prevalence of risk factors among stroke subtypes, adjusted for age and sex

Your comments

The mortality rate of ischemic stroke and risk characteristics must vary by its subtypes, such as embolic stroke and lacunar stroke. The authors should discuss it in the discussion section.

Response

We totally agree your comment saying that the mortality rate of ischemic stroke and risk characteristics must vary by its subtypes, such as embolic stroke and lacunar stroke. We added this matter in the discussion section. One of the strengths of a stroke registry in Japan is a high availability of CT and MRI. However, we don't have sufficient information to classify ischemic stroke into more detailed categories.

Your comments

Generally, J- or U-shaped association was observed between alcohol intake and stroke incidence. Why the authors did not analyse the association between amount of alcohol intake and stroke prognosis?

Response

Your comments are interesting and important.
We are sorry for that we do not have enough information on the amount of alcohol intake to clarify J- or U-shaped association between alcohol intake and stroke prognosis.

Your comments

Minor comments-
In Abstract, in the results section,
A total of 13,788 confirmed stroke patients in the study cohort comprised 9,011 (86.3%) CI, 3,549 (25.7%) CH and 1,197 (8.7%) SAH cases. I think that "86.3%" is incorrect. Concerning the hazard ratios (HR), two places of decimals must be enough, not three.

Response

We deeply appreciate your kind advice.
Corrections have been done.

References

1. Izumi M, Suzuki K, Sakamoto T, et al. Advantages and limitations of antihypertensive treatment for stroke risk in a general population: the Akita Stroke Registry. Acta cardiologica 2011;66(6):729-35
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http://www.msuisin.jp/blog/21nousochu.pdf.
3. Iwate Cancer and Stroke Registry. Secondary Iwate Cancer and Stroke Registry.
http://www.iwate.med.or.jp/gan_nou/index.html.
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REVIEWER	Turin, Tanvir Chowdhury Shiga University of Medical Science, Health Science
REVIEW RETURNED	21-Jan-2013

GENERAL COMMENTS	The authors will need to check the writing style of Reference and modify the references of their manuscript accordingly.

REVIEWER	Shigenobu NAKAMURA, MD, PhD Emeritus Professor of Hiroshima University Director of Rakuwa Kyoto Clinical Trial Centre Japan
REVIEW RETURNED	15-Jan-2013

THE STUDY	1. The difference/OR in Table 2 should be defined more clearly: *1Mean difference (Group-A – Group-B) with 95% confidence interval of the difference *2 Mantel-Haenszel common odds ratio (Group-B/Group-A) with 95% confidence interval. 2. (p.20, line 1) OR of hypertension history is missing. 3. (p.10) Criteria to diagnose diabetes mellitus should be described. 4. (p.13) The method should be described how strokes combined are dealt with. Are combined strokes counted in both subtypes? 5. (p.18, line 12 and 13 and supplementary table 3) *2 and *3. Sig. had better be replaced by significant. 6. (p.23, line 9) Is Table 3 mistaken for a Table 4? 7. Supplementary Table 2-C. CH in age 70-79: 3.801 to 3.80, 2.824 to 2,82 8. English expression is poor in some parts, especially in newly added sentences. Brush-up English.
RESULTS & CONCLUSIONS	1. Further discussions are necessary concerning the difference between Group A and B. 2. Discussion is necessary to explain the difference among Supplementary Table 2-C, Supplementary Table 2-F and Supplementary Table 2-I.
REPORTING & ETHICS	This paper has revealed important characteristics with a large number of stroke patients living in Kyoto, Japan. Results presnted in this paper have comfirmed data already presented by ohter researches. Moreover, the present study has elucidated the lower mortality of cerebral hemorrhage, compared with studies conducted in other countries than Japan. However, the incidence of stroke does not represent an acurate number in this area, since only a part of stroke patients are registered and there are many missing data for stroke patients.
GENERAL COMMENTS	This revised article is much improved, compared with the former article. The new one is worth publishing in BMJ open. However, there still exist some parts which should be revised before publication.

REVIEWER	Tetsuya Ohira, MD, PhD. Associate Professor Department of Social and Environmental Medicine, Osaka University Graduate School of Medicine, Japan

	No conflict interest
REVIEW RETURNED	25-Jan-2013

- The reviewer completed the checklist but made no further comments.

VERSION 2 – AUTHOR RESPONSE

Reviewer: Shigenobu NAKAMURA, MD, PhD, Emeritus Professor of Hiroshima University, Director of Rakuwa Kyoto Clinical Trial Centre Japan

1. The difference/OR in Table 2 should be defined more clearly:
*1Mean difference (Group-A – Group-B) with 95% confidence interval of the difference
*2 Mantel-Haenszel common odds ratio (Group-B/Group-A) with 95% confidence interval.

Response

Thank you for your advice.
We corrected according to your suggestion.

2. (p.20, line 1) OR of hypertension history is missing.

Response

OR of hypertension history is 1.27.
I am sorry for that.

3. (p.10) Criteria to diagnose diabetes mellitus should be described.

Response

Diagnosis of diabetes mellitus is based on the Diagnostic Criteria of Diabetes Mellitus [1]
We added the following sentence in the method section:

Diabetes mellitus: fasting plasma glucose is 126mg/dl or higher, and/or plasma glucose 2 hours after 75g glucose load is 200 mg/dl or higher [1]

4. (p.13) The method should be described how strokes combined are dealt with. Are combined strokes counted in both subtypes?

Response:
A small number of patients had a combination of stroke types as follows: 12 with CI and CH, 4 with CI and SAH, and 15 with CH and SAH. We excluded them from the further study.

5. (p.18, line 12 and 13 and supplementary table 3) *2 and *3. Sig. had better be replaced by significant.

Response

We corrected following your suggestion.

6. (p.23, line 9) Is Table 3 mistaken for a Table 4?

I am sorry for that. Table 4 is correct.

7. Supplementary Table 2-C. CH in age 70-79: 3.801 to 3.80, 2.824 to 2,82

Response

Thank you for your corrections.
We rewrote 3.801 to 3.8 and 2.824 to 2.82.

8. Further discussions are necessary concerning the difference between Group A and B.

Response

A significant increase in odds ratio is observed in histories of hypertension and hyperlipemia and a significant decrease is observed in use of tobacco and alcohol. Although delay time is shorter in Group-B than Group-A, there is no significant improvement in mortality.

9. Discussion is necessary to explain the difference among Supplementary Table 2-C, Supplementary Table 2-F and Supplementary Table 2-I.

Response

There are some resemblance and differences among prefectural stroke registries in various ways, such as age and sex distribution of strokes and annual monitoring rates of subtype in stroke. Although, it is difficult to explain the differences sufficiently, factors which possibly influence the registries and stroke incidence include regional medical services, socio-epidemiological factors, including industries and climates, prevalence of risk factors and constitution of societies. Prefectural stroke registries continue efforts to register as many stroke events as possible, which is, however, often difficult to accomplish. Nevertheless, since stroke incidence and characteristics may differ from area to area and from period to period, it is important to continue the registries in order to elucidate the current situation of stroke and subsequently improve stroke care in each prefecture.

However, the incidence of stroke does not represent an accurate number in this area, since only a part of stroke patients are registered and there are many missing data for stroke patients.
This revised article is much improved, compared with the former article. The new one is worth publishing in BMJ open. However, there still exist some parts which should be revised before publication.>

Response

We deeply appreciate your revising our manuscript and do hope our research will interest readers and contribute to improving stroke care.

1. Kuzuya T. [Outline of revision of classification and diagnostic criteria of diabetes mellitus in Japan]. Nihon rinsho. 1999;57(3):561-6

Reviewer: Dr Tanvir Chowdhury Turin

The authors will need to check the writing style of Reference and modify the references of their manuscript accordingly.

Response

Thank you for your advice. We carefully checked the writing style of References and modified the references accordingly.