Characteristics, risk factors and mortality of stroke patients in Kyoto, Japan

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Characteristics, risk factors and mortality of stroke patients in Kyoto, Japan

Short title: Characteristics, risk factors and mortality of Stroke

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Article Summary

Article focus

The focus on this study is on:

The characteristics, risk factors and outcome of contemporary stroke patients:

Age, sex, vital signs

Histories of hypertension, arrhythmia, diabetes mellitus and hyperlipemia

Usages of tobacco and alcohol

Hazard ratio for death

Key messages

About two thirds of patients have hypertension history, whereas only about one fifth have histories of arrhythmia, diabetes mellitus and hyperlipemia.

About one tenth of patients died within a month.

Hazard ratio for death is highest in subarachnoid hemorrhage, followed by cerebral hemorrhage and lowest in cerebral infarction.

Strengths and limitations of this study

This study provided quantitative data on fundamentals of contemporary stroke in a very large cohort in Kyoto Japan.

Detailed information on size and localization of stroke and on treatment and complication was not available in this population based study.

Objectives: The aim of the study is to evaluate characteristics, risk factors and outcome of recent stroke patients in Kyoto Japan.

Design: We analyzed stroke patients in the registry in a quantitative manner with regard to their characteristics, risk factors, and mortality. Cox proportional hazards regression was used to calculate adjusted hazard ratios for death and their 95% confidence intervals.

Settings: Kyoto Stroke Registry registers all new stroke patients in Kyoto prefecture with about 2,630,000 residents.

Participants: The registry now has data on 14.268 patients enrolled from January 1, 1999 to December 31, 2009. Of these 12,774 (89.5%), 9232 (64.7%), 2504 (17.5%), and 342 (2.4%) underwent CT, MRI scan, angiography, and scintigraphy for blood flow. Excluding 480 (3.3%) unclassified patients, 13,788 (96.6%) patients formed the basis of further analyses dividing then into three subtypes of stroke, cerebral infarction (CI), cerebral hemorrhage (CH), and subarachnoid hemorrhage (SAH).

Results: 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. The mean age was oldest in the CI cases, and youngest in the SAH cases. In the CI and CH cases, males were predominant, whereas in the SAH cases, females were predominant. Frequencies of risk factors, including tobacco and alcohol usage, were also different among the subtypes. Mortality was worst in the SAH, followed by the CH, and least in the CI. Adjusted hazard ratios for death showed a significant (P<0.001) difference among CI (a reference), CH (1.745; 1.454-2.094) and SAH (2.966; 2.384-3.690).

Conclusions: Characteristics, risk factors, and mortality were evaluated in a quantitative manner in a large Japanese study cohort to shed light on the present status of stroke medicine. Hazard ratios for death were about three times worse in SAH than in CI.

Introduction

Stroke, the third major cause of death, constitutes the largest cause of acquired disability in Japan [1]. According to a report of the Ministry of Health, Labor and Welfare, about 123,400 people died from stroke in 2010. About 10.3% of the total national death resulted from stroke. Sustained exposure to risk factors associated with lifestyle which patients live in play an important role in stroke incidence. Stroke is regarded as one of the diseases developed by long lasting exposure to risk factors associated with lifestyle. The incidence, as well as mortality, should be greatly affected by society, regions and times[2 3]. The updated detailed information on stroke events in each society is required. A long-term surveillance of stroke, comparing characteristics, risk factors, and mortality, based on the entire population in a prefecture as large as Kyoto, which has about 2,630,000 residents, should provide a fundamental database of stroke. Stroke consists of three major distinct subtypes, namely, cerebral infarction (CI), cerebral hemorrhage (CH), and subarachnoid hemorrhage (SAH). Although these subtypes, as disorders of the cerebral arteries, have many things in common, distinct characteristics prevail. Quantitative measurement of these differences in the same large cohort should help characterize three stroke subtypes [4]. The strength of comparing these three stroke subtypes in the same large cohort is that, by doing so, we can evaluate the relative strength of the risk factors influencing each subtype. These data also should help confirm a higher mortality rate in hemorrhagic stroke than ischemic stroke, and elucidate hazard ratios for death estimated simultaneously among major stroke subtypes, which should reflect relative severities of stroke.

The Kyoto prefecture of Japan has established a registry to enroll all new stroke patients in cooperation with the Kyoto Medical Association and its affiliated hospitals with help from the data collecting agency known as the Kyoto Stroke Registry [5]. We studied all patients registered during the past 11 years in the prefecture of Kyoto to document characteristics, risk factors, and hazard ratios in the three major stroke subtypes.

Methods

We analyzed all stroke patients identified from January 1999 to December 2009 in the entire Kyoto prefecture and registered in the Kyoto Stroke Registry run by the local government of Kyoto prefecture. The diagnosis of stroke was confirmed by local neurologists and/or neurosurgeons based on the WHO definition [6].

We classified the patients into CI (ICD-9 code 433 and 434, ICD-10 code I63), CH (ICD-9 code 431, ICD-10 code I61), SAH (ICD-9 code 430, ICD-10 code I60) [7,8] and others by neurological examination and the findings of CT scans, MRI scans, angiographies, and scintigraphies. Each registry recorded age, sex, date of stroke onset, blood pressure and arrhythmia on arrival, history of hypertension, arrhythmia, diabetes mellitus and hyperlipemia, tobacco and alcohol use, type of paresis, consciousness levels and clinical outcome 30 days after the onset.

For the purpose of this entry, we used the following definitions.

1) Systolic and diastolic hypertension: blood pressure exceeding 140 and 90 mmHg,
2) Arrhythmia: any types of irregularity,
3) Diabetes mellitus: both type 1 and type 2 based on the patient medical record,
4) Hyperlipemia: serum cholesterol level of 220 mg/dl or higher and/or triglyceride exceeding 150mg/dl,
5) Smoking: divided into four categories, non smokers, and former smokers for more than a year, light smokers with 20 or less cigarettes a day and heavy smokers with more than 20 cigarettes a day.

6) Alcohol consumption: divided into three categories, non drinkers, occasional drinkers (less than three time a week), and daily drinkers (more than four times a week).

7) Paresis: any distribution including unilateral or bilateral limb or face,

8) Consciousness levels onset based on the Japan Coma Scale (JCS) [9 10], the most widely used Japanese scale composed of the four levels,

1; JSC 0 (alert),

2; JCS 1-digit code (disoriented but awake),

3; JCS 2-digit code (arousable with stimulation),

4; JSC 3-digit code (unarousable)

Statistical Analysis

Statistical analyses used include Fisher exact tests for frequencies of listed characteristics among the three stroke types, Student-t test for such numerical variables as age and systolic- and diastolic-blood pressures, a log-rank test for Kaplan-Meier curves of estimated survival. Cox proportional hazards regression was used to calculate age-, sex-, systolic and diastolic blood pressure-, and consciousness levels-adjusted hazard ratios and their 95% confidence intervals for the risk of death. Analyses were performed using SPSS ver.19 and statistical significance was set at $p<0.05$. All reported p values are 2-sided.

Ethics Statement

This research was performed in accordance with the ethical principles for medical research involving human subjects outlined in the Declaration of Helsinki. This research was approved by the Board of Directors, the Kyoto Medical Association, the Department of Health and Welfare, Kyoto Prefecture and Ethics Committee of the National Hospital Organization, Minami Kyoto Hospital. Since all identifying personal information was stripped from the secondary files before analysis, the boards waived the requirement for written informed consent from the patients involved.

Results

We reviewed 14,268 stroke patients newly identified in Kyoto prefecture from January 1999 to December 2009. Of these 12,774 (89.5%), 9232 (64.7%), 2504 (17.5%), and 342 (2.4%) underwent CT, MRI scan, angiography, and scintigraphy for blood flow.

Excluding 480 (3.3%) unclassified patients, 13,788 (96.6%) patients formed the basis of further analyses dividing then into three subtypes of stroke, CI, CH, and SAH categories.

The study cohort had 13,788 patients divided into 9011 (65.4%) CI, 3549 (25.7%) CH and 1197 (8.7%) SAH. 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. Table 1 summarizes the characteristics, risk factors, symptoms, and mortality rate.

Table 1 Characteristics of Stroke Patients (n=13788)

	Overall n=13788	**Cerebral Infarction n=9011 (65.4%)**	**Cerebral Hemorrhage n=3549 (25.7%)**	**Subarachnoid Hemorrhage n=1197 (8.7%)**
Age (SD)	71.3 (12.9)	73.3 (11.8)*1*3	69.1 (13.6) *1*2	62.7 (13.5) *2*3
Sex, % female (n=female/male)	45.2 (6233/7555)	42.3*1*3 (3815/5196)	45.9*1*2 (1630/1919)	64.6*2*3 (773/424)
Systolic blood pressure (SD)	161.3 (35.5)	157.5 (28.3)*1	172.1 (34.8) *1*2	157.9 (37.0)*2

Diastolic blood pressure (SD)	87.6 (18.63)	85.6 (17.0) [*1*3]	93.1 (21.1) [*1*2]	86.8 (21.8) [*2*3]
Hypertension history, % (n=with/without)	62.6 (8005/4780)	62.0[*1*3] (5285/3242)	68.5[*1*2] (2183/1006)	49.9[*2*3] (520/522)
Arrhythmia, % (n=with/without)	14.5 (1932/11352)	18.9[*1*3] (1647/7064)	5.9[*1*2] (200/3209)	7.2[*2*3] (82/1052)
Arrhythmia history, % (n=with/without)	18.5(2357/10415)	24.3[*1*3] (2060/6432)	7.5[*1*2] (240/2971)	5.3[*2*3] (55/985)
Diabetes mellitus history, % (n=with/without)	20.9 (2689/10198)	24.8[*1*3] (2138/6475)	14.8[*1*2] (474/2738)	6.9[*2*3] (71/963)
Hyperlipemia history, % (n=with/without)	19.2 (2419/10198)	23.1[*1*3] (1951/6503)	11.9[*1*2] (371/2755)	9.2[*2*3] (93/918)
Tobacco	32.4 (3665/7642)	32.6[*1*3]	30.1[*1*2]	37.1[*2*3]

usage, % (n=with/without)		(2455/5077)	(843/1956)	(354/599)
Non smoker, % (n)	67.6 (7642)	67.4 (5077) *3	69.9 (1956) *2	62.9 (599) *2*3
Former smoker, % (n)	5.4 (615)	5.8 (435) *3	5.7 (159) *2	2.1 (20) *2*3
Light smoker, % (n)	17.0 (1918)	17.0 (1281) *1*3	14.6 (409) *1*2	23.3 (222) *2*3
Heavy smoker, % (n)	10.0 (1132)	9.8 (739)	9.8 (275)	11.8 (112)
Alcohol usage, % (n=with/without)	38.0 (4202/6851)	36.3*1*3 (2654/4655)	40.5*1*2 (1124/1650)	43.6*2*3 (412/533)
Non drinker, % (n)	62.0 (6851)	63.7 (4655) *1*3	59.5 (1650) *1	56.4 (533) *3
Occasional drinker, % (n)	15.3 (1692)	15.5 (1131) *1*3	13.5 (374) *1*2	18.9 (179) *2*3
Every day drinker, % (n)	22.7 (2510)	20.8 (1523) *1*3	27.0 (750) *1	24.7 (233) *3

Paresis, % (n=with/without)	73.3 (9670/3525)	76.8[*1*3] (6750/2041)	78.5[*1*2] (2624/717)	26.8[*2*3] (73.2)
Consciousness disturbance, % (n=with/without)	43.5 (5914/7676)	31.8[*1*3] (2815/8863)	65.7[*1] (2305/1201)	65.1[*3] (775/415)
JCS 0, % (n)	55.7 (7676)	67.1[*1*3] (6048)	33.8[*1*2] (1201)	35.6[*2*3] (415)
JSC 1-digit code, % (n)	19.0 (2619)	16.7[*1] (1508)	26.0[*1*2] (921)	15.9[*2] (185)
JSC 2-digit code, % (n)	11.6 (1602)	8.6[*1*3] (774)	17.5[*1] (622)	16.7[*3] (200)
JSC 3-digit code, % (n)	10.9 (1509)	4.7[*1*3] (421)	20.2[*1*2] (716)	30.5[*2*3] (365)
JSC undetermined, % (n)	1.3 (184)	1.2[*3] (112)	1.3[*2] (46)	2.1[*2*3] (25)
Mortality, % (n=dead/alive)	9.8 (1344/12391)	5.2[*1*3] (467/8981)	15.2[*1*2] (536/2997)	28.4[*2*3] (338/853)

When the numbers entered in the above table are significantly different statistically between different types of strokes, they are marked as follows:

*1: significant difference between Cerebral Infarction and Cerebral Hemorrhage;

*2: sig. difference between Cerebral Hemorrhage and Subarachnoid Hemorrhage;

*3: sig. difference between Subarachnoid Hemorrhage and Cerebral Infarction;

SD = Standard Deviation

Table 1 also shows historical account on hypertension in 12,785 (92.7%), arrhythmia in 12,772 (92.6%), diabetes mellitus in 12,887 (93.5%), hyperlipemia in 12,617 (91.5%), tobacco usage in 11,307 (82.0%), alcohol usage in 11,053 (80.2%), and paresis in 13,195 (96.7%). We were able to classify 13,406 (97.2%) patients into four consciousness levels, excluding 184 (1.3%) patients with uncategorized stroke and 580 (4.2%) patients with no reliable information on conscious levels. Calculation of the mean delay time excluded 4964 (36.0%) patients of unknown onset. Patients received primary medical care within 3 hours of CI in 54.3%, of CH in 68.5% in CH, and of SAH in 76.4%.

Of 13,788 patients, 13,735 (99.6%) had a confirmed record of survival or death 30 days after stroke onset. A total of 1344 (9.8%) patients died within this time period.

Figure 1 shows Kaplan-Meier Survival curves, comparing stroke subtypes, showing a significant difference (p<0.001) between any two subtypes based on Log-rank tests.

Compared to CI, CH and SAH hazard ratios for fatality of 1.446 (1.255-1.667), and 2.287 (1.922-2.722) p<0.001), when adjusted for age, sex, systolic and diastolic blood pressures and consciousness levels, showing significant differences (p<0.001) (Table 2).

Table 2 Hazard ratios for death, comparing stroke subtypes, adjusted to age, sex, systolic and diastolic blood pressures and consciousness levels

	Hazard Ratio	**95% Confidence Intervals**		**p**
		Lower	Upper	
Cerebral Infarction		Reference		
Cerebral Hemorrhage	1.446	1.255	1.667	<0.001
Subarachnoid Hemorrhage	2.287	1.922	2.722	<0.001

Discussion

The study summarized the stroke registry covering entire prefecture for 11 years. Such data set depends on the society and the times. More than 100 hospitals affiliated to the Kyoto Medical Association, virtually all major hospitals in the prefecture, registered all new stroke patients based on the inclusion and exclusion criteria in accordance with the Kyoto municipal ordinance, avoiding area or hospitals preferences.

The two major findings are as follows:

First, we calculated hazard ratios for death was highest in SAH, followed by CH and lowest in CI as shown in Table 2.

Second, the study clarified characteristics, risk factors, paresis, depth of consciousness impairment and delay time among three subtypes as summarized in Table 1.

Our study is based on the very large number of stroke patients, which allows for sufficient statistical power.

In agree with previous reports, CI showed higher incidence followed by CH and SAH, which constitutes a fourth of hemorrhagic strokes [11]. The result adds the information that SAH constitutes about a fourth of hemorrhagic strokes. Age distribution also confirm the result of previous reports, the oldest mean age in CH and youngest in SAH [12]. The elderly patients showed a greater difference in proportion in stroke subtypes. For example, in patients who were 71 years or older, the proportions were 73.1% (n=5616), 22.3% (n=1709), and 4.6% (n=353), as compared to younger group who showed 55.8% (n=3395), 30.3% (n=1840) and 13.9% (n=844).

Most of the other characteristics also showed significant difference among three stroke subtypes. The overall registry had more male patients than female, except almost two-thirds of SAH cases were female. The initial medical examination revealed higher systolic and diastolic blood pressures in CH than in CI, possibly reflecting intracranial mass effect on brain edema [13 14].

Patients with disturbed consciousness had a higher ($p<0.001$) systolic/diastolic blood pressure (mean±SD: 164.0±35.2/88.6±20.9) than the remainder (159.3±28.2/87.0±17.1), implying possible association between stroke severity and degree of hypertension.

Risk factors for stroke include hypertension [15], arrhythmia [16], diabetes mellitus [17 18], hyperlipemia [19], alcohol usage [20 21], and tobacco usage . Except for tobacco and alcohol usage, most often seen in SAH, these factors were noted most often seen in CI, followed by CH, and least in SAH. Hypertension, probably plays the most important role, was found in more than 60 % of all stroke patients. A history of arrhythmia and diabetes mellitus, relatively high in CI and lower in CH, was rarely found in SAH. These data suggest a limited association between these three factors and hemorrhagic strokes. The Ministry of Health, Labour and Welfare of Japan, has estimated morbidity rates of hypertension diabetes mellitus and hyperlipemia among Japanese aged from 40 to 74 as 49.9%, 11.4%, and 17.7%. In our series, a history of hypertension exceeded this estimate in CI and CH. A history of diabetes mellitus was higher in CI and CH, but lower in SAH, suggesting that this may not be a risk factor in SAH. A history of hyperlipemia was also lower in SAH than the morbidity rate, also suggesting that this may not a risk factor in SAH.

Alcohol and tobacco usage showed a higher correlation to SAH than the other types in the surveillance conducted under the same conditions for the three subtypes of stroke. Alcohol and tobacco usage may therefore increase the risk of SAH more than CI or CH.

The proportion of heavy smokers was not different among stroke subtypes, whereas the proportion of every day drinkers was higher in hemorrhagic strokes than in ischemic stroke. Paresis developed more often in CI and CH compared to SAH. Hemorrhagic stroke caused consciousness disturbance more than ischemic stroke.

We calculated mortality based on the information up to 30 days after the stroke event, excluding those who died later. Early mortality indicates stroke events themselves, whereas long term mortality reflects aftereffects and complications. Thus, early mortality serves well to evaluate the severity of the three major stroke subtypes. Death in the first month after stroke mainly results from neurological causes such as brain edema[22], followed by complications of immobility including pneumonia [23].

Limitations

1) There may be missing data for stroke patients; for example, patients who died before arriving to hospitals and patients who went to hospital outside of the prefecture. Patients with mild symptoms might not have visited hospitals and patients with atypical symptoms might not have been diagnosed as such, and subsequently might not have been registered [5].

2) The study did not encompass the effects of therapeutic interventions, which must have affected on mortality. It is virtually impossible to adjust all the treatments in a very large population based study. Treatments should be studied in randomized controlled studies. The causes of death in the study cohort were not investigated either. Possible bias exists in the assessment of variables, such as history of habits, which largely depend on patients' self report or information from their families. The study, however, showed the overall characteristics and mortality in stroke and in major subtypes, which should shed light on the difference among the major subtypes as a whole, since the comparison was done otherwise in the same condition.
3) The outcomes assessment limited to 30 days after onset leaves the majority of patients (n=11869, 86.1%) who survived the first month out of consideration. However, early mortality evaluation within 30-day should reflect cause of death directly associated with stroke and therefore correlate severity in more direct way.

Major conclusions of the study should prevail as a report based on a very large number of patients analyzed under the same conditions.

Conclusion

We have presented population based data for the span of 11 years covering the entire Kyoto prefecture in Japan. Among stroke major subtypes, hazard ratio for death was highest in SAH, followed by CH and lowest in CI.

Acknowledgments

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Figure Legends

Kaplan-Meier survival curves of stroke patients

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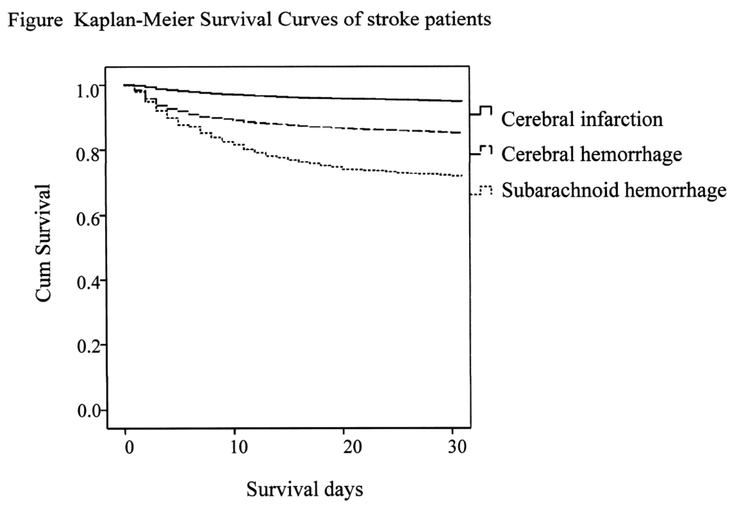

Kaplan-Meier survival curves of stroke patients
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Article Summary

Article focus

We examined the characteristics, risk factors and outcome of contemporary stroke patients based on the Kyoto Stroke Registry for recent 11 years. The study cohort has 12,774 cerebral infarction (CI), 9,232 cerebral hemorrhage (CH) and 2,540 subarachnoid hemorrhage (SAH) patients.

Key messages

About two thirds of patients have hypertension history, whereas only about one fifth have histories of arrhythmia, diabetes mellitus and hyperlipemia. The prevalence of risk factors was different among stroke subtypes.

Mortality on 30 days after the onset is 5.2% in CI, 15.2% in CH and 28.4% in SAH.

Hazard ratios for death adjusted for age, sex, histories of hypertension, arrhythmia, diabetes mellitus and hyperlipemia and uses of tobacco and alcohol, showed a significant (P<0.001) difference among CI (a reference), CH (3.66; 3.07-4.37) and SAH (8.91; 27.18-11.06).

Strengths and limitations of this study

This study provided quantitative data on fundamentals of contemporary stroke in a very large cohort in Kyoto Prefecture, Japan.

Detailed information on size and localization of stroke and on treatment and complication was not available in this population based study.

Objectives: The aim of the study is to evaluate characteristics, risk factors and outcome of recent stroke patients in Kyoto Japan.

Design: We analyzed stroke patients in the registry with regard to their characteristics, risk factors, and mortality. Cox proportional hazards regression was used to calculate adjusted hazard ratios for death.

Settings: The Kyoto prefecture of Japan has established a registry to enroll new stroke patients in cooperation with the Kyoto Medical Association and its affiliated hospitals

Participants: The registry now has data on 14.268 patients enrolled from January 1, 1999 to December 31, 2009. Of these 12,774 (89.5%), 9,232 (64.7%), 2,504 (17.5%), and 342 (2.4%) underwent CT, MRI, angiography, and scintigraphy. Excluding 480 (3.3%) unclassified patients, 13,788 (96.6%) patients formed the basis of further analyses divided then into three subtypes of stroke, cerebral infarction (CI), cerebral hemorrhage (CH), and subarachnoid hemorrhage (SAH).

Results: 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. The mean age was

73.3±11.8, 69.1±13.6 and 62.7±13.5 in the CI, CH and SAH cases, respectively. In the CI and CH cases, males were predominant, whereas in the SAH cases, females were predominant. Frequencies of risk factors were different among the subtypes. Mortality was worst in the SAH, followed by the CH, and least in the CI. Hazard ratios for death adjusted for age, sex, histories of hypertension, arrhythmia, diabetes mellitus and hyperlipemia and uses of tobacco and alcohol, showed a significant (P<0.001) difference among CI (a reference), CH (3.66; 3.07-4.37) and SAH (8.91; 27.18-11.06).

Conclusions: Characteristics, risk factors, and mortality were evaluated in a quantitative manner in a large Japanese study cohort to shed light on the present status of stroke medicine.

Introduction

Stroke, the third major cause of death, constitutes the largest cause of acquired disability in Japan [1]. According to a report of the Ministry of Health, Labor and Welfare, about 123,400 people died from stroke in 2010. About 10.3% of the total national death resulted from stroke. Sustained exposure to risk factors associated with lifestyle which patients live in play an important role in stroke incidence. Stroke is regarded as one of the diseases developed by long lasting exposure to risk factors associated with lifestyle. The incidence, as well as mortality, should be greatly affected by society, regions and times [2 3]. The updated detailed information on stroke events in each society is required. A long-term surveillance of stroke, comparing characteristics, risk factors, and mortality, based on the entire population in a prefecture as large as Kyoto, which has about 2,630,000 residents, should provide a fundamental database of stroke. Stroke consists of three major distinct subtypes, namely, cerebral infarction (CI), cerebral hemorrhage (CH), and subarachnoid hemorrhage (SAH). Although these subtypes, as disorders of the cerebral arteries, have many things in common, distinct characteristics prevail. Quantitative measurement of these differences in the same large cohort should help characterize three stroke subtypes [4]. The strength of comparing these three stroke subtypes in the same large cohort is that, by doing so, we can evaluate the relative strength of the risk factors influencing each subtype. These data also should help confirm a higher mortality rate in hemorrhagic stroke than ischemic stroke, and elucidate hazard ratios for death estimated simultaneously among major stroke subtypes, which should reflect relative severities of stroke.

The Kyoto prefecture of Japan has established a registry to enroll all new stroke patients in cooperation with the Kyoto Medical Association and its affiliated hospitals with help from the data collecting agency known as the Kyoto Stroke Registry (KSR) [5]. We studied all patients registered during the past 11 years in the prefecture of Kyoto to document characteristics, risk factors, and hazard ratios in the three major stroke subtypes.

Methods

We analyzed all stroke patients identified from January 1999 to December 2009 in the entire Kyoto prefecture and registered in the KSR run by the local government of Kyoto prefecture. 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 A. 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.

The diagnosis of stroke was confirmed by local neurologists and/or neurosurgeons based on the WHO definition [6]. Stroke patients who lived in Kyoto prefecture were registered regardless to their age and sex. Conditions such as shock, Adam-Strokes Syndrome or hypertensive encephalopathy are excluded as they are not caused directly by cerebrovascular events. TIA is also excluded as the symptoms cease within 24 hours after onset. Differential diagnoses are made by attending physicians based on CT/MRI images and other clinical examinations. Inclusion and exclusion criteria for KSR were shown in supplementary Table 1B.

We classified the patients into CI (ICD-9 code 433 and 434, ICD-10 code I63), CH

(ICD-9 code 431, ICD-10 code I61), SAH (ICD-9 code 430, ICD-10 code I60) [7 8] and others by neurological examination and the findings of CT scans, MRI scans, angiographies, and scintigraphies. In order to clarify trends over time, we also 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.

Each registry recorded age, sex, date of stroke onset, blood pressure and arrhythmia on arrival, history of hypertension, arrhythmia, diabetes mellitus and hyperlipemia, tobacco and alcohol use, type of paresis, consciousness levels and clinical outcome 30 days after the onset.

For the purpose of this entry, we used the following definitions.

1) Systolic and diastolic hypertension: blood pressure exceeding 140 and 90 mmHg,

2) Arrhythmia: any types of irregularity,

3) Diabetes mellitus: both type 1 and type 2 based on the patient medical record,

4) Hyperlipemia: serum cholesterol level of 220 mg/dl or higher and/or triglyceride exceeding 150mg/dl,
5) Smoking: divided into four categories, non smokers, and former smokers for more than a year, light smokers with 20 or less cigarettes a day and heavy smokers with more than 20 cigarettes a day.
6) Alcohol consumption: divided into three categories, non drinkers, occasional drinkers (less than three time a week), and daily drinkers (more than four times a week).
7) Paresis: any distribution including unilateral or bilateral limb or face,
8) Consciousness levels onset based on the Japan Coma Scale (JCS) [9] [10], the most widely used Japanese scale composed of the four levels,

   1; JSC 0 (alert),

   2; JCS 1-digit code (disoriented but awake),

   3; JCS 2-digit code (arousable with stimulation),

   4; JSC 3-digit code (unarousable)

Statistical Analysis

Statistical analyses used include Fisher exact tests for frequencies of listed characteristics among the three stroke types, Student-t test for such numerical variables as age and systolic- and diastolic-blood pressures, a log-rank test for Kaplan-Meier curves of estimated survival. The Mantel-Haenszel method and a logistic regression model were used to estimate univariate and multivariate odds ratios. Cox proportional hazards regression was used to calculate age-, sex-, systolic and diastolic blood pressure-, and consciousness levels-adjusted hazard ratios and their 95% confidence intervals for the risk of death. Analyses were performed using SPSS ver.19 and statistical significance was set at $p<0.05$. All reported p values are 2-sided.

Ethics Statement

This research was performed in accordance with the ethical principles for medical research involving human subjects outlined in the Declaration of Helsinki. This research was approved by the Board of Directors, the Kyoto Medical Association, the Department of Health and Welfare, Kyoto Prefecture and Ethics Committee of the National Hospital Organization, Minami Kyoto Hospital. Since all identifying personal information was stripped from the secondary files before analysis, the boards waived the requirement for written informed consent from the patients involved.

Results

We reviewed 14,268 stroke patients newly identified in Kyoto prefecture from January 1999 to December 2009. Of these 12,774 (89.5%), 9,232 (64.7%), 2,504 (17.5%), and 342 (2.4%) underwent CT, MRI scan, angiography, and scintigraphy for blood flow. Excluding 480 (3.3%) unclassified patients, 13,788 (96.6%) patients formed the basis of further analyses dividing then into three subtypes of stroke, CI, CH, and SAH categories.

The study cohort had 13,788 patients divided into 9,011 (65.4%) CI, 3,549 (25.7%) CH and 1,197 (8.7%) SAH cases. 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. Table 1 summarizes the characteristics, risk factors, symptoms, and mortality rate.

Table 1 Characteristics of Stroke Patients (n=13,788)

	Overall	Cerebral infarction n=9,011	Cerebral hemorrhage n=3,549	Subarachnoid hemorrhage n=1,197

		(65.4%)	(25.7%)	(8.7%)
Age (mean± SD)	71.3 (12.9)	73.3 (11.8)*1*3	69.1 (13.6) *1*2	62.7 (13.5) *2*3
Sex, % female (n=female: male)	45.2 (6,233:7,555)	42.3*1*3 (3,815:5,196)	45.9*1*2 (1,630:1,919)	64.6*2*3 (773:424)
Systolic blood pressure (mean± SD)**, mmHg**	161.3 (35.5)	157.5 (28.3)*1	172.1 (34.8) *1*2	157.9 (37.0)*2
Diastolic blood pressure (mean± SD)**, mmHg**	87.6 (18.63)	85.6 (17.0) *1*3	93.1 (21.1) *1*2	86.8 (21.8) *2*3
Hypertension history, % (n=with: without)	62.6 (8,005:4,780)	62.0*1*3 (5,285:3,242)	68.5*1*2 (2,183:1,006)	49.9*2*3 (520:522)
Arrhythmia, % (n=with:	14.5 (1,932:11,352)	18.9*1*3 (1,647:7,064)	5.9*1*2 (200:3,209)	7.2*2*3 (82:1,052)

without)				
Arrhythmia history, % (n=with: without)	18.5(2,357:10,415)	24.3^{*1*3} (2,060:6,432)	7.5^{*1*2} (240:2,971)	5.3^{*2*3} (55:985)
Diabetes mellitus history, % (n=with: without)	20.9 (2,689:10,198)	24.8^{*1*3} (2,138:6,475)	14.8^{*1*2} (474:2,738)	6.9^{*2*3} (71:963)
Hyperlipemia history, % (n=with: without)	19.2 (2,419:10,198)	23.1^{*1*3} (1,951:6,503)	11.9^{*1*2} (371:2,755)	9.2^{*2*3} (93:918)
Tobacco use, % (n=with: without)	32.4 (3,665:7,642)	32.6^{*1*3} (2,455:5,077)	30.1^{*1*2} (843:1,956)	37.1^{*2*3} (354:599)
Non smoker, %	67.6 (7,642)	67.4 (5,077)^{*3}	69.9 (1,956)^{*2}	62.9 (599)^{*2*3}

(n)				
Former smoker, % (n)	5.4 (615)	5.8 (435) *3	5.7 (159) *2	2.1 (20) *2*3
Light smoker, % (n)	17.0 (1,918)	17.0 (1,281) *1*3	14.6 (409) *1*2	23.3 (222) *2*3
Heavy smoker, % (n)	10.0 (1,132)	9.8 (739)	9.8 (275)	11.8 (112)
Alcohol use, % (n=with: without)	38.0 (4,202/6,851)	36.3*1*3 (2,654:4,655)	40.5*1*2 (1,124:1,650)	43.6*2*3 (412:533)
Non drinker, % (n)	62.0 (6,851)	63.7 (4,655) *1*3	59.5 (1,650) *1	56.4 (533) *3
Occasional drinker, % (n)	15.3 (1,692)	15.5 (1,131) *1*3	13.5 (374) *1*2	18.9 (179) *2*3
Every day drinker, % (n)	22.7 (2,510)	20.8 (1,523) *1*3	27.0 (750) *1	24.7 (233) *3
Paresis, % (n=with:	73.3 (9,670:3,525)	76.8*1*3 (6,750:2,041)	78.5*1*2 (2,624:717)	26.8*2*3 (277:756)

without)				
Consciousness disturbance, % (n=with: without)	43.5 (5,914: 7,676)	31.8[*1*3] (2,815: 8,863)	65.7[*1] (2,305: 1,201)	65.1[*3] (775: 415)
JCS 0, % (n)	55.7 (7,676)	67.1[*1*3] (6,048)	33.8[*1*2] (1,201)	35.6[*2*3] (415)
JSC 1-digit code, % (n)	19.0 (2,619)	16.7[*1] (1,508)	26.0[*1*2] (921)	15.9[*2] (185)
JSC 2-digit code, % (n)	11.6 (1,602)	8.6[*1*3] (774)	17.5[*1] (622)	16.7[*3] (200)
JSC 3-digit code, % (n)	10.9 (1,509)	4.7[*1*3] (421)	20.2[*1*2] (716)	30.5[*2*3] (365)
JSC undetermined, % (n)	1.3 (184)	1.2[*3] (112)	1.3[*2] (46)	2.1[*2*3] (25)
Delay time (mean± SD)	3.91±4.82	4.20±5.21	3.50±4.13	3.13±3.77
CT, % (n)	89.7 (12,365)	85.1 (7,668)	98.2 (3,485) [*1]	98.8 (1,183) [*3]

		*1*3		
MRI, % (n)	64.5 (8,891)	79.8 (7,148) *1*3	40.3 (1,429) *1*2	25.1 (300) [*1*3]
Surgery % **(n=with: without)**	16.0 (2,171:11,399)	4.2 (374:8,495) *1*3	26.1 (915:2,588) *1*2	74.6 (871:297) *1*3
Mortality, % **(n=dead: alive)**	9.8 (1,344:12,391)	5.2[*1*3] (467:8,981)	15.2[*1*2] (536:2,997)	28.4[*2*3] (338:853)

When the numbers entered in the table above are significantly different between different types of strokes, they are marked as follows:

*1: significant difference between cerebral infarction and cerebral hemorrhage;

*2: sig. difference between cerebral hemorrhage and subarachnoid hemorrhage;

*3: sig. difference between subarachnoid hemorrhage and cerebral infarction;

SD = Standard Deviation

Temporal trends of characteristics of stroke patients, comparing Group-A and Group-B, are summarized in Table 2 and hazard ratios for death, comparing the two groups are summarized in Table 3. Characteristics of stroke patients in Group-A and Group-B are summarized in supplementary Table 3.

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

	Group-A	Group-B	P	Difference/OR
Age (mean± SD)	70.5±12.7	72.3±13.0	<0.001	-1.85 (-2.28~-1.41) *[1]
Sex, % female (n=female: male)	44.8 (3,531:4,349)	45.7 (2,702:3,206)	0.505	1.02 (0.96~1.09)*[2]
Systolic blood pressure (mean± SD), mmHg	161.5±31.6	161±31.5	0.449	0.41 (-0.66~1.49)*[1]
Diastolic blood pressure (mean± SD), mmHg	87.3±18.7	88.0±19.0	0.036	-0.69 (-1.33~-0.05)*[1]

Hypertension history, % (n=with: without)	60.2 (4,379:2,900)	65.9 (3,626:1,880)	<0.001	1.19~1.38*[2]
Arrhythmia, % (n=with: without)	14.9 (1,132:6,446)	14.0 (800:4,906)	0.079	0.92 (0.83~1.01) *[2]
Arrhythmia history, % (n=with: without)	19.0 (74.7)	17.7 (974:4,531)	0.059	0.92 (0.84~1.00) *[2]
Diabetes mellitus history, % (n=with: without)	20.5 (1,500:5,827)	21.4 (1,189:4,371)	0.327	1.04 (0.96~1.14) *[2]
Hyperlipemia history, %	17.5 (1,250:5,910)	21.4 (1,169:4,288)	<0.001	1.27 (1.16~1.39) *[2]

(n=with: without)				
Tobacco use, % (n=with: without)	33.6 (2,152:4,259)	30.9 (1,513:3,383)	0.001	0.88 (0.81~0.95) *[2]
Alcohol use, % (n=with: without)	39.5 (2,478:3,797)	36.1 (1,724)	0.002	0.89 (0.82~0.96) *[2]
Paresis, % (n=with: without)	73.7 (5,581:1,987)	72.7 (4,087:1,534)	0.116	0.94 (0.87~1.02)*[2]
Consciousness disturbance, % (n=with: without)	42.4 (3,290:4,463)	45.0 (2,624:3,207)	0.055	1.07 (1.00~1.14) *[2]
Delay time (mean± SD)	4.15±5.03	3.60±4.54	<0.001	-0.55 (-0.73~-0.38)*[1]
CT, % (n)	92.4 (7,285)	86.1 (5,080)	<0.001	0.51

				(0.45~0.57) *[2]
MRI, % (n)	59.4 (4,682)	71.3 (4,209)	<0.001	1.68
				(1.56~1.80) *[2]
Surgery %	17.6	13.9	<0.001	0.76
(n=with:	(1,356:6,339)	(815:5,060)		(0.69~0.83) *[2]
without)				
Mortality, %	9.5 (745:7,097)	10.2	0.771	1.02
(n=dead: alive)		(599:5,294)		(0.91~1.14) *[2]

*[1]Mean difference (95% confidence interval of the difference)

*[2]Mantel-Haenszel common odds ratio (95% confidence interval)

OR= Odds Ratio

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

	Hazard Ratio (Group-B/Group-A)	**95% Confidence Interval**		**p**
		Lower	Upper	
Over all	1.33	1.15	1.55	<0.001

Cerebral infarction	1.33	1.04	1.70	0.021
Cerebral hemorrhage	1.06	0.83	1.34	0.650
Subarachnoid hemorrhage	1.25	0.92	1.70	0.147

Adjusted for age, sex, histories of hypertension, arrhythmia, diabetes mellitus and hyperlipemia, and uses of tobacco and alcohol

Odds ratios for the prevalence of risk factors among stroke subtypes, adjusted for age and sex, were calculated using a logistic regression model and are summarized in Table 3.

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

	Odds Ratio	**95% Confidence Interval**		**p**
		Lower	Upper	
History of hypertension				
Cerebral infarction (CI)	Reference			
Cerebral hemorrhage (CH)	1.36	1.25	1.49	<0.001
Subarachnoid hemorrhage	0.65	0.57	0.74	<0.001

(SAH)				
History of arrhythmia				
CI	Reference			
CH	0.28	0.24	0.33	<0.001
SAH	0.26	0.19	0.34	<0.001
History of diabetes mellitus				
CI	Reference			
CH	0.49	0.44	0.55	<0.001
SAH	0.20	0.16	0.26	<0.001
History of hyperlipemia				
CI	Reference			
CH	0.40	0.35	0.45	<0.001
SAH	0.24	0.19	0.30	<0.001

Table 1 also shows historical account on hypertension in 12,785 (92.7%), arrhythmia in 12,772 (92.6%), diabetes mellitus in 12,887 (93.5%), hyperlipemia in 12,617 (91.5%), tobacco usage in 11,307 (82.0%), alcohol usage in 11,053 (80.2%), and paresis in

13,195 (96.7%). We were able to classify 13,406 (97.2%) patients into four consciousness levels, excluding 184 (1.3%) patients with uncategorized stroke and 580 (4.2%) patients with no reliable information on conscious levels. Calculation of the mean delay time excluded 4964 (36.0%) patients of unknown onset. Patients received primary medical care within 3 hours of CI in 54.3%, of CH in 68.5% in CH, and of SAH in 76.4%.

Of 13,788 patients, 13,735 (99.6%) had a confirmed record of survival or death 30 days after stroke onset. A total of 1,344 (9.8%) patients died within this time period.

Figure 1 shows Kaplan-Meier Survival curves, comparing stroke subtypes, showing a significant difference ($p<0.001$) between any two subtypes based on Log-rank tests.

Compared to CI, CH and SAH hazard ratios for fatality of 3.66 (3.07-4.37), and 8.91 (7.18-11.06) $p<0.001$), when adjusted for age, sex, histories of hypertension, arrhythmia, diabetes mellitus and hyperlipemia and uses of tobacco and alcohol, showing significant differences ($p<0.001$) (Table 5).

Table 5 Hazard ratios for death, comparing stroke subtypes

	HR	**95% Confidence Interval**	**p**

		Lower	Upper	
Cerebral infarction	Reference			
Cerebral hemorrhage	3.66	3.07	4.37	<0.001
Subarachnoid hemorrhage	8.91	7.18	11.06	<0.001

Adjusted for age, sex, histories of hypertension, arrhythmia, diabetes mellitus and hyperlipemia, and uses of tobacco and alcohol

Hazard ratios for death, comparing stroke subtypes, in Group-A and Group-B are summarized in Supplementary Table 4 A and B.

Discussion

The study summarized the stroke registry covering entire prefecture for 11 years. Such data set depends on the society and the times. Hospitals affiliated to the Kyoto Medical Association registered new stroke patients based on the inclusion and exclusion criteria in accordance with the Kyoto municipal ordinance, avoiding area or hospitals preferences.

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. 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) [11-14], Iwate Stroke Registry (ISR) [15], Tochigi Stroke Registry (TSR) [16 17], Miyazaki Stroke Registry (MSR) [18] and KSR. 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. We summarized incidence information based on KSR in supplementary Tables 2 A, B and C. 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 and I. ISR says that their reports will be ready [19]. 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 on more restricted area should be more suitable to clarify stroke incidence in a community. The incidence rates of stroke reported from the Takashima Stroke Registry [20-22] and the Hisayama Study [23-25] 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 [26]. 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 [23]. Among subtypes of stroke, they are 357:77, 130:21 and 42:13 (men: women) in cerebral infarction, cerebral hemorrhage and subarachnoid hemorrhage, respectively [23].

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 [11]. Some prefectural stroke registries reported mortality rates. In TSR, they were 10%, 16% and 29% in CI, CH and SAH, respectively [16]. 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 [13 14], 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. Strengths of stroke registry in Japan include a high availability of CT and MRI. Japan has the most MRI units (40 U per million population) and CT scanners (93 U per million populations) among the developed countries [27]. 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.

In agree with previous reports, CI showed higher incidence followed by CH and SAH, which constitutes a fourth of hemorrhagic strokes [24]. The result adds the information that SAH constitutes about a fourth of hemorrhagic strokes. Age distribution also confirm the result of previous reports, the oldest mean age in CH and youngest in SAH [28]. The elderly patients showed a greater difference in proportion in stroke subtypes. For example, in patients who were 71 years or older, the proportions were 73.1% (n=5616), 22.3% (n=1709), and 4.6% (n=353), as compared to younger group who showed 55.8% (n=3,395), 30.3% (n=1,840) and 13.9% (n=844).

Most of the other characteristics also showed significant difference among three stroke subtypes. The overall registry had more male patients than female, except almost two-thirds of SAH cases were female. The initial medical examination revealed higher systolic and diastolic blood pressures in CH than in CI, possibly reflecting intracranial mass effect on brain edema [29 30].

Patients with disturbed consciousness had a higher ($p<0.001$) systolic/diastolic blood pressure (mean ± SD: 164.0 ± 35.2/88.6 ± 20.9) than the remainder (159.3 ± 28.2/87.0 ± 17.1), implying possible association between stroke severity and degree of hypertension.

Risk factors for stroke include hypertension [31], arrhythmia [32], diabetes mellitus [33 34], hyperlipemia [35], alcohol use [36 37], and tobacco use . Except for tobacco and alcohol uses, these factors were noted most often in CI, followed by CH, and least in SAH. Hypertension, probably plays the most important role, was found in more than 60 % of all stroke patients. A history of arrhythmia and diabetes mellitus, relatively high in CI and lower in CH, was rarely found in SAH. These data suggest a limited association between these three factors and hemorrhagic strokes. The Ministry of Health, Labour and Welfare of Japan, has estimated morbidity rates of hypertension, diabetes mellitus and hyperlipemia among Japanese aged from 40 to 74 as 49.9%, 11.4% and 17.7%, respectively. In our series, a history of hypertension exceeded this estimate in CI and CH. A history of diabetes mellitus was higher in CI and CH, but lower in SAH, suggesting that this may not be a risk factor in SAH. A history of hyperlipemia was also lower in SAH than the morbidity rate, also suggesting that this may not a risk factor in SAH. Regarding the risk factor of stroke, the data may not add sufficient information on the effect of risk factors on stroke occurrence. The registry data are not meant to do that type of study. The registry data, however, are appropriate to present the prevalence of different risk factors among the stroke patients. The higher prevalence of a factor in a certain group may support the higher association between the factor and the group. This study added information on the prevalence of risk factors among stroke patients and clarified the differences among stroke subtypes. We also added multivariate analyses. Using a logistic regression model, we estimated odds ratios and 95% confidence intervals for the prevalence of these risk factors comparing each stroke subtype after adjusted for age and sex.

Alcohol and tobacco use showed a higher correlation to SAH than the other types in the surveillance conducted under the same conditions for the three subtypes of stroke. Alcohol and tobacco usage may therefore increase the risk of SAH more than CI or CH. The proportion of heavy smokers was not different among stroke subtypes, whereas the proportion of every day drinkers was higher in hemorrhagic strokes than in ischemic stroke. Paresis developed more often in CI and CH compared to SAH. Hemorrhagic stroke caused consciousness disturbance more than ischemic stroke.

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 adjusted for age, sex, histories of risk factors and uses of tobacco and alcohol.

We calculated mortality based on the information up to 30 days after the stroke onset, excluding those who died later. Early mortality indicates stroke events themselves, whereas long term mortality reflects aftereffects and complications. Thus, early mortality serves well to evaluate the severity of the three major stroke subtypes. Death in the first month after stroke mainly results from neurological causes such as brain edema[38], followed by complications of immobility including pneumonia [39]. The mortality rate of ischemic stroke and risk characteristics must vary by its subtypes, such as embolic stroke and lacunar stroke. However, sufficient information to classify ischemic stroke into more detailed categories was not available in this study.

Limitations

Firstly, there may be missing data for stroke patients; for example, patients who died before arriving to hospitals and patients who went to hospital outside of the prefecture. Patients with mild symptoms might not have visited hospitals and patients with atypical symptoms might not have been diagnosed as such, and subsequently might not have been registered [5].

Secondary, the study did not encompass the effects of therapeutic interventions, which must have affected on mortality. It is virtually impossible to adjust all the treatments in a very large population based study. Treatments should be studied in randomized controlled studies. The causes of death in the study cohort were not investigated either. Possible bias exists in the assessment of variables, such as history of habits, which largely depend on patients' self report or information from their families. The study, however, showed the overall characteristics and mortality in stroke and in major subtypes, which should shed light on the difference among the major subtypes as a whole, since the comparison was done otherwise in the same condition.

Lastly, the outcomes assessment limited to 30 days after onset leaves the majority of patients (n=11,869, 86.1%) who survived the first month out of consideration. However, early mortality evaluation within 30-day should reflect cause of death directly associated with stroke and therefore correlate severity in more direct way.

Major conclusions of the study should prevail as a report based on a very large number of patients analyzed under the same conditions.

Conclusion

We have presented population based data for the span of 11 years covering the entire Kyoto prefecture in Japan. Among stroke major subtypes, hazard ratio for death was highest in SAH, followed by CH and lowest in CI.

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Figure Legends

Kaplan-Meier survival curves of stroke patients

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Characteristics, risk factors and mortality of stroke patients in Kyoto, Japan

Short title: Characteristics, risk factors and mortality of Stroke

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Article Summary

Article focus

We examined the characteristics, risk factors and outcome of contemporary stroke patients based on the Kyoto Stroke Registry for recent 11 years. The study cohort has 12,774 cerebral infarction (CI), 9,232 cerebral hemorrhage (CH) and 2,540 subarachnoid hemorrhage (SAH) patients.

Key messages

About two thirds of patients have hypertension history, whereas only about one fifth have histories of arrhythmia, diabetes mellitus and hyperlipemia. The prevalence of risk factors was different among stroke subtypes.

Mortality on 30 days after the onset is 5.2% in CI, 15.2% in CH and 28.4% in SAH.

Hazard ratios for death adjusted for age, sex, histories of hypertension, arrhythmia, diabetes mellitus and hyperlipemia and uses of tobacco and alcohol, showed a significant (P<0.001) difference among CI (a reference), CH (3.66; 3.07-4.37) and SAH (8.91; 27.18-11.06).

Strengths and limitations of this study

This study provided quantitative data on fundamentals of contemporary stroke in a very large cohort in Kyoto Prefecture, Japan.

Detailed information on size and localization of stroke and on treatment and complication was not available in this population based study.

Objectives: The aim of the study is to evaluate characteristics, risk factors and outcome of recent stroke patients in Kyoto Japan.

Design: We analyzed stroke patients in the registry with regard to their characteristics, risk factors, and mortality. Cox proportional hazards regression was used to calculate adjusted hazard ratios for death.

Settings: The Kyoto prefecture of Japan has established a registry to enroll new stroke patients in cooperation with the Kyoto Medical Association and its affiliated hospitals

Participants: The registry now has data on 14.268 patients enrolled from January 1, 1999 to December 31, 2009. Of these 12,774 (89.5%), 9,232 (64.7%), 2,504 (17.5%), and 342 (2.4%) underwent CT, MRI, angiography, and scintigraphy. Excluding 480 (3.3%) unclassified patients, 13,788 (96.6%) patients formed the basis of further analyses divided then into three subtypes of stroke, cerebral infarction (CI), cerebral hemorrhage (CH), and subarachnoid hemorrhage (SAH).

Results: 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. The mean age was

73.3±11.8, 69.1±13.6 and 62.7±13.5 in the CI, CH and SAH cases, respectively. In the CI and CH cases, males were predominant, whereas in the SAH cases, females were predominant. Frequencies of risk factors were different among the subtypes. Mortality was worst in the SAH, followed by the CH, and least in the CI. Hazard ratios for death adjusted for age, sex, histories of hypertension, arrhythmia, diabetes mellitus and hyperlipemia and uses of tobacco and alcohol, showed a significant ($P<0.001$) difference among CI (a reference), CH (3.66; 3.07-4.37) and SAH (8.91; 27.18-11.06).

Conclusions: Characteristics, risk factors, and mortality were evaluated in a quantitative manner in a large Japanese study cohort to shed light on the present status of stroke medicine.

Introduction

Stroke, the third major cause of death, constitutes the largest cause of acquired disability in Japan [1]. According to a report of the Ministry of Health, Labor and Welfare, about 123,400 people died from stroke in 2010. About 10.3% of the total national death resulted from stroke. Sustained exposure to risk factors associated with lifestyle which patients live in play an important role in stroke incidence. Stroke is regarded as one of the diseases developed by long lasting exposure to risk factors associated with lifestyle. The incidence, as well as mortality, should be greatly affected by society, regions and times [2 3]. The updated detailed information on stroke events in each society is required. A long-term surveillance of stroke, comparing characteristics, risk factors, and mortality, based on the entire population in a prefecture as large as Kyoto, which has about 2,630,000 residents, should provide a fundamental database of stroke. Stroke consists of three major distinct subtypes, namely, cerebral infarction (CI), cerebral hemorrhage (CH), and subarachnoid hemorrhage (SAH). Although these subtypes, as disorders of the cerebral arteries, have many things in common, distinct characteristics prevail. Quantitative measurement of these differences in the same large cohort should help characterize three stroke subtypes [4]. The strength of comparing these three stroke subtypes in the same large cohort is that, by doing so, we can evaluate the relative strength of the risk factors influencing each subtype. These data also should help confirm a higher mortality rate in hemorrhagic stroke than ischemic stroke, and elucidate hazard ratios for death estimated simultaneously among major stroke subtypes, which should reflect relative severities of stroke.

The Kyoto prefecture of Japan has established a registry to enroll all new stroke patients in cooperation with the Kyoto Medical Association and its affiliated hospitals with help from the data collecting agency known as the Kyoto Stroke Registry (KSR) [5]. We studied all patients registered during the past 11 years in the prefecture of Kyoto to document characteristics, risk factors, and hazard ratios in the three major stroke subtypes.

Methods

We analyzed all stroke patients identified from January 1999 to December 2009 in the entire Kyoto prefecture and registered in the KSR run by the local government of Kyoto prefecture. **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 A. 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.

The diagnosis of stroke was confirmed by local neurologists and/or neurosurgeons based on the WHO definition [6]. **Stroke patients who lived in Kyoto prefecture were registered regardless to their age and sex. Conditions such as shock, Adam-Strokes Syndrome or hypertensive encephalopathy are excluded as they are not caused directly by cerebrovascular events. TIA is also excluded as the symptoms cease within 24 hours after onset. Differential diagnoses are made by attending physicians based on CT/MRI images and other clinical examinations. Inclusion and exclusion criteria for KSR were shown in supplementary Table 1B.**

We classified the patients into CI (ICD-9 code 433 and 434, ICD-10 code I63), CH

(ICD-9 code 431, ICD-10 code I61), SAH (ICD-9 code 430, ICD-10 code I60) [7 8] and others by neurological examination and the findings of CT scans, MRI scans, angiographies, and scintigraphies. **In order to clarify trends over time, we also 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.**

Each registry recorded age, sex, date of stroke onset, blood pressure and arrhythmia on arrival, history of hypertension, arrhythmia, diabetes mellitus and hyperlipemia, tobacco and alcohol use, type of paresis, consciousness levels and clinical outcome 30 days after the onset.

For the purpose of this entry, we used the following definitions.

1) Systolic and diastolic hypertension: blood pressure exceeding 140 and 90 mmHg,

2) Arrhythmia: any types of irregularity,

3) Diabetes mellitus: both type 1 and type 2 based on the patient medical record,

4) Hyperlipemia: serum cholesterol level of 220 mg/dl or higher and/or triglyceride exceeding 150mg/dl,

5) Smoking: divided into four categories, non smokers, and former smokers for more than a year, light smokers with 20 or less cigarettes a day and heavy smokers with more than 20 cigarettes a day.

6) Alcohol consumption: divided into three categories, non drinkers, occasional drinkers (less than three time a week), and daily drinkers (more than four times a week).

7) Paresis: any distribution including unilateral or bilateral limb or face,

8) Consciousness levels onset based on the Japan Coma Scale (JCS) [9] [10], the most widely used Japanese scale composed of the four levels,

   1; JSC 0 (alert),

   2; JCS 1-digit code (disoriented but awake),

   3; JCS 2-digit code (arousable with stimulation),

   4; JSC 3-digit code (unarousable)

Statistical Analysis

Statistical analyses used include Fisher exact tests for frequencies of listed characteristics among the three stroke types, Student-t test for such numerical variables as age and systolic- and diastolic-blood pressures, a log-rank test for Kaplan-Meier curves of estimated survival. The Mantel-Haenszel method and a logistic regression model were used to estimate univariate and multivariate odds ratios. Cox proportional hazards regression was used to calculate age-, sex-, systolic and diastolic blood pressure-, and consciousness levels-adjusted hazard ratios and their 95% confidence intervals for the risk of death. Analyses were performed using SPSS ver.19 and statistical significance was set at $p<0.05$. All reported p values are 2-sided.

Ethics Statement

This research was performed in accordance with the ethical principles for medical research involving human subjects outlined in the Declaration of Helsinki. This research was approved by the Board of Directors, the Kyoto Medical Association, the Department of Health and Welfare, Kyoto Prefecture and Ethics Committee of the National Hospital Organization, Minami Kyoto Hospital. Since all identifying personal information was stripped from the secondary files before analysis, the boards waived the requirement for written informed consent from the patients involved.

Results

We reviewed 14,268 stroke patients newly identified in Kyoto prefecture from January 1999 to December 2009. Of these 12,774 (89.5%), 9,232 (64.7%), 2,504 (17.5%), and 342 (2.4%) underwent CT, MRI scan, angiography, and scintigraphy for blood flow. Excluding 480 (3.3%) unclassified patients, 13,788 (96.6%) patients formed the basis of further analyses dividing then into three subtypes of stroke, CI, CH, and SAH categories.

The study cohort had 13,788 patients divided into 9,011 (65.4%) CI, 3,549 (25.7%) CH and 1,197 (8.7%) SAH cases. 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. Table 1 summarizes the characteristics, risk factors, symptoms, and mortality rate.

Table 1 Characteristics of Stroke Patients (n=13,788)

	Overall	Cerebral infarction n=9,011	Cerebral hemorrhage n=3,549	Subarachnoid hemorrhage n=1,197

		(65.4%)	(25.7%)	(8.7%)
Age (mean± SD)	71.3 (12.9)	73.3 (11.8)*1*3	69.1 (13.6) *1*2	62.7 (13.5) *2*3
Sex, % female (n=female: male)	45.2 (6,233:7,555)	42.3*1*3 (3,815:5,196)	45.9*1*2 (1,630:1,919)	64.6*2*3 (773:424)
Systolic blood pressure (mean± SD)**, mmHg**	161.3 (35.5)	157.5 (28.3)*1	172.1 (34.8) *1*2	157.9 (37.0)*2
Diastolic blood pressure (mean± SD)**, mmHg**	87.6 (18.63)	85.6 (17.0) *1*3	93.1 (21.1) *1*2	86.8 (21.8) *2*3
Hypertension history, % (n=with: without)	62.6 (8,005:4,780)	62.0*1*3 (5,285:3,242)	68.5*1*2 (2,183:1,006)	49.9*2*3 (520:522)
Arrhythmia, % (n=with:	14.5 (1,932:11,352)	18.9*1*3 (1,647:7,064)	5.9*1*2 (200:3,209)	7.2*2*3 (82:1,052)

without)				
Arrhythmia history, % (n=with: without)	18.5(2,357:10,415)	24.3^{*1*3} (2,060:6,432)	7.5^{*1*2} (240:2,971)	5.3^{*2*3} (55:985)
Diabetes mellitus history, % (n=with: without)	20.9 (2,689:10,198)	24.8^{*1*3} (2,138:6,475)	14.8^{*1*2} (474:2,738)	6.9^{*2*3} (71:963)
Hyperlipemia history, % (n=with: without)	19.2 (2,419:10,198)	23.1^{*1*3} (1,951:6,503)	11.9^{*1*2} (371:2,755)	9.2^{*2*3} (93:918)
Tobacco use, % (n=with: without)	32.4 (3,665:7,642)	32.6^{*1*3} (2,455:5,077)	30.1^{*1*2} (843:1,956)	37.1^{*2*3} (354:599)
Non smoker, %	67.6 (7,642)	67.4 (5,077) ^{*3}	69.9 (1,956) ^{*2}	62.9 (599) ^{*2*3}

(n)				
Former	5.4 (615)	5.8 (435) ^{*3}	5.7 (159) ^{*2}	2.1 (20) ^{*2*3}
smoker, % (n)				
Light smoker, %	17.0 (1,918)	17.0 (1,281) ^{*1*3}	14.6 (409) ^{*1*2}	23.3 (222) ^{*2*3}
(n)				
Heavy smoker, %	10.0 (1,132)	9.8 (739)	9.8 (275)	11.8 (112)
(n)				
Alcohol use, %	38.0 (4,202/6,851)	36.3^{*1*3}	40.5^{*1*2}	43.6^{*2*3}
(n=with:		(2,654:4,655)	(1,124:1,650)	(412:533)
without)				
Non drinker, %	62.0 (6,851)	63.7 (4,655) ^{*1*3}	59.5 (1,650) ^{*1}	56.4 (533) ^{*3}
(n)				
Occasional	15.3 (1,692)	15.5 (1,131) ^{*1*3}	13.5 (374) ^{*1*2}	18.9 (179) ^{*2*3}
drinker, % (n)				
Every day	22.7 (2,510)	20.8 (1,523) ^{*1*3}	27.0 (750) ^{*1}	24.7 (233) ^{*3}
drinker, % (n)				
Paresis, %	73.3 (9,670:3,525)	76.8^{*1*3}	78.5^{*1*2}	26.8^{*2*3}
(n=with:		(6,750:2,041)	(2,624:717)	(277:756)

without)				
Consciousness disturbance, % (n=with: without)	43.5 (5,914: 7,676)	31.8[*1*3] (2,815: 8,863)	65.7[*1] (2,305: 1,201)	65.1[*3] (775: 415)
JCS 0, % (n)	55.7 (7,676)	67.1[*1*3] (6,048)	33.8[*1*2] (1,201)	35.6[*2*3] (415)
JSC 1-digit code, % (n)	19.0 (2,619)	16.7[*1] (1,508)	26.0[*1*2] (921)	15.9[*2] (185)
JSC 2-digit code, % (n)	11.6 (1,602)	8.6[*1*3] (774)	17.5[*1] (622)	16.7[*3] (200)
JSC 3-digit code, % (n)	10.9 (1,509)	4.7[*1*3] (421)	20.2[*1*2] (716)	30.5[*2*3] (365)
JSC undetermined, % (n)	1.3 (184)	1.2[*3] (112)	1.3[*2] (46)	2.1[*2*3] (25)
Delay time (mean± SD**)**	3.91±4.82	4.20±5.21	3.50±4.13	3.13±3.77
CT, % (n)	89.7 (12,365)	85.1 (7,668)	98.2 (3,485) [*1]	98.8 (1,183) [*3]

		*1*3		
MRI, % (n)	64.5 (8,891)	79.8 (7,148)	40.3 (1,429)	25.1 (300) *1*3
		*1*3	*1*2	
Surgery %	16.0 (2,171:11,399)	4.2	26.1	74.6 (871:297)
(n=with: without)		(374:8,495)	(915:2,588)	*1*3
		*1*3	*1*2	
Mortality, %	9.8 (1,344:12,391)	5.2 *1*3	15.2 *1*2	28.4 *2*3
(n=dead: alive)		(467:8,981)	(536:2,997)	(338:853)

When the numbers entered in the table above are significantly different between different types of strokes, they are marked as follows:

*1: significant difference between cerebral infarction and cerebral hemorrhage;

*2: sig. difference between cerebral hemorrhage and subarachnoid hemorrhage;

*3: sig. difference between subarachnoid hemorrhage and cerebral infarction;

SD = Standard Deviation

Temporal trends of characteristics of stroke patients, comparing Group-A and Group-B, are summarized in Table 2 and hazard ratios for death, comparing the

two groups are summarized in Table 3. Characteristics of stroke patients in Group-A and Group-B are summarized in supplementary Table 3.

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

	Group-A	Group-B	P	Difference/OR
Age (mean± SD)	70.5±12.7	72.3±13.0	<0.001	-1.85 (-2.28~-1.41) *[1]
Sex, % female (n=female: male)	44.8 (3,531:4,349)	45.7 (2,702:3,206)	0.505	1.02 (0.96~1.09)*[2]
Systolic blood pressure (mean± SD), mmHg	161.5±31.6	161±31.5	0.449	0.41 (-0.66~1.49)*[1]
Diastolic blood pressure (mean± SD), mmHg	87.3±18.7	88.0±19.0	0.036	-0.69 (-1.33~-0.05)*[1]

Hypertension history, % (n=with: without)	**60.2 (4,379:2,900)**	**65.9 (3,626:1,880)**	**<0.001**	**1.19~1.38*[2]**
Arrhythmia, % (n=with: without)	**14.9 (1,132:6,446)**	**14.0 (800:4,906)**	**0.079**	**0.92 (0.83~1.01) *[2]**
Arrhythmia history, % (n=with: without)	**19.0 (74.7)**	**17.7 (974:4,531)**	**0.059**	**0.92 (0.84~1.00) *[2]**
Diabetes mellitus history, % (n=with: without)	**20.5 (1,500:5,827)**	**21.4 (1,189:4,371)**	**0.327**	**1.04 (0.96~1.14) *[2]**
Hyperlipemia history, %	**17.5 (1,250:5,910)**	**21.4 (1,169:4,288)**	**<0.001**	**1.27 (1.16~1.39) *[2]**

(n=with: without)				
Tobacco use, % (n=with: without)	33.6 (2,152:4,259)	30.9 (1,513:3,383)	0.001	0.88 (0.81~0.95) *[2]
Alcohol use, % (n=with: without)	39.5 (2,478:3,797)	36.1 (1,724)	0.002	0.89 (0.82~0.96) *[2]
Paresis, % (n=with: without)	73.7 (5,581:1,987)	72.7 (4,087:1,534)	0.116	0.94 (0.87~1.02)*[2]
Consciousness disturbance, % (n=with: without)	42.4 (3,290:4,463)	45.0 (2,624:3,207)	0.055	1.07 (1.00~1.14) *[2]
Delay time (mean± SD)	4.15±5.03	3.60±4.54	<0.001	-0.55 (-0.73~-0.38)*[1]
CT, % (n)	92.4 (7,285)	86.1 (5,080)	<0.001	0.51

				(0.45~0.57) *[2]
MRI, % (n)	59.4 (4,682)	71.3 (4,209)	<0.001	1.68 (1.56~1.80) *[2]
Surgery % (n=with: without)	17.6 (1,356:6,339)	13.9 (815:5,060)	<0.001	0.76 (0.69~0.83) *[2]
Mortality, % (n=dead: alive)	9.5 (745:7,097)	10.2 (599:5,294)	0.771	1.02 (0.91~1.14) *[2]

*[1]Mean difference (95% confidence interval of the difference)

*[2]Mantel-Haenszel common odds ratio (95% confidence interval)

OR= Odds Ratio

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

	Hazard Ratio (Group-B/Group-A)	95% Confidence Interval		p
		Lower	Upper	
Over all	1.33	1.15	1.55	<0.001

Cerebral infarction	1.33	1.04	1.70	0.021
Cerebral hemorrhage	1.06	0.83	1.34	0.650
Subarachnoid hemorrhage	1.25	0.92	1.70	0.147

Adjusted for age, sex, histories of hypertension, arrhythmia, diabetes mellitus and hyperlipemia, and uses of tobacco and alcohol

Odds ratios for the prevalence of risk factors among stroke subtypes, adjusted for age and sex, were calculated using a logistic regression model and are summarized in Table 3.

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

	Odds Ratio	95% Confidence Interval		p
		Lower	Upper	
History of hypertension				
Cerebral infarction (CI)	Reference			
Cerebral hemorrhage (CH)	1.36	1.25	1.49	<0.001

Subarachnoid hemorrhage (SAH)	**0.65**	**0.57**	**0.74**	**<0.001**
History of arrhythmia				
CI	**Reference**			
CH	**0.28**	**0.24**	**0.33**	**<0.001**
SAH	**0.26**	**0.19**	**0.34**	**<0.001**
History of diabetes mellitus				
CI	**Reference**			
CH	**0.49**	**0.44**	**0.55**	**<0.001**
SAH	**0.20**	**0.16**	**0.26**	**<0.001**
History of hyperlipemia				
CI	**Reference**			
CH	**0.40**	**0.35**	**0.45**	**<0.001**
SAH	**0.24**	**0.19**	**0.30**	**<0.001**

Table 1 also shows historical account on hypertension in 12,785 (92.7%), arrhythmia in 12,772 (92.6%), diabetes mellitus in 12,887 (93.5%), hyperlipemia in 12,617 (91.5%), tobacco usage in 11,307 (82.0%), alcohol usage in 11,053 (80.2%), and paresis in 13,195 (96.7%). We were able to classify 13,406 (97.2%) patients into four consciousness levels, excluding 184 (1.3%) patients with uncategorized stroke and 580 (4.2%) patients with no reliable information on conscious levels. Calculation of the mean delay time excluded 4964 (36.0%) patients of unknown onset. Patients received primary medical care within 3 hours of CI in 54.3%, of CH in 68.5% in CH, and of SAH in 76.4%.

Of 13,788 patients, 13,735 (99.6%) had a confirmed record of survival or death 30 days after stroke onset. A total of 1,344 (9.8%) patients died within this time period.

Figure 1 shows Kaplan-Meier Survival curves, comparing stroke subtypes, showing a significant difference (p<0.001) between any two subtypes based on Log-rank tests.

Compared to CI, CH and SAH hazard ratios for fatality of 3.66 (3.07-4.37), and 8.91 (7.18-11.06) p<0.001), when adjusted for age, sex, histories of hypertension, arrhythmia, diabetes mellitus and hyperlipemia and uses of tobacco and alcohol, showing significant differences (p<0.001) (Table 5).

Table 5 Hazard ratios for death, comparing stroke subtypes

	HR	95% Confidence Interval		p
		Lower	Upper	
Cerebral infarction	Reference			
Cerebral hemorrhage	3.66	3.07	4.37	<0.001
Subarachnoid hemorrhage	8.91	7.18	11.06	<0.001

Adjusted for age, sex, histories of hypertension, arrhythmia, diabetes mellitus and hyperlipemia, and uses of tobacco and alcohol

Hazard ratios for death, comparing stroke subtypes, in Group-A and Group-B are summarized in Supplementary Table 4 A and B.

Discussion

The study summarized the stroke registry covering entire prefecture for 11 years. Such data set depends on the society and the times. Hospitals affiliated to the Kyoto Medical Association registered new stroke patients based on the inclusion and exclusion criteria in accordance with the Kyoto municipal ordinance, avoiding area or hospitals preferences.

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. 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) [11-14], Iwate Stroke Registry (ISR) [15], Tochigi Stroke Registry (TSR) [16 17], Miyazaki Stroke Registry (MSR) [18] and KSR. 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. We summarized incidence information based on KSR in supplementary Tables 2 A, B and C. 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 and I. ISR says that their reports will be ready [19]. 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 on more restricted area should be more suitable to clarify stroke incidence in a community. The incidence rates of stroke reported from the Takashima Stroke Registry [20-22] and the Hisayama Study [23-25] 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 [26]. 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 [23]. Among subtypes of stroke, they are 357:77, 130:21 and 42:13 (men: women) in cerebral infarction, cerebral hemorrhage and subarachnoid hemorrhage, respectively [23].

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

[11]. Some prefectural stroke registries reported mortality rates. In TSR, they were 10%, 16% and 29% in CI, CH and SAH, respectively [16]. 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 [13 14], 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. Strengths of stroke registry in Japan include a high availability of CT and MRI. Japan has the most MRI units (40 U per million population) and CT scanners (93 U per million populations) among the developed countries [27]. 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.

In agree with previous reports, CI showed higher incidence followed by CH and SAH, which constitutes a fourth of hemorrhagic strokes [24]. The result adds the information that SAH constitutes about a fourth of hemorrhagic strokes. Age distribution also confirm the result of previous reports, the oldest mean age in CH and youngest in SAH [28]. The elderly patients showed a greater difference in proportion in stroke subtypes. For example, in patients who were 71 years or older, the proportions were 73.1% (n=5616), 22.3% (n=1709), and 4.6% (n=353), as compared to younger group who showed 55.8% (n=3395), 30.3% (n=1840) and 13.9% (n=844).

Most of the other characteristics also showed significant difference among three stroke subtypes. The overall registry had more male patients than female, except almost two-thirds of SAH cases were female. The initial medical examination revealed higher systolic and diastolic blood pressures in CH than in CI, possibly reflecting intracranial mass effect on brain edema [29 30].

Patients with disturbed consciousness had a higher ($p<0.001$) systolic/diastolic blood pressure (mean±SD: 164.0±35.2/88.6±20.9) than the remainder (159.3±28.2/87.0±17.1), implying possible association between stroke severity and degree of hypertension.

Risk factors for stroke include hypertension [31], arrhythmia [32], diabetes mellitus [33 34], hyperlipemia [35], alcohol use [36 37], and tobacco use . Except for tobacco and alcohol uses, these factors were noted most often in CI, followed by CH, and least in SAH. Hypertension, probably plays the most important role, was found in more than 60 % of all stroke patients. A history of arrhythmia and diabetes mellitus, relatively high in CI and lower in CH, was rarely found in SAH. These data suggest a limited association between these three factors and hemorrhagic strokes. The Ministry of Health, Labour and Welfare of Japan, has estimated morbidity rates of hypertension, diabetes mellitus and hyperlipemia among Japanese aged from 40 to 74 as 49.9%, 11.4% and 17.7%, respectively. In our series, a history of hypertension exceeded this estimate in CI and CH. A history of diabetes mellitus was higher in CI and CH, but lower in SAH, suggesting that this may not be a risk factor in SAH. A history of hyperlipemia was also lower in SAH than the morbidity rate, also suggesting that this may not a risk factor in SAH. **Regarding the risk factor of stroke, the data may not**

add sufficient information on the effect of risk factors on stroke occurrence. The registry data are not meant to do that type of study. The registry data, however, are appropriate to present the prevalence of different risk factors among the stroke patients. The higher prevalence of a factor in a certain group may support the higher association between the factor and the group. This study added information on the prevalence of risk factors among stroke patients and clarified the differences among stroke subtypes. We also added multivariate analyses. Using a logistic regression model, we estimated odds ratios and 95% confidence intervals for the prevalence of these risk factors comparing each stroke subtype after adjusted for age and sex.

Alcohol and tobacco use showed a higher correlation to SAH than the other types in the surveillance conducted under the same conditions for the three subtypes of stroke. Alcohol and tobacco usage may therefore increase the risk of SAH more than CI or CH. The proportion of heavy smokers was not different among stroke subtypes, whereas the proportion of every day drinkers was higher in hemorrhagic strokes than in ischemic stroke. Paresis developed more often in CI and CH compared to SAH. Hemorrhagic stroke caused consciousness disturbance more than ischemic stroke.

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 adjusted for age, sex, histories of risk factors and uses of tobacco and alcohol.

We calculated mortality based on the information up to 30 days after the stroke onset, excluding those who died later. Early mortality indicates stroke events themselves, whereas long term mortality reflects aftereffects and complications. Thus, early mortality serves well to evaluate the severity of the three major stroke subtypes. Death in the first month after stroke mainly results from neurological causes such as brain edema[38], followed by complications of immobility including pneumonia [39]. **The mortality rate of ischemic stroke and risk characteristics must vary by its subtypes, such as embolic stroke and lacunar stroke. However, sufficient information to classify ischemic stroke into more detailed categories was not available in this study.**

Limitations

Firstly, there may be missing data for stroke patients; for example, patients who died before arriving to hospitals and patients who went to hospital outside of the prefecture. Patients with mild symptoms might not have visited hospitals and patients with atypical symptoms might not have been diagnosed as such, and subsequently might not have been registered [5].

Secondary, the study did not encompass the effects of therapeutic interventions, which must have affected on mortality. It is virtually impossible to adjust all the treatments in a very large population based study. Treatments should be studied in randomized controlled studies. The causes of death in the study cohort were not investigated either. Possible bias exists in the assessment of variables, such as history of habits, which largely depend on patients' self report or information from their families. The study, however, showed the overall characteristics and mortality in stroke and in major subtypes, which should shed light on the difference among the major subtypes as a whole, since the comparison was done otherwise in the same condition.

Lastly, the outcomes assessment limited to 30 days after onset leaves the majority of patients (n=11,869, 86.1%) who survived the first month out of consideration. However, early mortality evaluation within 30-day should reflect cause of death directly associated with stroke and therefore correlate severity in more direct way.

Major conclusions of the study should prevail as a report based on a very large number of patients analyzed under the same conditions.

Conclusion

We have presented population based data for the span of 11 years covering the entire Kyoto prefecture in Japan. Among stroke major subtypes, hazard ratio for death was highest in SAH, followed by CH and lowest in CI.

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Figure Legends

Kaplan-Meier survival curves of stroke patients

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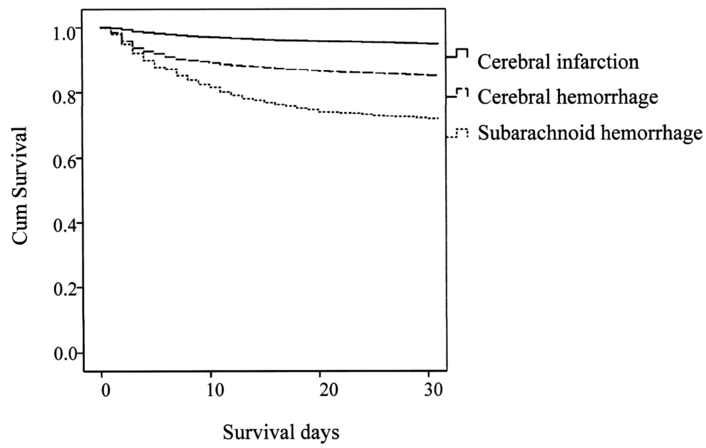
Figure Kaplan-Meier Survival Curves of stroke patients



Kaplan-Meier survival curves of stroke patients
215x156mm (300 x 300 DPI)

Supplementary Table 1A 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

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

Supplementary Table 2

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

Supplementary Table 2-A. Age and Sex Distribution of Strokes in the Kyoto Stroke Registry

Age group	**Cerebral infarction**			**Cerebral hemorrhage**			**Subarachnoid hemorrhage**		
	Men	Women	Total	Men	Women	Total	Men	Women	Total
<20	5	2	7	7	3	10	0	0	0
20-29	10	4	14	13	7	20	4	4	8
30-39	40	22	62	24	27	51	20	17	37
40-49	122	66	188	105	59	164	72	76	148
50-59	608	204	812	374	220	594	138	180	318
60-69	1,516	539	2,055	622	293	915	116	194	310
70-79	1,706	1,131	2,937	498	449	947	53	174	227
80-89	927	1,417	2,344	219	450	669	21	105	126
>90	160	1417	2344	57	122	179	0	23	23

Supplementary Table 2-B. Population by Sex and Age, Kyoto Prefecture, Japan (2010)

	Age group

	20-29	30-39	40-49	50-59	60-69	70-79	80-89	>90
Men	153,750	180,802	161,356	147,768	186,956	119,094	48,383	6,030
Women	152,528	184,729	167,751	158,029	206,016	144,563	87,673	23,313

Supplementary Table 2-C. Annual Monitoring Rates of Subtype in Stroke per 10,000 populations in Kyoto Stroke Registry

Sub-type		**Age group**							
	Sex	20-29	30-39	40-49	50-59	60-69	70-79	80-89	>90
CI	Men	0.06	0.20	0.69	3.74	7.37	13.02	17.43	24.12
	Women	0.02	0.11	0.36	1.17	3.10	7.11	14.69	55.26
CH	Men	0.08	0.12	0.59	2.30	3.03	3.801	4.12	8.59
	Women	0.04	0.13	0.32	1.27	1.29	2.824	4.67	4.76
SAH	Men	0.02	0.10	0.41	0.85	0.56	0.41	0.40	0.00
	Women	0.02	0.08	0.41	1.04	0.86	1.09	1.09	0.90

Supplementary Table 2-D. Age and Sex Distribution of Strokes in Tochigi Stroke Registry

Age group	**Cerebral infarction**			**Cerebral hemorrhage**			**Subarachnoid hemorrhage**		
	Men	Women	Total	Men	Women	Total	Men	Women	Total
-39	15	4	19	13	2	15	5	7	12
40-49	42	10	52	33	7	40	10	14	24
50-59	118	30	148	78	42	120	13	22	33
60-69	300	83	383	110	56	166	23	43	66
70-79	334	199	533	89	77	166	5	36	41
80-89	262	322	584	59	85	144	7	32	39
>90	34	103	137	4	9	13	0	4	4

Supplementary Table 2-E. Population by Sex and Age, Tochigi Prefecture, Japan (2010)

	Age group						
	-39	40-49	50-59	60-69	70-79	80-89	>90
Men	493,600	128,100	147,400	141,000	84,700	38,500	4,000
Women	447,100	120,200	141,200	139,400	105,200	74,700	17,500

Supplementary Table 2-F. Annual Monitoring Rates of Subtype in Stroke per 10,000

Populations in Tochigi Stroke Registry

Sub -type	Sex	-39	40-49	50-59	60-69	70-79	80-89	>90
CI	Men	0.30	3.28	8.01	21.28	39.43	68.05	80.00
	Women	0.09	0.83	2.13	5.95	18.92	43.11	58.86
CH	Men	0.26	2.58	5.29	7.80	10.51	15.36	10.00
	Women	0.04	0.08	2.98	4.02	7.32	11.38	5.14
SAH	Men	0.10	0.78	0.88	1.63	0.59	1.82	0.00
	Women	0.16	1.16	1.56	3.08	3.42	4.28	2.29

Supplementary Table 2-G. Age and Sex Distribution of Strokes in Miyazaki Stroke Registry

Age group	Cerebral infarction			Cerebral hemorrhage			Subarachnoid hemorrhage		
	Men	Women	Total	Men	Women	Total	Men	Women	Total
<20	0	0	0	0	1	1	0	0	0
20-29	0	0	0	0	0	0	1	0	1
30-39	2	3	5	5	2	7	4	0	4
40-49	11	7	18	13	10	23	5	4	9
50-59	60	21	81	49	15	64	3	8	11
60-69	97	64	161	78	33	111	7	20	27
70-79	222	144	366	73	69	142	3	33	36
80-89	150	177	327	39	66	105	3	20	23
>90	23	60	83	11	14	25	0	3	3

Supplementary Table 2-H. Population by Sex and Age, Miyazaki Prefecture, Japan (2010)

	Age group							
	20-29	30-39	40-49	50-59	60-69	70-79	80-89	>90
Men	19,314	26,526	23,726	26,037	25,650	16,164	7,337	982
Women	22,034	28,537	26,656	28,889	28,656	20,935	13,219	3,544

Supplementary Table 2-I. Annual Monitoring Rates of Subtype in Stroke per 10,000 Populations in Miyazaki Stroke Registry

Sub	Age group

-type	Sex	20-29	30-39	40-49	50-59	60-69	70-79	80-89	>90
CI	Men	0.00	0.75	4.64	23.04	37.82	137.34	204.44	234.22
	Women	0.00	1.05	2.63	7.27	22.33	68.78	133.90	169.30
CH	Men	0.00	1.88	5.48	18.82	30.41	45.16	53.16	112.02
	Women	0.00	0.75	3.75	5.19	11.52	32.96	49.93	39.50
SAH	Men	0.52	1.51	2.11	1.15	2.73	1.86	1.36	0.00
	Women	0.00	0.00	1.50	2.77	6.98	15.76	15.13	8.47

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

Group-A	**Overall n=7,886**	**Cerebral infarction n= 5,247(66.6%)**	**Cerebral hemorrhage n=1,896 (24.1%)**	**Subarachnoid hemorrhage n=711 (9.0%)**
Age (mean± SD)	70.5±12.7	72.5±11.6	68.5±13.3	61.2±13.5
Sex, % female (n=female: male)	44.8 (3,531:4,349)	41.9 (2,196:3,051)	46.1 (875:1,021)	62.9 (447:264)
Systolic blood pressure (mean± SD**), mmHg**	161.5±31.6	158.1±28.5	172.4±35.1	157.2±36.7
Diastolic blood pressure (mean± SD**), mmHg**	87.3±18.7	85.8±17.2	92.4±20.6	85.4±21.8
Hypertension history, % (n=with: without)	60.2 (4379:2,900)	59.2 (2,922:2,016)	67.3 (1,148:557)	48.3 (296:317)
Arrhythmia, % (n=with: without)	14.9 (1,132:6,446)	19.4 (988:4,110)	5.4 (97:1,694)	6.9 (46:617)
Arrhythmia history, % (n=with: without)	19.0 (74.7)	25.1 (1,243:3,704)	6.3 (107:1,580)	5.3 (32:576)
Diabetes mellitus history, % (n=with: without)	20.5 (1,500:5,827)	24.2 (1,209:3,796)	14.5 (245:1,447)	6.8 (41:565)
Hyperlipemia history, % (n=with: without)	17.5 (1,250:5,910)	21.0 (1,028:3,869)	10.7 (177:1,472)	7.1 (42:547)
Tobacco use, %	33.6	33.6	30.6	40.0 (218:327)

(n=with: without)	(2,152:4,259)	(1,482:2,925)	(441:998)	
Non smoker, % (n)	60.5 (3,797)	66.4 (2,925)	69.4 (998)	60.0 (327)
Former smoker, % (n)	4.4 (281)	4.6 (202)	4.9 (70)	1.7 (9)
Light smoker, % (n)	17.7 (1,132)	17.7 (782)	15.0 (216)	23.5 (128)
Heavy smoker, % (n)	11.5 (739)	11.3 (498)	10.8 (155)	14.9 (81)
Alcohol use, % (n=with: without)	39.5 (2,478:3,797)	37.8 (1,624:2,669)	41.3 (585:832)	47.5 (258)
Non drinker, % (n)	60.5 (3,797)	62.2 (2,669)	58.7 (832)	52.5 (285)
Occasional drinker, % (n)	17.6 (1,105)	17.6 (754)	15.8 (224)	22.1 (120)
Every day drinker, % (n)	21.9 (1,373)	20.3 (870)	25.5 (361)	25.4 (138)
Paresis, % (n=with: without)	73.7 (5,581:1,987)	78.0 (3,996:1,129)	78.8 (1,417:382)	24.4 (151:467)
Consciousness disturbance, % (n=with: without)	42.4 (3,290:4,463)	31.7 (1,634:3,518)	64.9 (1,213:657)	60.4 (426:279)
JCS 0, % (n)	58.6 (4,463)	69.3 (3,518)	35.7 (657)	40.8 (279)
JSC 1-digit code, % (n)	18.5 (1,409)	16.5 (837)	25.5 (468)	14.5 (99)
JSC 2-digit code, % (n)	11.8 (896)	9.1 (462)	17.8 (327)	14.8 (101)
JSC 3-digit code, % (n)	11.2 (853)	5.1 (257)	21.0 (386)	30.0 (205)
Delay time (mean± SD**)**	4.15±5.03	4.55±5.42	3.48±4.12	3.40±4.23
CT, % (n)	92.4 (7,285)	89.4 (4,969)	98.0 (1,860)	98.9 (704)

MRI, % (n)	59.4 (4,682)	74.4 (3,907)	33.7 (639)	17.6 (125)
Surgery % (n=with: without)	17.6 (1,356:6,339)	4.8 (244:4,885)	69.1 (573:1,282)	77.1 (529:157)
Mortality, % (n=dead: alive)	9.5 (745:7,097)	5.0 (262:4,965)	15.5 (292:1,592)	26.9 (190:516)

When the numbers entered in the table above are significantly different between different types of strokes, they are marked as follows:

*1: significant difference between cerebral infarction and cerebral hemorrhage;

*2: sig. difference between cerebral hemorrhage and subarachnoid hemorrhage;

*3: sig. difference between subarachnoid hemorrhage and cerebral infarction;

SD = Standard Deviation

Supplementary Table 3: *continue*

Group B	**Overall n=5907**	**Cerebral Infarction n= 3,764(%)**	**Cerebral Hemorrhage n=1,653 (%)**	**Subarachnoid Hemorrhage n=486 (%)**
Age (mean± SD)	72.3±13.0	74.4±12.0	69.8±13.9	64.9±13.3
Sex, % female (n=female: male)	45.7 (2,702:3,206)	43.0 (1,619:2,145)	45.7 (755:898)	67.1 (326:160)
Systolic blood pressure (mean± SD), mmHg	161±31.5	156.6±28.0	171.9±34.5	159.0±37.4
Diastolic blood pressure (mean± SD), mmHg	88.0±19.0	85.3±16.7	93.9±21.6	88.9±21.6
Hypertension history, % (n=with: without)	65.9 (3,626:1,880)	65.8 (2,363:1,226)	69.7 (1,035:449)	52.2 (224:205)
Arrhythmia, % (n=with: without)	14.0 (800:4,906)	18.2 (659:2,954)	6.4 (103:1,515)	7.6 (36:435)
Arrhythmia	17.7 (974:4,531)	23.0	8.7	5.3 (23:409)

history, % (n=with: without)		(817:2,728)	(133:1,391)	
Diabetes mellitus history, % (n=with: without)	21.4 (1,189:4,371)	25.7 (929:2,679)	15.1 (229:1,291)	7.0 (30:398)
Hyperlipemia history, % (n=with: without)	21.4 (1,169:4,288)	26.0 (923:2,631)	13.1 (194:1,283)	12.1 (51:371)
Tobacco use, % (n=with: without)	30.9 (1,513:3,383)	31.1 (973:2,152)	29.6 (402:958)	33.3 (136:272)
Non smoker, % (n)	69.1 (3,383)	68.9 (2,152)	70.4 (958)	66.7 (272)
Former smoker, % (n)	6.8 (334)	7.5 (233)	6.5 (89)	2.7 (11)
Light smoker, % (n)	16.1 (786)	16.0 (499)	14.2 (193)	23.0 (94)
Heavy smoker, % (n)	8.0 (393)	7.7 (241)	8.8 (120)	7.6 (31)
Alcohol use, % (n=with: without)	36.1 (1,722:3,051)	34.2 (1,030:1,986)	39.7 (539:818)	38.3 (154:248)
Non drinker, % (n)	63.9 (3,054)	65.8 (1,986)	60.3 (818)	61.7 (248)
Occasional drinker, % (n)	12.3 (587)	12.5 (377)	11.1 (150)	14.7 (59)
Every day drinker, % (n)	23.8 (1,137)	21.7 (653)	28.7 (389)	23.6 (95)
Paresis, % (n=with: without)	72.7 (4,087:1,534)	75.1 (2,754:912)	78.3 (1,207:335)	30.4 (126:289)
Consciousness	45.0	31.8	66.7	72.0

disturbance, % (n=with: without)	(2,624:3,207)	(1,181:2,530)	(1,092:544)	(349:136)
JCS 0, % (n)	55.5 (3,213)	68.8 (2,530)	33.5 (544)	28.3 (136)
JSC 1-digit code, % (n)	20.9 (1,210)	18.2 (671)	27.9 (453)	17.9 (86)
JSC 2-digit code, % (n)	12.2 (706)	8.5 (312)	18.2 (295)	20.6 (99)
JSC 3-digit code, % (n)	11.3 (656)	4.5 (164)	20.3 (330)	33.3 (481)
Delay time (mean± SD)	3.60±4.54	3.76±4.88	3.52±4.13	2.75±2.99
CT, % (n)	86.1 (5,080)	79.0 (2,972)	98.4 (1,625)	98.8 (479)
MRI, % (n)	71.3 (4,209)	86.2 (3,241)	47.8 (790)	36.1 (175)
Surgery % (n=with: without)	13.9 (815:5,060)	3.5 (130:3,610)	20.8 (342:1,306)	71.0 (342:140)
Mortality, % (n=dead: alive)	10.2 (599:5,294)	5.5 (205:3,549)	14.8 (244/1,405)	30.5 (148:337)

When the numbers entered in the table above are significantly different between different types of strokes, they are marked as follows:

*1: significant difference between cerebral infarction and cerebral hemorrhage;

*2: sig. difference between cerebral hemorrhage and subarachnoid hemorrhage;

*3: sig. difference between subarachnoid hemorrhage and cerebral infarction;

SD = Standard Deviation

Supplementary Table 4 A

Hazard Ratios for death in Group A, comparing stroke subtypes

	Hazard Ratio	95% Confidence Interval		P
		Lower	Upper	
Cerebral infarction	Reference			
Cerebral hemorrhage	4.48	3.46	5.79	<0.001
Subarachnoid hemorrhage	9.39	6.88	12.82	<0.001

Adjusted for age, sex, histories of hypertension, arrhythmia, diabetes mellitus and hyperlipemia, and uses of tobacco and alcohol

Supplementary Table 4 B

Hazard Ratios for death in Group B, comparing stroke subtypes

	HR	95% Confidence Interval		P
		Lower	Upper	
Cerebral infarction	Reference			
Cerebral hemorrhage	3.01	2.35	3.85	<0.001
Subarachnoid hemorrhage	8.36	6.16	11.34	<0.001

Adjusted for age, sex, histories of hypertension, arrhythmia, diabetes mellitus and hyperlipemia, and uses of tobacco and alcohol

Characteristics, risk factors and mortality of stroke patients in Kyoto, Japan

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Characteristics, risk factors and mortality of stroke patients in Kyoto, Japan

Short title: Characteristics, risk factors and mortality of Stroke

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Article Summary

Article focus

We examined the characteristics, risk factors and outcome of contemporary stroke patients based on the Kyoto Stroke Registry for recent 11 years. The study cohort has 12,774 cerebral infarction (CI), 9,232 cerebral hemorrhage (CH) and 2,540 subarachnoid hemorrhage (SAH) patients.

Key messages

About two thirds of the patients have a history of hypertension, whereas only about one fifth have histories of arrhythmia, diabetes mellitus or hyperlipemia. The prevalence of risk factors was different among stroke subtypes.

Mortality within 30 days after the onset was 5.2% in CI, 15.2% in CH and 28.4% in SAH.

Hazard ratios for death adjusted for age, sex, histories of hypertension, arrhythmia, diabetes mellitus and hyperlipemia and use of tobacco and/or alcohol, showed a significant (P<0.001) difference among CI (as reference), CH (3.71; 3.11-4.43) and SAH (8.95; 7.21-11.11).

Strengths and limitations of this study

This study provided quantitative data on the fundamentals of contemporary stroke in a very large cohort in Kyoto Prefecture, Japan.

Detailed information on the size and localization of the stroke and on treatment and complications was not available in this population based study.

Objectives: The aim of the study was to evaluate characteristics, risk factors and outcome of recent stroke patients in Kyoto Japan.

Design: We analyzed stroke patients in the registry with regard to their characteristics, risk factors and mortality. The Cox proportional hazards regression was used to calculate adjusted hazard ratios for death.

Settings: The Kyoto prefecture of Japan has established a registry to enroll new stroke patients in cooperation with the Kyoto Medical Association and its affiliated hospitals

Participants: The registry now has data on 14,268 patients enrolled from January 1, 1999 to December 31, 2009. Of these, 12,774 (89.5%) underwent CT, 9,232 (64.7%) MRI, 2,504 (17.5%) angiography, and 342 (2.4%) scintigraphy. Excluding 480 (3.3%) unclassified patients, 13,788 (96.6%) patients formed the basis of further analyses divided then into three subtypes: cerebral infarction (CI), cerebral hemorrhage (CH), and subarachnoid hemorrhage (SAH).

Results: 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. The mean age ±

SD was 73.3±11.8, 69.1±13.6 and 62.7±13.5 in the CI, CH and SAH cases, respectively. Males were predominant in the CI and CH cases, whereas females were predominant in the SAH cases. The frequencies of risk factors were different among the subtypes. Mortality was worst in SAH, followed by CH, and least in CI. Hazard ratios for death adjusted for age, sex, histories of hypertension, arrhythmia, diabetes mellitus and hyperlipemia and use of tobacco and/or alcohol, showed a significant ($P<0.001$) difference among CI (as reference), CH (3.71; 3.11-4.43) and SAH (8.94; 7.21-11.11).

Conclusions: The characteristics, risk factors, and mortality were evaluated in a quantitative manner in a large Japanese study cohort to shed light on the present status of stroke medicine.

Introduction

Stroke, the third major cause of death, is the largest cause of acquired disability in Japan [1]. According to a report of the Ministry of Health, Labor and Welfare, about 123,400 people died from stroke in 2010. About 10.3% of all national deaths resulted from stroke. Stroke is regarded as one of the diseases developed by long lasting exposure to risk factors associated with lifestyle. The incidence, as well as mortality, should be greatly affected by society, regions and times [2 3]. Updated detailed information on stroke events is required. A long-term surveillance of stroke, comparing characteristics, risk factors and mortality, based on the entire population in a prefecture as large as Kyoto, which has about 2,630,000 residents, should provide a fundamental database for stroke. Stroke consists of three major distinct subtypes: namely, cerebral infarction (CI), cerebral hemorrhage (CH), and subarachnoid hemorrhage (SAH). Although these subtypes have many things in common, distinct characteristics prevail. Quantitative measurement of these differences in the same large cohort should help characterize the three stroke subtypes [4]. The strength of comparing these three stroke subtypes in the same large cohort is that, by doing so, we can evaluate the relative influence of the risk factors on each subtype. These data may also help to elucidate hazard ratios for death among major stroke subtypes.

The Kyoto prefecture of Japan has established a registry to enroll all new stroke patients in cooperation with the Kyoto Medical Association and its affiliated hospitals, with help from the data collecting agency known as the Kyoto Stroke Registry (KSR) [5]. We studied all patients registered during the past 11 years in the prefecture of Kyoto to document characteristics, risk factors, and hazard ratios in the three major stroke subtypes.

Methods

We analyzed all stroke patients identified from January 1999 to December 2009 in the entire Kyoto prefecture and registered in the KSR run by the local government of Kyoto prefecture. 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 supply a summary of the KSR Program in supplementary Table 1 A. This summary has been distributed to all hospitals affiliated with the Kyoto Medical Association and to public health centers in the Kyoto Prefecture. It is also attached to the annual reports published by the Kyoto Prefecture.

The diagnosis of stroke was confirmed by local neurologists and/or neurosurgeons based on the WHO definition [6]. Stroke patients who lived in the Kyoto prefecture were registered regardless of their age and sex. Conditions such as shock, Adam-Strokes syndrome or hypertensive encephalopathy are excluded, as they are not caused directly by cerebrovascular events. Transient ischemic attack (TIA) is also excluded as the symptoms cease within 24 hours after onset. Differential diagnoses were made by the attending physicians, based on CT/MRI images and other clinical examinations. Inclusion and exclusion criteria for the KSR are shown in supplementary Table 1B.

We classified the patients into CI (ICD-9 code 433 and 434, ICD-10 code I63), CH (ICD-9 code 431, ICD-10 code I61), SAH (ICD-9 code 430, ICD-10 code I60) [7 8] and others by neurological examination and the findings of CT scans, MRI scans, angiographies, and scintigraphies. In order to clarify trends over time, we also 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 strokes between January 1999 and June 2004, and Group-B comprises patients who developed strokes 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.

Each registry recorded age, sex, date of stroke onset, blood pressure and arrhythmia on arrival, history of hypertension, arrhythmia, diabetes mellitus and hyperlipemia, tobacco and alcohol use, type of paresis, consciousness levels and clinical outcome 30 days after the onset.

For the purpose of this entry, we used the following definitions.

1) Systolic and diastolic hypertension: blood pressure is 140 and 90 mmHg or higher,
2) Arrhythmia: any types of irregularity,
3) 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 [9],
4) Hyperlipemia: serum cholesterol level is 220 mg/dl or higher and/or triglyceride is 150mg/dl or higher,

5) Smoking was divided into four categories: non-smokers, and former smokers for more than a year, light smokers with 20 or less cigarettes a day and heavy smokers with more than 20 cigarettes a day,

6) Alcohol consumption was divided into three categories: non-drinkers, occasional drinkers (less than three time a week), and daily drinkers (more than four times a week),

7) Paresis: any distribution, including unilateral or bilateral effect on limb or face,

8) Consciousness levels based on the Japan Coma Scale (JCS) [10] [11], the most widely used Japanese scale which is composed of four levels:

 1; JSC 0 (alert),

 2; JCS 1-digit code (disoriented but awake),

 3; JCS 2-digit code (arousable with stimulation),

 4; JSC 3-digit code (unarousable)

Statistical Analysis

Statistical analyses used included Fisher exact tests for frequencies of listed characteristics among the three stroke types, Student-t test for such numerical variables as age and systolic- and diastolic-blood pressures, and a log-rank test for Kaplan-Meier curves of estimated survival. The Mantel-Haenszel method and a logistic regression model were used to estimate univariate and multivariate odds ratios. Cox proportional hazards regressions were used to calculate age-, sex-, histories of hypertension, arrhythmia, diabetes mellitus and hyperlipemia, and use of tobacco and/or alcohol-adjusted hazard ratios and their 95% confidence intervals for the risk of death. Analyses were performed using SPSS ver.19 and statistical significance was set at $p<0.05$. All reported p values are 2-sided.

Ethics Statement

This research was performed in accordance with the ethical principles for medical research involving human subjects outlined in the Declaration of Helsinki. This research was approved by the Board of Directors, the Kyoto Medical Association, the Department of Health and Welfare, Kyoto Prefecture and Ethics Committee of the National Hospital Organization, Minami Kyoto Hospital. Since all identifying personal information was stripped from the secondary files before analysis, the boards waived the requirement for written informed consent from the patients involved.

Results

We reviewed 14,268 stroke patients newly identified in Kyoto prefecture from January 1999 to December 2009. Of these 12,774 (89.5%) underwent CT, 9,232 (64.7%) an MRI scan, 2,504 (17.5%) angiography, and 342 (2.4%) scintigraphy for blood flow. Excluding 480 (3.3%) unclassified patients, the study cohort had 13,788 patients divided into 9,011 (65.4%) CI, 3,549 (25.7%) CH and 1,197 (8.7%) SAH cases. 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. They were omitted. Table 1 summarizes the characteristics, risk factors, symptoms and mortality rate.

Table 1 Characteristics of Stroke Patients (n=13,788)

	Overall	**Cerebral infarction n=9,011 (65.4%)**	**Cerebral hemorrhage n=3,549 (25.7%)**	**Subarachnoid hemorrhage n=1,197 (8.7%)**
Age (mean± SD)	71.3 (12.9)	73.3 (11.8)*1*3	69.1 (13.6) *1*2	62.7 (13.5) *2*3

Sex, % female (n=female: male)	45.2 (6,233:7,555)	42.3^{*1*3} (3,815:5,196)	45.9^{*1*2} (1,630:1,919)	64.6^{*2*3} (773:424)
Systolic blood pressure (mean± SD)**, mmHg**	161.3 (35.5)	157.5 (28.3)^{*1}	172.1 (34.8) ^{*1*2}	157.9 (37.0)^{*2}
Diastolic blood pressure (mean± SD)**, mmHg**	87.6 (18.63)	85.6 (17.0) ^{*1*3}	93.1 (21.1) ^{*1*2}	86.8 (21.8) ^{*2*3}
Hypertension history, % (n=with: without)	62.6 (8,005:4,780)	62.0^{*1*3} (5,285:3,242)	68.5^{*1*2} (2,183:1,006)	49.9^{*2*3} (520:522)
Arrhythmia, % (n=with: without)	14.5 (1,932:11,352)	18.9^{*1*3} (1,647:7,064)	5.9^{*1*2} (200:3,209)	7.2^{*2*3} (82:1,052)
Arrhythmia history, %	18.5(2,357:10,415)	24.3^{*1*3} (2,060:6,432)	7.5^{*1*2} (240:2,971)	5.3^{*2*3} (55:985)

(n=with: without)				
Diabetes mellitus history, % (n=with: without)	20.9 (2,689:10,198)	24.8*1*3 (2,138:6,475)	14.8*1*2 (474:2,738)	6.9*2*3 (71:963)
Hyperlipemia history, % (n=with: without)	19.2 (2,419:10,198)	23.1*1*3 (1,951:6,503)	11.9*1*2 (371:2,755)	9.2*2*3 (93:918)
Tobacco use, % (n=with: without)	32.4 (3,665:7,642)	32.6*1*3 (2,455:5,077)	30.1*1*2 (843:1,956)	37.1*2*3 (354:599)
Non smoker, % (n)	67.6 (7,642)	67.4 (5,077) *3	69.9 (1,956) *2	62.9 (599) *2*3
Former smoker, % (n)	5.4 (615)	5.8 (435) *3	5.7 (159) *2	2.1 (20) *2*3

Light smoker, % (n)	17.0 (1,918)	17.0 (1,281) ^{*1*3}	14.6 (409) ^{*1*2}	23.3 (222) ^{*2*3}
Heavy smoker, % (n)	10.0 (1,132)	9.8 (739)	9.8 (275)	11.8 (112)
Alcohol use, % (n=with: without)	38.0 (4,202/6,851)	36.3 ^{*1*3} (2,654:4,655)	40.5 ^{*1*2} (1,124:1,650)	43.6 ^{*2*3} (412:533)
Non drinker, % (n)	62.0 (6,851)	63.7 (4,655) ^{*1*3}	59.5 (1,650) ^{*1}	56.4 (533) ^{*3}
Occasional drinker, % (n)	15.3 (1,692)	15.5 (1,131) ^{*1*3}	13.5 (374) ^{*1*2}	18.9 (179) ^{*2*3}
Every day drinker, % (n)	22.7 (2,510)	20.8 (1,523) ^{*1*3}	27.0 (750) ^{*1}	24.7 (233) ^{*3}
Paresis, % (n=with: without)	73.3 (9,670:3,525)	76.8 ^{*1*3} (6,750:2,041)	78.5 ^{*1*2} (2,624:717)	26.8 ^{*2*3} (277:756)
Consciousness disturbance, %	43.5 (5,914: 7,676)	31.8 ^{*1*3} (2,815:	65.7 ^{*1} (2,305: 1,201)	65.1 ^{*3} (775: 415)

(n=with: without)		8,863)		
JCS 0, % (n)	55.7 (7,676)	67.1[*1*3] (6,048)	33.8[*1*2] (1,201)	35.6[*2*3] (415)
JSC 1-digit code, % (n)	19.0 (2,619)	16.7[*1] (1,508)	26.0[*1*2] (921)	15.9[*2] (185)
JSC 2-digit code, % (n)	11.6 (1,602)	8.6[*1*3] (774)	17.5[*1] (622)	16.7[*3] (200)
JSC 3-digit code, % (n)	10.9 (1,509)	4.7[*1*3] (421)	20.2[*1*2] (716)	30.5[*2*3] (365)
JSC undetermined, % (n)	1.3 (184)	1.2[*3] (112)	1.3[*2] (46)	2.1[*2*3] (25)
Delay time (mean± SD)	3.91±4.82	4.20±5.21	3.50±4.13	3.13±3.77
CT, % (n)	89.7 (12,365)	85.1 (7,668) *1*3	98.2 (3,485) [*1]	98.8 (1,183) [*3]
MRI, % (n)	64.5 (8,891)	79.8 (7,148) *1*3	40.3 (1,429) *1*2	25.1 (300) [*1*3]

Surgery %	16.0 (2,171:11,399)	4.2	26.1	74.6 (871:297) *1*3
(n=with: without)		(374:8,495) *1*3	(915:2,588) *1*2	
Mortality, %	9.8 (1,344:12,391)	5.2 *1*3	15.2 *1*2	28.4 *2*3
(n=dead: alive)		(467:8,981)	(536:2,997)	(338:853)

When the numbers entered in the table above are significantly different between different types of strokes, they are marked as follows:

*1: significant difference between cerebral infarction and cerebral hemorrhage;

*2: significant difference between cerebral hemorrhage and subarachnoid hemorrhage;

*3: significant difference between subarachnoid hemorrhage and cerebral infarction;

SD = Standard Deviation

Temporal trends of characteristics of stroke patients, comparing Group-A and Group-B, are summarized in Table 2 and hazard ratios for death, comparing the two groups are summarized in Table 3. The characteristics of stroke patients in Group-A and Group-B are summarized in supplementary Table 3.

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

	Group-A	Group-B	P	Difference/OR
Age (mean± SD)	70.5±12.7	72.3±13.0	<0.001	-1.85 (-2.28~-1.41) *[1]
Sex, % female (n=female: male)	44.8 (3,531:4,349)	45.7 (2,702:3,206)	0.505	1.02 (0.96~1.09)*[2]
Systolic blood pressure (mean± SD), mmHg	161.5±31.6	161±31.5	0.449	0.41 (-0.66~1.49)*[1]
Diastolic blood pressure (mean± SD), mmHg	87.3±18.7	88.0±19.0	0.036	-0.69 (-1.33~-0.05)*[1]
Hypertension history, % (n=with:	60.2 (4,379:2,900)	65.9 (3,626:1,880)	<0.001	1.27 (1.19~1.38)*[2]

without)				
Arrhythmia, % (n=with: without)	14.9 (1,132:6,446)	14.0 (800:4,906)	0.079	0.92 (0.83~1.01) *[2]
Arrhythmia history, % (n=with: without)	19.0 (74.7)	17.7 (974:4,531)	0.059	0.92 (0.84~1.00) *[2]
Diabetes mellitus history, % (n=with: without)	20.5 (1,500:5,827)	21.4 (1,189:4,371)	0.327	1.04 (0.96~1.14) *[2]
Hyperlipemia history, % (n=with: without)	17.5 (1,250:5,910)	21.4 (1,169:4,288)	<0.001	1.27 (1.16~1.39) *[2]
Tobacco use, %	33.6	30.9	0.001	0.88

(n=with: without)	(2,152:4,259)	(1,513:3,383)		(0.81~0.95) *[2]
Alcohol use, % (n=with: without)	39.5 (2,478:3,797)	36.1 (1,724)	0.002	0.89 (0.82~0.96) *[2]
Paresis, % (n=with: without)	73.7 (5,581:1,987)	72.7 (4,087:1,534)	0.116	0.94 (0.87~1.02)*[2]
Consciousness disturbance, % (n=with: without)	42.4 (3,290:4,463)	45.0 (2,624:3,207)	0.055	1.07 (1.00~1.14) *[2]
Delay time (mean± SD)	4.15±5.03	3.60±4.54	<0.001	-0.55 (-0.73~-0.38)*[1]
CT, % (n)	92.4 (7,285)	86.1 (5,080)	<0.001	0.51 (0.45~0.57) *[2]
MRI, % (n)	59.4 (4,682)	71.3 (4,209)	<0.001	1.68 (1.56~1.80) *[2]

Surgery %	17.6	13.9	<0.001	0.76
(n=with: without)	(1,356:6,339)	(815:5,060)		(0.69~0.83) *[2]
Mortality, %	9.5 (745:7,097)	10.2	0.771	1.02
(n=dead: alive)		(599:5,294)		(0.91~1.14) *[2]

*[1]Mean 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

OR= Odds Ratio

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

	Hazard Ratio (Group-B/Group-A)	**95% Confidence Interval**		**p**
		Lower	Upper	
Over all	1.33	1.15	1.55	<0.001
Cerebral infarction	1.33	1.04	1.70	0.021
Cerebral hemorrhage	1.06	0.83	1.34	0.650

Subarachnoid hemorrhage	1.25	0.92	1.70	0.147

Adjusted for age, sex, histories of hypertension, arrhythmia, diabetes mellitus and hyperlipemia, and use of tobacco and/or alcohol

Odds ratios for the prevalence of risk factors among stroke subtypes, adjusted for age and sex, were calculated using a logistic regression model and are summarized in Table 4.

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

	Odds Ratio	**95% Confidence Interval**		**p**
		Lower	Upper	
History of hypertension				
Cerebral infarction (CI)	Reference			
Cerebral hemorrhage (CH)	1.36	1.25	1.49	<0.001
Subarachnoid hemorrhage (SAH)	0.65	0.57	0.74	<0.001
History of arrhythmia				

CI	Reference			
CH	0.28	0.24	0.33	<0.001
SAH	0.26	0.19	0.34	<0.001
History of diabetes mellitus				
CI	Reference			
CH	0.49	0.44	0.55	<0.001
SAH	0.20	0.16	0.26	<0.001
History of hyperlipemia				
CI	Reference			
CH	0.40	0.35	0.45	<0.001
SAH	0.24	0.19	0.30	<0.001

Table 1 also shows a history of hypertension in 12,785 (92.7%), arrhythmia in 12,772 (92.6%), diabetes mellitus in 12,887 (93.5%), hyperlipemia in 12,617 (91.5%), tobacco usage in 11,307 (82.0%), alcohol usage in 11,053 (80.2%), and paresis in 13,195 (96.7%). We were able to classify 13,406 (97.2%) patients into four consciousness levels, excluding 184 (1.3%) patients with uncategorized stroke and 580

(4.2%) patients with no reliable information on consciousness levels. Calculation of the mean delay time excluded 4,964 (36.0%) patients with unknown onset. Patients received primary medical care within 3 hours of onset in 54.3% of CI, 68.5% of CH, and 76.4% of SAH.

Of 13,788 patients, 13,735 (99.6%) had a confirmed record of survival or death 30 days after stroke onset. A total of 1,344 (9.8%) patients died within this time period.

Figure 1 shows Kaplan-Meier Survival curves, comparing stroke subtypes, and reveals a significant difference ($p<0.001$) between any two subtypes by the log-rank test.

Compared to CI, CH and SAH hazard ratios for fatality were 3.66 (3.07-4.37, $p<0.001$), and 8.91 (7.18-11.06, $p<0.001$), when adjusted for age, sex, histories of hypertension, arrhythmia, diabetes mellitus and hyperlipemia and use of tobacco and/or alcohol (Table 5).

Table 5 Hazard ratios for death, comparing stroke subtypes

	HR	**95% Confidence Interval**		**p**
		Lower	Upper	
Cerebral infarction	Reference			

Cerebral hemorrhage	3.71	3.11	4.43	<0.001
Subarachnoid hemorrhage	8.95	7.21	11.11	<0.001

Adjusted for age, sex, histories of hypertension, arrhythmia, diabetes mellitus and hyperlipemia, and use of tobacco and/or alcohol

Hazard ratios for death, comparing stroke subtypes, in Group-A and Group-B are summarized in Supplementary Table 4 A and B.

Discussion

The study summarized the stroke registry covering the entire prefecture for 11 years. Hospitals affiliated to the Kyoto Medical Association registered new stroke patients based on inclusion and exclusion criteria in accordance with the Kyoto municipal ordinance, avoiding area or hospital preferences.

One of the major purposes of these prefectural stroke registries is to clarify the current situation concerning stroke events in order to maintain and improve health care. In Japan, health care systems largely depend on the prefectural governments, and information on each prefecture is therefore important. Japan has 47 prefectures. There are five stroke registries based on populations in the entire prefectures: the Akita Stroke Registry (ASR) [12-15], the Iwate Stroke Registry (ISR) [16], the Tochigi Stroke Registry (TSR) [17 18], the Miyazaki Stroke Registry (MSR) [19] and the KSR. Although each prefectural registry reports the result annually to the local government, to health care centers, and to the public, most are not available in scientific English literature. We summarize incidence information based on the KSR in supplementary Tables 2 A, B and C. The ASR has published age-adjusted gender-specific incidence. Although we could not find age-adjusted gender-specific incidence among the other prefectural stroke registries, the TSR and MSR have reported data on the numbers of patients they registered. We calculated age-adjusted gender-specific incidence in the TSR and MSR based on their annual reports and summarize them in supplementary Tables 2 D-I. The ISR says that their reports will soon be ready [20]. All the prefectural registries ask as many hospitals and facilities as possible to register all stroke events. Registration, however, is not mandatory but depends on the voluntary contributions of the hospitals. Therefore, registries for more restricted areas may be better suited to clarify stroke incidence in a community. Takashima and Hisayama are two such areas. The incidence rates of stroke reported from the Takashima Stroke Registry [21-24] and the Hisayama Study [25-27] are higher than those from the prefectural stroke registries. The Hisayama study is reported to cover about 80 % of the residents (aged 40 or over) of the area, which has a population of about 8,400 [28]. 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 [25]. The incidence ratios for men:women for the subtypes of stroke are 357:77 for CI, 130:21 for CH and 42:13 for SAH [25].

The average annual mortality from CH is 3.9 per 1,000 person-years of experience (PYE), whereas that from CI is 6.5 in the Hisayama population aged 40 and over [12]. Some prefectural stroke registries report mortality rates. In the TSR, they were 10%, 16% and 29% in CI, CH and SAH, respectively [17]. According to the 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 [14 15]. These figures generally agree with the results for the KSR. The present study added age, sex, histories of hypertension, arrhythmia, diabetes, hyperlipemia, and use of tobacco and/or alcohol as adjusted hazard ratios for death in each stroke subtype.

In the KSR, voluntary contributions have built up a registry of 14,268 stroke patients over 11 years. Compared with the other prefectural registries, one of the outstanding strengths of the KSR is that it has information on survival up to 30 days after the onset in 13,735 patients out of the 13,788 patients in this cohort (99.6%). These data make it possible to analyse relationships between various factors and early mortality. A strength of stroke registry in Japan is that it includes a large amount of CT and MRI data. Japan has the most MRI units (40 U per million population) and CT scanners (93 U per million population) among developed countries [29]. In the study cohort, 12,365 patients (89.7%) had a CT examination and 8,891 patients (64.5%) had a MRI examination. The study added information on recent trends on the usage of these examinations. As expected, the usage of CT declined whereas the usage of MRI increased with time over the study period of 11 years.

In agreement with previous reports, CI had the highest incidence, followed by CH and SAH [26]. The data add the information that SAH constitutes about a fourth of hemorrhagic strokes. The age distribution also confirms the result of previous reports, the oldest mean age being in CH and the youngest in SAH [30]. The elderly patients showed a greater proportional difference in stroke subtypes. For example, in patients who were 71 years or older, the proportions were 73.1% CI (n=5,616), 22.3% CH (n=1,709), and 4.6% SAH (n=353), as compared to the younger group who showed 55.8% (n=3,395), 30.3% (n=1,840) and 13.9% (n=844).

Most of the other characteristics also showed significant differences among the three stroke subtypes. The overall registry had more male patients than female, except that almost two-thirds of the SAH cases were female. The initial medical examination revealed higher systolic and diastolic blood pressures in CH than in CI, possibly reflecting an intracranial mass effect on brain edema [31 32].

Patients with disturbed consciousness had a higher ($p<0.001$) systolic/diastolic blood pressure (mean ± SD: 164.0 ± 35.2/88.6 ± 20.9) than the remainder (159.3 ± 28.2/87.0 ± 17.1), implying possible association between stroke severity and degree of hypertension.

Risk factors for stroke include hypertension [33], arrhythmia [34], diabetes mellitus [35 36], hyperlipemia [37], alcohol use [38 39], and tobacco use. Except for tobacco and alcohol use, these factors were noted most often in CI, followed by CH, and least in SAH. Hypertension probably plays the most important role since it was found in more than 60 % of all stroke patients. A history of arrhythmia and diabetes mellitus, relatively high in CI and lower in CH, was rarely found in SAH. These data suggest a limited association between these three factors and hemorrhagic strokes. The Ministry of Health, Labour and Welfare of Japan, has estimated morbidity rates of hypertension, diabetes mellitus and hyperlipemia among Japanese aged from 40 to 74 as 49.9%, 11.4% and 17.7%, respectively. In our series, a history of hypertension exceeded this estimate in CI and CH. A history of diabetes mellitus was higher in CI and CH, but lower in SAH, suggesting that this may not be a risk factor in SAH. A history of hyperlipemia was also lower in SAH than the morbidity rate, also suggesting that this may not a risk factor in SAH. These data may not add sufficient information on the effect of risk factors on stroke occurrence. The registry data are not meant to correlate factors with the risk of stroke. The registry data, however, are appropriate to determine the prevalence of different risk factors among stroke patients. The higher prevalence of any factor in a certain group may indicate a higher association between that factor and that group. This study added information on the prevalence of various risk factors among stroke patients and clarified differences among stroke subtypes. We also added multivariate analyses. Using a logistic regression model, we estimated odds ratios and

95% confidence intervals for the prevalence of these risk factors comparing each stroke subtype after adjusting for age and sex.

Alcohol and tobacco use showed a higher correlation with SAH than with the other types of stroke in a surveillance conducted under the same conditions for the three subtypes of stroke. Alcohol and tobacco use may therefore increase the risk of SAH more than the risk of CI or CH. The proportion of heavy smokers was not different among stroke subtypes, whereas the proportion of every day drinkers was higher in hemorrhagic strokes than in ischemic stroke. Paresis developed more often in CI and CH than in SAH. Hemorrhagic stroke caused more consciousness disturbance than ischemic stroke did.

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. The hazard ratio for death in cerebral infarction was significantly higher in Group-B than in Group-A after adjustment for age, sex, histories of risk factors and use of tobacco and alcohol. Although delay time is shorter in Group-B than Group-A, there is no significant improvement in mortality.

We calculated mortality based on the information up to 30 days after the stroke onset, excluding those who died later. Early mortality suggests stroke effects, whereas long term mortality reflects aftereffects and complications. Thus, early mortality serves to evaluate the severity of the three major stroke subtypes. Death in the first month after stroke mainly results from neurological causes such as brain edema[40], followed by complications of immobility including pneumonia [41].

The mortality rate of ischemic stroke and risk characteristics must vary by subtypes, such as embolic stroke and lacunar stroke. However, sufficient information to classify ischemic stroke into more detailed categories was not available in this study. 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.

Limitations

Firstly, there may be missing data for stroke patients; for example, patients who died before arriving in hospitals and patients who went to hospitals outside of the prefecture. Patients with mild symptoms may not have visited hospitals and patients with atypical symptoms may not have been diagnosed as such, and consequently, may not have been registered [5].

Secondarily, the study did not include the types of therapeutic interventions, which must have an effect on mortality. It is virtually impossible to adjust for all the treatments in a very large population based study. Treatments should be studied in randomized controlled studies. The causes of death in the study cohort were also not investigated.

A possible bias exists in the assessment of variables, such as in the history of habits, which largely depends on the patients' self reports or information from their families. The problem, however, applied equally to all three subtypes. The study did show the overall characteristics and mortality in stroke and in major subtypes, which should shed light on the differences.

Lastly, the outcome assessment limited to 30 days after onset leaves the majority of patients (n=11,869, 86.1%) who survived the first month out of consideration. However, early mortality should reflect a cause of death directly associated with stroke and therefore correlate with severity in a direct way.

Conclusion

We have presented population based data accrued over 11 years in the Kyoto prefecture in Japan. As for the major stroke subtypes, the hazard ratio for death was highest in SAH, followed by CH and lowest in CI.

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Figure Legends

Kaplan-Meier survival curves of stroke patients

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Characteristics, risk factors and mortality of stroke patients in Kyoto, Japan

Short title: Characteristics, risk factors and mortality of Stroke

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Article Summary

Article focus

We examined the characteristics, risk factors and outcome of contemporary stroke patients based on the Kyoto Stroke Registry for recent 11 years. The study cohort has 12,774 cerebral infarction (CI), 9,232 cerebral hemorrhage (CH) and 2,540 subarachnoid hemorrhage (SAH) patients.

Key messages

About two thirds of the patients have a history of hypertension ~~history~~, whereas only about one fifth have histories of arrhythmia, diabetes mellitus ~~and~~or hyperlipemia. The prevalence of risk factors was different among stroke subtypes.

Mortality ~~on~~within 30 days after the onset ~~is~~was 5.2% in CI, 15.2% in CH and 28.4% in SAH.

Hazard ratios for death adjusted for age, sex, histories of hypertension, arrhythmia, diabetes mellitus and hyperlipemia and ~~uses~~use of tobacco and/or alcohol, showed a significant (P<0.001) difference among CI (~~a~~as reference), CH (3.~~66~~71; 3.~~07~~11-4.~~37~~43) and SAH (8.~~91; 27.18~~95; 7.21-11.~~06~~11).

Strengths and limitations of this study

This study provided quantitative data on the fundamentals of contemporary stroke in a very large cohort in Kyoto Prefecture, Japan.

Detailed information on the size and localization of the stroke and on treatment and ~~complication~~complications was not available in this population based study.

Objectives: The aim of the study ~~is~~was to evaluate characteristics, risk factors and outcome of recent stroke patients in Kyoto Japan.

Design: We analyzed stroke patients in the registry with regard to their characteristics, risk factors~~,~~ and mortality. The Cox proportional hazards regression was used to calculate adjusted hazard ratios for death.

Settings: The Kyoto prefecture of Japan has established a registry to enroll new stroke patients in cooperation with the Kyoto Medical Association and its affiliated hospitals

Participants: The registry now has data on 14~~.~~,268 patients enrolled from January 1, 1999 to December 31, 2009. Of these, 12,774 (89.5~~%), ~~%) underwent CT, 9,232 (64.7~~%),~~%) MRI, 2,504 (17.5~~%), and 342 (2.4%) underwent CT, MRI, ~~%) angiography, and 342 (2.4%) scintigraphy. Excluding 480 (3.3%) unclassified patients, 13,788 (96.6%) patients formed the basis of further analyses divided then into three subtypes~~ of stroke,~~: cerebral infarction (CI), cerebral hemorrhage (CH), and subarachnoid hemorrhage (SAH).

Results: 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. The mean age ± SD was 73.3±11.8, 69.1±13.6 and 62.7±13.5 in the CI, CH and SAH cases, respectively. ~~In~~Males were predominant in the CI and CH cases, ~~males were predominant,~~ whereas ~~in the SAH cases,~~ females were predominant~~. Frequencies~~ in the SAH cases. The frequencies of risk factors were different among the subtypes. Mortality was worst in ~~the~~ SAH, followed by ~~the~~ CH, and least in ~~the~~ CI. Hazard ratios for death adjusted for age, sex, histories of hypertension, arrhythmia, diabetes mellitus and hyperlipemia and ~~uses~~use of tobacco and/or alcohol, showed a significant (P<0.001) difference among CI (~~a~~as reference), CH (3.~~66~~71; 3.~~07~~11-4.~~37~~43) and SAH (8.~~91; 27.18~~94; 7.21-11.~~06~~11).

Conclusions: ~~Characteristics~~The characteristics, risk factors, and mortality were evaluated in a quantitative manner in a large Japanese study cohort to shed light on the present status of stroke medicine.

Introduction

Stroke, the third major cause of death, constitutesis the largest cause of acquired disability in Japan [1]. According to a report of the Ministry of Health, Labor and Welfare, about 123,400 people died from stroke in 2010. About 10.3% of the totalall national deathdeaths resulted from stroke. Sustained exposure to risk factors associated with lifestyle which patients live in play an important role in stroke incidence. Stroke is regarded as one of the diseases developed by long lasting exposure to risk factors associated with lifestyle. The incidence, as well as mortality, should be greatly affected by society, regions and times [2 3]. The updatedUpdated detailed information on stroke events in each society is required. A long-term surveillance of stroke, comparing characteristics, risk factors, and mortality, based on the entire population in a prefecture as large as Kyoto, which has about 2,630,000 residents, should provide a fundamental database offor stroke. Stroke consists of three major distinct subtypes,: namely, cerebral infarction (CI), cerebral hemorrhage (CH), and subarachnoid hemorrhage (SAH). Although these subtypes, as disorders of the cerebral arteries, have many things in common, distinct characteristics prevail. Quantitative measurement of these differences in the same large cohort should help characterize the three stroke subtypes [4]. The strength of comparing these three stroke subtypes in the same large cohort is that, by doing so, we can evaluate the relative strengthinfluence of the risk factors influencingon each subtype. These data may also should help confirm a higher mortality rate in hemorrhagic stroke than ischemic stroke, andto elucidate hazard ratios for death estimated simultaneously among major stroke subtypes, which should reflect relative severities of stroke.

The Kyoto prefecture of Japan has established a registry to enroll all new stroke patients in cooperation with the Kyoto Medical Association and its affiliated hospitals, with help from the data collecting agency known as the Kyoto Stroke Registry (KSR) [5]. We studied all patients registered during the past 11 years in the prefecture of Kyoto to document characteristics, risk factors, and hazard ratios in the three major stroke subtypes.

Methods

We analyzed all stroke patients identified from January 1999 to December 2009 in the entire Kyoto prefecture and registered in the KSR run by the local government of Kyoto prefecture. 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~~supply a summary of ~~Kyoto Stroke Registry~~the KSR Program in supplementary Table 1 A. This summary has been distributed to all hospitals affiliated ~~to~~with the Kyoto Medical Association and to public health centers in the Kyoto Prefecture. It is also attached to the annual reports published by the Kyoto Prefecture.

The diagnosis of stroke was confirmed by local neurologists and/or neurosurgeons based on the WHO definition [6]. Stroke patients who lived in the Kyoto prefecture were registered regardless ~~to~~of their age and sex. Conditions such as shock, Adam-Strokes ~~Syndrome~~syndrome or hypertensive encephalopathy are excluded, as they are not caused directly by cerebrovascular events. Transient ischemic attack (TIA) is also excluded as the symptoms cease within 24 hours after onset. Differential diagnoses ~~are~~were made by the attending physicians, based on CT/MRI images and other clinical examinations. Inclusion and exclusion criteria for the KSR ~~were~~are shown in supplementary Table 1B.

We classified the patients into CI (ICD-9 code 433 and 434, ICD-10 code I63), CH (ICD-9 code 431, ICD-10 code I61), SAH (ICD-9 code 430, ICD-10 code I60) [7 8] and others by neurological examination and the findings of CT scans, MRI scans, angiographies, and scintigraphies. In order to clarify trends over time, we also 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~~strokes between January 1999 and June 2004, and Group-B comprises patients who developed ~~stroke~~strokes 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.

Each registry recorded age, sex, date of stroke onset, blood pressure and arrhythmia on arrival, history of hypertension, arrhythmia, diabetes mellitus and hyperlipemia, tobacco and alcohol use, type of paresis, consciousness levels and clinical outcome 30 days after the onset.

For the purpose of this entry, we used the following definitions.

1) Systolic and diastolic hypertension: blood pressure ~~exceeding~~is 140 and 90 mmHg or higher,

2) Arrhythmia: any types of irregularity,

~~3) Diabetes mellitus: both type 1 and type 2 based on the patient medical record,~~

3) 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 [9],

4) Hyperlipemia: serum cholesterol level ~~of~~is 220 mg/dl or higher and/or triglyceride ~~exceeding~~is 150mg/dl or higher,

5) Smoking~~:~~ was divided into four categories~~,~~: non~~-~~-smokers, and former smokers for more than a year, light smokers with 20 or less cigarettes a day and heavy smokers with more than 20 cigarettes a day~~.~~,

6) Alcohol consumption~~:~~ was divided into three categories~~,~~: non~~-~~-drinkers, occasional drinkers (less than three time a week), and daily drinkers (more than four times a week~~).~~),

7) Paresis: any distribution, including unilateral or bilateral effect on limb or face,

8) Consciousness levels ~~onset~~ based on the Japan Coma Scale (JCS) [~~9~~10] [~~10~~11], the most widely used Japanese scale which is composed of ~~the~~ four levels~~,~~:

1; JSC 0 (alert),

Field Code Changed
Field Code Changed
Field Code Changed
Field Code Changed

2; JCS 1-digit code (disoriented but awake),

3; JCS 2-digit code (arousable with stimulation),

4; JSC 3-digit code (unarousable)

Statistical Analysis

Statistical analyses used ~~include~~included Fisher exact tests for frequencies of listed characteristics among the three stroke types, Student-t test for such numerical variables as age and systolic- and diastolic-blood pressures, and a log-rank test for Kaplan-Meier curves of estimated survival. The Mantel-Haenszel method and a logistic regression model were used to estimate univariate and multivariate odds ratios. Cox proportional hazards ~~regression was~~regressions were used to calculate age-, sex-, ~~systolic~~histories of hypertension, arrhythmia, diabetes mellitus and ~~diastolic blood pressure ,~~hyperlipemia, and ~~consciousness levels~~use of tobacco and/or alcohol-adjusted hazard ratios and their 95% confidence intervals for the risk of death. Analyses were performed using SPSS ver.19 and statistical significance was set at p<0.05. All reported p values are 2-sided.

Ethics Statement

This research was performed in accordance with the ethical principles for medical research involving human subjects outlined in the Declaration of Helsinki. This research was approved by the Board of Directors, the Kyoto Medical Association, the Department of Health and Welfare, Kyoto Prefecture and Ethics Committee of the National Hospital Organization, Minami Kyoto Hospital. Since all identifying personal information was stripped from the secondary files before analysis, the boards waived the requirement for written informed consent from the patients involved.

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Results

We reviewed 14,268 stroke patients newly identified in Kyoto prefecture from January 1999 to December 2009. Of these 12,774 (89.5%), 9,232 (64.7%), 2,504 (17.5%), and 342 (2.4%) %) underwent CT, 9,232 (64.7%) an MRI scan, 2,504 (17.5%) angiography, and 342 (2.4%) scintigraphy for blood flow. Excluding 480 (3.3%) unclassified patients, 13,788 (96.6%) patients formed the basis of further analyses dividing then into three subtypes of stroke, CI, CH, and SAH categories.

Thethe study cohort had 13,788 patients divided into 9,011 (65.4%) CI, 3,549 (25.7%) CH and 1,197 (8.7%) SAH cases. 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. They were omitted. Table 1 summarizes the characteristics, risk factors, symptoms, and mortality rate.

Table 1 Characteristics of Stroke Patients (n=13,788)

	Overall	**Cerebral infarction n=9,011 (65.4%)**	**Cerebral hemorrhage n=3,549 (25.7%)**	**Subarachnoid hemorrhage n=1,197 (8.7%)**
Age (mean± SD)	71.3 (12.9)	73.3 (11.8)*1*3	69.1 (13.6) *1*2	62.7 (13.5) *2*3
Sex, % female (n=female: male)	45.2 (6,233:7,555)	42.3*1*3 (3,815:5,196)	45.9*1*2 (1,630:1,919)	64.6*2*3 (773:424)
Systolic blood pressure (mean±	161.3 (35.5)	157.5 (28.3)*1	172.1 (34.8) *1*2	157.9 (37.0)*2

SD), **mmHg**				
Diastolic blood pressure (mean± SD), **mmHg**	87.6 (18.63)	85.6 (17.0) *1*3	93.1 (21.1) *1*2	86.8 (21.8) *2*3
Hypertension history, % (n=with: without)	62.6 (8,005:4,780)	62.0*1*3 (5,285:3,242)	68.5*1*2 (2,183:1,006)	49.9*2*3 (520:522)
Arrhythmia, % (n=with: without)	14.5 (1,932:11,352)	18.9*1*3 (1,647:7,064)	5.9*1*2 (200:3,209)	7.2*2*3 (82:1,052)
Arrhythmia history, % (n=with: without)	18.5(2,357:10,415)	24.3*1*3 (2,060:6,432)	7.5*1*2 (240:2,971)	5.3*2*3 (55:985)
Diabetes mellitus history, %	20.9 (2,689:10,198)	24.8*1*3 (2,138:6,475)	14.8*1*2 (474:2,738)	6.9*2*3 (71:963)

(n=with: without)				
Hyperlipemia history, % (n=with: without)	19.2 (2,419:10,198)	23.1*1*3 (1,951:6,503)	11.9*1*2 (371:2,755)	9.2*2*3 (93:918)
Tobacco use, % (n=with: without)	32.4 (3,665:7,642)	32.6*1*3 (2,455:5,077)	30.1*1*2 (843:1,956)	37.1*2*3 (354:599)
Non smoker, % (n)	67.6 (7,642)	67.4 (5,077) *3	69.9 (1,956) *2	62.9 (599) *2*3
Former smoker, % (n)	5.4 (615)	5.8 (435) *3	5.7 (159) *2	2.1 (20) *2*3
Light smoker, % (n)	17.0 (1,918)	17.0 (1,281) *1*3	14.6 (409) *1*2	23.3 (222) *2*3
Heavy smoker, % (n)	10.0 (1,132)	9.8 (739)	9.8 (275)	11.8 (112)
Alcohol use, %	38.0 (4,202/6,851)	36.3*1*3	40.5*1*2	43.6*2*3

(n=with: without)		(2,654:4,655)	(1,124:1,650)	(412:533)
Non drinker, % (n)	62.0 (6,851)	63.7 (4,655) [*1*3]	59.5 (1,650) [*1]	56.4 (533) [*3]
Occasional drinker, % (n)	15.3 (1,692)	15.5 (1,131) [*1*3]	13.5 (374) [*1*2]	18.9 (179) [*2*3]
Every day drinker, % (n)	22.7 (2,510)	20.8 (1,523) [*1*3]	27.0 (750) [*1]	24.7 (233) [*3]
Paresis, % (n=with: without)	73.3 (9,670:3,525)	76.8[*1*3] (6,750:2,041)	78.5[*1*2] (2,624:717)	26.8[*2*3] (277:756)
Consciousness disturbance, % (n=with: without)	43.5 (5,914: 7,676)	31.8[*1*3] (2,815: 8,863)	65.7[*1] (2,305: 1,201)	65.1[*3] (775: 415)
JCS 0, % (n)	55.7 (7,676)	67.1[*1*3] (6,048)	33.8[*1*2] (1,201)	35.6[*2*3] (415)
JSC 1-digit code, % (n)	19.0 (2,619)	16.7[*1] (1,508)	26.0[*1*2] (921)	15.9[*2] (185)

JSC 2-digit code, % (n)	11.6 (1,602)	8.6*1*3 (774)	17.5*1 (622)	16.7*3 (200)
JSC 3-digit code, % (n)	10.9 (1,509)	4.7*1*3 (421)	20.2*1*2 (716)	30.5*2*3 (365)
JSC undetermined, % (n)	1.3 (184)	1.2*3 (112)	1.3*2 (46)	2.1*2*3 (25)
Delay time (mean± SD)	3.91±4.82	4.20±5.21	3.50±4.13	3.13±3.77
CT, % (n)	89.7 (12,365)	85.1 (7,668) *1*3	98.2 (3,485) *1	98.8 (1,183) *3
MRI, % (n)	64.5 (8,891)	79.8 (7,148) *1*3	40.3 (1,429) *1*2	25.1 (300) *1*3
Surgery % (n=with: without)	16.0 (2,171:11,399)	4.2 (374:8,495) *1*3	26.1 (915:2,588) *1*2	74.6 (871:297) *1*3
Mortality, % (n=dead: alive)	9.8 (1,344:12,391)	5.2*1*3 (467:8,981)	15.2*1*2 (536:2,997)	28.4*2*3 (338:853)

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When the numbers entered in the table above are significantly different between different types of strokes, they are marked as follows:

*1: significant difference between cerebral infarction and cerebral hemorrhage;

*2: ~~sig.~~significant difference between cerebral hemorrhage and subarachnoid hemorrhage;

*3: ~~sig.~~significant difference between subarachnoid hemorrhage and cerebral infarction;

SD = Standard Deviation

Temporal trends of characteristics of stroke patients, comparing Group-A and Group-B, are summarized in Table 2 and hazard ratios for death, comparing the two groups are summarized in Table 3. ~~Characteristics~~The characteristics of stroke patients in Group-A and Group-B are summarized in supplementary Table 3.

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

	Group-A	Group-B	P	Difference/OR
Age (mean± SD)	70.5±12.7	72.3±13.0	<0.001	-1.85 (-2.28~-1.41)

				*[1]
Sex, % female (n=female: male)	44.8 (3,531:4,349)	45.7 (2,702:3,206)	0.505	1.02 (0.96~1.09)*[2]
Systolic blood pressure (mean± SD), mmHg	161.5±31.6	161±31.5	0.449	0.41 (-0.66~1.49)*[1]
Diastolic blood pressure (mean± SD), mmHg	87.3±18.7	88.0±19.0	0.036	-0.69 (-1.33~-0.05)*[1]
Hypertension history, % (n=with: without)	60.2 (4,379:2,900)	65.9 (3,626:1,880)	<0.001	1.27 (1.19~1.38*)*[2]
Arrhythmia, % (n=with: without)	14.9 (1,132:6,446)	14.0 (800:4,906)	0.079	0.92 (0.83~1.01) *[2]
Arrhythmia	19.0 (74.7)	17.7	0.059	0.92

history, % (n=with: without)		(974:4,531)		(0.84~1.00) *[2]
Diabetes mellitus history, % (n=with: without)	20.5 (1,500:5,827)	21.4 (1,189:4,371)	0.327	1.04 (0.96~1.14) *[2]
Hyperlipemia history, % (n=with: without)	17.5 (1,250:5,910)	21.4 (1,169:4,288)	<0.001	1.27 (1.16~1.39) *[2]
Tobacco use, % (n=with: without)	33.6 (2,152:4,259)	30.9 (1,513:3,383)	0.001	0.88 (0.81~0.95) *[2]
Alcohol use, % (n=with: without)	39.5 (2,478:3,797)	36.1 (1,724)	0.002	0.89 (0.82~0.96) *[2]

Paresis, % (n=with: without)	73.7 (5,581:1,987)	72.7 (4,087:1,534)	0.116	0.94 (0.87~1.02)*[2]
Consciousness disturbance, % (n=with: without)	42.4 (3,290:4,463)	45.0 (2,624:3,207)	0.055	1.07 (1.00~1.14) *[2]
Delay time (mean± SD)	4.15±5.03	3.60±4.54	<0.001	-0.55 (-0.73~-0.38)*[1]
CT, % (n)	92.4 (7,285)	86.1 (5,080)	<0.001	0.51 (0.45~0.57) *[2]
MRI, % (n)	59.4 (4,682)	71.3 (4,209)	<0.001	1.68 (1.56~1.80) *[2]
Surgery % (n=with: without)	17.6 (1,356:6,339)	13.9 (815:5,060)	<0.001	0.76 (0.69~0.83) *[2]
Mortality, % (n=dead: alive)	9.5 (745:7,097)	10.2 (599:5,294)	0.771	1.02 (0.91~1.14) *[2]

*[1]Mean 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)

OR= Odds Ratio

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

	Hazard Ratio (Group-B/Group-A)	**95% Confidence Interval**		**p**
		Lower	Upper	
Over all	1.33	1.15	1.55	<0.001
Cerebral infarction	1.33	1.04	1.70	0.021
Cerebral hemorrhage	1.06	0.83	1.34	0.650
Subarachnoid hemorrhage	1.25	0.92	1.70	0.147

Adjusted for age, sex, histories of hypertension, arrhythmia, diabetes mellitus and hyperlipemia, and usesuse of tobacco and/or alcohol

Odds ratios for the prevalence of risk factors among stroke subtypes, adjusted for age and sex, were calculated using a logistic regression model and are summarized in Table ~~3~~4.

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

	Odds Ratio	95% Confidence Interval		p
		Lower	Upper	
History of hypertension				
Cerebral infarction (CI)	Reference			
Cerebral hemorrhage (CH)	1.36	1.25	1.49	<0.001
Subarachnoid hemorrhage (SAH)	0.65	0.57	0.74	<0.001
History of arrhythmia				
CI	Reference			
CH	0.28	0.24	0.33	<0.001
SAH	0.26	0.19	0.34	<0.001
History of diabetes mellitus				

CI	Reference			
CH	0.49	0.44	0.55	<0.001
SAH	0.20	0.16	0.26	<0.001
History of hyperlipemia				
CI	Reference			
CH	0.40	0.35	0.45	<0.001
SAH	0.24	0.19	0.30	<0.001

Table 1 also shows ~~historical account on~~a history of hypertension in 12,785 (92.7%), arrhythmia in 12,772 (92.6%), diabetes mellitus in 12,887 (93.5%), hyperlipemia in 12,617 (91.5%), tobacco usage in 11,307 (82.0%), alcohol usage in 11,053 (80.2%), and paresis in 13,195 (96.7%). We were able to classify 13,406 (97.2%) patients into four consciousness levels, excluding 184 (1.3%) patients with uncategorized stroke and 580 (4.2%) patients with no reliable information on ~~conscious~~consciousness levels. Calculation of the mean delay time excluded ~~4964~~4,964 (36.0%) patients ~~of~~with unknown onset. Patients received primary medical care within 3 hours of ~~CI~~onset in 54.3~~%,~~% of ~~CH in~~CI, 68.5% ~~in~~of CH, and 76.4% of SAH~~ in 76.4%.~~.

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Of 13,788 patients, 13,735 (99.6%) had a confirmed record of survival or death 30 days after stroke onset. A total of 1,344 (9.8%) patients died within this time period.

Figure 1 shows Kaplan-Meier Survival curves, comparing stroke subtypes, showingand reveals a significant difference (p<0.001) between any two subtypes based on Logby the log-rank teststest.

Compared to CI, CH and SAH hazard ratios for fatality ofwere 3.66 (3.07-4.37, p<0.001), and 8.91 (7.18-11.06), p<0.001), when adjusted for age, sex, histories of hypertension, arrhythmia, diabetes mellitus and hyperlipemia and usesuse of tobacco and/or alcohol, showing significant differences (p<0.001) (Table 5).

Table 5 Hazard ratios for death, comparing stroke subtypes

	HR	95% Confidence Interval		p
		Lower	Upper	
Cerebral infarction	Reference			
Cerebral hemorrhage	3.6671	3.0711	4.3743	<0.001
Subarachnoid hemorrhage	8.9195	7.1821	11.0611	<0.001

Adjusted for age, sex, histories of hypertension, arrhythmia, diabetes mellitus and hyperlipemia, and usesuse of tobacco and/or alcohol

Hazard ratios for death, comparing stroke subtypes, in Group-A and Group-B are summarized in Supplementary Table 4 A and B.

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Discussion

The study summarized the stroke registry covering the entire prefecture for 11 years. Such data set depends on the society and the times. Hospitals affiliated to the Kyoto Medical Association registered new stroke patients based on the inclusion and exclusion criteria in accordance with the Kyoto municipal ordinance, avoiding area or hospitalshospital preferences.

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

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prefectural ~~government~~governments, and ~~therefore~~ information on each prefecture is therefore important. Japan has 47 prefectures. ~~To our knowledge, there~~ There are five stroke registries based on ~~a population~~populations in the entire ~~prefecture in recent years;~~prefectures: the Akita Stroke Registry (ASR) [~~11-14~~12-15], the Iwate Stroke Registry (ISR) [~~15~~16], the Tochigi Stroke Registry (TSR~~) —~~) [~~16~~17 ~~17~~18], ~~-~~the Miyazaki Stroke Registry (MSR) [~~18~~19] and the KSR. Although each prefectural registry ~~reported~~reports the result annually to the local government, to health care centers, and to the public, most ~~of them~~ are not available in scientific English literature. We ~~summarized~~summarize incidence information based on the KSR in supplementary Tables 2 A, B and C. The 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, the TSR and MSR have reported data on the numbers of patients they registered. We calculated age-adjusted gender~~-~~-specific incidence in the TSR and MSR based on their annual ~~report~~reports and ~~summarized~~summarize them in supplementary Tables 2 D~~, E, F, G, H and ~~-I. The ISR says that their reports will soon be ready [~~19~~20]. All the prefectural registries ask as many hospitals and facilities as possible to register all ~~the~~ stroke events ~~as possible~~. Registration, however, is not mandatory but depends on the voluntary contributions of

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the hospitals. ~~Some hospitals might be difficult to undertake this social work.~~ Therefore, registries ~~on~~for more restricted ~~area should~~areas may be ~~more suitable~~better suited to clarify stroke incidence in a community. Takashima and Hisayama are two such areas. The incidence rates of stroke reported from the Takashima Stroke Registry [~~20-22~~21-24] and the Hisayama Study [~~23-~~25-27] are higher than those from the prefectural stroke registries. The Hisayama study is reported to ~~examine~~cover about 80 % of the residents (~~at age of~~aged 40 or over) of the area, which has a population of about 8,400 [~~26~~28]. 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 [~~23~~25]~~. Among~~ The incidence ratios for men:women for the subtypes of stroke~~, they~~ are 357:77 for CI, 130:21 for CH and 42:13 ~~(men: women) in cerebral infarction, cerebral hemorrhage and subarachnoid hemorrhage, respectively~~for SAH [~~23~~25].

The average annual mortality ~~of cerebral hemorrhage~~from CH is 3.9 per 1,000 person-years of experience (PYE), whereas that ~~of cerebral infarction~~from CI is 6.5 in the Hisayama population aged 40 and over [~~11~~12]. Some prefectural stroke registries ~~reported~~report mortality rates. In the TSR, they were 10%, 16% and 29% in CI, CH and SAH, respectively [~~16~~17]. According to the ASR, survival rates were 94%, 92%, 83%,

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84%, 70% and 70% in CI-men, CI-women, CH-men, CH-women, SAH-men and SAH-women, respectively [~~13~~14 ~~14~~15]~~, which~~. These figures generally ~~agrees~~agree with the results ~~of~~for the KSR. The present study added ~~the~~ age, sex, histories of hypertension, arrhythmia, diabetes ~~and~~, hyperlipemia, and ~~uses~~use of tobacco and/or alcohol as adjusted hazard ratios for death in each stroke subtype.

In the KSR, voluntary ~~contribution mentioned above has~~contributions have built up a registry of 14,268 stroke patients over 11 years. ~~To be compared~~Compared with the other prefectural registries, one of the outstanding strengths of the KSR is that it has information on survival ~~days~~ up to 30 days after the onset in 13,735 patients out of the 13,788 patients ~~of~~in this ~~study~~ cohort (99.6%). ~~KSR makes~~These data make it possible to analyse relationships between ~~a certain factor~~various factors and early mortality. ~~Strengths~~A strength of stroke registry in Japan ~~include a high availability~~is that it includes a large amount of CT and MRI data. Japan has the most MRI units (40 U per million population) and CT scanners (93 U per million ~~populations~~population) among ~~the~~ developed countries [~~27~~29]. In the study cohort, 12,365 patients (89.7%) had a CT examination and 8,891 patients (64.5%) had a MRI examination. The study added ~~the~~ information on recent trends on the usage of these examinations. As expected, ~~but~~

~~interestingly,~~ the usage of CT declined whereas the usage of MRI increased with time ~~during~~over the study period of 11 years.

In ~~agree~~agreement with previous reports, CI ~~showed higher~~had the highest incidence, followed by CH and SAH~~, which constitutes a fourth of hemorrhagic strokes~~ [~~24~~26]. The ~~result adds~~data add the information that SAH constitutes about a fourth of hemorrhagic strokes. ~~Age~~The age distribution also ~~confirm~~confirms the result of previous reports, the oldest mean age being in CH and the youngest in SAH [~~28~~30]. The elderly patients showed a greater proportional difference in ~~proportion in~~ stroke subtypes. For example, in patients who were 71 years or older, the proportions were 73.1% CI (n=~~5616~~5,616), 22.3% CH (n=~~1709~~1,709), and 4.6% SAH (n=353), as compared to the younger group who showed 55.8% (n=3,395), 30.3% (n=1,840) and 13.9% (n=844).

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Most of the other characteristics also showed significant ~~difference~~differences among the three stroke subtypes. The overall registry had more male patients than female, except that almost two-thirds of the SAH cases were female. The initial medical examination revealed higher systolic and diastolic blood pressures in CH than in CI, possibly reflecting an intracranial mass effect on brain edema [~~29~~31 ~~30~~32].

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Patients with disturbed consciousness had a higher ($p<0.001$) systolic/diastolic blood pressure (mean±SD: 164.0±35.2/88.6±20.9) than the remainder (159.3±28.2/87.0±17.1), implying possible association between stroke severity and degree of hypertension.

Risk factors for stroke include hypertension [3133], arrhythmia [3234], diabetes mellitus [3335 3436], hyperlipemia [3537], alcohol use [3638 3739], and tobacco use-. Except for tobacco and alcohol usesuse, these factors were noted most often in CI, followed by CH, and least in SAH. Hypertension, probably plays the most important role, since it was found in more than 60 % of all stroke patients. A history of arrhythmia and diabetes mellitus, relatively high in CI and lower in CH, was rarely found in SAH. These data suggest a limited association between these three factors and hemorrhagic strokes. The Ministry of Health, Labour and Welfare of Japan, has estimated morbidity rates of hypertension, diabetes mellitus and hyperlipemia among Japanese aged from 40 to 74 as 49.9%, 11.4% and 17.7%, respectively. In our series, a history of hypertension exceeded this estimate in CI and CH. A history of diabetes mellitus was higher in CI and CH, but lower in SAH, suggesting that this may not be a risk factor in SAH. A history of hyperlipemia was also lower in SAH than the morbidity rate, also suggesting that this may not a risk factor in SAH. Regarding the risk factor of

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~~stroke, the~~These data may not add sufficient information on the effect of risk factors on stroke occurrence. The registry data are not meant to ~~do that type~~ correlate factors with the risk of ~~study~~stroke. The registry data, however, are appropriate to ~~present~~determine the prevalence of different risk factors among ~~the~~ stroke patients. The higher prevalence of ~~a~~any factor in a certain group may ~~support the~~indicate a higher association between ~~the~~that factor and ~~the~~that group. This study added information on the prevalence of various risk factors among stroke patients and clarified ~~the~~ differences among stroke subtypes. We also added multivariate analyses. Using a logistic regression model, we estimated odds ratios and 95% confidence intervals for the prevalence of these risk factors comparing each stroke subtype after ~~adjusted~~adjusting for age and sex.

Alcohol and tobacco use showed a higher correlation ~~to~~with SAH than with the other types of stroke in ~~the~~a surveillance conducted under the same conditions for the three subtypes of stroke. Alcohol and tobacco ~~usage~~use may therefore increase the risk of SAH more than the risk of CI or CH. The proportion of heavy smokers was not different among stroke subtypes, whereas the proportion of every day drinkers was higher in hemorrhagic strokes than in ischemic stroke. Paresis developed more often in CI and CH ~~compared to~~than in SAH. Hemorrhagic stroke caused more consciousness disturbance ~~more~~ than ischemic stroke did.

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~~The hazard ratio for death in cerebral infarction was significantly higher in Group-B than ~~that~~ in Group-A after ~~adjusted~~adjustment for age, sex, histories of risk factors and ~~uses~~use of tobacco and alcohol. Although delay time is shorter in Group-B than Group-A, there is no significant improvement in mortality.

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We calculated mortality based on the information up to 30 days after the stroke onset, excluding those who died later. Early mortality ~~indicates~~suggests stroke ~~events themselves~~effects, whereas long term mortality reflects aftereffects and complications. Thus, early mortality serves ~~well~~ to evaluate the severity of the three major stroke subtypes. Death in the first month after stroke mainly results from neurological causes such as brain edema[~~38~~40], followed by complications of immobility including pneumonia [~~39~~41].

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The mortality rate of ischemic stroke and risk characteristics must vary by ~~its~~ subtypes, such as embolic stroke and lacunar stroke. However, sufficient information to classify ischemic stroke into more detailed categories was not available in this study. 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.

Limitations

Firstly, there may be missing data for stroke patients; for example, patients who died before arriving toin hospitals and patients who went to hospitalhospitals outside of the prefecture. Patients with mild symptoms mightmay not have visited hospitals and

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patients with atypical symptoms ~~might~~may not have been diagnosed as such, and ~~subsequently might~~consequently, may not have been registered [5].

~~Secondary~~Secondarily, the study did not ~~encompass~~include the ~~effects~~types of therapeutic interventions, which must have ~~affected~~an effect on mortality. It is virtually impossible to adjust for all the treatments in a very large population based study. Treatments should be studied in randomized controlled studies. The causes of death in the study cohort were also not investigated~~ either. Possible~~.

A possible bias exists in the assessment of variables, such as in the history of habits, which largely ~~depend~~depends on the patients' self ~~report~~reports or information from their families. The ~~study~~problem, however, ~~showed~~applied equally to all three subtypes. The study did show the overall characteristics and mortality in stroke and in major subtypes, which should shed light on the ~~difference among the major subtypes as a whole, since the comparison was done otherwise in the same condition~~differences.

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Lastly, the ~~outcomes~~outcome assessment limited to 30 days after onset leaves the majority of patients (n=11,869, 86.1%) who survived the first month out of consideration. However, early mortality ~~evaluation within 30-day~~ should reflect a cause of death directly associated with stroke and therefore correlate with severity in ~~more~~a direct way.

~~Major conclusions of the study should prevail as a report based on a very large number of patients analyzed under the same conditions.~~

Conclusion

We have presented population based data ~~for the span of~~accrued over 11 years ~~covering~~in the ~~entire~~ Kyoto prefecture in Japan. ~~Among~~As for the major stroke ~~major~~ subtypes, the hazard ratio for death was highest in SAH, followed by CH and lowest in CI.

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We acknowledge the contribution of participating institutions and their staffs who provided the data in the Kyoto Stroke Registry.

Figure Legends

Kaplan-Meier survival curves of stroke patients

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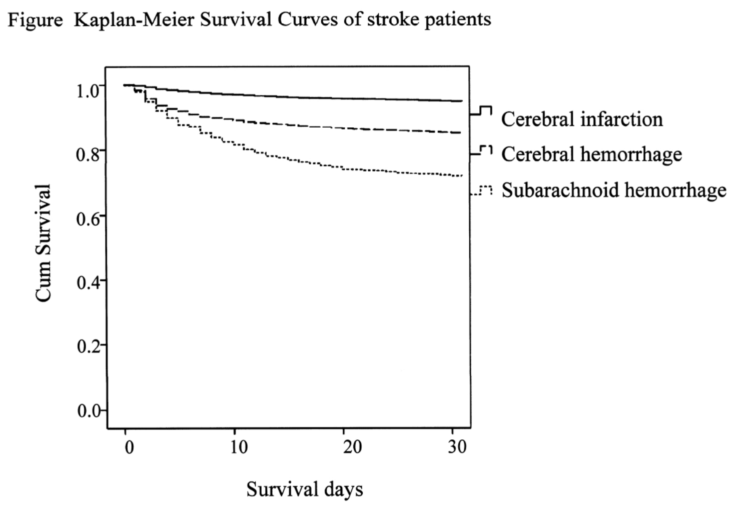

Kaplan-Meier survival curves of stroke patients
215x156mm (300 x 300 DPI)

Supplementary Table 1A Summary of the Kyoto Stroke Registry Program

1. Purpose

   The purpose of this registry is to register and analyze all stroke patients in the Kyoto prefecture with the 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

   The 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 go to medical institutions that belong to the Kyoto Medical Association may be registration.

5. Methods

(1) The Kyoto Medical Association distributes stroke patients registration forms to the affiliated medical institutions

(2) The medical institutions fill in and submit the registration forms when their patients fulfill 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 the information

(4) The Kyoto Medical Association queries the medical institutions if crucial information, such as a patients' address or date of birth, is missing

(5) The Kyoto Medical Association informs the medical institutions of the results of its registry

6. Death records

The registry is referred with death records

7. Follow-up study

If needed, a supplementary study and follow-up study are conducted by the Kyoto Medical Association with the cooperation of the attending physicians

8. Cooperation of related associations and organizations

This project is conducted with the 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 patient privacy

10. Contact with patients

Patients must not be contacted without the permission from the attending physicians

Supplementary Table 1B Inclusion and Exclusion criteria for the 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 of their age.
3 Patients are registered regardless of their sex.
4 Patients must have lived in the Kyoto Prefecture.
5 Differential diagnoses have been made by attending physicians based on CT/MRI images and other clinical examinations.

[Exclusion criteria]

1 When patients are diagnosed with some disorder other than stroke
2 When patients move out of the Kyoto prefecture
3 When patients have stroke-like symptoms but they are caused by non

cerebrovascular factors

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

Caused by shock, Adam-Strokes syndrome or hypertensive encephalopathy

4 TIA is also excluded as the symptoms cease within 24 hours after onset

Supplementary Table 2

Supplementary Table 2-A. Age and Sex Distribution of Strokes in the 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 the 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 the 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

Supplementary Table 2-A. Age and Sex Distribution of Strokes in the Kyoto Stroke Registry

Age group	Cerebral infarction			Cerebral hemorrhage			Subarachnoid hemorrhage		
	Men	Women	Total	Men	Women	Total	Men	Women	Total
<20	5	2	7	7	3	10	0	0	0
20-29	10	4	14	13	7	20	4	4	8
30-39	40	22	62	24	27	51	20	17	37
40-49	122	66	188	105	59	164	72	76	148
50-59	608	204	812	374	220	594	138	180	318
60-69	1,516	539	2,055	622	293	915	116	194	310
70-79	1,706	1,131	2,937	498	449	947	53	174	227
80-89	927	1,417	2,344	219	450	669	21	105	126
>90	160	1417	2344	57	122	179	0	23	23

Supplementary Table 2-B. Population by Sex and Age, Kyoto Prefecture, Japan (2010)

	Age group

	20-29	30-39	40-49	50-59	60-69	70-79	80-89	>90
Men	153,750	180,802	161,356	147,768	186,956	119,094	48,383	6,030
Women	152,528	184,729	167,751	158,029	206,016	144,563	87,673	23,313

Supplementary Table 2-C. Annual Monitoring Rates of Subtype in Stroke per 10,000 populations in the Kyoto Stroke Registry

Sub -type	**Age group**								
	Sex	20-29	30-39	40-49	50-59	60-69	70-79	80-89	>90
CI	Men	0.06	0.20	0.69	3.74	7.37	13.02	17.43	24.12
	Women	0.02	0.11	0.36	1.17	3.10	7.11	14.69	55.26
CH	Men	0.08	0.12	0.59	2.30	3.03	3.80	4.12	8.59
	Women	0.04	0.13	0.32	1.27	1.29	2.82	4.67	4.76
SAH	Men	0.02	0.10	0.41	0.85	0.56	0.41	0.40	0.00
	Women	0.02	0.08	0.41	1.04	0.86	1.09	1.09	0.90

Supplementary Table 2-D. Age and Sex Distribution of Strokes in the Tochigi Stroke Registry

Age group	**Cerebral infarction**			**Cerebral hemorrhage**			**Subarachnoid hemorrhage**		
	Men	Women	Total	Men	Women	Total	Men	Women	Total
-39	15	4	19	13	2	15	5	7	12
40-49	42	10	52	33	7	40	10	14	24
50-59	118	30	148	78	42	120	13	22	33
60-69	300	83	383	110	56	166	23	43	66
70-79	334	199	533	89	77	166	5	36	41
80-89	262	322	584	59	85	144	7	32	39
>90	34	103	137	4	9	13	0	4	4

Supplementary Table 2-E. Population by Sex and Age, Tochigi Prefecture, Japan (2010)

	Age group						
	-39	40-49	50-59	60-69	70-79	80-89	>90
Men	493,600	128,100	147,400	141,000	84,700	38,500	4,000
Women	447,100	120,200	141,200	139,400	105,200	74,700	17,500

Supplementary Table 2-F. Annual Monitoring Rates of Subtype in Stroke per 10,000

Populations in the Tochigi Stroke Registry

Sub -type	Sex	Age group -39	40-49	50-59	60-69	70-79	80-89	>90
CI	Men	0.30	3.28	8.01	21.28	39.43	68.05	80.00
	Women	0.09	0.83	2.13	5.95	18.92	43.11	58.86
CH	Men	0.26	2.58	5.29	7.80	10.51	15.36	10.00
	Women	0.04	0.08	2.98	4.02	7.32	11.38	5.14
SAH	Men	0.10	0.78	0.88	1.63	0.59	1.82	0.00
	Women	0.16	1.16	1.56	3.08	3.42	4.28	2.29

Supplementary Table 2-G. Age and Sex Distribution of Strokes in the Miyazaki Stroke Registry

Age group	Cerebral infarction			Cerebral hemorrhage			Subarachnoid hemorrhage		
	Men	Women	Total	Men	Women	Total	Men	Women	Total
<20	0	0	0	0	1	1	0	0	0
20-29	0	0	0	0	0	0	1	0	1
30-39	2	3	5	5	2	7	4	0	4
40-49	11	7	18	13	10	23	5	4	9
50-59	60	21	81	49	15	64	3	8	11
60-69	97	64	161	78	33	111	7	20	27
70-79	222	144	366	73	69	142	3	33	36
80-89	150	177	327	39	66	105	3	20	23
>90	23	60	83	11	14	25	0	3	3

Supplementary Table 2-H. Population by Sex and Age, Miyazaki Prefecture, Japan (2010)

	Age group 20-29	30-39	40-49	50-59	60-69	70-79	80-89	>90
Men	19,314	26,526	23,726	26,037	25,650	16,164	7,337	982
Women	22,034	28,537	26,656	28,889	28,656	20,935	13,219	3,544

Supplementary Table 2-I. Annual Monitoring Rates of Subtype in Stroke per 10,000 Populations in the Miyazaki Stroke Registry

Sub	Age group

-type	Sex	20-29	30-39	40-49	50-59	60-69	70-79	80-89	>90
	Men	0.00	0.75	4.64	23.04	37.82	137.34	204.44	234.22
CI	Women	0.00	1.05	2.63	7.27	22.33	68.78	133.90	169.30
	Men	0.00	1.88	5.48	18.82	30.41	45.16	53.16	112.02
CH	Women	0.00	0.75	3.75	5.19	11.52	32.96	49.93	39.50
	Men	0.52	1.51	2.11	1.15	2.73	1.86	1.36	0.00
SAH	Women	0.00	0.00	1.50	2.77	6.98	15.76	15.13	8.47

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

Group-A	**Overall n=7,886**	**Cerebral infarction n= 5,247(66.6%)**	**Cerebral hemorrhage n=1,896 (24.1%)**	**Subarachnoid hemorrhage n=711 (9.0%)**
Age (mean± SD)	70.5±12.7	72.5±11.6	68.5±13.3	61.2±13.5
Sex, % female (n=female: male)	44.8 (3,531:4,349)	41.9 (2,196:3,051)	46.1 (875:1,021)	62.9 (447:264)
Systolic blood pressure (mean± SD), mmHg	161.5±31.6	158.1±28.5	172.4±35.1	157.2±36.7
Diastolic blood pressure (mean± SD), mmHg	87.3±18.7	85.8±17.2	92.4±20.6	85.4±21.8
Hypertension history, % (n=with: without)	60.2 (4379:2,900)	59.2 (2,922:2,016)	67.3 (1,148:557)	48.3 (296:317)
Arrhythmia, % (n=with: without)	14.9 (1,132:6,446)	19.4 (988:4,110)	5.4 (97:1,694)	6.9 (46:617)
Arrhythmia history, % (n=with: without)	19.0 (74.7)	25.1 (1,243:3,704)	6.3 (107:1,580)	5.3 (32:576)
Diabetes mellitus history, % (n=with: without)	20.5 (1,500:5,827)	24.2 (1,209:3,796)	14.5 (245:1,447)	6.8 (41:565)
Hyperlipemia history, % (n=with: without)	17.5 (1,250:5,910)	21.0 (1,028:3,869)	10.7 (177:1,472)	7.1 (42:547)
Tobacco use, %	33.6	33.6	30.6	40.0 (218:327)

(n=with: without)	(2,152:4,259)	(1,482:2,925)	(441:998)	
Non smoker, % (n)	60.5 (3,797)	66.4 (2,925)	69.4 (998)	60.0 (327)
Former smoker, % (n)	4.4 (281)	4.6 (202)	4.9 (70)	1.7 (9)
Light smoker, % (n)	17.7 (1,132)	17.7 (782)	15.0 (216)	23.5 (128)
Heavy smoker, % (n)	11.5 (739)	11.3 (498)	10.8 (155)	14.9 (81)
Alcohol use, % (n=with: without)	39.5 (2,478:3,797)	37.8 (1,624:2,669)	41.3 (585:832)	47.5 (258)
Non drinker, % (n)	60.5 (3,797)	62.2 (2,669)	58.7 (832)	52.5 (285)
Occasional drinker, % (n)	17.6 (1,105)	17.6 (754)	15.8 (224)	22.1 (120)
Every day drinker, % (n)	21.9 (1,373)	20.3 (870)	25.5 (361)	25.4 (138)
Paresis, % (n=with: without)	73.7 (5,581:1,987)	78.0 (3,996:1,129)	78.8 (1,417:382)	24.4 (151:467)
Consciousness disturbance, % (n=with: without)	42.4 (3,290:4,463)	31.7 (1,634:3,518)	64.9 (1,213:657)	60.4 (426:279)
JCS 0, % (n)	58.6 (4,463)	69.3 (3,518)	35.7 (657)	40.8 (279)
JSC 1-digit code, % (n)	18.5 (1,409)	16.5 (837)	25.5 (468)	14.5 (99)
JSC 2-digit code, % (n)	11.8 (896)	9.1 (462)	17.8 (327)	14.8 (101)
JSC 3-digit code, % (n)	11.2 (853)	5.1 (257)	21.0 (386)	30.0 (205)
Delay time (mean± SD**)**	4.15±5.03	4.55±5.42	3.48±4.12	3.40±4.23
CT, % (n)	92.4 (7,285)	89.4 (4,969)	98.0 (1,860)	98.9 (704)

MRI, % (n)	59.4 (4,682)	74.4 (3,907)	33.7 (639)	17.6 (125)
Surgery % (n=with: without)	17.6 (1,356:6,339)	4.8 (244:4,885)	69.1 (573:1,282)	77.1 (529:157)
Mortality, % (n=dead: alive)	9.5 (745:7,097)	5.0 (262:4,965)	15.5 (292:1,592)	26.9 (190:516)

When the numbers entered in the table above are significantly different between different types of strokes, they are marked as follows:

*1: significant difference between cerebral infarction and cerebral hemorrhage;

*2: sig. difference between cerebral hemorrhage and subarachnoid hemorrhage;

*3: sig. difference between subarachnoid hemorrhage and cerebral infarction;

SD = Standard Deviation

Supplementary Table 3: *continue*

Group B	**Overall n=5907**	**Cerebral Infarction n= 3,764(%)**	**Cerebral Hemorrhage n=1,653 (%)**	**Subarachnoid Hemorrhage n=486 (%)**
Age (mean± SD)	72.3±13.0	74.4±12.0	69.8±13.9	64.9±13.3
Sex, % female (n=female: male)	45.7 (2,702:3,206)	43.0 (1,619:2,145)	45.7 (755:898)	67.1 (326:160)
Systolic blood pressure (mean± SD), mmHg	161±31.5	156.6±28.0	171.9±34.5	159.0±37.4
Diastolic blood pressure (mean± SD), mmHg	88.0±19.0	85.3±16.7	93.9±21.6	88.9±21.6
Hypertension history, % (n=with: without)	65.9 (3,626:1,880)	65.8 (2,363:1,226)	69.7 (1,035:449)	52.2 (224:205)
Arrhythmia, % (n=with: without)	14.0 (800:4,906)	18.2 (659:2,954)	6.4 (103:1,515)	7.6 (36:435)
Arrhythmia	17.7 (974:4,531)	23.0	8.7	5.3 (23:409)

history, % (n=with: without)		(817:2,728)	(133:1,391)	
Diabetes mellitus history, % (n=with: without)	21.4 (1,189:4,371)	25.7 (929:2,679)	15.1 (229:1,291)	7.0 (30:398)
Hyperlipemia history, % (n=with: without)	21.4 (1,169:4,288)	26.0 (923:2,631)	13.1 (194:1,283)	12.1 (51:371)
Tobacco use, % (n=with: without)	30.9 (1,513:3,383)	31.1 (973:2,152)	29.6 (402:958)	33.3 (136:272)
Non smoker, % (n)	69.1 (3,383)	68.9 (2,152)	70.4 (958)	66.7 (272)
Former smoker, % (n)	6.8 (334)	7.5 (233)	6.5 (89)	2.7 (11)
Light smoker, % (n)	16.1 (786)	16.0 (499)	14.2 (193)	23.0 (94)
Heavy smoker, % (n)	8.0 (393)	7.7 (241)	8.8 (120)	7.6 (31)
Alcohol use, % (n=with: without)	36.1 (1,722:3,051)	34.2 (1,030:1,986)	39.7 (539:818)	38.3 (154:248)
Non drinker, % (n)	63.9 (3,054)	65.8 (1,986)	60.3 (818)	61.7 (248)
Occasional drinker, % (n)	12.3 (587)	12.5 (377)	11.1 (150)	14.7 (59)
Every day drinker, % (n)	23.8 (1,137)	21.7 (653)	28.7 (389)	23.6 (95)
Paresis, % (n=with: without)	72.7 (4,087:1,534)	75.1 (2,754:912)	78.3 (1,207:335)	30.4 (126:289)
Consciousness	45.0	31.8	66.7	72.0

disturbance, % (n=with: without)	(2,624:3,207)	(1,181:2,530)	(1,092:544)	(349:136)
JCS 0, % (n)	55.5 (3,213)	68.8 (2,530)	33.5 (544)	28.3 (136)
JSC 1-digit code, % (n)	20.9 (1,210)	18.2 (671)	27.9 (453)	17.9 (86)
JSC 2-digit code, % (n)	12.2 (706)	8.5 (312)	18.2 (295)	20.6 (99)
JSC 3-digit code, % (n)	11.3 (656)	4.5 (164)	20.3 (330)	33.3 (481)
Delay time (mean± SD**)**	3.60±4.54	3.76±4.88	3.52±4.13	2.75±2.99
CT, % (n)	86.1 (5,080)	79.0 (2,972)	98.4 (1,625)	98.8 (479)
MRI, % (n)	71.3 (4,209)	86.2 (3,241)	47.8 (790)	36.1 (175)
Surgery % (n=with: without)	13.9 (815:5,060)	3.5 (130:3,610)	20.8 (342:1,306)	71.0 (342:140)
Mortality, % (n=dead: alive)	10.2 (599:5,294)	5.5 (205:3,549)	14.8 (244/1,405)	30.5 (148:337)

When the numbers entered in the table above are significantly different between different types of strokes, they are marked as follows:

*1: significant difference between cerebral infarction and cerebral hemorrhage;

*2: sig. difference between cerebral hemorrhage and subarachnoid hemorrhage;

*3: sig. difference between subarachnoid hemorrhage and cerebral infarction;

SD = Standard Deviation

Supplementary Table 4 A

Hazard Ratios for death in Group A, comparing stroke subtypes

	Hazard Ratio	95% Confidence Interval		P
		Lower	Upper	
Cerebral infarction	Reference			
Cerebral hemorrhage	4.48	3.46	5.79	<0.001
Subarachnoid hemorrhage	9.39	6.88	12.82	<0.001

Adjusted for age, sex, histories of hypertension, arrhythmia, diabetes mellitus and hyperlipemia, and uses of tobacco and alcohol

Supplementary Table 4 B

Hazard Ratios for death in Group B, comparing stroke subtypes

	HR	95% Confidence Interval		P
		Lower	Upper	
Cerebral infarction	Reference			
Cerebral hemorrhage	3.01	2.35	3.85	<0.001
Subarachnoid hemorrhage	8.36	6.16	11.34	<0.001

Adjusted for age, sex, histories of hypertension, arrhythmia, diabetes mellitus and hyperlipemia, and uses of tobacco and alcohol