■ Original Article ■

The Comparison of Risk Factors for Ischemic Stroke or Intracranial Hemorrhage in Korean Stroke Patients: A Nationwide Population-based Study

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Stroke is a leading cause of death in the Korean population and remains a major health burden worldwide. The two main pathologic types of stroke are ischemic stroke and intracranial hemorrhage (ICH), but comparisons of risk factors for these have been limited. We under took a nationwide population-based study to analyze the relationship between these risk factor sand ischemic stroke and ICH. From January 2003 to December 2013, a total of 37,561 patients with newly diagnosed ischemic stroke or ICH were identified using the National Health Insurance Service data base as the study population. Multivariable logistic regression analysis was used to determine the association between baseline risk factors and presentation with ICH versus ischemic stroke. The incidence of ischemic stroke showed an increasing rend every year, while there was no significant change in the incidence of ICH. Of the several risk factors associated with stroke, old age (OR 2.35, 95% CI 2.12~2.49, $P < 0.001$) was more closely associated with ischemic stroke than ICH, whereas renal disease (OR 0.74, 95% CI 0.55~0.99, $P = 0.04$) and carotid disease (OR 0.25, 95% CI 0.17~0.35, $P < 0.001$) were more strongly associated with ICH. In addition, diabetes mellitus, dyslipidemia, hypertension, ischemic heart disease and male sex was associated with an increased risk of ischemic stroke. Old age was more strongly associated with ischemic stroke than ICH, while carotid stenosis and renal impairment were more closely associated with ICH risk. Classic risk factors for stroke have considerably different associations with the two main pathologic types of stroke.

Key Words: Stroke, Intracranial hemorrhage, Risk factor

INTRODUCTION

Stroke is the leading cause of death in the Korean population and represents one of the biggest healthcare burdens worldwide (Go et al., 2013; Bennett et al., 2014; Krishnamurthi et al., 2014). There are two categories of stroke, referred to as ischemic stroke and intracranial hemorrhage (ICH). The cause of ischemic stroke is insufficient blood supply to keep the brain nourished with oxygen and nutrients, while hemorrhagic stroke is characterized by bleeding within the enclosed cranial cavity (Caplan, 1989). Atrial fibrillation (AF), heart disease, hypertension, and diabetes mellitus are known to be associated with a greater overall risk of stroke (Meschia et al., 2014). A major contributor to ischemic stroke, AF, is associated with a five-fold higher risk. To reduce the risk of ischemic stroke in AF patients, the majority is discharged with antithrombotic treatment, but ICH is the most feared complication of anticoagulant therapy (Hart et al., 1995). Therefore, for optimal prescribing of oral anticoagulants in

AF patients, clinicians must carefully consider the competing risks of ischemic stroke and ICH. The primary risk factors for ischemic stroke are also risk factors for ICH. Some of these shared risk factors (eg, age, hypertension, diabetes mellitus, and renal impairment) are included in clinical prediction rules for both ischemic stroke (eg, CHA_2DS_2VASc score; Lip et al., 2010) and major bleeding including ICH (HAS-BLED score; Pisters et al., 2010). Although ischemic stroke and ICH are associated with distinct independent risk factors due different pathological mechanisms, precisely how these risk factors differ has yet to be fully understood. The aim of this study was to further investigate the risk factors associated with the two stroke types in Korean patients.

MATERIALS AND METHODS

Data sources and study population

From January 2003 to December 2013, a total of 37,561 stroke patients were identified from the National Health Insurance Service (NHIS) database as the study population. Prevalent stroke events were identified using International Classification of Disease, Tenth Revision (ICD-10) code for ischemic stroke (ICD-10 codesI63 or I64) or for ICH (ICD-10 codesI60-62). We excluded patients who had a history of previous ischemic stroke or ICH. The clinical endpoint was the occurrence of all-cause death during the 10-year follow-up period (from January 2003 to December 2013).

Statistical analysis

Continuous variables are expressed as mean values with standard deviations, and categorical variables are presented as frequencies (percentages). The adjusted incidence rate for the clinical endpoint was calculated by dividing the number of events by 100 person-years at risk with a 95% confidence interval (CI). The risk of events was assessed using Logistic regression analysis. Odds ratios (OR) were calculated to represent the risk of ischemic stroke relative to ICH. Relative risk (RR) estimated the risk of ischemic stroke or ICH according to the risk factors. P values of <0.05 were considered to indicate significance. Statistical analyses were performed using SPSS Version 18.0 (SPSS Inc., Chicago, IL, USA) and Med Calc Version 12.2.1 (Med Calc software, Mariakerke, Belgium).

RESULTS

Baseline characteristics

Table 1 summarizes the characteristics of the 37,561

Table 1. Baseline characteristics

Variable	Total stroke (n=37,561)	Ischemic stroke (n=29,277)	ICH (n=8,284)
Age, yrs	58.1 ± 14.9	60.4 ± 13.1	49.9 ± 17.7
Male	18,420 (49%)	14,249 (49%)	4,171 (51%)
Diabetes mellitus	8,649 (23%)	6,594 (23%)	2,055 (25%)
Hypertension	17,636 (47%)	14,272 (48%)	3,364 (41%)
Dyslipidemia	9,834 (26%)	7,581 (26%)	2,253 (27%)
Ischemic heart disease	8,946 (24%)	6,843 (23%)	2,103 (25%)
Atrial fibrillation/atrial flutter	6,607 (18%)	4,774 (16%)	1,833 (22%)
Heart failure	7,704 (21%)	5,751 (20%)	1,953 (24%)
Valvular heart disease	6,421 (17%)	4,606 (16%)	1,815 (22%)
Renal failure	6,472 (17%)	4,646 (16%)	1,826 (22%)
Peripheral vascular disease	7,338 (20%)	5,412 (19%)	1,926 (23%)
Carotid stenosis	6,196 (17%)	4,416 (15%)	1,780 (22%)
All-cause death	9,811 (26.1%)	7,590 (25.9%)	2,221 (26.8%)

Values are n (%) or mean ± standard deviation. ICH, intracranial hemorrhage

stroke patients included in the current analysis. Of the total number of stroke patients, 29,277 were ischemic stroke patients (78%). There was an increasing trend for ischemic stroke every year, while there was no significant change in the incidence of ICH (Fig. 1). The mean age of all patients was 58.1, with ischemic stroke patients on average being older than ICH patients. The proportion of male gender (approximately 50%) was similar for both stroke types. Hypertension was the most prevalent risk factor for ischemic stroke and ICH (49% and 41%, respectively). All-cause death occurred in 7,590 of the ischemic stroke patients (25.9%) and 2,221 (26.8%) of the ICH patients at full follow-up.
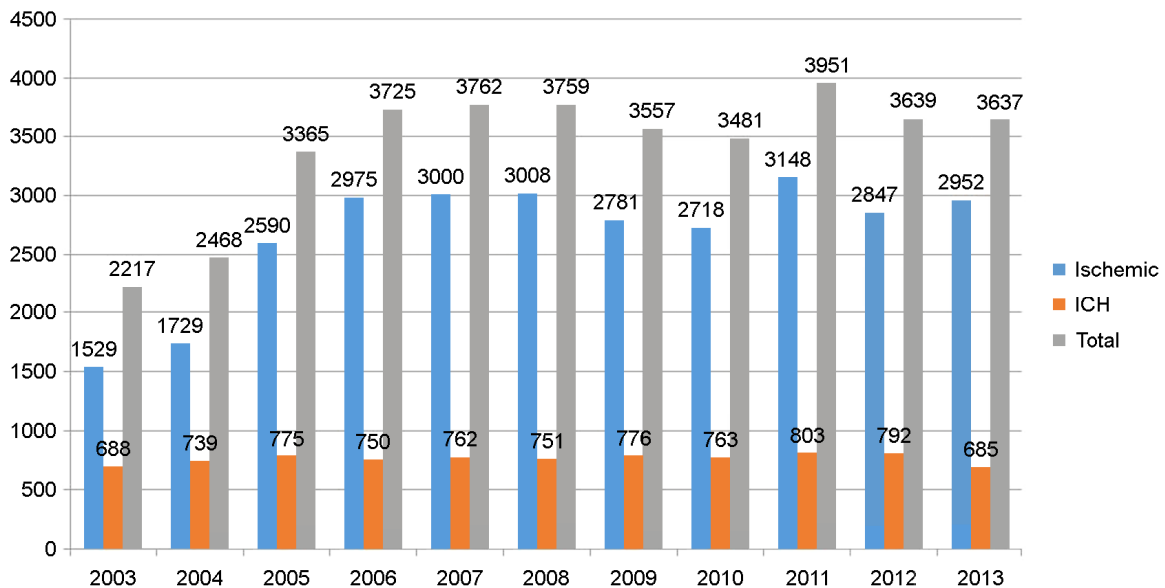

Fig. 1. Stroke incidence over time.

Table 2. Relative risk of ischemic stroke and ICH according to risk factor

Variable	Ischemic stroke		ICH	
	No. of events	RR (95% CI)	No. of events	RR (95% CI)
Old age (≥65)	1,2421	1.21 (1.20~1.22)	1,809	0.46 (0.44~0.48)
Male	14,269	0.97 (0.96~0.98)	4,308	1.11 (1.07~1.15)
Diabetes mellitus	6,594	0.97 (0.96~0.99)	2,055	1.10 (1.06~1.15)
Hypertension	14,272	1.08 (1.06~1.09)	3,364	0.77 (0.74~0.80)
Dyslipidemia	7,581	0.99 (0.97~1.00)	2,253	1.05 (1.01~1.10)
IHD	6,843	0.98 (0.96~0.99)	2,103	1.09 (1.04~1.14)
AF	4,774	0.91 (0.90~0.93)	1,833	1.33 (1.27~1.39)
Heart failure	5,751	0.95 (0.93~0.96)	1,953	1.20 (1.14~1.25)
VHD	4,606	0.91 (0.89~0.92)	1,815	1.36 (1.30~1.42)
Renal disease	4,646	0.91 (0.89~0.92)	1,826	1.36 (1.30~1.45)
PVD	5,412	0.93 (0.92~0.95)	1,926	1.25 (1.19~1.30)
Carotid disease	4,416	0.90 (0.88~0.91)	1,780	1.39 (1.33~1.45)

IHD, ischemic heart disease; AF, atrial fibrillation; VHD, valvular heart disease; PVD, peripheral vascular disease; ICH, intracranial hemorrhage; RR, relative risk. RR is the relative risk for each risk factor compared to no risk factor
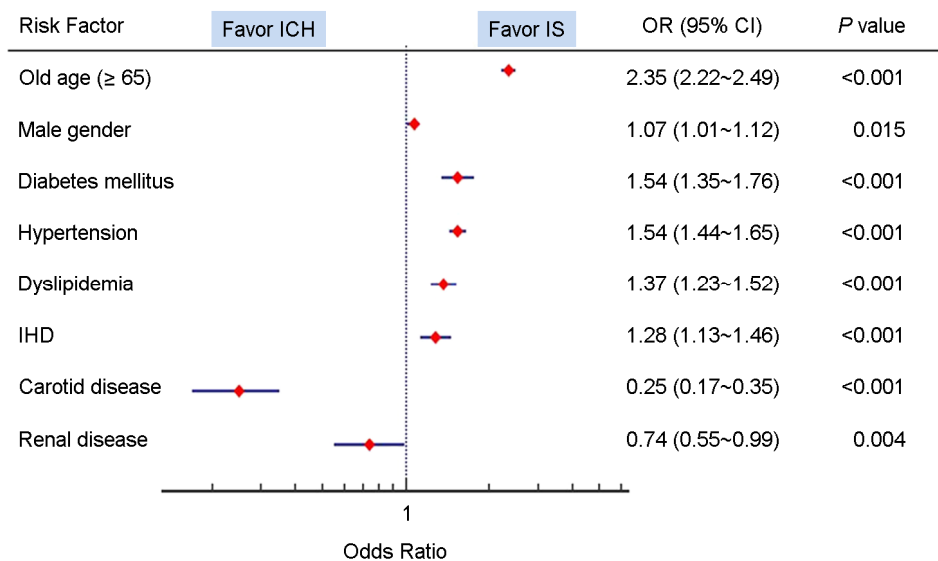
Fig. 2. Odds ratio of risk factors for ischemic stroke relative to ICH. DM, diabetes mellitus; HTN, hypertension; IHD, ischemic heart disease; ICH, intracranial hemorrhage; IS, ischemic stroke; OR, odds ratio.

Relative risk of ischemic stroke and ICH according to risk factors

In old age (≥ 65), the risk of ischemic stroke was substantially increased (RR 1.21, 95% CI 1.20~1.22), but the risk of ICH was reduced (RR 0.46, 95% CI 0.44~0.48). Higher AF (RR 1.33, 95% CI 1.27~1.39), heart failure (RR 1.20, 95% CI 1.14~1.25), valvular disease (RR 1.36, 95% CI 1.30~1.42), renal impairment (RR 1.36, 95% CI 1.30~1.42), peripheral vascular disease (RR 1.25, 95% CI 1.19~1.30) and carotid disease (RR 1.39, 95% CI 1.33~1.45) was associated with an increased risk of ICH (Table 2).

Comparison of risk factors for ischemic stroke and ICH

In the multivariable analysis, age (OR 2.35, 95% CI 2.22~2.49, *P* < 0.001) was strongly associated with an increased risk of ischemic stroke compared to ICH, whereas carotid disease (OR 0.25, 95% CI 0.17~0.35, *P* < 0.001) and renal impairment (OR 0.74, 95% CI 0.55~0.99, *P* = 0.04) were more closely associated with ICH than ischemic stroke. Diabetes mellitus (OR 1.54, 95% CI 1.35~1.76, *P* < 0.001), hypertension (OR 1.54, 95% CI 1.44~1.65, *P* < 0.001), dyslipidemia (OR 1.37, 95% CI 1.23~1.52, *P* < 0.001) and ischemic heart disease (OR 1.28, 95% CI 1.13~1.46, *P* <

0.001) were more closely related to ischemic strokethan ICH (Fig. 2).

DISCUSSION

Ischemic stroke and hemorrhagic stroke can be further subdivided based on different etiologies, clinical courses and outcomes. Oral anticoagulation is recommended for AF patients to prevent ischemic stroke but can increase major bleeding events such as ICH. Of the common risk factors associated with stroke (age, gender, hypertension, diabetes mellitus, IHD, renal impairment, carotid disease), older age was more strongly associated with ischemic stroke than ICH, while renal impairment and carotid disease was associated with an increased risk of ICH.

Previous studies have suggested that hypertension is a stronger risk factor for ICH than ischemic stroke (Lewington et al., 2002; Song et al., 2004; Zia et al., 2007). In our analyses, a history of hypertension was not more closely associated with ischemic stroke than ICH. However, a limitation of this study was that the severity of hypertension and blood pressure information was not known. Previously published prospective studies have demonstrated an association between diabetes mellitus and stroke risk. There was a small

increase in risk of hemorrhagic stroke and a doubling in the risk of ischemic stroke. The increased risk of ischemic stroke in people with diabetes mellitus has been well established and believed to share a common mechanism with ischemic heart disease (Grundy et al., 1999). A reduced risk of hemorrhagic stroke associated with diabetes mellitus has been reported in several retrospective and prospective studies (Feigin et al., 2005), but some prospective studies have directly compared diabetes mellitus-associated risk for hemorrhagic stroke with the risk of other types of stroke (Cui et al., 2011; Shah et al., 2015). The mechanism for the observed reduction in diabetes mellitus-associated risk for hemorrhagic stroke remains unclear. In our study, diabetes mellitus was more associated with ischemic stroke than ICH. Although old age is known to be an important risk factor for ICH, a previous study has suggested that advanced age is a more potent risk factor for ischemic stroke than ICH (McGrath et al., 2012). Our findings were consistent with this suggestion. For renal impairment and carotid stenosis, there was a trend toward an increased risk of ICH compared with ischemic stroke, which likely represents evidence of underlying vascular disease. The strengths of our study include the large sample size, and the large number of ICH and ischemic stroke events compared with previous studies. The findings provide further guidance to clinicians when making decisions about suitability for antithrombotic therapy in patients with AF.

In conclusion, old age was more strongly associated with ischemic stroke than ICH, while carotid stenosis and renal impairment was associated with an increased ICH risk. Classic risk factors for stroke have considerably different relationships with the two main pathologic types of stroke.

Study limitations

We note several limitations to our findings as intrinsic limitations exist in nationwide cohort study like this. First, the NHIS data does not contain laboratory or clinical measurements. Therefore, important information was not available for analysis, including serum hemoglobin, renal and liver function, blood pressure, and body weight. Second, our registry data did not provide details regarding drug changes over time or the quality of anticoagulation control (e.g., time-in-therapeutic range), which is important for warfarin management. Third, we were not able to clearly confirm the cause of ischemic stroke, which could be due to AF-related thromboembolism or atherosclerosis and thrombosis of the cerebral artery. This has also been a common limitation in previous randomized trials.

CONFLICT OF INTEREST

None of the authors declare any personal or financial conflicts of interest in relation to the data presented in this study.

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