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CLINICAL RESEARCH

Secondary prevention by stroke subtype: a nationwide follow-up study in 46 108 patients after acute ischaemic stroke

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Aims Although use of antithrombotic agents is recommended after ischaemic stroke or transient ischaemic attack (TIA), long-term outcome of secondary prevention between stroke subtypes has not yet been explored.

Methods and results We used data from the Korean Stroke Registry (KSR), a nationwide, multicentre, prospective registry for acute stroke patients. Patients with acute ischaemic stroke or TIA within 7 days of onset were consecutively enrolled between January 2002 and September 2010. A total of 46 108 patients with ischaemic stroke and TIA were included in this study. Among the major stroke subtypes, stroke due to small vessel occlusion (SVO) showed the lowest mortality, whereas cardioembolic stroke (CE) was associated with the fatal prognosis during the follow-up [for SVO: hazard ratio (HR) 0.66, 95% CI 0.62–0.71; for CE: HR 1.41, 95% CI 1.30–1.53; large artery atherosclerosis (LAA) group as a reference]. Regarding secondary prevention, antiplatelet polytherapy was better than monotherapy in the patients with LAA-related stroke in prognosis [HR 0.89, 95% CI 0.80–0.98]. Anticoagulant therapy was associated with better outcome than antiplatelet monotherapy in CE-related stroke [HR 0.66, 95% CI 0.59–0.74]. In SVO-related stroke group, antiplatelet polytherapy failed to show benefits over monotherapy. Additionally, the risk of death was higher with anticoagulant therapy in the patients with SVO-related stroke [HR 1.44, CI 95% 1.06–1.97].

Conclusions Our study demonstrated that stroke subtype affects prognosis and also determines the effectiveness of secondary prevention.

Keywords Ischaemic stroke • Stroke prevention • Antiplatelet

Introduction

Stroke is a disastrous disease with major mortality and severe morbidity worldwide.[1] However, not all strokes are associated with poor outcome. Because stroke is a clinical syndrome comprised of heterogeneous subtypes including ischaemic strokes due to large artery atherosclerosis (LAA), small vessel occlusion (SVO), and cardioembolism (CE) as proposed by the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria,[2] outcomes are quite variable.[3–5] In general, ischaemic stroke caused by SVO has the best prognosis with mild neurological disability, and stroke caused by CE has the poorest prognosis with a high risk of recurrent vascular events. However, outcome studies on the stroke subtypes have been rare, and prognosis of strokes due to undetermined (UD) or other determined (OD) causes has not been clearly demonstrated.

The core strategy for ischaemic stroke secondary prevention includes antiplatelet agents and anticoagulation using warfarin.[6,7] Dual or triple antiplatelet therapy using different antiplatelet mechanisms had been believed to have additional effects on ischaemic stroke prevention, but unfortunately have never been successful in most clinical trials.[8–10] In this context, the clinical practice guidelines for stroke prevention recommend single drug medication such as

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aspirin or clopidogrel in any case of ischaemic stroke except cardioembolic stroke.[11] However, in specific cases such as acute coronary syndromes, dual antiplatelet therapy is recommended, and it is theoretically understood that dual antiplatelet therapy is more powerful than single antiplatelet therapy.[12,13]

We started a nationwide stroke registry in 1999, the Korean Stroke Registry (KSR), to investigate characteristics, mechanisms, risk factors, neurological disability, and treatment strategy of stroke in Korea.[14] Using accumulated data from a large sample of representative hospitals in Korea, we sought to find whether stroke subtype affects long-term mortality and also determine the effectiveness of secondary prevention.

Methods

Study population

The KSR covers patients with acute ischaemic stroke patients admitted to major university and tertiary hospitals in Korea within 7 days after symptom onset. The registration data were gathered in the centralized web-based database. Participating centres were required to use a standardized case registration form to collect a predefined set of data. Trained physicians or research nurses recorded patients' information into the KSR database, and the consecutiveness and fidelity of data were confirmed by experienced vascular neurologists in each stroke centre. Between January 2002 and September 2010, 30 stroke centres with nationwide coverage registered 56 230 acute stroke patients consecutively. Among them, we excluded 10 122 patients because of haemorrhagic stroke ($n = 2680$), paediatric stroke ($n = 10$), unavailable mortality data ($n = 4983$), and delayed admission after 7 days from symptom onset ($n = 2440$). As a result, a total of 46 108 acute ischaemic stroke patients were finally included in the analysis. This study was approved by the local ethics committee and Institutional Review Board [H-0911-065-301]. This study complied with the Declaration of Helsinki, and informed consent has been obtained from the participants or their next of kin.

Data collection

Data on clinical, laboratory, radiological, treatment and neurological information for all subjects were collected. Collected data included age, sex, height, weight, date and time of stroke onset, time of hospital arrival, stroke subtype classification, risk factors such as hypertension, diabetes, hyperlipidaemia, smoking, cardioembolic risk factors, and history of a stroke or transient ischaemic attack (TIA), lesion location and angiographic findings, thrombolytic treatment, angioplasty, secondary preventive medication during admission and after discharge, and National Institute of Health Stroke Scale (NIHSS) at admission. Body mass index (BMI) was calculated using height and weight (kg/m^2). The stroke aetiology was based on clinical, medical, and radiological data and was assessed by stroke physicians according to the TOAST criteria.[2] All five original subtypes were included in the analysis plus TIA: (1) LAA, (2) CE, (3) SVO, (4) OD, and (5) UD. Stroke due to UD includes three subgroups; (5a) multiple aetiologies (ME), (5b) negative aetiology with extensive workup (NE), (5c) undetermined aetiology but incomplete evaluation (IE). The patients with LAA will have clinical findings of cerebral cortical impairment (aphasia, neglect, etc.) or brainstem or cerebellar dysfunction. There should be significant stenosis (>50%) or occlusion of a major brain artery, and corresponding infarcts greater than 1.5 cm in diameter on brain imaging. Potential source of cardiogenic embolism

Table 1 Baseline characteristics of study subjects

	Value	Total *N* available
Demographic information		
Age, years	66.1 ± 12.3	46 106 (100)
Male sex, *n* (%)	26 567 (57.6)	46 103 (100)
BMI, kg/m^2	23.7 ± 3.3	39 233 (85.1)
Mechanism of stroke		38 322 (83.1)
Large artery atherosclerosis, *n* (%)	13 066 (34.1)	
Small vessel occlusion, *n* (%)	9208 (24.0)	
Cardioembolism, *n* (%)	6197 (16.2)	
Other determined aetiology, *n* (%)	650 (1.7)	
Undetermined aetiology, *n* (%)		
2 or more, *n* (%)	1976 (5.2)	
Negative, *n* (%)	2589 (6.8)	
Incomplete, *n* (%)	1960 (5.1)	
TIA, *n* (%)	2676 (7.0)	
Risk factors		
History of TIA or stroke, *n* (%)	8081 (20.6)	39 305 (85.2)
Hypertension, *n* (%)	29 274 (67.4)	43 413 (94.2)
Diabetes, *n* (%)	13 867 (33.7)	41 121 (89.2)
Dyslipidaemia, *n* (%)	8888 (21.3)	41 722 (90.5)
Smoking, *n* (%)	15 197 (36.2)	41 948 (91.0)
Potential cardioembolic sources, *n* (%)	8967 (28.4)	41 948 (91.0)
Stroke management		
Intravenous rt-PA use, *n* (%)	2581 (8.8)	29 345 (63.6)
Intraarterial thrombolysis	1535 (5.4)	28 610 (62.0)
Angioplasty	528 (1.9)	28 475 (61.8)
Preventive medication during admission		40 203 (87.2)
Antiplatelet, *n* (%)	29 157 (74.4)	39 201 (85.0)
Anticoagulants, *n* (%)	7942 (26.7)	29 712 (64.4)
Secondary preventive medication		36 637 (79.5)
Antiplatelet monotherapy, *n* (%)	15 630 (42.7)	
Antiplatelet polytherapy, *n* (%)	13 990 (38.2)	
Anticoagulants, *n* (%)	5778 (15.8)	
Antiplatelet and anticoagulant, *n* (%)	1239 (3.4)	
Stroke severity		
NIHSS at admission, median (SD)	4 (2–8)	43 713 (94.8)
mRS at discharge, median (SD)	2 (1–3)	36 633 (79.5)
Long-term outcome		
All cause death, *n* (%)	10 366 (22.5)	46 108 (100)
Vascular death, *n* (%)	5196 (11.9)	43 708 (94.8)
Non-vascular death, *n* (%)	2770 (6.3)	43 708 (94.8)
Follow-up duration, years	2.4 (1.0–4.3)	46 102 (100)

BMI, body mass index; mRS, modified Rankin scale; NIHSS, National Institutes of Health stroke scale; rt-PA, recombinant tissue-plasminogen activator; TIA, transient ischaemic attack.

should be excluded to diagnose stroke with LAA. Clinical and radiologic presentations of stroke due to CE are similar to stroke due to LAA, except for positive CE source and negative atherosclerotic lesion. Small vessel occlusion is diagnosed when patients have lacunar syndromes and brain lesion less than 1.5 cm in diameter without having significant stenosis (>50%) or potential cardioembolic source. Stroke due to OD is diagnosed if stroke has occurred due to unusual causes such as non-atherosclerotic vasculopathy, hypercoagulable states, or haematologic disorders. If no cause of stroke is found despite an extensive evaluation, the patient was classified as having a stroke with NE. Stroke due to ME includes patients with two or more potential causes of stroke. When no cause of stroke is found and evaluation is incomplete to make a correct diagnosis, patients are classified as undetermined stroke due to IE. Secondary preventive medication was further categorized into antiplatelet monotherapy, antiplatelet polytherapy, anticoagulation, and combination treatment of antiplatelet agent and anticoagulant (Supplementary material online, *Table S6*). Antiplatelet polytherapy means that a patient was taking more than two antiplatelet agents.

Mortality information was gathered from the Statistics Korea, a governmental statistics office in South Korea, current as of December 2010.[15,16] The date of death and cause of death according to the International Classification of Diseases, 10th Revision, were recorded. We divided mortality data into vascular death and non-vascular death. Vascular death was defined as death caused by stroke, myocardial infarction, heart failure, pulmonary embolism, cardiac arrhythmia, or other definite vascular causes. Non-vascular death was defined as death caused by accidents, cancer, pulmonary causes (such as pneumonia or chronic obstructive pulmonary disease), and other miscellaneous causes.

Statistical analysis

For statistical analyses, the patients were subdivided into eight groups according to the aetiology. The distributions of demographic, clinical, laboratory, stroke, and treatment data by the TOAST classification were analysed using the χ^2 test, or one-way analysis of variance (ANOVA), as appropriate. To impute missing values, a multiple imputation method was used, assuming that data were missing at random. We imputed five data sets using clinical, treatment, and outcome information by IVEware 0.2. In the imputation model, the event indicator and the Nelson–Aalen estimator of the cumulative hazard to the survival were included.[17]

The Kaplan–Meier product-limit method was used to estimate survival rates after stroke in terms of long-term mortality. And the survival rates of patients according to the aetiology, or secondary preventive medication were compared using the log-rank test. In addition, cumulative incidence curves adjusted for competing risk of death were estimated according to the secondary preventive medication.

To examine the relationship between secondary preventive medication and mortality subdivided by the stroke aetiology during the follow-up, the Cox proportional regression analysis was used to calculate the unadjusted and adjusted hazard ratios (HRs) with 95% confidence intervals (CIs). Log-minus-log plots were used to check proportional hazards assumptions. We also used the propensity score analysis to minimize the selection bias and to adjust for baseline differences. We estimated the propensity score between antiplatelet monotherapy and polytherapy, using all potential variables; age, sex, BMI, history of prior stroke, hypertension, diabetes, smoking, and dyslipidaemia, admission NIHSS, rt-PA and stroke subtype. And we then made a 1:1 matched pair set using greedy matching algorithm. We used paired *t*-test or McNemar test to analyse the post-match data set. To calculate the competing risk of vascular and nonvascular death, we used a modified Cox regression analysis, using SAS macro 'criskcox' which was publicly available. Two-tailed *P*-values <0.05 were considered significant. Data analysis was performed using SAS 9.3 (SAS Institute, Cary, NC, USA).

Results

Of the 46 108 subjects with acute ischaemic stroke, distributions of baseline characteristics from analysed patients are presented in *Table 1* and Supplementary material online, *Table S1*. According to the TOAST classification, there were 34% with LAA aetiology (n = 13 066), 24% with SVO (n = 9208), 16% with CE (n = 6197), 1.7% with OD (n = 650), 14.2% with UD (n = 6525), and 7% with TIA (n = 2676). Median follow-up was 2.4 years, during which 22.5% patient died. Admission NIHSS score was 4 (median, IQR 2–8), and discharge modified Rankin Scale (mRS) score was 2 (median, IQR 1–3). These were significantly different among TOAST subtypes. Mortalities were much higher in the CE and IE subtypes. Cardioembolic

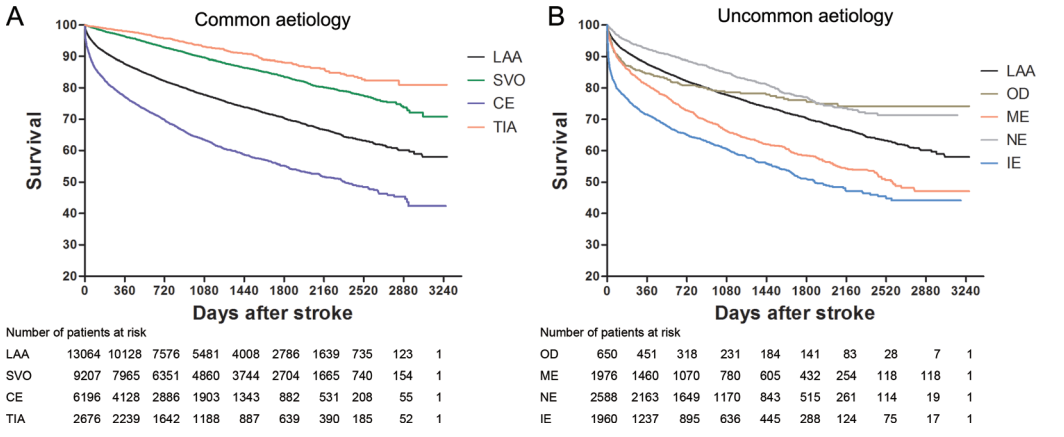

Figure 1 Kaplan–Meier curves of long-term mortality between TOAST subtypes. (*A*) Common TOAST subtypes (LAA, SVO, and CE). (*B*) Uncommon TOAST subtypes. LAA, large artery atherosclerosis; SVO, small vessel occlusion; CE, cardioembolism; TIA, transient ischaemic attack; OD, other determined aetiology; ME, multiple aetiologies; NE, negative aetiology; IE, undetermined aetiology but incomplete evaluation.

Table 2 Multivariable model hazard ratios for long-term outcomes by stroke subtype and secondary preventive medication

	HR (95% CI)[a]		
	All death	**Vascular death**	**Non-vascular death**
Large artery atherosclerosis	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Small vessel occlusion	0.66 (0.62–0.71)	0.55 (0.50–0.60)	0.81 (0.73–0.89)
Cardioembolism	1.41 (1.30–1.53)	1.47 (1.34–1.61)	1.22 (1.07–1.38)
Other determined aetiology	1.85 (1.56–2.20)	1.19 (0.91–1.55)	3.16 (2.48–4.03)
Undetermined aetiology			
Two or more	1.29 (1.18–1.42)	1.30 (1.14–1.48)	1.25 (1.06–1.49)
Negative	0.97 (0.88–1.08)	0.78 (0.68–0.90)	1.28 (1.10–1.49)
Incomplete	1.61 (1.47–1.77)	1.60 (1.39–1.85)	1.61 (1.39–1.87)
TIA	0.62 (0.54–0.71)	0.43 (0.33–0.55)	0.86 (0.69–1.07)
Secondary preventive medication			
Antiplatelet monotherapy	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Antiplatelet polytherapy	0.90 (0.85–0.96)	0.93 (0.86–1.00)	0.85 (0.76–0.95)
Anticoagulants	0.82 (0.75–0.91)	0.83 (0.75–0.93)	0.84 (0.72–0.97)
Antiplatelet and anticoagulant	0.86 (0.77–0.96)	0.80 (0.68–0.94)	1.01 (0.82–1.24)

HR, hazard ratio; CI, confidence interval; TIA, transient ischaemic attack.
[a]Hazard ratios were adjusted for age, sex, BMI, history of prior stroke, hypertension, diabetes, smoking, and dyslipidaemia, admission NIHSS, rt-PA, and secondary preventive medication at discharge.

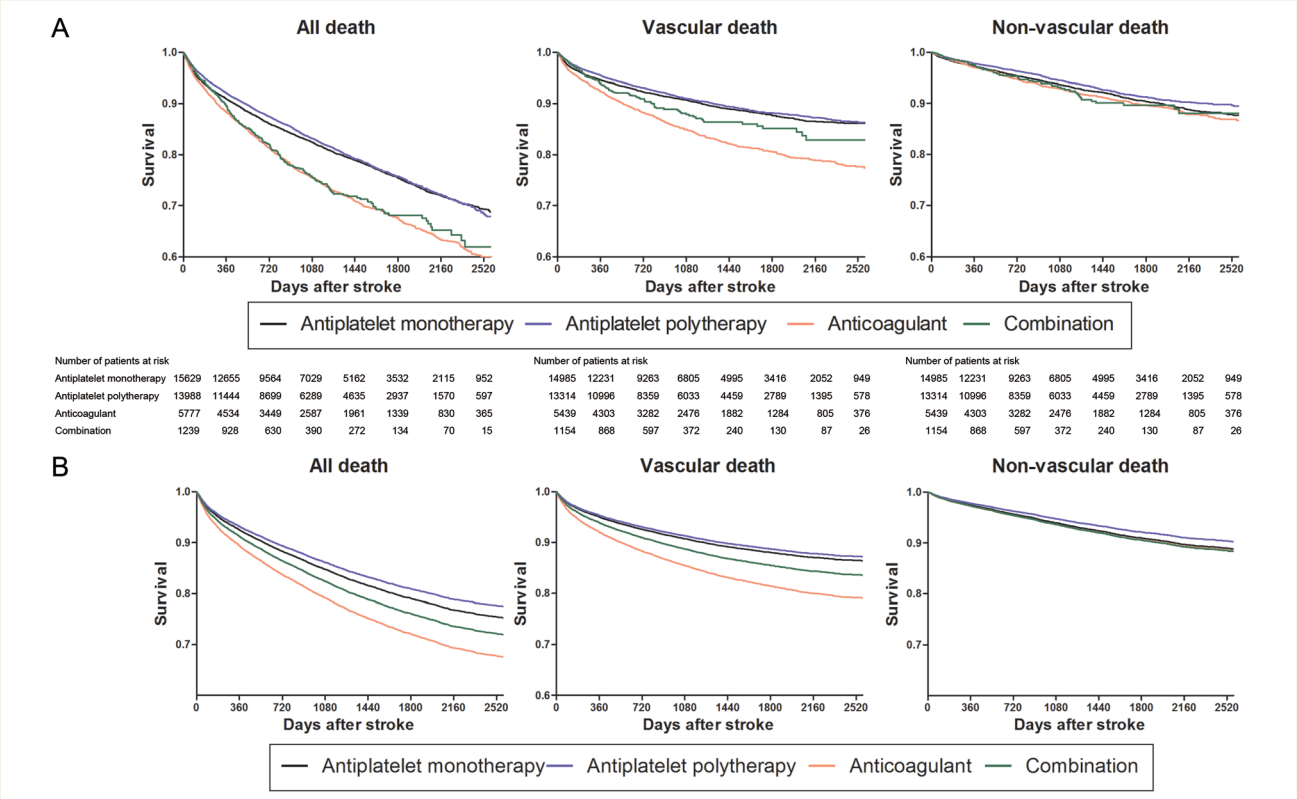

Figure 2 (*A*) Kaplan–Meier curves of long-term mortality by secondary preventive medications. (*B*) Cumulative incidence curves adjusted for competing risk of death by secondary preventive medications.

Table 3 **Long-term outcomes between secondary preventive medications by TOAST subtypes**

	HR (95% CI)[a]								
	All	Large artery atherosclerosis	Small vessel occlusion	Cardioembolism	Other determined aetiology	Undetermined aetiology			TIA
						Two or more	Negative	Incomplete	
All death									
Antiplatelet monotherapy	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Antiplatelet polytherapy	0.90 (0.85–0.96)	0.89 (0.80–0.98)	0.97 (0.83–1.12)	0.79 (0.66–0.95)	0.73 (0.40–1.34)	0.88 (0.71–1.11)	0.90 (0.74–1.10)	0.97 (0.81–1.15)	1.20 (0.91–1.59)
Anticoagulants	0.82 (0.75–0.91)	0.97 (0.77–1.23)	1.44 (1.06–1.97)	0.66 (0.59–0.74)	0.50 (0.24–1.08)	0.92 (0.77–1.10)	0.87 (0.58–1.30)	1.00 (0.76–1.32)	1.42 (0.97–2.10)
Antiplatelet and anticoagulant	0.86 (0.77–0.96)	1.14 (0.89–1.45)	0.74 (0.25–2.18)	0.66 (0.53–0.82)	0.69 (0.18–2.73)	0.84 (0.60–1.18)	1.60 (0.88–2.90)	0.63 (0.30–1.34)	0.91 (0.26–3.20)
Vascular death									
Antiplatelet monotherapy	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Antiplatelet polytherapy	0.93 (0.86–1.00)	0.90 (0.80–1.03)	1.11 (0.92–1.34)	0.79 (0.64–0.97)	0.82 (0.32–2.14)	0.90 (0.67–1.20)	1.02 (0.77–1.36)	1.00 (0.83–1.21)	1.37 (0.84–2.22)
Anticoagulants	0.83 (0.75–0.93)	0.97 (0.73–1.29)	1.71 (1.06–2.76)	0.65 (0.57–0.74)	0.48 (0.22–1.06)	0.95 (0.76–1.18)	0.81 (0.49–1.34)	1.04 (0.74–1.45)	2.32 (1.19–4.51)
Antiplatelet and anticoagulant	0.80 (0.68–0.94)	1.06 (0.67–1.68)	0.77 (0.20–3.04)	0.60 (0.46–0.78)	1.25 (0.31–5.12)	0.82 (0.56–1.19)	1.34 (0.46–3.89)	0.48 (0.11–2.10)	1.18 (0.08–17.7)
Non-vascular death									
Antiplatelet monotherapy	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Antiplatelet polytherapy	0.85 (0.76–0.95)	0.89 (0.74–0.99)	0.84 (0.68–1.05)	0.78 (0.55–1.11)	0.69 (0.32–1.50)	0.84 (0.60–1.19)	0.81 (0.60–1.09)	0.90 (0.60–1.35)	1.11 (0.77–1.61)
Anticoagulants	0.84 (0.72–0.97)	0.97 (0.76–1.24)	1.23 (0.76–2.01)	0.71 (0.56–0.89)	0.53 (0.19–1.46)	0.88 (0.63–1.21)	0.94 (0.54–1.62)	0.92 (0.53–1.62)	0.92 (0.44–1.93)
Antiplatelet and anticoagulant	1.01 (0.82–1.24)	1.27 (0.85–1.90)	0.68 (0.14–3.29)	0.86 (0.61–1.20)	Could not be estimated	0.86 (0.48–1.54)	1.78 (0.76–4.18)	0.91 (0.24–3.54)	0.62 (0.10–3.78)

HR, hazard ratio; CI, confidence interval; TIA, transient ischaemic attack.
[a]Hazard ratios were adjusted for age, sex, BMI, history of prior stroke, hypertension, diabetes, smoking, and dyslipidaemia, admission NIHSS, rt-PA, and secondary preventive medication at discharge.

stroke patients suffered 1.8 times higher mortality risk, and IE patients 1.9 times more compared with the LAA reference group.

As the survival curves illustrated in *Figure 1*, overall survival rates were significantly different among the stroke subtypes (the log-rank test, $P < 0.001$). Adjusted long-term outcome rates in the stroke subtypes were produced by Cox proportional hazard regression analyses (*Table 2*), with the LAA group was used as a reference. Other determined aetiology showed the highest risk of death (adjusted HR, 1.85; 95% CI, 1.56–2.20), and CE, ME, and IE aetiologies also showed increased risks of death. Surviving patients were likely to be female, younger, and non-diabetic and also likely to have higher BMI and lower NIHSS at admission (Supplementary material online, *Table S2*). In terms of treatment, survived patients were likely to be treated with intravenous thrombolytics using the recombinant tissue-plasminogen activator (rt-PA).

We analysed the effects of secondary preventive medication on long-term outcome (*Table 2*, Supplementary material online, *Tables S2–S3*, and *Figure 2*). In general, intensive antithrombotic treatments (antiplatelet polytherapy, anticoagulation, or combination of antiplatelet and anticoagulants) was associated with a lower risk of death, after adjusting for age, sex, BMI, history of prior TIA or stroke, hypertension, diabetes, smoking, dyslipidaemia, NIHSS on admission, and rt-PA use. When we divided the whole population according to the stroke subtypes, the effects of secondary preventive medications produced heterogeneous results, as shown in *Table 3*, Supplementary material online, *Tables S4–S5* and *Figure 3*. Stroke patients due to LAA aetiology were associated with better outcomes when they were treated with antiplatelet polytherapy than antiplatelet monotherapy (HR 0.89, CI 0.80–0.98). The Cox regression model adjusted for propensity score and matched Cox regression model also gave comparable results (Supplementary material online, *Tables S8 and S9*). Anticoagulant treatment was associated with poor long-term outcome in the SVO-related stroke patients, when compared with antiplatelet monotherapy (HR 1.44, CI 1.06–1.97). In CE-related stroke patients, intensive antithrombotic treatment using anticoagulation showed better outcomes (HR 0.66) than antiplatelet treatment. In other aetiologic

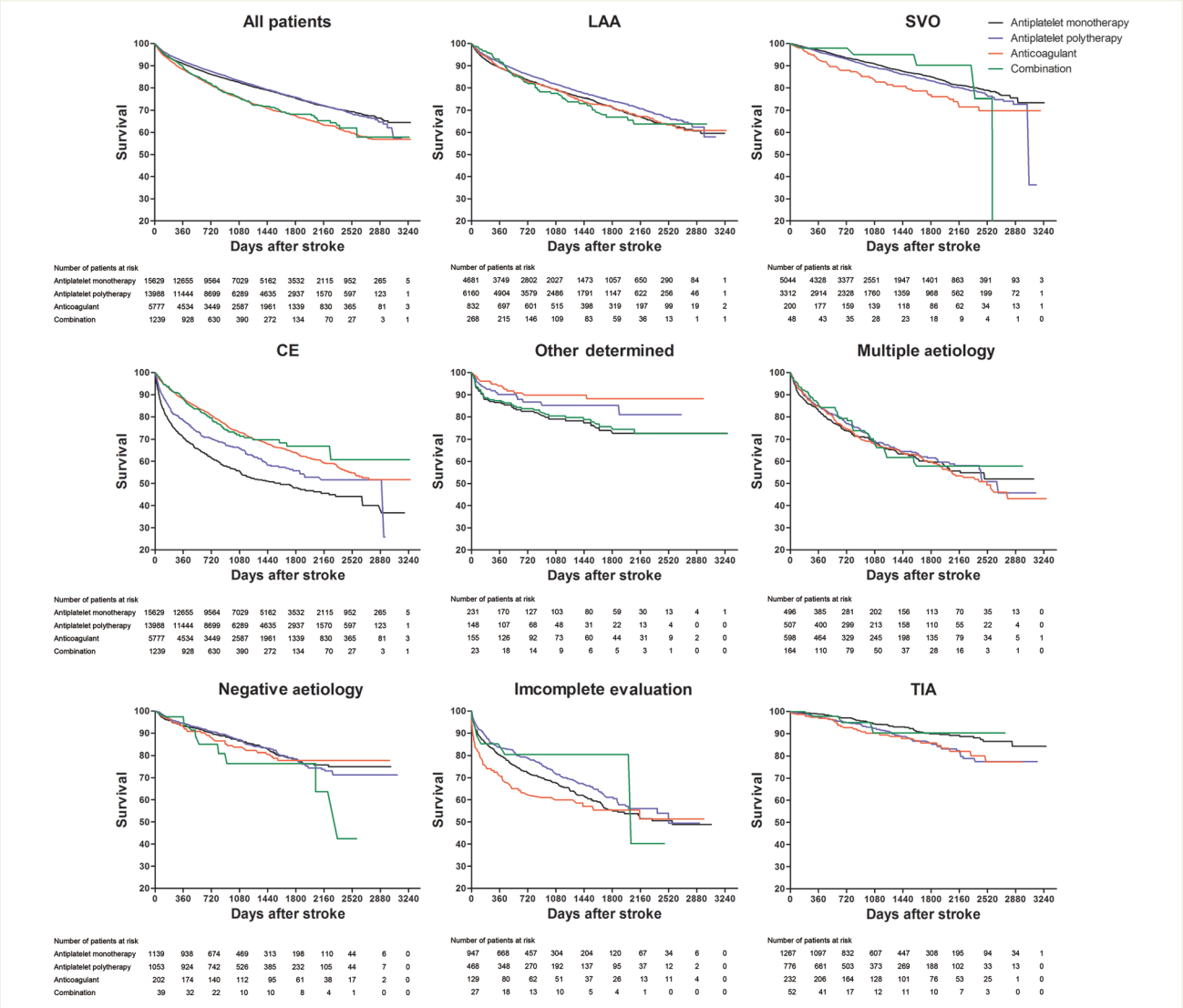

Figure 3 Kaplan–Meier curves of long-term mortality between secondary preventive medications by TOAST subtypes.

subtypes, secondary preventive medications had no association with the long-term outcome. Results were also comparable when we restricted our subjects over a year of follow-up (Supplementary material online, *Table S10*).

Medical treatment of antiplatelet and anticoagulants during admission also produced heterogeneous impacts on patients' long-term outcome by stroke subtype (Supplementary material online, *Table S4*). In regard to bleeding complications, compared with antiplatelet monotherapy, anticoagulants were significantly associated with the risk of haemorrhagic stroke, whereas antiplatelet polytherapy was not (*Table 4*).

Discussion

Using the nationwide stroke registry in Korea, we analysed the data of 46 108 patients with acute ischaemic stroke or TIA, and demonstrated several important findings. First, among the three major stroke subtypes (LAA, SVO, and CE), SVO-related stroke showed the most favourable prognosis, whereas CE-related stroke showed the poorest. Second, intensive antithrombotic strategies (antiplatelet polytherapy, anticoagulation, or combination of antiplatelet and anticoagulants) were generally superior to monotherapy regardless of causes of death. Third, antiplatelet polytherapy was associated with better prognosis than monotherapy in the patients with LAA-related stroke. And intensive antithrombotic strategies were also better than antiplatelet monotherapy in CE-related stroke.

It is noteworthy that antiplatelet polytherapy was superior to monotherapy in 'real' clinical practice, not recommended in the guidelines. In fact, in Korea, regardless of the recommendation of the guidelines, antiplatelet polytherapy for stroke patients is not prohibited by law, and had been freely prescribed in clinical practice during the study period. Heterogeneity of stroke patients in the previous clinical trials was indeed one of the major obstacles to reach proper evidence. The CHARISMA trial failed to show an additional benefit of dual antiplatelet treatment with aspirin and clopidogrel over aspirin monotherapy, although a *post hoc* analysis indicated small significant efficacy in the subpopulation with established vascular diseases.[9] More importantly, in the MATCH trial for secondary prevention in stroke patients, dual antiplatelet treatment with aspirin and clopidogrel was not better in efficacy and more harmful in safety (significantly increased fatal haemorrhage) than clopidogrel monotherapy.[8] However, in the trial, as many as 53% out of the enrolled patients had lacunar infarction due to SVO, which is the most serious problem in conducting clinical trials of stroke.[18] Small vessel occlusion is not related to plaque rupture and platelet activation, and is, at least pathologically, fairly closely associated with development of intracerebral haemorrhage. Consistent with this consideration, the recent SPS3 trial also failed to show benefit from the dual antiplatelet in the patients with SVO.[10] In this context, some recent trials made an effort to limit the enrolled population to patients with LAA-related stroke.[19,20] These repeated failures of large clinical trials on dual antiplatelet treatment led to the global recommendation in the clinical practice guideline that dual antiplatelet treatment should be banned in any case of stroke.[11] However, considering superiority of dual antiplatelet in coronary artery disease,[12] which is similar to LAA-related stroke in mechanism, we should have deliberated over the heterogeneous stroke subtypes.

Table 4 Death due to haemorrhagic stroke between secondary preventive medications by TOAST subtypes

	HR (95% CI)[a]				
	All	Large artery atherosclerosis	Small vessel occlusion	Cardioembolism	Other determined aetiology
Antiplatelet monotherapy	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Antiplatelet polytherapy	1.03 (0.79–1.33)	1.03(0.63–1.69)	1.29 (0.74–2.26)	0.97 (0.38–2.45)	Could not be estimated
Anticoagulants	1.61 (1.10–2.36)	1.73 (0.68–4.42)	2.01 (0.62–6.55)	1.05 (0.51–2.18)	1.00 (0.07–15.1)
Antiplatelet and anticoagulants	1.42 (0.73–2.76)	1.81 (0.50–6.48)	Could not be estimated	0.94 (0.20–4.34)	Could not be estimated
		Undetermined aetiology			**TIA**
		Two or more	**Negative**	**Incomplete**	
Antiplatelet monotherapy		1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Antiplatelet polytherapy		0.54 (0.15–1.88)	0.76 (0.25–2.33)	1.29 (0.43–3.86)	0.72 (0.14–3.71)
Anticoagulants		1.80 (0.81–4.03)	0.92 (0.10–8.38)	2.43 (0.58–10.2)	2.73 (0.59–12.5)
Antiplatelet and anticoagulants		Could not be estimated	3.92 (0.45–34.5)	Could not be estimated	Could not be estimated

HR, hazard ratio; CI, confidence interval; TIA, transient ischaemic attack.
[a]Hazard ratios were adjusted for age, sex, BMI, history of prior stroke, hypertension, diabetes, smoking, and dyslipidaemia, admission NIHSS, rt-PA, and secondary preventive medication at discharge.

The second major finding is the differential impacts of stroke subtypes on mortality after stroke. Mild neurological severity may give the best prognosis in SVO-related stroke, and the poor prognosis in CE-related stroke is consistent with the previous results, with patients prone to have cardiogenic vascular death caused by ischaemic heart disease or severe arrhythmia. Interestingly, we found that patients with OD or UD had heterogeneous outcomes, quite different from the homogeneous data in strokes related to LAA, SVO, or CE. The poor outcome in stroke with OD cause might be explained by the severity of underlying diseases such as systemic or cerebral vasculitis, cancer, moyamoya disease, hypercoagulant states, and other specific cerebrovascular diseases. In addition, stroke with UD cause is a kind of waste-basket diagnosis which includes multiple established aetiologies; no known cause and incomplete investigations, and their outcomes were highly heterogeneous. We hypothesize that patients undergoing incomplete investigation might have a variety of serious comorbidities, and that stroke with two or more aetiologies might include serious cardiac diseases. These hypotheses remain to be delineated.

There are several caveats in this study. First, we have prospectively collected the data using the established protocols before the enrolment, but the study idea was generated after the enrolment as a retrospective cohort study. In comparison with randomized clinical trials, this population-based observational study might have hidden confounding factors that cannot be fully adjusted by statistical methods. And hidden confounders which could not be expected at the beginning of this study may affect the results. Second, at the timing of our protocol development, statin, a HMG-CoA reductase inhibitor, was rarely prescribed in Korea, because the SPARCL study was published in 2006.[21] It is likely that during the first half of the study, statin was rarely prescribed, but during the latter half, considerable number of patients had received statin treatment. Third, we do not have information about bleeding complications during follow-up periods. Despite these concerns, our study has a few strong points. Sufficient number of stroke patients was enrolled in representative centres with nationwide coverage in Korea, and we used a very reliable mortality censoring method that is guaranteed by the national governmental system.[15,16]

In management of acute stroke patients, classification of stroke subtype is the beginning, but the most critical element. These outcome results should be used in prediction of stroke patients' prognosis and in education of stroke patients. Furthermore, we demonstrated that intensive antithrombotic treatment may offer a better chance to the patients with LAA-related stroke, which has been hypothesized, but failed for a long time. Because the current guidelines do not consider antiplatelet polytherapy for stroke patients, this option, potentially powerful, may lead to increase the survival after stroke, and should be reassessed promptly, especially in the LAA-related stroke.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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