Stroke subtype predicts outcome in young and middle-aged stroke sufferers

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Abstract

Objectives—There are few studies on long-term outcome after ischemic stroke (IS) for young and middle-age stroke sufferers in relation to etiologic subtypes. Here, we report 2-year outcome in the Sahlgrenska Academy Study on Ischemic Stroke (SAHLSIS).

Materials and methods—SAHLSIS comprises 600 patients with IS before the age of 70 years. Etiologic subtype of IS was classified according to TOAST. Recurrent vascular events and death were registered using several overlapping methods. Functional outcome was assessed according to the modified Rankin Scale (mRS).

Results—After 2 years, 55 (9.2%) patients had suffered a recurrent stroke, 15 (2.5%) a transient ischemic attack (TIA), 4 (0.7%) a coronary event, and 24 (4.0%) had died. The number of recurrent stroke, TIA, and death differed significantly between etiologic stroke subtypes. The highest rates were observed in large-vessel disease (LVD), whereas small-vessel disease and cryptogenic stroke showed the lowest recurrence and mortality rates. LVD was a significant predictor of the composite outcome (recurrent stroke, TIA, coronary event and/or death) independently of cardiovascular risk factors and stroke severity. Stroke subtype also predicted functional outcome two years after index stroke, but this association was not retained after adjustment for stroke severity.

Conclusions—In young and middle-aged stroke patients, stroke subtype predicts recurrent vascular events and/or death 2 years after index stroke independently of cardiovascular risk factors and stroke severity. Thus, it is important to take the etiologic subtype of IS in account when assessing the risk of recurrence both in the clinical setting and in future studies.

Introduction

Worldwide, stroke is a leading cause of death and disability. It is also a highly heterogeneous disorder; a broad spectrum of underlying etiologies poses challenge on the development of effective prophylaxis and treatment. In ischemic stroke (IS), the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification (1) is increasingly being used for classification of the etiologic subtype of IS. Previous studies have reported that etiologic subtypes of IS differ with respect to risk factor profiles (2-5), short time functional outcome and rate of early recurrence, with the best short-time prognosis in stroke due to small vessel disease (SVD) (3-6), whereas there is a high risk for early recurrence in stroke due to large vessel disease (6, 7).

Less information is available on prognosis in relation to etiologic subtype of IS beyond 6 months after index stroke and long-term outcome may show a different subtype-specific pattern compared to outcome after 3-6 months. For instance Staaf el al reported that, from 5 years and onward, the mortality rate in lacunar infarction is higher than previously thought (8). Furthermore, despite the fact that stroke incidence increases sharply at 40 years of age (9), few studies have focused on younger and middle-aged patients. In this age group the case-fatality is low. It follows that the patients live with the consequences of stroke and exposure to risk of a recurrent vascular event for a long time. Therefore, reliable data on long-term outcome with respect to risk of recurrent events as well as to functional outcome are wanted.

In this study, we used data from the Sahlgrenska Academy Study on Ischemic Stroke (SAHLSIS) (3), a sample of well characterized patients with IS <70 years, in order to assess functional outcome and recurrent vascular events in different etiologic subtypes of IS during 2 years follow-up.

Material and methods

Study Population

The study population comprised patients who participated in SAHLSIS, the design of which has been reported elsewhere (3). Six hundred patients who presented with first-ever or recurrent acute IS before reaching the age of 70 years were recruited consecutively from 1998 to 2003 at four Stroke Units in Western Sweden. IS was defined as an episode of focal neurological deficits with acute onset and lasting > 24 hours or until death, with no apparent non-vascular cause, and no signs of primary hemorrhage on brain-imaging. All patients were included within 10 days from the index stroke. Stroke severity at inclusion was scored using the Scandinavian Stroke Scale (SSS), a scale that describes no clinical deficit with a maximum score of 58 points. The study was approved by the Ethics Committee of the University of Gothenburg. All participants provided written informed consent prior to enrolment. For participants who were unable to communicate, consent was obtained from their next-of-kin.

Risk Factor Definition and Stroke Subtyping

Information on risk factors was collected as previously described in detail (3). All patients underwent computed tomography of the brain and ECG, and magnetic resonance imaging of the brain was performed in 62% (3). The etiologic subtypes of IS were classified according to the modified Trial of Org 10172 in Acute Stroke Treatment (TOAST) system. Cryptogenic stroke was defined when no cause was identified despite extensive evaluation. Other determined cause of stroke and undetermined stroke were merged into one category. For more details regarding diagnostic work-up and subtyping, please refer to the supporting information file.

Follow-up

Two years after the inclusion in the study, the survival rates of patients and controls as well as new or recurrent vascular events among patients were assessed using several overlapping methods. Survival rates were obtained from the Swedish population register (Folkbokföringen). For all non-survivors, cause of death was obtained from the Swedish Cause of Death Register, with death certificates, autopsy protocols, and medical records reviewed by a neurologist (P.R.) to establish the underlying cause of death. The Swedish Cause of Death Register is based on International Classification of Diseases version 10 (ICD 10), contains data on underlying cause of death, and is estimated to be 99% complete. Seven (29%), of the non-survivors were autopsied. All surviving patients were contacted by a study nurse trained in stroke medicine for a structured telephone interview that involved questions on recurrent stroke, transient ischemic attack (TIA), coronary events, and an assessment of functional outcome according to the modified Rankin Scale (mRS) (10). Approximately 5% of the patients were unable to provide an answer, and in these cases a relative, mainly spouses, were interviewed. The Swedish Hospital Discharge register, which has almost complete data (99%) for all hospital discharges in Sweden according to ICD 9 and 10, was screened for all patients and all diagnoses. When a cerebrovascular or other cardiovascular event was identified in this register or when there was a self-reported event, the medical records, including results from neuroimaging, from all the relevant hospitals and primary care units were reviewed by a neurologist (P.R.) to confirm the diagnosis according to criteria specified below. Given that some very early cardiovascular events may have gone undetected using this approach, all the medical records from hospitals and primary care units collated from presentation to 3 months after the index stroke, were reviewed for early stroke recurrence, TIA or coronary events by two neurologists (P.R. and K.J.).

Recurrent stroke was defined as a new sudden neurologic deficit or a deterioration of the previous deficit, which was not attributable to edema, hemorrhagic transformation, or concomitant illness. Both fatal and non-fatal stroke were included. The new neurologic deficit had to occur after > 24 hours of neurological stability and in non-fatal stroke the duration had to be > 24 hours. For TIA, the neurologic deficit had to have resolved completely within 24 hours. A coronary event was defined as a myocardial infarction (MI), hospitalization for unstable angina, acute coronary-artery bypass grafting or percutaneous coronary intervention. MI was defined as markers of myocardial damage indicative of myocardial ischemia with at least 1 of the following; symptoms of ischemia or electrocardiogram changes indicative of new ischemia (11).

Statistical Analyses

Differences in outcome based on etiologic subtype of IS were examined with the χ^2-test for proportions and Fisher´s exact test, as appropriate. The Kaplan-Meier method was used for each subtype, and heterogeneity was tested with the log-rank test. Cox proportional hazards multivariable analyses with stepwise forward selection of predefined variables (age sex, hypertension, smoking, diabetes, hyperlipdemia, SSS and stroke subtype) were used to identify variables associated with vascular events or death and with recurrent stroke or TIA. Multivariable analyses were not performed on the outcomes death or coronary events separately, due to a small number of events. Multivariable binary logistic regression with stepwise forward selection of predefined variables was used to calculate the odds ratios (OR) for a poor functional outcome (mRS 3-6). As the SSS at inclusion is expected to be highly correlated with the mRS score at follow-up, multivariable analysis was performed both without and with SSS as a covariate. For the etiologic subtypes of IS, SVD was used as the reference category. Variables that showed a *P*-value <0.1 were included in the final models. Missing values are reported and handled as described previously (3). All statistical analyses were performed using SPSS for Windows version 18.0.

Results

Two-year follow-up data were obtained for 594 patients. The distribution of the etiologic subtypes of IS as well as baseline characteristics of the whole sample and stroke subtypes are shown in Table 1. The mean SSS score at admission was 47. Data for SSS were missing for 16 participants. The SSS score differed significantly by stroke subtype ($P<0.01$, by Kruskal Wallis test).

Two years after the index stroke, 82 patients had suffered a recurrent stroke, TIA, coronary event and/or death, i.e. the composite outcome (Table 2). Four of the recurrent strokes were hemorrhagic and 11 were fatal. Overall, 71% of the deaths were due to cardiovascular disease, with 14 cases due to complications from the index stroke (3) or a recurrent stroke (11), one to congestive heart failure, one to aortic aneurysmal bleeding, and one to intestinal ischemia. Thus, all the coronary events were non-fatal MIs. In patients aged <45 years, there were no deaths or coronary events during the follow-up period, although 7.0% of these patients experienced a recurrent stroke and 1.4% had a TIA. The corresponding percentages for patients aged 45-69 years were: 4.6% for death, 9.5% for recurrent stroke, 2.7% for TIA, and 0.8% for coronary event.

The proportion of patients who suffered the composite outcome within 2 years after the index stroke differed significantly between the etiologic subtypes of IS (Table 2). Patients with LVD had the highest event rates for the composite outcome and for recurrent stroke after 3 months as well as after 2 years, and for death after 2 years. In the LVD group 24% underwent carotid endarterectomy, and two of the recurrent strokes were procedure-related. Patients with SVD had the lowest event rates of recurrent stroke/TIA whereas patients with cryptogenic stroke had the lowest mortality event rate. Figure 1 presents the cumulative proportion of patients surviving free of recurrent stroke or TIA.

Table 3 shows that age, SSS score at inclusion and etiologic subtype of IS are significant predictors of the composite outcome in the univariate and the multivariable analyses. Similar predictors were found when analyzing the outcome of recurrent stroke and/or TIA separately; multivariable HR (95% CI) 0.98 (0.96-1.00) for SSS and 3.05 (1.27-7.31) for the subtype of LVD. Excluding TIA from the model did not change the results (data not shown). Multivariable analysis including only patients with first-ever stroke showed similar results both for the composite outcome and for the outcome recurrent stroke or TIA (data not shown).

With regard to functional outcome after 2 years, 134 patients (23%) had a poor functional outcome (mRS 3-6). Among patients aged <45 years, 21% showed a poor outcome compared to 24% of the patients aged 46-69 years. The proportion of patients with a poor functional outcome differed between the etiologic subtypes of IS ($P<0.001$, χ^2-test). Figure 2 shows mRS scores after 2 years for the stroke subtypes. The proportion of patients with a poor functional outcome was as follows; LVD 34%, CE stroke 28%, other/undetermined stroke 27%, cryptogenic stroke 18%, and SVD 12%. Age, stroke subtype, diabetes and SSS score at inclusion showed associations with functional outcome (Table 3). Furthermore, when excluding SSS as a covariate, both age and stroke subtype predicted functional outcome independent of cardiovascular risk factors (hypertension, diabetes, hyperlipidemia and smoking), and LVD showed the poorest functional outcome (multivariable OR (95% CI) 3.08 (1.39-6.80) for LVD, 2.57 (1.20-5.48) for CE stroke, and 2.68 (1.32-5.43) for other/undetermined stroke compared to SVD). However, the association between etiologic subtype of IS and functional outcome did not remain when adjustment was also made for stroke severity measured as SSS at inclusion (Table 3).

Discussion

In this prospective 2-year follow-up cohort study of young and middle-aged patients with IS, we found that etiologic subtype of IS and SSS at admission were independent predictors of the composite outcome vascular events and/or death. This was also true when analyzing the outcome of recurrent stroke or TIA. Patients with LVD had a threefold increased risk of both recurrent stroke and death compared to the SVD group.

To the best of our knowledge, this is the first study showing that etiologic subtype of IS predicts the long-term risk of vascular events and/or death after IS, independently of stroke severity and cardiovascular risk factors. In line with the present results, two studies on IS before the age of 45 years reported that LVD had the highest rate of recurrent stroke or death (12) and of recurrent stroke (13) in long-term follow-up. However, both studies were small and the study by Kappelle et al (12) did not adjust for cardiovascular risk factor or stroke severity.

In contrast, two previous studies did not identify etiologic subtype of IS as a significant and independent predictor of long-term stroke recurrence (6, 14). Although the IS subtype of LVD displayed the highest stroke recurrence rate after 2 years in the study from Rochester, stroke subtype was not an independent predictor of this outcome (6). Both these studies included patients without an upper age limit, which increases the prevalence of comorbidity and combined stroke etiologies that may blur the effect of stroke subtypes on long-term outcome.

A high risk for early stroke recurrence (i.e. within 3 months) in the LVD group has been described in previous studies (6, 7). However, in the present study, LVD was associated with the highest rates of stroke recurrence and death during a more extended period of 3 months to 2 years following the index event. This indicates that the higher risk for stroke recurrence and death noted after 2 years of follow-up for patients with LVD cannot be attributed entirely to a high rate of early recurrence.

With respect to death, multivariable analyses were not applicable due to the small number of events. However, for death univariate analysis confirmed results from previous studies showing a comparatively favorable prognosis for SVD (6, 12, 14, 15). A more novel finding was that outcome in cryptogenic stroke is as favorable as for SVD with respect to survival. In previous studies, this subtype has usually been included in the undetermined stroke group.

Compared to previous studies we recorded a low rate of MIs (16, 17). A possible explanation is the considerably lower age in our cohort. In the study by Jackson et al a trend toward a lower incidence of MI after lacunar compared to nonlacunar stroke was reported (16). The low number of MIs precluded a similar comparison in the present study.

Age and etiologic subtype of IS predicted functional outcome independent of cardiovascular risk factors, and LVD showed the poorest functional outcome. However, the association between stroke subtype and functional outcome did not remain after adjustment for stroke severity as measured by SSS at inclusion. This does not imply that stroke subtype is unimportant with respect to long-term outcome, but rather that it exerts an effect on outcome through initial case severity, with both LVD and CE causing more damage than SVD. The distinction is not unimportant, because, as shown in a previous analysis from the same study population (3), risk factor - stroke associations differed by etiologic subtype of IS with e.g. smoking being more important for LVD than for SVD. Accordingly, decreasing rates of

smoking in the population might mean fewer severe stroke cases (18). There are few data on stroke subtype-specific long-term functional outcome (6, 13, 19). In the Rochester study (6), Petty et al. reported similar results to ours one year after stroke although multivariable analysis was not applied in this study.

A major strength of the present study is that we had complete follow-up with regard to death and cardiovascular events, and that only 1% of the patients were lost to follow-up with regard to functional outcome. However, the study also has some limitations. First, it is based on hospitalized cases. Nevertheless, the stroke admission rate in Sweden is high, with 87-94% of the cases <75 years being admitted to hospital (20, 21). Second, we used retrospective ascertainment of vascular events, and the event rate may be underestimated using a telephone interview. However, we used several overlapping sources to identify all events including the Cause of Death Register and the Hospital Discharge Register which both has an estimated completeness of 99%. All medical records were scrutinized for possible events to achieve an almost complete ascertainment of symptomatic events. Third, the mortality and event rates were low. Consequently, in the multivariable analyses it cannot be excluded that some associations were neglected due to lack of power.

In conclusion, in this cohort of young and middle-aged IS sufferers, we show that the etiologic subtype of IS predicts vascular events or death as well as recurrent stroke or TIA after 2 years independently of cardiovascular risk factors and stroke severity as assessed by SSS. Although the proportion of IS caused by LVD is relatively small in young and middle-aged stroke sufferers (3, 9), our results highlight a significant contribution of LVD to the burden of stroke also in these age groups, as the prognosis is poor particularly with respect to recurrent vascular events. Thus, in these age groups, etiologic subtype of IS should be considered with respect to prognosis, both in the clinical setting and in future studies.

TABLE 1. Baseline characteristics of overall ischemic stroke and the major etiologic subtypes of ischemic stroke

	Ischemic Stroke	**LVD**	**SVD**	**CE stroke**	**Cryptogenic stroke**	**Other/ Undetermined stroke**
	n=594	n=73 (12%)	n=122 (21%)	n=97 (16%)	n=161 (27%)	n=141 (24%)
Age, mean y (SD)	57 (10)	59 (8)	59 (7)	58 (10)	54 (12)	56 (11)
Male sex, no. (%)	380 (64)	54 (74)	75 (62)	66 (68)	94 (58)	91 (65)
Hypertension, no (%)	352 (60)	44 (63)	89 (73)	49 (52)	87(55)	83 (59)
Diabetes, no (%)	114 (19)	25 (34)	26 (21)	19 (20)	23 (14)	21 (15)
Hyperlipidemia, no (%)	410 (76)	53 (82)	76 (71)	73 (82)	106 (71)	102 (78)
Smoking, no (%)	228 (39)	39 (54)	53 (43)	33 (34)	59 (37)	44 (31)
Personal history of stroke, no (%)	113 (19)	21 (29)	24 (20)	22 (23)	18 (11)	28 (20)
SSS, mean score (SD)	47 (13)	45 (15)	52 (7)	45 (16)	48 (12)	45 (14)

LVD indicates large vessel disease; SVD small vessel disease; CE cardioembolic; SD standard deviation; SSS Scandinavian Stroke Scale. Risk factors were defined as described (3).

TABLE 2. Events recorded within 3 months and 2 years after the index ischemic stroke

	Ischemic Stroke	**LVD**	**SVD**	**CE stroke**	**Cryptogenic stroke**	**Other/ Undetermined stroke**	*P*-value
	n=594	n=73	n=122	n=97	n=161	n=141	
Composite outcome, n (%)							
3 months	38 (6.4)	9 (12.3)	1 (0.8)	7 (7.2)	8 (4.9)	13 (9.1)	<0.01
2 years	82 (13.8)	20 (27.4)	11 (9.0)	12 (12.4)	17 (10.6)	22 (15.6)	<0.01
Recurrent stroke, n (%)							
3 months	31 (5.2)	8 (11.0)	1 (0.8)	5 (5.2)	5 (3.1)	12 (8.5)	<0.01
2 years	55 (9.3)	14 (19.2)	6 (4.9)	8 (8.2)	9 (5.6)	18 (12.8)	<0.01
TIA, n (%)							
3 months	6 (1.0)	2 (2.7)	0	1 (1.0)	3 (1.9)	0	NS
2 years	15 (2.5)	3 (4.1)	2 (1.6)	1 (1.0)	8 (5.0)	1 (0.7)	<0.05
Coronary event, n (%)							
3 months	0	0	0	0	0	0	
2 years	4 (0.7)	1 (1.4)	2 (1.6)	1 (1.0)	0	0	NS
Death, n (%)							
3 months	7 (1.2)	1 (1.2)	0	3 (3.1)	0	3 (2.1)	NS
2 years	24 (4.0)	7 (9.6)	2 (1.6)	7 (7.1)	1 (0.6)	7 (4.9)	<0.01

Composite outcome describes patients suffering a recurrent stroke, a transient ischemic attack, a coronary event and/or death during follow-up. TIA indicates transient ischemic attack: other abbreviations, as in Table 1. Differences between etiologic subtypes of ischemic stroke were examined using the χ^2-test and Fisher's exact test.

TABLE 3. Predictors of the composite outcome, i.e. recurrent vascular events (stroke, TIA, coronary event) and/or death, and predictors of poor functional outcome (modified Rankin Scale score 3-6) 2 years after the index ischemic stroke.

	Recurrent vascular events and/or death		**Poor functional outcome**	
	Univariate HR (95% CI)	**Multivariable** HR (95% CI)	**Univariate** OR (95% CI)	**Multivariable** OR (95% CI)
Age	1.03 (1.01-1.06)*	1.03 (1.01-1.06)*	1.03 (1.01-1.05)**	1.04 (1.00-1.07)*
Sex (male)	1.03 (0.66-1.62)	0.86 (0.54-1.37)	1.02 (0.68-1.52)	0.78 (0.46-1.33)
Etiologic subtype of IS:				
SVD (reference)	1	1	1	1
LVD	3.47 (1.66-7.24)***	2.89 (1.36-6.16)**	3.72 (1.80-7.67)**	1.29 (0.51-3.26)
CE stroke	1.46 (0.50-3.55)	1.35 (0.59-3.10)	2.89 (1.44-5.81)**	0.88 (0.35-2.22)
Cryptogenic stroke	1.67 (0.64-2.59)	1.28 (0.60-2.77)	1.52 (0.77-3.00)	1.06 (0.47-2.37)
Other/Undetermined stroke	1.87 (0.90-3.85)	1.57 (0.74-3.35)	2.63 (1.37-5.07)**	1.33 (0.60-2.96)
Diabetes	1.60 (0.98-2.61)	1.40 (0.84-2.31)	1.72 (1.09-2.72)*	1.31 (0.71-2.41)
Hyperlipidemia	0.84 (0.49-1.44)	0.75 (0.43-1.31)	1.39 (0.83-2.33)	1.18 (0.61-2.27)
Hypertension	1.26 (0.79-2.01)	1.07 (0.65-1.77)	1.41 (0.94-2.13)	1.84 (1.01-3.34)*
Smoking	1.21 (0.78-1.89)	1.30 (0.82-2.07)	1.27 (0.86-1.88)	1.52 (0.89-2.58)
SSS at inclusion	0.98 (0.97-0.99)**	0.98 (0.97-1.00)*	0.91 (0.90-0.93) ***	0.90 (0.89-0.92) ***

HR indicates hazard ratio; IS ischemic stroke; other abbreviations, as in Table 1. For recurrent vascular events and/or death, Cox regression with stepwise forward selection of variables was used for multivariable analyses; age, etiologic subtype of IS and SSS are included in the final model. Multivariable logistic regression with stepwise forward selection of variables was used for poor functional outcome; age, hypertension and SSS are included in the final model (Hosmer and Lemeshow test=0.16).
* P<0.05, ** P<0.01, *** P<0.001.

Figure 1

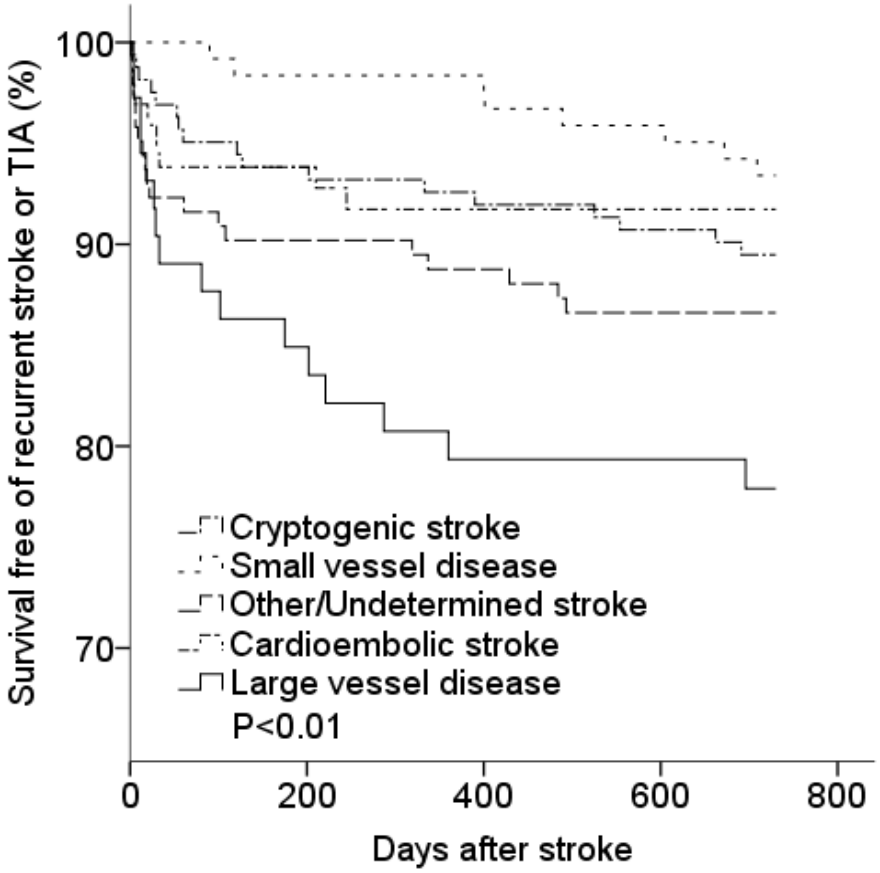

Figure 1
The Kaplan-Meier estimates of the probability of surviving free of recurrent stroke or TIA after the index IS according to etiologic subtype of IS. Log rank *P*<0.01.

Figure 2

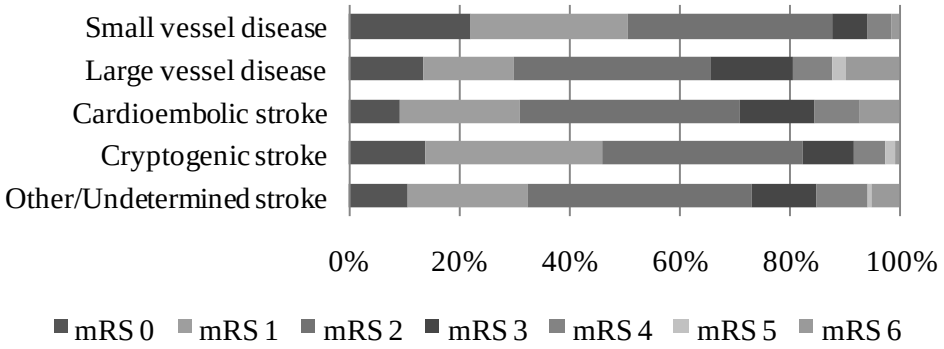

Figure 2
Distribution of modified Rankin Scale (mRS) scores by etiologic subtype of IS 2 years after the index IS.

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