Supplementary Material

Stroke Outcomes Are Worse with Larger Leukoaraiosis Volumes

Supplementary Table 1. Category of early neurological deterioration

Category	Definition
Stroke progression	Early neurological deterioration event in neurologically stable patients ≥24 hours - May be attributable to peri-lesional oedema - For cases with ≤ 24 hours after onset, early neurological deterioration events not attributable to recurrent stroke or peri-lesional oedema
Stroke recurrence	Development of early neurological deterioration associated with new lesions documented by relevant neuroimaging study - Discrete new lesions documented by diffusion-weighted image or computed tomography - If discrete, new lesions within the vascular territory of the index stroke lesion may be counted - Do not count for increased volume of the index stroke lesions - Do not count for oedema, mass effect, herniation, or haemorrhagic transformation of the index stroke lesions
Symptomatic haemorrhagic transformation	Early neurological deterioration events attributable to documented haemorrhagic transformation and associated with NIHSS score increase ≥ 4 points
Other causes of early neurological deterioration	Defined as early neurological deterioration attributable to other medical illness including pneumonia, deep vein thrombosis, urinary tract infection, sepsis, metabolic or electrolyte imbalance, and so on
Unknown	Early neurological deterioration events not specified above

Supplementary Table 2. Comparison of the baseline characteristics of the included vs. excluded patients

	Included (n = 5035)	Excluded[a] (n = 1117)	P-value[b]	Adjusted P-value[d]
Age, years	66.3 (12.8)	69.0 (13.5)	< 0.001	NA
Sex, male	3003 (59.6%)	614 (55.0%)	0.004	NA
Hypertension	3250 (64.6%)	745 (66.7%)	0.17	0.75
Diabetes	1363 (27.1%)	370 (33.1%)	< 0.001	< 0.001
Hyperlipidemia	1587 (31.5%)	346 (31.0%)	0.73	0.85
Smoking	1951 (38.8%)	414 (37.1%)	0.30	0.14
Coronary artery disease	375 (7.5%)	108 (9.7%)	0.012	0.038
Atrial fibrillation	989 (19.6%)	264 (23.6%)	0.003	0.17
Prior use of statin	558 (11.1%)	185 (16.6%)	< 0.001	< 0.001
Previous use of antiplatelet	1049 (20.8%)	347 (31.1%)	< 0.001	< 0.001
Thrombolysis	910 (18.1%)	159 (14.2%)	0.002	0.003
NIHSS score	3 (1–7)	5 (2–11)	< 0.001[c]	

NA = not available. Data are mean (SD), number (percentage), or median (IQR).

[a]Excluded due to contraindications to MRI (n = 234), poor quality or unavailability of MRI (n = 636), MRI scans not registered (n = 25), and lost to follow-up (n = 222).

[b]P-values by Student's t-test or χ^2 test, unless otherwise indicated.

[c]Wilcox Rank-Sum test.

[b]Adjusted for age and sex.

Supplementary Table 3. Bivariable and multivariable ordinal logistic regression analyses between covariates and modified Rankin Scale score at 3 months

	Bivariable analysis		Multivariable analysis*	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age, years	1.05 (1.04–1.05)	< 0.001	1.03 (1.02–1.03)	< 0.001
Sex, male	0.64 (0.58–0.71)	< 0.001	0.90 (0.80–1.02)	0.11
Hypertension	1.31 (1.20–1.45)	< 0.001	0.98 (0.88–1.08)	0.64
Diabetes	1.25 (1.12–1.39)	< 0.001	1.22 (1.08–1.38)	0.002
Hyperlipidemia	0.73 (0.63–0.84)	< 0.001	0.85 (0.67–1.06)	0.15
Smoking	0.69 (0.63–0.76)	< 0.001	1.06 (0.94–1.20)	0.32
Coronary artery disease	1.56 (0.31–1.84)	< 0.001	1.02 (0.85–1.22)	0.87
Atrial fibrillation	2.60 (2.23–3.03)	< 0.001	1.04 (0.88–1.23)	0.61
Stroke subtype				
Large artery atherosclerosis	Reference			
Small vessel occlusion	0.49 (0.43–0.56)	< 0.001		
Cardioembolism	1.73 (1.52–1.97)	< 0.001		
Undetermined	1.18 (1.04–1.35)	0.01		
Other determined	0.80 (0.58–1.10)	0.17		
Prior use of statin	0.81 (0.70–0.94)	0.006	0.72 (0.56–0.92)	0.01
Previous use of antiplatelet	1.01 (0.90–1.13)	0.92		
Thrombolysis	2.28 (2.01–2.58)	< 0.001	0.65 (0.56–0.75)	< 0.001
NIHSS score	1.26 (1.24–1.27)	< 0.001	1.22 (1.21–1.24)	< 0.001
Log infarct volume, 1 log	1.70 (1.64–1.75)	< 0.001	1.24 (1.19–1.29)	< 0.001
Body mass index, kg/m^2	0.92 (0.91–0.94)	< 0.001	0.98 (0.97–1.00)	0.041
Haemoglobin, g/dl	0.84 (0.82–0.86)	< 0.001	0.94 (0.91–0.97)	< 0.001
Fasting glucose, mmol/l	1.09 (1.07–1.11)	< 0.001	1.07 (1.05–1.09)	< 0.001
Total cholesterol, mmol/l	0.91 (0.87–0.95)	< 0.001	1.01 (0.96–1.05)	0.82

ORs (95% CI) were derived from imputed dataset (n = 5035). Results for WMH quintiles were not shown. Ordinal logistic regression analysis was performed using 3-month modified Rankin Scale score as a dependent variable. *Covariates with $P < 0.2$ in the bivariable analysis were entered into the multivariable model.

Supplementary Table 4. Generalized estimating equations on association between quintiles of WMH volume and dichotomized modified Rankin Scale score (0–2 vs. 3–6) at 3 months after stroke

	All (*n* = 5035)		Large artery atherosclerosis (*n* = 1965)		Small vessel occlusion (*n* = 895)		Cardioembolism (*n* = 1035)	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
First quintile	Reference		Reference		Reference		Reference	
Second quintile	1.17 (0.91–1.49)	0.22	1.33 (0.89–1.99)	0.17	1.10 (0.39–3.10)	0.86	0.98 (0.58–1.68)	0.95
Third quintile	1.36 (1.06–1.75)	0.014	1.67 (1.11–2.50)	0.013	1.40 (0.52–3.76)	0.51	1.07 (0.62–1.82)	0.81
Fourth quintile	1.67 (1.30–2.14)	< 0.001	2.11 (1.40–3.17)	< 0.001	2.12 (0.80–5.62)	0.13	1.14 (0.66–1.96)	0.65
Fifth quintile	1.96 (1.51–2.53)	< 0.001	2.06 (1.35–3.14)	< 0.001	3.03 (1.12–8.22)	0.029	1.38 (0.79–2.40)	0.25
*P** for trend	< 0.001		0.001		0.014		0.87	

ORs (95% CI) were derived from imputed dataset (*n* = 5035). Generalized estimating equations for the entire study population and each stroke subtype were performed using dichotomized modified Rankin Scale score (0–2 vs. 3–6) at 3 months after ischaemic stroke as a dependent variable. Data for patients with undetermined (*n* = 1021) or other determined (*n* = 119) strokes are not shown. ORs were adjusted for age, admission NIHSS score, sex, body mass index, hypertension, diabetes, hyperlipidemia, smoking, coronary artery disease, atrial fibrillation, prior use of statin, haemoglobin, total cholesterol, fasting glucose, and log-transformed infarct volume (on diffusion-weighted MRI). * χ^2 trend test across quintiles.

Supplementary Table 5. Multivariable analysis between quintiles of WMH volume vs. modified Rankin Scale score at 3 months or early (onset to 3 weeks) neurological deterioration: further adjustment for the degree of relevant artery stenosis in the large artery atherosclerosis group

	Modified Rankin Scale score at 3 months		Early neurological deterioration	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
First quintile	Reference		Reference	
Second quintile	1.18 (0.87−1.60)	0.28	1.05 (0.66−1.68)	0.84
Third quintile	1.24 (0.90−1.69)	0.18	1.27 (0.79−2.02)	0.32
Fourth quintile	1.88 (1.35−2.62)	< 0.001	1.74 (1.07−2.83)	0.026
Fifth quintile	2.00 (1.42−2.82)	< 0.001	1.72 (1.03−2.86)	0.037
*P** for trend	< 0.001		0.045	

ORs (95% CI) were derived from imputed dataset (n = 1921; 44 patients without angiographic data were excluded). Ordinal and binary logistic regression analyses were performed using 3-month modified Rankin Scale and early neurological deterioration (categorical yes/no) as dependent variables, respectively. Covariates included were age, admission NIHSS score, sex, body mass index, hypertension, diabetes, hyperlipidemia, smoking, coronary artery disease, atrial fibrillation, prior use of statin, thrombolysis, haemoglobin, total cholesterol, fasting glucose, log-transformed infarct volume on diffusion-weighted MRI, and the presence vs. absence of significant (≥ 50%) stenosis or occlusion of symptomatic intracranial or extracranial artery. * χ^2 trend test across quintiles.

Supplementary Table 6. Simple and multiple linear regression analyses between covariates and admission NIHSS score

	Bivariable analysis		Multivariable analysis*	
	Coefficient (95% CI)	*P*-value	Coefficient (95% CI)	*P*-value
Age, years	0.081 (0.069–0.093)	< 0.001	0.048 (0.037–0.060)	< 0.001
Sex, male	-0.573 (-0.894–-0.251)	< 0.001	-0.289 (-0.601–0.023)	0.07
Hypertension	0.437 (0.118–0.756)	0.007	-0.078 (-0.034–0.187)	0.57
Diabetes	-0.114 (-0.470–0.241)	0.53		
Hyperlipidemia	-0.297 (-0.767–0.172)	0.21		
Smoking	-0.616 (-0.939–-0.292)	< 0.001	0.079 (-0.221–0.380)	0.61
Coronary artery disease	2.031 (1.466–2.596)	< 0.001	0.686 (0.226–1.145)	0.003
Atrial fibrillation	4.038 (3.545–4.532)	< 0.001	0.605 (0.177–1.032)	0.006
Stroke subtype				
Large artery atherosclerosis	Reference			
Small vessel occlusion	-2.064 (-2.490–-1.638)	< 0.001		
Cardioembolism	3.884 (3.478–4.289)	< 0.001		
Undetermined	1.012 (0.605–1.420)	< 0.001		
Other determined	-0.328 (-1.325–0.668)	0.52		
Prior use of statin	0.123 (-0.380–0.626)	0.63		
Previous use of antiplatelet	0.525 (0.137–0.914)	0.008	-0.214 (-0.546–0.118)	0.21
Thrombolysis	6.618 (6.250–6.986)	< 0.001	4.656 (4.324–4.989)	< 0.001
Log WMH volume	0.321 (0.142–0.500)	< 0.001	0.050 (-0.109–0.210)	0.54
Log infarct volume	2.180 (2.095–2.264)	< 0.001	1.759 (1.673–1.846)	< 0.001
Body mass index, kg/m^2	-0.206 (-0.255–-0.157)	< 0.001	-0.077 (-0.119–-0.036)	< 0.001
Haemoglobin, g/dl	-0.231 (-0.313–-0.149)	< 0.001	0.014 (-0.061–0.089)	0.72
Fasting glucose, mmol/l	0.167 (0.110–0.223)	< 0.001	0.106 (0.063–0.149)	< 0.001
Total cholesterol, mmol/l	-0.304 (-0.452–-0.155)	< 0.001	-0.011 (-0.134–0.112)	0.86

Coefficients (95% CI) were derived from imputed dataset (n = 5035). WMH volume and infarct volume (on diffusion-weighted MRI) were transformed into a logarithmic scale. *Covariates with P < 0.2 in the simple linear regression analysis were entered into the multivariable model.

Supplementary Table 7. Multivariable analysis between quintiles of WMH volume and early (admission to 72 hours) neurological deterioration with / without stratification by stroke subtype

	All patients (n = 5035)	Large artery atherosclerosis (n = 1965)	Small vessel occlusion (n = 895)	Cardioembolism (n = 1035)
WMH quintile	Adjusted OR of early neurological deterioration (95% CI)			
First quintile	Reference	Reference	Reference	Reference
Second quintile	1.03 (0.77–1.39)	1.11 (0.71–1.73)	0.82 (0.34–1.99)	0.61 (0.32–1.17)
Third quintile	1.38 (0.99–1.78)	1.56 (0.97–2.51)	1.14 (0.50–2.58)	0.85 (0.47–1.56)
Fourth quintile	1.44 (1.07–1.94)	1.72 (1.10–2.71)	1.66 (0.74–3.74)	0.73 (0.39–1.37)
Fifth quintile	1.40 (1.03–1.90)	1.59 (1.02–2.48)	1.62 (0.68–3.87)	0.82 (0.45–1.52)
P^* for trend	0.04	0.09	0.38	0.64

ORs (95% confidence interval) were derived from imputed dataset (n = 5035). Results are from binary logistic regression analysis using early neurological deterioration (categorical yes/no) as a dependent variable. Data for patients with undetermined (n = 1021) or other determined (n = 119) strokes are not shown. ORs were adjusted for age, admission NIHSS score, sex, body mass index, hypertension, diabetes, hyperlipidemia, smoking, coronary artery disease, atrial fibrillation, prior use of statin, haemoglobin, total cholesterol, fasting glucose, and log-transformed infarct volume (on diffusion-weighted MRI), while using early neurological deterioration (presence / absence) as a dependent variable. $^*\chi^2$ trend test across quintiles.

Supplementary Table 8. WMH volume quintiles and symptomatic haemorrhagic transformation after intravenous tissue plasminogen activator therapy with or without intra-arterial intervention

	All (*n* = 910)	Intravenous tissue plasminogen activator without intra-arterial intervention (*n* = 566)	Intravenous tissue plasminogen activator with intra-arterial intervention (*n* = 208)
Symptomatic haemorrhagic transformation	48 (5.3%)	22 (3.9%)	15 (7.2%)
WMH quintile			
First quintile	11 (5.5%)	1 (0.9%)	5 (9.1%)
Second quintile	10 (5.2%)	4 (3.4%)	4 (9.1%)
Third quintile	10 (5.7%)	9 (8.6%)	1 (2.2%)
Fourth quintile	8 (4.5%)	4 (3.5%)	3 (8.3%)
Fifth quintile	9 (5.4%)	4 (3.5%)	2 (7.1%)
P-value	0.99[a]	0.078[b]	0.65[b]

Data are number (percentage). Symptomatic haemorrhagic transformation was defined as a cerebral haemorrhage documented by neuroimaging study and accompanied by an increase of ≥ 4 points on the NIHSS score compared with the baseline score or from the lowest NIHSS score in the individual subject before the development of haemorrhagic transformation.

[a]χ^2 test.

[b]Fisher's exact test.

Supplementary Table 9. Frequency and classification of early (from onset to 3 weeks) and late (from 3 weeks to 3 months) stroke recurrence in each quintile of WMH volume with or without stratification by stroke subtype

	All (*n* = 5035)	Large artery atherosclerosis (*n* = 1965)	Small vessel occlusion (*n* = 895)	Cardioembolism (*n* = 1035)
Stroke recurrence	167 (3.3%)	80 (4.1%)	8 (0.9%)	39 (3.8%)
Classification of recurrent stroke				
Large artery atherosclerosis	60 (35.9%)	51 (63.8%)	1 (12.5%)	1 (2.6%)
Small vessel occlusion	15 (9.0%)	6 (7.5%)	4 (50.0%)	3 (7.7%)
Cardioembolism	26 (15.6%)	4 (5.0%)	0	20 (51.3%)
Other determined	5 (3.0%)	1 (1.3%)	0	0
Undetermined	21 (12.6%)	6 (7.5%)	1 (12.5%)	3 (7.7%)
Haemorrhagic stroke	7 (4.2%)	3 (3.8%)	1 (12.5%)	1 (2.6%)
Transient ischaemic attack	3 (1.8%)	1 (1.3%)	0	0
Unknown	30 (18.0%)	0 (10.0%)	1 (12.5%)	11 (28.2%)
WMH quintile				
First quintile	29 (2.9%)	13 (3.4%)	1 (0.6%)	8 (4.0%)
Second quintile	29 (2.9%)	14 (3.5%)	1 (0.6%)	9 (4.7%)
Third quintile	34 (3.4%)	17 (4.4%)	1 (0.5%)	7 (3.3%)
Fourth quintile	34 (3.4%)	17 (4.2%)	1 (0.5%)	7 (3.3%)
Fifth quintile	41 (4.1%)	19 (4.8%)	4 (2.6%)	8 (3.7%)
P-value	0.56[a]	0.86[a]	0.20[b]	0.94[a]

Data are number (percentage).

[a]χ^2 trend test.

[b]Fisher's exact test.

Supplementary Table 10. Time from admission to discharge, stratified by stroke subtype and WMH volume quintiles

Days	All	Large artery atherosclerosis	Small vessel occlusion	Cardioembolism
	7.3 (5.3–11.1)	7.3 (5.3–10.7)	5.6 (4.3–8.0)	8.6 (6.0–13.9)
WMH quintiles				
First quintile	6.9 (5.1–10.4)	7.2 (5.4–10.4)	5.4 (4.2–6.8)	8.2 (5.5–13.1)
Second quintile	6.9 (5.2–10.4)	7.1 (5.3–10.5)	5.5 (4.3–7.5)	8.4 (5.6–11.9)
Third quintile	7.3 (5.3–11.5)	7.2 (5.4–11.0)	5.8 (4.5–7.7)	9.1 (6.0–15.0)
Fourth quintile	7.4 (5.2–11.3)	7.4 (5.3–11.4)	6.3 (4.4–8.5)	8.6 (6.2–14.3)
Fifth quintile	7.5 (5.4–11.5)	7.5 (5.4–11.2)	6.3 (4.2–9.6)	9.3 (6.3–14.6)
P-value[a]	0.001	0.67	0.02	0.32

Data are presented as median (IQR). Time from admission to discharge was significantly different between stroke subtypes ($P < 0.001$ by the Kruskal-Wallis test).

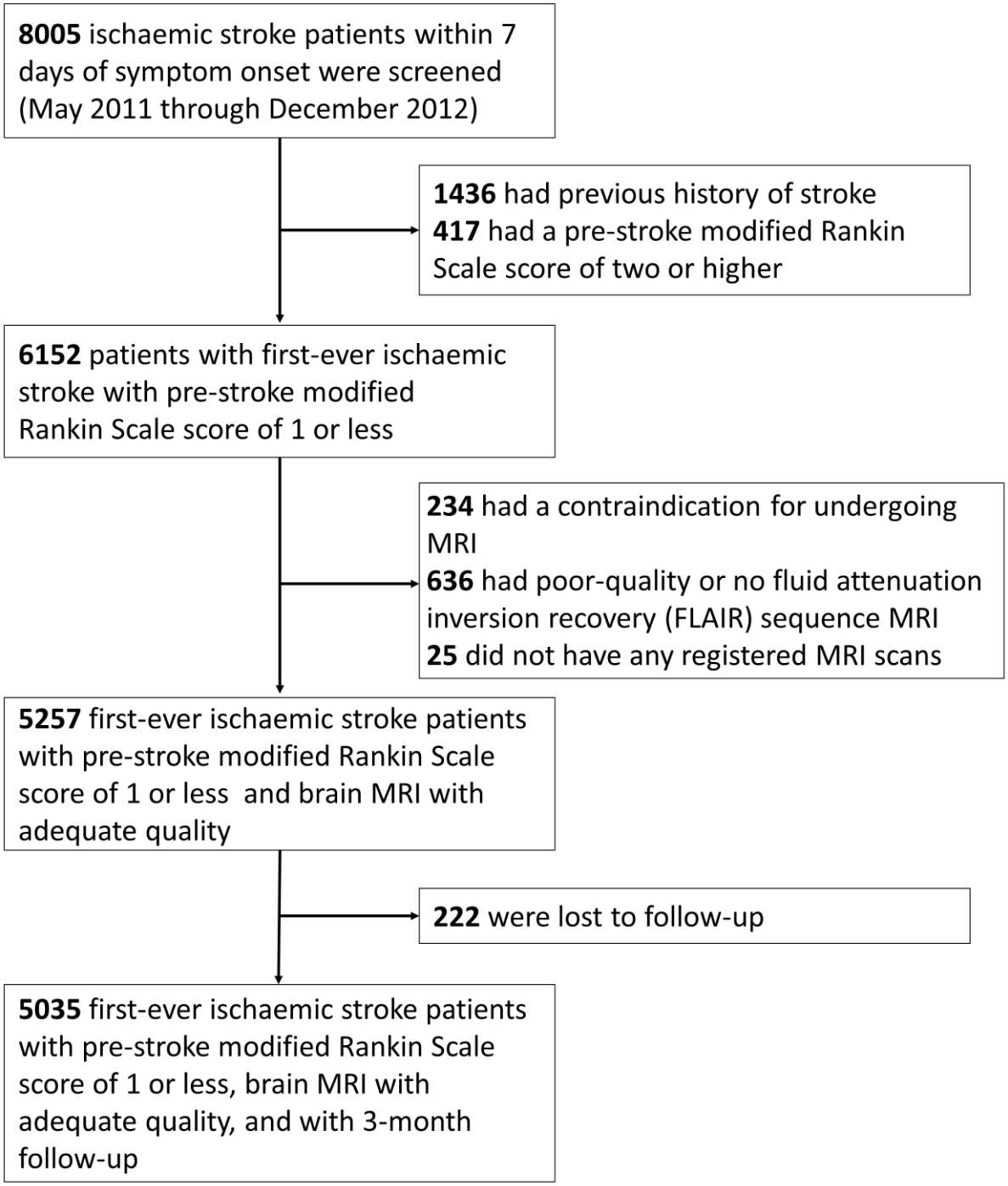
[a]Kruskal-Wallis test.

Supplementary Table 11. Multivariable analysis between quintiles of WMH volume and 3-month modified Rankin Scale score after stratification by stroke subtype: further adjustment for early neurological deterioration

	Large artery atherosclerosis (*n* = 1965)		Small vessel occlusion (*n* = 895)		Cardioembolism (*n* = 1035)	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
First quintile	Reference		Reference		Reference	
Second quintile	1.25 (0.96–1.63)	0.09	1.18 (0.78–1.78)	0.44	1.27 (0.88–1.85)	0.21
Third quintile	1.39 (1.06–1.84)	0.019	1.40 (0.93–2.11)	0.10	1.19 (0.81–1.74)	0.38
Fourth quintile	1.66 (1.26–2.21)	< 0.001	1.29 (0.83–2.02)	0.25	1.30 (0.88–1.92)	0.19
Fifth quintile	1.75 (1.30–2.34)	< 0.001	1.84 (1.14–2.96)	0.012	1.68 (1.13–2.50)	0.011
P for trend*	<0.001		0.22		0.35	

Ordinal logistic regression analysis was performed using 3-month modified Rankin Scale score as a dependent variable. Data for patients with undetermined (*n* = 1021) or other determined (*n* = 119) strokes are not shown. ORs were adjusted for age, admission NIHSS score, sex, body mass index, hypertension, diabetes, hyperlipidemia, smoking, coronary artery disease, atrial fibrillation, prior use of statin, thrombolysis, haemoglobin, total cholesterol, fasting glucose, log-transformed infarct volume on diffusion-weighted MRI, and early neurological deterioration.

*χ^2 trend test across quintiles



Supplementary Figure 1. Study flow chart

From May-2011 to December-2012, a total of 8005 patients with acute ischaemic stroke were admitted to 11 participating stroke centres within 7 days after symptom onset. Among 7354 consecutive patients with acute first-ever ischaemic stroke and pre-stroke modified Rankin Scale score of 1 or less, we analysed 5305 patients after excluding 1,117 patients whose MRIs or 3-month modified Rankin Scale score were unavailable.