

Table S1 Associations between PCSK9 and stroke recurrence at 12 months according to TOAST etiological subtype

	PCSK9 level	Events (%)	Model 1			Model 2			Model 3		
			HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
LAA	Q1	104 (15.0)	Ref.	Ref.		Ref.	Ref.		Ref.	Ref.	
	Q2	87 (13.2)	0.87	0.66–1.16	0.35	0.87	0.65–1.15	0.32	0.87	0.65–1.15	0.32
	Q3	62 (10.5)	0.68	0.50–0.93	0.02	0.67	0.49–0.92	0.01	0.67	0.48–0.91	0.01
	Q4	68 (11.9)	0.78	0.57–1.06	0.11	0.77	0.57–1.05	0.10	0.78	0.57–1.06	0.12
	Per 1 ng/mL		0.97	0.93–1.01	0.15	0.97	0.93–1.01	0.13	0.97	0.93–1.01	0.14
	Per 1-SD		0.92	0.82–1.03	0.15	0.92	0.82–1.03	0.13	0.92	0.82–1.03	0.14
CE	Q1	25 (13.1)	Ref.	Ref.		Ref.	Ref.		Ref.	Ref.	
	Q2	23 (14.7)	1.12	0.63–1.97	0.71	1.09	0.62–1.92	0.77	1.10	0.62–1.94	0.75
	Q3	23 (15.2)	1.14	0.65–2.01	0.64	1.16	0.65–2.05	0.62	1.16	0.65–2.06	0.61
	Q4	10 (6.9)	0.52	0.25–1.07	0.08	0.52	0.25–1.10	0.09	0.53	0.25–1.11	0.09
	Per 1 ng/mL		0.93	0.85–1.01	0.09	0.93	0.85–1.01	0.09	0.93	0.85–1.01	0.10
	Per 1-SD		0.82	0.66–1.03	0.09	0.82	0.66–1.03	0.09	0.83	0.66–1.04	0.10
SAO	Q1	48 (8.7)	Ref.	Ref.		Ref.	Ref.		Ref.	Ref.	
	Q2	36 (6.8)	0.79	0.51–1.21	0.27	0.79	0.51–1.21	0.29	0.79	0.51–1.21	0.28
	Q3	31 (5.9)	0.67	0.43–1.05	0.08	0.66	0.42–1.04	0.08	0.66	0.42–1.04	0.08
	Q4	30 (5.3)	0.59	0.38–0.94	0.03	0.61	0.38–0.96	0.03	0.61	0.38–0.96	0.03
	Per 1 ng/mL		0.95	0.89–1.01	0.13	0.96	0.90–1.02	0.17	0.96	0.90–1.02	0.17
	Per 1-SD		0.88	0.74–1.04	0.13	0.89	0.75–1.05	0.17	0.89	0.75–1.05	0.17
SOE	Q1	2 (8.7)	Ref.	Ref.		Ref.	Ref.		Ref.	Ref.	
	Q2	1 (3.7)	0.42	0.03–4.65	0.48	0.40	0.04–4.69	0.47	0.60	0.04–8.17	0.70
	Q3	0 (0.0)	–	–	–	–	–	–	–	–	–
	Q4	9 (28.1)	3.79	0.81–17.64	0.10	4.06	0.76–21.79	0.10	7.12	0.99–51.43	0.051
	Per 1 ng/mL		1.24	1.06–1.44	0.0058	1.29	1.07–1.57	0.01	1.32	1.08–1.62	0.01
	Per 1-SD		1.77	1.18–2.66	0.0058	1.99	1.18–3.34	0.01	2.12	1.24–3.63	0.01
SUE	Q1	96 (9.7)	Ref.	Ref.		Ref.	Ref.		Ref.	Ref.	
	Q2	114 (10.6)	1.08	0.83–1.42	0.56	1.09	0.83–1.42	0.56	1.07	0.82–1.41	0.61
	Q3	106 (9.2)	0.93	0.70–1.23	0.60	0.97	0.74–1.28	0.83	0.96	0.73–1.27	0.80
	Q4	101 (8.9)	0.89	0.67–1.17	0.40	0.93	0.70–1.23	0.59	0.92	0.69–1.21	0.54
	Per 1 ng/mL		0.98	0.95–1.02	0.35	0.99	0.95–1.03	0.55	0.99	0.95–1.02	0.51
	Per 1-SD		0.96	0.87–1.05	0.35	0.97	0.88–1.07	0.55	0.97	0.88–1.07	0.51

Model 1: adjusted for age and sex; Model 2: adjusted for age, sex, NIHSS and medical histories (diabetes mellitus, dyslipidemia, known atrial fibrillation, previous ischemic stroke and previous coronary artery disease); Model 3: adjusted for age, sex, NIHSS, medical histories (diabetes mellitus, dyslipidemia, known atrial fibrillation, previous ischemic stroke and previous coronary artery disease) and pre-hospitalization medication (antihypertensive drugs, lipid-lowering drugs, antiplatelet drugs, hypoglycemic drugs). PCSK9, protein convertase subtilisin/kexin type 9; LAA, large artery atherosclerosis; CE, cardioembolism; SAO, small artery occlusion; SOE, stroke of other determined etiology; SUE, stroke of undetermined etiology; HR, hazard ratio; OR, odds ratio; CI, confidence interval.

Table S2 Allele frequency and Hardy-Weinberg equilibrium

PCSK9 SNP	Minor allele	Minor allele frequency-N (%)	HWE-P value
rs2479394	T	39	0.1285
rs11206510	C	6	0.299
rs2479415	T	15	0.3051
rs2149041	G	34	0.2274
rs2479409	A	31	0.06619
rs11591147	T	0	1.000
rs11583680	T	11	0.3397
rs10888897	T	19	0.3309
rs7552841	T	16	0.8653
rs562556	G	1	1.000
rs505151	G	6	0.1508

PCSK9, protein convertase subtilisin/kexin type 9; SNP, single-nucleotide polymorphism.

Table S3 Concentrations of PCSK9 according to genotypes and genetic scores used as instrumental variables in genetic analyses

	Genotype	Patients (n)	PCSK9 level (95%CI)	P	F test	R ²
rs2479394	CC	3,247	(372.84, 382.01)	0.12	4.04	0.000931
	CT	4,051	(367.92, 376.12)			
	TT	1,365	(358.48, 372.62)			
rs11206510	TT	7,726	(372.80, 378.74)	<0.001	14.56	0.003353
	TC	901	(342.83, 360.21)			
	CC	34	(293.43, 382.92)			
rs2479415	CC	6,224	(371.09, 377.72)	1.71	0.1816	0.000394
	CT	2,250	(363.30, 374.33)			
	TT	192	(361.05, 398.81)			
rs2149041	CC	3,716	(380.78, 389.32)	<0.001	32.95	0.007553
	CG	3,867	(363.50, 371.87)			
	GG	1,079	(343.28, 359.12)			
rs2479409	GG	4,049	(375.31, 383.50)	<0.001	20.32	0.004679
	GA	3,781	(367.90, 376.38)			
	AA	819	(337.95, 356.18)			
rs11591147	GG	8,701	(370.38, 375.99)	0.36	0.84	0.000097
	GT	3	(292.94, 594.90)			
rs11583680	CC	6,885	(376.83, 383.09)	<0.001	51.14	0.011629
	CT	1,700	(343.13, 355.73)			
	TT	110	(279.66, 329.19)			
rs10888897	CC	5,629	(377.93, 384.86)	<0.001	42.39	0.009723
	CT	2,670	(355.86, 365.92)			
	TT	338	(313.26, 341.54)			
rs7552841	CC	6,153	(369.60, 376.27)	0.58	0.54	0.000124
	CT	2,302	(366.65, 377.55)			
	TT	221	(364.25, 399.42)			
rs562556	AA	8,560	(369.98, 375.63)	0.13	2.35	0.000271
	GA	121	(367.77, 415.30)			
rs505151	AA	7,668	(369.20, 375.17)	0.19	1.68	0.000388
	AG	950	(370.93, 387.89)			
	GG	22	(343.86, 455.30)			

PCSK9, protein convertase subtilisin/kexin type 9; CI, confidence interval.