

SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Methods

Assessment of Cause of Death

Deaths and causes of death were ascertained through monthly visits to the coroner's office, review of all death certificates in the study's general practices, practice-specific listings of all ICD-10 (International Classification of Diseases) death codes registered centrally, and daily identification via bereavement officers of patients who were dead on arrival at the hospital or who died soon after. If a patient died before assessment, we obtained an eyewitness account of the clinical event and reviewed any relevant records. If death took place outside the hospital or before investigation, the autopsy result was reviewed. Clinical details were sought from primary-care physicians or other clinicians on all deaths occurring in this cohort of ischaemic stroke survivors.

A list of all deaths occurring in Oxfordshire with a vascular ICD-10 code in any position on the death certificate is generated by the local Department of Public Health. These anonymised data are provided on a three-monthly basis. After a patient dies their GP notes are sent to central storage at the Thames Valley Health Authority headquarters. These notes were used to collect further past medical history, supplement missing data, and ensure accurate diagnosis of cause of death.

For the purposes of this analysis, deaths were coded as related to: (1) a recurrent ischaemic or haemorrhagic stroke, either acutely (<30 days) or non-acutely as a result of further stroke-related disability (ICD I607, I609, I610, I619, I620, I634, I635, I639, I64X, I678, I679, I694, I698); (2) a cardiac cause if the primary cause of death was deemed to be related to heart disease, including acute coronary syndromes (ICD I219, I251) and congestive heart failure; (3) pneumonia or other chest infection; (4) sepsis or other severe infection including meningitis and endocarditis; (5) dementia; (6) pulmonary embolism and/or deep-vein thrombosis (PE/DVT); (7) peripheral vascular disease (ICD I709, I710, I711, I713, I714, I718, I719, I728, I739); (8) cancer; (9) renal failure from acute or chronic kidney disease; (10) gastro-intestinal bleeding; (11) fall or similar trauma, including traumatic subdural haematoma or traumatic subarachnoid haemorrhage; (12) chronic obstructive pulmonary disease or other chronic lung disease; or (13) other cause, if the death did not fall into any of the aforementioned categories.

Table S1. Patient sample and characteristics for all 3-month survivors of ischaemic stroke and subgroups of interest

	Treatable major stroke patients (n=183)	Non-hyperacute/minor stroke patients (n=1,243)	Age- and sex-adjusted P	AF-related stroke patients (n=329)	Non-AF-related stroke patients (n=1,096)	Age- and sex-adjusted P	Lacunar stroke patients (n=234)	Non-lacunar stroke patients (n=1,191)	Age- and sex-adjusted P
Age, mean (S.D.)	75.3 (11.9)	72.9 (12.8)		78.3 (9.8)	71.7 (13.1)		69.9 (12.0)	73.8 (12.8)	
Sex – male (%)	90 (49.2)	663 (53.3)		168 (51.1)	585 (53.4)		143 (61.1)	610 (51.2)	
Previous history(%):									
MI	31 (16.9)	146 (11.8)	0.060*	61 (18.5)	116 (10.6)	0.001*	13 (5.6)	164 (13.8)	0.002*
Angina	30 (16.4)	209 (16.8)	0.71	79 (24.0)	160 (14.6)	0.007*	32 (13.7)	207 (17.4)	0.46
Atrial Fibrillation	54 (29.5)	206 (16.6)	<0.001*	257 (78.1)	3 (0.3)	<0.001*	2 (0.9)	258 (21.7)	<0.001*
Hypertension	120 (65.6)	769 (61.9)	0.63	231 (70.2)	658 (60.0)	0.10	145 (62.0)	744 (62.5)	0.87
Dyslipidemia	60 (32.8)	409 (32.9)	0.98	118 (35.9)	351 (32.0)	0.11	72 (30.8)	397 (33.3)	0.45
Diabetes	23 (12.6)	183 (14.7)	0.48	50 (15.2)	155 (14.1)	0.64	42 (17.9)	163 (13.7)	0.10
PVD	15 (8.2)	93 (7.5)	0.75	31 (9.4)	77 (7.0)	0.21	13 (5.6)	95 (8.0)	0.31
Stroke	19 (10.4)	139 (11.2)	0.54	53 (16.1)	105 (9.6)	0.03*	22 (9.4)	136 (11.4)	0.66
TIA	26 (14.2)	179 (14.4)	0.74	67 (20.4)	138 (12.6)	0.02*	29 (12.4)	176 (13.8)	0.75
Smoking	108 (59.0)	729 (58.7)	0.57	186 (56.5)	650 (59.3)	0.98	147 (62.8)	689 (57.9)	0.70
Cancer	37 (20.2)	184 (14.8)	0.15	61 (18.5)	160 (14.6)	0.90	32 (13.7)	189 (15.9)	0.61
Prior disability (mRS ≥3)	38 (20.8)	206 (16.6)	0.62	76 (23.2)	168 (15.4)	0.45	17 (7.3)	227 (19.1)	0.003*
NIHSS, median (IQR)	10 (7-15)	2 (0-3)	<0.001*	3 (1-8)	2 (0-4)	<0.001*	2 (1-3)	2 (1-5)	<0.001*

Significant differences ($p < 0.05$) between groups are indicated by an asterisk (*). For each subgroup pair (Treatable major strokes versus non-hyperacute/minor strokes, AF-related versus non-AF-related strokes, and lacunar versus non-lacunar strokes), age was compared using an independent samples T-test, while median and distribution of NIHSS were compared using independent-samples Median and Mann-Whitney U Tests respectively. The remaining dichotomous variables were compared using the Chi-squared test. Abbreviations: AF – Atrial Fibrillation, S.D. – Standard deviation, MI – Myocardial Infarction, PVD – Peripheral Vascular Disease, TIA – Transient Ischaemic Attack, mRS – modified Rankin scale, NIHSS – National Institutes of Health Stroke Scale, IQR – Inter-quartile range.

Table S2. Impact of 3-month mRS (>2 versus 0-2) on disability/death at 5-years (logistic regression) and 5-year mortality (Cox regression) for all 3-month ischaemic stroke survivors and subgroups, adjusted for age and sex

mRS >2 versus 0-2		Age		Male		N	c-statistic	
aOR/HR(95%CI)	p> z	aOR/HR	p> z	aOR/HR	p> z			
All stroke patients								
aOR (death/disability)	34.15 (23.57-49.48)	<0.0001*	1.08 (1.06-1.09)	<0.0001*	0.81(0.60-1.10)	0.180	1403	0.90
aHR(death)	2.93 (2.38-3.60)	<0.0001*	1.08 (1.07-1.09)	<0.0001*	1.25(1.03-1.52)	0.022*		
Treatable major strokes								
aOR	41.65(13.31-130.36)	<0.0001*	1.08 (1.03-1.12)	<0.0001*	2.08(0.68-6.37)	0.198	181	0.91
aHR	2.40 (1.19-4.86)	0.015*	1.10 (1.07-1.14)	<0.0001*	1.83(1.13-2.95)	0.015*		
Non-hyperacute/minor strokes								
aOR	29.00 (19.37-43.42)	<0.0001*	1.08 (1.06-1.10)	<0.0001*	0.74 (0.54-1.02)	0.068	1222	0.89
aHR	2.92 (2.33-3.66)	<0.0001*	1.07 (1.06-1.09)	<0.0001*	1.19 (0.96-1.47)	0.119		
AF-related strokes								
aOR	27.64 (13.09-58.35)	<0.0001*	1.08 (1.04-1.12)	<0.0001*	1.01(0.53-1.90)	0.988	320	0.89
aHR	2.65 (1.81-3.87)	<0.0001*	1.07 (1.05-1.10)	<0.0001*	1.44(1.04-1.99)	0.030*		
Non-AF-related strokes								
aOR	35.19 (22.94-53.99)	<0.0001*	1.07 (1.06-1.09)	<0.0001*	0.76(0.54-1.07)	0.117	1083	0.90
aHR	2.92 (2.28-3.75)	<0.0001*	1.08 (1.06-1.09)	<0.0001*	1.15(0.90-1.47)	0.255		
Lacunar strokes								
aOR	8.97 (4.13-19.49)	<0.0001*	1.09 (1.04-1.13)	<0.0001*	0.72(0.35-1.47)	0.369	234	0.85
aHR	1.18 (0.59-2.35)	0.633	1.11 (1.06-1.16)	<0.0001*	1.32(0.68-2.56)	0.417		
Non-lacunar strokes								
Aor	45.89 (29.54-71.30)	<0.0001*	1.08 (1.06-1.10)	<0.0001*	0.86(0.61-1.20)	0.377	1169	0.91
Ahr	3.16 (2.53-3.94)	<0.0001*	1.07 (1.06-1.09)	<0.0001*	1.27(1.04-1.56)	0.021*		

p>|X²| was <0.0001 for all the models. Significant p-values (<0.05) are indicated by an asterisk(*)

Abbreviations: aOR – adjusted odds ratio from logistic regression for 5-year disability/death, aHR – adjusted hazard ratio from Cox regression for 5-year mortality

Table S3. Impact of dichotomized 3-month mRS (>2 vs 0-2) on mortality for post-stroke years 1 to 4 for 3-month stroke survivors – controlling for age and sex – including treatable major strokes and related subgroups.

	mRS >2 versus 0-2		Age		Male		Total (n)
	Adj. HR (95% CI)	p> z	Adj. HR (95% CI)	p> z	Adj. HR (95% CI)	p> z	
All stroke patients							
Year 1	6.67 (4.16-10.69)	<0.0001*	1.06 (1.04-1.08)	<0.0001*	1.55 (1.09-2.20)	0.014*	1403
Year 2	4.80 (3.43-6.71)	<0.0001*	1.07 (1.05-1.08)	<0.0001*	1.32 (1.01-1.74)	0.046*	
Year 3	3.86 (2.94-5.08)	<0.0001*	1.07 (1.06-1.09)	<0.0001*	1.17 (0.93-1.49)	0.186	
Year 4	3.34 (2.64-4.22)	<0.0001*	1.08 (1.07-1.09)	<0.0001*	1.26 (1.02-1.56)	0.032*	
Treatable major strokes							
Year 1	9.61 (1.31-70.43)	0.026*	1.09 (1.04-1.14)	<0.0001*	1.75 (0.86-3.53)	0.120	181
Year 2	14.2 (1.95-103.2)	0.009*	1.10 (1.05-1.14)	<0.0001*	2.06 (1.12-3.78)	0.020*	
Year 3	2.51 (1.14-5.55)	0.023*	1.11 (1.07-1.15)	<0.0001*	1.83 (1.07-3.12)	0.027*	
Year 4	2.42 (1.15-5.09)	0.020*	1.11 (1.07-1.15)	<0.0001*	1.70 (1.02-2.81)	0.040*	
Non-hyperacute/minor strokes							
Year 1	5.97 (3.59-9.93)	<0.0001*	1.05 (1.03-1.08)	<0.0001*	1.59 (1.06-2.40)	0.027*	1222
Year 2	4.34 (3.03-6.21)	<0.0001*	1.06 (1.04-1.08)	<0.0001*	1.22 (0.89-1.67)	0.210	
Year 3	3.87 (2.87-5.23)	<0.0001*	1.07 (1.05-1.09)	<0.0001*	1.09 (0.83-1.42)	0.544	
Year 4	3.35 (2.60-4.32)	<0.0001*	1.08 (1.06-1.09)	<0.0001*	1.21 (0.96-1.54)	0.107	
AF-related strokes							
Year 1	10.48 (3.20-34.3)	<0.0001*	1.06 (1.02-1.10)	0.006*	1.55 (0.86-2.81)	0.148	320
Year 2	5.20 (2.64-10.25)	<0.0001*	1.07 (1.04-1.11)	<0.0001*	1.56 (0.99-2.47)	0.056	
Year 3	3.85 (2.29-6.49)	<0.0001*	1.07 (1.04-1.10)	<0.0001*	1.37 (0.92-2.03)	0.117	
Year 4	3.21 (2.08-4.96)	<0.0001*	1.07 (1.05-1.10)	<0.0001*	1.40 (0.98-2.00)	0.061	
Non-AF-related strokes							
Year 1	5.94 (3.51-10.07)	<0.0001*	1.06 (1.03-1.08)	<0.0001*	1.54 (1.00-2.38)	0.051	1083
Year 2	4.55 (3.07-6.73)	<0.0001*	1.06 (1.04-1.08)	<0.0001*	1.19 (0.84-1.68)	0.333	
Year 3	3.74 (2.70-5.16)	<0.0001*	1.07 (1.06-1.09)	<0.0001*	1.06 (0.79-1.44)	0.681	
Year 4	3.27 (2.47-4.32)	<0.0001*	1.08 (1.06-1.10)	<0.0001*	1.18 (0.90-1.53)	0.227	
Lacunar strokes							
Year 1	Only 1 death, so N/A						234
Year 2	1.99 (0.52-9.55)	0.389	1.15 (1.03-1.28)	0.011*	2.31(0.52-10.21)	0.269	
Year 3	1.68 (0.68-4.19)	0.262	1.12 (1.06-1.20)	<0.0001*	1.00 (0.41-2.43)	0.996	
Year 4	1.50 (0.67-3.34)	0.324	1.12 (1.06-1.19)	<0.0001*	1.14 (0.52-2.49)	0.739	
Non-lacunar strokes							
Year 1	6.66 (4.13-10.75)	<0.0001*	1.05 (1.03-1.08)	<0.0001*	1.57 (1.11-2.23)	0.011*	1169
Year 2	4.78 (3.39-6.74)	<0.0001*	1.06 (1.04-1.08)	<0.0001*	1.33 (1.01-1.76)	0.046*	
Year 3	4.06 (3.04-5.41)	<0.0001*	1.07 (1.05-1.09)	<0.0001*	1.21 (0.95-1.55)	0.126	
Year 4	3.51 (2.74-4.48)	<0.0001*	1.07 (1.06-1.09)	<0.0001*	1.29 (1.04-1.61)	0.021*	

p>|X²| was <0.0001 for each regression presented, except for Lacunar Strokes in Year 2, for which it was 0.0027.

Table S4. Impact of the 3-month mRS (using the full range of scores from 0 to 5) on 1-year and 5-year mortality for 3-month stroke survivors – controlling for age and sex.

	1-year Mortality		5-year Mortality	
	aHR(95%CI)	p> z	aHR(95%CI)	p> z
3-month mRS	0=Reference		0=Reference	
1	1.57 (0.35-7.08)	0.560	1.36 (0.73-2.52)	0.337
2	1.53 (0.33-7.12)	0.587	1.89 (1.02-3.49)	0.042*
3	4.62 (1.09-19.67)	0.038*	3.53 (1.93-6.43)	<0.0001*
4	11.15 (2.66-46.73)	0.001*	4.58 (2.49-8.43)	<0.0001*
5	26.24 (6.27-109.76)	<0.0001*	9.00 (4.84-16.74)	<0.0001*
Age	1.07 (1.04-1.09)	<0.0001*	1.08 (1.07-1.09)	<0.0001*
Male	1.95 (1.36-2.80)	<0.0001*	1.39 (1.14-1.69)	0.001*
	p> X ² <0.0001*		p> X ² <0.0001*	
	n 1403		n 1403	

Table S5. mRS changes between 3 months and 5 years (or 1 year if censored) for 3-month stroke survivors

All stroke patients

3-month mRS	mRS 5 years after index stroke						Death (%)	Total
	0	1	2	3	4	5		
0	55	60	10	0	0	0	12 (8.8)	137
1	67	218	64	11	6	1	60 (14.1)	427
2	25	84	93	19	8	2	74 (24.3)	305
3	0	8	29	53	29	6	126 (50.2)	251
4	0	0	7	23	47	11	92 (51.1)	180
5	0	0	0	3	10	20	70 (68.0)	103
Total	147	370	203	109	100	40	434 (30.9)	1403

3-month mRS missing in 22 cases; n=348 censored; for all of them, mRS at 1 year was available and this was used instead. p<0.0001.

Treatable major stroke patients

3-month mRS	mRS 5 years after index stroke						Death (%)	Total
	0	1	2	3	4	5		
0	2	1	0	0	0	0	0	3
1	2	8	0	1	1	0	2 (14.3)	14
2	1	6	6	2	0	0	7 (31.8)	22
3	0	1	5	11	2	1	18 (47.4)	38
4	0	0	2	7	17	5	24 (43.6)	55
5	0	0	0	1	6	10	32 (65.3)	49
Total	5	16	13	22	26	16	83 (45.9)	181

3-month mRS missing in 2 cases; n=36 censored; for all of them, mRS at 1 year was available and this was used instead. p<0.0001.

Non-hyperacute/minor stroke patients

3-month mRS	mRS 5 years after index stroke						Death (%)	Total
	0	1	2	3	4	5		
0	53	59	10	0	0	0	12 (9.0)	134
1	65	210	64	10	5	1	58 (14.0)	413
2	24	78	87	17	8	2	67 (23.7)	283
3	0	7	24	42	27	5	108 (50.7)	213
4	0	0	5	16	30	6	68 (54.4)	125
5	0	0	0	2	4	10	38 (70.4)	54
Total	142	354	190	87	74	24	351 (28.7)	1222

3-month mRS missing in 21 cases; n=312 censored; for all of them, mRS at 1 year was available and this was used instead. p<0.0001.

AF-related stroke patients

3-month mRS	mRS 5 years after index stroke						Death (%)	Total
	0	1	2	3	4	5		
0	8	6	0	0	0	0	3 (17.7)	17
1	7	33	11	3	0	0	15 (21.7)	69
2	1	15	15	4	3	1	20 (33.9)	59
3	0	1	8	13	12	1	50 (58.8)	85
4	0	0	1	4	11	4	32 (61.5)	52
5	0	0	0	0	3	6	29 (76.3)	38
Total	16	55	35	24	29	12	149 (46.6)	320

3-month mRS missing in 9 cases; n=59 censored; for all of them, mRS at 1 year was available and this was used instead. p<0.0001.

Non-AF-related stroke patients

3-month mRS	mRS 5 years after index stroke						Death (%)	Total
	0	1	2	3	4	5		
0	47	54	10	0	0	0	9 (7.5)	120
1	60	185	43	8	6	1	45 (12.6)	358
2	24	69	78	15	5	1	54 (22.0)	246
3	0	7	21	40	17	5	76 (45.8)	166
4	0	0	6	19	36	7	60 (46.9)	128
5	0	0	0	3	7	14	41 (63.1)	65
Total	131	315	168	85	71	28	285	1083

3-month mRS missing in 13 cases; n=289 censored; for all of them, mRS at 1 year was available and this was used instead. p<0.0001.

Lacunar stroke patients

3-month mRS	mRS 5 years after index stroke						Death (%)	Total
	0	1	2	3	4	5		
0	12	7	0	0	0	0	1 (5.0)	20
1	19	48	15	1	2	1	10 (10.4)	96
2	8	18	22	1	1	0	12 (19.4)	62
3	0	3	11	10	0	1	12 (32.4)	37
4	0	0	0	5	5	1	4 (26.7)	15
5	0	0	0	1	1	2	0	4
Total	39	76	48	18	9	5	39 (16.7)	234

3-month mRS available for all cases; n=55 censored; for all of them, mRS at 1 year was available and this was used instead. p<0.0001.

Non-lacunar stroke patients

3-month mRS	mRS 5 years after index stroke						Death (%)	Total
	0	1	2	3	4	5		
0	43	53	10	0	0	0	11 (9.4)	117
1	48	170	49	10	4	0	50 (15.1)	331
2	17	66	71	18	7	2	62 (25.5)	243
3	0	5	18	43	29	5	114 (53.3)	214
4	0	0	7	18	42	10	88 (53.3)	165
5	0	0	0	2	9	18	70 (70.7)	99
Total	108	294	155	91	91	35	395 (33.8)	1169

3-month mRS missing in 22 cases; n=293 censored; for all of them, mRS at 1 year was available and this was used instead. p<0.0001.

Table S6. Impact of dichotomized 3-month mRS (0-2 versus >2) on disability or death at 5 years for 3-month stroke survivors , for the overall cohort and relevant subgroups – controlling for age and sex, and excluding patients with premorbid disability

	mRS >2		Age		Male		Total (n)	c-statistic
	Adj. OR (95% CI)	p> z	Adj. OR (95% CI)	p> z	Adj. OR (95% CI)	p> z		
All stroke patients	25.22 (16.85-37.74)	<0.0001*	1.08 (1.06-1.09)	<0.0001*	0.80 (0.59-1.10)	0.172	1171	0.87
Treatable major strokes	31.49 (10.02-98.93)	<0.0001*	1.07 (1.03-1.12)	0.001*	1.96 (0.54-6.00)	0.237	145	0.90
Non-hyperacute/ minor strokes	19.80 (12.65-30.99)	<0.0001*	1.08 (1.06-1.10)	<0.0001*	0.74 (0.53-1.03)	0.074	1026	0.85
AF-related strokes	31.86 (12.71-79.90)	<0.0001*	1.08 (1.03-1.12)	<0.0001*	1.00 (0.51-1.97)	0.997	249	0.87
Non-AF-related strokes	22.52 (14.31-35.42)	<0.0001*	1.07 (1.06-1.09)	<0.0001*	0.74 (0.52-1.06)	0.101	922	0.86
Lacunar strokes	6.42 (2.79-14.81)	<0.0001*	1.09 (1.04-1.13)	<0.0001*	0.64 (0.30-1.33)	0.230	217	0.83
Non-lacunar strokes	35.52 (21.83-57.78)	<0.0001*	1.08 (1.06-1.10)	<0.0001*	0.87 (0.61-1.23)	0.429	954	0.88

p>|X²| was <0.0001 for each regression presented. Significant differences (p<0.05) between groups are indicated by an asterisk (*).

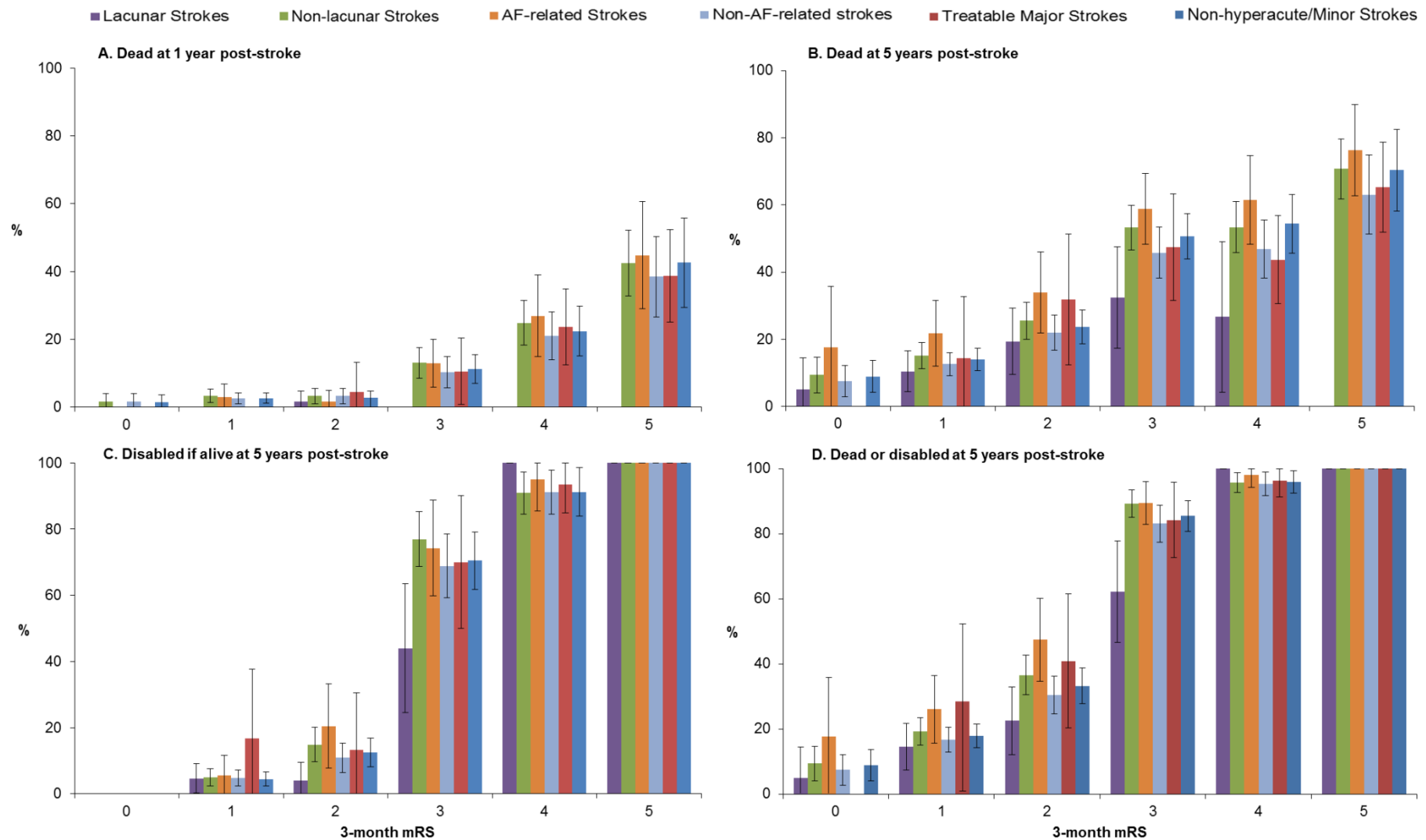


Figure S1. Proportions of 3-month ischaemic stroke survivors in subgroups, stratified by 3-month mRS, who were: (A) dead at 1-year; (B) dead at 5-years; (C) disabled (mRS>2) at 5-years, only including those alive at 5-years; and (D) dead/disabled at 5-years.

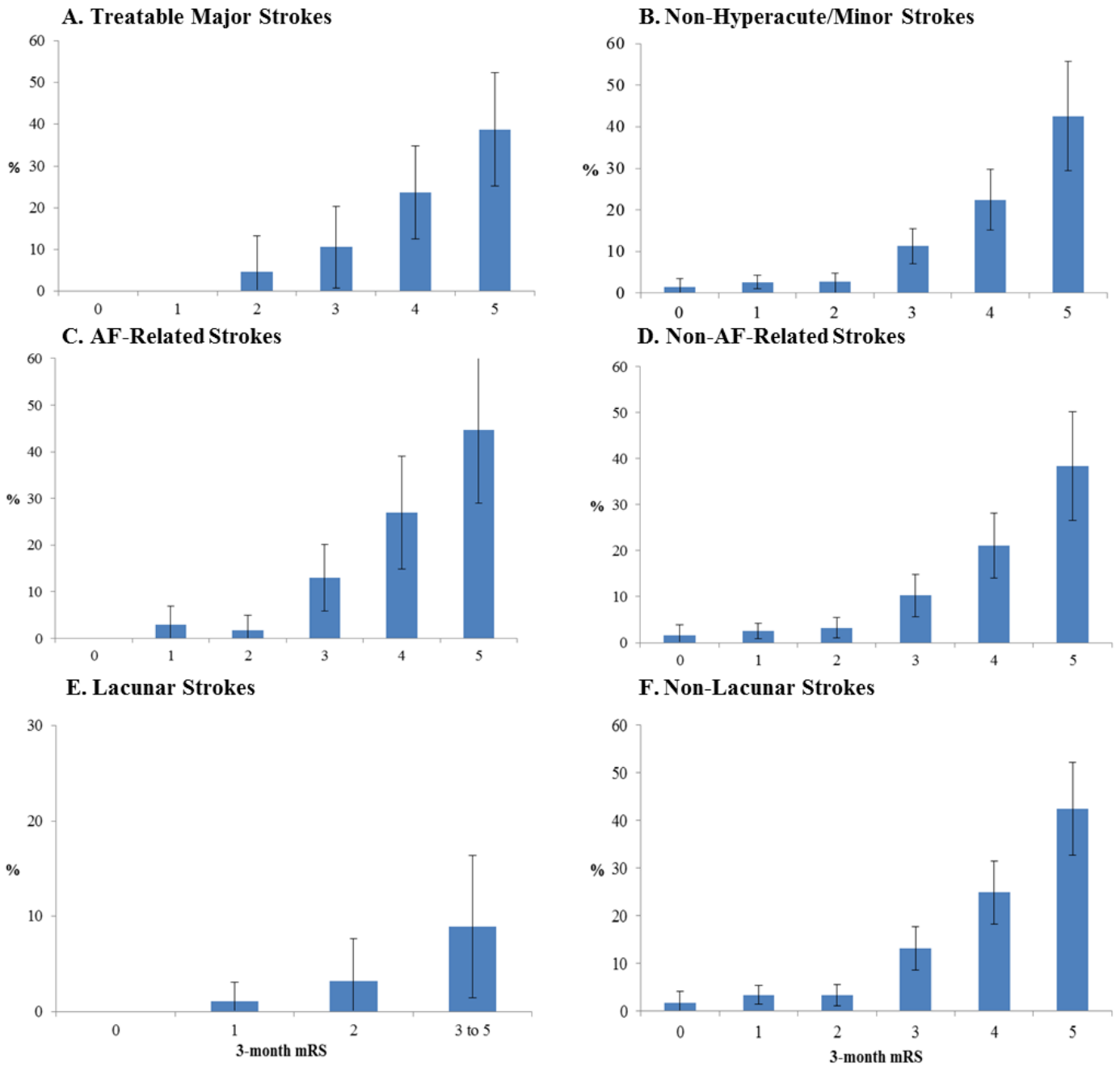


Figure S2. Proportions of 3-month survivors of ischaemic stroke for key subgroups, stratified by 3-month mRS, who were dead at 1 year (2 years for the lacunar subgroup, as there was only 1 death in the first year). Bars represent 95% confidence intervals.

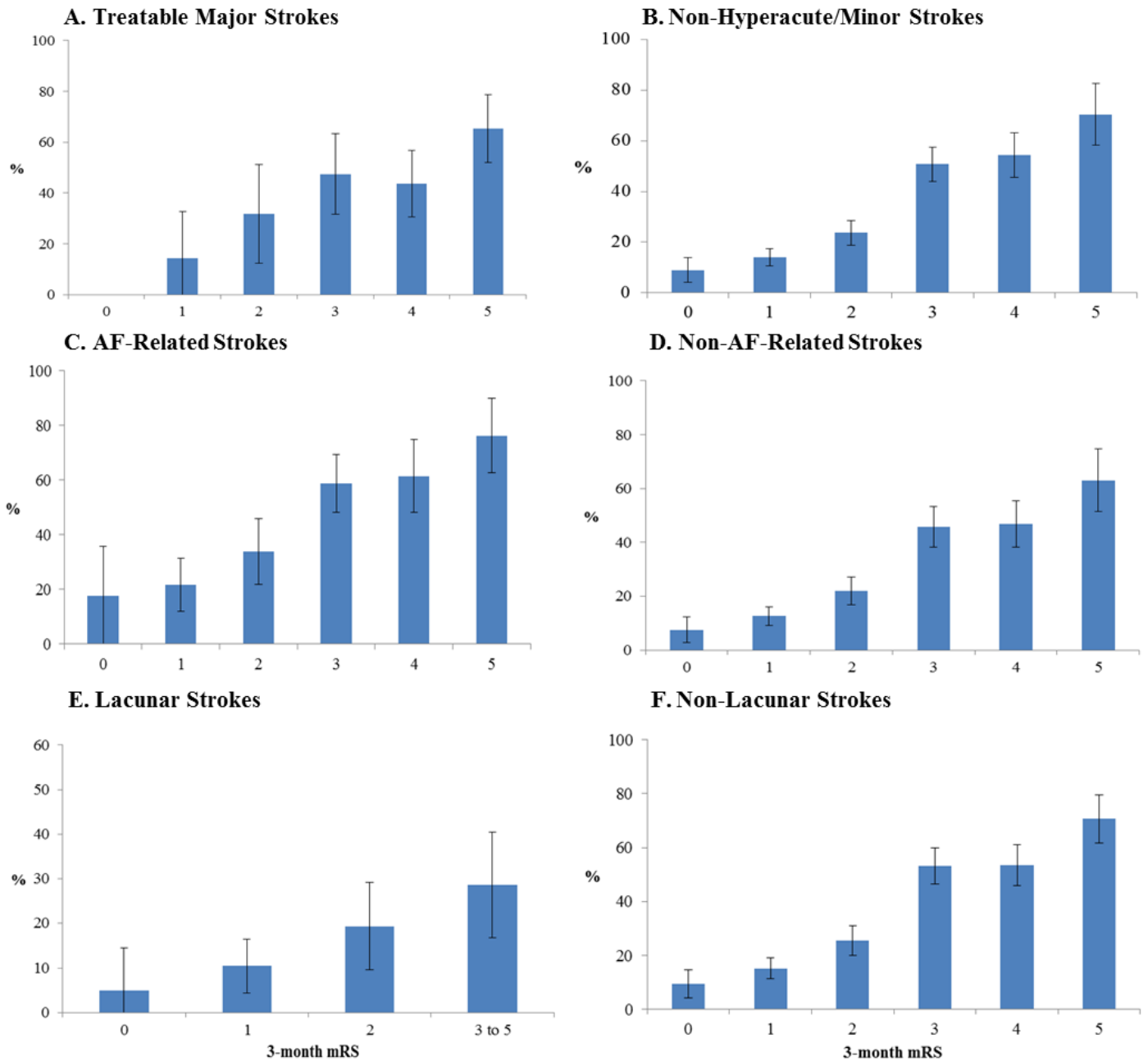


Figure S3. Proportions of 3-month survivors of ischaemic stroke for key subgroups, stratified by pre-3-month mRS, who were dead at 5 years. Bars represent 95% confidence intervals.

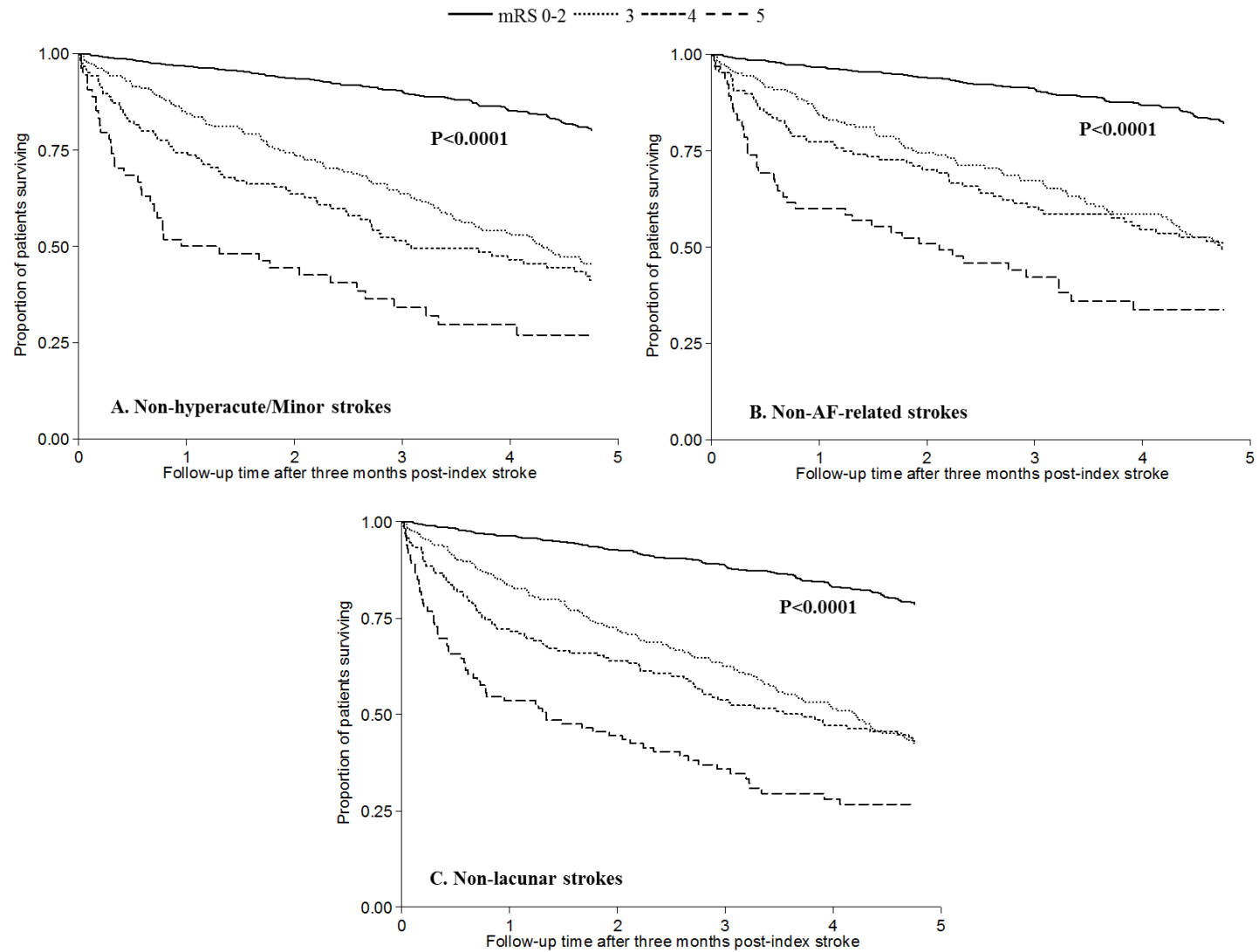


Figure S4. Kaplan-Meier survival curves after index stroke for 3-month survivors (mRS 0-2 versus 3, 4, 5), for (A) non-hyperacute/minor strokes, (B) non-AF-related strokes, and (C) non-lacunar stroke subgroups. P values obtained from the log-rank test for each group are displayed.

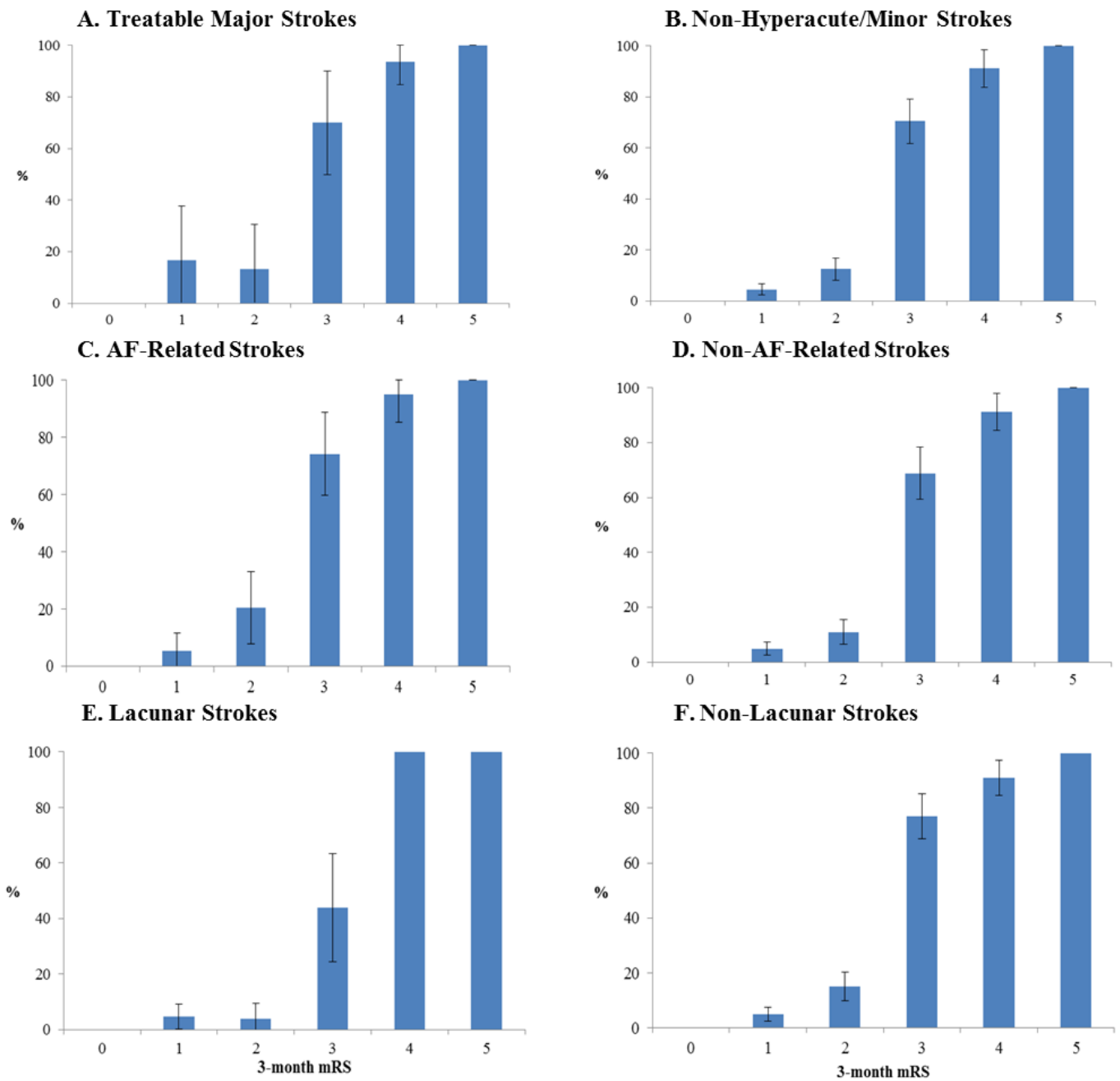


Figure S5. Proportions of 3-month survivors of ischaemic stroke for key subgroups, stratified by pre-3-month mRS, who were disabled (mRS >2) at 5 years, only including those alive at 5 years in the total. Bars represent 95% confidence intervals.

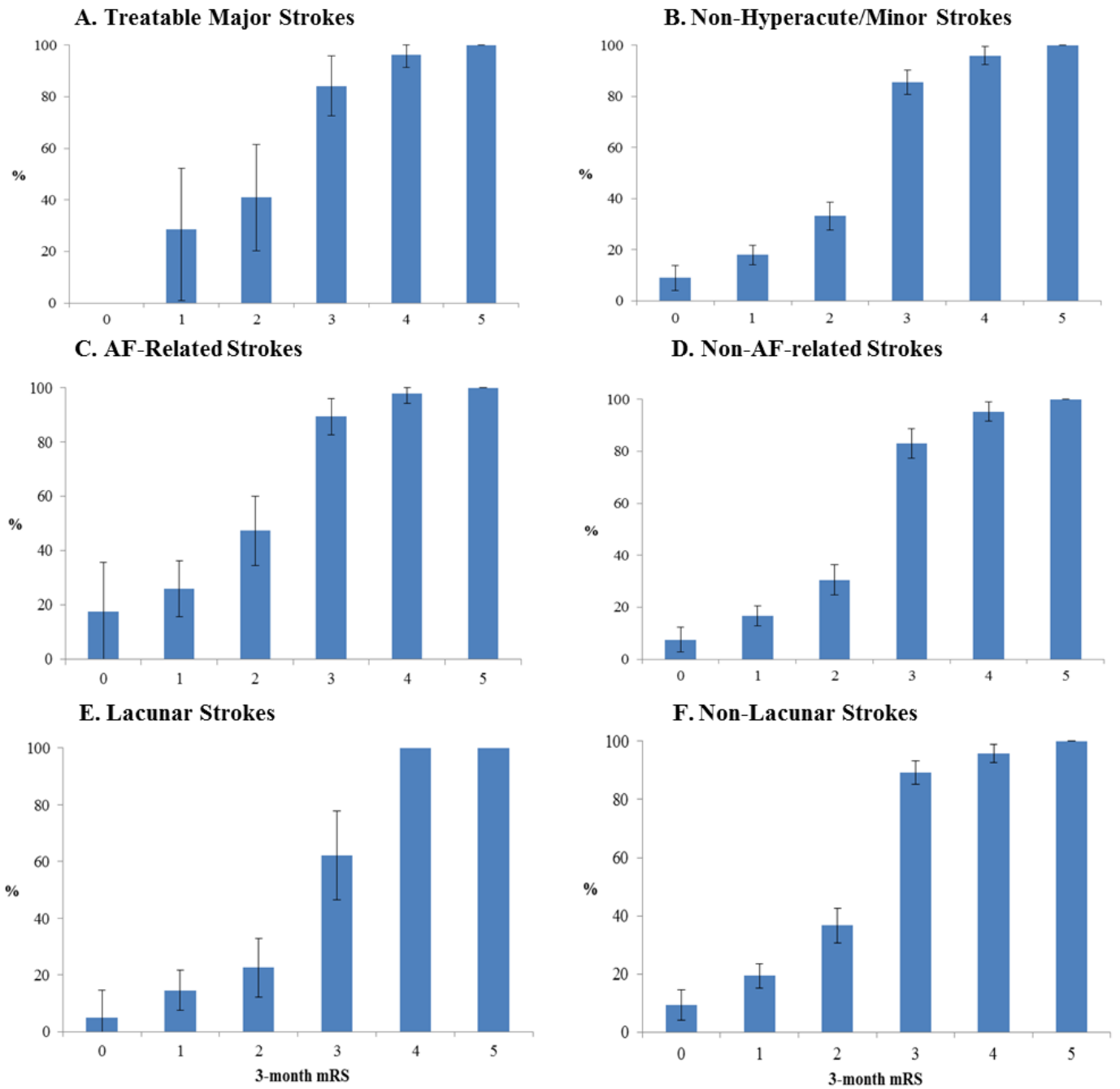


Figure S6. Proportions of 3-month survivors of ischaemic stroke for key subgroups, stratified by pre-3-month mRS, who were dead or disabled at 5 years. Bars represent 95% confidence intervals.