

## **SUPPLEMENTAL MATERIAL**

### **Stroke and Vascular Neurology**

#### **Retinal microvascular signs and recurrent vascular events in patients with TIA or minor stroke**

Supplemental table 1. Baseline characteristics by fundus groups

	No or mild vascular retinopathy		Moderate vascular retinopathy		Vascular retinopathy with vessel rarefaction	
	Yes (n=155)	No (n=567)	Yes (n=473)	No (n=249)	Yes (n=94)	No (n=628)
Age (years), mean (±SD)	64 (±11)	70 (±9)	70 (±10)	67 (±11)	72 (±7)	68 (±10)
Sex, n (%)						
Female	59 (38.1)	192 (33.9)	160 (33.8)	91 (36.5)	32 (34.0)	219 (34.9)
Male	96 (61.9)	375 (66.1)	313 (66.2)	158 (63.5)	62 (66.0)	409 (65.1)
Study arm, n (%)						
Conventional care	67 (56.8)	285 (50.3)	235 (49.7)	114 (45.8)	47 (50.0)	305 (51.4)
Intensified care	88 (43.2)	282 (49.7)	238 (50.3)	135 (54.2)	47 (50.0)	323 (48.6)
BMI (kg/m <sup>2</sup> ), mean (±SD)	29 (±5)	28 (±4)	28 (±4)	28 (±5)	27 (±4)	28 (±4)
ABCD2, median (IQR)	4 (3-5)	4 (4-5)	4 (4-5)	4 (4-5)	5 (4-6)	4 (4-5)
NIHSS, median (IQR)†	1 (0-2)	1 (0-2)	1 (0-2)	1 (0-2)	1 (0-2)	1 (0-2)
Carotid surgery, n (%)	5 (3.2)	17 (3.0)	13 (2.7)	9 (3.6)	4 (4.3)	18 (2.9)
Vascular risk factors, n (%)						
Hypertension	127 (81.9)	513 (90.5)	423 (89.4)	217 (87.1)	90 (95.7)	550 (87.6)
Diabetes mellitus	41 (26.5)	133 (23.5)	116 (24.5)	58 (23.3)	17 (18.1)	157 (25.0)
Atrial fibrillation	27 (17.4)	100 (17.6)	88 (18.6)	39 (15.7)	12 (12.8)	115 (18.3)
Smoking	43 (27.7)	84 (14.8)	72 (15.2)	55 (22.1)	12 (12.8)	115 (18.3)
Index event, n (%)						
TIA	71 (45.8)	255 (45.0)	223 (47.1)	103 (41.4)	32 (34.0)	294 (46.8)
Minor stroke	84 (54.2)	312 (55.0)	250 (52.9)	146 (58.6)	62 (66.0)	334 (53.2)
Stroke etiology, n (%)						
Large vessel atherosclerosis	16 (10.3)	51 (9.0)	40 (8.5)	27 (10.8)	11 (11.7)	56 (8.9)
Cardioembolism	30 (19.4)	103 (18.2)	88 (18.6)	45 (18.1)	15 (16.0)	118 (18.8)
Small vessel disease	8 (5.2)	51 (9.0)	39 (8.2)	20 (8.0)	12 (12.8)	47 (7.5)
Other etiology	0 (0)	11 (1.9)	11 (2.3)	0 (0)	0 (0)	11 (1.8)
Undetermined cause	101 (65.2)	351 (61.9)	295 (62.4)	157 (63.1)	56 (59.6)	396 (63.1)
Previous vascular event, n (%)						
TIA‡	9 (5.8)	31 (5.7)	24 (5.3)	16 (6.6)	7 (7.6)	33 (5.5)
Stroke§	25 (16.2)	92 (16.5)	70 (15.1)	47 (19.0)	22 (23.7)	95 (15.4)
Myocardial infarction	12 (7.7)	45 (8.1)	37 (7.9)	20 (8.1)	8 (8.6)	49 (7.9)

†Data available for 720 patients

‡Data available for 696 patients

§Data available for 710 patients

||Data available for 714 patients

SD, standard deviation; BMI, body mass index; IQR, interquartile range; NIHSS, National Institute of Health stroke scale; TIA, transient ischemic attack.

Supplemental table 2. Cox proportional hazards for bivariate hazard ratios

	Composite events (N=109)		Recurrent stroke (N=74)		Acute coronary syndrome (N=20)		Vascular death (N=15)	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Age	1.04 (1.01-1.06)	0.001	1.04 (1.01-1.07)	0.004	1.03 (0.98-1.09)	0.230	1.03 (0.97-1.09)	0.398
Sex	0.93 (0.62-1.38)	0.703	0.95 (0.58-1.53)	0.819	0.65 (0.23-1.78)	0.396	1.28 (0.46-3.59)	0.640
Study arm (conventional care)	1.08 (0.74-1.57)	0.699	1.02 (0.64-1.61)	0.941	1.53 (0.63-3.75)	0.351	0.90 (0.33-2.48)	0.835
BMI (kg/m <sup>2</sup> )	1.00 (0.96-1.04)	0.988	0.99 (0.94-1.04)	0.747	1.00 (0.90-1.10)	0.930	1.05 (0.94-1.16)	0.417
ABCD2	1.16 (0.99-1.36)	0.062	1.27 (1.05-1.54)	0.014	1.04 (0.72-1.52)	0.821	0.86 (0.55-1.33)	0.484
NIHSS†	1.04 (0.97-1.12)	0.284	1.06 (0.97-1.15)	0.202	1.01 (0.84-1.21)	0.928	1.00 (0.81-1.23)	1.000
Carotid surgery	2.06 (0.95-4.48)	0.068	1.18 (0.37-3.82)	0.780	6.06 (1.77-20.74)	0.004	2.36 (0.31-17.98)	0.406
Vascular risk factors								
Hypertension	1.04 (0.54-1.99)	0.914	0.96 (0.44-2.10)	0.920	2.06 (0.28-15.37)	0.483	0.79 (0.18-3.50)	0.757
Diabetes mellitus	1.58 (1.06-2.35)	0.024	1.47 (0.90-2.40)	0.121	1.65 (0.66-4.13)	0.287	2.09 (0.74-5.86)	0.163
Atrial fibrillation	1.07 (0.63-1.83)	0.793	1.41 (0.77-2.59)	0.263	0.67 (0.16-2.90)	0.594	0.36 (0.05-2.76)	0.327
Smoking	1.15 (0.73-1.83)	0.548	0.81 (0.44-1.51)	0.510	1.87 (0.71-4.89)	0.204	2.41 (0.82-7.04)	0.109
Index event (minor stroke)	1.53 (1.04-2.27)	0.033	1.28 (0.80-2.04)	0.298	2.44 (0.89-6.71)	0.084	2.23 (0.71-7.00)	0.170
Stroke etiology								
Large vessel atherosclerosis	1.45 (0.80-2.63)	0.225	1.21 (0.57-2.57)	0.615	4.71 (1.33-16.68)	0.016	0.66 (0.09-5.10)	0.689
Cardioembolism	1.14 (0.67-1.95)	0.634	1.05 (0.54-2.03)	0.888	2.77 (0.78-9.85)	0.114	0.66 (0.15-2.99)	0.592
Small vessel disease	1.05 (0.55-2.00)	0.880	0.52 (0.19-1.45)	0.210	5.59 (1.80-17.37)	0.003	0.63 (0.08-4.88)	0.658
Other etiology	3.73 (1.16-11.95)	0.027	5.69 (1.74-18.57)	0.004	0	0	0	0
Undetermined cause	Reference		Reference		Reference		Reference	
Previous vascular event								
TIA‡	1.90 (1.01-3.55)	0.046	2.39 (1.18-4.83)	0.015	0	0	2.54 (0.57-11.34)	0.223
Stroke§	1.61 (1.03-2.51)	0.037	1.38 (0.79-2.41)	0.259	4.37 (1.77-10.75)	0.001	0.40 (0.05-3.04)	0.374
Myocardial infarction	1.98 (1.14-3.42)	0.015	1.31 (0.60-2.86)	0.498	4.12 (1.48-11.45)	0.007	2.89 (0.82-10.25)	0.100
<b>Fundus group</b>								
<b>No or mild vascular retinopathy</b>	<b>Reference</b>		<b>Reference</b>		<b>Reference</b>		<b>Reference</b>	
<b>Moderate vascular retinopathy</b>	<b>1.19 (0.75-1.88)</b>	<b>0.469</b>	<b>1.55 (0.86-2.78)</b>	<b>0.143</b>	<b>0.51 (0.18-1.47)</b>	<b>0.214</b>	<b>1.00 (0.31-3.21)</b>	<b>0.998</b>
<b>Vascular retinopathy with vessel rarefaction</b>	<b>1.40 (0.79-2.47)</b>	<b>0.248</b>	<b>1.54 (0.76-3.15)</b>	<b>0.234</b>	<b>1.64 (0.55-4.89)</b>	<b>0.374</b>	<b>0.45 (0.05-4.02)</b>	<b>0.474</b>

†Data available for 720 patients

‡Data available for 696 patients

§Data available for 710 patients

||Data available for 714 patients

HR, hazard ratio; CI, confidence intervals; BMI, body mass index; NIHSS, National Institute of Health stroke scale; TIA, transient ischemic attack.

Supplemental table 3. Post-hoc analysis: Baseline characteristics of patients with diabetes mellitus and hypertension

	Total (n=154)	Composite events		Recurrent stroke	Acute coronary syndrome	Vascular death
		Yes (n=32)	No (n=122)	Yes (n=20)	Yes (n=7)	Yes (n=5)
Age (years), mean ( $\pm$ SD)	69 ( $\pm$ 10)	70 ( $\pm$ 11)	69 ( $\pm$ 9)	71 ( $\pm$ 12)	68 ( $\pm$ 10)	70 ( $\pm$ 9)
Sex, n (%)						
Female	47 (30.5)	10 (31.3)	37 (30.3)	5 (25.0)	2 (28.6)	3 (60.0)
Male	107 (69.5)	22 (68.8)	85 (69.7)	15 (75.0)	5 (71.4)	2 (40.0)
Study arm, n (%)						
Conventional care	77 (50.0)	20 (37.5)	57 (46.7)	13 (65.0)	4 (57.1)	3 (60.0)
Intensified care	77 (50.0)	12 (62.5)	65 (53.3)	7 (35.0)	3 (42.9)	2 (40.0)
BMI (kg/m <sup>2</sup> ), mean (SD)	30 ( $\pm$ 5)	30 ( $\pm$ 4)	30 ( $\pm$ 5)	29 ( $\pm$ 4)	33 ( $\pm$ 4)	30 ( $\pm$ 5)
ABCD2, median (IQR)	5 (4-6)	5 (4-6)	5 (4-6)	5 (4-6)	5 (4-6)	4 (3.5-6)
NIHSS, median (IQR)	1 (0-2)	1 (0-2)	1 (0-2)	1 (0-1)	1 (1-3)	2 (0-2.5)
Carotid surgery, n (%)	7 (4.5)	1 (3.1)	6 (4.9)	0 (0)	1 (14.3)	0 (0)
Vascular risk factors, n (%)						
Atrial fibrillation	21 (12.6)	1 (3.1)	20 (16.4)	1 (5.0)	0 (0)	0 (0)
Smoking	25 (16.2)	11 (34.4)	14 (11.5)	5 (25.0)	4 (57.1)	2 (40.0)
Index event, n (%)						
TIA	71 (46.1)	15 (46.9)	56 (45.9)	13 (65.0)	1 (14.3)	1 (20.0)
Minor stroke	83 (54.9)	17 (53.1)	66 (54.1)	7 (35.0)	6 (85.7)	4 (80.0)
Stroke etiology, n (%)						
Large vessel atherosclerosis	25 (16.2)	5 (15.6)	20 (16.4)	3 (15.0)	1 (14.3)	1 (20.0)
Cardioembolism	25 (16.2)	4 (12.5)	21 (17.2)	3 (15.0)	1 (14.3)	0 (0)
Small vessel disease	15 (9.7)	5 (15.6)	10 (8.2)	1 (5.0)	3 (42.9)	1 (20.0)
Other etiology	1 (0.6)	0 (0)	1 (0.8)	0 (0)	0	0 (0)
Undetermined cause	88 (57.1)	18 (56.3)	70 (57.4)	13 (65.0)	2 (28.6)	3 (60.0)
Previous vascular event, n (%)						
TIA <sup>†</sup>	6 (4.0)	1 (3.3)	5 (4.1)	1 (5.6)	0 (0)	0 (0)
Stroke <sup>‡</sup>	26 (17.1)	7 (22.6)	19 (15.7)	3 (15.8)	4 (57.1)	0 (0)
Myocardial infarction <sup>  </sup>	19 (12.6)	6 (18.8)	13 (10.7)	2 (10.0)	2 (28.6)	2 (40.0)
Fundus groups, n (%)						
No or mild vascular retinopathy	34 (22.1)	8 (25.0)	26 (21.3)	2 (10.0)	5 (71.4)	1 (20.0)
Moderate vascular retinopathy	103 (66.9)	18 (56.3)	85 (69.7)	13 (65.0)	2 (28.6)	3 (60.0)
Vascular retinopathy with vessel rarefaction	17 (11.0)	6 (18.8)	11 (9.0)	5 (25.0)	0 (0)	1 (20.0)

<sup>†</sup>Data available for 151 patients

<sup>‡</sup>Data available for 152 patients

<sup>||</sup>Data available for 151 patients

SD, standard deviation; BMI, body mass index; IQR, interquartile range; NIHSS, National Institute of Health stroke scale; TIA, transient ischemic attack.

Supplemental table 4. Secondary prevention targets at 1 year follow-up by fundus category

	Total (n=722)	No or mild vascular retinopathy			Moderate vascular retinopathy			Vascular retinopathy with vessel rarefaction		
		Yes (n=155)	No (n=567)	p-value	Yes (n=473)	No (n=249)	p-value	Yes (n=94)	No (n=628)	p-value
Systolic blood pressure (mmHg), mean (SD)	130.4 (±14.9)	126.8 (±15.5)	131.4 (±14.6)	0.002	131.1 (±14.5)	129.0 (±15.5)	0.088	132.5 (±15.0)	130.1 (±14.9)	0.158
Diastolic blood pressure (mmHg), mean (SD)	78.7 (±9.6)	77.7 (±10.0)	78.9 (±9.4)	0.197	78.7 (±9.5)	78.5 (±9.8)	0.737	79.7 (±9.4)	78.5 (±9.6)	0.276
Blood pressure target achieved†	59.7% (368/616)	67.7% (90/133)	57.6% (278/483)	0.035	59.1% (237/401)	60.9% (131/215)	0.659	50.0% (41/82)	61.2% (327/534)	0.053
LDL (mg/dl), mean (SD)	93.7 (±34.0)	91.5 (±33.2)	94.3 (±34.3)	0.401	94.1 (±33.6)	93.1 (±35.0)	0.752	95.7 (±37.6)	93.4 (±33.5)	0.570
LDL target achieved‡	54.5% (324/594)	58.9% (76/129)	53.3% (248/465)	0.260	53.4% (206/384)	56.2% (118/210)	0.552	51.9% (42/81)	55.0% (282/513)	0.621
Smoking abstinence	88.3% (564/639)	79.4% (108/136)	90.7% (456/503)	0.001	90.6% (378/417)	83.8% (186/222)	0.010	90.7% (78/86)	87.9% (486/553)	0.451
HbA1c (%), mean (SD)	5.9 (±0.8)	6.0 (±0.9)	5.9 (±0.8)	0.418	5.9 (±0.8)	6.0 (±0.8)	0.810	5.9 (±0.7)	6.0 (±0.8)	0.520
HbA1c target achieved§	95.7% (553/578)	92.7% (115/124)	96.5% (438/454)	0.070	96.3% (364/378)	94.5% (189/200)	0.313	97.4% (74/76)	95.4% (479/502)	0.436
Patients taking platelet inhibitors of all patients not taking oral anticoagulation	93.9% (460/490)	95.2% (99/104)	93.5% (361/386)	0.529	92.8% (297/320)	95.9% (163/170)	0.177	97.0% (64/66)	93.4% (396/424)	0.260
Patients with atrial fibrillation taking oral anticoagulation	91.2% (135/148)	93.8 (30/32)	90.5% (105/116)	0.567	89.7% (87/97)	94.1% (48/51)	0.366	94.7% (18/19)	90.7% (117/129)	0.561
Physical activity target achieved	21.3% (136/639)	27.5% (38/138)	19.6% (98/501)	0.043	20.0% (83/415)	23.7% (53/224)	0.281	17.4% (15/86)	21.9% (121/553)	0.349

†<140/85 mmHg in patients who are not diabetic and <130/80 mmHg in patients who are diabetic.

‡Target for LDL was <100 mg/dl and <70 mg/dl in patients with coronary artery disease or symptomatic intracranial or extracranial artery stenosis.

§Target in patients with diabetes was less than 58.5 mmol/mol.

||Target for physical activities (self-reported) was ≥30 min per day at least three times per week

Statistical tests used: independent t test for continuous variables and Pearson Chi square test for categorical variables.

SD, standard deviation; LDL, low density lipoprotein.

Supplemental table 5. Secondary prevention targets at 2 year follow-up by fundus category

	Total (N=722)	No or mild vascular retinopathy			Moderate vascular retinopathy			Vascular retinopathy with vessel rarefaction		
		Yes (N=155)	No (N=567)	p-value	Yes (N=473)	No (N=249)	p-value	Yes (N=94)	No (N=628)	p-value
Systolic blood pressure (mmHg), mean (SD)	130.0 (±16.0)	126.8 (±15.8)	131.1 (±15.9)	0.015	130.1 (±15.8)	130.0 (±16.3)	0.937	135.1 (±15.7)	129.2 (±15.9)	0.005
Diastolic blood pressure (mmHg), mean (SD)	78.4 (±8.4)	77.3 (±8.3)	78.7 (±8.4)	0.115	78.4 (±8.3)	78.4 (±8.3)	0.947	80.2 (±8.4)	78.1 (±8.3)	0.046
Blood pressure target achieved†	59.4% (277/466)	65.2% (73/112)	57.6% (204/354)	0.156	60.4% (172/285)	58.0% (105/181)	0.616	46.4% (32/69)	61.7% (245/397)	0.017
LDL (md/dl), mean (SD)	94.6 (±34.7)	90.4 (±32.0)	96.0 (±35.5)	0.140	95.6 (±34.9)	93.2 (±34.5)	0.475	97.9 (±38.2)	94.1 (±34.1)	0.412
LDL target achieved‡	54.1% (242/447)	56.8% (63/111)	53.3% (179/336)	0.523	53.7% (146/272)	54.9% (96/175)	0.807	51.6% (33/64)	54.6% (209/383)	0.655
Smoking abstinence	87.5% (443/506)	81.8% (99/121)	89.4% (344/385)	0.029	89.6% (284/317)	84.1% (159/189)	0.072	88.2% (60/68)	87.4% (383/438)	0.854
HbA1c (%), mean (SD)	5.9 (±0.8)	6.0 (±0.8)	5.9 (±0.8)	0.245	5.9 (±0.8)	5.9 (±0.8)	0.891	5.8 (±0.7)	5.9 (±0.8)	0.109
HbA1c target achieved§	96.3% (418/434)	97.1% (102/105)	96.1% (317/330)	0.608	96.3% (257/267)	96.4% (162/168)	0.925	95.2% (60/63)	96.5% (359/372)	0.621
Patients taking platelet inhibitors of all patients not taking oral anticoagulation	95.5% (359/376)	95.5% (84/88)	95.5% (275/288)	0.990	94.5% (222/235)	97.2% (137/141)	0.223	100% (53/53)	94.7% (306/323)	0.087
Patients with atrial fibrillation taking oral anticoagulation	96.6% (113/117)	96.8% (30/31)	96.5% (83/86)	0.945	95.8% (68/71)	97.8% (45/46)	0.551	100% (15/15)	96.1% (98/102)	0.435
Physical activity target achieved	21.1% (108/511)	22.1% (27/122)	20.8% (81/389)	0.757	21.7% (69/318)	20.2% (39/193)	0.689	16.9% (12/71)	21.8% (96/440)	0.346

†<140/85 mmHg in patients who are not diabetic and <130/80 mmHg in patients who are diabetic.

‡Target for LDL was <100 mg/dl and <70 mg/dl in patients with coronary artery disease or symptomatic intracranial or extracranial artery stenosis.

§Target in patients with diabetes was less than 58.5 mmol/mol.

||Target for physical activities (self-reported) was ≥30 min per day at least three times per week

Statistical tests used: independent t test for continuous variables and Pearson Chi square test for categorical variables.

SD, standard deviation; LDL, low density lipoprotein.

Supplemental table 6. Secondary prevention targets at 3 year follow-up by fundus category

	Total (N=722)	No or mild vascular retinopathy			Moderate vascular retinopathy			Vascular retinopathy with vessel rarefaction		
		Yes (N=155)	No (N=567)	p-value	Yes (N=473)	No (N=249)	p-value	Yes (N=94)	No (N=628)	p-value
Systolic blood pressure (mmHg), mean (SD)	131.0 (±16.0)	129.1 (±13.8)	131.6 (±16.6)	0.196	131.0 (±16.4)	131.1 (±15.3)	0.894	134.5 (±17.3)	130.4 (±15.7)	0.077
Diastolic blood pressure (mmHg), mean (SD)	78.7 (±9.6)	79.2 (±8.6)	78.6 (±9.8)	0.599	78.4 (±10.1)	79.3 (±8.7)	0.342	79.5 (±8.9)	78.6 (±9.7)	0.500
Blood pressure target achieved†	59.6% (227/381)	64.5% (60/93)	58.0% (167/288)	0.265	59.2% (138/233)	60.1% (89/148)	0.860	52.7% (29/55)	60.7% (198/326)	0.263
LDL (mg/dl), mean (SD)	97.0 (±34.4)	95.5 (±33.7)	97.4 (±34.6)	0.651	97.6 (±34.0)	96.1 (±35.2)	0.684	96.9 (±37.8)	97.0 (±33.9)	0.986
LDL target achieved‡	50.0% (185/370)	52.9% (45/85)	49.1% (140/285)	0.537	49.1% (114/232)	51.4% (71/138)	0.667	49.1% (26/53)	50.2% (159/317)	0.882
Smoking abstinence	89.4% (380/425)	82.0% (82/100)	91.7% (298/325)	0.006	91.7% (242/264)	85.7% (138/161)	0.053	91.8% (56/61)	89.0% (324/364)	0.512
HbA1c (%), mean (SD)	6.0 (±0.8)	6.0 (±0.8)	5.9 (±0.8)	0.732	6.0 (±0.8)	5.9 (±0.7)	0.798	5.9 (±0.6)	6.0 (±0.8)	0.440
HbA1c target achieved§	95.5% (341/357)	93.8% (75/80)	96.0% (266/277)	0.386	95.2% (217/228)	96.1% (124/129)	0.677	100% (49/49)	94.8% (292/308)	0.103
Patients taking platelet inhibitors of all patients not taking oral anticoagulation	94.7% (302/319)	94.4% (68/72)	94.7% (234/247)	0.923	94.0% (188/200)	95.8% (114/119)	0.489	97.9% (46/47)	94.1% (256/272)	0.290
Patients with atrial fibrillation taking oral anticoagulation	94.2% (98/104)	96.0 (24/25)	93.7% (74/79)	0.663	95.4% (62/65)	92.3% (36/39)	0.515	85.7% (12/14)	95.6% (86/90)	0.142
Physical activity target achieved	19.1% (82/429)	23.2% (23/99)	17.9% (59/330)	0.235	18.3% (49/268)	20.5% (33/161)	0.572	16.1% (10/62)	19.6% (72/367)	0.518

†<140/85 mmHg in patients who are not diabetic and <130/80 mmHg in patients who are diabetic.

‡Target for LDL was <100 mg/dl and <70 mg/dl in patients with coronary artery disease or symptomatic intracranial or extracranial artery stenosis.

§Target in patients with diabetes was less than 58.5 mmol/mol.

||Target for physical activities (self-reported) was ≥30 min per day at least three times per week

Statistical tests used: independent t test for continuous variables and Pearson Chi square test for categorical variables.

SD, standard deviation; LDL, low density lipoprotein.