

## Supplemental material

### Supplemental Figure Legends

**Supplemental Figure 1:** CADISP centers

**Supplemental Figure 2:** Flow diagram of the participant selection and exclusion process

**Supplemental Figure 3:** CADISP inclusion criteria

CEAD: Cervical Artery Dissection; IS: Ischemic Stroke; MR: Magnetic Resonance; CT: Computed Tomography; \* Mural hematoma, aneurysmal dilatation, long tapering stenosis, intimal flap, double lumen, or occlusion > 2 cm above the carotid bifurcation revealing an aneurysmal dilatation or a long tapering stenosis after recanalization; † Mechanical prosthetic valves, mitral stenosis with atrial fibrillation, intracardiac tumor, infectious endocarditis, myocardial infarction < 4 months; ‡ e.g. CADASIL, Fabry disease, MELAS, homocystinuria, sickle cell disease

## Supplemental Tables

**Supplemental Table 1:** Comparison of vascular risk factors in CEAD patients versus referents in a multivariable stepwise logistic regression

	OR (95%CI)*	p
Hypertension	1.81 (1.33-2.45)	0.0001
Hypercholesterolemia	0.53 (0.40-0.70)	<0.0001
Obesity	0.35 (0.23-0.53)	<0.0001
Overweight	0.64 (0.49-0.83)	0.0009

BMI: Body Mass Index; CEAD: Cervical Artery Dissection; CI: confidence interval; IS: ischemic stroke; OR: odds ratio; \*multivariable stepwise logistic regression comparing CEAD patients to referents and including age, gender, country of inclusion, hypertension, diabetes, current smoking, hypercholesterolemia and obesity/overweight as covariates, with age, gender and country of inclusion forced in: only the vascular risk factors retained in the final model are shown in the table (significance levels for entering into and staying in the model were set at 0.10).

**Supplemental Table 2:** Association of vascular risk factors with CEAD according to the recruitment type and the age at inclusion

	OR <sup>†</sup> (95%CI)	p		OR <sup>†</sup> (95%CI)	p	p heterogeneity <sup>§</sup>
<i>Prospective CEAD patients (N=232 CEAD patients, N=1170 referents)</i>			<i>Retrospective CEAD patients (N=458 CEAD patients, N=1170 referents)</i>			
Hypertension	1.50 (1.05-2.14)	0.03	Hypertension	1.70 (1.31-2.22)	<0.0001	0.39
Diabetes	0.95 (0.41-2.16)	0.90	Diabetes	0.35 (0.15-0.84)	0.02	0.17
Current smoking	1.27 (0.93-1.73)	0.13	Current smoking	1.17 (0.92-1.49)	0.20	0.53
Hypercholesterolemia <sup>†</sup>	0.43 (0.28-0.65)	<0.0001	Hypercholesterolemia <sup>†</sup>	0.61 (0.45-0.83)	0.002	0.24
Obesity	0.49 (0.30-0.81)	0.005	Obesity	0.31 (0.20-0.48)	<0.0001	0.13
Overweight	0.60 (0.43-0.85)	0.003	Overweight	0.76 (0.59-0.98)	0.03	
BMI <sup>*</sup>	0.93 (0.89-0.96)	0.0001	BMI <sup>*</sup>	0.92 (0.89-0.95)	<0.0001	0.76
<i>After exclusion of persons aged &lt; 35 (N=562 CEAD patients, N=1112 referents)</i>						
Hypertension	1.54 (1.20-1.96)	0.0006				
Diabetes	0.51 (0.27-0.97)	0.04				
Current smoking	1.20 (0.96-1.51)	0.11				
Hypercholesterolemia <sup>†</sup>	0.51 (0.38-0.68)	<0.0001				
Obesity	0.34 (0.23-0.49)	<0.0001				
Overweight	0.73 (0.57-0.92)	0.007				
BMI <sup>*</sup>	0.92 (0.89-0.95)	<0.0001				

BMI: Body Mass Index; CEAD: Cervical Artery Dissection; CI: confidence interval; OR: Odds Ratio; <sup>\*</sup>per kg/m<sup>2</sup> increase; <sup>†</sup>N=188 prospective CEAD patients, N=327 retrospective

CEAD patients, N=419 CEAD patients and 890 referents aged <35 years; <sup>†</sup>multinomial logistic regression for CEAD subgroups vs. all referents adjusted for country of inclusion, age

and gender; <sup>§</sup>assessed using logistic regression restricted to CEAD patients with the CEAD characteristic as the outcome variable

**Supplemental Table 3:** Association of vascular risk factors with cervical artery dissection (CEAD) compared to non-CEAD IS, by country of inclusion

	France-Belgium		Finland		Italy		p for interaction
	OR* (95%CI)	p	OR* (95%CI)	p	OR* (95%CI)	p	
Hypertension	0.49 (0.33-0.73)	0.0004	0.77 (0.49-1.22)	0.26	0.51 (0.30-0.87)	0.01	0.24
Diabetes	0.33 (0.13-0.84)	0.02	0.03 (0.005-0.26)	0.001	0.36 (0.12-1.09)	0.07	0.11
Current smoking	0.30 (0.21-0.42)	<0.0001	0.88 (0.56-1.36)	0.56	0.58 (0.36-0.94)	0.03	0.0004
Hypercholesterolemia	0.55 (0.37-0.81)	0.002	NA		0.40 (0.23-0.69)	0.001	0.60
Obesity	0.39 (0.22-0.66)	0.0006	0.28 (0.14-0.58)	0.0005	0.46 (0.17-1.21)	0.11	0.85
Overweight	0.70 (0.48-1.03)	0.07	0.51 (0.32-0.83)	0.006	0.65 (0.38-1.10)	0.11	
BMI, kg/m <sup>2</sup>	0.93 (0.89-0.97)	0.001	0.92 (0.88-0.97)	0.002	0.92 (0.87-0.99)	0.02	0.71

BMI: body mass index; OR: odds ratio; CI: confidence interval; NA: not available; \* Multinomial logistic regression comparing CEAD patients to non-CEAD IS patients, adjusted for age and gender and stratified on the country of inclusion

**Supplemental Table 4:** Comparison of vascular risk factors in CEAD patients who sustained an IS (N=454) versus non-CEAD IS patients

	OR (95%CI) *	p
Hypertension	0.51 (0.38-0.69)	<0.0001
Diabetes	0.22 (0.10-0.45)	<0.0001
Current smoker	0.50 (0.39-0.65)	<0.0001
Hypercholesterolemia	0.46 (0.34-0.64)	<0.0001
Obesity	0.35 (0.23-0.56)	<0.0001
Overweight	0.68 (0.51-0.91)	0.008
BMI, kg/m <sup>2</sup>	0.93 (0.90-0.96)	<0.0001

BMI: Body Mass Index; CEAD: Cervical Artery Dissection; CI: confidence interval; IS: ischemic stroke; OR: odds ratio; \* Logistic regression comparing CEAD patients with an IS to non-CEAD IS patients, adjusted for age, gender and country of inclusion.

**Supplemental Table 5:** Association of vascular risk factors with non-CEAD IS, by country of inclusion

	France-Belgium		Finland		Italy		p for interaction
	OR* (95%CI)	p	OR* (95%CI)	p	OR* (95%CI)	p	
Hypertension	2.39 (1.70-3.35)	<0.0001	2.68 (1.73-4.15)	<0.0001	6.30 (3.48-11.38)	<0.0001	0.10
Diabetes	2.27 (1.15-4.48)	0.02	2.31 (1.18-4.55)	0.01	4.03 (1.32-12.32)	0.01	0.86
Current smoking	3.01 (2.23-4.07)	<0.0001	2.19 (1.44-3.33)	0.0003	2.29 (1.44-3.64)	0.0004	0.30
Hypercholesterolemia	1.33 (0.96-1.84)	0.08	NA		0.72 (0.46-1.15)	0.17	0.01
Obesity	1.03 (0.67-1.57)	0.90	1.29 (0.75-2.23)	0.36	0.75 (0.34-1.66)	0.48	0.08
Overweight	0.98 (0.69-1.37)	0.89	1.85 (1.18-2.89)	0.007	0.89 (0.54-1.46)	0.65	
BMI, kg/m <sup>2</sup>	0.98 (0.95-1.02)	0.37	1.03 (0.98-1.07)	0.25	0.98 (0.93-1.04)	0.51	0.15

BMI: body mass index; CEAD: cervical artery dissection; CI: confidence interval; IS: ischemic stroke; NA: not available; OR: odds ratio; \* Multinomial logistic regression comparing non-CEAD IS patients to referents, adjusted for age and gender and stratified on the country of inclusion

**Supplemental Table 6:** Association of vascular risk factors with non-CEAD IS, according to the etiology of IS

	OR (95%CI) †	p		OR (95%CI) †	p	p heterogeneity §
<i>TOAST = LAA, SVD, or CE (N=321 non-CEAD IS patients)</i>			<i>TOAST = Other determined or undetermined (N=235 non-CEAD IS patients)</i>			
Hypertension	2.95 (2.21-3.95)	<0.0001	Hypertension	3.23 (2.32-4.49)	<0.0001	0.67
Diabetes	2.39 (1.42-4.01)	0.001	Diabetes	3.06 (1.76-5.30)	<0.0001	0.46
Current smoker	2.46 (1.90-3.18)	<0.0001	Current smoker	2.82 (2.10-3.78)	<0.0001	0.36
Hypercholesterolemia	1.19 (0.90-1.57)	0.22	Hypercholesterolemia	0.89 (0.64-1.24)	0.49	0.14
Obesity	1.18 (0.82-1.70)	0.38	Obesity	0.86 (0.55-1.35)	0.52	0.40
Overweight	1.20 (0.90-1.59)	0.21	Overweight	1.07 (0.78-1.48)	0.68	
BMI	1.00 (0.97-1.03)	0.84	BMI	0.99 (0.96-1.03)	0.69	0.73

BMI: body mass index; CEAD: cervical artery dissection; CE: cardioembolism; CI: confidence interval; IS: ischemic stroke; LAA: large artery atherosclerosis; OR: odds ratio;

SVD: small vessel disease; TOAST: Trial of Org 10172 in Acute Stroke Treatment <sup>20</sup>; \* Italian and Finnish participants are not included in these analyses; † Italian participants

are not included in these analyses; ‡ Multinomial logistic regression comparing non-CEAD IS subgroups to all referents, adjusted for country of inclusion, age and gender; §

assessed using logistic regression analysis restricted to CEAD patients (case-only analysis) with the CEAD characteristic as the outcome variable

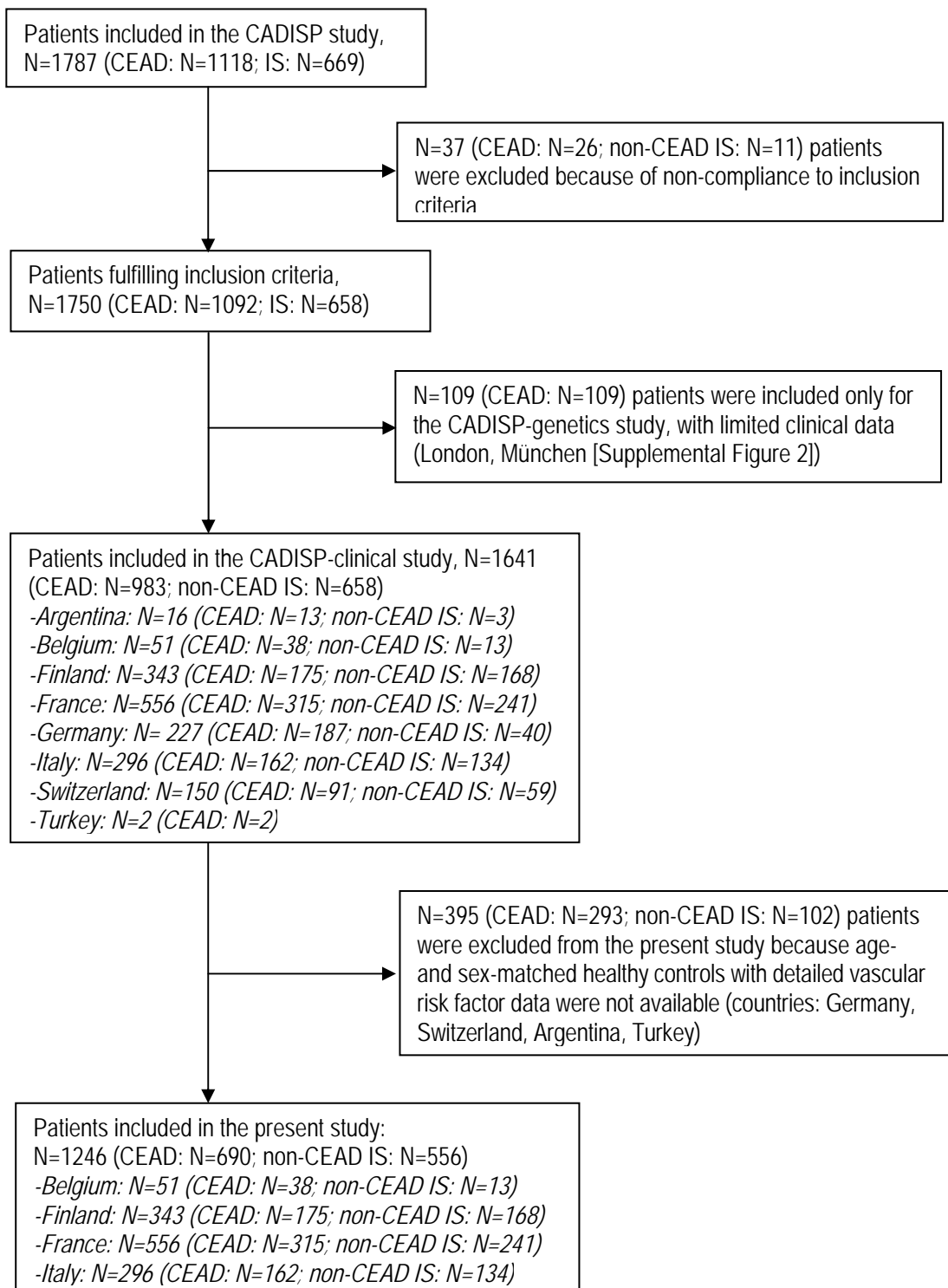
Supplemental Figures

Supplemental Figure 1: CADISP centers





Supplemental Figure 2: Flow diagram of the participant selection and exclusion process



Supplemental Figure 3: CADISP inclusion criteria

	CEAD patients	Non-CEAD IS patients
<i>Inclusion criteria</i>	<ul style="list-style-type: none"> <li>▪ Typical radiological aspect of dissection* in a cervical artery (carotid, vertebral)</li> </ul>	<ul style="list-style-type: none"> <li>▪ Recent ischemic stroke</li> <li>▪ No signs of CEAD on ultrasound and angiography (MR or CT or conventional), performed &lt; 7 days after the stroke</li> </ul>
<i>Exclusion criteria</i>	<ul style="list-style-type: none"> <li>▪ Purely intracranial dissection</li> <li>▪ Iatrogenic dissection after endovascular procedure</li> <li>▪ Age &lt;18 years at inclusion</li> <li>▪ <b>For the genetic study only</b> : monogenic disorder known to cause CEAD (e.g. vascular Ehlers-Danlos syndrome)</li> </ul>	<ul style="list-style-type: none"> <li>▪ Possible IS with normal cerebral imaging</li> <li>▪ CEAD cannot be ruled out (e.g. persistent arterial occlusion without mural hematoma)</li> <li>▪ Endovascular or surgical procedure on coronary, cervical or cerebral arteries &lt;48h</li> <li>▪ Cardiopathies with very high embolic risk †</li> <li>▪ Arterial vasospasm after subarachnoid hemorrhage</li> <li>▪ Auto-immune disease possibly explaining IS</li> <li>▪ Monogenic disease explaining IS †</li> <li>▪ Age &lt; 18 years at inclusion</li> </ul>