Supplementary

Table S1. Serum biomarkers related to clinical outputs of carotid artery disease.

Type of Biomarkers	Biomarkers	Diagnosis of Carotid Artery Disease	Plaque Vulnerability	Symptomatic Carotid Artery Disease	Future Stroke Event	Stroke Severity	Cardiovascular Mortality
Inflammatory	hs-CRP	[1] [2, 3]	[4] [5]		[6] [7] [8]		[9]
	PTX 3	[10] [11]	[5]				
	IL-6	[1] [12]	[4] [5]				
	TNF-α	[10]	[5] [13] [14]	[15] [16]			
Endothelial and Cell Adhesion Biomarkers	NGAL		[17]				
	VCAM-1		[5]				[18]
	ICAM-1	[12]					[18]
	E-selectin	[12]	[5]				
	L-selectin		[13]				
Matrix Degrading or Proteolysis	MMP-1		[14]				
	TIMP-1		[14]				
	MMP-2		[19]	[20]			
	MMP-3	[12]					
	MMP-7		[14] [19]	[15]			[15]
	MMP-9	[12]	[20] [19] [21]	[20]			[22]
	MMP-14		[19]				
Lipid Related	LDL-C	[10]			[23]		
	TC				[23]		
	triglyceride				[23]		
	ox-LDL		[24]	[21]	[25]		[26]
	HDL-C		[27] [28]			[29] [23]	
	TRL	[30]	[31] [30]				
	Lp-PLA2	[32]	[32] [8]	[33]	[34] [35]		
	apoA-I					[36] [37]	
	apoE						
	PCSK9	[38]					
Metabolic Biomarkers	restinin		[39]	[39]			
	adiponectin	[40]		[41] [42]			
	leptin			[42]			
	FABP4	[43]	[43]	[43]			
	homocysteine	[44] [45]			[45]		
	osteoprotegerin		[46]	[46] [47]			

Table S2. A summary of studies investigating biomarkers related to carotid artery disease diagnosis.

Study	Biomarker	Methodology	Dataset	Output
Puz et al. [2]	hs-CRP	laboratory tests, ultrasound examination, statistical analysis	65 patients with ICA stenosis > 50% (39 symptomatic) and 30 healthy	Patients with ICA stenosis had significantly higher serum concentrations and CRP values than the individuals from the control group ($p = 0.009$)
Horn et al. [3] (2009)	hs-CRP	laboratory tests, ultrasound examination, statistical analysis	subclinical and advanced (INVADE study-n = 3,092, > 55 years)	rate of both subclinical and advanced stages of atherosclerosis was higher in patients with pathological hs-CRP
Debing et al. [1] (2008)	hs-CRP, IL-6, sVCAM-1	statistical analysis, high-resolution B-mode ultrasound	180 patients with ICA stenosis, 180 age-matched and sex-matched controls.	levels of hs-CRP, sVCAM-1, and IL-6 in the CEA group were significantly higher than in the control group
Yi et al. [10] (2020)	PTX 3, TNF-a, LDL-C	computed tomography angiography (CTA), statistical analysis	206 patients with ischemic stroke	plasma levels of PTX 3, TNF-α, and low-density lipoprotein cholesterol (LDL-C) were increased significantly in the CAS group patients vs. the CAS-free
Knoflach et al. [11] (2012)	PTX 3	statistical analysis, high-resolution B-mode ultrasound	132 young men, 205 young women, 562 individuals 55 to 94 years old	PTX 3 level was independently associated with prevalent
Biscetti et al. [12] (2015)	IL-6, ICAM-1, E-selectin, MMP-3, MMP-9	genetic association study	933 individuals (344 patients with ICAS-CEA endarterectomy and 589 controls)	IL-6, ICAM-1, MMP-3, and MMP-9 gene polymorphisms were independently associated with ICAS
Kofoed et al. [30] (2002)	TRL	high-resolution B-mode ultrasound and computerized image analysis	66 controls and 323 patients with carotid artery stenosis ≥ 50%	fasting and postprandial triglyceride-rich lipoproteins are elevated in patients with carotid artery stenosis of ≥ 50%
Chan et al. [38] (2016)	PCSK-9	biochemical analysis, carotid ultrasound	95 asymptomatic subjects	serum PCSK-9 remained an independent predictor of mean carotid IMT
Saarikoski et al. [40] (2010)	adiponectin	ultrasound data on carotid IMT	2,147 young adults	low serum adiponectin concentration is independently related with increased carotid IMT early atherosclerosis

Study	Biomarker	Methodology	Dataset	Output
Holm et al. [43] (2011)	FABP4	enzyme immunoassay, statistical analyses	28 asymptomatic, 31 symptomatic, 202 patients with acute ischemic stroke	FABP4 levels were higher in patients with carotid atherosclerosis
Jia et al. [44] (2016)	homocysteine	carotid duplex ultrasound examination	5393 Chinese participants	Hcy > 19.3μmol/L was considered as an independent indicator of asymptomatic CAS
Alsulaimani et al. [45] (plaque area) (2013)	homocysteine	ultrasonographic assessment of plaque morphology measured by gray-scale median	1327 stroke-free subjects	increasing Hcy was associated with an increasing risk

Table S3. A summary of studies investigating biomarkers related to carotid atherosclerotic plaque vulnerability

Study	Biomarker	Methodology	Dataset	Output
Yamagami et al. [4] (2004).	hs-CRP, IL-6	statistical analyses	246 patients, including 80 patients with a history of stroke/TIA	IL-6 and hs-CRP were negatively correlated with carotid plaque echogenicity
Shindo et al. [5] (2014)	hs-CRP, PTX 3, IL-6, TNF-a, VCAM-1	histological analysis, statistical analysis	58 patients with carotid stenosis	vulnerable group showed upregulation of proinflammatory cytokines, endothelial activation markers and inflammation markers. and downregulation of anti-inflammatory markers
Andersson et al. [13] (2009)	TNF-a	ultrasound procedure, measurement serum markers, statistical analysis	1,016 subjects	Plaque size was also related to increased levels of TNF-alpha
Pelisek et al. [14] (2009)	TNF-a, MMP-1, TIMP-1, MMP-7	Measurement of serum markers by ELISA assays, Multiscore analysis	patients (n = 101) were classified as histologically stable (n = 37) or unstable (n = 64).	Circulating levels of MMP-1, MMP-7, TIMP-1, and TNF-α were significantly enhanced in patients with unstable plaques
Guo et al. [19] (2018)	MMP-2, MMP-7, MMP-14	carotid plaque specimens, histology and	64 patients	The mRNA levels of MMP-2, MMP-7, MMP-9 and MMP-14 were

Study	Biomarker	Methodology	Dataset	Output
		immunohistochemistry analysis		elevated in vulnerable plaques
Alvarez et al. [20] (2004)	MMP-9	histopathologic analysis, immunohistochemistry (macrophage count, T lymphocytes, activated T lymphocytes)	40 patients with carotid artery stenosis	MMP-9 was also significantly higher in the symptomatic group and in patients with unstable plaques
Eilenberg et al. [17] (2019)	NGAL, MMP-9	histological investigation, statistical analysis	83 patients with asymptomatic carotid artery stenosis	Circulating NGAL and MMP-9/NGAL are significantly increased in asymptomatic patients with vulnerable carotid atherosclerotic plaques
Sarlon-Bartoli et al. [32] (2012)	Lp-PLA2	laboratory measurements, histological assessment and immunohistochemistry of carotid plaques, statistical analyses	42 patients (neurological symptoms were present in 16, unstable plaques in 23)	Plasma Lp-PLA2 level was independently associated with unstable carotid plaques
Yang et al. [8] (2017)	Lp-PLA2	laboratory examination, carotid ultrasonography and grouping, statistics analysis	100 patients with acute anterior circulation stroke and 50 noninfarction subjects (control group)	Hs-CRP and Lp-PLA2 levels were significantly higher in vulnerable plaque group than in mixed plaque group and stable plaque group
K. Nishi et al. [24] (2002)	Ox-LDL	histopathological characteristics of plaques, immunohistochemical analysis, statistical analysis	44 patients	The ox-LDL level was significantly higher in vulnerable than stable plaques
Mathiesen et al. [28] (2001)	HDL-C	ultrasonography, statistical Analysis	216 with carotid stenosis, 223 control subjects	Low levels of HDL-C are associated with an increased risk of having echolucent, rupture-prone atherosclerotic plaques
Peters et al. [27] (2012)	HDL-C	measurement of intima-media thickness, statistical analysis	984 individuals	Low levels of HDL-C are related to echolucency of the carotid intima-media

Study	Biomarker	Methodology	Dataset	Output
Nordestgaard et al. [31] (2003)	TRL, HDL	ultrasound imaging methods, histological characterization	111 asymptomatic, 135 symptomatic patients with carotid artery stenosis, 44 ipsilateral ischaemic strokes	Vulnerable plaques are associated with elevated levels of triglyceride-rich lipoproteins and with reduced levels of HDL
Kofoed et al. [30] (2002)	TRL	high-resolution B-mode ultrasound and computerized image analysis	66 controls and 323 patients with carotid artery stenosis ≥ 50%	Fasting and postprandial triglyceride-rich lipoproteins are elevated in patients with carotid artery stenosis of ≥ 50% compared with controls
Gasbarrino et al. [39] (2016)	Restinin, Chemerin	association of circulating adipokines and carotid plaque instability	n=165 symptomatic and asymptomatic patients	Low chemerin and high resistin levels were associated with plaque instability
Holm et al. [43] (2011)	FABP4	enzyme immunoassay, statistical analyses	28 asymptomatic, 31 symptomatic, 202 acute ischemic stroke	FABP4 is linked to plaque instability in patients with carotid atherosclerosis
Davaine et al. [46] (2014)	Osteoprotegerin	OPG measurement, histological and immunological analyses, statistical analysis	73 carotid plaques (49 asymptomatic and 24 symptomatic)	Circulating OPG levels were higher in the plasma of asymptomatic patients

Table S4. A summary of studies investigating biomarkers related to symptomatic carotid artery disease.

Study	Biomarkers	Methodology	Dataset	Output
Abbas et al. [15] (2014)	MMP-7	immunohistochemistry, statistical analyses	182 consecutive patients with moderate (50–69%), 23 healthy controls	MMP-7 could contribute to plaque instability
Schneiderman et al. [16] (2012)	TNF-α	lesion analysis, statistical analysis	40 symptomatic, 38 asymptomatic patients with	TNF-α was significantly increased in

Study	Biomarkers	Methodology	Dataset	Output
			progressive stenosis	symptomatic patients
B. Alvarez et al. [20] (2004)	MMP-2, MMP-9	MMP-2 and MMP-9 measurement, statistical analysis	40 patients with carotid artery stenosis	Elevated MMP-9 concentration is associated with carotid plaque instability
Sigala et al. [21] (2010)	Ox-LDL	Immunohistochemistry, data analysis and statistics	36 patients undergoing endarterectomy, 20 controls	Ox-LDL was increased in symptomatic patients
Gasbarrino [61] (2016)	Restinin	Measurement of circulation adipokines, data analysis and statistics	165 neurologically symptomatic and asymptomatic patients	resistin levels were significantly elevated in symptomatic
A. Schiro et al. [47] (2015)	Osteopontin, Osteoprotegerin	Measurement of circulating EMPs, platelet MPs (PMPs) and inflammatory markers, statistical analysis	-	Osteopontin and osteoprotegerin were significantly elevated in the symptomatic

Table S5. A summary of studies investigating biomarkers related to future stroke event.

Study	Biomarkers	Methodology	Dataset	Output
Zhou et al. [6] (2016)	hs-CRP	Meta-analysis	2436 ischemic strokes, 655 hemorrhagic strokes from 66,560 participant	When comparing the highest with the lowest hs-CRP category, the pooled RR of ischemic strokes was 1.46
Yang et al. [8] (2017)	hs-CRP	Laboratory examination, carotid ultrasonography and grouping, statistics analysis	100 patients with acute anterior circulation stroke and 50 controls	Hs-CRP and Lp-PLA2 are among the risk factors for anterior circulation stroke

Study	Biomarkers	Methodology	Dataset	Output
Ma et al. [7] (2020)	hs-CRP, TNF-α, IL-6	Data collection, statistical analysis	288 ischemic stroke patients and 300 controls	Hs-CRP, TNF-α, and IL-6 are considered to be important markers of the body's inflammatory state in ischemic stroke
Gu et al. [23] (2019)	LDL-C, TC, triglyceride	Baseline information collection, statistical analysis	Six cohort studies in China with 267, 500 participants	TC, LDL-C, and triglyceride showed positive associations with ischemic stroke
Markstad et al. [25] (2019)	Ox-LDL	Analyses of the plaque tissue: cytokines and chemokines, measurement of sLOX-1 in blood samples, statistical analysis	202 patients undergoing carotid endarterectomy	Ox-LDL induces the release of sLOX-1 from endothelial cells and that
Oei et al. [34] (2005)	Lp-PLA2	Measurement of Lp-PLA2 activity, statistical analysis	308 coronary heart disease cases, 110 ischemic stroke cases, and a random sample of 1820 subjects	Lp-PLA2 activity is an independent predictor of ischemic stroke
Elkind et al. [35] (2009)	Lp-PLA2	Measurement of Lp-PLA2 activity, statistical analysis	467 patients	Stroke patients with Lp-PLA2 activity levels in the highest quartile had an increased risk of recurrence after first ischemic stroke
Alsulaimani et al. [45] (2013)	Homocysteine	Assessment of homocysteine, assessment of carotid	1327 stroke-free subjects	elevated homocysteine was

Study	Biomarkers	Methodology	Dataset	Output
		atherosclerosis, statistical analysis		independently associated with plaque morphology
Gorgui et al. [62] (2017)	Adiponectin	systematic review and meta-analysis	-	increased adiponectin levels were associated with an increase in risk for ischemic stroke
Gairolla et al. [63] (2017)	Adiponectin, leptin	systematic review	-	levels of adiponectin and leptin are significantly associated with ischemic stroke

Table S6. A summary of studies investigating biomarkers related to cardiovascular mortality.

Study	Biomarkers	Methodology	Dataset	Output
Mayer et al. [9] (2016)	hs-CRP	Clinical and laboratory data collection, statistical analysis	1065 patients with neurological asymptomatic carotid atherosclerosis	The risk of all-cause and cardiovascular mortality significantly increased in patients with elevated serum levels of hs-CRP
Hoke et al. [18] (2015)	VCAM-1, ICAM-1	Measurement of cellular adhesion molecules, statistical analysis	855 patients	significant association between cardiovascular mortality and ICAM-1
Abbas et al. [15] (2014)	MMP-7	Immunohistochemistry, statistical analyses	182 consecutive patients with moderate (50–69%) levels, 23 healthy controls	high plasma levels of MMP-7 were independently associated with total mortality
Zhong et al. [22] (2017)	MMP-9	Data collection, statistical analysis	3186 participants, 767 participants (24.6%) experienced major disability or died	Higher log MMP-9 was associated with death and major disability.
Wang et al. [26] (2017)	Ox-LDL	Biochemical indicators, diagnosis of stroke and	3688 patients	Patients in the highest ox-LDL

Study	Biomarkers	Methodology	Dataset	Output
		stroke subtype classification, statistical analysis		quartile had a higher risk of 1-year stroke mortality
Holm et al. [43] (2011)	FABP4	Enzyme immunoassay, statistical analyses	asymptomatic (n = 28), symptomatic (n = 31), patients with acute ischemic stroke (n = 202)	levels of FABP4 were significantly associated with total and cardiovascular mortality

Table S7: Biomarkers related with different clinical outputs of carotid artery disease in i)Symptomatic, Asymptomatic & Controls, ii) Asymptomatic, iii) Symptomatic and in iv) General population

i) Symptomatic, Asymptomatic & Controls	
Carotid Artery Disease Diagnosis	hs-CRP [2] [3] [1], IL-6 [1] [12], sVCAM-1 [1], ICAM-1 [12], E-selectin [12], MMP-3 [12], MMP-9 [12], TRL [30], FABP4 [43]
Carotid Atherosclerotic Plaque Vulnerability	hs-CRP [4] , IL-6 [4], TRL [31] [30], HDL [31] [28], Restinin [39], Chemerin [39], FABP4 [43], Osteoprotegerin [46], Lp-PLA2 [32] ,TNF-a [14], MMP-1 [14], TIMP-1 [14], MMP-7 [14]
Symptomatic Carotid Artery Disease	MMP-7 [15], TNF-α [16] [7], hs-CRP [7], IL-6 [7], Ox-LDL [21], Restinin [61]
Cardiovascular Mortality	MMP-7 [15], FABP4 [43]
ii) Asymptomatic	
Carotid Artery Disease Diagnosis	PCSK-9 [38], homocysteine [45]
Carotid Atherosclerotic Plaque Vulnerability	NGAL [17], MMP-9 [17]
Future Stroke Event	Homocysteine [45]
Cardiovascular mortality	hs-CRP [9]
iii) **Symptomatic patients (either with diagnosis of carotid artery disease or undergoing CEA)**	
Carotid Artery Disease Diagnosis	PTX 3 [10], TNF-a [10], LDL-C [10]
Carotid Atherosclerotic Plaque Vulnerability	MMP-9 [20], Lp-PLA2 [8]
Future Stroke Event.	hs-CRP [6] [8], MMP-2 [20], MMP-9 [20], Ox-LDL [25], Lp-PLA2 [34]
iv) **General population**	
Carotid Artery Disease Diagnosis	Adiponectin [40], homocysteine [44], PTX 3 [11]
Carotid Atherosclerotic Plaque Vulnerability	MMP-2 [19], MMP-7 [19], MMP-14 [19], Ox-LDL [24], HDL-C [27], TNF-a [13]
Future Stroke Event.	LDL-C [23], TC [23], triglycerides [23], Lp-PLA2 [35]
Cardiovascular Mortality	MMP-9 [22], Ox-LDL [26], VCAM-1 [18], ICAM-1 [18]

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