

ADDITIONAL FILE 1.

Table S1: Clinical characteristics of study population relative to PCSK9 quartiles

	Total Population n=539	Quartile I <138 ng/L n=135	Quartile II 138-183.8 ng/L n=135	Quartile III 183.9-264 ng/L n=135	Quartile IV >264 ng/L n=134	P value
Demographics						
Age, years	60±9	61±9	58±10	62±8	61±8	ns
Male gender	326 (60)	88 (65)	82 (61)	84 (62)	72 (58)	ns
Clinical characteristics						
Typical angina	140 (26)	30 (22)	34 (25)	32 (24)	44 (33)	
Atypical angina	321 (60)	78 (58)	87 (64)	79 (58)	77 (57)	
Non-anginal chest pain	78 (14)	27 (20)	14 (10)	24 (18)	13 (10)	
LVEF%	60±8	60±9	60±9	59±9	61±7	ns
Pre-test probability of CAD	48±19	48±18	47±19	49±19	49±20	ns
Cardiovascular risk factors						
Family history of CAD	189 (35)	40 (30)	48 (36)	42 (31)	59 (44)	0.0596
Diabetes	181 (34)	44 (33)	53 (39)	45 (33)	39 (29)	ns
Hypercholesterolemia	322 (60)	77 (57)	82 (61)	81 (60)	82 (61)	ns
Hypertension	360 (67)	88 (65)	93 (69)	88 (65)	91 (68)	ns
Smoking	133 (25)	30 (22)	42 (31)	27 (20)	34 (25)	ns
BMI, kg/m ²	27.7±4.3	27.9±4.0	28.2±4.1	27.7±4.5	26.8±4.6	ns
Metabolic Syndrome	185 (34)	54 (40)	54 (40)	46 (34)	31 (23)	0.0102
Pharmacological therapies						
Beta-blockers	215 (40)	64 (47)	51 (38)	54 (40)	46 (34)	ns
Calcium channel blockers	74 (14)	21 (16)	16 (12)	16 (12)	21 (15)	ns
ACE Inhibitors	166 (31)	43 (32)	39 (29)	48 (36)	36 (27)	ns
ARBs	91 (17)	23 (17)	26 (19)	27 (13)	25 (19)	ns
Diuretics	93 (17)	27 (20)	24 (18)	20 (15)	22 (16)	ns
Anti-diabetic	98 (18)	25 (19)	30 (22)	25 (18)	18 (13)	ns
Statins	279 (52)	72 (53)	77 (57)	71 (53)	59 (44)	ns
Aspirin	316 (59)	94 (70)	66 (49)	81 (60)	75 (56)	0.0058
Anti-coagulants	11 (2)	2 (1)	3 (2)	2 (1)	4 (3)	ns

Continuous variables are presented as mean ± standard deviation, categorical variables as absolute N and (%).

Table S2. Bio-humoral characteristics of clinical population relative to PCSK9 quartiles.

	Total Population n=412	Quartile I <136 ng/L n=103	Quartile II 136-183.8 ng/L n=206	Quartile III 183.9-264 ng/L n=206	Quartile IV >264 ng/L n=103	P value
Renal						
Creatinine, mg/dL	0.88±0.23	0.91±0.27	0.87±0.24	0.88±0.21	0.86±0.19	ns
Hepatic						
AST, IU/L	24±10	24±11	23±7	26±11	26±9	0.0062
ALT, IU/L	21±13	19±11	19±11	22±16	22±13	0.0111
ALP, IU/L	51±18	47±17	47±17	51±15	60±20	<0.0001
Metabolic (glucose)						
FPG, mg/dL	112±35	109±30	117±43	116±38	109±29	ns
†FPG ≥ 100 mg/dL	339 (63)	82 (61)	81 (60)	93 (69)	83 (62)	ns
Insulin, µUI/mL	11.5±10.8	13.3±12.5	12.6±12.2	10.0±7.2	10.3±10.1	0.0344*
HOMA index	3.4±4.1	3.9±4.5	4.0±5.2	2.9±2.6	2.9±3.2	0.0566*
Metabolic (lipid)						
Total cholesterol, mg/dL	183±49	171±43	179±46	182±44	201±55	<0.0001
LDL, mg/dL	106±40	100±37	103±38	105±38	118±45	0.0043
HDL, mg/dL	53±17	47±13	51±16	52±14	61±19	<0.0001
†HDL ≤ 40 mg/dL, male or HDL ≤ 50 mg/dL, female	160 (30)	60 (44)	47 (34)	34 (26)	19 (14)	<0.0001
Apo A1, mg/dL	143±32	132±32	139±32	148±27	155±35	<0.0001
Apo B, mg/dL	87±28	82±28	86±26	88±27	93±29	0.0048
Lipoprotein (a)	21.3±23.2	16.1±18.3	21.6±21.6	22.9±22.0	24.6±26.5	0.0052
Tryglicerides, mg/dL	124±81	125±85	127±83	127±89	118±68	ns
†Tryglicerides ≥150 mg/dL	131 (24)	34 (25)	36 (25)	31 (23)	30 (23)	ns
Inflammatory and vascular						
hs-CRP, mg/dL	0.40±1.09	0.41±0.61	0.30±0.34	0.47±1.89	0.43±0.84	ns
Interleukin 6, ng/L	1.35±2.53	1.56±2.71	1.10±1.25	1.46±3.24	1.30±1.67	ns
Adipokines						
Adiponectin, µg/mL	9.81±6.92	8.11±5.06	10.21±8.04	9.74±6.28	11.19±7.62	0.0019
Leptin, ng/mL	9.93±10.66	11.38±13.01	9.06±8.89	9.27±9.15	9.99±10.98	ns

Continuous variables are presented as mean ± standard deviation, categorical variables as absolute N and (%); * I vs. IV quartile; † criteria of Metabolic Syndrome.

Table S3. Angiography imaging results relative to PCSK9 groups.

	CTA Population (n=412)	Quartile I <136 ng/L n=103	Quartile II-III 136-183.8 ng/L n=103	Quartile III 183.9-266 ng/L n=103	Quartile IV >266 ng/L n=103	P value
Obstructive CAD at CTA						
Stenosis >50%	144 (35)	40 (39)	31 (30)	40 (38)	33 (32)	ns
Stenosis >70%	45 (11)	12 (12)	12 (12)	11 (11)	10 (10)	ns
Coronary plaques						
Total N. of plaques	3.9±3.8	4.36±3.89	3.70±3.63	4.23±3.90	3.37±3.77	0.0621*
N. of non-obstructive plaques	3.03±3.0	3.33±2.89	2.96±2.89	3.14±3.31	2.43±2.93	0.0323*
N. of obstructive plaques	0.9±1.7	0.94±1.57	0.63±1.43	0.84±1.43	0.85±1.87	ns
N. of calcified plaques	0.9±1.7	0.85±1.84	0.83±1.42	1.04±1.93	0.81±1.74	ns
N. of mixed plaques	2.6±3.2	3.14±3.42	2.45±3.14	2.54±3.14	2.19±3.15	0.0358*
N. of non-calcified plaques	0.5±0.9	0.38±0.85	0.43±0.78	0.66±1.21	0.38±0.72	ns
CTA risk score	11.71±11.05	13.17±11.53	10.88±10.43	12.77±10.95	9.99±11.11	0.0390*

Continuous variables are presented as mean ± standard deviation, categorical variables as absolute N and (%); * I vs. IV quartile.

Table S4: Univariate analysis of the association between clinical variables and CTA risk score

	Univariate analysis	
	Coefficient (SE)	P Value
Age	0.067 (0.007)	<0.0001
Male gender	0.774 (0.131)	<0.0001
Typical angina	-0.340 (0.155)	0.0288
LVEF	-0.022 (0.008)	0.0059
Pre-test probability of CAD	0.005 (0.003)	0.0609
Family history of CAD	-0.298 (0.139)	0.0326
Diabetes	0.458 (0.152)	0.0028
Hypercholesterolemia	0.157 (0.134)	ns
Hypertension	0.478 (0.133)	0.0004
Smoking	0.074 (0.152)	ns
BMI	0.016 (0.017)	ns
Metabolic Syndrome	0.373 (0.152)	0.0143
Beta-blockers	0.386 (0.134)	0.0041
Calcium channel blockers	0.380 (0.203)	ns
ACE Inhibitors	0.355 (0.145)	0.0146
ARBs	0.386 (0.179)	0.0318
Diuretics	-0.269 (0.178)	ns
Anti-diabetic	0.0465 (0.167)	0.0056
Statins	0.543 (0.130)	<0.0001
Aspirin	0.535 (0.131)	<0.0001
Anti-coagulants	0.670 (0.156428)	ns

Table S5: Univariate analysis of the association between biohumoral variables and CTA risk score

	Univariate analysis	
	Coefficient (SE)	P Value
Creatinin	1.069 (0.599)	0.0750
AST	0.036 (0.186)	ns
ALT	-0.119 (0.138)	ns
ALP	-0.083 (0.185)	ns
Glicemia	0.514 (0.259)	0.0475
Insulin	0.249 (0.086)	0.0041
HOMA index	0.322 (0.107)	0.0029
Total cholesterol	-0.859 (0.244)	0.0005
LDL cholesterol	-0.519 (0.166)	0.0019
HDL cholesterol	-0.829 (0.207)	< 0.0001
Apo A1	-0.911 (0.253)	0.0004
Apo B	-0.308 (0.202)	ns
Lipoprotein (a)	0.016 (0.065)	ns
Triglycerides	0.143 (0.121)	ns
hs-CRP	0.0152 (0.036)	ns
Interleukin-6	0.496 (0.137)	0.0003
Adiponectin	-0.118 (0.105)	ns
Leptin	-0.318 (0.073)	<0.0001
PCSK9	-0.277 (0.135)	0.0408

Table S6. Univariate and multivariate analyses of the association between PCSK9 and statins or all drugs.

	PCSK9	
	Coefficient± SE	P
AST	0.202±0.056	0.0004
AST + statins	0.201±0.056	0.0004
AST + all drugs	0.205±0.057	0.0003
	Coefficient± SE	P
ALT	0.142±0.042	0.0009
ALT + statins	0.143±0.042	0.0008
ALT + all drugs	0.142±0.042	0.0008
	Coefficient± SE	P
ALP	0.389±0.055	0.0001
ALP + statins	0.387±0.056	<0.0001
ALP + all drugs	0.389±0.055	<0.0001

Table S7. Univariate and multivariate analyses of the association among PCSK9 and hepatic enzymes, risk factors, CTA risk score.

	PCSK9	
	Coefficient± SE	P
AST	0.202±0.056	0.0004
AST + risk factors*	0.205±0.056	0.0003
AST + CTA score	0.183±0.066	0.0059
	Coefficient± SE	P
ALT	0.142±0.042	0.0009
ALT + risk factors*	0.157±0.043	0.0002
ALT + CTA score	0.131±0.050	0.0085
	Coefficient± SE	P
ALP	0.389±0.055	0.0001
ALP + risk factors*	0.372±0.057	<0.0001
ALP + CTA score	0.389±0.064	<0.0001

*Risk factors included Diabetes, Hypecholesterolemia, Hypertriglyceridemia, Obesity, and Metabolic Syndrome