Supplementary material

Mołek P, Żmudzki P, Machnik A, et al. Thin-cap fibroatheroma and increased coronary intima-media thickness are associated with an altered balance of arginine metabolites. Pol Arch Intern Med. 2023; 133: 16356. doi:10.20452/pamw.16356

Figure S1. Optical coherence tomography image analysis.

Abbreviations: The longitudinal view was used to identify the culprit lesion, and region adjacent to the culprit. Within the culprit lesion (representative frames E-H), the outlines of a lumen, vessel, and thrombus were contoured on each frame by multiple points trace function (according to B1). Within the non-culprit segment of infarct-related artery the contours of a lumen, intima layer and media layer were drawn (according to B1) on the most proximal frame (A), on the most available distal frame (L), on the three frames (B-D) within the 10-mm adjacent to the culprit proximal segment and on the three frames (I-K) within the 10-mm distal adjacent segment. The obtained contours were used for the calculation of the areas of the intima, media, intima-media, lumen, and vessel while their mean diameters were calculated from measurements performed every 90 degrees at the same frames (according to B2). Mean values for the adjacent to the culprit region were derived from measurements B-D and I-K.

Figure S1.

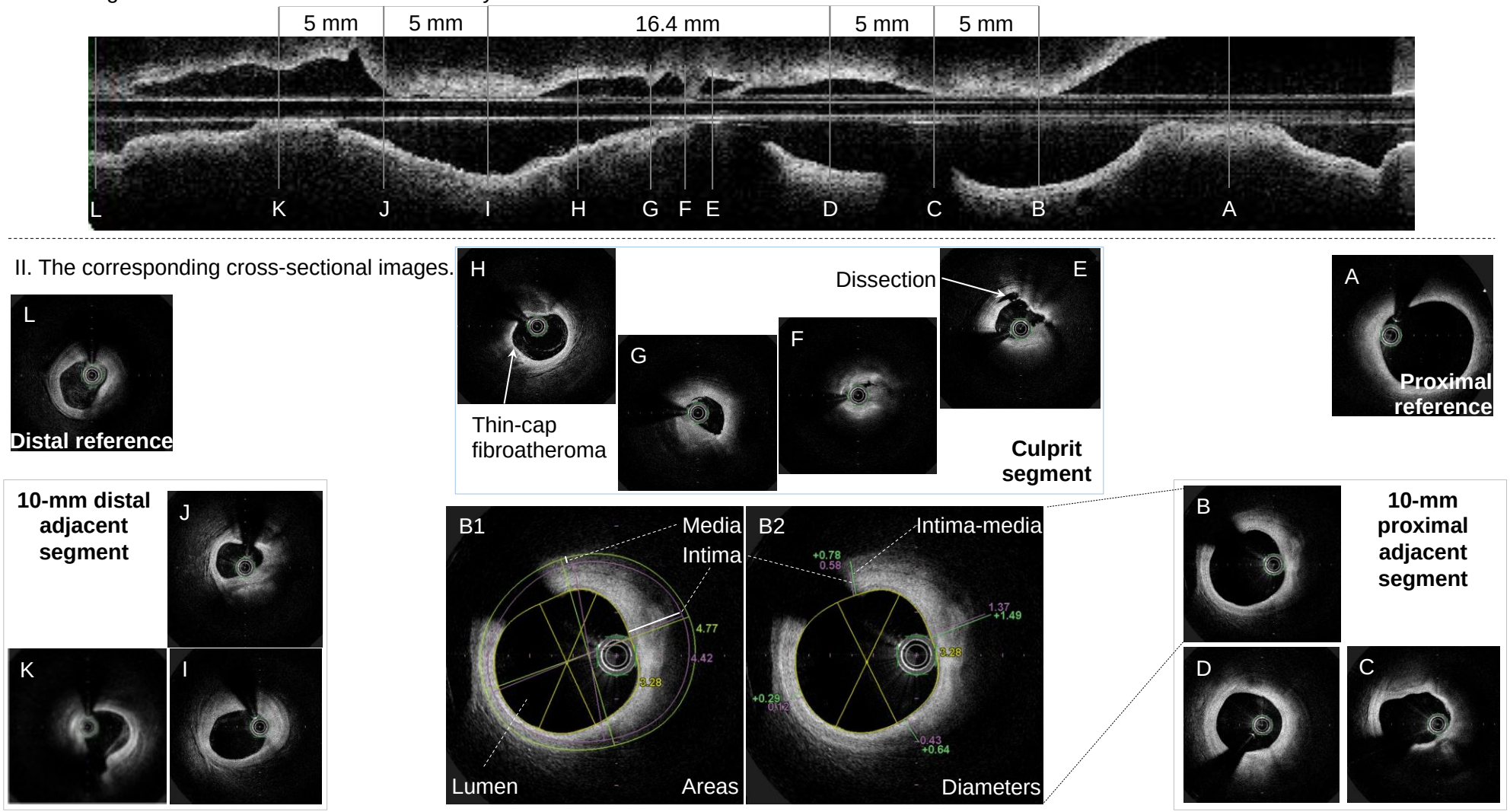
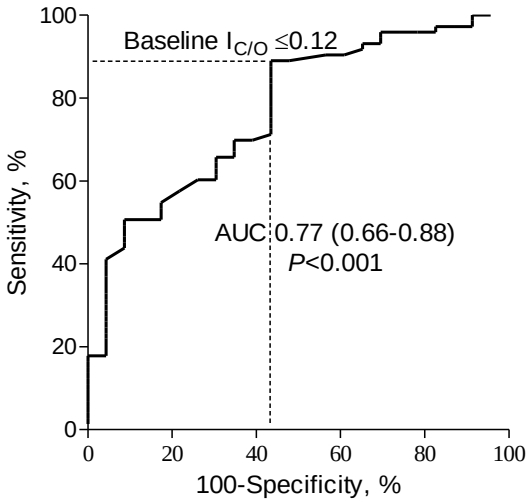
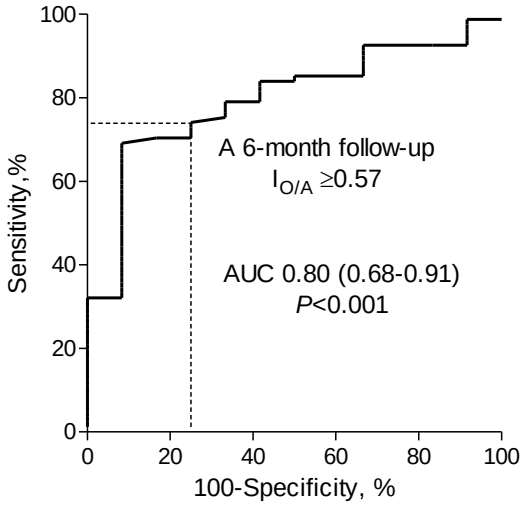

I. The longitudinal view of an infarct-related artery.
5 mm
5 mm
16.4 mm
5 mm
5 mm
L
K
J
I
H
G
F
E
D
C
B
A
II. The corresponding cross-sectional images.
L
Distal reference
H
Thin-cap fibroatheroma
G
F
Dissection
E
Culprit segment
A
Proximal reference
10-mm distal adjacent segment
J
K
I
B1
Media
Intima
4.77
4.42
3.28
Lumen
Areas
B2
Intima-media
+0.78
0.58
1.37
+1.49
3.28
+0.29
0.43
+0.64
Diameters
B
10-mm proximal adjacent segment
D
C

Figure S2. Prognostic value of arginine indices.

A



B



Abbreviations: A. Acute phase of MI $I_{C/O}$ reached the area under the ROC curve of 0.77 (95% CI 0.66-0.88) for prediction of TCFA with a cut-off value of ≤0.12, and a sensitivity of 89.0% and specificity of 57.1%. B. 6-month $I_{O/A}$ reached the area under the ROC curve of 0.80 (95% CI 0.68-0.91) for prediction of composite ischemic endpoint with a cut-off value of ≥0.57, a sensitivity of 74.1% and specificity of 75.0%. $I_{C/O}$: citrulline/ornithine ratio, $I_{O/A}$: ornithine/arginine ratio, AUC: area under the curve, ROC: receiver operating characteristic.

Table S1. Arginine metabolites in acute phase of myocardial infarction and in stable chronic phase.

		Citrulline	Ornithine	Proline	ADMA	MMA	Spermidine	Agmatine	Creatinine
Acute phase of myocardial infarction									
Arginine	R	0.312	0.367	0.369	0.503	0.532	0.308	0.383	0.001
	P	0.004	0.001	0.001	<0.001	<0.001	0.005	<0.001	0.97
Citrulline	R		0.467	0.477	0.421	0.455	0.306	0.056	0.287
	P		<0.001	<0.001	<0.001	<0.001	0.005	0.614	0.004
Ornithine	R			0.396	0.332	0.372	0.340	0.478	0.222
	P			<0.001	0.002	<0.001	0.002	<0.001	0.04
Proline	R				0.374	0.390	0.325	0.073	0.195
	P				<0.001	<0.001	0.003	0.51	0.06
ADMA	R					0.668	0.455	0.121	0.289
	P					<0.001	<0.001	0.28	0.004
MMA	R						0.463	0.101	0.318
	P						<0.001	0.20	0.003
Spermidine	R							0.012	0.003
	P							0.92	0.77
Agmatine	R								0.128
	P								0.251
6-month follow-up									
Arginine	R	0.564	0.344	0.568	0.289	0.322	0.154	0.186	0.131
	P	<0.001	0.002	<0.001	0.009	0.005	0.17	0.10	0.33
Citrulline	R		0.21	0.99	0.26	0.27	-0.07	0.17	0.43

	P		0.063	<0.001	0.023	0.011	0.548	0.142	<0.001
Ornithine	R			0.198	0.251	0.261	0.213	0.124	0.473
	P			0.08	0.02	0.02	0.06	0.27	<0.001
Proline	R				0.273	0.283	-0.057	0.170	0.365
	P				0.01	0.009	0.61	0.13	0.001
ADMA	R					0.710	0.444	-0.011	0.312
	P					<0.001	<0.001	0.92	0.002
MMA	R						0.401	-0.121	0.301
	P						<0.001	0.31	0.006
Spermidine	R							-0.014	0.015
	P							0.90	0.52
Agmatine	R								0.113
	P								0.45

Abbreviations: arginine metabolites were expressed in μM, ADMA: asymmetric dimethylarginine, MMA: monomethyl arginine, r: correlation coefficient.

Table S2. The infarct-related artery characteristics obtained from the non-culprit regions in relation to the sex.

	Male	Female	*P*-value
Proximal reference of the IRA			
Diameters			
Vessel	5.14 (4.75; 5.63)	4.78 (4.34; 5.10)	**0.01**
Lumen	3.81 (3.44; 4.52)	3.78 (3.16; 4.09)	0.19
Intima	0.44 (0.33; 0.68)	0.36 (0.20; 0.43)	0.08
Media	0.12 (0.10; 0.13)	0.13 (0.11; 0.14)	0.22
Intima-media	0.58 (0.43; 0.78)	0.47 (0.37; 0.54)	0.12
Lumen/Vessel	0.77 (0.71; 0.84)	0.80 (0.72; 0.85)	0.33
Intima/Vessel	0.09 (0.06; 0.13)	0.08 (0.04; 0.11)	0.23
Media/Vessel	0.020 (0.023; 0.027)	0.028 (0.022; 0.033)	0.08
Intima-media/Vessel	0.12 (0.08; 0.16)	0.10 (0.07; 0.14)	0.43
Areas			
Vessel	20.5 (17.7; 24.9)	17.9 (14.3; 20.9)	**0.01**
Lumen	11.3 (9.3; 16.0)	11.3 (7.7; 13.8)	0.20
Intima	6.5 (3.9; 8.5)	3.9 (2.8; 5.1)	**0.02**
Media	2.0 (1.7; 2.3)	1.8 (1.4; 2.6)	0.69
Intima-media	8.8 (6.1; 10.5)	5.8 (4.7; 7.1)	**0.02**
Lumen/Vessel	0.59 (0.51; 0.70)	0.65 (0.52; 0.73)	0.31
Intima/Vessel	0.29 (0.19; 0.40)	0.27 (0.13; 0.38)	0.23
Media/Vessel	0.09 (0.08; 0.11)	0.09 (0.08; 0.11)	0.98

Intima-media/Vessel	0.41 (0.30; 0.49)	0.35 (0.28; 0.49)	0.31
Adjacent segment of the IRA			
Diameters			
Vessel	4.34 (3.96; 4.79)	3.92 (3.59; 4.36)	**0.006**
Lumen	3.09 (2.78; 3.47)	3.07 (2.51; 3.28)	0.22
Intima	0.51 (0.35; 0.62)	0.34 (0.28; 0.44)	**<0.001**
Media	0.13 (0.11; 0.16)	0.12 (0.11; 0.15)	0.35
Intima-media	0.64 (0.49; 0.75)	0.48 (0.39; 0.61)	**0.002**
Lumen/Vessel	0.72 (0.67; 0.77)	0.75 (0.71; 0.79)	**0.049**
Intima/Vessel	0.11 (0.09; 0.14)	0.09 (0.07; 0.12)	**0.01**
Media/Vessel	0.030 (0.026; 0.033)	0.032 (0.029; 0.035)	**0.004**
Intima-media/Vessel	0.14 (0.12; 0.17)	0.12 (0.12; 0.15)	0.065
Areas			
Vessel	15.5 (12.6; 18.3)	12.3 (10.2; 15.2)	**0.005**
Lumen	7.7 (6.6; 9.9)	7.4 (5.1; 8.7)	0.18
Intima	5.6 (4.2; 6.9)	3.5 (3.0; 4.2)	**<0.001**
Media	1.7 (1.4; 2.0)	1.5 (1.4; 2.0)	0.57
Intima-media	7.0 (5.7; 8.7)	5.5 (4.2; 6.4)	**<0.001**
Lumen/Vessel	0.54 (0.47; 0.59)	0.58 (0.51; 0.62)	0.08
Intima/Vessel	0.34 (0.30; 0.41)	0.29 (0.22; 0.35)	**0.005**
Media/Vessel	0.11 (0.10; 0.13)	0.13 (0.12; 0.14)	**0.002**
Intima-media/Vessel	0.45 (0.39; 0.53)	0.41 (0.37; 0.49)	0.25
Distal reference of the IRA			
Diameters			

Vessel	3.14 (2.79; 3.63)	2.98 (2.52; 3.32)	0.39
Lumen	2.29 (1.97; 2.61)	2.27 (1.91; 2.74)	0.50
Intima	0.30 (0.16; 0.40)	0.20 (0.17; 0.28)	0.30
Media	0.10 (0.08; 0.13)	0.11 (0.09; 0.13)	0.65
Intima-media	0.41 (0.24; 0.52)	0.32 (0.26; 0.42)	0.44
Lumen/Vessel	0.76 (0.69; 0.83)	0.78 (0.71; 0.82)	0.80
Intima/Vessel	0.08 (0.06; 0.12)	0.07 (0.05; 0.11)	0.42
Media/Vessel	0.033 (0.028; 0.040)	0.037 (0.034; 0.044)	0.35
Intima-media/Vessel	0.12 (0.09; 0.16)	0.11 (0.09; 0.14)	0.65
Areas			
Vessel	7.7 (6.1; 10.3)	7.0 (5.0; 8.7)	0.35
Lumen	4.2 (3.0; 5.4)	4.1 (3.0; 6.0)	0.51
Intima	2.3 (1.0; 3.3)	1.6 (1.1; 2.4)	0.26
Media	1.0 (0.7; 1.5)	1.1 (0.7; 1.2)	0.94
Intima-media	3.4 (1.7; 4.7)	2.6 (2.0; 4.3)	0.37
Lumen/Vessel	0.58 (0.48; 0.69)	0.61 (0.52; 0.66)	0.78
Intima/Vessel	0.28 (0.19; 0.38)	0.22 (0.19; 0.35)	0.42
Media/Vessel	0.13 (0.11; 0.15)	0.14 (0.13; 0.17)	0.16
Intima-media/Vessel	0.42 (0.31; 0.52)	0.39 (0.34; 0.49)	0.77

Abbreviations: IRA: infarct-related artery.

Table S3. The correlations between follow-up arginine metabolites or their indices versus mean diameters and areas of non-culprit regions of the infarct-related artery.

		Mean diameters					**Mean areas**				
		Lumen	Vessel	Intima	Intima media	Media	Lumen	Vessel	Intima	Intima media	Media
Adjacent segment of the IRA											
Arginine	R	-0.001	-0.099	**-0.246**	**-0.271**	**-0.236**	0.052	-0.076	-0.177	-0.203	**-0.233**
	P	0.99	0.39	**0.03**	**0.02**	**0.04**	0.66	0.51	0.12	0.08	**0.04**
Citrulline	R	-0.086	-0.133	-0.166	**-0.231**	-0.122	-0.085	-0.145	-0.163	-0.172	-0.158
	P	0.46	0.25	0.15	**0.04**	0.29	0.46	0.21	0.16	0.14	0.17
Ornithine	R	0.128	0.108	0.016	0.063	-0.016	0.155	0.136	0.071	0.076	0.060
	P	0.27	0.35	0.89	0.59	0.89	0.18	0.24	0.54	0.51	0.61
Proline	R	-0.074	-0.123	-0.159	-0.223	-0.120	-0.078	-0.135	-0.153	-0.162	-0.152
	P	0.53	0.29	0.17	0.05	0.30	0.50	0.24	0.183	0.16	0.19
ADMA	R	-0.033	-0.116	-0.130	-0.125	-0.116	-0.055	-0.115	-0.136	-0.152	-0.160
	P	0.78	0.32	0.26	0.28	0.31	0.64	0.32	0.24	0.19	0.16
MMA	R	-0.011	-0.137	-0.220	-0.173	-0.151	-0.025	-0.140	-0.195	**-0.252**	-0.180
	P	0.90	0.27	0.05	0.12	0.17	0.82	0.25	0.10	**0.03**	0.12
GABR	R	-0.045	-0.129	**-0.230**	**-0.275**	**-0.239**	-0.003	-0.115	-0.179	-0.211	**-0.257**
	P	0.70	0.26	**0.04**	**0.02**	**0.04**	0.98	0.32	0.12	0.07	**0.02**
Ornithine/Arginine	R	0.074	0.185	**0.291**	**0.337**	0.172	0.045	0.176	**0.265**	**0.278**	**0.229**
	P	0.52	0.11	**0.009**	**0.003**	0.13	0.70	0.13	**0.02**	**0.02**	**0.04**
Citrulline/Ornithine	R	-0.111	-0.205	**-0.243**	**-0.278**	-0.173	-0.109	-0.204	**-0.239**	**-0.256**	**-0.240**
	P	0.34	0.07	**0.03**	**0.02**	0.13	0.35	0.078	**0.04**	**0.03**	**0.04**

Proline/Arginine	R	-0.093	-0.053	0.055	0.004	0.041	-0.131	-0.079	-0.003	0.004	0.006
	P	0.42	0.65	0.64	0.97	0.73	0.26	0.50	0.98	0.97	0.96
Citrulline/Arginine	R	-0.090	-0.023	0.092	0.116	0.117	-0.126	-0.050	0.028	0.061	0.089
	P	0.40	0.83	0.40	0.28	0.27	0.24	0.64	0.79	0.57	0.40
Distal reference of the IRA											
Arginine	R	-0.158	**-0.310**	**-0.272**	**-0.308**	**-0.356**	-0.162	**-0.299**	**-0.288**	**-0.321**	**-0.358**
	P	0.22	**0.02**	**0.03**	**0.02**	**0.005**	0.21	**0.02**	**0.02**	**0.01**	**0.004**
Citrulline	R	0.003	**-0.276**	**-0.436**	**-0.455**	**-0.369**	-0.019	**-0.313**	**-0.444**	**-0.454**	**-0.388**
	P	0.98	**0.03**	**<0.001**	**<0.001**	**0.003**	0.88	**0.02**	**<0.001**	**<0.001**	**0.002**
Ornithine	R	0.0147	-0.056	-0.080	-0.108	-0.232	0.0105	-0.063	-0.071	-0.102	-0.180
	P	0.91	0.66	0.54	0.40	0.07	0.94	0.63	0.58	0.43	0.16
Proline	R	0.0069	**-0.278**	**-0.447**	**-0.466**	**-0.371**	-0.017	**-0.316**	**-0.450**	**-0.460**	**-0.388**
	P	0.96	**0.03**	**<0.001**	**<0.001**	**0.003**	0.90	**0.01**	**<0.001**	**<0.001**	**0.002**
ADMA	R	-0.083	-0.146	-0.142	-0.141	-0.141	-0.095	-0.154	-0.147	-0.156	-0.152
	P	0.52	0.26	0.27	0.28	0.27	0.46	0.23	0.26	0.23	0.24
MMA	R	-0.121	-0.167	-0.155	-0.165	-0.166	-0.120	-0.170	-0.197	-0.201	-0.172
	P	0.22	0.15	0.17	0.16	0.15	0.23	0.14	0.12	0.12	0.18
GABR	R	-0.172	**-0.267**	-0.191	-0.221	-0.241	-0.169	-0.239	-0.205	-0.225	-0.241
	P	0.18	**0.04**	0.14	0.09	0.06	0.19	0.06	0.11	0.08	0.06
Ornithine/Arginine	R	0.1415	**0.266**	**0.258**	**0.273**	0.235	0.142	0.246	**0.252**	**0.258**	0.218
	P	0.27	**0.04**	**0.04**	**0.03**	0.07	0.27	0.05	**0.04**	**0.04**	0.09
Citrulline/Ornithine	R	-0.180	**-0.339**	**-0.316**	**-0.334**	**-0.294**	-0.187	**-0.359**	**-0.381**	**-0.392**	**-0.34**
	P	0.16	**0.007**	**0.01**	**0.008**	**0.02**	0.15	**0.004**	**0.002**	**0.002**	**0.007**
Proline/Arginine	R	0.109	-0.083	**-0.291**	**-0.285**	-0.144	0.082	-0.145	**-0.299**	**-0.282**	-0.162
	P	0.40	0.52	**0.02**	**0.03**	0.27	0.53	0.26	**0.02**	**0.03**	0.21

Citrulline/Arginine	R	0.112	0.012	-0,170	-0.140	0.038	0.100	-0.036	-0.170	-0.138	-0.011
	P	0.32	0.92	0.15	0.23	0.75	0.40	0.76	0.14	0.24	0.93
Proximal reference of the IRA											
Arginine	R	0.150	0.078	-0.114	-0.010	-0.016	0.140	0.082	-0.056	-0.060	-0.006
	P	0.23	0.53	0.36	0.43	0.90	0.26	0.51	0.66	0.63	0.97
Citrulline	R	0.0931	0.033	-0.088	-0.060	-0.023	0.065	0.026	-0.033	-0.050	-0.028
	P	0.46	0.79	0.49	0.63	0.85	0.60	0.84	0.80	0.69	0.83
Ornithine	R	-0.187	-0.115	0.133	0.141	0.072	-0.194	-0.116	0.095	0.079	-0.070
	P	0.13	0.36	0.29	0.26	0.57	0.12	0.35	0.45	0.53	0.58
Proline	R	0.099	0.044	-0.081	-0.055	-0.030	0.072	0.036	-0.025	-0.041	-0.016
	P	0.43	0.73	0.52	0.66	0.81	0.57	0.77	0.84	0.74	0.90
ADMA	R	-0.023	-0.016	0.037	0.035	-0.083	-0.029	-0.016	0.041	0.015	-0.084
	P	0.85	0.90	0.77	0.78	0.51	0.82	0.90	0.75	0.90	0.50
MMA	R	-0.032	-0.022	0.056	0.100	-0.112	-0.036	-0.024	0.081	0.065	-0.131
	P	0.79	0.81	0.73	0.48	0.40	0.78	0.79	0.44	0.68	0.37
GABR	R	**0.301**	0.184	-0.202	-0.203	-0.082	**0.302**	0.192	-0.119	-0.110	0.038
	P	**0.02**	0.14	0.10	0.10	0.51	**0.02**	0.12	0.34	0.38	0.76
Ornithine/Arginine	R	**-0.250**	-0.101	0.232	0.228	0.088	**-0.250**	-0.105	0.189	0.185	-0.001
	P	**0.04**	0.42	0.06	0.07	0.48	**0.04**	0.40	0.13	0.14	0.99
Citrulline/Ornithine	R	0.114	0.088	0.001	0.008	-0.183	0.097	0.086	0.047	0.009	-0.122
	P	0.36	0.48	0.99	0.98	0.14	0.44	0.49	0.71	0.95	0.33
Proline/Arginine	R	-0.022	-0.001	0.053	0.069	-0.010	-0.042	-0.012	0.061	0.039	-0.032
	P	0.86	0.99	0.67	0.58	0.94	0.74	0.92	0.63	0.75	0.80
Citrulline/Arginine	R	-0.084	-0.029	0.093	0.116	0.095	-0.100	-0.040	0.077	0.076	0.057
	P	0.47	0.80	0.43	0.32	0.42	0.40	0.73	0.51	0.52	0.63

Abbreviations: ADMA; asymmetric dimethylarginine, MMA: monomethyl arginine, GABR: global arginine bioavailability ratio.

Table S4. Arginine metabolites and their indices measured in acute phase of MI and after 6-month follow-up in patients with and without ischemic composite endpoint.

	With ischemic endpoint n=14	**Without ischemic endpoint** n=86	***P*-value**
Acute phase of MI			
Arginine, μM	6.58 (4.94; 7.37)	5.56 (4.16; 7.19)	0.33
Citrulline, μM	0.72 (0.51; 1.13)	0.56 (0.44; 0.74)	0.06
Ornithine, μM	10.01 (6.34; 14.23)	4.78 (4.37; 5.57)	0.26
Proline, μM	0.87 (0.57; 1.35)	0.73 (0.51; 0.90)	0.18
ADMA, μM	0.36 (0.31; 0.48)	0.33 (0.26; 0.42)	0.20
MMA, μM	0.60 (0.22; 0.70)	0.48 (0.20; 0.58)	0.22
Spermidine, μM	14.02 (6.72; 21.69)	10.36 (4.87; 23.00)	0.67
Agmatine, μM	54.20 (15.92; 66.89)	47.88 (7.82; 61.50)	0.41
Citrulline/Arginine	0.12 (0.07; 0.16)	0.10 (0.08; 0.15)	0.51
Ornithine/Arginine	1.52 (1.04; 1.89)	1.24 (1.03; 2.07)	0.88
Citrulline/Ornithine	0.11 (0.07; 0.12)	0.09 (0.07; 0.12)	0.31
Arginine/ADMA	12.60 (9.08; 23.52)	15.13 (10.97; 18.50)	0.81
GABR	0.61 (0.51; 0.89)	0.69 (0.40; 0.87)	0.93
Agmatine/Arginine	9.26 (3.05; 11.53)	7.95 (2.17; 10.44)	0.73
Proline/Arginine	0.14 (0.10; 0.21)	0.12 (0.09; 0.20)	0.64
Spermidine/Arginine	2.11 (1.09; 3.41)	2.11 (0.94; 3.92)	0.84
Spermidine/Ornithine	1.28 (0.70; 1.83)	1.20 (0.78; 3.09)	0.79

6-month follow-up			
Arginine, μM	8.07 (7.66; 10.29)	10.06 (8.60; 11.99)	0.17
Citrulline, μM	2.08 (1.56; 2.66)	2.30 (1.83; 2.74)	0.31
Ornithine, μM	5.10 (4.78; 6.08)	4.78 (4.37; 5.57)	0.26
Proline, μM	0.37 (0.24; 0.53)	0.42 (0.32; 0.55)	0.34
ADMA, μM	0.53 (0.48; 0.64)	0.58 (0.52; 0.73)	0.49
MMA, μM	0.75 (0.35; 0.90)	0.60 (0.23; 0.78)	0.18
Spermidine, μM	11.92 (10.68; 13.51)	11.72 (11.08; 13.56)	0.98
Agmatine, μM	25.63 (9.68; 28.24)	26.95 (19.63; 30.73)	0.55
Citrulline/Arginine	0.22 (0.15; 0.28)	0.23 (0.18; 0.26)	0.86
Ornithine/Arginine	0.62 (0.56; 0.79)	0.48 (0.41; 0.57)	<0.001
Citrulline/Ornithine	0.40 (0.30; 0.52)	0.49 (0.36; 0.57)	0.11
Arginine/ADMA	12.98 (10.68; 16.56)	14.70 (10.56; 18.74)	0.60
GABR	1.16 (1.09; 1.35)	1.42 (1.27; 1.59)	0.02
Agmatine/Arginine	2.86 (2.28; 3.61)	2.46 (2.02; 3.23)	0.30
Proline/Arginine	0.04 (0.03; 0.05)	0.04 (0.03; 0.05)	0.95
Spermidine/Arginine	1.39 (1.06; 1.60)	1.18 (0.94; 1.46)	0.34
Spermidine/Ornithine	2.19 (2.03; 2.5)	2.41 (2.12; 2.90)	0.29

Abbreviations: data are shown as median (interquartile range), ADMA; asymmetric dimethylarginine, MMA: monomethyl arginine, GABR: global arginine bioavailability ratio.