Supplemental table 1. Characteristics of all study subjects.

	Control (n=9)	AS before AVR (n=10)	AS after AVR (n=10)
Age (years)	51 ± 9	62 ± 10*	62 ± 10
Men (%)	6 (67%)	7 (70%)	7 (70%)
BMI (kg/m²)	26 ± 3	28 ± 3	28 ± 4
Heart rate (beats per minute)	66 ± 10	66 ± 7	66 ± 6
Systolic blood pressure (mm Hg)	124 ± 14	120 ± 11	122 ± 12
Diastolic blood pressure (mm Hg)	69 ± 4	69 ± 10	72 ± 9
Cardiac parameters			
LVEF (%)	61 ± 6	58 ± 7	61 ± 5
LVEDV (mL)	201 ± 42	202 ± 46	178 ± 40
LVESV (mL)	79 ± 25	87 ± 32	71 ± 21
LV mass	103 ± 18	209 ± 50*	151 ± 38#
E	78 ± 11	72 ± 17	81 ± 13
A	60 ± 10	76 ± 15*	77 ± 17
E/A	0.98 ± 0,3	1.34 ± 0,3*	1.1 ± 0,3
Septal e'	9 ± 2,1	6 ± 2*	8 ± 1#
Lateral e'	14 ± 3	6 ± 2*	10 ± 2#
E/e'	7 ± 1	12 ± 3*	10 ± 2#
Laboratory data			
Hemoglobin (mmol/L)	8 ± 0,5	9 ± 0,7*	9 ± 1
Hematocrit	0.39 ± 0,02	0.43 ± 0,04*	0.42 ± 0,05
Kreatinine (mmol/L)	94 ± 8	74 ± 10*	78 ± 13
Ureum (mmol/L)	5 ± 1	6 ± 1	6 ± 1
Glucose (mmol/L)	6 ± 0,4	6 ± 0,7	6 ± 0,6
Free fatty acids (mmol/L)	0.5 ± 0,3	0.7 ± 0,3	0.6 ± 0,2
Lactate (mmol/L)	1 ± 0,6	1 ± 0,5	2 ± 1
NT-pro-BNP	54 ± 58	439 ± 537*	247 ± 151

Values are depicted as mean ± SD.
BMI = Body mass index, LVEF = Left Ventricular Ejection Fraction, LVEDV = Left Ventricular End Diastolic Volume, LVESV = Left Ventricular End Systolic Volume, E = early diastolic mitral flow velocity, A = late diastolic mitral flow velocity, e' = early diastolic mitral annulus velocity, NT-pro-BNP = N-terminal fragment B-type natriuretic peptide. *=p<0.05 AS before AVR compared to control, #=p<0.05 AS after AVR compared to AS before AVR.

Supplemental table 2. List of possible annotations for identical masses.

Metabolite 1	Metabolite 2	Metabolite 3	Metabolite 4	Metabolite 5
5(S)-Hydroperoxy-eicosatetraenoic acid	8,9-Epoxyeicosatrienoic acid	17a-Hydroxypregnenolone	Biopterin	5b-Cholestane-3a,7a,12a,25-tetrol
8-iso-PGA1	14R,15S-EpETrE	3a,7a-Dihydroxy-5b-cholestanate	D-Biopterin	Cholestane-3,7,12,25-tetrol
Prostaglandin A1	15(S)-HETE	21-Hydroxypregnenolone	Orinapterin	27-Deoxy-5b-cyprinol
Prostaglandin B1	14,15-Epoxy-5,8,11-eicosatrienoic acid	17-alpha,20-alpha-Dihydroxypregn-4-en-3-one	Dyspropterin	5b-Cholestane-3a,7a,12a,23-Tetrol
12(S)-HPETE	11,12-Epoxyeicosatrienoic acid	5alpha-Dihydrodeoxycorticosterone	Primapterin	5a-Cholestane-3a,7a,12a,25-tetrol
15(S)-HPETE	8-HETE	7alpha-Hydroxypregnenolone	Sepiapterin	
Hepoxilin A3	16(R)-HETE	16-a-Hydroxypregnenolone		
Hepoxilin B3	11(R)-HETE			
12(R)-HPETE	20-Hydroxyeicosa-tetraenoic acid			
11H-14,15-EETA	12-HETE			
11(R)-HPETE	18-Hydroxyarachidonic acid			
8(S)-HPETE	9-HETE			
15H-11,12-EETA	11,12-EpETrE			
6-trans-Leukotriene B4	5-HETE			
6-trans-12-epi-Leukotriene B4	19(S)-HETE			
12(S)-Leukotriene B4	10-HETE			
14,15-DiHETE	13-HETE			
17,18-DiHETE	17-HETE			
5,15-DiHETE	12 Hydroxy arachidonic acid			
8,15-DiHETE	Arachidonate			
5-HPETE	5,6-Epoxy-8,11,14-eicosatrienoic acid			
10,11-dihydro-12-oxo-LTB4				
6,7-dihydro-5-oxo-12-epi-LTB4				
9-Deoxy-delta12-PGD2				
Prostaglandin C1				
12,20-DiHETE				
Leukotriene B4				

Supplemental Table 3. Overview of top 30 metabolite changes in AS patients relative to controls (before AVR)(shown in Figure 2), and changes 4 months after AVR relative to AS before AVR.

	Metabolite	Before AVR	After AVR	p value Before vs after AVR
Nitric oxide synthesis	Homo-L-Arginine	↑	=	0.45
	D-Arginine / L-Arginine	↑	↑	0.006*
	(A)symmetric dimethylarginine	↑	=	0.07
BH4 metabolism	Nicotinamide riboside	↑	=	0.41
	Phenylalanyl-Asparagine / Asparaginyl-Phenylalanine	↑	↓	**0.03***
	Metabolite 4	↑	↓	**0.04***
	Dihydropteridine	↑	↓	**0.004***
Anti-oxidants	**Alpha-Tocotrienol**	↑	↓	**0.0002***
	9'-Carboxy-alpha-tocotrienol / 12a-Hydroxy-3-oxocholadienic acid	↑	=	0.05
	9'-Carboxy-gamma-tocotrienol	↑	↓	**0.02***
	Alpha-CEHC / Monoethylhexyl phthalic acid	↑	↑	0.008*
	3-Hydroxymelatonin	↓	↑	**0.01***
Homocysteine metabolism	L-Homocysteine sulfonic acid	↓	=	0.45
	Cysteinyl-Alanine / Alanyl-Cysteine	↓	=	0.08
	1-Methylhypoxanthine / 7-Methylhypoxanthine	↓	↓	0.004*
	Diphthamide	↑	=	0.15
	3-Polyprenyl-4,5-dihydroxybenzoate	↑	↓	**<0.0001***
Eicosanoids	Metabolite 1	↑	↑	0.04*
	Metabolite 3	↑	↑	0.03*
	13,14-Dihydro PGE1 / 13,14-Dihydro PGF2a / Prostaglandin F1a	↑	↓	**0.02***
Fatty acids	trans-Dodec-2-enoic acid / 5-Dodecenoic acid	↑	↑	0.04*
	LPA(16:0/0:0) / LPA(0:0/16:0)	↑	=	0.28
	2,3-Methylene suberic acid / 3,4-Methylene suberic acid	↑	↑	0.02*
	Alpha-linolenyl carnitine / Gamma-linolenyl carnitine	↑	↓	**0.03***
	14-HDoHE	↑	↓	**0.007***
Steroids	**Metabolite 2**	↑	↓	**<0.0001***
	Metabolite 5	↓	↑	**0.006***
	24,25,26,27-Tetranor-23-oxo-hydroxyvitamin D3	↑	↓	**0.01***
	11beta,20-Dihydroxy-3-oxopregn-4-en-21-oic acid	↑	↓	**0.0004***
Unknown	4-Hydroxy-3-methoxy-cinnamoylglycine	↑	=	0.08

P values from one-tailed paired t-tests between metabolites in AS patient sera taken before and 4 months after AVR.
*Significant difference (increase or decrease indicated by the arrows) at p<0.05. Unchanged (=) when p>0.05. Metabolites which show a significant reversal after AVR are indicated in bold.

Supplemental Table 4. Correlation between the top 30 metabolites of the metabolic profile and left ventricular mass (LVM) indexed for body surface area (BSA) and myocardial external efficiency indexed for BSA, respectively LVMi and MEEi.

Metabolite	Before AVR	After AVR	LVMi			MEEi		
			R^2	P value	FDR	R^2	P value	FDR
Homo-L-Arginine	↑	=	0.62	<0.0001	0.048204	0.49	0.0009	0.179834
L-Arginine	↑	↑	0.6	<0.0001	0.048204	0.51	0.0006	0.155335
(A)symmetric dimethylarginine	↑	=	0.57	0.0002	0.069656	0.4	0.0035	0.343254
Nicotinamide riboside	↑	=	0.11	0.1677	0.77763	0.11	0.167	0.813088
Phenylalanyl-Asparagine / Asparaginyl-Phenylalanine	**↑**	**↓**	**0.55**	**0.0003**	**0.070049**	**0.66**	**<0.0001**	**0.049699**
Metabolite 4	↑	↓	0.39	0.0043	0.230593	0.3	0.0152	0.569802
Dihydropteridine	↑	↓	0.37	0.0054	0.274244	0.28	0.0207	0.569802
Alpha-Tocotrienol	↑	↓	0.32	0.0119	0.461431	0.13	0.1224	0.765295
9'-Carboxy-alpha-tocotrienol / 12a-Hydroxy-3-oxocholadienic acid	↑	=	0.53	0.0004	0.074217	0.28	0.021	0.569802
9'-Carboxy-gamma-tocotrienol	**↑**	**↓**	**0.6**	**0.0001**	**0.048204**	**0.43**	**0.0025**	**0.306104**
Alpha-CEHC / Monoethylhexyl phthalic acid	↑	↑	0.51	0.0006	0.092942	0.31	0.0126	0.569802
3-Hydroxymelatonin	↓	↑	0.2	0.0524	0.666301	0.26	0.0252	0.604403
L-Homocysteine sulfonic acid	↓	=	0.15	0.0965	0.693427	0.18	0.0722	0.722006
Cysteinyl-Alanine / Alanyl-Cysteine	↓	=	0.37	0.0061	0.292895	0.32	0.0109	0.569802
1-Methylhypoxanthine / 7-Methylhypoxanthine	↓	↓	0.2	0.0555	0.666301	0.33	0.0108	0.569802
Diphthamide	↑	=	0.23	0.0377	0.663081	0.23	0.0393	0.685654
3-Polyprenyl-4,5-dihydroxybenzoate	**↑**	**↓**	**0.55**	**0.0003**	**0.070049**	**0.51**	**0.0006**	**0.155335**
trans-Dodec-2-enoic acid / 5-Dodecenoic acid	↑	↑	0.54	0.0004	0.074217	0.499	0.0007	0.168447
LPA(16:0/0:0) / LPA(0:0/16:0)	↑	=	0.45	0.0016	0.143242	0.25	0.0284	0.645321
2,3-Methylene suberic acid / 3,4-Methylene suberic acid	↑	↑	0.31	0.0126	0.477657	0.39	0.0041	0.379805
Alpha-linolenyl carnitine / Gamma-linolenyl carnitine	↑	↓	0.21	0.0501	0.666301	0.17	0.0841	0.722006
14-HDoHE	↑	↓	0.47	0.0013	0.131652	0.29	0.0184	0.569802
Metabolite 1	↑	↑	0.27	0.0239	0.604347	0.24	0.032	0.650984
Metabolite 2	↑	↑	0.41	0.0031	0.292895	0.3	0.0158	0.569802
13,14-Dihydro PGE1 / 13,14-Dihydro PGF2a / Prostaglandin F1a	↑	↓	0.22	0.0419	0.663081	0.2	0.0537	0.700883
Metabolite 3	↑	↓	0.36	0.0064	0.201124	0.29	0.0179	0.569802
Metabolite 5	↓	↑	0.15	0.0976	0.693427	0.23	0.0373	0.685654
24,25,26,27-Tetranor-23-oxo-hydroxyvitamin D3	↑	↓	0.49	0.0008	0.100121	0.25	0.031	0.650984
11beta,20-Dihydroxy-3-oxopregn-4-en-21-oic acid	↑	↓	0.496	0.0008	0.100121	0.41	0.0033	0.342398
4-Hydroxy-3-methoxy-cinnamoylglycine	↑	=	0.4	0.0037	0.212982	0.48	0.0011	0.198779

A linear regression analysis was performed with Pearson correlation and p-values were adjusted for False Discovery Rate (FDR) using the Benjami-Hochberg correction.

For overview purposes, the arrows indicate whether a metabolite is increased or decreased compared to controls (before AVR) and compared to after AVR. The colours correspond to the categories of metabolites shown in figures 3 through 11.
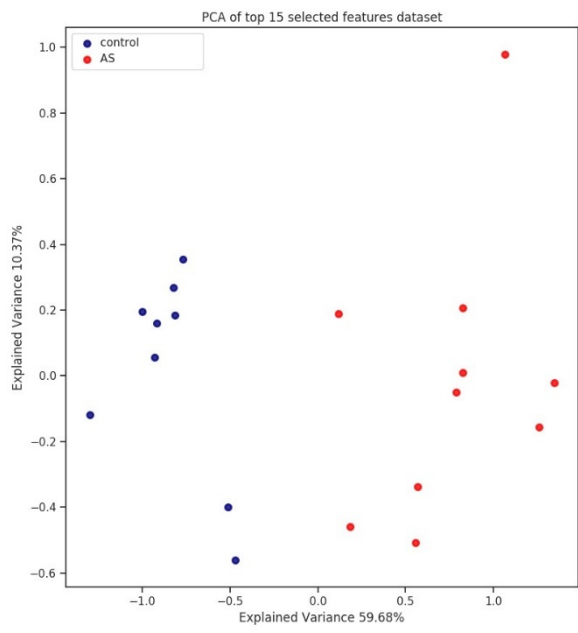
Figure S1. Principal component analysis (PCA) plot shows good separation of the model between controls and AS patients.
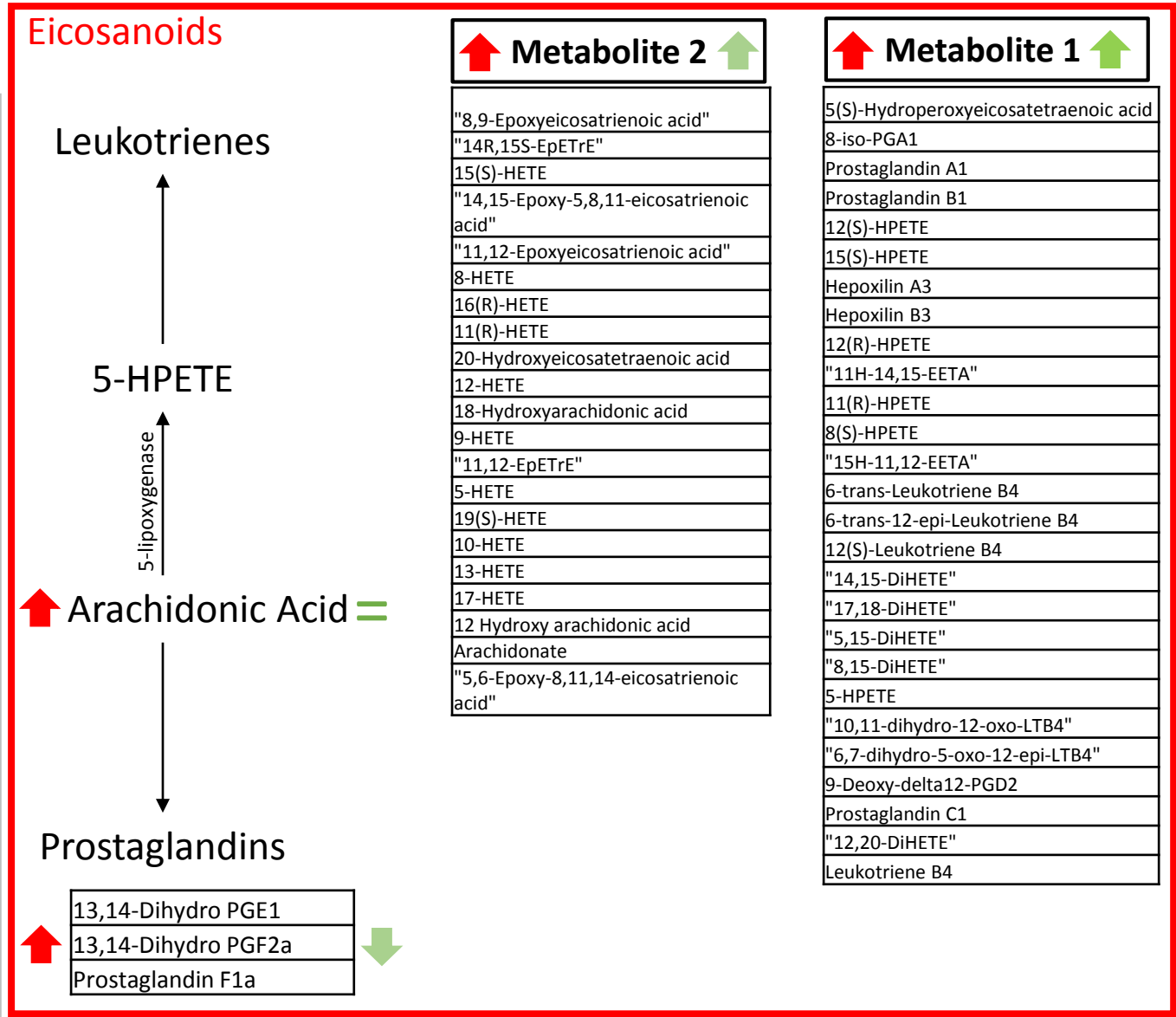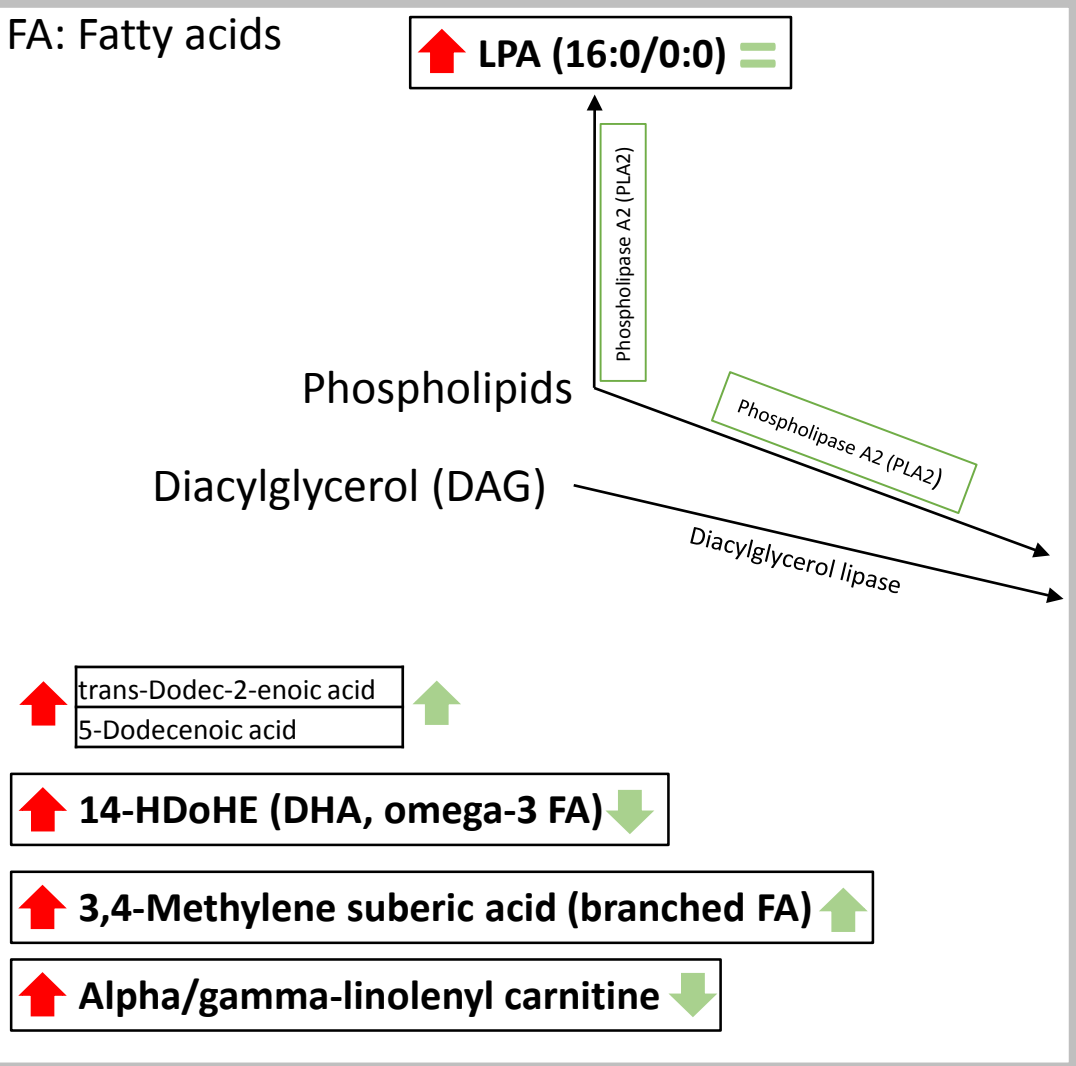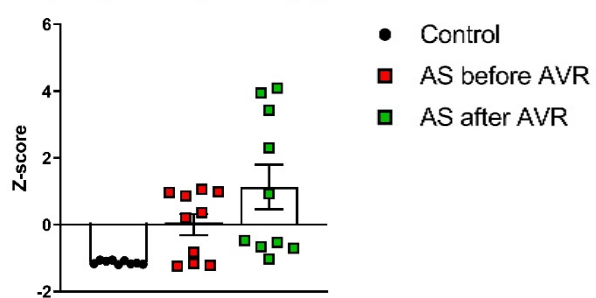
Figure S2.

LEGEND

⬆ Increased
⬇ Decreased
= No difference

⬆ **Metabolite** ⬆

AS vs. Control | AS after vs. before AVR

FA: Fatty acids

⬆ **LPA (16:0/0:0)** =

Phospholipase A2 (PLA2)

Phospholipids

Diacylglycerol (DAG)

Phospholipase A2 (PLA2)

Diacylglycerol lipase

⬆ trans-Dodec-2-enoic acid
⬆ 5-Dodecenoic acid ⬆

⬆ **14-HDoHE (DHA, omega-3 FA)** ⬇

⬆ **3,4-Methylene suberic acid (branched FA)** ⬆

⬆ **Alpha/gamma-linolenyl carnitine** ⬇

Eicosanoids

⬆ **Metabolite 2** ⬆

"8,9-Epoxyeicosatrienoic acid"
"14R,15S-EpETrE"
15(S)-HETE
"14,15-Epoxy-5,8,11-eicosatrienoic acid"
"11,12-Epoxyeicosatrienoic acid"
8-HETE
16(R)-HETE
11(R)-HETE
20-Hydroxyeicosatetraenoic acid
12-HETE
18-Hydroxyarachidonic acid
9-HETE
"11,12-EpETrE"
5-HETE
19(S)-HETE
10-HETE
13-HETE
17-HETE
12 Hydroxy arachidonic acid
Arachidonate
"5,6-Epoxy-8,11,14-eicosatrienoic acid"

⬆ **Metabolite 1** ⬆

5(S)-Hydroperoxyeicosatetraenoic acid
8-iso-PGA1
Prostaglandin A1
Prostaglandin B1
12(S)-HPETE
15(S)-HPETE
Hepoxilin A3
Hepoxilin B3
12(R)-HPETE
"11H-14,15-EETA"
11(R)-HPETE
8(S)-HPETE
"15H-11,12-EETA"
6-trans-Leukotriene B4
6-trans-12-epi-Leukotriene B4
12(S)-Leukotriene B4
"14,15-DiHETE"
"17,18-DiHETE"
"5,15-DiHETE"
"8,15-DiHETE"
5-HPETE
"10,11-dihydro-12-oxo-LTB4"
"6,7-dihydro-5-oxo-12-epi-LTB4"
9-Deoxy-delta12-PGD2
Prostaglandin C1
"12,20-DiHETE"
Leukotriene B4

Leukotrienes

5-HPETE

5-lipoxygenase

⬆ Arachidonic Acid =

Prostaglandins

⬆
13,14-Dihydro PGE1
13,14-Dihydro PGF2a
Prostaglandin F1a
⬇

4-Hydroxy-3-methoxy-cinnamoylglycine

Figure S3. 4-hydroxy-3-methoxy-cinnamoylglycine is of unknown biological relevance.