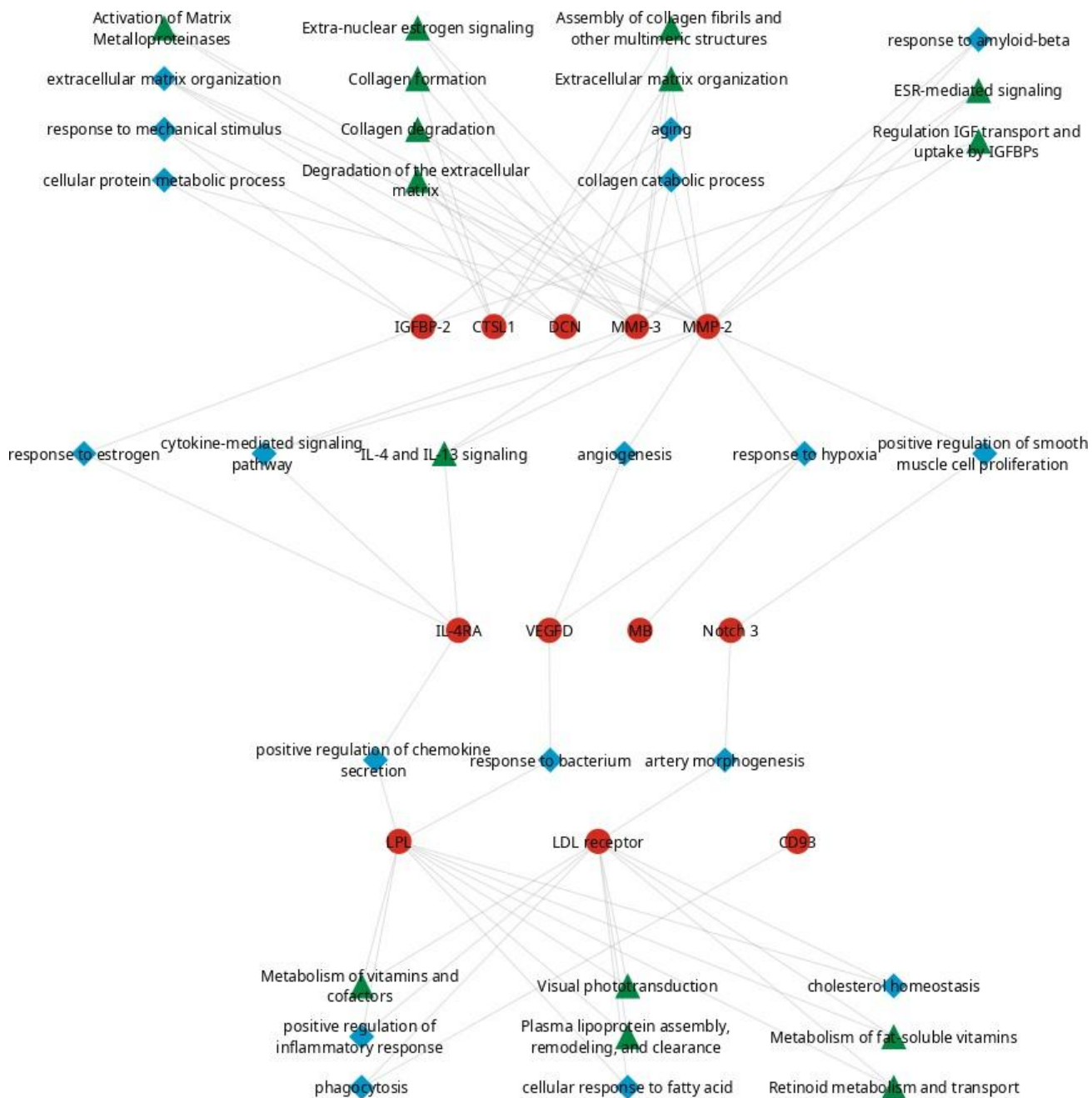


## Supplemental materials

**Supplemental Figure 1. A complex network analysis for pathways linked to LAVi-**



**associated biomarkers**

**Supplemental Table 1. Protein names and respective Olink® panel sorted in alphabetical order**

Full protein name	Entry name	Olink® Panel*	Uniprot ID**
Angiotensin-converting enzyme 2	ACE2	CVD II	Q9BYF1
Adenosine Deaminase	ADA	INF	P00813
Adisintegrin and metalloproteinase with thrombospondin motifs 13	ADAMTS13	CVD II	Q76LX8
Adrenomedullin	ADM	CVD II	P35318
Agouti-related protein	AGRP	CVD II	O00253
CD166 antigen	ALCAM	CVD III	Q13740
Protein AMBP	AMBP	CVD II	P02760
Angiopoietin-1	ANG1	CVD II	Q15389
Aminopeptidase N	APN	CVD III	P15144
Axin-1	AXIN1	INF	O15169
Tyrosine-protein kinase receptor UFO	AXL	CVD III	P30530
Azurocidin	AZU1	CVD III	P20160
Brain-derived neurotrophic factor	BDNF	INF	P23560
Beta-nerve growth factor	BETANGF	INF	P01138
Bleomycin hydrolase	BLMHYDROLASE	CVD III	Q13867
Bone morphogenetic protein 6	BMP6	CVD II	P22004
Natriuretic peptides B	BNP	CVD II	P16860
Eukaryotic translation initiation factor 4E-binding protein 1	BP1_4E	INF	Q13541
Carbonic anhydrase 5A, mitochondrial	CA5A	CVD II	P35218
Caspase-3	CASP3	CVD III	P42574
Caspase 8	CASP8	INF	Q14790
Eotaxin-1	CCL11	INF	P51671
C-C motif chemokine 15	CCL15	CVD III	Q16663
C-C motif chemokine 16	CCL16	CVD III	O15467
C-C motif chemokine 17	CCL17	CVD II	Q92583
C-C motif chemokine 19	CCL19	INF	Q99731
C-C motif chemokine 20	CCL20	INF	P78556
C-C motif chemokine 22	CCL22	CVD III	O00626
C-C motif chemokine 23	CCL23	INF	P55773
C-C motif chemokine 24	CCL24	CVD III	O00175
C-C motif chemokine 25	CCL25	INF	O15444
C-C motif chemokine 28	CCL28	INF	Q9NRJ3
C-C motif chemokine 3	CCL3	CVD II	P10147
C-C motif chemokine 4	CCL4	INF	P13236
Scavenger receptor cysteine-rich type 1 protein M130	CD163	CVD III	Q86VB7
Natural killer cell receptor 2B4	CD244	INF	Q9BZW8
T-cell surface glycoprotein CD4	CD4	CVD II	P01730
CD40L receptor	CD40	INF	P25942
CD40 ligand	CD40L	CVD II	P29965
T-cell surface glycoprotein CD5	CD5	INF	P06127
T cell surface glycoprotein CD6	CD6	INF	P30203
SLAM family member 5	CD84	CVD II	Q9UIB8
Complement component C1q receptor	CD93	CVD III	Q9NPY3
CUB domain-containing protein 1	CDCP1	INF	Q9H5V8
Cadherin-5	CDH5	CVD III	P33151

Carcinoembryonic antigen-related cell adhesion molecule 8	CEACAM8	CVD II	P31997
Chitinase-3-like protein 1	CHI3L1	CVD III	P36222
Chitotriosidase-1	CHIT1	CVD III	Q13231
Contactin-1	CNTN1	CVD III	Q12860
Collagen alpha-1(I) chain	COL1A1	CVD III	P02452
Carboxypeptidase A1	CPA1	CVD III	P15085
Carboxypeptidase B	CPB1	CVD III	P15086
Macrophage colony-stimulating factor 1	CSF1	INF	P09603
Cystatin D	CST5	INF	P28325
Cystatin-B	CSTB	CVD III	P04080
Chymotrypsin C	CTRC	CVD II	Q99895
Cathepsin D	CTSD	CVD III	P07339
Cathepsin L1	CTSL1	CVD II	P07711
Cathepsin Z	CTSZ	CVD III	Q9UBR2
Fractalkine	CX3CL1	INF	P78423
C-X-C motif chemokine 1 (CVD2)	CXCL1	CVD II	P09341
C-X-C motif chemokine 10	CXCL10	INF	P02778
C-X-C motif chemokine 11	CXCL11	INF	O14625
C-X-C motif chemokine 16	CXCL16	CVD III	Q9H2A7
C-X-C motif chemokine 5	CXCL5	INF	P42830
C-X-C motif chemokine 6	CXCL6	INF	P80162
C-X-C motif chemokine 9	CXCL9	INF	Q07325
Decorin	DCN	CVD II	P07585
2,4-dienoyl-CoA reductase, mitochondrial	DECR1	CVD II	Q16698
Dickkopf-related protein 1	DKK1	CVD II	O94907
Azurocidin	DLK1	CVD III	P80370
Delta and Notch-like epidermal growth factor-related receptor	DNER	INF	Q8NFT8
Epidermal growth factor receptor	EGFR	CVD III	P00533
Protein S100-A12	ENRAGE	INF	P80511
Epithelial cell adhesion molecule	EPCAM	CVD III	P16422
Ephrin type-B receptor 4	EPHB4	CVD III	P54760
Fatty acid-binding protein, intestinal	FABP2	CVD II	P12104
Fatty acid-binding protein, adipocyte	FABP4	CVD III	P15090
Tumor necrosis factor receptor superfamily member 6	FAS	CVD III	P25445
Fibroblast growth factor 19	FGF19	INF	O95750
Fibroblast growth factor 21 (CVD2)	FGF21	CVD II	Q9NSA1
Fibroblast growth factor 23 (CVD2)	FGF23	CVD II	Q9GZV9
Fibroblast growth factor 5	FGF5	INF	P12034
Fms-related tyrosine kinase 3 ligand	FLT3L	INF	P49771
Follistatin	FS	CVD II	P19883
Galectin-3	GAL3	CVD III	P17931
Galectin-4	GAL4	CVD III	P56470
Galectin-9	GAL9	CVD II	O00182
Growth/differentiation factor 15	GDF15	CVD III	Q99988
Growth/differentiation factor 2	GDF2	CVD II	Q9UK05
Growth hormone	GH	CVD II	P01241
Gastric intrinsic factor	GIF	CVD II	P27352
Lactoylglutathione lyase	GLO1	CVD II	Q04760
Granulins	GRN	CVD III	P28799

Gastrotropin	GT	CVD II	P51161
Hydroxyacid oxidase 1	HAOX1	CVD II	Q9UJM8
Proheparin-binding EGF-like growth factor	HBEGF	CVD II	Q99075
Glial cell line-derived neurotrophic factor	HGDNF	INF	P39905
Hepatocyte growth factor	HGF	INF	P14210
Heme oxygenase 1	HO1	CVD II	P09601
Osteoclast-associated immunoglobulin-like receptor	HOSCAR	CVD II	Q8IYS5
Heat shock 27 kDa protein	HSP27	CVD II	P04792
Intercellular adhesion molecule 2	ICAM2	CVD III	P13598
Alpha-L-iduronidase	IDUA	CVD II	P35475
Insulin-like growth factor-binding protein-1	IGFBP-1	CVD III	P08833
Insulin-like Growth Factor-Binding Protein-2	IGFBP-2	CVD III	P18065
Insulin-like growth factor-binding protein-7	IGFBP-7	CVD III	Q16270
Low affinity immunoglobulin gamma Fc region receptor II-b	IGGFCRECEPTOR I IB	CVD II	P31994
Interleukin-10	IL10	INF	P22301
Interleukin-10 receptor subunit alpha	IL10RA	INF	Q13651
Interleukin-10 receptor subunit beta	IL10RB	INF	Q08334
Interleukin-12 subunit beta	IL12B	INF	P29460
Interleukin-13	IL13	INF	P35225
Interleukin-15 receptor subunit alpha	IL15RA	INF	Q13261
Pro-interleukin-16	IL16	CVD II	Q14005
Interleukin-17A	IL17A	INF	Q16552
Interleukin-17C	IL17C	INF	Q9P0M4
Interleukin-17D	IL17D	CVD II	Q8TAD2
Interleukin-17 receptor A	IL17RA	CVD III	Q96F46
Interleukin-18 (CVD2)	IL18	CVD II	Q14116
Interleukin-18-binding protein	IL18BP	CVD III	O95998
Interleukin-18 receptor 1	IL18R1	INF	Q13478
Interleukin-1 receptor antagonist protein	IL1RA	CVD II	P18510
Interleukin-1 receptor-like 2	IL1RL2	CVD II	Q9HB29
Interleukin-1 receptor type 1	IL1RT1	CVD III	P14778
Interleukin-1 receptor type 2	IL1RT2	CVD III	P27930
Interleukin-20 receptor subunit alpha	IL20RA	INF	Q9UHF4
Interleukin-27	IL27	CVD II	Q8NEV9
Interleukin-2 receptor subunit alpha	IL2RA	CVD III	P01589
Interleukin-4 receptor subunit alpha	IL4RA	CVD II	P24394
Interleukin-6 (CVD2)	IL6	CVD II	P05231
Interleukin-6 receptor subunit alpha	IL6RA	CVD III	P08887
Interleukin-7	IL7	INF	P13232
Interleukin-8	IL8	INF	P10145
Melusin	ITGB1BP2	CVD II	Q9UKP3
Integrin beta-2	ITGB2	CVD III	P05107
Junctional adhesion molecule A	JAMA	CVD III	Q9Y624
Kidney injury molecule 1	KIM1	CVD II	Q96D42
Kallikrein-6	KLK6	CVD III	Q92876
Latency-associated peptide transforming growth factor beta 1	LAPTGF BETA1	INF	P01137
Low-density lipoprotein receptor	LDLRECEPTOR	CVD III	P01130
Leptin	LEP	CVD II	P41159
Leukemia inhibitory factor receptor	LIFR	INF	P42702

Lectin-like oxidized LDL receptor 1	LOX1	CVD II	P78380
Lipoprotein lipase	LPL	CVD II	P06858
Lymphotoxin-beta receptor	LTBR	CVD III	P36941
Macrophage receptor MARCO	MARCO	CVD II	Q9UEW3
Myoglobin	MB	CVD III	P02144
Monocyte chemotactic protein 1	MCP1_CVD3	CVD III	P13500
Monocyte chemotactic protein 2	MCP2	INF	P80075
Monocyte chemotactic protein 3	MCP3	INF	P80098
Monocyte chemotactic protein 4	MCP4	INF	Q99616
Matrix extracellular phosphoglycoprotein	MEPE	CVD III	Q9NQ76
Tyrosine-protein kinase Mer	MERTK	CVD II	Q12866
Matrix metalloproteinase-1	MMP-1	INF	P03956
Matrix metalloproteinase-10	MMP-10	INF	P09238
Matrix metalloproteinase-12	MMP-12	CVD II	P39900
Matrix metalloproteinase-2	MMP-2	CVD III	P08253
Matrix metalloproteinase-3	MMP-3	CVD III	P08254
Matrix metalloproteinase-7	MMP-7	CVD II	P09237
Matrix metalloproteinase-9	MMP-9	CVD III	P14780
Myeloperoxidase	MPO	CVD III	P05164
NF-kappa-B essential modulator	NEMO	CVD II	Q9Y6K9
Neurogenic locus notch homolog protein 3	NOTCH3	CVD III	Q9UM47
Neurotrophin-3	NT3	INF	P20783
N-terminal prohormone brain natriuretic peptide	NTPROBNP	CVDII	P16860
Osteoprotegerin	OPG_CVD3	CVD III	O00300
Osteopontin	OPN	CVD III	P10451
Oncostatin-M	OSM	INF	P13725
Plasminogen activator inhibitor 1	PAI	CVD III	P05121
Pappalysin-1	PAPPA	CVD II	Q13219
Proteinase-activated receptor 1	PAR1	CVD II	P25116
Poly [ADP-ribose] polymerase 1	PARP1	CVD II	P09874
Proprotein convertase subtilisin/kexin type 9	PCSK9	CVD III	Q8NBP7
Platelet-derived growth factor subunit A	PDGFSUBUNITA	CVD III	P04085
Platelet-derived growth factor subunit B	PDGFSUBUNITB	CVD II	P01127
Programmed cell death 1 ligand 1	PDL1	INF	Q9NZQ7
Programmed cell death 1 ligand 2	PDL2	CVD II	Q9BQ51
Platelet endothelial cell adhesion molecule	PECAM1	CVD III	P16284
Peptidoglycan recognition protein 1	PGLYRP1	CVD III	O75594
Elafin	PI3	CVD III	P19957
Polymeric immunoglobulin receptor	PIGR	CVD II	P01833
Perlecan	PLC	CVD III	P98160
Placenta growth factor	PLGF	CVD II	P49763
Paraoxonase (PON 3)	PON3	CVD III	Q15166
Prolargin	PRELP	CVD II	P51888
Brother of CDO	PROTEINBOC	CVD II	Q9BWW1
Serine protease 27	PRSS27	CVD II	Q9BQR3
Prostasin	PRSS8	CVD II	Q16651
Myeloblastin	PRTN3	CVD III	P24158
P-selectin glycoprotein ligand 1	PSGL1	CVD II	Q14242
Pulmonary surfactant-associated protein D	PSPD	CVD III	P35247
Pentraxin-related protein PTX3	PTX3	CVD II	P26022
Receptor for advanced glycosylation end products	RAGE	CVD II	Q15109

Retinoic acid receptor responder protein 2	RARRES2	CVD III	Q99969
Renin	REN	CVD II	P00797
Resistin	RETN	CVD III	Q9HD89
Stem cell factor (CVD2)	SCF	CVD II	P21583
Secretoglobin family 3A member 2	SCGB3A2	CVD III	Q96PL1
E-selectin	SELE	CVD III	P16581
P-selectin	SELP	CVD III	P16109
Serpin A12	SERPINA12	CVD II	Q8IW75
Tyrosine-protein phosphatase non-receptor type substrate 1	SHPS1	CVD III	P78324
SIR2-like protein 2	SIRT2	INF	Q8IXJ6
Signaling lymphocytic activation molecule	SLAMF1	INF	Q13291
SLAM family member 7	SLAMF7	CVD II	Q9NQ25
Superoxide dismutase [Mn], mitochondrial	SOD2	CVD II	P04179
Sortilin	SORT1	CVD II	Q99523
Spondin-1	SPON1	CVD III	Q9HCB6
Spondin-2	SPON2	CVD II	Q9BUD6
Proto-oncogene tyrosine-protein kinase	SRC	CVD II	P12931
Sulfotransferase 1A1	ST1A1	INF	P50225
ST2 protein	ST2	CVD III	Q01638
STAM-binding protein	STAMPB	INF	O95630
Serine/threonine-protein kinase 4	STK4	CVD II	Q13043
Tissue factor	TF	CVD II	P13726
Trefoil factor 3	TFF3	CVD III	Q07654
Tissue factor pathway inhibitor	TFPI	CVD III	P10646
Transforming growth factor alpha	TGFALPHA	INF	P01135
Protein-glutamine gamma-glutamyltransferase 2	TGM2	CVD II	P21980
Thrombospondin-2	THBS2	CVD II	P35442
Thrombopoietin	THPO	CVD II	P40225
Angiopoietin-1 receptor	TIE2	CVD II	Q02763
Metalloproteinase inhibitor 4	TIMP4	CVD III	Q99727
Trem-like transcript 2 protein	TLT2	CVD III	Q5T2D2
Thrombomodulin	TM	CVD II	P07204
Tumor necrosis factor	TNF	INF	P01375
TNF-beta	TNFB	INF	P01374
Tumor necrosis factor receptor 1	TNFR1	CVD III	P19438
Tumor necrosis factor receptor 2	TNFR2	CVD III	P20333
Tumor necrosis factor receptor superfamily member 10A	TNFRSF10A	CVD II	O00220
Tumor necrosis factor receptor superfamily member 10C	TNFRSF10C	CVD III	O14798
Tumor necrosis factor receptor superfamily member 11A	TNFRSF11A	CVD II	Q9Y6Q6
Tumor necrosis factor receptor superfamily member 13B	TNFRSF13B	CVD II	O14836
Tumor necrosis factor receptor superfamily member 14	TNFRSF14	CVD III	Q92956
Tumor necrosis factor receptor superfamily member 9	TNFRSF9	INF	Q07011
Tumor necrosis factor ligand superfamily member 13B	TNFSF13B	CVD III	Q9Y275
Tumor necrosis factor ligand superfamily member 14	TNFSF14	INF	O43557

Tissue-type plasminogen activator	TPA	CVD III	P00750
Transferrin receptor protein 1	TR	CVD III	P02786
TNF-related apoptosis-inducing ligand	TRAIL	INF	P50591
TNF-related apoptosis-inducing ligand receptor 2	TRAILR2	CVD II	O14763
TNF-related activation-induced cytokine	TRANCE	INF	O14788
Tartrate-resistant acid phosphatase type 5	TRAP	CVD III	P13686
Tumor necrosis factor (Ligand) superfamily, member 12	TWEAK	INF	O43508
Urokinase-type plasminogen activator	UPA_CVD3	CVD III	P00749
Urokinase plasminogen activator surface receptor	UPAR	CVD III	Q03405
Vascular endothelial growth factor A	VEGFA	INF	P15692
Vascular endothelial growth factor D	VEGFD	CVD II	O43915
V-set and immunoglobulin domain-containing protein 2	VSIG2	CVD II	Q96IQ7
von Willebrand factor	VWF	CVD III	P04275
Lymphotoxin	XCL1	CVD II	P47992



**Supplemental Table 2. Baseline characteristics according to LAVi tertiles in STANISLAS**

	Left atrial volume index				p-value
	Overall (N=1,640)	T1 <19ml/m <sup>2</sup> (N=547)	T2 19-25ml/m <sup>2</sup> (N=546)	T3 >25ml/m <sup>2</sup> (N=547)	
Age, years	49 ± 14	48 ± 14	48 ± 14	52 ± 14	<0.001
Men, N (%)	827 (48.5 %)	245 (44.8 %)	260 (47.6 %)	294 (53.7 %)	0.01
BMI, kg/m <sup>2</sup>	26 ± 5	25 ± 5	26 ± 4	27 ± 5	<0.001
Medical history, N (%)					
Hypertension	337 (19.8 %)	94 (17.2 %)	90 (16.5 %)	135 (24.7 %)	<0.001
Diabetes mellitus	70 (4.1 %)	22 (4.0 %)	22 (4.0 %)	23 (4.2 %)	0.98
Dyslipidemia	402 (23.6 %)	128 (23.4 %)	118 (21.6 %)	135 (24.7 %)	0.48
Coronary artery disease	42 (2.5 %)	10 (1.8 %)	7 (1.3 %)	23 (4.2 %)	0.004
Current smoker	363 (21.5 %)	112 (20.7 %)	132 (24.4 %)	108 (19.9 %)	0.16
Physical assessment					
Systolic BP, mmHg	120 ± 16	119 ± 15	119 ± 16	123 ± 18	<0.001
Heart rate, bpm	63 ± 9	65 ± 9	63 ± 9	60 ± 9	<0.001
Laboratory data					
HbA1c, %	5.6 ± 0.5	5.6 ± 0.6	5.6 ± 0.5	5.7 ± 0.5	0.34
Total cholesterol, mg/dl	213 ± 40	214 ± 39	211 ± 39	212 ± 41	0.42
LDL cholesterol, mg/dl	134 ± 34	135 ± 33	133 ± 34	133 ± 36	0.47
eGFR, ml/min/1.73m <sup>2</sup>	96 ± 17	95 ± 17	97 ± 18	97 ± 17	0.25
NT-proBNP (NPX)	3.6 ± 1.0	3.5 ± 0.9	3.5 ± 0.9	3.8 ± 1.0	<0.001
Echocardiogram					
LVEDVi, ml/m <sup>2</sup>	49 ± 13	48 ± 12	48 ± 12	52 ± 14	<0.001
LVEF, %	65 ± 7	65 ± 7	65 ± 6	65 ± 7	0.13
LVMi, g/m <sup>2</sup>	76 ± 19	71 ± 17	74 ± 17	83 ± 21	<0.001
Men	83 ± 19	78 ± 17	80 ± 16	91 ± 21	<0.001
Women	69 ± 17	66 ± 14	69 ± 16	74 ± 18	<0.001
LV hypertrophy, N (%)	117 (7.0 %)	17 (3.1 %)	33 (6.1 %)	63 (11.6 %)	<0.001
LAVi, ml/m <sup>2</sup>	23 ± 7	16 ± 3	22 ± 2	31 ± 6	<0.001
E wave, cm/s	70 ± 15	69 ± 15	71 ± 15	70 ± 16	0.055
A wave, cm/s	63 ± 17	62 ± 16	62 ± 16	64 ± 18	0.02
E/A ratio	1.2 ± 0.4	1.2 ± 0.4	1.2 ± 0.4	1.2 ± 0.4	0.21
Septal e', cm/s	9.9 ± 2.9	10.1 ± 3.0	10.0 ± 2.8	9.5 ± 3.0	0.003
Lateral e', cm/s	12.9 ± 4.2	13.1 ± 4.1	13.1 ± 4.0	12.4 ± 4.4	0.007
Septal e' <7cm/s or lateral e' <10cm/s, N (%)	503 (30.4 %)	144 (26.9 %)	153 (28.1 %)	194 (35.7 %)	0.003
E/e' mean	6.5 ± 1.9	6.2 ± 1.7	6.4 ± 1.6	6.8 ± 2.2	<0.001
E/e' mean >14	9 (0.5 %)	2 (0.4 %)	1 (0.2 %)	5 (0.9 %)	0.20
Peak TR velocity, m/sec (N=841)	2.1 ± 0.4	2.1 ± 0.3	2.1 ± 0.4	2.1 ± 0.4	0.22
Peak TR velocity >2.8m/sec, N (%) (N=841)	11 (1.3 %)	0 (0.0 %)	4 (1.5 %)	7 (2.5 %)	0.035

Values are expressed as mean ±SD, n (%) or median (25th to 75th percentile)

LAVi, left atrial volume indexed by body surface area; HbA1c, glycosylated hemoglobin; LDL, low-density lipoprotein; eGFR, estimated glomerular filtration rate; SP, systolic pressure; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVMi, left ventricular mass index; LV, left ventricular; LAVi, left atrial volume index; E/A, ratio of peak early and late diastolic velocities; e' mean, mean value of early diastolic velocity at the septal and lateral sites of the mitral annulus; E/e' ratio, ratio of early mitral inflow velocity and mitral annular early diastolic velocity; TR, tricuspid regurgitation.

**Supplemental Table 3. Clinical characteristics at baseline, month 1 and month 9 across baseline LAVi tertiles**

	Baseline variables			Month 1 variables			Month 9 variables			P-value among baseline, month 1 and month 9 variables		
	Baseline left atrial volume index			Baseline left atrial volume index			Baseline left atrial volume index			T1	T2	T3
	T1 <28 ml/m <sup>2</sup>	T2 28-34 ml/m <sup>2</sup>	T3 >34 ml/m <sup>2</sup>	T1 <28 ml/m <sup>2</sup>	T2 28-34 ml/m <sup>2</sup>	T3 >34 ml/m <sup>2</sup>	T1 <28 ml/m <sup>2</sup>	T2 28-34 ml/m <sup>2</sup>	T3 >34 ml/m <sup>2</sup>			
<b>Physical assessment</b>												
Systolic BP, mmHg	140 ± 20	142 ± 22	146 ± 21	133 ± 19	138 ± 20	139 ± 19	134 ± 19	133 ± 19	136 ± 18	<0.001*\$	<0.001*\$	<0.001*\$
Heart rate, bpm	63 ± 8	61 ± 10	60 ± 10	62 ± 8	61 ± 9	60 ± 9	63 ± 8	60 ± 10	60 ± 11	<0.001*\$	<0.001*\$	<0.001*\$
<b>Laboratory data</b>												
Hemoglobin, g/dl	14 ± 1	14 ± 1	14 ± 2	14 ± 1	14 ± 1	13 ± 1	14 ± 2	14 ± 1	13 ± 1	<0.001*\$	<0.001*\$	<0.001*\$
Sodium, mmol/L	139 ± 2	139 ± 3	140 ± 3	139 ± 2	138 ± 3	140 ± 3	139 ± 2	139 ± 3	139 ± 3	0.15	<b>0.01*\$</b>	0.06\$
Potassium, mmol/L	4.3 ± 0.4	4.4 ± 0.4	4.3 ± 0.3	4.4 ± 0.4	4.4 ± 0.4	4.4 ± 0.4	4.5 ± 0.4	4.4 ± 0.4	4.4 ± 0.4	<0.001*\$	<b>0.02*\$</b>	0.11\$
eGFR, ml/min/1.73m <sup>2</sup>	70 ± 15	71 ± 16	72 ± 16	68 ± 15	69 ± 17	70 ± 17	67 ± 15	69 ± 17	67 ± 17	<0.001*\$	<0.001*\$	<0.001*\$
NT-proBNP, pg/ml	18 (13 - 30)	25 (14 - 44)	30 (19 - 47)	18 (12 - 29)	20 (13 - 38)	27 (16 - 46)	20 (13 - 32)	22 (14 - 37)	30 (17 - 47)	<0.001*\$	<0.001*\$	<0.001*\$
<b>Echocardiographic variables</b>												
LVEDVi, mL/m <sup>2</sup>	38 ± 9	43 ± 11	48 ± 12	38 ± 9	42 ± 9	46 ± 11	37 ± 8	42 ± 10	46 ± 11	0.49	<0.001*\$	<0.001*\$
LVEF, %	62 ± 6	62 ± 7	62 ± 7	63 ± 6	63 ± 7	63 ± 7	62 ± 7	63 ± 6	62 ± 7	0.86	0.47	0.27
LVMi, g/m <sup>2</sup>	90 ± 21	96 ± 24	106 ± 29	89 ± 22	94 ± 22	102 ± 27	88 ± 22	95 ± 24	103 ± 28	0.23	0.63	0.14
LAVi, ml/m <sup>2</sup>	24 ± 3	31 ± 2	41 ± 7	24 ± 4	31 ± 4	38 ± 8	24 ± 4	31 ± 5	38 ± 8	0.15	0.61	<0.001*\$
E wave, cm/s	65 ± 15	69 ± 17	73 ± 20	64 ± 15	68 ± 17	70 ± 20	64 ± 17	68 ± 19	70 ± 20	0.70	0.57	<b>0.03*\$</b>
A wave, cm/s	80 ± 19	80 ± 19	83 ± 22	78 ± 20	79 ± 18	78 ± 21	80 ± 19	79 ± 19	79 ± 23	0.35	0.69	0.08\$
E/A ratio	0.8 ± 0.3	0.9 ± 0.3	0.9 ± 0.3	0.9 ± 0.3	0.9 ± 0.2	1.0 ± 0.5	0.8 ± 0.4	0.9 ± 0.3	0.9 ± 0.4	0.83	0.74	0.94
Lateral e', cm/sec	8.5 ± 2.4	8.6 ± 2.6	9.1 ± 3.1	8.8 ± 2.4	8.8 ± 2.7	8.9 ± 2.9	8.5 ± 2.8	8.6 ± 2.3	9.0 ± 3.2	0.71	0.68	0.20
Septal e', cm/sec	6.0 ± 1.6	6.1 ± 1.6	5.9 ± 1.6	6.2 ± 1.6	6.1 ± 1.6	6.0 ± 1.5	6.2 ± 1.7	6.0 ± 1.4	5.9 ± 1.6	0.40	0.98	0.99
E/e' mean	9 ± 3	10 ± 3	10 ± 3	9 ± 3	10 ± 3	10 ± 3	9 ± 3	10 ± 3	10 ± 3	0.21	0.22	0.40
TAPSE, mm	22 ± 6	23 ± 6	22 ± 7	22 ± 5	23 ± 6	23 ± 7	21 ± 6	23 ± 6	22 ± 7	0.09	0.53	0.28

\*p-value &lt;0.05 compared between baseline value and month 1 value.

\$p-value &lt;0.05 compared between baseline value and month 9 value.

**Supplemental Table 4. Circulating biomarkers significantly associated with LAVi in HOMAGE in multivariable models**

<b>Name</b>	<b>beta (95%CI)</b>	<b>P-value</b>
<b>B-type natriuretic peptide</b>	2.93 (2.23 to 3.64)	<0.001
<b>Leptin</b>	-2.85 (-3.93 to -1.76)	<0.001
<b>Interleukin-2 receptor subunit alpha</b>	3.23 (1.55 to 4.91)	<0.001
<b>N-terminal prohormone brain natriuretic peptide</b>	3.66 (2.69 to 4.62)	<0.001
<b>Matrix metalloproteinase-2</b>	3.82 (1.53 to 6.11)	0.001
<b>Insulin-like Growth Factor-Binding Protein-2</b>	2.46 (1.03 to 3.89)	0.001
<b>Resistin</b>	2.46 (0.90 to 4.02)	0.002
<b>Cathepsin L1</b>	3.18 (0.95 to 5.42)	0.005
<b>Collagen alpha-1(I) chain</b>	3.07 (0.95 to 5.18)	0.005
<b>C-C motif chemokine 4</b>	-1.60 (-2.70 to -0.49)	0.005
<b>Interleukin-1 receptor antagonist protein</b>	-1.99 (-3.41 to -0.56)	0.006
<b>C-C motif chemokine 15</b>	2.64 (0.77 to 4.50)	0.006
<b>Vascular endothelial growth factor D</b>	2.82 (0.78 to 4.87)	0.007
<b>Interleukin-8</b>	-1.64 (-2.87 to -0.42)	0.009
<b>Procollagen type I C-terminal propeptide*</b>	2.58 (0.66 to 4.49)	0.009
<b>Matrix metalloproteinase-3</b>	1.72 (0.41 to 3.03)	0.01
<b>Neurogenic locus notch homolog protein 3</b>	2.81 (0.63 to 4.99)	0.012
<b>Lipoprotein lipase</b>	2.07 (0.44 to 3.71)	0.013
<b>Growth hormone</b>	0.57 (0.11 to 1.02)	0.014
<b>Decorin</b>	2.94 (0.54 to 5.33)	0.016
<b>Complement component C1q receptor</b>	3.07 (0.47 to 5.67)	0.021
<b>Gastric intrinsic factor</b>	-0.86 (-1.60 to -0.12)	0.022
<b>Low-density lipoprotein receptor</b>	-1.88 (-3.50 to -0.26)	0.023
<b>Thrombomodulin</b>	2.76 (0.37 to 5.16)	0.024
<b>Myoglobin</b>	1.59 (0.21 to 2.96)	0.024
<b>Carcinoembryonic antigen-related cell adhesion molecule 8</b>	1.58 (0.20 to 2.97)	0.025
<b>Matrix metalloproteinase-7</b>	-1.77 (-3.32 to -0.22)	0.025
<b>Receptor for advanced glycosylation end products</b>	2.22 (0.26 to 4.18)	0.027
<b>Hydroxyacid oxidase 1</b>	-0.71 (-1.35 to -0.07)	0.03
<b>Interleukin-4 receptor subunit alpha</b>	2.45 (0.16 to 4.73)	0.036
<b>Interleukin-15 receptor subunit alpha</b>	3.04 (0.16 to 5.92)	0.039
<b>Brother of CDO</b>	2.76 (0.04 to 5.47)	0.047
<b>Tyrosine-protein kinase receptor UFO</b>	2.25 (0.02 to 4.48)	0.048

\*variables were transformed using natural logarithm.

**Supplemental Table 5. Circulating biomarkers significantly associated with LAVi in STANISLAS in multivariable models**

<b>Name</b>	<b>beta (95%CI)</b>	<b>P-value</b>
<b>N-terminal prohormone brain natriuretic peptide</b>	2.06 (1.66 to 2.46)	<0.001
<b>Insulin-like Growth Factor-Binding Protein-2</b>	1.07 (0.49 to 1.64)	<0.001
<b>Procollagen type I C-terminal propeptide*</b>	1.07 (0.51 to 1.64)	<0.001
<b>Fibroblast growth factor 23</b>	1.48 (0.61 to 2.34)	0.001
<b>Decorin</b>	2.45 (0.97 to 3.92)	0.001
<b>Neurogenic locus notch homolog protein 3</b>	1.72 (0.72 to 2.73)	0.001
<b>Matrix metalloproteinase-2</b>	1.87 (0.72 to 3.02)	0.001
<b>Oncostatin-M</b>	-0.66 (-1.04 to -0.27)	0.001
<b>Lipoprotein lipase</b>	1.24 (0.46 to 2.03)	0.002
<b>Matrix metalloproteinase-9</b>	-0.66 (-1.08 to -0.24)	0.002
<b>Adrenomedullin</b>	1.45 (0.50 to 2.41)	0.003
<b>Interleukin-10 receptor subunit alpha</b>	-0.76 (-1.26 to -0.27)	0.003
<b>Interleukin-4 receptor subunit alpha</b>	1.87 (0.61 to 3.14)	0.004
<b>Chitinase-3-like protein 1</b>	0.73 (0.24 to 1.23)	0.004
<b>Prolargin</b>	2.57 (0.77 to 4.37)	0.005
<b>Lymphotactin</b>	0.85 (0.25 to 1.44)	0.005
<b>Myoglobin</b>	1.06 (0.32 to 1.80)	0.005
<b>Complement component C1q receptor</b>	1.74 (0.52 to 2.95)	0.005
<b>Procollagen type III N-terminal propeptide*</b>	1.28 (0.36 to 2.20)	0.006
<b>Insulin-like growth factor-binding protein-7</b>	1.54 (0.42 to 2.65)	0.007
<b>Interleukin-17D</b>	1.69 (0.42 to 2.97)	0.009
<b>Cathepsin L1</b>	1.42 (0.35 to 2.49)	0.009
<b>Low-density lipoprotein receptor</b>	-0.86 (-1.50 to -0.21)	0.01
<b>Gastrotropin</b>	0.80 (0.18 to 1.43)	0.012
<b>Perlecan</b>	1.65 (0.35 to 2.95)	0.013
<b>E-selectin</b>	-0.80 (-1.44 to -0.16)	0.014
<b>Spondin-2</b>	2.01 (0.36 to 3.67)	0.017
<b>Neurotrophin-3</b>	-0.93 (-1.68 to -0.17)	0.017
<b>Insulin-like growth factor-binding protein-1</b>	0.51 (0.09 to 0.93)	0.018
<b>Vascular endothelial growth factor D</b>	1.01 (0.11 to 1.91)	0.028
<b>Tartrate-resistant acid phosphatase type 5</b>	-1.03 (-1.97 to -0.10)	0.03
<b>Platelet-derived growth factor subunit B</b>	-0.41 (-0.79 to -0.03)	0.034
<b>Renin</b>	0.59 (0.03 to 1.14)	0.038
<b>Signaling lymphocytic activation molecule</b>	0.79 (0.04 to 1.53)	0.039
<b>Beta-nerve growth factor</b>	1.04 (0.05 to 2.03)	0.039
<b>Matrix metalloproteinase-10</b>	0.63 (0.03 to 1.23)	0.039
<b>Matrix extracellular phosphoglycoprotein</b>	-0.93 (-1.81 to -0.04)	0.04
<b>Tumor necrosis factor receptor superfamily member 13B</b>	0.99 (0.04 to 1.93)	0.041
<b>Tumor necrosis factor receptor 2</b>	1.12 (0.05 to 2.19)	0.041
<b>Matrix metalloproteinase-3</b>	0.66 (0.03 to 1.28)	0.041
<b>Hepatocyte growth factor</b>	-0.98 (-1.94 to -0.03)	0.043
<b>Osteoclast-associated immunoglobulin-like receptor</b>	1.27 (0.02 to 2.53)	0.047
<b>V-set and immunoglobulin domain-containing protein 2</b>	0.79 (0.01 to 1.56)	0.048
<b>P-selectin glycoprotein ligand 1</b>	1.34 (0.01 to 2.66)	0.048
<b>Placenta growth factor</b>	1.21 (0.01 to 2.41)	0.049
<b>Programmed cell death 1 ligand 2</b>	1.06 (0.01 to 2.11)	0.049

\*variables were transformed using natural logarithm.