

SUPPLEMENTAL MATERIAL

	LA			RA		
	Total ECM			Total ECM		
	effect (%)	SE	p value	effect (%)	SE	p value
<i>Sex*:M</i>	-3.97	1.47	0.011	-4.74	2.06	0.029
<i>Age* (/5years increase)</i>	0.25	0.31	0.291	0.49	0.38	0.178
<i>Weight[§] (/5kg increase)</i>	-0.14	0.24	0.331	-0.77	0.24	0.003
<i>Height[§] (/5cm increase)</i>	-0.57	0.36	0.115	-0.94	0.39	0.022
<i>CHA₂DS₂-VAsc</i>	-0.17	0.49	0.374	1.04	0.52	0.054
<i>Hatch</i>	-0.41	0.68	0.335	0.26	0.73	0.374
<i>Rhythm*: par.AF</i>	-1.71	1.62	0.229	0.32	2.02	0.393
<i>Rhythm*: pers.AF</i>	1.86	1.68	0.216	3.55	2.14	0.101
<i>Concomitant PVI</i>	-1.95	1.69	0.205	2.31	3.13	0.303
<i>CABG[§]</i>	-0.59	1.69	0.375	2.28	1.66	0.155
<i>MV surgery[§]</i>	1.43	1.57	0.263	1.31	2.18	0.333
<i>MV stenosis</i>	0.44	4.46	0.396	-0.72	4.56	0.393
<i>MV insufficiency</i>	2.79	1.41	0.058	0.52	1.91	0.384
<i>AV surgery[§]</i>	-1.89	1.73	0.219	0.11	1.84	0.398
<i>AV stenosis</i>	-1.42	1.85	0.296	0.75	1.99	0.371
<i>AV insufficiency</i>	0.36	1.67	0.389	-1.36	1.94	0.311
<i>TV insufficiency[§]</i>	0.44	1.51	0.382	1.92	1.98	0.248
<i>Heart failure*</i>	3.04	1.41	0.038	-2.49	1.71	0.137
<i>EF (/5% increase)</i>	-0.12	0.19	0.325	0.45	0.24	0.071
<i>NYHA</i>	-0.64	0.64	0.239	-0.35	0.81	0.363
<i>HTX</i>	2.08	1.48	0.148	-4.13	1.91	0.039
<i>coronary artery Disease</i>	-0.38	1.42	0.384	2.61	1.69	0.122
<i>prior myocardial infarction[§]</i>	-1.21	1.67	0.306	-1.71	2.14	0.289
<i>periferal artery disease</i>	5.58	3.91	0.143	3.34	2.67	0.182
<i>Diabetes[§]</i>	1.93	1.78	0.221	1.51	2.26	0.318
<i>hypertension[§]</i>	1.42	1.51	0.255	1.72	1.85	0.258
<i>COPD</i>	6.21	3.15	0.058	1.56	3.6	0.363
<i>hypothyroidism[§]</i>	1.94	1.87	0.232	1.99	3.25	0.329
<i>chronic kidney failure[§]</i>	7.03	2.63	0.012	-0.31	3.32	0.396
<i>prior stroke[§]</i>	-4.29	2.16	0.056	5.55	3.64	0.125
<i>prior TIA</i>	-1.69	3.96	0.363	2.91	2.63	0.217

Table S1: Univariate associations between clinical parameters and total ECM, stratified by atrial side. Univariate associations between clinical parameters and total ECM were obtained with univariate regression analysis. LA/RA: Left/Right atrial appendage, par.AF: paroxysmal AF, pers.AF: persistent AF/ permanent AF; PVI: pulmonary vein isolation; CABG: coronary artery bypass graft; MV: mitral valve; AV: aortic valve; TV: tricuspid valve; EF: ejection fraction; NYHA: New York Heart Association; HTX: heart transplant surgery; COPD: chronic obstructive pulmonary disease; TIA: transient ischemic attack. SE: standard error; * will be explicitly modeled in multivariate models; §: will be included in principal component modeling

	LA			RA		
	Endomysial fibrosis			Endomysial fibrosis		
	effect (μm)	SE	p value	effect (μm)	SE	p value
<i>Sex*:M</i>	-0.82	0.59	0.161	-1.11	0.61	0.074
<i>Age* (/5years increase)</i>	-0.11	0.13	0.266	0.01	0.11	0.398
<i>Weight[§] (/5kg increase)</i>	-0.03	0.09	0.368	-0.21	0.07	0.006
<i>Height[§] (/5cm increase)</i>	-0.23	0.14	0.096	-0.32	0.11	0.008
<i>CHA₂DS₂-VASc</i>	0.06	0.19	0.377	0.15	0.16	0.256
<i>Hatch</i>	0.44	0.25	0.084	-0.01	0.22	0.398
<i>Rhythm*: par.AF</i>	-0.25	0.64	0.368	1.31	0.57	0.029
<i>Rhythm*: pers.AF</i>	1.48	0.63	0.027	1.28	0.59	0.039
<i>Concomitant PVI</i>	-1.02	0.67	0.124	-0.02	0.94	0.398
<i>CABG[§]</i>	-1.04	0.64	0.107	0.48	0.49	0.244
<i>MV surgery[§]</i>	-0.14	0.62	0.388	-0.52	0.62	0.281
<i>MV stenosis</i>	0.69	1.61	0.362	-0.08	1.31	0.398
<i>MV insufficiency</i>	0.72	0.56	0.176	0.41	0.56	0.305
<i>AV surgery[§]</i>	-1.69	0.65	0.015	-0.43	0.52	0.281
<i>AV stenosis</i>	-1.38	0.69	0.056	-0.96	0.57	0.094
<i>AV insufficiency</i>	0.51	0.66	0.293	0.22	0.56	0.369
<i>TV insufficiency[§]</i>	-0.29	0.58	0.351	1.62	0.55	0.006
<i>Heart failure*</i>	2.41	0.51	<0.001	0.16	0.51	0.379
<i>EF (/5% increase)</i>	-0.21	0.07	0.005	0.07	0.07	0.246
<i>NYHA</i>	-0.22	0.26	0.279	0.27	0.23	0.201
<i>HTX</i>	2.51	0.53	<0.001	0.21	0.57	0.373
<i>coronary artery Disease</i>	-0.73	0.55	0.167	0.04	0.49	0.397
<i>prior myocardial infarction[§]</i>	-1.69	0.64	0.014	-0.11	0.63	0.392
<i>periferal artery disease</i>	3.53	1.47	0.024	-0.02	0.79	0.398
<i>Diabetes[§]</i>	0.75	0.68	0.217	0.82	0.64	0.175
<i>hypertension[§]</i>	0.21	0.61	0.377	0.13	0.54	0.387
<i>COPD</i>	1.39	1.19	0.211	-0.08	1.02	0.397
<i>hypothyroidism[§]</i>	-0.09	0.72	0.394	1.71	0.91	0.071
<i>chronic kidney failure[§]</i>	4.26	0.96	<0.001	0.77	0.96	0.288
<i>prior stroke[§]</i>	-0.77	0.85	0.264	0.17	1.06	0.393
<i>prior TIA</i>	-1.89	1.46	0.172	-0.18	0.77	0.388

Table S2: Univariate associations between clinical parameters and endomysial fibrosis, stratified by atrial side. Univariate associations between clinical parameters and endomysial fibrosis were obtained with univariate regression analysis. LA/RA: Left/Right atrial appendage, par.AF: paroxysmal AF, pers.AF: persistent AF/permanent AF; PVI: pulmonary vein isolation; CABG: coronary artery bypass graft; MV: mitral valve; AV: aortic valve; TV: tricuspid valve; EF: ejection fraction; NYHA: New York Heart Association; HTX: heart transplant surgery; COPD: chronic obstructive pulmonary disease; TIA: transient ischemic attack. SE: standard error; * will be explicitly modeled in multivariate models; §: will be included in principal component modeling

	LA			RA		
	fibroblast signal			fibroblast signal		
	effect	SE	p value	effect	SE	p value
<i>Sex*:M</i>	0.11	0.06	0.098	0.07	0.06	0.248
<i>Age* (/5years increase)</i>	-0.03	0.01	0.031	-0.02	0.01	0.093
<i>Weight[§] (/5kg increase)</i>	0.01	0.01	0.212	0.02	0.06	0.531
<i>Height[§] (/5cm increase)</i>	0.03	0.05	0.652	0.01	0.04	0.675
<i>CHA₂DS₂-VASc</i>	0.01	0.02	0.882	-0.02	0.01	0.114
<i>Hatch</i>	0.06	0.02	0.009	<0.01	0.02	0.936
<i>Rhythm*: par.AF</i>	-0.05	0.07	0.431	0.06	0.05	0.278
<i>Rhythm*: pers.AF</i>	0.04	0.06	0.488	0.14	0.05	0.011
<i>Concomitant PVI</i>	-0.09	0.06	0.119	-0.01	0.08	0.958
<i>CABG[§]</i>	-0.06	0.06	0.325	-0.08	0.04	0.078
<i>MV surgery[§]</i>	-0.04	0.06	0.532	-0.06	0.05	0.251
<i>MV stenosis</i>	-0.11	0.17	0.522	-0.11	0.12	0.375
<i>MV insufficiency</i>	0.09	0.05	0.111	0.09	0.05	0.078
<i>AV surgery[§]</i>	-0.14	0.06	0.031	-0.01	0.05	0.861
<i>AV stenosis</i>	-0.12	0.06	0.063	-0.03	0.05	0.599
<i>AV insufficiency</i>	0.07	0.07	0.299	0.08	0.05	0.118
<i>TV insufficiency[§]</i>	0.01	0.06	0.861	0.09	0.05	0.087
<i>Heart failure*</i>	0.21	0.05	<0.001	0.12	0.04	0.007
<i>EF (/5% increase)</i>	-0.02	0.01	0.022	-0.01	0.01	0.363
<i>NYHA</i>	0.03	0.02	0.181	0.06	0.02	0.002
<i>HTX</i>	0.24	0.05	<0.001	0.15	0.05	0.003
<i>coronary artery Disease</i>	-0.04	0.05	0.466	-0.11	0.04	0.032
<i>prior myocardial infarction[§]</i>	-0.07	0.06	0.262	0.04	0.05	0.477
<i>periferal artery disease</i>	0.31	0.16	0.061	-0.11	0.08	0.193
<i>Diabetes[§]</i>	0.01	0.07	0.823	0.01	0.06	0.821
<i>hypertension[§]</i>	0.08	0.06	0.169	-0.07	0.05	0.113
<i>COPD</i>	-0.02	0.11	0.839	-0.09	0.09	0.322
<i>hypothyroidism[§]</i>	-0.09	0.07	0.198	0.18	0.07	0.014
<i>chronic kidney failure[§]</i>	0.27	0.11	0.009	-0.09	0.08	0.291
<i>prior stroke[§]</i>	0.06	0.08	0.441	-0.09	0.11	0.403
<i>prior TIA</i>	-0.11	0.13	0.421	0.01	0.07	0.941

Table S3: Univariate associations between clinical parameters and fibroblast expression, stratified by atrial side. Univariate associations between clinical parameters and fibroblast expression were obtained with univariate regression analysis. LA/RA: Left/Right atrial appendage, par.AF: paroxysmal AF, pers.AF: persistent AF/ permanent AF; PVI: pulmonary vein isolation; CABG: coronary artery bypass graft; MV: mitral valve; AV: aortic valve; TV: tricuspid valve; EF: ejection fraction; NYHA: New York Heart Association; HTX: heart transplant surgery; COPD: chronic obstructive pulmonary disease; TIA: transient ischemic attack. SE: standard error; * will be explicitly modeled in multivariate models; §: will be included in principal component modeling

	LA			RA		
	myocyte diameter			myocyte diameter		
	effect (µm)	SE	p value	effect (µm)	SE	p value
Sex*:M	1.26	0.44	0.006	0.69	0.56	0.219
Age* (/5years increase)	-0.09	0.11	0.372	-0.02	0.09	0.832
Weight [§] (/5kg increase)	0.02	0.01	0.141	0.02	0.01	0.056
Height [§] (/5cm increase)	0.03	0.02	0.195	0.02	0.02	0.299
CHA ₂ DS ₂ -VASc	0.09	0.15	0.548	-0.14	0.14	0.336
Hatch	0.21	0.19	0.308	0.18	0.19	0.349
Rhythm*: par.AF	-0.13	0.51	0.801	0.37	0.53	0.486
Rhythm*: pers.AF	-0.44	0.51	0.395	0.07	0.58	0.905
Concomitant PVI	-0.15	0.52	0.767	-0.26	0.78	0.737
CABG [§]	-0.08	0.51	0.873	-0.81	0.43	0.061
MV surgery [§]	-0.22	0.47	0.635	0.02	0.55	0.999
MV stenosis	-0.46	1.15	0.689	-0.11	1.06	0.924
MV insufficiency	-0.02	0.45	0.968	0.33	0.46	0.483
AV surgery [§]	0.03	0.52	0.952	0.01	0.48	0.993
AV stenosis	0.18	0.53	0.743	-0.26	0.49	0.598
AV insufficiency	0.85	0.49	0.091	0.58	0.48	0.231
TV insufficiency [§]	0.11	0.45	0.815	-0.19	0.51	0.711
Heart failure*	0.16	0.44	0.717	0.81	0.44	0.077
EF (/5% increase)	-0.07	0.06	0.199	-0.07	0.06	0.263
NYHA	0.38	0.21	0.054	-0.01	0.21	0.961
HTX	0.32	0.46	0.49	0.82	0.51	0.112
coronary artery Disease	0.32	0.43	0.461	-0.76	0.43	0.085
prior myocardial infarction [§]	0.29	0.51	0.561	0.04	0.55	0.939
periferal artery disease	-0.54	1.15	0.636	-0.89	0.77	0.257
Diabetes [§]	0.21	0.56	0.712	-0.54	0.61	0.373
hypertension [§]	0.52	0.47	0.266	0.13	0.49	0.795
COPD	-1.14	0.99	0.255	-0.48	0.94	0.611
hypothyroidism [§]	-0.01	0.56	0.982	-0.79	0.84	0.355
chronic kidney failure [§]	1.05	0.99	0.292	-0.3	0.85	0.728
prior stroke [§]	0.93	0.65	0.154	-1.26	0.93	0.181
prior TIA	0.08	1.15	0.947	0.04	0.73	0.962

Table S4: Univariate associations between clinical parameters and myocyte diameter, stratified by atrial side. Univariate associations between clinical parameters and myocyte diameter were obtained with univariate regression analysis. LA/RA: Left/Right atrial appendage, par.AF: paroxysmal AF, pers.AF: persistent AF/permanent AF; PVI: pulmonary vein isolation; CABG: coronary artery bypass graft; MV: mitral valve; AV: aortic valve; TV: tricuspid valve; EF: ejection fraction; NYHA: New York Heart Association; HTX: heart transplant surgery; COPD: chronic obstructive pulmonary disease; TIA: transient ischemic attack. SE: standard error; * will be explicitly modeled in multivariate models; §: will be included in principal component modeling

	LA			RA		
	capillary density			capillary density		
	effect	SE	p value	effect	SE	p value
Sex*:M	0.04	0.05	0.448	0.06	0.04	0.179
Age* (/5years increase)	-0.01	0.01	0.411	0.01	0.01	0.629
Weight [§] (/5kg increase)	0.03	0.03	0.282	0.04	0.03	0.524
Height [§] (/5cm increase)	0.02	0.04	0.839	0.02	0.04	0.899
CHA ₂ DS ₂ -VASc	0.01	0.02	0.613	-0.01	0.01	0.196
Hatch	0.04	0.02	0.068	-0.02	0.01	0.291
Rhythm*: par.AF	-0.06	0.06	0.289	-0.01	0.04	0.764
Rhythm*: pers.AF	0.05	0.06	0.411	0.07	0.04	0.105
Concomitant PVI	-0.11	0.05	0.041	-0.08	0.06	0.161
CABG [§]	0.02	0.06	0.996	0.01	0.03	0.895
MV surgery [§]	-0.07	0.05	0.177	-0.11	0.04	0.021
MV stenosis	-0.11	0.12	0.423	-0.08	0.09	0.375
MV insufficiency	0.06	0.05	0.237	-0.03	0.04	0.413
AV surgery [§]	-0.11	0.05	0.055	-0.01	0.04	0.812
AV stenosis	-0.11	0.06	0.082	-0.04	0.04	0.238
AV insufficiency	0.02	0.06	0.729	0.04	0.04	0.247
TV insufficiency [§]	0.01	0.05	0.975	-0.01	0.04	0.749
Heart failure*	0.12	0.05	0.011	0.04	0.03	0.279
EF (/5% increase)	-0.02	0.01	0.009	0.01	0.01	0.948
NYHA	0.05	0.02	0.031	-0.02	0.02	0.319
HTX	0.17	0.05	0.011	0.04	0.04	0.341
coronary artery Disease	-0.01	0.05	0.819	-0.05	0.04	0.187
prior myocardial infarction [§]	0.02	0.06	0.975	-0.03	0.04	0.488
periferal artery disease	0.05	0.12	0.651	0.02	0.05	0.957
Diabetes [§]	0.09	0.06	0.117	0.02	0.05	0.621
hypertension [§]	0.04	0.05	0.403	-0.02	0.03	0.603
COPD	0.07	0.11	0.526	-0.05	0.07	0.504
hypothyroidism [§]	-0.09	0.06	0.181	0.17	0.06	0.007
chronic kidney failure [§]	0.17	0.09	0.061	-0.04	0.06	0.498
prior stroke [§]	0.02	0.07	0.738	-0.06	0.07	0.447
prior TIA	-0.06	0.12	0.624	-0.03	0.05	0.621

Table S5: Univariate associations between clinical parameters and capillary density, stratified by atrial side. Univariate associations between clinical parameters and capillary density were obtained with univariate regression analysis. LA/RA: Left/Right atrial appendage, par.AF: paroxysmal AF, pers.AF: persistent AF/permanent AF; PVI: pulmonary vein isolation; CABG: coronary artery bypass graft; MV: mitral valve; AV: aortic valve; TV: tricuspid valve; EF: ejection fraction; NYHA: New York Heart Association; HTX: heart transplant surgery; COPD: chronic obstructive pulmonary disease; TIA: transient ischemic attack. SE: standard error; * will be explicitly modeled in multivariate models; §: will be included in principal component modeling

	LA			RA		
	capillary size			capillary size		
	effect (µm)	SE	p value	effect (µm)	SE	p value
<i>Sex*:M</i>	0.11	0.21	0.591	0.02	0.16	0.998
<i>Age* (/5years increase)</i>	-0.09	0.04	0.035	0.02	0.03	0.583
<i>Weight[§] (/5kg increase)</i>	0.02	0.02	0.952	0.01	0.01	0.441
<i>Height[§] (/5cm increase)</i>	-0.02	0.01	0.254	0.01	0.01	0.734
<i>CHA₂DS₂-VASc</i>	-0.08	0.06	0.232	-0.04	0.04	0.355
<i>Hatch</i>	-0.04	0.09	0.678	0.02	0.06	0.992
<i>Rhythm*: par.AF</i>	-0.51	0.22	0.026	0.02	0.16	0.912
<i>Rhythm*: pers.AF</i>	-0.24	0.21	0.263	0.09	0.16	0.584
<i>Concomitant PVI</i>	-0.34	0.21	0.121	0.11	0.22	0.651
<i>CABG[§]</i>	-0.18	0.22	0.413	-0.19	0.12	0.124
<i>MV surgery[§]</i>	-0.25	0.21	0.226	0.21	0.16	0.201
<i>MV stenosis</i>	1.31	0.45	0.005	-0.16	0.38	0.668
<i>MV insufficiency</i>	0.21	0.19	0.293	0.31	0.14	0.028
<i>AV surgery[§]</i>	-0.16	0.22	0.481	-0.09	0.14	0.508
<i>AV stenosis</i>	0.01	0.23	0.974	-0.02	0.16	0.918
<i>AV insufficiency</i>	-0.38	0.22	0.087	0.11	0.15	0.478
<i>TV insufficiency[§]</i>	-0.11	0.19	0.586	0.24	0.14	0.102
<i>Heart failure*</i>	0.51	0.18	0.005	0.29	0.13	0.024
<i>EF (/5% increase)</i>	-0.07	0.02	0.002	-0.03	0.01	0.096
<i>NYHA</i>	0.12	0.09	0.188	0.14	0.29	0.021
<i>HTX</i>	0.44	0.19	0.022	0.34	0.15	0.023
<i>coronary artery Disease</i>	0.17	0.18	0.358	-0.09	0.13	0.507
<i>prior myocardial infarction[§]</i>	0.24	0.21	0.254	0.25	0.16	0.113
<i>periferal artery disease</i>	-0.24	0.48	0.621	-0.19	0.21	0.367
<i>Diabetes[§]</i>	0.38	0.23	0.096	-0.29	0.18	0.111
<i>hypertension[§]</i>	0.07	0.21	0.739	-0.15	0.14	0.265
<i>COPD</i>	0.77	0.36	0.037	-0.35	0.29	0.245
<i>hypothyroidism[§]</i>	0.51	0.25	0.042	0.11	0.22	0.635
<i>chronic kidney failure[§]</i>	1.01	0.36	0.006	0.01	0.23	0.969
<i>prior stroke[§]</i>	-0.29	0.27	0.296	-0.02	0.31	0.959
<i>prior TIA</i>	0.37	0.47	0.441	-0.21	0.21	0.333

Table S6: Univariate associations between clinical parameters and capillary diameter, stratified by atrial side. Univariate associations between clinical parameters and capillary diameter were obtained with univariate regression analysis. LA/RA: Left/Right atrial appendage, par.AF: paroxysmal AF, pers.AF: persistent AF/permanent AF; PVI: pulmonary vein isolation; CABG: coronary artery bypass graft; MV: mitral valve; AV: aortic valve; TV: tricuspid valve; EF: ejection fraction; NYHA: New York Heart Association; HTX: heart transplant surgery; COPD: chronic obstructive pulmonary disease; TIA: transient ischemic attack. SE: standard error; * will be explicitly modeled in multivariate models; §: will be included in principal component modeling

LA

	total ECM				endomysial fibrosis				fibroblast signal				myocyte diameter			
	β (%)	SE	p	padj	β (μ m)	SE	p	padj	β (%)	SE	p	padj	β (μ m)	SE	p	padj
<i>intercept</i>	26.97	3.63			4.77	1.25			2.78	3.45			14.31	1.36		
<i>age</i>	0.43	0.26	0.125	0.107	0.06	0.06	0.534	0.745	0.32	0.26	0.225	0.313	-0.11	0.13	0.384	0.426
<i>sex:F</i>	4.56	1.47	0.003	<0.001	0.99	0.51	0.048	0.002	1.26	-1.07	0.247	0.234	-1.87	0.72	0.012	<0.001
<i>heart failure</i>	2.93	1.15	0.014	0.013	1.79	0.41	<0.001	<0.001	3.12	1.12	0.006	0.011	0.45	0.57	0.431	0.151
<i>parAF</i>	-1.05	1.27	0.412	0.804	0.37	0.44	0.414	0.056	-0.01	1.22	0.992	0.981	0.33	0.62	0.645	0.556
<i>persAF</i>	1.07	1.23	0.387	0.203	1.07	0.41	0.014	0.042	0.86	1.14	0.454	0.331	0.01	0.58	0.994	0.941
<i>PC1</i>	0.66	0.39	0.095	0.162	0.15	0.13	0.282	0.326	0.21	0.35	0.916	0.886	-0.07	0.19	0.723	0.725
<i>PC2</i>	0.29	0.41	0.486	0.448	0.11	0.29	0.408	0.478	0.14	0.18	0.328	0.285	-0.03	0.2	0.871	0.841
<i>PC3</i>	-0.13	0.45	0.781	0.724	-0.27	0.15	0.077	0.114	-0.06	0.08	0.349	0.387	-0.3	0.21	0.158	0.268
<i>PC4</i>	0.74	0.43	0.094	0.103	0.23	0.15	0.139	0.196	0.24	0.22	0.783	0.774	-0.08	0.21	0.719	0.728

RA

	total ECM				endomysial fibrosis				fibroblast signal				myocyte diameter			
	β (%)	SE	p	padj	β (μ m)	SE	p	padj	β (%)	SE	p	padj	β (μ m)	SE	p	padj
<i>intercept</i>	33.86	4.51			8.29	1.3			5.88	2.87			11.84	1.57		
<i>age</i>	0.03	0.06	0.661	0.161	-0.01	0.02	0.368	0.638	0.24	4.02	0.323	0.237	0.01	0.02	0.569	0.638
<i>sex:F</i>	2.22	1.89	0.252	0.094	0.35	0.54	0.524	0.473	-0.61	-1.52	0.191	0.998	-0.69	0.7	0.328	0.191
<i>heart failure</i>	-0.7	1.49	0.639	0.571	-0.16	0.43	0.712	0.824	-0.93	1.32	0.181	0.466	0.93	0.55	0.107	0.104
<i>parAF</i>	-0.42	1.62	0.795	0.462	0.86	0.48	0.083	0.172	2.85	1.48	0.132	0.829	1.13	0.6	0.061	0.186
<i>persAF</i>	2.14	1.65	0.215	0.227	0.89	0.43	0.032	0.044	4.21	1.55	0.021	0.007	0.15	0.6	0.814	0.442
<i>PC1</i>	-0.06	0.45	0.896	0.779	-0.12	0.13	0.378	0.436	-0.27	0.18	0.224	0.255	-0.01	0.16	0.927	0.905
<i>PC2</i>	0.89	0.46	0.068	0.186	0.19	0.13	0.164	0.255	-0.17	0.13	0.344	0.412	-0.35	0.19	0.072	0.138
<i>PC3</i>	-0.67	0.53	0.214	0.178	-0.12	0.15	0.444	0.478	-0.08	0.11	0.962	0.846	0.08	0.19	0.704	0.746
<i>PC4</i>	-0.5	0.55	0.363	0.423	-0.04	0.15	0.781	0.913	-0.15	0.06	0.693	0.712	0.08	0.2	0.674	0.631

Table S7: Multivariate models describing the association between clinical traits and structural properties of the myocardium in left (LA) and right (RA) atrial appendages. Age, sex, heart failure and rhythm history were modeled explicitly. A combination of 13 additional clinical traits was combined in 4 principal components (PCs). B: Degree of change in the outcome variable for every unit of change in the predictor variable. SE: standard error, ECM: extracellular matrix, parAF: paroxysmal atrial fibrillation, persAF: persistent atrial fibrillation, PC: principal component

LA

	capillary density				capillary size			
	β (n)	SE	p	p _{adj}	β (μ m)	SE	p	p _{adj}
<i>intercept</i>	0.49	0.19			5.62	0.76		
<i>age</i>	1.50E-04	0.01	0.991	0.863	-0.02	0.05	0.736	0.505
<i>sex:F</i>	-0.05	0.08	0.523	0.843	-0.03	0.29	0.932	0.581
<i>heart failure</i>	0.14	0.06	0.032	0.007	0.48	0.23	0.041	0.016
<i>parAF</i>	-0.03	0.07	0.694	0.403	-0.28	0.25	0.257	0.064
<i>persAF</i>	0.06	0.06	0.308	0.059	-0.21	0.23	0.369	0.377
<i>PC1</i>	0.03	0.02	0.124	0.183	0.03	0.08	0.712	0.618
<i>PC2</i>	-0.01	0.02	0.776	0.795	0.04	0.08	0.594	0.716
<i>PC3</i>	-0.02	0.02	0.361	0.335	-0.11	0.08	0.163	0.264
<i>PC4</i>	0.01	0.02	0.693	0.675	0.07	0.08	0.393	0.366

RA

	capillary density				capillary size			
	β (n)	SE	p	p _{adj}	β (μ m)	SE	p	p _{adj}
<i>intercept</i>	0.28	0.13			4.89	0.46		
<i>age</i>	0.01	0.01	0.591	0.379	0.05	0.03	0.171	0.686
<i>sex:F</i>	-0.08	0.05	0.012	0.156	-0.02	0.19	0.911	0.997
<i>heart failure</i>	0.03	0.04	0.516	0.064	0.31	0.16	0.047	0.084
<i>parAF</i>	-0.01	0.04	0.794	0.765	-0.08	0.17	0.661	0.548
<i>persAF</i>	0.09	0.04	0.061	0.058	0.01	0.16	0.942	0.922
<i>PC1</i>	0.02	0.01	0.974	0.913	-0.03	0.05	0.518	0.476
<i>PC2</i>	-0.01	0.01	0.398	0.415	0.01	0.05	0.837	0.835
<i>PC3</i>	0.01	0.01	0.878	0.836	0.06	0.05	0.291	0.225
<i>PC4</i>	0.01	0.01	0.632	0.689	-0.004	0.06	0.939	0.899

Table S8 (continuation S7): Multivariate models describing the association between clinical traits and structural properties of the myocardium in left (LA) and right (RA) atrial appendages. Age, sex, heart failure and rhythm history were modeled explicitly. A combination of 13 additional clinical traits was combined in 4 principal components (PCs). B: Degree of change in the outcome variable for every unit of change in the predictor variable. SE: standard error, ECM: extracellular matrix, parAF: paroxysmal atrial fibrillation, persAF: persistent atrial fibrillation, PC: principal component

	LA			RA		
	Total ECM			Total ECM		
	Estimate (%)	SE	p value	Estimate (%)	SE	p value
Sex*:M	-4.70	1.37	1.56E-03	-1.12	0.67	9.92E-02
Age* (/5years increase)	0.53	0.37	1.44E-01	0.27	0.15	8.62E-02
Weight [§] (/5kg increase)	-0.69	0.23	5.36E-03	-0.18	0.08	3.65E-02
Height [§] (/5cm increase)	-0.76	0.35	3.77E-02	-0.28	0.13	4.72E-02
CHA ₂ DS ₂ -VASc	0.02	0.50	3.97E-01	0.40	0.18	4.01E-02
Hatch	-0.60	0.68	2.70E-01	0.28	0.25	2.10E-01
Rhythm*: par.AF	-1.28	1.65	2.94E-01	1.70	0.63	1.11E-02
Rhythm*: pers.AF	1.39	1.90	3.04E-01	1.60	0.69	2.86E-02
Concomitant PVI	-1.19	1.54	2.95E-01	0.03	0.96	3.97E-01
CABG [§]	0.34	1.54	3.88E-01	0.70	0.55	1.76E-01
MV surgery [§]	2.95	1.43	4.92E-02	-0.47	0.65	3.06E-01
MV stenosis	3.06	4.40	3.11E-01	-0.55	1.63	3.75E-01
MV insufficiency	2.22	1.48	1.30E-01	0.14	0.66	3.89E-01
AV surgery [§]	-1.15	1.57	3.03E-01	-0.42	0.57	3.02E-01
AV stenosis	-0.47	1.68	3.82E-01	0.33	0.64	3.48E-01
AV insufficiency	0.02	1.49	3.98E-01	1.22	0.64	6.45E-02
TV insufficiency [§]	0.25	1.99	3.95E-01	0.32	0.88	3.71E-01
Heart failure*	1.50	5.38	3.82E-01	-0.38	1.18	3.78E-01
EF (/5% increase)	0.07	0.33	3.89E-01	0.02	0.01	3.93E-01
NYHA	9.49	4.89	6.17E-02	1.35	1.08	1.82E-01
coronary artery Disease	-0.92	0.72	1.77E-01	0.31	0.28	2.17E-01
prior myocardial infarction [§]	0.47	1.95	3.86E-01	0.78	0.75	2.31E-01
periferal artery disease	-0.07	1.79	3.97E-01	0.67	0.74	2.61E-01
Diabetes [§]	-3.73	1.85	5.38E-02	0.24	1.08	3.88E-01
hypertension [§]	-0.99	3.35	3.80E-01	-0.11	0.79	3.93E-01
COPD	0.01	0.07	3.89E-01	0.00	0.03	3.93E-01
hypothyroidism [§]	0.07	0.14	3.58E-01	0.00	0.05	3.97E-01
chronic kidney failure [§]	9.49	4.89	6.18E-02	1.35	1.08	1.81E-01
prior stroke [§]	-3.73	1.85	5.41E-02	0.24	1.08	3.88E-01
prior TIA	-0.99	3.45	3.81E-01	-0.11	0.79	3.93E-01

Table S9: Univariate associations between clinical parameters and total ECM, stratified by atrial side, excluding HTX patients. Univariate associations between clinical parameters and total ECM were obtained with univariate regression analysis. LA/RA: Left/Right atrial appendage, par.AF: paroxysmal AF, pers.AF: persistent AF/permanent AF; PVI: pulmonary vein isolation; CABG: coronary artery bypass graft; MV: mitral valve; AV: aortic valve; TV: tricuspid valve; EF: ejection fraction; NYHA: New York Heart Association; HTX: heart transplant surgery; COPD: chronic obstructive pulmonary disease; TIA: transient ischemic attack. SE: standard error; * will be explicitly modeled in multivariate models; §: will be included in principal component modeling

	LA			RA		
	Endomysial fibrosis			Endomysial fibrosis		
	Estimate (µm)	SE	p value	Estimate (µm)	SE	p value
Sex*:M	-4.48	2.29	5.98E-02	-0.96	2.88	2.05E-03
Age* (/5years increase)	0.60	0.53	2.13E-01	1.45	0.82	8.45E-02
Weight [§] (/5kg increase)	-0.76	0.28	1.07E-02	-1.53	0.47	2.45E-03
Height [§] (/5cm increase)	-0.85	0.47	7.83E-02	-1.87	0.69	1.12E-02
CHA ₂ DS ₂ -VASc	1.23	0.64	6.18E-02	0.32	0.10	2.48E-03
Hatch	1.10	0.85	1.71E-01	0.33	0.14	2.84E-02
Rhythm*: par.AF	0.89	2.25	3.67E-01	0.45	0.34	1.65E-01
Rhythm*: pers.AF	5.72	2.51	3.15E-02	1.02	0.38	1.14E-02
Concomitant PVI	1.29	3.19	3.66E-01	1.00	3.30	3.80E-01
CABG [§]	0.81	1.90	3.62E-01	-1.55	3.30	3.55E-01
MV surgery [§]	0.20	2.26	3.96E-01	0.82	0.30	1.13E-02
MV stenosis	0.78	5.59	3.94E-01	1.70	0.91	7.16E-02
MV insufficiency	-0.52	2.21	3.87E-01	0.63	0.31	5.28E-02
AV surgery [§]	-1.38	1.95	3.09E-01	-0.53	0.32	1.03E-01
AV stenosis	-3.00	2.19	1.55E-01	0.31	0.35	2.72E-01
AV insufficiency	0.06	2.22	3.97E-01	-0.06	0.32	3.98E-01
TV insufficiency [§]	-0.34	2.92	3.95E-01	-0.98	0.38	1.55E-02
Heart failure*	2.85	4.08	3.11E-01	-1.33	1.07	1.83E-01
EF (/5% increase)	-0.34	0.54	3.25E-01	0.10	0.75	3.94E-01
NYHA	-1.32	3.73	3.73E-01	0.31	0.17	3.36E-03
coronary artery Disease	0.15	0.98	3.93E-01	-0.25	0.15	1.08E-01
prior myocardial infarction [§]	1.12	2.62	3.62E-01	0.60	0.41	1.33E-01
periferal artery disease	-0.76	2.57	3.80E-01	0.57	0.39	1.40E-01
Diabetes [§]	4.90	3.77	1.71E-01	0.23	0.40	3.36E-01
hypertension [§]	2.08	2.76	2.99E-01	-0.62	0.63	2.57E-01
COPD	-0.07	0.11	3.25E-01	0.02	0.15	3.94E-01
hypothyroidism [§]	-0.23	0.19	1.88E-01	0.59	0.26	2.91E-02
chronic kidney failure [§]	-1.32	3.73	3.74E-01	0.39	0.12	3.32E-03
prior stroke [§]	4.90	3.77	1.71E-01	0.23	0.40	3.35E-01
prior TIA	2.08	2.76	2.99E-01	-0.62	0.66	3.68E-01

Table S10: Univariate associations between clinical parameters and endomysial fibrosis, stratified by atrial side, excluding HTX patients. Univariate associations between clinical parameters and endomysial fibrosis were obtained with univariate regression analysis. LA/RA: Left/Right atrial appendage, par.AF: paroxysmal AF, pers.AF: persistent AF/ permanent AF; PVI: pulmonary vein isolation; CABG: coronary artery bypass graft; MV: mitral valve; AV: aortic valve; TV: tricuspid valve; EF: ejection fraction; NYHA: New York Heart Association; HTX: heart transplant surgery; COPD: chronic obstructive pulmonary disease; TIA: transient ischemic attack. SE: standard error; * will be explicitly modeled in multivariate models; §: will be included in principal component modeling

	LA			RA		
	fibroblast density			fibroblast density		
	Estimate	SE	p value	Estimate	SE	p value
Sex*:M	0.03	0.05	5.61E-01	0.03	0.05	5.63E-01
Age* (/5years increase)	0.01	0.01	4.84E-01	0.02	0.01	7.37E-02
Weight [§] (/5kg increase)	0.02	0.02	1.71E-01	<0.01	0.01	9.51E-01
Height [§] (/5cm increase)	0.02	0.02	3.12E-01	-0.01	0.00	7.65E-01
CHA ₂ DS ₂ -VASc	0.04	0.01	2.15E-02	0.01	0.02	5.72E-01
Hatch	0.05	0.02	6.53E-03	0.02	0.02	3.17E-01
Rhythm*: par.AF	0.06	0.05	2.59E-01	0.07	0.05	2.18E-01
Rhythm*: pers.AF	0.09	0.06	1.32E-01	0.04	0.05	4.74E-01
Concomitant PVI	-0.01	0.05	8.72E-01	0.04	0.07	5.43E-01
CABG [§]	0.03	0.05	4.93E-01	-0.02	0.04	6.51E-01
MV surgery [§]	0.06	0.05	1.89E-01	-0.02	0.05	6.48E-01
MV stenosis	-0.12	0.17	4.63E-01	-0.07	0.11	5.31E-01
MV insufficiency	0.11	0.04	2.04E-02	0.07	0.05	1.55E-01
AV surgery [§]	-0.05	0.05	2.71E-01	0.04	0.04	3.27E-01
AV stenosis	-0.04	0.05	4.65E-01	0.03	0.05	6.28E-01
AV insufficiency	0.13	0.05	1.11E-02	0.09	0.05	8.21E-02
TV insufficiency [§]	0.08	0.05	8.88E-02	0.03	0.05	5.16E-01
Heart failure*	0.05	0.07	4.34E-01	0.04	0.06	5.09E-01
EF (/5% increase)	0.00	0.01	6.70E-01	0.01	0.01	6.39E-01
NYHA	0.02	0.02	4.56E-01	0.05	0.02	2.00E-02
coronary artery Disease	-0.03	0.05	5.07E-01	-0.06	0.04	2.12E-01
prior myocardial infarction [§]	-0.06	0.06	3.07E-01	0.04	0.06	4.91E-01
periferal artery disease	0.55	0.15	4.35E-04	-0.08	0.08	3.31E-01
Diabetes [§]	0.01	0.06	9.30E-01	0.00	0.06	9.68E-01
hypertension [§]	0.11	0.05	3.89E-02	0.02	0.05	7.12E-01
COPD	-0.25	0.16	1.28E-01	-0.06	0.08	4.77E-01
hypothyroidism [§]	-0.07	0.06	3.02E-01	0.00	0.08	9.94E-01
chronic kidney failure [§]	-0.12	0.17	4.59E-01	-0.05	0.08	5.20E-01
prior stroke [§]	0.15	0.06	1.13E-02	-0.06	0.10	5.37E-01
prior TIA	-0.04	0.10	6.90E-01	0.04	0.06	4.80E-01

Table S11: Univariate associations between clinical parameters and fibroblast expression, stratified by atrial side, excluding HTX patients. Univariate associations between clinical parameters and fibroblast expression were obtained with univariate regression analysis. LA/RA: Left/Right atrial appendage, par.AF: paroxysmal AF, pers.AF: persistent AF/permanent AF; PVI: pulmonary vein isolation; CABG: coronary artery bypass graft; MV: mitral valve; AV: aortic valve; TV: tricuspid valve; EF: ejection fraction; NYHA: New York Heart Association; HTX: heart transplant surgery; COPD: chronic obstructive pulmonary disease; TIA: transient ischemic attack. SE: standard error; * will be explicitly modeled in multivariate models; §: will be included in principal component modeling

	LA			RA		
	myocyte diameter			myocyte diameter		
	Estimate (μm)	SE	p value	Estimate (μm)	SE	p value
Sex*:M	1.06	0.47	2.58E-02	0.79	0.57	1.77E-01
Age* (/5years increase)	-0.05	0.13	7.25E-01	0.10	0.13	4.70E-01
Weight [§] (/5kg increase)	0.04	0.01	7.68E-03	0.02	0.01	2.66E-01
Height [§] (/5cm increase)	0.03	0.02	1.56E-01	0.02	0.02	4.49E-01
CHA ₂ DS ₂ -VASc	0.17	0.17	3.17E-01	-0.09	0.16	5.55E-01
Hatch	0.30	0.22	1.77E-01	0.02	0.21	9.42E-01
Rhythm*: par.AF	0.35	0.56	5.27E-01	0.41	0.56	4.67E-01
Rhythm*: pers.AF	-0.15	0.62	8.08E-01	-0.74	0.64	2.58E-01
Concomitant PVI	-0.03	0.51	9.49E-01	-0.07	0.75	9.30E-01
CABG [§]	0.05	0.51	9.18E-01	-0.63	0.46	1.76E-01
MV surgery [§]	-0.11	0.48	8.29E-01	0.24	0.54	6.51E-01
MV stenosis	-1.42	1.30	2.80E-01	-0.73	1.17	5.37E-01
MV insufficiency	0.43	0.50	3.89E-01	0.43	0.48	3.70E-01
AV surgery [§]	0.18	0.51	7.29E-01	0.29	0.48	5.50E-01
AV stenosis	-0.01	0.54	9.90E-01	-0.01	0.50	9.98E-01
AV insufficiency	0.93	0.53	8.65E-02	0.82	0.49	9.84E-02
TV insufficiency [§]	0.33	0.48	4.92E-01	0.08	0.51	8.83E-01
Heart failure*	-0.30	0.73	6.83E-01	0.59	0.63	3.55E-01
EF (/5% increase)	-0.06	0.11	6.05E-01	0.03	0.11	7.68E-01
NYHA	0.32	0.23	1.82E-01	0.07	0.24	7.69E-01
coronary artery Disease	-0.09	0.48	8.54E-01	-0.59	0.48	2.29E-01
prior myocardial infarction [§]	-0.80	0.65	2.22E-01	0.09	0.70	8.98E-01
periferal artery disease	2.12	1.81	2.44E-01	-0.67	0.90	4.57E-01
Diabetes [§]	-0.26	0.63	6.81E-01	-0.81	0.65	2.20E-01
hypertension [§]	1.03	0.59	8.80E-02	0.16	0.63	8.06E-01
COPD	-2.86	1.79	1.16E-01	-0.99	1.02	3.39E-01
hypothyroidism [§]	-0.32	0.63	6.10E-01	-0.31	0.90	7.31E-01
chronic kidney failure [§]	-1.67	1.81	3.62E-01	0.35	0.90	6.99E-01
prior stroke [§]	1.11	0.61	7.42E-02	-1.08	0.89	2.28E-01
prior TIA	0.18	1.07	8.66E-01	0.25	0.70	7.28E-01

Table S12: Univariate associations between clinical parameters and myocyte diameter, stratified by atrial side, excluding HTX patients. Univariate associations between clinical parameters and myocyte diameter were obtained with univariate regression analysis. LA/RA: Left/Right atrial appendage, par.AF: paroxysmal AF, pers.AF: persistent AF/permanent AF; PVI: pulmonary vein isolation; CABG: coronary artery bypass graft; MV: mitral valve; AV: aortic valve; TV: tricuspid valve; EF: ejection fraction; NYHA: New York Heart Association; HTX: heart transplant surgery; COPD: chronic obstructive pulmonary disease; TIA: transient ischemic attack. SE: standard error; * will be explicitly modeled in multivariate models; §: will be included in principal component modeling

	LA			RA		
	capillary density			capillary density		
	Estimate	SE	p value	Estimate	SE	p value
Sex*:M	-0.02	0.05	6.37E-01	0.05	0.04	2.45E-01
Age* (/5years increase)	0.01	0.01	3.78E-01	0.01	0.01	4.37E-01
Weight [§] (/5kg increase)	0.01	0.02	5.41E-01	<0.01	0.01	8.67E-01
Height [§] (/5cm increase)	-0.01	0.02	7.60E-01	<0.01	0.02	9.47E-01
CHA ₂ DS ₂ -VASc	0.03	0.02	8.61E-02	-0.01	0.01	4.48E-01
Hatch	0.03	0.02	2.35E-01	-0.02	0.02	2.19E-01
Rhythm*: par.AF	-0.03	0.06	6.49E-01	-0.01	0.04	8.29E-01
Rhythm*: pers.AF	0.02	0.06	8.07E-01	0.00	0.04	9.19E-01
Concomitant PVI	-0.05	0.05	3.22E-01	-0.07	0.05	1.71E-01
CABG [§]	0.08	0.05	1.32E-01	0.02	0.03	6.46E-01
MV surgery [§]	0.00	0.05	9.89E-01	-0.09	0.04	1.89E-02
MV stenosis	-0.05	0.12	6.95E-01	-0.07	0.08	4.17E-01
MV insufficiency	0.08	0.05	1.05E-01	-0.05	0.04	1.93E-01
AV surgery [§]	-0.04	0.05	3.84E-01	0.02	0.04	9.55E-01
AV stenosis	-0.03	0.05	5.00E-01	-0.02	0.04	6.57E-01
AV insufficiency	0.02	0.05	7.01E-01	0.05	0.04	2.10E-01
TV insufficiency [§]	0.05	0.05	3.43E-01	-0.05	0.04	2.23E-01
Heart failure*	-0.03	0.07	6.35E-01	0.03	0.04	5.35E-01
EF (/5% increase)	-0.01	0.01	3.19E-01	0.01	0.01	5.93E-01
NYHA	0.04	0.02	1.43E-01	-0.03	0.02	1.28E-01
coronary artery Disease	0.04	0.05	9.33E-01	-0.03	0.04	4.98E-01
prior myocardial infarction [§]	0.05	0.06	4.68E-01	-0.04	0.05	4.91E-01
periferal artery disease	-0.09	0.17	6.00E-01	0.06	0.06	3.40E-01
Diabetes [§]	0.07	0.06	2.85E-01	-0.01	0.05	9.86E-01
hypertension [§]	0.08	0.06	1.91E-01	-0.03	0.04	4.42E-01
COPD	NA	NA	NA	-0.04	0.07	5.48E-01
hypothyroidism [§]	-0.07	0.06	2.67E-01	0.13	0.08	9.86E-02
chronic kidney failure [§]	-0.18	0.17	3.04E-01	-0.01	0.06	8.92E-01
prior stroke [§]	0.09	0.06	1.30E-01	-0.05	0.07	4.83E-01
prior TIA	-0.04	0.10	9.68E-01	-0.02	0.05	7.23E-01

Table S13: Univariate associations between clinical parameters and capillary density, stratified by atrial side, excluding HTX patients. Univariate associations between clinical parameters and capillary density were obtained with univariate regression analysis. LA/RA: Left/Right atrial appendage, par.AF: paroxysmal AF, pers.AF: persistent AF/ permanent AF; PVI: pulmonary vein isolation; CABG: coronary artery bypass graft; MV: mitral valve; AV: aortic valve; TV: tricuspid valve; EF: ejection fraction; NYHA: New York Heart Association; HTX: heart transplant surgery; COPD: chronic obstructive pulmonary disease; TIA: transient ischemic attack. SE: standard error; * will be explicitly modeled in multivariate models; §: will be included in principal component modeling

	LA			RA		
	capillary size			capillary size		
	Estimate (μm)	SE	p value	Estimate (μm)	SE	p value
Sex*:M	-0.23	0.21	2.78E-01	-0.13	0.16	4.20E-01
Age* (/5years increase)	-0.08	0.06	2.20E-01	0.06	0.04	1.25E-01
Weight [§] (/5kg increase)	-0.01	0.01	4.10E-01	-0.03	0.04	3.77E-01
Height [§] (/5cm increase)	-0.02	0.01	9.31E-02	-0.04	0.01	5.42E-01
CHA ₂ DS ₂ -VASc	<0.01	0.07	9.99E-01	0.00	0.05	9.26E-01
Hatch	-0.03	0.10	7.36E-01	0.03	0.06	6.23E-01
Rhythm*: par.AF	-0.31	0.24	2.12E-01	0.02	0.17	9.28E-01
Rhythm*: pers.AF	-0.22	0.27	4.11E-01	0.05	0.17	7.86E-01
Concomitant PVI	-0.18	0.22	4.24E-01	0.19	0.20	3.63E-01
CABG [§]	<0.01	0.22	9.98E-01	-0.07	0.13	5.79E-01
MV surgery [§]	-0.07	0.21	7.55E-01	0.32	0.15	3.74E-02
MV stenosis	1.10	0.51	3.73E-02	-0.07	0.36	8.35E-01
MV insufficiency	-0.07	0.21	7.40E-01	0.18	0.15	2.25E-01
AV surgery [§]	0.03	0.22	8.95E-01	0.03	0.14	9.83E-01
AV stenosis	0.23	0.22	3.07E-01	-0.06	0.17	7.25E-01
AV insufficiency	-0.26	0.23	2.79E-01	-0.01	0.16	9.95E-01
TV insufficiency [§]	-0.13	0.21	5.49E-01	0.35	0.14	1.88E-02
Heart failure*	0.50	0.30	9.82E-02	0.17	0.18	3.51E-01
EF (/5% increase)	-0.03	0.05	4.89E-01	-0.01	0.04	8.89E-01
NYHA	-0.04	0.11	7.13E-01	0.10	0.07	1.30E-01
coronary artery Disease	0.05	0.21	8.25E-01	-0.09	0.14	5.45E-01
prior myocardial infarction [§]	0.08	0.28	7.81E-01	0.13	0.22	5.50E-01
periferal artery disease	-0.69	0.76	3.68E-01	-0.20	0.24	4.18E-01
Diabetes [§]	0.33	0.27	2.38E-01	-0.37	0.18	4.69E-02
hypertension [§]	0.07	0.26	7.87E-01	-0.09	0.17	6.21E-01
COPD	-0.57	0.76	4.60E-01	-0.27	0.28	3.31E-01
hypothyroidism [§]	0.59	0.28	3.84E-02	0.18	0.25	4.75E-01
chronic kidney failure [§]	1.79	0.72	1.64E-02	-0.05	0.24	8.53E-01
prior stroke [§]	-0.13	0.26	6.20E-01	0.06	0.28	8.21E-01
prior TIA	0.53	0.44	2.41E-01	-0.13	0.20	5.24E-01

Table S14: Univariate associations between clinical parameters and capillary diameter, stratified by atrial side, excluding HTX patients. Univariate associations between clinical parameters and capillary diameter were obtained with univariate regression analysis. LA/RA: Left/Right atrial appendage, par.AF: paroxysmal AF, pers.AF: persistent AF/ permanent AF; PVI: pulmonary vein isolation; CABG: coronary artery bypass graft; MV: mitral valve; AV: aortic valve; TV: tricuspid valve; EF: ejection fraction; NYHA: New York Heart Association; HTX: heart transplant surgery; COPD: chronic obstructive pulmonary disease; TIA: transient ischemic attack. SE: standard error; * will be explicitly modeled in multivariate models; §: will be included in principal component modeling

LA																
	Total ECM				endomysial fibrosis				Fibroblast density				Myocyte diameter			
	β (%)	SE	p	padj	β (μm)	SE	p	padj	β	SE	p	padj	β (μm)	SE	p	padj
<i>intercept</i>	24.96	3.12			4.97	1.23			0.38	0.22			14.07	2.12		
<i>age</i>	0.58	0.24	0.02	0.05	0.13	0.06	0.05	0.04	0.001	0.02	0.96	0.95	-0.10	0.17	0.54	
<i>Sex: F</i>	4.27	1.27	0.001	0.001	0.82	0.40	0.03	0.02	0.02	0.08	0.77	0.71	-1.46	0.56	0.04	0.04
<i>Heart Failure</i>	4.24	1.35	0.002	0.001	1.18	0.50	0.02	0.03	0.04	0.07	0.55	0.51	-0.50	0.86	0.56	0.61
<i>par.AF</i>	-1.72	1.07	0.11	0.10	0.36	0.41	0.38	0.35	0.07	0.07	0.29	0.26	0.85	0.72	0.24	0.20
<i>pers.AF</i>	-0.12	1.20	0.92	0.74	0.96	0.44	0.04	0.04	0.11	0.07	0.10	0.16	0.75	0.77	0.34	0.35
<i>PC1</i>	0.32	0.34	0.35	0.39	0.02	0.13	0.85	0.88	0.02	0.02	0.45	0.39	-0.02	0.23	0.94	1.00
<i>PC2</i>	0.90	0.52	0.09	0.19	0.31	0.20	0.08	0.19	-0.01	0.02	0.68	0.76	-0.25	0.24	0.31	0.36
<i>PC3</i>	0.19	0.43	0.67	0.65	-0.28	0.16	0.08	0.15	-0.01	0.02	0.58	0.65	-0.19	0.28	0.50	0.49
<i>PC4</i>	0.19	0.41	0.65	0.73	0.12	0.16	0.45	0.49	-0.01	0.02	0.75	0.78	-0.02	0.27	0.93	0.95

RA																
	Total ECM				endomysial fibrosis				Fibroblast density				Myocyte diameter			
	β (%)	SE	p	padj	β (μm)	SE	p	padj	β	SE	p	padj	β (μm)	SE	p	padj
<i>intercept</i>	35.66	6.67			6.55	1.94			-0.01	0.21	0.98		9.10	2.46		
<i>age</i>	-0.02	0.50	0.97	0.96	0.18	0.11	0.04	0.03	0.03	0.003	0.10	0.12	0.28	0.18	0.13	0.16
<i>Sex: F</i>	-2.14	2.27	0.35	0.40	0.12	0.50	0.80	0.78	0.03	0.06	0.59	0.52	0.58	0.80	0.48	0.41
<i>Heart Failure</i>	1.54	2.03	0.45	0.47	0.23	0.36	0.53	0.49	0.05	0.07	0.45	0.41	-0.04	0.71	0.96	0.93
<i>par.AF</i>	0.17	1.93	0.93	0.85	0.92	0.40	0.02	0.03	0.05	0.06	0.45	0.47	1.03	0.69	0.14	0.17
<i>pers.AF</i>	3.17	2.12	0.14	0.08	0.97	0.41	0.02	0.01	0.03	0.06	0.59	0.61	-0.56	0.75	0.46	0.41
<i>PC1</i>	0.07	0.57	0.90	0.85	0.07	0.17	0.70	0.77	0.01	0.02	0.51	0.53	0.04	0.21	0.87	0.83
<i>PC2</i>	0.95	0.55	0.09	0.11	0.19	0.15	0.21	0.26	-0.03	0.02	0.14	0.17	-0.28	0.19	0.15	0.20
<i>PC3</i>	-0.52	0.62	0.41	0.39	-0.03	0.17	0.86	0.85	-0.003	0.02	0.88	0.86	0.07	0.22	0.75	0.82
<i>PC4</i>	-0.57	0.61	0.36	0.29	-0.11	0.17	0.53	0.52	-0.01	0.02	0.56	0.53	0.08	0.22	0.72	0.73

Table S15: Multivariate models describing the association between clinical traits and structural properties of the myocardium in left (LA) and right (RA) atrial appendages, excluding HTX patients. Age, sex, heart failure and rhythm history were modeled explicitly. A combination of 13 additional clinical traits was combined in 4 principal components (PCs). B: Degree of change in the outcome variable for every unit of change in the predictor variable. SE: standard error, ECM: extracellular matrix, parAF: paroxysmal atrial fibrillation, persAF: persistent atrial fibrillation, PC: principal component

LA

	capillary density				capillary size			
	β (n)	SE	p	p _{adj}	β (μ m)	SE	p	p _{adj}
<i>intercept</i>	0.35	0.21			6.02	0.90		
<i>age</i>	0.017	0.02	0.30	0.36	-0.04	0.07	0.59	0.57
<i>sex:F</i>	-0.13	0.08	0.12	0.16	-0.25	0.34	0.47	0.47
<i>heart failure</i>	-0.02	0.07	0.78	0.73	0.52	0.31	0.10	0.16
<i>parAF</i>	-0.05	0.07	0.43	0.55	-0.29	0.29	0.32	0.32
<i>persAF</i>	0.02	0.07	0.77	0.74	-0.23	0.30	0.44	0.40
<i>PC1</i>	0.05	0.02	0.07	0.10	0.02	0.09	0.87	0.83
<i>PC2</i>	<0.001	0.02	1.00	0.99	0.05	0.09	0.60	0.68
<i>PC3</i>	-0.002	0.02	0.94	0.95	-0.06	0.10	0.55	0.50
<i>PC4</i>	-0.01	0.02	0.73	0.77	0.02	0.10	0.87	0.91

RA

	capillary density				capillary size			
	β (n)	SE	p	p _{adj}	β (μ m)	SE	p	p _{adj}
<i>intercept</i>	0.18	0.18			4.94	0.68		
<i>age</i>	0.01	0.00	0.30	0.37	0.05	0.05	0.35	0.41
<i>sex:F</i>	0.05	0.06	0.35	0.32	-0.10	0.21	0.64	0.69
<i>heart failure</i>	0.02	0.05	0.68	0.63	0.10	0.19	0.60	0.50
<i>parAF</i>	-0.03	0.05	0.58	0.51	-0.05	0.20	0.82	0.75
<i>persAF</i>	0.01	0.05	0.88	0.86	-0.06	0.19	0.76	0.78
<i>PC1</i>	0.004	0.02	0.81	0.76	-0.03	0.06	0.64	0.63
<i>PC2</i>	-0.003	0.02	0.88	0.84	0.01	0.06	0.89	0.86
<i>PC3</i>	0.005	0.02	0.76	0.72	0.07	0.06	0.23	0.27
<i>PC4</i>	0.002	0.01	0.88	0.80	-0.02	0.06	0.73	0.68

Table S16 (continuation S15): Multivariate models describing the association between clinical traits and structural properties of the myocardium in left (LA) and right (RA) atrial appendages, excluding HTX patients. Age, sex, heart failure and rhythm history were modeled explicitly. A combination of 13 additional clinical traits was combined in 4 principal components (PCs). B: Degree of change in the outcome variable for every unit of change in the predictor variable. SE: standard error, ECM: extracellular matrix, parAF: paroxysmal atrial fibrillation, persAF: persistent atrial fibrillation, PC: principal component

	LA				RA			
	Fibrotic atCM (n=22)	hypertrophic atCM (n=69)	p	padj	fibrotic atCM (n=45)	hypertrophic atCM (n=29)	p	padj
capillary density	0.584±0.184	0.451±0.176	<0.001	<0.001	0.449±0.175	0.468±0.175	0.011	0.013
capillary size	5.545±1.166	5.493±1.062	0.821	0.857	5.498±1.059	5.506±1.093	0.524	0.648
endomysial fibrosis	7.955±1.851	4.784±1.791	<0.001	<0.001	8.234±1.835	5.462±1.786	<0.001	<0.001
total ECM	32.451±5.252	28.924±5.253	<0.001	<0.001	34.662±5.321	28.264±5.448	<0.001	<0.001
Vimentin signal	10.613±4.830	6.236±3.872	<0.001	<0.001	10.868±4.053	8.709±5.084	0.788	0.776
Myocyte Diameter	10.948±1.872	12.106±1.904	0.009	0.01	10.944±1.632	13.524±2.098	<0.001	<0.001

Table S17: Univariate structural differences between left and right atrial appendage samples clustered in unique clusters. NoAF: No history of AF, pAF: paroxysmal AF, persAF: persistent/permanent AF; AV/MV aortic/mitral valve; PVI: concomitant pulmonary vein isolation; HTX: Heart Transplant Xenograft; CAD: Coronary artery disease; CABG: Coronary artery bypass graft; CKD: chronic kidney disease TIA: Transient ischemic attack; atCM: atrial cardiomyopathy. *Variables that were explicitly modeled in multivariate logistic regression model (table 4). Values are presented as (mean ± SD) for continuous traits, or in absolute number and as percentage for dichotomous traits.

	LA				RA			
	Fibrotic atCM (n=22)	hypertrophic atCM (n=69)	p	padj	fibrotic CM atCM (n=45)	hypertrophic CM atCM (n=29)	p	padj
Age*	63.0±9.40	62.9±11.4	0.971	0.998	64.8±11.8	64.1±12.2	0.806	0.823
weight	75.4±17.3	78.1±14.5	0.469	0.315	77.6±17.1	83.9±15.1	0.111	0.118
height	169.6±10.9	173.4±9.18	0.109	0.107	171.4±11.5	175.9±7.2	0.064	0.053
bmi	25.9±4.1	26.2±4.1	0.766	0.996	26.4±4.7	26.9±3.8	0.633	0.613
Sex (F)*	9 (41%)	17 (25%)	0.141	0.138	14 (31%)	0 (0%)	0.002	<0.001
<u>Rhythm</u> *			0.041	0.015			0.683	0.515
• noAF	9 (41%)	31 (45%)			23 (51%)	18 (62%)		
• pAF	4 (18%)	21 (30%)			11 (24%)	7 (24%)		
• persAF	9 (41%)	17 (25%)			11 (24%)	4 (14%)		
<u>HF</u> *	14 (64%)	23 (33%)	0.008	0.008	13 (29%)	13 (45%)	0.161	0.165
<u>HF category</u>			0.011	0.024			0.341	0.355
• noHF	8 (36%)	46 (67%)			32 (71%)	16 (59%)		
• HFpEF	2 (9%)	5 (7%)			1 (3%)	2 (7%)		
• HFrfEF	12 (55%)	18 (26%)			12 (27%)	11 (41%)		
<u>EF category</u>			0.034	0.046			0.321	0.342
• mildly reduced	1 (5%)	3 (4%)			5 (11%)	4 (15%)		
• moderately reduced	5 (23%)	8 (12%)			2 (4%)	5 (19%)		
• severely reduced	6 (27%)	7 (10%)			5 (11%)	2 (7%)		
<u>primary indication</u>			0.041	0.034			0.364	0.376
• CABG only	3 (14%)	12 (17%)			16 (36%)	6 (21%)		
• MVS	6 (27%)	17(25%)			9 (20%)	5 (17%)		
• AVS	1 (5%)	17 (25%)			8 (18%)	8 (28%)		
• HTX	12 (55%)	19 (28%)			9 (20%)	8 (28%)		
• PVI	0 (0%)	2 (3%)			0 (0%)	1 (3%)		
• donor	0 (0%)	2 (3%)			0 (0%)	1 (3%)		
CAD	8 (36%)	32 (47%)	0.081	0.334	27 (60%)	18 (62%)	0.751	0.795
prior MI	3 (14%)	19 (28%)	0.063	0.209	7 (16%)	7 (24%)	0.572	0.546
PAD	2 (9%)	1 (1%)	0.072	0.069	6 (13%)	1 (4%)	0.221	0.218
diabetes	5 (23%)	13 (19%)	0.994	0.944	8 (17%)	2 (7%)	0.239	0.214
hypertension	14 (64%)	48 (69%)	0.839	0.795	32 (71%)	21 (72%)	0.858	0.863

<i>COPD</i>	2 (9%)	3 (4%)	0.373	0.394	3 (6%)	0 (0%)	0.181	0.179
<i>thyroid dysf</i>	2 (9%)	13 (19%)	0.719	0.744	8 (17%)	1 (4%)	0.091	0.067
<i>CKD</i>	4 (18%)	2 (3%)	0.010	0.014	4 (9%)	1 (4%)	0.432	0.369
<i>stroke</i>	1 (5%)	9 (13%)	0.275	0.316	3 (6%)	0 (0%)	0.189	0.191
<i>TIA</i>	0 (0%)	3 (4%)	0.324	0.324	5 (11%)	3 (11%)	0.905	0.923

Table S18: Univariate clinical differences between left and right atrial appendage samples clustered in unique clusters. NoAF: No history of AF, pAF: paroxysmal AF, persAF: persistent/permanent AF; AV/MV aortic/mitral valve; PVI: concomitant pulmonary vein isolation; HTX: Heart Transplant Xenograft; CAD: Coronary artery disease; CABG: Coronary artery bypass graft; CKD: chronic kidney disease TIA: Transient ischemic attack; CM: cardiomyopathy; MI: myocardial infarction. *Variables that were explicitly modeled in multivariate logistic regression model (table 4). Values are presented as (mean \pm SD) for continuous traits, or in absolute number and as percentage for dichotomous

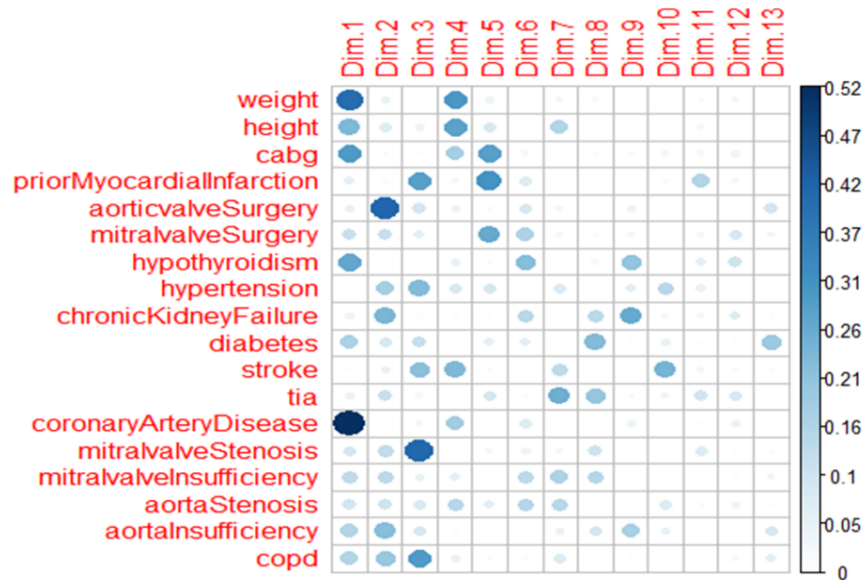
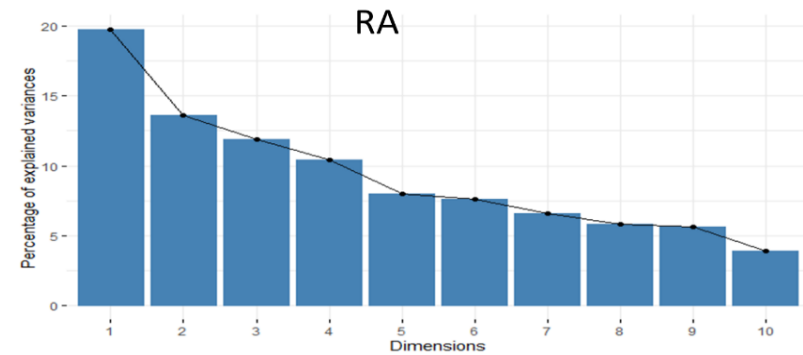
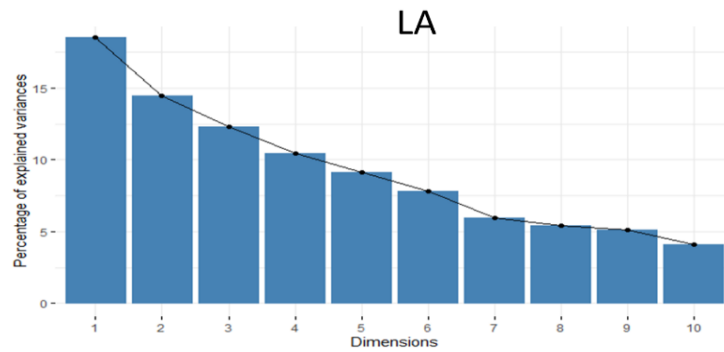


Figure S1: Principal component analyses for reduction of dimensionality. Orthogonal principal component analysis was performed in order to model the cumulative variance of 13 clinical traits into principal components. Variants were scaled. Based on the scree plots for LA and RA (top), 4 Principal components were selected, covering a cumulative variance of respectively 56 and 57%. Representation of each variable in each principal component was shown in the corrplots (bottom). cabg: coronary artery bypass graft, tia: transient ischemic attack, copd: chronic obstructive pulmonary disease, LA/RA: left/right atrium

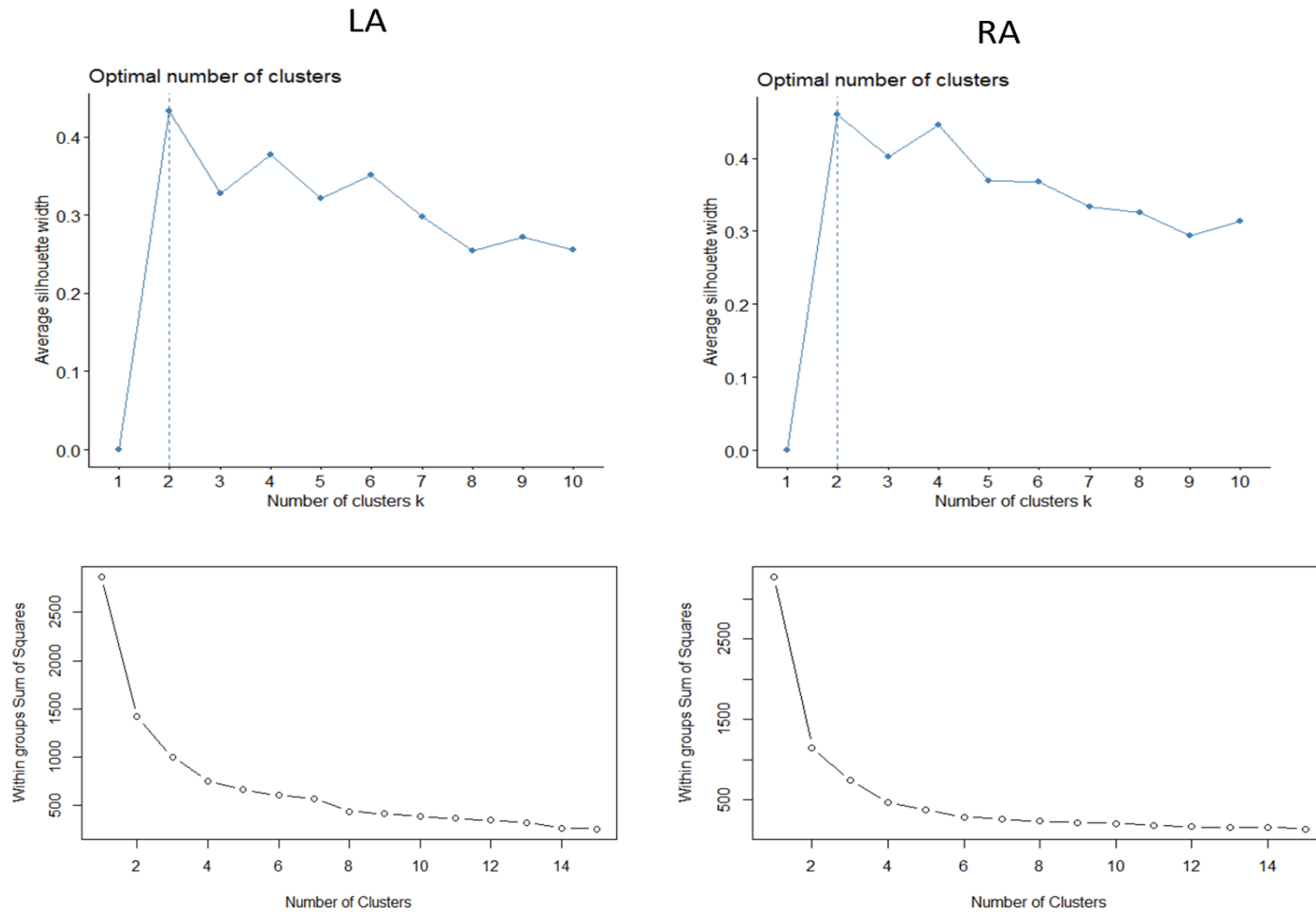


Figure S2: Optimal cluster size in Fuzzy k-means clustering. Left and Right atrial appendage samples (LA, RA) where clustered based on structural features (endomysial fibrosis, total extracellular matrix content, fibroblast signal, capillary density and size, cardiomyocyte size). Optimal cluster size was automatically determined at 2 clusters per side, resulting in an optimal silhouette score (top). Within-group sum of squares was sufficiently low with 2 clusters, representing sufficiently low variability of the observations within each cluster (bottom).