

Appendices

Appendix Ia. Aortic thoracic diameter at multiple levels – measured at CT or TTE

	All patients (n=158)	Males (n=99)	Females (n=59)	P-value	Missing (%)
Maximal diameter thoracic aorta (mm)	43.2 ± 5.2	43.9 ± 5.2	41.9 ± 5.1	0.030	3.8
Indexed diameter thoracic aorta (mm/m ²)	21.2 ± 2.9	20.5 ± 2.9	22.5 ± 3.5	<0.001	4.4
Maximal diameter ascending aorta (mm)	42.92 (5.14)	43.82 (5.17)	41.31 (4.70)	0.004	5.1
Indexed diameter max. ascending aorta (mm/m ²)	21.0 [19.0, 22.6]	20.6 [18.9, 22.1]	21.8 [19.7, 24.4]	0.007	5.7
Annulus	30.0 [25.50, 32.00]	30.0 [28.0, 32.5]	28.0 [25.0, 32.0]	0.474	81.0
Sinus of Valsalva	39.0 [36.0, 43.0]	42.0 [38.0, 46.0]	36.0 [34.0, 39.0]	<0.001	11.4
Sinotubular junction	35.0 [33.0, 39.0]	37.0 [34.0, 41.0]	34.0 [31.0, 36.0]	<0.001	48.1
Ascending aorta	41.0 [37.0, 44.0]	41.0 [37.0, 44.3]	40.0 [33.0, 44.0]	0.528	5.7
Aortic arch	32.0 [29.0, 35.0]	32.0 [30.0, 36.0]	31.0 [27.0, 34.0]	0.049	23.4
Descending aorta	29.0 [26.0, 32.0]	29.0 [27.0, 32.0]	28.0 [25.0, 32.0]	0.344	34.2

Normally distributed continuous variables are expressed as mean ± SD, skewed continuous variables are expressed as median and 25th–75th percentile. CT = cardiac tomography, TTE = transthoracic echocardiography.

Appendix Ib. Aortic thoracic diameter at multiple levels – measured at CT only

	All patients (n=158)	Males (n=99)	Females (n=59)	P-value	Missing (%)
CTA performed	106 (67.1)	64 (64.6)	42 (71.2)	0.502	0.0
Annulus	30.00 [38.00, 32.75]	32.00 [29.50, 33.00]	28.00 [25.00, 32.00]	0.099	83.5
Sinus of Valsalva	39.00 [36.00, 43.00]	42.00 [38.00, 47.00]	36.00 [34.00, 38.75]	<0.001	39.9
Sinotubular junction	35.00 [33.00, 39.00]	37.50 [34.00, 41.00]	34.00 [31.00, 35.75]	<0.001	48.1
Ascending aorta	39.82 (5.97)	39.98 (5.41)	39.57 (6.79)	0.731	33.5

Aortic arch	32.00 [29.00, 35.00]	32.00 [30.00, 35.25]	31.00 [27.00, 34.25]	0.116	36.7
Descending aorta	29.00 [26.00, 32.00]	29.00 [27.00, 32.00]	28.00 [25.00, 32.00]	0.344	34.2
Aorta abdominals	22.00 [19.00, 25.00]	23.00 [21.00, 27.00]	21.00 [18.00, 24.00]	0.023	41.1

Normally distributed continuous variables are expressed as mean \pm SD, skewed continuous variables are expressed as median and 25th–75th percentile. CT = cardiac tomography, TTE = transthoracic echocardiography.

Appendix Ic. Aortic thoracic diameter at multiple levels – measured at TTE only

	All patients (n=158)	Males (n=99)	Females (n=59)	P- value	Missing (%)
TTE performed	108 (68.4)	73 (73.7)	35 (59.3)	0.088	0.0
Annulus	25.17 (4.12)	25.20 (4.60)	25.00 (NA)	NA	96.2
Sinus of Valsalva	40.46 (5.88)	41.92 (5.70)	36.75 (4.64)	<0.001	46.2
Sinotubular junction	36.00 (4.76)	37.67 (4.16)	31.00 (NA)	NA	97.5
Ascending aorta	41.00 [37.00, 43.00]	41.00 [37.00, 43.00]	41.00 [37.00, 44.25]	0.821	39.2
Aortic arch	32.15 (5.28)	32.84 (4.76)	29.00 (6.73)	0.081	75.3

Normally distributed continuous variables are expressed as mean \pm SD, skewed continuous variables are expressed as median and 25th–75th percentile. CT = cardiac tomography, TTE = transthoracic echocardiography.

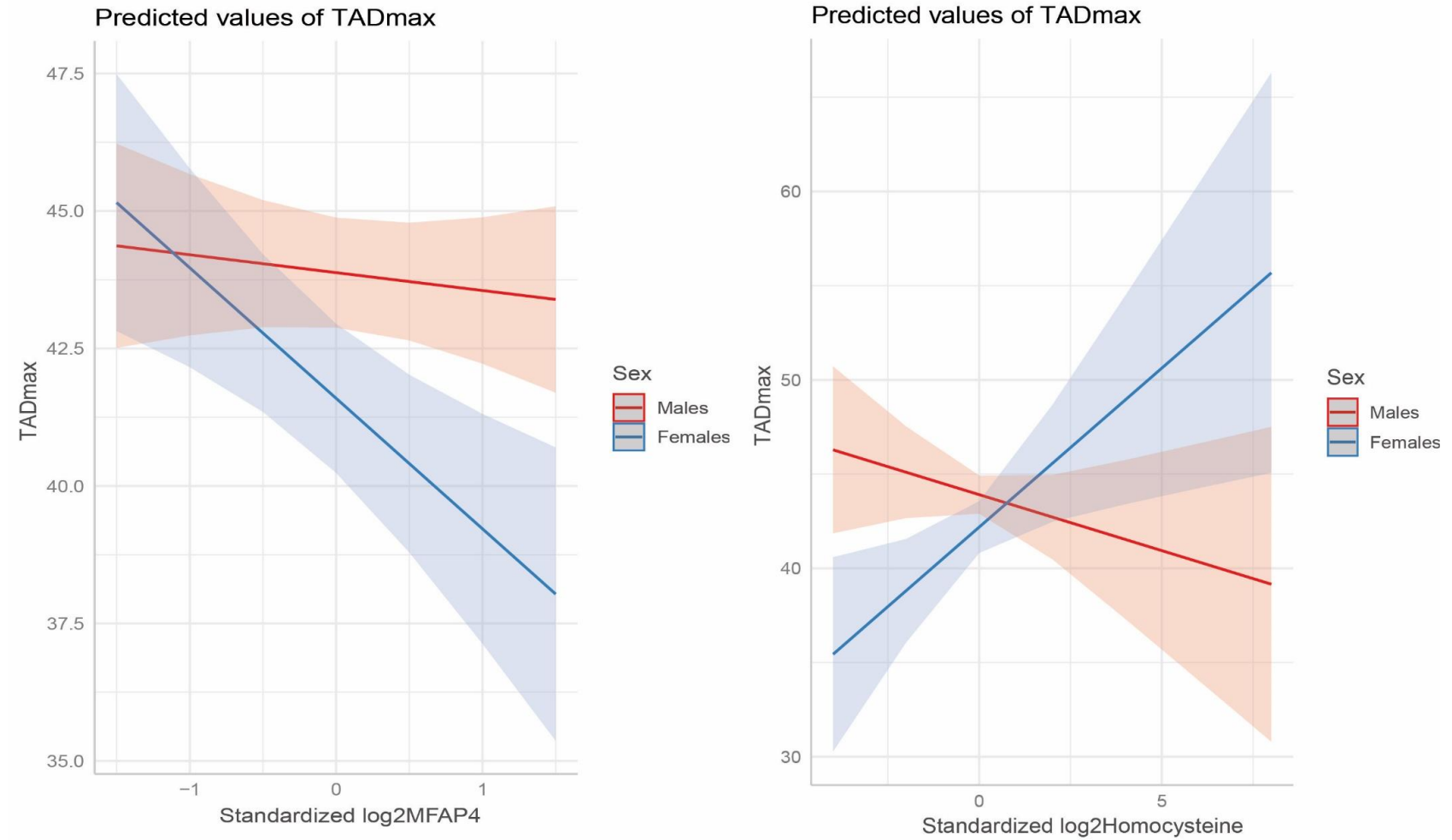
Appendix II. Circulating biomarker levels stratified by sex

Biomarker	All patients (n=158)	Males (n=99)	Females (n=59)	P-value	Missing %
MFAP4 (ng/ml)	0.48 [0.08, 5.61]	0.80 [0.08, 6.92]	0.20 [0.08, 3.17]	0.102	0.0
FBN1 (ng/ml)	1908.00 [1698.00, 2313.50]	2055.00 [1728.00, 2454.00]	1829.00 [1612.50, 2044.50]	0.002	0.0
PIIINP (pg/ml)	13.20 [10.53, 15.20]	13.60 [11.40, 15.70]	11.80 [9.30, 14.65]	0.011	0.0
hsTNT (ng/l)	6.00 [4.00, 10.00]	8.00 [5.00, 12.00]	5.00 [1.50, 7.50]	<0.001	0.0
NT-pro BNP (pmol/L)	10.00 [5.75, 18.25]	8.50 [4.00, 15.00]	13.50 [7.00, 25.25]	0.012	8.9
IL-6 (pg/ml)	2.00 [1.00, 3.00]	2.00 [1.00, 3.00]	2.00 [1.00, 3.00]	0.910	0.0
GDF-15 (pg/ml)	855.00 [654.00, 1222.25]	849.00 [638.00, 1324.50]	864.00 [686.00, 1156.00]	0.695	0.0
hsCRP (mg/L)	1.10 [0.60, 2.50]	1.10 [0.60, 1.98]	1.40 [0.70, 3.25]	0.077	0.6
Triglycerides (mmol/L)	1.58 [1.07, 2.06]	1.73 [1.20, 2.19]	1.32 [0.98, 1.84]	0.012	7.6
Total cholesterol (mmol/L)	4.77 (0.96)	4.63 (0.96)	4.99 (0.94)	0.025	7.6
HDL-cholesterol (mmol/L)	1.30 [1.10, 1.57]	1.15 [1.02, 1.43]	1.51 [1.26, 1.83]	<0.001	7.6
LDL-cholesterol (mmol/L)	3.10 (0.90)	3.02 (0.91)	3.22 (0.88)	0.196	7.6
Total cholesterol/HDL	3.41 [2.87, 4.28]	3.64 [2.95, 4.54]	3.18 [2.69, 3.90]	0.008	7.6
Homocysteine (µmol/L)	14.40 [12.31, 17.25]	14.70 [12.70, 17.15]	13.85 [11.35, 17.48]	0.160	0.0
Haemoglobin (mmol/L)	8.83 (0.91)	9.20 (0.80)	8.26 (0.75)	<0.001	8.2
RDW (%)	12.90 [12.40, 13.50]	12.80 [12.40, 13.40]	12.90 [12.40, 13.53]	0.515	8.2
TSH (mU/L)	1.58 [1.22, 2.09]	1.62 [1.21, 2.07]	1.57 [1.24, 2.46]	0.921	36.1
fT4 (pmol/L)	16.10 (3.11)	16.17 (3.18)	15.99 (3.01)	0.792	36.1
T4 (nmol/L)	99.96 (22.53)	96.87 (21.25)	105.28 (23.95)	0.075	38.0
T3 (nmol/L)	1.88 [1.68, 2.07]	1.91 [1.70, 2.07]	1.81 [1.68, 2.02]	0.234	37.3
Creatinine (µmol/L)	81.50 [69.00, 92.00]	87.00 [80.00, 98.25]	69.50 [62.00, 77.00]	<0.001	5.1
eGFR (mL/min)	83.55 (18.60)	82.23 (19.75)	85.64 (16.58)	0.276	5.1
Ureum (mmol/L)	5.60 [4.80, 6.60]	5.70 [5.20, 6.60]	5.20 [4.40, 6.38]	0.008	6.3

Normally distributed continuous variables are expressed as mean \pm SD, skewed continuous variables are expressed as median and 25th–75th percentile.

P-values < 0.05 are depicted in bold.

MFAP4 = microfibrillar-associated protein 4, FBN1 = human fibrillin-1, PIIINP = procollagen III, hsTnT = high-sensitivity troponin-T, NT-pro BNP = N-Terminal Propeptide, IL-6 = interleukin-6, GDF-15 = growth-differentiation factor-15, hsCRP = high-sensitivity C-reactive protein, HDL = high-density lipoprotein, LDL = low-density lipoprotein, RDW = red cell distribution width, TSH = thyroid stimulating hormone, fT4 = free thyroxin, T4 = thyroxin, T3 = triiodothyronine, eGFR = estimated glomerular filtration rate

Appendix III. Plotting interaction with sex and MFAP4 and homocysteine

Appendix IV. Univariable and multivariable model clinical factors associated with TADmax.

Variable	Univariable analysis		Final multivariable model	
	Mean difference (95%CI) in TADmax per unit	P-value	Mean difference (95%CI) in TADmax per unit	P value
Age per 10 years*	1.400 (0.850-1.940)	<0.001	0.450 (-0.140-1.040)	0.137
Sex:Female*	-1.921 (-3.655—0.187)	0.030	-0.997 (-2.509-0.514)	0.194
Height (m)	-1.215 (-7.112-4.681)	0.684	-	-
Weight (kg)*	0.057 (0.012-0.103)	0.014	-	-
BSA (mm/m ²)	3.238 (-0.592-7.069)	0.097	-	-
Systolic blood pressure per 10 mmHg	0.251 (-0.227-0.729)	0.301	-	-
Diastolic blood pressure per 10 mmHg*	0.785 (0.060-1.510)	0.034	-	-
Hypertension	0.579 (-1.130-2.288)	0.504	-	-
Hyperlipidaemia*	3.642 (1.937-5.348)	<0.001	1.940 (0.279-3.600)	0.022
Active smoking	-1.992 (-4.850-0.867)	0.17	-	-
Diabetes*	4.340 (0.067-8.613)	0.047	-	-
CVA	0.705 (-2.547-3.957)	0.669	-	-
COPD	0.255 (-2.354-2.864)	0.847	-	-
BAV	0.037 (-4.690-4.764)	0.988	-	-
Renal dysfunction	1.484 (-3.236-6.205)	0.535	-	-
LVEF ¹ not normal vs normal	0.205 (-3.265-3.674)	0.907	-	-

Beta blocker use	1.051 (-0.710-2.812)	0.24	-	-
ARB use	3.043 (0.892-5.193)	0.006	-	-
ACEi use	0.563 (-1.527-2.654)	0.595	-	-
Diuretics	3.107 (0.888-5.325)	0.006	-	-
Cholesterol	3.159 (1.371-4.947)	<0.001	-	-
Antitrombotics	0.645 (-1.082-2.372)	0.461	-	-
Hereditary TAD diagnosis *	-6.184 (-7.899— 4.471)	<0.001	-4.873 (-6.771- - 2.975)	<0.001
Positive family history aortic disease	-2.802 (-4.453- - 1.151)	0.001	-	-
Abdominal aortic aneurysm	1.391 (-1.855-4.637)	0.399	-	-
Peripheral aneurysm	-1.132 (-3.735- 1.471)	0.392	-	-
Previous aortic surgery or aortic dissection	-1.435 (-3.490- 0.629)	0.17	-	-

*= variables entered in full model.

Estimates can be interpreted as follows: an increase in age of 10 years (one unit) results in a mean difference of 1.40 mm in TADmax.

BSA = body surface area, CVA = cerebrovascular accident, COPD = chronic obstructive pulmonary disease, BAV = bicuspid aortic valve, LVEF = left ventricle ejection fraction, ARB = angiotensin receptor blocker, ACEi = angiotensin-converting enzyme inhibitor, TAD = thoracic aortic disease

Appendix Va. –Univariable linear regression analysis circulating biomarkers excluding patients with prior aortic dissection or surgery (n=120)

Biomarker	Mean difference (95%CI) in TADmax per doubling of the standardized biomarker	P-value
MFAP4	-0.588 (-1.412-0.236)	0.160
FBN1	-0.021 (-0.849-0.808)	0.961
PIIINP	0.596 (-0.181-1.372)	0.131
HsTnT	0.773 (-0.030-1.575)	0.059
NT-pro BNP	-0.237 (-1.227-0.754)	0.636
IL-6	0.530 (-0.267-1.327)	0.190
hsCRP	-1.021 (-1.800- -0.243)	0.011
GDF-15	0.490 (-0.319-1.298)	0.233
Triglycerides	0.309 (-0.518-1.336)	0.496
Total cholesterol	0.409 (-0.518-1.336)	0.384
HDL	-0.362 (-1.257-0.532)	0.424
LDL	0.255 (-0.661-1.171)	0.582
Chol/HDL	0.573 (-0.336-1.482)	0.214
Homocysteine	0.373 (-0.433-1.179)	0.362
Haemoglobin	0.821 (-0.160-1.801)	0.100
RDW	0.368 (-0.622-1.359)	0.463
TSH	0.355 (-0.636-1.347)	0.478
fT4	-0.084 (-1.115-0.947)	0.872
T4	-0.761 (-1.837-0.315)	0.163
T3	-1.407 (-2.560- -0.255)	0.017
Creatinine	0.806 (-0.089-1.701)	0.077
eGFR	-0.868	0.082

	(-1.847-0.111)	
Ureum	0.210 (-0.703-1.122)	0.650

Estimates and corresponding 95% CI are derived from linear regression analysis with log₂ transformed and standardized biomarkers as independent variables, i.e. a doubling of the standardized MFAP4 value, results in a decrease of 0.588 mm in TAD_{max}.

P-values < 0.05 are depicted in bold.

CI = confidence interval, MFAP4 = microfibrillar-associated protein 4, FBN1 = human fibrillin-1, PIIINP = procollagen III, hsTnT = high-sensitivity troponin-T, NT-pro BNP = N-Terminal Propeptide, IL-6 = interleukin-6, GDF-15 = growth-differentiation factor-15, hsCRP = high-sensitivity C-reactive protein, HDL = high-density lipoprotein, LDL = low-density lipoprotein, RDW = red cell distribution width, TSH = thyroid stimulating hormone, fT4 = free thyroxin, T4 = thyroxin, T3 = triiodothyronine, eGFR = estimated glomerular filtration rate

Appendix Vb. - Univariable linear regression analysis biomarkers excluding patients with hereditary thoracic aortic disease (n=122)

	Mean difference (95%CI) in TADmax per doubling of the standardized biomarker	P-value
Biomarker		
MFAP4	-0.141 (-0.967-0.685)	0.736
FBN1	0.121 (-0.690-0.932)	0.768
PIIINP	0.017 (-0.749-0.784)	0.965
HsTnT	0.228 (-0.628-1.084)	0.599
NT-pro BNP	0.177 (-0.693-1.046)	0.688
IL-6	0.950 (0.186-1.713)	0.015
hsCRP	-0.416 (-1.230-0.397)	0.313
GDF-15	0.465 (-0.534-1.464)	0.359
Triglycerides	0.747 (-0.258-1.751)	0.144
Total cholesterol	0.019 (-0.873-0.911)	0.966
HDL	-0.396 (-1.300-0.508)	0.387
LDL	-0.071 (-0.918-0.775)	0.868
Chol/HDL	0.339 (-0.547-1.225)	0.450
Homocysteine	0.478 (-0.329-1.286)	0.243
Haemoglobin	0.386 (-0.542-1.313)	0.412
RDW	-0.131 (-1.024-0.762)	0.771
TSH	0.719 (-0.262-1.700)	0.148
ft4	0.702 (-0.709-1.313)	0.553
T4	0.582 (-0.555-1.719)	0.311
T3	-0.892 (-2.187-0.403)	0.174
Creatinine	0.474 (-0.383-1.330)	0.275
eGFR	-0.528 (-1.445-0.388)	0.256
Ureum	-0.308 (-1.185-0.569)	0.488

Estimates and corresponding 95% CI are derived from linear regression analysis with log₂ transformed and standardized biomarkers as independent variables, i.e. a doubling of the standardized MFAP4 value, results in a decrease of 0.141 mm in TADmax.

P-values < 0.05 are depicted in bold.

CI = confidence interval, MFAP4 = microfibrillar-associated protein 4, FBN1 = human fibrillin-1, PIIINP = procollagen III, hsTnT = high-sensitivity troponin-T, NT-pro BNP = N-Terminal Propeptide, IL-6 = interleukin-6, GDF-15 = growth-differentiation factor-15, hsCRP = high-sensitivity C-reactive protein, HDL = high-density lipoprotein, LDL = low-density lipoprotein, RDW = red cell distribution width, TSH = thyroid stimulating hormone, ft4 = free thyroxine, T4 = thyroxine, T3 = triiodothyronine, eGFR = estimated glomerular filtration rate

Appendix Vc. - Univariable linear regression analysis max thoracic aortic diameter – only CT (n=106)

	Mean difference (95%CI) in TADmax per doubling of the standardized biomarker	P-value
Biomarker		
MFAP4	-0.991 (-1.971- -0.010)	0.048
FBN1	-0.072 (-1.146-1.003)	0.895
PIIINP	0.305 (-0.586-1.196)	0.499
HsTnT	0.614 (-0.405-1.633)	0.235
NT-pro BNP	0.259 (-0.962-1.479)	0.675
IL-6	1.287 (0.360-2.214)	0.007
hsCRP	-0.263 (-1.232-0.705)	0.591
GDF-15	1.196 (0.125-2.268)	0.029
Triglycerides	1.032 (-0.072-2.135)	0.067
Total cholesterol	0.576 (-0.495-1.648)	0.288
HDL	-0.028 (-1.169-1.113)	0.961
LDL	0.248 (-0.837-1.333)	0.651
Chol/HDL	0.417 (-0.706-1.540)	0.463
Homocysteine	1.288 (0.141-2.434)	0.028
Haemoglobin	0.494 (-0.645-1.634)	0.391
RDW	0.359 (-0.792-1.510)	0.537
TSH	1.803 (0.097-3.508)	0.039
ft4	0.139 (-1.319-1.597)	0.849
T4	-0.477 (-1.819-0.865)	0.480
T3	-1.914 (-2.992- -0.836)	<0.001
Creatinine	1.370 (0.239-2.501)	0.018
eGFR	-2.052 (-3.141- -0.962)	<0.001
Ureum	0.623 (-0.515-1.761)	0.280

Estimates and corresponding 95% CI are derived from linear regression analysis with log₂ transformed and standardized biomarkers as independent variables, i.e. a doubling of the standardized MFAP4 value, results in a decrease of 0.991 mm in TADmax.

P-values < 0.05 are depicted in bold.

CI = confidence interval, MFAP4 = microfibrillar-associated protein 4, FBN1 = human fibrillin-1, PIIINP = procollagen III, hsTnT = high-sensitivity troponin-T, NT-pro BNP = N-Terminal Propeptide, IL-6 = interleukin-6, GDF-15 = growth-differentiation factor-15, hsCRP = high-sensitivity C-reactive protein, HDL = high-density lipoprotein, LDL = low-density lipoprotein, RDW = red cell distribution width, TSH = thyroid stimulating hormone, ft4 = free thyroxin, T4 = thyroxin, T3 = triiodothyronine, eGFR = estimated glomerular filtration rate