

Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

eTable 1. ICD-9 And ICD-10 Codes Used To Identify Syndromic Patients For Exclusion

ICD9	759.82	MARFANS SYNDROME
ICD10	Q87.4	MARFANS SYNDROME
ICD10	Q87.40	MARFANS SYNDROME UNSPECIFIED
ICD10	Q87.41	MARFANS SYNDROME W/CV MANIFESTATIONS
ICD10	Q87.410	MARFANS SYNDROME WITH AORTIC DILATION
ICD10	Q87.418	MARFANS SYNDROME W/OTH CV MANIFESTATIONS
ICD10	Q87.42	MARFANS SYNDROME WITH OCULAR MANIFESTATIONS
ICD10	Q87.43	MARFANS SYNDROME WITH SKELETAL MANIFESTATION
ICD10	Q79.6	EHLERS DANLOS SYNDROME
ICD9	758.6	TURNER SYNDROME
ICD10	Q96	TURNER SYNDROME
ICD10	Q96.0	KARYOTYPE 45 X
ICD10	Q96.1	KARYOTYPE 46 X ISO XQ
ICD10	Q96.2	KARYOTYPE 46 X W/ABNORMAL SEX CHROMOSOME NO ISO
ICD10	Q96.3	MOSAICISM 45 X/46 XX OR XY
ICD10	Q96.4	MOSAICISM 45 X/OTH CELL LINES W/ABN SEX CHROMOSM
ICD10	Q96.8	OTHER VARIANTS OF TURNERS SYNDROME
ICD10	Q96.9	TURNERS SYNDROME UNSPECIFIED
ICD10	Q87.89	LOEYS DIETZ SYNDROME

Note: We excluded all patients with known predisposition to TAA, whom we identified using a combination of manual review of health plan databases, including registries from cardiovascular genetics clinics, in combination with searches of relevant ICD-9/10 codes included in eTable1.

eMethods

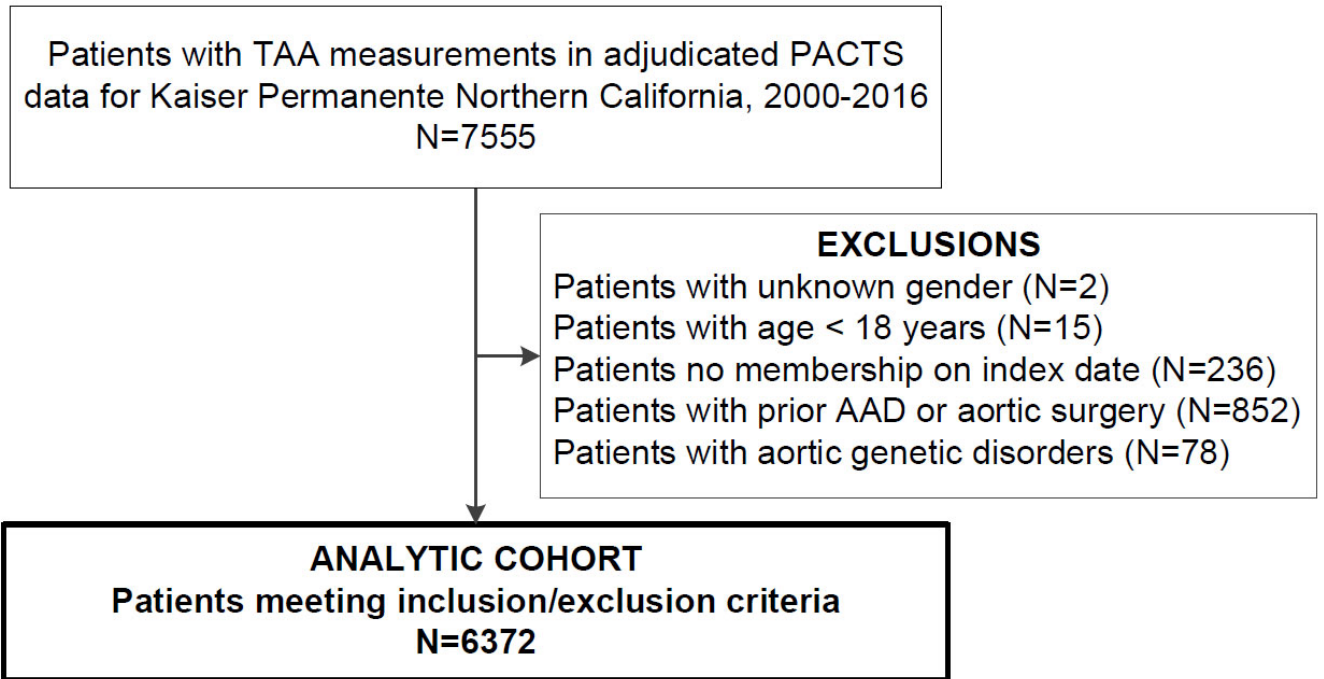
Covariates

We used health plan administrative and clinical data, pharmacy databases, and laboratory databases from our comprehensive KPNC EHR to obtain baseline demographics, medications, laboratory values, and vital signs for our study population. Race and ethnicity are self-reported in our data. Race refers to the categories of: African American/Black, Asian/Pacific Islander, White, Other, and Unknown. "Other" for race refers to any self-identification not listed previously, which may include Native American, a subset of Latino/a individuals who do not identify as one of the previously defined races, and multiracial. "Unknown" indicates missing race or ethnicity. Ethnicity is dichotomized as Hispanic vs. not-Hispanic.

Using validated algorithms,¹⁷⁻²¹ we identified multiple comorbid conditions before the index date acute myocardial infarction (AMI); unstable angina; ischemic stroke or transient ischemic attack; peripheral artery disease; mitral or aortic valve disease; atrial fibrillation; heart failure; coronary artery bypass surgery (CABG); percutaneous coronary intervention (PCI); hypertension; dyslipidemia; hospitalized bleed; liver disease; lung disease; thyroid disease; depression; cognitive impairment/dementia; diabetes mellitus; and history of abdominal aortic aneurysm.

Using pharmacy databases, we also identified receipt of relevant medications before the index date including angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, beta blockers, calcium channel blockers, diuretics, aldosterone receptor antagonists, hydralazine, vasodilators, alpha blockers, other hypertension medications, nitrates, statins, other lipid-lowering agents, non-aspirin antiplatelet agents, anticoagulants, digoxin, antiarrhythmic agents, diabetes therapies, and non-steroidal anti-inflammatory drugs (NSAIDs).

eFigure 1. Cohort Assembly



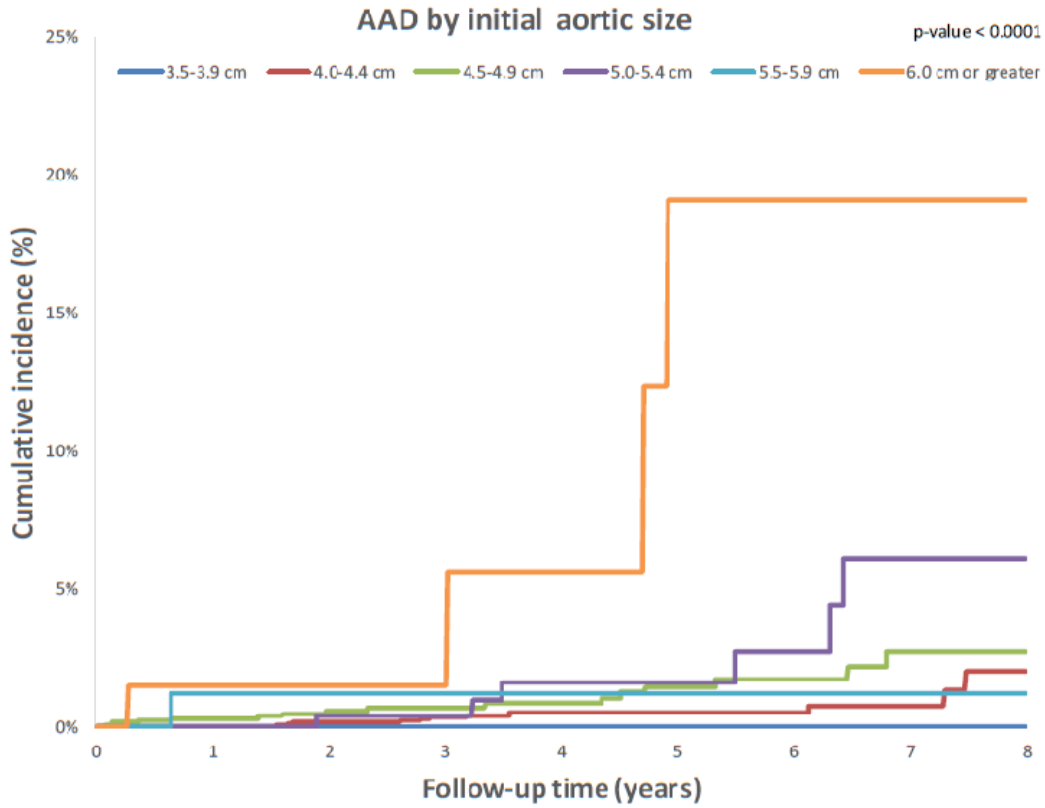
eTable 2. Additional Baseline Characteristics for Patients with Thoracic Aortic Aneurysm

	Overall (N=6372)	3.5-3.9 cm (N=726)	4.0-4.4 cm (N=3120)	4.5-4.9 cm (N=1698)	5.0-5.4 cm (N=548)	5.5-5.9 cm (N=156)	Over 6.0 cm (N=124)	P
Demographics								
Median (IQR) age, yr	69.2 (60.4-77.9)	68.8 (59.8-77.7)	68.8 (60.5-77.1)	69.6 (60.6-78.2)	69.9 (60.5-78.8)	68.2 (58.3-79.9)	76.8 (61.8-83.8)	<0.01
Age category, yr								<0.001
Age 21-49	498 (7.8)	69 (9.5)	231 (7.4)	127 (7.5)	45 (8.2)	12 (7.7)	14 (11.3)	
Age 50-64	1797 (28.2)	192 (26.4)	919 (29.5)	463 (27.3)	146 (26.6)	53 (34.0)	24 (19.4)	
Age 65-74	1962 (30.8)	237 (32.6)	985 (31.6)	530 (31.2)	152 (27.7)	36 (23.1)	22 (17.7)	
Age 75-84	1528 (24.0)	168 (23.1)	721 (23.1)	419 (24.7)	147 (26.8)	35 (22.4)	38 (30.6)	
Age ≥85	587 (9.2)	60 (8.3)	264 (8.5)	159 (9.4)	58 (10.6)	20 (12.8)	26 (21.0)	
Vital signs								
Systolic blood pressure category, mmHg								0.07
<120	2210 (34.7)	265 (36.5)	1069 (34.3)	592 (34.9)	201 (36.7)	53 (34.0)	30 (24.2)	
120-129	1335 (21.0)	137 (18.9)	674 (21.6)	361 (21.3)	110 (20.1)	26 (16.7)	27 (21.8)	
130-139	1656 (26.0)	198 (27.3)	831 (26.6)	416 (24.5)	120 (21.9)	49 (31.4)	42 (33.9)	
140-159	765 (12.0)	77 (10.6)	348 (11.2)	219 (12.9)	86 (15.7)	18 (11.5)	17 (13.7)	
160-179	159 (2.5)	20 (2.8)	77 (2.5)	35 (2.1)	19 (3.5)	4 (2.6)	4 (3.2)	
≥180	50 (0.8)	7 (1.0)	25 (0.8)	15 (0.9)	2 (0.4)	0 (0.0)	1 (0.8)	
Unknown	197 (3.1)	22 (3.0)	96 (3.1)	60 (3.5)	10 (1.8)	6 (3.8)	3 (2.4)	
Diastolic blood pressure category, mmHg								0.78
<80	4730 (74.2)	566 (78.0)	2277 (73.0)	1255 (73.9)	416 (75.9)	117 (75.0)	99 (79.8)	
81-84	564 (8.9)	58 (8.0)	287 (9.2)	158 (9.3)	45 (8.2)	10 (6.4)	6 (4.8)	
85-89	511 (8.0)	44 (6.1)	270 (8.7)	132 (7.8)	39 (7.1)	15 (9.6)	11 (8.9)	
90-99	275 (4.3)	27 (3.7)	144 (4.6)	67 (3.9)	28 (5.1)	6 (3.8)	3 (2.4)	
100-109	68 (1.1)	7 (1.0)	32 (1.0)	19 (1.1)	6 (1.1)	2 (1.3)	2 (1.6)	
≥110	26 (0.4)	2 (0.3)	14 (0.4)	7 (0.4)	3 (0.5)	0 (0.0)	0 (0.0)	
Unknown	198 (3.1)	22 (3.0)	96 (3.1)	60 (3.5)	11 (2.0)	6 (3.8)	3 (2.4)	
Body mass index category, kg/m ²								<0.001
<18.5	109 (1.7)	20 (2.8)	59 (1.9)	17 (1.0)	9 (1.6)	2 (1.3)	2 (1.6)	
18.5-24.9	1751 (27.5)	252 (34.7)	870 (27.9)	433 (25.5)	129 (23.5)	35 (22.4)	32 (25.8)	
25.0-29.9	2211 (34.7)	240 (33.1)	1072 (34.4)	614 (36.2)	196 (35.8)	47 (30.1)	42 (33.9)	
30.0-39.9	1754 (27.5)	156 (21.5)	855 (27.4)	488 (28.7)	166 (30.3)	52 (33.3)	37 (29.8)	
≥40	196 (3.1)	21 (2.9)	94 (3.0)	52 (3.1)	18 (3.3)	8 (5.1)	3 (2.4)	
Unknown	351 (5.5)	37 (5.1)	170 (5.4)	94 (5.5)	30 (5.5)	12 (7.7)	8 (6.5)	
Laboratory results								
Total cholesterol, mg/dL								0.26
>240	232 (3.6)	37 (5.1)	104 (3.3)	64 (3.8)	17 (3.1)	6 (3.8)	4 (3.2)	
200-240	839 (13.2)	98 (13.5)	420 (13.5)	208 (12.2)	80 (14.6)	20 (12.8)	13 (10.5)	
<200	3239 (50.8)	345 (47.5)	1580 (50.6)	875 (51.5)	301 (54.9)	74 (47.4)	64 (51.6)	
Unknown	2062 (32.4)	246 (33.9)	1016 (32.6)	551 (32.4)	150 (27.4)	56 (35.9)	43 (34.7)	
Low density lipoprotein, mg/dL								0.24

≥200	28 (0.4)	5 (0.7)	9 (0.3)	9 (0.5)	2 (0.4)	1 (0.6)	2 (1.6)
160-199	171 (2.7)	25 (3.4)	80 (2.6)	51 (3.0)	12 (2.2)	1 (0.6)	2 (1.6)
130-159	569 (8.9)	67 (9.2)	273 (8.8)	156 (9.2)	47 (8.6)	15 (9.6)	11 (8.9)
100-129	1286 (20.2)	142 (19.6)	655 (21.0)	316 (18.6)	115 (21.0)	40 (25.6)	18 (14.5)
70-99	1670 (26.2)	183 (25.2)	810 (26.0)	439 (25.9)	158 (28.8)	39 (25.0)	41 (33.1)
<70	808 (12.7)	85 (11.7)	390 (12.5)	234 (13.8)	75 (13.7)	12 (7.7)	12 (9.7)
Unknown	1840 (28.9)	219 (30.2)	903 (28.9)	493 (29.0)	139 (25.4)	48 (30.8)	38 (30.6)

eFigure 2. Cumulative Incidence of Aortic Dissection, All-Cause Mortality, and Elective Aortic Surgery, by Initial TAA size

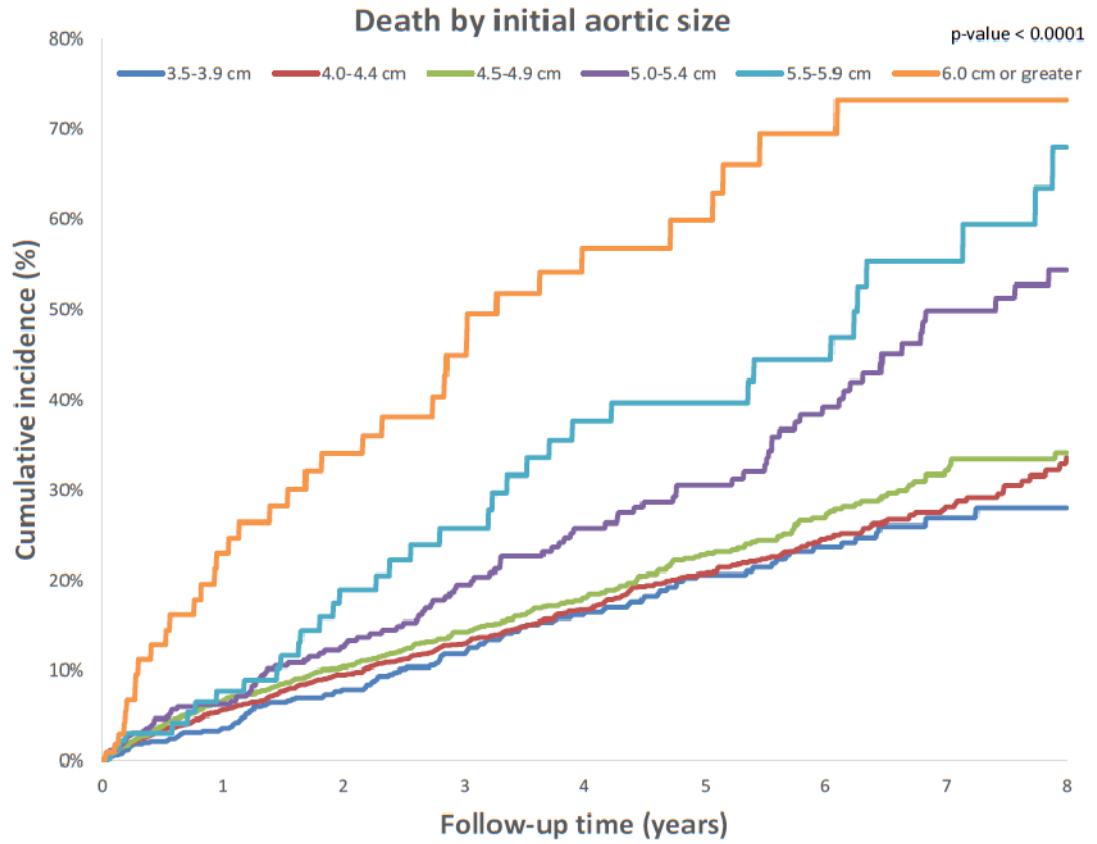
A. Aortic Dissection



Patients at risk									
	0	1	2	3	4	5	6	7	8
3.5-3.9 cm	726	630	503	400	304	219	155	76	43
4.0-4.4 cm	3120	2604	1954	1416	990	681	454	222	96
4.5-4.9 cm	1698	1312	996	782	566	400	285	164	95
5.0-5.4 cm	548	323	239	186	136	104	70	40	26
5.5-5.9 cm	156	76	54	40	31	25	22	12	7
6.0 cm or greater	124	45	33	24	16	12	8	4	1

Follow-up censored at end of study, disenrollment, death, or aortic surgery

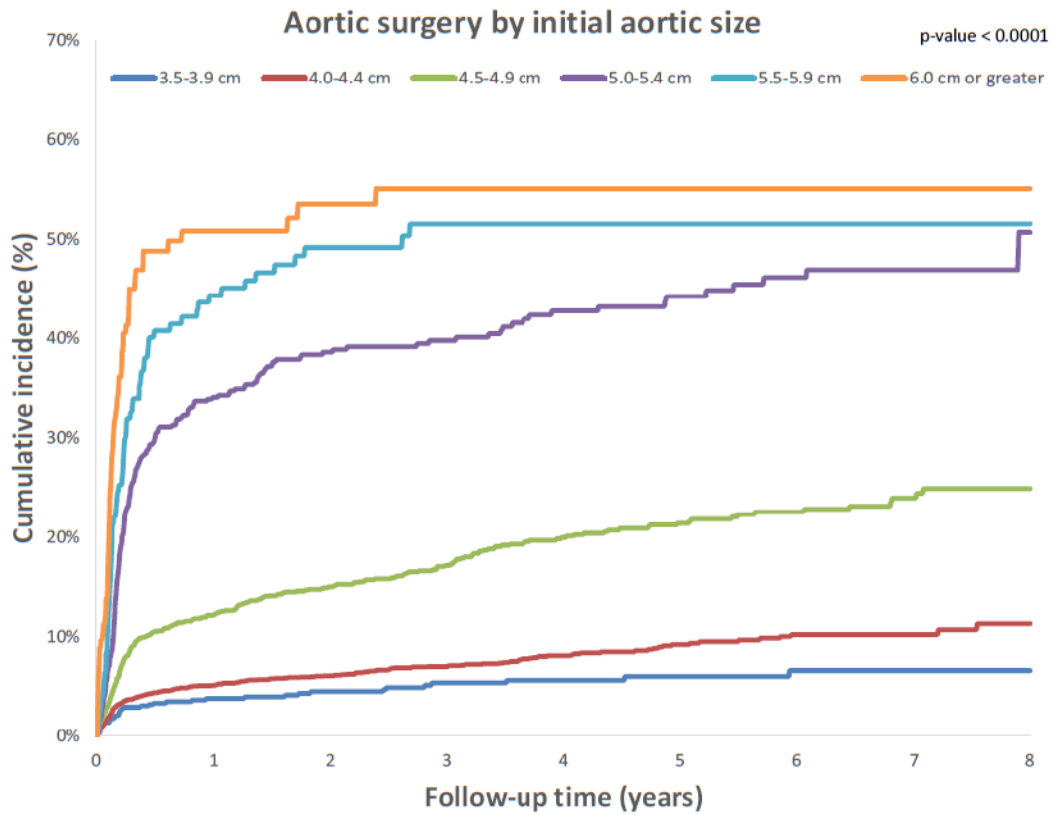
B. All-Cause Mortality



Patients at risk									
	0	1	2	3	4	5	6	7	8
3.5-3.9 cm	726	630	503	400	304	219	155	76	43
4.0-4.4 cm	3120	2605	1956	1418	992	683	455	223	96
4.5-4.9 cm	1698	1314	998	767	567	401	286	165	96
5.0-5.4 cm	548	323	239	186	136	104	70	40	26
5.5-5.9 cm	156	76	54	40	31	25	22	12	7
6.0 cm or greater	124	45	33	24	16	13	9	5	2

Follow-up censored at end of study, disenrollment, or aortic surgery

C. Receipt of Elective Aortic Surgery



Patients at risk

3.5-3.9 cm	726	630	503	400	304	219	155	76	43
4.0-4.4 cm	3120	2604	1954	1416	990	681	454	222	96
4.5-4.9 cm	1698	1312	996	766	566	400	285	164	95
5.0-5.4 cm	548	323	239	186	136	104	70	40	26
5.5-5.9 cm	156	76	54	40	31	25	22	12	7
6.0 cm or greater	124	45	33	24	16	12	8	4	1

Follow-up censored at end of study, disenrollment, death, or aortic dissection/rupture

eTable 3. Surgery among bicuspid aortic valve patients

Initial aortic size, cm	Total, N	BAV, N	BAV (%)	Total aortic surgeries, N (%)	Aortic surgeries in BAV patients, N (%)	% of Total surgeries accounted for by BAV patients
3.5-3.9	726	56	7.7	38 (5.2)	15 (26.8)	39.4
4.0-4.4	3120	269	8.6	237 (7.6)	83 (30.9)	35
4.5-4.9	1698	266	15.7	313 (18.4)	132 (49.6)	42.2
5.0-5.4	548	119	21.7	225 (41.1)	80 (67.2)	35.6
5.5-5.9	156	24	15.4	78 (50.0)	17 (70.8)	21.8
≥ 6.0	124	13	10.5	64 (51.6)	11 (84.6)	17.2

eTable 4. Model Discrimination Parameters (C-statistics) for Models Using Aortic Size vs Aortic Size Index

Model and Outcome	Aortic size	ASI
Baseline model - AD	0.8521 (0.7922-0.9120)	0.8596 (0.8021-0.9171)
Baseline model - AD/death	0.8215 (0.8053-0.8377)	0.8228 (0.8061-0.8396)
Time-varying model - AD	0.8538 (0.7973-0.9104)	0.8748 (0.8209-0.9287)
Time-varying model - AD/death	0.8213 (0.8052-0.8374)	0.8203 (0.8035-0.8372)

ASI = aortic size index; AD = aortic dissection

Note: For the ASI models, we used the categories <2.00, 2.00-2.74, 2.75-3.49, >=3.50 in our analyses as there were only 17 patients in the 4.25-4.99 and >= 5.00 categories, none of whom had an aortic dissection.

eTable 5. Multivariable Association of Initial Aortic Size Index (ASI) and Most Recent ASI Prior to Outcome with Clinical Outcomes

Aortic Dissection ^a					
	Initial ASI Models			Time Updated Models Using Most Recent ASI	
Aortic size index (cm/m ²)	Adjusted HR (95% CI)	P		Adjusted HR (95% CI)	P
< 2.00	(ref)			(ref)	
2.00-2.74	4.10 (1.29-13.03)	0.017		5.40 (1.47-19.88)	0.011
2.75-3.49	13.28 (3.12-56.49)	<0.001		47.44 (10.73-209.67)	<0.001
≥3.50	28.86 (3.79-219.85)	0.001		101.72 (16.46-628.62)	<0.001
Aortic Dissection or All-Cause Death ^b					
	Initial ASI Models			Time Updated Models Using Most Recent ASI	
Aortic size index (cm/m ²)	Adjusted HR (95% CI)	P		Adjusted HR (95% CI)	P
< 2.00	(ref)			(ref)	
2.00-2.74	1.34 (1.11-1.62)	0.002		1.78 (1.46-2.17)	<0.001
2.75-3.49	1.69 (1.29-2.20)	<0.001		2.51 (1.93-3.26)	<0.001
≥3.50	3.95 (2.69-5.79)	<0.001		5.36 (3.75-7.67)	<0.001

Abbreviations: ASI, aortic size index; HR, hazard ratio

a. Model adjusted for baseline variables of index age, gender, race, smoking status, BMI, heart rate, SBP, LDL, atrial flutter or fibrillation, peripheral artery disease, mitral or aortic valvular disease, heart failure, hypertension, dyslipidemia, diabetes mellitus, chronic lung disease, hypothyroidism, diagnosed depression, abdominal aortic aneurysm, and bicuspid aortic valve

b. Model adjusted for baseline variables of index age, gender, race, smoking status, BMI, heart rate, SBP, LDL, acute coronary syndrome, ischemic stroke, atrial flutter or fibrillation, peripheral artery disease, mitral or aortic valvular disease, heart failure, hypertension, dyslipidemia, diabetes mellitus, chronic liver disease, chronic lung disease, hypothyroidism, diagnosed depression, abdominal aortic aneurysm and bicuspid aortic valve

For the ASI models, we used the categories <2.00, 2.00-2.74, 2.75-3.49, ≥3.50 in our analyses as there were only 17 patients in the 4.25-4.99 and ≥ 5.00 categories, none of whom had an aortic dissection

