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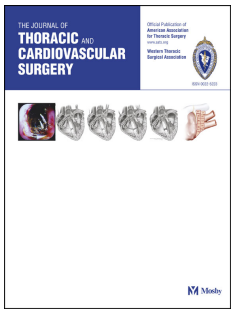

Aortic enlargement in two weeks is associated with subsequent aortic events in patients with type B acute aortic syndrome

Yutaro Miyoshi, MD, Shuichiro Kaji, MD, PhD, Akiko Masumoto, MD, Kitae Kim, MD, Takeshi Kitai, MD, PhD, Makoto Kinoshita, MD, PhD, Yutaka Furukawa, MD, PhD

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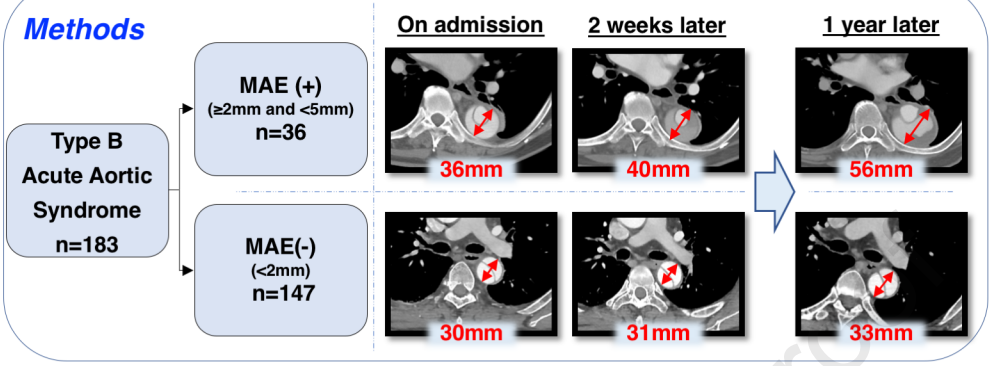
Graphical Abstract

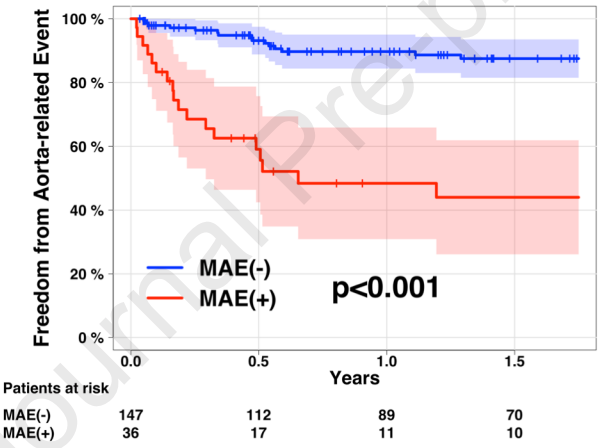
Moderate Aortic Enlargement (MAE) in 2 Weeks

Methods



Results

Aorta-related adverse event



Implications

Aortic enlargement in 2 weeks is associated with subsequent aorta-related adverse events in patients with uncomplicated type B acute aortic syndrome.

Aortic enlargement in two weeks is associated with subsequent aortic events in patients with type B acute aortic syndrome

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Department of Cardiovascular Medicine

Kobe City Medical Center General Hospital, Kobe, Japan

Authors' conflicts of interest: None

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Address for correspondence: Shuichiro Kaji, MD, PhD

Department of Cardiovascular Medicine, Kobe City Medical Center General Hospital, 2-1-1 Minatojima-minamimachi, Chuo-ku 650-0047, Kobe, Japan

Tel.: +81-78-302-4321, Fax: +81-78-302-2487

E-mail: skaji@theia.ocn.ne.jp

Date and number of IRB approval: 2/1/2021 and zn210222

The need to obtain informed consent was waived because of the retrospective nature of the study.

Manuscript word count: 2982 words, Structured abstract word count: 250 words

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Department of Cardiovascular Medicine

Kobe City Medical Center General Hospital, Kobe, Japan

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Address for correspondence: Shuichiro Kaji, MD, PhD

Department of Cardiovascular Medicine, Kobe City Medical Center General Hospital, 2-1-1 Minatojima-minamimachi, Chuo-ku 650-0047, Kobe, Japan

Tel.: +81-78-302-4321, Fax: +81-78-302-2487

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Keywords

aorta, acute aortic syndrome, imaging, prognosis, follow-up studies

Glossary of Abbreviations

AAS: acute aortic syndrome

AD: aortic dissection

IMH: intramural hematoma

TBAD: type B aortic dissection

TEVAR: thoracic endovascular aortic repair

OMT: optimal medical therapy

Central Message

Aortic enlargement in 2 weeks is associated with subsequent aorta-related adverse events in patients with uncomplicated type B acute aortic syndrome.

Perspective statement

Moderate aortic enlargement in two weeks is strongly associated with subsequent aorta-related adverse events in patients with uncomplicated type B acute aortic syndrome. These patients could be candidates for preemptive thoracic endovascular aortic repair.

Abstract

Objectives: This study aimed to determine whether aortic enlargement in 2 weeks in patients with type B acute aortic syndrome is associated with aorta-related adverse events.

Methods: This retrospective single-center study included 183 patients who were diagnosed with uncomplicated type B acute aortic syndrome (classic aortic dissection and intramural hematoma) between 2010 and 2019 and had follow-up computed tomography at second or third week. Aortic diameter was measured at admission and at pre-discharge follow-up. Aorta-related adverse events were defined by a composite of aortic rupture, surgical or endovascular aortic repair, re-dissection, severe intestinal malperfusion, and aortic enlargement.

Results: The patients whose aortic diameter enlarged ≥ 2 mm but < 5 mm in 2 weeks were categorized as moderate aortic enlargement group. During follow-up, 51 patients (28%) had aorta-related adverse events and 36 patients (20%) had moderate aortic enlargement. Patients with moderate aortic enlargement showed lower aorta-related event-free survival rates than those without moderate enlargement (48 ± 9% vs. 90 ± 3% at 1 year, p<0.001). On multivariable analysis, moderate aortic enlargement (subhazard ratio, 3.64; 95% confidence interval, 2.08–6.35; p < 0.001) and aortic diameter ≥ 40 mm

at admission (subhazard ratio, 2.96; 95% confidence interval, 1.60–5.48; $p < 0.001$) were associated with aorta-related adverse events.

Conclusions: Moderate aortic enlargement in 2 weeks is a significant risk factor of aorta-related adverse events in patients with uncomplicated type B acute aortic syndrome. Patients with moderate aortic enlargement should be followed up carefully and may be candidates for subsequent endovascular treatment.

(250 words)

INTRODUCTION

Stanford type B acute aortic syndrome (B-AAS), including classic aortic dissection (AD) and aortic intramural hematoma (IMH), is a life-threatening disease. Initial medical therapy and blood pressure control is recommended for patients with uncomplicated B-AAS [1, 2]. However, it has been reported that 5-year mortality in patients with B-AAS has remained at about 20% and considerable portion of patients who survived acute phase without complications have aorta-related events that need surgical repair or thoracic endovascular aortic repair (TEVAR) [3, 4]. Previous randomized trials, which compared the clinical outcomes in patients treated with optimal medical therapy (OMT) and those treated with TEVAR, suggest that preemptive TEVAR should be considered in uncomplicated B-AAS with suitable aortic anatomy [5, 6]. However, these trials failed to show improvement in early mortality in patients treated with TEVAR compared with those treated with OMT, which suggest the importance of patient selection in TEVAR. Thus, predicting the risk factors for future aorta-related adverse events in patients with uncomplicated B-AAS is crucial to determine a therapeutic strategy. Several clinical and imaging-related risk factors have been shown to be associated with early disease progression [7-12]. Of these, imaging-related risk factors are considered to be crucial. Although these imaging-related risk factors are

frequently useful to make clinical decisions, many of these are based on one-time image findings on admission and do not consider temporal changes in aortic size during the acute phase. Changes in aortic size in a short period of time might be a good prognostic indicator. In particular, the clinical significance of moderate aortic enlargement in the acute phase has not been well understood. The purpose of this study was to investigate whether moderate aortic enlargement is associated with aorta-related adverse events in patients with B-AAS.

METHODS

Patient Characteristics

We retrospectively reviewed 201 consecutive patients admitted to our hospital, who were diagnosed with uncomplicated type B acute aortic syndrome, defined as classic aortic dissection (AD) and intramural hematoma (IMH), between April 2010 and October 2019. Diagnoses were established by contrast-enhanced computed tomography (CT) at admission. Patients who had aortic enlargement ≥ 5 mm within 2 weeks were regarded as having complicated B-AAS and excluded from the study (n=7). In addition, patients in whom pre-discharge follow-up CT was not obtained at second or third week after the symptom onset were excluded (n=11). The reasons for missing CT examination during that period included early discharge (n=5), patients' unstable condition (n=2),

and unknown factors (n=4). Consequently, we retrospectively enrolled 183 patients in whom follow-up computed tomography (CT) was repeated between 7 and 20 days after the symptom onset before discharge (Figure 1). This study was approved by the institutional review board of Kobe City Medical Center General Hospital.(zn210222) The need to obtain informed consent was waived because of the retrospective nature of the study.

Treatment

All patients received medical therapy initially. The therapeutic goal was pain relief and control of systolic blood pressure under 120 mmHg. Intravenous calcium channel antagonist was mainly used in controlling blood pressure during the acute phase. Oral antihypertensive drugs such as calcium channel antagonists, β-blockers, and angiotensin-converting enzyme inhibitors were added in the acute and chronic phases. In general, plain or contrast-enhanced CT was repeated within a week and at the second or third week (pre-discharge follow-up) after the symptom onset. Patients were discharged unless they had any serious complication. During hospitalization or outpatient follow-up, surgical or endovascular aortic repair was performed in the case of aortic rupture or large aortic enlargement.

Clinical Follow-up and CT evaluation

The patients had follow-up visits at the outpatient clinic every 4 to 8 weeks after discharge to check the adequacy of blood pressure control and the presence of symptoms. Multi-detector row CT or magnetic resonance imaging (MRI) were performed at 1, 3, 6, and 12 months after discharge, and annually thereafter. Aorta-related adverse events were defined by a composite of aortic rupture, surgical or endovascular aortic repair, re-dissection, severe intestinal malperfusion, and aortic enlargement (≥ 55 mm or ≥ 5 mm per 6 months). Maximum aortic and false lumen diameters were measured in the same plane at the timing of admission, pre-discharge follow-up, and the last follow-up. AD was defined as a double-channel aorta that typically shows contrast enhancement or visible intimal tear. IMH was defined as crescentic aortic wall thickening without direct flow communication [11, 13, 14]. The location of maximum aortic diameter was decided by using visual inspection and was recorded subdividing into 5 segments: proximal descending thoracic aorta (PD), mid descending thoracic aorta (MD), distal descending thoracic aorta (DD), suprarenal abdominal aorta (SR), and infrarenal abdominal aorta (IR) as previously reported [11]. The CT scans were performed with various scanners with contiguous 2.5 to 10 mm thick sections. Axial images were used to measure diameters because it was easy to compare different images of the same patient. To adjust different follow-up timing, we calculated

adjusted aortic enlargement at 2 weeks by multiplying daily aortic growth rate by 14.

Statistical Analysis

Categorical variables were expressed as numbers and percentages and compared by chi-square test or Fisher's exact test, as appropriate. For the continuous variables, normality of distribution was tested using Shapiro-Wilk test. Normally distributed variables were expressed as mean and standard deviation (mean ± SD) and compared by unpaired *t* tests. Repeated measurements of aortic diameter during follow-up were compared by repeated analysis of variance. Non-normally distributed variables were expressed as median with interquartile range (IQR) and compared between the groups using Wilcoxon rank-sum test. For freedom from aorta-related events, Kaplan-Meier survival analysis was performed and differences between two groups were assessed using log-rank test. In addition, nonparametric estimates of cumulative incidence (probability of aorta-related adverse events) were calculated considering mortality as competing risk event. Survival regression used competing risk analysis with the Fine-Gray model. Results are presented as subhazard ratios (SHRs) and 95% confidence intervals (CIs). The following variables were selected: age, sex, Marfan syndrome, classic AD or IMH, hypertension, dyslipidemia, diabetes mellitus, smoking history, chronic obstructive pulmonary disease, hemodialysis, previous coronary artery disease,

previous stroke, aortic diameter ≥40mm[7, 12], true lumen diameter, false lumen thickness or hematoma thickness, true lumen diameter/false lumen thickness (TL/FL ratio) and aortic enlargement at 2 weeks. No patients had missing data on these variables. The variables whose proportional assumptions were generally fair and probability values were ≤ 0.10 on univariable analysis were included in the multivariable analysis. The multivariable model was constructed by stepwise variable selection using Akaike's information criterion. To evaluate multicollinearity, variance inflation factor was calculated for each variable, and the results were used to determine the final multivariable model. A receiver-operating characteristics (ROC) curve analysis was used for the calculation of cut-off values. Cut-off values were chosen based on the Youden index. The expect (E) value represents the minimum magnitude of association required between an unmeasured confounder and the exposure and outcome, which is conditional to measured covariates, to completely attenuate the observed exposure-outcome association [15]. An E value was calculated for the observed overall association between aortic enlargement and aorta-related events using a publicly available online calculator [16].

In all analyzes, a p-value of < 0.05 was considered statistically significant. All statistical analyzes were performed using SPSS Statistics version 25.0 (IBM Corp.,

Armonk NY, USA) or R package version 3.3.0 softwares.

RESULTS

Overall patient characteristics

Of the 201 patients, 7 patients who showed aortic enlargement ≥ 5 mm within 2 weeks after symptom onset were regarded as complicated B-AAS and excluded from the study. Pre-discharge follow-up CT scans were not obtained between 7 to 20 days after symptom onset in 11 patients, and they were also excluded. The study population consisted of 183 patients (126 men and 57 women) with a mean age of 70 (IQR: 59-81) years. Seventy patients (38%) were diagnosed with classic AD and 113 patients (62%) with IMH; 4 patients (2%) were diagnosed with or clinically suspected of Marfan syndrome. Pre-discharge follow-up CT scans were performed at a median of 14 days (7-20 days, interquartile range: 11-16 days) after the initial CT scans. Maximum aortic diameters in patients with aorta-related adverse events at admission, pre-discharge follow-up, and at the latest timing were 43 ± 10 mm, 44 ± 9 mm, and 48 ± 11 mm ($p<0.001$), respectively. As is the case with those without events, maximum aortic diameters at admission, pre-discharge follow-up, and at the latest timing were 37 ± 6 mm, 37 ± 6 mm, and 38 ± 7 mm ($p=0.14$), respectively. Clinical features and CT measurement of patients with aorta-related adverse event and those without events are

shown in Table 1. There were 4 patients with Marfan syndrome, including suspected cases. Clinical outcomes of these patients are summarized in Supplemental table 1.

In addition, aortic growth rate was different in acute and chronic phases. The mean aortic growth rate in the acute phase in patients with and without events were 1.8 mm/2 weeks (46.9 mm/year) and 0.31 mm/2 weeks (8.0 mm/year). On the other hand, the mean aortic growth rate in the chronic phase in patients with and without events were 0.26 mm/2 weeks (6.9 mm/year) and 0.01 mm/2 weeks (0.27 mm/year).

Aorta-related adverse events

Follow-up was completed in 139 patients and the median follow-up period was 2.1 years (range 0.02–10.7 years). A total of 44 (24%) patients were lost to follow-up. The reasons for lost follow-up were patients' refusal (n=23) and transfer to different hospital or clinic in another area (n=21). Comparison of patient characteristic between patients who were lost to follow-up and those who completed follow-up are shown in Supplemental table 2. Patients lost to follow-up had similar clinical demographics compared to those who were followed-up with respect to age, gender, comorbidities and aortic measurements except for prevalence of dyslipidemia and previous stroke. Moderate aortic enlargement was observed less frequently in the patients lost to follow-up compared to those who were followed up. Fifty-one patients (28%) had aorta-related

adverse events during follow-up. Of these, 4 (2%) had aortic rupture, 19 (10%) underwent surgical repair, 15 (8%) underwent endovascular repair, 2 (1%) had re-dissection, 4 (2%) had severe intestinal malperfusion, and 7 (4%) had aortic enlargement. Five patients died because of aortic rupture (n = 3) and severe intestinal malperfusion (n = 2).

Risk factors of aorta-related adverse events

ROC curve analysis identified adjusted aortic enlargement at 2 weeks ≥ 2.0 mm as a good cut-off for predicting aorta-related adverse events. Thus, we defined adjusted aortic enlargement at 2 weeks ≥ 2 mm and < 5 mm as moderate enlargement and aortic enlargement at 2 weeks < 2 mm as no or mild enlargement. A total of 36 patients (20%) had moderate aortic enlargement, while the other 147 patients (80%) had mild or no aortic enlargement (Figure 1). Figure 2 depicts Kaplan-Meier curves of aorta-related adverse events according to moderate aortic enlargement. Patients with moderate aortic enlargement showed lower aorta-related event-free survival rates than patients with no or mild enlargement (48 ± 9% vs. 90 ± 3% at 1 year, $p < 0.001$). The results of competing risk univariable and multivariable analyses for risk factors of aorta-related adverse events are shown in Table 2. In multivariable analysis with death as the competing risk, moderate aortic enlargement (SHR, 3.64; 95% confidence interval (CI),

223 2.08–6.35; $p < 0.001$) and aortic diameter ≥ 40 mm at admission (SHR, 2.96; 95% CI,
224 1.60–5.48; $p < 0.001$) were associated with aorta-related adverse events. Table 3
225 summarizes the relationship between moderate aortic enlargement with or without aortic
226 diameter ≥ 40 mm and aorta-related events. Figure 3 illustrates cumulative incidence of
227 aorta-related events with death as the competing risk according to moderate aortic
228 enlargement and aortic diameter ≥ 40 mm at admission. The 1-year cumulative
229 incidence of aorta-related events with death as the competing risk was higher in patients
230 with moderate aortic enlargement than those with no or mild enlargement (51 ± 9% vs.
231 10 ± 3% at 1 year, $p < 0.001$). Similarly, the 1-year cumulative incidence of aorta-
232 related events with death as the competing risk was higher in patients with aortic
233 diameter ≥ 40 mm at admission than those with aortic diameter < 40 mm (23 ± 5% vs.
234 16 ± 4% at 1 year, $p < 0.001$).

235 Subgroup analysis for aorta-related events according to disease entities of acute
236 aortic syndrome (IMH/classic AD) are shown in Table 4. There was no interaction
237 between IMH/classic AD and, moderate aortic enlargement and aortic diameter ≥40mm
238 at admission.

239 **Sensitivity analysis**

240 The E value for the adverse aorta-related events point estimate was high (5.01),

as was the E value for the 95% CI(3.22), indicating a less probability that an unmeasured variable explained the observed association between aortic enlargement and aorta-related events.

DISCUSSION

The main findings of the study were as follows; (1) one-fifth of patients with uncomplicated B-AAS had moderate aortic enlargement (≥ 2 mm and < 5 mm) at 2 weeks of onset. (2) moderate aortic enlargement at 2 weeks was associated with aorta-related adverse events in patients with uncomplicated B-AAS. (Figure 4)

Several imaging-related risk factors have been shown to be associated with early disease progression in patients with B-AAS, such as aortic diameter ≥ 40 mm [7, 12], false lumen diameter of the proximal descending aorta ≥ 22 mm [8], patent false lumen [17, 18], partially thrombosed false lumen [19], ulcer-like projection [11, 17], and large entry tear ≥ 10 mm in the proximal descending aorta [10]. Although these imaging-related risk factors are useful to predict future aortic events, all of these are based on one-time image findings during admission. Evaluating temporal change in aortic diameter might be more useful in predicting future aorta-related events. In the present study, moderate aortic enlargement in the acute phase had strong prognostic information. The possible explanation is that temporal change in aortic diameter might be strongly associated with

distensibility of dissected aortic wall. Our findings suggested that damaged dissected aorta with moderate enlargement might be more prone to adverse aorta-related events.

Previous studies showed that the rate of aortic enlargement in patients with B-AAS was reported as 1.35-3.3 mm/year [6, 20-22]. In the present study, the median of the chronic aortic enlargement rate was 0.91 mm/year, which was consistent with previous results. Although many studies reported chronic aortic growth rates, little is known about acute growth rates in patients with B-AAS. Besides, it is not well elucidated whether the aortic growth rate would be constant throughout acute and chronic phases. In this study, the median of the rate of acute aortic enlargement for first 2 weeks was larger than that of chronic phase. These results indicate that the rate of aortic enlargement might be different between the acute and chronic phases and aortic dilatation should be carefully monitored during first two weeks. Further studies are necessary for time course of aortic remodeling in B-AAS patients.

False lumen thrombosis is a crucial factor for predicting clinical outcome. In comparison with patients with patent or partially thrombosed false lumen, those with TBAD having closed and thrombosed false lumen, which are identical to IMH and characterized by the absence of intimal tear and continuous flow communication, have different clinical features and outcomes [18, 23]. We previously reported that patients with

277 type B IMH have better short- and long-term prognoses than patients with AD [17].
278 Compared to patients with AD, patients with IMH have less opportunity of branch
279 occlusion and subsequent malperfusion and more chance of aortic remodeling [17, 23, 24].
280 These clinical features may be associated with better clinical outcome. In the present
281 study, similar to previous studies, patent false lumen, which is observed in patients with
282 AD, was a significant risk factor and could be included into the final predictive model,
283 including large aortic diameter (≥ 40 mm) and moderate enlargement. Our result
284 suggested that false lumen status should be precisely assessed by serial CT images as well
285 as aortic diameter.

286 In the present study, we chose 2 weeks as the time interval for comparing aortic
287 diameter. This is partially because 1 week or less might be too short to detect significant
288 aortic remodeling. Besides, in the clinical settings, patients' poor conditions including
289 deoxygenation, systemic inflammatory responses, and acute renal failure may hamper
290 pre-discharge follow-up CT within a week after the symptom onset. Thus, we suggest
291 that evaluation of aortic diameter at 2 weeks is reasonable and clinically appropriate.

292 **Study limitations**

293 This study has several limitations. First, we evaluated aortic diameters by
294 conventional axial CT images. Recently, measurement in aortic axial images with three-

dimensional reconstruction has been recommended. However, to measure aortic diameters at the same positions through various timings in one patient, conventional axial CT images would be more accurate due to difficulty in matching the measured position in aortic axial images. Second, the timing of follow-up CT was not predetermined due to retrospective nature of the study. In order to adjust the follow-up timing, we included patients in whom follow-up CT images were obtained between the second and third week after symptom onset. In addition, we adjusted aortic enlargement with the follow-up timing, assuming that aortic growth rate is constant during the second to third week after the symptom onset. Aortic enlargement during this period might not be constant even in uncomplicated patients. Third, this study is a single-center retrospective study. Because of the retrospective study design, 44 (24%) patients were lost to follow-up, which might have affected the study results. Patients who were lost to follow-up, however, had comparable clinical characteristics to those who were followed up. Thus, it is unlikely that the patients lost to follow-up had a greater rate of aorta-related events than those who completed followed-up. Further prospective studies with multi-center settings might be necessary.

Conclusions

Moderate aortic enlargement in 2 weeks is a significant risk factor of aorta-related

313 adverse events in patients with uncomplicated B-AAS. Considering strong prognostic

314 information, patients with moderate aortic enlargement could be regarded as

315 complicated cases and might be possible candidates for preemptive TEVAR.

316

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Tables

Table 1. Baseline characteristics of patients according to aorta-related adverse events

	Event (+) (n=51)	**Event (-) (n=132)**	***P* value**
Age, years, median (IQR)	70 (56-80)	71 (60-82)	0.29
Male, n (%)	41 (80%)	85 (64%)	0.04
Marfan syndrome, n(%)	2 (4%)	2 (2%)	0.31
Hypertension, n (%)	43 (84%)	113 (86%)	0.83
Dyslipidemia, n (%)	21 (41%)	48 (36%)	0.55
Diabetes Mellitus, n (%)	6 (12%)	24 (18%)	0.29
COPD, n(%)	1 (2%)	6 (5%)	0.37
Hemodialysis, n(%)	1 (2%)	0 (0%)	0.28
Previous coronary artery disease, n (%)	9 (18%)	9 (7%)	0.03
Previous stroke, n (%)	7 (14%)	4 (3%)	0.01
Smoking history, n (%)	22 (43%)	54 (41%)	0.78
Classic aortic dissection, n (%)	31 (61%)	39 (30%)	<0.001

Maximum aortic diameter (mm)			
at admission	43±10	37±6	<0.001
pre-discharge follow-up	44±9	37±6	<0.001
latest follow-up	48±11	38±7	<0.001
False lumen thickness* (mm)	16±8	12±5	<0.001
True lumen diameter (mm)	26±10	25±6	0.49
True lumen/false lumen ratio	2.2±1.7	2.4±1.1	0.30
Adjusted aortic enlargement (for 2 weeks)			
2-5 mm	24 (47%)	12 (9%)	<0.001
0-2 mm	15 (29%)	77 (58%)	<0.001
< 0 mm	12 (24%)	43 (33%)	0.23

384 COPD: chronic obstructive pulmonary disease; IQR: interquartile range

385 * hematoma thickness in patients with intramural hematoma.

386 **Table 2. Competing risk univariable and multivariable analyses of risk factors of adverse aorta-related events**

	Univariable model			Multivariable model	
	Subhazard Ratio (95% CI)	***P****		**Subhazard Ratio (95% CI)**	***P****
Age (≥ 75 years)	1.51 (0.86–2.64)	0.15			
Male	1.74 (0.86–3.55)	0.13			
Marfan syndrome	1.64 (0.34–7.86)	0.54			
Hypertension	0.76 (0.36–1.63)	0.49			
Dyslipidemia	1.42 (0.81–2.49)	0.22			
Diabetes Mellitus	0.76 (0.32–1.77)	0.52			
Smoking history	1.26 (0.72–2.18)	0.42			
Chronic obstructive pulmonary disease	0.96 (0.12–7.84)	0.97			

Hemodialysis	10.3 (6.29–16.70)	<0.001			
Previous Coronary artery disease	3.01 (1.39–6.53)	0.005		2.34 (0.90–6.07)	0.08
Previous stroke	2.3 (1.14–4.64)	0.02			
Classic aortic dissection**	2.44 (1.40–4.26)	0.002		3.12 (1.75–5.54)	<0.001
Aortic diameter ≥ 40 mm at admission	2.75 (1.57–4.82)	<0.001		2.96 (1.60–5.48)	<0.001
False lumen thickness	1.06 (1.03–1.09)	<0.001			
True lumen diameter	1.02 (0.98–1.07)	0.30			
True lumen/false lumen ratio	0.88 (0.68–1.15)	0.36			
Moderate aortic enlargement	4.55 (2.56–8.10)	<0.001		3.64 (2.08–6.35)	<0.001

387 * The Fine-Gray model with death as competing risk; CI: confidence interval.

388 ** Reference: aortic intramural hematoma

Table 3. Aorta-related adverse events according to moderate aortic enlargement in 2 weeks and aortic diameter at admission

	Total n=183	**Event (+)** n=51	**Event (-)** n=132	***P* value**
Moderate aortic enlargement (+) and aortic diameter ≥40mm	15 (8%)	10 (20%)	5 (4%)	0.001
Moderate aortic enlargement (+) and aortic diameter <40mm	21 (11%)	14 (28%)	7 (5%)	<0.001
Moderate aortic enlargement (-) and aortic diameter ≥40mm	54 (30%)	19 (37%)	35 (27%)	0.15
Moderate aortic enlargement (-) and aortic diameter <40mm	93 (51%)	8 (16%)	85 (64%)	<0.001

Table 4. Subgroup analysis for aorta-related events between intramural hematoma and classic aortic dissection

	IMH (n=113)		AD (n=70)		
	Subhazard Ratio (95% CI)	***P****	**Subhazard Ratio (95% CI)**	***P****	***P* for interaction**
Age (≥ 75 years)	1.76 (0.71–4.35)	0.22	1.92 (0.86–4.26)	0.11	0.73
Male	2.12 (0.70–6.40)	0.18	1.22 (0.47–3.19)	0.69	0.48
Marfan syndrome	NA	NA	1.07 (0.23–4.96)	0.93	NA
Hypertension	1.43 (0.33–6.16)	0.63	0.55 (0.23–1.27)	0.16	0.23
Dyslipidemia	1.33 (0.53–3.33)	0.54	1.37 (0.66–2.86)	0.40	0.93
Diabetes Mellitus	0.30 (0.04–2.07)	0.22	1.11 (0.39–3.19)	0.84	0.25
Smoking history	1.02 (0.43–2.42)	0.96	2.01 (0.97–4.19)	0.06	0.24

COPD	NA	NA	16.54 (6.26–43.68)	<0.001	NA
Hemodialysis	16.69 (7.54–36.91)	<0.001	NA	NA	NA
Previous Coronary artery disease	5.45 (2.09–14.19)	<0.001	2.41 (0.48–12.2)	0.29	0.50
Previous stroke	3.28 (1.73–6.22)	<0.001	1.76 (0.40–7.77)	0.46	0.44
Aortic diameter ≥ 40 mm at admission	3.86 (1.49–9.98)	0.005	2.61 (1.21–5.61)	0.01	0.47
False lumen thickness	1.08 (1.03–1.13)	<0.001	1.03 (1.00–1.07)	0.06	0.09
True lumen diameter	1.10 (1.03–1.17)	0.003	1.03 (0.99–1.08)	0.18	0.12
True lumen/false lumen ratio	1.16 (0.82–1.64)	0.42	0.98 (0.58–1.65)	0.93	0.63
Moderate aortic enlargement	3.35 (1.33–8.45)	0.01	4.76 (2.26–10.03)	<0.001	0.55

* The Fine-Gray model with death as competing risk; CI: confidence interval; COPD: chronic obstructive pulmonary disease

Figure Legends

Central Picture Legend:

Freedom from aorta-related adverse events with/without moderate aortic enlargement (MAE).

Figure 1:

Flow chart of patient selection and distribution of patients with and without moderate aortic enlargement. Moderate aortic enlargement is defined as aortic enlargement at 2 weeks ≥ 2 mm and < 5 mm. B-AAS indicates type B acute aortic syndrome.

Figure 2:

Kaplan-Meier curves for freedom from aorta-related adverse events between patients with and without moderate aortic enlargement in 2 weeks. MAE indicates moderate aortic enlargement, which is defined as aortic enlargement at 2 weeks ≥ 2 mm and < 5 mm.

Figure 3:

Considering non-aorta-related death as the competing risk, cumulative incidence of aorta-related adverse events between patients with and without moderate aortic enlargement in 2 weeks (A) and between patients with aortic diameter on admission ≥40mm and <40mm (B). MAE indicates moderate aortic enlargement, which is defined

as aortic enlargement at 2 weeks ≥ 2 mm and < 5 mm.

Figure 4:

In type B acute aortic syndrome, patients who showed moderate aortic enlargement (≥ 2 mm and < 5 mm) in 2 weeks had lower aorta-related event-free survival rates than those without moderate enlargement (<2 mm). Aortic enlargement in 2 weeks is associated with subsequent aorta-related adverse events in patients with uncomplicated type B acute aortic syndrome.

Supplemental Video:

Two model cases with/without moderate aortic enlargement.

Supplemental table 1. Clinical outcome of patients with Marfan syndrome

Case	Age	Sex	Comorbidity	Aortic enlargement at 2 weeks	Aortic diameter at admission	Classic AD or IMH	Aorta-related event
1	51	Female	Hypertension	0.2 mm	26 mm	IMH	None
2	47	Female	Hypertension, smoking	1.4 mm	27 mm	Classic AD	Surgical aortic repair
3	35	Male	Hypertension, dyslipidemia	0.8 mm	36 mm	Classic AD	TEVAR
4	31	Female	None	1.0 mm	25 mm	Classic AD	None

AD: aortic dissection; IMH: intramural hematoma; TEVAR: thoracic endovascular aortic repair

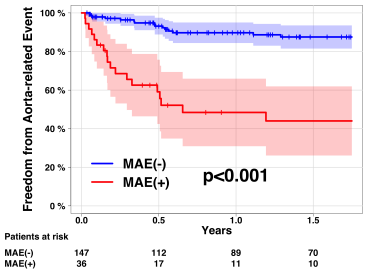
Supplemental Table 2. Baseline characteristics between patients who were lost to follow-up and followed-up

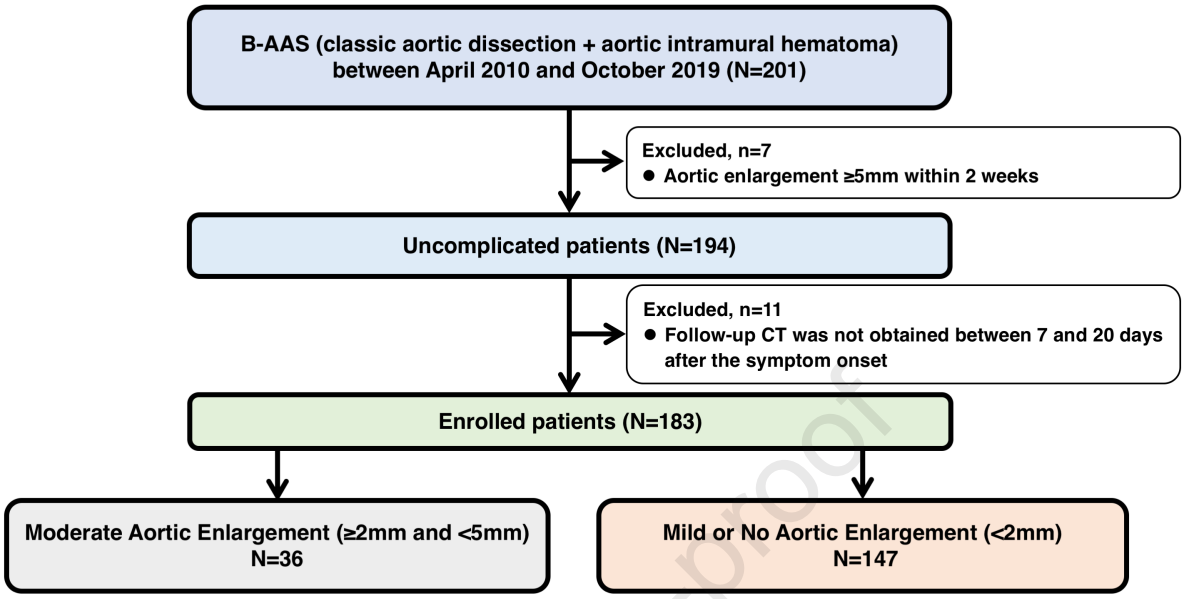
	Lost to follow-up group (n=44)	**Followed-up group (n=139)**	***P* value**
Age, years, median (IQR)	76 (59-82)	69 (59-80)	0.22
Male, n (%)	31 (70%)	95 (68%)	0.79
Marfan syndrome, n(%)	0 (0%)	4 (3%)	0.33
Hypertension, n (%)	37 (84%)	119 (86%)	0.80
Dyslipidemia, n (%)	10 (23%)	59 (42%)	0.02
Diabetes Mellitus, n (%)	4 (9%)	26 (19%)	0.13
COPD, n(%)	2 (5%)	5 (4%)	0.53
Hemodialysis, n(%)	0 (0%)	1 (1%)	0.76
Previous coronary artery disease, n (%)	2 (5%)	16 (12%)	0.14
Previous stroke, n (%)	0 (0%)	11 (8%)	0.04
Smoking history, n (%)	19 (43%)	57 (41%)	0.80
Classic aortic dissection, n (%)	17 (39%)	53 (38%)	0.95

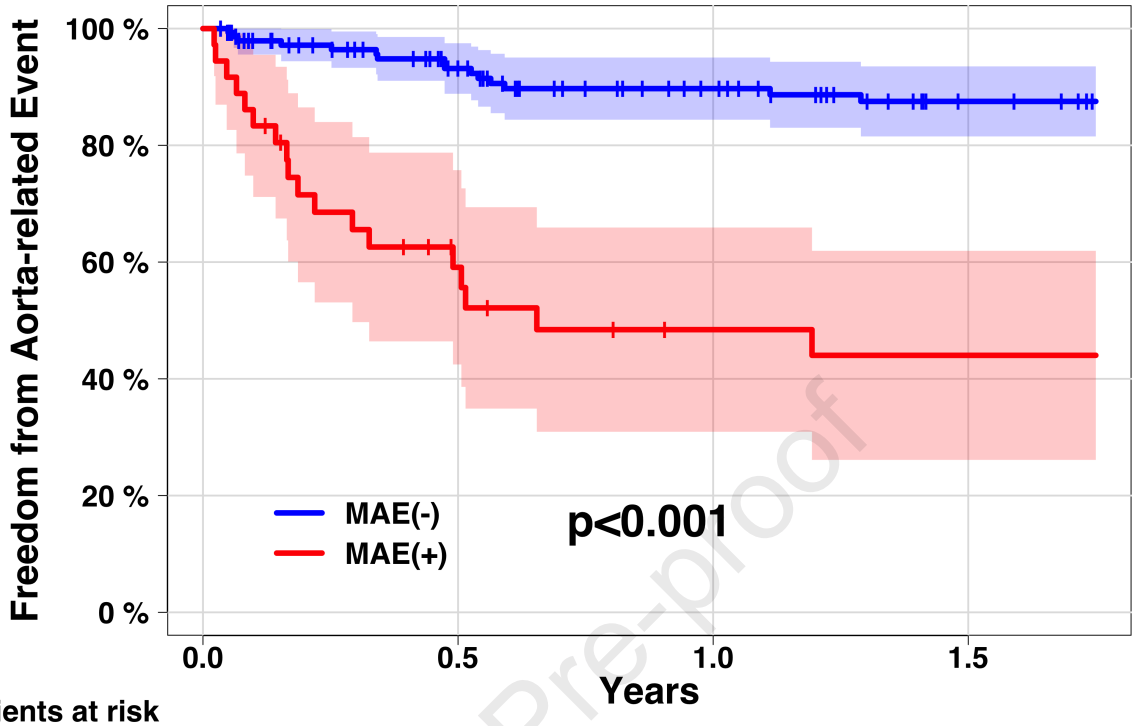
Maximum aortic diameter (mm)			
at admission	40±8	38±8	0.36
pre-discharge follow-up	40±8	39±8	0.47
latest follow-up	40±8	40±10	0.99
False lumen thickness* (mm)	14±7	13±6	0.38
True lumen diameter (mm)	26±7	25±8	0.80
True lumen/false lumen ratio	2.2±1.2	2.4±1.4	0.44
Adjusted aortic enlargement (for 2 weeks)			
2-5 mm	4 (9%)	32 (23%)	0.04
0-2 mm	25 (57%)	67 (48%)	0.32
< 0 mm	15 (34%)	40 (29%)	0.50
Others			
Follow-up period, years, median (IQR)	1.4 (0.4-2.7)	2.4 (0.8-4.3)	0.009
Aorta-related adverse events	6 (14%)	45 (32%)	0.016

COPD: chronic obstructive pulmonary disease; IQR: interquartile range

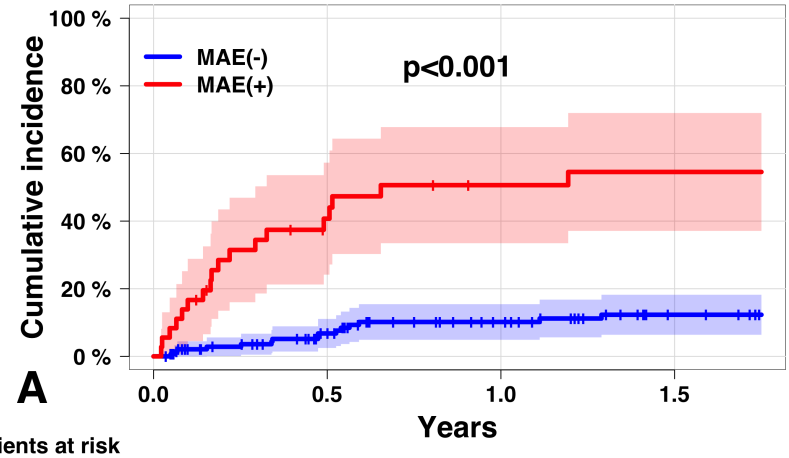
* hematoma thickness in patients with intramural hematoma







Patients at risk				
MAE(-)	147	112	89	70
MAE(+)	36	17	11	10



Patients at risk

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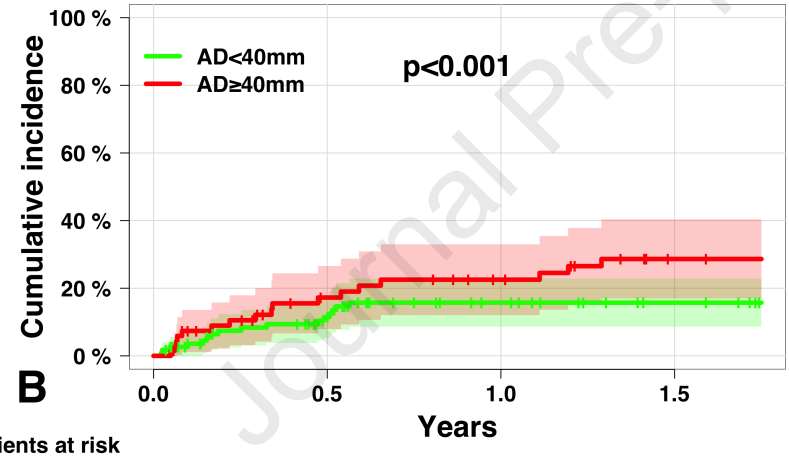


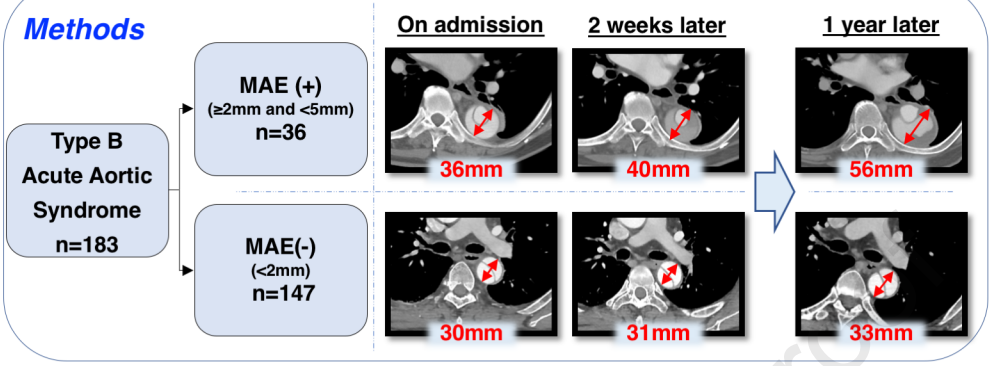
Patients at risk

AD<40mm	114	82	62	52
AD≥40mm	69	47	38	28

Graphical Abstract

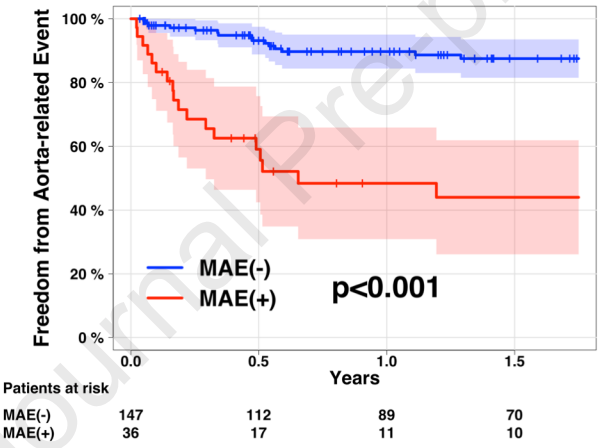
Moderate Aortic Enlargement (MAE) in 2 Weeks

Methods



Results

Aorta-related adverse event



Implications

Aortic enlargement in 2 weeks is associated with subsequent aorta-related adverse events in patients with uncomplicated type B acute aortic syndrome.