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ORIGINAL ARTICLE

Relationship Between Heart Rate at Discharge and Long-Term Outcomes of Surgically Treated Patients With Type A Acute Aortic Dissections

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Background: Resting heart rate (HR) at discharge is an important predictor of mortality after acute myocardial infarction. However, in patients with Stanford type A acute aortic dissections (TA-AADs), the relationship between HR and long-term outcomes is unclear. Therefore, this relationship was investigated in the present study.

Methods and Results: Surgically treated consecutive patients with TA-AAD (n=721) were retrospectively categorized according to HR quartiles, recorded within 24 h before discharge (<70, 70–77, 78–83, and ≥84 beats/min). The study endpoints included aortic aneurysm-related deaths, sudden deaths, aortic surgeries, and hospitalizations for recurrence of acute aortic dissections. The mean (±SD) patient age was 65.8±13.0 years. During a median observation period of 5.8 years (interquartile range 3.9–8.5 years), 17.2% of patients (n=124) experienced late aortic events. Late aortic surgery was performed in 14.0% of patients. After adjusting for potential confounders, including *β*-blocker use, HR at discharge remained an independent predictor of long-term aortic outcomes. Patients with discharge HR ≥84 beats/min had a higher risk (hazard ratio 1.86; 95% confidence interval 1.06–3.25; P=0.029) of long-term aortic events than those with HR <70 beats/min; the cumulative survival rates were similar among the groups (log-rank, P=0.905).

Conclusions: In surgically treated patients with TA-AAD, HR at discharge independently predicted long-term aortic outcomes. Consequently, HR in patients with TA-AAD should be optimized before discharge, particularly if the HR is ≥84 beats/min.

Key Words: Aortic outcome; Discharge; Heart rate; Long term; Stanford type A acute aortic dissection

Despite recent improvements in diagnostic imaging, perioperative management, and operative techniques for Stanford type A acute aortic dissections (TA-AADs), the in-hospital mortality of patients with TA-AADs remains high, even after surgical treatment.[1–3] Furthermore, residual aortic dissection in the distal aorta, after surgical repair of a TA-AAD, poses a potential risk for reoperation or late death due to aneurysm formation or rupture.[4–6] Therefore, long-term regular assessments and optimal medical management may be required to prevent late aortic adverse events.

Numerous epidemiological studies have demonstrated a significant association between resting heart rate (HR) and various cardiovascular diseases, including acute myocardial infarction (AMI), heart failure, and left ventricular dysfunction.[7–9] Several clinical studies have reported that an increased HR is associated with an increased risk of mortality in patients with AMI or heart failure. Moreover, recent studies have reported that HR at discharge is an important predictor of long-term mortality in patients with AMI.[8,9] However, the relationship between the HR and long-term outcomes in patients with acute aortic dissections (AADs) is not well understood.

Therefore, we conducted this retrospective analysis to determine the correlation between HR at discharge and the long-term outcomes of TA-AAD.

Methods

Study Population and Data Collection

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and the guidelines

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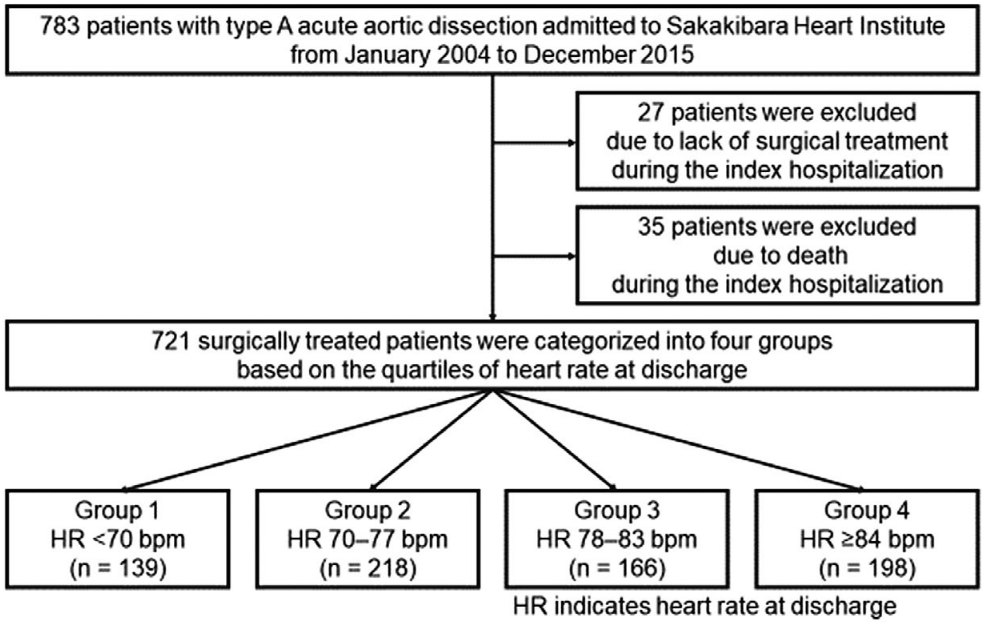


Figure 1. Flow chart for the selection and categorization of the study population. HR, heart rate.

of the Japanese Ministry of Health, Labour, and Welfare. The Institutional Review Board of the Sakakibara Heart Institute approved this retrospective study (Reference no. 19-066), and all patients provided written informed consent to use their medical records for research purposes.

We retrospectively analyzed the data of 783 consecutive patients with TA-AADs who were admitted to the Sakakibara Heart Institute between January 2004 and December 2015. Aortic dissection was diagnosed using enhanced computed tomography (CT) and categorized according to the Stanford classification.[10] Of these 783 patients, 27 did not undergo surgical treatment and 35 died during the index hospitalization. These 62 patients were excluded from further analysis (in-hospital mortality rate 4.4%). The remaining 721 patients who underwent surgical treatment during the index hospitalization were divided into 4 groups (quartiles) based on HR at discharge (Group 1, <70 beats/min; Group 2, 70–77 beats/min; Group 3, 78–83 beats/min; and Group 4, ≥84 beats/min), and each group's long-term clinical outcomes were investigated. Because our aim was to evaluate how HR at discharge was associated with the long-term risk of aortic events, patients were categorized into discharge HR quartiles, where discharge HR was defined as the last recorded HR, measured within 24 h before discharge from hospital.

In principle, we considered a TA-AAD to be an indication for surgery; however, conservative management was selected in the presence of a completely thrombosed false lumen, an ascending aortic diameter <50 mm, and a stable hemodynamic state, without pericardial effusion.

Clinical data (patient demographic characteristics, presentation histories, clinical presentations, physical examinations, laboratory findings, echocardiogram findings, details of medical and surgical treatments, hospital outcomes, and follow-up) were collected.

Follow-up

All patients were followed up through outpatient clinic visits or telephonic interviews using a standardized questionnaire. The follow-up period was defined as the time between admission and the event or the last follow-up; patients not reaching an endpoint were censored. The study endpoint was defined as an aortic event, including aortic aneurysm-related death, any sudden death, aortic surgery, or hospitalization for AAD recurrence. Any sudden death was considered to be an aneurysm-related death because of the difficulty in completely ruling out a residual aneurysm rupture as the cause of sudden death. Aortic surgery was performed due to aortic dilatation, aortic rupture, anastomotic pseudoaneurysm, or infection. The flow chart for patient selection is shown in **Figure 1**.

Definitions

A communicating aortic dissection was defined as one with a connection between the true and false lumens, confirmed using enhanced CT. However, a non-communicating aortic dissection was defined as one that was completely thrombosed, with a false lumen and without a connection between the true and false lumens. Hypertension was defined based on a history of antihypertensive medication use. Diabetes was defined either based on a history of antidiabetic medication use or a history of HbA1c ≥6.5%. Dyslipidemia was defined either on the basis of a blood total cholesterol level ≥220 mg/dL or a history of relevant medication use. Coronary artery disease was defined based on a history of percutaneous coronary intervention, coronary artery bypass graft, or old myocardial infarction. Cerebrovascular disease was defined based on a history of stroke; peripheral artery disease was defined as a confirmed history of endovascular treatment, bypass, or an ankle-brachial pressure index <0.9. A known aortic aneurysm was defined as an aortic

Table 1. Baseline Characteristics of the Patients

	All patients (n=721)	HR at discharge quartiles				P value
		Group 1 (n=139)	Group 2 (n=218)	Group 3 (n=166)	Group 4 (n=198)	
HR at discharge (beats/min)	77.2±10.7	63.1±4.1	71.8±2.0	79.6±1.3	91.0±6.3	
Demographics at admission						
Age (years)	65.8±13.0	68.9±12.7	65.6±13.3	65.3±13.5	64.4±12.0	0.014
Female sex	347 (48.1)	70 (50.4)	111 (50.9)	75 (45.2)	91 (46.0)	0.592
BMI (kg/m²)	23.5±3.9	23.3±3.7	23.6±3.9	23.4±3.7	23.9±4.0	0.526
Communicating type	516 (71.6)	101 (72.7)	149 (68.3)	122 (73.5)	144 (72.7)	0.663
Hypertension	589 (81.7)	113 (81.3)	177 (81.2)	137 (82.5)	162 (81.8)	0.989
Diabetes	44 (6.1)	7 (5.0)	15 (6.9)	5 (3.0)	17 (8.6)	0.140
Dyslipidemia	188 (26.1)	27 (19.4)	58 (26.6)	46 (27.7)	57 (28.8)	0.229
ESRD	7 (1.0)	0 (0)	1 (0.5)	4 (2.4)	2 (1.0)	0.175
COPD	20 (2.8)	4 (2.9)	8 (3.7)	3 (1.8)	5 (2.5)	0.759
Coronary artery disease	39 (5.4)	7 (5.0)	10 (4.6)	13 (7.8)	9 (4.5)	0.514
Cerebrovascular disease	64 (8.9)	14 (10.0)	18 (8.3)	23 (13.9)	9 (4.5)	0.016
Peripheral artery disease	6 (0.8)	0 (0)	2 (0.9)	2 (1.2)	2 (1.0)	0.707
AF on admission	35 (4.9)	7 (5.0)	12 (5.5)	10 (6.0)	6 (3.0)	0.526
Prior aortic dissection	17 (2.4)	4 (2.9)	5 (2.3)	3 (1.8)	5 (2.5)	0.937
Known aortic aneurysm	48 (6.7)	14 (10.1)	18 (8.3)	8 (4.8)	8 (4.0)	0.088
Marfan syndrome	16 (2.2)	4 (2.9)	6 (2.8)	2 (1.2)	4 (2.0)	0.708
Bicuspid aortic valve	12 (1.7)	1 (0.7)	1 (0.5)	3 (1.8)	7 (3.5)	0.087
Previous cardiovascular surgery	32 (4.4)	10 (7.2)	9 (4.1)	9 (5.4)	4 (2.0)	0.115
Examination on admission						
Chest pain	491 (68.1)	103 (74.1)	146 (67.0)	116 (69.9)	126 (63.6)	0.214
Back pain	383 (53.1)	74 (53.2)	107 (49.1)	100 (60.2)	102 (51.5)	0.170
Syncope	78 (10.8)	12 (8.6)	21 (9.6)	22 (13.3)	23 (11.6)	0.553
All neurological deficits	57 (7.9)	8 (5.8)	15 (6.9)	16 (9.6)	18 (9.1)	0.525
Shock or tamponade	154 (21.4)	29 (20.9)	38 (17.4)	35 (21.1)	52 (26.3)	0.187
Preoperative CPR	19 (2.6)	4 (2.9)	6 (2.8)	4 (2.4)	5 (2.5)	1.000
Malperfusion						
Renal malperfusion	49 (6.8)	10 (7.2)	12 (5.5)	12 (7.2)	15 (7.6)	0.827
Mesenteric malperfusion	9 (1.2)	1 (0.7)	2 (0.9)	3 (1.8)	3 (1.5)	0.811
Lower limb malperfusion	62 (8.6)	18 (12.9)	16 (7.3)	15 (9.0)	13 (6.6)	0.198
Laboratory findings						
WBC count (/μL)	12,741±4,758	12,179±4,375	12,716±5,003	12,476±4,655	13,384±4,786	0.108
Hematocrit (%)	37.3±5.4	36.7±5.1	37.4±5.4	37.3±5.7	37.8±5.4	0.472
Albumin (mg/L)	3.7±0.5	3.7±0.4	3.7±0.5	3.7±0.5	3.7±0.5	0.737
Glucose (mg/dL)	162±66	160±76	155±53	158±54	173±77	0.067
hs-CRP (mg/dL)	1.98±4.53	1.91±3.99	2.27±5.09	1.80±4.26	1.86±4.46	0.726
BUN (mg/dL)	18.4±8.0	17.9±6.3	18.2±7.8	18.7±7.6	18.6±9.5	0.781
Creatinine (mg/dL)	1.04±1.09	0.89±0.33	1.03±1.05	1.17±1.43	1.04±1.17	0.189
eGFR (mL/min/m²)	62.3±22.3	63.6±20.6	63.2±24.1	60.2±22.5	62.0±21.2	0.519
Echocardiogram findings						
Low EF (LVEF <50%)	51 (7.1)	7 (5.0)	14 (6.4)	19 (11.4)	11 (5.6)	0.117
AR (moderate/severe)	153 (21.2)	25 (18.0)	49 (22.5)	38 (22.9)	41 (20.7)	0.712

Data are presented as n (%) or mean ± SD. Patients were divided into 4 groups based on quartiles of heart rate (HR) at discharge: Group 1, <70 beats/min; Group 2, 70–77 beats/min; Group 3, 78–83 beats/min; and Group 4, ≥84 beats/min. AF, atrial fibrillation; AR, aortic regurgitation; BMI, body mass index; BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease; CPR, cardiopulmonary resuscitation; EF, ejection fraction; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease (regular dialysis); hs-CRP, high-sensitivity C-reactive protein; LVEF, left ventricular ejection fraction; WBC, white blood cell.

aneurysm recognized before the initial hospitalization. Neurological deficits were defined as permanent or transient losses of neurological function. Marfan syndrome was diagnosed using the revised Ghent criteria (including suspicious cases).[11] Shock was defined as systolic blood pressure (BP) <90 mmHg at the time of admission. Cardiac tamponade was defined as hemodynamic instability, with pericardial effusion confirmed using echocardiography or CT. Emergency surgery was defined as a surgery performed within 24 h of hospital admission. Performance status was classified using the Eastern Cooperative Oncology Group performance status scale.[12]

Table 2. Operative Findings, In-Hospital Events, and Details at Discharge

	All patients (n=721)	HR at discharge quartiles				P value
		Group 1 (n=139)	Group 2 (n=218)	Group 3 (n=166)	Group 4 (n=198)	
Emergency surgery	709 (98.3)	134 (96.4)	215 (98.6)	165 (99.4)	195 (98.5)	0.266
In-hospital events						
Stroke	73 (10.1)	13 (9.4)	17 (7.8)	15 (9.0)	28 (14.1)	0.183
Repeat thoracotomy	52 (7.2)	9 (6.5)	12 (5.5)	13 (7.8)	18 (9.1)	0.538
Sepsis	66 (9.2)	11 (7.9)	21 (9.6)	14 (8.4)	20 (10.1)	0.896
Hospitalization period (days)	21.0±15.8	20.5±11.5	21.7±19.5	19.9±13.1	21.5±16.0	0.671
Demographics at discharge						
Discharge to home	453 (62.8)	91 (65.5)	142 (65.1)	104 (62.7)	116 (58.6)	0.490
Performance status (pts)	1.6±0.8	1.6±0.8	1.5±0.8	1.7±0.9	1.7±0.9	0.069
SBP (mmHg)	114.5±14.5	113.0±14.6	113.7±12.6	115.5±13.6	115.5±16.7	0.278
DBP (mmHg)	62.7±9.0	60.9±7.3	61.2±8.5	63.5±8.7	65.1±10.1	<0.001
Medications at discharge						
ACEI	30 (4.2)	8 (5.8)	8 (3.7)	6 (3.6)	8 (4.0)	0.768
ARB	340 (47.2)	60 (43.2)	108 (49.5)	84 (50.6)	88 (44.4)	0.432
CCB	480 (66.6)	93 (66.9)	145 (66.5)	115 (69.3)	127 (64.1)	0.786
β-blockers	587 (81.4)	121 (87.1)	192 (88.1)	136 (81.9)	138 (69.7)	<0.001
Statin	89 (12.3)	14 (10.1)	26 (11.9)	18 (10.8)	31 (15.7)	0.413
Aspirin	139 (19.3)	22 (15.8)	40 (18.3)	43 (25.9)	34 (17.2)	0.106
Warfarin/DOAC	162 (22.5)	36 (25.9)	54 (24.8)	32 (19.3)	40 (20.2)	0.369

Data are presented as n (%) or the mean ± SD. Patients were divided into 4 groups based on quartiles of heart rate (HR) at discharge: Group 1, <70 beats/min; Group 2, 70–77 beats/min; Group 3, 78–83 beats/min; and Group 4, ≥84 beats/min. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; DBP, diastolic blood pressure; DOAC, direct oral anticoagulant; SBP, systolic blood pressure.

Table 3. Long-Term Outcomes

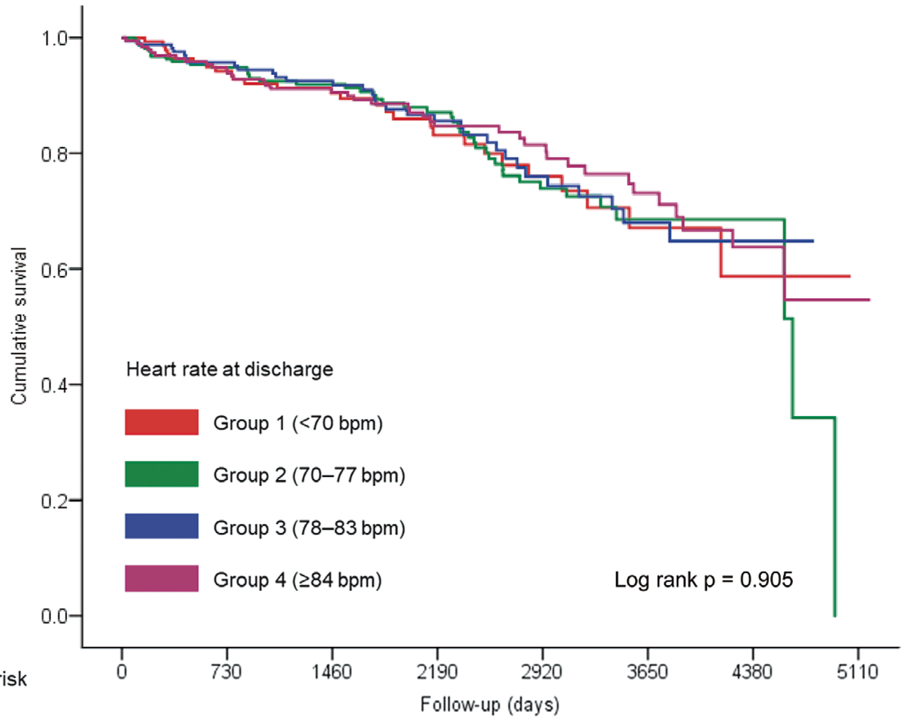
	All patients (n=721)	HR at discharge quartiles				P value
		Group 1 (n=139)	Group 2 (n=218)	Group 3 (n=166)	Group 4 (n=198)	
Aortic events	124 (17.2)	18 (12.9)	29 (13.3)	25 (15.1)	52 (26.3)	0.002
Aortic event-related death	13 (1.8)	3 (2.2)	4 (1.8)	3 (1.8)	3 (1.5)	0.980
Recurrence of AAD	11 (1.5)	3 (2.2)	1 (0.5)	3 (1.8)	4 (2.0)	0.422
Aortic surgery	101 (14.0)	12 (8.6)	24 (11.0)	20 (12.0)	45 (22.7)	0.001
Indications for surgery						
Aortic dilatation	70 (9.7)	8 (5.8)	14 (6.4)	16 (9.6)	32 (16.2)	0.003
Rupture	11 (1.5)	1 (0.7)	3 (1.4)	2 (1.2)	5 (2.5)	0.628
Pseudo aneurysm	8 (1.1)	0 (0)	2 (0.9)	1 (0.6)	5 (2.5)	0.186
ULP	1 (0.1)	0 (0)	1 (0.5)	0 (0)	0 (0)	1.000
Infection	7 (1.0)	3 (2.2)	2 (0.9)	0 (0)	2 (1.0)	0.299
Others	4 (0.6)	0 (0)	2 (0.9)	1 (0.6)	1 (0.5)	0.911
AMI	9 (1.2)	4 (2.9)	1 (0.5)	2 (1.2)	2 (1.0)	0.271
Stroke	100 (13.9)	19 (13.7)	23 (10.6)	22 (13.3)	36 (18.2)	0.168
All-cause death	144 (20.0)	27 (19.4)	44 (20.2)	32 (19.3)	41 (20.7)	0.988

Data are presented as n (%) or the mean ± SD. Patients were divided into 4 groups based on quartiles of heart rate (HR) at discharge: Group 1, <70 beats/min; Group 2, 70–77 beats/min; Group 3, 78–83 beats/min; and Group 4, ≥84 beats/min. AAD, acute aortic dissection; AMI, acute myocardial infarction; ULP, ulcer-like projection.

Statistical Analysis

Data are presented as the mean ± SD, median with interquartile range (IQR), or percentages, as appropriate. One-way analysis of variance (ANOVA) was used to compare continuous variables. Levene's test was used to evaluate the homogeneity of variances, and Welch's test was used when data did not show homogeneity of variances. Fisher's exact test was used for categorical variables to test the homogeneity of frequencies across the groups. Paired t-tests were used to compare the severity of echocardiographic aortic regurgitation (AR) between the pre- and postoperative states and to compare HR at discharge with that recorded in the outpatient clinic.

Cumulative survival and aortic event-free survival rates were evaluated using Kaplan-Meier analyses, and differences in survival curves were assessed using the log-rank



No. at risk	0	730	1460	2190	2920	3650	4380	5110
<70 bpm	139	131	105	58	35	14	6	0
70–77 bpm	218	200	158	104	63	22	6	0
78–83 bpm	166	152	127	81	48	21	9	0
≥84 bpm	198	181	150	105	69	39	17	2

Figure 2. Kaplan-Meier curves for cumulative survival.

test. Cox proportional hazards models were used to assess the association of discharge HR with long-term aortic events. Crude and adjusted hazard ratios and 95% confidence intervals (CIs) were estimated.

Multivariable models were used to adjust for potential confounders. The selection of confounders entered into the multivariable models was based on clinical judgment. Model 1 included sex and age. Model 2 included the variables in Model 1 and the use of β-blockers. Model 3 included the variables in Model 2, as well as systolic and diastolic BP and the presence of a history of Marfan syndrome. Model 4 included all variables in Model 3, as well as false lumen patency, the use of calcium channel blockers, the need for emergency surgery, and sepsis during the index hospitalization.

Receiver operating characteristic (ROC) analysis was performed to confirm that HR contributes to the prognosis of aortic events at a median observational period of 5.8 years, and to determine the appropriate HR for predicting long-term aortic events. Patients were divided into 2 groups, namely those who developed aortic events up to 5.8 years and those who did not. To compare the 2 groups, the area under the curve (AUC) and 95% CIs were calculated. In addition, the optimum cut-off point was identified based on Youden's index.

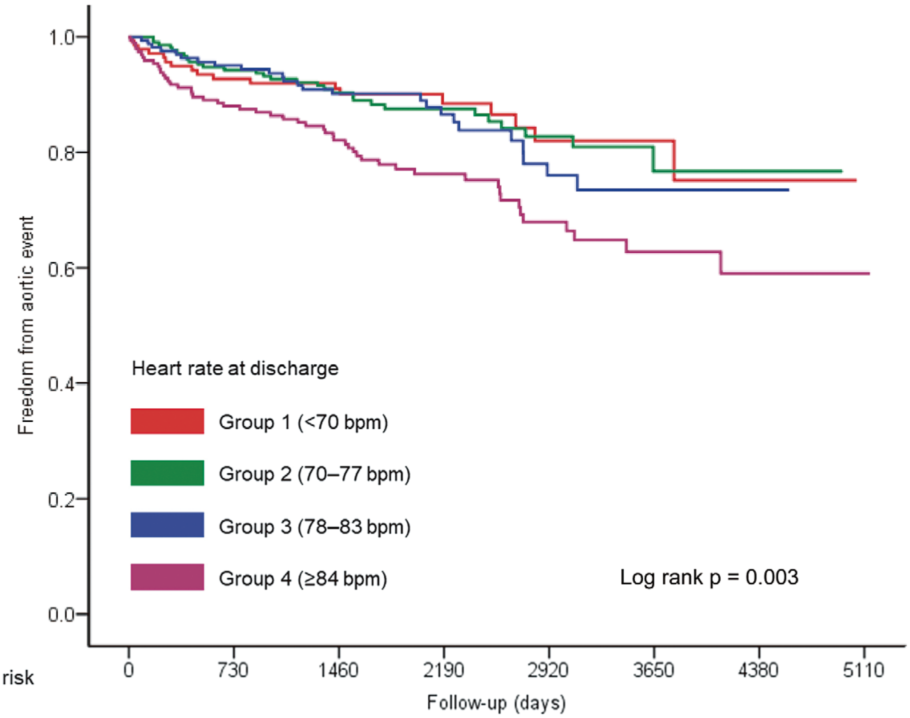
Two-sided $P<0.05$ was considered significant. All statistical analyses were performed in IBM SPSS Statistics for Windows, Version 24.0 (IBM, Armonk, NY, USA).

Results

Baseline Characteristics

The baseline (admission) characteristics of the total patient population are given in **Table 1**. The mean age of patients was 65.8±13.0 years, and almost half the cohort was female. The mean HR at discharge was 77.2±10.7 beats/min. Based on HR at discharge quartiles, patients were divided into 4 groups (Groups 1–4). Mean age differed significantly among the 4 groups (P=0.014), being highest in Group 1. Most patients had the communicating type (C type) of dissection, with a similar percentage across all groups (P=0.663). The proportion of patients with a history of cerebrovascular disease differed significantly among groups (P=0.016), being lowest in Group 4. Conversely, there were no significant differences in the prevalence of hypertension, diabetes, coronary artery disease, or atrial fibrillation among the 4 groups (P=0.989, P=0.140, P=0.514, and P=0.526, respectively).

In the clinical examinations, approximately 21.4% of patients (n=154) presented with shock or tamponade upon



No. at risk	0	730	1460	2190	2920	3650	4380	5110
<70 bpm	139	124	97	54	33	14	5	0
70–77 bpm	218	188	146	90	54	17	3	0
78–83 bpm	166	144	114	69	37	13	4	0
≥84 bpm	198	163	129	81	48	22	10	1

Figure 3. Kaplan-Meier curves for aortic event-free survival.

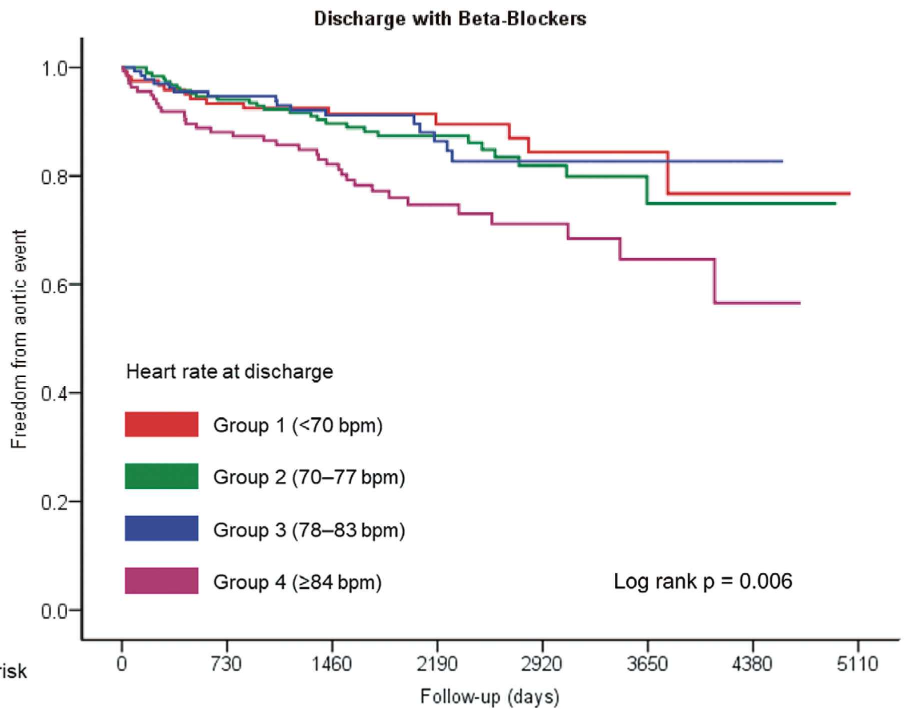
admission, whereas 2.6% (n=19) received preoperative cardiopulmonary resuscitation; neither characteristic differed significantly among the 4 groups (P=0.187 and P=1.000, respectively). With regard to laboratory findings, mean white blood cell count and glucose level did not differ significantly among the groups (P=0.108 and P=0.067, respectively), but both tended to be higher in Group 4.

Operative Findings, In-Hospital Events, and Details at Discharge

Table 2 shows the operative findings, in-hospital events, and discharge details. Overall, 98.3% of patients (n=709) underwent surgical treatment within 24 h of hospital admission. The percentage of patients undergoing emergency surgery was not significantly different among the 4 groups (P=0.266). Ascending aortic replacements were performed in 51.3% of patients (n=370), partial or total aortic arch replacements were performed in 35.6% (n=257), and ascending aorta replacements and separate aortic valve replacements were performed in 1.2% (n=9). Composite aortic root replacements, such as the Bentall procedure or valve-sparing aortic root replacement, were performed in 10.1% of patients (n=73). Of these, Bentall procedures were performed in 6.6% of patients (n=48) and valve-sparing aortic root replacements were performed in 3.4% (n=25). Conversely, 27 patients were treated non-surgically: 20 patients met the criteria for conservative (non-surgical) management and 7 did not undergo surgery because of advanced age, comorbidities, or a refusal to do so. The rates of in-hospital events were not significantly different among the 4 groups, including stroke, repeat thoracotomy, and sepsis (P=0.183, P=0.538, and P=0.896, respectively).

The mean hospitalization period was similar among the groups and approximately two-thirds of patients were discharged home; neither characteristic showed significant differences among the 4 groups (P=0.671 and P=0.490, respectively). The mean performance scores at discharge were not significantly different among the groups (P=0.069). Although mean systolic BP values was not significantly different among the 4 groups (P=0.278), mean diastolic BP differed significantly (P<0.001), with Group 4 having the highest mean diastolic BP. Prior to discharge, echocardiographic findings of moderate or severe AR were observed in only 1.1% of patients (n=8; paired t-test, P<0.001) and were similar among the 4 groups (P=0.333).

At discharge, most patients were prescribed β-blockers, followed by calcium channel blockers and angiotensin receptor blockers. Some patients were prescribed angiotensin-converting enzyme inhibitors. The percentage of



No. at risk	0	730	1460	2190	2920	3650	4380	5110
<70 bpm	121	111	85	47	30	13	4	0
70–77 bpm	192	167	129	80	48	14	2	0
78–83 bpm	136	115	91	52	27	8	3	0
≥84 bpm	138	114	90	52	30	12	4	0

Figure 4. Kaplan-Meier curves for aortic event-free survival in patients discharged with β-blockers.

patients treated with β-blockers at discharge was significantly different among the 4 groups (P<0.001) and was lowest in Group 4.

Long-Term Outcomes

Table 3 summarizes the long-term outcomes. Follow-up observations were completed in 99.3% of patients (n=716). The median observational period was 5.8 years (IQR 3.9–8.5 years). During the observation period, 17.2% of patients (n=124) experienced late aortic events. Late aortic surgeries were performed in 14.0% of patients, mainly due to dilatation of the diseased aorta (n=70). Of those, 67 patients required aortic surgeries due to enlargement of the distal diseased aorta. In the other 3 patients, aortic surgeries were performed for aortic root dilatation. AMI, stroke, and all-cause deaths were not significantly different among the 4 groups (P=0.271, P=0.168, and P=0.988, respectively).

HR at Discharge and Long-Term Outcomes

To assess the relationship between HR at discharge and HR in the outpatient clinic, we focused on checking HR approximately 1 year postoperatively, with HR confirmed in 90.8% of patients (n=655). The median observational period was 377 days (IQR 361–392 days). The mean HR in the outpatient clinic was 64.9±10.9 beats/min, and a paired t-test showed a significant difference between the HR at discharge and that recorded in the outpatient clinic (P<0.001). In addition, the HR in the outpatient clinic differed significantly among the 4 groups (P=0.001) and was highest in Group 4.

In this study, the cumulative survival rate was 96.6% at 1 year, 88.1% at 5 years, and 69.4% at 10 years. Kaplan-Meier survival curves, categorized by HR at discharge, are shown in **Figure 2**. The cumulative survival rates were not significantly different among the 4 groups (log-rank test, P=0.905).

In this study, the cumulative freedom from aortic reoperations was 95.9% at 1 year, 87.7% at 5 years, and 78.2% at 10 years. **Figure 3** shows the Kaplan-Meier curves for the cumulative aortic event-free survival, stratified by HR at discharge. The cumulative aortic event-free survival rates were significantly different among the 4 groups (log-rank test, P=0.003) and the rate was the lowest in Group 4 patients. The aortic event-free survival rate in Group 4 was 91.2% at 1 year, with further separation from the curves of other groups at 5 years; the aortic event-free survival rate for Group 4 was 77.9% at 5 years. Moreover, we analyzed the cumulative aortic event-free survival rate according to the use of β-blockers at discharge. Among patients who

Table 4. Hazard Ratios of Long-Term Aortic Events, According to Heart Rate at Discharge

	Heart rate at discharge (beats/min)						
	<70 (n=139)	70–77 (n=218)		78–83 (n=166)		≥84 (n=198)	
	HR	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Crude	1.00	1.02 (0.56–1.84)	0.939	1.16 (0.63–2.12)	0.629	2.06 (1.20–3.52)	0.008
Model 1	1.00	0.95 (0.53–1.72)	0.882	1.07 (0.58–1.97)	0.818	1.86 (1.08–3.19)	0.024
Model 2	1.00	0.95 (0.52–1.71)	0.871	1.04 (0.56–1.91)	0.896	1.74 (1.00–3.03)	0.048
Model 3	1.00	1.01 (0.55–1.82)	0.973	1.09 (0.59–2.02)	0.765	1.88 (1.08–3.28)	0.026
Model 4	1.00	0.97 (0.53–1.76)	0.933	1.07 (0.58–1.98)	0.822	1.86 (1.06–3.25)	0.029

Model 1 was adjusted for sex and age. Model 2 was further adjusted for the use of β-blockers. Model 3 was further adjusted for systolic blood pressure, diastolic blood pressure, and Marfan syndrome. Model 4 was further adjusted for false lumen patency, calcium channel blockers, emergency surgery, and sepsis during index hospitalization. CI, confidence interval; HR, Hazard ratio.

used β-blockers at discharge, the cumulative aortic event-free survival rates were significantly different among the 4 groups (log-rank test, P=0.006, **Figure 4**). Conversely, no significant between-group differences were observed among those not using β-blockers at discharge (log-rank test, P=0.374; **Supplementary Figure**).

According to the crude Cox proportional hazards regression analysis model, compared with the lowest HR group (Group 1), the highest group (Group 4) had a significantly higher risk of aortic events (hazard ratio 2.06; 95% CI 1.20–3.52; **Table 4**). This positive association remained significant even after adjusting for potential confounding factors, such as sex and age (Model 1; hazard ratio 1.86; 95% CI 1.08–3.19), the use of β-blockers (Model 2; hazard ratio 1.74; 95% CI 1.00–3.03), BP and Marfan syndrome (Model 3; hazard ratio 1.88; 95% CI 1.08–3.28), and false lumen patency, the use of calcium channel blockers, emergency surgery, and sepsis during the index hospitalization (Model 4; hazard ratio 1.86; 95% CI 1.06–3.25).

Furthermore, we categorized patients into 2 groups for ROC analysis and examined the frequency distribution of both the groups. One group comprised patients who developed aortic events up to 5.8 years (n=94) and the other group comprised patients who were confirmed to be free of aortic events at 5.8 years (n=278). ROC analysis revealed that the AUC was 0.588 (95% CI 0.519–0.657; P=0.011) and significantly higher than 0.5. The ROC curve indicated that the cut-off point of discharge HR that demonstrated the maximum sensitivity and specificity for separating patients with and without aortic events was 81 beats/min.

Discussion

This study produced 2 main findings. First, the HR at discharge in surgically treated patients with TA-AADs was an independent predictor of long-term aortic outcomes, after adjusting for potential confounders. Second, long-term aortic events occurred significantly more frequently in patients with HR at discharge ≥84 beats/min than in those with HR <84 beats/min.

The in-hospital mortality rate for surgically treated patients with TA-AADs remained high in recent large-scale observational studies.[1,13,14] Furthermore, residual aortic dissection in the distal aorta poses a potential risk of reoperation or aneurysm formation/rupture-related death.[4–6] Previous studies reported that the actuarial rate of freedom from cardiac or aortic reoperations after surgical repair for TA-AADs ranged from 61% to 85% at 10 years.[15–17] In the present study, the cumulative freedom from aortic reoperations was 78.2% at 10 years, which is comparable to that in previous reports. The most common cause for reoperation was aortic dilatation of the residual diseased aorta, which was observed in 70 of 101 patients (69.3%). The next most common cause was a ruptured aorta, which was observed in 11 of 101 patients (10.8%). Several risk factors have been identified for distal reoperations of the dissecting diseased aorta after surgery for TA-AADs, such as younger age and more distal extent of the dissection.[18,19] Other studies have described several risk factors for secondary dilatation of the non-dissecting diseased aorta, such as age, aorta diameter, the presence of chronic obstructive pulmonary disorder, and a patent false lumen.[20–24] Moreover, previous reports indicated that late mortality due to rupture was significantly higher in patients with chronic dissection than in those with non-dissecting aneurysms.[20,22–24]

The specific mechanism of dilatation of the residual diseased aorta, which may cause aneurysm formation and aortic rupture, remains unclear. Conversely, aortic wall stress may be a potential underlying reason for dilatation of the diseased aorta. Increased aortic wall stress induces aortic dilatation and causes further expansion of the aneurysm, according to the law of Laplace.[18] Experimental models of aortic dissection have revealed that 2 interrelated forces, pulsatile load and BP, play integral roles in the propagation of aortic dissections.[18] Therefore, to prevent dilatation of the diseased aorta, a long-term pharmacological approach during the chronic phase is primarily aimed at regulating BP and the pulsatile load, thereby limiting aortic wall stress.

Previous observational studies have shown that among various antihypertensive drugs, β-blockers significantly improve the long-term outcomes of patients with TA-AADs who undergo surgical treatment compared with those not using β-blockers.[25–27] The presumptive benefits of β-blockers derive not only from their efficacy in reducing both BP and HR, but also from their negative inotropic and chronotropic effects.[18] Several observational studies have demonstrated the importance of BP control in improving long-term survival and aortic outcomes in patients after repair of TA-AADs.[20,25,28] Conversely, little is known about the relationship between HR and long-term outcomes of TA-AAD. Although the current guidelines for patients with thoracic aortic disease in Europe and the US recommend a target level for BP control, HR control is not a recognized factor involved in reducing risk in aortic disease.[29,30]

Resting HR is a well-known prognostic factor for various cardiovascular diseases.[7–9] Numerous previous studies have demonstrated that the HR at discharge is significantly associated with all-cause mortality in patients with AMI, after adjusting for potential confounders.[8,9] As previously mentioned, the relationship between HR and long-term outcomes in TA-AAD has not been established, and very few studies have investigated the relationship between HR control and long-term outcomes in patients with AAD.[31,32] In patients with type B AADs, strict HR control (<60 beats/min) during the early phase improves long-term aortic outcomes compared with conventional HR control (≥60 beats/min), regardless of β-blocker administration.[31] In contrast, HR control during the early postoperative period is not significantly associated with long-term outcomes in patients with TA-AADs.[32] Because these previous studies used HRs measured within 1 week after the onset or after surgical repair, their findings were possibly markedly influenced by the acute stage. We focused on HR at discharge, which has not been previously reported, and revealed that it is a prognostic factor for long-term aortic outcomes in surgically treated patients with TA-AADs.

Some potential mechanisms may underlie the association between HR at discharge and long-term aortic outcomes. First, HR at discharge may reflect a condition in which the effect of the acute phase has subsided to some extent. Second, lowering the HR may contribute to diminishing the effect of hemodynamic stress on the diseased aorta. The progression of aortic disease during the chronic phase probably results from a combination of hemodynamic stress, aortic injury, chronic inflammation, genetic propensity, and epidemiological risk factors.[33] Some experimental data have demonstrated the pathophysiological benefits of reduced HR for atherosclerosis and arterial stiffness.[7,34,35] Similarly, an increased HR, associated with endothelial dysfunction, is an integral part of the pathogenesis of atherosclerosis.[36] Therefore, an increase in HR is an important risk factor for long-term aortic dilatation of the diseased aorta, with direct effects on the diseased arterial wall.

In this study, patients with HR ≥84 beats/min had a relative risk of 1.86 for a long-term aortic event compared with those with HR <70 beats/min after adjusting for potential confounders in the multivariable Cox proportional hazards models. In addition, the ROC analysis confirmed that HR at discharge contributes to the prognosis of long-term aortic events, and 81 beats/min was the cut-off point of HR at discharge with the maximum sensitivity and specificity for identifying patients who had aortic events. However, because the present study used data from the existing medical records and the observational period was not fixed, there was a large variation in the follow-up period among patients.

The results of the present study suggest that the HR in surgically treated patients with TA-AADs should be optimized before discharge, particularly in those with a discharge HR ≥84 beats/min; however, the target HR remains unclear. Further investigations are necessary to clarify this issue.

Study Limitations

This study has several limitations. First, this was a single-center observational study that lacked treatment randomization. Further investigations at multiple centers are needed. Second, the β-blocker prescription rate at hospital discharge was significantly different among the groups and was especially low in patients with a discharge HR ≥84 beats/min. We assumed that the high-HR group would include a large number of young patients with arch replacements, poor preoperative condition, and who developed surgical complications (e.g., stroke). As a result, many of these patients may not have been prescribed β-blockers at discharge, based on the doctor's decision, potentially affecting long-term outcomes.

Conclusion

In conclusion, this study demonstrated that HR at discharge in surgically treated patients with TA-AADs is an independent predictor of long-term aortic outcomes. Discharge HR ≥84 beats/min was significantly associated with an increased risk of long-term aortic events. Consequently, the HR in surgically treated patients with TA-AADs should be optimized before discharge, particularly if the HR is ≥84 beats/min.

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Disclosures

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IRB Information

The Institutional Review Board of Sakakibara Heart Institute approved this retrospective study (Reference no. 19-066).

Data Availability

The deidentified participant data will not be shared.

References

1. Pape LA, Awais M, Woznicki EM, Suzuki T, Trimarchi S, Evangelista E, et al. Presentation, diagnosis, and outcomes of acute aortic dissection: 17-year trends from the International Registry of Acute Aortic Dissection. *J Am Coll Cardiol* 2015; **66:** 350–358.
2. Boening A, Karck M, Conzelmann LO, Easo J, Kruger T, Rylski B, et al. German registry for acute aortic dissection type A: Structure, results, and future perspectives. *J Thorac Cardiovasc Surg* 2017; **65:** 77–84.
3. Yamaguchi T, Nakai M, Sumita Y, Miyamoto Y, Matsuda H, Inoue Y, et al. Current status of the management and outcomes of acute aortic dissection in Japan: Analyses of nationwide Japanese Registry of All Cardiac and Vascular Diseases-Diagnostic Procedure Combination data. *Eur Heart J Acute Cardiovasc Care* 2020; **9**(3_suppl)**:** S21–S31.
4. Yang B, Norton EL, Hobbs R, Farhat L, Wu X, Hornsby WE, et al. Short- and long-term outcomes of aortic root repair and replacement in patients undergoing acute type A aortic dissection repair: Twenty-year experience. *J Thorac Cardiovasc Surg* 2019; **157:** 2125–2136.
5. Kobuch R, Hilker M, Rupprecht L, Hirt S, Keyser A, Puehler T, et al. Late reoperations after repaired acute type A aortic dissection. *J Thorac Cardiovasc Surg* 2012; **144:** 300–307.
6. Chen SW, Lin YS, Wu VC, Lin MS, Chou AH, Chu PH, et al. Effect of beta-blocker therapy on late outcomes after surgical repair of type A aortic dissection. *J Thorac Cardiovasc Surg* 2020; **159:** 1694–1703.
7. Fox K, Borer JS, Camm AJ, Danchin N, Ferrari R, Lopez Sendon

JL, et al. Resting heart rate in cardiovascular disease. *J Am Coll Cardiol* 2007; **50:** 823–830.
8. Antoni ML, Boden H, Delgado V, Boden H, Delgado V, Boersma E, et al. Relationship between discharge heart rate and mortality in patients after acute myocardial infarction treated with primary percutaneous coronary intervention. *Eur Heart J* 2012; **33:** 96–102.
9. Alapati V, Tang F, Charlap E, Chan PS, Heidenreich PA, Jones PG, et al. Discharge heart rate after hospitalization for myocardial infarction and long-term mortality in 2 US registries. *J Am Heart Assoc* 2019; **8:** e010855.
10. Daily PO, Trueblood HW, Stinson EB, Wuerflein RD, Shumway NE. Management of acute aortic dissections. *Ann Thorac Surg* 1970; **10:** 237–247.
11. Loeys BL, Dietz HC, Braverman AC, Callewaert BL, De Backer J, Devereux RB, et al. The revised Ghent nosology for the Marfan syndrome. *J Med Genet* 2010; **47:** 476–485.
12. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982; **5:** 649–655.
13. Reutersberg B, Salvermoser M, Trenner M, Geisbusch S, Zimmermann A, Eckstein HH, et al. Hospital incidence and in-hospital mortality of surgically and interventionally treated aortic dissections: Secondary data analysis of the nationwide German diagnosis-related group statistics from 2006 to 2014. *J Am Heart Assoc* 2019; **8:** e011402.
14. McClure RS, Ouzounian M, Boodhwani M, El-Hamamsy I, Chu MWA, Pozeg Z, et al. Cause of death following surgery for acute type A dissection: Evidence from the Canadian Thoracic Aortic Collaborative. *Aorta* 2017; **5:** 33–41.
15. Kirsch M, Soustelle C, Houel R, Hillion ML, Loisance D. Risk factor analysis for proximal and distal reoperations after surgery for acute type A aortic dissection. *J Thorac Cardiovasc Surg* 2002; **123:** 318–325.
16. Concistre G, Casali G, Santaniello E, Montalto A, Fiorani B, Dell'Aquila A, et al. Reoperation after surgical correction of acute type A aortic dissection: Risk factor analysis. *Ann Thorac Cardiovasc Surg* 2012; **93:** 450–455.
17. Suzuki T, Asai T, Kinoshita T. Predictors for late reoperation after surgical repair of acute type A aortic dissection. *Ann Thorac Cardiovasc Surg* 2018; **106:** 63–69.
18. Genoni M, Paul M, Jenni R, Graves K, Seifert B, Turina M. Chronic beta-blocker therapy improves outcome and reduces treatment costs in chronic type B aortic dissection. *Eur J Cardiothorac Surg* 2001; **19:** 606–610.
19. Geirsson A, Bavaria JE, Swarr D, Keane MG, Woo YJ, Szeto WY, et al. Fate of the residual distal and proximal aorta after acute type a dissection repair using a contemporary surgical reconstruction algorithm. *Ann Thorac Surg* 2007; **84:** 1955–1964.
20. Immer FF, Hagen U, Berdat PA, Eckstein FS, Carrel TP. Risk factors for secondary dilatation of the aorta after acute type A aortic dissection. *Eur J Cardiothorac Surg* 2005; **27:** 654–657.
21. Juvonen T, Ergin MA, Galla JD, Lansman SL, Nguyen KH, McCullough JN, et al. Prospective study of the natural history of thoracic aortic aneurysms. *Ann Thorac Surg* 1997; **63:** 1533–1545.
22. Juvonen T, Ergin MA, Galla JD, Lansman SL, McCullough JN, Nguyen K, et al. Risk factors for rupture of chronic type B dissections. *J Thorac Cardiovasc Surg* 1999; **117:** 776–786.
23. Griepp RB, Ergin MA, Galla JD, Lansman SL, McCullough JN, Nguyen KH, et al. Natural history of descending thoracic and thoracoabdominal aneurysms. *Ann Thorac Surg* 1999; **67:** 1927–1930.
24. Akutsu K, Nejima J, Kiuchi K, Sasaki K, Ochi M, Tanaka K, et al. Effects of the patent false lumen on the long-term outcome of type B acute aortic dissection. *Eur J Cardiothorac Surg* 2004; **26:** 359–366.
25. Melby SJ, Zierer A, Damiano RJ Jr, Moon MR. Importance of blood pressure control after repair of acute type A aortic dissection: 25-year follow-up in 252 patients. *J Clin Hypertens* 2013; **15:** 63–68.
26. Suzuki T, Isselbacher EM, Nienaber CA, Pyeritz RE, Eagle KA, Tsai TT, et al. Type-selective benefits of medications in treatment of acute aortic dissection (from the International Registry of Acute Aortic Dissection [IRAD]). *Am J Cardiol* 2012; **109:** 122–127.
27. Fukui T, Tabata M, Morita S, Takanashi S. Gender differences in patients undergoing surgery for acute type A aortic dissection. *J Thorac Cardiovasc Surg* 2015; **150:** 581–587.
28. Tsai TT, Evangelista A, Nienaber CA, Trimarchi S, Sechtem U, Fattori R, et al. Long-term survival in patients presenting with type A acute aortic dissection: Insights from the International Registry of Acute Aortic Dissection (IRAD). *Circulation* 2006; **114:** I350–I356.
29. Erbel R, Aboyans V, Boileau C, Bossone E, Bartolomeo RD, Eggebrecht H, et al. 2014 ESC guidelines on the diagnosis and treatment of aortic diseases: Document covering acute and chronic aortic diseases of the thoracic and abdominal aorta of the adult. The Task Force for the Diagnosis and Treatment of Aortic Diseases of the European Society of Cardiology (ESC). *Eur Heart J* 2014; **35:** 2873–2926.
30. Hiratzka LF, Bakris GL, Beckman JA, Bersin RM, Carr VF, Casey DE, et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with thoracic aortic disease: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, and Society for Vascular Medicine. *Circulation* 2010; **121:** e266–e369.
31. Kodama K, Nishigami K, Sakamoto T, Sawamura T, Hirayama T, Misumi H, et al. Tight heart rate control reduces secondary adverse events in patients with type B acute aortic dissection. *Circulation* 2008; **118**(Suppl)**:** S167–S170.
32. Ohnuma T, Kimura N, Sasabuchi Y, Asaka K, Shiotsuka J, Komuro T, et al. Lower heart rate in the early postoperative period does not correlate with long-term outcomes after repair of type A acute aortic dissection. *Heart Vessels* 2015; **30:** 355–361.
33. Wu D, Shen YH, Russell L, Coselli JS, LeMaire SA. Molecular mechanisms of thoracic aortic dissection. *J Surg Res* 2013; **184:** 907–924.
34. Huikuri HV, Jokinen V, Syvanne M, Nieminen MS, Airaksinen KE, Ikaheimo MJ, et al. Heart rate variability and progression of coronary atherosclerosis. *Arterioscler Thromb Vasc Biol* 1999; **19:** 1979–1985.
35. Giannattasio C, Vincenti A, Failla M, Capra A, Ciro A, De Ceglia S, et al. Effects of heart rate changes on arterial distensibility in humans. *Hypertension* 2003; **42:** 253–256.
36. Tardif JC. Heart rate and atherosclerosis. *Eur Heart J Suppl* 2009; **11:** D8–D12.

Supplementary Files

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