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Risk Model of Cardiovascular Surgery in 845 Marfan Patients Using the Japan Adult Cardiovascular Surgery Database

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SUMMARY

The aim of this study was to evaluate the short-term operative results of patients with Marfan syndrome who underwent thoracic or abdominal aortic surgery in a 4-year period in Japan. Data were collected from the Japan Cardiovascular Surgery Database (JCVSD). We retrospectively analyzed the data of 845 patients with Marfan syndrome who underwent cardiovascular surgery between January 2008 and January 2011. Logistic regression was used to generate risk models. The early mortality rate was 4.4% (37/845). Odds ratios (OR), 95% confidence intervals (CI), and *P* values for structures and processes in the mortality prediction model were as follows: renal insufficiency (OR, 11.37; CI, 3.72-34.66; $P < 0.001$); respiratory disorder (OR, 11.12; CI, 3.20-38.67; $P < 0.001$); aortic dissection (OR, 13.02; CI, 2.80-60.60; $P = 0.001$); pseudoaneurysm (OR, 11.23; CI, 1.38-91.66; $P = 0.024$); thoracoabdominal aneurysm (OR, 2.67; CI, 1.22-5.84; $P = 0.014$); and aortic rupure (OR, 4.23; CI, 1.26-14.23; $P = 0.002$). The mortality prediction model had a C-index of 0.82 and a Hosmer–Lemeshow *P* value of 0.56. In conclusion, this study demonstrated that renal insufficiency and respiratory disorder had great impact on the operative mortality of Marfan patients undergoing cardiovascular surgery. Because patients with aortic dissection or aortic rupture showed high operative mortality, close follow-up to avoid emergency operation is mandatory to improve the operative results. Achieving good results from surgery of the thoracoabdominal aorta was quite challenging, also in Marfan patients. (Int Heart J 2013; 54: 401-404)

Key words: JACVSD

Marfan syndrome (MFS) is the most common multisystem disorder of connective tissue that affects 1 in 5000 individuals.[1)] It is inherited as an autosomal dominant trait and displays a variety of clinical manifestations in the ocular, musculoskeletal, and cardiovascular systems. Aortic root aneurysm and subsequent aortic dissection are the leading cause of morbidity and mortality in MFS patients. Aortic aneurysm in MFS is typically pear-shaped and involves progressive dilatation of the sinus of Valsalva. Early diagnosis and advances in surgical treatment, in particular the Bentall procedure and more recently the valve-sparing procedure, have significantly improved life expectancy in MFS.[2)] There has been no report of any nationwide study in Japan, presumably because the number of operations on MFS patients at each institute is limited. In the present study, risk analysis was performed for MFS patients who had undergone cardiovascular surgery between January 2008 and January 2011, using the Japan Adult Cardiovascular Surgery Database (JACVSD).

METHODS

Study population: The JACVSD was initiated in 2000 to estimate surgical outcomes after cardiovascular procedures in many centers throughout Japan. The JACVSD adult cardiovascular division currently captures clinical information from nearly half of all Japanese hospitals (235 hospitals) performing cardiovascular surgery. The data collection form has a total of 255 variables (definitions are available online at http://www.jacvsd.umin.jp), and these are almost identical to those in the STS National Database (definitions are available online at http://sts.org). The JACVSD has developed software for the Web-based data collection system through which the data manager of each participating hospital submits their data electronically to the central office. Although participation in the JACVSD is voluntary, data completeness is a high priority. Accuracy of the submitted data is maintained by a data audit that is achieved by monthly visits by administrative office members to the participating hospital to check data against clinical records. Data validity is further confirmed by an independent comparison of the volume of cardiac surgery at a particular

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hospital entered in the JACVSD versus that reported to the Japanese Association for Thoracic Surgery annual survey.[3]

We examined all MFS patients who had undergone cardiovascular surgery between 1 January 2008 and 31 December 2011. First, those JACVSD records that were obtained without informed consent were excluded from this analysis. Records with missing age (or which were out of range), sex, or 30-day status were also excluded. After this data cleaning, the population for this risk model analysis consisted of 845 patients from 235 participating sites throughout Japan.

Endpoints: The primary outcome measure of the JACVSD was 30-day operative mortality, which was defined exactly the same as the 30-day operative mortality in the Society of Thoracic Surgeons National Database. This includes any patient who died during the index hospitalization, regardless of the length of hospital stay, and any patient who died within 30 days of the operation after being discharged from the hospital. By using the definition from a previous study,[4,5] major morbidity was defined as any of the following 5 postoperative in-hospital complications: stroke, reoperation for any reason, need for mechanical ventilation for more than 24 hours after surgery, renal failure, or deep sternal wound infection.

Statistical analysis: The statistical model was multiple logistic regression; variables entered in the model were selected from all variables shown in Table I using bivariate tests. The chi-square test analyzed categoric covariates, and the unpaired *t* test or Wilcoxon rank-sum test was used for continuous covariates. A multivariate stepwise logistic regression analysis was then performed for each outcome. Stability of the model was checked every time a variable was eliminated. When all statistically nonsignificant variables had been eliminated from the model, "goodness-of-fit" was evaluated and the area under the receiver operating characteristic (ROC) curve was used to assess how well the model could discriminate between patients who lived and patients who had died. To evaluate model calibration, the Hosmer–Lemeshow test was applied.[6]

Results

Patient characteristics: Patient characteristics and outcomes of each procedure are shown in Table I. Patient median age was 41.9 ± 13.9 years, and the percentage of male patients was as 59.7%.

Early mortality and morbidity: As shown in Table II, 30-day operative mortality rates and composite rates for mortality or major morbidity were 4.4% and 23.0% respectively.

Model results and performance: Multiple regression analyses for all patients identified 6 preoperative risks affecting operative mortality (Table III). Preoperative comorbid conditions such as high creatinine levels ≧ 3.0 mg/dL or severe chronic lung disease significantly increased the surgical risks. Types of aortic disease such as dissecting aortic aneurysm, pseudoaneurysm, and thoracoabdominal aneurysm, and also mode of surgery such as emergency surgery for rupture of the aneurysm did as well. Model performance was evaluated using the C-index (area under the ROC curve) as a measure of model discrimination and the Hosmer–Lemeshow test as a measure of "goodness-of-fit." The C-index was 0.82 for the mortality model and 0.76 for the composite mortality or morbidity model; the Hosmer–Lemeshow test *P* value was 0.56 for the mortality model and 0.35 for the composite mortality or morbidity model. Details of model performance metrics are shown in Table IV.

Discussion

A clinical diagnosis of MFS is made according to the Ghent nosology when major manifestations are present in 2 organ systems and a third organ system is involved.[7] The cardinal features of MFS involve the ocular, cardiovascular, and skeletal systems,[1] but aortic enlargement and dissection, mostly of the ascending aorta, are the primary cause of early death.[8] In

Table I. Patient Characteristics ($n = 845$)

Variable	*n*	%
Male sex	507	59.7
Age (years)	41.9 ± 13.9	
Redo	326	38.4
Aortic dissection	487	57.4
Pseudoaneurysm	30	3.5
Rupture	24	2.8
Dilatation	560	66
Aortic root	432	50.9
Ascending aorta	359	42.3
Aortic arch	254	29.9
Descending aorta	165	19.4
Thoracoabdominal	118	13.9
Abdominal aorta	23	2.7
CABG	62	7.3
Mechanical valve	268	31.6
Bioprosthetic valve	48	5.7
Aortic regurgitation ≧ 2	371	43.7
Aortic regurgitation ≧ 3	245	28.9
Emergent operation	169	19.9
NYHA class ≧ 2	244	28.7
LVEF < 50%	18	2.1
Endocarditis	19	2.2
Hypertension	356	41.9
Associated coronary disease	18	2.2
History of myocardial infarction	19	2.2
Smoking	104	12.2
COPD	83	9.8
Diabetes	17	2
Renal insufficiency	24	2.8
Cerebrovascular accident	45	5.3
Aortic valve stenosis	4	0.5
Preoperative congestive heart failure	77	9.1
Prior cardiac operation	50	5.8
Hypercholesterolemia	89	10.5

Table II. Procedural Outcomes ($n = 845$)

	30-day operative mortality (%)	Composite results (%)
All patients	4.4	23
Thoracic aneurysm		
Root	2.1	23.1
Ascending	3.5	31
Arch	5.4	45.1
Descending	8.6	36.4
TAAA	12.4	68.6

Table III. Description of each prediction model ($n = 845$)

	30-day operative mortality				Composite mortality or major morbidity			
			95%CI				95%CI	
	P	OR	Lower	Upper	*P*	OR	Lower	Upper
Age	—	—	—	—	0.033	1.292	1.02	1.64
Gender	—	—	—	—	0.002	1.829	1.26	2.66
Myocardial infarction	—	—	—	—	0.011	3.566	1.34	9.52
Poor LV function	—	—	—	—	0.032	3.105	1.1	8.76
NYHA ≧ 2	—	—	—	—	0.007	1.688	1.15	2.47
Renal failure	0	11.37	3.727	34.66	—	—	—	—
Respiratory insufficiency	0	11.12	3.195	38.67	—	—	—	—
Reoperation	—	—	—	—	0.001	2.02	1.36	3.01
Rupture	0.02	4.225	1.256	14.22	0	6.975	2.61	18.7
Acute aortic dissection	—	—	—	—	0	2.339	1.53	3.59
Dissecting aortic aneurysm	0.001	13.02	2.796	60.6	—	—	—	—
Pseudoaneurysm	0.024	11.23	1.377	91.66	—	—	—	—
Aortic arch	—	—	—	—	0	2.376	1.61	3.51
Thoracoabdominal aneurysm	0.014	2.668	1.22	5.835	0	3.511	2.12	5.81

Table IV. Performance of each prediction model ($n = 845$)

	30-day operative mortality	Composite mortality or major morbidity
C-statistic	0.82	0.76
Hosmer-Lemeshow test	0.56	0.35

1968, Bentall reported a technique for the combined treatment of diseases of the aortic valve and the segment of the ascending aorta using a valvulated tube in which the coronary artery ostia were reimplanted.[2] In the years since, this technique has gone through several modifications and has become the procedure of choice for the treatment of aortic valve disease associated with the involvement of the ascending aorta.[9-12] Thus, the life expectancy of patients with MFS has dramatically improved from about 45 years in 1972[8] to 72 years in 1995.[13]

This study demonstrated that the 30-day operative mortality of aortic root surgery including both dissecting and nondissecting aneurysm in MFS patients was 2.1%. The JATS publishes an Annual Report of all Registry data, and the most recent version reported that the 30-day operative mortality of aortic root surgery performed for acute dissecting aneurysm and nondissecting, unrupturred aneurysm was 16.3% and 2.7%, respectively.[1] The better results in our study than the JATS Registry report might be attributed to the younger ages, less atherosclerotic changes of the aortic wall, and less opportunity for accompanying diseases in MFS patients. However, the operative mortality of thoracoabdominal aneurysm in MFS patients was 12.4%, which is not better than the number reported in the JATS Registry report; the 30-day operative mortality of thoracoabdominal procedures for chronic Stanford type B aortic dissection and nondissecting unruptured thoracoabdominal aneurysm was 10.7% and 6.9%, respectively.[1] It is likely that the thoracoabdominal aneurysms in MFS patietns in our study included more extensive types than the JATS Registry report, although classification of thoracoabdominal aneurysms was not clarified in either study.

There were two important variables affecting both the 30-day operative mortality rates and the composite results; ruputure for operative indication (OR, 3.67; 95% CI, 2.80 to 4.81 and OR, 3.67; 95% CI, 2.80 to 4.81) and thoracoabdominal aortic aneurysm (OR, 3.67; 95% CI, 2.80 to 4.81 and OR, 3.67; 95% CI, 2.80 to 4.81). Other factors, like preoperative high creatinine levels ≧ 3.0 mg/dL, severe chronic lung disease, dissecting aortic aneurysm, and pseudoaneurysm were also significant risk factors for the 30-day operative mortality in our study.

Aortic root dilatation, with subsequent aortic valve regurgitation, aortic dissection, or rupture, is a common and morbid cardiovascular abnormality in MFS patients.[14] As shown in our study, because the morbidity and mortality rates in MFS patients undergoing elective root surgery is low, and besides, emergency operation for aneurysmal rupure or acute dissection worsens the clinical results, early recognition of the disorder, identification of presymptomatic patients, and subsequent institution of surgical therapy is mandatory to reduce the frequency of catastrophic aortic events.

Symptomatic aneurysms have a much worse prognosis than asymptomatic ones, and should be resected regardless of size. There is an operative mortality of up to 20% for acute ascending aortic dissection in MFS. MFS patients who suffer aortic dissection have a significantly reduced long term survival, reported at 50–70% at 10 years.[15] These facts emphasise the importance of prophylactic aortic surgery before aortic dissection occurs in MFS. Recent guidelines have suggested that prophylactic aortic surgery be performed in adults with MFS when the aortic root diameter exceeds 5 cm.[15] Aortic surgery should also be considered in MFS when the aortic root exceeds 4.5 cm and there is a family history of aortic dissection, when there is rapid aortic growth (> 5–10 mm per year), and when significant aortic insufficiency is present. Aortic diameter should be measured serially by a transthoracic echocardiogram at multiple levels and compared to normal values based on age and body surface area. Unfortunately, there is no information about size criteria for operative indication in the study. Because Japanese people are generally smaller than people in western countries and the size of the vasculature might be accordingly smaller, further investigation is warranted to elucidate the true criteria of aortic size for operative indication in Japanese people.

Our study found that the operative mortality of thoracoabdominal aneurysm in MFS patients was not better than the JATS Registry report in the general population. Although en-

dovascular treatment has been demonstrated to be effective in type B aortic dissection and descending thoracic aneurysms in non-Marfan patients, it may have limited durability in MFS patients, because the aorta is prone to dilate in these connective tissue disorders.[16,17]

The validity of our study is limited because the odds ratio of several factors for the 30-day operative mortality were quite high (> 10) and suboptimal. These high odds ratios are attributed to the small number of each factor and therefore the figures themselves are not reliable, although these factors surely affect the results significantly. Additional limitation is that we did not divide our data into analyzing and validation data sets because of the relatively small volume of data. It would be possible to perform a validation of our risk model by dividing into the 2 data sets when the volume of data becomes large enough.

In conclusion, we have reported a risk stratification study on cardiovascular surgery that uses a nationwide cardiovascular surgery database. By analyzing 845 patients, the 30-day operative mortality rate was 4.4%. Renal insufficiency and respiratory disorder had great impacts on the operative mortality of MFS patients undergoing cardiovascular surgery. Because patients with aortic dissection or aortic rupture showed high operative mortality, close follow-up to avoid emergency operation is mandatory to improve the operative results in MFS patients. Achieving good results from surgery of the thoracoabdominal aorta was also quite challenging in MFS patients.

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Pulse Pressure and Type A Acute Aortic Dissection In-Hospital Outcomes (from the International Registry of Acute Aortic Dissection)

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Little is known about the relation between type A acute aortic dissection (TAAAD) and pulse pressure (PP), defined as the difference between systolic and diastolic blood pressure. In this study, we explored the association between PP and presentation, complications, and outcomes of patients with TAAAD. PP at hospital presentation was used to divide 1,960 patients with noniatrogenic TAAAD into quartiles: narrowed (≤39 mm Hg, n = 430), normal (40 to 56 mm Hg, n = 554), mildly elevated (57 to 75 mm Hg, n = 490), and markedly elevated (≥76 mm Hg, n = 486). Variables relating to index presentation and in-hospital outcomes were analyzed. Patients with TAAAD in the narrowed PP quartiles were frequently older and Caucasian, whereas patients with markedly elevated PPs tended to be male and have a history of hypertension. Patients who demonstrated abdominal vessel involvement more commonly demonstrated elevated PPs, whereas patients with narrowed PPs were more likely to have periaortic hematoma and/or pericardial effusion. Narrowed PPs were also correlated with greater incidences of hypotension, cardiac tamponade, and mortality. Patients with TAAAD who were managed with endovascular and hybrid procedures and those with renal failure tended to have markedly elevated PPs. No difference in aortic regurgitation at presentation was noted among groups. In conclusion, patients with TAAAD in the third PP quartile had better in-hospital outcomes than patients in the lowest quartile. Patients with narrowed PPs experienced more cardiac complications, particularly cardiac tamponade, whereas those with markedly elevated PPs were more likely to have abdominal aortic involvement. Presenting PP offers a clue to different manifestations of acute aortic dissection that may facilitate initial triage and care. **(Am J Cardiol 2014;113:1255–1259)**

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See page 1258 for disclosure information.

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Pulse pressure (PP) has been the focus of a number of studies in several populations of cardiovascular disease.[1,2] PP, the force that a heart generates with each contraction, is defined as the difference between systolic and diastolic blood pressure. Wide PP is strongly correlated with long standing hypertension where there is a loss of aortic elasticity in chronic disease.[3,4] Wide PP has been associated with cardiovascular, coronary, and all-cause mortality in various patient populations.[5–9] A narrow PP at hospital admission is an independent predictor of mortality in patients with acute coronary syndrome.[10] Little is known about the relation between PP and type A acute aortic dissection (TAAAD). We hypothesized that patients with TAAAD who presented with a narrow PP would be more likely to have cardiac tamponade and experience negative outcomes and increased mortality compared with patients who exhibited normal and mildly elevated PPs.[11] We also believe that patients with a wide PP might have increased age, more malperfusion, or aortic valve disruption leading to aortic valve regurgitation and worse outcomes.

Methods

The International Registry of Acute Aortic Dissection (IRAD) has collected data on patients with acute aortic dissection at 24 aortic referral centers in 11 countries since

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Table 1
Demographics and patient history for all patients with type A aortic dissection

Variable	PP (mm Hg)				p Value
	≤39	40–56	57–75	≥76	
Number of patients	430 (21.9)	554 (28.2)	490 (25.0)	486 (24.8)	—
Demographics					
Age (yrs)	63.6 ± 13.477	62.04 ± 14.848	59.74 ± 14.794	60.78 ± 13.640	<0.001*
Age (≥70 yrs)	147 (34.2)	183 (33.0)	124 (25.3)	134 (27.6)	0.006*
Men	276 (64.2)	361 (65.2)	339 (69.2)	357 (73.5)	0.008*
White	376 (91.7)	468 (90.0)	404 (87.4)	378 (84.6)	0.006*
History					
Hypertension	301 (71.7)	382 (69.8)	350 (72.5)	385 (79.9)	0.002*
Atherosclerosis	94 (22.7)	106 (19.8)	83 (17.5)	104 (21.7)	0.224
The Marfan syndrome	13 (3.1)	31 (5.7)	30 (6.2)	14 (2.9)	0.021
Bicuspid aortic valve	17 (4.6)	20 (4.3)	16 (3.9)	15 (3.7)	0.924
Other aortic disease	9 (2.1)	8 (1.5)	8 (1.7)	6 (1.3)	0.756
Smoker: current	34 (28.3)	54 (36.2)	46 (32.4)	54 (37.2)	0.409
Cocaine abuse	4 (1.0)	8 (1.5)	8 (1.7)	9 (1.9)	0.702
Family history of aortic disease	9 (6.2)	17 (9.2)	23 (14.3)	10 (6.1)	0.036
Known aortic aneurysm	50 (12.1)	73 (13.5)	54 (11.3)	49 (10.2)	0.403
Previous aortic dissection	13 (3.1)	20 (3.7)	22 (4.6)	19 (4.0)	0.704
Aortic aneurysm/dissection surgery	22 (5.2)	37 (6.9)	30 (6.3)	31 (6.5)	0.742
Previous cardiac surgery	41 (9.7)	69 (12.9)	58 (12.3)	69 (14.4)	0.191

Data are presented as mean ± SD or n (%).
* Variables that have both a p value of <0.05 and a linear-by-linear association of <0.05.

Table 2
Findings on diagnostic imaging for all patients with type A aortic dissection

Variable	PP (mm Hg)				p Value
	≤39	40–56	57–75	≥76	
True intramural hematoma on first imaging study	21 (5.3)	26 (5.1)	17 (3.7)	17 (3.9)	0.567
True intramural hematoma progressing to dissection	4 (19.0)	4 (16.0)	3 (17.6)	2 (14.3)	1.000
Intramural hematoma (any study)	81 (18.8)	112 (20.2)	84 (17.1)	76 (15.6)	0.248
Pre-/postoperative extension of dissection	38 (9.4)	40 (7.7)	34 (7.3)	35 (7.6)	0.679
Any aneurysm	198 (51.0)	259 (51.8)	230 (51.3)	220 (50.2)	0.971
False lumen patency					
Patent	193 (72.3)	272 (71.0)	222 (73.3)	228 (71.0)	0.905
Partial thrombosis	44 (16.5)	66 (17.2)	61 (20.1)	67 (20.9)	0.423
Complete thrombosis	30 (11.2)	45 (11.7)	20 (6.6)	26 (8.1)	0.075
Abdominal vessel involvement	94 (22.1)	95 (17.3)	101 (20.8)	133 (27.6)	0.001*
Right renal	26 (6.1)	35 (6.4)	36 (7.4)	45 (9.3)	0.206
Left renal	56 (13.1)	48 (8.7)	59 (12.1)	85 (17.6)	<0.001*
Distal communication	69 (27.2)	92 (26.3)	73 (26.7)	83 (28.8)	0.906
Arch vessel involvement	147 (46.2)	166 (39.2)	128 (37.0)	135 (37.2)	0.052
Coronary artery compromised	32 (9.9)	53 (12.8)	35 (10.2)	48 (13.6)	0.337

Data are presented as n (%).
* Variables that have both a p value of <0.05 and a linear-by-linear association of <0.05.

January 1, 1996. Patients are enrolled if they present with nontraumatic, spontaneous, or iatrogenic dissections within 14 days of symptom onset. They are identified prospectively by physicians or retrospectively through discharge diagnoses, imaging, and/or surgical databases. Diagnosis is based on symptom onset, patient history, imaging, surgical examination, and/or autopsy. All sites have received approval from each hospital's institutional review board to participate in IRAD. A comprehensive description of the organization and methods of the IRAD database have been detailed previously.[12]

A standardized form with 290 variables was used to record information on patient demographics, medical history, clinical presentation, physical findings, imaging study results, medical and interventional management, and in-hospital outcomes. Data were collected at presentation or retrospectively through medical record analysis and reviewed for face validity and completeness at the coordinating center at the University of Michigan.

This study included patients with TAAAD enrolled in IRAD from January 1, 1996 to July 26, 2012. Patients with type B dissections and/or iatrogenic dissections were excluded, resulting in 1,960 study patients. These patients were arranged into quartiles based on PP at hospital presentation: narrow (≤39 mm Hg, n = 430), normal (40 to 56 mm

Table 3
Management, in-hospital pre- and/or postoperative complications, and mortality for all patients with type A aortic dissection

Variable	PP (mm Hg)				p Value
	≤39	40–56	57–75	≥76	
Management					
Medical	51 (11.9)	75 (13.5)	54 (11.0)	57 (11.7)	0.642
Surgical	372 (86.5)	475 (85.7)	426 (87.1)	410 (84.4)	0.639
Endovascular	4 (0.9)	1 (0.2)	7 (1.4)	9 (1.9)	0.031*
Hybrid	3 (0.7)	3 (0.5)	2 (0.4)	10 (2.1)	0.047*
Complications					
Aortic regurgitation	194 (55.1)	239 (51.3)	231 (57.5)	241 (57.5)	0.139
Periaortic hematoma	105 (30.2)	93 (20.2)	70 (17.9)	70 (17.7)	<0.001*
Pericardial effusion	224 (58.8)	235 (47.2)	153 (35.1)	138 (32.2)	<0.001*
Cerebrovascular accident: 1-h outcome	41 (10.5)	43 (8.7)	36 (8.1)	41 (9.3)	0.653
Coma: 1-h outcome	8 (2.1)	14 (2.8)	6 (1.4)	9 (2.1)	0.478
Spinal cord ischemia	4 (1.0)	4 (0.8)	4 (0.9)	4 (0.9)	0.986
Myocardial ischemia	51 (12.4)	61 (11.6)	53 (11.3)	35 (11.3)	0.078
Myocardial infarction	33 (8.0)	33 (6.3)	29 (6.2)	20 (4.3)	0.152
Mesenteric ischemia/infarction	25 (6.1)	30 (5.7)	19 (4.1)	36 (7.7)	0.126
Pre-/postoperative renal failure	102 (24.9)	141 (26.7)	94 (20.1)	136 (29.1)	0.014*
Pre-/postoperative extension of dissection	38 (9.4)	40 (7.7)	34 (7.3)	35 (7.6)	0.680
Pre-/postoperative hypotension	223 (53.9)	171 (32.4)	79 (17.0)	77 (16.6)	<0.001*
Cardiac tamponade	32 (7.5)	17 (3.1)	0 (0.0)	3 (0.6)	<0.001*
Limb ischemia	56 (13.8)	56 (10.7)	57 (12.2)	74 (15.9)	0.097
Complications (any)	34 (8.0)	33 (6.0)	27 (5.6)	44 (9.1)	0.099
In-hospital mortality	133 (30.9)	141 (25.5)	80 (16.3)	114 (23.5)	<0.001*
Cause of death: aortic rupture	23 (26.7)	27 (29.7)	16 (29.1)	15 (21.7)	0.700
5-yr Kaplan-Meier survival estimates (n at risk)	77.7 (19)	81.0 (21)	84.5 (19)	84.2 (16)	0.507

Data are presented as n (%).
* Variables that have both a p value of <0.05 and a linear-by-linear association of <0.05.

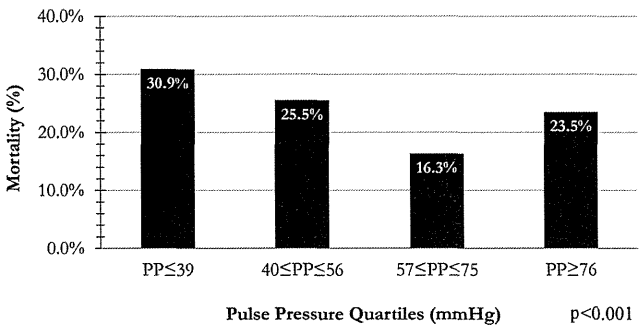

Figure 1. In-hospital mortality (%) among patients with acute type A aortic dissection in narrow, normal, mildly elevated, and markedly elevated PP quartiles.

Hg, n = 554), mildly elevated (57 to 75 mm Hg, n = 490), and markedly elevated (≥76 mm Hg, n = 486). When patients fell between quartiles, they were assigned to the higher grouping resulting in a slightly uneven sample size between quartiles.

Categorical variables were compared across PP quartiles using Pearson's chi-square test or Fisher's exact test as appropriate. Continuous variables were examined using analysis of variance. Linear-by-linear association was used to study linear trends across quartiles. The tables are marked with an asterisk to indicate variables that have both a p value of <0.05 and a linear-by-linear association of <0.05. Variables detailing demographics, patient history, presentation, imaging results, complications, and outcomes were analyzed for their relation to PP in patients with TAAAD. All statistical analyses were performed using SPSS, version 20.0 (IBM Corp.).

Results

The study cohort consisted of 1,960 subjects with TAAAD including 21.9% of patients in the narrow quartile, 28.3% in the normal quartile, 25.0% in the mildly elevated quartile, and 24.8% in the markedly elevated quartile. Patients in the narrow quartile (PP ≤39 mm Hg) were typically aged >70 years, women, a race other than Caucasian, and had an average age of 63.6 years (Table 1). Patients in the markedly elevated quartile (PP ≥76 mm Hg) had an average age of 60.8 years and tended to be Caucasian, men, and have a history of hypertension (Table 1). There was no correlation seen between PP and a history of atherosclerosis, previous smoking, or any previously diagnosed aortic conditions (Table 1).

Patients who presented with a narrow PP tended to have more cardiac complications in comparison with those in the other 3 quartiles (Tables 2 and 3). Specifically, they had greater incidences of periaortic hematoma, pericardial effusion, and cardiac tamponade than patients with normal, mildly elevated, and markedly elevated PPs (Table 3). Patients with TAAAD in the narrow PP quartile had a greater risk of in-hospital mortality than patients in the other quartiles (Figure 1). There was no relation between narrow PP and false lumen patency, coronary artery compromise, or long-term mortality (Tables 2 and 3).

Patients with TAAAD who had markedly elevated PPs at presentation were more inclined to have abdominal aorta involvement and distal complications compared with patients with narrow, normal, and mildly elevated PPs (Tables 2 and 3). These patients had greater incidences of abdominal vessel involvement, left renal artery involvement, and in-hospital renal failure than patients in the other 3 quartiles (Table 2). The selection of endovascular and hybrid managements was also correlated with wide PP at presentation (Table 3). There was no link between wide PP and aortic regurgitation, right renal involvement, or distal communication (Tables 2 and 3).

Discussion

This is the first comprehensive assessment of the association of presenting PP with in-hospital complications and mortality of patients with acute type A aortic dissection. As expected, the quartile with the narrowest PPs ($\leq$39 mm Hg) had the highest mortality rate (30.9%). This subgroup was characterized by a high incidence of pericardial effusion and hypotension. Such patients typically have pericardial bleeding as a result of leakage from the tear in the aortic wall into the pericardial sac's reflection, which extends up into the ascending aorta. This often leads to early death, but for a percentage of patients, the leakage is modest at first, leading to hemodynamic blunting of cardiac systolic function but not frank tamponade.

We had also hypothesized that patients in the markedly elevated PP quartile would have increased mortality compared with those in the middle 2 quartiles owing to several other factors. We believed that wider PPs would be seen more often in patients with greater underlying aortic stiffness, loss of peripheral resistance owing to malperfusion or extensive dissection, and/or possibly due to development of aortic valve regurgitation in a subset of patients. Also, because PP widens with age, we expected that older patients would be found in the markedly elevated PP quartile. Interestingly, the quartile with widest PP did not have the highest average age, but it did contain the greatest number of men (73.5% compared with 64.2% in quartile 1). Expectedly, this group experienced higher rates of abdominal artery involvement, renal artery compromise, and renal failure. We believe that such malperfusion syndromes are associated with release of various cytokines, which lower peripheral arterial resistance and accordingly elevate PP in affected patients. This association could influence therapeutic approaches including site of aortic access for endovascular therapy (e.g., axillary artery vs femoral artery). No association between wider PPs and aortic valve insufficiency was found. This likely relates to the notion that a lowering of peripheral arterial resistance and therefore diastolic blood pressure represents an adaptation to chronic aortic valve regurgitation but not acute aortic valve incompetence.

A high PP has been linked to cardiovascular risk in a number of populations. The Framingham Study discovered that elevated PP is an important risk predictor for cardiovascular events in patients living in Massachusetts.[13] Similarly, Benetos et al[14] showed that PP elevation predicts increased cardiovascular risk in a cohort of French men. Domanski et al[7] showed that elevated PP provided independent risk predictability for cardiovascular events over 16.5 years in a cohort of subjects enrolled in the National Health and Nutrition Examination Survey registry. Zakopoulos et al[15] observed that a widened PP predicted elevated cardiovascular risk even in normotensive subjects. PP appears to be a better predictor of myocardial infarction,[5] left ventricular hypertrophy,[5] and cardiovascular death [4,5,16] than either diastolic or systolic blood pressure alone.

Each of these associations underlines the general notion that PP reflects 2 mechanisms of cardiovascular physiology, which are strongly correlated with end organ risk.[1,2] The first is development of a high-pressure aortic wave by the left ventricle (proximal compartment) leading to the recorded systolic pressure. Left ventricular hypertrophy is more common in patients with widened PP and, of course, such hypertrophy correlates with long-term risk of heart failure, both diastolic and systolic. The second association is indirect and relates to the distal compartment of arterial function. As arteries stiffen and lose their natural elasticity, diastolic blood pressure decreases, again leading to a widened PP. Thus, both cardiac and arterial physiologies are tightly connected over time as recorded through serial measurement of PP.

Our data suggest that in addition to frank hypotension, a narrow PP indicates a high likelihood of pericardial involvement, and a narrow PP should compel the care team to arrange for the most expeditious aortic repair possible. Second, clinicians should also glean from our study that a markedly elevated pulse may be associated with malperfusion conditions affecting the mesentery, renal bed, limbs, or other vital structures.

There are several limitations to our study. First, we analyzed blood pressure and its associated PP at a single point in time, the first recorded measurement. This ignores the notion that PP is a dynamic measurement, varying beat by beat. Second, our associations of PP with patient outcomes have excluded the effects of diagnostic testing, medical treatment, surgical treatment, and complications. However, overall treatment (surgery in approximately 85%) was relatively similar across all 4 quartiles.

Disclosures

The authors have no conflicts of interest to disclose.

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Stroke and Outcomes in Patients With Acute Type A Aortic Dissection

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Background—Stroke is a highly dreaded complication of type A acute aortic dissection (TAAAD). However, little data exist on its incidence and association with prognosis.

Methods and Results—We evaluated 2202 patients with TAAAD (mean age 62±14 years, 1487 [67.5%] men) from the International Registry of Acute Aortic Dissection to determine the incidence and prognostic impact of stroke in TAAAD. Stroke was present at arrival in 132 (6.0%) patients with TAAAD. These patients were older (65±12 versus 62±15 years; P=0.002) and more likely to have hypertension (86% versus 71%; P=0.001) or atherosclerosis (29% versus 22%; P=0.04) than patients without stroke. Chest pain at arrival was less common in patients with stroke (70% versus 82%; P<0.001), and patients with stroke presented more often with syncope (44% versus 15%; P<0.001), shock (14% versus 7%; P=0.005), or pulse deficit (51% versus 29%; P≤0.001). Arch vessel involvement was more frequent among patients with stroke (68% versus 37%; P<0.001). They had less surgical management (74% versus 85%; P<0.001). Hospital stay was significantly longer in patients with stroke (median 17.9 versus 13.3 days; P<0.001). In-hospital complications, such as hypotension, coma, and malperfusion syndromes, and in-hospital mortality (adjusted odds ratio, 1.62; 95% confidence interval, 0.99–2.65) were higher among patients with stroke. Among hospital survivors, follow-up mortality was similar between groups (adjusted hazard ratio, 1.15; 95% confidence interval, 0.46–2.89).

Conclusions—Stroke occurred in >1 of 20 patients with TAAAD and was associated with increased in-hospital morbidity but not long-term mortality. Whether aggressive early invasive interventions will reduce negative outcomes remains to be evaluated in future studies. ***(Circulation.* 2013;128[suppl 1]:S175-S179.)**

Key Words: aortic dissection ■ mortality ■ stroke management

Stroke is a highly dreaded complication of type A acute aortic dissection (TAAAD). Brain tissue ischemia from hypotension and direct compromise of cerebral circulation are believed to be the underlying mechanisms of stroke in patients with TAAAD.[1] Single-center studies of few patients have reported a stroke incidence between 3% and 32% and demonstrated increased morbidity and mortality in these patients.[2–5] Accordingly, we evaluated a large cohort of >2000 patients with TAAAD enrolled in the International Registry of Acute Aortic Dissection (IRAD)[6–8] to determine the incidence, presentation, management, prognosis, and outcomes of stroke in this cohort.

Methods

Study Population

We analyzed data on 2202 TAAAD IRAD patients enrolled from January 1, 1996, to August 18, 2012, at 25 aortic centers. The structure and methods of IRAD have been previously published.[6–8] Patients were identified prospectively at presentation and retrospectively via discharge diagnoses, imaging, and hospital databases. Diagnosis was confirmed by imaging, surgical visualization, or autopsy. Each site's institutional review committee approved participation.

Data Collection and Definitions

Data on 290 variables were recorded on a standardized form detailing demographics, history, clinical presentations, imaging results,

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treatment, and outcomes. TAAAD was defined as any nontraumatic dissection of the aorta proximal to the left subclavian artery presenting within 14 days of symptom onset. Stroke was defined in the database lexicon as a cerebrovascular accident representing a loss of neurological function (loss or slurring of speech, altered state of consciousness) caused by an ischemic event, confirmed by computed tomography or MRI. This definition of stroke was formulated to be conservative, considering that not all patients had routine neurological consults postdissection. Therefore, we have probably somewhat underestimated the incidence of less obvious neurological injuries. Other definitions were similar to those in previous publications.[6–8]

Statistical Analysis

Data are shown as frequencies and percentages, mean±SD, or medians with first and third quartiles. Univariate comparisons between patients with and without stroke were performed using the χ^2 test for categorical data and Student t test for continuous variables with normal data distributions. Nonparametric test of medians was used for data with skewed distributions. In all cases, missing data were not defaulted to negative, and denominators reflect cases for which information was reported. Binary logistic regression analysis was performed to determine the independent correlates of presenting stroke and to assess the independent association of presenting stroke with in-hospital mortality. Cox proportional hazard models were used to identify the independent association of stroke with long-term mortality among patients discharged alive at hospitalization. Odds ratios and hazard ratios with their corresponding 95% confidence intervals were generated to provide an estimate of these associations. All P values were 2-sided, with values <0.05 considered statistically significant. Analyses were performed using SPSS 20.0 statistical analysis software (IBM Corporation).

Results

Incidence, Demographics, History, and Clinical Symptoms and Signs

Among 2202 patients with TAAAD enrolled in IRAD, 132 (6.0%) had stroke at presentation (Table 1). These patients were older, with only 1 stroke patient <40 years of age. A history of hypertension was 1.2× more common in patients with stroke, and atherosclerosis was ≈1.4-fold higher in the stroke cohort compared with nonstroke patients. Presentation with chest or back pain was less frequent, whereas presentation with syncope was 3-fold higher among TAAAD patients with stroke. Shock and pulse deficit were 2-fold higher, and the combination of shock, hypotension, and cardiac tamponade was 1.4× higher among patients with stroke. Other demographics, clinical features, and presenting symptoms were similar between groups (Table 2).

Table 1. Patient Characteristics in TAAAD Patients With and Without Presenting Stroke

Variable	Overall n (%)	Stroke n (%)	No Stroke n (%)	P
n (%)	n=2202 (100)	n=132 (6.0)	n=2070 (94.0)	Value
Demographics				
Age, mean±SD, y	61.9±14.4	65.0±11.5	61.7±14.6	0.002
Age <40 y	167 (7.6)	1 (0.8)	166 (8.0)	0.002
Male	1487 (67.5)	82 (62.1)	1405 (67.9)	0.17
White	1837(89.0)	109 (88.6)	1728 (89.1)	0.88
Transferred to IRAD sites	1654 (75.1)	95 (72.0)	1559 (75.3)	0.39
Medical history				
Marfan syndrome	88 (4.1)	2 (1.6)	86 (4.3)	0.14
Hypertension	1554 (72.3)	110 (85.9)	1444 (71.4)	<0.001
Cocaine abuse	27 (1.3)	2 (1.6)	25 (1.3)	0.68
Atherosclerosis	470 (22.1)	37 (29.4)	433 (21.6)	0.04
Bicuspid aortic valve	86 (4.6)	7 (6.4)	79 (4.5)	0.38
Iatrogenic dissection	56 (2.6)	1 (0.8)	55 (2.8)	0.26
Prior aortic dissection	89 (4.2)	4 (3.1)	85 (4.2)	0.56
Prior aortic aneurysm	269 (12.6)	13 (10.3)	256 (12.7)	0.43
Diabetes mellitus	125 (5.9)	10 (7.8)	115 (5.7)	0.33
Prior cardiovascular surgery	291 (13.8)	12 (9.5)	279 (14.0)	0.15

IRAD indicates International Registry of Acute Aortic Dissection.

Diagnostic Imaging and Use of Medications

The use of diagnostic imaging techniques was similar in patients with and without stroke. Chest radiograph, ECG, and imaging study findings were also similar between cohorts, with the exception of more arch involvement in patients with stroke (Table 3).

Patients with stroke had lower in-hospital β-blocker use; otherwise, use of evidence-based medical therapies at presentation and discharge was similar between groups (Table 4). Patients with stroke were twice as likely to undergo nonoperative management compared with those without stroke.

Complications and In-Hospital Mortality

In-hospital complications, such as hypotension and coma, were significantly higher in patients with stroke, who also demonstrated a trend toward greater incidence of malperfusion syndrome (Table 5). Although almost all other complications were higher in patients with stroke, these differences did not reach statistical significance. Median length of stay was 4.8 days longer in patients with stroke (17.8 days with stroke, Q1–Q3: 12.1–31.1 days; 13.0 days without, Q1–Q3: 8.6–21.0 days; P<0.001). Finally, overall mortality was 1.8-fold higher in patients with stroke (adjusted odds ratios, 1.62; 95% confidence interval, 0.99–2.65; P=0.055). Mortality was higher in patients with stroke compared with nonstroke patients with

Table 2. Presenting Sign and Symptoms in TAAAD Patients With and Without Stroke

Variable	Overall n (%)	Stroke n (%)	No Stroke n (%)	P Value
Presenting symptoms and signs				
Chest pain	1744 (81.6)	85 (69.7)	1659 (82.3)	<0.001
Back pain	889 (42.8)	36 (32.4)	853 (43.4)	0.023
Abrupt onset of pain	1729 (83.4)	95 (84.1)	1634 (83.4)	0.85
Migrating pain	284 (14.1)	17 (16.0)	267 (14.0)	0.56
Syncope	358 (17.0)	54 (43.5)	304 (15.3)	<0.001
Congestive heart failure	151 (6.9)	10 (8.1)	141 (6.9)	0.61
Mean systolic blood pressure±SD mm Hg	122.3±18.2	127.7±41.6	122.1±16.3	0.31
Mean diastolic blood pressure±SD mm Hg	69.7±11.4	69.3±10.3	69.7±11.4	0.80
Shock	154 (7.4)	17 (13.8)	137 (7.0)	0.005
Hypotension/tamponade/shock	565 (27.2)	46 (37.4)	519 (26.5)	0.009
Any pulse deficit	504 (29.9)	54 (50.5)	450 (28.5)	<0.001

TAAAD indicates type A acute aortic dissection.

Table 3. Diagnostic Imaging in TAAAD Patients With and Without Stroke

Variable	Overall n (%)	Stroke n (%)	No Stroke n (%)	*P* Value
Chest radiograph				
Normal	358 (22.0)	20 (20.8)	338 (22.0)	0.78
Widened mediastinum	832 (53.0)	55 (59.8)	777 (52.6)	0.18
Abnormal aortic contour	633 (41.6)	44 (47.8)	589 (41.2)	0.21
Abnormal cardiac contour	363 (23.8)	28 (30.8)	335 (23.3)	0.11
Pleural effusion	186 (12.2)	12 (13.0)	174 (12.2)	0.80
ECG				
Normal	648 (32.3)	35 (31.0)	613 (32.3)	0.76
NSST	752 (39.6)	37 (34.6)	715 (39.9)	0.28
LVH	382 (20.4)	29 (27.4)	353 (20.0)	0.07
Prior infarction	121 (6.5)	9 (8.3)	112 (6.3)	0.42
ST elevation or new infarct	132 (7.0)	9 (8.3)	123 (6.9)	0.60
Diagnostic imaging				
Any imaging study	2063 (98.4)	124 (97.6)	1939 (98.4)	0.46
Computed tomography	1784 (81.5)	113 (86.3)	1671 (81.2)	0.15
Echocardiography (TEE and TTE)	1609 (73.5)	88 (66.7)	1521 (73.9)	0.07
Aortography	249 (11.5)	22 (16.7)	227 (11.1)	0.054
MRI	88 (4.2)	8 (6.2)	80 (4.0)	0.23
Diagnostic imaging findings				
Widest diameter of ascending aorta median (Q1–Q3), cm	5.0 (4.5–5.7)	5.0 (4.2–5.4)	5.0 (4.5–5.8)	0.07
Pericardial effusion	819 (41.9)	53 (46.5)	766 (41.6)	0.30
Arch vessel involvement	628 (39.0)	66 (68.0)	562 (37.1)	<0.001
Aortic regurgitation	996 (54.3)	52 (49.1)	944 (54.6)	0.26

LVH indicates left ventricular hypertrophy; NSST, nonspecific ST-T changes; Q1–Q3, first quartile–third quartile; TAAAD, type A acute aortic dissection; TEE, transesophageal echocardiogram; and TTE, transthoracic echocardiogram.

similar management. Among hospital survivors, follow-up mortality (median follow-up 2 years, Q1–Q3: 1 –4 years) was not different between groups (adjusted hazard ratio, 1.15; 95% confidence interval, 0.46–2.89; P=0.76). Estimates using Cox proportional hazard model suggested excellent 5-year survival in 4 of 5 TAAAD surgically treated stroke patients who survived past index hospitalization; conversely, 5-year survival among medically managed stroke patients was dismal (estimated mortality of 100%).

Independent Clinical Correlates of Presenting Stroke and In-Hospital Mortality

Arch vessel involvement on imaging was the greatest predictor of stroke (Table 6). In addition, syncope, abdominal pain, presenting pulse deficit, abnormal chest radiograph without accompanying pain, and history of hypertension had significant independent adjusted correlations with stroke in our cohort.

In TAAAD patients presenting with stroke, surgical management had strong independent adjusted associations with improved survival (Table 7). Variables with independent adjusted associations with decreased survival included coma, pleural effusion, pulse deficit on presentation, and mesenteric ischemia.

Table 4. Treatment of TAAAD Patients With and Without Stroke

Variable	Overall n (%)	Stroke n (%)	No Stroke n (%)	*P* Value
Medical therapies: in hospital				
β-Blockers	1055 (53.6)	46 (42.6)	1009 (54.2)	0.018
ACE inhibitors	68 (10.3)	2 (6.1)	66 (10.5)	0.56
Angiotension II antagonist	27 (4.1)	2 (6.1)	25 (4.0)	0.64
Calcium antagonists	223 (11.8)	15 (14.0)	208 (11.6)	0.46
Statins	33 (5.8)	2 (8.0)	31 (5.7)	0.65
Medical therapies: discharge				
β-blockers	1269 (83.0)	57 (81.4)	1212 (83.1)	0.71
ACE inhibitors	599 (40.3)	25 (35.7)	574 (40.5)	0.43
Angiotension II antagonist	74 (13.0)	4 (16.0)	70 (12.9)	0.55
Calcium antagonists (Ca channel blocker)	536 (35.8)	21 (29.6)	515 (36.1)	0.26
Statins	127 (26.0)	9 (45.0)	118 (25.2)	0.048
Definitive management				
Surgery	1863 (84.6)	97 (73.5)	1766 (85.4)	<0.001
Medical therapy only	284 (12.9)	31 (23.5)	253 (12.2)	<0.001
Percutaneous	29 (1.3)	2 (1.5)	27 (1.3)	0.69

ACE indicates angiotension-converting enzyme; and TAAAD, type A acute aortic dissection.

Discussion

Our study, the largest to date, suggests that stroke at hospital admission is observed in 6% of patients with TAAAD. These patients were older, more often had hypertension and atherosclerosis, and presented more frequently with symptoms such as syncope rather than the more classic presentation of chest or back pain. Patients with stroke were also likely to have signs of hypotension, shock, and pulse deficit. Except aortic arch involvement, imaging study findings were similar between groups. Medical therapies in hospital and at discharge were similar in the 2 groups, with the lower use of in-hospital β-blocker among stroke patients likely a reflection of the more frequent hypotension and shock in these patients. Patients with stroke were more likely to be managed medically and had greater length of stay. In-hospital mortality was higher in patients with stroke compared with nonstroke patients, regardless of the management strategy; however, postdischarge mortality did not differ between groups.

Few studies have focused on stroke in patients with TAAAD, most of which are single-center case reports[9–15] evaluating a small number of patients with few stroke events.[2–5,16] These studies described a stroke incidence between 3% and 32% in 24 to 174 patients with TAAAD. Similar to our findings, some studies reported more frequent painless presentation, syncope, and hypotension in patients with stroke. Furthermore, most studies suggested a higher mortality for patients with stroke compared with those without it. Most of these reports focused primarily on patients undergoing surgery, and many did not characterize the factors associated with risk of presenting stroke and mortality in those with stroke.

Table 5. Outcomes in TAAAD Patients With and Without Stroke

Variable	Overall n (%)	Stroke n (%)	No Stroke n (%)	*P* Value
In-hospital complications				
Malperfusion	696 (33.1)	50 (41.0)	646 (32.6)	0.056
Coma	121 (5.5)	24 (18.2)	97 (4.7)	<0.001
Myocardial ischemia/ infarction	294 (14.0)	23 (19.2)	271 (13.6)	0.09
Mesenteric ischemia/ infarction	130 (6.2)	13 (11.0)	117 (5.9)	0.024
Acute kidney failure	521 (24.7)	36 (29.8)	485 (24.3)	0.18
Hypotension	641 (30.4)	52 (43.3)	589 (29.6)	0.002
Cardiac tamponade	388 (18.4)	28 (23.1)	360 (18.1)	0.17
Limb ischemia	273 (13.0)	20 (16.8)	253 (12.7)	0.20
In-hospital mortality				
Overall	555 (25.2)	56 (42.4)	499 (24.1)	<0.001
Surgically treated patients	371 (19.9)	30 (30.9)	341 (19.3)	0.005
Medically treated patients	160 (56.3)	24 (77.4)	136 (53.8)	0.012
5-year mortality estimate (Kaplan–Meier)				
Overall	17.6%	24.1%	17.2%	0.30
Surgery	14.1%	22.1%	14.1%	0.51
Medical therapy only	62.0%	100.0%	58.7%	0.56

TAAAD indicates type A acute aortic dissection.

Our findings may have several implications for patients with TAAAD and presenting stroke. In addition to chest or back pain preceding the stroke, this and other studies suggest that a high index of suspicion should also be made for TAAAD in stroke patients who present with syncope hypotension, pulse deficit, and a murmur of aortic regurgitation. In patients with these symptoms, early imaging would enable diagnosis of TAAAD if present and help prevent inadvertent use of fibrinolytic therapy that could lead to fatal outcomes in this cohort.[10,12,17–19]

Urgent surgical repair is required for TAAAD because conservative management is associated with a high incidence of early mortality.[6] However, some studies have suggested that immediate surgical repair of TAAAD in the presence of stroke has a prohibitive risk associated with hemorrhagic worsening of an ischemic infarction after reperfusion subsequent to cardiopulmonary bypass and full anticoagulation.[20,21] Others have suggested that delaying repair until cerebral injury stabilizes may minimize these concerns, albeit exposing patients to an early hazard of death from rupture.[22] However, Fann et al[3] reported no worsening of cerebral symptoms in 7 surgically treated patients with TAAAD. Several small studies have since corroborated the feasibility and safety of early surgical repair in TAAAD patients with stroke.[9,13,16,23,24] In fact, 1 study suggested no benefit of surgery beyond 12 hours when cerebral damage is almost complete.[16] Deeb et al[25] have suggested good results with a hybrid approach involving fenestrations for immediate percutaneous reperfusion followed by surgery after the brain tissue has healed. Although our data suggest that surgically treated TAAAD patients with stroke had higher mortality than those without stroke, surgical patients had much lower mortality than patients treated medically, regardless of whether they presented with stroke. Furthermore, adjusted survival estimates for patients with TAAAD suggested that among surgically treated patients with TAAAD discharged alive at index hospitalization, ≈4 of 5 patients survived at 5-year follow-up, whereas long-term outcomes were dismal among stroke patients treated medically (100% mortality). Our results and those of previous studies suggest, compared with medical therapy, that definitive early repair in TAAAD patients presenting with stroke is safe and likely associated with lower short- and long-term mortality. Further studies are warranted in TAAAD patients presenting with stroke to determine which stroke patients will benefit more from surgery and whether or not stroke severity impacts outcomes. In addition, analyses should be performed to determine the optimal timing of surgery (early versus late) and to compare outcomes between surgical strategies used in this cohort.

Table 6. Independent Clinical Correlate of Presenting Stroke Among These TAAAD Patients

Independent Adjusted Effects of Clinical Correlates of Presenting Stroke					
		95% CI for Odds Ratio			
Variable	Odds Ratio	Lower	Upper	Wald χ^2	*P* Value
Any arch vessel involvement	3.393	1.932	5.961	18.063	<0.001
Syncope on presentation	3.117	1.781	5.457	15.845	<0.001
History of hypertension	3.275	1.450	7.397	8.149	0.004
Abdominal pain on presentation	0.347	0.165	0.729	7.800	0.005
Any pulse deficit	2.019	1.172	3.479	6.410	0.011
Abnormal chest radiograph without associated pain	1.932	1.077	3.466	4.874	0.027

Hosmer–Lemeshow test *P*=0.525. C=0.780. CI indicates confidence interval; and TAAAD, type A acute aortic dissection.

Table 7. Independent Clinical Correlate of In-hospital Death Among TAAAD Patients Presenting With Stroke

Independent Adjusted Effects of Clinical Correlates of In-Hospital Death in Patients With Stroke					
		95% CI for Odds Ratio			
Variable	Odds Ratio	Lower	Upper	Wald χ^2	*U* Value
Age ≥70 y	1.622	0.379	6.937	0.426	0.514
Surgical management	0.015	0.002	0.129	14.555	<0.001
Coma	10.081	1.317	77.161	4.952	0.026
Pleural effusion on any test	4.303	1.031	17.959	4.007	0.045
Any pulse deficit	6.629	1.483	29.624	6.130	0.013
Mesenteric ischemia	47.605	3.458	655.452	8.336	0.004

Hosmer–Lemeshow test *P*=0.387. C=0.908. CI indicates confidence interval; and TAAAD, type A acute aortic dissection.

Limitations

Patients in this study had TAAAD and were admitted to centers specializing in aortic disease. Thus, our results may not be applicable to those with chronic TAAAD, type B AAD,

or those treated at smaller centers. IRAD data are collected retrospectively and prospectively through voluntary site participation and are subject to incomplete information, particularly with regard to long-term outcomes. As such, some strokes may have not been adequately captured in the registry. Furthermore, because IRAD is composed of tertiary care centers, patients with TAAAD and stroke who died at primary care centers or who were unable to be transferred secondary to their acute illness were not included. Treatment strategies were not protocol driven and were determined by the treating physicians. Thus, inference regarding the effectiveness of various strategies on outcomes in these patient cohorts should be made with caution. Imaging results were based on interpretation at the IRAD center and were not independently adjudicated. We are also unable to provide any details on stroke size, extent of debilitation after stroke, or improvement or resolution of neurological symptoms.

Conclusions

Stroke occurred in >1 of 20 patients with TAAAD and was associated with increased morbidity and in-hospital mortality, but not higher long-term mortality among survivors. Our data suggest that aggressive early intervention with rapid establishment of cerebral flow and surgical repair of dissection have significant potential for reducing morbidity and improving mortality.

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Disclosures

None.

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Extent of Preoperative False Lumen Thrombosis Does Not Influence Long–Term Survival in Patients With Acute Type A Aortic Dissection

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ORIGINAL RESEARCH

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Extent of Preoperative False Lumen Thrombosis Does Not Influence Long-Term Survival in Patients With Acute Type A Aortic Dissection

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Background—Partial thrombosis of the false lumen has been related to aortic growth, reoperations, and death in the chronic phase of type B and repaired type A aortic dissections. The impact of preoperative false lumen thrombosis has not been studied previously. We used data from a contemporary, multinational database on aortic dissections to evaluate whether different degrees of preoperative false lumen thrombosis influenced long-term prognosis.

Methods and Results—We examined the records of 522 patients with surgically treated acute type A aortic dissections who survived to discharge between 1996 and 2011. At the preoperative imaging, 414 (79.3%) patients had patent false lumens, 84 (16.1%) had partial thrombosis of the false lumen, and 24 (4.6%) had complete thrombosis of the false lumen. The annual median (interquartile range) aortic growth rates were 0.5 (−0.3 to 2.0) mm in the aortic arch, 2.0 (0.2 to 4.0) mm in the descending thoracic aorta, and similar regardless of the degree of false lumen thrombosis. The overall 5-year survival rate was 84.7%, and it was not influenced by false lumen thrombosis (P=0.86 by the log-rank test). Independent predictors of long-term mortality were age >70 years (hazard ratio [HR], 2.34; 95% confidence interval [CI], 1.20 to 4.56, P=0.012) and postoperative cerebrovascular accident, coma, and/or renal failure (HR, 2.62; 95% CI, 1.40 to 4.92, P=0.003).

Conclusions—Patients with acute type A aortic dissection who survive to discharge have a favorable prognosis. Preoperative false lumen thrombosis does not influence long-term mortality, reintervention rates, or aortic growth. **(*J Am Heart Assoc.* 2013;2: e000112 doi: 10.1161/JAHA.113.000112)**

Key Words: aortic dissection • prognosis • surgery • thrombosis

Acute type A aortic dissection (AAAD) is a challenging clinical emergency. Despite continuous improvements in diagnosis, surgical treatment, and perioperative management, the latest report from the International Registry of Acute Aortic Dissection (IRAD) revealed an in-hospital surgical mortality of 23.9%.[1] This is similar to that found in a more recent study from another large registry,[2] while several single-center series report mortality well below 10%.[3–5] Patients who survive to discharge have reasonable intermediate and long-term survival rates.[6,7]

Several reports[8–12] have indicated that patients with a residual patent false lumen following an AAAD repair have an increased risk of distal aortic enlargement and death. In addition, the IRAD data have shown that in patients with acute type B aortic dissections, partial thrombosis, more than a completely patent false lumen, predicts a higher follow-up mortality.[13] As an extension of this observation, Song et al[14] found that partial thrombosis of the false lumen after an extensive Stanford type A (DeBakey type I) aortic dissection repair is a predictor of aortic enlargement, aorta-related procedures, and poor long-term survival. Different factors have been proposed to account for this increased risk, and one possible mechanism could be that the thrombus itself is a risk factor by enhancing the coagulation system.[15]

In this context, we anticipated that a partial thrombosis of the false lumen observed at the first hospitalization would negatively affect the remodeling of the distal aorta, increase

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the need for reintervention, and negatively influence the long-term survival of AAAD patients. To assess this hypothesis, in the IRAD database, we analyzed the patients with surgically treated AAAD who were discharged alive from their primary hospitalization.

Methods

IRAD Registry

IRAD is a multinational registry that collects consecutive and unselected cases of acute aortic dissection at 30 aortic centers in 10 countries. Participation in the registry does not per se imply treatment standardization. Further details about the IRAD structure and data collection have been previously published.[16] The study was approved by the institutional review board or ethics committee at each participating center.

Study Population

We screened the data records for all patients who were enrolled in IRAD between January 1, 1996 and January 31, 2011. We identified 2380 patients with an AAAD, which was defined as any nontraumatic dissection involving the ascending aorta and presenting within 14 days of symptom onset. Iatrogenic dissections were included. The patients were identified prospectively at presentation or retrospectively from discharge diagnoses. The diagnosis was based on imaging, intraoperative findings, and/or autopsy.

The patients who were exclusively managed medically, had intramural hematomas, died during the index hospitalization, or for whom follow-up or information on false lumen status was lacking were excluded from the analysis (Figure 1). Our final study population included 522 patients. Of these patients, 414 (79.3%) had a patent, 84 (16.1%) a partially thrombosed, and 24 (4.6%) a completely thrombosed false lumen.

Data Collection

A standardized form with 290 variables was used at all IRAD centers to describe the index hospital stay. This form included patient demographics, past medical histories, presenting symptoms, physical findings, imaging results, treatments, and outcomes (including complications and mortality).

All of the patients underwent computed tomography, magnetic resonance imaging, angiography, and/or echocardiography. The false lumen was classified as patent when flow was present without evidence of thrombus at any level of the aorta, as partially thrombosed when both flow and thrombus were present, and completely thrombosed in the absence of flow in the false lumen at any aortic level. Intramural

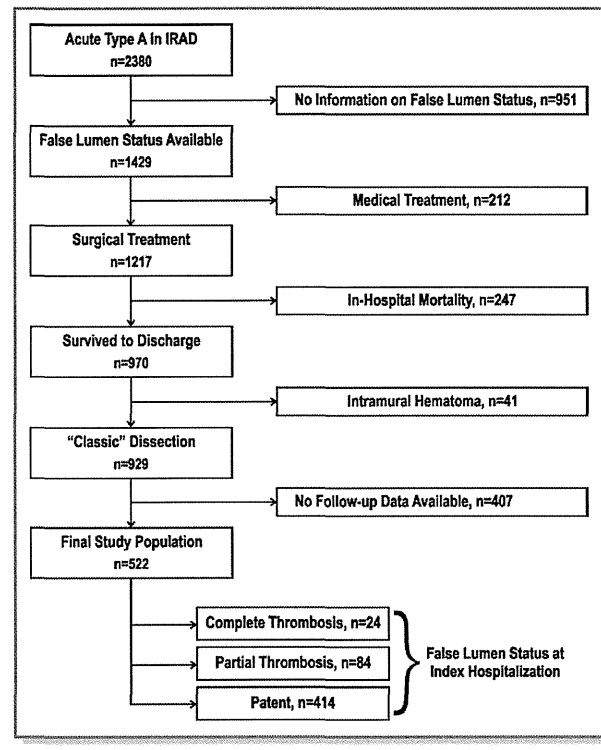

Figure 1. Study inclusion flow-chart. IRAD indicates International Registry of Acute Aortic Dissection.

hematoma was defined as an aortic wall hematoma without an intimal flap or tear on any imaging study. The distinction between an intramural hematoma and a classic double-barrel dissection with complete thrombosis of the false lumen was determined by experts at each IRAD center.

Follow-up data were obtained annually for up to 5 years using a standardized form to record clinical variables, imaging data, reoperations (including endovascular and/or open repair), and mortality.

Aortic Growth Analysis

The growth rate was calculated for the aortic arch and the descending thoracic aorta. Aortic size was measured as the largest transversal diameter perpendicular to the flow axis for each segment. Patients who underwent arch replacement at the index hospitalization were only included in the growth calculations for the descending thoracic aorta. For patients who underwent reintervention during follow-up, the latest diameter measure before reintervention was used. The growth rate was calculated as the difference between the most recent diameter measure and the diameter at the index hospitalization at the same aortic level, divided by the time interval between the 2 measurements and expressed as millimeters per year.