



# Clinical Investigation of Recurrent Arterial Dissection

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**Scholarly Report submitted in partial fulfilment of the MD Degree at Harvard Medical  
School**

**Date:** 1 March 2018

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**Scholarly Report Title:** Clinical Investigation of Recurrent Arterial Dissection

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**TITLE:** Clinical Investigation of Recurrent Aortic Dissection

Mohammad H. Abbasi, Yisha Cheng and Mark E. Lindsay

**Background:** Recurrent arterial dissection (RAD) after thoracic aortic dissection is poorly understood.

**Methods:** We used the Research Patient Data Registry (RPDR) tool to identify 954 patients with acute, imaging-confirmed, thoracic aortic dissection. We characterised dissection anatomy and elucidated the prevalence and incidence of cardiovascular risk factors and events prior to and in the peri-dissection period based on ICD-9 codes. We compared these findings between patients who experienced RAD versus a single thoracic aortic dissection (SAD).

**Results:** RAD occurred in 117 patients (12.3 %). RAD patients were younger ( $49.21 \pm 15.65$  years vs  $63.20 \pm 15.19$  years,  $p < 0.0001$ ), more likely to be male (73.5 % vs 64.8 %,  $p = 0.0476$ ), more likely to have Stanford Type A dissection (77.8 % vs 57.1 %,  $p < 0.0001$ ) and more likely to have extension of dissection flap into the cervical arteries (25.0 % vs 15.0 %,  $p = 0.0207$ ). Prior to dissection, RAD patients were less likely to have a history of hypertension (29.1 % vs 53.5 %,  $p < 0.0001$ ), diabetes mellitus (2.56 % vs 7.77 %,  $p = 0.0355$ ), dyslipidaemia (12.0 % vs 23.2 %,  $p = 0.0041$ ), cerebrovascular accident (6.84 % vs 14.2 %,  $p = 0.0223$ ), heart failure (5.98 % vs 18.5 %,  $p = 0.0005$ ), disorders of the mitral valve (4.27 % vs 11.2 %,  $p = 0.0172$ ), disorders of the aortic valve (12.8 % vs 25.7 %,  $p = 0.0014$ ) and atrial fibrillation (4.27 % vs 16.1 %,  $p = 0.0005$ ), but were more likely to have Marfan syndrome (26.5 % vs 4.30 %,  $p < 0.0001$ ). RAD patients also had a lower incidence of new hypertension (13.3 % vs 49.4 %,  $p < 0.0001$ ), diabetes mellitus (0 % vs 4.53 %,  $p = 0.0200$ ), dyslipidaemia (0.97 % vs 14.0 %,  $p = 0.0001$ ), first-time cerebrovascular accident (3.67 % vs 11.8 %,  $p = 0.0088$ ), heart failure (7.27 % vs 20.1 %,  $p = 0.0008$ ) and disorders of the mitral valve (2.68 % vs 11.3 %,  $p = 0.0039$ ) in the first 30 days after thoracic aortic dissection. Most RAD events consisted of recurrent aortic dissection (88.0 %).

**Conclusions:** The first 30 days following thoracic aortic dissection is a perilous time with a high incidence of new cardiovascular events in previously healthy patients. RAD may be a marker for underlying aberrations in vascular connective tissue integrity.

## Introduction

Arterial dissection remains a poorly understood and challenging disease. Stemming either from a tear in the vascular intima or from the rupture of the vasa vasorum, dissection propagates via haemorrhage into and further separation of the layers of the arterial wall.<sup>1</sup> This complex phenomenon can be complicated by frank rupture and extravascular haemorrhage, obstruction of the native vessel lumen, stagnation of native flow and generation of thrombus, all of which may lead to distal malperfusion syndromes. Acute thoracic aortic dissection is a particularly perilous manifestation of arterial dissection. Though relatively uncommon with an incidence of 2.53 per 100,000 patient-years,<sup>2</sup> acute thoracic aortic dissection continues to portend a poor prognosis. Data from the International Registry of Acute Aortic Dissection (IRAD) demonstrate an in-hospital mortality rate of 32.5 % (26 % for patients managed surgically and 58 % for patients managed medically).<sup>3,4</sup> Strikingly, autopsy studies of acute thoracic aortic dissection reveal a pre-hospital mortality rate of 21.4 % and a 30-day mortality rate of 54.9 %.<sup>2</sup> Despite recent advances and improvements in surgical technique and technologies, thoracic aortic dissection continues to be associated with a mortality rate of at least 1 % per hour amongst patients who arrive alive to hospital until definitive surgical intervention is initiated.<sup>5</sup>

Previously, we described the prevalence of recurrent aortic dissection in the IRAD database and found that Marfan syndrome is a strong clinical marker for this otherwise rare phenomenon.<sup>6</sup> However, the total risk of recurrent arterial dissection (RAD) in any vascular bed following thoracic aortic dissection remains unclear. In addition, the relationship between vascular connective tissue diseases, including Marfan syndrome, and propensity for RAD remains largely uncharacterised. Given that clinical care often remains focused on the aorta, current interventions in the management of acute thoracic aortic dissection may be insufficient to protect survivors of thoracic aortic dissection from concomitant or additional dissection events and malperfusion syndromes. For example, peri-dissection cerebral ischaemia has been described to occur in as many as 15.7 % of patients with acute Type A dissection in one study.<sup>7</sup> In particular, in patients with Marfan syndrome, aneurysm and dissection of the carotid arteries has been reported both as a complication of and independently of an acute aortic syndrome.<sup>8, 9, 10, 11,</sup>  
<sup>12</sup> Likewise, peri-dissection myocardial ischaemia has also been observed.<sup>13, 14, 15, 16, 17, 18, 19, 20</sup>

In this observational study, we aim to study patients with thoracic aortic dissection to quantify the risk of RAD. We also aim to characterise the anatomy of dissection in patients both with a single aortic dissection (SAD) and with RAD, and to determine the prevalence of Marfan syndrome in the RAD population. Finally, we aim to empirically describe the rate of peri-dissection malperfusion syndromes—including cerebral and myocardial infarction—in patients presenting with acute thoracic aortic dissection and to describe the rate at which these events occur in the SAD and RAD cohorts.

## **Student Role**

This study was student-driven. The medical student investigated the literature and compiled all references, designed the Research Patient Data Registry query, identified and isolated the patient cohort of interest, performed chart review (personally reviewed the medical record and all radiographic data for approximately 500 patients, and trained and assisted the co-author in chart review of the remaining patients), performed the initial data analysis (including statistical analysis) and proposed all initial conclusions. The medical student wrote the entirety of the first draft of the manuscript and revised it with appropriate guidance from the Faculty Mentor.

Co-author Yisha Cheng was an invaluable asset to the study. She worked under the medical student to collect data from the electronic medical record and independently performed chart review for approximately 1200 patients.

## **Methods**

### *Patient Selection*

Using the Research Patient Data Registry (RPDR) tool, we queried the electronic medical record at Massachusetts General Hospital and Brigham and Women's Hospital for "Thoracic Aortic Dissection" on 7 July 2015. We then investigated the medical record of each identified patient to confirm the presence of acute thoracic aortic dissection. Only patients who were both

acutely symptomatic and had imaging-confirmed thoracic aortic dissection, defined as visualisation of a dissection flap on computerised tomography (CT), magnetic resonance imaging (MRI), aortic angiography or transoesophageal echocardiography (TEE), were included for further analysis.

### *Data Collection*

Demographic information including sex and date of birth and all clinical diagnoses in the form of ICD-9 codes were collected using the RPDR data request feature on 19 July 2015. Specific clinical diagnoses of interest included hypertension (ICD-9 codes 401.0 to 401.9), diabetes mellitus (ICD-9 codes 250.0-250.93), dyslipidaemia (ICD-9 codes 272.0 to 272.9), personal history of tobacco use (ICD-9 code V15.82), cerebrovascular accident (ICD-9 codes 433.0 to 434.91 and 436), myocardial infarction (ICD-9 codes 410.0-410.92), heart failure (ICD-9 codes 428.0 to 428.9), disorders of the mitral valve (ICD-9 code 424.0), disorders of the aortic valve (ICD-9 code 424.1), atrial fibrillation (ICD-9 427.31), ventricular tachycardia or ventricular fibrillation (ICD-9 codes 427.4 to 427.42), cardiac arrest (ICD-9 code 427.5), Ehlers-Danlos syndrome (ICD-9 code 756.83) and Marfan syndrome (ICD-9 759.82). Prevalence prior to the dissection event was determined by the presence of the appropriate ICD-9 code at least 5 days prior to the date of thoracic aortic dissection. Incidence within 30 days of the dissection event was determined by the new presence of the appropriate ICD-9 code within 30 days of the date of the thoracic aortic dissection.

Review of all imaging modalities at the time of presentation with dissection was used to characterise dissection anatomy. Chart review was then performed for additional arterial dissection events after the initial thoracic aortic dissection. Patients with no additional arterial dissection events were assigned to the Single Aortic Dissection (SAD) Group whereas patients with at least one additional arterial dissection event were assigned to the Recurrent Arterial Dissection (RAD) Group.

### *Statistical Analysis*

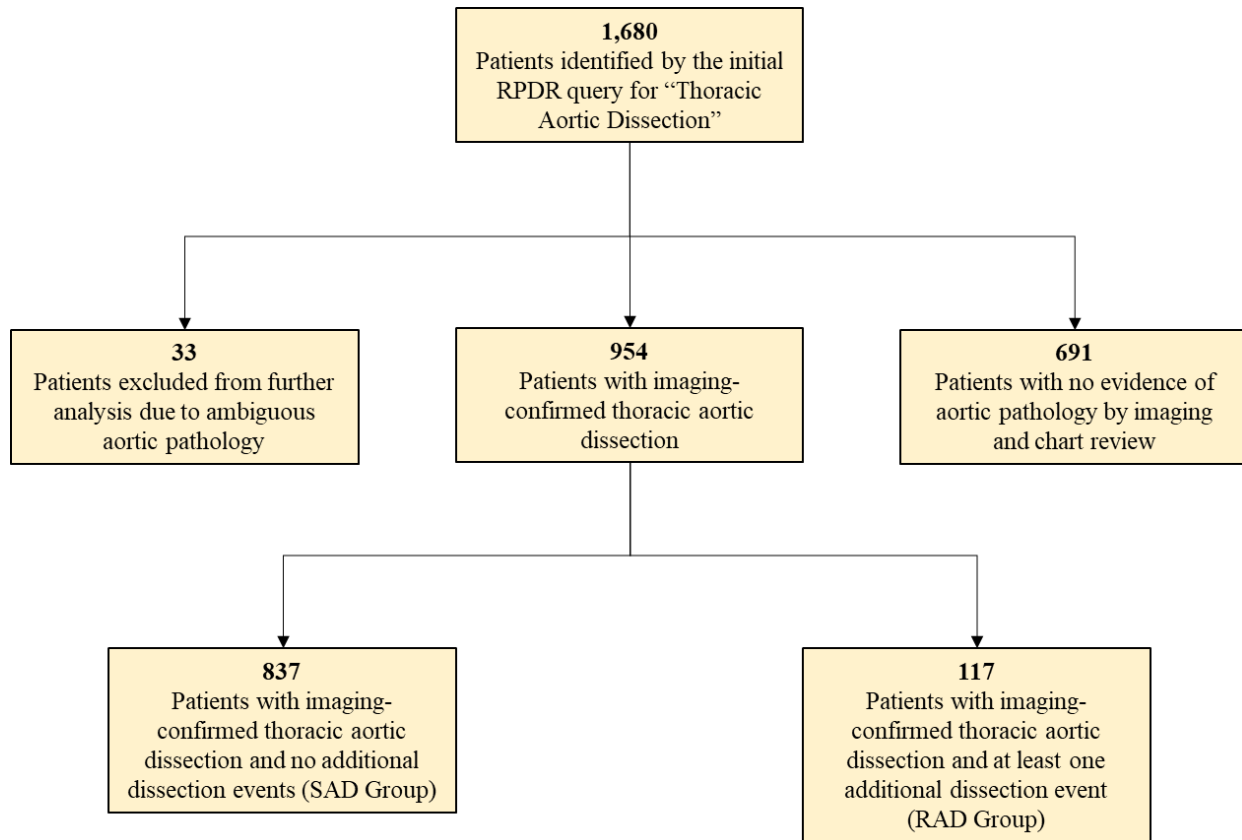
Mean age at time of dissection between SAD Group and RAD Group were compared using a two-sample Student's *t*-test. All categorical variables, including dissection anatomy and prevalence/incidence of clinical diagnoses, were compared using chi-square testing.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written. The protocol was approved by an Institutional Review Board at each participating clinical site.

## **Results**

### *Patient Identification*

As presented in **Figure 1**, 1,680 patients were identified by the initial RPDR query for “Thoracic Aortic Dissection.” Chart review of this group revealed 691 patients with no evidence of acute aortic pathology and 954 patients with imaging-confirmed thoracic aortic dissection (56.8 %). A total of 33 additional patients were excluded from further analysis. Eleven had an iatrogenic thoracic aortic dissection. Seven patients had mention of thoracic aortic dissection in clinic notes but no imaging to confirm this diagnosis. Seven patients underwent non-diagnostic or inconclusive non-contrast chest CT. Five patients were identified to have a non-dissecting thoracic aortic ulcer or haematoma. Four asymptomatic patients had an incidental finding of thoracic aortic dissection of unknown age discovered by CT chest for another indication. One patient was excluded as there were major discrepancies between the radiographic images and the radiographic imaging reports. The earliest thoracic aortic dissection event included for further analysis occurred on 1 January 1979 and the most recent thoracic aortic dissection event included for further analysis occurred on 1 April 2015. Further chart review of the 954 patients with imaging-confirmed thoracic aortic dissection revealed no additional non-iatrogenic dissection events in 837 patients (87.7 %) and an additional, non-iatrogenic dissection event in 117 patients (12.3 %). The 837 patients with no additional non-iatrogenic arterial dissection events comprised the SAD Group and the 117 patients with an additional, non-iatrogenic arterial dissection event after thoracic aortic dissection comprised the RAD Group. One patient experienced an initial non-iatrogenic thoracic aortic dissection and later had an iatrogenic thoracic aortic dissection; this patient was assigned to the SAD Group.



**Figure 1.** Patient isolation and group designation following the initial RPDR query. Excluded patients included: 11 patients with iatrogenic thoracic aortic dissection, 7 patients with thoracic aortic dissection mentioned in notes but no confirmatory imaging, 7 patients with non-diagnostic or inconclusive non-contrast chest CT, 5 patients with non-dissecting aortic ulcer or haematoma, 4 patients with an incidental finding of a thoracic aortic dissection of unknown age, and 1 patient for whom there were major discrepancies between the radiology images and reports.

### Overview of All Patients

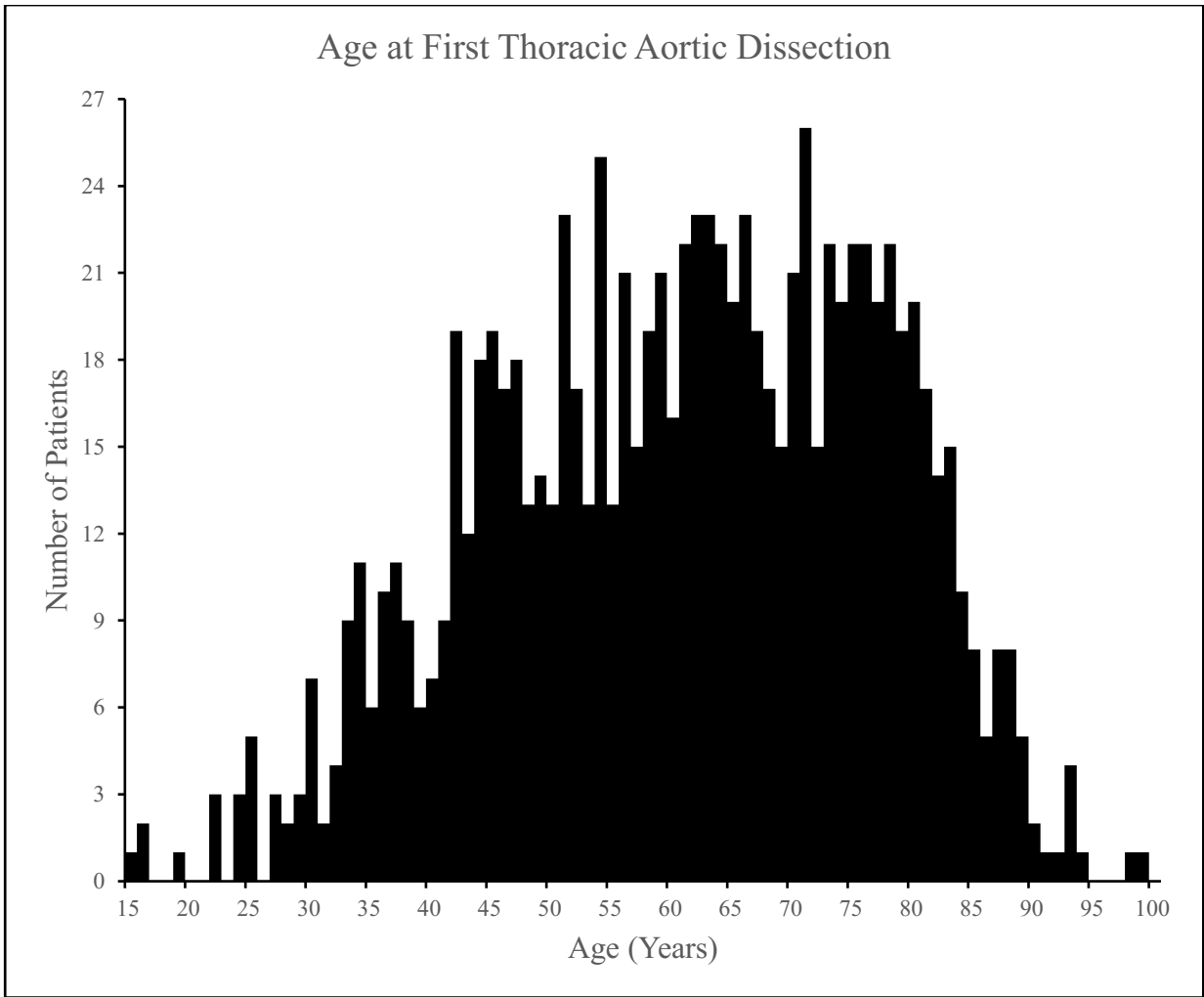
Demographic and general dissection characteristics for all patients are presented below in **Table 1**. The age distribution at time of thoracic aortic dissection is presented below in **Figure 2**. Amongst the 954 total patients with imaging-confirmed thoracic aortic dissection, the mean age at the time of initial thoracic aortic dissection was  $61.45 \pm 15.91$  years. There were 628 male patients and 326 female patients (male-to-female ratio 1.93). There were 569 patients with Stanford Type A dissection (59.6 %) and 385 patients with Stanford Type B dissection (40.4 %). Amongst the 882 patients who underwent cervical imaging as part of the diagnostic evaluation at the time of presentation with acute thoracic aortic dissection, 139 had extension of the thoracic aortic dissection flap to involve the cervical arteries (15.8 %), defined as either the carotid or vertebral arteries.



**Table 1.** Patient demographics and general dissection characteristics in all patients.

	<b>All Patients</b>
<b>Age (years)</b>	61.45 ± 15.91
<b>Female</b>	326/954 (34.2 %)
<b>Stanford Type A Dissection</b>	569/954 (59.6 %)
<b>Stanford Type B Dissection</b>	385/954 (40.4 %)
<b>Involvement of Cervical Arteries*</b>	139/882 (15.8 %)

\*Includes the carotid and vertebral arteries. Cervical arterial involvement was unable to be determined in 72 patients who did not undergo cervical arterial imaging at the time of diagnosis.



**Figure 2.** Age distribution for the 954 patients with imaging-confirmed thoracic aortic dissection. Mean age was  $61.45 \pm 15.91$  years.

Of the 954 identified total patients with imaging-confirmed thoracic aortic dissection, 836 underwent imaging that allowed a more detailed description of dissection anatomy, as presented below in **Table 2**. There were 223 patients (26.7 %) with dissection arising in the aortic root, 164 patients (19.6 %) with dissection arising in the ascending aorta, 88 patients (10.5 %) with dissection arising in the aortic arch and 361 patients (43.2 %) with dissection arising in the descending thoracic aorta.

**Table 2.** Anatomic characteristics of the initial thoracic aortic dissection event in the 836 patients with imaging-confirmed thoracic aortic dissection.

<b>Dissection Start Site</b>	<b>Dissection End Site</b>	<b>No. (%)</b>
<b>Aortic Root</b>		223 (26.7)
	Aortic Root*	1 (0.12)
	Ascending Aorta	34 (4.07)
	Aortic Arch	37 (4.43)
	Descending Thoracic Aorta	15 (1.79)
	Suprarenal Abdominal Aorta	24 (2.87)
	Infrarenal Aorta	17 (2.03)
Aortic Bifurcation and below	95 (11.4)	
<b>Ascending Aorta</b>		164 (19.6)
	Ascending Aorta*	29 (3.47)
	Aortic Arch	39 (4.67)
	Descending Thoracic Aorta	21 (2.51)
	Suprarenal Abdominal Aorta	6 (0.72)
	Infrarenal Aorta	15 (1.79)
Aortic Bifurcation and below	54 (6.46)	
<b>Aortic Arch</b>		88 (10.5)
	Aortic Arch*	13 (1.56)
	Descending Thoracic Aorta	11 (1.32)
	Suprarenal Abdominal Aorta	13 (1.56)
	Infrarenal Aorta	13 (1.56)
Aortic Bifurcation and below	38 (4.55)	
<b>Descending Thoracic Aorta</b>		361 (43.2)
	Descending Thoracic Aorta*	116 (13.9)
	Suprarenal Abdominal Aorta	56 (6.70)
	Infrarenal Aorta	60 (7.18)
Aortic Bifurcation and below	129 (15.4)	

\*Indicates focal dissection

The prevalence of specific cardiovascular diagnoses prior to thoracic aortic dissection and the incidence of new diagnoses within 30 days of the dissection for all patients are presented below in **Table 3**. Prior to dissection, atherosclerotic risk factors included hypertension in 482 patients (50.5 %), diabetes mellitus in 68 patients (7.13 %), dyslipidaemia in 208 patients (21.9 %) and current or former tobacco use in 218 patients (22.9 %). Within 30 days of dissection, newly diagnosed atherosclerotic risk factors included hypertension in 203 of 472 patients (incidence 43.0 %), diabetes mellitus in 35 of 886 patients (incidence 3.95 %) and dyslipidaemia in 91 of 746 patients (incidence 12.2 %). One hundred and twenty-seven patients (13.3 %) had a history of cerebrovascular accident prior to dissection, and 89 patients had a first acute cerebrovascular accident within 30 days of dissection (incidence 10.8 %). Eighty-five patients (8.91 %) had a history of myocardial infarction prior to dissection, and 61 patients had a first acute myocardial infarction within 30 days of dissection (incidence 7.02 %). Heart failure was diagnosed in 162 patients (17.0 %) prior to dissection, and 145 patients had a new diagnosis of heart failure within 30 days of dissection (incidence 18.3 %). Disorders of the mitral valve were present in 99 patients (10.4 %) prior to dissection, and 87 new cases were diagnosed within 30 days of dissection (incidence 10.2 %). Disorders of the aortic valve were present in 230 patients (24.1 %) prior to dissection, 172 new cases were diagnosed within 30 days of dissection (incidence 23.8 %). Cardiac dysrhythmias included a history of atrial fibrillation in 140 patients (14.7 %) and an episode of ventricular tachycardia or ventricular fibrillation in 4 patients (0.42 %) prior to dissection. In the 30 days following dissection, there were 103 new cases of atrial fibrillation (incidence 12.7 %) and 11 new cases of ventricular tachycardia or ventricular fibrillation (incidence 1.16 %). Although there were no patients with a history of cardiac arrest prior to dissection, cardiac arrest occurred in 19 patients within 30 days of dissection (incidence 1.99 %).

**Table 3.** Prevalence of cardiovascular disease prior to dissection and incidence of new cardiovascular disease within 30 days of dissection in the 954 patients with imaging-confirmed thoracic aortic dissection.

	<b>Prevalence Prior to Dissection No. (%)</b>	<b>Incidence within 30 Days of Dissection No./At Risk (%)</b>
<b>Hypertension</b>	482 (50.5)	203/472 (43.0)
<b>Diabetes Mellitus</b>	68 (7.13)	35/886 (3.95)
<b>Dyslipidaemia</b>	208 (21.9)	91/746 (12.2)
<b>Current or Former Tobacco Use</b>	218 (22.9)	
<b>Cerebrovascular Accident</b>	127 (13.3)	89/827 (10.8)
<b>Myocardial Infarction</b>	85 (8.91)	61/869 (7.02)
<b>Heart Failure</b>	162 (17.0)	145/792 (18.3)
<b>Disorders of the Mitral Valve</b>	99 (10.4)	87/855 (10.2)
<b>Disorders of the Aortic Valve</b>	230 (24.1)	172/724 (23.8)
<b>Atrial Fibrillation</b>	140 (14.7)	103/814 (12.7)
<b>Ventricular Tachycardia or Ventricular Fibrillation</b>	4 (0.42)	11/950 (1.16)
<b>Cardiac Arrest</b>	0 (0)	19/954 (1.99)

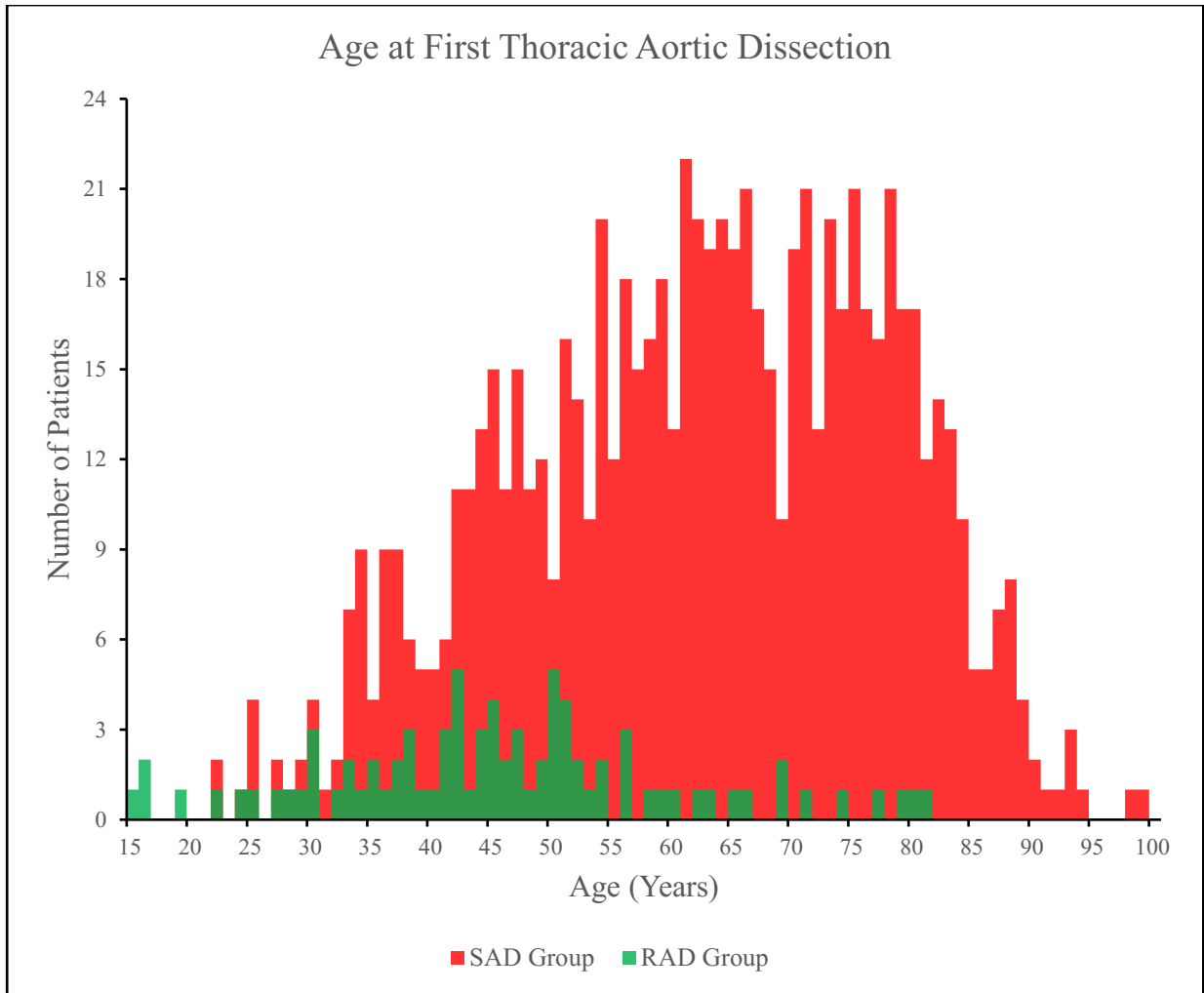
*Cardiovascular Disease by Patient Groups*

Demographic and general dissection characteristics for the SAD Group and RAD Group are presented below in **Table 4**. The age distribution at time of initial thoracic aortic dissection is presented below in **Figure 3**. Patients in the RAD Group were significantly younger (mean age  $49.21 \pm 15.65$  years vs  $63.20 \pm 15.19$  years,  $p < 0.0001$ ) and more likely to experience a Stanford Type A dissection (77.8 % vs 57.1 %,  $p < 0.0001$ ) than patients in the SAD Group. Although the majority of patients in both groups were male, the SAD Group was enriched for female sex (35.2 % vs 26.5 %,  $p = 0.0476$ ). Stanford Type B dissection was also more common in the SAD Group (42.9 % vs 22.2 %,  $p < 0.0001$ ). In the 68 patients in the RAD Group and the 814 patients in the SAD Group who underwent cervical imaging at time of diagnosis of thoracic aortic dissection, extension of the dissection into the cervical arteries was more common in the RAD Group than in the SAD Group (25.0 % vs 15.0 %,  $p = 0.0207$ ).

**Table 4.** Patient demographics and general dissection characteristics in the SAD Group ( $n = 837$ ) and RAD Group ( $n = 117$ ).

	<b>SAD Group</b>	<b>RAD Group</b>	<b><i>p</i></b>
<b>Age (years)</b>	63.20 ± 15.19	49.21 ± 15.65	< 0.0001
<b>Female</b>	295/837 (35.2 %)	31/117 (26.5 %)	0.0476
<b>Stanford Type A Dissection</b>	478/837 (57.1 %)	91/117 (77.8 %)	< 0.0001
<b>Stanford Type B Dissection</b>	359/837 (42.9 %)	26/117 (22.2 %)	< 0.0001
<b>Involvement of Cervical Arteries*</b>	122/814 (15.0 %)	17/68 (25.0 %)	0.0207

\*Cervical arterial involvement was unable to be determined in 23 patients in the SAD Group and 49 patients in the RAD Group.



**Figure 3.** Age distribution at the time of initial thoracic aortic dissection by patient group. Mean age was  $63.20 \pm 15.19$  years in the SAD Group and  $49.21 \pm 15.65$  years in the RAD Group ( $p < 0.0001$ ).

Detailed dissection anatomy was then reanalysed after segregation by patient group. Data were available for 778 patients in the SAD Group and the 58 patients in the RAD Group and are presented below in **Table 5**. There was no difference in the rate of dissections originating at the aortic root (27.0 % vs 22.4 %,  $p = 0.4322$ ). Dissections originating in the ascending aorta (31.0 % vs 18.8 %,  $p = 0.0167$ ) and aortic arch (22.4 % vs 9.64 %,  $p = 0.0010$ ) were more common in the RAD Group, whereas dissections originating in the descending thoracic aorta were more common in the SAD Group (44.6 % vs 24.1 %,  $p = 0.0017$ ).

**Table 5.** Anatomic characteristics of the initial thoracic aortic dissection event in the SAD Group ( $n = 778$ ) and the RAD Group ( $n = 58$ ).

<b>Dissection Start Site</b>	<b>Dissection End Site</b>	<b>SAD Group No. (%)</b>	<b>RAD Group No. (%)</b>	<b><i>p</i></b>
<b>Aortic Root</b>		210 (27.0)	13 (22.4)	0.4322
	Aortic Root*	1 (0.13)	0 (0)	0.7847
	Ascending Aorta	33 (4.24)	1 (1.72)	0.3414
	Aortic Arch	31 (3.98)	6 (10.3)	0.0133
	Descending Thoracic Aorta	14 (1.80)	1 (1.72)	0.9656
	Suprarenal Abdominal Aorta	22 (2.83)	2 (3.45)	0.7756
	Infrarenal Aorta	16 (2.06)	1 (1.72)	0.8584
Aortic Bifurcation and below	93 (12.0)	2 (3.45)	0.0459	
<b>Ascending Aorta</b>		146 (18.8)	18 (31.0)	0.0167
	Ascending Aorta*	27 (3.47)	2 (3.45)	0.9926
	Aortic Arch	31 (39.8)	8 (13.8)	0.0001
	Descending Thoracic Aorta	18 (2.31)	3 (5.17)	0.1476
	Suprarenal Abdominal Aorta	5 (0.64)	1 (1.72)	0.3027
	Infrarenal Aorta	15 (1.93)	0 (0)	0.2856
	Aortic Bifurcation and below	50 (6.43)	4 (6.90)	0.8840
<b>Aortic Arch</b>		75 (9.64)	13 (22.4)	0.0010
	Aortic Arch*	9 (1.16)	4 (6.90)	< 0.0001
	Descending Thoracic Aorta	10 (1.29)	1 (1.72)	0.7667
	Suprarenal Abdominal Aorta	12 (1.54)	1 (1.72)	0.9106
	Infrarenal Aorta	10 (1.29)	3 (5.17)	0.0086
	Aortic Bifurcation and below	34 (4.37)	4 (6.90)	0.3466
<b>Descending Thoracic Aorta</b>		347 (44.6)	14 (24.1)	0.0017
	Descending Thoracic Aorta*	111 (14.3)	5 (8.62)	0.2188
	Suprarenal Abdominal Aorta*	56 (7.20)	0 (0)	0.0339
	Infrarenal Aorta*	57 (7.33)	3 (5.17)	0.5290
	Aortic Bifurcation and below*	123 (15.8)	6 (10.3)	0.2540

\*Indicates focal dissection



The prevalence of specific cardiovascular diagnoses as documented in the medical record at least 5 days prior to thoracic aortic dissection are presented below in **Table 6** for patients in the SAD Group and RAD Group. Hypertension (53.5 % vs 29.1 %,  $p < 0.0001$ ), diabetes mellitus (7.77 % vs 2.56 %,  $p = 0.0355$ ) and dyslipidaemia (23.2 % vs 12.0 %,  $p = 0.0041$ ) were more common in the SAD Group, but current or former tobacco use (22.0 % vs 29.1 %,  $p = 0.0646$ ) was not. The percentage of patients with at least one previous cerebrovascular accident was higher in the SAD Group (14.2 % vs 6.84 %,  $p = 0.0223$ ). Although the percentage of patients with at least one previous myocardial infarction was also nominally higher in the SAD Group (9.32 % vs 5.98 %), this difference was not statistically significant. However, patients in the SAD Group had higher rates of heart failure (18.5 % vs 5.98 %,  $p = 0.0005$ ), disorders of the mitral valve (11.2 % vs 4.27 %,  $p = 0.0172$ ) and disorders of the aortic valve (25.7 % vs 12.8 %,  $p = 0.0014$ ). Atrial fibrillation was also more common in the SAD Group (16.1 % vs 4.27 %,  $p = 0.0005$ ), but ventricular tachycardia or ventricular fibrillation was not (0.36 % vs 0.85 %). No patients in either the SAD Group or RAD Group had a history of previous cardiac arrest. The RAD Group was significantly enriched for both Marfan syndrome (26.5 % vs 4.30 %,  $p < 0.0001$ ) and Ehlers-Danlos syndrome (3.42 % vs 0.12 %,  $p < 0.0001$ ).

**Table 6.** Prevalence of cardiovascular risk factors and pre-existing cardiovascular disease as documented at least 5 days prior to the initial thoracic aortic dissection event in the SAD Group ( $n = 837$ ) and RAD Group ( $n = 117$ ).

	<b>SAD Group</b> No. (%)	<b>RAD Group</b> No. (%)	<b><i>p</i></b>
<b>Hypertension</b>	448 (53.5)	34 (29.1)	< 0.0001
<b>Diabetes Mellitus</b>	65 (7.77)	3 (2.56)	0.0355
<b>Dyslipidaemia</b>	194 (23.2)	14 (12.0)	0.0041
<b>Current or Former Tobacco Use</b>	184 (22.0)	34 (29.1)	0.0646
<b>Cerebrovascular Accident</b>	119 (14.2)	8 (6.84)	0.0223
<b>Myocardial Infarction</b>	78 (9.32)	7 (5.98)	0.2145
<b>Heart Failure</b>	155 (18.5)	7 (5.98)	0.0005
<b>Disorders of the Mitral Valve</b>	94 (11.2)	5 (4.27)	0.0172
<b>Disorders of the Aortic Valve</b>	215 (25.7)	15 (12.8)	0.0014
<b>Atrial Fibrillation</b>	135 (16.1)	5 (4.27)	0.0005
<b>Ventricular Tachycardia or Ventricular Fibrillation</b>	3 (0.36)	1 (0.85)	0.3690
<b>Cardiac Arrest</b>	0	0	-
<b>Marfan Syndrome</b>	36 (4.30)	31 (26.5)	< 0.0001
<b>Ehlers-Danlos Syndrome</b>	1 (0.12)	4 (3.42)	< 0.0001

The incidence of specific cardiovascular diagnoses as documented in the medical record within 30 days of thoracic aortic dissection are presented below in **Table 7** for patients in the SAD Group and RAD Group. First-time diagnoses of hypertension (incidence 49.4 % vs 13.3 %,  $p < 0.0001$ ), diabetes mellitus (incidence 4.53 % vs 0 %,  $p = 0.0200$ ) and dyslipidaemia (incidence 14.0 % vs 0.97 %,  $p = 0.0001$ ) within 30 days of thoracic aortic dissection were more common in the SAD Group. Rate of first cerebrovascular accident was significantly higher in the SAD Group (incidence 11.8 % vs 3.67 %,  $p = 0.0088$ ), whereas rate of first myocardial infarction was nominally, but not statistically, higher in the SAD Group (incidence 7.51 % vs 3.64 %,  $p = 0.1232$ ). New diagnoses of heart failure (incidence 20.1 % vs 7.27 %,  $p = 0.0008$ )

and disorders of the mitral valve (incidence 11.3 % vs 2.68 %,  $p = 0.0039$ ) were more common in the SAD Group. Although incidence of new disorders of the aortic valve was nominally higher in the SAD Group (incidence 24.9 % vs 16.7 %,  $p = 0.0540$ ), this difference was not statistically significant. Likewise, incidence of new atrial fibrillation (13.2 % vs 8.93 %,  $p = 0.1775$ ), ventricular tachycardia or ventricular fibrillation (1.20 % vs 0.86 %,  $p = 0.7388$ ) and cardiac arrest (2.15 % vs 0.85 %,  $p = 0.5538$ ) were not different between the SAD Group and the RAD Group.

**Table 7.** Incidence of new cardiovascular diagnoses within the first 30 days following the initial thoracic aortic dissection event in the SAD Group and RAD Group.

	<b>SAD Group No./At Risk (%)</b>	<b>RAD Group No./At Risk (%)</b>	<b><i>p</i></b>
<b>Hypertension</b>	192/389 (49.4)	11/83 (13.3)	< 0.0001
<b>Diabetes Mellitus</b>	35/772 (4.53)	0/114 (0)	0.0200
<b>Dyslipidaemia</b>	90/643 (14.0)	1/103 (0.97)	0.0001
<b>Acute Cerebrovascular Accident</b>	85/718 (11.8)	4/109 (3.67)	0.0088
<b>Acute Myocardial Infarction</b>	57/759 (7.51)	4/110 (3.64)	0.1232
<b>Heart Failure</b>	137/682 (20.1)	8/110 (7.27)	0.0008
<b>Disorders of the Mitral Valve</b>	84/743 (11.3)	3/112 (2.68)	0.0039
<b>Disorders of the Aortic Valve</b>	155/622 (24.9)	17/102 (16.7)	0.0540
<b>Atrial Fibrillation</b>	93/702 (13.2)	10/112 (8.93)	0.1775
<b>Ventricular Tachycardia or Ventricular Fibrillation</b>	10/834 (1.20)	1/116 (0.86)	0.7388
<b>Cardiac Arrest</b>	18/837 (2.15)	1/117 (0.85)	0.5538

*Group Comparisons after Exclusion of Patients with Marfan Syndrome*

Demographic and general dissection characteristics after exclusion of patients with Marfan syndrome are presented below in **Table 8**. Patients in the RAD Group continued to be

significantly younger (mean age  $54.69 \pm 13.61$  years vs  $64.13 \pm 14.71$  years,  $p < 0.0001$ ) and more likely to experience a Stanford Type A dissection (75.6 % vs 56.3 %,  $p = 0.0002$ ) than patients in the SAD Group. Female sex was no longer different between the two groups (35.2 % in SAD Group vs 26.7 % in RAD Group,  $p = 0.1004$ ). Stanford Type B dissection was again more common in the SAD Group (43.7 % vs 24.4 %,  $p = 0.0004$ ). In the 53 patients in the RAD Group and the 778 patients in the SAD Group who underwent cervical imaging at time of diagnosis of thoracic aortic dissection, extension of the dissection into the cervical arteries was again more common in the RAD Group (24.5 % vs 14.7 %,  $p = 0.0421$ ).

**Table 8.** Patient demographics and general dissection characteristics in the SAD Group ( $n = 801$ ) and RAD Group ( $n = 86$ ) after exclusion of all patients with Marfan syndrome.

	SAD Group	RAD Group	<i>p</i>
<b>Age (years)</b>	64.13 ± 14.71	54.69 ± 13.61	< 0.0001
<b>Female</b>	282/801 (35.2 %)	23/86 (26.7 %)	0.1004
<b>Stanford Type A Dissection</b>	451/801 (56.3 %)	65/86 (75.6 %)	0.0002
<b>Stanford Type B Dissection</b>	350/801 (43.7 %)	21/86 (24.4 %)	0.0004
<b>Involvement of Cervical Arteries*</b>	114/778 (14.7 %)	13/53 (24.5 %)	0.0421

\*Includes the carotid and vertebral arteries. Cervical arterial involvement was unable to be determined in 23 patients in the SAD Group and 33 patients in the RAD Group who did not undergo cervical imaging.

The prevalence of specific cardiovascular diagnoses as documented in the medical record at least 5 days prior to thoracic aortic dissection are presented below in **Table 9** after exclusion of all patients with Marfan syndrome in the SAD Group and RAD Group. Hypertension continued to be more common in the SAD Group (54.1 % vs 33.7 %,  $p = 0.0002$ ), but diabetes mellitus (7.99 % vs 3.49 %,  $p = 0.1236$ ) and dyslipidaemia (23.5 % vs 16.3 %,  $p = 0.1156$ ) were no longer more common in the SAD Group. Current or former tobacco use was now less common in the SAD Group (22.3 % vs 32.6 %,  $p = 0.0230$ ). The proportion of patients who had experienced at least one previous cerebrovascular accident (14.7 % vs 9.30 %,  $p = 0.1554$ ) or myocardial infarction (9.36 % vs 8.14 %,  $p = 0.6969$ ) continued to be nominally, but not significantly, higher in the SAD Group as compared to the RAD Group. However, patients in the SAD Group continued to have higher rates of heart failure (18.9 % vs 6.98 %,  $p = 0.0049$ ), disorders of the mitral valve (10.4 % vs 3.49 %,  $p = 0.0365$ ) and disorders of the aortic valve (24.8 % vs 11.6 %,  $p = 0.0046$ ). Atrial fibrillation continued to be more common in the SAD Group (16.2 % vs 5.81 %,  $p = 0.0088$ ) and ventricular tachycardia or ventricular fibrillation continued to be no

different between the two groups (0.37 % vs 1.16 %,  $p = 0.2314$ ). As stated previously, no patients in the SAD Group or RAD Group had a history of cardiac arrest prior to thoracic aortic dissection.

**Table 9.** Prevalence of cardiovascular risk factors and pre-existing cardiovascular disease as documented at least 5 days prior to the initial thoracic aortic dissection event in the SAD Group ( $n = 801$ ) and RAD Group ( $n = 86$ ) after exclusion of all patients with Marfan Syndrome.

	<b>SAD Group</b>	<b>RAD Group</b>	<b><i>p</i></b>
	<b>No. (%)</b>	<b>No. (%)</b>	
<b>Hypertension</b>	433 (54.1)	29 (33.7)	0.0002
<b>Diabetes Mellitus</b>	64 (7.99)	3 (3.49)	0.1236
<b>Dyslipidaemia</b>	188 (23.5)	14 (16.3)	0.1156
<b>Current or Former Tobacco Use</b>	179 (22.3)	28 (32.6)	0.0230
<b>Cerebrovascular Accident</b>	118 (14.7)	8 (9.30)	0.1554
<b>Myocardial Infarction</b>	75 (9.36)	7 (8.14)	0.6969
<b>Heart Failure</b>	151 (18.9)	6 (6.98)	0.0049
<b>Disorders of the Mitral Valve</b>	83 (10.4)	3 (3.49)	0.0365
<b>Disorders of the Aortic Valve</b>	199 (24.8)	10 (11.6)	0.0046
<b>Atrial Fibrillation</b>	130 (16.2)	5 (5.81)	0.0088
<b>Ventricular Tachycardia or Ventricular Fibrillation</b>	3 (0.37)	1 (1.16)	0.2314
<b>Cardiac Arrest</b>	0 (0)	0 (0)	-

The incidence of specific cardiovascular diagnoses as documented in the medical record within 30 days of thoracic aortic dissection are presented below in **Table 10** for patients in the SAD Group and RAD Group after exclusion of all patients with Marfan syndrome. As previously observed, the incidence of new hypertension (50.0 % vs 12.3 %,  $p < 0.0001$ ), diabetes mellitus (4.75 % vs 0 %,  $p = 0.0419$ ) and dyslipidaemia (14.5 % vs 1.39 %,  $p = 0.0016$ ) within 30 days of thoracic aortic dissection were more common in the SAD Group. Rates of first cerebrovascular accident (incidence 12.0 % vs 5.13 %,  $p = 0.0616$ ) and first myocardial

infarction (incidence 7.71 % vs 2.53 %,  $p = 0.0843$ ) were again nominally, but not significantly, higher in the SAD Group. New diagnoses of heart failure (incidence 20.0 % vs 10.0 %,  $p = 0.0253$ ) and disorders of the mitral valve (incidence 11.7 % vs 2.41 %,  $p = 0.0085$ ) were again more common in the SAD Group. In addition, though incidence of new disorders of the aortic valve was nominally higher in the SAD Group (24.9 % vs 15.8 %,  $p = 0.0658$ ), this difference was not statistically significant. Incidence of new atrial fibrillation (13.4 % vs 8.64 %,  $p = 0.2077$ ), ventricular tachycardia or ventricular fibrillation (1.25 % vs 1.18 %,  $p = 0.9493$ ) and cardiac arrest (2.12 % vs 1.16 %,  $p = 0.5370$ ) were again not different between the SAD Group and the RAD Group.

**Table 10.** Incidence of new cardiovascular diagnoses within the first 30 days following thoracic aortic dissection in the SAD Group and RAD Group after exclusion of all patients with Marfan syndrome.

	<b>SAD Group No./At Risk (%)</b>	<b>RAD Group No./At Risk (%)</b>	<b><i>p</i></b>
<b>Hypertension</b>	184/368 (50.0)	7/57 (12.3)	< 0.0001
<b>Diabetes Mellitus</b>	35/737 (4.75)	0/83 (0)	0.0419
<b>Dyslipidaemia</b>	89/613 (14.5)	1/72 (1.39)	0.0016
<b>Acute Cerebrovascular Accident</b>	82/683 (12.0)	4/78 (5.13)	0.0616
<b>Acute Myocardial Infarction</b>	56/726 (7.71)	2/79 (2.53)	0.0843
<b>Heart Failure</b>	130/650 (20.0)	8/80 (10.0)	0.0253
<b>Disorders of the Mitral Valve</b>	84/718 (11.7)	2/83 (2.41)	0.0085
<b>Disorders of the Aortic Valve</b>	150/602 (24.9)	12/76 (15.8)	0.0658
<b>Atrial Fibrillation</b>	90/671 (13.4)	7/81 (8.64)	0.2077
<b>Ventricular Tachycardia or Ventricular Fibrillation</b>	10/798 (1.25)	1/85 (1.18)	0.9493
<b>Cardiac Arrest</b>	17/801 (2.12)	1/86 (1.16)	0.5370

## Recurrent Arterial Dissection

The mean time to recurrent dissection was  $6.88 \pm 6.29$  years in the RAD Group. Dissection details are presented in **Table 11**. Sixty-six patients (56.4 %) had recurrent Stanford Type A thoracic aortic dissection. Of these 66 patients, 22 had extension of the thoracic aortic dissection flap to involve the cervical arteries. Thirty-seven patients (31.6 %) had recurrent Stanford Type B aortic dissection. Eleven patients (9.40 %) had recurrent dissection of the cervical arteries without involvement of the aorta. Of these 11 patients, 3 had dissection of the right common carotid artery, 2 had dissection of the right internal carotid artery, 2 had dissection of the left common carotid artery, 2 had dissection of the left internal carotid artery, 1 had bilateral common carotid artery dissection and 1 had bilateral internal carotid artery dissections. There was 1 patient (0.85 %) with left main coronary artery dissection, 1 patient (0.85 %) with pulmonary artery dissection and 1 patient (0.85 %) with superior mesenteric artery dissection.

**Table 11.** Recurrent arterial dissection characteristics in the RAD Group ( $n = 117$ ).

	<b>RAD Patients</b>
	<b>No. (%)</b>
<b>Stanford Type A Aortic Dissection</b>	66 (56.4)
With Cervical Involvement	22 (18.8)
<b>Coronary Artery Dissection</b>	1 (0.85)
<b>Pulmonary Artery Dissection</b>	1 (0.85)
<b>Cervical Artery Dissection</b>	11 (9.40)
<b>Stanford Type B Aortic Dissection</b>	37 (31.6)
<b>Mesenteric Artery Dissection</b>	1 (0.85)

## Discussion

In this study, we identified a large cohort of 954 patients with acute, imaging-confirmed thoracic aortic dissection and characterised the extent of propagation and anatomy of each dissection event. We investigated the baseline prevalence and incidence of cardiovascular disease within this cohort. We then divided our large cohort into two distinct groups: 837 patients who experienced a single aortic dissection (SAD) and 117 patients who experienced a subsequent recurrent arterial dissection (RAD) after the initial thoracic aortic dissection in order to better elucidate the clinical characteristics and behaviours of these two distinct patient populations. We then re-performed our analyses after the exclusion of patients with Marfan syndrome in order to understand the contribution of Marfan syndrome to the trends we observed. Finally, we characterised the extent and anatomy of the RAD event.

### *Patient Demographics and Dissection Anatomy*

Initial observations by Hagan *et al.* from the International Registry of Acute Aortic Dissection (IRAD) database described aortic dissection as a disease predominantly affecting the proximal aorta in men in the seventh decade of life (464 patients, 62.3 % Stanford Type A dissection, 65.3 % male, mean age  $63.1 \pm 14.0$  years).<sup>3</sup> We observed similar trends in our cohort of 954 patients with acute, imaging-confirmed, thoracic aortic dissection (59.6 % Stanford Type A dissection, 65.8 % male, mean age  $61.45 \pm 15.91$  years). A large proportion of patients (882 of 954, 92.5 %) underwent imaging that allowed visualisation of the cervical vessels (computerised tomography [CT], magnetic resonance imaging [MRI], or aortic angiography) at the time of diagnosis of thoracic aortic dissection. Although cervical arterial involvement, defined in this study as extension of the thoracic aortic dissection flap into the carotid or vertebral arteries, has been described in case reports,<sup>21, 22</sup> this phenomenon has not been otherwise robustly described. In our cohort, cervical arterial involvement occurred in 15.8 % of patients, which suggests that compromise of the cervical arteries may be a more common complication of acute thoracic aortic dissection than previously believed. Among patients who did not undergo cervical vessel imaging, most were diagnosed with thoracic aortic dissection by transoesophageal echocardiography (TEE). Nicosia *et al.* have shown TEE to be a powerful tool in the diagnosis of



aortic dissection with a sensitivity of 100 % and specificity of 94 %, though it remains an unreliable tool for correctly identifying dissections in the aortic arch (62.5 % accurate) or arch branch vessels (71.4 % accurate).<sup>23</sup> Although TEE remains a rapid and accessible tool to diagnose aortic dissection at the bedside in the unstable patient, our results suggest that these patients may require broader vascular imaging in order to assess the integrity of the cervical vessels.

Detailed dissection anatomy was determined by direct visualisation of the dissection origin site and following of the dissection flap to the termination site. Data were available in 836 of the 954 total patients (87.6 %). Extension of the dissection flap to the aortic bifurcation was the most common occurrence in patients with Stanford Type A dissection regardless of dissection origin site (95 of 223 patients with dissection originating at the aortic root, 42.6 %; 54 of 164 patients with dissection originating in the ascending aorta, 32.9 %; 38 of 88 patients with dissection originating in the aortic arch, 43.2 %), whereas focal dissection was a relatively rare occurrence (1 of 223 patients with dissection originating at the aortic root, 0.45 %; 29 of 164 patients with dissection originating in the ascending aorta, 17.7 %; 13 of 88 patients with dissection originating in the aortic arch, 14.8 %). Although extension of the dissection flap to the aortic bifurcation was also the most common occurrence in patients with Stanford Type B thoracic aortic dissection (129 of 361 patients, 35.7 %), focal dissection was also very common (116 of 361 patients, 32.1 %). In models of aortic dissection constructed from harvested human aortas, Tiessen and Roach have found that the location of dissection origin site and presence of plaque, but not age or dissection origin tear depth, are predictive of pressure required to overcome aortic medial integrity and therefore of dissection propagation patterns. More specifically, they report higher pressures required for medial separation in thoracic as compared to abdominal aorta in both men and women.<sup>24</sup> Although extent of dissection propagation *in vivo* is likely highly variable and dependent on individual patient factors (including heart rate, vascular tone, position, local wall pressures, presence of other aortic and connective tissue disease, among other factors), it is plausible to suggest that proximal aortic dissections stem from more severe pressure aberrations and therefore are more likely to propagate extensively whereas distal aortic dissection stem from less severe pressure aberrations and therefore are less likely to propagate extensively. More research in the mechanisms and determinants of dissection propagation are needed.

## *Cardiovascular Disease in Patients with Thoracic Aortic Dissection*

Cardiovascular disease was common in patients with thoracic aortic dissection. Hypertension, previously reported at rates of 70-75 % in patients with aortic dissection,<sup>1,3</sup> was documented in only 50.5 % of patients in our cohort. Hypertension is believed to be the single most important modifiable risk factor for aortic dissection,<sup>25</sup> as chronic aortic wall shear stress results in intimal thickening, calcification and adventitial fibrosis, all of which promotes dissection formation.<sup>1</sup> In addition, chronic hypertension is believed to act as an indirect proinflammatory trigger by inducing macrophage recruitment to and activation within the aortic wall, ultimately leading to aortic remodelling which may compromise wall integrity.<sup>25</sup> Of note, of the 472 patients within our cohort without a diagnosis of hypertension prior to thoracic aortic dissection, 203 were newly diagnosed with hypertension within 30 days of aortic dissection. Thus, of the 954 patients in our cohort, 685 patients had a diagnosis of hypertension prior to or within 30 days of aortic dissection (71.8 %). This most likely suggests that a significant proportion of patients in the cohort had undiagnosed, underlying hypertension, which may have contributed to the development and propagation of dissection. Proactive monitoring and treatment of hypertension remains essential.

Diabetes mellitus was present in 7.13 % of patients prior to thoracic aortic dissection and was newly diagnosed in an additional 35 patients within 30 days of the dissection event (incidence 3.95 %). The relationship between diabetes and thoracic aortic dissection remains under investigation. Some studies have suggested that diabetes is protective against aneurysm and dissection formation and that patients with diabetes have improved outcomes, including lower mortality, following aortic dissection.<sup>26,27,28</sup> One theory for this observation is that glycated cross-links in aortic wall connective tissue may enhance structural integrity,<sup>28</sup> though further research is needed to better understand the relationship between diabetes mellitus and thoracic aortic dissection. Similarly, dyslipidaemia, a known risk factor for abdominal aortic aneurysm<sup>29</sup> and a possible risk factor for thoracic aortic dissection, was present in 21.9 % of patients prior to thoracic aortic dissection and was newly diagnosed in an additional 91 patients within 30 days of the dissection event (incidence 12.2 %). As with hypertension, new diagnoses of diabetes mellitus and dyslipidaemia likely represented underlying, undiagnosed disease that was newly recognised in the peri-dissection period rather than truly new disease processes

triggered by the thoracic aortic dissection. This highlights the need to carefully screen patients with thoracic aortic dissection for modifiable cardiovascular risk factors in order to improve future cardiovascular outcomes. Finally, current or former tobacco use was present in 22.9 % of patients in our cohort. Smoking has been strongly linked to abdominal aortic aneurysm (confers greater population-attributable risk than hypertension) and with thoracic aortic dissection (confers lower population-attributable risk than hypertension).<sup>29</sup> Smoking cessation remains paramount to the prevention and mitigation of cardiovascular disease and ought to remain a primary target for therapeutic interventions.

Many patients in our cohort had a history of previous major ischaemic events (13.3 % with previous cerebrovascular accident and 8.91 % with previous myocardial infarction). Strikingly, 89 patients with no history of previous cerebrovascular accident had a first-time cerebrovascular accident within 30 days of dissection (incidence 10.8 %), and 61 patients with no history of previous myocardial infarction had a first-time myocardial infarction within 30 days of dissection (incidence 7.02 %). Gaul *et al.* report a similar rate (albeit in a slightly different patient population) of cerebral ischaemia in 15.7 % (16 out of 102 patients) of patients presenting with acute Stanford Type A dissection,<sup>7</sup> and while the rate of myocardial ischaemia in patients with aortic dissection remains largely undescribed, this phenomenon is well-documented in case reports.<sup>13, 14, 15, 16, 17, 18, 19, 20</sup> Aortic dissection, and particularly thoracic aortic dissection, results in abrupt changes in cardiovascular anatomy and haemodynamics. Specifically, invasion of a critical vessel, such as a cervical or coronary artery, by a propagating dissection flap with thrombosis and compression of the native vessel lumen can directly precipitate a local ischaemic event. In addition, aortic rupture and massive haemorrhage can precipitate shock and global ischaemia. Finally, acute aortic insufficiency resulting from thoracic aortic dissection can acutely volume overload the left ventricle, subsequently leading to an acute increase in left ventricular end diastolic pressure, while simultaneously dropping diastolic blood pressure due to regurgitation into the left ventricle during diastole. Because coronary perfusion pressure decreases with increasing left ventricular end diastolic pressure and increases with diastolic blood pressure, acute aortic insufficiency can dramatically suppress coronary perfusion pressure. This abrupt fall in coronary perfusion pressure can directly precipitate myocardial ischaemia and indirectly (due to the development of contractile dysfunction or frank cardiogenic shock)

precipitate global ischaemia. Ultimately, our observations demonstrate that ischaemic cardiovascular events may be a common complication of acute thoracic aortic dissection.

Heart failure was also common in our patient cohort, with 17.0 % of patients having a previous history of heart failure and 145 patients with no previous history of heart failure having heart failure within 30 days of thoracic aortic dissection (incidence 18.3 %). The mechanism of heart failure precipitated by thoracic aortic dissection is likely similar to that discussed above (acute aortic insufficiency and myocardial ischaemia). However, our observed rate of new heart failure within 30 days of dissection is much higher than the rate of heart failure at time of presentation with acute aortic dissection of 6 % (64 of 1,069 patients in the IRAD database) reported by Januzzi *et al.*<sup>30</sup> This suggests that the development of the clinical syndrome of heart failure may not be readily apparent at the time of diagnosis and that the absence of clinical heart failure at the time of thoracic aortic dissection may not prevent the development of new heart failure within ensuing days or weeks. This may be particularly true for patients who undergo surgical interventions that drastically alter cardiovascular anatomy and haemodynamics.

Many patients in our cohort had valvular heart disease prior to thoracic aortic dissection (10.4 % with a disorder of the mitral valve and 24.1 % with a disorder of the aortic valve). Bicuspid aortic valve is a well-known and well-characterised risk factor for thoracic aortic aneurysm and dissection.<sup>1, 29, 31</sup> Though the exact mechanism of bicuspid aortic valve in predisposing to aortopathy remains under investigation, patients with bicuspid aortic valve generate abnormally high levels of shear stress in the tubular ascending aorta.<sup>32</sup> In addition, genetic factors associated with bicuspid aortic valve may predispose to development of thoracic aortic aneurysm independently of mechanical factors.<sup>32</sup> Previous studies have estimated bicuspid aortic valve to occur in 5-7 % of all patients with thoracic aortic dissection.<sup>1</sup> However, due to the fact that bicuspid aortic valve lacks a unique ICD-9 code, we were unable to determine the prevalence or incidence of bicuspid aortic valve in our cohort and report instead the prevalence and incidence of the general category of disorders of the aortic valve. New diagnoses of mitral and aortic valve disorders likely resulted from the combination of truly new disease in the setting of altered haemodynamics and possible cardiac surgery and incidental detection of underlying valvular disease during cardiac and aortic imaging.

Atrial fibrillation, but not ventricular tachyarrhythmias, were common in our cohort. Prior to dissection, 14.7 % of patients had a history of atrial fibrillation and only 0.42 % (4

patients) had a history of ventricular tachycardia or ventricular fibrillation. No patients had a history of cardiac arrest prior to thoracic aortic dissection. In the 30 days after dissection, 103 patients had new atrial fibrillation (incidence 12.7 %), 11 patients had new ventricular tachycardia or ventricular fibrillation (incidence 1.16 %) and 19 patients had new cardiac arrest (incidence 1.99 %). Atrial fibrillation is largely a disease of atrial stretch, scar or inflammation. As discussed above, acute thoracic aortic dissection can lead to abrupt changes in cardiovascular anatomy, including the development of acute aortic insufficiency. This can subsequently lead to dilation of both the left ventricle and the left atrium, thereby precipitating new atrial fibrillation via acute atrial stretch. In addition, atrial fibrillation is a common and known complication following cardiac surgery. Matsuura *et al.* report an incidence of 52.7 % for new onset atrial fibrillation after surgery involving the aortic arch.<sup>33</sup> Given the large proportion of patients in our cohort who presented with Stanford Type A aortic dissection and likely underwent some surgical intervention, we would have expected more new atrial fibrillation in this cohort. This suggests that our observed incidence of atrial fibrillation may underestimate the true risk of atrial fibrillation in the peri-dissection period. Furthermore, atrial fibrillation can both be caused by heart failure (due to increased pressure and chamber size of the left heart) and result in heart failure (due to loss of active ventricular filling and development of tachycardiomyopathy). Thus, part of the prevalence and incidence of atrial fibrillation we observed in our cohort of patients may have been linked to the prevalence and incidence of heart failure. Appropriate stroke prevention in patients with atrial fibrillation and aortic dissection represents a particularly perplexing clinical problem, as has been described in case reports.<sup>34</sup> Inability to tolerate anticoagulation in patients with previous or new atrial fibrillation may be contributing to the high incidence of new cerebrovascular accidents in the peri-dissection period observed in our cohort. Matsuura *et al.* observed longer ICU stay and longer hospital stay in patients with atrial fibrillation after aortic arch surgery,<sup>33</sup> though it was unclear to what extent these trends were driven by new acute cerebrovascular events.

Ventricular tachycardia or ventricular fibrillation was an uncommon occurrence in the peri-dissection period. Unlike atrial fibrillation, ventricular tachyarrhythmias result from re-entry (in the presence of scar, or functional re-entry in the presence of a critical mass of heterogeneously conducting ventricular myocardium), increased automaticity or triggered activity.<sup>35,36</sup> Although always possible secondary to myocardial ischaemia during acute thoracic

aortic dissection, our cohort remained relatively protected from ventricular tachyarrhythmias. However, 19 patients (1.99 %) experienced cardiac arrest within 30 days of acute thoracic aortic dissection. This may have resulted either from ventricular tachycardia or ventricular fibrillation, or from cardiac tamponade secondary to haemopericardium. Cardiac tamponade remains the most common cause of death (87.1 %) in patients with aortic dissection,<sup>37</sup> and likely was a significant cause of morbidity and mortality in the patients in this cohort.

### *Group Comparisons*

Patients with RAD were significantly younger—on average by nearly 14 years—than patients with SAD. This finding is consistent with our previous findings in the IRAD population.<sup>6</sup> Patients with RAD were also more likely to be male (73.5 % vs 64.8 %,  $p = 0.0476$ ), to have Stanford Type A dissections (77.8 % vs 57.1 %,  $p < 0.0001$ ), and to have extension of the thoracic aortic dissection flap to involve the cervical arteries (25.0 % vs 15.0 %,  $p = 0.0207$ ). Based on these initial findings, we suspected that RAD may represent a unique vascular phenotype rather than merely being the result of increased survivorship after thoracic aortic dissection.

Further investigation of dissection anatomy revealed that it was dissections originating in the ascending aorta or aortic arch (31.0 % vs 18.8 % and 22.4 % vs 9.64 %, respectively), but not dissections originating at the aortic root, that drove the proclivity for Stanford Type A dissection in patients with RAD as compared to patients with SAD. In addition, whereas extensive dissection to the aortic bifurcation or below continued to be the most likely occurrence in SAD patients with Type A dissection (93 of 210 patients when dissection originated at the aortic root, 44.3 %; 50 of 146 patients when dissection originated in the ascending aorta, 34.2 %; 34 of 75 patients when dissection originated in the aortic arch, 45.3 %), focal or local dissection confined to the thoracic aorta was the most likely occurrence in RAD patients (8 of 13 patients when dissection originated at the aortic root, 61.5 %; 13 of 18 patients when dissection originated in the ascending aorta, 72.2 %; 5 of 13 patients when dissection originated in the aortic arch, 38.5 %). These differences in dissection propagation trends despite similar dissection origin sites suggest that RAD patients and SAD patients may have had differences in underlying aortic structure and integrity prior to the dissection event.

RAD patients were also less likely to have hypertension, diabetes mellitus, dyslipidaemia, previous cerebrovascular accident, heart failure, disorders of the mitral valve, disorders of the aortic valve or atrial fibrillation prior to dissection. These trends were likely driven at least in part by younger age, as age is the most significant non-modifiable risk factor for many types of cardiovascular disease. Furthermore, RAD patients had lower incidence of new hypertension, diabetes mellitus, dyslipidaemia, first cerebrovascular accident, new heart failure and disorders of the mitral valve than SAD patients within 30 days of dissection. This suggests that younger age and the absence of cardiovascular risk factors at least partially protected RAD patients from some of the acute cardiovascular events precipitated by thoracic aortic dissection observed in SAD patients. Most strikingly, 72 of the 117 RAD patients (61.5 %) remained free of hypertension 30 days after dissection. This observation suggests that the traditional mechanism of chronic hypertension-induced aortic changes that allow for the development of dissection cannot be the driving force behind dissection formation in most RAD patients. In addition, we were surprised to see a lower incidence of first acute cerebrovascular accident in the RAD patients (3.67 %) as compared to the SAD patients (11.8 %) despite the fact that RAD patients were more likely to have extension of the aortic dissection flap into the cervical vessels than SAD patients (25.0 % vs 15.0 %). This suggests that underlying cardiovascular disease and risk factors, rather than dissection anatomy, drives cerebral ischaemia after acute thoracic aortic dissection. Furthermore, whereas the peri-dissection incidence of first-time cerebrovascular accident was nearly identical to the peri-dissection incidence of first-time myocardial infarction in RAD patients (4 of 109 patients, 3.67 %, vs 4 of 110, 3.64 %), the peri-dissection incidence of first-time cerebrovascular accident was higher than the peri-dissection incidence of first-time myocardial infarction in SAD patients (85 of 718 patients, 11.8 %, vs 57 of 759 patients, 7.51 %). This suggests that increasing age and increasing prevalence of cardiovascular risk factors and disease prior to thoracic aortic dissection increases the risk of new cerebral ischaemia out-of-proportion to the risk of new myocardial ischaemia. New atrial fibrillation (incidence of which was nominally, but not significantly, higher in SAD patients in the peri-dissection period) may have been one such factor, as this would be expected to increase the risk of cerebral ischaemia more than it increased the risk of myocardial ischaemia.

## *Marfan Syndrome*

Previously, we showed that patients who experience recurrent aortic dissection are enriched for Marfan syndrome (42 of 204 patients, 21.5 %).<sup>6</sup> Consistent with that finding, we observed in this study that RAD patients are enriched for Marfan syndrome (26.5 % vs 4.30 % in SAD patients). Marfan syndrome is an autosomal dominant disorder that results from mutations in the fibrillin-1 (FBN1) gene that interrupt normal FBN1 interactions with transforming growth factor- $\beta$  (TGF- $\beta$ )-binding proteins.<sup>1</sup> This results in excess free TGF- $\beta$  and unregulated aortic remodelling, culminating in cystic medial necrosis and a proclivity for aneurysm formation and dissection.<sup>1</sup> Mechanical factors and dampened ability of vascular endothelial cells to respond appropriately to local aberrations in shear forces may also play a role.<sup>38</sup> This state of promiscuous TGF- $\beta$  signalling and cystic medial necrosis is likely responsible for the additional aortic dissection events and may play a role in the dissection events in remote vascular beds observed in the RAD Group in this study. Investigations to better characterise TGF- $\beta$  signalling in extra-aortic vessels remain ongoing. Ultimately, in our study, of the 67 total patients with Marfan syndrome who experienced a thoracic aortic dissection, 31 patients (46.3 %) survived to experience a RAD event. This suggests that current interventions in the management of acute thoracic aortic dissection in patients with Marfan syndrome do not protect these patients from future dissection events.

After the exclusion of all patients with Marfan syndrome, many of the differences between the RAD Group and SAD Group persisted. More specifically, RAD patients continued to be younger, more likely to have a Stanford Type A dissection and more likely to have extension of the thoracic aortic dissection flap into the cervical arteries than SAD patients. RAD patients continued to have lower rates of hypertension, heart failure, disorders of the mitral valve, disorders of the aortic valve or atrial fibrillation prior to dissection. However, the RAD patients no longer had lower rates of diabetes mellitus, dyslipidaemia or previous cerebrovascular accident than SAD patients, and RAD patients were now more likely to have current or former tobacco use. Thus, baseline cardiovascular health was less disparate between RAD and SAD patients after the exclusion of patients with Marfan syndrome. RAD patients continued to have lower incidence of new hypertension, diabetes mellitus, dyslipidaemia, heart failure and disorders of the mitral valve than SAD patients within 30 days of thoracic aortic



dissection. Though the incidence of new cerebrovascular accident was nominally lower in RAD patients as compared to SAD patients, this difference was no longer significant after the exclusion of patients with Marfan syndrome. The persistence of many of the differences in age, dissection anatomy and baseline cardiovascular health between the SAD Group and RAD Group after the exclusion of patients with Marfan syndrome suggests that Marfan syndrome alone was not the primary driving force for the unique clinical behaviours in patients with RAD.

Ehlers-Danlos syndrome was also more common in the RAD Group as compared to the SAD Group. Although Ehlers-Danlos syndrome is a known risk factor for thoracic aortic aneurysm,<sup>1</sup> given the very few number of total cases (4 patients in the RAD Group and 1 patient in the SAD Group), it is difficult to determine the actual significance of this finding in our cohort of patients. Similarly, though Loeys-Dietz syndrome is also a well-known risk factor for thoracic aortic aneurysm and dissection,<sup>1</sup> it does not have an ICD-9 code designation. We were thus unable to determine the prevalence of Loeys-Dietz syndrome in our cohort.

The young age, relative paucity of typical risk factors, unique anatomy of dissection, dissonance with descriptions of traditional cohorts of patients, clear differences in cardiovascular events and outcomes in the peri-dissection period, and tendency to be enriched for patients with known vascular connective tissue disease all together raise the possibility that the mechanism of thoracic aortic dissection is different in RAD patients as compared to SAD patients. More specifically, RAD patients appear to clinically resemble patients with Marfan syndrome, which suggests that underlying, possibly genetically-triggered, aberrancies in vascular connective tissue may play a prominent role in the development and propagation of thoracic aortic dissection in RAD patients.

### *Recurrent Arterial Dissection*

Of the 954 patients in our cohort with acute, imaging-confirmed thoracic aortic dissection, 117 patients survived the initial dissection event and experienced a subsequent arterial dissection event (12.3 %). This is far higher than the ~5 % rate of recurrent aortic dissection we observed in the IRAD population.<sup>6</sup> Interestingly, the majority of RAD events were recurrent aortic dissection (in 103 of 117 patients, 88.0 %). This suggests that our initial findings in the IRAD population may not only have underestimated the risk for RAD, they may also have

underestimated the risk for recurrent aortic dissection. One possible reason for this may be that RAD may be a relatively late occurrence (mean time to RAD was  $6.88 \pm 6.29$  years). Ultimately, our observations from this study suggest that RAD may be a common and underappreciated long-term risk of thoracic aortic dissection, particularly in young patients without traditional risk factors for aortic dissection.

All RAD events in this study occurred in critical vascular beds—including the aorta, coronary arteries, carotid arteries and the superior mesenteric artery—in which perturbation of flow and loss of vessel integrity may result in critical malperfusion syndromes. It is possible that asymptomatic RAD events in non-critical vascular beds were more common than we observed. These events may have remained undiscovered due to their inability to cause symptomatic malperfusion syndromes. Thus, we may be underestimating the true prevalence of RAD after thoracic aortic dissection in this study. In contrast, if our suspicion regarding the role of underlying vascular connective tissue disease as the driving force for dissection formation and propagation in RAD patients is true, perhaps such vascular connective tissue disease may manifest most prominently in these specific vascular beds (aorta, coronaries, cervical arteries and mesenteric arteries). With improvement in surgical technologies and screening methods and better outcomes following acute thoracic aortic dissection, we hope to better understand the prevalence of and mechanisms underlying RAD.

### *Limitations*

One major limitation of this study involved its use of ICD-9 codes, which have been demonstrated to be of varying reliability. Birman-Deych *et al.* report a  $> 95\%$  positive predictive value for ICD-9 codes in determining true presence of hypertension, diabetes mellitus and heart failure, all of which were employed in this study.<sup>39</sup> Overall, Birman-Deych *et al.* described a low sensitivity of  $76\%$  but high specificity of  $95\%$  in the use of ICD-9 codes to identify cardiovascular risk factors.<sup>39</sup> This suggests that our study may be underestimating the burden of cardiovascular disease in our thoracic aortic dissection cohort. Goldstein describes a combined sensitivity of  $81\%$  and specificity of  $90\%$  for ICD-9 codes 433, 434 and 436 in identifying acute stroke.<sup>40</sup> This paper was our rationale for selecting to use these three specific ICD-9 codes to identify acute cerebrovascular accident. Accordingly, the true prevalence and incidence of

cerebrovascular events during the peri-dissection period may have been higher than what we observed.

In addition to reliability, a major limitation of ICD-9 codes is that they do not distinguish between an acute event and history of an acute event (for example, new acute cerebrovascular accident vs history of cerebrovascular accident). Therefore, we were unable to determine the incidence of recurrent myocardial infarction or recurrent cerebrovascular accident in patients with a history of myocardial infarction or cerebrovascular accident, respectively. Myocardial and cerebral ischaemic events are the most commonly the most extreme manifestation of atherosclerosis within the coronary and cerebrovascular vessels, respectively. Patients with a previous history of an ischaemic event are at greatest risk for repeat ischaemic events. Therefore, we suspect that our findings underestimate the true incidence of peri-dissection myocardial infarction and cerebrovascular accidents.

Another limitation of our study was incomplete aortic imaging in patients with imaging-confirmed thoracic aortic dissection. More specifically, many patients (49 in the RAD Group and 23 in the SAD Group) underwent TEE as the means for diagnosis of acute thoracic aortic dissection. This modality does not allow visualisation of the cervical arteries, and therefore cervical involvement was unable to be determined in these patients.

In addition, there is no unique ICD-9 code for bicuspid aortic valve, Loeys-Dietz syndrome and death. Thus, we were unable to determine or even estimate the prevalence of bicuspid aortic valve and Loeys-Dietz syndrome in our cohort. Perhaps more importantly, we were unable to evaluate mortality rate following dissection. It is possible that the lower incidence of peri-dissection ischaemic and non-ischaemic cardiovascular events observed in RAD patients as compared to SAD patients in this study was actually due to increased rates of fatal ischaemic and non-ischaemic cardiovascular events in the RAD Group that were left uncoded or indeterminate after the patient's death.

Finally, as is true by design for all observational studies, our study is primarily hypothesis-generating, not hypothesis-testing. Our study allows the exploration of the clinical profile of patients who experience RAD and the suggests possible and plausible disease mechanisms in this unique and underrepresented population, but more work is needed to truly elucidate mechanisms of disease in patients with RAD.

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