Acute Aortic Syndromes: State of the Art

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Disclosures: Kim A. Eagle

**Registry**

**IRAD**
International Registry of Aortic Dissection
Role: *Founder*

**GenTAC**
Genetically Triggered Aortic Conditions
Role: *Study Chair*

**Research Grants**

- Gore (Major Sponsor)
- Mardigian Foundation
- Hewlett Foundation
- Medtronic
- Robert & Anne Aikens
- National Heart, Lung, & Blood Institute
- National Institute of Arthritis & Musculoskeletal & Skin Diseases
- Terumo
- Varbedian Fund
- University of Michigan (Founding Sponsor)
Lecture Outline

• Where have we been?
  – Epidemiology
  – Classification
  – Clinical Presentation/ECG/Chest X-Ray
  – Static Imaging
  – Treatments
    ➢ Medical
    ➢ Non-Medical

• Where are we headed?
  – Genetics
  – Acute Biomarkers
  – Chronic Biomarkers
  – Dynamic Imaging

• Reflections on the Theme
Understanding Acute Aortic Syndromes... Where Have We Been?

- Predisposing Conditions
- Static Imaging Results
- Chest X-Ray
- Clinical Presentation
- Diagnosis using all inputs
- Medical Rx-All
- Intervention? (some)
- ECG Results
- Physical Findings
- Routine Laboratory Tests
- Long Term Follow-Up, Treatment, & Surveillance
Epidemiology: Incidence and Outcomes of Aortic Dissection

- 9 general practice sites – UK; 2002-12
- 52 incident dissections *(6/100,000/yr)*
- Risk factors
  - HTN – 67%
  - Smoking – 62%
  - BP poorly controlled pre-AoD
    - 56% BP’s > 140/90;
- 33/52 died, 18 (>50%) at home
- Hospital survivors: 5yr. survival
  - Type A – 86%
  - Type B – 83%
“Acute Aortic Syndromes”

- Classic Aortic Dissection
- Intramural Hematoma
- Penetrating Aortic Ulcer
Classic Intimal Tear

Intima

Media

Adventitia

Cystic Medial Necrosis

Intimal Tear

Intimal Medial Hemorrhage

Cystic Medial Necrosis

Medial Hemorrhage
Current Classification by Time From Symptom Onset - Outdated

Acute AoD

- Presentation within 14 days of onset

**Stanford Type A**
Involves the ascending aorta with or without descending aorta

**Stanford Type B**
Confined to descending aorta

Aortic Dissection:
Mortality vs. Time from Symptom Onset

Mortality rate ....425 Cases

Chronic (> 15 days)
ESC
Acute (≤14 days)
Sub-acute (2-6 weeks)
Chronic (>6 weeks)
IRAD
Hyperacute (<24 hours)
Acute (2-7 days)
Sub-acute (8-30 days)
Chronic (>30 days)


## Demographics and Past History

<table>
<thead>
<tr>
<th>Variable</th>
<th>All</th>
<th>Type A</th>
<th>Type B</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=7331)</td>
<td>(n=4837)</td>
<td>(n=2494)</td>
<td></td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>61.9</td>
<td>61.3</td>
<td>63.0</td>
<td>&lt;0.003</td>
</tr>
<tr>
<td>Male</td>
<td>65.9%</td>
<td>66.20%</td>
<td>65.6%</td>
<td>NS</td>
</tr>
<tr>
<td>HTN</td>
<td>78.3%</td>
<td>75.5%</td>
<td>83.4%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Marfan</td>
<td>4.0%</td>
<td>3.9%</td>
<td>4.81%</td>
<td>NS</td>
</tr>
<tr>
<td>Prior Heart</td>
<td>16.4%</td>
<td>14.2%</td>
<td>20.3%</td>
<td>0.001</td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iatrogenic</td>
<td>2.7%</td>
<td>3.1%</td>
<td>2.0%</td>
<td>0.009</td>
</tr>
</tbody>
</table>

IRAD Investigators.
How Common is Aortic Dissection in ED Patients with Thoracic Pain?


<table>
<thead>
<tr>
<th>Condition</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic Dissection</td>
<td>122</td>
<td>0.3%</td>
</tr>
<tr>
<td>No Aortic Dissection</td>
<td>128</td>
<td>0.3%</td>
</tr>
<tr>
<td>Suspicious</td>
<td>250</td>
<td>0.6%</td>
</tr>
<tr>
<td>Other Disease</td>
<td>38,819</td>
<td>93%</td>
</tr>
<tr>
<td>Not suspicious for Aortic Dissection</td>
<td>2,426</td>
<td>5.8%</td>
</tr>
</tbody>
</table>
Pain attending the splitting of the aortic wall is usually excruciating and extensive, radiating from midthorax front or back through the chest, down the back, and even into the thighs or up into the neck. The pain in the thorax or back comes suddenly at its maximum and is often prostrating, inducing a state of shock or even death.

- Paul Dudley White, 1944
## IRAD Presenting Symptoms

<table>
<thead>
<tr>
<th>Variable</th>
<th>All</th>
<th>Type A</th>
<th>Type B</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pain</strong></td>
<td>94.6%</td>
<td>93.8%</td>
<td>96.1%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Abrupt</td>
<td>84.0%</td>
<td>83.3%</td>
<td>85.2%</td>
<td>0.050</td>
</tr>
<tr>
<td>Anterior</td>
<td>82.1%</td>
<td>86.9%</td>
<td>72.1%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Back</td>
<td>52.8%</td>
<td>42.7%</td>
<td>70.2%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Abdominal</td>
<td>30.9%</td>
<td>25.0%</td>
<td>41.3%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sharp</td>
<td>54.0%</td>
<td>49.8%</td>
<td>61.3%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tearing</td>
<td>30.4%</td>
<td>27.8%</td>
<td>35.0%</td>
<td>0.004</td>
</tr>
<tr>
<td><strong>Syncope</strong></td>
<td>12.7%</td>
<td>17.6%</td>
<td>3.6%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

(n=6917)

IRAD Investigators
# IRAD Physical Exam

<table>
<thead>
<tr>
<th>Variable</th>
<th>All</th>
<th>Type A</th>
<th>Type B</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>High BP</td>
<td>41.1%</td>
<td>28.4%</td>
<td>65.1%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Low BP</td>
<td>11.4%</td>
<td>15.6%</td>
<td>3.5%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Shock/Tamponade</td>
<td>10.4%</td>
<td>15.3%</td>
<td>1.4%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Murmur AI</td>
<td>23.4%</td>
<td>32.2%</td>
<td>8.0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulse Deficit</td>
<td>31.8%</td>
<td>35.8%</td>
<td>25.3%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroke</td>
<td>6.5%</td>
<td>9.3%</td>
<td>1.3%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

(n=6339)
Sensitivity of ACC/AHA Guidelines for Acute Aortic Dissection


2538 (100%)

High Risk Conditions
- Marfan Syndrome
- Family History Aortic Disease
- Known Aortic Valve Disease
- Recent Aortic Manipulation
- Known Thoracic Aortic Aneurysm

713 (28.1%)

High Risk Pain Features
- Chest, back, or abdominal pain described as any of the following:
  - Abrupt onset
  - Severe intensity
  - Ripping or tearing

2220 (87.5%)

High Risk Exam Features
- Evidence of Perfusion Deficit
  - Pulse Deficit
  - Systolic BP differential
  - Focal Neurologic Deficit (in conjunction with pain)
- Murmur of Aortic Insufficiency (new and with pain)
- Hypotension or Shock state

1294 (51%)

Add Risk Score

Score = 0
108 (4.3%)

Score = 1
927 (36.5%)

Score = 2 or 3
1503 (59.2%)

Chest X-Ray
- Yes – Widened Mediastinum
  - 35 (48.6%)
- No – Widened Mediastinum
  - 37 (51.4%)

No Chest X-Ray
- 72
- 36

# IRAD

## EKG & CXR

<table>
<thead>
<tr>
<th>Variable</th>
<th>All</th>
<th>Type A</th>
<th>Type B</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CXR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>29.7%</td>
<td>29.2%</td>
<td>30.3%</td>
<td>NS</td>
</tr>
<tr>
<td>Wide Mediast.</td>
<td>49.1%</td>
<td>53.5%</td>
<td>42.3%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>or Aorta</td>
<td>14.5%</td>
<td>12.4%</td>
<td>17.7%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>EKG</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>39.0%</td>
<td>38.5%</td>
<td>40.0%</td>
<td>NS</td>
</tr>
<tr>
<td>NSST-T △’s</td>
<td>44.4%</td>
<td>43.7%</td>
<td>45.6%</td>
<td>NS</td>
</tr>
<tr>
<td>Ischemia</td>
<td>14.3%</td>
<td>17.2%</td>
<td>8.6%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>New MI</td>
<td>7.4%</td>
<td>9.7%</td>
<td>3.0%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

(n=5516)

IRAD Investigators
IRAD Diagnostic Tests
Imaging test 1.8/case (60% > 1)

First Modality

MRI 2%
AG 4%
TEE 33%
CT 61%

Sensitivity of the First Imaging Study to Detect AoD and Intramural Hematoma

<table>
<thead>
<tr>
<th>Imaging Study</th>
<th>Sensitivity (%)</th>
<th>Number of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEE</td>
<td>88.8%</td>
<td>935 / 1053</td>
</tr>
<tr>
<td>CT</td>
<td>97.6%</td>
<td>2625 / 2690</td>
</tr>
<tr>
<td>MRI</td>
<td>97.8%</td>
<td>44 / 45</td>
</tr>
<tr>
<td>Cath</td>
<td>89.8%</td>
<td>88 / 98</td>
</tr>
</tbody>
</table>

(n=3886)

IRAD Investigators
My aorta is huge! It’s bigger than any of the presidents before me! Small aortas are for losers. Sad.
What is the Size of a Normal Aorta?

- How Measured?
- Where Measured?
- In Who?
Who are You Measuring?
Aortic Diameter at Sinuses of Valsalva by Gender (Adjusted for BSA)

Devereux et al. J Am Coll Cardiol 2010;55:A87. [Epub on DVD]
How Are You Measuring?

Oblique Imaging Can Cause Over-Estimation of Aortic Diameter: A GenTAC Substudy

How Are You Measuring?

Patients Meeting Surgical Criteria (%)

All Segments

Segments Meeting Surgical Criteria (%)

Sinuses of Valsalva

Sinotubular Junction

Mid Ascending Aorta

Axial Method

Double Oblique Method

p = 0.03

p < 0.001

p = 1.0

Weinsaft et al. JACC 2010.
Maximum Aorta Diameter: Type A Dissection

(59% < 5.5 cm)

One Proposed Management Pathway for Acute Aortic Dissection

Suspected Dissection

Directed History and Exam: ECG, Biomarker Testing, Diagnostic Imaging (CTA>TEE), initiate intravenous medical treatment

Step 1

Step 2

Ascending Aortic Involvement?

Yes (Type A) → Emergency Surgical Consultation OR Intraop TEE

No (Type B) → Complicated?

- Malperfusion Syndrome Syndrome
- Rupture
- Rapid Expansion
- Refractory Pain

Uncomplicated?

- Pain, HR, BP controlled
- Operative Management
- Cannulation, Perfusion
- Aortic Valve Considerations
- Management of Arch Complications

- Endovascular (TEVAR) >> Open Repair

Step 3

Step 4

Long-Term Medical Treatment
Radiologic Surveillance

### Surgical Indications for Acute and Chronic Aortic Dissection

<table>
<thead>
<tr>
<th>Acute Dissection</th>
<th>Chronic Dissection</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type A:</strong> All patients</td>
<td><strong>Type A:</strong></td>
</tr>
<tr>
<td></td>
<td>• Maximal dimension ≥ 5.5 cm</td>
</tr>
<tr>
<td></td>
<td>• Marfan syndrome with maximum dimension ≥ 4.5-5 cm</td>
</tr>
<tr>
<td></td>
<td>• Increase in dimension ≥ 1 cm/yr</td>
</tr>
<tr>
<td></td>
<td>• Severe aortic regurgitation</td>
</tr>
<tr>
<td></td>
<td>• Symptoms suggestive of expansion or compression</td>
</tr>
<tr>
<td><strong>Type B:</strong> With complications</td>
<td><strong>Type B:</strong></td>
</tr>
<tr>
<td></td>
<td>• Rupture</td>
</tr>
<tr>
<td></td>
<td>• Extension</td>
</tr>
<tr>
<td></td>
<td>• Rapid aneurysm expansion</td>
</tr>
<tr>
<td></td>
<td>• Malperfusion syndrome</td>
</tr>
<tr>
<td></td>
<td>• Marfan syndrome?</td>
</tr>
<tr>
<td></td>
<td>• Maximal dimension ≥ 6 cm</td>
</tr>
<tr>
<td></td>
<td>• Increase in dimension ≥ 1 cm/yr</td>
</tr>
<tr>
<td></td>
<td>• Symptoms suggestive of expansion or compression</td>
</tr>
</tbody>
</table>

Challenges of Repair in Acute Proximal Dissection

- Friable fragile tissue
- Cardiac tamponade
- Distal malperfusion
- Aortic valve compromise
- Aortic valve pathology
- Stroke
- Prior cardiac surgery
- Annuloaortic ectasia
Percentage of Non-operative TA-AAD Patients Over Time

- Type A Operative Patients: p < 0.001
- Type A Non-operative Patients: p < 0.001

Percentage of In-hospital Mortality of All TA-AAD Patients Over Time

- In-hospital Mortality: p = 0.001

Sinha S, presented ACC 2011.
In Hospital Mortality: Operated Type A Dissection

Linear Trend  $p=0.013$

<table>
<thead>
<tr>
<th>Year Range</th>
<th>Frequency (%)</th>
<th>Count (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996-2003</td>
<td>17.5</td>
<td>229</td>
</tr>
<tr>
<td>2004-2009</td>
<td>15.8</td>
<td>692</td>
</tr>
<tr>
<td>2010-2016</td>
<td>12.2</td>
<td>811</td>
</tr>
</tbody>
</table>

Aortic Dissection: Mortality is Falling!

Overall Mortality, TASR, TBSR, TEVAR, MM

Endovascular Stent Grafting for Ascending Aortic Repair in High Risk Patients

22 Patients

Early Outcomes
- 3 Deaths
- 3 Strokes
- 2 MI’s
- 2 Tracheostomies

Later Outcomes (One-Year)
- 6 Type 1 Endoleaks
- 2 Open Repair
- 2 Reoperations (Stent Migration–1)
- 3 Deaths

Type A Aortic Dissection

Type B Dissection

- Uncomplicated - No false lumen: Medical
- Uncomplicated - False channel +/- aneurysm - consider stent
- Complicated - stent +/- surgery

# Outcomes of Stent-Graft Treatment of Acute Type B Dissection in Various Centers

<table>
<thead>
<tr>
<th>Indication</th>
<th>In-Hospital mortality</th>
<th>Complete false lumen thrombosis</th>
<th>Mean follow-up (months)</th>
<th>Late re-operation</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rupture</td>
<td>Malperfusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>aortic dilatation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sweden</td>
<td>32(42%)</td>
<td>20(30%)</td>
<td>12(18%)</td>
<td>21(49%)</td>
<td>14</td>
</tr>
<tr>
<td>Beijing</td>
<td>4(6%)</td>
<td>0</td>
<td>2(3%)</td>
<td>62(98%)</td>
<td>12</td>
</tr>
<tr>
<td>Nanjing</td>
<td>15(24%)</td>
<td>NS</td>
<td>3(5%)</td>
<td>NS</td>
<td>27</td>
</tr>
<tr>
<td>EUROSTAR</td>
<td>57(95%)</td>
<td>17(28%)</td>
<td>7(12%)</td>
<td>56(93%)</td>
<td>12</td>
</tr>
<tr>
<td>Total</td>
<td>108(43%)</td>
<td>37(19%)</td>
<td>24(10%)</td>
<td>139(73%)</td>
<td>16</td>
</tr>
</tbody>
</table>

INSTEAD XL – Trial: Kaplan-Meier Estimates of Aortic Progression and Adverse Events

### INSTEAD XL – Trial Results

<table>
<thead>
<tr>
<th></th>
<th>OMT (n=68)</th>
<th>OMT + TEVAR (n=72)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>5 year follow-up</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum aortic diameter</td>
<td>56.4±6.8</td>
<td>44.5±11.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>True lumen diameter at level A</td>
<td>18.7±6.7</td>
<td>32.6±5.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>False lumen diameter at level A</td>
<td>37.1±9.1</td>
<td>10.4±13.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>True lumen diameter at level B</td>
<td>16.9±7.2</td>
<td>28.6±6.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>False lumen diameter at level B</td>
<td>31.2±11.9</td>
<td>13.4±13.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>False lumen thrombosis at 5 year</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete, number (%)</td>
<td>11/50 (22.0)</td>
<td>48/53 (90.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Partial, number (%)</td>
<td>6/50 (12.0)</td>
<td>5/53 (9.4)</td>
<td>0.76</td>
</tr>
</tbody>
</table>

Comparison of Medical Therapy to Endovascular Treatment in Type B Dissection: Long Term Follow-Up

False Lumen Expansion is the Main Complication of Chronic Type B Dissection

Treatment with Stent Graft
National Trends in Type B Aortic Dissection Management

Type B Aortic Dissection Repair in Medicare Patients, 2000-2010

- Total Repair Rate Ratio 1.2 (95% CI 1.16-1.25)
- Open Repair Rate Ratio 0.9 (95% CI 0.86-0.93)
- TEVAR Rate Ratio 25.0 (95% CI 19.5-30.5)

* P ≤ .001
** P < .01
Interventions Among All Type B Patients Over Time

Procedures Over Time (Interventional Patients Only)

Kaplan-Meier Post-Discharge Mortality

Misirliyan S, (in press).
Retrograde Dissection after TEVAR
How to Follow?

1. Treatment
2. Surveillance
3. Patient Education
Type A and Type B Post-discharge Survival

The IRAD Investigators.
Natural History of Distal Aorta After Operated Type A Aortic Dissection

Distal false lumen patency:

Incidence of partial or complete distal false lumen patency is reported between: 31% and 89%.

Survival After Type A Dissection: False Lumen

Actuarial survival rates are shown for patients with patent false lumen (solid line) vs occluded (dashed line) false lumen.

Hazard Risk 15.2

224 pts acute DeBakey I dissection (early death 16%)
189 survivors followed, 48 with Marfan syndrome
Reintervention After Type A Dissection: False Lumen

224 pts acute DeBakey I dissection (early death 16%)
189 survivors followed, 48 with Marfan syndrome
# Acute DeBakey Type I Aortic Dissection: Frequency of Late Distal Reintervention

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>DeBakey I of Total # Dissections* n</th>
<th>DTA/TAAA Aortic Reintervention n (%)</th>
<th>Mean F/U</th>
<th>Completed F/U</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crawford</td>
<td>1992</td>
<td>65 of 82</td>
<td>7 (9%)</td>
<td>35.5 m</td>
<td>100%</td>
</tr>
<tr>
<td>Geirsson</td>
<td>2007</td>
<td>159 of 221</td>
<td>12 (5%)</td>
<td>39.7 m</td>
<td>99%</td>
</tr>
<tr>
<td>Zierer</td>
<td>2007</td>
<td>157 of 201</td>
<td>15 (9%)</td>
<td>78 m</td>
<td>100%</td>
</tr>
<tr>
<td>Stevens</td>
<td>2009</td>
<td>162 of 195</td>
<td>8 (4%)</td>
<td>8.1 y</td>
<td>91%</td>
</tr>
<tr>
<td>Song</td>
<td>2010</td>
<td>118 of 118</td>
<td>13 (11%)</td>
<td>3.5 y</td>
<td>100%</td>
</tr>
<tr>
<td>Kim</td>
<td>2012</td>
<td>129 of 129</td>
<td>23 (18%)**</td>
<td>30 m</td>
<td>N/A</td>
</tr>
<tr>
<td>Kimura</td>
<td>2014</td>
<td>472 of 534</td>
<td>30 (6%)</td>
<td>5.6 y</td>
<td>N/A</td>
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<tr>
<td>Rylski</td>
<td>2015</td>
<td>357 of 534</td>
<td>26 (7%)</td>
<td>3 y</td>
<td>N/A</td>
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</table>

Rupture not included

*Several reports include DeBakey type I and II

** Percent with aneurysm formation
Entry Tear Size and Proximal Location

Prox tear > 10 mm: 3 yrs later = 6.8cm

Cumulative survival free from sudden death and surgical/endovascular treatment by entry tear pattern (size and location). Prox indicates proximal.

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Type B Survival Related to Total Aortic Diameter

What’s the Best Long-Term Medical Therapy for Aortic Dissection?
Medical Therapy of Thoracic Aortic Aneurysms: Are We there Yet?

ACEI → ↑ Angiotensin II → AT1 → ↑ TGF beta → ↑ psmad2 → Cellular proliferation Matrix degradation

β-blocker → Fibrillin 1 mutation → ↑ TGF beta

Statin → ↓ NADH/NADPH → ↑ ROS → ↑ Cyclophilin A → Inflammatory reaction

ARB → Tetracyclines/ Macrolides → ↑ MMP → Cystic medial necrosis

Shear stress → ↑ TGF beta

↑ Angiotensin II → ↑ NADH/NADPH

↑ Angiotensin II → ↑ ROS

Beta Adrenergic Blockade Slows Aorta Growth in Marfan’s Syndrome

Randomized trial of propranolol in 70 adolescent and adult patients with classic Marfan's syndrome

Beta-Blockers Lower Risk in Ehler-Danlos

Kaplan-Meier curves of event-free survival in 53 patients with vascular Ehlers-Danlos Primary endpoint (A). Primary and secondary endpoints (B).

Importance of Blood Pressure Control After Repair of Acute Type A Aortic Dissection: 25-Year Follow-Up in 252 Patients

Reoperation rates:
- SBP <120 mm Hg: 3/85 (4%)
- SBP 120-140 mm Hg: 13/63 (21%)
- SBP >140 mm Hg: 10/30 (33%)

Freedom from Adverse Clinical Outcomes, According to Treatment Group

Marfan Syndrome: Primary Outcomes in the Intention-to-Treat Population During the Study Period

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Control</th>
<th>Losartan</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td></td>
<td><em>n</em>=105</td>
<td><em>n</em>=113</td>
<td></td>
</tr>
<tr>
<td>Aortic dilatation rate by MRI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic root</td>
<td>1.35±1.55</td>
<td>0.77±1.36</td>
<td>0.014</td>
</tr>
<tr>
<td>Ascending aorta</td>
<td>0.85±1.23</td>
<td>0.78±1.32</td>
<td>0.726</td>
</tr>
<tr>
<td>Aortic arch</td>
<td>0.61±1.35</td>
<td>0.52±1.37</td>
<td>0.598</td>
</tr>
<tr>
<td>Descending aorta</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulm. artery</td>
<td>0.72±1.40</td>
<td>0.54±1.40</td>
<td>0.366</td>
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<tr>
<td>Diaphragm</td>
<td>0.43±1.13</td>
<td>0.31±1.13</td>
<td>0.472</td>
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<tr>
<td>Abdominal</td>
<td>0.37±1.12</td>
<td>0.51±2.18</td>
<td>0.594</td>
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<tr>
<td>Aortic dilatation rate by TTE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic root</td>
<td>1.93±1.39</td>
<td>1.34±1.51</td>
<td>0.021</td>
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# GenTAC Human Data

<table>
<thead>
<tr>
<th></th>
<th>Aortic Dissection</th>
<th></th>
<th>Aortic Surgery</th>
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<tr>
<td></td>
<td><em>Marfan</em></td>
<td><em>Other</em></td>
<td><em>Marfan</em></td>
<td><em>Other</em></td>
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<tr>
<td></td>
<td>n=531</td>
<td>n=1819</td>
<td>n=531</td>
<td>n=1819</td>
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<tr>
<td>Odds in CCB</td>
<td>5.1%</td>
<td>0.57%</td>
<td>28.1%</td>
<td>10.70%</td>
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<tr>
<td>Odds in non-CCB</td>
<td>0.41%</td>
<td>0.12%</td>
<td>5.1%</td>
<td>4.4%</td>
</tr>
<tr>
<td>Odds Ratio-CCB</td>
<td>12.5</td>
<td>4.7</td>
<td>5.5</td>
<td>2.4</td>
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<tr>
<td><em>p-Value</em></td>
<td>0.032</td>
<td>NS</td>
<td>&lt;0.001</td>
<td>&lt;0.01</td>
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<tr>
<td>Odds Ratio (BP)</td>
<td>12.7</td>
<td>5.6</td>
<td>5.4</td>
<td>2.2</td>
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<tr>
<td><em>p-Value</em></td>
<td>0.06</td>
<td>NS</td>
<td>&lt;0.001</td>
<td>0.016</td>
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<tr>
<td>Odds Ratio (Aortic Size)</td>
<td>11.2</td>
<td>4.1</td>
<td>5.0</td>
<td>2.2</td>
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<tr>
<td><em>p-Value</em></td>
<td>0.08</td>
<td>NS</td>
<td>&lt;0.01</td>
<td>0.017</td>
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</table>

Surveillance Imaging of Aorta Following Acute Aortic Syndrome

• Serial CTAs early post-AoD to rule out rapid growth
  – Pre-discharge
  – 1, 3, and 6 months (consider 2 and 6 months)
  – Annually for first 2-3 years
• Consider switch to MRA once aorta is stable
• Alternatives
  – Iodinated contrast allergy: MRA for all follow-up
  – Renal insufficiency: MRI (no gadolinium)
Long Term Management of Aortic Dissection

- Medical management
  - Decrease dP/dT with beta blockers
  - Additional antihypertensives: ACE inhibitors, calcium channel blockers, etc
  - Goal is HR in 50’s-60’s, SBP 110-125
- Avoid heavy lifting or strain
  - Occupational responsibilities may be an issue
- Serial imaging studies to follow remaining aortic segments for aneurysm growth
  - Contrast-enhanced CT or MRI
  - Image abdominal aorta also if involved
Conclusions

• Aortic dissection is a chronic disease
• Regular surveillance is indicated
• Modality is less important than accuracy
• Medical management and lifestyle recommendations are important
• More data are needed
• More study is needed
Understanding Acute Aortic Syndromes: Where Are We Headed?

Clinical Presentation

- Initial Diagnosis
- Initial Prognostication
- Initial Treatment
  - Medical
  - Surgical
  - Interventional
  - Combinations

- Response to Initial Therapy
- Individualized Long Term Therapy
- Targeted Family Screenings

Pre-Existing Conditions

Genetic Predisposition

Static Imaging Result

Dynamic Imaging Result

Clinical Evaluation

Static Imaging Result

Dynamic Imaging Result

Physical Findings

ECG Testing

Routine Laboratory Tests

Acute Biomarkers

Genetic Predisposition

Chronic Biomarkers
Heritable Thoracic Aortic Diseases

Genetic Variants (12 Genes)

- Vascular Smooth Muscle Cell Contraction and Adhesion to ECM
- TGF-B Signaling
- Smooth Muscle Cell Metabolism or Survival
### Genetic Disorders: Thoracic Aortic Disease

<table>
<thead>
<tr>
<th>Genetic Syndrome</th>
<th>Common Clinical Features</th>
<th>Genetic Defect</th>
<th>Diagnostic Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marfan Syndrome</td>
<td>Skeletal features, Ectopic lentle</td>
<td><em>FBN1</em> mutations*</td>
<td>Ghent diagnostic Criteria, DNA for sequencing</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loeys-Dietz Syndrome</td>
<td>Bifid uvula or cleft palate, Arterial tortuosity, Hypertelorism</td>
<td><em>TGFBR2</em> or <em>TGFBR1</em> mutations</td>
<td>DNA for sequencing</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ehlers-Danios Syndrome</td>
<td>Thin, translucent skin, GI rupture, Rupture of gravid uterus, Rupture of medium to large arteries</td>
<td><em>COL3A1</em> mutations</td>
<td>DNA for sequencing, Dermal fibroblasts for analysis of type 3 collagen</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Turner Syndrome</td>
<td>Short stature, Primary amenorhea, BAV, Aortic coarctation</td>
<td>45 X karyotype</td>
<td>Cells for karyotype analysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*The defective gene at a second locus for MFS is TGFBR2 but the clinical phenotype as MFS is debated.*
• Ascending Ao Aneurysm
• AR, Dissection,
• MVP and MR,
• Pulmonary Artery Dilatation

Armspan > Height
Pectus excavatum
Scoliosis
Arachnodactyly (long fingers and toes)
Hyper-reflexic
High arched palate

Marfan Syndrome
Extensive aortic, carotid, subclavian aneurysms. Prone to dissection. No Marfan’s skeletal features.
The Dirty Dozen!

- **FBN 1** – Fibrillin I
- **LOX** – Lysyl oxidase
- **MYH II** – Smooth muscle myoxin heavy chain
- **ACTA 2** – Smooth muscle oc actin
- **MYLK** – Myosin light chain kinase
- **PRKG1** – cGMP dependent protein kinase type 1
- **COL3A1** – Collagen, type III, alpha -1
- **TGFBR2** – Transforming growth factor, β receptor II
- **TGFBR1** – Transforming growth factor, β receptor I
- **TGFB2** – Transforming growth factor, beta – 2
- **SMAD3** – Mothers against decapentaplegic homolog 3
- **FOXE3** – Forkhead box E3

Guo et al. Submitted.
### Familial TAAD Genes: Genetic Heterogeneity

<table>
<thead>
<tr>
<th>Gene</th>
<th>Description</th>
<th>Frequency</th>
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<tbody>
<tr>
<td>ACTA2</td>
<td>α-actin</td>
<td>10-14%</td>
</tr>
<tr>
<td>MYH11</td>
<td>myosin heavy chain</td>
<td>1%</td>
</tr>
<tr>
<td>MYLK</td>
<td>myosin light chain kinase</td>
<td>1%</td>
</tr>
<tr>
<td>PRKG1</td>
<td>cGMP-dependent kinase I</td>
<td>1%</td>
</tr>
<tr>
<td>TGFBR1</td>
<td>TGF-β receptor type I</td>
<td>2%</td>
</tr>
<tr>
<td>TGFBR2</td>
<td>TGF-β receptor type I</td>
<td>4%</td>
</tr>
<tr>
<td>SMAD3</td>
<td>Smad3</td>
<td>3%</td>
</tr>
<tr>
<td>TGFB2</td>
<td>TGF-β2</td>
<td>1%</td>
</tr>
<tr>
<td>FBN1</td>
<td>fibrillin-1</td>
<td>&lt;1%</td>
</tr>
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</table>

FTAAD families with identified gene: 25%

Non Syndromic Aortic Dissection in Young (≤ 55 Years) Patients

355 Patients

Pathogenic Rare Variants

TGFB2-1
TGFB2-1
FBN1-15
TGFB1-5
COL3A1-4
MYH11 Duplication-1
MYLK Deletion-1
ACTA2-3
SMAD3-3

33 (9.3%)

Guo et al. Submitted.
Genetics of Aortic Diseases: An Emerging Science

Hard to Identify: Rare Variants with Small Effects

Mendelian Families (Single Gene Disorders)

Missing Heritability
Intermediate Frequency, Moderate Effects (Rare Variants, CNV's)

GWAS loci e.g. (Common Variants; SNP's)

Effect Size

High

Intermediate

Modest

Low

Allele Frequency

Rare

Low Frequency

Common

The Complicated Genetics of Thoracic Aortic Disease

Indexed Aortic Root Dimensions of 3 Study Groups

- Indexed Aortic Dimensions (cm/m)
  - BAVs (53% Abnormal)
  - FDRs (32% Abnormal)
  - Controls (0% Abnormal)

- BAVs (n=54)
- FDRs (n=48)
- Controls (n=45)

Indications for Aortic Root Repair in Bicuspid Aortic Valve are:

1. Maximal diameter of > 5.5cm (Class I).

2. Maximal diameter of > 5cm with family history of aortic dissection or annual increase in size of > 0.5cm (Class IIa).

3. Maximal diameter of 4.5cm if patient undergoing surgery for aortic stenosis or regurgitation (Class IIa).

Surveillance and Surgical Indication Work-up of Ascending Aorta Dilation

- **TTE**

  - <45mm
    - Consider Baseline CT/MRI
    - TTE Biannually
    - CV Risk Factor Assessment and Control
  - Root / Ascending Aorta
  - ≥45mm
    - CT / MRI

  - 45-49mm
    - TTE Annually
    - Ao coarctation
    - Systemic Arterial Hypertension
    - FDR with Ao dissection/rupture
    - Growth rate > 3mm/y
    - Severe AVD

  - 50-54mm
    - TTE 6 Monthly
    - BAV
    - Marfan S

  - ≥55mm
    - Surgical Treatment

Evangelista A. *Heart* 2014;100:909-915.
Searching for A Biomarker?

- Endothelium
- Elastin laminae (sheets)
- Vascular smooth muscle cells
Biomarkers “Targets” in Acute and Chronic Thoracic Aortic Disease

Diagnosis and/or Risk Prediction

- Regulatory Proteins (TGFB)
- Smooth Muscle Cells (Myosin Heavy Chain)
- Inflammation (CRP)
- Elastic Fibers (Fibrillin Fragments)
- Clotting Factors (D-Dimer)

- Elastic Fibers (Fibrillin Fragments)
Aortic Dissection Biomarkers

- Smooth muscle myosin
- Creatine kinase-BB isozyme
- Calponin (smooth muscle troponin-like protein)
- GM-CSF
- TGFβ
- D-dimer

Circulating levels vs. time after onset

References:
# D-Dimer in Acute Aortic Dissection

<table>
<thead>
<tr>
<th>Author/Year</th>
<th># Cases</th>
<th>A/B</th>
<th># Ctrl</th>
<th>Onset</th>
<th>Sens</th>
<th>Spec</th>
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<td>Weber 2003</td>
<td>24</td>
<td>12/12</td>
<td>30</td>
<td>24</td>
<td>100%</td>
<td>69</td>
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<tr>
<td>Eggebrecht 2004</td>
<td>16</td>
<td>6/10</td>
<td>48</td>
<td>16</td>
<td>100%</td>
<td>81%</td>
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<tr>
<td>Hazui 2005</td>
<td>29</td>
<td>29/0</td>
<td>-</td>
<td>4</td>
<td>93%</td>
<td>-</td>
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<tr>
<td>Akutsu 2005</td>
<td>30</td>
<td>12/18</td>
<td>48</td>
<td>4.5</td>
<td>100%</td>
<td>54%</td>
</tr>
<tr>
<td>Ohlman 2006</td>
<td>94</td>
<td>67/27</td>
<td>94</td>
<td>29</td>
<td>99%</td>
<td>34%</td>
</tr>
<tr>
<td>Weigand 2007</td>
<td>25</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>88%</td>
<td>-</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>218</strong></td>
<td></td>
<td></td>
<td></td>
<td><strong>97%</strong></td>
<td><strong>34-81%</strong></td>
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</table>
Bio – IRAD:
D-Dimer Levels in Aortic Dissection

Emergency Room: Acute Chest Pain

ACUTE CHEST PAIN

Medical history + clinical examination + ECG

STEMI*: see ESC guidelines

UNSTABLE

TTE + TOE/CT*

AAS confirmed
AAS excluded
Consider alternate diagnosis

HAEMODYNAMIC STATE

Low probability (score 0-1)

D-dimers** + TTE + Chest X-ray

No argument for AD
Look for signs of AD
Widened mediastinum
Consider alternate diagnosis

STABLE

High probability (score 2-3) or typical chest pain

TTE

Definite Type A-AD c
Refer on emergency to surgical team and pre-operative TOE

CT (or TOE)

AAS confirmed
Consider alternate diagnosis; repeat CT if necessary

www.escardio.org/guidelines

Granulocyte macrophage colony-stimulating factor is required for aortic dissection/intramural haematoma

Bo-Kyung Son¹, Daigo Sawaki¹, Shota Tomida¹, Daishi Fujita¹, Kenichi Aizawa¹,², Hiroki Aoki³, Masahiro Akishita⁴, Ichiro Manabe¹, Issei Komuro¹, Scott L. Friedman⁵, Ryozo Nagai² & Toru Suzuki¹,²,⁶,⁷
Fibrillin Fragments in Thoracic Aortic Disease

Fibrillin Fragments in Thoracic Aortic Disease

Potential Biomarkers of Chronic Dissection

GM-CSF/IL-6
IL-17?
G-CSF?
TGFβ
MMPs
TIMPs
elastin
D-dimer
CRP

Need for biomarkers of progression and speed

Normal | Chronic inflammation | Tissue Remodeling | Dissection (rupture)

Partial Thrombosis of False Lumen in Acute Type B Dissection

Dynamic Imaging: A Key Concept for Personalized Treatment and Follow-Up?
Helicity Quantification

A, Aortic valve images (shown at every 3 times steps starting from left ventricular contraction) were (B) coregistered with the 4D flow data for 3D flow visualization of a normal subject with a tricuspid aortic valve.
A–C, Coregistered steady-state free precession images provide anatomic landmarks to locate (D and E) the direction and propagation of a systolic flow jet.

Helicity

\[ y = 31.24x + 792.8 \]
\[ r = 0.83 \]
\[ P = 0.0154 \]

On the death of King George II in 1760: Aortic Dissection in Perspective

“On the 25th of October he [King George II] rose as usual at six, and drank his chocolate; for all his actions were invariably methodic. A quarter after seven he went into a little closet. His German valet de chambre in waiting heard a noise, and running in, found the King dead on the floor.”¹ Nichols was directed to open and embalm the royal body. What he found (and meticulously described²) was the first clear account of the condition we now know (after Laennec) as aortic dissection (AD): “...the pericardium was found distended with a quantity of coagulated blood, nearly a pint...; the whole heart was so compressed as to prevent any blood contained in the veins from being forced into the auricles; therefore the
Disease is very old, and nothing about it has changed. It is we who change as we learn to recognize what was formerly imperceptible.

- Charcot
<table>
<thead>
<tr>
<th>University of Michigan Collaborators</th>
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</thead>
<tbody>
<tr>
<td><strong>IRAD Core</strong></td>
</tr>
<tr>
<td>Jim Froehlich</td>
</tr>
<tr>
<td>Eva Kline-Rogers</td>
</tr>
<tr>
<td>Dan Montgomery</td>
</tr>
<tr>
<td>Elise Woznicki</td>
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<tr>
<td><strong>UM Aortic Program</strong></td>
</tr>
<tr>
<td>Santhi Ganesh</td>
</tr>
<tr>
<td>Kristen Willer</td>
</tr>
<tr>
<td>Stan Chetcuti</td>
</tr>
<tr>
<td>Bill Armstrong</td>
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<tr>
<td>David Bach</td>
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<td>G. Michael Deeb</td>
</tr>
<tr>
<td>Jon Eliason</td>
</tr>
<tr>
<td>David Williams</td>
</tr>
<tr>
<td>Himanshu Patel</td>
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“There is no disease more conducive to clinical humility than aneurysm of the aorta”

- Sir William Osler
# Acknowledgements

<table>
<thead>
<tr>
<th>Mentorship</th>
<th>Support</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Dr. Larry Cohen – Joy of Cardiology &amp; Professionalism</td>
<td>- Mr. &amp; Mrs. Walter Eagle – Value of hard work, honesty &amp; family</td>
</tr>
<tr>
<td>- Dr. Roman DeSanctis – My “Medical” Father</td>
<td>- Mr. Donald S. Hopkins – Invested in my career</td>
</tr>
<tr>
<td>- Dr. George Thibault – Outcomes &amp; Guidelines</td>
<td>- Mrs. Darlene Farrell Eagle – Lifelong companion</td>
</tr>
<tr>
<td>- Dr. Valentin Fuster – Think Global – Anything possible!</td>
<td>- Mr. Taylor Eagle – My greatest legacy?</td>
</tr>
<tr>
<td></td>
<td>- Countless others: Colleagues, students, patients, and family members</td>
</tr>
</tbody>
</table>

*Faith, family, friends, colleagues… These are the “things” that matter…*