Key to Optimal Medical Treatment for Patients with TBADs: Where does it usually go wrong?

Professor Christoph A. Nienaber, Dr. Xun Yuan, Dr Andreas Mitsis

The Royal Brompton and Harefield NHS Trust
Cardiology and Aortic Centre

C.Nienaber@rbht.nhs.uk
Does intensive medical treatment improve outcomes in aortic dissection?

Frank A Lederle professor of medicine, Janet T Powell professor of vascular biology and medicine, Christoph A Nienaber professor of internal medicine/cardiology

1Center for Chronic Disease Outcomes Research, VA Health Care System (111-O), Minneapolis, MN 55417, USA; 2Vascular Surgery Research Group, Imperial College, London W6 8RP, UK; 3Heart Center Rostock, University of Rostock, 18055 Rostock, Germany

This is one of a series of occasional articles that highlight areas of practice where management lacks convincing supporting evidence. The series adviser is David Tovey, editor in chief, the Cochrane Library. To suggest a topic for this series, please email us at uncertainties@thebmj.com

Each year, aortic dissection affects one in 20 000 people, resulting in 3000 deaths in the United States. Men are affected twice as often as women, and most people affected are over the age of 65 years. Two thirds of dissections involve the ascending aorta (type A), and many of these patients die before reaching hospital. The survivors, who are usually treated with immediate surgery (open or endovascular) unless contraindicated, have a 30 day mortality of 20-50%. Dissections confined to the descending aorta (type B) are usually managed without repair unless complications develop, and with this approach they have a 30 day mortality of about 12%. For nearly half a century, the recommended initial medical lowered to <100 mmHg if tolerated. The first line use of β-blockers also differs from recommendations for patients without aortic dissection who have hypertension or are undergoing surgery, for whom this practice is discouraged because of evidence of increased cardiovascular morbidity and mortality.

Long term control of systolic blood pressure to below 120 mm Hg after aortic dissection (with or without surgery) is also widely recommended, often requires five or more drugs, and contrasts with recommendations for patients over age 60 without aortic dissection, for whom the systolic blood pressure goal has recently been raised to 150 mm Hg.

What is the evidence of uncertainty?

We sought evidence in Medline (Aneurysm, Dissecting), in the Cochrane Library, and in the reference lists of pertinent articles. Neither we nor a recent Cochrane review found any randomised trials on the medical management of aortic dissection.
Renal Sympathetic Denervation in Patients with Aortic Dissection

DIMITAR DIVCHEV, M.D., GÖKMEN TURAN, M.D., TIM REH德ERS, M.D., and CHRISTOPH A. NIENABER, M.D., Ph.D.

From the Department of Cardiology, University Heart Center Rostock, Rostock, Germany

**Background:** We report on feasibility, safety, and mid-term outcomes of renal sympathetic denervation (RSD) in hypertensive patients after endovascular treatment for aortic dissection.

**Methods:** Six patients were subjected to RSD after receiving endovascular treatment for complicated aortic dissection. Between April 2011 and May 2012, RSD procedure was applied for persistent hypertension despite maximized antihypertensive drug therapy using the Symplicity™ catheter system. Endovascular aortic treatment was performed for malperfusion or rapid expansion by virtue of a stent-graft system (Valiant®, n = 5) or an open cell stent (Smart®, n = 1).

**Results:** Systolic blood pressure (BP) was 189.8 ± 32.2 mmHg and diastolic BP 96.2 ± 11.1 mmHg at baseline on 24 hours readings; after RSD, a successful reduction to 129.5 ± 11.8 mmHg (P = 0.004) for systolic and to 77.7 ± 10.7 (P = 0.004) for diastolic BP at 3-month follow-up was documented on ambulatory 24-hour BP readings with sustained reduction at 1-year follow-up (127.2 ± 11.8 mmHg [P = 0.002] and 77.7 ± 7.7 [P = 0.011]).

**Conclusion:** RSD using the Symplicity™ catheter system is feasible and safe in hypertensive patients previously subjected to endovascular repair for complicated aortic dissection. (J Interv Cardiol 2014;27:334-339)
Medical Management of Thoracic Aortic Dissection

1. Diagnosis of underlying disease
2. Pharmacologic therapy
3. Lifestyle modification
4. Long-term surveillance
5. Timing of prophylactic aortic repair
Shear stresses on the aortic wall are highest at sites of increased dilatation.

dP/dt, which is affected by wave reflections, is greatest in areas of aortic dilatation (Yin FC et al. Circulation 1989;79:854).
Patients with aortic dissection are at risk for late aortic events

Medical management to prevent ... rupture, aneurysm, aortic repair
# Recommendations for treatment of aortic dissection

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>In all patients with AD, medical therapy including pain relief and blood pressure control is recommended.</td>
<td>I</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>In patients with Type A AD, urgent surgery is recommended.</td>
<td>I</td>
<td>B</td>
<td>1,2</td>
</tr>
<tr>
<td>In patients with acute Type A AD and organ malperfusion, a hybrid approach (i.e. ascending aorta and/or arch replacement associated with any percutaneous aortic or branch artery procedure) should be considered.</td>
<td>IIa</td>
<td>B</td>
<td>2, 118, 202–204, 227</td>
</tr>
<tr>
<td>In uncomplicated Type B AD, medical therapy should always be recommended.</td>
<td>I</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>In uncomplicated Type B AD, TEVAR should be considered.</td>
<td>IIa</td>
<td>B</td>
<td>218, 219</td>
</tr>
<tr>
<td>In complicated Type B AD, TEVAR is recommended.</td>
<td>I</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>In complicated Type B AD, surgery may be considered.</td>
<td>IIb</td>
<td>C</td>
<td></td>
</tr>
</tbody>
</table>

*a* Class of recommendation.  
*b* Level of evidence.  
*c* Reference(s) supporting recommendations.  
AD = aortic dissection; TEVAR = thoracic endovascular aortic repair.
**Multiple guidelines:** IV beta-blockers as first-line therapy based on theoretical ability to decrease aortic wall shear stress (Labetalol).

- HR <60 bpm
- Systolic BP of 100-120 mm Hg or as tolerated while maintaining adequate end-organ perfusion

CCB (diltiazem, verapamil) suggested as alternatives if intolerance to beta-blockers.

If BP remains over target, ACE-inhibitors and other IV vasodilators can be used.

Once stable, transition to oral medications and continue long-term. Beta-blockers are recommended long-term.
What are the data on antihypertensive therapy after aortic dissection?

RCT: none
Non-randomized studies of antihypertensive medications in aortic dissection


2. Takeshita 2008. ACE-inhibitor treatment may reduce the risk of long-term aortic events after type B aortic dissection.

3. Sakakura K 2009. CCB use at discharge is associated with increased survival in type B aortic dissection.


Chronic beta-blocker therapy improves outcome and reduces treatment costs in chronic type B dissection


Increasing diameter of the aorta was the most important indication for surgery in both groups.

<table>
<thead>
<tr>
<th>Indication for aortic surgery</th>
<th>Beta-blocker use (n=51)</th>
<th>Other anti-hypertensive use (n=20)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic diameter</td>
<td>6 (12%)</td>
<td>8 (40%)</td>
<td>P=0.002</td>
</tr>
<tr>
<td>Persistent pain</td>
<td>2 (4%)</td>
<td>1 (5%)</td>
<td></td>
</tr>
<tr>
<td>Rupture</td>
<td>0</td>
<td>1 (5%)</td>
<td></td>
</tr>
<tr>
<td>Malperfusion</td>
<td>1 (2%)</td>
<td>1 (5%)</td>
<td></td>
</tr>
</tbody>
</table>
Angiotensin-Converting Enzyme Inhibitors Reduce Long-Term Aortic Events in Patients With Acute Type B Aortic Dissection


Medications at hospital discharge:

- Beta-blockers: 89%
- CCB: 47%
- ACE-i: 29%
- ARB: 27%
- Diuretic: 8%

Multivariate analysis for independent predictors of aortic events:

<table>
<thead>
<tr>
<th></th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 70 years</td>
<td>2.12</td>
<td>0.63-7.10</td>
<td>0.22</td>
</tr>
<tr>
<td>Beta-blocker use</td>
<td>0.26</td>
<td>0.06-1.04</td>
<td>0.06</td>
</tr>
<tr>
<td>ACE-inhibitor use</td>
<td>0.18</td>
<td>0.04-0.85</td>
<td>0.03</td>
</tr>
<tr>
<td>ARB use</td>
<td>1.27</td>
<td>0.37-4.31</td>
<td>0.70</td>
</tr>
</tbody>
</table>
Angiotensin-Converting Enzyme Inhibitors Reduce Long-Term Aortic Events in Patients With Acute Type B Aortic Dissection


Patients receiving ACEI had a significantly lower incidence of dissection-related aortic events than those not receiving ACEI (6% vs 28%, p=0.02)

Events:
- Aortic rupture in 3%
- Aneurysmal enlargement ≥ 60 mm in 10%
- Rapid enlargement of the dissected aorta in 4%
- Visceral/limb ischemia in 1%

Fig 1. Kaplan-Meier curve showing dissection-related aortic event-free survival during the follow-up. ACEI, angiotensin-converting enzyme inhibitor.
Determinants of Long-Term Mortality in Patients with Type B Acute Aortic Dissection


Median follow-up 55 months:

44 post-DC deaths:
   21/44 CV deaths (9 complications from AD, 5 sudden death, 7 cardiac cause).
   1-, 3-, and 5-year survival: 96%, 92%, and 88%, respectively.

Multivariate analysis predicting all cause mortality:

Use of beta blocker at DC (80%): HR 0.6  (95% CI, 0.29-1.24), p = 0.17
Use of CCB at DC (93%): HR 0.38  (95% CI 0.15-0.97), p = 0.04
No anti-hypertensive meds at DC (2%): HR 9.5   (95% CI 1.85-48.8), p <0.007
Type-Selective Benefits of Medications in Treatment of Acute Aortic Dissection (from IRAD)


1301 pts who survived acute AD with information about medications at discharge.

Median f/u: 26 months (interquartile range 12-48)

At DC, most patients normotensive (124 + 18/71 + 11 mm Hg)

Meds upon DC:
- Beta-blockers 89%
- CCB 50% [not specified by type or dose]
- ACE-i 47%
- diuretics 29%
- vasodilators 22%
- ARBs 8%
Kaplan-Meier survival curves for effects of medications on mortality. β Blockers in patients with (A) type A dissection and (B) type B dissection; and calcium channel blockers in those with (C) type A and (D) type B.

Type-Selective Benefits of Medications in Treatment of Acute Aortic Dissection (from IRAD)

Type-Selective Benefits of Medications in Treatment of Acute Aortic Dissection (from IRAD)


Effects of medications on outcomes. (A) Patients with type A who underwent surgery; and (B) those with type B treated medically. ACE = angiotensin-converting enzyme; BB = β blocker; CCB = calcium channel blocker

Study not powered to examine which combinations of drugs showed most benefit.
Importance of Blood Pressure Control After Repair of Acute Type A Aortic Dissection: 25-Year Follow-Up in 252 Patients


1984-2009, 252 patients underwent repair of type A AD at Washington University

Operative mortality 16%
Mean f/u for reoperation or death 6.9 ± 5.9 years

For operative survivors:
5-, 10-, and 20 year survival was 78%, 59%, and 24%, respectively.

Risk factors for late reoperation:
- male sex (OR 2.9)
- Marfan syndrome (OR 7.8)
- SBP >120 at late f/u (OR 8.9)
- Absence of beta-blocker therapy (OR 6.1)
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%)
Group A included 2340 patients (25.74%) treated surgically for type A AD.

Group B included 1144 patients (12.58%) treated endo/surgically for type B AD.

Group C included 5608 patients (61.68%) with any type of AD treated with medical therapy only.

Overall survival rates of the three study groups in 9092 patients with aortic dissection in Taiwan.
Medical Management of Thoracic Aortic Dissection

1. Diagnosis of underlying disease
2. Pharmacologic therapy
3. Lifestyle modification
4. Long term surveillance
5. Referral for prophylactic aortic repair
Survivors of Aortic Dissection: Activity, Mental Health, and Sexual Function


314 survivors of acute aortic dissection surveyed regarding lifestyle modifications, exercise practice and emotional state.

Response rate was 42%.

32% with new-onset depression
32% with new onset anxiety
24% no longer engaged in any exercise
Majority of patients no longer sexually active after aortic dissection

Those who exercised routinely had less depression and lower BP.
“Medical” Management after Aortic Dissection

E - Establish the underlying diagnosis
A - Achieve normal blood pressure (regardless of drug!)
S - Stop cigarette smoking
Y - Yearn to exercise moderately
T - Test 1ˢᵗ degree relatives for TAA disease
I - Image the aorta over time
P - Perform aortic repair when appropriate
Key to Optimal Medical Treatment for Patients with TBADs: Where does it usually go wrong?

Professor Christoph A. Nienaber,
Dr. Xun Yuan, Dr Andreas Mitsis

The Royal Brompton and Harefield NHS Trust
Cardiology and Aortic Centre

C.Nienaber@rbht.nhs.uk
Estimation of risk in type B aortic dissection

Rare diseases: facts and figures

The UK defines a ‘rare disease’ as one that affects 1 in 2,000 or less of the population...

... so, collectively, rare disease will affect 1 in 17 of the population at some point in their life.

In total, that’s about 3 million people currently in the UK who will be affected by a rare disease.

50% of newly diagnosed cases of rare diseases are in children.

There are between 5,000 and 8,000 different rare diseases...

... and 80% of them have a known genetic origin.

"Your disease is so rare, there hasn't even been a TV drug-ad for it yet."
Propranolol on Progression (in MFS)

**Abstract**

*Background.* The aortic root enlarges progressively in Marfan’s syndrome, and this enlargement is associated with aortic regurgitation and dissection. Long-term treatment with β-adrenergic blockade, by reducing the impulse (i.e., the rate of pressure change in the aortic root) of left ventricular ejection and the heart rate, may protect the aortic root.

*Methods.* We conducted an open-label, randomized trial of propranolol in adolescent and adult patients with classic Marfan’s syndrome (32 treated and 38 untreated [control] patients). Aortic-root dimensions and clinical end points (aortic regurgitation, aortic dissection, cardiovascular surgery, congestive heart failure, and death) were monitored for an average of 9.3 years in the control group and 10.7 years in the treatment group. All 70 patients were included in the analysis according to the intention-to-treat principle.

*Results.* The dose of propranolol was individualized; the mean (±SE) dose was 212±68 mg per day. The mean slope of the regression line for the aortic-root dimensions, which reflect the rate of dilatation, was significantly lower in the treatment group than in the control group (0.023 vs. 0.084 per year, P<0.001). Clinical end points were reached in five patients in the treatment group and nine in the control group. The Kaplan-Meier survival curve for the treatment group differed significantly from that for the control group during the middle years of the trial and remained better for the treatment group throughout the study.

*Conclusions.* Prophylactic β-adrenergic blockade is effective in slowing the rate of aortic dilatation and reducing the development of aortic complications in some patients with Marfan’s syndrome. (N Engl J Med 1994;330:1335-41.)

Propranolol @ 212±68mg/d had marginal effect on progression of aortic root dimension

Effect only seen in juveniles
## Use of antihypertension therapy and Outcomes - A mixed Bag

### Treatment strategy of antihypertensive drugs and event rate.

<table>
<thead>
<tr>
<th>Treatment strategy</th>
<th>Number of patients</th>
<th>%</th>
<th>Primary endpoints</th>
<th>Hosp.</th>
<th>Death</th>
<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>11</td>
<td>10.4%</td>
<td>5 (45.5%)</td>
<td>3 (27.3%)</td>
<td>2 (18.2%)</td>
<td>1 (9.1%)</td>
</tr>
<tr>
<td>Monotherapy</td>
<td>10</td>
<td>9.4%</td>
<td>2 (20.0%)</td>
<td>1 (10.0%)</td>
<td>1 (10.0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>β-blocker</td>
<td>5</td>
<td>50.0%</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>CCB</td>
<td>1</td>
<td>10.0%</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Others</td>
<td>4</td>
<td>40.0%</td>
<td>1 (25.0%)</td>
<td>1 (25.0%)</td>
<td>1 (25.0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Dual therapy</td>
<td>31</td>
<td>29.3%</td>
<td>8 (25.8%)</td>
<td>6 (19.4%)</td>
<td>3 (9.7%)</td>
<td>4 (12.9%)</td>
</tr>
<tr>
<td>β-blocker + CCB</td>
<td>18</td>
<td>58.1%</td>
<td>3 (16.7%)</td>
<td>3 (16.7%)</td>
<td>0 (0%)</td>
<td>2 (11.1%)</td>
</tr>
<tr>
<td>β-blocker + Others</td>
<td>5</td>
<td>16.1%</td>
<td>2 (40.0%)</td>
<td>2 (40.0%)</td>
<td>2 (40.0%)</td>
<td>2 (40.0%)</td>
</tr>
<tr>
<td>CCB + RAS</td>
<td>3</td>
<td>9.7%</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>CCB + Others</td>
<td>4</td>
<td>12.9%</td>
<td>1 (25.0%)</td>
<td>1 (25.0%)</td>
<td>1 (25.0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>RAS + Others</td>
<td>1</td>
<td>3.2%</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Triple therapy</td>
<td>42</td>
<td>39.6%</td>
<td>12 (28.6%)</td>
<td>9 (21.4%)</td>
<td>4 (9.5%)</td>
<td>3 (7.1%)</td>
</tr>
<tr>
<td>β-blocker + CCB + RAS</td>
<td>14</td>
<td>33.3%</td>
<td>3 (21.4%)</td>
<td>3 (21.4%)</td>
<td>0 (0%)</td>
<td>3 (21.4%)</td>
</tr>
<tr>
<td>β-blocker + CCB + Others</td>
<td>20</td>
<td>47.6%</td>
<td>5 (25.0%)</td>
<td>5 (25.0%)</td>
<td>1 (5.0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>β-blocker + RAS + Others</td>
<td>4</td>
<td>9.5%</td>
<td>1 (25.0%)</td>
<td>1 (25.0%)</td>
<td>2 (50.0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>CCB + RAS + Others</td>
<td>4</td>
<td>9.5%</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (25.0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Quadruple therapy</td>
<td>12</td>
<td>11.3%</td>
<td>3 (25.0%)</td>
<td>1 (8.3%)</td>
<td>2 (16.7%)</td>
<td>1 (8.3%)</td>
</tr>
</tbody>
</table>

CCB: calcium channel blockers; RAS: drugs acting on the rennin-angiotensin system.

*Antihypertensive drugs divided into β-blockers, drugs acting on the rennin-angiotensin system (including angiotensin converting enzyme inhibitors, angiotensin receptor blocker, and direct rennin inhibitors), calcium channel blockers, and all other antihypertensive classes (including diuretics, α-blockers, vasodilators, and central α_2_ agonists).

Hospitalization associated with aortic dissection (primary endpoint). All-cause mortality and admission to hospital because of aortic dissection.

Hospitalization associated with aortic dissection. All-cause mortality. Referred to surgery repair.
Medical Management of Thoracic Aortic Dissection

1. Diagnosis of underlying disease
2. Pharmacologic therapy
3. Lifestyle modification
4. Long term surveillance
5. Referral for prophylactic aortic repair
TEVAR in complex complicated type B dissection (IC)

Malperfusion syndrome treated with endovascular stent-graft and PETTICOAT; a) angiography of lower body malperfusion; b) reperfusion after proximal stent-graft; c) 3D CT reconstruction of acute complicated dissection with malperfusion; d) reconstructed aorta and abolished malperfusion after stent-graft and PETTICOAT.
PETTICOAT for malperfusion resolution
Dual stent-graft procedure in type A aortic dissection
INSTEAD-XL: Landmark analysis

CV death (2nd EP)

Nienaber CA et al, Circulation CV Int 2013
Longterm outcomes in IRAD

TEVAR versus medical management of type B dissection

Fattori R, JACC CV Int 2013
Chronic type B dissection on drugs!
Algorithm...role of medical management?

- Patient with chest pain
  - Blood biomarkers, ECG
    - Urgent CT scan
      - Triple rule out CT if intermediate pre-test probability of CAD
      - Negative initial imaging, high clinical suspicion – add TTE
  - Pulmonary embolus
  - Aortic dissection
    - Stanford type A
      - Open surgery after initial risk assessment
    - Stanford type B
      - Complications:
        - Aortic rupture
        - End-organ ischaemia
        - On-going pain and hypertension despite full medical therapy
        - Early false lumen expansion
        - Large single entry
      - Uncomplicated Medical treatment
      - Complicated Endovascular treatment
  - Acute Coronary Syndrome
20% of individuals with a Thoracic Aortic Aneurysm disease will have an affected 1st degree relative

Risk Factors for Aortic Dissection: Bicuspid Aortic Valve Disease

Genes associated with BAV and TAA Disease:

*NOTCH1, TGFBR1, TGFBR2, TGFBR2, TGFBR3, ACTA2, MAT2A, GATA5, SMAD6, LOX*
Remodeling with TEVAR...

Complete false lumen thrombosis in the descending thoracic aorta.

Pre-procedure  Post-procedure  24 months
New high risk group: Pain & persisting hypertension

Trimarchi S et al. Circulation 2009
Panel 1: Contributing disorders for aortic dissection

- Long-term arterial hypertension
- Smoking
- Dyslipidaemia
- Cocaine, crack cocaine, or amphetamine use
- Connective tissue disorders
  - Hereditary disorders
    - Marfan’s syndrome
    - Loeys-Dietz’s syndrome
    - Ehlers-Danlos syndrome
    - Turner’s syndrome
  - Hereditary vascular disease
    - Bicuspid aortic valve
    - Coarctation

Vascular inflammation
- Autoimmune disorders
  - Giant-cell arteritis
  - Takayasu’s arteritis
  - Behçet’s disease
  - Ormond’s disease
- Infection
  - Syphilis
  - Tuberculosis

Deceleration trauma
- Car accident
- Fall from height

Iatrogenic factors
- Catheter or instrument intervention
- Valvular or aortic surgery
  - Side-clamping, cross-clamping, or aortotomy
  - Graft anastomosis
  - Patch aortoplasty

Risk Assessment:

Contributing disorders for aortic dissection
In presence or absence of a dilated aorta

Nienaber CA, Clough RA, Lancet 2015
## Genetic Profiling

### List of monogenetic disorders that cause acute aortic dissection by site and gene

<table>
<thead>
<tr>
<th>Function</th>
<th>Clinical manifestation (OMIM number)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ascending aorta</strong></td>
<td></td>
</tr>
<tr>
<td><strong>FBN1</strong></td>
<td>Microfibrils, elastogenesis, TGF-β bioavailability, and smooth muscle cell phenotype</td>
</tr>
<tr>
<td><strong>EFEMP2</strong></td>
<td>Fibulin 4, elastic fibres</td>
</tr>
<tr>
<td><strong>Thoracic aorta</strong></td>
<td></td>
</tr>
<tr>
<td><strong>FBN1</strong></td>
<td>Microfibrils, elastogenesis, TGF-β bioavailability</td>
</tr>
<tr>
<td><strong>TGFB1, TGFB2, TGF</strong></td>
<td>Signalling domain of TGF-β receptor</td>
</tr>
<tr>
<td><strong>MYH11</strong></td>
<td>Smooth muscle cell contraction</td>
</tr>
<tr>
<td><strong>ACTA2</strong></td>
<td>Smooth muscle cell contraction</td>
</tr>
<tr>
<td><strong>COL3A1</strong></td>
<td>Type III collagen, altered extracellular matrix fibres</td>
</tr>
<tr>
<td><strong>Aorta and other arteries</strong></td>
<td></td>
</tr>
<tr>
<td><strong>SLC2A10</strong></td>
<td>Decreased GLUT1.0 protein in TGF-β pathway</td>
</tr>
<tr>
<td><strong>Aorta</strong></td>
<td></td>
</tr>
<tr>
<td><strong>SMAD3</strong></td>
<td>Impaired TGF-β signal transmission</td>
</tr>
</tbody>
</table>

OMIM = Online Mendelian Inheritance in Man.

*Table: Monogenetic disorders that cause acute aortic dissection by site and gene*

Nienaber CA, Clough RA, Lancet 2015
Pre-TEVAR | Post-TEVAR | Erosion @ 16m

Nonsyndromic

69 years old lady

BP normalised using BB, ARB and diuretics

Symptom free until relapse of dissection

No genetic underpinning
IRAD: 1996 - 2016

Active IRAD Sites [49]
Uncomplicated Type B Dissection: In-H mortality/compl.

IRAD, unpublished
Algorithm

Patient with chest pain
Blood biomarkers, ECG
Urgent CT scan

Pulmonary embolus
Aortic dissection
Acute Coronary Syndrome

Triple rule out CT if intermediate pre-test probability of CAD

Negative initial imaging, high clinical suspicion – add TTE

Stanford type A
Open surgery after initial risk assessment

Stanford type B

Complications:
- Aortic rupture
- End-organ ischaemia
- On-going pain and hypertension despite full medical therapy
- Early false lumen expansion
- Large single entry

Uncomplicated
Medical treatment

Complicated
Endovascular treatment
A, Thoracic aortic dilations in interleukin-1β (IL-1β) knockout (KO) and IL-1 receptor (IL-1R) KO mice exposed to elastase were significantly less than wild-type (WT) thoracic aortic aneurysm (TAA) mice. *P<0.0001, †P<0.001. B, By immunohistochemistry, representative samples demonstrated increased staining of elastin fibers (black) and smooth muscle cells (brown) in IL-1β KO and IL-1R KO mice compared with WT TAAs. IL-1β KO and IL-1R KO aortas also had decreased macrophage staining and neutrophil staining (brown). Scale bar, 100 μm.
Aortic Dissection – inflammatory process?