Surgical Thresholds for proximal aortic disease—Search for an aortic fingerprint to track a Silent Killer

Jehangir J. Appoo
Libin Cardiovascular Institute
University of Calgary
www.aorta.ca

September 16, 2016
Genetic Aortic Diseases Association of Canada
Toronto, Ontario
Purpose

1. Where we are
   Review the latest guidelines from Canada, US and Europe Societies

2. How we got here
   Reveal gaps in knowledge

3. Where we may be going
   Speculate on future care paradigms
Why understanding aortic behaviour is important?

Intervention is invasive – has some risks

Dilemma:

Young patients with small aneurysms are running into trouble
vs.
Denominator is very large – many patients have large aortic aneurysms that are stable for prolonged periods of time

If we operated on every dilated aorta, we may do more harm than benefit
Why predicting aortic behaviour will be even more important in the future
# 2014 ESC Guidelines on the diagnosis and treatment of aortic diseases

## Recommendations on interventions on ascending aortic aneurysms

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery is indicated in patients who have aortic root aneurysm, with maximal aortic diameter$^c \geq 50$ mm for patients with Marfan syndrome.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Surgery should be considered in patients who have aortic root aneurysm, with maximal ascending aortic diameters:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• ≥45 mm for patients with Marfan syndrome with risk factors.$^d$</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>• ≥50 mm for patients with bicuspid valve with risk factors.$^e$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• ≥55 mm for other patients with no elastopathy.$^{e,h}$</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td>Lower thresholds for intervention may be considered according to body surface area in patients of small stature or in the case of rapid progression, aortic valve regurgitation, planned pregnancy, and patient’s preference.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Aortic root ≠ Asc Aorta
Position Statement

Canadian Cardiovascular Society Position Statement on the Management of Thoracic Aortic Disease

Primary Panel: Munir Boodhwani, MD, MMSc (Co-Chair),\textsuperscript{a} Gregor Andelfinger, MD, PhD,\textsuperscript{b} Jonathon Leipsic, MD,\textsuperscript{c} Thomas Lindsay, MD, MSc,\textsuperscript{d} M. Sean McMurtry, MD, PhD,\textsuperscript{e} Judith Therrien, MD,\textsuperscript{f} and Samuel C. Siu, MD, SM (Co-Chair)\textsuperscript{g}

\textsuperscript{a}Division of Cardiac Surgery, University of Ottawa Heart Institute, Ottawa, Ontario, Canada
\textsuperscript{b}Department of Pediatrics, University of Montreal, Montreal, Québec, Canada
\textsuperscript{c}Department of Radiology, University of British Columbia, Vancouver, British Columbia, Canada
\textsuperscript{d}Division of Vascular Surgery, University Health Network, Toronto, Ontario, Canada
\textsuperscript{e}Division of Cardiology, University of Alberta, Edmonton, Alberta, Canada
\textsuperscript{f}Division of Cardiology, McGill University, Montreal, Québec, Canada
\textsuperscript{g}Division of Cardiology, Western University, London, Ontario, Canada
Position Statement

Canadian Cardiovascular Society Position Statement on the Management of Thoracic Aortic Disease

Table 2. Recommended size thresholds for intervention for asymptomatic thoracic aortic aneurysms*

<table>
<thead>
<tr>
<th>Condition</th>
<th>Aortic root</th>
<th>Ascending</th>
<th>Arch</th>
<th>Descending</th>
</tr>
</thead>
<tbody>
<tr>
<td>Degenerative</td>
<td>5.5 cm</td>
<td>5.5 cm</td>
<td>6.0 cm</td>
<td>6.5 cm</td>
</tr>
<tr>
<td>Bicuspid aortic valve</td>
<td>5.0-5.5 cm</td>
<td>5.0-5.5 cm</td>
<td>5.5 cm</td>
<td>6.5 cm</td>
</tr>
<tr>
<td>Marfan syndrome</td>
<td>5.0 cm†</td>
<td>5.0 cm</td>
<td>5.5-6.0 cm</td>
<td>5.5-6.0 cm</td>
</tr>
<tr>
<td>Familial aortopathy</td>
<td>4.5-5.0 cm</td>
<td>4.5-5.0 cm</td>
<td>5.5-6.0 cm</td>
<td>5.5-6.0 cm</td>
</tr>
<tr>
<td>Other genetic syndromes†</td>
<td>4.0-5.0 cm</td>
<td>4.2-5.0 cm</td>
<td>5.5-6.0 cm</td>
<td>5.5-6.0 cm</td>
</tr>
<tr>
<td>Undergoing cardiac surgery</td>
<td>—</td>
<td>4.5 cm</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

* Size thresholds for intervention should take patient body size into consideration, either empirically or using proposed formulas for adjustment.
† For women anticipating pregnancy, the threshold is 4.1-4.5 cm.
‡ Loeys-Dietz, Turner, Ehlers-Danlos.

Distinguish between root and ascending but size indications are same
Surgery for Aortic Dilatation in Patients With Bicuspid Aortic Valves

A Statement of Clarification From the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>B-NR</td>
<td>1. Operative intervention to repair or replace the aortic root (sinuses) or replace the ascending aorta is indicated in asymptomatic patients with BAV if the diameter of the aortic root or ascending aorta is 5.5 cm or greater.</td>
</tr>
</tbody>
</table>
1. Operative intervention to repair or replace the aortic root (sinuses) or replace the ascending aorta is reasonable in asymptomatic patients with BAV if the diameter of the aortic root or ascending aorta is 5.0 cm or greater and an additional risk factor for dissection is present (eg, family history of aortic dissection or aortic growth rate ≥0.5 cm per year) or if the patient is at low surgical risk and the surgery is performed by an experienced aortic surgical team in a center with established expertise in these procedures.²⁻⁷⁻⁹
Summary of 2014-2016 Guidelines for Prox Ao Intervention:

Asc Ao > 5.5cm

Asc Ao > 5.0cm with some risk factors (rate of growth, family history of dissection, hypertension, patient preference...)

Asc Ao 4.5 – 5.0cm for Connective Tissue Disease

Probably don’t need to be more aggressive if bicuspid valve
Summary of 2014-2016 Guidelines on Prox Aortic Intervention:

Level of scientific evidence is poor
- no randomized data
- no large non randomized studies
- small, retrospective studies
- consensus opinions

Lots of room for flexible interpretation including patient preference, aortic shape, rate of growth, patient size
What 2014-2016 Guidelines are not telling us:

Difference of size indication between root vs. ascending aorta

What annual risk of rupture/dissection truly is

Are these guidelines valid only for a N. American population or range of BSAs?

Is there something magical about an aortic diameter of 5.5cm? If so, what??
Share 2 recent case where guidelines leave us confused
Aug 2016

29 y.o VACTERL Syndrome

R sided aortic arch
Bicuspid valve with mild stenosis
Asymptomatic
Petite stature

Does she have an indication for surgery?
The Asc Ao is 2.7x the size of desc aorta!
Do the Guidelines convince us that this 29 y.o is safe?
July 2016

50 y.o active female

BSA 1.53m2
Bicuspid valve with mild to moderate AI
asymptomatic
normal lv size and function
family history of bicuspid valve and ascending aortic aneurysm repair (brother)

Does she have an indication for surgery?
According to Guidelines does this 50y.o have an indication for surgery?

- <5.5cm
- <5.0cm
- No known history of rapid growth
- Family history of elective aneurysm repair – no family history of dissection

Indexed to BSA: 3.24!
One publication suggests >2.75cm/m2 is high risk
Why do Aneurysms Rupture?

Risk stratification of Aortic Aneurysms – *Indolent but Catastrophic*

Size & growth rate not great predictors of rupture/dissection

Need more science
How robust are the natural history data of Ascending Aortic Aneurysms? A Systematic Review – CCC 2016

Search Strategy

Studies Identified:
2321 by primary search
4 by reference search
Total: 2325

Duplicated Studies Removed: 50

Abstract Reviewed: 2275

Excluded by Title & Abstract: 2205

Full Text Reviewed: 70

Eliminated by Full Text Review: 59

Studies Included in Systematic Review: 11
<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Data Collection Period</th>
<th>Study Design</th>
<th>No of Patients</th>
<th>Imaging Modality</th>
<th>Thoracic vs ascending Ao</th>
<th>Follow up</th>
<th>Surgical Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joyce (1964)</td>
<td>1945-1955</td>
<td>-</td>
<td>-</td>
<td>Fluoroscopy, aortography</td>
<td>Mixed</td>
<td>-</td>
<td>N</td>
</tr>
<tr>
<td>Coady (1997)</td>
<td>1985-1996</td>
<td>Retrospective</td>
<td>174</td>
<td>CT, MRI, echo</td>
<td>Mixed</td>
<td>25.9 mos</td>
<td>Mixed</td>
</tr>
<tr>
<td>Coady (1999)</td>
<td>1985-1997</td>
<td>Retrospective</td>
<td>294</td>
<td>CT, MRI, echo</td>
<td>Mixed</td>
<td>29.4 mos</td>
<td>Mixed</td>
</tr>
<tr>
<td>Eleftheriades (2002)</td>
<td>-</td>
<td>Prospective database</td>
<td>1600</td>
<td>-</td>
<td>Thoracic</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Bassano (2005)</td>
<td>1995-2002</td>
<td>-</td>
<td>38</td>
<td>Echo</td>
<td>Ascending</td>
<td>42 mos</td>
<td>Y (operated at 5.5cm)</td>
</tr>
<tr>
<td>Matsuyama (2005)</td>
<td>1990-2000</td>
<td>-</td>
<td>35</td>
<td>CT</td>
<td>Ascending</td>
<td>8.1 years</td>
<td>-</td>
</tr>
<tr>
<td>Davies (2006)</td>
<td>1985-2005</td>
<td>Prospective database</td>
<td>805</td>
<td>CT, MRI, echo</td>
<td>Thoracic</td>
<td>31.4 mos</td>
<td>-</td>
</tr>
<tr>
<td>Pape (2007)</td>
<td>1996-2005</td>
<td>Prospective database</td>
<td>591</td>
<td>CT, MRI, echo</td>
<td>Ascending ao (dissection)</td>
<td>-</td>
<td>Y</td>
</tr>
<tr>
<td>Hornick (2012)</td>
<td>2003-2010</td>
<td>Retrospective</td>
<td>612</td>
<td>CT, MRI</td>
<td>Mixed</td>
<td>31.6 mos</td>
<td>-</td>
</tr>
<tr>
<td>Geisbusch (2014)</td>
<td>2009-2011</td>
<td>Retrospective</td>
<td>232</td>
<td>CT</td>
<td>Mixed (all &lt;5cm)</td>
<td>-</td>
<td>Mixed (3 patients)</td>
</tr>
</tbody>
</table>
Table 1. Summary of the 11 studies included in the systematic review. No. = Number; AsAA = Ascending Aortic Aneurysm; AD = Aortic Dissection; R = Aortic Rupture.

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Centres</th>
<th>Study Design</th>
<th>No of Patients with AsAA</th>
<th>% male</th>
<th>Surgical Intervention at operative threshold</th>
<th>Mean Initial Aneurysm Diameter (cm)</th>
<th>Mean Growth Rate (cm/year)</th>
<th>Mean Size at AD or R</th>
<th>Incidences of AD or R</th>
<th>Predictor of Increased Aneurysm Growth Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joyce (1994)</td>
<td>1</td>
<td>Retrospective</td>
<td>26</td>
<td>74%</td>
<td>No</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Coady (1997)</td>
<td>1</td>
<td>Retrospective</td>
<td>111</td>
<td>60%</td>
<td>Yes</td>
<td>NR</td>
<td>0.10</td>
<td>5.9</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Coady (1999)</td>
<td>1</td>
<td>Retrospective</td>
<td>201</td>
<td>60%</td>
<td>Yes</td>
<td>NR</td>
<td>0.09</td>
<td>5.9</td>
<td>NR</td>
<td>25% higher in &gt;6.0cm than 4.0-4.9cm</td>
</tr>
<tr>
<td>Davies (2002)</td>
<td>1</td>
<td>Retrospective</td>
<td>219</td>
<td>58.8%</td>
<td>Yes</td>
<td>NR</td>
<td>0.07</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Eleftheriades (2002)</td>
<td>1</td>
<td>Retrospective</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>0.07</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Bassano (2005)</td>
<td>1</td>
<td>Retrospective</td>
<td>38</td>
<td>81.6%</td>
<td>Yes</td>
<td>4.5</td>
<td>0.024+/-.34</td>
<td>NR</td>
<td>NR</td>
<td>2.63% (5 years) Aortic Regurgitation &amp; Initial aortic diameter</td>
</tr>
<tr>
<td>Matsuyama (2005)</td>
<td>1</td>
<td>Retrospective</td>
<td>35</td>
<td>60%</td>
<td>Yes</td>
<td>4.4±/4.4</td>
<td>0.026</td>
<td>4.65</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Davies (2006)</td>
<td>1</td>
<td>Retrospective</td>
<td>335</td>
<td>62.9%</td>
<td>Yes</td>
<td>5</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Pipe (2007)</td>
<td>11 (IRAD)</td>
<td>Retrospective</td>
<td>591</td>
<td>66%</td>
<td>Yes</td>
<td>NR</td>
<td>NR</td>
<td>5.5</td>
<td>&lt;5cm: 40%; 5.0-5.5cm: 20%</td>
<td>NR</td>
</tr>
<tr>
<td>Hornick (2012)</td>
<td>1</td>
<td>Retrospective</td>
<td>495</td>
<td>67.6%</td>
<td>Yes</td>
<td>NR</td>
<td>Bovine’s arch: 0.06; Non-Bovine’s arch: 0.12</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Godsbusch (2014)</td>
<td>1</td>
<td>Prospective</td>
<td>282</td>
<td>72%</td>
<td>Yes</td>
<td>Volume: 132.8+/4.0ml.</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>
Conclusions of our systematic review:

No single study reported all of: aneurysm growth rate, size at dissection or rupture, incidences of dissection or rupture, predictors of increase rate of growth, rupture and dissection, and overall survival.

Discrepancies between results from different studies

Data not robust enough to do a meta-analysis on topic
CTAC – Canadian Thoracic Aortic Collaborative proposal of a Nationwide Registry:

Establishment of a Capacity for Co-ordination of National Clinical Trials in the Treatment of Ascending Aortic Aneurysms
Establishment of a Capacity for Co-ordination of National Clinical Trials in the Treatment of Ascending Aortic Aneurysms

Objectives of Nationwide Online Registry:

- Describe natural history
- Establish core CT lab
- Determine a NNT for asc ao aneurysms
- Risk profile aneurysms beyond size
- Forum for prospective trials of medical and surgical therapy
Establishment of a Capacity for Co-ordination of National Clinical Trials in the Treatment of Ascending Aortic Aneurysms

Letters of Intent to participate from Cardiac Surgeons at 15 Canadian institutions

- Memorial University of Newfoundland
- New Brunswick Heart Centre
- Laval University
- Royal Victoria Hospital, McGill University
- Montreal Heart Institute
- Queens University
- Ottawa Heart Institute
- Toronto General Hospital
- Northern Ontario School of Medicine
- London Health Sciences Centre
- University of Manitoba
- University of Calgary
- University of Alberta
- St. Paul’s Hospital, University of British Columbia
- Royal Jubilee Hospital, University of British Columbia
Establishment of a Capacity for Co-ordination of National Clinical Trials in the Treatment of Ascending Aortic Aneurysms

Estimated cost: $187,000 for first 2 years

Current status: Applying for seed funding
Conference call with industry next week to explore partnership
Biomechanical Engineering Analysis as a tool to determine Aortic “fingerprint”
Aneurysms rupture/dissect when wall stress > wall strength

Collaboration with Biomedical Engineering, Histo-Pathology & Imaging colleagues
3D Growth

Multidimensional growth estimation

Non linear growth measure

$$g_d = \frac{1}{t} \log \left( \frac{D_{i \text{ follow-up}}}{D_{i \text{ post operation}}} \right)$$

100 observations

Post operation

1 year follow-up
3D Growth

Results

Growth rate (mm/y)

Maximum diameter

Outer diameter (mm)
“Aorta at Risk” Project
Personalized Medicine – “fingerprint”

Prospective tissue sample from asc ao aneurysms
Multimodality imaging
HistoPath analysis
Tissue strength & stiffness testing

Once we understand properties of asc ao, can we determine a non invasive risk profile?
Early work indicates that aneurysmal tissue from bicuspid aortas may in fact be stronger than aneurysms associated with trileaflet valves

To be presented at STS 2017

Ex-Vivo Assessment of Material Characteristics in Ascending Aortic Aneurysm Tissue for Bicuspid and Trileaflet Valve Groups

R. Beddoes1, Jehangir J. Appoo1,2, Elena S. Di Martino1,3
1 Schulich School of Engineering, University of Calgary, AB, 2 Division of Cardiac Surgery, Cumming School of Medicine, University of Calgary, 3 Libin Cardiovascular Institute of Alberta, University of Calgary

Purpose:
Risk of rupture or dissection of dilated ascending aortas is poorly understood. Debate exists whether aneurysms associated with bicuspid aortic valves behave differently than aneurysms with trileaflet valves. To help understand rupture risk, biomechanical analysis was performed to assess tissue strength and stiffness of human ascending aortic aneurysms.

Methods:
Ascending aortic aneurysm samples obtained from 32 patients were cut into 56 circumferential specimens. Uniaxial tensile strength testing was performed by first preconditioning and then stretching to failure at rate of 5mm/min. Material strength was defined as the first discontinuous portion of stress-strain curve. Stiffness was assessed from the linear region of stress-strain curve. Neo-Hookean parameter, a surrogate for stiffness for materials exhibiting non-linear behaviour, was fit to the data. Corresponding goodness of fit, R², was computed via linear regression analysis. Results of material strength and stiffness were compared in patients with bicuspid aortic valves vs. trileaflet aortic valves.

Results:
Uniaxial tensile tests were performed on 22 trileaflet valve and 34 bicuspid valve specimens. Median ascending aortic diameters were 5.6cm vs. 5.2cm for trileaflet and bicuspid valves respectively (P<0.05). Median material strength was 0.737 MPa in trileaflet vs. 1.196 MPa in bicuspid (P<0.05). Median material stiffness in the linear region was 3.253 MPa (R²=____) in trileaflet and 4.194 MPa (R²=____) in bicuspid (P<0.05). The median neo-Hookean parameter for non-linear region for trileaflet and bicuspid was found to be 0.0318 MPa (R²=0.90) vs. 0.0513 MPa (R²=0.99) (P<0.05).

Conclusions:
Ex-vivo biomechanical assessment of ascending aortic aneurysms indicate bicuspid aortas may be stronger and stiffer than aortic tissue associated with trileaflet valves. This is contrary to popular clinical belief that aneurysms associated with bicuspid valves are at higher rupture or dissection risk. Further studies will control for maximal aortic diameter.

Table

<table>
<thead>
<tr>
<th>Trileaflet N=22</th>
<th>Bicuspid N=34</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Provocative Question:

Histopath (eg: fibrillin deficiency) may explain why patients with CT disorders develop aneurysms - but for the same size ascending aorta why is that the Marfan’s aorta is much more to rupture/dissection?

Recall that aneurysms rupture when wall strength < wall stress
Screening

How can we appropriately screen a population to prevent disasters?

Caveat: Will also discover a lot of aortas that may not benefit from treatment
March 2016

20 y.o male abdo pain

Lap Appendectomy at Rural Hospital

Repeat CT POD4 for CP/unwell

Died prior to transfer
In retrospect, root dilatation and abdo aortic dissection could be appreciated on preop CT at time of abdo pain presentation

March 2016

Questions:

What kind of systematic screening program can identify him early?

How did aorta get to 8cm in young man without rupturing?
Sept 2016

46y.o Type A and GI bleed – died prior to transfer from RGH
Screening at FMC:

Working with DI to develop “White Papers”

   incidental finding of aortic aneurysms

   screening of first degree relatives
Conclusions:

Recent interest in aortic pathology/surgery has led to formation of new guidelines

Current guidelines are based on low quality evidence

More subtleties to aneurysm rupture than just aortic diameter

Perhaps aneurysms in young patients behave differently than in older patients

More tools are needed to assess risk profile of this silent killer
Future:

1. Prospective multicentre natural history registry to determine a NNT
2. Biomechanical assessment may help stratify risk assessment along with size, growth rate, indexed size, pt. age, biomarkers to develop a “Fingertip”
3. Appropriate Screening protocols are to be determined