MHIF FEATURED STUDY: CLBS16-P02 FREEDOM Study

DESCRIPTION: Blinded randomized study comparing IC delivery of apheresis derived (after G-CSF administration) autologous CD34+ cells versus placebo.

Reduced CFR is a risk factor and these are patients with chronic chest pain thought to be secondary to microvascular dysfunction. This disease adversely affects women; typical patients experience angina without obstructive coronary artery disease (CAD).

CRITERIA LIST/ QUALIFICATIONS:

Inclusion

- Age > 18
- Experiencing angina > 3 times a week
- No obstructive CAD
- CCS Class II-IV

Exclusion

- Active Inflammatory or autoimmune disease
- Sickle Cell disease
- LVEF < 30%
DEMONSTRATING THE VALUE OF IMAGING: THE ROLE OF OUTCOMES RESEARCH AND BIG DATA IN CARDIAC IMAGING

Jordan B. Strom, MD, MSc, FACC, FASE
Director of Echocardiographic Research, Beth Israel Deaconess Medical Center
Richard A. and Susan F. Smith Center for Outcomes Research in Cardiology
Assistant Professor of Medicine, Harvard Medical School

May 24, 2021
Disclosures

Grant support: NIH/NHLBI K23, Edwards Lifesciences (Co-PI), HeartSciences, Ultromics

Consulting: Philips Healthcare, Bracco

Speaker’s Bureau: Northwest Imaging Forums

Other: ASE Board of Directors (2021-22), JRC-DMS Board of Directors (2019-2022)
The Hierarchy of Imaging Evidence
The Thornbury and Frybeck Pyramid

Available Evidence

Clinical impact

Technical efficacy
Diagnostic accuracy efficacy
Diagnostic thinking efficacy
Therapeutic efficacy
Patient efficacy
Societal efficacy
The Hierarchy of Imaging Evidence

The Fordyce and Douglas Circle

1. Improved Mortality and Morbidity
2. Additional Non-invasive Imaging
3. Adequate Technical Efficiency for the Accurate Diagnosis of Obstructive CAD
4. Change in Medical Therapy
5. Referral for Revascularization
6. Improved Quality of Life
7. Long-term Safety
8. Lifestyle Changes

Maximize Efficiency and Minimize Cost
## The Hierarchy of Imaging Evidence
### Domains of Diagnostic Evidence

<table>
<thead>
<tr>
<th>Domain</th>
<th>Questions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Test Attributes</strong></td>
<td>Can the test detect the target condition</td>
</tr>
<tr>
<td></td>
<td>Is the test accurate?</td>
</tr>
<tr>
<td></td>
<td>Is the test reproducible?</td>
</tr>
<tr>
<td></td>
<td>Is the test available?</td>
</tr>
<tr>
<td><strong>Clinician Behavior</strong></td>
<td>Does the test alter clinical diagnosis?</td>
</tr>
<tr>
<td></td>
<td>Does the test alter clinical management?</td>
</tr>
<tr>
<td><strong>Health Outcomes</strong></td>
<td>Does the test alter patient outcomes?</td>
</tr>
<tr>
<td></td>
<td>Does the test improve resource utilization?</td>
</tr>
<tr>
<td></td>
<td>Is the test cost-effective?</td>
</tr>
</tbody>
</table>

Adapted from Wallbridge, Resp Medicine, 2018
Why do imagers need to demonstrate value?

**Growth in Volume of Physician Services per Beneficiary, 1999-2004**

---

**MHIF Cardiovascular Grand Rounds | May 24, 2021**

Iglehart, NEJM, 2006

The Value of Imaging | May 2021

Richard A. and Susan F. Smith Center for Outcomes Research in Cardiology

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL
Why do imagers need to demonstrate value?

Trends in Imaging: the Scene from Canada

Year

Rate of Echo/1000 persons

Year

Relative Rate to 2002

- All Echocardiogram
- Repeat Echocardiogram
Why do imagers need to demonstrate value?
Trends in Imaging: the Scene from Canada

Table 2. Characteristics of Repeat Echocardiograms in Ontario

<table>
<thead>
<tr>
<th></th>
<th>2002</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of echocardiograms</td>
<td>371,356</td>
<td>382,187</td>
<td>431,716</td>
<td>459,692</td>
<td>504,581</td>
<td>536,655</td>
<td>571,520</td>
<td>630,692</td>
</tr>
<tr>
<td>Percent repeats</td>
<td>18.5</td>
<td>18.4</td>
<td>19.1</td>
<td>20.3</td>
<td>21.3</td>
<td>22.6</td>
<td>23.5</td>
<td>25.3</td>
</tr>
<tr>
<td>Adjusted rate of repeat (per 1,000 people)</td>
<td>7.6</td>
<td>7.6</td>
<td>8.7</td>
<td>9.7</td>
<td>10.9</td>
<td>12.0</td>
<td>12.9</td>
<td>15.1</td>
</tr>
<tr>
<td>Repeats (%) performed by same physician</td>
<td>43.4</td>
<td>45.3</td>
<td>46.3</td>
<td>45.6</td>
<td>48.0</td>
<td>47.6</td>
<td>46.5</td>
<td>46.5</td>
</tr>
<tr>
<td>Number of persons with echocardiogram</td>
<td>338,055</td>
<td>348,181</td>
<td>390,220</td>
<td>413,157</td>
<td>449,277</td>
<td>474,264</td>
<td>500,432</td>
<td>543,772</td>
</tr>
<tr>
<td>Percent of persons with repeat echocardiogram</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 repeat</td>
<td>83.4</td>
<td>83.5</td>
<td>82.8</td>
<td>81.7</td>
<td>80.9</td>
<td>79.5</td>
<td>79.0</td>
<td>77.5</td>
</tr>
<tr>
<td>1 repeat</td>
<td>13.7</td>
<td>13.5</td>
<td>13.9</td>
<td>14.8</td>
<td>15.3</td>
<td>16.4</td>
<td>16.5</td>
<td>17.3</td>
</tr>
<tr>
<td>2 repeats</td>
<td>2.5</td>
<td>2.5</td>
<td>2.7</td>
<td>2.9</td>
<td>3.1</td>
<td>3.3</td>
<td>3.6</td>
<td>4.0</td>
</tr>
<tr>
<td>3 repeats</td>
<td>0.4</td>
<td>0.4</td>
<td>0.5</td>
<td>0.5</td>
<td>0.6</td>
<td>0.6</td>
<td>0.7</td>
<td>0.9</td>
</tr>
<tr>
<td>≥4 repeats</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
<td>0.3</td>
</tr>
</tbody>
</table>

> 1/2 of all echocardiograms were performed by a different physician
Why do imagers need to demonstrate value?
Trends in Imaging: the Scene from Canada

Annual rate of change per year (%):

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cardiology</th>
<th>Internal Medicine</th>
<th>Radiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physicians billing echo - no.</td>
<td>3%</td>
<td>3%</td>
<td>-6%</td>
</tr>
<tr>
<td>Echo - no.</td>
<td>8%</td>
<td>6%</td>
<td>1%</td>
</tr>
<tr>
<td>Echos per physician – mean</td>
<td>5%</td>
<td>3%</td>
<td>8%</td>
</tr>
<tr>
<td>Repeat Echo - no.</td>
<td>13%</td>
<td>11%</td>
<td>16%</td>
</tr>
<tr>
<td>Repeat echo per physician - mean</td>
<td>9%</td>
<td>8%</td>
<td>27%</td>
</tr>
</tbody>
</table>

Adapted from Blecker, JACC Imaging, 2013
Why do imagers need to demonstrate value?

Trends in Imaging: the Scene from Canada

Utilization of Multimodality Imaging

Costs of Multimodality Imaging
Why do imagers need to demonstrate value?

Trends in Imaging: Back to the US in 2011

80% of Medicare FFS beneficiaries receive at least one echo per year and 15% receive two.
Why do imagers need to demonstrate value?

The Mortality Effect: Caution Advised

Echo only performed in 8% of HF hospitalizations

The problem: individuals must survive long enough to receive an echo
Why do imagers need to demonstrate value?  
The Mortality Effect: Caution Advised

SPECIAL ARTICLE

Demonstrating the Value of Outcomes in Echocardiography: Imaging-Based Registries in Improving Patient Care

Jordan B. Strom, MD, MSc, Varsha K. Tanguturi, MD, Sherif F. Nagueh, MD, Allan L. Klein, MD, and Warren J. Manning, MD, Boston, Massachusetts; Houston, Texas; and Cleveland, Ohio

• Underutilization is harder to measure than overutilization
• It is hard to separately value proper diagnosis vs. treatment (e.g. ICDs and LVEF)
• Impact of mistakes is harder to measure – what is ground truth?
• Imagers nevertheless need to study outcomes to justify the cost and inconvenience of testing
How do imagers demonstrate value?
Value of Linking Outcomes to Imaging

Uses of Imaging as a Biomarker
- Pre-operative risk stratification
- Guide shared decision making
- Guide use of treatments or other diagnostic tests
- Understand cardiac structure and function

Uses of Imaging as Raw Data
- Images as High Resolution Data Arrays

Use of Outcomes to Understand Variation in Imaging

Use of Outcomes to Identify Areas of Underutilization in Imaging

Use of Outcomes to Define Normality in Imaging
- Example: ageing and diastolic function

Use of Imaging as a Surrogate Outcome
- Provide outcomes (e.g. LV mass, LGE) for trials and other studies
How do imagers demonstrate value?

Why Big Data?

- Outcomes of interest to cardiology are generally uncommon.

- Central limit theorem – unless collected in a biased manner, imaging measurements in large numbers will approach population means.

- Technology advances have made large data analysis feasible.

- Large, multicenter registries can improve generalizability of results and can improve understanding of subgroups.

- Large data repositories are increasingly being built through human interactions with the healthcare system, though relatively few have been linked.
## How do imagers demonstrate value?

### Sources of Data

<table>
<thead>
<tr>
<th>Data source</th>
<th>Outcomes data</th>
<th>Advantages and disadvantages</th>
<th>Echocardiographic data</th>
<th>Advantages and disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient self-report</strong></td>
<td>• Well-validated and reliable questionnaires available</td>
<td>• Patient self-report of imaging data is not validated and likely biased by recall</td>
<td>• Predominant source of large aggregated imaging data</td>
<td>• Site variation in acquisition and recording of data</td>
</tr>
<tr>
<td></td>
<td>• Difficult to capture in practice</td>
<td></td>
<td>• Frequently includes nonstructured data</td>
<td>• Variables may require mapping across sites</td>
</tr>
<tr>
<td><strong>Electronic health records</strong></td>
<td>• Detailed patient information (e.g., diagnoses, testing, treatments)</td>
<td>• Site variation in acquisition and recording of data</td>
<td>• Interoperability and privacy concerns limit sharing across sites</td>
<td>• Frequent missing data</td>
</tr>
<tr>
<td></td>
<td>• Outcomes may be incompletely recorded or captured</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Challenging to extract information</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Privacy concerns involving data access and sharing across sites</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Clinical trials</strong></td>
<td>• Gold standard for evaluation of efficacy</td>
<td>• Imaging data often adjudicated at central core laboratories</td>
<td>• Limited number of subjects with echocardiograms and limited data obtained from images</td>
<td>• May lack generalizability and expensive to conduct</td>
</tr>
<tr>
<td></td>
<td>• Detailed, adjudicated outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• May lack generalizability and expensive to conduct</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Registries or cohort studies</strong></td>
<td>• May enroll generalizable, “real-world” populations</td>
<td>• Large echocardiography databases (e.g., ImageGuidedEcho registry) in development</td>
<td>• May enroll generalizable, “real-world” populations</td>
<td>• May lack generalizability and expensive to conduct</td>
</tr>
<tr>
<td></td>
<td>• Relies on site participation, complete and accurate data entry, and inclusion of generalizable populations</td>
<td>• Relies on site participation, complete and accurate data entry, and inclusion of generalizable populations</td>
<td>• Relies on site participation, complete and accurate data entry, and inclusion of generalizable populations</td>
<td>• Variables collected may differ by site</td>
</tr>
<tr>
<td><strong>Administrative billing claims</strong></td>
<td>• Capture of outcomes across sites</td>
<td>• Claims for echocardiographic examinations contain cost and billing data</td>
<td>• Limited information on imaging variables</td>
<td>• Few repositories of multipayer claims</td>
</tr>
<tr>
<td></td>
<td>• Cost and billing data included</td>
<td>• Limited information on imaging variables</td>
<td>• Few repositories of multipayer claims</td>
<td>• Subject to coding errors and incomplete capture of number and severity of comorbidities</td>
</tr>
<tr>
<td></td>
<td>• Few repositories of multipayer claims</td>
<td>• Limited information on imaging variables</td>
<td>• Few repositories of multipayer claims</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Subject to coding errors and incomplete capture of number and severity of comorbidities</td>
<td>• Limited information on imaging variables</td>
<td>• Subject to coding errors and incomplete capture of number and severity of comorbidities</td>
<td></td>
</tr>
<tr>
<td><strong>Mobile or wearable technology</strong></td>
<td>• Provides near continuous or continuous physiologic information</td>
<td>• None currently available for echocardiography</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Few metrics are validated against clinical outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Proprietary control limits access to data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>National health/Vital status repositories</strong></td>
<td>• Source of death information across sites (e.g., National Death Index or Social Security Death Master File)</td>
<td>• None currently available for echocardiography</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Comprehensiveness and data quality vary</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
How do imagers demonstrate value?

Unique Challenges with Imaging Data

- Data only actionable if diagnosis/misdiagnosis recognized
- Large amounts of missing data
- Hierarchical data structures
- Large amounts of collinearity
- Differences in variable names and conventions
- Data entry errors
- Different study types within a given modality (e.g. TEE, TTE, stress echo)

- Large amounts of unstructured data
- Size and complexity of images
- Referral bias
- Imaging “leakage”
How do imagers demonstrate value?

Existing Registries: Institutional Registries and BIDMC

ENCOR (2000-2018) – 271,618 echocardiograms on 135,792 individuals

- Linked to 26,163 deaths in SSDI
- Linked to 100% Medicare FFS claims from 2003-2017
- Includes information on 133,168 echocardiogram reports from 64,063 individuals
- Claims algorithms used to generate 23 clinical covariates (e.g. hypertension, smoking, diabetes), and 20 outcomes (e.g. MACCE, AKI, acute MI, HF, stroke)

MIMIC (2003-2018) – Contains clinical and lab data from > 60,000 ICU admissions

- MIMIC-III features 350,000 de-identified chest x-ray DICOM images linked to patient information and clinical data from over 260,000 ED visits
- MIMIC-IV (in development) will add 145,000 TTEs, 980,000 ECGs
How do imagers demonstrate value?

Existing Registries: Others

**Foundations and Non-for-profit Companies**

- SCMR Registry - > 62k CMRs
- ImageGuide Registry (ASE and ASNC)
- UK Biobank
- National Echo Database Australia (NEDA)
  - > 40 million echocardiographic reports
  - 14 clinical laboratories
  - 60,000 deaths

**Governmental Federated Data Networks**

- Sentinel network
- PCORNet
- NIH Collaboratory
How do imagers demonstrate value?  
Existing Registries: Challenges

The National Quality Registry Network (NQRN) surveyed 152 societies/associations:

- Response Rate 52%
- 32% spent $1-9.9 million per year
- Average registry had 3 FTEs
- 88% used manual data entry
- 18% linked to external data sources
- Mostly used for QI, benchmarking, and clinical decision support
- Cost, interoperability, and vendor management were barriers to continued development

<table>
<thead>
<tr>
<th>MEASURE TYPES</th>
<th>USING TODAY</th>
<th>PLANNING TO USE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Process</td>
<td>86% (30/35)</td>
<td>6% (3/35)</td>
</tr>
<tr>
<td>Outcome</td>
<td>74% (26/35)</td>
<td>20% (7/35)</td>
</tr>
<tr>
<td>Safety</td>
<td>62% (21/34)</td>
<td>26% (9/34)</td>
</tr>
<tr>
<td>Structure</td>
<td>46% (16/35)</td>
<td>9% (3/35)</td>
</tr>
<tr>
<td>Patient-reported outcome</td>
<td>47% (16/34)</td>
<td>29% (10/34)</td>
</tr>
<tr>
<td>Utilization</td>
<td>41% (14/34)</td>
<td>38% (13/34)</td>
</tr>
<tr>
<td>Other</td>
<td>12% (4/33)</td>
<td>9% (3/33)</td>
</tr>
<tr>
<td>Cost</td>
<td>6% (2/34)</td>
<td>53% (18/34)</td>
</tr>
<tr>
<td>Personalized medicine</td>
<td>6% (2/33)</td>
<td>15% (5/33)</td>
</tr>
</tbody>
</table>
How do imagers demonstrate value?
Defining a Field: Outcomes Research in Cardiac Imaging

A multidisciplinary field that seeks to:

1. Evaluate the relationship of cardiac structure and function to health outcomes
2. Evaluate the use of imaging to guide medical decision making and prognostication
3. Understand the use, cost, and sources of variation of cardiac imaging in practice
4. Identify optimal imaging intervals and the cost-effectiveness of diagnostic strategies related to imaging.
5. Conduct trials of diagnostic imaging strategies.

These goals are accomplished through a hybrid of methods including epidemiology and biostatistics, cost effectiveness, and data science techniques (e.g. machine learning, database management) and using a variety of data sources including registries of structured or unstructured images or image reports, trials, claims, and multicenter registries.
A use case of imaging registries

Moderate Aortic Stenosis

72 year old M with HTN, HL, DM2 and moderate AS (AVA 1.3 cm2) who presents with dyspnea on exertion x 1 year.

- TTE with no significant AS progression (AVA 1.2 cm2) but LVEF 35%
- Coronary angiography without obstructive CAD
- ETT with limiting dyspnea at 5 METs, no ECG changes, no changes on TTE
- CPET demonstrates cardiac limitation

Should we consider AVR in moderate AS?
A use case of imaging registries
Natural History of Severe AS

MHIF Cardiovascular Grand Rounds | May 24, 2021

Ross and Braunwald, Circulation, 1968
## A use case of imaging registries
### Natural History of severe AS

<table>
<thead>
<tr>
<th>Author</th>
<th>Title</th>
<th>N Value</th>
<th>Journal and Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pellikka et al</td>
<td>The Natural history of Adults with Asymptomatic, haemodynamically significant Aortic Stenosis</td>
<td>N = 143</td>
<td>JACC 1990</td>
</tr>
<tr>
<td>Pellikka et al</td>
<td>Outcomes of 622 patients with asymptomatic haemodynamically significant Aortic Stenosis</td>
<td>N = 622</td>
<td>Circulation 2005</td>
</tr>
<tr>
<td>Lancellotti et al</td>
<td>Risk Stratification of Moderate to Severe Aortic Stenosis</td>
<td>N = 163</td>
<td>Heart 2010</td>
</tr>
<tr>
<td>Lancellotti et al</td>
<td>Outcomes for Patients with Asymptomatic Aortic Stenosis followed in heart centres</td>
<td>N = 1375</td>
<td>JAMA Cardiology 2018</td>
</tr>
</tbody>
</table>
A use case of imaging registries
What is the risk of moderate AS?

316 asymptomatic patients with moderate to severe AS underwent ETT (mean age 65, 67% men):

Outcome of mortality (67% CV related) or AVR
Followed for 3 years

During serial testing, symptoms identified in 55% with moderate AS

Symptom free survival at 24 months:

Moderate AS: 52% ± 4%
Severe AS: 26% ± 6%
A use case of imaging registries
What is the risk of moderate AS?

176 asymptomatic patients (58 ± 19 years; 41.4% female) with mild-moderate AS (peak AV velocity 2.5-3.9 m/s):

- 48 ± 19 month follow-up
- Evaluated hemodynamic progression
- Outcome: death or AVR
- Compared with age-, gender- matched controls

34 deaths (15 CV deaths)
Severe AS only in 7/15 premortem
One with SCD

Event-free survival only 55% ± 5% at 5 years if velocity > 3 m/s
## A use case of imaging registries

### What is the risk of moderate AS?

<table>
<thead>
<tr>
<th>Author</th>
<th>Years</th>
<th>N</th>
<th>Echo or Cath</th>
<th>AV parameter</th>
<th>Follow-up</th>
<th>Event free survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Horstkotte and Loogen</td>
<td>1978-1988</td>
<td>236</td>
<td>Cath</td>
<td>0.8 – 1.5 (AVA)</td>
<td>10 years</td>
<td>80% at 10 years</td>
</tr>
<tr>
<td>Chizner</td>
<td>1980</td>
<td>42</td>
<td>Cath</td>
<td>0.71-1.09 (AVA)</td>
<td>64.4 months</td>
<td>57% mortality at 3 years (56% SCD)</td>
</tr>
<tr>
<td>Kennedy</td>
<td>1980-1985</td>
<td>66</td>
<td>Cath</td>
<td>0.7-1.2 (AVA)</td>
<td>35 months</td>
<td>59% at 4 years</td>
</tr>
<tr>
<td>Kearney</td>
<td>1988-1994</td>
<td>55</td>
<td>Echo</td>
<td>1-1.5 (AVA) or 25-40 mmHg (MG)</td>
<td>6.5 years</td>
<td>23% at 5 years</td>
</tr>
<tr>
<td>Otto</td>
<td>1989-1995</td>
<td>68</td>
<td>Echo</td>
<td>3-4 m/s (peak velocity)</td>
<td>2.5 years</td>
<td>66% at 2 years</td>
</tr>
<tr>
<td>Livanainen</td>
<td>1990-1991</td>
<td>26</td>
<td>Echo</td>
<td>0.9-1.2 (AVA)</td>
<td>4 years</td>
<td>65% at 4 years</td>
</tr>
<tr>
<td>Rossebo</td>
<td>2001-2002</td>
<td>948</td>
<td>Echo</td>
<td>3-4 m/s (peak velocity)</td>
<td>5 years</td>
<td>49.1% at 5 years</td>
</tr>
<tr>
<td>Minners</td>
<td>2001-2002</td>
<td>948</td>
<td>Echo</td>
<td>3-4 m/s (peak velocity)</td>
<td>4 years</td>
<td>94.1% at 4 years</td>
</tr>
<tr>
<td>Lancellotti</td>
<td>2001-2014</td>
<td>1375</td>
<td>Echo</td>
<td>1-1.5 (AVA)</td>
<td>8 years</td>
<td>30% at 8 years</td>
</tr>
<tr>
<td>Yechoor</td>
<td>2006</td>
<td>104</td>
<td>Echo</td>
<td>1-1.5 (AVA)</td>
<td>22 months</td>
<td>15% at 5 years</td>
</tr>
<tr>
<td>Van Gils</td>
<td>2010-2015</td>
<td>305</td>
<td>Echo</td>
<td>1-1.5 (AVA)</td>
<td>4 years</td>
<td>39% at 4 years</td>
</tr>
<tr>
<td>Strange</td>
<td>2000-2017</td>
<td>241, 303</td>
<td>Echo</td>
<td>1-1.5 (AVA)</td>
<td>5 years</td>
<td>56% at 5 years</td>
</tr>
</tbody>
</table>
A use case of imaging registries
What is the risk of moderate AS?

Excess Mortality Associated with Progression Rate in Asymptomatic Aortic Valve Stenosis

Giovanni Benfari, MD, Stefano Nistri, MD, PhD, Federico Marin, MD, Luca F. Cerrito, MD, Luca Maritan, MD, Elvin Tafciu, MD, Ilaria Franzese, MD, Francesco Onorati, MD, Martina Setti, MD, Michele Pighi, MD, Andrea Rossi, MD, and Flavio L. Ribichini, MD, PhD, Verona and Vicenza, Italy
A use case of imaging registries
Moderate Aortic Stenosis

Circulation

PERSPECTIVE

Aortic Stenosis
Then and Now

Historical operative mortality for AVR = ~ 15%

Current operative mortality in low-risk TAVR population = ~1%
A use case of imaging registries
Moderate Aortic Stenosis

Does risk/benefit now favor early intervention?

Moderate AS trial:
TAVR UNLOAD trial - Sapien 3 THV in HF, moderate AS (AVA 1-1.5 cm²), and HF

Asymptomatic severe AS trials:
- EARLY-TAVR trial
- EVoLVeD trial
- AVATAR trial
- ESTIMATE trial
- RECOVERY trial (very severe: Vmax > 5 m/s)
A use case of imaging registries

Moderate Aortic Stenosis: The Final Nail?

Documented or calculable Mean Aortic Gradient (n = 110,197), Peak Velocity (n = 235,430), or Aortic Valve Area (n = 52,175) for AVA using VTI & n = 84,656 for AVA using Peak velocity)

No AS (n = 215,478)
Age 60 ± 15 years
Mild AS (n = 16,129)
Age 72 ± 14 years
Moderate AS (n = 3,315)
Age 74 ± 15 years
Severe AS (n = 6,383)
Age 78 ± 15 years

Mortality inflection at MG = 20 mmHg
A use case of imaging registries
Moderate Aortic Stenosis: Size Does Matter

1. All those in Rosenhek and Lancellotti studies who had AVR had severe AS pre-operatively.
2. Noncardiac death high in moderate AS group as well.

BUT

1. Moderate AS still associated with higher mortality than age-, sex-, and comorbidity-adjusted controls.
2. Half of deaths in Rosenhek study did not have severe AS
3. If there is an associated SCD risk in moderate AS, it is likely small and large numbers are needed for detection.
4. Ascertainment bias: those with OHCA may not present to medical attention; autopsies rarely performed.
5. Confirmation bias: we don’t associate moderate AS with mortality.

Is the moderate AS the issue or the company it keeps?

STUDY FOLLOW-UP: All individuals were followed up from the date of their last recorded echocardiogram to the point of death or being censored alive at the census point. The pattern of all-cause and cardiovascular-related mortality during >1 million person-years of follow-up (derived from 44,235 case-
A use case for imaging registries
Moderate Aortic Stenosis: the iENHANCED-AS study

Redefining the clinical consequences Aortic Stenosis:
The International ENHancing the ANalysis of Clinical Events & Death in Aortic Stenosis (I-ENHANCED-AS) Study

Co-PIs: Geoff Strange (NEDA), Jordan Strom (Smith Center)
A use case for imaging registries
The iENHANCED-AS study: Time-Dependent Covariates

Example Survival Plot

Individuals with AS are only given “credit” for the alive time they spend in each severity stage

Time-invariant interpretation

Time-varying interpretation

HR = weighted average of time window-specific HRs

Follow-up (years)

Baseline

1 2 3 4 5 6

Start of study

Time

End of study

○ = drop-out/censored

● = event

Unexposed/Untreated

Exposed/Treated
A use case for imaging registries
The iENHANCED-AS study: Results

ENCOR-CMS / NEDA v2.0
Equivalent Linked Data (2000-2017)

135,481 echocardiograms from 66,846 people (US cohort) / 1,077,145 echocardiograms from 631,824 people (Australian cohort)

17,428 / 31,468 Non-study period
4,445 / 125,606 No AV profiling

44,973 / 474,750 people with Aortic Valve profiling

12,634 / 243,023 Aged <65 years
1,081 / 18,405 Prior AVR

393 / 5,454 people aged ≥ 65 years with native Aortic Valve → AVR
127 / 2,422 all-cause deaths over 633 / 38,000 person-years follow-up

30,865 / 217,599 people aged ≥ 65 years with native Aortic Valve on last echo
14,481 / 89,054 all-cause deaths over 97,576 / 1.1 million person-years follow-up

Peak AV Velocity (30,810 / 211,635) or Mean AV Gradient (5,063 / 118,133) to determine grade of AS according to hemodynamic profile as per clinical guidelines

NO AS
26,682 / 173,776
MILD AS
2,440 / 27,921
Mild AS
1,198 / 10,789
SEVERE AS
545 / 5,113

AVA measurements in 3,976 / 104,689 cases to reclassify severe AS if AIA <1.0 cm²
A use case for imaging registries
The iENHANCED-AS study: Results
A use case for imaging registries

The iENHANCED-AS study: Gradient-based classification
A use case for imaging registries
The iENHANCED-AS study: AVA-based classification

---

**Cox Proportional Hazards Model**
- Demography (age/sex/race)
- Body mass index
- AV area (continuous variable)
- Left heart (e.g., LVES/TVS) & right heart (TR velocity) profile

![Graphs showing cumulative all-cause survival over follow-up years for Australian and US patients](image-url)
A use case for imaging registries
The iENHANCED-AS study: Results

• Results consistent across subgroups:
  • First vs. last echo as baseline
  • Adjusting & not adjusting for time in stage
  • CV-specific death (AU cohort)
  • Age < 65 (AU cohort)

• Interaction by CAD/HF status
  • Significant interaction by prevalent HF and CAD

• Importance of gradients to risk

• Impact of sex and race on risk
The case for imaging registries
iENHANCED AS – Caution: Not a Prescription

Correlation ≠ Causation. | Risk ≠ Benefit from AVR

Data sources: National Spelling Bee and Centers for Disease Control & Prevention

Source: tylergiven.com
Summary

• Rising costs of cardiac imaging have forced the hand of imagers to justify the value of imaging.

• Imaging registries, especially when linked with outcomes, can be used to demonstrate value through better risk stratification and prognostication for patients, pathophysiologic insights into diseases, and understanding of care gaps and variation in imaging.

• Outcomes research in cardiac imaging is a unique discipline with a distinct set of methodologies, challenges, and questions.

• Aortic stenosis represents a powerful and important use case for use of such methodologies to answer clinically relevant questions, but results must be interpreted cautiously.
Acknowledgements

Smith Center
• Robert Yeh
• Dhruv Kazi
• Joanne Healy
• Linda Valsdottir
• Changyu Shen
• Eric Secemsky
• Rishi Wadhera
• Hector Tamez-Aguilar
• Eunhee Choi
• Yuansong Zhao
• Jiaman Xu

Cardiovascular Division
• Robert Gerszten
• Peter Zimetbaum
• Jeffrey Popma

Advisory Council
• David Cohen
• John Spertus

Imaging Mentors
• Warren Manning
• Madhav Swaminathan
• Allan Klein
• Sherif Nagueh
• Vic Ferrari

Collaborators
• Geoff Strange
• David Playford
• Simon Smith

Life Mentors
• Bess Gutter
• Lily Strom
• Brian and Lani Strom