Preoperative Assessment of Older Patients Undergoing TAVR

The Geriatrician’s Role in the Heart Team

Catherine Talbot-Hamon, MD, FRCP
Assistant Professor, Department of Geriatric Medicine McGill University
CGS Resident Day
April 19, 2018
Faculty/Presenter Disclosure

- **Faculty:** Catherine Talbot-Hamon

- **Relationships with commercial interests:**
  - Grants/Research Support: none
  - Speakers Bureau/Honoraria: none
  - Consulting Fees: none
  - **Other:** Assistant Professor, Division of Geriatric Medicine, McGill University
Disclosure of Commercial Support

- This speaker has received financial support from the Richard and Edith Strauss Foundation in the form of an educational grant.

- **Potential for conflict(s) of interest:**
  - None to disclose.
Mitigating Potential Bias

- Nor the Strauss Foundation or McGill University have interests in the subjects to be discussed during this presentation.
Objectives

- At the end of the session, the participant will be able to:
  - describe TAVR procedure and expected outcomes in older patients;
  - discuss factors related to poor prognosis in TAVR;
  - and discuss the pertinence and components of a preoperative geriatric assessment in patients undergoing TAVR.
Outline

- Overview of aortic stenosis
- Before TAVR - historical perspective on treatment of aortic stenosis
- TAVR - what it’s about
- TAVR outcomes review
- Trying to predict outcomes in TAVR - the input of geriatrics.
Fall 2009 - GIM residents longitudinal clinic - JGH

- 99M, referred by cardiologist
  
  “Critical aortic stenosis, for medical management”

- Accomplished musician (violinist), composer

- Blind, 24 hour caregiver

- Exhaustion from minimal effort, angina at rest

- Goal to get to 100...

  “…to get my letter from the Queen. She writes personally, you know…”
Aortic stenosis

- Aortic valve thickening and calcification, causing a decrease in AVA and a pressure gradient
- Etiology
  - Congenital valve abnormalities
  - Calcific disease of a normal trileaflet valve
  - Rheumatic valve disease
- Prevalence
  - 70-79 y: 3.9%
  - 80-89 y: 9.8%

1. Eveborn et al, Heart, 2013

Fig 1 Anatomy and function of the aortic valve. The valve controls blood forward flow during systole and preventing blood return to the heart during diastole. In aortic stenosis, calcific degeneration of the aortic leaflets results in narrowing of the aortic valve orifice, increasing pressure and causing angina or dyspnea. (Zakkar et al. BMJ 2016)
### Aortic stenosis - stages

<table>
<thead>
<tr>
<th>Stage of aortic valve stenosis</th>
<th>Symptoms and severity</th>
<th>Aortic valve anatomy and hemodynamics</th>
</tr>
</thead>
<tbody>
<tr>
<td>At risk of AS</td>
<td>Examples: aortic sclerosis or congenital bicuspid valve</td>
<td></td>
</tr>
<tr>
<td>Progressive AS (mild-moderate)</td>
<td>Mild AS: abnormal valve with ( V_{\text{max}} ) 2–2.9 m/s, mean ( \Delta P &lt; 20 ) mm Hg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Moderate AS: abnormal valve with reduced leaflet motion and ( V_{\text{max}} ) 3–3.9 m/s, mean ( \Delta P &lt; 20–40 ) mm Hg</td>
<td></td>
</tr>
<tr>
<td>Asymptomatic severe AS</td>
<td>Calcified and thickened leaflets with limited mobility and ( V_{\text{max}} ) ( \geq 4.0 ) m/s or mean ( \Delta P \geq 40 ) mm Hg (AVA usually ( &lt; 1.0 ) cm(^2))</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C1: normal LV systolic function</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C2: LV EF (&lt; 50%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Very severe ( V_{\text{max}} ) ( \geq 5.0 ) m/s, mean ( \Delta P \geq 60 ) mm Hg</td>
<td></td>
</tr>
<tr>
<td>Symptomatic severe AS</td>
<td>Severely thickened and calcified aortic valve leaflets with reduced systolic opening with:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>D1: high gradient severe AS: ( V_{\text{max}} ) ( \geq 4.0 ) m/s or mean ( \Delta P \geq 40 ) mm Hg (AVA usually ( &lt; 1.0 ) cm(^2) but not needed for diagnosis)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>D2: low-flow low-gradient severe AS (low EF): LV EF (&lt; 50%) with a resting AVA ( &lt; 1.0 ) cm(^2) and ( V_{\text{max}} ) 3 to 4 m/s. On low dose DSE there is a ( V_{\text{max}} ) ( \geq 4.0 ) m/s with an AVA ( &lt; 1.0 ) cm(^2) at any flow rate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>D3: low-flow low-gradient severe AS (normal EF): ( V_{\text{max}} ) 3 to 4 m/s, AVA ( &lt; 1.0 ) cm(^2), indexed AVA ( &lt; 0.6 ) cm(^2)/m(^2), and indexed SV ( &lt; 35 ) mL/m(^2), all measured when patient is normotensive</td>
<td></td>
</tr>
</tbody>
</table>

In gradient, AS: aortic stenosis, AVA: aortic valve area, DSE: dobutamine stress echocardiography (maximum dose 20 mcg/mg/min), EF: ejection fraction, LV: left ventricular, SV: stroke volume, \( V_{\text{max}} \): maximum aortic velocity

Aortic stenosis - symptoms and prognosis
Historical perspective - cardiac procedures

- First successful open-heart procedure - Capellen, 1895
- Angiography - Moniz, 1927
- First surgical aortic valve replacement (SAVR) - Harken, 1960
- Coronary artery angiogram - Sones, 1960
- First angioplasty - Gruentzig, 1977
Aortic stenosis - treatment

- Medical
- Aortic valve replacement
  - Indications
    - Severe high gradient AS with symptoms on history or exercise testing
    - Asymptomatic severe AS with EF < 50%
    - Severe AS undergoing other cardiac surgery
    - Asymptomatic very severe AS and low surgical risk
    - Asymptomatic AS with decreased exercise tolerance or fall in systemic BP with exercise
    - Asymptomatic AS, rapid progression, low surgical risk
    - Moderate AS undergoing other cardiac surgery

Decision to replace valve based on:
1. Symptoms
2. AS grade/severity
3. Individual patient’s surgical risk
4. Other

(Nishimura et al. Circulation. 2014)
Surgical Risk Assessment

TS Risk Score
- Patient, cardiac and surgery-related risk factors (50 variables)
- % 30 day mortality*
- Performance in older patients undergoing AVR
  - In ≥ 80 y, AUC 0.81 (Vanhuyse et al, 2013)
  - Superior to EuroSCORE for high risk patients (Kuwaki et al, 2015)

Logistic EuroSCORE II
- Patient, cardiac and surgery-related risk factors (17 variables)
- % 30 day mortality*
- Performance in older patients undergoing AVR
  - In ≥ 70y, AUC <0.7 (Pullis et al, 2015)
  - In ≥ 80 y, same poor AUC, worse in high risk category (Provenchere et al, 2017)
Limits of SAVR

- ‘Futility’
  - Limited life expectancy (< 12 mo)
- Risk-related contra-indications
  - Prohibitive (extreme) risk patients (Estimated risk of mortality or major morbidity > 50% at 30 d)
- Non-risk-related contra-indications
  - Absolute
    - Porcelain aorta
    - Hostile chest
  - Relative
    - Frailty, severe liver disease/cirrhosis, severe PH, etc.

2014 AHA/ACC Guideline for the Management of Patients with Valvular Heart Disease - JACC (2014)
Historical perspective - cardiac procedures

- Balloon aortic valvuloplasty - 1991
- First transcatheter aortic valve replacement (TAVR) on a human - Cribier, 2002
PARTNER 1 - trial

Symptomatic Severe Aortic Stenosis

A

n = 699

High risk

ASSESSMENT: High-risk AVR candidate
3105 total patients screened

Yes

ASSESSMENT: Transfemoral access

No

Transfemoral (TF)

1:1 Randomization

n = 244

TF TAVR vs AVR

Transfemoral (TA)

1:1 Randomization

n = 248

n = 104

n = 103

Primary end point: All-cause mortality at 1 year (noninferiority)

B

Total = 1057 patients

2 Parallel trials: Individually powered

Inoperable

n = 358

ASSESSMENT: Transfemoral access

Yes

1:1 Randomization

n = 179

TF TAVR vs Standard therapy

No

n = 179

Not in study

Primary end point: All-cause mortality over length of trial (superiority)
Coprimary end point: Composite of all-cause mortality and repeat hospitalization (superiority)

CoreValve trial

CoreValve US Pivotal Trials

Extreme Risk

Iliofemoral Access > 18 Fr Sheath

YES

CoreValve ileofemoral
n=487

Primary Endpoint: All-Cause Mortality or major stroke at 1 year (Superiority)

NO

CoreValve non ileofemoral
n=147

High Risk

1:1 Randomization

CoreValve
n=390

Primary Endpoint: All-Cause Mortality at 1 year (Non-inferiority)

SAVR
n=357

(Haussig and Linke, Circulation, 2014)
# LANDMARK STUDIES - OUTCOMES

<table>
<thead>
<tr>
<th></th>
<th>PARTNER 1A</th>
<th>COREVALVE US PIVOTAL TRIAL</th>
<th>PARTNER 1B</th>
<th>COREVALVE EXTREME RISK</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ONE YEAR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All cause mortality (%)</td>
<td>24.2 vs 26.6</td>
<td>13.9 vs 18.7*</td>
<td>30.7 vs 50.7*</td>
<td>24,3</td>
</tr>
<tr>
<td>Death + rehospit. (%)</td>
<td>34.6 vs 35.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Δ KCCQ</td>
<td>31.8 vs 4.1*</td>
<td>24.0 vs 21.9</td>
<td>24.2 vs 10.4*</td>
<td>27.4</td>
</tr>
<tr>
<td><strong>COMPLICATIONS (30d)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major stroke (%)</td>
<td>3.8 vs 2.1</td>
<td>4.9 vs 6.2</td>
<td>5.0% vs 1.1</td>
<td>2.3</td>
</tr>
<tr>
<td>Vascular complications (%)</td>
<td>11.0 vs 3.2*</td>
<td>5.9 vs 1.7*</td>
<td>16.2 vs 1.1*</td>
<td>8.2</td>
</tr>
<tr>
<td>Major bleeding (%)</td>
<td>9.3 vs 19.5*</td>
<td>28.1 vs 34.5*</td>
<td>16.8 vs 3.9*</td>
<td>36.7</td>
</tr>
</tbody>
</table>

KCCQ: Kansas City Cardiomyopathy Questionnaire

(Leon, Smith et al. NEJM. 2010)  
(Leon, Smith et al. NEJM 2011)  
(Adams, Popma et al. JACC. 2014)  
(Popma, Adams et al. NEJM 2014)
Historical perspective - cardiac procedures

- FDA approval of TAVR - 2011 (inoperable)
  - 2012 (high risk)
- Creation of the STS/ACC TVT registry - 2012
TAVR - Procedure

- https://www.youtube.com/watch?v=csxJYTLXNJY
TAVR - “long term” outcomes

Extreme risk

(Makkar, Fontana et al. NEJM, 2012)
TAVR - “long term” outcomes

(Kodali et al. NEJM, 2012.
Reardon et al. JACC, 2015
Deeb et al. JACC, 2016)
Quality of Life in TAVR

- Inoperable patients

**Figure 3: Generic Health Status After TAVR**

**A** SF-12 Physical component
- CoreValve
- Baseline

**B** SF-12 Mental component

**C** EQ-5D Utilities

Changes in generic health status according to the Short Form-12 (SF-12) (A and B) and Euroqol-5D (EQ-5D) (C) at 1, 6, and 12 months after TAVR. Baseline values, as indicated by the dashed line, correspond to the evaluable patient population at each time point. Mean values and p values are derived from paired t tests comparing each patient with his or her own baseline value.
Quality of Life in TAVR

- High risk patients

![Graphs showing treatment differences in KCCQ scores over time.](image-url)
Concept of “poor outcome” in TAVR

- Came from realization that in patients undergoing TAVR (older, multiple comorbidities):

  ‘survival alone (without improved QoL) would not be viewed as a desirable outcome’ - Arnold

- Redefined ‘successful outcome’ in TAVR as the composite of:

  Death
  Very poor QoL (KCCQ OS < 45)
  Important decline in QoL compared to baseline (decrease of 10 points on KCCQ OS)
Prevalence of poor outcome

**PARTNER**
- 6 months: 33%
- One year: 50%

**COREVALVE**
- 6 months: 31.2%
- One year: 50.8%

(Arnold et al. Circulation. 2014)
(Arnold et al. JACC. 2016)
Poor outcomes in TAVR -

- Predictors
  - 6 min walk test (per 10 m) – OR 0.97* (0.96–0.98)
  - Mean aortic valve gradient (per 10 mmHg) – OR 0.82* (0.75–0.89)
  - MMSE (per 1 point) – OR 0.96* (0.92–1.00)
  - O2 dependent lung disease – OR 1.77* (1.23–2.54)
  - Serum creat (per 1mg/dL) – OR 1.32* (1.03–1.70)
  - Major arrhythmia – OR 1.29* (1.02–1.63)

- CoreValve
  - Same as PARTNER plus:
    - Frailty (Fried) – OR 1.29* (1.08–1.55)
    - Disability (per 1ADL) – OR 1.29* (1.19–1.39)
    - Unintentional weight loss – OR 1.51* (1.17–1.95)

- C-statistic = 0.64
- C-statistic = 0.65
- C-statistic 0.67
Geriatric measures in outcome prediction - TAVR

- Frailty
  - Psoas muscle area
  - Gait speed
- Mood
- Comprehensive Geriatric Assessment
Frailty-TAVR

1. Why bother so much?

- It's prevalent
  - 33-76% patients (depending on definition)
- It adds predictive value to traditional risk scores
- It's perceived as easily measurable in the office
- It's potentially reversible

(Talbot-Hamon et al. JAGS. 2017)
(Afilalo et al. JACC. 2014)
Frailty - TAVR

2. Associated Outcomes

Early (30 d)
- Mortality
  - 17 vs 6% (Puls, 2014)
- Length of stay
  - 9 vs 6 d (Green, 2012)
- Discharge to facility
  - OR 4.8 (Huded, 2016)

Intermediate (6 months)
- Mortality
  - OR 1.8 (Osnabrugge, 2015)
- Poor outcome
  - OR 2.1 (Green, 2015)
  - ADL Δ ≥ 1
  - OR 3.34 (Schoenenberger, 2013)

Long (1 year)
- Mortality
  - HR 2.5-3.5 (Green, 2012) (Green, 2015)
- Poor outcome
  - OR 1.42-2.93 (Arnold, 2016) (Stortecky, 2012)

Longer (2 years)
- Mortality
  - HR 2.28 (Bogdan, 2016)
- OR 2.15 (Cockburn)
Frailty-TAVR
3. How to measure

In 2017 review:

- Fried scale: 2
- Custom scale - Fried adaptation: 3
- Gait speed alone: 1
- Katz ADL disability: 2
- Albumin (different thresholds): 3
- ‘poor mobility’: 1
- Recent fall: 1
- SHERPA scale: 1
- Psoas muscle area: 2
- Total muscle area at L3: 1
- Wheelchair bound: 1
- Custom scale (CGA-derived): 2
- Subjective: 2
Frailty in AVR - parenthesis on psoas muscle area

2 studies\(^2,3\)

Rationale: 1/5 patients cannot undergoing assessment for TAVR cannot perform 5 m gait speed test\(^1\)

Psoas muscle area good surrogate for muscle mass\(^4\) -> frailty

Readily available with routine CT scans pre-TAVR

In Mamane et al:

- Associated with mortality in females HR 0.88/cm\(^2\) (CI 0.78-0.99) but not in males HR 1.01/cm\(^2\) (CI 0.93-1.10)

In Paknikar et al:

- Gender-standardized TPA (total psoas area) associated with mortality HR 0.47, p = 0.02 and resource utilization OR 0.6 p < 0.001

Gait speed alone as outcome predictor in TAVR/STS/ACC Transcatheter Valve Therapy Registry (USA)1 Optimized Catheter Valvular Intervention–Transcatheter Aortic Valve Implantation (OCEAN-TAVI, Japan)2

5 m gait speed cutoffs:
- Not able to walk
- Slowest walkers (< 0.5 m/s)
- Slow walkers (0.5-0.83 m/s)
- Normal walkers (> 0.83 m/s)

Outcomes:
- Slowest walkers aHR 1.35 (1.01-1.80) 30 d mortality1
- Slowest walkers or unable to walk: aHR 2.01 (1.20-3.38) 1 y mortality2
- Longer LOS (7 vs 5 days) and higher discharge to facility in slowest group2

Frailty - TAVR

4. Latest news

Use of FORECAST score to predict short term outcomes in TAVR

- **FORECAST** (Frailty predicts death One yeaR after Elective Cardiac Surgery Test)
  - Chair rise (3) - timed
  - Weakness - subjective, past 2 weeks
  - Stairs - as many as possible
  - Clinical frailty scale (CFS) - Rockwood and al, 2005.
  - Creatinine

- Initially tested in patients undergoing cardiac surgery\(^1\):
  - Best predictor of one year mortality (compared to EuroScore and STS) - AUC 0.76, vs 0.67

- Now tested in TAVR as predictor of 30 day mortality\(^2\):
  - ROC 0.73 alone and 0.77 when combined with STS (p=0.021)

The Essential Frailty Tool (EFT) as predictor of mortality and disability in TAVR or SAVR (FRAILTY AVR study)

- Large longitudinal cohort (>1000 patients)
- Four items
- Compared to other scales (Fried, Rockwood, SPPB, etc.) and found to have best fit.
- Best predictor of:
  - 30 d mortality: aOR 3.29 (1.73-6.26)
  - 1 year mortality: aOR 3.72 (2.54-5.45)
  - 1 year disability: aOR 2.13 (1.57-2.87)

(Afilalo et al. JACC. 2017)
Frailty and TAVR - what do guidelines say?

2017 ACC Expert Consensus Decision Pathway for Transcatheter Aortic Valve Replacement in the Management of Adults With Aortic Stenosis

- Complete section on patient selection and evaluation, suggesting:
  - Team-based approach
  - Functional assessment
    - Frailty
      - gait speed <0.5 m/s or <0.83 m/s with disability or cognitive impairment
      - Another scale
    - Nutritional risk status (albumin, BMI, MNA, history of weight loss)
  - Physical function (6MWT and functional assessment)
  - Cognitive function (MMSE, depression screen)
  - Futility (life expectancy)
- Integrated risk-benefit and shared decision-making
  - Severe frailty considered prohibitive risk

(Otto et al. JACC. 2017)
Importance of preoperative mood in TAVR

- Subgroup analysis FRAILTY-AVR
- GDS SF or history of depression
- Outcomes with depression:
  - 30 d mortality
    - aOR 2.20 (1.18-4.10)
  - 1 year mortality
    - aOR 1.532 (1.03-2.24)
    - If persistent depression (6 months post-procedure) - aOR 2.98 (1.08-8.20)

(Drudi et al. JAMA Cardiol. 2018)
Benefits of involving geriatricians in patient selection

- If many studies report on utility of a Geriatric Assessment (GA) in patient selection, only one was found reporting outcomes of a Comprehensive Geriatric Assessment (CGA)
- France, outpatient geriatric assessment clinic
- Study pop: 21 patients, mean age 85 y, mean gait speed 0.66 m/s, median MMSE 21/30.

Results:
- Cardiologists followed 100% recommendations of NOT performing TAVR, and 50% other recommendations.
- Lower LOS than national mean
- All TAVR patients alive at one year, 75% had rehab.

TAVR - “Geriatric” Outcome Predictors - Recap

- Frailty and individual criteria
  - Gait speed
  - Sarcopenia
  - Malnutrition
- Mood
- Functional impairment
- Geriatric assessments
  - Cognition?
When to involve the geriatrician?

Older Patient (> 70 years old) with AS

5-m gait speed test

- < 0.83 m/s (or > 6 sec to complete the test)
  - Comprehensive Geriatric Assessment
    - HIGH-RISK
      - Medical treatment
      - Percutaneous balloon valvuloplasty
      - Multidisciplinary management
    - FRAIL
      - AVR
      - Geriatric intervention before and after procedure
    - ROBUST
      - AVR
      - Standard care
- ≥ 0.83 m/s (or ≤ 6 sec to complete the test)

(Lilamand et al. Int J Cardiol, 2014)
Components of a preoperative geriatric assessment in TAVR

- Reassess symptoms and confirm cardiac etiology
- Assess comorbidities to optimize management
- Perform CGA, including measures of frailty, function, cognition, mood, nutrition, social context
- If possible prognosticate on life expectancy
- Clarifying goals of care
- Make recommendations
  - Whether or not to proceed (under which reserves)
  - How to proceed to minimize complications
  - On how to optimize management of other conditions

(Otto et al. JACC. 2017)
Potential areas where geriatric expertise may be beneficial

Preoperatively
- Patient selection
- Optimization (Delirium prevention, medication review, prehab?, control of comorbid diseases, etc.)

Perioperatively
- Preventing delirium and other complications, advise on benefits of rehab.

Post-operatively
- Accompany in rehab process, manage long term care of complex cases

If no surgery
- Palliative care

Higher levels
- Involvement in research and program development
- Teaching
# TAVR - What`s in the loop

<table>
<thead>
<tr>
<th>Title</th>
<th>Recruitment</th>
<th>Study Results</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Geriatric Assessment and Outcome in Patients Undergoing Transcatheter Aortic Valve Replacement</td>
<td>Recruiting</td>
<td>No Results Available</td>
<td>-1</td>
</tr>
<tr>
<td>2. Clinical and Genetic Assessment in Elderly Patients Before and After TAVR or Mitral Clip Positioning</td>
<td>Recruiting</td>
<td>No Results Available</td>
<td>+1</td>
</tr>
<tr>
<td>3. Physical Therapy and Occupational Therapy After Transcatheter Aortic Valve Replacement</td>
<td>Enrolling by invitation</td>
<td>No Results Available</td>
<td>+1</td>
</tr>
<tr>
<td>4. Prehabilitation for Patients Undergoing Transcatheter Aortic Valve Replacement</td>
<td>Recruiting</td>
<td>No Results Available</td>
<td>+1</td>
</tr>
<tr>
<td>5. Geriatric Care Management for Cardiology Patients in the Hospital</td>
<td>Recruiting</td>
<td>No Results Available</td>
<td>+1</td>
</tr>
<tr>
<td>6. Home-Based Exercise Program For Recovery After Transcatheter Aortic Valve Replacement</td>
<td>Recruiting</td>
<td>No Results Available</td>
<td>+1</td>
</tr>
<tr>
<td>7. Emphy and Cognitive Function Assessment of TAVI Patients</td>
<td>Recruiting</td>
<td>No Results Available</td>
<td>+1</td>
</tr>
<tr>
<td>8. COA-TAVI Registry to Evaluate the Predictive Value of a COA in Predicting TAVI Outcomes</td>
<td>Completed</td>
<td>No Results Available</td>
<td>+1</td>
</tr>
<tr>
<td>9. Exercise Training After Transcatheter Aortic Valve Implantation</td>
<td>Completed</td>
<td>No Results Available</td>
<td>+1</td>
</tr>
</tbody>
</table>
- Actually 2010, 3 months before patient`s 100\textsuperscript{th} birthday
  - Acute CHFE requiring hospitalization
  - Patient demanded BiPap while attempts at diuresis
  - Continued to worsen and passed away, without his letter from the Queen...
Small advertisement

- McGill fellowship in Geriatric Cardiology
- Contact: jonathan.afilalo@mcgill.ca
Questions/Comments


References


References


References


References


77. Arnold SV, Reynolds MR, Wang K, et al. Health Status After Transcatheter or Surgical Aortic Valve Replacement in Patients With Severe Aortic Stenosis at Increased Surgical Risk: Results From the CoreValve US Pivotal Trial. JACC Cardiovascular interventions 2015;8:1207-7.


