

# Valvular Heart Disease – The Basics and New Therapies

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## Presenter Disclosure

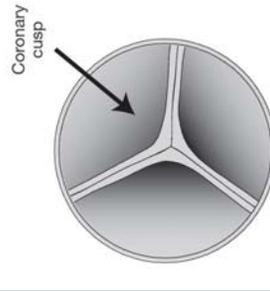
- Presenter's Name: Heather Kertland
- I have no current or past relationships with commercial entities
- Speaking Fees for current program:
  - I have received a speaker's fee for this learning activity

## Outline

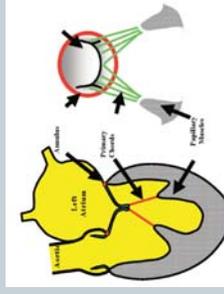
- Review physiology
- Review transcatheter Aortic Valve Implantation (TAVI)
- Highlight developments on percutaneous mitral valve repair
- Discuss the definition of heart disease

## Valvular Heart Disease

Aortic & Pulmonic



Mitral & Tricuspid



## Common valvular abnormalities

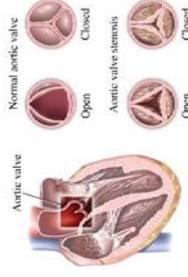
- Stenotic (too tight)
  - Aortic stenosis
  - Mitral stenosis
- Regurgitation (valve leaks)
  - Aortic regurgitation (insufficiency)
  - Mitral regurgitation

## Screening/Diagnosis

- **Physical Exam**
  - Murmurs
  - Other findings
- **Imaging**
  - Echocardiography (TTE)
    - × Imaging of valve structures
    - × Flow velocity across
    - × Valve area
  - Additional tests
    - × Transesophageal echo (TEE)
    - × Cardiac cath
    - × MRI

## Aortic Stenosis

- **Most common valvular problem**
  - Age > 75 years – 12.4% (0.4% general population)
- **Calcification of valve (cusps)**
  - Risk factor – congenital bicuspid valve
    - × 1 – 2% of population
- **Commissural fusion (due to rheumatic heart disease)**



Pharmacotherapy 2011;33(1):76–91, <http://heart surgeryinfo.com>

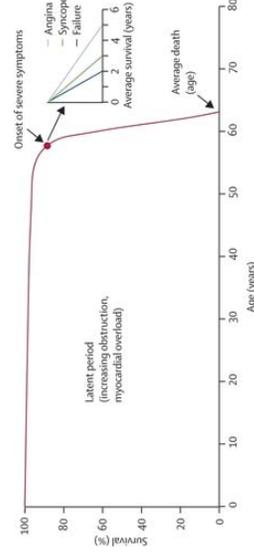
- **Progression**
  - Increased afterload → increased left ventricular systolic pressure generated by LV hypertrophy
  - Increased oxygen demand
  - Eventually – decreased cardiac output, left atrial enlargement
- **Unpredictable rate of progression**
- **Signs and Symptoms**
  - Angina
  - Syncope
  - Heart failure
  - Dyspnea

## Aortic Stenosis

Stage	Valve anatomy	Valve hemodynamics	Consequences and Symptoms
A At risk	Bicuspid valve, sclerosis	normal	none
B Progressive	Mild to moderate calcification Rheumatic changes – commissural fusion	Valve area < 2 cm <sup>2</sup>	Early diastolic dysfunction Normal EF Asymptomatic
C Severe asymptomatic	Severe calcification Reduced leaflet opening	Valve area < 1.6 cm <sup>2</sup>	LV diastolic dysfunction Mild LVH EF normal or < 50 % Asymptomatic
D Severe Symptomatic	Severe calcification Reduce leaflet motion	Valve area < 1 cm <sup>2</sup>	Dyspnea, angina, HF, syncope

JACC 2014;63:e57-185

## Natural History



Once symptomatic - Mean survival 5 years (angina), 3 years (syncope), 2 years (clinical heart failure)

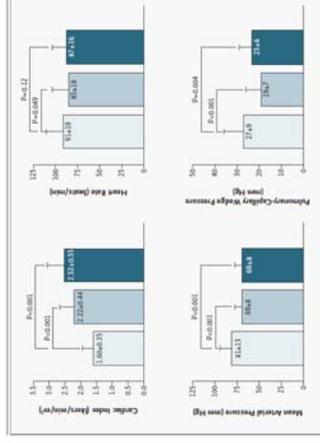
Ross J Jr, Braunwald E. Aortic Stenosis. Circulation 1968;38: 61-67

## Natural History

• Can we alter natural history?

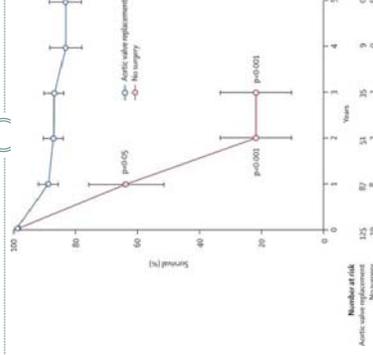
- **Statins**
  - No benefit
    - × Intensive Lipid Lowering with Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) N Engl J Med 2008;359:1343-56
    - × ASTRONOMER trial Circulation 2010;121:306-14
  - Started late in disease process
- **Hypertension**
  - Use of vasodilators
    - × Concern with severe/critical aortic stenosis
    - × Blood pressure = cardiac output X mean vascular resistance

## UNLOAD study - Nitroprusside in severe AS



N Engl J Med 2003;348:1756-63.

## Treatment alternatives

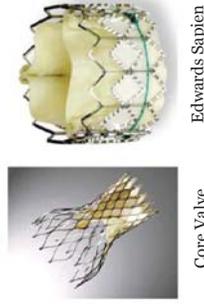


## Indications for surgery

- **Symptomatic individuals with severe AS**
  - Decreased systolic opening
  - Aortic velocity > 4 m/s, mean pressure gradient > 40 mmHg
  - Symptoms of heart failure, syncope, exertional dyspnea, angina or presyncope
- **Benefits of surgery**
  - Improved survival
  - Reduced symptoms

JACC 2014;63:857-185

## Transcatheter Aortic Valve Implantation (TAVI) (TAVR)



Core Valve

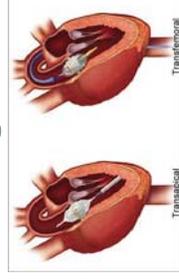
Edwards Sapien

## TAVI complications

- **Median age - 83 years**
- **Death (5 - 10%)**
  - Early - cardiac (heart failure, tamponade, arrhythmias)
  - Late - infection, sepsis, stroke
- **Bleeding (41%)**
  - Life-threatening 16%
  - Access site bleeding (59% of patients), GI, retroperitoneal, pleura
  - Tamponade (3 - 4%)
    - Bivalirudin (BRAVO - 3) no difference
- **Acute kidney injury 22%**
  - Dialysis therapy - 5%
  - DM, CKD, PVD, aortic plaque embolization, hypoperfusion, intramop blood transfusions
  - Stop nephrotoxic medications pre-op
- **Pacemaker 11%**
- **Periprocedural MI (1,1%)**
  - Ischemia due to hypotension or rapid ventricular pacing, myocardial compression by prosthesis, microembolism, direct trauma
- **Cerebrovascular events (3 - 7%)**
  - Later strokes often associated with a fib
  - Distal embolization of native aortic valves
  - Distal protection devices

Nature Review Cardiology 2013;10:685-695. JACC 2015;66:2860-8

- **In high risk surgical candidates:**
  - Reduced mortality, rehospitalization and symptom burden compared to medical management
  - Non-inferior to surgical aortic valve replacement
  - Access - femoral, transapical + others (aorta)



## Valve thrombosis prophylaxis

- Denuded native valve leaflets behind prosthetic valve
- Accelerate neointimal tissue growth/endothelialization
- **PARTNER** trial
  - Encouraged but did not require DAPT
    - × ASA + possible clopidogrel (3 – 6 months)
  - ASA 80- 325 mg
  - Clopidogrel 75 mg daily

## Is DAPT necessary?

Meta-analysis  
2 RCT + 2 quasi-experimental  
N=662

### All cause mortality

Study or Subgroup	Events	Total	DAPT	Events	Total	Weight	M-H, Random, 95% CI	Risk Ratio
Ueda 2011	4	40	5	39	18.6%		0.78 (0.23, 2.69)	
Wang 2012	1	25	1	24	1.7%		1.00 (0.10, 10.00)	
Ponikvar 2013	6	35	4	31	15.1%		2.50 (0.69, 7.98)	
Dargatzis 2014	12	128	13	164	50.7%		1.18 (0.56, 2.50)	
<b>Total (95% CI)</b>	<b>286</b>	<b>354</b>	<b>100.0%</b>	<b>354</b>	<b>100.0%</b>		<b>1.22 (0.72, 2.09)</b>	

Total events: 286 (DAPT) vs 354 (Control)  
Heterogeneity: Tau<sup>2</sup> = 0.06, Chi<sup>2</sup> = 1.68, df = 3 (P = 0.64), I<sup>2</sup> = 0%  
Test for overall effect: Z = 0.14 (P = 0.88)

- No difference in major coronary or cerebrovascular events (MACCE)
- Higher risk of bleeding of any severity with DAPT
- Risk of major of life threatening bleeding varied (1 increased risk, 2 no difference)
- Evaluate need for DAPT on individual patient basis

Clin Cardiol 2015;38:629-34

## Guideline recommendations

- **ACC/AHA**
  - Clopidogrel 75 mg daily may be reasonable for the first 6 months after TAVR in addition to life-long aspirin 75 mg to 100mg daily. Grade IIb (Level of Evidence: C)
- **CCS statement**
  - indefinite low-dose aspirin is recommended along with 1-3 months of a thienopyridine. For patients in whom there are indications for oral anticoagulants (such as atrial fibrillation) the need for adjunctive antiplatelet agents is controversial and triple therapy should be avoided unless definite indications exist.

JACC 2015;66:2860-8, Can J Cardiol 2012;28:520-28.

But wait....

## Possible Subclinical Leaflet Thrombosis in Bioprosthetic Aortic Valves

R.R. Makkani, G. Fontana, H. Jilali, T. Chakravarthy, K.F. Kofoed, O. de Backer, F.M. Asch, C.E. Ruiz, N.T. Olsen, A. Trento, J. Friedman, D. Berman, W. Cheng, M. Kashif, V. Jehlin, C.A. Kilger, H. Guo, A.D. Pichard, N.J. Weissman, S. Kapadia, E. Manasse, D.L. Bhatt, M.B. Leon, and L. Sondergaard

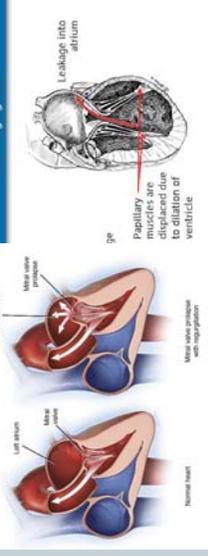
### CONCLUSIONS

Reduced aortic valve leaflet motion was shown in patients with bioprosthetic aortic valves. The condition resolved with therapeutic anticoagulation. The effect of this finding on clinical outcomes including stroke needs further investigation. (funded)

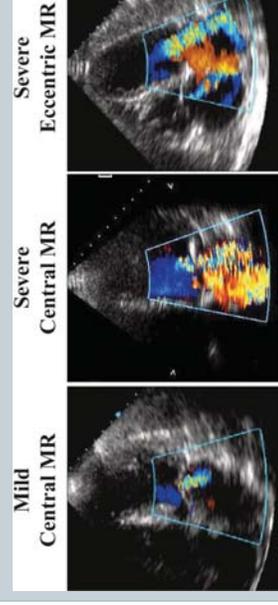
DOI: 10.1056/NEJMoa1509233

## Mitral regurgitation

- **Causes**
  - Primary
    - × Mitral valve prolapse (mechanical problem)
  - Secondary
    - × Papillary muscle dysfunction due to ischemia (ischemic MR)
    - × Dilatation of the left of ventricle (functional MR)



DOI: 10.1161/JCEI.2003.07.001.237-261



- **Consequences**
  - Left atrial dilatation
    - ✦ To receive extra volume
  - Left ventricular dilatation
    - ✦ To ensure adequate preload to maintain forward output
  - Ejection fraction may remain low normal (50 – 60%)
  - Can remain asymptomatic (with mild to moderate MR)
  - Eventually pulmonary congestion, heart failure, pulmonary hypertension

## Primary Mitral Regurgitation

Grade/Definition	Valve anatomy	Valve hemodynamics	Hemodynamic consequence	Symptoms
A: At Risk	Mild MVP, normal coaptation	No/small MR jet < 20% of LA	None	None
B: Progressive MR	Severe MVP, normal coaptation	Central jet 20-40% of LA	Mild LA enlargement	None
C: Asymptomatic severe MR	Severe MVP, Loss of coaptation or flail leaflet	Central jet > 40%	Mod/severe LA enlarged LV enlarged Pul HTN may be present	None
D: symptomatic severe MR	Severe MVP Loss of coaptation		Mod/Severe LA enlarged LV enlarged Pul HTN present	Decreased exercise tolerance, exertional dyspnea

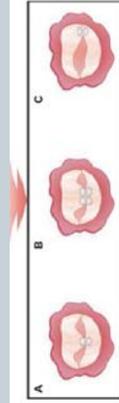
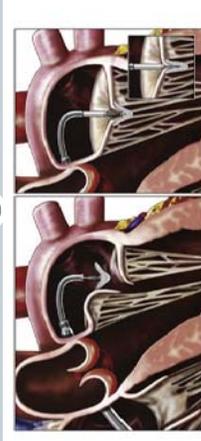
## Mitral Regurgitation

- **Indications for surgery**
  - Primary MR
    - ✦ Symptomatic patients with severe MR
    - ✦ Asymptomatic patients with abnormal LV function
    - ✦ Asymptomatic patients with normal LV function with high likelihood of successful repair
- **Types of surgery**
  - Mitral valve replacement
    - ✦ Mitral valve repair – often preferred
    - ✦ Mitral apparatus
    - ✦ LV function better preserved
    - ✦ Lower mortality
    - ✦ Avoids long term anticoagulation
- **Goal of surgery**
  - Improved symptoms



J Am Coll Cardiol 2009;54:686-94, JACC 2014, 63:e57-185

## Non-invasive mitral valve repair (Mitra Clip)



JACC 2014;63:2057-68, European Heart Journal 2011;32:2350-57

## Outcomes

- **Indicated for those with Grade 3 – 4 MR**
  - Improvement in MR ≤ Grade 2 MR
  - Improvement in NYHA classification
  - Improvement in LV measurements
- **Guideline recommendations;**
  - NYHA class III – IV with severe Primary MR with prohibitive surgical risk (considered inoperable) Grade IIb

## Impact for Pharmacists

- General anesthesia
- Trans-septal puncture
- Peri-procedural heparin
- ASA < 100 mg x 6 months
- Clopidogrel 75 mg x 1 month
- Endocarditis prophylaxis recommended during the first 6 months
- Reassessment of medications – improved cardiac output

## Mitral Stenosis

- **Rheumatic heart disease**

- **Mitral stenosis**

- Leaflet thickening
- Commissural fusion
- Delayed onset of symptoms
- **20 – 40 years**

- **Consequences**

- Left atrium enlarges
- Increased pulmonary venous pressure
- 30 – 40 % develop a fib

Mitral Stenosis



Source: Mayo Clinic

## What is valvular atrial fibrillation?

- **Why is this important?**

- Rheumatic heart disease (mitral stenosis) + A Fib
- **Stroke rate – 20% - 30%/year**

- **Choice of therapy**

- Warfarin vs NOACs

- **CCS recommendations:**

- Rheumatic a fib
- Mitral valve repair
- Mechanical or bioprosthetic heart valve

Can J Cardiol 2015;31:1207-18

## What is valvular A fib? – recent trials

Study/ Medication	Definition
RELY (Dabigatran)	History of heart valve disorders (prosthetic valve or hemodynamically relevant disease)
ROCKET-AF (Rivaroxaban)	Hemodynamically significant mitral stenosis or prosthetic heart valve
ARISTOTLE (Apixaban)	Moderate or severe mitral stenosis, conditions other than a fib that require anticoagulation
AVERROES (Apixaban)	Valvular disease requiring surgery, prosthetic mechanical heart valve, conditions other than atrial fibrillation that require anticoagulation

Can J Cardiol 2015;31:1207-18

## What is valvular a fib? - recent trials

Trial	Valvular Heart disease incidence/type
RELY (dabigatran)	21.8% mitral regurgitation, tricuspid regurgitation, aortic regurgitation, aortic stenosis, mitral stenosis
ARISTOTLE (apixaban)	26.4% Mitral regurgitation, tricuspid regurgitation, aortic regurgitation, aortic stenosis, mitral stenosis, previous valve surgery
ROCKET-AF (rivaroxaban)	14.1% Mitral regurgitation +/- aortic stenosis or regurgitation

- Efficacy - No difference in primary outcome (stroke/systemic embolism)
- Safety – Rocket AF – higher rates of clinically relevant bleeding with VHD

Can J Cardiol 2015;31:1207-18

## Expert Opinion

NOAC use is contraindicated	NOAC use is reasonable
Mechanical heart valves	Bioprosthetic heart valve
• In any position (100% agreement)	• Aortic position (82% agreement)
Rheumatic mitral stenosis	• Mitral position (73% agreement)
• Mild (67% agreement)	Mitral annuloplasty
• Moderate-severe (88% agreement)	• With or without prosthetic ring (60% agreement)
• After commissurotomy (42% agreement)	Non-rheumatic mitral stenosis
	• Mild (97% agreement)
	• Moderate-severe (>90% agreement)
	Tricuspid regurgitation
	• Mild (98% agreement)
	Aortic stenosis or regurgitation
	• Mild (98% agreement)
	• Moderate to severe (69% agreement)
	• Moderate to severe (80% agreement)

NOAC, novel non-vitamin K antagonist.

Can J Cardiol 2015;31:1207-18

## Summary

- **New less invasive treatments available for patients with valvular disease**
  - TAVI
  - Mitra clip
  - Next??
- **Limited data to identify optimal therapies**
  - Valve thrombosis
- **Recent new concerns identified**
- **Valve disease ≠ Valve disease with respect to SPAF**
- **Important for pharmacists to have an understanding of valvular disease and its management as can impact therapy**

## Questions

