Learning Objectives

- By the end of this 45-minute session, the audience should be able to:
  - State the common causes of valvular heart disease
  - List the complications of valvular heart disease
  - Describe the hemodynamic consequences of valvular heart disease
  - Describe the indication for and alternatives of pharmacotherapy in valvular heart disease, specifically in aortic stenosis, aortic regurgitation, mitral stenosis and mitral regurgitation
  - Describe the principles of pharmacotherapy after valve surgery
  - State the antithrombotic recommendations for various prosthetic valve replacements, including transcatheter valve implantation
  - Explain when ASA should or should not be added to the vitamin K antagonist in patients with prosthetic heart valves

Guidelines and Resources

- 2014 AHA/ACC Valvular Heart Disease Guidelines
  - Full: Circulation 2014;129(23):e521-643
  - Executive Summary: Circulation. 2014;129(23):2440-92
- 2012 ESC Valvular Heart Disease Guidelines
  - Eur Heart J 2012;33(19):2451-96
- 2012 CHEST Guidelines for Valvular Heart Disease
  - CHEST 2012;141(2)(Suppl):e576S–e600S
- 2006 AHA/ACC Valvular Heart Disease Guidelines
  - J Am Coll Cardiol 2006;48(3);e1-148
- Canadian Cardiovascular Pharmacist Network (CCPN) Antithrombotic Guidelines Pocket Reference 2008
  - http://ccpn.ca/docs/AntithromboticThrombolyticTxPocketcard.pdf

Introduction

- Valvular heart disease (VHD) affects > 100 million people worldwide
- In Canada, VHD is less common than other cardiac conditions like CAD, HF, HTN
- The burden of VHD is increasing
  - High incidence of rheumatic heart disease in developing countries
  - ↑ burden of degenerative valve disease in developed countries
  - Patients with valve disease are living longer and diagnosis is often made at an older age
    - ↑ frequency of comorbidity, ↑ risk of intervention
  - ↑ in previously operated patients who require re-operation

Figure: Number waiting for and completed open heart surgeries in BC (CABG, valve, other)
Heart Valve Anatomy

- Right Heart
  - Tricuspid Valve
  - Pulmonary Valve
- Left Heart
  - Mitral Valve
  - Aortic Valve

Valve Physiology

Valve Function

Valve Pathology

Diagnosis and Types of VHD

- Identification
  - On physical exam (e.g. heart murmur)
  - Symptoms (e.g. syncope, CP, SOB, ↓ exercise tolerance, HF)
    - May not be recognized by the patient due to progressive nature valve disease
  - Incidental finding (e.g. chest imaging)
- Diagnosis
  - Echo (TTE or TEE)
    - Tricuspid valve regurgitation or stenosis
    - Pulmonary valve regurgitation or stenosis
    - Mitral regurgitation or stenosis
    - Aortic regurgitation or stenosis
  - Other: CXR, ECG, coronary angiogram, cardiac CT, cardiac MRI

Valve Disease Classification

- Classification of valve disease severity:
  - Mild, moderate, severe
- Based on:
  - Symptoms
  - Echocardiography findings
    - Valve anatomy
    - Gradients: Pressure difference across the valve
    - Valve area
      - More applicable in valve stenosis
      - Measured when the valve is open
    - Hemodynamic complications

Circulation. 2014 Jun 10;129(23):e521-643

http://www.ssmhealth.com/heart/PublishingImages/heart.jpg


http://www.drugs.com/health-guide/images/205521.jpg

http://www.drugs.com/health-guide/images/205522.jpg

http://www.ssmhealth.com/heart/PublishingImages/heart.jpg


http://www.drugs.com/health-guide/images/205521.jpg

http://www.drugs.com/health-guide/images/205522.jpg
Complications of Valvular Heart Disease

- Symptoms
  - Due to ↓ in cardiac output
- HF
  - With preserved EF
    - ↓ in cardiac output, but LV function and size remain normal
  - With ↓ EF and/or ↓ LV function
    - Will occur over time if the VHD remains untreated
- AF
  - Especially with mitral stenosis
  - Pulmonary hypertension
  - Stroke
  - Mortality

Management Strategies

- Monitoring
  - Asymptomatic valve disease
  - Echo every 1-5 years
- Medical management
  - For those awaiting surgical intervention
  - Valve not amenable to surgical intervention
  - Decreased life expectancy
- Valve repair or replacement
  - Symptomatic or severe valve disease
  - Reasonable life expectancy and quality of life

Circulation. 2014 Jun 10;129(23):e521-643

Aortic Valve

- Normal aortic valve
  - Open
  - Closed

Aortic Stenosis

- Aortic Stenosis (AS)
- Aortic Regurgitation (AR)
- Mitral Stenosis (MS)
- Mitral Regurgitation (MR)

Specific Valve Pathologies
Aortic Stenosis

- Most common type of VHD
- Etiology
  - Calcified disease of normal leaflet (80%)
  - 2-7% in those > 65y: generally present when 70-80y
  - Inflammatory condition similar to atherosclerosis
    - Risk factors: older age, male, smoking, HTN, diabetes, LDL, lipoprotein and CRP
  - Calcified disease of bileaflet valve
    - Present in 2% of population; present in 10% of 1st degree relatives
    - More common in men; presents earlier (ie. 50-60y)
  - Rheumatic: rare (except in India)
- AS is a chronic, progressive condition with a long latency period
  - Aortic sclerosis: leaflet thickening without obstruction (5% progress to AS)
  - Mortality 15-50% over 5 years once symptomatic

Circulation. 2014 Jun 10;129(23):e521-643

Aortic Regurgitation

- Having bicuspid AV ↑ risk of AR, aortic dilatation and dissection
- 2 types: chronic and acute
- Etiology
  - Primary disease of aortic valve or aortic root
    - Calcified disease, annuloaortic ectasia (root dilatation due to HTN or aging), Marfan’s syndrome, aortic dissection, collagen vascular disease, syphilis
  - Rheumatic disease
  - Infective endocarditis (IE)
  - Post-TAVI or valvuloplasty
- Once symptoms present, mortality is 10-20% per year without surgery

Circulation. 2014 Jun 10;129(23):e521-643
Mitral Valve

Mitral Stenosis

Mitral Regurgitation

Mitral Valve

Mitral Stenosis

Mitral Regurgitation

http://www.merckmanuals.com/media/home/figures/CVS_stenosis_regurgitation_valves_b.gif


http://circ.ahajournals.org/content/120/13/1287/F1.large.jpg

http://dokterpenulis.files.wordpress.com/2008/03/mitral-stenosis-lg.jpg

http://circ.ahajournals.org/content/120/13/1287/F1.large.jpg

Mitral Stenosis

Etiology

- Rheumatic heart disease (most common; in women)
- Calcification

Survival in asymptomatic patients is generally up to 10 years

Progression is highly variable with sudden deterioration

- Precipitated by pregnancy, AF or embolism

LV function is generally normal

Most common complication: AF

Mainstay of therapy is valve replacement

- High operative mortality 3-10%

Mitral Regurgitation

Primary MR

Secondary MR

Acute MR

Chronic MR

2nd most common type of VHD requiring surgery

Circulation. 2014 Jun 10;129(23):e521-643

Circulation. 2014 Jun 10;129(23):e521-643

Mitral Stenosis

Medical Management

- Diuretics or nitrates to relieve symptoms
- 40% of patients with MS will develop AF
  - Anticoagulation regardless of CHADS2 score
    • Mitral stenosis = "Valvular" AF
  - HR control
  - Patients with MS are at high risk of atrial arrhythmias
- In patients with NSR
  - HR control if symptomatic with exercise
- Secondary prevention of Rheumatic fever
  - For at least 10y or until patient is 40y (which ever is longer)
  - Pen G, Pen V, Sulfadiazine, Macrolide

Medical Management

Diuretics or nitrates to relieve symptoms

40% of patients with MS will develop AF

Anticoagulation regardless of CHADS2 score

Mitral stenosis = "Valvular" AF

HR control

Patients with MS are at high risk of atrial arrhythmias

In patients with NSR

HR control if symptomatic with exercise

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Pen G, Pen V, Sulfadiazine, Macrolide


Mitral Regurgitation

Primary MR

- Disruption to various parts of the mitral apparatus
- Etiology
  - Rheumatic (↓ incidence)
  - Degenerative (myxomatous degeneration) or collagen vascular disease
  - IE
  - Trauma or radiation (e.g. chordae rupture)
- Acute or chronic
  - Acute: Leaflet perforation, chordae rupture, papillary muscle dysfunction or rupture; may result in acute pulmonary edema
    - Poorly tolerated, poor prognosis
  - Chronic: may progress insidiously, causing LV dysfunction before symptoms
- High risk of mortality and morbidity
  - 14% CV death, 22% all-cause death; 33% cardiac event

Primary MR

Management strategy

- Replacement
- Repair
  - Lower peri-op mortality, improved survival, better preservation of post-op LV function, lower risk of long term morbidity
- Medical management
  - Reduce filling pressures with nitrates and diuretics
  - Nitroprusside for reducing preload and afterload (↓ regurgitant fraction)
  - Inotropes for hemodynamic support
  - Medical therapy for systolic dysfunction if not a valve surgery candidate and EF < 60% (BB, ACEI/ARB, aldosterone antagonists)
  - BB improve surgical outcomes, delays onset of LV dysfunction, reverse LV dysfunction
  - No evidence for ACEI in chronic MR without HF

Secondary (Functional) MR

- Also known as: ischemic MR
- MV leaflets and chordae are structurally normal
- MR caused by LV dysfunction (secondary to CAD, MI, cardiomyopathy)
- Generally poor prognosis compared to primary MR
  - Not improved by revascularization
- Myocardial viability imaging should be performed pre-surgery
- Operative mortality is higher
  - Presence of comorbidities
  - Repair yields better outcomes than replacement
    - High risk of MR recurrence
- Medical Management
  - Treat LV dysfunction (ACEI/ARB, BB, aldosterone antagonists)
  - Treat cause of LV dysfunction
- Operative mortality is higher
  - Presence of comorbidities
  - Repair yields better outcomes than replacement
    - High risk of MR recurrence
- Medical Management
  - Treat LV dysfunction (ACEI/ARB, BB, aldosterone antagonists)
  - Treat cause of LV dysfunction

Basic Principles of Medical Management in VHD

- Risk factor management
  - Treat HTN, dyslipidemia, diabetes
- Treat the altered hemodynamics in each specific valve pathology
- Treat LV dysfunction if present
  - Diuresis, ACEI/ARB, BB, aldosterone blockers
- Rheumatic fever prophylaxis
  - Prompt treatment of streptococcal pharyngitis
- Infective endocarditis prophylaxis (for those with prosthetic heart valves only)
  - Oral health is key
- Vaccinations
  - Influenza and pneumococcal
- Exercise
  - Lack of studies in VHD
  - May suggest regular aerobic exercise for select VHD patients

Open Heart Surgery History

- 1895: First Open Heart Surgery
- 1925: First Valve Surgery
- 1990s: First off-pump open heart surgeries
- 2005: First transapical valve in Canada
- 2013: First "tara device" mitral valve
Open Heart Surgery

Introduction

• Valve surgery is the mainstay of therapy for severe VHD
  – 30% of VHD patients receive a prosthetic heart valve
• Over the last 50 years, there have been major advances in surgical techniques and post-operative care for the VHD patient
• Generally, the risk of mortality of severe VHD greatly outweighs the risk of perioperative mortality
• In BC, 30-day adjusted mortality remains low compared to society of thoracic surgeon (STS) reports
  – Valve surgery: 2-3% (STS 3.4%)
  – CABG + Valve surgery: 4-6% (STS 6.8%)


Open Heart Surgery

Operation

• Sedation
• Mechanical Ventilation
• Sternotomy or thoracotomy
  – Tranexamic acid
• Cardiopulmonary bypass machine
  – Heparinized circuit
  • Protamine to reverse
  – Fluids and blood products PRN
  – Vasopressors (no inotropes)
• Cardioplegia
  – Potassium
  – Hypothermia
• Pre-, intra-, and post-op transesophageal echo (TEE)
• Chest tubes

http://mehmanesh.com/wp-content/uploads/2013/05/open-heart.png

Post Open Heart Surgery

Medical Management

Post-op Care

• Inotropes and vasopressors
• Diuretics
• AF prophylaxis
• Stress ulcer prophylaxis
• DVT prophylaxis
• Post-op complications management
  – Delirium
  – Arrhythmias or heart block
  – AKI
  – Nausea and vomiting
  – Bleeding
  – Hyperglycemia
  – Skin and soft tissue infection
• Home meds restarted

On Discharge

• Diuresis
• Change in antithrombotics
• Change in BP meds
• AF
  – Treatment
  – Prophylaxis
• Change in diabetes meds
• Stress ulcer prophylaxis

Prosthetic Heart Valves

<table>
<thead>
<tr>
<th>Types</th>
<th>Selection Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioprosthetic</td>
<td>~10-20 year life span More physiological hemodynamics</td>
</tr>
<tr>
<td>Mechanical</td>
<td>Indefinite life span Patient has another indication for warfarin</td>
</tr>
<tr>
<td>Transcatheter</td>
<td>Recommended in those who are high risk surgical candidates Expected life expectancy &gt; 12 months post-surgery</td>
</tr>
</tbody>
</table>

Bioprosthetic (1970)

<table>
<thead>
<tr>
<th>Types</th>
<th>Selection Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caged-ball</td>
<td>Transfemoral (AV) Porcine pericardium</td>
</tr>
<tr>
<td>Tilling disc single leaflet</td>
<td>Bileaflet</td>
</tr>
<tr>
<td>Bileaflet</td>
<td>Transcatheter (AV, MV) Sapien XT THV</td>
</tr>
</tbody>
</table>


Transcatheter Valves

Transapical

https://encrypted-tbn1.gstatic.com/images?q=tbn:ANd9GcR4bfMO0p97BSFFz-035ce1nnvCulPQmpC7FE6ewV1JipamAc
**Anticoagulation in Prosthetic Valves**

- **Goals of Therapy**
  - Prevent thrombosis
    - Valve thrombosis (<2-4% per year)
    - Major embolism (<4-8% per year)
    - Total embolism (<9-18% per year)
  - Prevent thromboembolic stroke
  - Minimize bleeding
    - <1 to 2% yearly
  - Prevent mortality

**Therapeutic Alternatives**

- **ASA**
  - ↓ major embolism by 40%
  - Total bleeding < 1% per year
- **Warfarin**
  - ↓ major embolism by 75%
  - Total bleeding 2% per year
- **ASA + Warfarin**
  - ↓ major embolism by > 75%
  - Total bleeding ~5% per year

**Approach to Anticoagulation in Prosthetic Heart Valves**

- Risk of thrombogenicity determines choice of antithrombotic therapy
  - Location of valve
    - Mitral (2x) > Aortic
  - Type of valve
    - Mechanical (m) > Tissue (t)
      - Mechanical: caged-ball (5x) > tilting disc > bileaflet
    - Generation of valve
  - Timing of valve replacement / repair
  - Risk of thrombosis highest in first 3 months
  - Presence of additional thromboembolism risk factors

**Choice of Antithrombotic**

<table>
<thead>
<tr>
<th>Risk of Thrombosis</th>
<th>Location &amp; Type</th>
<th>+ RF?</th>
<th>Antithrombotic Recommendation</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>MVR(m) or AVR(m) – caged ball or tilting disc</td>
<td>VKA to INR 3 + ASA</td>
<td>Indefinite</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AVR(m) – bileaflet</td>
<td>VKA to INR 3 + ASA</td>
<td>Indefinite</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MVR(t) or MV Repair</td>
<td>VKA to INR 2.5 + ASA</td>
<td>VKA x &gt; 3 mos, ASA indefinitely</td>
<td></td>
</tr>
<tr>
<td>Lower</td>
<td>MV Repair or AVR(t)</td>
<td>VKA to INR 2.5 + ASA</td>
<td>VKA x &gt; 3 mos, ASA indefinitely</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ASA alone</td>
<td>VKA x 3 mos, ASA</td>
<td>ASA indefinitely</td>
<td></td>
</tr>
</tbody>
</table>

**Additional Risk Factors (RF) for Thrombosis**

- AF
- Enlarged left atria (>4.5-5cm in diameter)
- Reduced EF
- Hypercoagulable state
- Hx thromboembolism
- Atherosclerotic vascular disease
  - Cerebrovascular disease
  - Coronary artery disease
  - Peripheral arterial disease

**Evidence for Adding ASA?**

- 2003 Cochrane review of 11 RCTs (N=2428) in prosthetic valve patients found that adding ASA to OAC vs OAC alone:
  - ↓ mortality (RR 0.58, 95% CI 0.4-0.86)
  - ↓ thromboembolism (RR 0.42, 95% CI 0.21-0.81)
  - ↑ bleeding (RR 1.44, 95% CI 1.2-2.08)
- Adding low dose ASA (<100mg) did not ↑ bleeding in this population

**Adding ASA to VKA**

- Additional risk factors for thrombosis:
  - AF
  - Hypercoagulable state (e.g. thrombophilias)
  - Low EF
  - Vascular disease (e.g. CAD)
  - Hx embolism (e.g. VTE)
- Elderly (>80 years)
- Hx recent or severe bleeding (e.g. GIB)
- Other risk factors for bleeding
  - Abnormal renal or liver function
  - Other medications that ↑ bleeding risk
Anticoagulation in AVR(t) without additional thromboembolic risk factors

- 2014 AHA guidelines recommend VKA x 3-6 months then ASA
  - 2008 AHA, 2012 ESC: ASA alone
  - 2012 ESC: VKA x 3 months then ASA
- Aramendi et al. 2005
  - P, R, OL, N=191 with bioprosthetic valves (94% AVR(t))
  - triflusal 600mg daily vs. acenocoumarol (INR 2-3) x 3 mos
  - Outcome: Thromboembolism, hemorrhage, valve-related death at 180d = NSS
- Merie et al. 2012
  - Retrospective cohort (Danish Registry), N=4075 AVR(t)+CABG, no previous indication for warfarin, no POAF
  - ASA, VKA, ASA + VKA, no ASA or VKA x 6.6y
    - Analyses done on VKA vs ASA vs ASA or No antithrombotic
      (N=2278+916 vs. N=181+700)
    - VKA x 30-89d, 90-179d, 180-364d, 365-729d, 730d
    - Outcomes: ↓ stroke, ↓ thromboembolism, ↓ bleeding, ↓ CV death

JAMA. 2012;308(20):2118-25

Merie et al. 2012

- There is controversy about the optimal antithrombotic in mitral valve repair
  - ASA + Warfarin x 3 months, then ASA alone
  - Warfarin x 3 months, then ASA
  - ASA
- Observational studies demonstrate that risk of thromboembolism and bleeding are both low
  - Thromboembolism 0.4-3% per patient year
  - Bleeding 0.3-0.8% per year
  - Confounded by 1/3 of patients developing AF during first 3 months

JAMA. 2012;308(20):2118-25

Anticoagulation in Mitral Valve Repair

Anticoagulation in Transcatheter Valves

- St. Paul’s Hospital first pioneered the transfemoral and transapical approaches for TAVI in 2005
  - > 200 TAVIs have been completed since
- Major complications: stroke, bleeding, hypotension, conduction disturbances, AF, AKI, vascular injury; anemia, paravalvular leak
  - Stroke rates and bleeding rates > 15% at 30d, which are independent risk factors for mortality
- Antithrombotic alternatives
  - ASA 50-100mg daily + clopidogrel 75mg daily x 3-6 months then ASA indefinitely (guideline recommended)
    - 2 RCTs and 1 prospective observational trial
    - ASA alone
    - ASA + warfarin
    - Clopidogrel + warfarin
    - Warfarin alone

Investigational Transcatheter Valves

Bridging of Anticoagulation

- Bridging ↑ risk of bleeding; unknown whether the ↑ risk of bleeding is off-set by the benefits of ↓ thrombosis
- Bridging is not required for procedures that are low risk of bleeding (e.g. dental extractions); warfarin should be continued
- 2012 CHEST recommends bridging for risk of thrombosis 5 to > 10% yearly
  - Any MVR(m), bileaflet AVR(m) with AF, cage-ball or tilting disc AVR(m),
  any AVR and recent CVA (<6 months), AF with Rheumatic valve disease
- Pre-op: stop warfarin x 3-5 days, LMWH bridging
- Post-op management varies
  - Bridging depends on the risk of bleeding from the surgery
  - Heterogeneous definitions exist depending on type of surgery
  - Post open heart surgery (OHS)
    - Generally risk of bleeding > thrombosis post-OHS
    - Do not bridge with LMWH; low target IV heparin protocol to start POD 1-3

Novel Oral Anticoagulants (NOACs) in Prosthetic Heart Valves

- Studies with NOACs in AF excluded patients with valvular heart disease (e.g. mitral stenosis) and prosthetic heart valves
- Dabigatran is contraindicated in those with mechanical valves
  - RE-ALIGN Trial prematurely terminated
  - Phase II, Dabi in mechanical valves
- Unknown if Factor Xa Inhibitors provide adequate anticoagulation
  - Ongoing: Rivaroxaban in mechanical AVR (NCT02128841)
- Lack of evidence in bioprosthetic valves or valve repairs
  - Possible NOAC use in AF and AVR(t)
    - AVR(t) is the least thrombogenic prosthetic valve
    - Low dose ASA daily
    - Select surgeons have been recommending ASA + warfarin x 3 months then resume NOAC

Prosthetic Heart Valves

- Small sample size, non-randomized trials
  - Observational trials or case series
- Risk of thrombosis comes from studies with 1st generation valves
  - For newer valves, company may conduct biased in-house studies and make recommendations
- Heterogeneous valve types (AV and MV) studied with different baseline thrombosis or bleeding risks
- Target INRs, frequency of INR checks, TTR infrequently reported
- Other risks of thrombosis or bleeding poorly documented or uncontrolled for
- Advances in surgical techniques and post-surgical care will affect thrombosis and bleeding outcomes

General Pharmacotherapeutic Approach to the VHD Patient

- Pre-surgical intervention
  - Mild to moderate (watch and wait)
    - Risk factor management
  - Educate patient on important signs and symptoms
  - Moderate to severe (surgery is imminent)
    - Support hemodynamics with pharmacotherapy specific to the pathophysiology
    - Stop anticoagulation in preparation for surgery
- Post-surgical intervention
  - Re-evaluate need for pre-op medical management medications
  - Treat LV dysfunction if present
  - Assess need for anticoagulation and duration
  - Risk factor management
  - Minimize risk for infective endocarditis
    - Recommend routine dental care
    - Antibiotic prophylaxis for dental procedures in those with prosthetic heart valves

Summary

- Valvular heart disease encompasses many valvular pathologies
- Making pharmacotherapeutic decisions in VHD is complex
- Pharmacotherapy has a distinct role in the overall management of VHD patients
- Choice of antithrombotic to balance the risks of thrombosis and bleeding takes into account a variety of factors
- Novel surgical techniques (e.g. TAVI) will pose new therapeutic challenges
- The pharmacist can play an important role in optimizing pharmacotherapy wherever the patient may be in their valvular heart disease journey