The Role of Anti-Coagulation in Patients with Prosthetic Valve Replacement

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Anticoagulation Symposium & Workshop 2015
Introduction

- First successful mitral valve surgery for rheumatic mitral stenosis was performed by Dr. Elliot Cutler in 1923 on 12 years old girl (Cutler et al)
Introduction

• The introduction of commercial valve replacement surgery in the early 1960s has dramatically improved the outcome of patients with valvular heart disease

• Approximately 280,000 valve substitutes are now implanted worldwide each year;

• Approximately half are mechanical and another half are bioprosthetic valves.
Introduction

• Despite the marked improvements in prosthetic valve design and surgical procedures over the past decades, valve replacement does not provide a definitive cure to the patient.

• Instead, native valve disease is traded for “prosthetic valve disease,” and the outcome of patients undergoing valve replacement is affected by prosthetic valve hemodynamics, durability, and thrombogenicity.

• Nonetheless, many of the prosthesis-related complications can be prevented or their impact minimized through optimal prosthesis selection in the individual patient and careful medical management and follow-up after implantation.
Anatomy of Heart & Prosthetic Valves
Heart Valves
What is an ideal prosthetic valve?
The ideal valve substitute should mimic the characteristics of a normal native valve.

It should have excellent hemodynamics, provide unimpeded forward flow with minimal transvalvular gradient upon opening and a competent valve with minimal regurgitation upon closing.

Unfortunately, this ideal valve substitute does not exist, Available prosthetic valves have inherent limitations.
Types of Prosthetic valves

Mechanical Valves
- Caged Ball Valves
- Monoleaflet Valves
- Bileaflet Valves

Bioprosthetic Valves
- Stented Bioprostheses
- Stentless Bioprostheses
- Percutaneous Bioprostheses
Different types of prosthetic valves.
Long established Valve History

1965
Starr-Edwards (Model 6120, 1260)

1975
- St. Jude Medical
- Medtronic-Hall D-16 (Mfg. Change)
- Bjork-Shiley Spherical

1985
- Bjork-Shiley C-C (60°)
- Bjork-Shiley C-C (70°)
- Baxter Duromedics (Original)

1995
- Bjork-Shiley Monostrut
- Baxter Tekna
- CarboMedics
- Sorin Bicarbon
- ATS
- Medtronic Parallel
- On-X
Selecting the Optimal Prosthesis in the Individual Patient? Bioprosthetic Versus Mechanical Valve
Algorithm for the selection of the optimal prosthesis in the individual patient.

**PATIENT**
- Age, life expectancy, preference
- Indication / contra-indication for warfarin therapy

**IN FAVOR OF BIOPROSTHESIS**
- Desire of the patient
- Age ≥ 65 or limited life expectancy
- Warfarin therapy not available or contra-indicated
- Woman of child bearing age

**SELECT THE PROSTHESIS MODEL BASED ON:**
- LONG DURABILITY
- HEMODYNAMIC PERFORMANCE (Prevention of PPM)
- IMPLANTABILITY

**IN FAVOR OF MECHANICAL PROSTHESIS**
- Desire of the patient
- No contra-indication for warfarin therapy
- Already on warfarin therapy
- Age < 65 and long life expectancy

**SELECT THE PROSTHESIS MODEL BASED ON:**
- LOW THROMBOGENICITY
- PATIENT
  - Body size
  - Valve annulus size
  - Age
  - Lifestyle
  - Comorbidities
  - LV function

**HEMODYNAMIC PERFORMANCE (Prevention of PPM)**
**IMPLANTABILITY**
In the recent American College of Cardiology/American Heart Association and European guidelines, the weight given to patient age has been reduced, whereas much greater importance is now given to patient’s preference.


Is Prosthetic Valve Replacement a traded Prosthetic Valve Disease?
Prosthetic Valve Related Complications

- Thromboembolism
- Valve Thrombosis
- Anticoagulant-Related Hemorrhage
- Prosthetic Valve Endocarditis
- Hemolysis
- Structural Valve Degeneration
Thromboembolism

- **A prosthesis-related thromboembolic** event is defined as any new, permanent or transient, focal or global neurologic deficit, or a peripheral embolus in the absence of another clear-cut embolic source.

- The risk of thromboembolism depends not only on **prosthesis type** but also on **valve position**, **thrombogenicity**, **patient risk factors**, and **antithrombotic treatment**.

- **All prosthetic valves** are susceptible to the formation of thrombus that can subsequently embolize.

- **Thrombus** can form on the polished **metal components** of mechanical valves, the Dacron sewing rings, areas of **pannus ingrowth**, or on areas of **tissue valve degeneration and calcification**.
Thromboembolism

- The thromboembolic risk does appear to have decreased with some of the newer mechanical prostheses, such as the St. Jude, Medtronic-Hall valves and On-X.

- Tissue valves are more resistant to thromboembolism, but the sewing ring is a nidus for thrombus formation in the early postoperative period.

- Thromboembolism is more common in the mitral position (2-5%/patient-year) than the aortic position (1-2%/patient-year) and is more common with mechanical valves (2-4%/patient-year), even with the use of warfarin, than with tissue valves without warfarin (1-2%/patient-year).

- The risk of thromboembolism with mechanical valves increases about threefold in both aortic and mitral positions if anticoagulation is stopped.
Minimized Risk of Thromboembolism

Unique pivot guards create passive and active washing of butterfly recesses which may reduce the potential for thromboembolic complications.

Thromboresistance – Material Biocompatibility

Orifice and leaflets Pyrolytic Carbon

Sewing ring Double velour polyester fiber
Thromboresistance

Studies confirm that valve-related events with St. Jude Medical mechanical heart valves are low.

<table>
<thead>
<tr>
<th></th>
<th>AVR</th>
<th>MVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valve Thrombosis</td>
<td>0.06%</td>
<td>0.18%</td>
</tr>
<tr>
<td>Thromboembolism</td>
<td>1.9%</td>
<td>2.8%</td>
</tr>
<tr>
<td>Bleeding</td>
<td>2.7%</td>
<td>2.7%</td>
</tr>
</tbody>
</table>

# Clinical Data Comparison MHV

## Thromboembolism (TE) / Bleeding (BL) Rate Comparison

<table>
<thead>
<tr>
<th>Primary author</th>
<th>St. Jude Medical</th>
<th>Medtronic (ATS Medical)</th>
<th>Sorin</th>
<th>Sorin (Carbomedics)</th>
<th>On-X</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of publication</td>
<td>2007</td>
<td>2007</td>
<td>2009</td>
<td>2005</td>
<td>2007</td>
</tr>
<tr>
<td>Study duration (years)</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Number of patients</td>
<td>604</td>
<td>601</td>
<td>587</td>
<td>505</td>
<td>428</td>
</tr>
<tr>
<td>Mean patient age (years)</td>
<td>62.3</td>
<td>63.7</td>
<td>61.5</td>
<td>57</td>
<td>62.7</td>
</tr>
<tr>
<td>Mean follow-up period (years)</td>
<td>4.8</td>
<td>4.8</td>
<td>5.8</td>
<td>5.1</td>
<td>3.9</td>
</tr>
<tr>
<td>Total patient years</td>
<td>5624 (SJ and ATS)</td>
<td>5624 (SJ and ATS)</td>
<td>2474</td>
<td>2590</td>
<td>1626</td>
</tr>
<tr>
<td>Aortic valve replacement (AVR) thromboembolism rate (%/patient-years)</td>
<td>0.8</td>
<td>1.1</td>
<td>1.2</td>
<td>1.45</td>
<td>1.49</td>
</tr>
<tr>
<td>Mitral valve replacement (MVR) thromboembolism rate (%/patient-years)</td>
<td>1.4</td>
<td>1.3</td>
<td>1.18</td>
<td>1.78</td>
<td>1.61</td>
</tr>
<tr>
<td>AVR bleeding rate (%/patient-years)</td>
<td>0.3</td>
<td>0.3</td>
<td>1.31</td>
<td>0.52</td>
<td>0.93</td>
</tr>
<tr>
<td>MVR bleeding rate (%/patient-years)</td>
<td>0</td>
<td>0.6</td>
<td>0.99</td>
<td>0.85</td>
<td>1.43</td>
</tr>
</tbody>
</table>

Valve Thrombosis

- The risk of mechanical valve thrombosis is very low during satisfactory anticoagulation, but it has been reported in patients with therapeutics prothrombin times at the time of hospital admission.

- The risk is higher in the mitral position than in the aortic position and is greatest in the tricuspid position.

- The risk of thrombosis on mechanical valves is raised about five to tenfold if anticoagulation is stopped.
Valve Thrombosis

- Thrombosis of a mechanical valve may occur as a catastrophic event with the acute onset of heart failure, pulmonary oedema, or cardiogenic shock. However, it is often heralded by nonspecific cardiac complaints, or the indolent development of congestive heart failure.

- There has been limited but favourable experience with the use of thrombolytic therapy to treat acute valve thrombosis.

- More commonly, valve thrombosis requires emergency surgery that carries up to a 50% mortality rate.
Anticoagulant-Related Hemorrhage

- The use of anticoagulant to reduce thromboembolic risk occasionally results in internal or external bleeding episodes that can cause death, stroke, reoperation, hospitalization, or require blood transfusion.

- The annual risk of fatal, major, and minor bleeding episodes during anticoagulation is approximately 0.5%, 1-2%, and 4 – 8%, respectively.

- The risk of bleeding is even higher in elderly patients, approximating 9%/patient-year in patients older than age 70.
• What is the role of anticoagulation after prosthetic valve replacement?


Antithrombotic Therapy for Prosthetic Valves
Class 1 Evidence

- Anticoagulation with a **VKA** and international normalized ratio (INR) monitoring is recommended in patients with a mechanical prosthetic valve. (Level of Evidence: A)

- Anticoagulation with a **VKA** to achieve an **INR of 2.5** is recommended in patients with a **mechanical AVR** (bileaflet or current-generation single tilting disc) and no risk factors for thromboembolism. (Level of Evidence: B)

- Anticoagulation with a **VKA** is indicated to achieve an **INR of 3.0** in patients with a **mechanical AVR** and additional risk factors for thromboembolic events (AF, previous thromboembolism, LV dysfunction, or hypercoagulable conditions) or an **older-generation mechanical AVR** (such as ball-in-cage). (Level of Evidence: B)
Class 1 Evidence

- Anticoagulation with a **VKA** is indicated to achieve an **INR of 3.0** in patients with a **mechanical MVR** (Level of Evidence: B)

- **Aspirin 75 mg to 100 mg daily** is recommended in addition to anticoagulation with a **VKA** in patients with a **mechanical valve prosthesis**. (Level of Evidence: A)
CLASS IIa Evidence

- Aspirin 75 mg to 100 mg per day is reasonable in all patients with a bioprosthetic aortic or mitral valve. (Level of Evidence: B)

- Anticoagulation with a VKA is reasonable for the first 3 months after bioprosthetic MVR or repair to achieve an INR of 2.5 (Level of Evidence: C)
• Anticoagulation, with a VKA, to achieve an INR of 2.5 may be reasonable for the first 3 months after bioprosthetic AVR (Level of Evidence: B)

• Clopidogrel 75 mg daily may be reasonable for the first 6 months after TAVR in addition to life-long aspirin 75 mg to 100 mg daily. (Level of Evidence: C)
CLASS III: Harm

• Anticoagulant therapy with oral direct thrombin inhibitors or anti-Xa agents should not be used in patients with mechanical valve prostheses (Level of Evidence: B)
Bridging Therapy for Prosthetic Valves
CLASS I

- **Continuation of VKA anticoagulation** with a therapeutic INR is recommended in patients with mechanical heart valves undergoing minor procedures (such as dental extractions or cataract removal) where bleeding is easily controlled. (Level of Evidence: C)

- **Temporary interruption of VKA anticoagulation**, without bridging agents while the INR is subtherapeutic, is recommended in patients with a bileaflet mechanical AVR and no other risk factors for thrombosis who are undergoing invasive or surgical procedures. (Level of Evidence: C)

- Bridging anticoagulation with either intravenous unfractionated heparin (UFH) or subcutaneous low-molecular-weight heparin (LMWH) is recommended during the time interval when the INR is subtherapeutic preoperatively in patients who are undergoing invasive or surgical procedures with a 1) mechanical AVR and any thromboembolic risk factor, 2) older generation mechanical AVR, or 3) mechanical MVR. (Level of Evidence: C)
CLASS II a

- Administration of *fresh frozen plasma or prothrombin complex concentrate* is reasonable in patients with mechanical valves receiving VKA therapy who require [emergency non-cardiac surgery or invasive procedures]
Excessive Anticoagulation and Serious Bleeding With Prosthetic Valves
CLASS IIa

- Administration of **fresh frozen plasma or prothrombin complex concentrate** is reasonable in patients with mechanical valves and **uncontrollable bleeding who require reversal of anticoagulation** (Level of Evidence: B)
Figure 6. Anticoagulation for Prosthetic Valves
Heart Valve Replacement in National Heart Institute, Kuala Lumpur, Malaysia
Figure for MVR, AVR and DVR operations in IJN(NHI) from 2000-2012.

MVR, AVR and DVR Operation in 2000-2012

Average: 300 cases/year
Average: 200 cases/year

70%-80% of mechanical valves used in IJN: SJMV
A Personal Experience of Heart Valve Replacement Surgery.
Methods

• It is a retrospective study of 203 patients who underwent heart valve replacement by a surgeon at the National Heart Institute (NHI), Kuala Lumpur, Malaysia from 2002 to June 2012.

• It is the preference of the surgeon to repair the diseased valve both in mitral and aortic position whenever possible.

• Valve replacement was performed only for very severe rheumatic valvular disease in both aortic and mitral positions, calcified aortic valvular disease, valve not amenable for repair and failed repair.

• The patients were divided into 3 groups:
  Group A: Mitral valve replacement [n = 70 patients (34.5%)]
  Group B: Aortic valve replacement [n = 68 patients (33.5%)]
  Group C: Mitral and Aortic valves replacement [n = 65 patients (32%)]
Results

- 30-day mortality: n= 4/203 (1.9%) (Post MVR: 2; Post DVR: 2)
- Median ICU stay (day): 1 (Range 1-32)
- Mean hospital stay (day): 11.7 ± 7 (1-63)

Early deaths were from:
1. Septic shock secondary to pneumonia (n=1) (0.5%)
2. Acute fulminant pancreatitis (n=1) (0.5%)
3. Acute abdomen perforated bowel (n=1) (0.5%)
4. Right heart failure (n=1) (0.5%)

Major complications:
- Bleeding (Chest Reopen): n=14 (4.9%)
- Pericardial Effusion (Open PE Drainage): n=9 (4.4%)
- Sepsis: n=1 (0.5%)
- Renal Impairment: n=5 (2.5%)
- AF: n=38 (18.7%)
### Clinical Outcome

<table>
<thead>
<tr>
<th>Mean follow-up (year)</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Late Mortality:</td>
<td></td>
</tr>
<tr>
<td>Acute Myocardial Infarction</td>
<td>2</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>3</td>
</tr>
<tr>
<td>Sepsis (Bacterial Endocarditis)</td>
<td>1</td>
</tr>
<tr>
<td>Retroperitoneal Bleeding</td>
<td>1</td>
</tr>
</tbody>
</table>

- Survivors (n=192):
  - Follow-up complete in 187/203 (92.1%).
  - 91.1% of survivors in NYHA I
Follow-up

Number of reoperation: n=1 (0.5%)

Redo-operation details
  Redo-Mitral Valve Replacement: n=1 (0.5%)

Cause of redo-operation
  Clot on the prosthetic valve (16 months after the initial operation)

Valve related complications
  • Bleeding (n=1)
  • Valve Thrombosis (n=1)
  • Bacterial Endocarditis (n=1)
Freedom from valve related complication (Bleeding; Thromboembolism; Endocarditis)

<table>
<thead>
<tr>
<th>Month</th>
<th>No at risk</th>
<th>Estimate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>183</td>
<td>100.0</td>
</tr>
<tr>
<td>12</td>
<td>135</td>
<td>100.0</td>
</tr>
<tr>
<td>60</td>
<td>38</td>
<td>99.2</td>
</tr>
<tr>
<td>120</td>
<td>12</td>
<td>93.3</td>
</tr>
</tbody>
</table>

Freedom from valve related complication: 5 years: 99.2%; 10 years: 93.3%
Conclusions

• This study on valve replacement has been encouraging despite the surgeon’s preference is to repair the diseased valves especially the mitral and tricuspid valves.

• The outcomes of early mortality, survival, freedom from the reoperation were all comparable or even better than other studies.

• Improvements in ICU and ward managements have resulted in minimal or no complications with shorter stay.

• Structured patient education, anticoagulation counseling, home INR monitoring and careful follow-up plan helped in care of patients with prosthetic heart valve.

• This approach has produced good results with a low mortality, reasonable long term survival rate and minimal valve related complications.
Future Perspectives
Importance of Anticoagulation

- High variability of the INR is the strongest independent predictor of reduced survival after mechanical valve replacement.

Self-Monitoring Anti-Coagulation

- In patients with mechanical prosthetic valves, the Early Self-Controlled Anticoagulation Trial (ESCAT) has revealed that self-management of anticoagulation allows patients to be maintained within a lower and smaller INR range, which results in fewer thromboembolic events rates and in a 23% improvement in long-term survival.


- Although these results are encouraging, it is important to emphasize that self-management is not feasible for all patients and that it requires proper identification and education of suitable candidates.

Future Perspectives

- In addition, alternatives to warfarin therapy are now under investigation, including the use of direct thrombin inhibitors administered at fixed doses that do not require regular monitoring.

  Dabigatran received FDA approval in October 2010 for use in patients with atrial fibrillation, after the RE-LY trial showed that it is a clinically acceptable alternative to warfarin in this setting. When early animal studies showed promising results for dabigatran in preventing valve thrombosis, it was hoped that dabigatran might replace warfarin for patients with mechanical heart valves. But that hope has dimmed.

- The use of antiplatelet drugs or lower doses of warfarin in newer-generation bi-leaflet prosthesis with a low thrombogenicity profile.

The Prospective Randomized On-X Valve Anticoagulation Clinical Trial (PROACT) The US FDA approved the first and only IDE (Investigational Device Exemption) lowered anticoagulation trial for a mechanical heart valve to be conducted at 40 sites in the United States and Canada for the On-X Prosthetic Heart Valve. Successful completion of the clinical trial could result in the On-X heart valve becoming the only mechanical valve approved for low-dose anticoagulation therapy.
Future Hope

- Valve replacement can be performed with no or minimal valve-related complications

- Availability of an “ideal valve“

- No need any form of anticoagulation or presence of a drug that can be given at fixed doses with no monitoring and effectively prevent thromboembolism.