VALVE EMERGENCIES

Prosthetic valve thrombosis

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Institute of Cardiology, Warsaw, Poland

ESC CONGRESS 2010, STOCKHOLM
<table>
<thead>
<tr>
<th>Company</th>
<th>Relationship</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boehringer Ingelheim</td>
<td>speaker fees, consultant</td>
</tr>
<tr>
<td>Bayer</td>
<td>speaker fees, consultant</td>
</tr>
<tr>
<td>Novartis</td>
<td>research grant</td>
</tr>
<tr>
<td>Orion</td>
<td>speaker fees</td>
</tr>
</tbody>
</table>
Complications following mechanical prosthetic valve replacement (PVR)

1. Dysfuncion/disruption/dehisence
2. Infection
3. Embolism
4. Thrombosis
Incidence of valve thrombosis

Obstruction of a tricuspid mechanical prosthesis is 20 x more frequent than left-sided PVT

Heart 2007; 93: 137-142
lifelong for all patients with mechanical valve
for 3 months for all patients with bioprostheses
lifelong for patients with bioprostheses who have other indications for anticoagulation

Butchart EG et al. Eur Heart J. 2005, 26, 2463
Valve thrombosis – risk factors

- Inadequate oral anticoagulant therapy
- Interruption of oral anticoagulant treatment
Valve thrombosis – risk factors

- Inadequate oral anticoagulant therapy
- Interruption of oral anticoagulant treatment
INR Recommendations

1. Prosthetic thrombogenicity

2. Intracardiac Conditions = Patient - related risk factors

Butchard EG et al, Eur Heart J 2005, 26, 2463-2471
INR Recommendations

1. Prosthetic thrombogenicity

- **Low** (Medtronic Hall, SJM, Carbomedics, AVR, bioprosthesis)
- **Medium** (Bileaflet valves with insufficient data, Björk-Shiley)
- **High** (Lillehei Kaster, Omniscience, Starr Edwards)

*Butchard EG et al, Eur Heart J 2005, 26, 2463-2471*
INR Recommendations

2. Intracardiac Conditions = Patient - risk factors

- Atrial fibrillation
- Left atrium >50 mm
- Mitral valve gradient
- EF <35%
- Spontaneous echo contrast
- MVR, TVR, PVR

Butchard EG et al, Eur Heart J 2005, 26, 2463-2471
## Target INR for mechanical prostheses

<table>
<thead>
<tr>
<th>Adjust targeted INR to intracardiac conditions and prosthesis hrombogenicity</th>
<th>Without risk factors</th>
<th>With risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prosthesis thrombogenicity (as determined by valve thrombosis rates)</td>
<td>Low</td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td>Medium</td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>3.5</td>
</tr>
</tbody>
</table>

Butchart E. et al. Eur Heart J 2005; 26: 2463-71
Kaplan Meier curve of event-free period for all thromboembolism by Risk Score (total number of risk factors) for patients who underwent aortic, mitral or double valve replacement. For each curve, freedom from TE at 4 years is indicated by (●).

VALVE THROMBOSIS INR<1.5

507 pts, prospective F-U for 10 years

DISC – bileaflet valve
B&C ball-and-cage

Ann Thorac Cardiovasc Surg 2009, 15, 10-17
Fifteen years of experience with ATS mechanical heart valve prostheses

Akira Sezai, MD, a Mitsumasa Hata, MD, a Tetsuya Niino, MD, a Isamu Yoshitake, MD, a
Yuji Kasamaki, MD, b Atsushi Hirayama, MD, b and Kazutomo Minami, MD b

Freedom from valve-related complications

Freedom from thromboembolic events

J Thorac Cardiovasc Surg 2010; 139, 1494-1500
RISK OF THROMBOEMBOLIC AND BLEEDING COMPLICATIONS

Cumulative hazard rates for bleeding and thromboembolic events with higher and lower target

INR below 2.0 results in a higher risk of stroke

The estimated odds ratio subdural hemorrhage increased fold as INR increased above


Valve thrombosis – risk factors

Inadequate oral anticoagulant therapy

Interruption of oral anticoagulant treatment:
- non-cardiac surgery
- pregnancy
To bridge or not to bridge – what to do in case of noncardiac surgical procedures?
Low thromboembolic risk/low bleeding risk
Continue anticoagulant therapy eith INR in therapeutic range

Low thromboembolic risk/high bleeding risk
Discontinue VKA 5 days before the procedure
Start LMWH once daily or UFH iv 1day after acenokumarol and 2 days after warfarin interruption.
Last dose LMWH-12h before, stop UFH iv 4h before; resume at least 12h according to haemostatic status.
VKA 1-2 days after surgery at the preprocedual dose+50%.
Continue LMWH or UFH until the INR has returned to therapeutic levels.
High thromboembolic risk/high bleeding risk

Discontinue VKA 5 days before the procedure
Start LMWH twice daily or UFH iv 1 day after acenokumarol and 2 days after warfarin interruption.
Last dose LMWH-12h before, stop UFH iv 4h before; resume at least 12h according to haemostatic status.
VKA 1-2 days after surgery at the preprocedual dose+50%.
Continue LMWH or UFH until the INR has returned to therapeutic levels.
Prosthetic heart valves should not be used in young women likely to become pregnant

Pregnancy is a hypercoagulable state

↑ factor VII
↑ factor VIII
↑ X
↑ fibrinogen

Heart 2001, 85, 710-715
Fetal complications in % (n) with different anticoagulation regimes

<table>
<thead>
<tr>
<th>Regime</th>
<th>Embryopathy</th>
<th>Spontaneous abortion</th>
<th>Spontaneous fetal death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral anticoagulation during whole pregnancy</td>
<td>6.4 (35/549)</td>
<td>24.7 (196/792)</td>
<td>33.6 (266/792)</td>
</tr>
<tr>
<td>UFH during whole pregnancy</td>
<td>0.0 (0/17)</td>
<td>23.8 (5/21)</td>
<td>42.9 (9/21)</td>
</tr>
</tbody>
</table>

Chan et al., Eur Heart J 2003, 24, 761
### Maternal complications in % (n) with different anticoagulation regimes

<table>
<thead>
<tr>
<th>Regime</th>
<th>Thromboembolic complications</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral anticoagulation during whole pregnancy</td>
<td>3.9 (31/788)</td>
<td>1.8 (10/561)</td>
</tr>
<tr>
<td>UFH during whole pregnancy</td>
<td>33 (7/21)</td>
<td>15 (3/20)</td>
</tr>
<tr>
<td>UFH 1st trimester, oral anticoagulation</td>
<td>9.2 (57/230)</td>
<td>4.2 (7/167)</td>
</tr>
</tbody>
</table>

*Chan et al., Eur Heart J 2003, 24, 761*
ANTICOAGULATION DURING PREGNANCY

weeks
1 2 24 35 40

LMWH* bid

VKA
INR 2,0-3,0

LMWH* bid

* Anty-Xa level 4h after the dose -1,0 U/mL or 0,6 U/mL before
VKA -4-8h after delivery (INR 2,0-3,0)

De Caterina et al. EHJ 2007, 28, 880-913,
Elkayam U et al. JACC, 2005, 46, 403-410
PVT-clinical presentation

Massive valve thrombosis = severe symptoms

embolism
dyspnea
pulmonary edema
pulmonary edema with hypotension
Suspected PVT-diagnostic procedures

1. To assess hemodynamic severity
   - TTE and Doppler echo

2. To assess valve motion and clot burden
   - TEE and/or fluoroscopy
ECHOCARDIOGRAPHIC SIGNS OF OBSTRUCTIVE PVT

- reduced valve mobility
- presence of thrombus
- abnormal transprosthetic flow
- central prosthetic regurgitation
- elevated transprosthetic gradients
- reduced prosthetic area

Heart J 2007, 93, 137-142
Suspected PVT-TTE aortic valve
Suspected PVT-TTE aortic valve
Suspected PVT-TEE mitral valve
In prosthetic valve thrombosis, the size of thrombus is a significant independent predictor of outcome. Incidence of complications rate and death according to the thrombus area $\geq 0.8$ cm and previous stroke.
Suspected PVT-FLUOROSCOPY
Differentiation of thrombus and pannus on CT?
Prosthetic valve thrombosis – TREATMENT

Left-sided/right sided

Obstructive/non-obstructive
Risks and Benefits of Adding Anti-Platelet Therapy to Warfarin Among Patients With Prosthetic Heart Valves: A Meta-Analysis

David Massel, MD, FRCPC, Stephen H. Little, MD
London, Ontario, Canada

Odds ratio for thromboembolism

Odds ratio for major bleeding

JACC 2001, 37, 569-78
Management of left-sided obstructive prosthetic thrombosis

Suspicion of thrombosis

Echo (TTE + TEE)/fluoroscopy

Obstructive thrombus

Critically ill

Yes

No

TTE - transhoracic echocardiography
TEE - transoesophageal echocardiography

ESC Guidelines, Eur Heart J 2007, 28,230-268
Management of left-sided obstructive prosthetic thrombosis

1. Critically ill
   - Yes
     - Surgery immediately available
       - Yes
         - Surgery*
       - No
         - Fibrinolysis*

* Risk and benefits of both treatments should be individualised. The presence of a first-generation prosthesis is an incentive to surgery.
Fibrinolysis should be considered in:

- Critically ill patients unlikely to survive surgery
- Surgery is not immediately available and the patient cannot be transferred.
- Thrombosis of tricuspid or pulmonary valve replacements, because of the higher success rate and low incidence of embolism.

ESC Guidelines, Eur Heart J 2007, 28, 230-268
Fibrinolysis of Mechanical Prosthetic Valve Thrombosis
A Single-Center Study of 127 Cases
Raymond Roudaut, MD, FESC,* Stéphane Lafitte, MD, PhD,* Marie-Françoise Roudaut, MD,* Carine Courtault, MD,* Jean-Marie Perron, MD,* Catherine Jaïs, MD,* Xavier Pillois, PhD,* Pierre Coste, MD,* Anthony DeMaria, MD, FACC†
Pessac, France; and San Diego, California

Figure 2. Efficacy of fibrinolysis of prosthetic valve thrombosis.

Figure 3. Efficacy according to fibrinolytic agent: on the left, after the first single fibrinolysis treatment (FT); on the right, after complementary FT (combined therapy). rtPA = recombinant tissue-type plasminogen activator; SK = streptokinase; UK = urokinase.

mortality-10%
systemic embolism – 12.5%
JACC 1997: 30, 1521-6


**Accelerated Infusion of Streptokinase for the Treatment of Left-Sided Prosthetic Valve Thrombosis**

**A Randomized Controlled Trial**

Ganesan Karthikeyan, MD, DM, MSc; Ravi S. Math, MD, DM; Navin Mathew, MD, DM; Bhima Shankar, MD, DM; Mani Kalaivani, MSc; Sandeep Singh, MD, DM; Vinay K. Bahl, MD, DM; Jack Hirsh, MD; John W. Eikelboom, MBBS, MSc

*(Circulation. 2009;120:1108-1114.)*

**Table 3. Adverse Events With Treatment**

<table>
<thead>
<tr>
<th>Outcome, n (%)</th>
<th>Accelerated Infusion (n=60)</th>
<th>Conventional Infusion (n=60)</th>
<th>Unadjusted HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death, major bleeding, embolic stroke, or non-CNS embolism</td>
<td>11 (18)</td>
<td>9 (15)</td>
<td>1.4 (0.5–3.5)</td>
<td>0.50</td>
</tr>
<tr>
<td>Death</td>
<td>5 (8)</td>
<td>4 (7)</td>
<td>1.3 (0.3–5.2)</td>
<td>0.71</td>
</tr>
<tr>
<td>Embolic stroke or non-CNS embolic event</td>
<td>4 (7)</td>
<td>2* (3)</td>
<td>2.7 (0.5–14.8)</td>
<td>0.26</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>7 (12)</td>
<td>4 (7)</td>
<td>2.2 (0.8–7.7)</td>
<td>0.24</td>
</tr>
<tr>
<td>Intracranial bleeding</td>
<td>4 (7)</td>
<td>1 (2)</td>
<td>4.5 (0.5–43.4)</td>
<td>0.19</td>
</tr>
<tr>
<td>Other major bleeding</td>
<td>3 (5)</td>
<td>3 (5)</td>
<td>1.4 (0.3–7.0)</td>
<td>0.69</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>8 (13)</td>
<td>5 (8)</td>
<td>2.1 (0.7–6.5)</td>
<td>0.19</td>
</tr>
</tbody>
</table>

CNS indicates central nervous system.

*Values are n (%). *

*One patient had coronary embolism.

**Table 4. Independent Predictors of a Complete Clinical Response**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted HR* (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accelerated infusion</td>
<td>1.5 (0.9–2.4)</td>
<td>0.15</td>
</tr>
<tr>
<td>Better functional class (NYHA class I/II)</td>
<td>3.5 (1.7–7.2)</td>
<td>0.001</td>
</tr>
<tr>
<td>Sinus rhythm</td>
<td>1.2 (0.7–2.1)</td>
<td>0.48</td>
</tr>
<tr>
<td>Aortic PVT</td>
<td>1.3 (0.7–2.3)</td>
<td>0.37</td>
</tr>
<tr>
<td>Early PVT (within 12 mo after valve replacement)</td>
<td>1.2 (0.7–2.0)</td>
<td>0.62</td>
</tr>
</tbody>
</table>

*HRs from a Cox regression model.

**Conclusions**—The large number of patients recruited from a single center underscores the massive burden of prosthetic valve thrombosis in developing countries. Fibrinolytic therapy with streptokinase is less efficacious than previously believed. The accelerated streptokinase infusion is not better than the standard infusion for left-sided prosthetic valve thrombosis. Developing countries urgently need more effective strategies to prevent and treat prosthetic valve thrombosis. *(Circulation. 2009;120:1108-1114.)*
Management of left-sided obstructive prosthetic thrombosis

Critically ill

No

Recent inadequate anticoagulation

Yes

Heparin ± aspirin

Success

Failure

No

High risk for surgery

Yes

Fibrinolysis*

No

Surgery*

* Risk and benefits of both treatments should be individualised. The presence of a first-generation prosthesis is an incentive to surgery.
Management of left-sided non-obstructive prosthetic thrombosis – with thromboembolism

Large thrombus (≥ 10 mm)

No

Optimize anticoagulation follow-up

Yes

Disappearance or decrease of thrombus

Persistence of thrombus

Recurrent TE?

No

Follow-up

Yes

Consider surgery or fibrinolysis if surgery is at high risk

Surgery if no high-risk

ESC Guidelineres, Eur Heart J 2007, 28,230-268

TE - thromboembolism
Self-managed patients more often achieved an INR within the target range.

GELIA 4 Database
2024 patients

Figure 1  International Normalized Ratio (INR) measurements for oral anticoagulation after aortic valve replacement with a St. Jude Medical prosthesis, according to target INR range.

Huth C et al. Eur Heart J 2001, 3, Q33-Q38
NEW ORAL ANTICOAGULANTS – ALTERNATIVES TO VKA IN PATIENTS WITH MECHANICAL VALVES?

- TTP889
- Rivaroxaban
- Apixaban
- LY517717
- YM150
- DU-176b
- Betrixaban
- TAK 422
- Dabigatran
- Ximelagatran

Adapted from Weitz JI. J Thromb Haemost. 2007;5:65-7
NEW ORAL ANTICOAGULANTS – ALTERNATIVES TO VKA IN PATIENTS WITH MECHANICAL VALVES?
Summary

• Adequate anticoagulant therapy after valve replacement is obligatory

• PVT is an urgent clinical condition

• Therapeutic strategy depends on prosthesis location, valvular obstruction and patient’s clinical condition
Prof. Andrzej Biederman  
Dr Lidia Greszata  
Prof. Piotr Hoffman  
Dr Ilona Michałowska  
Prof. Adam Witkowski  

THANK YOU!