Antithrombotic Therapy in patients with Valvular Heart Disease

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Introduction:
Thromboembolism and anticoagulant related bleeding are the most common life threatening complications in patients with valvar heart disease. The optimal anticoagulant intensity, define as, the level at which thromboembolic complications are effectively prevented without excessive bleeding. We will examine various forms of valvular heart disease and their antithrombotic therapy.

Mitral stenosis:
The identification of risk factors for systemic embolism in patients with mitral stenosis in sinus rhythm are age, left atrial size (>55mm by echocardiography based on grade 2C given by American College of Chest Physicians Sixth Consensus Conference on Antithrombotic Therapy (ACCP) [4] and >50 mm by echocardiography, a lower threshold of the atrial size for the European Society of Cardiology), and previous or embolic event. These risk factors supports the use of anticoagulation International normalized ratio (INR) 2.5 (range 2 to 3), a IIb recommendation for left atrial size and I por previous embolism for the American College of Cardiology and American Heart Association (ACC/AHA) [5] and a grade 2C recommendation for the ACCP [7].

If recurrent systemic embolism occurs despite adequated anticoagulation, the addision of aspirin 100mg/d or increase the target INR to 3.0 (range 2.5 to 3.5) (figure 1).

<table>
<thead>
<tr>
<th>European Society of Cardiology INR range</th>
<th>British Society of Haematology INR target</th>
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<tbody>
<tr>
<td>Rheumatic valvar heart disease</td>
<td>3.0-4.5</td>
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<tr>
<td>Patients with recurrent emboli under adequate anticoagulation</td>
<td>3.0-4.5 + 100 mg/d aspirin</td>
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Percutaneous balloon valvuloplasty:
In patients with mitral stenosis, transesophageal echocardiography needs to rule out the presence of left atrial thrombus, in it presence, valvuloplasty is deferred and anticoagulatnt treatment started with a target INR 2.0
In the absence of atrial thrombus but in presence of risk factors (previous thromboembolism, atrial fibrillation, enlarged left atrium) oral anticoagulant treatment should be started.

**Mitral Valve Prolapse:**
Mitral valve prolapse is the most common form of valve disease in adults, the risk of stroke is only 1/6.000/yr [8]. At the time, to be no clinical or echocardiographic marker that clearly identifies patients at risk for ischemic events [7] ACCP recommendation grade 1C. In patients with Mitral Valve prolapse who have documented but unexplained transient ischemic attacks the recommendation is long-term low-dose aspirin therapy (grade 2C) or class I [5] long-term oral anticoagulant is recommend target INR 2.5 rge 2 to 3 for those who have documented systemic embolism or atrial fibrillation despite aspirin therapy. Grade 1C recommendation.

**Mitral Annular calcification (MAC):**
The estimate of thromboembolic potential of mitral annular calcification comes from the Framingham Heart study [10], the relative risk (rr) of stroke in those with MAC was 2.1 times that without MAC (p=0.006).

There is little reason to believe that anticoagulant therapy would be effective in preventing calcific emboli, established by pathological examination of the embolus [23] The anticoagulation therapy should be discouraged merely on the basis of radiographic evidence of MAC.

Patients with MAC and associated atrial fibrillation should be treated with oral anticoagulation INR 2.5 (range 2.0 to 3.0) grade 1C+ [7].

**Antithrombotic therapy in prosthetic heart valves:**
**Bioprosthetic valves:**
There are different types of bioprosthetic valves (figure 2).

The frequency of long-term thromboembolic events/year (3 months after valve insertion) is 0.2 to 2.6%/yr [24,25,26, 27,28,29] but is high in the first 3 months 5.0% specially for mitral position [11,12] an INR of 2.0 to 2.3 was safe [12] The ACCP recommended INR target 2.5 (range 2.0 to 3.0) during the first 3 months, grade 1A [14] for bioprosthetic valves in aortic or mitral position. The same recommendations are for the ACC/AHA task force [5] because of the high risk of thromboembolism after valve replacement, heparin therapy (low molecular weight or unfractionate d) might be used until INR is at therapeutic levels (grade 2 C recommendation) Patients with bioprosthetic valves who have thromboembolic risk factors (atrial fibrillation) long-term oral anticoagulation is recommended, allof the patients with thromboemboli had atrial fibrillation [13].
The ACCP recommended oral anticoagulation in patients with bioprosthetic valves and evidence of atrial thrombus at surgery (grade 1C), previous thromboembolus (grade 2C), permanent pacemaker (grade 2C). These recommendations are not based on published studies. The duration of the therapy is uncertain [14].

Aspirin therapy may reduce the long-term frequency of thromboembolism in patients with bioprosthetic valves [15]. The ACCP, ACC/AHA recommended it.

**Mechanical Prosthetic Heart Valves:**
There are different types of mechanical valves (figure 3).

The first prosthetic cardiac valve was implanted in 1952 [1] since then different types have developed the difference between them are their lasting, the thrombogenicity, and hemodynamic conditions. Mechanical valves are more durable than bioprosthetic valves, but the thrombogenicity is great, patients require lifelong anticoagulation therapy (Figure 4.5) [1,2].
According to valves classification antithrombotic therapy can be optimised

The frequency of thromboembolic events in old generation valves or first generation are 2.5 per 100 patients -year compared with single tilting disc 0.7 per 100 patients-year and 0.5 per 100 patients-year in bileaflet. The overall risk of thromboembolism is influenced by the position of the valve, 0.5 per 100 patients-year for aortic position, 0.9 per 100 patients-year for mitral and 1.2 per 100 patients-year among with aortic and mitral valve [16]. The risk of thromboembolism is very low among younger patients, an incidence 0.1 per 100 patients-year.
in younger than 50, 0.8 per 100 patients-year among patients between 50 and 69, and 11.1 per 100 patients-year among those 70 or older.

Multiple trials compared different intensity of anticoagulant therapy in patients with mechanical heart valve [30,31,32]. The analysis of results of several investigations suggests that an INR of 2.2.5 to 3.5 is satisfactory.

The European guidelines, European Society of Cardiology (1995) and The British Society of Haematology (1998) suggest INR 3.4 (range 3.0 to 4.5) among patients with first generation valves. The AHA/ACC (1998) and ACCP (2001) suggest INR 2.0 to 3.0 for aortic position and 2.5 to 3.5 to mitral position (figure 6,7,8).

<table>
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<tr>
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<th>European Society of Cardiology</th>
<th>British Society of Haematology</th>
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<tbody>
<tr>
<td>mechanical</td>
<td></td>
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<tr>
<td>First generation</td>
<td>3.0 to 4.5</td>
<td>3.5</td>
</tr>
<tr>
<td>Aortic second and third generation</td>
<td>2.5 to 3.5</td>
<td>3.5</td>
</tr>
<tr>
<td>Mitral</td>
<td>3.0 to 3.5</td>
<td>3.5</td>
</tr>
<tr>
<td>biological</td>
<td></td>
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</tr>
<tr>
<td>Aortic</td>
<td>2.5 to 3.0 for 3 months</td>
<td>Aspirin 100mg/d</td>
</tr>
<tr>
<td>Mitral</td>
<td>3.0 to 3.5 for 3 months</td>
<td>2.5 for 3 months</td>
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Aspirin combination with oral anticoagulants in patients with mechanical heart valves:
Turpie et al. [17] showed that 100 mg/d in combination with oral anticoagulants at an INR of 3.0 to 4.5 was associated with fewer major systemic thromboemboli or death from vascular causes than oral anticoagulant alone, 1.9%/yr vs 8.5%/yr (p=0.001). The rate of major bleeding, 8.5%/yr vs 6.6%/yr (p=NS). Meschengieser et al. [18] showed that aspirine 100 mg/d in combination with oral anticoagulants at INR of 2.5 to 3.5 was as effective as oral anticoagulants at INR of 3.5 to 4.5.
At INR of 2.0 to 3.5 the frequency of bleeding is no greater with aspirin 325 mg to 660 mg/d than with 100 mg/d [33,34]. Low doses of aspirin did not increase the risk of major bleeding. The combination of oral anticoagulant with aspirin may be particularly useful in patients with prosthetic valves who have coronary artery disease or stroke [14].

For patients with mechanical prosthetic heart valves who suffer systemic embolism despite adequate therapy with oral anticoagulants, 100 mg/d of aspirin is recommended.

**Antithrombotic therapy in special circumstances:**

**Dental procedures:**
Measure INR before the procedure is recommended. It should be adjusted to therapeutic range where blood loss is expected to be minimal. Bleeding can be stopped with oral tranexamic acid mouth wash [35], local hemostasis is recommended. Antimicrobial prophylaxis should be given.

**Surgical procedures:**
For major non-cardiac surgical procedure, in which there is a substantial risk of bleeding, anticoagulant should be discontinued for 4 to 5 days before surgery and INR should be normalized at 1.0. The risk of thromboembolism increases, and so interim heparin treatment should be given in a dosage that prolongs aPTT to twice the control value. The aPTT should be near normal at the time of surgery.

**Antithrombotic therapy during pregnancy in patients with prosthetic heart valves:**
The oral anticoagulants cross the placenta and are associated with bleeding and teratogenicity, the embryopathy, which consist of nasal hypoplasia and or stippled epiphyses, between 6 and 12 weeks of gestation [37] in 6.4% of live births [36].

Unfraction heparins (UFH) and low molecular weight heparins (LMWH) do not cross the placenta, the LMWH is not approved by FDA to be use in pregnancy, they are safe for the fetus [38].

Three approaches of clinical practice are described by the ACCP, oral anticoagulants throughout pregnancy (in widespread use in Europe) that was associated with the lowest risk of thromboembolic complications (3.9%) and overall mortality 1.8%. The second approach is replacing oral anticoagulant with UFH from 6 to 12 weeks, this was associated with increased risk of thromboembolism (9.2%) with overall mortality rate 4.2%. The third approach is UFH throughout pregnancy that needs aggressive monitoring and appropriate dose adjustment, long-term heparin therapy cause osteoporosis (Figure 9).

<table>
<thead>
<tr>
<th>Anticoagulation regimen</th>
<th>Thromboembolic complications</th>
<th>Mortality</th>
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<tbody>
<tr>
<td>Oral anticoagulation throughout pregnancy</td>
<td>31/788 (3.9)</td>
<td>10/561 (1.8)</td>
</tr>
<tr>
<td>Heparin use in first trimester then oral anticoagulant</td>
<td>21/229 (9.2)</td>
<td>7/167 (4.2)</td>
</tr>
<tr>
<td>Heparin throughout pregnancy</td>
<td>7/21 (33.3)</td>
<td>3/20 (15.0)</td>
</tr>
<tr>
<td>no anticoagulation</td>
<td>6/38 (15.8)</td>
<td>2/37 (5.4)</td>
</tr>
<tr>
<td>Only aspirin</td>
<td>20/69 (29.0)</td>
<td>3/69 (4.4)</td>
</tr>
</tbody>
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Slide 9: Maternal mortality and thromboembolic complications with various anticoagulant regimens.
Antithrombotic therapy in prosthetic valve endocarditis:

The ACCP recommended long-term oral anticoagulant in mechanical prosthetic endocarditis unless there are contraindications (grade 2C).

References

7. Salem et al Antithrombotic Therapy in valvular Heart Disease; Chest; 119 (1) 207-2155, 2001
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