Early antithrombotic management after valve replacement

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Because of the substantial risk of thromboembolism early after valve replacement, perioperative initiation of anticoagulation is necessary, despite the increased risk for bleeding. Anticoagulation should be initiated within 24 h after the procedure with unfractionated heparin or low-molecular-weight heparin (LMWH). Subcutaneous LMWH appears more beneficial than intravenous heparin therapy, but this approach requires further evaluation. Oral anticoagulants, preferably at low dosage, are added following the removal of chest tubes. Heparin anticoagulation is monitored by checking the activated partial thromboplastin time or anti-Xa activity, and the International Normalized Ratio (INR) is used to measure the effects of oral anticoagulants. Heparin treatment should be continued until the INR is stable in the therapeutic range in order to avoid hypercoagulable conditions caused by varying degrees of decay in coagulation factors.

Key Words: Early antithrombotic management, heart valve replacement, monitoring of oral anticoagulation.

Introduction

The risk for thrombus formation associated with prosthetic heart valves is up to seven times greater within the first month after valve replacement than it is during the following months and years, irrespective of the intra-cardiac position of the device[1]. Underlying pathophysiological factors are activation of the extrinsic and intrinsic coagulation systems by synthetic surfaces of the extracorporeal circulation, or by contact of blood with foreign surfaces (sutures, sewing ring, occluder), or at sites of collagen or denuded tissue[2–4]. Shear stress arising in the vicinity of valvular implants adds activated platelets as a source of thrombus[5]. Frequently, arrhythmias and perioperative haemodynamic disturbances further increase the thromboembolic risk. Coagulopathy results from activation of coagulation and decrease in inhibitors, and a reactive increase in fibrinogen and platelet count (following an initial decrease caused by platelet consumption and complement activation during extra-corporeal circulation)[6].

The importance of chronic anticoagulation after heart valve replacement with mechanical devices is generally accepted; recommendations for anticoagulation[7–11] have been formulated by several working groups (Table 1). Those guidelines were recently redefined with respect to the level of anticoagulation and laboratory monitoring required, but provide only scarce information regarding early management of anticoagulation after heart valve replacement. This is due to a lack of randomized studies that address this important issue.

The following aspects of anticoagulation management during the immediate postoperative period are of major interest: when anticoagulation should be started; what dosage of oral anticoagulant is appropriate; how anticoagulation should be monitored; and how anticoagulation should be managed until stable oral anticoagulation is achieved.

Introduction of anticoagulation during the immediate postoperative period

Early anticoagulation with unfractionated heparin (UFH) is recommended[7–11], but great variation exists among protocols in various surgical units and countries. A substantial number of surgeons favour delay of anticoagulation because of the risk of bleeding. The incidence of pericardial tamponade and surgical reintervention is up to eight times greater in patients treated with high-dose heparin than in those treated with low-dose heparin for prevention of venous thrombosis[12,13]. Clinical symptoms of tamponade can be delayed by several weeks...
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is generally greater following heart valve surgery
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decrease in albumin, reduced concentrations of coagulation
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factors, the state of the protein C system at the end of extra-
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necrosis with higher warfarin loading doses in patients with
loading doses of warfarin in order to shorten the time period
until the desired level of anticoagulation is achieved. This
strategy has obvious disadvantages; an International
Normalized Ratio (INR) greater than 2 is achieved
significantly earlier with a loading dose of 10 mg or greater
than with a dose of 5 mg, but higher INR values do not
indicate sufficient antithrombotic effects[14,15]. INR increase
reflects early reduction in factor VII (half-life 5 h), whereas
factor II (half-life 72 h) is still in a non-therapeutic range.
Also, further depression of thrombin formation cannot be
achieved with higher loading doses of oral anticoagulant[16].
Combined with a rapid decrease in levels of vitamin K
dependant inhibitor protein C, a temporary hypercoagulable
state can result. Furthermore, the higher incidence of cutis
necrosis with higher warfarin loading doses in patients with
protein C deficiency supports the recommendation to
employ low-dose initiation protocols. In addition, high-dose
protocols may result in hypocoagulation and increased risk
for bleeding, because the individual response to coumarins
is generally greater following heart valve surgery[17]. A
decrease in albumin, reduced concentrations of coagulation
factors, the state of the protein C system at the end of extra-
corporeal circulation, and advanced age account for this
finding[17–19]. Current guidelines recommend that dosage
regimens be adapted to the patient’s condition, age, and
heart and liver function. For the majority of patients after
heart valve replacement, doses of less than 10 mg warfarin
appear preferable[8,20]. That finding is from studies that
addressed the use of warfarin, but no similar studies that
address use of phenprocoumon exist.
Platelet activation caused by shear stress may be
anticipated as a source of thrombus formation on mechanical
heart valve surfaces[5]. This has led to the recommenda-
tion to administer a platelet inhibitor to patients with
significant risk factors or previous thromboembolic
events[8]. Studies that added aspirin to warfarin showed
benefits with regard to thromboembolic complications, but
also reported increased risk of bleeding[21]. Therefore, at
present, platelet inhibitors cannot be recommended during
the early postoperative period.

**Dosage regimen of coumarins**

In the past, oral anticoagulation was initiated with high
loading doses of warfarin in order to shorten the time period
until the desired level of anticoagulation is achieved. This
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**Concomitant heparin therapy**

In the current guidelines the use of UFH is recommended
early after the procedure[7–11]. As additional experience is
gained with other indications, the use of low-molecular-
weight heparin (LMWH) must be considered. Thus far no
controlled studies have been conducted regarding LMWH
and the initiation of oral anticoagulation. The following
characteristics support the use of LMWH during the
induction of oral anticoagulation[22]; longer half-life; more
 predictable dose responses; reduction in the need for
laboratory monitoring; and greater bioavailability following
subcutaneous administration, allowing a more convenient
mode of administration without the need for an intravenous
line.
LMWH has been used in selected cases after the
immediate postoperative period, when anticoagulation
stabilizes, because of pregnancy[23] or contraindications to
coumarins[24], with favourable results. Cases of treatment

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**Table 1 Guidelines for the management of patients with prosthetic heart valves**

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<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Type of heparin</td>
<td>UFH</td>
<td>UFH</td>
<td>UFH</td>
</tr>
<tr>
<td>Start of heparin</td>
<td>Heparin and coumarins on first postoperative day, or heparin on first postoperative and coumarins later</td>
<td>–</td>
<td>Controversial</td>
</tr>
<tr>
<td>Duration of heparin therapy</td>
<td>Until therapeutic INR is reached</td>
<td>Until INR is within the therapeutic range for more than 2 days</td>
<td>Controversial</td>
</tr>
<tr>
<td>Coumarin dosage</td>
<td>No recommendation for starting dose, because it depends on the indication, coagulative and clinical status, age and heart failure; oral anticoagulation should be initiated cautiously</td>
<td>10 mg warfarin, unless elderly, congestive cardiac failure, liver disease, or weight less than average body weight</td>
<td>No recommendation for starting dose. INR level depends on valve type (bileaflet versus tilting disk) and position</td>
</tr>
<tr>
<td>Monitoring</td>
<td>UFH: aPTT (double aPTT)</td>
<td>UFH: aPTT Warfarin: INR</td>
<td>Warfarin: INR</td>
</tr>
</tbody>
</table>

aPTT=activated partial thromboplastin time; INR=International Normalized Ratio; UFH=unfractionated heparin.

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following the start of anticoagulation. Occurrence of this threatening complication is frequently associated with episodes of hyper-anticoagulation[13]. Therefore, protocols should aim to avoid over-aggressive anticoagulation.
failure can clearly be attributed to inadequate doses\textsuperscript{[25]}. Montalescot \textit{et al.}\textsuperscript{[26]} conducted a comparative, non-randomized study in patients following after heart valve replacement. Those investigators demonstrated that therapeu tic anti-Xa levels can be achieved within 2 days after starting LMWH administration in more than 90% of patients treated with weight-adjusted doses, without an increase in bleeding or incidence of thromboembolic complications.

LMWH may carry a substantial economic advantage in the present era of diminishing resources. Intravenous heparin therapy often prolongs hospital stay, whereas the use of LMWH could allow ambulatory care and thereby might significantly reduce hospital costs. Laboratory controls are not needed (as demonstrated with treatment of deep vein thrombosis\textsuperscript{[27]}), except for conditions that lead to the accumulation of LMWH, thus making treatment easier. More intensive use of LMWH requires further evaluation in prospective randomized studies, however.

### Monitoring

Currently, INR has replaced partial thromboplastin time as a laboratory parameter for monitoring anticoagulation with oral anticoagulants\textsuperscript{[7-11]}. During the initial phase of oral anticoagulation, however, INR in the therapeutic range does not necessarily indicate sufficient anticoagulation because of the different half-lives of the coagulation factors\textsuperscript{[28]}. Continuation of heparin therapy for 2 consecutive days once INR is in the therapeutic range is advisable to prevent potential thromboembolic events\textsuperscript{[8,28]}. If intravenous UFH is used, then partial thromboplastin time should be measured\textsuperscript{[9]}. LMWH requires laboratory testing (anti-Xa activity) only in those patients with an increased risk of accumulation (renal insufficiency, pregnancy, very high/low body weight) or abnormal bleeding characteristics\textsuperscript{[29]}.

### Conclusion

In order to prevent early thromboembolic complications after heart valve replacement, anticoagulation should be started within 24 h after the procedure using intravenous UFH or subcutaneous LMWH. Sufficient anticoagulation can be achieved with subcutaneous LMWH. Laboratory testing is only necessary in those cases in which there is a risk of LMWH accumulation. With UFH, frequent monitoring of partial thromboplastin time is mandatory. Further studies are necessary to evaluate whether LMWH is associated with a higher incidence of bleeding complications. Oral anticoagulation should be initiated preferably with low doses of coumarins in order to avoid hypercoagulable conditions. INR levels measured early post-operatively do not represent the actual coagulation status because of the high sensitivity of the thromboplastin reagents to factor VII. Therefore, heparin treatment should be continued until INR is within the therapeutic range for more than 2 days, or molecular markers should be recorded to improve management. There is a need for further data regarding the management of early anticoagulation following heart valve replacement.

### References


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