

## PRACTICE REVIEWED

## Anticoagulation after intracoronary stent insertion

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Early indications from trials suggest that elective stent implantation may prevent restenosis after percutaneous transluminal coronary angioplasty (PTCA).<sup>1,2</sup> None the less the subacute thrombotic closure rate was 4% in patients in these trials. When stents are placed because of a poor angiographic result or as a bail-out procedure (currently the most accepted uses for stents) 4-14% become thrombosed.<sup>3,4</sup> Stent placement is thus associated with a relatively high risk of thrombosis. We believe that the risk of this potentially lethal process (myocardial infarction rate 4%<sup>5</sup> to 75%<sup>3</sup> and mortality as high as 20%<sup>6</sup>) may be reduced by careful attention to anticoagulation control. Based on advice from haematologists and on haematological principles, we devised an anticoagulation protocol for stent implantation. This protocol is now established in our unit and we have had no stent thrombosis in our last 50 procedures. Because randomised trials of anticoagulant strategies after stenting are difficult to perform we report on the protocol used in our unit and invite debate.

**A proposed anticoagulant strategy****PRE STENT DELIVERY**

The day before elective stenting patients are given a first dose of warfarin (10 mg). This is given with aspirin (300 mg) and an infusion of dextran 40 is started at a rate of 50 ml/h and continued for 24 hours. After the arterial sheath is inserted we give a bolus of 10 000 IU of heparin intravenously. Though this usually produces effective anticoagulation by the time of stent insertion, the activated clotting time (ACT) must be measured. If the bolus dose does not produce an ACT of >300s a further bolus of 2500 IU heparin is given. In unplanned stenting it is important to check that the patient has received aspirin and that the ACT is >300 seconds.

**POST PROCEDURE**

Measurements in our last 50 cases indicated that after a bolus of 10 000 IU of heparin it takes a mean 3.5 hours (range 3-7 hours) before the activated partial thromboplastin time (APTT) falls within the laboratory range. Once the patient returns to the ward we measure the APTT every 90 minutes. Femoral sheaths should be removed on the

day of stent implantation once the APTT has fallen (probably about 4 hours after the heparin bolus). Four to six hours after removal of the femoral sheath (to ensure good haemostasis) we give a further bolus of 2 500 IU of heparin followed by an intravenous infusion of heparin, initially at a dose of 1000 IU/h. The APTT ratio is maintained within the range of 2.0:1-2.5:1 which allows subsequent accurate INR measurements. An initial dose (10 mg) of warfarin is given (this will be the first dose if the stent has been unplanned) and thereafter appropriate daily doses are given to achieve an INR of 2.5:1-3.0:1.

When the risk of stent thrombosis is F1 and F2 (see below), high assays of prothrombin if available, are performed each day. To ensure complete warfarin inhibition of prothrombin intravenous heparin is generally required for between 72 hours and 96 hours after the first dose of warfarin. Even though the INR may be within the therapeutic range after the second dose, the half life of factor II is 96 hours and complete anticoagulant control cannot be guaranteed until after this time. In our experience the mean time taken to achieve a "steady state" for anticoagulation in unplanned stents is 4 days. If the assays show an increase in prothrombin F1 and F2 during this time we increase the heparin dose after a further bolus of 2500-5000U IV. It has been suggested that when concentrations of the F1 and F2 fragments increase to more than 1.0 nmol/l intravenous urokinase (500 000 units) should be given because such a high concentration indicates active thrombus formation. Heparin can be stopped once it has been given for up to 96 hours after start of warfarin and the INR is stable at 2.5:1-3.0:1. Six hours later we routinely recheck the INR because heparin may have induced a falsely high result, and the INR should not be allowed to fall to below 2.0:1. The warfarin dosage should be tailored to maintain the appropriate INR for one month after the procedure.

Patients with suboptimal angiographic outcome after stent insertion are at even greater risk of subacute stent thrombosis. Either these patients can be regarded as now having had a temporary stent with coronary artery surgery scheduled for the next available space, or vigorous treatment with urokinase

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Accepted for publication  
9 February 1994

can be attempted to reduce any thrombotic tendency. There are no trials to indicate that this is the correct thing to do, however. When the result seen after stenting is less than perfect we re-examine these patients with a 5F catheter while they are being treated with warfarin. The result of this examination helps us to decide whether to discharge them or to refer them for surgery.

### Anticoagulants and stents

#### WHAT TO USE AND WHY?

Heparin and warfarin remain the mainstay of anticoagulation but the interaction between them may be more complex than appreciated. Heparin binds to antithrombin III and this complex inactivates several coagulation enzymes, including thrombin and activated factors X, XII, XI, and IX.<sup>7</sup> Heparin treatment is routinely monitored by measuring the APTT, ratio which should be kept within the range of approximately 1.5:1–2.5:1. We have tested a commercially available bedside kit for its accuracy against laboratory values. The kit values for 82 separate values correlated well with laboratory values ( $r = 0.8$ ), and we now use these kits for the rapid determination of APTT ratios (<3 minutes). After an initial capital outlay the kits are cheaper than laboratory assays when used out of normal working hours. Warfarin is rapidly absorbed from the gastrointestinal tract and there is a direct relation between the dose of warfarin and the anticoagulant response, although there is considerable variation in dose response between subjects.<sup>8</sup> Warfarin exerts its effect by limiting the carboxylation of the vitamin-K-dependent coagulation proteins, prothrombin, factor VII, factor IX, and factor X. The anticoagulant effect of warfarin may be delayed until clotting factors already circulating are completely inhibited.<sup>9</sup> Warfarin also inhibits the production of anticoagulant proteins C and S and because proteins C, like prothrombin, has a short half life the protective effects of protein C pathways may be lost before the coagulant pathways are inhibited. This may result in a paradoxical hypercoagulable state during the first 24–48 hours of oral anticoagulant therapy.<sup>10</sup> Though some anticoagulation occurs within 24 hours, peak anticoagulant activity may be delayed for between 72 and 96 hours because of the longer half lives of factors II, IX, and X<sup>11</sup> (half life of prothrombin 96 hours). There is good evidence to suggest that an important and underestimated effect of heparin on the coagulation system may be through its inhibition of thrombin-induced activation of factor V and factor VIII, which thus extends the effect of heparin into the “extrinsic” system, though it acts primarily through the intrinsic system.<sup>12–14</sup> This means that methods of monitoring the extrinsic system (INR) may give falsely high results during the concurrent administration of heparin.

Because we cannot be sure that the INR value accurately reflects warfarin anticoagulation, it has been suggested that heparin treat-

ment should be stopped for 4 hours or until the effects of heparin are negligible before the INR is measured. But this would increase the risk of thrombus production and bolus doses of heparin will be needed to re-establish adequate anticoagulation once the sample has been taken for INR measurement. Because this protocol is likely to result in peaks and troughs in heparin concentrations it cannot be recommended. It is better to titrate the heparin dose carefully so that the APTT ratio is maintained in the range of 2.0:1–2.5:1. Within this range the expected maximum percentage increase in the INR will be about 3% (range up to 17%).<sup>15</sup> Because the INR may fall after the heparin infusion is stopped, it should be rechecked after 6 hours. When an INR result is needed urgently and the APTT ratio is high the laboratory can be asked to add protamine to the sample to remove any heparin effect.

### Other methods of monitoring anticoagulation

#### ACTIVATED CLOTTING TIME MEASURED AT THE BEDSIDE

The activated clotting time (ACT) is a simple test that can be done in the catheter laboratory and at the bedside. There is no direct relation between the ACT value and the APTT, however. This is to be expected since the APTT is essentially monitoring the intrinsic pathway and the ACT is monitoring both the intrinsic and extrinsic pathways. An ACT of >300 seconds is, however, desirable before the stent is inserted. When the ACT has fallen to <150 seconds it is probably safe to remove the femoral sheaths, though in our unit we measure the APTT ratio too because there is no correlation between the two measurements. Currently it is routine clinical practice to measure the ACT at stent placement and the APTT thereafter. This approach is the result of kits for measuring ACT being available and giving a quick result.

#### PROTHROMBIN FRAGMENTS F1 AND F2

The conversion of prothrombin to thrombin produces prothrombin fragments F1 and F2. This conversion can be used as a marker for activation of the coagulation system.<sup>16</sup> Both oral anticoagulants<sup>17</sup> and heparin<sup>18</sup> reduce F1 and F2 concentrations. F1 and F2 concentrations have been used to monitor anticoagulation after stent insertion<sup>19</sup> and it has been suggested that the concentration of F1 and F2 should be maintained below 0.8 nmol/l by increasing the heparin dose. We believe that when subacute thrombosis is likely (say after stent implantation for acute closure secondary to dissection) the expense and effort required to monitor F1 and F2 concentrations and adjust the heparin dose can be justified.

#### THROMBIN-ANTITHROMBIN COMPLEX

The thrombin-anti-thrombin (TAT) complex has also been used as a marker for evolving

stent thrombosis. In their study Gulba *et al* increased the heparin dose by 250 IU/h from a baseline heparin dose of 1250 IU/h when the TAT concentration exceeded  $6 \mu\text{g/l}$ .<sup>20</sup> In 24% of patients dose increases were required to suppress the TAT and F1 + F2 concentrations. No controlled study to date has confirmed that monitoring either F1 + 2 or TAT significantly reduces thrombotic occlusion rate.

### Summary

Stents rarely thrombose in the first 24 hours after implantation; secondly, heparin has some influence on the extrinsic pathway. Additionally, if too much heparin is present it interferes with the INR, and the half life of prothrombin suggests that the patient should be anticoagulated with heparin for up to 96 hours after starting warfarin. This is the evidence on which our standard protocol is based.

### Areas of controversy

Debate about the use of anticoagulants and stents continues. Researchers in Italy using intravascular ultrasound to ensure full and accurate stent placement<sup>21</sup> reported that anticoagulation with warfarin may not be required. This claim needs to be supported by large multicentre trials. The group in Italy still uses aspirin and ticlopidine.

The eventual aim must be to produce a non-thrombogenic stent. Trials are about to start to measure the incidence of stent thrombosis and restenosis with polymer coated stents with incorporated heparin (Benestent II). The results of this and other trials are awaited with interest, but it will be surprising if heparin is a powerful enough antithrombotic agent to inhibit the degree of platelet rich thrombus formation that results in stent occlusion. Much of the experimental work on heparin-coated stents is based on a model of normal coronary arteries,<sup>22</sup> in which stent thrombosis is much less likely than in the prothrombotic local environment found after angioplasty. Early experimental work is underway to assess the effect of the more powerful antithrombins (such as hirudin). Their efficacy may be increased when they are used with powerful antiplatelet agents (such as the glycoprotein IIb/IIIa receptor blockers). In addition limitation of thrombin generation may have an important impact on subsequent smooth muscle cell proliferation.<sup>23</sup>

Other groups in Europe are using low molecular weight heparin or ticlopidine, and

some are starting trials to compare ticlopidine with aspirin.

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