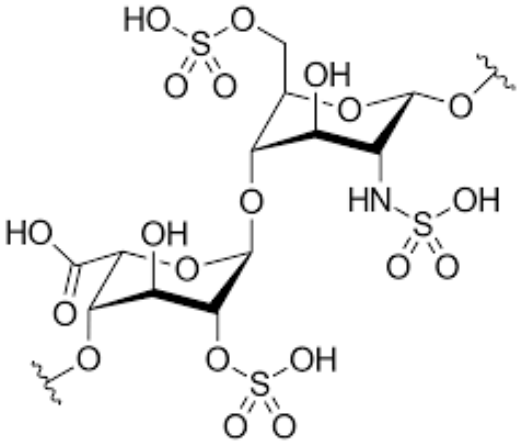
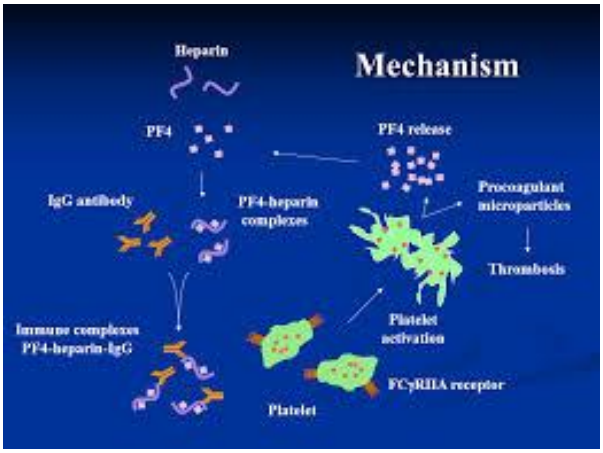
# The Royal Melbourne Hospital

## Management of Heparin Induced Thrombocytopenia (HIT) Patients undergoing Cardiac Surgery



# Management of Heparin Induced Thrombocytopenia (HIT) Patients undergoing Cardiac Surgery

## Protocol for Bivalirudin Anticoagulation during Cardiac Surgery

### CPB dosing and monitoring protocol:

Systemic Bolus (Anaesthesia – Central line): 1.0mg/kg body weight
Infusion: 2.5mg/kg/hour
CPB Prime: 50mg

Bivalirudin level monitoring by ACT: 2.5 or more (480 sec) then baseline ACT indicates adequate anticoagulation, once on CPB check ACT every 20 minutes.

If ACT drops below target, increase bivalirudin infusion rate alternatively, maintain the same infusion rate and give repeat boluses of 0.25mg/kg to maintain ACT in therapeutic range, do not reduce infusion rate if ACT exceeds target.

As with all current direct thrombin inhibitor, there is no known reversal agent, for this reason it is expected that patients may experience more than normal amount of post-operative bleeding.

Bivalirudin infusion is discontinued when it is estimated that 15 minutes remain prior to the discontinuation of CPB. If CPB is not terminated within 20 minutes following discontinuation of the infusion, an additional bolus of 0.5mg/kg of bivalirudin is to be administered and the infusion restarted at 2.5mg/kg/hr until CPB is terminated.

Alternatively: Bivalirudin infusion is discontinued at cessation of bypass. The circuit should be flushed through with Plasmalyte 148 and the blood collected in a blood transfer bag to be transfused back into the patient. If you need to run back on bypass, then the above protocol applies to restarting bivalirudin.

After discontinuation of bypass ACT should be monitored for few hours and transfusion protocol for bleeding is the same as any post cardiac surgery protocol. Platelets should be maintained >100,000.

## Management of CPB:

- Due to the unique pharmacology of bivalirudin, stasis in the CPB circuit should be minimised**.**
- Maintain a constant flow through recirculation line in cardioplegia circuit.
- When repeating cardioplegia doses, discard the stagnant blood in the cardioplegic lines from heat exchanger to cardioplegic cannula (use discard sucker to eliminate it from operation table) to avoid danger of thromboembolism of coronary arteries.

- Due to the fact that bivalirudin can be eliminated by hemofiltration, the use of ultrafiltration/haemoconcentration is discouraged during CPB.
- Due to enzymatic metabolism of bivalirudin, hypothermia may lead to drug accumulation therefore periods of hypothermia should be brief, and if possible only mild hypothermia (30-34) should be instituted.
- Cell saver should be used with a citrate-based solution (citrate phosphate dextrose [CPD}, acid citrate dextrose [ACD], Sodium citrate) is recommended for flushing line.
- Recirculate the CPB circuit after coming off bypass with 50 mg bolus of bivalirudin with 50mg/hr infusion.
- Not to use heparin-bonded circuits and to remove all heparin from Perfusion cart prior to the patient entering the room.
- Patients with creatinine clearance below 30ml/min have not been studied in cardiac surgery.

## Considerations for grafts handling in CABGs

Assessments of grafts for patency and leakage should be performed with saline or, if bivalirudin containing blood is used, grafts should thereafter be flushed with saline and “bulldogged” while applying pressure on the saline syringe. If a mammary artery is used for grafting, the vessel should be transacted shortly before grafting in order to avoid stasis and potential risk of thrombus formation in the graft.

## Bivalirudin dose for Off-pump Surgery

- 0.75mg/kg bolus, followed by
- 1.75mg/kg/hr infusion with option to adjust by 0.25mg/kg/hr, or
- To administer additional boluses 0.1 to 0.5mg/kg to maintain ACT > 300 seconds.
- Discontinue bivalirudin at discretion of surgeon / anaesthetist, normally stopped 15 minutes before flow is restored to all grafts or at a time protamine would have normally been given.

## Bivalirudin in ECMO

Bivalirudin as the sole anticoagulant can be safely used for post-cardiotomy ECMO, with a better coagulation profile, less bleeding, and allogeneic transfusions. Bivalirudin dose of 0.1 – 0.2 mg/kg/hr is adequate to maintain a target ACT of 200-220 seconds (J Extra Corporeal Technology 2014 Mar; 46(1): 94-97).

During ECMO, leaving a minimal degree of intracardiac blood flow may help in preventing stagnation of blood in cardiac chambers.

## BACKROUND INFORMATION

### Introduction

Heparin (McLean) remains the drug of choice for more than 60 years required for anticoagulation during cardiopulmonary bypass (CPB) because of its rapid onset of action after intravenous administration, reliable effect, rapid reversibility with protamine and low cost. However, hypersensitivity (anaphylaxis) to heparin poses substantial challenges for cardiac surgical interventions, although rare, has been reported.

Heparin-induced thrombocytopenia (HIT) is caused by auto-antibodies directed against endogenous platelet factor 4 (PF4) after heparin administration. HIT antibodies cause PF4 to be released from endothelial cell surfaces. A complex is formed by the binding of the antibodies with PF4, heparin and the surface of platelets and/or the endothelial cell surface. These complexes cause platelet activation, further release of PF4 and a positive feedback loop resulting in antibody coated platelets being removed by the reticulo-endothelial system. This eventually causes thrombocytopenia, a significant increased risk of venous and/or arterial thrombosis and possibly death. A more rapid onset of HIT may be seen in some patients who have received heparin previously, usually within the past three months. (Warkentin, 2003, Keeling et al 2006)

### Ideal Anticoagulant

An ideal anticoagulant for cardiopulmonary bypass would have the following properties:

- Clearance that is not dependant on organ-based excretion.
- Effective in minimising the activation of coagulation during CPB.
- A rapid and simple method of monitoring its anticoagulant effects should be available.
- Rapid and complete reversibility of the anticoagulant effects.
- Low immunological reactivity.
- No cross reactivity with HIT antibodies.
- Not dependant on a co-factor for anticoagulant action.

Anticoagulation with unfractionated heparin (UFH), point-of-care monitoring by activated clotting time (ACT) systems and reversal of anticoagulation with protamine comprise a longstanding and well-established strategy permitting cardiac surgery.

This approach is so universally entrenched that there is only limited experience with other forms of anticoagulation for this indication.

There are three alternative anticoagulation protocols for cardiac surgery with CPB in patients diagnosed with HIT that are currently most often used and they are well-described in recent literature.

- Use any direct thrombin inhibitor for anticoagulation to avoid any heparin exposure
- Choose a combination of heparin with a potent, short-acting antiplatelet agent such as a platelet GPIIb/IIIa antagonist, or use a prostaglandin of procoagulant activity
- Wait until the transient HIT antibodies are no longer detectable, perform CPB with heparin, and establish an alternative anticoagulation in the postoperative period.

### Diagnosis

A diagnosis of HIT can be made when HIT antibodies are detected in association with one of the following:

- An unexplained platelet count fall of > 50% from the baseline platelet count. This is taken to be the highest count in the period after heparin treatment commenced.
- Venous or arterial thrombosis
- Skin lesions at site of injection
- Acute, systemic anaphylactic reactions that occur after IV heparin administration.

## Guidelines for Surgery on HIT Patients

Both the American College of Chest Physicians and the British Committee for standards in Haematology have recommended Bivalirudin as the preferred anticoagulant for HIT patients requiring CPB during surgery.

- Patients with history of HIT that test negative for HIT antibodies, it is recommended that unfractionated heparin is used, but heparin must be avoided in the pre and post-surgery phases, as it takes up to 5 days for significant levels of HIT antibodies to be generated, by which time the circulating heparin received during surgery will have been eliminated and should not be present to react with HIT antibodies. (Selleng et al, 2008). This option requires authorisation from the Surgeon, Haematologist and the Perfusionist prior to initiating CPB with heparin.
- Patients presenting with HIT and currently test positive for HIT antibodies, if possible, delay surgery until HIT antibodies are not present and then perform surgery using unfractionated heparin, but avoiding heparin in the pre and post-surgery phases.
- Patients presenting with HIT, who are antibody positive and for whom surgery cannot be delayed, the use of Bivalirudin is recommended (Keeling et al, 2006, Warkentin et al, 2008).

## Bivalirudin

Bivalirudin (Angiomax) is a short-acting, bivalent, reversible direct thrombin inhibitor. Its pharmacokinetics is characterized by a rapid onset of effect and a short half-life of approximately 25 minutes. It interferes with fibrin formation, platelet aggregation, factor XII activation, and other effects associated with blood coagulation. Since it binds reversibly to thrombin, the anticoagulant effects of bivalirudin disappear soon after treatment is discontinued. The drug's elimination is predominately achieved by proteolytic cleavage and, to a minor extent, by renal excretion.

Bivalirudin has been safely studied in large studies enrolling more than 40,000 patients (Reference needed) and is approved by the FDA in patients undergoing percutaneous coronary intervention, including those with or at risk of HIT. In pilot investigations and a recent multicentre study comparing bivalirudin and heparin-protamine in non-HIT patients, protocols for CPB anticoagulation with bivalirudin have been established and successfully used for anticoagulation during CPB. The coronary artery bypass (CABG) HIT thrombosis syndrome (TS) on – and off-pump (OPCAB) safety and efficacy (CHOOSE-ON Dyke et al 2006, Smedira et al 2006, Koster et al, 2007) trial was designed to assess the safety and efficacy of bivalirudin anticoagulation during CPB in patients with confirmed or suspected HIT and (or) antiplatelet factor 4/heparin (anti-PF4/H) antibodies.

The results of the EVOLUTION trials (Quote the reference here) show that bivaluridin is a safe and effective anticoagulant for patients undergoing OPCAB and CPB procedures. A rapid onset of action, along with rapid elimination essentially independent of specific organ involvement, renders bivalirudin a potentially valuable alternative to heparin for high-dose anticoagulation during cardiovascular surgery and CPB.

No anaphylactic reactions to bivalirudin have been reported. Moreover, standard ACT assays have been shown to provide satisfactory point-of-care monitoring of bivalirudin anticoagulation during CPB.

Angiomax should be administered via an intravenous line. No incompatibilities have been observed with glass bottles or polyvinyl chloride bags and administration sets. The following nine drugs should not be administered in the same intravenous line with Angiomax, since they resulted in haze formation, microparticulate formation, or gross precipitation when mixed with Angiomax: alteplase, amiodarone HCl, amphotericin B, chlorpromazine HCl, diazepam, prochlorperazine edistylate, reteplase, streptokinase, and vancomycin HCl.
The following six drugs show dose-concentration physical incompatibility

**Contraindications**

- Hypersensitivity
- Uncontrollable active bleeding
- Major blood clotting disorders
- Acute gastric or duodenal ulcer

- Cerebral haemorrhage
- Severe cerebro-spinal trauma
- Bacterial endocarditis
- Severe uncontrolled hypertension
- Diabetic or haemorrhagic retinopathy
- Proximal use of spinal/epidural anaesthesia

**Special Populations**
*Pregnant Women***:** There are no studies available evaluating bivalirudin in pregnant women.
*Nursing Women*: It is not known whether bivalirudin is excreted in human milk.
*Paediatrics (<18 years of age):* The safety and efficacy of bivalirudin in children have not been established.
*Geriatrics (>65 years of age):* Across studies approximately 45% of patients were >_ 65years of age and 18% of patients were >_75 years old. Elderly patients experienced more bleeding events than younger patients.